Dose-Response Study of Recombinant Factor VIIa/Tissue Factor Inhibitor Recombinant Nematode Anticoagulant Protein c2 in Prevention of Postoperative Venous Thromboembolism in Patients Undergoing Total Knee Replacement

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Background—With the best prophylactics now available, venous thromboembolism after total knee replacement remains substantial (25% to 27%). Recombinant nematode anticoagulant protein c2 (rNAPc2) is a potent inhibitor of factor VIIa/tissue factor complex that has the potential to reduce this risk. The present study was performed to determine an efficacious and safe dose of rNAPc2 for prevention of venous thromboembolism after elective, unilateral total knee replacement.

Methods and Results—This open-label, sequential dose-ranging study was conducted in 11 centers in Canada, Europe, and the United States. Five regimens were tested. Injections were administered subcutaneously on the day of surgery (day 1) and days 3, 5, and optionally, day 7. Primary efficacy outcome was a composite of overall deep vein thrombosis based on mandatory unilateral venography (day 7 ±2) and confirmed symptomatic venous thromboembolism recorded ≥48 hours after the last dose of rNAPc2. Primary safety outcome was major bleeding ≥72 hours after the last dose. An independent, blinded Central Adjudication Committee assessed all outcome events. Of 293 patients studied, 251 (86%) could be evaluated for primary efficacy analysis. A dosage of 3.0 μg/kg administered within 1 hour after surgery provided the best observed results, with an overall deep vein thrombosis rate of 12.2%, a proximal deep vein thrombosis rate of 1.3%, and a major bleeding rate of 2.3%.

Conclusions—A randomized, double-blind trial that compared rNAPc2 with current best prophylactics is warranted based on encouraging, first-reported clinical results for a factor VIIa/tissue factor inhibitor evaluated for thrombosis prophylaxis. (Circulation. 2001;104:74-78.)

Key Words: thrombosis • anticoagulants • replacement, knee

Recent clinical trials of low-molecular-weight heparin (LMWH) prophylaxis in patients undergoing total knee replacement (TKR) report overall deep vein thrombosis (DVT) rates of 25% to 27% and proximal DVT rates of 6% to 12% in the operated leg based on mandatory venography.1-3 These rates are appreciably lower than rates seen without prophylactic treatment (40% to 70% and 10% to 20%, respectively) but are still substantial.1 We hypothesized that a mechanism for this high failure rate was that local tissue factor (TF) expression in the operated area activates the extrinsic pathway of coagulation and results in continual thrombin generation. Because currently available antithrombotic agents do not suppress TF pathway activity, an agent that can block extrinsic pathway–mediated thrombin generation may be more effective for prevention of breakthrough or delayed thrombus formation after surgery.

Recombinant nematode anticoagulant protein c2 (rNAPc2) is an 85–amino acid serine protease inhibitor that directly inhibits the catalytic complex of activated factor VII/TF (FVIIa/TF).4,5a The natural peptide originally was isolated from the hematophagous hookworm Ancylostoma caninum, and it is now produced in stable recombinant form. This novel
anticoagulant potently inhibits FVIIa/TF ($K_i, 10\text{ pmol/L}$) by a unique mechanism that requires initial binding of rNAPc2 to activated orzymogen factor X before formation of a ternary complex with FVIIa/TF.\textsuperscript{5a} The drug has a pharmacokinetic half-life of $>50$ hours and a bioavailability of 90% to 100% after subcutaneous injection. Because it blocks coagulation activation by inhibiting the TF pathway, rNAPc2 may be effective for thrombosis prophylaxis through attenuation of the initiation and propagation of thrombin generation after surgery. The present sequential dose-ranging study was designed to test this hypothesis and to evaluate the safety and efficacy of rNAPc2 for prevention of venous thromboembolism (VTE) after unilateral TKR.

Methods

Patients

Consecutive patients undergoing elective, unilateral TKR were potentially eligible. Preoperative exclusion criteria were active bleeding or previous history of abnormal bleeding, uncontrolled hypertension, clinically significant abnormalities in hematological or biochemical measurements, significant renal dysfunction, inability to undergo venography (including contrast allergy), required anticoagulation, known to be pregnant, and enrolled in another study. Postoperative exclusions included use of an epidural catheter for anesthesia or analgesia, traumatic spinal anesthesia, and failure to achieve primary or surgical hemostasis.

All patients provided written informed consent, and each was considered to be enrolled after he or she received 1 dose of rNAPc2. Study protocol was conducted according to the International Conference on Harmonisation Good Clinical Practice Guideline\textsuperscript{5b} and was approved by the institutional review boards of each clinical center.

Study Intervention

Each enrolled patient received 1 of 3 dosages of rNAPc2: 1.5, 3.0, or 5.0 $\mu$g/kg. Dosage administered to patients who weighed $>120$ kg was calculated at 120 kg. The first subcutaneous dose was administered initially within 6 to 12 hours after end of surgery (defined as time of leaving the operating room) and, later in the study, within the first hour after surgery. Because of the long half-life of rNAPc2, patients received a single dose on the day of surgery (day 1) and on days 3 and 5 and sometimes day 7. To ensure the safety of patients, rNAPc2 was given only in hospital, and patients were not discharged until $>24$ hours after the last dose.

Except for graduated (nonpneumatic) compression stockings, additional prophylactic methods were not permitted. Concomitant antiplatelet agents were allowed at the discretion of the attending physician.

Sequential Dose-Adjustment Rationale

The first dosage of rNAPc2 tested was 1.5 $\mu$g/kg SC, the lowest dosage level considered likely to be efficacious based on phase I and preclinical pharmacological data. By use of the principle of maximizing efficacy with acceptable safety, dose-adjustment decisions were made by the Steering Committee on the basis of regular review of the site and adjudicated overall DVT and major bleeding rates and in comparison to expected rates (25% to 27% and 2% to 3%, respectively) reported with LMWH.

After 167 patients were studied at 3 dosage levels, timing of the initial dose of rNAPc2 was advanced to within 1 hour after surgery, provided that unusual or excessive bleeding did not occur during or immediately after surgery. The rationale for this time change was 3-fold: (1) increasing the dose of rNAPc2 without changing the time of initiating prophylaxis did not appear to decrease the DVT rate substantially, but some increase in major bleeding occurred; (2) emerging data about LMWH prophylaxis indicated that a lower dose of anticoagulant started earlier postoperatively would enhance antithrombotic efficacy without increasing major bleeding\textsuperscript{6}; and (3) local TF release was likely to be greatest intraoperatively and immediately postoperatively, so that earlier drug administration would have a greater likelihood of controlling “downstream” thrombin generation and, hence, postoperative VTE.\textsuperscript{7} The 2 lower dosages, 1.5 and 3.0 $\mu$g/kg, were evaluated at this earlier injection time. Further dosage levels were not tested because a priori determination of rNAPc2 availability necessitated patient enrollment termination on May 31, 2000.

Patient Surveillance

While in hospital, patients were examined daily for evidence of thrombosis and bleeding, and laboratory investigations were performed to monitor patient safety. Before discharge, patients were instructed in the signs and symptoms of DVT, pulmonary embolism (PE), and bleeding and were asked to contact the investigator if any of these symptoms developed. Appropriate investigations would then be performed. Telephone contact or clinic visit was completed for all patients at day 30 to 35.

Outcome Measures

Primary efficacy outcome was a composite of overall DVT diagnosed on mandatory and technically adequate venography of the operated leg on day 7 to 2 and confirmed symptomatic DVT or PE recorded $\leq 48$ hours after the last dose of rNAPc2 was given. Symptomatic events that occurred $\geq 48$ hours after the last dose of rNAPc2 up to day 30 to 35 that were confirmed as DVT or PE by objective testing were considered to be secondary efficacy outcome events.

For suspected symptomatic VTE events, compression ultrasonography, ventilation-perfusion scintigraphy, and pulmonary angiography, if necessary, were to be performed as appropriate. Standard criteria were used by the Central Adjudication Committee for evaluation of these investigations for the diagnosis of DVT and symptomatic PE.\textsuperscript{9}

Primary outcome for safety was major bleeding. All bleeding events that occurred after the first dose and $\leq 72$ hours after the last dose of rNAPc2 were included. A bleeding event was defined as clinically overt bleeding in excess of the usual amount expected for the particular surgical procedure. To qualify for a major bleeding episode, 1 of the following criteria also had to be satisfied: a fall in hemoglobin of $\geq 20$ g/L; packed red-cell transfusion of $\geq 2$ units with a bleeding index of $\geq 2.0$; or bleeding in a critical site, such as intra-articular or intracranial bleeding. By convention, the bleeding index was calculated as Number of Units of Red Cells Transfused+(Prebleed Hemoglobin−Postbleed Hemoglobin), where hemoglobin is calculated in grams per deciliter. All other overt bleeding events were considered to be minor. Details of unusual bleeding were reported by the investigators and were adjudicated by the Central Adjudication Committee.

Avoidance of Bias

All mandatory venograms, suspected DVT or PE events, and bleeding events were reviewed by a Central Adjudication Committee whose members were blinded to the regimen of rNAPc2 and to local interpretation of the events. Because this was an open-label study, agreement between the on-site interpretation and central review was determined at the end of the study to address the possibility of bias caused by selective underreporting or overreporting of venography results by the Central Adjudication Committee.

Statistical Analysis

Point estimates of the rates of overall DVT, proximal DVT, and bleeding (major, minor, any) were made separately for each of the 5 regimens. Because patients were enrolled sequentially into different regimens and not randomized, we evaluated a priori–selected, clinically sensible baseline variables (type of anesthesia, previous VTE, presence of active cancer, center, sex, age, height, and weight) as potential confounders by fitting a logistic regression model to the data with DVT as the outcome and the odds ratio as the measure of
treatment effect. Because 3.0 \( \mu g/kg \) within 1 hour of surgery was the most efficacious regimen, the DVT rate in that group was compared with each of the other 4 groups. The model-fitted odds ratios were assessed with and without inclusion of the 8 baseline variables.

**Results**

**Patients**

The study started in January 1999 in 6 clinical centers; 5 more centers were added later. A total of 819 patients satisfied inclusion criteria, of whom 172 were excluded preoperatively, the main reasons for which included enrollment in another study (n = 37), allergy to radiopaque dye (n = 31), or need for anticoagulation therapy (n = 28). Of the 647 remaining patients, 353 (55%) provided informed consent. Of these, 60 patients were excluded postoperatively, the main reasons for which included use of epidural anesthesia or analgesia (n = 43) or traumatic spinal anesthesia (n = 9) and failure to achieve primary or surgical hemostasis (n = 4). Baseline characteristics of the 293 enrolled patients are shown in Table 1.

The most important baseline difference among the 5 regimens was type of anesthesia used. As the study progressed, a strong shift occurred toward overall use of general anesthesia and away from spinal or regional techniques. This temporal shift reflected center-specific anesthesia practice, with the centers that joined later in the study performing only general anesthesia in study patients. Within each clinical center, the predominant type of anesthesia performed was unchanged throughout the study.

Overall, 41.8% of the patients received 3 doses of rNAPc2, and 53.8% received 4 doses. No important differences occurred in the proportion of patients receiving 3 or 4 doses of rNAPc2 among the 5 regimens (range, 92.9% to 97.7%). One patient missed the day 1 dose and was excluded from efficacy analyses but included in safety assessments. For the remaining patients who were to begin treatment 6 to 12 hours after surgery, mean time between leaving the operating room and receiving the first injection was 8.5 hours (range, 5.5 to 18.2 hours), whereas mean time was 0.6 hours (range, 0.17 to 1.5 hours) for those who were to be treated within the 1-hour time window. Mean time from initiation of prophylactic treatment to venography was consistent across the 5 regimens, ranging from 5.0 to 6.2 days.

**DVT and Symptomatic PE**

Of the 293 patients studied, 251 (86%) could be evaluated for the primary efficacy analysis. Twenty-nine patients did not have their mandatory unilateral venogram due to patient refusal (n = 18), technical difficulties (n = 9), or early death (n = 2). An additional 13 patients had venograms considered to be indeterminate by central review. One of these patients underwent compression ultrasonography, which was unequivocal for proximal DVT as confirmed by the Central Adjudication Committee.

Table 2 summarizes thromboembolic outcomes for each of the 5 regimens. Three of the 49 DVTs (6%) were symptomatic and occurred in hospital. Observed rates of overall DVT were similar across the 3 regimens in which rNAPc2 was administered within 6 to 12 hours after surgery (mean, 21.5%). When rNAPc2 was initiated within 1 hour after surgery, the overall DVT rate for the 3.0-\( \mu g/kg \) dosage group fell to 12.2% (95% CI, 5.7% to 21.8%). Upper limit of this CI is well below the expected rate of 25% to 27% for LMWH. Observed rate of proximal DVT was 6.9% in the 2 groups

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1.5 mg/kg (n=42)</th>
<th>3.0 mg/kg (n=59)</th>
<th>5.0 mg/kg (n=66)</th>
<th>1.5 mg/kg (n=40)</th>
<th>3.0 mg/kg (n=86)</th>
<th>All (n=293)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>66.9</td>
<td>69.5</td>
<td>69.4</td>
<td>70.9</td>
<td>69.8</td>
<td>69.4</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>25 (59.5)</td>
<td>42 (71.2)</td>
<td>41 (62.1)</td>
<td>25 (62.5)</td>
<td>49 (57.0)</td>
<td>182 (62.1)</td>
</tr>
<tr>
<td>Previous DVT, n (%)</td>
<td>1 (2.4)</td>
<td>2 (3.4)</td>
<td>8 (12.1)</td>
<td>2 (5.0)</td>
<td>6 (7.0)</td>
<td>19 (6.5)</td>
</tr>
<tr>
<td>Active cancer, n (%)</td>
<td>0 (0.0)</td>
<td>1 (1.7)</td>
<td>2 (3.0)</td>
<td>3 (7.5)</td>
<td>2 (2.3)</td>
<td>8 (2.7)</td>
</tr>
<tr>
<td>Anesthesia, n (%)</td>
<td>General 12 (28.6)</td>
<td>10 (17.0)</td>
<td>38 (57.6)</td>
<td>24 (60.0)</td>
<td>64 (74.4)</td>
<td>148 (50.5)</td>
</tr>
<tr>
<td></td>
<td>Spinal/regional 30 (71.4)</td>
<td>49 (83.0)</td>
<td>28 (42.4)</td>
<td>16 (40.0)</td>
<td>22 (25.6)</td>
<td>145 (49.5)</td>
</tr>
</tbody>
</table>

### Table 2. Rates of DVT With Each rNAPc2 Regimen in Patients Evaluable for Efficacy Analysis

<table>
<thead>
<tr>
<th>rNAPc2 Regimen, ( \mu g/kg )</th>
<th>6–12 h After Operation</th>
<th>Within 1 h After Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, n (%)*</td>
<td>9/39 (23.1)</td>
<td>12/52 (23.1)</td>
</tr>
<tr>
<td>Proximal, n (%)*</td>
<td>3/40 (7.5)</td>
<td>1/53 (1.9)</td>
</tr>
</tbody>
</table>

*Denominators differ because a venogram may be evaluable for overall DVT but not proximal DVT and vice versa.
TABLE 3. rNAPc2 Regimen Comparisons Based on Modeling of Overall DVT Risk

<table>
<thead>
<tr>
<th>rNAPc2 Regimen vs 3.0 μg/kg at 1 h, μg/kg (h*)</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 (6–12)</td>
<td>2.17 (0.78, 6.01)</td>
<td>3.08 (0.77, 12.34)</td>
</tr>
<tr>
<td>3.0 (6–12)</td>
<td>2.17 (0.84, 5.60)</td>
<td>2.32 (0.65, 8.21)</td>
</tr>
<tr>
<td>5.0 (6–12)</td>
<td>1.68 (0.63, 4.47)</td>
<td>1.87 (0.63, 5.58)</td>
</tr>
<tr>
<td>1.5 (1)</td>
<td>2.71 (0.96, 7.63)</td>
<td>3.71 (1.21, 11.38)</td>
</tr>
</tbody>
</table>

N=251.  
*No. of hours after operation that first dose was administered.  
†Adjusted for type of anesthesia, previous venous thrombosis, active cancer, center, sex, age, height, and weight.

at the 1.5-μg/kg dosage level compared with 1.6% in the 3 groups at the higher dosages. After mandatory venography at day 7±2 and continuing through day 30 to 35, no confirmed cases occurred of symptomatic DVT or PE (95% CI, 0.0% to 1.2%).

Agreement in categorization of venographic outcomes between local interpretation and central review was high for all 5 regimens (86%). In addition, no evidence occurred of the central review overcalling the first 4 regimens or undercalling the last regimen.

Logistic modeling of the overall DVT risk was done to adjust for regimen differences in 8 baseline variables. Table 3 shows observed and model-fitted odds ratios and corresponding 95% CIs for the separate regimens versus the 3.0-μg/kg dosage level within first-hour dosage group. Without adjustment, odds ratios ranged from 1.68 to 2.71, and substantial overlap existed among 95% CIs. In contrast, covariate adjustment produced larger odds ratio estimates and demonstrated a dose-related trend in efficacy.

Bleeding
Table 4 summarizes rates of major, minor, and any bleeding episodes observed with each regimen. These 31 episodes were confirmed by the Central Adjudication Committee. The 14 major bleeding events were categorized as intra-articular or wound hematoma (n=3), excessive bruising (n=4), or excessive drainage (n=7). No substantial differences occurred in rates of minor bleeding among the 5 regimens, but evidence was seen of increased major bleeding, at 10.6% (95% CI, 4.4% to 20.6%), at the highest dosage of rNAPc2 (5.0 μg/kg). The lower limit of this CI is greater than the expected rate of 2% to 3% for LMWH. Timing of the first dose of rNAPc2 did not significantly affect the risk of bleeding, at least with the 3.0-μg/kg dosage.

TABLE 4. Rates of Bleeding With Each rNAPc2 Regimen

<table>
<thead>
<tr>
<th>rNAPc2 Regimen, μg/kg</th>
<th>6–12h After Operation</th>
<th>Within 1h After Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 (n=42)</td>
<td>3.0 (n=59)</td>
<td>5.0 (n=66)</td>
</tr>
<tr>
<td>Major</td>
<td>0 (0.0)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Minor</td>
<td>3 (7.1)</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>Any</td>
<td>3 (7.1)</td>
<td>5 (8.5)</td>
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<td>6 (7.0)</td>
</tr>
<tr>
<td>Any</td>
<td>4 (10.0)</td>
<td>8 (9.3)</td>
</tr>
</tbody>
</table>

Deaths
During the study, 2 deaths occurred: 1 was confirmed on autopsy to be due to myocardial infarction (day 1), and the other was attributed to cardiac arrest secondary to aspiration (day 2).

Laboratory Results
Administration of rNAPc2 resulted in modest prolongation of the prothrombin time ranging from 1.1-fold to 1.4-fold baseline at the highest dosage level (5.0 μg/kg). The most promising dosage level, 3.0 μg/kg, produced maximum elevations in prothrombin time of 1.2 times baseline. No effect on activated partial thromboplastin time was observed at any dosage level.

Discussion
Our present study is the first to show that inhibition of the fVIIa/TF complex is efficacious for prevention of VTE after unilateral TKR. These findings are also the first evidence in humans that ongoing TF expression plays an important role in the pathogenesis of acute VTE after surgery. Moreover, our results demonstrate that inhibition of the TF pathway can have a clinically significant effect on abrogating thrombus formation.

When rNAPc2 was administered 6 to 12 hours postoperatively, we observed rates of overall DVT that were similar across the 3 doses studied. However, a dose-related trend in efficacy was evident in the modeled analysis. Furthermore, evidence was seen of a dose-related effect on both major and any bleeding, with rates of 10.6% and 16.7%, respectively, at the highest dosage of 5.0 μg/kg. The observed bleeding rates at the 2 lower dosage levels were consistent with current best prophylactics. Thus, considering these results and to test the hypothesis that earlier administration of a fVIIa/TF inhibitor might be more effective for reduction of thrombus formation, we advanced the administration of the initial rNAPc2 dosage to within the first hour after surgery and reevaluated the 2 lower doses. Resulting data showed no increase in bleeding and a lower rate of overall DVT in the 3.0-μg/kg dosage level group. Evidence of superior efficacy with this dosage level compared with the dosage of 1.5 μg/kg is strengthened when pooled data on proximal DVT are compared (ie, 1.6% versus 6.9%, respectively). Thus, the rNAPc2 regimen of 3.0 μg/kg administered within 1 hour after TKR appears at least as favorable as published results for LMWH prophylaxis.

These observed trends in efficacy and safety support a biological effect of rNAPc2 consistent with its known mechanism of action. Because high levels of fVIIa/TF are released locally during and immediately after surgery, early administration of rNAPc2 is more likely to be efficacious for reduction of thrombus formation and subsequent development of VTE associated with surgery. We hypothesize that improved efficacy observed at the early 3.0-μg/kg dosage of rNAPc2 is due to abrogation of ongoing TF-mediated thrombin generation after surgery and, hence, reduction in thrombus formation and propagation. The 1.5-μg/kg dosage might not have been sufficient at the earlier injection time, because a higher concentration of rNAPc2 may be necessary to inhibit
maximal levels of TF that are expressed during and immediately after surgery.

On the basis of our observed data, rNAPc2 compares favorably with currently available antithrombotic agents in a number of ways. First, the efficacy and safety profile demonstrated at the 3.0-μg/kg dosage level given within 1 hour after surgery is comparable or superior to results reported with LMWH, 1–3 warfarin, 1–3 and direct thrombin inhibitors that inactivate both free and clot-bound thrombin. 10 Second, administration of rNAPc2 requires subcutaneous administration only once every 2 days. Third, unlike oral anticoagulant therapy, laboratory monitoring is not required. One potential safety concern is the prolonged half-life of rNAPc2. However, phase I studies suggest that recombinant fVIIa can reverse anticoagulant effects of rNAPc2 in normal volunteers. 11

Several methodological features of the present study warrant discussion. First, a concurrent control group was not included because providing an active control group for each of the rNAPc2 regimens tested would have increased substantially the total sample size, and the thrombotic and bleeding events rates for LMWHs, considered by most clinicians to be the best prophylactics available, are already well established in patients undergoing TKR. 1–3 Second, a sequential, dosage-ranging design was chosen over a parallel design because prior information on the efficacy and safety of rNAPc2 in this patient population was not available and a sequential design allowed us to respond to accumulating data in a timely and appropriate fashion. Our logistic regression analysis showed that temporal changes in baseline variables (eg, type of anesthesia) did not influence the direction of the results, but enhanced the magnitude of effect. Third, bias in the open-label design was reduced by having all reported events reviewed by a blinded central committee. The agreement between local interpretations and central review was high. Fourth, although the number of patients in each regimen was relatively small, the results were not intended to be definitive. The purpose of the present study was to assess the efficacy and safety of rNAPc2 and to seek a regimen that is likely to be at least comparable to results with LMWH. On the basis of our study design and approach, we were able to identify a reasonable dose regimen for future study in a randomized trial. Fifth and finally, we considered it prudent to exclude patients who received epidural anesthesia or analgesia because of the lack of prior safety data, even though this limits the generalizability of our findings.

The present study provides the first clinical evidence that inhibition of the fVIIa/TF complex is effective for reduction of the development of postoperative VTE. Our results show that 3.0 μg/kg of rNAPc2 administered within the first hour after elective, unilateral TKR has the potential to reduce significantly the incidence of venographically confirmed DVT and symptomatic PE. This was achieved with an acceptable rate of bleeding. A double-blind, randomized trial that compared rNAPc2 with best current prophylactics is warranted to confirm these promising results.

Appendix

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Central Adjudication Committee: J. Hirsh, C. Kearon, and J. Weitz.

Coordinating and Methods Center: The Clinical Trials Methodology Group, Hamilton Civic Hospitals Research Center, McMaster University; Dr Gent, L. Constantini, S. Haley, J. Julian, H. Nelson, N. Bedek, and W. Yacura.

Clinical Centers: Bone and Joint/St. Anthony’s Hospitals and University Hospital/Veterans Affairs Medical Center, Okla: Dr Comp, S. Farriester, M. Vowell; Hamilton Health Sciences Corporation Henderson and McMaster Sites, Hamilton, Canada: Dr Ginsberg, Dr Lee, J. deBeer, and the Hamilton Arthroplasty Group, D. Donovan and J. Joval; IRCSS Policlinico San Matteo, University of Pavia, Italy: Dr Piovella, M. Barone, S. Serafini, and P. Jelmoni; Centro Ortopedico Umbro Perugia, Perugia, Italy: S. Cecconi, D. Biagini, S. Lupparelli; Perugia University: Dr Agnelli, G.B. Mancini, and S. Lazzeri; Mayo Clinic, Minn: Dr Heit and S. Ward; Tulsa Regional Medical Center, Tulsa, Okla: Dr Raskob and D. Braletzler; Academic Hospital, Groningen, Netherlands: Dr van der Meer; and St. John Medical Center, Okla: S.J. Dunitz and K. Buchanan.

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References


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