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ORIGINAL ARTICLE

Combination of enoxaparin and low-dose aspirin for thromboprophylaxis in selective patients after primary total joint arthroplasty in a Taiwanese population

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ABSTRACT

Background: The incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) after total joint arthroplasty (TJA) procedures are lower in Asian populations than in Caucasian populations. Therefore, the need for thromboprophylaxis in Asian patients undergoing TJA remains inconclusive. The aim of this study was to validate the clinical outcomes of thromboprophylaxis in selective TJA patients in a Taiwanese population.

Methods: We retrospectively reviewed records of patients who underwent TJA procedures performed by a single-surgeon between January 2010 through December 2019. Patients received thromboprophylaxis with a combination of enoxaparin and low-dose aspirin if they fulfilled any of the following criteria: 1) body mass index >30 (kg/m^2), 2) presence of varicose veins, 3) history of DVT or PE, or 4) simultaneous bilateral TJA procedure. We assessed the incidence of DVT and PE, 90-day postoperative complications, length of stay, in-hospital mortality, 30-day and 90-day readmission, and 1-year reoperation.

Results: Of the 7511 patients included in this study, 2295 (30.6%) patients received thromboprophylaxis. For patients who received thromboprophylaxis(N = 2295), the incidence of DVT and PE were 0.44% and 0%, respectively. For patients who did not receive thromboprophylaxis (N = 5216), the incidence of DVT and PE was 0.46% and 0.04%, respectively. The overall rates of 90-day postoperative complications (2.3%), 30-day (1.8%) and 90-day readmission (2.3%), and 1-year reoperation (1.1%) were low.

Conclusion: Providing thromboprophylaxis for selective TJA patients within the Taiwanese population was effective, as indicated by the low incidence of DVT and PE. Complications, such as surgical site infection, should be carefully weighed and managed.

Keywords: Aspirin; Deep vein thrombosis; Low molecular weight heparin; Pulmonary embolism; Total hip arthroplasty; Total knee arthroplasty

1. INTRODUCTION

Patients undergoing elective total joint arthroplasty (TJA), including total knee arthroplasty (TKA) and total hip arthroplasty (THA), are at high risk of venous thromboembolism (VTE).[1–3] According to clinical practice guidelines from the American Academy of Orthopaedic Surgeons and the American College of Chest Physicians (ACCP), pharmacologic agents are recommended for every patient undergoing elective TJA whose bleeding risk is lower than the risk of developing VTE, including symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE).[4,5] Interestingly, the overall rates of VTE in Asian countries (13.8-17.1, per 100,000 individuals) are generally lower than that of Western countries (approximately 100, per 100,000 individuals).[6–9] Data from nationwide population-based studies also indicate that the incidence of VTE following TJA procedures in Asian populations are low, ranging from 0.4 to 1.4%.[3,10–12] Additionally, thromboprophylaxis with antiplatelet or anticoagulant agents might be associated with adverse events, such as hematoma or seroma, persistent wound drainage, delayed wound healing, infection, or the need for transfusions.[10–12] The risks and benefits of thromboprophylaxis in a population with a low incidence of VTE should be weighed carefully. Therefore, we developed criteria for prescribing pharmacologic thromboprophylaxis after TJA in Taiwanese patients.

In this study, we aimed to validate the clinical outcomes of thromboprophylaxis in selective TJA patients in a Taiwanese population over a 10-year study period. We hypothesize that our criteria for thromboprophylaxis can be performed safely with low rates of VTE and associated adverse events.

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2. METHODS

This single-surgeon, case series study was conducted in Taipei Veterans General Hospital, a single tertiary referral hospital in Taipei, Taiwan. The study was approved by the Taipei Veterans General Hospital Institutional Review Board (TVGH-IRB: 2022-04-011BC). Because of the retrospective design of this observational study, TVGH-IRB approved our request to waive the requirement for informed consent. All methods were carried out in accordance with the Declaration of Helsinki. We obtained medical records and images from the Taipei Veterans General Hospital Orthopaedic Database dated between January 2010 and December 2019. We reviewed records of patients who had undergone unilateral or simultaneous bilateral primary total knee arthroplasty (TKA) or THA procedures during this period, according to Taiwan National Health Insurance procedure codes PCS-64169B or PCS-64162B. We included patients who had primary TKA procedures for primary or secondary knee osteoarthritis (ICD-10-CM code: M17), spontaneous osteonecrosis of the knee (SONK, ICD-10-CM code: M90.55, M90.56) and rheumatoid arthritis of knee joint (RA, ICD-10-CM code: M05.76, M05.86, M06.86, M06.9). We included patients that underwent primary THA procedures for primary or secondary hip osteoarthritis (ICD-10-CM code M16), osteonecrosis of the femoral head (ICD-10-CM code: M87.05, M87.15, M87.25, M87.35, M87.85) and RA of hip joint (ICD-10-CM code: M05.75, M05.85, M06.85, M08.45, M08.85, M08.95). We excluded patients who 1) underwent TJA after resection of musculoskeletal tumor; 2) underwent TJA for acute fractures; 3) are allergic to low molecular weight heparin (LMWH) or aspirin; 4) have bleeding disorders (e.g., hemophilia); 5) have Child-Pugh class B or C cirrhosis; or 6) have active, or history of, knee infection.

2.1. Criteria VTE prophylaxis

During our first study period (from January 2010 to December 2017), the criteria for VTE prophylaxis included: 1) body mass index (BMI) >30 (kg/m^2), 2) presence of varicose veins, or 3) history of DVT or PE. However, in December 2017, there was a patient who underwent a simultaneous bilateral TKA procedure who did not fulfill any of the above criteria for prophylaxis but developed PE during the perioperative period. Therefore, we adjusted our criteria for prophylaxis of VTE during the second study period (from January 2018 to December 2019) to 1) BMI > 30 (kg/m^2), 2) presence of varicose veins, 3) history of DVT or PE, or 4) simultaneous bilateral TKA or THA procedures.

2.2. Operative procedure

All procedures were performed under spinal or general anesthesia by a single fellowship-trained, orthopedic surgeon (W.M.C.). A minimally invasive mid-vastus approach was used for all TKA procedures.[13] The distal femoral cut was performed using an intramedullary guide at 6 degrees of valgus. An extramedullary guide was used to perform a perpendicular cut in line with the mechanical axis. The patella was resurfaced with an onlay technique. Tourniquets and closed-suction drains were used in all TKA procedures. All the TKA implants were fixed with cement. Three types of TKA prosthesis were used, including NexGen (Zimmer Biomet, Warsaw, IN, USA), NRG (Stryker, Mahwah, NJ, USA), and Triathlon (Stryker).

A minimally invasive trans-gluteal approach was used for all THA procedures in a lateral decubitus position.[14] A closed-suction drain was used in all THA procedures. Trident cup (Stryker) and SecurFit femoral stem (Stryker) were the only types of THA implants used in all procedures. The fixation method for all THA procedures was cementless.

2.3. Postoperative protocols

All patients adhered to a standard postoperative protocol. All patients began ambulation within 24 hours after TJA. Each patient received postoperative prophylactic antibiotics for 1 day unless there was evidence of infection (e.g., pneumonia, urinary tract infection or surgical site infection). A standard thromboprophylaxis protocol was given to patients who fulfilled the criteria for prophylaxis. The protocol consisted of an injection of low molecular weight heparin (Enoxaparin, Clexane, 2000 IU, 0.2 cc) immediately after surgery and every day after up to and including POD3, before then transitioning to low-dose aspirin (Bokey, 100 mg) for 2 weeks. If the patient was diagnosed with DVT based on clinical symptoms and positive findings on doppler ultrasonography, low-dose aspirin would then be administered for a total of 5 weeks.

If the patient presented with signs of hypovolemia in the operating room or post-anesthesia care unit secondary to excessive intraoperative blood loss or drainage amount, packed red blood cells were transfused accordingly. The hemoglobin level was measured on POD1. If the patient had a 1) hemoglobin <9.0 g/dL or 2) hemoglobin between 9.0–10.0 g/dL and symptoms suggestive of anemia (e.g., dizziness, malaise, pale conjunctiva, tachycardia, hypotension), 1–2 units of packed red blood cells were transfused.

2.4. Perioperative outcome

All medical records were reviewed by three authors (W.L.C., F.Y.P., and S.W.T.). Primary outcome domains include incidence of DVT and PE within the 90-day postoperative period. The diagnosis of DVT was based on positive clinical symptoms (e.g., severe pain, swelling, warm, erythematous, or discolored skin) and positive findings on Doppler ultrasonography. We only performed Doppler ultrasonography on patients with positive symptoms. We screened and diagnosed PE with computed tomography pulmonary angiography in patients displaying positive symptoms, including sudden onset of shortness of breath, dyspnea, chest tightness, desaturation, or hypotension. Secondary outcome domains include postoperative complications that occurred within 90 days after the surgery, 30-day and 90-day readmission, 1-year reoperation, length of stay, and in-hospital mortality. The 90-day postoperative complications and reasons for readmission include surgical site complications (SSC), periprosthetic joint infection (PJI), gastrointestinal (GI) bleeding, urinary tract infection, pneumonia, periprosthetic fracture, extensor mechanism failure, coronary artery disease and cerebrovascular disease. SSCs were defined as delayed wound healing, superficial wound infection, hematoma or seroma formation that required additional wound care, systemic antibiotics, or a surgical debridement procedure. PJI is a more severe type of infection involving the bone and prosthesis surface that required extensive debridement or removal of prosthesis. Common types of extensor mechanism failures include patella fracture or rupture of quadriceps or patellar tendon. Patients were diagnosed with unstable TKA if they exhibited the typical signs or symptoms, such as giving way, difficulty climbing stairs, fear of knee buckling under stress, recurrent joint effusion, joint laxity, or positive stress test upon physical examination.

2.5. Statistical analysis

Statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY). Descriptive statistics were performed for all available data. The Student's *t*-test was used for comparing continuous variables. The Chi-square test was used for comparing discrete variables. When one or more of the cells in the contingency table had an expected frequency of less than 5, we performed the Fisher's exact test. Statistical significance was

defined as p-value <0.05. Multivariate logistic regression analysis was performed to validate whether pharmacologic prophylaxis was associated with SSC. The forward variable selection method was employed to choose the 'best' model, with the significance test for a risk factor entering and remaining at the significance level of 0.10. The results were expressed in odds ratio (OR) with a 95% confidence interval (CI).

3. RESULTS

During the first study period (January 2010 to December 2017), we included 5724 patients for analysis. A total of 1448 (25.3%) patients fulfilled the criteria for prophylaxis. There were significant differences in patient demographics between the prophylaxis and non-prophylaxis groups, with regards to age (70.2 ± 7.8 vs 68.2 ± 12.3 years), female sex (80.0% vs 73.5%), height (154.3 ± 8.2 vs 155.8 ± 8.5 cm), weight (77.8 ± 11.4 vs 61.3 ± 9.2 kg), BMI (32.6 ± 3.6 vs 25.2 ± 2.8 kg/m^2), type of TJA procedure, and whether or not the procedure was unilateral or bilateral (p < 0.05). The number of patients that fulfilled each distinct criteria were, 1) BMI > 30 (N = 1300, 89.8%), 2) presence of varicose veins (N = 139, 9.6%), and 3) history of DVT or PE (N = 15, 1.0%). The non-adherence rate for the protocol was 4.8% (N = 275), which were all unintentional (Table 1).

In the prophylaxis group, the incidence of DVT and PE was 0.35% and 0%, respectively. In the non-prophylaxis group, the incidence of DVT and PE was 0.49% and 0.02%, respectively. The length of stay was slightly longer in the prophylaxis group (4.9 ± 1.2 vs 4.8 ± 2.0 days, p = 0.003), because a greater proportion of patients received bilateral TJA procedures in this group, which was associated with a longer length of stay. There were 3 (0.07%) in-hospital mortality events in the non-prophylaxis group. The were no differences in the rates of transfusion, 90-day complications, 30-day readmission, 90-day readmission, and 1-year reoperation. Notably, the SSC rate in the early postoperative period was higher in the prophylaxis group (1.45% vs 0.82%, p = 0.035). After controlling for several variables including age, sex, height, weight, BMI, TKA or THA procedure, unilateral or bilateral procedure, and transfusion, thromboprophylaxis was associated with increased risk of SSC in the early postoperative period (adjusted OR: 1.78, 95% CI 1.14-2.78) (Table 2).

During the second study period (January 2018 to December 2019), we included 1787 patients for analysis. A total of 847 patients (47.4%) received prophylaxis. Patient age (71.1 ± 7.0 vs 68.8 ± 11.1 years), height (154.3 ± 7.7 vs 155.8 ± 8.0 cm), weight (71.5 ± 12.9 vs 61.1 ± 9.0 kg), BMI (30.0 ± 4.5 vs 25.1 ± 2.8 kg/m^2), type of TJA procedure, and proportion of unilateral or bilateral procedures were different (p < 0.05) between the prophylaxis and non-prophylaxis group. The number of patients that fulfilled the criteria were, 1) BMI > 30 (N = 437, 51.6%), 2) bilateral TJA procedure (N = 416, 49.1%), 3) presence of varicose vein (N = 96, 11.3%), 4) history of DVT or PE (N = 1, 0.1%). The protocol non-adherence rate was 3.4% (N = 61), which were all unintentional (Table 1).

In the prophylaxis group, the incidence of DVT and PE was 0.59% and 0%, respectively. In the non-prophylaxis group, the incidence of DVT and PE was 0.32% and 0.11%, respectively. The length of stay was longer in the prophylaxis group (4.7 vs 4.2 days, p < 0.001) since this group included patients that received bilateral TJA procedures, which normally results in longer length of stay. The transfusion rate was higher in the prophylaxis group (43.5% vs 13.8%, p < 0.001). This can be attributed to a higher rate of intraoperative transfusion associated with a bilateral TJA procedure. The postoperative transfusion rate was similar (10.7% vs 11.3%, p = 0.720). There were no in-hospital mortality events. The 90-day complication, 30-day readmission, 90-day readmission and 1-year reoperation rates were similar between the prophylaxis and non-prophylaxis

Table 1

Patient demographics

	Study period #1 January 2010 through December 2017(N = 5724)			Study period #2 January 2018 through December 2019 (N = 1787)		
Variables	**Prophylaxis (N = 1448)**	**Non-prophylaxis (N = 4276)**	***p***	**Prophylaxis (N = 847)**	**Non-prophylaxis (N = 940)**	***p***
Age (years)	70.2 ± 7.8 (range 21–93)	68.2 ± 12.3 (range 17–97)	<0.001	71.1 ± 7.0 (range 24–90)	68.8 ± 11.1 (range 22–93)	<0.001
Sex			<0.001			0.061
Female	1159 (80.0%)	3141 (73.5%)		684 (80.8%)	725 (77.1%)	
Male	289 (20.0%)	1135 (26.5%)		163 (19.2%)	215 (22.9%)	
Height (cm)	154.3 ± 8.2 (range118.4–195.0)	155.8 ± 8.5 (range 128.0–190.0)	<0.001	154.3 ± 7.7 (range 134.0–183.0)	155.8 ± 8.0 (range 129.0–181.7)	<0.001
Weight (kg)	77.8 ± 11.4 (range47.2–160.0)	61.3 ± 9.2 (range 31.4–97.7)	<0.001	71.5 ± 12.9 (range 39.9–130.0)	61.1 ± 9.0 (range 35.0–93.3)	<0.001
Body mass index (kg/m^2)	32.6 ± 3.6 (range 17.1–50.0)	25.2 ± 2.8 (range 14.2–29.9)	<0.001	30.0 ± 4.5 (range 17.7–45.0)	25.1 ± 2.8 (range 15.8–29.9)	<0.001
Procedure (%)		2	<0.001			<0.001
TKA	1234 (85.2%)	902 (67.9%)		748 (88.3%)	602 (64.0%)	
THA	214 (14.8%)	1374 (32.1%)		99 (11.7%)	338 (36.0%)	
Uni vs Bil (%)			<0.001			<0.001
Unilateral	1056 (72.9%)	3486 (81.5%)		424 (50.1%)	940 (100%)	
Bilateral	392 (27.1%)	790 (18.5%)		423 (49.9%)	0	
Criteria for prophylaxis (%)						
BMI > 30	1300 (89.8%)			437 (51.6%)		
Bilateral TJA	-			416 (49.1%)		
Varicose vein	139 (9.6%)			96 (11.3%)		
History of DVT/PE	15 (1.0%)			1 (0.1%)		

BMI = body mass index; DVT = deep vein thrombosis; PE = pulmonary embolism; THA = total hip arthroplasty; TJA = total joint arthroplasty; TKA = total knee arthroplasty.

Table 2

Perioperative outcomes of patients from study period #1 (January 2010 to December 2017, N = 5724)

	Prophylaxis group (n = 1448)	Non-prophylaxis group (n = 4276)	*p*
Symptomatic DVT (%)	5 (0.35%)	21 (0.49%)	0.476
Pulmonary embolism (%)	0	1 (0.02%)	1.000
90-day complication rate (%)	40 (2.76%)	88 (2.06%)	0.117
Surgical site complication	21 (1.45%)	35 (0.82%)	0.035
Gastrointestinal bleeding	5 (0.35%)	12 (0.28%)	0.696
Periprosthetic fracture	3 (0.21%)	5 (0.12%)	0.426
Extensor mechanism failure	1 (0.07%)	2 (0.05%)	1.000
Periprosthetic joint infection	2 (0.14%)	10 (0.23%)	0.742
Urinary tract infection	4 (0.28%)	16 (0.37%)	0.797
Pneumonia	3 (0.21%)	3 (0.07%)	0.174
Cerebrovascular disease	0	3 (0.07%)	1.000
Coronary artery disease	1 (0.07%)	2 (0.05%)	1.000
Length of stay (days)	4.9 ± 1.2 (range 3-15)	4.8 ± 2.0 (range 2-91)	0.003
In-hospital mortality (%)	0	3 (0.07%)	0.576
Transfusion rate (%)	536 (37.0%)	1595 (37.3%)	0.846
Transfusion at the operation room	422 (29.1%)	1089 (25.5%)	0.006
Postoperative transfusion	180 (12.4%)	690 (16.1%)	<0.001
30-day readmission (%)	29 (2.00%)	66 (1.54%)	0.237
Surgical site complication	17 (1.17%)	25 (0.58%)	0.023
Gastrointestinal bleeding	4 (0.28%)	10 (0.23%)	0.762
Symptomatic DVT	2 (0.14%)	4 (0.09%)	0.647
Periprosthetic fracture	0	4 (0.09%)	0.578
Extensor mechanism failure	1 (0.07%)	1 (0.02%)	0.442
Periprosthetic joint infection	2 (0.14%)	5 (0.12%)	1.000
Urinary tract infection	2 (0.14%)	12 (0.28%)	0.539
Pneumonia	1 (0.07%)	2 (0.05%)	1.000
Cerebrovascular disease	0	1 (0.02%)	1.000
Coronary artery disease	0	1 (0.02%)	1.000
Pulmonary embolism	0	1 (0.02%)	1.000
90-day readmission (%)	40 (2.76%)	86 (2.01%)	0.092
Surgical site complication	19 (1.31%)	31 (0.72%)	0.038
Gastrointestinal bleeding	5 (0.35%)	11 (0.26%)	0.583
Symptomatic DVT	2 (0.14%)	6 (0.14%)	1.000
Periprosthetic fracture	3 (0.21%)	5 (0.12%)	0.426
Extensor mechanism failure	1 (0.07%)	2 (0.05%)	1.000
Periprosthetic joint infection	2 (0.14%)	6 (0.14%)	1.000
Urinary tract infection	4 (0.28%)	16 (0.37%)	0.797
Pneumonia	3 (0.21%)	3 (0.07%)	0.174
Cerebrovascular disease	0	3 (0.07%)	0.576
Coronary artery disease	1 (0.07%)	2 (0.05%)	1.000
Pulmonary embolism	0	1 (0.02%)	1.000
1-year reoperation (%)	19 (1.31%)	44 (1.03%)	0.372
Periprosthetic fractures	6 (0.41%)	8 (0.19%)	0.130
Surgical site complications	2 (0.14%)	7 (0.16%)	1.000
Periprosthetic joint infections	4 (0.28%)	16 (0.37%)	0.797
Extensor mechanism failure	2 (0.14%)	2 (0.05%)	0.267
Joint instability	0	1 (0.02%)	1.000
Stem subsidence	3 (0.21%)	6 (0.14%)	0.701
Soft tissue impingement	0	1 (0.02%)	1.000
Synovitis	1 (0.07%)	1 (0.02%)	0.442
DVT[a]	1 (0.07%)	2 (0.05%)	1.000

DVT = deep vein thrombosis.

[a]The patients underwent percutaneous transluminal angioplasty with iliac vein stenting for deep vein thrombosis.

groups. SSC accounted for the most common 90-day complication and was also the most common reason for 30-day and 90-day readmission in both groups (Table 3).

The results of the sensitivity analyses, including intention-to-treat, per-protocol, and as-treated analysis, are presented in Supplementary Table S1–3, http://links.lww.com/JCMA/A201. The results from these sensitivity analyses were consistent, which revealed that the rates of primary outcomes (DVT and PE) were similar between the prophylaxis and non-prophylaxis groups throughout this study period.

Table 3

Perioperative outcomes of patients from study period #2 (January 2018 to December 2019, N = 1787)

	Prophylaxis group (n = 847)	Non-prophylaxis group (n = 940)	*p*
Symptomatic DVT (%)	5 (0.59%)	3 (0.32%)	0.488
Pulmonary embolism (%)	0	1 (0.11%)	1.000
90-day complication rate (%)	26 (3.07%)	21 (2.23%)	0.270
Surgical site complication	14 (1.65%)	10 (1.06%)	0.280
Gastrointestinal bleeding	4 (0.47%)	3 (0.32%)	0.714
Periprosthetic fracture	1 (0.12%)	1 (0.11%)	1.000
Extensor mechanism failure	3 (0.35%)	1 (0.11%)	0.351
Periprosthetic joint infection	3 (0.35%)	1 (0.11%)	0.351
Urinary tract infection	0	3 (0.32%)	0.252
Pneumonia	0	1 (0.11%)	1.000
Cerebrovascular disease	1 (0.12%)	1 (0.11%)	1.000
Coronary artery disease	0	0	
Length of stay (days)	4.7 ± 0.9 (range 3-11)	4.2 ± 1.0 (range 2-25)	<0.001
In-hospital mortality (%)	0	0	-
Transfusion rate (%)	368 (43.5%)	130 (13.8%)	<0.001
Transfusion at the operation room	312 (36.8%)	30 (3.2%)	<0.001
Postoperative transfusion	91 (10.7%)	106 (11.3%)	0.720
30-day readmission (%)	19 (2.24%)	18 (1.91%)	0.626
Surgical site complication	9 (1.06%)	7 (0.74%)	0.476
Gastrointestinal bleeding	4 (0.47%)	2 (0.21%)	0.431
Symptomatic DVT	2 (0.24%)	0	0.225
Periprosthetic fracture	1 (0.12%)	1 (0.11%)	1.000
Extensor mechanism failure	2 (0.24%)	1 (0.11%)	0.606
Periprosthetic joint infection	1 (0.12%)	1 (0.11%)	1.000
Urinary tract infection	0	3 (0.32%)	0.252
Pneumonia	0	1 (0.11%)	1.000
Cerebrovascular disease	0	1 (0.11%)	1.000
Coronary artery disease	0	0	1.000
Pulmonary embolism	0	1 (0.11%)	
90-day readmission (%)	28 (3.31%)	20 (2.13%)	0.124
Surgical site complication	13 (1.53%)	8 (0.85%)	0.180
Gastrointestinal bleeding	4 (0.47%)	2 (0.21%)	0.431
Symptomatic DVT	3 (0.35%)	1 (0.11%)	0.351
Periprosthetic fracture	1 (0.12%)	1 (0.11%)	1.000
Extensor mechanism failure	3 (0.35%)	1 (0.11%)	0.351
Periprosthetic joint infection	3 (0.35%)	1 (0.11%)	0.351
Urinary tract infection	0	3 (0.32%)	0.252
Pneumonia	0	1 (0.11%)	1.000
Cerebrovascular disease	1 (0.12%)	1 (0.11%)	1.000
Coronary artery disease	0	0	1.000
Pulmonary embolism	0	1 (0.11%)	
1-year reoperation (%)	15 (1.77%)	13 (1.38%)	0.510
Periprosthetic fractures	3 (0.35%)	4 (0.43%)	1.000
Surgical site complications	3 (0.35%)	0 (%)	0.106
Periprosthetic Joint Infections	4 (0.47%)	5 (0.53%)	1.000
Extensor mechanism failure	3 (0.35%)	4 (0.43%)	1.000
Joint instability	1 (0.12%)	0	0.474
Stem subsidence	0	0	0.474
Soft tissue impingement	0	0	
Synovitis	0	0	
DVT[a]	1 (0.12%)	0	

DVT = deep vein thrombosis.

[a]The patient underwent percutaneous transluminal angioplasty with iliac vein stenting for deep vein thrombosis.

4. DISCUSSION

In this single-surgeon case series of 7511 patients, we provided thromboprophylaxis for patients within the Taiwanese population that received a TJA procedure over a 10-year study period, while adhering to a consistent protocol. For patients who received thromboprophylaxis, the incidence of DVT and PE were 0.44% and 0%, respectively. For patients who did not receive thromboprophylaxis, the incidence of DVT and PE was 0.46% and 0.04%, respectively. These results might indicate that a TJA procedure can be safely performed in a selective group of Asian patients without thromboprophylaxis according to our criteria.

The VTE prophylaxis protocol and outcomes in this study are consistent with both regional (Asian) and global clinical practice standards. The VTE protocol used in current practice remains highly variable amongst orthopedic surgeons.[15,16] For example, not all TJA patients in Asian countries receive VTE prophylaxis.[17–19] Although this practice may deviate from the American Academy of Orthopaedic Surgeon and ACCP guidelines, several studies have supported this, and this practice is based on evidence that Asian populations have lower overall and postoperative VTE rates.[2,3,9,20–22] Therefore, the VTE criteria for prophylaxis applied in this study were based on known VTE risk factors,[23] including high BMI, varicose veins, history of VTE; and later included patients undergoing a bilateral TJA procedure. The inclusion for bilateral TJA was added after a bilateral TJA patient within our study developed a PE. In this study, all patients initially received LMWH before transitioning to aspirin, which is consistent with current trends.[24] In terms of safety and effectiveness, both agents were given Grade 1B in the most recent ACCP guidelines, indicating a strong recommendation, over other agents with Grade 2B/2C.[25] A large Korean population study identified the most common and third most common VTE pharmacologic agents for THA were LMWH (34%) and aspirin (19%), respectively.[26] Lastly, this study's VTE outcomes are consistent, if not lower, with global clinical practice standards. We compared the overall incidence rates (including both prophylaxis and non-prophylaxis groups) of DVT and PE in both our study periods to the incidence rates of DVT and PE in western (United States) and eastern (Japan, Korea, and China) countries obtained from modern, large-scale studies.[18,19,27,28] In our study, the overall incidence of DVT was 0.45%. The incidence of DVT was similar in the prophylaxis (0.44%) and non-prophylaxis groups (0.46%). The incidence of DVT was consistent with the results (0.2–1.15%) from national, large-scale studies.[18,19,27,28] The overall incidence of PE was 0.03%. The incidence of PE was low in both the prophylaxis (0%) and non-prophylaxis (0.04%) groups. The results were similar to the incidence of PE (0–0.72%) reported in those large-scale studies.[18,19,27,28] Even though other confounding variables, such as different surgical techniques and prophylaxis protocols used, prohibit a direct comparison, the low rates among our non-prophylaxis group is encouraging, as it suggests our selection criteria allow a portion of the Taiwanese population to remain safe from developing VTE without incurring the additional health risks and medical costs associated with the prophylactic drugs.[10–12]

Pharmacological thromboprophylaxis was associated with a higher risk of hematoma or seroma formation, persistent wound drainage, wound healing problems, or even infection.[11,12,29] SSCs was the most common reason for early readmission, but most patients can be managed conservatively without the need for further surgical procedures.[30,31] The SSC rates (90-day, range: 1.45%-1.65%) in this study were similar to studies that reported the rates associated with the use of LMWH or LMWH plus aspirin for thromboprophylaxis (30 to 90-day, range: 0.33%-2.81%).[30,31] In comparison with the use of rivaroxaban, the wound complication rate associated with the use of LMWH appeared to be lower (LMWH vs rivaroxaban, 2.81% vs 3.84%).[30] Notably, we have validated that providing thromboprophylaxis was associated with an increased risk of SSC (adjusted OR: 1.78, 95% CI 1.14-2.78), even after controlling for known risk factors such as age, BMI, and blood transfusion.[12,32–34] Although thromboprophylaxis was as an independent risk factor for SSC, very few patients in this study subsequently developed PJI, and the rates of early postoperative PJI (N = 14, 0.19%) and need for additional procedures because of PJI (N = 29, 0.39%) or SSC (N = 12, 0.16%) within 1 year was relatively low. To identify patients at risk of SSC and provide proper wound care would be important to minimize the risk of developing PJI.

Patients who received thromboprophylaxis might be at risk of GI bleeding because of concomitant use of non-steroidal anti-inflammatory drugs for pain management.[35] The rates of GI bleeding in this study were low (0.39%) and similar to the reported rates in patients who received thromboprophylaxis from the National Administrative database,[36] indicating that the combination of these agents short term did not lead to higher risks for GI complications. With appropriate evaluation and patient selection before a TJA procedure, reported mortality rates during admission or the early postoperative period (0.07%-0.34%) are very low,[30,31,37] and similar to the mortality rate (0.04%) in this study.

There are some limitations in this study. First, of the 7511 patients included in this study, 336 (4.5%) did not adhere to the criteria for prophylaxis due to unintentional reasons. To evaluate the impact of these patients on our results, we performed sensitivity analyses for the primary outcome domains, including incidence of DVT and PE (Supplementary Table S1–3, http://links.lww.com/JCMA/A201). The findings were consistent among the intention-to-treat, per-protocol, and as-treated analyses, indicating that the incidence of DVT and PE was similar between patients who had or had not received prophylaxis during each study periods. Second, a control group including patients that received pharmacologic thromboprophylaxis in every of them was lacking. There was also a lack of studies from Asian countries with 1) clearly stated, consistent criteria and regimens for thromboprophylaxis, and 2) a large study size for comparison. Alternatively, we evaluated the VTE rates based on procedure type (TKA or THA) and each study period with large-scale population studies from the USA, Japan, China, and Korea.[18,19,27,28] The VTE rates in our study, specifically the non-prophylaxis group, were all relatively low and consistent with these studies.[18,19,27,28] Third, our transfusion criteria were more liberal than the American Association of Blood Banks clinical practice guidelines on transfusion,[38] and thus our transfusion rates were relatively higher. Even though intraoperative bleeding that requires two or more units of transfusion has been listed as one of the major bleeding complications,[39] these differing transfusion criteria prevented us from directly comparing the incidence of major bleeding complications associated with pharmacologic thromboprophylaxis with other studies. Interestingly, none of the patients in this study experienced 1) fatal bleeding; 2) bleeding that occurred in a critical area, such as intracranial, intraspinal, retroperitoneal, etc.; 3) extra-surgical site bleeding that required transfusion, or 4) surgical site bleeding that required a second intervention.

In conclusion, we recommend thromboprophylaxis with a combination of enoxaparin and low-dose aspirin in a selective group of TJA patients within the Taiwanese population who fulfill the following criteria: 1) BMI > 30 (kg/m^2), 2) presence of varicose veins, 3) history of DVT or PE, or 4) simultaneous bilateral TJA procedure. This protocol can lead to low VTE rates with minimal risk for major bleeding events.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A201.

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