The Risk of Upper Extremity Deep Vein Thrombosis and Primary Thromboprophylaxis with Low Dose Rivaroxaban in Oncology Patients with Central Venous Catheters

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ABSTRACT

Venous thromboembolism (VTE) is a common disorder which causes significant morbidity and mortality. Upper extremity deep vein thrombosis(UEDVT) is a relatively understudied subtype of VTE which is commonly associated with central venous catheters, cancer, and thrombophilia.

The goal of this project was to better characterize the risk of UEDVT and to design and execute a pilot study that will demonstrate the efficacy of a strategy preventing the occurrence of VTE in a high-risk population for UEDVT.

This M.Sc project, was conducted in three parts.

Chapter 1 of the thesis outlines a systematic review of the literature which assessed the risk of VTE in UEDVT patients by search for and including data from studies with patients with prospectively enrolled symptomatic UEDVT.

Chapter 2 describes the development and final protocol of the TRIM-Line pilot study, a randomized open-label study comparing 90 days of rivaroxaban 10mg po daily against the current standard of care (observation) in patients with active cancer and central venous catheters, two known risk factors for VTE. Finally in Chapter 3 the TRIM-Line study was executed as a pilot trial involving The Ottawa Hospital and the Juravinski Cancer Centre located in Hamilton. The study was conducted from March 2019 until February 2020. 105 patients underwent randomization at the two Canadian centres. The study met its prespecified feasibility endpoint average enrolment rate of 7.5 per month (95% CI:4.56, 10.44) at the coordinating Ottawa Hospital site and 2.0 per month (95% CI:0.87, 3.13) for the Juravinski Cancer Centre site. The randomized controlled trial met its enrollment targets and demonstrated that a full scale randomized controlled trial on the topic of prevention of cancer associated venous thromboembolism is feasible.

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THESIS INTRODUCTION

Venous thromboembolism is a common disorder which causes significant morbidity and mortality across a broad range of age groups and patient types. Compared to lower extremity deep vein thrombosis (DVT), upper extremity DVT (UEDVT) is not well studied with poor estimates for risk of thromboembolism. The UEDVT patient population has a higher prevalence of risk factors such as cancer, presence of central venous catheters, thrombophilia and structural obstruction, compared to lower extremity DVT.

The goal of this project is to better characterize the risk of UEDVT and to design and execute a pilot study that will demonstrate the efficacy of a strategy preventing the occurrence of VTE in a high-risk population for UEDVT

This thesis consists of three parts:

Chapter 1 of the thesis outlines a systematic review of the literature which assessed the risk of VTE in UEDVT patients.

Chapter 2 describes the protocol of the TRIM-Line pilot study, a randomized open-label study comparing 90 days of rivaroxaban 10mg po daily against the current standard of care (observation) in patients with active cancer and central venous catheters, two known risk factors for VTE.

Finally, Chapter 3 reports on the execution and findings of the TRIM-Line study outlined in the Section 2 protocol.

CHAPTER 1: SYSTEMATIC REVIEW AND META-ANALYSIS

Introduction

Venous thromboembolism (VTE) is a medical condition that results when a thrombus occurs in a deep vein or embolizes to the pulmonary circulation. VTE can be subdivided into deep vein thrombosis (DVT) and pulmonary embolism(PE) depending on the location of the thrombus in the venous circulation(1).

The deep veins are the primary vascular path for blood to return from the extremities to the right heart where blood is pumped to the lungs for gas exchange. The deep veins are commonly divided into those of the lower extremity which involves the deep veins of the leg (popliteal, femoral, iliac) and upper extremity (brachial, axillary, subclavian). Lower extremity DVT involves a thrombosis in the deep veins of the leg whereas upper extremity DVT (UEDVT) represents a thrombus in one of the deep veins of the arm(2). Pieces of thrombus can break of the primary clot and travel to the lungs where they can form a PE as the thrombus becomes trapped in the pulmonary arteries(1).

The pathophysiology of formation of VTE is often summarized by the Virchow's Triad of endothelial injury, hypercoagulable state and venous stasis(3, 4). The occurrence of VTE is associated with significant morbidity, mortality and health care costs(5-8).

The risk of recurrent VTE in patients with lower extremity deep vein thrombosis (DVT) is well established but the risk in patients with UEDVT is poorly described and the optimal treatment regimen is not known. Currently, guidelines suggest treatment of the UEDVT similarly to a lower extremity DVT with a minimum of 3 months of anticoagulation(9). However, compared to lower extremity DVT, UEDVT have been associated with a lower incidence of PE (10-12). Moreover, as many of the patients with UEDVT have concomitant malignancy their prognosis may be more associated with the progression of their underlying disease rather than the venous thrombosis(13). Finally, patients with malignancy have

`a higher bleeding risk(14). Therefore, a better understanding of the risk of recurrent VTE and of bleeding risk is important for balancing the benefits and risks of therapy in this population.

To better fill this knowledge gap, we conducted a systematic review of the literature review to determine the risk of recurrent VTE and bleeding among patients treated for an UEDVT. The details of the systematic review are detailed below in the literature review section.

Search Strategy

A systematic search of MEDLINE (1966-Sept 19, 2020), EMBASE (1975-Sept 19, 2020) and the Cochrane Central Register of Controlled Trials) was conducted. In addition, relevant studies were searched by hand within the last 2 years of the International Society of Thrombosis and Haemostasis (ISTH) conference proceedings in the Journal of Thrombosis and Haemostasis. The bibliographies of review articles found in the search were examined for potentially relevant studies not captured in the initial search. Additional studies of UEDVT recommended by expert opinion of members of the Canadian Venous Thromboembolism Research Network (CanVECTOR) were also evaluated for eligibility.

Relevant trials and studies that prospectively enrolled patients with UEDVT and reported events of recurrent VTE and bleeding were included. When needed, authors were contacted to attempt to obtain missing data.

Registration number

The protocol for this review was registered on PROSPERO CRD42017060849.

Eligibility Criteria

Full publications, conference proceedings, peer reviewed abstracts and letters reporting randomized controlled trials or prospective observational studies were considered for inclusion in the review.

To be selected for inclusion in this systematic review studies needed to meet the following criteria:

1. Inclusion of patients with symptomatically objectively diagnosed acute UEDVT.

2. Prospective enrollment of patients with objectively confirmed UEDVT.

3. Report of one or more of the primary or secondary outcomes of interest.

Exclusion Criteria

Case Reports, retrospective studies, prospective studies not following consecutive patients, studies enrolling <10patients and animal studies were excluded from the review.

The search was not limited by language and there were no limitations on year of publication.

The population of interest for the review were patients (adults and children) diagnosed with acute objectively confirmed symptomatic UEDVT. Proximal UEDVT was defined as thrombosis in the jugular, subclavian, axillary and/or brachiocephalic veins. Distal UEDVT was defined as thrombosis in the brachial vein, cephalic vein or basilic vein. The diagnosis of UEDVT had to be objectively determined as an incompressible venous segment on ultrasound examination or a filling defect on contrast venography, computed tomography(CT) venography or magnetic resonance(MR) imaging in ordered to be considered for inclusion.

As numerous treatments are available for the management of UEDVT, a broad search of different therapies was conducted. There were no specific exclusions. The interventions of interest for this review were as follows:

(1) thrombolytic therapy

(2) surgical rib resection

(3) thrombectomy

Treatment with:

(4) at least 5 days of intravenous (IV) or subcutaneous (SC) unfractionated heparin (UFH) followed by oral vitamin k antagonist (VKA) anticoagulant therapy with a target INR 2-3

(5) weight-adjusted doses of low molecular weight heparin (LMWH) SC for at least 5 days followed by three months of oral VKA with a target INR between 2.0-3.0

(6) weight-adjusted doses of low molecular weight heparin (LMWH) SC;

(7) weight-adjusted pentasaccharide (e.g. Fondaparinux,) SC for at least 5 days followed by oral VKA with a target INR between 2.0-3.0

(8) weight-adjusted pentasaccharide SC

(9) an oral or SC direct thrombin inhibitor

(10) a direct Xa inhibitor (e.g. apixaban/ rivaroxaban)

Outcomes

Outcomes related to efficacy, specifically the risk of having a recurrent VTE, and safety outcomes of bleeding were the outcomes of interest. The primary and secondary outcomes were defined as the frequency of the following events as follows.

Primary Outcomes

-Recurrent VTE (diagnosed by contrast venography, ultrasound, CT scanning, MR imaging, ventilation perfusion lung scanning, pulmonary angiography or post-mortem autopsy)

-Recurrent UEDVT (new incompressible venous segment on compression ultrasonography, a new filling defect on contrast venography or CT venography or filling defect consistent with thrombosis on magnetic resonance imaging)

Secondary Outcomes

- Major bleeding as defined by the ISTH definition (clinical or radiographic evidence of bleeding with at least one of the following criteria

1. Associated with a fall in hemoglobin of 2g/dl or more

2. Leading to a transfusion of 2 or more units of packed red blood cells or whole blood

3. Symptomatic bleeding occurring in a critical site area (intracranial, intra-spinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome or retroperitoneal)

4. Fatal bleeding (15)

-Clinically relevant non-major bleeding (CRNMB) as defined by the ISTH: Any sign or symptom of hemorrhage (e.g. more bleeding that would be expected for a clinical circumstance, including bleeding found by imaging alone that does not fit the ISTH criteria for major bleeding but does meet at least one of:

1. Requiring medical intervention by a health professional

2. Leading to hospitalization or increased level of care

3. Prompting a face to face evaluation my medical personnel (16)

-Death from any cause

-Fatal bleeding

-Fatal pulmonary embolism

These primary outcomes were chosen as, in general, they are objective, and these outcomes are the standard way in which events are reported in the field of thrombosis medicine. Since most therapy in the field of thrombosis requires anticoagulant therapy, safety is of critical importance in order to assess the benefit risk ratio or treatment and therefore the bleeding outcomes are our secondary outcomes. The ISTH definitions were selected as bleeding is a difficult outcome to quantify reliably and this definition is well accepted across the research community for assessing degree of bleeding.

Data Management

Through the OVID interface used to search the above strategy, relevant citations were uploaded into EndNote with removal of duplicate publications. Citations were then uploaded into Covidence for the screening.

Selection Process

Two reviewers (RI, MC) independently assessed eligibility of articles identified in the original search strategy for inclusion. Abstracts were screened by title, abstract and keywords. Citations of potential relevance or those for which there was disagreement between the two reviewers were obtained in full length for detailed review.

Full manuscripts were reviewed independently by the same two reviewers and applicable manuscripts were selected for inclusion into the review. Discrepancies were resolved by discussion and consensus. If this was unsuccessful a third party (single coinvestigator for all review discrepancies, MR) decided on whether the study would be included. Conference proceedings were included should adequate data be available to determine their relevance to the study and inclusion criteria.

Data Extraction

Data was independently extracted by both reviewers using a standardized data extraction sheet by both reviewers. The drug name, dose, route of administration and frequency/duration of the intervention treatments in addition to event numbers of the outcomes specified in the above outcome section were extracted.

Assessment of Study Quality

Each reviewer assessed the included studies for quality. As no randomized controlled trials met the inclusion criteria, all included studies were observational. Thus, study quality was assessed using the Newcastle-Ottawa scale for observational nonrandomized studies(17).

Statistical Analysis and Heterogeneity

When the baseline characteristics were extracted and the studies were analyzed prior to analysis, it became evident that significant concern for heterogeneity existed between the studies, based on clinical and methodologic design issues such that they should not be pooled. Instead, studies could be classified into different categories based on the underlying etiology of UEDVT: Paget-Schroetter, exertional, or thoracic outlet syndrome, 2: Studies which enrolled UEDVT regardless of cause or only enrolled non-catheter associated thrombosis and 3: Central venous catheter (CVC) associated thrombosis. Meta-analyses were performed for each category separately for the primary outcome.

After meta-analyses, the thresholds used to assess the degree of heterogeneity were defined as follows: I^2 < 25% was considered as “might not be important”, 26% to 50% was considered as “may represent moderate heterogeneity”, 51%-75% was considered as “may represent substantial heterogeneity” and greater than 75% was deemed considerable heterogeneity.

Open Meta-Analyst(18) software was used for meta-analysis and generation of the Forest plots. As each group of meta-analyzed studies included was of less than ten studies, funnel plots to investigate for publication bias could not be generated as these would be difficult to interpret with small study number.

In order to estimate the weighted rate of recurrent VTE, major bleeding, fatal bleeding, overall mortality, fatal PE and their associated 95% confidence intervals, results from the individual studies were extracted

and pooled by single proportion random-effects model. Although the initial plan was to express the results in “events per 100-patient-years” this was not conducted as many of the studies either did not report the follow up duration or reported the minimum and maximum follow up durations with no median or patient level information that would allow for calculation of this value. Therefore, the rates of the outcomes of interest are reported as the number or proportion of individuals who developed the outcome regardless of study duration. When available, the follow-up duration or ranges were reported.

Rates of recurrent VTE, bleeding, mortality and other primary and secondary outcomes were calculated with 95% confidence intervals for all dichotomous outcome variables. No continuous outcome measures were extracted for this systematic review.

Results

A total of 2961 citations were identified by the systematic literature search. (1222 from MEDLINE, 1729 from EMBASE, 10 from Cochrane Register of Controlled Trials and 6 additions from hand searches and expert recommendations). After 588 duplicates were removed and screening by authors (RI and MC) a total of 102 articles were deemed potentially eligible for inclusion into the review.

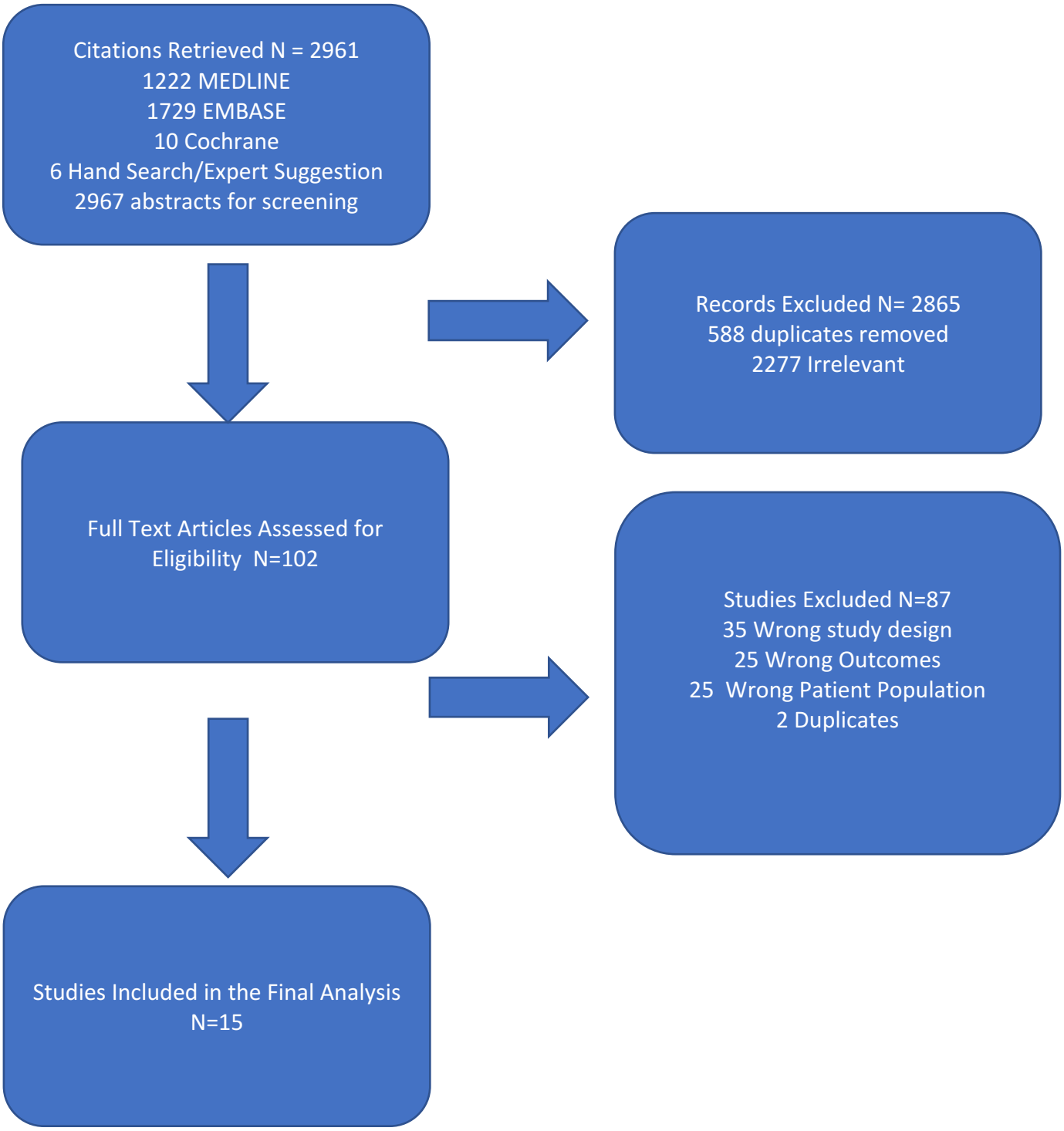

Figure 1. Flow-Diagram of Screened and Included Studies with Reasons for Exclusion.

A total of 15 articles were deemed to meet inclusion criteria and were included in the final review. The study selection process is documented in a flow chart as per the PRISMA statement(19) in Figure 1. As outlined in the methods section, studies were meta-analyzed in three distinct groups due to concerns of clinical heterogeneity.

Study Characteristics

There were no randomized controlled trials found that met the inclusion criteria. All 15 studies were prospective cohort studies. Evaluation of risk of bias by Newcastle-Ottawa Scale for observational cohort studies is located in the Appendix Table 4. Overall study quality denoted a low risk of bias for most studies. Exceptions included Desancho 2014(20) which was only available as an abstract and the studies investigating Paget-Schroetter which demonstrated lower quality.

Baseline characteristics of the included patients of the 15 included studies are reported in Table 1. Patient weight was not documented in any of the included studies.

Study, year	N	Treatment (n)	Duration on treatment (months)	CVC n (%)	Malignancy n (%)	Age (years)	Male Gender
Paget-Schroetter Studies							
Kreienberg, 2001(21)	23	Thrombolysis-Urokinase followed by 1st rib resection(n=9)/vein stenting (n=14) then IV heparin bridge to warfarin. Total (n=23)	6-18	101 (100)	NR	Mean 30.3 Range 18-58	47.8%
Lee J, 2006(22)	35	Thrombolysis + IV heparin +Warfarin (n=35) Subsequently then had 1st rib resection (n=8)	Mean 5.2 months	0 (0)	0(0)	Mean 31	38%

Lee W, 2000(23)	32	Thrombolysis N=22	NR	0 (0)	0 (0)	Mean 28.8 Range 18-47	59%
Unselected Enrolment Studies							
Castenada, 2002 (24)	10	Reteplase 10U + infusion protocol with low dose UFH infusion.	0	3 (30)	NR	16-78 mean 53.3	48%
Cote, 2017(25) Non CVC related	1334	LMWH or Warfarin	3	0(0)	334 (25)	Mean 54.4	53.5%
Desancho, 2014 (20)	25	VKA (n=13) LMWH (n=6) Thrombolysis (n=3) Rivaroxaban (n=1) Removal catheter only (n=2)	NR	6(24)	0	16-86	20%
Harley, 1984(26)	14	IV heparin + warfarin (n=14)	3	0 (0)	3 (21)	Mean 37 Range 18-72	71.4%
Houghton, 2020 (27)	210	Apixaban/Rivaroxaban (n=102) LMWH + Warfarin (n= 108)	3	107 (51)	125 (59.5)	Median 60.4	59.3%
Karabay, 2004(28)	36	LMWH + VKA; in case of malignancy: LMWH (n=36)	4.7	23 (64)	6 (17)	Mean 54 +/- 12.3	52.7%
Prandoni, 1997(29)	27	IV UFH + VKA (n = 27)	≥ 3	8 (30)	6 (22)	Median 53(19-79)	70.4%
Rathbun, 2011(30)	67	Dalteparin + VKA (n = 28) vs. Dalteparin (n = 39)	3	52 (79)	31 (47)	Dalteparin + VKA (n = 28) Median 48(18-82) Dalteparin (n = 39) Median 53(20-77) Total 52(18-82)	Dalteparin + VKA (n = 28) 43% Dalteparin (n = 39) 49% Total 52(18-82) 46%
Savage, 1999(31)	46	Dalteparin + VKA (n=46)	3	16 (35)	34 (74)	Range 18-87	53%
CVC Associated Thrombosis							
Cote, 2017(25) CVC related	938	LMWH or Warfarin	3	938 (100)	491 (52)	Mean 59.0	55.0%
Davies, 2016 (32)	70	Rivaroxaban 15mg BID x 3 weeks then 20mg daily x 9 weeks	3	70 (100)	70 (100)	Median 54.1	32.9%

Kovacs, 2007(33)	74	Dalteparin + VKA (n = 74)	3	74 (100)	74 (100)	Median 54.1	33.4%
Monreal, 1994(34)	86	IV UFH (8 days) + VKA (n 86)	NR	86 (99)	27 (32)	NR	NR

Table 1. Baseline Characteristics of included studies.

UFH=unfractionated heparin, LMWH=low molecular weight heparin, VKA= vitamin K antagonist(e.g. warfarin)

Study Outcomes

Study, year	Recurrent UEDVT	LEDVT	PE	Fatal PE	Major bleeding	Clinically Relevant Non-Major Bleeding (CRNMB)	Fatal bleeding	Duration of Follow Up
Paget-Schroetter Studies								
Kreienberg 2001(21)	Resection only = 0 Resection and stenting = 5	0	0	0	0	4	0	Mean 4 years Range 2-6 years
Lee J 2006(22)	8	0	0	0	NR	NR	NR	1-12 months
Lee W, 2000(23)	1	0	0	0	NR	NR	NR	Follow-up ranged from 5 to 40 months and averaged 25.8 months
Unselected Enrolment Studies								
Castenada, 2002 (24)	0	0	0	0	1	0	0	NR
Cote, 2017(25) Non-CVC Associated	29		9	7	27	NR	6	Non-catheter unprovoked UEDVT = 230 days +/-SD 263 Non-catheter provoked UEDVT = 178 days +/-SD 190
Desancho 2014 (20)	2	0	2	0	0	0	0	NR

Harley 1984(26)	1	0	0	0	NR	NR	NR	3-24 months but only for 10/14 patients
Houghton, 2020(27)	2 recurrent VTE site not specified			NR	3	3	NR	3 months
Karabay, 2004(28)	0	0	0	0	NR	NR	NR	3-6 months Mean 4.7 +/- 2.2months
Prandoni, 1997(29)	0	1	1	1	NR	NR	NR	1-6 years
Rathbun, 2011(30)	0	0	0	0	1	1	0	3 months
Savage, 1999(31)	1	0	0	0	1	1	0	12 weeks
CVC Associated Thrombosis								
Cote, 2017(25) CVC Associated	13		16	5	30	NR	8	Catheter associated UEDVT = 166 days +/-SD 202
Davies, 2016 (32)	0	0	1	1	7	4	0	6 months
Kovacs, 2007(33)	0	0	0	0	3	0	1	3 months
Monreal, 1994(34)	0	0	3	2	0	0	0	NR

Table 2. Recurrent Thrombosis, Bleeding Outcomes and Duration of Follow Up

Paget-Schroetter/Thoracic Outlet

There were 3 studies which primarily enrolled patients with Paget-Schroetter syndrome and thoracic outlet obstruction. The patient population of these studies was approximately aged 30 which is lower than the in the other studies and very few of these patient's UEDVTs were associated with CVCs or cancer. Characteristics of age, gender, weight, presence of a Central venous catheter or malignancy are depicted in Table 1. Duration of follow up depicted above in Table 2 varied from 1-6 years for these three studies.

Meta-analysis results for all recurrent VTE events of these studies are reported below in Figure 2. I^2 value was 33.9 % denoting moderate heterogeneity. Estimate of recurrent events of VTE was 16.4% with (95%CI: 7.1%, 25.8%). All recurrent events in these three studies were UEDVT. There were no LEDVT or PE events. There were no fatal recurrent PE. in this patient group. I^2 value was 33.9% denoting moderate heterogeneity. Bleeding events were only reported in the Kreienberg study with no major bleeding events and 4 CRNMB events among the 23 study participants.

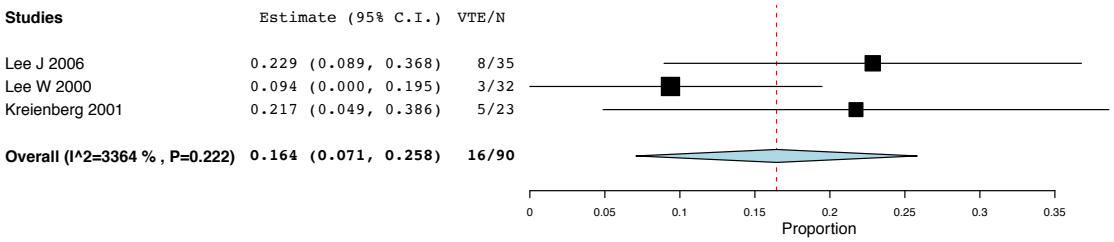

Figure 2. Forest Plot of All Recurrent Venous Thrombosis in Paget-Schroetter Studies.

Unselected UEDVT-Recurrent DVT

There were 8 studies which enrolled any UEDVT patients (i.e. did not select patients with Paget-Schroetter or those with CVC). Meta-analysis results for all recurrent VTE events in studies including patients with unselected UEDVT are reported in Figure 3. Estimate of all recurrent VTE was 1.7% (95% CI:0.8%, 2.6%). The measurements of heterogeneity for this analysis gave I^2 value of 14.9%.

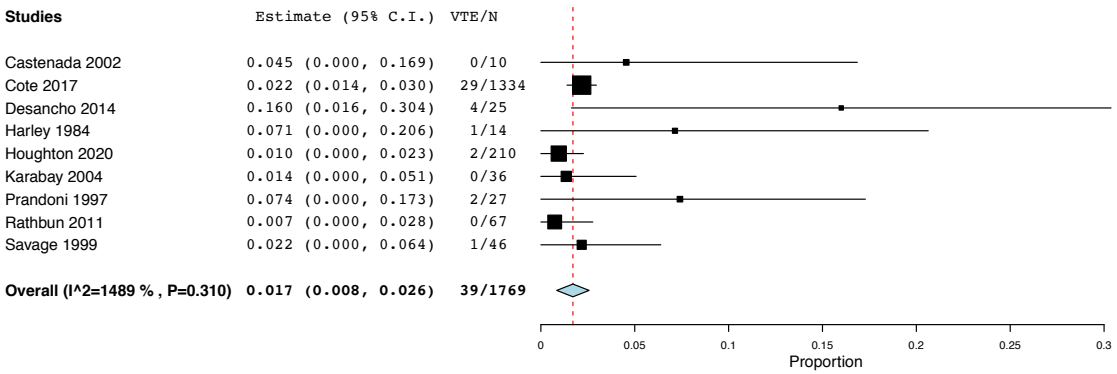

Figure 3. Forest Plot of All Recurrent Venous Thrombosis in Studies with Unselected Patients.

Unselected UEDVT-Recurrent UEDVT

UEDVT data could be extracted from 7 studies with unselected patient enrollment. Meta-analysis of these results are reported in Figure 4. Estimate of recurrent UEDVT events occurring in this population was 1.4% (95% CI: -0.1%, 2.9%). Duration of follow up for this group was 3-12 months. The measurement of heterogeneity for this analysis determined an I^2 of 0%.

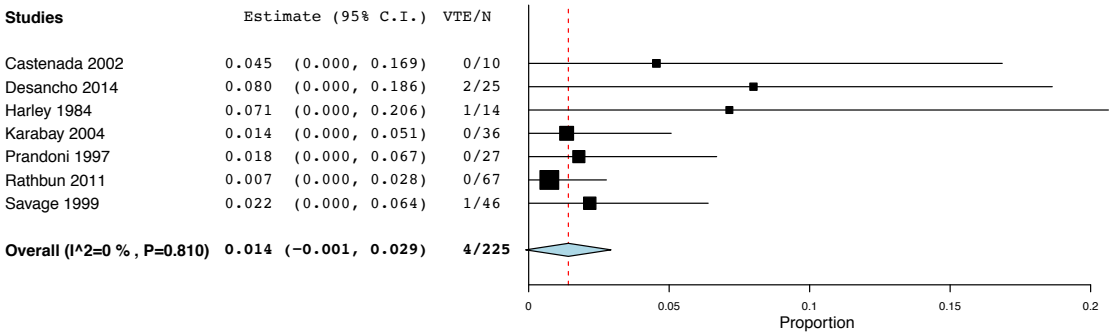

Figure 4. Forest Plot of Recurrent Upper Extremity Venous Thrombosis in Studies with Unselected Patients.

Unselected UEDVT-Major Bleeding

Major bleeding was reported in 6 of the 9 studies with unselected patient enrollment. Meta-analysis of these results is reported in Figure 5. The estimate of major bleeding events was 1.9% (95%CI: 1.3%, 2.6%). Heterogeneity for this analysis determined an I^2 of 0%.

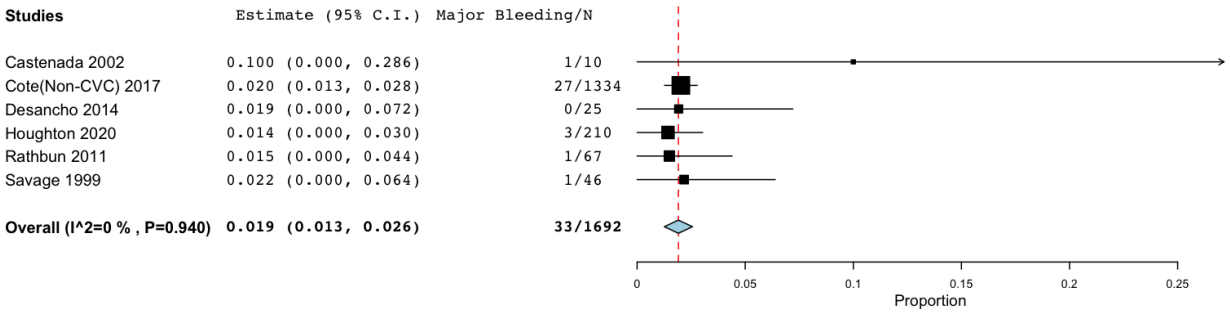

Figure 5. Forest Plot of Major Bleeding in Studies with Unselected Patients.

Unselected UEDVT-CRNMB

CRNMB was reported in 5 of 9 of the unselected enrollment studies. Meta-analysis results for CRNMB events are reported in Figure 6. The estimate of CRNMB was 1.6% with (95%CI:0.3%, 2.9%). The measurement of heterogeneity gave an I^2 value of 0%.

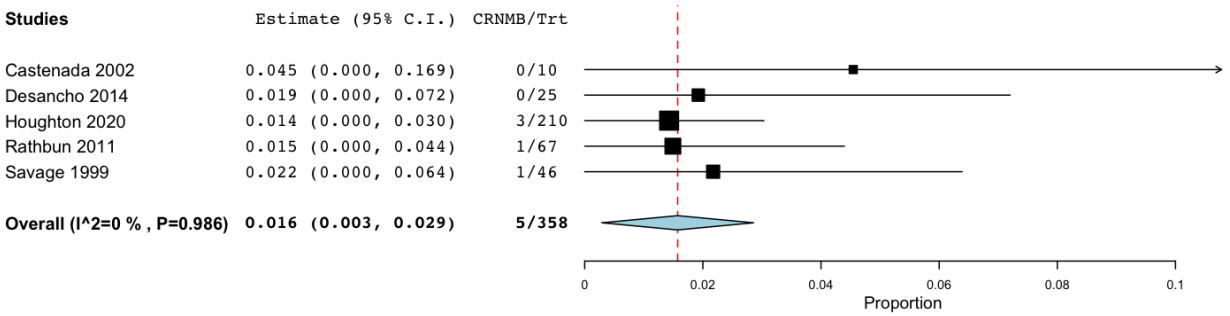

Figure 6. Forest Plot of CRNMB in Studies with Unselected Patients.

CVC Associated Thrombosis Studies-Recurrent VTE

Four studies included patients with CVC associated thrombosis patients. A large number of patients with cancer were enrolled in these studies (Table 1). Meta-analysis results for recurrent VTE events are reported in Figure 7. Estimate of recurrent VTE was 1.4% with (95% CI: 0.7%, 2.0%). None of the recurrent events was reported as an UEDVT. One fatal PE occurred in the Davies(35) study. Duration of follow up was 3-6 months for all included studies. The measurements of heterogeneity gave an I^2 value of 0%.

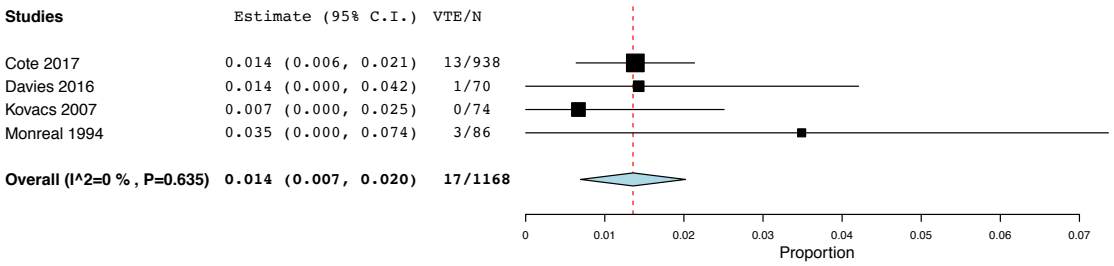

Figure 7. Forest Plot of All Venous Thrombosis in Catheter Associated Thrombosis Studies.

CVC Associated Thrombosis Studies-Major Bleeding

The same four studies reported major bleeding in the CVC associated thrombosis population. Meta-analysis results for major bleeding events are reported in Figure 8. The estimate of major bleeding was 2.2% with (95%CI:0.0%, 4.3%). The measurement of heterogeneity gave an I^2 value of 79.1%.

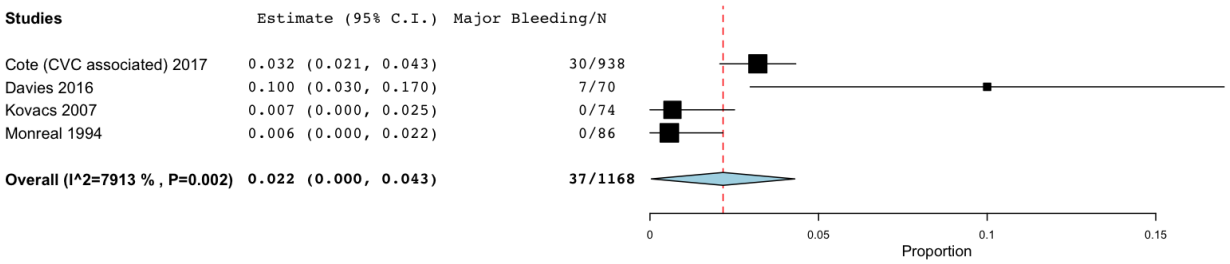

Figure 8. Forest Plot of Major Bleeding in Catheter Associated Thrombosis Studies.

Three of the four studies reported CRNMB in the CVC associated thrombosis population. Meta-analysis results for CRNMB events are reported in Figure 9. The estimate of CRNMB was 1.1% with (95%CI:0.0%, 2.7%). The measurement of heterogeneity gave an I^2 value of 38.0%.

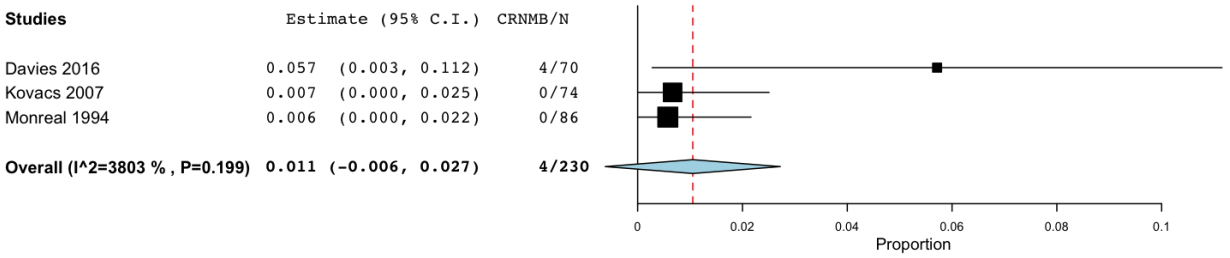

Figure 9. Forest Plot of CRNMB in Catheter Associated Thrombosis Studies.

The event rates of recurrent VTE and bleeding outcomes of the meta-analysis are summarized in Table 2. Regarding the *a priori* specified possible subgroup analysis, there were no studies that reported distal DVT and studies which included cancer patients did not specify whether the recurrence or bleeding occurred in an individual with cancer or without. Therefore, these subgroup analyses were not conducted. The group with catheter associated thrombosis was analyzed as a distinct subgroup.

Discussion

Our systematic review and meta-analysis of patients with UEDVT showed that the risk of recurrent VTE is higher in patients with Paget-Schroetter syndrome than in those with UEDVT related to other causes. Overall, the rates of recurrent VTE in patients with UEDVT appeared to be low in the patients without Paget-Schroetter syndrome. Both major bleeding and CRNMB rates were low in patients with diagnosed UEDVT and were similar to what is usually observed in patients with other types of VTE (e.g. LEDVT, PE, etc.).

The studies investigating Paget-Schroetter syndrome and thoracic outlet syndrome of the upper extremity reported a much higher risk of recurrent VTE and UEDVT than CVC associated and unselected UEDVT patient studies. There may be multiple reasons for this finding. First, most of these studies are primarily surgical trials investigating surgical decompression of the thoracic outlet by rib resection or endovascular stenting. Second, several also used warfarin therapy which could have led to suboptimal anticoagulation. The time in therapeutic range for the warfarin management was not reported in the included studies. Third, in some studies, the treatment was primary thrombolysis without starting anticoagulation therapy afterwards. These patients would be at elevated risk for recurrent VTE or UEDVT as compared to patients on anticoagulation. Furthermore, surgery is also a known risk factor for VTE (36) and some patients had venous stenting procedures completed which may have left potentially thrombogenic stent material at the site increasing the risk of recurrent VTE. Finally, the quality of the studies in this subgroup was inferior compared to the other groups (unselected and CVC-related) particularly with regards to outcome assessment. The observational nature of all studies included in the review prevents the determination of whether the high recurrence rate is related to an intrinsically high recurrent thrombotic risk in the younger patient population with thoracic outlet syndrome or whether complications from the therapy such as surgery or stenting may be contributing to the adverse outcomes.

The Paget-Schroetter and thoracic outlet patients were the only group with a risk of recurrent VTE that outweighed the risk of major bleeding. However, the management of this patient population in these studies consisted of a surgical intervention or thrombolysis with no specific recommendation for long term anticoagulation in two of the three studies which may have led to a higher rate of recurrent VTE.

Studies that enrolled an unselected population of patients and those that enrolled CVC associated thrombosis had a low risk of recurrent VTE (<2%). Since the patient level data from many of the non-selected studies was not available, it is unknown whether the event rates in the studies with non-selected patients were driven by events from patients with Paget-Schroetter or thoracic outlet syndrome.

The sites of recurrent VTE were different in the three groups of studies analyzed. The CVC associated thrombosis studies had no reported recurrent UEDVT events and the non-selected populations had a low recurrent UEDVT rate of 1.4%. This is in stark contrast to the studies investigating the young patient population with thoracic outlet obstruction as these patients had most of the recurrent UEDVT. We theorize this may be related the persistent structural defect, surgical injury or stent thrombogenicity in the group that had an UEDVT in the context of a thoracic outlet obstruction or Paget-Schroetter syndrome.

With regards to bleeding outcomes, the meta-analysis estimate of 2.0% for major bleeding events is consistent with results of other studies of patients on warfarin(37). Only two studies of the group used the direct oral anticoagulant class of medication that has been associated with a lower bleeding risk than warfarin in recent studies(37), thus the actual bleeding rate may be lower than the one that we reported. Overall, the low rate of bleeding found is reassuring that this population of UEDVT is not more likely to suffer from complications of therapy than other types of VTE.

All values of the I^2 except for CRNMB demonstrated low or moderate heterogeneity except for CRNMB and thus may not be important in interpreting the results. The higher heterogeneity for CRNMB may be

related to heterogeneity of definitions as not all studies used the ISTH definition and to the difficulty in classifying non-life-threatening bleeding events.

There are several limitations of the current study: No randomized controlled trials were found on this topic and the evidence currently relies on observational studies of varying quality. Using the GRADE system, since all of the included studies were observational and there were some methodologic concerns particularly in the surgical trials evaluating thoracic outlet syndrome, the overall assessment of the quality of the evidence was low. A major problem area that arose during extraction is the poor reporting of follow up and treatment duration in the studies included. Given the poor reporting and missing values of this data we are unable to report the rates per patient time of exposure and correct for differences in treatment or follow up duration. Clearly, studies that follow patients for longer periods are more likely to detect more recurrent VTE as there is more monitored time at risk for an event to occur. In addition, clinically it is critically important to know if the patient was actively on anticoagulation at the time of sustaining their recurrent VTE as the risk of recurrent VTE while on and off treatment is expected to be very different. In some cases, this was not able to be determined and could adversely bias the event estimates. As seen in Table 3, most of the studies that reported treatment did so for 3 months which would be consistent with the current guidelines of the American College of Chest Physicians Antithrombotic Guidelines(38) for the treatment of upper extremity venous thrombosis. If studies followed patients for longer than 3 months after ending their anticoagulation then the rate of VTE would be higher in the post termination period biasing the estimates higher. Finally, this review investigated the efficacy and safety outcomes of recurrent VTE and bleeding. Long term morbidity related to symptoms of post thrombotic syndrome was not assessed. While not usually life threatening, post thrombotic syndrome is difficult to treat and is a major concern to patients experiencing a VTE.

Conclusion

Even with the above limitations, this systematic review is among the first in the field to estimate the risk of recurrence of VTE after experiencing an UEDVT. The results suggest that the population of patients who experience UEDVT are heterogeneous with a higher recurrence rate for patients with Paget-Schroetter or thoracic outlet syndrome rather than other etiologies. Further well-designed studies are needed to confirm the high recurrence risk of patients experiencing UEDVT related to thoracic outlet syndrome in light of the poor quality of the included studies of that group. For all other groups experiencing UEDVT, both the recurrence risk of UEDVT and all DVT as well as the rate of bleeding was reassuringly low supporting the overall good prognosis of this condition. These estimates will assist in clinical risk assessment and treatment decision making balancing the risk of recurrent thromboembolism with the risk of bleeding.

After completion of this systematic review which gave a better estimate of the risk of complications associated with UEDVT, the recurrent VTE rates among patients with UEDVT were lower than expected, thus, in order to demonstrate the effectiveness of a primary prophylaxis strategy, a high-risk population would be required. Given UEDVT is a frequent complication of CVC and cancer is an additional risk factor for VTE, a search of ClinicalTrials.gov was conducted to ensure that no in progress randomized controlled trials were in progress on the topic of cancer associated UEDVT associated with CVC. No studies were found and thus it was decided to proceed with the design of the TRIM-Line pilot trial.

CHAPTER 2: Primary thromboprophylaxis of UEDVT: The TRIM-Line Trial Protocol

Introduction

VTE is a common complication among patients with cancer and while UEDVT accounts for approximately 4-11% of all deep vein thrombosis this prevalence is higher in patients with cancer (10, 11). They are a source of significant morbidity and mortality(39) and are associated with the risk factors of thoracic outlet obstruction, cancer, and presence of CVC (40-42). The CVC itself predisposes to endothelial injury due to direct irritation and venous stasis due to slower venous flow by the space occupying nature of the catheter in the vein. (12, 13, 43). Rising rates of CVC usage have coincided with an increase in UEDVT diagnosis(10, 12, 44). With an aging population in Western countries and subsequent rise in cancer diagnoses requiring CVC for chemotherapy, it is expected the burden of disease caused by UEDVT will increase.

CVCs are often needed in oncology patients to maintain venous access, administer chemotherapy and provide supportive care. These devices are a known risk factor for the development of VTE and studies have suggested that approximately 7% of patients with active cancer and a newly inserted CVC will have a VTE complication over a 3-month follow-up period(45). Over 600,000 CVCs are inserted yearly in Canada and their use is increasing(46).

The majority of CVCs used among patients with cancers are either peripherally inserted central catheters (PICC) or infusion ports (e.g. Port-a-Cath) (47). All CVCs share similar complications. VTE is a common complication which usually includes UEDVT and/or pulmonary embolism (PE). Vessel injury caused by the catheter insertion, venous stasis caused by the catheter, on-going movements of the catheter within the vein, and cancer-related hypercoagulability all contribute to the development of UEDVT(48, 49).

The reported frequency of UEDVT with CVCs is variable and highly dependent on the presence of symptoms, the type of CVC and the presence of cancer. The reported incidence of CVC-associated VTE is 1% to 18% in symptomatic patients versus 27% to 66% in asymptomatic patients undergoing screening ultrasound. PICCs appear to increase the risk of symptomatic VTE by 2.6-fold when compared to other types of CVCs (e.g. infusion ports) and cancer patients with CVCs have a higher rate of VTE complications compared to non-cancer patients.(50, 51).

A recent systematic review and meta-analysis including 12 randomized controlled trials and over 3000 patients reported an overall rate of symptomatic VTE of 6.8% (95% CI: 5.5 to 8.3%)(45).This study also demonstrated that thromboprophylaxis with unfractionated heparin, LMWH or VKA for the prevention of VTE in patients with cancer and newly inserted CVC was associated with a significantly reduced risk of symptomatic VTE (risk ratio (RR) 0.61 95% CI: 0.45 to 0.88) when compared with observation(45). There was a decrease in the incidence of VTE from 6.8% to 3.7% ($p< 0.001$). In addition, a Cochrane review reported a lower risk of symptomatic VTE amongst patients with cancer and CVC receiving parenteral thromboprophylaxis with LMWH compared to observation (RR: 0.43; 95% CI, 0.22 to 0.81) (52). This also demonstrated that LMWH was associated with a small and not statistically significant increase in the risk of major bleeding complications (RR: 1.49; 95% CI, 0.06 to 36.28)(52). Therefore, these two meta-analyses suggest that the use of thromboprophylaxis is safe and effective in this patient population.

However, despite evidence of benefit, the use of routine thromboprophylaxis has not translated into clinical practice. Currently, in patients with cancer and newly inserted CVCs, thromboprophylaxis is not recommended by guidelines due to the need for daily subcutaneous injections and high costs associated with LMWH and the difficulty managing anticoagulation with VKA in cancer patients receiving chemotherapy due to drug interactions (53). Direct oral Xa-inhibitor anticoagulants such as rivaroxaban, apixaban, and edoxaban are oral medications which have predictable pharmacokinetics that eliminate the

need for routine laboratory monitoring and have minimal drug-to-food or drug-to-drug interactions(54) and may present an attractive option for thromboprophylaxis.

In 2019, two randomized controlled trials AVERT(55) and CASSINI (56)were published investigating VTE prevention with low dose apixaban and rivaroxaban respectively versus placebo in ambulatory cancer patients undergoing chemotherapy, regardless of the presence of a CVC. These demonstrated a reduced rate of VTE in intermediate-to-high risk cancer patients as defined by a Khorana risk score of 2 or more (57). This risk stratification integrates tumor type, biomarkers and BMI and is outlined below in Table 3.

Khorana Risk Score	
Site of Cancer	Risk Score
Very high risk(stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count $350x10^9$/L or more	1
Hemoglobin level less than 100g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count more than $11x10^9$/L	1
BMI 35kg/m2 or more	1

Table 3. The Khorana Risk Score (57)

This clinical prediction rule does not include CVCs despite the fact they are a major risk for VTE and therefore, patients with CVCs were under-represented in these clinical trials (< 40%). As a result, patients with cancer types and clinical factors associated with a lower risk of VTE but in whom CVCs were employed for chemotherapy (e.g. breast and colorectal), were excluded from AVERT and CASSINI.

Results of the AVERT and CASSINI trials led to changes in the 2019 clinical practice guidelines from the American Society of Clinical Oncology (ASCO) and the International Initiative on Thrombosis and Cancer (ITAC); both suggest that high-risk ambulatory patients with cancer initiating chemotherapy

might be considered for primary thromboprophylaxis(53, 58). The same guidelines currently state that the use of thromboprophylaxis for prevention of CVC-related thrombosis is not routinely recommended (Grade 1A)(53). However, there is no evidence for the use of direct oral Xa-inhibitor anticoagulants in this setting.

Since rivaroxaban is a promising agent for primany thromboprophylaxis in patients with cancer, the TRIM-Line Pilot trial aims to assess the feasibility of a large scale multicentre randomized controlled trial investigating the efficacy and safety of a direct oral Xa-inhibitor to enable informed decisions about the optimal thromboprophylaxis strategy for patients with cancer and a new CVC.

Research Hypothesis

Thus, the research hypothesis is that primary thromboprophylaxis with rivaroxaban 10 mg daily for 3 months will decrease the number of major VTE complications over a 3-month follow-up period when compared to standard of care in patients with cancer and a newly inserted CVC.

To investigate this question, we conceived the Thromboprophylaxis with Rivaroxaban in Patients with Malignancy and Central Venous Lines (TRIM-Line) Pilot Randomized Controlled Trial was conceived. This is a Canadian, multicentre, open-label randomized controlled trial comparing rivaroxaban 10mg daily for 90 days with the current standard of care which is observation.

Objectives

Objectives of the Pilot Trial

To determine the feasibility of conducting a multicenter randomized open label-controlled trial evaluating the use of prophylactic dose rivaroxaban to prevent CVC associated VTE among cancer

patients.

Objectives of the Full Trial

The purpose of the full trial is to determine the efficacy and safety of prophylactic dose rivaroxaban to prevent CVC associated VTE among cancer patients.

Trial Design

The TRIM-Line Pilot Study is an open blinded endpoint pilot randomized controlled trial. A pilot study is needed before a full RCT can be completed as recruitment of patients to a prophylaxis study which would add an additional medication to their existing cancer regimen may further burden or complicate the care of patients which may lead patients to feel overwhelmed or unwilling to accept the bleedings risks of rivaroxaban for a condition they do not have. In addition, the results of the pilot study will be used to demonstrate feasibility and assist in the applications for funding of the full-scale trial. A randomized controlled trial design was chosen for its superior ability to control bias as compared to retrospective trials. This study will be conducted at 2 Canadian centres. The Ottawa Hospital and the Juravinski Cancer Centre in Hamilton.

Trial Intervention

Eligible and consenting patients will receive **one tablet of rivaroxaban 10 mg daily** starting within 72 hours of CVC placement **or standard of care (observation)** for a treatment course of 90 days (+/- 3 days). The study drug will be continued until the CVC is removed, one of the primary study outcomes is achieved, or the end of the follow-up (90 days +/- 3 days). All patients will be observed until the development of a major VTE, until the patient dies, or until the end of follow-up (90 days +/- 3 days). At the end of the trial, thromboprophylaxis was left to the discretion of the local investigator.

Participant Allocation

Patients will be randomly assigned in a 1:1 ratio to one of the two study groups. The randomization list will be created centrally by an independent statistician using computer-generated permutation blocks of different sizes. Randomization will be stratified by sex, center and type of CVC (PICC or infusion ports) and concealed from all study personnel before allocation(51).

Patients will be approached by the attending physician for participation in the study. After written informed consent is obtained, eligible participants will be enrolled. A secure, dedicated, central web-based randomization system through the Ottawa Hospital Research Institute (Method Center) will be used. A unique study participant number and study group allocation will be given after the study personnel entered the patient's basic information, sex, and type of catheter, and confirmed that the patient meets eligibility criteria.

Study Outcomes

The primary feasibility outcome for the pilot study is the number of participants recruited per centre per month. We will obtain baseline details of the patient's type, location and treatment of cancer, and medications. Secondary feasibility outcomes of the pilot study will include, consent rates, loss to follow up, adherence to therapy defining 80% or greater medication taken as having good adherence to study drug, proportion of screened patients who meet eligibility criteria. We will document reasons for non-consent in order to assist recruitment for the larger multicentre trial.

For the full multicentre trial the outcomes would be as follows: primary outcome of radiographically confirmed VTE. Secondary outcomes include major and CRNMB, CVC life span, premature CVC removal, CVC lumen occlusion, CVC associated infection and death.

Methods for Protection Against Source of Bias

For this pilot trial, the primary outcome of enrollment rate at each centre is objective making bias less likely. We attempted to choose sites similar to those that would conduct the full-scale trial to obtain an accurate measurement of the enrolment rates at CanVECTOR member affiliated sites.

While not a specific outcome of this pilot trial, clinical outcomes will be the outcomes of interest for the full-scale trial. These outcomes will be collected as a part of this pilot trial. For the trial design PROBE design was chosen as it associated with lower costs and greater similarity to standard clinical practice which could make the results more easily applicable in routine medical care. (59) Although an open-label design is potentially more prone to biasing the true frequency of the outcome than a placebo-controlled trial, the primary endpoint (major VTE) in this study is a hard outcome, making bias by unblinded study personnel less likely. This type of bias will also be minimized by instructing all trial participants on the signs and symptoms of primary and secondary outcomes and safety events, with explicit instruction to contact study staff should these arise. Importantly, the PROBE design features blinded outcome assessment; an independent Central Adjudication Committee will be assembled via CanVECTOR and will blindly adjudicate all study outcomes. Committee members will include experts in cancer and in thrombosis. The CanVECTOR research network uses an online adjudication portal whereby studies in their network requiring event adjudication will be blinded and adjudicated by expert physicians at other Canadian centres of the network. No events at the either study site will be adjudicated by a physician from that centre. Finally, crossover is unlikely in the TRIM-Line trial since the intervention (rivaroxaban) is not indicated (or reimbursed) for this specific indication nor for thromboprophylaxis in ambulatory cancer patients in Canada. Differential withdrawal remains a possibility, however the follow-up is relatively short and identical for both groups and should not lead to an imbalance between the two groups.

It is not expected that a high risk of differential discontinuation or loss to follow up would be an issue with this trial. The rate of adherence was high (over 80%) in similar trials of AVERT and CASSINI(55, 56). However, 43.7% of patients on rivaroxaban (CASSINI) and 36% on apixaban (AVERT) discontinued the trial regimen before the end of the study period(55, 56). The reasons for premature discontinuation were similar between the groups (rivaroxaban or apixaban *versus* placebo) and the most common reasons were patients' wishes and end of life issues. Most of the study drug discontinuation occurred at the end of the follow-up period. The TRIM-Line pilot trial has a follow-up of 90 days instead of 180 days and an open-label design which limited study drug discontinuation.

Inclusion and Exclusion Criteria

Inclusion criteria

Consenting patients 18 years of age or older with a new or existing diagnosis of cancer and with a CVC inserted no more than 72 hours prior to obtaining consent were eligible to participate in the study.

Exclusion criteria. These criteria would be considered in clinical practice before prescribing rivaroxaban for thromboprophylaxis: 1) anticoagulation required for another indication; 2) concomitant use of dual antiplatelet therapy; 3) prior VTE; 4) history of condition at increased bleeding risk; 5) concomitant use of strong inducers or inhibitors of CYP3A4 or glycoprotein-P (known interaction with rivaroxaban); 6) pregnancy; 7) severe renal insufficiency (Creatinine clearance <30 mL/min (defined by Cockcroft-Gault)); 8) severe liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis); 9) thrombocytopenia < 50x 10^9/L; 10) history of a condition that increases bleeding risk including, but not limited to: a) history of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding; b) chronic hemorrhagic disorder; c) sustained uncontrolled hypertension defined as systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg. 11) CVC in place >72 hours. 12) Allergy to Rivaroxaban 13) Life expectancy<6months 14) primary malignancy diagnosis of basal cell or squamous cell carcinoma

of the skin or acute leukemia or myelodysplastic syndrome. 15) geographic inaccessibility 16) refused or unable to obtain consent.

Duration of treatment

The duration of the trial treatment (rivaroxaban 10 mg daily) is **90 days** (+/- 3 days). Most randomized controlled trials assessing primary thromboprophylaxis in patients with CVC and cancer have a follow-up period of 90 days.(52) Given previous studies have demonstrated that the mean duration from CVC insertion to VTE is approximately 10 days and that a majority of VTE occur within the initial 100 days following insertion,(51, 60) a follow up of 90 days is adequate to capture most events and appropriately assess the efficacy and safety of primary thromboprophylaxis with rivaroxaban in this patient population.

Frequency and duration of follow up

In addition to the initial enrollment visit, patients received a telephone follow up at Day 30 +/- 3 days and a final in-person follow-up at Day 90 +/- 3 days. At each visit, patients were asked standardized questions to capture the presence of primary or secondary outcomes. During these interviews the study coordinator collected data on the diagnosis of VTE, bleeding events or CVC-related complications (e.g. premature removal, occlusion, infections, etc.).

Safety surveillance: Any complications or adverse events associated with rivaroxaban were captured and reported to the Data and Safety Monitoring Board.

SCHEDULE OF MANDATORY EVENTS

	Screening, Baseline and Randomization	Day 30 +/- 3 days	Day 90 +/- 3 days
Consent	x		
Inclusion/Exclusion	x		
Demographic	x		
Randomization	x		
Labs	x		
History	x		
Cancer Treatments	x		
Dispense IP (Group 1)	x		
Concomitant Medications	x	x	x
IP Compliance		x	x
Outcome Information (Section 4.5)		x	x
Adverse Events		x	x

Table 4. Schedule of Mandatory Events

Individual Participant Compliance

Participants will be given a diary and will record the date and time of administration of each dose. If a dose is missed the participant should take it as soon as it is remembered and record the time. The next dose should be taken at the new time. Non-adherent participants may be removed from the study at the discretion of the primary investigator. In order to allow drug accountability by research staff participants will be instructed to return all bottles of study medication.

Withdrawal of Subjects

A subject has completed the study once all follow-up procedures have been completed. Study drug is discontinued, and appropriate clinical management is initiated in the case of the following outcome events.

For the subjects who reach a study endpoint, subsequent treatment will be left up to the discretion of the treating physician and documented. If the subject is prematurely discontinued from participation in the study, the study personnel will make every effort to obtain, and record, information about the reasons for discontinuation and any adverse events and if possible perform all safety assessments.

A subject may voluntarily withdraw participation in this study at any time, including for future data collection. If the subject does not return for a scheduled visit, every effort will be made to contact the subject. In any circumstance, every effort will be made to document the reason for withdrawal and when possible, all safety assessments will be done. All data will be reported for any subject randomized and not completing the study. Subjects withdrawn as a result of an adverse event thought to be related to the study drug will not be replaced. All safety data collected from all subjects during the study will be analyzed.

Safety

The adverse event reporting period will begin with the first dose of study medication and end on Day-90 +/- 3 days. Adverse events may be collected from participant report or by review of the clinical chart. Adverse events will be documented in the CRF.

Clinical investigators and ultimately the Qualified Investigator (QI) have the primary responsibility for

adverse event identification, documentation, grading, assignment of attribution and reporting.

Primary and Secondary Outcome Measures

The primary feasibility outcome for the pilot trial was enrolment rate. A prespecified target of 5 patients per month at the coordinating centre and 1.5 enrolments/month for additional centres was set as the cut-off for determination of trial feasibility. This was estimated based on the number of possible enrolling sites in the CanVECTOR network and the estimated time to trial enrolment completion being planned for 4 years or less. This timeline of feasibility was chosen due to limitations on funding duration if sought through Canadian Institutes of Health Research (61). Secondary feasibility outcomes included the loss to follow up and adherence to therapy defined as over 80% of study drug taken.

Clinical data which will be the outcomes for the full-scale TRIM-Line trial were also collected. These included, VTE, DVT, PE, UEDVT along with major bleeding and clinically relevant non-major bleeding, as per the standardized definition by the ISTH (15, 16), distal upper or lower extremity DVT. Major VTE was defined as a proximal leg DVT, or segmental or larger vessel pulmonary embolism as these are VTE which would clearly require anticoagulation. Superficial upper or lower extremity vein thrombosis, and catheter associated complications (CVC life span, CVC lumen occlusion, CVC associated infection and death).

Statistical Analysis Plans

Sample Size and Power Calculation

The sample size for the pilot trial was calculated based on the primary outcome, enrolment rate. An estimate for the full-scale trial was also conducted. The rate of symptomatic VTE among patient with cancer and CVC has been reported to be 6.8% in recent studies with a rate of 3.7% in those on anticoagulant treatment (45). With 0.05 (2-sided) alpha-significance and 80% power and estimating a

conservative loss to follow up rate of 10%, the predicted sample size required to complete the full-scale trial was 1892 (61).

Agreement in principle to participate has been obtained from nine centres of the pan-Canadian CanVECTOR thrombosis research network for the full trial pending obtaining funding and success of the pilot study. Given these site numbers and if the minimum enrolment rates specified it is expected the full trial could be completed in under 5 years which is a reasonable time span for a large multicentre randomized controlled trial. Additional sites would be available to be added should enrolment fall below target. Given the expected rates and the budget available, the pilot trial would aim to enrol 100 patients to provide an assessment on the feasibility of the full scale trial(61).

Analysis of Baseline Characteristics

Descriptive statistics will be used to examine the baseline characteristics of excluded subjects and those in the experimental and standard of care arm. Standard deviations will be reported for all characteristics expressed as continuous variables. Medians and ranges will be presented for discrete data.

Pilot Trial Primary Analysis

The primary analysis will involve a simple estimate of the mean monthly recruitment rate per site along with the 95% confidence interval of the mean.

Pilot Trial Secondary Analyses

Proportions with 95% confidence intervals will be calculated using Wilson's score method for the

following secondary analyses: 1) proportion of screened subjects who meet eligibility criteria, 2) proportion of eligible subjects who provide consent, 3) proportion of withdrawals/losses to follow-up among randomized subjects, 4) proportion of sites requiring >18 months to obtain all required approvals/contracts from time of delivery of all study documents, and 5) proportion of crossover between study arms. Reasons for non-consent will be collected and analyzed using qualitative thematic analysis.

Planned Trial Management

The trial will be coordinated from the Ottawa Hospital Research Institute's (OHRI) Clinical Epidemiology Unit, where the nominated Principal Investigator (Dr. Rick Ikesaka) is based. OHRI will act as the study sponsor. Dr. Ikesaka will train a Multicenter Trial Coordinator with expertise in VTE clinical studies to this trial. The Multicenter Trial Coordinator, supervised by the co-PIs, will be responsible for overseeing the day-to-day conduct of the study in the participating centers. At each study site, study coordinators will carry out patient screening, recruitment, case report form completion, initiation of study interventions, patient education, and arranging follow-up visits. The OHRI Data Management Services group, under the supervision of Dr. Ikesaka, will be responsible for the design, implementation and maintenance of the web-based randomization system and for data management, including quality assurance. This will involve developing the electronic case report forms and database, including queries, audit trail, quality control, security, and backup. Randomization and data management will be overseen by the study statistician.

A *Data and Safety Monitoring Board (DSMB)* will be created. The DSMB will be independent and composed of 3 members: an expert in thrombosis medicine and clinical trials (Chair), a biostatistician and an expert in thromboembolic diseases. All members will remain at arms-length from the study. All serious adverse events will be reported to and reviewed by the DSMB.

Monitoring

The investigator/institution will permit trial-related monitoring, audits, REB review and regulatory inspections(s), and will provide direct access to source data/documents as required.

The multicentre research coordinator will be responsible for the training of research staff and conducting monitoring visits in the anticipated 3 centers. Remote monitoring methods will be used. An initiation teleconference will be performed in each center before commencement of the trial. Monitoring at each center will be performed to ensure that patient safety, study procedures, and data collection are performed in accordance with the research protocol and GCP/ICH guidelines.

Ethics

Ethical Conduct of the Trial

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly (Helsinki, Finland, 1964 and later revisions), the Tri-Council Policy Statement and the ICH GCP Guidelines.

Research Ethics Board

This study will be and approved with annual renewal by the Ottawa Health Science Network Research Ethics Board. REB approval will be obtained from all other participating centres prior to initiating the study at these sites.

Subject Information and Consent

The investigator, or his designee, will inform each subject (or the subject's acceptable representative) prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The subjects must be informed about their right to withdraw from the trial at any time. Written subject information will be given to each subject before enrolment.

Furthermore, it is the responsibility of the investigator or his designee to obtain signed informed consent (or witnessed verbal consent according to applicable regulations) from all subjects prior to inclusion in the trial.

Data Handling and Record Keeping

Personal Health Information

Personal health information including Case Report Forms (CRF), evaluation forms, reports, etc. will be kept strictly confidential. All records will be stored on-site in a secure, locked facility.
Records will be destroyed after 25 years, in accordance with Health Canada Regulations.

Case Report Forms

A CRF is required and will be completed for each randomized subject. The completed original CRFs are the sole property of The Ottawa Hospital and are not to be made available in any form to third parties, except for authorized representatives of appropriate Regulatory Authorities.

Record Retention

To enable evaluations and/or audits, the investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs and detailed records of drug disposition. To comply with international regulations, the records are to be retained for 25 years.

Study Dissemination Plan

The results of our trial will be used by the investigators to evaluate the feasibility of a larger trial evaluating the role of the prophylactic dose rivaroxaban to reduce upper extremity DVT in cancer patients with central venous catheters. The results will provide justification to external funding agencies before a commitment is made to fund a full trial. Regardless of the results of the trial, we will strive to publish and present our data and conclusions about feasibility such that future researchers might benefit from this work.

Next Steps

Given the success of direct oral Xa-inhibitors in preventing VTE ambulatory cancer patients in the AVERT and CASSINI (55, 56) trials during the formation of this trial protocol and the concerns regarding increased thrombogenicity of newly inserted CVC and active cancer, it seemed like an opportune time to test this class of medication in a high-risk oncology population. With the completion of the TRIM-Line Pilot trial study protocol outlined in in this chapter, funding was obtained through CanVECTOR and the pilot trial was conducted with the goal of providing evidence that a multicentre randomized controlled trial to investigate the efficacy and safety of a direct oral Xa-inhibitor to enable informed decisions about the optimal thromboprophylaxis strategy for patients with cancer and a newly inserted CVC would be feasible.

CHAPTER 3: Execution of the TRIM-Line Pilot Randomized Controlled Trial

No changes were made to the study protocol outlined in Chapter 2 prior to the execution of the Pilot RCT. Therefore, the TRIM-Line pilot trial is a multicentre, two-arm, PROBE randomized controlled trial conducted at two Canadian Centres, The Ottawa Hospital and the Juravinski Cancer Centre which are members of the CanVECTOR research network. The coordinating centre was the Ottawa Hospital Research Institute and the secondary site was the Juravinski Cancer Centre in Hamilton Ontario.

Methods

The study protocol was described in Section 2 and registered on ClinicalTrials.gov with identifier NCT3506815.

Funding

Given the significant costs associated with recruitment and the operation of large multicentre trials, it is common for a pilot trial to be conducted to support the grant applications for large trials. Funding for the pilot randomized controlled trial was obtained through the author's successful application to the CanVECTOR Research Start-up fund competition ($2,500) and the CanVECTOR Pilot Trials competitions ($52,224).

Ethics

Ethics approval was obtained from the Ottawa Hospital Research Ethics Board and the Hamilton Health Sciences Research Ethics board prior to study initiation at the respective sites. At the time conception and execution of the study the use of rivaroxaban for prophylactic use in cancer patients with CVC was an off-label indication, an application with subsequent issuing of a Health Canada Division 5 Non-objection letter was obtained prior to enrollment of patients into the study.

Results

Patients were enrolled at The Ottawa Hospital and Juravinski Cancer Centre from March 2019 until February 2020. A total of 105 patients underwent randomization at 2 centres in Canada. The baseline characteristics of the two groups were well balanced (Table 4). 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 to 90). The median follow-up duration was 90 days in both groups. The study drug was discontinued as per participants' wish in 2 patients (adherence of 96%). Compliance was high in the experimental group at 96.7%

The study met its prespecified feasibility endpoint average enrolment rate of 7.5 per month (95% CI:4.56, 10.44) at the coordinating Ottawa Hospital site and 2.0 per month (95% CI:0.87, 3.13) for the Juravinski Cancer Centre site. No patients were lost to follow up over the course of the trial.

Thrombotic complications occurred in 3 of 52 patients in the rivaroxaban arm (5.8%, 95%CI: 1.2-16.0%) including 2 major VTE(PE,DVT,UEDVT) (3.9% 95%CI: 0.5-13.2). In contrast, patients in the control group had 5 of 53 patients develop VTE (9.4%, 95% CI: 3.1-20.7) including 3 major VTE (5.7%, 95% CI: 1.2-15.7) (Table 2). One UEDVT occurred in the rivaroxaban group following discontinuation of the study drug (>30 days) during a prolonged hospitalization. The hazard ratios for thrombotic complications and major VTE were 0.58 (95% CI: 0.14-2.5) (Figure 1) and 0.66 (95% CI: 0.11-3.9), respectively. One patient (1.9%) receiving rivaroxaban had a major bleeding episode. Two patients in both groups 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 5 of 53 patients in the control group (9.4%, 95% CI: 3.1-20.7) compared to 0 of 51 patients (0%, 95% CI, 0 to 7.0) in the rivaroxaban group.

	Rivaroxaban 10mg N=52	Standard of Care N = 53
Age (mean +/- SD)	60.0 (11.9)	61.6 (12.7)
Female (%)	36 (69.9)	36 (67.9)
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)

CVC: central venous catheter; SD: Standard deviation; PICC – Peripherally Inserted Central Catheter

Table 5. Baseline Characteristics of the TRIM-Line Patients

	Rivaroxaban 10mg N=52	Standard of Care N = 53	Hazard Ratio
Thrombotic complications (n, %):			0.58(95% CI: 0.14-2.5)
Major VTE (n, %):	2* (3.9)	3 (5.7)	0.66 (95% CI: 0.11-3.9)
Upper extremity DVT	2* (3.9)	2 (3.7)	
PE	0	1 (1.9)	
Other thrombotic events (n, %):			
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 (95% CI: 0.14-7.24)

* One upper extremity DVT occurred following rivaroxaban discontinuation for prolonged hospitalization

CRNMB: Clinically-relevant non-major bleeding; CVC: central venous catheter. DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: Venous thromboembolism

Table 6. Clinical Outcomes at 90 Days

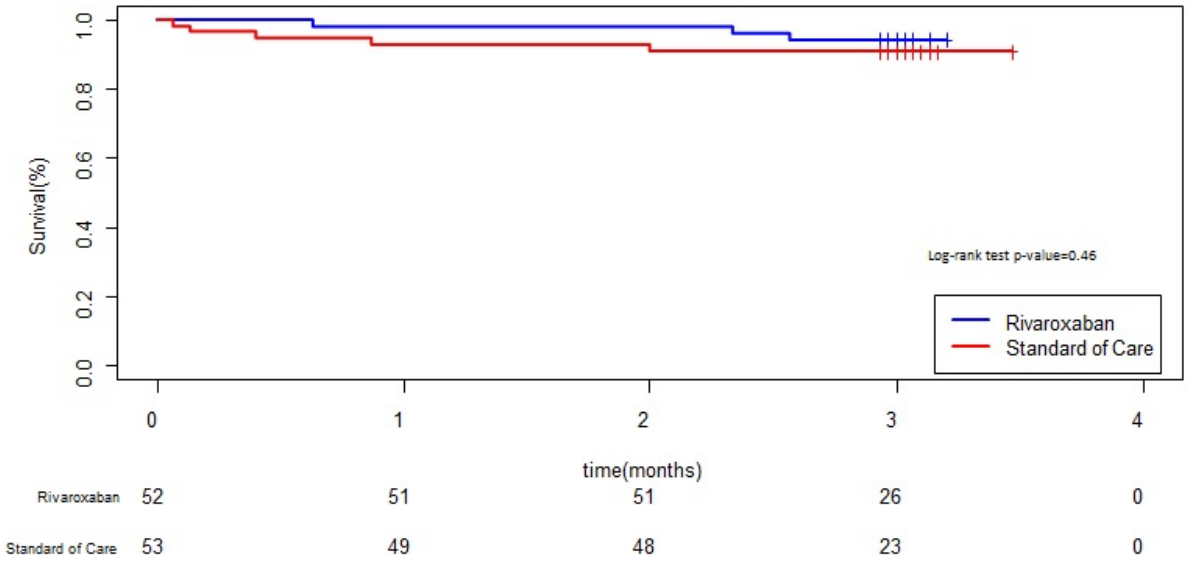

Figure 10. Kaplan Meier Event Curve for all Thrombotic Complications

Analysis of the pre-specified secondary outcomes demonstrated that the proportion of eligible subjects which provided consent and were enrolled into the study was 0.35 (95%CI: 0.28, 0.42). The most common themes for patients not enrolling in the study were the patient were: 1) overwhelmed with the cancer diagnosis and treatment; 2) already being on an anticoagulant for an alternate indication; and 3) not wanting to take additional pills during their cancer treatments.

Discussion

The TRIM-Line Pilot Trial met its feasibility outcome and support that a full-scale definitive multicentre randomized controlled trial with a PROBE design investigating the efficacy and safety of low-dose rivaroxaban for preventing VTE in patients with active cancer and newly inserted CVC would be feasible. The hypothesis of the full-scale trial would be the primary prevention with rivaroxaban 10mg daily would reduce the rate of symptomatic VTE in cancer patients with a recently inserted CVC. For the TRIM-Line trial, based on an estimate of 6.8% VTE events from a recent systematic review(45) for the control group at 3 months and with 0.05 (2-sided) alpha- significance and 80% power with a conservative loss to follow up rate of 10% the estimated sample size required to complete the full scale trial is 1892 patients.

With the enrolment rates achieved in this study of 7.5 participants a month at the coordinating centre and 2 participants/month at the secondary site and 9 sites of the existing pan-Canadian CANVECTOR thrombosis research network expressing interest, conservatively over 40 patients per month could be enrolled into the full-scale trial allowing for completion of target enrolment within 4 years and trial completion within a reasonable timeline of 5 years.

Although CVC-associated VTE is associated with significant harms, primary thromboprophylaxis is not currently recommended due to uncertainty about overall net clinical benefit. Based on the AVERT and CASSINI trials the ASCO clinical practice guidelines now suggest the use of thromboprophylaxis in high-risk ambulatory cancer patients initiating systemic therapy(58). Patients enrolled in the TRIM-Line trial have a different VTE risk profile than those in the AVERT and CASSINI trials which did not specifically report the rates of VTE of cancer patients with CVC in the study(55, 56). Further, these studies chose high risk cancer patients as defined as Khorana score greater than or equal to 2 which stratifies patients based on tumor type, complete blood count parameters and body mass index (57). The Khorana score does not include CVC as a risk factor and therefore patients with lower risk tumor types

included in the pilot TRIM-Line trial (e.g. breast and colorectal carcinomas) remain high risk due to the indwelling CVC .

A previously conducted systematic review and meta-analysis has reported the rate of symptomatic VTE in patients with cancer and CVC to be 6.8% (45) emphasizing the importance of CVC as a major risk factor for VTE in this population. In the TRIM-Line pilot study, 5 patients in the control group experience thrombotic complications (9.4%, 95%:CI 3.1-20.7) consistent with the results of other studies. This review (45) and previous studies using LMWH and VKA have previously reported efficacy as primary prophylaxis for ambulatory cancer patients but have never seen widespread clinical adoption due to the difficulty managing VKA in cancer patients and the inconvenience of daily self-injection and cost of LMWH(62, 63). The most recent version of the International Initiation on Thrombosis and Cancer (ITAC)(53) guidelines does not recommend routine use of thromboprophylaxis in patients with cancer and a newly inserted CVC, therefore, the premise of the full-scale TRIM-Line trial still remains a valid research question as the efficacy and safety of using prophylactic dosing of DOACs in patients with cancer and CVC remains an important question of clinical importance.

Potential challenges of the full-scale TRIM-Line trial are study drug adherence and potential high rates of rivaroxaban discontinuation. The AVERT and CASSINI trials reported high rates of study drug discontinuation, 36% in AVERT and 43.7% in CASSINI, (55, 56). This was not noted in the TRIM-Line pilot trial with high compliance in the experimental arm of 96% of the rivaroxaban group were adherent. This study has a shorter treatment course of 90 days vs 180 days which may have improved patient adherence to therapy. The open label design may improve adherence as patients may be motivated to prevent catheter complications and VTE if they know they are on a treatment medication rather than a placebo. Also, with increasing utilization of the DOACs in a variety of settings for the prevention of VTE (e.g. high-risk cancer, post orthopedic surgery) it is likely that these agents will be more acceptable to patients than in the past. Hence, study drug adherence and discontinuation should not be an important issue for the full-scale TRIM-Line trial.

Study weaknesses included the lack of a placebo control. However, a PROBE study design(59) was chosen in order to be pragmatic and to reflect current standard practice which could make the study results more easily applicable to clinical practice. While the open label design is more likely to bias the frequency of an outcome compared to a placebo-controlled trial, the clinical endpoints of VTE trials are objective and blindly adjudicated without knowledge of treatment allocation using standard definitions based on objective testing, thus reducing the risk of bias. In addition, crossover is unlikely in the TRIM-Line trial since the intervention (rivaroxaban) is not indicated (or reimbursed) for this specific indication nor for thromboprophylaxis in ambulatory cancer patients in Canada and therefore would be unlikely to be prescribed for this indication. Differential withdrawal remains a possibility, however given that follow-up is relatively short and identical for both groups it should not lead to an imbalance between the two groups. Furthermore, differential withdrawal was not observed in the AVERT or CASSINI studies or the pilot TRIM-Line trial (55, 56).

This pilot trial featured, blinded computer-generated randomization and therefore any differences in baseline characteristics between the two arms of the study would likely be related to random chance. There does not appear to be any major between group differences in terms of baseline characteristics of the enrolled patients but due to the very small number of enrolled patients in the pilot trial, the standard deviation is large.

Finally, this was a pilot feasibility study and thus designed to assess feasibility and not to determine difference in the risk of clinical events between the treatment groups. Clinical events were collected to simulate the research coordinator workload of operating the trial as well as it was hoped that this pilot study could be rolled into the full-scale trial. Funding could not be obtained prior to exhaustion of the pilot trial funds and therefore the study was closed. Therefore, the number of clinical outcome events in

this pilot study was relatively small leading to wide confidence intervals. The reported difference in outcomes between the groups are presented only to be hypothesis generating.

Conclusion

In conclusion, the work of this M.Sc. Epidemiology thesis demonstrates a lack of high quality randomized controlled data on the risk of upper extremity deep vein thrombosis and that the risk profile of different types of upper extremity DVT vary by cause. Subsequently, the protocol of TRIM-Line was conceived, designed and used to achieve funding for the TRIM-Line pilot trial. This pilot study was successful at meeting its primary feasibility outcome supporting that a definitive full-scale multicentre randomized controlled trial investigating low-dose rivaroxaban prophylaxis in cancer patients with newly inserted CVC is feasible in Canada.

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Appendix A Search Strategy for MEDLINE

1. Venous Thrombosis/
2. Venous thrombosis.tw.
3. Pulmonary Embolism/
4. Pulmonary Emboli$.tw.
5. Venous thrombosis.tw.
6. Vein thrombosis.tw.
7. Thrombophlebitis/
8. Upper Extremity Deep Vein Thrombosis/
9. Or/1-8
10. Upper Extremity/
11. Jugular Veins/
12. Jugular vein$.tw.
13. Axillary Vein/
14. Axillary vein$.tw.
15. Axillary ven$.tw.
16. Jugular ven$.tw.
17. Brachiocephalic Veins/
18. Brachiocephalic ven$.tw.
19. Brachiocephalic ven$.tw.
20. Subclavian Vein/
21. Subclavian vein$.tw.
22. Subclavian ven$.tw.
23. Cephalic ven$.tw.
24. Cephalic vein$.tw.
25. Basilic vein$.tw.
26. Basilic ven$.tw.
27. Heparin, Low-Molecular-Weight/
28. Heparin/
29. Heparin.tw.
30. Dalteparin/
31. Daltepearin.tw.
32. Enoxaparin/
33. Enoxaparin.tw.
34. Tinzaparin.tw.
35. Warfarin/
36. Warfarin.tw.
37. Coumadin.tw.
38. Mechanical Thrombolysis/
39. Thrombectomy.tw.
40. Thrombolysis.tw.
41. Thrombolytic Therapy/
42. Tissue Plasminogen Activator/
43. Tissue plasminogen activator.tw.
44. Rib resection.tw.
45. Anticoagulants/
46. Anticoagul$.tw.
47. Factor Xa Inhibitors/

48. Rivaroxaban/
49. Factor Xa inhibitor$.tw.
50. Rivaroxaban.tw.
51. Apixaban.tw.
52. Edoxaban.tw.
53. Antithrombins/
54. Dabigatran/
55. Dabigatran.tw.
56. Argatroban.tw.
57. Fondaparinux.tw.
58. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
59. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
60. 9 and 58 and 49

Appendix B. Search Strategy for EMBASE

1. Vein Thrombosis/
2. Lung embolism/
3. Vein thrombo$.ab,ti.
4. Pulmonary embol$.ab,ti.
5. Venous thromboembol$.ab,ti.
6. Thrombophlebitis/
7. Upper extremity deep vein thrombosis/
8. Venous thrombosis.ab,ti.
9. Upper limb/
10. Jugular vein/
11. jugular ven$.ab,ti.
12. Jugular vein$.ab,ti.
13. Axillary vein/
14. Axillary vein$
15. Axillary ven$.ab,ti.
16. Brachiocephalic vein/
17. Brachiocephalic vein$.ab,ti.
18. brachiocephalic ven$.ab,ti.
19. Subclavian Vein/
20. Subclavian vein$.ab,ti.
21. Subclavian ven$.ab,ti.
22. Cephalic vein/
23. Cephalic ven$.ab,ti.
24. Cephalic vein$.ab,ti.
25. Basilic vein$.ab,ti.
26. Basilic ven$.ab,ti.
27. Brachial vein/
28. Brachial vein$.ab,ti.
29. Low molecular weight heparin/
30. heparin/
31. low molecular weight heparin .ab,ti.
32. Heparin.ab,ti.
33. Dalteparin
34. Dalteparin.ab,ti.
35. Tinzaparin/
36. Tinzaparin.ab,ti.
37. Enoxaparin/
38. Enoxaparin.ab,ti.
39. Warfarin/
40. warfarin.ab,ti.
41. Coumadin.ab,ti.
42. Blood clot lysis/
43. mechanical thrombectomy/
44. thrombolysis.ab,ti.
45. Tissue plasminogen activator/
46. Tissue plasminogen activator.ab,ti.
47. Rib resection/
48. blood clotting factor 10a inhibitor/

49. rivaroxaban/
50. rivaroxaban.ab,ti.
51. Apixaban/
52. Apixaban.ab,ti.
53. Edoxaban/
54. edoxaban.ab,ti.
55. Antithrombin/
56. dabigatran/
57. argatroban/
58. argatroban.ab,ti.
59. dabigatran.ab,ti.
60. Fondaparinux/
61. Fondaparinux.ab,ti.
62. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
63. or /9-28
64. or /29-61
65. 62 and 63 and 64

Appendix C. Quality Assessment of Included Trials

Study	Selection				Comparability	Outcome		
	Representativeness of exposed cohort	Representativeness of non-exposed cohort	Ascertainment of exposure	Outcome not present at beginning of study	Comparability of cohorts	Assessment of Outcome	Was follow-up long enough?	Adequacy of follow-up
Castenada 2002 (24)	*	N/A	*	*	N/A	*		
Cote 2017 (25)	*	N/A	*	*	N/A	*	*	*
Davies, 2017 (32)	*	N/A	*	*	*	*	*	*
Desancho (20)2014		N/A	*		N/A	*		
Harley 1984(26)	*	N/A	*	*	N/A	*	*	*
Houghton 2020 (27)	*	N/A	*	*	N/A	*	*	*
Karabay, 2004(28)	*	N/A	*	*	N/A	*	*	*
Kovacs, 2007(33)	*	*	*	*	*	*	*	*
Kreienberg 2001(21)	*	*	*	*	*	*	*	*
Lee J 2006(22)	*	*	*	*	*		*	*
Lee W, 2000(23)	*	*	*	*			*	*
Monreal, 1994(34)	*	N/A	*	*	N/A	*		
Prandoni, 1997(29)	*	*	*	*	*	*	*	*
Rathbun, 2011(30)	*	*	*	*	*	*	*	*
Savage, 1999(31)	*	N/A	*	*	N/A	*	*	*

Table 7. Newcastle-Ottawa Risk of Bias Assessment for Included Studies

Appendix D - Contribution of Authors

Rick Ikesaka is the principle investigator of all research presented in this M.Sc. manuscript. Rick Ikesaka was responsible for the design and execution of the systematic review, the conception of the TRIM-Line study, funding application, design of the study protocol, acquisition, execution and interpretation of study data. Rick Ikesaka was responsible for the writing of this thesis manuscript.

Marc Carrier is the M.Sc. thesis supervisor and provided guidance in the conception, design and execution of the TRIM-Line pilot study. He also assisted as the second reviewer in the systematic review. Marc Carrier participated in the revision and approval of the final written manuscripts.

Gregoire Le Gal is a member of the M.Sc. thesis advisory committee and provided guidance on the study design, and revision and approval of the final written manuscript

Sudeep Shivakumar is a member of the M.Sc. thesis advisory committee and provided guidance on the study design, and revision and approval of the final written manuscript