Rationale and Design of the Rivaroxaban Post-Transradial Access for the Prevention of Radial Artery Occlusion Trial (CAPITAL-RAPTOR)

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ABSTRACT

Introduction Transradial access (TRA) has rapidly emerged as the preferred vascular access site for coronary angiography and percutaneous coronary intervention. Radial artery occlusion (RAO) remains an important complication of TRA as it precludes future ipsilateral transradial procedures. While intraprocedural anticoagulation has been studied extensively, the definitive role of postprocedural anticoagulation has not yet been established.

Methods and analysis The Rivaroxaban Post-Transradial Access for the Prevention of Radial Artery Occlusion trial is a multicentre, prospective, randomised, open-label, blinded-endpoint design study investigating the efficacy and safety of rivaroxaban to reduce the incidence of RAO. Eligible patients will undergo randomisation to receive either rivaroxaban 15 mg once daily for 7 days or to no additional postprocedural anticoagulation. Doppler ultrasound to assess radial artery patency will be performed at 30 days.

Ethics and dissemination The study protocol has been approved by the Ottawa Health Science Network Ethics Board (approval number 2018S0319-01H). The study results will be disseminated via conference presentations and peer-reviewed publications.

Trial registration number NCT03630055.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be the largest randomised trial to date assessing postprocedure anticoagulation in patients undergoing transradial access and should provide a definitive answer to this question.

⇒ If proven safe and efficacious, rivaroxaban may impact millions of patients worldwide undergoing coronary angiography and percutaneous coronary intervention.

⇒ A potential limitation of this study is the absence of a placebo arm, which may overestimate self-reported bleeding events in the treatment group.

INTRODUCTION

Transradial access (TRA) has rapidly emerged as the preferred vascular access site for coronary angiography (CA) and percutaneous coronary intervention (PCI).1 Advantages of TRA include rapid haemostasis, early ambulation after the intervention (PCI).1 Advantages of TRA include rapid haemostasis, early ambulation after the intervention (PCI). Advantages of TRA include rapid haemostasis, early ambulation after the intervention (PCI). TRA over TFA in patients presenting with an acute coronary syndrome.5 However, radial artery occlusion (RAO) remains an important complication of TRA as it precludes future ipsilateral transradial procedures, utilisation of the vessel as a conduit for coronary artery bypass grafting (CABG) or for the creation of an arteriovenous fistula in patients requiring haemodialysis.6,7

Reports of RAO following TRA varies between 1% and 10% in observational and randomised trials.8–18 In the largest systematic review published to date, the overall rate of RAO was 5.2% among the 46631 subjects across 92 studies between 1989 and 2016.6 This study also noted that the rate of early RAO (ie, within 7 days) was significantly higher than late RAO (ie, after 7 days) which is suggestive of late recanalisation in some patients. The factors which affect recanalisation are not clear; however, current standard of care to reduce RAO involves administration of intraprocedural unfractionated anticoagulation and postprocedural patent haemostasis.7
Numerous trials have explored the role of intraprocedural anticoagulation during angiography to reduce RAO. A recent meta-analysis demonstrated high-dose unfractionated heparin (UFH) is associated with less incidence of RAO compared with low-dose UFH. Additionally, there were higher rates of RAO with diagnostic CA compared with PCI purportedly as the latter involves higher doses of anticoagulation. Two randomised trials including the Short-Term Postoperative Use of Rivaroxaban to Prevent Radial Artery Occlusion After Transradial Coronary Procedure (RESTORE) and the Prevention of Radial Artery Occlusion With Rivaroxaban After Transradial Coronary Procedures (RIVARAD) trials examined short-term anticoagulation with rivaroxaban in patients following TRA and observed trends towards reduced rates of RAO with use of anticoagulation. Here, we describe the rationale and design of the randomised Rivaroxaban Post-Transradial Access for the Prevention of Radial Artery Occlusion Trial (CAPITAL-RAPTOR)—the largest proposed study evaluating postprocedural anticoagulation following TRA.

METHODS AND ANALYSIS

Trial design and methods

The CAPITAL-RAPTOR trial is a multicentre, international, prospective, randomised, open-label, blinded-endpoint (PROBE) design study investigating the efficacy and safety of rivaroxaban to reduce the incidence of RAO. There are three participating study sites—the University of Ottawa Heart Institute in Ottawa, Canada, Kingston Health Sciences Centre in Kingston, Canada and Mayo Clinic in Rochester, Minnesota, USA. All study sites have received local ethics board approvals prior to any participant enrolment. While the recruitment period was initially planned to be completed by 2023, the COVID-19 pandemic resulted in slower recruitment than had been anticipated. As such, the study continues recruitment and is anticipated to be completed by 2025. Patients who have undergone CA or PCI via TRA will be screened for eligibility using predefined inclusion and exclusion criteria (Box 1). Patients who are eligible and agree to participate will provide written informed consent. All participants will receive the same intraprocedural standard of care which currently involves administration of 3000–5000 international units (IU) of UFH during CA and patent haemostasis following the procedure.

All patients will undergo patent haemostasis on arrival to the postprocedure recovery unit. A pulse oximeter will be placed on the participant’s index finger, followed by manual compression of both the radial and ulnar arteries simultaneously. Once the plethysmography waveform is flat, the pressure over the radial artery will be released and the plethysmography will be observed to ensure a waveform is present. If there is no waveform, 1 mL of air will be removed from the postprocedure band at a time until a waveform appears. After 120 min, half the volume from the compressive device will be removed while assessing for bleeding. If no bleeding is seen after 15 min, the remained of the air from the compressive device will be removed.

Randomisation and study procedures

Randomisation will take place following completion of the postprocedure patent haemostasis period to ensure only patients without concerns regarding haemostoma or bleeding complications are enrolled. Eligible patients will undergo randomisation in a 1:1 fashion using a centralised, computer-generated sequence to receive either rivaroxaban 15 mg once daily for 7 days or to no additional postprocedural anticoagulation (figure 1). Stratification will be performed by study site only. The stratified randomisation will be generated using varying block sizes to make the sequence difficult to predict without leading to

Box 1 Eligibility Criteria for the Rivaroxaban Post-Transradial Access for the Prevention of Radial Artery Occlusion trial

Inclusion criteria

Willing and able to provide written informed consent.
Age ≥18 years old.
Diagnostic coronary angiography or percutaneous coronary intervention via the transradial approach.

Exclusion criteria

Presence of a palpable haematoma or clinical concern of haemostasis at the transradial access site.
Unsuccessful or abandoned attempt at a secondary arterial access site.
Planned staged procedure, coronary artery bypass grafting or non-cardiac surgery within 30 days.
Contraindication or high risk of bleeding with anticoagulation, including any of the following:
1. Any bleeding requiring medical attention in the previous 6 months.
2. Thrombocytopenia with platelets <50×10^9/L.
3. Any prior intracranial haemorrhage.
4. Use of glycoprotein IIb/IIIa inhibitor during percutaneous coronary intervention.
5. Administration of thrombolytic therapy in the preceding 24 hours.
7. Ischaemic stroke or transient ischaemic attack diagnosed in the last 3 months.
Cardiogenic shock.
Ventricular arrhythmias refractory to treatment.
Liver dysfunction (Child-Pugh class B or C).
Unexplained anaemia with a haemoglobin less than 100 g/L.
History of medication non-compliance or risk factor for non-compliance.
Active malignancy.
Another indication for anticoagulation therapy.
CYP3A4 and P-glycoprotein inhibitor use.
Life expectancy <30 days.
Female capable of pregnancy not on birth control.
Chronic kidney disease with creatinine clearance of less than 30 mL/min.
History of antiphospholipid syndrome, in particular triple positive (lupus anticoagulant, anticardiolipin antibodies and anti-beta 2-glycoprotein I antibodies).
a major imbalance in numbers between treatment groups if a block is incomplete at the end of recruitment.

Study participants will be seen in follow-up at 30 days where assessment of RAO will be performed using Doppler ultrasound by a trained study member. During the assessment, the accessed radial artery will be visualised and measured in both short and long axis views. Maximum lumen diameter, intimal thickness and colour Doppler will be measured at 1 cm proximal to the styloid process of the radius. RAO will be adjudicated in a blinded fashion by core laboratory and defined as an absence of documented Doppler flow in the radial artery. In addition to static testing, methods that employ dynamic assessment of Doppler signals during radial artery assessment have been described; thus we will use the most extreme case (ie, absence of flow) as our standard.

Study intervention

Participants in the treatment arm will receive rivaroxaban 15 mg daily for 7 days (figure 1). The dose of rivaroxaban was selected based on numerous factors, including the inclusion of post-PCI patients who will require dual-antiplatelet therapy. Reduced dose rivaroxaban at 15 mg daily has demonstrated safety in conjunction with antiplatelet therapy and remains guideline recommended for post-PCI patients with atrial fibrillation. Additionally, reduced dose rivaroxaban is recommended for atrial fibrillation patients with creatinine clearance 30–60 mL/min thereby permitting the inclusion of patients with moderate renal dysfunction. As such, it was determined by the trial steering committee that rivaroxaban 15 mg daily would provide the optimal balance between efficacy and safety while permitting maximal generalisability of the study results to patients who undergo CA and PCI.

The 7-day treatment course was selected as peak RAO rates are observed at 7 days suggesting the optimal period for intervention may occur in this time period. Doppler ultrasound will be performed at 30 days to avoid capturing early RAO which may resolve as late recanalisation may be observed in some patients.

Data collection

Baseline demographics of the study participants will include age, sex, height and weight. The participant’s ethnicity will be collected voluntarily. Medical history regarding cardiovascular risk factors, previous myocardial infarction, previous PCI, previous CABG surgery or previous stroke/transient ischaemic attack will also be collected. Renal function will be collected based on the study participant’s preprocedure serum creatinine. Additionally, the participant’s baseline medications including use of common cardiovascular medications, antiplatelets and nitrates will be gathered. Procedural details will include type of procedure (eg, CA or PCI), maximal sheath diameter, maximal catheter size and dose of intraprocedural UFH administration will also be collected.

Endpoints

The CAPITAL-RAPTOR has two primary endpoints. The primary efficacy outcome is the incidence of RAO at 30 days post-TRA as determined by Doppler ultrasound assessment. The primary safety outcome is the International Society on Thrombosis and Haemostasis definition of major bleeding, which includes fatal bleeding; symptomatic bleeding in a critical area or organ such as intracranial, spinal, ocular, retroperitoneal, pericardial or intraarticular, or intramuscular with compartment syndrome; and/or bleeding causing a fall in haemoglobin.

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Figure 1 Flow of patient screening and enrolment. ISTH, International Society on Thrombosis and Haemostasis.
level of ≥2 g/L or transfusion of ≥2 units of packed red blood cells in a 48-hour period.

In addition, there are several secondary 30-day outcomes in the trial:
1. All-cause mortality.
2. Stroke (ischaemic or uncertain).
5. Symptomatic bleeding in a critical area or organ.
6. Bleeding requiring medical attention.
7. Global Utilization Of Streptokinase And TPA For Occluded Arteries (GUSTO) bleeding criteria.
8. Thrombolysis In Myocardial Infarction (TIMI) bleeding criteria.
10. Myocardial infarction.
11. Stent thrombosis as defined by the Academic Research Consortium criteria.

All outcomes will be adjudicated by a centralised adjudication committee which will be blinded to treatment assignment.

Sample size and data analysis
Using a modified Delphi process, the minimal clinically important difference (MCID) for the reduction of RAO was identified as a 50% relative risk reduction. Specifically, a 2-round process was used whereby 10 experts including interventional cardiologists, general cardiologists and internists were asked a series of survey questions regarding TRA best practices and to determine what each expert felt was the minimal clinically important difference. Using the information obtained in the first round, a second questionnaire was distributed with prespecified MCID values, and the experts were asked to select only one value which corresponded to what they felt was the most appropriate. The MCID value selected by at least 80% of respondents after the second round was determined to represent the MCID of our research question. Using an estimated RAO occurrence rate of 5.2% (the event rate reported in the most comprehensive meta-analysis to date), a power of 0.80 with an alpha of 0.05 and assuming a 5% lost to follow-up, a total of 913 participants per study arm for a grand total of 1826 participants will need to be recruited.

The statistical analysis plan will be reviewed by trial investigators and finalised prior to unblinding of the study data. In brief, the analysis of the primary efficacy and safety outcomes will be based on the intention-to-treat principle. A χ² test will be used for the primary efficacy and safety analyses. We will use multiple imputation for patients lost to follow-up. A planned interim analysis using O’Brien-Fleming bounds for efficacy will be undertaken at 50% participant recruitment. A critical value of 2.782 corresponding to p=0.0054 will be considered significant at the interim analysis. A final analysis will be performed at study completion with a critical value of 1.967 corresponding to p=0.0492 for significance.

Prespecified subgroup analysis will also be carried out based on criteria below:
1. Type of procedure (CA or PCI).
2. Sex.
3. Age group <65, 65–75 years and >75 years.
4. Weight >70 kg.
5. Estimated glomerular filtration rate <50 mL/min.
8. Type of coronary disease (acute coronary syndrome or stable coronary artery disease).

Patient and public involvement
No patients or members of the public were involved in study design or conduct.

Current state of the trial
Enrolment commenced in October 2018 but was paused in March 2020 due to the COVID-19 pandemic. Recruitment resumed in July 2021 and at time of the publication of this study protocol, over 600 participants have been recruited at participating study sites.

Ethics and dissemination
The study protocol has been approved by the Ottawa Health Science Network Research Ethics Board (approval number 20180319-01H), and will be conducted in accordance with the Good Clinical Practice standards specified in the Declaration of Helsinki. Informed consent will be obtained from all participants prior to enrolment. Study results will be disseminated via publication in a peer-reviewed medical journal and conference presentations. Data sharing statement can be found in online supplemental material.

DISCUSSION
RAO is the most common complication after TRA, with an estimated incidence of approximately 5%. While most RAOs are asymptomatic, they remain an important complication of TRA as it precludes future use of the ipsilateral radial artery for repeat CA or PCI, as a conduit for CABG or for arteriovenous fistula formation in patients requiring haemodialysis. The CAPITAL-RAPTOR study aims to evaluate the efficacy and safety of short-term rivaroxaban in preventing RAO following TRA.

While the pathophysiology of RAO is complex and multifactorial, TRA results in structural changes to the radial artery. Yonetsu et al examined 69 patients immediately post-TRA with optical coherence tomography and demonstrated 67% of radial arteries had intimal tears and 36% had medial dissections. The primary mechanism of early RAO after TRA is purported to be a combination of catheter-induced endothelial damage, resultant local hypercoagulable state and reduced blood flow from compressive haemostasis. The process of sheath insertion and instrumentation during TRA causes repeated...
endothelial damage, leading to vessel remodelling and thrombosis. This phenomenon is supported by Sakai et al, who demonstrated the rate of successful radial access decreases with successive procedures in patients who underwent repeat transradial catheterisation. There were many studies that evaluated the risk factors and predictors of RAO. Baseline characteristics such as age, female, low body mass index, diabetes and previous radial artery access are associated with higher RAO rate.\(^\text{28-29}\) Procedural risk factors for RAO include repeated unsuccessful puncture attempt, larger sheath size, absence of pretreatment aspirin and lack of periprocedural intravascular coagulation.\(^\text{30-32}\) Postprocedural variables that are associated with an increased risk of RAO include non-patent haemostasis\(^\text{10,33}\) and longer duration of compressive haemostasis.\(^\text{34}\)

Direct oral anticoagulant (DOAC) therapy has emerged as the preferred oral anticoagulation over vitamin K antagonists due to its comparable efficacy and better safety profile. The use of DOACs in cardiovascular medicine includes stroke prevention in atrial fibrillation\(^\text{18,35-39}\) and venous thromboembolism.\(^\text{40-43}\) Recently, low-dose rivaroxaban in combination with aspirin has been shown to reduce cardiovascular outcomes compared with aspirin alone among patients with stable cardiovascular disease.\(^\text{44}\) Given emerging evidence suggestive of late RAO recanalisation\(^\text{6}\) and higher-dose intraprocedural anticoagulation in preventing RAO,\(^\text{11}\) we hypothesised that a 7-day postprocedure course of rivaroxaban will reduce the incidence of RAO at 30 days following TRA. Certainly, the use of an anticoagulant may result in increased rates of bleeding, particularly in patients who are post-PCI and on dual-antiplatelet therapy. However, given the relatively short course of anticoagulation (ie, 7 days) and based on the better safety profile of DOACs, a significant increase in the rate of clinically significant bleeding is not expected.

Recent studies have begun to examine the role of postprocedural anticoagulation in reducing RAO post TRA. The Short-Term Postoperative Use of Rivaroxaban to Prevent Radial Artery Occlusion After Transradial Coronary Procedure (RESTORE) trial randomised a population of 382 patients to receive rivaroxaban at a dose of 10mg daily or placebo for 7 days following TRA, and observed no difference in the primary outcome of 24-hour RAO, however 1-month RAO was significantly reduced in the group that received rivaroxaban.\(^\text{13}\) The Prevention of Radial Artery Occlusion With Rivaroxaban After Transradial Coronary Procedures (RIVARAD) trial randomised 521 patients to rivaroxaban 10mg daily versus placebo and observed significant reduction in 1-month RAO with anticoagulation.\(^\text{14}\) Our trial will use a unique dosing regimen of rivaroxaban in conjunction with standard of care practices including patent haemostasis and intraprocedural anticoagulation. Finally, as the largest study to date, RAPTOR will be the only study adequately powered to determine the definitive role of postprocedural anticoagulation following TRA.

**Implication**
To our knowledge, the CAPITAL-RAPTOR trial is the largest study to date evaluating the impact of a short-course of postprocedural oral anticoagulation on the incidence of RAO after TRA. Preservation of the radial artery for future medical uses has implications for future cardiac interventions and ongoing medical care with an increasing unmet clinical need as more patients benefit from TRA. If proven safe and efficacious in the CAPITAL-RAPTOR study, rivaroxaban may impact millions of patients worldwide who undergo CA and PCI.

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**Contributors** PDS, OA-R, RJ, SP, TS and BH: writing, editing and revision of present manuscript. PDS, OA-R, RJ, SP, JB, DAF, DC, KK, JA, GAW, TS and BH: critical trial design and statistical analysis plan, assistance with writing analysis section of present manuscript. PDS, OA-R, RJ, SP, AP, BM, LP, HF, JW, CYG, KS, MF, ML, TS and BH: assistance with conduct of the trial. All authors contributed to the refinement of the study methods and critical revision of the manuscript. All authors read and approved the final version of the manuscript.

**Funding** This study is funded in part by the CCS-Bayer Cardiovascular Research Award.

**Disclaimer** The authors are solely responsible for the drafting and editing of the paper.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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Radial versus femoral access


