Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association®
Learn and Live℠

Low-Molecular-Weight Heparin as a Bridging Anticoagulant Early After Mechanical Heart Valve Replacement

Philippe Meurin, Jean Yves Tabet, Hélène Weber, Nathalie Renaud and Ahmed Ben Driss

Circulation 2006;113;564-569
DOI: 10.1161/CIRCULATIONAHA.105.575571
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
Copyright © 2006 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/cgi/content/full/113/4/564

Subscriptions: Information about subscribing to Circulation is online at
http://circ.ahajournals.org/subscriptions/

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
http://www.lww.com/reprints

Downloaded from circ.ahajournals.org by on February 1, 2010

Low-Molecular-Weight Heparin as a Bridging Anticoagulant Early After Mechanical Heart Valve Replacement

Philippe Meurin, MD; Jean Yves Tabet, MD; Hélène Weber, MD;
Nathalie Renaud, MD; Ahmed Ben Driss, MD, PhD

Background—After mechanical heart valve replacement (MHVR), long-term use of unfractionated heparin is sometimes required because vitamin K antagonists (VKA) are temporarily contraindicated or because the time to reach the target international normalized ratio is long. The aim of this study was to investigate the feasibility of low-molecular-weight heparin treatment in these patients.

Methods and Results—This work was conducted as a prospective study. We selected all patients (n=695) who underwent MHVR and were transferred to a postoperative cardiac rehabilitation center between January 2000 and January 2005. The study focused on patients who had not yet started VKA therapy or who had a below-target international normalized ratio despite VKA therapy. Unfractionated heparin was replaced by enoxaparin (100 IU/kg BID) until VKA treatment was fully effective. Two hundred fifty patients (60±11 years old) were enrolled 16±11 days after surgery (aortic valve replacement, n=190; mitral valve replacement, n=34; double valve replacement, n=26). Of these, 50% had permanent or transient atrial fibrillation, 40% had hypertension, 13% had diabetes, and 19% had a history of cardiac surgery. The mean duration of low-molecular-weight heparin treatment was 8.3±6.0 days. Patients were followed for 90 days, during which there were two major and three minor bleeding episodes and one transient ischemic attack. There were no cases of valve thrombosis and no deaths.

Conclusions—After MHVR, one third of patients leave the cardiac surgery unit before VKA treatment is fully effective. Bridging anticoagulation therapy with enoxaparin appears to be feasible during this high-risk period for thromboembolism and could shorten the length of hospital stay. **(*Circulation*. 2006;113:564-569.)**

Key Words: valves ■ prosthesis ■ heparin

Low-molecular-weight heparins (LMWH) have been tested in the treatment and prevention of deep vein thrombosis and pulmonary embolism, the treatment of stroke and unstable angina,[1] and, more recently, in acute myocardial infarction[2,3] and atrial fibrillation.[4] LMWH had at least as good a risk-to-benefit ratio as unfractionated heparin (UH) in all these settings.

Editorial p 470
Clinical Perspective p 569

Few data on the use of LMWH after mechanical valve insertion exist.[5–8] The risk of thromboembolism is particularly high during the first month after mechanical prosthetic valve surgery,[9,10] but only two nonrandomized studies have tested LMWH in this setting.[5,8] Only 131 patients received LMWH in these studies, and the proportion of high-risk patients was low (eg, only 15 patients with mitral valve replacement). The results suggested that therapeutic levels were more rapidly and more predictably achieved with LMWH than with UH[5] and that the LMWH regimen was as effective and as safe as the UH regimen.[5,8]

Owing to this paucity of data, practice guidelines are imprecise and somewhat conflicting: The American College of Chest Physicians endorses LMWH administration (with the same low grade of recommendation as for UH) as a possible strategy until the international normalized ration (INR) is stable at therapeutic levels,[11] but, the American Heart Association/American College of Cardiology does not compel to use any heparin[12]: "It is important to note that thromboembolic risk is increased early after insertion of the prosthetic valve. The use of heparin early after prosthetic valve replacement before warfarin achieves therapeutic levels is controversial. In some patients, achievement of therapeutic INR can be delayed several days postoperatively because of mitigating complications."

The aim of this study was to evaluate the feasibility of LMWH therapy as a bridge between immediate postsurgical UH and fully effective oral anticoagulation in a larger population of high-risk patients who recently underwent mechanical heart valve replacement (MHVR).

Methods

Study Population and Anticoagulation

This prospective, single-center study was conducted between January 2000 and January 2005. All consecutive patients who underwent

Received July 19, 2005; revision received October 24, 2005; accepted October 25, 2005.
From Les Grands Prés, Villeneuve Saint Denis, France.
Correspondence to Philippe Meurin, MD, Les Grands Prés, 27 rue Sainte Christine, 77174 Villeneuve Saint Denis, France. E-mail philippemeurin@hotmail.com
© 2006 American Heart Association, Inc.

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.105.575571**

Downloaded from circ.ahajournals.org by on February 1, 2010

MHVR and were transferred to a postoperative cardiac rehabilitation center (POCRC) were selected. Patients with the following characteristics were excluded: (1) renal failure (serum creatinine >150 μm/L) precluding LMWH administration, (2) previous heparin-induced thrombocytopenia, (3) pregnancy, or (4) vitamin K antagonist (VKA) treatment already fully efficient. Moreover, patients with LMWH treatment of less than 2 days (4 injections) were eliminated (n=10).

UH therapy was started on the first postoperative day and was continued (intravenously or subcutaneously, targeting an activated partial-thromboplastin time [APTT] of between 1.5 and 2.5) until either VKA therapy achieved the target INR or the patient was admitted to the POCRC.

VKA therapy was usually started during the first postoperative week, unless temporarily contraindicated. Patients were enrolled on their admission to the POCRC if VKA treatment had not yet been started or if VKA treatment had not yet achieved the target INR (2.5 to 3.5 after mitral valve replacement or double valve replacement; 2.0 to 3.0 after aortic valve replacement).[11]

After enrollment, UH was withdrawn and replaced by LMWH (enoxaparin: 100 IU/kg BID). The dose of enoxaparin used was the usual dose administered in studies when an efficient anticoagulation is required for atrial fibrillation[4] or acute coronary syndromes[13,14] and is the same dose used in the two previous studies conducted on the same topic.[5,8]

As recommended, anticoagulation was checked in obese patients (body mass index >30 kg/m^2) by measuring anti-Xa activity 4 hours after the third injection.[15] The therapeutic range was 0.5 to 1.0 IU/mL, as defined in studies of LMWH for treatment of deep vein thrombosis[15] acute coronary syndromes[13,14] and in the two pilot studies focusing on LMWH use after MHVR.[5,8] The LMWH dose was adjusted when the anti-Xa level was not within the target range.

Platelet counts were performed twice per week during LMWH therapy, and the INR was determined 3 times per week during the first 3 weeks and twice per month afterward. Enoxaparin treatment was stopped when the INR remained at the target level for 2 consecutive days.

Outcome Measures

The main end point for efficacy was the occurrence of symptomatic arterial thromboembolism from the first day of LMWH treatment (enrollment) until the 90th postoperative day. The patients had daily physical evaluations while in the POCRC (mean follow-up, 20±7 days), and their status 3 months after surgery was determined by contacting their cardiologists. Arterial thromboembolism was defined as ischemic stroke, transient ischemic attack, myocardial infarction, systemic embolism, or prosthetic valve thrombosis.

The main end point for safety was major hemorrhaging during LMWH treatment, defined as (1) overt bleeding with a hemoglobin fall of >2 g/dL within a 24-hour period or transfusion of at least 2 U of blood; (2) intraspinal, retroperitoneal, or pericardial bleeding; or (3) fatal bleeding.

Statistical Analysis

Results are expressed as mean±SD.

Results

A total of 695 patients who were transferred to the POCRC after MHVR were selected. Sixteen patients were excluded because of a creatinine level >150 μm/L, 4 because of suspected heparin allergy and 425 because oral anticoagulant treatment was already fully effective. Therefore, 250 patients were enrolled, 16±11 days (range, 3 to 52), on average after surgery. The mean age was 60±11 years, and 60% were men. Aortic valve replacement (AVR) was performed in 76% of patients (n=190), mitral valve replacement (MVR) in 13.6% (n=34), and double valve replacement in 10.4% (n=26).

The most commonly used prostheses for AVR (n=216) were bileaflet (St Jude, 34%; Bicarbon, 26%; Carbomedics, 16%; Mira, 9%; ATS, 5%; ONX, 2%; Advantage, 2%); monoleaflet prostheses (Medtronic) were used in 6% of cases.

MVR (n=60) involved use of only bileaflet prostheses (St Jude, 41%; Bicarbon, 35%; Mira, 6%; ATS, 6%; Carbomedics, 12%).

The types of surgery are listed in Table 1. As shown in Table 2, the study population had a particularly high-risk profile for thromboembolism.[5]

Anticoagulant Management

In most cases (n=190: 76%), VKA treatment was started during the first postoperative week (day 5±2). On arrival in the POCRC, these patients' mean INR was 1.5±0.3.

In 60 cases (24%), VKA therapy had not been started on arrival in the POCRC because of early postoperative events, namely, pacemaker implantation (n=12), monitoring of large pericardial effusion (n=19), hematemesis (n=3), inguinal hematoma (n=2), arterial limb ischemia (n=1), multiple postoperative dental extractions (n=2), ischemic colitis (n=1), and mediastinitis (n=2) or because of the standard practices of one surgical team (n=18). In these 60 patients, VKA treatment was started the day after their arrival.

In every case, anticoagulation therapy with UH (intravenous, n=74; subcutaneous, n=176) was stopped and replaced by LMWH (enoxaparin, 100 IU/kg BID subcutaneously) on arrival in the POCRC (postoperative day 16±11). Enoxaparin was continued until the target INR was reached with VKA. The mean duration of LMWH treatment was 8.3±6.0 days and the mean duration of bridging was 7.9±5.8 days. Eighty-one patients (33%) received low-dose aspirin. Acenocoumarol was provided in 41 patients (16.4%; mean dose, 3.3±1.7 mg) and fluindione in 209 patients (83.6%; mean dose, 19.9±8.2 mg).

Clinical Outcome

No thromboembolic events and no deaths occurred in the POCRC (20±7 days after LMWH treatment began).

At 3 months, outcome information was available for 247 patients (98.8%). One patient (with AVR) had a transient ischemic attack (transient left hemiparesis) within 30 days after enoxaparin treatment cessation; the INR was 2.6, and computerized tomography of the brain, transesophageal echocardiography, and Holter ECG were normal; carotid Doppler ultrasonography showed a significant (70%) contralateral carotid stenosis. This event probably was not caused by valve thrombosis.

Two major bleeding episodes (one tamponade requiring pericardiotomy and one abdominal muscle hematoma requiring blood transfusion) occurred during the switch from enoxaparin to VKA. Three minor bleeding episodes occurred (one hemoptoic spit; one minor bleeding from a tonsillar wound caused during intubation; and one abdom-

Downloaded from circ.ahajournals.org by on February 1, 2010

TABLE 1. Characteristics of the 250 Patients

	Patients Without Major Adverse Outcomes (n=247)	Patients With Major Adverse Outcomes (n=3)
Mean age, y	60±11	65±4
Mean weight, kg	71±15	72±2
Mean BMI	25±5	24±1
Gender, No. (%)		
Men	148 (60)	2(66)
Women	99 (40)	1(33)
Surgical procedures: AVR	188	2
AVR alone	126	2
AVR+CABG	31	0
AVR+Bentall	29	0
AVR+Bentall+CABG	2	0
MVR	33	1
MVR alone	20	1
MVR+TV	8	0
MVR+CABG	5	0
DVR	26	0
DVR alone	21	0
DVR+CABG	3	0
DVR+Bentall	1	0
DVR+TV	1	0
Echographic data		
LVEF, %	55±7	56±15
LVEDD, mm	50±7	52±7
LAD, mm	45±5	50±8
Mean transprosthetic aortic gradient (n=216), mm Hg	13±5	12±3
Mean transprosthetic mitral gradient (n=60), mm Hg	4±1.5	3±0

BMI indicates body mass index (kg/m^2); AVR, aortic (mechanical) valve replacement; MVR, mitral (mechanical) valve replacement; DVR, double (mechanical) valve replacement; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; and LAD, left atrial diameter.

Major averse outcomes were tamponade, n=1; abdominal muscle hematoma requiring blood transfusion, n=1; transient ischemic attack, n=1. Multivariate analysis is impossible given the small number of adverse outcomes.

inal muscle hematoma not requiring blood transfusion). Anti-Xa activity was within the target range in all these patients.

There were no cases of heparin-induced thrombopenia.

Discussion

This study involved 250 patients who had recently undergone single or double mechanical heart valve replacement and who were at an increased risk of arterial thromboembolism. A standardized LMWH-based bridging anticoagulation regimen, between the end of standard postoperative UH therapy and the onset of full oral anticoagulant efficacy, was associated with a low incidence of major bleeding (2/250, 0.8%) and with no thromboembolic events.

UH is widely used during this period, but this practice raises two main concerns. First, very few controlled studies have ascertained the optimal condition of UH use or the required degree of anticoagulation. Second, the bioavailability and predictability of UH anticoagulation are poor. Indeed, in the ESSENCE study[16] and the TIMI 9B study,[17] in about 50% of patients receiving intravenous UH, effective anticoagulation was achieved on day 3. Hull et al,[18] using subcutaneous UH administration, observed that only in 37% of patients with recent deep venous thrombosis was the target APTT achieved on day 2, despite an additional intravenous bolus of 5000 IU. Finally, Montalescot et al[5] reported that only 9% and 27% of patients had an APTT value within the therapeutic range (1.5 to 2.5 times control) after 2 and 13 days, respectively, of subcutaneous UH therapy.

Downloaded from circ.ahajournals.org by on February 1, 2010

TABLE 2. Baseline Risk Factors for Thromboembolic and Hemorrhagic Complications in the 250 Patients

Risk Factors	Patients, n (%)
Age >70 y	51(20.4%)
Hypertension	100 (40%)
LVEF<45%	29 (11.6%)
Prior ischemic stroke	31 (12.4%)
Atrial fibrillation	125 (50%)
Enlarged LA (LAD>45 mm)	133 (53.2%)
Redo cardiac surgery	47 (19%)
Diabetes	32 (13%)
MVR	34 (13.6%)
DVR	26 (10.4%)

LVEF indicates left ventricular ejection fraction; LAD, left atrial diameter; MVR, mitral (mechanical) valve replacement; and DVR, double (mechanical) valve replacement.

UH has not been shown to be superior (or even noninferior) to other anticoagulant regimens pending achievement of the target INR in patients who recently underwent MHVR. The only study comparing LMWH and UH for the prevention of thrombus formation on mechanical heart valves was based on an ex vivo rabbit model[19]; the authors concluded that subcutaneous enoxaparin was as effective as intravenous UH.

Because there is no gold standard in this setting, the use of LMWH instead of UH as a bridge pending full VKA efficacy warrants evaluation, especially because LMWH has several potential advantages in patients with mechanical heart valves[1]: (1) a better safety profile, with less frequent thrombocytopenia and bleeding in pooled analyses, and less osteoporosis during chronic therapy; (2) a more predictable and rapid anticoagulant effect; and (3) the possibility of self-administration without daily laboratory monitoring.

It must be stressed that medicolegal issues have recently arisen as a result of labeling modifications for an LMWH (Lovenox for injection package insert, Aventis Pharmaceuticals, 2002). According to the product label, the use of enoxaparin is not recommended for thromboprophylaxis in all patients with prosthetic heart valves. These modifications were based on 2 cases of valve thrombosis in pregnant women.[20] However, this labeling revision seems to be unsubstantiated, considering that an ample number of cases of similar complications, including deaths, have been reported in comparable groups of pregnant women under UH therapy.[20,21] In fact, available data suggest that neither adjusted-dose UH nor fixed-dose LMWH provides adequate protection in pregnant women with mechanical heart valves, but it has been suggested that LMWH may provide superior protection against thromboembolism if the dose is adjusted throughout pregnancy on the basis of anti-Xa levels, body weight changes, and D-dimer levels.[11,22] Moreover, this recommendation should at least be followed only in pregnant patients.

In nonpregnant patients having undergone MHVR, LMWH could be valuable in 2 situations. The first situation is for patients operated on previously who require temporary VKA withdrawal for extracardiac surgery. Despite its historic use in this situation, the efficacy and safety of bridging therapy with UH is not properly documented. By contrast, 2 large prospective surveys including a total of 327 patients with prosthetic mechanical heart valves treated with LMWH in this situation have recently been published.[6,7] They concluded that a standardized periprocedural LMWH-based anticoagulant regimen is associated with a low risk of thromboembolism and major bleeding complications. The second situation is immediately after valve implantation, when patients normally receive concomitant anticoagulation treatment with heparin and VKA until a target INR is achieved with the VKA alone. Only 2 retrospective, nonrandomized studies with a total of 131 patients receiving LMWH have been published.[5,8] Montalescot et al[5] conducted a comparative nonrandomized study in which patients who underwent single or double heart valve replacement received subcutaneous UH in the first study phase (n=106) and LMWH in the second phase (n=102). Two major bleeding events occurred in each group, and one stroke occurred in the UH group. On the second day of treatment, only 9% of patients receiving UH had an APTT within the therapeutic range (1.5 to 2.5 times control), whereas 87% of patients treated with LMWH had an anti-Xa factor activity within the therapeutic range (0.5 to 1.0 IU/mL). However, follow-up was short (14 days), and the number of MVR recipients was low (n=10).

In the Fanikos study,[8] 29 patients received LMWH and were matched with 34 control patients who were given UH. After 90 days of follow-up, the number of events (deaths + thromboembolic events + bleeding events) was slightly but not significantly lower in the LMWH group than in the control group (4 versus 9 cases). The authors concluded that patients who received LMWH had a shorter hospital stay and lower postoperative costs than control subjects receiving UH.

Our study provides significant additional information over the previous studies. First, our study population was larger (n=250). Second, the patients were at a higher risk for thromboembolism. Indeed, 90% of our patients had at least one of the thromboembolic risk factors described by Montalescot et al[5] in the above-mentioned study (MVR, double valve replacement, atrial fibrillation, enlarged cavities, prior embolic stroke, or prior heart failure) (versus 45% in the Montalescot study), whereas 61% and 24% of patients had two or more risk factors (versus 21% and 11%, respectively, in the Montalescot study). In particular, 60 of our patients had undergone MVR (versus 10 patients in the Montalescot study). This high-risk profile is probably one reason why the patients were transferred to a POCRC and not sent home directly. Third, follow-up was longer in our study (3 months), thus reducing the risk of missing late thromboembolic events (including valve thrombosis).[23] Finally, LMWH treatment began on postoperative day 16 on average (after UH treatment), whereas

Downloaded from circ.ahajournals.org by on February 1, 2010

it began on about postoperative day 2 to 6 in the 2 studies described above.[5,8] This period (16 days) is longer than the mean postoperative stay after valve replacement (11 days after AVR, 13 days after MVR[24]) and was due to a high incidence of postoperative complications before LMWH introduction, further illustrating the high-risk profile of our patients. Therefore, our results correspond to a "real-world" anticoagulation profile after mechanical valve prosthesis surgery in the specific population of patients in whom target INR has not been achieved 16 days after surgery (250/695, 36% of the total population).

Study Limitations

Because this study did not include a control group, we cannot comment on the efficacy or safety of this anticoagulant regimen relative to other strategies based on intravenous or subcutaneous heparin. However, no study evaluating UH itself and no randomized double-blinded studies comparing LMWH and UH after heart valve replacement have been conducted, more than 15 years after LMWH first became available. This situation exists, first because such studies are difficult to perform (blinded adjustment of the intravenous drug dose regimen) and also perhaps because this clinical situation is not financially interesting. It is noteworthy that no thromboembolic events related to valve thrombosis occurred in our study, which possibly lessens the need for a control group.

Conclusions

LMWH therapy as a bridge between immediate postoperative UH administration and full effectiveness of oral anticoagulation seems to be feasible in preventing thromboembolic events in patients who recently underwent mechanical heart valve replacement. These results warrant a randomized double-blinded study comparing LMWH and UH for this indication.

Disclosures

None.

References

1. Weitz JL. Low molecular weight heparins. *N Engl J Med*. 1997;337:688–698.
2. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, Bogaerts K, Danays T, Lindahl B, Makijarvi M, Verheugt F, Van de Werf F. Efficacy and safety of tenecteplase in combination with the low molecular weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)3- plus randomized trial in acute myocardial infarction. *Circulation*. 2003;108:135–42.
3. Petersen JL, Mahaffey KW, Hasselblad V, Antman EM, Cohen M, Goodman SG, Langer A, Blazing MA, Le-Moigne-Amrani A, de Lemos JA, Nessel CC, Harrington RA, Ferguson JJ, Braunwald E, Califf RM. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non ST segment elevation acute coronary syndromes: a systematic overview. *JAMA*. 2004;292:89–96.
4. Stellbrink C, Nixdorff U, Hofmann T, Lehmacher W, Daniel WG, Hanrath P, Geller C, Mugge A, Sehnert W, Schmidt-Lucke C, Schmidt-Lucke JA; ACE (Anticoagulation in Cardioversion using Enoxaparin) Study Group. Safety and efficacy of enoxaparin compared with unfractionated heparin and oral anticoagulants for prevention of thromboembolic complications in cardioversion of non valvular atrial fibrillation: the Anticoagulation in Cardioversion using Enoxaparin (ACE) trial. *Circulation*. 2004;109:997–1003.
5. Montalescot G, Polle V, Collet JP, Leprince P, Bellanger A, Gandjbakhch I, Thomas D. Low molecular weight heparin after mechanical heart valve replacement. *Circulation*. 2001;101:1083–1086.
6. Kovacs MJ, Kearon C, Rodger M, Anderson DR, Turpie AG, Bates SM, Desjardins L, Douketis J, Kahn SR, Solymoss S, Wells PS. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. *Circulation*. 2004;110:1658–1663.
7. Douketis JD, Johnson JA, Turpie AG. Low molecular weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized periprocedural anticoagulation regimen. *Arch Intern Med*. 2004;164:1319–1326.
8. Fanikos J, Tsilimingras K, Kucher N, Rosen AB, Hieblinger MD, Goldhaber SZ. Comparison of efficacy, safety, and cost of low molecular weight heparin with continuous infusion unfractionated heparin for initiation of anticoagulation after mechanical prosthetic valve implantation. *Am J Cardiol*. 2004;93:247–250.
9. Laffort P, Roudaut R, Roques X, Lafitte S, Deville C, Bonnet J, Baudet E. Early and long term (one year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St Jude medical prosthesis: a clinical and transesophageal echocardiographic study. *J Am Coll Cardiol*. 2000;35:739–746.
10. Ionescu A, Payne N, Fraser AG, Giddings J, Grunkemeier GL, Butchart EG. Incidence of embolism and paravalvular leak after St Jude Silzone valve implantation: experience from the Cardiff Embolic Risk Factor Study. *Heart*. 2003;89:1055–1061.
11. Salem DN, Stein PD, Al-Ahmad A, Bussey HI, Horstkotte D, Miller N, Pauker SG Antithrombotic therapy in valvular heart disease-native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(Suppl 3):457S-482S.
12. Bonow RO, Carabello B, de Leon AC Jr, Edmunds LH Jr, Fedderly BJ, Freed MD, Gaasch WH, McKay CR, Nishimura RA, O'Gara PT, O'Rourke RA, Rahimtoola SH, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Gibbons RJ, Russell RO, Ryan TJ, Smith SC Jr. Guidelines for the management of patients with valvular heart disease: executive summary: a report of the Am College of Cardiology/Am Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation*. 1998;98:1949–1984.
13. Montalescot G, Collet JP, Tanguy ML, Ankri A, Payot L, Dumaine R, Choussat R, Beygui F, Gallois V, Thomas D. Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin. *Circulation*. 2004;110:392–398.
14. The TIMI 11A Trial Investigators. Dose ranging trial of enoxaparin for unstable angina: results of TIMA 11A. *J Am Coll Cardiol*. 1997;29:1474–1482.
15. Hirsh J, Raschke B. Heparin and low molecular weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(Suppl 3):188S-203S.
16. Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KA, Premmereur J, Bigonzi F. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease: Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med*. 1997;337:447–452.
17. Antman EM, for the TIMI 9B Investigators. Hirudin in acute myocardial infarction: Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. *Circulation*. 1996;94:911–921.
18. Hull RD, Raskob GE, Hirsh J, Jay RM, Leclerc JR, Geerts WH, Rosenbloom D, Sackett DL, Anderson C, Harrison L. Continuous intravenous heparin compared with subcutaneous heparin in the initial treatment of proximal vein thrombosis. *N Engl J Med*. 1986;315:1109–1114.
19. Schlitt A, Buerke M, Hauroeder B, Peetz D, Hundt F, Bickel C, Schaefer I, Meyer J, Rupprecht HJ. Fondaparinux and enoxaparin in comparison to unfractionated heparin in preventing thrombus formation on mechanical heart valves in an ex-vivo rabbit model. *Thromb Haemost*. 2003;90:245–251.

Downloaded from circ.ahajournals.org by on February 1, 2010

20. Anticoagulation and enoxaparin use in patients with prosthetic heart valves and/or pregnancy. An evidence-based review and focused analysis of current controversies and clinical strategies. Clin Consensus Rep. 2002;1–18. Published by American Health Consultants, 3525 Piedmont Road, NE, Six Piedmont Center, Suite 400, Atlanta, GA 30305.
21. Salazar E, Izaguirre R, Verdejo J, Mutchinick O. Failure of adjusted doses of subcutaneous heparin to prevent thromboembolic phenomena in pregnant patients with mechanical cardiac prostheses. *J Am Coll Cardiol*. 1996;27:1698–1703.
22. Laurent P, Dussarat GV, Bonal J, Jego C, Talard P, Bouchiat C, Cellarier G. Low molecular weight heparin: a guide to their optimum use in pregnancy. *Drugs*. 2002;62:463–477.
23. Gohlke-Barwolf C. Anticoagulation in valvar heart disease: new aspects and management during non cardiac surgery. *Heart*. 2000;84:567–572.
24. Goodney PP, Stukel TA, Lucas FL, Finlayson EV, Birkmeyer JD. Hospital volume, length of stay and readmission rates in high risk surgery. *Ann Surg*. 2003;238:161–167.

CLINICAL PERSPECTIVE

After MHVR, long-term use of UH is sometimes required because VKA are temporarily contraindicated or because the time to reach the target INR is long. The aim of this study was to investigate the feasibility of LMWH treatment in these patients. Two hundred fifty consecutive patients were enrolled 16±11 days after surgery (aortic valve replacement, n=190; mitral valve replacement, n=34; double valve replacement, n=26) and received enoxaparin (100 IU/kg BID during 8.3±6.0 days on average) until VKA treatment was fully effective. During a 90-day follow-up, there were 2 major and 3 minor bleeding episodes and 1 transient ischemic attack. There were no cases of valve thrombosis and no deaths. Because this study did not include a control group, we cannot comment on the efficacy or safety of this anticoagulant regimen relative to other strategies based on intravenous or subcutaneous heparin. However, no study evaluating UH itself and no randomized double-blinded studies comparing LMWH and UH after heart valve replacement have been conducted. In conclusion, LMWH therapy as a bridge between immediate postoperative UH administration and full effectiveness of oral anticoagulation appears to be feasible in preventing thromboembolic events in patients who recently underwent MHVR and could shorten the length of hospital stay. These results warrant a randomized double-blinded study comparing LMWH and UH for this indication.

Downloaded from circ.ahajournals.org by on February 1, 2010