COBRRA

COmparison of Bleeding Risk between Rivaroxaban and Apixaban for the Treatment of Acute Venous Thromboembolism: The Pilot Study

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List of Abbreviations

ACCP	American College of Chest Physicians
AE	Adverse Event
ALT	Alanine aminotransferase
BID	Twice daily
CrCl	Creatinine clearance
CRF	Case Report Forms
CRNMB	Clinically relevant non-major bleeding
CT	Computed tomography
CUS	Compression ultrasound
DOAC	Direct oral anticoagulant
DSM	Data management services
DSMB	Data safety monitoring board
DVT	Deep vein thrombosis
e-CRF	Electronic case report form
GCP/ICH	Good Clinical Practise/International Conference of Harmonization
INR	International Normalized Ratio
LMWH	Low molecular weight heparin
OAC	Oral Anticoagulants
PCC	Prothrombin Complex Concentrate
PE	Pulmonary embolism
P-gp	P-glycoprotein
PO	Per os
PROBE	Prospective randomised open, blinded end-point
QD	Once daily
RCT	Randomized controlled trial
RR	Relative risk
SAE	Serious Adverse Event
SAE	Serious adverse event
V/Q	Ventilation/perfusion
VECTOR	VEnous thromboembolism Clinical Trials ORganization
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

Protocol Synopsis

Title	Comparison of Bleeding Risk between Rivaroxaban and Apixaban for the Treatment of Acute Venous Thromboembolism: The Pilot Study
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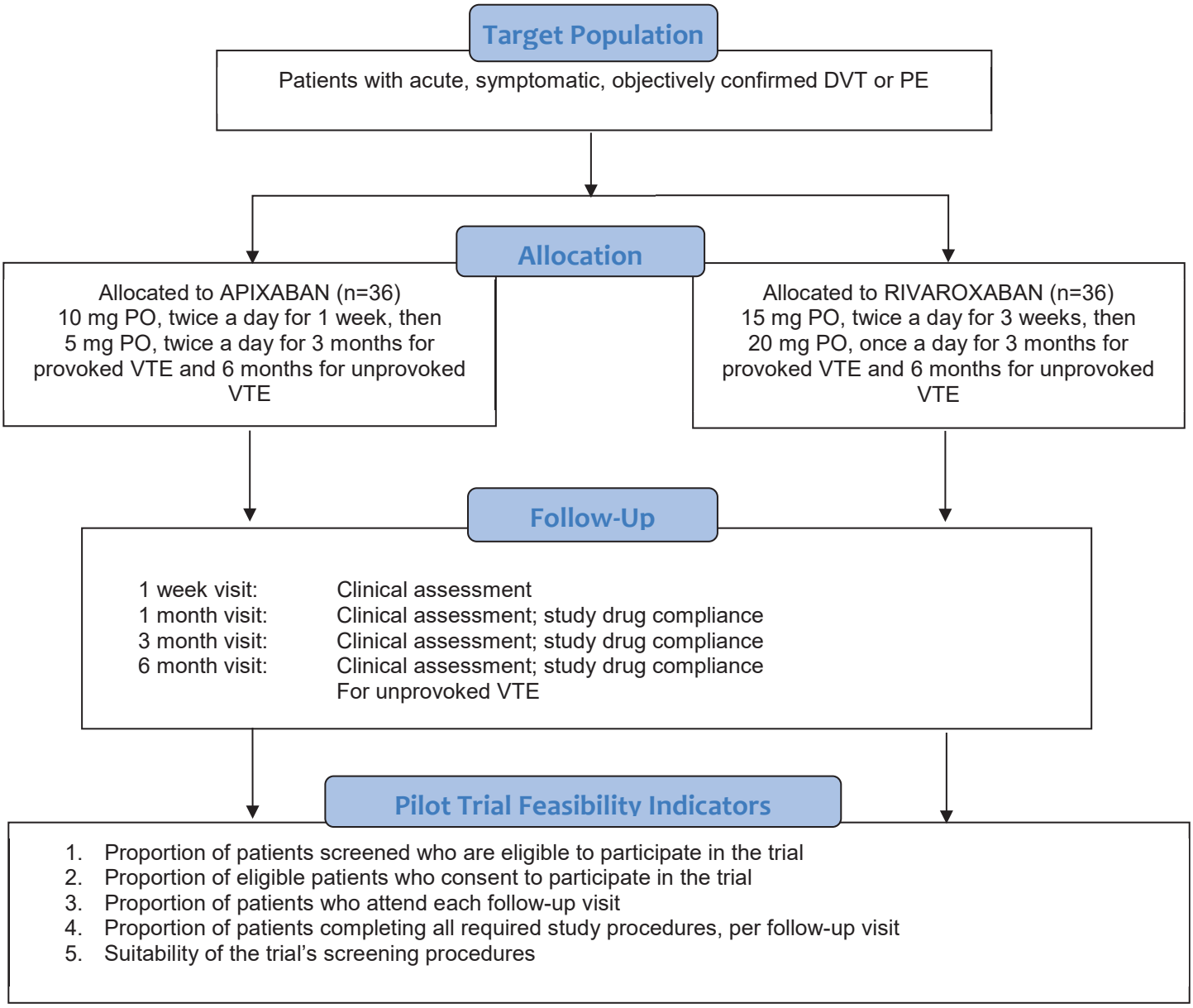
Background	Recently developed new oral anticoagulants (OAC) overcome some of the limitations of established therapy with vitamin K antagonists (VKA) and low molecular weight heparin (LMWH) for treatment of acute venous thromboembolism (VTE), due to ease of administration and more predictable pharmacokinetic properties. Many clinical questions about the new OAC remain unanswered because there have not been direct head-to-head comparison trials. For example, although studies have shown that rivaroxaban and apixaban are at least as effective and safe as LMWH and VKA, meta-analyses suggest that apixaban may be associated with lower bleeding risk. Concerns about the potential impact of medication non-adherence have been raised. Compliance with twice daily medications (e.g. apixaban) is often worse than once daily medications (e.g. rivaroxaban). Both of these medications are approved by Health Canada for treatment of VTE yet there is genuine uncertainty about which of the two direct OAC confer the best risk-to-benefit ratio.
Study Objectives	•The primary objective of the study is to determine if it is feasible to conduct a large randomized multicenter trial comparing apixaban vs. rivaroxaban for the treatment of acute VTE. •The secondary objectives are to assess safety and superiority of apixaban vs rivaroxaban.
Study Design	This is a multi-centre, prospective randomized open blinded end-point (PROBE) trial assessing clinical feasibility for a larger multi-centered trial comparing bleeding outcomes using apixaban vs. rivaroxaban for treatment of acute VTE.
Study Population	<u>Inclusion Criteria</u> •Confirmed newly diagnosed symptomatic acute VTE (proximal lower extremity DVT or segmental or greater PE) •Age ≥ 18 years old •Written informed consent <u>Exclusion Criteria</u> • Any contraindication for anticoagulation with apixaban or rivaroxaban such as active bleeding, weight >120 kg, etc. • Another indication for long-term anticoagulation (e.g. AFib) •Clinically significant liver disease or alanine aminotransferase (ALT) levels ≥ 3 times the upper limit of normal range •Creatinine clearance < 30 ml/min calculated with the Cockcroft-Gault formula •Known allergies to either apixaban or rivaroxaban •Pregnancy or breastfeeding •Use of contraindicated medications with apixaban or rivaroxaban •Active malignancy in the last 6 months (excluding localized skin malignancy) •No private insurance coverage for the study drug or not willing to pay for

	study drug •Have received > 72 hours of therapeutic anticoagulation
Study Intervention	Patients will be randomized to one of these 2 groups: 1)Apixaban group:10 mg PO twice-a-day for 1 week, then 5 mg PO, twice daily for 3 or 6 months of treatment. 2)Rivaroxaban group: 15 mg PO twice-a-day for 3 weeks, then 20 mg PO once daily for 3 or 6 months of treatment.
Study Outcomes	Primary outcome measures: •Proportion of patients screened who are eligible to participate in the trial •Proportion of eligible patients who consent to participate in the trial •Proportion of patients who attend each follow-up visit •Proportion of patients completing all required study procedures, per follow-up visit •Suitability of the trial's screening procedures Secondary outcomes: •Major bleeding events, clinically relevant non-major and minor bleeding episodes •Recurrent VTE and VTE related-death •All-cause mortality rates •Individual rates of death related to VTE, cardiovascular disease, bleeding or other causes •Medication compliance •The time-to-first occurrence of secondary outcomes between randomization and end of follow-up (time-to-event analysis)
Total # of Patients	A total of 72 patients will take part in this study conducted in 4 Canadian centres.
Follow-Up	3 months for provoked VTE, 6 months for unprovoked VTE

STUDY FLOW CHART



PROTOCOL SYNOPSIS **5**

STUDY FLOW CHART **7**

ALLOCATION 7
PILOT TRIAL FEASIBILITY INDICATORS 7
TARGET POPULATION 7
FOLLOW-UP 7

1 BACKGROUND AND SCIENTIFIC RATIONALE **10**

1.1 BACKGROUND 10
1.2 RATIONALE 11
1.3POTENTIAL RISKS AND BENEFITS 12
1.3.1 Potential Risks *12*
1.3.2 Known Benefits *12*

2 OBJECTIVES **12**

3 STUDY DESIGN **12**

3.1 DESIGN 12
3.2 RATIONALE FOR SELECTED DOSE OF STUDY DRUGS 13
3.3 RATIONALE FOR USE OF A PROBE DESIGN 13

4 SELECTION OF SUBJECTS **14**

4.1 INCLUSION CRITERIA 14
4.2 EXCLUSION CRITERIA 14

5 RANDOMIZATION **15**

6 TRIAL TREATMENT/ STUDY PROCEDURES **15**

6.1 SCREENING AND ENROLMENT 15
6.1.1 Screening *15*
6.1.2 Enrolment *15*
6.1.3 Pregnancy *16*

7 TRIAL TREATMENT /STUDY PROCEDURES **16**

7.1 TRIAL INTERVENTION 16
7.2 Follow-Up *16*
7.3 Concomitant Medications/Treatment *17*
7.4 Compliance to Study Drug *17*

8 INVESTIGATIONAL PRODUCTS **18**

8.1 PACKAGING AND LABELLING 18
8.2 DRUG ACCOUNTABILITY 18

9 ASSESSMENT OF SCIENTIFIC OBJECTIVES **18**

9.1 STUDY OUTCOME MEASURES 18
9.2 ASSESSMENT AND ANALYSIS OF SECONDARY OUTCOMES MEASURES 19
9.2.1 Methods for Assessing Secondary Outcome Measures *19*

10 DISCONTINUATION OF STUDY DRUG **19**

11 ASSESSMENT OF SAFETY **20**

11.1 ADVERSE EVENT 20
11.2 SERIOUS ADVERSE EVENT 20
Intensity, Causality and Grading *20*
11.3 RECORDING AND REPORTING OF SAES 21

12 CLINICAL MONITORING 22
12.1 MONITORING 22
12.2 DATA AND SAFETY MONITORING BOARD (DSMB) 22
13 PROTOCOL DEVIATIONS/VIOLATIONS 22
13.1 PROTOCOL DEVIATIONS 23
13.2 PROTOCOL VIOLATIONS 23
14 STATISTICAL CONSIDERATIONS 24
14.1 SAMPLE SIZE 24
14.2 ANALYSIS 24
15 ETHICS 24
15.1 RESEARCH ETHICS BOARD 24
15.2 INFORMED CONSENT 24
16 DATA HANDLING AND RECORD KEEPING 25
16.1 CASE REPORTS FORMS 25
16.2 CONFIDENTIALITY 25
16.3 STUDY RECORDS RETENTION 25
17 APPENDIX 26
18 REFERENCES 27

1 BACKGROUND AND SCIENTIFIC RATIONALE

1.1 Background

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common, potentially fatal yet treatable condition. VTE is the third leading cause of mortality by cardiovascular disease (1-3). The incidence of VTE (DVT ± PE) in the general population is reported in 1 to 2 persons per 1000 people(1). VTE is etiologically classified as unprovoked, provoked or malignancy associated. In ~50% of patients it is unprovoked, ~30% it is malignancy associated and ~20% it is provoked (defined as associated with fracture or plaster casting of a lower limb, hospitalization with confinement to bed for 3 days, or use of general anesthesia, each within the previous three months(4;5). Without treatment, the rate of VTE recurrence is about 25%, but this incidence decreases to 3% with anticoagulation therapy. Standard anticoagulation treatment for acute VTE uses a combination of parenteral low molecular weight heparin (LMWH) with transition to oral vitamin K antagonists (VKA) (henceforth LMWH/VKA)(2;3). This regimen, however, exposes patients to significant risk of bleeding. The composite rate of major and/or clinically-relevant non-major bleeding in the first 6 months of treatment ranges between 8.1% and 9.7% (6;7), with associated rates of fatal bleeding events of 0.2% and case-fatality rates of 11.0%(8). While the combination of LMWH/VKA is the standard of care for most patients with acute VTE, this treatment is burdensome as it initially requires subcutaneous injections, laboratory monitoring and frequent dose adjustments due to a number drug-drug and food-drug interactions with VKA.

The recently developed direct oral anticoagulants (DOACs) overcome several of these limitations as some do not require initial parenteral LMWH, and they have more predictable pharmacokinetics properties eliminating the need for laboratory monitoring(9). Several clinical trials (6;10-13), and meta-analyses (14-17) have evaluated the efficacy and safety of DOACs for the treatment of acute VTE compared with standard care. These studies have shown that rivaroxaban and apixaban, two DOACs targeting Factor Xa, are at least as equally effective and safe as LMWH/VKA(6;10;11). Although analysis of the composite bleeding outcomes from these trials demonstrated less bleeding with twice daily dosed apixaban (4.3%) vs. LMWH/VKA (9.3%) (11), and 8.1% with once daily rivaroxaban vs. LMWH/VKA (8.1%) (6), there were several methodological limitations associated with selection bias, heterogeneity of the populations, differences in treatment duration (6;10;14), and lack of face-to-face comparison between these agents, making it difficult to conclusively establish the superiority of apixaban over rivaroxaban. This issue represents a dilemma in real practice because in the absence of convincing evidence of their differences in safety, there is genuine uncertainty about which of the two DOACs will result in the best risk-to-benefit ratio. Moreover, in the absence of direct comparisons between these agents, it is difficult to estimate if differences in their daily prescription (twice daily

versus once daily) would lead to changes in safety due to medication non-adherence. All trials to date have been sponsored by the pharmaceutical industry and there is no interest by the industry to sponsor head-to-head comparisons.

A meta-analysis that included 45 clinical trials (44,989 patients and 20,842 patient-years of follow-up) compared dabigatran, rivaroxaban, apixaban or edoxaban against LMWH/VKA during the first 3 months of treatment of acute VTE, was associated with a similar risk of recurrent VTE; however, only rivaroxaban and apixaban were associated with the lowest risk of bleeding (rivaroxaban; hazard ratio (HR): 0.55; 95% CI: 0.35-0.89; apixaban; HR: 0.31; 95% CI: 0.15-0.62) (14). Using indirect comparison to other DOAC treatments, rates of major bleeding were significantly lower with apixaban (LMWH-dabigatran: HR: 0.42; 95% CI: 0.17-0.99; LMWH-edoxaban; HR: 0.37; 95% CI: 0.15-0.89), with the exception of comparison to rivaroxaban (HR: 0.56; 95% CI: 0.24-1.33). This meta-analysis is limited by use of indirect comparisons of safety outcomes.

Evaluating the relative safety of apixaban and rivaroxaban anticoagulants is important because of the potential morbidity, mortality and health-care costs associated bleeding events may impart.

Depending on the anatomical location major bleeding events can be devastating to individuals and their families, while clinically relevant non-major bleeding (CRNMB) events are often considered a nuisance to patients. In addition to being bothersome, CRNMB events often lead to patients seeking unscheduled medical attention or intervention, frequently in emergency rooms at an unexpected and increased cost to the healthcare system. Such bleedings would include epistaxis, hematuria, and gastrointestinal bleedings. A large multi-center Canadian trial conduction by the VEnous thromboembolism Clinical Trials ORganization (VECTOR) group will evaluate such events and provide much needed information about which anticoagulant has the safest risk-to-benefit profile.

1.2 Rationale

To address the limitations of RCTs, we propose a pragmatic trial to determine the safety (i.e. bleeding risk) of twice daily apixaban compared to once daily rivaroxaban during the first 3-6 months of treatment for the prevention of recurrent VTE. The results of this trial are relevant to clinical practice as these agents are approved in Canada for treatment of VTE and it is expected that the number of patients eligible to use these drugs and those switching from VKA to these new therapies will increase in the next few years. Since these new oral agents are simpler to use and do not require drug monitoring, identifying the DOAC with the safest risk profile would confidently support longer periods of patient-self management and the role of this agent as first line of treatment for acute VTE. In order to prepare for such a large multi-center trial and address these limitations, we propose a pilot feasibility trial to evaluate recruitment rates and resource utilization during follow up.

1.3Potential Risks and Benefits

1.3.1 Potential Risks

All options for long term anticoagulation carry the risks of major or minor bleeding. Although all DOACs have no direct antidote, several phase III trials are underway/upcoming evaluating potential antidote therapies (18-20). There is conflicting evidence in animal and ex vivo studies using Prothrombin Complex Concentrates (PCCs; Octaplex®) and activated PCCs (aPCCs; FEIBA®) for DOAC reversal (21-23). Small case reports have shown bleeding control in DOAC-associated bleeding using aPCCs (24;25). There is limited experience with managing major bleeding events in patients using rivaroxaban and apixaban. However, management of bleeding has not been a significant concern in previous trials which demonstrated low rates of fatal bleeding and major bleeding rates that are lower or comparable to those seen with standard LMWH/VKA therapies.

1.3.2 Known Benefits

Several RCTs conducted in patients with acute VTE have demonstrated that DOACs have comparable efficacy with LMWH/VKAs in terms of VTE recurrence rates and lower risks of bleeding complications ranging from 0.6% for fatal bleeding to 10.6% for a first major or clinically relevant non-major bleeding (6;10-13;26).

2 OBJECTIVES

- The primary objective of the study is to determine if it is feasible to conduct a large randomized multicenter trial comparing apixaban vs. rivaroxaban for the treatment of acute VTE.
- The secondary objectives are to assess safety and superiority of apixaban vs rivaroxaban.

The study objectives will be met by assessing the following outcomes:

- The primary outcome is to evaluate recruitment rates and resource utilization to carry the study procedures and follow-up.
- The secondary outcomes are expected rates of major bleeding episodes, and symptomatic VTE.

3 STUDY DESIGN

3.1 Design

This is a multi-centre, prospective randomized open blinded end-point (PROBE) trial assessing clinical feasibility for a larger multi-centered trial comparing bleeding outcomes using apixaban vs. rivaroxaban for treatment of acute VTE. A total of 72 patients (36 per arm) will take part in this study conducted in 4 Canadian centres.

The larger trial will be a superiority study to determine if twice daily apixaban is safer than once daily rivaroxaban during the first 6 months of anticoagulation treatment for reducing the rates of clinically relevant bleeding in patients with acute VTE. The PROBE design is used to eliminate any possible bias making it comparable to a double-blind RCT and follow up will be conducted openly in a way that is similar to clinical practice.

Arm 1	Arm 2
36 patients	36 patients
Apixaban 10 mg PO twice daily for 1 week, then 5 mg PO, twice daily for 3-6 months	**Rivaroxaban** 15 mg PO twice daily for 3 weeks, then 20 mg PO once daily for 3-6 months

3.2 Rationale for selected dose of study drugs

The rationale for selecting 10 mg of apixaban twice a day for 1 week followed by 5 mg PO twice daily and 15 mg of rivaroxaban PO twice a day for 3 weeks followed by 20 mg PO once daily are based on the favourable safety and efficacy outcomes reported in previous RCTs and meta-analyses. In the Amplify study (11) the recurrent symptomatic VTE rate was 2.3% for apixaban and 2.7% in the conventional-therapy LMWH/VKA group (RR: 0.85, 95% CI: 0.60-1.18). Major bleeding occurred in 0.6% in apixaban and 1.9% in LMWH/VKA groups (RR: 0.31, 95% CI: 0.17-0.55; p <0.01). The composite outcome of major bleeding and clinically relevant non-major bleeding was 4.3% in apixaban and 9.7% in the LMWH/VKA groups (RR: 0.44, 95% CI: 0.36-0.55; p <0.001). Based on the Einstein Study (6), rivaroxaban was as effective as the standard therapy (LMWH/VKA) in preventing secondary VTE (2.1% vs 3.0% during 6 to 12 months of treatment, respectively) (HR: 0.68, 95% CI: 0.44-1.04; p<0.001, one sided) with similar safety for the risk of bleeding (8.1% vs 8.1%) (HR: 0.97, 95% CI: 0.76 to 1.22; p=0.77). These dosing regimens are recommended by the respective pharmaceutical manufacturers (27;28) and are approved by Health Canada for treatment of acute VTE.

3.3 Rationale for use of a PROBE design

The PROBE design is a highly cost-effective approach that offers several advantages compared to the double-blind prospective RCT: a) it will use a strict randomization procedure through randomly selected block sizes to allocate patients to the 2 treatments. This will eliminate any possible bias and will make it comparable to a double-blind RCT; b) follow-up and treatment will be conducted openly in a way that is

similar to regular clinical practice. This will make the results more applicable to the practical management of patients; c) strictly defined outcomes will be blinded to the adjudicators allowing unbiased comparison of these two therapies; d) we will use an open management of DOACs through their approved regulatory doses which will result in lower costs compared to the complicated packing and distribution of double-blind medication. Expenses will be lower, but without compromising study quality; e) our PROBE design will increase simplicity by reducing the number of exclusion criteria as much as possible in an attempt to reflect real clinical practice; and f) we will openly use commercially available approved drugs, which may positively affect compliance.

4 SELECTION OF SUBJECTS

The study will be conducted at the Ottawa Hospital with a volume of approximately 700 with VTE annually, with 300 new diagnoses of VTE. Potential eligible patients will be identified by a healthcare professional according to institutional policy on privacy.

4.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

- Confirmed newly diagnosed symptomatic acute VTE (proximal lower extremity DVT or segmental or greater PE)
- Age ≥ 18 years old
- Written informed consent

4.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria will be excluded from study participation

- Any contraindication for anticoagulation with apixaban or rivaroxaban such as active bleeding, weight >120 kg, etc.
- Another indication for long-term anticoagulation (e.g. AFib)
- Clinically significant liver disease or alanine aminotransferase (ALT) levels ≥ 3 times the upper limit of normal range
- Creatinine clearance < 30 ml/min calculated with the Cockcroft-Gault formula (29)
- Known allergies to either apixaban or rivaroxaban
- Pregnancy* or breastfeeding
- Use of contraindicated medications with apixaban or rivaroxaban
- Active malignancy in the last 6 months (excluding localized skin malignancy)
- No private insurance coverage for the study drug or not willing to pay for study drug
- Have received > 72 hours of therapeutic anticoagulation

*As reported by the patient or a pregnancy test will be ordered by the treating physician for women of childbearing potential as per standard of care

5 RANDOMIZATION

We will use block randomization with blocks of randomly selected block sizes through a central randomization system by a customized web-based program in a 1:1 ratio for the two treatments. Since antiplatelet use and renal dysfunction are proven risk factors that could affect the risk of bleeding, blocks will be stratified by antiplatelet use (yes/no) and renal dysfunction (creatinine clearance (CrCl): ≥ 60 ml/min; < 60 ml/min) and by centre. Central randomization will be conducted using the COBRRA web-based program. The randomization process will be initiated by the local study coordinator who will access the web-based system and enter the patient's information on antiplatelet use, creatinine results and confirmation of eligibility. The patient's open-label study treatment allocation will then be electronically delivered to the local research coordinator.

6 TRIAL TREATMENT/ STUDY PROCEDURES

6.1 Screening and Enrolment

6.1.1 Screening

Potentially eligible patients will be identified by a healthcare professional according to institutional policy on privacy. After obtaining verbal consent from the patient to be contacted for the study, a research staff will approach the patient to participate in the study. The research staff will obtain written informed from the patient before collecting any data and performing any study procedures.

6.1.2 Enrolment

The following clinical evaluations/data collection will be performed during the enrolment visit:

- Eligibility Assessment (inclusion/exclusion criteria)
- Assessment of CBC, creatinine (done within one month prior to start of study treatment)
- Medical History(medical comorbidities, bleeding history)
- Concomitant medications
- Patient's demographics (age, gender, BMI, race)
- Imaging confirming diagnosis of VTE

6.1.3 Pregnancy

Females of childbearing potential must agree to utilize highly effective contraception methods or practice sexual abstinence throughout the duration of the study treatment and for 30 days following the last dose of study drug.

7 TRIAL TREATMENT /STUDY PROCEDURES

7.1 Trial Intervention

Patients will be allocated by the web-based system to one of the following groups:

1) **Apixaban group**:10 mg PO twice-a-day for 1 week, then 5 mg PO, twice daily for 3 or 6 months of treatment.
2) **Rivaroxaban group**: 15 mg PO twice-a-day for 3 weeks, then 20 mg PO once daily for 3 or 6 months of treatment.

The minimum duration of the anticoagulation treatment will be 3 months for provoked VTE and 6 months for unprovoked VTE in accordance with the 2012 American College of Chest Physicians (ACCP) guidelines (30). If clinically indicated, treatment will continue up to 12 months or longer at discretion of the attending physician.

Randomization will occur at the enrolment visit. Following randomization, patients will receive teaching about the study drug including potential side effects, and signs and symptoms of recurrent VTE. The first dose of the study drug will be administered within 12 hours after randomization. All participating patients will continue to self-administer the study drug until completion of the study or if a an event warrant for premature discontinuation. Appropriate clinical management will be initiated for patients who discontinue the study drug prematurely.

7.2 Follow-Up

All enrolled patients will be followed for the entire study treatment period, for 3 months or 6 months. Patients will be scheduled for an in-person visit at:

- 1 week (± 3 days) (this follow-up can also be performed by phone call/email)
- 30 days (± 10 days)
- Study treatment completion 3 or 6 months(+ 1 month)

For patients who will complete their study treatment at 6 months, a 3 month follow-up visit will be performed in the clinic or by phone call/email .

The following evaluations will occur at all study visits (see table 1 in appendix):

- Surveillance for adverse events
- Clinical manifestations of bleeding events and symptomatic VTE
- Investigations of in-hospital admission
- Assessment of compliance to the study drug by pill count and review of medication diary **only at the 1 month visit and study completion visit (3 or 6 months)**

Patients will be instructed to contact the study team if events occur between visits or phone calls.

7.3 Concomitant Medications/Treatment

Concomitant medications/treatments will be assessed by the physician at the screening period.

The following is a brief guideline of all medications/treatments that are contraindicated with apixaban and rivaroxaban:

- Systemic treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, voriconazole) and HIV protease inhibitors (e.g. ritonavir)
- Systemic treatment with strong CYP 3A4 and P-glycoprotein inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort)
- Other anticoagulants co-administered (LMWH, VKA)

7.4 Compliance to Study Drug

We will keep accurate records of the quantities of the study drug prescribed to patients and will keep track of the patient's compliance to medication on the basis of dose-taking. Dose-taking will be defined by the percentage of the prescribed doses of pills actually taken by the patient over a specified period of time and this will be achieved by reviewing the quantities of the medication prescribed and returned. At the initiation of treatment and during regular visits we will emphasize the importance of taking the medication as prescribed and remind patients that the research nurse will be available to answer any questions. A dose-taking of less than 80% will be considered non-compliant. If a patient is non-compliant, he/she will be followed until the end of the treatment, but we will investigate the reasons for non-compliance. Based on our literature review on compliance with DOACs (31) we should expect an average of 11% non-compliance (range: 2% to 29%) as reported in previous studies.

At selected sites, compliance will also be assessed with the use of electronic monitoring devices. The Medication Event Monitoring System (MEMS) is composed of a SmartCap and reader. The MEMS will record and imprint the time of opening the medication container on multiple occasions. This method of recording data on adherence will

provide preliminary data about rates of non-compliance and will be compared to the conventional methods of self-reporting and pill count for efficacy and safety.

8 INVESTIGATIONAL PRODUCTS

Once allocation of the study drug is determined, the patient will be prescribed the commercially available medication.

8.1 Packaging and Labelling

The packaging and labelling for apixaban and rivaroxaban will be done in accordance with its marketing authorization.

8.2 Drug Accountability

Drug pill count will be performed and documented for the assessment of medication compliance.

9 ASSESSMENT OF SCIENTIFIC OBJECTIVES

9.1 Study Outcome Measures

Clinical feasibility for a larger multi-center trial is the primary outcome of this pilot study. The primary outcome measures are:

- Proportion of patients screened who are eligible to participate in the trial
- Proportion of eligible patients who consent to participate in the trial
- Proportion of patients who attend each follow-up visit
- Proportion of patients completing all required study procedures, per follow-up visit
- Suitability of the trial's screening procedures

The secondary outcomes measures are:

- Major bleeding events, clinically relevant non-major and minor bleeding episodes
- Recurrent VTE and VTE related-death
- All-cause mortality rates
- Individual rates of death related to VTE, cardiovascular disease, bleeding or other causes
- Medication compliance
- The time-to-first occurrence of secondary outcomes between randomization and end of follow-up (time-to-event analysis)

9.2 Assessment and Analysis of Secondary Outcomes Measures

9.2.1 Methods for Assessing Secondary Outcome Measures

Major bleeding and clinically relevant non-major bleeding will be confirmed with investigational reports including clinic notes, hemoglobin results and imaging.

Major Bleeding will be defined as:

- Clinically overt and associated with a decreased in the hemoglobin level of 2.0 g per deciliter or more, if bleeding led to the transfusion of 2 or more units of red cells, and/or
- Bleeding was intracranial or retroperitoneal, occurred in another critical site or contributed to death (32).

Clinically relevant non-major bleeding will be defined as :

- Overt bleeding that did not meet the criteria for major bleeding but was associated with medical intervention or unscheduled contact with a physician, and/or
- Interruption or discontinuation of anticoagulants, and/or
- Discomfort or impairment of activities of daily life.

Minor bleeding will be defined as:

- Overt bleeding not fulfilling the definition of major bleeding or clinically relevant non-major bleeding.

Diagnosis of DVT will be confirmed by new findings on ultrasonography. Diagnosis of PE will be confirmed by new findings on computed tomographic pulmonary angiography or ventilation perfusion (V/Q) lung scanning that indicates a high probability of PE or a non-normal lung scan finding coinciding with objectively confirmed DVT.

VTE-related death (fatal PE or unexplained deaths) will be confirmed using death certificates and/or autopsy findings.

At any time during the study course, if a patient experiences signs or symptoms suggestive of bleeding or VTE, diagnostic tests will be performed and all events independently of their seriousness will be treated according to the standard of care at the local institution by the primary physician. All secondary outcomes will be sent to the blinded CIAC for review.

10 DISCONTINUATION OF STUDY DRUG

Study treatment may be stopped temporarily due to a medical event/procedure (ex. surgery). The discontinuation procedures will be performed as per the treating

physician. The details of the temporary discontinuation will be documented in the source documents and CRFs.

Study treatment will be stopped permanently if any of the following events occur:

- Clinically significant bleeding
- Pregnancy
- With the administration of a contraindicated medication (see section 7.3)
- medical event (ex. Clinically significant bleeding) warranting permanent discontinuation as per the investigator's judgment

11 ASSESSMENT OF SAFETY

11.1 Adverse Event

For this study, bleeding and VTE events are recorded and reported as secondary outcomes. However if the bleeding or VTE event meets the definition of an SAE, the event will be recorded and reported as an SAE as well.

11.2 Serious Adverse Event

The following events will be recorded and reported as an SAE:

- Life-threatening (subject at immediate risk of death)
- Requires in-patient hospitalization* or prolongation of existing hospitalization
- Results in congenital anomaly/birth defect
- Results in a persistent or significant disability or incapacity
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require a surgical intervention to prevent one of the outcomes listed in this definition.

*Any pre-scheduled procedures which requires hospitalization will be not reported as an SAE.

Death will not be recorded be as an SAE since it sit recorded as a secondary outcome.

Intensity, Causality and Grading

The following will be used to describe the maximum intensity of the AE: MILD, MODERATE, or SEVERE. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with participant's usual function
MODERATE	Interferes to some extent with participant's usual function
SEVERE	Interferes significantly with participant's usual function

The following will be used to describe the causality of the AE: UNRELATED, POSSIBLY RELATED, or RELATED. For the purpose of consistency, the causality grades are defined as follows:

UNRELATED	There is not a reasonable possibility that the adverse event may have been caused by the study drug/intervention.
POSSIBLY RELATED	The adverse event may have been caused by the study drug/intervention; however there is insufficient information to determine the likelihood of this possibility.
RELATED	There is reasonable possibility that the adverse event may have been caused by the study drug/intervention.

The following will be used to describe the grading of the AE: EXPECTED/ANTICIPATED or UNEXPECTED/UNANTICIPATED. For the purpose of consistency grading will be defined as follows:

EXPECTED/ANTICIPATED	Identified in nature, severity, or frequency in the current protocol, informed consent, product monograph or within other current risk information.
UNEXPECTED/UNANTICIPATED	Not identified in nature, severity, or frequency in the current protocol, informed consent or product monograph or within other current risk information.
MORE PREVALENT	Occurs more frequently than anticipated or at a higher prevalence than expected.

11.3 Recording and reporting of SAEs

SAEs are to be recorded on the SAE worksheet, in the source documents at the trial site and in the eCRFs. The local investigator is responsible for documenting and assessing each SAE for intensity, causality and grading. The local investigator will report to their individual REB as per their institutional policy on safety reporting.

In turn, the principal investigator will:

- Review all SAEs and request changes if applicable
- If the SAE is felt to be possibly related/related and unexpected, the principal investigator will inform the manufacturers of the study drug.

Table 1 REPORTING REQUIREMENTS FOR ADVERSE EVENTS		
Gravity	**Reporting Time**	**Type of Report**
SERIOUS	Within 24 hours*	Initial report on SAE
	Within 15 days*	Final report on SAE
SERIOUS (life-threatening)	Within 24 hours*	Initial report on SAE
	Within 7 days*	Final report on SAE

*After being aware of the event and receiving the information

12 CLINICAL MONITORING

12.1 Monitoring

The multicentre coordinator will be responsible for the training of the research staff and the monitoring at the 4 centres. Remote monitoring methods will be used. An initiation training in each centre will be performed before commencement of the trial. Monitoring will be performed to ensure that patient safety, study procedures and data collection are performed in accordance with the research protocol ,GCP/ICH and Health Canada Division 5 guidelines.

12.2 Data and Safety Monitoring Board (DSMB)

The DSMB will be comprised of clinicians and methodologists who are independent of the trial and study investigators but have experience with clinical trials and can be relied upon to exercise good judgment in weighing the potential risks and benefits to patients as data accumulate in the trial. The committee will review data on a regular basis for monitoring safety of the patients exposed to the study medication. The DSMB will have an independent associated statistician who will receive study data from the central database and will remain independent of the trial management team. An interim safety analyses will occur after the recruitment of the first 25 patients.

13 PROTOCOL DEVIATIONS/VIOLATIONS

Study related procedures must be conducted in compliance with the protocol, amendments, regulations and guidelines, in order to ensure participant safety and data integrity. Any deviations from the protocol, or violations of the protocol, will be accurately documented, reported and reconciled.

13.1 Protocol Deviations

Protocol deviations refer to incidents involving non-compliance with the protocol that are unlikely to have a significant impact on the participant's rights, safety or welfare, or on data integrity. Examples of deviations include: forgetting to complete a procedure at a specified visit (weight, missing lab value, etc.).

If a protocol deviation occurs the following procedures will be followed:

- The local investigator or delegate will document and explain any deviation from the approved protocol
- Deviations from the protocol must be reported in the study source document and case report forms

13.2 Protocol Violations

Protocol violations refer to more serious incidents involving non-compliance with the protocol that may result in significant effect on the participant's rights, safety, or welfare or data integrity.

Protocol violations could result in the participant being excluded from the eligibility analysis and/or result in the participant being discontinued from the trial. Examples of violations include: non-compliance with inclusion/exclusion criteria and dosing administration.

If non-compliance is identified, the following procedures will be followed:

- The site investigator or delegate will notify the coordinating centre in Ottawa as soon as possible after discovering the violation.
- The site investigator or delegate will document: the details and reason for the protocol violation. The documentation will also include an assessment by the site investigator with regards to the impact of the protocol deviation on the participant or trial data. Follow-up procedure and corrective action to prevent future violations will also be documented.
- Violations will be recorded in the study source document and case report forms
- All violations will be reported to the local research ethics board (according to local policies)
- All violations will be reported and reviewed by the Data and Safety Monitoring Board.

14 STATISTICAL CONSIDERATIONS

14.1 Sample size

We propose a sample size of 72 patients for the pilot study, with an estimated recruitment rate of 4 patients per month. This number would demonstrate ease of recruitment and provide direct comparison of which anticoagulant is safest.

14.2 Analysis

An estimate of the proportion of patients who meet the criteria for the adjudicated secondary outcomes stratified by treatment groups ("2 x 2" table) according to the intention-to-treat principle. The cumulative rates of the adjudicated clinically relevant bleedings within the first 6- months after randomization for the 2 treatment groups will be analyzed with a chi-square ($\chi 2$) test. An estimation of the treatment effect will be done through a stratified Cox proportional hazard regression model and its 95% confidence interval adjusted by the VTE condition (PE ± DVT or DVT alone) at baseline. The risk of bleeding over time (time-to-event) will be estimated according to the Kaplan-Meier method and the treatment groups will be compared with the 2- sided log-rank test.

15 ETHICS

15.1 Research Ethics Board

This study will be reviewed and approved by the Ottawa Health Science Network Research Ethics Board before commencement of the trial. Each participating center must also obtain Ethics Board approval before trial initiation. Annual ongoing renewals will also be performed. Any amendment to the protocol or informed consent form must be approved by the local Research Ethics Board before implementation.

15.2 Informed Consent

Eligible participants will be identified by a healthcare professional or by research personnel as per institutional policy on privacy. They will then be asked if they can be approached by research personnel to obtain their written informed consent. Study objectives, procedures and possible risks and benefits will be discussed extensively with the patient. The patient will be given sufficient time to read and ask all questions they might have concerning their participation in the study. Written consent must be

obtained and documented prior to enrollment. The participant may withdraw at any given time during the trial. The subject's medical care will not be influenced by their decision to participate in the clinical trial.

16 DATA HANDLING AND RECORD KEEPING

16.1 Case Reports Forms

Data collection will be performed using a web-based system. Only trained research personnel from each center will have authorization with an access password to enter and modify case report forms. The web based system functions with a secure server and backups will be done regularly. An audit trial will be implemented that will track who enters the data and when. All data queries, responses to queries and changes to the data will be captured in the eCRF.

16.2 Confidentiality

To protect the participant's confidentiality, source documents and informed consent forms will be kept separate from case report forms. Case report forms will not contain any identifying information. The identification log which links the identification of the participant to the assigned participant code will be kept in a secure cabinet or electronic drive kept under lock and key according to local policy.

16.3 Study Records Retention

To enable regulatory audits, the Principal Investigator and each local co-investigator will have the responsibility to retain study related documents according to Health Canada regulations. All study records will be kept for 25 years as per Health Canada regulations. After 25 years, records will be destroyed.

17 APPENDIX

Table 1: Schedule of Study Procedures

Procedures	Screening/Enrolment	1 week (+/- 3 days)	4 weeks (+/- 10 days)	3 months (+1 month)	6 months (+1 month)
Assessment for Eligibility	x				
Written Informed Consent	x				
Assessment of CBC, creatinine	x				
Medical History	x				
Concomitant Medications	x				
Patient's demographics	x				
Randomization	x				
Study Drug Intervention[a]	←==========				→
Surveillance for AEs		x	x	x	x
Assessment of bleeding and VTE		x	x	x	x
Investigations of in-hospital admissions		x	x	x	x
Assessment of compliance to study drug			x	x[b]	x

a)For provoked VTE; study treatment and follow-up will be for 3 months; for unprovoked VTE, study treatment and follow-up will be for 6 months.

b)For patients completing study at 3 months, drug compliance must be performed at this visit. For patients completing treatment at 6 months, drug compliance is not performed at this visit.

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