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Is Pharmacological Thromboprophylaxis Truly Necessary: Predictive Factors for Venous Thromboembolic Events Post-Total Knee Arthroplasty in an Asian Population

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Abstract

Introduction: Venous thromboembolic prophylaxis is routinely used in elective total knee arthroplasty (TKA) patients worldwide, and current guidelines vary from aspirin to low molecular weight heparin in combination with mechanical prophylaxis, and direct oral anticoagulants. This study aimed to identify predictive or protective factors for VTEs in an Asian hospital and examine the efficacy of pharmacological VTE prophylaxis.

Materials and Methods: A retrospective cohort study of 2,014 patients who underwent primary TKAs between 2017 and 2022 was performed. All patients received mechanical thromboprophylaxis postoperatively. Patients who were symptomatic were referred for radiological investigations to exclude VTE. We evaluated patient demographics, co-morbidities, and surgical parameters to establish the overall incidence of symptomatic VTEs and risk factors for VTEs.

Results: There were 23 (1.14%) incidences of symptomatic VTEs, of which 1 patient developed pulmonary embolism, and 22 deep vein thrombosis. The incidence of VTE was 0.69% (10/1449) for patients on mechanical prophylaxis only, 2.08% (9/432) for patients on aspirin, 3.67% (4/109) for patients on clexane, 0% (0/19) for patients on clopidogrel, and 0% (0/5) for patients on DOACs. Multivariate analysis revealed length of stay ($P < 0.001$), the need for blood transfusion ($P = 0.007$), choice of thromboprophylaxis ($P = 0.049$), and diagnosis ($P = 0.048$) were independent risk factors for VTE. The use of tranexamic acid did not significantly affect VTE rates in the model ($P = 0.059$).

Conclusion: Pharmacological thromboprophylaxis may not be required post-operative in the Asian population. The identification of risk factors in this study allows surgeons to individualise risk counselling for patients listed for elective TKAs and choose appropriate thromboprophylaxis methods.

Keywords: Knee arthroplasty, arthroplasty, replacement, knee, thromboprophylaxis, venous thrombosis, asians

Introduction

Total knee arthroplasty (TKA) is associated with 22 adverse events and complications, including bleeding, stiffness, periprosthetic fractures, revisions, and thromboembolic disease [1]. The incidence of venous thromboembolic events (VTEs), including deep vein thrombosis (DVT) and pulmonary embolism (PE) post-total knee arthroplasty can be as high as 35.7–62.5% in patients without any form of thromboprophylaxis [2,3] In Asian population studies, however, post-operative DVT rates ranged from 0.15% to 1.35%, at only 15–20% of the incidence recorded in Western populations [4].

The development of VTE significantly increases 30-day mortality [5]. Furthermore, symptomatic PE patients are at an 18-fold increased risk of mortality compared to DVT patients, and VTE recurs in about 30% of patients, develop recurrence within 10 years [6]. The development of VTE hence comes at a significant cost to patients and healthcare systems, increases length of stay (LOS), and worsens clinical outcomes, while subjecting patients to increased morbidity and mortality [7, 8]. DVT also places patients at risk of developing post-thrombotic syndrome, where patients develop symptoms similar

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to those of venous insufficiency, including pain and leg swelling [9].

Enhanced Recovery after Surgery (ERAS) protocols are comprehensive protocols for the pre-operative, peri-operative and post-operative stages - each aimed at improving clinical outcomes, and improving patients' wellbeing. They include nutritional support, multi-modal analgesia, reducing fasting time, among others [10].

Glassou et al., and Millar et al., both showed that VTE incidence decreased with the introduction of ERAS concepts in their TKA and total hip arthroplasty (THA) patient populations [11, 12]. In addition, the Asian venous thromboembolism guidelines 2017 recommend that early mobilization is highly recommended and should be the primary method of prophylaxis in Trauma and Orthopaedic patients [13]. However, the overall incidence and impact of other factors on incidence rates are still not well established – with the International Consensus Meeting on Venous Thromboembolism (ICM-VTE) recommendation on ERAS protocols decreasing VTE risk still limited [14]. Hence, this study aims to investigate the incidence of VTEs in an Asian population who underwent ERAS protocol, with a secondary aim to identify preventive/protective factors for VTE in this population.

Materials and Methods

A retrospective study was performed of patients who underwent TKAs between 2017 and 2022. Patients who underwent same-day bilateral TKRs, or revision surgeries were excluded. The total number of patients who developed VTEs, including DVT or PE were recorded. The demographics of these patients, including age, body mass index, type of anesthesia, tranexamic acid use, diagnoses, use of tourniquet, and the type of thromboprophylaxis were recorded and analyzed.

All patients underwent standard Enhanced Recovery after surgery protocol (ERAS) for knee arthroplasty as described in Fig. 1 (Tan Tock Seng Hospital, Singapore's ERAS Protocol). This includes pre-operative patient education, physiotherapist and dietician optimization, use of intra-operative regional anesthesia and multi-modal analgesia, and post-operative early mobilization and rehabilitation and nutrition optimization. This protocol aims to promote faster functional recovery, lower post-operative complications, decrease LOS, and readmission rates.

Fasting time pre-operative was minimized including allowing patients to stay hydrated with up to 250 ml of plain water until 2 h pre-operative. Routine intravenous tranexamic acid (TXA) was given preoperatively unless contraindicated. Post-operatively, patients are allowed early oral intake and calf compressors and TED stockings are applied in the post-operative anesthesia recovery unit, (PACU). All patients were mobilized 4–6 h post-operative unless they arrived in the ward after office hours, for which they were mobilized the following day. In patients with increased risk of VTE such as history of VTEs, morbid obesity, patients are started on additional chemical prophylaxis according to surgeons' preferences,

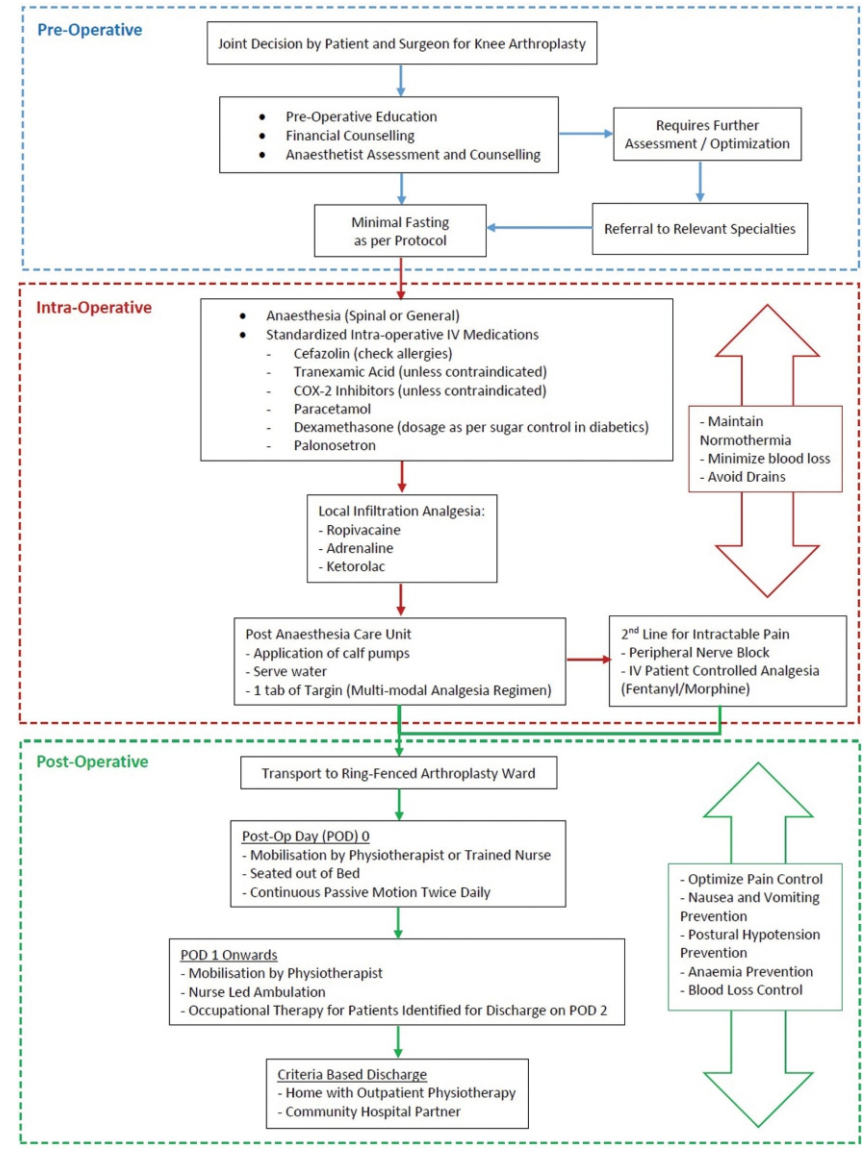

Figure 1: Tan Tock Seng Hospital, Singapore's TKA enhanced recovery after surgery (ERAS) protocol.

usually on post-operative day 1, once the wound is assessed to be stable. Patients are monitored clinically for deep vein thrombosis symptoms. Further imaging is obtained if there is clinical suspicion in the form of a duplex ultrasound study or high-resolution contrast scan of the thorax if pulmonary embolism is suspected.

Statistical analysis was performed using Microsoft Excel 2016 and SPSS Statistics 28. Parametricity of the data was determined using Shapiro–Wilk test, and descriptive statistics including median and interquartile range reported. Single variable analysis was performed using Mann–Whitney U test for continuous variables, or Fisher's Exact test for discrete variables on patient comorbidities, diagnoses, and operative techniques and factors. Factors significant with $P < 0.20$ were included for multivariate logistic regression analysis, which was then performed to determine significant protective or predictive factors, and its associated odds ratio for developing VTEs. A $P < 0.05$ was considered statistically significant.

This study is approved by the ethics board.

Results

A total of 2,014 primary unilateral TKRs were performed in the period of 2017 to 2022 and included for analysis. The demographics of the patients included is shown in Table 1. The median age of the patients was 69.0 (inter-quartile range IQR: 63.8-74.0), and BMI 26.92 (24.39–30.10). 31.8% (641/2014) were male, while 68.2% (1373/2014) were female. 71.9% (1449/2014) patients were placed on IPCD only with no pharmacological thromboprophylaxis.

There was no statistically significant difference in the baseline demographics including the BMI ($P = 0.387$) or age ($P = 0.252$) of patients between patients placed on or without pharmacological thromboprophylaxis.

The incidence of VTEs was 1.14% (23/2014), including 22 DVTs and 1 PE. Table 2 shows the breakdown of DVT and PE incidences by thromboprophylaxis. There was a statistically significant difference in VTE incidence depending on choice of thromboprophylaxis ($P = 0.015$). Patients on clexane had the highest incidence of VTEs at 3.67%, with 1 patient developing PE.

Table 3 shows the demographics and background comorbidities of patients with VTE events depending on thromboprophylaxis choice. There was a very high proportion of known cardiovascular risk factors amongst patients who developed VTEs, with 65.2% (15/23) VTE patients with underlying hypertension. In our univariate analysis, the diagnosis ($P = 0.025$), use of TXA ($P = 0.004$), tourniquet use ($P = 0.042$), blood transfusion ($P = 0.004$), use of chemical thromboprophylaxis ($P = 0.004$), and LOS ($P < 0.001$) were significant risk factors in the development of VTE. Table 4 shows the single-variable analysis results for the other factors analyzed. Other comorbidities included in the univariate analysis include respiratory and psychiatric diseases but were not significant.

Table 1: Demographic table of patients

	IPCD only	Aspirin	Clexane	DOACs	Clopidogrel	Total
No.	1,449	432	109	5	19	2,014
Gender						
Male	456	150	32	0	3	641
Female	993	282	77	5	16	1,373
Median Age (IQR)	69.0 (63.0–74.0)	69.0 (64.0–73.3)	69.0 (63.0–73.0)	76.0 (67.0–84.0)	71.0 (68.5–74.0)	69.0 (63.8–74.0)
Median BMI (IQR)	26.9 (24.2–30.0)	26.9 (24.9–30.2)	26.7 (25.1–31.0)	28.3 (25.1–29.3)	27.3 (26.3–29.5)	26.9 (24.4–30.1)
Race						
Chinese	1180	359	84	5	13	1,641
Malay	144	42	18	0	3	207
Indian	104	28	6	0	2	140
Others	21	3	1	0	1	26
Diagnoses						
Osteoarthritis	1387	422	103	5	18	1,935
Rheumatoid arthritis	35	7	4	0	0	46
Non-RA Inflammatory arthritis	21	1	2	0	0	24
Traumatic arthritis	1	1	0	0	1	3
Osteonecrosis	5	1	0	0	0	6
Anaesthesia						
General	474	129	32	2	5	642
Spinal	975	303	77	3	14	1,372
Tranexamic Acid						
Yes	1,328	421	104	4	17	1,874
No	121	11	5	1	2	140
Tourniquet Use						
Yes	1,410	420	92	5	18	1,945
No	39	12	17	0	1	69
Tourniquet Time (IQR)	88.5 ± 31.1	61.2 ± 35.3	64.4 ± 39.1	70.8 ± 37.9	79.7 ± 34.8	82.7 ± 33.8
Operation Time	102.5 ± 33.8	106.7 ± 33.2	107.3 ± 32.6	93.4 ± 27.6	111.6 ± 30.9	103.7 ± 33.6

We adopted a more lenient P-value cutoff as supported by literature and included variables significant with $P < 0.020$ in the single-variable analysis for multivariate analysis, and a binomial logistic regression was performed. In the model, the patient's diagnosis ($P = 0.012$), need for blood transfusion ($P = 0.007$),

Table 2: Number of deep vein thrombosis and pulmonary embolism cases by thromboprophylaxis

	IPCD only	Aspirin	Clexane	Clopidogrel	DOACs	Total
Total VTE	10	9	4	0	0	23
DVT	10	9	3	0	0	22
Proximal	6	3	1			10
Distal	3	6	2			11
No data	1	0	0			1
PE	0	0	1	0	0	1
No VTE	1439	423	105	5	19	1991

Table 3: Demographic table of venous thromboembolism incidents

	IPCD only	Pharmacological	Total
Anesthesia			
General	8	1	9
Spinal	2	12	14
Tranexamic Acid			
Yes	6	11	17
IV	4	6	10
IA	1	0	1
PO	0	0	0
IV + IA	1	5	6
IV + PO	0	0	0
No	4	2	6
Tourniquet Use			
Yes	10	10	20
No	0	3	3
Comorbidities			
Previous Stroke	2	1	3
Diabetes Mellitus	4	1	5
Hypertension	5	10	15
Hyperlipidemia	5	8	13
Ischemic Heart Disease	0	1	1
Peripheral Vascular Disease	0	1	1

Table 4: Single-variable analysis

	Total	VTE	No VTE	*P*-value
Gender				
Male	641	5	636	0.372 (Fisher)
Female	1,373	18	1,355	
Age	Median (IQR)			
*Shapiro-wilk < 0.001	69.0 (63.8–74.0)	71.0 (67.0–78.0)	69.0 (63.0–74.0)	0.062 (Mann Whitney)
Race				
Chinese	1,641	19	1,622	0.935 (Fisher)
Malay	207	2	205	
Indian	140	2	138	
Others	26	0	26	
BMI	Median (IQR)			
*Shapiro wilk < 0.001	26.92 (24.39– 30.10)	26.36 (25.10–28.56)	26.93 (24.39–30.10)	0.706 (Mann Whitney)
Smoker				
Yes	26	0	26	1.000 (Fisher)
No	1,988	23	1,965	
Comorbidities				
Hypertension				
Yes	1,392	15	1,377	0.656 (Fisher)
No	622	8	614	
Hyperlipidemia				
Yes	1,239	13	1,226	0.669 (Fisher)
No	775	10	765	
Diabetes Mellitus				
Yes	554	5	549	0.644 (Fisher)
No	1,460	18	1,442	
Previous Stroke				
Yes	94	3	91	0.089 (Fisher)
No	1,920	20	1,900	
Peripheral Vascular Disease				
Yes	30	1	29	0.293 (Fisher)
No	1,984	22	1,962	
Parkinson's Disease				
Yes	19	1	18	0.197 (Fisher)
No	1,995	22	1,973	
Malignancy				
Yes	113	0	113	0.636 (Fisher)
No	1,901	23	1,878	
Diagnosis				
Osteoarthritis	1,935	20	1,915	0.025 (Fisher)
Rheumatoid arthritis (RA)	46	2	44	
Non-RA Inflammatory Arthritis	24	0	24	
Spontaneous Osteonecrosis of the Knee (SONK)	6	1	5	
Traumatic Arthritis	3	0	3	
Method of Operation				
Conventional	285	7	278	0.093 (Fisher)
Navigated	1,508	15	1,493	
Robotic	221	1	220	
Anesthesia				
General	642	9	633	0.501 (Fisher)
Spinal	1,372	14	1,358	
Tranexamic Acid				
Yes	1,874	17	1,857	0.004 (Fisher)
No	140	6	134	
Tourniquet Use				
Yes	1,945	20	1,925	0.042 (Fisher)
No	69	3	66	
Tourniquet Time	Median (IQR)			
*Shapiro-wilk < 0.001	81.0 (59.0–103.0)	72.0 (39.0–90.0)	81.0 (60.0–104.0)	0.077 (Mann Whitney)
Operative Time	Median (IQR)			
*Shapiro-wilk < 0.001	100.0 (80.0–122.0)	80.0 (74.5–103.5)	100.0 (80.0–122.0)	0.059 (Mann-Whitney)
Transfusion				
Yes	59	4	55	0.004 (Fisher)
No	1,955	19	1,936	
Chemical Thromboprophylaxis				
Yes	565	13	552	0.004 (Fisher)
No	1,449	10	1,439	
Intraoperative Dexamethasone				
Yes	1,125	8	1,117	0.056 (Fisher)
No	889	15	874	
Length of Stay	Median (IQR)			
*Shapiro-wilk < 0.001	4.0 (3.0–5.0)	7.0 (5.0–10.5)	4.0 (3.0–5.0)	<0.001 (Mann Whitney)
Discharge Destination				
Home	1,374	11	1,363	0.105 (Fisher)
Community Hospital	634	12	622	
Others	6	0	6	

choice of thromboprophylaxis (P = 0.049) and length of stay (P < 0.001) were significant predictors in the development of VTE. For the underlying diagnosis, rheumatoid arthritis (RA) had an 8.90-fold increased odds than OA for development of VTE (P = 0.012). On the use of thromboprophylaxis, aspirin and IPCD had a 4.35-fold increased odds of developing VTE (P = 0.007) than IPCD alone, while clexane and IPCD had a 5.29-fold increased odds of developing VTE (P = 0.015) than IPCD alone.

Patient's age (P = 0.567), previous stroke (P = 0.169), method of surgery (P = 0.539), use of tourniquet (P = 0.059), use of tranexamic acid (P = 0.059), use of dexamethasone (P = 0.930), and operative time (P = 0.60) were not significant factors in predicting risk of VTE.

Discussion

Our study aimed to evaluate the incidence of VTE in a large number of Asian patients undergoing knee arthroplasty in a tertiary hospital with well-developed ERAS protocols. ERAS has been shown to reduce the risk of VTEs in patient undergoing various surgeries including lung cancer resection from 11.67% to 1.54% [15], 2.17% in ovarian cancer patients undergoing cytoreductive surgery [16], 0.167% in patients undergoing curative colorectal malignancy resection. There are limited studies directly investigating VTE rates in patients with and without ERAS protocols, however, a meta-analysis of 74 random-controlled trials including 9076 patients showed ERAS reduced LOS by 1.88 days (P < 0.001) and risk of complications (risk ratio 0.71, P < 0.001).

We found that the incidence of symptomatic VTEs in our study over the past 5 years was low (1.14%) and did not identify any protective factors for VTE events in our model. In our model, the choice of thromboprophylaxis contributed significantly to the development of symptomatic VTE events (P = 0.007).

The use of aspirin and clexane increased the odds of patients developing VTEs (P = 0.007 and 0.015, respectively). This could be attributable to the fact that aspirin and clexane are utilized in patients identified at risk of VTE with risk factors such as hypertension, hyperlipidemia and 1 patient with peripheral vascular disease.

A 2022 meta-analysis of 14 studies and 4,259 Asian post-TKA patients by Wong et al showed no significant difference in symptomatic VTE rates and deaths depending on choice of thromboprophylaxis (DOACs, LMWH, mechanical only, and no thromboprophylaxis), although the study did not specify how different prophylaxis options were chosen in patients. However, they found that overall, mechanical only thromboprophylaxis had lower venography-diagnosed asymptomatic VTE incidents as compared to DOACs, LMWH and no thromboprophylaxis. LMWH and DOACs also had a higher minor bleeding incidence than no prophylaxis (11.71% and 6.33% difference respectively), while there were no significant differences in major bleeding events [17].

The 2021 Asia-Pacific VTE in knee and hip arthroplasty and hip

fracture surgery consensus statement recommended that mechanical devices for VTE thromboprophylaxis should be routinely applied, and mechanical only prophylaxis is an option for patients of standard VTE risk or elevated VTE risk but have increased bleeding risk. However, they concurred that there is inconclusive evidence whether mechanical only thromboprophylaxis can be effective in all Asian patients [18, 19].

This is of important consideration as in addition to its usual risks of bleeding and adverse drug reactions, the use of pharmacological thromboprophylaxis is also a risk factor for 90-day readmission for surgical site complication and prosthetic joint infection (adjusted OR 1.753 and 3.267, respectively). This could possibly due to post-operative hematomas which acts as a nidus for bacteria, and prolonged wound drainage which increases risk of wound dehiscence and provides retrograde pathway for pathogens, but the reasons are not well evaluated [20]. Therefore, significant consideration for the use of pharmacological thromboprophylaxis should be made, factoring in the patient profile, comorbidities, and operative factors.

Furthermore, we also identified LOS ($P < 0.001$), the diagnosis ($P = 0.048$) and the need for blood transfusion ($P = 0.007$) as significant predictive factors for VTE events. LOS as a predictive factor may however be confounded an increased LOS as a consequence of the DVT requiring treatment. Our study did not differentiate this. However, there is little doubt that increased LOS increases risk of hospital-acquired VTE [21].

Patients with RA also had an increased risk of VTE as compared to OA patients ($P = 0.012$). In a 2021 meta-analysis by Hu et al. including 272,884 RA patients, RA patients had an 2.23 times increased odds of developing VTE than control patients, due to the inflammatory state of RA patients contributes to endothelial injury, upregulates procoagulants, downregulates anticoagulants and suppresses fibrinolysis [22]. Some RA patients may also have antiphospholipid antibodies expressed which can contribute to this [23].

The need for blood transfusion hinders post-operative mobility until a satisfactory hemoglobin target is achieved. Lin et al., also concurred that blood transfusion increased the risk of VTE with a 2.98 times higher risk. This could be attributed to the increased hematocrit, enhanced collagen-induced platelet sensitivity due to red blood cells, increased red cell distribution width due to transfusion positively associated with the risks of VTE, and membrane changes and hemolysis of red blood cells that could enhance adhesive interaction and promote thrombosis [24]. Our study noted a longer operative time in patients who did not develop VTE than patients who developed VTE, although not statistically significant. This could potentially be due to the small number of VTE patients in our study.

TXA use was also not associated with increased VTE risk ($P = 0.059$), reassuring that TXA is safe for use to decrease blood loss and risk of transfusion without increasing the risk of VTE [25].

A large retrospective study of 13,969 TJA patients found that the strongest predictors of VTE post-discharge were increased LOS and increased severity of comorbidities [26]. Xu et al. reported increased DVT rates with delayed post-operative ambulation, likely due to venous stasis [27].

Underlying these risk factors however, our study, as well as multiple other studies, concurred that Asians generally have a low prevalence of VTEs, and lower inherent risk compared to Whites due to a combination of genetic and environmental factors, including obesity rates, oral contraceptive pill use, diet, and exercise. Genetic factors include the rarity of activated Protein C anticoagulant system dysfunction in Asians, lower mean fibrinogen levels, and lower prevalence of Factor VIIc, VIIIc, and prothrombin gene mutation G20210A in Asians (2–4% of Caucasians vs 0% in Asians) [28-32]. Other conventional established risk factors for VTE such as obesity and age were not found to be statistically significant in our study, and this is in concordance with other Asian studies, possibly due to the overall underlying low risk in Asians [33].

Pearse et al., reported lower DVT incidence in patients' mobilization immediately post-operative on post-operative day 0 at 1.0% as compared to 27.6% of patients who were not ($P < 0.001$) [34].

Overall, current literature remains divided and limited with regards to best choice of thromboprophylaxis for TKA patients, particularly in Asian populations. Discrepancies in efficacy of prophylaxis options also exist depending on VTE diagnostic modalities studied [17]. Given the wide myriad and variance in patients' risk profile including patient demographic, comorbidities, underlying disease, and planned operation, fundamentally the balance between the risk of VTE and risk of bleeding should be considered and individualized for each patient when choosing thromboprophylaxis. There are also promising early studies emerging regarding the application of machine learning and artificial intelligence software to aid in the prediction of VTE events, and hence aid in decision making for pharmacological thromboprophylaxis [35].

Our study had its strengths in the large number of patients and comprehensive perioperative data available for study. However, limitations include the retrospective design of the study, an overall low incidence VTE, and that only symptomatic cases were investigated for VTEs and included in our study. Furthermore, patients on pharmacological thromboprophylaxis may have had higher underlying risk of VTE. Further research can be performed with a propensity matched study, performing radiological investigation for all

patients to study asymptomatic VTEs, and performing further analysis to study the impact of ERAS.

In conclusion, there may be no need for chemical thromboprophylaxis in Asian populations post-TKA. The authors believe an individualized approach should be undertaken when selecting thromboprophylaxis based on stratification of VTE and bleeding risk.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Conflict of Interest: NIL; **Source of Support:** NIL

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