Evaluation of Low-Molecular-Weight Heparin Dose Adjusted by Weight for Patients with Cardiovascular Disease

Thromboembolic diseases are a common cause of cardiovascular morbidity and mortality, and their prevention depends on adequate antithrombotic therapy. Drug dose recommendations are based on clinical trials evaluating the risk-benefit of the therapies employed. This is particularly important for heparins that require doses adjusted by body weight. Precise weight-adjusted dosing has been performed in randomized trials testing these drugs. Based on these results, recommendation guidelines for atrial fibrillation (AF), pulmonary thromboembolism (PTE), deep vein thrombosis (DVT), and acute coronary syndromes (ACS) suggest anticoagulation therapy with low-molecular-weight heparin (LMWH) at 1 mg/kg body weight every 12 hours to prevent thromboembolic events with low risk of bleeding.

This study has been conducted to determine the actual usefulness of LMWH depending on estimated weight-adjusted dosing.

To understand the usefulness of LMWH in patients requiring anticoagulation for cardiac reasons, an analysis of patients under LMWH was performed by comparing estimated weight-adjusted dosing versus actual weight-adjusted dosing.

Before discharge, inpatient data with conditions requiring LMWH were collected from both public and private tertiary cardiology services. The administered dose and its relationship with the body weight estimated by the attending physician were evaluated, and the actual patients' weight was measured with an analog scale. A range of±10 kg of the estimated weight compared with the actual weight was considered adequate. Patients with contraindications for LMWH, creatinine clearance (Cockcroft-Gault equation) <30 ml/min, or weighing >100 kg were excluded from the study. Continuous variables were expressed as mean ± standard deviation, and events, in percentages.

A total of 102 patients were included with mean age of 68 years; 33% were women. The reason for anticoagulation was 1 patient with left ventricular thrombus, 11 patients with mechanical valve, 19 patients with acute coronary syndromes, 27 patients with DVT/PTE, and 43 patients with atrial flutter/AF (Table 1). Mean creatinine clearance was 89.2 ml/min, and enoxaparin was the heparin used in all patients. After adjusting LMWH dose by actual weight (1 mg/kg every 12 h), it was seen that 62.8% of patients were improperly anticoagulated. Among the anticoagulated patients under improper dosage, 95.2% was receiving only one dose.

This series revealed that estimated weight entails incorrect LMWH anticoagulation doses in patients with cardiovascular diseases. Not measuring patients' weight systematically is the major determinant of proper dosage failure. In a study of patients with ACS, Macie et al. observed that only 1 out of 10 patients treated with LMWH had had their weight measured in the Coronary Care Unit. (1) In this regard, weight estimation implies an error of 9-10 kg, even reaching an interindividual variability of up to 20%. This estimation differs depending on who calculates it. Patients' own weight estimates are likely to be more accurate than those of physicians or nurses. (2, 3) There are other factors involved in correct dosing; weight changes during the course of hospitalization, generally decreasing as a result of diet, and in patients with cardiovascular disease, weight is related to heart failure treatment. This is a very important aspect to be considered in daily dose adjustment. In our registry, patients were weighed within two days of hospitalization, so as to prevent weight changes from influencing the results.

Another factor is that LMWH comes in fixed doses, which prevents an accurate weight adjustment without drug discarding. All these factors generally determine subtherapeutic anticoagulation doses, and to a lesser extent, doses higher than suggested. The Thrombolysis in Myocardial Infarction (TIMI) 11A trial revealed that a 25% increase in the dose of heparin increased the rate of bleeding without reducing thrombotic events; however, the thrombotic effect of lower dosing is controversial. (4) Xu et al. have demonstrated that lower-than-required dose in anticoagulated patients with LMWH was not associated with increased risk of thrombotic events, whereas an overdose caused major bleeding according to multivariate analysis. Neverthe-

Table 1. Baseline characteristics and results

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Patients (n)	102
Male (%)	67.6
Mean age (years)	68 ± 12
Reason for anticoagulation (n)	
*Atrial fibrillation/Atrial flutter	43
*DVT/PTE	27
*ACS	19
*Mechanical valve	11
*LV thrombus	1
Cr Clearance (mean ml/min)	89.2 ± 56
Mean weight (kg)	77.7 ± 13
Sub-therapeutic range (%)	95.2
Enoxaparin (%)	100

ACS: Acute coronary syndrome. Cr Clearance: Creatinine clearance. DVT/PTE: Deep vein thrombosis/Pulmonary thromboembolism. LV thrombus: Left ventricular thrombus

less, the sub-therapeutic LMWH dose is associated with the individual effect on anti-Xa activity. Although low anti-Xa activity increases 30-day mortality, implications in our series are unkown because it was not measured. (5)

This report evidences the value of using weight-adjusted LMWH dosing and the difficulty of such adjustment in daily practice, which may require anti-Xa activation measurement. Another possibility is to consider the use of new oral anticoagulation agents that do not involve weight adjustment or factor measurement to prevent thromboembolic events with low bleeding risk.

Anticoagulation with estimated weight-based LMWH dosing entails an inadequate dose of heparin, generally due to weight underestimation. Measuring actual body weight, not usually performed, is essential for a correct anticoagulation therapy.

Conflicts of interest

None declared.
(See authors' conflicts of interest forms on the website/Supplementary material).

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Prosthetic Dehiscence as Cause of Acute Coronary Syndrome

Prosthetic dehiscence is a complication consisting in a solution of continuity of the sutures that connect the valve prosthesis with its ring, resulting in eccentric valve regurgitation.

The incidence of significant paravalvular regurgitation in a prosthetic valve is 1-5%. (1, 2) It can be mild and have a benign course or present symptoms of heart failure or hemolytic anemia, which is the complication reflected in our uncommon clinical case. Some of the predisposing factors include a severely calcified valve annulus, infective endocarditis (IE), chronic use of steroids, and poor surgical technique. (3) Its early postoperative onset is common in patients with severe mitral annulus calcification, making prosthesis fixation difficult. If there is no hemodynamic involvement, and if failure is not severe, the treatment approach can be conservative, since it is usually mild and decreases, or even disappears with time. Late dehiscence occurs commonly as the result of IE and its diagnosis is clinical and echocardiographic.

Transthoracic echocardiography (TTE) is useful to identify paravalvular prosthetic valve regurgitation. Acoustic shadowing, so problematic in mitral prosthesis, is a minor inconvenience for prosthetic aortic regurgitation. However, transesophageal echocardiography (TEE) provides uniform, better images than those from TTE for prosthetic valve assessment, given the proximity of the esophagus to cardiac structures. Two-dimensional (2D)-TEE can miss significant findings as it only presents images from one plane of the heart. Three-dimensional (3D) TEE, on the other hand, provides improved spatial resolution compared to conventional 2D TEE, allowing a complete visualization of the prosthesis. (4, 5)

Echocardiographic findings will include a high velocity and intense eccentric regurgitant jet, which usually courses adhered to the receptive chamber wall and its level can be determined using the usual criteria for valve diseases. If dehiscence is significant, pros-

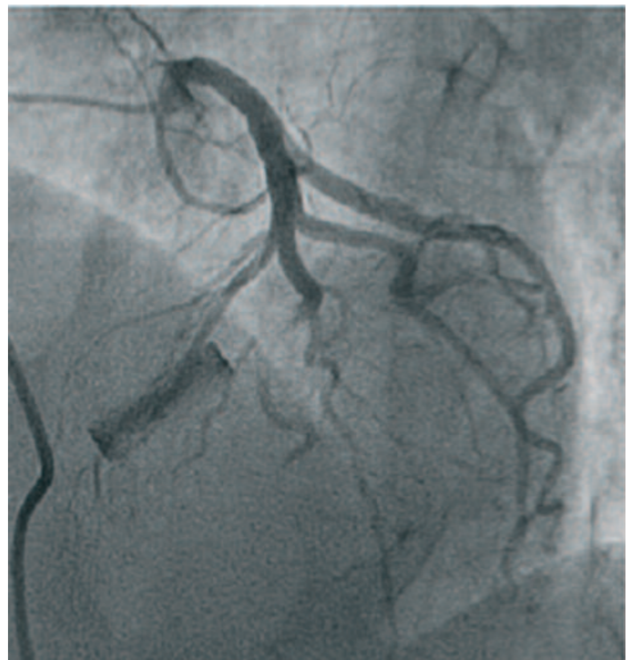

Fig. 1