How I treat recurrent venous thromboembolism in patients on anticoagulant therapy

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Abstract

Oral anticoagulant therapy for venous thromboembolism (VTE) is very effective. When oral anticoagulants are managed well, the risk of recurrence is approximately 2 per 100 patient-years. The main reasons for a breakthrough event can be split into underlying disease and subtherapeutic drug levels. The most common underlying disease that results in recurrence on treatment is cancer. Subtherapeutic drug levels can be caused by poor adherence to the drug regimen, interactions with other drugs or food, or inappropriate dosing. It is important to investigate and understand the cause whenever such an event occurs, in order to provide improved anticoagulant management, thereby avoiding further recurrences. Four illustrative cases will be presented here together with a discussion around the underlying pathology. Whereas the mechanisms are usually quite well understood, the management of further anticoagulation after a breakthrough event is based on minimal or no clinical trial evidence.

**Key words:** Venous thromboembolism, recurrence, cancer, vasculitis, Behçet’s disease, lupus anticoagulant
Introduction

Risk of recurrence in different populations

Vitamin K antagonists (VKA) have a long track record of providing effective protection against recurrences after venous thromboembolism (VTE). In a Cochrane meta-analysis of studies comparing shorter versus longer duration of treatment with VKA the risk of recurrence in the long arm was 1.6%.¹ These studies generally excluded patients with known cancer. In 5 randomized trials in patients with cancer, recurrent VTE occurred in 82 of 571 patients (14%) on treatment with VKA versus 42 of 591 patients (7.1%) on low-molecular-weight heparin (LMWH) during the first 3 to 6 months of treatment.²

The non-vitamin K antagonist oral anticoagulants (NOACs) have not shown superiority versus VKA regarding efficacy in the treatment of VTE. In the treatment of acute VTE the relative risk for recurrence with NOACs versus VKA was 0.85 (95% confidence interval [CI], 0.55-1.31).³ Based on subgroup analyses from some of these studies the corresponding relative risk in patients with cancer was 0.77 (95% CI, 0.44-1.33).⁴ This was, however, mainly in cancers without metastases and not with LMWH as a comparator. Results from clinical practice studies show also similar efficacy for rivaroxaban versus VKA; rivaroxaban being the only NOAC approved for a sufficiently long time to allow for such observations. Thus in the international XArelto for Long-term and Initial Anticoagulation in venous thromboembolism (XALIA) cohort study the adjusted hazard ratio for VTE recurrence with rivaroxaban versus VKA was 0.91 (95% CI, 0.54-1.54)⁵ and in The SWIss Venous ThromboEmbolism Registry (SWIVTER) it was 0.55 (0.18–1.65).⁶

New symptoms of deep vein thrombosis or pulmonary embolism are not proof of recurrent events, even when there seems to be support from diagnostic imaging. In the RE-COVER study,⁷ comparing dabigatran with warfarin for the treatment of acute VTE, all patients had at
baseline ultrasonography of both legs and computed tomography (CT) or ventilation-perfusion scanning of the lungs, whether they had symptoms or not. Central adjudication of locally suspected recurrences on diagnostic imaging, using comparisons with baseline did not confirm suspected recurrent pulmonary embolism in 7.5% and did not confirm suspected recurrent deep vein thrombosis in 11.8% (unpublished data). Especially ipsilateral recurrence of thrombosis poses a diagnostic challenge. When there is questionable difference in extension of the VTE between the images from the first event and the recurrence a negative D-dimer in a patient with onset of symptoms within the last few days speaks against a true recurrence.

Patients admitted to hospital with new diagnosis of pulmonary embolism while already on warfarin have, compared to those admitted with pulmonary embolism not on anticoagulation, after discharge from the hospital a 4.4-fold higher risk of fatal recurrent pulmonary embolism. These deaths are mainly related to cardiovascular disease, malignancy and sepsis.

**Causes for breakthrough thromboembolism**

*Underlying condition or disease.* There are many potential causes for recurrence of VTE despite anticoagulant therapy. From the above-mentioned trial data it is obvious that presence of cancer increases the risk of recurrence. In the largest registry of VTE treatment in clinical practice, Registro Informatizado de la Enfermedad Trombo Embolica (RIETE), every third patient with recurrence on VKA therapy had cancer. This is the cardinal example of an underlying disease exhibiting pronounced thrombogenicity that overcomes the protective effect of anticoagulants. The malignant tumors exert this effect through several mechanisms that among others involve activation of coagulation and obstruction of blood flow, extensively reviewed elsewhere. For patients with myeloproliferative neoplasms (polycythemia vera and essential thrombocythemia) molecular profiling with analysis of JAK2, CALR and MPL mutations can add information on the risk of thrombosis that often occurs in atypical sites. Diseases or conditions with an increased risk of recurrent VTE on anticoagulation are summarized in Table
1. The mechanism behind the increased thrombogenicity is sometimes unclear, such as in Behçet’s disease and antiphospholipid syndrome and many alternatives have been proposed (Table 1). For heparin-induced thrombocytopenia the pathogenesis has, however, been explained – IgG antibodies recognizing the multimolecular complexes between heparin and platelet factor 4 assemble on the surface of platelets that become activated and release procoagulant microparticles. A minority of patients with antiphospholipid syndrome display a falsely elevated international normalized ratio (INR), possibly due to antibodies against tissue factor, and they may thus have recurrent events despite “optimal” INRs. They would typically have demonstrated a prolonged prothrombin time before starting on an anticoagulant and alternative thromboplastins that are insensitive to the lupus anticoagulant should then be used for monitoring warfarin therapy. INR results from point-of-care instruments are variable and not reliable for patients with lupus anticoagulant.

Paroxysmal nocturnal hemoglobinuria, diagnosed in 1/100,000/year, caused by the expansion of an abnormal hematopoietic clone, is characterized by intravascular hemolysis, cytopenias and thrombosis. The latter often occur in unusual sites (intraabdominal or intracranial veins) and treatment failures on anticoagulant therapy have been reported at 10.6 events per 100 patient-years. In one study 9 of 41 patients with thrombosis experienced recurrences on anticoagulants. A concomitant bleeding tendency makes it often difficult to increase the anticoagulant intensity and targeting of the terminal complement activation complex by addition of eculizumab is probably the best solution.

During pregnancy many changes occur in the prohemostatic direction, essentially preparing the woman for childbirth without massive bleeding but with a concomitant increase in risk of thrombosis (Table 1). Furthermore, presence of the antiphospholipid syndrome will increase the risk of gestational venous thromboembolism as well as unexplained fetal death, spontaneous
abortions and premature birth. In the RIETE registry with 607 women suffering VTE during pregnancy or puerperium, 16 had a recurrence and 11 of those occurred during anticoagulant treatment. However, only one of the patients with recurrence on anticoagulation had antiphospholipid syndrome.

Thrombophilia, other than antiphospholipid syndrome, is sometimes found in patients with breakthrough events but there is no convincing evidence that such events are more common in patients with hereditary thrombophilic defects. It has been speculated that deficiency of antithrombin may be associated with heparin resistance. In a retrospective review of 70 patients with congenital antithrombin deficiency we found 8 cases were there was some clinical deterioration on treatment with unfractionated heparin.

Finally, vascular anomalies with chronic obstruction of the venous flow may cause recurrences while on anticoagulation, typically in young patients. These abnormalities include the thoracic outlet syndrome and May-Thurner syndrome (compression of the left common iliac vein by the right iliac artery). Several options for the management of these thrombotic events exist, including initial thrombolysis, pharmaco-mechanical clot removal, endovascular stenting or decompressive surgery (thoracic outlet syndrome).

Inappropriate dosing of anticoagulant. For patients treated with VKA it is crucial to remember that it takes at least 5 days for all the vitamin K dependent coagulation factors to decrease to sufficiently low activity in order to provide a therapeutic anticoagulant effect. Therefore, overlap with a parenteral anticoagulant for at least 5 days and until the INR has reached 2.0 for at least 24 h is recommended (Grade 1B – explained in Table 2).

It may take 4-6 weeks until treatment with a VKA results in stable therapeutic INRs, i.e. maintaining the range of 2.0-3.0. Many patients will have one or several subtherapeutic INRs during this first treatment phase, which could explain the frontloaded trend to superior efficacy of
NOACs seen in the studies with rivaroxaban in deep vein thrombosis\textsuperscript{27} and with apixaban in VTE.\textsuperscript{28}

Patients on anticoagulation with VKA, as well as physicians managing them need to be aware of the large number of drug-drug interactions that can affect the INR levels and require dose adjustments. This often becomes demanding when patients start treatment with an interacting drug that has a slow, progressive interaction that requires repeated dose adjustments over weeks or even months. An example of this is rifampicin, which causes a delayed induction of the microsomal enzyme CYP2C9, responsible for most of the metabolism of warfarin.\textsuperscript{29} A reverse example is amiodarone, a general inhibitor of cytochrome P450 catalyzed oxidation, thereby decreasing the effect of CYP2C9.\textsuperscript{30} When amiodarone is discontinued there is a delayed increase in dose requirements to maintain therapeutic warfarin effect. In both cases frequent monitoring of anticoagulation during several months is required to avoid suboptimal dosing and recurrent VTE.

The importance of drug-food interactions with VKA, involving the vitamin K rich dark green vegetables, has often been exaggerated to the extent that some patients stopped the intake of any vegetables when taking warfarin. The patients should be encouraged to keep a rather consistent, healthy diet. If the patient, however, decides to embark on a vegetarian diet there might be a need to increase the dose of VKA. Avocado was reported to antagonise warfarin, perhaps more from the oil inhibiting warfarin absorption than via vitamin K.\textsuperscript{31}

The NOACs have definitely fewer drug-drug interactions than VKAs. Concomitant use of rifampicin, phenytoin, carbamazepine, St. John’s Wort and possibly phenobarbital will cause strong induction of CYP3A4. This leads to a decrease of the area under the curve, i.e. exposure, by 50% or more for rivaroxaban and apixaban, as described in the respective product monographs. Edoxaban is much less dependent on CYP3A4 metabolism but it is a substrate for the P-glycoprotein (P-gp) efflux transporter like all other NOACs and rifampicin will cause a 33%
increase of the clearance of edoxaban. Dabigatran is not metabolized via the CYP3A4 pathway but again a substrate for P-gp. Concomitant use of rifampicin or any of the other strong CYP3A4 or P-gp inducers is therefore not recommended with any of the NOACs.

Thus, one of the above-mentioned interactions could be the explanation for a VTE recurrence on anticoagulation with a NOAC and the current medication list should be carefully reviewed before prescribing an alternative oral anticoagulant or intensifying current anticoagulation therapy. For rivaroxaban there is an additional caveat. At the 15-20 mg doses used for treatment of VTE (as opposed to 10 mg in VTE prophylaxis) rivaroxaban depends on presence of food for optimal intestinal absorption, as already reported from studies in healthy volunteers. The exposure to rivaroxaban, taken without food, might be even lower in patients than in healthy volunteers, as described in a case with recurrent pulmonary embolism on rivaroxaban, and I have in my clinical practice identified several cases with recurrent VTE or cardioembolic stroke under the same circumstances.

Another scenario with suboptimal exposure is the morbidly obese patient. There are no recommendations for dose adjustments of NOACs for this population that was underrepresented in the clinical trials.

Patients with major gastrointestinal tract surgery might have reduced absorption of a NOAC. In a review of the literature only case series or single case reports were identified. It appeared that reduced anticoagulant efficacy could be experienced with dabigatran, and possibly also with rivaroxaban after Roux-en-Y gastric by-pass or after gastrectomy. There was no information regarding the absorption of apixaban or edoxaban in such cases.

In the setting of stroke prophylaxis in atrial fibrillation it has been shown that patients are more stroke averse than physicians but physicians are more bleeding averse than patients, leading to underdosing. The NOACs are typically labelled for a standard dose and a reduced dose
regimen according to specific criteria for the indication stroke prophylaxis in atrial fibrillation and in some countries also for VTE. Retrospective chart reviews have shown a high degree of inappropriate dose selection even in hospitals, with many of those patients receiving a suboptimal dose. This may be true also for the patients with VTE and thus another explanation for breakthrough events. The approved dose regimens for treatment of VTE with NOACs differ somewhat between the United States and other countries. For example, dabigatran is only approved at a dose of 150 mg twice daily in the United States whereas other countries have in the label a dose reduction to 110 mg twice daily for patients over 80 years of age or over 75 years of age in combination with increased risk of bleeding. This dose reduction is not based on data from the studies on treatment in VTE and only observational studies will confirm if this dose is sufficiently effective. There are also criteria based on low body weight, impaired renal function, and/or old age for reduction of the dose of rivaroxaban or apixaban in patients with atrial fibrillation but not in patients with VTE, which is bound to result in confusion. Conversely, for edoxaban, the dose reduction is recommended for both indications for patients with moderate renal impairment, low body weight and/or concomitant use of P-gp inhibitors (Table 3).

**Evaluation and Investigation of the patient**

A suggested algorithm for evaluation of the cause for recurrent VTE on anticoagulation is shown in Figure 1. Rare causes for breakthrough events may have been missed. Further details regarding evaluation and management will be discussed in association with the case examples below. The reason for the therapeutic failure may not be apparent at the first encounter with the patient. While investigations are continuing the most appropriate and effective anticoagulant therapy should be provided. If a malignancy is highly suspected but not yet proven it would be appropriate to treat according to that hypothesis – see Case 1. In general, LMWH at a
therapeutic dose, sometimes higher, is a good option unless heparin-induced thrombocytopenia is a possibility.

Some investigations are not feasible or fraught with misinterpretation while on anticoagulant treatment. For example, the antithrombin level is reduced during treatment with heparin. Lupus anticoagulant testing may become false positive on any anticoagulant treatment, but it is not advisable to hold treatment in order to obtain this test, in view of the very hypercoagulable state of the patient.

**Case 1: cancer and recurrent thrombosis**

A 56-year-old male is diagnosed with proximal deep vein thrombosis in the right leg, confirmed with compression ultrasonography. He was diagnosed with an unprovoked thrombosis in the left leg 3 months earlier and has since then been treated with warfarin after an initial overlap with LMWH. His INR is now 2.9 and has been in the therapeutic range most of the time. The patient also complains of upper abdominal pain, poor appetite and has since the last visit lost about 5 kg.

**Initial investigation and anticoagulation**

We suspect a malignancy and order a CT of the abdomen and pelvis. In the SOMIT study this was the investigation with the highest yield in the group allocated to extensive screening for cancer. While awaiting the CT result we stop warfarin and start LMWH at a therapeutic dose. The CT demonstrates pancreas cancer with liver metastases. Therefore, the patient will continue on LMWH at a therapeutic dose rather than going back to an oral anticoagulant for now. This is in accordance with the recommendations by guidelines from the American College of Chest Physicians (ACCP) (Grade 2C), a guidance document supported by the International Society on Thrombosis and Haemostasis (ISTH), a guidance document by Anticoagulation FORUM, and an informal suggestion from the American Society of Clinical Oncology.
(ASCO).\(^4^4\) The recommendations or suggestions are based on superior efficacy of LMWH compared to VKA in patients with cancer and mainly first event of VTE. An ISTH registry on patients with cancer and recurrent VTE on anticoagulation confirmed that these patients also experience fewer recurrences over the next 3 months on LMWH versus warfarin (hazard ratio [HR], 0.28; 95\% CI, 0.11–0.70).\(^4^5\) Nevertheless, additional recurrences on anticoagulation are not uncommon – 11\% during 3 months in the ISTH registry.\(^4^5\)

**Beyond the acute phase**

The CLOT study used a protocol with the LMWH dalteparin at full therapeutic dose for 1 month, followed by 75\% of the dose for the next 2-5 months.\(^4^6\) In the CATCH study patients in the LMWH arm received tinzaparin at full therapeutic dose for the entire 6 months.\(^4^7\) The guideline and guidance documents do not express any suggestion regarding dose reduction after a certain number of months.\(^4^1,4^2,4^4\) This has left me in my practice with a choice to maintain the dose at 100\% or reduce to 75\% after 1 month depending on the perceived risk of recurrence (thrombogenic tumor type, extensive thromboembolism) and risk of bleeding.

For patients with a calculated creatinine clearance below 30 mL/min, corresponding to severe renal impairment, the dose of enoxaparin should be reduced to 1 mg/kg once daily. The product monographs for dalteparin and tinzaparin recommend that for patients with severe renal impairment a dose reduction should be considered without specifying by how much. Nadroparin is contraindicated in severe renal impairment.

**Recurrent venous thromboembolism on therapeutic dose LMWH**

In a retrospective study of patients with cancer and with recurrent VTE on anticoagulation, 47 patients that already were receiving treatment with therapeutic dose LMWH had dose escalation of 20-25\% for 4 weeks.\(^4^8\) Some patients were on a prophylactic dose and others on a therapeutic dose LMWH when the breakthrough event happened. Only the latter subset were
escalated to a supratherapeutic LMWH dose of about 120%. The recurrence rate beyond this dose escalation was 8.6% during 3 months with 3 patients each receiving therapeutic dose or 120% of therapeutic dose. In the international ISTH registry there was no significant difference in the risk of further recurrences over 3 months between patients who had a dose escalation of ≥20% (or ≥25%) and those with unchanged dose of LMWH. The ACCP guidelines recommend a dose escalation of LMWH by “one-quarter to one-third” (Grade 2C) and ASCO recommends a 20-25% increase (no grade).

In clinical practice it is often difficult to maintain patients on a twice-daily injection regimen for prolonged periods. After a recurrence on enoxaparin at 1.5 mg/kg daily one can change to either enoxaparin 1 mg/kg twice daily, or for patients that are not overweight to tinzaparin at slightly more than 200 units/kg once daily, which still might fit into one prefilled syringe.

Insertion of vena cava filter is not recommended for these patients unless there is a contraindication to anticoagulation or if there is recurrent pulmonary embolism on adequate anticoagulation.

The NOACs are not yet recommended for the initial treatment in the absence of any study comparing such a drug head-to-head with LMWH. In the near future results are expected from such a study comparing edoxaban with LMWH, and another study comparing apixaban with LMWH (NCT03045406). After the first 3-6 months of treatment patients that still have active cancer continue to have a high risk of recurrent VTE. It is unlikely that we will see a study comparing different anticoagulants for this extended phase. Here, NOACs are a valid option in view of the data from a meta-analysis of subgroups from the phase III trials with NOACs, but VKA or, for patients that still tolerate it, LMWH are other options. Treatment suggestions for recurrent VTE in patients with cancer on anticoagulation are summarized in Fig. 2. Decisions on dose reductions should take into account the bleeding risk and renal function.
Case 2: antiphospholipid syndrome

A 33-year-old female is seen in the Emergency Room for acute shortness of breath and fatigue. She has a history of recurrent spontaneous abortions and investigation has demonstrated that she is positive for lupus anticoagulant and antibodies against cardiolipin. She has recently had a successful pregnancy, managed with LMWH and aspirin throughout and until 6 weeks post-partum. At 3 months post-partum she developed deep vein thrombosis in the right leg and was treated initially with LMWH, overlapping to warfarin. The patient has continued breast-feeding the baby. She is now 5 months post-partum and her INRs have been difficult to maintain between 2.0 and 3.0, now being 1.6, a typical finding in patients with the antiphospholipid syndrome. Ventilation-perfusion lung scanning demonstrates bilateral segmental defects on the perfusion but not on the ventilation scan, thus high probability for pulmonary embolism.

Treatment should now be switched back to LMWH at a therapeutic dose for 1 week. Once the symptoms have abated, the dose can be reduced to a prophylactic level, for example dalteparin 5000-7500 IU daily or enoxaparin 40-60 mg daily. In a systematic review, long-term anticoagulation with LMWH was similarly effective and had a lower risk of bleeding than VKA. Although several of the 15 included studies had used a therapeutic dose LMWH also in the long term, there are similar results for efficacy after pooling the 6 studies with a prophylactic dose – odds ratio for recurrent VTE 0.91 (95% CI, 0.50-1.60) for LMWH versus VKA. In a case series with 24 patients with antiphospholipid syndrome and thrombosis, long-term secondary prophylaxis was given with dalteparin, 5000 units daily for a mean of 309 days with only one failure reported. For patients like the one in this example with a recurrence on VKA I would give the higher prophylactic dose, e.g. dalteparin 7500 IU or enoxaparin 60 mg daily long-term.

One of the NOACs could be a more convenient alternative for this patient once she stops breast-feeding, and there are emerging data from case series and subgroup analyses from...
larger trials that NOACs are similarly effective in patients with antiphospholipid syndrome. However, until a current randomized trial has demonstrated efficacy results, NOACs should not be the first line of treatment since failures have been reported.

**Case 3: suspected Behçet’s disease**

A 39-year-old male, immigrant from Syria, was diagnosed with deep vein thrombosis in the popliteal vein of the right leg 2 months ago. It was apparently unprovoked and he was treated initially with LMWH overlapping with warfarin. The last month his INRs have been between 2.0 and 3.0. He has now more pain in the right thigh and the calf is more swollen. Ultrasonography confirms progression of the thrombus up to mid-femoral vein. He has not lost any weight, has good appetite and normal bowel function. 5 years ago, in his home country, he had some kind of inflammation in one eye. Upon further questioning, he admits to having had some ulcers in his mouth that he thought were “cold sores”. On physical examination there are no current mouth sores or genital sores but there is acne. The visual acuity is decreased on the eye where he had the inflammation.

Behçet’s disease is suspected since the patient appears to fulfil the obligatory criterion of mouth sores and 2 of the additional 4 signs required (possible uveitis and acne but not genital sores and no pathergy test yet). The pathology of venous thrombosis in Behçet’s disease is mainly attributed to inflammation of the vessel wall and the thrombi become very adherent with a low risk for pulmonary embolism. Anticoagulants have not provided good protection against recurrences in reported cases. In the recommendations of the European League Against Rheumatism (EULAR) for management of Behçet’s disease from 2008, anticoagulation received the weakest strength of recommendation (D) based on the lowest level of evidence (IV). Instead, immunosuppressive agents are recommended (Table 4). The monoclonal antibody against tumor necrosis factor alpha, infliximab, has more recently been used with success in
some cases with venous thrombosis.\textsuperscript{60,61} I have personally used colchicine with good effect in such a patient with anticoagulant refractory deep vein thrombosis, and similar experiences have been published.\textsuperscript{62}

**Case 4: recurrence on treatment with a NOAC**

A 42-year-old male was previously healthy until he suffered an unprovoked, deep vein thrombosis in the left leg 4 months ago. Compression ultrasonography showed lack of compressibility from the mid-femoral vein to the trifurcation. He was started on rivaroxaban 15 mg twice daily, switching after 3 weeks to rivaroxaban 20 mg daily. The past 4 days he has experienced increasing pain in the same leg and difficulty to walk. On physical examination the left leg is 3 cm larger than the right at the maximum calf level and 2 cm larger at the ankle, slight reddish discoloration, no pitting edema. Body weight is 142 kg. Repeat ultrasonography shows extension of the thrombosis to the proximal femoral and the common femoral vein.

The patient has not had any weight loss, and review of systems is negative. He works as a taxi driver. The patient claims that he is taking rivaroxaban diligently once daily and his pharmacy verifies that he renewed his prescription on the expected date. However, he admits that he does not always have time to eat breakfast in the morning when he takes his medication. We have thus a patient that appears compliant but has a body weight at the extreme of the population in the clinical trials (14\% weighed >100 kg) and the absorption of the drug has been suboptimal part of the time. Pharmacokinetic results from human volunteers showed that the peak concentration of rivaroxaban (C\textsubscript{max}) was unaffected in subjects >120 kg,\textsuperscript{63} but only 12 subjects had a body weight >100 kg. A guidance document from ISTH on the use of NOACs for obese patients suggests that these drugs should not be used for a body weight >120 kg.\textsuperscript{64} It also suggests that if a NOAC anyhow is used, drug-specific levels at peak and trough should be obtained. Pharmacokinetic studies in healthy subjects also showed that the absorption of the 20
mg dose of rivaroxaban taken on a fasting stomach is 66% of the absorption when taken with food and in patients the difference might be greater.\textsuperscript{34}

We obtained a rivaroxaban-calibrated drug level 3 hours after the patient took a dose with food and it was 55 ng/mL, which is quite low. Thus, it is reasonable to follow the ISTH guidance document\textsuperscript{64} and abandon further treatment with a NOAC and continue instead with warfarin, overlapping initially with LMWH.

**Conclusion**

Recurrent VTE on anticoagulation is not very common and new symptoms from the leg could be a manifestation of post-thrombotic syndrome. For chest pain or shortness of breath there are several differential diagnoses. When a recurrence is confirmed by differences in VTE extent compared to the diagnostic imaging before anticoagulation was started the cause should be carefully investigated, since the management differs. The first step is to identify inappropriate anticoagulation, i.e. incorrect dose, poor adherence, drug interactions that may reduce the anticoagulant effect. Once any of these have been excluded the investigation should be focused on diseases or conditions with hypercoagulability, of which cancer is the most common. The recommendations regarding continued management are usually weak due to low-quality level of evidence.

**Disclosures**

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References


Legends to figures

Fig. 1. Suggested algorithm for investigation of cause for recurrent venous thromboembolism (VTE) on anticoagulation.

VTE – venous thromboembolism; VKA – vitamin K antagonist; NOAC – non-vitamin K antagonist oral anticoagulant; CT – computed tomography

*Antithrombin level becomes falsely low during treatment with heparin.

**Testing for lupus anticoagulant is not possible while on any anticoagulant.

Fig. 2. Suggested management of recurrent venous thromboembolism on anticoagulation in cancer, from the acute phase via the intermediate and long-term.

LMWH – low-molecular-weight heparin; NOAC – non-vitamin K oral anticoagulant; VKA – vitamin K antagonist; VTE - venous thromboembolism
Table 1. Causes for recurrent venous thromboembolism on appropriate anticoagulation

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>Mechanisms</th>
</tr>
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<tbody>
<tr>
<td>Cancer</td>
<td>Activation of coagulation factors and platelets, inflammatory cytokines with endothelial cell activation, neutrophil extracellular traps, adhesion molecules&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>Annexin V shield disruption, neutrophil extracellular traps, endothelial cell activation, inhibition of protein C or fibrinolysis&lt;sup&gt;65&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vasculitis (Behçet’s disease)</td>
<td>Diminished nitric oxide, impaired protein C pathway, elevated platelet-derived microparticles&lt;sup&gt;66&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Complement activation, ADP release from lysed red cells, decreased fibrinolysis&lt;sup&gt;67&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>Platelet activation, platelet-derived microparticles&lt;sup&gt;68&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Increased coagulation factors, impaired protein C pathway, inhibition of fibrinolysis, compression of left iliac vein&lt;sup&gt;69&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vascular abnormalities</td>
<td>Venous compression in May-Thurner- and thoracic outlet syndromes&lt;sup&gt;25&lt;/sup&gt;</td>
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Table 2. Explanation of the recommendations grading system, modified from\(^{70}\)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
<th>Benefit vs. Risk and Burdens</th>
<th>Methodologic Strength of Supporting Evidence</th>
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<tbody>
<tr>
<td>1A</td>
<td>Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh</td>
<td>Consistent evidence from RCTs without important limitations or exceptionally strong evidence from OS</td>
</tr>
<tr>
<td>1B</td>
<td>Strong recommendation, moderate-quality evidence</td>
<td>risk and burdens or vice versa</td>
<td>Evidence from RCTs with important limitations* or very strong evidence from OS.</td>
</tr>
<tr>
<td>1C</td>
<td>Strong recommendation, low/very low-quality evidence</td>
<td>vice versa</td>
<td>Evidence for at least one critical outcome from OS, case series, or RCTs, with serious flaws or indirect evidence</td>
</tr>
<tr>
<td>2A</td>
<td>Weak recommendation, high-quality evidence</td>
<td>Benefits closely balanced</td>
<td>Consistent evidence from RCTs without important limitations or exceptionally strong evidence from OS</td>
</tr>
<tr>
<td>2B</td>
<td>Weak recommendation, moderate-quality evidence</td>
<td>with risks and burden</td>
<td>Evidence from RCTs with important limitations* or very strong evidence from OS.</td>
</tr>
<tr>
<td>2C</td>
<td>Weak recommendation, low/very low-quality evidence</td>
<td>Evidence for at least one critical outcome from OS, case series, or RCTs, with serious flaws or indirect evidence</td>
<td></td>
</tr>
</tbody>
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RCTs – randomized controlled trials; OS – observational studies

*Important limitations are inconsistent results, methodologic flaws, indirect or imprecise results
Table 3. Criteria for dose reduction of non-vitamin K antagonist oral anticoagulants in the treatment of acute venous thromboembolism

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&gt;80 or</td>
<td>No</td>
<td>No*</td>
<td>No</td>
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<tr>
<td></td>
<td>&gt;75 + history of bleeding</td>
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<td></td>
<td></td>
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<tr>
<td><strong>Weight ≤60 kg</strong></td>
<td>No</td>
<td>No</td>
<td>No*</td>
<td>Yes</td>
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<tr>
<td><strong>Moderate renal impairment</strong> †</td>
<td>No</td>
<td>Only for SPAF</td>
<td>No*</td>
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</tr>
<tr>
<td><strong>Concomitant P-gp inhibitors</strong> †</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Increased risk of bleeding</strong> ‡</td>
<td>No</td>
<td>In Europe</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>After 6 months of treatment</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

b.i.d. – twice daily; SPAF – stroke prophylaxis in atrial fibrillation; P-gp – P-glycoprotein

*Only approved in countries outside of the United States

†Calculated creatinine clearance of 30-50 mL/min

‡Apixaban is only dose-reduced for stroke prophylaxis and only if 2 of the 3 criteria are fulfilled.

§Strong P-gp-inhibitors with recommended dose reduction of edoxaban are cyclosporine, dronedarone, erythromycin, ketokonazole, and quinidine
In the European product monograph for rivaroxaban “increased risk of bleeding” is examplified as patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis.
Table 4. Suggested and discouraged antithrombotic management after recurrence on anticoagulation

<table>
<thead>
<tr>
<th>Cause</th>
<th>Suggested management</th>
<th>Discouraged management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Switch to LMWH, perhaps escalate dose of LMWH, see Fig. 2 (ACCP Grade 2C)(^{41,42,44})</td>
<td>Vitamin K antagonists or NOACs during the first 3 months</td>
</tr>
<tr>
<td></td>
<td>For myeloproliferative neoplasm also cytoreduction and antiaggregants(^{71})</td>
<td></td>
</tr>
<tr>
<td>Behçet's disease</td>
<td>glucocorticoids, azathioprine, cyclophosphamide, cyclosporine A (all recommended by EULAR(^ {58})); colchicine, or infliximab</td>
<td>Anticoagulants alone</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>If on VKA or a NOAC – switch to LMWH</td>
<td>Monitoring of warfarin with a point-of-care instrument or with a thromboplastin sensitive to lupus anticoagulant(^{14})</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Anticoagulation and eculizumab(^ {18})</td>
<td>Anticoagulation alone</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>Argatroban, lepirudin, danaparoid (all ACCP Grade 2C)(^ {68}), fondaparinux(^ {72})</td>
<td>Heparin or LMWH</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Check anti-Xa level, escalate dose of LMWH</td>
<td>NOACs - contraindicated, VKA or heparin</td>
</tr>
<tr>
<td>Vascular abnormalities</td>
<td>Endovascular stent, possibly decompression surgery, and higher intensity anticoagulation&lt;sup&gt;73&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>

NOAC and

<table>
<thead>
<tr>
<th>Inappropriate dose</th>
<th>Increase to recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight &gt;120 kg</td>
<td>Switch to VKA</td>
</tr>
<tr>
<td>Use of strong inducer of CYP3A4 or of P-gp</td>
<td>Switch to VKA</td>
</tr>
<tr>
<td>Rivaroxaban taken without food</td>
<td>Instruct patient to take rivaroxaban with food</td>
</tr>
<tr>
<td>Poor adherence</td>
<td>Consider switch to VKA for better supervision</td>
</tr>
</tbody>
</table>

LMWH – low-molecular-weight heparin; ACCP – American College of Chest Physicians; EULAR – European League Against Rheumatism; NOAC – non-vitamin K oral anticoagulant; VKA – vitamin K antagonist; P-gp – P-glycoprotein
Recurrent VTE on anticoagulant treatment

Is the patient taking the drug?

Yes: Inappropriate dosing?

Yes: The patient is on: Heparin  VKA  NOAC

Antithrombin deficiency?*
INR below 2.0

No: Underlying condition or disease

1. Cancer
   a. Consider CT chest-abdomen-pelvis
   b. Age- and sex-appropriate work-up

2. Vasculitis, specifically Behçet

3. Antiphospholipid syndrome
   a. History, pregnancy complications?
   b. Antibodies against cardiolipin and beta2-glycoprotein I**

4. Paroxysmal nocturnal hemoglobinuria

5. Pregnancy

6. Vascular malformation

7. Heparin-induced thrombocytopenia
Recurrence on VKA, NOAC or subtherapeutic LMWH

LMWH at therapeutic dose

Recurrence on therapeutic dose LMWH

LMWH at therapeutic or 120-125% therapeutic dose

LMWH without dose reduction for at least 1 month. Optional dose reduction by 25% after that.

Recurrence with massive VTE

Consider thrombolysis or pharmaco-mechanic clot removal

LMWH with or without further dose reduction, or NOAC, or VKA, as long as active cancer

Figure 2
How I treat recurrent venous thromboembolism in patients on anticoagulant therapy

Sam Schulman