Low Molecular Weight Heparin After Mechanical Heart Valve Replacement

Gilles Montalescot, MD, PhD; Valérie Polle, PharmD; Jean P. Collet, MD, PhD; Pascal Leprince, MD; Agnès Bellanger, PharmD; Iradj Gandjbakhch, MD; Daniel Thomas, MD

Background—Patients with mechanical heart valves require life-long anticoagulation. We report here the first large and comparative series of consecutive patients anticoagulated with low molecular weight heparin (LMWH) after mechanical heart valve replacement.

Methods and Results—In this comparative, nonrandomized study, 208 consecutive patients who underwent a single or double heart valve replacement with mechanical prostheses were anticoagulated subcutaneously with unfractionated heparin (UH) in the first period (n = 106) and LMWH in the second phase (n = 102) of the study. Baseline characteristics were similar in the 2 groups. The mean durations of UH and LMWH treatments were 13.6 ± 0.5 and 14.1 ± 0.6 days, respectively (not significant). On the second day of treatment, 87% of patients treated with LMWH had an anti-Xa activity within the range of efficacy (0.5 to 1 IU/mL), but only 9% of UH-treated patients had an activated partial-thromboplastin time value within the therapeutic range (1.5 to 2.5 times control, P < 0.0001 between the 2 groups). On the last day of prescription, all LMWH-treated patients had anti-Xa activity above 0.5 IU/mL, but 19% were above 1 IU/mL. In the UH group, 27% of patients had an activated partial-thromboplastin time above 1.5 times control, but 62% were overanticoagulated. Two major bleedings occurred in each group, and one stroke occurred in the UH group.

Conclusions—In this first comparative study, anticoagulation with LMWHs after mechanical heart valve replacement appears feasible, provides adequate biological anticoagulation, and compares favorably with UH anticoagulation. Randomized studies are now needed to further evaluate this new therapeutic approach. (Circulation. 2000;101:1083-1086.)

Key Words: heparin ■ prosthesis ■ valves

In recent years, low molecular weight heparins (LMWH) have been tested in the prevention and treatment of deep vein thrombosis and pulmonary embolism, as well as in the treatment of stroke and unstable angina.1 In all these situations, LMWH had a similar or even a better risk/benefit ratio than unfractionated heparin (UH). Acute myocardial infarction and coronary angioplasty are among the new targets presently under investigation with various LMWH.

In contrast, little attention has been paid to other thrombogenic clinical situations representing often little market shares for the pharmaceutical companies. Patients with mechanical heart valve prostheses have a high thromboembolic potential requiring life-long anticoagulation, but the use of LMWH in place of UH has not been examined yet. The implantation of a large artificial device in contact with the bloodstream expose to the risk of valve thrombosis and embolism mainly in the central nervous system. The risk of thromboembolism is particularly elevated in the postoperative period, when oral anticoagulation is not effective yet. UH is largely prescribed over this period, although little controlled data are available to ascertain the optimal use and the necessary degree of anticoagulation. The published experience with LMWH is limited only to a few case reports. Lee et al2 have reported the use of LMWH in 2 pregnant women with mechanical heart valves, Harenberg et al3 described in his largest series 16 patients with mechanical heart valves in a population of 120 patients receiving long-term LMWH therapy because of contraindications to oral anticoagulants and only two cases of LMWH prescription in the postoperative period of mechanical heart valve replacement have been published.4,5 We report here the first large series of patients treated consecutively with LMWH after mechanical heart valve replacement, and we compare the results with a series of similar patients treated classically with UH in the same department.

Methods

Study Population
We studied 208 consecutive patients who underwent a single or double heart valve replacement with mechanical prostheses. This
population included 142 men (68%) and mean age was 57.6 ± 1.5 years without difference between the 2 treatment groups. Mean body weight was 72 ± 1.5 and 70 ± 1.6 kg in the LMWH and UH groups, respectively (not significant between groups). The operative technique included median sternotomy, cardiopulmonary bypass, and anticoagulation for extracorporeal circulation circuitry, which was provided with UH at a commencement dose of 300 U/kg with continued anticoagulation to maintain activated coagulation time above 450 seconds. Heparin anticoagulation was reversed after discontinuation of extracorporeal circulation circuitry by administration of protamine sulfate (dose/dose). The most commonly used prostheses were bileaflet prostheses; St Jude (65%) and Carbomedics (27%) prostheses were the most frequently implanted in mitral position, whereas Medtronic (33%), St Jude (30%), and Bicarbon (18%) prostheses were mostly used in aortic position. Single aortic valve replacement was performed in 157 patients, mitral valve replacement in 29 patients, and double valve replacement in 22 patients. Intravenous UH anticoagulation was resumed as soon as possible after operation according to postoperative blood loss from chest tubes and activated partial-thromboplastin time (APTT) values (≈day 2).

In patients returning from heart valve surgery, with no more need for an IV line, subcutaneous UH or LMWH injections were started with oral anticoagulation given without loading dose (≈day 6). Over the first period of the study, patients (n = 106) were classically anticoagulated with UH, and in the second phase of the study, anticoagulation was provided with LMWH in similar patients (n = 102). Subcutaneous heparin treatments with either UH or LMWH were given until oral anticoagulant treatment was fully effective. During these 2 treatment periods, no patient selection was made according to the clinical status, medical history, type of surgery, or risk factors of thrombosis. The type of heparin was the only major change over this period in the management of our patients operated with 1 or 2 mechanical heart valves. No other major changes occurred in both surgical and medical managements. We collected all clinical, echocardiographic, and follow-up data for all patients over the 2 treatment periods.

Study Design
Patients treated with UH (Calciparine, Sanofi-Winthrop, France) received 3 subcutaneous injections a day, at a dose of 500 IU · kg⁻¹ · 24hrs⁻¹, adjusted to the APTT with a target range of 1.5 to 2.5 times control. APTT measurements were repeated as often as necessary with a last measurement before stopping UH treatment when oral anticoagulants were effective. Most of the patients (72%) treated with LMWH received enoxaparin (Lovenox, Rhone-Poulenc-Rorer, France), which was given at a dose of 100 anti-Xa IU/kg (1 mg/kg), subcutaneously at 12-hour intervals. The other patients received nadroparin (Fraxiparin, Sanofi-Winthrop, France) at a dose of 87 anti-Xa IU/kg subcutaneously at 12-hour intervals. Anticoagulation was checked by measuring anti-Xa activity 4 hours after the third injection. Our therapeutic range was 0.5 to 1 IU/mL as previously defined in studies with LMWH in the treatment of deep vein thrombosis and recently confirmed in studies in unstable angina.⁶ ⁷ When anti-Xa levels were not in the target range, the doses of LMWH were adjusted. Anti-Xa was measured again before stopping LMWH treatment when oral anticoagulants were effective.

In-hospital follow-up was performed looking at death, stroke (transient or permanent), any peripheral embolism, valve thrombosis, mechanical prostheses failure, endocarditis, reintervention, and major bleedings defined as any bleeding requiring transfusion, surgical operation, or prolongation of hospitalization.

Anti-Xa Measurements
Blood (9 vol) was collected 4 hours after the morning injection in 0.109 mol/L trisodium citrate anticoagulant (1 vol) and centrifuged at 3000g for 20 minutes. The anti-Xa activity of LMWH was measured with a colorimetric assay with a synthetic chromogenic substrate (Rotachrom, Diagnostica Stago, Asnieres, France) using STA analysers. The therapeutic range recommended by the manufacturer with 2 injections/day is 0.5 to 1 anti-Xa IU/mL.

Baseline Risk Factors for Thromboembolic or Hemorrhagic Complications in the 2 Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>LMWH</th>
<th>UH</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.8 ± 1.4</td>
<td>55.3 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>37.2</td>
<td>27.3</td>
<td>NS</td>
</tr>
<tr>
<td>Prior heart failure, %</td>
<td>11.7</td>
<td>8.5</td>
<td>NS</td>
</tr>
<tr>
<td>Prior ischemic stroke, %</td>
<td>3.9</td>
<td>2.8</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>19.6</td>
<td>20.7</td>
<td>NS</td>
</tr>
<tr>
<td>LA or LV thrombus, %</td>
<td>3.9</td>
<td>4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Endocarditis, %</td>
<td>8.8</td>
<td>7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Enlarged LA, %</td>
<td>28.4</td>
<td>33.0</td>
<td>NS</td>
</tr>
<tr>
<td>LV dysfunction, %</td>
<td>37.3</td>
<td>47.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

LMWH indicates low molecular weight heparin; UH, unfractionated heparin; LA, left atrium; LV, left ventricle; and NS, not significant.

Statistical Analysis
Results are expressed as mean ± SEM. Potential associations between clinical or biological parameters were tested by univariate procedures using Student’s t or χ² tests. The alpha level was set at 0.05.

Results
Clinical Characteristics
Two hundred and eight consecutive patients were studied after mechanical heart valve replacement. Despite the lack of randomization, the 2 treatment groups were well balanced for the baseline clinical characteristics. Aortic valve replacement was performed in 68% and 83% of patients treated with UH and LMWH, respectively; mitral valve replacement was done in 18% and 10%, double valve replacement in 14% and 7% of patients given UH and LMWH, respectively. Patients at high risk of thromboembolic events were treated like patients at lower risk, and all of them received LMWH during the second period of the study. Subsequently, no difference was observed between the 2 groups for the percentage of atrial fibrillation, prior heart failure, prior history of stroke, intracardiac thrombus, enlarged cardiac cavities, or left ventricular dysfunction (see Table). In each group, 45% of patients had at least 1 of the following risk factors for thromboembolic events: (1) mitral valve replacement, (2) double valve replacement, (3) atrial fibrillation, (4) enlarged cavities, (5) prior embolic stroke, (6) intracardiac thrombosis, or (7) episode of heart failure; 21% and 11% patients cumulated 2 or more of these risk factors in the LMWH and UH groups, respectively.

The mean duration of heparin treatment was 13.6 ± 0.5 and 14.1 ± 0.6 days in the UH and LMWH groups, respectively (not significant between the 2 groups).

Levels of Anticoagulation
At the initiation of treatment, an effective anticoagulation was rapidly reached with LMWH because most patients (87%) had an anti-Xa activity within the range of efficacy (0.5 to 1 IU/mL) on the second day of treatment (Figure 1). In contrast, at the same time period, only 9% of UH-treated patients had an APTT value within the therapeutic range (1.5 to 2.5 times control), most patients (91%) not being enough anticoagulated.
On the last day of UH and LMWH treatments, when oral anticoagulants were effective allowing interruption of heparin administration, all LMWH-treated patients had anti-Xa activity above 0.5 IU/mL (Figure 2); however, 19% were above 1 IU/mL of anti-Xa activity. In the UH group, 27% of patients had an APTT between 1.5 and 2.5 times control, but more patients (62%) were overanticoagulated (above 2.5 times control).

**Clinical Outcome**

Only 1 patient presented a thrombotic event in our study population of 208 patients. This patient treated with UH suffered 2 successive transient ischemic strokes 17 days after a single aortic valve replacement. No valve thrombosis and no mechanical prosthesis failure was observed on the echocardiogram. Computed tomography scan confirmed the diagnosis. Both the APTT and international normalized ratio values were below the lower limit of anticoagulation demonstrating that both UH and oral anticoagulants were ineffective before the neurologic event.

Four major bleedings occurred, two in each treatment group; there were 2 gastrointestinal bleedings in the LMWH group, 1 gastrointestinal bleeding and one thigh hematoma in the UH group. Only 1 patient (UH group) was significantly overanticoagulated on the day of bleeding.

**Discussion**

This is the first report of a large use of LMWH after heart valve replacement by mechanical prostheses using doses shown to be effective in the treatment of thromboembolic disease and unstable angina. Systematic laboratory monitoring showed a more rapid and more constant biological efficacy with LMWH than with UH. The good safety/efficacy profile with LMWH suggests the feasibility of this therapeutic option.

Patients with mechanical prostheses need life-long anticoagulation, and heparin administration is required when oral anticoagulation must be interrupted (eg, noncardiac surgery, catheterization, coloscopy) and of course in the postoperative period after implantation of the mechanical prosthesis. During this period, patients are at high risk of thromboembolic complications, and heparin is prescribed until oral anticoagulants are effective. Although literature is scarce,2–5 LMWH have the following potential advantages that may be relevant for patients with mechanical heart valves1: (1) a better safety profile with less thrombocytopenias, less bleedings in pooled analyses, and less osteoporosis with prolonged treatments; (2) a more predictable and rapidly reached anticoagulant effect; and (3) the possibility of self-administration of anticoagulation without laboratory monitoring. The pharmacokinetic and biological advantages of LMWH may even be more relevant in the postoperative period of heart valve replacement, which is associated with severe inflammation and platelet and coagulation disorders related to cardiopulmonary bypass, making adequate anticoagulation with UH more difficult. Large clinical studies have always demon-
strated that LMWH are at least as safe and effective as UH in the prevention and treatment of deep venous thrombosis and in the treatment of pulmonary embolism, ischemic stroke, and unstable angina. Moreover, LMWH with a safe out-hospital administration without laboratory monitoring could shorten the hospital stay and the financial costs as it has been shown for the treatment of deep vein thrombosis.

We demonstrate in our study population that LMWH in the high-risk postoperative period is at least as safe and effective as UH in a comparable group of patients managed in the same department. The main limitation of our study is the lack of randomization. However, our patients were not selected for the allocation to LMWH, and our data represent a “real world” approach of anticoagulation after implantation of mechanical valve prostheses; subsequently, the LMWH group had the same risk profile as the group of patients previously treated with UH. Anti-Xa activity in the LMWH group was more frequently in the range of efficacy than was APTT in the UH group, both at the initiation and the end of treatment, confirming the more predictable anticoagulant response with LMWH. This more rapid and more constant efficacy of LMWH anticoagulation might provide a better efficacy/safety profile with a larger population compared with UH. Although the present work represents the largest group ever reported of patients with mechanical prostheses anticoagulated with LMWH, the amount of clinical information remains limited and the small number of events impact the power of the study, which should be considered as a pilot study. Our report points out the urgent need for collection of more clinical data and for well designed randomized trials.

References

Low Molecular Weight Heparin After Mechanical Heart Valve Replacement
Gilles Montalescot, Valérie Polle, Jean P. Collet, Pascal Leprince, Agnès Bellanger, Iraj Gandjbakhch and Daniel Thomas

Circulation. 2000;101:1083-1086
doi: 10.1161/01.CIR.101.10.1083

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/101/10/1083

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

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

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