


**BRIEF REPORT**

# Thromboprophylaxis with rivaroxaban in patients with malignancy and central venous lines (TRIM-Line): A two-center open-label pilot randomized controlled trial

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**Abstract**

**Background:** Central venous catheter (CVC) insertion is an important risk factor for venous thromboembolism (VTE) among patients with cancer. Routine use of primary thromboprophylaxis in this patient population is not currently recommended. We sought to assess the feasibility of conducting a randomized controlled trial (RCT) assessing the safety and efficacy of rivaroxaban (10 mg daily) to prevent VTE complications in this patient population.

**Methods:** This is a two-center prospective, randomized, open blinded end point pilot trial including patients with active cancer and a newly inserted CVC. Patients were randomly assigned 1:1 to rivaroxaban or observation for 90 days. The primary feasibility outcome of this pilot study was the number of participants recruited per month. Secondary clinical outcomes included thrombotic complications, major VTE, and major bleeding episodes.

**Results:** Overall, 105 patients were enrolled over 11 months. The average enrollment rates were 7.5 and 2 patients per month at the two participating centers, respectively. Overall, thrombotic complications occurred in 3 patients in the rivaroxaban group (5.8%; 95% confidence interval [CI], 1.2-16.0) compared with 5 patients in the control group (9.4%; 95% CI, 3.1-20.7) (HR, 0.58; 95% CI, 0.14-2.5). Major VTE occurred in 2 (3.9%; 95% CI, 0.5-13.2) and 3 (5.7%; 95% CI, 1.2-15.7) patients in the rivaroxaban and control group, respectively (HR, 0.66; 95% CI, 0.11-3.9). One patient (1.9%) receiving rivaroxaban had a major bleeding event.

**Conclusions:** Thrombotic complications are common in patients with cancer and a newly inserted CVC. The pilot trial achieved its enrollment targets and supports that a large multicenter RCT is feasible in this area. ClinicalTrials.gov (NCT03506815).

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**KEYWORDS**

hemorrhage, neoplasia, rivaroxaban, venous thromboembolism, venous thrombosis

**Essentials**

- Thrombotic complications are common among patients with cancer with central venous catheters (CVCs).
- Rivaroxaban may be an appealing option for primary thromboprophylaxis in this patient population.
- A trial assessing the use of rivaroxaban for primary thromboprophylaxis was feasible.
- Rivaroxaban may be safe and effective to prevent CVC-related thrombosis.

## 1 | BACKGROUND

Venous thromboembolism (VTE) is a common complication among patients with cancer and is associated with significant morbidity, mortality, and health care costs.<sup>1-4</sup> Many patients with cancer require a central venous catheter (CVC), including peripherally inserted central catheters (PICCs) or infusion ports (eg, Port-a-Cath),<sup>5</sup> to maintain venous access and receive chemotherapy and other supportive care (eg, transfusions, antibiotics, nutrition, etc). The presence of a CVC is an important risk factor for VTE among patients with cancer. Vessel injury caused by insertion, venous stasis, repeated catheter movements within the vein, and cancer-related hypercoagulability all contribute to the development of VTE.<sup>6,7</sup> Furthermore, chemotherapy deliverance is a well-known additional risk factor for VTE.<sup>8</sup>

Two recent double-blind randomized controlled trials (RCTs) have reported that direct oral Xa inhibitor anticoagulants (ie, rivaroxaban and apixaban) at prophylactic dosing were safe and effective to prevent cancer-associated VTE in high-risk ambulatory patients initiating systemic chemotherapy.<sup>9,10</sup> The use of thromboprophylaxis was associated with a lower rate of VTE (relative risk [RR], 0.56; 95% confidence interval [CI], 0.38-0.83; number needed to treat = 24) and a reassuring rate of major bleeding (RR, 1.96; 95% CI, 0.88-4.33; number needed to harm = 77).<sup>11</sup> The results of these RCTs led to changes in recent clinical practice guidelines from the American Society of Clinical Oncology (ASCO) and the International Initiative on Thrombosis and Cancer (ITAC), and both suggest that high-risk ambulatory patients with cancer initiating chemotherapy be considered for primary thromboprophylaxis.<sup>12,13</sup> However, given that patients with CVCs were underrepresented in these trials, the same guidelines currently state that the use of thromboprophylaxis for prevention of CVC-related VTE is not routinely recommended.<sup>12</sup> Hence, we sought to assess the feasibility of conducting a two-center RCT assessing the safety and efficacy of rivaroxaban (10 mg daily) to prevent VTE complications among patients with cancer.

## 2 | METHODS

The Thromboprophylaxis With Rivaroxaban in Patients With Malignancy and Central Venous Lines (TRIM-Line) trial was a

two-center prospective, randomized, open blinded end point (PROBE) pilot trial conducted comparing rivaroxaban 10 mg daily to observation in patients with cancer and a newly inserted CVC. Inserted CVCs included BioFlo PICC (Angiodynamics, United States of America) or Power PICC Solo 2 (BD, United States of America) and Smart Port CT-Injectable Port (Angiodynamics, United States of America) or Bard Ports (BD, United States of America). The institutional review boards at both participating sites approved the protocol (ClinicalTrials.gov [NCT03506815]). A central adjudication committee through the CanVECTOR (Canadian Venous Thromboembolism Research; www.canvector.ca) platform whose members were unaware of treatment assignment reviewed all suspected outcome events. An independent Data Safety Monitoring Board periodically reviewed trial outcomes. The trial was sponsored by the Ottawa Hospital Research Institute.

### 2.1 | Study population

Adult ( $\geq 18$  years) patients with active cancer who had a CVC inserted within 72 hours of enrollment and had the capacity to provide written informed consent were potentially eligible. Patients were excluded if they had conditions putting them at increased risk of clinically significant bleeding, had an indication for anticoagulation (prophylactic or therapeutic dosing), had hepatic disease associated with coagulopathy, had a planned stem cell transplant, were diagnosed with myelodysplastic syndrome or acute leukemia, had a life expectancy of  $< 6$  months, or had renal insufficiency with a glomerular filtration rate of  $< 30$  mL/min or a platelet count  $< 50 \times 10^9$ /L. Other exclusion criteria included use of medications contraindicated with rivaroxaban, pregnancy or potential pregnancy, and breast feeding.

### 2.2 | Randomization and trial intervention

Eligible patients were randomly assigned using a centralized web-based randomization system to rivaroxaban or observation (standard of care) in a 1:1 ratio at two different sites (Ottawa Hospital [Ottawa, ON] and Juravinski Hospital [Hamilton, ON]) in Canada.

Randomization was stratified by sex, participating center, and type of CVC (PICC or infusion ports). Patients in the experimental arm received rivaroxaban (10 mg daily) with an intended treatment duration of 90 days ( $\pm 3$  days). Rivaroxaban was started within 72 hours of CVC placement. The study drug was continued until the earliest of one of these milestones occurred: (i) CVC was removed, (ii) thrombotic complication occurred, or (iii) the end of the follow-up (90 days  $\pm 3$  days).

### 2.3 | Study outcomes

The primary feasibility outcome of this pilot study was the number of participants recruited per month ( $>8$  patients per month). The recruitment rate was established to ensure that the recruitment for the full-scale trial including centers with comparable volumes could be completed within 4 years. Secondary feasibility outcomes included loss to follow-up, adherence to therapy ( $>80\%$ ), and clinical end points.

Clinical end points included thrombotic complications, major VTE events, major bleeding episodes, clinically relevant nonmajor bleeding (CRNMB), and CVC-related complications within 90  $\pm 3$  days of randomization. Thrombotic complication was defined as a combination of major VTE (any symptomatic or incidentally detected proximal deep vein thrombosis of the lower or upper limbs, any nonfatal symptomatic or incidental pulmonary embolism, and pulmonary embolism-related death) and any other deep (ie, distal, splanchnic, or cerebral) or superficial venous thromboses. CVC occlusion was defined as an obstruction of the CVC lumen that prevents or limits the ability to flush, withdraw blood, and/or administer solutions or medications. The main safety outcome was a major bleeding event defined by the ISTH as overt bleeding associated with a decrease in the hemoglobin level of  $\geq 2$  g/dL, which led to transfusion of two or more units of packed red blood cells, occurred in a critical site, or contributed to death.<sup>14</sup> Other safety outcomes included CRNMB (ISTH definition)<sup>15</sup> and CVC-related complications. Compliance with the study drug was estimated using pill count recorded by patients in a medication diary and defined as high if  $\geq 80\%$  of the study drug was taken.

### 2.4 | Statistical analysis

A convenience sample size of 100 patients was chosen to allow reporting of the average monthly recruitment. The study was designed to assess feasibility and, therefore, not powered to detect differences in clinical outcomes between groups, although these were measured and presented descriptively. Secondary analyses were performed on the intention-to-treat population, which included all patients who underwent randomization. We performed a time-to-event analysis on the clinical end points. The hazard ratio (HR) for major VTE was estimated using a Cox proportional hazard model controlling for sex, center, and type of CVC. Time to the first outcome event

was described by the Kaplan-Meier method. The statistical analyses were performed using SAS Enterprise Guide (version 7.15; SAS Institute, Cary, NC, USA) and R software (version 3.5.1).

## 3 | RESULTS AND DISCUSSION

From March 2019 through February 2020, 385 patients were assessed for eligibility for study participation. The two most common reasons for ineligibility included “not interested/overwhelmed” (N = 190) followed by “already on anticoagulation” (N = 32). A total of 105 patients underwent randomization at 2 centers in Canada. The baseline characteristics of the patients were well balanced (see Table 1). The mean age was 61 years, and more patients were women (68.5%). The most common primary cancer types were colorectal (29.5%) and breast (27.6%). A total of 82 patients (78.1%) had a PICC line, whereas 23 (22%) had an infusion port. The median duration of rivaroxaban was 88 days (interquartile range, 50.3-90). The median follow-up duration was 90 days in both groups. The study drug was discontinued as per participant’s wish in 2 patients (adherence of 96%). Compliance was high in the experimental group, at 96.7%.

Average enrollment rates were 7.5 and 2.0 patients per month (overall, 9.5 patients per month) at the participating centers, respectively. No patients were lost to follow-up during the course of the trial.

**TABLE 1** Baseline characteristics of included patients

	Rivaroxaban 10 mg N = 52	Standard of care N = 53
Age, mean(SD)	60.0 (11.9)	61.6 (12.7)
Female, n (%)	36 (69.9)	36 (67.9)
Race, n (%) <sup>a</sup>		
White	50 (96.2)	49 (92.4)
Black	0	1 (1.9)
Asian	0	3 (5.7)
Other	2 (3.8)	0
Cancer type, n (%)		
Breast	15 (28.9)	14 (26.4)
Colorectal	15 (28.9)	16 (30.2)
Stomach	5 (9.6)	2 (3.8)
Gynecological	6 (11.5)	5 (9.4)
Pancreas	3 (5.8)	7 (13.2)
Other	8 (15.4)	9 (17.0)
CVC types		
PICC	40 (76.9)	42 (79.3)
Port-a-Cath	12 (23.1)	11 (20.8)
Metastatic disease, n (%)	14 (34.2)	19 (43.2)

Abbreviations: CVC, central venous catheter; SD, standard deviation.

<sup>a</sup>Race was reported by the patients.

TABLE 2 Clinical outcomes

	Rivaroxaban 10 mg N = 52	Standard of care N = 53	Hazard ratio (95% CI)
Thrombotic complications, n (%)	3 (5.8)	5 (9.4)	0.58 (0.14-2.5)
Major VTE	2 <sup>a</sup> (3.9)	3 (5.7)	0.66 (0.11-3.9)
Upper-extremity DVT <sup>b</sup>	2 <sup>a</sup> (3.9)	2 (3.7)	
PE	0	1 (1.9)	
Other thrombotic events			
Splanchnic vein thrombosis	1 (1.9)	1 (1.9)	
Superficial vein thrombosis	0	1 (1.9)	
CVC-related complications, n (%)	0	5 (9.4)	
CVC-associated infection	0	2 (3.7)	
CVC migration	0	1 (1.9)	
CVC positional occlusion	0	1 (1.9)	
CVC occlusion	0	1 (1.9)	
Major bleeding	1 (1.9)	0	
CRNMB	2 (3.9)	2 (3.7)	1.02 (0.14-7.24)

Abbreviations: CI, confidence interval; CRNMB, clinically relevant nonmajor bleeding; CVC, central venous catheter; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

<sup>a</sup>One upper-extremity DVT occurred following rivaroxaban discontinuation for prolonged hospitalization.

<sup>b</sup>All upper-extremity DVT occurred in the presence of and around a CVC.

Symptomatic thrombotic complications occurred in 3 of 52 patients in the rivaroxaban group (5.8%; 95% CI, 1.2-16.0) including 2 with symptomatic major VTE (3.9%; 95% CI, 0.5-13.2) compared with 5 of 53 patients in the control group (9.4%; 95% CI, 3.1-20.7) including 3 with symptomatic major VTE (5.7%; 95% CI, 1.2-15.7) (Table 2). One upper extremity deep vein thrombosis in the rivaroxaban group occurred over 30 days after discontinuation of the study drug for prolonged hospitalization. The HRs for symptomatic thrombotic complications and major VTE were 0.58 (95% CI, 0.14-2.5) and 0.66 (95% CI, 0.11-3.9), respectively. One patient (1.9%) receiving rivaroxaban had a major bleeding complication. Two patients in each group had CRNMB (HR, 1.02; 95% CI, 0.14-7.24) (Table 2). CVC-related complications, including CVC-associated infection, migration, positional occlusion or occlusions, occurred in 0 of 51 patients (0%; 95% CI, 0-7.0) in the rivaroxaban group compared with 5 of 53 patients in the control group (9.4%; 95% CI, 3.1-20.7).

Symptomatic thrombotic complications are common in patients with cancer and a newly inserted CVC. CVC is an important risk factor for VTE in patients with cancer that increases the risk of VTE incrementally through distinct pathophysiological mechanisms (ie, vein trauma, venous stasis, contact activation by a foreign body). Although CVC-related VTE is associated with significant harms, routine primary thromboprophylaxis is not recommended due to uncertainty about overall net clinical benefit. The results of the TRIM-Line pilot trial support the feasibility of a planned full-scale, definitive, multicenter trial to assess the efficacy and safety of low-dose

rivaroxaban for preventing VTE in patients with cancer and a recently inserted CVC. The ASCO clinical practice guidelines now suggest the use of thromboprophylaxis in high-risk ambulatory patients with cancer initiating systemic therapy based on a modest relative risk of 0.56.<sup>13</sup> Using the same HR of 0.56 with 80% power and two-sided alpha of 0.05, 1768 patients are needed. After adjustment for loss to follow-up, the final sample-size estimate for the TRIM-Line trial is 1828 patients. Overall, nine sites have expressed interest in participating and can conservatively recruit >40 patients per month with expectation of completing recruitment within 4 years and trial completion in 5 years.

Patients enrolled in TRIM-Line have a different VTE risk profile than those included in previous trials assessing thromboprophylaxis among ambulatory patients with cancer initiating systemic therapy.<sup>9,10</sup> In the Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients (AVERT) and Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer (CASSINI) trials, the risk factors used to stratify patients according to their underlying risk of VTE included tumor type, complete blood count parameters, and body mass index.<sup>9,10</sup> Patients with lower-risk tumor types included in TRIM-Line pilot trial (eg, breast and colorectal carcinomas) remain at high risk of VTE because of the indwelling CVC. Overall, five patients in the control group experienced thrombotic complications (9.4%; 95% CI, 3.1-20.7). This is also consistent with previous literature assessing the efficacy and safety of low-molecular-weight heparin (LMWH) or vitamin K

antagonist (VKA) in patients with cancer and a newly inserted CVC. A previous systematic review and meta-analysis has reported the rate of symptomatic VTE among patients with cancer and CVC to be 6.8%,<sup>5</sup> which is emphasizing the importance of CVC as an independent risk factor for VTE in this patient population. This review has also reported that the use of VKA or LMWH as primary thromboprophylactic agents were associated with a significant reduction in symptomatic VTE (risk ratio, 0.61; 95% CI, 0.42-0.88).<sup>5</sup> However, these findings were never incorporated in clinical practice due to the difficulty to manage VKA in patients with cancer, the inconvenience of daily self-injection with LMWH and the uncertainty about the potential risk of bleeding complications in this patient population. The most recent version of the ITAC clinical practice guideline does not recommend routine use of thromboprophylaxis in patients with cancer and a newly inserted CVC (grade 1A). Given the convenience of direct oral anticoagulants and their previously reported efficacy and safety as primary thromboprophylactic agents in ambulatory patients with cancer initiating systemic therapy, trials assessing their use (ie, rivaroxaban and apixaban) in patients with cancer and CVC are desperately needed.

It is important to acknowledge the limitations of the TRIM-Line pilot RCT. A PROBE design was chosen in order to be pragmatic and to reflect standard clinical practice, which could make the results more easily applicable to routine medical care.<sup>16</sup> Although an open-label design is potentially more prone to biased estimates of the frequency of clinical outcomes than a blinded placebo-controlled trial, the clinical end points (thrombotic complications, major VTE, etc) in this study are hard outcomes blindly adjudicated without knowledge of treatment allocation using standardized definitions based on objective testing, thereby making bias less likely. Finally, the study was designed to assess feasibility and not to determine differences in the risk of clinical events between treatment groups. As a result, the number of clinical outcome events was relatively small, leading to imprecision and wide confidence intervals. The reported difference in outcomes between groups should be considered only as hypothesis generating.

In conclusion, thrombotic complications appear to be common in patients with cancer and a newly inserted CVC. The TRIM-Line pilot trial confirms feasibility and supports a large, multicenter RCT to definitely answer this research question.

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## AUTHOR CONTRIBUTIONS

RI and MC designed the study, performed the data extraction and data analysis, and wrote the manuscript. DS was involved in study design and data analysis and provided critical revisions to the manuscript. RM was involved in data analysis and provided critical revisions to the manuscript. TFW, DW, and CW were involved in study design and provided critical revisions to the manuscript.

## RELATIONSHIP DISCLOSURE

RI, DS, RM, TFW, CW, and DW declare no conflicts of interest. MC has received research funding from BMS, Pfizer, and Leo Pharma. He has also received honoraria from Bayer, Pfizer, BMS, Servier, and Leo Pharma.

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