Review

Treatment of Venous Thromboembolism

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IMPORTANCE Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common, potentially lethal condition with acute morbidity.

OBJECTIVE To review the etiology of VTE and the 3 phases of VTE treatment: acute (first 5-10 days), long-term (from end of acute treatment to 3-6 months), and extended (beyond 3-6 months).

EVIDENCE REVIEW Cochrane reviews, meta-analyses, and randomized controlled trials, as well as other clinical trials for topics not covered by the former, were reviewed. Literature searches using broad terms were used to find meta-analyses published in the last 15 years. The ninth edition of the American College of Chest Physicians Antithrombotic Therapy Guidelines was used to supplement the literature search. Guidelines from specialty organizations were consulted when relevant. The Canadian Agency for Drugs and Technologies in Health was searched for relevant cost-effectiveness studies. We also searched our own literature database of 8386 articles for relevant research.

FINDINGS Low-molecular-weight heparin (LMWH) along with with vitamin K antagonists and the benefits and proven safety of ambulation have allowed for outpatient management of most cases of DVT in the acute phase. Development of new oral anticoagulants further simplifies acute-phase treatment and 2 oral agents can be used as monotherapy, avoiding the need for LMWH. Patients with PE can also be treated in the acute phase as outpatients, a decision dependent on prognosis and severity of PE. Thrombolysis is best reserved for severe VTE; inferior vena cava filters, ideally the retrievable variety, should be used when anticoagulation is contraindicated. In general, DVT and PE patients require 3 months of treatment with anticoagulants, with options including LMWH, vitamin K antagonists, or direct factor Xa or direct factor IIa inhibitors. After this time, decisions for further treatment are based on balancing the risk of VTE recurrence, determined by etiology of the VTE (transient risk factors, unprovoked or malignancy associated), against the risk of major hemorrhage from treatment. Better prediction tools for major hemorrhage are needed. Experience with new oral anticoagulants as acute, long-term, and extended therapy options is limited as yet, but as a class they appear to be safe and effective for all phases of treatment.

CONCLUSIONS AND RELEVANCE The mainstay of VTE treatment is anticoagulation, while interventions such as thrombolysis and inferior vena cava filters are reserved for limited circumstances. Multiple therapeutic modes and options exist for VTE treatment with small but nonetheless important differential effects to consider. Anticoagulants will probably always increase bleeding risk, necessitating tailored treatment strategies that must incorporate etiology, risk, benefit, cost, and patient preference. Although great progress has been made, further study to understand individual patient risks is needed to make ideal treatment decisions.

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Section Editor: Mary McGrae McDermott, MD, Senior Editor.

JAMA. 2014;311(7):717-728. doi:10.1001/jama.2014.65

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Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), has an estimated annual incidence of 0.1% to 0.27%, affecting up to 5% of the population during their lifetimes.[1,2] Approximately 20% of patients with PE die before diagnosis or on the first day after diagnosis; for those surviving more than 1 day, up to 11% may die in the first 3 months, even with adequate therapy, although many of these deaths are due to comorbidities associated with VTE.[3] Acute morbidity from DVT may include pain and swelling, which may limit ambulation or, in extreme cases, lead to arterial compromise. Acute PE may cause chest pain, at times necessitating analgesia; dyspnea and hypoxia necessitating oxygen therapy; or hypotension and shock. Long-term complications of VTE include postphlebitic syndrome from DVT in up to 40% and chronic thromboembolic pulmonary hypertension after PE in 1% to 4% of cases.[4,5] Prior to the development of anticoagulant therapy, untreated VTE was often fatal (30% of cases),[6] but anticoagulant therapy effectively treats symptoms and decreases recurrent VTE and death; however, its use increases the risk of major hemorrhage, which may be fatal in up to 25% of cases.[7] Understanding the balance of risk and benefit of treatment options informs management decisions. This balance is best evaluated from the perspectives of 3 phases: acute (first 5-10 days), long-term (first 3 months), and extended (beyond 3 months) and by etiology; ie, whether the initial VTE was provoked (by transient risk factors), unprovoked, or associated with malignancy. The acute and long-term phases are treated the same for provoked and unprovoked VTE. Etiology becomes relevant for the extended phase; malignancy-associated VTE has different recommendations in all phases of treatment.

DVT *deep vein thrombosis*

INR *international normalized ratio*

LMWH *low-molecular-weight heparin*

PE *pulmonary embolism*

PTS *postthrombotic syndrome*

VKE *vitamin K antagonist*

VTE *venous thromboembolism*

Methods

A PubMed search was conducted from inception to November 30, 2013, to find studies in humans on treatment of VTE using the terms relevant to VTE and all categories of anticoagulation and thrombolysis; studies were limited to clinical trials, meta-analyses, and randomized trials. This search resulted in 1535 articles. We also searched the Cochrane reviews database to find meta-analyses published in the last 15 years, the ninth edition of the American College of Chest Physicians Antithrombotic Therapy Guidelines, and our own literature database (Refman version 12) of 8753 articles for relevant research. The latter 2 in particular were used when no relevant randomized trials or meta-analyses were available. The search selected 222 articles as meta-analyses. These were reviewed, and only 80 were related to treatment; 68 were actual meta-analyses and 57 were relevant to this article. For treatment-related issues that were not covered by the meta-analyses, the 1287 articles selected as clinical trials or randomized trials were reviewed. The abstracts of the remaining articles after exclusion of the 222 meta-analyses were reviewed for relevant studies not covered by the included meta-analyses. PubMed, the National Institutes of Health databases, the Canadian Agency for Drugs and Technologies in Health, the UK National Institute for Health and Care Excellence, and our Refman database were searched for relevant cost-effectiveness studies (eFigure in the Supplement).

Treatment of Acute VTE

Initial Treatment

When VTE is first diagnosed, the objectives of its initial therapy are prevention of DVT extension or prevention of PE occurrence or recurrence and relief of acute symptoms while averting hemodynamic collapse or death. These indications are compelling, and when diagnostic testing for VTE is delayed, empirical administration of therapeutic dosages of low-molecular-weight heparin (LMWH) is indicated.[8]

Initial VTE treatment requires therapeutic dosages of unfractionated heparin (intravenous, subcutaneous monitored, or subcutaneous fixed dose), LMWH, rivaroxaban, or fondaparinux.[9-11] Although any of these drugs can be used, a recent meta-analysis comparing fixed-dose LMWH with unfractionated heparin administered as either an adjusted dose intravenously or an adjusted or fixed dose subcutaneously found that LMWH was associated with significantly fewer deaths (odds ratio, 0.76), less major hemorrhage (odds ratio, 0.57), and lower rates of recurrent VTE (odds ratio, 0.68).[12] Low-molecular-weight heparin is effective and easily administered, making it the preferred anticoagulant irrespective of VTE treatment in the outpatient or inpatient setting. Unfractionated heparin should be given to patients with renal insufficiency because LMWH is predominantly excreted in the urine. Details on the medications used to treat VTE are shown in **Table 1**.

Initial therapy with vitamin K antagonists (VKA) alone is not recommended because a randomized trial demonstrated significantly more recurrent symptomatic and asymptomatic VTE events in patients treated with VKAs alone.[13] When VTE is suspected, therapeutic dosages of unfractionated heparin or LMWH for a minimum of 5 days are given and continued until the international normalized ratio (INR) from the concomitant VKA therapy is therapeutic.[9] Low-molecular-weight heparin is given once daily. A meta-analysis suggested that fewer hemorrhages and recurrences might occur with twice-daily dosing of LMWH, but the differences between outcomes with once- and twice-daily dosing were not statistically significant.[14]

Oral Anticoagulants in the Acute Phase of Treatment

Once systemic anticoagulation is initiated and after initiation of parenteral therapy, VKAs can be started, except in malignancy-associated VTE (see below). A nomogram for optimizing VKA dosing was developed and validated by a randomized trial and subsequent observational studies. A nomogram using 10 mg of warfarin on days 1 and 2 is safe and achieves therapeutic INRs more rapidly than a 5-mg nomogram.[15] Difficulties associated with outpatient INR testing preclude use of this approach for all patients and in these, lower starting dosages are recommended.[16]

Insufficient evidence exists to support the use of VKA pharmacogenetic testing.[17] These tests are expensive, limiting their cost-effectiveness. Vitamin K antagonist pharmacogenetic testing may

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Table 1. Drugs for Treatment of Venous Thromboembolism

Drug by Class	Treatment Dosage	Pharmacokinetics		Pharmacokinetic Drug Interactions
		Half-Life	Renal Clearance, %	
Direct factor Xa inhibitors				All drugs in this class have increased levels with strong inhibitors of CYP3A4 and P-Gp and decreased levels with inducers of CYP3A4 and P-Gp
Rivaroxaban	15 mg orally, twice daily for 3 wk, then 20 mg orally every 24 h	7-11 h	33[a]	
Apixaban	10 mg orally, twice daily for 10 d, then 5 mg twice daily	8-12 h	25[a]	
Edoxaban	60 mg orally every 24 h after 7 to 10 d of low-molecular-weight heparin	6-11 h	35[a]	
Direct factor IIa inhibitors				Increased levels with strong inhibitors of P-Gp and amiodarone; decreased levels with inducers of P-Gp
Dabigatran	150 mg orally, twice daily after 7 to 10 d of low-molecular-weight heparin	14-17 h	80[a]	
Indirect factor Xa inhibitors				None
Fondaparinux	Weight <50 kg: 5 mg subcutaneously every 24 h Weight 50-100 kg: 7.5 mg subcutaneously every 24 h Weight >100 kg: 10 mg subcutaneously every 24 h	17-21 h	100	
Low-molecular-weight heparins				None
Dalteparin	200 IU/kg subcutaneously every 24 h or 100 IU/kg twice daily	3-4 h	Approximately 80	
Enoxaparin	1 mg/kg subcutaneously twice daily or 1.5 mg/kg subcutaneously every 24 h	3-4 h	Approximately 80	
Nadroparin	86 IU/kg subcutaneously twice daily or 171 IU/kg subcutaneously every 24 h	3-4 h	Approximately 80	
Tinzaparin	175 IU/kg subcutaneously every 24 h	3-4 h	Approximately 80	
Thrombolytics				None
Alteplase	For pulmonary embolism: 100 mg intravenously over 2 h	5 min	Approximately 2	
Unfractionated heparin	Treatment: weight-based bolus followed by weight-based continuous infusion adjusted to maintain therapeutic activated partial thromboplastin time or anti-Xa level Fixed subcutaneous dosing: 333 U/kg as first dose, then 250 U/kg twice daily	1.5 h	Approximately 30	
Vitamin K antagonists				Numerous drug interactions
Warfarin	Usual dose: 0.5-6 mg/d orally Adjust dose to maintain INR of 2-3; higher doses may be necessary in some patients	Approximately 36 h	Approximately 2	
Nicoumalone	As for warfarin	9 h	Approximately 2	
Phenprocoumon	As for warfarin	5.5 d	Approximately 2	

Abbreviations: CYP34A, cytochrome P450 34A; INR, international normalized ratio; P-Gp, P-glycoprotein.

[a] There are limited data in patients with creatinine clearance of less than 30 mL/min.

cost as much as $172 000 per quality-adjusted life-year.[18] Two randomized trials[19,20] were recently published that suggested that with pharmacogenetic-based dosing the INR was in the therapeutic range for a greater percentage of time but, as noted in the accompanying editorial, "these trials indicate that pharmacogenetic testing has either no ... or marginal usefulness, given the cost and effort required to perform this testing."[21]

Rivaroxaban, an oral direct factor Xa inhibitor, is a monotherapy (ie, acute and long-term treatment) useful for treating both DVT and PE. Compared with LMWH/VKA treatment, rivaroxaban was noninferior for (ie, not worse than) recurrent VTE rates and had similar or fewer major hemorrhages.[10,11] The ease of administration of this new drug coupled with the lack of a need to monitor the degree of anticoagulation makes rivaroxaban an attractive option for VTE treatment. However, the medication is costly in the United States, which may limit its overall utility. As with LMWH, rivaroxaban may not be appropriate for patients with renal insufficiency. The pivotal trials demonstrating the efficacy of rivaroxaban excluded patients with creatinine clearance levels less than 30 μmol/L. Only 5% of study patients had creatinine clearance levels ranging between 30 and 50 μmol/L.

Rivaroxaban has no reversal agent similar to vitamin K and clotting factors for warfarin. This could also limit the usefulness of the drug. However, warfarin reversibility does not improve outcomes in warfarin-related intracranial hemorrhage, suggesting that anticoagulation reversal may not influence outcomes when bleeding occurs.[22] Also, major hemorrhage mortality is similar in all the studies of new oral anticoagulants and is similar to death rates observed in patients with major hemorrhage attributable to VKAs (Table 2 and Table 3).

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Table 2. Results of Phase 3 Trials With New Oral Anticoagulants (NOACs)—Acute VTE

Source	Dosage	Treatment Duration, mo	Recurrent VTE (Fatal Events), %		Major Hemorrhage, %		Major Hemorrhage + CRNM, %		ICH, No.		No. of Fatal Major Bleeds (Case-Fatality Rate, %)	
			NOAC	SC[a]	NOAC	SC[a]	NOAC	SC[a]	NOAC	SC[a]	NOAC	SC[a]
Prins et al,[23] 2013 (n=8282)	Rivaroxiban, 15 mg twice daily for 3 wk, then 20 mg once daily (vs SC)	3, 6, or 12	2.1 (0.08)	2.3 (0.03)	1.0	1.7	9.4	10	5	13	3 (7.5)	8 (11.1)
Agnelli et al,[24] 2013 (n=5244)	Apixaban, 10 mg twice daily for 1 wk, then 5 mg twice daily (vs SC)	6	2.3 (<0.1)	2.7 (0.1)	0.6	1.8	4.3	9.7	3	6	1 (6.6)	2 (4)
Schulman et al,[25] 2009 (n=2539)	LMWH for 1 wk, then dabigatran, 150 mg twice daily (vs SC)	6	2.4 (0.1)	2.1 (0.2)	1.6	1.9	5.6	8.8	0	3	1 (5)	1 (4.2)
Büller et al,[26] 2013 (n=8240)	LMWH for 1 wk, then 60 mg edoxaban once daily[b] (vs SC)	3, 6, or 12	3.2 (0.1)	3.5 (0.1)	1.4	1.6	8.5	10.3	6	18	2 (3.6)	10 (15.2)

Abbreviations: CRNM, clinically relevant nonmajor hemorrhage; ICH, intracranial hemorrhage; LMWH, low-molecular weight heparin; VTE, venous thromboembolism.

[a] Standard care is LMWH followed by vitamin K antagonist.

[b] Patients aged ≥75 y or with weight ≤60 kg received edoxaban, 30 mg once daily.

Table 3. Results of Phase 3 Trials With New Oral Anticoagulants (NOACs)—Extended VTE

Source	Dosage	Treatment Duration	Recurrent VTE, %		Major Hemorrhage, %		Major Hemorrhage + CRNM, %		ICH, No.		No. of Fatal Major Bleeds (Case-Fatality Rate, %)	
			NOAC	Placebo	NOAC	Placebo	NOAC	Placebo	NOAC	Placebo	NOAC	Placebo
Agnelli et al,[27] 2013 (n=2486)[a]	Apixaban, 5 mg twice daily or 2.5 mg twice daily (vs placebo)	1 y	5 mg: 1.7 2.5 mg: 1.7	8.8	5 mg: 0.1 2.5 mg: 0.2	0.5	5 mg: 3.2 2.5 mg: 4.3	2.3	NA	NA	5 mg: 0 2.5 mg: 0	0
Bauersachs et al,[10] 2010 (n=1196)[a]	Rivaroxiban, 20 mg once daily (vs placebo)	6 or 12 mo	1.3	7.1	0.7	0	6.0	1.2	0	0	0	0
Schulman et al,[28] 2013 (RE-SONATE) (n=1343)[b]	Dabigatran, 150 mg twice daily vs placebo	≥6 mo	0.4	5.6	0.3	0	5.3	1.8	NA	NA	0	0
Schulman et al,[28] 2013 (RE-MEDY) (n=2586)[b]	Dabigatran, 150 mg twice daily (vs vitamin K antagonist [INR, 2-3])	0-36 mo	1.8	1.3	0.9	1.8	5.6	10.2	0	0	0	1 (4)

Abbreviations: CRNM, clinically relevant nonmajor hemorrhage; ICH, intracranial hemorrhage; INR, international normalized ratio; NA, data not available; VTE, venous thromboembolism.

[a] Patients had undergone 6 to 12 mo of anticoagulant treatment prior to study entry.

[b] Patients had undergone ≥3 mo of anticoagulant treatment prior to study entry.

Thrombolysis

Thrombolysis is an attractive therapy because it may restore patency in occluded veins, potentially reducing postthrombotic syndrome (PTS). Thrombolysis leads to earlier patency of an occluded vein but it does not decrease the rate of PE, and although meta-analyses suggest that it may decrease PTS at the expense of an increase in major bleeding, it has not been demonstrated to reduce the rate of recurrence, PE, or death.[29] Thrombolytic-associated reductions in PTS were seen in a recent randomized trial comparing catheter-directed thrombolysis with standard therapy for iliofemoral DVT.[30] Thrombolytic therapy almost doubled vein patency at 6 months (66% vs 47%) and was associated with significantly less PTS at 24 months (41% vs 56%). Thrombolysis was associated with more bleeding complications and did not prevent recurrent events, and mortality was no different in the 2 groups.

Retrospective and observational data suggest that catheter-directed thrombolysis may be preferred over systemic therapy, but the evidence for this is inadequate. Catheter-directed treatments have better rates of early vein patency and less bleeding risk, but the 2 delivery modes have not been directly compared with each other in any studies. Catheter-directed lysis may be useful if patients meet all of the following criteria: iliofemoral DVT, symptoms for less than 14 days, good functional status, life expectancy greater than 1 year, and low risk of bleeding.[9] Given the success of thrombolysis at establishing earlier vein patency, it is recommended for cases of impending venous gangrene with threatened limb loss.[9]

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Thrombolytic therapy as initial therapy for acute upper extremity DVT has been used with some success, but no randomized trials comparing thrombolysis with anticoagulation alone have been performed. There are no randomized trials of any treatment for upper extremity DVT.[9]

Systemic administration of thrombolysis for submassive PE has been studied in 2 well-performed randomized trials. Systemic thrombolysis does not reduce mortality and is associated with a greater risk of significant hemorrhage. Thrombolysis is recommended only for patients with PE who experience hemodynamic compromise or deterioration while receiving standard anticoagulant therapy.[31,32]

Vena Cava Filters

Retrievable or permanent inferior vena cava filters may be used when there is a contraindication to anticoagulation therapy (eg, recent hemorrhage, impending surgery) for patients with newly diagnosed proximal DVT or PE. One risk of these devices is development of thrombosis at the filter itself.[33] Consequently, a standard course of anticoagulant therapy should be administered if the contraindications to anticoagulation resolve.[34] If possible, the filter should be removed once therapy is safely accomplished. It is not known if retrievable filters placed in patients at high risk of death (eg, limited cardiopulmonary reserve) reduce PE-related mortality. Inferior vena cava filter placement in addition to anticoagulation does not improve survival in patients with DVT except in those with hemodynamically unstable PE or after thrombolytic therapy.[35,36] Insertion of filters increase the risk of recurrent DVT, an effect that offsets some of the benefits attributable to reduced PE.[35]

Postthrombotic Syndrome

Postthrombotic syndrome is a clinically important and frequent complication of DVT that has received relatively little attention. Prediction of which patients will develop PTS is not possible. It is also not known how to prevent PTS when VTE occurs. It was thought that graduated compression stockings reduced the risk of PTS following DVT, but this was shown to not be the case in a recent randomized, double-blind, placebo-controlled trial of more than 800 patients with DVT.[37] The cumulative incidence of PTS was 14.2% in the active compression stocking group (30-40 mm Hg compression stockings) and 12.7% in the placebo stocking group. Compression stockings can improve edema and pain in the acute stage of DVT and can also relieve symptoms in patients who develop PTS. However, stockings do not prevent the development of PTS.

One systematic review did identify 2 studies suggesting that 6 months of therapeutic dosages of tinzaparin compared with VKA therapy were more effective in reducing the risk of PTS.[38]

Inpatient vs Outpatient Treatment of VTE

Initial VTE treatment used to require hospitalization to administer heparin. Low-molecular-weight heparin has enabled outpatient management of VTE and also provides an alternative means of long-term anticoagulation for patients in whom warfarin treatment either is not optimal or is contraindicated. A meta-analysis identified 6 randomized trials comparing outpatient LMWH treatment with inpatient treatment demonstrated the safety and efficacy of this approach.[39] Avoiding hospitalization and managing DVT entirely through outpatient treatment using LMWH improves quality of life and reduces health care system expenditures.[40-42] Patients with DVT are unlikely to be suitable for outpatient treatment if they have severe symptoms, renal impairment, poor social circumstances, or a high risk of bleeding. Although the evidence supporting early ambulation following DVT is less than optimal, meta-analyses suggest that it has benefits, and it has been standard practice in many centers for decades.[43] A meta-analysis of early ambulation studies demonstrated that it reduced the severity of PTS at 1 month when high levels of physical activity were applied. If edema and pain are severe, delay in ambulation may be required and effective pain management implemented.

Outpatient treatment of PE is not universally accepted but has been standard practice in many Canadian centers.[37] Recent studies, including 2 randomized trials, support the safety and efficacy of outpatient PE management.[44-46] A systematic review of observational studies[47] combined with 4 more recent publications[44,48-50] supports the efficacy of outpatient management of PE because about 30% to 50% of all PE cases qualify as having a low risk of death. A recent meta-analysis showed that several prediction rules accurately select patients who are at low risk of death and therefore appropriate for outpatient PE management.[51] The Geneva, Pulmonary Embolism Severity Index, Aujesky, and Murugappan clinical prediction rules all identified patients with an in-hospital mortality risk of less than 1% who are suitable candidates for outpatient therapy (**Table 4**). **Figure 1** outlines a strategy for acute treatment of VTE.

Isolated calf DVT is less well studied than is PE or proximal vein DVT. In general, isolated calf DVT without severe symptoms or associated risk factors for extension of thrombus into proximal veins is managed by observation of the thrombus using serial ultrasound; ie, surveillance for proximal DVT. If a repeat ultrasound after 1 week of observation and conservative treatment demonstrates no extension, distal DVT patients rarely develop proximal DVT and anticoagulation can be withheld. Some studies suggest surveillance should be continued for 2 weeks.[56] If the clot causes severe symptoms or extends proximally, then it is treated like a proximal DVT as outlined above.[9] Upper extremity DVT occurs in 5% to 10% of all DVT and is subdivided into catheter-related (75% of cases) and non–catheter-related thrombosis. The axillary and more proximal veins are involved and there is a risk of PE, necessitating anticoagulation treatment using the same treatment regimens used for lower extremity DVT. The minimum duration of anticoagulation recommended is 3 months, and in the case of upper extremity DVT associated with a central catheter, therapy should be continued as long as the catheter remains in place. Catheter removal is not necessary if it remains functional.[9] Catheter-directed thrombolysis is sometimes advocated for so-called effort-induced upper extremity DVT in younger patients, presumed to be caused by thoracic outlet obstruction, but there are no randomized trials to support this. Thrombolysis is associated with higher costs and more adverse events in the short term.

Long-term and Extended Treatment of VTE

For most patients with VTE, VKAs such as warfarin effectively prevent recurrent thrombosis. New oral anticoagulant medications are now available for long-term prevention of recurrent thrombosis. The duration of long-term treatment and the decision for extended treat-

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Table 4. Prognostic Clinical Prediction Rules Identifying In-Hospital All-Cause Mortality of <1% (Low Risk) After Pulmonary Embolism

Geneva Prognostic Score[52]		Pulmonary Embolism Severity Index[53]		Aujesky et al, 2006[54]		Murugappan et al, 2008[55]	
Variables	No. of Points	Variables	No. of Points	Variables	No. of Points	Variables	No. of Points
Cancer	2	Age	No. of Years	Age >70 y	1	Need for hospitalization	NA
Heart failure	1	Male	10	Cancer	1	Anticoagulant allergy	NA
Previous DVT	1	Cancer	30	Heart failure	1	Pregnancy	NA
Systolic BP <100 mm Hg	2	Heart failure	10	Chronic obstructive lung disease	1	Venous thromboembolism recurrence risk predictors	NA
Pao_2 <8 kPa (60 mm Hg)	1	Chronic obstructive lung disease	10	Renal disease	1	Bleeding predictors	NA
DVT on ultrasound	1	Pulse >110/min	20	Cerebrovascular disease	1	Massive pulmonary embolism	NA
		Systolic BP <100 mm Hg	30	Pulse >110/min	1	Limited cardiopulmonary reserve	NA
		Respiratory rate	20	Systolic BP <100 mm Hg	1		
		Temperature <36°C	20	Altered mental status	1		
		Altered mental status	60	Arterial blood oxygen saturation <90%	1		
		Arterial blood oxygen saturation <90%	20				
Risk Class	**No. of Points**	**Risk Class**	**No. of Points**	**Risk Class**	**No. of Points**	**Risk Class**	**No. of Points[a]**
Low	≤2	I: very low	≤65	Low	0	Eligible for outpatient treatment	None of the above risk factor variables
High	>2	II: low	66-85	High	≥1	Ineligible for outpatient treatment	At least 1 of the above risk factor variables
		III: intermediate	86-105				
		IV: high	106-125				
		V:very high	≥126				
		I-II: low	≤85				
		III-IV: high	>85				

Abbreviations: BP, blood pressure; DVT, deep vein thrombosis; NA, not applicable.

[a] The Murugappan rule is a narrative score in that a patient is eligible if he or she has none of the described risk factors.

ment vary depending on risk of recurrent VTE.[9] Three months is usually recommended as the shortest treatment duration. Extended treatment for more than 3 months may be warranted if the anticipated benefits of continued anticoagulation outweigh potential harm from hemorrhage. Two meta-analyses have been influential on treatment decisions for anticoagulation duration for VTE.[57,58] These studies were limited because each VTE risk category included only a few hundred patients, resulting in wide confidence intervals for point estimates and uncertainty regarding optimal treatment duration. Studies examining 3 months vs 6 months of therapy are equivocal because of small numbers of participants in the various studies.[59] Nevertheless, some experts continue to recommend a minimum of 6 months of anticoagulation for treating VTE.

Aspirin has been studied for extended treatment of VTE. A recent network meta-analysis showed that the risk reduction for recurrent VTE is not significant for aspirin (odds ratio, 0.65; 95% CI, 0.39-1.03) but is significant for VKAs and the new oral anticoagulants (odds ratios of 0.07-0.18).[60] **Figure 2** summarizes an approach for long-term and extended phases of treatment.

Provoked (Transient Risk Factor) VTE

Transient risk factors increase thrombotic risk briefly and reversibly while a patient is exposed to a discrete event. After the event, thrombotic risk abates. Surgery is a transient risk factor and itself is associated with a very low thrombotic recurrence risk after adequate treatment (<1% at 1 year and 3% at 5 years after surgery). Surgery-induced VTE requires only 3 months of anticoagulation.[61]

When a patient has a first VTE following a nonsurgical event such as pregnancy, major trauma, or significant immobilization after medical illness, they have an intermediate risk of recurrent VTE (5% after 1 year and 15% after 5 years).[61] Despite the higher risk, 3 months of anticoagulation is still adequate. There is a slight mortality benefit for longer than 3 months of anticoagulation (2 fewer deaths per 1000 years of patient observations) but only if the risk of major bleeding is less than 1% per year.[9]

Pulmonary embolism is the leading cause of maternal mortality in the Western world. Venous thromboembolism incidence in pregnancy ranges from 0.6 to 1.7 episodes per 1000 deliveries, with one-third occurring postpartum.[62] Vitamin K antagonists should not be used during pregnancy because of their teratogenic effects in the first trimester of pregnancy. There are also risks of fetal intracranial bleeding in the third trimester. Low-molecular-weight heparin can be safely administered during pregnancy and is now the treatment of choice for VTE during pregnancy.[63,64] The twice-daily treatment dosage of LMWH is preferred over the once-daily treatment dosage to account for the more rapid peak and trough of LMWH levels

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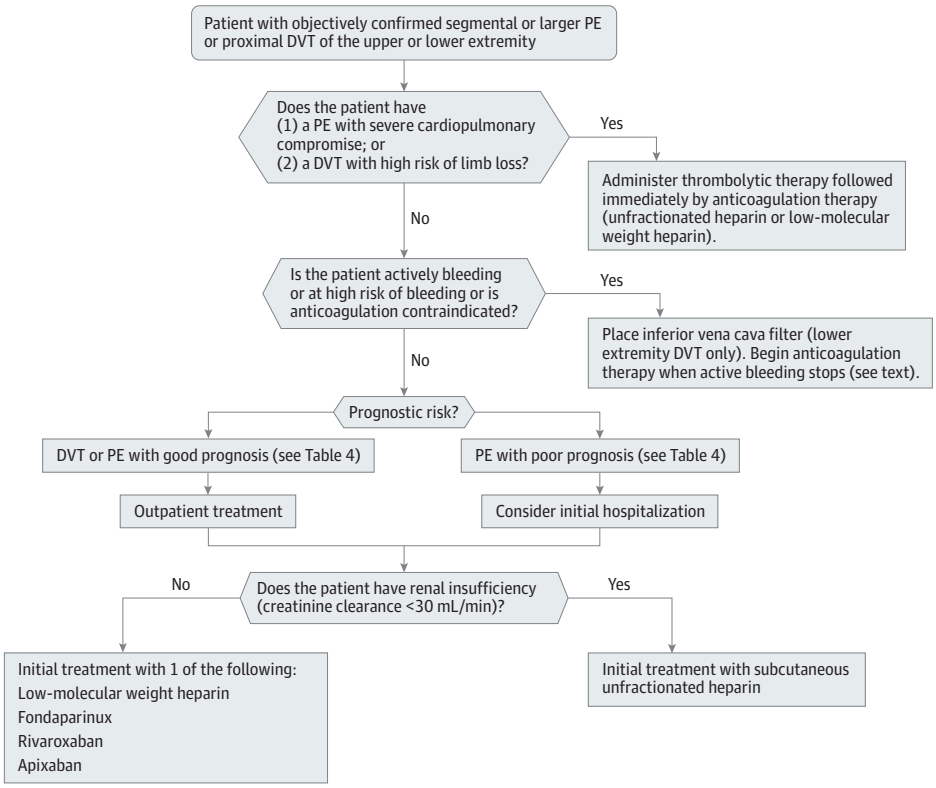
Figure 1. Approach to Acute Treatment of Venous Thromboembolism (Onset Through Days 5 to 10)



DVT indicates deep vein thrombosis; PE, pulmonary embolism.

occurring with pregnancy. Low-molecular-weight heparin is given for at least 1 month and then reduced to 75% of a full treatment dose. This approach borrows from experience with patients with cancer who receive long-term anticoagulation because of a high risk of recurrent VTE that can be reduced with less than full doses of LMWH. This empirical treatment approach is not well supported by evidence. Unlike the activated partial thromboplastin time and INR for heparin and warfarin, respectively, there is no optimal anti-Xa LMWH range or other clinical end point to support LMWH dose adjustment. Given the cost and inconvenience of monitoring, it is difficult to justify. Anticoagulant treatment is continued for at least 6 weeks postpartum and for a minimum of 3 months. If acute DVT or PE occurs close to the delivery date, interrupting anticoagulation may be hazardous because of a high risk of PE. Under these circumstances, a temporary inferior vena cava filter should be considered.[64,65]

Unprovoked VTE

When a patient's first VTE occurs without any identifiable thrombotic risk factor, the VTE is classified as unprovoked. Unprovoked VTE has a significant recurrence risk of at least 10% after 1 year and at least 30% at 5 years. Consequently, most such patients require extended if not indefinite anticoagulation. To justify indefinite anticoagulation, the risk of VTE and its consequences should be offset by the risks of bleeding. The estimated case-fatality rate for major hemorrhage is 12% and is 4% for recurrent DVT and 8% for PE.[1] Therefore, to justify indefinite anticoagulation, the recurrence risk of DVT must exceed 3 times the major hemorrhage rate and should exceed 1.5 times the PE rate. Although bleeding risk prediction tools have been proposed, they lack validation.[9,66] However, the hemorrhage risk is low for most patients.[67,68]

Prediction of an individual patient's risk of recurrent VTE remains elusive. Low D-dimers level 1 month after discontinuing anticoagulants,[69] residual venous occlusion,[70] and male sex[71] (in patients with a first unprovoked VTE, men have a 2.2-fold higher risk of recurrent VTE than do women) have been tested as risk predictors, but none are useful in isolation because they do not predict a low enough recurrence rate. Using methodologically rigorous methods, the Reverse study resulted in the HERDOO2 clinical decision tool for predicting recurrent VTE.[72] This tool is able to predict women who have a risk of recurrent VTE that is less than 3%. Low risk of recurrent VTE in women exists when no more than 1 of the following risk factors are present: signs of PTS (skin hyperpigmentation, erythema, edema, etc), Vidas D-dimer greater than 250 μg/L, age older than 65 years, or body mass index greater than 30 (calculated as weight in kilograms divided by height in meters squared). This tool has yet to be validated and studies to overcome this limitation are ongoing. To date, other risk prediction tools have not been properly validated.[73,74]

In one study, patients with persistently elevated antiphospholipid antibodies had a 29% recurrence rate compared with 14% in the control VTE population (risk ratio, 2.1; 95% CI, 1.3-3.3) within 4 years following cessation of anticoagulation; such patients should be treated indefinitely.[75] A recent systematic review suggests that the risk ratio is 2.83 in the presence of persistently positive lupus anticoagulant, but the review notes that the data are of low quality.[76]

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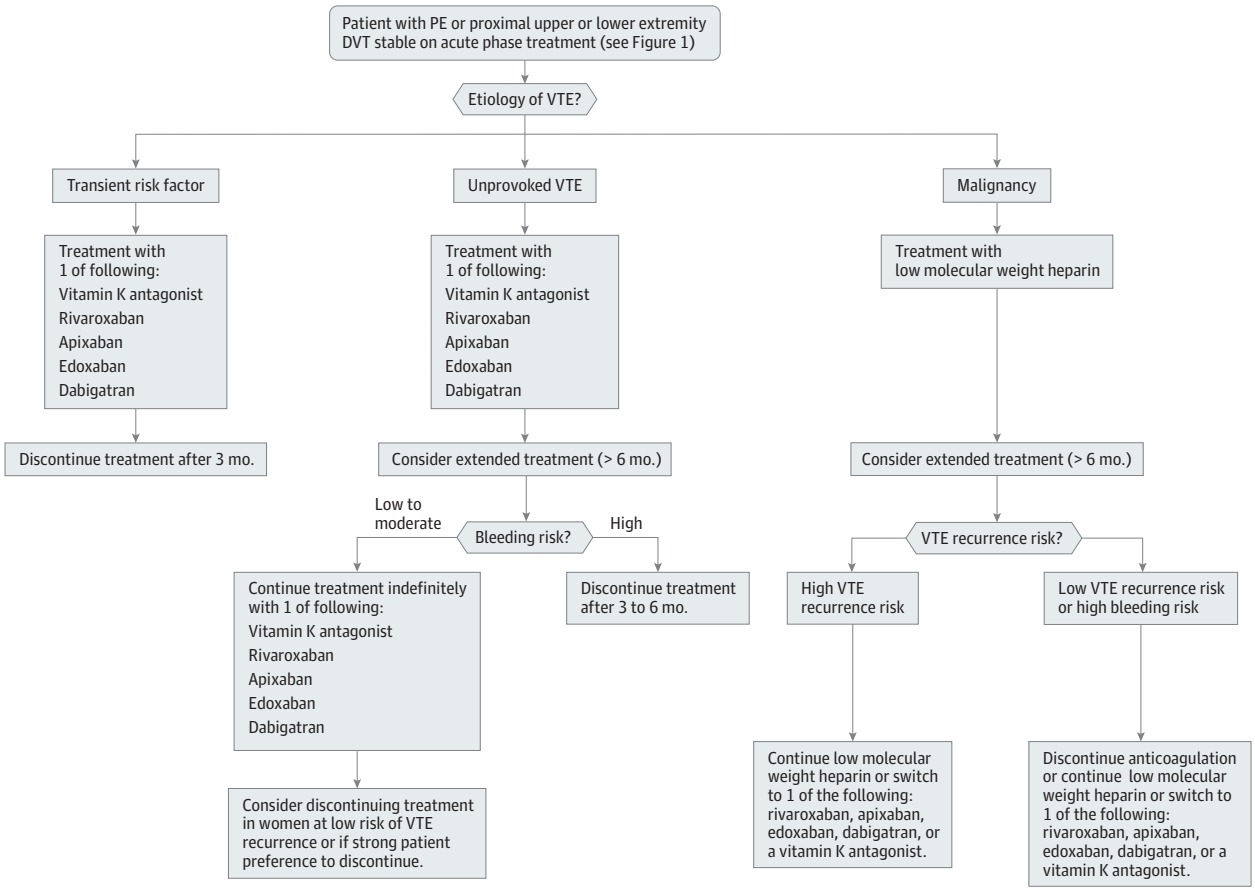
Figure 2. Approach to Long-term and Extended Treatment of Venous Thromboembolism (After Acute Treatment Through 3 to 6 Months After Diagnosis)



DVT indicates deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

It is not clear if more potent thrombophilias (protein C, protein S, antithrombin deficiency, and homozygous factor V Leiden or prothrombin gene defect) have an effect on VTE recurrence and should be a consideration when deciding about long-term anticoagulation. This remains true when there is a strong family history of VTE.[77] In recent studies, factor V Leiden, prothrombin gene mutation heterozygosity, and increased factor VIII levels were not helpful in predicting recurrent VTE and are not useful in decision making about long-term anticoagulation.

Patients who have a second unprovoked VTE have a substantial risk of recurrent VTE. These patients should receive indefinite anticoagulation.[78] In contrast, if an unprovoked VTE occurs as a second VTE event in a patient whose first event was provoked (ie, after surgery or pregnancy), the risk of recurrent VTE is not elevated. The recurrence risk is the same as if the patient was having their first unprovoked VTE. A third scenario in which a patient who had his or her first VTE during a transient risk period has a second VTE during a transient risk period has not been investigated. In absence of firm evidence, it seems reasonable to administer anticoagulation for a shorter duration (3-6 months). Patients who are recommended to receive indefinite anticoagulation should have yearly visits to assess bleeding risk and patient preference/quality of life to determine if anticoagulation should continue.

Patient preference should always be a strong consideration when deciding on extended anticoagulation. Guidelines recommend placing great importance on patient preference when recommending extended anticoagulation because[79] the importance of patient preference has been demonstrated in decision analysis modeling in patients with VTE.[80,81] Factoring patient preferences into clinical decision making requires balancing the patient's preferences with the outcomes of recurrent VTE, major bleeding, PTS, and other risks, but as yet, methods to achieve this are not well developed.[82] Physicians should present to patients an unbiased perspective on treatment including the benefits and harms, effect on quality of life, and cost.

Vitamin K Antagonists for Long-term and Extended Therapy

Although VKAs have been used in clinical practice for many years, their therapeutic range is narrow and there is a wide range of dose requirements. They are very inexpensive and their utility would be greatly improved if better management practices resulted in improved safety. Point-of-care monitoring of anticoagulation is more effective than other strategies for monitoring patients[83] and is cost-effective from a societal viewpoint.[84] Dedicated anticoagulation clinics are superior to other strategies for providing VKA care. A systematic review of the literature showed that time in the therapeutic

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range was 57% in community practices but was 66% when anticoagulation clinics were available.[85] The implications of this on the outcomes of recurrent VTE and major bleeding are unknown. Various algorithms predicting maintenance dosing exist but are not widely used. These deserve greater consideration.[86] Maintaining good INR control decreases the risk of developing postphlebitic syndrome, highlighting the need for better INR monitoring.[87]

It is generally recommended that INR be maintained in the 2 to 3 range. Some have advocated for more aggressive anticoagulation when antiphospholipid antibodies are present but 2 randomized controlled trials found that standard anticoagulation (INR range of 2-3) is as effective as maintaining an INR higher than 3.0.[88,89] Anticoagulation with a target INR of higher than 3.0 is not recommended in any patient with VTE. Long-term therapy with reduced-intensity INR (1.5-1.9) to prevent recurrent thrombosis while reducing the risk of bleeding has been advocated. A large randomized trial showed that lower-intensity anticoagulation is less effective at preventing recurrent thrombosis than standard anticoagulation and does not lead to a lower risk of bleeding, dispelling the notion that lesser-intensity anticoagulation is beneficial.[90] Although low-intensity therapy is not recommended, it is more effective than no therapy at all.[68]

New Oral Anticoagulants

A new class of oral anticoagulant drugs is now available; these drugs are direct inhibitors of either factor Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran). These drugs share in common low molecular weight, reasonably short half-lives of 8 to 16 hours, direct inhibition of activated clotting factors, oral administration, and no need to monitor the anticoagulant effect. Monitoring is not required because the predictable pharmacokinetic profile gives minimal variability in drug response, and regardless, standard coagulation assays correlate poorly with drug levels and clinical outcomes. Rivaroxaban and apixaban are used as monotherapy (ie, 1 drug for acute, long-term, and extended anticoagulation) for DVT and PE and have demonstrated noninferiority to (ie, are not worse than) combination therapy with enoxaparin and VKAs for the prevention of recurrent symptomatic VTE. These drugs were superior for major and nonmajor clinically relevant bleeding events.[10,11,23,24]

When studied for prevention of recurrent VTE, predominantly in patients with unprovoked VTE, 6 to 12 months of extended therapy with rivaroxaban, 20 mg/d, was more effective than placebo (1.3% VTE recurrences with rivaroxaban vs 7.1% with placebo), with no differences in bleeding events between the 2 groups. Apixaban for extended therapy compared with placebo resulted in a recurrent VTE rate of 1.7% vs 8.8% with placebo; bleeding rates were extremely low in both the apixaban group (0.2% with 2.5 mg twice daily and 0.1% with 5 mg twice daily) and placebo group (0.5%).[27] Dabigatran was extensively studied in the long-term phase of treatment in the RECOVER I and RECOVER II trials. It was not used as a monotherapy because patients initially underwent anticoagulation with unfractionated heparin or LMWH and then transitioned to dabigatran or warfarin. Recurrent VTE rates were similar, as were major bleeding rates. Extended therapy with dabigatran was also demonstrated to be as effective as VKA and superior to placebo in the REMEDY and RE-SONATE studies.[28]

Dabigatran may be associated with an increased risk of acute coronary syndromes relative to warfarin but not compared with placebo.[25] Edoxaban is effective as an initial therapy after 1 week of LMWH and also for extended therapy.[26] As with the other new oral anticoagulants, it was noninferior with respect to recurrent VTE and noninferior for major and clinically relevant nonmajor bleeding. Patients with large PE, determined by high levels of *N*-terminal pro-brain natriuretic peptide levels, had fewer recurrent VTE events with edoxaban than with warfarin. These trials are summarized in Table 2 and Table 3. All of these drugs can be recommended for extended therapy and rivaroxaban and apixaban can be recommended as monotherapy for VTE. To date, experience with these drugs in large patient populations is lacking, and real-world patient outcomes will need to be carefully monitored. In practice, major hemorrhage rates seemed higher with dabigatran when used for atrial fibrillation than those observed in clinical trials, but the US Food and Drug Administration suggests that this is not the case and these clinical observations mirror those observed in randomized trials.[91] It is possible, but as yet unproven, that these drugs will be especially useful alternatives for adherent patients experiencing poor INR control with VKAs. The trials with the new oral anticoagulants are summarized in Table 2 and Table 3.

Malignancy-Associated VTE

Compared with patients with unprovoked VTE, patients with malignancy have a higher incidence of recurrent VTE and bleeding complications while receiving anticoagulation therapy.[92] Long-term anticoagulation with LMWH instead of warfarin appears to be more effective at preventing recurrent venous thrombosis without a statistically significant increase in bleeding risk.[93] All patients with active malignancy should be treated with at least 6 months of LMWH if there is adequate renal function. Low-molecular-weight heparin rather than VKAs also facilitates the management of these complex patients, who often undergo procedures and who have periodic chemotherapy-induced thrombocytopenia. Because the risk of recurrence is 3 times higher in patients with vs without cancer, treatment with anticoagulation is recommended if the cancer is thought to be active. It is recommended to wait 6 months after cure or complete remission before stopping therapy but consideration should be given to stopping therapy earlier in patients with a high bleeding risk, if the VTE occurred postsurgery, if the VTE was an isolated calf DVT, and in those with lower risk of recurrence.[94] Recurrence risk is defined through a scoring system in which 1 point is given for previous VTE, female sex, or lung cancer, minus 1 point for breast cancer and minus 2 points for TNM stage 1. Patients scoring 0 or lower have a recurrence risk of less than 5%; ie, similar to those with transient nonsurgical risk factors.

Conclusions

Therapeutic management of VTE continues to evolve as anticoagulant options increase. Prior to the 1960s, when no options existed, patients almost universally experienced poor short- and long-term outcomes. Now, multiple therapeutic modes and options exist. Anticoagulants will probably always increase bleeding risk, necessitating tailored treatment strategies that must incorporate etiology, risk, benefit, cost, and patient preference. Although great progress has been made, further study to understand individual patient risk is needed to make the ideal treatment decisions.

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ARTICLE INFORMATION

Author Contributions: Drs Wells and Forgie had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition of data: Wells, Forgie.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
Administrative, technical, and material support: Wells.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Correction: This article was corrected for a misplaced heading and a wording error on April 23, 2014.

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

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