Pulmonary embolism: update on management and controversies

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ABSTRACT

Pulmonary embolism is a common and potentially fatal cardiovascular disorder that must be promptly diagnosed and treated. The diagnosis, risk assessment, and management of pulmonary embolism have evolved with a better understanding of efficient use of diagnostic and therapeutic options. The use of either clinical probability adjusted or age adjusted D-dimer interpretation has led to a reduction in diagnostic imaging to exclude pulmonary embolism. Direct oral anticoagulation therapies are safe, effective, and convenient treatments for most patients with acute venous thromboembolism, with a lower risk of bleeding than vitamin K antagonists. These oral therapeutic options have opened up opportunities for safe outpatient management of pulmonary embolism in selected patients. Recent clinical trials exploring the use of systemic thrombolysis in intermediate to high risk pulmonary embolism suggest that this therapy should be reserved for patients with evidence of hemodynamic compromise. The role of low dose systemic or catheter directed thrombolysis in other patient subgroups is uncertain. After a diagnosis of pulmonary embolism, all patients should be assessed for risk of recurrent venous thromboembolism to guide duration of anticoagulation. Patients with a venous thromboembolism associated with a strong, transient, provoking risk factor can safely discontinue anticoagulation after three months of treatment. Patients with an ongoing strong risk factor, such as cancer, or unprovoked events are at increased risk of recurrent events and should be considered for extended treatment. The use of a risk prediction score can help to identify patients with unprovoked venous thromboembolism who can benefit from extended duration therapy. Despite major advances in the management of pulmonary embolism, up to half of patients report chronic functional limitations. Such patients should be screened for chronic thromboembolic pulmonary hypertension, but only a small proportion will have this as the explanation of their symptoms. In the remaining patients, future studies are needed to understand the pathophysiology and explore interventions to improve quality of life.

Introduction

Venous thromboembolism, which includes deep venous thrombosis (DVT) and pulmonary embolism, is the third most common cardiovascular disorder and affects up to 5% of the population during their lifetime.[1] The increased sensitivity of imaging modalities has more than doubled rates of hospital admission for pulmonary embolism in the past 10 years, although the case fatality rate has remained stable or decreased.[2-4] Embolization of a DVT in the lower extremity into the pulmonary arteries is thought to be the most common mechanism for pulmonary embolism. Registry studies found that up to 17% of patients die within three months of diagnosis of venous thromboembolism,[5] although many of these deaths may be due to associated comorbidities rather than direct causation. For those patients included in the more recent large randomized controlled trials (RCTs), the three month all cause mortality has been approximately 2%.[6-9]

Careful clinical assessment is needed for diagnosis of pulmonary embolism, as the presentation can mimic other common medical conditions. Clinical probability scores in combination with D-dimer

testing improve the use and interpretation of diagnostic imaging.[10] Important recent advances in diagnosis of pulmonary embolism have been the use of clinical probability adjusted, or age adjusted, D-dimer interpretation.[11-13] Only a small proportion of patients with acute pulmonary embolism will have high risk features associated with short term clinical deterioration, but identification of such patients and consideration of therapies in addition to anticoagulation, such as thrombolysis, are important.[14-16] Various risk prediction scores, serum biomarkers, and imaging abnormalities such as right ventricular strain can identify patients at higher short term risk for all cause mortality.[10 14 16] What interventions can be made to alter this prognosis remains unclear.

The major advance in management for patients with pulmonary embolism in the past decade has been the introduction of direct oral anticoagulants (DOACs). This class of drugs includes direct Xa inhibitors (apixaban, edoxaban, rivaroxaban) and a direct thrombin inhibitor (dabigatran). Large RCTs have shown these therapies to be non-inferior to vitamin K antagonists (warfarin).[6-8 17] Rates of major bleeding seem to be similar or reduced in patients treated with DOACs compared with warfarin, but whether this is a class effect or whether differences exist between drugs is uncertain. Duration of anticoagulation should be determined after weighing the risk of recurrent venous thromboembolism against the risk of bleeding, along with the associated morbidity and mortality of each outcome. In the era of DOAC therapy, weighing the risk of recurrent venous thromboembolism against that of bleeding remains a challenge as data on bleeding risk and direct comparisons between types and doses of DOACs are lacking. This review is aimed at clinicians caring for patients with pulmonary embolism and researchers interested in recent advances in its management.

Epidemiology

The annual incidence of pulmonary embolism in the population is 1 per 1000 people, but this increases sharply with age, from 1.4 per 1000 people aged 40-49 to 11.3 per 1000 aged 80 years or over.[1 18 19] Recurrent venous thromboembolism occurs in 30% of people, making the attack rate (including incident and recurrent venous thromboembolism) higher, estimated as up to 30 per 1000 person years.[19] The influence of race on venous incidence of thromboembolism is uncertain, but incidence may be higher in white and African-American populations and lower in Asians and Native Americans.[19] Overall, the incidence of venous thromboembolism in men is slightly higher than in women, but the balance changes according to age categories.[19] Among women under 45 years or over 80 years, the incidence of venous thromboembolism is higher than in men. This interaction with age and sex is likely related to estrogen and pregnancy related risk factors at a young age and longer life expectancy of women at advanced ages. Vital registration data indicate that women aged 15-55 and over 80 years have an excess pulmonary embolism related mortality compared with men.[20] Although increased incidence of pulmonary embolism in women among both of these age groups may be contributing to this, whether true sex and/or gender differences exist in case fatality rates remains to determined. Data from registry studies have suggested a higher in-hospital and 30 day pulmonary embolism related mortality in women,[21] whereas other studies have not observed a difference.[22] Subgroup analyses of RCTs comparing warfarin and DOAC therapy have not suggested a difference.

Fifty per cent of venous thromboembolism events are associated with a transient risk factor, such as recent surgery or hospital admission for medical illness, 20% are associated with cancer, and the remainder are associated with minor or no risk factors and are thus classified as unprovoked.[23] Box 1 summarizes common risk factors for venous thromboembolism.[19 24] Despite comprehensive literature on the epidemiology of venous thromboembolism and its risk factors, public awareness is poor compared with other health conditions with comparable incidence. This was illustrated in an international survey of more than 7000 people in nine countries. Half of respondents had no awareness of venous thromboembolism conditions and risk factors, and less than 30% knew the signs and symptoms of venous thromboembolism.[25]

Box 1: Transient risk factors for venous thrombosis[16]

Strong risk factor (odds ratio >10)
- Hip or leg fracture
- Hip or leg joint replacement
- Major general surgery
- Major trauma
- Spinal cord injury

Moderate risk factor (odds ratio 2-9)
- Arthroscopic knee surgery
- Central venous lines
- Congestive heart or respiratory failure
- Hormone replacement therapy
- Malignancy
- Oral contraceptive therapy
- Paralytic stroke
- Postpartum
- Previous venous thromboembolism
- Thrombophilia

Weak risk factor (odds ratio <2)
- Bed rest >3 days
- Immobility due to sitting (eg, prolonged road or air travel)
- Increasing age
- Laparoscopic surgery (eg, cholecystectomy)
- Obesity
- Pregnancy (antepartum)
- Varicose veins

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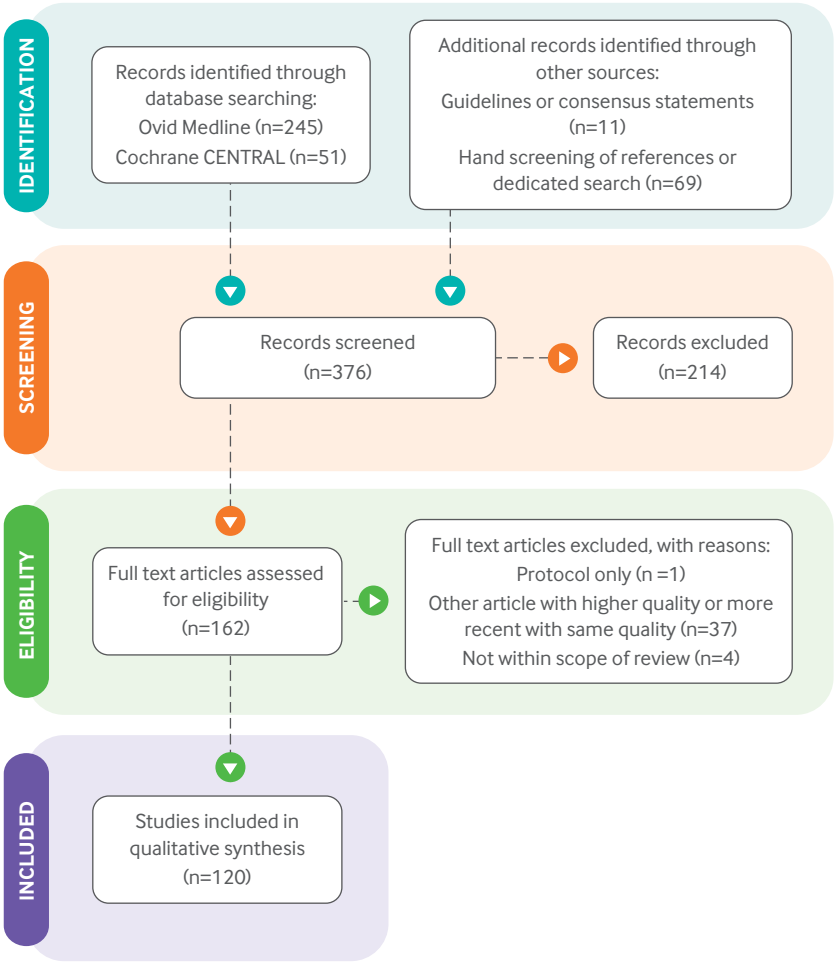

Fig 1 | PRISMA flow diagram

Sources and selection criteria

We searched Ovid Medline, Cochrane CENTRAL, and other non-indexed citations from 1 January 2010 to 7 August 2019 to find English language systematic reviews, meta-analyses, and RCTs that evaluated management of pulmonary embolism. We included clinical practice guidelines (American College of Chest Physicians, American Society of Hematology, and European Society of Cardiology), as well as screening them to identify additional studies. We used Ovid Medline and PubMed for dedicated search strategies of selected topics thought not to be included in the above search. These topics included inferior vena cava filters, bleeding and anticoagulation, post-thrombotic syndrome, post-pulmonary embolism syndrome, chronic thromboembolic pulmonary hypertension, quality of life and patient experience, cancer, inherited thrombophilia, and antiphospholipid syndrome. A health sciences librarian did all the searches. Additional references were suggested during the peer review process.

Two authors (LD and LAC) independently evaluated the 360 non-duplicate references retrieved and identified 162 articles as potentially related to our overview. We focused our search on systematic reviews and meta-analyses judged to be of medium or high quality by the AMSTAR tool or as of acceptable quality by the SIGN-50 tool.[26 27] When multiple systematic reviews or meta-analyses covered the same topic, we chose the study with the best methodological quality; when studies had similar quality, we chose the most recent. If topic advances were not fully covered by a systematic review, meta-analysis, or RCT, we included observational studies or expert consensus and opinion. In the end, 11 endorsed clinical practice guidelines/consensus statements, 24 systematic reviews/meta-analysis, 25 randomized trials, 39 prospective studies, and 21 retrospective/secondary analysis studies informed our overview (fig 1). We also included six actively recruiting clinical trials, identified using NCT registration numbers (clincaltrials.gov). These registered clinical trials were either selected by the authors or suggested through the peer review process as having the potential to affect the field, and the conclusions of this review, on completion. After this review was accepted for publication, one of these clinical trials, CARAVAGGIO, was completed and its results published; we updated the manuscript to include the details of this trial and its results.

Diagnosis

Prompt recognition of a constellation of nonspecific signs and symptoms is needed for diagnosis of pulmonary embolism. Prompt initiation of anticoagulation while awaiting investigations is prudent because of the high risk of early mortality with untreated pulmonary embolism.[28-30] Although this approach for starting anticoagulation in patients in whom a pulmonary embolism is suspected has been shown to be safe in outpatient settings,[31] risks of bleeding and overuse of diagnostic tests remain. Inappropriately proceeding down a diagnostic pathway for pulmonary embolism may also distract clinicians from identifying the alternative causes of the symptoms.

Clinical probability scores

Clinical probability scores can be used to assign a pre-test probability for pulmonary embolism. Consideration of the probability of pulmonary embolism before testing (that is, pre-test probability) avoids unnecessary testing and is critical to the interpretation of results. This was first illustrated in the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study. A high probability planar ventilation-perfusion lung scan was almost as likely to give a false positive result as a true positive one if the pre-test probability was low, with 44% having no evidence of pulmonary embolism on angiography. Conversely, with a low probability ventilation-perfusion lung scan and a high pre-test probability, 60% had pulmonary embolism by angiography.[32]

The Geneva and Wells rules are among the most commonly cited clinical probability scores (table 1).[10 34 37] Both the Geneva rule and the Wells rule have been studied in more than 55 000 patients and have been shown to be reliable, accurate, and superior to a gestalt, non-standardized, clinical assessment.[37]

Table 1 | Comparison of pulmonary embolism clinical probability scores

Variable	Points
Modified Geneva rule*[33]	
Age ≥65 years	1
Previous DVT or PE	3
Surgery or fracture within 1 month	2
Active cancer	2
Unilateral lower limb pain	3
Pain on deep palpation of lower limb and unilateral edema	4
Hemoptysis	2
Heart rate 75-94 beats/min	3
Heart rate ≥95 beats/min	5
Simplified Geneva rule†[34]	
Age >65 years	1
Surgery or fracture within 1 month	1
Active cancer	1
Unilateral lower limb pain	1
Hemoptysis	1
Pain on deep vein palpation of lower limb and unilateral edema	1
Heart rate 75-94 beats/min	1
Heart rate >94 beats/min	2
Wells rule‡[35 36]	
Signs or symptoms of DVT	3
Alternative diagnosis is less likely than PE	3
Heart rate >100 beats/min	1.5
Immobilization/surgery in previous 4 weeks	1.5
History of DVT or PE	1.5
Hemoptysis	1
Active cancer	1

DVT=deep venous thrombosis; PE=pulmonary embolism.
*Using modified score, <3 points indicates low probability, 4-10 points indicates intermediate probability, and >10 points indicates high probability. Using simplified score, ≤2 points indicates that PE is unlikely.
†Using simplified score, ≤2 points indicates that PE is unlikely.
‡Using traditional score, >6.0 points indicates high probability, 2.0-6.0 points indicates moderate probability, and <2.0 points indicates low probability of PE. Using simplified score, >4 points indicates that PE is likely and ≤4 points indicates that PE is unlikely.

An adaption of the Wells rule, keeping three items only (clinical signs of DVT, hemoptysis, and whether pulmonary embolism is the most likely diagnosis), the YEARS rule, has been evaluated in one observational study of 3465 patients with suspected pulmonary embolism.[13] In this study, pulmonary embolism was excluded if patients had either absence of all three criteria and a D-dimer less than 1000 ng/mL or one or more criteria and a D-dimer less than 500 ng/mL. Of the patients in whom pulmonary embolism was ruled out at baseline and remained untreated, 0.61% (95% confidence interval 0.36% to 0.96%) were diagnosed as having venous thromboembolism during the three month follow-up. Limitations of this study include that investigators were not blinded to the D-dimer results when making the assessment of the most likely diagnosis, small numbers of patients with cancer, and the absence of a control arm.

Despite the routine use of clinical probability scores, only 8% of patients in the US and 27% in Europe investigated for pulmonary embolism will have the diagnosis confirmed.[38] To overcome this, the pulmonary embolism rule-out criteria (PERC rule) were studied in a crossover cluster RCT of 1916 patients who were judged by treating physicians to have a gestalt probability of pulmonary embolism of less than 15%.[39] The PERC rule consists of eight clinical variables (hypoxia, unilateral leg swelling, hemoptysis, previous venous thromboembolism, recent surgery or trauma, age >50, hormone use, tachycardia), and further testing (D-dimer and/or imaging) was withheld if all eight variables were absent. This study showed that in patients deemed to be at very low risk of pulmonary embolism by gestalt, the PERC rule was non-inferior to standard of care for the primary outcome of venous thromboembolism rate during three months of follow-up (mean difference 0.2, one sided upper 95% confidence limit 1.6%). The PERC rule should not be applied to patients at higher risk of pulmonary embolism, defined as gestalt pre-test probability of pulmonary embolism higher than 15%.

D-dimer testing

Physiologically, the activation of coagulation and generation of cross linked fibrin simultaneously leads to the activation of fibrinolysis. The D-dimer is a degradation product of fibrinolysis and is increased in patients with acute venous thromboembolism as well other non-thrombotic disorders.[40] D-dimer is a helpful diagnostic tool, and a negative value in combination with a low clinical probability score is useful for excluding a diagnosis of venous thromboembolism. D-dimer should not be used as a screening tool in patients in whom venous thromboembolism is not clinically suspected. Clinicians should assess the clinical pre-test probability of pulmonary embolism before ordering D-dimer testing, as knowledge of D-dimer results can influence the assessment of the clinical probability score.[41]

D-dimer is a sensitive but not specific diagnostic test. Improvements to the specificity can be made by using a dichotomized cut-off value according to the pre-test probability. A recent observational study of 2017 patients with suspected pulmonary embolism showed that a cut-off of 1000 ng/mL in patients with a low pre-test clinical probability score (traditional Wells) and 500 ng/mL in patients with a moderate clinical probability score could safely exclude pulmonary embolism without the need for further diagnostic imaging.[11] All other patients (high clinical probability score) underwent diagnostic imaging. In this study, no patients with low or moderate clinical probability score had a recurrent venous thromboembolism event in the three months of study follow-up (0%, 95% confidence interval 0.00% to 0.29%) and the dichotomized D-dimer cut-off strategy reduced the use of diagnostic imaging by 17.6% (15.9% to 19.2%) compared with the reanalysis of results with a single 500 ng/mL cut-off. Alternatively, D-dimer concentrations increase with age, and specificity can be improved with an age adjusted cut-off value.[42] An observational study of 3346 patients evaluated an age adjusted D-dimer (500 µg/L cut-off for patients ≤50 or age×10 µg/L for patients >50 years), whereby patients with a negative D-dimer and an unlikely (Wells) or non-high (revised Geneva) clinical probability did not undergo diagnostic imaging.[12] This age adjusted D-dimer approach increased the number of patients

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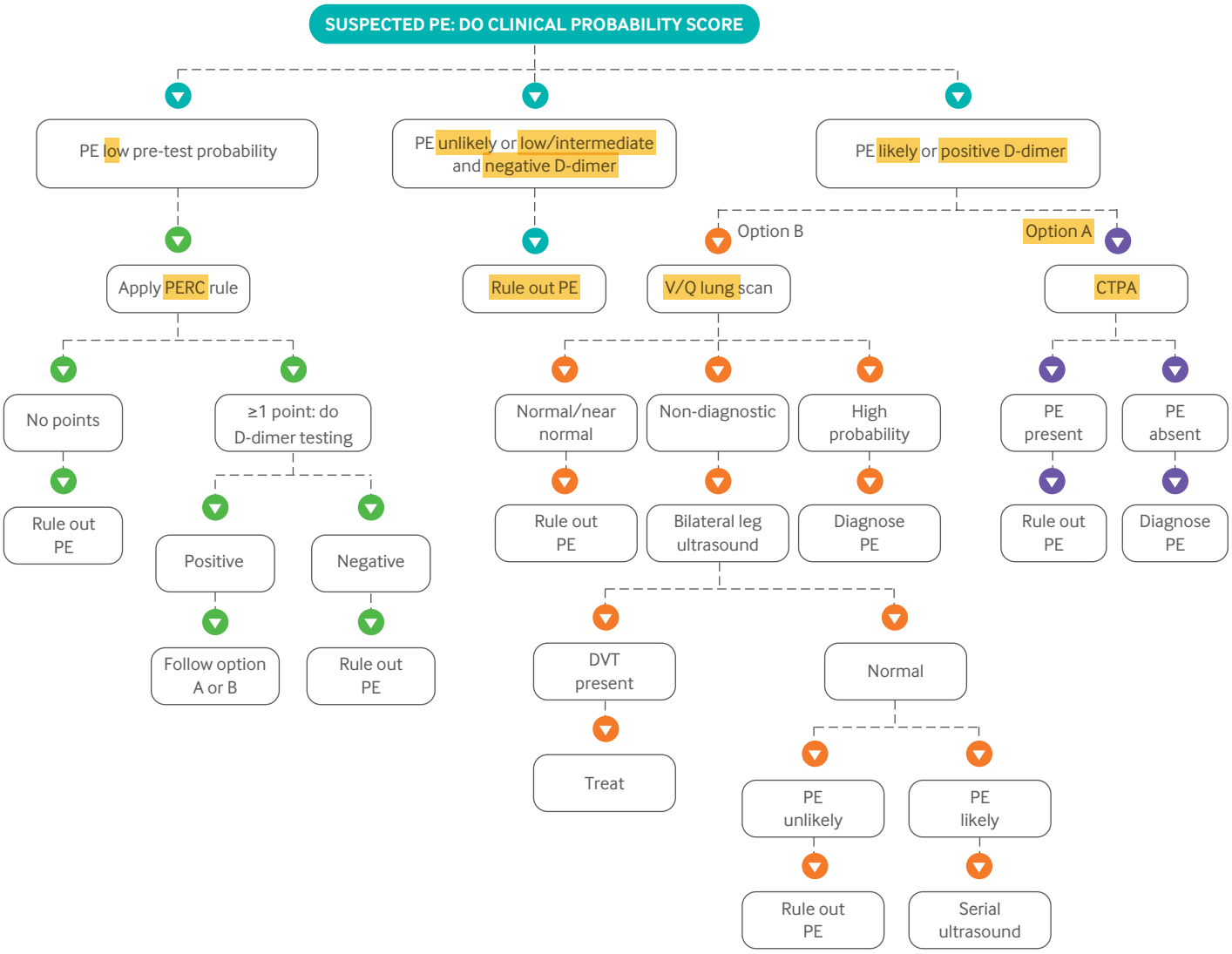

Fig 2 | Diagnostic work-up of patients with suspected pulmonary embolism (PE). CTPA=computed tomography pulmonary angiography; PERC=pulmonary embolism rule-out criteria; V/Q=ventilation-perfusion. Adapted from Wells PS, et al. *Ann Intern Med* 2018[44]

in whom pulmonary embolism could be excluded without diagnostic imaging from 6% to 30% without additional false negative findings. The three month venous thromboembolism rate in patients with a D-dimer concentration higher than 500 µg/L but below the age adjusted cut-off was 1 in 331 patients (0.3%, 0.1% to 1.7%).

Imaging for suspected pulmonary embolism

The gold standard diagnostic test for pulmonary embolism has historically been interventional pulmonary angiography. This invasive procedure has been largely abandoned, and diagnostic management studies have used the clinical safety measurement of frequency of venous thromboembolism events in the three months after evaluation in patients in whom pulmonary embolism is considered ruled out. The target is to match what was historically observed in similar patients after a negative pulmonary angiography—that is, 1.6% (0.3% to 2.9%) venous thromboembolism rate in the three month follow-up period.[43] Planar ventilation-perfusion lung scans and computed tomography pulmonary angiography (CTPA) are validated imaging tests. Both should be used in combination with the probability scores and D-dimer testing to accurately interpret results, as both false negative and false positive results can be observed when test results are discordant with clinical probability scores (fig 2).[44]

On the basis of a meta-analysis of observational and randomized studies, a normal CTPA is associated with a pooled incidence of venous thromboembolism at three months of 1.2% (0.8% to 1.8%) and negative predictive value of 98.8% (98.2% to 99.2%).[45] A ventilation-perfusion lung scan in a validated diagnostic algorithm performs equally well as CTPA in the diagnosis of pulmonary embolism.[46-48] Patients with pulmonary embolism excluded by a diagnostic algorithm combining ventilation-perfusion lung scan, D-dimer, compression ultrasound, and clinical probability score had an incidence of venous thromboembolism at three months of 0.1% (0.0% to 0.7%) with a negative predictive value of 99.5% (99.1% to 100%).[48]

An RCT comparing CTPA and ventilation-perfusion lung scanning found that CTPA detected 5% (1.1% to 8.9%) more pulmonary embolisms, but patients in whom pulmonary embolism was excluded by a diagnostic algorithm based on ventilation-perfusion lung scanning did not have a higher three month incidence of venous thromboembolism during follow-up: 2/561 (0.4%) patients randomized to CTPA versus 6/611 (1.0%) patients undergoing ventilation-perfusion lung scan (difference −0.6%, −1.6% to 0.3%).[46] This calls into question the clinical significance of these pulmonary embolisms "missed" by ventilation-perfusion lung scans. Nevertheless, the wide availability, fewer non-diagnostic results, and ability to provide alternative diagnoses have made CTPA the most common diagnostic modality. Important limitations to CTPA, however, should cause clinicians to reassess this shift in choice of tests, including exposure to ionizing radiation and risk of secondary malignancy,[49] renal toxicity with pre-existing renal disease, and risk of over-diagnosis and over-treatment of clinically insignificant pulmonary embolism.

Single photon emission computed tomography (SPECT) ventilation-perfusion scanning is proposed as an alternative to planar ventilation-perfusion scanning, as this technique may reduce the proportion of non-diagnostic results. The technique and diagnostic criteria for reporting SPECT ventilation-perfusion scans are variable and have not been validated sufficently.[16] On this basis, we suggest favoring planar ventilation-perfusion lung scans over SPECT.

Diagnosis of pulmonary embolism in pregnancy

Pregnancy and the postpartum period confer an increased risk of venous thromboembolism, but only 4-7% of women investigated are diagnosed as having pregnancy associated pulmonary embolism.[50 51] Diagnosing pulmonary embolism in pregnancy is challenging, as shortness of breath and lower extremity swelling are common complaints and D-dimer concentration is increased in normal pregnancies. Diagnostic management studies have either excluded or included very few pregnant women, and safe diagnostic strategies were lacking until recently. Two large observational studies specific to pregnant women have recently been published. The first evaluated the use of the modified Geneva score and a high sensitivity D-dimer in 441 pregnant patients.[51] Women with a low or intermediate clinical probability and negative D-dimer (<500 µg/L) had pulmonary embolism excluded; all others underwent bilateral lower limb compression ultrasonography and, if this was negative, CTPA. Although this approach was safe, with no venous thromboembolism events (0.0%, 0.0% to 1.0%), in three months of follow-up among untreated women in whom pulmonary embolism was excluded, the algorithm could avoid diagnostic imaging in only 10% of patients. This was because D-dimer testing was positive in 87% of women who underwent testing and was more likely to be positive with advanced gestation.

A second observational study of 510 pregnant women applied the YEARS probability score and D-dimer with a stratified cut-off (1000 ng/mL if no criteria were met or 500 ng/mL if one or more criteria were met).[50] Compression ultrasonography was performed only in women with symptoms of DVT. Using this approach, 39% of women were able to avoid diagnostic imaging, with an acceptably low three month venous thromboembolism incidence of 0.21% (0.04% to 1.2%). Furthermore, post hoc retrospective application of this pregnancy adapted YEARS algorithm to the cohort of patients in the first study showed similar findings, with 21% of women meeting criteria for exclusion of pulmonary embolism without diagnostic imaging and no venous thromboembolism events during follow-up.[52] Limitations of these studies include relative small sample sizes and possible bias for inclusion of patients at lower risk. Nevertheless, a pregnancy adapted YEARS algorithm seems to be safe and effective at reducing the need for diagnostic imaging in some patients.

Diagnostic imaging choices for suspected pulmonary embolism in pregnancy are similar to those in non-pregnant patients. Pregnancy alone does not increase the occurrence of non-diagnostic imaging results, and both ventilation-perfusion lung scans and CTPA are safe and accurate diagnostic imaging modalities in pregnancy.[53 54] Fetal exposure to radiation is well under acceptable limits for both tests.[53] Given the younger age, and thus longer lifetime risk for secondary malignancies, we favor the use of ventilation-perfusion lung scans in pregnant women, a position similar to the American Society of Hematology guidelines.[53] First investigating for DVT with compression ultrasonography can be considered in patients who have symptoms suggestive of a DVT. The absence of DVT does not exclude the need for chest imaging, but if a proximal DVT is confirmed then a presumptive diagnosis of pulmonary embolism may be made without dedicated imaging.

Thrombophilia testing

Family history of venous thromboembolism portends higher risk,[55] particularly when the venous thromboembolism is unprovoked or the patient is under 50 years of age.[56] Despite this, considerable controversy remains around the value of inherited thrombophilia testing (factor V Leiden mutation, prothrombin gene mutation, protein C deficiency, protein S deficiency, and antithrombin deficiency), as evidence suggests that the presence of thrombophilia does not alter management.[56] Furthermore, thrombophilia testing does not identify all inherited causes of venous thromboembolism.[57 58] This is illustrated by the observation that only 30% of people with a family history of a first degree relative with venous thromboembolism will have a positive thrombophilia screen.[59]

Patients who have a venous thromboembolism diagnosed in the context of a strong provoking risk

factor, such as major surgery, are at a low risk for recurrence, and this risk is not significantly altered by the presence of an inherited thrombophilia.[56] Patients who have a venous thromboembolism that is classified as unprovoked are at a significant increased risk of recurrence, but testing for inherited thrombophilia has not been shown to alter this risk in a way that might guide decisions about duration of anticoagulation.[60 61] Relatives identified as asymptomatic carriers of thrombophilia are at increased lifetime risk of venous thromboembolism (factor V Leiden mutation: 0.58-0.67% per year; protein C deficiency: 1.0-2.5% per year; protein S deficiency: 0.7-2.2% per year; antithrombin deficiency: 4% per year), but half of all events occur with additional provoking risk factors.[62] The presence of a positive family history remains significant, as such patients are more likely to develop a venous thromboembolism event compared with those with an inherited thrombophilia with no family history.[59 62] How thrombophilia testing informs the care of family members without symptoms beyond consideration of the risk imposed by a positive family history is therefore unclear.

If thrombophilia testing is used, it should be done after completion of treatment for an acute venous thromboembolism event and preferably in the absence of anticoagulation therapy, as false positive results are associated with warfarin (protein C deficiency, protein S deficiency), heparin (lupus anticoagulant), and DOACs (lupus anticoagulant).[56] We suggest that inherited thrombophilia testing should not be done when venous thromboembolism is associated with a strong provoking factor, as such patients have a low risk of recurrent venous thromboembolism, even when an inherited thrombophilia is identified.[60] We also suggest that thrombophilia testing should not be done in patients with unprovoked venous thromboembolism who already have an indication for long term anticoagulation (based on sex or risk predictions scores). In the remaining patients with unprovoked venous thromboembolism and no indication for indefinite anticoagulation, we suggest discussing inherited thrombophilia testing with them. In most cases, testing will not change the decision on duration of anticoagulation, but rare exceptions include high risk inherited thrombophilia such as antithrombin deficiency, or combined thrombophilia. In the absence of high quality evidence, the patient's preference should be considered in such decisions. Genetic counseling should be offered to patients undergoing testing, with acknowledgment of the psychological effects such results can have.[63-66]

Antiphospholipid syndrome

Antiphospholipid syndrome is a thrombophilia that should be considered separately. It is acquired, so most affected people will not have a family history of venous thromboembolism. Antiphospholipid syndrome is thought to be associated with a high risk for both recurrent venous thromboembolism and arterial thrombosis.[67] The presence of persistently elevated antiphospholipid antibodies with a first venous thromboembolism is an acceptable indication for indefinite duration of anticoagulation.[16 67] A diagnosis of antiphospholipid syndrome is made on the basis of laboratory and clinical criteria.[68] Laboratory criteria include the presence of at least one associated antibody on two or more occasions and at least 12 weeks apart: lupus anticoagulant (detected according to the guidelines of the International Society on Thrombosis and Hemostasis (ISTH)),[69] anti-β2-glycoprotein I (>99th centile of controls), or anti-cardiolipin antibodies (>40 GPL units or >99th centile of controls). Clinical criteria include one or more episodes of arterial, venous, or small vessel thrombosis or one or more defined pregnancy morbidities. In patients presenting with an unprovoked venous thromboembolism event, 6% of patients overall and up to 19% of those under 50 years old will meet the criteria for antiphospholipid syndrome.[70 71]

The identification of antiphospholipid syndrome may be important to guide decisions on choice of anticoagulant therapy. A randomized controlled, non-inferiority trial compared rivaroxaban and warfarin in patients with high risk antiphospholipid syndrome, defined as positive for all three laboratory criteria, for the primary outcome of cumulative incidence of thrombotic events, major bleeding, and vascular death.[72] This trial was terminated after 120 patients were enrolled, as interim analyses showed excess events in the rivaroxaban arm (hazard ratio 6.7, 95% confidence interval 1.5 to 30.5). All trial participants discontinued the assigned study drug and switched to a non-study vitamin K antagonist (VKA). Another non-inferiority RCT of 190 patients with thrombotic antiphospholipid syndrome (required one laboratory criterion: lupus anticoagulant, or moderate to high titer IgG anti-cardiolipin or anti-β2-glycoprotein I antibodies), randomized participants to rivaroxaban or warfarin.[73] The primary outcome of proportion of patients with new thrombotic events during three years of follow-up occurred more frequently in the rivaroxaban arm (risk ratio 1.83, 0.71 to 4.76). Most patients (96%) were positive for lupus anticoagulant, and 60% were triple positive. Both trials showed a trend of increased arterial rather than venous thrombotic events.

Given the high prevalence of antiphospholipid syndrome among patients under 50 years old with unprovoked venous thromboembolism, and implications for duration and choice of anticoagulation, screening for antiphospholipid syndrome should be considered in these patients. Further studies are needed to determine the efficacy of DOACs in lower risk antiphospholipid syndrome (for example, non-lupus anticoagulant, IgM class, and low titer antibodies) and to identify subpopulations of patients with antiphospholipid syndrome in whom DOACs might be acceptable (for example, non-arterial thrombotic history). Until such time, we discuss the risk and benefits of therapeutic

options with patients with venous thromboembolism associated with antiphospholipid syndrome and suggest the use of VKAs over other therapies in most patients with antiphospholipid syndrome associated with lupus anticoagulant and triple positive serology.

Diagnosis of recurrent pulmonary embolism

Patients who have a history of a previous DVT or pulmonary embolism are at a lifetime increased risk of recurrent events.[29 74] Anticoagulation reduces the incidence of recurrent venous thromboembolism by about 80-85%.[75] Nevertheless, patients often present with symptoms of recurrent DVT and pulmonary embolism, and differentiating symptoms related to chronic complications of venous thromboembolism, such as post-thrombotic syndrome and post-pulmonary embolism syndrome, represents a diagnostic challenge. Because a history of previous venous thromboembolism is a variable in some clinical probability scores (table 1), such patients are often categorized as having a high probability, necessitating further diagnostic imaging. The most commonly used clinical probability scores were derived in, and are therefore generalizable to, cohorts that included patients with previous venous thromboembolism. Additionally, the D-dimer concentration remains elevated in many patients after completion of a standard treatment course for acute venous thromboembolism, limiting its usefulness for excluding recurrent events.[76 77] Nevertheless, in a combined subgroup analysis of observational studies (1721 patients in total), patients with a previous history of venous thromboembolism and clinically suspected pulmonary embolism (306 patients) were safely managed using a clinical probability and D-dimer diagnostic approach (three month venous thromboembolism incidence in patients with pulmonary embolism excluded by negative D-dimer 0%, 0% to 7.9%). However, only 16% (compared with 33% of those without previous venous thromboembolism history) were able to have pulmonary embolism excluded without imaging tests.[78] Another observational study included 516 patients with clinically suspected recurrent pulmonary embolism while not on anticoagulation therapy.[79] This diagnostic strategy excluded pulmonary embolism on the basis of a Wells pulmonary embolism score of 4 or lower ("pulmonary embolism unlikely") and a negative D-dimer test; all other patients underwent CTPA. The prevalence of pulmonary embolism in the study was 33%, and the primary outcome of three month recurrent venous thromboembolism in patients with pulmonary embolism excluded was 2.8% (1.2% to 5.5%). The strategy was able to exclude pulmonary embolism without imaging tests in only 17% of patients. Additionally, none of the patients was on anticoagulation at the time of D-dimer testing, so whether this strategy can be generalized to patients who are on anticoagulation is unknown. We support the position endorsed by the ISTH that a combination of low clinical probability score and negative D-dimer test can be used to exclude pulmonary embolism in patients with a history of previous venous thromboembolism, but patients with an intermediate or high clinical probability score should undergo diagnostic imaging.[76]

As residual defects often persist on CTPA and ventilation-perfusion lung scans six to 12 months after the initial diagnosis, interpretation of diagnostic imaging for suspected recurrent events requires prudent comparison with previous imaging to prevent over-diagnosis. The rate of complete resolution on baseline imaging varies from about 50% to 84%.[80-83] Differentiating acute pulmonary embolism from residual thrombi is difficult, and inter-observer agreement between radiologists is poor.[82] Characteristics of thrombi such as density, intramural calcification, or eccentric filling defects have been proposed but never validated.[76] We would advise caution in relying on such descriptive features. The availability, and careful review with an experienced radiologist, of previous imaging and ideally baseline imaging performed six to 12 months after an acute pulmonary embolism is advised when evaluating a patient for recurrent pulmonary embolism and has been shown to be a safe and accurate approach.[84] We routinely do a baseline ventilation-perfusion lung scan six to 12 months after an acute pulmonary embolism. Although this may not be a widely adopted approach, the risk of radiation exposure with ventilation-perfusion lung scans is low and the availability of such baseline imaging has been shown to improve the interpretation of diagnostic tests for suspected recurrent venous thromboembolism.[84 85]

Initial treatment for pulmonary embolism

Pulmonary embolism risk assessment

Pulmonary embolism remains a heterogeneous condition, ranging from presentation with sudden death to incidental findings with no symptoms. Initial hemodynamic instability, defined as systolic blood pressure below 90 mm Hg for 15 minutes or more, is an important marker of prognosis. However, this presentation is uncommon, being found in only 5% of cases; the short term mortality exceeds 15%.[14-16 86] For the remaining 95% of cases, several risk prediction scores have been proposed to estimate the risk of an adverse outcome (table 2).[33 88-90]

A systematic review assessing the characteristics and quality of pulmonary embolism risk prediction scores identified 17 models in the literature.[91] Of these, the Pulmonary Embolism Severity Index (PESI) and the simplified-PESI (sPESI) had the most robust evidence and validation. Both risk prediction scores were able to differentiate between low and high risk of 30 day mortality in patients with pulmonary embolism.[91] The PESI and the Hestia criteria have been used in randomized studies to select patients with low risk pulmonary embolism suited to outpatient care (discussed below).[92 93] Biomarkers have also been studied. A systematic review of cardiac troponin as a predictor of early mortality showed that in patients otherwise classified as being

Table 2 | Comparison of pulmonary embolism risk prediction scores

Variable	Points
Pulmonary Embolism Severity Index (PESI)*[87]	
Age, per year	Age, in years
Male sex	+10
History of cancer	+30
History of heart failure	+10
History of chronic lung disease	+10
Pulse rate ≥110/min	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate ≥30/min	+20
Temperature <36°C	+20
Altered mental status	+60
Arterial oxygen saturation <90%	+20
Simplified Pulmonary Embolism Severity Index (sPESI)†[88]	
Age >80 years	1
History of cancer	1
History of chronic lung disease	1
Pulse rate ≥110 beats/min	1
Systolic blood pressure <100 mm Hg	1
Arterial oxygen saturation <90%	1
Hestia criteria‡[89]	
Is the patient hemodynamically unstable?	–
Is thrombolysis or embolectomy necessary?	–
Active bleeding or high risk of bleeding?	–
>24 h of oxygen supply to maintain oxygen saturation >90%?	–
Is pulmonary embolism diagnosed during anticoagulant treatment?	–
Severe pain needing intravenous pain medication for >24 h?	–
Medical or social reason for treatment in the hospital for >24 h (infection, malignancy, no support system)?	–
Does the patient have a creatinine clearance of <30 mL/min?	–
Does the patient have severe liver impairment?	–
Is the patient pregnant?	–
Does the patient have a documented history of heparin induced thrombocytopenia?	–

*66-85 class I; 86-105 class II; 106-125 class III; >125 class IV; class V. Class I and II defined as low risk.
†0 low risk; ≥1 high risk.
‡Yes to any question, admission required.

at low risk by the PESI or sPESI score, the presence of a positive troponin had a pooled fivefold increased odds of 30 day mortality (odds ratio 4.79, 1.11 to 20.68), although the wide confidence interval casts doubt on the reliability of this estimate.[94]

Other prognostic markers have been proposed for risk stratification, including B-type natriuretic peptide and N-terminal pro-b-type natriuretic peptide (NT-proBNP). Evidence of right ventricular dysfunction by echocardiography and CTPA are also indicators of worse prognosis.[16 95] The combination of the prognostic markers of positive cardiac troponin and right ventricular dysfunction was used in an RCT of 1005 patients identified as having "intermediate risk" pulmonary embolism who were candidates for thrombolysis therapy.[96] The results of the thrombolysis arm are discussed below in the section "Thrombolytic therapy for pulmonary embolism." In the control arm, a 5% rate of hemodynamic decompensation (25/499 patients) was seen within the first seven days; most of these patients (23/499) went on to need rescue thrombolytic therapy. Although this observation might justify the combination of right ventricular dysfunction and cardiac troponin as predicators of early decompensation, whether clinical characteristics alone would have also identified these patients at high risk is unclear. Although opinion on their usefulness diverges, right ventricular imaging and cardiac biomarkers may be considered for selecting patients who need cardiac monitoring, should close follow-up be unavailable.

Outpatient versus inpatient management of acute pulmonary embolism

Risk stratification has been used to identify patients with a low short term mortality risk to select for outpatient management. The availability of DOACs has simplified outpatient management of pulmonary embolism because some DOACs do not require initial self-administration of parenteral therapies. RCTs have compared outpatient versus inpatient management of pulmonary embolism and found no difference in outcomes in selected patients. A randomized controlled non-inferiority trial allocated 344 patients with low risk pulmonary embolism (PESI class I or II; table 2) to inpatient or outpatient treatment, with patients in both arms receiving low molecular weight heparin before transition to an oral agent.[92] No significant difference was seen in the primary outcome of three month incidence of recurrent venous thromboembolism in outpatients versus inpatients (difference 0.6%, 95% upper confidence limit 2.7%, meeting non-inferiority margin of 4%). The Hestia criteria (table 2) have been combined with cardiac troponin and NT-proBNP, with no added benefit of either marker seen compared with the Hestia criteria alone.[93 97] An RCT

of 114 patients with low risk pulmonary embolism, no Hestia criteria, and a negative troponin reported a reduction in the primary outcome of time spent in the hospital for venous thromboembolism or bleeding events 30 days after randomization (difference 28.8 (95% confidence interval 16.2 to 41.5) hours lower in outpatient arm). No difference was seen in the three month event rate of venous thromboembolism (predefined secondary outcome).[93] A non-inferiority RCT of 550 patients with no Hestia criteria and negative NT-proBNP compared inpatient and outpatient treatment. The composite primary outcome was 30 day pulmonary embolism or bleeding related mortality, cardiopulmonary resuscitation, or intensive care unit admission.[97] Although the lower than expected positive NT-proBNP concentrations (12% *v* 40% expected) prevented the trial from being powered to conclude non-inferiority, the primary endpoint occurred in none of the 275 patients (0%, 0% to 1.3%) who had NT-proBNP testing, compared with 3/275 patients (1.1%, 0.2% to 3.2%) in the direct discharge group (P=0.25). The authors speculate that the lower than expected positive biomarkers observed could be because the Heista criteria alone identified a low risk population, so lower amounts of NT-proBNP were detected. On the basis of this evidence, we support the recommendations for outpatient management of pulmonary embolism.[14 16] The identification and outpatient management of appropriate pulmonary embolisms will represent a significant cost savings without compromise to patient safety.[98]

Subsegmental pulmonary embolism

The increased use and sensitivity of CTPA has seen an increase in single or multiple pulmonary emboli isolated to the smaller, subsegmental pulmonary arteries.[99] Despite this increase, overall pulmonary embolism related mortality has not changed, and this may account for the decrease in case fatality.[100-102] The clinical significance of subsegmental pulmonary emboli remains uncertain, and recommendations are extrapolated mainly from historical ventilation-perfusion lung scan trials.

In the PIOPED study, 17% of patients had defects isolated to the subsegmental pulmonary arteries, which corresponds to a "low probability" ventilation-perfusion lung scan.[32] In observational studies, these low probability ventilation-perfusion patients were not treated if bilateral leg compression ultrasonography and serial compression ultrasonography were performed.[48] This was shown to be a safe strategy and remains the current management of such patients.[16] A systematic review and meta-analysis of observational studies and RCTs showed that the rate of subsegmental pulmonary embolism was higher when multi-row detector computed tomography was used compared with single detector computed tomography, but the three month incidence of recurrent venous thromboembolism in patients left untreated was the same in both groups (0.9% (0.4% to 1.4%) and 1.1% (0.7% to 1.4%) for single and multi-row detectors respectively), suggesting that the extra subsegmental pulmonary embolisms detected may not have the same clinical significance.[99] Similarly, another systematic review and meta-analysis of observational studies and RCTs showed no difference between patients with subsegmental pulmonary embolism who were treated with anticoagulation and those not treated for the pooled outcomes of three month incidence of recurrent venous thromboembolism (5.3% (1.6% to 10.9%) treated, 3.9% (4.8% to 13.4%) untreated) and all cause mortality (2.1% (3.4% to 5.2%) treated, 3.0% (2.8% to 8.6%) untreated).[103] The diagnosis of subsegmental pulmonary embolism is complicated by low inter-observer agreement between radiologists and the recognition that many subsegmental pulmonary embolisms are interpreted as false positives by more experienced radiologists.[100] Collectively, this has led to the recommendation that subsegmental pulmonary embolism in the absence of DVT may not need to be treated with anticoagulation.[14] Until further research is completed, we suggest that isolated subsegmental pulmonary embolism on CTPA, in the absence of cancer or high risk features such as poor cardiopulmonary reserve, may be approached as one would a non-diagnostic ventilation-perfusion lung scan: with baseline and serial bilateral leg compression ultrasonography and no anticoagulation treatment unless DVT is found. An ongoing observational study is assessing the safety of such a management strategy (clinicaltrials.gov NCT01455818).

Box 2: Phases of pulmonary embolism treatment[104]

Initial (0-7 days)
- Apixaban 10 mg BID for 7 days
- Rivaroxaban 15 mg BID for 21 days
- LMWH/fondaparinux for minimum 5 days* and INR ≥2 for 2 days

Long term (1 week to 3 months)
- Apixaban 5 mg BID
- Dabigatran 150 mg BID
- Edoxaban 60 mg daily†
- Rivaroxaban 20 mg daily
- Warfarin for INR 2-3

Extended (3 months to indefinite)
- Apixaban 5 mg BID or 2.5 mg BID‡
- Acetylsalicylic acid 81-100 mg daily, if anticoagulation not possible
- Dabigatran 150 mg BID
- Edoxaban 60 mg daily†
- Rivaroxaban 20 mg daily or 10 mg daily‡
- Warfarin for INR 2-3

BID=twice daily; INR=international normalized ratio; LMWH=low molecular weight heparin
*LMWH is needed for 5-10 days before starting dabigatran or edoxaban
†30 mg daily if creatinine clearance is 30-50 mL/min or weight <60 kg
‡Dose reduction may be considered after 6 months of therapy

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Table 3 | Characteristics of direct oral anticoagulant drugs

Drug	Target	Peak effect (hours)	Half life (hours)	Renal clearance (%)	Protein binding (%)
Dabigatran	Factor IIa (thrombin)	1.5	14-17	>80	35
Apixaban	Factor Xa	3	8-14	25	85
Edoxaban	Factor Xa	4	8-11	35	55
Rivaroxaban*	Factor Xa	2-3	7-11	33	90

*Rivaroxaban 15 mg and 20 mg tablets should be taken with food for maximum absorption and efficacy.

Choice of anticoagulation for acute pulmonary embolism

Anticoagulation therapy for confirmed acute pulmonary embolism is the mainstay of treatment and can be divided into three phases: initial phase from zero to seven days, long term therapy from one week to three months, and extended therapy from three months to indefinite.[14] Box 2 shows anticoagulation options and dosing during each phase. Parenteral anticoagulation with low molecular weight heparin (LMWH), fondaparinux, or intravenous unfractionated heparin is typically used in patients admitted to hospital for initial management of pulmonary embolism. Stable patients on discharge from hospital or those patients suitable for outpatient treatment from the time of diagnosis of acute pulmonary embolism may be treated with DOACs. DOACs are given at fixed doses and do not necessitate routine laboratory monitoring (table 3).[105] Each DOAC has been deemed non-inferior to the VKA/LMWH combination in phase III RCTs for the prevention of symptomatic recurrent venous thromboembolism in patients with an acute venous thromboembolism). DOACs also have significantly fewer major bleeding events compared with VKAs (table 4).[6-8 17] Limitations of these trials include heterogeneous populations and lack of direct comparisons between DOACs. An RCT comparing rivaroxaban and apixaban for patients with acute venous thromboembolism is ongoing (NCT03266783), evaluating the differences in clinically relevant bleeding with these anticoagulants.

Until the past decade, VKAs were the only oral anticoagulants available for treatment of venous thromboembolism, used concurrently with parenteral anticoagulation for at least five days and until two consecutive international normalized ratio readings are between 2 and 3. Although VKA use has diminished with the availability and relative simplicity of DOACs, they remain a critical part of pulmonary embolism management in patients with severe renal insufficiency, antiphospholipid syndrome,[72 73] or inability to cover the cost of DOACs.

Treatment of cancer associated pulmonary embolism

Patients with cancer have a sevenfold increased risk for venous thromboembolism, with an overall absolute risk of 7% within the first year of a cancer diagnosis and up to 20% depending on type of cancer and treatments used.[108-110] Pulmonary embolism may be symptomatic or found incidentally on imaging to assess response to cancer treatment. Symptomatic or incidental pulmonary embolisms have similar high risk for recurrence.[111] Major bleeding complications are also more common with venous thromboembolism in patients with cancer.[112 113] Treatment of acute symptomatic and incidental pulmonary embolism is individualized according to risk of recurrent pulmonary embolism and bleeding. Prolonged use of LMWH dominated the cancer associated venous thromboembolism field for a long time, on the basis of the results of trials comparing LMWH and VKAs.[114] Since then, four RCTs have compared DOACs and LMWH in patients with cancer associated venous thromboembolism. The HOKUSAI VTE Cancer RCT randomized 1050 patients with cancer and acute venous thromboembolism and showed that edoxaban (after a five day lead-in with LMWH) was non-inferior to LMWH for the primary outcome of recurrent venous thromboembolism or major bleeding during 12 month follow-up (hazard ratio 0.97, 95% confidence interval 0.70 to 1.36; P=0.006 for non-inferiority).[115] A non-significant lower venous thromboembolism rate was seen (difference in risk −3.4 (−7.0 to 0.2) percentage points), but the major bleeding rate was significantly higher (difference in risk 2.9 (0.1 to 5.6) percentage points) in the edoxaban treated patients. Major bleeding events were mostly seen in the subgroup of patients with upper gastrointestinal tract malignancies.

A second RCT, SELECT-D, compared rivaroxaban and LMWH for the acute treatment of cancer associated venous thromboembolism in 406 patients. This pilot trial was originally designed to inform feasibility of recruiting patients to a phase III RCT. It was powered to estimate venous thromboembolism recurrence

Table 4 | Phase III randomized controlled trials comparing direct oral anticoagulants and vitamin K antagonists

Trial characteristics	Dabigatran[6 106]	Apixaban[8]	Edoxaban[17]	Rivaroxaban[7 107]
Sample size	5132	5395	8292	8281
Single agent (ie, no LMWH or UFH lead-in)	No	Yes	No	Yes
Duration of treatment (months)	6	6	3–12	3, 6 or 12
Primary outcome: non-inferior efficacy *v* VKA (recurrent or fatal VTE)	HR 1.09 (0.76 to 1.57)	RR 0.84 (0.60 to 1.18)	HR 0.89 (0.70 to 1.13)	HR 0.89 (0.66 to 1.19)
Major bleeding *v* VKA	HR 0.73 (0.48 to 1.11)	RR 0.31 (0.17 to 0.55)	HR 0.84 (0.59 to 1.21)	HR 0.54 (0.37 to 0.79)
Major or CRNM bleeding *v* VKA	HR 0.56 (0.45 to 0.71)	RR 0.44 (0.36 to 0.55)	HR 0.81 (0.71 to 0.94)	HR 0.93 (0.81 to 1.06)
Dosing schedule	BID	BID	OD	BID then OD

BID=twice a day; CRNM=clinically relevant non-major; HR=hazard ratio; LMWH=low molecular weight heparin; OD=once a day; RR=relative risk; UFH=unfractionated heparin; VKA=vitamin K antagonist; VTE=venous thromboembolism.

rates at six months to within an 8% width of the 95% confidence interval within each arm, assuming a recurrent venous thromboembolism rate of 10% at six months. As a result of slow recruitment, it was later modified to within 9% width. The cumulative venous thromboembolism recurrence rate at six months was 11% (7% to 16%) for dalteparin and 4% (2% to 9%) for rivaroxaban, with fewer recurrent venous thromboembolisms in patients treated with rivaroxaban (hazard ratio 0.43, 0.19 to 0.99). A non-significant increase in major bleeding was seen in patients treated with rivaroxaban (hazard ratio 1.83, 0.68 to 4.96) and a significant increase in clinically relevant non-major bleeding with rivaroxaban (3.76, 1.63 to 8.69).[116] A planned interim safety analysis identified a non-significant difference in major bleeding between arms in patients with esophageal cancers, and these cancers were later excluded from the trial. Unfortunately, slow recruitment in the SELECT-D pilot trial resulted in an inability to definitively compare the efficacy and safety of rivaroxaban and LMWH.

Two RCTs have compared apixaban and LMWH for the treatment of cancer associated venous thromboembolism. The ADAM VTE trial randomized 300 patients to either apixaban or LMWH for six months' treatment of cancer associated venous thromboembolism.[117] Recurrent thrombosis was more common in the LMWH group (hazard ratio 0.099, 0.013 to 0.780). No differences were seen in safety outcomes of major bleeding or clinically relevant non-major bleeding rates at 6% in each group. The CARAVAGGIO trial randomized 1170 patients to apixaban or LMWH for six months' treatment.[118] Apixaban was non-inferior to LMWH for the primary outcome of recurrent venous thromboembolism during the trial period of six months (hazard ratio 0.63, 0.37 to 1.07; P<0.001 for non-inferiority). No difference in major bleeding, the primary safety outcome, was observed (hazard ratio 0.82, 0.40 to 1.69).[118]

Caution should be applied in making indirect comparisons of the major bleeding rate in CARAVAGGIO with those in other trials, as important differences in enrolled patients exist. Notably, CARAVGGIO excluded patients with either primary or metastatic central nervous system disease and acute leukemia. There was also an imbalance with less upper gastrointestinal malignancies in the apixaban arm than in the LMWH arm (4.0% *v* 5.4%), whereas HOKUSAI VTE had an imbalance in the opposite direction for edoxaban compared with LMWH (6.3% *v*. 4.0%).

Consensus from Canadian clinical experts provides a treatment algorithm for patients with cancer and acute venous thromboembolism, considering the risk of bleeding, informed patient preferences, and reimbursement of drugs (fig 3).[112] Of note, this consensus statement was made before the publication of the ADAM VTE and CARAVAGGIO trials, the results of which would also support apixaban for the treatment of cancer associated venous thromboembolism. In general, patients with cancer associated pulmonary embolism without contraindication to anticoagulation are assessed for bleeding risk on the basis of a previous history of bleeding, comorbidities, and type of malignancy. Drug-drug interactions are another consideration, particularly for DOACs. All DOACs are substrates of

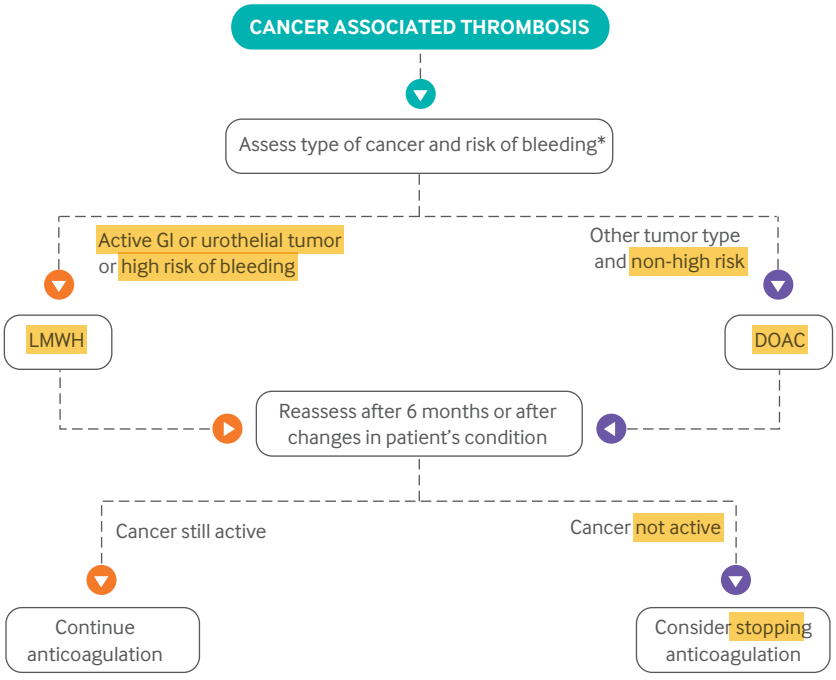

Fig 3 | Suggested algorithm for management of cancer associated thrombosis. DOAC=direct oral anticoagulant; LMWH=low molecular weight heparin. *Consider risk factors for bleeding including gastrointestinal (GI) toxicity (previous GI bleed, treatment associated with GI toxicity), thrombocytopenia (<50 000 platelets/mL), renal impairment, recent and/or life threatening bleeding, intracranial lesion, and use of antiplatelet agents. Adapted from Carrier M, et al. *Curr Oncol* 2018[112]

Box 3: Phases of cancer associated pulmonary embolism treatment

Initial (0-7 days)
- LMWH/fondaparinux for minimum 5 days*
- Apixaban 10 mg BID for 7 days†
- Rivaroxaban 15 mg BID for 21 days

Long term (1 week to 6 months)
- LMWH
- Apixaban 5 mg PO BID†
- Edoxaban 60 mg daily‡
- Rivaroxaban 20 mg daily
- VKA for INR 2-3

Extended (6 months to indefinite)
- LMWH
- Apixaban 5 mg PO BID†
- Edoxaban 60 mg daily‡
- Rivaroxaban 20 mg daily
- VKA for INR 2-3

BID=twice daily; INR=international normalized ratio; LMWH=low molecular weight heparin; VKA=vitamin K antagonist
*LMWH is needed for 5-10 days before starting edoxaban
†Not included in original Canadian expert consensus recommendations
‡30 mg daily if creatinine clearance 30-50 mL/min or weight <60 kg

P-glycoprotein; apixaban and rivaroxaban are also substrates of cytochrome P450 (CYP3A4), whereas edoxaban and dabigatran are not. Determination of clinically relevant drug interactions is complex in patients with cancer, as they are often treated with many anticancer therapies that may compete for a common metabolic pathway. The choice of anticoagulant should be made on an individual basis and in consultation with a pharmacist for assessment of drug-drug interactions.[112] A list of common drug-drug interactions for direct Xa inhibitors can be found in the Canadian expert consensus.[112] The initial phase of cancer associated pulmonary embolism treatment requires use of parenteral anticoagulation (LMWH, fondaparinux) or rivaroxaban in patients without significant renal impairment, according to the algorithm proposed. The choice of long term anticoagulant can include LMWH, edoxaban, or rivaroxaban over VKAs, which are inferior to LMWH. VKAs may be used if LMWH or DOACs are unavailable or contraindicated, such as with severe renal impairment or drug-drug interactions. Duration of therapy for acute venous thromboembolism in cancers patients is usually six months, and extended treatment is individualized on the basis of the patient's cancer status and treatments (box 3). An ongoing RCT is comparing low dose apixaban with standard dose apixaban in cancer patients treated beyond six months (NCT03692065).

Treatment of pregnancy associated pulmonary embolism

DOACs and fondaparinux cross the placenta and should be avoided in pregnancy. Unfractionated heparin and LMWH are safest during pregnancy as they do not cross the placenta; LMWH is the mainstay of treatment owing to its once daily dosing and self-administered subcutaneous route. Management of anticoagulation around the time of delivery requires close coordination with a multidisciplinary team of obstetrics, anesthesia, thrombosis, and maternal fetal medicine. A recent RCT of 3062 low risk pregnancies showed that scheduled induction of labor is safe, does not increase the risk for cesarean section delivery, and had a small benefit on the primary outcome of perinatal death or severe neonatal complications (relative risk 0.80, 0.64 to 1.00).[119] In patients with an acute venous thromboembolism event in the current pregnancy that occurred more than a month before the expected delivery date, we suggest a scheduled induction of labor with the last dose of LMWH administered 24 hours before. Stopping LMWH 24 hours before delivery allows the safe use of neuro-axial anesthesia if needed.[120 121] In the absence of any postpartum hemorrhage, LMWH is restarted six hours after delivery and continued for at least six weeks post partum. In patients who have an acute pulmonary embolism within one month of expected delivery, we also suggest scheduled induction of labor but administration of unfractionated heparin at therapeutic dose until active labor to avoid prolonged interruptions of therapy. If pulmonary embolism occurred less than two weeks from time of delivery, an inferior vena cava (IVC) filter may be considered.[122] Post partum, anticoagulant treatment options for women who are breast feeding include unfractionated heparin, LMWH, VKA, fondaparinux, or danaparoid. DOACs concentrate in breast milk and are contraindicated but can be considered in women who are not breast feeding or after completion of breast feeding in those who have an indication for longer term treatment. Antepartum and postpartum venous thromboembolism prophylaxis with LMWH are recommended for future pregnancies.[53]

Thrombolysis for acute pulmonary embolism

Thrombolytic therapy, either systemic (most common) or directed by a catheter into the pulmonary arteries, can be used to accelerate the resolution of acute pulmonary embolism, lower pulmonary artery pressure, and increase arterial oxygenation.[123] Five per cent of patients with acute pulmonary embolism will present with hemodynamic compromise with systolic blood pressure persistently less than 90 mm Hg; they represent the subgroup at the highest risk for early mortality from pulmonary embolism, thus standing to benefit the most from thrombolytic therapy.[124] Bleeding is the major limitation of thrombolytic therapy, with major bleeding rates reported to be 10% or greater.[125] Overall, a systolic blood pressure persistently less than 90 mm Hg for at least 15 minutes and without high risk for bleeding is considered to be an indication for immediate treatment with systemic thrombolytic therapy.[14 15] This recommendation, however, is based on poor quality evidence, likely because of challenges in studying patients presenting with acute instability.

The results of the International Cooperative Pulmonary Embolism Registry (ICOPER), showed no benefit in terms of 90 day mortality with thrombolytic therapy in hemodynamically unstable pulmonary embolism but should be interpreted with caution as only 32% of all such patients received thrombolysis and selection bias is likely present.[124] A systematic review identified 18 randomized trials using thrombolytic therapy for the treatment of pulmonary embolism, including both hemodynamically stable and unstable pulmonary embolism.[123] Overall a reduction in death with thrombolytic therapy was observed (odds ratio 0.51, 0.29 to 0.89; P=0.02; 1898 participants; low quality evidence), but this overall effect was lost when studies with a high risk of bias were excluded (odds ratio 0.66, 0.42 to 1.06; P=0.08; 2054 participants).

The use of thrombolytic therapy in selected hemodynamically stable patients with high risk features has been better studied in clinical trials. The largest RCT to evaluate the benefit of thrombolysis in hemodynamically stable patients was the Pulmonary Embolism Thrombolysis (PEITHO) trial, which randomized 1005 patients with right ventricular dysfunction on either CTPA or echocardiogram or an elevated troponin to receive thrombolysis (tenecteplase) in addition to unfractionated heparin,

compared with unfractionated heparin alone.[96] This study showed a benefit in the study's composite primary outcome of death or hemodynamic decompensation within seven days (odds ratio 0.44, 0.23 to 0.87; P=0.02) but at a significant cost of major bleeding (major extracranial bleeding: odds ratio 5.55, 2.3 to 13.39; P<0.001). The most notable finding of this trial was that no difference in overall death was seen between the two groups, perhaps because patients randomized to the heparin only group successfully received rescue thrombolysis on development of hemodynamic decompensation. This would suggest that a strategy of close observation of such patients with escalation to systemic thrombolysis in those who decompensate is worthy of study. Three year follow-up in PEITHO showed no effect of thrombolysis therapy on residual dyspnea, right ventricular dysfunction, or overall mortality.[126]

Catheter directed thrombolysis (CDT) is an alternative method for delivery of thrombolysis with potentially a lower risk of bleeding (one third the dose of thrombolytic drug compared with systemic delivery). This approach has been studied in an RCT of 59 patients with acute pulmonary embolism without evidence of hemodynamic compromise on presentation, and CDT showed a benefit in the primary outcome of improved right ventricular function (right ventricular/left ventricular ratio) at 24 hours (mean difference 0.30 (SD 0.20) versus 0.03 (0.16), heparin and CDT respectively; P<0.001).[127] Cohort and registry studies have shown improvement in surrogate outcomes of right ventricular function but no difference in recurrent pulmonary embolism or mortality.[15] Major bleeding rates are variable across studies but reported by some to be similar to those with systemic thrombolysis.[128 129] The role for CTD remains unclear, and we do not recommend its routine use except in experienced centers when a patient has hemodynamic compromise and a high risk of bleeding and therapy can be started without delay.

A network meta-analysis of all RCTs that compared recanalization procedures for acute pulmonary embolism (full dose systemic thrombolysis, low dose systemic thrombolysis, and catheter directed thrombolysis) found no significant benefit on overall mortality for any thrombolysis methods (full dose systemic thrombolysis: odds ratio 0.60, 0.36 to 1.01; low dose thrombolysis: 0.47, 0.14 to 1.59; catheter directed thrombolysis: 0.31, 0.01 to 7.96) and a significantly increased risk of bleeding, especially with full dose systemic thrombolysis (odds ratio 2.00, 1.06 to 3.78).[125] For patients presenting with persisting hemodynamic instability for at least 15 minutes, in the absence of high quality evidence, but also considering the high short term mortality of this group, we suggest the use of systemic thrombolysis in patients without absolute contraindication.[16] For patients with persisting hemodynamic instability but at high risk or with contraindications to systemic thrombolysis, we suggest that catheter directed thrombolysis may be considered on an individual case basis, where available. For all other patients deemed to be at high risk for short term deterioration (see "Pulmonary embolism risk assessment" above), we suggest observation in a monitored setting with thrombolytic therapy reserved for hemodynamic deterioration.

Surgical embolectomy

Surgical embolectomy with cardiopulmonary bypass can be performed in patients with acute pulmonary embolism associated with hemodynamic instability and contraindication to thrombolytic therapy.[14 16] Published case series have shown variable results, with perioperative mortality ranging from 4% to 59%.[130 131] Advanced age, pre-surgical cardiac arrest, and pre-surgical thrombolytic therapy are associated with worse outcomes. Extracorporeal membrane oxygenation (ECMO) either alone or as a bridge to surgical embolectomy has also shown benefit in case reports and small case series.[130] ECMO requires continuous anticoagulation and can induce a consumptive coagulopathy, resulting in high risk of bleeding. In a patient with significant hemodynamic instability and contraindication to thrombolysis, surgical embolectomy and/or ECMO may be considered.

Vena cava filters

IVC filters were first introduced in 1973 and designed to mechanically trap venous emboli from the lower extremities to prevent pulmonary embolism.[122] Since this time, the use of IVC filters has dramatically increased, despite a lack of evidence for an effect on venous thromboembolism related mortality.[132] Guidelines from major clinical societies differ in their suggested indication for IVC filters but generally agree on their use in patients with an acute proximal DVT or pulmonary embolism and a contraindication to anticoagulation.[122] The use of IVC filters for other indications, such as failure of anticoagulation, massive pulmonary embolism clot burden with residual DVT, severe cardiopulmonary disease, use before thrombolysis, or prophylaxis in patients at high risk, has expanded greatly in recent years but is not driven by evidence.[122 133]

Pre-emptive placement of a permanent IVC filter in addition to standard anticoagulation in patients at high risk with acute proximal DVT was investigated in the Prévention du Risque d'Embolie Pulmonaire par Interruption Cave (PREPIC) study, an RCT of 400 patients, which showed a reduction in the primary outcome of early pulmonary embolism diagnosed within the first 12 days (odds ratio 0.22, 0.05 to 0.90) but no difference in mortality (odds ratio 0.99, 0.29 to 3.42).[134] Longer term follow-up data showed similar results, with reduction of pulmonary embolism in the IVC filter arm but a significant increase in recurrent DVT and no difference in overall mortality.[47] A follow-up RCT, PREPIC-2, studied removable IVC filters in 399 patients with high risk pulmonary embolism and showed no benefit in the use of the filter combined with standard anticoagulation

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compared with anticoagulation alone on the primary outcome of recurrent pulmonary embolism at three months (relative risk 2.00, 0.51 to 7.89; P=0.50).[135] We suggest that IVC filters should be restricted to patients with an acute proximal DVT or pulmonary embolism in whom full dose anticoagulation cannot be given because of uncontrollable active bleeding or a high risk for life threatening bleeding (for example, coagulation defect, severe thrombocytopenia, recent intracerebral hemorrhage, or cerebral lesion at high risk of bleeding) or urgent surgery requiring interruption of anticoagulation. In such patients, the safety of starting or resuming anticoagulation should be assessed frequently. Once full dose anticoagulation can be restarted without recurrence of major bleeding, the IVC filter should be promptly removed to reduce the chance of IVC filter related complications, which are increased over time.[122]

Duration of treatment for pulmonary embolism

The duration of treatment depends on the presence or absence of risk factors at the time of diagnosis of the index pulmonary embolism (see box 1). The ISTH Scientific Subcommittee suggests evaluating patients' risk for recurrent venous thromboembolism.[14] In patients with less than 5% risk at one year or less than 15% at five years, the recommendation is to stop anticoagulation. In pulmonary embolism provoked by major transient risk factors such as major surgery, the risk of recurrent pulmonary embolism at one year is less than 1%, favoring discontinuation of anticoagulation after three months. In those with minor transient risk factors such as hormone associated pulmonary embolism, the risk of recurrent venous thromboembolism is approximately 15% at five years and consideration of the risks of anticoagulation related major bleeding is important when recommending extended treatment in this intermediate group.

In patients without an identifiable risk factor (unprovoked pulmonary embolism), a recent systematic review and meta-analysis of 18 studies (RCTs and observational studies) evaluated the risk of recurrent venous thromboembolism in patients with a first unprovoked venous thromboembolism.[74] In total, 7515 patients were included, and all completed at least three months' anticoagulation before discontinuing therapy. In the first year after stopping anticoagulation, the pooled rate of recurrent venous thromboembolism was 10.3 (95% confidence interval 8.6 to 12.1) events per 100 person years and the rate of recurrent pulmonary embolism was 3.3 (2.4 to 4.2) events per 100 person years. Table 5 shows the cumulative incidence of recurrent venous thromboembolism and recurrent pulmonary embolism. The case fatality rate of recurrent venous thromboembolism was 3.8% (2.0% to 6.1%). These data suggest that patients with a first unprovoked venous thromboembolism are at substantial risk for recurrent thrombosis, and this should guide decisions on extended anticoagulation therapy. Intermediate duration anticoagulation, such as extending the initial treatment period to one or two years before discontinuing therapy, does not reduce the subsequent risk of recurrent venous thromboembolism after anticoagulation is discontinued.[136]

Risk stratification for patients with unprovoked venous thromboembolism may also help to determine the risk of recurrent thrombosis. Prognostic markers of recurrent venous thromboembolism include male sex, advanced age,[137 138] inherited thrombophilia,[70] obesity,[70] persistently positive D-dimer,[77 139] and residual pulmonary obstruction on ventilation-perfusion lung scan.[140] Individually, these risk factors are insufficient to recommend long term anticoagulation; however, risk prediction models incorporating various combinations have been proposed.[137 138] The largest prospectively validated (2785 patients) clinical decision rule is the "Men Continue and HERDOO-2."[75 141] In the derivation cohort of this prediction rule, stratifying men into high and low risk categories was not possible; men had an annual risk of recurrent venous thromboembolism of 13.9% (10.8% to 17.0%) while off anticoagulation, so they remained on anticoagulation in the validation cohort. Women, on the other hand, were stratified into risk groups, such that anticoagulation could be discontinued in women with 0 or 1 HERDOO points (hyperpigmentation, edema or redness of either leg, D-dimer >250 µg/L, obesity (body mass index >30), older age (≥65 years)). The annual risk of recurrent venous thromboembolism in women at low risk was 1.6% (0.3% to 4.6%) in the derivation cohort and 3% (1.8% to 4.8%) in the validation cohort. Women with 2 or more HERDOO points were deemed to be at high risk and had an annual recurrent venous thromboembolism rate of 14.1% (10.9% to 17.3%) in the derivation cohort and remained on anticoagulation in the validation study. Limitations to this rule include the misclassification of women at high and low risk of recurrent venous thromboembolism risk with use of non-VIDAS D-Dimer assays (bioMérieux, Marcy L'Etoile, France),[142] and D-dimer testing was done on anticoagulation at six months after the initial venous thromboembolism event. Use of the rule at other time points or off anticoagulation has not been validated. Anticoagulant options for extended venous thromboembolism treatment are shown in box 2.

Oral anticoagulation reduces the risk of recurrent venous thromboembolism only during therapy. Identifying patients with unprovoked index venous thromboembolism who would benefit from

Table 5 | Risk of recurrent venous thromboembolism (VTE) and pulmonary embolism (PE) after discontinuing anticoagulation*[74]

Time interval after anticoagulation stopped	Cumulative incidence, % (95% CI)	
	Recurrent VTE	Recurrent PE
1 year	10.3 (8.6 to 12.1)	3.3 (2.4 to 4.2)
2 year	16.0 (13.3 to 18.8)	5.2 (3.7 to 6.7)
5 year	25.2 (21.3 to 29.3)	8.0 (4.0 to 11.6)
10 year	36.1 (27.8 to 45.0)	11.2 (5.9 to 18.4)

*In patients after first unprovoked VTE.

prolonged anticoagulation for extended treatment and secondary prevention needs to be balanced with risk of bleeding while on anticoagulation. Risk factors for bleeding include age over 75 years, history of bleeding, chronic liver disease, chronic renal disease, previous stroke, and use of concurrent antiplatelet agents or non-steroidal anti-inflammatory drugs.[16] As the bleeding risks and associated case fatality rates are lower for DOACs than VKAs,[143 144] when possible, DOACs should be considered over VKAs.

Box 2 shows the DOAC dosing options for extended treatment, including continuation of the same dosing as for long term treatment or reduced dosing for rivaroxaban and apixaban. The EINSTEIN CHOICE RCT compared rivaroxaban 20 mg daily and rivaroxaban 10 mg daily against aspirin 100 mg daily for extended treatment of venous thromboembolism in 3400 participants who completed at least six to 12 months of anticoagulation for acute venous thromboembolism.[145] The trial was not sufficiently powered to compare the different doses of rivaroxaban with each other. For the primary efficacy outcome of recurrent/fatal venous thromboembolism, each dose of rivaroxaban was associated with fewer events compared with aspirin (hazard ratio 0.34 (0.20 to 0.59) for rivaroxaban 20 mg versus aspirin and 0.26 (0.14 to 0.47) for rivaroxaban 10 mg compared with aspirin). The primary safety outcome of major bleeding was not different for either dose of rivaroxaban compared with aspirin (hazard ratio 2.01 (0.50 to 8.04) for rivaroxaban 20 mg compared with aspirin and 1.64 (0.39 to 6.84) for rivaroxaban 10 mg compared with aspirin). Limitations of EINSTEIN CHOICE are centered on the predominantly provoked venous thromboembolism population (60% of participants). The benefit of extended therapy in this population is less clear, as the risk of recurrent venous thromboembolism is lower in patients with provoked index venous thromboembolism. Whether rivaroxaban 10 mg daily is as effective as 20 mg daily in unselected high risk patients with unprovoked venous thromboembolism is also unknown.

The AMPLIFY EXT RCT compared two doses of apixaban, 5 mg twice daily and 2.5 mg twice daily, with placebo for 12 months for prevention of recurrent venous thromboembolism/all cause mortality.[146] Participants were randomized after completing six to12 months of therapy for acute venous thromboembolism and received either dose of apixaban or placebo for 12 months. Apixaban at both doses resulted in fewer recurrent primary outcome events compared with placebo (hazard ratio 0.36 (0.25 to 0.53) for apixaban 5 mg versus placebo and 0.33 (0.22 to 0.48) for apixaban 2.5 mg versus placebo). Major bleeding was the primary safety outcome and occurred with similar frequency in each apixaban group (hazard ratio 0.25 (0.03 to 2.24) for apixaban 5 mg versus placebo and 0.49 (0.09 to 2.64) for apixaban 2.5 mg versus placebo). More than 90% of participants in AMPLIFY EXT had unprovoked index venous thromboembolism, providing reassurance that both doses of apixaban reduce the risk of recurrent venous thromboembolism in this high risk patient population, without increasing bleeding events. Unfortunately, the study was not sufficiently powered to compare the apixaban doses with each other. Ongoing studies such as RENOVE (NCT03285438) are evaluating extended therapy of full dose DOAC compared with reduced dose DOAC for patients with unprovoked index venous thromboembolism. In the meantime, patients' preferences and regular evaluation of bleeding risks should be incorporated into decisions about extended therapy. We recommend annual reassessment of risks of bleeding and recurrent venous thromboembolism to inform decisions about prolonged anticoagulation.

In cancer associated pulmonary embolism, cancer is a major persistent risk factor and the need for extended anticoagulation therapy, beyond six months, is suggested for patients with active cancer (metastatic disease) or receiving chemotherapy.[112] Box 3 shows the options for extended therapy. To ensure that the benefit of continuing anticoagulation outweighs the potential harm of bleeding, we suggest that the decision to continue anticoagulation should be regularly reassessed. Figure 4 summarizes our suggested approach to duration of anticoagulant treatment.[147]

Long term effect of pulmonary embolism

Post-pulmonary embolism syndrome

As many as 50% of patients report long term sequelae after pulmonary embolism.[148- 150] Post-pulmonary embolism syndrome has been defined by suboptimal cardiac function, pulmonary artery flow dynamics, or pulmonary gas exchange at rest or during exercise, in combination with dyspnea, decreased exercise tolerance, or diminished functional status or quality of life, without an alternative explanation.[148 149] At the extreme end, chronic thromboembolic pulmonary hypertension (CTEPH) occurs in an estimated 3% of patients surviving after a six month treatment period for acute pulmonary embolism.[151] The exact pathophysiology of why CTEPH occurs in a minority of patients remains unknown. Risk factors for development of CTEPH after acute pulmonary embolism include diagnostic delay, high thrombus load, recurrent symptomatic pulmonary embolism, pulmonary hypertension or right ventricular dysfunction at baseline, and failure to achieve thrombus resolution.[148 152 153] A diagnosis of CTEPH is confirmed by showing a mean pulmonary artery pressure above 25 mm Hg combined with thrombotic pulmonary vascular obstructions. Planar ventilation-perfusion lung scanning is the preferred imaging modality, with high sensitivity and specificity for CTEPH.[15] Bilateral pulmonary endarterectomy through the medial layer of the pulmonary arteries is a curative treatment for CTEPH, but most patients need lifelong anticoagulation because of the risk of recurrent venous thromboembolism.[15]

A second subset of patients is those with evidence of chronic thromboembolic disease without pulmonary

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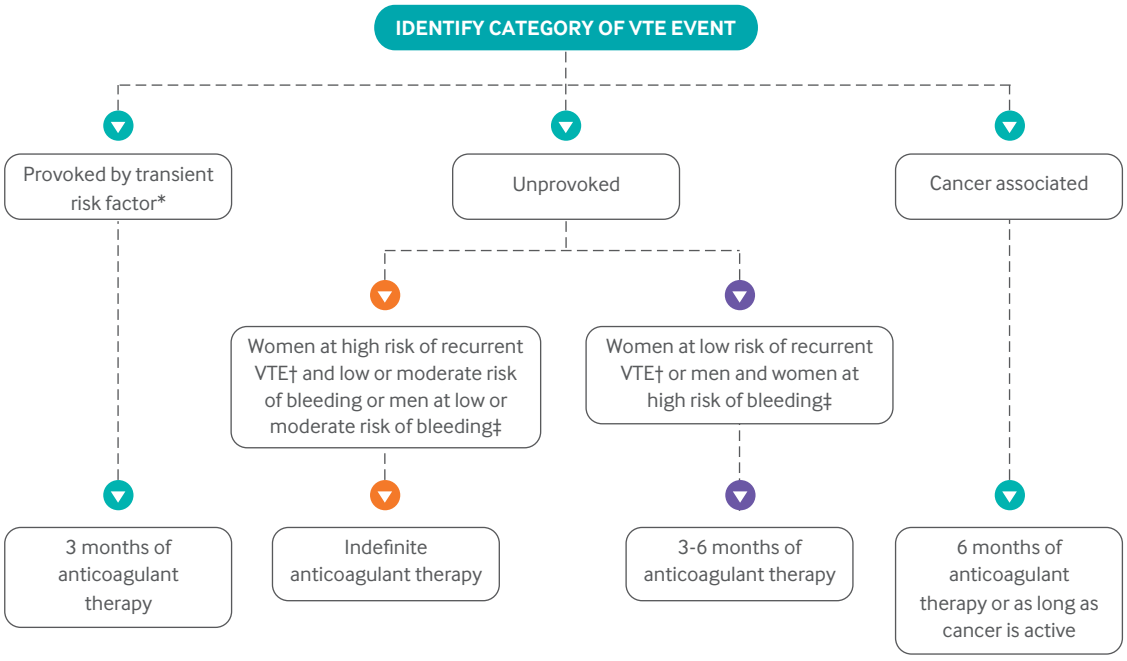

Fig 4 | Approach to duration of treatment of venous thromboembolism (VTE). *If transient risk factor is non-surgical (eg, immobilization, pregnancy, or estrogen therapy), extended treatment can be considered given the safety profile of direct oral anticoagulants. †According to "Men continue and HERDOO2" risk prediction score: low=women with 0-1 points; high risk=all men and women with ≥2 points. ‡Bleeding risk according to HAS-BLED score: low risk 0-2 points or high risk ≥3 points. Adapted from Tritschler T, et al. *JAMA* 2018[147]

hypertension. Cardiopulmonary functional testing suggests that this is an intermediate clinical phenotype in response to exercise.[154] The relation between residual pulmonary obstruction and the patient's risk of developing CTEPH and how the prognosis differs from those with functional symptoms without evidence of residual pulmonary obstruction remain unclear. An observational study, the Prospective Evaluation of Long-term Outcomes After Pulmonary Embolism (ELOPE), followed 100 unselected patients with an acute pulmonary embolism and did cardiopulmonary exercise testing at one and 12 months.[150] Consistent with self-reported symptoms at one year, almost 50% of these patients had evidence of diminished exercise capacity. The observed reduced cardiopulmonary exercise capacity correlated well with several quality of life measurements and the six minute walk test. Baseline residual pulmonary obstruction was not associated with the exercise limitation, and nor were pulmonary function testing or echocardiographic results.[155] Predictors of exercise limitations were age, body mass index, and smoking history. These observations led the investigators to speculate that general deconditioning may be the cause of the patient's reported dyspnea and exercise limitation. The absence of association with baseline residual clot burden and cardiopulmonary exercise capacity is also consistent with the long term follow-up study of patients with pulmonary embolism who had systemic thrombolysis, as no benefit was seen on reported dyspnea or exercise capacity.[126]

Post-pulmonary embolism syndrome describes a heterogeneous consolidation of symptoms and objective findings that has an important effect on the quality of life of patients with pulmonary embolism. Following patients beyond the acute pulmonary embolism period and screening for persisting dyspnea and functional limitations at three to six months is recommended. An ongoing observational study is evaluating a CTEPH clinical prediction score to select patients for screening with echocardiography (NCT02555137). Until these results are available, we continue to screen all patients reporting persisting dyspnea with a ventilation-perfusion lung scan to evaluate for persistent mismatched defects and transthoracic echocardiogram for pulmonary hypertension. If these are found, these patients are referred to a CTEPH expert center for further diagnostic work-up and treatments. Targeted cardiopulmonary rehabilitation and lifestyle modifications may be offered to the remaining patients, although future research is needed to determine the benefits of such programs.

Psychological impact and quality of life

The diagnosis of a pulmonary embolism has a significant psychological effect on patients, who often refer to such an event as a near-miss death experience. The above described ELOPE study followed a cohort of patients with acute pulmonary embolism over one year and showed an acute decline in both generic and pulmonary embolism specific quality of life scores, but these scores then improved over the one year follow-up.[156] Cancer patients with venous thromboembolism also experience a decline in quality of life scores.[157] Qualitative interviews of

Table 6 | Comparison of guideline recommendations from ASH*, CHEST†, and ESC‡ for diagnosis and treatment of pulmonary embolism

Parameter	Recommendation
Diagnosis: D-dimer use	Both ASH and ESC make recommendations to include use of age adjusted D-dimer§ for patients with low PTP to exclude diagnosis of PE but conflict on the strength of the recommendation (ASH: strong recommendation; ESC: class IIa)
Diagnosis: imaging modality	ASH suggests the use of V/Q scan over CTPA to limit radiation exposure in patients with low PTP who need imaging. If V/Q is not available, CTPA is preferred
Diagnosis: pregnancy	Guidelines differ as to use of D-dimer for diagnosis of PE in pregnancy: ESC suggests incorporating its use into the work-up of PE, and ASH makes no recommendation. ESC suggests either V/Q scan or CTPA as equal preference, whereas ASH recommends V/Q scan over CTPA for imaging
Subsegmental PE	Both CHEST and ESC state that the clinical importance of subsegmental PE is uncertain. CHEST suggests clinical surveillance with serial bilateral leg ultrasound for possible DVT in low risk patients and use of anticoagulation in high risk patients
Choice of anticoagulant therapy	CHEST and ESC recommend DOAC over VKA. ESC does not recommend DOACs in patients with antiphospholipid antibody syndrome
Treatment of cancer associated PE	CHEST and ESC suggest that for patients with cancer, weight adjusted subcutaneous LMWH should be considered over VKAs for the first 6 months. ESC suggests the use of edoxaban and rivaroxaban in patients without gastrointestinal cancer. CHEST and ESC are conflicting on the strength of the recommendations for extended anticoagulation beyond 3-6 months for active cancer (CHEST: strong recommendation in absence of high bleeding risk and weak/conditional in presence of high bleeding risk; ESC: class IIa without comment on bleeding risk)
Treatment of PE in pregnancy	ASH and ESC are conflicting on the strength of the recommendation for use of weight based therapeutic LMWH for treatment of PE in pregnancy (ASH: conditional recommendation; ESC: class I). ASH suggests either daily or twice daily LMWH dosing and to avoid anti-FXa monitoring to guide dosing. ASH and ESC suggest thrombolysis be considered for pregnant women with PE and hemodynamic instability
Thrombolysis of PE	CHEST and ESC are conflicting on the strength of recommendation for systemic thrombolytic therapy for patients with hemodynamic instability (systolic blood pressure <90 mm Hg for 15 min, high risk PE) (CHEST: grade 2; ESC: class I). CHEST and ESC recommend against routine use of primary systemic thrombolysis in patients without hemodynamic instability (intermediate risk or low risk PE)
Duration of treatment	CHEST and ESC recommend 3 months' treatment for patients with first PE/VTE secondary to a major transient/ reversible risk factor. CHEST and ESC suggest extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and no identifiable risk factor. CHEST suggests 3 months' treatment for patients with high risk of bleeding and a first episode of PE/VTE and no identifiable risk factor. ESC suggests extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a persistent risk factor other than antiphospholipid antibody syndrome. ESC suggests extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a minor transient or reversible risk factor. ESC suggests that, for extended duration anticoagulation in a patient without cancer, a reduced dose of apixaban (2.5 mg BID) or rivaroxaban (10 mg OD) should be considered after 6 months of therapeutic anticoagulation

anti-FXa=anti-factor Xa; ASH=American Society of Hematology; BID=twice a day; CHEST=American College of Chest Physicians; CTPA=computed tomography pulmonary angiography; DOAC=direct oral anticoagulant; DVT=deep venous thrombosis; ESC=European Society of Cardiology; LMWH=low molecular weight heparin; OD=once a day; PE=pulmonary embolism; PTP=pre-test probability; VKA=vitamin K antagonist; V/Q=ventilation-perfusion lung scan; VTE=venous thromboembolism.
*GRADE approach and recommendations expressed as either strong or conditional.
†GRADE approach and recommendations expressed as strong (grade 1) or weak/conditional (grade 2).
‡Pre-defined scale for recommendations expressed as class I: evidence and/or general agreement that given treatment or procedure is beneficial, useful, effective; class II: conflicting evidence and/or divergence of opinion about usefulness/efficacy of given treatment or procedure; class IIa: weight of evidence/opinion is in favor of usefulness/efficacy; class IIb: usefulness/efficacy is less well established by evidence/opinion; class III: evidence or general agreement that given treatment or procedure is not useful/effective, and in some cases may be harmful.
§Age adjusted D-dimer, age×10 µg/L, in patients aged >50 years.

patients six to 12 months after a diagnosis of venous thromboembolism reported a major theme of "life changing and forever changed" when describing their lived experience with venous thromboembolism.[158] Some patients also noted a "post-thrombotic panic," describing feelings of hypervigilance and panic related to fear of illness recurring. A need for greater recognition of patients' psychological wellness and research into potential targeted supports clearly exists.

Guidelines

Table 6 summarizes the guidelines that seem to be the most relevant, updated, and endorsed by leading international societies concerning management of patients with pulmonary embolism.[14 16 159] Of these, the guidelines from the European Society of Cardiology (ESC) and the American Society of Cardiology (ASH) have been updated within the last one or two years and are thus based on the most recent clinical trials. The completed ASH guidelines are in progress, with six of 10 intended sections published at this time (prophylaxis for medical patients,[160] diagnosis,[161] anticoagulation therapy,[162] pediatrics,[163] heparin induced thrombocytopenia,[164] and pregnancy[53]). The remaining four sections are expected to be released later in 2020 (treatment, cancer, thrombophilia, prophylaxis in surgical patients). The completed ASH guidelines will represent the most comprehensive and updated guideline set. The guidelines released by the American College of Chest Physicians in 2016 are a partial update of the comprehensive 2012 guidelines.[165] The field of pulmonary embolism has had several important advances in the four years since this release.

Emerging treatments

Anticoagulant therapies targeting coagulation factors IX, XI, and XII are under research and development.[166 167] Of these, factor XIa inhibition is most developed and includes targeted strategies such as antisense oligonucleotide agents to reduce hepatic biosynthesis, aptamers to target DNA or RNA expression, and monoclonal antibodies and small molecules that block activity of factor XIa.[168 169] Two phase II RCTs of novel factor XI inhibitors have been published, both testing various doses after elective knee arthroplasty for the primary outcome of new venous thromboembolism (symptomatic and asymptomatic). Büller et al randomized 300 patients to either 200 mg or 300 mg of FXI-ASO, given as a series of subcutaneous injections staring 36 days preoperatively, or enoxaparin prophylaxis.[170] The 200 mg regimen was non-inferior and the 300 mg regimen superior to enoxaparin (P<0.001). Weitz et al randomized 813 patients post-elective knee arthroplasty to enoxaparin, apixaban, or single intravenous infusions of the factor XIa inhibitor

GLOSSARY OF ABBREVIATIONS

- ASH—American Society of Cardiology
- CDT—catheter directed thrombolysis
- CTEPH—chronic thromboembolic pulmonary hypertension
- CTPA—computed tomography pulmonary angiography
- DOAC—direct oral anticoagulant
- DVT—deep venous thrombosis
- ECMO—extracorporeal membrane oxygenation
- ESC—European Society of Cardiology
- ISTH—International Society on Thrombosis and Hemostasis
- IVC—inferior vena cava
- LMWH—low molecular weight heparin
- NT-proBNP—N-terminal pro-b-type natriuretic peptide
- PERC—pulmonary embolism rule-out criteria
- PESI—Pulmonary Embolism Severity Index
- pro-BNP—pro-B-type brain natriuretic peptide
- RCT—randomized controlled trial
- SPECT—Single photon emission computed tomography
- sPESI—simplified Pulmonary Embolism Severity Index
- VKA—vitamin K antagonist

osocimab (BAY1213790) at various dose and schedules (preoperative/postoperative).[171] In this open label dose finding study, osocimab at doses of 0.6 mg/kg, 1.2 mg/kg, and 1.8 mg/kg given postoperatively met criteria for non-inferiority compared with enoxaparin for the primary outcome of new venous thromboembolism (symptomatic or asymptomatic), and the preoperative 1.8 mg/kg dose of osocimab met criteria for superiority compared with enoxaparin (risk difference 10.6, 95% confidence interval −1.2 to 22.4; P=0.07). Further studies are needed to determine the true efficacy and bleeding risk of these novel anticoagulants.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The authors of this clinical review are members of Canadian Venous Thromboembolism Clinical Trials and Outcomes Research (CanVECTOR) network. This network includes patient partner members. Three CanVECTOR patient partners were consulted for the preparation of the manuscript and were asked to review a proposed outline of topics to include and provided their contributions and feedback. Specifically, patients were asked to review the manuscript outline with the following question in mind: "If your clinicians were to read one review paper for the purpose of updating their knowledge of pulmonary embolism management, which topics do you feel are most important to include?" Additions to the manuscript as a direct result of this engagement with patient partners included a discussion of thrombophilia testing, with specific reference to benefits of thrombophilia testing in patients with identified transient provoking risk factors; a discussion of the detailed management of pregnancies in patient with pulmonary embolism; and a discussion of the psychological impact of a diagnosis of pulmonary embolism in survivors. The final manuscript of this article was reviewed and approved by one lead patient partner from this group.

QUESTIONS FOR FUTURE RESEARCH

- Can the use of clinical probability score and D-dimer testing be optimized for the diagnosis of pulmonary embolism in subgroups of patients such as those with a previous history of pulmonary embolism and pregnant women?
- What is the appropriate management of a patient with pulmonary emboli located to within the subsegmental pulmonary arteries?
- How can clinicians recognize and manage the long term sequelae of pulmonary embolism such as chronic thromboembolic pulmonary hypertension and post-pulmonary embolism syndrome?

Conclusion

The management of pulmonary embolism has changed considerably over the past decade, most substantially driven by the introduction of direct oral anticoagulation therapies. The convenience of use, lack of routine laboratory monitoring, and lower bleeding rates have allowed a greater acceptance by patients compared with VKAs. Extended treatment duration in selected patients with pulmonary embolism has had a significant effect on risk of recurrent venous thromboembolism. Other important management updates include a recognition of over-investigation and perhaps over-treatment of pulmonary embolism in some patients. The use of clinical probability scores and advances in the interpretation of D-dimer results reduces the use of diagnostic imaging to exclude pulmonary embolism. Recognition of subsegmental pulmonary embolism as a distinct entity and careful evaluation of need for anticoagulation have been important to avoid over-diagnosis and over-treatment. Despite a decade of advances, however, pulmonary embolism continues to have important long term consequences for patients, including chronic dyspnea, diminished exercise capacity, and effects on quality of life. Future research is needed to identify targeted interventions and supports.

Contributors: LD and LAC did the primary literature search in collaboration with a health information librarian. LD was the lead author of the manuscript, and LAC wrote the sections on choice of anticoagulation for acute pulmonary embolism, treatment of cancer associated pulmonary embolism, and duration of treatment for pulmonary embolism. MAF guided the writing of the full manuscript. All authors reviewed the full manuscript and contributed to its content and references.

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