

Anticoagulant bridging: Prosthetic heart valves, labeling changes, and limiting issues of liability

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Recently, enoxaparin (Lovenox) product labeling has been revised to address this anticoagulant's use in patients with prosthetic heart valves.¹ The package labeling now states the use of enoxaparin injection is not recommended for prophylaxis in patients with prosthetic heart valves. It also states that pregnant women with prosthetic heart valves may be at higher risk for thromboembolism.¹ This change has prompted many questions, including the following:

- what is the background that precipitated the recent "Dear Health Care Professional Letter,"
- which patients are affected,
- what are the options and limitations for bridging patients based upon recommendations of the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy,
- what is the evidence to support the role of LMWH in bridge therapy, and
- how may we limit liability and yet best serve the interest of the patient?

Responses to these questions are addressed in this commentary.

LABELING CHANGE BACKGROUND

The labeling change was primarily brought about by a few events observed in a clinical study of pregnant women with prosthetic heart valves. The study was an independent, open randomized study conducted in South Africa that

evaluated enoxaparin with warfarin and unfractionated heparin (UFH) in pregnant patients with prosthetic heart valves. After 12 patients were enrolled (out of a planned 110), the study was terminated because of two deaths in the enoxaparin group.

Patient 1 received 80 mg twice daily and succumbed at 12 weeks gestation (32-year-old pregnant woman with prosthetic mitral [Carbomedics 31-mm] valve). Anti-Xa levels were taken 2 days prior to her death and were 0.33 IU/ml and 0.78 IU/ml.

Patient 2 received 80 mg twice daily and died at 31 weeks gestation (36-year-old pregnant woman with prosthetic mitral and aortic [Hall Kaster] valves). An anti-Xa level taken 20 days prior to her death was 0.43 IU/ml. The anti-Xa levels were subtherapeutic in each patient report, though the exact timing of the samples was not reported in either case. It is interesting that while each of these patients died within different trimesters of pregnancy, the reported dosing had not been weight-adjusted throughout the pregnancy.²

In the setting of pregnancy, patients' weight increased, which would suggest a continued increase in dose and close follow-up for assured maintenance of therapeutic anti-Xa levels. As a result of increasing weight and increased production of clotting factors, these women were in a very high-risk patient population.³

Concerns about teratogenicity also prompted another labeling change. Revised labeling in the pregnancy subsection of the precautions section states that there have been reports of congenital anomalies—including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defects—in infants born to women who received enoxaparin during pregnancy. Labeling adds that no cause and effect relationship has been established and that the incidence is not higher than in the general population.¹

FOCUS ON PATIENTS WITH PROSTHETIC HEART VALVES

Each organization must carefully review these adverse effect case reports, assess ramifications on their own patient population, and distinguish three distinct patient categories.

1. Patients who have prosthetic heart valves.
2. Patients who are pregnant.
3. Patients who are pregnant and have prosthetic heart valves.

The greatest impact of this labeling change—because of the sheer numbers—is on patients who have prosthetic heart valves. However, therapeutic options are limited.

BRIDGING OPTIONS LIMITED

Specific to bridging, the recommendations of the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy suggest "UFH or LMWH be used until the INR is at a therapeutic level for 2 consecutive days (grade 2C)."⁴ Since the use of continuous infusion UFH cited in the guidelines invariably results in increased lengths of stay for

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hospitalized patients and adjusted-dose subcutaneous UFH has little data to support its use, many have turned to LMWH in the outpatient setting for bridging—though this is not an FDA labeled indication for LMWH therapy. Although not found currently in the labeling of dalteparin (Fragmin) or tinzaparin (Innohep), this concern regarding the use of LMWH in this situation cannot be ruled out unequivocally for all LMWHs.

LMWH EVIDENCE IN BRIDGING THERAPY

Numerous case series⁵⁻⁸ report the safe and effective use of LMWHs in non-pregnant patients with prosthetic heart valves. Montalescot et al⁵ in a comparative, nonrandomized study, enrolled 208 consecutive patients who underwent a single or double heart valve replacement with mechanical prostheses. Patients received subcutaneous anticoagulation with UFH in the first period (n = 106) and LMWH in the second phase (n = 102) of the study. Baseline characteristics were similar for the two groups. The mean duration of UFH and LMWH treatments were 13.6 ± 0.5 and 14.1 ± 0.6 days, respectively (not statistically different). On the second day of treatment, only 9% of patients on UFH had an activated partial-thromboplastin time (aPTT) value within the therapeutic range (1.5 to 2.5 times control); however, 87% of patients treated with LMWH had an anti-Xa activity within the range of efficacy (0.5 to 1 IU/ml). On the last day of prophylaxis, all LMWH-treated patients had anti-Xa activity above 0.5 IU/ml but 19% were above 1 IU/ml. In the UFH treated group, 27% of patients had aPTTs above 1.5 times control, but 62% were over-anticoagulated. Two major bleeds occurred in each group, and one stroke occurred in the UFH group. The author concluded that anticoagulation

with LMWHs after mechanical valve replacement appeared feasible, provided adequate biological anticoagulation, and compared favorably with UFH anticoagulation.

Johnson and Turpie⁶ evaluated the outpatient use of LMWH in 515 chronically anticoagulated patients, including those with mechanical heart valves (n = 209), who required temporary discontinuation of long-term anticoagulant therapy. Patients received enoxaparin 1 mg/kg subcutaneously twice daily (n = 372) or dalteparin 100 anti-Xa units per kg subcutaneously twice daily (n = 143). LMWH was administered a mean of five times prior to the procedure and 5.2 times post-procedure. The last dose was administered 12 hours before the procedure and resumed 8 to

24 hours after the procedure until a therapeutic INR was achieved; oral anticoagulation was restarted 6 to 24 hours after the procedure. There were no thromboembolic complications. Among the entire study population (n = 515), there were 2 major bleeding events, 17 minor

bleeds, and 22 reports of bruising at the injection site, and no deaths.

Berdague et al⁷ evaluated the use of LMWH (15 received enoxaparin, 62 received nadroparin, and 33 received dalteparin) in the immediate postoperative period following valve replacement with a St. Jude mitral valve or combined aortic and mitral mechanical valves. Data regarding the efficacy and safety of individual agents were not provided. However, of the 110 patients treated, ischemic complications (stroke) were reported in 1 patient (0.9%), bleeding complications in 6 patients (5.4%), and death occurred in 6 patients (5.3%). The author cited none of the 6 deaths as being related to LMWH therapy.

Ferriera et al⁸ in a prospective, observational study evaluated LMWHs

(enoxaparin or fraxiparin) in 20 patients with prosthetic mechanical heart valves admitted for procedures necessitating interruption of chronic oral anticoagulation. The dose of LMWH was dependent on the patient's weight and INR before starting treatment. The mean duration of LMWH therapy was 10 ± 7 days. There were no thromboembolic events or deaths documented during the mean 3.6 month follow-up period.

Thus, the above studies suggest that LMWHs are both safe and effective in bridging prosthetic valve patients. They are also convenient for the patient and represent a less costly alternative for full anticoagulation protection. Larger randomized trials that are definitive in identifying the best LMWH bridging regimen are awaited.

INHERENT RISK OF ANTICOAGULATION

These patient populations (patients with mechanical prosthetic heart valves, pregnant patients, and pregnant patients who have mechanical prosthetic heart valves) are all at heightened risk for therapeutic misadventure. This would also be the case if such patients were being bridged with continuous infusion UFH prior to discharge on warfarin, and indeed, even after establishing such patients on oral anticoagulation. Warfarin is a known teratogen in the first trimester of pregnancy and has been associated with fetal and neonatal hemorrhage. Using a LMWH or UFH until the 13th week of pregnancy, changing to warfarin until the middle of the third trimester, and then restarting LMWH or UFH therapy until delivery is associated with significant risk. As such, hypervigilant monitoring in anticoagulation clinics or the healthcare provider's office setting is warranted with the use of any anticoagulant regimen in these patients.

LIMITING LIABILITY AND SERVING THE PATIENT

The anticoagulant options in bridging prosthetic valve patients into and out of the hospital are very limited. The cli-

■ If a patient is brought into the treatment [decision-making] loop, the probability of later legal retaliation is dramatically minimized.

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nician must carefully consider each option in identifying the therapy of choice in the individual patient. If, in the clinician's medical judgment, LMWH therapy is the appropriate mode of bridge therapy, the physician should be sensitive to the potential liability risk. As with any therapy, liability risks are minimized by patient involvement in the therapeutic decision process. If a patient is brought into the treatment decision loop, the probability of later legal retaliation is dramatically minimized. The patient should be advised of the potential benefits of LMWH bridging and the risks of such therapy, especially if a prosthetic heart valve is involved. The benefits and risks of alternatives to such therapy (IV UFH in-hospital, subcutaneous UFH, warfarin) should also be discussed. If adequate information is provided, such that the patient can make an informed decision, the doctrine of "assumption of the risk" may well be available to the clinician in the unlikely incident where an adverse event occurs. As informed consent requirements are not uniform across the country, providers are encouraged to contact their institutions legal counsel to determine local requirements.

Now that the FDA has approved revised labeling (see first paragraph of this commentary), clinicians may specifically question if this *official* change in labeling puts them at any increased liability risk should they wish to use LMWHs in these clinical situations. We believe that LMWH use is the best alternative for nonpregnant patients. Further, we believe that with so few options available to pregnant patients with prosthetic valves, the evidence of safety and the obtainment of informed consent limits an institution's liability with LMWH products. However, admitting the patient and using heparin is an alternative.

The high-risk prosthetic valve patient receiving chronic anticoagulation must be safely and effectively managed before, during, and after invasive procedures. The patients depend on the practicing clinician to apply their knowledge and experience in manag-

ing their anticoagulant therapy in these situations. There is no regimen free of risk in these situations; however, the related benefits of LMWH in this setting appear to outweigh the limited concerns in our opinion.

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