Contemporary Treatment of Venous Thromboembolic Disease

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KEYWORDS

• Venous thromboembolism • Deep vein thrombosis • Pulmonary embolism • Anticoagulation • Thrombolysis • Inferior vena cava filter

KEY POINTS

- The routine use of thrombolysis for lower-extremity deep vein thrombosis (DVT) is not recommended.
- Catheter-directed thrombolysis is suggested in patients with impending venous gangrene whose symptom duration is less than 14 days and who have a low risk of bleeding.
- Systemic thrombolysis, administered through a peripheral intravenous line, is recommended in patients with hemodynamic collapse (ie, persistent hypotension).
- The new target-specific oral anticoagulants have been shown to be as safe and effective as standard anticoagulation for the treatment of acute venous thromboembolism (VTE).
- Indefinite anticoagulation is suggested in patients with an unprovoked or recurrent VTE and in patients with an active malignancy.

INTRODUCTION

Venous thromboembolism (VTE) encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). The incidence of VTE is approximately 1 per 1000 person-years.[1,2] The case-fatality rate in patients presenting with an acute DVT and PE during the first 3 months of anticoagulation is 9.0% and 30.1%, respectively.[3] In addition to mortality, the cumulative incidence of chronic thromboembolic pulmonary hypertension is approximately 4% at 2 years following a diagnosis of PE.[4] Furthermore, postthrombotic syndrome (PTS) occurs in 20% to 50% of patients diagnosed with a symptomatic DVT.[5] The treatment of VTE is divided into 3 phases (**Fig. 1**).[6] Several target-specific oral anticoagulants (TSOACs) have been studied for the treatment of VTE during these phases of therapy (**Tables 1** and **2**) and have been shown to be as noninferior in safety and efficacy as conventional therapy. This article reviews the contemporary treatment of VTE.

RISK STRATIFICATION (INPATIENT VS OUTPATIENT TREATMENT)

A *Cochrane Review* of randomized controlled trials (RCTs) demonstrated the efficacy and safety of the outpatient treatment of DVT with low-molecular-weight heparin (LMWH) compared with inpatient anticoagulation.[7] Several clinical prediction rules have been established to stratify PE-related mortality risk,[8–10] of which the Pulmonary Embolism Severity Index seems to be the best validated

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(Table 3).[6] The use of LMWH as outpatient treatment of patients with low-risk PE has been shown to be safe and effective in several RCTs and a systematic review.[11–13]

THROMBOLYSIS FOR LOWER EXTREMITY DEEP VEIN THROMBOSIS

There are no RCTs comparing catheter-directed thrombolysis (CDT) with systemic thrombolysis for lower-extremity DVT. Lower-quality evidence suggests that CDT is more effective in establishing vein patency and is associated with a lower risk of bleeding compared with systemic thrombolysis.[6] A meta-analysis of thrombolysis (either systemic or catheter-directed) for lower-extremity DVT demonstrated a significant difference in clot lysis, vein patency, and reduction of PTS in patients treated with lytic therapy compared with standard anticoagulation at the expense of more bleeding complications.[14] There are insufficient data to recommend one thrombolytic agent over others. CDT is suggested in patients with an ileofemoral DVT with the following criteria: impending venous gangrene, symptom duration less than 14 days, good functional capacity, life expectancy greater than 1 year, and low risk of bleeding. In the absence of impending limb gangrene, standard anticoagulation is an acceptable, initial form of treatment.[6] The use of venous stents following balloon angioplasty in patients with residual occlusion after CDT has not been studied in prospective, randomized trials.

THROMBOLYSIS FOR PULMONARY EMBOLISM

Features of right ventricular dysfunction as determined by echocardiography, CT scanning, or an elevation of cardiac biomarkers (ie, troponins, brain natriuretic peptide) are associated with worse outcomes in patients with an acute PE.[15] However, systemic thrombolysis was not associated with a reduction in mortality in patients with a submassive PE (abnormal right ventricular dysfunction without arterial hypotension) in 2 randomized, double-blind studies.[16,17] In the most recent RCT using thrombolysis in patients with a submassive PE, major bleeding and hemorrhagic stroke occurred in approximately 12% and 2%, respectively, in patients treated with thrombolysis (statistically significant).[17] Systemic thrombolysis is recommended in patients who experience hemodynamic compromise.[6] There is insufficient evidence to recommend the administration of

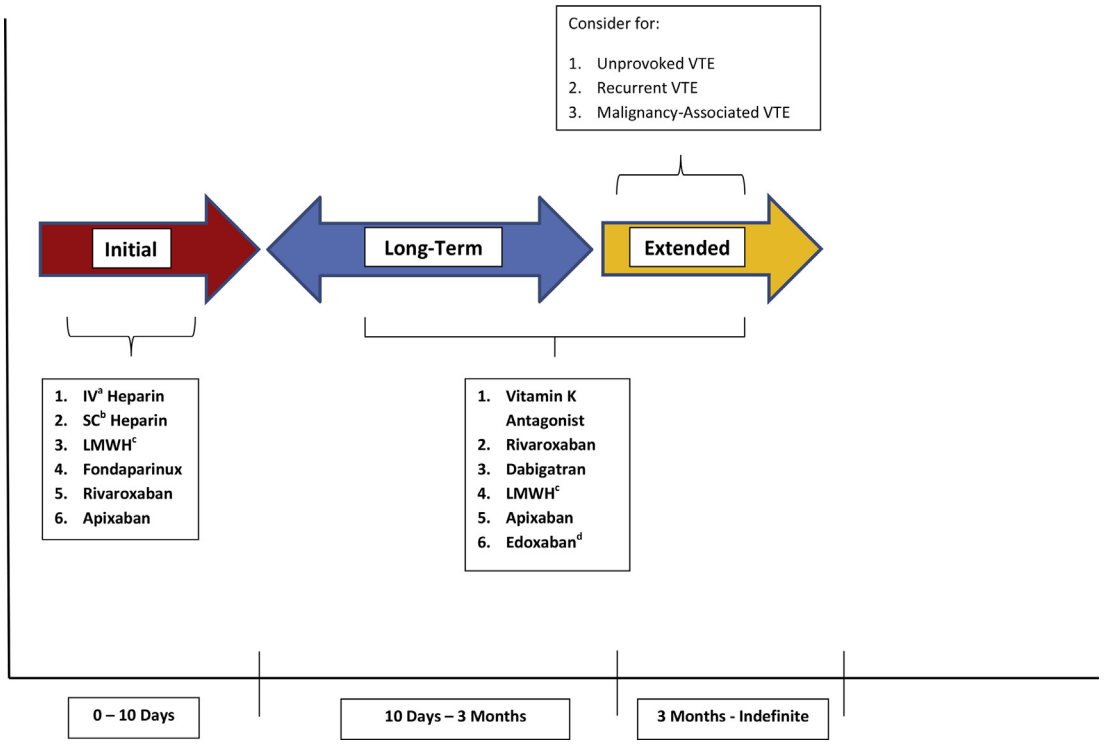

Fig. 1. Phases of anticoagulant treatment. (a) Intravenous; (b) subcutaneous; (c) LMWH, preferred in patients with a malignancy; (d) edoxaban has not yet been approved for VTE treatment.

Table 1
Clinical trials comparing the new oral anticoagulants to standard therapy in acute venous thromboembolism[a]

	Einstein-DVT	Einstein-PE	Amplify	Re-Cover	Re-Cover II	Hokusai-VTE
Trial design	Open-label, randomized	Open-label, randomized	Double-blind, randomized	Double-blind, randomized	Double-blind, randomized	Double-blind, randomized
Regimen	Rivaroxaban 15 mg BID × 3 wk, then 20 mg daily	Rivaroxaban 15 mg BID × 3 wk, then 20 mg daily	Apixaban 10 mg BID × 7 d, then 5 mg BID	Standard therapy for median 9 d, then Dabigatran 150 mg BID	Standard therapy for median 9 d, then Dabigatran 150 mg BID	Standard therapy for median 7 d, then edoxaban 60 mg daily (30 mg daily if CrCl 30–50 mL/min or weight ≤60 kg)
Average age	55–58 y old	58 y old	57 y old	54–55 y old	55 y old	56 y old
PE only	—	All patients	25%	21%	23%	30%
DVT + PE	All patients (no PE)	25%	8%–9%	10%	8%–9%	10%
Unprovoked VTE	61%–63%	64%–65%	90%	Undefined	Undefined	65%–66%
Prior VTE	19%	19%–20%	15%–17%	25%–26%	16%–19%	18%–19%
Malignancy	5%–7%	5%	3%	5%	4%	9%
Thrombophilia	6%–7%	5%–6%	2%–3%	Undefined	Undefined	Undefined
% TTR for INR[b]	57.7%	62.7%	61%	60%	57%	63.5%
Efficacy outcome[c]	Rivaroxaban: 2.1% Standard Tx: 3.0%	Rivaroxaban: 2.1% Standard Tx: 1.8%	Apixaban: 2.3% Standard Tx: 2.7%	Dabigatran: 2.4% Standard Tx: 2.1%	Dabigatran: 2.3% Standard Tx: 2.2%	Edoxaban: 3.2% Standard Tx: 3.5%
Major bleeding[d]	Rivaroxaban: 0.8% Standard Tx: 1.2%	Rivaroxaban: 1.1% Standard Tx: 2.2%	Apixaban: 0.6% Standard Tx: 1.8%	Dabigatran: 1.6% Standard Tx: 1.9%	Dabigatran: 1.2% Standard Tx: 1.7%	Edoxaban: 1.4% Standard Tx: 1.6%
Clinically relevant bleeding[e]	Rivaroxaban: 8.1% Standard Tx: 8.1%	Rivaroxaban: 10.3% Standard Tx: 11.4%	Apixaban: 4.3% Standard Tx: 9.7%	Dabigatran: 5.6% Standard Tx: 8.8%	Dabigatran: 5.0% Standard Tx: 7.9%	Edoxaban: 8.5% Standard Tx: 10.3%

Abbreviation: Amplify, Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy.
[a] Standard therapy is defined as the use of a short-acting anticoagulant (ie, intravenous heparin, low-molecular-weight heparin) followed by a vitamin K antagonist.
[b] TTR is defined as time in therapeutic range for vitamin K antagonism.
[c] Efficacy outcome = symptomatic VTE.
[d] Major bleeding is defined as per the International Society of Thrombosis and Haemostasis guidelines.
[e] Clinically relevant bleeding is defined as the composite of major and clinically relevant nonmajor bleeding as per the International Society of Thrombosis and Haemostasis guidelines.

Table 2
Clinical trials investigating the new oral anticoagulants for the extended treatment of venous thromboembolism[a]

	Einstein-Ext	Amplify-Ext	Re-Medy	Re-Sonate
Trial design	Double-blind, randomized	Double-blind, randomized	Double-blind, randomized	Double-blind, randomized
Regimen	Rivaroxaban 20 mg daily vs Placebo	Apixaban 2.5 mg or 5 mg BID vs Placebo	Dabigatran 150 mg BID vs warfarin	Dabigatran 150 mg BID vs placebo
Average age	58 y old	56–57 y old	54–55 y old	56 y old
Index event[b]	DVT: 60%–64% PE: 36%–40%	DVT: 65%–67% PE: 34%–35%	DVT: 65%–66% PE: 34%–35%	DVT: 63%–67% PE: 32%
Unprovoked VTE	73%–74%	91%–93%	Undefined	Undefined
Prior VTE	14%–18%	12%–15%	52%–55%	2 patients
Malignancy	4%–5%	Excluded (1%–2%)	4%	Excluded
Thrombophilia	8%	Excluded (3%–4%)	18%	10%–13%
% TTR for INR[c]	—	—	65.3%	—
Efficacy outcome[d]	Rivaroxaban: 1.3%, Placebo: 7.1%	Apixaban 2.5 mg: 3.8%, Apixaban 5 mg: 4.2%, Placebo: 11.6%	Dabigatran: 1.8%, warfarin: 1.3%	Dabigatran: 0.4%, placebo: 5.6%
Major bleeding[e]	Rivaroxaban: 0.7%, Placebo: 0%	Apixaban 2.5 mg: 0.2%, Apixaban 5 mg: 0.1%, Placebo: 0.5%	Dabigatran: 0.9%, warfarin: 1.8%	Dabigatran: 0.3%, placebo: 0%
Clinically relevant bleeding[f]	Rivaroxaban: 6.0%, Placebo: 1.2%	Apixaban 2.5 mg: 3.2%, Apixaban 5 mg: 4.3%, Placebo: 2.7%	Dabigatran: 5.6%, warfarin: 10.2%	Dabigatran: 5.3%, placebo: 1.8%

[a] Patients were treated with either a standard anticoagulant or study drug for at least 3 months before being randomized in the extended treatment trials.
[b] PE = PE ± DVT, DVT = DVT only.
[c] TTR is defined as time in therapeutic range for vitamin K antagonism.
[d] Efficacy outcome = symptomatic VTE.
[e] Major bleeding is defined as per the International Society of Thrombosis and Haemostasis guidelines.
[f] Clinically relevant bleeding is defined as the composite of major and clinically relevant nonmajor bleeding as per the International Society of Thrombosis and Haemostasis guidelines.

Table 3
Simplified Pulmonary Embolism Severity Index

Variable	Points
Age >80 y	1
History of cancer	1
Chronic cardiopulmonary disease	1
Pulse ≥110 beats per minute	1
Systolic blood pressure <100 mm Hg	1
Pulse oximetry <90%	1
PE Risk	**Score**
Low risk	0
High risk	≥1

Adapted from Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170(15):1383–9.

thrombolysis through a pulmonary artery catheter rather than through a peripheral vein.

INITIAL PHASE OF TREATMENT (FIRST 5–10 DAYS)

A meta-analysis comparing LMWH versus adjusted-dose unfractionated heparin (UFH; intravenous or subcutaneous) for the initial treatment of VTE showed a statistically significant advantage of LMWH in preventing recurrent VTE, major bleeding, or death compared with UFH.[18] Furthermore, a meta-analysis comparing once-daily versus twice-daily LMWH revealed that the once-daily regimen was associated with less recurrent VTE and major hemorrhage. However, the difference for both endpoints did not reach statistical significance.[19] UFH is the drug of choice in

patients with renal insufficiency given the renal excretion of LMWH, fondaparinux, and the TSOACs.

As shown in **Table 1**, several of the TSOACs have been studied for the treatment of an acute DVT and/or PE. In all of these trials, the new anticoagulants were shown to be at least as safe and effective as conventional therapy.[6] A recent, pooled analysis confirmed the noninferiority of rivaroxaban for the treatment of VTE compared with vitamin K antagonism. Rivaroxaban was associated with a statistically significant reduction in major bleeding compared with conventional therapy, and its efficacy as well as safety profile did not vary according to thrombus burden, patient frailty, or the presence of a malignancy.[20] Dabigatran was shown to be as effective and safe as warfarin for the treatment of VTE in a recent pooled analysis as well. Although the rate of clinically significant bleeding was significantly less in patients treated with dabigatran, there were numerically more acute coronary syndromes in patients treated with this new anticoagulant (which did not reach statistical significance).[21,22] A meta-analysis of noninferiority trials comparing dabigatran to various therapies, including placebo, in different populations showed a higher risk of acute coronary syndrome in patients exposed to the direct-thrombin inhibitor.[23]

Apixaban, edoxaban, and rivaroxaban were shown to be as safe and effective in patients with renal impairment (creatinine clearance <50 mL/min) for the treatment of VTE compared with vitamin K antagonism in a recent metaregression and meta-analysis. Data were not available for dabigatran in the VTE population. As shown in **Table 1**, the trial designs of the acute-phase studies differed. Although apixaban and rivaroxaban were started at the time of randomization, dabigatran and edoxaban were initiated after patients received lead-in therapy with a conventional anticoagulant for at least 5 days (ie, with LMWH). Of all the TSOACs studied for VTE, a subgroup analysis for drug efficacy in patients with a submassive PE was only provided for edoxaban. In this specific population, edoxaban was more effective than standard therapy in reducing the risk of symptomatic, recurrent VTE. At the time of this writing, apixaban, rivaroxaban, and dabigatran have been approved for the treatment of VTE during the initial phase of therapy. Based on the aforementioned differences in the trial designs, dabigatran should not be started for an acute VTE until the patient has been treated with a conventional anticoagulant for at least 5 days. On the other hand, apixaban and rivaroxaban can be immediately given at the time of diagnosis.

Although, historically, compression stockings were recommended in patients with symptomatic DVT to prevent PTS, a recent randomized, double-blind study of compression stockings did not reduce the risk of PTS.[24] Despite these results, compression therapy is generally recommended in patients with a symptomatic DVT to improve symptoms. In a systematic review, early ambulation led to a more rapid resolution of limb pain in patients with a DVT and potentially reduced the risk of PTS.[25] Thus, patients should be encouraged to ambulate during this phase of treatment.

LONG-TERM PHASE OF TREATMENT (DAY 10 TO 3 MONTHS)

In addition to the newly approved anticoagulants, warfarin remains a viable option for treatment during this phase of therapy, particularly in patients with renal insufficiency. Although there is evidence that a 10-mg loading dose of warfarin achieves a therapeutic level faster, there are insufficient data to recommend one specific nomogram for warfarin dosing. Pharmacogenetic testing to guide warfarin dosing is not recommended given the results of trials and high cost.[26] LMWH is recommended over vitamin K antagonism in patients with a malignancy for at least the first 3 months of therapy. The TSOACs have not been well-studied in patients with cancer and should likely not be used in this patient population until further evidence supports their use for this indication. A 3-month duration of anticoagulation is suggested in patients with a provoked VTE.[6]

EXTENDED TREATMENT PHASE (3 MONTHS TO INDEFINITELY)

Extended treatment is suggested in patients with unprovoked VTE, recurrent VTE, or malignancy.[6] Results demonstrating an increased risk of VTE recurrence in patients with thrombophilia are inconsistent.[6,27–29] Several meta-analyses and systematic reviews have confirmed the correlation of a positive d-dimer assay after stopping anticoagulation and a higher risk of VTE recurrence in patients with an unprovoked thrombotic event.[30–32] However, the presence of residual vein obstruction (RVO) has not been consistently shown to predict recurrence of VTE after withdrawal of anticoagulation, particularly in patients with unprovoked VTE.[33–35] These factors (hereditary and acquired thrombophilia, abnormal d-dimer testing, and RVO) do not appear individually to be strong enough risk factors to determine the duration of anticoagulation, whereas the combination of these factors may be more predictive.[6] Low-dose aspirin

(100 mg daily) has been studied for secondary prevention of VTE in patients with an unprovoked thrombotic event after completing at least 3 months of treatment.[36,37] The efficacy of aspirin for this indication has not been consistently demonstrated in pooled analyses.[38] Most recently, apixaban 2.5 mg twice daily has been approved for treatment during this phase of therapy based on the results of the Amplify-Extend trial. In this trial, apixaban was found to be more effective than and just as safe as placebo in preventing recurrent VTE in patients who completed the long-term phase of treatment (ie, at least 3 months of therapy).

INFERIOR VENA CAVA FILTERS

There are no randomized studies comparing the use of inferior vena cava (IVC) filters to anticoagulation. IVC filters are associated with a reduction in PE at the expense of an increased risk of a recurrent DVT over a period of 8 years.[39] Lower-quality evidence suggests a mortality benefit with IVC filters in patients with a massive PE (ie, with

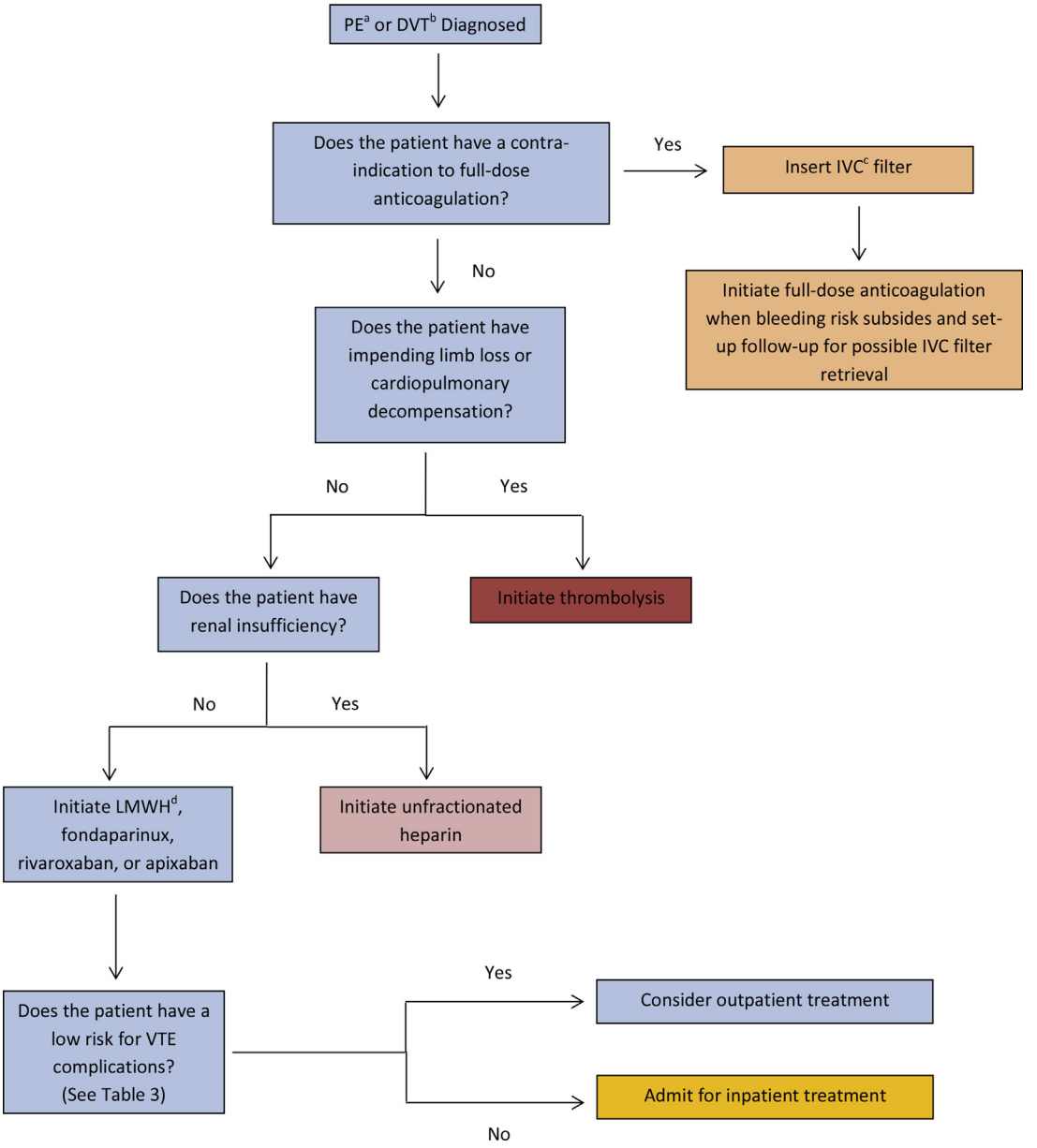

Fig. 2. Algorithm for treatment of VTE. (a) PE; (b) DVT; (c) IVC; (d) LMWH.

persistent hypotension) or in those patients with a PE who are receiving thrombolysis therapy.[40,41] In patients with a DVT or PE who have a contraindication to anticoagulation therapy, an IVC filter is indicated. Initiation of a conventional course of anticoagulation is suggested once the contraindication resolves.[6] The reported rates of filter complications vary widely. Of 921 complications listed in a 2010 report issued by the US Food and Drug Administration, the following complications were noted: 35.6% device migration, 15.8% filter embolization, 7.6% perforation of the IVC, and 6% filter fractures.[42] IVC filter thrombosis is also not an uncommon complication.[39] The risks and benefits of retrieving IVC filters should be reviewed. Institutional programs may increase the probability of successful filter retrieval.[43]

SUMMARY

The treatment armament for VTE has increased dramatically during recent years owing to the results of several phase III clinical trials. Although all of the TSOACs have been shown to be safe and effective for the treatment of DVT and PE, these medications have not been well studied in certain patient populations, including the elderly, those with cancer, as well as those with renal insufficiency. Conventional anticoagulation, such as warfarin or LMWH, likely will continue to be the anticoagulant of choice in these patient groups. **Fig. 2** summarizes a proposed algorithm for the treatment of VTE. Owing to the results of RCTs, many patients with VTE can be treated in the outpatient setting. Thrombolysis is generally reserved for patients with either impending limb gangrene or hemodynamic collapse. IVC filters should generally be avoided unless there is a contraindication to full-dose anticoagulation.

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