Adjustments in the diagnostic work-up, treatment and prognosis of pulmonary embolism
van Es, Josien

Citation for published version (APA):
van Es, J. (2013). Adjustments in the diagnostic work-up, treatment and prognosis of pulmonary embolism

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
How to prevent, treat, and overcome current clinical challenges of VTE

J. van Es
E.S. Eerenberg
P.W. Kamphuisen
H.R. Büller

Journal of Thrombosis and Haemostasis 2011
**Abstract**

Venous thromboembolism (VTE) is most commonly initially treated with low molecular weight heparin (LMWH), fondaparinux, or unfractionated heparin, in combination with vitamin-K antagonists (VKA) for the long-term treatment. VKA have some drawbacks however, which has led to the development of new anticoagulants. Most of these new drugs can be administered orally, and they have been investigated in many phase III clinical trials. The benefits of the anticoagulants are the stable therapeutic effect, little interactions with other medication and food, and therefore no regular monitoring is required. The duration of anticoagulant treatment for VTE is usually 3-12 months, and depends on the balance between the risks of recurrent thrombosis, major bleeding, and the patient’s preference. Clinical decision rules to assess the risk of recurrence to tailor the duration of anticoagulant treatment, are being investigated. The beneficial aspects of novel anticoagulants may prolong the duration of treatment. VTE treatment should be adjusted in special patient groups, such as in case of malignancy, renal failure, pregnancy, or extreme bodyweight. This article gives an overview of current and future aspects of the treatment of VTE.
**INTRODUCTION**

Pulmonary embolism (PE) and deep-vein thrombosis (DVT) are considered to be two manifestations of the same condition: venous thromboembolism (VTE) – which has an incidence of 1-3 per 1000 of the general population per year, and is the third most common cardiovascular disorder in industrialized countries. With the aging of the current population, the incidence is expected to increase further (1, 2). Anticoagulant treatment in patients with VTE is highly effective, as it reduces the incidence of recurrent disease from about 25% to about 3% during the first 6-12 months of therapy (3). Since 1960, treatment with oral vitamin K antagonists (VKA) remained the mainstay of long-term anticoagulation therapy for hemodynamic stable patients with VTE, for both prevention of thrombus extension, and recurrence of the disease (3). There are well-known disadvantages notable with the use of VKA. Although VKA administration usually can be started immediately after diagnosis, the slow onset and offset of action often requires bridging with parental or subcutaneous anticoagulant drugs, which challenges outpatient treatment (4). The initial treatment with low molecular weight heparin (LMWH), fondaparinux or unfractionated heparin (UFH) can only be stopped after the International Normalized Ratio (INR) remains above 2.0 for at least 24 h (4), which usually takes 5-10 days (5, 6). LMWH or fondaparinux are usually preferred to intravenous UFH because they rarely require monitoring and are both associated with fewer recurrent thrombotic events, and less major bleeding (7). However, dose adjustments for severe renal impairment and extreme obesity are not standardized for LMWH, and there is no antidote unlike for UFH, which can be directly reversed with protamine sulphate. A rare but serious complication of UFH, LMWH, and in extreme rare situations of fondaparinux, is heparin-induced thrombocytopenia (HIT) (8, 9). Besides the need for additional bridging, other drawbacks of VKA therapy include the interactions with other drugs and food, and the narrow therapeutic window, which leads to a great inter-individual variability in dose-response rate. The risk for either under- and overtreatment consequently is high and therefore routine monitoring and dose adjustments are necessary (10). Patients taking VKA spend at least one third of the time outside the therapeutic INR range (11). Therefore, the development of new anticoagulants in the last decade was welcome. In contrast to VKA these new drugs, (in-)direct Factor Xa and thrombin inhibitors, have less disadvantages, as they all have predictable pharmacological profiles (Table 1) (12, 13). Currently, many clinical trials with new anticoagulants have been published or are on-going. Factor Xa inhibitors
most advanced in clinical development are rivaroxaban, apixaban, idrabiotaparinux and edoxaban. Dabigatran is the most advanced thrombin inhibitor (12,13). Critically, there is a lack of information on the appropriate antidote, and on reliable monitoring for special circumstances, such as in case of a major bleeding or when an urgent invasive procedure is required (14).

Initial anticoagulant treatment is different for patients with massive PE with hemodynamic instability and a high mortality risk. Systemic thrombolysis is recommended as first-line treatment, because of the short-term resolution of emboli and the beneficial hemodynamic effect of thrombolysis (4;15-17). However, the available evidence on the benefit of thrombolytic therapy in patients with massive PE is modest, let alone in patients with right ventricular dysfunction and a normal blood pressure (submassive PE). Embolectomy (surgically, by aspiration of the clot, or by angioplasty) is indicated in patients with PE and arterial hypotension in whom thrombolysis has failed or is contraindicated (4). However, a randomized clinical trial to compare the efficacy of the surgical and the catheter-based techniques has not been performed (4).

Table 1; Pharmacokinetic and pharmacodynamic properties of novel anticoagulants. *From phase II studies with Idraparinux. **After a single bolus, from phase I studies.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Steady state levels</th>
<th>Ttpeak (hours)</th>
<th>½ life (hours)</th>
<th>excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>After 3 days</td>
<td>2</td>
<td>14-17</td>
<td>80% kidneys, 20% biliary system</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>After the first dosage</td>
<td>2-4</td>
<td>5-9 young, 9-13 elderly subjects</td>
<td>66% kidneys, 28% intestines</td>
</tr>
<tr>
<td>Apixaban</td>
<td>After 3 days</td>
<td>1</td>
<td>12</td>
<td>25-29% kidneys, 46-56% intestines</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>After 2 days</td>
<td>1-3</td>
<td>9-11</td>
<td>35-39% kidneys</td>
</tr>
<tr>
<td>Idrabiotaparinux</td>
<td>3-4 months*</td>
<td>1.5 h</td>
<td>120 h**, 60 days*</td>
<td>Idraparinux: Mainly kidneys</td>
</tr>
</tbody>
</table>

If anticoagulant or thrombolytic therapy is contraindicated, VTE can also be treated with an inferior vena cava (IVC) filter. Patients with an IVC filter are recommended to receive a conventional course of anticoagulant therapy when the risk of bleeding is diminished (4;18). No randomized trials or prospective cohort studies have been performed to evaluate IVC filters as monotherapy of VTE, without concurrent anticoagulation.
Consequently, the use of IVC filters is restricted to patients with VTE who have a temporary contraindication to anticoagulant treatment (4).

In this state of the art, the results from large clinical trials with new anticoagulants will be outlined. Additionally, the optimal duration of anticoagulant treatment of VTE will be discussed; with a focus on special patient groups, such as cancer, renal failure, obesity and antiphospholipid syndrome, as well as the use of anticoagulant treatment in pregnant women.

Clinical implementation of novel anticoagulants

Over the last decade, a new generation of anticoagulants has emerged, with favourable characteristics to their predecessors, the VKAs. These novel anticoagulants directly inhibit one specific coagulation factor, and have stable pharmacokinetic and pharmacodynamic properties. Due to the absence of major interactions with food or other drugs, they do not require frequent monitoring. Several phase III trials have shown efficacy and safety for prophylaxis and treatment of VTE, and for the prevention of stroke in atrial fibrillation, as the following chapter further describes.

**Dabigatran**

Dabigatran is a novel direct thrombin inhibitor, administered orally as a prodrug, dabigatran etexilate. Its properties are listed in Table 1 (19;20). Dabigatran is licensed for the prevention of VTE after planned knee or hip surgery, following the results of several phase III studies. Both dabigatran 150 mg and 220 mg administered once daily were shown to be non-inferior to enoxaparin 40 mg subcutaneous once daily, and bleeding risks were similar (the RE-MODEL trial, see Table 2) (21). In the RE-MOBILIZE study, with a higher enoxaparin dosage of 30 mg twice daily, both dosages of dabigatran were found to be inferior to enoxaparin, without a difference in the major bleeding risk (22). Furthermore, the same dosages of dabigatran were as effective and safe as enoxaparin 40 mg once daily for the prevention of VTE after hip replacement (The RENOVATE and RENOVATE-II) (23;24).

In patients with acute VTE, dabigatran was also non-inferior to VKA in preventing recurrent VTE (in the RECOVER trial). Subjects were randomized double-blind to 6 months of treatment with either dabigatran 150 mg bid or warfarin (target INR 2-3). LMWH was administered to all patients at the beginning of treatment. Dabigatran had the same recurrence rate of VTE and the same major bleeding rate as warfarin (Table 2) (25). Results of two other studies for the (extended) treatment of VTE with dabigatran are eagerly awaited (http://clinicaltrials.gov, NCT00329238, NCT00558259).
Dabigatran was also assessed for the prevention of stroke in atrial fibrillation. The RE-LY study included 18,000 patients, randomised between dabigatran 110 mg or 150 mg bd, and warfarin (target INR 2-3). The study had a double blind, double-dummy design, and subjects were treated for 2 years. Dabigatran 110 mg bid gave a significant lower incidence of major bleeding than warfarin, and a similar occurrence of stroke or systemic embolism (Table 2). The higher dosage of dabigatran 150 mg bd was as safe as warfarin in terms of bleeding risk, but more effective in the prevention of stroke or systemic embolism. Notable side effect was dyspepsia, occurring in 12% of all dabigatran recipients (26). Based on these results, dabigatran was registered for the prevention of stroke in atrial fibrillation, in Canada and USA. The licensed dosage was 150 mg twice daily, an adjusted dose of 75 mg twice daily was suggested for patients with severe renal impairment. The 75 mg dose was however not assessed in the RE-LY study, in which patients with a creatinine clearance of < 30 mL per minute were excluded.

Rivaroxaban

One of the most advanced direct factor Xa inhibitors is rivaroxaban, a novel oral anticoagulant known for causing steady state levels after the first dose. See Table 1 for its other properties (27;28). Rivaroxaban 10 mg once daily has been shown superior to LMWH in preventing VTE after knee and hip surgery, with similar bleeding risks as 40 mg enoxaparin once daily (the phase III RECORD studies) (29;30) (Table 2). A meta-analysis of eight randomised controlled trials involving rivaroxaban for VTE prophylaxis underlined these results (31). The combined endpoint of the VTE rate and all cause mortality was lower for rivaroxaban than for enoxaparin (RR 0.56, 95% CI 0.39-0.80), and both drugs had comparable risks of major (RR 1.65, 95% CI 0.93-2.93) and clinically relevant non-major bleeding (RR 1.21, 95% CI 0.98-1.50) (31). Rivaroxaban has therefore been registered for the prevention of VTE after elective orthopaedic surgery in both Europe and Canada, for a dosage of 10 mg once daily.

The EINSTEIN investigators showed that rivaroxaban 20 mg once daily was as effective and safe as VKA for treating acute DVT. Recurrences of VTE were similar for both drugs, as was the incidence of the total of major and clinically relevant non-major bleeding (Table 2). In contrast to other new anticoagulants or VKA, rivaroxaban does not require additional LMWH at the onset of treatment. The trial was therefore designed as open-label (32). In the first 3 weeks patients received a higher dose of 15 mg rivaroxaban twice daily, followed by 20 mg once daily for the rest of the treatment period. In the EINSTEIN-Extension study, patients were randomized double-blind to the same dosage of rivaroxaban, or placebo for the extended treatment of symptomatic VTE.
Subjects had either participated in the original EINSTEIN acute DVT study, or had taken VKA for 6-12 months. Rivaroxaban significantly reduced the recurrence of VTE, without a different risk of major bleeding (Table 2). The net clinical benefit, the composite of recurrent VTE or major bleedings, was 2.0% for the rivaroxaban group and 7.1% for the placebo group (HR 0.28, 95% CI 0.15 to 0.53, p <0.001). The EINSTEIN-PE study in patients with pulmonary embolism is still ongoing.

Rivaroxaban was also investigated for the prevention of stroke in patients with atrial fibrillation. The double-blind, double-dummy ROCKET AF trial contained a relatively vulnerable patient population, with an average age of 73 years, and a 90% incidence of a CHADS 2 score of ≥ 3. Rivaroxaban 20 mg once daily was non-inferior in comparison to warfarin (target INR 2-3) for the prevention of stroke and systemic embolism, and the risk for major bleeding was also comparable in both treatment arms. The discontinuation of treatment was relatively high for the total study population (22%), and less than 57.8% of the warfarin treated subjects had an INR in the therapeutic range (33;34).

Apixaban
Apixaban is an oral anticoagulant that directly inhibits factor Xa, its details are described in Table 1 (35). Apixaban was shown to be superior to enoxaparin for VTE prevention after both hip and knee replacement surgery. The occurrence of the composite of major and clinically relevant bleeding was similar for both drugs (see Table 2) (36;37). For the treatment of symptomatic deep vein thrombosis with apixaban, only dose-ranging studies have been performed (7). Further results from phase III studies will follow (AMPLIFY and AMPLIFY-EXT) (38). In the AVERROES study, in which apixaban 5 mg bid was evaluated vs. aspirin (80-320 mg) for patients with non-valvular atrial fibrillation and who were unsuitable for VKA treatment, the prevalence of stroke and/or systemic embolism was significantly lower in the apixaban study group, while major bleeding rates were similar for both treatment arms (Table 2). Apixaban resulted in more minor bleeding events than aspirin (HR for apixaban 1.24, 95% CI 1.00-1.53). The double-blind double-dummy study was stopped prematurely because of the efficacy of apixaban (39). The ARISTOTLE study that compares apixaban to warfarin in patients with atrial fibrillation is currently ongoing (38).

Edoxaban
Another novel oral direct factor Xa inhibitor is edoxaban (Table 1) (40). There are no available results from phase III studies for the prevention of VTE after elective hip or knee replacement. The HOKUSAI study currently investigates the efficacy and safety of
edoxaban vs. warfarin for the treatment of symptomatic VTE in a randomised, double-blind, double-dummy design. All patients are initially treated with 5-12 days of (LMWH) heparin (http://clinicaltrials.gov, NCT00986154).

Edoxaban has been assessed in a phase II study for the prevention of stroke in atrial fibrillation, with various dosages. The highest doses, 30 mg and 60 mg bid, resulted in significant more bleeding events in comparison to warfarin. The dosages of 30 mg and 60 mg once daily had similar outcomes as the vitamin K antagonist, for bleeding as well as thrombosis (41).

Idrabiotaparinux

Idrabiotaparinux was created by biotinylation of idraparinux, enabling reversal by means of avidin, its unique antidote. It indirectly inhibits activated FXa via selective antithrombin binding and therefore this pentasaccharide inhibits thrombin generation via both the extrinsic and intrinsic pathway, is administered subcutaneously, and has a very long half-life, which facilitates a once weekly dosing (42). Idrabiotaparinux shares its pharmacokinetic and pharmacodynamic properties with idraparinux, some of which are notable. It takes substantial time before the anticoagulant reaches steady state levels, after which its half-life expands to 60 days. Whether or not this increases the risk of bleeding after a long treatment period, is not clear. It may require dose adjustments for patients with long-term therapy (see also Table 1) (43). There are no studies performed with idrabiotaparinux for the prevention of VTE. Idrabiotaparinux was compared to idraparinux in the EQUINOX study for the treatment of DVT (Table 2). Idraparinux was shown effective and safe in comparison to VKA in the treatment of DVT (Van Gogh DVT study) (44). During 6 months of treatment, idrabiotaparinux 3 mg once weekly was as efficient and safe as idraparinux 2.5 mg once weekly, in terms of recurrent VTE and major bleeding, although the composite of all bleedings and major bleedings was higher for idraparinux than previously found in the Van Gogh trial (45). The CASSIOPEA study is investigating the treatment of pulmonary embolism with idrabiotaparinux in comparison to standard therapy with warfarin. In this double-blind, double-dummy, parallel group trial subjects will be treated for 3 or 6 months. Primary outcome will be the recurrence of VTE at 3 months. Secondary outcome will be the recurrence of VTE at 6 months, and bleeding risk (http://clinicaltrials.gov, NCT00345618). The BOREALIS-AF was designed to investigate whether idrabiotaparinux could prevent the occurrence of stroke or other systemic embolism in patients with atrial fibrillation. Unfortunately this trial was terminated prematurely due to financial issues.
Table 2. Results from phase III clinical trial programs for most advanced novel anticoagulants. Dosages of novel anticoagulants are mentioned in the corresponding chapter.

<table>
<thead>
<tr>
<th>Novel anticoagulant</th>
<th>VTE prevention after orthopaedic surgery*</th>
<th>VTE treatment**</th>
<th>Stroke prevention in AF***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total VTE events</td>
<td>Major Bleeding</td>
<td>VTE recurrence</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Knee surgery</td>
<td>36.4% vs 37.7% (p=0.017 for non-inferiority)</td>
<td>Knee surgery</td>
</tr>
<tr>
<td></td>
<td>Hip surgery</td>
<td>6.0% vs 6.7% (p &lt; 0.001 for non-inferiority)</td>
<td>Hip surgery</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Knee surgery</td>
<td>9.6% vs 18.9% (p=0.01)</td>
<td>Knee surgery</td>
</tr>
<tr>
<td></td>
<td>Hip surgery</td>
<td>1.1% vs 3.7% (p=0.01)</td>
<td>Hip surgery</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Knee surgery</td>
<td>No data available</td>
<td>No data available</td>
</tr>
<tr>
<td></td>
<td>Hip surgery</td>
<td>No data available</td>
<td>No data available</td>
</tr>
<tr>
<td>Idarbiotaparinux</td>
<td>No data available</td>
<td>No data available</td>
<td>No data available</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism. AF: atrial fibrillation. *versus enoxaparin 40 mg qd **versus LMWH/VKA (INR 2-3) except for ***versus aspirin 80-320 mg ****versus idraparinux 2,5 mg weekly #versus placebo
Challenges in daily practice

The introduction of new anticoagulants in clinical practice presents several challenges. First, the favourable results of the phase II and III trials may not necessarily sustain in clinical practice, where patients with high risk of thrombosis or bleeding will be treated. Also, new anticoagulants still have an increased risk of bleeding, and in case of a major hemorrhage or the need for an emergency intervention, the anticoagulant effect should be directly and completely reversed. Today, a proper method to reverse novel anticoagulants is unknown (46).

Although these agents may not require routine monitoring, this may still be needed for special conditions. In a debate published in 2010, both parties (for and against) agreed that laboratory testing should be performed in specific circumstances (47;48). Examples are extreme body weight, renal impairment, or potential drug interactions. Also in the case of major bleeding or a possible overdose, or when emergency surgery is necessary, monitoring of the anticoagulant effect may provide relevant information prior to any reversal attempts. Furthermore, assessing compliance with anticoagulant treatment will become more difficult without monitoring. Finally, the information regarding the pharmacokinetic and pharmacodynamic properties of these drugs comes from a selected study population. In clinical practice, patients who would have been disqualified for such studies may not have a similar response. It remains to be shown whether these novel anticoagulants remain as beneficial and safe for their clinical implementations. Results regarding long term effects are therefore eagerly awaited.

Duration of treatment

Long-term anticoagulant therapy is required to prevent (symptomatic) extension of the thrombus and recurrence of the disease. The continuation of treatment is based on the balance between recurrent VTE and anticoagulant-related major bleeding, and the preference of patients (3;49). International guidelines on the treatment of VTE base the duration of treatment first of all on the existence and absence of an underlying cause, classifying VTE in unprovoked or provoked by risk factors such as surgery, malignancy, pregnancy or the puerperium (4). Furthermore, provoked VTE can be categorised in VTE caused by temporary or reversible risk factors, and VTE caused by persistent risk factors. In general, when a persistent risk factor is present such as malignancy, treatment should be continued as long as the risk factor is present (4;50). In patients with VTE caused by temporary and reversible risk factors, treatment duration of three months is recommended, as the incidence of recurrence is low (0% versus 19% for unprovoked VTE, two years after stopping treatment) (51).
When thrombotic events are unprovoked, VTE recurs in about a quarter of patients within 5 years (52-54). Based on the number of VTE episodes, as well as the consequences of VTE and anticoagulant-related major bleedings, anticoagulant treatment should be continued for at least 3-12 months, when risk factors for bleeding are absent and good anticoagulant monitoring is achievable (55-57). In clinical practice, most patients are treated 6-12 months (58). The decision to prolong treatment and even consider indefinite treatment, should be based on the individual recurrence and bleeding risk, together with the preference of patients (3;4;58). Agnelli et al. (55) clearly showed that the recurrence rate after stopping anticoagulant treatment, is comparable between three months (5.1%, 95% CI 3.2-7.5) and 12 months of therapy (5.0%, 95% CI 3.1-7.8).

The introduction of new anticoagulants may shift the balance to longer treatment duration. Extension of anticoagulant treatment with rivaroxaban, for instance, reduced the recurrence of VTE with acceptable bleeding rates in comparison with placebo (32). It should be noted that data on bleeding risk for the new anticoagulants is based on trials where high bleeding risk patients were excluded. Efficacy and safety data from clinical practice are needed before definite conclusions can be drawn. If the risk of bleeding is proven lower in daily practice for novel anticoagulants, prolonging anticoagulant treatment may be beneficial.

Ideally, a more individual treatment approach may be applied, where the risk of recurrence is based on patient specific characteristics. Gender, D-dimer levels measured shortly after cessation of anticoagulant therapy, and residual thrombosis in the leg veins seem all associated with a higher risk of recurrence. The PROLONG study showed that an abnormal D-dimer level, measured after the cessation of anticoagulant therapy, correlated with a higher recurrence rate (adjusted HR 1.70, p=0.045) (59). Thus far, two studies have attempted to improve the prediction of the recurrence risk by the use of risk assessment models. First, Rodger et al. designed a clinical decision rule to predict the risk of recurrence VTE after 5-7 months of VKA (60). They concluded that for women, it might be safe to discontinue anticoagulant therapy after 5-7 months, when a maximum of one of the following features is present: post-thrombotic signs, D-dimer level ≥ 250µg/L, BMI ≥ 30 kg\(^{-1}\), or age ≥ 65 years (60). More recently, another risk assessment model was developed by Eichinger et al., (52) based on 929 patients with unprovoked VTE and without thrombophilic factors. Only the combination of the location of initial VTE, male gender, and peak thrombin levels were found to discriminate well between low- and high risk of recurrence of VTE. Age, BMI, and Factor V Leiden did not enter the final risk models (Table 3) (52). On the other hand, treatment duration
will also be affected by an increased bleeding risk, but a bleeding risk prediction model of anticoagulant treatment in patients with VTE has not been assessed. Consequently, a precise instrument to weigh benefit and risk of anticoagulant treatment is urgently needed.

Table 3. Multivariable Cox Regression prediction models for recurrent VTE, including D-Dimer (A) and Peak Thrombin Levels (B) (51) (with permission).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs female sex</td>
<td>1.90</td>
<td>1.31-2.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary embolism vs distal thrombosis</td>
<td>2.60</td>
<td>1.49-4.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proximal vs distal thrombosis</td>
<td>2.08</td>
<td>1.16-3.74</td>
<td>0.01</td>
</tr>
<tr>
<td>D-dimer (per doubling)</td>
<td>1.27</td>
<td>1.08-1.51</td>
<td>0.005</td>
</tr>
<tr>
<td>Model B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs female sex</td>
<td>2.05</td>
<td>1.36-3.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary embolism vs distal thrombosis</td>
<td>2.32</td>
<td>1.32-4.09</td>
<td>0.004</td>
</tr>
<tr>
<td>Proximal vs distal thrombosis</td>
<td>1.88</td>
<td>1.03-3.44</td>
<td>0.04</td>
</tr>
<tr>
<td>Peak thrombin (per 100 nmol/L)</td>
<td>1.38</td>
<td>1.17-1.63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Treatment in specific circumstances

General guidelines do not apply to all patient groups, and the balance between recurrence of thrombosis and the risk of bleeding may vary with special circumstances, leading to a different choice of anticoagulant, dose regime, or duration of therapy.

Pregnancy

Pregnancy and the postpartum period are associated with an increased risk of VTE, which is the leading cause of maternal mortality in the developed world (61;62). The increased risk of VTE during pregnancy results from procoagulant changes in the haemostatic and fibrinolytic systems, in combination with venous stasis in the lower extremities (63;64). Pregnant patients with VTE are treated with LMWH, because this agent does not cross the placenta in contrast to VKA, exposure to which is associated with small negative effects on neurodevelopment in the first trimester and gives an unacceptable risk of hemorrhage during delivery. VKA can, only if necessary, be safely administered in the 17th to 36th week of the pregnancy. As a result of increased renal perfusion, clearance of
How to prevent, treat, and overcome current clinical challenges of VTE

LMWH increases during pregnancy. Most centres, therefore, measure the anti-factor Xa (anti FXa) levels at regular intervals to monitor the therapeutic effect. However, there seems to be a wide variation in LMWH dosage and monitoring, together with a low rate of recurrences, and there is controversy to the clinical representation of the anti-FXa levels. It is therefore questionable whether anti-Xa monitoring is really mandatory (65-67). Another point of discussion is whether monitoring of platelets in patients using LMWH is required in order to assess the presence of HIT, a rare side effect of LMWH with an even lower incidence during pregnancy (65;66).

In pregnant women with HIT or with a history of HIT, the heparinoid danaparoid sodium can be administered, although only limited data exist describing use during pregnancy (68). In these cases of a history of HIT, platelet monitoring could be useful, but evidence about the frequency of monitoring is lacking.

LMWH should preferably be discontinued 24 h before the expected time of labour. However, in case of a very high risk of recurrent VTE, e.g. if the VTE occurred after week 36 of the pregnancy, unfractionated heparin (UFH) should be considered. Ideally, UFH should be discontinued four to 6 h prior to elective induction or caesarean section, in order to limit the duration of time without therapeutic anticoagulation. Additionally, a retrievable inferior vena cava (IVC) filter could be inserted within a week of elective induction or caesarean section (69). In the postpartum period, the duration of the anticoagulant therapy should be administered for at least 6 weeks, either with LMWH or VKA, a total duration of at least 3 months (70).

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by vascular thrombosis and/or pregnancy morbidity in the presence of circulating antiphospholipid antibodies, lupus anticoagulant, anticardiolipin or anti-β2-glycoprotein 1. Patients with APS have an increased risk of VTE recurrence ranging from 10-70% (71-73). Patients with APS are usually treated with VKA, with an INR range between 2.0 and 3.0 (15). The optimal duration of anticoagulant treatment for prevention of recurrent VTE in patients with APS is unclear, but considering the high recurrence rate, a minimal duration of one year is generally recommended, depending on the circumstances of the thrombotic event and the risk of bleeding (71;74).

Cancer

Patients with cancer and particularly those with metastatic disease have a high risk of VTE with an incidence of 4-20%, which is caused by the prothrombotic effects of the tumor and treatment with chemotherapy and radiotherapy (75-77). In patients with
cancer, VTE is an important cause of morbidity and mortality, and may be a predictor of worse prognosis (78).

It is generally recommended that patients with cancer and thrombosis are treated with LMWH for at least 6 months, because the risk of recurrent VTE is reduced to 9% with LMWH compared to a 17% recurrence rate with VKA (79). The risk of major hemorrhage with LMWH and VKA in patients with cancer and VTE are comparable (79). After 6 months of LMWH, indefinite anticoagulant therapy is recommended as long as the cancer is active (50). Whether LMWH is still more effective than VKA in the prevention of VTE after the first 6 months is under investigation. At present, the relative benefits and risks of continuing LMWH beyond 6 months versus switching to oral VKA remains a clinical judgment per individual patient.

Obesity

Obese subjects have a lower proportion of highly vascular and lean body mass as a percentage of total body weight. It is therefore possible that in obese subjects treatment with LMWH could lead to an overdose, since LMWH treatment is based on body weight. Conversely, arbitrary dose reduction or capping could lead to sub-therapeutic anticoagulation and increased risk of recurrent VTE. Therefore, there is an ongoing debate whether the dose should be increased linearly, adjusted for weight or capped at some point at a maximum allowable dose. Furthermore, extreme bodyweight is a risk factor for VTE (80-83). Obese subjects with VTE are mostly excluded from clinical trials and therefore the information on the efficacy and safety of anticoagulants is scarce and inconclusive (84). Three studies showed that there is no need to adjust the currently recommended dose of therapeutic dalteparin and tinzaparin in obese people with (near) normal renal function (85-87). However, monitoring may not have been properly assessed, as Bazinet et al. found that the increase of anti FXa levels with higher body mass index is not significant (88). Whether these discrepant results depend on the pharmacokinetic properties of the different LMWHs remains to be determined (89).

Renal Insufficiency (RI)

As in patients with obesity, patients with RI are excluded in most clinical trials, so the optimal dose of the (new) anticoagulants and monitoring in the setting of RI is lacking. Anticoagulant treatment in patients with RI is also challenging because of the associated hypercoagulable state and increased risk of bleeding (90;91). Most LMWHs, with the exception of tinzaparinsodium, undergo renal clearance. In patients with non severe renal insufficiency, (glomerular filtration rate (GFR) > 30mL-1), and VTE, dose-adjustment of LMWH according to anti-Xa levels is necessary due to the risk of accumulation of LMWH.
How to prevent, treat, and overcome current clinical challenges of VTE
(88;92). However, due to the inter-individual variation of LMWH accumulation, no simple dosing scheme can be recommended (92). Therapeutic subcutaneous bemiparin is currently investigated among others severe RI (GFR < 30mL$^{-1}$), but to date, no data have been evaluated yet (93). Due to the accumulation of LMWH in patients with severe RI (GFR < 30mL$^{-1}$) (92), UFH is indicated as bridging therapy (4). UFH can be administered subcutaneously as an unmonitored, fixed, weight-based dose (5;94;95). Although VKA are predominantly metabolized by the liver, renal failure can decrease non-renal clearance and alter the bioavailability of and response to VKA. Therefore, a dose reduction of 10-20% is required, depending on the severity of the renal failure (90;91).

**Reference List**


How to prevent, treat, and overcome current clinical challenges of VTE


(38) Pfizer Press Release. Bristol-Myers Squibb and Pfizer Initiate New Study in the Apixaban Phase 3 Clinical Trial Program. 12-6-2008.

(39) Ref Type: Online Source


How to prevent, treat, and overcome current clinical challenges of VTE


