

## ORIGINAL RESEARCH

# Mechanical and Suboptimal Pharmacologic Prophylaxis and Delayed Mobilization but Not Morbid Obesity Are Associated With Venous Thromboembolism After Total Knee Arthroplasty: A Case-Control Study

Banafsheh Sadeghi, MD, PhD<sup>1\*</sup>, Patrick S. Romano, MD, MPH<sup>1</sup>, Gregory Maynard, MD, MS<sup>2</sup>, Amy L. Strater, MPH, MBA<sup>3</sup>, Laurie Hensley, MHA<sup>3</sup>, Julie Cerese, RN, MSN<sup>3</sup>, Richard H. White, MD, FACP<sup>1</sup>

<sup>1</sup>School of Medicine, Department of Internal Medicine, Division of General Medicine; <sup>2</sup>School of Medicine, Division of Hospital Medicine; <sup>3</sup>University HealthSystem Consortium, Chicago, Illinois.

**BACKGROUND:** The FDA-approved dose of low-molecular-weight heparin (LMWH) may not provide adequate thromboprophylaxis in morbidly obese patients after total knee arthroplasty (TKA). Suboptimal dosing, delayed initiation, and overreliance on mechanical methods may also limit the effectiveness of thromboprophylaxis.

**OBJECTIVE:** We explored the associations between the type of thromboprophylaxis, obesity, time of mobilization, and undergoing bilateral TKA on development of symptomatic venous thromboembolism (VTE) after TKA.

**DESIGN/SETTING/PATIENTS:** This was a case-control study of patients undergoing TKA in 15 teaching hospitals between October 2008 and March 2010. Cases were screened using the Agency for Healthcare Research and Quality's Patient Safety Indicator 12 and had objectively documented acute VTE within 9 days of surgery; controls were randomly selected from the same hospital. Multivariable logistic regression was used to analyze risk factors for postoperative VTE, adjusted for age and gender.

**RESULTS:** Among 130 cases with and 463 controls without acute VTE, body mass index (BMI) ranged from 17 to 61 (median = 34). Thromboprophylaxis was LMWH in 284 (48%), warfarin in 189 (32%), both in 55 (10%), and mechanical prophylaxis alone in 120 (20%). Overall, 77% ambulated on day 1 or 2 after surgery. Factors significantly associated with VTE were bilateral simultaneous TKA (odds ratio [OR] = 4.2; 95% confidence interval [CI]: 1.9–9.1), receipt of FDA-approved pharmacological prophylaxis (OR = 0.5; 95% CI: 0.3–0.8), and ambulation by postoperative day 2 (OR = 0.3; 95% CI: 0.1–0.9). Obesity was neither a significant confounder nor a modifier of these effects.

**CONCLUSIONS:** Severe obesity was not a significant independent predictor for VTE and did not modify the beneficial effect of FDA-approved pharmacological thromboprophylaxis. Bilateral TKA and failure to ambulate by the second day after surgery were significant risk factors. *Journal of Hospital Medicine* 2012;7:665–671. © 2012 Society of Hospital Medicine

Symptomatic venous thromboembolism (VTE) is a common complication following total knee arthroplasty (TKA).<sup>1–7</sup> In fact, the high incidence of thrombosis after TKA has made this operation the principal condition used to study the efficacy of new anticoagulants, and it is a principal target of quality improvement oversight and measurement.<sup>8</sup> The Agency for Healthcare Research and Quality (AHRQ) has developed a Patient Safety Indicator (PSI-12) to assist hospitals, payers, and other stakeholders identify patients who experienced VTE after major surgery. The Centers for Medicare \* Medicaid Services has deemed that because a VTE that develops after TKA is

“potentially preventable,” it withholds the additional payment for this complication.<sup>9</sup>

Prior the introduction of new oral anticoagulants, most guidelines from North America recommended the use of postoperative low-molecular-weight heparin (LMWH), fondaparinux, or warfarin for at least 10 days after TKA.<sup>2,10</sup> However, there is some ongoing controversy about whether pharmacological prophylaxis is necessary after total joint replacement surgery, and whether it is effective in preventing pulmonary embolism.<sup>11–14</sup> In addition, there is controversy regarding the effectiveness of mechanical prophylaxis alone as a means of preventing VTE.<sup>2,4,14,15</sup>

Pharmacological thromboprophylaxis using LMWH or fondaparinux calls for using a fixed-dose that does not depend on the patient's weight or body mass index (BMI). This stands in sharp contrast to the consistent recommendation to use weight-based dosing of LMWH/fondaparinux in patients who have acute VTE.<sup>16</sup> The absence of any adjustment in the dose of thromboprophylaxis based on weight may be particularly important after TKA because the majority of these patients are obese or extremely obese,<sup>17–19</sup> making the dose of LMWH/fondaparinux potentially insufficient. It is noteworthy that surgeons who perform bariatric

\*Address for correspondence and reprint requests: Banafsheh Sadeghi, MD, PhD, Department of Internal Medicine, University of California Davis, 4150 V St, PSSB Suite 2400, Sacramento, CA 95817; Telephone: 916-734-7005; FAX (916) 734-2732; E-mail: bsadeghi@ucdavis.edu

Additional Supporting Information may be found in the online version of this article.

Received: January 26, 2012; Revised: May 5, 2012 and 10 June 2012; Accepted: June 14, 2012

2012 Society of Hospital Medicine DOI 10.1002/jhm.1962

Published online in Wiley Online Library (Wileyonlinelibrary.com).

surgery currently recommend a higher dose of LMWH, usually 40 mg of enoxaparin every 12 hours.<sup>20,21</sup>

We conducted this case-control study to address 3 hypotheses. First, we hypothesized that use of standard pharmacologic thromboprophylaxis drugs is associated with a lower risk of acute VTE compared with mechanical prophylaxis alone. Second, we hypothesized that among patients given LMWH/fondaparinux, excessive obesity (BMI >35) is associated with a higher risk of developing VTE. Third, based on prior studies that identified immobilization as a risk factor for VTE, we hypothesized that delayed ambulation after TKA is associated with higher risk for VTE.

## METHODS

### Study Design

The University of California Davis, in partnership with the University HealthSystem Consortium (UHC), conducted a retrospective case-control study of risk factors for acute symptomatic VTE within 90 days following TKA. Fifteen volunteer hospitals nationwide agreed to abstract medical records of up to 40 sampled cases or controls. Inclusion criteria were admission between October 1, 2008 and March 31, 2010; presence of a principal *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) procedure code of 81.54 or 81.55; and age 40 years or more. Patients with a pregnancy-related principal diagnosis (Major Diagnostic Category 14) or inferior vena cava interruption on or before the date of the first operating room procedure were excluded.

Cases were defined as having: a) one or more secondary diagnosis codes for acute VTE, as defined by AHRQ PSI-12, version 4.1 (415.11, 415.19, 451.11, 451.19, 451.2, 451.81, 451.9, 453.40–453.42, 453.8, 453.9), coupled with a “present-on-admission” flag of “no” (POA = N); or b) were readmitted with a principal diagnosis of VTE (same codes) within 90 days of the date of surgery. A probability sample of VTE cases (up to a maximum of 20), and 20 eligible TKA patients who did not develop acute VTE during the index hospitalization or within 90 days of surgery, were randomly selected for abstraction. Only 1 case flagged by the PSI algorithm was excluded because VTE could not be confirmed by abstraction.

### Chart Abstraction

A chart abstraction tool was constructed and personnel at each site were taught how to obtain the desired information. Data elements included age, gender, height and weight, and type of TKA (unilateral, bilateral, or revision). BMI was calculated and categorized as severely obese (World Health Organization [WHO] class II or more, BMI  $\geq 35$ ) versus not severely obese (BMI <35), and as morbidly obese (WHO class III, BMI >40) or not morbidly obese (<40). Information about use of pharmacologic (LMWH, fondaparinux,

or warfarin) and mechanical thromboprophylaxis was collected and classified as follows. First, the type of prophylaxis was categorized as: (1) LMWH (enoxaparin, dalteparin)/fondaparinux with or without mechanical prophylaxis (pneumatic compression devices, graduated compression stockings, or foot pump); (2) warfarin alone, with or without mechanical prophylaxis; (3) LMWH/fondaparinux and warfarin with or without mechanical pharmacologic prophylaxis; (4) mechanical prophylaxis alone (without any pharmacological prophylaxis but with or without aspirin); and (5) aspirin only, without any other pharmacologic or mechanical prophylaxis. Second, patients who received LMWH, fondaparinux, or warfarin pharmacologic prophylaxis were further classified as receiving “FDA-approved pharmacologic prophylaxis” or “other prophylaxis.” The criteria for FDA-approved pharmacologic prophylaxis were receipt of the recommended dose at the recommended starting time (per package insert), either before or after surgery, and continued administration until at least the day of hospital discharge, consistent with the 2008 American College of Chest Physicians (ACCP) guidelines for prevention of VTE in orthopedic patients.<sup>2</sup> For warfarin, FDA-approved dosing required a starting dose of 2–10 mg per day beginning either preoperatively or on the evening after surgery, and given daily thereafter, targeting an international normalized ratio (INR) of 2.0–3.0. No patient received aspirin alone for prophylaxis. In the analysis of risk factors for VTE, the effect of FDA-approved pharmacologic prophylaxis was compared against other pharmacologic prophylaxis or mechanical prophylaxis alone. Time of ambulation was defined as “early” if it occurred on or before the second postoperative day, “late” if it occurred after the second postoperative day, or “none” if the patient did not ambulate before discharge.

### Outcomes

The principal outcome was validated symptomatic objectively confirmed VTE, manifested as either pulmonary embolism (PE) or lower extremity deep vein thrombosis (DVT) or both. Patients who were diagnosed with VTE on the day of surgery or the day after surgery were not included in the principal analysis, reasoning that postoperative prophylaxis started 12–24 hours after surgery is unlikely to prevent early VTE events. In a secondary sensitivity analysis, the effect of including these early postoperative VTE events on the estimated risk was determined.

### Statistical Analysis

For continuous variables, bivariate comparisons were made with the use of Student *t* test. For categorical variables, we applied the chi-square test and estimated unadjusted odds ratios (ORs) and Cornfield’s 95% confidence intervals (CIs). We specifically analyzed whether gender, age, type of TKA, race/ethnicity,

primary payer, severe or morbid obesity, postoperative ambulation, personal or family history of VTE, and comorbid conditions were associated with the development of any VTE, DVT, or PE.

Multivariable models were developed using logistic regression. In addition to age and gender, other terms included receipt of FDA-approved pharmacologic prophylaxis, degree of obesity (severe if BMI >35, morbid if BMI >40), type of TKA (unilateral vs bilateral) and early versus late versus no ambulation. A patient was considered receiving FDA-approved pharmacologic prophylaxis if the first postoperative dose and the last postoperative dose before discharge of LMWH, fondaparinux, or warfarin were given based on the recommended time and dose. Two-way interactions between FDA-approved pharmacologic prophylaxis and extent of obesity were tested, as well as interactions between LMWH/fondaparinux prophylaxis and extent of obesity. We adjusted all of the point estimates and confidence intervals for the correlation of data within each hospital by using the STRATA option in SAS; statistical analyses were performed using the SAS-PC program, SAS 9.2 (SAS Institute, Inc, Cary, NC).

## RESULTS

A total of 593 TKA records were abstracted by the 15 participating hospitals. All patients underwent TKA on the day of admission or the day after admission. A total of 16 cases (12 PE and 4 DVT) were diagnosed with VTE on the day of surgery, or the day after surgery, and were deemed nonpreventable in the multivariable analysis. There were 114 additional cases with VTE (44 PE, 68 DVT, 2 both) diagnosed 2 or more days after surgery, and 463 controls that had no VTE diagnosed by the index hospital within 90 days after surgery.

In bivariate analyses (Table 1), the mean age of cases was significantly greater for controls ( $65.5 \pm 10.4$  vs  $63.5 \pm 10.4$ ,  $P < 0.05$ ). More cases underwent bilateral simultaneous TKA compared with controls (23% vs 7%,  $P < 0.001$ ). The mean BMI was marginally higher among VTE cases than among controls ( $34.6 \pm 8.0$  vs  $33.3 \pm 7.1$ ,  $P = 0.07$ ). Among cases with PE, a significantly greater percentage were morbidly obese than among controls (30% vs 16%,  $P$  value = 0.01), whereas there was not a difference for the DVT cases.

Fewer VTE cases began ambulation on or before the second postoperative day compared with controls (47% vs 73%,  $P < 0.001$ ). There was no difference in the number or types of comorbidities between cases and controls. All patients received at least 1 type of pharmacologic or mechanical prophylaxis within the first 24 hours after TKA. Although the difference was not statistically significant, controls had marginally higher odds of receiving FDA-approved pharmacologic prophylaxis than cases ( $P = 0.07$ ; Table 2). Table 3

presents the criterion that led to 242 cases not meeting the definition of FDA-approved pharmacologic prophylaxis definition. Administering a suboptimal dose was the most common reason. Also, about half of the patients received only mechanical prophylaxis.

In the primary multivariable analysis (Table 4), neither age, gender, nor obesity (defined as BMI >30, BMI >35, or BMI >40) was a significant predictor of VTE. Undergoing bilateral simultaneous TKA versus unilateral TKA was associated with higher risk of VTE (OR = 4.2; 95% CI: 1.90–9.10), whereas early ambulation on or before the second postoperative day versus later (OR = 0.30; 95% CI: 0.10–0.90). Receiving FDA-approved pharmacologic prophylaxis (right dose and time described in Table 4) versus any other prophylaxis regimen was adversely associated with VTE (OR = 0.50; 95% CI: 0.30–0.80,  $P = 0.01$ ). There was no significant effect of receipt of FDA-approved pharmacologic prophylaxis on being diagnosed with VTE among the cases that were severely or morbidly obese ( $P$  for interaction = 0.92). In a secondary analysis, the adjusted odds of being diagnosed with VTE were not significantly different for severely (OR = 0.9; CI 0.53–1.5) or morbidly obese (OR = 1.5; CI 0.80–2.80) patients.

In a sensitivity analysis, we did not find any significant changes in the results when the 12 cases that developed VTE on the day of, or day after, TKA were included.

## DISCUSSION

Venous thromboembolism is a frequent and potentially serious complication following TKA. In population-based studies that report the number of patients who develop symptomatic acute VTE, the incidence is approximately 2.0%–2.5%.<sup>3,22–24</sup> Thromboprophylaxis reduces the risk of developing asymptomatic VTE by more than 60%, and pharmacologic prophylaxis using LMWH, fondaparinux, or warfarin alone is recommended by the ACCP and other organizations, with use of mechanical pneumatic compression, low-dose unfractionated heparin, or aspirin as alternative options.<sup>25</sup> Nevertheless, because extremely obese patients are not commonly enrolled in clinical trials and because current guidelines do not recommend any adjustment in the dose of LMWH or fondaparinux based on weight, we hypothesized that LMWH/fondaparinux would be significantly less effective in severely or morbidly obese patients. We also hypothesized that pharmacologic prophylaxis would be superior to mechanical prophylaxis alone,<sup>26</sup> and that delayed ambulation after TKA would be associated with a higher risk of developing VTE.

Two widely cited clinical guidelines that pertain to prophylaxis of venous thromboembolism after total knee arthroplasty are the ACCP guidelines<sup>2</sup> and the American Academy of Orthopedic Surgeons (AAOS) guidelines.<sup>27</sup> Although we acknowledge that there are

**TABLE 1.** Results of Bivariate Analysis of Clinical and Demographic Variables in Relation to Case (VTE) or Control (no VTE) Status After TKA

Variable		VTE n = 130 (%)	No VTE n = 463 (%)	Total N = 593 (%)
Gender	Male	45 (34)	175 (38)	220 (37)
	Female	85	288	373
Age (y)*	Mean	65.5	63.5	63.9
	Standard deviation	10.4	10.4	10.5
LOS (d)*	Mean	6.1	3.4	4.0
	Standard deviation	4.7	1.5	2.8
Type of TKR†	Primary TKR-unilateral	100 (76)	425 (92)	525 (89)
	Primary TKR-bilateral	29 (23)	35 (7)	64 (11)
	Revision for mechanical problem	1 (1)	3 (1)	4 (1)
	African American	25 (19)	80 (17)	105 (18)
Race	Asian	4 (3)	8 (2)	12 (2)
	White	91 (70)	337 (73)	428 (72)
	Hispanic	7 (5)	28 (6)	35 (6)
	Unknown/others	5 (4)	18 (4)	23 (4)
Primary payer	Uninsured/self-pay	2 (1)	2 (<1)	4 (1)
	Medicaid/managed care	11 (8)	40 (7)	51 (9)
	Medicare/managed care	66 (52)	220 (47)	286 (48)
	Private	44 (34)	156 (34)	200 (34)
	US/state/local government	1 (1)	5 (1)	6 (1)
	Others/unknown	6 (4)	40 (8)	46 (8)
BMI	Mean	34.6	33.3	33.6
	Standard deviation	8.0	7.1	7.3
Obesity	BMI			
	≤30	51 (38)	172 (37)	223 (38)
	30 to <35	29 (22)	122 (26)	151 (25)
	35 to ≤40	21 (18)	95 (20)	116 (20)
	>40	29 (22)	74 (16)	103 (17)
Ambulation	Taking steps with or without walker (day 1 or 2 after surgery)	62 (47)	340 (73)	402 (77)
	Taking steps with or without walker (day 3 or more after surgery)	58 (45)	106 (23)	164 (28)
	Weight bearing only or no ambulation predischarge	10 (8)	17 (4)	27 (5)
No. of days from surgery to taking steps	Mean	2.0	1.3	1.45
	Standard deviation	2.3	0.7	1.4
Comorbidities/risk factors	Diabetes	30 (22)	99 (22)	129 (22)
	Hypertension	90 (70)	313 (67)	403 (68)
	History of malignancy	9 (8)	54 (11)	63 (11)
	Current neoplasm	4 (3)	9 (2)	13 (2)
	Documented history/risk of bleeding or hematoma	3 (2)	7 (2)	10 (2)
	History of any other surgery	1 (1)	1 (<1)	2 (<1)
	Baseline inability to ambulate without assistance from staff	0	3 (1)	3 (<1)
	Trauma, head trauma, new fractures	0	0	0
	Current use of oral contraceptive or system estrogen	0	8 (2)	8 (1)
	Past stroke/CVA with residual weakness	1 (1)	7 (2)	8 (1)
	Prior history of DVT	6 (5)	20 (4)	26 (4)
	Prior history of PE	2 (2)	11 (2)	13 (2)
	Family history of VTE	0	5 (1)	5 (1)
	Known thrombophilia	0	1 (<1)	1 (<1)
	None of the above	33 (25)	96 (21)	129 (22)

Abbreviations: BMI, body mass index; CVA, cerebrovascular accident; DVT, deep vein thrombosis; LOS, length of stay; PE, pulmonary embolism; TKA, total knee arthroplasty; TKR, total knee replacement; VTE, venous thromboembolism. \*P value between VTE and no VTE, <0.05. †P value between VTE and no VTE groups, <0.001.

differences in these and other guidelines, recommendations and quality measures,<sup>13,28,29</sup> the aim of the current study was not to evaluate or compare specific guidelines. We simply classified the thromboprophylaxis regimens into logical groups, the 2 most frequent being use of LMWH/fondaparinux (±mechanical) and mechanical prophylaxis alone, and then performed the case-control analysis. We followed FDA-approved labeling to assess whether

pharmacologic therapy was provided at the proper dose in the proper time period.

A principal finding of this study was that FDA-approved pharmacologic prophylaxis using LMWH, fondaparinux, or warfarin, was associated with significantly lower odds of developing VTE compared to all other prophylaxis regimens.

When the effect of FDA-approved pharmacologic prophylaxis was analyzed in severely or morbidly



**TABLE 2.** Pharmacological and Nonpharmacological Prophylaxis, and FDA-Approved Pharmacologic vs All Other Prophylaxis, in TKA Cases With Thromboembolism and TKA Controls Without Thromboembolism

Thromboprophylaxis	Thromboembolism	
	VTE = Yes n = 130 (%)	VTE = No n = 463 (%)
Pharmacologic prophylaxis		
LMWH/fondaparinux	61 (46)	223 (48)
Warfarin alone (no LMWH)*	44 (33)	145 (31)
None	25 (19)	95 (20)
Nonpharmacologic prophylaxis		
Intermittent pneumatic compression or graduated compression stockings/foot pump	27 (21)	93 (20)
FDA-approved pharmacologic prophylaxis		
LMWH/fondaparinux/warfarin prophylaxis	67 (48)	284 (61)
No FDA-approved pharmacologic prophylaxis		
Suboptimal pharmacologic or mechanical prophylaxis	63 (52)	179 (39)

NOTE: Numbers are mutually exclusive within each column. Abbreviations: FDA, US Food and Drug Administration; LMWH, low-molecular-weight heparin; TKA, total knee arthroplasty; VTE, venous thromboembolism. \*There was no case of aspirin alone in our sample.

**TABLE 3.** Patients Who Did Not Receive FDA-Approved Pharmacologic Prophylaxis Based on the FDA-Approved Labeling for Proper Dose, Timing, and Duration

Cases and Controls Who Did Not Receive FDA-Approved Pharmacologic Prophylaxis (N = 242)			
Prophylaxis Status		Variable	n*
Received FDA-approved pharmacologic prophylaxis but did not meet FDA-approved proper dose, timing, and duration	118 (49%)	Wrong dose†	87
		Dose not within the recommended time window‡	17
		Not continued at discharge	50
Received no pharmacologic prophylaxis (only mechanical)	124 (51%)		

Abbreviations: FDA, US Food and Drug Administration. \*Numbers are not mutually exclusive. †Wrong dose if did not meet FDA-recommended dose: First post-op dose of enoxaparin was 30 mg per 12 hours, or last post-op dose before discharge was 30 mg per 12 hours, or 40 mg per day; or first post-op dose of fondaparinux was 2.5 mg per day; or first post-op dose of warfarin was 2–10 mg per day; or first post-op dose of dalteparin was 2500 mg per 12 hours. ‡Wrong time window if did not meet FDA-recommended timing: First post-op dose of enoxaparin was given between 720 and 1440 minutes postsurgery; or first post-op dose of fondaparinux was given less than or equal to 480 minutes postsurgery; or first post-op dose of warfarin was given between 0 and 720 minutes postsurgery; or first post-op dose of dalteparin was given between 240 and 360 minutes postsurgery.

obese patients versus less obese patients, there was no significant difference in the risk of VTE across the BMI levels that were compared. Further, among the patients whose pharmacologic prophylaxis was LMWH or fondaparinux, severe or morbid obesity was not associated with significantly higher odds of developing VTE. Although it is logical to think that heavier patients require a larger dose of LMWH or fondaparinux, the findings of this study suggest that current FDA-approved doses of these drugs are adequate even in morbidly obese patients.

Two other findings were noteworthy. First, early mobilization with active ambulation in the first 2 days after TKA was strongly associated with lower odds of

**TABLE 4.** Results of Multivariable (Conditional Logit) Analysis of Factors Associated With Thromboembolism After TKA

Variable	Odds Ratio	P Value
Older age	1.02 (0.99–1.05)	0.20
Female gender	1.70 (0.9–2.9)	0.90
BMI over 35 (vs 35 or less)	0.9 (0.5–1.6)	0.66
Bilateral TKA (vs unilateral TKA)	4.2 (1.9–9.1)	0.0004
Receiving FDA-approved pharmacologic prophylaxis* vs mechanical	0.5 (0.3–0.8)	0.01
Ambulation on or before second postoperative day	0.3 (0.1–0.9)	0.005

Abbreviations: BMI, body mass index; FDA, US Food and Drug Administration; TKA, total knee arthroplasty.

\*If the first post-op dose of enoxaparin was given between 720 and 1440 minutes postsurgery, or the first post-op dose of enoxaparin was 30 mg per 12 hours, or last post-op dose before discharge was 30 mg per 12 hours or 40 mg per day; or the first post-op dose of fondaparinux was given less than or equal to 480 minutes postsurgery, or the first post-op dose of fondaparinux was 2.5 mg per day; or the first post-op dose of dalteparin was 2500 mg per 12 hours, or the first post-op dose of dalteparin was given between 240 and 360 minutes postsurgery; or the first post-op dose of warfarin was given between 0 and 720 minutes postsurgery, or the first post-op dose of warfarin was 2–10 mg per day.

developing VTE. This finding is similar to the report by Chandrasekaran et al that sitting out of bed or walking for at least 15–30 minutes twice a day on the first postoperative day after TKA significantly reduced the incidence of thromboembolic complications (OR = 0.35; 95% CI: 0.11, 1.03,  $P = 0.03$ ) compared those confined to bed.<sup>22,30</sup> In our study, the beneficial effect of mobilization disappeared if ambulation commenced on day 3 or later after surgery. This finding emphasizes the importance of early mobilization in prevention of VTE, as has been reported after total hip arthroplasty.<sup>31</sup>

The other important finding was that bilateral simultaneous TKA was strongly associated with VTE, with over 4-fold greater odds of developing VTE compared with unilateral TKA. This effect did not disappear when we adjusted for obesity or the time to mobilization. This finding was not unexpected and is consistent with other reports in the literature showing a higher incidence of VTE after bilateral TKA compared with unilateral TKA.<sup>32–35</sup>

This study has several limitations. We were unable to ascertain postdischarge VTE unless a patient was readmitted to the same hospital. It has been reported that between 35% to 45% of postoperative VTEs occur after hospital discharge,<sup>22,23</sup> and some of these complications are treated at other institutions or in the outpatient arena.<sup>36</sup> Second, it has been shown that hospital volume and hospital specialization are associated with the incidence of VTE after TKA procedures.<sup>37,38</sup> To minimize the risk of confounding by hospital characteristics, we conditioned our analysis on hospital and adjusted for the clustering effect of hospitals. Third, all data were collected by individuals employed by and working at the participating hospitals, with no mechanism for duplicate abstraction to ensure reliability. Fourth, only teaching hospitals participated in this study. Adherence to guidelines and use of prophylaxis may be higher at teaching hospitals

than at nonteaching hospitals.<sup>39</sup> As a result, our sample may have less variation than the general population of TKA patients, limiting our power to detect associations between thromboprophylaxis and VTE. Finally, the case-control design has inherent limitations in detecting causal associations, largely due to its susceptibility to unmeasured confounders and incorrect ascertainment of pre-outcome exposures. To avoid the latter problem, we excluded VTEs that were diagnosed on the date of surgery, before prophylaxis is routinely started.

Despite these limitations, our findings suggest that there may be opportunities to prevent postoperative VTE, even among high-risk patients at teaching hospitals that have achieved 100% compliance with The Joint Commission's Surgical Care Improvement Project process measures.<sup>40,41</sup> Specifically, delivery of FDA-approved pharmacologic prophylaxis (vs mechanical prophylaxis alone) and early ambulation (vs later) may further decrease the risk of postoperative VTE. These hypotheses merit further testing in randomized controlled trials or cluster-randomized quality improvement trials. Patients should be informed of the increased risk of VTE after bilateral TKA, although this additional risk may be outweighed by a reduction in the cumulative recovery time and a lower cumulative risk of developing a prosthetic joint infection.<sup>42,43</sup> Finally, AHRQ's PSI-12 appears to be a useful tool for ascertaining VTE cases and identifying potential opportunities for improvement, when the "present-on-admission" status is also available.

Disclosure: Nothing to report.

## References

- Bjornara BT, Gudmundsen TE, Dahl OE. Frequency and timing of clinical venous thromboembolism after major joint surgery. *J Bone Joint Surg Br.* 2006;88(3):386–391.
- Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). *Chest.* 2008;133(6 suppl):381S–453S.
- Howie C, Hughes H, Watts AC. Venous thromboembolism associated with hip and knee replacement over a ten-year period: a population-based study. *J Bone Joint Surg Br.* 2005;87(12):1675–1680.
- 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.
- Watanabe H, Sekiya H, Kariya Y, Hoshino Y, Sugimoto H, Haya-saka S. The incidence of venous thromboembolism before and after total knee arthroplasty using 16-row multidetector computed tomography. *J Arthroplasty.* 2011;26(8):1488–1493.
- 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(14):1525–1531.
- Milbrink J, Bergqvist D. The incidence of symptomatic venous thromboembolic events in orthopaedic surgery when using routine thromboprophylaxis. *Vasa.* 2008;37(4):353–357.
- White RH, Sadeghi B, Tancredi DJ, et al. How valid is the ICD-9-CM based AHRQ patient safety indicator for postoperative venous thromboembolism? *Med Care.* 2009;47(12):1237–1243.
- Department of Health and Human Services, Centers for Medicare & Medicaid Services. Hospital-Acquired Conditions (HAC) in Acute Inpatient Prospective Payment System (IPPS) Hospitals. Available at: <http://www.cms.gov/Medicare/Medicare-Fee-for-Service-payment/HospitalAcqCond/downloads/hacfactsheet.pdf>. Accessed September 2012.
- Parvizi J, Kahl L, Dalsey C. Aggressive anticoagulation after TJA: an evaluation of the ACCP guidelines for thromboprophylaxis. *J Long Term Eff Med Implants.* 2007;17(4):359–365.
- Eikelboom J, Karthikeyan G, Fagel N, Hirsh J. American Association of Orthopedic Surgeons and American College of Chest Physicians guidelines for venous thromboembolism prevention in hip and knee arthroplasty differ. What are the implications for clinicians and patients? *Chest.* 2009;135(2):1512–1520.
- Jämsen E, Varonen M, Huhtala H, et al. Incidence of prosthetic joint infections after primary knee arthroplasty. *J Arthroplasty.* 2010;25(1):87–92.
- Lachiewicz PF. Comparison of ACCP and AAOS guidelines for VTE prophylaxis after total hip and total knee arthroplasty. *Orthopedics.* 2009;32(12 suppl):74–78.
- Sobieraj-Teague M, Eikelboom JW, Hirsh J. How can we reduce disagreement among guidelines for venous thromboembolism prevention? *J Thromb Haemost.* 2010;8(4):675–677.
- Limpus A, Chaboyer W, McDonald E, Thalib L. Mechanical thromboprophylaxis in critically ill patients: a systematic review and meta-analysis. *Am J Crit Care.* 2006;15(4):402–410; quiz/discussion, 411–412.
- Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). *Chest.* 2008;133(6 suppl):454S–545S.
- Altıntaş F, Gürbüz H, Erdemli B, et al. Venous thromboembolism prophylaxis in major orthopaedic surgery: a multicenter, prospective, observational study. *Acta Orthop Traumatol Turc.* 2008;42(5):322–327.
- Namba RS, Paxton L, Fithian DC, Stone ML. Obesity and perioperative morbidity in total hip and total knee arthroplasty patients. *J Arthroplasty.* 2005;20(suppl 3):46–50.
- White RH, Henderson MC. Risk factors for venous thromboembolism after total hip and knee replacement surgery. *Curr Opin Pulm Med.* 2002;8(5):365–371.
- Simone E, Madan A, Tichansky D, Kuhl D, Lee M. Comparison of two low-molecular-weight heparin dosing regimens for patients undergoing laparoscopic bariatric surgery. *Surg Endosc.* 2008;22(11):2392–2395.
- Rowan B, Kuhl D, Lee M, Tichansky D, Madan A. Anti-Xa levels in bariatric surgery patients receiving prophylactic enoxaparin. *Obes Surg.* 2008;18(2):162–166.
- Samama CM, Ravaud P, Parent F, Barre J, Mertl P, Mismetti P. Epidemiology of venous thromboembolism after lower limb arthroplasty: the FOTO study. *J Thromb Haemost.* 2007;5(12):2360–2367.
- White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost.* 2003;90(3):446–455.
- White RH. The epidemiology of venous thromboembolism. *Circulation.* 2003;107(23 suppl 1):14–18.
- Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 suppl):e278S–e325S.
- Blanchard J, Meuwly J-Y, Leyvraz P-F, et al. Prevention of deep-vein thrombosis after total knee replacement: randomised comparison between a low-molecular-weight heparin and mechanical prophylaxis with a foot-pump system. *J Bone Joint Surg Br.* 1999;81-B(4):654–659.
- AAOS. Pulmonary Embolism After Knee Arthroscopy: Rare but Serious. American Academy of Orthopaedic Surgeons/American Association of Orthopaedic Surgeons Web site. Available at: <http://www.6aas.org/news/pemr/releases/releasecfm?releasenum=9692011>.
- Eikelboom JW, Karthikeyan G, Fagel N, Hirsh J. American Association of Orthopedic Surgeons and American College of Chest Physicians guidelines for venous thromboembolism prevention in hip and knee arthroplasty differ: what are the implications for clinicians and patients? *Chest.* 2009;135(2):513–520.
- Premier—A supporting partnership organization of the Surgical Care Improvement Project (SCIP). Premier Inc Web site. Available at: <http://www.premierinc.com/safety/topics/scip/>. Accessed April 10, 2012.
- Chandrasekaran S, Ariaretnam SK, Tsung J, Dickson D. Early mobilization after total knee replacement reduces the incidence of deep venous thrombosis. *Aust N Z J Surg.* 2009;79(7–8):526–529.
- 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(24):1758–1764.
- Barrett J, Baron JA, Losina E, Wright J, Mahomed NN, Katz JN. Bilateral total knee replacement: staging and pulmonary embolism. *J Bone Joint Surg Am.* 2006;88(10):2146–2151.
- Kim YH, Kim JS. Incidence and natural history of deep-vein thrombosis after total knee arthroplasty. A prospective, randomised study. *J Bone Joint Surg Br.* 2002;84(4):566–570.
- Memtoudis SG, Gonzalez Della Valle A, Besculides MC, Gaber L, Sulco TP. In-hospital complications and mortality of unilateral, bilateral, and revision TKA: based on an estimate of 4,159,661 discharges. *Clin Orthop Relat Res.* 2008;466(11):2617–2627.

35. Restrepo C, Parvizi J, Dietrich T, Einhorn TA. Safety of simultaneous bilateral total knee arthroplasty. A meta-analysis. *J Bone Joint Surg Am.* 2007;89(6):1220–1226.
36. Dushey CH, Bornstein LJ, Alexiades MM, Westrich GH. Short-term coagulation complications following total knee arthroplasty: a comparison of patient-reported and surgeon-verified complication rates. *J Arthroplasty.* 2011 Jan 20.
37. Baser O, Supina D, Sengupta N, Wang L, Kwong L. Clinical and cost outcomes of venous thromboembolism in Medicare patients undergoing total hip replacement or total knee replacement surgery. *Curr Med Res Opin.* 2011;27(2):423–429.
38. Hagen TP, Vaughan-Sarrazin MS, Cram P. Relation between hospital orthopaedic specialisation and outcomes in patients aged 65 and older: retrospective analysis of US Medicare data. *BMJ.* 2010;340: c165.
39. Amin A, Stemkowski S, Lin J, Yang G. Thromboprophylaxis rates in US medical centers: success or failure? *J Thromb Haemost.* 2007; 5(8):1610–1616.
40. Knapp RM. Quality and safety performance in teaching hospitals. *Am Surg.* 2006;72(11):1051–1054; discussion 1061–1059, 1133–1048.
41. Pardini-Kiely K, Greenlee E, Hopkins J, Szaflarski NL, Tabb K. Improving and sustaining core measure performance through effective accountability of clinical microsystems in an academic medical center. *Jt Comm J Qual Patient Saf.* 2010;36(9):387–398.
42. Fabi DW, Mohan V, Goldstein WM, Dunn JH, Murphy BP. Unilateral vs bilateral total knee arthroplasty risk factors increasing morbidity. *J Arthroplasty.* 2011;26(5):668–673.
43. Powell RS, Pulido P, Tuason MS, Colwell CW Jr, Ezzet KA. Bilateral vs unilateral total knee arthroplasty: a patient-based comparison of pain levels and recovery of ambulatory skills. *J Arthroplasty.* 2006; 21(5):642–649.