

# The clinical challenge of bridging anticoagulation with low-molecular-weight heparin in patients with mechanical prosthetic heart valves: An evidence-based comparative review focusing on anticoagulation options in pregnant and nonpregnant patients

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**Background** Recent labeling changes for enoxaparin, a low-molecular-weight heparin (LMWH), have prompted a reexamination of its role in patients with mechanical prosthetic heart valves (MPHVs). Healthcare providers are faced with the challenge of weighing favorable trial results with LMWHs and balancing their clinical experiences with these agents as a bridge to oral anticoagulation in patients with prosthetic heart valves. This review will provide evidence-based guidance on issues surrounding the use of LMWH that require bridging anticoagulant therapy in the setting of cardiac surgery (MPHVs), cardiovascular disease, and during temporary interruption of oral anticoagulants in patients requiring periprocedural bridging therapy.

**Methods** A Medline search was conducted of articles appearing in the medical literature published in English between 1992 and 2004. Approximately 120 clinical trials, case reports, editorials, and/or guideline statements were retrieved and reviewed by the authors as to their relevance for the subject under review, ie, bridging anticoagulation in patients with MPHVs. Approximately 80 of these publications were selected for detailed review, analysis, and discussion in a consensus format.

**Results** This review addresses the controversy surrounding the divergence between the new labeling recommending against the use of LMWH in patients with MPHVs as well as the ongoing clinical experience and evidence in the medical literature. The clinical challenges in the use of LMWH and unfractionated heparin (UFH) in pregnant patients with MPHVs are presented; the evidence for LMWHs in nonpregnant patients with prosthetic valves is described; and the role of LMWH for bridging immediately after mechanical valve surgery and its periprocedural and perioperative uses are discussed. Based on an expert consensus panel, clinical algorithms for the use of LMWH in pregnant and nonpregnant patients with MPHVs are also illustrated.

**Conclusions** Based on the available data sets, clinical trials, reviews, and registry data, the evidence suggests that LMWH compared to UFH may be a safe and effective agent in patients with MPHVs. Future large-scale, randomized trials are warranted. (*Am Heart J* 2005;150:27-34.)

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## Background and overview

Identifying safe, evidence-based, and outcome-effective approaches to managing patients who are at risk of developing arterial thromboembolism represents a formidable clinical challenge. It is likely that in no patient subgroup are the therapeutic challenges associated with anticoagulation more complex or problematic than in individuals with mechanical prosthetic heart valves (MPHVs). Low-molecular-weight heparins (LMWHs) and unfractionated heparin (UFH) have been used in these clinical settings, although recent labeling changes in the case of enoxaparin have prompted a reexamination of its role in high-risk subgroups, including pregnant and nonpregnant patients with MPHVs.<sup>1,2</sup> Healthcare providers are faced with the difficult challenge of weighing favorable published trial results with LMWH for indications such as prophylaxis against perioperative and postoperative thromboembolism after abdominal, hip, and knee surgeries,<sup>3-9</sup> in the treatment of deep venous thrombosis,<sup>10</sup> for acute coronary syndromes<sup>11</sup> and ST-segment elevation myocardial infarction,<sup>12</sup> and balancing their clinical experiences with this agent as a bridge to oral anticoagulation instead of UFH in nonpregnant patients with prosthetic valves. There are also medicolegal issues that have been introduced as a result of recent labeling modifications for enoxaparin.<sup>2</sup> In addition, LMWH may be more advantageous than UFH because of a better safety profile with less thrombocytopenia, less bleeding, less osteoporosis with prolonged treatment, a more predictable and rapidly reached anticoagulant effect, and the possibility of self-administration of anticoagulant therapy without laboratory monitoring.<sup>13</sup>

This review addresses the controversy surrounding the divergence between the new labeling recommending against the use of LMWH in patients with MPHVs and the ongoing clinical experience and evidence in the medical literature demonstrating that LMWH, compared with available alternatives, may potentially be a safe and effective agent in patients with MPHVs. We will analyze the available data sets, clinical trials, reviews, and registry data that can provide evidence-based guidance on issues surrounding the use of LMWH in patients who require bridging anticoagulant therapy in the setting of (a) cardiac surgery (MPHVs), (b) cardiovascular disease (ie, atrial fibrillation), and (c) temporary interruption of chronic oral anticoagulant therapy in patients requiring periprocedural bridging therapy for either cardiac or noncardiac procedures.

## Methods

A Medline search was conducted of articles appearing in the medical literature published in English between 1992 and 2004. The search was conducted using the keywords, "bridging/heparin/prosthetic valves," "bridging/LMWH/prosthetic valves," "thromboembolism/prosthetic valves," "thromboembolism/pregnancy/prosthetic valves," "heparin/

LMWH/bridging," "bridging/prosthetic valve/guidelines," and "thromboembolism/valves/pregnancy/warfarin." Approximately 120 clinical trials, case reports, editorials, and/or guideline statements were retrieved and reviewed by the authors as to their relevance for the subject under review, that is, bridging anticoagulation in patients with MPHVs. Approximately 80 of these publications were selected for detailed review, analysis, and discussion in a consensus format. Publications were not included if they were felt to be of poor study design or failed to monitor necessary parameters, that is, anti-factor Xa levels, if such monitoring was deemed necessary to draw conclusions about therapeutic implications of certain agents. The final manuscript was reviewed and approved by all authors.

## Clinical challenges in response to labeling change: LMWHs in pregnant patients with MPHVs

According to the new product labeling,<sup>1,14</sup> the use of Lovenox (enoxaparin) injection is "not recommended for thromboprophylaxis in patients with prosthetic heart valves." Cases of prosthetic heart valve thrombosis have been reported in patients with MPHVs who have received enoxaparin for thromboprophylaxis. Some of these cases were of pregnant women in whom thrombosis led to maternal and fetal deaths.<sup>1</sup>

The clinical study cited in the "precautions" section of the product labeling was an independent, open-label, randomized study conducted in South Africa to evaluate the use of enoxaparin compared with warfarin and UFH in pregnant women with prosthetic heart valves. After 12 patients were enrolled (of a planned 110), the Aventis Safety Board requested that the study be terminated because of 2 deaths in the enoxaparin group.<sup>1,15</sup> These deaths prompted the Food and Drug Administration to add this information to the enoxaparin package insert.<sup>1,14</sup> In addition to these reports, the American College of Cardiology/American Heart Association (ACC/AHA) Task Force (1998) has specifically advised against using LMWH for pregnant patients with MPHVs.<sup>16</sup> The labeling revision did not take into account the many other cases with similar complications including death that have been reported in a comparable population of pregnant patients managed with UFH.<sup>17-20</sup>

## Analysis of index cases

The 2 deaths in the South African study were considered by the investigators to be caused by prosthetic heart valve thrombosis. In patient 1 (32-year-old pregnant woman with prosthetic mitral [CarboMedics, 31 mm; CarboMedics, Inc., Austin, Tex] valve), anti-factor Xa levels were taken approximately 2 days before her death and were 0.33 and 0.78 IU/mL, respectively (recommended therapeutic range 0.5-1.0 IU/mL). The exact timing of the anti-factor Xa levels was not reported clearly. In patient 2 (36-year-old pregnant woman with

prosthetic mitral and aortic [Hall Kaster, Medtronic, Minneapolis, Minn] valves), the anti-factor Xa level taken 20 days before her death was 0.43 IU/mL. A dose of 80 mg enoxaparin subcutaneously (SC) every 12 hours was used in both patients. In these patients, 2 of the 3 available anti-factor Xa levels were subtherapeutic. Despite anti-factor Xa levels being drawn, they were not used to make adjustments in dosing.<sup>1,15</sup>

Based on current recommendations for such high-risk patient populations, optimal and appropriate anticoagulation strategy would have necessitated using more appropriate treatment doses of the LMWH using levels of anti-factor Xa to guide dosing. These 2 cases could well have represented clinical failure caused by inadequacy of drug dosing.

It is extremely difficult to interpret the clinical significance of these 2 cases, given the inherently high-risk nature of thrombosis in a pregnant patient with a prosthetic valve using UFH or warfarin. The level of anticoagulation with enoxaparin may have been insufficient. Furthermore, this clinical setting is one of exceptional risk for thrombotic and/or other adverse fetal and/or maternal events. Some studies using UFH in this population have shown a 35% risk of adverse events.<sup>17,20-23</sup> As a result, the extrapolation of these 2 case histories to all subsets of patients with prosthetic heart valves seems debatable. Specifically, the appropriateness of extrapolating these 2 index case findings to larger subsets of patients, in particular, those with prosthetic heart valves without pregnancy, is questionable, because these patient subsets may well have entirely different (ie, lower) risk profiles for thromboembolism than individuals who are pregnant and have a prosthetic heart valve.<sup>24</sup>

### **Pregnancy with MPHVs: evidence for thrombosis-related complications in patients treated with other anticoagulants (UFH)**

A substantial number of valvular thromboses, venous thromboembolism prophylaxis failures, and thromboembolic events have been reported in pregnant patients with prosthetic valves treated with UFH.<sup>17-20</sup> Sadler et al<sup>17</sup> found that UFH treatment of pregnancies in women with mitral mechanical valves is associated with high fetal survival but a clinically problematic and significant (29%) risk of thromboembolic complications. Examining 79 women who underwent 147 pregnancies, this comparative study reported that cardiac complications occurred in 10 (20%) pregnancies in women with mitral mechanical valves and 4 (13%) with mitral bioprosthetic valves. All 4 thromboembolic complications with MPHVs occurred among the 14 women treated with UFH throughout pregnancy. Three of the 4 thromboembolic

complications in women with mechanical valves transpired in the antepartum period and occurred while the patients were on UFH. The 3 antenatal thrombotic events included a coronary artery embolus resulting in both maternal and fetal death at 13 weeks' gestation, a valve thrombosis (presenting as a transient ischemic attack at 32 weeks), and a cerebral embolic event. The fourth patient, who delivered by cesarean section, had valve thrombosis 7 days postpartum, necessitating urgent valve replacement. At the time of diagnosis of valve thrombosis, she was on warfarin (7 mg/d) and UFH, and her activated partial thromboplastin time was 121 seconds (>3 times baseline). Furthermore, there was 1 maternal death among the 4 patients with mechanical valves (Starr-Edwards, Baxter Healthcare, Edwards CVS Division, Santa Ana, Calif) who were treated with UFH.<sup>17</sup> This cohort study, albeit small, highlights the extraordinarily high risk of thromboembolic complications in pregnant patients with mechanical valves, despite prophylaxis with adequate doses of UFH. Based on this study, the rate of thromboembolism in pregnant women with prosthetic valves exposed to long-term UFH therapy during pregnancy was 29%, which is not statistically different from the 26% valvular thrombosis rate observed among the initial 7 patients entered into the South African study.<sup>15</sup>

Characterization of enoxaparin as a uniquely problematic anticoagulant in pregnant patients with prosthetic valves is inconsistent with the reports citing UFH-linked failures, including patients whose activated partial thromboplastin time was therapeutic at the time of valvular thrombosis. Accordingly, information identifying risks and precautions should be provided for all products used in pregnant patients with prosthetic heart valves. Prosthetic valvular thromboses, cerebral thromboembolism, myocardial infarctions, and pregnancy complications, as well as maternal deaths, have been reported in a number of published reviews evaluating the safety and efficacy of UFH—a widely used “gold standard” for prophylaxis—in pregnant patients with MPHVs.<sup>17-20</sup> Moreover, because of the thrombogenic environment induced by pregnancy—complicated by other hemodynamic and pharmacokinetic factors—this subgroup represents an ultrahigh risk stratum in which no single agent or combination thereof has been shown to be uniformly effective in producing consistently favorable outcomes for both fetus and mother in the setting of mechanical valves and pregnancy. The most rational management strategy for this patient population is to inform the patients on the risks involved in using each of the available anticoagulation regimens during pregnancy both to the mother and to the fetus.

### **ACC/AHA**

The choice of anticoagulant therapy for all pregnant patients, and pregnant women with mechanical valves, in particular, must be carefully considered and indi-

**Table 1.** Summary of clinical trials evaluating use of LMWH in patients with prosthetic heart valves

Reference	Patient description	Enoxaparin dosing	
		Schedule	Outcome
Spandorfer et al <sup>33</sup> Berdaguè et al <sup>29</sup>	12 Valve patients of 20 total studied 15 Valve patients treated with enoxaparin of 110 total with multiple therapies	1 mg/kg SC BID for 10 ± 7 d 1 mg/kg SC BID for 10 ± 6 d	No thromboembolic events One thromboembolic event (transient ischemic stroke) unknown if occurred in the enoxaparin arm
Montalescot et al <sup>30</sup>	208 Single or double heart valve replacements; 102 of these in the LMWH group, of which 73 treated with enoxaparin	14 d	No thromboembolic events in the enoxaparin group
Johnson and Turpie <sup>26</sup>	209 Valve patients of 515 total studied; one third of all patients were treated with enoxaparin	1 mg/kg SC BID for 10 ± 7 d	No thromboembolic events
Ferreira et al <sup>31</sup>	82 Valve patients	1 mg/kg SC BID for 10 ± 7 d	No thromboembolic events

vidualized for the patient. The ACC/AHA report,<sup>16</sup> although published >5 years ago, has issued recommendations for anticoagulation during pregnancy for women with mechanical valves: “Women at high risk (a history of thromboembolism or/and older-generation mechanical prosthesis in the mitral position) who choose not to take warfarin should receive continuous UFH intravenously in a dose to prolong the midinterval activated partial thromboplastin time to 2 to 3 times control,” continuing, “Women at low risk (no history of thromboembolism) may be managed with an adjusted dose of UFH given SC (17 500-20 000 U BID) to prolong the midinterval activated partial thromboplastin time to 2 to 3 times control.” The cautionary note of the ACC/AHA regarding the using of LMWH in the pregnant patient with mechanical valves is sounded because of lack of data 5 years ago: “There are no data to guide their (LMWHs) use in the management of patients with mechanical heart valves. Therefore, it is not advisable to use LMWHs in pregnant patients with MPHVs until more data are available.”<sup>16</sup> More recently, a consensus statement from the seventh American College of Chest Physicians conference on antithrombotic and thrombolytic therapy suggests that LMWH gives adequate protection in nonpregnant patients with MPHVs and in pregnant patients provided that the changing pharmacokinetics of LMWH during pregnancy are accounted for by adjusting the dose according to LMWH levels.<sup>25</sup>

Although no conclusive, prospectively generated evidence or trial data exist to support the effective and safe use of LMWHs in pregnant patients with prosthetic valves, similarly, there is no body of evidence suggesting that it is any less effective, safe, or problematic than UFH. In the case of pregnant patients with MPHVs, enoxaparin should more appropriately be considered an unproven and imperfectly studied alternative among a trio of suboptimal options (warfarin, UFH, and LMWH) for managing a high-risk population characterized by predictably unfavorable outcomes.

### LMWHs in nonpregnant patients with prosthetic valves: evidence for comparable safety and clinical efficacy

Extrapolation of the 2 South African index cases (ie, pregnant patients with MPHVs) to the nonpregnant valve population and the resulting label changes warning, advising, and recommendation against enoxaparin use in nonpregnant prosthetic-valve patients may be inconsistent with recently available data confirming the safety and efficacy of enoxaparin in patients with prosthetic valves (see Table 1).

One of the largest institutional data sets of LMWHs for periprocedural management of anticoagulation in patients on long-term oral anticoagulants undergoing noncardiac surgery prospectively evaluated 1082 patients (618 men/464 women; average age 66 years) undergoing temporary discontinuation of oral anticoagulation and prophylactically “bridged” with LMWH on an outpatient basis. Patients were started on a LMWH (70% with enoxaparin at a dose of 1 mg/kg SC every 12 hours and 30% with dalteparin at a dose of 100 anti-factor Xa U/kg SC twice daily). The study cohort included 65 patients with mechanical mitral valve replacement in sinus rhythm, 61 patients with mechanical mitral valve replacement in atrial fibrillation, 170 patients with mechanical aortic valve replacement in sinus rhythm, 29 patients with mechanical aortic valve replacement in atrial fibrillation, 2 patients with bioprosthetic mitral valve replacement in sinus rhythm, 12 patients with bioprosthetic mitral valve replacement in atrial fibrillation, 6 patients with bioprosthetic aortic valve replacement in sinus rhythm, 9 patients with bioprosthetic aortic valve replacement in atrial fibrillation, and 47 patients with other valve combinations or valvular architecture. An additional 681 patients without valves demonstrated other indications for “bridging” therapy. Overall, minor bleeding was seen in 7.6% of patients, major bleeding in 0.3%, and bruising at the injection site in 3.5% of patients. Of special significance

was the observation that no thromboembolic events were seen in any of the patients during the bridging period.<sup>1,26</sup> In a more recently published, multicenter, prospective study involving 224 patients, the feasibility and safety of short-term bridging with LMWHs was reported.<sup>27</sup>

In another large institutional data set, 532 patients were managed with periprocedural anticoagulation because of the need to interrupt chronic oral anticoagulation. Of these patients, 185 (35%) had MPHVs. Among these, 135 (73%) had valves in the aortic position (83 bileaflet St Jude valves (St Jude Medical, Inc., St. Paul, Minn), 15 Starr-Edwards ball valves, and 26 tilting Bjork-Shiley valves, Pfizer, Inc., New York, NY). Low-molecular-weight heparins used were dalteparin (80%) and enoxaparin (20%). There were no cases of prosthetic valve thrombosis.<sup>1</sup>

Another large study evaluated the outpatient use of LMWH (enoxaparin 1 mg/kg SC every 12 hours [n = 372], dalteparin 100 anti-factor Xa U/kg SC BID [n = 143]) in 515 chronically anticoagulated patients, including those with MPHVs (n = 209), who required temporary discontinuation of long-term anticoagulant therapy. The length of the bridging period was the time until effective anticoagulation (primary end point of the study). This was significantly shorter for enoxaparin compared with UFH ( $1.1 \pm 0.4$  vs  $3.7 \pm 2.5$  days,  $P < .0001$ ). Anti-factor Xa levels were  $0.79 \pm 0.18$  IU/mL on day 3 of treatment and  $0.8 \pm 0.18$  IU/mL on the last day of treatment ( $P = \text{NS}$ ). In this study, there were no thromboembolic complications. There were 2 major bleeding events, 17 minor bleeding events, 22 reports of bruising at the injection site, and no mortality.<sup>28</sup>

Thus, LMWH appears to be an evidence-supported option in nonpregnant patients with MPHVs. Although large-scale randomized trial data are lacking for any specific strategy, current data are sufficiently favorable to suggest LMWH use as an alternative among currently available options.

## LMWH for bridging immediately after mechanical heart valve surgery

Numerous case series<sup>28-31</sup> have reported the safe and effective use of LMWH in nonpregnant patients with MPHVs. Much of these data support the safety and efficacy of LMWH for immediate postoperative prophylaxis.

Montalescot et al<sup>30</sup> studied 208 consecutive patients undergoing a single or double heart valve replacement with MPHVs anticoagulated with UFH in the first phase (n = 106) and LMWH in the second phase (n = 102) of the study. Most of the patients (72%) treated with LMWH received enoxaparin, which was administered at a dose of 1 mg/kg SC every 12 hours. Baseline characteristics were similar for the 2 groups. On the

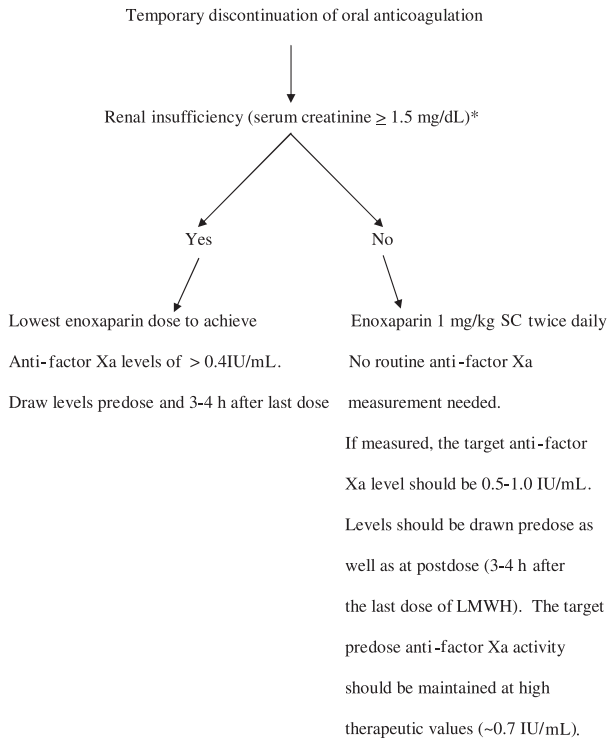
second day of treatment, only 9% of patients on UFH had an activated partial thromboplastin time within the therapeutic range (1.5-2.5 times control); however, 87% of patients treated with LMWH had anti-factor Xa activity within the range of efficacy (0.5-1.0 IU/mL). On the last day of their prescription, all LMWH-treated patients had anti-factor Xa activity above 0.5 IU/mL, and only 19% were above 1 IU/mL. Two major bleeds occurred in each group, and 1 stroke occurred in the UFH group.

The use of LMWH, including enoxaparin (n = 15), nadroparin (n = 62), and dalteparin (n = 33) in the postoperative period after valve replacement with a St Jude mitral valve (St. Jude Medical Inc., was evaluated in another study.<sup>29</sup> Of the 110 patients treated, there was 1 ischemic cerebrovascular accident (0.9%), 6 patients had bleeding complications (5.4%), and there were 6 deaths (5.3%). However, none of the 6 deaths were related to LMWH therapy.<sup>29</sup>

## Periprocedural and perioperative anticoagulation with LMWH

There is also evidence supporting safety, clinical outcomes comparable with those seen with UFH, and cost-effectiveness of LMWH in perioperative management of patients requiring chronic anticoagulation. A prospective cohort study was conducted to assess the efficacy, safety, and cost of using LMWH on an outpatient basis in place of inpatient continuous UFH as a “bridge” to warfarin therapy after cardiac surgery.<sup>32</sup> Fifty-five cardiac surgery patients (44 with prosthetic heart valves, and 11 with coronary artery bypass grafting and postoperative atrial fibrillation) received enoxaparin postoperatively in the outpatient setting until target international normalized ratio was achieved with warfarin. One patient who underwent coronary artery bypass surgery and mitral valve repair and had new-onset atrial fibrillation developed a small embolic stroke without neurological deficit 3 days postdischarge. Two patients had bloody pleural effusions necessitating thoracentesis after hospital discharge. Use of enoxaparin reduced the length of hospital stay after surgery with an estimated cost-avoidance with enoxaparin therapy of US\$323 300, an average of US\$5878 per patient. The primary reason for cost savings was decreased length of stay.<sup>32</sup>

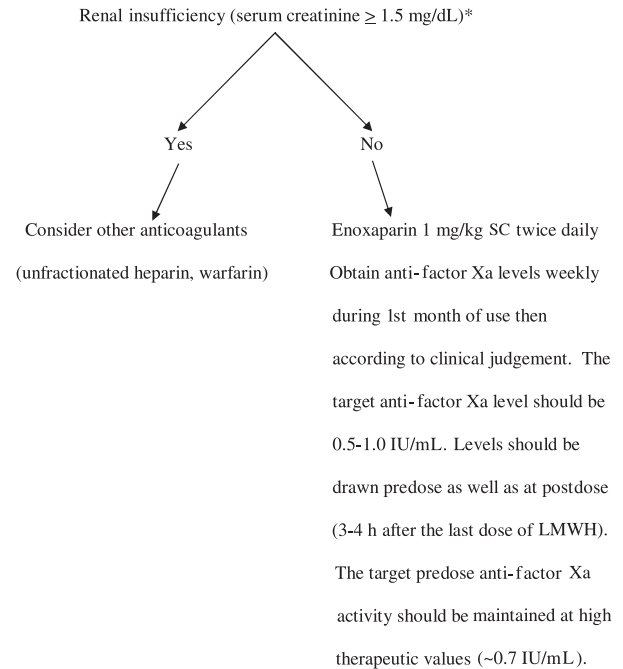
Another prospective randomized study compared the efficacy of enoxaparin with UFH for intermittent therapy before cardiac catheterization in patients who had been receiving long-term oral anticoagulation. Twenty-seven consecutive patients with atrial fibrillation or MPHVs were randomized to receive weight-adjusted enoxaparin SC twice daily (SC every 12 hours) or weight-adjusted intravenous UFH. Cardiac catheterization was performed when international normalized

**Figure 1**

Suggested algorithm for the use of enoxaparin in nonpregnant patients with MPHVs. The Lovenox package insert (14) recommends decreasing the dosage of enoxaparin (1 mg/kg SC once daily) with a creatinine clearance = 30 mL/min. It may be reasonable to use a lower threshold (ie, serum creatinine of = 1.5 mg/dL to make dosage changes to enoxaparin in higher-risk patients (31).

ratio was  $< 1.5$ . The primary end point was time (days) to effective anticoagulation with both treatment arms. The secondary outcome measure was the percentage of days of ineffective treatment. The time to reaching therapeutic anticoagulation was significantly shorter in the enoxaparin group compared with the UFH group. In addition, the percentage of days of ineffective anticoagulation was significantly lower in the enoxaparin group. Enoxaparin was superior to UFH in rapidly achieving and maintaining effective anticoagulation in patients receiving chronic oral anticoagulation therapy before cardiac catheterization. There were no thromboembolic complications in this study.<sup>28</sup>

In a prospective observational study, use of enoxaparin was evaluated in 82 patients with mechanical heart valves requiring temporary interruption of warfarin for various invasive cardiac and noncardiac procedures. All patients received periprocedural enoxaparin at a dose of 1 mg/kg SC twice daily. The mean duration of LMWH therapy was 11 days. There were 8 minor and

**Figure 2**

Suggested algorithm for the use of enoxaparin in pregnant patients with MPHVs. The Lovenox package insert (14) recommends decreasing the dosage of enoxaparin (1 mg/kg SC once daily) with a creatinine clearance = 30 mL/min. It may be reasonable to use a lower threshold (ie, serum creatinine of = 1.5 mg/dL to make dosage changes to enoxaparin in higher-risk patients (31).

1 major bleeding episodes during the follow-up period, and there were no thromboembolic events.<sup>31</sup>

Another group of investigators studied 20 chronically anticoagulated patients who underwent major surgery or moderately invasive procedures including cardiac procedures requiring discontinuation of their warfarin therapy.<sup>33</sup> Patients included those with mechanical heart valves, atrial fibrillation with risk factors for stroke, deep vein thrombosis within the past 3 months, or known hypercoagulable states and history of life-threatening thrombosis. Enoxaparin 1 mg/kg SC every 12 hours was initiated 36 hours after discontinuing warfarin therapy on an outpatient basis. No thrombotic or hemorrhagic complications were reported during the procedures. No thrombotic events occurred after procedures, but 1 episode of major bleeding and 2 episodes of minor bleeding occurred postoperatively.<sup>33</sup> This study supports the concept that outpatient management of periprocedural anticoagulation with enoxaparin is convenient and may be cost-effective relative to inpatient management.

Sixteen cases of mechanical heart valve thrombosis during enoxaparin therapy have been reported between

1986 and 2002. Eight of the 16 patients were pregnant at the time of the event, and the remaining 8 patients were either not pregnant or pregnancy was not specified.<sup>1</sup> Overall, the lack of sufficient information about patient demographics, medical history, concomitant conditions, enoxaparin dosing regimens and duration, diagnostic monitoring, event treatment, and outcomes limit evaluation of these reports. Finally, there is no denominator; hence, incidence data are impossible to obtain.

Data from published clinical trials, expert opinion, and institutional data sets suggest that enoxaparin 1 mg/kg SC every 12 hours is safe and effective bridging therapy for patients who are not pregnant and require interruption of oral anticoagulation for a number of clinical indications, including those who require interruption because of the presence of prosthetic heart valves, atrial fibrillation, and other clinical conditions.

## Summary and conclusions

Recommendations for use of LMWH in patients with mechanical prostheses

Based on currently available evidence, what recommendations can be made on the use of LMWH in patients with MPHVs? Clearly, there is a need for a definitive, large-scale, randomized, controlled trial of LMWH versus UFH to settle this issue. However, within the constraints of the available data, one approach would be to risk-stratify patients into low-risk and high-risk groups and tailor the anticoagulation regimen appropriately. Risk stratification would depend on the indications for anticoagulation, the clinical scenario, any accompanying risk factors including the types of MPHVs, and whether they are pregnant.

Algorithms for the use of LMWH in nonpregnant and pregnant patients with MPHVs are shown in [Figures 1 and 2](#). These are general recommendations based on an expert clinical consensus panel and should not be construed as definitive guidelines. The majority of patients with MPHVs requiring enoxaparin when oral anticoagulation is discontinued would be nonpregnant patients, with the pregnant patients forming a minority. In nonpregnant patients requiring temporary interruption of oral anticoagulation for noncardiac surgery, including those with MPHVs, a regimen consisting of enoxaparin at a dose of 1 mg/kg SC every 12 hours appears to be safe, despite the relative paucity of data from controlled trials. Anti-factor Xa levels need not be measured routinely if patients have normal renal function. Extra caution should be exercised in patients with older generation MPHVs especially in the mitral position. In the immediate postoperative period after implantation of MPHVs, there is no strong evidence to base any firm recommendations for the use of LMWH compared with UFH. The use of LMWH during pregnancy needs extremely careful monitoring. However, pending results

of randomized controlled trial, no definitive recommendations on the use of LMWH can be made.

As pregnancy advances, the volume of distribution of the LMWH increases necessitating appropriate dose adjustments. If there is renal impairment, dosing should be further adjusted, and use of LMWH may even need to be discontinued. Anti-factor Xa levels should be obtained weekly for the first month and thereafter depending on clinical judgement. Levels should be drawn predose as well as at 3 to 4 hours after the last dose of LMWH, and the target predose anti-factor Xa activity should be maintained at high therapeutic values (~0.7 IU/mL, range of usual therapeutic levels 0.5-1.1 IU/mL). Some authors recommend higher ranges such as 0.6 to 1.2 IU/mL. The safety of this dose range, however, has not been fully characterized. Those requiring LMWH for prophylactic reasons such as prevention of deep venous thrombosis could be given enoxaparin at a dose of 40 mg SC every 12 hours. Full therapeutic doses of enoxaparin (1 mg/kg SC every 12 hours) may be required in those with high risk such as those with active thromboembolic disease.

There are insufficient data to reliably predict, compare clinical outcomes, or confirm the safety or effectiveness of enoxaparin, UFH, or warfarin in pregnant patients with MPHVs. Each option has potentially adverse consequences, which must be weighed carefully when deciding upon drug selections for individual patients.

Based on available data sets, clinical trials, reviews, and registry data, the evidence suggests that LMWH compared to UFH may be a safe and effective agent in patients with MPHVs. Future large-scale, randomized trials are warranted.

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