REVIEW

CME CREDIT

AMIR K. JAFFER, MD
Medical Director, The Internal Medicine Preoperative Assessment Consultation and Treatment (IMPACT) Center and the Anticoagulation Clinic, Section of Hospital and Preoperative Medicine, Department of General Internal Medicine, The Cleveland Clinic

DANIEL J. BROTMAN, MD
Section of Hospital and Preoperative Medicine, Department of General Internal Medicine, The Cleveland Clinic

NKEM CHUKWUMERIJE, MD
Kaiser Permanente Medical Center, Panorama, CA

When patients on warfarin need surgery

ABSTRACT

When a patient who has been taking warfarin long-term needs to undergo surgery, how to manage his or her anticoagulation is controversial. We believe most patients should stop taking warfarin 5 days before elective surgery, and most do not need to receive heparin in the perioperative period as a bridge to surgery.

KEY POINTS

Some procedures, such as some ophthalmic, endoscopic, and dermatologic procedures, entail a low risk of bleeding and do not require that warfarin therapy be interrupted.

If warfarin is withheld for 5 days, the international normalized ratio usually falls to less than 1.5, and surgery is usually safe.

Infusions of fresh-frozen plasma or intravenous or oral vitamin K can reverse anticoagulation quickly before emergency surgery.

The need for bridging therapy depends on the patient's calculated risk of thromboembolism without it, the risk of bleeding with it, and other factors.

When bridging therapy is needed, we use subcutaneous doses of a low-molecular-weight heparin.

Anticoagulation therapy should usually be restarted on the day after surgery.

Dr. Jaffer has indicated that he has received grant or research support from Astra Zeneca, serves as a consultant for Aventis and Astra Zeneca, and is on the speakers' bureau of Aventis.
This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

THE MORE THAN 2 million patients in North America who take warfarin[1] face a major problem should they need surgery or an invasive procedure.

On one hand, if they continue taking warfarin up to the time of surgery, they face an increased risk of bleeding. Therefore, most patients need to stop taking warfarin about 5 days before surgery—the time it takes for its antithrombotic effect to wear off.

During this time and afterward, however, they may be at increased risk of thromboembolism, as stopping warfarin may cause a rebound hypercoagulable state (which has been described but not validated in clinical practice).[2–4] Moreover, prolonged immobility during surgery and afterward increases the risk for venous thromboembolism.

To bridge the gap in protection against thromboembolism, patients can receive heparin in the perioperative period, but questions abound about who should receive it, whether to use unfractionated heparin or one of the low-molecular-weight heparins, and the optimal regimen.

In this article we discuss:

- Which surgical procedures can be performed without stopping warfarin
- The optimal times to stop and restart warfarin
- The use of heparin as a bridge to surgery, including our recommendations and the protocol we use at the Anticoagulation Clinic of The Cleveland Clinic.

FOR SOME PROCEDURES, WARFARIN CAN BE CONTINUED

Although warfarin should be stopped before most invasive procedures,[5] it can be continued before some procedures, as shown by a few prospective and retrospective studies, case reports, and anecdotal evidence—but no randomized clinical trials.

Ophthalmic procedures

Cataract extractions and trabeculectomies can be performed without withholding anticoagulation.[5,6] In several small series in which these procedures were performed in patients on warfarin therapy,[5] the rates of retrobulbar hemorrhage, subconjunctival hemorrhage, and mild hyphema were low, and even when these complications occurred, the prognosis was good.

On the other hand, the risk of bleeding in vitreoretinal, complex lid, lacrimal, and orbital surgical procedures has not been adequately studied; therefore, warfarin should be stopped in these cases.[6]

Gastrointestinal endoscopy

Gastroenterologists differ widely in what they do about anticoagulation before endoscopic procedures.[7,8]

In its 2002 guidelines on this topic,[9] the American Society of Gastrointestinal Endoscopy divided endoscopic procedures into those that pose a low risk for bleeding (which do not require a change in anticoagulation therapy—although some doctors might disagree[10]) and those that pose a high risk.

Usually, surgery is safe if the INR is < 1.5

Low bleeding-risk endoscopic procedures:

- Upper endoscopy with or without biopsy
- Flexible sigmoidoscopy with or without biopsy
- Colonoscopy with or without biopsy
- Endoscopic retrograde cannulation of the pancreatic duct without sphincterotomy
- Biliary stent insertion without sphincterotomy
- Endosonography without fine-needle aspiration
- Push enteroscopy of the small bowel.

High bleeding-risk procedures:

- Polypectomy
- Laser ablation and coagulation
- Endoscopic sphincterotomy
- Pneumatic or bougie dilation
- Percutaneous endoscopic gastrostomy tube placement
- Treatment of varices.

Dental procedures

No change in the intensity of anticoagulation is needed before most dental procedures,[11] eg:

- Restorations
- Endodontics
- Prosthetics
- Uncomplicated extractions
- Dental hygiene treatment
- Periodontal therapy.[12]

On the other hand, warfarin therapy may need to be stopped before other procedures such as complicated extractions and gingival and alveolar surgeries. The decision needs to be made in consultation with the dentist or oral surgeon after determining the risk of bleeding from the specific procedure.

Some dentists give antifibrinolytic agents such as tranexamic acid mouthwash to control local bleeding without stopping the warfarin. In a small study,[13] patients who underwent oral surgery used this mouthwash for 2 minutes four times a day for 1 week afterward, and none of them developed postoperative bleeding or systemic side effects.

Dermatologic procedures

Dermatologic procedures that have been performed safely without stopping warfarin include Mohs micrographic surgery and simple excisions and repairs.[14] A prospective study[14] showed an increase in intraoperative bleeding but no increase in postoperative bleeding.

In more complex procedures (eg, hair transplantation, blepharoplasty, or facelifts), it may be necessary to stop warfarin perioperatively.

Other procedures

Joint and soft-tissue aspirations and injections can be safely performed without altering oral anticoagulation. In a small study,[15] 25 patients on warfarin underwent 32 procedures without any joint or soft-tissue hemorrhage.

Minor podiatric procedures (eg, nail avulsions and phenol matrixectomy) can also be safely performed without stopping warfarin therapy.[16]

STOPPING WARFARIN

After deciding to withhold warfarin preoperatively, the clinician must decide if the goal is to reverse anticoagulation fully or just to decrease its intensity. Usually, surgery can be safely performed if the international normal-

ized ratio (INR) is lower than 1.5.[17] White et al[17] found that if the patient's INR is 2 to 3 while on warfarin, it almost always falls to less than 1.5 within 115 hours (4.8 days) after the last dose.

At our institution, patients take their last dose of warfarin 5 days before surgery. However, if the steady-state INR is greater than 3.0 or the patient is elderly, more time may be required to lower the INR to less than 1.5. Moreover, with neurosurgical procedures and certain major noncardiac surgeries, near-normal INRs (ie, < 1.2) may be desirable. Therefore, it is important to routinely check the INR immediately before surgery to ensure that anticoagulation has been reversed.

Reversing anticoagulation quickly before emergency surgery

If the patient needs an emergency procedure while his or her INR is in the therapeutic range, one must reverse the anticoagulation quickly.

Fresh-frozen plasma can reverse anticoagulation immediately without causing any resistance to warfarin or heparin later. However, it carries the known risks of transfusion, and its effects are short-lived.

Check the INR immediately after fresh-frozen plasma is given and every few hours thereafter if there is ongoing bleeding or a high risk for bleeding.

Vitamin K can be used in semiurgent situations (ie, if surgery or an invasive procedure must be done within 24–96 hours). Because high doses (5–10 mg) can cause postoperative resistance to warfarin,[18] smaller doses (1–2.5 mg) should be used if the patient is expected to restart anticoagulation therapy within a few days after the procedure.

In a retrospective study,[19] the median time to reversal of anticoagulation after a 1-mg intravenous dose of phytonadione (vitamin K) was approximately 27 hours (range 0.7–147 hours). Dyspnea and chest tightness during infusion developed in 2 of the 105 patients, both of whom had preexisting lung disease. At this dosage, the use of vitamin K before surgery did not prolong the time for the INR to return to the therapeutic range afterward.

Oral vitamin K is well absorbed and does not cause the same adverse effects as intravenous vitamin K. At present, only 5-mg tablets are available in the United States. One study using 1 mg of oral vitamin K[18] used an intravenous preparation, which the patients drank, while another study[20] used 5-mg tablets broken in half to supply 2.5 mg. Both these studies showed that oral vitamin K brought supratherapeutic INRs (> 4.5) down into the therapeutic range within 24 hours.[12,20] Likewise, it can be given to patients with INRs in the therapeutic range (2.0–3.0) who need semiurgent or elective surgery.

In general, we use vitamin K only if surgery is urgently or semiurgently needed, not before elective surgery.

Recombinant activated factor VII (rFVIIa) is indicated to stop bleeding in patients with hemophilia who have acquired inhibitors of factor VIII and factor IX. A multicenter pilot study is under way to determine the effect of this drug in patients on vitamin K antagonists (eg, warfarin) who experience bleeding.

A case series of 13 patients showed this drug to be a safe, rapid, and effective means of lowering INRs higher than 10 and for reducing bleeding during diagnostic and therapeutic procedures.[21]

Limitations to its use: it is expensive ($3,500 for the mean dose used in the case series), and one cannot monitor or predict its hemostatic efficacy.

Check the INR immediately before surgery

THROMBOSIS RISK WHILE OFF WARFARIN

Since most surgical procedures require that anticoagulation be reversed, patients taking warfarin long-term generally face an unavoidable risk of thromboembolism when they stop taking it to undergo surgery. The risk of thrombosis during this period depends on:

- The reason the patient is taking warfarin
- The patient's risk factors for thromboembolism
- How long the patient remains off anticoagulation therapy
- The degree of anticoagulation reversal
- The type of surgical procedure (this factor mainly determines the risk of venous thrombosis).

TABLE 1

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 (not including primary atherosclerotic events, such as stroke or myocardial infarction due to intrinsic cerebrovascular or coronary disease)
- Venous or arterial thromboembolism within the preceding 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 (eg, ejection fraction < 40%, diabetes, hypertension, nonrheumatic valvular heart disease, transmural myocardial infarction within preceding month)
- Venous thromboembolism > 3–6 months ago*

Low risk for thromboembolism: bridging not advised

- One remote venous thromboembolism (> 6 months ago)*
- Intrinsic cerebrovascular disease (such as carotid atherosclerosis) without recurrent strokes or transient ischemic attacks
- Atrial fibrillation without multiple risks for cardiac embolism
- Newer-model prosthetic valve in aortic position

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

We have defined three risk categories for thromboembolism

Using evidence from the literature, we have defined three risk categories for thromboembolism:

- **High:** 1-year risk of arterial embolism greater than 10%, or 1-month risk of venous thromboembolism greater than 10%
- **Intermediate:** 1-year risk of arterial embolism 5% to 10%, or 1-month risk of venous thromboembolism 2% to 10%
- **Low:** 1-year risk of arterial embolism less than 5%, or 1-month of venous thromboembolism < 2% (TABLE 1).

HEPARIN AS A BRIDGE TO SURGERY

Using heparin, which has a faster onset and offset of action than warfarin, we can shorten the time the patient is unprotected against thromboembolism in the perioperative period. Formerly, virtually all patients requiring bridging were hospitalized to receive unfractionated heparin intravenously; now, many give themselves subcutaneous doses of low-molecular-weight heparin at home (TABLE 2).

TABLE 2

Cleveland Clinic Anticoagulation Clinic protocol for low-molecular-weight heparin as a bridge to surgery in patients on warfarin

Inclusion criteria

- Age > 18 years, needing to undergo therapy with low-molecular-weight heparin
- Treating physician thinks patient needs bridging therapy (see TABLE 1)
- Medically and hemodynamically stable
- Scheduled for elective procedure or surgery

Exclusion criteria

- Allergy to unfractionated heparin or low-molecular-weight heparin
- Weight > 150 kg
- Pregnant woman with a mechanical valve
- History of bleeding disorder or intracranial hemorrhage
- Creatinine clearance < 30 mL/minute
- Gastrointestinal bleeding within the last 10 days
- Major trauma or stroke within the past 2 weeks
- History of heparin-induced thrombocytopenia or severe thrombocytopenia
- Language barrier
- Potential for medication noncompliance
- Unsuitable home environment to support therapy
- Severe liver disease

Before surgery

- If preoperative international normalized ratio (INR) is 2.0–3.0, stop warfarin 5 days before surgery (ie, hold four doses)
- If preoperative INR is 3–4.5, stop warfarin 6 days before surgery (hold five doses)
- Start low-molecular-weight heparin 36 hours after last warfarin dose, ie:
  - Enoxaparin 1 mg/kg subcutaneously every 12 hours,* or
  - Enoxaparin 1.5 mg/kg subcutaneously every 24 hours, or
  - Dalteparin 120 U/kg subcutaneously every 12 hours, or
  - Dalteparin 200 U/kg subcutaneously every 24 hours, or
  - Tinzaparin 175 U/kg subcutaneously every 24 hours
- Give last dose of low-molecular-weight heparin approximately 24 hours before procedure
- Educate patient in self-injection and provide with written instructions
- Discuss plan with surgeon and anesthesiologist
- Check INR in morning of surgery to ensure that it is less than 1.5, or in some cases (eg, neurologic surgery) less than 1.2

After surgery

- Restart low-molecular-weight heparin approximately 24 hours after procedure or consider thromboprophylactic dose of low-molecular-weight heparin on first postoperative day if patient is at high risk for bleeding
- Discuss above with surgeon
- Start warfarin at patient's preoperative dose on postoperative day 1
- Daily prothrombin time and INR until patient is discharged and periodically thereafter until INR is in the therapeutic range
- Daily phone follow-up with patient by the Anticoagulation Clinic pharmacist to assess for adverse effects such as bleeding
- Complete blood cell count with platelets on day 3 and day 7
- Discontinue low-molecular-weight heparin when INR is 2–3 for 2 consecutive days

*Most of our experience is with enoxaparin 1 mg/kg subcutaneously every 12 hours

Data and consensus are lacking

There is a complete lack of randomized controlled data to guide recommendations about bridging therapy, and experts disagree widely about who should and who should not receive it.

For example, Kearon and Hirsh[22] recommend that no patient with a prosthetic heart valve receive intravenous heparin before or after elective surgery unless he or she has had a cardioembolic event in the preceding month. However, many cardiologists[23] *do* use

heparin as bridging therapy in patients with heart valves who have never had an embolic event, especially patients with older valve models in the mitral position.

We recommend a middle-ground position based on the current evidence and on both expert and consensus opinions. We also wish to emphasize that clinical decisions should always be individualized and that bridging anticoagulation is not always "playing it safe," since it may confer unnecessary risk in some patients.

WHO SHOULD RECEIVE BRIDGING THERAPY?

We believe that most patients receiving warfarin long-term can stop taking it 5 days before elective surgery. Most patients do not need bridging therapy, as their risk of thromboembolism is low, and bridging therapy may involve unnecessary risk of bleeding and heparin-induced thrombocytopenia.

However, common sense dictates that patients at very high risk for thromboembolism should receive heparin as a bridge while off warfarin. In this situation, it is imperative to discuss the strategy for managing perioperative anticoagulation with the patient, the surgeon, and the anesthesiologist.

Bridging therapy is not always 'playing it safe,' since it can confer risk

In intermediate-risk patients, the decision should be individualized on the basis of the risk of thromboembolism without bridging, the risk of bleeding with it, and the patient's preferences, after a detailed discussion of risks and benefits.

Patients with a history of deep vein thrombosis or pulmonary embolism

Before surgery, the risk of another venous thromboembolic event when warfarin is stopped depends primarily upon how recently the previous event occurred. The risk is highest in the first 4 weeks[24]: an estimated 0.3% to 1.3% per day without anticoagulation,[22,25,26] dropping to 0.03% to 0.2% per day in the next 4 to 12 weeks,[22,25] and to less than 0.05% per day after 12 weeks.[22,25]

Elective surgery should therefore be postponed for at least 1 month if the event occurred in the past month so that the patient can receive uninterrupted anticoagulation for this time. A vena cava filter can be considered if the patient needs urgent or emergency surgery or cannot receive effective anticoagulation.[27]

We recommend preoperative heparin bridging therapy for patients with a venous thromboembolic event in the past 1 to 3 months and in those with a hypercoagulable state marked by recurrent life-threatening thromboses. Bridging therapy should also be considered for patients with an active malignancy who have had an episode of venous thromboembolism within the past 3 months.

After surgery, patients with a history of venous thromboembolism are at high risk for more episodes if their surgery is for cancer or involves extended bed rest or trauma to veins in the leg (eg, hip or knee arthroplasty). If full-dose anticoagulation cannot be started at 24 hours, these patients should receive aggressive prophylactic treatment for venous thromboembolism with a low-molecular-weight heparin (eg, enoxaparin 40 mg subcutaneously every day or dalteparin 5,000 IU subcutaneously every day).

In contrast, the risk of thrombosis is probably trivial after minimally invasive procedures.

Patients at risk for cardioembolism due to atrial fibrillation or prosthetic valves

Dunn and Turpie,[5] in a pooled analysis, found that thromboembolic events occurred in 30 (1.6%) of 1,868 patients who had warfarin therapy stopped, with or without bridging, and 7 (0.4%) had strokes. These numbers may be overestimates or underestimates, owing to the heterogeneity and poor quality of identified studies.

Since no randomized trials have examined the different strategies for interrupting anticoagulation in patients at risk for cardioembolism, we believe the estimates of the relative risk of stroke or other cardioembolic events should be based on the annual stroke rates observed when patients are not anticoagulated for extended periods of time. One can assume that 1 day off anticoagulation carries a thrombosis risk that is 1/365th of the annual risk,[22] although this assumption has not been clinically validated and in theory may not reflect the true risk.

For example, cardioversion without anticoagulation is generally accepted as safe in patients with new-onset atrial fibrillation of less than 48 hours' duration,[28] since an intracardiac thrombus takes time to form. By this reasoning, we might assume that 48 hours off anticoagulation should be safe for most patients at risk for cardioembolism.

On the other hand, there is biochemical evidence of a "rebound" phenomenon after warfarin is stopped that may lead to a prothrombotic state and increase the risk of thrombosis.[3] A handful of thrombotic events have been reported in case series of patients in whom anticoagulation was stopped because of major hemorrhage (eg, intracranial bleeding) or surgery,[29–37] but available reports do not permit a precise calculation of the average rate of cardioembolism in this setting.

While it is impossible to know the exact risk of cardioembolism during a brief period of interrupted anticoagulant therapy, it is possible to identify patients at high risk for thrombosis and those at relatively low risk.

Prosthetic heart valves, atrial fibrillation. On warfarin, patients with prosthetic heart valves have a risk of cardioembolism similar to that in patients with atrial fibrillation—approximately 4% per year, with a lifetime risk of up to 35%.[38–41] The risk is higher with older types of valves, especially the ball-in-cage type (eg, Starr-Edwards) and the Björk-Shiley valves, than with tilting disk or bileaflet valves.[41] In addition, the risk is approximately twice as high with prosthetic mitral valves than with prosthetic aortic valves.[41]

If there are no other risk factors for cardioembolism, warfarin therapy can be safely interrupted without bridging therapy in most patients with either a prosthetic heart valve or atrial fibrillation. However, if the two coexist, the patient's risk is higher and bridging therapy is appropriate.

Tinker et al[35] reported that 159 patients with previously implanted mechanical valves had their warfarin therapy stopped while they underwent 180 surgeries without bridging. The thromboembolic complication rate was 10%, but the earliest complication was seen 2 years later. In terms of bleeding, about "13% experienced various difficulties with hemostasis," and the bleeding episodes were not categorized as major or minor.

In another retrospective study,[36] 35 patients with mechanical valves underwent 44 noncardiac procedures without bridging anticoagulation. Thromboembolism developed in 2 of the 10 patients with mechanical mitral valves (all older valve models), vs none of the 25 patients with mechanical aortic valves.

Prior embolic events are the most important risk factor for cardioembolism.[42] The annual risk of recurrent events is about three times as high in patients with atrial fibrillation with a history of a cardioembolic stroke than in those without[43]; the same probably also applies to patients with mechanical valves.

Other risk factors that should be considered in deciding whether to use bridging heparin in patients with prosthetic heart valves or atrial fibrillation include:

- Rheumatic atrial fibrillation, particularly with mitral stenosis, poses an especially high risk for cardiac embolism[44]
- Congestive heart failure
- Hypertension
- Age greater than 65 years
- Diabetes
- The combination of prosthetic heart valves plus concurrent atrial fibrillation or systolic dysfunction[39,44]
- Valve replacement in the preceding few months.[39]

As a general rule, the more risk factors present, the more seriously bridging therapy should be considered.

Wait at least 1 month for elective surgery after any venous thromboembolism

Nonembolic strokes

It is unclear whether warfarin prevents strokes due to atherosclerotic disease of the carotid or vertebral arteries any better than aspirin does.[45] Furthermore, cerebrovascular disease may increase the rate of heparin-associated intracranial hemorrhage.[46]

In the absence of a compelling clinical history (such as recurrent strokes or transient ischemic attacks while off anticoagulation and none while on anticoagulation), the risks of bridging therapy probably outweigh the benefits for most patients on long-term anticoagulation for cerebrovascular disease.

If a patient has risk factors for both cardioembolism and nonembolic stroke (eg, atrial fibrillation and carotid stenosis), it may be unclear whether a prior event was due to cardioembolism. Unless there is a compelling history to suggest that prior events were due to intrinsic cerebral atherosclerosis (eg, if the patient has recurrent transient ischemic attacks ipsilateral to a known carotid stenosis),[44] such patients should probably be assumed to have had cardioembolic events, and bridging treatment should be considered.

UNFRACTIONATED VS LOW-MOLECULAR-WEIGHT HEPARIN FOR BRIDGING

The two main options for bridging therapy are low-molecular-weight heparins and unfractionated heparin. If the patient has a history of heparin-induced thrombocytopenia, however, it may be necessary to use danaparoid or intravenous direct thrombin inhibitors, or perhaps a synthetic pentasaccharide such as fondaparinux. Only the intravenous direct thrombin inhibitors are FDA-approved for treatment of heparin-induced thrombocytopenia.

Prior embolic events are the most important risk factor for cardioembolism

Advantages of low-molecular-weight heparins

Compared with unfractionated heparin, low-molecular-weight heparins have better bioavailability, more predictable dose responses, and longer plasma half-lives, and they interact less with platelets, endothelial cells, macrophages, and plasma proteins.[47]

Moreover, unlike unfractionated heparin, which should be given intravenously in the hospital for full protection, the low-molecular-weight heparins can be given subcutaneously on an outpatient basis.[47]

Clinical trials suggest that low-molecular-weight heparins may be safer and more effective than unfractionated heparin in the outpatient treatment of deep venous thrombosis.[48,49] They also pose less risk of causing heparin-induced thrombocytopenia.[49]

However, the safety and efficacy of low-molecular-weight heparins as bridging therapy have not been established in randomized clinical trials. Before low-molecular-weight heparins became available, only intravenous unfractionated heparin was used for bridging.

Nonrandomized studies of heparin bridging

In a prospective study by Katholi et al,[37] 39 patients with mechanical valves underwent 45 noncardiac procedures. Patients with aortic mechanical valves had their warfarin stopped without bridging, while patients with mitral mechanical valves received parenteral vitamin K before surgery and intravenous unfractionated heparin afterward. There was one case of major bleeding in the mitral valve group. No thromboembolic events occurred in this study.

More recent studies[50–56] included a total of 745 surgical patients with who were receiving warfarin for various medical conditions including mechanical heart valves, atrial fibrillation, stroke, cardiomyopathy, coronary artery disease with apical thrombus, and a history of prior venous thromboembolism. They received low-molecular-weight heparins preoperatively as outpatients and postoperatively as inpatients and outpatients. There were 3 episodes of major bleeding and 21 cases of minor bleeding, and two patients experienced transient ischemic attacks. This translates into a major bleeding rate of 0.4% and a thromboembolic rate of 0.3%.

None of these studies followed patients long-term to look for thrombosis in mechanical valves. Furthermore, without randomized studies and stratification according to thromboembolic risk, the possibility of selection bias cannot be excluded. Nevertheless, we believe the pooled results of these studies suggest that low-molecular-weight heparin is safe and effective for short-term perioperative bridging therapy and is simpler and less costly to use than unfractionated heparin.

On the basis of this limited evidence and our own experience,[52] we developed a bridging protocol that is similar but distinct from the one developed by Spandorfer et al,[54] and which we use in our anticoagulation clinic (TABLE 2).

RISKS OF BRIDGING THERAPY

Bleeding

In clinical trials, the incidence of major bleeding during initial heparin treatment for acute deep venous thrombosis was quite similar with both low-molecular-weight heparin and

unfractionated heparin, ranging from 0.5% to 5.0%.

One trial[57] found that the incidence of major bleeding with the low-molecular-weight heparin tinzaparin was only 0.5%, vs 5.0% with unfractionated heparin. A meta-analysis,[58] however, found no difference in bleeding risk between the two types of heparin.

Postoperatively, the nature of the surgery also affects bleeding risk, and this must be considered when a decision to use bridging therapy is made.

When a patient changes over from a stable warfarin regimen to a low-molecular-weight heparin or unfractionated heparin, the risk of bleeding may be consequential, since the intensity of anticoagulation may be higher with a heparin product in full doses. The targets for the prothrombin time (PT) and PT ratios that were used in the past, if converted into today's INR, would be higher than they are now; for example, an INR greater than 4.0 was not always considered overanticoagulation.[59] These targets were reduced because of an unacceptable bleeding risk during long-term treatment.

The rates of bleeding with warfarin vs heparin have not been directly compared in clinical trials. However, rates of major spontaneous hemorrhage were as high as 5% in patients receiving intravenous heparin for 5 to 10 days to treat venous thromboembolism in clinical trials.[57] This rate is comparable to bleeding rates observed in clinical trials during a full year of warfarin therapy.[59]

Although this comparison may overestimate the risk of bleeding with heparin compared with warfarin, we certainly cannot assume the risks are equivalent—especially when intravenous heparin is used and the activated partial thromboplastin time may be occasionally supratherapeutic.[60] We also believe that these rates of bleeding observed in clinical trials may be lower than what we observe in clinical practice and especially in patients at high risk.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia, which may be associated with thrombosis in 30% to 80% of cases, needs to be considered in deciding whether to use bridging anticoagulation. About 3% of patients treated with unfractionated heparin develop heparin-induced thrombocytopenia, while the incidence with low-molecular-weight heparin is closer to 1%.[61]

Consequently, in patients at very low risk for thrombosis, we may actually increase the risk of thromboembolism when we use bridging therapy. This risk can be minimized by using a low-molecular-weight heparin but may still exceed the risk of thrombosis incurred by simply stopping warfarin.

Many patients placed on a bridging protocol may develop heparin-induced thrombocytopenia as early as 1 day into therapy because of prior exposure to heparin. Therefore, close monitoring of the platelet count is recommended on days 1, 3, and 7 after surgery.

Precautions with epidural catheters when using low-molecular-weight heparins

Symptomatic epidural hematomas can develop when a spinal or epidural catheter is inserted or removed in a patient receiving anticoagulation therapy. Therefore, the American Society of Regional Anesthesia[62,63] recommends the following for patients receiving a low-molecular-weight heparin preoperatively:

- Coadministration of antiplatelet or oral anticoagulant medication is contraindicated
- Lumbar puncture should be delayed at least 12 hours after the last thromboprophylactic dose of low-molecular-weight heparin (enoxaparin 40 mg or dalteparin 5,000 U), and at least 24 hours if treatment doses of low-molecular-weight heparin are being used (eg, enoxaparin 1 mg/kg every 12 hours, enoxaparin 1.5 mg/kg every 24 hours, dalteparin 120 U/kg every 12 hours, dalteparin 200 U/kg every 24 hours, or tinzaparin 175 U/kg every 24 hours).

If a low-molecular-weight heparin is used postoperatively:

- The first dose should be given no earlier than 24 hours after surgery if being given twice daily for thromboprophylaxis or at treatment doses
- Indwelling catheters may be safely maintained if low-molecular-weight heparins are given as a single daily thromboprophylactic dose
- In general, the epidural catheter should be removed about 12 hours after the last prophylactic dose

Measure platelets on days 1, 3, and 7 after surgery on bridging therapy

- The first dose of a low-molecular-weight heparin should be given no earlier than 2 hours after the catheter is removed
- Concurrent use of a low-molecular-weight heparin and indwelling epidural catheter is generally not recommended
- Low-molecular-weight heparin use should be delayed for 24 hours if the patient experienced excessive trauma to the epidural space during attempted epidural or spinal anesthesia.

Low-molecular-weight heparins are not recommended in pregnant patients with prosthetic heart valves

The Lovenox (enoxaparin) package insert states: "The use of Lovenox Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. Although a causal relationship has not been established these deaths may have been due to therapeutic failure or inadequate anticoagulation. No patients in the heparin/warfarin group (0 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion and premature delivery. Therefore, frequent monitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may be needed."

A consensus group[64] recently reviewed the literature and details of the two deaths reported to the FDA and noted that in both pregnant patients some of the recorded anti-Xa levels (a test used to measure the therapeutic efficacy of low-molecular-weight heparin) prior to valve thrombosis were subtherapeutic, suggesting that weight-based dosing alone may be suboptimal in pregnancy.

If low-molecular-weight heparins are used in pregnant patients, anti-Xa levels (peaks and troughs) should be checked frequently and dose changes made to achieve a therapeutic level between 0.5 and 1.2 anti-Xa units. Pregnancy is associated with biochemical, autonomic, and physiological changes that can affect the pharmacokinetics of many drugs, including enoxaparin. This may lead to lower anti-Xa levels.[65,66]

We believe that until more safety data are available, bridging therapy with low-molecular-weight heparins should be avoided in pregnant patients with prosthetic valves undergoing surgery. Instead, this patient group should be hospitalized to receive intravenous unfractionated heparin.

We and this consensus group, however, still maintain that low-molecular-weight heparins are safe to use without monitoring in nonpregnant patients with prosthetic valves. Although some clinicians are reluctant to embrace this practice on the basis of the limited available data,[50–56] it should be noted that there are actually fewer total patients in published case series in which unfractionated heparin was used[35–37] than in studies with low-molecular-weight heparin. The pooled outcomes looking at the rate of thromboembolism and major bleeding favor the use of low-molecular-weight heparin. Therefore, the use of unfractionated heparin for bridging therapy in patients with prosthetic heart valves should not be considered an evidence-based standard of care.

Before restarting anticoagulation, discuss it with the surgeon

RESUMING ANTICOAGULATION AFTER SURGERY

The nature of the surgery often dictates the timing and intensity of postoperative anticoagulation.

For patients at high risk for thromboembolism, full-dose (therapeutic) anticoagulation should be started as soon as hemostasis has been achieved; discussion with the surgeon prior to resuming anticoagulation is always advisable.

For uncomplicated nonintracranial surgeries, intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin can usually be safely restarted 24 hours after surgery.

If full-dose anticoagulation is desired, unfractionated heparin without bolus is pre-

ferred over low-molecular-weight heparin during the first 24 hours postoperatively, since it is more easily reversed should postoperative bleeding occur. Alternatively, prophylactic doses of a low-molecular-weight heparin can be started during the first 24 hours after surgery.

For patients who were on warfarin for venous thromboembolism, full-dose anticoagulation should be initiated as soon as possible after surgical procedures involving trauma to leg veins or postoperative bed rest, since this is a very high-risk time for venous thromboembolism recurrence. Full-dose anticoagulation should be considered in these patients, even if they did not require preoperative heparin bridging. Since warfarin does not have immediate anticoagulant effects, it can be resumed the day after surgery unless prolonged postoperative bleeding is anticipated.

REFERENCES

1. **Waterman AD, Banet G, Milligan PE, et al.** Patient and physician satisfaction with a telephone-based anticoagulation service. J Gen Intern Med 2001; 16:460–463.
2. **Palareti G, Legnani C, Guazzaloca G, et al.** Activation of blood coagulation after abrupt or stepwise withdrawal of oral anticoagulants—a prospective study. Thromb Haemost 1994; 72:222–226.
3. **Palareti G, Legnani C.** Warfarin withdrawal. Pharmacokinetic-pharmacodynamic considerations. Clin Pharmacokinet 1996; 30:300–313.
4. **De Groot MR, Van Marwijk NT, et al.** Abrupt versus gradual withdrawal of vitamin K antagonist treatment in patients with venous thromboembolic disease: assessment of hypercoagulability and clinical outcome. Clin Lab 2000; 46:575–581.
5. **Dunn AS, Turpie AG.** Perioperative management of patients receiving oral anticoagulants: a systematic review. Arch Intern Med 2003; 163:901–908.
6. **Konstantatos A.** Anticoagulation and cataract surgery: a review of the current literature. Anaesth Intensive Care 2001; 29:11–18.
7. **Kadakia SC.** Gastrointestinal endoscopy in patients taking antiplatelet agents and anticoagulants: survey of ASGE members. American Society for Gastrointestinal Endoscopy. J Clin Gastroenterol 1995; 20:139–141.
8. **Kadakia SC, Angueira CE, Ward JA, Moore M.** Gastrointestinal endoscopy in patients taking antiplatelet agents and anticoagulants: survey of ASGE members. American Society for Gastrointestinal Endoscopy. Gastrointest Endosc 1996; 44:309–316.
9. **Eisen GM, Baron TH, Dominitz JA, et al.** Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. Gastrointest Endosc 2002; 55:775–779.
10. **Ansell JE.** The perioperative management of warfarin therapy. Arch Intern Med 2003; 163:881–883.
11. **Wahl MJ.** Dental surgery in anticoagulated patients. Arch Intern Med 1998; 158:1610–1616.
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. **Sindet-Pedersen S, Ramstrom G, Bernvil S, Blomback M.** Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. N Engl J Med 1989; 320:840–843.
14. **Billingsley EM.** Intraoperative and postoperative bleeding problems in patients taking warfarin, aspirin, and nonsteroidal antiinflammatory agents. A prospective study. Dermatol Surg 1997; 23:381–383.
15. **Thumboo J, O'Duffy JD.** A prospective study of the safety of joint and soft tissue aspirations and injections in patients taking warfarin sodium. Arthritis Rheum 1998; 41:736–739.
16. **Lanzat M, Danna AT, Jacobson DS.** New protocols for perioperative management of podiatric patients taking oral anticoagulants. J Foot Ankle Surg 1994; 33:16–20.
17. **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.
18. **Martin JE, Lutomski DM.** Warfarin resistance and enteral feedings. JPEN J Parenter Enteral Nutr 1989; 13:206–208.
19. **Shields RC.** Efficacy and safety of intravenous phytonadione (vitamin K1) in patients on long-term oral anticoagulant therapy. Mayo Clin Proc 2001; 76:260–266.
20. **Crowther MA, Donovan D, Harrison L, McGinnis J, Ginsberg J.** Low-dose oral vitamin K reliably reverses over-anticoagulation due to warfarin. Thromb Haemost 1998; 79:1116–1118.
21. **Deveras RA, Kessler CM.** Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. Ann Intern Med 2002; 137:884–888.
22. **Kearon C, Hirsh J.** Management of anticoagulation before and after elective surgery. N Engl J Med 1997; 336:1506–1511.
23. **Douketis JD, Crowther MA, Cherian SS.** Perioperative anticoagulation in patients with chronic atrial fibrillation who are undergoing elective surgery: results of a physician survey. Can J Cardiol 2000; 16:326–330.
24. **Levine MN, Hirsh J, Gent M, et al.** Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. Thromb Haemost 1995; 74:606–611.
25. **Coon WW, Willis PW 3rd.** Recurrence of venous thromboembolism. Surgery 1973; 73:823–827.
26. **Hull R, Delmore T, Genton E, et al.** Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. N Engl J Med 1979; 301:855–858.
27. **Bergqvist D.** The role of vena caval interruption in patients with venous thromboembolism. Prog Cardiovasc Dis 1994; 37:25–37.
28. **Weigner MJ, Caulfield TA, Danias PG, Silverman DI, Manning WJ.** Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. Ann Intern Med 1997; 126:615–620.
29. **Ananthasubramaniam K, Beattie JN, Rosman HS, Jayam V, Borzak S.** How safely and for how long can warfarin therapy be withheld in prosthetic heart valve patients hospitalized with a major hemorrhage? Chest 2001; 119:478–484.
30. **Crawley F, Bevan D, Wren D.** Management of intracranial bleeding associated with anticoagulation: balancing the risk of further bleeding against thromboembolism from prosthetic heart valves. J Neurol Neurosurg Psychiatry 2000; 69:396–398.
31. **Phan TG, Wijdicks EF.** Management of intracranial bleeding associated with anticoagulation: balancing the risk of further bleeding against thromboembolism from prosthetic heart valves. J Neurol Neurosurg Psychiatry 2001; 70:820–821.
32. **Phan TG, Koh M, Wijdicks EF.** Safety of discontinuation of anticoagulation in patients with intracranial hemorrhage at high thromboembolic risk. Arch Neurol 2000; 57:1710–1713.
33. **Wijdicks EF, Schievink WI, Brown RD, Mullany CJ.** The dilemma of discontinuation of anticoagulation therapy for patients with intracranial hemorrhage and mechanical heart valves. Neurosurgery 1998; 42:769–773.
34. **Butler AC, Tait RC.** Restarting anticoagulation in prosthetic heart valve patients after intracranial haemorrhage: a 2-year follow–up. Br J Haematol 1998; 103:1064–1066.
35. **Tinker JH, Tarhan S.** Discontinuing anticoagulant therapy in surgical patients with cardiac valve prostheses. Observations in 180 operations. JAMA 1978; 239:738–739.

36. **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.
37. **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.
38. **Shapira Y, Sagie A, Battler A.** Low-molecular-weight heparin for the treatment of patients with mechanical heart valves. Clin Cardiol 2002; 25:323–327.
39. **Bettadapur MS, Griffin BP, Asher CR.** Caring for patients with prosthetic heart valves. Cleve Clin J Med 2002; 69:75–87.
40. **Cannegieter SC, van der Meer FJ, Briet E, Rosendaal FR.** Warfarin and aspirin after heart-valve replacement. N Engl J Med 1994; 330:507–508.
41. **Cannegieter SC, Rosendaal FR, Briet E.** Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994; 89:635–641.
42. **Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ.** Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001; 285:2864–2870.
43. **Atrial Fibrillation Investigators.** Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials [erratum appears in Arch Intern Med 1994; 154:2254]. Arch Intern Med 1994; 154:1449–1457.
44. **Cerebral Embolism Task Force.** Cardiogenic brain embolism. Arch Neurol 1986; 43:71–84.
45. **Mohr JP, Thompson JL, Lazar RM, et al.** A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001; 345:1444–1451.
46. **Levine MN, Raskob G, Landefeld S, Hirsh J.** Hemorrhagic complications of anticoagulant treatment. Chest 1995; 108(suppl 4):276S–290S.
47. **Hirsh J, Dalen J, Anderson DR, et al.** Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001; 119(suppl 1):8S–21S.
48. **Koopman MM, Prandoni P, Piovella F, et al.** Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. N Engl J Med 1996; 334:682–687.
49. **Levine M, Gent M, Hirsh J, et al.** A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996; 334:677–681.
50. **Ferreira IJ, Dos L, Tornos MP, Soler J.** Is low-molecular-weight heparin a safe alternative to unfractionated heparin in patients with prosthetic mechanical heart valves who must interrupt antithrombotic therapy? [abstract]. Eur Heart J 2000; 21:301.
51. **Galla JM, Fuhs BE.** Outpatient anticoagulation protocol for mechanical valve recipients undergoing non-cardiac surgery [abstract]. J Am Coll Cardiol 2000; 135:531A.
52. **Jaffer A, Ahmed M, Bragg L, et al.** Safety and efficacy of using low-molecular-weight heparins to bridge patients on long-term warfarin [abstract]. J Thromb Haemost 2003; 1(suppl 1):1862.
53. **Johnson JTA.** Temporary discontinuation of oral anticoagulants: role of low-molecular-weight heparin [abstract]. Thromb Haemost 2001; 62(suppl):62–63.
54. **Spandorfer J.** The management of anticoagulation before and after procedures. Med Clin North Am 2001; 85(5):1109–1116.
55. **System UH.** Home LMWH bridge therapy in cardiac valve replacement: safe, effective and cost saving. Formulary 2000; 35:990–991.
56. **Tinmouth AH, Morrow BH, Cruickshank MK, Moore PM, Kovacs MJ.** Dalteparin as periprocedure anticoagulation for patients on warfarin and at high risk of thrombosis. Ann Pharmacother 2001; 35:669–674.
57. **Hull RD, Raskob GE, Pineo GF, et al.** Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992; 326:975–982.
58. **Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM.** Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. Ann Intern Med 1999; 130:800–809.
59. **Levine MN, Raskob G, Landefeld S, Kearon C.** Hemorrhagic complications of anticoagulant treatment. Chest 2001; 119(suppl 1):108S–121S.
60. **Siragusa S, Cosmi B, Piovella F, Hirsh J, Ginsberg JS.** Low-molecular-weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: results of a meta-analysis. Am J Med 1996; 100:269–277.
61. **Warkentin TE, Levine MN, Hirsh J, et al.** Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995; 332:1330–1335.
62. **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.
63. **Horlocker TT.** Thromboprophylaxis and neuraxial anesthesia. Orthopedics 2003; 26(suppl 2):243–249.
64. **Topol E.** Anticoagulation and enoxaparin use in patients with prosthetic heart valves and/or pregnancy. Clinical Cardiology Consensus Reports. October 2002:1–19.
65. **Laifer SA, Casele HL.** Puerperal thromboprophylaxis: comparison of the anti-Xa activity of enoxaparin and unfractionated heparin. Br J Obstet Gynaecol 1999; 106:614–615.
66. **Casele HL, Laifer SA, Woelkers DA, Venkataramanan R.** Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy. Am J Obstet Gynecol 1999; 181:1113–1117.

ADDRESS: *Amir K. Jaffer, MD, Department of General Internal Medicine, A72, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail jaffera@ccf.org.*