

# Risk Factors for Clinically Relevant Pulmonary Embolism and Deep Venous Thrombosis in Patients Undergoing Primary Hip or Knee Arthroplasty

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**Background:** Prevention of thromboembolic complications after elective lower extremity arthroplasty has increasingly relied on routine thromboprophylaxis in all patients. Not all patients are at equal risk, however, and prophylaxis is not devoid of complications. The aim of this study was to examine the risk factors for clinically relevant pulmonary embolism and deep venous thrombosis after elective primary hip or knee arthroplasty in a large patient population.

**Methods:** During the 10-yr study period, 116 of 9,791 patients undergoing primary hip or knee arthroplasty at the authors' institution who experienced pulmonary embolism or deep venous thrombosis within 30 days of surgery were matched at a 1:1 ratio with patients undergoing the same surgery with the same surgeon who did not experience an adverse event. Medical records were reviewed, with data abstracted using a standardized data collection form.

**Results:** Increased body mass index ( $P = 0.031$ ; odds ratio = 1.5 for each 5-kg/m<sup>2</sup> increase) and American Society of Anesthesiologists physical status classification of 3 or greater ( $P = 0.005$ ; odds ratio = 2.6) were found to independently increase the likelihood of pulmonary embolism or deep venous thrombosis. In addition, use of antithrombotic prophylaxis was found to decrease the likelihood of these thromboembolic events ( $P = 0.050$ ; odds ratio = 0.2 for aspirin or subcutaneous heparin, and odds ratio = 0.4 for warfarin or low-molecular-weight heparin).

**Conclusions:** In patients undergoing primary elective lower extremity arthroplasty, obesity, poor American Society of Anesthesiologists physical status classification, and lack of thromboprophylaxis are independent risk factors for clinically relevant thromboembolic events.

A LARGE number of studies have examined the incidence of thromboembolic complications after lower extremity orthopedic surgery.<sup>1-4</sup> Early studies reported a high frequency of symptomatic deep venous thrombosis and pulmonary embolism in patients after hip or knee arthroplasty.<sup>5,6</sup> More recent studies have demonstrated a significant reduction in the frequency of deep venous

thrombosis (as diagnosed by contrast venography or ultrasonography) after hip and knee arthroplasty when mechanical or medical thromboprophylaxis is used.<sup>7-11</sup> It remains controversial whether the reduction in asymptomatic deep venous thrombosis results in a similar decrease in the frequency of clinically significant thromboembolic events such as fatal pulmonary embolism or postphlebotic syndrome. In a recent study, we demonstrated a consistent frequency of clinically relevant deep venous thrombosis (1.5%) and pulmonary embolism (0.7%) within 30 days of elective primary hip or knee arthroplasty over a 10-yr period that spanned the widespread adoption of routine thromboprophylactic strategies used in contemporary practice.<sup>12</sup>

Not all patients undergoing elective lower extremity joint replacement surgery are necessarily at the same risk for venous thromboembolism. Genetic influences may place specific patient populations at increased thromboembolic risk.<sup>13</sup> Other suggested risk factors for venous thromboembolic events in the general and surgical population include history of cigarette smoking,<sup>14</sup> malignancy,<sup>15</sup> hormone therapy,<sup>16</sup> obesity,<sup>17,18</sup> immobility,<sup>18</sup> and use of general instead of regional anesthetic techniques.<sup>19</sup> Additional risk factors for adverse thromboembolic events may be present after primary elective hip or knee arthroplasty, including surgeon-specific effects.<sup>20</sup> Optimization of perioperative treatment strategies may result in improved patient outcomes and decreased cost.

The purpose of this study was to evaluate the medical, surgical, and anesthetic risk factors potentially associated with increased frequency of clinically relevant thromboembolic complications in the perioperative period for patients undergoing lower extremity joint replacement. A case-control methodology is especially useful when the outcome/condition of interest (*i.e.*, cases) occurs infrequently.<sup>21</sup> This methodology is well suited for the study of clinically significant thromboembolic events, because prospective ascertainment of surrogate markers may result in additional diagnosed events of undetermined clinical relevance.<sup>21</sup> In addition, the availability at our institution of a large and broadly based patient population allows retrospective examination of multiple potential risk factors. Therefore, we designed a case-control study of patients undergoing primary elective primary hip or knee arthroplasty who developed clinically relevant venous thromboembolism within 30 days of the surgical procedure.

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## Materials and Methods

### Patients

This investigation includes patients who underwent primary elective total hip or knee arthroplasty at Mayo Clinic between January 1, 1986, and December 31, 1995.<sup>12</sup> All patients who underwent one or more elective primary total hip or knee replacements at our institution in the 10-yr study period were identified using prospectively collected databases, after review board approval. Patients who had denied research access to their medical records were excluded from the study (Minnesota state law [Minnesota Statute 144.335 Subd. 3a. (d)]). Our institutional total joint registry is a prospectively collected computerized database of all joint replacements performed at our institution since 1969 and has been validated previously.<sup>22</sup> Joint registry personnel abstract detailed information on surgical approach, prosthesis data operative indication, preoperative diagnoses, and postoperative medical and surgical complications and perform a formal chart review at 1, 2, and 5 yr and every 5 yr thereafter using a standardized data collection form. In a previous study, the overall rate of clinical follow-up within the total joint registry was greater than 95%.<sup>22</sup> The total joint registry was used to identify all patients who received one or more elective primary hip or knee joint replacements in the 10-yr study period. We excluded patients who received nonelective arthroplasty for fracture management. For patients who underwent more than one lower extremity arthroplasty during the study period, only the most recent procedure was considered. Thus, only one joint replacement episode was examined for each patient. All patients with evidence of a potential thromboembolic complication within the first year after the date of operation as documented in the total joint registry were identified, and their medical records were examined. As a cross-reference to the total joint registry, the institutional unified medical record system, which contains information on all patients who have ever been examined at Mayo Clinic,<sup>23</sup> was used to identify all patients treated with total hip or knee arthroplasty at our institution who had a diagnosis of pulmonary embolism or deep venous thrombosis at any time during the previous year, the year of, or the year after the surgical event. The medical records of all patients identified in either database search were retrospectively reviewed. Strict and validated criteria were used for the definition of adverse thromboembolic events. The level of diagnostic certainty was determined for each episode of pulmonary embolism or deep venous thrombosis occurring during the initial 30 days after the date of operation using previously defined criteria.<sup>24</sup> Patients meeting diagnostic criteria for probable events were not included as cases and were also excluded from the pool of potential controls. The patients meeting

**Table 1. Definition of Adverse Thromboembolic Events**

Perioperative pulmonary embolism	Episode occurring within 30 days of the date of operation <i>and</i> : 1. confirmation by pulmonary angiography, computed tomographic scan, magnetic resonance imaging, echocardiographic visualization, or pathologic examination of thrombus removed at surgery or autopsy, <i>or</i> 2. onset of new symptoms highly suggestive of acute pulmonary embolism associated with a perfusion or ventilation-perfusion lung scan interpreted as high probability for pulmonary embolism.
Perioperative deep venous thrombosis	Episode occurring within 30 days of the date of operation and the onset of local or systemic symptoms suggestive of venous thromboembolism: 1. confirmed by venography, computed tomographic scan, magnetic resonance imaging, or pathologic examination of thrombus removed at surgery or autopsy, <i>or</i> 2. associated with a documented positive noninvasive diagnostic test: impedance plethysmography, continuous wave Doppler ultrasound, compression duplex ultrasonography, radionuclide venography, or radiolabeled fibrinogen leg scan.

diagnostic criteria for definite thromboembolic events (table 1) make up the cases for the current investigation.

For each case, we identified a pool of potential controls who had undergone the same surgery with the same surgeon. Using 1:1 matching of cases and controls, a control was selected as the individual with the closest surgery date before the surgery date for the case. The records of selected controls were reviewed to confirm the absence of noncoded thromboembolic events. Thus, each patient experiencing a definite adverse event was matched with a patient who underwent the same surgical procedure with the same surgeon, without an adverse event, and within a narrow time frame. All patient records were abstracted by a single investigator using standardized data collection forms. Demographic data and information on comorbid diseases, medications, and laboratory results were noted. Surgical procedure; anesthetic technique; and surgical, anesthetic, and recovery duration were recorded. Additional intraoperative and immediately postoperative information, including monitoring used and amount and type of fluids administered, was noted. Postoperative disposition, use of in-hospital thromboprophylaxis, postoperative analgesia, and duration of stay were also recorded.

### Statistical Analysis

Statistical analyses were performed using SAS<sup>®</sup> Software Release 6.12 (SAS Institute Inc., Cary, NC). Potential risk factors for perioperative thromboembolic events were assessed using conditional logistic regression, mak-

**Table 2. Univariate Analysis of Patient and Procedural Characteristics**

Characteristic	Controls (n = 116)*	Cases (n = 116)*	OR	95% CI	P
Gender					
Female	69 (59)	59 (51)			
Male	47 (41)	57 (49)	1.5	0.8, 2.6	0.168
Age, yr	68.9 ± 12.1	69.5 ± 11.0	1.0†	0.8, 1.3†	0.680
Body mass index, kg/m <sup>2</sup>	28.5 ± 5.0	30.0 ± 5.2	1.5‡	1.1, 2.0‡	0.012
Preoperative anticoagulant use	28 (24)	29 (25)	1.0	0.6, 1.9	0.882
Coronary artery disease	19 (16)	30 (26)	1.8	0.9, 3.6	0.075
Previous thromboembolic event	3 (3)	11 (9)	3.7	1.0, 13.1	0.046
Diabetes mellitus	7 (6)	11 (9)	1.7	0.6, 4.5	0.323
Smoking status					0.495
Never	89 (77)	84 (72)			
Former	21 (18)	28 (24)	1.4	0.7, 2.7	
Current	6 (5)	4 (3)	0.8	0.2, 2.8	
ASA physical status classification ≥ 3	43 (37)	67 (58)	2.6	1.4, 4.7	0.002
Use of regional anesthesia <sup>§</sup>	53 (46)	49 (42)	0.9	0.5, 1.5	0.580
Use of arterial catheter monitoring	8 (7)	19 (16)	2.8	1.1, 7.2	0.028
Duration of surgery, h	2.9 ± 0.8	2.9 ± 1.0	1.0	0.6, 1.5	0.885
Duration of anesthesia, h	3.9 ± 0.9	3.9 ± 1.0	1.0	0.7, 1.4	0.855
Red blood cell use					0.172
None	42 (36)	52 (45)			
Intraoperative autotransfusion only	9 (8)	11 (9)	0.9	0.3, 2.6	
Banked blood	65 (56)	53 (46)	0.5	0.3, 1.1	
Postoperative characteristics					
Intensive care unit admission	2 (2)	10 (9)	5.0	1.1, 22.8	0.038
Hemoglobin, g/dl	10.7 ± 1.7	10.9 ± 1.5	1.1	0.9, 1.3	0.333
Use of neuraxial analgesia <sup>§</sup>	5 (4)	8 (7)	2.0	0.5, 8.0	0.327
Thromboembolic prophylaxis used					0.038
None	8 (7)	19 (16)			
Aspirin/subcutaneous heparin#	39 (34)	27 (23)	0.2	0.1, 0.7	
Warfarin/low-molecular-weight heparin#	68 (59)	70 (60)	0.5	0.1, 1.5	

Data are reported as number of patients (percentage) for categorical variables and mean ± SD for continuous variables. The odds ratio (OR) and 95% confidence interval (CI) were obtained from conditional logistic regression, taking into account the matched-pair study design.

\* Duration of surgery, duration of anesthesia, and use of thromboembolic prophylaxis were missing for one control, use of neuraxial analgesia was missing for two controls, and postoperative hemoglobin concentration was missing for two controls and six cases. † OR is for every 10-year increase in age. ‡ OR is for every 5-kg/m<sup>2</sup> increase in body mass index. § Regional anesthesia includes intraoperative delivery of local anesthetics via the subarachnoid or epidural routes, resulting in adequate surgical anesthesia. Neuraxial analgesia includes postoperative use of continuous subarachnoid or epidural infusion of solutions containing local anesthetics and/or opioids. # Of the 39 controls and 27 cases in the aspirin/subcutaneous heparin subgroup, only 3 (1 control, 2 cases) received subcutaneous heparin. Of the 68 controls in the warfarin/low-molecular-weight heparin subgroup, 66 received warfarin. Of the 70 cases in the warfarin/low-molecular-weight heparin subgroup, 65 are known to have received warfarin, 3 are known to have received low-molecular-weight heparin, and 2 participated in a blind study and received either warfarin or low-molecular-weight heparin.

ASA = American Society of Anesthesiologists.

ing use of the 1:1 matched-pair study design. Age, body mass index (weight in kilograms divided by the square of height in meters), hemoglobin concentration, duration of anesthesia, and duration of surgery were treated as continuous variables in the logistic regression analysis. The American Society of Anesthesiologists (ASA) physical status classification was adopted in 1962 for the grading of patients based on severity of illness and physiologic reserve.<sup>25</sup> For analysis purposes, ASA physical status was dichotomized ( $\leq 2$  vs.  $\geq 3$ ). Other potential risk factors included in the logistic regression analysis were treated as categorical variables as presented in table 2. Characteristics found to be statistically significant from the univariate analysis were included in a multivariate analysis with stepwise backward elimination of non-significant variables. To assess consistency in variable selection, a multivariate analysis was also performed using a stepwise forward procedure. To assess whether

the effect of any potential risk factor changed over calendar time, two additional sets of analyses were performed. For each potential risk factor, an additional analysis was performed, which included the two-way interaction of the given risk factor with calendar time. In addition, because the use of routine thromboprophylactic strategies is known to have changed over the study period, the cases were separated into two groups, 1986–1990 (n = 66) and 1991–1995 (n = 50), to represent the periods before and after routine thromboprophylactic strategies were employed. Univariate analysis of risk factors was then performed separately for each group. In all cases, two-sided tests were used, with P values  $\leq 0.05$  denoting statistical significance.

## Results

A total of 116 of 9,791 eligible patients undergoing elective primary hip or knee arthroplasty surgery in the

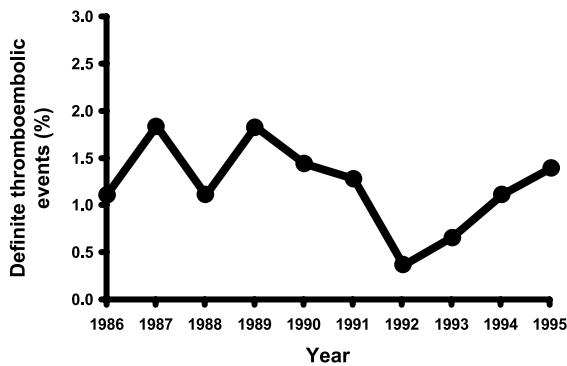


Fig. 1. Frequency of adverse thromboembolic events according to calendar year.

10-yr study period were found to have experienced one or more definite adverse thromboembolic events. The frequency of definite adverse thromboembolic events is displayed in figure 1 according to calendar time. There were 56 patients who experienced a definite pulmonary embolism and 68 patients who experienced a definite deep venous thrombosis, with 8 patients experiencing both events. There were an additional 34 patients who met criteria for a probable event but did not meet criteria for a definite event (24 for both pulmonary embolism and deep venous thrombosis, 10 for deep venous thrombosis only). These patients were not included as cases and were also not included in the pool of potential controls. Of the 116 cases, 39 patients underwent elective primary total hip arthroplasty, 49 underwent unilateral knee arthroplasty, and 28 underwent bilateral knee arthroplasty. Of the 68 patients who experienced deep venous thrombosis, 56 (82%) developed the thrombosis in an operative leg and 12 (18%) developed the thrombosis in a nonoperative leg. Overall, 43 patients (of the 116 cases [37%]) experienced the first venous thromboembolic event within 3 days after surgery, 43 (37%) from 4 to 10 days after surgery, and 30 (26%) from 11 to 30 days after surgery.

A summary of the univariate analysis of potential risk factors for thromboembolic events is presented in table 2. The distribution of age and gender was similar for cases and controls. Treated as a continuous variable, larger body mass index was a significant risk factor for thromboembolic events ( $P = 0.012$ ; odds ratio [OR] = 1.5, 95% confidence interval (CI): 1.1-2.0 for each 5-kg/m<sup>2</sup> increase). Obesity, defined as body mass index  $\geq 30$  kg/m<sup>2</sup>, was observed in 56% of cases and 34% of controls ( $P < 0.001$ ; OR = 3.4, 95% CI: 1.7-6.6). A history of previous thromboembolic events was present for 9% of cases and 3% of controls ( $P = 0.046$ ; OR = 3.7, 95% CI: 1.0-13.1). The percentage of patients using antithrombotic agents (aspirin, warfarin, unfractionated heparin, or low-molecular-weight heparin preparations) on admission for lower extremity arthroplasty surgery was similar for cases (25%) and controls (24%), however.

The percentages of patients classified as having ASA physical status 1, 2, 3, 4, and 5 were 3%, 39%, 55%, 3%, and 0% for cases and 0%, 63%, 35%, 2%, and 0% for controls, respectively. An ASA physical status classification of 3 or greater was significantly associated with an increased likelihood of a thromboembolic event ( $P = 0.002$ ; OR = 2.6, 95% CI: 1.4-4.7). Coronary artery disease, diabetes mellitus, and smoking status were not found to differ significantly between cases and controls.

Anesthetic technique (regional *vs.* general), duration of surgery, duration of anesthesia, transfusion of blood products, and use of postoperative neuraxial analgesia were similar in cases and controls and did not significantly alter the frequency of pulmonary embolism or deep venous thrombosis. The intraoperative use of invasive blood pressure monitoring *via* arterial cannulation was univariately associated with an increased risk for these adverse postoperative thromboembolic events ( $P = 0.028$ ; OR = 2.8, 95% CI: 1.1-7.2), however. Other invasive intraoperative monitoring modalities, including central venous pressure and pulmonary artery catheters or transesophageal echocardiography, were used infrequently (<5% of cases) and not evaluated as potential risk factors. Postoperative intensive care unit admission was infrequent (2% of controls, 9% of cases) but was significantly associated with an increased likelihood of pulmonary embolism or deep venous thrombosis ( $P = 0.038$ ; OR = 5.0, 95% CI: 1.1-22.8). All intensive care unit admissions in both groups were scheduled for patients thought to benefit from increased postoperative monitoring based on the preoperative medical assessment. No unplanned admissions based solely on intraoperative events were found in either group.

As expected, the use and choice of postoperative pharmacologic antithrombotic prophylaxis among cases and controls changed over calendar time (fig. 2). The use of antithrombotic agents was found to be protective against the occurrence of clinically relevant thromboembolic events ( $P = 0.038$ ; OR = 0.2, 95% CI: 0.1-0.7 for aspirin or standard dose subcutaneous unfractionated heparin; OR = 0.5, 95% CI: 0.1-1.5 for warfarin or low-molecular-weight heparin). In patients who received aspirin or subcutaneous heparin thromboprophylaxis, the median time to initiation of treatment was the operative day in both cases and controls, and 89.0% of patients had it initiated by the first postoperative day. For patients receiving warfarin or low-molecular-weight heparin therapy, the median time to initiation was the operative day for both the cases and controls, and 99.3% of patients had it initiated by the first postoperative day.

From multivariate analysis after eliminating nonsignificant variables, body mass index ( $P = 0.031$ ; OR = 1.5, 95% CI: 1.0-2.0 for each 5-kg/m<sup>2</sup> increase), ASA physical status classification of 3 or greater ( $P = 0.005$ ; OR = 2.6, 95% CI: 1.3-4.7), and use of antithrombotic prophylaxis ( $P = 0.050$ ; OR = 0.2, 95% CI: 0.1-0.7 for aspirin or

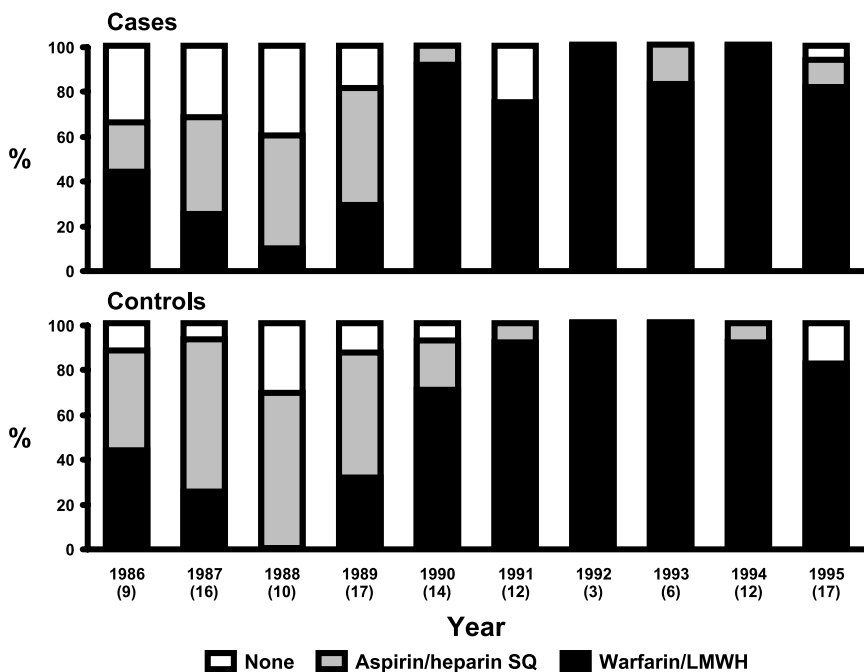


Fig. 2. Frequency of anticoagulant use for patients who experienced adverse thromboembolic events (cases) and controls according to calendar year. The number of cases for each calendar year is provided in parentheses. For each year, the height of the bar was set at 100%. Shading is used to indicate the percentage of patients receiving warfarin or low-molecular-weight heparin (LMWH) (black), aspirin or standard dose subcutaneous heparin (heparin SQ) (gray), or no pharmacologic thromboprophylaxis (white). The date of surgery for case and control patients differed by less than 12 months for 99% of the matched pairs. To ensure consistency, controls are presented according to the calendar year of their matched case.

subcutaneous heparin; OR = 0.4, 95% CI: 0.1-1.4 for warfarin or low-molecular-weight heparin) were found to be independently associated with clinically relevant thromboembolic events. Using a stepwise forward selection procedure, the same set of independent predictors was identified. The effects of body mass index and ASA physical status classification  $\geq 3$  were found to change significantly over the 10-yr study period ( $P = 0.016$  and  $P = 0.012$  for the two-way interaction of calendar time with ASA physical status classification and body mass index, respectively). For each of these risk factors, the effect was significantly greater during the later years of the study. For body mass index, the OR increased from 1.1 (95% CI: 0.7-1.6) per 5-kg/m<sup>2</sup> increase in the 1986-1990 period to 2.3 (95% CI: 1.4-3.9) per 5-kg/m<sup>2</sup> increase in the 1991-1995 period. For ASA physical status classification  $\geq 3$ , the OR increased from 1.5 (95% CI: 0.7-3.0) during the early period to 10.0 (95% CI: 2.3-42.8) during the 1991-1995 period. No other statistically significant risk factors were identified when analyses were performed separately for the 1986-1990 and 1991-1995 periods. Among cases, the duration of time from surgery to event diagnosis did not change significantly over calendar time ( $P = 0.171$ ) and was not found to be associated with the use of pharmacologic antithrombotic prophylaxis ( $P = 0.172$ ), ASA physical status classification ( $P = 0.877$ ), or body mass index ( $P = 0.471$ ).

Although the current study has limited statistical power to assess interaction effects, a question of specific interest is whether the use of regional *versus* general anesthesia reduces the risk of clinically relevant thromboembolic events in patients who do not receive pharmacologic antithrombotic prophylaxis. In the control

group, regional anesthetic techniques were used in 6 of 8 (75%) patients not receiving prophylactic antithrombotic agents, in 13 of 39 (33%) patients receiving aspirin or subcutaneous heparin, and in 34 of 68 (50%) patients receiving warfarin or low-molecular-weight heparin. Among cases, regional anesthetic techniques were used in 8 of 19 (42%) patients not receiving prophylactic antithrombotic agents, in 9 of 27 (33%) patients receiving aspirin or subcutaneous heparin, and in 32 of 70 (46%) patients receiving warfarin or low-molecular-weight heparin. From an unmatched analysis of those who did not receive pharmacologic antithrombotic prophylaxis, the type of anesthetic technique was not found to differ significantly between cases and controls (use of regional technique in 8 of 19 patients *vs.* 6 of 8 patients for cases and controls, respectively; Fisher exact test,  $P = 0.21$ ).

## Discussion

This study provides physicians involved in the perioperative care of arthroplasty patients information on the risk factors for clinically relevant perioperative thromboembolic morbidity after major elective orthopedic surgery of the lower extremities has been performed. An accurate assessment of the risks associated with these elective orthopedic surgeries should assist clinicians and their patients in decisions regarding treatment options and optimization of perioperative care. Anesthesiologists are increasingly involved in the preoperative preparation of their patients, improving both efficiency and cost-effectiveness.<sup>26</sup> The institution of therapeutic interventions geared toward improved perioperative outcomes

might be critically dependent on the identification of patients at highest risk and timely initiation of appropriate therapies. Anesthesiologists might be best suited for this role.

The occurrence of pulmonary embolism and deep venous thrombosis within 30 days after elective primary total hip or knee arthroplasty was more frequent in patients with increasing body mass index, specifically those with a body mass index greater than 30 kg/m<sup>2</sup>, and in patients with moderate or severe systemic disease resulting in some functional limitation as defined by an ASA physical status classification greater than or equal to 3. For each of these risk factors, the effect was found to be significantly greater during the later years of the study, when pharmacologic antithrombotic prophylaxis with warfarin was common. In contrast, the use of pharmacologic antithrombotic prophylaxis after lower extremity orthopedic surgery was found to be protective. The choice of anesthetic technique, regional or general, did not measurably affect the risk of adverse thromboembolic events in this study. Although only in the univariate analysis, history of a previous venous thromboembolic event was associated with increased thromboembolic risk. Certainly, congenital and acquired thrombophilic disorders may contribute to venous thromboembolism. The interaction between hypercoagulable states and surgical procedures remains to be explored, however.

In several studies,<sup>20,27,28</sup> obesity was not found to be a risk factor for perioperative thromboembolic events in patients undergoing primary hip or knee replacement surgery. Benjamin *et al.*<sup>29</sup> examined obesity as an independent risk factor for patients undergoing simultaneous bilateral knee replacement surgery in 455 patients but did not find significantly different rates of venous thromboembolism. Other studies,<sup>17,18,30,31</sup> including the present report, have found increased risk of pulmonary embolism or deep venous thrombosis in obese patients after lower extremity orthopedic surgery. In a survey of orthopedic surgeons, Rodgers *et al.*<sup>32</sup> found that the majority of practitioners thought gross obesity was a risk factor for thromboembolic events. In fact, some authors have advocated the selective use of antithrombotic prophylaxis after total knee arthroplasty only in those patients with a history of previous deep venous thrombosis or obesity.<sup>33</sup> The present study specifically examined the risk of perioperative thromboembolic events in patients undergoing elective primary total hip or knee arthroplasty using a quantifiable grading of the extent of obesity. We also found that the association between obesity and perioperative thromboembolic events changed over time, with a larger effect observed during the later years of the study. Differences in the definition of obesity may underlie some of the reported differences in results. In addition, potential differences in patient populations (*e.g.*, use of pharmacologic antithrombotic prophylaxis) may account for the disparity in results. Nevertheless,

the conflicting results cannot be ascribed to differences in prospective ascertainment<sup>18,27,30</sup> or clinical diagnosis<sup>17,20,28,29,34</sup> of events.

In our study, the use of aspirin or subcutaneous heparin was as protective against the occurrence of clinically relevant pulmonary embolism or deep venous thrombosis within 30 days of elective primary total hip or knee replacement surgery as thromboprophylaxis with warfarin or low-molecular-weight heparin (OR = 0.2 and OR = 0.5, respectively). During the period of study, the First (1986) and Second (1988) American College of Chest Physicians Consensus Conferences recommended that patients undergoing elective knee arthroplasty surgery receive intermittent pneumatic compression, whereas those undergoing hip replacement receive either heparin or warfarin in doses sufficient to produce moderate anticoagulant effects.<sup>35,36</sup> Only the Fourth American College of Chest Physicians Consensus Conference (1995) included fixed-dose low-molecular-weight heparin as an alternative to any of these thromboprophylactic treatments. The incorporation of these recommendations into clinical practice at our institution is reflected by the increase in the use of pharmacologic thromboprophylaxis evident during the 10-yr study period (fig. 2). The Sixth American College of Chest Physicians Consensus Conference on antithrombotic therapy evaluated available literature and reported results on specific strategies geared toward the prevention of venous thromboembolism in the general and surgical populations.<sup>37</sup> For instance, the use of mechanical and pharmacologic interventions was considered effective, and in specific high-risk groups, including the lower extremity orthopedic population, the use of pharmacologic antithrombotic therapy was highly recommended. Reductions of greater than 50% in the rate of asymptomatic prospectively ascertained pulmonary embolism and deep venous thrombosis are cited.<sup>37</sup> Despite the successful reduction of asymptomatic thromboembolic disease with the use of routine anticoagulation, an actual reduction of clinically relevant adverse events has been difficult to demonstrate in everyday medical practice.<sup>38</sup> Although there is a large amount of clinical data documenting the efficacy and cost-effectiveness of routine thromboprophylaxis in patients undergoing elective total hip or knee replacement surgery,<sup>37</sup> it is likely that selected patient populations might receive the most benefit from specific prophylactic measures.<sup>12,38</sup> A targeted selective approach to perioperative thromboprophylaxis may reduce the incidence of hemorrhagic complications<sup>39</sup> resulting from unnecessary therapy in patients at low risk of thromboembolic complications while appropriately treating those patients at higher risk. In addition, the delayed occurrence of a number of thromboembolic events (28% of cases occurred more than 10 days after surgery) would suggest that additional antithrombotic prophylaxis beyond the duration of hospitalization

might be warranted in certain patient populations. These hypotheses remain to be tested.

Multiple studies have found a surgery-specific association between ASA physical status classification and perioperative morbidity and mortality.<sup>40-42</sup> The ASA physical status classification subjectively stratifies patients independent of the surgical procedure planned according to their severity of illness, which, in turn, may determine the occurrence of adverse outcomes. In our study, patients undergoing primary elective lower extremity arthroplasty surgery with an ASA physical status classification of 3 or greater were found to be at increased risk of clinically relevant deep venous thrombosis or pulmonary embolism within 30 days. Similarly, intraoperative placement of an arterial line for continuous arterial blood pressure monitoring and/or repeated sampling and planned postoperative intensive care unit admission were predictive of an increased risk of thromboembolic events within 30 days of elective primary hip or knee arthroplasty surgery. It is likely that these findings represent surrogate markers for other variables, including patient sickness profile. Accordingly, increasing age has been associated with increased thromboembolic risk in the orthopedic population.<sup>12,31</sup> In the present study, we did not observe a measurably increased frequency of deep venous thrombosis or pulmonary embolism in older patients. It is possible that differences in overall well-being (*i.e.*, sickness profile) rather than age determine the perioperative risk of thromboembolic complications.

Earlier studies had suggested that the use of regional anesthetic techniques such as the subarachnoid or epidural administration of local anesthetics for the administration of surgical levels of anesthesia was associated with reduced risk of perioperative thromboembolic events in the lower extremity arthroplasty population.<sup>19,43</sup> In the present study, we did not observe a measurable effect of anesthetic technique on the risk of deep venous thrombosis or pulmonary embolism in patients treated with elective lower extremity arthroplasty. Differences in patient selection or use of adjuvant measures, including early ambulation or pneumatic compression, may have been responsible for the reported protective effect. By matching on surgeon and type of surgery, we have likely accounted for these differences in patient management and thus are better able to define the specific role of regional anesthesia (including postoperative neuraxial analgesia) in the prophylaxis against deep venous thrombosis or pulmonary embolism after lower extremity arthroplasty.

There are limitations inherent to the design of this study. As with all case-control studies, our findings only provide information on relative risk rather than on absolute risk; this limits the applicability to clinical practice. Similarly, the quality of the data is dependent on the accuracy and completeness of the medical record. Our investigation was restricted to data routinely collected as

part of the medical record or the total joint registry. In addition, a single investigator abstracted all the data using standardized data collection forms. It is possible that a previous thromboembolic event or other variable may have led to specific changes in the management of the patient(s). In the present study, there were no differences in the history of thromboembolism between the cases and controls.

The effective sample size for assessing a given risk factor in a matched case-control study is determined by the number of discordant matched pairs (*i.e.*, the number of matched pairs in which the value of the given risk factor differs for case and control). For this investigation, matching on surgeon, surgical procedure, and calendar time resulted in a small effective sample size for assessing some risk factors such as type of antithrombotic prophylaxis used. We also have limited power to assess interaction effects such as whether regional anesthesia is protective in the absence of anticoagulant use. Among those who did not receive pharmacologic antithrombotic prophylaxis, the use of regional anesthetic techniques did not differ significantly between cases and controls. Given the small sample size, however, this observation should not be interpreted as evidence of no association.

In the present study, although nonpharmacologic antithrombotic measures were not routinely used at our institution, it is possible that some patients might have received intermittent pneumatic compression devices during their hospital course. Documentation of their use was not performed in a standardized fashion, however, and thus was not available for review. Although several small studies have shown that intermittent pneumatic compression is an effective form of prophylaxis (specifically after total knee replacement surgery), its effectiveness depends on continuous wear immediately after surgery (both in the hospital and after discharge). Thus, current recommendations indicate that these devices are most useful when used concurrently with pharmacologic antithrombotic regimens. Nonetheless, a significant protective effect of the use of some form of thromboprophylaxis is evident in the present study. Other studies have demonstrated similar reductions in the rates of clinically relevant thromboembolic events in patients receiving aspirin, warfarin, or low-molecular-weight heparin.<sup>44,45</sup>

The results of the present study are consistent with a significant reduction in the rate of clinically relevant adverse thromboembolic events with the use of aspirin. The Pulmonary Embolism Prevention Trial Collaborative Group examined the frequency of symptomatic deep venous thrombosis and pulmonary embolism in patients receiving elective hip or knee arthroplasty or after hip fracture and reported reductions in these adverse outcomes with the use of aspirin (when compared with placebo)<sup>45</sup> similar to those reported for prophylactic

warfarin or low-molecular-weight heparin.<sup>44</sup> The actual impact on disease prevention of routine warfarin and low-molecular-weight heparin thromboprophylaxis in the orthopedic population needs further study. In fact, the clinical relevance of venographically or ultrasonographically ascertained lower extremity thrombi after hip or knee arthroplasty surgery remains to be determined, because most of these thrombi resolve without coming to clinical attention.<sup>44</sup> In the present study, the effects of body mass index and ASA physical status classification  $\geq 3$  were greater during the time when the thromboprophylactic use of warfarin or low-molecular-weight heparin became routine. The prevention of clinically relevant venous thromboembolic events after lower extremity arthroplasty might need optimization, because not all patients receiving pharmacologic thromboprophylaxis are at equal risk. For instance, a weight-based and/or sickness-adjusted thromboprophylactic regimen may further reduce thromboembolic risk while avoiding unnecessary treatment of low-risk patients. These hypotheses remain to be explored.

In conclusion, this study demonstrates the existence of specific risk factors within the general orthopedic population for the occurrence of adverse perioperative thromboembolic events in patients undergoing elective lower extremity joint replacement surgery managed with current operative and perioperative care. The routine use of antithrombotic prophylaxis might require optimization in specific patient populations, as suggested by the findings of increased risk in obese patients, defined by a body mass index greater than 30 kg/m<sup>2</sup>, and in patients with higher sickness profiles, as determined by an ASA physical status classification of 3 or greater.

## References

- Warwick D, Williams MH, Bannister GC: Death and thromboembolic disease after total hip replacement: A series of 1162 cases with no routine chemical prophylaxis. *J Bone Joint Surg (Br)* 1995; 77:6-10
- Fender D, Harper WM, Thompson JR, Gregg PJ: Mortality and fatal pulmonary embolism after primary total hip replacement: Results from a regional hip register. *J Bone Joint Surg (Br)* 1997; 79:896-9
- White RH, Romano PS, Zhou H, Rodrigo J, Bargar W: Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med* 1998; 158:1525-31
- Wroblewski BM, Siney PD, Fleming PA: Fatal pulmonary embolism after total hip arthroplasty: Diurnal variations. *Orthopedics* 1998; 21:1269-71
- Stulberg BN, Insall JN, Williams GW, Ghelman B: Deep-vein thrombosis following total knee replacement: An analysis of six hundred and thirty-eight arthroplasties. *J Bone Joint Surg (Am)* 1984; 66:194-201
- Planes A, Vochelle N, Fagola M: Total hip replacement and deep vein thrombosis: A venographic and necropsy study. *J Bone Joint Surg (Br)* 1990; 72:9-13
- Levine MN, Hirsh J, Gent M, Turpie AG, Leclerc J, Powers PJ, Jay RM, Neemeh J: Prevention of deep vein thrombosis after elective hip surgery: A randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med* 1991; 114:545-51
- Francis CW, Pellegrini VD Jr, Marder VJ, Totterman S, Harris CM, Gabriel KR, Azodo MV, Leibert KM: Comparison of warfarin and external pneumatic compression in prevention of venous thrombosis after total hip replacement. *JAMA* 1992; 267:2911-5
- Hull R, Raskob G, Pineo G, Rosenbloom D, Evans W, Mallory T, Anquist K, Smith F, Hughes G, Green D, Elliott CG, Panju A, Brant R: A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *N Engl J Med* 1993; 329:1370-6
- Imperiale TF, Speroff T: A meta-analysis of methods to prevent venous thromboembolism following total hip replacement. *JAMA* 1994; 271:1780-5
- Colwell CW Jr, Collis DK, Paulson R, McCutchen JW, Bigler GT, Lutz S, Hardwick ME: Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty: Evaluation during hospitalization and three months after discharge. *J Bone Joint Surg (Am)* 1999; 81:932-40
- Mantilla CB, Horlocker TT, Schroeder DR, Berry DJ, Brown DL: Frequency of myocardial infarction, pulmonary embolism, deep venous thrombosis, and death following primary hip or knee arthroplasty. *ANESTHESIOLOGY* 2002; 96:1140-6
- Seligsohn U, Lubetsky A: Genetic susceptibility to venous thrombosis. *N Engl J Med* 2001; 344:1222-31
- Goldhaber SZ, Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Willett WC, Hennekens CH: A prospective study of risk factors for pulmonary embolism in women. *JAMA* 1997; 277:642-5
- Piccioli A, Prandoni P, Ewenstein BM, Goldhaber SZ: Cancer and venous thromboembolism. *Am Heart J* 1996; 132:850-5
- Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S: Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996; 348:977-80
- Kelsey JL, Wood PH, Charnley J: Prediction of thromboembolism following total hip replacement. *Clin Orthop* 1976; 247-58
- Kim YH, Kim VE: Factors leading to low incidence of deep vein thrombosis after cementless and cemented total knee arthroplasty. *Clin Orthop* 1991; 119-24
- Sharrock NE, Haas SB, Hargett MJ, Urquhart B, Insall JN, Scuderi G: Effects of epidural anesthesia on the incidence of deep-vein thrombosis after total knee arthroplasty. *J Bone Joint Surg (Am)* 1991; 73:502-6
- Sharrock NE, Hargett MJ, Urquhart B, Peterson MG, Ranawat C, Insall J, Windsor R: Factors affecting deep vein thrombosis rate following total knee arthroplasty under epidural anesthesia. *J Arthroplasty* 1993; 8:133-9
- Schlesselman JJ, Stolley PD: *Research strategies, Case Control Studies—Design, Conduct, Analysis*. Edited by Schlesselman JJ. New York, Oxford University Press, 1982, pp 7-26
- Berry DJ, Kessler M, Morrey BF: Maintaining a hip registry for 25 years: Mayo Clinic experience. *Clin Orthop* 1997; 344:61-8
- Melton LJ III: History of the Rochester Epidemiology Project. *Mayo Clin Proc* 1996; 71:266-74
- Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III: Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population-based study. *Arch Intern Med* 1998; 158:585-93
- American Society of Anesthesiologists: New classification of physical status. *ANESTHESIOLOGY* 1963; 24:111
- Starsnic MA, Guarnieri DM, Norris MC: Efficacy and financial benefit of an anesthesiologist-directed university preadmission evaluation center. *J Clin Anesth* 1997; 9:299-305
- Lemos MJ, Sutton D, Hozack WJ, Balderston RA, Booth RE Jr, Rothman RH: Pulmonary embolism in total hip and knee arthroplasty: Risk factors in patients on warfarin prophylaxis and analysis of the prothrombin time as an indicator of warfarin's prophylactic effect. *Clin Orthop* 1992; 282:158-63
- Jiganti JJ, Goldstein WM, Williams CS: A comparison of the perioperative morbidity in total joint arthroplasty in the obese and nonobese patient. *Clin Orthop* 1993; 289:175-9
- Benjamin J, Tucker T, Ballesteros P: Is obesity a contraindication to bilateral total knee arthroplasties under one anesthetic? *Clin Orthop* 2001; 392:190-5
- Lowe GD, Haverkate F, Thompson SG, Turner RM, Bertina RM, Turpie AG, Mannucci PM: Prediction of deep vein thrombosis after elective hip replacement surgery by preoperative clinical and haemostatic variables: The ECAT DVT Study. *European Concerted Action on Thrombosis. Thromb Haemost* 1999; 81:879-86
- White RH, Gettner S, Newman JM, Trauner KB, Romano PS: Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. *N Engl J Med* 2000; 343:1758-64
- Rodgers A, Gray H, MacMahon S: Pharmacological thromboprophylaxis in hip and knee surgery: A survey of New Zealand orthopaedic surgeons. *Aust NZ J Surg* 1994; 64:167-72
- Ansari S, Warwick D, Ackroyd CE, Newman JH: Incidence of fatal pulmonary embolism after 1,390 knee arthroplasties without routine prophylactic anticoagulation, except in high-risk cases. *J Arthroplasty* 1997; 12:599-602
- Stern SH, Bowen MK, Insall JN, Scuderi GR: Cemented total knee arthroplasty for gonarthrosis in patients 55 years old or younger. *Clin Orthop* 1990; 260:124-9
- Hyers TM, Hull RD, Weg JG: Antithrombotic therapy for venous thromboembolic disease. *Chest* 1986; 89(suppl):26-35
- Hyers TM, Hull RD, Weg JG: Antithrombotic therapy for venous thromboembolic disease. *Chest* 1989; 95(suppl):37-51
- Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr,



- Wheeler HB: Prevention of venous thromboembolism. *Chest* 2001; 119(supp): 132-75
38. Murray DW, Britton AR, Bulstrode CJ: Thromboprophylaxis and death after total hip replacement. *J Bone Joint Surg (Br)* 1996; 78:863-70
39. Levine MN, Raskob G, Landefeld S, Kearon C: Hemorrhagic complications of anticoagulant treatment. *Chest* 2001; 119(supp):108-21
40. Klotz HP, Candinas D, Platz A, Horvath A, Dindo D, Schlumpf R, Largiader F: Preoperative risk assessment in elective general surgery. *Br J Surg* 1996; 83:1788-91
41. Wolters U, Wolf T, Stutzer H, Schroder T: ASA classification and perioperative variables as predictors of postoperative outcome. *Br J Anaesth* 1996; 77:217-22
42. Leung JM, Dzankic S: Relative importance of preoperative health status versus intraoperative factors in predicting postoperative adverse outcomes in geriatric surgical patients. *J Am Geriatr Soc* 2001; 49:1080-5
43. Sharrock NE, Cazan MG, Hargett MJ, Williams-Russo P, Wilson PD Jr: Changes in mortality after total hip and knee arthroplasty over a ten-year period. *Anesth Analg* 1995; 80:242-8
44. Leclerc JR, Gent M, Hirsh J, Geerts WH, Ginsberg JS: The incidence of symptomatic venous thromboembolism during and after prophylaxis with enoxaparin: A multi-institutional cohort study of patients who underwent hip or knee arthroplasty. Canadian Collaborative Group. *Arch Intern Med* 1998; 158: 873-8
45. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000; 355: 1295-302