

Extended Prophylaxis with Low-Molecular-Weight Heparin Versus Oral Anticoagulation Following Hip Replacement

Samama CM, Vray M, Barré J, et al. Extended venous thromboembolism prophylaxis after total hip replacement: a comparison of low-molecular-weight heparin with oral anticoagulant. *Arch Intern Med* 2002;162:2191–6.

Study Overview

Objective. To compare thromboembolic and bleeding outcomes following total hip replacement in patients receiving extended prophylaxis with low-molecular-weight heparin (LMWH) or oral anticoagulation (OA).

Design. Randomized trial of 2 active treatment groups. Treating physicians and patients were not blinded to treatment. The results of diagnostic testing (venography, lower extremity duplex ultrasound, ventilation-perfusion scanning, or angiography) were assessed by blinded interpreters.

Setting and participants. Adults scheduled for elective total hip replacement at 65 French centers were eligible. Exclusion criteria included fracture, active bleeding, contraindication to study drugs, history of prior thromboembolic event, heparin-induced thrombocytopenia, peptic ulcer disease, contrast allergy, renal failure, liver failure, endocarditis, recent stroke, uncontrolled hypertension, pregnancy, alcoholism, treatment with aspirin or ticlopidine, or inability to follow instructions.

Intervention. All patients not receiving regional anesthesia were given the LMWH reviparin (4200 anti-Xa IU) subcutaneously 12 hours preoperatively. All patients received reviparin 6 to 10 hours postoperatively. After 2 to 4 days, if no complications developed, patients were randomized to continue with daily reviparin or to take overlapping reviparin and OA with acenocoumarol until the international normalized ratio (INR) was 2.0 to 3.0 for 2 consecutive days, when reviparin was discontinued. Reviparin or OA was continued until 6 weeks after surgery.

Main outcome measures. Patients with signs or symptoms of deep venous thrombosis or pulmonary embolism received diagnostic testing. Major bleeding was defined as overt bleeding with any of the following: a hemoglobin drop of 2.0 g/dL; requirement of a 2- or more unit blood transfusion; gastrointestinal, intracranial, retroperitoneal, or intraocular location; surgical site bleeding requiring repeat

operation; or bleeding leading to drug discontinuation. The primary endpoint was the combination of confirmed symptomatic thromboembolism, major bleeding, or death. Analysis was by intention-to-treat.

Main results. 1279 patients were randomized to the LMWH ($n = 643$) and OA ($n = 636$) groups. The primary endpoint was reached in 3.7% in the reviparin group and 8.3% in the OA group ($P = 0.001$). Compared with OA, the reviparin group had a nonsignificant reduction in thromboembolism (2.3% versus 3.3% [95% confidence interval, -0.8% to 2.8%]), and significantly fewer major bleeding events (1.4% versus 5.5%; $P = 0.001$).

Conclusion. Extended prophylaxis with reviparin following hip replacement led to fewer episodes of major bleeding than did oral anticoagulation begun with overlapping LMWH. There was a significant reduction in the combined endpoint of thromboembolism, major bleeding, or death.

Commentary

At first glance, this study is eye-catching because its findings differ from earlier trials comparing LMWH with OA prophylaxis in hip replacement. On closer examination, however, it does not address the most clinically relevant question. Prior short-term studies showed that thromboembolism rates were similar or lower with LMWH treatment compared with OA, and bleeding rates were higher, especially for surgical site bleeding [1]. In contrast, this study showed fewer bleeding episodes in the LMWH group. Differences between the design of this study and earlier ones likely accounts for the finding of a lower bleeding rate with LMWH. Here, all patients received initial treatment with LMWH for 2 to 4 days, then were randomized to overlapping LMWH and OA or LMWH alone. Patients who had early symptomatic clotting or bleeding were not randomized. Treatment in earlier studies as well as general practice in North America usually has been to use either LMWH or an oral anticoagulant prior to or following surgery and to continue the same medication for the duration of prophylactic therapy [1]. For this reason, this study is not a direct comparison of treatments commonly in use.

The new contribution of this study to the literature is the comparison of prolonged treatment in the 2 groups. Examination of the Kaplan-Meier curves from the 2 treatment groups, however, demonstrates that the majority of the difference in the combined endpoint results from events occurring in the first 10 days of treatment. Since the major findings of this study were due to differences in bleeding and because of the timing of the events in the OA group, overlapping of OA may have been an important factor producing differences between the 2 groups. After the first 2 weeks of treatment, there seems to be little difference in the event rates between the groups. Now that data have emerged demonstrating prolonged (4–6 weeks) prophylaxis following hip surgery improves outcomes [1,2], direct comparison of LMWH and OA prophylaxis would be welcome, but that was not the kind of study performed here. For this reason, and because of lack of true blinding, it is hard to apply the findings of this study to contemporary practice.

Applications for Clinical Practice

Overlapping LWMH and oral anticoagulation followed by prolonged OA for prophylaxis of venous thromboembolism after hip replacement led to more bleeding complications than did extended use of the LMWH alone. A large trial comparing extended treatment with either LMWH or OA alone would be valuable. Physicians should continue to follow the recommendations of the Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy [1].

—Review by Stephen D. Persell, MD

References

1. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest* 2001;119(1 Suppl):132S–175S.
2. Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular-weight-heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med* 2001;135:858–69.

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