

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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## Anticoagulation Therapy in Patients With Prosthetic Heart Valves

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### **H&O** How is thromboprophylaxis achieved in patients with prosthetic heart valves?

**JD** Patients with prosthetic heart valves, whether mechanical or biologic, typically receive thromboprophylaxis with an anticoagulant to prevent blood clots in the valve itself or embolization of such clots, which can cause a stroke. In patients with a mechanical prosthetic heart valve, lifelong thromboprophylaxis is recommended with an oral vitamin K antagonist such as warfarin. For short-term anticoagulation, typically when warfarin therapy is initiated or temporarily interrupted, low-molecular weight heparins (LMWHs) are used as “bridging anticoagulation” during the time patients are not therapeutically anticoagulated with warfarin. Warfarin and other vitamin K antagonists are used in patients with prosthetic heart valves because these are the best-studied agents, with established efficacy in preventing thromboembolic events. In addition, vitamin K antagonists have a well-defined safety profile. Other than potential bleeding complications, which can occur with administration of all antithrombotic agents, vitamin K antagonists have no significant long-term drug-related adverse effects. The risk of anticoagulant-related bleeding can be minimized by monitoring the level of anticoagulation with periodic blood tests, typically every 3–6 weeks, with the international normalized ratio (INR). Evidence is limited in regard to the efficacy and safety of long-term use of LMWH or other antithrombotic drugs like aspirin or clopidogrel (Plavix, Sanofi-Aventis/Bristol-Myers Squibb) in patients with prosthetic heart valves.

### **H&O** Are there particular situations when a LMWH may be chosen as a thromboprophylactic agent in a patient with a prosthetic heart valve?

**JD** LMWHs may be used in lieu of warfarin during pregnancy because warfarin is associated with embryopathy, particularly if it is administered during the first trimester. Controversy exists, however, regarding the magnitude of this risk. Recently, the US Food and Drug Administration (FDA) issued a warning concerning the use of one particular LMWH, enoxaparin (Lovenox, Sanofi-Aventis), during pregnancy due to several reports that pregnant women with a prosthetic heart valve who received this drug developed valve thrombosis, which in some cases was fatal. However, the evidence that these deaths were attributable to a treatment failure rather than inadequate dosing or monitoring, or some other factor, is not compelling. As a consequence of these reports, concern has arisen in regard to the use of LMWH in non-pregnant patients with a mechanical heart valve. On the other hand, this concern has been tempered by studies involving, in total, approximately 2,500 patients, which have shown that short-term (6–10 days) use of LMWH is safe for bridging anticoagulation, with no reported episodes of valve thrombosis.

Rarely, LMWH is used in patients who have allergies to warfarin, but even in this clinical setting, other alternatives to warfarin exist (eg, anisindione), although such agents are not widely available for clinical use.

### **H&O** Could you elaborate on the use of LMWH as a bridging anticoagulant?

**JD** LMWH may be used as bridging anticoagulation because of its rapid and short-acting blood-thinning

effect, whereas with warfarin or other vitamin K antagonists, the blood-thinning effect takes several days to be induced. LMWH can be used as bridging anticoagulation in three clinical settings. The first setting is in a warfarin-treated patient who experiences a stroke or transient ischemic attack when the patient's level of anticoagulation, as measured by the INR, is subtherapeutic (ie, INR <2.0). In this setting, LMWH may be administered to supplement the anticoagulation effect of the vitamin K antagonist. Increasing the dose of warfarin may be inadequate in an acute situation such as a stroke or valve thrombosis because of its delayed anticoagulant effect.

The second setting in which LMWH can be used as bridging anticoagulation is in a patient with a prosthetic heart valve when such a patient requires an elective surgical or other invasive procedure that necessitates warfarin interruption, in order to minimize the risk of perioperative bleeding. In this clinical setting, warfarin is typically stopped approximately 5 days before the procedure to allow adequate time for the anticoagulant effect to recede. During the time that the anticoagulant effect is receding, LMWH is administered in order to sustain a therapeutic level of anticoagulation for the longest possible time in the perioperative period, with the intent of minimizing the risk of thromboembolism. LMWH is typically stopped the morning of the day before the procedure, so as to ensure no residual anticoagulant effect at the time of surgery. After surgery, LMWH is administered for approximately the first 5 days in conjunction with warfarin because the latter's anticoagulation effect does not begin until after that period. In these perioperative situations, it is necessary to exercise caution in administering any anticoagulants in order to minimize the bleeding risk. Studies have shown that the closer the proximity of the administration of LMWH to surgery, the higher the risk of bleeding. Clinicians must balance the risk of thromboembolism with the risk for bleeding accompanying the procedure and additionally account for any unexpected bleeding that occurs during the procedure.

The third setting in which LMWH can be used as bridging anticoagulation is in a patient with a newly implanted prosthetic heart valve, in whom LMWH after surgery may be used until a therapeutic level of anticoagulation has been achieved with warfarin, which is also initiated with heparin or LMWH after surgery.

In the clinical settings of perioperative bridging anticoagulation, where LMWH is used during temporary interruption of warfarin, we lack comparative data from randomized trials assessing this approach with other management strategies. Is LMWH better for bridging than, for example, unfractionated heparin? Is bridging anticoagulation necessary at all? Is simply stopping warfarin without bridging anticoagulation sufficient? Though answers to

these questions have not been addressed by randomized trials, it should be acknowledged that conducting trials is problematic from a methodologic and ethical standpoint. In a nutshell, we do not know categorically that LMWHs are effective (or ineffective) in preventing valve thrombosis or stroke. The use of LMWH in patients with a prosthetic heart valve is not an indication approved by the FDA. Therefore, in general, the dose regimen that would be administered is extrapolated from that used to treat people with other thromboembolic conditions, such as deep vein thrombosis, pulmonary embolism, myocardial infarction, or acute coronary syndrome.

### **H&O** What concerns exist regarding the use of LMWH in patients with comorbidities?

**JD** Doses of LMWH are modified in patients with renal dysfunction, but there are not many high-quality data on the treatment of such individuals. It is known that enoxaparin, in particular, may accumulate in patients with severe renal insufficiency. This risk may not exist with other LMWHs. In general, though, for all LMWHs, some caution must be exercised when administering the agents in the setting of renal dysfunction. The dose must either be reduced empirically by 33–50%, or it is necessary to monitor the anticoagulant effect of LMWHs with the antifactor Xa level, which indicates if too much or too little LMWH is being administered.

A more common scenario is in patients who are very obese or, to a lesser extent, underweight. With the typical patient, who weighs approximately 75 kg, the dose regimen used is that used in other conditions. Many of the trials that evaluated LMWHs excluded patients over a certain weight, typically 100 kg. However, people over this weight level are common in North America and, at present, it is unclear if an obese or, otherwise, very heavy, patient should simply receive a weight-based dose of LMWH without dose capping. Thus, a patient who weighs 75 kg would receive 75 mg (1 mg/kg) enoxaparin; however, should a patient who weighs 150 kg, for example, receive 150 mg of enoxaparin? The general consensus is that it is acceptable to dose according to weight, rather than to use a capped dose, but there are not many high-quality data on the efficacy and safety of weight-based dosing in individuals at the extremes of body weight.

There are no age-related effects on the pharmacokinetics or pharmacodynamics of LMWHs, as with warfarin, except in the setting of impaired renal function. If a person is frail or debilitated, a caregiver is required to administer the LMWH, whereas it is typically self-administered in healthier patients. The pharmacokinetics or pharmacodynamics of LMWH during pregnancy are less studied. Consequently, clinicians may perform

antifactor Xa level testing during pregnancy to ensure the level of anticoagulation is appropriate. LMWHs do not affect the pharmacodynamics of other drugs per se, but the risk for bleeding is increased with co-administration of antithrombotic drugs, such as adding aspirin or clopidogrel to warfarin.

Patients with mechanical heart valves, particularly older-generation valves (eg, ball-cage valve, tilting-disc valve), are at a higher risk of developing thromboembolic sequelae due to the increased thrombogenicity of the valve itself. It is recommended that these individuals receive daily low-dose aspirin (ie, 81 mg) to supplement their anticoagulation therapy with warfarin, as the increased risk for bleeding with combined therapy is offset by the decreased risk for thromboembolism. In patients with a newer-generation aortic valve replacement (eg, bileaflet valve), the indication for aspirin use is not as strong, though it still may be considered in selected patients, particularly those at lower risk for bleeding.

### **H&O** Could you discuss malignant proliferation in the setting of prosthetic heart valves?

**JD** Malignancies in patients with prosthetic heart valves appear to be very rare but such reports exist in the medical literature. There are isolated reports of non-Hodgkin lymphoma and myocardial sarcoma in patients with prosthetic heart valves, which have been thought to be related

to the foreign substance material of the heart valve, either the Dacron fabric used to sew the valve onto the tissue ring or the silver coating of the valve. It is possible these foreign substances generate an immune-mediated reaction that, in turn, leads to local malignant proliferation either in a cardiac lymph gland or in the muscles of the heart itself. Due to the scarcity of such reports, coupled with the large number of patients with mechanical prosthetic heart valves who never experience such conditions, it is difficult to know whether these reported malignancies are associated with the mechanical valve or if they are due to other patient-related factors.

### **Suggested Reading**

Douketis JD. Perioperative anticoagulant management in patients who are receiving oral anticoagulant therapy: a practical guide for clinicians. *Thomb Res.* 2002;108:3-13.

Descarries LM, Leduc L, Khairy P, Mercier LA. Low-molecular-weight heparin in pregnant women with prosthetic heart valves. *J Heart Valve Dis.* 2006;15:679-685.

Meurin P, Tabet JY, Weber H, Renaud N, Ben Driss A. Low-molecular-weight heparin as a bridging anticoagulant early after mechanical heart valve replacement. *Circulation.* 2006;113:564-569.

Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation in patients who require temporary interruption of warfarin for an elective surgical or invasive procedure: assessment of a standardized peri-procedural anticoagulation regimen. *Arch Intern Med.* 2004;169:1319-1326.

Ginsberg JS, Chan WS, Bates SM, Kaatz S. Anticoagulation of pregnant women with mechanical heart valves. *Arch Intern Med.* 2003 24;163:694-698.