

## Criteria for Use of Enoxaparin in Mechanical Heart Valve Patients

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

*These criteria were based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. These guidelines are intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. They are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.*

### Introduction

Patients receiving oral anticoagulation with warfarin often require invasive diagnostic tests or surgery. If anticoagulant therapy is not held for these interventions the patient is at a higher risk of developing bleeding complications. However, this interruption in anticoagulation places the patient at a higher risk for thromboembolic complications.<sup>1,2</sup> This risk can vary with the indication for long-term oral anticoagulation.<sup>3</sup> An alternative form of anticoagulation for these procedures involves the administration of heparin (UFH) or low molecular weight heparins (LMWH). The administration of LMWH can be done as an outpatient while UFH is commonly given in the hospital by intravenous infusion with laboratory monitoring. The use of LMWH is less costly than a hospitalization and has proven efficacy in the anticoagulation of patients with prosthetic heart valves.<sup>4,5</sup> Recently, enoxaparin (Lovenox®) has had an FDA mandated labeling change that could impact its use in short-term anticoagulant bridge therapy. In February of 2002 the labeling of enoxaparin was changed as follows;

**"Prosthetic Heart Valves:** *The use of Lovenox Injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal deaths and fetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism (see PRECAUTIONS: Pregnancy).*

*In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events resulted in maternal death or surgical interventions. The use of Lovenox Injection is not recommended for thromboprophylaxis in pregnant women with prosthetic heart valves (see WARNINGS: Prosthetic Heart Valves)."*<sup>6</sup>

This new labeling raises concerns regarding the use of LMWH for bridge therapy in prosthetic valve patients, a population that commonly requires this intervention.

### Clinical Evidence

There have been reports of both clinical success<sup>7-9</sup> and failure<sup>9-12</sup> with enoxaparin in pregnant women. In a retrospective review of 624 pregnancies, Lepage et al,<sup>13</sup> documented a low incidence of maternal adverse effects (bleeding, thrombocytopenia) and no relation of enoxaparin use to the fetal and neonatal adverse effects noted. Various case reports have documented adverse effects (fetal loss, new thrombus formation, maternal death) with LMWH use during pregnancy. The pharmacokinetic changes seen in pregnancy may provide a complicating variable to the use of LMWH in this population. The increased clearance and volume of distribution commonly seen with pregnancy would support increased dose requirements for this population. Indeed, increased dosage requirement were supported by a changes in D-dimer and thrombin-antithrombin complex levels during pregnancy.<sup>14</sup>

The use of LMWH in non- pregnant mechanical valve patients is well supported by consensus guideline statements.<sup>15-17</sup> The 2001 Sixth ACCP Consensus Conference on Antithrombotic Therapy and the 2002 ACC/AHA Guidelines support the use of LMWH in patients with mechanical valve replacement,

bioprosthetic valves, atrial fibrillation and Unstable angina/NSTEMI. Additionally, several clinical trials have documented the safety and efficacy of LMWH in non-pregnant patients receiving chronic oral anticoagulation who received short-term therapy with LMWH prior to invasive procedures. The adverse events noted in these trials were minor with bruising at the injection site and minor bleeding being the most common.<sup>18-21</sup>

### Conclusions

1. The majority of therapeutic failures with LMWH in mechanical valve patients have been reported in pregnant females.
2. There is documented clinical safety and efficacy of LMWH bridge therapy in non-pregnant mechanical valve patients.
3. There is support of major consensus guidelines from ACCP/AHA/ACC regarding the use of LMWH in short term anticoagulation for invasive procedures.
4. The use of LMWH bridge therapy can decrease hospitalization costs.
5. The therapeutic failures reported appear associated with changing volume of distribution; increased clearance, subtherapeutic Anti-Xa levels and previous failures of therapy.

### Treatment Considerations

1. There are risks associated with hospitalization and unfractionated heparin use. The new labeling of enoxaparin highlights the risks associated with its use. The decision to use a LMWH heparin for bridge therapy should be considered on a case-by-case basis, recognizing the risk/benefit ratio for each patient. These issues should also be discussed with the patient prior to therapy initiation.
2. Treatment doses of LMWH should be employed (enoxaparin 1mg/kg, dalteparin 100IU/kg) and given BID.
3. Patients with renal impairment or obesity may need altered doses to insure efficacy.
4. The LMWH should not be discontinued until a therapeutic INR is achieved post procedure.
5. In most cases, oral therapy is stopped four days prior to the procedure with the first dose of LMWH given 2 days prior and no dose given the day of the procedure. Oral anticoagulant therapy is re-initiated when post-operative hemostasis is insured.
6. Patients with prior therapeutic failure of LMWH should be considered for alternate anticoagulation protocols.

### References

1. Kearon C, Hirsh J. management of anticoagulation before and elective surgery. *N Engl J Med* 1997;336:1506-1511.
2. Katholi RE, Nolan SP, McGuire LB. The management of anticoagulation during noncardiac operations in patients with prosthetic heart valves. *Am Heart J* 1978;96:163-165.
3. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation* 1994;89L:635-641.
4. Lee LH. Low molecular weight heparin for thromboprophylaxis during pregnancy in 2 patients with mitral valve replacement. *Thromb Haemostas* 1996;76:628-630.
5. Maharaj S, Bayliff CD, Kovacs MJ. Successful anticoagulation in a patient with mechanical heart valves. *Ann Pharmacotherapy* 1999;33:1188-1191.
6. Lovenox® (enoxaparin) product information. Aventis Pharmaceuticals. Feb 2002.
7. Tenconi PM, Gatti L, Acacia B. Low molecular weight heparin in a pregnant woman with mechanical heart valve prosthesis case report. (Abstract) *Thromb Haemost* 1997;734 Abstract PS-2996.
8. Ellison J, Thomson AJ, Walker ID, et al. Use of enoxaparin in a pregnant woman with a mechanical heart valve prosthesis. *Br J Obstet Gynecol* 2001;108:757-759.
9. Rowan JA, McGowan LME, Raudkivi PJ, et al. Enoxaparin treatment in mechanical heart valves during pregnancy. *Am J Obstet Gynecol* 2001;185:633-637.
10. Lev-Ran O, Kramer A, Gurevitch J, et al. Low-molecular weight heparin for prosthetic heart valves; treatment failure. *Ann Thorac Surg* 2000;69:264-246.

11. Berndt N, Khan I, Gallo R. A complication in anticoagulation using low molecular weight heparin in a patient with a mechanical valve; a case report. *J Heart Valve Disease* 2000;9:844-846.
12. Oles D, Berryessa R, Campbell K, et al. Emergency redo mitral valve replacement in a 27 year old pregnant female with a clotted prosthetic mitral valve, preoperative fetal demise and postoperative ventricular assist device; a case report. *Perfusion* 2001;16:159-164.
13. Lepercq J, Conard J, Borel-Derlon A, et al. Venous Thromboembolism during pregnancy; a retrospective study of enoxaparin safety in 624 pregnancies. *Int J Obstet Gynecol* 2001;108(11):1134-1140.
14. Bombeli T, Raddatz P, Fehr J. Evaluation of an optimal dose of low molecular heparin for thromboprophylaxis in pregnant women at risk of thrombosis using coagulation activation markers. *Haemostasis* 2001;31(2):90-98.
15. ACC/AHA Guideline Update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. ACC/AHA Practice Guidelines. Accessed from the World Wide Web. <http://www.acc.org>
16. ACC/AHA/ESC Guidelines for the management of patients with atrial fibrillation; Executive Summary. Accessed from the World Wide Web. <http://.acc.org>
17. Stein PD, Alpert JS, Bussey HI, et al. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. *Chest* 2001;119:220S-227S.
18. Spandorfer JM, Lynch S, Weitz HH et al. Use of enoxaparin for the chronically anticoagulated patient before and after procedures. *Am J Cardiol* 1999;84:478-480
19. Anonymous. Home LMWH bridge therapy in cardiac replacement; safe, effective and cost saving. *Formulary* 2000;35:990-991.
20. Galla JM, Fuhs BE. Outpatient anticoagulation protocol for mechanical valve recipients undergoing cardiac surgery. (Abstract) *J Am Coll Cardiol* 2000;13 (2 suppl A) 531A.
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.