Anticoagulation management strategies for patients on warfarin who need surgery

AMIR K. JAFFER, MD

Surgical candidates who are receiving chronic warfarin therapy pose a management dilemma to the perioperative consultant. Continuing warfarin up to the time of surgery increases the risk of bleeding, so these patients' warfarin traditionally was stopped 5 days before surgery. Yet during this time and afterward, these patients are believed to be at increased risk of thromboembolism.

In light of this dilemma, 250,000 surgical patients in North America on warfarin therapy are assessed annually for perioperative anticoagulation with a heparin product to bridge the gap in thromboembolic protection if warfarin is stopped.[1] This review explores key issues and questions surrounding "bridging" anticoagulation and describes the bridge therapy protocol in use at The Cleveland Clinic.

PERIOPERATIVE THROMBOEMBOLISM IN WARFARIN RECIPIENTS: RISK IS LOW BUT RESULTS CAN BE DEVASTATING

A systematic review published in 2003[2] reveals that the risk of perioperative thromboembolism among patients receiving long-term anticoagulation therapy is low. The limitations of this review are that no randomized controlled trials could be identified for inclusion and the overall quality of the reports was deemed poor. The overall thromboembolic event rate was 1.6%. The rates of major bleeding were approximately 2% to 4% in patients undergoing major surgery and 0% to 2% in those undergoing invasive procedures, but interpretation of the bleeding rates is difficult because the studies identified included surgical procedures with varying risks of bleeding and, as stated, none was randomized.

The consequences of interrupting warfarin therapy must be understood for effective decision making. In patients with a previous episode of venous thromboembolism (VTE), 5% to 10% of recurrent VTEs are fatal.[3] Twenty percent of arterial thromboembolic events are fatal, and more than 50% result in permanent disability.[4] Bridge therapy with heparin can reduce this risk of thromboembolism by nearly 70% but may lead to an increased risk of bleeding. Nine percent to 13% of patients with a major bleed will die, but major bleeding events rarely result in permanent disability because resuscitation with fresh frozen plasma or other blood products is possible.[5]

WHAT DO THE GUIDELINES SAY?

In its recent consensus guidelines, the American College of Chest Physicians (ACCP) suggests various management options for oral anticoagulation during invasive procedures.[6]

For patients at low risk of thromboembolism, it recommends stopping warfarin 4 days preoperatively and considering unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) postoperatively, and perhaps preoperatively as well, although preoperative use is not well explained.

For patients at intermediate risk of thromboembolism, it suggests stopping warfarin 4 days preoperatively, starting a prophylactic dose of UFH or LMWH pre- and postoperatively, and restarting warfarin postoperatively.

For patients at high risk of thromboembolism, its guidelines recommend stopping warfarin 4 days preoperatively, starting full-dose UFH or LMWH preoperatively and then full-dose UFH or LMWH postoperatively, and restarting warfarin postoperatively.

The 1998 American College of Cardiology/

From the IMPACT (Internal Medicine Preoperative Assessment, Consultation, and Treatment) Center and Anticoagulation Clinic, Department of General Internal Medicine, Cleveland Clinic Foundation, Cleveland, OH.

Address: Amir K. Jaffer, MD, Medical Director, IMPACT Center and Anticoagulation Clinic, Cleveland Clinic Foundation, 9500 Euclid Avenue, A13, Cleveland, OH 44195; jaffera@ccf.org.

Disclosure: Dr. Jaffer reported that he is a consultant to the Sanofi-Aventis and AstraZeneca corporations, receives grant support from AstraZeneca, and is on the Sanofi-Aventis speakers' bureau.

American Heart Association (ACC/AHA) guidelines[7] for the management of valvular heart disease state that LMWH is not recommended for perioperative bridge therapy. Bridging with UFH is recommended for patients with Bjork-Shiley valves, atrial fibrillation and two or more risk factors for thromboembolism, or a mechanical mitral valve plus one risk factor.

New data that contradict the ACCP and ACC/AHA guidelines suggest that LMWH is both safe and efficacious for perioperative bridge therapy and are reviewed later in this article.

CASE 1: MINOR SURGERY IN A PATIENT WITH AF

An 85-year-old man with a history of atrial fibrillation, stroke, and congestive heart failure is scheduled for cataract surgery. He is on warfarin with a target INR of 2.0 to 3.0. How should this patient be managed?

A. Stop warfarin 5 days before surgery (ie, hold for four doses before surgery)
B. Use UFH or LMWH as bridge therapy
C. No reason to discontinue warfarin therapy

The aforementioned systematic review[2] demonstrated that major bleeding while receiving oral anticoagulation was rare for cataract surgery and other minor procedures, and therefore can be continued without alteration. Because these data are not well known, educating patients and ophthalmologists that cataract surgery can be performed safely with anticoagulation on board is wise.

In addition to cataract surgery, procedures that can be performed on full-dose anticoagulation include various dental, dermatologic, and gastrointestinal procedures. The decision to continue anticoagulation in patients undergoing gastrointestinal procedures is especially controversial. Guidelines from the American Society of Gastrointestinal Endoscopy[8] state that low-risk procedures such as diagnostic endoscopies and colonoscopies (even with biopsies) can be performed without adjusting warfarin. Despite this recommendation, many gastroenterologists don't agree. A classic example is the patient on long-term warfarin therapy who needs a surveillance colonoscopy following polyp removal in the past; in such a patient, warfarin need not be stopped unless another polypectomy is anticipated. On the other hand, if another polypectomy is anticipated, then withholding anticoagulation is reasonable.

INR nomogram

A nomogram has been developed to decrease the international normalized ratio (INR) in patients undergoing dental surgery, another low-risk procedure.[9] The daily warfarin dose is decreased by 50% on days 4, 3, and 2 before surgery; the original warfarin dose is resumed 1 day before surgery; and the dose of warfarin is doubled on the day of surgery followed by the usual maintenance dose on the day after. This nomogram would be appropriate for other minor surgeries as well. It was tested in 80 consecutive anticoagulated patients who were scheduled for minor surgery, and resulted in no thromboembolic events up to 1 month after surgery, with the caveat that the study contained no control group. In addition to being safe, this strategy is inexpensive.

Timing of warfarin discontinuation

The timing of warfarin discontinuation in patients undergoing elective surgery has been studied by White et al.[10] Among 22 patients on a fixed evening dose of warfarin who had warfarin temporarily discontinued, interpatient variation in the rate of INR decrease was wide, especially among the elderly, but some general rules for interrupting therapy could be established from this small study. To ensure that the INR is less than 1.2 at the time of surgery, warfarin should be withheld for four doses if the steady-state INR is 2.0 to 3.0 and for five doses if the INR is 3.0 to 4.0.

CASE 2: URGENT SURGERY IN A PATIENT WITH AF

An 82-year-old woman with a history of atrial fibrillation, hypertension, and coronary disease is admitted to the hospital with hip fracture. She had a stress test in the past year which was negative. Her INR is 5.5 on admission, and the surgery is scheduled in approximately 18 hours. How should the INR be reduced to less than 1.5 so that the surgeon can operate on this patient?

A. Use fresh frozen plasma
B. Use 10 mg vitamin K subcutaneously
C. Use 2.5 mg vitamin K orally
D. Use 2.5 mg vitamin K intravenously (IV)

Although subcutaneous vitamin K is widely used to reduce the INR prior to surgery, absorption through the subcutaneous route is not predictable.[11] The route of administration of vitamin K that acts most rapidly to reduce the INR is IV, followed by oral and subcutaneous.[11–13] Fresh frozen plasma is probably necessary for surgeries within 12 hours. For surgeries more than 24 hours away, oral vitamin K is usually an effective option.

The proper way to manage this patient is to administer IV vitamin K and recheck the INR in the early morning. In this patient, administering IV vitamin K immediately will most likely result in an INR of 1.5 to 2.0 in 24 hours. If the INR is still close to 2.0, order 2

TABLE 1
Estimated rates of thromboembolism and risk reduction with anticoagulation

Indication	Rate without therapy (%)	Risk reduction with therapy (%)
Acute VTE*		
Month 1	40	80
Months 2 and 3	10	80
Recurrent VTE*†	15‡	80
Nonvalvular AF	4.5‡	66
Nonvalvular AF and previous embolism	12‡	66
Mechanical heart valve	8‡	75
Acute arterial embolism		
Month 1	15	66

VTE = venous thromboembolism; AF = atrial fibrillation

* Surgery-associated increase in risk of VTE (estimated to be 100-fold) is not included in these rates.

† Refers to patients whose last episode of VTE occurred more than 3 months before evaluation but who require long-term anticoagulation because of high risk of recurrence.

‡ Annual rate.

TABLE 2
Which patients on warfarin should receive heparin bridging before surgery?

High risk for thromboembolism: bridging advised

Known hypercoagulable state as documented by a thromboembolic event and one of the following:
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Homozygous factor V Leiden mutation
- Antiphospholipid-antibody syndrome

Hypercoagulable state suggested by recurrent (two or more) arterial or idiopathic venous thromboembolic events*

Venous or arterial thromboembolism in prior 1–3 months

Rheumatic atrial fibrillation

Acute intracardiac thrombus visualized by echocardiogram

Atrial fibrillation plus mechanical heart valve in any position

Older mechanical valve model (single-disk or ball-in-cage) in mitral position

Recently placed mechanical valve (< 3 months)

Atrial fibrillation with history of cardioembolism

Intermediate risk for thromboembolism: bridging on a case-by-case basis

Cerebrovascular disease with multiple (two or more) strokes or transient ischemic attacks without risk factors for cardiac embolism

Newer mechanical valve model (eg, St. Jude) in mitral position

Older mechanical valve model in aortic position

Atrial fibrillation without a history of cardiac embolism but with multiple risks for cardiac embolism†

Venous thromboembolism > 3–6 months ago‡

Low risk for thromboembolism: bridging not advised

One remote venous thromboembolism (> 6 months ago)‡

Intrinsic cerebrovascular disease (eg, carotid atherosclerosis) without recurrent strokes or transient ischemic attacks

Atrial fibrillation without multiple risks for cardiac embolism

Newer-model prosthetic valve in aortic position

* Not including primary atherosclerotic events, such as stroke or myocardial infarction due to cerebrovascular or coronary disease.

† For example, ejection fraction < 40%, diabetes, hypertension, nonrheumatic valvular heart disease, transmural myocardial infarction within preceding month.

‡ For patients with a history of venous thromboembolism undergoing major surgery, consideration can be given to postoperative bridging therapy only (without preoperative bridging).

Reprinted, with permission, from reference 15.

U of fresh frozen plasma to be given to the patient on call to the operating room.

Hypotension and allergic reactions are a small risk in patients who receive IV vitamin K, occurring in about 1% to 2% of these patients.

IDENTIFY THE WARFARIN INDICATION, ASSESS PATIENT RISK

Identify the indication for anticoagulation

When managing the patient on warfarin who is undergoing an elective procedure, identifying the indication for anticoagulation is most important. The risk of thrombosis needs to be quantified, which involves understanding the patient's risk factors for thromboembolism, considering the type of surgery/procedure to be performed, and determining how long the patient needs to be off anticoagulation. For example, the primary risk in a patient with AF in whom anticoagulation must be interrupted prior to surgery is arterial thromboembolism from removal of the anticoagulation plus the risk of VTE related to the surgery. The risk of bleeding from the procedure also needs to be quantified, and the consequences of thromboembolism and bleeding need to be weighed.

Risk determines bridge strategy

The risk of thromboembolism will determine the need for anticoagulation bridging, the risks and benefits of which must also be weighed. Use of a perioperative anticoagulant will decrease the risk of a perioperative thromboembolic event but carries the potential risks of postoperative bleeding and development of heparin-induced thrombocytopenia.

For bridge therapy, outpatient UFH is not practical given the need for partial thromboplastin time measurements, leaving LMWH as the best option for out-

TABLE 3
Published bridging studies of low-molecular-weight heparin

Author	No. patients (no. valves)	Low-molecular-weight heparin	Rate of bleeding	Rate of thromboembolism
Spandorfer[20]	20	Enoxaparin	5% major, 10% minor	0%
Tinmouth[21]	24 (12)	Dalteparin	0% major, 8.3% minor	4.2%
Dotan[22]	20 (3)	Enoxaparin	0% major, 10% minor	0%
Ferreira[23]	74 (74)	Enoxaparin	1.35% major, 10.8% minor	0%
Jaffer[24]	69 (21)	Enoxaparin or tinzaparin	2.8% major, 1.3% minor	0%
Spyropoulos[25]	84 (27)	Enoxaparin	3.5% major, 3.5% minor	0%
Douketis[26]	650 (215)	Dalteparin	1.85%*, 0.74%†	1.85%*, 0.74%†
Kovacs[27]	224 (112)	Dalteparin	6.7% major	3.6%

* Procedures with high bleeding risk (received only preprocedural bridging therapy).
† Procedures with high bleeding risk plus nonsurgical procedures without high bleeding risk.

patient therapy. Inpatient IV UFH is another option.

The rates of thromboembolism and the reductions in risk with bridge therapy have been quantified by Kearon and Hirsh (Table 1).[14] They state that patients who have had VTE or arterial thromboembolic events in the past month are at extremely high risk for thromboembolism, as are patients with AF who have had a prior stroke. They also believe that bridge therapy decreases the risk of a perioperative thromboembolic event by 70% to 80%, on average.

Thromboembolism risk stratification

An extensive literature review has helped define the risk of perioperative thromboembolism in patients on chronic anticoagulation.[15] Patients were classified as low risk, intermediate risk, and high risk based on their annual risk of an arterial thromboembolic event or their monthly risk of VTE (Table 2).

Low-risk patients in this classification are those with a less than 5% per year risk of an arterial thromboembolic event or a less than 2% per month risk of VTE.

Intermediate-risk patients are those with a 5% to 10% per year risk of an arterial thromboembolic event or a 2% to 10% per month risk of VTE.

High-risk patients are those with a greater than 10% per year risk of an arterial thromboembolic event or a greater than 10% per month risk of VTE.

The CHADS 2 risk classification scheme can be used to estimate the annual (not perioperative) risk of stroke in atrial fibrillation patients by assigning point values to stroke risk factors. It assigns 1 point each for the presence of Congestive heart failure, Hypertension, Age 75 years or older, and Diabetes mellitus; and 2 points for a history of Stroke or transient ischemic attack. Anticoagulation as a bridge to surgery may be reasonable in patients with a CHADS 2 score of 3 or greater, which indicates a 6% annual risk of stroke.[16]

CASE 3: COLECTOMY IN A PATIENT WITH A MECHANICAL VALVE: UFH OR LMWH FOR BRIDGE THERAPY?

A 65-year-old man with an older-generation valve, a Starr-Edwards, is diagnosed with colon cancer and needs a colectomy. The patient's personal physician recommends stopping warfarin 5 days before surgery and admitting the patient for IV UFH therapy because LMWH is not shown to be safe and effective for patients with mechanical heart valves. How should you, the medical consultant, advise the patient's physician?

A. Tell him he is right—there is little evidence to support the use of LMWHs in mechanical valve patients.

B. Tell him there is in fact more evidence in the literature to support the use of LMWHs than UFH for bridging with mechanical valves.

The better answer is B. Bridge studies using IV UFH are few and poorly done.[17–19] In these studies, the rate of bleeding was 2.6% and the overall rate of thromboembolism was 3.4% in patients bridged with UFH.

Published bridge studies of LMWH have demonstrated very acceptable rates of major bleeding (Table 3) and a rate of thromboembolism of 0% to 4%.[20–27] In a large unpublished registry[28] in which enoxaparin 1.5 mg/kg once daily was used for bridging, the rate of major bleeding was 22% with major surgery and 0% with minor surgery, although the overall rate of major bleeding was only 3.6%. The rate of thromboembolic events in this registry was 2.6% and the rate of VTE was 1%. In another large unpublished registry (REGIMEN),[29] the rates of major bleeding were 3.3% with major surgery and 10% with minor surgery, and the rate of thromboembolism was 0.9%.

Perioperative anticoagulation strategies and adverse events were examined in a preliminary analy-

TABLE 4
Exclusion criteria for bridge therapy with low-molecular-weight heparin

- Weight > 150 kg
- Pregnancy or childbearing potential without adequate contraception
- History of heparin-induced thrombocytopenia
- End-stage renal disease
- Allergy to low-molecular-weight heparin or unfractionated heparin
- History of noncompliance, language barriers, or unsuitable home environment
- Gastrointestinal bleeding in last 10 days
- Major trauma or stroke in past 2 weeks

Reprinted, with permission, from reference 15.

sis of 425 of 500 planned patients from nine anticoagulation clinics.[30] Patients were stratified a priori according to bridge strategy, procedure/surgery using the Johns Hopkins bleeding classification scheme, and their risk of thromboembolism and VTE. Of the patients in this registry, 46% did not receive bridge therapy, 30% received bridge therapy, and 3.8% had warfarin continued. The others received various combinations of no anticoagulation, intermediate-intensity anticoagulation, and high-intensity anticoagulation pre- and postoperatively.

Overall, mortality was 0.5%, the thromboembolic event rate was 0.9%, and the rate of major bleeding was 2.1%. Eight of the nine major bleeding events and 12 of the 15 bleeding events overall occurred in the 40% of patients who received full-dose bridge therapy.

Interpretation of bridge studies

Bridge therapy must be tailored to the individual patient. Careful selection of patients for bridge therapy is required, with resumption of the anticoagulant postoperatively when hemostasis has been achieved.

Cost considerations. Admitting patients for anticoagulation is costly and therefore discouraged. In a managed care setting, Spyropoulos et al[31] determined that use of LMWH as opposed to UFH for bridge therapy, starting 10 days before an elective surgical procedure and continued for 30 days after the procedure, can achieve a cost saving of approximately $13,000, taking into account expected differences in the rates of adverse events and the costs associated with inpatient/outpatient care, outpatient surgery, and laboratory, pharmacy, and professional fees.

CLEVELAND CLINIC ANTICOAGULATION CLINIC BRIDGE THERAPY PROTOCOL

The Cleveland Clinic Anticoagulation Clinic has a bridge therapy protocol in which the timing of warfarin interruption is based on the preoperative INR.[15] If the preoperative INR is 2.0 to 3.0, warfarin is stopped 5 days before surgery (four doses); if the preoperative INR is 3.0 to 4.5, warfarin is stopped 6 days before surgery (five doses). Enoxaparin 1 mg/kg or dalteparin 100 IU/kg, delivered subcutaneously every 12 hours, is started 36 hours after the last warfarin dose. The final dose of LMWH is administered 24 hours before surgery. The plan is discussed with the surgeon, the anesthesiologist, and the patient, during which time the risks and benefits of LMWH are outlined. Patients receive instruction on self-administration, the signs and symptoms of bleeding, and the course of action in the event of an emergency.

The postoperative protocol calls for restarting LMWH at full doses approximately 24 hours after the procedure only if hemostasis has been achieved. Prophylactic doses on postoperative days 1 and 2 should be considered if patients are at high risk for bleeding. Warfarin is restarted at preoperative doses on postoperative day 1. The INR should be monitored daily until the patient is discharged and periodically thereafter until it is in the therapeutic range. Patients should be screened for heparin-induced thrombocytopenia with platelet counts at days 3 and 7. LMWH should be discontinued when the INR is 2.0 to 3.0 for 2 consecutive days.

Exclusions to bridge therapy

Table 4 provides a list of exclusion criteria for bridge therapy with LMWH. Body weight greater than 150 kg is an exclusion for practical reasons; two syringes of enoxaparin would be required in such a patient. Also, the risk of overdosing increases with increasing weight because the relationship between volume of distribution of LMWH and weight is not linear. Patients who are heavier than 150 kg are admitted to the hospital and treated with UFH, after which their partial thromboplastin time is monitored every 6 hours and the UFH is discontinued 5 hours before surgery.

REGIONAL ANESTHESIA CONSIDERATIONS

Recommendations to minimize risk in anticoagulated patients undergoing regional anesthesia have been published by the American Society of Regional Anesthesia and Pain Medicine.[32] Preoperative recommendations include needle placement 12 hours after prophylactic LMWH (24

hours if the dose is ≥ 1 mg/kg). Postoperatively, an indwelling catheter must be removed prior to starting twice-daily LMWH, with the first dose of LMWH to be given 2 hours after catheter removal; once-daily LMWH is acceptable, but the first dose should be given 6 to 8 hours postoperatively and the second dose 24 hours later. Concurrent use of an indwelling catheter and once-daily LMWH is acceptable, but not twice-daily LMWH. The catheter should be removed 12 to 24 hours after the last dose.

CONCLUSION

The risk of thromboembolism is small but real in patients undergoing procedures or surgeries off their chronic warfarin therapy. This risk ranges from 1% to 2%, and is possibly even greater. If the patient is not comfortable with this level of risk, bridge therapy should be offered, with the knowledge that it will slightly raise the risk of minor or major bleeding. Until a randomized controlled trial is published, the risk of bleeding and thromboembolism should be balanced in every patient, which requires an individualized, tailored approach.

REFERENCES

1. 2002 Heart and Stroke Statistical Update. Dallas, TX: American Heart Association; 2001.
2. Dunn AS, Turpie AGG. Perioperative management of patients receiving oral anticoagulants: a systematic review. Arch Int Med 2003; 163:901–908.
3. Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. N Engl J Med 1995; 332:1661–1665.
4. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994; 154:1449–1457.
5. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern Med 2003; 139:893–900.
6. Ansell J, Hirsh J, Poller L, et al. The pharmacology and management of the vitamin K antagonists. Chest 2004; 126(suppl):204S–233S.
7. Bonow RO, Carabello B, de Leon AC, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 1998; 98:1949–1984.
8. Zuckerman MJ, Hirota WK, Adler DG, et al. ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. Gastrointest Endosc 2005; 61:189–194.
9. Marietta M, Bertesi M, Simoni L, et al. A simple and safe nomogram for the management of oral anticoagulation prior to minor surgery. Clin Lab Haematol 2003; 25:127–130.
10. White RH, McKittrick T, Hutchinson R, Twitchell J. Temporary discontinuation of warfarin therapy: changes in the international normalized ratio. Ann Intern Med 1995; 122:40–42.
11. Crowther MA, Douketis JD, Schnurr T, et al. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy. A randomized, controlled trial. Ann Intern Med 2002; 137:251–254.
12. Weibert RT, Le DT, Kayser SR, Rapaport SI. Correction of excessive anticoagulation with low-dose oral vitamin K1. Ann Intern Med 1997; 126:959–962.
13. Shields RC, McBane RD, Kuiper JD, et al. Efficacy and safety of intravenous phytonadione (vitamin K1) in patients on long-term oral anticoagulant therapy. Mayo Clin Proc 2001; 76:260–266.
14. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997; 336:1506–1511.
15. Jaffer AK, Brotman DJ, Chukwumerije N. When patients on warfarin need surgery. Cleve Clin J Med 2003; 70:973–984.
16. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001; 285:2864–2870.
17. Tinker JH, Tarhan S. Discontinuing anticoagulant therapy in surgical patients with cardiac valve prostheses. Observations in 180 operations. JAMA 1978; 239:738–739.
18. Katholi RE, Nolan SP, McGuire LB. Living with prosthetic heart valves. Subsequent noncardiac operations and the risk of thromboembolism or hemorrhage. Am Heart J 1976; 92:162–167.
19. Katholi RE, Nolan SP, McGuire LB. The management of anticoagulation during noncardiac operations in patients with prosthetic heart valves. A prospective study. Am Heart J 1978; 96:163–165.
20. Spandorfer JM, Lynch S, Weitz HH, Fertel S, Merli GJ. Use of enoxaparin for the chronically anticoagulated patient before and after procedures. Am J Cardiol 1999; 84:478–480.
21. Tinmouth AH, Morrow BH, Cruickshank MK, et al. Dalteparin as periprocedure anticoagulation for patients on warfarin and at high risk of thrombosis. Ann Pharmacother 2001; 35:669–674.
22. Dotan ZA, Mor Y, Leibovitch I, et al. The efficacy and safety of perioperative low molecular weight heparin substitution in patients on chronic oral anticoagulant therapy undergoing transurethral prostatectomy for bladder outlet obstruction. J Urol 2002; 168:610–613.
23. Ferriera I, Dos L, Tornos P, et al. Experience with enoxaparin in patients with mechanical heart valves who must withhold acenocumarol. Heart 2003; 89:527–530.
24. Jaffer AK, Ahmed M, Brotman DJ, et al. Low-molecular-weight-heparins as periprocedural anticoagulation for patients on long-term warfarin therapy: a standardized bridging therapy protocol. J Thromb Thrombolysis 2005; 20:11–16.
25. Spyropoulos AC, Jenkins P, Bornikoya L. A disease management protocol for outpatient perioperative bridge therapy with enoxaparin in patients requiring temporary interruption of long-term oral anticoagulation. Pharmacotherapy 2004; 24:649–658.
26. Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized periprocedural anticoagulation regimen. Arch Intern Med 2004; 164:1319–1326.
27. Kovacs MJ, Kearon C, Rodger M, et al. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. Circulation 2004; 110:1658–1663.
28. Dunn AS, Spyropoulos AC, Sirko SP, et al. Perioperative bridging therapy with enoxaparin in patients requiring long-term oral anticoagulant therapy: a multicenter cohort study [abstract]. Blood 2004; 104:488A.
29. Spyropoulos AC, Turpie AGG, Dunn AS, et al. Clinical outcomes with unfractionated heparin or low-molecular-weight heparin as bridging therapy in patients on long-term oral anticoagulants: results from the REGIMEN registry [abstract]. Blood 2004; 104(11 Pt 1):203a–204a.
30. Jaffer AK, Brotman DJ, White RH. The perioperative and periprocedural management of warfarin: the PPMW study [abstract]. Presented at: XXth Congress of the International Society on Thrombosis and Haemostasis; August 6–12, 2005; Sydney, Australia.
31. Spyropoulos AC, Frost FJ, Hurley JS, et al. Costs and clinical outcomes associated with low-molecular-weight heparin vs unfractionated heparin for perioperative bridging in patients receiving long-term oral anticoagulant therapy. Chest 2004; 125:1642–1650.
32. Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain Med 2003; 28:172–197.