How I manage recurrent deep-vein thrombosis

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Deep-vein thrombosis (DVT) is regarded a chronic disease as it often recurs. DVT affects most frequently the lower limbs and hence DVT of the leg will be the focus of this article. Whereas algorithms were developed and validated for the diagnosis of a first DVT, no such well-defined strategies exist in the case of recurrence of DVT. Likewise, the scientific evidence regarding the treatment of recurrent DVT is sparse, in particular when it comes to deciding on the duration of anticoagulation. Two typical cases of recurrent DVT, one with an unprovoked DVT and one with DVT during anticoagulation, will be presented. Based on these two clinical scenarios algorithms for the diagnosis and treatment of recurrent DVT will be put forward. The purpose of this article is to discuss strategies that can be applied in daily clinical practice by physicians who do not have access to means and measures available in specialized thrombosis centers.

Case 1

A 59-year-old man presented for pain and swelling of the left calf. He had been doing fine until 3 days earlier when symptoms all of a sudden began. He did not have surgery, or an injury to the leg, or a medical illness requiring prolonged bed rest during the previous months. He did report, however, that he had had similar symptoms approximately 3 years ago in the same leg after a skiing accident. According to a medical record from that time, he had been diagnosed with isolated DVT in the posterior tibial veins and was treated with a “blood thinner” for several months. Physical examination revealed tenderness and warmth of the calf and an increase in calf diameter of 3 cm compared to the other leg. Deep palpation of the calf muscles was painful. Recurrent DVT was suspected. What are the next diagnostic steps?

Diagnosis of recurrent DVT

The diagnosis of recurrent DVT is of particular clinical importance. Many patients in whom such a diagnosis is established will receive extended and sometimes life-long anticoagulant therapy, which means that they will be exposed to a considerable bleeding risk. Conversely, if the diagnosis is missed, untreated patients have a high risk of thrombus progression and embolization. In contrast to the diagnosis of a first DVT of the leg, which follows validated algorithms including a pretest probability assessment, measurement of D-Dimer and compression ultrasonography (CUS), no such strategies are established for the diagnosis of recurrent DVT. This diagnostic ambiguity can be explained by the absence of clinical studies...
defining a valid clinical endpoint. A pretest probability score has never been developed for patients with suspected recurrent DVT. Nevertheless, an individual clinical judgment of the likelihood of recurrent thrombosis taking into account signs and symptoms indicative for DVT as well as strong risk factors of thrombosis such as recent surgery, trauma, prolonged bedrest, or active cancer should always be the first step during the diagnostic work-up. The history of a previous venous thromboembolism (VTE) per se classifies such patients at risk of thrombosis.

The role of D-Dimer is less well studied in patients with a recurrent DVT. Incorporating D-Dimer in an algorithm to diagnose or exclude recurrent DVT could nevertheless be potentially helpful: none of 16 untreated patients with a low clinical likelihood of recurrence according to the modified Well’s score and a negative D-Dimer had recurrent DVT during a 3-months follow-up. Only one of 134 patients with a negative D-Dimer experienced recurrence during a follow-up of 3 months, but recurrence could not be definitively ruled out in another 6 patients. A failure rate of only 1% was recorded among almost 1.000 untreated patients with suspected recurrent DVT, who had a negative D-Dimer and a low pretest probability. D-Dimer levels may remain elevated for a long time after a first VTE thereby possibly deflating the diagnostic utility for the second event.

The mainstay of DVT diagnosis, also in the scenario of recurrence, is imaging. Several methods to detect DVT have been studied including venography, CUS, computer tomography (CT) venography and magnetic resonance direct thrombus imaging (MRDTI). Venography was used as an outcome standard in several accuracy studies of patients with suspected recurrent DVT, but has never been validated for this purpose. Venography is invasive and can be associated with serious complications. It is often complicated by technical problems and, in the era of CUS, the expertise among radiologists to perform and interpret a venogram has declined. Nowadays, the gold standard for diagnosing a first DVT has become CUS with a sensitivity for proximal and distal DVT of greater than 90% and 60%, respectively, and a specificity of almost 100%. Approximately half of the DVT recurrences occur in the so far unaffected contralateral leg. There is nothing to assume that in this case CUS would not perform equally as well as in a first DVT. The diagnosis of an ipsilateral recurrent DVT is far more challenging. The finding of non-compressibility of an ipsilateral femoral or popliteal vein segment, which was previously not affected, can be considered diagnostic. Sometimes the initial thrombus does not completely resolve resulting in residual vein thrombosis. For diagnosing recurrent DVT in a previously affected vein segment the criterion of an increase in thrombus diameter of at least 4 mm on (serial) CUS, possibly in combination with a D-Dimer...
measurement, has been put forward.\textsuperscript{12,17,18} In a validation study, 8 of 284 patients in whom recurrent VTE had been excluded by this approach and who were left untreated had a VTE with a 3-month risk of 2.8\% and an upper 95\% confidence interval (CI) of 5.5\%.\textsuperscript{17} Its applicability is dependent upon a highly experienced investigator and the availability of a previous CUS result. It also cannot be used to detect recurrent calf vein thrombosis. A guidance panel suggests that proximal CUS should be performed at the time of withdrawal of anticoagulation to obtain a baseline measurement.\textsuperscript{19} This is, however, rarely done in everyday practice.

Figure 1 suggests an algorithm for the diagnosis of recurrent DVT in routine clinical practice. The first step is to estimate the clinical likelihood of DVT. In the absence of a validated clinical prediction rule, this should be done by a thorough individual clinical judgment looking for symptoms and signs indicative for DVT as well as for important risk factors. The second step is whole-leg CUS. If the deep leg veins are fully compressible, DVT is ruled out. In case of non-compressibility of a vein segment not affected by the first DVT, the diagnosis is established. If CUS is non-diagnostic (i.e. non-compressibility of a previously affected vein segment or non-compressibility of any vein segment in the ipsilateral leg in the absence of a previous CUS result), a strategy combining clinical assessment and D-Dimer is followed. For patients in whom the diagnosis is still ambiguous, serial CUS or alternative imaging tests can be considered although they rarely offer an additional diagnostic certainty.

\textbf{Case 1 continued}

The clinical likelihood of recurrent DVT was considered high. On whole-leg CUS non-compressibility of the femoral and the popliteal vein was found. Upon the basis of non-compressibility of a previously unaffected vein segment the diagnosis of recurrent DVT was made. The positive D-Dimer supported the presence of a thrombosis, but had no part in deciding on the diagnostic work-up. What are the treatment options for a patient with a recurrent DVT?

\textbf{Anticoagulant treatment of recurrent DVT}

\textit{How to estimate the bleeding risk?}
Deciding on the mode and duration of anticoagulation entails balancing the risk of recurrent thromboembolism against the risk of bleeding. It is, therefore, mandatory to evaluate the bleeding risk not only before anticoagulation is installed but also at regular intervals thereafter. Scoring systems to estimate the bleeding risk exist for patients with venous thrombosis, but, unfortunately, perform poorly, are not validated and cannot be recommended for use in daily practice. The annual long-term risk of major bleeding during anticoagulation ranges between less than 1% and greater than 6.5% and is dependent upon the presence or absence of various risk factors, including advanced age, previous bleeding, cancer, thrombocytopenia, antiplatelet therapy, recent surgery, previous stroke or other comorbidities. These bleeding risk percentages may not be valid for patients with a second DVT who already tolerated prior anticoagulation well. Ultimately, the estimation of the bleeding risk relies on the discretion of the treating physician rather than on scientific evidence.

*Which anticoagulant regimen should be used for the acute treatment?*

Data on the treatment of acute recurrent DVT is scarce. Only a small number of patients with a history of previous VTE were included in the large treatment trials. It, thus, remains that considerations and treatment options for a recurrent acute DVT will not be different to that of a first event and immediate and intensive anticoagulation is mandatory. Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux followed by a vitamin K antagonist (VKA) were the only treatment options until recently. The field of anticoagulation has lately changed with the appearance of the direct oral anticoagulants (DOACs). Four DOACs (rivaroxaban, apixaban and edoxaban are direct factor Xa inhibitors; dabigatran is a direct thrombin inhibitor) gained approval in many countries worldwide. DOACs are equally effective as heparin followed by a VKA but confer a lower risk of major and fatal bleeding. Dabigatran and edoxaban are started after a lead-in phase with heparin. Rivaroxaban and apixaban are administered as an all-oral regimen with a higher dose at the beginning.

Figure 2 suggests an algorithm for the treatment of recurrent DVT in routine clinical practice. In the absence of a contraindication, anticoagulation is started as soon as possible. If the patient does not need to be admitted or can be discharged early, an all-oral regimen with a DOAC is more convenient. In patients in whom a DOAC is not given, LMWH at a therapeutic dose followed by a VKA is an alternative. Pregnant women must not be treated
with a DOAC but should receive LMWH at a therapeutic dose. In patients with cancer treatment with a DOAC is seen controversially and guidelines recommend against its use.\textsuperscript{31,32} Consequently, cancer patients with a recurrent DVT should receive LMWH at a therapeutic dose. Thrombolysis or thrombectomy can be considered in younger patients with extensive DVT, who have a low bleeding.

*What is the optimal duration of anticoagulation?*

The duration of anticoagulation is largely dependent upon the risk of recurrent VTE. In contrast to patients with a first VTE, the recurrence risk is less well studied in patients with a second event. Patients with a thrombosis history usually receive thromboprophylaxis when they are later exposed to transient risk conditions such as surgery, trauma, hospitalization, or pregnancy. Provoked recurrences, i.e. events that occur in association with a transient risk factor, are, therefore, seen infrequently. In the Austrian Study of Recurrent Venous Thrombosis (AUREC) only 10\% of VTE recurrences were rated as “provoked”. In the absence of clinical studies, the recurrence risk can only be extrapolated from patients with a first provoked DVT. There is evidence that patients with a first provoked DVT have a lower recurrence risk than patients with a first unprovoked event. Surgical patients have by far the lowest recurrence risk.\textsuperscript{33} It is, therefore, justified to treat patients with recurrent DVT associated with a transient risk factor (surgical or non-surgical) for only a limited period of time (3 to 6 months) as the thrombosis risk in this patient population is outweighed by the risk of bleeding associated with long-term anticoagulation. In patients in whom DVT recurred in the presence of a persistent risk factor such as active cancer, autoimmune disease or inflammatory bowel disease, long-term anticoagulation is reasonable as long as the bleeding risk does not increase (Figure 2).

Patients in whom the first VTE was unprovoked (i.e. occurred in the absence of a transient risk factor) have a recurrence risk as high as 30\% over 5 years after discontinuation of anticoagulation.\textsuperscript{34-36} There is circumstantial evidence that a second episode of unprovoked VTE inflicts 1.5 the risk of recurrent VTE relative to a first episode of unprovoked VTE resulting in a calculated recurrence risk of almost 50\% over 5 years.\textsuperscript{26} The Duration of the Anticoagulant Trial Study Group (DURAC II) performed the only randomized controlled trial comparing short-term oral anticoagulant therapy with warfarin with long-term anticoagulation.\textsuperscript{37} The majority of patients had an unprovoked VTE as the second event. After a mean follow-up of almost 4 years, patients treated for 6 months had a much higher
incidence of recurrence than patients treated infinitely (20.7% vs. 2.6%). One major bleed occurred in the short-term treatment group and 2 fatal bleeds and 8 major bleeds in the long-term treatment group. Taken together, the recurrence risk among patient with an unprovoked second DVT has to be considered as very high, although this notion is largely based upon indirect evidence. Nevertheless, it is commonly agreed upon that these patients should receive long-term anticoagulation. The presence of a post-thrombotic syndrome would strengthen this decision even more as DVT recurrence in the same leg would further impair venous flow.

Before deciding on long-term anticoagulant treatment, the patient’s preferences and concerns need to be discussed as this decision may have major life-style implication. Once therapy is begun, patients have to be followed-up at regular intervals to evaluate the quality of anticoagulation and the adherence to treatment, and also to capture the appearance of new risk factors of bleeding which could necessitate interruption or discontinuation of anticoagulation.

**Which anticoagulant regimen should be used for the long-term treatment?**

Until recently, VKA were regarded first choice for the long-term treatment of VTE. Lately, several DOACs were investigated also for extended anticoagulation. Approximately two thirds of patients included in these trials had a first DVT. Table 1 provides an overview of 3 trials comparing rivaroxaban, dabigatran and apixaban with placebo for extended VTE prevention after an initial course of 6 months anticoagulation. The intended treatment durations ranged from 6 to 12 months. Apixaban was given at a therapeutic dose (i.e. at the same dose that was used for the treatment of acute VTE) and also at a lower dose. Rivaroxaban and dabigatran were given at a therapeutic dose. DOACs conferred substantial risk reductions ranging between 64% and 92% compared to placebo. Fatal bleeding occurred in none of the patients and major or clinical relevant non-major bleeding was infrequent. The incidence of bleeding was not higher in patients treated with apixaban than in the placebo group. RE-MEDY compared dabigatran at a therapeutic dose with warfarin in patients who have completed at least 3 months of anticoagulation. The duration of treatment (up to 36 months) was longer than in the other studies. Recurrent VTE was recorded in 1.8% patients assigned to dabigatran and in 1.3% of warfarin-treated patients for a hazard ratio (HR) of 1.4 (95% CI 0.8-2.6). Major bleeding and major or clinically relevant non-major bleeding were less frequent among patients treated with dabigatran (0.9% vs. 1.8%; HR 0.5, 90% CI 0.3 to 1.0 and 5.6% vs.10.2%; HR 0.5, 95% CI 0.4-0.7, respectively). Therefore, in the setting of extended anticoagulation DOACs effectively prevent recurrent VTE at an acceptable bleeding
risk. Some caveats require to be mentioned. The treatment duration of all studies was limited and it is unknown if patients who receive long-term anticoagulation benefit to the same extent. The majority of patients included in these trials experienced only one thrombotic event and it remains to be seen if DOACs are also as effective and safe in patients with multiple events. DOACs are partly cleared from the circulation via the kidneys. Caution should, therefore, be exercised in prescribing DOACs to patients with a creatinine clearance of less than 30 ml/min in the case of the factor Xa inhibitors or 50 ml/min when dabigatran is chosen. Routine monitoring of kidney function at least once or twice a year is prudent, in particular in older patients. Nevertheless, DOACs are an appealing alternative to VKA also in the setting of long lasting DVT therapy (Figure 2).

Case 1 continued

The patient was otherwise healthy and risk factors of bleeding were absent. Because there was no need for admission an all-oral DOAC regimen was started. The patient consented to long-term anticoagulant therapy after having been informed that due to the fact that his second episode was unprovoked his risk of recurrent DVT is high and most likely outweighs the risk of bleeding. He was advised to take his medication regularly and that missing doses could result in thrombus progression, embolization or recurrence. Appointments were arranged for the time-point of dose reduction and for regular check-ups thereafter.

Case 2

A 27-year old male presented with swelling and pain of the right leg. Physical examination revealed warmth, edema from the distal thigh downwards to the ankle, and tenderness on palpation of the calf. He is a musician and is regularly on tour for longer periods often traveling by plane over long distances. The D-Dimer was elevated and CUS showed femoral vein thrombosis. He had already been diagnosed with unprovoked proximal DVT of the left leg one year earlier and long-term anticoagulation had been recommended. At the time of presentation he was still on VKA treatment.

Recurrent DVT during anticoagulant therapy

What could be the reason for a recurrent DVT during anticoagulation?
Anticoagulants, when given at a therapeutic dose, are highly effective to prevent recurrence. In the DURAC II trial none of the patients with a second VTE who were given warfarin for up to 4 years had another event during anticoagulation. DVT during anticoagulant therapy is, therefore, rare and most disturbing for both patients and physicians. The most likely explanation in patients treated with a VKA or a DOAC alike is insufficient intensity of anticoagulation most often because of non-adherence to the medication. The half-life of DOACs is short and missing doses may increase the susceptibility for recurrence. In a patient who has recurrence while treated with a VKA the first step is to assess the quality of treatment by checking the international normalized ratio (INR) determined at the time of recurrence as well as those measured earlier. In rare cases the INR is within the therapeutic range. One explanation for a DVT at therapeutic INR could be that a patient who had been incompliant with VKAs developed symptoms of DVT and restarted VKAs, which then led to a therapeutic INR when seeking medical attention. Alternatively, in such a situation hypercoagulability as the consequence of a risk factor potent enough to overcome the usual intensity of anticoagulation is often suspected. Indeed, cancer patient were found to have a more than 3-fold higher risk of recurrent VTE than non-cancer patients and more than 80% of events occurred at an anticoagulation level within or above the therapeutic range. According to an international registry, 80% of cancer patients who were treated with a VKA for an incident VTE had their “breakthrough” recurrence at an INR greater than 2. In a randomized trial in patients with cancer-associated VTE, the probability of recurrent thrombosis at 6 months was 17% in the VKA group and 9% in patients treated with a LMWH. Thus, the finding of failures of VKA anticoagulation in patients with cancer infers that DVT recurrence in a patient with a therapeutic INR should raise the suspicion for the presence of a thus far unknown hidden malignancy. Other conditions that may be considered as predisposing for a DVT recurrence during adequate anticoagulation - although there is no scientific evidence for this assumption - are anatomical abnormalities such as the May-Thurner syndrome, blood diseases including myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria, or phospholipid antibodies (Table 2). Notably, in some patients with a phospholipid antibody syndrome, recurrence could be explained by underanticoagulation due to a falsely therapeutic (or even supra-therapeutic) INR resulting from interference of a lupus anticoagulant with the INR test system. In case of prolongation of the baseline PT by a lupus anticoagulant, which causes difficulty in establishing the true degree of anticoagulation, amidolytic factor X assays can be used aiming at a therapeutic factor Xa.
range of 20-40%. In patients who develop recurrent DVT while on heparin, heparin-induced thrombocytopenia should be suspected.

**How should a recurrent DVT which occurred during anticoagulation be treated?**

An algorithm for the treatment of patients with recurrent DVT during anticoagulant treatment is suggested in Figure 3. In case of a sub-therapeutic INR the patient should be immediately started on full-dose LMWH. If VKAs are considered for long-term treatment again, all efforts to improve the quality of anticoagulation should be made. These include intense counseling, INR monitoring at closer intervals, or inclusion in a self-monitoring or self-management program. In case the patient is dissatisfied with VKA treatment, switching to a DOAC may be reasonable. In case of an INR equal to or greater than 2, vitamin K followed by full-dose LMWH should be given. The presence of a hidden cancer needs to be taken into consideration. Patients, in whom such a diagnosis is suspected or even established, should continue full-dose LMWH. If a cancer patient recurs with DVT despite full-dose LMWH treatment, an increase in the LMWH dose by 25% is suggested. There are several therapeutic alternatives if active cancer is unlikely, none of them studied in greater detail: long-term LMWH at a therapeutic dose, LMWH followed by a VKA with either an upward adjustment of the therapeutic INR range or combined with aspirin, or fondaparinux at a therapeutic dose. In case of recurrence during anticoagulation with one of the DOACs, anticoagulation with LMWH at full dose followed by a VKA aiming at an INR range of 2 to 3 together with intense counseling regarding adherence to the treatment seems to be the best available option.

A permanent vena cava filter in addition to anticoagulant therapy appears to be, at first glance, a promising tool to protect patients from recurrent PE. There are, however, several arguments against this approach. In a randomized trial in patients with proximal DVT, vena cava filters together with standard anticoagulation reduced the risk of PE, but increased that of DVT and did not confer a survival benefit. DVT patients have more often DVT than PE as the recurrent event, and will therefore benefit from filter insertion to a much lesser extent than PE patients. Most importantly, there are safety concerns regarding filter embolization, fracturing and device migration, which have led to a Food and Drug Association safety alert. As a consequence, vena cava filter should be used with great caution in patients with (recurrent) DVT and, if at all, only in patients with a very high risk of PE such as in patients who have a contraindication against anticoagulation.
Case 2 continued

At presentation the INR was 1.4. The patient had stopped INR monitoring several months before because of interference with his professional commitments. He refused to take VKA any longer. He was once again counseled with regard to his high thrombosis risk, started on an all-oral DOAC regimen and instructed that missing doses could result in thrombus progression or recurrence.

Conclusion

The diagnosis of recurrent DVT can be challenging, in particular if it is suspected in the same leg as the first event. In this article a diagnostic strategy is proposed which can be applied in routine daily practice without knowing the diagnostic details of the previous event. The treatment of acute recurrent DVT is not different from that of a first DVT. Many patients with a second DVT have to be regarded at high risk of another recurrence and are candidates for long-term anticoagulation. DOACs are a reasonable choice for extended anticoagulant therapy because they are convenient to patients and their physicians, are as effective as the VKAs and confer a lower risk of bleeding. Their performance over a long period of time however remains unknown.

In conclusion, the scientific evidence for diagnosis and treatment of recurrent DVT is scarce. The algorithms proposed in this article are therefore in large part not evidence-based and are likely to change when more data become available.

Authorship

Contribution: P.A.K. wrote the article.

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References


Table 1: Double-blind randomized trials comparing a direct oral anticoagulant with placebo in patients with proximal DVT and/or PE

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Dose (mg)</th>
<th>N</th>
<th>Intended treatment duration (mo)</th>
<th>Recurrent VTE % vs. placebo; HR (95% CI)</th>
<th>Major bleeding % vs. placebo; HR (95% CI)</th>
<th>Major or CRNM bleeding % vs. placebo; HR (95% CI)</th>
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<tr>
<td>EINSTEIN</td>
<td>Rivaroxaban</td>
<td>20 OD</td>
<td>1196</td>
<td>6-12</td>
<td>1.3 vs. 7.1; 0.18 (0.09-0.39)</td>
<td>0.7 vs. 0</td>
<td>6 vs. 1.2; 5.19 (2.3-11.7)</td>
</tr>
<tr>
<td>extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-SONATE</td>
<td>Dabigatran</td>
<td>150 BID</td>
<td>1343</td>
<td>6-12</td>
<td>0.4 vs. 5.6; 0.08 (0.02-0.25)</td>
<td>0.3 vs. 0</td>
<td>5.3 vs. 1.8; 2.92 (1.52-5.60)</td>
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<td>AMPLIFY</td>
<td>Apixaban</td>
<td>2.5 BID</td>
<td>2486</td>
<td>12</td>
<td>3.8 vs. 11.6; 0.33 (0.22-0.48)</td>
<td>0.2 vs. 0.5</td>
<td>3.2 vs. 2.7; 1.20 (0.69-2.10)</td>
</tr>
<tr>
<td>extension</td>
<td></td>
<td>5 BID</td>
<td></td>
<td></td>
<td>4.2 vs. 11.6; 0.36 (0.25-0.53)</td>
<td>0.25 vs. 0.5</td>
<td>4.3 vs. 2.7; 1.62 (0.96-2.73)</td>
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VTE, venous thromboembolism; OD, once daily, BID = twice daily; CRNM, clinically relevant non-major; HR (95% CI), hazard ratio (95% confidence interval)
Table 2: Possible underlying conditions for recurrent VTE during anticoagulation

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Insufficient intensity of anticoagulation</td>
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<tr>
<td>Active cancer</td>
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<tr>
<td>Anatomical abnormalities (i.g. May-Thurner syndrome)*</td>
</tr>
<tr>
<td>Myeloproliferative neoplasms (i.g. polycythemia vera, essential thrombocythemia)*</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria*</td>
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<tr>
<td>Phospholipid antibody syndrome*</td>
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<tr>
<td>Heparin-induced thrombocytopenia</td>
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</table>

* low level of scientific evidence
Legends to the figures

Figure 1. Suggested procedure to diagnose recurrent deep-vein thrombosis. DVT, deep-vein thrombosis; DD, D-Dimer; CUS, compression ultrasonography; a) non-compressibility of a previously affected vein segment or non-compressibility of any vein segment in the ipsilateral leg in the absence of a previous CUS result; b) alternative imaging techniques include venography, computer tomography venography, and magnetic resonance direct thrombus imaging.

Figure 2. Suggested treatment protocol for recurrent deep-vein thrombosis. DVT, deep-vein thrombosis; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; INR, international normalized ration; a) apixaban 10 mg twice daily for 1 week followed by 5 mg twice daily, reduce dose to 2.5 mg twice daily after 6 months; rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily; LMWH once or twice daily at therapeutic dose for at least 5 days followed by 150 mg dabigatran twice daily or by 60 mg edoxaban once daily; b) LMWH once or twice daily at therapeutic dose together with a VKA (target INR 2.0-3.0) and continue LMWH until a stable INR has been reached, but for a minimum of 5 days; c) LMWH at therapeutic dose until 24 h before induction of labor or caesarean section and restart LMWH at a reduced dose; d) LMWH at therapeutic dose, reduced to about 75% at 4 weeks for at least 6 months or as long as it is safe to do so; e) transient risk factors include surgery, trauma, prolonged bed rest, oral contraceptives, hormone replacement therapy, pregnancy/puerperium; f) persistent risk factors include inflammatory bowel disease, antiphospholipid syndrome, nephrotic syndrome, paroxysmal nocturnal haemoglobinuria, myeloproliferative neoplasma, Behçet’s syndrome, postthrombotic syndrome, congenital venous malformation.

Figure 3. Suggested treatment protocol for recurrent deep-vein thrombosis during anticoagulant treatment. DVT, deep-vein thrombosis; VKA, vitamin K antagonist; DOAC; direct oral anticoagulant; LMWH, low-molecular-weight heparin; INR, international normalized ratio; a) LMWH once or twice daily at therapeutic dose together with a VKA (target INR 2.0-3.0) and continue LMWH until a stable INR has been reached, but for a minimum of 5 days; b) apixaban 10 mg twice daily for 1 week followed by 5 mg twice daily; rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily; LMWH once or twice daily at therapeutic dose for at least 5 days followed by 150 mg dabigatran twice daily
or by 60 mg edoxaban once daily; c) 10 mg vitamin K orally or intravenously, d) LMWH dose increase by approximately 25% ; e) LMWH once or twice daily at therapeutic dose together with a VKA (target INR 2.5-4.0) and continue LMWH until a stable INR has been reached, but for a minimum of 5 days; f) LMWH once or twice daily at therapeutic dose together with a VKA (target INR 2.0-3.0) and aspirin (100 mg once daily) and continue LMWH until a stable INR has been reached, but for a minimum of 5 days; g) LMWH once or twice daily at therapeutic dose; h) fondaparinux weight-adjusted at a therapeutic dose.
Suspected recurrent DVT

Perform clinical assessment and measure DD

Refer to whole-leg CUS

Full compressibility
- Exclude DVT

Non-compressibility of a vein segment not affected by the 1st DVT
- Treat

Non-diagnostic
- Re-consider clinical assessment
  - "Likely"
    - DD Positive: Treat
    - DD Negative: Consider serial CUS or alternative imaging
  - "Unlikely"
    - DD Positive: Exclude DVT
    - DD Negative: Exclude DVT
Confirmed diagnosis of recurrent DVT

- Start DOAC \(^a\)
  - Consider all-oral regimen if admission is not required

- Start LMWH/VKA \(^b\)
  - Do not use VKA in pregnancy \(^c\) or cancer \(^d\)

Evaluate duration of anticoagulation after 3 months

- DVT triggered by a transient risk factor \(^e\)
  - Discontinue

- DVT unprovoked
  - Continue

- DVT triggered by a persistent risk factor \(^f\)
  - Continue as long as risk factor persists and/or it is safe to do so
Figure 3

Recurrent DVT during anticoagulation

While on VKA

At an INR < 2
- Start LMWH/VKA

Start LMWH/high intensity VKA e

While on a DOAC

At an INR ≥ 2
- Start a DOAC

Start LMWH/VKA plus aspirin f

Start LMWH g

While on LMWH

High-dose LMWH d

Start Fondaparinux h
How I manage recurrent deep-vein thrombosis

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