Multimodal Thromboprophylaxis for Total Hip and Knee Arthroplasty Based on Risk Assessment

By Lawrence D. Dorr, MD, Vlad Gendelman, MD, Aditya V. Maheshwari, MD, Myriam Boutary, BS, Zhinian Wan, MD, and William T. Long, MD

Investigation performed at the Arthritis Institute, Inglewood, California

Background: Orthopaedic surgeons are increasingly challenged to find a prophylaxis regimen that protects patients from thromboembolism while minimizing adverse clinical outcomes such as bleeding. We used a multimodal approach in which the treatment regimen is selected according to patient risk factors.

Methods: We retrospectively reviewed the records on 1179 consecutive total joint arthroplasties in 970 patients who had undergone primary and revision total hip and total knee replacement. Preoperatively, patients were assigned to one of two deep venous thrombosis prophylactic regimens on the basis of an assessment of their risk factors. Eight hundred and fifty-six patients (1046 operations) were considered to be low risk and were managed with aspirin, dipyridamole, or clopidogrel bisulfate as well as intermittent pneumatic calf compression devices. One hundred and fourteen patients (133 operations) were considered to be high risk and were managed with low-molecular-weight heparin or warfarin and intermittent calf compression. All patients were mobilized from bed within twenty-four hours after surgery, and all underwent Doppler ultrasonography within the twenty-four hours before hospital discharge. All of the patients were followed for six months postoperatively. The prevalence of asymptomatic and symptomatic distal and proximal deep venous thrombosis, symptomatic and fatal pulmonary emboli, overall mortality, and bleeding complications was determined. Thrombotic events were expressed as a percentage of 1179 operations because some patients had two or more operations.

Results: Overall, there were no fatal pulmonary emboli, three symptomatic pulmonary emboli (prevalence, 0.25%), and five clinically symptomatic deep venous thrombi (0.4%). Sixty-one asymptomatic deep venous thrombi (5.2%) were found with use of routine postoperative Doppler ultrasound scans. There were three deaths (prevalence, 0.25%) that were unrelated to thromboembolism, and there were two nonfatal gastrointestinal bleeding events (prevalence, 0.17%). Wound hematomas occurred in association with five (0.4%) of the 1179 operations. Three nonfatal pulmonary emboli (prevalence, 0.3%) were detected in association with the 1046 procedures in the low-risk group, and none were detected in association with the 133 operations in the high-risk group ($p = 0.767$). Clinically symptomatic deep venous thrombosis was detected in association with four (0.38%) of the 1046 operations in the low-risk group and one (0.75%) of the 133 operations in the high-risk group ($p = 0.93$). Asymptomatic distal deep venous thrombosis was detected in association with thirty-seven (3.5%) of the 1046 procedures in the low-risk group and four (3.0%) of the 133 operations in the high-risk group. Asymptomatic proximal thrombosis was detected in association with fourteen (1.3%) of the 1046 procedures in the low-risk group and six (4.5%) of the 133 procedures in the high-risk group ($p = 0.03$). Wound hematomas occurred only in patients being managed with warfarin or low-modular-weight heparin ($p = 0.0001$).

Conclusions: A multimodal thromboembolic prophylactic regimen is consistent with protecting patients while limiting adverse clinical outcomes secondary to thromboembolic, vascular, and bleeding complications.

Level of Evidence: Therapeutic Level III. See Instructions to Authors for a complete description of levels of evidence.

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The constituents of an optimal regimen that prevents thromboembolic complications after total hip and knee replacement remain controversial[1]. Symptomatic pulmonary emboli occur in association with all treatments and in the absence of evidence of venous thrombosis[2-6]. With chemical prophylaxis, the threat of postoperative bleeding must be balanced against the risk of thrombotic events[1,7,8]. Today, with better pain management, rapid mobilization of patients postoperatively, and shorter hospital stays[7-10], some authors have questioned whether routine chemoprophylaxis is necessary, especially because of the potential for complications such as bleeding, prolonged wound drainage, and hematomas[1-3,6,8,11]. Thus, while the American College of Chest Physicians has concluded that chemical prophylaxis is the recommended safe and effective protection against thrombotic events[12,13], some within the orthopaedic community have challenged these recommendations as being not entirely applicable to patients undergoing total hip and total knee arthroplasty[1].

An ideal deep venous thrombosis prophylactic program would prevent thromboembolic disease while avoiding postoperative bleeding complications. The senior author (L.D.D.) has employed a multimodal program for low-risk patients that involves the use of aspirin as an antiplatelet, antithrombotic drug; intermittent pneumatic compression; early mobilization of the patient; hypotensive epidural anesthesia; and donated autologous blood. Our program reserves the prophylactic treatment that is associated with the highest risk of bleeding and other complications for patients with the highest risk of venous thrombotic embolism. Patients who are deemed to be at high risk for deep venous thromboembolism receive chemical anticoagulation prophylaxis with low-molecular-weight heparin (enoxaparin; sanofi-aventis, Bridgewater, New Jersey) or warfarin (Coumadin; Bristol-Myers Squibb, Princeton, New Jersey) and the same adjunctive regimen of intermittent pneumatic compression and rapid mobilization. With this program, there have been no known deaths resulting from venous thrombotic emboli associated with primary or revision total hip or knee replacement operations in our practice since 1985. In the current report, we present a retrospective review of a consecutive series of patients who underwent primary and revision total hip and total knee arthroplasty with use of this multimodal thromboprophylaxis approach. Our hypothesis was that this cohort of patients would have no greater risk of death, readmission, and reoperation and would have a lower risk of hematoma and bleeding complication than the historically published risk associated with the use of chemical anticoagulation for all patients.

Materials and Methods

Demographic Characteristics

Nine-hundred and seventy patients underwent 1179 consecutive total hip and knee arthroplasties at our institution between January 2002 and July 2003. The study group included 418 men and 552 women. The procedures included 448 primary total hip arthroplasties, 152 revision total hip arthroplasties, 481 primary total knee arthroplasties, seventy-two revision total knee arthroplasties, and twenty-six unicompartmental knee arthroplasties. One hundred and ninety-eight patients had multiple operations: 189 patients had two procedures, eight patients had three, and one patient had five. One hundred and twenty-nine patients had two joint arthroplasties under the same anesthetic. The mean age of the patients (and standard deviation) was 64.9 ± 11.9 years (range, 21.8 to 94.7 years). The mean body mass index was 28.9 ± 6.2 (range, 16.1 to 60.6), with a mean weight of 83.9 ± 21.2 kg (range, 36.3 to 180.5 kg) and a mean height of 170.1 ± 11.1 cm (range, 116.8 to 198.1 cm).

The outcomes for these patients were reviewed retrospectively, and the institutional review board approved the review of their records. Each patient had signed a consent form for the review of their data. All patients had data available with follow-up to six months. The data from the time of hospitalization were obtained from the hospital chart, and follow-up data to six months were obtained from a review of the office records as well as from telephone responses from those who did not have sufficient office follow-up.

Treatment Regimen

All patients were instructed to stop taking any nonsteroidal anti-inflammatory medications and/or aspirin or warfarin five days before surgery, regardless of whether these medications were being used for the treatment of an unrelated medical condition. Preoperatively, all patients were managed with a multimodal pain-relief program that included the oral analgesic OxyContin (20 mg) (oxycodone CR; Purdue Pharma, Stamford, Connecticut) and Bextra (40 mg) (valdecoxib; Pfizer, New York, New York). Postoperatively, patients were given the oral analgesic regimens of either Darvon (65 mg) (propoxyphene; AAIPharma, Wilmington, North Carolina) or Norco (hydrocodone/acetaminophen; Watson Pharmaceuticals, Corona, California) or Vicodin (hydrocodone/acetaminophen; Abbott Laboratories, Abbott Park, Illinois) or Tylenol (acetaminophen; McNeil PPC, Fort Washington, Pennsylvania) for pain management with the avoidance of parenteral narcotics[14,15]. Each patient received Bextra (10 mg daily) unless medically contraindicated.

Eight hundred and one (82.6%) of the 970 patients underwent surgery with a combination of epidural anesthesia and supplemental general anesthesia to provide sedation. Eighteen patients (1.9%) had epidural anesthesia alone, and 151 patients (15.6%) had general anesthesia alone. The mean anesthesia time was 155.6 ± 41.8 minutes (range, sixty to 415 minutes). Intraoperatively, patients wore an elastic compression thromboembolic disease stocking (TED hose; Kendall, Mansfield, Massachusetts) on the uninvolved leg. The mean duration of hospitalization was 5 ± 2 days (range, zero to thirty-six days). Postoperatively, physical therapy was begun on the day of surgery or the following morning. We did not use continuous passive range of motion machines for patients undergoing knee replacement.

All patients were mobilized from bed within twenty-four hours after surgery, and all patients had a Doppler ultrasound

(ACUSON Sequoia C512; Siemens, Mountain View, California) examination of the venous system of both lower extremities within the twenty-four hours before hospital discharge. Real-time imaging was obtained from the external iliac vein through the proximal portions of the calf veins. A scan was considered to be negative if it showed complete patency of the lumen. All scans were performed by specialized technicians and were read by experienced radiologists postoperatively. Patients who had symptoms of pain and swelling consistent with a clinical suspicion of deep venous thrombosis underwent Doppler ultrasonography for diagnostic purposes. Patients who had symptoms suggestive of pulmonary embolism had ventilation-perfusion scans for diagnosis.

Preoperatively, patients were divided into two treatment groups on the basis of their risk for venous thromboembolism. The low-risk group comprised 504 patients (607 procedures) with no risk factors and 352 patients (439 procedures) with low-risk factors. The low-risk factors were cardiac disease (congestive heart failure) that was classified as Class I according to the system of the New York Heart Association[16] (eighty-three patients, 106 procedures), prior deep venous thrombosis that had occurred more than five years previously (fifteen patients, seventeen procedures), inactive malignant disease (eighty-two patients, 105 procedures), current use of hormone replacement therapy (ninety-four patients, 116 procedures), chronic tobacco use (seventy-four patients, ninety procedures), and blood disorders of the sickle-cell trait, polycythemia vera, or thrombocytopenia (four patients, five procedures). Some patients had a combination of these factors.

In the low-risk group, 856 patients (1046 procedures) received antiplatelet chemoprophylaxis and were managed with an intermittent pneumatic compression device (PlexiPulse foot compression [KCI, San Antonio, Texas] or Flowtron calf compression [Huntleigh Healthcare, Eatontown, New Jersey]). Eight hundred and fourteen patients (999 procedures) received aspirin, forty-one patients (forty-six procedures) received dipyridamole (Persantine; Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut), and one patient was maintained on clopidogrel bisulfate (Plavix; Bristol-Myers Squibb, Princeton, New Jersey). On the day of surgery, patients were given a 600-mg aspirin suppository in the recovery room and then were given aspirin (Ecotrin; GlaxoSmithKline, Pittsburgh, Pennsylvania) at a dosage of 325 mg orally twice each day postoperatively for one month. Patients who were intolerant of aspirin preoperatively or who had development of intolerance to aspirin postoperatively were converted to treatment with dipyridamole at a dosage of 25 mg three times a day. For all patients, intermittent pneumatic compression devices were applied in the recovery room to both legs, and these remained in place day and night for the duration of the acute hospitalization.

All low-risk patients who had the occurrence of a *proximal* deep venous thrombosis as diagnosed with Doppler ultrasound or who had a pulmonary embolism were converted to chemical prophylaxis (Fig. 1). Patients who had a distal (calf) deep venous thrombosis as diagnosed with Doppler ultrasound were not managed with chemical prophylaxis if they had no risk factors.

One hundred and fourteen patients (133 operations) constituted the high-risk group. The high-risk factors were a history of a venous thromboembolic event that had occurred within the previous five years (thirty-one patients, forty-two procedures), congestive heart failure that was classified as Class II or III according to the system of the New York Heart Association (fifty-two patients, fifty-six procedures), atrial fibrillation with cardiac disease and use of Coumadin preoperatively (sixteen patients, eighteen procedures), recent surgery for the treatment of malignant disease or current adjuvant drug treatment (ten patients, twelve procedures), and thrombophilia, including factor V Leiden, prothrombin disorders, protein-C and S deficiency, antithrombin disorders, or hypercoagulability states (five patients, five procedures). Some patients had a combination of these factors.

High-risk patients were managed postoperatively with enoxaparin (40 mg per day) or Coumadin (with a target international normalized ratio of 2 to 2.5) and the same intermittent pneumatic compression regimen as was used for low-risk patients. They were initially managed with aspirin for twenty-four to forty-eight hours, at which time the anticoagulation drug was initiated and aspirin was discontinued. This delay was an attempt to prevent wound hematoma as well as to provide protection against epidural hematoma for patients who had an epidural catheter in place for twenty-four hours for the postoperative administration of pain medication. Enoxaparin was continued for ten days, and then the patient was again placed on aspirin for one month. Coumadin was continued for six weeks or as prescribed for medical conditions. Patients who had deep venous thrombosis during the study and were being managed with low-molecular-weight heparin were converted to warfarin and continued to receive that agent for three to six months; patients who were already receiving warfarin continued to receive that agent for three to six months.

Regardless of the treatment group, the rehabilitation protocol encouraged each patient to begin walking out of doors upon return to home. Supervised physical therapy was used only for patients who required it, who were primarily those who had been treated with knee arthroplasty. Patients who had been managed with either a primary total hip or total knee replacement were allowed to be fully weight-bearing upon return to home and were encouraged to advance to a cane as quickly as was safe. Patients who had had a revision operation were mobilized in the same way as patients who had had primary arthroplasty but used two crutches for six weeks with 50% weight-bearing on the involved limb.

Data Collection

All 970 consecutive patients were included in the study. All were followed for at least the first six months postoperatively. Patients who had more than one operation during the course of the study were evaluated separately during each hospitalization, and all operations were considered as separate events.

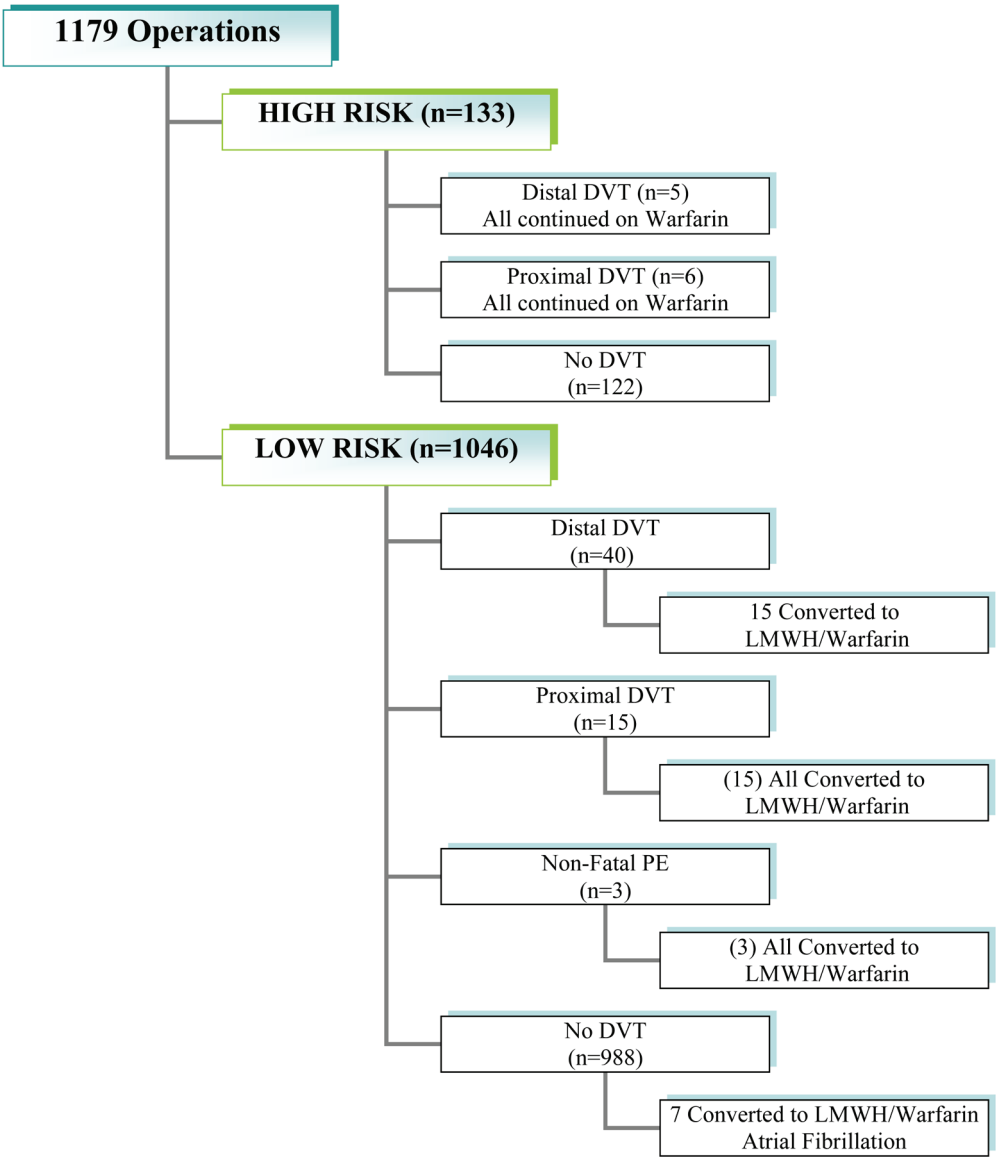

Fig. 1

Treatment flowchart and venous thromboembolic event distribution. DVT = deep venous thrombosis, PE = pulmonary embolism, and LMWH = low-molecular-weight heparin.

Data that were retrieved from the hospital chart included demographic characteristics, the risk factors for venous thromboembolic disease as recorded by the internist, the type and duration of anesthesia, the presence or absence of deep venous thrombosis or pulmonary embolism, the occurrence of other complications (particularly bleeding complications, including hematomas), the necessity for reoperation, and the length of stay.

Review of office charts, and direct communication with patients when necessary, provided the information on any venous thromboembolic complications that occurred after discharge from the hospital. The treatment for each of these complications was determined, including readmission to the hospital or reoperation.

Statistical Analysis

The Pearson chi-square test was performed to analyze the distribution frequency of deep venous thrombosis among variables such as gender, the location of the procedure (hip or knee), the type of anesthesia (general or regional), the type of surgery (primary or revision), the operating surgeon, associated risk factors, a history of deep venous thromboembolism, associated "at risk" medical conditions, a history of thrombophilia, a history of tobacco use, and concurrent use of risk medications. The Student t test was used to analyze the occurrence of deep venous thrombosis on the basis of age, height, weight, body mass index, anesthesia time, and duration of hospital stay. Discriminant analysis was performed to find the correlation between the risk factors and the occurrence of

TABLE I Prevalence of Venous Thromboembolic Events (VTE) in Low-Risk-Factor Group*

Low-Risk Factor	No VTE	Asymptomatic Distal VTE	Symptomatic Distal VTE	Asymptomatic Proximal VTE	Symptomatic Proximal VTE	Pulmonary Embolism	Total
No risk factors	593	11	2	1	0	0	607
Congestive heart failure	86	10	0	9	0	1	106
Deep venous thrombosis >5 years previously	15	1	0	1	0	0	17
Inactive malignant disease	98	4	1	0	1	1	105
Blood dyscrasias	4	0	0	1	0	0	5
Hormone replacement therapy	108	6	0	2	0	0	116
Tobacco use	84	5	0	0	0	1	90
Total	988	37	3	14	1	3	1046

*N = 856 patients (1046 operations). The results are reported as the number of procedures.

deep venous thrombosis. For the low-risk group, Logit log-linear analysis was used to assess the odds of development of a venous thromboembolism, to evaluate the interactive effects between age and each risk factor, and to determine the odds of development of a proximal deep venous thrombosis.

Results

Occurrence

Symptomatic pulmonary emboli occurred in three patients (three operations; 0.25%) after discharge, at a mean of 45.3 days (range, four to ninety days) postoperatively. All three nonfatal pulmonary emboli were in the low-risk group ($p = 0.77$) (Fig. 1, Tables I and II). The pulmonary emboli occurred after total knee replacement in two patients (at four days and six weeks postoperatively) and after total hip replacement in one patient (at three months postoperatively).

In the entire group, symptomatic and asymptomatic deep venous thrombi (proximal and distal) occurred in association with sixty-six (5.6%) of the 1179 procedures. Fifty-five deep venous thrombi occurred in the low-risk group, and eleven occurred in the high-risk group ($p = 0.21$) (Fig. 1). Clinically symptomatic proximal or distal deep venous thrombosis was detected in association with four (0.38%) of the 1046 operations in the low-risk group (Table I) and one (0.75%) of the 133 operations in the high-risk group ($p = 0.93$) (Table II). Overall, asymptomatic deep venous thrombosis (either proximal or distal) was identified on discharge Doppler ultrasonography in association with sixty-one (5.2%) of the 1179 operations (Tables I and II). Asymptomatic deep venous thrombi occurred in association with fifty-one (4.9%) of the 1046 operations in the low-risk group and ten (7.5%) of the 133 operations in the high-risk group ($p = 0.26$). Proximal thrombi occurred in association with fifteen (1.4%) of the 1046 procedures in the low-risk group, compared with six (4.5%) of the 133 procedures in the high-risk group; this difference was significant ($p = 0.029$) (Table III). The occurrence of venous thrombi according to the type of operation is presented in Table IV. Deep venous thrombosis occurred in association with twelve (2%) of 600 hip procedures and fifty-four (9.3%) of 579 knee procedures ($p = 0.001$).

Treatment

In the high-risk group, the patients with symptomatic and asymptomatic deep venous thrombi were managed with war-

TABLE II Prevalence of Venous Thromboembolic Events (VTE) in High-Risk-Factor Group*

High-Risk Factor	No VTE	Asymptomatic Distal VTE	Symptomatic Distal VTE	Asymptomatic Proximal VTE	Symptomatic Proximal VTE	Pulmonary Embolism	Total
Congestive heart failure	56	0	0	0	0	0	56
Atrial fibrillation/cardiac	18	0	0	0	0	0	18
Deep venous thrombosis ≤5 years previously	33	4	1	4	0	0	42
Malignant disease	12	0	0	0	0	0	12
Thrombophilia (with malignant disease or deep venous thrombosis)	3	0	0	2	0	0	5
Total	122	4	1	6	0	0	133

*N = 114 patients (133 operations). The results are reported as the number of procedures.

TABLE III Comparison of Prevalence of Venous Thromboembolic Events in Low and High-Risk Groups

Venous Thromboembolic Event	Venous Thromboembolic Events: Low-Risk Group (N = 1046)*	High-Risk Group (N = 133)	P Value†
Pulmonary embolism (nonfatal)	3 (0.3%)	0	0.767
Deep venous thrombosis			
Proximal	15 (1.4%)	6 (4.5%)	0.029
Distal	40 (3.8%)	5 (3.8%)	0.839
Total	55 (5.3%)	11 (8.3%)	0.212

*Antiplatelet agents include aspirin, dipyridamole, and clopidogrel. †The level of significance was set at $p < 0.05$.

farin for six weeks. No venous thromboembolic disease occurred in association with 122 of the 133 procedures (Fig. 1). In the low-risk group, 822 patients (representing 1006 [96.2%] of the 1046 procedures) did not require conversion to anticoagulant chemoprophylaxis (Fig. 1). Overall, thirty-four patients in the low-risk group (representing forty of the 1046 operations) were switched to low-molecular-weight heparin or warfarin because they had development of symptomatic or asymptomatic venous thromboembolic disease (thirty-three procedures) or postoperative atrial fibrillation (seven procedures) (Fig. 1). Symptomatic and asymptomatic patients with distal clots were followed with Doppler ultrasonography seven to twelve days later, and there was no proximal progression or increase in the size of the clot in any of these patients.

Risk Factors and Thrombosis

Overall, there was no significant difference between patients with or without a thrombotic event with respect to gender, body mass index, height, type of anesthesia, prior medications, tobacco use, anesthesia time, duration of hospitalization, primary or revision surgery, bilateral simultaneous or unilateral surgery, or surgeon. The relative risk of development of deep venous thrombosis (as measured with the Lambda coefficient) was strongest for location (knee, 0.964); a history of venous thrombotic embolism (0.959); a history of the medical risks of congestive heart failure, malignancy, or blood dyscrasias (0.956); and a history of thrombophilia (0.948).

In the low-risk group, three risk factors increased the odds of development of a venous thromboembolism as compared with the odds when there was no risk factor: congestive heart failure (odds ratio, 7.7; $p = 0.0001$), inactive malignant disease (odds ratio, 3.1; $p = 0.014$), and hormone replacement therapy (odds ratio, 3.2; $p = 0.008$). Only congestive heart failure (odds ratio, 6.2; $p = 0.0005$) increased the risk of a proximal deep venous thrombosis. The general Logit loglinear analysis of the low-risk group showed that age was not related to any risk factor and was not itself a risk factor.

In the high-risk group, the only risk factor associated with deep venous thrombosis was a history of deep venous thrombosis that had occurred within the previous five years. Two of the patients with prior deep venous thrombosis also had thrombophilia. No odds ratio could be calculated because there were no patients with no risk factors. There was no identified progression of clots in any of these patients on follow-up Doppler ultrasound.

Complications (Table V)

Five (0.4%) of the 1179 operations were associated with a wound hematoma, necessitating three reoperations and one readmission. All five hematomas occurred in patients receiving low-molecular-weight heparin (three patients) or warfarin (two patients). Three of the five patients with a hematoma had been converted from treatment with aspirin to treatment with low-molecular-weight heparin, and two were in the high-risk group. Therefore, overall, hematoma developed in association with five (2.9%) of the 173 procedures in patients receiving warfarin or low-molecular-weight heparin. In comparison, none of the 1006 procedures in patients receiving aspirin or dipyridamole were associated with a hematoma ($p = 0.0001$). Two of the five hematomas occurred in patients managed with total knee replacement, and three occurred in patients managed with total hip replacement. Both patients with a total knee replacement ultimately had reduced range of motion after the hematoma, with a range of 5° to 95° in one patient and of 0° to 85° in the other patient. All three patients with a total hip replacement had a satisfactory outcome.

There were two gastrointestinal bleeding events (prevalence, 0.17%). One occurred in a patient with a history of thyroid carcinoma who was receiving aspirin and ibuprofen (Advil; Wyeth Pharmaceuticals, Collegeville, Pennsylvania), and the other occurred in a patient who was receiving low-molecular-weight heparin. Thrombocytopenia developed in one patient (0.1%) who was receiving low-molecular-weight heparin, and the prophylaxis was changed to warfarin. These complications did not influence the patients' ultimate function.

TABLE IV Prevalence of Thrombosis According to Type of Operation

Operation	Number of Operations	Deep Venous Thrombosis	Pulmonary Embolism
Total hip replacement			
Primary	448	8 (1.8%)	1
Revision	152	4 (2.6%)	0
Total knee replacement			
Primary	481	47 (9.8%)	2
Revision	72	4 (5.6%)	0
Unicondylar	26	3 (11.5%)	0
Total	1179	66	3

TABLE V Complications According to Treatment Regimen

Complication	Low-Molecular-Weight Heparin/ Warfarin (173 Procedures*)	Antiplatelet Agents (1006 Procedures)	P Value†
Bleeding complications			
Hematoma	5 (2.9%)	0	0.0001
Gastrointestinal bleeding	1 (0.6%)	1 (0.1%)	0.68
Total	6 (3.5%)	1 (0.1%)	0.0001
Compromised joint function	2 (1.2%)	0	0.01
Thrombocytopenia	1 (0.6%)	0	0.32
Death	1 (0.6%)†	2 (0.2%)§	0.92

*Includes 133 high-risk procedures and forty procedures in patients who had been converted from treatment with aspirin. †The level of significance was set at $p < 0.05$. ‡Chronic renal disease. §Acute dissecting aortic aneurysm (one patient) and fat embolism (one patient).

TABLE VI Summary of Chemical Anticoagulation Studies 1996 to Present*

Study	Prescribed Prophylaxis	Number of Procedures	Prevalence of Deep Venous Thrombosis *(%)*		Prevalence of Pulmonary Embolism *(%)*
			Overall	Symptomatic	
Our study	Multimodal	1179 total hip and total knee replacements	5.6	0.4	0.25 nonfatal
Warwick et al.[25]†	"No routine chemoprophylaxis"	1162 total hip replacements	N/A	1.89	1.20 nonfatal, 0.34 fatal
Lieberman et al.[21]	Low-dose warfarin	1099 total hip replacements	N/A	0.5 ($p = 1.0$)	1.1 nonfatal ($p = 0.02$), 0.1 fatal
Fitzgerald et al.[19]	Enoxaparin	108 total knee replacements	38.0 ($p < 0.001$)	N/A	0.0
	Warfarin	122 total knee replacements	59.0 ($p < 0.001$)	N/A	0.0
Colwell et al.[18]	Enoxaparin	1516 total hip replacements	2.6 ($p = 0.003$‡)	N/A	0.4 nonfatal ($p = 0.66$), 0.1 fatal
	Warfarin	1495 total hip replacements	2.9 ($p = 0.0002$‡)	N/A	0.6 nonfatal ($p = 0.07$), 0.1 fatal
Pellegrini et al.[7]	Warfarin	1079 total hip replacements	6.1 ($p = 0.66$)	1.2 ($p < 0.0001$)	1 nonfatal ($p = 0.08$), 0.2 fatal
Colwell et al.[17]	Warfarin	960 total knee replacements	21.9 ($p < 0.001$)	1.3 ($p = 0.047$)	0.4 nonfatal ($p = 0.71$)
	Ximelagatran	976 total knee replacements	31.4 ($p < 0.0001$)	0.7 ($p = 0.4$)	0.2 nonfatal ($p = 1.0$)
Francis et al.[20]	Warfarin	190 total hip replacements	26.0 ($p < 0.0001$)	NA§	NA§
	Dalteparin	192 total hip replacements	15.0 ($p < 0.0001$)	NA§	NA§

*Meta-analyses not included. †This study was published in 1995 but is included as a benchmark for a study that involved the use of no prophylaxis at all. ‡These values are significantly better than those in the present study, whereas all other statistical results are equivalent or significantly worse than those in the present study. (The level of significance was set at $p < 0.05$) §NA = not available.

TABLE VII Summary of Multimodal Studies from 1999 to Present

Study	Prescribed Prophylaxis*	Number of Cases	Prevalence of Deep Venous Thrombosis† *(%)*		Prevalence of Pulmonary Embolism† *(%)*
			Overall	Symptomatic	
Present study	Aspirin + intermittent pneumatic compression	1179 total hip and total knee replacements	5.6	0.4	0.25 nonfatal
Lotke and Lonner[23]	Aspirin + intermittent pneumatic compression	3473 total knee replacements	NA‡	0.2 (p = 0.19)	0.26 nonfatal (p = 1.0), 0.06 to 0.14 fatal
DiGiovanni et al.[22]	Aspirin + intermittent pneumatic compression	1021 total hip replacements	8.0 (p = 0.03)	0.85 (p = 0.18)	0.5 nonfatal (p = 0.48)
Westrich et al.[24]	Aspirin + intermittent pneumatic compression	2037 total hip replacements	10.3 (p < 0.0001)	NA‡	2.0 nonfatal (p < 0.0001), 0.04 fatal
Lachiewicz and Soileau[4]	Intermittent pneumatic compression (aspirin at home)	1032 total hip replacements	3.9 (p = 0.073)	0.4 (p = 1.0)	0.7 nonfatal (p = 0.2), 0.09 fatal

*In these studies, high-risk patients were managed with warfarin or enoxaparin. †All statistical values were either equivalent or significantly worse than our data. (The level of significance was set at p < 0.05) ‡NA = not available.

There were three deaths (prevalence, 0.25%). One patient in the low-risk group had development of an acute dissecting aortic aneurysm on the first postoperative day after a unicompartmental knee arthroplasty. Another patient, who was receiving low-molecular-weight heparin, had a revision total hip arthroplasty and died on the eighth postoperative day as a result of previously existing renal complications. The third patient, who was on an aspirin regimen, underwent bilateral total knee replacement and had symptoms of fat embolism with shortness of breath and right-sided hemiparesis in the first twenty-four hours after surgery. The patient had a computed tomography scan of the brain that was not diagnostic and a ventilation-perfusion scan that was not diagnostic. The patient died on the fifth postoperative day.

Comparison of Our Results with Historical Data

We compared our results with those from six studies involving use of chemical anticoagulation (enoxaparin or warfarin) that were published from 1996 to 2005[7,17-21] (Table VI). The total prevalence of asymptomatic and symptomatic proximal and distal deep venous thrombosis was 5.6% in the present study, compared with a range of 3.1% to 59% in those studies. In one study[18], the prevalence of deep venous thrombosis was 3.1% among patients receiving warfarin and 3.2% among those receiving enoxaparin. Those rates were significantly lower than the prevalence of 5.6% in the present study (p = 0.003 and p = 0.0002). There was no significant difference in the prevalence of nonfatal pulmonary embolism between the two studies.

In two studies[3,7], the prevalence of symptomatic deep venous thrombosis ranged from 0.7% to 5.7%; the prevalence in the present study was 0.4%. The rate of nonfatal pulmonary embolism in the present study (0.3%) was not significantly different from the prevalence of nonfatal pulmonary embolism (range, 0.0% to 0.8%) as reported in three of the studies that used chemoprophylaxis exclusively[7,18,21].

The results of the present study are statistically equivalent to or better than those of other studies on multimodal prophylaxis[4,22-24] (Table VII). All of those studies involved the use of aspirin and intermittent pneumatic compression for patients who were not deemed to be at high risk. In those studies and in ours, the prevalence of nonfatal pulmonary emboli ranged from 0.25% to 2.0%; fatal pulmonary emboli occurred in three studies[4,23,24]. The rate of symptomatic deep venous thrombosis was listed in four of the five studies and ranged from 0.2% to 0.85%. The prevalence of proximal and distal deep venous thrombosis was reported in four of the five studies and ranged from 3.9% to 10.3%.

Discussion

The hypothesis of the present study was that a multimodal thromboprophylaxis treatment regimen, based on risk assessment for venous thromboembolism, would protect patients undergoing total hip and total knee replacement from venous thrombosis and pulmonary embolism as effectively as does a regimen of chemical anticoagulation drugs alone, while limiting adverse clinical outcomes. Comparison of our data with historical data showed that our multimodal treatment was just as effective, and at least as safe, as regimens involving the use of chemical anticoagulation drugs alone[7,17-21,25].

An important aspect of the present study is that it included a consecutive patient population, which represents the usual practice of total hip and total knee replacement surgeons. The advantages of this study population are that it represents the clinical outcome of treatment of "all-comers," it does not exclude high-risk patients (as most randomized chemoprophylaxis studies do), and it does not represent the results for just one operative group, for example, only patients

managed with total hip replacement[22,24]. The second important finding of the present study is that the low-risk group had a significantly lower prevalence of proximal deep venous thrombosis and a nonsignificant difference in the prevalence of nonfatal pulmonary embolism when compared with the high-risk group (Table III), without being subjected to the risks of bleeding from chemoprophylaxis.

The first limitation of the present study was that it was not randomized. However, a weakness of previous randomized studies is that they excluded at-risk patients, combined symptomatic and asymptomatic thrombi in the analyses, and did not include clinical outcomes (with the exception of death) for patients with complications, especially hematomas[17-20]. The second limitation was that we studied only antiplatelet drugs for the low-risk group. Pellegrini et al.[7] used low-dose warfarin (international normalized ratio, 1.3 to 1.5) instead of full anticoagulation with warfarin or low-molecular-weight heparin and reported a 0.2% prevalence of fatal pulmonary embolism, a 0.8% prevalence of symptomatic pulmonary embolism, a 1.2% prevalence of bleeding complications, and no deaths as a result of bleeding. Both aspirin and low-dose warfarin are more protective against proximal clots than they are against distal clots, so we believe that the combination of either of these drugs with intermittent pneumatic compression is protective against clots while providing safety from bleeding[2,8,11]. We prefer to use aspirin because it is protective against bleeding[2,3,5,6,26-29], arterial complications[26-30], and heterotopic ossification[8]. It is also less expensive and less cumbersome to use than low-dose warfarin because blood levels do not need to be monitored. The third limitation is that our study cannot be considered to be conclusive because of its design and the number of patients. However, the present study suggests that total hip arthroplasty and total knee arthroplasty patients can be managed effectively and safely without following American College of Chest Physician guidelines. The studies in Table VII support our findings[4,22-24], and we believe that it is now time to perform a multicenter prospective, randomized study of the efficacy of multimodal prophylaxis.

Our data were obtained with use of Doppler ultrasound examinations, which have been validated as an accurate measurement for deep venous thrombosis[13,31,32]. Routine screening with venous Doppler ultrasonography is controversial, but we found it to be helpful for assessing and then modifying our treatment regimen when it showed proximal deep venous thrombosis. For example, nine patients with New York Heart Association Class-I congestive heart failure (low-risk group) had asymptomatic *proximal* deep venous thrombi that were discovered on the discharge Doppler ultrasound. Our data suggest that Class-I congestive heart failure can be clinically safely treated as a low-risk factor if routine screening is performed to detect proximal clots. The present study, however, did not address the question of the necessity of treating asymptomatic distal venous clots with conversion to chemoprophylaxis.

In a meta-analysis, Imperiale and Speroff reported the prevalence of major bleeding episodes after total hip replacement to be 0.3% in association with no prophylaxis, 0.4% in association with aspirin, 1.3% in association with warfarin, 1.8% in association with low-molecular-weight heparin, and 2.5% in association with unfractionated heparin[3]. Since 1996, studies on the routine use of heparin agents or normal-dose warfarin have shown a total rate of major bleeding events of 1.3% (100 of 7737) (clinical outcomes not reported), with three deaths from bleeding (prevalence, 0.04%)[7,17-21]. Two of the three patients who died were receiving warfarin, and the third was receiving ximelagatran therapy. Fifty-four (54%) of these 100 major bleeding events occurred in patients who were being managed with warfarin, and forty-six (46%) occurred in patients who were being managed with heparin agents. The patients in those studies were considered to be healthy because high-risk patients were excluded. In contrast, four multimodal studies[4,22-24] demonstrated a rate of major bleeding events of 0.2% (fifteen of 7563), with no deaths from bleeding (Table VII). Nine (60%) of these fifteen major bleeding events occurred in patients who were being managed with aspirin, and six (40%) occurred in patients who were being managed with warfarin or enoxaparin. In the study by Lotke and Lonner[23], thirteen (0.38%) of 3473 patients who had been managed with total knee replacement required a reoperation because of deep wound hematoma; nine were receiving aspirin, two were receiving enoxaparin, and two were receiving warfarin.

The prevalence of bleeding and hematomas in our study was thirty-five times higher in patients managed with chemoprophylaxis either for prophylaxis (high-risk group) or for treatment. A recently published report on chemoprophylaxis in which warfarin was compared with ximelagatran (Exanta; AstraZeneca, Mölndal, Sweden) in patients managed with total knee replacement[17] showed no improvement with ximelagatran as compared with our multimodal results. In that study of 2303 patients[17], there were seventeen major bleeding events (twelve in patients being managed with ximelagatran and five in patients being managed with warfarin), with one death from gastrointestinal bleeding and three knee hematomas (outcomes not reported).

On the basis of the findings of our study and the results of studies in the literature[8,22,24,33], we conclude that safe and effective prophylaxis can be achieved with use of multimodal therapy. We continue to use this method of venous embolic prophylaxis, and we believe it is time to perform a prospective, randomized, multicenter trial to assess its efficacy in a larger cohort of patients. ■

Lawrence D. Dorr, MD
Vlad Gendelman, MD
Aditya V. Maheshwari, MD
Myriam Boutary, BS
Zhinian Wan, MD
William T. Long, MD
The Arthritis Institute, 501 East Hardy Street, 3rd Floor, Inglewood, CA 90301. E-mail address for L.D. Dorr: patriciajpaul@yahoo.com

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