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# Venous thrombosis in Emergency Department: diagnosis, treatment, and disposition

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**Abstract. – *Aim:*** **The Authors describe diagnosis, treatment and therapy of deep venous thrombosis in Emergency Department following the last guidelines indications.**

***Discussion:*** **Deep venous thrombosis of the legs, ranges from asymptomatic, incidentally discovered emboli to massive embolism causing immediate death. Chronic sequelae of venous thromboembolism (deep venous thrombosis and pulmonary embolism) include the post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension. Acute pulmonary embolism may occur rapidly and unpredictably and may be difficult to diagnose. Diagnosis and treatment can reduce the risk of death, and appropriate primary prophylaxis is usually effective. Patients treated for acute pulmonary embolism appear to be more times as likely to die of recurrent thromboembolism in the next year.**

*Key Words:*

TDeep venous thrombosis, Pulmonary embolism, Emergency Department.

## Introduction

People aging with the increase of chronic diseases such as cardiac failure, COPD, or neoplasm, or risk diseases as stroke, pneumonia and obesity had lead to Deep Venous Thrombosis (DVT) raise and sequel venous thromboembolic diseases.

The symptoms of these diseases can lead patients to ask help to Emergency Departments (ED), or may be in in-hospital patients in Internal Medicine ward.

DVT may causes pulmonary embolism (PE) – sometimes the first clinic expression of that disease – should be suspected in all patients who present with new or worsening dyspnea, chest pain, or sustained hypotension without an alternative cause. PE unfortunately is one of the main in and out hospital reason of death[1].

Beside DVT may result in an imperfect healing as chronic venous failure and post-thrombotic syndrome[2].

Recognition and correct treatments of DVT in ED today is considered essential to prevent PE and, therefore, with the current know-how is mostly important physicians evaluate DVT risk and adjust thromboprophylaxis therapy.

Risk factors for an event of Venous Thromboembolism[3] may be congenital or acquired as shows Table I.

## Diagnosis

### Deep Venous Thrombosis Diagnostic Path

Symptoms and clinical signs who arise DVT suspicious are represented: rest and/or walking pain, foot dorsiflexion (Homan's sign), oedema, skin hyperesthesia, redness or other modifications of skin color, the presence of skin venous network. (The Wells clinical decision rule criteria for deep vein thrombosis: Table II)[4].

It useful say these signs and symptoms are not specific and then the clinical hypothesis of DVT must be always confirmed with the results of objective diagnostic tools.

Patients with signs and symptoms compatible with DVT are many (e.g. 4-5 per 1000 habitant), but usually only 1 out of 5 has a truly DVT, while the others have additional diseases (usually skin or muscle-skeleton problems which mime DVT).

It is an evident problem of diagnostic accuracy we meet in appropriate treating of patients suffering of thrombosis.

It is essential use a tested diagnostic procedure with objective and significant methods allowing to rule in or out the diagnosis of DVT.



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**Table I.** Risk Factors for Venous Thromboembolism*.

| Hereditary factors | Acquired factors | Probable factors |
|---|---|---|
| Antithrombin deficiency | Reduced mobility | Elevated levels of lipoprotein(a)† |
| Protein C deficiency | Advanced age | Low levels of tissue factor–pathway inhibitor |
| Protein S deficiency | Cancer | Elevated levels of homocysteine; |
| Factor V Leiden | Acute medical illness | Elevated levels of factors VIII, IX, and XI; |
| Activated protein C resistance without factor V Leiden | Major surgery | Elevated levels of fibrinogen; |
| Prothrombin gene mutation | Trauma | Elevated levels of thrombin-activated fibrinolysis inhibitor |
| Dysfibrinogenemia | Heparins | |
| Plasminogen deficiency | Hormone-replacement therapy<br>Oral contraceptives<br>Polycythemia vera<br>Pregnancy and postpartum period<br>Antiphospholipid antibody syndrome<br>Spinal cord injury<br>Chemotherapy<br>Obesity | |
| | Central venous catheterization<br>Immobilizer or cast | At present, the associated risk of venous thromboembolism is not clear† |

*It remains unclear whether some of the disorders listed are hereditary, acquired, or both (from[3]).

In patients with compatible signs and symptoms of DVT of lower leg we shall use non-invasive diagnostic tools: Compression ultrasonography (CUS) has showed high sensitivity (97-100%) and specificity (97-100%) for proximal DVT (e.g. from poplyteal vein included and up); otherwise, this technique is far less sensible in the study of calf veins, where it can't exclude at all the presence of alone distal thrombosis (only inside deep calf veins: anterior and posterior tibial, peroniere).

The distal DVT may, also rarely, spread the venous tree: the embolic risk increases when the thrombosis process extends to proximal deep veins.

Guidelines suggest diagnostic strategy with use of clinical decision rule criteria, and measure of D-Dimers, technology with high negative predictive value[5].

### D-Dimer Dosage

D-dimer are degradation products of stable fibrin.

**Table II.** The Wells clinical decision rule criteria for deep vein thrombosis (DVT)[4].

| Clinical feature | Score |
|---|---|
| Active cancer (treatment ongoing or within previous 6 months, or palliative) | 1 |
| Paralysis, paresis or recent plaster immobilisation of lower extremities | 1 |
| Recently bedridden > 3 days or major surgery within 4 weeks | 1 |
| Localised tenderness along the distribution of the deep venous system | 1 |
| Entire leg swollen | 1 |
| Calf swelling 3 cm greater than the asymptomatic side (measured 10 cm below tibial tuberosity) | 1 |
| Pitting oedema confined to the symptomatic leg | 1 |
| Collateral superficial veins (not varicose) | 1 |
| Alternative diagnosis as likely as or greater than that of DVT – i.e. cellulitis, phlebitis, Baker's cyst, oedema | -2 |
| Probability: 3, High; 1-2 intermediate; 0 low | |

D-dimer levels we measure in blood are results of balance between their formation and their clearance; and usually their half-life is about 48 hours.

High plasmatic levels of D-dimer, apart from presence of venous and arterial thrombi, may be caused by many other conditions with fibrin formation in vascular space or reabsorption of degradation products from extravascular spaces (e.g. subcutaneous hematomas, surgical wounds, skin necrosis, large burns, lung effusion, ascites).

An increase of D-dimer values we can observe frequently in many diseases (DIC, neoplasms, unstable angina, myocardial infarction, infections, renal and hepatic failure, eclampsy, surgical patients).

Then, the D-dimer dosage is extremely sensible when thrombi are present, but few specific (e.g. positive in too many situations).

In Table III there are conditions with usually elevations of D-dimer plasma levels.

### Ultrasonography

Ultrasonography (B-mode echography, echocolor Doppler) is non invasive first choice tool for the diagnosis of proximal DVT of lower legs (thrombosis from popliteal veins to iliac-femoral segments).

Ultrasonography has high diagnostic accuracy, is practical and simply, low expensive, harmless, and it may repeat without limits. It allows get image of venous system (venous wall and valves) and representation in real time of blood flow in static or dynamic conditions.

Operators carry out US examination with patient supine position for studying of thigh, then prone position for studying of popliteal segment, and then in stand up or seat position for studying of deep distal veins (the veins relaxation promote anatomic details view).

It is possible explore completely the common femoral vein, deep femoral vein when join with the common one, the superficial femoral vein, the popliteal vein, the underpopliteal veins when join with popliteal vein, and then the calf veins.

Calf exploration of underpopliteal veins take a lot of time, and needs examinator skills with a suitable machine. Beside the Doppler is the main device for studying of valvular function and flow we see in post-thrombosis syndrome.

Abdominal iliac veins exploration needs probe of kind sectorial or convex (2.5-5 MHz), with the highest power of sight in deep abdomen, but with reduced power of resolutions.

The positive or negative main diagnosis criterion for DVT is compression test (Compression UltraSonography = CUS): operator makes a soft pressure with the probe on venous line: a completely flattened venous has not thrombus. Still we must bear in mind some venous line (e.g. superficial femoral on Hunter channel, deep femoral, iliac, cava veins) we can not flattened for many reasons: extremely deep positions, overlap with bone-tendon structure, scar tissue around the veins.

A good quality examinations of distal veins bear on operator training and use of good and last generation machines[6-8].

### Spiral TC Angiography

Multi slice spiral Computed Tomography (CT) angiography can study completely iliac-cava venous axis.

Direct sign of intraluminal thrombus looks as area without filling inside veins, with around an hyperdensity ring, who represents the iodine media laminar flow around thrombus.

Beside this diagnosis tool can show intra abdominal and intra thoracic organs.

**Table III.** Conditions with usually elevations of D-dimer plasma levels.

| Advanced age | Newborn | Pregnancy |
|---|---|---|
| Hospital in-patients | Functional disability patients | Infections (gram negative sepsis) |
| Neoplasm | Surgical operation | Trauma |
| DIC | DVT | Ischemic Cardiac Disease |
| Stroke | Peripheral arterial disease | Aneurysm |
| Congestive heart failure | Hemolytic crisis in sickle cell anemia | Subarachnoid hemorrage and subdural hematoma |
| Hemorrage | ARDS | Hepatic diseases |
| Renal diseases | Chronic flogistic diseases (e.g. SEL, reumatoid arthritis) | Trombolytic terapy |

Then in emergency and urgent room when we have suspicion of DVT and thrombus-embolic disease, multi slice spiral CT angiography is the first choice examination[9-11].

### Thromboembolic Risk

A lot of studies assessed thromboembolic risk both in medical than surgical area, in order it may suggest procedures of prophylaxis. Table IV shows a meta-analysis about incidence of DVT when prophylaxis is missing in internal diseases[12].

Currently it has suggested probability indexes of pulmonary embolic disease: the following are the two most used in clinical practice.

The Wells Criteria and Revised Geneva score established the concept of risk stratifying patients with suspected PE to allow physician to determine a patient's pretest likelihood of having the disease based on a small number of risk factors (Table V).

Postthrombotic syndrome is a potentially debilitating chronic cluster of lower-extremity symptoms occurring in 20% to 50% of deep venous thrombosis patients subsequent to the acute insult, sometimes not until years later. A strategy of early thrombus burden reduction or frank removal might reduce the appearance of postthrombotic syndrome (Table VI)[13].

### Prophylaxis

The last guide line evidences are in the Table VII.

### Thromboprophylaxis

Large randomized clinical trials have demonstrated the efficacy of Low Dose Unfraction Heparin (LDUH), of LMWH (enoxaparin at 40 mg qd, dalteparin at 5.000 UI qd, and fondaparinux at 2.5 mg qd) compared with placebo in medical patients[15-18].

### Recommendations 1A

- For acutely ill medical patients admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, thromboprophylaxis with LMWH, LDUH, or fondaparinux.
- For all major trauma patients, if thromboprophylaxis is possible.
- We recommend against the use of aspirin alone as thromboprophylaxis for any patient group[14].

### Recommendations 1A

Mechanical methods of thromboprophylaxis must be used primarily in patients at high risk for bleeding with graduated compression stockings (GCS); and/or intermittent pneumatic compression (IPC) at least until the bleeding risk decreases[14].

#### Note on Specific Situations

1. Prophylaxis with enoxaparin in patients with ischemic stroke joins with a reduced frequency of DVT versus patients treated with unfraction heparin 5000 UI b.i.d.
2. Association Low Molecular Weight Heparin (LMWH) + aspirin is effective in venous thromboembolism without increase in the hemorrhagic risk.
3. 40 days prophylaxis with enoxaparin in bedridden patients reduces DVT prevalence against 10 days treatment.
4. Cancer patients are at higher risk of DVT and/or fatal event: in chemotherapy, in radiotherapy or after surgical procedure.
5. Pregnancy and puerperium: if present personal history or family story of past VTE or with other risk factors, woman must receive prophylaxis with LMWH during pregnancy and after delivery for six weeks. Useful elastic socks. Oral Anticoagulant Therapy (OAT) must turn to LMWH when pregnancy come, because coumarin may damages embryo.
6. Higher risk patients: Body Mass Index > 40, thrombophilia.

**Table IV.** (Adapted by[12]).

| Disease | Study | Patients | Incidence |
|---|---|---|---|
| Stroke | 8 | 395 | 56% |
| Myocardial infarction | 4 | 180 | 22% |
| Geriatrics ward patients | 1 | 131 | 9% |
| Internal ward patients | 10 | 2822 | 8.1% |

**Table V.** (Adapted by[5]).

| Wells score: clinical decision rule criteria for PE | | Revised Geneva score: clinical decision rule criteria for PE | |
|---|---|---|---|
| **Variables** | **Points** | **Variables** | **Points** |
| Previous PE o DVT | +1.5 | Age > 65 years | +1 |
| Recent surgery or immobilization | +1.5 | Previous DVT or PE | +3 |
| Cancer | +1 | Surgery or fracture within one mont | +2 |
| Haemoptysis | +1 | Active malignancy | +2 |
| Heart rae > 100 beats per minute | +1.5 | Unilateral lower limb pain | +3 |
| Clinical sign of DVT | +3 | Haemoptysis | +2 |
| Antenative diagnosis less likely of PE | +3 | | |
| | | **Heart rate** | |
| *Probability:* Low 0-1, intermediate 2-6, high > 7 | | 75 to 94 beats per minute | +3 |
| | | > 95 beats per minute | +5 |
| | | Pain on lower limb deep vein at palpation and unilateral oedema | +4 |
| | | *Probability:* Low 0-3, Intermediate 4 to 10, high > 11 | |

## Deep Venous Thrombosis Therapy

Treatment aims of Deep Venous Thrombosis, both proximal and distal, are: prevent the local extension of thrombus and prevent emboli leaving; promote and accelerate fibrinolysis, prevent recurrences and complications as post-thrombotic syndrome.

Therapeutic directory usually used includes anticoagulant drugs, thrombolytic drugs and caval filters.

Beside the compressive procedures are used mainly in patients with hemorrhagic risk.

**Table VI.** Risk factors for post-thrombotic syndrome. (Adapted by[5]).

| Factors apparent at DVT diagnosis thrombosis |
|---|
| Previous ipsilateral DVT |
| Extent of index DVT |
| Proximal DVT |
| Older age |
| Male sex |
| High body mass index |
| Thrombophilia |
| **Factors that become manifest during long-term follow-up** |
| Presence of DVT symptoms and clinical signs at 1 mo after initial treatment |
| Poor quality of early anticoagulant therapy (e.g., > 50% of time with subtherapeutic INR |
| Precence of residual thrombus on ultrasonography |
| Increased D-dimer 3 weeks after withdrawal of oral VKA anticoagulant |

Therapy of DVT and PE established on appropriate levels of intravenous unfractionated heparin, or low molecular weight heparins s.c. for at least five days, associated with oral anticoagulant for at least 4-5 days.

Initially in the most of the patients heparins and oral anticoagulant can administered together, stopping heparins in fifth day if INR is in therapeutic range for two consecutive days.

Oral anticoagulant therapy must go on at least three months with target to keep INR on 2.5 (range useful between 2 and 3).

## Isolated Calf DVT Must Take Anticoagulant Therapy at Least Three Months

Patients with reversible or limited in time risk factors must take therapy for three to six months.

Patients with story of previous episode of unknown DVT must be treated at least six months.

Patients with frequent venous thrombosis and with persistent risk factors (neoplasms, inhibitory factor deficiency, anti phospholipids syndrome) must be treated lifetime.

The use of thrombolytic agents prosecutes in highly individual manners and physicians must be flexible when need use them: the best candidates are patients with instable EP or massive ileo-femoral thrombosis.

Contraindications to thrombolytic therapy:

- Hemorrhagic diseases both acquired or congenital
- Recent major surgery
- Recent stroke

**Table VII.**

| Risk levels | DVT risk without prophylaxis (%) | Suggested prophylaxis |
|---|---|---|
| **Low** | | |
| Mobilized internist ward patients | < 10 | Mobilization of patients |
| **Middle** | | |
| Bedridden internist ward patients | 10-40 | UFH, LMWH, Fondaparinux |
| **High** | | |
| Major and oncologic surgery ward patients | 40-80 | LMWH, Fondaparinux, K vitamin antagonist (INR 2-3) |

*Note:* When hemorrhagic risk is high use mechanical prophylaxis. (Adapted by[14]).

- Intracranial neoplasm
- Gastric and/or duodenal ulcer
- Diabetic retinal hemorrhage
- Serious non treated arterial hypertension
- Bacterial endocarditis
- Serious hepatic or renal failure

Filter positioning on vena cava is recommended when:
- Contraindications to or failure of anticoagulant therapy
- Chronic recurrent pulmonary embolism
- Contemporary operation of pulmonary embolectomy or endarterectomy

### *Acute Phase DVT*

Anticoagulation is the main therapy for acute DVT of the leg. The main objectives of anticoagulant therapy in the initial treatment of this disease are to prevent thrombus extension and early and late recurrences of VTE.

### *Unfraction Heparin (UFH) IV – Class 1A*

SC – Class 1A

Actions and features:
- Inactive both Xa and IIa factors
- Low bioavailability by subcutaneous (~30%)
- Strong link to endothelium, plasma proteins
- Non linear ratio dosage-answer
- Need monitoring
- IV initial IV bolus (80 U/kg or 5,000 U), it be administered by continuous infusion (initially at a dose of 18 U/kg/h or 1.300 U/h) with dose adjustment to achieve and maintain an activated partial thromboplastin time (APTT) prolongation to 1.5-2.5
- SC weight-adjusted dose of approximately 250 U/kg bid, with dose adjustment to achieve and maintain an APTT prolongation
- No intermittent dosage (e.g.: it increases bleeding risk)

### *Low Molecular Weight Heparin (LMWH) – Class 1A*

Actions and features:
- Inactive mainly Xa factor
- High bioavailability by subcutaneous (> 90%)
- Weak link to endothelium, plasma proteins
- Linear ratio dosage-answer
- Monitoring not needed
- Dosage (enoxaparin) 1 mg/kg sc every 12 h;

### *Fondaparinux – Class 1A*
- Synthetic pentasaccharide with high affinity to Anti Thrombin (AT)
  – More activity against Xa factor than LMWH (700 U/mg vs 100 U/mg)
  – More long haf-life than LMWH (17hs vs 4hs)
- Doses:
  – 7.5 mg/die sc (if body weight 50-100 kg)
  – 10 mg/die sc (if body weigh > 100 kg)
- Indications:
  – DVT;
  – Pulmonary embolim;
  – Patients with documented allergy to LMWH.
- Contraindications:
  – Serious renal failure (Creatinine clearance under 30 ml/min)
  – Patients weight < 50 kg.

## Thrombolytic Therapy

### *Systemic Thrombolytic Therapy*
- In selected patients with extensive proximal DVT (e.g., symptoms for < 14 days, good

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***Note:*** In patients with acute DVT and severe renal failure, guidelines[5] suggest UFH over LMWH (Grade 2C).

- Functional status, life expectancy of > 1 year) who have a low risk of bleeding, guidelines suggest that systemic thrombolytic therapy may be used to reduce acute symptoms and post-thrombotic morbidity if catheter-directed thrombolysis (CDT) is not available (Grade 2C)[19-20].

### Catheter-Directed Thrombolysis (CDT)

In selected patients with extensive acute proximal DVT (e.g., iliofemoral DVT, symptoms for < 14 days, good functional status, life expectancy > 1 year) who have a low risk of bleeding, guidelines suggest that CDT may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available (Grade 2B) (Table VIII).

### Thrombectomy

In selected patients with acute iliofemoral DVT (e.g., symptoms for < 7 days, good functional status, and life expectancy > 1 year), guidelines suggest that operative venous thrombectomy may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available (Grade 2B). If such patients do not have a high risk of bleeding, we suggest that CDT is usually preferable to operative venous thrombectomy (Grade 2C).

## Vena Caval Filters for the Initial Treatment of DVT

For patients with acute proximal DVT if anticoagulant therapy is not possible because of risk of bleeding, guidelines recommend placement of an IVC filter (Grade 1C)[22].

### Elastic Compression

For a patient who has had a symptomatic proximal DVT, guidelines recommend the use of an elastic compression stocking with an ankle pressure gradient of 30 to 40 mm Hg if feasible (Grade 1A). Compression therapy, which may include use of bandages acutely, should be started as soon as feasible after starting anticoagulant therapy and should be continued for a minimum of 2 years, and longer if patients have symptoms of PTS. (Chest guideline 2008)[14].

### Vitamin K Antagonist (VKA)

For patients with DVT secondary to a transient (reversible) risk factor, guidelines recommend treatment with a VKA for 3 months over treatment for shorter periods (Grade 1A).

For patients with unprovoked DVT, guidelines recommend treatment with a VKA for at least 3 months (Grade 1A). After 3 months of anticoagulant therapy, all patients with unprovoked DVT should be evaluated for the risk-to-benefit ratio of long-term therapy (Grade 1C). For patients with a first unprovoked VTE that is a proximal DVT, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, guidelines recommend long-term treatment (Grade 1A)[23-25].

Finally, we report in Figure 1 a flow-chart with a usefull algorithm for ED management of acute iliofemoral deep venous thrombosis.

**Table VIII.** Pharmacological profile of plasminogen-activating fibrinolytic agents.

| Fibrinolytic | FDA indication for PE | Direct plasminogen activator | Fibrinolytic dose | Fibrin specificity | PAI resistance |
|---|---|---|---|---|---|
| Streptokinase | Yes | No | 250.000 IU bolus followed by 100.000 IU/h infusion for 12-24 h | – | – |
| Urokinase | Yes | No | 4400 IU/kg bolus followed by 4400 IU/kg/h for 12-24 h | – | – |
| Alteplase | Yes | Yes | 100 mg IV infusion over 2 h | ++ | ++ |
| Reteplase | No | Yes | Double 10 U IV bolus 30 min apart | + | + |
| Tenecteplase | No | Yes | Weight adjusted IV bolus over 5 s (30-50 mg with a 5 mg step every 10 kg From < 60 to > 90 kg | +++ | +++ |

PAI – plasminogen activator inhibitor, is 52 kDa circulating glycoprotein that is the primary native of plasminogen-activating enzymes, and greater PAI resistance confers a longer duration of fibrinolysis. (Adapted from[21]).

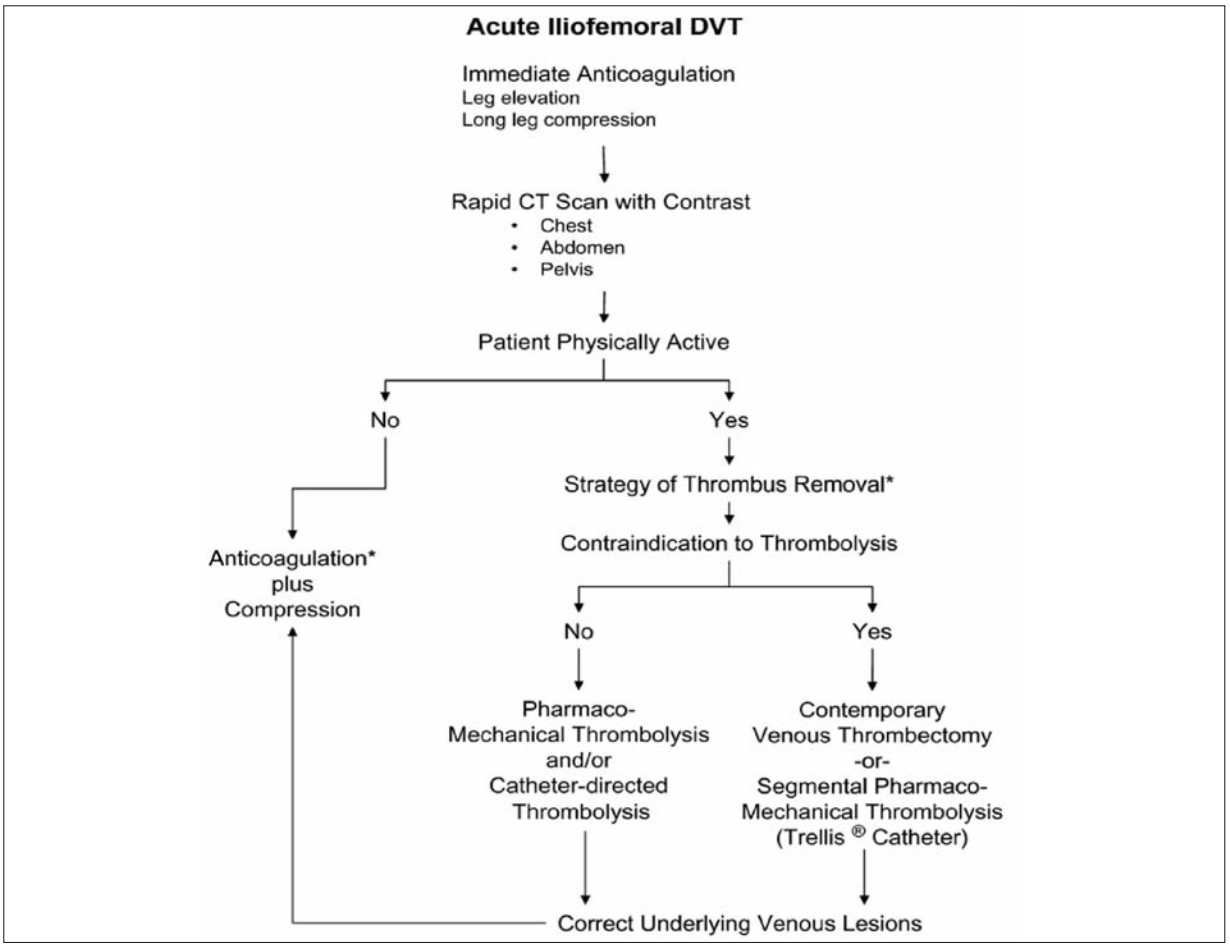


***Figure 1.*** Suggested algorithm for ED management of acute iliofemoral deep venous thrombosis, including possible referral in appropriate cases for endovascular thrombus removal. *Vena caval filter for free-floating vena caval thrombus. CT, Computed tomography. (Reprinted from[25]).

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