REVIEW ARTICLE

Managing challenging patients with venous thromboembolism: a practical, case-based approach

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KEY WORDS

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ABSTRACT

The management of patients with venous thromboembolism (VTE) is a common clinical scenario that, for the most part, involves well-established, evidence-based treatment pathways. However, important unanswered clinical questions remain that are the focus of ongoing research. The aim of this narrative review is to provide a practical, case-based approach to the following clinical scenarios in which therapeutic management pathways are less well established: How long to administer anticoagulation to patients with a first unprovoked VTE? How to manage complex patients with cancer-associated VTE? When and how to treat patients with splanchnic vein thrombosis? When to use thrombolytic therapy for deep vein thrombosis?

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Introduction The diagnosis and management of venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is considered a mature clinical domain that, for the most part, has attained the status of having established diagnostic and treatment algorithms. One might claim that the pivotal clinical questions relating to the management of patients with VTE have been answered, with the focus now shifting to ensuring that this knowledge is incorporated into clinical practice.[1] On the other hand, finding solutions to one clinical problem creates opportunities for additional research; moreover, clinically important unanswered questions remain. These include deciding on the duration of anticoagulation after unprovoked VTE, the role of catheter-directed thrombolysis for DVT and PE, and the role of the newer direct oral anticoagulants (DOACs) in patients with cancer or unusual site thrombosis.[2]

There are well-developed algorithms for the assessment of patients with suspected DVT or PE, which encompasses the diagnosis of initial and recurrent disease and deals with special populations that include suspected upper extremity DVT and suspected VTE during pregnancy.[3] What remains to be addressed, perhaps, are more nuanced issues that include how D-dimer-based diagnostic algorithms can be applied in the elderly or in patients with low, as opposed to moderate, clinical pretest probability, in whom different D-dimer positivity thresholds may be warranted.[3]

As regards the treatment of acute VTE, improvements in the initial anticoagulant management have led to a lowering of adverse outcomes, with the rates of recurrent VTE and major bleeding of 2% to 3% and 1% to 2%, respectively, during the initial 3-month treatment period.[4-6] Moreover, the recent cluster of clinical trials examining the effects of DOACs, which comprise dabigatran, rivaroxaban, apixaban, and edoxaban, for the treatment of acute VTE have provided a more convenient (though more costly) and slightly safer alternative to treatment with a low-molecular-weight heparin (LWMH) and vitamin K antagonist (VKA). Indeed, the 2016 American College of Chest Physicians practice guidelines for antithrombotic therapy provide a weak recommendation (grade 2B) in favor of DOACs over LMWH and a VKA for the initial treatment of VTE.[7] There is active research assessing important unresolved

treatment questions. Thus, the HOKUSAI-VTE cancer study[8] is assessing the use of a DOAC (edoxaban) compared with LMWH therapy for the long-term treatment of patients with cancer-associated thrombosis (CAT), the ATTRACT trial[9] will better define the role of catheter-directed thrombolysis for extensive DVT, single-arm trials are assessing the use of rivaroxaban for acute and chronic portal vein thrombosis (RIVASVT-100, NCT02 627 053 and RIPORT, NCT02555111), and the COBRRA trial is comparing DOACs (rivaroxaban vs apixaban) for acute VTE treatment (NCT02559856).

Against this background, the aim of this narrative review is to provide a practical, case-based approach to the management of 4 common clinical scenarios involving patients with VTE that are considered both clinically challenging and active in terms of current research. These scenarios are: 1) How long should patients receive anticoagulant therapy after a first unporvoked VTE?; 2) How to manage complex patients with cancer-associated VTE?; 3) When and how to treat patients with splanchnic vein DVT?; and 4) When to use thrombolytic therapy for DVT?

Duration of anticoagulation after unprovoked venous thromboembolism and related management

Case example A 50-year-old, previously well male patient presents with left calf swelling and is diagnosed with DVT (popliteal to distal femoral vein) and has neither antecedent VTE risk factors nor any other comorbid conditions. He has now completed 3 uneventful months of anticoagulant therapy and has some mild residual leg edema but no other symptoms. Should this patient continue or stop anticoagulant therapy?

Comment The past 2 decades have witnessed intense research investigating the optimal duration of anticoagulant therapy for patients with a first unprovoked VTE, which comprise 45% to 55% of all patients with VTE.[10,11] With this research we have learned 3 important things. First, at least 3 months of anticoagulant therapy is needed for the treatment of VTE but any additional anticoagulation, though preventing disease recurrence during the on-treatment period (risk reduction, 80%–90%), only postpones the development of recurrent VTE after anticoagulation is stopped.[12] Second, although done to identify cancers at an earlier stage that may be more amenable to treatment, there is no benefit from intensive screening with abdominopelvic computed tomography and gastrointestinal endoscopy, as it does not improve cancer outcomes above that of age- and sex-appropriate cancer screening.[13] Similarly, screening for thrombophilia does not appear to have utility because, with the exception of rare patients with severe thrombophilia such as antiphospholipid syndrome, the identification of more common abnormalities (factor V Leiden or prothrombin mutations) does not materially affect the risk of recurrent VTE.[14,15] Third, we are now better at estimating patients' risk for recurrent VTE after 3 months of anticoagulant therapy, which helps us decide whether patients should stop anticoagulants or continue them indefinitely.[14,16,17]

The decision to continue or stop anticoagulant therapy is anchored on estimating the risk of recurrent VTE if anticoagulation is stopped alongside an estimate of major (or life-threatening) bleeding if anticoagulation is continued. Estimates of bleeding risk, which are usually expressed as the annual risk of major bleeding, are 1% to 3% after an initial 3 months of treatment.[18-20] Emerging bleeding prediction rules for VTE patients will further refine this assessment, as bleeding risk scores for patients with atrial fibrillation have limited applicability for those patients with VTE[4] who tend to be younger and with fewer comorbidities.[21] Coupled with the risk for major bleeding is an assessment of the associated case-fatality of such bleeds, which is approximately 10%.[18,19] Consequently, the annual risk for fatal bleeding with extended anticoagulation for VTE is estimated at 0.1% to 0.3%.

On the other side of the risk ledger is the estimated risk for recurrent VTE in patients with unprovoked VTE who stop anticoagulant therapy after 3 to 6 months of treatment. In such patients, the annual risk for recurrent VTE varies widely from 2% to 12% per year, during the initial 2 to 3 years after treatment is stopped.[14,16,17,22] After this initial 2- to 3-year period, there are less data to provide precise estimates of this risk. Thus, the 5-year risk for recurrent VTE may be as low as 5% and as high as 40%. With a case-fatality rate of recurrent VTE of approximately 5%,[18,23,24] the risk for death from disease recurrence is estimated at 0.25% to 2.0%.

Factors that consistently appear to increase recurrence risk are extensive VTE at presentation (ie, proximal DVT or PE versus isolated distal DVT), male sex, and positive D-dimer following anticoagulation, when measured approximately 1 month after anticoagulant therapy is interrupted. These and other factors have been incorporated into clinical prediction rules aimed at estimating the risk of recurrence after a first unprovoked VTE, and comprise the HER-DOO2 score, Vienna prediction score, and DASH score.[25] The HER-DOO2 score applies only to women and incorporates signs and symptoms of the post-thrombotic syndrome, and D-dimer that is measured during anticoagulant therapy.[26] The Vienna prediction score uses patient sex, posttreatment D-dimer, and thrombosis location to estimate the risk of recurrent VTE over a 5-year period (www.meduniwien.ac.at/user/georg.heinze/zipfile/).[27] The DASH score incorporates patient age and sex, posttreatment D-dimer, and estrogen use in women.[28] Of these scores, only the HER-DOO2 score has been prospectively validated in an independent patient population (http://congress365.escardio.org/Presentation/142 492#).

The "tipping point" as to when to recommend continuing or stopping anticoagulant therapy can be anchored on the annual risk for disease recurrence, which can be estimated by 1 or more of the above clinical prediction rules. It has been suggested that if the annual risk for recurrence is 5% or lower,[29] this would justify stopping anticoagulation, although others have suggested continuing treatment unless the annual risk is 3% or lower per year.[30] Another way to frame this decision is to consider indefinite anticoagulant therapy if the cumulative risk of recurrent VTE is higher than 24% at 5 years.[31] The presentation of VTE, whether as DVT or PE, also may influence decisions about indefinite therapy because patients presenting with PE are about 3 times as likely to develop PE rather than DVT as the manifestation of disease recurrence[23,32] Although the risk of recurrence is about 50% lower after an isolated distal (or calf) DVT than after a proximal DVT, the risk for recurrence does not appear to differ between patients who initially presented as proximal DVT or PE.[32] Finally, the decision to continue or stop anticoagulation may also depend on the patient's perspective and preferences. Thus, patients who place a high value on preventing recurrence may accept the associated bleeding risk, cost, and inconvenience of continuing anticoagulant therapy, whereas other patients may prefer to stop therapy and accept the risk of recurrent VTE.

Back to the case After a discussion about the potential benefits of ongoing anticoagulant therapy and estimated risk for recurrent VTE if anticoagulation is stopped (~35% over 5 years), the patient decided to decline D-dimer testing for further risk stratification and elected to discontinue anticoagulation as he places a high value on preventing bleeding due to a lifestyle that includes motorcycle riding and heli-skiing. Other patients in this clinical scenario may choose to continue anticoagulation. For patients without risk factors for bleeding who stop anticoagulation, acetylsalicylic acid (81 mg) daily should be considered,[7] as it provides a 25% to 35% reduction of recurrent VTE risk compared to no treatment.[33,34]

Anticoagulant management for cancer-associated thrombosis

Case example A 68-year-old male patient (73 kg) is diagnosed with small cell lung cancer metastatic to the brain and is started on chemotherapy using a peripherally inserted central catheter. Within 2 weeks, he develops arm swelling and pain in the central catheter line arm and is diagnosed with axillary-subclavian DVT. His hemoglobin level is 98 g/l, platelet count is 69×10^9/l, and serum creatinine level is 80 μmol/l. The peripherally inserted catheter line remains functional.

Comment In patients with CAT, treatment with LMWH for at least 3 months remains the first-line anticoagulant management. LMWH can be administered as once-daily regimens (eg, dalteparin, 200 IU/kg; tinzaparin, 175 IU/kg; enoxaparin, 1.5 mg/kg), which have been shown in well-designed randomized trials to be more effective and safer than treatment with an LMWH for 5 to 7 days followed by a VKA.[7,35] In the case of dalteparin, the dose is reduced to 150 IU/kg after the initial 4 weeks of treatment.[36] In general, the duration of the LWMH therapy is predicated on whether the cancer is "active" (metastatic, progressing, or requiring ongoing antineoplastic therapy) or "inactive". Most patients with CAT, however, fall into the "active cancer" category and indefinite treatment is recommended.[37] An example of a patient where a limited duration of anticoagulant therapy may be reasonable is when VTE occurs in the presence of transient risk factors, such as VTE after cancer resection surgery with curative intent.

Patients with treated CAT have a 3- to 5-fold higher risk for bleeding and recurrent VTE than patients with VTE and no cancer.[35,36] As in our case example, thrombocytopenia is common among patients with CAT. Full-dose anticoagulation can be initiated in patients with a platelet count exceeding 50×10^9/l, with the provisos that there are no concomitant factors that may inhibit hemostasis and that platelet count recovery is likely (eg, postchemotherapy). In patients with a platelet count between 30×10^9/l and 50×10^9/l, a 50% reduction in the dose of LMWH is considered appropriate, whereas in those with a platelet count of less than 30×10^9/l, consideration should be given to either a prophylaxis-dose LMWH regimen (eg, dalteparin, 5000 IU; enoxaparin, 40 mg/d) or placement of a temporary inferior vena cava filter in patients with acute lower extremity DVT. If recurrent VTE develops despite LMWH therapy, increasing the dose of LMWH by 25% is a reasonable treatment option.[37]

In patients with CAT, treatment with a DOAC is an appealing option, which can circumvent the need for daily subcutaneous injections. However, there are no direct comparisons of a DOAC against treatment with an LMWH. Such studies are ongoing but until then LMWHs remain the go-to treatment for CAT, and DOACs should be reserved as a second- or third-line treatment option.

Back to the case This patient was initiated on treatment with subcutaneous LMWH and responded well to treatment, with a reduction in signs and symptoms. The peripherally inserted central catheter line was maintained for chemotherapy and blood product transfusion. It was removed within the subsequent month, and anticoagulation was discontinued after 3 months of treatment since the CAT involved the upper extremity and was considered secondary to a reversible risk factor.

Anticoagulant management for splanchnic vein thrombosis

Case example A 55-year-old male patient with alcohol-related cirrhosis and stable portal

hypertension (ie, nonbleeding esophageal varices and mild ascites) undergoes a surveillance abdominal ultrasound to screen for hepatoma, which shows a nonocclusive thrombosis of the portal vein that was not present a year earlier. He has not had any recent abdominal pain or other gastrointestinal symptoms. The ultrasound also shows cavernous transformation of the portal vein. His international normalized ratio (INR) is 1.7, and platelet count is 90×10^9/l.

Comment The incidence of splanchnic vein thrombosis is increasing, in part due to the increasing use of diagnostic imaging modalities that are used to screen patients with chronic disease such as cirrhosis, or for staging and assessing treatment response in patients with cancer.

In patients who are symptomatic with thrombosis involving 1 or more of the portal, mesenteric, and splenic veins, typically presenting with abdominal pain due to upstream end-organ injury (ie, intestinal or splenic congestion or ischemia), anticoagulant management is recommended. Long-term use of LMWH is preferred in patients with cancer. Moreover, LMWH may be a safer treatment option for patients with thrombocytopenia, in whom a reduced dose can be administered, and in patients with abnormal coagulation test results related to liver disease, in whom INR monitoring of a VKA may be problematic. Nonrandomized, observational studies suggest that anticoagulant therapy reduces the risk for thrombus extension, recurrence, and overall mortality. DOACs may be an appealing treatment option in patients without advanced liver disease, but have not been assessed in patients with splanchnic vein thrombosis.[38,39] A prospective cohort study is currently assessing rivaroxaban for the treatment of acute, symptomatic splanchnic vein thrombosis (RIVASVT-100, NCT02627053). The optimal duration of anticoagulation for splanchnic vein thrombosis is not well defined, as randomized trials of different treatment durations are lacking; however, the same principles can be applied as in patients with nonsplanchnic vein thrombosis. Thus, patients with concomitant cancer or cirrhosis appear to be at high risk (10% per year after 2 years) for recurrent disease and indefinite anticoagulation may be warranted.[38] The need for ongoing anticoagulation should be balanced against patients' risk for bleeding, particularly in the setting of portal hypertension and prior bleeding from esophageal varices.

Asymptomatic patients, such as the case example herein, require a more nuanced management approach. Thus, in patients with active cancer or with a known thrombophilia, anticoagulant therapy is warranted.[39] In patients with cirrhosis and evidence of chronic thrombosis, manifest by collateralization around the portal veins, the need for anticoagulant management is less compelling. In such patients, clinical monitoring and, perhaps, serial imaging of the portal veins to assess thrombus progression, is reasonable. An ongoing randomized trial (RIPORT, NCT02555111) is comparing rivaroxaban to no anticoagulation for asymptomatic, presumed chronic, splanchnic vein thrombosis.

The presence of mild cirrhosis-associated coagulopathy (eg, INR, 1.4–1.7) and mild to moderate thrombocytopenia (eg, platelet count, $50–100 \times 10^9$/l) should not discourage the use of anticoagulation since such patients may, in fact, have an overall hypercoagulable state due to decreased production of the endogenous anticoagulants, protein C, protein S, and antithrombin, decreased clearance of von Willebrand factor, and higher factor VIII levels, which are increased as acute phase reactants.

Back to the case This patient was considered to have chronic portal vein thrombosis based on the lack of associated symptoms and cavernous transformation around the thrombosed portal vein. Anticoagulant therapy was not administered as there was no evidence for cancer or thrombophilia, and the pathogenesis was deemed related to stasis associated with the underlying portal hypertension, which was now stable. The patient underwent clinical follow-up and had a repeat Doppler ultrasound of the portal vein 3 to 4 months later, which was unchanged and thereby supported the chronic, nonprogressive nature of the thrombosis.

Management of patients with massive deep vein thrombosis

Case example A 25-year-old obese woman (body mass index, 35 kg/m^2), who works as a chef, presents with a 1-week history of progressive left leg swelling and pain, extending from the calf to the inguinal area. She is taking an oral contraceptive but is on no other medications. The symptoms have become unbearable in the last 24 hours. A venous ultrasound shows noncompressibility extending from the popliteal to the common femoral vein with a Doppler finding of thrombus extension into the iliac vein.

Comment The management of patients with clinically massive DVT, which typically involves the common femoral or iliofemoral veins, should consider a different paradigm than the management of patients with less extensive DVT, especially in the setting of severe leg symptoms or phlegmasia cerulea dolens.[40] Involvement of the iliofemoral vein will greatly restrict venous return because bypass vein channels, such as the profunda femoris, are distal to the obstruction. In such patients, catheter-directed thrombolytic therapy should be considered, especially in patients with recent (within 7 days) symptom onset who are at low risk for bleeding and have a high level of physical functioning.[7] Catheter-directed thrombolysis via the popliteal vein allows the delivery of lower doses of thrombolytic therapy than systemic administration (eg, tissue plasminogen activator infusion at 0.5 to 1.0 mg/h, with a total dose of 25 mg or lower) and may be

combined with mechanical thrombus dissolution (ie, pharmacomechanical catheter-directed thrombolysis).[41] Venography is performed before and after the intervention to assess venous patency and if additional lytic therapy, mechanical dissolution, balloon dilation, or venous stenting is warranted. Despite the intuitive appeal of this treatment, and evidence from a moderate-size randomized trial that catheter-directed thrombolysis reduces the postthrombotic syndrome from 71% to 43% at 5 years,[42] there are several caveats before considering such treatment. First, it should be limited to patients with extensive (eg, iliofemoral) DVT. Second, placement of venous stents is empiric, with limited evidence for added therapeutic benefit, but may be indicated in patients with evidence of iliac vein stenosis, for example, with left-sided iliac vein compression by an overlying right iliac artery (May–Thurner syndrome). Third, catheter-directed thrombolysis may rapidly improve acute symptoms but should be administered with the aim of reducing long-term symptoms due to the postthrombotic syndrome. Finally, catheter-directed thrombolysis is likely to be associated with an increase in bleeding compared to anticoagulation alone and is less attractive if there are risk factors for bleeding.

Back to the case This patient received catheter-directed thrombolysis, which resulted in rapid symptom improvement. She was then treated with an LMWH and a VKA. In addition, an aerobic exercise and weight loss program was empirically recommended to improve venous collateral circulation and to reduce venous hypertension in an effort to mitigate morbidity related to the post-thrombotic syndrome, especially as her occupation requires prolonged periods of standing. Knee-length compression stockings were also recommended to reduce leg edema.

Conclusions Although there have been many advances in the diagnosis and treatment of the "typical case of VTE" in the past 3 decades, important unanswered questions remain, as illustrated by the cases we have presented. Recently completed and ongoing studies are addressing these and other related questions. Thus, the SOX trial[43] has questioned the routine use of graduated compression stockings to prevent postthrombotic syndrome, although it is reasonable to use compression stockings in patients with ongoing leg edema and heaviness.[44] The soon-to-be-completed ATTRACT trial[9] aims to provide robust evidence as to whether catheter-directed thrombolysis prevents this debilitating sequela of DVT. The SOME trial[13] does not support extensive imaging to detect occult cancer in patients with unprovoked VTE, and ongoing trials are assessing the use of DOACs for the treatment of symptomatic CAT and asymptomatic thrombi in patients with or without cancer. The CACTUS trial[45] does not support the routine use of anticoagulant therapy in low-risk patients, defined as without active cancer or prior VTE, who have symptomatic isolated distal (calf) DVT,[45] which is being increasingly detected with the availability of whole-leg venous ultrasound. Finally, the SSPE study (NCT01455818) will determine the safety of withholding anticoagulant therapy in patients with isolated symptomatic subsegmental PE.

In summary, the large global burden of VTE has only recently been recognized as a public health problem that affects millions of people worldwide.[46] The scope of VTE mandates the need for ongoing research, such as that which we have described herein, but also makes it incumbent on health care professionals in this field to take this cumulative research to the next level, that is, to ensure it is being translated and acted upon at the point of care.

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