Rivaroxaban plus Acetylsalicylic Acid Versus Standard of Care for Arterial and Venous Cardiovascular Prevention After Hip Fracture Surgery in Patients with Myocardial Injury: a Pilot Randomized Trial (HIPSTER-Pilot)

Protocol Number: HIPSTER-2024

Sponsor: Dr. Federico Germini, MD, McMaster University

Name and title of the person(s) authorized to sign the protocol: Dr. Federico Germini, MD

CONFIDENTIAL

DECLARATION AND SIGNATURE PAGE

Title: Rivaroxaban plus Acetylsalicylic Acid Versus Standard of Care for Arterial and Venous Cardiovascular Prevention After Hip Fracture Surgery in Patients with Myocardial Injury: a Pilot Randomized Trial (HIPSTER-Pilot)

The study will be conducted in accordance with the International Council for Harmonisation Guidelines for Good Clinical Practice and applicable local and federal regulations. The study will not commence without the prior written approval of a properly constituted Research Ethics Board (REB), Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the REB, IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects.

Sponsor Signature: _____ _____
Dr. Federico Germini, MD Date

I have read, understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study centre: _____
Name, Title

_____ _____ _____
Institution Signature Date

Abstract

Background: A third of patients undergoing surgery for a hip fracture develop a myocardial injury (i.e., an elevated troponin measurement), and these patients are at substantial risk of death and morbidity. Current prophylaxis strategies focus on preventing venous thromboembolism (VTE); however, arterial events are more common and carry a poor prognosis. The association of acetylsalicylic acid (ASA) 75-100 mg once daily and rivaroxaban 2.5 mg twice a day (the regimen used in the COMPASS trial) might prevent both VTE and arterial cardiovascular events.
Objective: Among patients who have undergone hip fracture surgery and have evidence of myocardial injury, to explore the feasibility of a randomized controlled trial (RCT) comparing rivaroxaban 2.5 mg twice daily + low-dose ASA (75-100 mg) for 90 days, with standard VTE thromboprophylaxis for 30 days, for prevention of major cardiovascular events.
Methods: The HIPSTER-Pilot is a multicenter, international, open-label, pilot RCT with blinded outcome adjudication. A total of 100 participants aged ≥45 years who received hip fracture surgery and experienced a myocardial injury will be randomized to receive either rivaroxaban 2.5 mg twice daily plus ASA 75-100 mg daily for 90 days or standard VTE prophylaxis with an anticoagulant for 30 days. The primary feasibility outcome will be the recruitment rate. Other feasibility measures include completeness of follow-up and adherence to the treatment. Exploratory clinical outcomes will be assessed.
Conclusion: This pilot trial will provide information on the feasibility of conducting a larger RCT to evaluate the efficacy and safety of the COMPASS regimen for preventing arterial and venous thrombotic events after hip fracture surgery in patients who have had myocardial injury. The results of this feasibility study will inform the design of the full-scale trial.
Funding: Canadian Venous Thromboembolism Research Network
Registration: This study will be registered on ClinicalTrials.gov.

List of abbreviations

AE: Adverse reaction

ASA: acetylsalicylic acid

ASH: American Society of Hematology

BIMS: bleeding associated with mortality after non-cardiac surgery

BID: bis in die (twice daily)

CanVECTOR: Canadian Venous Thromboembolism Research Network

CI: confidence interval

CRF: case report form

CV: cardiovascular

CYP3A4: Cytochrome P450 3A4

DOAC: direct oral anticoagulant

DVT: deep vein thrombosis

EDI: equity, diversity, and inclusion

FTE: full-time equivalent

HIPSTER: HIP fracture Surgery Thromboembolism prevention Randomized controlled trial

HR: hazard ratio

ICH-GCP: International Council for Harmonisation- Good Clinical Practice

ISTH: International Society on Thrombosis and Haemostasis

LMWH: low molecular weight heparin

MI: myocardial infarction

MINS: myocardial injury after non-cardiac surgery

NICE: National Institute for Health and Care Excellence

OD: once daily

OR: odds ratio

PE: pulmonary embolism

P-gp: P-glycoprotein

PI: principal investigator

POD: postoperative day

PreOD: preoperative day

RCT: randomized controlled trial

REB: Research Ethics Board

REDCap: Research Electronic Data Capture

SAE: Serious adverse reaction

SOP: standard operating procedure

SUADR: serious unexpected adverse drug reactions

UFH: unfractionated heparin

VTE: venous thromboembolism

Synopsis

Title	Rivaroxaban plus acetylsalicylic acid versus standard of care for arterial and venous cardiovascular prevention after hip fracture surgery in patients with myocardial injury: a pilot randomized trial (HIPSTER-Pilot)
Study objective	To determine the feasibility of a randomized controlled trial (RCT) on the use of rivaroxaban 2.5 mg twice daily + low-dose acetylsalicylic acid (ASA 75-100 mg) compared with standard thromboprophylaxis for cardiovascular prevention after surgery for hip fracture in patients with myocardial injury.
Study design	Multicenter, international, pilot RCT, open label, with blinded outcome adjudication.
Sample size	100 participants.
Study population	Inclusion criteria: - Age ≥45 years, - Received surgery for a hip fracture due to a low-energy mechanism, and - myocardial injury (i.e., an elevated troponin measurement) Main exclusion criteria: - Contraindications to the use of rivaroxaban or ASA; - Indication for full dose anticoagulation; or for dual antiplatelet therapy or a P2Y12 inhibitor; - Patients already on rivaroxaban 2.5 mg twice daily + ASA before the fracture Bleeding diathesis;Previous participation in HIPSTER trial.
Study intervention	Rivaroxaban 2.5 mg twice daily + low-dose ASA (75-100 mg) for 90 days or standard prophylaxis for venous thromboembolic events for 30 days.
Outcomes	The primary feasibility outcome will be recruitment rate. Other feasibility measures include completeness of follow-up and adherence to the treatment. We will also undertake exploratory measurement of clinical outcomes.
Follow-up	In hospital and at 30 and 90 days after randomization.

1. Introduction

1.1 Background and rationale

More than 1.6 million persons worldwide and almost 30,000 Canadians experience hip fractures each year.[1,2] The incidence of hip fractures is expected to increase dramatically, from 1.6 million cases in 2000 to an estimated 6.3 million by 2050, largely due to an aging global population.[3] A study analyzing postoperative mortality from hip fracture surgeries in Denmark (2000-2014) using national health registries revealed mortality rates of 9.6% at 30 days, 16.2% at 90 days, and 26.8% at one year, with stable risk over time.[4] The HIP ATTACK-1 trial, a multi-center study across 69 hospitals in 17 countries, enrolled 2970 patients to compare the outcomes of accelerated surgery (within 6 hours of diagnosis) versus the standard of care for hip fracture. [5] After 90 days from the surgery, the all-cause mortality across both groups was 9.5%. The following major vascular complications occurred within 90 days: vascular death 5.5% of patients, myocardial infarction (MI, fatal and non-fatal) 5.5% of participants, and myocardial injury not fulfilling the universal definition of myocardial infarction 30.3% of patients. In contrast, the rate of venous thromboembolism (VTE) was low, at 1.1%.

Despite the high frequency of arterial cardiovascular (CV) events and their poor prognosis, research has mainly focused on preventing VTE, the combination of deep vein thrombosis (DVT) and pulmonary embolism (PE), rather than on CV morbidity and mortality in general. Patients with hip fractures face a risk of VTE driven by a combination of factors, including regional tissue injury from the fracture and the surgery, comorbidities, prolonged immobility, and systemic complications associated with the intervention. In the absence of thromboprophylaxis, the

estimated risk of PE and proximal DVT is about 1% and 3%, respectively.[67]Pharmacological thromboprophylaxis has been shown to significantly reduce this risk, with relative risks of 0.49 [95% confidence interval (CI) 0.33-0.72] for symptomatic PE and 0.51 (95% CI 0.38-0.69) for symptomatic proximal DVT, although there is very low certainty around these estimates due to risk of bias and imprecision. These benefits must be weighed against the bleeding risk. The baseline risk of major bleeding events in this population is approximately 5%.[8] Pharmacological prophylaxis can increase this risk by an estimated 24% (relative increase, 95% CI 12-37%; very low certainty evidence due to risk of bias and indirectness or imprecision).[7,9]

The American Society of Hematology (ASH) guidelines recommend using low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) for VTE prophylaxis in hip surgery patients, based on very low certainty of evidence.[10] The National Institute for Health and Care Excellence (NICE) guidelines propose offering VTE prophylaxis for a duration of one month to individuals with fragility fractures of the pelvis, hip, or proximal femur, provided the risk of VTE exceeds the risk of bleeding.[11] Suggested prophylactic options include LMWH (initiated 6 to 12 hours postoperatively), or fondaparinux sodium (administered 6 hours postoperatively, contingent on low bleeding risk).[11] Consideration should be given to preoperative VTE prophylaxis in cases of delayed surgery beyond the day following admission. In this population, there is a lack of trials that directly compare these agents with each other, or with alternatives such as the antiplatelet agent, acetylsalicylic acid (ASA) or direct oral anticoagulants (DOACS) inhibiting thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, and edoxaban).[10]

A few trials have evaluated the effects on venous or arterial thrombotic/ischemic events of antithrombotic agents other than LMWH or fondaparinux (i.e., antiplatelets or other anticoagulants) in this patient population. In the Pulmonary Embolism Prevention (PEP) trial, a total of 13,356 patients with hip fractures were randomized to receive ASA or placebo for the prevention of venous and arterial thrombotic events.[9] The study drug was started before the surgery, as soon as possible after admission. Concomitant discretionary use of UFH or LMWH occurred in 43.8% of participants. VTE occurred in 105 participants (1.6%) in the intervention group and 165 (2.5%) in the control group, with a hazard ratio (HR) of 0.64 (95% CI 0.50-0.81). Fatal and non-fatal MI occurred in 105 (1.6%) assigned to ASA and 79 (1.2%) assigned to placebo (HR 1.33; 95% CI 1.00-1.78). There was no statistically significant difference in the risk of stroke, death from vascular or non-vascular causes between the two groups. The incidence of major bleeds was similar, although there was an increase in postoperative bleeds requiring transfusions, occurring in 197 (2.9%) patients assigned ASA and 157 (2.4%) assigned placebo, with an absolute (standard error) increase of 6 (3) per 1000 and a relative increase of 24% (95% CI 1; 53).

The POISE-2 and MANAGE studies were international, randomized, blinded, placebo-controlled trials that investigated the efficacy of perioperative or postoperative antithrombotic therapy for the prevention of CV events in non-cardiac surgery.[12,13] The POISE-2 trial had a 2-by-2 factorial design, assessing the effect of ASA versus placebo and clonidine versus placebo in patients undergoing non-cardiac surgery. The study included 10,010 patients at risk for vascular complications, divided into an initiation stratum (n=5,628, not taking ASA before the trial) and a

continuation stratum (n=4,382, taking ASA before the trial). Patients in the initiation stratum received a 200 mg dose of ASA/placebo just before surgery, followed by 100 mg daily for 30 days. Those in the continuation stratum had to stop ASA at least three days before randomization, and they were then given ASA/placebo for seven days after the surgery before resuming their regular regimen. We don't have details about the proportion of participants with a hip fracture, but 7.2% required urgent surgery, and 38.7% of surgeries were classified as orthopedic procedures. The primary composite outcome of death or nonfatal MI showed an HR of 0.99 (95% CI 0.86-1.15) between the ASA and placebo groups. Secondary and tertiary outcomes, including overall death, CV death, nonfatal MI, nonfatal stroke, and a combination of these, also showed no statistically significant benefit from ASA, with HRs close to 1. There was no statistically significant difference in life-threatening bleeding events, but major bleeding occurred in 230 (4.6%) participants on ASA and 188 (3.8%) on placebo, with an HR of 1.23 (95% CI 1.01-1.49). The definition of major bleeding represented severe bleeding.

The MANAGE trial investigated the effect of dabigatran on major vascular complications in patients who experienced myocardial injury after non-cardiac surgery (MINS).[12] Participants (≥45 years, within 35 days of MINS diagnosis) were given either dabigatran (110 mg twice daily) or placebo for a median duration of 474 days. The primary outcome was a composite of major vascular events that included vascular mortality and non-fatal MI, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic VTE. The median number of days from surgery to dabigatran initiation was six, 38.2% of participants received orthopedic surgery. Dabigatran significantly reduced the risk of major vascular events, with an HR of 0.72 (95% CI

0.55-0.93). The HR for the primary safety outcome (a composite of life-threatening, major, and critical organ bleeding) was 0.92 (95% CI 0.55-1.53). Therefore, the MANAGE trial highlighted the potential for oral anticoagulation to prevent CV events in the postoperative period. Fifty-eight percent of patients (in both groups) were on ASA before randomization, and, during the study period, 74% took ASA or a P2Y12 inhibitor, which suggest that a combination of anticoagulation and ASA could be safe long-term in patients with a recent history of major non-cardiac surgery. The participants' mean age in MANAGE was 70 years and patients were excluded if their estimated glomerular filtration rate was <35 mL/min.

Moving outside the postoperative setting, the COMPASS trial was a randomized controlled trial (RCT) that compared the efficacy and safety of rivaroxaban 2.5 mg twice daily (bis in die, BID) plus ASA 100 mg once daily (OD) - from now on referred to as the "COMPASS regimen" -, rivaroxaban 5 mg BID, or ASA 100 mg OD for secondary CV prevention in 27,395 participants with stable atherosclerotic vascular disease.[14] The primary outcome was a composite of CV death, stroke, or MI. The trial was stopped early for efficacy, with the primary composite outcome occurring in 4.1% of participants receiving the COMPASS regimen compared with 5.4% in those receiving ASA alone, with an HR of 0.76 (95% CI 0.66-0.86). The COMPASS regimen resulted in increased major bleeding events [International Society on Thrombosis and Haemostasis (ISTH) definition in non-surgical patients][15] compared with ASA alone, 3.1% vs. 1.9%; HR 1.70 (95% CI 1.40-2.05). Notably, a mortality benefit was seen with the COMPASS regimen, 3.4% vs. 4.1%; HR 0.82 (95% CI 0.71-0.96).[14] The trial was not designed to compare the COMPASS regimen with rivaroxaban 5 mg BID on its own. However, rivaroxaban 5 mg BID is a dose that can

be considered equivalent to the 10 mg OD dose currently used for VTE prophylaxis. This comparison is of interest to us, as it can provide an indirect estimate of the possible benefits of the use of the COMPASS regimen as compared with rivaroxaban alone for thromboprophylaxis and CV prevention in people undergoing surgery for hip fracture. We extrapolated crude odds ratios (ORs) for this comparison using published data from the COMPASS trial, reported in **Figure 1.** This analysis suggests that the COMPASS regimen, compared with rivaroxaban 5 mg BID, reduced the likelihood of CV complications such as death, stroke, or MI, as indicated by an OR of 0.84 (95% CI 0.73-0.96), and death from any cause, with an OR of 0.85 (95% CI 0.73-0.99). There was a potential trend toward reduced CV mortality (OR 0.81, 95% CI 0.66-1.01) and VTE (OR 0.69; 95% CI 0.41-1.15). However, the COMPASS regimen increased the risk of minor bleeding events (OR 1.14; 95% CI 1.03-1.26), and there was a potential trend for an increase in major bleeding (OR 1.13, 95% CI 0.95-1.34).

The COMPASS regimen was used in the postoperative setting in the VOYAGER PAD trial, an RCT that compared the efficacy and safety of the COMPASS regimen with ASA alone in a blinded manner in patients with peripheral artery disease who had undergone lower-extremity revascularization.[16] The three-year incidence of the primary composite outcome of acute limb ischemia, major amputation, MI, ischemic stroke, or CV death was 17.3% in the intervention group and 19.9% in the control group (HR 0.85; 95% CI 0.76-0.96). There was an increase in major bleedings as defined using the ISTH criteria, the incidence at 3 years being 5.9% with rivaroxaban and 4.1% with placebo (HR 1.42; 95% CI 1.10-1.84).[16] The VTE rate in participants on the COMPASS regimen was 0.8%.[16] The COMPASS regimen is approved for the prevention of stroke,

myocardial infarction (MI) and cardiovascular (CV) death; and the prevention of acute limb ischemia and mortality in patients with coronary artery disease (CAD) and/or peripheral artery disease (PAD) at high-risk with small regulatory differences in Canada, Europe, and the United States.[17–19]

The benefits of the COMPASS regimen observed in the COMPASS and VOYAGER trials may extend to the high-risk population of people with hip fractures. Compared with the current standard of care for VTE prophylaxis, the COMPASS regimen might offer comparable or better VTE prevention, prevention of arterial CV events, improvement in quality of life and treatment adherence because of oral administration instead of daily subcutaneous injection of LMWH (the current standard of care according to guidelines), as well as cost savings over injectables. Considering the clinical characteristics of this patient population, including older age, comorbidities such as dementia, and the need for urgent surgical treatment, it is crucial to determine the feasibility of enrolling and retaining such patients in a trial. Additionally, a feasibility study will allow us to evaluate the acceptability of using the COMPASS regimen after surgery, identifying potential compliance issues or concerns. Our goal is to establish a new, more effective and comprehensive approach to thrombosis prevention in hip fracture patients with myocardial injury by simultaneously preventing venous and arterial CV events.

Before designing this study, we conducted a survey to assess physician practices surrounding VTE prophylaxis for patients undergoing hip fracture surgery to define the current standard of care. Unpublished data from the survey showed that of the 204 physicians from 28 countries who completed the survey, 175 (85.8%) were responsible for prescribing postoperative

VTE prophylaxis and 172 (84.3%) supported the need for an RCT in this field. LMWH was the most frequently used VTE prophylaxis regimen (58.8%), DOACs (rivaroxaban or apixaban) (25.0%), ASA alone (9.8%), and sequential treatments (LMWH followed by either an oral anticoagulant or ASA, 37.7%). Fondaparinux, dabigatran, and other regimens were less commonly used. As expected, the COMPASS regimen is not used for VTE prophylaxis.

There was some variability in the duration of prophylaxis, with 58.9% of physicians prescribing the treatment for four weeks or 35 days, 9.8% until weight-bearing status, 10.3% until discharge from rehabilitation, and the remaining 21.0% spread among other options. While 30 days are likely appropriate for VTE prophylaxis, the risk of arterial cardiovascular events remains high for at least 90 days.5 The COMPASS regimen can prevent cardiovascular events in this setting, but one should select a population with high risk of such events and try minimizing the risk of bleeding. People who develop ischemic myocardial injury (35% on the population with a low-energy hip fracture), are the ones at higher risk of a recurrent cardiovascular events at 90 days: 29.6% as compared with 14.6% in people without myocardial injury.[21] Targeting a similar group was a successful strategy in the MANAGE trial.[12] However, approximately 80% of the initial myocardial injuries after non-cardiac surgery start off as supply-demand mismatch. Antithrombotic treatment is not only unlikely to prevent these events but may cause them through bleeding. This could explain the neutral effect of ASA on MI in the POISE-2 trial and the increased occurrence of MI in the ASA arm of the PEP trial. [12,13] The COMPASS regimen can be beneficial in people who had a myocardial injury on presentation to the hospital with their hip

fracture or in the days after their hip fracture surgery, if started not too soon after the surgery to reduce the risk of bleeding and administered for 90 days.

1.2 Objectives

Our primary objective is to determine the feasibility of an RCT comparing rivaroxaban 2.5 mg BID + ASA 75 to 100 mg daily for 90 days with standard thromboprophylaxis with a low-dose anticoagulant for 30 days in people who received surgery for low-energy hip fracture and experienced a myocardial injury. Our secondary objective is to describe the frequency of clinical outcomes.

Our research question in a PICOTS format:

- **Population:** Individuals who received surgery for low energy hip fracture and experienced a myocardial injury.
- **Intervention:** Oral rivaroxaban 2.5 mg BID + ASA 75 to 100 mg daily for 90 days.
- **Comparison:** Institutional standard thromboprophylaxis with a low-dose anticoagulant for 30 days
- **Outcomes:**
    - **Feasibility:** recruitment rate (primary), medication adherence, and retention of participants.
    - **Exploratory:** all-cause mortality, symptomatic VTE, arterial vascular events, and bleeding events.
- **Time of Follow-up:** in hospital, 30 days and 90 days.
- **Setting:** in-hospital and post discharge.

2. Methods

2.1 Study design.

This will be a pilot open-label RCT. The study design is described in **Figure 2**.

2.2 Study setting

We will enroll patients admitted to the hospital.

2.3 Eligibility criteria

2.3.1 Inclusion criteria

We will include patients satisfying the following criteria:

1. Age ≥45 years;
2. who received urgent surgery for a hip fracture due to a low energy mechanism; and,
3. who had a myocardial injury (not meeting the diagnostic criteria for myocardial infarction) on presentation to the hospital with their hip fracture or in the first three days after their hip fracture surgery.

2.3.2 Exclusion criteria

We will exclude centers in which the standard of care for VTE prophylaxis after hip fractures is ASA, alone or in combination with other drugs.

We will exclude patients based on the following criteria:

1. Renal Function: Measured or estimated glomerular filtration rate (GFR) <15 mL/min.
2. Drug interactions and conditions that prevent the use of the standard of care or intervention:
    a. Known allergy to the study drugs;

b. Pregnancy;

c. An indication for anticoagulation, for dual antiplatelet therapy, for a P2Y12 inhibitor;

d. Already on rivaroxaban 2.5 mg twice daily + ASA before the fracture;

e. Bleeding diathesis that in the judgment of the investigator precludes the use of anticoagulant prophylaxis;

f. History of significant hepatic disease (Child-Pugh B or C, see supplementary material) or any other condition that, in the judgment of the investigator, precludes the use of the intervention. We will collect information about the specific reason;

g. Concomitant use of drugs that are strong inhibitors or strong inducers of P-glycoprotein (P-gp, e.g., systemic azole antimycotics, such as ketoconazole, and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir) and/or Cytochrome P450 3A4 (CYP3A4).

3. Other Factors:

a. Expected requirement for major surgery post-arthroplasty within 90 days;

b. Persons of childbearing potential who are not abstinent or do not use appropriate contraception or are breast-feeding;

c. Patient is unable or unwilling to consent;

d. Previous participation in the HIPSTER trial;

e. Participation in another anticoagulant or antiplatelet study.

2.4 Trial intervention

Intervention Arm: Patients randomized to the intervention will receive rivaroxaban 2.5 mg orally BID and ASA 75-100 mg OD for 90 days, to be started between postoperative day (POD) three and five. The exact dose of ASA will depend on local formulary and clinical practice at each participating site. A maximum of four postoperative days of any anticoagulant (LMWH, UFH, fondaparinux or a DOAC) will be allowed in the meantime.

Control Arm: Patients in the control arm will receive the institution's standard of care for thromboprophylaxis for up to 30 days. While the study team will encourage a 30-day duration to align with guideline recommendations and ensure consistency with the intervention arm, it will not be mandated as there are variations in the duration of postoperative VTE prophylaxis across institutions. Actual practices at each site will be documented and analyzed. The following regimens are provided as guidance only, and actual clinical practices will be recorded and analyzed.

- **Low-molecular-weight heparin (LMWH)**
  - Enoxaparin: 40 mg subcutaneously OD (or 30 mg subcutaneously BID);
  - Dalteparin: 5000 IU subcutaneously OD (or alternative dosing based on institutional protocol);
  - Tinzaparin: 4500 IU subcutaneous OD;
- **Fondaparinux:** 2.5 mg subcutaneously OD; or
- **Direct oral anticoagulant (DOAC):** Rivaroxaban 10 mg OD or apixaban 2.5 mg BID, started after surgery or after a period of LMWH.

2.4.1 People already on ASA:

For people already on ASA at the time of the hip fracture diagnosis, who are eligible for the study, we will suggest holding it preoperatively. In the intervention arm, ASA will be restarted as planned after randomization. In the control arm, if the indication to ASA is confirmed, it can be restarted at physician's discretion.

2.5 Standardization of co-interventions

To minimize the potential for co-interventions and detection bias, we will promote adherence to evidence-based perioperative management in accordance with national and international guidelines, as summarized below. Data on co-interventions will be collected, but non-adherence to these measures will not be considered a protocol violation. Where available, the perioperative and thrombosis services will continue to follow patients as per routine clinical practice. This includes assessment of signs and symptoms of VTE, arterial cardiovascular events, and bleeding. For the duration of the study period, the study team will follow patients. The study team will assume the responsibility for initiating and managing the assigned thromboprophylaxis in the interventional arm. The study team will remain in communication with the treating team.

2.5.1 Preoperative VTE prophylaxis

The American Society of Hematology (ASH) 2019 guidelines and American College of Chest Physicians recommend - Prophylactic UFH or LMWH before surgery. The last dose should be administered at least four hours before the procedure.[7,19]

2.5.2 Intra-operative bleeding prevention

The NICE guideline recommend that all patients should receive 1 g of tranexamic acid intravenously at the beginning of the surgery and 1 g at wound closure.[22,23] Patients with an absolute contraindication to its use will not receive it and the reason will be documented.

2.5.3 Measuring Troponins for Cardiac Risk Assessment

We will suggest measuring troponin (I or T, high-sensitivity or not, as available to the institution) after hip fracture diagnosis (before surgery) and daily after surgery (POD 1 to 3), for the detection of myocardial injury.[24,25]

2.5.4 Postoperative VTE prophylaxis

The American Society of Hematology (ASH) 2019 guidelines recommend that patients should receive daily VTE prophylaxis with LMWH or a DOAC starting ~12-24 hours after the surgery up to randomization.[7] The study team will provide the required prescriptions, medications, and instructions prior to discharge, in consultation with the thrombosis service where available.

2.5.5 Pregnancy test

Pregnancy is an exclusion criterion, and rivaroxaban is contraindicated in pregnancy.[26] Therefore, pregnancy testing will be mandated for all individuals of child-bearing potential, prior to enrollment, unless it has already been performed for clinical reasons as part of standard of care.

2.6 Outcomes

2.6.1 Feasibility outcomes

The primary feasibility outcome will be the recruitment rate. Other feasibility outcomes will be complete 30 and 90 days follow up, treatment adherence. We will also measure the working time

for the research coordinator and research assistant, to obtain a precise estimate of the time commitments for the full-scale trial.

2.6.2 Progression criteria.

We will adopt a traffic light system for our feasibility outcomes: green (go) indicates that the criteria have been met and we should proceed, amber (amend) indicates that some changes should be made to proceed to the larger trial, and red (major amendments or stop) indicates that we should not move forward with the full-scale trial without major amendments.[27] **Table 1** reports the formula for calculating the feasibility outcomes with the thresholds for progression. For recruitment rate, we aim at recruiting two (one) patients per month per site. For the 30 and 90 days follow up, we aim at 95% (85%) of the patients. For treatment adherence we aim at 85% (75%).

2.6.3 Exploratory clinical outcomes

The primary clinical outcome will be a composite of all-cause mortality, MI, non-hemorrhagic stroke, peripheral arterial thrombosis, and symptomatic, objectively confirmed VTE (DVT and/or PE). These outcomes will be monitored from randomization and over the specified follow-up period and will also be analyzed as individual outcomes, with the addition of CV mortality. We will also collect data on the length of stay and on re-hospitalizations, as measures of resource utilization.

2.6.4 Exploratory safety outcomes

The primary safety outcome will be bleeding independently associated with mortality after non-cardiac surgery (BIMS).[28] Secondary safety outcomes will be major bleeding events as defined by the ISTH, clinically relevant nonmajor bleeding, and minor bleeding.[29,30]

The appendix contains detailed outcomes definitions.

Decisions regarding holding or discontinuing (and eventually restarting) either study drug rest with the attending physician and the patient. If a patient experiences a life-threatening or clinically relevant bleed, study personnel will recommend that the patient have their trial medication(s) held until the bleeding is stabilized. If a patient experiences a minor bleed, physicians may continue, temporarily interrupt, or permanently discontinue the trial medication. It is not a requirement, however, that the study medication is stopped for minor bleeding. The study personnel will be available for discussion about the best course of action. Participants will continue to be followed up for outcomes by the study team, unless they choose to withdraw from the study entirely.

2.7 Recruitment

Physicians and nurses working in the orthopedic, thrombosis and perioperative services (as appropriate and applicable for each site) will receive training on the HIPSTER study from the local investigators and study material prepared centrally. Health care providers who are part of the circle of care will identify potential participants, and if the potential participant provides permission to be approached for the study, the study team will be notified to seek informed consent. At sites where allowed by local policies, trained study personnel will also screen patient

charts for potentially eligible patients and approach where appropriate. If an eligible patient is missed, the research staff will discuss with the relevant stakeholders to reduce the potential for this to reoccur. A screening log will be kept as allowed per local institutional practices to document missed patients.

2.8 Participant timeline

The study schedule is reported in **Figure 3**.

Randomization will occur three to five days after surgery and will be timed to allow starting the intervention as soon as possible after allocation. The study personnel will follow patients throughout their hospital stay assessing the participants and reviewing their medical records, ensuring trial orders are followed, and noting any outcome. The study personnel will contact the patients via telephone (or in person, if the patient will not be discharged) 30 and 90 days after randomization and will obtain documentation as appropriate.

2.9 Sample size

For this study, we set the target of enrolling 100 patients as a pragmatic sample size. This will allow us to show a complete 90-day follow-up in 95% of participants with a 95% CI ranging from 89% to 98%. We also calculated possible sample sizes for the full-scale trial. **Table 2** reports the sample size for different scenarios. We used the rate of cardiovascular events reported in the HIP-ATTACK trial: 0.18 overall, 0.30 in the subgroup with myocardial injury. For the effect size, we used the one reported in the COMPASS study, adding a more conservative and a more optimistic estimate. This provides the rationale for only including people with myocardial injury.

2.10 Assignment of the interventions

Participants will be randomized to a control or experimental group with a 1:1 ratio using a computer-generated randomization schedule. The allocation sequence will be generated by a statistician and imported into the web application Research Electronic Data Capture (REDCap), which will function as a web-based randomization system and data collection tool. Participants will be stratified by center and the use of ASA at baseline or at the time of enrolment (yes or no). The stratification will be implemented using permuted blocks of variable size in random order, to ensure allocation concealment. Randomization will occur after a patient is deemed eligible and provides informed consent.

2.11 Blinding

The care providers, on-site study personnel, and participants will not be blinded to the treatment allocation, the outcome adjudicators will be.

2.12 Data collection and management

All data collection and management will be performed in accordance with International Council for Harmonisation - Good Clinical Practice (ICH-GCP) and applicable local privacy and personal health information protection regulations to maintain patient confidentiality and privacy. Each patient will be assigned a unique study ID and no direct patient identifiers will be collected as part of the study data. No patients will be recruited before institutional approval is obtained.

The study personnel at participating sites will input the data into online CRFs through REDCap. REDCap is a browser-based, meta-driven electronic data capture (EDC) software and workflow methodology for designing clinical research databases. REDCap can be installed in a variety of

environments for compliance with standards such as Health Insurance Portability and Accountability Act (HIPAA) and FDA 21 CFR Part 11. Within REDCap, user privileges are utilized to maintain data integrity and confidentiality (e.g. each user has an individual account with unique username and password; a site research coordinator will only be able to access data from their site). REDCap implements authentication to validate the identity of end-users that log in to the system, as well as an auto-logout feature after a period of inactivity. REDCap has a built-in audit trail that automatically logs all user activity and logs all pages viewed by every user. The Computer Services Unit at McMaster University has the appropriate license agreement and is password protected on a secure site and on a separate server. Any hard copy documents will be stored in a locked, secure location at each site with access restricted to the study team only.

2.13 Statistical analysis

Baseline patient characteristics will be reported using means and standard deviations or medians and ranges as appropriate for continuous variables, and percentages with 95% CI for dichotomous and categorical variables. Feasibility and clinical outcomes will be reported using percentages with 95% CI. We will not look at clinical outcomes by group, as data from this feasibility study will be included in the analysis of a later full-scale multicenter study if its design will not change.

2.14 Monitoring

Both rivaroxaban and ASA are approved for prevention of arterial and venous thrombosis and have been extensively used, and the combination of low dose rivaroxaban and ASA is approved for prevention of arterial thrombosis. The overall adverse profiles of each agent and in

combination have been well described in broad populations, with the most common side effect being bleeding. Given the approved status and known risk profiles of rivaroxaban and ASA as well as the small sample size of this pilot study, we are not planning to set up a data monitoring committee, nor to implement formal interim analyses. However, at 50% recruitment, we will ask a person with expertise in cardiovascular medicine and clinical trials to review the event rates. This person will be independent of the study team. If there is a safety concern, the study will be paused and the protocol will be reconsidered. If there is no major concern, the study investigators will remain blinded.

2.14.1 Documenting and Reporting of Adverse Events

An Adverse Event (AE), as defined by GCP, is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease having been absent at baseline, or, if present at baseline, appears to worsen and is temporally associated with medical treatment or procedure, regardless of the attribution (i.e., relationship of event to medical treatment or procedure). Because of the extensive safety data available on ASA, rivaroxaban, and their combination, AE collection in HIPSTER pilot is limited to changes in health status that require permanent drug discontinuation. This ensures that only those events the investigator thinks are related to the study medication are considered an adverse event. These AEs will be collected during the whole treatment period, and will be followed to resolution or stabilization. Data on AEs will be collected during the hospital stay and at the follow-up assessments. Moreover, study participants will be able to report AEs by contacting their local study team or the coordinating center.

A serious adverse event (SAE) is classified as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, is a congenital anomaly / birth defect and/or is another medically important serious event representing a significant hazard, which is comparable to the aforementioned criteria.

All unexpected and related or possibly related SAEs will be reported by the site PI to their local REB within **7** business days of awareness. The sponsor will report these SAEs to HiREB within **15** business days of awareness if they require a change to the research and/or informed consent form and/or requires immediate notification to participants for safety reasons. Follow-up reports will be submitted as required.

2.14.2 Protocol-specific exceptions to expedited SAE reporting

For the purpose of this trial, expected events will be captured on the CRFs as study outcome events only and will be exempted from the expedited reporting but will be included in the final study report. This includes:

- Primary or secondary efficacy outcomes for the full trial:
    - Overall mortality
    - Cardiovascular mortality
    - All thrombosis or thromboembolism (arterial and venous)
    - Hospitalization
- Safety outcomes:
    - Bleeding events

- Expected Events: Events that are expected to occur in high frequency in the population under study, including:
    - Planned hospitalization (e.g., surgery, rehabilitation, respite care)
    - Conditions e.g., chronic obstructive pulmonary disease, hypertension, diabetes and trauma

The sponsor will report all serious unexpected adverse drug reactions (SUADRs) to the regulatory authorities and REB. If the SUADR is neither fatal nor life-threatening, the sponsor will report the SUADR to Health Canada within **15** calendar days of awareness. If the SUADR is fatal or life-threatening, Health Canada will be advised within **7** calendar days of awareness. Follow-up reports will be submitted as required. In addition, as required by ICH-GCP, the sponsor will expedite reporting of all SUADRs to all concerned institutions and REBs.

2.14.3 Audits and Inspections

Authorized representatives of a regulatory authority and/or an REB may visit the sites to perform audits or inspections, including source data verification. The medical records of participating study subjects are considered confidential and disclosure to third parties other than those noted is prohibited. The ethics-approved informed consent form will clearly indicate
that the subject's medical records will be inspected by said parties, and permission for such review and use of personal information is a requirement for study participation.

2.15 Ethics

Research personnel will approach all eligible patients to obtain informed consent. In accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – TCPS 2

(2022), if the patient is legally competent but not competent to provide informed consent, we will inform and obtain consent from a family member. In case of legal incompetence, we will inform and obtain consent from the patient's authorized representative.

Study participants will have the possibility to withdraw from the study at any time they decide to do so, contacting their local study team or the coordinating center. They will have the possibility to withdraw from treatment but continue the follow-up, or to also stop the follow-up. They will decide if they want the study team to also delete the data already collected (right to be forgotten). These participants will not be replaced.

2.16 Record retention

The PI will retain and maintain all documentation relating to the study for a period of 15 years as per C.05.012 (4) of the Food and Drug Regulations (FDR). Any additional applicable regulatory requirements in other relevant jurisdictions will also be adhered to.

3. Trial registration

The trial will be registered on ClinicalTrials.gov.

4. Funding

This project received funding from the Canadian Venous Thromboembolism Research Network (CanVECTOR) pilot trial competition.

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Tables

Table 1:calculation and progression criteria for the feasibility outcomes.

Outcome	Calculation	No modifications	Minor modifications	Major modifications
Recruitment rate	(n of participants recruited)/month/site	≥ 2/month	1-2/month	<1/month
Screening to enrollment ratio	(n of eligible participants)/(n enrolled)	NA	NA	NA
30 days FUP	(n of participants with complete follow-up data)/(n of enrolled participants)	≥ 95%	95-85%	< 85%
90 days FUP		≥ 95%	95-85%	< 85%
Treatment adherence	(n of pills/syringes prescribed – n of pills/syringes administered*)/(n of pills/syringes prescribed)	≥ 85%	85-75%	< 75%

FUP: follow-up, NA: not applicable.
*Based on hospital records for the inpatient period and on patient-reported for the period after discharge.

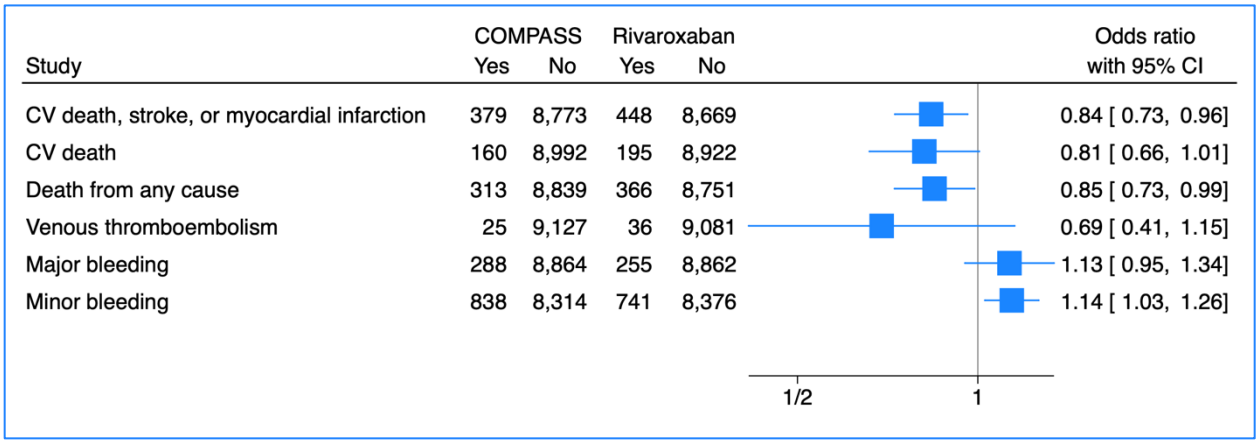
Table 2: effect size for the full-scale trial, for different event rates and effect sizes.

Control event rate	Effect size (HR)	Sample size
0.30	0.70	1215
	0.75	1826
	0.80	2967
0.25	0.70	1409
	0.75	2115
	0.80	3434
0.18	0.70	1860
	0.75	2789
	0.80	4524

Based on the composite outcome measured in the HIP-ATTACK study: all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, and non-fatal congestive heart failure. 0.30 was the event rate in people with baseline troponin elevation, 0.18 was the event rate in unselected patients with a baseline troponin measurement.
HR: hazard ratio
Power set at 0.80.

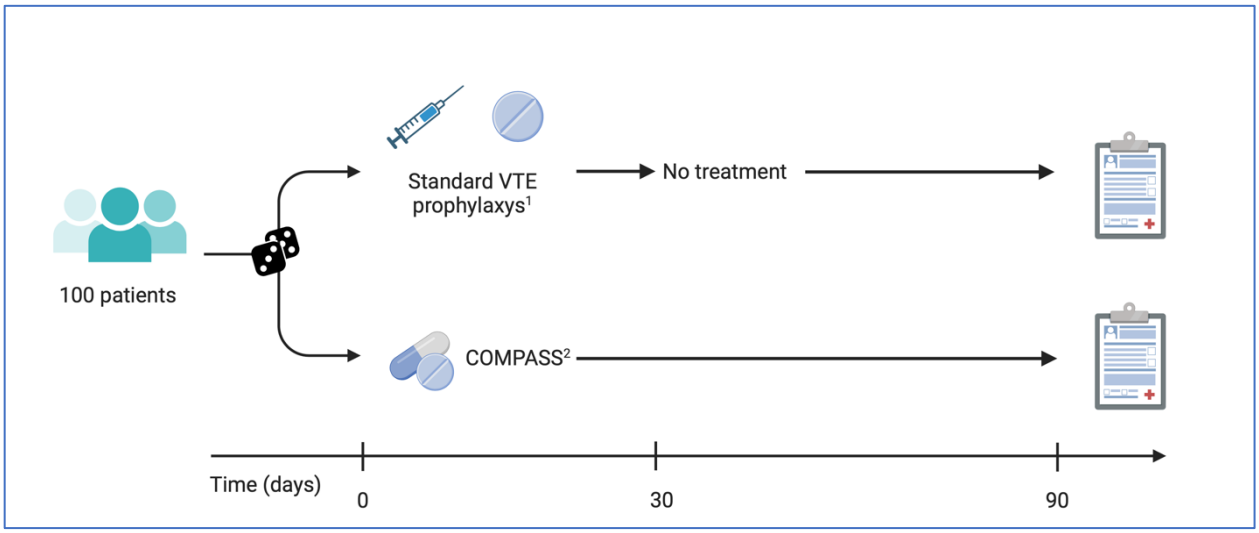
Figures

Figure 1: comparison of rivaroxaban 2.5 mg BID + ASA 100 mg OD with rivaroxaban 5 mg BID, data from the COMPASS trial



CI: confidence interval; CV: cardiovascular.

Figure 2: HIPSTER Pilot design



[1]With low-molecular weight heparin (LMWH) or a direct oral anticoagulant (DOAC)
[2]ASA 75-100 mg once daily + Rivaroxaban 2.5 mg twice daily
Figure created with BioRender.com, dice by Marie Van den Broeck from Noun Project

Figure 3: study schedule.

	STUDY PERIOD							
		Enrolment	Allocation[1]	Post-allocation				Close-out
TIMEPOINT**	PreOD -1 to POD3	POD 3-5		POD 3-5	*POD 30*		*POD 90*	t_x[2]
ENROLMENT:								
Eligibility screen		X						
Troponin measurement[3]	X	X						
Informed consent		X						
2 gr Tranexamic acid IV[4]	X							
Allocation			X					
INTERVENTIONS:								
Rivaroxaban 2.5 mg BID + ASA 75-100 mg daily				♦—	—		—♦	
Standard of Care[5]				♦—	—♦			
ASSESSMENTS:								
List baseline variables		X						
Feasibility outcomes		X	X	X	X		X	X
Efficacy outcomes				X	X		X	
Safety outcomes				X	X		X	

ASA: acetylsalicylic acid, BID: bis in die; POD: post operative day; PreOD: preoperative day.

[1] As close as possible to the start of the intervention.

[2] tx: 90 days after the enrolment of the last participant.

[3] At diagnosis and daily on POD 1-3

[4] 1 g of tranexamic acid intravenously at the beginning of the surgery and 1 g at wound closure

[5] Standard of Care for Thromboprophylaxis: Includes low molecular weight heparin (e.g., enoxaparin 40mg daily/30mg BID, dalteparin 5000 IU daily, tinzaparin 4500 IU daily), fondaparinux 2.5 mg daily, or direct oral anticoagulants (rivaroxaban 10 mg or Apixaban 2.5 mg BID) post-surgery or following low molecular weight heparin.