Extending enoxaparin 1 month after hospital discharge reduced thromboembolism after elective hip surgery

Bergqvist D, Benoni G, Björgell O, et al. **Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement.** N Engl J Med. 1996 Sep 5;335:696-700.

Objective
To compare the effectiveness of 1 month of anticoagulant therapy with enoxaparin with enoxaparin given only during hospitalization in patients having elective total hip replacement.

Design
Randomized, double-blind, placebo-controlled trial with maximum 23-day follow-up after discharge from the hospital.

Setting
Hospital in Sweden.

Patients
262 patients who were aged > 39 years (median age 70 y, 57% women) and weighed > 60 kg having elective hip arthroplasty. Exclusion criteria were renal insufficiency; hypersensitivity to contrast medium, heparin, or low-molecular-weight heparin (LMWH); risk for hemorrhage; endocarditis; severe liver disease; untreated hypertension; venous thromboembolism in the past 3 months; receipt of heparin, LMWH, oral anticoagulants, or nonsteroidal anti-inflammatory drugs within 5 days of surgery; ipsilateral hip surgery in the past 6 months; or pregnancy or lactation. 89% of patients were included in the analysis.

Intervention
While in the hospital, patients received enoxaparin, 40 mg injected subcutaneously once daily. At the end of hospitalization, 131 patients were assigned to continue receiving enoxaparin, 40 mg/d, and 131 were assigned to placebo. Outpatient prophylaxis was scheduled to last 21 days or until the time of phlebography.

Main outcome measures
Deep venous thrombosis (DVT), distal and proximal thrombosis, pulmonary embolism, hemorrhage, and death.

Main results
21 patients (18%) receiving enoxaparin developed DVT or pulmonary embolism compared with 45 patients (39%) receiving placebo ($P < 0.001$). {This absolute risk reduction (ARR) of 21% means that 5 patients would need to be treated (NNT) with enoxaparin (compared with placebo for 1 month to prevent 1 additional patient from developing DVT or pulmonary embolism, 95% CI 3 to 11; the relative risk reduction (RRR) was 54%, CI 28% to 71%.}* 8 patients (7%) receiving enoxaparin developed proximal DVT compared with 28 patients (24%) receiving placebo ($P < 0.001$) {ARR 17%; NNT 6, CI 4 to 12; RRR 72%, CI 42% to 86%}. Hematomas occurred at the injection site in 6 patients in the enoxaparin group and in 1 patient in the placebo group. No patients in either treatment group died or had major complications.

Conclusion
One month of enoxaparin, compared with enoxaparin alone during hospitalization, led to fewer venous thromboembolic complications in patients having elective hip replacement.

Sources of funding: Swedish Medical Research Council; Swedish Heart and Lung Foundation; Rhône-Poulenc Rorer.

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*Numbers calculated from data in article.

Abstract and Commentary also published *ACP Journal Club.* 1997;126:11.

Commentary
The study by Bergqvist and colleagues is the latest in a number of recent randomized trials (1–3) that assess the risk for thromboembolism after hospital discharge and the efficacy of continued prophylaxis with LMWH. Like the previous trials, this study confirmed both the substantial incidence of thrombosis in patients with arthroplasty despite receiving prophylaxis with LMWH until hospital discharge and the reduction in venous thrombosis overall with prolonged prophylaxis. Unlike the recent study by Planes and colleagues (1), however, this study showed a substantial reduction in the incidence of proximal DVT. This difference in results may be because of differences in study design. For instance, Planes and colleagues only randomized patients with normal venography at discharge, and the study had a longer period of in-hospital prophylaxis (13 to 15 d).

The findings by Bergqvist and colleagues raise several clinical issues: Are thrombi found after hospital discharge clinically significant? Does the high incidence of thrombosis despite 4 weeks of prophylaxis suggest that even longer periods of prophylaxis are required? Although this study showed a reduction in the incidence of proximal thrombosis, the placebo group had a higher incidence of proximal DVT (24%) than did the placebo group in the study by Planes and colleagues (8%). However, the treatment groups had similar rates. Does this reflect efficacy of prophylaxis after hospital discharge or failure of the shorter period of hospital prophylaxis? The latter possibility has ramifications because of the current trend toward shorter hospital stays.

Until these issues are addressed, the optimal duration and method of prophylaxis for patients with arthroplasty after surgery remains to be determined. However, when combined with those of previous studies, the results of this trial support a potential benefit for prophylaxis after hospital discharge, especially when patients are discharged shortly after surgery.

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Bypass surgery and angioplasty led to similar 5-year mortality rates in multivessel coronary artery disease

The Bypass Angioplasty Revascularization Investigators. **Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease.** N Engl J Med. 1996 Jul 25;335:217-25.

Objective
To compare the effectiveness of coronary artery bypass grafting (CABG) with percutaneous transluminal coronary angioplasty (PTCA) in patients with multivessel coronary artery disease (CAD).

Design
Randomized controlled trial with a mean follow-up of 5.4 years.

Setting
16 U.S. and 2 Canadian centers.

Patients
1829 patients (mean age 62 y, 73% men) with angiographically documented multivessel CAD and clinically severe angina or objective evidence of ischemia that required revascularization who were suitable candidates for CABG or PTCA. Vital status was ascertained for 1792 patients (98%).

Intervention
914 patients were assigned to CABG, and 915 were assigned to PTCA.

Main outcome measures
All-cause mortality, cumulative survival, Q-wave myocardial infarction (MI), survival free of Q-wave MI, and subsequent revascularization.

Main results
1796 patients (98%) had the assigned treatment. In-hospital death (1.3% vs 1.1%, {$P = 0.67$}*) and in-hospital stroke (0.8% vs 0.2%, {$P = 0.09$}*) were similar between the CABG and PTCA groups. Patients assigned to CABG were more likely to have an in-hospital Q-wave MI than patients assigned to PTCA (4.6% vs 2.1%, $P < 0.01$). No difference existed between the CABG and PTCA groups in the 5-year mortality rate (12.1% vs 14.3%, $P = 0.19$), the 5-year cumulative survival rate (89.3% vs 86.3%, CI for the 3% absolute difference −0.2% to 6.0%, $P = 0.19$), the rate of survival free of Q-wave MI (80.4% vs 78.7%, CI for the 1.6% absolute difference −2.2% to 5.4%, $P = 0.84$), or the cumulative rate of Q-wave MI (11.7% vs 10.9%, $P = 0.45$). At 5 years, 8% of the patients assigned to CABG had subsequent revascularization compared with 54% of those assigned to PTCA ($P < 0.001$). Patients treated for diabetes who were assigned to CABG had a greater 5-year survival rate than those who were assigned to PTCA (80.6% vs 65.5%, CI for the 15.1% absolute difference 1.4% to 28.9%, $P = 0.003$).

Conclusions
Mortality rates were similar among patients with multivessel coronary artery disease who were assigned either to CABG or to an initial strategy of PTCA. Patients treated with PTCA, however, were more likely to receive subsequent CABG. CABG improved survival in patients with diabetes.

Source of funding: National Heart, Lung, and Blood Institute.

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*Numbers calculated from data in article.

Abstract and Commentary also published in *ACP Journal Club.* 1997;126:12.

Commentary
The Bypass Angioplasty Revascularization Investigation (BARI) brings the number of reported randomized trials comparing PTCA with CABG for the treatment of CAD to 9 (1). It is the largest study to date and the only multicenter, North American trial. The authors conclude that PTCA is an acceptable alternative to CABG for the treatment of all patients with CAD except those with diabetes. Although this result is similar to that reported in the other studies, it does not mean that there was no difference, as noted in an accompanying editorial (2). CABG was associated with a survival advantage of 2.9% at 5 years, largely because of its benefit in patients with diabetes. However, perhaps because of the lower-than-expected mortality rates, the study was underpowered to show statistically significant differences.

Anticipating concerns about generalizability, the BARI investigators compared the current practice of revascularization in the BARI centers with a sample of U.S. hospitals (3). The patients and the choice of revascularization procedures were found to be similar. The investigators estimated that 12% of candidates for revascularization would meet eligibility criteria for the BARI. Unfortunately, no information was available on whether success or complication rates were comparable. Also relevant to the generalizability of the study is that options for revascularization have changed. Stents have been shown to improve the outcomes of percutaneous interventions, and surgeons are becoming more aggressive with the use of arterial conduits.

Trials comparing treatment strategies are difficult to do, and the first-rate work of the BARI investigators is commendable. It is hoped that additional trials will assess the newer options for revascularization. In the interim, the BARI provides us with important insights that can guide our practice of evidence-based medicine.

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