Does International Normalized Ratio Level Predict Pulmonary Embolism?

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Abstract

Background Preventing pulmonary embolism is a priority after major musculoskeletal surgery. The literature contains discrepant data regarding the influence of anticoagulation on the incidence of pulmonary embolism after joint arthroplasty. The American College of Chest Physicians guidelines recommend administration of oral anticoagulants (warfarin), aiming for an international normalized ratio (INR) level between 2 and 3. However, recent studies show aggressive anticoagulation (INR > 2) can lead to hematoma formation and increased risk of subsequent infection.

Questions/purposes We asked whether an INR greater than 2 protects against pulmonary embolism.

Patients and Methods We identified 9112 patients with 10,122 admissions for joint arthroplasty between 2004 and 2008. All patients received warfarin for prophylaxis, aiming for an INR level of 2 or lower. We assessed 609 of 10,122 admissions (6%) for pulmonary embolism using

CT, ventilation/perfusion scan, or pulmonary angiography, and 163 of 10,122 admissions (1.6%) had a proven pulmonary embolism.

Results Fifteen of 163 admissions (9%) had an INR greater than 2 before or on the day of workup compared to 35 of 446 admissions (8%) who were negative. We observed no difference between the INR values in patients with or without pulmonary embolism.

Conclusions We found no clinically relevant difference in the INR values of patients who did or did not develop pulmonary embolism. The risk of bleeding should be weighed against the risk of pulmonary embolism when determining an appropriate target INR for each patient, as an INR less than 2 may reduce the risk of bleeding while still protecting against pulmonary embolism.

Level of Evidence Level III, therapeutic study. See Instructions to Authors for a complete description of levels of evidence.

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Each author certifies that his/her institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

Pulmonary embolism (PE) is a serious and potentially fatal complication that can develop after total joint arthroplasty (TJA), with an incidence of symptomatic PE of 1.1% to 1.82% after TKA and 0.51% to 0.9% after THA [12, 18, 19]. Patients undergoing TJA are considered to be at higher risk for PE. Prevention of PE after orthopaedic procedures continues to be a priority. For this reason, various scientific groups have devised guidelines for implementation of anticoagulation prophylaxis to minimize this complication [10, 11].

In 2008, the American College of Chest Physicians (ACCP) issued updated guidelines regarding postoperative PE prophylaxis in elective hip or knee arthroplasty [10].

These guidelines endorse the use of low-molecular-weight heparin (LMWH), fondaparinux, or vitamin K antagonists to achieve an international normalized ratio (INR) between 2 and 3. These guidelines, however, make the assumption that deep venous thrombosis (DVT) and PE should be treated as the same entity and that the former is likely to lead to the latter. A recently published study discredited this relationship [16]. Further, the ACCP guidelines do not account for the risk or severity of bleeding complications associated with anticoagulation. At an INR 2 to 3, the incidence of major bleeding complications ranges from 5.0% to 5.6% after TKA and 0.6% to 1.6% after THA [8, 9, 17]. In those same studies, the rate of minor bleeding complications after TKA and THA reportedly ranges from 21% to 28% and 4.6% to 13.5%, respectively. With the increased risk of bleeding complications, it is important to understand the effectiveness of therapeutic anticoagulation in minimizing PE. We previously demonstrated the low risk of complications with the use of low-dose warfarin (ie, aiming for an INR < 2) for preventing PE [1]. That study was the basis for implementing the use of low-dose warfarin (aiming for an INR < 2) in patients undergoing TJA in 1990.

We therefore asked whether an INR level of greater than 2, as dictated by the ACCP guidelines, after TJA is protective against PE.

Patients and Materials

From our institutional database, we retrospectively identified 9112 patients who underwent TJA between January 2004 and June 2008 and had at least a single postoperative INR value available. Those patients who underwent workup for PE yet did not have an INR value on the day of or before PE scan were excluded. During that same time, we treated 9973 patients with TJA. Therefore, 861 patients were excluded due to lack of complete data. The demographics of these two groups were investigated (Table 1). The 9112 patients had an average age of 64 years (range, 11–103 years) and had 10,122 admissions for 11,300 procedures (4727 primary hips, 5079 primary knees, 803 revision hips, 615 revision knees, and 76 hemiarthroplasties). Patients were followed until discharge from the hospital for a minimum of 2 days (average, 6.3 days; range, 2–56 days). Any patients with symptoms indicative of PE were investigated. Since this study's observational window ended at discharge, no patients were lost to followup. No patients were recalled specifically for this study; all data were obtained from medical records.

The protocol for anticoagulation at our institution throughout the study period consisted of administration of 1000 IU intravenous LMWH at the time of dislocation of

Table 1. Demographic distribution among included and excluded admissions

Variable	Included admissions	Excluded admissions
Number	10,122	1041
Age (years)*	64.2 (64.0–64.4)	63.3 (62.5–64.0)
Charlson comorbidity index [†]	2 (0–8)	2 (0–8)
Sex (number)		
Male (%)	4362 (43.1%)	434 (41.7%)
Female (%)	5759 (56.9%)	607 (58.3%)
Joint (number)		
Hip (%)	5074 (50.1%)	558 (53.6%)
Knee (%)	5047 (49.9%)	483 (46.4%)
Procedure (number)		
Primary (%)	8788 (86.8%)	925 (88.9%)
Revision (%)	1256 (12.4%)	113 (10.9%)
Hemiarthroplasty (%)	77 (0.8%)	3 (0.3%)

* Values are expressed as mean, with 95% confidence interval in parentheses; [†] values are expressed as median, with range in parentheses.

the hip during THA and before inflation of the tourniquet during TKA. In addition, we placed patients on oral anticoagulation (warfarin), aiming for an INR level of 2 or lower. Patients continued on the anticoagulation for a period of 6 weeks. The institutional guidelines are modeled after the recommendations from the American Academy of Orthopaedic Surgeons (AAOS) [11] for prevention of PE after TJA. These guidelines were developed without regard for the prevention of DVT. This conflicts with the recommendations made by the ACCP [10], whose means of PE prevention include prophylaxis against DVT. There were variations based on the risk profile of patients for PE and bleeding. We gave patients at higher risk of PE LMWH in addition to oral anticoagulation until their INR level reached therapeutic levels. We considered patients at high risk for PE as those with previous PE or polycythemia vera and those in a hypercoagulable state. On the other hand, we gave patients at high risk of bleeding aspirin for anticoagulation. We considered patients at high risk for bleeding as those with recent craniospinal surgery, active gastric ulcer, and hemophilia. Prophylaxis with warfarin involved administration of the drug on the operative day. We monitored the INR daily while the patients were in the hospital and dosed warfarin according to their INR levels. The mean preoperative INR for the entire cohort of 10,122 admissions was 1.09. The median daily postoperative values for INR were 1.13 (range, 0.67–3.04) on Postoperative Day (POD) 0, 1.24 (range, 0.6–5.8) on POD 1, 1.39 (range, 0.4–7.0) on POD 2, 1.32 (range, 0.7–5.3) on POD 3, 1.33

Fig. 1 A graph shows median INR versus day of surgery (columns, left axis) and a histogram displaying PE workup day of scan relative to POD (area curve; right axis). POD 2 was the maximum day of scans for both PE-positive and PE-negative patients.

Fig. 2 A graph shows percentage of patients with an INR greater than 2 from preoperative to POD 5.

(range, 0.9–5.2) on POD 4, and 1.41 (range, 0.8–4.3) on POD 5 (Fig. 1). The proportion of admissions with an INR greater than 2 was 0.7%, 0.2%, 6.4%, 3.1%, 4.5%, and 8.6% for POD 0 through 5, respectively (Fig. 2).

The workup for PE at our institution followed a standard protocol as well. This protocol underwent some modification over time. In general, we first administered oxygen to patients with hypoxia and monitored them closely (Appendix 1). If within 5 to 10 minutes of oxygen therapy hypoxia was not resolved, we imaged these patients for PE,

which included multidetector CT (MDCT), ventilation/perfusion (VQ) scan, and in rare cases pulmonary angiography. We then thoroughly evaluated patients with other signs suggesting PE, such as tachycardia, tachypnea, and dyspnea, and based on the judgment of the evaluating internist, performed further evaluations for PE.

From among the 10,122 admissions, 600 patients (609 admissions; 6.0%) were scanned for PE. This subset had an average age of 69 years (range, 24–96 years) and consisted of 424 (73.5%) women. These patients had 710 arthroplasty

Table 2. Risk factors for developing PE

Variable	Scanned		Not scanned
	PE-positive	PE-negative	
Number of admissions	163	446	9513
Age (years)*	68.9 (67.4–68.9)	69.0 (68.0–70.1)	63.4 (63.1–63.6)
Charlson comorbidity index†	3 (0–6)	3 (0–7)	2 (0–8)
Gender (number)			
Male (%)	57 (35.0%)	133 (29.8%)	4172 (43.9%)
Female (%)	106 (65.0%)	313 (70.2%)	5341 (56.1%)
Procedure (number)			
Primary THA	33	147	4286
Revision THA	7	28	759
Hemiarthroplasty	0	5	69
Primary TKA	113	242	3919
Revision TKA	10	26	500
Body mass index*	32.0 (27.8–36.1)	30.6 (27.7–33.5)	30.1 (29.5–30.6)

* Values are expressed as mean, with 95% confidence interval in parentheses; †values are expressed as median, with range in parentheses; PE = pulmonary embolism.

Table 3. Variables between admissions with INR ≥ 2 and INR < 2

Variable	INR ≥ 2	INR < 2
Number	950	9172
Age (years)*	68.6 (67.9–69.4)	63.2 (62.9–63.4)
Charlson comorbidity index†	3 (0–8)	2 (0–8)
Gender (number)		
Male (%)	287 (30.2%)	4075 (44.4%)
Female (%)	663 (69.8%)	5097 (55.6%)
Procedure (number)		
Primary THA	321	4145
Revision THA	103	691
Hemiarthroplasty	24	50
Primary TKA	447	3827
Revision TKA	59	477
Body mass index*	28.6 (26.3–30.9)	30.3 (28.0–32.6)

* Values are expressed as mean, with 95% confidence interval in parentheses; †values are expressed as median, with range in parentheses; INR = international normalized ratio.

procedures (194 primary hips, 428 primary knees, 38 revision hips, 42 revision knees, and eight hemiarthroplasties) in 621 admissions. After workup for PE, 163 of the 10,122 admissions (1.6%) were positive for PE and were included in the PE-positive subgroup. Among the 609 admissions that received workup for PE, the majority (41.2%; 251 of 609) were scanned on POD 2 (Fig. 1). We assessed their daily INR values to identify any variations in their INR relative to the remaining admissions who were negative for PE and the entire arthroplasty cohort. We utilized the

Charlson comorbidity index [3], as modified by Deyo et al. [5], to assess comorbidities. This index is adjusted for age. Variables describing differences between PE-positive and PE-negative admissions are reported (Table 2). Furthermore, the same variables are reported for admissions with a postoperative INR greater than 2 versus INR less than 2 (Table 3).

To analyze the anticoagulation (INR) levels and confounding variables of the three cohorts, we utilized a series of statistical tests. First, the data were tested for normality using the Kolmogorov-Smirnov test. Normal continuous data were assessed using Student's t test, and confidence intervals provided clinical significance of variations. Nonnormal continuous data were assessed with the Mann-Whitney test, and 25th and 75th percentiles were used to represent the variation of data. Chi square analysis was used for categorical data. All data analysis was performed using SPSS® 16.0 (SPSS, Inc, Chicago, IL).

Results

Female gender ($p = 0.04$), body mass index ($p < 0.001$), THA ($p < 0.001$), increasing age ($p < 0.001$), and an increase in age-adjusted Charlson comorbidity index ($p < 0.0001$) were risk factors for developing PE (Table 2). Type of arthroplasty (revision versus primary) did not predict development of PE. When we plotted the percentage of admissions who had an INR greater than 2 in the PE-positive and PE-negative groups against the day of scan, including the 5 days before and after the scan, we observed

Fig. 3 A graph shows percentage of patients with INR greater than 2 by day of scan (lines; right axis) and median INR related to the day of scan (columns; left axis). Day of scan is 0, the 5 days before the scan are in reverse chronological order as -1 through -5, and the 5 days after the scan are Days 1 through 5. Median values between PE-positive and PE-negative PE patients are shown. On the day of scan, there was no difference ($p = 0.63$) between INR values. PE-positive patients had higher ($p = 0.009$, $p < 0.001$, and $p < 0.001$, respectively) INR values 3, 4, and 5 days after the scan.

no differences ($p = 0.55$) on the day of or before the workup between the confirmed PE-positive group (9.2%) and confirmed PE-negative group (7.9%). On the first day after the scan, the PE-negative group tended to have a higher percentage of admissions ($p = 0.11$) with an INR greater than 2. At 3, 4, and 5 days after the scan, there was a higher percentage ($p = 0.009$, 0.0001 , and 0.0002 , respectively) of PE-positive admissions with an INR greater than 2 (Fig. 3). Admissions with confirmed PE had a higher ($p = 0.02$) INR on POD 5 than the confirmed PE-negative admissions. When aggregating confirmed PE-negative admissions with admissions who were not worked up, PE-positive admissions had a higher INR on POD 2, 3, 4, and 5 ($p = 0.012$, $p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively).

Discussion

PE is a dreaded and life-threatening complication that can develop after TJA, with an incidence of 1.1% to 1.82% after TKA and 0.51 to 0.9% after THA [12, 18, 19]. The 2008 updated ACCP guidelines regarding postoperative PE prophylaxis in musculoskeletal patients [10] endorsed the use of LMWH, fondaparinux, or vitamin K antagonists to achieve an INR between 2 and 3. These guidelines, however, assume DVT is a proxy for PE. Even more, the ACCP guidelines do not consider the risk of severe bleeding associated with anticoagulation, which ranges from 5.0% to 5.6% after TKA and 0.6% to 1.6% after THA [8, 9, 17], as well as the risk for minor bleeding complications after

TKA and THA (21%–28% and 4.6%–13.5%, respectively). Safety and low risk of complications with the use of low-dose warfarin (ie, aiming for an INR < 2) for preventing PE has been demonstrated [1]. We therefore asked whether an INR level of greater than 2, as dictated by the ACCP guidelines, after TJA is protective against PE.

This study is limited by a number of issues. First, while the relatively large size of patients undergoing evaluation for PE adds to its strength, some patients in this study may have received workup for PE after discharge from the hospital, which was not disclosed to their treating surgeon. Second, due to the fact that our observational window was focused on in-hospital data only, incidence of PE may be skewed, and PE occurring up to 3 or more months post-operatively was not captured. Third, due to the retrospective nature of the study, it is not possible to provide an accurate number (although small) of those patients who deviated from the main anticoagulation protocol (ie, patients with previous PE or polycythemia vera and those in a hypercoagulable state) who received an alternate anticoagulation protocol. Fourth, there are no set standards in defining PE and it is plausible some of the emboli seen on lung scans (MDCT) were fat emboli that could not be distinguished from venous emboli. Fifth, not all patients in this study had pulmonary angiography, which is considered the gold standard for diagnosis of PE. Due to the invasive nature of the test and the costs involved, pulmonary angiography is reserved for only a limited number of patients. Furthermore, not all patients included in this analysis underwent workup for PE. This led us to separate the cohort into three groups (PE-positive, PE-negative, and not

scanned). While we make the assumption that asymptomatic patients were PE-negative, this cannot be truly confirmed without invasive workup. Sixth, this study only evaluated the efficacy of an INR target (< 2) set at our institution. These results do not exclude the possibility that a lower INR target would be as efficacious at preventing PE. Seventh, the incidence of PE was low, thus limiting the power of the study to observe some predictive correlations with the possibility of a Type II error. This would non-likely be the case with a single-institution study since the total number of patients in the pool (9112) was relatively large. Finally, we did not assess the incidence of minor or major bleeding since our sole purpose was to determine the protective value of an INR greater than 2 for PE. A number of studies, however, show a relationship between INR and bleeding [8, 9, 17].

This study highlights some important findings. First, we observed a low incidence of PE (1.6%), comparable to those reported in the literature [14, 19] using low-dose warfarin, with no fatal PE during the study period. Second, there is no correlation between the level of INR and the development of PE. It appears PE could develop in any patient, including those with an INR greater than 2. These findings raise the possibility that either INR fails to measure the efficacy of warfarin as an anticoagulant or that prophylactic anticoagulation has no effect on the incidence of PE. A study (130,000 patients) demonstrated the incidence of PE among patients without anticoagulation prophylaxis (0.12%) is the same as those receiving it (0.095%) [13]. Although there is a division among orthopaedic surgeons regarding the most effective modality, they agree some form of venous thromboembolism prophylaxis is warranted. Some believe improvements in surgical and anesthesia care for patients undergoing TJA have made administration of chemical anticoagulation unnecessary [2].

Orthopaedic surgeons consistently take an active role in preventing PE; however, there are key differences between the manner that they and medical physicians approach this complication. First, they observe 8.9% to 25.6% of patients undergoing TJA develop DVT, while only 0.5% to 2.0% developed PE [14, 19]. For this reason, the AAOS

recommends treating DVT and PE as separate entities. Second, they are committed to minimizing bleeding complications in their surgical patients; these can be as devastating to patients as PE [15]. A study comparing low-dose warfarin with a target INR 1.5 to 2 to a historical control group with a target INR 2 to 3 found no difference in the incidence of DVT, PE, or death [4, 7]. Expectedly though, a higher incidence of bleeding complications occurs in the higher-target INR group. Major bleeding complications can be a foundation for infection, wound-healing problems, functional disability, and prosthetic loosening [7]. All of these consequences can lead to reoperation and increase in morbidity and mortality. Third, pneumatic compression boots and aspirin, along with regional anesthesia, are suggested as being noninferior to chemoprophylactic anticoagulants at preventing PE without the increased bleeding complications [6]. Interestingly, potent anticoagulants such as warfarin and LMWH are associated with increased all-cause mortality rates, including PE, when compared to pneumatic compression boots and aspirin [20]. It is from this point of view that the AAOS created the guidelines stating patients at a standard risk of both PE and bleeding can be given aspirin, LMWH, synthetic pentasaccharides, or warfarin to reach an INR goal of 2 or lower [11]. A previous prospective study from this institution that involved performing preoperative and postoperative VQ scans in a consecutive series of patients undergoing TJA found low-dose warfarin (with an INR goal < 2) is effective at minimizing development of PE, with a low (2.4%) bleeding complication [1]. Based on these findings, we have used low-dose warfarin as a prophylaxis for prevention of PE in our patients over the last two decades.

The most pertinent finding of this study is that an INR greater than 2 does not appear to protect against PE. Thus, implementing the recommendations of the ACCP [10] in aiming for an INR greater than 2 may not protect these patients against PE, while exposing them to the undue risk of bleeding and all untoward consequences that may ensue [8, 9]. Despite the limitations, we believe our results and those in the literature cast doubt on the belief that administration of aggressive anticoagulation can and does protect patients against development of PE.

Appendix 1

Algorithm for Pulse Oximetry.

Routine pulse oximetry only for patients given Depodur and when clinically indicated (i.e. morbid obesity, sleep apnea, respiratory disease, patient requiring high dose opioids).

RR = Respiratory rate;
HR = Heart rate;
EKG = Echocardiogram;
CXR = Chest X-Ray;
Pox = Pulse oximetry reading; PE = Pulmonary embolism.

Management of a patient diagnosed with PE

- In the first week after surgery, the diagnosis of PE must be clear (based on unambiguous clinical signs or a positive diagnostic test) before treatment can be initiated.
 - a. The patient is to be started on a Heparin Drip or have a retrievable IVC filter placed based on the Medical Consultant's opinion.
 - b. If a retrievable IVC filter is placed, then the new goal INR will be between 2-3.
 - c. If a Heparin gtt is started then:
 - i. NO HEPARIN BOLUS
 - ii. aPTT between 60-90
 - iii. New goal INR of 2-3

References

1. Balderston RA, Graham TS, Booth RE Jr, Rothman RH. The prevention of pulmonary embolism in total hip arthroplasty: evaluation of low-dose warfarin therapy. *J Arthroplasty*. 1989;4: 217-221.
2. Callaghan JJ, Dorr LD, Engh GA, Hanssen AD, Healy WL, Lachiewicz PF, Lonner JH, Lotke PA, Ranawat CS, Ritter MA, Salvati EA, Sculco TP, Thornhill TS. Prophylaxis for thromboembolic disease: recommendations from the American College of Chest Physicians—are they appropriate for orthopaedic surgery? *J Arthroplasty*. 2005;20:273-274.

3. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373–383.
4. Clark NP, Witt DM, Delate T, Trapp M, Garcia D, Ageno W, Hylek EM, Crowther MA. Thromboembolic consequences of subtherapeutic anticoagulation in patients stabilized on warfarin therapy: the low INR study. *Pharmacotherapy.* 2008;28:960–967.
5. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45:613–619.
6. Dorr LD, Gendelman V, Maheshwari AV, Boutary M, Wan Z, Long WT. Multimodal thromboprophylaxis for total hip and knee arthroplasty based on risk assessment. *J Bone Joint Surg Am.* 2007;89:2648–2657.
7. Enyart JJ, Jones RJ. Low-dose warfarin for prevention of symptomatic thromboembolism after orthopedic surgery. *Ann Pharmacother.* 2005;39:1002–1007.
8. Fitzgerald RH Jr, Spiro TE, Trowbridge AA, Gardiner GA Jr, Whitsett TL, O'Connell MB, Ohar JA, Young TR. Prevention of venous thromboembolic disease following primary total knee arthroplasty: a randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. *J Bone Joint Surg Am.* 2001;83:900–906.
9. Freedman KB, Brookenthal KR, Fitzgerald RH Jr, Williams S, Lonner JH. A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. *J Bone Joint Surg Am.* 2000;82:929–938.
10. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133:381S–453S.
11. Johanson NA, Lachiewicz PF, Lieberman JR, Lotke PA, Parvizi J, Pellegrini V, Stringer TA, Tornetta P 3rd, Haralson RH 3rd, Watters WC 3rd. American Academy of Orthopaedic Surgeons Clinical Practice Guideline on prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. *J Bone Joint Surg Am.* 2009;91:1756–1757.
12. 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;96:1140–1146.
13. Murray DW, Britton AR, Bulstrode CJ. Thromboprophylaxis and death after total hip replacement. *J Bone Joint Surg Br.* 1996;78:863–870.
14. O'Reilly RF, Burgess IA, Zicat B. The prevalence of venous thromboembolism after hip and knee replacement surgery. *Med J Aust.* 2005;182:154–159.
15. Parvizi J, Azzam K, Rothman RH. Deep venous thrombosis prophylaxis for total joint arthroplasty: American Academy of Orthopaedic Surgeons guidelines. *J Arthroplasty.* 2008;23:2–5.
16. Parvizi J, Jacovides CL, Bican O, Purtill JJ, Sharkey PF, Hozack WJ, Rothman RH. Is deep vein thrombosis a good proxy for pulmonary embolus? *J Arthroplasty.* 2010;25:138–144.
17. Pellegrini VD Jr, Sharrock NE, Paiement GD, Morris R, Warwick DJ. Venous thromboembolic disease after total hip and knee arthroplasty: current perspectives in a regulated environment. *Instr Course Lect.* 2008;57:637–661.
18. Phillips CB, Barrett JA, Losina E, Mahomed NN, Lingard EA, Guadagnoli E, Baron JA, Harris WH, Poss R, Katz JN. Incidence rates of dislocation, pulmonary embolism, and deep infection during the first six months after elective total hip replacement. *J Bone Joint Surg Am.* 2003;85:20–26.
19. Pulido L, Parvizi J, Macgibeny M, Sharkey PF, Purtill JJ, Rothman RH, Hozack WJ. In hospital complications after total joint arthroplasty. *J Arthroplasty.* 2008;23:139–145.
20. Sharrock NE, Gonzalez Della Valle A, Go G, Lyman S, Salvati EA. Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty. *Clin Orthop Relat Res.* 2008;466:714–721.