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Timing of Symptomatic Pulmonary Embolism with Warfarin Following Arthroplasty

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ABSTRACT

The purpose is to determine the incidence and timing of pulmonary embolism for patients receiving warfarin for thrombo-prophylaxis following total joint arthroplasty (TJA). Current guidelines for duration of prophylaxis are nonspecific. Chemical prophylaxis carries the risk of bleeding and associated periprosthetic joint infection. We retrospectively studied 26,415 primary and revision TJA cases performed at our institution between 2000 and 2010. The overall 90-day rate of symptomatic PE was 1.07%. Fatal PE rate was 0.02%. Out of 283 documented symptomatic PE cases, 81% occurred within three postoperative days, 89% within one postoperative week, and 94% within two postoperative weeks. The risk of symptomatic PE appears to be highest during the first week after TJA. Efforts must be made to minimize risk during this period.

The elevated risk of postoperative venous thromboembolism (VTE) has been clearly established in total joint arthroplasty (TJA) patients. This risk is reported to be as high as 20% after TJA when patients do not receive VTE prophylaxis [1]. For this reason, prophylactic measures have been introduced to minimize the risk of postoperative VTE. These include the intraoperative administration of heparin, the minimization of operative time, the use of regional anesthesia, the use of lower extremity sequential compression devices, the early mobilization of patients, and the use of pharmacologic anticoagulants [2–4]. Despite the success of these measures in reducing the incidence of postoperative VTE to approximately 1%, VTE prophylaxis is not without risk [3,5]. Specifically, studies have shown that the administration of aggressive anticoagulation agents such as low molecular weight heparin (LMWH) or warfarin may dramatically increase the risk of major and minor bleeding complications, including hematoma formation and prolonged wound drainage [3,5,6]. The latter is not without consequence since it may lead to possible re-operation in the case of hematoma formation as well as an increased risk of infection in cases of prolonged wound drainage [7].

Because of this balance of benefit and risk, significant controversy exists as to the most effective means of pharmacologic prophylaxis in TJA. Both the American College of Chest Physicians (ACCP) and the American Academy of Orthopaedic Surgeons (AAOS) have published guidelines regarding pharmacologic anticoagulation prophylaxis in TJA patients [8,9]. These guidelines present recommendations both with regard to the choice of pharmacologic agent as well as to the length of time postoperatively during which these agents need to be administered. Whereas the recommendations as to the choice of pharmacologic agent have generated significant debate in the literature, less data has been published regarding the duration of prophylaxis. Despite this discrepancy, these concerns are not mutually exclusive. Regardless of the specific pharmacologic agent employed, the risk of its use can be decreased by minimizing its administration to the shortest time postoperatively that is necessary to provide a therapeutic benefit. Studies have found that the vast majority of cases of pulmonary embolism (PE) occur early in the postoperative course, suggesting that extended prophylaxis may not be warranted [10,11]. In 2006, Bjørnarå et al. reported that pulmonary emboli occurred at a median of 12 days following major joint arthroplasty [10]. In 2007, Hope et al. found that the timing of PE varied significantly with the age of the patients: in patients younger than the age of 40 years, the majority of PEs occurred around day 3; however, in patients between the ages of 40 to 60 years, PEs tended to occur later, around day 11 [11]. Current ACCP guidelines recommend pharmacologic anticoagulation for TKA and THA for a minimum of 10 to 14 days, and up to 35 days [12]. The current AAOS guidelines for the duration of pharmacologic prophylaxis are less specific with a range of two to six weeks [9]. Given these non-specific duration recommendations and lack of consensus, this study was conceived to determine the incidence and timing of pulmonary embolism after TJA in

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Table 1
Demographics of Patients With and Without PE.

Variable		No PE (N = 26132)	PE (N = 283)	P-Value
Age		64.0 ± 12.2	68.8 ± 10.3	<0.001
BMI		30.1 ± 6.7	31.6 ± 6.3	<0.001
Gender	Male	11268 (43.1%)	98 (34.6%)	0.004
	Female	14864 (56.9%)	185 (65.4%)	
Procedure	Primary Hip	11975 (45.8%)	50 (17.7%)	<0.001
	Primary Knee	10657 (40.8%)	198 (70.0%)	
	Revision Hip	2178 (8.3%)	16 (5.6%)	
	Revision Knee	1322 (5.1%)	19 (6.7%)	
Procedure	<40	759 (2.9%)	3 (1.1%)	<0.001
	40-49	2522 (9.7%)	6 (2.1%)	
	50-59	6434 (24.6%)	45 (16.0%)	
	60-69	7721 (29.5%)	87 (30.6%)	
	70-79	6242 (23.9%)	101 (35.9%)	
	80-89	2344 (9.0%)	40 (13.9%)	
	90-99	116 (0.4%)	1 (0.4%)	
Anticoagulation	Warfarin	24290 (93.0%)	277 (97.9%)	0.892
	Aspirin	1820 (7.0%)	4 (1.4%)	
	Heparin + Derivatives	22 (0.1%)	2 (0.7%)	

order to provide a basis for future studies to clarify the appropriate duration of postoperative VTE prophylaxis.

Materials and Methods

Following institutional review board approval, we identified and retrospectively reviewed the medical records of 26,415 consecutive patients who underwent primary and revision TJA at our institution between January 2000 and December 2010. Symptomatic pulmonary emboli that occurred within 90 days of total joint replacement were documented. All patients in the cohort were identified in our electronic medical record (EMR) system and a search tool was used to extract discrete and non-discrete data from different locations within the EMR, including post-hospital discharge data.

Patients were not routinely scanned for PE. Clinical work-up for PE was based on an established institutional protocol that endorses investigation for PE when clinical symptoms such as tachypnea, new onset arrhythmia, dyspnea, tachycardia and chest pain exist [13]. If any of these symptoms were present, the patient was assessed with pulse oximetry, vital signs, an electrocardiogram (ECG), a chest x-ray (CXR) and a set of cardiac enzymes. Patients with an oxygen saturation of less than 90% were placed on 2 L oxygen by nasal cannula for 10 minutes. If the hypoxia persisted, a multi-detector computed tomography (MDCT) of the chest, or a ventilation-perfusion (VQ) scan was performed.

Patients received 1000 IU of intravenous (IV) heparin intraoperatively at the time of hip dislocation during THA or before tourniquet inflation for TKA. Postoperatively, 24,567 of the total 26,415 cases were anticoagulated with warfarin beginning the evening of the surgery. Warfarin prophylaxis continued for a period of six weeks postoperatively with a targeted international normalized ratio (INR) of 1.5 to 2.0. The consulting medical physician and more recently, a specialized clinic monitored bi-weekly INR levels in patients receiving warfarin and adjusted doses accordingly. Another 1,824 patients were treated with a modified aspirin protocol (single dose of low dose warfarin the night of surgery, followed by 325 mg aspirin twice daily for six weeks postoperatively). This protocol was utilized during the time period of this study to comply with the Surgical Care Improvement Project (SCIP) guidelines, but has since been changed to remove the dose of warfarin following the recent addition of aspirin to acceptable forms of VTE prophylaxis in SCIP guidelines. The remaining 24 patients received subcutaneous heparin or heparin derivatives. Patients were treated with a standard postoperative protocol with regard to early mobilization by postoperative day 1.

Descriptive statistics were utilized to report the incidence of PE in TJA and the time to occurrence of PE after surgery. Log rank tests were used to compare the timing of PE between THA and TKA groups. Additionally, Cox regression was used to determine the association of age, BMI, procedure, postoperative prophylaxis, CCI, diabetes, heart disease and atrial fibrillation with the timing of PE.

Results

Of the 26,391 consecutive primary and revision TJA procedures performed, 12,025 were primary THA, 2,194 were revision THA, 10,855 were primary TKA, and 1,341 were revision TKA. Symptomatic PE was confirmed by MDCT or VQ scan in 283 patients (1.07%); 185 (66%) of these patients were women and 98 (34%) were men.

The incidence of symptomatic PE in patients undergoing knee procedures was 1.77% (217/12,196). The incidence of symptomatic PE in patients undergoing hip procedures was 0.46% (66/14,219). The average age of patients who developed a PE was 68.8 years (range: 19 to 92 years) compared with an average age of 64.0 years (range: 11 to 99 years) for patients without PE. Average body mass index (BMI) was also slightly higher in the PE group at 31.6 Kg/m^2 (range: 10.2 to 77.5 Kg/m^2) compared to 30.1 Kg/m^2 (range: 10.2 to 112.5 Kg/m^2) in those without PE (Table 1). Incidence of fatal PE was 0.02% (4 of 26,415). One case of fatal PE occurred at postoperative day 1, two cases occurred on day 11, and one case occurred on day 48.

Our cohort of 26,415 cases included more women than men (56.9% and 43.1%, respectively). Women were noted to exhibit a higher tendency to develop PE following TJA (1.21%) when compared to men (0.84%). There was also a higher incidence of PE with increasing age. The highest incidence of PE was in the 71–80 year old group (1.61%) and the lowest was in the 41–50 year old group (0.36%) (Table 1).

The median time at which PE occurred was 2 days postoperatively (range: 1–87 days). Of the 283 documented PE cases, 81% (228/283) occurred within the first 3 postoperative days, 89% (251/283) occurred within the first postoperative week, and 94% (264/283) occurred by the end of the second postoperative week (Fig. 1). There was no statistical difference in PE timing between men and women at day 3 (81% and 81% respectively), day 7 (91% and 88% respectively) and day 14 (93% and 94% respectively). In patients receiving aspirin prophylaxis, PEs occurred on postoperative days 3, 4, 6, and 11. In patients receiving heparin based prophylaxis, PEs occurred on postoperative days 2 and 43.

Factors that showed statistical significance on multivariate analysis in association with later timing of PE occurrence included revision TJA (Fig. 2; $p < 0.001$), Charlson Comorbidity Index (CCI) greater than or equal to 3 (Fig. 3; $p < 0.001$), and a difference between patients with or without atrial fibrillation (Fig. 4; $p < 0.001$). Age, BMI, diabetes, and heart disease did not have a statistically significant effect upon the timing of PE.

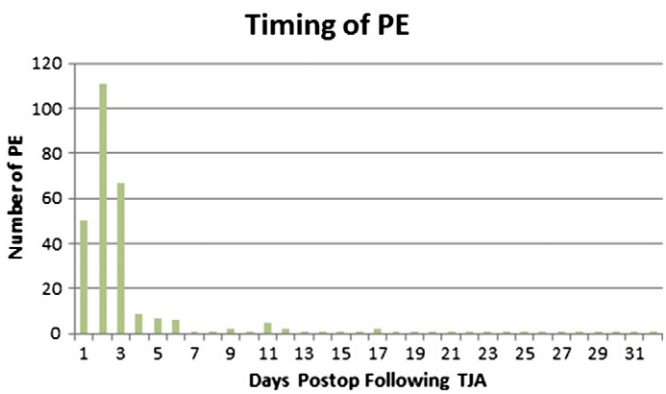

Fig. 1. Timing of PE.