

# Potential Risk Factors Contributing to Development of Venous Thromboembolism for Total Knee Replacements Patients Prophylaxed With Rivaroxaban: A Retrospective Case-Control Study

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## Abstract

Rivaroxaban after total knee arthroplasty (TKA) is used to prevent postoperative venous thromboembolism (VTE); however, despite thromboprophylaxis, some patients still develop postoperative VTE. To determine whether tourniquet time, time to initiate rivaroxaban (TTI<sub>RIV</sub>), or Body Mass Index (BMI) was associated with postoperative VTE. A retrospective case-control study was conducted. Those patients that developed VTE despite prophylaxis (cases) were compared to controls (no VTE). A univariate analysis was conducted ( $p \leq 0.05$  statistically significant). Seven VTE cases were identified from 234 TKA-patients. Patients with and without VTE had BMI of  $40.1 \pm 9.1$  and  $32.8 \pm 7.5$ , respectively ( $p = 0.064$ ). TTI<sub>RIV</sub> in VTE and control group was  $28.2 \pm 4.7$  hours and  $26.4 \pm 4.2$  hours, respectively ( $p = 0.39$ ). Mean tourniquet time in VTE and control group was  $65.0 \pm 8.7$  minutes and  $49 \pm 8.8$  minutes, respectively ( $p = 0.0007$ ). Statistically significant differences in tourniquet times were noted between VTE and non-VTE group but not for TTI<sub>RIV</sub> and BMI. Prolonged tourniquet use could pose a potential risk factor for postoperative VTE. Thromboprophylaxis management may need to be adjusted, based on patient-specific factors that could include increasing doses of oral anticoagulants and/or mechanical prophylaxis. However, further large-scale studies are required to establish pathophysiology.

## Keywords

venous thromboembolism, orthopedic surgery, tourniquet, body mass index, rivaroxaban thromboprophylaxis

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## Background

Venous thromboembolism (VTE) is a major postoperative complication for patients undergoing total knee arthroplasty (TKA). Current guidelines require that all TKA patients be given thromboprophylaxis therapy following surgery to minimize the risk of postoperative VTE.<sup>1</sup> Previously, various parenteral anticoagulants were commonly administered as a part of therapy but required extensive monitoring and administration protocols. As a result of these limitations, over the last decade, clinicians have adopted novel oral anticoagulants (NOACs) into their routine practice.<sup>2</sup>

Rivaroxaban was approved in the United States by the Food and Drug Administration in 2011.<sup>3</sup> Marketed as Xarelto, it was

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the first oral direct factor Xa inhibitor and is commonly used for anticoagulation therapy following TKA as a replacement for older parenteral anticoagulants. The results of the phase 3 RECORD trials were promising, indicating that rivaroxaban was superior to subcutaneous enoxaparin in preventing postoperative VTE while having a similar bleeding risk in TKA patients.<sup>4,5</sup> In some situations, however, despite using Rivaroxaban therapy, some patients still develop VTE during the immediate postoperative period.<sup>1</sup> Scientific research on risk factors potentially causing postoperative VTE while receiving rivaroxaban prophylaxis is lacking or inconclusive. This study explores mechanical, time-dependent intraoperative factors and patient-specific risk factors which may lead to the development of postoperative VTE in patients who have undergone TKA, despite receiving rivaroxaban therapy.

Currently at our center, routine preop screening for VTE is conducted. Patients with thromboembolic disease are identified and management may be altered in that set of patients. Those that are either asymptomatic or with no known pro-thrombotic comorbidities proceed with routine management of their TKA. Postoperatively, all patients are provided with oral thromboprophylaxis and are screened for any symptoms or signs of thromboembolic disease. However, the reason why initially asymptomatic patients with no known pro-thrombotic comorbidities may still develop postoperatively VTE is the rationale for this study.

The results from clinical trials using NOACs have suggested optimum first dose administration times but quality scientific research is lacking.<sup>6</sup> The average time to initiate rivaroxaban prophylaxis after wound closure in the RECORD trials was within 6-8 hours.<sup>4,5</sup> However, observations at clinical institutions illustrated that initiation time of rivaroxaban is not consistent as outlined in the clinical trials and often varies. In addition, previous studies have shown intraoperative development of asymptomatic deep venous thrombosis (DVT).<sup>7</sup> Venography and imaging studies have demonstrated images of DVT formation at early stages of the knee surgery.<sup>8</sup> This supports nursing and thrombosis staff reporting that some postoperative TKA patients developed clinical signs and symptoms of VTE prior to initiation of rivaroxaban. In addition, this observation suggests that certain intraoperative factors may increase the risk of VTE in the immediate postoperative period, ultimately resulting in the failure of rivaroxaban. Studies have examined thrombotic events resulting from intraoperative factors such as prolonged tourniquet application, but conclusions are unclear and conflicting.<sup>9-12</sup> Previous literature has also suggested that a high body mass index (BMI) is an independent risk factor for VTE but does not show the exact effects of BMI on the incidence of VTE after knee surgery.<sup>13</sup> Moreover, a post-hoc analysis published after the RECORD trial showed the potential effect BMI may have on VTE, but data did not permit an analysis on the different classes of obesity and VTE.<sup>14</sup>

A few studies have specifically analysed the role of these independent factors on postoperative VTE in TKA patients who receive standard rivaroxaban prophylaxis. However, the results of these studies are comparatively conflicting. In addition, no

scientific research was found on what the combined effects of these independent factors may have on postoperative VTE, relative to each other. The aim of our pilot study was to analyze the independent effects of time to initiate rivaroxaban prophylaxis ( $TTI_{RIV}$ ), patient BMI, and duration of intraoperative tourniquet use on the development of postoperative symptomatic VTE in patients receiving standard rivaroxaban therapy after knee surgery. Using the results of this study, we hope to further conduct a larger study to understand the exact pathophysiology of postoperative VTE and ultimately work toward improving guidelines for thromboprophylaxis therapy given to patients undergoing TKA.

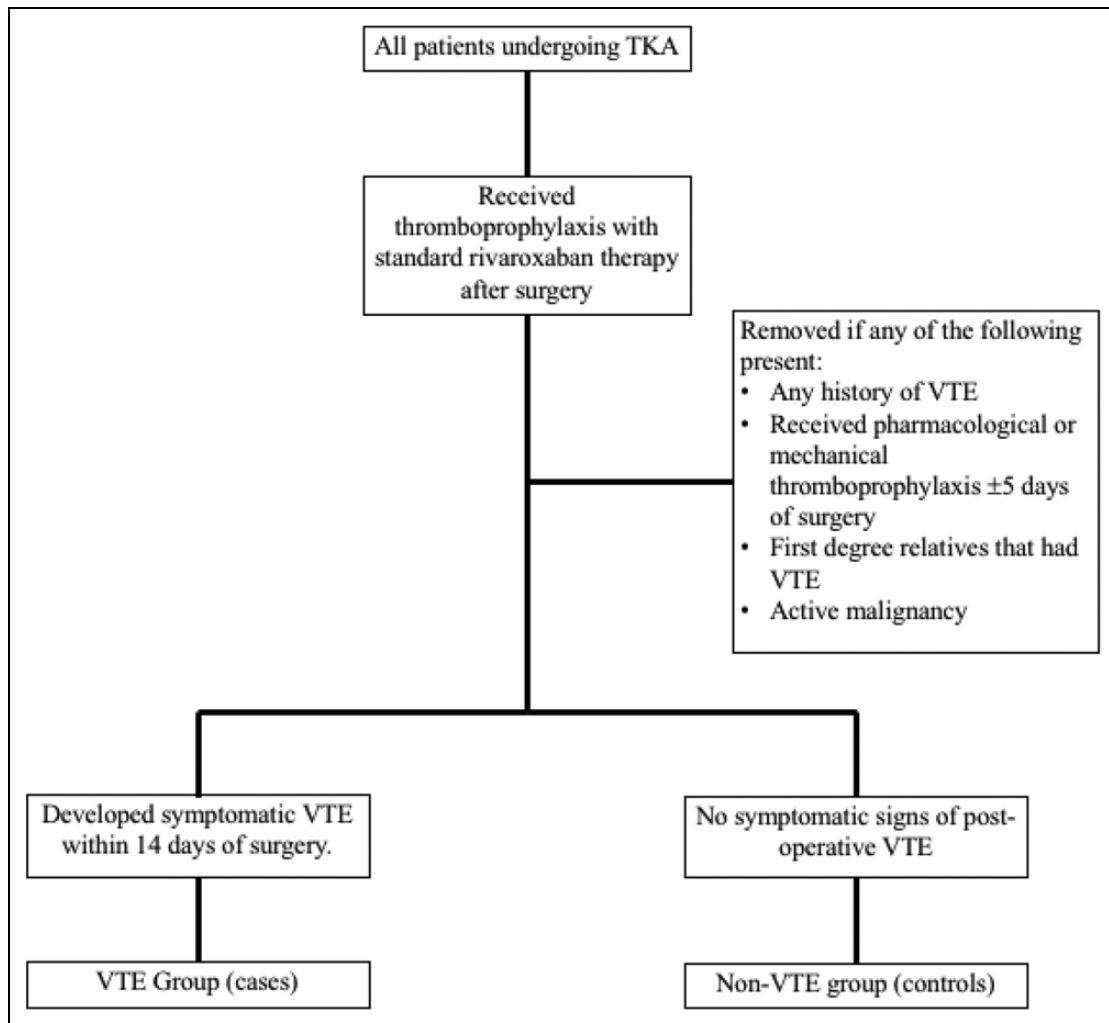
## Methods

### Study Design

A retrospective case-control study at St. Joseph's Health Care (Hamilton, ON, Canada) was conducted using patients who underwent TKA and received standard rivaroxaban administration after surgery. The database was compiled by identifying TKA patients from the records of thrombosis service who received the standardized dose of rivaroxaban (10 mg daily) for postoperative anticoagulation therapy. Relevant data were extracted directly from patient charts and stored in an online protected database. To ensure reliability and accuracy of the database, the data were collected independently by two experienced and trained data abstractors, an experienced thrombosis nurse, and an academic research student. The two individual databases from each data collector were then compared using statistical measures for reliability. An inter-rater reliability test was conducted to judge the homogeneity of the data. In the case of any disagreement, the data collectors jointly reviewed the patient chart to arrive at a consensus. All data collection was completed in accordance with appropriate practices outlined and approved by the Hamilton Integrated Research Ethics Board.

### Eligible Patients

The event in the case group for this study was defined as the patient having their first lifetime episode of symptomatic VTE within 14 days of TKA despite receiving rivaroxaban prophylaxis (VTE group). Each VTE patient was then compared with two randomly selected control patients who underwent the same surgery, received the same rivaroxaban anticoagulation therapy, but experienced no postoperative VTE complication (control group). Any patients who experienced prior VTE, were on any other forms of pharmacological or mechanical thromboprophylaxis within 5 days of surgery, had any first degree relatives with history of VTE, or had any active malignancy were excluded from the study. All treatment dose anticoagulation patients were also excluded. To ensure homogeneity of the surgical procedure and intraoperative factors, data was only collected retrospectively from patients who had the same surgeon. A study design graphic is seen in Figure 1.



**Figure 1.** Study design.

### Data Collection

Data on patient demographics (age, gender, body weight, and BMI), medical history (known thrombophilia conditions, prothrombotic medical comorbidity, patient and family history of VTE), surgical details (type of surgery, surgery duration, estimated blood loss, duration of intraoperative tourniquet use, units of packed red blood cell administered, preoperative and postoperative hemoglobin) and postoperative details (time to initiate rivaroxaban dose, duration of hospital stay) were extracted.

Patient demographic data were recorded from the preoperative assessment reports. Medical history and prothrombotic comorbidities were obtained from the Department of Internal Medicine's consult reports or Department of Vascular Medicine anticoagulation consultation form. Information on other prothrombotic medical comorbidities that was extracted from the patient chart included presence of high blood pressure (HTN), heparin-induced thrombocytopenia (HIT), active cancer, estrogen/hormone therapy, peripheral vascular disease, mechanical heart valve, coronary arterial disease (CAD), peripheral

vascular disease (PVD), cardiomyopathy, congestive heart failure (CHF), atrial fibrillation, diabetes mellitus (DM) and prior stroke. Extracted data also included information on known thrombophilia conditions such as information on prior VTE, family history of VTE, prothrombin gene mutation (PGM), factor V Leiden (FVL), protein C deficiency (PC def), protein S deficiency (PS def), antithrombin deficiency (AT def), antiphospholipid syndrome (APLS), hyperhomocysteinemia.

Surgical details such as start and end times of the operation, total blood loss, length of tourniquet use, and any intraoperative complications were obtained from the patient's intraoperative report. Davol (surgical drain) output in the first 24 hours was also noted as per the nursing assessment charts. Pre and postoperative hemoglobin levels were also recorded using the most recent laboratory test results for surgery. The duration of time between the end of surgery and first administration of rivaroxaban was defined as the time to initiate rivaroxaban prophylaxis (TTI<sub>RIV</sub>). The time of the first dose of rivaroxaban administered to the patient was obtained as per the computer-generated patient medication record (C-MAR). Information on specific cause for delay in prophylaxis was also noted.

For patients who had postoperative VTE, data on type and location of VTE in addition to the type and duration of anticoagulation therapy prescribed were also collected. This information was collected from the physician order sheet and patient discharge summary. All symptomatic VTE cases were objectively diagnosed using ultrasound imaging. Specifically, data on type and location of VTE were obtained from the summary of the ultrasound report. The weight bearing status (WBS) for all patients before surgery and through recovery was also recorded as per the orthopedic assessment consultation form.

### Statistical Measures

Mean  $\pm$  SD for each group (case versus control) was calculated for each variable. A univariate analysis was done using Student's *t*-test (assuming equal variances) to determine the independent association of each casual variable (BMI, TTI<sub>RIV</sub>, and duration of intraoperative tourniquet use) on postoperative symptomatic VTE. SAS was used to set up this model and determine the above values. A *p* value of  $\leq 0.05$  was considered statistically significant.

## Results

There were 234 patients who underwent total joint replacement at St. Joseph Health Care Hamilton from 2012-2015. From this pool of patients, the records of thrombosis service identified 7 patients meeting our inclusion criteria (experienced first lifetime episode of postoperative VTE, were given no other type of pharmacological or mechanical thromboprophylaxis within 5 days of surgery, had operation by same surgeon, had no first degree relatives who had prior VTE, no active malignancy or other bleeding disorder) who experienced VTE within 14 days of surgery despite receiving rivaroxaban prophylaxis, showing an incidence of 3%.

Among TKA patients who did not develop postoperative VTE (control group), 14 patients were randomly selected as controls who met the same inclusion criteria as the VTE group. The surgeon selected for the study performed the most TKA procedures during the time period of this study, giving the maximum sample size possible.

### Results: Baseline Patient Characteristics

The baseline characteristics of the enrolled patients are shown in Table 1. The mean age for the VTE and control groups was 61.4 and 65.4 years old, respectively. Twenty-nine percent of the patients in the VTE group and 36% of patients in the control group were males. The VTE group had a higher mean body weight (106.4 kg) than the control group (87.05 kg). Approximately 40% of patients in the VTE group and 80% of the control group had clinically diagnosed high blood pressure. Only one patient in the control group was on hormone (estrogen) therapy and one patient had coronary arterial disease. Furthermore, there was also one patient in each group who was diagnosed with diabetes mellitus. Other common medical comorbidities

**Table 1.** Baseline Patient Characteristics.

Baseline Demographic Variable	VTE Group (n = 7)	Non-VTE Group (control: n = 14)
Age (mean, range)	61.4 (52, 75)	65.4 (50, 81)
Sex-Male (n, %)	2 (29)	5 (36)
Body weight (kg) (Mean, range)	106.4 (85.3, 132.5)	87.1 (63.5, 130)
BMI (mean, range)	40.13 (26, 50.4)	32.81 (22.9, 48.3)
Surgical procedure		
Right total knee replacement (n, %)	6 (86%)	3 (21%)
Weight bearing as tolerated	7 (100)	14 (100)
Other prothrombotic medical comorbidity		
– High Blood Pressure (HTN)	3 (38%)	11 (78%)
– Estrogen / hormone therapy	0	1 (7%)
– Diabetes mellitus (DM)	1 (13%)	1 (7%)
– Coronary arterial disease (CAD)	0	1 (7%)
– Family history of VTE	0	0
Venous Thromboembolism (n, %)		
– Ipsilateral deep vein thrombosis (relative to TKA)	1 (14%)	
– Pulmonary embolism	6 (86%)	

presented in both groups were immobility, obesity, hyperlipidemia, and osteoarthritis. The internist's consult report had no indication of any patients having a family history of VTE, either in the VTE group or the control group. Furthermore, orthopedic assessments classified all patients in both groups as weight bearing as tolerated (WBAT). Within the VTE group, six had objectively diagnosed pulmonary embolism and one patient had ipsilateral DVT. A wide variety of anticoagulants were given as treatment to patients who had postoperative VTE. There were also no reported fatalities in any patient groups (Table 1).

### Results: Relevant Surgical Data

All patients underwent standard TKA completed by the same surgeon with the administration of 30 mL of tranexamic acid. The mean surgery time were 71 minutes and 62 minutes for the VTE and the control groups, respectively (*p* = 0.036). Tourniquet was used in all surgeries at a constant pressure of 350 mmHg. Patients in both groups had uneventful surgeries with no intraoperative complications, as indicated on the postoperative reports. In both groups, there were no major blood losses reported or any administration of packed red blood cells.

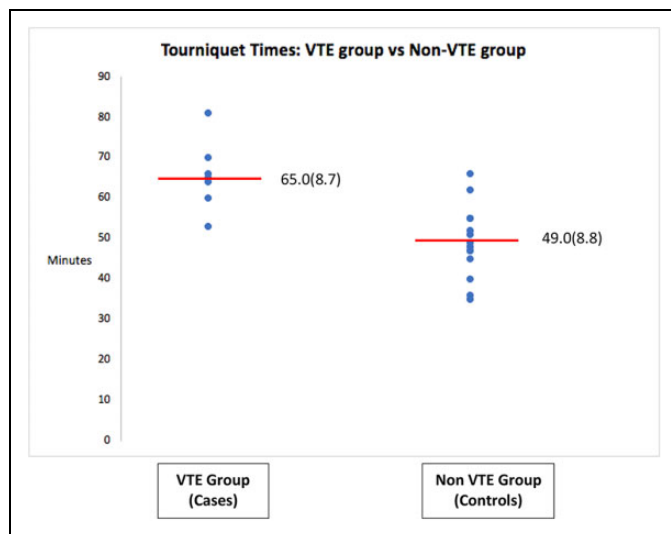
### Results: Time Duration of Tourniquet Use, BMI, and TTI<sub>RIV</sub>

Results from the Student's *t*-test for each independent variable are listed in Table 2. Patients in the VTE group tended to be

**Table 2.** Results of Student's t-Test Showing Means  $\pm$  SD of the Predictor Variables (BMI, Time Duration of Tourniquet Use, TTI<sub>RIV</sub>) by VTE Group and Control Group.

Variables	Case (n = 7)	Control (n = 14)	P value
BMI	40.1 $\pm$ 9.1*	32.8 $\pm$ 7.5	0.064
TTI <sub>RIV</sub> (Hours)	28.2 $\pm$ 4.7	26.4 $\pm$ 4.2	0.39
Time duration of tourniquet (minutes)	65.0 $\pm$ 8.7	49.0 $\pm$ 8.8	0.0007

(\*Mean  $\pm$  SD).



**Figure 2.** Individual Tourniquet Times \*MEAN (SD) \*\*They are two data points in the controls measuring 47 minutes which are super-imposed on each other.

heavier than the controls with the average BMI of  $40.1 \pm 9.1$  and  $32.8 \pm 27.5$  in the VTE and control groups, respectively ( $p = 0.064$ ). The TTI<sub>RIV</sub> was numerically lower in the control ( $26.4 \pm 4.2$  hours) compared to the VTE group ( $28.2 \pm 4.7$  hours), but the difference was not significant ( $p = 0.39$ ). In addition, there were no indications for specifying the delay of prophylaxis initiation in any of the patients. The time duration of intraoperative tourniquet use showed a significant difference between the VTE and the control group. Mean tourniquet time was  $65.0 \pm 8.7$  minutes in the VTE group, but only  $49.0 \pm 8.8$  minutes in the control group ( $p < 0.001$ ). Consequently, the length of the operation was longer for the VTE group (71 minutes) compared to the control group (61 minutes). The individual tourniquet times are displayed in Figure 2 and show very little overlap in the distributions for both VTE cases and controls. An exploratory step-wise analysis between the three pre-specified risk factors and tourniquet time suggested that TTI<sub>RIV</sub> and BMI provided little explanatory information over and above tourniquet time.

In summary, there were statistically significant differences between the VTE group and control group in terms of time duration of tourniquet application, however, there was no statistical difference between both TTI<sub>RIV</sub> and BMI in the VTE vs. non-VTE group. In addition, a stepwise logistic regression model supported the univariate finding that tourniquet time was the only variable exhibiting statistically important influences on VTE incidence in our patient population.

## Discussion

This study investigated the potential association of three key factors which may increase the risk of postoperative VTE despite receiving rivaroxaban prophylaxis. The results of this study suggest the potential effect of time duration of intraoperative tourniquet use on the incidence of postoperative VTE. The results are discussed below.

### Time Duration of Intraoperative Tourniquet Use

The results of our study suggest a potential association between prolonged tourniquet time and incidence of postoperative VTE. In this study, it was observed by the nursing staff that patients experienced clinical signs and symptoms of VTE before the initiation of rivaroxaban. In addition, the patient that experienced DVT had the clot in the operative leg.

This study illustrates that prolonged tourniquet application is associated with early postoperative VTE despite routine rivaroxaban prophylaxis. Specifically, our results show an average 16 minute longer tourniquet use in patients that developed postoperative VTE than in the controls. Controlling for the homogeneity of the surgical procedure by using data from a single surgeon suggests that potentially, one avenue of reducing postoperative VTE may be minimizing tourniquet use during surgery; however, larger scale studies are needed.

### Intraoperative Tourniquet Use—Benefits Versus Harms

The benefit or advantage of using intraoperative tourniquet and its effect on postoperative VTE in TKA patients is conflicting, with some studies suggesting benefits and some suggesting harm.<sup>10-12</sup> A study that included over 500 total knee replacement patients found an increasing incidence of postoperative VTE in patients who had tourniquet applied for more than 60 minutes.<sup>15</sup> This is consistent with the results of our study, as patients who experienced VTE in our study had a mean tourniquet application of greater than 60 minutes and those who did not experience VTE had a mean tourniquet application of less than 60 minutes. In addition, another randomized clinical trial with 50 patients that measured outcomes of tourniquet use during knee replacements showed a higher amount of postoperative pain with less range of motion compared to the non-tourniquet group.<sup>16</sup> Furthermore, a meta-analysis involving 13 randomized control trials with almost 900 patients showed an increased risk ratio of postoperative complications like VTE in the tourniquet group vs non-tourniquet group.<sup>12</sup>

However, this analysis also reported lower amounts of intraoperative blood loss in the tourniquet group, which has been consistent in other studies.<sup>17</sup> Another study found excellent clinical outcomes in patients who had undergone total knee replacement without tourniquet use.<sup>18</sup>

The use of intraoperative tourniquet and its effect on postoperative VTE in TKA patients is conflicting.<sup>9-12</sup> There have been past studies that have suggested tourniquet use to be a contributing factor to postoperative VTE. Wilson et al. reported that compression of the blood vessels closer to the bone through the use of tourniquet could increase blood vessel lesions.<sup>9</sup> Another study found that tourniquet use on the superficial femoral artery during knee surgery may actually lead to atheromatous and subsequent plaque embolization.<sup>19</sup> The results of our study support this, as 85 percent of our index patients experienced pulmonary embolism, likely resulting from thrombus embolization in the vessel.

Using prolonged length of tourniquet application during surgery has been shown to have benefits as well. For example, a randomized blind clinical trial comparing a short duration vs a long duration of tourniquet application found that a short duration of tourniquet use was associated with increased blood loss and increased operating time due to lack of a clear operative field relative to long duration of tourniquet use.<sup>20</sup>

Evidently, results from studies on the use of tourniquet in surgery is controversial. It seems that prolonged use of tourniquet during surgery may help to lower total blood loss but may lead to increase in postoperative complications in specific patients. Therefore, the results of our study, along with other studies, suggest that further optimization of tourniquet timing may have to be adjusted to individual patients. However, our study warrants additional larger scale studies to explore further associations between prolonged tourniquet use and VTE.

### *Time to Initiate Prophylaxis (TTI<sub>RIV</sub>)*

This study illustrates the real-world practice of rivaroxaban prophylaxis, as the literature suggests times for initiation of prophylaxis vary across institutions.<sup>6</sup> The results of our study indicated a non-significant difference between the TTI<sub>RIV</sub> of the index and the control group. However, the TTI<sub>RIV</sub> in our study was significantly longer compared to the 6-8 hour window described in the RECORD trials.<sup>4,5</sup> Even with the prolonged TTI<sub>RIV</sub> in our study, there was no increase in incidence of postoperative VTE among our patients. This finding suggests that delaying rivaroxaban prophylaxis may not directly increase the risk of postoperative VTE, however, further larger scale studies are warranted.

### *Body Mass Index*

Previous studies have shown that obese patients are more likely to undergo major orthopedic surgery like TKA than less heavy patients.<sup>21</sup> Since being overweight is considered an independent risk factor for VTE,<sup>13</sup> one of the aims of this study was to investigate the association between larger body weight and

postoperative VTE. The results of our study did not show a statistically significant difference between the BMI of patients who had postoperative VTE and those who did not, despite receiving rivaroxaban treatment.

Our results are consistent with the post hoc analysis of the RECORDS trials (14) which showed that BMI >30 is not a risk factor for postoperative VTE after knee surgery.<sup>14</sup> In addition, our results are in agreement with a large database study that included more than 200,000 TKA patients. This database analysis showed that there was no association with an increased rate of DVT resulting in treatment identified in obese patients classified according to the World Health Organization obesity BMI criteria. However, this analysis did show an association between increase risk of pulmonary embolism resulting in treatment in obese patients undergoing TKA vs non-obese patients.<sup>22</sup> In addition, another study with over 12,000 patients showed that they were no significant differences between asymptomatic or symptomatic VTE in obese vs non-obese patients.

Many studies have shown that obesity is an independent risk factor for post-operative VTE after orthopedic surgery. A study that included almost 10,000 patients showed that obesity was an independent risk factor for postoperative VTE after a hip replacement surgery.<sup>23</sup> In addition, a large meta-analysis which included over 14 million hip and knee replacement surgeries indicated an increase in relative risk of postoperative VTE associated with increasing BMIs.<sup>24</sup> This analysis suggested that modifiable risk factors such as BMI should be addressed prior to orthopedic surgery. The results of our study did not show a significant difference in the incidence of VTE between different BMIs. Two possible reasons for the fact that no association was found between BMI and VTE incidence are the small sample size or the fact that obese individuals may have had subclinical DVT which did not develop to symptomatic presentation. However, larger studies are needed for further exploration.

The results of our study indicate that prolonged time duration of tourniquet use may be a risk factor for postoperative VTE. Specifically, our results shed more light on the discussion of possibly minimizing tourniquet time during TKA for high-risk patients. A prospective double-blinded study including 150 patients who underwent TKA with or without tourniquet showed that the non-tourniquet group displayed better range of motion in the initial 3 postoperative days and earlier straight-leg raising.<sup>25</sup> Moreover, the benefit of tourniquet use remains controversial. Some studies suggest that tourniquet use may reduce blood loss<sup>26</sup> but there are also studies that suggest use of tourniquet makes no difference to total blood loss during TKA.<sup>27</sup>

We hope that the results of this study will facilitate the discussion of brainstorming possible ways to help minimize the incidence of postoperative VTE despite the use of routine anticoagulants. This also opens the door to additional research on the efficacy of adding different forms of anticoagulation treatment such as increasing dosages of oral anticoagulants or including mechanical thromboprophylaxis in routine patient

management. Thus, we propose that slight alterations in thromboprophylaxis treatment plans based on patient-specific outcomes may be beneficial for patients who are at high risk for VTE, such as morbidly obese patients but additional studies are needed.

### Limitations

Our study is not without its limitations. Firstly, the most significant limitation of this study is the limited sample size. The reason our sample size is small is because we aimed to ensure as much homogeneity among our VTE patients as possible. In addition, since we analyzed intraoperative factors, it was important to ensure homogeneity of the surgical procedure to reduce other confounding variables. Consequently, we limited our patients to those who had the same surgeon. The aim of this study was not to present firm recommendations to change thromboprophylaxis management guidelines, but merely to introduce the discussion of potentially minimizing the use of tourniquet when considering the risk of postoperative VTE after TKA. Given our study design and sample size, we recognize our limitations, however, do have a better understanding of the thrombosis management in our center. We hope that this study, along with other larger scaled studies, would stimulate discussion of having patient-specific thromboprophylaxis protocols that may include optimizing tourniquet application times.

### Conclusion

In conclusion, our study explored the independent association of certain intraoperative factors such as tourniquet use, BMI, and time to initiate prophylaxis with postoperative VTE in TKA patients who received rivaroxaban. Our results indicate that time of tourniquet use was largely associated with postoperative VTE; however, the start time of prophylaxis or BMI was not a risk factor for VTE. Thus, we propose that further studies are required to address these aspects and that a patient-specific thromboprophylaxis protocol taking into account the risk factors outlined above be developed.

### Authors' Note

Ethical approval to report this case was obtained from Hamilton Integrated Research Ethics Board (APPROVAL 14 850C).


### Declaration of Conflicting Interests

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