Antithrombotic therapy for venous thromboembolic disease

The purpose of this guideline is to present recommendations based on current evidence in order to help clinicians in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). This field is highly dynamic however, and new evidence is emerging periodically that may change the recommendations.

The following tables are based on the last American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) (1) after discussion by the Belgian Thrombosis Guidelines Group and adaptation to Belgian specificities.

Grade 1 recommendations are strong and indicate that the benefits do or do not outweigh risks, burden, and costs.

Grade 2 suggests that individual patient values may lead to different choices (for a full understanding of the grading, see "Grades of Recommendation" chapter) (2).

Anticoagulation therapy is considered as the standard treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Other treatment options such as thrombolytic therapy, surgical thrombectomy or placement of an inferior vena cava filter might be suggested in selected patients.

References

(1) Kearon C et al. Antithrombotic Therapy for Venous Thromboembolic disease. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:454S-545S.

(2) Guyatt GH et al. Grades of Recommendation for Antithrombotic Agents. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:123S-131S.

Treatment of Deep Vein Thrombosis of the lower limb

- For patients with a DVT of the lower limb, we recommend an <u>anticoagulant therapy:</u>
    - o In case of an objectively confirmed DVT, treatment as in table 1
    - o In case of a high clinical suspicion of DVT, initiate anticoagulant therapy as in table 1 while awaiting the outcome of diagnostic tests. Confirmatory diagnostic tests should be performed within 24 hours.

- In addition, for the prevention of postthrombotic syndrome (PTS), we recommend the use of an <u>elastic compression stocking</u> with an ankle pressure gradient of 30 to 40 mm Hg (usually type 2 compression) if feasible. Compression therapy, which may include the use of bandages acutely, should be started as soon as feasible* after starting anticoagulation and should be continued for a minimum of 2 years in case of symptomatic proximal DVT, and longer if patients have symptoms of PTS.

- We recommend <u>early ambulation</u> in preference to bed rest when this is feasible.

- Don't use VKA during pregnancy.

- The duration of anticoagulant therapy depends on the risk of recurrent VTE after stopping VKA. The factors that influence this risk are the following :
    - o Presence of a reversible provoking risk factor (eg, recent surgery, immobilization, use of oestrogen therapy...)
    - o Unprovoked VTE (= idiopathic VTE)
    - o Presence of active cancer

Hereditary thrombophilia has not been used as a major factor to guide duration of anticoagulation for VTE in these recommendations because evidence from prospective studies suggests that these factors are not a major determinant of the risk of recurrence.

The concept of indefinite (or long-term) anticoagulation has been introduced with the following definition: continued anticoagulation without a scheduled stop date, but which may be stopped because of a subsequent increase in the risk of bleeding or change in the patient's preference.

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* Feasibility, both short and long term, refers to ability of patients and their caregivers to apply and remove stockings.

Table 1: Anticoagulation treatment recommendations in DVT

Diagnosis	Initial treatment	Treatment duration
DVT secondary to reversible risk factor	• Short-term treatment with SC LMWH or IV UFH and initiation of VKA on the 1st treatment day	3 months rather than shorter periods
Unprovoked DVT • First episode	• Maintain LMWH or UFH for at least 5 days and until the INR is ≥ 2 for 24h • In case of severe renal failure (MDRD-GF < 30ml/min), UFH is preferred over LMWH	• At least 3 months, then evaluation of the risk-benefit ratio of long-term therapy • Long-term treatment in case of 1st unprovoked proximal DVT if risk factors for bleeding are absent and if good anticoagulant monitoring is achievable
• Second episode		• Long-term treatment
Asymptomatic DVT		Same schedule as for symptomatic DVT
DVT and cancer	SC LMWH for the first 3 to 6 months and then VKA or LMWH indefinitely or until the cancer is resolved	

LMWH SC	Once or twice daily, as an outpatient if possible, or as an inpatient if necessary, according to one of the following dosages : • Dalteparin 100 IU anti-Xa/kg/12h or 200 IU anti-Xa/kg/24h • Enoxaparin 100 IU anti-Xa/kg/12h or 150 IU anti-Xa/kg/24h • Nadroparin 86 IU anti-Xa/kg/ 12h or 171 IU anti-Xa/kg/24h • Tinzaparin 175 IU anti-Xa/kg/24h
UFH IV	Initial IV bolus (80 IU/kg or 5000 IU) followed by a continuous infusion (18 IU/kg/h or 1300 IU/kg/h) with adjustment to obtain an APTT that corresponds to plasma heparin levels of 0.3 to 0.7 IU/ml anti-Xa activity by the amidolytic assay
VKA	Use acenocoumarol, phenprocoumon or warfarin and adjust the dose to maintain a target INR of 2.5 (range 2.0 to 3.0)

In selected patients with extensive iliofemoral acute DVT (eg. symptoms for less than 7 to 14 days, good functional status, life expectancy of ≥ 1 year), an alternative treatment may be suggested in the acute phase according to Table 2.

Table 2. Alternative treatment for acute proximal DVT of the lower limb in selected patients
• If the risk of bleeding is low, <u>catheter-directed thrombolysis</u> or pharmacomechanical thrombolysis (fragmentation, aspiration) may be used to reduce acute symptoms and post-thrombotic morbidity if appropriate expertise and resources are available. This procedure may be completed by correction of underlying venous lesions (balloon angioplasty, stents).   • <u>Operative venous thrombectomy</u> may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available. Catheter-directed thrombolysis is usually preferable if the risk of bleeding is low.

If anticoagulant therapy is not possible because of the risk of bleeding in patients with acute proximal DVT, we recommend placement of an inferior vena cava (IVC) filter.

Discuss retrievable filter in the setting of transient contraindication to anticoagulation.

For patients with acute DVT who have an IVC filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if their risk of bleeding resolves.

Treatment of Pulmonary embolism

Treatment regimens for DVT and PE are similar but there are some important differences between patients who present with PE and with DVT that justify separate consideration of treatment for PE:

- The risk of early death (within 1 month) is much greater after presenting with PE than after DVT; this difference may justify more agressive initial treatment (eg, thrombolytic therapy, insertion of an IVC filter).

- Recurrent episodes are about 3 times as likely to be PE after an initial PE than after an initial DVT.

- Long-term sequelae of PE are cardiorespiratory impairment, especially due to pulmonary hypertension.

All the patients presenting with PE should undergo rapid risk stratification to select those who could benefit from thrombolytic therapy.

The main recommendations for initial anticoagulant therapy do not differ for proximal DVT or PE (Table 3).

- For patients with a PE , we recommend an <u>anticoagulant therapy:</u>
    - In case of an objectively confirmed PE, treatment as in table 3
    - In case of a high clinical suspicion of PE, anticoagulant therapy should be initiated while awaiting the outcome of diagnostic tests.
      Confirmatory diagnostic tests should be performed within 24 hours.
- The recommendations for anticoagulation in clinical practice, the duration and the intensity of the anticoagulation do not differ for proximal DVT or PE. (Table 3)

Table 3: Anticoagulation treatment recommendations in PE

Diagnosis	Initial treatment	Treatment duration
PE secondary to reversible risk factor	• Short-term treatment with SC LMWH or IV UFH and initiation of VKA on the 1st treatment day • Maintain LMWH or UFH for at least 5 days and until the INR is ≥ 2 for 24h • In case of severe renal failure (MDRD-GF < 30ml/min), UFH is preferred over LMWH	3 months rather than shorter periods
Unprovoked PE • First episode		• At least 3 months, then evaluation of the risk-benefit ratio of long-term therapy • Long-term treatment in case of 1st unprovoked PE if risk factors for bleeding are absent and if good anticoagulant monitoring is achievable
• Second episode		• Long-term treatment
Asymptomatic PE		Same schedule as for symptomatic PE
Massive PE • If concern about SC absoption • If possible thrombolytic therapy	Prefer IV UFH rather than SC LMWH	Same schedule as for unprovoked PE
PE and cancer	SC LMWH for the first 3 to 6 months and then VKA or LMWH indefinitely or until the cancer is resolved	

LMWH SC	Once or twice daily, as an outpatient if possible, or as an inpatient if necessary, according to one of the following dosages : • Dalteparin 100 IU anti-Xa/kg/12h or 200 IU anti-Xa/kg/24h • Enoxaparin 100 IU anti-Xa/kg/12h or 150 IU anti-Xa/kg/24h • Nadroparin 86 IU anti-Xa/kg/ 12h or 171 IU anti-Xa/kg/24h • Tinzaparin 175 IU anti-Xa/kg/24h
UFH IV	Initial IV bolus (80 IU/kg or 5000 IU) followed by a continuous infusion (18 IU/kg/h or 1300 IU/kg/h) with adjustment to obtain an APTT that corresponds to plasma heparin levels of 0.3 to 0.7 IU/ml anti-Xa activity by the amidolytic assay
VKA	Use acenocoumarol, phenprocoumon or warfarin and adjust the dose to maintain a target INR of 2.5 (range 2.0 to 3.0)

Table 4. Thrombolytic therapy of pulmonary embolism

- For patients with <u>evidence of hemodynamic compromise</u>, we recommend use of thrombolytic therapy unless there are major contraindications owing to bleeding risk.
- In selected high-risk patients without hypotension who are judged to have a low risk of bleeding, thrombolytic therapy can be considered. The decision to use thrombolytic therapy depends on the clinician's assessment of PE severity, prognosis, and risk of bleeding.
- For the majority of patients with PE, we recommend against using thrombolytic therapy.
- When a thrombolytic agent is used, we recommend that treatment be administered via a peripheral vein rather than placing a pulmonary artery catheter to administer treatment.
- We recommend use of thrombolytic regimens with short infusion times (*eg*, a 2-h infusion) over those with prolonged infusion times (*eg*, a 24-h infusion).

In selected highly compromised patients in the acute phase who are unable to receive thrombolytic therapy because of bleeding risk, an alternative treatment may be suggested according to Table 5.

Table 5. Alternative treatment for severe PE in selected high risk patients

- In selected highly compromised patients who are unable to receive thrombolytic therapy because of bleeding risk, or whose critical status does not allow sufficient time for systemic thrombolytic therapy to be effective, we suggest use of <u>interventional catheterization techniques</u> (catheter extraction or fragmentation) if appropriate expertise is available.
- In selected highly compromised patients who are unable to receive thrombolytic therapy because of bleeding risk, or whose critical status does not allow sufficient time for systemic thrombolytic therapy to be effective, we suggest that <u>pulmonary embolectomy</u> may be used if appropriate expertise is available.

For patients with acute PE, <u>if anticoagulant therapy is not possible</u> because of the risk of bleeding, we recommend placement of an <u>inferior vena cava (IVC) filter.</u>

Discuss retrievable filter in the setting of transient contraindication to anticoagulation.

For patients with acute PE who have an IVC filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if their risk of bleeding resolves.

For patients with chronic thromboembolic pulmonary hypertension, we recommend or suggest the following (Table 6).

Table 6. Treatment of chronic thromboembolic pulmonary hypertension (CTPH)
• In selected patients with CTPH, such as those with central disease under the care of an experienced surgical/medical team, we recommend pulmonary thromboendarterectomy.
• For all patients with CTPH, we recommend life-long treatment with a VKA targeted to an INR of 2.0 to 3.0.
• For patients with inoperable CTPH, we suggest referral to a center with expertise in pulmonary hypertension so that patients can be evaluated for alternative treatments, such as vasodilator therapy or balloon pulmonary angioplasty.

Treatment of Upper-extremity Deep Vein Thrombosis (UEDVT)

For patients with an UEDVT, we recommend an <u>anticoagulant therapy</u> for at least 3 months as described for lower limbs DVT (Table 1).

Other recommendations and suggestions are given in Table 7.

Table 7. Treatment of Upper-extremity deep vein thrombosis

• We recommend anticoagulant therapy for ≥ 3 months (as described for DVT of the lower limb).
 	
 • We recommend against the routine use of systemic or catheter-directed thrombolytic therapy.
 	
 • We recommend against the routine use of catheter extraction, surgical thrombectomy, transluminal angioplasty, stent placement, staged approach of lysis followed by interventional or surgical procedure, or superior vena cava filter placement.
 	
 • We suggest the following approach if UEDVT is associated with an indwelling catheter :
      o the catheter has not to be removed if it is functional and there is an ongoing need for the catheter;
      o if the catheter is removed, the duration of long-term anticoagulation has not to be shortened to less than 3 months.