# Exclusive Low-Molecular-Weight Heparin as Bridging Anticoagulant After Mechanical Valve Replacement

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*Background.* **Unfractionated heparin has been the standard anticoagulant used immediately after mechanical heart valve replacement (MHVR). The purpose of this study was to assess a postoperative anticoagulation protocol with low-molecular-weight heparin (LMWH) immediately after MHVR without the use of unfractionated heparin or anti-factor Xa monitoring.**

*Methods.* **We performed a prospective, single-center, observational study of 1,063 consecutive patients undergoing elective MHVR with postoperative LMWH anticoagulation treatment. The exclusion criteria were as follows: renal failure, intraaortic balloon counterpulsation, critical perioperative state, or a recent neurologic event. The postoperative anticoagulation protocol used subcutaneous enoxaparin as a bridging anticoagulant treatment beginning on the first postoperative day and continuing until vitamin K antagonist treatment was fully effective. Patients were followed for 6 weeks. The primary endpoints were the incidence of thromboembolic or major bleeding events.**

*Results.* **Eleven (1%) thromboembolic events occurred. Ten of these events were transient or permanent strokes. Major bleeding events occurred in 44 patients (4.1%), 7 of which were observed before the enoxaparin treatment period. At the time of discharge, 570 patients (53.6%) were no longer receiving LMWH treatment due to achieving the target international normalized ratio. The mean length of hospital stay was 8.5 ± 2.9 days. There were no deaths during the 6-week follow-up period.**

*Conclusions.* **In our highly selected population, after MHVR, postoperative anticoagulation using LMWH is associated with a low rate of thromboembolic and major bleeding events. This large observational study demonstrates that the use of LMWH as an anticoagulant is effective and safe after MHVR.**

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The immediate administration of anticoagulation therapy after mechanical heart valve replacement (MHVR) remains under discussion, and no consensus exists [1, 2]. Worldwide, unfractionated heparin (UH) is still the standard drug used as a bridging anticoagulant after MHVR. Recently, it has become increasingly apparent that low-molecular-weight heparin (LMWH) is safe and effective for the treatment of deep vein thrombosis, pulmonary embolism, stroke, and unstable angina [3–7]. Compared with UH, LMWH anticoagulation is associated with a more predictable and rapidly reached anticoagulation target level in addition to its better bioavailability and improved risk to benefit ratio [7, 8].

Managing anticoagulation immediately after MHVR remains a challenge because of the risk of bleeding early after surgery and the risk of thromboembolic events in the subsequent days [9]. Despite the potential interest in using LMWH as a bridging anticoagulant after MHVR, few studies have analyzed this application [8, 10–13]. In those studies, the population sizes were small, and most patients received LMWH anticoagulation after an initial UH anticoagulation period [8, 12].

Considering the good risk to benefit ratio of LMWH, we decided to anticoagulate our patients after MHVR using an anticoagulation protocol that exclusively used LMWH. Therefore, the purpose of this study was to assess the efficacy and safety of LMWH as a bridging anticoagulant immediately after MHVR without the use of UH or anti-factor Xa activity monitoring.

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## Patients and Methods

### Study Population

The rationale for our bridging anticoagulant protocol with LMWH after MHVR was based on studies that demonstrated the safety and efficiency of LMWH for the treatment of deep vein thrombosis, pulmonary embolism, stroke, and unstable angina [3–5, 14]. Furthermore, Montalescot and colleagues [8] published a pilot study where LMWH was used as a bridging anticoagulant after MHVR. They demonstrated that LMWH was safe and effective compared with unfractionated heparin. Nonetheless, LMWH in their study was started after approximately 6 days of treatment with unfractionated heparin [8]. The study procedures were approved by the Institutional Review Board of our institution.

From January 1, 2000 through November 1, 2010, a total of 1,374 patients underwent mechanical heart valve replacement (MHVR) at our institution. Within this population, 1,063 patients (77.3%) met the inclusion (MHVR surgery; age ≥18 years) and exclusion criteria and received exclusively LMWH as a bridging anticoagulant immediately after MHVR without the use of UH or anti-factor Xa activity monitoring. Exclusion criteria were a recent neurologic event, preoperative or postoperative severe renal insufficiency (serum creatinine >200 μmol/L), dialysis, aortic dissection, critical perioperative state, intraaortic balloon counterpulsation, or duration of intubation of more than 48 hours. Baseline demographic, clinical, and operative characteristics are reported in Tables 1, 2, and 3.

*Table 1. Patient Baseline Characteristics*

| Variable | Number (%) |
|---|---|
| Age, years | 59.2 ± 11.1 |
| Body mass index (kg/m$^2$) ≥35 kg/m$^2$, n (%) | 27.0 ± 4.9 |
| Male gender, n (%) | 56 (6.1) |
| New York Heart Association class III or IV, n (%) | 683 (64.3) |
| Canadian Cardiovascular Society class III or IV, n (%) | 380 (35.7) |
| Asymptomatic, n (%) | 40 (3.8) |
| Coronary artery disease, n (%) | 89 (8.4) |
| Current smoker, n (%) | 116 (10.9) |
| Hypertension, n (%) | 401 (37.7) |
| Dyslipidemia, n (%) | 458 (43.1) |
| Diabetes, n (%) | 408 (38.4) |
| Chronic obstructive pulmonary disease, n (%) | 164 (15.4) |
| Cerebral vascular disease, n (%) | 81 (7.6) |
| Previous cardiovascular surgery, n (%) | 59 (5.6) |
| Previous myocardial infarction, n (%) | 135 (12.7) |
| Percutaneous coronary intervention, n (%) | 44 (4.1) |
| Prior heart failure | 48 (4.5) |
| Atrial fibrillation, n (%) | 139 (13.1) |
| $CHADS_2$ score ≥2, n (%)[a] | 142 (13.4) |
| Peripheral vascular disease, n (%) | 36 (3.3) |
| Active endocarditis, n (%) | 65 (6.1) |
| Echographic data | 37 (3.5) |
| Left ventricular ejection fraction | 61.2 ± 12.3 |
| Left ventricular ejection fraction <0.35, n (%) | 32 (3.0) |
| Left ventricular end-diastolic diameter, mm | 57.1 ± 10.2 |
| Biologic data | |
| Hemoglobin, g/dL | 13.6 ± 1.6 |
| Platelet count, $10^3$/mm$^3$ | 238.8 ± 72.7 |
| Prothrombin time, % | 85.0 ± 17.9 |
| Activated partial thromboplastin time, sec | 37.1 ± 10.5 |
| Creatinine - μmol/L | 89.0 ± 20.4 |
| Fibrinogen, g/L | 3.6 ± 1.0 |
| 30-day operative mortality predicted by EuroSCORE I, % | 4.6 ± 4.9 |

[a] $CHADS_2$ is a risk-prediction score ranging from 0 to 6 that gives 1 point each for congestive heart failure, hypertension, age of 75 years or older, and diabetes, and 2 points for either stroke or transient ischemic attack.

EuroSCORE = European System for Cardiac Operative Risk Evaluation.

### Study Design

We enrolled all consecutive patients who met the inclusion and exclusion criteria into a prospective, single-center, observational study. The surgical procedure was performed using UH anticoagulation to maintain an activated coagulation time above 400 seconds. At the end of the surgery, when the cardiopulmonary bypass was stopped, protamine sulfate (dose/dose) was given to reverse heparin anticoagulation. Small surgical drains (8 to 14 drains, each 3 mm in diameter; Peters Surgical, France) were placed around the heart and, if necessary, in the pleural cavities. The surgical drains were removed on the second postoperative day.

Our institutional postoperative anticoagulation protocol was started on postoperative day 1, with 1 subcutaneous enoxaparin injection per day at a dose of 4,000 IU of anti-Xa. vitamin K antagonist (VKA; fluindione) was started as soon as the patients were extubated on the first or second postoperative day. On postoperative day 2, subcutaneous enoxaparin was administered at 12-hour intervals. The LMWH dose was determined based on body weight, as described in Table 4. The LMWH was given until the international normalized ratio (INR) was within the target range for 2 consecutive days (2 to 3 after aortic valve replacement or 2.5 to 3.5 after mitral or tricuspid valve replacement). Antiplatelet therapy was only prescribed in case of concomitant peripheral vascular disease or coronary artery disease. Cardiac echocardiography was systematically performed prior to discharge, usually on postoperative day 5. A transesophageal echocardiography was performed only in case of uncertain transthoracic echocardiography findings. All patients underwent follow-up evaluations at 6 weeks.

### Endpoints

All outcome definitions follow the "Guidelines for reporting mortality and morbidity after cardiac valve interventions" [15]. The primary endpoints of this study were the 6-week time point and the occurrence of a thromboembolic (efficacy endpoint) or major bleeding (safety endpoint) event during the 6-week follow-up. Thromboembolic events were defined as a transient or