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JACC FOCUS SEMINAR: VENOUS THROMBOEMBOLISM

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Antithrombotic Management of Venous Thromboembolism

JACC Focus Seminar

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ABSTRACT

Venous thromboembolism (VTE) is a significant public health burden. Management of anticoagulation is the mainstay of treatment for the vast majority of patients. The introduction of 4 direct oral anticoagulants beginning in 2010 has significantly affected selection of anticoagulants for patients with VTE. Treatment of VTE consists of 3 phases: the initial treatment (first 5 to 21 days), primary treatment (first 3 to 6 months), and secondary prevention (after the initial 3 to 6 months). Oral-only anticoagulation strategies are now available, using apixaban or rivaroxaban therapy, beginning in the initial treatment phase. In addition, low-dose anticoagulation with either apixaban or rivaroxaban can be used in the secondary prevention phase for appropriate patients. Use of the direct oral anticoagulants is now supported for many patients with cancer-associated VTE. Appropriate selection and monitoring of anticoagulants remains a critical element of high-quality care for patients with VTE. (J Am Coll Cardiol 2020;76:2142–54)

Venous thromboembolism (VTE) results when a thrombus forms inside a vein, usually in the lower extremities. Disruptions in normal venous physiology, such as vascular injury, venous stasis, or hypercoagulability, increase the risk of developing VTE. When a thrombus forms, it can remain stationary or embolize to the lungs. As such, VTE encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE).

VTE is a common diagnosis, afflicting nearly 1,000,000 people annually in the United States (1). Risk of mortality varies widely but can be as high as 10% to 30% within 1 month for the highest-risk patients. Between one-quarter and one-half of patients continue to have debilitating symptoms or functional limitations following VTE events, contributing to more than $1.5 billion annual direct medical costs (2–6).

For some patients, a precipitating cause of their VTE event can be identified (**Table 1**) (7,8). These patients are considered to have "provoked" VTE. For many other patients, no precipitating event is identifiable. These patients are often categorized as having "unprovoked" or "idiopathic" VTE. These patients have a high risk of VTE recurrence, estimated at 30% over 5 years (9). Yet, for most patients, a combination of risk factors (both identifiable and unidentifiable) likely contributes to VTE events. Patients experiencing VTE events associated with reversible risk factors (e.g., recent casting or immobilization,

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HIGHLIGHTS

- VTE is a leading cause of cardiovascular death and disability.
- Anticoagulation is the mainstay of treatment for VTE.
- Further efforts are needed to increase safe use of anticoagulation for treatment of VTE.

estrogen hormone use) have a very low risk of VTE recurrence (<3 per 100 patient-years) as long as the precipitating risk factor is resolved (10). Of note, the most recent VTE guidelines from the European Society of Cardiology have transitioned from the "provoked" and "unprovoked" descriptors to use of the terms "major," "transient or reversible," and "persistent" risk factors. Similarly, "transient" and "persistent" risk factor descriptors are used by the American Society of Hematology 2020 Guidelines for Management of Venous Thromboembolism: Treatment of Deep Vein Thrombosis and Pulmonary Embolism document (11).

Selecting antithrombotic therapy is influenced by a number of key factors (**Central Illustration**). These include the presence of any precipitating factors, the phase of treatment, the various options for oral anticoagulants, and a few other key considerations.

OVERVIEW OF ANTICOAGULATION IN VENOUS THROMBOEMBOLISM

Anticoagulation therapy is the mainstay of treatment for the vast majority of patients with VTE. However, some patients are at sufficiently low risk for progression or recurrence so that anticoagulation therapy may not be recommended. These include select patients with DVT confined to the distal veins of the leg (isolated distal DVT) and patients with uncomplicated subsegmental PE. As recommended by recent guidelines, patients with low risk of VTE recurrence are recommended either for serial ultrasound (isolated distal DVT) or clinical surveillance rather than anticoagulation therapy. However, some patients have risk factors for progression of a distal DVT and therefore should be considered for anticoagulation rather than clinical or ultrasound surveillance (**Table 2**) (7,11). For patients who undergo serial ultrasound surveillance, this is typically performed at 1 and 2 weeks following diagnosis. Anticoagulation is typically initiated if any extension of the thrombus is identified.

For patients treated with anticoagulation therapy, this can be conceptualized in 3 phases (**Figure 1**). Initially, any active thrombus formation must be halted through rapid and intensive anticoagulation ("initial management" phase). Traditionally, this was achieved using either intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin (LMWH). More recently, 2 oral anticoagulation strategies have been shown efficacious in this phase. All patients with acute VTE are recommended to receive at least 3 to 6 months of anticoagulation in the "primary treatment" phase. This represents the period of highest risk of recurrence, when the body's natural thrombolytic processes are recanalizing the vein and converting acute thrombus to chronic fibrin. Finally, many patients with persistent recurrence risk will benefit from "secondary prevention" beyond the initial 3 to 6 months. With the introduction of the direct oral anticoagulants (DOACs), including low-dose options for apixaban and rivaroxaban, more patients are candidates for secondary prevention therapy as their risk of recurrence outweighs the relatively lower risk of anticoagulant-related serious bleeding. It should be noted that these same 3 phases have previously been referred to as the "acute," "long-term," and "extended" phases in previous guideline documents (7). However, because of the confusion over "long-term" referring to the initial 3 months of therapy, the more recent American Society of Hematology 2020 Guidelines for Management of Venous Thromboembolism: Treatment of Deep Vein Thrombosis and Pulmonary Embolism use the terms *initial management*, *primary treatment*, and *secondary prevention* (11).

ABBREVIATIONS AND ACRONYMS

CT = computed tomography
DOAC = direct oral anticoagulant
DVT = deep vein thrombosis
HIT = heparin-induced thrombocytopenia
INR = international normalized ratio
LMWH = low molecular weight heparin
PE = pulmonary embolism
VTE = venous thromboembolism

TABLE 1 Venous Thromboembolism Risk Factors (7,8)

Surgical Transient Risk Factor	Nonsurgical Transient Risk Factor	Nontransient Risk Factor
Surgery	Estrogen therapy	Cancer
Trauma	Pregnancy	Advanced age
	Leg injury	Obesity
	Air travel >8 h	Frailty and chronic medical illness
	Acute medical illness	Previous venous thromboembolism
		Genetic thrombophilia (e.g., protein C or S deficiency)
		Acquired thrombophilia (e.g., antiphospholipid antibody syndrome)
		Chronic medical illness (e.g., nephrotic syndrome, vasculitis, inflammatory bowel disease)

Some patients with cancer-associated venous thromboembolism (VTE) may not have long-term VTE recurrence risk if the cancer is cured with early treatment.

CENTRAL ILLUSTRATION **Selecting Venous Thromboembolism Anticoagulant and Duration**

Determine Phase of Treatment
- Initial (first 5-21 days)
- Primary (first 3-6 months)
- Secondary (beyond 3-6 months)

Assess Risk for Recurrence
- Surgical, transient factors → very low
- Non-surgical, transient factors → low
- Persistent factors → moderate
- No identifiable factors → moderate
- Cancer → high
- High-risk thrombophilia → high

Screen for Bleeding Risk
- Recent bleeding
- Anemia
- Renal dysfunction
- Antiplatelet therapy
- Older age
- Cancer

Anticoagulant Options

Oral Anticoagulant	Initial Phase: Oral Only?	Secondary Phase: Reduced Dose?	Cancer-associated VTE RCT Data?
Apixaban	Yes	Yes	Yes
Dabigatran	No	No	No
Edoxaban	No	No	Yes
Rivaroxaban	Yes	Yes	Yes
VKA	No	No	No

Duration of Anticoagulation

	Initial Phase	Primary Phase	Secondary Phase
Very low or low recurrence risk	Yes	Yes	No
Moderate recurrence risk	Yes	Yes	Consider based on bleed risk
High	Yes	Yes	Usually

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When considering the most appropriate anticoagulant and duration of treatment for patients with venous thromboembolism (VTE), clinicians should determine the phase of treatment, assess for the risk of recurrence of VTE, and screen for bleeding risk. Based on that information, an oral anticoagulation strategy can be selected. The duration of anticoagulation therapy is guided based on the risk of recurrence of VTE and risk of bleeding. RCT = randomized clinical trial; VKA = vitamin K antagonists (including warfarin).

No matter what anticoagulation strategy is selected, 1 key decision in the initial treatment phase is the best location for treatment: at home or in a hospital setting. The introduction of oral-only anticoagulation strategies now allows for diagnosis and treatment without hospital admission. For patients with DVT, this can be accomplished in the outpatient clinic as long as duplex ultrasound studies are readily available. For patients with PE, the diagnosis is typically made with the emergency department's computed tomography (CT) scanner. Various protocols have been developed to identify low-risk patients for whom outpatient treatment is reasonable (12–14). Clinicians considering home treatment for acute VTE should ensure that patients will be able to obtain anticoagulation medications without significant cost burden and have reliable clinical follow-up in a primary care office or with an anticoagulation or thrombosis clinic provider.

TABLE 2 **Risk Factors for Progression of Distal DVT**

Elevated D-dimer
Extensive thrombosis
>5 cm in length
Multiple veins involved
>7 mm maximal diameter
Close to proximal (above knee) veins
No reversible provoking factor for DVT
Active cancer
Previous history of VTE
Inpatient status

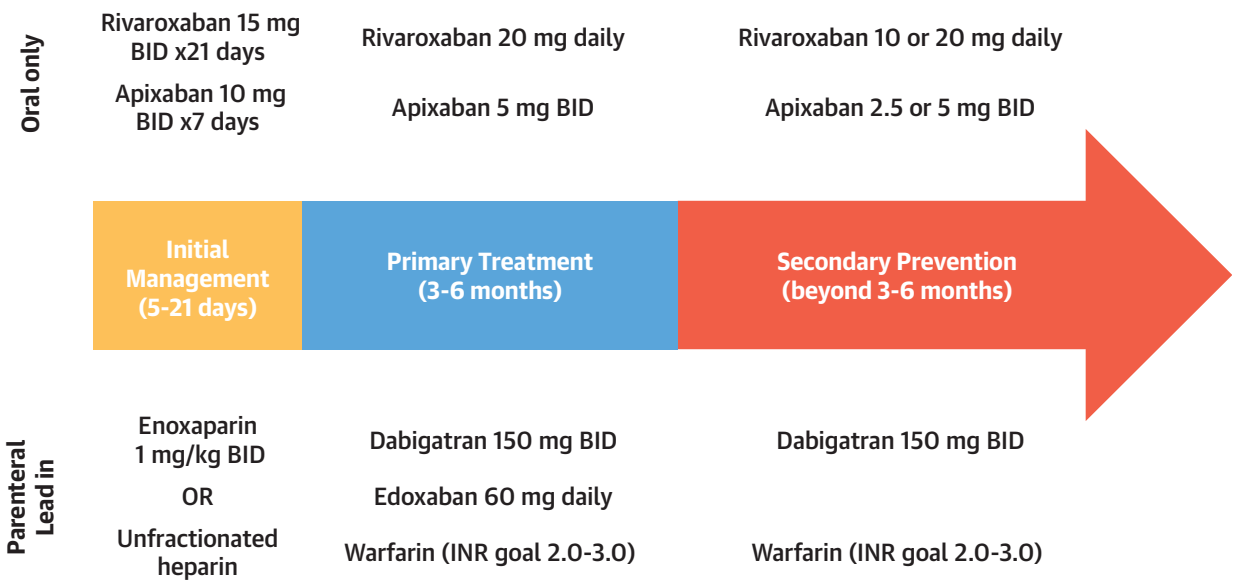
Given the increased risk of progression of DVT associated with the risk factors listed here, anticoagulation therapy may be preferential to serial ultrasound or clinical monitoring.

DVT = deep vein thrombosis; VTE = venous thromboembolism.

INITIAL MANAGEMENT AND PRIMARY TREATMENT WITH ANTICOAGULATION

INITIAL MANAGEMENT: PARENTERAL AND ORAL OPTIONS. The initial anticoagulation management of VTE refers to the first 5 to 21 days in which a more intensive regimen of anticoagulation is recommended, consisting of either parenteral therapy or higher-dose oral therapy. Patients treated in the acute-care setting are likely to be treated with a parenteral anticoagulant such as heparin. Heparin

FIGURE 1 Strategies for Anticoagulation Treatment by Phase of VTE



Initial management refers to the initial 5 to 21 days when anticoagulation therapy aims to stop any active clotting. Primary treatment encompasses the first 3 to 6 months and addresses periods of highest risk of recurrence. Secondary prevention extends beyond the initial 3 to 6 months and addresses ongoing risk of recurrence. In Europe, use of apixaban 2.5 mg twice daily rather than 5 mg twice daily is recommended during secondary prevention. BID = twice daily; INR = international normalized ratio; VTE = venous thromboembolism.

offers the advantage of being rapidly effective. It is also rapidly cleared from circulation upon discontinuation, which makes it an attractive option for patients who may require urgent invasive procedures or surgeries. Disadvantages of heparin include the risk of allergy or intolerance such as heparin-induced thrombocytopenia (HIT), the need for intravenous administration, frequent monitoring, and dose adjustments. Long-term use of heparin is additionally undesirable because of the risk of side effects such as osteoporosis. Patients who require intravenous anticoagulation but have a history of HIT should be given non-heparin anticoagulants such as argatroban or bivalirudin.

LMWHs (e.g., enoxaparin) are administered subcutaneously, carry a lower risk of HIT, have a longer duration of action suitable for once- or twice-daily administration, do not require routine monitoring, and may be used long-term with low concern for osteoporosis. A key advantage of LMWH over unfractionated heparin is the predictable anticoagulation level when dosed based on a patient's actual body weight. LMWH is commonly used for inpatients or outpatients who will be transitioning to select oral anticoagulants (warfarin, dabigatran, edoxaban) in the primary treatment phase of anticoagulation. A growing number of interventionalists are comfortable performing venous and pulmonary artery interventions on LMWH, making this an increasingly used option for hospitalized patients with acute VTE.

Two oral factor Xa inhibitors—apixaban and rivaroxaban—may also be used in the initial management phase without the need for parenteral treatment. This oral-only strategy is advantageous for patients with strong desire to avoid parenteral therapy, especially those who are suitable candidates for VTE treatment at home. The other DOACs (dabigatran and edoxaban) require a 5- to 10-day lead-in with either heparin or LMWH before initiating oral therapy. It should be noted that when using DOACs for treatment of VTE, dose adjustments used commonly in atrial fibrillation do not apply. Prescribing information should be consulted carefully to avoid inappropriate dose adjustments.

PRIMARY TREATMENT WITH ANTICOAGULATION. After the initial management phase, the primary treatment phase of anticoagulation begins. This phase continues until 3 to 6 months from the date of diagnosis. Options for primary treatment with oral anticoagulation include warfarin and DOACs, including the direct thrombin inhibitor dabigatran

TABLE 3 Oral Anticoagulant Medications

Generic name	Common Brand names	Mechanism of action	Dose and Regimen	Considerations for Renal Dysfunction	Considerations for Hepatic Dysfunction	Other Considerations
Warfarin	Coumadin (off-market), Jantoven	Vitamin K antagonist	5 mg daily for most patients, adjusted to target INR 2.0-3.0	None	Use caution, especially in patients with baseline elevations in INR	Consider reducing starting dose to 2.5 mg for patients with advanced age, frailty, advanced end-organ dysfunction, multiple comorbidities, or drug-drug interactions expected to increase exposure to warfarin.
Dabigatran	Pradaxa	Direct thrombin inhibitor	150 mg twice daily after 5-10 days of parenteral anticoagulation	Avoid in CrCl ≤ 30 ml/min	Not studied in patients with ALT >2x ULN	Patients taking p-glycoprotein inhibitors should avoid dabigatran if CrCl ≤50 ml/min. Patients taking p-glycoprotein inducers should avoid dabigatran.
Rivaroxaban	Xarelto	Factor Xa inhibitor	15 mg twice daily for 21 days, then 20 mg once daily	Avoid in CrCl ≤ 15 ml/min	Avoid in Childs-Pugh Class B-C	Administer with food. Avoid use in patients taking strong dual inhibitors or inducers of CYP 3A4 and p-glycoprotein. Use caution in patients taking moderate dual inhibitors of CYP 3A4 and p-glycoprotein if CrCl ≤80 ml/min.
Apixaban	Eliquis	Factor Xa Inhibitor	10 mg twice daily for 7 days, then 5 mg twice daily	Not studied in patients with SCr ≥2.5 mg/dl or CrCl <25 ml/min	Avoid in Childs-Pugh Class C	Reduce dose by 50% in patients taking dual inhibitors of CYP 3A4 and p-glycoprotein. Avoid use in patients taking strong dual inducers of CYP 3A4 and p-glycoprotein.
Edoxaban	Savaysa, Lixiana	Factor Xa inhibitor	60 mg once daily after 5-10 days of parenteral anticoagulation	Reduce dose to 30 mg once daily for CrCl 15-50 ml/min. Avoid in CrCl <15 ml/min	Avoid in Childs-Pugh Class B-C	Reduce dose to 30 mg daily for body weight ≤ 60 kg or in patients taking p-glycoprotein inhibitors. Avoid use with p-glycoprotein inducers.

Based on Food and Drug Administration package label prescribing instructions. Accessed on March 25, 2020.
ALT = alanine transaminase; CrCl = creatinine clearance as calculated by the Cockcroft-Gault equation; SCr = serum creatinine; ULN = upper limits of normal.

and factor Xa inhibitors apixaban, rivaroxaban, and edoxaban (Table 3). It should be noted that other vitamin K antagonists, including phenprocoumon and acenocoumarol, are prescribed globally. The remaining sections of this review will exclude these.

Warfarin. Warfarin acts by inhibiting vitamin K epoxide reductase, which is responsible for reduction of vitamin K into the form used in the production of active clotting factors by the liver. Inhibiting this enzyme results in a functional deficiency of the vitamin K-dependent clotting factors (factors II, VII, IX, and X). Warfarin has a narrow therapeutic index and high interpatient dosing variability. Thus, therapeutic drug monitoring is critical for safe and effective use. The preferred monitoring parameter for warfarin is the international normalized ratio (INR) with a recommended target of 2.5 (therapeutic range 2.0 to 3.0).

Warfarin has a long elimination half-life of 20 to 60 h, and the aforementioned clotting factors have half-lives that vary from 4 to 60 h. This results in a prolonged time to warfarin effectiveness of 5 to 10 days. In addition, warfarin inhibits the natural anticoagulant proteins C and S. With their relatively short half-lives, these proteins are inhibited early in the course of warfarin treatment, theoretically inducing a transient prothrombotic effect during the first days. Thus, parenteral anticoagulant therapy must be maintained for at least 5 days and until the INR has reached the therapeutic range.

If patients have taken warfarin previously, they should start with the dose they previously used that resulted in a therapeutic INR. Most warfarin-naive patients should start 5 mg daily, with INR testing to guide subsequent dosing. INR testing should be done frequently (at least weekly) until a stable INR has been achieved. Dose adjustments and monitoring guidance should come from trained anticoagulation care providers when possible.

DOACs. At present, 4 DOACs are FDA approved for treatment of DVT and PE. In their relevant clinical trials (Table 4), they were compared with LMWH-bridged warfarin therapy and found to be non-inferior (15-20). Rates of major bleeding were also similar among treatment groups. DOACs lack the narrow therapeutic index and high interpatient

TABLE 4 Overview of Anticoagulation Clinical Trials in Venous Thromboembolism

Clinical Trial (Ref. #) (Study Drug)	Included Patients	Trial Design	Length of follow-up	N	Treatment Groups	TTR	Primary Efficacy Outcome	Rate of Primary Outcome	Rate of Major Bleeding
RE-COVER (15) (dabigatran)	Acute symptomatic proximal DVT or PE	Double-blind, double-dummy RCT	6 months	2,564	Dabigatran 150 mg twice daily. After 5-10 days of parenteral anticoagulation versus parenterally bridged, adjusted-dose warfarin targeting INR 2.0-3.0	60%	Composite of symptomatic VTE or death associated with VTE	Dabigatran: 2.4% Warfarin: 2.1% HR: 1.10 (0.65-1.84)	Dabigatran: 1.6% Warfarin: 1.9% HR: 0.82 (0.45-1.48)
RE-COVER II (16) (dabigatran)	Acute symptomatic proximal DVT or PE	Double-blind, double-dummy RCT	6 months	2,568	Dabigatran 150 mg twice daily after 5-10 days of parenteral anticoagulation versus parenterally bridged, adjusted-dose warfarin targeting INR: 2.0-3.0	57%	Composite of symptomatic VTE or death associated with VTE	Dabigatran: 2.3% Warfarin: 2.2% HR: 1.08 (0.64-1.8)	Dabigatran: 1.2% Warfarin 1.7% HR: 0.69 (0.36-1.32%)
EINSTEIN DVT (17) (rivaroxaban)	Acute symptomatic proximal DVT without PE	Open-label RCT	3, 6, or 12 months	3,449	Rivaroxaban 15 mg twice daily x 21 days, then 20 mg daily versus enoxaparin-bridged, adjusted-dose warfarin targeting INR: 2.0-3.0	58%	Recurrent symptomatic VTE	Rivaroxaban: 2.1% Warfarin: 3.0% HR: 0.68 (0.44-1.04)	Rivaroxaban: 0.8% Warfarin: 1.2% HR: 0.65 (0.33-1.30)
EINSTEIN PE (18) (rivaroxaban)	Acute symptomatic PE with or without DVT	Open-label RCT	3, 6, or 12 months	4,832	Rivaroxaban 15 mg twice daily x 21 days, followed by 20 mg daily versus enoxaparin-bridged, adjusted-dose warfarin targeting INR: 2.0-3.0	63%	Recurrent symptomatic VTE	Rivaroxaban: 2.1% Warfarin: 1.8% HR: 1.12 (0.75-1.68)	Rivaroxaban: 1.1% Warfarin: 2.2% **HR: 0.49 (0.31-0.79)**
AMPLIFY (19) (apixaban)	Acute symptomatic proximal DVT or PE	Double-blind double-dummy RCT	6 months	5,395	Apixaban 10 mg twice daily x 7 days followed by 5 mg twice daily versus enoxaparin-bridged, adjusted-dose warfarin targeting INR: 2.0-3.0	61%	Composite of symptomatic VTE or death associate with VTE	Apixaban: 2.3% Warfarin: 2.7% HR: 0.84 (0.6-1.18)	Apixaban: 0.6% Warfarin: 1.8% **HR: 0.31 (0.17-0.55)**
Hokusai VTE (20) (edoxaban)	Acute symptomatic DVT of popliteal, femoral or iliac veins, or acute symptomatic PE	Double-blind double-dummy RCT	3-12 months	8,240	Edoxaban 60 mg daily after 5-10 days of parenteral anticoagulation versus parenterally bridged, adjusted-dose warfarin targeting INR: 2.0-3.0	64%	Composite of recurrent symptomatic VTE or VTE-related death	Edoxaban: 3.2% Warfarin: 3.5% HR: 0.89 (0.70-1.13)	Edoxaban: 1.4% Warfarin: 1.6% HR: 0.81 (0.59-1.21)

Bold refers to values that are statistically significant.

DVT = deep vein thrombosis; HR = hazard ratio; INR = international normalized ratio; PE = pulmonary embolism; RCT = randomized controlled trial; TTR = time in therapeutic range; VTE = venous thromboembolism.

dosing variability of warfarin and thus offer patients freedom from routine therapeutic drug monitoring. However, baseline and periodic monitoring of renal function is recommended (21).

When used for VTE treatment, dabigatran and edoxaban require 5 to 10 days of parenteral drug therapy run-in. This does not overlap or "bridge" as with warfarin. Most patients take LMWH on days 1 through 5, then stop and initiate either dabigatran or edoxaban on day 6.

As mentioned previously, apixaban and rivaroxaban offer an oral-only VTE-treatment strategy. With both of these oral factor Xa inhibitors, a higher dose is taken for the first 1 to 3 weeks, during the acute treatment phase, before the standard dose is given during long-term treatment.

Drug selection. The most recent American College of Chest Physicians and American Society of Hematology guideline notes a preference for DOAC treatment over warfarin, based primarily on the perception of improved convenience for patients and providers (7,11). It should be noted that there are groups of patients, including those with severe renal dysfunction and those who lack adequate prescription drug insurance coverage, for whom warfarin remains the preferred long-term treatment of VTE.

TABLE 5 Factors Influencing Selection of Oral Anticoagulants

Patient-Specific Motivation/Factor	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Avoidance of injections			X	X	
Cost barrier (Medicare patients with coverage gap)	X				
Once-daily dosing	X		X		X
History of GERD or PPI use	X		X	X	X
Desire for close monitoring, including patients with history of poor medication adherence	X				
Dose timing without regard to food or other meds	X	X		X	X
Inconsistent or poor nutrition, especially with respect to vitamin K		X	X	X	X

Patients with specific health factors or preferences may be best suited for specific oral anticoagulants.
GERD = gastro-esophageal reflux disease; PPI = proton-pump inhibitor.

Warfarin is also the drug of choice in patients with specific high thrombotic-risk conditions such as triple-positive antiphospholipid antibody syndrome, owing to trial data indicating higher rates of arterial thrombosis in high-risk patients treated with rivaroxaban compared with those treated with warfarin (22). It is less clear if warfarin should be preferred over DOACs for patients with lower-risk antiphospholipid antibody syndrome such as those without arterial thrombotic events and only 1 or 2 antibodies that are persistently positive (23).

Many patients are candidates for warfarin and DOACs. These patients should be actively involved in treatment decisions. Failure to involve patients in treatment decisions has been shown to negatively affect medication adherence. High drug costs and complex medication regimens have also been shown to decrease adherence (24). Patients should be asked about their motivations and preferences (Table 5).

All patients on therapeutic anticoagulation should be educated on the potential safety concerns of treatment. Patients should also be engaged in diagnosis-specific and drug-specific education to ensure optimal adherence and treatment outcomes. Patients on warfarin require extensive education because of the nature of lifestyle factors on INR stability. Table 6 includes suggested patient education topics for anticoagulated patients.

VTE IN CANCER. Because the risk of VTE recurrence is significantly higher in patients with cancer compared with those without, special consideration must be given to patients experiencing a cancer-

TABLE 6 Important Patient-Education Topics

For patients taking ANY anticoagulants	Signs and symptoms of worsening or recurrent thrombosis
	Signs and symptoms of bleeding
	Potential for heavier menstrual bleeding, if applicable
	Pregnancy prevention, if applicable
	Expected duration of therapy
	Importance of contacting anticoagulation care provider for changes in medications or upcoming procedures or surgeries
	Avoidance of over-the-counter medications that increase bleeding risk (NSAIDs)
	Avoidance of behaviors that increase bleeding risk (overuse of alcohol, contact sports)
	What to do in case of a missed dose
	When to seek emergency care (in case of head trauma or severe bleeding)
For patients on any DOAC	Importance of strict medication adherence
For patients on dabigatran	Storage in original container, not in pill boxes
	Capsules may not be broken, open, or split
For patients on rivaroxaban	Switch from 15 mg twice daily to 20 mg once daily after 3 weeks
	Administer with food
For patients on apixaban	Switch from 10 mg twice daily to 5 mg twice daily after 1 week
For patients on warfarin	Importance of INR monitoring and target range
	Consistent intake of dietary vitamin K
	Awareness of sources of vitamin K including nutritional shakes, supplements, vitamins
	Awareness of lifestyle factors that affect INR (exercise, alcohol, tobacco, stress, acute illness, interacting medications)
	Notify anticoagulation care provider if warfarin tablets appear different in color or shape with each medication refill

DOAC = direct oral anticoagulant; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug.

TABLE 7 Randomized Trials of Oral Anticoagulant Use on Cancer Patients With Venous Thromboembolism

Clinical Trial (Ref. #) (Study Drug)	Included Patients	Trial Design	Length of Follow-Up	N	Treatment Groups	Efficacy Outcome	Rate of Efficacy Outcome	Rate of Major Bleeding
Hokusai VTE Cancer (28) (edoxaban)	Patients with active cancer and symptomatic or incidental popliteal, femoral or iliac or IVC DVT, symptomatic or incidental PE	Open-label RCT	12 months	1,050	Edoxaban 60 mg daily after 5–10 days of parenteral anticoagulation versus dalteparin 200 IU/kg x 30 days, then 150 IU/kg	Recurrent VTE (secondary)	Edoxaban: 7.9% Dalteparin: 11.3% HR: 0.71 (0.48–1.06)	Edoxaban: 6.9% Dalteparin: 4.0% **HR: 1.77 (1.03–3.04)**
SELECT-D (29) (rivaroxaban)	Patients with active cancer and symptomatic DVT, symptomatic PE, or incidental PE	Open-label RCT	6 months	406	Rivaroxaban 15 mg twice daily x 21 days, then 20 mg daily versus dalteparin 200 IU/kg x 30 days, then 150 IU/kg	Recurrent VTE	Rivaroxaban: 4% Dalteparin: 11% **HR: 0.43 (0.19–0.99)**	Rivaroxaban: 6% Dalteparin: 4% HR: 1.83 (0.68–4.96)
ADAM VTE (30) (apixaban)	Active cancer patients with acute DVT (including upper extremity), PE, splanchnic or cerebral vein thrombosis	Open-label RCT	6 months	300	Apixaban 10 mg twice daily x 7 days then 5 mg twice daily versus dalteparin 200 IU/kg x 30 days, then 150 IU/kg	Venous or arterial thrombo-embolism (secondary outcome)	Apixaban: 6% Dalteparin: 6% HR: 0.931 (0.43–2.02)	Apixaban: 0% Dalteparin: 1.4% HR: not estimable
Caravaggio (31) (apixaban)	Patients with active or recent cancer and acute DVT or PE	Open-label RCT	6 months	1,155	Apixaban 10 mg twice daily x 7 days then 5 mg twice daily versus dalteparin 200 IU/kg x 30 days, then 150 IU/kg	Recurrent VTE	Apixaban: 5.6% Dalteparin: 7.9% HR: 0.63 (0.37–1.07)	Apixaban: 3.8% Dalteparin: 4.0% HR: 0.82 (0.40–1.69)

Bold refers to values that are statistically significant.

DVT = deep vein thrombosis; HR = hazard ratio; IVC = inferior vena cava; PE = pulmonary embolism; RCT = randomized controlled trial; VTE = venous thromboembolism.

associated VTE. In the pre-DOAC era, clinical trials in this population compared LMWH monotherapy with LMWH-bridged warfarin. The CLOT (Comparison of Low-Molecular-Weight versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) (25) and CATCH (Comparison of Acute Treatments in Cancer Haemostasis) (26) studies both compared the efficacy of LMWH treatment with warfarin in patients with cancer-associated VTE. A meta-analysis confirmed that LMWH treatment offers a 40% relative risk reduction in recurrence of VTE compared with warfarin in patients with cancer-associated VTE (27). In addition to considering differences in efficacy, patients with intolerance to oral therapies, including those on highly emetogenic cancer treatment regimens, might prefer a parenteral option.

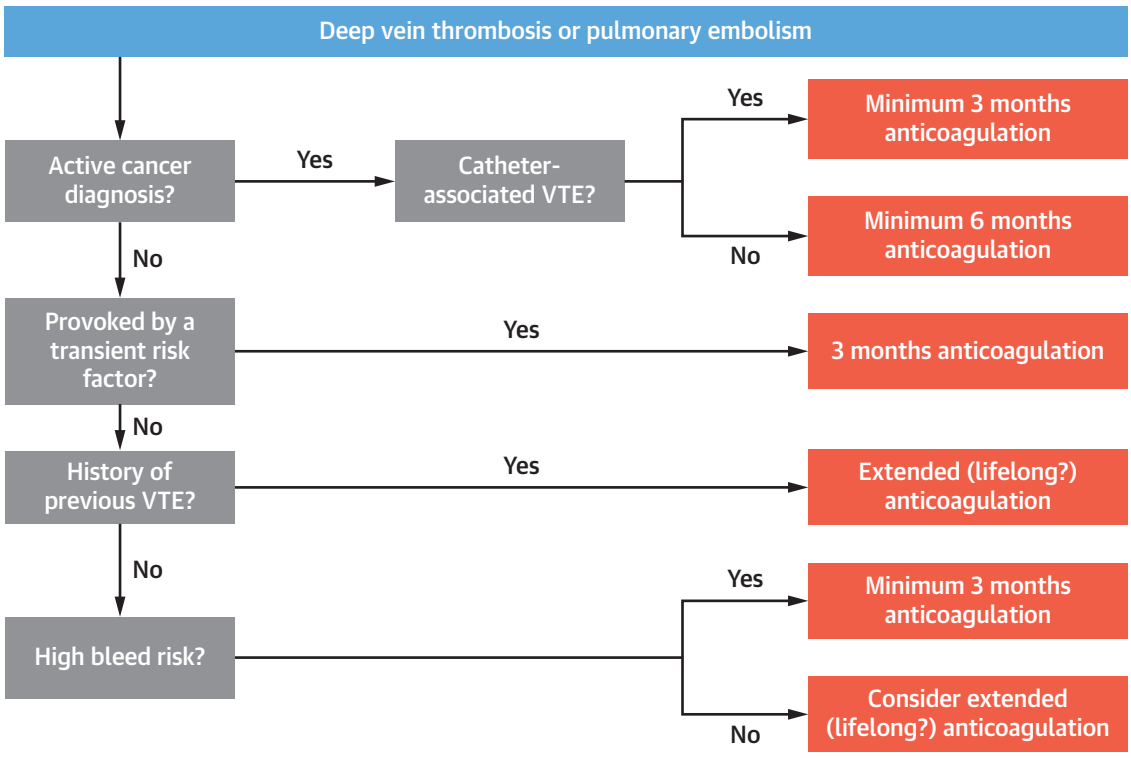
More recent trials (**Table 7**) have compared LWMH with DOACs in cancer-associated VTE (28-31). In the Hokusai VTE Cancer study, edoxaban started after a 5- to 10-day run-in period of dalteparin was compared with dalteparin monotherapy for a period of 6 to 12 months. Patients in the edoxaban arm were less likely to have recurrent VTE but more likely to have a major bleeding event compared with patients in the dalteparin arm. The Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism (SELECT-D) pilot study compared an oral-only rivaroxaban VTE treatment approach with dalteparin monotherapy and found that rivaroxaban-treated patients had fewer recurrent VTEs over 6 months but had higher rates of bleeding, particularly clinically relevant nonmajor bleeding (CRNMB). Apixaban and Dalteban in Active Malignancy (ADAM) VTE was a relatively small trial investigating apixaban VTE treatment versus dalteparin and demonstrated a lower risk of recurrent VTE in the apixaban group over 6 months of follow-up. Major bleeding events were rare and rates of CRNMB were similar between groups. The Caravaggio trial expanded upon ADAM VTE with a larger number of subjects and found a numerically lower rate of recurrent VTE in the apixaban group, which demonstrated statistical noninferiority to the dalteparin treatment arm. In contrast to the other trials mentioned in this paragraph, there was no difference in major bleeding between treatment arms of the Caravaggio study.

DOACs appear to be reasonable alternatives to LMWH in the treatment of cancer-associated VTE. Higher bleeding rates seen among the DOAC-treated groups in cancer-associated VTE trials are largely of gastrointestinal (GI) or urinary origin. A meta-analysis of the Hokusai VTE Cancer and SELECT-D pilot trials found bleeding events to be most common among patients with GI malignancies (32). Patients requiring VTE treatment with these types of cancers require special consideration, given their higher bleeding risk in the setting of anticoagulation.

SECONDARY PREVENTION OF VTE

DURATION OF ANTICOAGULATION. Whether or not to continue anticoagulation after the initial 3 to 6 months (primary treatment phase) from diagnosis is

FIGURE 2 Decision Tool for Shorter Versus Longer Course of Anticoagulation



For patients with lower extremity deep vein thrombosis or pulmonary embolism, length of anticoagulation therapy can be guided by 3 key factors. Those with presence of active cancer should receive a minimum of 3 months (if catheter-associated) or 6 months (it not catheter-associated) of anticoagulation. Those with surgical or nonsurgical transient risk factors should receive only 3 months of anticoagulation. Those with high bleeding risks, which can be estimated using various scores or clinical gestalt, should receive only 3 months of anticoagulation. All others should be considered for extended courses of anticoagulation beyond 3 to 6 months. Extended courses of anticoagulation may end up being lifelong but require period reassessment of risk and benefit.

best determined by review of an individual patient's risk of recurrent VTE if therapy is discontinued and their risk of bleeding if therapy is prolonged. **Figure 2** represents a simplified decision tree for determining treatment length based on the most recent American College of Chest Physicians guideline (7).

Several risk-scoring algorithms exist to help quantify risk of recurrence of VTE. These include the Men Continue and HERSOO2 score, Vienna Risk Model, and DASH Prediction Score (33-35). These risk scores consider various patient-specific factors that may increase risk of recurrence of VTE including male sex, elevated D-dimer, presence of post-thrombotic syndrome, obesity, age <50 years at index event, location of thrombus (distal vs. proximal), and presence of provoking factors.

Patients with low risk of recurrence of VTE, especially those with a first VTE provoked by a reversible risk factor such as surgery, prolonged travel or immobility, or presence of a thrombogenic medication (e.g., estrogen-containing oral contraceptives), should generally not continue anticoagulation beyond the initial 3 months of therapy if the risk factor can be removed. Patients without an identified provoking factor for their VTEs are generally more challenging because their risk of recurrence is uncertain. In these patients, it may be helpful to quantify risk of bleeding on anticoagulation. The RIETE and VTE-BLEED bleeding risk scores (**Table 8**) have been tested in VTE populations and use conditions and risk factors that are readily available in a primary care setting (36,37). It is important to differentiate between early versus late predictors of bleeding as well as modifiable (e.g., concurrent antiplatelet medications) and nonmodifiable factors (e.g., chronic kidney disease). It is important to know that none of the bleeding risk scores has been studied in prospective clinical decision-making studies (38).

DRUG SELECTION IN SECONDARY PREVENTION OF VTE. All available oral anticoagulants have been used

TABLE 8 RIETE and VTE-BLEED Bleeding Risk Scores

RIETE Score (36)

Condition	Points	Total Points	3-Month Major Bleeding Risk (%)	Risk Level
Recent major bleeding (<15 days before VTE)	2	0	0.1	Low
Creatinine >1.2 mg/dl	1.5	1	1.4	Moderate
Anemia (Hgb <13 g/dl in men or <12 g/dl in women)	1.5	1.5–2	2.2	
Cancer	1	2.5–3	4.4	
Clinically overt pulmonary embolism	1	3.5–4	4.2	
Age >75 yrs	1	4.5–5	4.9	High
		5.5–6	11	
		>6	20	

VTE-BLEED Risk Score (37)

Condition	Points	Total Points	6-Month Major Bleeding Risk (%)	Risk Level
Active cancer	2	0–1.5	1.4	Low
Creatinine clearance 30–60 ml/min	1.5	≥ 2	2.8	High
Anemia (Hgb <13 g/dl in men or <12 g/dl in women)	1.5			
Age ≥60 yrs	1.5			
History of major or nonmajor clinically relevant bleeding	1.5			
Male with uncontrolled hypertension (SBP ≥140 mm Hg)	1			

Hgb = hemoglobin; SBP = systolic blood pressure; VTE = venous thromboembolism.

successfully in primary treatment of VTE as well as in secondary prevention. If patients are continuing therapy beyond the primary treatment period, it is reasonable for them to continue to use the same anticoagulant. If patients or providers are significantly motivated to transition to another medication, this can also be done.

Warfarin. Warfarin has been used in the setting of secondary prevention of VTE for many years. Although lower-intensity regimens (targeting INR: 1.5 to 2.0) have been studied and shown to lower risk of recurrent VTE more than placebo, these regimens remain inferior to the standard INR target (2.0 to 3.0). Thus, if patients opt to continue warfarin as their extended secondary prevention of VTE, it is recommended to continue targeting an INR of 2.5 throughout treatment.

DOACs. As shown in **Table 9**, dabigatran is the only available DOAC to have been studied versus an active comparator (warfarin) in secondary prevention of VTE. As in its initial VTE treatment trial program, dabigatran performed as well as warfarin in reducing recurrent VTE and had similar rates of major bleeding. Dabigatran, rivaroxaban, and apixaban have all been studied in trials that showed their comparative efficacy versus placebo in the setting of prevention of secondary VTE in patients for whom discontinuation of anticoagulation was being considered (17,39–41). Unsurprisingly, all 3 were superior to placebo in reduction in the rate of recurrent VTE. Rates of major bleeding were sufficiently low in all trials that no differences in risk were noted among groups.

Two factor Xa inhibitors—rivaroxaban and apixaban—have been studied in secondary VTE prevention studies in doses that are lower than those prescribed in their initial VTE treatment studies. In EINSTEIN CHOICE, rivaroxaban, 20 mg daily (standard dose), was compared with rivaroxaban 10 mg daily (low dose) and aspirin 100 mg daily. Both doses of rivaroxaban were found to reduce the risk of recurrent VTE similarly and to a greater degree than aspirin. There was no difference found in rate of major bleeding for any group. In AMPLIFY-EXT, apixaban 5 mg twice daily (standard dose) was compared with apixaban 2.5 mg twice daily (low dose) and with placebo. Both apixaban groups had similarly low rates of recurrent VTE and both were superior to placebo. Rates of major bleeding were numerically lower in the apixaban groups than in the placebo group, although this was not found to be a statistically significant difference.

Because of these favorable secondary prophylaxis trials, both apixaban and rivaroxaban are labeled in the United States for use in their lower doses (2.5 mg twice daily and 10 mg daily, respectively) after 6 months of therapy at the standard doses (5 mg twice daily and 20 mg daily, respectively). Low-dose DOACs are a good option for patients with weakly provoked VTE events (e.g., long car travel) or patients with unprovoked VTE and no high-risk features (e.g., active cancer, antiphospholipid antibody syndrome).

TABLE 9 Randomized Trials of Oral Anticoagulants in Secondary Prevention

Trial (Ref. #) (Study Drug)	Included Patients	Design	Treatment Duration	N	Treatment Groups	TTR	Primary Efficacy Outcome	Rate of Primary Outcome	Rate of Major Bleeding
RE-MEDY (39) (dabigatran)	Patients previously enrolled in RE-COVER or RE-COVER II at with continued risk of VTE after 3–12 months	Double-blind, double-dummy RCT	6–36 months	2,866	Dabigatran 150 mg twice daily vs. adjusted-dose warfarin targeting INR: 2.0–3.0	65%	Composite of symptomatic VTE or death associated with VTE	Dabigatran: 1.8% Warfarin: 1.3% HR: 1.44 (0.78–2.64)	Dabigatran: 0.9% Warfarin: 1.8% HR: 0.52 (0.27–1.02)
RE-SONATE (39) (dabigatran)	Patients previously in RE-COVER or RE-COVER II being considered for therapy discontinuation after 6–18 months	Double-blind RCT	6 months	1,353	Dabigatran 150 mg twice daily versus placebo	n/a	Composite of symptomatic VTE or death associated with VTE	Dabigatran: 0.4% Placebo: 5.6% **HR: 0.08 (0.02–0.25)**	Dabigatran: 0.3% Placebo: 0% HR: nonestimable
EINSTEIN-EXT (17) (rivaroxaban)	Patients on warfarin 6–12 months after a VTE (may have been in EINSTEIN program) or rivaroxaban (all from EINSTEIN)	Open-label RCT	6 or 12 months	1,197	Rivaroxaban 20 mg daily vs. placebo	n/a	Recurrent symptomatic VTE	Rivaroxaban: 1.3% Placebo: 7.1% **HR: 0.18 (0.09–0.39)**	Rivaroxaban: 0.7% Placebo: 0% HR: nonestimable
AMPLIFY-EXT (40) (apixaban)	Patients on apixaban who had received 6–12 months of treatment after VTE	Double blind, double dum-dum RCT	12 months	2,486	Apixaban 5 mg twice daily, 2.5 mg twice daily, or placebo	n/a	Symptomatic recurrent VTE or death	Apixaban 5 mg twice daily: 4.2% Apixaban 2.5 mg twice daily: 3.8% Placebo: 11.6% **Placebo HR 0.33 (0.22–0.48) for 2.5 mg BID vs. placebo**	Apixaban 5 mg twice daily: 0.1% Apixaban 2.5 mg twice daily: 0.2% Placebo: 0.05% HR: 0.25 (0.03–2.24) for apixaban 5 mg twice daily vs. placebo HR: 0.49 (0.09–2.64) for apixaban 2.5 mg twice daily vs. placebo
EINSTEIN (41) CHOICE (rivaroxaban)	Patients who were on an anticoagulant 6–12 months after a VTE	Double-blind RCT	Up to 12 months	3,365	Rivaroxaban 20 mg daily, 10 mg daily, or aspirin 100 mg daily	n/a	Symptomatic recurrent fatal or nonfatal VTE	Rivaroxaban 20 mg daily: 1.5% Rivaroxaban 10 mg daily: 1.2% Aspirin 100 mg daily: 4.4% **HR: 0.34 (0.20–0.59) for 20 mg daily vs. aspirin** **HR: 0.26 (0.14–0.47) for 10 mg daily vs. aspirin**	Rivaroxaban 20 mg daily: 0.5% Rivaroxaban 10 mg daily: 0.4% Aspirin 100 mg daily: 0.3% HR: 2.01 (0.50–8.04) for rivaroxaban 20 mg daily vs. aspirin HR: 1.64 (0.39–6.84) for rivaroxaban 10 mg daily vs. aspirin

Bold refers to values that are statistically significant.

HR = hazard ratio; INR = international normalized ratio; RCT = randomized-controlled trial; TTR = time in therapeutic range; VTE = venous thromboembolism.

Use of standard dosing (apixaban 5 mg twice daily, rivaroxaban 20 mg daily) is also permitted, particularly if there is concern about high ongoing VTE risk. In Europe, rivaroxaban can be prescribed at either the standard (20 mg daily) or reduced dose (10 mg daily) after 6 months, whereas apixaban is recommended to have a dose reduction (2.5 mg twice daily) in secondary prophylaxis.

Aspirin. The WARFASA (Warfarin and Aspirin [42]) and ASPIRE (Anticoagulation in ICH Survivors for Stroke Prevention and Recovery [43]) trials showed that in patients who are no longer anticoagulated following a VTE, aspirin 100 mg daily may provide some protection against recurrent events. Although the relative risk reduction provided by aspirin (~30%) does not approach that of therapeutic anticoagulation (~80% to 90%), the risk of major bleeding is low and similar to placebo. Aspirin may be considered for recurrent VTE risk reduction in patients who have opted not to continue

anticoagulation and who do not carry a high risk of bleeding.

DISCONTINUATION OF ANTICOAGULATION. Although some providers use imaging such as ultrasonography or blood tests such as D-dimer to help determine when discontinuation of anticoagulation is appropriate, the 2020 American Society of Hematology guidelines recommend against these tests routinely, given low certainty of the evidence supporting their use (11). Use of sex and D-dimer to guide duration of anticoagulation in patients with unprovoked VTE is supported in the 2016 American College of Chest Physicians guidelines. However, use of low-dose DOAC therapy may reduce the number of patients with unprovoked VTE for whom full anticoagulation discontinuation is considered. In patients for whom the decision is made to terminate anticoagulation after VTE, education should be provided regarding future risk for thrombosis. Signs and symptoms of VTE should be reviewed, and patients should be made aware of future situations that might put them at higher risk, including long-distance travel, prolonged immobility, surgeries or hospitalizations, and use of hormonal therapies such as estrogens.

CATHETER-ASSOCIATED VTE. Indwelling catheters remain a common cause of provoked VTE, especially in the upper extremities. This is especially true for peripherally inserted central catheters (44). When a symptomatic catheter-associated DVT is identified, 3 months of anticoagulation therapy should be initiated (45). Despite limited efficacy evidence, DOAC therapy can be considered in this clinical scenario. Anticoagulation can be continued beyond 3 months if the catheter cannot be removed. Cather removal is not mandatory if it is well positioned, necessary for medical therapy, and functional.

FUTURE WORK

In the past decade, the DOACs have revolutionized care of patients with VTE. Their rapid onset of action and stable dosing regimens allow for easier outpatient treatment of VTE. At the same time, they have introduced new complexities for management of anticoagulation. These include different doses and regimens for different indications (e.g., atrial fibrillation vs. VTE), different approaches to peri-procedural management, and the need to understand complex drug-drug interactions. Efforts are ongoing to optimize safe anticoagulant prescribing and monitoring through important collaboration with expert pharmacists and nurses in anticoagulation clinics.

At the same time, new classes of antithrombotic medications are under development. These include novel direct thrombin antibodies (46), inhibitors of Factor XI and XII (47,48), and selectin antagonists (49). The goal of these antithrombotic medications is to prevent thrombus formation while further reducing bleeding risk. Given their mechanisms of action, their eventual indications are likely to be more limited than DOACs.

CONCLUSIONS

VTE represents a significant public health burden, especially for an aging population. Although many patients have identifiable provoking factors, it is increasingly recognized that unidentified factors likely contribute to an individual's risk of initial and recurrent VTE. In the past decade, the DOAC medications have transformed both acute treatment and secondary prevention of VTE with oral-only strategies and reduced doses, respectively. Additional antithrombotic therapies are currently under development and offer hope for treatments with lower risks of bleeding complications.

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