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Venous Thromboembolism
Advances in Diagnosis and Treatment

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IMPORTANCE Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal disease.

OBJECTIVE To summarize the advances in diagnosis and treatment of VTE of the past 5 years.

EVIDENCE REVIEW A systematic search was conducted in EMBASE Classic, EMBASE, Ovid MEDLINE, and other nonindexed citations using broad terms for diagnosis and treatment of VTE to find systematic reviews and meta-analyses, randomized trials, and prospective cohort studies published between January 1, 2013, and July 31, 2018. The 10th edition of the American College of Chest Physicians Antithrombotic Therapy Guidelines was screened to identify additional studies. Screening of titles, abstracts, and, subsequently, full-text articles was performed in duplicate, as well as data extraction and risk-of-bias assessment of the included articles.

FINDINGS Thirty-two articles were included in this review. The application of an age-adjusted D-dimer threshold in patients with suspected PE has increased the number of patients in whom imaging can be withheld. The Pulmonary Embolism Rule-Out Criteria safely exclude PE when the pretest probability is low. The introduction of direct oral anticoagulants has allowed for a simplified treatment of VTE with a lower risk of bleeding regardless of etiology or extent of the VTE (except for massive PE) and has made extended secondary prevention more acceptable. Thrombolysis is best reserved for patients with massive PE or those with DVT and threatened limb loss. Insertion of inferior vena cava filters should be avoided unless anticoagulation is absolutely contraindicated in patients with recent acute VTE. Graduated compression stockings are no longer recommended to treat DVT but may be used when acute or chronic symptoms are present. Anticoagulation may no longer be indicated for patients with isolated distal DVT at low risk of recurrence.

CONCLUSIONS AND RELEVANCE Over the past 5 years, substantial progress has been made in VTE management, allowing for diagnostic and therapeutic strategies tailored to individual patient characteristics, preferences, and values.

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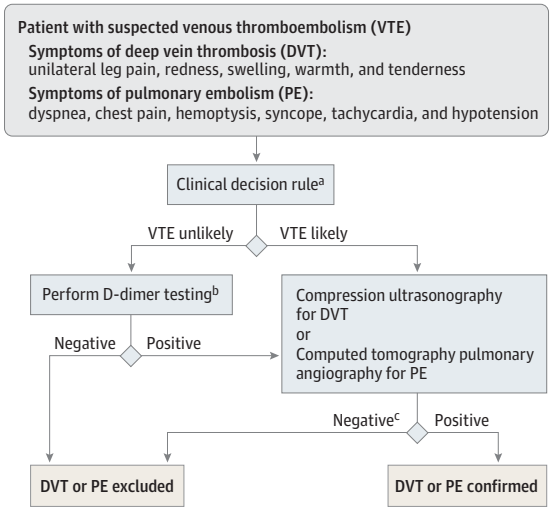
Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal disease. The estimated incidence of a first acute VTE is 0.7 to 1.4 per 1000 person-years and is mostly observed in patients older than 55 years.[1-4] While the incidence of DVT has remained constant over time,[5] hospital admissions for PE in the United States more than doubled over the last decades,[6] partly because of widespread use of sensitive imaging techniques detecting smaller, potentially insignificant emboli.[7] Even though the in-hospital case-fatality rate of PE has decreased in the United States between 1999 and 2008,[8] about 30% of patients with PE die within the first year after diagnosis.[4] The socioeconomic effect of VTE is significant, with estimated annual costs ranging from $13.5 billion to $27.2 billion in the United States.[9]

Clinical signs and symptoms of DVT include unilateral leg pain, redness, swelling, edema, warmth, and tenderness. Pulmonary embolism may present with dyspnea, chest pain, hemoptysis, syncope, tachycardia, and hypotension. The clinical presentation of VTE is often not specific, and DVT can be indistinguishable from cellulitis, hematoma, superficial thrombophlebitis, and congestive heart failure. Pulmonary embolism presents similarly to myocardial infarction, congestive heart failure, and other diseases. Consequently, imaging is needed to confirm the diagnosis of VTE. The diagnosis of VTE is made in a sequence of steps including assessment of the pretest probability, followed by D-dimer testing and imaging as appropriate (**Figure 1**). When VTE is diagnosed, immediate initiation of anticoagulant therapy is imperative. The choice among different anticoagulant agents and the duration of treatment are based

Figure 1. Diagnostic Management of Patients With Suspected DVT or PE



[a] Wells score for suspected DVT and Wells score or revised Geneva score for suspected PE.

[b] Age-adjusted D-dimer threshold, calculated as the patient's age multiplied by 10 ng/mL (fibrinogen-equivalent units) for patients older than 50 years with suspected PE.

[c] Repeat compression ultrasonography 1 week after initially normal finding in patients with high clinical probability and positive D-dimer levels if initial imaging was not whole-leg ultrasonography.

on clinical presentation, etiology of the VTE event, bleeding risk, and patient preference. This review focuses on advances in diagnosis and treatment of VTE during the past 5 years.

Methods

A systematic search was conducted in EMBASE Classic, EMBASE, Ovid MEDLINE, and other nonindexed citations from January 1, 2013, to July 31, 2018, combining terms for diagnosis and treatment of VTE, to find prospective cohort studies, randomized trials, systematic reviews, and meta-analyses (eAppendix in the Supplement). Articles were restricted to humans, adults, and studies published in English, French, Dutch, German, and Italian. In addition, the 10th edition of the American College of Chest Physicians Antithrombotic Therapy Guidelines was screened for studies not found by the initial search.[10] Titles, abstracts, and, subsequently, full-text articles were screened independently by 2 authors (T.T. and N.K.) for eligibility. Data extraction and quality assessment were independently performed in duplicate (T.T. and N.K.) using the AMSTAR tool for systematic reviews and meta-analyses[11] and the SIGN-50 tool for randomized trials and cohort studies[12]; disagreements were resolved by discussion.

To be eligible, studies had to be rated as at least medium quality by the AMSTAR tool or as acceptable quality by the SIGN-50 tool.[11,12] When multiple systematic reviews or meta-analyses covered the same topic, the study with the best methodological quality was included, and in cases of similar quality, the most recent study was selected. If advances were not covered by a systematic review or meta-analysis, we included randomized trials or prospective cohort management studies.

Key Points

Question What advances in diagnosis and treatment of venous thromboembolism have occurred in the past 5 years?

Findings Alternative approaches have been developed for improvement and simplification of currently recommended diagnostic algorithms and for assessment of specific subgroups. The introduction of direct oral anticoagulants has resulted in simplified treatment of venous thromboembolism with a lower risk of bleeding. Decisions on initiation and duration of therapy can now be more carefully implemented.

Meaning Advances in diagnosis and treatment enabled more patient-specific management of venous thromboembolism.

Results

Of the 2009 citations identified by the literature search, 32 articles were included in the review (eFigure in the Supplement). Characteristics and results of the included studies are provided in **Table 1** and **Table 2** and quality assessment of included studies in eTable 1, eTable 2, and eTable 3 in the Supplement.

Major Diagnostic Advances

Deep vein thrombosis and PE cannot be diagnosed based on signs and symptoms alone. Prompt and accurate diagnosis is crucial to provide appropriate treatment and avoid thrombus extension or embolization, disease-related morbidity, and mortality. However, because VTE diagnosis is frequently suspected but confirmed in less than 20% of suspected cases,[13,14] it is not ideal to perform imaging in every suspected case. Overall, VTE can be excluded in 29% (95% CI, 20%-40%) of patients with suspected DVT and in 28% (95% CI, 20%-37%) of those with suspected PE using diagnostic algorithms including pretest probability assessment and D-dimer testing (Figure 1).[15,16] The remaining patients require compression ultrasonography or computed tomography pulmonary angiography (CTPA) to determine whether VTE is present.[17-20]

Clinical Decision Rules

In settings with low VTE prevalence (eg, emergency departments in the United States), an alternative approach to management of patients with suspected PE was proposed with the introduction of the Pulmonary Embolism Rule-Out Criteria (PERC), which aimed to rule out PE without testing.[21] The 8 PERC criteria are (1) age 50 years or older; (2) pulse rate of at least 100/min; (3) pulse oximetry oxygen saturation of less than 95%; (4) unilateral leg swelling; (5) hemoptysis; (6) recent surgery or trauma; (7) prior PE or DVT; and (8) exogenous estrogen use.[21] When none of these are present in a patient with suspected PE, the PERC rule safely excludes PE with a false-negative rate of less than 1%, a sensitivity of 97% (95% CI, 96%-98%), and a specificity of 22% (95% CI, 22%-23%).[22] When the prevalence of PE is high, as occurs in many European emergency departments (>20%), PERC should be applied only when a treating clinician believes that the probability of PE is

Table 1. Major Diagnostic Advances in Venous Thromboembolism

Source	Type of Evidence	No. of Studies	No. of Patients	Diagnostic Management	Conclusion
Clinical Decision Rules					
Singh et al,[22] 2013	Meta-analysis	12	14 844	PERC rule	PERC can safely rule out PE in low-clinical-probability populations.
Penaloza et al,[25] 2017	Cohort	1	1773	PERC rule	PERC may safely rule out PE in patients with low implicit clinical probability in a European setting.
Freund et al,[26] 2018	Cluster randomized trial	1	1916	PERC rule	PERC safely rules out PE in patients with low implicit clinical probability in a European setting.
D-Dimer Testing					
Van Es et al,[16] 2016	Meta-analysis	6	7268	Conventional vs age-adjusted D-dimer threshold	Age-adjusted D-dimer threshold increases proportion of patients in whom imaging can be withheld, and also in high-risk subgroups
Diagnostic Algorithm					
Van der Hulle et al,[27] 2017	Cohort	1	3465	Diagnostic algorithm	YEARS diagnostic algorithm can safely rule out PE.
Imaging for Suspected DVT					
Pomero et al,[28] 2013	Meta-analysis	16	2379	Emergency physician-performed ultrasonography	Emergency physician–performed ultrasonography has a high sensitivity and specificity for diagnosis of DVT.
Abdalla et al,[29] 2015	Meta-analysis	23	1121	Magnetic resonance venography	Magnetic resonance venography is a potential alternative for diagnosis of DVT when ultrasonography is not feasible.
Imaging for Suspected PE					
Da Costa Rodrigues et al,[30] 2016	Meta-analysis	15	6991	Lower limb ultrasonography	Proximal lower limb ultrasonography can confirm but cannot rule out PE.
Squizzato et al,[31] 2017	Meta-analysis	13	1170	Magnetic resonance imaging	Magnetic resonance imaging has high specificity but limited sensitivity for diagnosis of PE, and one-fifth of results are inconclusive.
Phillips et al,[32] 2015	Meta-analysis	19	5923	Ventilation/perfusion SPECT	Ventilation/perfusion SPECT and computed tomography pulmonary angiography have similar performance and are both superior to planar ventilation/perfusion imaging.

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; PERC, Pulmonary Embolism Rule-Out Criteria; SPECT, single-photon emission computed tomography.

low.[23-26] PERC has been validated in a cluster-randomized trial,[26] but it should be used only in low-prevalence settings or for patients considered to have a low probability of PE.

D-Dimer Testing

D-dimer is a sensitive marker for VTE and excludes VTE without need for further testing among patients with a low clinical probability of PE.[17-20] D-dimer levels greater than 500 ng/mL suggest the presence of PE. However, as D-dimer increases with age, older patients more often have false-positive test results, which lowers the test's specificity in these patients. The false-positive rate can be reduced by using an age-adjusted D-dimer threshold, calculated as the patient's age multiplied by 10 ng/mL (fibrinogen-equivalent units) for patients older than 50 years. When tested, the proportion of patients in whom imaging could safely be withheld based on a "PE-unlikely" Wells score and age-adjusted normal D-dimer levels increased from 28% to 33%.[16] Age-adjusted D-dimer testing is useful when PE is suspected, although this approach appears to be less successful for inpatients and patients with previous VTE or cancer.[16] Prospective validation of the age-adjusted D-dimer threshold to rule out DVT is currently ongoing (ClinicalTrials.gov identifier: NCT02384135).

Diagnostic Strategies for Suspected PE

Aiming to simplify diagnostic management of suspected PE, the YEARS diagnostic algorithm includes presence of clinical signs of DVT, presence of hemoptysis, determination of PE to be the most likely diagnosis, and D-dimer level at 2 different thresholds. Pulmonary embolism is excluded if (1) none of these criteria are present and the D-dimer level is less than 1000 ng/mL or (2) there are 1 or more criteria present and the D-dimer level is less than 500 ng/mL. When YEARS was tested in a Netherlands-based multicenter cohort study, 48% of patients could be managed without imaging with a false-negative rate lower than 1%.[27] However, D-dimer was measured before clinical assessment was performed, hemoptysis was uncommon, and the a priori knowledge of the existing clinical prediction rules may have influenced the determination of PE as the most likely diagnosis.[27] Further validation is needed before YEARS is used in clinical practice.

Imaging for Suspected DVT

Emergency Physician–Performed Ultrasonography | Ultrasonography is time consuming and generally performed by dedicated, trained technicians. This requirement and lack of 24-hour availability has led to bedside testing by emergency physicians. Emergency physicians can perform compression ultrasonography of the proximal veins within 15 minutes with good overall diagnostic accuracy; the pooled sensitivity is 96% and specificity is 97% for DVT diagnosis, suggesting potential clinical utility with the caveat that diagnostic accuracy is operator dependent.[28]

Magnetic Resonance Venography | Magnetic resonance venography may be a valuable alternative test for those in whom ultrasonography results are inconclusive and DVT cannot be ruled out. A meta-analysis reported a promising diagnostic accuracy with

Table 2. Major Therapeutic Advances in VTE

Source	Type of Evidence	No. of Studies	No. of Patients (% With PE)	Phase of Treatment	Intervention	Control	Occurrence Rate or RR/OR/HR (95% CI) for Primary Outcome
Oral Anticoagulants							
Gomez-Outes et al,[39] 2014	Meta-analysis	6	27 127 (43)	Initial and long-term	DOAC	LMWH/VKA	Recurrent VTE: RR, 0.91 (0.79-1.06); major bleeding: RR, 0.62 (0.45-0.85)
Gomez-Outes et al,[40] 2015	Meta-analysis	6	27 127 (NR)	Initial and long-term	DOAC	LMWH/VKA	Case-fatality recurrent VTE: RR, 1.09 (0.77-1.55); case-fatality major bleeding: RR, 0.57 (0.25-1.30)
		4	5036 (NR)	Extended	DOAC	VKA or placebo	Case-fatality recurrent VTE: RR, 2.02 (0.75-5.43); no fatal bleeding during extended treatment
Garcia et al,[42] 2016	Meta-analysis	3	383 (NR)	Initial	10-mg nomogram	5-mg nomogram	Therapeutic INR by day 5: RR, 1.27 (1.05-1.54)
Li et al,[43] 2015[a]							
	Meta-analysis	6	2029[b]	Initial	Pharmacogenetic testing	Standard anticoagulation strategy	Thromboembolic events: RR, 0.38 (0.17-0.85)
	Meta-analysis	6	2029[b]	Initial	Pharmacogenetic testing	Standard anticoagulation strategy	Major bleeding: RR, 0.57 (0.37-0.90)
	Meta-analysis	9	2278[b]	Initial	Pharmacogenetic testing	Standard anticoagulation strategy	Time in therapeutic INR range: 4.65% (0.01%-9.29%)[c]
	Meta-analysis	6	2043[b]	Initial	Pharmacogenetic testing	Standard anticoagulation strategy	INR >4: RR, 0.92 (0.81-1.06)
Marik and Cavallazzi,[68] 2015[a]							
	Meta-analysis	2	533 (78)	Extended	VKA	Placebo	Recurrent VTE: OR, 0.09 (0.03-0.25); major bleeding: OR, 5.13 (0.87-30.15)
	Meta-analysis	3	5021 (36)	Extended	DOAC	Placebo	Recurrent VTE: OR, 0.16 (0.11-0.24); major bleeding: OR, 1.88 (0.19-18.06)
	Meta-analysis	2	1224 (41)	Extended	Aspirin	Placebo	Recurrent VTE: OR, 0.62 (0.44-0.87); major bleeding: OR, 1.28 (0.47-3.48)
Schulman et al,[70] 2013	RCT	1	2856 (35)	Extended	Dabigatran	VKA	Recurrent VTE: RR, 1.44 (0.78-2.64); major bleeding: RR, 0.52 (0.27-1.02)
Weitz et al,[69] 2017							
	RCT	1	3365 (50)	Extended	Rivaroxaban, 20 mg/d	Aspirin	Recurrent VTE: HR, 0.34 (0.20-0.59); major bleeding: HR, 2.01 (0.50-8.04).
	RCT	1	3365 (50)	Extended	Rivaroxaban, 10 mg/d	Aspirin	Recurrent VTE: HR, 0.26 (0.14-0.47); major bleeding: HR, 1.64 (0.39-6.84)
Thrombolysis							
Watson et al,[46] 2016[a]							
	Meta-analysis	9	529 (0)	Initial	Thrombolysis plus anticoagulation	Anticoagulation	All-cause mortality: RR, 0.76 (0.31-1.89)
	Meta-analysis	17	1103 (0)	Initial	Thrombolysis plus anticoagulation	Anticoagulation	Major bleeding: RR, 2.23 (1.41-3.52)
	Meta-analysis	3	306 (0)	Initial	Thrombolysis plus anticoagulation	Anticoagulation	Postthrombotic syndrome: RR, 0.66 (0.53-0.81)
Vedantham et al,[47] 2017	RCT	1	692 (0)	Initial	Catheter-directed thrombolysis	Anticoagulation	Postthrombotic syndrome: RR, 0.96 (0.82-1.11)
Engelberger et al,[48] 2015	RCT	1	48 (0)	Initial	Ultrasound-assisted catheter-directed thrombolysis	Catheter-directed thrombolysis	Thrombus load reduction: 55% vs 54% (P = .91)

(continued)

Table 2. Major Therapeutic Advances in VTE (continued)

Source	Type of Evidence	No. of Studies	No. of Patients (% With PE)	Phase of Treatment	Intervention	Control	Occurrence Rate or RR/OR/HR (95% CI) for Primary Outcome
Engelberger et al,[49] 2017	RCT	1	45 (0)	Initial	Ultrasound-assisted catheter-directed thrombolysis	Catheter-directed thrombolysis	Venous patency: 100% vs 100% (*P* = .91); postthrombotic syndrome: 17% vs 5% (*P* = .47); Chronic Venous Insufficiency Questionnaire–20 score: 29 points vs 26 points (*P* = .30)
Hao et al,[50] 2015[a]							
	Meta-analysis	10	1841 (100)[d]	Initial	Thrombolysis plus anticoagulation	Anticoagulation	All-cause mortality: OR, 0.60 (0.36-1.01)
	Meta-analysis	8	1707 (100)[d]	Initial	Thrombolysis plus anticoagulation	Anticoagulation	Recurrent PE: OR, 0.39 (0.17-0.86)
	Meta-analysis	8	1699 (100)[d]	Initial	Thrombolysis plus anticoagulation	Anticoagulation	Major bleeding: OR, 3.35 (2.06-5.45)
Konstantinides et al,[52] 2017	RCT	1	709 (100)	Initial	Thrombolysis plus anticoagulation	Placebo plus anticoagulation	All-cause mortality: 20% vs 18% (*P* = .43); clinical symptoms: 36% vs 30% (*P* = .23); right ventricular dysfunction: 44% vs 37% (*P* = .20)
Vena Cava Filters							
Mismetti et al,[53] 2015	RCT	1	399 (100)	Initial	Inferior vena cava filter plus anticoagulation	Anticoagulation	Recurrent PE: RR, 2.00 (0.51-7.89)
Compression Stockings							
Subbiah et al,[56] 2016	Meta-analysis	6	1462 (0)	Initial and long-term	Compression stockings	No stockings/placebo	Postthrombotic syndrome: OR, 0.56 (0.27-1.16)
Cancer-Associated VTE							
Raskob et al,[57] 2018	RCT	1	1046 (63)	Initial and long-term	LMWH/edoxaban	Dalteparin	Recurrent VTE or major bleeding: HR, 0.97 (0.70-1.36)
Young et al,[58] 2018	RCT	1	406 (73)	Initial	Rivaroxaban	Dalteparin	Recurrent VTE: HR, 0.43 (0.19-0.99); major bleeding: HR, 1.83 (0.68-4.96)
Isolated Distal DVT							
Franco et al,[60] 2017	Meta-analysis	20	2936 (100)	Initial and long-term	Anticoagulation	No treatment	Recurrent VTE: OR, 0.50 (0.31-0.79); major bleeding: OR, 0.64 (0.15-2.73)
Righini et al,[61] 2016	RCT	1	259 (100)	Initial and long-term	LMWH	Placebo	Proximal clot extension, contralateral proximal DVT, or symptomatic PE: 3% vs 5% (*P* = .54); major or clinically relevant nonmajor bleeding: 4% vs 0% (*P* = .26)
Unprovoked VTE							
Palareti et al,[62] 2014	Cohort	1	1010 (46)	Extended	D-dimer testing	NA	Recurrent VTE in patients with negative D-dimer and no anticoagulation: 3.0% (2.2%-4.4%) per patient-year
Kearon et al,[63] 2015	Cohort	1	410 (55)	Extended	D-dimer testing	NA	Recurrent VTE in patients with negative D-dimer and no anticoagulation: 6.7% (4.8%-9.0%) per patient-year
Rodger et al,[65] 2017	Cohort	1	2747 (55)	Extended	HERDOO2 rule	NA	Recurrent VTE in low-risk women and no anticoagulation: 3.0% (1.8%-4.8%) per patient-year

Abbreviations: DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; HR, hazard ratio; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NA, not applicable; NR, not reported; OR, odds ratio; PE, pulmonary embolism; RCT, randomized clinical trial; RR, relative risk; VKA, vitamin K antagonist; VTE, venous thromboembolism.

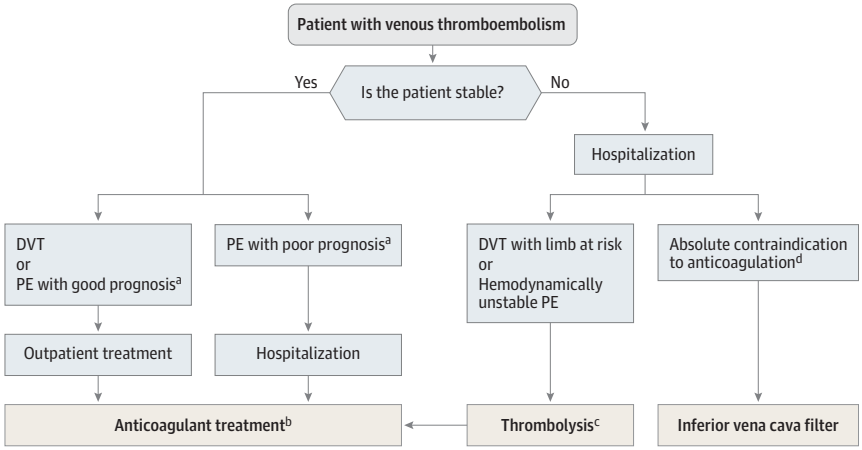
[a] Pooling of studies for meta-analyses was done only when outcome measures were sufficiently similar across included studies. Therefore, the number of studies and number of patients differ for different outcomes.

[b] Indication for anticoagulation included VTE, atrial fibrillation/flutter, preoperative orthopedics, heart valve replacement, thromboembolic disease, congestive heart failure, and rheumatic heart disease.

[c] Mean difference.

[d] Subgroup analysis of patients with submassive PE only.

Figure 2. Approach to Initial Treatment of Venous Thromboembolism (Onset Through Days 5-10)



Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

[a] Assessment of 30-day mortality risk with the Pulmonary Embolism Severity Index score or its simplified version or the Hestia criteria.

[b] Initiate treatment with direct oral anticoagulants (rivaroxaban or apixaban, or initial low-molecular-weight heparin followed by dabigatran or edoxaban). Vitamin K antagonists, following a low-molecular-weight heparin lead-in, are indicated for patients with a creatinine clearance of less than 30 mL/min and those with concomitant use of potent P-glycoprotein inhibitors or cytochrome P450 3A4 inhibitors or inducers.

[c] Catheter-directed thrombolysis for DVT and systemic thrombolysis for PE.

[d] Active bleeding, high risk of bleeding, or other contraindication to anticoagulant therapy.

summary estimate sensitivity and specificity of 93% and 96% for DVT, respectively.[29] However, the heterogeneity and quality of the included studies, as well as the small number of patients evaluated, warrant caution. Furthermore, magnetic resonance venography has not been validated in a management study, so it cannot be recommended for routine use.[17,18,20] It may benefit specific populations in whom ultrasonography is not feasible, such as morbidly obese patients.

Imaging for Suspected PE

Computed tomography pulmonary angiography has a good diagnostic accuracy for PE, is widely available, is relatively easy to perform, and, therefore, in most situations has replaced ventilation/perfusion ($\dot{V}/\dot{Q}$) scintigraphy and pulmonary angiography as the first-choice imaging test for suspected PE.[18,19] However, it exposes patients to ionizing radiation, and contrast medium is contraindicated in patients with severe renal impairment and has the risk of renal toxicity and allergic reactions. Alternative tests may overcome these disadvantages.

Compression Ultrasonography of the Lower Limb | Because a confirmed diagnosis of proximal DVT in patients with suspected PE is highly predictive of PE and warrants treatment with an anticoagulant, compression ultrasonography may also be used to establish a diagnosis of PE.[19] Importantly, a negative result does not exclude PE and requires further investigation, as confirmed by a meta-analysis in which the sensitivity of proximal ultrasonography was low (41%) although specificity was high (96%).[30]

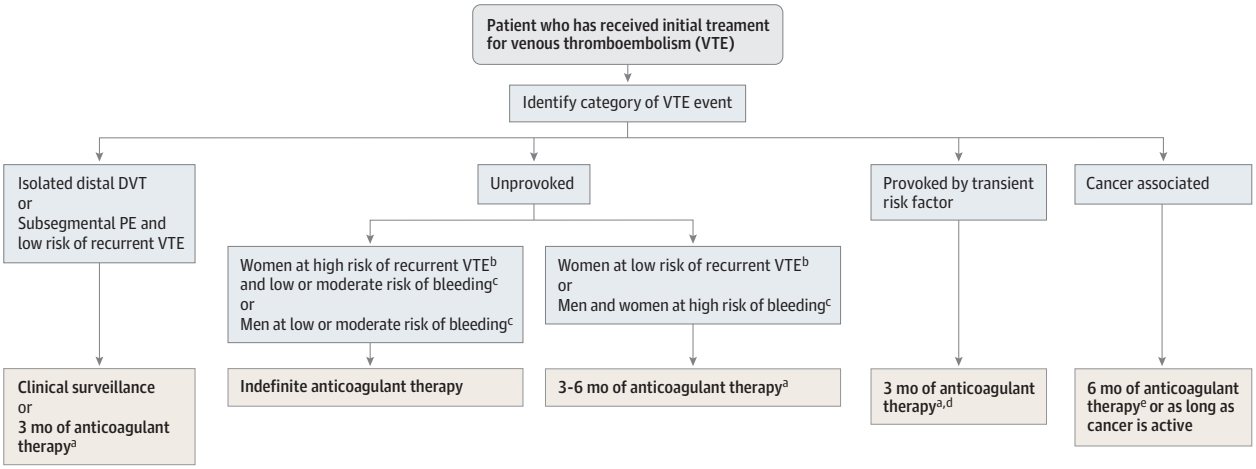
Magnetic Resonance Imaging | Magnetic resonance imaging avoids ionizing radiation and intravenous contrast providing a theoretical advantage over CTPA. A meta-analysis assessing the efficacy of MRI for establishing the diagnosis of PE showed the test to be inconclusive in 19% of cases limiting its ability for use in diagnosing PE.[19,31]

$\dot{V}/\dot{Q}$ Scintigraphy and $\dot{V}/\dot{Q}$ Single-Photon Emission Computed Tomography | Ventilation/perfusion single-photon emission computed tomography is an emerging technique that results in considerably less radiation exposure than CTPA and avoids the need for intravenous contrast. The diagnostic accuracy of PE in terms of sensitivity and specificity is similar to CTPA, and both perform better than planar $\dot{V}/\dot{Q}$ scintigraphy.[32] However, the efficacy and safety of this technology has not been sufficiently validated for use in routine clinical practice.

Major Therapeutic Advances

There are 3 phases of VTE treatment: the initial (first 5-10 days), long-term (from end of acute treatment to 3-6 months), and extended (beyond 3-6 months) periods. The benefits of anticoagulation, including prevention of clot extension, PE, recurrent VTE, hemodynamic collapse, and death, should be carefully weighed against the risk of bleeding to determine the choice of anticoagulant and the duration of therapy. Most patients with DVT and many with PE can be treated as outpatients (**Figure 2** and **Figure 3**).[33-36] To estimate the risk of recurrent VTE and guide decisions on treatment duration, VTE events are classified as being "provoked" by a transient or persistent risk factor or as "unprovoked" in the absence of any identifiable risk factors for VTE.[37] In patients with VTE provoked by surgery, the risk of recurrence after treatment is low (<1% after 1 year and 3% after 5 years); those with VTE caused by a nonsurgical transient risk factor, such as immobilization, pregnancy, or estrogen therapy, have an intermediate risk of recurrent VTE (5% after 1 year and 15% after 5 years).[10] In both situations, anticoagulation is recommended for only 3 months, as previous randomized trials showed that major bleeding risk during extended anticoagulant treatment beyond this period outweighed the risk of recurrent VTE.[10,18-20] Patients with cancer-associated VTE have a high risk of recurrence (15% annualized), and therapy may be given until the cancer is cured,[10,18-20] although clinical trials supporting

Figure 3. Approach to Long-term and Extended Treatment of VTE (After Initial Treatment)



Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

[a] Anticoagulation with direct oral anticoagulants (rivaroxaban or apixaban, or initial low-molecular-weight heparin followed by dabigatran or edoxaban). Vitamin K antagonists are indicated for patients with a creatinine clearance of less than 30 mL/min and those with concomitant use of potent P-glycoprotein inhibitors or cytochrome P450 3A4 inhibitors or inducers.

[b] If transient risk factor is nonsurgical (eg, immobilization, pregnancy, or estrogen therapy), extended treatment can be considered given the safety profile of direct oral anticoagulants.

[c] Edoxaban or low-molecular-weight heparin.

[d] Low-risk women according to the HERDOO2 rule.

[e] Bleeding risk according to HAS-BLED score. HAS-BLED categorizes patients into low (score, 0-2) or high (score, ≥3) risk.

this recommendation are lacking. When a patient does not have any identifiable risk factors for VTE, the event is classified as unprovoked. Patients with a first unprovoked VTE have a high risk of recurrence of VTE (10% after 1 year and 30% at 5 years) and should therefore receive indefinite therapy unless bleeding risk is high.[10,18-20] The risk in men is at least double that in women.

Initial and Long-term Treatment of VTE

Oral Anticoagulants

Over the past decade, direct oral anticoagulants (DOACs), including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, have been studied and are now recommended by the 2016 American College of Chest Physicians and 2014 and 2017 European Society of Cardiology guidelines for both DVT and PE.[10,19,20] These anticoagulant agents have several advantages over vitamin K antagonists (VKAs), including a rapid onset of action and predictable pharmacokinetic profile, which allow for simplified drug administration in a standardized dose and avoid the need for laboratory monitoring and dose adjustments. Dabigatran and edoxaban were studied for treatment of acute VTE following initial low-molecular-weight heparin (LMWH) treatment for at least 5 days and rivaroxaban and apixaban without antecedent LMWH. There has been no direct comparison of DOACs with one another, and the choice for one drug over another is based on different treatment regimens, patient characteristics, and patient preference. Vitamin K antagonists remain the preferred treatment for patients with severe renal impairment. Similarly, DOACs are generally avoided in patients with concomitant use of potent P-glycoprotein inhibitors or cytochrome P450 3A4 inhibitors or inducers, including azole antimycotics (eg, ketoconazole), several protease inhibitors used for human immunodeficiency virus treatment (eg, ritonavir), and antiepileptic drugs (in particular, phenytoin and carbamazepine), because they can alter plasma levels of DOACs.

Compared with initial LMWH followed by long-term VKA treatment, DOACs are noninferior for recurrent VTE and are associated with a lower risk of major bleeding, as defined by the International Society on Thrombosis and Hemostasis[38] (absolute risk, 1.1% vs 1.8%; risk ratio, 0.62; 95% CI, 0.45-0.85) in the first months of VTE treatment.[39] All-cause mortality and case-fatality rates of recurrent VTE or major bleeding with DOACs are comparable with rates with LMWH/VKA.[40] DOAC therapy is currently more expensive than treatment with VKAs. Monthly costs range between $333 and $419 with DOACs, whereas generic VKAs cost $8 per month.[41]

In patients treated with VKA after initiation of parenteral anticoagulant therapy, use of a 10-mg warfarin nomogram—ie, a loading dose of 10 mg warfarin on days 1 and 2 with subsequent doses depending on the international normalized ratio value on day 3—more rapidly achieves a therapeutic international normalized ratio on day 5 than does a 5-mg nomogram, without adverse outcomes.[42]

Pharmacogenetic testing for variations of cytochrome P450 2C9 and vitamin K epoxide reductase complex subunit 1 genes in patients initiating VKA therapy may have the potential to reduce thromboembolic events and major bleeding compared with a standard dosing strategy,[43] but adequate comparisons with validated dose-response nomograms have not been performed and pharmacogenetic testing is unlikely to be cost-effective.[44]

A table summarizing the oral anticoagulants used to treat VTE is partially reprinted from *The Medical Letter on Drugs and Therapeutics* in this issue of *JAMA*.[45]

Thrombolysis

Deep Vein Thrombosis | Catheter-directed thrombolysis as initial treatment of acute DVT is currently recommended only for patients with threatened limb loss.[10] A Cochrane review including patients with acute proximal DVT showed that thrombolysis plus anticoagulation compared with anticoagulation alone may reduce postthrombotic

syndrome by one-third (risk ratio, 0.66; 95% CI, 0.53-0.81).[46] However, thrombolysis appeared to have no effect on occurrence of PE, recurrent DVT, or death and, moreover, has an increased bleeding risk.[39] Results did not differ between thrombolytic agents or route of administration (systemic vs locoregional vs catheter directed).[46] The recent randomized trial ATTRACT confirmed these findings, as pharmacomechanical catheter-directed thrombolysis (ie, local administration of thrombolytic agent with concomitant thrombus aspiration or maceration) compared with anticoagulation alone did not lead to better results with regard to VTE recurrence or mortality and led to an increased risk of major bleeding in the first 10 days.[47] Notably, the occurrence of postthrombotic syndrome after 24 months was similar in both treatment groups, suggesting no role for catheter-directed thrombolysis in routine management of DVT.[47] Similarly, because ultrasound-assisted thrombolysis appears to have no benefit over conventional catheter-directed thrombolysis, it should not be used.[48,49] Whether any subgroup of patients with DVT without threatened limb loss may benefit from systemic or catheter-directed thrombolysis remains to be determined.

Pulmonary Embolism | Systemic thrombolysis as initial therapy is currently recommended by the 2016 American College of Chest Physicians and 2014 European Society of Cardiology guidelines only for patients with acute massive or high-risk PE; ie, those presenting with hemodynamic compromise, broadly defined as a systolic blood pressure of less than 90 mm Hg.[10,19] For patients with intermediate-risk or submassive PE (ie, hemodynamically stable patients with signs of right ventricular dysfunction on imaging and elevated cardiac biomarkers), thrombolysis is not recommended because in these patients the benefits from reperfusion are counterbalanced by the high risk of intracranial hemorrhage and nonintracranial major bleeding.[10,19,50] Systemic administration of thrombolysis plus heparin compared with heparin reduced the risk of recurrent PE at the expense of an increase in major bleeding.[50] Conflicting results have been published with regard to overall mortality and a lack of evidence limits comparison of PE-related mortality.[51] Two-year follow-up of the large PEITHO study in patients with intermediate-risk PE, in which systemic thrombolysis plus heparin was compared with placebo plus heparin, showed no difference with regard to all-cause mortality or right ventricular dysfunction, confirming that thrombolysis should not be used in non–high-risk patients.[52]

Vena Cava Filters

Inferior vena cava filters may be used in patients with proximal DVT or PE who have an absolute contraindication to anticoagulant therapy but are not recommended in those who can receive anticoagulation.[10,18-20] The use of a retrievable inferior vena cava filter for 3 months in addition to standard anticoagulation compared with anticoagulation alone was recently evaluated in a randomized trial including 399 hospitalized patients with severe acute PE.[53] There was no reduction in recurrent PE or death at 3- and 6-month follow-up.[53] The use of inferior vena cava filters in patients with a contraindication to anticoagulation remains controversial. Recent retrospective data suggest that in these patients, inferior vena cava filters are associated with an increased 30-day mortality rate.[54] Despite compelling evidence, guideline recommendations, and the US Food and Drug Administration warning about filter complications in 2010, usage rates across the United States remain high.[55]

Compression Stockings

The use of graduated compression stockings after acute proximal DVT does not reduce the incidence of postthrombotic syndrome compared with placebo or no stockings.[56] Accordingly, compression stockings are recommended only as symptomatic treatment in patients with acute or chronic symptoms, such as swelling and discomfort.[10,18,20]

Cancer-Associated VTE

Cancer patients have an increased risk of both recurrent VTE and bleeding complications. The 2016 American College of Chest Physicians and 2014 and 2017 European Society of Cardiology guidelines recommend long-term daily subcutaneous LMWH as the first-choice drug in patients with cancer-associated VTE.[10,18,19] Recently, 2 randomized trials compared DOACs with LMWH for treatment of VTE in cancer patients. The Hokusai VTE Cancer trial showed that the factor Xa inhibitor edoxaban, given orally once daily, was noninferior to the LMWH dalteparin, given as a subcutaneous injection once daily, for the composite outcome of recurrent VTE or major bleeding.[57] The absolute rate of recurrent VTE at 12 months was lower with edoxaban (7.9% vs 11.3%; hazard ratio [HR], 0.71; 95% CI, 0.48-1.06; $P = .09$), while the absolute rate of major bleeding was higher (6.9% vs 4.0%; HR, 1.77; 95% CI, 1.03-3.04; $P = .04$), mainly because of upper gastrointestinal tract bleeding in patients with gastrointestinal cancer. The SELECT-D pilot trial, in which rivaroxaban was compared with dalteparin for treatment of cancer-associated VTE, reported similar results.[58] The absolute rate of recurrent VTE at 6 months was lower with rivaroxaban (4% vs 11%; HR, 0.43; 95% CI, 0.19-0.99) at the expense of a higher major bleeding rate (6% vs 4%; HR, 1.83; 95% CI, 0.68-4.96).[58] The 2018 guidance of the International Society on Thrombosis and Hemostasis suggests specific DOACs (edoxaban or rivaroxaban) for treatment of cancer-associated VTE in patients with a low risk of bleeding and no drug-drug interactions with DOACs.[59] In the United States, edoxaban costs $337, rivaroxaban $333, and dalteparin $3527 per month,[41] so in addition to having similar efficacy, DOACs are less expensive than dalteparin. Apixaban is currently being evaluated in cancer-associated VTE (ClinicalTrials.gov identifiers: NCT03045406, NCT03080883).

Isolated Distal DVT

The 2016 American College of Chest Physicians guidelines suggest that ultrasound surveillance of isolated distal DVT to monitor for thrombus extension to the proximal veins is preferred over anticoagulation in patients with a low risk of extension.[10] However, a meta-analysis suggested that anticoagulation may reduce risk of VTE recurrence without increasing risk of bleeding.[60] This meta-analysis was limited by substantial heterogeneity across the included studies, mainly due to differences in study design, patient characteristics, and treatment regimens. In contrast, the only double-blind, randomized, placebo-controlled trial to date examining this question showed that LMWH therapy for 6 weeks was not superior to placebo in reducing risk of proximal extension, contralateral DVT, or symptomatic PE in low-risk outpatients with symptomatic distal DVT, and risk of bleeding was increased with LMWH.[61] This study was prematurely terminated because of slow recruitment, expiration of the study drug, and lack of funding to manufacture new study drug batches, precluding arriving at definitive conclusions about the best approach for managing isolated distal DVT.[61]

Extended Treatment

Unprovoked VTE

Extended treatment for long-term prevention of recurrent VTE is indicated for patients with unprovoked VTE, unless bleeding risk is high.

Negative (normal) D-dimer levels measured serially after stopping anticoagulation are associated with a low risk of recurrent VTE and may be used to guide the decision to stop anticoagulant treatment in women but not in men, because they have an unacceptably high risk of recurrent VTE even if D-dimer levels are normal (9.7% per patient-year; 95% CI, 6.7%-13.7%).[62,63] However, the requirement for measurement of D-dimers while not receiving treatment, the use of different cutoffs to define a normal test result, and the use of different D-dimer assays in the validation studies call into question the utility of this approach.

The HERDOO2 clinical decision rule was developed to identify patients with a first unprovoked VTE who have a low recurrence risk that may not require extended anticoagulation.[64] Women with 0 or 1 of the following criteria have a low risk of recurrent VTE: signs of postthrombotic syndrome in either leg (hyperpigmentation, edema, or redness), a VIDAS D-dimer level of at least 250 µg/L while taking an anticoagulant 6 months after initiation of treatment, a body mass index of at least 30, and age 65 years or older.[65] Women with scores of 2 or more have a high risk of recurrent VTE. HERDOO2 cannot be applied to men because when it was developed, no subgroup of men with unprovoked VTE had an annual VTE recurrence risk of less than 3%. A recent prospective management study demonstrated that HERDOO2 effectively predicted a low risk of recurrence for women who had unprovoked VTE and subsequently had less than 3.0% annual risk of recurrent VTE while not receiving anticoagulant treatment.[65] The DASH and Vienna prediction scores for recurrent VTE have not been externally validated in prospective management studies, limiting their utility.[66,67]

Oral Anticoagulants

The 2016 American College of Chest Physicians and 2014 and 2017 European Society of Cardiology guidelines suggest extended therapy with DOACs over VKAs or low-dose aspirin in patients without cancer.[10,19,20] Compared with placebo or aspirin, extended therapy with DOACs or VKAs significantly reduces the risk of recurrent VTE.[68-71] Compared with VKAs, dabigatran and edoxaban are as effective and are associated with a lower risk of major bleeding (0.9% vs 1.8%; HR, 0.52; 95% CI, 0.27-1.02 for dabigatran; 0.3% vs 0.7%; HR, 0.45; 95% CI, 0.22-0.92 for edoxaban).[70-72] In contrast to extended treatment with VKAs,[73] the introduction of DOACs has enabled extended anticoagulant therapy at a lower dosage, as apixaban and rivaroxaban at prophylactic dosages (10 mg once daily and 2.5 mg twice daily, respectively) are associated with similar efficacy as at therapeutic dosages (20 mg once daily and 5 mg twice daily, respectively) and a bleeding risk comparable with placebo and aspirin (absolute risk of major bleeding <0.5% per year).[69,74]

Discussion

Improvement of existing diagnostic algorithms to reduce the number of unnecessary imaging examinations is desirable because the widespread use of advanced imaging techniques may lead to detection of clinically insignificant clots, resulting in patients undergoing anticoagulation therapy with the risks of treatment outweighing the benefits. There is a particular need to improve the specificity of clinical decision rules and D-dimer thresholds for inpatients and patients with cancer or previous VTE, who are susceptible to false-positive imaging results. An ongoing study is evaluating which predictors may improve existing clinical prediction rules for patients with prior VTE who have a suspected recurrence (ClinicalTrials.gov identifier: NCT02297373).

Evidence for withholding anticoagulant therapy in specific subgroups is emerging, especially for those with small VTE. For patients with isolated distal DVT, the most recent American College of Chest Physicians antithrombotic therapy guidelines suggest that patients with isolated subsegmental PE at low risk of progression or recurrence may not require anticoagulation.[10] The safety of withholding anticoagulation in patients with subsegmental PE and negative bilateral ultrasonography of the proximal leg veins is currently under investigation (ClinicalTrials.gov identifier: NCT01455818).

To better guide decisions on the duration of anticoagulant therapy in patients with unprovoked VTE, the lack of a bleeding risk score that has been prospectively validated in a management study remains an important knowledge gap. In the forthcoming years, bleeding risk assessment should be improved to tailor individual treatment strategies. However, given the lower bleeding risk with DOACs, the benefit-risk profile of anticoagulant treatment may have shifted, and patients with an intermediate risk of recurrent VTE, such as patients with VTE provoked by a nonsurgical transient risk factor, may now benefit from extended treatment because bleeding risk may no longer exceed risk of recurrence.

A concern regarding DOACs is the lack of agents to reverse the anticoagulant effect. Idarucizumab has been approved for reversal of dabigatran[75] and andexanet alfa for reversal of apixaban and rivaroxaban,[76] but the need for these products will be difficult to evaluate. Given the short half-life of DOACs, cessation of the drug and supportive care may be sufficient for the majority of bleeding cases. Despite no specific reversal agents for the thousands of patients in the original trials of DOACs in VTE and atrial fibrillation, the risk of death due to major bleeding was substantially less than those that occurred with VKAs.[77]

Direct oral anticoagulants are currently associated with higher treatment costs than VKAs and may therefore not be affordable to all patients.[41]

There is currently insufficient evidence to support the use of DOACs in patients with significant renal impairment, antiphospholipid syndrome, heparin-induced thrombocytopenia, or venous thrombosis at unusual sites, such as splanchnic vein thrombosis. Large trials assessing the efficacy and safety of DOACs in these specific patient populations are ongoing.

Conclusions

In the past 5 years, substantial progress has been made in the management of VTE, allowing for diagnostic and therapeutic strategies tailored to individual patient characteristics, preferences, and values. Further studies should aim to improve VTE management and will need to target specific issues as outlined in this review.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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