# Tratamiento del Tromboembolismo Venoso: que hay de nuevo

## Update in the treatment of venous thromboembolism

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**Abstract**

The treatment of venous thromboembolism has today reached a high degree of simplification with outpatient management, often with oral treatment only. There is still uncertainty regarding the patients with more extensive venous thromboembolism and possible thrombolytic or pharmacomechanic therapy. Indefinite duration of anticoagulation will dramatically reduce the risk of recurrence after unprovoked thromboembolism but has had limited acceptance. With the newer oral anticoagulants that provide a lower risk of bleeding, particularly intracranial haemorrhage, together with convenience we should see more patients continuing secondary prophylaxis very long-term. Large clinical trials with negative results have recently been published on the use of compression stockings and on extensive cancer screening.

**Introduction**

The treatment of venous thromboembolism (VTE) has become safer and substantially more convenient than two decades ago with preserved efficacy. There were two major steps in this development. The first was the switch from infusion of unfractionated heparin to subcutaneous injection with low-molecular-weight heparin (LMWH) without the need for daily laboratory monitoring, enabling outpatient treatment of the majority of patients. The second and most recent step was from vitamin K antagonists to the non-vitamin K antagonist oral anticoagulants (NOACs) eliminating the need for frequent laboratory monitoring and also reducing the risk of intracranial bleeding. With the high risk of recurrence after unprovoked VTE we can now seriously consider and offer these patient indefinite duration of a therapy that is no longer inconvenient and with benefits clearly outweighing the potential harms.

In this review the treatment of VTE will be discussed from diagnosis and progressively to the decision on long-term management, with emphasis on newer developments.

**Initial treatment of acute VTE – pulmonary embolism**

The management of pulmonary embolism, which can be life-threatening, is discussed separately from deep vein thrombosis (DVT), which only rarely can be limb-threatening. Pulmonary embolism with hemodynamic compromise, most importantly expressed as hypotension, carries a high mortality. For patients requiring inotropic drugs the mortality has been estimated at 30% and for those with cardiopulmonary arrest as high as 70%.[1] Thrombolytic therapy should be strongly considered for these patients as the first line of therapy. The contraindication is a high risk of bleeding. Most of the documentation is for recombinant tissue plasminogen activator (rtPA), for example alteplase at a dose of 100 mg, of which 10 mg is given as a bolus and the rest as an infusion of 2 hours, all into a peripheral vein. For patients in an immediately life-threatening condition treatment should be given as a bolus dose alone but at a lower total dose (i.e. 50 mg in 15 minutes). Streptokinase is still an alternative to rtPA.

For patients with right ventricle strain but without hypotension there has been a debate whether thrombolytic therapy should be recommended to reduce mortality. In a randomized, controlled trial with over 1000 patients with right ventricle dysfunction and elevated cardiac troponin I or T, tenecteplase gave an absolute reduction of the composite outcome of death or hemodynamic decompensation of 3% (P=0.02) but no significant reduction of all-cause mortality.[2] Major bleeding was increased by 9.1% (absolute) and hemorrhagic stroke by 1.8%, both statistically significant. It remains a challenge to select the patients with benefit and minimal harm in this subset.

In case of uncertainty regarding the need for thrombolytic therapy it is recommendable to start with intravenous infusion of unfractionated heparin, which can be rapidly switched to thrombolysis or transitioned to LMWH subcutaneously.

Patients with less serious clinical manifestations of pulmonary embolism the management should be similar to that for DVT, as described below. However, specifically for pulmonary embolism, there are prediction scores that can be used for risk stratification before sending the patient home from the Emergency Department. These are helpful to document the patients at very low risk for fatal outcome, for whom outpatient treatment is equally safe. The user-friendliest one is the simplified version of Pulmonary Embolism Severity Index (PESI) [3] with 1 point each for age >80, cancer (including history of it), chronic heart or lung disease, heart rate >110/min, systolic blood pressure <100 mmHg and oxygen saturation <90%. Patients scoring 0 can be safely treated at home.

**Initial treatment of acute VTE – DVT**

The most serious forms of DVT are the rarely occurring *phlegmasia coerulea dolens* and *phlegmasia alba dolens*. In the former the massive thrombosis occludes essentially all deep veins and collaterals from the leg, which becomes cyanotic an, very swollen and painful. In the latter the arterial flow is also impaired. The result is a limb-threatening situation for which intravenous infusion with unfractionated heparin may give relief but thrombolytic therapy should be considered. In many such cases there is an underlying malignancy that can confer a high risk of bleeding, e.g. if brain metastases are present. It is in those cases better to give heparin infusion a chance and monitor the viability of the leg closely.

Furthermore, patients with large, proximal thrombi in the leg but without circulatory compromise might also warrant consideration of thrombolytic therapy to reduce the risk of post-thrombotic syndrome (PTS). The population of greatest interest here are the young and with low risk of bleeding. A randomized, controlled trial comparing catheter-directed thrombolysis with standard treatment in 209 patients showed an absolute risk reduction of 14.4% (P=0.047) after 2 years of follow-up.[4] The population included was highly selected and standard therapy is still the recommended one for these patients.[1] Additional benefit might be achieved with the combination of local thrombolysis and rotating catheters that fragment the thrombus – pharmaco-mechanic removal. This is currently investigated in a large randomized trial (ClinicalTrials.gov NCT00790335).

Standard initial treatment for patients with DVT or with pulmonary embolism that is not associated with right ventricle strain has since many years been LMWH subcutaneously once daily and overlapping initiation of a vitamin K antagonist until the international normalized ratio (INR) is at least 2.0 for 2 days. The first dose of LMWH can be given already on clinical suspicion of VTE, particularly if it is pulmonary embolism, when there is anticipated delay until imaging diagnostics can be obtained. There is no need to split the daily dose of LMWH into 2 doses per day. The only exception is patients at a very

high risk of bleeding, such as VTE very shortly after major surgery.

For patients with severe renal failure (calculated creatinine clearance <30 mL/min) there is a risk of bioaccumulation of LMWH. It is unclear how to optimally reduce the dose of LMWH for these patients. Unfractionated heparin is not eliminated renally and can be administered subcutaneously at a dose that is adjusted to body weight and does not require monitoring with activated partial thromboplastin time. Based on a randomized clinical trial comparing this regimen versus LMWH in 708 patients *without* severe renal failure,[5] we have developed a protocol with slightly lower doses of heparin (**Table 1**). The dose reduction takes into account the increased risk of bleeding with any anticoagulant in patients with severe renal failure.

**Table 1:** Treatment protocol with unfractionated heparin subcutaneously without laboratory monitoring for VTE in patients with severe renal failure – in comparison with the FIDO Study protocol[5]

| | Severe renal failure | Other patients (FIDO study) |
|---|---|---|
| First dose | 250 units/kg | 333 units/kg |
| Following doses | 200 units/kg every 12 h | 250 units/kg |

**Continued therapy for VTE**

Initial heparin therapy followed by ineffective dose of subcutaneous heparin[6] or by no anticoagulation[7] is associated with a 20-30% risk of recurrence during 3 months. It is therefore necessary to continue anticoagulation for at least 3 months, after which point the risk of recurrence decreases. The only exception is calf vein DVT that is clearly provoked, such as after surgery, in which case 6 weeks of therapy may suffice [Kearon] although most physicians treat these for 3 months as well. The main choice at this point is whether the patient should have a vitamin K antagonist (warfarin, acenocoumarol, phenprocoumon) or a NOAC (dabigatran, rivaroxaban, apixaban, edoxaban) or continue with LMWH.

**Long-term LMWH**

This should be considered for the following subsets of patients:

1) Active malignancy with VTE. A study in 672 patients demonstrated that dalteparin 200 units/kg for 1 month and then at 150 units/kg for another 5 months, all once daily, reduced the absolute risk of recurrence by 8% (P=0.002) compared to dalteparin for 1 week followed by warfarin for 6 month.[8] The risk of bleeding was similar for the two strategies. In a similar study with 900 patients treated with tinzaparin at 175 units/kg for 6 months versus the same for 1 week followed by warfarin there was a trend to lower risk of recurrence with an absolute risk reduction of 3.1% (P=0.07).[9] Thus, LMWH is considered the preferred anticoagulant for the first 3-6 months in cancer and VTE.
2) Splanchnic vein thrombosis with liver cirrhosis can be complicated by hypoprothrombinemia so that monitoring of vitamin K antagonists becomes impossible. The reduced synthesis of vitamin K-dependent factors may not in itself prvide an antithrombotic effect since the vitamin K-dependent coagulation inhibitors, protein C and protein S also are reduced. For those patients LMWH for 3-6 months is an alternative.[10]
3) Patients with antiphospholipid syndrome have sometimes a lupus anticoagulant directed against coagulation factors that will prolong the prothrombin time and thus give false elevation of the INR with increased risk of recurrent VTE. Here again LMWH is an alternative.
4) Pregnant patients should avoid vitamin K antagonists – definitely during the first trimester due to the risk for warfarin embryopathy and preferably also in trimester 2 and 3 due to increased risk for fetal intracranial hemorrhage. For these patients LMWH should be used at therapeutic dose until delivery, after which substitution with a vitamin K antagonist is possible.[11]

**Long-term vitamin K antagonist**

This has been the standard for many decades and is probably still prescribed for the majority of patients in many countries in view of the low direct cost. Vitamin K antagonists should be started early in the management of the patient to give sufficient time for overlapping with LMWH until INR is therapeutic for 2 days. For outpatients a starting "loading" dose of 10 mg for 2 days, followed by dosing according to the INR leads to faster achievement of the ther-

apeutic range.[12] Pharmacogenetic testing has not been convincingly shown to improve clinical outcomes.[12]

In countries and for patients that prescription of NOACs is not a financial problem, vitamin K antagonists still have to be used for the following:

1) Severe renal failure will result in bioaccumulation of NOACs whereas the elimination of vitamin K antagonists is independent of the kidney function.
2) Patients with other indications necessitating vitamin K antagonists, such as mechanical heart valves.
3) In addition, it is prudent to use vitamin K antagonists for patients with known or suspected poor adherence, since with the use of a NOAC that will go undetected with high risk for treatment failure.

**Long-term NOAC**

Patients with initial parenteral treatment can easily be switched over to a NOAC without any overlap. Dabigatran and edoxaban have only been studied with lead-in parenteral treatment[13-15] and are therefore not recommended for monotherapy. Rivaroxaban was studied as monotherapy with more intensive dosing the first 3 weeks at 15 mg twice daily, followed by 20 mg daily.[16, 17] Apixaban was similarly studied at 10 mg twice daily, although only the first week, and then 5 mg twice daily.[18] It is unclear whether the lead-in parenteral treatment provides any antithrombotic advantage for the NOAC regimen. In the study with edoxaban, a pre-specified analysis of the patients with pulmonary embolism with right ventricle dysfunction showed significantly lower risk of recurrence with edoxaban than with warfarin (absolute risk reduction 2.9%).[15] In all other subgroups and studies the efficacy was NOACs was non-inferior to vitamin K antagonist. However, the risk of bleeding, measured as major or clinically relevant, was in most studies lower with NOACs. Importantly, the risk of intracranial bleeding was shown in a meta-analysis to be significantly reduced with NOACs with a 63% relative risk reduction although in absolute terms only 0.2% during 6 months.[19] In view of the convenience of using NOACs for patients with VTE this will become increasingly popular.

**Duration of anticoagulation**

It is recommended to reassess the duration of anticoagulation after 3 months for patients with unprovoked VTE to decide whether to discontinue or to proceed with indefinite duration of treatment to minimize the otherwise high risk of recurrence, which is 10% during the first year after discontinuation.[20] Factors to take into account are the increased risk of recurrence for males,[21] the increased risk of bleeding in case of a history of bleeding, in the presence of antiplatelet therapy, renal or liver disease, old age, alcohol or drug abuse, and finally the increased risk of both bleeding and VTE recurrence with poor compliance. Additional decision support, at least for females can be obtained by testing the D-dimer before and one month after discontinuing anticoagulation.[22] If the level is normal on both occasions the risk of recurrence is low.

Dabigatran is the only NOAC that has been studied long-term versus warfarin and it was non-inferior in efficacy with a reduced risk of bleeding.[23] In comparison with placebo all NOACs tested were very effective with a 70-90% risk reduction.[16, 23, 24] This can be compared with approximately 30% risk reduction from aspirin.[25] Aspirin is an option for patients with a relatively low risk of VTE recurrence and presence of cardiac risk factors.

**Compression stockings**

In a randomized clinical trial with compression stockings versus placebo stockings for 2 years in 800 patients with first proximal DVT there was no reduction of PTS.[26] These may still be indicated to reduce symptoms for patients with pain or swelling from PTS.

**Investigation of malignancy**

Twenty percent of patients with VTE have a malignancy but several studies have failed to demonstrate benefit from extensive investigations to screen for cancer in patients with unprovoked VTE. The largest study with 854 patients evaluated the addition of comprehensive computed tomography but without demonstrating any benefit.[27] Therefore, basic medical history, physical exam, routine blood tests and age-and sex-specific investigations should be sufficient. More extensive investigation could be warranted in patients with recurrent VTE despite adequate anticoagulation.

**Declaration of conflict of interest:**
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## References


1. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e419S-94S.
2. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402-11.
3. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170:1383-9.
4. Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 2012;379:31-8.
5. Kearon C, Ginsberg JS, Julian JA, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. JAMA 2006;296:935-42.
6. Hull RD, Raskob GE, Hirsh J, et al. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. N Engl J Med 1986;315:1109-14.
7. Lagerstedt CI, Olsson CG, Fagher BO, Öqvist BW, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. Lancet 1985;2:515-8.
8. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-53.
9. Lee AYY, Kamphuisen PW, Meyer G, et al. A randomized trial of long-term tinzaparin, a low molecular weight heparin (LMWH), versus warfarin for treatment of acute venous thromboembolism (VTE) in cancer patients - the CATCH study. Blood 2014;124:LBA-2 (abstract).
10. Ageno W, Riva N, Schulman S, et al. Long-term clinical outcomes of splanchnic vein thrombosis: results of an international registry. JAMA Intern Med 2015:{Epub ahead of print].
11. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e351S-418S.
12. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e152S-84S.
13. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014;129:764-72.
14. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-52.
15. The Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406-15.
16. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.
17. Buller HR, Prins MH, Lensing AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.
18. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.
19. van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute symptomatic venous thromboembolism: evidence from phase 3 trials. Blood 2014;124:1968-75.

20. Kearon C. A conceptual framework for two phases of anticoagulant treatment of venous thromboembolism. J Thromb Haemost 2012;10:507-11.

21. McRae S, Tran H, Schulman S, Ginsberg J, Kearon C. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. Lancet 2006;368:371-8.

22. Kearon C, Spencer FA, O'Keeffe D, et al. D-dimer testing to select patients with a first unprovoked venous thromboembolism who can stop anticoagulant therapy: a cohort study. Ann Intern Med 2015;162:27-34.

23. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin or placebo in venous thromboembolism. N Engl J Med 2013;368:709-18.

24. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708.

25. Simes J, Becattini C, Agnelli G, et al. Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. Circulation 2014;130:1062-71.

26. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet 2014;383:880-8.

27. Carrier M, Lazo-Langner A, Shivakumar S, et al. Screening for occult cancer in unprovoked venous thromboembolism. N Engl J Med 2015;373:[Epub ahead of print].