COmparison of Bleeding Risk between Rivaroxaban and Apixaban for the treatment of acute venous thromboembolism (COBRRA Study)

Version 1, 04OCT2017

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Signature:_____ Date:_____

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
CTO	Clinical Trials Ontario
CUS	Compression ultrasound
DOAC	Direct oral anticoagulant
DSM	Data management services
DSMB	Data safety monitoring board
DVT	Deep vein thrombosis
eCRF	Electronic case report form
ICH/GCP	International Conference of Harmonization/Good Clinical Practice
INR	International Normalized Ratio
LMWH	Low molecular weight heparin
MCID	Minimal clinically important difference
OAC	Oral anticoagulants
OD	Once daily
PCC	Prothrombin complex concentrate
PE	Pulmonary embolism
P-gp	P-glycoprotein
PO	Per os, by mouth
PROBE	Prospective randomized open blinded end-point
RCT	Randomized controlled trial
RR	Relative risk
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
Short title	COBRRA Study
ClinicalTrials.gov Identifier	NCT03266783
CTO Identifier	901
Background	VTE is the third leading cause of mortality by cardiovascular disease. Standard treatment for acute VTE uses a combination of parenteral Low-Molecular-Weight Heparin (LMWH) and oral vitamin K antagonists (VKA) for 3 months, and carries significant bleeding risk. The major and/or clinically-relevant non-major bleeding (CRNMB) event rate is reported between 8.1-9.7% during initial treatment. This treatment is burdensome owing to subcutaneous injections, drug interactions, and laboratory monitoring. Direct oral anticoagulants (DOACs) are simpler to use and do not require laboratory monitoring. Rivaroxaban and apixaban are two DOACs targeting Factor Xa. Each DOAC was separately proven effective and safe when compared to standard treatment. Comparison of the bleeding rates between studies would favour use of apixaban over rivaroxaban (4.3% vs 8.1%); however, trial limitations and lack of direct comparison between these two agents makes it impossible to draw firm conclusions and both are considered standard of care medications. This represents a dilemma in clinical practice because the absence of convincing differences in safety has led to genuine uncertainty about which DOAC has the best risk-to-benefit ratio. To address this clinical equipoise, a head-to-head randomized controlled trial (RCT) between apixaban and rivaroxaban with safety as primary outcome is needed.
Primary Objective	To compare the safety of apixaban and rivaroxaban for treatment of VTE.
Study Intervention	Patients will be randomized to one of 2 groups: 1. Apixaban group: 10 mg PO twice-a-day for 1 week, then 5 mg PO, twice daily for 3 months of treatment, or 2. Rivaroxaban group: 15 mg PO twice-a-day for 3 weeks, then 20 mg PO once daily for 3 months of treatment.
Primary Outcome	The rate of adjudicated clinically relevant bleeding (CRB) events defined as the composite of major bleeding (MB) events and/or clinically relevant non-major bleeding events (CRNMB).

Secondary Outcomes	1. adjudicated MB events; 2. adjudicated CRNMB events; 3. adjudicated recurrent VTE events; 4. adjudicated VTE-related deaths; 5. all-cause mortality; 6. medication adherence-; 7. incremental cost-effectiveness ratios, including cost per one CRB case prevented, cost per one life year saved and cost per one quality-adjusted life year (QALY) gained; 8. impact of verbal consent on patient participation in comparison with participants from sites using written informed consent.
Study design	This is a multi-centre, pragmatic, prospective randomized, open label, blinded end-point (PROBE) trial comparing bleeding outcomes using apixaban vs. rivaroxaban for treatment of acute VTE. Patients will be stratified during randomization based on antiplatelet use (yes/no), and renal disease (CrCl <50mL/min, ≥50mL/min). Central randomization will be conducted using a customized web-based program designed for the study.
Study population	<u>Inclusion Criteria</u> • symptomatic acute VTE (proximal lower extremity DVT or segmental or greater PE) • Age ≥ 18 years old • Provide informed consent <u>Exclusion Criteria</u> • Have received > 72 hours of therapeutic anticoagulation • Creatinine clearance < 30 ml/min calculated with the Cockcroft-Gault formula • Any contraindication for anticoagulation with apixaban or rivaroxaban as determined by the treating physician such as, but not limited to: ◦ active bleeding, ◦ active malignancy defined as the following: a) diagnosed with cancer within the past 6 months; or b) recurrent, regionally advanced or metastatic disease; or c) currently receiving treatment or have received treatment for cancer during the 6 months prior to randomization; or d) a hematological malignancy not in complete remission, ◦ weight >120 kg, ◦ known liver disease (Child-Pugh B or C), ◦ use of contraindicated medications, ◦ another indication for long-term anticoagulation (e.g. atrial fibrillation), ◦ pregnant or breastfeeding.
Number of subjects	We aim to include and follow 2760 patients; 1380 participants per group.
Primary endpoints	The primary safety outcome will be defined by the 3 month cumulative rate of the adjudicated composite outcome of major bleeding and/or CRNMB events.

Study duration and planning	The total duration of this study is expected to be 45 months. Ethics approval in the primary research centre (OHRI) is aimed to be achieved by fall 2017, and by winter 2017 for the remaining participating centres. Subject recruitment is planned to start in fall 2017 and end in summer 2021. The follow-up period will end in fall 2021, allowing for the analysis of data and first assessment and presentation of results in spring 2022. The Ottawa Hospital Thrombosis clinic (trial coordinating center) and 7 other Thrombosis Clinics of the CanVECTOR group (a national CIHR-funded research network) have committed to the study, with another 6 Canadian centers considering their participation. The estimated monthly accrual rate needed is 60 patients per month.
Sample size consideration	The rates of CRB in EINSTEIN (rivaroxaban) and AMPLIFY (apixaban) acute VTE trials were 8.1% and 4.3%, respectively[1;2]. Several systematic reviews and meta-analyses show that the CRB rate is lower with apixaban and rivaroxaban compared to VKA therapy, with apixaban having the greatest risk reduction[22-25]. Based on this, an informal survey of thrombosis experts determined that a 33% risk reduction in the 3-month cumulative rate of CRB events would be clinically meaningful (minimal clinically important difference (MCID) of 2.7%) and result in a change in practice. This clinically significant reduction would be sufficient to support use of apixaban as first line treatment (under superiority) for acute VTE. A minimum of 1352 subjects in each study arm will have 80% power to demonstrate a minimum 33% reduction in CRB events from an 8.1% with rivaroxaban to 5.4% with apixaban, with 0.05 (2-sided) alpha-significance. The Einstein and Amplify trials reported <1% loss to follow-up; given the short treatment period of 3 months we expect few patients will be lost to follow-up. A conservative 2% lost-to-follow-up has been included in the sample size for a total of 1380 participants in each treatment arm.
Statistical analysis	Descriptive statistics will be used for patient baseline characteristics. The primary outcome analysis will be based on intention-to-treat. The cumulative rates of adjudicated CRB events during the 3-month period after randomization for the 2 treatment groups will be analysed with a chi-square ($\chi 2$) test. The treatment effect estimate will be done through a stratified Cox-proportional hazard regression model and its 95% confidence interval (CI). Bleeding risk over time (time-to-event) will be estimated with Kaplan-Meier method and treatment groups will be compared with the 2-sided log-rank test. For secondary outcomes, t-tests or Wilcoxon rank sum tests for comparing groups on continuous outcomes and $\chi 2$ tests for all binary outcomes. Pre-specified subgroup analyses will be conducted in the following patient groups: renal disease (CrCl <50mL/min, ≥50mL/min), elderly age (<75 years, ≥75 years), and antiplatelet use (yes/no).

STUDY FLOW CHART

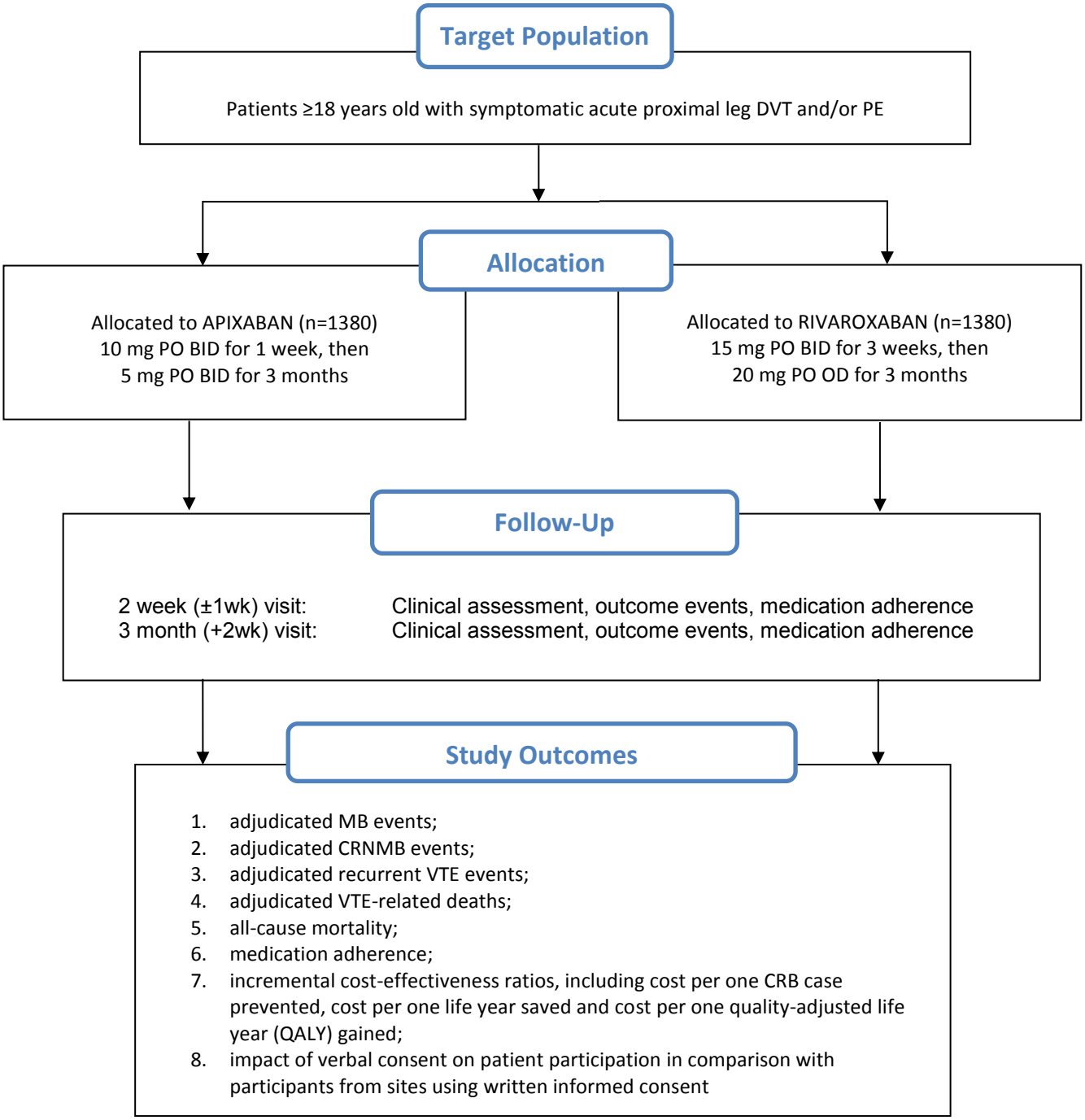


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1 BACKGROUND AND SCIENTIFIC RATIONALE

1.1 Background

VTE comprising deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common, lethal, costly, yet treatable condition and is the third leading cause of mortality by cardiovascular disease[3-5]. The incidence of VTE (DVT ± PE) in the general population is reported in 1 to 2 persons per 1000 people[3;6;7]. VTE is predominantly a disease of older people as the incidence rates increase exponentially with age for both men and women and for both DVT and PE[8]. As the proportion of aged Canadians continue to increase, it is expected that the number of annual deaths associated with PE will increase during the next 10 years.

Patients who experience VTE are at risk for serious and costly effects of recurrent VTE during their initial 3 month anticoagulant treatment (3-13% risk of recurrent VTE)[9;10] and thereafter (2-10% per year)[11;12]. VTE is fatal in 5-10% of patients who experience recurrent VTE[10] and is associated with early morbidity and an estimated cost of $33,000 per event[13]. Recurrent VTE also increases the risk of the common and disabling post-thrombotic syndrome (PTS) which negatively affects quality of life[14].

Standard anticoagulation for acute VTE uses a combination of parenteral low-molecular-weight-heparin (LMWH) with oral vitamin K antagonists (VKA)[4; 5] for 3 months and carries significant bleeding risk. During initial therapy bleeding rates range between 8.1% -9.7%[1; 2], with a fatal bleeding rate of 0.2% and a case-fatality rate of 11.3%[10]. Intracranial bleeding accounts for 8.7% of all major bleeding events and is associated with a mortality rate of 46%[15]. This combination LMWH/VKA therapy is burdensome, potentially life-threatening, and may negatively impact quality of life owing to the need for subcutaneous LMWH injections, laboratory monitoring and frequent dosing adjustments due to many VKA-related food and drug interactions.

1.1.1 DOACs

Direct oral anticoagulants (DOACs) are simpler to use and overcome several of the challenges noted above with LMWH/VKA therapy. They have fixed dosing regimens, do not require laboratory monitoring, and have fewer drug- drug interactions[16]. Several clinical trials have compared DOACs to LMWH/VKA for acute VTE[1;2;17-20] and DOACs are non-inferior to standard treatment of acute VTE and they are associated with lower bleeding rates.

The anti-Factor Xa drugs rivaroxaban and apixaban demonstrated a comparable clinically relevant bleeding [(CRB); composite of major bleeding (MB) and/or clinically relevant non-major bleeding (CRNMB)] rate compared to VKA with 9.7% for VKA vs 4.3% for apixaban[1] and 8.1% for VKA vs 8.1% for rivaroxaban[2]. Several meta-analyses have confirmed these findings for individual DOACs and when grouped together for a DOAC class effect (Appendix A: Table 1. Summary of Relevant Systematic Reviews and Meta-analyses of Phase 3 Trials Comparing DOACs vs Standard Therapy (VKA) for Acute VTE); however, the greatest limitation is lack of head-to-head comparisons between DOACs. We performed a network meta-analysis of 45 clinical trials that compared dabigatran, rivaroxaban, apixaban or edoxaban against LMWH/VKA during the first 3 months of treatment; all were associated with a similar risk of

recurrent VTE. However, only rivaroxaban and apixaban were associated with the lowest risk of major bleeding (rivaroxaban; hazard ratio (HR): 0.55; 95% CI: 0.35-0.89; apixaban; HR: 0.31; 95% CI: 0.15-0.62)[21]. Using indirect comparison to other DOAC treatments, rates of major bleeding were significantly lower with apixaban (dabigatran: HR: 0.42; 95% CI: 0.17-0.99; 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). The CRB rates in Phase 3 studies (4.3%1 vs 8.1%), and MB and CRNBM rates in meta-analyses (Appendix A: Table 1. Summary of Relevant Systematic Reviews and Meta-analyses of Phase 3 Trials Comparing DOACs vs Standard Therapy (VKA) for Acute VTE) would support use of apixaban over rivaroxaban, yet trial limitations (selection bias, differences in treatment duration, heterogeneous populations) and lack of direct comparison between these two agents makes it impossible to provide sound treatment recommendations[21-25]. This gap in evidence highlights the decisional dilemma patients, clinicians, and stakeholders are faced with when choosing an anticoagulant. Evaluating the comparative safety of apixaban and rivaroxaban is important because of the potential morbidity, mortality and health-care costs associated with bleeding events. Depending on the anatomical location, MB events can be devastating to individuals and their families, while clinically relevant non-major bleeding (CRNMB) events are less severe but are characterized by more bleeding than expected in a given clinical circumstance[26]. CRNMB events lead to patients seeking unscheduled medical attention or intervention, frequently in emergency rooms at an unexpected and increased cost to the healthcare system.

Uncertainty about the use of rivaroxaban and apixaban is with respect to little guidance for clinicians on which agent to use according to specific patient characteristics. Although results from RCTs and meta-analyses reassuringly favour DOACs over LMWH/VKA therapy, the effect size on CRB events is quite different between studies[1;2;17-25;27]. These safety concerns lead to challenges in daily practice because patients have multiple comorbidities and polypharmacy which could increase bleeding risks. Patients participating in industry-funded RCTs are highly selected and do not present the same risk profile as those encountered in daily practice, leading to concerns about generalizability.

It is not known why apixaban appears to be associated with fewer MB and CRNMB events than rivaroxaban for acute VTE treatment. Comparison of the exclusion criteria for AMPLIFY[1] and EINSTEIN[2] trials reveals that patients with findings associated with increased bleeding risk were excluded from AMPLIFY: platelet count <100,000/mL, gastrointestinal bleeding within the prior 6 months, and use of dual-antiplatelet therapy (aspirin and clopidogrel); such exclusions were not used in the EINSTEIN trials.

1.1.2 Other DOACs:

Two other DOACs have been compared to LMWH/VKA for treatment of acute VTE: dabigatran and edoxaban[18;20]. Both anticoagulants require a LMWH lead-in period of at least 5 days for treatment of acute VTE, unlike rivaroxaban and apixaban which can be started at diagnosis. Edoxaban is only recently available for use in Canada and dabigatran has been associated with increased rates of myocardial infarction[28;29]. For these reasons we have chosen not to evaluate these anticoagulants. There are currently no new DOACs in Phase 2 or Phase 3 clinical trials (review of Clinicaltrials.gov) for treatment of acute VTE. Given the duration of time required for new anticoagulants to complete Phase 2 or 3 trials, we do not anticipate any industry funded competing trials during the time course of our proposed trial that could reduce accrual rates.

1.1.3 DOAC Utilization for VTE:

A study evaluating prescribing patterns of dabigatran and rivaroxaban in Ontario, between 2010 and 2012, for stroke prevention in atrial fibrillation demonstrated a 20-fold increase in use compared to warfarin[30]. This corresponded to 21% of all anticoagulant prescriptions by September 2012, only two years since dabigatran became available for use. It is expected that these numbers will continue to rise as other DOACs are available for additional clinical indications. No data is yet available on prescribing patterns for VTE associated anticoagulation.

1.1.4 DOAC Antidotes and Bleeding Events:

Although the DOACs are associated with fewer bleeding events than VKA, there has been significant concern from patients, physicians, and policy makers over the lack of reversal agents. One phase 3 trial is now complete evaluating idarucizumab antidote for dabigatran (ClinicalTrials.gov number, NCT02104947) and one is underway to evaluate reversal of rivaroxaban/apixaban (ClinicalTrials.gov number, NCT02329327). Results of these studies demonstrated high mortality rates and have shown risk of systemic embolism in the form of stroke and recurrent VTE[31;32]. Similar findings were shown in patients with VKA associated intracranial hemorrhage[33]. Despite appropriate reversal of anticoagulant effect, there was high morbidity and mortality of nearly 45% suggesting that other factors, despite reversal, are contributing to these findings. Based on that experience, it is possible that administration of DOAC antidotes may not reduce the clinical burden associated with bleeding events.

The availability of antidotes will be reassuring yet it is important to remember that their role is limited to preventing ongoing bleeding. In addition, they are costly ($4000 USD) which may be prohibitive, limiting widespread use to large tertiary centers. It is of greater value to prevent and reduce bleeding by identifying DOACs with lower bleeding risk at the outset of anticoagulation treatment, which the proposed trial aims to do.

1.2 Rationale

Secondary prevention is the most effective way to decrease the burden caused by VTE and to reduce the risk of recurrence. In previous RCTs, rivaroxaban and apixaban have shown to be at least equally effective and safe as standard therapy for acute VTE. A detailed analysis of the composite bleeding outcomes from these trials suggest that the use of twice daily-dosed apixaban results in lower rates of bleeding (4.3%[1]) over once daily dose rivaroxaban (8.1%[2]). However, there is no evidence on the superiority of these agents with respect to safety from direct comparisons in clinical trials. While meta-analyses provide some insight into this issue, there are limitations in our ability to compare these trials based on several components:

- Time in therapeutic range of VKA differed between trials
- Study populations were heterogeneous
- Cumulative bleeding rates were derived from different treatment duration
- Methodological differences in trial design: AMPLIFY was a double-blind RCT and EINSTEIN was PROBE design, accounting for possible risk of reporting bias and differences in exclusion criteria.

These limitations in extrapolating results based on indirect comparisons and the potential to establish superiority based on the safety profile strongly supports a head-to-head comparison between rivaroxaban and apixaban. The DOACs are increasingly being used for VTE treatment without data to inform use of one agent over another. Members of the CanVECTOR (Canadian Venous Thromboembolism Clinical Trials and Outcomes Research) Network have recognized this knowledge gap and identified this direct comparison safety trial between rivaroxaban and apixaban for acute VTE as a top research priority.

All trials to date have been sponsored by the pharmaceutical industry, and there is no interest in sponsoring the proposed head-to-head comparison safety trial of rivaroxaban to apixaban for acute VTE.

1.3 Potential Risks and Benefits

1.3.1 Potential Risks

All options for long term anticoagulation carry the risks of major or minor bleeding. Although rivaroxaban and apixaban have no direct antidote, phase III trials are underway/upcoming evaluating potential antidote therapies[34-36]. There is conflicting evidence in animal and ex vivo studies using Prothrombin Complex Concentrates (PCCs; Octaplex®) and activated PCCs (aPCCs; FEIBA®) for DOAC reversal[37-39]. Small case reports have shown bleeding control in DOAC-associated bleeding using aPCCs[40;41]. 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 Potential Benefits

The results of this trial have the potential to impact the treatment of acute VTE. Since our trial will compare the safety between two DOACs that have been equally effective as compared to standard anticoagulation for prevention of recurrent VTE, results would provide valuable information on the expected rates of major and clinically relevant non-major bleeding events, sites of bleeding, and associated health care costs.

Our results would also determine if recommended doses of these two DOACs are sufficient to reduce the rate of VTE as suggested by previous clinical trials. Since our study aims to be a more pragmatic RCT, it is expected that it will be more applicable to patients encountered in practice, improving the generalizability of results. The number of patients for whom long-term anticoagulation is indicated has increased dramatically over the past decade in Canada. Approximately 500,000 Canadians are taking oral anticoagulants and the numbers continue to increase by about 10% each year. Results of the proposed trial in patients with acute VTE will inform patients, physicians, stakeholders, and guideline makers on the relative safety of these DOACs.

2 OBJECTIVES

- The primary objective of the study is to assess safety and superiority of apixaban versus rivaroxaban

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

- The primary outcome is the rate of adjudicated clinically relevant bleeding (CRB) events defined as the composite of major bleeding (MB) events and/or clinically relevant non-major bleeding events (CRNMB). ISTH MB is defined as clinically overt and associated with: a fall in hemoglobin of ≥20 g/L; transfusion of ≥2 units of red cells; or if bleeding was in a critical site or contributed to death[42]. ISTH CRNMB is defined as overt bleeding not fitting criteria for MB but associated with medical intervention, unscheduled in-person contact with a physician, or need for hospitalization[26].

- The secondary outcomes include: a) adjudicated MB events; b) adjudicated CRNMB events; c) adjudicated recurrent VTE events; d) adjudicated VTE-related deaths; e) all-cause mortality; f) medication adherence; g) incremental cost-effectiveness ratios, including cost per one CRB case prevented, cost per one life year saved and cost per one quality-adjusted life year (QALY) gained; h) impact of verbal consent on patient participation in comparison with participants from sites using written informed consent.

Recurrent VTE will be confirmed by diagnostic imaging. VTE related death (fatal PE or unexplained deaths) will be confirmed with death certificates and autopsy findings. If patients experience signs or symptoms of bleeding or recurrent VTE, diagnostic tests will be performed and events will be treated as per standard of care at the local center. All outcome events will be sent to the blinded adjudication committee for review.

3 STUDY DESIGN

3.1 Design

This is a multi-center, pragmatic, prospective randomized open blinded end-point (PROBE) trial comparing bleeding outcomes using apixaban vs. rivaroxaban for treatment of acute VTE. A total of 2760 patients (1380 per arm) will take part in this study conducted in 8 or more Canadian centers.

This trial will be a superiority study to determine if twice daily apixaban is safer than once daily rivaroxaban during the first 3 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
1380 patients	1380 patients
Apixaban 10 mg PO twice daily for 1 week, then 5 mg PO BID for 3 months	**Rivaroxaban** 15 mg PO BID for 3 weeks, then 20 mg PO OD for 3 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 [1] 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[2], 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[44;45] 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[46]: 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

Potentially eligible patients will initially be approached by a person within their circle of care (nurse, physician, etc.) unless they have provided their consent for research staff to contact them directly (according to approved institutional procedures). Eligibility will be confirmed by a study investigator.

4.1 Inclusion Criteria

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

- Symptomatic acute VTE (proximal lower extremity DVT or segmental or greater PE)
- Age ≥ 18 years old
- Provide informed consent

4.2 Exclusion Criteria

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

- Have received > 72 hours of therapeutic anticoagulation
- Creatinine clearance < 30 ml/min calculated with the Cockcroft-Gault formula
- Any contraindication for anticoagulation with apixaban or rivaroxaban as determined by the treating physician such as, but not limited to:
  - active bleeding,
  - active malignancy, defined as the following: a) diagnosed with cancer within the past 6 months; or b) recurrent, regionally advanced or metastatic disease; or c) currently receiving treatment or have received any treatment for cancer during the 6 months prior to randomization; or d) a hematologic malignancy not in complete remission,
  - weight >120 kg,
  - known liver disease (Child-Pugh B or C),
  - use of contraindicated medications (see Section 6.4)
  - another indication for long-term anticoagulation (e.g. atrial fibrillation)
  - pregnant* or breastfeeding

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

5 SCREENING AND ENROLLMENT

5.1 Subject Screening

The research staff or site investigators will obtain informed consent from the patient prior to any data collection or study procedures in accordance with Health Canada regulations and applicable guidelines. After the patient's eligibility has been confirmed by a site investigator, the patient may be approached by the study coordinator in accordance with the institutional policy on privacy.

5.2 Enrollment

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
- Concomitant medications
- Patient demographics
- Imaging confirming diagnosis of VTE (proximal DVT defined as the popliteal vein or more proximal vein and/or PE involving a segmental vessel or greater)

5.3 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. The requirement for a pregnancy test at enrolment and during follow up will be determined by the treating physician.

6 TRIAL TREATMENT AND STUDY PROCEDURES

6.1 Trial Intervention

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

1) **Apixaban group**: 10 mg PO BID for 1 week, then 5 mg PO BID for 3 months of treatment
2) **Rivaroxaban group**: 15 mg PO BID for 3 weeks, then 20 mg PO OD for 3 months of treatment

These doses align with the product monographs[44;45] and have Health Canada approval. The duration of therapy is in accordance with the 2016 ACCP guidelines[47].

6.2 Randomization

A stratified randomization list with variable and permuted blocks (1:1 ratio) will be generated by an independent statistician. Patients will be stratified based on antiplatelet use (yes/no) and renal dysfunction (CrCl <50mL/min, ≥50mL/min), as either factor may increase bleeding risk. Central randomization will be conducted using a customized web-based program designed for the study. The randomization process will be initiated by the site investigator or delegate who will access the web-based system and enter the patient's confirmation of eligibility and informed consent. The patient's unique study identifier and open-label study treatment allocation will then be electronically delivered to the local site investigator or delegate.

Randomization will occur at the enrolment visit. Following randomization, patients will receive teaching about the study drug they are allocated including potential side effects, and signs and symptoms of recurrent VTE and bleeding.

All participating patients will continue to self-administer the study drug until completion of the study or until an event warrants premature discontinuation at the discretion of the treating physician. Appropriate clinical management will be initiated by the treating physician for patients who discontinue the study drug prematurely.

6.3 Follow-up

All enrolled patients will be followed for the entire 3-month study treatment period. Patients will complete a study follow-up at:

- 2 week (±7 days) – phone call OR in-person clinical visit
- 90 days (+14 days) – in-person clinical visit
- Unscheduled visits, when medically necessary

The following evaluations will occur at all study visits:

- Clinical manifestations of bleeding events and symptomatic recurrent VTE
- Surveillance for serious adverse events
- Investigations of in-hospital admissions or other unscheduled in-person contact with a physician
- Assessment of medication adherence

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

6.4 Concomitant Medications/Treatment

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

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

- Systemic treatment with strong inhibitors of both CYP 3A4/5 and P-glycoprotein (e.g. ketoconazole, itraconazole, voriconazole, posaconazole) and HIV protease inhibitors (e.g. ritonavir)
- Systemic treatment with strong CYP 3A4/5 and P-glycoprotein inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort)
- Other anticoagulants co-administered (LMWH, VKA)

6.4.1 Antiplatelet and NSAID Use

Concomitant use of single or dual antiplatelet drugs or non-steroidal anti-inflammatory agents are permitted in this study, as participants are stratified during randomization based on their use. Concomitant use of antiplatelet agents or NSAIDS must be documented in the patient's study record and carefully monitored by the treating physician/site investigator.

6.5 Compliance to Study Drug

Compliance will be monitored and assessed from randomization until last scheduled dose of study drug during the follow-up period. The study investigator or delegate will assess participant compliance by inquiring about any missed doses and recording the drug accountability in the eCRF.

7 INVESTIGATIONAL PRODUCTS

Once allocation of the study drug is determined, the patient will be prescribed the commercially available medication. The medications in this trial will not be provided to the patient by the Sponsor. Should the patient choose to participate, then the patient's private drug insurance would cover the costs of the medication or the patient would pay for the medication himself or herself. This payment structure for medications would apply even if the patient did not participate in this trial.

8 ASSESSMENT OF SCIENTIFIC OBJECTIVES

8.1 Study Outcomes

The primary outcome is the rate of adjudicated clinically relevant bleeding (CRB) events defined as the composite of major bleeding (MB) events and/or clinically relevant non-major bleeding events (CRNMB).

The secondary outcomes measures are:

- adjudicated MB events
- adjudicated CRNMB events
- adjudicated recurrent VTE events
- adjudicated recurrent VTE-related deaths
- all-cause mortality
- medication adherence
- incremental cost-effectiveness ratios, including cost per one CRB case prevented, cost per one life year saved and cost per one quality-adjusted life year (QALY) gained
- impact of verbal consent on patient participation in comparison with participants from sites using written informed consent

8.2 Assessment and Analysis of Secondary Outcomes Measures

At any time during the study follow-up period, if a patient experiences signs or symptoms suggestive of bleeding or recurrent VTE, diagnostic tests will be performed at the discretion of the treating physician. All events, independent of their seriousness, will be treated according to the standard of care at the local institution by the treating physician. Secondary outcomes (suspected MB, CRNMB, recurrent VTE events and suspected recurrent VTE-related deaths) will be sent to the blinded adjudication committee for review.

8.2.1 Methods for Assessing Secondary Outcome Measure: Bleeding

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

Major Bleeding will be defined as[42]:

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin of ≥20 g/L, or leading to transfusion of ≥2 units of whole blood or red cells

Clinically relevant non-major bleeding will be defined as[26]:

- Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:
  - Requiring medical intervention by a healthcare professional
  - Leading to hospitalization or increased level of care
  - Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

Bleeding is a known side effect of all anticoagulation medications, including apixaban and rivaroxaban, and therefore, bleeding events will not qualify as Adverse Events (AEs). For this study, bleeding events meeting criteria for major bleeding and/or clinically relevant non-major bleeding will be recorded as primary and secondary outcomes. However, if a bleeding event meets criteria for a Serious Adverse Event (SAE) (i.e. it is fatal, bleeding results in inpatient hospitalization or prolongation of hospitalization, or places the participant at immediate risk of death) it will be recorded and reported as an outcome and as a SAE.

Minor bleeding is any bleeding that does not meet the criteria for being clinically relevant but is abnormal for the patient compared to their baseline. This includes “nuisance bleeding”, such as bleeding gums or increased bleeding while shaving, that does not require any evaluation or intervention as described above.

Abnormal uterine bleeding (AUB) in menstruating women is a common complication in premenopausal women receiving anticoagulation for VTE. AUB will be recorded even if the events do not meet the criteria for major bleeding or clinically relevant non-major bleeding (i.e. prolonged or intermenstrual bleeding).

8.2.2 Methods for Assessing Secondary Outcome Measure: Recurrent VTE

Recurrent VTE will be will be confirmed with investigational reports including clinic notes, D-dimer results and imaging as per standard of care.

Recurrent DVT will be confirmed by compression ultrasound revealing a new (compared to baseline/index ultrasound) area of non-compressibility in the popliteal vein or more proximal vein, or venography demonstrating a constant intraluminal filling defect in the popliteal vein or more proximal veins.
Recurrent PE will be diagnosed if the V/Q scan is non-normal and a new unmatched segmental or greater perfusion defect is documented, or an intraluminal filling defect is seen on CTPA in a segmental or greater vessel that was previously free of thrombus, or pulmonary angiography demonstrating a constant intraluminal filling defect or a cutoff of a vessel >2.5 mm in diameter will be considered diagnostic for PE.

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

9 DISCONTINUATION OF STUDY DRUG

Study treatment may be stopped temporarily due to a medical event/procedure (eg. surgery). The instructions for temporary interruption will be provided by the treating physician. The details of the temporary discontinuation will be documented in the eCRFs.

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

- Bleeding or recurrent VTE warranting permanent discontinuation as per the treating physician's judgment
- Pregnancy or breastfeeding
- With the administration of a contraindicated medication (see Section 6.4)

10 ASSESSMENT OF SAFETY

10.1 Adverse Event

An AE can be classified by the treating physician as serious or non-serious by the gravity of the event. Apixaban and rivaroxaban are marketed drugs in Canada and, as such, adverse event reporting will be restricted to SAEs only.

For this study, bleeding and VTE events are recorded and reported as primary and 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.

10.2 Serious Adverse Event

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

- Death
- Life-threatening (subject at immediate risk of death)

- Requires in-patient hospitalization* or prolongation of existing hospitalization
- Congenital anomaly/birth defect
- 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.

10.2.1 Intensity, Causality and Grading

The following will be used to describe the maximum intensity of the SAE: 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

A distinction is made between the gravity and the intensity of an AE. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but is not to be classified as serious unless it meets one of the criteria for serious events listed in Section 10.2.

The following will be used to describe the causality of the SAE: 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 SAE: 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.

10.2.2 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 Lead Qualified Investigator will:

- Review all SAEs and request corrections or additional information, if applicable
- If the SAE is felt to be related and unexpected, the Lead Qualified Investigator will inform the manufacturers of the study drug.

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

*After becoming aware of the event

11 QUALITY ASSURANCE

The trial will be conducted as per ICH-GCP guidelines and applicable Health Canada regulations.

In addition, regulatory agencies may conduct an inspection of this study. If such an inspection occurs, the investigator agrees to allow the inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the inspector to discuss findings of any relevant information.

11.1 Monitoring

The multicenter coordinator will be responsible for the training of the research staff and the monitoring at all centers. Remote monitoring methods with a risk-based approach will be used and outlined in the study's monitoring plan. Study initiation training at each center 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, ICH/GCP guidelines and Health Canada Division 5 regulations.

11.2 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 first 500 patients are recruited, then yearly or at intervals of 1000 patients recruited, whichever is accomplished earlier. A total of 3-4 DSMB meetings will be held during the completion of the study.

12 PROTOCOL DEVIATIONS/VIOLATIONS

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

12.1 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 documents

12.2 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 center 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
- 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

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size

We propose a sample size of 2760 patients for the study (1380 per group), with an estimated recruitment rate of 60 patients per month once all sites are actively recruiting. This number would demonstrate ease of recruitment and provide direct comparison of which anticoagulant is safest.

13.1.1 Sample Size and Power

The rates of CRB in EINSTEIN (rivaroxaban) and AMPLIFY (apixaban) acute VTE trials were 8.1% and 4.3%, respectively[1;2]. Several systematic reviews and meta-analyses show that the CRB rate is lower with apixaban and rivaroxaban compared to VKA therapy, with apixaban having the greatest risk reduction[22-25]. Based on this, an informal survey of thrombosis experts determined that a 33% risk reduction in the 3-month cumulative rate of CRB events would be clinically meaningful (minimal clinically important difference (MCID) of 2.7%) and result in a change in practice. This clinically significant reduction would be sufficient to support use of apixaban as first line treatment (under superiority) for acute VTE.

A minimum of 1352 subjects in each study arm will have 80% power to demonstrate a minimum 33% reduction in CRB events from an 8.1% with rivaroxaban to 5.4% with apixaban, with 0.05 (2-sided) alpha-significance. The Einstein and Amplify trials reported <1% loss to follow-up; given the short treatment period of 3 months we expect few patients will be lost to follow-up. A conservative 2% lost-to-follow-up has been included in the sample size for a total of 1380 participants in each treatment arm.

13.2 Analysis

Descriptive statistics will be used for patient baseline characteristics. The primary outcome analysis will be based on intention-to-treat. The cumulative rates of adjudicated CRB events during 3 months after randomization for the 2 treatment groups will be analyzed with a chi-square ($\chi 2$) test. The treatment effect estimate will be done through a stratified Cox-proportional hazard regression model and its 95% confidence interval (CI). Bleeding risk over time (time-to-event) will be estimated with Kaplan-Meier method and treatment groups will be compared with the 2-sided log-rank test. For secondary outcomes, t-tests or Wilcoxon rank sum tests for comparing groups on continuous outcomes and $\chi 2$ tests for all binary outcomes. Pre-specified subgroup analyses will be conducted in the following patient groups: renal disease (CrCl <50mL/min, ≥50mL/min), elderly age (<75 years, ≥75 years), and antiplatelet use (yes/no).

13.3 Economic Evaluation

The economic research question is whether using apixaban for treatment of acute VTE is cost-effective compared to rivaroxaban. We will perform a cost-utility analysis and a cost-effectiveness from the perspective of the publicly-funded health care system. A Markov model will be used to simulate costs and health outcomes of patients receiving each treatment option. The Markov model involves dividing a patient's possible prognoses into a series of health states. The probabilities defining transition between each of these states are specified over a cycle of one month. Transition probabilities used in the model will be obtained from the COBRRA Study. The model will be run over a large number of cycles to see how a hypothetical cohort of patients would move between states. Patients could move between health states within the model until they all die. In this study, the cohort of patients will be modeled over their lifetime.

We will include the costs of medications, health events and adverse events associated with each treatment option. We will include all health services that are covered by the Ontario Health Insurance Plan, including inpatient stays, outpatient attendances, day hospital treatment, medications rehabilitation and physician visits. Unit costs for all resources will be obtained from relevant sources, such as Ontario Case Costing, Ontario Schedule of Benefits and Ontario Drug Benefit Formulary. All costs will be expressed in 2017 Canadian Dollars.

We will obtain the efficacy of apixaban vs. rivaroxaban for treatment of acute VTE from the COBBRA study. We will measure health utility values using the EuroQoL-5D-5L [51] at baseline, 2 week (± 7 days), and 90 days (+14 days). We will model the prognosis of a cohort of patients receiving rivaroxaban as a baseline against the potential impact of apixaban. The results will be presented as incremental cost per QALY gained, incremental costs per one CRB cases prevented, and incremental cost per one life year saved. Both costs and health outcomes will be discounted at 1.5% annually as recommended by the Canadian guideline[52]. The incremental cost per one unit of health outcome gained will be calculated over 10,000 iterations using a Monte Carlo probabilistic analysis. All parameters will be varied according to the derived 95% confidence intervals, distribution obtained from the COBBRA Trial and the published literature. A cost-effectiveness acceptability curve will be included to show the probability of apixaban being cost-effective according to a willingness to pay threshold of any values between $10,000per QALY and $100,000 per QALY. Health economic evaluation will be conducted using Microsoft Excel with Visual Basic Applications.

14 ETHICS

14.1 Research Ethics Board

REB approval will be obtained and maintained annually with the REB board of record selected by Clinical Trial Ontario (CTO) for CTO-qualified sites. If a participating site is not CTO-qualified, REB approval will be obtained and maintained with its local REB separately.

14.2 Informed Consent

The informed consent process will be conducted in accordance with ICH/GCP guidelines, and will take place before collecting any data or performing any study procedures. Eligible participants will be identified by a healthcare professional or by research personnel as per institutional policy on privacy. All pertinent study information (study objectives, procedures, risks, benefits, alternatives to participation, etc.) will be provided to the potential study participant in an REB approved format. The patient will be given sufficient time to ask all questions they might have concerning their participation in the study. Only patients who have provided consent will be enrolled into the study. The participant may withdraw at any time during the study. The participant's medical care will not be influenced by their decision to participate in the study. If the study participant decides to leave the study, the information that was collected before the participant left the study will still be used in order to help answer the research question unless the participant provides written documentation of their wish to have the data removed.

15 DATA HANDLING AND RECORD KEEPING

15.1 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 eCRFs. The web based system functions with a secure server and backups will be done regularly. An audit trail 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.

15.2 Confidentiality

Medical records will be reviewed in compliance with applicable provincial privacy laws as well as local hospital privacy policies. All personal health information will be treated in a confidential manner with respect to its collection, use, and disclosure. Participant names or potentially identifying personal health information will not leave the institution. Any source documents provided to the sponsor for monitoring purposes must first be de-identified. A master list that links participant identifiers to their unique participant number will be maintained at all study sites and stored separately from all other study records according to local institutional policies.

15.3 Study Records Retention

To enable regulatory audits, the Lead Qualified Investigator and each Site Qualified 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 in accordance with local institutional policies.

16 APPENDICES

Appendix A: Table 1. Summary of Relevant Systematic Reviews and Meta-analyses of Phase 3 Trials Comparing DOACs vs Standard Therapy (VKA) for Acute VTE

Author (Reference)	**# RCTs**	**# Patients**	**DOACs**	**Efficacy (recurrent VTE) vs VKA**	**Major Bleeding vs VKA***	**Clinically Relevant Non- Major Bleeding vs VKA***
Castellucci 2014[21] Network meta-analysis	45	44,989	Dabigatran Rivaroxaban Apixaban Edoxaban	No differences among each DOAC	Rivaroxaban: HR: 0.55 (95% CrI: 0.35-0.89); Apixaban: HR: 0.31 (95% CrI: 0.15-0.62); Apixaban vs Rivaroxaban: HR: 0.56 (95% CrI: 0.24-1.33)	NA
Kakkos 2014[22]	10	38,000	Dabigatran Rivaroxaban Apixaban Edoxaban	Pooled DOACs: RR: 0.89 (95% CI: 0.75-1.05)	Pooled DOACs: RR: 0.63 (95% CI: 0.51-0.77); pooled Rivaroxaban & Apixaban vs VKAs: RR: 0.45 (95% CI, 0.33-0.62)	Pooled DOACs: RR: 0.74 (95% CI: 0.59-0.93); pooled Rivaroxaban & Apixaban vs VKAs: RR: 0.75 (95% CI, 0.66-0.84)
Cohen 2015[23] Network meta-analysis	6	26,997	Dabigatran Rivaroxaban Apixaban Edoxaban	No differences among each DOAC	Rivaroxaban: RR: 0.55 (95% CrI:0.37-0.81) Apixaban: RR: 0.30 (95% CrI: 0.16-0.53); Apixaban vs Rivaroxaban: RR: 0.55 (95% CrI: 0.27-1.09)	Rivaroxaban: RR: 1.02 (95% CrI:0.88-1.18) Apixaban: RR: 0.48 (95% CrI: 0.38-0.60); Apixaban vs Rivaroxaban: RR: 0.47 (95% CrI: 0.36-0.62)
Van Es 2014[24]	6	27,023	Dabigatran Rivaroxaban Apixaban Edoxaban	Pooled DOACs: RR: 0.90 (95% CI: 0.77-1.06)	Pooled DOACs: RR: 0.61 (95% CI: 0.45-0.83)	Pooled DOACs: RR: 0.73 (95% CI: 0.58-0.93)
van der Hulle 2014[25]	5	24,455	Dabigatran Rivaroxaban Apixaban Edoxaban	Pooled DOACs: RR: 0.88 (95% CI: 0.74-1.05)	Pooled DOACs: RR: 0.60 (95% CI: 0.41-0.88)	Pooled DOACs: RR: 0.78 (95% CI: 0.58-0.99)

Abbreviations: CI: confidence interval; CrI: credible interval; DOACs: direct oral anticoagulants; HR: hazard ratio; NA: not available; RCTs: randomized control trials; RR: relative risk; VKAs: vitamin K antagonists; VTE: venous thromboembolism. *results for apixaban and rivaroxaban are presented for network meta-analyses.

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