CLINICAL ARTICLE

Risk-Stratified Venous Thromboembolism Prophylaxis after Total Joint Arthroplasty: Low Molecular Weight Heparins and Sequential Aspirin *vs* Aggressive Chemoprophylaxis

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Objective: Venous thromboembolism (VTE) is a significant concern post total joint arthroplasty (TJA). However, the optimal prevention method of VTE remains controversial at present. This study aims to evaluate a risk-stratified VTE prophylaxis protocol for patients undergoing TJA.

Methods: A total of 891 TJA patients from January 2011 to November 2019 were retrospectively investigated. The study was divided into two cohorts. In cohort 1, 410 patients (250 females and 160 males, mean age 64.32 years) were treated with an aggressive VTE chemoprophylaxis protocol. In cohort 2, 481 patients were treated with a risk-stratified protocol that utilized low molecular weight heparins (LMWH) and sequential aspirin (ASA) for standard-risk patients (a total of 288 containing 177 females and 111 males, mean age 65.4 years), and targeted anticoagulation for high-risk patients (a total of 193 containing 121 females and 72 males, mean age 66.8 years). The patients were followed up at 2–4 weeks for an initial visit and at 6–10 weeks for a subsequent visit after surgery. A chart review of all patient medical records was performed to record the demographics, comorbidities, deep vein thrombosis, pulmonary embolus, superficial infection, deep infection, bleeding complications, and 90-day readmissions.

Results: The VTE rate was 1.71% (7/410) in cohort 1 and 1.46% (7/481) in cohort 2 respectively. For cohort 2, the VTE rate was 2.07% (4/193) in high-risk group and 1.04% (3/288) in standard-risk group. The readmission rate was 2.44% (10/410) in cohort 1 and 2.08% (10/481) in cohort 2. For cohort 2, the readmission rate was 2.07% (4/193) in high-risk group and 2.08% (6/288) in standard-risk group. The reasons for readmission were as follows: infection, 1.3% (5/410) in cohort 1 and 1.3% (6/481) in cohort 2; wound or bleeding complications, 0.48% (2/410) in cohort 1 and 0.2% (1/481) in cohort 2; trauma, 0.2% (1/410) in cohort 1 and 0.2% (1/481) in cohort 2; VTE, 0.2% (1/410) in cohort 1 and 0.2% (1/481) in cohort 2; others, 0.2% (1/410) in cohort 1 and 0.6% (3/481) in cohort 2. There was a decrease in VTE events and readmissions in the risk-stratified cohort, although this did not reach statistical significance. However, it was found that there was a significant reduction in costs ($P < 0.001$) with the use of LMWH/ASA, when compared with aggressive anticoagulation agents in the risk-stratified cohort.

Conclusion: The use of LMWH/ASA in a risk-stratified TJA population is a safe and cost-effective method of VTE prophylaxis.

Key words: Deep venous thrombosis; Pulmonary embolism; Risk stratification; Total joint arthroplasty; Venous thromboembolism

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Orthopaedic Surgery

Introduction

Total joint arthroplasty (TJA) is a new technique for the treatment of hip and knee disease after the successful application of modern artificial hip and knee implants in patients. It can effectively eradicate late hip and knee pain and greatly improve the quality of life of patients. However, due to the lack of mobility in a short period of time after TJA, patients need to stay in bed for a long time, which makes it easy to form venous thromboembolism (VTE). VTE comprises of pulmonary embolism (PE) and deep venous thrombosis (DVT), and this has been identified as a significant public health concern[1]. How to prevent the formation of postoperative VTE is also a hot topic in the medical field[2].

As the present understanding of the risk of VTE improves, the available prophylactic options increase gradually. At present, multimodal thrombosis prevention strategy is advocated to reduce the incidence of VTE after TJA by: (i) emphasizing the risk stratification of VTE before operation; (ii) stopping the use of coagulant drugs before operation; (iii) choosing epidural anesthesia as much as possible; (iv) avoiding rough operation and tissue trauma during operation, especially avoiding traction, clamping, and electric burn of important veins; (v) reducing intraoperative blood loss; (vi) handling femur or tibia carefully; and (vii) adopting early ambulation and chemical prevention for 4–6 weeks. However, the optimal VTE prevention protocol remains unknown. The incidence of VTE among TJA patients without prophylaxis has been reported to be nearly 50%[3]. Despite the advances in VTE prevention with present prophylaxis measures, approximately 0.3%–4.3% of patients had clinically symptomatic deep vein thrombosis (DVT)[4], while 0.14%–1.10% of patients experienced asymptomatic PE after TJA[5]. The incidence of VTE increased the morbidity and mortality associated with TJA[6]. Furthermore, patients who sustained a VTE had more extended hospital stays, increased rates of readmission, and had overall higher health care costs. A vast increase in the number of primary hip/knee replacements is predicted in the coming years[7], which necessitates the optimization of prophylaxis methods, in order to decrease health care burden and improve the morbidity and mortality associated with TJA operations.

Choosing a proper VTE prophylaxis method is a balance between safety and efficacy. Traditionally, aggressive anticoagulation agents, such as low molecular weight heparins (LMWH), vitamin K antagonists, and factor Xa inhibitors, have been the standard of care in the prevention of the VTE disease. Previous studies have confirmed that aspirin (ASA) is an effective drug for the prevention of VTE, with a low risk of bleeding or wound-related complications. ASA is a commonly used non-steroidal anti-inflammatory drug, which can inhibit the synthesis of platelet cyclooxygenase and thromboxane A2. It is mature, cheap, has no need to monitor, and has good anticoagulant effect. The retrospective analysis results of Raphael *et al.*[8] showed that the incidence of PE in patients receiving ASA anticoagulation was lower than that in patients receiving warfarin, and ASA anticoagulation had a lower incidence of symptomatic DVT and fewer wound-related problems. Bala *et al.*[9] used a large number of databases to analyze ASA, warfarin, enoxaparin, or factor Xa inhibitors, and the results showed that ASA, warfarin, enoxaparin, or factor Xa inhibitors were significantly lower than those receiving warfarin. Compared with warfarin, ASA has the lowest risk of bleeding, and has the same VTE prevention effect as Xa inhibitor. Despite the proven efficacy in VTE prevention, the increase in complications are potentially associated with these agents: bleeding, infection, wound problems, and the need for readmission and reoperation[10, 11]. In order to reduce these complications, the use of less aggressive means of prophylaxis has become popular. These methods include LMWH or Xa inhibitors, and sequential ASA[12].

The latest VTE prevention guidelines released by the Chinese Orthopaedic Association (COA)[13] and the American College of Chest Physicians (ACCP)[1] does not recommend ASA alone as an acceptable form of VTE prophylaxis after TJA. Despite several studies that evaluated the efficacy and safety profile of anticoagulation, there is still no clear consensus on the ideal strategy for each patient. In our institution, a risk-stratified VTE prophylaxis protocol consistent with the guidelines from the COA and ACCP was applied. Patients were divided into high-risk group and standard-risk group according to their past medical history and health status. Patients in the high-risk group received aggressive prophylaxis with either enoxaparin or rivaroxaban. Patients in the standard-risk group were treated with LMWH and/or ASA protocol. The effectiveness and safety of this risk-stratified VTE prevention protocol were evaluated by comparing it with the preventive effect without a risk-stratified scheme.

The main purpose of this study is as follows: (i) to compare the incidence of VTE rate between patients receiving risk-stratified VTE prevention protocol and patients receiving aggressive prophylaxis protocol; (ii) to prove the effectiveness and safety of the risk-stratified VTE prevention protocol; and (iii) to provide a valuable protocol for VTE prevention in clinic.

Material and Methods

Patients

The present study was approved by the institutional review board, and conducted at a single academic institution. All procedures were performed by one senior surgeon (WW Qian, MD). Using the institution's electronic medical record system, patients who underwent TJA between January 2011 and November 2019 were identified. The month of April 2014 was excluded, because this period was a transition month when the postoperative VTE prophylaxis protocol was updated to implement the risk-stratification strategy based on the presence of risk factors. Patients who received primary total knee or hip arthroplasty were selected for the present study. The inclusion criteria were as follows:

(i) patients are in line with hip and knee osteoarthritis and rheumatoid arthritis diagnostic criteria for inflammation and traumatic arthritis; (ii) primar unilateral hip and knee replacement operation; (iii) the preoperative color Doppler ultrasonography was negative for deep vein thrombosis of the lower limbs; (iv) a retrospective study. The exclusion criteria were as follows: (i) preexisting thromboembolic diseases, varicose veins of the lower extremities and arterial vascular diseases of the lower extremities; (ii) patients with long-term use of anticoagulants before admission, patients with a history of bleeding disorders or bleeding tendency in the preoperative coagulation test; (iii) lost to follow-up or incomplete data; (iv) patients with a history of joint replacement surgery; (v) patients using other drugs that may affect the results. A total of 891 patients who underwent total knee or hip arthroplasty were included in the present study.

These patients were divided into two cohorts; patients who received TJA from October 2011 to March 2014 (cohort 1) and patients who received TJA from May 2014 to November 2019 (cohort 2). All patients in cohort 1 received aggressive anticoagulation, regardless of the presence of risk factors. A department-wide risk-stratification protocol was adopted during the period for cohort 2. TJA patients were classified as high or standard risk for VTE (Fig. 1).

Risk Stratification

The patients in cohort 1 received aggressive prophylaxis with either enoxaparin (40 mg, subcutaneous, daily for 2–4 weeks) or rivaroxaban (10 mg, oral, daily for 14–21 days).

The medical charts of patients in cohort 2 were reviewed, and patients with one or more of the following risk factors were assigned to the high-risk group: a history of prior DVT or PE, a history of cancer, a body mass index of >35 kg/m^2, or current smoker. These patients received aggressive prophylaxis with either enoxaparin (40 mg, subcutaneous, daily for 2–4 weeks), or rivaroxaban (10 mg, oral, daily for 14–21 days). Patients with no risk factors were deemed a standard risk and placed on the LMWH and ASA protocol. Standard-risk patients were instructed to receive enoxaparin (40 mg, subcutaneous, daily for 3 days). Then, for sequential, a 100-mg enteric-coated aspirin (Bayer) was given once daily for 30 days. All patients received an intermittent pneumatic foot vein pump and stretched socks for the period until discharge.

Perioperative Care and VTE Surveillance

Each patient in both cohorts received the same perioperative care. This included receiving 1,000 mg of tranexamic acid (TXA) during surgery, and the use of stretched socks on the non-operative limb during the operation. There was no difference in the physical therapy and rehabilitation of patients among these two cohorts. Standard VTE monitoring with no additional surveillance measures was applied.

Outcome Measurement

Demographics

The descriptive demographics of the two cohorts included age, gender, body mass index, and comorbidities.

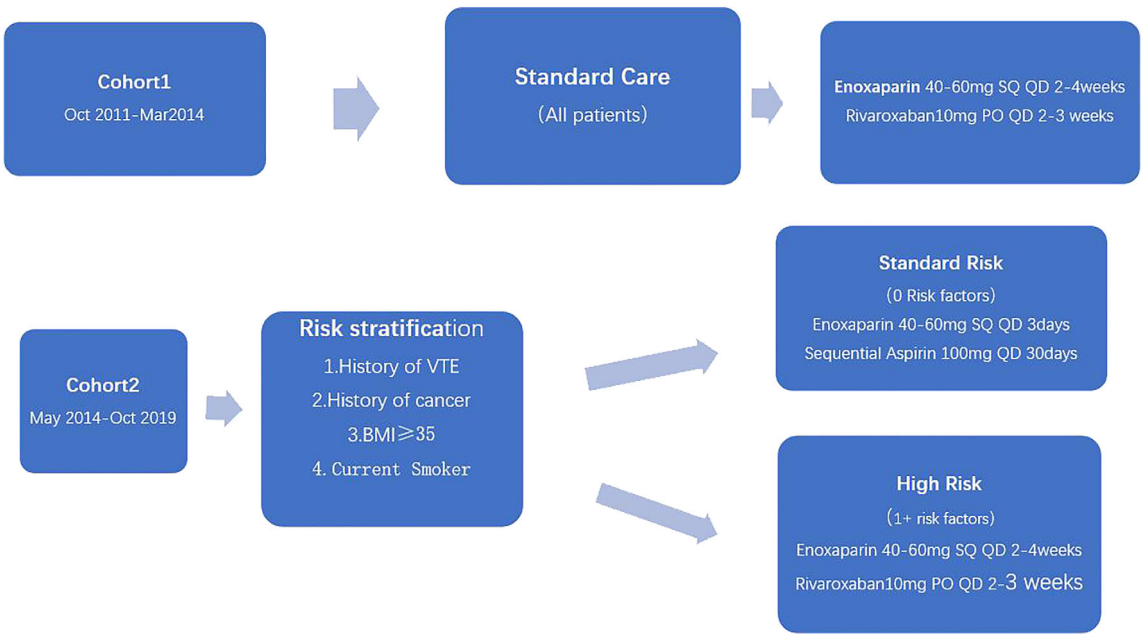

Fig. 1 Flowchart illustrating the VTE prophylaxis protocol before (cohort 1) and after (cohort 2) the implementation of a risk-stratification approach based on the presence of patient risk factors for VTE. BMI, body mass index.

VTE Events

The DVT was assessed before performing the TJA. Patients were assessed using the Wells score to determine whether there was visible swelling of the lower limbs (more significant than the preoperative value of 3 cm), pain, or Homan positiveness, while Doppler ultrasonography was used to investigate the DVT. The various scores indicated different probabilities of DVT diagnosis. A score dated a determined probability, while >6.0 indicated a high probability. Diagnostic criteria: (i) the venous lumen could not be closed; (ii) the cavity was hypoechoic or echoless; (iii) there was no or only a small amount of blood flow signal within the venous thrombosis; (iv) the pulse of the Doppler revealed no blood flow, or the spectrum did not change with respiration. If chest pain and chest tightness occurred, the patient was immediately tested for PE using a computed tomography pulmonary angiogram (CTPA).

Patients with clinical symptoms of DVT received duplex ultrasonography, while patients with clinical symptoms that suggested a PE received a spiral computed tomography PE protocol scan.

Postoperative clinical follow-up care: an initial visit at 2–4 weeks after surgery, and a subsequent visit at 6–10 weeks after surgery. All VTE results during the follow-up period were recorded.

Postoperative Complications and Readmission Rate

A chart review of all patient medical records was performed to record the DVT, pulmonary embolus, superficial infection, deep infection, bleeding complications, and 90-day readmissions.

Readmission was defined as unplanned re-admission for any reason within 90 days after operation, which included emergency room visit. If a patient was readmitted, the reason for readmission was recorded as either infection, wound/bleeding-related, trauma, VTE, or other. The "other" category included medical complications or issues unrelated to DVT prophylaxis.

Total Hospital Costs

The data of total hospital cost of patients who were enrolled in this study were obtained by using the institution's electronic medical record system. Billing data were used to obtain the quality assessment.

Statistical Analysis

All demographics were summarized using descriptive statistics. The statistical analysis between these cohorts was performed using the Fisher's exact test for categorical variables and independent *t*-test for continuous variables. The results were deemed to be significant at a *P*-value of <0.05 ($\boldsymbol{\alpha = 0.05}$). All statistical analyses were performed using the IBM SPSS software version 22 (IBM, Armonk, NY, USA).

Results

Demographics of the Two Cohorts

A total of 891 consecutive TJA patients were enrolled between 1 January 2011 and 31 October 2019, excluding April 2014. Cohort 1 (aggressive-only prophylaxis patients, 410 cases) consisted of patients who received aggressive modes of VTE prophylaxis. Cohort 2 (risk-stratified patients, 481 cases) consisted of patients who were risk-stratified, and subsequently given the appropriate type of VTE prophylaxis. In the risk-stratified group, 193 high-risk patients received aggressive prophylaxis, and 288 standard-risk patients received prophylaxis with LMWH (3 days) and ASA (100 mg daily, 30 days). The descriptive statistics between these two cohorts, which included age ($P = 0.439$), gender ($P = 0.772$), and body mass index ($P = 0.502$), were not statistically significant (Table 1).

Comparison of VTE Events

A total of seven VTE events occurred in 410 patients in the aggressive-only prophylaxis cohort, with a VTE rate of 1.71%. A total of seven VTE events occurred in 481 patients in the risk-stratified cohort, with a VTE rate of 1.46%. There was no statistically significant difference in the incidence of VTE between the aggressive- only and risk-stratified cohorts ($P = 0.855$). Patients in the risk-stratified cohort had no statistical difference in terms of the VTE rate ($P = 0.249$) between high-risk patients treated with aggressive prophylaxis (2.07%, 4/193) and standard-risk patients treated with LMWH/ASA (1.04%, 3/288) (Table 2).

TABLE 1 Descriptive statistics of the preoperative demographics of the aggressive-only VTE prophylaxis patients (Cohort 1) and the risk-stratified patients (Cohort 2)

Groups	PPx	*n*	Age (years, mean±SD)	Female (%)	BMI (kg/m^2, mean±SD)
Cohort 1	Aggressive	410	63.72 ± 11.1	61.01	28.7 ± 6.7
Cohort 2	Aggressive	193	64.9 ± 11.2	64.60	32.7 ± 7.9
	LMWH/ASA	288	63.4 ± 11.0	59.55	26.8 ± 5.5
P value			0.489	0.769	0.552

Note: ASA, aspirin; BMI, body mass index; LMWH, Low Molecular Weight Heparins; PPx, Prophylaxis; VTE, venous thromboembolism.

TABLE 2 The rate of VTE, readmissions, hospital costs, and adverse events among the aggressive-only VTE prophylaxis patients (Cohort 1) and the risk-stratified patients (Cohort 2)

Groups	PPx	*n*	Total VTE	VTE (%)	Readmit	RR (%)	Adverse Events	AE (%)	Cost (¥%)
Cohort1	Aggressive	410	7	1.70	10	2.49	16	3.99	+7.83
Cohort2	Aggressive	193	3	1.55		2.28	9	4.25	+17.14
	LMWH/ASA	288	4	1.38		2.01	9	3.21	_
	Total	481	7	1.45	10	2.13	18	3.62	+7.29
Total		891	14	1.57	20	2.31	34	3.79	+7.51
P value			0.855		0.622		0.624		0.674

Note: ASA, aspirin; LMWH, Low Molecular Weight Heparins; PPx, Prophylaxis; VTE, venous thromboembolism.

Comparison of Readmission Rates

It was found that the 30-day all-cause readmission rates decreased in risk-stratified patients. However, this did not reach statistical significance (P = 0.822). Patients in the aggressive-only cohort experienced a 2.44% (10/410) readmission rate, while patients in the risk-stratified cohort experienced a 2.08% (10/481) readmission rate. Among patients in the risk-stratified cohort, the readmission rates between high- and standard-risk patients again did not favor the LMWH/ASA group, and the difference was not statistically significant (P = 0.563), with high-risk patients treated with aggressive prophylaxis having a readmission rate of 2.07% (4/193) and standard-risk patients treated with LMWH/ASA having a readmission rate of 2.08% (6/288).

Comparison of Reasons for Readmission

The reasons for readmissions in the aggressive-only prophylaxis cohort were as follows: infection, 1.3% (5/410) of patients; wound or bleeding complications, 0.48% (2/410) of patients; trauma, 0.2% (1/410) of patients; VTE, 0.2% (1/410) of patients; other, 0.2% (1/410) of patients. The reason for readmission in the risk-stratified cohort was as follows: infection, 1.3% (6/481) of patients; wound or bleeding complications, 0.2% (1/481) of patients; trauma, 0.2% (1/481) of patients; VTE, 0.2% (1/481) of patients; other, 0.6% (3/481) of patients. None of the differing rates between cohorts reached a statistical significance. A comprehensive list of VTE events and readmissions experienced by patients in each cohort and subgroup are summarized in Table 3.

Comparison of Total Hospital Costs

The total hospital costs between these two cohorts were not statistically significant (P = 0.604). However, in the risk-stratified cohort, standard-risk patients treated with LMWH/ASA had a 13.14% lower cost when compared to high-risk patients who received a more aggressive VTE prophylaxis. This cost difference was clinically significant (P < 0.001).

Discussion

Risk-stratified VTE Prophylaxis Protocol Can Reduce Readmission and Adverse Events

The ideal VTE prophylaxis following TJA remains unknown[14]. The present study aims to review our institution's risk-stratification protocol, in order to provide effective VTE prophylaxis, while lowering the potential complications related to chemo-anticoagulation. The present study demonstrated that there was no difference in VTE rate between the risk-stratified combination of LMWH and ASA for standard-risk patients, and the aggressive anticoagulation in high-risk patients, when compared to non-risk-adjusted aggressive anticoagulation agents, for all TJA patients. However, there was a statistically similar readmission rate and overall adverse event rate between both cohorts. The readmissions and adverse events were lesser in the risk-stratified cohort. However, the size of the study was underpowered to achieve a statistical significance.

Risk-stratified VTE Prophylaxis Protocol Can Reduce the Cost and Complications of Treatment

Most importantly, in the present value-based health care system, the episode of care costs of standard-risk patients treated with ASA and LMWH in the risk-stratified cohort were significantly lesser (18%) than high-risk patients treated with aggressive anticoagulation. Furthermore, an increasing amount of data supports the use of LMWH in combination with ASA as a valid form of VTE prophylaxis with a lower complication rate after TJA. The present study was underpowered, and was not able to show a significant reduction in wound complications with the use of less aggressive VTE prophylaxis. However, other studies have demonstrated this reduction. Nam *et al.*[15] conducted a prospective study of 1,859 patients who underwent THA by utilizing similar risk-stratification measures, with the "routine"-risk cohort prescribed with LMWH/ASA and the "high"-risk cohort was prescribed with warfarin. It was found that there was a significantly lower rate of significant bleeding and wound complication in the "routine"-risk cohort, when compared with the "high"-risk cohort. Similar to the present findings, there

TABLE 3 The number of VTE cases among the aggressive-only VTE prophylaxis patients (Cohort 1) and the risk-stratified patients (Cohort 2) along with the reasons for readmission

Groups	PPx	*n*	VTE			Readmission				
			DVT	PE	Total	Infection	Wound/bleeding	VTE	Trauma	Other
Cohort1	Aggressive	410	6	1	7	5	2	1	1	1
Cohort2	Aggressive	193	2	1	3	3	1	1	0	1
	LMWH/ASA	288	4	0	4	3	0	0	1	2
Total		481	6	1	7	6	1	1	1	3

Note: ASA, aspirin; DVT, deep vein thrombosis; LMWH, Low Molecular Weight Heparins; PPx, Prophylaxis; VTE, venous thromboembolism.

was no difference in VTE event rate among the two cohorts. In 2018, a randomized controlled trial that involved patients who were undergoing total hip or knee arthroplasty revealed that for patients who received 5 days of rivaroxaban prophylaxis after TJA, extended prophylaxis with ASA was not significantly different from rivaroxaban in the prevention of symptomatic VTE[12]. In the present study, it was also found that the inexpensive and widely available ASA was not significantly different from the more expensive agents (rivaroxaban or LMWH).

Risk-stratified VTE Prophylaxis Protocol Is a Valuable Management Scheme

The optimum duration for VTE prophylaxis remains controversial, because the appropriate length of ASA prophylaxis after TJA has not be well-studied. The studies included in this systematic review reported various durations of ASA prophylaxis, which included 14 days, 21 days, 3 weeks, 1 month/4 weeks, 5 weeks, and 6 weeks[16, 17]. The ASA has also been shown to be a cardio-protective drug that can effectively prevent occlusive vascular events. The Antithrombotic Trialists' (ATT) collaboration meta-analysis revealed a 12% reduction in serious vascular complications, which included myocardial infarction (MI), stroke, or vascular death, when ASA was used for primary prevention, in addition to the one-fifth reduction in non-fatal MI[18].

The VTE rate was 1.59% in the present aggressive-only cohort and 1.49% in the present risk-stratified cohort, with no significant difference between groups. In the risk-stratified cohort, the VTE rate of standard-risk patients (1.19%) was lower than that of high-risk patients (1.95%). This was predicted, but was not statistically significant, which was likely due to the underpowered nature of the study. Brown *et al.*[19] conducted a pooled analysis of 14 randomized control trials of VTE prophylaxis among patients undergoing TJA. They found no difference in symptomatic DVTs, PEs, and fatal PEs among patients who were given aspirin, when compared with warfarin, enoxaparin, and fondaparinux. Bozic *et al.*[20] investigated 93,840 primary TKA patients, and patients prescribed with aspirin for VTE prophylaxis had identical or lower rates of VTE when compared to patients who received aggressive agents. In addition, similar large-scale studies have revealed the same result among THA patients[21]. The present study adds to the literature that the use of LMWH/ASA provides equivalent prophylaxis for VTE among standard-risk patients.

The present VTE prophylaxis risk-stratification protocol demonstrated cost savings without affecting quality, thereby increasing the value. It was found that there was a significant cost decrease in the LMWH/ASA subgroup in the risk-stratified cohort. It is noteworthy that the cost savings identified in the present study were not solely attributed to the use of LMWH/ASA, but likely multi-factorial, as it shows that patients with fewer medical comorbidities generally had lower costs of care. Other studies have compared the costs of aggressive chemoprophylaxis and LMWH/ASA. Kapoor *et al.*[22] similarly reported a cost savings of US$1,300 for the 4-week use of ASA, when compared to enoxaparin, after THA and TKA.

Strengths and Limitations

Several strengths and limitations of the present study should be noted. The strengths of the present study include the single-surgeon nature of the study. Therefore, the variation in both surgical approaches and type of implants used for the procedures could be reduced to a minimum. Furthermore, the present study conducted a pragmatic analysis that closely mirrored the practice of a typical joint replacement surgeon. Certain limitations were acknowledged for the present study. First, the most important issue that arose in all observational studies was selection bias. Second, the present study was a retrospective study that assessed the effectiveness of our institution's risk-stratification VTE protocol. Thus, the present data collection relied on the accuracy of our electronic medical record, which may have contained errors in terms of coding or documentation. In addition, these two cohorts were not concurrent. Hence, the investigators were not aware of any other treatment variables that changed between the periods of these two cohorts, and it was considered that the consecutive nature of these cohorts minimized any unrecognized treatment differences.

No additional DVT/PE surveillance measures were conducted in addition to the typical standard of care. Although this limited the identification of the exact number

of possible VTE events, the screening focused on clinical events that impacted patient care, and this was uniformly applied for all patients in both cohorts. This was consistent with the COA and ACCP guidelines, which recommend no routine postoperative duplex ultrasonography for patients undergoing TKA and THA[13, 19]. Although oral warfarin itself is available in inexpensive generic forms, its use added to the costs of routine testing for patients.

Conclusion

The present study demonstrated that the use of a VTE risk-stratification protocol designed to provide the appropriate intensity of VTE prophylaxis for individual patients after TJA is safe and cost-effective. The combination of LMWH and ASA provides a reasonable alternative to the traditional aggressive chemoprophylaxis agents, while avoiding bleeding-associated complications in selected standard-risk patients. Further large-sample prospective studies are needed to determine the optimal prophylaxis algorithm that would allow for a personalized, efficacious, and safe thromboprophylaxis regimen.

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