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PREVENTING AND TREATING THROMBOEMBOLISM IN THE 21ST CENTURY

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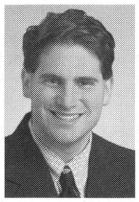

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Venous and arterial thromboembolism are important causes of morbidity and mortality in the United States. Since the first randomized trial in 1960 establishing the life-saving role of heparin in patients with pulmonary embolism, the diagnosis and treatment of thromboembolism have undergone major advances. In particular, new parenteral anticoagulant therapies have revolutionized the care of patients with venous thromboembolism. Currently available agents include the low-molecular-weight heparins, the direct thrombin inhibitors, and a synthetic pentasaccharide. Other new anticoagulant classes are under development. In contrast, since their development 60 years ago, vitamin K antagonists have remained the only commercially available oral antithrombotic drugs in the United States.

Despite its unpredictable anticoagulant response, narrow therapeutic range, and many drug and food interactions, warfarin remains the most widely used vitamin K antagonist in North America. Late last year the US Food and Drug Administration unanimously rejected approval of an oral direct thrombin inhibitor, ximelagatran, because of concerns over hepatotoxicity. However, ximelagatran has demonstrated equivalent efficacy to conventional therapy in more than a dozen clinical trials among patients at risk for venous and arterial thromboembolism. Thus, there is good reason to continue the quest for a safe and convenient oral alternative to warfarin.

This supplement brings together experts in thromboembolism and anticoagulation to lay out this changing landscape through seven state-of-the-art, evidence-based reviews addressing common clinical problems. Our topics include the pharmacology of anticoagulants; advances in the prevention, diagnosis, and management of thromboembolism; heparin-induced thrombocytopenia; and anticoagulant dosing in patients who are obese, pregnant, or who suffer from renal impairment or cancer. We conclude by presenting economic considerations to help physicians choose among various anticoagulation strategies.

I am excited that this supplement is being distributed to nearly 100,000 physicians around the nation. I hope you find our efforts useful, and I encourge readers to e-mail me with feedback or questions.

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A pharmacologic overview of current and emerging anticoagulants

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ABSTRACT

For over 50 years, anticoagulant options for the treatment and prevention of thrombosis have been limited mainly to traditional agents such as unfractionated heparin and oral vitamin K antagonists such as warfarin. These traditional agents are fraught with limitations that complicate their clinical use. A variety of novel anticoagulants with improved pharmacologic and clinical profiles have recently been introduced or are in development, offering benefits over traditional therapies. Specifically, progress has been made in the development of low-molecular-weight heparins, factor Xa inhibitors, and direct thrombin inhibitors. Because of their convenience and ease of use, some of these novel compounds are competing with the traditional anticoagulants and are needed additions to the antithrombotic arsenal.

Anticoagulant therapy has historically consisted of heparins for the treatment of acute thrombosis and vitamin K antagonists for long-term or chronic treatment.[1] Though effective if appropriately dosed and monitored, these traditional agents have shortcomings that stem mainly from their nonspecific mechanisms of action and variable pharmacodynamics. This has left a persisting need for novel anticoagulants that have more specific and targeted action and are easier to administer and manage.[2] Recent efforts have focused on the development of more specific agents that may offer benefits over traditional anticoagulants. As a result, today there are four major classes of anticoagulants available in the United States for the prevention and treatment of thrombosis:

- Vitamin K antagonists such as warfarin
- Indirect thrombin inhibitors such as unfractionated heparin and low-molecular-weight heparins
- Direct thrombin inhibitors
- Factor Xa inhibitors.

This article reviews and compares pharmacologic characteristics among these various traditional and novel anticoagulants. These agents' modes of action are depicted in **Figure 1** and their clinical and pharmacologic profiles are outlined in **Table 1**.

VITAMIN K ANTAGONISTS

The first vitamin K antagonists (VKAs), or coumarin derivatives, were developed in the early 1940s, and the first clinical trials began in 1954. Sweet clover disease, a malady in which cattle died of hemorrhagic complications after ingesting spoiled sweet clover, led to the discovery of dicumarol and its congener warfarin by Dr. Karl Paul Link in 1940. For the last 50 years VKAs have been the mainstay oral anticoagulants in North America.

Two classes of VKAs have been approved by the US Food and Drug Administration (FDA), the coumarins and the indandiones. One drug from each class, warfarin and anisindione, is available in the United States, but warfarin is by far the most commonly used oral agent. Warfarin is the anticoagulant of choice when long-term or extended anticoagulation is indicated.

The VKAs' efficacy has been demonstrated for the primary and secondary prevention of venous thromboembolism (VTE), prevention of systemic VTE in patients with atrial fibrillation or prosthetic heart valves, prevention of thromboembolic stroke, and primary and secondary prevention of acute myocardial infarction.[3]

Warfarin exerts its anticoagulant effect by inhibiting activation of the vitamin K–dependent clotting factors II, VII, IX, and X as well as the anticoagulant proteins C and S. The degree of depression of clotting factors is dose-dependent, with a decrease in each factor of approximately 30% to 50% at therapeutic doses.

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When warfarin therapy is initiated, attainment of complete antithrombotic effect is usually delayed for several days, owing to the various half-lives of the clotting factors (6 to 72 hours). Proteins C and S are inhibited more rapidly because of their shorter half-lives, which may potentially lead to a "paradoxical" procoagulant state during the first few days of therapy. It is therefore crucial that patients with acute thrombosis receive a parenteral anticoagulant (heparin or low-molecular-weight heparin) while transitioning to therapeutic doses of warfarin.[3,4]

Why alternatives are needed

Although warfarin is effective, its use is limited by various challenges:

- The need for frequent monitoring of anticoagulant effect via the international normalized ratio
- Large interindividual dosing differences
- A narrow therapeutic index
- Slow onset and offset of action
- Interactions with dietary vitamin K and many other medications, vitamins, and herbal supplements
- Drug-disease interactions
- Genetic variations in anticoagulant response
- The need for constant dose adjustments, patient education, strict compliance, and frequent follow-up.[2,3,5]

These limitations render VKAs cumbersome for day-to-day clinical use and cumbersome for patients, underscoring the need for novel oral agents that are more convenient and less complex to use.

HEPARINS: UNFRACTIONATED AND FRACTIONATED

Discovered in the early 20th century, unfractionated heparin (UFH) is commercially isolated from porcine or bovine mucosa. Heparin exerts its anticoagulant effect via a plasma cofactor, antithrombin, inhibiting thrombin (factor IIa) and factor Xa in an equal (1:1) ratio. It binds nonspecifically to a number of plasma and cellular proteins, resulting in decreased bioavailability and substantial interpatient variability in anticoagulant response. Thus, when given at therapeutic doses, UFH requires frequent laboratory monitoring to assess the level of anticoagulation, as measured by the activated partial thromboplastin time (aPTT).[6]

Fractionated or low-molecular-weight heparins (LMWHs) are derived by chemical or enzymatic depolymerization of UFH, resulting in shorter heparin chains that have an enhanced affinity for inhibiting factor Xa relative to their activity against thrombin. The factor Xa:IIa ratios for LMWHs are agent-specific and range from 4:1 to 2:1. Three LMWHs are currently available in the United States: dalteparin, enoxaparin, and tinzaparin.[6,7]

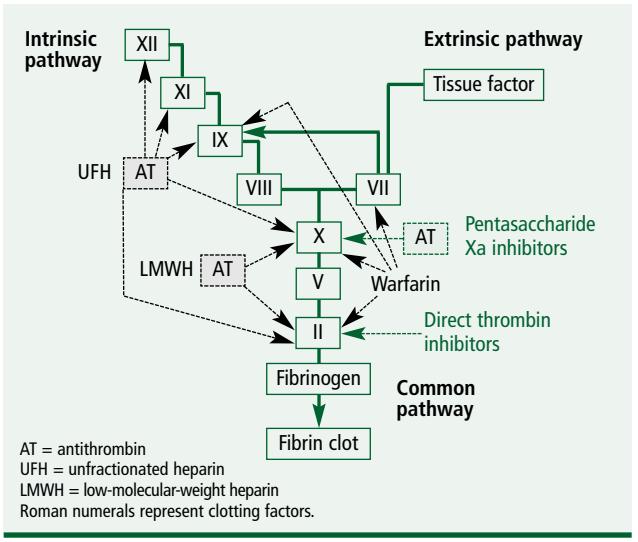

FIGURE 1. The pathways of coagulation and the modes of action of various anticoagulant classes. The coagulation cascade comprises two independent pathways—intrinsic and extrinsic—that converge on the activation of factor X and initiate the common pathway that leads to thrombin generation and fibrin formation.

Advantages of LMWHs

LMWHs have substantially improved pharmacodynamic and pharmacokinetic properties as compared with UFH. They exhibit less binding to plasma and cellular proteins, resulting in a more predictable anticoagulant response. Consequently, routine monitoring of anticoagulation intensity and dose adjustment are not required in most patients. LMWHs also have longer plasma half-lives, allowing once- or twice-daily administration (vs twice or thrice daily with UFH), improved subcutaneous bioavailability, and dose-independent renal clearance. Because of their ease of use, LMWHs can be given more readily on an outpatient basis, providing patients a more convenient and less complex form of therapy. LMWHs also have a more favorable side-effect profile than does UFH, including a lower incidence of heparin-induced thrombocytopenia (HIT) and osteopenia. However, LMWHs cross-react with UFH and should not be given as alternative anticoagulants in patients with documented HIT.[8,9]

Other factors to consider

Additional factors to weigh when considering LMWHs relative to UFH are their higher acquisition costs; the more limited data on their use in high-risk populations such as obese patients, pregnant women, and pediatric patients; and the fact that they, unlike UFH, are only partially reversible with protamine. In addition, LMWHs require dose adjustment in patients with renal impairment, owing to their renal elimination.[10,11]

TABLE 1
Pharmacologic and clinical profiles of anticoagulant agents

Characteristic	Warfarin	Unfractionated heparin	Low-molecular-weight heparins	Factor Xa inhibitors	Direct thrombin inhibitors
No. of targets in coagulation cascade, specificity of activity	Multiple, nonspecific	Multiple, nonspecific	Relatively few and specific	Few, specific	Few, specific
No. of times dosed daily	1	2–3*	1–2	1	1–2*
Route of administration	Oral	IV or SC	SC	SC or oral	IV, SC, or oral
Laboratory monitoring requirements	INR	aPTT, platelet count	Platelet count; anti-Xa monitoring in special groups	None	Varies†
Variability in response	High	High	Relatively low	None	Relatively low
Risk of thrombocytopenia	None	2%–5%	1%–2%	None	None

*Or continuous infusion (for select indications)
†aPTT for parenteral agents; liver function testing for argatroban and possibly for oral agents
aPTT = activated partial thromboplastin time; INR = international normalized ratio; IV = intravenous; SC = subcutaneous

Because of their quick onset of action, UFH and LMWHs are the anticoagulants of choice when a rapid anticoagulant effect is required. Both types of heparins are used for treatment of venous thrombosis and acute myocardial ischemia in higher "therapeutic" doses, as well as for VTE prevention in lower "prophylactic" doses. Even though UFH was the gold standard for anticoagulation for more than 60 years, its role is now challenged by the LMWHs, which have demonstrated at least comparable safety and efficacy, an improved side-effect profile, and more convenient dosing. Based on recently published and ongoing clinical trials, LMWHs are competing with UFH in all therapeutic and surgical interventions requiring anticoagulation.[1,6,12–14]

FACTOR Xa INHIBITORS

The factor Xa inhibitors are a novel class of anticoagulants; the first such agent was approved by the FDA in late 2001. They are synthetic versions of the five-sugar sequence of heparin and are thus referred to as pentasaccharides. Because of their very small molecular size, they exert their inhibitory activity specifically on activated factor X (Xa) and, unlike heparins, have no direct effect on factor IIa.[15,16]

Pentasaccharides can inhibit factor Xa directly or indirectly. The direct inhibitors bind to factor Xa without a cofactor, thus blocking its activity. Direct factor Xa inhibitors currently in development include tick anticoagulant peptide, YM-60828, and DX-9065a. The indirect inhibitors bind to antithrombin with high affinity, causing a permanent conformational change in antithrombin and increasing its rate of factor Xa inhibition. Because they are selective for factor Xa, they reduce thrombin generation without affecting circulating thrombin. Fondaparinux is the only member of the class that is commercially available in the United States. Additional agents such as idraparinux and razaxaban (formerly DPC-906) are undergoing clinical trials. Fondaparinux and idraparinux are given subcutaneously, whereas razaxaban is an oral formulation.[17–20]

As synthetic compounds, factor Xa inhibitors offer several advantages: no risk of animal pathogen transmission, batch-to-batch consistency, and unlimited sourcing. Other favorable attributes include a predictable and linear dose-response relationship, a quick time to maximum concentration, and a long half-life. Because of their predictable anticoagulant effect, factor Xa inhibitors, like LMWHs, do not require routine coagulation monitoring or dose adjustment. Fondaparinux has a half-life of 17 to 21 hours, allowing once-daily dosing, and idraparinux (an extended-release formulation) is being developed for administration as a once-weekly injection. Neither fondaparinux nor idraparinux is metabolized in the liver, so each has few drug interactions. Unlike the heparins, factor Xa inhibitors do not affect platelet function and do not react with heparin–platelet factor 4 (PF4) antibodies, thus reducing the risk of HIT. There has been no in vitro cross-reactivity with fondaparinux and antibodies to the heparin–PF4 complex, suggesting that this agent might be useful for treatment of patients with HIT and for prophylaxis in patients with a history of HIT.[19–22]

Fondaparinux is indicated for prophylaxis of venous thrombosis in patients undergoing hip replacement surgery, knee replacement surgery, and hip fracture surgery (including extended prophylaxis after hip fracture surgery). It also recently gained FDA approval for treatment of acute deep vein thrombosis and pulmonary embolism.[17] Idraparinux is being investigated for the treatment of VTE and for stroke prevention in patients with atrial fibrillation.

While a once-weekly agent such as idraparinux

would improve convenience and perhaps patient compliance, a potential drawback of these long-acting anticoagulants is that there is no antidote if the patient bleeds or requires an invasive procedure.[22,23] Clinically significant bleeding would require fresh frozen plasma and, potentially, red blood cell replacement. In the case of a life-threatening bleeding episode, one potential option to minimize bleeding is the use of recombinant factor VIIa, although this is very costly and can also increase the risk of thrombosis.[23]

In addition, since factor Xa inhibitors are renally eliminated, accumulation can occur in patients with renal dysfunction if there is not appropriate dose adjustment. Because of a current lack of specific dosing guidelines in special populations, fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) and in orthopedic surgery patients weighing less than 50 kg.[24]

Nonetheless, because of their convenience of use, factor Xa inhibitors are a welcome addition to the more traditional anticoagulants for the treatment and prevention of VTE.[17,21,24]

DIRECT THROMBIN INHIBITORS

Because thrombin is the central effector of coagulation and amplifies its own production, it is a natural target for direct pharmacologic intervention. Direct thrombin inhibitors (DTIs) bind with thrombin to prevent an interaction between the enzyme and substrates. Several parenteral DTIs are approved for use in the United States, including lepirudin, bivalirudin, argatroban, and desirudin.[25,26]

The advantages of DTIs include a targeted specificity for thrombin, the ability to inactivate clot-bound thrombin, and an absence of plasma protein and platelet interactions that can lead to complications such as HIT. Unlike heparins, DTIs do not require antithrombin as a cofactor and do not bind to plasma proteins. Therefore, they produce a more predictable anticoagulant effect, and variability of patient response is low relative to other drug classes.[25,26]

Lepirudin has a short half-life—approximately 80 minutes following intravenous administration. Its elimination is primarily renal, so dosing must be adjusted according to the patient's renal function. The dose should be monitored and adjusted to an aPTT ratio of 1.5 to 2.5 because bleeding risk increases above this range without an increase in efficacy. Lepirudin is approved for use in patients with HIT and related thrombosis.[25–27]

Bivalirudin, a DTI with a smaller molecular weight, is also given intravenously. It has a shorter elimination half-life than lepirudin (≈25 min), and its elimination is only partially renal. Patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min) may require dose adjustment and monitoring of anticoagulation status since clearance of bivalirudin is reduced by approximately 20% in these patients. The activated clotting time can be used to monitor bivalirudin's anticoagulant effect during percutaneous coronary intervention (PCI). Bivalirudin is approved for use in patients undergoing percutaneous transluminal coronary angioplasty.[25–27]

Argatroban, a small-molecule DTI, is also given intravenously. It has an elimination half-life of 40 to 50 minutes. Monitoring of the aPTT is required to assess its anticoagulant activity. Argatroban is hepatically metabolized, so dose reductions and careful monitoring are recommended in patients with hepatic dysfunction. Renal impairment has no influence on its elimination half-life and so does not require dose adjustment. Like the other DTIs, argatroban has no known antidote. Argatroban is approved for the prevention and treatment of thrombosis in patients with HIT and in patients with HIT undergoing PCI.[25–27]

Desirudin is the first subcutaneously administered DTI and also the first DTI approved for prevention of VTE after hip replacement surgery, but it is not yet commercially available in the United States. However, it is available in several European countries. Desirudin has an elimination half-life of 2 to 3 hours and is typically dosed every 12 hours. It is primarily eliminated and metabolized by the kidney, so dose reduction is needed in patients with renal impairment. The aPTT is the test used to measure desirudin's anticoagulant activity.[25]

The quest for oral DTIs

DTIs can be structurally modified for oral administration. Approximately 10 oral DTIs are reported to be in development, of which ximelagatran is the furthest along.

Ximelagatran is a small-molecule prodrug that is rapidly absorbed following oral administration and converted to melagatran, its active form, achieving peak plasma concentrations in 1.6 to 1.9 hours. Ximelagatran has several advantages compared with the mainstay oral anticoagulant, warfarin:

- A predictable dose response, requiring no dose adjustment or coagulation monitoring
- A wider therapeutic index
- A rapid onset and offset of effect
- An apparent lack of clinically significant interactions with drugs and foods metabolized via the CYP450 isoenzyme.[28,29]

Stable, fixed doses of ximelagatran without monitor-

ing of coagulation parameters have been successfully studied in large phase 3 trials in various clinical settings, including stroke prevention in patients with atrial fibrillation, VTE prevention after major joint replacement, acute VTE treatment and secondary prevention of VTE after idiopathic VTE, and secondary prevention of myocardial infarction.[30–32] While these studies indicate that the drug can potentially be used in these clinical settings, the FDA recently refused to approve ximelagatran over concerns about liver toxicity.

Specifically, ximelagatran is associated with a 6% to 10% increase in hepatic transaminase levels in the first 2 to 6 months of long-term therapy, which is likely to require intensive liver function monitoring. The true clinical significance of these findings remains unclear at this time. Also, melagatran is renally eliminated, so dose adjustment will be required in patients with renal impairment. Without laboratory indicators of coagulation, getting the dose right is crucial. Finally, there is no known antidote for reversal of ximelagatran's effect, though it is much shorter-acting than warfarin.[32] Even with these hurdles, ximelagatran's advantages would most likely make its use attractive in clinical practice, as it is more convenient and less complicated to administer on a chronic basis than is warfarin.

SUMMARY

Novel anticoagulants have been developed to overcome the limitations of nonspecific traditional anticoagulants. They offer more specific activity on the coagulation cascade, predictable pharmacodynamics and pharmacokinetics, simpler dosing regimens, and few or no laboratory monitoring requirements. Some of these agents, such as factor Xa inhibitors and parenteral DTIs, are already available and are clearly improved additions to the antithrombotic arsenal.

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Prevention of venous thromboembolism in medical and surgical patients

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ABSTRACT

Prophylaxis against venous thromboembolism (VTE) should be considered in all hospitalized patients, as VTE is a significant cause of morbidity and mortality in the hospital. Although VTE risk is greatest and VTE prophylaxis is more established in surgical patients, most hospitalized medical patients have one or more risk factors for VTE and are candidates for prophylaxis. Selection of a prophylaxis strategy should be guided by the patient's risk factors for VTE and the risks associated with prophylaxis options. This review surveys evidence and recommendations for various VTE prophylaxis methods in medical and surgical patients.

The importance of venous thromboembolism (VTE) as a preventable cause of morbidity and mortality in hospitalized patients cannot be overstated. Although not all patients in the hospital need to receive prophylaxis against VTE, prophylaxis needs to be considered in all hospitalized patients. While recent years have seen significant strides in the use of VTE prophylaxis in many hospital settings, thanks in part to the work of hospitalists,[1] many patients—particularly medical patients—still do not receive adequate prophylaxis in community or tertiary care settings.

This review surveys pharmacologic and nonpharmacologic methods of prophylaxis against VTE (including pulmonary embolism [PE] and deep vein thrombosis [DVT]) in surgical and medical patients. It also discusses considerations for prophylaxis in special surgical situations and identifies general strategies for optimizing VTE prophylaxis.

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RELATIONSHIPS MATTER IN THE SURGICAL SETTING

One of the keys to successful VTE prophylaxis in surgical patients is a close working relationship among the surgeon, the anesthesiologist, nurses, and medical consultants. Because evidence and guidelines support many methods of prophylaxis in a variety of surgical settings, individual practice preferences need to be considered and respected. If a medical consultant recommends a form of prophylaxis that the surgeon is not comfortable with or the anesthesiologist is not aware of, complications or management conflicts can occur.

NONPHARMACOLOGIC PROPHYLAXIS IN SURGICAL PATIENTS

Aggressive postoperative ambulation and physical therapy should be an integral part of all postsurgical management as well as of a global approach to VTE prophylaxis. Although there are scant data from randomized trials showing that early ambulation and physical therapy reduce the risk of VTE, the nonambulatory postoperative period is a high-risk time for thrombosis development and venous stasis. Physical therapists, nurses, and nurses' aides should all work together to get patients out of bed and ambulating as soon as possible. Moreover, early postoperative ambulation helps to reduce length of stay in the hospital, and optimizing mobility prior to discharge is important to patients.[2] For surgical patients considered to be at low risk (ie, < 40 years of age with no VTE risk factors), early ambulation is adequate VTE prophylaxis.

Elastic stockings have been shown to be effective in reducing VTE risk by reducing venous stasis through provision of compression gradients on the legs.[3] Stockings should be applied before surgery, continued throughout the hospitalization, and continued into the

TABLE 1
Summary of options for prophylaxis of venous thromboembolism

	Nonpharmacologic methods			Pharmacologic methods				
	Early ambulation	Elastic stockings	SCD	Aspirin	LDUFH	Warfarin	LMWH	Pentasaccharide
General surgery								
Low risk	A	A	A					
Moderate risk	X	B	B		A*		A	
High risk	X	X	B		A**		A	
Very high risk	X	X	B§		A**+		A+	
Gynecologic surgery								
Low risk	A							
Moderate risk	X	X	B		A*		B	
High risk	X	X	A		A** or +		A or +	
Urologic surgery								
Low risk	A							
Moderate risk	X	B	B		A* or **		B	
High risk	X	X	B§		A**+		A+	
Orthopedic surgery								
Hip fracture#	X	X	B§	X	B** or +	B or +	B or +	A
Total hip arthroplasty#	X	X	B§	X		A or +	A or +	A
Total knee arthroplasty	X	X	B	X		A or +	A or +	A
Neurosurgery	X	X	A or +		B+		B+	
Trauma	X	B or +	B or +				A	
Medical patients								
Low risk	A							
High risk	X		B§		A* or **		A	

Recommendation grades and notes
A = acceptable for solo prophylaxis with highest level of evidence
B = acceptable as an alternative method of prophylaxis with less evidence than grade A
+ = combine with a nonpharmacologic method (ie, elastic stockings, SCD, or both)
X = beneficial but inadequate for solo prophylaxis
* LDUFH at 5,000 U twice daily
** LDUFH at 5,000 U three times daily
§ If pharmacologic prophylaxis is contraindicated
# These patients should be considered for extended prophylaxis (ie, 28–35 days postoperatively).
If no grade is provided, then that form of prophylaxis is not indicated either due to low risk of VTE or because its efficacy for that condition is not established.

Abbreviations/identifications
SCD = sequential compression device
LDUFH = low-dose unfractionated heparin
LMWH = low-molecular-weight heparins:
- enoxaparin 40 mg/day subcutaneously (or 30 mg twice daily for total knee arthroplasty)
- dalteparin 5,000 IU/day subcutaneously

Pentasaccharide = fondaparinux 2.5 mg once daily subcutaneously

Risk definitions for surgical patients
General surgery: Low risk = minor procedure, <40 years of age, and no risk factors for venous thromboembolism (VTE). Moderate risk = minor procedure but with VTE risk factors; *or* minor procedure between ages 40 and 60 with no additional risk factors; *or* major procedure but <40 years of age. High risk = minor procedure and over age 60 or other VTE risk factors; *or* major procedure and over age 40 or with additional risk factors. Very high risk = major procedure with multiple VTE risk factors.

Gynecologic surgery: Low risk = brief procedure for benign disease. Moderate risk = major procedure for benign disease without additional VTE risk factors. High risk = extensive procedure for malignancy.

Urologic surgery: Low risk = transurethral resection of the prostate or other low-risk urologic procedure. Moderate risk = major open urologic procedure. High risk = major procedure with additional VTE risk factors.

Adapted from Kaboli P et al, Med Clin North Am 2003; 87:77–110.

posthospitalization period if ambulation remains limited. Although effective, elastic stockings are not without risk. If not fitted properly, they can produce a reverse pressure gradient and increase the risk of VTE, as has been shown in orthopedic patients.[4] For patients with very large legs or other reasons why stockings cannot be fitted properly, they should be avoided. Finally, elastic stockings likely have a synergistic effect when used with other methods of VTE prophylaxis, although data supporting this are lacking.

Pneumatic compression devices, also referred to as sequential compression devices (SCDs) or intermittent pneumatic compression devices, are available as foot pumps and in calf or thigh lengths. These devices reduce the risk of VTE by squeezing the venous system (ie, plantar plexus, calf and thigh veins) to combat venous stasis, and they may promote the clearance of prothrombotic factors from the vasculature.[5]

SCDs have been studied in many surgical settings and are considered by the American College of Chest Physicians in their guidelines on antithrombotic therapy[6] as a 1A recommendation (highest level of evi-

dence) for patients undergoing gynecologic surgery for malignancy or intracranial neurosurgery **(Table 1)**. SCDs are also the method of choice when pharmacologic prophylaxis is contraindicated because of bleeding risk or other factors. Emerging data also support the use of SCDs as adjunctive prophylaxis with pharmacologic methods, such as in neurosurgical procedures, in which SCDs can be started preoperatively and continued until unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) therapy can be initiated.[7] They have also been shown to be effective in total hip and knee replacement when used in conjunction with a LMWH, significantly reducing thrombosis rates relative to a LMWH alone.[8]

Comparisons between foot pumps and calf or thigh devices are limited, but one study in trauma patients showed a higher rate of DVT in patients randomized to foot pumps.[9] Although foot pumps offer slightly greater ease of use and comfort, they may not be as effective as calf or thigh devices.

A fundamental limitation of SCDs is that they cannot be worn while the patient is ambulatory and they must be worn at all times when the patient is in bed to be maximally effective. While use of up to 15 hours per day has been achieved in clinical trials, this is unlikely in clinical practice.[10] If SCDs are to be used, nurses must be able to keep the SCDs on patients when they are in bed while still encouraging ambulation as much as possible. As patients become more ambulatory, the clinical utility of SCDs declines.

PHARMACOLOGIC PROPHYLAXIS IN SURGICAL PATIENTS

Aspirin. The routine use of aspirin alone as VTE prophylaxis is not recommended.[6] However, aspirin (160 mg daily) was shown to reduce the risk of PE following hip fracture surgery when added to routine prophylaxis, resulting in a 58% relative reduction in fatal PE compared with placebo (from 1.2% to 0.7%).[11] Use of aspirin in the postoperative setting, especially in patients with cardiovascular risks who may benefit from it, should be considered.

Low-dose UFH has been a standard and well-accepted mode of VTE prophylaxis in a wide range of surgical procedures for decades.[12] In moderate-risk surgical patients, 5,000 U twice daily is effective, but in higher-risk patients, the dosage should be 5,000 U three times daily.

LMWHs are replacing UFH for prophylaxis in most surgical settings, owing to their improved efficacy, especially in orthopedic patients,[13] and their modestly lower rates of bleeding complications,[13–15] reduced incidence of heparin-induced thrombocytopenia,[15,16] and convenient once-daily dosing.

Two important considerations influence LMWH dosing for VTE prophylaxis: timing (preoperative vs postoperative) and frequency (once vs twice daily). For general surgical patients, initiating a LMWH 2 hours before surgery is recommended. For orthopedic surgical patients, the timing of dosing has been debated because thrombus formation begins intraoperatively, but preoperative dosing is associated with increased bleeding complications. A recent pooled analysis found no reduction in VTE rates with preoperative dosing for elective hip surgery and suggested that it may be associated with an increase in postoperative bleeding.[17] For this reason, and because of issues related to neuraxial anesthesia, postoperative dosing is often preferred.

SCDs, elastic stockings, or both are often used intraoperatively until postoperative LMWH dosing can begin, usually 12 to 24 hours after surgery, provided that adequate hemostasis has been established. For other high-risk bleeding conditions (eg, neurosurgery, multiple trauma), postoperative initiation is indicated once the bleeding risk is minimized, with concomitant use of SCDs and/or elastic stockings.

Once-daily dosing of LMWHs has replaced twice-daily dosing for most indications, with the exception of total knee replacement. In general, once-daily dosing is more convenient, has equal efficacy, and costs one third less.

Vitamin K antagonists such as warfarin are often used in orthopedic surgery; they were the most common form of prophylaxis for total hip and knee arthroplasty in a recent survey of orthopedic surgeons.[18] Warfarin is typically initiated immediately after surgery to achieve an international normalized ratio (INR) of 2.0 to 3.0, often in conjunction with SCDs and/or elastic stockings. Though it can be started at a low dose 10 to 14 days before surgery and then increased postoperatively to achieve an INR of 2.0 to 3.0, this is less frequently done, and reportedly only in higher-risk patients.[18] Because warfarin takes up to 5 days to achieve its maximal antithrombotic effect, it may leave patients relatively unprotected compared with immediately acting anticoagulants such as LMWH or nonpharmacologic methods. This risk was demonstrated in a recent case-control study of patients undergoing lower extremity total joint arthroplasty in which prophylactic warfarin monotherapy initiated postoperatively had an odds ratio of 11.3 for proximal VTE compared with postoperative enoxaparin.[19]

Besides orthopedic surgery, there are no other well-studied indications for warfarin for VTE prophylaxis in surgical patients.

Fondaparinux is a pentasaccharide approved for VTE prophylaxis in total hip or knee arthroplasty and hip fracture surgery. It was shown to be more efficacious than the LMWH enoxaparin in a meta-analysis of orthopedic trials, though the risk of major bleeding was increased.[20] Fondaparinux has 100% bioavailability when given subcutaneously, a rapid onset of effect, a long half-life allowing for once-daily dosing, and no association with HIT. In spite of these potential benefits, it has not been widely adopted, in part because of concerns over increased bleeding rates,[21] lack of an antidote, acquisition cost, risks associated with neuraxial anesthesia, and delayed clearance in patients with renal impairment.

The oral direct thrombin inhibitor ximelagatran has been approved in some European nations for VTE prophylaxis in patients undergoing orthopedic surgery, but it has not been approved in the United States because of safety concerns.[22] Oral direct thrombin inhibitors hold considerable promise for VTE prophylaxis and other indications but are not likely to be available in the United States in the near future.

SPECIAL CONSIDERATIONS IN SURGICAL SETTINGS

Bariatric surgery for weight reduction is increasing in popularity. Because this surgery is extensive and obesity is an independent risk factor for VTE, patients undergoing gastric bypass surgery are at high risk for VTE and require aggressive prophylaxis. In an observational study of 481 patients undergoing bariatric surgery, enoxaparin was associated with fewer postoperative DVT complications when dosed at 40 mg twice daily than at 30 mg twice daily.[23] All patients also received elastic stockings and SCDs. This study supports the use of a higher prophylactic dose of enoxaparin in bariatric surgery, but further studies are needed.

Neuraxial anesthesia, when used concomitantly with anticoagulation, increases the risk of epidural hematomas and subsequent spinal cord injury. Good communication among the anesthesia team, surgeons, medical consultants, and nurses is critical. Guidelines for the use of neuraxial anesthesia when anticoagulation is indicated have been developed by the American Society of Regional Anesthesia and Pain Medicine.[24] Specific recommendations include avoiding needle placement for 24 hours after a full dose of LMWH and for 12 hours after the last prophylactic dose of LMWH, waiting at least 2 hours to give LMWH after removal of an epidural catheter, and avoiding anticoagulants in patients who have had traumatic needle or catheter insertion.

Inferior vena cava (IVC) filters are not recommended for primary prophylaxis in any surgical setting.[6] An evaluation of 2,868 consecutive trauma patients, 10% of whom were considered to be at high risk for VTE, found the use of prophylactic IVC filters to be unjustified.[25] However, a temporary IVC filter should be considered for PE prevention in the presence of DVT in patients who cannot receive anticoagulant therapy or in those who have received less than 6 weeks of anticoagulant therapy. Temporary filters can be retrieved within 2 to 3 weeks, allowing patients to be safely started on anticoagulation without requiring lifelong anticoagulation for an IVC filter. Alternatively, the filter can be left in permanently. Temporary IVC filters have been studied as primary prophylaxis in high-risk trauma patients,[26] but not in randomized trials comparing them with the current standard of care (SCDs combined with a LMWH once bleeding risk is minimized).

Routine screening duplex ultrasonography of the lower extremities is also not recommended as part of routine prophylaxis in surgical patients.[6] It has been studied most extensively in orthopedic surgery, but it is not cost-effective, does not reduce symptomatic VTE, and is limited by considerable interobserver variability.

The duration of VTE prophylaxis in surgical patients is controversial. All surgical patients except those at low thromboembolic risk should receive, at minimum, VTE prophylaxis while hospitalized and nonambulatory. High-risk patients and those undergoing orthopedic surgery should receive prophylaxis for a minimum of 7 to 10 days. The highest-risk patients, such as those undergoing hip arthroplasty or hip fracture surgery, deserve consideration for longer postdischarge prophylaxis. One month of VTE prophylaxis with a LMWH, warfarin, or fondaparinux (all of which can be given on an outpatient basis) reduces VTE risk relative to in-hospital prophylaxis.[6] Moreover, a recent study of patients undergoing surgery for abdominal or pelvic cancer showed that 4 weeks of LMWH therapy reduced the rate of venographically documented VTE compared with 1 week of LMWH therapy.[27]

VTE IN MEDICAL PATIENTS: WHAT IS THE RISK?

Hospitalized medical patients are at increased risk for VTE because of immobility, stasis, and the potential release of procoagulant mediators during acute illness,[28] though the risk is lower than in patients hospitalized for surgery.[29] However, because medical admissions are more common than surgical admissions, it is estimated that hospitalization for medical illness accounts for a greater number of fatal pulmonary emboli than does hospitalization for surgery, and that hospital admissions for medical illness and for surgery account for similar proportions of all VTE events (22% and 24%, respectively).[30]

Most studies of VTE prophylaxis in medical

patients have excluded patients with no risk factors for VTE and thus give a reasonable estimate of the VTE rate for the target population in clinical practice. These trials have found the incidence of asymptomatic VTE (based on screening tests) in the absence of prophylaxis to be approximately 15%.[31,32]

Asymptomatic vs symptomatic VTE

The asymptomatic event rate, however, appreciably overestimates the incidence of potentially clinically significant events. Researchers from a university hospital in the Netherlands assessed the rate of symptomatic VTE among all medical patients admitted to the hospital from 1992 through 1996, reporting a hospital-acquired VTE rate of 0.6% (39/6,332).[33] Of the 39 patients with a symptomatic VTE event, 24 (61%) had a malignancy. Most patients did not receive prophylaxis; those who did received a regimen—enoxaparin 20 mg once daily—later shown to be ineffective.[31]

In a randomized study of 11,693 patients aged 55 years or older admitted to six hospitals in Sweden, Gardlund and the Heparin Prophylaxis Study Group[34] reported a 2.0% incidence of symptomatic VTE in patients randomized to no prophylaxis. A large cross-sectional study of patients admitted to the medical wards of a university hospital in France found the incidence of hospital-acquired VTE to be 1.4%.[35] A higher VTE incidence was noted among patients receiving prophylaxis with UFH than those not receiving prophylaxis (3.5% vs 0.8%), indicating that UFH was given primarily to patients deemed by the treating physician to be at increased risk for VTE.

Based on these studies, the rate of *symptomatic* VTE *without* prophylaxis is estimated at 0.5% to 1.0% for low-risk general medical inpatients and at 2.0% to 3.0% for patients with VTE risk factors. This suggests that:

- There is a subgroup of general medical inpatients without risk factors who are at very low risk of a clinical event and for whom VTE prophylaxis is unwarranted.
- Patients with VTE risk factors have a small but clinically important risk of symptomatic events and are expected to gain a substantial benefit from prophylaxis.

The VTE risk factors listed in major guidelines have been derived largely from data in surgical settings, although a limited number of studies examining general medical inpatients have reported factors associated with an increased incidence of VTE in medical patients **(Table 2)**.[33,35–37]

TABLE 2
Risk factors for hospital-acquired VTE

Active cancer[33]	Immobility[35]/paralysis
Acute ischemic stroke	Inflammatory bowel disease
Acute MI	Nephrotic syndrome
Age > 60 years[35]	Obesity
Central venous catheter	Prior ischemic stroke with paresis
Congestive heart failure[36]	Prior VTE[35,37]
Estrogen therapy	Thrombophilia
	Varicose veins

MI = myocardial infarction; VTE = venous thromboembolism

PROPHYLAXIS IN MEDICAL PATIENTS

Nonpharmacologic prophylaxis

We are unaware of any published randomized trials examining mechanical methods of prophylaxis, including elastic stockings and SCDs, for hospitalized general medical patients. These methods have been shown, however, to reduce the incidence of VTE in patients with acute stroke[38] and acute myocardial infarction.[39]

Pharmacologic prophylaxis

UFH and LMWH. Several studies have investigated the use of subcutaneous UFH and LMWH for general medical inpatients.

A large randomized study of patients aged 40 years or older admitted to medical wards of an Israeli hospital showed UFH (5,000 U twice daily) to significantly reduce mortality compared with no prophylaxis (8% vs 11%), although the study design was potentially limited by a lack of investigator blinding to patients' treatment assignment.[40] In contrast, Gardlund and the Heparin Prophylaxis Study Group[34] found that UFH did not reduce mortality or rates of autopsy-proven fatal PE compared with no prophylaxis among patients admitted to infectious disease wards. Additionally, a study of 2,472 general medical inpatients randomized to LMWH or to placebo found no difference in mortality.[15]

The large and rigorous study by Gardlund and the Heparin Prophylaxis Study Group[34] is the only trial we have identified that randomized patients to either prophylaxis or no prophylaxis, did not screen for asymptomatic events, and examined symptomatic VTE as an end point. It found that UFH (5,000 U twice daily) reduced the incidence of symptomatic VTE to 1.2% from 2.0% with no prophylaxis, a statistically significant difference.

Several trials have examined the efficacy of UFH and LMWHs for the reduction of asymptomatic events in medical patients. A small randomized trial found that UFH reduced the incidence of DVT from 26% to 4% compared with no prophylaxis.[32] Two larger randomized trials[31,41] found prophylaxis with LMWH to

reduce VTE rates by two thirds compared with placebo (from 15% to 5%[31] and from 9% to 3%[41]). The large randomized PREVENT study[42] found that prophylaxis with the LMWH dalteparin reduced the VTE rate to 2.8%, vs 5.0% with placebo. These lower VTE rates in the PREVENT study relative to other trials may have been due to this study's use of ultrasonography (rather than venography) as a screening test.

Several trials examining asymptomatic VTE have directly compared prophylactic UFH and LMWH; most used three-times-daily dosing for UFH. None of these studies in general medical patients found a significant difference in VTE incidence between the two prophylactic therapies. One study examining patients after acute stroke did find a lower incidence of VTE with LMWH (20%) than with UFH (35%).[43] In contrast, another trial found twice-daily UFH and enoxaparin (20 mg once daily) to have similar efficacy in VTE prevention among elderly hospitalized medical patients.[15] Despite the higher drug-acquisition cost of LMWHs, they are considered more cost-effective than UFH for prophylaxis in medical patients because of their lower complication rates.[44]

Newer and investigational anticoagulants. Newer anticoagulants that may enhance the prevention and treatment of VTE in medical patients are under investigation. We are unaware of published trials examining the efficacy or safety of the investigational oral direct thrombin inhibitor ximelagatran for prevention of VTE in medical inpatients. However, fondaparinux, which has been approved in the United States for VTE prophylaxis in orthopedic surgery patients (as well as for VTE treatment), has been evaluated in the ARTEMIS study[45] of hospitalized medical patients aged 60 years or older who were expected to be at bed rest for at least 4 days. In a preliminary report,[45] fondaparinux was associated with a 51% relative risk reduction for asymptomatic VTE compared with placebo (incidence of 5.6% vs 10.5%).

The bottom line on prophylaxis in medical patients

Although mortality reduction from VTE prophylaxis has not been definitively established in medical patients, prevention of symptomatic and asymptomatic DVT is an important goal of prophylaxis in view of the substantial morbidity associated with DVT, including leg pain and swelling due to the acute thrombosis, risk of PE, and development of the postthrombotic syndrome (PTS). PTS is a common sequela of DVT, occurring in up to 30% of patients.[46] PTS results from incomplete venous recanalization and destruction of valve cusps in the deep veins of the leg, leading to chronic leg edema, pain, induration, and, when severe, venous ulceration.

Most hospitalized medical patients have one or more risk factors for VTE **(Table 2)** and are at moderate (2.0% to 3.0%) risk of a symptomatic event. Since prophylaxis is often overlooked,[47] it should be considered at the time of admission for all hospitalized patients, and administered to those with risk factors for VTE who are nonambulatory. Prophylaxis may be unnecessary for medical patients without any risk factors, as the incidence of symptomatic VTE in this population is low (< 1.0%). Both UFH and LMWH are efficacious in preventing VTE in hospitalized medical patients, although there is no established reduction in mortality. Neither therapy has been proven superior to the other in this population. Data from other settings suggest that mechanical methods of prophylaxis are likely to be effective for patients who cannot tolerate anticoagulants because of bleeding risk.

FUTURE DIRECTIONS

Although VTE prophylaxis in surgical and medical patients is improving, VTE remains a significant patient safety concern and is at the center of efforts by the federal Agency for Healthcare Research and Quality to improve the care of hospitalized patients.[48] Systems-based approaches, including use of automated computer prompts and admission protocols, are more likely to lead to routine prophylaxis than is the sporadic implementation often seen in current practice. Ensuring adequate VTE prophylaxis involves a concerted effort of all interested parties, including physicians, nurses, patients, hospitals, and health systems.[1]

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Current and emerging options in the management of venous thromboembolism

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ABSTRACT

Venous thromboembolism (VTE) is a common disease whose diagnosis is challenging. The best diagnostic approaches combine the patient's pretest clinical probability of disease with D-dimer testing and/or diagnostic imaging. In light of several advantages, low-molecular-weight heparins are now recommended over unfractionated heparin for most patients with acute VTE. Newer anticoagulants such as the factor Xa inhibitor fondaparinux also show promise for acute VTE. For chronic management, the duration and intensity of warfarin therapy should be tailored to the individual patient.

New drug classes and diagnostic tests for the management of venous thromboembolism (VTE) have proliferated in the 45 years since parenteral heparin was first shown to have a life-saving role in the treatment of pulmonary embolism. At the same time, clinical trials with older anticoagulants such as warfarin have helped to define and refine the optimal duration of therapy in patients with idiopathic VTE. In this article we review the latest evidence on the diagnosis and treatment of this common disease and provide practical recommendations on key aspects of its management.

EPIDEMIOLOGY OF VTE: WIDESPREAD, OFTEN DEADLY

VTE, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease in the United States, with an average annual incidence of more than 100 cases per 100,000 population.[1] Autopsy studies demonstrate large numbers of silent events,[2,3] leading to the widely reported estimates of 2 million DVT cases and up to 200,000 deaths from PE annually.[4] The aging of the US population will only cause these numbers to grow.

VTE accounts for about 10% of all in-hospital deaths, with a long-term case-fatality rate of about 19% to 30% at 1 to 3 years,[5] presuming the patient survives the initial thrombotic event. However, it is estimated that up to one quarter of all PE cases present as sudden death.[6] Even after 6 months or more of anticoagulation following a first VTE event, there is a persistently elevated risk (5% to 12% annually) for subsequent VTE.[7]

Age and the presence of identifiable VTE risk factors both influence the incidence of first-time VTE. The annual incidence of first-time VTE rises exponentially from fewer than 5 cases per 100,000 population in persons younger than 20 years of age to nearly 500 cases per 100,000 for those 80 years of age or older.[5] Most first-time VTE events occur in patients with an identifiable risk factor. Nursing home residents or persons recently discharged from the hospital accounted for almost 60% of first-time VTE events in the community in a recent population-based study.[8] That same study found the incidence of VTE to be 135-fold higher in hospitalized patients than in community residents.[8]

RISK FACTORS FOR VTE: VARYING MAGNITUDES, UNCERTAIN INTERACTION

Virchow's triad describes three etiologic factors for thrombosis: stasis of blood flow, endothelial injury, and hypercoagulability. Established VTE risk factors reflect these underlying pathophysiologic processes. Important risk factors for VTE include increased age (especially beyond age 40), prolonged immobility, malignancy, major surgery, multiple traumas, prior VTE, and chronic heart failure.[9] However, the magnitude of risk conferred by these and other factors varies **(Table 1)**. It is not yet known how these factors interact to determine a given patient's individual risk, but there is evidence that VTE risk increases in proportion to the number of predisposing factors present.[10]

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DIAGNOSIS: COMBINE PRETEST PROBABILITY WITH DIAGNOSTIC TESTING

Accurate diagnosis of VTE remains challenging since symptoms of VTE may be atypical or absent and because noninvasive diagnostic tests have imperfect accuracy. Furthermore, since VTE can be fatal, and since effective treatments are available, it is an important diagnosis not to miss.

For these reasons, serial noninvasive diagnostic testing is often used, which may include D-dimer testing, compression ultrasonography, helical computed tomography (CT) of the chest, and nuclear lung scans. However, the cornerstone of VTE diagnosis remains assessment of pretest clinical probability.

Without standardized diagnostic algorithms (simply using clinical impression), the PIOPED investigators[11] classified patients as having low, intermediate, or high pretest probabilities of PE with remarkable accuracy. Of those patients deemed to be at high risk, 68% had PE, in contrast to 9% of those deemed to be at low risk. Formal algorithms have since been created and validated to help even novice clinicians estimate the pretest probability for VTE.[12–17]

Bayes' theorem dictates that the posttest odds of disease is equal to the pretest odds of disease multiplied by the likelihood ratio of the diagnostic test used.[17,18] Likelihood ratios of various diagnostic tests used in the evaluation of VTE are shown in **Table 2**.[11,18–24]

A key concept is that a diagnosis of VTE can generally be secured or excluded when the pretest clinical probability is concordant with an appropriate diagnostic test.[18] For example, a high pretest clinical suspicion of PE in conjunction with a high-probability lung scan is adequate to confirm the diagnosis of PE (> 95% certainty), while a low pretest clinical suspicion of DVT in conjunction with a negative D-dimer test can exclude the diagnosis. When the clinical impression is discordant with the diagnostic test result (eg, a high pretest clinical suspicion of PE in the setting of a negative helical CT scan), further diagnostic testing is often warranted. This applies even to noninvasive tests that are often thought to "rule in" the diagnosis when positive: a positive helical CT or high-probability lung scan in the context of a low pretest suspicion for PE does not rule in the diagnosis of PE.[11,25] In such cases, it is reasonable to order a pulmonary arteriogram.

Whether pulmonary CT angiography is accurate enough to render conventional angiography obsolete is being addressed in an ongoing prospective, multicenter trial (PIOPED II). Until its results are available, we may still need to pursue pulmonary angiography in patients with high clinical suspicion for PE but negative helical CT findings, and most current diagnostic algorithms still rely on angiography as a gold standard fall-back test when the diagnosis remains ambiguous after multiple noninvasive tests.[26–28]

TABLE 1
Risk factors for venous thromboembolism

Strong risk factors (odds ratio ≥ 10)

- Fracture (hip or leg)
- Hip or knee replacement
- Major general surgery
- Major trauma
- Spinal cord injury

Moderate risk factors (odds ratio 2 to 9)

- Arthroscopic knee surgery
- Central venous lines
- Chemotherapy
- Congestive heart or respiratory failure
- Hormone replacement therapy
- Malignancy
- Oral contraceptive therapy
- Paralytic stroke
- Pregnancy/postpartum
- Previous venous thromboembolism
- Thrombophilia

Weak risk factors (odds ratio < 2)

- Bed rest > 3 days
- Immobility due to sitting (eg, prolonged car or air travel)
- Increased age
- Laparoscopic surgery (eg, cholecystectomy)
- Obesity
- Pregnancy/antepartum
- Varicose veins

INITIAL THERAPY: OPTIONS ARE EXPANDING

Prompt initiation of anticoagulant therapy is essential in the management of acute VTE, except in patients who are actively bleeding or in whom the risk of bleeding outweighs the benefits of anticoagulation.

Several groups of drugs are commercially available to treat acute DVT and PE: unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs) and factor Xa inhibitors (pentasaccharides). Parenteral direct thrombin inhibitors are approved for use in patients with acute VTE in the setting of heparin-induced thrombocytopenia (HIT). The oral direct thrombin inhibitor ximelagatran was recently denied FDA approval due to concerns over liver toxicity. The pharmacologic profiles of these drug classes are discussed in detail by Nutescu et al in the first article in this supplement. We have summarized the

TABLE 2
Approximate likelihood ratios of commonly used diagnostic tests for venous thromboembolism

Diagnostic test	Likelihood ratio*	Clinical setting	Comments
D-dimer[19]		Evaluation of suspected acute DVT or PE in symptomatic nonanticoagulated outpatients	Questionable reliability in patients on anticoagulant drugs, those with nonacute symptom onset, and hospitalized patients[20]
• Quantitative ELISA			
—Negative test	0.07–0.12		
—Positive test	1.5–3.0		
• Other assays			
—Negative test	0.11–0.36		
—Positive test	1.6–5.0		
Helical chest CT[21]		Suspected PE	Accuracy is user-dependent.[22] Best for ruling in or ruling out large (central) emboli. Likelihood ratio for a positive study may greatly exceed 7.1 if multiple unambiguous large filling defects are seen. However, confirmatory pulmonary angiography may be indicated in a patient with low pretest suspicion of PE and only 1 or 2 small filling defects on CT.[22,23] May reveal alternate source of dyspnea, hypoxia, or chest pain.
—Negative study	0.29		
—Positive study	7.1		
Nuclear lung scan[11]		Suspected PE	Patients with known pulmonary disease (eg, chronic obstructive pulmonary disease) may be unlikely to have normal or near-normal scans
High probability	23		
Intermediate	0.87		
Low probability	0.26		
Normal/near-normal	0.17		
Duplex ultrasonography[24]		Suspected symptomatic proximal lower extremity DVT	Accuracy may be lower for distal DVT, asymptomatic DVT (eg, postoperative surveillance), and upper extremity thrombosis. Since most PEs arise from thrombi in the legs, duplex ultrasonography can also be used in the evaluation of suspected PE.
—Negative	0.05		
—Positive	24		

* When likelihood ratios were not specifically reported, they were calculated using standard formulas.[18] Likelihood ratios are interpreted as follows using Bayes' theorem: *(pretest odds of disease) × (likelihood ratio for given finding) = posttest odds of disease*. Odds and probabilities can be interconverted using the following formulas: *odds = probability/(1 – probability)* or *probability = odds/(1 + odds)*.

Example: In a patient with an estimated pretest probability of 80% for PE (very high pretest suspicion), the probability of PE after a negative helical CT of the chest is calculated as follows: Pretest probability of 80% is converted to pretest odds of 80/20 (= 4). Likelihood ratio of disease with a negative helical CT of the chest is approximately 0.29. Posttest odds of PE is 4 × 0.29 = 1.16. Posttest probability of PE is 1.16 /(1 + 1.16) = 54%. Further testing is clearly indicated, since this patient still has a greater than 50% chance of having a PE despite the negative helical CT.

CT = computed tomography; DVT = deep vein thrombosis; ELISA = enzyme-linked immunosorbent assay; PE = pulmonary embolism

available options for initial VTE therapy in **Table 3**.

Unfractionated heparin

Until 1996, when LMWHs were approved by the US Food and Drug Administration (FDA) for the outpatient treatment of DVT, patients with DVT were generally treated in the hospital with UFH.

Studies demonstrate that 5 to 7 days of intravenous (IV) UFH is as effective as longer treatment durations.[29] Moreover, use of a weight-based nomogram helps to achieve a therapeutic activated partial thromboplastin time (aPTT) within the first 24 hours more quickly than fixed dosing does. Compared with fixed dosing (5,000-U bolus followed by IV infusion of 1,000 U/hr), weight-based nomogram dosing (bolus of 80 U per kilogram of ideal body weight followed by IV infusion of 18 U/kg/hr) decreases the rate of recurrent thromboembolism in patients with underlying VTE, arterial thromboembolism, or unstable angina.[30] Each laboratory should determine its own therapeutic aPTT range, corresponding to a heparin level of 0.3 to 0.7 U/mL of anti-Xa activity.

Problems associated with UFH use include its higher incidence of HIT (≈3%) relative to other anticoagulants, its variable bioavailability, bone demineralization, and the need for inpatient treatment (for IV dosing and frequent laboratory monitoring).[31]

Low-molecular-weight heparins

These shortcomings of UFH spurred the development of LMWHs, whose advantages relative to UFH include once- or twice-daily subcutaneous (SC) dosing; more predictable pharmacokinetics and bioavailability; a lower incidence of HIT (≈1%); and freedom from laboratory

monitoring requirements in most clinical situations.[31]

Outpatient DVT therapy. Two landmark studies established the safety and efficacy of LMWHs for the outpatient treatment of DVT.[32,33] One study compared SC weight-based enoxaparin to IV UFH.[32] There were no differences between the groups in the incidence of recurrent VTE, major bleeding, or death. However, length of stay was approximately 1 day in the enoxaparin group compared with 6.5 days in the UFH group. In the other study,[33] 500 patients were randomized to SC nadroparin (a LMWH not available in the United States) or IV UFH. Again, there was no difference between the groups in rates of recurrent VTE, bleeding, or mortality.

Gould et al[34] conducted a meta-analysis comparing a variety of LMWHs with UFH for the treatment of acute DVT across 11 trials comprising 3,566 patients. The results indicated that LMWH therapy was superior to UFH, reducing mortality by approximately 30% (absolute risk reduction, 1.65%; number needed to treat to prevent a death, 61; $P = .02$). Rates of recurrent thromboembolism and major bleeding were similar between the LMWH and UFH groups, although there was a trend toward reduction in both of these outcomes in the LMWH group.

VTE therapy in cancer patients. Rates of warfarin-resistant thrombosis and warfarin-associated bleeding are elevated in patients with cancer,[35] and results from meta-analyses[36,37] have suggested that cancer patients may achieve a particular mortality benefit from LMWH therapy. This has prompted recent investigations of LMWHs specifically in cancer patients.

The CLOT investigators[38] randomized cancer patients with acute VTE to either the LMWH dalteparin (200 IU/kg/day for 1 month, followed by 150 IU/kg/day for 5 months) or traditional therapy, consisting of dalteparin for 5 to 7 days followed by oral anticoagulation for 6 months. During the 6-month study period, recurrent VTE occurred in 27 of 336 patients (8.0%) in the LMWH group compared with 53 of 336 (15.8%) in the oral anticoagulation group (hazard ratio, 0.48; $P = .002$). Most recurrences occurred while patients were on anticoagulation. Rates of major and minor bleeding were similar between the groups. A smaller study comparing enoxaparin 1.5 mg/kg/day with warfarin in cancer patients demonstrated a similar risk reduction with LMWH therapy, though it failed to reach statistical significance.[35] However, any increased efficacy of LMWHs over oral anticoagulation in the treatment of cancer-associated VTE must be weighed against the cost of LMWHs and the willingness of the patient or caregiver to administer daily injections.

TABLE 3
Options for initial therapy for venous thromboembolism

Unfractionated heparin

Use nomogram—bolus of 80 U/kg ideal body weight followed by continuous IV drip of 18 U/kg/hr

Goal activated partial thromboplastin time*: 60–80 sec

Low-molecular-weight heparins

Enoxaparin: 1 mg/kg SC twice daily or 1.5 mg/kg SC once daily

Dalteparin: 200 IU/kg SC once daily†

Tinzaparin: 175 IU/kg SC once daily

Factor Xa inhibitor

Fondaparinux: 5 mg SC once daily (if body weight < 50 kg), 7.5 mg SC once daily (if body weight 50–100 kg), or 10 mg SC once daily (if body weight > 100 kg)

* May vary from institution to institution. Maintain in therapeutic range, which must correspond to heparin levels of 0.3–0.7 U/mL.
† Not FDA-approved for treatment of venous thromboembolism.

Acute PE therapy. The safety of LMWHs for treating acute PE has been established in two large clinical trials[39,40] and confirmed in a recent meta-analysis.[41] The Columbus Investigators[39] randomized more than 1,000 patients to the LMWH reviparin (not available in the United States) or IV UFH. Rates of recurrent VTE, bleeding, and death were similar between the two groups. The authors concluded that reviparin and UFH are equally effective and safe. Similarly, Simonneau et al[40] compared the LMWH tinzaparin with IV UFH for the treatment of acute symptomatic PE in 612 patients. The two groups had similar rates of VTE recurrence, major bleeding, and death. The meta-analysis[41] concluded that fixed-dose LMWH therapy appears to be as effective and safe as IV UFH for the initial treatment of nonmassive PE, and showed a nonsignificant trend toward improved outcomes in LMWH recipients.

Although the outpatient use of LMWHs is not yet approved for treating acute PE, we believe that off-label outpatient treatment is reasonable in selected patients at low risk for clinical deterioration (see below).

Fondaparinux, a factor Xa inhibitor

Fondaparinux is the first synthetic selective inhibitor of factor Xa available for patients. It inhibits both free and platelet-bound factor Xa. It binds antithrombin with high affinity, has close to 100% bioavailability, and is given by once-daily SC administration. It does not bind platelet factor 4 and therefore should not cause HIT. There is currently no antidote for fondaparinux, although factor VIIa infusion might be effective.[42]

Fondaparinux was recently approved by the FDA for treatment of acute DVT and PE on the basis of two randomized noninferiority trials.[43,44]

In the Mattise-DVT trial,[43] 2,205 patients with acute DVT were treated with once-daily SC fondaparinux (dosed as outlined in **Table 3**) or enoxaparin 1 mg/kg SC twice daily for 5 days, followed in each group by a 3-month course of an oral vitamin K antagonist. Recurrent thromboembolic events occurred in 43 (3.9%) of 1,098 fondaparinux recipients compared with 45 (4.1%) of 1,107 enoxaparin recipients, for an absolute difference of –0.15% in favor of fondaparinux (95% confidence interval [CI], –1.8% to 1.5%). Major bleeding occurred in 1.1% of fondaparinux recipients and in 1.2% of enoxaparin recipients. Mortality rates were 3.8% and 3.0%, respectively. The authors concluded that once-daily fondaparinux was at least as effective and safe as twice-daily, weight-adjusted enoxaparin in the initial treatment of patients with symptomatic DVT.

In another study by the Matisse investigators,[44] 2,213 patients with acute symptomatic PE were randomized in an open-label fashion to continuous IV infusion of UFH or once-daily SC fondaparinux (dosed as in **Table 3**), each given for at least 5 days and until vitamin K antagonist therapy resulted in an international normalized ratio (INR) above 2.0. At 3 months, recurrent thromboembolism occurred in 42 of 1,103 fondaparinux recipients (3.8%) and in 56 of 1,110 UFH recipients (5.0%), for an absolute difference of –1.2% in favor of fondaparinux (95% CI, –3.0% to 0.5%). Major bleeding occurred in 1.3% of fondaparinux recipients and in 1.1% of UFH recipients. Mortality at 3 months was similar in the two groups. This study suggests that once-daily SC administration of fondaparinux without monitoring is at least as effective and safe as adjusted-dose IV UFH in the initial treatment of hemodynamically stable patients with PE.

Direct thrombin inhibitors

The direct thrombin inhibitors are another class of anticoagulants that can be used to treat VTE. All four FDA-approved direct thrombin inhibitors (argatroban, lepirudin, bivalirudin, and desirudin) are administered parenterally, and all are indicated for conditions other than initial VTE therapy, although some are approved to treat thrombosis in patients with HIT. Other articles in this supplement detail the pharmacology of the direct thrombin inhibitors (see Nutescu et al) and their use in HIT (see Bartholomew et al).

The oral direct thrombin inhibitor ximelagatran has been studied in phase 3 trials in patients without HIT, and appears to be effective for VTE prevention after orthopedic surgery, for stroke prevention in patients with atrial fibrillation, and for treatment of acute VTE.[45] Unlike other oral anticoagulants, ximelagatran can be given in fixed daily doses without laboratory monitoring. Although approved for use in several European countries for VTE prevention following major orthopedic surgery, ximelagatran was rejected by the FDA last fall because of concerns about liver enzyme elevations in up to 9% of patients receiving long-term therapy.

The THRIVE Treatment Study[46] was a double-dummy, randomized noninferiority study of 2,489 patients with acute VTE that compared oral ximelagatran (36 mg twice daily) with enoxaparin (1 mg/kg twice daily for a minimum of 5 days) followed by warfarin (to a target INR of 2.0 to 3.0). Treatment was for 6 months and patients were followed for an additional 40 days. Recurrent VTE occurred in 2.1% of ximelagatran recipients and in 2.0% of enoxaparin/warfarin recipients. All-cause mortality rates were 2.3% with ximelagatran and 3.4% with enoxaparin/warfarin; major bleeding rates were 1.3% and 2.2%, respectively. These results suggest that ximelagatran is an effective and safe alternative to LMWH for the acute treatment of VTE. However, the rate of elevated transaminase levels was as high as 9.6% in this study.

WHAT'S THE ROLE OF THROMBOLYSIS?

Over the last 30 years, clinical observations and randomized trials have consistently shown favorable effects of thrombolysis on angiographic, hemodynamic, and scintigraphic measures in patients with acute PE. Tissue-type plasminogen activator (tPA), streptokinase, and urokinase are thrombolytic agents that have been approved by the FDA for the treatment of PE. tPA is comparable to urokinase and streptokinase in thrombolytic capacity but can be administered over a shorter time period.[31]

A recent meta-analysis[47] of nine small randomized trials compared rates of death, recurrent PE, or major bleeding between patients with acute PE treated with thrombolytic agents plus heparin or with heparin alone. At least one of these events occurred in 56 (23.2%) of 241 patients in the thrombolysis group compared with 57 (25.9%) of 220 patients in the heparin group (relative risk [RR], 0.9; 95% CI, 0.57 to 1.32). Eleven thrombolytic recipients died (4.6%), compared with 17 heparin recipients (7.7%) (RR, 0.59; 95% CI, 0.27 to 1.25). However, the incidence of major bleeding was 12.9% in the thrombolysis group (31/241) compared with 8.6% in the heparin group (19/220) (RR, 1.49; 95% CI, 0.85 to 2.81). Five fatal

bleeding episodes occurred in the thrombolysis group (2.1% incidence), compared with none in the heparin group ($P = .06$). Six studies provided data on recurrent PE. Recurrence occurred in 14 (6.6%) of 214 thrombolytic recipients and in 22 (10.9%) of 201 heparin recipients (RR, 0.60; 95% CI, 0.29 to 1.15). The composite end point of recurrence or death occurred in 10.4% of the thrombolysis group (25/241) compared with 17.3% of the heparin group (38/220) (RR, 0.55; 95% CI, 0.33 to 0.96; $P = .03$).

The authors concluded that, in patients with PE, thrombolysis was associated with a lower risk of the composite of death or PE recurrence compared with heparin therapy alone.[47] However, excessive bleeding is the trade-off for this improved efficacy, which is a major concern for patients with risk factors for bleeding, who may have been excluded from the clinical trials.

In practice, thrombolysis is usually reserved as a last resort in cases of hemodynamically unstable PE. The current debate surrounding thrombolysis focuses on patients with submassive PE, with right ventricular dysfunction but without hypotension. Opponents of thrombolysis note that thrombolytic therapy can cause life-threatening bleeding and has not been proven to reduce mortality compared with UFH alone. However, a massive study would be needed to specifically show a reduction in mortality. Moreover, treatment allocation would be blurred when patients assigned to UFH alone suffered clinical deterioration and required rescue thrombolysis. Although MAPPET-3,[48] a randomized study of patients with submassive PE, was not powered to demonstrate a mortality benefit, it showed that tPA plus UFH was superior to UFH alone in preventing the composite primary end point of mortality or treatment escalation. Notably, no fatal or cerebral bleeding episodes were observed in the tPA group.

Potential indications for thrombolytic therapy in PE include hemodynamic instability[31] and right ventricular dysfunction. Thrombolysis should not be used routinely in patients with DVT but may be considered in patients with severe iliofemoral DVT who are at risk for limb ischemia.[31]

RISK STRATIFICATION IN PATIENTS WITH PE

All patients with confirmed PE should receive anticoagulation unless they have a major contraindication, such as active bleeding. There are, however, additional questions after the diagnosis is confirmed:

- Can the patient be treated with LMWH in the outpatient setting, or is continued hospitalization prudent?
- Is the patient at high enough risk of death to justify thrombolytic therapy?
- Is the patient at high risk for long-term complications?

Frank hemodynamic instability (tachycardia or hypotension) and classic electrocardiographic findings of right ventricular strain are insensitive for detecting impending right ventricular failure in patients with PE, but some newer diagnostic tools show promise. These include echocardiography, measurement of cardiac troponins, and measurement of B-type natriuretic peptide (BNP). All of these tests seek to quantify the degree of strain on the right ventricle, since it is the potential for acute right ventricular failure that makes PE deadly. Identification of patients at high risk for hemodynamic collapse and death allows for appropriate triage decisions (such as early discharge with LMWH therapy at home vs observation in the hospital) and may allow for timely escalation of therapy (ie, thrombolytics) in selected patients.[48]

A recent prospective study[49] of the prognostic utility of cardiac troponins and echocardiography in 106 patients with acute PE found that both troponin I and troponin T were associated with right ventricular dysfunction, especially when the enzyme elevations were more than 2 times the upper limit of normal. The study's two end points were in-hospital death or a "complicated" inpatient course (ie, death or the need for thrombolysis, pressor support, intubation, or cardiopulmonary resuscitation). Of the 7 patients who died, 6 (86%) had elevated cardiac enzyme levels at presentation (vs about 20% to 30% of those who survived). Of the 19 patients with a complicated hospital course, more than 70% had elevated enzyme levels, compared with less than 30% of patients with an uncomplicated course. Similar prognostication has been reported with BNP.[50] Evidence of right ventricular dysfunction on echocardiography is also associated with worse prognosis, although definitions of right ventricular dysfunction have been inconsistent.[51]

We suggest that at least two methods of risk stratification (echocardiography plus BNP or troponin measurement) be used in any hemodynamically stable patient with PE who is asymptomatic (not in pain and without dyspnea or hypoxia) in whom early discharge and home treatment are being considered.[51] If there is evidence of right ventricular dysfunction by any of these tests, we favor continued hospitalization for observation until target anticoagulation intensity is achieved. If early discharge treatment is not an option, risk stratification may still be appropriate if thrombolysis is being considered,[49,52] although thrombolysis for submassive PE remains controversial.[52] Finally, although symptomatic pulmonary hypertension may

develop in the months following PE,[53] there is no evidence that early risk stratification helps to predict this complication or influences clinical management.

INFERIOR VENA CAVA FILTERS

Use of inferior vena cava (IVC) filters has grown markedly over the last 2 decades in patients with PE, patients with DVT alone, and at-risk patients who have neither PE nor DVT.[54] We recommend reserving IVC filters for patients with contraindications to anticoagulation or those who develop recurrent thromboembolic disease despite anticoagulant therapy.[55] The FDA recently approved three types of retrievable filters. Although long-term safety data for these devices are not yet available, removable IVC filters may be attractive options for patients with transient contraindications to anticoagulation.

TESTING FOR HYPERCOAGULABILITY

It has long been known that some patients have a proclivity to develop thrombosis, but laboratory techniques to identify these coagulation defects have become available only relatively recently. More such defects are likely to be identified in the near future. But a laboratory diagnosis of a "hypercoagulable state" such as heterozygous factor V Leiden mutation, protein S deficiency, or heterozygous prothrombin gene mutation G20210A often does not change patient care, may not be cost-effective, and may cause needless anxiety among patients who test positive. Therefore, testing for hypercoagulability should be done only when it will directly impact the plan of care.

There is no role for screening for hypercoagulability in the general population, since many patients with so-called hypercoagulable states may never develop VTE[56,57] and since long-term anticoagulation for primary prevention of VTE would be costly and risky in these patients. But what about hypercoagulability testing after an episode of thrombosis? This, too, is usually not indicated. Even in patients with laboratory-diagnosed thrombophilia, thrombotic events are often triggered by a situational risk factor,[58,59] and once the situational factor is resolved and the thrombosis has been treated, there is little reason for indefinite anticoagulation. Most such patients do not suffer recurrent events.[60,61]

Although some authors recommend hypercoagulability testing in patients with unprovoked (idiopathic) thromboses,[62] this strategy is not universally accepted, and no management trials have shown that hypercoagulability testing improves the care of these patients.[63] Moreover, if lifelong anticoagulation is to be recommended solely because the episode was unprovoked,[7] then hypercoagulability testing is superfluous.

Two recent studies suggest that D-dimer elevations shortly after cessation of oral anticoagulation may be a better global indicator of hypercoagulability than any specific marker of thrombophilia.[61,64] In one of these studies, the absence of D-dimer elevations after withdrawal of anticoagulation carried a favorable prognosis, even in the presence of laboratory-confirmed thrombophilia (such as protein C deficiency or combined factor V Leiden/prothrombin mutation).[61] This strategy may help to inexpensively identify patients at risk for recurrent VTE without formal hypercoagulability testing.

In sum, definite indications for hypercoagulability testing remain elusive. It is clear, though, that such testing is not warranted in most patients with VTE and should be ordered selectively until management trials define clear indications for it. Gene assays for factor V Leiden and prothrombin gene mutation and testing for antiphospholipid antibodies can be performed in anticoagulated patients. However, testing for protein C and S levels should be done only after the patient has been off oral anticoagulants for at least 7 to 10 days, and this may be best accomplished after completing the course of warfarin therapy.

CHRONIC MAINTENANCE THERAPY

In 1992, Brandjes et al[65] showed that patients with acute VTE should not receive monotherapy with vitamin K antagonists such as warfarin. These drugs must be combined with an immediate-acting anticoagulant such as heparin since their optimal antithrombotic activity usually takes several days to achieve.

Debate over the appropriate starting dose of warfarin continues, as recent evidence suggests that a starting dose of 10 mg daily may achieve a therapeutic INR faster than 5 mg without increasing the risk of bleeding or thromboembolic complications. This may minimize the time on LMWH therapy.[66] However, previous randomized trials suggested that patients are more likely to have a therapeutic INR 3 to 5 days after initiating warfarin at 5 mg rather than 10 mg, in part because the higher dose carries a higher risk of supratherapeutic INR values.[67,68]

We recommend that clinicians consider patient-specific factors such as age, concomitant medications, and comorbidities when choosing the starting dose. Common medications that may require a lower starting warfarin dose include amiodarone, trimethoprim-sulfamethoxazole, and metronidazole. Lower starting doses may also be reasonable in patients with liver

TABLE 4
Bleeding risk index for outpatient warfarin therapy

What risk factors are present? (check all that apply)

- ❑ Age ≥ 65 years
- ❑ History of stroke
- ❑ History of gastrointestinal bleeding
- ❑ Recent myocardial infarction, hematocrit < 30%, serum creatinine > 1.5 mg/dL, history of diabetes mellitus

Sum the risk factors, classify patient by number of factors

Low bleeding risk: 0 factors
Intermediate bleeding risk: 1 or 2 factors
High bleeding risk: 3 or 4 factors

Estimated risk for major bleeding

	Low risk	Intermed. risk	High risk
In 3 months	2%	5%	23%
In 12 months	3%	12%	48%

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TABLE 5
Recommendations for optimal warfarin therapy duration for symptomatic venous thromboembolism

Indication/risk factor	Duration
Major transient risk factor (eg, surgery within 3 months, hospitalization, immobilization of leg)	3 months
Minor risk factor (eg, air travel, recent hormone replacement therapy, minor trauma or immobilization)	6 months
Unprovoked*, uncontrolled malignancy, or other factors (> 1 unprovoked venous thromboembolic episodes; antiphospholipid antibodies; protein C, protein S, or antithrombin deficiency; homozygous factor V Leiden or G20210A prothrombin mutation; inferior vena cava filter)	Indefinite†
Idiopathic calf vein thrombosis	6 months

*Consider target international normalized ratio of 1.5–2.0 after 6 months of therapy with a target of 2.0–3.0.

†If bleeding risk is high, consider 6 months of therapy instead.

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disease, congestive heart failure, or poor nutritional status, as well as in frail elderly patients. If a 10-mg starting dose is used, it is important that a detailed titration scheme be followed, as outlined in the 10-mg nomogram of Kovacs et al.[66]

Balance risk and benefit on a case-by-case basis

Choosing the duration of warfarin therapy requires estimating the risks of recurrent and fatal VTE if the patient were off warfarin and the competing risks of major and fatal bleeding while on therapy. This requires tailoring the therapy to the individual patient.

The rate of recurrent VTE at 1 year (after 3 months of therapy) is approximately 3% to 5% for patients with reversible risk factors such as surgery, trauma, hormone use, or acute illness. In contrast, the rate of recurrence after an episode of unprovoked VTE, even after 6 months of warfarin therapy, is approximately 10% at 1 year, and as high as 20% in those with cancer. In addition, about 5% to 10% of VTE events are fatal. On the other hand, the rate of major bleeding varies from 1% to 4% per patient-year in clinical trials, and the case-fatality rates for major bleeding range from 9% to 13%. The rate of intracranial bleeding is about 0.65% to 1% per year.[69,70] However, rates of major bleeding are often much higher in clinical practice than in clinical trials, probably owing to common comorbidities that predispose to anticoagulant-associated bleeding.[69] A validated outpatient bleeding risk index is shown in **Table 4**.[71]

Optimal dosing of warfarin for long-term VTE prevention following an unprovoked episode remains controversial. The PREVENT investigators[72] randomized 508 patients with idiopathic VTE to conventional warfarin therapy (target INR of 2.0 to 3.0) or to low-intensity warfarin therapy (target INR of 1.5 to 1.9) after an initial 3- to 6-month course of conventional therapy. This study showed that long-term, low-intensity warfarin therapy is highly effective in preventing recurrent VTE. However, 3 months later, the ELATE trial investigators[73] concluded that conventional warfarin therapy (INR of 2.0 to 3.0) is more effective than low-intensity therapy (INR of 1.5 to 1.9) for the long-term prevention of recurrent VTE following an unprecipitated thrombosis. In this study, low-intensity warfarin did not reduce the risk of clinically important bleeding. It is important to note that neither trial was powered to detect a difference in major bleeding.

These trials indicate that lifelong warfarin therapy for idiopathic VTE may be appropriate in selected patients at low risk of bleeding since these trials enrolled patients whose mean age was in the sixth decade of life (50 to 59 years) and who had few risk factors for bleeding. However, when we apply the outpatient bleeding risk index **(Table 4)** to our medical patients, we often estimate much higher rates of bleeding than observed in the selected patients in these trials.[71] Therefore, our recommendations for the duration of warfarin therapy are similar to those suggested by Kearon,[69] as outlined in **Table 5**.

COMPRESSION STOCKINGS

It is important to appreciate the chronic sequelae of DVT. The postthrombotic syndrome develops in approximately 40% of patients with proximal DVT and is charaterized by chronic venous stasis and sometimes by nonhealing ulcerations. A recent randomized study by Prandoni et al[74] demonstrated a 50% reduction in the risk of postthrombotic sequelae (P = .011) in patients with acute proximal DVT who used compression stockings. We therefore endorse the use of below-knee compression stockings (30 to 40 mm Hg at the ankle) in patients with acute DVT, particularly those who present with significant edema or skin changes.

SUMMARY AND RECOMMENDATIONS

VTE is a common disease. Its diagnosis can be challenging, but it is best approached using a clinical decision model to determine a pretest clinical probability of disease prior to any diagnostic testing. This clinical probability can then be combined with D-dimer testing, diagnostic imaging, or both. Some patients with PE require risk stratification, especially those who may be candidates for outpatient treatment or who may require thrombolysis. We recommend LMWH over UFH in most patients with acute VTE, in light of LMWH's multiple advantages. In addition, newer anticoagulants such as fondaparinux show promise, based on once-daily dosing and the lack of a reported association with HIT. The duration and intensity of warfarin therapy should be tailored to the individual patient, although the optimal target INR is 2.0 to 3.0 at least for the first several months of therapy.

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Stroke prevention in atrial fibrillation:

Current anticoagulation management and future directions

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ABSTRACT

Atrial fibrillation (AF) is an important cause of stroke, and stroke risk stratification is critical to the management of patients with AF. Anticoagulation with warfarin is the current standard of care for stroke prevention in these patients, despite the need for close monitoring. Aspirin alone is not as effective. Warfarin is recommended for patients with AF and valvular disease or with AF and one or more stroke risk factors. Other novel anticoagulants and antiplatelet combinations are under investigation. Curative procedures for AF are possible, but their long-term safety and effect on stroke risk are unknown.

Atrial fibrillation (AF) is a significant risk factor for the formation of atrial thrombi, which can lead to systemic emboli, including stroke.[1] For this reason, stroke prevention is a key consideration in managing patients with AF.

Anticoagulation successfully reduces the incidence of stroke in patients with AF,[2–7] but it carries risks of its own and is not accepted or tolerated by all, especially the elderly. There is also a problem with physician acceptance.[8] Other management options are under investigation. This article outlines considerations for stroke risk stratification in patients with AF and reviews stroke prevention options in these patients, with a focus on the role of anticoagulation within the evolving landscape of AF management.

OVERVIEW OF ATRIAL FIBRILLATION

Epidemiology and types of atrial fibrillation

AF is common, occurring in 2% to 5% of individuals 60 years of age or older and contributing to 10% to 20% of strokes in that population.[1,9–11] The prevalence of AF increases with age,[9–11] and the lifetime risk of developing AF is one in four for men and women over age 40.[11] Thus, AF is an important cause of stroke, and its significance increases with the aging process.

The condition encompasses many processes. *Paroxysmal AF* is self-terminating and generally lasts less than 24 hours (by definition, it lasts less than 7 days). *Persistent AF* lasts for longer than a week and is sustained (not self-terminating). Both paroxysmal and persistent AF can be recurrent. *Permanent AF* refers to AF that persists for longer than 1 year. *Lone AF* constitutes arrhythmia without underlying structural heart disease.

Mechanisms of atrial fibrillation

AF results in uncoordinated contraction of the atria, leading to blood stasis and clot formation.[12,13] Low left atrial appendage (LAA) peak velocities (< 20 cm/sec by pulsed-wave Doppler echocardiography) are associated with thrombus formation.[14] Another echocardiographic phenomenon seen in patients with AF is spontaneous echo contrast, ie, smoke-like images thought to represent increased red blood cell aggregation in the setting of low flow. The presence of spontaneous echo contrast is a predisposing factor for thrombus.[15]

AF also appears to activate the clotting system, further promoting thrombus formation. Thrombotic and fibrinolytic markers are increased in AF patients.[12,13]

STROKE RISK FACTORS AND RISK STRATIFICATION

A number of factors increase stroke risk in patients with nonvalvular AF: history of a previous stroke or stroke-like event, increased age, hypertension, diabetes mellitus, and history of heart failure.[16–18] The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators[16] identified female sex, systolic blood pressure greater than 160 mm Hg (with a history of hypertension), and an ejection fraction less than 25% as additional risk factors **(Table 1)**. The SPAF Investigators found that risk increases with each decade of life as one ages, with a relative risk of 1.8 per decade.[16]

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TABLE 1
Stroke risk calculations from two large atrial fibrillation trial groups[16–18]

Level of risk and risk factors	Annualized stroke rate	Strokes per 100 pt-yr*
Stroke Prevention in Atrial Fibrillation (SPAF) Investigators		
High risk	7.1%	5.7
• Female aged > 75 yr		
• Age > 75 yr + hypertension		
• Congestive heart failure		
• Left ventricular ejection fraction < 25%		
• Systolic blood pressure > 160 mm Hg		
Medium risk	2.6%	3.3
• Age < 75 yr + hypertension		
• Diabetes mellitus		
• Hypertension + diabetes mellitus		
Low risk	0.9%	1.5
• None of the above risk factors		
Atrial Fibrillation Investigators (AFI)		
High risk	—	5.4
• Previous stroke		
• Hypertension		
• Diabetes mellitus		
Medium risk	—	2.2
• Age > 65 yr		

*Modified by Gage et al[18] from the SPAF and AFI data.

TABLE 2
$CHADS_2$ scores, stroke risk, and risk levels[18,19]

$CHADS_2$ score*	Stroke risk per 100 pt-yr	$CHADS_2$ risk level	Warfarin recommended
0	1.9	Low	No
1	2.8	Low	No
2	4.0	Moderate	Yes
3	5.9	Moderate	Yes
4	8.5	High	Yes
5	12.5	High	Yes
6	18.2	High	Yes

*The $CHADS_2$ stroke risk index assigns 1 point for each of four risk factors (congestive heart failure, hypertension, age > 75 years, diabetes mellitus) and 2 points for a previous stroke.

Other clinical risk factors for AF include valvular heart disease, coronary artery disease, and obstructive sleep apnea.[1] Echocardiographic risk factors include left atrial enlargement, low LAA volume or flow velocity, the presence of left atrial or LAA thrombus or spontaneous echo contrast, valvular disease, left ventricular dysfunction or hypertrophy, and the presence of ascending aortic and aortic arch thrombus or plaque.[1,14,15]

Stroke rates vary significantly according to the patient's risk profile.[16–18] Patients at high risk may benefit from intervention,[2,3,5] whereas those at lower risk may not. Estimating the level of stroke risk is a critical part of assessing patients with AF.

The SPAF Investigators and Atrial Fibrillation Investigators identified risk factors and used clinical trial data to estimate stroke rates according to those factors **(Table 1)**.[16,17] Gage et al[18] identified independent risk factors for stroke and devised a scoring system, the $CHADS_2$ index, to assess the risk level for a given patient **(Table 2)**. The index assigns 1 point to each of four risk factors (congestive heart failure, hypertension, advanced age, and diabetes) and 2 points for a previous stroke-like event. The $CHADS_2$ index was validated with the $CHADS_2$ database and shown to be more accurate in predicting stroke rates in a Medicare population **(Table 2)** than the classifications from the SPAF Investigators or the Atrial Fibrillation Investigators.[18,19]

The most comprehensive but most complicated risk score for AF is based on Framingham Heart Study data and predicts 5-year risk of stroke or the composite of stroke and death on the basis of a patient's risk factors. This risk-analysis scoring system is available as an Excel spreadsheet on the National Institutes of Health Web site at **www.nhlbi.nih.gov/about/framingham/stroke.htm**.[20]

A RANGE OF MANAGEMENT OPTIONS

A variety of options are available for the prevention of stroke in patients with AF, including oral anticoagulation (warfarin or warfarin plus aspirin), antiplatelet therapy (aspirin, clopidogrel, ticlopidine, or dipyridamole), restoration of sinus rhythm, and procedural options (LAA ligation or amputation, LAA occlusion, surgical treatment for AF, or pulmonary vein ablation).

PHARMACOLOGIC OPTIONS

Oral anticoagulant therapy

Anticoagulation with warfarin has been shown to be beneficial in patients with AF and rheumatic valvular heart disease.[2]

A number of trials have evaluated warfarin for the primary prevention of stroke in patients with nonvalvular AF.[4,6,7,16,21–23] In these studies, warfarin (dosed to achieve an international normalized ratio [INR] between 2.0 and 5.0) significantly reduced the incidence of stroke and stroke-like events compared with placebo, aspirin, or aspirin combined with low-dose warfarin (INR < 2.0). Compared with placebo, warfarin reduced the annual rate of vascular events from 5%–8% to approximately 2% (relative risk reduction

TABLE 3

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Please see original source table (table 1) in: *McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. Ann Intern Med 2003; 139:1018–1033.*

of 62%).[4,6,7,16,21,22] However, warfarin increased the risk of intracranial hemorrhage relative to placebo, with rates ranging from 0.3% to 1.8% for INRs from 2.0 to 4.5. When the target INR was 2.0 to 3.0, rates of intracranial hemorrhage were only 0.3% to 0.6%.[6,16,21,22] Rates of major bleeding were 0.2% to 0.5% annually. Rates of minor bleeding also increased significantly with warfarin therapy.[6,7,16,21,22]

In patients with nonvalvular AF at moderate to high risk of stroke, warfarin is the recommended therapy for primary stroke prevention unless it is contraindicated; the target INR should be 2.0 to 3.0.[24–26] This includes patients with persistent or paroxysmal AF with one or more significant risk factors **(Tables 1 and 2)**.[19,24–26]

Antiplatelet therapy

For patients in whom warfarin is not an option, aspirin may be an alternative. The SPAF trials demonstrated a benefit for aspirin over placebo except in patients older than 75 years of age.[3,23] A recent meta-analysis[27] suggested a trend towards a benefit with aspirin relative to placebo **(Table 3)**. Aspirin may have a role for stroke risk reduction in low-risk patients. Aspirin combined with low-dose warfarin is not as effective as adjusted-dose warfarin (target INR of 2.0 to 3.0)[7,22,27,28] **(Table 3)**.

In patients who continue to have events despite appropriately dosed warfarin (INR 2.0 to 3.0), some physicians have advocated adding aspirin to the conventional warfarin regimen, although this has not been assessed in a clinical trial setting.

Combinations of aspirin and other antiplatelet agents (clopidogrel, ticlopidine, dipyridamole) have not yet been shown to be effective for patients with nonvalvular AF. Several trials are under way to assess the combination of aspirin and clopidogrel relative to warfarin. However, a study assessing the effect of aspirin and clopidogrel on platelet function and coagulation did not show equivalent effects on coagulation relative to warfarin,[29] suggesting that warfarin is likely to be superior for stroke prevention in this setting. Aspirin and clopidogrel may have a role in low-risk to moderate-risk patients, but this also needs to be tested. The combination could also be considered in patients for whom warfarin is not acceptable.

Warfarin has been shown to have a beneficial effect for patients who have had a recent cerebrovascular ischemic event associated with AF (ie, secondary prevention).[5,23] The secondary prevention data for aspirin from the European Atrial Fibrillation Trial suggest that it is a safe but less effective option than warfarin but better than placebo.[5]

Guidelines and pharmacologic therapy

A number of guidelines for the prevention of stroke in AF have been devised.[24–26] **Table 4** outlines the risk-based approach recommended in recent guidelines from the American College of Cardiology, American Heart Association, and European Society of Cardiology.[24] These guidelines are generally similar to the 2004 recommendations from the American College of Chest Physicians.[26] The American Academy of Family Physicians and American College of Physicians suggest defining risk for stroke according to the $CHADS_2$ classification **(Table 2)**.[19] Key recommendations from these guidelines are summarized in the "Recommendations" section below.

Perioperative bridging therapy

One of the dilemmas of warfarin therapy is what to do when a patient requires an intervention for which anticoagulation poses significant risk. In these situations, the risk of stroke resulting from warfarin discontinuation needs to be assessed. For those at low risk of thromboembolism, warfarin can be stopped for 4 to 5 days before the procedure and restarted after the procedure is completed. In high-risk patients, warfarin can be stopped and, once the INR has dropped below 2.0, intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin can be started. The US Food and Drug Administration has not approved these

TABLE 4

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Please see original source table (table 19) in: *Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences. Eur Heart J 2001; 22:1852–1923.*

agents for this indication, but guidelines do list them as options.[26] If low-molecular-weight heparin is used, it should be stopped 12 to 24 hours before the procedure. Unfractionated heparin can be discontinued several hours before the procedure. These medications and warfarin should be restarted as soon as adequate hemostasis is achieved. Unfractionated or low-molecular-weight heparin should be continued at least until the warfarin is therapeutic.[24–26]

Emerging antithrombotic therapies

Warfarin has a narrow therapeutic window and complex and variable pharmacodynamics and pharmacokinetics. It also interacts with many drugs and foods and requires regular blood level monitoring. As a result, there has been much interest in finding agents to replace warfarin.

Direct thrombin inhibitors. Ximelagatran is the first oral agent in the direct thrombin inhibitor class of anticoagulants. At a fixed dose, it has been shown to be noninferior to warfarin for stroke prevention in patients with nonvalvular AF.[30–32] It appears to have similar risks of intracranial bleeding and major bleeding relative to warfarin but a lower risk of minor hemorrhage.[31,32]

Unfortunately, ximelagatran has been shown to raise serum transaminase and bilirubin levels in 5% to 10% of patients. These abnormalities have been reported to improve whether or not the medication is continued.[30–32] However, recent analyses suggest that deaths due to liver failure have occurred.[33,34] These deaths may be preventable with more careful follow-up of transaminase levels, but more data are needed. The FDA also recently raised concerns over a possible increase in coronary events in patients receiving ximelagatran compared with those receiving warfarin, but these data are inconsistent.[34] As a result of these safety concerns, ximelagatran has not currently been approved by the FDA.

Factor Xa inhibitors. Another novel class of anticoagulants is the factor Xa inhibitors, or pentasaccharides. Fondaparinux, currently the only commercially available member of this class, is administered once daily by subcutaneous injection and has potential utility for stroke prevention in patients with AF. The long-acting, once-weekly subcutaneous agent idraparinux is in early phase 3 trials. Oral factor Xa inhibitors are still in phase 2 trials.

If a safe and effective oral agent becomes available, it will have the potential to revolutionize stroke prevention in patients with AF.

Rate control vs rhythm control

Another area of controversy is which of two strategies—maintenance of sinus rhythm ("rhythm control") or controlling the heart rate and continuing anticoagulation ("rate control")—is more beneficial for patients with AF. A number of studies have shown no mortality or stroke benefit with rhythm control,[35–39] and the AFFIRM trial[35] suggested a trend toward lower mortality with rate control. The main reason for these results has been the inability to maintain sinus rhythm in patients managed with rhythm control, and the subsequent thromboembolic events that occurred during AF after patients were taken off anticoagulant therapy.[35–37] There are, however, hemodynamic benefits to being in

TABLE 5
Summary of trials comparing rate control and rhythm control in patients with atrial fibrillation

Trial	N	Mean age (yr)	Follow-up	End point	Outcome
PIAF[39]	252	61	1 yr	Symptoms	No significant difference between rate and rhythm control groups
RACE[37]	522	68	2.3 yr	Composite*	No significant difference between rate and rhythm control groups
AFFIRM[35]	4,060	69.7	5 yr	Mortality	Trend toward lower mortality in rate control group (hazard ratio of 1.15 for rhythm group [95% CI, 0.99–1.34], $P = .08$)
STAF[36]	200	66	19.6 mo	Composite†	No significant difference between rate and rhythm control groups
HOT CAFE[38]	205	60.8	12 mo	Symptoms	No significant difference between rate and rhythm control groups
				Mortality	No significant difference between rate and rhythm control groups
				Hospitalizations	62% absolute risk reduction in rate control group ($P < .001$)
				LV function	Improvement in rhythm control group ($P < .01$)
				Exercise capacity	Improvement in rhythm control group ($P < .01$)

* Death, heart failure, and thromboembolic events

† Mortality, need for cardiopulmonary resuscitation, cerebrovascular events, and thromboembolic events

PIAF = Pharmacological Intervention in Atrial Fibrillation; **RACE** = Rate Control versus Electrical Cardioversion; **AFFIRM** = Atrial Fibrillation Follow-up Investigation of Rhythm Management; **STAF** = Strategies of Treatment of Atrial Fibrillation; **HOT CAFE** = How to Treat Chronic Atrial Fibrillation

sinus rhythm.[37,38] The trials investigating this problem enrolled patients with no symptoms or minimal symptoms. In patients for whom AF produces significant symptoms, restoration of sinus rhythm is still appropriate. The important message of these trials **(Table 5)**[35–39] is that in patients for whom a strategy of achieving sinus rhythm is chosen, continued anticoagulation should be recommended for the prevention of stroke.

CURATIVE APPROACHES TO ATRIAL FIBRILLATION

Surgical occlusion of the LAA may be attempted for patients with AF who are undergoing cardiac surgery for an indication other than AF. One study has shown a significant reduction of embolic events in patients who received this procedure compared with those who did not.[40] However, the significant risk of incomplete occlusion with this procedure (≈20%) may result in further thromboembolic events.[40]

Occlusion of the LAA can also be achieved percutaneously. This has been done safely and effectively without significant effect on the left atrium or the pulmonary veins.[41] Long-term safety data are not yet available, however, and the effect on stroke prevention is not yet known.

The maze procedure is a surgical intervention in which small incisions are made in the atria to interrupt the pathways that produce AF. It eliminates AF in more than 90% of patients.[42] Pulmonary vein ablation can also be done during or instead of the maze procedure. A small percentage of patients may require medical therapy or permanent pacemaker implantation for sinus node injury.[42] The maze procedure has been shown to significantly lower stroke rates both acutely (0.7% perioperative stroke rate) and over the long term (0.4% stroke rate over follow-up of up to 11.5 years).[43]

Percutaneous catheter ablation for AF is a procedure in evolution. Current techniques involve pulmonary vein isolation and atrial ablation. Success rates range from 60% to 90% during short-term follow-up. Long-term risks are not yet fully determined but so far seem minimal.[44–46] Nonrandomized trials have shown significantly improved survival, less heart failure, and less stroke with pulmonary ablation compared with conventional therapy.[44,46] Catheter ablation appears to offer substantial promise, at least for highly symptomatic patients.

Pacemaker implantation has a role in the management of AF. Options include physiologic pacing, dual-site atrial pacing, and overdrive pacing. Whether these options reduce stroke is currently unknown.[45] Atrioventricular node ablation and permanent pacemaker implantation is another strategy for patients with highly symptomatic AF that is unresponsive to other therapies. It does not cure AF or prevent stroke, however, and patients still require anticoagulation.

Implantable atrial defibrillators have been developed, but patient acceptance has been low. Most patients are conscious at the time of defibrillation. Even with low defibrillation outputs, patients have found the discharge uncomfortable.[45] These devices are still experimental, and their effect on stroke rates is unknown.

THE ROLE OF ECHOCARDIOGRAPHY

Transesophageal echocardiography (TEE) images the heart with a high level of resolution and readily detects thrombus in the left atrium and LAA.[47] It also can identify other echocardiographic risk factors for thrombus and emboli. The ACUTE trial[47] showed that TEE safely permits cardioversion in patients with new-onset

TABLE 6
Factors that guide cardioversion management in hemodynamically stable patients with atrial fibrillation

Patient factors that call for a TEE-guided strategy	Patient factors that call for conventional management
New-onset atrial fibrillation	Chronic or therapeutic anticoagulation
Uncertain anticoagulation status, subtherapeutic anticoagulation levels, or absence of anticoagulation therapy	High likelihood of spontaneous/chemical conversion with inciting factors for atrial fibrillation
Symptoms	Absence of symptoms or minimal symptoms
Hemodynamic effects, congestive heart failure, ischemia	Contraindications or intolerance to TEE
Hospitalized patients	Outpatient status
Elevated risk for long-term bleeding	Low risk for bleeding
Difficulty complying with anticoagulation therapy	Compliance with anticoagulation therapy
High risk for left atrial stroke*	Low risk for left atrial thrombi†

TEE = transesophageal echocardiography
*Valvular heart disease, left ventricular dysfunction, prior left atrial/left atrial appendage thrombi, prior stroke, advanced age, systolic hypertension
†No valvular heart disease, normal left ventricular function, no clinical risk factors for stroke

AF, for whom prolonged anticoagulation is not planned, when no left atrial or LAA thrombus has been identified **(Table 6)**. Postcardioversion embolic events occurred at a rate similar to that in patients treated conventionally (warfarin to an INR of 2.0 to 3.0 for at least 3 weeks before cardioversion), but with significantly fewer bleeding events.[47] Warfarin is still required for at least 3 weeks after cardioversion, owing to variability in the return to fully coordinated function, but the total duration of anticoagulation can be significantly reduced. TEE-guided cardioversion is an effective alternative to conventional management.[47,48]

TEE and intracardiac echocardiography can also be used to ensure the safety of other procedures for AF before those procedures are performed.[48] Echocardiography can guide the placement of percutaneous devices and surgical closure of intracardiac shunts, which may lessen stroke risk.[48]

RECOMMENDATIONS

Stroke prevention is possible and essential for almost all patients with AF. Warfarin remains the treatment of choice for patients in whom it is not contraindicated. It is the most effective approach currently available to prevent systemic thromboembolism. The desired treatment range is an INR of 2.0 to 3.0 (target of 2.5). Warfarin is recommended for patients with AF and valvular disease or with AF and at least one risk factor (see the guidelines discussed above[19,24–26] and **Tables 2 and 4**). It is also recommended in patients who have had a previous stroke or stroke-like event. However, warfarin is not indicated for young patients without risk factors (lone AF). Aspirin may have a role in this group. For patients already on therapeutic warfarin who continue to have recurrent events, the addition of aspirin may be beneficial. For patients with infrequent AF, the effectiveness of anticoagulation is unknown.

Attempting cardioversion for patients with persistent AF is quite reasonable. However, warfarin should be continued long-term in these patients for the prevention of stroke.

For patients with recurrent and significantly symptomatic AF despite attempts at reversion to sinus rhythm, a curative procedure can be contemplated. For patients requiring open heart surgery, a surgical approach at the same time may be warranted. Catheter-based techniques are emerging and may be the wave of the future. Whether these patients still require anticoagulation is currently unknown.

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Heparin-induced thrombocytopenia:

Principles for early recognition and management

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ABSTRACT

Heparin-induced thrombocytopenia (HIT) is a potentially devastating complication of therapy with either unfractionated or low-molecular-weight heparin. Thrombocytopenia is no longer essential for the diagnosis of HIT, since a 50% drop in the platelet count may be a more specific indicator. Once HIT is clinically suspected, heparin should be stopped immediately and direct thrombin inhibitor therapy started; waiting for laboratory confirmation may be catastrophic.

Heparin-induced thrombocytopenia (HIT) is one of the most important and potentially catastrophic drug complications known. Although first reported in 1958, it remains a diagnosis not frequently considered or even recognized by many physicians. This review briefly surveys the key issues surrounding HIT for clinicians: when to suspect it, how to approach its diagnosis, and strategies for its effective management.

HIT: WHAT IT IS AND WHY IT MATTERS

HIT is a serious complication of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) therapy that affects both the venous and arterial circulation. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are its most frequent sequelae, although arterial events—including loss of limb, myocardial infarction, and stroke—can also occur.

The incidence of HIT may be as high as 5% in patients receiving UFH but is lower (1% or less) with LMWH therapy.[1] Any route of administration (subcutaneous or intravenous) or amount of heparin (prophylactic doses, heparin flushes, small amounts on heparin-coated catheters) can cause HIT.

Historically, two types of HIT have been described.

Type I HIT, a non–immune-mediated form, results in a transient drop in the platelet count between days 1 and 4 of treatment. In this type, the platelet count seldom drops below 100,000 per µL, thrombocytopenia resolves without heparin discontinuation, and no thromboembolic events occur.

Type II HIT is an immune-mediated process that can result in devastating thromboembolic complications, including death. It develops within 5 to 14 days of heparin exposure, though it may occur within hours if the patient has had recent treatment, or days to weeks after heparin has been discontinued. In Type II HIT, administration of heparin stimulates the release of platelet factor 4 (PF4), a heparin-neutralizing protein found in the alpha granules of platelets. Heparin and PF4 form a complex that leads to development of HIT antibodies (immunoglobulin G [IgG]). These IgG-PF4-heparin immune complexes bind to the Fc receptors on platelet surfaces, resulting in platelet activation, aggregation, release of prothrombotic platelet-derived microparticles, and, eventually, the development of thrombocytopenia and thrombosis. These complexes also stimulate monocytes, resulting in tissue factor production, and activation of the extrinsic coagulation pathway system, increased thrombin generation, and thrombosis **(Figure 1)**.[2]

WHEN TO SUSPECT HIT

HIT should be suspected in any patient who develops thrombocytopenia (defined as a platelet count < 150,000 per µL) while receiving UFH or LMWH therapy. Although most patients do not develop the severe thrombocytopenia (or bleeding complications) often seen with other immune-mediated drug reactions, the median platelet count in one large series was 59,000 per µL, and counts under 15,000 were reported.[3] The thrombocytopenia is not always associated with thrombosis; when it is not, it is referred to as isolated HIT.

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The pathogenesis of heparin-induced thrombocytopenia

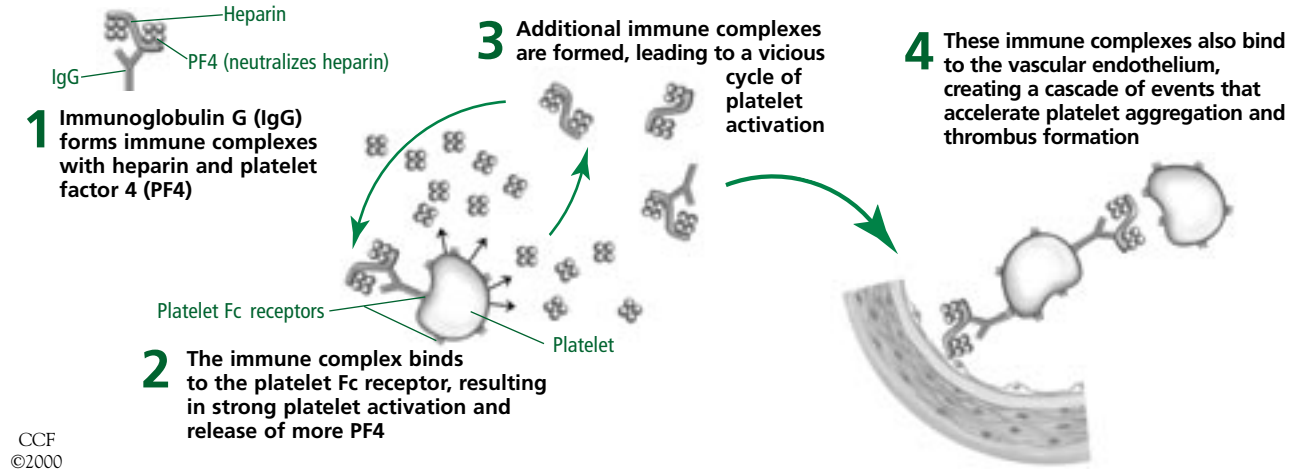

FIGURE 1. Adapted, with permission, from reference 2.

HIT can also occur in patients who have normal or even elevated platelet counts. These patients demonstrate a 50% or greater decline in their platelet count from their pretreatment level. Recent evidence-based guidelines suggest that the degree of this drop in platelet count may be a more sensitive predictor of HIT in postoperative patients than is absolute thrombocytopenia.[4]

HIT must also be considered in patients who develop new thrombosis or an extension of existing thrombosis despite adequate treatment with UFH or LMWH. It should also be considered when there is a resistance to UFH, defined as an inability to maintain therapeutic activated partial thromboplastin time (aPTT) levels despite increasing dosage.[5,6]

Three patterns of HIT presentation

In a heparin-naïve patient, HIT usually develops within the first 5 to 14 days after exposure. This classic presentation is referred to as **typical-onset HIT** and represents approximately 65% of all reported cases.[4]

Two other temporal patterns have recently been described. **Rapid-onset HIT**, which represents up to 30% of all cases, occurs within hours to days of heparin administration (median, 10.5 hours) in patients who have received prior heparin therapy within the previous 100 days.[7] It is attributable to the continued presence of circulating heparin-dependent antibodies following recent exposure. **Delayed-onset HIT** develops 9 to 40 days after UFH or LMWH has been withdrawn and is seen in 2% to 3% of all HIT patients.[7–9] These patients are often sent home off anticoagulants without complications, only to return later with a new thrombotic event. High antibody titers and low or borderline platelet counts are often identified on presentation.[9] Delayed-onset HIT must be differentiated from a delayed recognition of HIT in patients for whom the platelet count was not closely followed or the diagnosis not considered.

Thrombotic complications of HIT

More than half of all patients who develop HIT will experience a thrombotic complication.[10]

Venous thromboembolism (VTE) occurs four times more often than arterial events. DVT of the leg (often bilateral) is the most frequent clinical sequela, followed by upper extremity involvement, which often occurs at the site of a central venous catheter.[1,11] PE is more common than all of the arterial events combined and is reported to occur in up to 25% of all cases.[1] Additional reported VTE events include cerebral sinus thrombosis and adrenal vein thrombosis resulting in hemorrhagic necrosis of the adrenal gland.[1]

The most common arterial thrombosis is acute limb occlusion, which may occur at the site of an endovascular procedure or intravascular catheter insertion, or in areas of previous vascular trauma or surgery.[1,11] The iliac arteries and distal aorta are most often involved. HIT may also result in acute thrombotic stroke, myocardial infarction, an intracardiac thrombus, or thrombosis of a prosthetic graft or extracorporeal circuit.

A number of unusual complications have also been recognized with HIT, including warfarin-induced venous limb gangrene, warfarin-induced skin necrosis, heparin-induced skin necrosis, and an acute systemic reaction following an intravenous bolus of UFH.

Warfarin-induced venous limb gangrene or skin necrosis develop when patients receive unopposed warfarin or when this oral anticoagulant is initiated too early during active HIT.[12,13] Patients with warfarin-induced venous limb gangrene develop acral necrosis with DVT in an ipsilateral arm or leg, often accompanied by a supratherapeutic international normalized ratio (INR), whereas warfarin-induced skin necrosis affects fatty tissue areas, including the breast, buttocks, and thigh.[12]

Patients who develop heparin-induced skin lesions

TABLE 1
Using "the four T's" to estimate the pretest probability of HIT*

	2 Points	1 Point	0 Points
Thrombocytopenia	> 50% fall or platelet nadir of 20,000–100,000 per µL	30%–50% fall or platelet nadir of 10,000–19,000 per µL	Fall < 30% or platelet nadir < 10,000 per µL
Timing of platelet count fall or other sequelae	Clear onset between days 5 and 10; or less than 1 day if exposed to heparin within past 100 days	Consistent with immunization but not clear (eg, missing platelet counts); or onset after day 10	Fall in platelet count is too early (without recent heparin exposure)
Thrombosis or other sequelae (eg, skin lesions)	New thrombosis; skin necrosis; acute systemic reaction following heparin bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
O**T**her cause of thrombocytopenia	No other cause for fall in platelet count is evident	Possible other cause is evident	Definite other cause is present

* A patient's pretest probability equals the total points in all four categories: 0–3 points = low; 4–5 points = intermediate; 6–8 points = high.

Adapted, with permission, from reference 16.

present with erythematous plaques, nodules, or skin necrosis in areas where subcutaneous injections of UFH or LMWH were given. These lesions are usually painful and pruritic, and although as many as 75% of these patients will not develop thrombocytopenia, these skin changes should be considered a marker for HIT.[14]

An acute systemic reaction may occur within 5 to 30 minutes following an intravenous bolus of UFH. An abrupt fall in the platelet count is generally identified if the platelet count is assessed, while the most common signs include fever, chills, tachycardia, and hypertension. Flushing, headaches, nausea, vomiting, diarrhea, chest pain, and transient global amnesia have also been reported. Development of this reaction in association with HIT may result in sudden cardiorespiratory collapse and, rarely, death.[15]

Disseminated intravascular coagulation may also develop in patients with HIT. It is characterized by hypofibrinogenemia and a transient acquired natural anticoagulant deficiency including low levels of antithrombin and protein C. Patients may have a prolonged INR and aPTT. Schistocytes are often seen on the peripheral blood smear, and livedo reticularis, renal failure, and other signs of microvascular thrombosis may be present.[1]

DIAGNOSIS: COMBINE CLINICAL ASSESSMENT WITH LABORATORY TESTING

HIT is commonly referred to as a clinicopathologic syndrome and requires both clinical and laboratory findings to confirm the diagnosis.[1,4] Patients present with clinical evidence of thrombocytopenia or thrombosis, while the laboratory diagnosis relies on detection of HIT antibodies to UFH or LMWH.

Because thrombocytopenia is a common finding in the hospital setting, other possibilities must be considered in the differential diagnosis of HIT. These include pseudothrombocytopenia, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, infections, effects of other medications or alcohol, bone marrow failure, and dilution.

Warkentin and Heddle[16] recently recommended a clinical decision-making model to establish a pretest probability for HIT in patients who receive UFH or LMWH. This model is based on what they term the "four T's" (see **Table 1**). Points are given for each of these four categories, and point totals are summed to classify the likelihood of HIT as either low, intermediate, or high, as detailed in **Table 1**.

Two types of laboratory tests are readily available for the diagnosis of HIT: **functional tests**, which detect heparin-dependent platelet activation in the presence of the patient's sera and UFH or LMWH; and **antigen assays** (immunoassays), which measure IgG, IgM, or IgA antibodies that bind PF4 to UFH. It is important to recognize that these laboratory tests should be ordered only when there is a clinical suspicion of HIT.

Several functional assays are available, as detailed in **Table 2**. Of these, the washed-platelet assays have a higher sensitivity and specificity relative to the platelet aggregation test, and the serotonin release assay (SRA) is considered the gold standard among the washed-platelet tests.[17] Its major disadvantage, however, is that it is technically demanding, requires the use of radioisotopes and fresh donor platelets, and is not readily available in all laboratories. Most clinical laboratories do not perform the SRA, preferring the less demanding platelet aggregation test or

TABLE 2
Assays for use in laboratory testing for HIT

Functional assays	Antigen assays
Washed-platelet assays	• Solid-phase enzyme immunoassay —GTI-PF4 immunoassay —Asserachrom®
• Serotonin release assay	• PF4-polyvinylsulfonate antigen assay
• Heparin-induced platelet aggregation assay	• Fluid-phase immunoassay
Citrated plasma assays	• Particle gel immunoassay
• Platelet aggregation test	
Characteristics	Characteristics
• Less sensitive	• More sensitive
• More specific	• Less specific
• Technically demanding	• Technically simple
• Not standardized	• Standardized
• Expensive, not readily available	

heparin-induced platelet aggregation assay.

Four types of antigen assays are available, as detailed in **Table 2**. The two solid-phase enzyme immunoassays can detect clinically unimportant amounts of IgG, IgM, and IgA antibodies in patients exposed to UFH or LMWH, leading to high false-positive results and low specificity. More recently, a rapid antigen assay (particle gel immunoassay) has been developed.[18] It has a specificity similar to that of the functional assays with improved sensitivity, producing fewer false-positive results than the solid-phase immunoassays. This rapid antigen assay has the potential to fulfill a longstanding need for a quick (< 30 minutes) and reliable HIT assay.

Washed-platelet assays are recognized as more reliable than antigen assays because they have a better combined sensitivity and specificity, though no single test has 100% sensitivity and specificity.[16] Most reports recommend a combination of assays (a washed-platelet functional assay and an antigen assay) to help confirm the diagnosis of HIT.

HOW TO MANAGE ANTICOAGULATION IN HIT

Although the treatment of HIT has evolved over the past decade, the mainstay of therapy remains immediate discontinuation of UFH or LMWH once the diagnosis is suspected, followed by substitution of an alternative anticoagulant. Treatment should not be delayed while waiting for laboratory test results, as this only increases the risk of thrombosis. It is important that all sources of UFH or LMWH be removed, including any found in heparin flushes or total parenteral nutrition solutions, any that is bound to catheters, or any used intermittently during dialysis or angiography.

Simply discontinuing UFH is inadequate, even if there is no evidence of acute thrombosis (ie, isolated HIT). Three studies have found a cumulative thrombosis rate of 20% to 53% if this approach is followed.[10,19,20]

After many years of having few alternatives for treating HIT, clinicians now have several good options **(Table 3)**, owing largely to the development of the direct thrombin inhibitors (DTIs).

FDA-approved therapies

Lepirudin, a recombinant form of the leech-derived anticoagulant hirudin, was the first DTI approved by the US Food and Drug Administration (FDA) for anticoagulation in patients with HIT.[21–24] It has a relatively short half-life (80 minutes) and can be given intravenously or subcutaneously (though the latter route is not FDA-approved) and is monitored via the aPTT or the activated clotting time (ACT). The target aPTT is 1.5 to 2.5 times the baseline level and should be measured 4 to 6 hours after dose adjustments. Lepirudin is metabolized primarily by the kidney and requires significant dose adjustments in patients with renal insufficiency. In three studies comparing lepirudin-treated patients with historical controls, lepirudin was associated with significantly lower rates of the composite end point of mortality, limb amputation, or new thrombotic complications.[21–24]

Lepirudin lacks cross-reactivity with UFH or LMWH antibodies, but anti-hirudin antibodies develop in as many as 60% of patients.[25] These are not associated with increased risk for thrombosis, but anaphylaxis and death have been reported in patients who were reexposed to lepirudin.[26] Antibodies may extend the half-life of lepirudin, which requires closer monitoring of the aPTT.

Argatroban is a small synthetic molecule derived from L-arginine. It is FDA-approved for prevention and treatment of thrombosis in patients with HIT and for use in patients with HIT who require percutaneous coronary intervention. It has a short half-life **(Table 3)**, lacks cross-reactivity with UFH, and can be monitored via the aPTT or ACT. The target aPTT is 1.5 to 3.0 times the baseline level. Because argatroban prolongs the INR, assessing the anticoagulant effects of warfarin may be challenging in patients receiving argatroban. Therefore, the manufacturer recommends that a target INR greater than 4.0 be used during cotherapy before argatroban is discontinued, and that the INR be checked 4 to 6 hours after discontinuation to ensure that it remains within the therapeutic range.

Argatroban is metabolized in the liver and dose adjustments are recommended in patients with moderate liver disease. No antibody formation has been demonstrated. Similar to the data reported for lep-

TABLE 3
Comparison of available agents used in the treatment of HIT

	Argatroban*	Bivalirudin	Fondaparinux	Lepirudin*
Monitoring	aPTT, ACT	aPTT, ACT	None required	aPTT, ACT
Half-life	39–51 min	25 min	17 hr	80 min
Clearance	Hepatic	Proteolytic and renal	Renal	Renal
Dose adjustment	Moderate hepatic insufficiency	Moderate to severe renal insufficiency	Renal insufficiency	Renal insufficiency
Cross-reaction with HIT antibodies	No	No	Unknown in vivo, none in vitro	No
Antibody development	No	May cross-react with anti-hirudin antibodies	No	Anti-hirudin antibodies in up to 60% of patients

*FDA-approved for use in patients with HIT.

aPTT = activated partial thromboplastin time; ACT = activated clotting time

irudin, two studies of argatroban-treated patients with active or latent HIT have shown reductions in the risk of new thrombosis and thromboembolic complications compared with historical controls.[20,24,27]

Comparative considerations. Comparing the efficacy of lepirudin and argatroban is difficult because patients' baseline factors differed in the respective clinical trials. Neither agent has an antidote. Because of their differing dose adjustment requirements, argatroban may be better suited for patients with renal insufficiency and lepirudin for patients with hepatic dysfunction.[24]

'Off-label' therapies for HIT

Other anticoagulants have been used "off label" for treatment of patients with HIT.

Bivalirudin is a DTI designed from the structure of hirudin. It has the shortest half-life of the available DTIs (25 minutes), is metabolized by both proteolytic and renal mechanisms, and is monitored via the aPTT or ACT. Dose adjustments are necessary for patients with moderate to severe renal insufficiency. Bivalirudin has a minimal effect on the INR.

Experience with bivalirudin in patients with HIT is limited, though it has been used extensively to treat acute coronary syndrome in patients without HIT, and recent results from the ATBAT study were favorable for patients with HIT undergoing percutaneous coronary intervention.[28–30] It has also been used successfully in anecdotal cases of HIT patients requiring open-heart surgery,[31] and recent results on its use in patients without HIT who required off-pump coronary artery bypass surgery were encouraging.[32] Bivalirudin is currently under investigation as an alternative anticoagulant in both on-pump and off-pump cardiac surgery.

Fondaparinux is a synthetic pentasaccharide that binds to antithrombin. It is given subcutaneously, has 100% bioavailability, is excreted renally, and has only minimal effect on the prothrombin time, INR, aPTT, and bleeding time. It is currently approved for prevention of VTE in orthopedic patients and for treatment of DVT and PE in hospitalized patients. Fondaparinux does not appear to cross-react with HIT antibodies and may be an alternative to the DTIs, although experience with its use in HIT is limited.

Discontinued or nonrecommended options

Danaparoid, a low-molecular-weight heparinoid with a long half-life (18 to 24 hours), has also been used effectively in HIT patients. It has cross-reactivity with UFH in as many as 30% of cases, and although several studies have demonstrated its efficacy in the management of HIT, it is no longer commercially available in the United States.[17,33,34]

Warfarin remains the anticoagulant of choice for the long-term management of HIT, but it is now well recognized that warfarin should be avoided in patients with acute HIT, as it can precipitate warfarin-induced venous limb gangrene or skin necrosis.[12,13] Recent guidelines recommend not using warfarin as monotherapy, waiting until the platelet count has recovered (to ≈150,000 per μL), overlapping with an alternative anticoagulant for at least 5 days, starting with low doses (2.5 to 5 mg), and not discontinuing the alternative anticoagulant until the INR is therapeutic for 2 consecutive days.[4]

Platelet transfusions are not recommended even when thrombocytopenia is pronounced, both because bleeding complications are uncommon and because thrombotic events have been reported following such

transfusions. They should, however, be used in the rare patient with bleeding complications.

What about heparin reexposure?

Reexposure to UFH has generally been thought to be associated with a high risk of thrombocytopenia and thrombosis. In most patients, however, the UFH-dependent antibody will disappear within 100 days from the last dose. In certain clinical circumstances where anticoagulation is essential and the safety and efficacy of UFH is well established, such as cardiopulmonary bypass or vascular surgery, some investigators have advocated reexposure if certain conditions are met.[7] This is dependent upon demonstrating no antibody on sensitive laboratory tests and exposing the patient to UFH for only a short time (eg, during the surgical procedure).

SUMMARY

HIT is a serious complication of both UFH and LMWH therapy that occurs more than just rarely. It has recently been recognized to occur more frequently outside of its typical presentation within 5 to 14 days after heparin exposure. Thrombocytopenia is no longer essential for the diagnosis of HIT, as a 50% drop in the platelet count may be a more specific indicator. Once HIT is clinically suspected, heparin should be discontinued immediately and a DTI started; waiting for laboratory confirmation may be catastrophic. Failure to follow these guidelines may lead to VTE, stroke, myocardial infarction, loss of limb, or other devastating complications.

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Anticoagulation in special patient populations:

Are special dosing considerations required?

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ABSTRACT

Optimal dosing of low-molecular-weight heparin (LMWH) therapy has not yet been established for patients with morbid obesity or renal insufficiency or for pregnant women. Monitoring of anti-Xa levels appears to be helpful in guiding LMWH dosing in all of these patient groups. Use of fondaparinux in these populations has yet to be defined. Cancer patients are at particular risk of venous thromboembolism and generally require escalated and/or prolonged anticoagulation with intense monitoring of therapy.

The introduction of low-molecular-weight heparin (LMWH) was a turning point in the management of thrombotic disorders. Until 1987, the only parenteral anticoagulant was unfractionated heparin (UFH), which is limited by unpredictable pharmacokinetic and pharmacodynamic properties, as detailed earlier in this supplement. LMWH has more consistent and predictable anticoagulant activity, can be given subcutaneously once daily without laboratory monitoring, and has replaced UFH for most indications.

However, LMWH and other newer anticoagulants have not been well studied in several important patient populations, leaving questions as to efficacy, safety, and appropriate dosing. These special populations include morbidly obese patients (weight > 150 kg or body mass index > 50 kg/m^2), patients with severe renal insufficiency (creatinine clearance < 30 mL/min), and pregnant women. This article reviews special considerations for anticoagulant therapy—with LMWH and other options—in these populations as well as in cancer patients, who also appear to require escalated or prolonged anticoagulant therapy in the setting of venous thromboembolism (VTE).

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MORBIDLY OBESE PATIENTS

Obesity is an increasing health risk for Americans, occurring in approximately one third of both men and women. Obesity is an important risk factor for thrombosis, and VTE is common in obese patients.

LMWH has theoretic advantages in obese patients as a result of superior subcutaneous bioavailability. However, even LMWH at standard fixed doses may not be sufficient to prevent VTE in morbidly obese patients. Frederiksen et al[1] demonstrated a strong negative correlation between total body weight and heparin activity (as measured by anti-Xa assay) with fixed doses of the LMWH enoxaparin. This relationship has also been observed in obese patients who are critically ill.[2] These data suggest that weight-adjusted doses may be more appropriate than fixed doses for VTE prophylaxis in morbidly obese patients.

Scholten et al[3] conducted a nonrandomized retrospective study in 481 obese patients undergoing gastric bypass surgery. In addition to multimodal therapy with mechanical compression stockings, enoxaparin 40 mg every 12 hours was superior to enoxaparin 30 mg every 12 hours with respect to the incidence of postoperative deep vein thrombosis (DVT) (0.6% vs 5.4%; P = .01) without an increase in bleeding complications. Yet a smaller randomized study of the LMWH nadroparin (5,700 IU vs 9,500 IU) in 60 bariatric surgery patients failed to show a benefit from the higher dose in preventing postoperative DVT.[4]

It should be noted that heparin activity correlates with LMWH dose even in nonobese patients. Using data from the MEDENOX trial,[5] the efficacious prophylactic dose for enoxaparin (40 mg daily) translates to a dose of 0.5 mg/kg in a typical 80-kg patient. Similarly, an open-label trial evaluating two doses (75 and 175 IU/kg) of the LMWH tinzaparin given to otherwise healthy obese volunteers (100 to 165 kg) concluded that prophylactic tinzaparin dosing should be based on

TABLE 1
Therapeutic peak anti-Xa levels* with low-molecular-weight heparins for treatment of venous thromboembolism

Enoxaparin 1 mg/kg every 12 hours	0.6–1.0 IU/mL
Enoxaparin 1.5 mg/kg daily	1.0–1.5 IU/mL
Tinzaparin 175 IU/kg daily	0.85–1.0 IU/mL
Dalteparin 100 IU/kg every 12 hours	0.4–1.1 IU/mL
Dalteparin 200 IU/kg daily	1.0–2.0 IU/mL

* Via chromogenic anti-Xa assay drawn 4 hours after subcutaneous dose

actual body weight, independent of the presence of obesity, and that it need not be capped at a maximal absolute dose.[6] These studies support the notion that prophylactic LMWH doses (like therapeutic doses) should be weight-adjusted in all patients, with or without obesity. Although expert consensus generally recommends a heparin concentration of 0.1 to 0.6 IU/mL (by chromogenic anti-Xa assay) to prevent VTE, the optimal heparin activity needed for VTE prophylaxis remains unproven and can vary by LMWH.

Shepherd et al[7] recently found that subcutaneous adjusted-dose UFH, targeted to a partial thromboplastin time (PTT) 1.5 times control, is effective in reducing the risk of VTE in bariatric surgery patients. Unfortunately, the difficulties of titrating subcutaneous UFH to a target PTT are well documented,[8] raising questions about the overall feasibility of this approach.

To our knowledge, no published studies have looked at dosing of newer anticoagulants, such as the synthetic pentasaccharide fondaparinux, an indirect factor Xa inhibitor, in obese patients.

Recommendations

Without additional data, firm recommendations are difficult; however, clinicians should consider escalating standard recommended doses of LMWH in morbidly obese patients (ie, 0.5 mg/kg for enoxaparin) for thromboprophylaxis with or without adjunctive use of mechanical compression devices or anti-Xa monitoring. Alternatively, subcutaneous adjusted-dose UFH titrated to a PTT value 1.5 times control may be used.

Contemporary VTE treatment trials of LMWH generally used weight-adjusted doses without any ceiling for obese patients. However, few patients with a total body weight greater than 150 kg and a body mass index greater than 50 kg/m^2 were actually included. The relationship of intravascular volume and total body weight is not linear, and there is concern that dosing based on actual body weight could lead to excessive plasma concentrations of LMWH. However, post hoc analysis of cardiovascular patients using full weight-adjusted doses of LMWH and UFH found no differences in hemorrhage rates between obese and normal weight groups.[9] Similarly, anti-Xa activity is not significantly increased when LMWH is administered to obese patients based on total body weight.[6,10,11] Given the lack of clinical trial data for VTE treatment with LMWH in obese patients, it is still reasonable to monitor anti-Xa levels in such patients. Therapeutic anti-Xa levels depend on the specific LMWH preparation and dosing interval **(Table 1)**. Dose reduction should be considered if the anti-Xa level is excessive 4 hours after the subcutaneous LMWH dose.

PATIENTS WITH RENAL IMPAIRMENT

Because LMWH is cleared by the kidneys, patients with impaired renal function have prolonged elimination of LMWH agents. Thus, patients with severe renal insufficiency may be at increased risk for bleeding with standard doses of LMWH, particularly after multiple doses.

Post hoc analysis of cardiovascular trials using full weight-adjusted doses of LMWH and weight-adjusted and activated PTT (aPTT)-monitored UFH found significant increases in bleeding rates in renally impaired patients in both treatment groups.[9] A recent retrospective analysis using full weight-adjusted doses of LMWH or weight-adjusted and aPTT-monitored UFH confirmed this finding.[12] The study involved 620 patients with creatinine clearance (CrCl) rates of less than 60 mL/min, of which 331 received UFH, 250 received enoxaparin, and 39 received both. Rates of major bleeding were 26.3 per 1,000 patient-days for UFH and 20.7 per 1,000 patient-days for enoxaparin. Major bleeding complications were similarly increased with both UFH and enoxaparin across categories of worsening renal insufficiency. Among the subgroup of patients with severe renal insufficiency, the rate of minor bleeding was significantly higher in those treated with enoxaparin than in those treated with UFH (incidence ratio, 2.5; 95% confidence interval [CI], 1.01 to 6.36). These data suggest that patients with renal impairment are at increased risk for bleeding and that no specific heparin strategy is inherently safer than the other.

Although UFH has a dual clearance mechanism and may be less prone to accumulation than LMWH in patients with renal insufficiency, UFH has greater adverse effects on platelet function and capillary permeability with respect to bleeding. There is no evidence that UFH should be the "default" anticoagulant in renally impaired patients, provided that appropriate dosing and monitoring of LMWH is followed.

Large contemporary randomized trials of LMWH have generally excluded patients with significant renal impairment. However, sufficient pharmacokinetic and clinical data are available to make dosing recommendations. Pharmacokinetic studies confirm that the anti-Xa activity of LMWH is negatively correlated with CrCl.[13] For enoxaparin the relationship between anti-Xa activity and CrCl is linear in both single-dose and multiple-dose studies, with significantly increased anti-Xa levels in patients with a CrCl less than 30 mL/min.[14–16] Sanderink et al[17] reported a 39% decrease in anti-Xa clearance and a 35% increase in anti-Xa exposure with multiple prophylactic doses of enoxaparin in patients with a CrCl less than 30 mL/min relative to those with a CrCl of 31 mL/min or greater.

Recommendations

The aforementioned studies led to revised US Food and Drug Administration dosing guidelines for enoxaparin in the setting of renal insufficiency **(Table 2)**. It is important to note that the pharmacokinetic effect of impaired renal function may differ among LMWHs, and no such dosing guidelines exist for other LMWHs or for UFH. Moreover, the pentasaccharide fondaparinux is currently contraindicated in patients with renal impairment, owing to its much longer half-life than LMWH and a lack of safety and pharmacokinetic data in this patient group.

It should be emphasized that the dosing recommendations derived from pharmacokinetic studies have not been validated in randomized trials. The cutpoint of 30 mL/min for renal dose adjustment cannot be viewed dogmatically, as patients with a CrCl less than 10 mL/min may react differently from those with less renal impairment. Caution should be exercised in anticoagulation in all patients with renal impairment, and monitoring of heparin or anti-Xa activity remains the safest approach.

TABLE 2
FDA dosing guidelines for enoxaparin in patients with renal insufficiency*

Prophylaxis in the medically ill patient
• Enoxaparin 30 mg daily
Inpatient treatment of DVT with or without PE
• Enoxaparin 1 mg/kg daily
Outpatient treatment of DVT without PE
• Enoxaparin 1 mg/kg daily

*Creatinine clearance of less than 30 mL/min
DVT = deep vein thrombosis; PE = pulmonary embolism

PREGNANT WOMEN

The incidence of DVT in pregnant women is about six times the incidence in nonpregnant women.[18] Approximately one of every 100,000 pregnant women dies because of pulmonary embolism (PE), and in developed countries PE is the leading cause of death in pregnant women.[19,20] Often these events are sudden, occurring without premonitory signs or symptoms in what appeared to be an uneventful pregnancy. Several factors promote thrombosis during pregnancy, including reduced venous outflow from an expanding uterus (promoting stasis) and increased levels of almost all of the clotting proteins in the clotting cascade.[21,22]

Over the past few years, LMWH has become the choice for VTE treatment and prevention in pregnant women, owing to its improved bioavailability, better safety profile with regard to osteoporosis and thrombocytopenia,[23] and significantly reduced monitoring requirements relative to UFH. However, during pregnancy the volume of distribution and clearance of LMWH must be considered. The volume of distribution of LMWH is higher throughout pregnancy, and clearance may be higher in early pregnancy and then decline as pregnancy progresses to delivery. In light of this, anti-Xa levels should be assessed during the first week of pregnancy and then at least once per month in each trimester. The desired anti-Xa range for prophylaxis is 0.1 to 0.3 IU/mL, and the treatment range is 0.4 to 2.0 IU/mL **(Table 1)**.[23] In the postpartum period the volume of distribution and clearance will decrease further, requiring continued monitoring.

Intensity and duration of prophylaxis

The intensity and length of VTE prophylaxis in pregnancy depends on the patient's history of VTE. We recommend that pregnant women with a single previous VTE event secondary to a transient risk factor have clinical surveillance for signs and symptoms of VTE and receive 4 to 6 weeks of postpartum prophylaxis with LMWH (enoxaparin 40 mg or dalteparin 5,000 IU daily) as single-agent therapy or cross over to warfarin (dosed to achieve an international normalized ratio [INR] of 2.0 to 3.0). When the initial VTE event was secondary to prior pregnancy, estrogens, or additional risk factors (eg, obesity) or was a single idiopathic VTE event (and the patient is no longer on long-term anticoagulation), then antepartum prophylaxis is recommended with LMWH (enoxaparin 40 mg or dalteparin 5,000 IU daily) followed by postpartum prophylaxis as noted above. If the VTE event was secondary to thrombophilia or there is a strong family history of thrombotic events and a personal history of VTE, we

TABLE 3
Dosing regimens for LMWHs in pregnancy

Prophylactic LMWH
- Dalteparin 5,000 IU or enoxaparin 40 mg daily

Intermediate-dose prophylactic LMWH
- Dalteparin 5,000 IU or enoxaparin 40 mg twice daily

Adjusted-dose LMWH titrated via anti-Xa monitoring
- Dalteparin 100 IU/kg or enoxaparin 1 mg/kg twice daily

Postpartum prophylaxis
- Warfarin for 4 to 6 weeks to a target INR of 2.0 to 3.0 with initial UFH or LMWH overlap until INR is 2.0–3.0. Warfarin can be used safely in breast-feeding women.

Adapted from recommendations in reference 23.

LMWH = low-molecular-weight heparin; INR = international normalized ratio; UFH = unfractionated heparin

recommend intermediate-dose LMWH (see **Table 3**) plus postpartum prophylaxis. Similarly, women with antithrombin deficiency, prothrombin gene mutation, or factor V Leiden mutation (compound heterozygotes or homozygotes) with a history of VTE should receive intermediate-dose LMWH during pregnancy as well as postpartum prophylaxis for 4 to 6 weeks. For a patient with multiple episodes of VTE receiving long-term anticoagulation with warfarin, the warfarin should be discontinued and full weight-adjusted LMWH started. In the postpartum period, crossover to warfarin is recommended until an INR of 2.0 to 3.0 is achieved.

Pregnant women with additional considerations

We recommend that pregnant women with antiphospholipid antibodies and a history of two or more early or late pregnancy losses, preeclampsia, intrauterine growth retardation, or abruption receive antepartum aspirin plus LMWH (enoxaparin 40 mg or dalteparin 5,000 IU daily) and 4 to 6 weeks of postpartum prophylaxis. This is the same regimen recommended for women with known thrombophilia, recurrent miscarriages, a second-trimester or later loss, severe or recurrent preeclampsia, or abruption. Patients with antiphospholipid antibody syndrome who are receiving long-term warfarin therapy should be converted to adjusted-dose LMWH, which should be maintained up to the time of delivery and restarted after delivery with warfarin crossover until a therapeutic INR is achieved.

Pregnant women with mechanical heart valves should receive either adjusted-dose UFH targeted to a therapeutic aPTT (heparin level of 0.35 to 0.70 IU/mL) or adjusted-dose LMWH with a desired 4-hour postdose anti-Xa level of 1 to 1.2 IU/mL.[23] As the pregnancy progresses, bimonthly monitoring of anti-Xa levels with empiric dose adjustments is indicated, in light of the changes in the volume of distribution and clearance of LMWH as pregnancy progresses.

TABLE 4
VTE prophylaxis and treatment in cancer patients

VTE prophylaxis for the surgical patient

High-risk patient
- UFH 5,000 U 2 hr preoperatively, then every 8 hr
- Enoxaparin 40 mg or dalteparin 5,000 IU daily

Very-high-risk patient
- IPC sleeve ± gradient elastic stockings *plus*
  —UFH 5,000 U 2 hr preoperatively, then every 8 hr
  —Enoxaparin 40 mg or dalteparin 5,000 IU daily
- Extended prophylaxis (in selected high-risk patients):
  —Enoxaparin 40 mg daily for 1 month

VTE prophylaxis for the medical patient
- UFH 5,000 U every 8 hr
- Enoxaparin 40 mg daily
- Dalteparin 5,000 IU daily
- Fondaparinux 2.5 mg daily

VTE treatment
- UFH 80 U/kg bolus, 18 U/kg/hr infusion (aPTT every 6 hr for duration of infusion, adjust dose to a target heparin level) with concomitant warfarin*
- LMWH (enoxaparin 1 mg/kg every 12 hr, or tinzaparin 175 IU/kg daily) with concomitant warfarin*
- LMWH alone (dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily for 5 months, or enoxaparin 1.5 mg/kg once daily for 6 months)†

Adapted from recommendations in references 32 and 39.

*Continue warfarin indefinitely or until cancer has resolved.

†Although indefinite anticoagulation therapy is recommended in cancer patients, use of LMWH beyond 6 months has not been studied in clinical trials.

VTE = venous thromboembolism; UFH = unfractionated heparin; IPC = intermittent pneumatic compression; aPTT = activated partial thromboplastin time; LMWH = low-molecular-weight heparin

Pregnant women on prophylactic doses of LMWH have few bleeding complications with spontaneous delivery. Prophylactic doses can be held once labor begins. For patients on full weight-adjusted LMWH doses, the LMWH should be discontinued 24 hours before elective induction of labor; if the woman is deemed to have a very high risk of recurrent VTE, therapeutic UFH can be initiated intravenously and discontinued 4 to 6 hours before the expected time of delivery.

PATIENTS WITH CANCER

An association between venous thrombosis and malignant disease was first documented in the 1860s. Clinically manifested VTE has been reported in approximately 15% of cancer patients; rates including subclinical disease are probably even higher.[24,25] Some types of cancer have a higher prothrombotic tendency, but this feature is affected by disease staging, chemotherapy, surgical intervention, and generalized debility. Cancer patients with VTE who are receiving anticoagulation have twice the rate of recurrence on treatment as do noncancer patients; they also are hospitalized longer, pose more difficulties for maintenance

of anticoagulation, and have a poorer prognosis.[26,27] For these reasons, cancer patients should be viewed as being at especially high risk for VTE complications and in need of more intense anticoagulation monitoring.

The underlying etiology for cancer's prothrombotic tendency is the impact that malignant disease has on Virchow's triad of stasis, intimal injury, and hypercoagulability. The contributory effect of stasis to VTE in cancer patients stems from abnormalities in blood flow, immobility as a result of cancer-related debility, and compression of blood flow or invasion of vessels by expanding tumor growth. Vascular endothelium also plays a major role, with changes seen in concentrations of thrombosis-modulating factors such as von Willebrand factor, soluble thrombomodulin, soluble E selectin, and inflammatory cytokines.[28] In cancer, tumor cells can activate the coagulation system directly, through interactions with platelets, clotting factors, and the fibrinolytic system, to generate a hypercoagulable state.[29] In addition, two extrinsic causes of hypercoagulability are cancer surgery and chemotherapy. Approximately 60% of cancer patients undergo some sort of surgery, with all its attendant risks for VTE. Chemotherapies such as cisplatin, etoposide, medroxyprogesterone, and tamoxifen, as well as the vascular catheters through which these agents are delivered, have all been reported to increase the risk of thrombosis.[30,31]

Prophylaxis in cancer patients undergoing surgery

Because of cancer's association with increased thrombogenicity, cancer patients undergoing surgery should be considered at high or very high risk for VTE **(Table 4)**.[32] Cancer patients at high risk are generally those under 60 years of age without additional VTE risk factors. In the absence of prophylaxis, the incidences of proximal DVT and fatal PE in these patients are about 4% to 8% and 0.4% to 1%, respectively.[32] Most cancer patients undergoing surgery will be in the very-high-risk group, ie, over 60 years of age with multiple risk factors. In these patients the incidences of proximal DVT and fatal PE are about 10% to 20% and 0.2% to 5%, respectively.[32] Given these high rates of significant VTE events, all cancer patients undergoing major surgery should receive aggressive VTE prophylaxis, as represented in the regimens of choice detailed in **Table 4**. Once the patient is ambulatory, intermittent pneumatic compression sleeves (see **Table 4**) may be removed, but pharmacologic prophylaxis should be maintained at least until hospital discharge.[32]

Bergqvist et al[33] conducted a placebo-controlled study of extended out-of-hospital VTE prophylaxis with LMWH for 1 month following major abdominal or pelvic cancer surgery. The incidence of postdischarge VTE was 12.8% in the placebo group and 4.8% in LMWH group (P = .02). In new consensus guidelines from the American College of Chest Physicians,[32] extended out-of-hospital VTE prophylaxis with LMWH is recommended in selected high-risk general surgery patients **(Table 4)**. Cancer patients undergoing surgery should be strongly considered for such extended VTE prophylaxis.

Prophylaxis in medical patients with cancer

The hospitalized medical patient with cancer is also at increased risk for VTE. The overall reported prevalence of VTE in medical patients is about 10% to 20% in the absence of prophylaxis.[32] In a prospective placebo-controlled trial using bilateral leg venographic end points, Samama et al[34] documented a 15% incidence of DVT in the placebo group, with 5% of events being proximal in origin. In univariate analysis, cancer conferred a relative risk of 1.74 (95% CI, 1.13 to 2.68) for development of thrombotic events. A multivariate logistic regression model showed that the odds ratio for VTE in cancer patients was 1.62 (95% CI, 0.93 to 2.75).[35]

The recommendation for VTE prophylaxis in hospitalized medical patients with cancer is either escalated UFH 5,000 U every 8 hours or LMWH (enoxaparin 40 mg or dalteparin 5,000 IU) once daily until discharge **(Table 4)**. Recently the pentasaccharide fondaparinux (2.5 mg daily) was also shown to be effective and safe, relative to placebo, for prevention of VTE in 849 acutely ill medical patients.[36] The degree to which cancer patients were represented in this study has not yet been reported, but fondaparinux may be a reasonable alternative in this setting, based on proven efficacy in other high-risk groups, such as arthroplasty patients.

The optimal duration of prophylaxis in the medically ill patient is currently being studied, yet data from surgical trials suggest that extended out-of-hospital prophylaxis may also be appropriate for this patient group.

Treatment of acute VTE in cancer patients

Treatment of acute VTE in patients with malignancy should include weight-based UFH or weight-adjusted LMWH with concomitant warfarin. Either UFH or LMWH should be maintained until the INR is between 2.0 and 3.0 for 2 consecutive days. Strong consideration should be given, however, to continuing LMWH for at least the first 3 to 6 months of long-term anticoagulation.[37,38] This recommendation is based on warfarin's high reported failure rate in cancer patients and on evidence that LMWHs are more efficacious in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding.[38,39] LMWHs may also provide a mortality advantage in this popula-

tion.[39] Therefore, LMWH can be used alone to treat VTE in cancer patients, but since the cost of LMWH may not be covered by insurance providers, it may be more practical to bridge patients to warfarin (INR 2.0 to 3.0) indefinitely or until the cancer has resolved.

SUMMARY

Optimal dosing of LMWH has not yet been established for patients with morbid obesity or renal insufficiency or for pregnant women. Monitoring of anti-Xa levels may be warranted and helpful in all of these special groups. Use of fondaparinux in these special populations has yet to be defined, given that there is currently no measure of its biologic activity. Cancer patients are at especially high risk of VTE and its complications and therefore generally require escalated and prolonged anticoagulation and more intense monitoring of therapy.

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Cost considerations surrounding current and future anticoagulant therapies

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ABSTRACT

Because the costs of anticoagulation therapy are substantial and the difference between the risks and benefits of this therapy are often narrow, economic analyses are particularly valuable when weighing anticoagulation options. Economic analyses to date suggest that anticoagulation is most effective and results in the greatest cost savings when applied to populations at highest risk for thrombotic events. They also suggest that in situations where a more costly anticoagulant agent is available, that agent is cost-effective only if it is clearly more efficacious or if it substantially reduces costs in other areas, such as hospitalization. These principles should guide clinicians' choices of anticoagulation strategies.

Economic analyses are particularly important in anticoagulation because the difference between the risks and benefits of therapy can be quite narrow in relative terms, and because the costs of therapy are substantial, especially since therapy may be required for the rest of a patient's life.

For these reasons, standardized, systematic analyses that compare the risks, benefits, and costs of therapy can be valuable for the appropriate selection and use of anticoagulant medications. Empiric methods for comparing anticoagulation strategies will become even more relevant as new and equally effective but more costly anticoagulants become available.

This article addresses cost considerations for several common uses of anticoagulant drugs—the prevention of stroke in patients with nonvalvular atrial fibrillation and the treatment and prevention of venous thromboembolism. We also explore the evidence supporting differing systems for anticoagulation management and discuss cost-effectiveness considerations for new anticoagulant drugs.

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OVERVIEW OF ECONOMIC ANALYSES

Economic analyses help to prioritize health care decisions made at the *societal level*,[1] a perspective that is critical when considering anticoagulants, given the large numbers of patients potentially affected. In addition, the costs for anticoagulants are often borne by society (eg, via Medicare), making empiric comparison of costs and outcomes critically important. We suggest that readers gauge the quality and applicability of economic analyses to their individual practice using several simple questions outlined below and expanded in **Table 1**.[2]

Was the analysis explained clearly?

Economic models cannot account for individual patients' clinical situations but instead apply to "average" patients; thus, it is important to identify the assumptions on which the models are based. Assumptions should be clearly explained and represent accepted standards of practice.

Did the authors use the most broadly representative data available?

Examples of data sources include population-based trials or publicly available sources such as Medicare cost data; these data provide more useful estimates of effectiveness and cost than data from smaller studies and allow cross-comparability of findings across different regions or health care systems.

What kind of economic analysis was performed?

Cost-effectiveness analyses quantify effectiveness using quality-adjusted life-years (QALYs), which range from 0 (dead) to 1 (perfect health). The QALY weight for a year on warfarin therapy is surprisingly high (0.987, or 1.3% less than perfect health).[3,4] A high QALY weight for warfarin therapy is consistent with studies suggesting that patients rate quality of

TABLE 1
Elements of economic analyses that should guide decisions about anticoagulation

Does the analysis. . .	Points relevant to anticoagulation decisions
Clearly describe its patient population?	What were the characteristics of the hypothetical cohort in terms of age, indication for anticoagulation, and risks for benefits/adverse outcomes of therapy?
Compare strategies that are both effective and broadly acceptable in practice?	Strategies that are not considered effective or do not represent standard practice are not appropriate for economic analyses
Clearly explain its assumptions?	While simplifying assumptions is often necessary, assure yourself that the scenario studied would be reproducible in your clinic
Maintain a societal perspective?	Analyses that use data from small or single-site studies limit the generalizability of the results; population-derived data provide more stable and broadly useful information
Express results in quality-adjusted life-years (QALYs) (cost-effectiveness analysis) or costs per event (cost-benefit analysis)?	QALYs are a standard metric of effectiveness that allows for explicit comparisons of events that may have different clinical impact (eg, cerebral hemorrhage vs minor bleeding events)
Calculate incremental cost-effectiveness ratios (ICERs)?	ICERs using QALYs provide an estimate of how much more money it will cost to preserve one additional life at perfect health. ICERs using the costs required to prevent an event can be useful but do not include the potential differing impact of events.
Perform sensitivity analyses to test uncertainty in the source data and assumptions?	Sensitivity analyses provide a sense of which clinical variables influence cost-effectiveness most powerfully; these analyses provide data that clinicians can apply to patients more broadly

life on warfarin highly, and higher than their physicians do.[5–7] From a societal perspective, it is consistent with preference for avoiding stroke with permanent sequelae (eg, QALY weight = 0.6).[3,4]

Cost-benefit analyses, in contrast, express effectiveness in terms of the cost incurred per event (either prevented or caused by therapy). Cost-benefit analyses do not balance preferences for specific disease states (eg, intracranial hemorrhage and minor bleeding events are treated equally) and do not account for the impact of events that happen at different ages (eg, a paralyzing stroke at age 30 is equivalent to a death at age 90).

Were incremental cost-effectiveness ratios used to compare strategies?

When two therapies are being compared, the relevant metric is the incremental cost-effectiveness, ie, the additional costs incurred to achieve another year of perfect health (cost-effectiveness analyses) or to avert an adverse event (cost-benefit analyses). In cost-effectiveness analyses, incremental costs less than $50,000 per QALY gained are considered low cost, those between $50,000 and $100,000 per QALY gained are considered intermediate cost, and those greater than $100,000 per QALY gained are considered high cost. There are no standards for evaluating incremental cost-effectiveness ratios calculated in cost-benefit analyses; the relative value of events and costs in these analyses are left to readers to interpret.

Were sensitivity analyses done to test uncertainty in the model, its data inputs, or its assumptions?

Sensitivity analyses test the results by inputting broad ranges of key variables, thereby providing insight into how differing assumptions (or the use of estimates of risk/benefit from different trials) can influence the study's conclusions.

ANTICOAGULATION IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

Cost-effectiveness analyses are particularly appropriate for helping clinicians decide on optimal strategies to prevent stroke in patients with nonvalvular atrial fibrillation (AF), given that AF patients are generally older and at higher risk for adverse events related to therapy or to AF itself. In addition, treatment is generally lifelong, with patients exposed to the risks, benefits, and costs of treatment for longer periods of time.

Several authors have examined the cost-effectiveness of anticoagulation for prevention of stroke in patients with AF.[8–13]

Gage et al[9] compared warfarin, aspirin, and no therapy in a hypothetical cohort of 65-year-olds with chronic AF. For high-risk patients (those with an annual stroke rate of 4.9% to 17.6%), warfarin was both more effective and more cost-saving than either aspirin or no therapy. Among patients at medium risk (annual stroke rate of 2.6% to 4.6%), warfarin was better than aspirin in terms of quality-adjusted survival but cost more than aspirin, incurring an additional $8,000 per QALY saved. For patients at low risk of stroke, warfarin and aspirin were comparable in terms of quality-adjusted survival (and both were better than no therapy), but warfarin cost an additional $370,000 per QALY saved in the base case. The incremental costs of warfarin would be even higher if aspirin produced more than a 22% reduction in stroke risk, if hemorrhage rates on warfarin therapy were substantially higher than reported in randomized trial settings, or if warfarin resulted in greater disutility than the authors' base case assumptions.

Thomson et al[13] conducted a decision analysis to advise clinicians about appropriate treatment for AF by modeling various combinations of risk factors among people with AF using data inputs from a rigorous systematic review of the literature. Comparing only warfarin and no therapy, the results were consistent with those of Gage et al[9] in that warfarin led to both QALY gains and lower costs compared with no therapy in patients at high stroke risk, such as those with three or more stroke risk factors, and for most other combinations of risk factors. Again, this model was particularly sensitive to changes in patient quality of life on warfarin.

How does age affect cost-effectiveness?

Cost-effectiveness analyses have also examined how age influences the cost-effectiveness of anticoagulation. Desbiens[8] evaluated the costs of anticoagulation for AF and its impact on quality of life in older patients (up to age 100 years), comparing warfarin with no therapy. Despite assuming annual intracranial hemorrhage rates of 5.0% for patients aged 100 years, the analysis showed that warfarin resulted in improved quality-adjusted survival even among the "oldest old" who possessed significant risk factors for stroke. Warfarin led to worse or equivocal outcomes in younger patients and in older patients with fewer stroke risk factors. Notably, this study assumed fairly high rates of intracranial hemorrhage among older patients and acknowledged the need for more precise data on hemorrhagic complications and AF outcomes among the oldest old.

Conclusions

Studies of the cost-effectiveness of anticoagulation in patients with AF consistently suggest that warfarin improves quality-adjusted survival and reduces costs in patients at high risk for stroke; in patients at low risk for stroke, aspirin is a cost-effective alternative. For patients at moderate stroke risk, warfarin continues to be a cost-effective therapy compared with aspirin. Cost-effectiveness analyses of anticoagulation for AF in older patients are supported by fewer data, particularly because there are few studies of the risks and benefits of warfarin in the very old. However, warfarin does appear to be generally cost-effective in older patients because they are often at high risk for stroke. Notably, these studies were based on assumptions that strokes occurring on and off warfarin therapy result in equivalent decrements in quality of life and cost. Recent evidence suggesting that strokes that occur during warfarin therapy result in lower morbidity and mortality than those occurring off warfarin[14] would further tilt the balance in warfarin's favor.

ANTICOAGULATION FOR PREVENTION OF VENOUS THROMBOEMBOLISM

Surgical patients

Cost-effectiveness analyses of strategies for the prevention of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), in surgical patients have largely focused on warfarin and low-molecular-weight heparins (LMWHs) such as enoxaparin, as well as synthetic pentasaccharides such as fondaparinux. Cost-effectiveness analyses are particularly relevant in these cases because LMWHs are far more expensive but only slightly more effective than warfarin.

LMWH vs warfarin. Several published decision analyses of short-term prophylaxis (4 to 15 days) examining enoxaparin suggest that this balance is in enoxaparin's favor. One study suggested that the expected cost per VTE event avoided was $2,525 less and $87,201 less with enoxaparin than with warfarin for each DVT and PE prevented, respectively.[15] A cost-effectiveness analysis by Garcia-Zozaya[16] found that the overall cost of care for 15 days of prophylactic therapy in joint replacement patients was slightly lower with enoxaparin than with warfarin ($925 vs $972), but these results were not reported in QALYs or in cost-benefit terms. A recent cost-effectiveness analysis comparing 7 days of prophylaxis with warfarin 5 mg daily or enoxaparin 30 mg twice daily in hypothetical US patients undergoing hip replacement suggested that enoxaparin was associated with an incremental cost of $3,733 per QALY saved if only

short-term outcomes were considered.[17] When long-term complications were included, enoxaparin was both less expensive and more effective than warfarin ($89 lower costs per patient with net QALY benefits of 0.16 per patient).

Fondaparinux vs LMWH. A number of decision analyses have compared fondaparinux and enoxaparin for VTE prevention in the orthopedic population. A recent Canadian decision analysis[18] found that the use of fondaparinux in patients undergoing hip or knee surgery would prevent an additional 16 VTE events per 1,000 patients compared with enoxaparin, resulting in a cost savings of $55 (Canadian dollars) per patient. A cost-effectiveness analysis by Spruill et al[19] suggested that prophylactic fondaparinux resulted in an incremental cost savings of $1,081 per VTE event avoided compared with enoxaparin 30 mg twice daily; the incremental cost per life-year gained was $5,437 for enoxaparin and $4,925 for fondaparinux. Another decision analysis in joint replacement and hip fracture patients concluded that fondaparinux would be less costly overall than enoxaparin, largely owing to fewer VTE events and fewer VTE-related deaths.[20]

Prolonged prophylaxis. Recent recommendations from the American College of Chest Physicians[21] add yet another wrinkle to VTE prevention in surgical patients by advising prolonged VTE prophylaxis (28 to 35 days) in patients undergoing hip surgery. Sarasin et al[22] used a decision analysis to evaluate this strategy in patients undergoing hip replacement. Among patients without increased bleeding risks, extending prophylaxis with warfarin, LMWH, or aspirin to 4 weeks after discharge was cost-effective. LMWH was the most clinically effective regimen, and aspirin was the most cost-effective. The results of this analysis were most sensitive to the bleeding complication rate.

Medical patients

Although VTE prophylaxis in medical patients has gained prominence only recently, it has been the subject of a number of decision analyses. Four separate cost-benefit analyses suggest that, compared with aspirin or no therapy, LMWHs prevent VTE at reasonable additional cost;[23–26] those analyses conducted in North America suggest that the incremental cost to avoid a VTE ranges from $87 to $3,088. One cost-effectiveness analysis suggested that, compared with no prophylaxis, the incremental cost to avert a VTE-related death with enoxaparin 40 mg daily was $9,100.[27] In this analysis, enoxaparin was more cost-effective than unfractionated heparin 5,000 U twice daily because of greater efficacy and reduced costs of complications.

Conclusions

Most of the evidence for the cost-effectiveness of VTE prevention in surgical patients has focused on orthopedic patients, in whom enoxaparin appears to be more cost-effective than warfarin. In these same patients, fondaparinux appears to prevent VTE at a reasonably low cost, but there are few data to describe the effectiveness of fondaparinux in terms of QALYs. For prolonged prophylaxis in surgical patients, fondaparinux appears to be less costly and more effective than enoxaparin; again, these results are based more on cost-benefit methods than on QALY-based cost-effectiveness analysis.

Although LMWHs are less well studied in medical patients than in surgical patients, they appear to have similar advantages when used for VTE prevention in medical patients, where their higher costs relative to aspirin and unfractionated heparin are offset by cost savings due to VTE events averted.

ANTICOAGULATION FOR ACUTE MANAGEMENT OF VENOUS THROMBOEMBOLISM

The initial treatment of VTE is now dominated by anticoagulants that can be given subcutaneously and do not require laboratory monitoring—specifically, enoxaparin and fondaparinux. Use of these drugs has moved VTE treatment to the outpatient setting, avoiding the costs of lengthy hospital stays. A cost-effectiveness analysis by Gould et al[28] found that an enoxaparin-based approach is quite cost-effective when compared with usual (ie, inpatient) care with unfractionated heparin, incurring an incremental cost of $7,280 per QALY gained.

There are currently no data available for evaluating the cost-effectiveness of fondaparinux relative to enoxaparin for acute VTE treatment.

Conclusions

LMWH therapy is more expensive than older therapies but is more cost-effective, almost entirely because it obviates the need for prolonged hospital admission, not because of improved effectiveness.

ANTICOAGULATION FOR CHRONIC MANAGEMENT OF VENOUS THROMBOEMBOLISM

Recurrence of VTE is common, particularly among patients with idiopathic thromboses or predisposing hypercoagulable conditions. While longer courses of anticoagulation reduce recurrence, they also increase the costs of therapy and monitoring. In addition, patients with indications for lifelong anticoagulation (such as those with certain prothrombotic disorders)

TABLE 2
Summary of economic analyses of anticoagulation

Indication	Summary of evidence
Stroke prevention in patients with nonvalvular atrial fibrillation (AF)	Compared with aspirin, warfarin is cost-effective at an incremental cost of < $100,000 per QALY gained in patients at high and moderate risk for AF-related stroke. Warfarin is not as cost-effective in patients at low risk for AF-related stroke.
Prevention of venous thromboembolism	• *Surgical patients:* Enoxaparin is superior to unfractionated heparin for prophylaxis (incremental cost < $100,000 per QALY gained) in orthopedic surgical patients; fondaparinux is potentially cost-saving vs enoxaparin for short-term prophylaxis. For prolonged prophylaxis, use of any agent is cost-effective relative to usual care; enoxaparin may prevent additional events at reasonable cost. • *Medical patients:* Enoxaparin is superior to unfractionated heparin in high-risk medical patients
Acute treatment of venous thromboembolism	Enoxaparin is cost-effective relative to usual care, largely due to avoidance of hospital costs
Secondary prevention of venous thromboembolism	Little data to support cost-effectiveness of any anticoagulation approach; strategies that use warfarin in patients at highest risk for recurrence appear to be cost-effective
Anticoagulation management strategies (clinics, patient self-testing)	Mixed results—likely fewer emergency visits with anticoagulation clinics, but effectiveness of other strategies is sensitive to uncertainty in efficacy data

QALY = quality-adjusted life-year

tend to be younger, exposing them to risk for therapy-related adverse events for a longer time than patients with AF, for example. Once the decision is made to embark on long-term anticoagulation, warfarin remains standard therapy, as other options (eg, heparin pumps, LMWHs) are supported by too few data to allow cost-effectiveness analysis. The few studies examining secondary prevention suggest that the risk-benefit ratio of long-term warfarin therapy in these patients is influenced primarily by the baseline risk of VTE recurrence and lifetime risk for adverse events, and that long-term anticoagulation is less effective (and cost-effective) in patients at low risk for recurrence.[29,30]

ANTICOAGULATION CLINICS AND COST

Strategies for long-term oral anticoagulation management, such as the establishment of anticoagulation clinics or patient self-testing with home capillary blood monitors, are attractive options because they reduce patients' need for repeated clinic visits or hospitalizations. As such, they have been the subject of several economic analyses.

Chiquette et al[31] compared hospitalization and emergency department costs of hypothetical patients in an anticoagulation clinic with anticoagulated patients receiving usual medical care and found that anticoagulation clinics saved $1,620 per patient per year, largely owing to fewer hemorrhages and thromboembolic events. This study did not report results in terms of QALYs or the incremental cost of managing an anticoagulation clinic.

Another analysis compared usual care, care in an anticoagulation clinic, and patient self-testing; it assumed that patients would be in therapeutic international normalized ratio (INR) range 50% of the time with usual care, 65% of the time with anticoagulation clinic care, and 89% of the time with self-testing.[32] Using these assumptions, the authors calculated the anticipated number of hemorrhages and thromboembolic events and also tabulated costs from the patient, provider, and societal perspectives. Not surprisingly, costs in this study were highly sensitive to the perspective chosen and the type of costs included in the model (eg, direct medical costs only, or inclusion of indirect costs of traveling to clinic appointments). For instance, changing from usual care to an anticoagulation clinic was cost-saving from the individual provider perspective but shifted costs to the patient; changing to patient self-testing was cost-effective from the individual patient perspective because it reduced clinic visits and indirect costs. In general, more definitive data on outcomes associated with each strategy are needed before valid cost comparisons can be made.

INVESTIGATIONAL ANTICOAGULANTS

The orally administered direct thrombin inhibitor ximelagatran has been studied as an alternative to warfarin for several indications, notably stroke pre-

vention in patients with AF, chronic VTE treatment, and postoperative prevention of VTE.[33,34] Ximelagatran has substantial potential advantages over warfarin in that it does not require INR monitoring, has no known interactions with drugs metabolized via the cytochrome P450 isoenzyme, and produces reliable anticoagulation at fixed doses.

However, the US Food and Drug Administration has not approved the use of ximelagatran because of concerns about liver toxicity and coronary events. Even if eventually approved, ximelagatran is unlikely to be cost-effective compared with warfarin for most patients with AF. The exceptions may be patients who have low quality of life with warfarin therapy and those whose intracranial hemorrhage rates are lower on ximelagatran than on warfarin.[35] However, current cost-effectiveness analyses are limited by the lack of longer follow-up studies detailing the incidence of adverse events on ximelagatran therapy.

SUMMARY AND IMPLICATIONS

Results from a variety of economic analyses (summarized in **Table 2**) of anticoagulation for various indications suggest a couple of general themes:

- Anticoagulation is most effective and results in the greatest cost savings when applied to populations at highest risk for thrombotic events, a consistent finding in studies examining anticoagulation for nonvalvular AF.
- In situations where a more costly agent is available (eg, enoxaparin vs unfractionated heparin), the more costly agent is cost-effective only if it is truly more efficacious or if it can substantially reduce costs in other areas, such as by avoiding hospitalizations for treatment of VTE.

As newer anticoagulant agents become available, clinicians should consider these themes to maximize the cost-effectiveness of their anticoagulation strategies.

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