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ORIGINAL ARTICLE

The incidence of pulmonary embolism and deep vein thrombosis and their predictive risk factors after lower extremity arthroplasty: a retrospective analysis based on diagnosis using multidetector CT

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Abstract
Purpose The true incidence of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) events, and the predictive risk factors are not well-defined in patients who undergo major lower extremity arthroplasty such as total hip arthroplasty (THA) or total or partial knee arthroplasty (TPKA). Using multidetector computed tomography (MDCT), pulmonary angiography (CTA), and MDCT venography (CTV), we investigated the prevalence of VTE and its predictive risk factors in patients for whom the guideline recommends prophylaxis.
Methods The electronic records of patients who underwent elective THA or TPKA at our institution from April 2010 through July 2013 were surveyed. We examined a total of 1,163 patient records for 986 patients who had undergone MDCT seven days after THA or TPKA.
Results No PE-related deaths occurred in this study, though arterial embolization was needed for major bleeding in two cases. CTA-CTV revealed VTE in 51 (4.4 %) patients, PE in 20 (1.7 %), and DVT in 43 (3.3 %). Five of 51 patients had symptoms suggestive of DVT. In the logistic regression model, the type of surgery (TPKA > THA), patient age, and body mass index (BMI) were identified as predictive risk factors for VTE.
Conclusions This observational study showed that the overall incidence of VTE after THA and TPKA is 4.4 % in patients receiving recommended antithrombotic prophylaxis. TPKA is associated with a higher incidence of VTE than of THA, and greater BMI and older patient age are also independent risk factors.

Keywords Pulmonary embolism · Total hip arthroplasty · Total knee arthroplasty · Multislice computed tomography

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Introduction

Major lower extremity arthroplasty, such as total hip replacement (THA) and total or partial knee replacement (TPKA), is one of the most frequently performed procedures worldwide that substantially improves quality of life in aged people. However, these procedures carry a high risk for postoperative venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE),the occurrence of which is associated with potential fatality and long-term morbidity.

Several studies suggest that a routine antithrombotic strategy reduces the incidence of clinically significant VTE [1–3]. However, the true incidence of VTE and the predictive risk factors are not well-defined in patients, with guidelines recommending antithrombotic prophylaxes because most VTE are silent (i.e., asymptomatic) and the diagnostic sensitivity varies substantially among applied imaging modalities. The advent of enhanced, multidetector row computed tomography (MDCT) has revolutionized the diagnosis of VTE. In a single study, PE and DVT can be visualized by MDCT pulmonary angiography (CTA) and MDCT venography (CTV), respectively [4]. CTA is currently the gold standard for the diagnosis of PE [5]. The sensitivity and specificity of CTV for the diagnosis of DVT are similar to those of ultrasonography, the primary noninvasive imaging modality [4, 6].

At our institution, all patients received antithrombotic prophylaxes after THA and TPKA, as recommended by the guidelines, and they were scheduled to undergo postoperative CTA combined with CTV (CTA-CTV) to detect VTE. We performed this retrospective observational study to examine the incidence of VTE in this cohort. In addition, we sought to define the predictive risk factors for VTE. Previous studies have shown that several factors are associated with symptomatic VTE after THA or TPKA, including obesity, duration of surgery, poor physical status [7], anesthesia duration >3.5 h, absence of antithrombotic prophylaxis, and revision arthroplasty [8]. Risk factors for the overall incidence of VTE confirmed by CTA-CTV, irrespective of VTE symptoms, are not known. Thus, the objectives of this study were to elucidate the true incidence of VTE after lower extremity arthroplasty and to identify the perioperative risk factors in these patients with guideline-recommended thromboprophylaxis.

Methods

This observational study was approved by the institutional ethics committee of Kawasaki Medical School (No. 1584). We surveyed the electronic records of patients who underwent elective THA or TPKA at our institution from April 2010 through July 2013. During this period, a total of 1,263 THA and TPKA procedures were performed in 1,072 patients. According to the protocol at our hospital, patients underwent routine CTA-CTV for the diagnosis of DVT and PE seven days after THA or TPKA unless no contraindications were present, such as renal dysfunction and allergy to contrast media. A total of 100 patient records were excluded from the analysis because these patients did not have postoperative CTA-CTV. Consequently, a total of 1,163 patient records for 986 patients were included in the analysis (Fig. 1). We searched the electronic patient records and radiology reports for symptomatic and asymptomatic VTE, PE-related death or all cause deaths, and adverse events, such as bleeding and infection.

Patients underwent surgery under general anesthesia consisting of sevoflurane gas or continuous intravenous infusion of propofol with or without regional nerve blocks, such as continuous femoral nerve block or epidural block. Patients received anticoagulants, either subcutaneous enoxaparin (20 mg) twice a day or subcutaneous fondaparinux (1.5 mg) once a day, for seven days starting 24 h after surgery if they had no contraindications to anticoagulation, such as renal dysfunction or the use of anti-platelet medications [2]. Unfractionated heparin was infused intravenously at a dose of 18 IU kg/h in patients on chronic warfarin medication. All patients had pneumatic compression and used compression stockings until ambulation [13]. During the hospital stay, all patients were assessed daily in the ward by attending physicians for wounds, bleeding, symptoms of DVT and PE, and other serious complications.

CTA-CTV was performed on postoperative day 7 using either a 16-row CT scanner (LightSpeed Series, GE Medical Systems, Milwaukee, WI, USA) or a 64-row CT scanner (Aquilion TSX-101A, Toshiba Medical Systems, Tokyo, Japan) with the following protocol. A total volume of 2 ml kg^{-1} body weight non-ionic contrast material (iopamidol or iohexsol) containing 300 or 370 mg mL^{-1} iodine was used. Half of the dose was injected in the peripheral vein of the upper arm at a flow rate of 2.5 ml s^{-1} and the rest at a flow rate of 0.5 ml s^{-1}. CTA

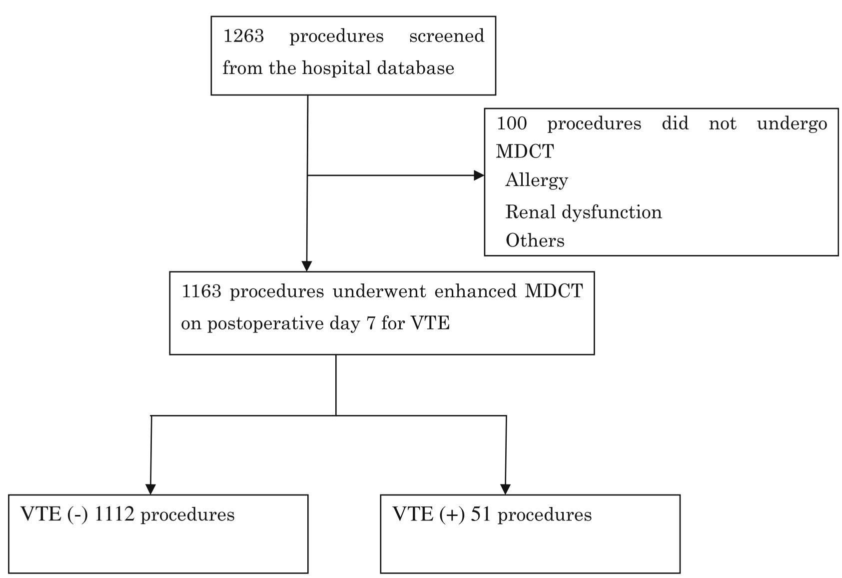

Fig. 1 Our study enrollment involved data extracted from the electronic patient records for elective total hip arthroplasty or total or partial knee arthroplasty from April 2010 through July 2013 at Kawasaki Medical School Hospital

started 20 s after initiation of the injection at a collimation of 5 mm in the cranial direction from the lowest diaphragm to the lung apex, and CTV started 4–4.5 min after initiation of the injection at a collimation of 2 or 2.5 mm (16-row or 64-row CT scanner, respectively) in the caudal direction from the iliac crest to the tibial plateau. CTA-CTV was performed with a 16-row CT scanner in 67 % of the 1,163 patients; the rest were examined with a 64-row CT scanner. CTA-CTV images were interpreted by staff radiologists as part of their routine clinical work. Representative images of PE and DVT are shown in Figs. 2 and 3, respectively. When PE or DVT was detected with CTA-CTV, the patients were treated with oral warfarin for at least 30 days.

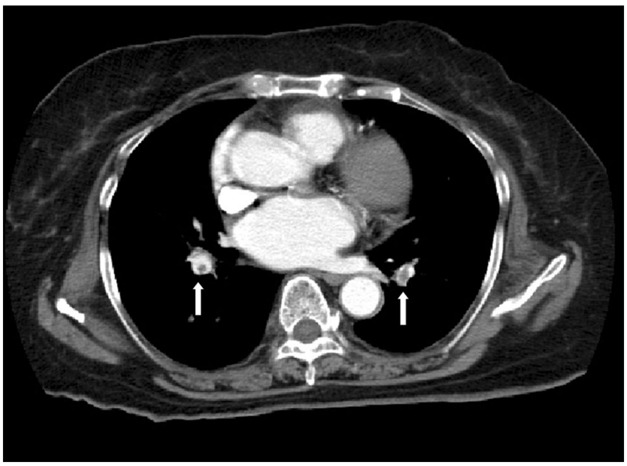

Fig. 2 Multidetector CT pulmonary arteriography showed a typical filling defect in the pulmonary arteries of this 71-year-old female; this patient had left-side total knee arthroplasty. Emboli are visible in the left and right pulmonary arteries of the lower lobes (*white arrows*)

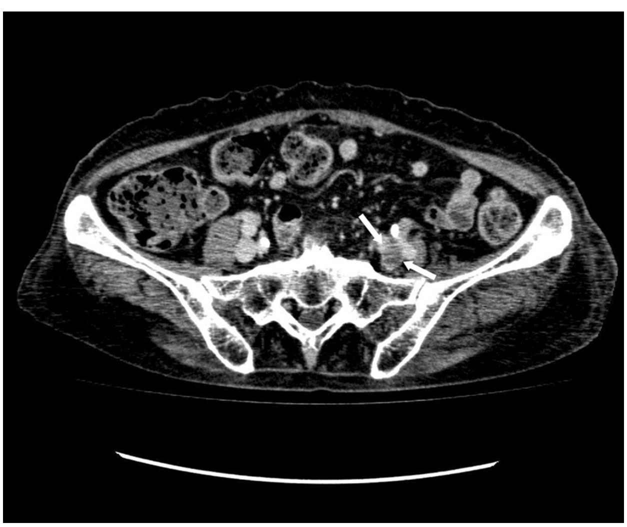

Fig. 3 Multidetector CT venography showed a typical filling defect in the left iliac vein of this 80-year-old female; this patient had left-side total hip arthroplasty. A thrombus is visible in the left iliac vein (*white arrows*)

DVT events were divided into two groups according to the location of the thrombus: proximal DVT (e.g., popliteal, femoral, or iliac-vein thrombi) and distal DVT (i.e., located only in the calf veins). Similarly, emboli in the main or lobar pulmonary arteries were categorized as proximal PE, and those in the segmental or subsegmental pulmonary arteries were labeled as distal PE.

Statistical analysis

Because some of the patients underwent either the same procedures (THA or TPKA) on the other side or a revision, data were assessed per procedure rather than per patient. Data were analyzed using Microsoft Excel (2007) and SPSS Statistics software (Version 22). We compared patient characteristics, types of anesthesia and surgery, duration of anesthesia, and hemoglobin levels the day after the surgery between patients with VTE and those without VTE based on the CTA-CTV diagnosis using the Student's *t* test and the chi-squared test, as appropriate. The *P*-values were not corrected for multiple comparisons. Subsequently, a stepwise, multivariate logistic regression analysis was performed to identify the independent predictive risk factors contributing to VTE. Variables associated with VTE in univariate analyses ($P < 0.10$) were included in the analysis. We included duration of surgery and excluded duration of anesthesia when building the multivariate models, because anesthesia duration is dependent on the duration of surgery. We also excluded duration of hospitalization, because it is obviously not the risk factor for VTE.

Results

A total of 591 of the 1,063 patients underwent 674 THAs, and 395 patients underwent 489 TPKAs. Among the 1,163 procedures in 986 patients, 614 patients (65.2 ± 11.1 years old) underwent 704 THAs, and 372 patients (73.9 ± 8.1 years old) underwent 459 TPKAs. Enoxaparin, fondaparinux, or heparin was administered as prophylactic anticoagulation in 665, 314, and 37 patients, respectively. The other 147 patients received no medication for anticoagulation. The patients' demographic and clinical data are summarized in Table 1.

Two patients died postoperatively, one from exacerbation of chronic pulmonary fibrosis 19 days after TKA and the other from sepsis 93 days after TKA. No VTE-related death was recorded. Major bleeding occurred in two patients with VTE after TKA detected by CTA-CTV: one had a hematoma in the retroperitoneal space on postoperative day 11 and was anticoagulated with fondaparinux, and the other had a hematoma between the genital and

Table 1 Characteristics of patients with or without VTE

	Total procedures ($N = 1{,}163$)	VTE (−) procedures ($N = 1{,}112$)	VTE (+) procedures ($N = 51$)	*P*-value
No. of patients	986	936	50	NA
Age (years)	69 ± 11	68 ± 11	73 ± 8.7	0.0011
Female gender *n* (%)	995 (86)	948 (85)	47 (92)	0.162
Weight (kg)	58 ± 12	58 ± 11	62 ± 24	0.0263
Height (cm)	153 ± 8	153 ± 8	151 ± 7	0.0768
BMI (kg m^{-2})	25 ± 4	25 ± 4	27 ± 5	0.0002
Hemoglobin POD 1 (g dL^{-1})	10.3 ± 1.5	10.0 ± 1.6	10.3 ± 1.5	0.1625
Duration of anesthesia (min)	168 ± 37	167 ± 37	179 ± 32	0.021
Duration of surgery (min)	102 ± 35	102 ± 35	112 ± 30	0.047
Types of arthroplasty				<0.0001
Single-side TPKA *n* (%)	421 (36.2)	388	33	
Bilateral TPKA *n* (%)	38 (3.3)	36	2	
Primary THA *n* (%)	659 (56.7)	648	11	
Revision THA *n* (%)	45 (3.9)	40	5	
Types of anesthesia				0.6608
General *n* (%)	490 (41.8)	466	24	
General+regional *n* (%)	673 (58.1)	647	27	
Anticoagulants				0.0289
Enoxaparin *n* (%)	665 (57.2)	632	33	
Fondaparinux *n* (%)	314 (27.0)	301	13	
Heparin *n* (%)	37 (3.2)	33	4	
No medication *n* (%)	147 (12.6)	146	1	
Duration of hospitalization (days)	25.3 ± 14.2	24.8 ± 13.2	37.1 ± 25.3	<0.0001
Mortality *n* (%)	2 (0.2)	2	0	
Major bleeding *n* (%)	2 (0.2)	1	1	

Data were assessed per procedure rather than per patient, except for the number of patients. Data are mean ± SD. *P*-values are for the comparison between patients without VTE and those with VTE, and calculated with the use of the Student's *t*-test. The *P*-values for the type of arthroplasty, type of anesthesia, and type of anticoagulants were calculated with the use of the chi-squared test

POD postoperative day, *VTE* venous thromboembolism, *TPKA* total or partial knee arthroplasty, *THA* total hip arthroplasty, *general* general anesthesia, *general+regional* general anesthesia with either epidural block or femoral nerve block

thigh on postoperative day 13 and was anticoagulated with enoxaparin. After seven days, the patients were switched to unfractionated heparin and warfarin for long-term anticoagulation, because DVT had been detected on CTV in both patients. Hemostasis was successfully achieved by transarterial embolization in both patients.

All CTA-CTV were performed on postoperative day 7 as scheduled. VTE was diagnosed in 51 of 1,163 patients. Although there were no cases of symptomatic VTE in which unscheduled imaging modalities were used for the diagnosis of VTE, there were symptoms compatible with DVT such as local swelling and tenderness in five of the 51 patients with VTE. Patients with VTE were significantly older, heavier, with greater BMI, and longer duration of surgery and anesthesia (Table 1). VTE diagnosis resulted in a longer hospital stay due to longer antithrombotic therapy. No difference was found between patients with VTE and those without VTE with respect to gender, height, or hemoglobin level the day after surgery.

CTA-CTV results are provided in Table 2. Proximal PE was not identified in patients after THA, whereas distal PE occurred after both THA and TPKA. The prevalence of VTE was greater after TPKA (7.2 %) compared to THA (2.4 %). Distal DVT occurred more frequently after TPKA than after THA, but no difference was found in the prevalence of proximal DVT between THA and TPKA.

In the logistic regression model, the type of surgery (TPKA > THA), patient age, and BMI were identified as predictive risk factors for VTE (Table 3). Though the duration of surgery was slightly longer for TPKA (108 ± 27 min) compared to THA (98 ± 37 min), the duration of surgery was not an independent risk factor for VTE.

Table 2 Details of VTE events ($n = 51$, 4.4 %)

	Total ($n = 1{,}163$)	THA ($n = 674$)	TPKA ($n = 489$)	*P*-value
VTE *n* (%)	51 (4.6)	16 (2.4)	35 (7.2)	0.0001
PE *n* (%)	20 (1.7)	1 (0.1)	19 (3.9)	<0.00001
Proximal PE *n*	5	0	5	
Distal PE *n*	15	1	14	
DVT *n* (%)	43 (3.7)	16 (2.4)	27 (5.5)	0.0050
Proximal DVT *n*	15	9	6	0.8716
Distal DVT *n*	28	7	21	0.0003
PE + DVT *n* (%)	12 (1.0)	1 (0.1)	11 (2.2)	0.0005

P-values are two-tailed tests comparing THA and TPKA

VTE venous thromboembolism, *PE* pulmonary embolism, DVT deep vein thrombosis, *proximal PE* thrombi in the main or lobar pulmonary artery, *proximal PE* thrombi located only in the segmental or subsegmental pulmonary artery, *PE + DVT* concomitant presence of pulmonary embolism and deep vein thrombosis

Table 3 Risk factors associated with VTE

Risk factor	OR	95 % CI	*P*-value
BMI (kg m^{-2})	1.089	1.020–1.163	0.011
Age (years)	1.036	1.010–1.072	0.043
Type of surgery (TPKA)	2.151	1.091–4.240	0.027

Logistic regression analysis for VTE after lower extremity arthroplasty revealed that TPKA (vs. THA), greater BMI, and older age are associated with a higher incidence of postoperative VTE

OR odds ratio, *CI* confidence interval, *VTE* venous thromboembolism, *BMI* body mass index

Discussion

This observational study using CTA-CTV for the diagnosis of VTE after THA or TPKA has two major findings. First, the overall incidences of VTE, PE, and DVT were 4.6, 1.7, and 3.7 %, respectively. These values were substantially lower than those of previous reports and a meta-analysis [9, 10]. Second, logistic regression analysis revealed that the type of surgery (TPKA > THA), age, and BMI are independent risk factors for VTE, whereas other patient characteristics and surgical and anesthesia variables are not directly associated with the incidence of VTE.

DVT occurs in 40–60 % of patients after lower major arthroplasty without antithrombotic prophylaxis [2]. A randomized, controlled trial from Japan that enrolled 832 patients demonstrated that the incidence of conventional venography in proven VTE was 36 (41.9 %) out of 86 patients who underwent THA and 48 (60.8 %) out of 79 patients that underwent TKA without antithrombotic prophylaxis, or 20.0 and 29.8 %, respectively, with anticoagulation via subcutaneous enoxaparin (20 mg) twice a day [11]. Although these incidences are similar to those reported in systematic reviews [2, 3], the incidence of VTE with anticoagulation was substantially higher in the reviews than in the current study. The higher incidence in the previous study may be explained by the use of conventional venography for screening, which detects mostly small thrombi in the calf veins with high sensitivity [1].

Using 16-row MDCT, Watanabe and others [12] examined the incidence of PE and DVT after TPKA in a prospective study of 64 patients and found rates of 3, 13, 34, and 51 % for PE alone, PE plus DVT, DVT, and asymptomatic VTE, respectively. Although there are differences in study designs (prospective vs. observational), the days on which MDCT was performed after surgery (4 vs. 7 days), and the numbers of patients (64 vs. 1,163 patients) between their study and the current study, given the fact that their patients had elastic stockings and intermittent pneumatic compression devices but no pharmacological anticoagulation, our results clearly demonstrate the efficacy of current pharmacological prophylaxis for preventing VTE in patients undergoing THA or TPKA.

Symptoms suggestive of VTE were recorded only in five out of 51 patients with VTE, although symptomatic VTE is reported to occur at a rate of 1.0 % after TPKA and 0.5 % after THA during hospital stays, even with modern antithrombotic prophylaxes as recommended by a recently published meta-analysis [1]. Because symptoms of VTE are non-specific, such as local pain, swelling, fever, shortness of breath, dyspnea, and sustained hypotension, the diagnosis of symptomatic VTE is affected by many factors, including the awareness of attending physicians, threshold differences for objective diagnostic testing among institutions, and the availability of imaging modalities. Scheduling postoperative CTA-CTV in all patients may have increased the trigger levels for ordering imaging, such as ultrasonography, conventional venography, or CTV, possibly resulting in the low incidence of symptomatic VTE among the 1,163 patients in our cohort.

Byun et al. [13] showed that the degradation of image quality due to hardening artifacts produced by orthopedic prosthesis does not play an important role in the diagnostic ability of CTV for DVT. The ability of CTV to detect DVT after lower extremity arthroplasty is comparable to that of ultrasound [6, 13]. A meta-analysis confirmed this finding and emphasized that CTV is appropriate for the diagnosis of proximal DVT [14]. We are aware of controversies regarding the routine use of CTV combined with CTA for the diagnosis of VTE. A meta-analysis showed that CTV detects 3 % of additional VTE cases if it is combined with CTA [15]. Similarly, the PIOPED II trial [4] reported that the negative predictive value increased from 60 to 82 % in a high-probability group for PE, but it did not increase in the low-probability group, suggesting that combining CTV with CTA was beneficial primarily in the high-probability group. The advantages of routine CTV-CTA over ultrasonography are as follows: a potential delay in waiting for ultrasound is avoided, pelvic and iliac veins can be assessed, and assessment of the culprit thrombus volume is helpful in later management of VTE. That the diagnostic accuracy of ultrasonography for detecting DVT is dependent on the examiners' skill must be considered when ordering the examination. Therefore, CTV is essential in the postoperative management of lower extremity arthroplasty, especially when PE is proven with CTA, and the additional radiation to the pelvis associated with CTV is offset by the advantages in postmenopausal patients undergoing THA or TPKA.

The thromboprophylaxis guidelines after major joint surgery are changing from a focus on the prevention of VTE to balancing efficacy and safety. Symptomatic, not asymptomatic, VTE is considered an efficacy point, and bleeding is an important safety concern [1]. The rate of major bleeding in our cohort (0.2 %) was less than the reported rates of 0.5–1.4 %, but we could not find an explanation for the difference. A low incidence of major bleeding combined with the low incidence of symptomatic VTE events, including all-cause death, in this study validates the current guidelines after THA and TPKA.

Age and obesity are well-recognized risk factors for VTE after surgery in general [16]. Mantilla et al. [7] showed that obesity, poor ASA physical status, and lack of thromboprophylaxis are independent risk factors for symptomatic VTE in their study of 9,791 patients with primary hip or knee arthroplasty. Although the latter two factors were not analyzed in this study, we confirmed the increased risk for VTE in obese patients after THA or TPKA. Obesity may have delayed the postoperative recovery in patients with lower extremity arthroplasty, resulting in venous stasis and DVT formation. Another case–control study of patients with lower extremity arthroplasty [8] showed an association between the duration of anesthesia and the incidence of postoperative VTE but found that other variables, such as type of anesthesia and laboratory data, do not predict VTE. The results of the current study confirmed their findings regarding anesthesia type and laboratory data. Duration of anesthesia/surgery was not related to the incidence of VTE in the current study. The difference may be due to the fact that VTE was diagnosed in patients with VTE-relevant symptoms in the previous case-controlled studies, whereas patients diagnosed with VTE in our cohort were mostly asymptomatic. The higher incidence of VTE after TPKA compared to THA in this study is in agreement with another report [11] and a recent meta-analysis [1]. This may reflect the ease with which calf vein injury occurs during TPKA surgery.

Limitations

The present study has some limitations. First, CTA-CTV was limited to one use on postoperative day 7. A prospective study of 70 patients using repeated ultrasonography revealed that DVT occurs mostly in the first two weeks after THP [8, 16]. Thus, the true incidence of asymptomatic VTE may be slightly higher than what we observed in our patients. Second, the follow-up period was limited to the hospital stay, which was significantly longer (25 days) than that of Western countries (nine days) [3]. Although new guidelines emphasize continued antithrombotic prophylaxis after hospital discharge [17], our results cannot provide any data on this issue.

In summary, this observational, single-center study using CTA-CTV showed that the overall incidence of VTE after THA and TPKA is approximately 4.4 % in patients receiving recommended antithrombotic prophylaxis. Compared to THA, TPKA is associated with a higher incidence of VTE, and greater BMI and older patient age are also independent risk factors. No PE-related deaths occurred in this study, though arterial embolization was needed for major bleeding in two cases. The results of the study validate the safety and efficacy of the current guideline-recommended strategy for thromboprophylaxis after major lower extremity arthroplasty, although vigilance for VTE and bleeding remains necessary.

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