Outpatient Management of Anticoagulation Therapy

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The Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy provides guidelines for outpatient management of anticoagulation therapy. The ACCP guidelines recommend short-term warfarin therapy, with the goal of maintaining an International Normalized Ratio (INR) of 2.5 ± 0.5, after major orthopedic surgery. Therapy for venous thromboembolism includes an INR of 2.5 ± 0.5, with the length of therapy determined by associated conditions. For patients with atrial fibrillation, the INR is maintained at 2.5 ± 0.5 indefinitely; for most patients with mechanical valves, the recommended INR is 3.0 ± 0.5 indefinitely. Use of outpatient low-molecular-weight heparin (LMWH) is as safe and effective as inpatient unfractionated heparin for treatment of venous thromboembolism. The ACCP recommends starting warfarin with unfractionated heparin or LMWH for at least five days and continuing until a therapeutic INR is achieved. Because patients with venous thromboembolism and cancer who have been treated with LMWH have a survival advantage that extends beyond their venous thromboembolism treatment, the ACCP recommends beginning their therapy with three to six months of LMWH. When invasive procedures require the interruption of oral anticoagulation therapy, recommendations for bridge therapy are determined by balancing the risk of bleeding against the risk of thromboembolism. Patients at higher risk of thromboembolization should stop warfarin therapy four to five days before surgery and start LMWH or unfractionated heparin two to three days before surgery. (Am Fam Physician 2007;75:1031-42.

Warfarin (Coumadin), unfractionated heparin, and low-molecular-weight heparins (LMWHs) are used for the treatment of venous thromboembolism (VTE), the prevention of systemic embolism associated with atrial fibrillation or the use of prosthetic heart valves, and the prevention of stroke and recurrent myocardial infarction in select patients.[1] The LMWHs have changed the course of outpatient anticoagulation therapy because patients no longer need to remain hospitalized for the initiation of oral therapy in acute VTE or for bridge therapy when undergoing invasive procedures that require temporary discontinuation of warfarin.

This article focuses on indications for warfarin and LMWH therapy, how to initiate therapy, therapeutic goals, troubleshooting common issues, and duration of therapy. Many of the recommendations are derived from a recent evidence-based practice guideline from the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy.[1-9]

Warfarin

MECHANISM OF ACTION

Warfarin interferes with the cyclic interconversion of vitamin K and vitamin K epoxide and subsequent modulation of the gamma carboxylation of the terminal regions of vitamin K proteins. This results in the reduction of clotting factors II, VII, IX, and X.[1] Carboxylation of the regulatory anticoagulant proteins C and S also is inhibited, potentially contributing to a procoagulant effect early in therapy.

Reduction of the clotting factors II, VII, and X is measured using the prothrombin time.[1] Because of interlaboratory variability in the thromboplastins used to measure the prothrombin time, use of the International Normalized Ratio (INR) has become the standard of practice, making values obtained from various laboratories comparable.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Warfarin (Coumadin) therapy should be initiated using validated 5-mg and 10-mg nomograms.	B	14
Outpatient LMWH is as safe and effective as inpatient unfractionated heparin for treatment of venous thromboembolism in most patients.	A	2
For treatment of acute deep venous thrombosis and pulmonary embolism, warfarin should be started with unfractionated heparin or LMWH for at least five days and until a therapeutic International Normalized Ratio (2.5 ± 0.5) is achieved.	A	2
For patients at higher risk of thromboembolism, invasive procedures requiring the interruption of anticoagulation therapy can be managed on an outpatient basis with LMWH.	C	1, 23
When determining whether to use bridge therapy, the risk of bleeding should be balanced against the risk of thromboembolism.	C	1, 22-26
Before invasive procedures, patients at high risk for thromboembolization should stop warfarin therapy four to five days preoperatively and start LMWH or unfractionated heparin two to three days before surgery. Warfarin and heparin are restarted postoperatively once hemostasis has been achieved.	C	1, 22, 23

LMWH = low-molecular-weight heparin.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 957 or http://www.aafp.org/afpsort.xml.

DRUG, FOOD, AND DISEASE-STATE INTERACTIONS

Medications, foods, and disease states can potentiate or inhibit the effects of warfarin *(Table 1*[1,10]*)*. Some of these interactions, such as those observed with metronidazole (Flagyl) and trimethoprim/sulfamethoxazole (Bactrim, Septra), occur via inhibition of warfarin metabolism. Amiodarone (Cordarone) potentiates the effects of warfarin and, because of the long half-life (i.e., 61 days) of its active metabolite, requires close monitoring of INR whenever this agent is added to or deleted from a warfarin regimen.

Other interactions, such as those observed with barbiturates, carbamazepine (Tegretol), and rifampin (Rifadin), occur when warfarin's hepatic metabolism is induced, resulting in less free, active warfarin and potentially increasing the required dosage. Alternatively, thyroid replacement medications such as levothyroxine may increase the metabolism of coagulation factors, reducing the amount of warfarin required.[1] The interaction observed with salicylates and nonsteroidal anti-inflammatory drugs is that of increased warfarin-associated bleeding via their inhibition of platelet activity and contribution to gastric erosion.

Most foods that affect the anticoagulant effect of warfarin are high in vitamin K. It is important that patients know they do not need to avoid these foods; rather, they may eat them in moderation, avoiding large fluctuations in intake that will lead to marked variation in INR results. A number of herbal medications, most commonly ginkgo, also affect the stability of warfarin therapy and may reduce the required dosage *(Table 1*[1,10]*)*.

Certain types of cancer, worsening or acute heart failure, hyper- and hypothyroidism, and liver disease may impact the expected therapeutic outcomes of warfarin. Hepatic congestion can reduce the metabolism of warfarin, resulting in higher levels of free, active warfarin. Hyperthyroidism increases the metabolism of coagulation factors, enhancing the effects of warfarin.[1]

INDICATIONS, GOALS, AND DURATION OF THERAPY

A variety of indications, therapeutic goals, and recommended durations of therapy exist for the use of warfarin. The ACCP publication addresses these issues in detail, and they are summarized in *Table 2*.[2,3,5,7,8]

DOSING

Two recent studies compared nomograms that initiate warfarin therapy with 5 or 10 mg.[11,12] In one study, the 5-mg initial dose helped patients more rapidly achieve a therapeutic level,[11] whereas the other study showed the 10-mg initial dose to be superior.[12] Because of differences between these studies, such as age and inpatient versus outpatient management,[13] either nomogram may be appropriate depending on the situation. In the older patient with atrial fibrillation, it may be appropriate to initiate warfarin in a dosage of 5 mg daily. However, for a younger patient being treated with LMWH for VTE,

initiating warfarin at a dosage of 10 mg daily may be preferred. An article in *AFP* presented these nomograms in a form easily applied in the primary care setting.[14]

INR monitoring does not occur until after the initial two or three doses of warfarin.[1] Although the ACCP recommendations are not specific about the frequency of monitoring, it is generally acceptable for patients to be monitored initially twice per week, then weekly, then every two to three weeks, and then monthly. The decision to extend future visits from, for example, weekly to every two weeks, is made when the patient's dosage and INR remain stable and therapeutic. Even when stable for long periods, the INR should continue to be monitored at least monthly.[1]

When the INR is not within the therapeutic range, attempts should be made to determine the cause. Adjustments to the dosage are typically a 5 to 20 percent increase or decrease in total weekly dosage. To improve patient adherence, the weekly regimen is kept as simple as possible. Supratherapeutic INRs may require that the dosage be withheld temporarily and, occasionally, that vitamin K be administered. A Point-of-Care Guide from *AFP* provides a tool to help physicians systematically monitor the INR and adjust warfarin dosages.[15]

Heparin

PHARMACOLOGY AND DOSING OF UNFRACTIONATED HEPARIN

Unfractionated heparin is a heterogeneous mixture of glycosaminoglycans with molecular weights ranging from 3,000 to 30,000 daltons with a mean molecular weight of 15,000 daltons.[6] It binds to antithrombin III in plasma by way of a pentasaccharide, and this catalyzes the inactivation of thrombin and other clotting factors.[6]

Use of unfractionated heparin requires careful monitoring because of its unpredictable anticoagulant effect.[6] Peak plasma activity occurs two to three hours after parenteral administration, and protocols for dosing and

Table 1. Warfarin (Coumadin) Interactions: Drugs, Herbs, and Food

Increase potency of warfarin		*Decrease potency of warfarin*
Drugs		**Drugs**
Acetaminophen	Propoxyphene (Darvon)	Azathioprine (Imuran)
Alcohol (if concomitant liver disease)	Quinidine	Barbiturates
Amiodarone (Cordarone)	Salicylates	Carbamazepine (Tegretol)
Anabolic steroids	Tamoxifen (Nolvadex)	Cholestyramine (Questran)
Cimetidine (Tagamet)	Tetracycline	Cyclosporine (Sandimmune)
Ciprofloxacin (Cipro)	Thyroxine	Dicloxacillin (Dynapen)
Disulfiram (Antabuse)	Trimethoprim/sulfamethoxazole (Bactrim, Septra)	Griseofulvin (Grisactin)
Erythromycin	**Herbal products**	Nafcillin
Fluconazole (Diflucan)	Danshen	Rifampin (Rifadin)
Influenza vaccine	Devil's claw	Sucralfate (Carafate)
Isoniazid (Nydrazid)	Dong quai	Trazodone (Desyrel)
Itraconazole (Sporanox)	Garlic	**Foods**
Lovastatin (Mevacor)	Ginkgo	Avocados (large amounts)
Metronidazole (Flagyl)	Papain	Enteral feeds with high vitamin K content
Miconazole (Monistat)	Vitamin E	Foods with high vitamin K content, such as broccoli, brussel sprouts, cabbage, collard greens, raw endive, kale, bib leaf and red leaf lettuce, mayonnaise, mustard greens, parsley, spinach, raw swiss chard, raw turnip greens, watercress
Nonsteroidal anti-inflammatory drugs		Green tea
Norfloxacin (Noroxin)		**Herbal products**
Ofloxacin (Floxin)		Coenzyme Q10
Omeprazole (Prilosec)		Ginseng
Phenytoin (Dilantin)		St. John's wort
Propafenone (Rythmol)		
Propranolol (Inderal)		

Information from references 1 and 10.

Table 2. Warfarin (Coumadin) Therapy: Indications, Goals, and Duration of Therapy

Indication for therapy	*Therapeutic INR goal* (recommendation grade if noted)*	*Duration of therapy (recommendation grade if noted)*
Prevention of venous thromboembolism[3]		
Orthopedic surgery		
Elective total hip replacement	2.5 (1A)	28 to 35 days (1A)
Elective total knee arthroplasty	2.5 (1A)	At least 10 days (1A)
Hip fracture surgery	2.5 (2B)	28 to 35 days (1C+)
Venous thromboembolic disease and pulmonary embolism[2]		
Deep venous thrombosis of the leg or pulmonary embolism†	2.5 (1A)	First episode secondary to reversible risk factor(s): three months (1A) First episode idiopathic: six to 12 months (1A); consider indefinite use (2A) In patients with cancer: LMWH for three to six months, then warfarin indefinitely (1C) In patients with antiphospholipid antibody *or* who have two or more thrombophilic conditions: 12 months (1C+); indefinite (2C) In patients with a deficiency of antithrombin or proteins C or S, gene mutation for factor V Leiden or prothrombin 2010, homocystinemia, or high factor VIII levels: six to 12 months (1A); indefinite (2C) Two episodes of objectively documented events: indefinite (1A)
Atrial fibrillation[8]		
High risk of stroke‡	2.5 (1A)	Indefinite
Persistent or paroxysmal atrial fibrillation§	2.5 (1A)	Indefinite
Atrial flutter	2.5 (1A)	Indefinite
Elective cardioversion	2.5 (1A)	Three weeks before; four weeks after conversion (1C+)

Table 2 continues

monitoring recommend testing every six hours to maintain the activated partial thromboplastin time (aPTT) in a range of 1.5 to 2.5 times normal.[6] Because of variability in the reagents used to check the aPTT, the ACCP recommends performing site-specific validation of the therapeutic range of aPTTs to monitor heparin dosing.[6] Dosing information is provided in *Table 3*.[16]

The adverse effects of unfractionated heparin include heparin-induced thrombocytopenia, a syndrome characterized by low platelet counts and a paradoxically hypercoagulable state. With long-term use, osteopenia may occur.[6] The anticoagulation effects of unfractionated heparin are reversed rapidly with protamine. The usual dose for heparin reversal is 1 mg of protamine to 100 U of unfractionated heparin.[6]

PHARMACOLOGY AND DOSING OF LMWH

LMWHs are heparin fragments with a mean molecular weights of 4,000 to 5,000 daltons (range: 2,000 to 9,000 daltons).[6] These smaller fragments do not bind well to plasma proteins, leading to a more predictable anticoagulant effect.[6] They also bind less effectively to macrophages and endothelial cells and, therefore, have a longer plasma half-life[6]; their peak plasma activity occurs three to five hours after subcutaneous injection.[6] Because LMWHs are cleared renally, their half-life is lengthened in patients with renal failure.[6] With the exception of severely obese patients (i.e., those whose total body weight is more than 330 lb [149.7 kg]) and those with renal failure, most patients receiving LMWHs do not require laboratory monitoring.[6] When monitoring is necessary, anti-factor Xa levels are measured four hours after injection.[6]

If the anticoagulation effects of LMWH urgently need to be reversed, protamine is given in a dose of 1 mg per 100 anti-factor Xa units (1 mg enoxaparin [Lovenox] equals 100 anti-factor Xa units).[6] However, protamine does not effect a complete reversal.

TREATMENT OF DEEP VENOUS THROMBOSIS AND NONMASSIVE PULMONARY EMBOLISM USING LMWH

The use of outpatient LMWH is as safe and effective as inpatient unfractionated heparin for treatment of

Table 2 *(continued)*

Indication for therapy	*Therapeutic INR goal* (recommendation grade if noted)*	*Duration of therapy (recommendation grade if noted)*
Valvular heart disease[7]		
Rheumatic mitral valve disease with atrial fibrillation or a history of systemic embolism	2.5 (1C+)	Long-term (1C+)
Patients undergoing mitral valvuloplasty	2.5 (2C)	Three weeks before and four weeks after (2C)
Mechanical prosthetic heart valves		
St. Jude Medical bileaflet in aortic position	2.5 (1A)	Long-term
Valve in mitral position	3.0 (1C+)	Long-term
Carbomedics bileaflet or Medtronic Hall tilting disk mechanical valves in the aortic position	2.5 (1C+)	Long-term
Ball/cage	3.0 with aspirin (2A)	Long-term
Mechanical valves *plus* an additional risk factor such as atrial fibrillation, myocardial infarction, left atrial enlargement, low ejection fraction	3.0 (1C+)	Long-term
Bioprosthetic valves	2.5	Three months (1C+)
Coronary heart disease[5]		
Patients with access to meticulous and routinely accessible INR monitoring	2.5 with aspirin (2B), 3.5 without aspirin (2B)	Long-term (up to four years)
High-risk patients‖ with myocardial infarction	2.0 to 3.0 with aspirin (2A)	Three months (2A)

INR = International Normalized Ratio; LMWH = low-molecular-weight heparin; RCT = randomized controlled trial.

Grade 1 = high certainty that benefits do, or do not, outweigh risks, burdens, and costs; grade 2 = less certainty that benefits do, or do not, outweigh risks, burdens, and costs; grade A = RCTs with consistent results; grade B = RCTs with inconsistent results or with major methodologic weaknesses; grade C = other observational and clinical trial evidence.

**—Therapeutic INR range = therapeutic goal ± 0.5.*

†*—Recommendation is to start warfarin therapy on the first treatment day with LMWH or unfractionated heparin (grade 1A).*

‡*—Defined as previous ischemic stroke, transient ischemic attack, systemic embolism; age older than 75 years; impaired left ventricular systolic function and/or congestive heart failure; history of hypertension or diabetes.*

§*—In patients 65 to 75 years of age without other risk factors; of note, aspirin (325 mg) is an acceptable alternative in this population (grade 1A).*

‖*—Patients with large anterior wall myocardial infarction, significant heart failure, intracardiac thrombus visible on echocardiography, history of thromboembolic event.*

acute VTE.[2,17] Its use decreases the need for patient hospitalization. In one meta-analysis, LMWH decreased overall mortality compared with unfractionated heparin, mainly because of reduced mortality in patients with cancer.[17] The likelihood of recurrent VTE, pulmonary embolism, major bleeding, minor bleeding, and thrombocytopenia was similar between LMWH and unfractionated heparin.[17] Once- versus twice-daily dosing of LMWH were compared with each other and with unfractionated heparin; no differences in clinical outcomes were noted among the three groups.[17] The ACCP recommends the use of LMWH once or twice daily with consideration of twice-daily dosing in patients with cancer.[2] A comparison of five LMWHs also failed to identify any significant differences.[17] *Table 3* describes available LMWHs and appropriate therapeutic and prophylactic dosing.[16]

Treatment of VTE *(Table 4[2,14])* is initiated with LMWH and warfarin, and patients who are stable are discharged directly from the emergency department or primary care setting (if adequate teaching and follow-up can be

Table 3. Anticoagulants: Dosages and Indications

Anticoagulant	*Prophylactic dosage*	*Therapeutic dosage*	*FDA-approved prophylactic conditions*
Warfarin (Coumadin)	Usual maintenance: 2 to 10 mg daily	Usual maintenance: 2 to 10 mg daily	See Table 2
Unfractionated heparin	5,000 U every eight to 12 hours	For DVT, start with 80 U per kg bolus, then 18 U per kg per hour infusion	Prophylaxis for patients at risk of developing DVT and PE Prophylaxis of peripheral artery embolization
Low-molecular-weight heparin Dalteparin (Fragmin)	5,000 IU daily	100 IU per kg every 12 hours *or* 200 IU per kg every 24 hours	Unstable angina and non–Q wave MI with ASA Conditions that predispose to DVT: joint replacement surgery, abdominal surgery, immobilized medical patients
Enoxaparin (Lovenox)	40 mg daily	1 mg per kg every 12 hours *or* 1.5 mg per kg every 24 hours	Unstable angina and non–Q wave MI with ASA Conditions that predispose to DVT: joint replacement surgery, abdominal surgery, immobilized medical patients
Nadroparin (not available in United States)	38 IU per kg daily	87 IU per kg every 12 hours	None
Tinzaparin (Innohep)	3,500 IU daily	175 IU per kg per 24 hours	None
Bivalirudin (Angiomax)	—	1 mg per kg IV bolus 2.5 mg per kg per hour for four hours; with ASA 325 mg May continue with 0.2 mg per kg for up to 20 hours	None
Desirudin (Ipravask)	15 mg every 12 hours	—	DVT prophylaxis after hip replacement
Lepirudin (Refludan)	—	0.4 mg per kg bolus (maximum: 45 mg) *or* 0.15 mg per kg per hour (maximum: 16.5 mg) for two to 10 days	Prophylaxis of venous thromboembolism in patients with HIT
Argatroban (Acova)	—	2 mcg per kg per minute	Prophylaxis of venous thromboembolism in patients with HIT
Ximelagatran (not available in United States)	24 to 36 mg twice daily	20 to 60 mg twice daily	None
Fondaparinux (Arixtra)	2.5 mg daily	5 mg for a patient less than 50 kg 7.5 mg for 50 to 100 kg 10 mg for more than 100 kg	DVT prophylaxis after hip or knee replacement or abdominal surgery

FDA = U.S. Food and Drug Administration; DVT = deep venous thrombosis; PE = pulmonary embolism; MI = myocardial infarction; ASA = aspirin; IV = intravenous; PTCA = percutaneous transluminal coronary angioplasty; HIT = heparin-induced thrombocytopenia.

**—Cost for 24-hour therapeutic dosage for 220-lb (99.8-kg) patient, except for bivalirudin, which is for a four-hour treatment.*

†—Estimated cost to the pharmacist based on average wholesale prices in Red Book. Montvale, N.J.: Medical Economics Data, 2006. Cost to the patient will be higher. Prices are rounded to the nearest dollar amount.

‡—Not listed in Red Book.

Information from reference 16.

FDA-approved therapeutic conditions	*Cost*†*
See Table 2	$1
Treatment of DVT and PE Atrial fibrillation with embolism Prevention of clotting during arterial and cardiac surgery Treatment of peripheral artery embolization Treatment of consumptive coagulopathies	9
None	117
Inpatient treatment of DVT with and without PE with warfarin Outpatient DVT without PE with warfarin	111
None	—
Treatment of DVT and PE with warfarin	71
During PTCA for unstable angina	2,204 for one four-hour treatment
None	‡
Treatment of thrombosis in patients with HIT	1,248
Treatment of thrombosis in patients with HIT	1,260
None	—
Bridge DVT or PE to warfarin	108

organized immediately) or after a 24-hour stay in the hospital. The ACCP recommends that treatment with unfractionated heparin or LMWH continue for at least five days and until a stable therapeutic INR is achieved.[2] Patients should be followed closely over the next seven to 10 days to ensure that they get appropriate laboratory tests, take their medications as prescribed, and achieve a therapeutic INR in as close to five days as possible. Outpatient treatment with LMWH is significantly less expensive than inpatient treatment with unfractionated heparin,[18] but its effectiveness mandates that: (1) the patient understands treatment and keeps frequent follow-up appointments, (2) consistent protocols ensure expeditious and safe transfer from injectable to oral anticoagulation, and (3) staff closely monitor patients. As noted earlier, validated protocols have been established to initiate warfarin in patients receiving LMWH and for warfarin maintenance.

Bed rest traditionally has been recommended for patients with VTE to prevent migration of clot to the lungs with ambulation. According to a large observational study, however, there is no evidence that bed rest improves outcomes.[19] In addition, several studies favor the use of support hose, particularly as a way to prevent postthrombotic syndrome.[20]

LMWH FOR PATIENTS WITH CANCER

Patients with cancer and VTE who are treated with LMWHs have an unexpected survival advantage that extends beyond the effect of treating their thrombotic diseases.[17] In recent double-blind, prospective studies, survival advantages were noted in patients who had solid

Table 4. Treatment of Deep Venous Thrombosis and Nonmassive Pulmonary Embolism

Initiate warfarin (Coumadin) and LMWH (or unfractionated heparin) on day 1; consider outpatient therapy if patient is stable, able to participate in care, and careful monitoring can be achieved as outpatient

Use 5-mg or 10-mg nomogram to initiate warfarin therapy and monitor INR per nomogram protocol to target of 2.0 to 3.0

Stop LMWH or unfractionated heparin after no less than five days and when INR is stable at 2.0 or more for two days

Use elastic compression stockings to prevent postthrombotic syndrome

Ambulate as tolerated

LMWH = low-molecular-weight heparin; INR = International Normalized Ratio.

Information from references 2 and 14.

tumors with advanced local disease or metastatic disease and were treated with LMWH.[21] These studies suggest that coagulation cascade activation may be involved in tumor growth, angiogenesis, and metastatic spread.[21] The ACCP recommends that patients with cancer and VTE be treated for the first three to six months with LMWH, rather than just five days, followed up by oral anticoagulation.[2]

Bridge Therapy

Temporary use of intravenous unfractionated heparin or LMWH for a patient on long-term anticoagulation who is about to undergo a surgical procedure is called bridge therapy. This type of therapy also has been simplified by the use of LMWHs. When determining whether to use bridge therapy, the risk of thromboembolism *(Table 5[1,22])* needs to be balanced with the risk of bleeding *(Table 6[1,22-26])*. The introduction of bridge therapy with LMWH has led to significant lowering of perioperative health care costs.[27] Recommendations for a bridge therapy protocol are summarized in *Table 7*.[1,22,23]

Some procedures have a minimal risk of bleeding complications.[1,22,24,25] For these procedures, warfarin does not need to be interrupted, but the INR should be checked the day of or the day before the procedure to ensure that it is not supratherapeutic. All other patients on anticoagulation therapy should discontinue warfarin for four to five days before the procedure and restart in the evening on the day of the procedure. No other therapy is necessary for patients at low risk of thromboembolism.[1,22,24,25]

Recommendations for patients with intermediate risk of thromboembolism are less clear. Recent trials have shown that the incidence of perioperative arterial thromboembolism is higher than would be expected based on calculations using annual risks of thromboembolism.[23] The trials also showed that the risk of major bleeding was low for minor surgical and invasive procedures but was significant for major surgery.[23] The increased risks of stroke and bleeding should be considered; therefore, the patient's preferred therapy should be taken into account when bridging patients with intermediate risk of thromboembolism, with an emphasis on no bridging before or after the procedure.[23] When the choice is to use perioperative anticoagulation, patients at intermediate risk of thromboembolism should be started on low-dose unfractionated heparin or prophylactic-dose LMWH two to three days before surgery. All anticoagulation is then held 12 to 24 hours preoperatively, with reinstitution of no or low-dose unfractionated heparin or LMWH following surgery.[1,22,23]

Patients at high risk of thromboembolism should start with full-dose unfractionated heparin or LMWH two to three days preoperatively. Unfractionated heparin is stopped five hours before surgery, and LMWH is stopped 12 to 24 hours before surgery. Prophylactic or full-dose unfractionated heparin or LMWH with warfarin therapy may be restarted postoperatively once hemostasis has been achieved.[23,25] If therapeutic unfractionated heparin or LMWH is used after major surgery, the patient must be monitored closely for bleeding.[23] Consider giving prophylactic-dose unfractionated heparin or LMWH for one to two days postoperatively before instituting therapeutic-dose unfractionated heparin or LMWH.[23]

No prospective, double-blind, randomized controlled studies have been performed to evaluate these bridge therapies. Recent trials suggest that the bleeding risk using perioperative unfractionated heparin or LMWH may lead to more bleeding complications than previously thought.[23] For these reasons, bridging anticoagulation should be approached more cautiously, using patient input once risks and benefits have been discussed. This means less bridging for intermediate-risk patients and more

Table 5. Risk Levels for Thromboembolism

Low
Atrial fibrillation without major risk factors for stroke
VTE more than three months earlier and no high-risk features
Intermediate
Atrial fibrillation and age older than 65 years, diabetes mellitus, coronary artery disease, or hypertension
Newer (second-generation) mechanical aortic valve in sinus rhythm without heart failure or previous thromboembolism
High
Atrial fibrillation with history of stroke or multiple risk factors for stroke
Older (first-generation) ball/cage aortic valves
Aortic mechanical valve with previous thromboembolism, atrial fibrillation, or congestive heart failure
Mitral mechanical valves
VTE less than three months earlier
VTE more than three months earlier with high-risk factors (active malignancy, multiple episodes of VTE, known thrombophilic state)

VTE = venous thromboembolism.

Information from references 1 and 22.

Table 6. Bleeding Risk Associated with Invasive Procedures and Recommendations for Perioperative Management

Bleeding risk category	*Invasive procedure*	*Recommendations*	*Grade*
High	Cardiac surgery, abdominal aortic aneurysm repair, neurosurgery, most cancer surgery, bilateral knee replacement, TURP, kidney biopsy	**Low-risk thromboembolism**	2C
		Stop warfarin (Coumadin) four to five days before surgery and allow INR to return to near normal	
		Restart warfarin after surgery	
		Use prophylactic LMWH or unfractionated heparin if procedure predisposes to thrombosis	
		Intermediate-risk thromboembolism	2C
		Stop warfarin four to five days before surgery	
		Consider no bridge therapy versus starting prophylactic LMWH or unfractionated heparin two to three days before surgery*	
		After surgery, start warfarin and prophylactic LMWH or unfractionated heparin	
		Alternatively follow bridge therapy protocol† using prophylactic LMWH or unfractionated heparin after surgery	
		High-risk thromboembolism	2C
		Follow bridge therapy protocol†	
		After surgery, await hemostasis before restarting LMWH or consider prophylactic dosages of LMWH or unfractionated heparin	
Intermediate (surgical)	Abdominal surgery, hemorrhoidal surgery, axillary node dissection, dilatation and curettage, hydrocele repair, orthopedic surgery, pacemaker insertion, internal cardiac defibrillator insertion, endarterectomy or carotid bypass surgery, noncataract eye surgery (complex lid, lacrimal, orbital), extensive dental surgery (multiple tooth extractions)	**Low-risk thromboembolism**	2C
		Stop warfarin four to five days before surgery and allow INR to return to near normal	
		Restart warfarin after surgery	
		Use prophylactic LMWH or unfractionated heparin if procedure predisposes to thrombosis	
		Intermediate-risk thromboembolism	2C
		Stop warfarin four to five days before surgery	
		Consider no bridging versus starting prophylactic LMWH or unfractionated heparin two to three days before surgery*	
		After surgery, restart warfarin and prophylactic LMWH or unfractionated heparin	
		Alternatively follow bridge therapy protocol†	
		High-risk thromboembolism	2C
		Follow bridge therapy protocol†	
		Await hemostasis before restarting LMWH and consider using therapeutic dosages of LMWH or unfractionated heparin	

Table 6 continues

TURP = transurethral resection of the prostate; INR = International Normalized Ratio; LMWH = low-molecular-weight heparin; RCTs = randomized controlled trials.

**—See further discussion in text.*
†—See Table 7 for bridge therapy protocol.

Grade 1 = high certainty that benefits do, or do not, outweigh risks, burdens, and costs; grade 2 = less certainty that benefits do, or do not, outweigh risks, burdens, and costs; grade A = RCTs with consistent results; grade B = RCTs with inconsistent results or with major methodologic weaknesses; grade C = other observational and clinical trial evidence.

use of prophylactic-dose unfractionated heparin or LMWH postoperatively except when a patient is at very high risk of thromboembolism such as a mitral valve replacement.[23] The recommendations in *Table 7* are based on the available literature.[1,22,23] There is room for interpretation by the physician managing anticoagulation and the surgeon or interventionalist.

New Anticoagulants

Several new anticoagulants have been developed to target specific sites on the coagulation cascade. These anticoagulants can be divided into direct thrombin inhibitors or factor Xa inhibitors. Hirudin, lepirudin (Refludan), bivalirudin (Angiomax), desirudin (Ipravask), argatroban (Acova), and ximelagatran (Exanta; not available in

Table 6 *(continued)*

Bleeding risk category	*Invasive procedure*	*Recommendations*	*Grade*
Intermediate to low (nonsurgical)	Coronary angiography with or without percutaneous coronary intervention, noncoronary angiography, upper endoscopy with endosphincterotomy, colonoscopy with polypectomy, bronchoscopy with or without biopsy, biopsy (prostate, bladder, thyroid, breast, lymph node, pancreas)	**Low-risk thromboembolism**	2C
		Stop warfarin four to five days before surgery and allow INR to return to near normal	
		Restart warfarin after surgery	
		Use prophylactic dosages of LMWH or unfractionated heparin if procedure predisposes to thrombosis	
		Intermediate-risk thromboembolism	2C
		Stop warfarin therapy four to five days before surgery	
		Consider no bridging versus starting prophylactic LMWH or unfractionated heparin two to three days before surgery*	
		After surgery, restart warfarin and prophylactic LMWH or unfractionated heparin	
		Alternatively follow bridge protocol†	
		High-risk thromboembolism	2C
		Follow bridge therapy protocol†	
		Await hemostasis before restarting LMWH and consider using therapeutic dosages of LMWH or unfractionated heparin	
Low to minimal	Arthrocentesis, general dental treatment (hygiene, restorations, endodontics, prosthetics, minor periodontal therapy, and uncomplicated extractions), ophthalmic procedures (cataract, trabeculectomy, vitreoretinal), TURP with laser surgery, upper and lower gastrointestinal endoscopy with or without mucosal biopsy	**All risks of thromboembolism**	2C
		Continue warfarin therapy	
		Check INR the day of or the day before surgery to be sure not supratherapeutic	

TURP = transurethral resection of the prostate; INR = International Normalized Ratio; LMWH = low-molecular-weight heparin; RCTs = randomized controlled trials.

**—See further discussion in text.*
†*—See Table 7 for bridge therapy protocol.*

Grade 1 = high certainty that benefits do, or do not, outweigh risks, burdens, and costs; grade 2 = less certainty that benefits do, or do not, outweigh risks, burdens, and costs; grade A = RCTs with consistent results; grade B = RCTs with inconsistent results or with major methodologic weaknesses; grade C = other observational and clinical trial evidence.

Information from references 1 and 22 through 26.

United States) are all direct thrombin inhibitors, whereas fondaparinux (Arixtra) is a factor Xa inhibitor.[28] *Table 3* lists dosages and indications for their use.[16]

Hirudin, lepirudin, bivalirudin, and desirudin are cleared renally and are monitored by measuring the aPTT.[28] Because hirudins are derived from peptides foreign to humans, allergies and antibodies can develop, even on first use.[28]

Argatroban is derived from L-arginine and is indicated for the treatment of heparin-induced thrombocytopenia.[28] It is cleared hepatically and is monitored using the aPTT.[28] Absorption of ximelagatran, an oral anticoagulant, is not affected by foods and does not appear to require monitoring.[9] Ximelagatran was studied extensively for prophylaxis in patients undergoing knee or hip arthroplasty; in the initial treatment and prevention of recurrent VTE; and in patients with atrial fibrillation, myocardial infarction, and acute coronary syndromes.[9] However, it failed to gain approval from the U.S. Food and Drug Administration in 2004 because of unexpected cardiovascular adverse effects and continued concerns with liver toxicity.

Table 7. Recommendations for Bridge Therapy Protocol* Based on Expert Opinion

Day	*Recommendation*
–7	Stop aspirin therapy and check INR
–5 or –4	Stop warfarin (Coumadin) therapy and check INR
–3 or –2	Start LMWH once or twice daily
–1	Last dose of LMWH 12 to 24 hours before procedure
	Check INR; if 1.5 or higher, give vitamin K (1 mg orally)
0 (day of surgery)	No LMWH
	Assess hemostasis
	Start regular warfarin dosage in evening
1	Continue regular warfarin dosage
	Restart LMWH therapeutic dosage (procedures with low risk of bleeding and/or patients or procedures with high risk of thrombosis)†
	or
	LMWH prophylactic dosage (procedures with high risk of bleeding)†
2	Check INR
4 to 10	Check INR
	Stop LMWH when INR is 2.0 or higher

INR = International Normalized Ratio; LMWH = low-molecular-weight heparin.

**—See Table 6 for when to use bridge therapy protocol.*
†—See further discussion in text.

Information from references 1, 22, and 23.

Fondaparinux, a synthetic analogue of heparin,[9] is effective for prophylaxis in orthopedic patients as well as in general medical and surgical patients. The safety of fondaparinux appears to be similar to that of LMWH for the treatment of acute VTE, and it is a viable option for patients with a history of heparin-induced thrombocytopenia.[9] Fondaparinux is cleared renally. The main limitation to its use is its lack of reversibility with protamine.[9]

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