TITLE: A Phase 2, open label, pilot study to examine the use of Rivaroxaban plus Aspirin vs. clopidogrel plus Aspirin for the Prevention of Restenosis after Infrainguinal Percutaneous Transluminal Angioplasty for Critical Limb Ischemia

SHORT TITLE: The RIFLE study

Clinical Phase: Phase 2

Protocol: Version: 3.0, 04 MAY 2015

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Sponsor: Ottawa Hospital Research Institute

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PROTOCOL SIGNATURE PAGE

Version 3.0 , 04 MAY 2015

A Phase 2, open label, pilot study to examine the use of Rivaroxaban plus Aspirin vs clopidogrel plus Aspirin for the Prevention of Restenosis after Infrainguinal Percutaneous Transluminal Angioplasty for Critical Limb Ischemia

My signature below confirms that I have reviewed and approved this protocol prior to submission to Health Canada, and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and all applicable local regulations.

F. GAWDAT.

Principal Investigator Name (Please Print)

Principal Investigator Signature

7/5/2015.

Date

P. JETTY

Principal Investigator Name (Please Print)

Principal Investigator Signature

18/5/15

Date

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ABBREVIATIONS & ACRONYMS

ABI	Ankle Brachial Index
ACS	Acute Coronary Syndrome
AE	Adverse Event/Adverse Experience
ALT	Alanine Transaminase
ASA	Acetyl Salicylic Acid
AST	Aspartate Amino Transferase
CBC	Cell Blood (Cells) Count
CEC	Clinical Event Committee
CIOMS	Council for International Organizations of Medical Sciences
CLI	Critical Limb Ischemia
CRF	Case Report Form
CTA	Clinical Trial Application
DSMB	Data and Safety Monitoring Board
DVT	Deep Vein Thrombosis
EGR-1	Early Growth Response 1
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HREB	Human Research Ethics Board
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
LMWH	Low Molecular Weight Heparin
MCP-1	Monocyte Chemostatic Protein -1
MOP	Manual of Procedures
N	Number (typically refers to Participants)
NEJM	New England Journal of Medicine
OHRI	Ottawa Hospital Research Institute
OHSNREB	Ottawa Health Research Science Network Research Ethics Board
PAD	Peripheral Arterial Disease
PI	Principal Investigator
PTA	Percutaneous Transluminal Angioplasty
QI	Qualified Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Smooth Muscle Cells
SOP	Standard Operating Procedure
TCPS	Tri-Council Policy Statement
TLR	Target Lesion Revascularization
TNF	Tumor Necrosis Factor
TVR	Target Vessel Revascularization
UFH	Unfractionated Heparin
ULN	Upper Limit of Normal

PROTOCOL SYNOPSIS

Title:	A Phase 2, open label, pilot study to examine the use of Rivaroxaban plus Aspirin vs clopidogrel plus Aspirin for the Prevention of Restenosis after Infrainguinal Percutaneous Transluminal Angioplasty for Critical Limb Ischemia
Short Title:	The RIFLE study
Clinical Trial Phase:	Phase 2
Sponsor:	OHRI
Principal Investigators:	Dr Esteban Gandara & Dr. Prasad Jetty
Indication:	Patients with Peripheral Artery Disease (PAD) requiring clopidogrel and aspirin following angioplasty
Objectives:	The aim of the trial is to measure the number of relevant clinical outcomes comparing Rivaroxaban plus Aspirin to clopidogrel plus aspirin in patients treated for CLI following PTA, to inform a large scale randomized controlled study.
Duration:	It is expected to take 12 months to enroll 40 participants. Each participant will be in the study for 12 months. The entire trial should be completed in 24 months.
Design:	This is a pilot study conducted at one center, The Ottawa Hospital. It is a Phase 2 open label randomized controlled trial. Consenting participants, meeting all eligibility criteria will be randomized, post PTA procedure, to one of two groups: Rivaroxaban 2.5 mg BID X 90 days plus ASA 81 mg daily OR Clopidogrel 75 mg daily X 90 days plus ASA 81 mg daily Participants will have study drug dispensed at Day 1 and take medication for 90 days. ASA may be continued after the study, for both groups, as per the standard of care. Visits will occur at 7 days, 30 days, 90 days, 6 months and 12 months. Participants will be followed for 12 months (± 14 days) in total. Adverse events will be collected for the first 90 days .
Intervention Description:	**Treatment Arm 1** Rivaroxaban 2.5 mg twice daily for 90 days (rivaroxaban will be started 6 to 8 hours after the finalization of the procedure) and 325mg of ASA on day 1 then 81 mg of ASA daily for 89 days **Treatment Arm 2** Clopidogrel 300mg on Day 1 (loading dose) then 75 mg daily for 89 days and 325mg of ASA on Day 1, then 81 mg of ASA daily for 89 days
Number of participants:	40

Inclusion and Exclusion Criteria	**Inclusion Criteria:** 1. Written informed consent and able to comply with protocol. 2. Infra-inguinal PAD presenting as CLI with Rutherford category ≥ 1. 3. More than 50% stenosis in the target infrainguinal vessel. 4. Good candidates for PTA using POBA (plain old balloon angioplasty) with or without stenting defined as TASC a, b, c and d lesions **Exclusion Criteria:** 1. Acute limb-threatening ischemia (e.g. embolic disease) 2. Hybrid procedures 3. Creatinine clearance < 30 mL/min 4. Platelet count <100x10^9/L; Hbg <100 g/L 5. INR >1.5; 6. History of or condition associated with increased bleeding risk including, but not limited to: a) Major surgical procedure or trauma within 30 days before the randomization visit b) Clinically significant gastrointestinal bleeding within 6 months before the randomization visit c) History of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding d) Chronic hemorrhagic disorder e) Known intracranial neoplasm, arteriovenous malformation, or aneurysm f) Sustained uncontrolled hypertension: systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg 7. Severe, disabling stroke (modified Rankin score of 4 to 5, inclusive) within 3 months or any stroke within 14 days before the randomization visit 8. Aspirin in combination with thienopyridines within 5 days before randomization 9. Intravenous antiplatelets within 5 days before randomization 10. Fibrinolytics within 10 days before randomization 11. Known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis or ALT >3ULN) 12. Childbearing potential without proper contraceptive measures, pregnancy or breast feeding 13. Drug addiction or alcohol abuse within 12 months before the randomization visit 14. Systemic treatment with strong CYP 3A4 and P-glycoprotein inhibitors : such as ketoconazole, itraconazole, posaconazole, or ritonavir 15. Known allergy or hypersensitivity to any component of rivaroxaban, ASA or clopidogrel 16. Need for long term anticoagulation or double antiplatelet agents for reasons other than PAD such as atrial fibrillation, heart valve replacement, acute coronary syndrome, stroke or venous thromboembolism 17. Anticipated need for chronic (> 4 weeks) therapy with non-steroidal anti-inflammatory drugs. 18. Concomitant treatment with any other anticoagulant, including oral anticoagulants, such as warfarin, dabigatran, apixaban, except under circumstances of switching therapy to or from study treatment. 19. Severe concomitant condition or disease (e.g. life expectancy <6 months secondary to cancer, advanced liver disease or dementia)

1 STUDY RATIONALE AND BACKGROUND

1.1 CRITICAL LIMB ISCHEMIA (CLI)

Peripheral arterial disease (PAD) affects over 27 million people in the industrialized world, and is associated with significant morbidity and mortality[1]. Up to 10% of patients with PAD[2]will develop critical limb ischemia (CLI) presenting as resting pain, ulcers, gangrene, and limb loss[1;3;4]. The typical prognosis of CLI is poor. Within 3 months of onset, 12% of patients will require an amputation and 9% will die; by one year the mortality rate is 22% [2]. With rates surpassing those of patients with coronary artery disease (CAD), patients with CLI are also at high risk of stroke, acute coronary syndrome (ACS), and cardiovascular (CV) death[5;6].

Treatment goals for CLI are to preserve life and limb; maintain function; relieve pain; and minimize the frequency and magnitude of repeated interventions[7;8]. Percutaneous transluminal angioplasty (PTA) procedures have revolutionized the management of patients with peripheral vascular disease and critical limb ischemia, providing a minimally invasive alternative to open bypass surgery in what is typically an elderly population with multiple co-morbidities and with limited life expectancy[8]. In addition, PTA has enabled treatment to be on an outpatient basis at a relatively low cost, and thus a low overall burden to the health care system. In the United States[9] the use of endovascular interventions grew substantially between 1996 and 2006, while bypass surgery decreased by 42%. Unfortunately, durability of these procedures is countered by restenosis and re-occlusions within the treated segment, ranging from ~40-60% primary patency rates at 1 year. Restenosis of the treated arterial segment is a major multi-factorial clinical problem following a PTA in patients with CLI, especially in those affected with infra-inguinal disease[2;10;11]. Acute restenosis of the treated segment (<4weeks post-PTA) is secondary to platelet and coagulation system activation whereas late restenosis is usually associated with myointimal proliferation, negative remodeling, and arterial recoil a process starting as early as 5 days post procedure[11]. In order to prevent early re-thrombosis, restenosis, and cardiovascular events, most guidelines agree that aspirin (ASA) or ASA-clopidogrel should be given to all patients undergoing PTA[7;12]. Based on the findings of the CHARISMA trial[13] (which suggest that patients with symptomatic PAD would benefit from the combination of ASA plus antiplatelet compared to ASA alone) and studies of post coronary PTA supporting the superiority of ASA-clopidogrel[14], the general consensus is that post lower limb PTA patients should receive ASA-clopidogrel over ASA alone[7;8]. According to a recent survey we conducted, in Canada, 44.6% of vascular surgeons use ASA-clopidogrel, 27.6% use ASA alone, and 23.4% use clopidogrel alone.

1.2 ROLE OF ANTICOAGULATION IN CLI PATIENTS TREATED WITH PTA

Although not fully understood, the complex pathogenesis of restenosis is most likely caused by one or more of the following: Platelet activation and aggregation, mural thrombus, myointimal hyperplasia. Active thrombin remains abundant in mural thrombi following PTA and may be important for vessel repair processes[15]as it directly stimulates vascular smooth muscle cell (SMC) proliferation and migration[15] via interaction and proteolytic activation of its direct cellular targets (PAR-1, 3, and 4). In animal models direct thrombin inhibition reduces atherosclerosis progression, promotes plaque stability, and reduces restenosis in rabbits with atherosclerosis after PTA. Compared to healthy controls, patients with PAD, especially those with CLI, have higher levels of circulating D-dimers and thrombin-AT complex suggesting a prothrombotic state[15;16], especially after a PTA. This prothrombotic state could have important prognostic implications. Namely, in patients with ACS, elevations of D-dimers are associated with higher risk of cardiovascular death, myocardial infarction, stroke and stent thrombosis[17;18]. Treatment with ASA[19] or clopidogrel[20] does

not reduce D-dimers levels, but the use of anticoagulant drugs has shown to reduce D-dimers and thrombin fragment levels[19]. Anticoagulant drugs are not usually recommended for the prevention of restenosis and vascular events following PTA for PAD[12;21] but small studies have suggested that anticoagulation with LMWH given to either surgical[22] or PTA[23-27]treated CLI patients improve restenosis rates in comparison to ASA, and also improve ulcer healing[28;29]. LMWHs produce their major anticoagulant effect by catalyzing antithrombin-mediated inhibition of coagulation factors. In addition to the antithrombotic properties, LMWH have SMC antiproliferative effects[19;30;31]; which could explain the benefits of anticoagulation in patients with CLI requiring PTA[18]. Although, the effects of LMWH on smooth muscle activation are not clearly understood, recent evidence has suggested that LMWH upregulates CD44 expression[32] leading to an antiproliferative function mediated by differential activation of ERK and Rac genes[33]. A recent randomized trial demonstrated that ERK 1/2 activation (a surrogate marker of smooth muscle cell proliferation) was increased post-PTA in patients with CLI and that the combination ASA-clopidogrel has no effects on its expression[30] thereby supporting the hypothesis that the use of anticoagulant drugs could be beneficial after PTA.

1.3 DIRECT FACTOR XA INHIBITORS IN PAD

Direct FXa inhibitors, such as rivaroxaban, are oral agents that inhibit factor Xa leading to a decrease in thrombin formation and potentially, a decrease in platelet activation. Rivaroxaban is detected 2–4 hours after oral administration, has half-life of 7 to 11 hours, and is associated with few drug interactions[34]. In phase III randomized trials; rivaroxaban and apixaban have shown to be effective for stroke prevention in patients with AFIB[35;36]; DVT prevention after surgery[37-39]; and treatment of VTE[40-42]. In patients with ACS[43], rivaroxaban reduced mortality, ACS, stroke, and stent thrombosis, although, along with these benefits is an increased risk of major bleeding[43]. It is widely believed that activated FXa has limited functions other than serving as the principal mediator of thrombin generation from prothrombin via the prothrombinase complex[44]. Factor Xa occupies a critical juncture in the coagulation cascade[45] and controls thrombin generation. The activation of one molecule of FXa results in the generation of 1000 molecules of FIIa[46]. FXa initiates intracellular signaling in various cell types of the cardiovascular system, preferentially mediated via PAR-2[47] which contributes to the production of proinflammatory cytokines, tissue factor up-regulation, SMC proliferation, and the release of vascular endothelial growth factor. Inhibition of FXa prevents thrombin generation via inhibition of free, prothrombinase-bound, and clot-associated Factor Xa and consequently attenuates thrombus-associated procoagulant activity[34] . This explains why compared to heparin, that allows persistent thrombin generation and direct thrombin inhibitors that aggravate thrombin generation, direct FXa inhibitors allow for small amounts of thrombin generation and protein C activation. The potential effects of FXa inhibition for the prevention of restenosis following PTA could be caused by the reduction of clot-induced mitogenesis and inflammatory gene expression in human vascular SMC[48];inhibition of the procoagulant activity of activated monocytes and macrophages[49]; and effects on the intrinsic coagulation pathways. To our knowledge only one study conducted in healthy volunteers suggested that rivaroxaban reduced thrombus associated mitosis of SMC of the aortic arch [48]. In animal models, vascular remodeling and myointimal formation were reduced on targeted delivery of nonspecific factor Xa inhibitors[34;44;50-52]. Animal models have suggested that rivaroxaban decreases mRNA expression of inflammatory mediators, such of IL-6, TNF-α, MCP-1, and Egr-1 promoting arterial plaque stability. In stent thrombosis models, rivaroxaban either alone or in combination with ASA+/-clopidogrel initiated a dose-dependent inhibition of FXa-induced, tissue factor-induced, thrombin-induced platelet aggregation, and ADP-induced platelet aggregation[53]. In conclusion, evidence suggests that

inhibition of Factor Xa with rivaroxaban could reduce major vascular outcomes and thrombin associated SMC proliferation leading to restenosis after PTA for CLI[24].

1.4 RATIONALE FOR TREATMENT SCHEDULES

We selected rivaroxaban 2.5mg twice daily because:

1. Rivaroxaban is the only FXa inhibitor that has shown to improve cardio-vascular outcomes in patients with[1] and without ACS[2, 3] ; furthermore, it has shown to reduce systemic non-CNS systemic[4] embolism and stent thrombosis post PTA[5].
2. A 2.5 mg twice daily dose appears to provide the best risk/ratio in combination with antiplatelet agents for the prevention of vascular events in patients treated with antiplatelet agents. The risk of bleeding in patients receiving rivaroxaban and antiplatelet appears to be increased regardless of the treatment indication. Mega et al suggested that a 10 mg daily dose of Rivaroxaban in combination with aspirin was associated with a 2.2% risk of TIMI major bleeding whereas it was 0% in those treated with a 5 mg daily dose plus aspirin. In participants treated with a total daily dose 5 mg of rivaroxaban, those who received 2.5 mg twice daily had a lower bleeding risk than those treated with 5 mg once daily (1.4 vs. 2.9%); furthermore twice daily dosing was associated with a lower number of cardiovascular events (6.6 vs. 9.4%)(6). In ATLAS ACS 2–TIMI 51, the 2.5-mg twice-daily dose of rivaroxaban compared with placebo was associated with reductions of 34% for cardiovascular death and 32% for all-cause death, which were not seen with the 5-mg twice-daily dose(1).
3. Although previous studies looking at the role of anticoagulation post PTA for CLI have used prophylactic doses of LMWH(7), our concern is that patients with CLI are older and sicker and a dose of rivaroxaban of 10 mg once daily in combination with aspirin will be associated with a higher bleeding risk without significant improvement in outcomes.

We selected ASA-clopidogrel as comparator because it is the treatment recommended by guidelines[7;8], and is used by 50% of vascular surgeons in Canada

Since optimal medical management to decrease restenosis and thrombosis rates following PTA would make an important contribution to the sustained success of endovascular treatment, the proposed study will evaluate indicators of the effect of rivaroxaban in patients with CLI requiring PTA.

2 HYPOTHESIS

We hypothesize that the addition of rivaroxaban to antiplatelet agents (ASA) following PTA will lead to a reduction in the rate of any/all of the following: restenosis , amputation, and/or major cardiovascular events in patients with CLI, as compared to the treatment of clopidogrel plus ASA.

3 STUDY OBJECTIVE

The aim of the trial is to establish if the use of rivaroxaban 2.5 mg twice a day plus ASA would improve relevant clinical outcomes, as compared to dual antiplatelet agents in patients treated with CLI following PTA. The data from this pilot trial will inform us if a multi center, large scale, randomized trial is warranted.

4 STUDY DESIGN

This is an open label single center randomized controlled pilot study.

4.1 INCLUSION CRITERIA:

1. Written informed consent and able to comply with protocol.
2. Infra-inguinal PAD presenting as CLI defined with Rutherford category of ≥ 1.
3. More than 50% stenosis in the target infrainguinal vessel
4. Participant must be a good candidate for PTA using POBA (plain old balloon angioplasty) with or without stenting defined as TASC a, b, c and d lesions.

4.2 EXCLUSION CRITERIA:

1. Acute limb-threatening ischemia (e.g. embolic disease)
2. Hybrid procedures
3. Creatinine clearance <30 mL/min
4. Platelet count <100x109/L; Hbg < 100 g/L.
5. INR >1.5
6. History of or condition associated with increased bleeding risk including, but not limited to:
    a. Major surgical procedure or trauma within 30 days before the randomization visit
    b. Clinically significant gastrointestinal bleeding within 6 months before the randomization visit
    c. History of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding
    d. Chronic hemorrhagic disorder
    e. Known intracranial neoplasm, arteriovenous malformation, or aneurysm
    f. Sustained uncontrolled hypertension: systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg
7. Severe, disabling stroke (modified Rankin score of 4 to 5, inclusive) within 3 months or any stroke within 14 days before the randomization visit
8. Aspirin in combination with thienopyridines within 5 days before randomization
9. Intravenous antiplatelets within 5 days before randomization
10. Fibrinolytics within 10 days before randomization
11. Known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis or ALT >3ULN)
12. Childbearing potential without proper contraceptive measures, pregnancy or breast feeding*
13. Drug addiction or alcohol abuse within 12 months before the randomization visit
14. Systemic treatment with strong CYP 3A4 and P-glycoprotein inhibitors : such as ketoconazole, itraconazole, posaconazole, or ritonavir
15. Known allergy or hypersensitivity to any component of rivaroxaban, ASA or clopidogrel
16. Need for long term anticoagulation or double antiplatelet agents for reasons other than PAD such as atrial fibrillation, heart valve replacement, acute coronary syndrome, stroke or venous thromboembolism
17. Anticipated need for chronic (> 4 weeks) therapy with non-steroidal anti-inflammatory drugs.
18. Concomitant treatment with any other anticoagulant, including oral anticoagulants, such as warfarin, dabigatran, apixaban, except under circumstances of switching therapy to or from study treatment.

19. Severe concomitant condition or disease (e.g. life expectancy <6 months secondary to cancer, advanced liver disease or dementia)

* Sexually active women of child bearing potential must undergo a serum pregnancy test ((β-HCG) before study entry and use highly effective methods of contraception. These may include: hormonal contraceptives (e.g. combined oral contraceptives, patch, vaginal ring, injectables, and implants); intrauterine device (IUD) or intrauterine system (IUS); vasectomy and tubal ligation. Highly effective methods of contraception might not always be achievable in the clinical trial setting and, therefore, the most effective alternative can be achieved using methods in combination.
The "double barrier" methods of contraception (e.g. male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above. The use of a male condom in association with spermicide should not be considered a suitable double barrier method for contraception.

5 STUDY MEDICATION

5.1 SCREENING MEDICATION/STANDARD OF CARE

Participants will be screened within 30 days prior to the PTA procedure. All participants enrolled in the study will receive a loading dose of 325 mg of ASA and IV heparin as per the TOH protocol during the procedure. The 325mg loading dose of ASA will be considered and recorded as the day 1 dose of ASA.

5.2 RANDOMIZATION

Participants will only be randomized once the surgeon has completed the PTA +/- stent . PTA will be considered successful once the target lesion is crossed with a wire and catheter and a balloon angioplasty has been successfully performed.
Randomization will be conducted using a customized web-based program developed for this study. The randomization process will be initiated by the local study coordinator who will access the web-based system and enter the patient's unique identifier and confirmation of eligibility and informed consent. Specific patient allocation will then be electronically delivered, to the research pharmacy who will prepare and dispense trial medication.

5.3 TREATMENT ARMS

5.3.1 Treatment Arm 1: Experimental

Rivaroxaban 2.5 mg twice daily for 90 days (rivaroxaban will be started 6 to 8 hours after the finalization of the procedure[37]) and 325mg of ASA on Day 1, plus 81 mg of ASA daily for 89 days. After 90 days, the study treatment will be discontinued and subsequent treatment will be at the discretion of the attending physician.

5.3.2 Treatment Arm 2: Standard of care

Clopidogrel 300mg on Day 1 (loading dose), then 75 mg daily for 89 days and 325mg of ASA on Day 1 then 81 mg of ASA daily for 89 days. After 90 days, the study treatment will be discontinued and subsequent treatment will be at the discretion of the attending physician

5.4 PROHIBITED MEDICATIONS DURING THE STUDY:

Systemic treatment with strong CYP 3A4 and P-glycoprotein inhibitors (such as ketoconazole, itraconazole, posaconazole, or ritonavir) is a contra-indication to treatment with Rivaroxaban and is therefore an exclusion criteria for study entry.
If a participant in the rivaroxaban arm requires initiation of treatment with strong CYP 3A4 and P-glycoprotein inhibitor while on study treatment the participant will be withdrawn from study treatment. The participant may then be switched to an alternative anticoagulant treatment at the discretion of the attending physician. See appendix 3 for a list of CYP 3A4 and P glycoprotein inhibitors.

5.5 FORMULATION PACKAGING AND LABELING

ASA and clopidogrel will be purchased and relabeled for this trial according to the template below. Rivaroxaban will be provided by Bayer and will be labeled according to the template below. All three study medications will be provided to the participants in bulk format. Each participant will be given a 90 day supply of study drug (according to the randomization scheme) at Day 1.

Product information for each of the study medications is listed in Appendix 4.

Rivaroxaban 2. 5 mg Expiration: DD-MMM-YYYY Store at room temperature between +15°C and +25°C Lot # ------- Protocol name : RIFLE Trial Sponsor: The Ottawa Hospital Research Institute, 725 Parkdale Ave, Ottawa ON K1Y 4E9 Investigational drug -- to be used only by a qualified Investigator	Rivaroxaban 2. 5 mg Expiration: DD-MM-YYYY Conserver au l'air ambient , entre +15°C et +25°C, Lot # ------- Nom du Protocole: RIFLE TrialCommenditaire: Institut de recherche de l'Hôpital d'Ottawa 725 Parkdale Ave. , Ottawa ON K1Y 4E9 Médicament expérimental -- à être utilisé seulement par un Investigateur qualifié

Clopidogrel 75 mg Expiration: DD-MMM-YYYY Store at room temperature between +15°C and +25°C Lot # ------- Protocol name : RIFLE Trial Sponsor: The Ottawa Hospital Research Institute, 725 Parkdale Avenue, Ottawa ON K1Y 4E9 Investigational drug -- to be used only by a qualified Investigator	Clopidogrel 75 mg Expiration: DD-MM-YYYY Conserver au l'air ambient , entre +15°C et +25°C, Lot # ------- Nom du Protocole: RIFLE Trial Commenditaire: Institut de recherche de l'Hôpital d'Ottawa 725 Parkdale Ave. , Ottawa ON K1Y 4E9 Médicament expérimental -- à être utilisé seulement par un Investigateur qualifié

ASA 81 mg Expiration: DD-MMM-YYYY Store at room temperature between +15°C and +25°C Lot # ------- Protocol name : RIFLE Trial Sponsor: The Ottawa Hospital Research Institute, 725 Parkdale Avenue, Ottawa ON K1Y 4E9 Investigational drug -- to be used only by a qualified Investigator	ASA 81 mg Expiration: DD-MM-YYYY Conserver au l'air ambient , entre +15°C et +25°C, Lot # ------- Nom du Protocole: RIFLE Trial Commenditaire: Institut de recherche de l'Hôpital d'Ottawa 725 Parkdale Ave. , Ottawa ON K1Y 4E9 Médicament expérimental -- à être utilisé seulement par un Investigateur qualifié

5.6 ACCOUNTABILITY AND STORAGE

Study drug will be stored and maintained by the Clinical Trial pharmacy technicians at The Ottawa Hospital. Bulk accountability logs and individual accountability logs will be completed and maintained by the pharmacy technicians. Participants will keep a diary card. Drug accountability (pill count & review of diary cards) will be done on Day 90 when the medication is returned.

Participants will be counseled to keep the study drug in room temperature conditions. The study medication which they take home should not be exposed to extreme temperatures.

5.7 Individual Participant Compliance

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

5.8 Concomitant Medications

Medication that the participant is taking from the screening time point until study end at 12 months will be recorded by the Research Coordinator. This includes any herbal supplements and vitamins and over the counter medications.

6 STUDY PROCEDURES AND EVALUATIONS

6.1 Study Visits

All participants will be followed for 12 months following their angioplasty. Participants will return to The Ottawa Hospital or will be evaluated as an inpatient at 7 days. There are follow up visits at 30 days, 90 days, 6 months, and 12 months post randomization. All primary and secondary outcome data will be collected during the trial (7 days, 30 days, 90 days, 6 months and 12 months) so that procedures can be evaluated and optimized for future studies. The schedule of study events is summarized in a table in appendix 1.

6.2 Screening (-30 days to -1 day of PTA)

Participants will be screened within 30 days of the PTA procedure.
The following will occur at the screening visit:

- Physical examination (Height and Weight plus BMI)
- Demographics (age, gender, race)
- Tobacco use
- Medical History including:
    - Bleeding history
    - History of stroke, TIA, CAD, CKD, COPD, Hypercholesterolemia
    - History of acute coronary syndrome
- Medication history
- Previous tissue loss
- Co-morbidities including
    - Exclusion criteria
    - Hypertension
    - Obesity
    - Diabetes
- Disease severity (Rutherford scale) and ABI index from medical record

- Anatomic level of disease[56].
- Obtain bloodwork results for CBC, coagulation tests (INR, PTT), and serum creatinine

6.2.1 Study Day 1: PTA, Randomization/Treatment Day 1

All participants enrolled in the study will receive a loading dose of 325 mg of ASA and IV heparin as per TOH protocol prior to the procedure.

Once the surgeon has completed the PTA +/- stent, participants will be randomized using a web-based program as per section 5.2. Participants will receive study medication as per section 5.3.1 and 5.3.2 for the group to which they are allocated.
At randomization the research coordinator will provide the appropriate training for each participant on:

- Monitoring of outcome events and adverse events.
- Review signs and symptoms of bleeding and provide instructions and study contact numbers.
- Details of the study requirements (follow-up schedule) and the importance of follow-up
- Storage and administration of study drug
- How to complete the Medication Diary

Data collected at Day 1 :

- Vascular access specifications: Access routes, size of introducer sheaths used, specifications of device used (length and diameters of balloons/devices implanted)
- Device to artery ratio for balloons and implants, length of treated segment
- Immediate procedural outcome
- Bleeding (approximate blood loss)
- Concomitant medications
- Blood collection (stored for future evaluation of platelet activation , coagulation markers. smooth muscle activation markers and inflammation markers)

6.2.2 Study Day 7 (+/-3 days)

Data collected :

- Adverse Events
- Drug compliance review
- Blood collection (stored for future evaluation of platelet activation , coagulation markers. smooth muscle activation markers and inflammation markers

6.2.3 Study Day 30 (+/- 14 days) (may be conducted by phone)

Data collected :

- Disease severity (Rutherford scale)
- Major Cardiac events
- TVR
- TLR
- Amputation
- Bleeding

- Adverse Events
- Compliance
- Concomitant medications
- Ultrasound + ABI index

6.2.4 Study Day 90 (- 14 days)

Data collected :

- Major Cardiac events
- TVR
- TLR
- Amputation
- Bleeding
- AEs
- Compliance
- Concomitant medications
- Blood collection (stored for future evaluation of platelet activation , coagulation markers. smooth muscle activation markers and inflammation markers

Study treatment will be discontinued and subsequent treatment will be at the discretion of the attending physician (long term use of ASA, as an example).

6.2.5 Study Month 6 (+/-30 days) (may be conducted by phone)

Data collected :

- Disease severity (Rutherford scale)
- Major Cardiac events
- TVR
- TLR
- Amputation
- Bleeding
- Ultrasound + ABI index (standard of care)

6.2.6 Study Month 12(+/-30 days): Final Visit (may be conducted by phone)

Data collected :

- Disease severity (Rutherford scale)
- Major Cardiac events
- TVR
- TLR
- Amputation
- Bleeding
- Ultrasound + ABI index (standard of care)

6.2.7 Premature Discontinuation Visit

In case of premature discontinuation participants will be asked to come for a final visit to assess potential adverse events and return unused study medication.

6.3 Outcome Measures

6.3.1 Rutherford scale

Participants will be evaluated according to Rutherford scale at screening, and at the day 30, month 6 and month 12 follow-up visits.
Classes in the Rutherford scale are defined as:

- Stage 0 – Asymptomatic
- Stage 1 – Mild claudication
- Stage 2 – Moderate claudication – The distance that delineates mild, moderate and severe claudication is not specified in the Rutherford classification, but is mentioned in the Fontaine classification as 200 meters.
- Stage 3 – Severe claudication
- Stage 4 – Rest pain
- Stage 5 – Ischemic ulceration not exceeding ulcer of the digits of the foot
- Stage 6 – Severe ischemic ulcers or frank gangrene

6.3.2 Blood samples

During the entire trial, a volume of approximately 40ml blood will be sampled from each participant for research purposes, in addition to standard of care blood samples: ~10ml of blood (2 x5 ml tubes) will be obtained for research purposes at Day 1, Day 7, and Day 90 for evaluation of platelet activation (including D-dimers), coagulation markers, smooth muscle activation markers (soluble CD40/44 ligands, and ERK ½) and inflammation markers.
All research blood samples will be processed and stored in a freezer at the Thrombosis Group Research Laboratory and analyzed at the conclusion of the study after enrollment has been completed.

6.3.3 Duplex ultrasound arterial examination

Duplex ultrasound arterial examination will be performed at the Ottawa Civic Hospital (Diagnostic Imaging) at 30 days, 6 and 12 months as part of the routine care. The following will be recorded in the CRF : re-stenosis as defined by peak velocity flow, and the Ankle Brachial Index (ABI).
The Ankle Brachial Index(ABI) is the ratio of the blood pressure in the lower legs to the blood pressure in the arms. The ABI is calculated by dividing the systolic blood pressure at the ankle by the systolic blood pressures in the arm.

6.4 Withdrawal / Discontinuation Criteria

Participants have the right to withdraw from the study treatment at any time for any reason. The Investigator has the right and obligation to withdraw participants from the study treatment in the event of:

1. Adverse event(s) which would, in the judgment of the investigator, require discontinuation of study product(s)
2. Request by the participant or their legally authorized representative (consent withdrawal)
3. Non compliance to the study protocol
4. Participants needs additional medication that would interfere with the study
5. Participant is lost to follow-up

6. The sponsor, or the principal investigator or the Data and Safety Monitoring Board or a government agency such as Health Canada cancels the study.

When a participant withdraws consent after starting the protocol treatment the investigator or delegate should make every effort to contact the participant to determine, as completely as possible, the reason for the withdrawal and to schedule an end-of-study visit for assessing potential adverse events. The participant will be asked to return unused study products and will be switched to standard of care, as per their own treating physician.

6.5 Management Of Major Bleeding

All participants with major bleeding will have study drug held until judged safe to resume by the investigator.

6.5.1 Treatment arm 1

In the event of hemorrhagic complications in a participant receiving Rivaroxaban, treatment should be temporarily discontinued, and the source of bleeding investigated. Rivaroxaban has a half-life of approximately 5 to 13 hours. Consideration should be given to the resumption of antithrombotic therapy at the discretion of the treating physicians, when clinically appropriate to adequately control risk of underlying thrombosis.
Management of bleeding should be individualized according to the severity and location of the bleeding. Appropriate symptomatic treatment should be used as needed, such as mechanical compression (eg, for severe epistaxis), surgical hemostasis with bleeding control procedures, fluid replacement and hemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anemia or coagulopathy) or platelets.
If bleeding cannot be controlled by the above measures, consider administration of one of the following pro-coagulants:

- activated prothrombin complex concentrate (APCC), eg., FEIBA
- prothrombin complex concentrate (PCC)
- recombinant Factor-VIIa (rFVIIa)

However, there is currently only very limited experience with the use of these products in individuals receiving Rivaroxaban. A specific antidote for Rivaroxaban is not available.

6.5.2 Treatment arm 2

In the event of hemorrhagic complications in a participant receiving Clopidogrel, treatment should be temporarily discontinued, and the source of bleeding investigated. A specific antidote for Clopidogrel is not available.
Management of bleeding should be individualized according to the severity and location of the hemorrhage. Appropriate symptomatic treatment should be used as needed, such as mechanical compression (eg, for severe epistaxis), surgical hemostasis with bleeding control procedures, fluid replacement and hemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anemia or coagulopathy).
Platelet transfusion may be used to reverse the pharmacological effects of clopidogrel and aspirin when quick reversal is required.

7 SAFETY

The adverse event reporting period will begin with the first dose of study medication and end on day 90 (at least 48 hours after last dose of study medication). Adverse events may be collected from participant report or by review of the clinical chart. Adverse events will be documented in the CRF.

Clinical investigators and ultimately the Qualified Investigator (QI) have the primary responsibility for adverse event identification, documentation, grading, assignment of attribution and reporting.

7.1 DEFINITIONS

7.1.1 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a participant administered at least one dose of study medication; the event does not necessarily have a causal relationship with that treatment or usage. An adverse event can therefore be:

- any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- pre-existing symptoms or conditions which worsen during a study.

7.1.2 Post-procedure adverse events

Bruising and discomfort at the puncture site is expected in the first week after the PTA procedure and will not be collected as an adverse event.

7.1.3 Serious Adverse Events

Serious Adverse Event (SAE)

- An event that results in death
- An event that places the participant at immediate risk of death (a life-threatening event). This does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires participant hospitalization or prolongation of existing hospitalization. For this study, the following exceptions apply to the index hospitalization:
    - The index hospitalization for PTA procedure will not be recorded as a serious adverse event
    - Prolonged hospitalization after the index hospitalization will not be recorded as a serious adverse event unless the prolongation is secondary to complications related to the study medication.
    - Hospitalizations for routine procedures and investigations are <u>not</u> considered a SAE in this protocol.
- Results in persistent or significant disability/incapacity. For_this study, the following exception applies to this criterion:
    - Disability/incapacity secondary to tissue loss (amputation) is not considered a SAE for this protocol.
- Is a congenital anomaly/ birth defect

- Other medically important events that, in the opinion of the Site Investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above.

Some conditions may not be immediately life threatening or require hospitalization. Should the investigator feel that the event may jeopardize the participant or may require intervention to prevent more serious outcomes, then it should be treated as serious.

7.1.4 Pre-Existing Conditions

In this trial, a pre-existing condition (i.e., a disorder present before the adverse event reporting period started) should not be reported as an adverse event unless the condition worsens during the adverse event reporting period.

7.1.5 Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy noted under Comments.

7.1.6 Laboratory Test Abnormalities

Laboratory test value abnormalities will be reported as an AE if they satisfy one or more of the following conditions for clinical significance:

1. Accompanied by clinical symptoms
2. Leading to a change in study medication (e.g. Dose modification, interruption or permanent discontinuation)
3. Requiring a change in concomitant therapy (e.g. Addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

Please note: any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an adverse event in the CRF.

7.2 Grading Of Adverse Events

All adverse events will be graded by the Investigator using the scale below.

1=Mild	Discomfort noticed but no disruption of normal daily activity
2=Moderate	Discomfort sufficient to reduce or affect daily activity
3=Severe	Inability to work or perform normal daily activity

7.3 Causality

Relationship of all adverse events and serious adverse events to the study interventions (causality) should be assessed by the investigator as follows:

• **Unrelated:** There is not a reasonable possibility that the adverse event may have been caused by the study drug.

• **Possibly related**: The adverse event may have been caused by the study drug, however there is insufficient information to determine the likelihood of this possibility.
• **Related**: There is a reasonable possibility that the adverse event may have been caused by the study drug.

7.4 EXPECTEDNESS

Adverse events and serious adverse events will also be assessed according to the following categories:
• **Expected (anticipated):** the event is identified in nature, severity, or frequency in the investigator brochure, product monograph or in the protocol .
• **Unexpected (unanticipated):** the event is not identified in nature, severity, or frequency in the investigator brochure, the product monograph or in the protocol.

7.5 RECORDING, REPORTING AND FOLLOW-UP OF ADVERSE EVENTS

7.5.1 Adverse Events Recording

Adverse events will be recorded on the CRF.
The investigator and delegates will record all directly observed adverse events and all adverse events spontaneously reported by the participant. In addition, each participant will be questioned about adverse events at each visit.

7.5.2 Adverse Events Reporting

The QI or delegate will be responsible for reporting the AEs to the OHSNREB, and the Data and Safety Monitoring Board (DSMB) as follows:

- Adverse events will be reported to the OHSNREB as per their guidelines
- Adverse events will be summarized in a table, and provided to the Data and Safety Monitoring Board (DSMB) before DSMB meetings.

7.5.3 Serious Adverse Events Reporting

SAEs require prompt or immediate reporting to the QI or delegate. The QI is ultimately responsible for reporting the SAEs to Health Canada, the OHSNREB, the Data and Safety Monitoring Board and Bayer.

Reporting to Health Canada
Serious adverse events that are both unexpected and related or possibly related are subject to expedited reporting to Health Canada. SAEs that are expected or that are unrelated to the study drug are not reportable.
Report must be filed in the cases:

I. where the SAE is neither fatal nor life-threatening; within 15 days after becoming aware of the information
II. where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information

Within 8 days after having informed Health Canada of the SAE, the Qualified investigator will submit as complete as possible, a report which includes an assessment of the importance and implication of any findings.

Each SAE which is subject to expedited reporting should be reported individually using the RIFLE SAE form (see Appendix 2).

Any updated follow up information that becomes available regarding the SAE should be reported in a follow up report.

Reporting to the OHSNREB
All SAEs, will be reported to the OHSNREB as per their guidelines.

Reporting to the Data Safety Monitoring Board (DSMB)
SAEs, that are related or possibly related and unexpected will be reported immediately to the Chair of the DSMB .
All SAEs, whether related to the study interventions or not will be summarized in a table, and provided to the DSMB before each scheduled DSMB meeting

Reporting to Bayer
SAEs will be reported to Bayer as per procedure outlined in the grant agreement.

7.5.4 Adverse Events Follow-Up

Follow-up of adverse events considered related or possibly related to study drugs should continue until they have returned to baseline status or stabilized or the causal relationship has been changed from related to unrelated to study drug.

7.6 Stopping Rules

The study has no formally defined stopping rules. Data will be monitored as they accumulate and the use of the experimental therapy will cease if there is clear evidence of rivaroxaban-related adverse events or of a lack of efficacy. This decision will be at the discretion of the DSMB as per section 9.5.1.

8 STATISTIC ANALYSIS

8.1 Study Outcomes

8.1.1 Primary Outcome

The primary outcome is a combined endpoint consisting of any Reintervention , Above ankle amputation and Stenosis (RAS) [2] at one year The 3 components of RAS are defined as follows:

8.1.1.1 Reintervention

Classified as major/minor and only considers first occurrence. Major reinterventions include placement of a new surgical bypass graft, use of thrombectomy or thrombolysis, or a major surgical revision (jump or interposition graft). Minor reinterventions include endovascular procedures without thrombectomy/thrombolysis and minor surgical revisions (patch angioplasty).

Re-interventions will be classified as target lesion revascularization (TLR), target vessel revascularization (TVR) and clinically-driven target lesion revascularization (CDTLR). TLR is defined as either repeat percutaneous or surgical revascularization for a lesion anywhere within previous treated area*. TVR is any repeat percutaneous intervention or surgical bypass of any segment of the target vessel**. CDTLR revascularization is a target lesion revascularization prompted by recurrent ipsilateral limb symptoms (intermittent claudication, critical limb ischemia) or objective imaging evidence of target lesion restenosis (i.e., most commonly with duplex ultrasonography).

*A target lesion is any lesion treated or attempted to be treated with PTA. The target lesion is the treated segment starting 5 mm proximal and ending 5 mm distal to the index procedure (stent, in most cases).

**A target vessel is the vessel that contains the target lesion. The target vessel includes the target lesion as well as the entire vessel upstream and downstream to the target lesion, including side branches (native vessel).

8.1.1.2 AMPUTATION

Minor and major amputations (above the ankle) differentiating below-the-knee vs. above-the-knee amputation will be collected at each follow-up visit.

8.1.1.3 RE-STENOSIS

Reported in a time-to-event fashion, defined as:

- Decrease in ABI by 0.15 (or TBI drop of 0.10) or greater as compared to post-procedure value
- Duplex ultrasound demonstrating occlusion of the graft or treated vessel
- Duplex ultrasound demonstrating critical graft stenosis (Peak Systolic Velocity _300 cm/s or velocity ratio 3.0)
- Angiogram, MRI or CTA demonstrating occlusion of graft or of any treated vessel, or >50% stenosis in the presence of recurrent clinical symptoms

8.1.2 Secondary Outcomes

1. Clinical improvement defined as cumulative improvement of 2 classes of the Rutherford scale without the need for repeated TLR in surviving patients.
2. Event-free survival
3. Overall survival
4. Target lesion revascularization (TLR) between day 1 and final visit
5. Target vessel revascularization (TVR between day 1 and final visit
6. Peri-procedure death within 30 days
7. Cumulative rate of major adverse cardiovascular events (as defined in 8.1.2.1) between day 1 and final visit
8. Cumulative rate of major bleeding (as defined in 8.1.2.2) between day 1 and day 90.
9. Cumulative rate of minor bleeding (as defined in 8.1.2.2) between day 1 and day 90
10. Biological plausibility by measuring coagulation changes and SMC proliferation markers within 7 and 90 days based on the following markers: D-dimer, soluble CD40/44 ligands, and ERK 1/2.
11. Patency rates based on the ABI index and with an ultrasound at 6 and 12 months
12. Information about feasibility of a future study:
    a. The total number of eligible candidates identified;

b. The percentage of eligible patients referred to our study;
c. The percentage of eligible patients who consent to be enrolled

8.1.2.1 MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

Any of the following events during follow up

1. Ischemic Stroke	Sudden onset of a neurological deficit that persists for more than 24 hours and involves one or more of the following: a) Hemiparesis: involving the face, arm and/or leg unilaterally b) Hemisensory loss; involving face, arm and/or leg unilaterally c) Speech impairment; (ie. Aphasia) d) Visuo-spatial impairment e) Visual loss (monocular or binocular) f) Two or more of the following symptoms which suggest vertebrobasilar involvement: i. incoordination/ataxia ii. cranial nerve abnormality iii. dysarthria iv. dysphagia v. vertigo vi. reduction/loss of consciousness vii. diplopia g) Objective and persistent (more than one week) worsening of a previous deficit or worsening associated with an appropriate new finding on CT scan or MRI.
2. Transient Ischemic Attack	A transient ischemic attack is defined for the purposes of this trial as a sudden onset of a neurological deficit lasting at least one minute but less than 24 hours. (Isolated syncope will not be considered a TIA unless this occurs with one or more of the following neurological symptoms suggesting vertebrobasilar involvement. a) Hemiparesis; involving face, arm and/or leg unilaterally b) Hemisensory loss; involving face, arm and/or leg unilaterally c) Speech impairment; (ie. Aphasia) d) Visuo-spatial impairment e) Visual Loss (monocular or binocular) f) Two or more of the following symptoms: i. Incoordination/ataxia, ii. Cranial nerve abnormality, iii. Dysarthria, iv. Dysphasia, v. Vertigo, vi. Reduction/loss of consciousness, vii. Diplopia

3. Myocardial Infarction	At least two of: a) Ischemic chest pain, b) EKG changes compatible with a MI(hyper acute T wave, elevated ST segment, T wave inversion, presence of new bundle branch block, loss of R wave height, development of Q waves) or c) elevation of cardiac enzymes (troponin, CK, CKMB isoenzyme, or other cardiac enzymes) to at least 2X the upper limit of the normal reference range or 3X the upper limit of normal within 48 hours after percutaneous coronary intervention (or if markers are already elevated, greater than 50% of the lowest recovery level from the index infarction
4. Vascular Death	Cardiac or cerebrovascular death excluding subarachnoid or primary intracranial haemorrhage or fatal pulmonary embolism.

8.1.2.2 BLEEDING

Bleeding will be classified as per the Thrombolysis in Myocardial Infarction (TIMI) bleeding classification scheme:

Major Bleeding:

- Any intracranial bleeding
- Clinically significant overt signs of bleeding associated with a drop in hemoglobin of > 50 g/L (or, when hemoglobin is not available, an absolute drop in hematocrit of > 15%),
- Fatal bleeding that directly results in death within 7 days.

Minor Bleeding:

- Any clinically overt sign of bleeding (including imaging) that is associated with a fall in hemoglobin of 30 to 50 g/L (or, when hemoglobin is not available, a fall in hematocrit of 9 to 15%).
- Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
  - Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
  - Leading to or prolonging hospitalization
  - Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

Minimal Bleeding:

- Any overt bleeding event that does not meet the criteria for major or minor bleeding listed above
- Any clinically overt sign of bleeding (including imaging) that is associated with a fall in hemoglobin < 30 g/L (or, when hemoglobin is not available, a fall in hematocrit of < 9%).

Bleeding will be further identified using the following criteria:

- Significant: major bleeding or minor bleeding requiring medical attention.
- Instrumented: any bleeding that occurs as a result of an invasive procedure.
- Spontaneous: any bleeding that is not the direct result of an invasive procedure (e.g. gingival bleeding, epistaxis, gastrointestinal bleeding).

8.2 Sample Size Calculation

Based on recent data published by Conte et al[2] we expect that during 1 year of follow up, 54% of participants will experience the primary outcome. A total sample of 40 participants was selected and is within the recommended approach for pilot studies evaluating effects when no prior information upon which to base the sample size is available. This sample size will allow us to detect an absolute 20% reduction in the main clinical outcome with a single sided alpha of 0.2 and power of 0.6 as recommended for pilots studies[59-61]. The study will be considered successful if we can demonstrate a reduction in events in the intervention group supported by changes in biomarkers levels (biological plausibility).

8.3 Statistical Analysis

All the continuous outcomes will be evaluated with the paired T-test or Wilcoxon-rank sum; proportions will be evaluated using the Fisher's exact test.

9 STUDY ADMINISTRATION

9.1 Applicable Standards And Regulations

The trial will be performed in compliance with the Canadian Tri-Council Policy Statement version 2 (TCPS2), the World Medical Association Declaration of Helsinki, adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and last amended by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, the Canadian Food and Drug Regulations, Division 5 Part C, the Canadian Ontario's Personal Health Information. Protection Act (PHIPA), and the ICH Good Clinical Practices (GCP).

9.2 Ethical Conduct Of The Study

9.2.1 Ethics Committee

The trial may only be initiated after the Investigator has obtained written approval of the protocol, Informed Consent form and other study documents, and any amendments (if applicable), by the Ottawa Health Science Network Research Ethics Board (OHSNREB). Changes in protocol (amendments) must be submitted to the OHSNREB for approval. Reports on, and reviews of, the trial, its safety aspects and its progress will be submitted to the OHSNREB by the Investigator at intervals according to the institutional guidelines.

9.2.2 Identification of potential participants

Enrollment will be conducted at the Vascular Surgery Outpatient Clinic and on the wards at the Ottawa Hospital Civic Campus. To increase our screening for eligible participants, all scheduled PTAs will be screened daily for eligibility and a screening log will be maintained.

9.2.3 Participant Information and Consent

All relevant study information will be summarized in an informed consent form. The investigator or delegate will explain all relevant aspects of the study to the patients prior to entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms). The patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for their decision.

9.3 Steering Committee

A Steering Committee comprised of the trial's co-investigators will manage the overall conduct of the trial. Drs. Gandara, Jetty and Ramsay will regularly review the progress of the trial. The Steering Committee will review how the trial was conducted and review the various outcomes of the trial to determine if the evidence justifies a full randomized trial.

9.4 Data Management

Data will be recorded on a paper case report form (CRF) by the research personnel according to the protocol. CRFs will be verified for completeness and accuracy by a research team member not involved in the data collection. Any changes to the CRF will be tracked. Upon completion of data collection and verification of the CRF by the Investigator or designee, data will be entered in an data analysis software. Data will be cleaned and coded prior to analysis by a statistician. Missing data will be queried. Data still missing after queries will be coded appropriately by the statistician.
Reports will be prepared prior to Data Safety Monitoring Board (DSMB) meetings including: enrollment per treatment arm, descriptive statistics for demographic data (and other relevant characteristic) to assess that randomization was effective, and a tabulated summary of AEs and SAEs per treatment arm.

9.5 Data Quality

9.5.1 Role of the Data Safety Monitoring Board

This study will be monitored by an independent Data Safety Monitoring Board (DSMB), consisting of an independent physician, and two other members not involved in this study. The DSMB will be immediately informed of any serious adverse events (SAEs), which are potentially related to study drug. If at any point the DSMB considers continuance of the study unacceptable, the steering committee will be immediately notified.

The DSMB will have a scheduled meeting midway through the trial (after ~20 participants have completed the first 90 days of the trial or after 6-months of active recruitment). An interim report will be prepared by the data management team for the study. The report will include data on recruitment, compliance, adverse events, baseline comparability and treatment comparisons.

If at any point the DSMB considers continuance of the study unacceptable, the steering committee will be immediately notified.

9.5.2 Monitoring

The investigator (or his/her delegate) agrees to cooperate with the OHRI monitor to schedule at least one monitoring visit during the course of the study and to ensure that any problems detected in the course of this monitoring visit are resolved. This monitoring by OHRI does not replace the routine quality control to be performed by the Qualified Investigator or his delegate.
Routine quality control will be completed by the Qualified Investigator or his delegate to ensure that the study is being run according to the protocol. The routine monitoring of the study will include:

- Verification of all inclusion and exclusion criteria to confirm that only eligible participants are participating in the trial
- Verification of source data to ensure accuracy of study data as per the monitoring plan
- Verification that adverse events are recorded, assessed and reported according to the protocol
- Verification of the case report forms to ensure that they are being completed according to the protocol

9.5.3 Audits

The Investigator should understand that OHRI or its delegates, after appropriate notification may audit the study for Quality Assurance purposes.

9.5.4 Adjudication of outcomes

The primary outcome, bleeding events and major adverse cardiovascular events will be adjudicated by a blinded expert adjudication committee.

10 RECORD RETENTION

To comply with Health Canada regulations, the trial related records will be retained for 25 years. Records will be kept to enable linkage of participants' identity to CRF data (master log). This includes sufficient information from hospital and clinic records such as all original signed informed consent forms, source records, and detailed records of cell manufacturing. After 25 years, all study records will be destroyed by shredding or incineration

11 ANTICIPATED RESULTS- DISSEMINATION PLAN

The results of our trial will be used by the investigators to evaluate the need for further studies evaluating the role of the addition of rivaroxaban to reduce clinically relevant outcomes in patients with CLI requiring PTA and will provide justification to external funding agencies before a commitment is made to fund a full trial.
Regardless of the results of the trial, we will make every effort to publish and present our data and conclusions about feasibility such that future researchers might benefit from this work.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. It is the responsibility of the QI to register this trial in an acceptable registry on or before patient enrollment.

12 CONFIDENTIALITY

All subject related information including Case Report Forms, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Subjects will be identified only by means of a coded number specific to each subject. All computerized databases will identify subjects by numeric codes only, and will be password protected or encrypted.

Upon request, subject records will be made available to the study sponsor, monitoring groups' representative of the study sponsor, and applicable regulatory agencies such as Health Canada.

APPENDIX I: REFERENCES

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APPENDIX 1: SCHEDULE OF EVENTS

	Screening Visit -30 days to -1 day	**PTA Baseline Day 1**	**Visit Day 7** (+/- 3 days)	**Visit Day 30 *** (+/- 14 days)	**Visit Day 90** (- 14 days)	**Visit 6 months*** (+/-30 days)	**Final Visit 12 months*** (+/-30 days)
Informed Consent	X						
Inclusion & Exclusion Criteria	X						
Physical Exam[1]	X						
Medical History	X						
Randomization		X					
Dispense study medication		X					
Study medication compliance review			X	X	X		
Rutherford Score	X	X		X		X	X
Review of bleeding events	X	X		X	X	X	X
Review of major cardiac events		X		X	X	X	X
Review of Re-interventions				X	X	X	X
Review of Adverse Events		X	X	X	X	X	X
Clinical Laboratory Tests Results[2]	X						
Review of Concomitant Medications	X	X		X	X	X	X
Collect Imaging Outcomes				X		X	X
Blood Work, research samples[3]		X	X		X		

[1] Height and weight

[2] CBC, coagulation tests, and serum creatinine

[3] Includes: Platelet activation, coagulation markers, smooth muscle activation, inflammation markers

*Visit may be completed in person or via telephone follow-up

APPENDIX 2: RIFLE SAE FORM

Complete one form for each SAE. Attach all supporting source documents (with no identifying information). The source documents must be signed and dated by the investigator.

1. SAE report type

☐ Initial ☐ Follow-Up

2.Condition/Diagnosis:

_____

3. Personal Data

Date of Birth (mmm/yyyy): ☐☐☐ / ☐☐☐☐

Gender: ☐ Male ☐ Female

Height(cm): ☐☐☐

Weight(kg): ☐☐☐

4. SAE Category

☐ Death
☐ Life-threatening
☐ New or prolonged hospitalization
☐ Other medically relevant condition judged or defined as serious
☐ Persistent or significant disability/incapacity
☐ Congenital anomaly/birth defect

If other: _____

5. Date and Time

Date of Onset: (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Onset Time: ☐☐ : ☐☐ (24 hour clock)

Date when event became serious: (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Time when event became serious: ☐☐ : ☐☐ (24 hour clock)

Location of onset of SAE(eg: home, hospital, car): _____

6. SAE status/clinical outcome

☐ Recovered/Resolved
☐ Not yet recovered
☐ Recovered with sequelae
☐ Fatal/Death
☐ Unknown

Date & Time:

Date (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Time: ☐☐ : ☐☐ (24 hour clock)

7. Event Description

Include a history of the event chronologically including signs and characteristics, severity, dates and outcomes of hospitalization and any other relevant information not captured elsewhere on the form. Include relevant tests/data, treatment/procedures, medical history, treatment history.

8. Relevant tests/data source documents have been attached? ☐ Yes ☐ No

9. Relevant treatment/procedures source documents have been attached? ☐ Yes ☐ No

10. Relevant medical history source documents have been attached? ☐ Yes ☐ No

11. Relevant previous treatment history (including operations or medical procedures) **source documents have been attached?** ☐ Yes ☐ No

12. Study Medication # 1

Study Medication Name: Aspirin

Dose: 81 mg Frequency: once daily

Route: oral

Lot number: ☐☐☐☐☐☐☐☐☐☐☐

Expiry date (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Indication for use: anti-platelet

Date of first dose: (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Time of first dose: ☐☐ : ☐☐ (24 hour clock)

Date of last dose prior to SAE: (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Time of last dose prior to SAE: ☐☐ : ☐☐ (24 hour clock)

13. Action taken with study drug #1 (Aspirin)

☐ Temporarily discontinued
☐ Permanently discontinued
☐ Nil
☐ Other:
_____

14. Is there a reasonable possibility that the SAE is related to study drug #1?

☐ **Yes** ☐ **No** ☐ **Not assessable**

15. If study drug #1 is temporarily interrupted:

Stopped on (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Restarted on (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Event abated after study drug #1 stopped? ☐Yes ☐No ☐N/A

Did event reappear after reintroducing study drug #1? ☐Yes ☐No ☐N/A

16. Study Medication # 2

Study Medication Name: _____

Dose: _____ Frequency: _____

Route: oral

Lot number: ☐☐☐☐☐☐☐☐☐☐☐

Expiry date (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Indication for use: _____

Date of first dose: (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Time of first dose: ☐☐ : ☐☐ (24 hour clock)

Date of last dose prior to SAE: (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Time of last dose prior to SAE: ☐☐ : ☐☐ (24 hour clock)

17. Action taken with study drug #2

☐Temporarily discontinued
☐Permanently discontinued
☐Nil
☐Other:
_____

18. Is there a reasonable possibility that the SAE is related to study drug #2?

☐ **Yes** ☐ **No** ☐ **Not assessable**

19. If study drug #2 is temporarily interrupted:

Stopped on (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Restarted on (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

Event abated after study drug #1 stopped? ☐ Yes ☐ No ☐ N/A

Did event reappear after reintroducing study drug #1? ☐ Yes ☐ No ☐ N/A

20. Concomitant Medications (exclude those used to treat reaction) source documents have been attached? ☐ Yes ☐ No

21. Intensity

☐ Mild ☐ Moderate ☐ Severe **To be completed by investigator only !**

22. Causality:

☐ Unrelated ☐ Possibly related ☐ Related **To be completed by investigator only !**

23. Expectedness

☐ Expected ☐ Unexpected ☐ More prevalent **To be completed by investigator only !**

24. Possible causes of the event (check all that apply): To be completed by investigator only !

☐ Pre-existing/Underlying disease: _____

☐ Study treatment: _____

☐ Other treatment (concomitant or previous): _____

☐ Protocol-related procedure: _____

☐ Other (e.g. accident, new or intercurrent illness) :_____

Research Staff's Name:_____

Research Staff Signature: _____

Investigator's Name: _____

Investigator's Signature: _____

Date (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐

APPENDIX 3 : CYP3A4 AND P GLYCOPROTEIN INHIBITORS

- Amiodarone
- Boceprevir
- Clarithromycin
- Cyclosporine
- Diltiazem
- Erythromycin
- Itraconazole
- Ketoconazole
- Nicardipine
- Nifedipine
- Posaconazole
- Quinine
- Ritonavir
- Saquinavir
- Telaprevir

Sources

(1) : Pharmacology Weekly COMPREHENSIVE DRUG REFERENCE TABLE (http://www.pharmacologyweekly.com/content/pages/drug-reference-table-cyp-p450-ugt-enzymes-transporters-ab)

(2) Rivaroxaban Product Monograph – Bayer Canada

APPENDIX 4: PRODUCT INFORMATION

Rivaroxaban 2.5 mg

Source:	Bayer Canada
Brand Name	**XARELTO**
Manufacturer	Bayer
Dosage form	Film-coated, round, biconvex, light red immediate release tablets of 6 mm diameter for oral use.
Daily dose:	2 tablets (2.50 mg twice daily every 12 hours)

Rivaxobaran will be supplied free of charge to all study participants randomized in treatment arm 1. Rivaxobaran tablets will be stored at the Ottawa Hospital Research Pharmacy. Each bottle will be labeled according to Food and Drug Regulations Division 5 Part C requirements as Rivoxabaran 2.5 mg is not a product currently approved in Canada.

Acetylsalicylic acid (ASA) 81 mg

Source:	Commercial
Brand Name	As per hospital formulary
Manufacturer	As per Hospital formulary
Dosage Form	Tablets
Daily dose:	1 tablet (ASA 81 mg) OD

ASA will be supplied free of charge to all study participants. Bottles will be labeled according to Food and Drug Regulations Division 5 Part C requirements as although ASA is standard of care for the proposed indication, it is an off label use according to the Product Monograph .

Clopidogrel 75 mg

Source:	Commercial
Brand Name	As per Hospital Formulary
Manufacturer	As per Hospital Formulary
Dosage Form	Tablets
Daily dose:	1 tablet (Clopidogrel 75 mg)OD

Clopidogrel will be supplied free of charge to all study participants randomized in treatment arm 2. Proposed indication, dose and route are within the parameters of the NOC : Clopidogrel is approved in Canada for the secondary prevention of atherothrombotic events (myocardial infarction, stroke and vascular death) in patients with atherosclerosis documented by stroke, myocardial infarction, or established peripheral arterial disease (Plavix Product monograph) . The recommended dose of is 75 mg once daily with or without food.