Extended Venous Thromboembolism Prophylaxis After Total Hip Replacement

A Comparison of Low-Molecular-Weight Heparin With Oral Anticoagulant

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Background: Oral anticoagulants and low-molecular-weight heparin are both recommended for venous thromboembolism prophylaxis after total hip replacement. To date, these regimens have not been compared by means of clinical end points in the extended prophylaxis setting.

Methods: We randomly assigned 1279 patients 3 days after total hip replacement surgery to fixed-dose subcutaneous low-molecular-weight heparin (reviparin sodium, 4200 anti-Xa IU) or adjusted-dose oral anticoagulant (international normalized ratio, 2-3; acenocoumarol) for a 6-week period. The primary end point was the failure rate, defined as the combined clinical events of a confirmed symptomatic thromboembolic event, a major hemorrhage, or death. All patients were followed up throughout the study interval. The primary objective was to compare the observed cumulative failure rate in the low-molecular-weight heparin vs oral anticoagulant group.

Results: In the intent-to-treat population, objectively documented symptomatic thromboembolic events occurred in 15 (2.3%) of 643 patients vs 21 (3.3%) of 636 patients receiving low-molecular-weight heparin or oral anticoagulants, respectively (P = 0.30; 95% confidence interval for the difference, −0.8% to 2.8%). Major bleeding occurred in 9 (1.4%) of 643 patients vs 35 (5.5%) of 636 patients receiving low-molecular-weight heparin or oral anticoagulants, respectively (P = .001). The failure rate was 24 (3.7%) of 643 patients compared with 53 (8.3%) of 636 patients who received low-molecular-weight heparin or oral anticoagulants (P = .001).

Conclusions: A significantly higher benefit-risk ratio was observed for patients undergoing elective hip replacement who received extended out-of-hospital prophylaxis with low-molecular-weight heparin vs acenocoumarol. Low-molecular-weight heparin prophylaxis was at least as effective as oral anticoagulants, but with a marked improvement in safety.

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POSTOPERATIVE DEEP vein thrombosis and pulmonary embolism are feared complications after orthopedic surgery. Patients who undergo total hip replacement are at high risk for complicating venous thromboembolic disease. Low-molecular-weight heparin regimens have simplified pharmacologic prophylaxis because of the use of a fixed-dose once-daily subcutaneous injection that does not require anticoagulant monitoring. Low-molecular-weight prophylaxis is effective, safe, and cost-effective in patients undergoing elective hip surgery. Clinical issues that are currently debated include the uncertainty as to the relative effectiveness and safety of extended low-molecular-weight heparin prophylaxis vs extended oral anticoagulant regimens after elective hip surgery. Multiple studies have compared extended out-of-hospital low-molecular-weight heparin prophylaxis against placebo in patients undergoing elective hip surgery with the use of a venographic end point. A significant and clinically important difference was consistently noted among the studies in favor of low-molecular-weight heparin prophylaxis. Extended low-molecular-weight heparin prophylaxis was effective and safe.

Adjusted-dose oral anticoagulant prophylaxis has been a standard of care in many countries for in-hospital thromboprophylaxis in patients undergoing elective hip surgery. Clinical custom has extended the use of oral anticoagulant out-of-hospital prophylaxis for many weeks after elective hip surgery. Oral anticoagulation avoids the need for a subcutaneous injection and is relatively inexpensive. Nevertheless, the use of oral anticoagulant regimens mandates frequent monitoring of international normalized ratio (INR) to maintain a therapeutic INR and
to minimize the risk of bleeding complications. In the postoperative setting, there has been considerable concern about an increased risk of major bleeding complications with the use of oral anticoagulant regimens. This is a more problematic issue once the patient leaves the hospital because of less frequent INR monitoring and subsequent dose adjustment of the oral anticoagulant. To date, the relative effectiveness and, in particular, safety of extended out-of-hospital low-molecular-weight heparin prophylaxis vs oral anticoagulants has not been compared in a large randomized trial in patients undergoing elective hip surgery.

Symptomatic deep vein thrombosis and pulmonary embolism occur infrequently in patients undergoing elective hip surgery and receiving pharmacologic prophylaxis. Accordingly, in designing and implementing a randomized trial of extended prophylaxis comparing active prophylactic regimens in patients undergoing elective hip surgery, it is relevant to report the individual findings for efficacy and safety and the cumulative failure rates.

We therefore performed a large randomized trial evaluating the effectiveness and safety in real-world practice conditions of a fixed-dose once-daily low-molecular-weight heparin regimen (reviparin sodium) compared with adjusted-dose oral anticoagulant therapy (acenocoumarol) for the prevention of objectively confirmed symptomatic venous thromboembolic disease during the 6-week postoperative period in patients undergoing elective hip surgery.

METHODS

STUDY DESIGN

The SACRE study (Study Comparing Oral Anticoagulants With Reviparin) was a multicenter, randomized trial comparing acenocoumarol (Sintron; Novartis Pharma, Rueil-Malmaison, France) in an adjusted dose with low-molecular-weight heparin (Cliva- rin; Knoll-France, Levallois-Perret, France) administered once daily for the 6-week interval after total hip replacement surgery. Sixty-five centers in France participated in the trial. The protocol was approved by the institutional review board at each center.

PATIENTS

Consecutive eligible patients 18 years or older scheduled to undergo elective unilateral primary total hip replacement surgery who gave an informed consent were enrolled in the study the day before surgery. Patients were eligible if they had none of the following: femoral neck fracture, current active bleeding or disorders contraindicating anticoagulant therapy, a history of deep vein thrombosis or pulmonary embolism, heparin-induced thrombocytopenia, peptic ulcer, allergy to radiopaque contrast medium, use of aspirin or ticlopidine hydrochloride, renal insufficiency, liver failure, acute endocarditis, recent stroke (<6 months), uncontrolled hypertension, pregnancy, alcoholism, or inability to follow instructions.

A randomized computer-derived treatment schedule was used to assign the patients to receive low-molecular-weight heparin subcutaneously or acenocoumarol orally. Central randomization was stratified for each center. Within each stratum the randomization schedule was balanced in blocks of 4.

TREATMENT REGIMENS

The patients received reviparin sodium (4200 anti-Xa IU, 1 subcutaneous injection) as an initial dose 12 hours preoperatively, except in patients undergoing regional anesthesia. After surgery was completed, patients received a once-a-day subcutaneous injection of reviparin sodium (4200 anti-Xa IU) for 3 ± 1 days. The first postoperative injection was performed in the evening, ie, between 6 and 10 hours after surgery. If no clinical symptoms or signs of deep vein thrombosis, pulmonary embolism, or major bleeding were reported, patients were randomized to either continue receiving reviparin at the same dosage or crossed over to acenocoumarol for a 6-week interval after surgery. In the patients crossed over to acenocoumarol, the dose of acenocoumarol was adjusted to achieve an INR between 2.0 and 3.0 for 2 consecutive days, and then reviparin treatment was discontinued when these 2 consecutive INRs were obtained.

SURVEILLANCE AND FOLLOW-UP

All patients were examined daily during the in-hospital period. Each patient was followed up during hospitalization and after discharge. At discharge, patients received a log book in which treatment and surveillance were recorded (ie, platelet count twice weekly during the first 3 weeks of reviparin treatment and once weekly thereafter, or weekly INR in the acenocoumarol group). To respect pragmatic conditions, no dosing algorithm was provided by the study committee for the acenocoumarol group. Patients were asked to report any bleeding or thromboembolic episode to their physician. In addition, any bleeding episode required a record of the complete blood cell count and (an INR in the acenocoumarol group). Four clinical visits were planned during the study: at preclusion, at randomization, at discharge, and at the end of the treatment period (between 6 and 9 weeks). Complete blood cell counts and INR estimates were obtained after surgery, at discharge, and if a bleeding episode occurred.

Patients with overt signs or symptoms of deep vein thrombosis or pulmonary embolism underwent objective testing. Patients with suspected deep vein thrombosis based on clinical findings underwent venography or duplex scanning. Patients with suspected pulmonary embolism based on clinical signs or symptoms underwent ventilation-perfusion scanning or angiography.

Bleeding was defined as major if it was clinically overt and met any of the following criteria: (1) it was associated with a decrease in the hemoglobin level of more than 20 g/L compared with the prerandomization level (day 3); (2) it required the transfusion of 2 U or more of packed red blood cells after randomization; (3) it was digestive, intracranial, retroperitoneal, or intraocular; (4) it was located at the surgical site and required a reoperation; or (5) according to the investigator’s opinion, it led to discontinuation of the study treatment. Clinically serious bleeding was also recorded and defined as (1) leading to reoperation, (2) leading to the transfusion of 3 U or more of packed red blood cells, or (3) responsible for delayed healing, prolonged hospitalization, rehospitalization, or sepsis. Bleeding was defined as minor if it was clinically overt without meeting any of the major bleeding criteria.

Data on the outcome measures of effectiveness (symptomatic venous thromboembolism), safety (bleeding complications), and death that provided the primary cumulative end point for the study were interpreted by a central adjudicating committee. The radiologic images were reviewed. Adjudication was made by 3 committee members not involved in the patient’s care. The results of objective tests were interpreted independently and without the interpreter’s knowledge of the other results, the patient’s clinical findings, or the patient’s treatment group.

STATISTICAL ANALYSIS

The primary end point was the cumulative rate of failure, which was defined as a combined outcome of a confirmed symptomatic thromboembolic event, major bleeding, or death. The study

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planned to include 1400 patients (700 in both arms) under the assumption of a failure rate of 4% with acenocoumarol and 1% with reviparin. From these assumptions, a study of 1280 patients would provide a 95% probability (power) of rejecting, with a 2-sided test at significance level of .05, the hypothesis that the rate of failure would be greater than 3% in one group compared with the other. With an expected percentage of patients not reaching the eligibility criteria of 10%, it was decided to include 1400 patients.

The recruitment of patients began September 1, 1997, and was completed in January 2000. A total of 1337 patients were included in the study. Of these patients, 1322 underwent total hip replacement surgery and 1289 were randomly assigned to receive either reviparin or acenocoumarol.

Thirty-three eligible patients undergoing total hip replacement were not randomized because of the following: death (n = 1), thromboembolic accident before randomization (n = 7), age younger than 18 years (n = 1), bleeding episode before randomization (n = 4), adverse effects (n = 6), declined participation (n = 3), physician decision (n = 2), use of other anticoagulant (n = 2), iodine allergy (n = 1), prothrombin time less than 70% (n = 1), forgotten randomization (n = 1), and local organization problems (n = 4).

Table 1 summarizes the patient populations included for both intent-to-treat and per-protocol analyses and the reasons for excluding patients from the efficacy analysis. The baseline characteristics of the patients were similar in the 2 treatment groups (Table 2).

### INTENT-TO-TREAT POPULATION

Among the 643 patients treated with reviparin, 15 (2.3%) developed at least 1 thromboembolic event, as compared with 21 (3.3%) of the 636 patients assigned to receive acenocoumarol, an absolute difference of 1.0% (95% confidence interval for the difference, −0.8% to 2.8%; \( \chi^2 \) test, \( P = .30 \)) (Table 3).

During the study at least 1 major bleeding event occurred in 9 patients (1.4%) treated with reviparin compared with 35 patients (5.5%) treated with acenocoumarol, an absolute difference of 4.1% (\( \chi^2 \) test, \( P = .001 \)) (Table 3). Five patients receiving reviparin had clinically serious bleeding, compared with 20 patients receiving acenocoumarol (including 1 fatal bleeding episode). In patients with major bleeding in the acenocoumarol group, the median (range) INR at discharge was 2.6 (1.0-15.2). The median

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### RESULTS

### STUDY PATIENTS

The recruitment of patients began September 1, 1997, and ended October 31, 1999. The follow-up of the patients was
During the study (intent-to-treat population), 60 patients (9.3%) required at least 1 blood transfusion in the reviparin group as compared with 65 (10.2%) in the acenocoumarol group (P=.59). The median number of units of packed red blood cells transfused was 2 (range, 1-3) in the reviparin group and 2 (range, 1-6) in the acenocoumarol group. In patients with at least 1 bleeding event (major or minor), the median number of units of packed red blood cells transfused was 2 (range, 2-3) in the reviparin group and 2 (range, 1-6) in the acenocoumarol group (Table 3).

Two patients in the acenocoumarol group died: on the 4th postoperative day and 18th postoperative day of myocardial infarction and gastrointestinal tract bleeding, respectively.

The failure rate was 24 (3.7%) of 643 patients compared with 53 (8.3%) of 636 patients who received low-molecular-weight heparin or oral anticoagulants, respectively, an absolute difference of 4.6% and relative risk reduction of 55% (χ² P=.001) (Table 3). Analysis by the log-rank test, which takes into account the duration until the first clinical event, showed a clinically and statistically significant difference between the groups (P<.001) in the frequency of the combined cumulative end point in favor of low-molecular-weight heparin.

In 2 patients receiving low-molecular-weight heparin, a low platelet count was observed at day 31 (110×10^3/µL) and day 36 (2×10^3/µL), respectively, leading to discontinuation of the treatment. However, according to the adjudication committee, the reviparin treatment was not thought to be involved in the occurrence of these events.

### PER-PROTOCOL POPULATION

The per-protocol analysis showed similar findings (Table 4). The failure rate in the reviparin group (4.2%) was significantly lower than the failure rate in the acenocoumarol group (10.3%). The absolute difference was 6.1% (95% confidence intervals of the difference, 2.8%-9.4%), with a χ² P=.001.

### DURATION OF TREATMENT AND DURATION OF FOLLOW-UP

The duration of the study treatment was similar in the 2 groups (mean±SD, 40.5±8.8 days in the reviparin group and 39.5±12.9 days in the acenocoumarol group).
The follow-up duration was similar between the 2 groups (mean ± SD, 53.9 ± 16.5 days in the reviparin group and 52.7 ± 19.2 days in the acenocoumarol group).

The findings of this multicenter clinical trial demonstrate that extended out-of-hospital prophylaxis with low-molecular-weight heparin is at least as effective as oral anticoagulant treatment (Table 3). The regimen of low-molecular-weight heparin in this trial resulted in significantly fewer major bleeding complications (P = .001). The incidence of clinically serious bleeding was also much less frequent in patients receiving low-molecular-weight heparin (P = .001) (Table 3). The failure rate was clinically and statistically significantly higher in patients receiving oral anticoagulants (P = .001) (Table 3, Figure).

Aacenocoumarol is a relatively short-acting oral anticoagulant. Its elimination half-life is close to 9 hours, and the effect duration reaches 68 to 72 hours. When the SACRE study was designed, oral anticoagulant agents were already no longer the standard anticoagulant agents in French orthopedic units; however, among vitamin K antagonists, acenocoumarol was well known and was the most prescribed agent.

To date, the debate as to whether extended out-of-hospital oral anticoagulant prophylaxis or low-molecular-weight heparin is preferred remains unresolved. To our knowledge, our randomized trial is the first to compare low-molecular-weight heparin vs oral anticoagulants for extended out-of-hospital prophylaxis in patients undergoing elective hip surgery. The superior benefit-risk ratio of the regimen of low-molecular-weight heparin used in this trial compared with acenocoumarol suggests that in this context low-molecular-weight heparin prophylaxis is preferred.

Our findings are based on objectively documented symptomatic events. Our findings cannot be attributed to bias; the randomization was successful because the baseline characteristics of the patients were comparable in each group, and the study was conducted rigorously to ensure that the participating clinicians adhered to the protocol. No systematic visit was scheduled between discharge and the end of the treatment period so as not to modify the usual patient care, and only the occurrence of a bleeding or thrombotic event could have led the patient to contact his or her physician. The symptomatic end points were adjudicated by a central committee without knowledge of the treatment groups, thus avoiding a diagnostic bias. The symptomatic end points were dispersed across centers rather than being confined to a few centers. For these reasons it is likely that our results are generalizable to the population at large.

Oral anticoagulant prophylaxis requires frequent monitoring of the INR and adjustment of the anticoagulant dose, aiming for a treatment range with the INR of 2.0 to 3.0 for optimal effectiveness and safety. However, prophylactic doses have to be adjusted to the same INR range (2–3) as therapeutic doses, and, accordingly, vitamin K antagonist–treated patients are exposed to a higher degree of anticoagulation. In contrast, low-molecular-weight heparin prophylaxis is administered in a fixed dose, using a high-risk rather than a treatment dose, and anticoagulant monitoring is not required. The increased frequency of major and serious bleeding associated with oral anticoagulant use in this trial likely reflects the inherent difficulties associated with the postoperative use of vitamin K antagonists in this clinical setting.

Our study provides clinically relevant information that is of practical value for physicians and surgeons. Multiple studies comparing low-molecular-weight heparin against placebo in the hospital and for an extended period out of the hospital demonstrate the need for extended prophylaxis. A recent trial comparing in-hospital prophylaxis with low-molecular-weight heparin in proximity to surgery (6 hours postoperatively) against oral anticoagulants showed superiority for low-molecular-weight heparin. Our trial extends this knowledge from an in-hospital setting to 6 weeks postoperatively and also favors low-molecular-weight heparin.

A potential limitation of low-molecular-weight heparin prophylaxis in the out-of-hospital setting is the need for subcutaneous administration of this regimen. This is more of a perceived than actual limitation; a recent randomized trial documented that self-administration by the patient or a family member is as efficacious as administration by a home care nurse. Low-molecular-weight heparin offers the simplicity of a once-daily injection without the need for anticoagulant monitoring and the close dependence on the primary care physician that monitoring requires. Oral anticoagulant prophylaxis is inexpensive, but the cost of its administration is increased by the need for monitoring of the INR.

A large epidemiologic study using a linked hospital discharge database provided by the State of California underpins the need for extended out-of-hospital prophylaxis in patients undergoing elective hip surgery. This epidemiologic study reported the outcomes in 19586 patients after total hip replacement, 95% of whom received in-hospital prophylaxis. Of the patients with symptomatic venous thromboembolism, 76% experienced these events after discharge from the hospital (median time, 17 days after surgery). The overall frequency of documented venous thromboembolism within 3 months of surgery was 2.8%. This symptomatic rate is lower than incidence rates in studies using screening venography reflecting that in most cases the venous thrombi do not cause symptoms that the patients or the physicians perceive as significant. However, these thrombi and, in particular, proximal thrombi are the source for fatal pulmonary embolism, which is often unrecognized clinically.

Because our SACRE study assessed the frequency of symptomatic objectively documented venous thromboembolic events rather than venous thrombotic events detected by screening venography, the observed overall rates were low. This was expected in planning the SACRE study, and for this reason the cumulative event rates were selected as the primary end point. Similarly, using symptomatic end points, a recent trial of in-hospital prophylaxis showed superiority of low-molecular-weight heparin vs oral anticoagulants in patients undergoing elective hip surgery. In the SACRE study, all patients received low-molecular-weight heparin prophylaxis for at least 31 days after surgery and were then randomized to continue low-
molecular-weight heparin prophylaxis or to receive oral anticoagulant prophylaxis. For this reason, the SACRE study addresses the commonly asked question as to the effectiveness and safety of oral anticoagulant prophylaxis after initial low-molecular-weight heparin prophylaxis.

In summary, our study shows that the extended use of low-molecular-weight heparin given in a single subcutaneous injection per day is superior to acenocoumarol prophylaxis in patients undergoing elective hip surgery and that it avoids the need to monitor the level of anticoagulation. These data, together with the cited literature, provide the clinician using evidence-based medicine with the opportunity to optimize the use and choice of extended out-of-hospital prophylaxis in patients undergoing elective hip surgery.

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