

# Deep Vein Thrombosis (DVT) clinical overview

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*Inspired from the ESC guidelines*

*doi:10.1093/eurheartj/ehx003*

## Introduction

- Venous thromboembolism (VTE) incidence increases sharply with **age** and appears steady over the last 25 years, despite preventive strategies.
- **Women** are more often affected at younger ages; this ratio reverses in the elderly.
- Incidence is similar in **Blacks** but lower in Asians.
- Almost two-thirds of VTE cases are **isolated deep vein thromboses** (DVTs), and 80% are proximal.

- Deep vein thrombosis is mostly **secondary to predisposing factors** common with pulmonary embolism (PE).
- **Distal (below knee)** DVTs are more frequently related to **transient situations** while proximal ones to chronic conditions.
- In 25–50% of first DVT episodes, **no predisposing factor** is identified.

- In patients with DVT without PE, short-term mortality rates of **2–5%** were reported, more frequent in proximal than distal DVT.
- **Recurrence risk is high**, especially within first 6 months.
- Early- and mid-term complications include **thrombosis extension, and PE and DVT recurrence.**

- **Long-term complications** include
- **post-thrombotic syndrome (PTS)**, defined as chronic venous symptoms and/or signs secondary to DVT.
- It represents the most frequent chronic DVT complication, occurring in 30–50% of patients within 2 years after proximal DVT.
- In 5–10% of cases, PTS is severe.
- Previous ipsilateral DVT, proximal location (ilio-femoral > popliteal), and residual veins obstruction are most significant PTS risk factors
- Obesity and poor INR control during the first 3-months treatment are additional independent risk factors.
- Villalta score is used for PTS diagnosis and treatment evaluation.

**Table 1 Villalta score<sup>11</sup>**

Symptoms and Clinical signs	None	Mild	Moderate	Severe
Symptoms				
Pain	0 points	1 points	2 points	3 points
Cramps	0 points	1 points	2 points	3 points
Heaviness	0 points	1 points	2 points	3 points
Paresthesia	0 points	1 points	2 points	3 points
Pruritus	0 points	1 points	2 points	3 points
Clinical signs				
Pretibial edema	0 points	1 points	2 points	3 points
Skin induration	0 points	1 points	2 points	3 points
Hyperpigmentation	0 points	1 points	2 points	3 points
Redness	0 points	1 points	2 points	3 points
Venous ectasia	0 points	1 points	2 points	3 points
Pain on calf compression	0 points	1 points	2 points	3 points
Venous ulcer	Absent	Present		

Points are summed into a total score (range 0–33). Post Thrombotic syndrome (PTS) is defined by a total score of  $\geq 5$  or the presence of a venous ulcer. PTS is classified as mild if Villalta score is 5–9, moderate if 10–14, and severe if  $\geq 15$  or venous ulcer is present.

# •Diagnosis

## 1-Deep vein thrombosis without pulmonary embolism

- *Clinical signs and symptoms* are highly variable and non-specific but remain the cornerstone of diagnostic strategy. Symptoms include pain, swelling, increased skin veins visibility, erythema, and cyanosis accompanied by unexplained fever

- *Probability assessment and D-dimer testing*

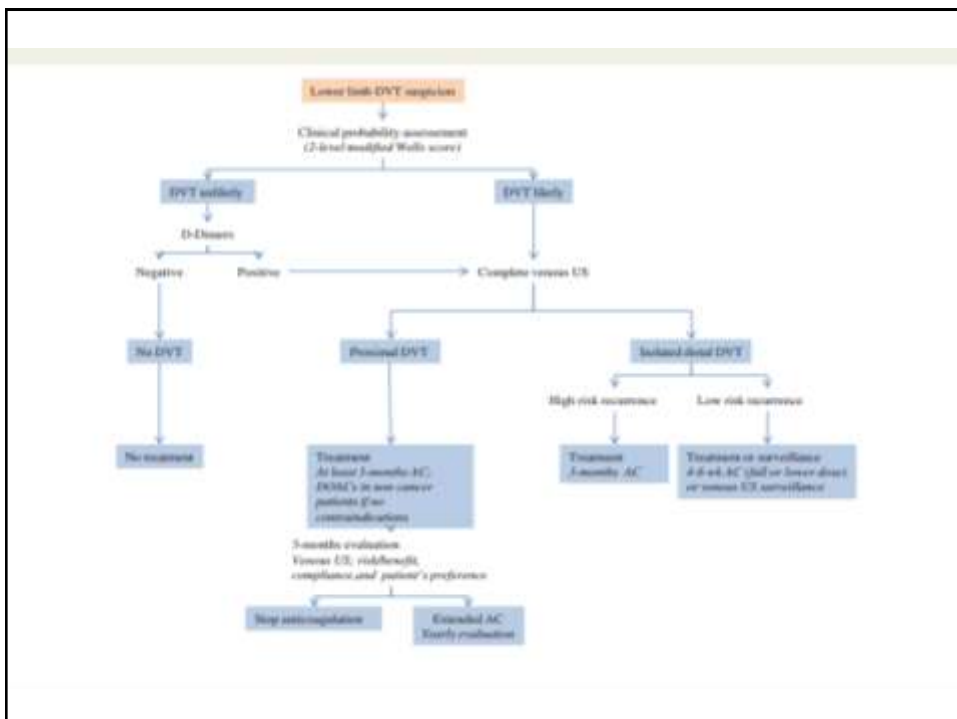
- Pre-test probability assessment is the first step in the diagnostic algorithm of DVT suspicion.
- Sensitivity and specificity of clinical symptoms are low when considered individually; however, their combination, using prediction rules, allows pre-test clinical probability classification into
- two- (DVT unlikely or likely) or
- three-categories (low-, intermediate-, or high-clinical probability) corresponding to increasing disease prevalence

- **Wells score** has been widely validated and can be applied both to out- and inpatients.
- The experts' panel favours the modified two-level pre-test probability as it is more straightforward
- Normal **D-dimers** render DVT unlikely however, D-dimers have low specificity

**Table 2 The Wells score<sup>12,13</sup>**

Clinical variable	Points
Active cancer (treatment ongoing or within previous 6 months or palliative)	+1
Paralysis, paresis or recent plaster immobilization of the lower extremities	+1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swelling	+1
Calf swelling at least 3 cm larger than that on the asymptomatic leg (measured 10 cm below the tibial tuberosity)	+1
Pitting edema confined to the symptomatic leg	+1
Collateral superficial veins (non varicose)	+1
Previously documented DVT	+1
Alternative diagnosis at least as likely as DVT	-2
<b>Three-level Wells score</b>	
Low	<-1
Intermediate	1-2
High	>2
<b>Two-level Wells score</b>	
Unlikely	≤1
Likely	≥2

- In patients with 'likely DVT, D-Dimer testing is not necessary: imaging is required.
- Therapeutic anticoagulation should be initiated, if not contraindicated, in patients with DVT 'likely' until imaging.



## • Imaging

- **Venous ultrasound (VUS)** is the first line DVT imaging modality.
- It is based on B-mode, combined or not with color-Doppler US, and power imaging techniques.
- DVT diagnostic criteria are cross-sectional vein incompressibility, direct thrombus imaging with vein enlargement, and abnormal spectral and color-Doppler flow.



- **VUS** can be performed by examining popliteal and common femoral veins only [2-point/2-region compression venous ultrasonography (CUS) or limited CUS], or by extended imaging of inferior vena cava, iliac and femoral veins, and calf veins (whole-leg VUS or complete VUS).
- There are controversies as to whether explore symptomatic leg only, or both.

- In clinically suspected DVT, VUS provides overall sensitivity of 94.2% for proximal, and 63.5% for isolated distal DVT, with an overall specificity of 93.8%.
- Combination with color-Doppler US increases sensitivity but lowers specificity.
- When DVT is suspected (without PE symptoms), anticoagulation may be safely withheld in patients with a single normal complete VUS

- In patients with clinically **suspected recurrent DVT**: comparison of test results with baseline imaging at discontinuation of anticoagulation can safely rule out diagnosis of recurrence. A **2- or 4-mm increase** in vein diameter between two measurements at the common femoral and popliteal veins, after full compression, is the most validated US criterion.

- **2-Deep vein thrombosis with pulmonary embolism symptoms**

- Proximal DVT confirmation in a normotensive patient with suspected PE essentially confirms VTE and justifies anticoagulation as after formal PE diagnosis.

- In **unstable patients with right ventricular overload** but no possibility to confirm PE, ***CUS showing proximal DVT*** facilitates initiation of reperfusion therapy.
- Presence of concomitant DVT has been suggested as an independent 30-days death risk factor following PE.

- Initial (first 5–21 days) and long-term (first 3–6 months) phase management.

- Deep vein thrombosis without pulmonary embolism

- ***Anticoagulation in non-cancer patients***

- Deep vein thrombosis treatment consists of three phases.
- ***Initial treatment*** (5–21 days following diagnosis); during this period, patients receive either parenteral therapy and are transitioned to vitamin K antagonists (VKA) or use high-dose direct oral anticoagulants (DOACs).
- ***Long-term treatment*** (following 3–6 months); patients are treated with VKA or DOACs. Initial and long-term treatments are mandatory for all DVT patients.
- Decision of ***extended treatment*** (beyond first 3–6 months) is based on benefit/risk balance of continued anticoagulation.

- Main disadvantage of UFH is its inter-individual dose variability requiring laboratory monitoring and dose adjustment. Additionally, UFH is associated with high risk of heparin-induced thrombocytopenia. For these reasons, low-molecular weight heparin (LMWH) is the parenteral treatment of choice.
- LMWHs are at least as effective as UFH and probably safer.
- Fondaparinux can also be used as parenteral agent.
- Both LMWH and fondaparinux do not have specific antidote.

- Recently, DOACs have emerged as valid options for DVT treatment.



- Thrombolysis/thrombectomy

- Early clot removal may prevent, at least partly, PTS development.
- Catheter-directed thrombolysis (CDT) is more efficient than systemic lysis, mainly due to less bleeding, as fibrinolytic agent is directly administered within the clot.
- Mechanical thrombus removal alone is not successful and needs adjuvant fibrinolytic therapy.
- Up to 83% of patients treated by any catheter-based therapy, need adjunctive angioplasty, and stenting.
- Primary acute DVT stenting is not recommended due to lack of data.

- **Vena cava filter:**
- may be used when anticoagulation is absolutely contraindicated in patients with newly diagnosed proximal DVT. One major complication is filter thrombosis.
- Therefore, anticoagulation should be started as soon as contraindications resolve and retrievable filter rapidly removed.
- Increased DVT recurrence has been shown with permanent but not with retrievable filters.

- **Compression**

- Goal of compression is to relieve venous symptoms and eventually prevent PTS.
- Although role of stockings in PTS prevention may be uncertain, their use remains **a reasonable option for controlling symptoms** of acute proximal DVT.
- Compression associated with **early mobilization and walking exercise** has shown significant efficacy in venous symptom relieve in patients with acute DVT.
- **Caution** should be used in patients with **severe peripheral artery disease**.

- **Home vs in-hospital management**

Most patients with DVT may be treated on a home basis.



- **Deep vein thrombosis with pulmonary embolism**  
Same management as pulmonary embolism.

- **Isolated distal deep vein thrombosis**

- Approach is to anticoagulate full-dose, for at least 3 months.
- All patients with acute isolated distal DVT should be recommended to wear elastic stockings. Follow up VUS is recommended to monitor thrombosis progression/evolution both in the presence or absence of anticoagulation.

**Table 3. Conditions or risk factors for complications after a first isolated distal DVT**

High-risk conditions	Low-risk conditions
Previous VTE events	Isolated distal DVT secondary to surgery or other transient risk factors (plasters, immobilization, traumas, long trip, etc.), provided complete mobilization is achieved
Males	Isolated distal DVT occurring during contraceptive or replacement hormonal therapy (provided therapy has been interrupted)
Age >50 years	
Cancer	
Unprovoked isolated distal DVT	
Secondary isolated distal DVT with persistently hampered mobilization	
Isolated distal DVT involving the popliteal trifurcation	
Isolated distal DVT involving >1 calf vein	
Isolated distal DVT present in both legs	
Presence of predisposing diseases (e.g. inflammatory bowel diseases)	
Known thrombophilic alterations	
Axial vs Muscular isolated distal DVT	

- Extended phase management  
(beyond first 3–6 months)

- *Duration of anticoagulation*

Once anticoagulation is stopped, risk of VTE recurrence over years after a first episode is consistently around 30%.

Risk is more than doubled in patients with unprovoked (annual rate >7.0%) vs those with (transient) provoked VTE, and among the latter in medical rather than surgical patients.

Patients with a first symptomatic unprovoked DVT are at higher risk of recurrence than those with a first unprovoked PE.

**Table 4. Risk of recurrence after a first episode of unprovoked VTE**

Risk factors for DVT recurrence			
Proximal DVT location	Male sex	Persistence of residual vein thrombosis at ultrasound	
Obesity	Non-zero blood group	High D-dimer values	
Old age	Early PTS development	Role of inherited thrombophilia is controversial	
Clinical prediction rules assessing risk of recurrent VTE after first episode of unprovoked VTE <sup>17</sup>			
Score	Vienna prediction model	DASH score	HERDOO-2
Parameters	<ul style="list-style-type: none"> <li>D-dimer level at 3 weeks and 3, 9, 15, 24 months after stopping anticoagulation</li> <li>Male sex</li> <li>VTE location (Distal DVT, Proximal DVT, PE)</li> </ul>	<ul style="list-style-type: none"> <li>Abnormal D-dimer 3–5 weeks after stopping anticoagulation</li> <li>Male sex</li> <li>Age &lt; 50 years</li> <li>VTE not associated with oestrogen-progestin therapy in women</li> </ul>	<ul style="list-style-type: none"> <li>Abnormal D-dimer before stopping anticoagulation</li> <li>Post thrombotic symptoms (hyperpigmentation, edema and redness)</li> <li>Age <math>\geq 65</math> years</li> <li>BPM <math>\geq 30</math></li> </ul>
Validation study	Yes	Yes	Yes
Commentaries	Different nomograms are available to calculate risk of VTE recurrence at different time	Patients with low score ( $\leq 1$ ) have an annual recurrence rate of 3.1%	It is applicable in women only. Women with low score ( $\leq 1$ ) have an annual recurrence rate of 1.3%

- For proximal DVT and/or PE, 3-months anticoagulation is the best option if transient and reversible risk factors were present. In all other patients, prolonging anticoagulation protects from recurrence (70–90%), but exposes to risk of unpredictable bleeding complications. Decision to discontinue anticoagulation or not should therefore be individually tailored and balanced against bleeding risk, taking also into account patients' preferences.

- Continuing **indefinite anticoagulation with the same drug administered during the first months** is the best option for patients with multiple VTE episodes or strong VTE familial history, those with major thrombophilia, or longstanding medical diseases at high thrombotic risk.
- Indefinite anticoagulation can also be considered in patients with first episode of unprovoked VTE, especially in those with severe presentation, provided they are at low bleeding risk.

- Discontinuing anticoagulation in non-cancer patients with repeatedly negative D-dimer (before drug interruption, 15, 30, 60, and 90 days following interruption) has proved to be safe in patients with unprovoked proximal DVT provided veins are re-canalized or remained stable for 1 year.

- Antithrombotics

- Vitamin K antagonists
- [target international normalized ratio (INR) 2.0–3.0].
- Recurrent VTE occurred less in the VKA groups.
- Bleeding was significantly higher.

- **Direct oral anticoagulants**

- Dabigatran (150 mg b.i.d.) was as effective as warfarin and more effective than placebo in preventing recurrent VTE. Risk of major bleeding was reduced compared with warfarin.
- With Rivaroxaban (20 mg o.d.), risk of VTE recurrence was lower compared with placebo, while bleeding risk was not increased.
- Standard and lower dose (10 mg od) also significantly reduced risk of recurrence compared to aspirin, without significant increase in bleeding.

- VTE recurrence occurred significantly less in standard and lower dose Apixaban (5 and 2.5 mg b.i.d.) vs placebo. Bleeding did not differ between groups.
- Recurrence rates with Edoxaban 60 mg were similar to the warfarin-treated group.
- Major bleeding was lower in the edoxaban group.

- *Aspirin.*
- *Sulodexide* can be used in patients with unprovoked VTE, who completed standard course of anticoagulation.

- *Venous occlusion recanalization*  
Endovascular techniques are available for selected patients with PTS.
- Case series and prospective cohort trials suggest that at least some subgroups of PTS patients may benefit from addition of endovascular therapy into overall management strategy.
- In patients with moderate-to-severe PTS and iliac vein obstruction, endovascular stent placement may be used to restore vein patency.



- *Follow-up*

Patients with DVT should be followed to avoid risk of recurrence as well as DVT and anticoagulation-related complications.

- Development of renal failure, changes in body weight, or pregnancy that may require anticoagulation adjustment should be monitored.
- Compliance as well as benefit/risk balance should be assessed regularly.
- VUS, at anticoagulation discontinuation, is useful in determining baseline residual vein thrombosis.

- *Special situations*

- *Upper extremities deep vein thrombosis*  
Upper extremities DVT (UEDVT) accounts for 10% of all DVTs with an annual incidence of 0.4–1.0/10,000 persons. Incidence rises because of increasing use of central venous catheters, cardiac pacemakers, and defibrillators.
- Complications are similar, although less frequent, to those of lower limb DVT.
- Secondary DVT include venous catheter- and devices-related complications, cancer, pregnancy, and recent arm/shoulder surgery or trauma.
- Most common clinical presentation includes pain, swelling, and skin discoloration.
- D-Dimer showed good negative predictive value in symptomatic DVT.
- VUS is the first choice exam for diagnosis.
- Anticoagulation is similar to that of lower limb DVT.

- *Deep vein thrombosis at unusual sites*
  - 1-Cerebral vein thrombosis
- Most common cerebral vein thrombosis (CVT) presentation includes severe headaches, seizures, focal neurological deficits, and altered consciousness.
- *2-Splanchnic vein thrombosis*
- Splanchnic vein thrombosis may present as sudden onset of abdominal pain with or without other non-specific abdominal symptoms.
- Upper gastrointestinal bleeding or abrupt ascites worsening may occur in cirrhotic patients, lower gastrointestinal bleeding, or acute abdomen may occur.

- *Deep vein thrombosis and cancer*

Cancer patients show four- to seven-fold increased VTE risk (second cause of death). Incidental VTE is increasingly diagnosed and associated with worse overall survival.

VTE risk varies from cancer diagnosis through treatment, with annual incidence rate of 0.5–20% according to cancer site and type, metastasis status, treatment (surgery, chemotherapy), use of central venous catheters, hospitalization, and patient-related factors.

- Cancer-related VTE is at high risk of recurrence and bleeding during treatment, risk of death increases up to eight-fold following acute VTE compared with non-cancer patients. LMWH is recommended for initial treatment (similar efficacy and higher safety than UFH).
- Fondaparinux in patients with history of heparin-induced thrombocytopenia, and UFH in case of renal failure are valid alternatives.
- Vena cava filter and thrombolysis should only be considered on a case-by case basis.

- In symptomatic catheter-related thrombosis, anticoagulation is recommended for at least 3-months. LMWHs are suggested although VKAs can also be used.
- Central vein-catheter can be maintained in place if it is functional, non-infected, and there is good thrombosis resolution. Optimal anticoagulation duration has not been determined, however, 3-months duration seems acceptable in analogy with upper extremity DVT.

- For VTE recurrence under proper anticoagulation (INR, antiXa within therapeutical range), 3 options are recommended: (i) switch from VKA to LMWH in patients treated with VKA; (ii) increase weight-adjusted dose of LMWH by 20–25%; (iii) vena cava filter use, although no specific results are available for cancer patients.

- **Deep vein thrombosis in pregnancy**

VTE remains the leading cause of maternal mortality

Although D-dimers increase during pregnancy, normal values exclude VTE with likelihood similar to non-pregnant women. VUS is the primary imaging test. Unless contraindicated, anticoagulation should be initiated until objective testing.

Treatment is based on heparin anticoagulation (no placenta crossing and not significantly found in breast milk). LMWHs are safe in pregnancy, anti-Xa monitoring, and dose adaptation cannot be recommended routinely, but may be considered in women at extremes of body-weight or renal disease.

- Dose reduction should be considered for women at high risk of bleeding, osteoporosis, or low VTE recurrence risk.
- Evidence is insufficient to recommend o.d. or b.i.d. LMWH, but b.i.d. may be more suitable perinatally to avoid high anti-Xa levels at time of delivery.
- Anticoagulation should be continued for at least 6 weeks postnatally and until at least a total of 3 months treatment.

Thank you