# Clinical aspects of recurrent venous thromboembolism

Tan, M.

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# Diagnostic management of clinically suspected acute deep vein thrombosis

M. Tan, C.J. van Rooden, R.E. Westerbeek, M.V. Huisman

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## ABSTRACT

Deep vein thrombosis (DVT) is a common disease that may lead to potentially fatal complications, such as pulmonary embolism. In the past decades several diagnostic tools and algorithms for DVT have been studied. Currently the combination of a clinical decision rule, D-dimer testing and compression ultrasonography has proved to be safe and effective for the diagnosis of DVT in the lower extremities.

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) can be useful as additional or secondary imaging modalities. This review will discuss the elements currently used in making the clinical diagnosis of DVT. These elements include clinical decision rules and D-dimer testing, different imaging investigations and the appropriate use of these within diagnostic algorithms in patients with clinically suspected DVT. Although current knowledge of the options available to diagnose DVT of the lower extremities is well established, there are still unresolved issues, including the optimal diagnosis of recurrent DVT and distal DVT. Furthermore, the diagnosis of DVT of the upper extremities will be discussed, including the different imaging modalities and the limitations of these techniques.

## INTRODUCTION

Deep vein thrombosis (DVT) of the lower extremities is a common disease with an estimated incidence between 0.5 and 1.6 per 1000 inhabitants in population-based studies.[1-3] Deep vein thrombosis of the upper extremity is relatively uncommon. About 4% of all DVT cases are located in the upper extremity.[4] Other conditions may simulate clinically manifest DVT, and in patients under suspicion of DVT based on clinical grounds, a definite diagnosis of DVT is confirmed in only 10–25% by imaging.[5,6] The consequence of falsely excluding DVT is a serious risk of pulmonary embolism, a potentially life-threatening disease, whereas a false positive diagnosis of DVT may lead to unnecessary anticoagulant related – sometimes major or fatal – haemorrhage.[7] Objective diagnosis of suspected DVT is therefore of great clinical significance and is mandatory. In the past decades several diagnostic tools and different algorithms have been proposed. The development of formal clinical decision rules and the D-dimer test have enabled a more structured clinical diagnosis of DVT. Furthermore, the introduction of ultrasonography (US) as an alternative to contrast venography facilitated the broad application of accurate noninvasive diagnosis. The use of an intravascular contrast agent with possible associated adverse events, and radiation exposure, is avoided by the use of US. Although many diagnostic aspects have been well established, several issues remain debated. This review aims to give an overview of the current knowledge of the diagnostic work-up of acute clinically manifest DVT, to address unresolved issues and give future perspectives of studies in the diagnosis of DVT.

## DIAGNOSIS OF A FIRST EPISODE LOWER EXTREMITY DEEP VEIN THROMBOSIS

### Clinical evaluation

*Clinical presentation*

Part of establishing the diagnosis of DVT is the medical history, physical examination and risk assessment of the patient. Several risk factors are known to increase the risk of developing a DVT. These risk factors are shown in Table 1.[2] Although many patients may present with one or several of these risk factors, a DVT can arise without any of these risk factors present, also known as an idiopathic DVT.

The symptoms of a DVT include pain in the affected leg, tenderness and swelling, increased warmth and changes in skin colour or a combination of these. However, such signs may also be observed in several other conditions and therefore simulate DVT. The differential diagnosis may include ruptured calf muscles or tendons, ruptured popliteal synovial membrane or Bakers cyst, muscle cramp, muscle hematoma, cellulitis, chronic

**Table 1.** Major and minor risk factors for DVT

| | |
|---|---|
| **Major risk factors** | |
| | Active malignancy |
| | Recent major surgery or trauma |
| | Recent hospitalization |
| | Prolonged immobilization |
| | Pregnancy and puerperium |
| | Hormonal therapy |
| | Positive family history |
| | Known thrombophilic factor |
| | Previous venous thromboembolism |
| **Minor risk factors** | |
| | Obesity |
| | Smoking |
| | Long distance flights |

venous insufficiency and lymphedema. Because of this broad spectrum of causes and the different management consequences, an objective establishment of the diagnosis of DVT is mandatory.

*Clinical decision rules*

Several clinical decision rules have been evaluated. The most widely tested and used clinical decision rule is the 'Wells decision rule'.[8] It utilizes information gathered by medical history and physical examination and consists of nine items. For each item one point is given; two points are deducted when an alternative diagnosis is considered more likely than DVT. The decision rule, initially divided patients into a low risk (≤0 points), an intermediate risk (1–2 points) and a high risk (≥3 points), was later dichotomized into a low probability (<2 points) or high probability (≥2 points). A high risk, as defined by a high probability Wells decision rule score, significantly increases the probability of DVT [posttest likelihood ratio, 5.2 (95% confidence interval (CI), 4.0–6.0%)], while a low probability risk score significantly reduces the probability of DVT [post-test likelihood ratio, 0.25 (95% CI, 0.21–0.29%).[9] The interobserver variability of the Wells decision rule is low ($\kappa = 0.85$) and assessing the score is independent of the experience of the physician.[8,10] Although the Wells decision rule brings advantages to the diagnostic work-up of DVT, there are some drawbacks. First, the Wells decision rule is not completely objective, due to the subjective element of considering an alternative diagnosis. Second, the Wells decision rule has not been validated to certain selected groups of patients with a different risk profile, including pregnant patients, patients with a history of DVT or pulmonary

embolism, patients who have used anticoagulant treatment for over 48 h, and older patients (>60 years).[9]

Several attempts have been carried out to simplify the Wells decision rule. Examples are the Kahn's decision rule – which uses four items, the St André decision rule – six items and Constans decision rule – five items.[11-13] Table 2 displays the clinical items of each of the four clinical decision rules. For all of these decision rules the performance was assessed for outpatients by plotting the Response Operating Curve (ROC) curve, i.e. a plot of proportion of true positive results versus the proportion of false positive results. The area under the ROC curve was 0.76 (95% CI, 0.70–0.81) for the Wells decision rule, 0.57 (95% CI, 0.50–0.63) for the Kahn decision rule, 0.67 (95% CI, 0.61–0.73) for the St Andre´ decision rule and 0.79 (95% CI, 0.74–0.84) for the Constans decision rule.[13] The Wells and Constans decision rule appear to be superior in performance than the St André and Kahn decision rule. In conclusion, the three simplified clinical decision rules seem to perform satisfactorily, with the Constans decision rule even slightly better than the Wells decision rule, however none of them have been adequately validated prospectively. Of

**Table 2.** Overview of the different clinical items in the four clinical decision rules.

| **Clinical items** | **Wells (points)** | **Kahn (points)** | **St Andre´ (points)** | **Ambulatory Constans (points)** |
|---|---|---|---|---|
| Male sex | - | 1 | - | 1 |
| Cancer | 1 | - | 1 | - |
| Lower limb paralysis or immobilization | 1 | - | 1 | 1 |
| Confinement to bed | 1 | - | - | 1 |
| Orthopaedic surgery <6 months | - | 1 | - | - |
| Unilateral lower limb pain | - | - | - | 1 |
| Local warmth | - | 1 | 1 | - |
| Localized tenderness | 1 | - | - | - |
| (Whole) limb enlargement | 1 | - | - | 1 |
| Calf enlargement ‡3 cm compared to the other site | 1 | - | - | - |
| Unilateral pitting edema | 1 | - | 1 | - |
| Superficial venous dilatation | 1 | 1 | 1 | - |
| Other diagnosis at least as plausible as DVT | -2 | - | -1 | -1 |
| *Cut-off points* | *≤ 0: low* | *0: low* | *≤ 0: low* | *≤ 0: low* |
| | *1–2: moderate* | *1–2: moderate* | *1–2: moderate* | *1–2: moderate* |
| | *≥ 3: high* | *≥ 3: high* | *≥ 3: high* | *≥ 3: high* |
| | *Or:* | | | |
| | *< 2: unlikely* | | | |
| | *≥ 2: likely* | | | |

DVT: deep vein thrombosis

note, both the St Andre´ and Constans decision rule include the subjective element of 'another diagnosis more likely than DVT'.

Another way to approach patients with a clinically suspected DVT is the physicians' empirical judgment. In this method the physician makes an estimation of the risk of DVT in the patient without using a standardized decision rule. The patients are classified as having a low (<20%), intermediate (21–79%) or high (>80%) probability of DVT according to the assessment of the clinician. Only a limited number of studies have been performed evaluating the empirical judgment. A meta-analysis of these studies shows a positive likelihood ratio of 6.2 (95% CI, 1.0–40.0%) and a negative likelihood ratio of 0.18 (95% CI, 0.133–0.26).[9] In comparison with the Wells score, the empirical judgment performed similarly. Drawbacks for the empirical judgment include interobserver variation, the dependency upon the experience of the physician and the lack of validation in studies.

Table 3 presents the four clinical decision rules and the empirical strategy with the proportion of patients categorized as low, intermediate and high risk and the percentage of patients with a DVT in each category.

In conclusion, while several clinical decision rules have been evaluated, in our opinion the Wells clinical decision rule is the preferred one, since it has been extensively validated in prospective management studies. Limitations of the Wells decision rule are the subjective element and the use in specific patient populations.

**Table 3.** Overview of different clinical decision rules for DVT: fraction of patients in three categories of pretest probability for DVT and incidence of DVT for each category.

| Rule | Study | N (% DVT) | Patient percentage in low category (% DVT) | Patient percentage in intermediate category (% DVT) | Patient percentage in high category (% DVT) |
|---|---|---|---|---|---|
| Wells | Goodacre et al [9]* | 271 (24) | 38 (7) | 39 (21) | 32 (62) |
| Kahn | Kahn et al [11] | 271 (27) | 20 (9) | 71 (26) | 9 (76) |
| St Andre | Constans et al [12] | 273 (24) | 52 (11) | 42 (33) | 6 (76) |
| Constans | Constans et al [13] | 282 (25) | 25 (4) | 64 (27) | 11 (58) |
| Empirical | Cornuz et al [10] | 278 (29) | 31 (13) | 46 (24) | 23 (63) |
| | Miron et al [75] | 270 (21) | 29 (1) | 61 (18) | 10 (100) |
| | Wells et al [76] | 527 (25) | 49 (5) | 33 (29) | 18 (73) |

*Depicted from meta-analysis; median prevalence for studies included in meta-analysis; N: number; DVT: deep vein thrombosis.

*D-dimer testing*

D-dimers are generated by fibrinolysis of a thrombus, in which cross-linked fibrin is degraded by plasmin. D-dimer tests recognize these D-dimers by monoclonal antibodies.

The main objective of D-dimer testing is to safely rule out DVT in correlation with a low to intermediate clinical prediction rule, because of its high sensitivity. Several D-dimer assays are available with different sensitivities and specificities. The D-dimer assays have either an intermediate sensitivity and specificity [semiquantitative latex (sensitivity 61–100%, specificity 22–92%), qualitative latex (sensitivity 77–87%, specificity 100–100%), whole blood assay (sensitivity 53–100%, specificity 20–94%) or a high sensitivity at cost of a low specificity [enzyme-linked immunosorbent assay (sensitivity 50–100%, specificity 5–82%), enzyme-linked fluorescence assay (sensitivity 88–100%, specificity 5–82%), quantitative latex (sensitivity 57–100%, specificity 26–97%).[14] A comparison of the different assays is difficult, because of the heterogeneity of the different tests. The semiquantitative and qualitative latex and whole blood assay are qualitative tests. Drawbacks of qualitative D-dimer tests are the high observer dependency, especially in case of an intermediate result.[15] Furthermore these tests have the inability to detect minimal elevations in D-dimer levels, resulting in a low sensitivity. For these reasons the preference exists for the quantitative assays. A normal D-dimer result as a sole diagnostic test cannot be used to withhold anticoagulant therapy in patients with a suspected DVT. The D-dimer test has always to be used with the combination of a clinical decision rule or US (see Diagnostic Algorithms).[16] Additionally, using an elevated D-dimer test alone to establish the diagnosis of DVT is also not appropriate, because of the low specificity. This low specificity is caused by the increase of the D-dimer level in other conditions, including infection, inflammation, cancer, surgery and trauma, extensive burns or bruises, ischemic heart disease, stroke, peripheral artery disease, ruptured aneurysm or aortic dissection or pregnancy.[17]

Furthermore the clinical usefulness of a D-dimer test is diminished in different settings, including inpatients, postoperative patients, during pregnancy or postpartum, in patients with a high clinical probability or with previous venous thromboembolic (VTE) event and in elderly patients. The proportion of patients with a high D-dimer result is greatly increased in these patient populations.[17] The extent and localization of the DVT also influence the sensitivity of the D-dimer test. The sensitivity of the D-dimer test in patients with a distal DVT is lower than in patients with a proximal DVT. The sensitivity of a D-dimer test for distal DVT is 86% (95% CI, 84–88%), while for proximal DVT the sensitivity is 98% (95% CI, 97–99%).[18] In most patients the levels of D-dimer remain elevated during the first days of treatment. However, there is an initial rapid decrease in D-dimer, which can cause the value of D-dimer to drop below the cut-off level.[19] With the use of intravenously administered heparin, the decline can be 30–40% in the first day after the start of the treatment.[20,21] The use of low molecular weight heparin (LMWH) and oral Vitamin K Antagonist (VKA) treatment may cause a drop in D-dimer levels as well. The sensitivity of the D-dimer test declines during the use of VKA treatment to 69.2% (95% CI, 42.2–87.3%).[19] Therefore a D-dimer cannot reliably be used to exclude a DVT during

anticoagulant therapy and US examination is mandatory in this group of patients. A final drawback of the D-dimer tests is the great diversity of tests being used. Because of a lack of a reference method for D-dimer assays, international standardization is not possible. Apart from the conventional D-dimer assays, very quick D-dimer tests have been evaluated. The advantage of these tests is the quick test result, especially suitable in emergency department setting. A limited amount of studies, which included small numbers of patients, have been performed. In these studies the near patient D-dimer test gave promising results (sensitivity 94.1–100%, specificity 40.4–52.9%).[22-24] However a drawback of these assays is the qualitative test result. A quantitative near patient D-dimer test has also been assessed with a high sensitivity and specificity (sensitivity 96.6%, specificity 60.8%).[25] These near patient D-dimer tests seem suitable for incorporation in the diagnostic strategy of DVT. However this has to be properly evaluated in prospective management studies.

In conclusion, a D-dimer test can be used to safely rule out acute DVT in combination with a low or intermediate clinical probability using Wells' decision rule (see Diagnostic Algorithms). The major limitation of the D-dimer testing is its low specificity and its limited value in specific patient populations and clinical settings. The near patient D-dimer tests seem promising, but have to be properly validated in prospective management studies.

## Imaging

*Contrast venography*

Traditionally, contrast venography has been used as the golden standard for diagnosing DVT. The diagnosis of DVT is confirmed with the finding of a constant intraluminal filling defect on two or more views. Treatment can be withheld safely when a technically adequate contrast venogram shows no evidence of DVT.[26,27] However, venography has many disadvantages. Not only the invasive nature of the technique, but also adverse reactions and venous endothelial toxicity following contrast administration are well known problems.[27] Furthermore contrast venography has a variation in interpretation in up to 10% of the cases and is relative expensive.[28] As a consequence contrast venography is now seldom used as a diagnostic investigation for the establishment of the diagnosis of DVT.

*Impedance plethysmography*

Occlusive-cuff impedance plethysmography (IPG) is a noninvasive technique for detecting a proximal DVT. The technique measures blood volume changes in the leg as a change in electrical resistance (impedance). Several studies demonstrated the value of IPG in the diagnosis of patients with suspected DVT.[29,30] Compared to venography the

technique has an overall sensitivity of 93% and a specificity of 95% for the diagnosis of proximal DVT.[31] Although IPG has proved its efficacy, it is hardly used anymore. This is mainly because US has shown a higher accuracy and is a simpler noninvasive technique.[32] IPG has therefore largely been replaced by US as a noninvasive technique for the diagnosis of acute DVT.

*Ultrasonography*

In routine clinical practice, ultrasonography has become a widely accepted and a primary diagnostic procedure for the work up of clinically suspected DVT. Initially, attempts were made to diagnose DVT by visualization of a thrombus. However this method performed relatively poorly, since its visibility may be dependent on the age of the clot. A fresh clot may appear almost anechoic and go unnoticed by visual inspection, leading to under diagnosis.[33] At present, several US techniques can be applied in the investigation of clinically suspected DVT. Methods commonly used, include compression ultrasonography (CUS), colour Doppler Flow Imaging (CDFI) and spectral Doppler.

Compression ultrasonography is commonly used in the radiological diagnosis of a first episode of clinically suspected DVT. In this technique, the femoral and popliteal veins are

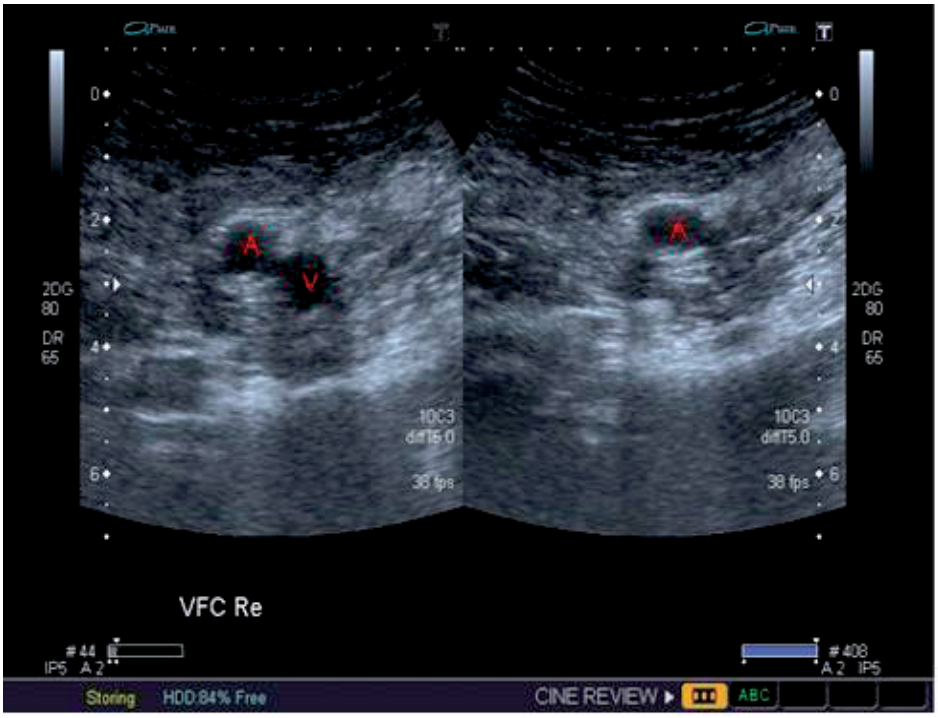


**Figure 1.** Compression ultrasonography. Left image is before compression, right image during compression. Compressible femoral vein. A, artery; V, vein.

directly visualized and subsequently assessed for their compressibility in the transverse plane (two-point CUS) (figure 1). Patients are preferably examined in supine position with the head of the bed raised 20–30º to enhance venous filling in the legs. In a two-point CUS strategy, the common femoral vein is identified first. The common femoral vein is positioned medially to the common femoral artery. Subsequently, the popliteal vein is identified by placing the transducer in the popliteal fossa in prone position (or in a sitting position with the legs slightly flexed). The vein is positioned above the popliteal artery. In the absence of a DVT, gentle pressure with the transducer (in a transverse plane) causes the venous lumen to completely collapse: the vein is compressible. When a thrombus is present, compression of the vein is not possible even with a more firm pressure. This inability to completely compress the vein, or non-compressibility, is the criterion in establishing the diagnosis of DVT (figure 2). Non-compressibility of either the femoral or popliteal vein, or both, is diagnostic for a first episode of acute proximal DVT in patients suspected for clinically manifest DVT, with a sensitivity of 93.8% (95% CI, 92–95.3%) and specificity of 97.8% (95% CI, 97–98.4%).[34] The interobserver agreement of CUS is excellent with a $\kappa = 1$ for proximal DVT of the leg.[35, 36] As an alternative for the two point strategy, extended CUS of the proximal deep venous system can be applied. Starting at the common femoral vein, subsequent stepwise compression is applied approxi-

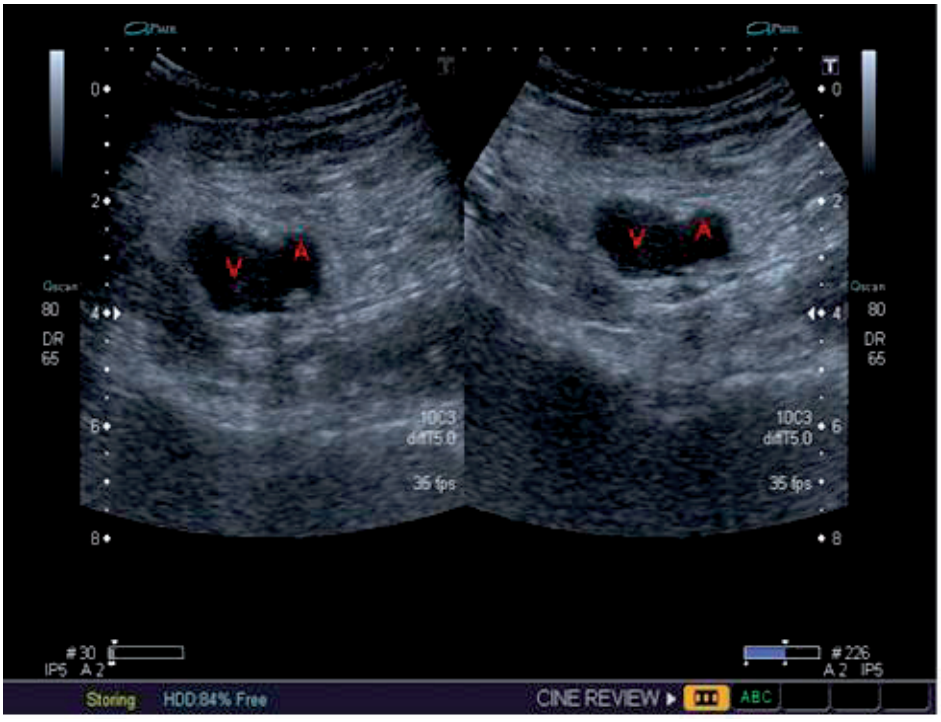


**Figure 2.** Compression ultrasonography. Non-compressible femoral vein. A, artery; V, vein.

mately every 1 cm along the course of the femoral and popliteal vein. An extended CUS examination could hypothetically lead to identification of more thrombosis. However, Cogo et al (1993) showed, by evaluating the distribution of DVT, that all proximal DVTs were located as follows: isolated popliteal vein (10%); popliteal and superficial femoral vein (42%); popliteal, superficial and common femoral vein (5%), entire proximal venous system (35%) and common femoral and superficial vein or iliac vein (8%).[37] Of note, no isolated superficial femoral vein thrombosis was detected. Based on this study, we prefer the two-point CUS method, which is time-efficient by limiting the examination of the proximal veins to the common femoral vein and popliteal vein. In summary, CUS is a simple, accurate and noninvasive diagnostic tool and serves as a first choice of imaging modality in the diagnostic work up of patients with a first episode of clinically suspected DVT of the lower extremities.[36]

Colour Doppler Flow Imaging may serve as an alternative or complementary technique in the diagnosis of thrombosis. CDFI provides colour code information about the velocity and direction of flow. Criteria in diagnosing thrombosis include absent (or partially absent) colour-coded flow. For CDFI, the sensitivity for the proximal deep veins of the legs is 95.8% (95% CI, 85.7–99.5%) with a specificity of 92.7% for all DVT (95% CI, 89.7–95.2%).[34] Subsequently, spectral Doppler examination can be added to the examination of CDFI. In a spectral Doppler, the spectrum of flow velocities is graphically represented and quantitatively and qualitatively analyzed. In summary, with US, the diagnostic criteria of a DVT include (a combination of) visualization of the thrombus, incompressibility of a venous segment and abnormal flow in Doppler examination.

Based on the reported high accuracy in literature and its widespread acceptance, CUS is a simple, robust and noninvasive diagnostic tool and serves as a first choice of imaging modality in the diagnostic work up of patients with a first episode of clinically suspected DVT of the lower extremities.[36] As an alternative, CDFI examination may be used, as it seems to perform equally well when compared to CUS.

*Isolated distal DVT*

In contrast to proximal DVT of the leg, distal DVT has been less well examined. Regardless of the method of US, accuracy is substantially lower as compared to proximal DVT. CUS and Doppler analysis were reported to have sensitivities that were just over 70% (73%; 95% CI, 54–93%).[3] In other studies, substantial numbers of examined cases were inconclusive.[38,39] Doppler US also has limited value with a sensitivity of 71% (95% CI, 64.6–77.2%) for distal DVT.[34] In addition, there is a high chance of false positive findings due to the complex anatomy of the distal veins.

*Complete compression ultrasonography (CCUS)*

Complete compression ultrasonography (CCUS) is a combination of the extended CUS of the proximal deep veins and CUS of the distal deep veins of the leg. CCUS was introduced by Elias et al (2003) to avoid the need for a repeat US in patients that had an initially normal CUS.[40] This second CUS is necessary to avoid a distal DVT propagating over days into the proximal–popliteal vein and above – system without being detected (see Diagnostic Algorithms). Of importance, no study has been performed in which CCUS has been compared with the reference method contrast venography. Therefore the sensitivity and specificity of CCUS are unknown. The main advantage of the use of the CCUS is the lack of necessity for a repeat US after 1 week. However, there are several drawbacks. Firstly, the technique is time consuming. The additional needed US time varies between 4 and 30 min, depending on the operators' personal skills and training.[41] Furthermore, these skills and training determine the accuracy of the examination of the distal deep vein system. Schellong reported very low rates of inadequate examinations of 0.4–1.4%.[41] These low rates are contradictory to the high inadequacy rates reported in other studies evaluating distal DVT. In these latter studies inadequacy rates between 32% and 55% were reported.[38,39] Finally, around 50% of DVTs diagnosed by CCUS are isolated distal DVT.[42] These cases of distal DVT can consist of either true positive small distal DVT that could also resolve spontaneously or false positive distal DVT. Therefore a risk of over diagnosing DVT is present with associated bleeding complications.[43]

In conclusion, although CCUS seemed to have promise because it is efficient (1 d testing) and can be performed adequately by experienced operators, there are many disadvantages to this technique. These include time-inefficiency, potential for over diagnosing and over treating patients with a distal DVT and a high rate of inadequate examinations. In routine practice the use of CCUS as an established test in DVT diagnosis cannot be recommended yet.

*Computed tomography and magnetic resonance imaging*

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) may serve as an alternative or complementary imaging tool to US. However, compared to US, both modalities are less well evaluated. In a recent meta-analysis, a pooled sensitivity for CT-venography was 96% (95% CI, 93–98%) with a pooled specificity of 95% (95% CI, 93.6–96.5%).[44] Of note, different techniques and different diagnostic criteria were used for the diagnosis of proximal DVT. Furthermore most studies were performed in patients with suspected pulmonary embolism, in which the CT scan was subsequently extended to the legs, usually in patients without symptoms or signs of a thrombosis of the leg. MR-venography can be performed with or without intravenously administered gadolinium and both techniques have been evaluated for their accuracy. The pooled sensitivity and specificity of MR-venography were reported to be 91.5% (95%CI, 87.5–94.5%) and 94.8%

(95% CI, 92.6–96.5%), respectively.[45] In conclusion, although the sensitivity and specificity of CT-venography and MR-venography are within the range of US; the safety of withholding anticoagulant treatment on the basis of a normal CT-venography or normal MR-venography has not been studied and therefore these modalities cannot be recommended as first line imaging approaches. CT-venography or MR-venography could be useful in patients with a suspected DVT in whom US cannot be performed or is less reliable, such as patients with morbid obesity, casts and patients with a suspected deep vein thrombosis in the iliac or inferior cava vein. Furthermore, patients with a suspected anatomical anomaly of a vein can be imaged by CT-venography or MR-venography.

## Diagnostic algorithms

Several diagnostic algorithms can be applied in patients with a first episode of clinically suspected acute DVT. The most validated approaches include the serial two point CUS

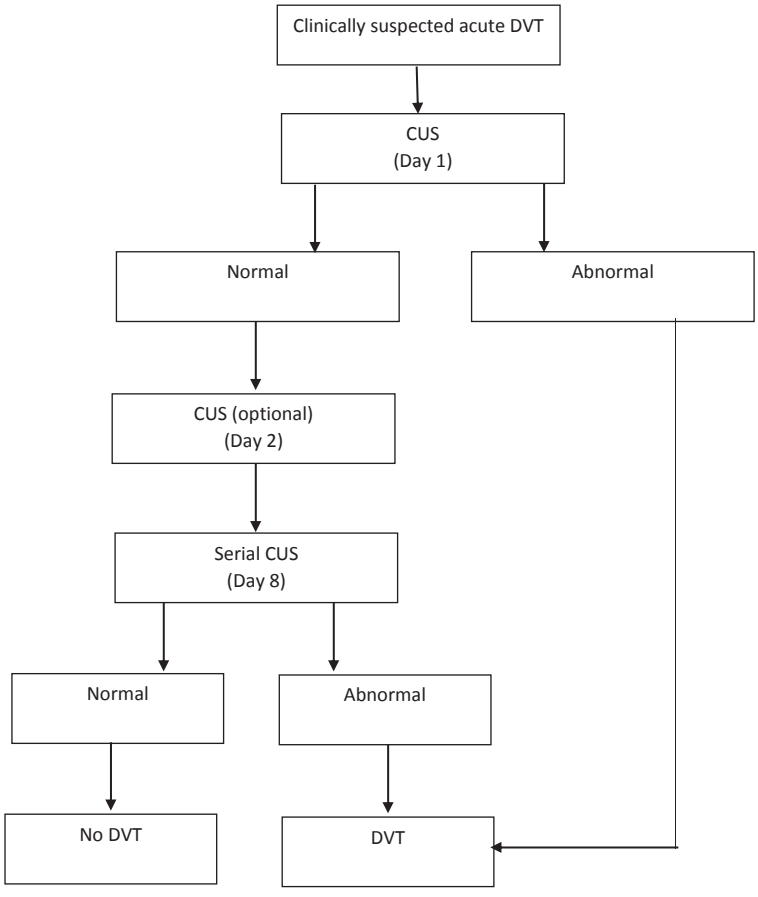


**Figure 3.** Algorithm 1; serial CUS.

and an algorithm consisting of a combination of clinical decision rule, D-dimer test and CUS. Recently algorithms with the use of CCUS have been studied. In order to detect distal DVT that has propagated into the proximal venous system, several algorithms that included a serial CUS have been proposed. First, an algorithm that solely constitutes of US tests was suggested (see Algorithm 1, figure 3). In this algorithm, CUS was performed in all patients with clinically suspected DVT. In case of an initial normal CUS, a second CUS was performed on the following day and, when still normal, after 1 week. A CUS indicating a DVT was followed by ascending venography to confirm the diagnosis. This algorithm was prospectively studied: of the 491 included patients, 490 underwent CUS of whom 78 were diagnosed with DVT on day 1 and 6 patients were diagnosed on day 2 and 8. The remaining 406 patients were left untreated. An abnormal CUS had a positive predictive value of 94% (95% CI, 87–98%). During 6 months follow-up 1.5% (95% CI, 0.5–3.3%) of patients with repeatedly normal tests were diagnosed with VTE.[46] This approach, of performing two ultrasonographies after a normal US is inconvenient for patients, labour intensive and expensive. The mean number of additional US is high, at 1.6.[5] Therefore a simpler algorithm was proposed in which one US test after 1 week was performed in case of an initially normal US (see Algorithm 1, figure 3). This algorithm was also studied prospectively; 1702 patients had an adequate CUS. Out of these patients, 412 patients had an abnormal CUS, of whom 400 were detected at presentation and 12 on repeat testing. The cumulative VTE failure rate using this approach was 0.7% (95% CI, 0.3–1.2%) after 3 months follow-up. The mean number of additional US was 0.8 using this algorithm.[5] To lower the additional US tests a combination with the D-dimer test was proposed. In this algorithm a CUS was performed in all patients with a clinical suspected DVT (see Algorithm 2, figure 4). The patients with an abnormal US were treated with anticoagulant treatment, while in patients with a normal US a D-dimer test was performed. If this D-dimer test was normal a DVT was excluded. In case of an abnormal D-dimer test repeat CUS was performed after 1 week. Depending on this CUS result patients were treated or treatment was withheld. With this strategy, 946 patients received a CUS, because of a clinical suspected DVT, of whom 260 patients had an abnormal CUS. The remaining 686 patients with a normal CUS result underwent D-dimer testing. In 598 patients the D-dimer test result was normal, so the diagnosis of DVT was excluded. The 88 patients with an abnormal D-dimer result underwent repeat CUS. In 83 patients the CUS was normal and DVT was excluded. In the remaining five patients the CUS became abnormal and DVT was confirmed. The cumulative 3-month VTE failure rate in patients with normal CUS and D-dimer test was 0.4% (95% CI, 0.0–0.9%) with a low mean number of 0.1 of additional US tests per referred patient.[47]

The third algorithm is the combination of a clinical decision rule, D-dimer test and CUS (see Algorithm 3, figure 5). The clinical decision rule divides patients into 'DVT likely' and 'DVT unlikely' groups. A low clinical decision rule (<2) and a normal high sensitive

quantitative D-dimer test can safely exclude a first DVT without additional imaging tests.[16] When a patient with a low clinical decision score has an elevated D-dimer test, additional imaging with CUS is indicated. A high clinical probability score (≥2) significantly increases the risk of a DVT, consequently an US examination has to be performed prior to performing a D-dimer test. When the CUS is abnormal, a DVT is diagnosed. A normal CUS cannot exclude a DVT, because of the risk of extension of a distal vein thrombosis into the proximal system. Therefore a D-dimer test has to be performed. A normal D-dimer test justifies withholding anticoagulant therapy. In case of an elevated D-dimer result a repeat US after 1 week has to be performed. In a prospective study, 317 patients had a low clinical decision score and underwent D-dimer testing. In 218 patients DVT was excluded by a negative D-dimer test result. This combination showed a 3-month VTE failure rate of 0.9% (95% CI, 0.1–3.3%). In 99 patients the D-dimer test was positive and consequently the patients underwent CUS, which confirmed the diagnosis of DVT in 14 patients. In the remaining 85 patients anticoagulant therapy was withheld; none of these patients subsequently had a VTE event in the 3 months of

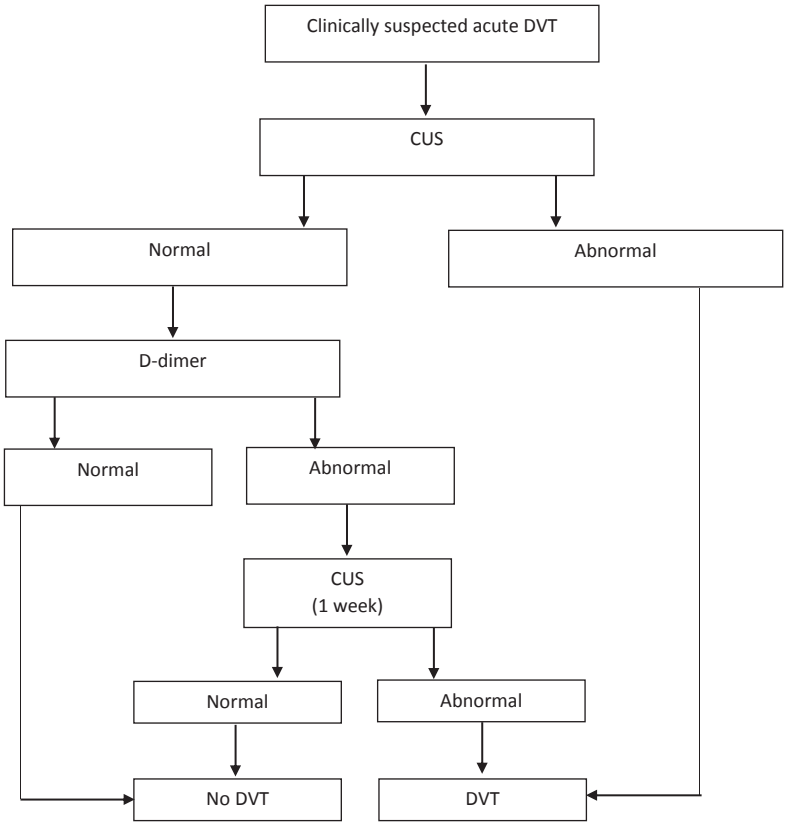


**Figure 4.** Algorithm 2; CUS and D-dimer test.

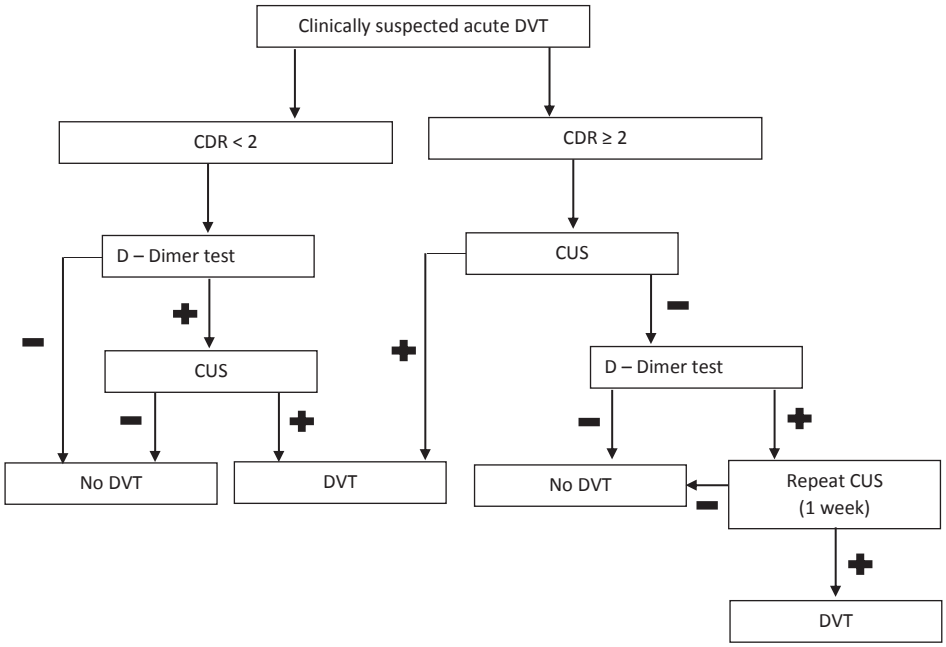


**Figure 5.** Algorithm 3; Clinical decision rule, D-dimer and CUS.

follow-up. Of the patients with a high clinical decision score, 249 patients underwent CUS, which confirmed the diagnosis of DVT in 68 patients. The remaining 181 patients underwent D-dimer testing; 81 patients had a negative result and DVT was ruled out, none of these patients developed a VTE event after 3 months of follow-up [0% (95% CI, 0–2%)]. The remaining 100 patients underwent repeat CUS and DVT was confirmed in three patients.[48] Alternatively, the use of CCUS in an algorithm has been assessed. In this technique anticoagulant therapy is withheld after a single negative CCUS. In a prospective study including 623 patients CCUS ruled out DVT in 410 patients. Its safety proved to be high, with a 0.5% (95% CI, 0.1–1.8%) VTE risk after 3 months.[40] These results were confirmed in a second study [3-month VTE failure rate 0.3% (95% CI, 0.1–0.8%).[49] In a randomized study, serial two-point US plus D-dimer has been compared with complete compression whole-leg colour-coded Doppler US. Both strategies performed similarly. The 3 months incidence of confirmed symptomatic VTE after an initially normal US result was 0.9% (95% CI, 0.3–1.8%) for the two-point strategy and 1.2% (95% CI, 0.5–2.2%) for the whole leg strategy.[50] Although the use of the CCUS seems promising, the risk of over diagnosing distal DVT is substantial and therefore an algorithm using CCUS is not recommended.

In conclusion, three well-validated algorithms exist, i.e. serial two-point proximal CUS, combined CUS and D-dimer test and combined clinical decision rule, D-dimer test and CUS. The addition of a clinical decision rule has made the diagnosis of DVT more struc-

tured and less (repeat) US examinations are needed to establish the diagnosis of a first episode DVT. Therefore we recommend the use of a combination of a clinical decision rule, D-dimer and CUS for the diagnosis of a first episode of symptomatic DVT



## DIAGNOSIS OF A RECURRENT EPISODE LOWER EXTREMITY DEEP VEIN THROMBOSIS

The clinical diagnosis of recurrent DVT alone is unreliable. Therefore, accurate objective testing is required to avoid the incorrect conclusion that recurrent DVT is absent and so placing the patient at high risk of potentially fatal pulmonary embolism, or misdiagnosing DVT and exposing the patient unnecessarily to the risks of lifelong anticoagulant therapy. Although several diagnostic algorithms for suspected first DVT have been validated, the diagnosis of recurrent DVT poses a significant clinical dilemma and the optimal approach is still debated. A randomized study has demonstrated the safety of combining clinical probability, D-dimer testing and US for a first episode DVT.[48] The clinical decision rules have not been formally validated for the use of a suspected recurrent DVT.

The D-dimer test has been studied regarding the exclusion of the diagnosis of recurrent DVT. This test showed a low incidence of venous thromboembolic complications (0.75%, 95% CI, 0.02–4.09%) after 3 months in patients with a suspected recurrent DVT and a negative D-dimer test. However, in seven of the 134 (5%) patients the diagnosis of recurrent DVT was inconclusive. If these patients were considered to have had a recurrence of DVT, eight of the 134 (6%) would have had a recurrence. Furthermore, as a positive D-dimer test is not suitable for establishing the diagnosis of DVT, a diagnostic dilemma exists in case of a positive D-dimer result and an inconclusive US.[51]

Compression ultrasonography is the most widely used noninvasive test for the investigation of a suspected first DVT, with non-compressibility of the common femoral vein or popliteal vein considered diagnostic of acute DVT in symptomatic patients. However, the diagnosis of ipsilateral recurrent DVT by means of CUS is problematic because persistent abnormalities are present in approximately 80% and 50% of patients at 3 months and 1 year respectively, after a proximal DVT.[52-54] Therefore, when a patient with suspected recurrence has a non-compressible venous segment, it can be difficult to determine whether this represents new disease or a residual abnormality from previous DVT with an inherent risk for false-positive US results. Similarly, persistent abnormalities as well as non-filling segments in patients with previous DVT often make contrast venography, the reference standard test for a suspected first episode of DVT, non-diagnostic. In addition, venography is seldom performed anymore. Recurrent DVT is diagnosed by CUS when a new vein segment has become non-compressible or a previously normalized

vein segment has become non-compressible.[55] An increase in thrombus diameter by a previously affected segment can also be considered diagnostic of recurrent DVT. Initially, a cut-off level of an increase of 2 mm in thrombus diameter was proposed[55], which was later increased to 4 mm. The positive predictive value of an abnormal US was 90% (95% CI, 77–97%) for recurrent DVT.[56] However, interobserver agreement of measurement of a thrombus diameter was found to be poor.[57] The mean difference between the measurements was 2.2 mm (95th centile 8.0 mm). Compression ultrasonography (CUS) is therefore only accurate when ipsilateral recurrent DVT occurs in another venous segment than at the time of the first DVT or when a previously normal venous segment is abnormal. As an alternative, 99mTC-recombinant tissue plasminogen activator (rt-PA) scintigraphy imaging has been evaluated. This technique relies on the uptake of 99mTC-rt-PA by C-terminal lysine residues on fibrin. In case of the ageing of a thrombus, less fibrin sites are available and a progressive decrease in 99mTC-rt-PA uptake is present when compared with fresh thrombus. It has been shown that the uptake of 99mTC-rt-PA was absent after 30 days.[58] This technique can potentially distinguish between an old and new thrombus. However a few limitations exist. First, the use of 99mTC-rt-PA is not widely available and there is a high chance for interobserver variability.[58]

A recent study using Magnetic Resonance Direct Thrombus Imaging (MRDTI) evaluated the MR signal change over 6 months.[59] This method is based upon the paramagnetic properties of methemoglobin, which gives a high signal on T1 weighted images. The intensity of this signal correlates with the amount of methemoglobin. In this study it was observed that after 6 months the abnormal MR signal of the acute DVT event had vanished in all 39 patients, while in 12 patients the CUS examination was still abnormal. This indicates that MRDTI may potentially be an accurate method to distinguish a new recurrent event from an old thrombus in patients with acute suspected recurrent DVT.[59]

**Summary**

In summary, the diagnosis of DVT of the lower extremity has made many advances in the past decades. The combination of a clinical decision rule, D-dimer test and CUS has proved to be safe and efficient for the diagnosis of first episode proximal DVT. The recent method of CCUS is potentially able to replace serial two-point proximal CUS. However the diagnosis of isolated distal DVT in this technique is still an aspect of debate, related to over diagnosis and therefore CCUS cannot yet be advised as a first line diagnostic technique. CT and MRI have sufficient accuracy in patients for whom CUS is not possible or less reliable, but is not suitable as first line diagnostic imaging modality. Finally the diagnosis of ipsilateral recurrent DVT remains a diagnostic dilemma as no uniformly available technique is available to establish an accurate diagnosis. The diagnosis has to be based on currently defined criteria for CUS. These criteria include a new vein segment that has become non-compressible, a previously normalized vein segment that has

become non-compressible or an increase in thrombus diameter by a previously affected segment of 4 mm. To implement these criteria correctly, accurately documented reports of previous CUS examinations have to be available. The use of MRI is not recommended yet, because this technique has not yet been prospectively validated for patients with clinically suspected ipsilateral recurrent DVT.

## DIAGNOSIS OF UPPER EXTREMITY DEEP VEIN THROMBOSIS

Upper Extremity Deep Vein Thrombosis (UE-DVT) is a relatively uncommon entity. Approximately 4% of all venous thrombo-embolic events affect the veins of the upper extremity (brachial, axillary and subclavian vein), neck (jugular vein) or central thoracic veins (brachiocephalic and superior caval vein).[4] However, due to the increase usage of Central Venous Catheters (CVCs), especially when used in high-risk patients, such as those with malignancies receiving (intensive) chemotherapy, the incidence of UE-DVT is rising. Similar to DVT of the lower extremity, there is a clear risk of pulmonary embolism in patients with UE-DVT. Within the population of patients with UE-DVT, the prevalence of PE might be as high as 15–33%.[60] Most documented PE are subclinical, however, associated fatal events have been reported.[61] Moreover, the prognosis in patients with UE-DVT is poor; a mortality rate up to one-third has been reported at 3 months after a confirmed diagnosis of UE-DVT.[62] In view of the diagnosis of UE-DVT, clinical parameters are known to be unreliable. Overt symptoms and signs, such as pain or tenderness, warmth, swelling or edema, bluish discolouration or visible collateral circulation have a limited specificity. The diagnosis was confirmed in only about a third to a half of all patients in whom UE-DVT was clinically suspected.[63-65] Besides, unlike patients with a clinical suspicion of DVT of the leg, D-dimer tests are not evaluated in patients in whom UE-DVT is clinically suspected. Similar to clinical parameters, a D-dimer test may lack specificity, since many patients have clear contributing factors to increased levels, such as malignancies, critical illness and CVCs or combinations of these. In the diagnostic work-up of UE-DVT, diagnostic imaging is mandatory upon a clinical suspicion of thrombosis. Contrast venography is still recognized as the reference standard in the diagnosis of thrombosis.[66] With regard to the UE-DVT, contrast venography has high to moderate interobserver agreement rates (71–83%) and can be used as a reference test in clinical practise.[67] However, US is most often used clinically and has many advantages. Ultrasonography is a noninvasive modality, does not expose to ionizing radiation or intravenous contrast, can easily be performed at the bedside and is well accepted by patients. Several studies have evaluated the diagnostic accuracy of US in UE-DVT (Table 4). However, comparative data in which contrast venography was used as a reference standard are relatively sparse. A summary of the available studies is listed in Table 4

**Table 4.** Diagnostic accuracy of Doppler-ultrasonography in the diagnosis of upper extremity thrombosis with routine contrast venography as the reference standard.

| References | Patients n | CVC % | Technique* | Sensitivity % | Specificity % | Manifest/subclinical** |
|---|---|---|---|---|---|---|
| Prandoni et al [64] | 58 | 14 | CUS | 96 | 94 | Manifest |
| Prandoni et al [64] | 47 | N.I. | Duplex | 81 | 77 | Manifest |
| Prandoni et al [64] | 34 | N.I. | CDFI | 100 | 93 | Manifest |
| Baarslag et al [65] | 99 | N.I. | CDFI | 82 | 82 | Manifest |
| Baxter et al [70] | 19 | 74 | CDFI | 100 | 100 | Manifest |
| Köksoy et al [71] | 44 | 100 | CDFI | 94 | 96 | Mixed |
| Haire et al [69] | 43 | 100 | Duplex | 56 | 100 | Mixed |
| Bonnet et al [68] | 40 | 100 | Doppler | 93 | 93 | Mixed |

CVC: central venous catheter; N.I.: Not Indicated;
*Technique; CUS: compression ultrasonography; CDFI: colour doppler flow imaging.
**For definition manifest/subclinical, see text.

limited to those studies in which a cohort of consecutive patients underwent both (US and contrast venography) and the results were independently evaluated by blinded observers. Overall, the reported sensitivity of US in the diagnosis of upper extremity DVT among these studies ranged from 56% to 100%, whereas the specificity ranged from 82% to 100%.[64,65,68-71] In symptomatic patients, the technique of CUS had a good performance with a reported sensitivity of 96%, and a specificity of 94%.[64] These were the results of a single study in 58 patients with axillary and subclavian vein thrombosis, of whom a minority had CVCs (14%). However, if thrombosis is located more centrally, the accuracy of CUS is only moderate to poor. Overlying anatomic bony structures limit the possibility of applying compression. Köksoy et al reported a sensitivity and specificity of only 56% and 54% of sole CUS, in a study of 44 patients – all with CVCs.[71] A possible explanation could be that thrombosis in patients with CVCs tends to more often be centrally located, and therefore inaccessible to compression.[65,71,72] Another explanation for the lower accuracy of US in some studies may be a substantial number of subclinical events in patients with CVCs, and therefore a limited extent of the thrombosis.[69,71] CDFI may add to an increased detection-rate in more centrally located thrombosis and groups of patients with large numbers of CVCs (82–100% sensitivity).[64,65,70,71]

CT-venography and MR-venography may serve as an alternative when US is inconclusive and venography is contra-indicated. Only a very limited number of studies have been performed with these modalities. Neither CT-venography nor MR-venography are therefore validated to replace contrast venography.73 Algorithm 4 (figure 6) shows the possible incorporation of the different imaging techniques for the diagnostic management of a clinically suspected UE-DVT.

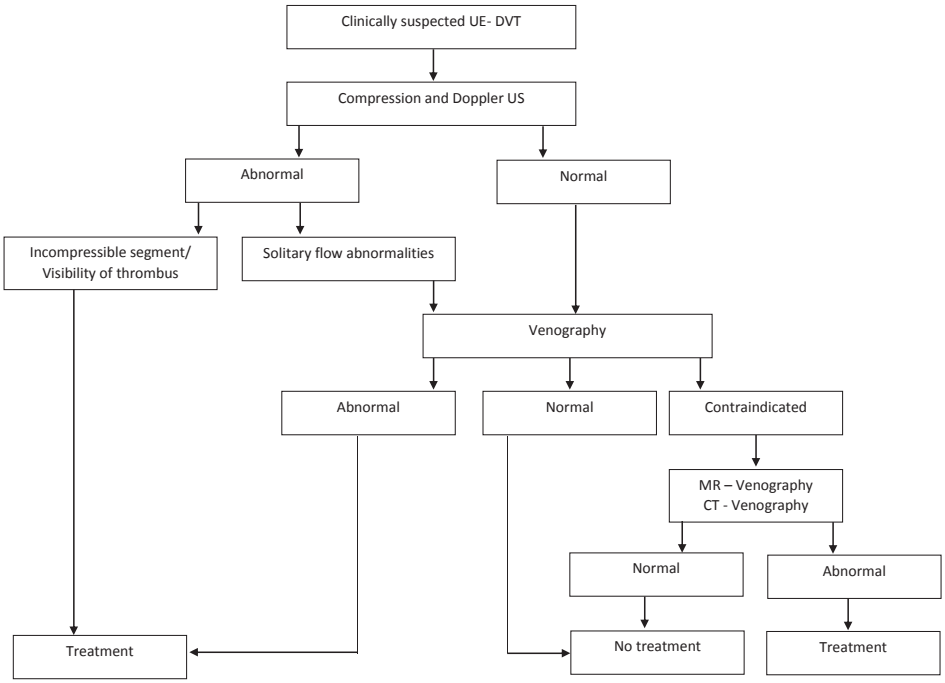


**Figure 6.** Algorithm 4; diagnostic management of UE-DVT.

## Summary

In summary, in the diagnostic work-up of UE-DVT, diagnostic imaging upon a clinical suspicion of thrombosis is mandatory. Available data on the accuracy of US in UE-DVT are relatively limited. In symptomatic UE-DVT, CUS was reported to have the best performance (sensitivity 96%, specificity 94%). However, application of CDFI is needed for the assessment of the more centrally located veins, which affects the overall accuracy of US in the diagnosis of UE-DVT (sensitivity and specificity >82%). In view of the mentioned advantages of US, patients with clinically suspected UE-DVT should undergo US initially. However, the safety of withholding treatment in case of a negative US in patients suspected for UE-DVT is uncertain, while the risk of pulmonary embolism is substantial.[60,74] As a consequence, in patients with normal US results, additional venography may be performed. Alternative strategies, such as serially performed US, spiral CT or MRI, may be useful and clearly of potential interest, but are not yet validated.

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