Guidelines

For The Management Of

Thromboembolic disorders

By

Dr. Sinan Butrus
F.I.C.M.S
Clinical Standards & Guidelines

Dr.Layla Al-Shahrabani
F.R.C.P (UK)
Director of Clinical Affairs

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For Medical Specialties

Venous thromboembolism (VTE) is a disease that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE).
VTE is a cardiovascular disease and the risk factors for arterial and venous thrombosis are similar.
The 2 most common genetic risk factors for VTE are factor V Leiden and the prothrombin gene mutation (G20210A).
The most common acquired (nongenetic) cause is antiphospholipid antibody syndrome.

Major Risk Factors for Venous Thromboembolism

Hereditary

- Factor V Leiden mutation
- Prothrombin gene mutation
- Protein C or S deficiency
- Antithrombin deficiency
- Hyperhomocysteinemia
- Elevated levels of factor VIII
- Dysfibrinogenemi

Acquired

- Age ≥ 65 yrs
- Body mass index ≥ 29 kg/m^2
- Surgery: more with general anesthesia, abdominal , pelvic or major orthopedic surgery of the leg
- Trauma
- Medical illness (heart failure,nephrotic syndrome, chronic obstructive pulmonary disease)
- Immobilization
- Oral contraceptives, hormone replacement therapy, pregnancy (third trimester of pregnancy and during the first 6 weeks after delivery)
- Indwelling central venous catheters or pacemakers
- Cancer: especially on immunosuppressive or cytotoxic chemotherapy
- Lupus anticoagulant , antiphospholipid antibody
- Heparin-induced thrombocytopenia
- Inflammatory bowel disease
- Myeloproliferative disorders
- Previous episode of venous thromboembolism
- Homocystinuria, and possibly hyperhomocysteinemia
- Air travel: especially over 6 hrs flight

Indications for screening for thrombophilias

- Venous or arterial thromboembolism before the age of 45 years.
- Recurrent venous thromboembolism or thrombophlebitis
- Venous thrombosis in an unusual site (e.g. mesenteric, cerebral)
- Unexplained neonatal thrombosis
- Skin necrosis, particularly if on coumarins
- Patients with family history of venous thrombosis
- Unexplained prolonged activated partial thromboplastin time (APTT) (lupus anticoagulants).

Clinical Decision Rules

Clinical probability of Deep Venous Thrombosis (Wells score)

Active cancer (treatment ongoing or within previous 6 months of palliative treatment	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than 3 days or major surgery, within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Calf swelling by > 3 cm compared with the asymptomatic leg (measured 10cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Entire leg swollen	1
Collateral superficial veins (not varicose)	1
Alternative diagnosis as likely or greater than that of deep-vein thrombosis	-2

Analysis High ≥ 3 Moderate 1 or 2 Low ≤ 0

Modified Score (adds one point if there is a previously documented DVT Likely ≥2 Unlikely ≤1

Clinical probability of pulmonary embolism(*The simplified Geneva score)*

Age >65	1
Previous DVT or PE	1
Surgery or fracture within 1 month	1
Active malignancy	1
Unilateral lower limb pain	1
Hemoptysis	1
Pain on deep vein palpation of lower limb and unilateral edema	1
Heart rate 75 to 94 bpm	1
Heart rate greater than 94 bpm	1

***** Heart rates of 75 to 94 bpm receive 1 point, while heart rates higher than 94bpm receive a further point i.e. 2 points in total

Patients with a score of 2 or less and a normal D-Dimer are unlikely to have a current PE

Baseline investigations:

1. FBC, platelet count, U&E, Creatinine, APTT, INR,liver function tests, chest x-ray

2. Investigation to confirm the diagnosis of DVT/ pulmonary embolism

A. D-dimer testing: negative value excludes the diagnosis of DVT.

B. Venous doppler study is a standard diagnostic test.

C. Pulmonary V/Q is indicated on the basis of symptoms and signs or when the supervising physician is concerned about high risk of pulmonary embolism

D. Computed tomography of the chest is the procedure of choice for PE diagnosis

E.Antithrombin III, protein C, and S protein assays before or at least two weeks after warfarin therapy has been discontinued.

F. A venogram or red cell scan may be necessary where there is a high index of suspicion and the doppler study is uninterpretable or inadequate.

3. Search for underlying cause in:

a. Idiopathic VTE in young patients (50 yrs of age)

b. Recurrent DVT without apparent cause

c. Family history of clotting disorders

d. Difficulties with anti-coagulation

Assess patient suitability for LMWH ; exclude:

* Renal failure
* Thrombocytopenia
* Concurrent NSAID therapy
* Significant bleeding risk

Thromboprophylaxis

Pre-operative

Low dose unfractionated heparin (LDUH) 5,000 U bid *OR*
Low-molecular-weight heparin (LMWH) 2500 -3500 U once daily
WITH the use of graduated compression stockings and/or intermittent pneumatic compression devices.

Postoperatively

high risk patients should receive thromboprophylaxis for at least 2- 3 weeks with one of the following three anticoagulant agents: LMWH, fondaparinux, or adjusted-dose vitamin K antagonist (VKA) i.e., warfarin [INR 2.0 - 3.0].

Long Air Travel

It is recommended for high-risk travelers, such as those with prior VTE, graduated compression stockings or a single prophylactic dose of low molecular weight heparin injected before departure, along with common sense measures applicable to all travelers: avoidance of constrictive clothing, ensuring adequate hydration, and undertaking periodic calf muscle contraction

Pregnant woman;

1.**With a single prior episode of VTE and no thrombophilia or thrombophilia but no prior VTE**; anticoagulant prophylaxis in the antepartum & postpartum period is indicated.

2. **With acute VTE**; subcutaneous LMWH or UFH should be continued throughout pregnancy and the anticoagulantion should be continued for at least 6 weeks postpartum (for a total minimum duration of therapy of 6 months).

3. **On oral anticoagulants**; should be substituted with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) during pregnancy, then resume oral anticoagulants in the postpartum period.

Those with mechanical heart valve give either adjusted-dose LMWH bid or adjusted-dose UFH throughout pregnancy, until the thirteenth week, then warfarin substitution with INR monitoring, then restart LMWH or UFH 4 weeks before delivery.

A thorough discussion with the patient for the risks and benefits of this approach is required.

4. For women with recurrent early pregnancy loss or unexplained late pregnancy loss, screening for **antiphospholipid antibodies** (APLAs) is recommended & if test positive; antepartum administration of prophylactic heparin combined with aspirin is recommended.

Therapeutic range

Unfractionated heparin (UFH) intravenous bolus dose (5,000 IU or 75 IU/kg body weight), followed by maintenance intravenous infusion (1,000-1,500 IU/hour),
if infusion set is not available; Unfractionated heparin (UFH) intravenously (5000 IU/4 hourly).

Low molecular weight heparin (LMWH); Enoxaparin (Lovenox): can be used as outpatient short-term anticoagulation for the treatment of DVT in patients who are hemodynamically stable, without renal failure, and not at high risk for bleeding; in a dosage of 1 mg/kg twice daily or 1.5 mg/kg once daily.

Monitoring parameters

The following patient parameters should be monitored during heparin therapy:
1- aPTT; obtain before initiation of heparin, every six hours thereafter until stable (two aPTT's drawn 24 hours apart are within the therapeutic range) then daily; aiming to have *aPTT* 1.5 - 2.5 to the control.
2- Platelet count, daily for early diagnosis of heparin-induced thrombocytopenia which typically occurs 2 - 5 days after heparin exposure, but can occur at any time.
3- Hematocrit, if bleeding is suspected.
4- Avoid the use of aspirin, dipyridamole, NSAID's.

Protamine (Heparin antidote)
- In the event of a critical bleed, 1mg of protamine will neutralize approximately 100 U of heparin.
- Protamine can cause severe, anaphylactoid reactions; use only when there is severe bleeding

Warfarin stabilization

Warfarin: starts on day 2 of Heparin therapy. Start at 5 mg daily for first two days.
Perform pretreatment INR, then daily INR with dose adjustment of warfarin according to INR from day 4 & then daily.
INR 5-8: stop warfarin for 24-72 hrs; recommence at half dose once INR< 5
INR >8: stop warfarin; administer Vitamin K 1mg (IV or SC) or FFP until INR< 5.

Graduated compression stockings are advised to reduce risk of post-phlebitic syndrome. Ideally should be worn for 2 years

Long term laboratory monitoring

Monitor INR A typical regimen is weekly for 4 weeks once in target range then monthly while stable. Increase monitoring frequency if there is intercurrent illness, change in drug therapy, change in alcohol intake and diet.

Duration of treatment for thromboembolic disease

- First episode: 3 – 6 months warfarin or duration of risk factor.
- Second episode: 6 - 12 months warfarin or longer if at increased risk of further recurrence.

- Three or more episodes: long term & according to the aetiology.
- Consider indefinite duration anticoagulation for those who have suffered a thrombotic event and high anticardiolipin antibody levels, homozygous factor V Leiden, homozygous prothrombin gene mutation, double heterozygote mutations, protein C, protein S, and antithrombin deficiency

Heparin Induced Thrombocytopenia (HIT)

HIT is a widely recognized is a **clotting disorder** disorder that is observed in 2 - 4% of patients who receive heparin & is associated with **high morbidity and mortality rates.**

Heparin-induced thrombocytopenia is a transient hypercoagulable state that occurs as a result of an immune mediated reaction to heparin and involves activation of platelets and massive thrombin generation.

Although HIT typically occurs 4 -14 days after heparin exposure, it can occur at any time. Thrombosis has been reported within 30 minutes after heparin re-exposure. Thrombosis can occur before the decline in platelet count or even when the platelet count is recovering and rising.

Heparin-induced thrombocytopenia is divided into 2 types:

Type I is an early-onset, mild decline in platelet count and is reversible. This condition is thought to be caused by the direct platelet-aggregating effect of heparin.

Type II is an immune-mediated reaction that typically occurs 2 - 5 days after the initial heparin exposure.

Diagnosis:

1.Clinical features.

2. Low platelet count or one that has decreased 30 - 50% from the baseline level.

3. New thrombotic event occurs while receiving heparin therapy.

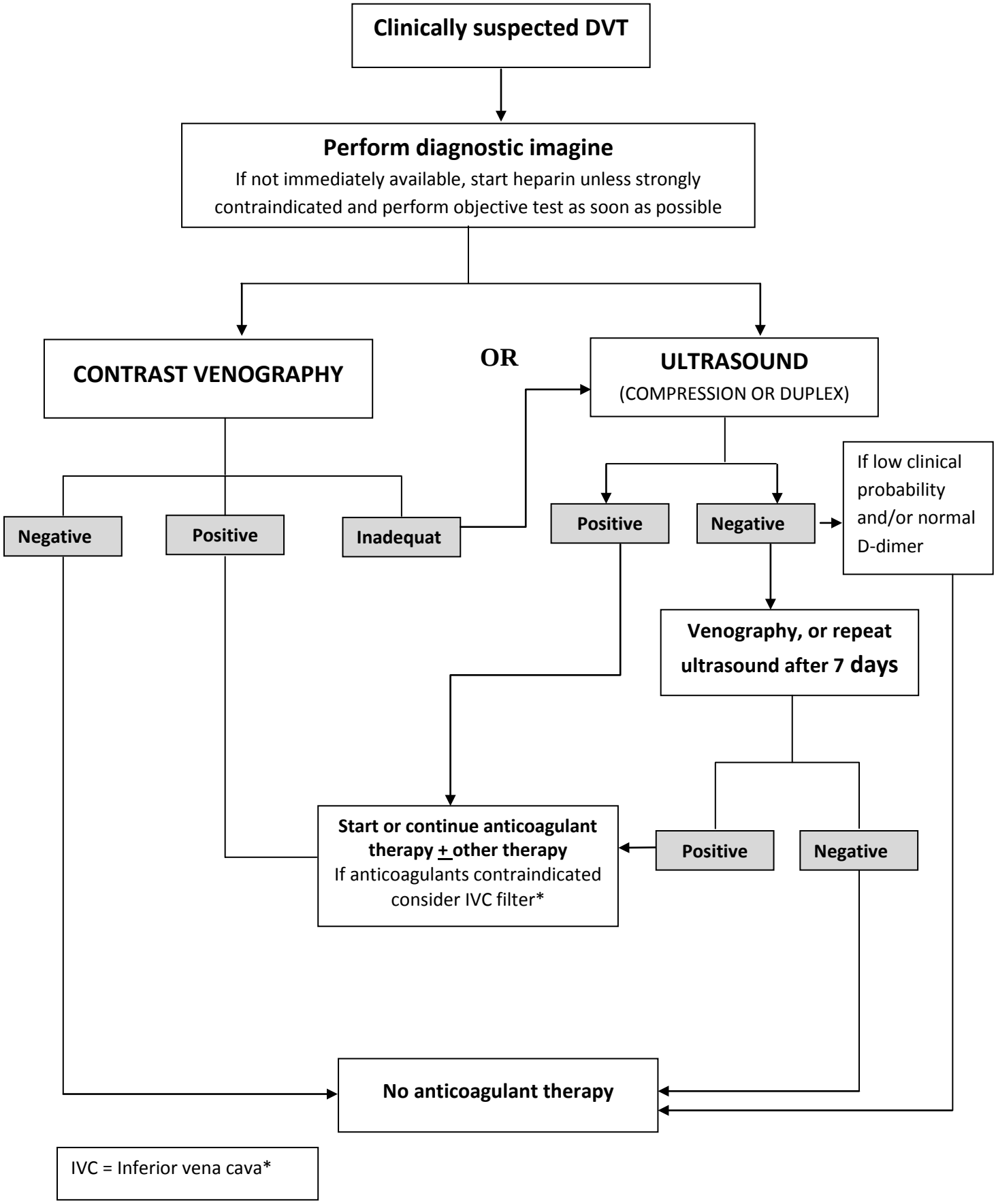
4. Acute systemic reaction within 5 to 30 minutes of heparin bolus:
    - Cardiorespiratory
    - Inflammatory
    - Gastrointestinal
    - Neurologic

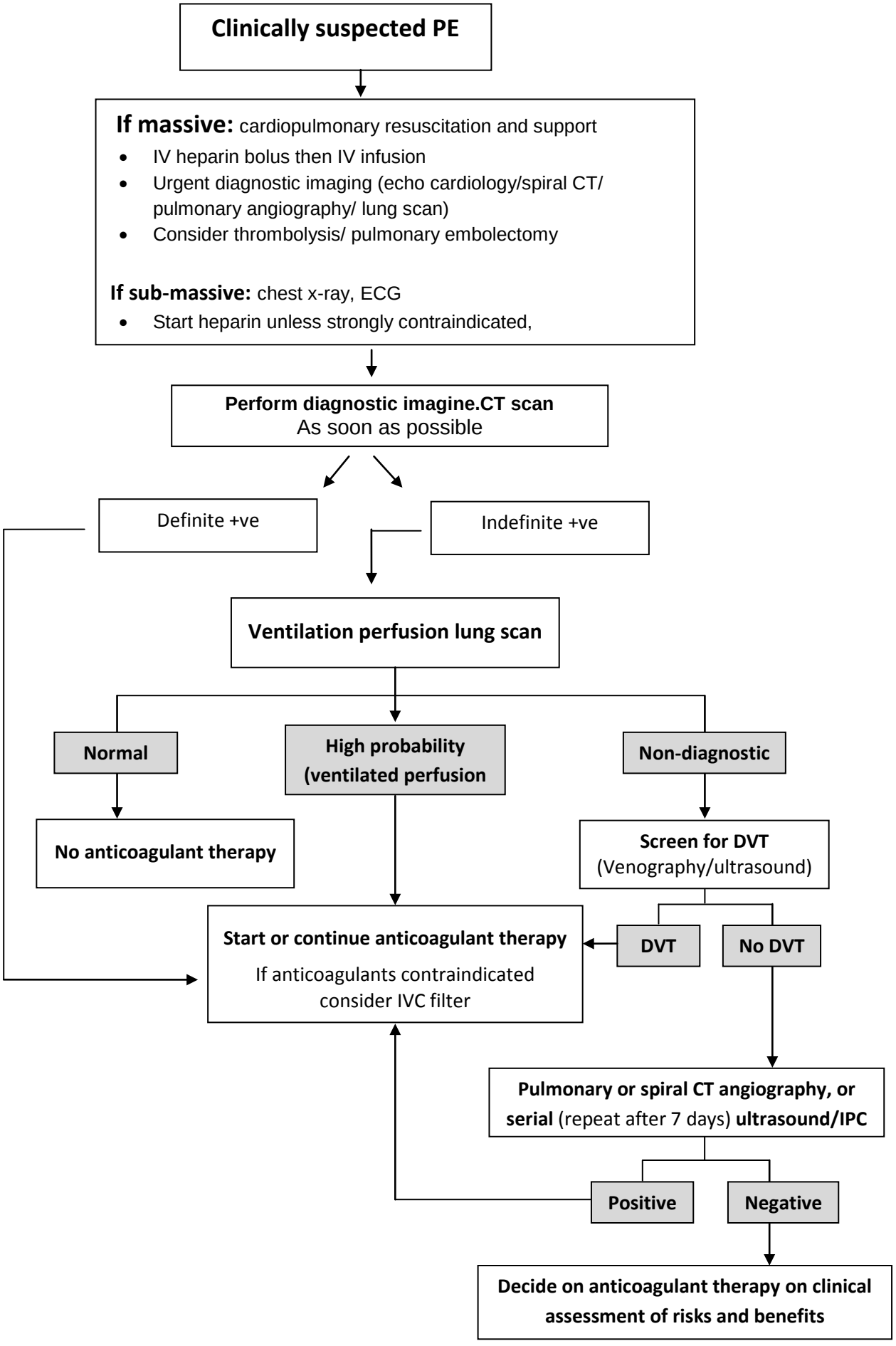
Treatment

Currently 2 agents are available to treat HIT: Lepirudin. Argatroban

Note:

- If HIT is suspected **do not** switch to a low-molecular-weight heparin, as LMWH's will cross-react with the antibody 90% of the time.
- Simply stopping heparin may not prevent thrombosis.
- Platelet transfusions can increase risk of thrombosis.
- Warfarin is contraindicated as acute monotherapy


Clinically suspected DVT
Perform diagnostic imagine
If not immediately available, start heparin unless strongly contraindicated and perform objective test as soon as possible
CONTRAST VENOGRAPHY
OR
ULTRASOUND
(COMPRESSION OR DUPLEX)
Negative
Positive
Inadequat
Positive
Negative
If low clinical probability and/or normal D-dimer
Venography, or repeat ultrasound after 7 days
Start or continue anticoagulant therapy + other therapy
If anticoagulants contraindicated consider IVC filter*
Positive
Negative
No anticoagulant therapy
IVC = Inferior vena cava*


Clinically suspected PE
If massive: cardiopulmonary resuscitation and support
IV heparin bolus then IV infusion
Urgent diagnostic imaging (echo cardiology/spiral CT/ pulmonary angiography/ lung scan)
Consider thrombolysis/ pulmonary embolectomy
If sub-massive: chest x-ray, ECG
Start heparin unless strongly contraindicated,
Perform diagnostic imagine.CT scan
As soon as possible
Definite +ve
Indefinite +ve
Ventilation perfusion lung scan
Normal
High probability (ventilated perfusion
Non-diagnostic
No anticoagulant therapy
Screen for DVT
(Venography/ultrasound)
Start or continue anticoagulant therapy
If anticoagulants contraindicated consider IVC filter
DVT
No DVT
Pulmonary or spiral CT angiography, or serial (repeat after 7 days) ultrasound/IPC
Positive
Negative
Decide on anticoagulant therapy on clinical assessment of risks and benefits

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