

The following abstracts, from medical journals containing literature on the use of heparin and low-molecular weight heparin, were selected for their relevance to this Special Report.

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### Heparin Regimen for Acute Coronary Syndromes

The authors evaluated regimens that adjusted heparin dosage for low body weight in a nonrandomized cohort of 80 patients with unstable angina and myocardial infarction (MI) who did not receive thrombolytic agents. They established a target activated partial thromboplastin time (aPTT) of 45 to 70 seconds with a dosage regimen of 60 U/kg intravenous bolus; 12 U/kg/hr infusion for patients < 70 kg and a capped 4000-U intravenous bolus; and 900 U/hr infusion for patients 70 kg. Results within the weight-adjusted group at 6 hours showed that 34% were within the target range vs. none of the patients undergoing standard heparin regimens. Within the weight-adjusted group, a significantly lower proportion (47%) were above the target range compared with 95% of those undergoing the standard heparin regimen ( $P < 0.0005$ ), but no statistical difference was found in the proportion below target range between groups. At 24 hours, 74% of patients undergoing the weight-adjusted dosage were within the target range compared with 52% of standard regimen patients. The weight-adjusted heparin nomogram resulted in fewer infusion adjustments over the first 24-hour period, and beyond 24 hours, there was reasonable maintenance of aPTT within target range without an increase in the rate of early aPTT below the target range. The authors conclude that the use of a lower-dose, weight-based heparin for patients

with low body weight is more effective in rapidly attaining aPTTs within the target range than are standard heparin regimens.

Hochman JS, Wali AU, Gavrilu D, et al. A new regimen for heparin use in acute coronary syndromes. *Am Heart J* 1999;138:313-318.

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### Preoperative Versus Postoperative Initiation of Low-Molecular Weight Heparin in Patients with Elective Hip Replacement

Low-molecular weight heparin (LMWH) is an effective prophylactic agent for patients undergoing elective hip replacement. However, clinical authorities have divergent views about whether to initiate prophylaxis of deep vein thrombosis (DVT) in high-risk surgical patients preoperatively, as administered in Europe, or postoperatively, as administered in the United States and Canada. Preoperative prophylaxis of DVT is based on the premise that it will optimize the antithrombotic effectiveness of the prophylactic agents. On the other hand, trials performed in the United States and Canada have evaluated postoperatively initiated prophylaxis with LMWH based on the premise that waiting 12 to 24 hours after surgery would minimize the risk of bleeding. Although clinical trials demonstrate both prophylactic approaches to be effective, the relative effectiveness and safety of these differing approaches are unknown. This meta-analysis reports that treatment with LMWH initiated preoperatively was associated with a DVT frequency of 10.0% compared with a frequency of 15.3% with postoperative administration of LMWH ( $P = 0.02$ ). Patients who received preoperatively initiated LMWH experienced major bleeding at a rate of 0.9% versus a 3.5% rate for those receiving LMWH postoperatively ( $P = 0.01$ ). The authors conclude that a

*randomized comparison of preoperative and postoperative initiation of pharmacological prophylaxis of DVT is necessary in order to resolve the divergent practices for DVT prophylaxis between the North American countries and Europe.*

Hull RD, Brant RF, Pineo GF, et al. Preoperative vs. postoperative initiation of low-molecular-weight heparin prophylaxis against venous thromboembolism in patients undergoing elective hip replacement. *Arch Intern Med* 1999;159:137-141.

### **Efficacy of a Very Low-Molecular Weight Heparin in Patients with Unstable Angina**

*Researchers compared the efficacy, tolerability, and safety of a very low-molecular weight heparin, OP 2000, with standard heparin in the treatment of unstable angina. OP 2000 has high antifactor Xa and antithrombin activities similar to those of low-molecular weight heparin. It may act on platelets and reduces thrombin-induced platelet aggregability as well as fibrinogen levels in patients with coronary artery disease. The study, an open-label, randomized, parallel-group trial, analyzed 120 patients suffering from unstable angina. Sixty of the patients received OP 2000 at a dosage of 200 mg intramuscular (IM) the first day followed by 150 mg IM/day. Sixty patients randomized to standard heparin treatment received an intravenous bolus injection of 5000 IU/mL standard heparin followed by continuous intravenous infusion at a dosage adjusted to maintain an activated partial thromboplastin time between 1.5 and 3 times the upper reference value. In all patients, aspirin was administered on the same day as heparin. The primary endpoints were death, acute myocardial infarction, urgent revascularization, and recurrence of angina. Tolerability was assessed using bleeding parameters, thrombocytopenia, and allergic reactions. Events were significantly less fre-*

*quent in patients receiving OP 2000—23.3% of cases versus 41.6% of cases receiving unfractionated heparin. The study provided evidence that fixed-dose, IM OP 2000, given once a day, is equivalent or potentially better than unfractionated heparin therapy in terms of cardiovascular events occurring during the acute phase of unstable angina.*

Mattioli AV, Castellani ET, Goedecke L, et al. Efficacy and tolerability of a very low molecular weight heparin compared with standard heparin in patients with unstable angina: A pilot study. *Clin Cardiol* 1999;22:213-217.

### **Thromboprophylaxis with Low-Molecular Weight Heparin in Pregnancy**

*Pulmonary embolism is the second leading cause of death during pregnancy and postpartum in the United States. Although prophylactic use of unfractionated heparin (UFH) is recommended for women at risk for venous thromboembolism, this randomized study was designed to determine whether low-molecular weight heparin is also suitable. One hundred and five pregnant women with current or previous thromboembolism received either dalteparin once daily subcutaneously or UFH twice daily, initiated prior to week 20 of gestation and continued for 6 weeks post delivery. Treatment with UFH was started at a dose of 7500 IU twice daily and then adjusted based on activated partial-thromboplastin time measurements, monitored every 2 weeks. Dalteparin was administered at a starting dose of 5000 IU for patients weighing less than 85 kg, or 7500 IU for those weighing 85 kg or more; the dose was adjusted on the basis of plasma antifactor Xa measurements. No thromboembolic complications were detected in either group during treatment. The number of bleeding complications differed significantly in the 2 groups, with 9 cases of bleeding in 9*

patients ( $n = 50$ ) in the dalteparin group versus 55 cases of bleeding in 35 patients ( $n = 55$ ) in the UFH group. However, only 2 of those bleedings were considered to be serious. The study also reports 2 compression fractures in the UFH-treated patients ( $n = 55$ ), and no fractures detected in the dalteparin group. The researchers conclude that dalteparin is safe and effective for thromboprophylaxis during pregnancy and has the advantage of a once-daily administration schedule.

Pettila V, Kaaja R, Leinonen P, et al. Thromboprophylaxis with low molecular weight heparin (Dalteparin) in pregnancy. *Thromb Res* 1999;96:275-282.

### Low-Molecular Weight Heparin Versus Heparin in the Treatment of Patients with Pulmonary Embolism

At least half of all patients with proximal deep vein thrombosis (DVT) experience pulmonary embolism (PE). Although low-molecular weight heparin's (LMWH) safety and efficacy in the treatment of DVT has been documented, researchers wished to compare its efficacy with that of intravenous heparin for the treatment of patients with PE associated with proximal DVT. In a double-blind, randomized trial of 200 patients with PE documented by lung scan, fixed-dose subcutaneous LMWH (tinzaparin sodium) was administered once daily to 97 patients and compared with dose-adjusted intravenous heparin given by continuous infusion to 103 patients. LMWH dosage was 175 International Factor Xa Inhibitory Units per kilogram of body weight subcutaneously once every 24 hours. The dose of intravenous heparin was adjusted according to the results of activated partial thromboplastin time laboratory monitoring obtained 4 hours after initiation of therapy and repeated every 4 to 6 hours until results reached the prescribed therapeutic range; thereafter, the aPTT was measured once daily. All patients received long-term therapy with warfarin sodium for at least 3 months.

None of the patients receiving LMWH experienced new episodes of venous thromboembolism compared with 6.8% of those who received intravenous heparin ( $P = 0.01$ ). Major bleeding occurred in one LMWH patient and in 2 patients who received intravenous heparin. The researchers conclude that LMWH administered once daily subcutaneously was equally, and probably more effective than the use of dose-adjusted intravenous heparin for preventing recurrent venous thromboembolism in patients with PE and associated proximal DVT. However, the authors caution their findings should not be generalized to patients with massive embolism who are hemodynamically unstable and state that the therapeutic role of LMWH in such patients still needs to be determined.

Hull RD, Raskob GE, Brant RF, et al. Low-molecular weight heparin vs. heparin in the treatment of patients with pulmonary embolism. *Arch Intern Med* 2000;160:229-236.

### Long-Term Low-Molecular Mass Heparin in Unstable Coronary Artery Disease

Although clinical trials have documented the efficacy of short-term low-molecular weight heparin (LMWH) therapy and aspirin in unstable coronary artery disease (CAD), the optimum duration of this combination therapy is undetermined. The objective of the Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) study, a prospective randomized multicenter study, was to assess the effects of long-term treatment with dalteparin compared with placebo in 2267 patients with unstable CAD undergoing a noninvasive treatment regimen. Researchers found that during 3 months of double-blind subcutaneous dalteparin twice daily adjusted for body weight and sex or placebo following at least 5 days' treatment with open-label dalteparin, a statistically insignificant decrease occurred in the

*composite endpoint of death or myocardial infarction of 6.7% and 8.0% in the dalteparin and placebo groups, respectively (P = 0.17). However, at 30 days the decrease was significant: 3.1% versus 5.9% (P = 0.002). The initial benefits were not sustained at 6 months. The researchers conclude that long-term dalteparin lowers the risk of death, myocardial infarction, and revascularization in unstable CAD at least during the first month of*

*therapy, and that these early protective effects could be used to lower the risk of events in patients waiting for invasive procedures.*

Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:701-707.