The Outpatient Management of Deep Venous Thrombosis and Venous Thromboembolism

Author John Reilly, MD, MSCE

Editor Amik Sodhi, MD

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Educational Objectives:

1. Review the long-term treatment options for acute PE and DVT
2. Discuss the relative benefits and evidence for each anticoagulant
3. Review the contraindications and concerns with each anticoagulant
4. Discuss the decision-making process for deciding on length of anticoagulation therapy
5. Review Hereditary Thrombophilia and when to test for them

Unless otherwise specified, the information provided herein is taken from the official American College of Chest Physicians' Guidelines and Expert Panel Review on Antithrombotic Therapy for VTE Disease first published in 2012 and subsequently updated in 2016 and 2021 (Stevens et al.,* CHEST *2021; 160(6):2247-2259).

Scenario:
Mr. S is a 27-year-old man who plays professional soccer . He had no past medical history and presents to the hospital with acute onset dyspnea and chest pain after a 12-hour flight from a soccer tournament in Asia. Physical examination reveals sinus tachycardia, tachypnea without respiratory distress or hypoxia, and a blood pressure within the limits of normal. Only his right lower extremity has trace to 1+ edema. CXR obtained on admission is clear but a CT angiogram reveals acute right lower lobe subsegmental PE as well as a right proximal lower extremity DVT. He is started on low molecular weight heparin (LMWH) in the Emergency Department and is admitted for overnight monitoring. His symptoms improve overnight, and so the primary team plans to discharge him with outpatient follow-up in your clinic, but they have some questions.

Question 1: Should Mr. S receive long-term outpatient anticoagulation? And if so, for how long? What is the evidence?

The decision to initiate long-term therapeutic anticoagulation for VTE should attempt to curb the *risk of recurrence of VTE* as long as it outweighs the bleeding risk, while also taking into account patient preference and patient-specific risk or mitigating/physiologic factors (i.e., Virchow's Triad).

The most recent ACCP Guidelines for risk stratification were published in 2016 and at that time, nomenclature for risk stratification continued to use designations for classifying of VTE dichotomously into either 'provoked' or 'unprovoked' classifications (Kearon et al., 2016) and have undergone two updates. For *provoked* proximal DVT or PE (occurring in the setting of a **transient risk factor**), guidelines recommend anticoagulation for 3 months rather than a shorter OR a longer duration (Grade 1B for surgical risk factor, Grade 2B for non-surgical, transient risk factor). On the other hand, guidelines currently recommend indefinite anticoagulation for any ***unprovoked*** VTE or VTE secondary to a **permanent risk factor** (Grade 1B).

Notably, 2016 ACCP Guidelines (Kearon et al., 2016) made a distinction regarding the need for outpatient anticoagulation in low-risk patients with either *asymptomatic isolated subsegmental PE without associated DVT* or *minimally symptomatic, isolated and provoked, distal DVT.* These two specific clinical scenarios carry low theoretical risk for conversion to life-threatening pathophysiology although there is limited evidence in support of that understanding. Guidelines nevertheless suggest close outpatient surveillance in place of anticoagulation as a viable potential management option for these two clinical scenarios. (Grade 2C). Serial imaging should be completed for distal DVT with weekly ultrasound or more frequently with change in symptoms. However, high-risk patients with isolated subsegmental PE and distal DVT should be anticoagulated (Stevens et al. 2021).

TABLE 11 Categorization of risk factors for venous thromboembolism based on the risk of recurrence over the long-term

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3-8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerpium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

PE: pulmonary embolism; VTE: venous thromboembolism. [a]If anticoagulation is discontinued after the first 3 months (based on data from Baglin *et al.* [340] and Iorio *et al.* [341]). [b]The categorization of risk factors for the index VTE event is in line with that proposed by the International Society on Thrombosis and Haemostasis [338]. The present Guidelines avoid terms such as "provoked", "unprovoked", or "idiopathic" VTE.

Image of Table 11 from 2019 European Respiratory Society Guidelines for VTE Management (Albertsen, Piazza, & Goldhaber, 2018; Konstantinides et al., 2019).

<u>Recurrence Risk (Baglin, Luddington, Brown, & Baglin, 2003; Iorio et al., 2010)</u>

I. Provoked (suspected cause or risk factor)
   A. Surgical (i.e., low risk cause): 1% at 1 year, 3% at 5 years
   B. Non-surgical (i.e., intermediate risk cause): 5% at 1 year, 15% at 5 years

II. Unprovoked VTE
   A. High risk cause: 10% at 1 year, 30% at 5 years

III. Unique Circumstances
   A. Low risk cause: isolated distal DVT (distal to popliteal)
      1. Carries half the recurrence risk of proximal DVT or PE
   B. High risk cause: Malignancy: Estimated 15% at 5 years.
   C. High risk cause: Recurrence of VTE (Second event, etc.)
      1. Each recurrence increases risk by 50%
   D. High risk cause: Hereditary Thrombophilia, Antiphospholipid antibodies

The greatest challenge in discontinuation of therapy or determining duration of therapy presents when faced with the clinical scenario of a 'possibly provoked or idiopathic' PE in patients with intermediate to high risk. Several prediction tools including the HERDOO2 Rule (Rodger et al., 2017), the DASH Prediction Score (Tosetto et al., 2017), and the Vienna Prediction Model (Tritschler, Méan, Limacher, Rodondi, & Aujesky, 2015) have been validated to assist clinicians with quantifying the risk of recurrent VTE after discontinuation of anticoagulation in patients with unprovoked VTE.

Recurrence of VTE typically resembles the initial presentation (i.e., DVT recurs as DVT, etc.), which by logical extension suggests that the case fatality rate of recurrent VTE will be higher in patients who have previously had a PE; in fact, case fatality rate of recurrence is almost twice that in patients with history of PE compared to those with history of DVT alone (Carrier, Le Gal, Wells, et al. 2010). And with respect to discontinuation of anticoagulation in this cohort, male sex and elevated D-dimer during or just after discontinuation of therapeutic anticoagulation is associated with a higher risk of recurrent VTE (>5% per year) and would merit ongoing treatment (Douketis et al., 2010). As such, obtaining D-Dimer levels 1 month after discontinuation of AC may be an acceptable clinical consideration.

Answer 1: *Yes, Mr. S should be prescribed outpatient anti-coagulation due to the presence of a proximal DVT with a PE. Duration of therapy is debatable, however. Although his presentation would most likely be classified as a provoked venous thromboembolism ("transient risk factor," in the parlance of the 2021 update to the ACCP recommendations), it nevertheless carries an intermediate risk of recurrence as well as an increased risk of morbidity/mortality were it to re-occur given that he is male and that the initial presentation this admission was with a symptomatic pulmonary embolism. According to 2021 ACCP updated guidelines he should be prescribed at least a 3-month long course of anticoagulation. At that time, ACCP recommendations would suggest re-assessment of the patient's risk factors, and if none present, discontinuation of anticoagulation. If permanent risk factors were to declare themselves or there was recurrence of VTE, then indefinite anticoagulation would be recommended. However, shared decision-making is an important aspect of this clinical scenario; if extended phase anticoagulation is pursued, it (and the patient's risk factors for bleeding as well as VTE recurrence) should be re-assessed annually.*

Question 2: Which anticoagulant would you choose for him to be discharged on? What are your options? What is the evidence?

In patients with acute DVT of the leg and/or PE, direct oral anticoagulants are recommended as initial outpatient therapy (rivaroxaban, apixaban, dabigatran, or edoxaban) over vitamin K antagonists (VKA) (all Grade 2B), which are in turn recommended over low-molecular weight heparin (LMWH) (Grade 2C).

The 2021 ACCP Guideline update indicates that the recommendation for DOAC as first-line agent over LMWH extends now to VTE in the setting of malignancy, as well (whereas previously, LMWH had been favored). DOACs have not been compared head to head in this setting. In the case of luminal gastrointestinal malignancy, apixaban is specifically recommended as the first-line DOAC agent to consider given data indicating similar risk of bleeding as LMWH. In those patients with luminal GI malignancy in whom apixaban is not an option, LMWH may be favored rather than other DOACs given that edoxaban and rivaroxaban showed higher rate of bleeding than LMWH in malignancy-associated VTE. In cases where enteral absorption of DOACs is a concern due to underlying malignancy, LMWH would be preferred, as well (Stevens et al. 2021).

Long Term Anticoagulation Choices:

I. Direct Oral Anticoagulants (Grade 2B rec, DOC for anticoagulation without malignancy). Oral administration.
    A. Factor Xa Inhibitors: Inactivate circulating and clot-bound factor Xa.
        1. RivaroXaban: Studied as an initial anticoagulant that continues as long-term.
            1. **EINSTEIN-DVT**: 3449 patients with acute, symptomatic DVT randomized to oral *rivaroxaban alone vs. enoxaparin* followed by VKA. Recurrent VTE 2.1% vs. 3%, bleeding 8.1% vs. 8.1%(Bauersachs et al., 2010).
            2. **EINSTEIN-PE:** 4,832 patients with acute, symptomatic PE randomized to *rivaroxaban versus enoxaparin* followed by VKA. Recurrent VTE 2.1% vs 1.8%, bleeding 10.3% vs 11.4%, major bleeding 1.1% vs 2.2% (Buller et al., 2012).
            3. **SELECT-D**: Pilot study of 406 pts randomized to rivaroxaban v. LMWH for VTE in malignancy reported reduced VTE recurrence (4% v. 11%) compared with LMW heparin, with similar (6% v. 4%) clinically significant bleeding, but with excess number of clinically relevant non-major bleeds with rivaroxaban (13% v. 4%), especially from upper GI tract malignancy (Young et al., 2018)
            4. Rivaroxaban v. VKA in Antiphospholipid Syndrome: randomized, open-label study in high-risk patients w/ APS (testing triple positive for lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein I), rivaroxaban had both increased VTE AND major bleeding events compared with warfarin (HR for the composite primary outcome 6.7; 95% CI 1.5–30.5) (Ordi-Ros et al. 2019)

        2. ApiXaban:
            1. **AMPLIFY:** 5395 patients with acute VTE randomized to *apixaban vs. enoxaparin followed by warfarin*. Recurrent VTE 2.3% vs. 2.7%, bleeding 4.3% vs. 9.7% (Agnelli et al., 2013)
            2. Apixaban V. Dalteparin in Malignancy-related VTE, open label non-inferiority trial in 576 patients. Recurrent VTE 5.6% v. 7.9% while major bleeding 3.8% v. 4.0% (Agnelli et al., 2020)
        3. EdoXaban
            1. RCT double blinded, noninferiority: 4921 patients with acute VTE randomized to *edoxaban vs. warfarin* for 3 to 12M. Recurrent VTE 3.2% vs. 3.5%, bleeding 8.5% vs. 10.3% (Investigators, 2013).

    B. Direct thrombin inhibitor. Thrombin (Factor IIa) is cleaved from prothrombin by factor Xa to become the final enzyme in the clotting cascade before provoking fibrin formation.
        1. Dabigatran:
            1. **RECOVER I** – 2539 patients with acute VTE randomized to six months of dabigatran (150 mg BID) vs. warfarin after 7 days of parenteral anticoagulation. Recurrent VTE occurred in 2.4% vs 2.1%, VTE-related deaths 0.1 vs. 0.2, major bleeding 1.6 vs. 1.9, any bleeding 16.1 vs. 21.9 (Shulman et al. 2009, NEJM).
            2. **RECOVER II** – 2589 patients with acute VTE: very similar results – recurrent VTE 2.3% vs 2.2%, major bleeding 1.2% vs 1.7% (Shulman et al. 2014, Circulation).

II. Vitamin K Antagonists: Grade 2B rec as DOC for anticoagulation without malignancy when contraindications to DOACs exist; Oral administration
    A. For decades coumadin was standard of care; landmark study of coumadin v. no AC in VTE was performed in 1960 & compared warfarin with observation in patients with acute DVT. AC w/ warfarin resulted in a dramatic reduction in recurrence to

0% from 26%, which translated into a mortality benefit of 26% v. 0% (Barritt & Jordan, 1960)

B. Since then almost all other AC has shown either similar or improved efficacy compared to coumadin w/ respect to VTE, with similar or improved safety profiles.
C. Category X in pregnancy.

III. Low Molecular Weight Heparin (LMWH): Grade 2B rec by ACCP as DOC for pregnancy related VTE, and is also generally preferred over unfractionated heparin when DOACs, VKAs are contraindicated; subcutaneous administration.
    A. 3299 patients, 16 studies in Cochrane meta-analysis for LMWH v warfarin in patients without malignancy; no difference in mortality or VTE recurrence; nonsignificant trend in lower bleeding rates and reduced post-thrombotic syndrome (Andras, Sala Tenna, & Stewart, 2017).
    B. Several RCTs compared LMWH to warfarin with malignancy; 2018 Cochrane Meta-analysis comparing UFH to LMWH for VTE in the setting of malignancy included 15 RCTs and 1615 patients.
        1. LMWH likely decreases mortality at 3 months compared to UFH (risk ratio (RR) 0.66, risk difference (RD) 57 fewer per 1000; but did not rule out a clinically significant increase or decrease in VTE recurrence (Hakoum et al., 2018).
    C. Recent meta-analysis by Giustozzi et al. comparing DOACs (apixaban, edoxaban or rivaroxaban) to LMWH (four RCTs included) with results indicating a reduced risk of recurrent VTE without a significantly higher likelihood of major bleeding at 6 months with DOACs. This was adopted into the 2021 ACCP guidelines.
        1. Edoxaban and rivaroxaban may have increased risk of GI bleed than LMWH in those with luminal GI malignancy, while apixaban does not. Apixaban or LMWH may be preferred for these patients.

IV. Fondaparinux (SC): Antithrombin III mediated selective inhibitor of factor Xa, drug class is known as pentasaccharides.
    A. 2017 Cochrane meta-analysis of 5 RCTs comparing pentasaccharides (fondaparinux, idraparinux, etc) for the treatment of VTE compared to coumadin at three- and six-month follow-up demonstrated no difference in risk of recurrent VTE or frequency of major bleeding among 6,981 patients.
        1. Two of the studies included in that analysis focused on safety and efficacy profile of fondaparinux
    B. The 2021 ACCP recommendations suggest fondaparinux as a possible option (compared to other anticoagulants) for those with superficial venous thrombosis (SVT) of the lower limb with concern for clot progression.
        1. This was based on the CALISTO study comparing fondaparinux v placebo in preventing VTE, recurrent SVT or extension int hose with SVT

V. Unfractionated Heparin (inpatient via IV, can be administered subcutaneous as outpatient)
    A. SC UFH is typically used inpatient for acute PE or for patient comfort rather than in the outpatient setting. Technically it can be administered in subcutaneous fashion as an outpatient to achieve therapeutic levels but requires frequent subcutaneous injections which is typically impractical for a patient. Other considerations for potentially choosing one anticoagulant regimen over another not discussed include the side-effect profile as well as the pharmacokinetics & pharmacodynamics of these medications.

Answer 2: *A first-line agent would be appropriate for Mr. S: Apixaban or Rivaroxaban.*

Scenario continued:
Mr. S was discharged on rivaroxaban and tolerated it well for three months. At his follow-up visit with you, a mutual decision is made to stop his anticoagulation due to the high risk of bleeding associated with his chosen profession. But before leaving, he confesses that he has been using 'Dr. Google' and has some questions to ask you based on his findings there:

Question 3: Are there any secondary prevention measures that he might be able to use while flying to soccer games that might prevent recurrence of VTE but have less bleeding risk than full anticoagulation?

In patients with unprovoked proximal DVT or PE (or those who have permanent risk factor for VTE) who are *stopping anticoagulant therapy* and do not have a contraindication to aspirin, current guidelines recommend aspirin over no aspirin to prevent recurrent VTE (Grade 2B). *NOTE: Aspirin is not an alternative to AC.* Additionally, though less relevant for this specific patient with a high-risk profession, low-dose anticoagulation (i.e., apixaban at 2.5 mg twice daily or rivaroxaban 10 mg daily) can also be considered in patients for who extended phase anticoagulation is recommended but who have clinical reasons to avoid full-dose anticoagulation (Stevens et al. 2021).

Aspirin for Secondary Prevention of VTE

I. INSPIRE/ASPIRE: International Collaboration of Aspirin Trials for Recurrent VTE: Aspirin for the Prevention of Recurrent Venous Thromboembolism. (Becattini et al., 2012; Brighton et al., 2012; Simes et al., 2014)
    A. Double-blind, randomized, placebo-controlled; 1224 patients evaluated for recurrent VTE at~30 months. Pooled results for various outcomes among the three studies: Aspirin reduced recurrent VTE 7.5%/yr versus 5.1%/yr; from 24 fewer cases per 1000 patients to 89 fewer per 1000 cases HR 0.65
II. Aspirin v. Rivaroxaban for Secondary prevention (Weitz et al., 2017):
    A. Patients who had received either 6 or 12 months of AC already, were randomized to either rivaroxaban 10mg or 20mg, or aspirin 100mg qD.
    B. Recurrent VTE at 12 months had occurred in 1.5% receiving 20 mg of rivaroxaban for & 1.2% receiving 10 mg of rivaroxaban, as compared with 4.4% receiving aspirin (hazard ratio for 20 mg of rivaroxaban vs. aspirin, 0.34; hazard ratio for 10 mg of rivaroxaban vs. aspirin, 0.26

Answer 3: *Given his choice of career, the bleeding risk may outweigh the benefit of AC or aspirin use. However, he should be encouraged to move during long flights and warned of the probable need for lifelong AC if VTE should recur.*

Question 4: Out of concern for his children, should he be tested for any inheritable causes of hypercoagulability that may have predisposed him to this presentation?

Inherited thrombophilia refers to a group of hereditary genetic mutations that generate increased risk of venous thromboembolism (VTE). These include Factor V Leiden, Prothrombin 20210, Protein C deficiency, Protein S deficiency, Antithrombin deficiency, and Methylenetetrahydrofolate reductase. Mr. S's question is often asked following diagnosis of an acute VTE, particularly when the patient with the VTE is young. However, ACCP guidelines recommend against testing routinely for these conditions, except perhaps in uniquely appropriate and equally rare situations, such as a pregnant woman with recurring VTE or unexplained etiology for multiple spontaneous abortions, or a woman with a known family history of VTE wanting to initiate either OCP or hormonal therapy.

In a large case-control study (MEGA) of patients with first time recurrence of VTE, thrombophilia tests were performed in 35% of cases and compared to 30% of controls (patients without recurrence), and the presence of testing was noted not to affect the rate of recurrence of VTE. The OR for recurrence was 1.2 for tested vs. non-tested patients (Coppens, Reijnders, Middeldorp, Doggen, & Rosendaal, 2008).

Regardless, by definition patients with first time *provoked* VTE likely have an explanation for development of VTE that is a more likely etiology than an undiagnosed thrombophilia. On the other hand, while patients with unprovoked VTE may indeed have an underlying inherited thrombophilia, inpatient testing is not indicated because results are not likely going to influence management since long-term anticoagulation will be the therapeutic recommendation.

Lastly, testing in hospitalized patients has even more limitations because many thrombophilia tests are inaccurate in the setting of acute VTE and/or anticoagulation (Petrilli et al., 2016).

TABLE 1. Limitations of Thrombophilia Workup in the Setting of Acute VTE or Anticoagulation

	Acute VTE	Anticoagulation With Warfarin	Anticoagulation With NOACs	Anticoagulation With Heparin/LMWH
FVL/PT20210/MTHFR gene mutations	No Impact	No Impact	No Impact	No Impact
Protein C*	Decreased	Decreased	No impact	No impact
Protein S*	Decreased	Decreased	No impact	No impact
ATIII activity	Decreased	Slight increase	Slight increase	Decreased
ATIII antigen	Decreased	Slight increase	Slight increase	Decreased

NOTE: **Abbreviations:** ATIII, antithrombin III deficiency; FVL, factor V Leiden gene mutation; LMWH, Low-molecular-weight heparin; MTHFR, methylenetetrahydrofolate reductase gene mutation; NOACs, novel oral anticoagulants (anti-Xa or direct thrombin inhibitors); PT20210, prothrombin 20210 gene mutation; VTE, venous thromboembolism.*Deficiency in both protein and functional assays.

Image of Table 1 from Petrilli et. al., 2016.

Answer 4: *Testing for thrombophilias is not indicated in this scenario. If the VTE or PE should recur, then he might be a candidate for testing.*

Question 5: What, if any, might be the long-term sequelae from having developed a VTE?

Chronic Thromboembolic Pulmonary Hypertension: It is estimated that approximately 3% of patients with acute symptomatic PE will develop CTEPH. Due to low prevalence and high rate of clearance of VTE with anticoagulation, screening for the condition is not recommended. In one prospective, multi-center cohort study, 157 patients with acute PE underwent follow-up CTPA-imaging after six months of anticoagulant treatment which demonstrated complete PE resolution in 84.1 % of the patients (95 % CI) (den Exter et al., 2015).

The diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation, to distinguish this condition from the cardiac findings of acute PE. As such, simple close clinical surveillance in the outpatient setting with follow-up visits is recommended.

Answer 5: *Minimal, if any, sequelae.*

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Pre/Post Test Questions:

1. A 60-year-old male with a history of diabetes and HTN has a new onset DVT post-op from a routine hernia repair. For how long should his anticoagulation be continued?
    a. 3 months
    b. 6 months
    c. 1 year
    d. Indefinitely

2. Which of the following patients is most likely to benefit from an extended course (>3 months) of anti-coagulation for DVT/PE?
    a. A 41-year-old male with a history of COPD has a CT chest for evaluation of mediastinal lymphadenopathy and has an incidentally discovered and asymptomatic subsegmental PE.
    b. A 32-year-old female who is 28 weeks pregnant has new onset dyspnea and a newly diagnosed PE. She has no other known risk factors.
    c. A 65-year-old male with a history of DVT one year ago (now off anticoagulation) and BPH has asymmetric LE edema and has a newly diagnosed DVT.
    d. A 85-year-old female with a history of an incidentally discovered subsegmental PE and history of recurrent diverticular bleeds.

3. Which of the following statements is true regarding the use of dabigatran for VTE?
    a. It is safe to use in patients with known renal dysfunction.
    b. The drug is metabolized by the kidney.
    c. It can be safely given to a patient being treated with first line therapy for TB.
    d. It can be safely given to a patient being treated for GERD with a PPI.