ACCESS SITE IN CORONARY ANGIOGRAPHY AND PERCUTANEOUS CORONARY INTERVENTION

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fulfillment of the requirements for the Doctorate of Philosophy

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DEDICATION

This thesis is dedicated to my wife, Assuntina, and our children, Carlos, Anita, and Angelina, who made this work possible.

ABSTRACT

Coronary angiography and percutaneous coronary intervention (PCI) are cornerstone procedures in the diagnosis and management of coronary artery disease, traditionally performed via transfemoral access (TFA). Over the past two decades, transradial access (TRA) has emerged as an alternative approach, supported by evidence demonstrating reduction in bleeding, vascular access complications, and even mortality, particularly in patients with acute coronary syndromes. Despite widespread adoption, important gaps remain regarding the comparative safety, assessment and management of complications, and cost effectiveness of TRA vs TFA across diverse clinical settings.

This Doctorate in Philosophy thesis evaluates vascular access strategies for coronary angiography and PCI through a comprehensive program of epidemiologic research integrating a systematic review and meta-analysis, observational studies, a prospective diagnostic evaluation study, economic modeling, and randomized clinical trial development. First, a systematic review and meta-analysis synthesizes randomized evidence comparing TRA and TFA in patients undergoing PCI for ST-elevation myocardial infarction, with a focus on short term mortality. Second, a large retrospective cohort study examines the incidence and predictors of catheter-induced coronary artery dissection (a rare but potentially catastrophic complication) by comparing TRA and TFA in a real-world practice. Third, a prospective cohort study evaluates the diagnostic accuracy of bedside point-of-care ultrasound for detecting access site complications which addresses an important gap in post-procedural management of patients. Fourth, a cost effectiveness analysis assesses TRA versus TFA in acute myocardial infarction from the perspective of the Canadian publicly funded healthcare system by incorporating clinical

outcomes, cost, and quality-adjusted life-years. Finally, the thesis includes the design and statistical analysis plan of a multicentre randomized clinical trial evaluating post-procedural anticoagulation for the prevention of radial artery occlusion (i.e. the most common complication following TRA).

Collectively, this thesis applies rigorous epidemiological and health economic methods to evaluate clinically relevant questions in interventional cardiology thereby generating evidence to inform procedural practice, optimize patient outcomes, and guide future clinical trials and health system decision making.

EXECUTIVE SUMMARY

Coronary angiography and percutaneous coronary intervention (PCI) are foundational diagnostic and therapeutic procedures in contemporary cardiovascular medicine. While these procedures are routinely performed via either transfemoral access (TFA) or transradial access (TRA), the choice of access site has important implications for patient safety, procedural complications, health system resource utilization, and vascular outcomes. Over the past two decades, TRA has emerged as the preferred access strategy in many clinical settings, driven by evidence demonstrating reductions in bleeding and vascular complications. However, the broader safety profile, downstream consequences, and system-level implications of access site selection have remained incompletely characterized.

This thesis examines the clinical, procedural, and health system consequences of access site selection for coronary angiography and PCI, with the overarching aim of generating rigorous evidence to inform practice, policy, and future research. To address this aim, five interrelated research questions were explored:

1. Does TRA improve short term mortality and safety outcomes compared with TFA in patients with ST-elevation myocardial infarction (STEMI)?
2. Is the risk of rare but catastrophic complications, specifically catheter-induced coronary artery dissection, influenced by access site?
3. Can point-of-care ultrasound improve the detection of clinically important vascular access complications following invasive cardiac procedures?

4. Is TRA a cost-effective strategy compared with TFA within a publicly funded Canadian healthcare system?
5. Can post-procedural oral anticoagulation reduce the incidence of radial artery occlusion (i.e. the most common complication of TRA)?

To answer these questions, this thesis comprises a series of complementary studies employing a systematic review and meta-analysis, large retrospective cohort analysis, prospective diagnostic accuracy study, decision analytic cost effectiveness modeling, and the design of a randomized clinical trial.

First, a systematic review meta-analysis of randomized clinical trials was conducted to evaluate 30-day all cause mortality and major complications in patients with STEMI undergoing PCI via TRA versus TFA. This analysis synthesized evidence from over 11,000 patients and demonstrated that TRA is associated with a significant reduction in short term mortality, major bleeding, and vascular access complications without an increase in ischemic events. These findings strengthen the guideline recommendations for a “radial-first” strategy in STEMI and addresses persistent concerns regarding the generalizability of prior data.

Second, a large retrospective cohort study spanning more than a decade of coronary angiography was performed to evaluate the association between access site and catheter-induced coronary artery dissection. This rare complication, which is associated with high procedural mortality, has been hypothesized to occur more frequently with TRA due to anatomic and mechanical factors. This analysis demonstrated that access site was not independently associated with an increased

risk of dissection in contemporary practice thereby providing important reassurance regarding the safety of TRA as its adoption as the preferred access site increases.

Third, recognizing that access site complications remain a major source of morbidity following invasive cardiac procedures, a prospective diagnostic accuracy study evaluated the use of point-of-care ultrasound (POCUS) as an adjunct to the physical examination for detecting vascular access complications. This study demonstrated that bedside ultrasound significantly improves diagnostic accuracy for detecting pseudoaneurysms compared with physical examination alone. The results of this study support the integration of POCUS into routine post-procedural assessment and highlight its potential to reduce patient care delays, unnecessary imaging, and healthcare costs.

Fourth, a decision analytic cost effectiveness analysis was conducted to evaluate TRA versus TFA from the perspective of the Canadian publicly funded health care system. Incorporating clinical event probabilities, health utilities, and Canadian cost data, this analysis demonstrated that TRA is economically dominant, yielding similar quality adjusted life years at lower overall costs. These findings underscore the system-level value of a “radial first” strategy, particularly when applied across the large number of patients undergoing coronary angiography annually.

Finally, this thesis includes the design and rationale of a multicentre randomized clinical trial evaluating post-procedural anticoagulation with rivaroxaban for the prevention of radial artery occlusion (RAO) following TRA. RAO is often clinically silent however, it has important implications for future vascular access, surgical conduit availability, and dialysis access. This

trial addresses a critical knowledge gap by testing a biologically plausible and scalable intervention aimed at mitigating the most common complication of TRA.

Collectively, the studies in this thesis provide a comprehensive and methodologically rigorous evaluation of arterial access site selection in coronary angiography and PCI. By examining outcomes ranging from mortality and rare catastrophic complications to economic implications and long-term vascular access preservation, this work advances understanding beyond traditional endpoints. The findings support the safety, efficacy, and value of TRA while identifying strategies to optimize its implementation and mitigate its limitations. This body of work informs clinical practice, strengthens clinical guideline recommendations, and establishes a foundation for future research aimed at improving procedural safety and patient-centred outcomes in interventional cardiology.

CONTRIBUTION OF THE AUTHORS

Five manuscripts were prepared as part of this thesis (presented in Chapters 3–7), all of which have been published or submitted for publication.

All manuscripts were conceived, implemented, and conducted under the leadership of Pietro Di Santo and were co-authored by at least one supervisor (George A. Wells or Benjamin Hibbert) and members of the thesis advisory committee (Doug Coyle, Dean Fergusson, Kwadwo Kyeremanteng). Pietro is first author on all publications, having been responsible for study design, data collection, analysis, and writing of the manuscripts. All studies were designed in consultation and discussion with members of the thesis advisor committee.

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TABLE OF CONTENTS

LIST OF TABLES

Chapter 3

Section 3.6

Section 3.8

Chapter 4

Section 4.6

Section 4.7

Chapter 5

Section 5.6

Section 5.7

Chapter 6

Section 6.5

Chapter 7

Section 7.6

LIST OF FIGURES

Chapter 3

Section 3.6

Chapter 4

Section 4.6

Chapter 5

Section 5.6

Chapter 6

Section 6.5

Chapter 7

Section 7.6

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ACS – acute coronary syndrome

AMI – acute myocardial infarction

BARC – Bleeding Academic Research Consortium

CABG – coronary artery bypass grafting

CCS – Canadian Cardiovascular Society

CI – confidence interval

CICAD – catheter-induced coronary artery dissection

CKD – chronic kidney disease

ESC – European Society of Cardiology

GPI – glycoprotein IIb/IIIa inhibitor

HORIZONS-AMI – Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction

IVUS – intravascular ultrasound

MI – myocardial infarction

NHLBI – National Heart, Lung, and Blood Institute

PCI – percutaneous coronary intervention

POCUS – point-of-care ultrasound

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QALY – quality adjusted life-year

RAO – radial artery occlusion

RCT – randomized clinical trial

RR – risk ratio/relative risk

RRA – right radial artery

SAP – statistical analysis plan

STEMI – ST-elevation myocardial infarction

TFA – transfemoral access

TIMI – Thrombolysis In Myocardial Infarction

TRA – transradial access

CHAPTER 1: INTRODUCTION

1.1 Statement of the problem

Coronary angiography and percutaneous coronary intervention (PCI) are cornerstone diagnostic and therapeutic procedures in the management of acute and chronic coronary artery disease. Over the past two decades, transradial access (TRA) has increasingly dominated as the preferred access site over transfemoral access (TFA). This has largely been driven by evidence demonstrating reductions in major bleeding, vascular complications, and all-cause mortality, particularly in patients presenting with acute coronary syndromes.[1-3] These findings have led to strong guideline recommendations favoring a "radial first" strategy in contemporary interventional cardiology practice.[4, 5]

Despite widespread adoption, arterial access site selection remains a clinically important decision with implications that extend beyond traditional bleeding-centric outcomes. As TRA has become the default approach in many centres, new and underexplored questions have emerged regarding its broader safety profile, long term vascular consequences, and economic impact within publicly funded health care systems. While the benefits of TRA are well established, important uncertainties remain regarding rare complications, optimal post-procedural assessment, preservation of future vascular access, and system-level value.

In particular, catheter-induced coronary artery dissection represents a rare but potentially fatal complication of coronary angiography with theoretical concerns that TRA may confer higher risk due to catheter manipulation through more torturous vascular anatomy.[6] Similarly, while vascular access complications such as pseudoaneurysms remain a significant source of

morbidity, post-procedural assessment continues to rely primarily on physical examination despite known limitations in sensitivity. Furthermore, radial artery occlusion (RAO), the most common complication of TRA, remains clinically important because it influences access site selection for repeat cardiovascular procedures, the availability of the radial artery as a conduit at time of coronary artery bypass graft surgery, and dialysis access in chronic kidney disease patients. Effective strategies to prevent RAO remain incompletely defined.[7-9]

Finally, although clinical benefits of TRA are well documented, the economic implications of access site selection particularly within publicly funded systems such as Canada have not been adequately characterized. Given the high procedural volume of coronary angiography and PCI at a national and international level, even modest differences in cost effectiveness may have substantial system-level consequences.[10]

Collectively, these unresolved issues highlight the need for a comprehensive evaluation of arterial access site selection that extends beyond short term procedural outcomes to encompass the detection and management of procedural complications, long term vascular preservation, and health system value.

1.2 Objective

The overarching objective of this thesis is to comprehensively evaluate the clinical, procedural, and health system consequences of arterial access site selection for coronary angiography and PCI. Specifically, this thesis aims to generate rigorous and clinically relevant evidence that informs access site decision making across the full continuum of invasive cardiovascular care

from procedural safety and rare adverse events to procedural assessment, long term vascular outcomes, and economic impact.

1.3 Research questions

To address this aim, five interrelated research questions were explored:

1. Does TRA improve short term mortality and safety outcomes compared with TFA in patients with ST-elevation myocardial infarction (STEMI)?
2. Is the risk of rare but catastrophic complications, specifically catheter-induced coronary artery dissection, influenced by access site?
3. Can point-of-care ultrasound improve the detection of clinically important vascular access complications following invasive cardiac procedures?
4. Is TRA a cost-effective strategy compared with TFA within a publicly funded Canadian healthcare system?
5. Can post-procedural oral anticoagulation reduce the incidence of radial artery occlusion (i.e. the most common complication of TRA)?

Each question addresses a distinct yet interrelated dimension of access site selection, collectively contributing to a unified framework for optimizing patient safety and health system efficiency in interventional cardiology.

1.4 Chapter outlines

This thesis is structured as a series of interrelated chapters, each addressing a specific aspect of access site selection.

Chapter 3 presents a systematic review and meta-analysis of randomized clinical trials comparing TRA and TFA for PCI in patients with STEMI. This chapter establishes the mortality and safety benefits of TRA in a high risk PCI patient population.

Chapter 4 examines the association between access site and catheter-induced coronary artery dissection using a large contemporary retrospective cohort. This chapter evaluates a rare but potentially catastrophic complication that has been a persistent concern with increasing adoption of TRA.

Chapter 5 evaluates the role of point-of-care ultrasound as an adjunct to the physical examination for the detection of vascular access complications following invasive cardiac procedures. This chapter focuses on early detection and mitigation of post-procedural morbidity.

Chapter 6 presents a cost effectiveness analysis comparing TRA and TFA for coronary angiography and acute myocardial infarction from a Canadian healthcare perspective. This chapter addresses the economic implications of access site selection at the system-level.

Chapter 7 describes the rationale, design, and prespecified statistical analysis plan of the Rivaroxaban Post-Transradial Access for the Prevention of Radial Artery Occlusion (RAPTOR) randomized clinical trial which evaluates short term post-procedural anticoagulation for the prevention of RAO. This chapter represents the translation of observational and mechanistic insights into prospective interventional research.

1.5 References

1. Jolly, S.S., et al., *Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial.* Lancet, 2011. **377**(9775): p. 1409–20.
2. Ferrante, G., et al., *Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials.* JACC Cardiovasc Interv, 2016. **9**(14): p. 1419–34.
3. Valgimigli, M., et al., *Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial.* Lancet, 2015. **385**(9986): p. 2465–76.
4. Rao, S.V., et al., *2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.* Circulation, 2025. **151**(13).
5. Wong, G.C., et al., *2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Guidelines on the Acute Management of ST-Elevation Myocardial Infarction: Focused Update on Regionalization and Reperfusion.* Can J Cardiol, 2019. **35**(2): p. 107–132.
6. Ramasamy, A., et al., *Iatrogenic catheter-induced ostial coronary artery dissections: Prevalence, management, and mortality from a cohort of 55,968 patients over 10 years.* Catheter Cardiovasc Interv, 2021. **98**(4): p. 649–655.
7. Kotowycz, M.A. and V. Dzavík, *Radial artery patency after transradial catheterization.* Circ Cardiovasc Interv, 2012. **5**(1): p. 127–33.

8. Rashid, M., et al., *Radial Artery Occlusion After Transradial Interventions: A Systematic Review and Meta-Analysis.* J Am Heart Assoc, 2016. **5**(1).

9. Bernat, I., et al., *Best Practices for the Prevention of Radial Artery Occlusion After Transradial Diagnostic Angiography and Intervention: An International Consensus Paper.* JACC Cardiovasc Interv, 2019. **12**(22): p. 2235–2246.

10. Faris, P.D., et al., *Diagnostic cardiac catheterization and revascularization rates for coronary heart disease.* Can J Cardiol, 2004. **20**(4): p. 391–7.

CHAPTER 2: BACKGROUND

2.1 Overview of arterial access for coronary angiography and PCI

Coronary angiography and percutaneous coronary intervention (PCI) require reliable arterial access to permit catheter manipulation, contrast delivery, and device deployment within the coronary artery circulation. Historically, transfemoral access (TFA) was the dominant approach due to the large caliber and relatively straight course of the common femoral artery, which facilitated catheter stability and procedural success. Over time, however, transradial access (TRA) has emerged as a widely adopted alternative. This evolution in preferred access site has been driven by advances in catheter technology, increasing operator experience, and an improved understanding of access site related complications. [1-6]

Despite their shared procedural objectives, TRA and TFA differ in vascular anatomy, technical execution, complication profiles, and downstream consequences. These differences underpin the nuanced clinical trade-offs explored in this thesis and motivate the need for a comprehensive evaluation of access site selection beyond traditional outcomes.

2.2 Technical considerations for TFA

TFA involves cannulation of the common femoral artery, typically below the inguinal ligament and above the femoral artery bifurcation. When performed correctly, this approach provides a direct and relatively non-tortuous pathway to the coronary ostia allowing for sufficient catheter support and ease of device delivery. As a result, TFA has been traditionally favoured for complex coronary interventions, large bore devices, and mechanical circulatory support.[4, 7]
However, TFA is associated with a higher risk of bleeding and vascular complications, including retroperitoneal hemorrhage, pseudoaneurysm formation, and arteriovenous fistula formation.

These complications are particularly important in patients with acute coronary syndromes, who frequently receive potent antithrombotic therapies.[2] Additionally, hemostasis following TFA often requires prolonged bed rest, contributing to patient discomfort, delayed mobilization, and longer hospital stays.

From a technical perspective, successful TFA requires accurate arterial puncture location, meticulous hemostasis, and careful post-procedural monitoring. While ultrasound-guided TFA and vascular closure devices have mitigated some risks, access site complications remain an important limitation of the femoral approach.[4, 7]

2.3 Technical considerations for TRA

TRA involves cannulation of the radial artery at the wrist and has become the preferred access site for coronary angiography and PCI in many centres worldwide.[4, 7] The superficial location of the radial artery allows for easy compression and rapid hemostasis, translating into lower rates of major bleeding and vascular complications. Additional advantages include early ambulation, improved patient comfort and reduced length of hospital stay.[2]

Nevertheless, TRA presents distinct technical challenges. The radial artery is smaller in caliber, more prone to spasm, and catheter manipulation requires navigation through the subclavian and brachiocephalic arteries, which may introduce tortuosity and anatomical variability. These factors have raised concerns regarding procedural complexity, catheter stability, and the potential for rare but serious complications such as catheter-induced coronary artery dissection.[8]

Importantly, TRA carries a unique long-term complication which is radial artery occlusion (RAO). While the pathophysiology of RAO is complex and multifactorial, TRA results in structural changes to the radial artery. 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 hemostasis. The process of sheath insertion and instrumentation during TRA causes repeated endothelial damage, leading to vessel remodeling and thrombosis. Although often clinically silent, RAO precludes future ipsilateral radial access and may limit the use of the artery for coronary artery bypass grafting or arteriovenous fistula creation in patients with chronic kidney disease requiring hemodialysis.[3, 9, 10] As TRA adoption increases, the preservation of radial artery patency has become an increasingly relevant clinical consideration.

2.4. The nuances of access site selection

While the superiority of TRA over TFA for reducing bleeding and major vascular complications is well established, access site selection remains nuanced and context dependent.[4, 7, 11] Decisions must account for patient characteristics, procedural complexity, operator experience, institutional resources, and anticipated future vascular needs. Furthermore, as access site related complications become less frequent, their relative importance may be underestimated despite their disproportionate impact on morbidity, mortality, and healthcare utilization.

Rare but potentially catastrophic complications, such as catheter-induced coronary artery dissection, may influence clinician perception and adoption of access site strategies despite their low absolute incidence. Similarly, vascular access complications such as pseudoaneurysms may

remain a significant source of post-procedural morbidity, yet bedside assessment continues to rely primarily on physical examination, which has limited diagnostic sensitivity. Additionally, RAO remains clinically important given its implications for future needs. Effective strategies for the prevention of RAO remain incompletely defined.

2.5 Overarching thesis framework

The overarching framework of this thesis is organized around the continuum of care associated with arterial access site selection for coronary angiography and PCI. Rather than focusing exclusively on intra-procedural outcomes, this thesis examines access site selection across four interrelated dimensions:

1. Clinical efficacy and safety, including mortality, bleeding, and vascular complications
2. Rare but serious complications which may influence clinician behavior and access site strategy adoption
3. Detection and management of access site complications, emphasizing diagnostic strategies that improve patient outcomes and efficiency within the healthcare system
4. Long term and system-level consequences including artery preservation and cost effectiveness

Each research question outlined in Chapter 1 maps onto one or more of these dimensions collectively forming a unified evaluation of access site selection for coronary angiography and PCI.

2.6 Methodological approaches used in this thesis

To address the research questions outlined in Chapter 1, this thesis implies a range of complementary methodological approaches, selected to align with the nature of each question.

A systematic review and meta-analysis of randomized clinical trials was used to summarize high-level evidence regarding mortality and major complications associated with TRA and TFA. This provides the strongest basis for causal inference in comparative effectiveness research.

Large respective cohort analyses are used to study rare complications which are not feasible to evaluate in randomized clinical trials due to low event rates.

Prospective diagnostic accuracy studies are used to evaluate point-of-care ultrasound for the detection of vascular access complications, consistent with established reporting standards for diagnostic research.

Decision analytic modeling is employed to assess cost effectiveness, integrating clinical outcomes, health utilities, and cost data to evaluate the economic implications of access site selection within a publicly funded Canadian health care system.

Finally, the design and prespecified statistical analysis plan of a randomized clinical trial are presented to address a critical unanswered question regarding prevention of RAO. This approach reflects best practices in clinical trial methodology and emphasizes transparency and reproducibility.

2.7 Summary

In summary, this chapter provides the technical and conceptual foundation for the work that follows within this thesis. By outlining key differences between TRA and TFA, highlighting the nuanced trade-offs inherent to access site selection, and describing the methodological framework of the thesis, this chapter establishes the context necessary to interpret the subsequent studies. Together, these elements position access site selection as a multifaceted determinant of patient outcomes and health system performance, setting the stage for the analyses presented in Chapters 3 to 7.

2.8 References

1. Campeau, L., *Percutaneous radial artery approach for coronary angiography.* Cathet Cardiovasc Diagn, 1989. **16**(1): p. 3–7.
2. Jolly, S.S., et al., *Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials.* Am Heart J, 2009. **157**(1): p. 132–40.
3. Bernat, I., et al., *Best Practices for the Prevention of Radial Artery Occlusion After Transradial Diagnostic Angiography and Intervention: An International Consensus Paper.* JACC Cardiovasc Interv, 2019. **12**(22): p. 2235–2246.
4. Mason, P.J., et al., *An Update on Radial Artery Access and Best Practices for Transradial Coronary Angiography and Intervention in Acute Coronary Syndrome: A Scientific Statement From the American Heart Association.* Circ Cardiovasc Interv, 2018. **11**(9): p. e000035.
5. Rao, S.V., et al., *2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.* Circulation, 2025. **151**(13).
6. Wong, G.C., et al., *2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Guidelines on the Acute Management of ST-Elevation Myocardial Infarction: Focused Update on Regionalization and Reperfusion.* Can J Cardiol, 2019. **35**(2): p. 107–132.
7. Rao, S.V., et al., *Best practices for transradial angiography and intervention: a consensus statement from the society for cardiovascular angiography and intervention's transradial working group.* Catheter Cardiovasc Interv, 2014. **83**(2): p. 228–36.

8. Ramasamy, A., et al., *Iatrogenic catheter-induced ostial coronary artery dissections: Prevalence, management, and mortality from a cohort of 55,968 patients over 10 years.* Catheter Cardiovasc Interv, 2021. **98**(4): p. 649–655.

9. Kotowycz, M.A. and V. Dzavík, *Radial artery patency after transradial catheterization.* Circ Cardiovasc Interv, 2012. **5**(1): p. 127–33.

10. Rashid, M., et al., *Radial Artery Occlusion After Transradial Interventions: A Systematic Review and Meta-Analysis.* J Am Heart Assoc, 2016. **5**(1).

11. Lawton, J.S., et al., *2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.* J Am Coll Cardiol, 2022. **79**(2): p. e21–e129.

CHAPTER 3: TRA VS. TFA IN STEMI - A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 Chapter overview

Chapter 3 addresses the research question: "Does TRA improve short term mortality and safety outcomes compared with TFA in patients with ST-elevation myocardial infarction (STEMI)?"

This chapter presents a systematic review and meta-analysis of randomized clinical trials comparing TRA with TFA for PCI in patients with STEMI. Given the high-risk nature of STEMI and the time sensitive need for reperfusion, access site selection in this population has remained an area of ongoing clinical debate, particularly considering conflicting evidence from large contemporary trials.

Building on prior meta-analyses that examined mixed acute coronary syndrome populations, this study was designed to provide a focused and methodologically rigorous synthesis of randomized evidence specific to STEMI. The primary outcome of interest was all cause mortality at 30-days with secondary outcomes including major bleeding, vascular access complications, myocardial infarction, and stroke. By incorporating recently published trials and applying strict eligibility criteria, this analysis provides the most contemporary and robust evaluation of access site strategy in STEMI patients undergoing PCI.

3.2 Importance of this study

This study has several important findings. First, it addresses a critical evidence gap by focusing exclusively on patients with STEMI which is a patient population that differs substantially from

other acute coronary syndrome cohorts in terms of bleeding risk, procedural urgency, and mortality. Prior randomized trials and pooled analyses often combine STEMI and non-STEMI populations limiting their applicability of their findings to primary PCI. Second, this study incorporates newly available randomized evidence, including large contemporary trials that were not included in earlier meta-analyses. By updating the evidence base and excluding nonrandomized and pseudo-randomized studies, this work provides a clear and more internally valid assessment of the association between access site and short-term mortality. Third, the findings have direct clinical and guideline relevance. The reductions in 30-day mortality, major bleeding, and vascular access complications associated with TRA supports international recommendations for a "radial first" strategy in STEMI and provides reassurance regarding its safety in higher risk PCI patient populations.

Finally, this chapter establishes a foundational pillar for the thesis, framing access site selection not merely as a technical choice but as a determinant of patient-centred outcomes. The results of this meta-analysis directly inform subsequent chapters to explore rare complications, cost effectiveness, and long-term vascular preservation associated with access site selection.

3.3 Manuscript status

This manuscript has been published:

> **Di Santo P**, Simard T, Wells GA, Jung RG, Ramirez FD, Boland P, Marbach JA, Parlow S, Kyeremanteng K, Coyle D, Fergusson D, Russo JJ, Chong AY, Froeschl M, So DY, Dick A, Glover C, Labinaz M, Hibbert B, Le May M. *Transradial versus transfemoral access for percutaneous coronary intervention in ST-elevation myocardial infarction: a*

systematic review and meta-analysis. Circulation: Cardiovascular Interventions (2021). 14(3):e009994

3.4 Author roles/contributions

PDS, TS, GAW, BH, and MLM conceived the study. PDS, TS, and MLM designed the search strategy. PDS drafted the protocol, which was reviewed and approved by all authors. PDS, TS, FDR, PB, JAM, SP, KK, JJR, AYC, MF, DYS, AD, CG, ML, BH, and MLM provided clinical perspective. PDS and TS selected studies for inclusion and assessed risk of bias. PDS extracted study data, which were checked by TS. PDS analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors provided comments on the draft and approved the version of the manuscript submitted for publication.

3.5 Related thesis appendices

Appendix A - Published manuscripts – The PDF of the systematic review/meta-analysis

3.6 Manuscript

Full Title: Transradial versus transfemoral access for percutaneous coronary intervention in ST-elevation myocardial infarction: a systematic review and meta-analysis

First author surname: Di Santo

Short title: TRA vs TFA for PCI in STEMI: a meta-analysis

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Abstract

Background

Transradial access (TRA) has emerged as the preferred vascular access site for coronary angiography and percutaneous coronary intervention (PCI). This systematic review and meta-analysis was performed to evaluate 30-day all-cause mortality comparing TRA with transfemoral access (TFA) for PCI in patients with ST-elevation myocardial infarction (STEMI).

Methods

We performed a systematic literature search and meta-analysis of randomized clinical studies published from inception until January 7, 2020 in MEDLINE, EMBASE, Cochrane Central Register of Clinical Trials, and Web of Science Core Collection. PRISMA guidelines were used for abstracting data. The primary outcome was all-cause mortality at 30-days. Secondary outcomes included myocardial infarction, major bleeding, stroke, and access site complications.

Results

A total of 14 studies representing 11,707 patients (5,802 patients with TRA; 5,905 patients with TFA) were included in this analysis. All-cause mortality was significantly reduced in the TRA group with an overall risk ratio (RR) of 0.72 (95% CI 0.56-0.92) in the pooled analysis. When stratified by glycoprotein IIb/IIIa use, there was no difference in mortality in the lowest usage quartile (RR 0.93, 95% CI 0.67-1.28). Major bleeding (RR 0.60, 95% CI 0.45-0.80) and access site complications (RR 0.40, 95% CI 0.30-0.53) were significantly higher in the TFA group. There was no statistical difference in re-infarction (RR 0.96, 95% CI 0.75-1.25) or stroke (RR 1.47, 95% CI 0.87-2.50).

Conclusions

Transradial access is associated with lower 30-day mortality when compared to TFA in STEMI patients who undergo PCI.

What is Known; What the Study Adds

What is Known:

- Transradial access has emerged as the preferred access site for coronary angiography and percutaneous coronary intervention, including in patients with ST-elevation myocardial infarction

What the Study Adds:

- In this meta-analysis of 14 randomized clinical trials including 11,707 patients, transradial access was associated with reduced all-cause mortality when compared to transfemoral access
- Transradial access was also associated with reductions in major bleeding and access site vascular complications
- There was no difference in re-infarction or stroke between transradial and transfemoral access

Introduction

Coronary angiography and percutaneous coronary intervention (PCI) are the gold standard for the treatment of obstructive lesions in ST-elevation myocardial infarction (STEMI).[1, 2] Transradial access (TRA) has emerged as the preferred vascular access site over transfemoral access (TFA) for coronary angiography and PCI[3, 4] with several international cardiology society guidelines now strongly recommending TRA over TFA in STEMI.[5, 6] Despite several reported advantages to TRA in STEMI, including a reduction in major bleeding, access site complications and a signal towards a reduction in all-cause mortality in the setting of primary PCI,[7-9] there has been a slow adoption of TRA for STEMI patients in the United States.[10]

Two of the largest studies to date evaluating the role of access site on the safety and efficacy of PCI are the Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) study[11] and the RadIal Vs femorAL access for coronary intervention (RIVAL) study.[12] Notably, both trials included patients with acute coronary syndromes (ACS) and were not limited solely to patients with STEMI. While the randomization in the MATRIX study was stratified by type of ACS, the RIVAL study only stratified by study centre. Moreover, STEMI patients in these trials encompassed both a cohort of patients undergoing primary PCI and those who had received fibrinolytic therapy prior to PCI. Most recently, the Safety and Efficacy of Femoral Access vs. Radial Access in ST-Elevation Myocardial Infarction (SAFARI-STEMI) trial has demonstrated no difference in 30-day all-cause mortality or major bleeding in a dedicated primary PCI STEMI population.[13] While previous systematic reviews in the field have been reported,[8, 9, 14] they were not specific to STEMI patients, did not include the SAFARI-STEMI study, and one review included studies

which did not meet their own eligibility criteria[14]. Hence, we sought to perform an updated systematic review and meta-analysis of randomized clinical trials in this field. For this study, we hypothesized that 30-day all-cause mortality in patients with STEMI who underwent PCI via the TRA would not be significantly different compared to TFA.

Methods

Search Strategy

This systematic review was conducted in accordance to the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix A).[15] We performed a computerized literature search of MEDLINE, EMBASE, Cochrane Central Register of Clinical Trials (CENTRAL), and Web of Science Core Collection from inception until January 7, 2020. No restrictions were placed on date or language of publication. A combination of both free text words and Medical Subject Heading terms were used in order to identify studies which assess TRA vs. TFA (Appendix B). Additionally, a manual search of all eligible articles' reference lists, articles citing eligible articles, and relevant review articles was carried out to identify additional literature. The resulting citations were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) with removed duplicates reviewed manually using the duplicate identification function.

Study Selection, Data Extraction, and Quality Assessment

The review was limited to randomized clinical trials (RCTs) examining TRA as compared to TFA for STEMI. All other study designs were excluded given the large volume of RCTs available on this subject. Titles, abstracts, and full texts were screened by two independent reviewers. Any discrepancies in the review stage were resolved by further discussion and consensus amongst

these two reviewers. Reference lists of all eligible studies were then screened to identify any additional publications meeting inclusion criteria. Data from articles were independently extracted by two reviewers. The primary outcome of interest was all-cause mortality at 30-days. Secondary outcomes included in-hospital all-cause mortality, greater than 30-day all cause mortality, myocardial infarction (MI), major bleeding as defined by each individual study, stroke (ischemic or hemorrhagic), and access site complications (e.g. bleeding, hematoma, pseudoaneurysm, distal limb ischemia) as defined by each study. All studies included in the final analysis were assessed according to the Cochrane Handbook for Systematic Reviews of Intervention[16] criteria in order to determine their relevance, risk of bias, and methodological validity.

Statistical Analyses

The Mantel-Haenszel method was used to calculate the pooled risk ratio (RR) and 95% confidence intervals (CIs) associated with TRA vs. TFA for all-cause mortality in PCI in STEMI patients using a random effects model. Risk ratios and 95% CIs were generated for our secondary outcomes. Additionally, pre-specified subgroup analyses evaluating trials with only primary PCI and glycoprotein IIb/IIIa inhibitor (GPI) use greater than 50% vs. less than 50% were evaluated. An additional *post-hoc* analysis was performed to further evaluate the impact of GPI use on mortality, bleeding, and access site complications by further stratifying the rates of usage into quartiles. This additional analysis was performed to further elucidate the impact of GPI given the degree of imbalance between the number of patients in the above and below 50% usage cut-off groups initially selected. Sensitivity analyses were performed excluding studies at high or unclear risk of bias and excluding studies with incomplete outcome data. Heterogeneity

among eligible studies was visually assessed through inspection of the forest plots and statistically assessed using the I^2 statistic. Publication bias was assessed using Egger's regression and visual inspection of funnel plots. Statistical analyses were conducted using Review Manager (RevMan version 5.3, Cochrane Collaboration, London, United Kingdom) and Meta-Essentials: Workbooks[17] for Egger's regression. Two-sided p values <0.05 were considered statistically significant.

Results

Study Selection and Characteristics

A total of 1,214 records were identified in our search after duplicates were removed (Figure 1). Full-text review was performed on 89 articles and a total of 14 studies were included in our meta-analysis (Supplemental Tables 1-3). Of the identified studies, two trials did not include only STEMI patients but rather included broader ACS populations which also included non-STEMI and unstable angina patients.[11, 12] As both trials were of considerable sample size and subgroup analyses of STEMI patients were reported,[18, 19] they were included in this systematic review. All included studies were parallel-group randomized clinical trials. There were nine multicentre studies[13, 18-25] and five single centre studies[26-30] from various countries. Follow-up duration ranged from in-hospital outcomes in six studies, 30-day outcomes in eight studies, and more than 30-day outcomes in four studies as some studies reported outcomes at various time intervals. With respect to reperfusion strategies, six studies included isolated primary PCI strategies, six studies included both primary PCI and combination fibrinolytic/PCI therapies, and the reperfusion strategy was unknown in one trial.

Patient population

Of the 11,707 patients included in this review, 5,802 (49.6%) underwent PCI with TRA approach and 5,905 (50.4%) with TFA (Table 1). The mean age of study participants across all studies was similar in both groups (60.5 ± 4.1 years in the TRA group vs. 61.0 ± 4.1 years in the TFA group). Most patients were male (77.6% in TRA and 77.0% in TFA) and more than 80% of patients in both groups presented Killip class I. Ten percent of all patients had a history of a previous myocardial infarction and/or previous PCI, and 1% had previous coronary artery bypass grafting. The reperfusion strategy was reported in only 50% of patients, of which 89.4% of patients in the TRA group underwent primary PCI as compared to 89.9% in the TFA group.

Mortality

All-cause mortality at 30-days was reported in seven of the included studies. One study reported only cardiac death, which was defined as any death due to cardiac cause, procedure-related death, and death of unknown cause.[24] As this study reported 30-day outcomes, it was included in the all-cause mortality outcome as part of this meta-analysis given their broad mortality definition. All-cause mortality at 30-days was low in both groups but was significantly reduced in the TRA group (RR 0.72, 95% CI 0.56-0.92) (Figure 2; Figure 3). Overall, there was low heterogeneity based on visual interpretation of the forest plot as well as statistical testing (I^2 = 8%, p=0.37). No statistical difference was observed between TRA and TFA with respect to in-hospital mortality (RR 0.78, 95% CI 0.32-1.91) or in mortality beyond 30-days (RR 0.62, 95% CI 0.35-1.10) (Supplemental Figure 1). With respect to differences in reperfusion strategies, all-cause mortality in the TRA and TFA groups was not different in the primary PCI population (RR 0.83, 95% CI 0.53-1.29) nor in the not exclusively primary PCI population (RR 0.73, 95% CI

0.53-1.00) when the longest time interval was considered in studies reporting outcomes at more than one follow-up duration (Supplemental Figure 2).

In the *post-hoc* analysis of 30-day all-cause mortality stratified by GPI use in quartiles (Supplemental Figure 3; Figure 2), there is a trend toward favoring TRA as the frequency of GPI use increased. In the three studies with the lowest GPI usage quartile, there was no difference between TRA and TFA (RR 0.93, 95% CI 0.67-1.28). In the second and third quartiles, the risk ratios were 0.59 (95% CI 0.35-1.00) and 0.57 (95% CI 0.36-0.90), respectively, in favour of TRA. In the fourth quartile, no significant difference was seen between TRA and TFA (RR 0.33, 95% CI 0.01-7.81); however, this highest usage quartile was only comprised of one small study with a total of 50 patients.

Major Bleeding

Major bleeding was reported in 12 of the trials. The definition of major bleeding was variable and included the Thombolysis in Myocardial Infarction (TIMI),[31] Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction Trial (HORIZONS-AMI),[32] Randomised Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events 2 (REPLACE-2),[33] Bleeding Academic Research Consortium (BARC),[34] and several trial-specific definitions. The overall incidence of major bleeding was low in both groups, but significantly less bleeding was seen in the TRA group (RR 0.60, 95% CI 0.45-0.80, $p<0.001$). Similar reductions in major bleeding in the TRA group were observed irrespective of stratification by frequency of GPI use (Figure 4 and Supplemental Figure 4). Overall, there was

low heterogeneity based on visual interpretation of the forest plot and statistical testing (I^2 = 16%, p=0.29).

Vascular access complications

Vascular access complications were reported in 13 studies. There were significantly fewer vascular access complications in TRA patients (1.4% vs. 3.5% in the TFA group) with an overall RR of 0.40 (95% CI 0.30-0.53) and TRA was favoured irrespective of GPI use (Figure 4 and Supplemental Figure 5). Radial artery occlusion, which is the most common vascular complication following TRA, was reported in four studies.[22, 23, 25, 26] There was low heterogeneity based on visual interpretation of the forest plot as well as statistical testing (I^2 = 0%, p=0.86).

Myocardial Infarction and Stroke

With respect to both re-infarction and stroke, there was no difference between TRA and TFA with an RR 0.96 (95% CI 0.75-1.25) and 1.47 (95% CI 0.87-2.50), respectively (Figure 4 and Supplemental Figures 6-7). There was low heterogeneity based on visual interpretation of both forest plots as well as statistical testing for re-infarction (I^2 0%, p=0.95) and stroke (I^2 0%, p=0.97).

Risk of Bias

All studies were at low risk of performance bias and most studies were at low risk of attrition bias, reporting bias, and detection bias with respect to all objective outcomes included in this review (Supplemental Figure 8). Only half of the included studies were at low risk of selection bias due to issues with random sequence generation and allocation concealment. Assessment of

publication bias was performed through visual inspection of the funnel plot for all-cause mortality (Supplemental Figure 9). The funnel plot appeared symmetrical suggesting an absence of publication bias, which was further supported by formal testing with Egger's regression (p=0.42).

Sensitivity Analyses

Sensitivity analyses were performed excluding studies with incomplete outcome data and excluding studies at high or unclear risk of bias (Supplemental Figure 10). Six studies with complete study follow up were included. Notably, these studies largely involved only in-hospital outcomes and had an overall RR of 0.63 (95% CI 0.36-1.11; Supplemental Figure 10A). Five studies were deemed to not be at high or unclear risk of bias, all of which reported 30-day outcomes. In this analysis, there was no difference between TRA and TFA (RR 0.79, 95% CI 0.62-1.02; Supplemental Figure 10B).

Discussion

In our systematic review and meta-analysis examining the differences between TRA and TFA for PCI in STEMI, patients who underwent TRA had a significantly lower 30-day all-cause mortality and were less likely to experience major bleeding or vascular access complications. Notably, radial artery occlusion was included as a vascular access complication in only four of the included trials. There were no statistical differences in the rates of stroke or myocardial infarction between these two strategies.

In previously reported pooled analyses, a significant reduction in all-cause mortality has been reported with use of the TRA in the primary PCI population.[35, 36] This mortality benefit is largely attributed to a reduction in both bleeding and vascular access complications.[37] As expected, our analysis demonstrates an increased risk of both complications with TFA, which may in part contribute to the lower 30-day all-cause mortality. Interestingly, despite the pooled analysis of eight studies reporting our primary outcome, the only trials that individually identified a mortality benefit were RIVAL[12, 19] (RR 0.39, 95% CI 0.20-0.76) and RIFLE-STEACS[24] (RR 0.57, 95% CI 0.36-0.93). Importantly, the RIVAL study was not limited to patients with STEMI but rather included patients with any ACS. Furthermore, this trial did not stratify by type of ACS as was done in the MATRIX trial. Finally, the RIFLE-STEACS study reported cardiac death, which given the broad definition and brief study follow-up duration, was used as a surrogate for all-cause mortality, although these may not be equivalent.

In studies performed in the past decade, there has been a trend away from favoring the TRA approach with respect to all-cause mortality at 30-days (Figure 3). In our *post-hoc* analysis, we demonstrated an increased trend in mortality with increasing GPI use (Supplemental Figure 3; Figure 2). In further subgroup analyses stratified by GPI use, there was no difference in major bleeding or access site complications across the frequency of GPI use and TRA was consistently favoured. Therefore, while the mechanism of increased mortality in TFA is thought to be attributable to higher rates of bleeding and access site complications, increased usage of GPI increased the risks of these complications in both groups. There was insufficient data provided to explore the relationship between vascular closure devices usage and access site sheath size usage with all-cause 30-day mortality (Supplemental Table 4). Ongoing use of both pharmacologic and

technological bleeding avoiding strategies may continue to further mitigate the differences in outcomes between access sites.

With respect to the incidence of stroke, our analysis demonstrated a trend towards increased stroke with TRA which did not meet statistical significant but we would argue has important clinical significance. The vast majority of TRA cases are performed via the right radial artery (RRA).[4] When compared to the left radial artery, RRA is preferred due to operator comfort, less fluoroscopy time, and limitations of typical catheterization laboratory radiation safety equipment design.[38] However, with RRA for TRA there are anatomic variations which may require extensive catheter manipulation and possibly lead to embolization through the right carotid artery. Interestingly, the use of the left radial artery for TRA appears to have lower stroke risk than via the RRA purportedly due to these anatomic differences.[39] Overall, the event rate for stroke in both TRA (0.6%) and TFA (0.4%) for STEMI patients is quite low; however, this remains an important consideration in the debate on access site selection.

Access site remains an important consideration in diagnostic coronary angiography and PCI with several international cardiology society guidelines now strongly recommending TRA over TFA in STEMI.[5, 6] While this systematic review further supports the use of TRA through a reduction in all-cause mortality at 30-days, major bleeding and vascular complications, it is important to consider the implications of maintaining competency in both access site options. It has been established that experience and procedural volume are the most important factors in reducing radiation exposure from coronary procedures to both patients and operators, irrespective of access site.[40] Additionally, despite potential benefits to a “radial first” approach to coronary

angiography and PCI in STEMI, it is important to recognize that there is a considerable rate of access site crossover in published trials (Supplemental Table 3), underscoring the importance of maintaining proficiency in both TRA and TFA, especially in centres using TRA as the default strategy for planned procedures. Lastly, there is a paucity of reported radial artery occlusion in these trials, potentially biasing comparisons between these two groups given that it is the most frequent post-procedure complication of TRA. This is an important complication of TRA as it restricts the use of the same radial artery for future procedures, including repeat angiography and coronary artery bypass grafting.[41]

Our analysis is not without limitations. First, the definitions of the two *a priori* secondary outcomes of interest (i.e. major bleeding and vascular access complications) varied between studies. However, there was low heterogeneity across the included studies with respect to these outcomes, suggesting a true association between access site and major bleeding or vascular access complications. Additionally, the indication for GPI as a routine strategy or as bail-out could not be evaluated in this systematic review which could impact outcomes. Second, patient-level data was not used for this meta-analysis – an analysis that could prove informative as it would allow for more robust statistical adjustments, given that STEMI patients were not sub-randomized in many studies. Finally, due to varying eligibility criteria in the included studies (Supplemental Table 1 and 3), patients who presented with STEMI and cardiogenic shock or required intra-aortic balloon pumps were largely excluded, thereby limiting the generalizability of these results to these patients.

Conclusion

Transradial access is associated with lower 30-day mortality when compared to TFA in STEMI patients who undergo PCI. Moreover, a significant reduction in major bleeding and vascular access complications with TRA is observed without any differences in myocardial infarction or stroke.

Disclosures

None

References

1. Keeley EC, Boura JA and Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *The Lancet*. 2003;361:13-20.

2. Simard T, Hibbert B, Ramirez FD, Froeschl M, Chen YX and O'Brien ER. The evolution of coronary stents: a brief review. *Can J Cardiol*. 2014;30:35-45.

3. Shroff AR, Fernandez C, Vidovich MI, Rao SV, Cowley M, Bertrand OF, Patel TM and Pancholy SB. Contemporary transradial access practices: Results of the second international survey. *Catheter Cardiovasc Interv*. 2018.

4. Bertrand OF, Rao SV, Pancholy S, Jolly SS, Rodés-Cabau J, Larose É, Costerousse O, Hamon M and Mann T. Transradial Approach for Coronary Angiography and Interventions: Results of the First International Transradial Practice Survey. *JACC Cardiovasc Interv*. 2010;3:1022-1031.

5. Wong GC, Welsford M, Ainsworth C, Abuzeid W, Fordyce CB, Greene J, Huynh T, Lambert L, Le May M, Lutchmedial S, et al. 2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Guidelines on the Acute Management of ST-Elevation Myocardial Infarction: Focused Update on Regionalization and Reperfusion. *Canadian Journal of Cardiology*. 2019;35:107-132.

6. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2018;39:119-177.

7. Schussler JM, Vasudevan A, von Bose LJ, Won JI and McCullough PA. Comparative Efficacy of Transradial Versus Transfemoral Approach for Coronary Angiography and Percutaneous Coronary Intervention. *Am J Cardiol*. 2016;118:482-488.

8. Ferrante G, Rao SV, Jüni P, Da Costa BR, Reimers B, Condorelli G, Anzuini A, Jolly SS, Bertrand OF, Krucoff MW, et al. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv*. 2016;9:1419-1434.

9. Kolkailah AA, Alreshq RS, Muhammed AM, Zahran ME, Anas El-Wegoud M and Nabhan AF. Transradial versus transfemoral approach for diagnostic coronary angiography and percutaneous coronary intervention in people with coronary artery disease. *Cochrane Database of Systematic Reviews*. 2018.

10. Howe MJ, Seth M, Riba A, Hanzel G, Zainea M and Gurm HS. Underutilization of Radial Access in Patients Undergoing Percutaneous Coronary Intervention for ST-Segment-Elevation Myocardial Infarction: Insights From the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. 2015;8:e002036-e002036.

11. Valgimigli M, Gagnor A, Calabro P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Ando G, Repetto A, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet*. 2015;385:2465-76.

12. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, Budaj A, Niemelä M, Valentin V, Lewis BS, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *The Lancet*. 2011;377:1409-1420.

13. Le May M, Wells G, So D, Chong AY, Dick A, Froeschl M, Glover C, Hibbert B, Marquis J-F, Blondeau M, et al. Safety and Efficacy of Femoral Access vs Radial Access in ST-Segment Elevation Myocardial Infarction: The SAFARI-STEMI Randomized Clinical Trial. *JAMA Cardiology*. 2020.

14. Singh S, Singh M, Grewal N and Khosla S. Transradial vs Transfemoral Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction: A Systemic Review and Meta-analysis. *Can J Cardiol*. 2016;32:777-790.

15. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P and Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*. 2015;4:1.

16. *Cochrane Handbook for Systematic Reviews of Interventions*: John Wiley & Sons Ltd; 2008.

17. Suurmond R, van Rhee H and Hak T. Introduction, comparison and validation of Meta-Essentials: A free and simple tool for meta-analysis. *Research Synthesis Methods*. 2017;8:537-533.

18. Vranckx P, Frigoli E, Rothenbühler M, Tomassini F, Garducci S, Andò G, Picchi A, Sganzerla P, Paggi A, Ugo F, et al. Radial versus femoral access in patients with acute coronary syndromes with or without ST-segment elevation. *European Heart Journal*. 2017;38:1069-1080.

19. Mehta SR, Jolly SS, Cairns J, Niemela K, Rao SV, Cheema AN, Steg PG, Cantor WJ, Dzavik V, Budaj A, et al. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *J Am Coll Cardiol*. 2012;60:2490-9.

20. Bernat I, Horak D, Stasek J, Mates M, Pesek J, Ostadal P, Hrabos V, Dusek J, Koza J, Sembera Z, et al. ST-Segment Elevation Myocardial Infarction Treated by Radial or Femoral

Approach in a Multicentre Randomized Clinical Trial. *Journal of the American College of Cardiology*. 2014;63:964-972.

21. Brasselet C, Tassan S, Nazeyrollas P, Hamon M and Metz D. Randomised comparison of femoral versus radial approach for percutaneous coronary intervention using abciximab in acute myocardial infarction: results of the FARMI Trial. *Heart*. 2006;93:1556-1561.

22. Cantor WJ, Puley G, Natarajan MK, Dzavik V, Madan M, Fry A, Kim HH, Velianou JL, Pirani N, Strauss BH, et al. Radial versus femoral access for emergent percutaneous coronary intervention with adjunct glycoprotein IIb/IIIa inhibition in acute myocardial infarction—the RADIAL-AMI pilot randomized trial. *American Heart Journal*. 2005;150:543-549.

23. Gan L, Lib Q, Liuc R, Zhaoc Y, Qiuc J and Liao Y. Effectiveness and feasibility of transradial approaches for primary percutaneous coronary intervention in patients with acute myocardial infarction. *Journal of Nanjing Medical University*. 2009;23:270-274.

24. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, Summaria F, Patrizi R, Borghi A, Di Russo C, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol*. 2012;60:2481-9.

25. Vazquez-Rodriguez J. Comparacion del acceso radial frente al acceso femoral en la revascularizacion precutánea durante la fase aguda del infarto agudo de miocardio con elevacion del segment ST [Comparison of radial access from access femoral in precutaneous revascularization during the acute phase of acute myocardial infarction ST segment elevation]. *Cardiology*. 2009;PhD.

26. Hou L, Wei YD, Li WM and Xu YW. Comparative study on transradial versus transfemoral approach for primary percutaneous coronary intervention in Chinese patients with acute myocardial infarction. *Saudi medical journal*. 2010;31:158-62.

27. Koltowski L, Filipiak K, Kochman J, Pietrasik A, Rdzanek A, Huczek Z, Scibisz A, Mazurek T and Opolski G. Access for percutaneous coronary intervention in ST segment elevation myocardial infarction: radial vs. femoral — a prospective, randomised clinical trial (OCEAN RACE). *Kardiol Pol*. 2014;72:604-611.

28. Li WM, Li Y, Zhao JY, Duan YN, Sheng L, Yang BF, Wang FL, Gong YT, Yang SS, Zhou LJ, et al. Safety and feasibility of emergent percutaneous coronary intervention with the transradial access in patients with acute myocardial infarction. *Chin Med J (Engl)*. 2007;120:598-600.

29. Saito S, Tanaka S, Hiroe Y, Miyashita Y, Takahashi S, Tanaka K and Satake S. Comparative study on transradial approach vs. transfemoral approach in primary stent implantation for patients with acute myocardial infarction: results of the test for myocardial infarction by prospective unicentre randomization for access sites (TEMPURA) trial. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2003;59:26-33.

30. Wang YB, Fu XH, Wang XC, Gu XS, Zhao YJ, Hao GZ, Jiang YF, Li SQ, Wu WL and Fan WZ. Randomized comparison of radial versus femoral approach for patients with STEMI undergoing early PCI following intravenous thrombolysis. *J Invasive Cardiol*. 2012;24:412-6.

31. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med*. 1985;312:932-6.

32. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358:2218-30.

33. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *Jama*. 2003;289:853-63.

34. Mehran R, Rao Sunil V, Bhatt Deepak L, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott Stephen D, Menon V, Nikolsky E, et al. Standardized Bleeding Definitions for Cardiovascular Clinical Trials. *Circulation*. 2011;123:2736-2747.

35. Joyal D, Bertrand OF, Rinfret S, Shimony A and Eisenberg MJ. Meta-analysis of ten trials on the effectiveness of the radial versus the femoral approach in primary percutaneous coronary intervention. *Am J Cardiol*. 2012;109:813-8.

36. Vorobcsuk A, Konyi A, Aradi D, Horvath IG, Ungi I, Louvard Y and Komocsi A. Transradial versus transfemoral percutaneous coronary intervention in acute myocardial infarction Systematic overview and meta-analysis. *Am Heart J*. 2009;158:814-21.

37. Mamas MA, Ratib K, Routledge H, Fath-Ordoubadi F, Neyses L, Louvard Y, Fraser DG and Nolan J. Influence of access site selection on PCI-related adverse events in patients with STEMI: meta-analysis of randomised clinical trials. *Heart*. 2012;98:303-311.

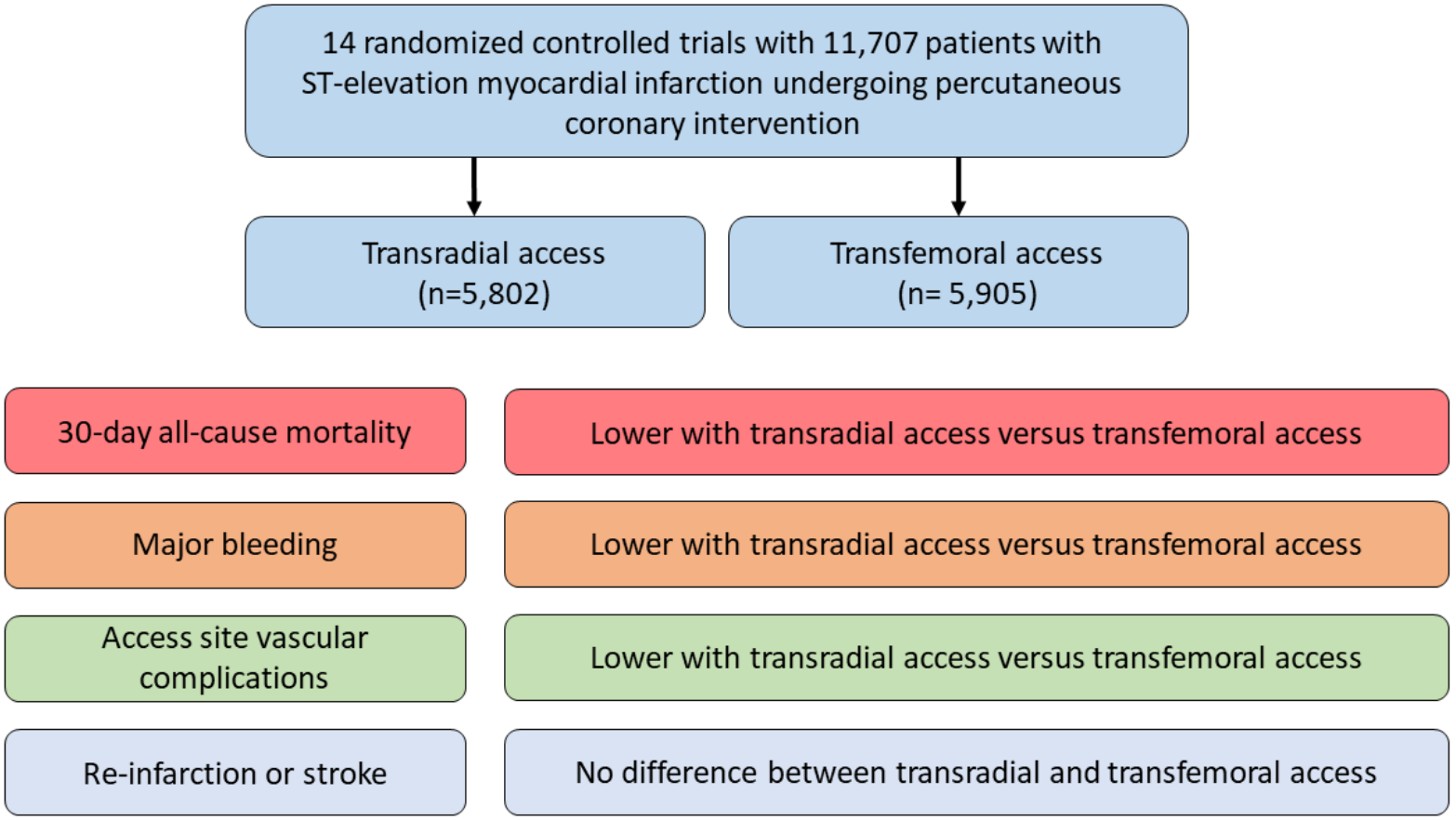
38. Kado H, Patel AM, Suryadevara S, Zenni MM, Box LC, Angiolillo DJ, Bass TA and Guzman LA. Operator Radiation Exposure and Physical Discomfort During a Right Versus Left Radial Approach for Coronary Interventions. *JACC: Cardiovascular Interventions*. 2014;7:810-816.

39. Rashid M, Lawson C, Potts J, Kontopantelis E, Kwok CS, Bertrand OF, Shoaib A, Ludman P, Kinnaird T, De Belder M, et al. Incidence, Determinants, and Outcomes of Left and Right Radial Access Use in Patients Undergoing Percutaneous Coronary Intervention in the United Kingdom. *JACC Cardiovasc Interv*. 2018;11:1021-1033.

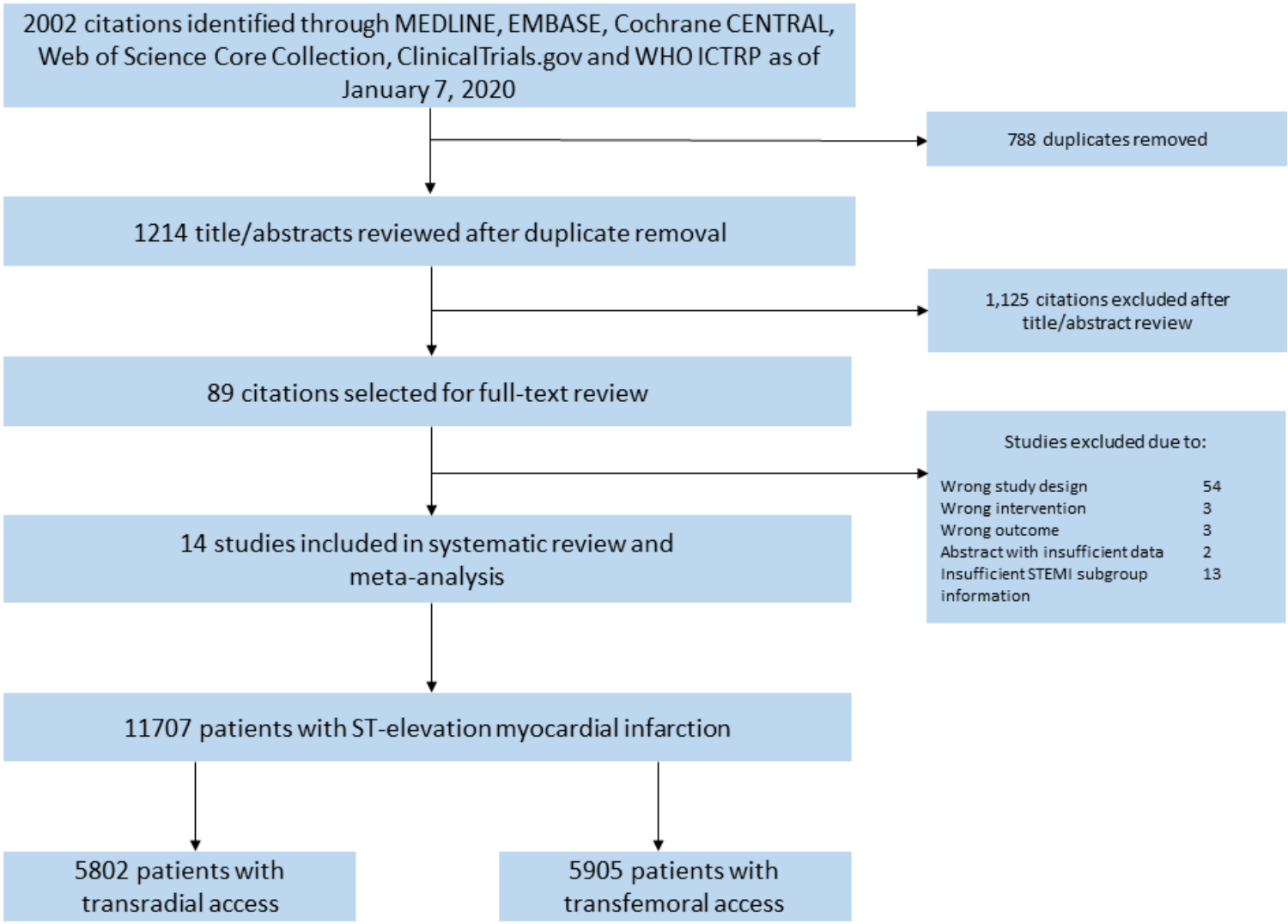
40. Jolly SS, Cairns J, Niemela K, Steg PG, Natarajan MK, Cheema AN, Rao SV, Cantor WJ, Dzavik V, Budaj A, et al. Effect of radial versus femoral access on radiation dose and the importance of procedural volume: a substudy of the multicentre randomized RIVAL trial. *JACC Cardiovascular interventions*. 2013;6:258-66.

41. Bernat I, Aminian A, Pancholy S, Mamas M, Gaudino M, Nolan J, Gilchrist IC, Saito S, Hahalis GN, Ziakas A, et al. Best Practices for the Prevention of Radial Artery Occlusion After Transradial Diagnostic Angiography and Intervention. *An International Consensus Paper*. 2019;12:2235-2246.

Figures



Visual Overview



1

2 Figure 1 – Flow diagram of the systematic review according to the PRISMA guidelines

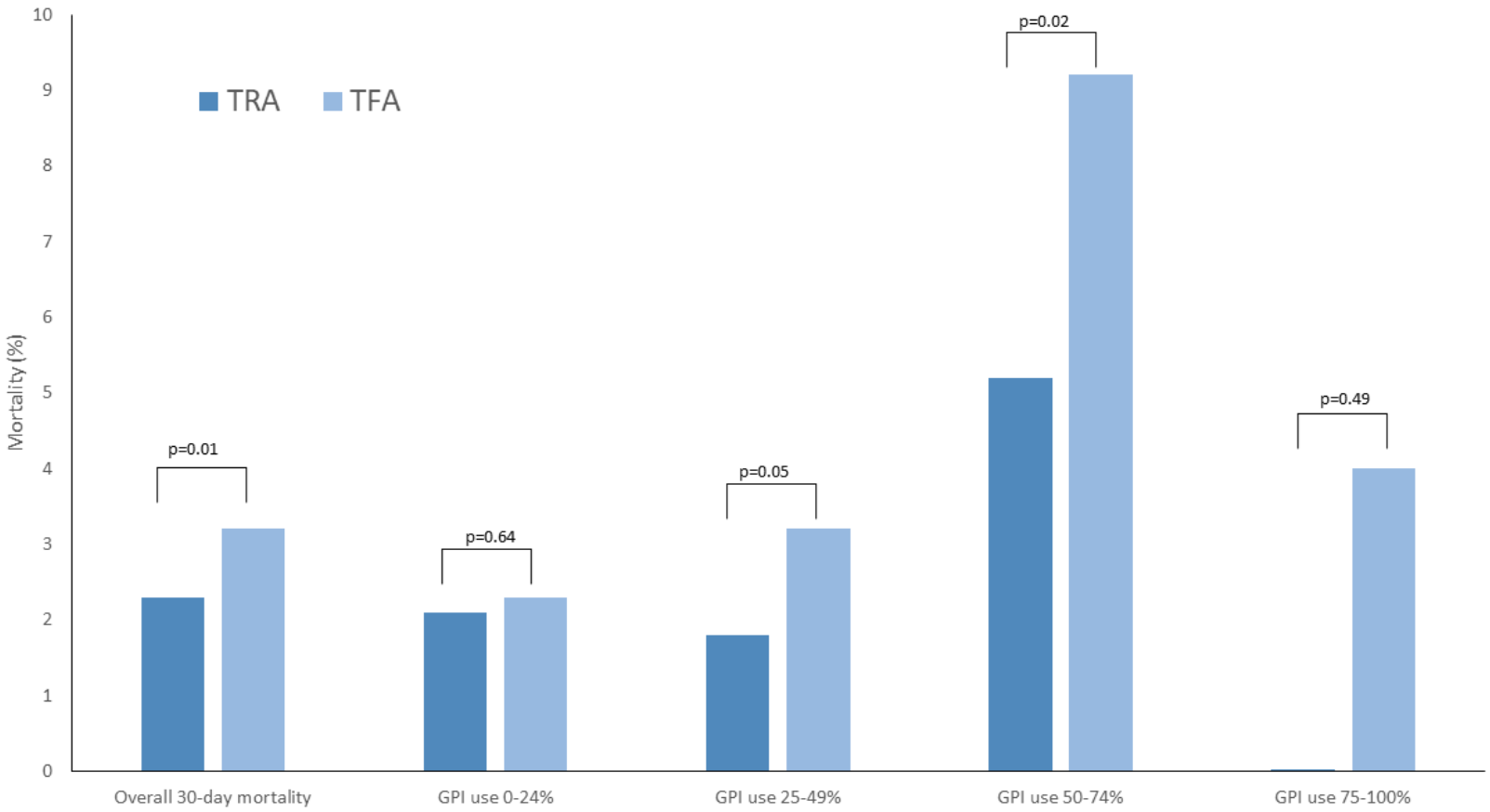


Figure 2 – The association between access site for percutaneous coronary intervention in patients with ST-elevation myocardial infarction and all-cause mortality at 30-days was assessed and stratified by frequency of glycoprotein IIb/IIIa inhibitor frequency of use.

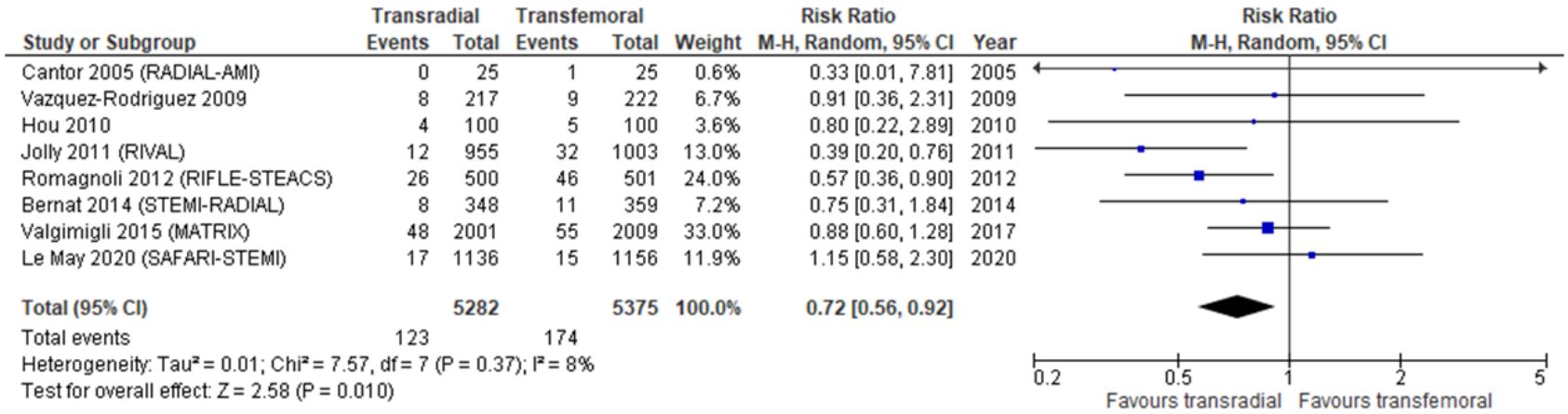


Figure 3 - The association between access site locations percutaneous coronary intervention in patients with ST-elevation myocardial infarction and all-cause mortality at 30-days was assessed. Transradial access was associated with reduced morality (RR 0.72; 95% CI 0.56-0.92) over TFA. CI=confidence interval; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction; TFA = transfemoral access; TRA = transradial access

Clinical outcome	No. of studies	Sample size	Forest plot	Risk ratio with TRA (95% CI)	p-value
Access site complications	**9**	**8674**		**0.40 (0.30-0.53)**	**<0.001**
0-24% GPI use	2	4210		0.49 (0.25-0.99)	0.05
25-49% GPI use	4	3299		0.32 (0.18-0.55)	<0.001
50-74% GPI use	1	1001		0.38 (0.20-0.72)	0.003
75-100% GPI use	2	164		0.37 (0.19-0.72)	0.003
Major bleeding	**12**	**11142**		**0.60 (0.45-0.80)**	**<0.001**
0-24% GPI use	4	6651		0.65 (0.46-0.93)	0.02
25-49% GPI use	3	3104		0.41 (0.16-1.05)	0.06
50-74% GPI use	3	1223		0.65 (0.45-0.94)	0.02
75-100% GPI use	2	164		1.00 (0.21-4.75)	1.00
Myocardial infarction	**10**	**11001**		**0.96 (0.75-1.25)**	**0.78**
Stroke	**8**	**10560**		**1.47 (0.87-2.50)**	**0.15**

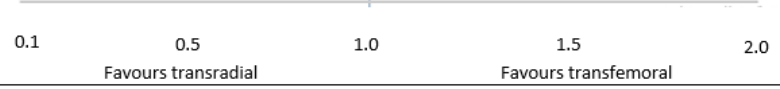


Figure 4 - Secondary outcomes. The association between access site for percutaneous coronary intervention in patients with ST-elevation myocardial infarction and access site complications, major bleeding, myocardial infarction, and stroke were assessed. CI=confidence interval; GPI=glycoprotein IIb/IIIa inhibitor; TRA=transradial access

Table 1 – Baseline characteristics of patients included in systematic review and meta-analysis

	Total no. of participants with available data	Transradial access	Transfemoral access
Total no. of participants	11707	5802	5905
Mean age (years)	11707	60.5 ± 4.1	61.0 ± 4.1
Males, n (%)	11485	4416/5690 (77.6%)	4462/5795 (77.0%)
Mean body mass index, kg/m^2	6157	27.5 ± 1.1	27.4 ± 0.6
Hypertension	9630	2553/4787 (53.3%)	2569/4843 (53.1%)
Diabetes	11588	1108/5742 (19.3%)	1084/5846 (18.5%)
Dyslipidemia	9630	1810/4787 (37.8%)	1880/4843 (38.8%)
Smoking	11588	2496/5742 (43.5%)	2509/5846 (42.9%)
Previous myocardial infarction	10854	543/5376 (10.1%)	562/5478 (10.3%)
Previous percutaneous coronary intervention	9406	419/4657 (9.0%)	480/4749 (10.1%)

Previous coronary artery bypass grafting	4717	30/2349 (1.3%)	28/2368 (1.2%)
Previous stroke	8598	161/4279 (3.8%)	180/4319 (4.2%)
Killip class			
I	6714	2805/3342 (83.9%)	2864/3372 (84.9%)
II	6714	362/3342 (10.8%)	366/3372 (10.9%)
III/IV	6714	175/3342 (5.2%)	142/3372 (4.2%)
Primary PCI	5768	2540/2840 (89.4%)	2632/2928 (89.9%)
Mean total procedure time (min)	1735	45.3 ± 9.2	44.9 ± 9.9
Mean total contrast volume used (mL)	5478	196.1 ± 26.0	198.7 ± 31.2

Weighted mean and standard deviations were calculated based on the sample size of the respective studies. Where median and interquartile range were reported in an individual study, the mean was assumed to be equal to the median and the standard deviation was calculated from interquartile range/1.3.

3.7 Supplemental file – Appendix A - Systematic review protocol

Protocol Number: Version 1 (March 21, 2019)

Title: Transradial vs. transfemoral access for percutaneous coronary intervention in ST-elevation myocardial infarction: a systematic review and meta- analysis protocol

Registration: PROSPERO Registration #127955

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ABBREVIATIONS

CA – coronary angiography
CAD – coronary artery disease
PCI – percutaneous coronary intervention TFA – transfemoral access
TRA – transradial access

INTRODUCTION

Rationale

Assessment of the coronary artery anatomy is commonly performed by coronary angiography (CA), which is the gold standard for evaluation of obstructive coronary artery disease (CAD). Coronary revascularization, which is the opening of obstructed vessels, is most commonly performed by percutaneous coronary intervention (PCI) in patients with obstructive CAD.[1] Traditionally, PCI is performed with implantation of one or more permanent metallic stents which act as a scaffold for arterial recoil and, in the case of drug eluting stents (DES), provide a platform for delivery of anti-proliferative agents. The transradial access (TRA) has rapidly emerged as the preferred vascular access site for CA and PCI with more than 50% of all coronary angiograms being performed via this approach.[2]

There are several reported advantages to TRA including rapid hemostasis, early ambulation after the procedure thereby improving patient comfort and experience, and a decrease in the length of hospital stay.[3] There is also a reported reduction in all-cause mortality, major adverse cardiovascular events, major bleeding, and vascular complications with TRA as compared to transfemoral access.[4]

Recently, a Cochrane review on the transradial vs transfemoral approach for CA and PCI demonstrated that TRA for diagnostic CA or PCI (or both) in all CAD may reduce short-term net adverse clinical events, cardiac death, all-cause mortality, bleeding, and access site complications however there is insufficient evidence regarding the long-term clinical outcomes (i.e. beyond 30 days of follow-up).[5]

This systematic review is being undertaken to update the body of literature pertaining specifically to ST-elevation myocardial infarction. Most recently, the SAFARI-STEMI trial, which is one of the largest studies in the STEMI population, has been presented at the 2019 American College of Cardiology Scientific Sessions.

Objective

To perform a systematic review and meta-analysis to assess the benefits and harms of transradial access vs. transfemoral access for percutaneous coronary intervention in ST-elevation myocardial infarction. The research question can be summarized in PICOS format as follows:

Population – Adult patients undergoing percutaneous coronary intervention for ST-

elevation myocardial infarction
Intervention – Transradial access
Comparator – Transfemoral access
Outcome (primary) – All-cause mortality
Study types – Published and unpublished randomized controlled trials

METHODS

Eligibility Criteria

The review will be limited to randomized control trials (RCTs) of good quality examining transradial access as compared to transfemoral access for ST-elevation myocardial infarction. All other study designs will be excluded given the large volume of RCTs available on this subject.
There will be no restriction based on date of publication or language.

Information Sources

Trials will be identified through systematic searches of the following electronic sources:

1. Cochrane Central Register of Controlled Trials (CENTRAL);
2. MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE;
3. Embase;
4. Web of Science Core Collection

Trial registry repositories will be searched:

1. Clinicaltrials.gov
2. WHO International Clinical Trials Registry Platform (ICTRP)

We will use a combination of both free text words and Medical Subject Heading (MeSH) terms in order to identify studies which assess transradial vs. transfemoral access. We will also systematically search conference proceedings and abstracts from key conferences in the field in order to identify relevant or unpublished literature. Additionally, a manual search of all eligible articles' reference lists, articles citing eligible articles as well as relevant review articles will be carried out in order to identify any additional literature.

Search Strategy See Appendix B

Study Records

Data management

All records retrieved by the searches for possible inclusion will be uploaded to Covidence. Covidence will allow for uploading of search results, screening of abstracts and full text,

completing data collection, conducting risk of bias assessment, resolving disagreements, and exporting data into Review Manager 5 (RevMan) software.

Selection Process

The titles and/or abstracts of all articles identified by the comprehensive search strategy will be screened independently by two reviewers in order to identify those which meet the predefined inclusion criteria. Following this, the full text versions of all potentially eligible studies will first be retrieved and then reviewed by two independent reviewers in duplicate in order to assess their eligibility. Any discrepancies over eligibility will be resolved through discussion and consensus with a third reviewer. If a study is included with more than two intervention arms, only the intervention and control groups that meet the eligibility criteria will be included.

Data Collection Process

A data extraction form will be piloted and agreed upon by the two reviewers screening the articles. Two reviewers will independently extract the predefined data in duplicate from all included studies and any disagreements will be resolved through discussion or through consensus with a third reviewer, if necessary. Any data missing from the reports of included studies will be requested from study authors. The information garnered through the data extraction process will be used to determine each study's quality as well as for synthesizing evidence.

Data Items

Using a predefined data extraction form, the following information will be extracted from all studies meeting the criteria for inclusion by two independent reviewers in duplicate:

- Year of publication
- Study country/setting/context
- Study population
- Sample size
- Participant recruitment procedures
- Baseline characteristics and participant demographics
- Description of interventions and comparators
- Study outcomes
- Funding source
- Author conflicts of interest

Outcomes and Prioritization

The primary outcome for this systematic review and meta-analysis will be all-cause mortality.

Secondary outcomes will be myocardial infarction, major bleeding as defined by each individual study, stroke (ischemic or hemorrhagic), and access site complications (bleeding, hematoma, pseudoaneurysm, distal limb ischemia).

Risk of Bias in Individual Studies

Two reviewers will independently assess the risk of bias in all included studies according to Cochrane Handbook for Systematic Reviews of Intervention criteria in order to determine their relevance and methodological validity. Any discrepancies will be resolved through discussion until consensus is reached, with the assistance of a third reviewer when necessary.

Data Synthesis

We will undertake a meta-analysis only if participants, interventions, comparisons and outcomes are judged to be sufficiently similar to ensure an answer that is clinically meaningful. Heterogeneity will be assessed using visual inspection of forest plots and calculation of statistical measures such as I^2. Meta-analysis will be performed using Review Manager 5 (RevMan) software. Should any cluster-randomized controlled trials be included in the systematic review, the impact of these trials will be specifically addressed so as to obtain precise point estimates.

Subgroup analyses will be performed if any outcome is found to have substantial heterogeneity as well as for the following groups:

- Primary PCI only
- Men vs. women
- Glycoprotein IIb/IIa inhibitor use >50% vs. <50% in the trial
- High vs. low volume femoral operator
- High vs. low volume radial operator

Sensitivity analyses will be performed with the following:

- Excluding studies at high or unclear risk of bias (selection bias)
- Excluding studies with incomplete outcome data (attrition bias)

Confidence in Cumulative Incidence

The five GRADE considerations (i.e. risk of bias, consistency of effect, imprecision, indirectness and publication bias) will be used to assess the quality of the body of evidence for each outcome, and to draw conclusions about the quality of evidence within the text of the review. Two independent reviewers in duplicate will use the online GRADEpro tool for assessment of GRADE.

REFERENCES

1. Simard T, Hibbert B, Ramirez FD, Froeschl M, Chen YX, O'Brien ER. The evolution of coronary stents: a brief review. *Can J Cardiol.* 2014;30(1):35-45.
2. Bertrand OF, Rao SV, Pancholy S, et al. Transradial Approach for Coronary Angiography and Interventions: Results of the First International Transradial Practice Survey. *JACC Cardiovasc Interv.* 2010;3(10):1022-1031.
3. Schussler JM, Vasudevan A, von Bose LJ, Won JI, McCullough PA. Comparative Efficacy of Transradial Versus Transfemoral Approach for Coronary Angiography and Percutaneous Coronary Intervention. *Am J Cardiol.* 2016;118(4):482-488.
4. Ferrante G, Rao SV, Jüni P, et al. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv.* 2016;9(14):1419-1434.
5. Kolkailah AA, Alreshq RS, Muhammed AM, Zahran ME, Anas El-Wegoud M, Nabhan AF. Transradial versus transfemoral approach for diagnostic coronary angiography and percutaneous coronary intervention in people with coronary artery disease. *Cochrane Database of Systematic Reviews.* 2018(4).

3.8 Supplemental file – Appendix B - Systematic review search strategy and results

Table S1 - MEDLINE Ovid – search run on March 25, 2019 and updated January 7, 2020

	Results
1. exp Percutaneous Coronary Intervention/	51861
2. (PCI or "percutaneous coronary intervention*").tw.	38560
3. "percutaneous coronary revascularization*".tw.	494
4. (balloon adj3 angioplast*).tw.	9662
5. atherectom*.tw.	2978
6. 1 or 2 or 3 or 4 or 5	75973
7. transradial.tw.	2266
8. Radial Artery/	6233
9. 7 or 8	7111
10. 6 and 9	1607
11. randomized controlled trial.pt.	498308
12. controlled clinical trial.pt.	93510
13. randomized.ab.	466241
14. placebo.ab.	204244
15. drug therapy.fs.	2171652
16. randomly.ab.	325015
17. trial.ab.	490112
18. groups.ab.	1995431
19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	4608065
20. Limit 19 to humans	3475611
21. 10 and 20	443

Table S2 - CENTRAL – search run on March 25, 2019 and updated January 7, 2020

	Results
1. exp Percutaneous Coronary Intervention/	5288
2. (PCI or "percutaneous coronary intervention*").tw.	10658
3. "percutaneous coronary revascularization*".tw.	120
4. (balloon adj3 angioplast*).tw.	1319
5. atherectom*.tw.	349
6. 1 or 2 or 3 or 4 or 5	14007
7. transradial.tw.	552
8. Radial Artery/	471
9. 7 or 8	870
10. 6 and 9	306
11. randomized controlled trial.pt.	484209
12. controlled clinical trial.pt.	91221
13. randomized.ab.	510806
14. placebo.ab.	262267
15. drug therapy.fs.	0
16. randomly.ab.	232373

17. trial.ab.	412753
18. groups.ab.	443090
19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1107010
20. Limit 19 to humans	1107010
21. 10 and 20	272

Table S3 - EMBASE – search run on March 25, 2019 and updated January 7, 2020

	Results
1. exp percutaneous coronary intervention/	98317
2. (PCI or "percutaneous coronary intervention*").tw.	77055
3. "percutaneous coronary revascularization*".tw.	693
4. (balloon adj3 angioplast*).tw.	13926
5. atherectom*.tw.	4388
6. 1 or 2 or 3 or 4 or 5	135145
7. transradial.tw.	4140
8. radial artery/	12790
9. 7 or 8	15051
10. 6 and 9	3296
11. random$.tw.	1502992
12. factorial$.tw.	37418
13. crossover$.tw.	74737
14. cross over$.tw.	32445
15. cross-over$.tw.	32445
16. placebo$.tw.	306702
17. (doubl$ adj blind$).tw.	210756
18. (singl$ adj blind$).tw.	24303
19. assign$.tw.	387054
20. allocat$.tw.	148508
21. volunteer$.tw.	258472
22. crossover procedure/	62156
23. double blind procedure/	171025
24. randomized controlled trial/	587998
25. single blind procedure/	37618
26. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	2297794
27. (animal/ or nonhuman/) not human/	5995304
28. 26 not 27	2041087
29. 10 and 28	693

Table S4 - Web of Science – search run on March 25, 2019 and updated January 7, 2020

	Results
# 11 #10 AND #9	594
# 10 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)	3771956
# 9 #8 AND #5	1542
# 8 #7 OR #6	10563
# 7 TS="radial arter*"	8611
# 6 TS=transradial	3057
# 5 #4 OR #3 OR #2 OR #1	81255
# 4 TS=atherectom*	4778
# 3 TS=(balloon NEAR/3 angioplast*)	16936
# 2 TS="percutaneous coronary revascularization*"	603
# 1 TS=(PCI or "percutaneous coronary intervention*")	63007

CHAPTER 4: CATHETER-INDUCED CORONARY ARTERY DISSECTION – A SINGLE CENTRE EXPERIENCE

4.1 Chapter overview

Chapter 4 addresses the research question: “Is the risk of rare but catastrophic complications, specifically catheter-induced coronary artery dissection, influenced by access site?”

This chapter examines the association between arterial access site in the occurrence of catheter-induced coronary artery dissection (CICAD), a rare but potentially catastrophic complication of coronary angiography and PCI. As TRA has become the dominant approach worldwide, concerns have persisted regarding whether it's distinct anatomic and mechanical characteristics may predispose patients to an increased risk of CICAD compared with TFA.

Using a large contemporary retrospective cohort spanning more than 15 years and nearly 90,000 consecutive cardiac catheterization procedures, this study evaluates the incidence of CICAD by access site and characterizes patient, procedural, and temporal factors associated with this complication. In addition to comparing TRA and TFA, the analysis explores changes in risk across distinct times of access site adoption, reflecting evolving operator experience and institutional practice patterns. Clinical management strategies and in hospital outcomes associated with CICAD are also described to contextualize the clinical significance of this event.

4.2 Importance of this study

This study addresses a longstanding and largely untested safety concern associated with TRA. Despite widespread adoption of TRA and its demonstrated benefits in reducing bleeding and

mortality, anecdotal reports and theoretical considerations have suggested an increased risk of CICAD. Prior to this study, no large-scale analysis has systematically evaluated this association by access site. Second, this work represents the largest reported series of CICAD to date and is the first to examine its incidence in relation to arterial access site selection. By leveraging a high-volume quaternary care centre with detailed procedural reporting, the study provides robust real-world estimates of CICAD incidence, risk factors, and outcomes. Third, the temporal analysis offers important insights into the role of operator and institutional experience. The finding of an apparent association between TRA and increase CICAD risk was present during the femoral predominant era, but not after a transition to a "radial first" strategy, suggesting that early signals of harm may reflect learning curve effects rather than intrinsic limitations of the access site itself. Finally, this chapter reinforces the clinical implications of CICAD demonstrating substantial in-hospital mortality and frequent need for bailout interventions. By quantifying these outcomes and identifying procedural correlates, this study underscores the importance of vigilance, technical expertise, and risk mitigation strategies regardless of access site selection.

Within the broader context of this thesis, this chapter complements earlier evidence demonstrating the benefits of TRA by rigorously evaluating one of its most feared complications. Together, these findings provide a balanced and comprehensive assessment of access site safety, informing clinical decision making in guiding future research on procedural optimization and interventional cardiology.

4.3 Manuscript status

This manuscript has been published:

Di Santo P, Boland PW, Abdel-Razek O, Simard T, Jung RG, Parlow S, Motazedian P, Joseph J, Theriault-Lauzier P, Alomar A, Hillani A, Alhassani S, Bayoumi M, Kyeremanteng K, Coyle D, Fergusson D, Wells GA, Froeschl M, Labinaz M, Russo JJ, Hibbert B. *Association between access site for coronary angiography and catheter-induced coronary artery dissection.* JSCAI (2023). 2(24):100606

4.4 Author roles/contributions

PDS, PWB, OAR, and BH conceived the study. PDS and PWB drafted the protocol, which was reviewed and approved by all authors. PDS, PWB, OAR, SP, PTL, AA, AH, SA, MB, KK, MF, ML, JJR and BH provided clinical perspective. PDS and PWB extracted study data. PDS analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors provided comments on the draft and approved the version of the manuscript submitted for publication.

4.5 Related thesis appendices

Appendix B - PDF of published manuscript – catheter-induced coronary artery dissection

4.6 Manuscript

Association between access site for coronary angiography and catheter-induced coronary artery dissection

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Word count: 2792

Declaration of Interests: None of the authors have any relevant disclosures

Highlights

- Catheter-induced coronary artery dissection (CICAD) is a feared complication of coronary angiography
- Access site was not associated with increased risk of CICAD
- Bailout stenting of the affected coronary artery is the most common treatment for CICAD
- CICAD is associated with an in-hospital mortality of 8.5%

Abstract

Introduction

Catheter-induced coronary artery dissection (CICAD) is a rare complication of coronary angiography. The association between access site and CICAD remains unclear; however, transradial access (TRA) may be associated with a higher incidence of CICAD due to access vessel tortuosity and the mechanical disadvantage of catheters designed for the transfemoral approach (TFA).

Methods

In this retrospective study, the reports of consecutive left heart catheterizations between April 2007 and December 2021 were reviewed for CICAD. Patients were excluded if the procedural report did not report arterial access site. Identified CICAD cases were reviewed in detail.

Results

There were 142/89,876 (0.16%) identified cases of CICAD. Access site was not associated with an increased risk of CICAD (0.18% with TRA vs. 0.15% with TFA, RR 1.18; 95% CI 0.84-1.65, p=0.34) over the entire study period. With respect to TRA-related CICAD, male sex was associated with a decreased risk of dissection (RR 0.64, 95% CI 0.41-0.99, p=0.04) but ST-elevation myocardial infarction at presentation was associated with an increased risk (RR 3.01, 95% CI 1.86-4.85, p<0.01). In the TFA predominant era, TRA was associated with an increased risk of CICAD (0.48% TRA vs. 0.11% TFA, RR 3.42, 95% CI 2.05-5.69, p<0.01) – an association that was not present in the TRA predominant era. In-hospital mortality in patients with CICAD was 8.5%.

Conclusions

CICAD is a rare complication of coronary angiography. Over a 15-year period, we did not demonstrate an association between access site and an increased risk of CICAD. There is substantial mortality associated with CICAD.

Keywords

Transradial approach

Transfemoral approach

Catheter-induced coronary artery dissection

Coronary angiography

Percutaneous coronary intervention

Introduction

Transradial access (TRA) has emerged over transfemoral access (TFA) as the preferred approach for coronary angiography. The advantages of TRA include lower access site complications, earlier patient ambulation and improved patient comfort.[1] Several randomized clinical trials and meta-analyses comparing TRA to TFA in acute coronary syndrome (ACS) have shown lower bleeding complications and reduced mortality favoring TRA.[2–6]

While there are numerous advantages to TRA, there are disadvantages associated with this access site that must be considered. Patient factors include difficulty obtaining radial artery access, radial artery spasm and difficulty with navigating tortuous upper extremity arterial anatomy. The catheters used for coronary angiography and percutaneous coronary angiography (PCI) were designed for use with TFA, contributing to increased difficulty with catheter manipulation and coronary intubation when utilized from a radial approach. Initial concerns about increased procedural failure, contrast use and radiation exposure have been mitigated by studies showing that these parameters improve with operator experience.[7,8]

Catheter-induced coronary artery dissection (CICAD) is a rare complication of coronary angiography and PCI. The incidence of left main involvement was estimated between 0.03% and 0.07% in large case series,[9–11] while the incidence of right coronary artery CICAD is estimated at 0.14%.[12] In a large contemporary series, the incidence of CICAD was 0.09% and most common with guide catheters.[13] Anecdotally, TRA is accompanied by an increased risk of CICAD, theoretically due to access vessel tortuosity and the mechanical disadvantage of catheters designed for TFA.

In the retrospective study herein, we aim to compare the risk of CICAD in TRA versus TFA, as well as describe the risk factors, management and clinical outcomes of CICAD at a large academic cardiac care centre.

Methods

The reports of consecutive cardiac catheterization procedures at a large quaternary care cardiac centre between April 2007 and December 2021 were obtained. Patients could be included more than once if they had repeat catheterizations performed during the study period. Patients were excluded if the procedural report did not report arterial access site. Reports with identified dissection were reviewed for mechanism of dissection (e.g. catheter-induced, spontaneous coronary artery dissection, post-intervention stent edge dissection, etc). Procedures involving transbrachial access were treated as TRA for the purpose of analysis. The study complied with the Declaration of Helsinki and was approved by the Ottawa Health Sciences Network Research Ethics Board. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

A "catheter-induced coronary artery dissection" was defined as an unplanned dissection of the left main, right coronary artery, left internal thoracic artery, right internal thoracic artery or aortic dissection/hematoma for which the catheter was identified as the cause by the operator's procedural report. In cases where both TRA and TFA were reported as being accessed, CICAD cases were further reviewed to identify the arterial access resulting in the dissection. Procedural details, including equipment information such as catheter type, size, and shape were obtained from the procedure log. Other key data, including age, height, weight, sex, procedure date, cardiovascular risk factors, operators, and presence of ST-elevation myocardial infarction were also collected from the catheterization reports and chart review.

The primary outcome of this study was the incidence of CICAD by TRA vs. TFA access sites. Secondary outcomes included evaluating risk factors for CICAD by access site. We also describe the management and clinical outcomes of patients with CICAD.

Outcomes were assessed using unadjusted chi-squared analyses to compare the CICAD and non-CICAD groups, and corresponding relative risks were generated along with 95% confidence intervals. A sensitivity analysis was performed to evaluate the association between CICAD and access site stratified according to most frequent access site utilized at our institution in a given year - a predominant TFA era (i.e. prior to 2012) and a predominant TRA era (i.e. 2012-2021; “radial first”). All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

Results

A total of 90,909 consecutive cardiac catheterizations were carried out between April 2007 and December 2021. There were 1,033 catheterizations without information on arterial access which were excluded (Figure 1). The baseline characteristics of the entire study cohort as well as cases with and without CICAD are presented in Table 1. The mean age of study patients was 66.1 ± 12.1 years, and most patients were males (68.2% across the entire study). Traditional cardiovascular risk factors were similar between the CICAD and non-CICAD groups.

A total of 142 cases were found to have CICAD (Table 2). Access site was not associated with an increased risk of CICAD (0.18% of all TRA cases vs. 0.15% of all TFA cases, relative risk [RR] 1.18; 95% confidence interval [CI] 0.84-1.65, p=0.34). Age was not associated with TRA-related CICAD (p=0.86) or TFA-related CICAD (p=0.30). With respect to TRA-related CICAD, male sex was associated with a decreased risk of dissection (RR 0.64, 95% CI 0.41-0.99, p=0.04), but not with TFA (p=0.84). STEMI was associated with an increased risk of dissection in TRA (RR 3.01, 95% CI 1.86-4.85, p<0.01) but not with TFA (RR 1.46, 95% CI 0.72-2.97, p=0.30). The right coronary artery was the most affected artery in both the TRA-related CICAD (54.1%) and TFA-related CICAD (43.9%). Guide catheters and 6-French catheters were used in approximately 80% of CICAD cases across both access site groups.

In terms of absolute numbers, the Extra Back Up (15.0% usage in the overall cohort) and Judkins Right (39.9% usage in overall cohort) were the two most common catheter designs associated with CICAD and comprised more than 50% of CICAD cases, followed by the Amplatz Left (4.7% usage in overall cohort) and Judkins Left (38.1% usage in overall cohort) (Table 2). The

rate of CICAD per 10,000 uses of the most commonly utilized catheters was greatest with the Amplatz Left (126.1 cases of CICAD per 10,000 uses) followed by the Extra Back Up (21.0 cases of CICAD per 10,000 uses), Judkins Left (9.9 cases of CICAD per 10,000 uses), and Judkins Right (3.6 cases of CICAD per 10,000 uses).

In a sensitivity analysis, the association between access site and CICAD was evaluated from 2007-2011 (i.e. TFA predominant era) and 2012-2021 (i.e. TRA predominant era) (Figure 2). In the TFA predominant era, there were a total of 59 cases of CICAD and TRA was associated with an increased risk of dissection (0.48% TRA vs. 0.11% TFA, RR 3.42, 95% CI 2.05-5.69, $p<0.01$). In the TRA predominant era, there were 83 cases of CICAD, with 0.13% in the TRA group and 0.16% in the TFA group and the association between access site and CICAD was no longer present ($p=0.40$).

The management of CICAD involved bailout stenting in 99 (69.7%) of cases and emergency coronary artery bypass graft (CABG) surgery in 18 (12.7%) of cases (Table 3). There were 21 patients (14.8%) in whom the CICAD was felt to be self-limited and improved during intra-procedural observation – notably, the majority of these were isolated aortic injury (n=12). Two patients required emergent mechanical circulatory support with veno-arterial extra-corporeal membrane oxygenation prior to revascularization. Two patients (1.4%) experienced immediate death at time of CICAD with inability to achieve revascularization. Of the 18 patients who were referred for CABG, 3 (17%) died during the surgery. In total, 12 patients (8.5%) with CICAD died in hospital. Of these 12 patients who died in hospital, 7 (58%) had retrograde extension of the CICAD into the aorta noted during the index procedure.

Discussion

We report a series of 142 catheter-induced coronary artery dissections at our institution over a 15-year period. To the best of our knowledge, this represents the largest reported series of CICAD in the literature to date and the first to evaluate the incidence by vascular access site. CICAD remains a very rare complication of coronary angiography, with an incidence of 16 cases per 10,000 procedures in our series, similar to the incident rates previously reported in the literature.[9–13]

The TRA approach has a significant learning curve due to various factors including catheter manipulation which is impeded by radial vasospasm, tortuous subclavian anatomy and the use of catheters designed for TFA.[7] Anecdotally, it has been felt that these factors increased the probability of suboptimal catheter engagement in non-coaxial or deep-seated positions, predisposing to CICAD. Similarly, torque introduced by catheter manipulation can transfer significant potential energy to the interface between the catheter and coronary wall. Despite these theoretical possibilities, we did not demonstrate an association between access site and CICAD over a 15-year period. However, when stratified by 'predominant femoral access' between the years 2007-2011, we found the risk of CICAD with TRA was nearly 3.5 times greater than with femoral access; however, this association was no longer present once our centre had transitioned to 'predominant radial access' (i.e. 2012 and onwards). Similar to the initial concerns about increased procedural failure, contrast use, and radiation exposure which have been refuted by studies showing that these parameters improve with operator experience,[7,8] perhaps the risk of CICAD with radial access is also reduced as we progress along the learning curve of this approach.

The most common catheter designs associated with CICAD were the Extra Back Up and Judkins Right. The Amplatz Left catheter has been postulated to cause a disproportionate number of iatrogenic dissections.[14] Our series corroborates this finding, with the Amplatz Left design implicated in 16.2% of CICAD cases, though it was used in only 4.7% of all procedures. The Special Curve design was the CICAD culprit in 4.9% of cases, though it was only used in 0.3% of procedures (206 cases of CICAD per 10,000 uses of the catheter), suggesting it is a particularly risky catheter. Though the EBU was responsible for nearly a quarter of all CICAD, this likely represents its widespread use at our institution (15.0% of procedures). Similarly, while the Judkins catheters are responsible for a combined 42% of CICAD, they are used in nearly 80% of cases at our institution, suggesting they have a lower risk of CICAD. However, the Judkins catheters have both diagnostic and guide designs, which we were unable to differentiate in the "overall" group data, and the lower frequency of CICAD might simply be reflective of a lower risk with diagnostic catheters. Similarly, aggressive catheters such as the Amplatz Left are used more frequently in complex disease where more support is required, which may also increase the risk of CICAD.

CICAD is a feared complication because of the perceived high morbidity and mortality.[11] Conservative management, bailout stenting and emergency CABG have all been described as CICAD treatment strategies.[9–12,15–17] In our series, the treatment strategy of choice was bailout stenting (69.7%) followed by conservative management (14.8%). The use of emergency CABG was less common (12.7%). CICAD was associated with an 8.5% in-hospital mortality, which is

slightly greater than previously reported.[11,13] The reason for the discrepancy is unclear and may reflect differences in practice or reporting patterns at our institutions. Additionally, of the 12 patients who died in hospital, 7 (58%) had retrograde extension of the CICAD into the aorta noted during their procedure. Clinicians should maintain a high index of suspicion of aortic involvement with CICAD and have a low threshold to pursue imaging of the ascending aorta as this may be a potentially modifiable target for intervention following CICAD. Based on our data, the mortality of CICAD is substantial and every step should be taken to mitigate the risk of this feared complication.

Our study is not without limitations. Firstly, we relied on catheterization reports to identify cases of reported CICAD, which are likely underreported and therefore our work likely represents an underestimate of the incidence of this complication. Secondly, angiographic images were only available from 2014 thereby limiting our ability to grade the CICAD events according to the National Heart, Lung and Blood Institute (NHLBI) system.[18] Similarly, we were unable to provide insight into factors described by other authors that may contribute to the risk of dissection, including ascending aorta configuration, aberrant anatomy of the coronary ostium, presence of proximal atherosclerosis or plaque rupture or non-coaxial catheter engagement.[16,19,20] Finally, this retrospective, observational study is hypothesis generating, and conclusions are limited by unforeseen bias and variables left unaccounted for.

Conclusions

CICAD is a rare complication of coronary angiography and PCI. Over a 15-year period, we did not demonstrate an association between access site and incidence of CICAD. There is considerable mortality associated with CICAD and bailout stenting is the most common treatment, when possible. All operators must remain vigilant and mitigate the risk of CICAD whenever possible.

References

1. Rao SV, Turi ZG, Wong SC, Brener SJ, Stone GW. Radial Versus Femoral Access. *Journal of the American College of Cardiology*. 2013;62(17_Supplement):S11-S20. doi:10.1016/j.jacc.2013.08.700

2. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial Versus Femoral Randomized Investigation in ST-Segment Elevation Acute Coronary Syndrome: The RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) Study. *Journal of the American College of Cardiology*. 2012;60(24):2481-2489. doi:10.1016/J.JACC.2012.06.017

3. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet (London, England)*. 2011;377(9775):1409-1420. doi:10.1016/S0140-6736(11)60404-2

4. Bernat I, Horak D, Stasek J, et al. ST-Segment Elevation Myocardial Infarction Treated by Radial or Femoral Approach in a Multicentre Randomized Clinical Trial: The STEMI-RADIAL Trial. *Journal of the American College of Cardiology*. 2014;63(10):964-972. doi:10.1016/J.JACC.2013.08.1651

5. Valgimigli M, Gagnor A, Calabró P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet (London, England)*. 2015;385(9986):2465-2476. doi:10.1016/S0140-6736(15)60292-6

6. Di Santo P, Simard T, Wells GA, et al. Transradial Versus Transfemoral Access for Percutaneous Coronary Intervention in ST-Segment–Elevation Myocardial Infarction. *Circulation: Cardiovascular Interventions*. 2021;14(3):e009994. doi:10.1161/CIRCINTERVENTIONS.120.009994

7. Simard T, Hibbert B, Natarajan MK, et al. Impact of Centre Experience on Patient Radiation Exposure During Transradial Coronary Angiography and Percutaneous Intervention: A Patient-Level, International, Collaborative, Multi-Centre Analysis. *Journal of the American Heart Association*. 2016;5(6). doi:10.1161/JAHA.116.003333

8. Hess CN, Peterson ED, Neely ML, et al. The learning curve for transradial percutaneous coronary intervention among operators in the United States: a study from the National Cardiovascular Data Registry. *Circulation*. 2014;129(22):2277-2286. doi:10.1161/CIRCULATIONAHA.113.006356

9. Cheng CI, Wu CJ, Hsieh YK, et al. Percutaneous coronary intervention for iatrogenic left main coronary artery dissection. *International Journal of Cardiology*. 2008;126(2):177-182. doi:10.1016/j.ijcard.2007.03.125

10. Lee SW, Hong MK, Kim YH, et al. Bail-out stenting for left main coronary artery dissection during catheter-based procedure: acute and long-term results. *Clinical cardiology*. 2004;27(7):393-395.

11. Eshtehardi P, Adorjan P, Togni M, et al. Iatrogenic left main coronary artery dissection: Incidence, classification, management, and long-term follow-up. *American Heart Journal*. 2010;159(6):1147-1153. doi:10.1016/j.ahj.2010.03.012

12. Chai HT, Yang CH, Wu CJ, et al. Utilization of a double-wire technique to treat long extended spiral dissection of the right coronary artery. Evaluation of incidence and mechanisms. *International heart journal*. 2005;46(1):35-44.

13. Ramasamy A, Bajaj R, Jones DA, et al. Iatrogenic catheter-induced ostial coronary artery dissections: Prevalence, management, and mortality from a cohort of 55,968 patients over 10

years. *Catheterization and Cardiovascular Interventions*. 2021;98(4):649-655. doi:10.1002/ccd.29382

14. Dunning DW, Kahn JK, Hawkins ET, O'Neill WW. Iatrogenic coronary artery dissections extending into and involving the aortic root. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2000;51(4):387-393.

15. Connors JP, Thanavaro S, Shaw RC, Sandza JG, Ludbrook PA, Krone RJ. Urgent myocardial revascularization for dissection of the left main coronary artery: a complication of coronary angiography. *The Journal of thoracic and cardiovascular surgery*. 1982;84(3):349-352.

16. Boyle AJ, Chan M, Dib J, Resar J. Catheter-induced coronary artery dissection: risk factors, prevention and management. *The Journal of invasive cardiology*. 2006;18(10):500-503.

17. Awadalla H, Sabet S, El Sebaie A, Rosales O, Smalling R. Catheter-induced left main dissection incidence, predisposition and therapeutic strategies experience from two sides of the hemisphere. *The Journal of invasive cardiology*. 2005;17(4):233-236.

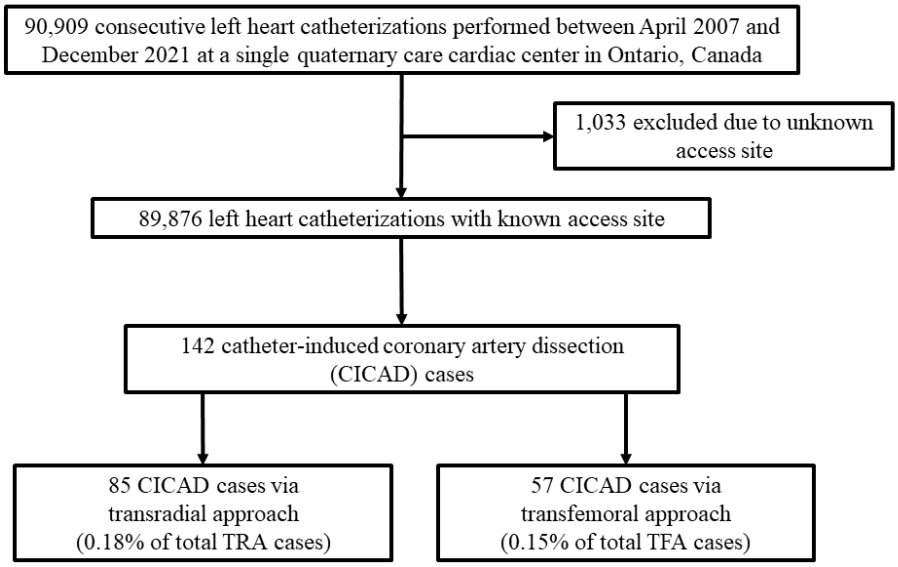
18. Rogers JH, Lasala JM. Coronary artery dissection and perforation complicating percutaneous coronary intervention. *The Journal of invasive cardiology*. 2004;16(9):493-499.

19. Ammann P, Brunner-La Rocca HP, Angehrn W, Roelli H, Sagmeister M, Rickli MD H. Procedural complications following diagnostic coronary angiography are related to the operator's experience and the catheter size. *Catheterization and Cardiovascular Interventions*. 2003;59(1):13-18. doi:10.1002/ccd.10489

20. Namazi MH, Rostami RT, Mohammadi A, et al. Iatrogenic left main artery dissection: A catastrophic complication. *Experimental and clinical cardiology*. 2012;17(4):254-256.

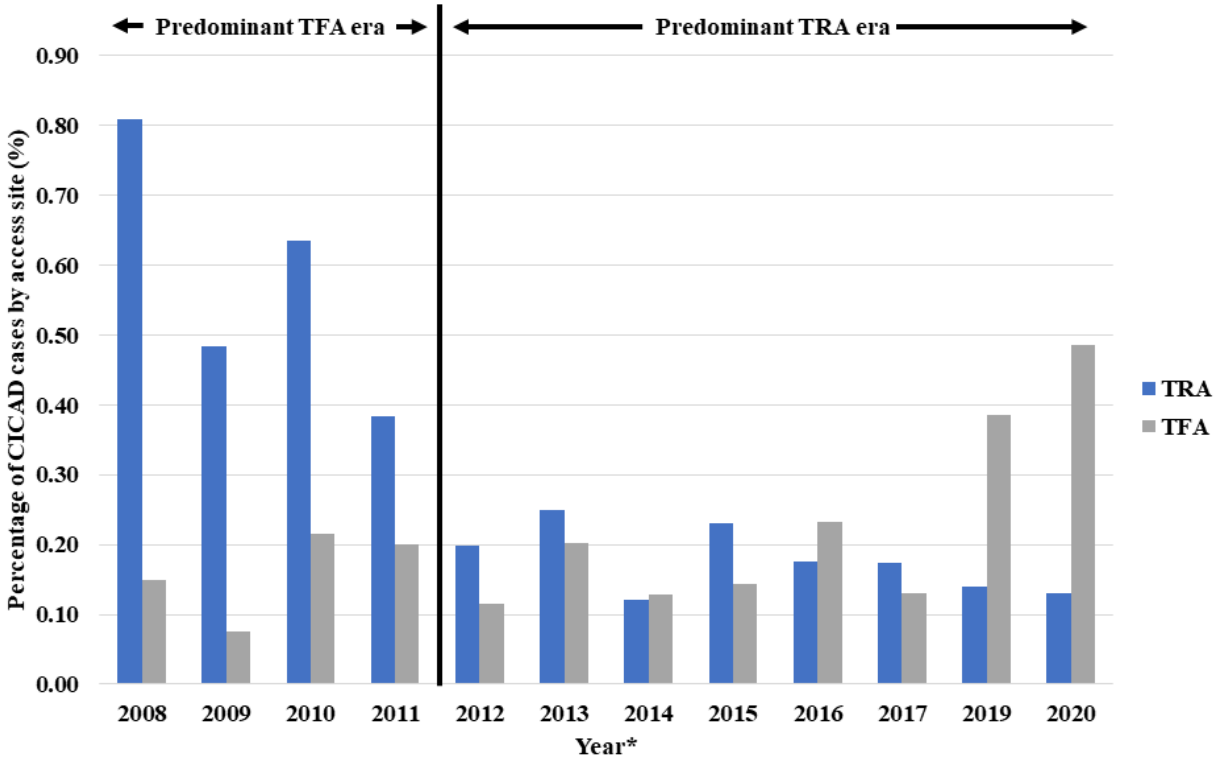
Figure Legends

Figure 1 – Flow diagram of study patients.



Legend: CICAD-catheter-induced coronary artery dissection; TFA-transfemoral access; TRA-transradial access

Figure 2 – Percentage of catheter-induced coronary artery dissection cases over study period stratified by access site. In the transfemoral access (TFA) predominant era, transradial access (TRA) was associated with an increased risk of dissection (0.48% TRA vs. 0.11% TFA, RR 3.42, 95% CI 2.05-5.69, p<0.01). In the TRA predominant era, the association between access site and CICAD was no longer present (p=0.40). *Only years in which there were more than 5 CICAD cases have been included in the figure



Legend: CICAD-catheter-induced coronary artery dissection; TFA-transfemoral access; TRA-transradial access

Tables

Table 1 – Baseline demographics of overall cohort as well as patients with and without catheter-induced coronary artery dissection

	Left heart catheterization (n=89,876)	**CICAD (n=142)**	**Non-CICAD (n=89,734)**
Age – (years) mean ± SD	66.1 ± 12.1	65.5 ± 12.9	65.9 ± 12.1
Males – no. (%)	60,956 (68.2%)	89 (63.1%)	60,867 (68.2%)
Height – (meters) mean ± SD	1.70 ± 0.10	1.69 ± 0.11	1.70 ± 0.10
Weight – (kilograms) mean ± SD	83.8 ± 19.8	81.8 ± 17.9	83.4 ± 19.8
Past medical history			
Hypertension – no. (%)	30,005 (33.4%)	43 (30.3%)	29,962 (33.4%)
Dyslipidemia – no. (%)	25,440 (28.3%)	30 (21.1%)	25,410 (28.3%)
Diabetes – no. (%)	23,047 (25.6%)	46 (32.4%)	23,001 (25.6%)
Active smoking – no. (%)	15,556 (17.3%)	24 (16.9%)	15,532 (17.3%)
Family history of premature coronary artery disease – no. (%)	4,428 (4.9%)	3 (2.1%)	4,425 (4.9%
Procedural details			
ST-elevation myocardial infarction at presentation – no. (%)	10,071 (11.2%)	32 (22.5%)	10,039 (11.2%)
Transradial access – no. (%)	47,826 (53.2%)	85 (59.9%)	47,741 (53.2%)
Transfemoral access – no. (%)	37,778 (42.0%)	57 (40.1%)	37,721 (42.0%)
Multiple access sites during procedure – no. (%)	4,272 (4.8%)	30 (21.1%)	4,272 (4.8%)
Percutaneous coronary intervention during procedure – no. (%)	38,985 (43.4%)	115 (81.0%)	38,870 (43.3%)

CICAD – catheter-induced coronary artery dissection; SD – standard deviation

Table 2 – Catheter-induced coronary artery dissection procedural details by access site

	Total CICAD (n=142)	Transradial access (n=85)	Transfemoral access (n=57)
Procedural characteristics			
ST-elevation myocardial infarction at presentation – no. (%)	35 (24.6%)	23 (27.1%)	9 (15.8%)
Coronary artery involved in CICAD			
Left coronary artery dissection – no. (%)	52 (36.6%)	32 (37.7%)	20 (35.1%)
Right coronary artery dissection – no. (%)	71 (50%)	46 (54.1%)	25 (43.9%)
Isolated aortic dissection – no. (%)	10 (7.0%)	6 (7.1%)	4 (7.1%)
Left internal thoracic artery dissection – no. (%)	6 (4.2%)	1 (1.2%)	5 (8.8%)
Right internal thoracic artery dissection – no. (%)	3 (2.1%)	0 (0.0%)	3 (5.3%)
Catheter type			
Diagnostic	31 (21.8%)	15 (17.6%)	16 (28.1%)
Guide	110 (77.5%)	69 (81.2%)	41 (71.9%)
Unknown	1 (0.7%)	1 (1.2%)	0 (0.0%)
Catheter design			
Amplatz Left	23 (16.2%)	11 (12.9%)	12 (21.1%)
Extra Back-Up	35 (24.6%)	22 (25.9%)	13 (22.8%)
Hockey Stick	3 (2.1%)	0 (0.0%)	3 (5.3%)
Judkins Left	15 (10.6%)	11 (12.9%)	4 (7.0%)
Judkins Right	44 (31.0%)	27 (31.8%)	17 (29.8%)
Multi-Aortic Curves	3 (2.1%)	3 (3.5%)	0 (0.0%)
Multipurpose	2 (1.4%)	1 (1.2%)	1 (1.8%)
Radial Curve	1 (0.7%)	1 (1.2%)	0 (0.0%)
Special Curve	7 (4.9%)	7 (8.2%)	0 (0.0%)
Internal Mammary	7 (4.9%)	0 (0.0%)	7 (12.3%)
Ikari Left	1 (0.7%)	1 (1.2%)	0 (0.0%)
Unknown	1 (0.7%)	1 (1.2%)	0 (0.0%)
Catheter size			
5-French	13 (9.2%)	11 (12.9%)	2 (3.5%)
6-French	123 (86.6%)	72 (84.7%)	51 (89.5%)
>6-French	5 (3.5%)	1 (1.2%)	4 (7.0%)
Unknown	1 (0.7%)	1 (1.2%)	0 (0.0%)

CICAD – catheter-induced coronary artery dissection

Table 3 – Outcomes of patients with CICAD

	Total CICAD (n=142)
Management of CICAD	
Medical therapy	21 (14.8%)
Bail-out stenting	99 (69.7%)
Coronary artery bypass graft surgery	18 (12.7%)
Extra-corporeal membrane oxygenation prior to revascularization	2 (1.4%)
None – death prior to revascularization established	2 (1.4%)
Clinical outcomes	
Death during index procedure	2 (1.4%)
Death during coronary artery bypass graft surgery	3 (2.1%)
Death in-hospital	12 (8.5%)

CICAD – catheter-induced coronary artery dissection

4.7 Supplemental file – Supplemental appendix

Supplemental Table 1: National Heart, Lung and Blood Institute (NHLBI) classification

NHLBI class	**Number of events**
Type A dissections (radiolucent areas within the coronary lumen during contrast injection, with minimal or no persistence of contrast)	7
Type B dissections (parallel tracts or double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence)	21
Type C dissections (contrast outside the coronary lumen with persistence of contrast in the area after clearance of contrast from the coronary lumen)	5
Type D dissections (spiral luminal filling defects, frequently with extensive contrast staining of the vessel)	5
Type E dissections (new, persistent filling defects)	1
Type F dissections (lead to total occlusion of the coronary artery, without anterograde flow)	15

Supplemental Table 2 – Proportion of access site by transradial and transfemoral approaches stratified by year of the procedure*

Year	% TRA	% TFA
2008	10%	87%
2009	13%	84%
2010	22%	74%
2011	46%	51%
2012	52%	43%
2013	53%	41%
2014	56%	38%
2015	62%	33%
2016	68%	26%
2017	71%	23%
2018	72%	22%
2019	81%	15%
2020	81%	14%

* - total per year may not equal 100% as procedures with multiple access sites were not included

Supplemental Table 3 – Procedural characteristics of catheter-induced coronary artery dissection cases that resulted in in-hospital death

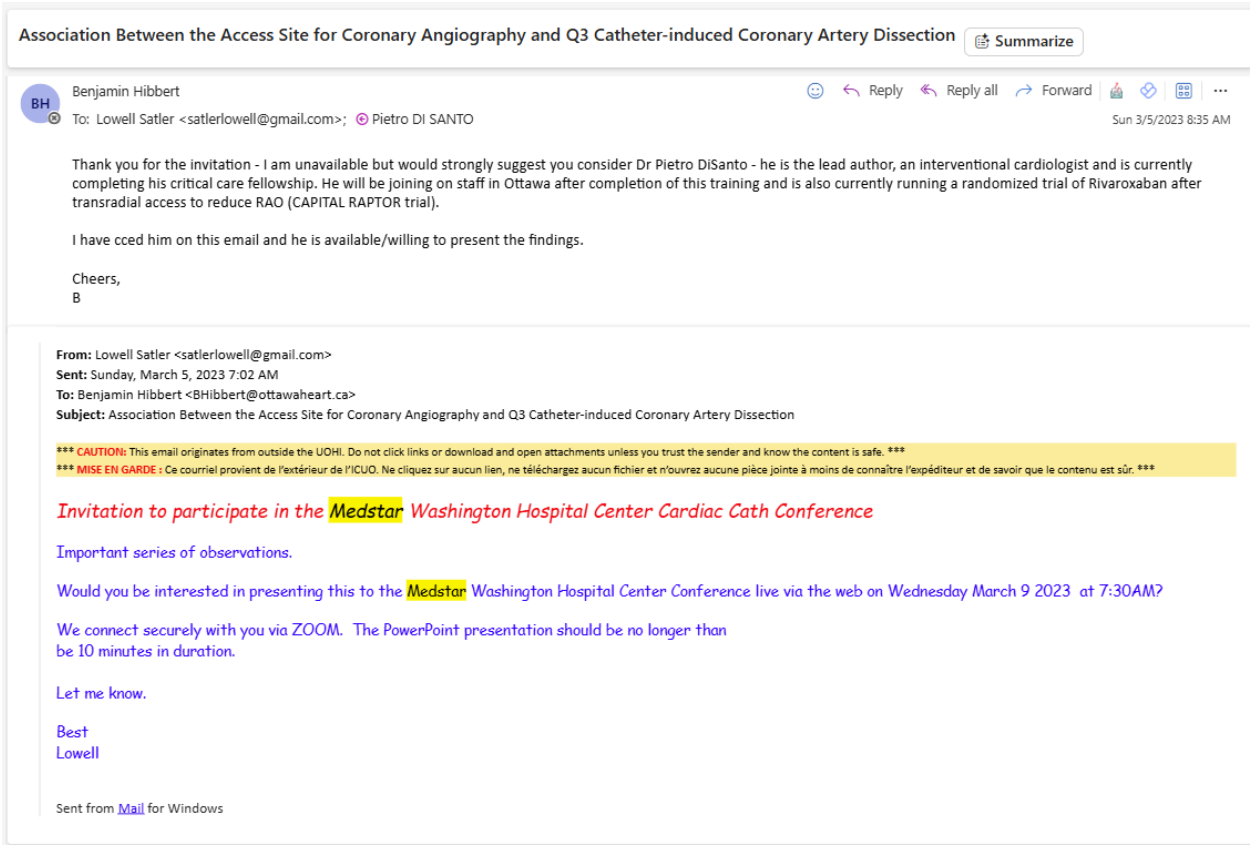
Year	Access site	Type of procedure	Catheter Design	Catheter Size	Artery involved
2008	TRA	PCI	Multi-Aortic Curve	6Fr	RCA
2009	TFA	PCI	Extra Back Up	6Fr	LCA
2009	TRA	PCI	Amplatz Left	6Fr	RCA
2010	TRA	PCI	Special Curve	6Fr	RCA
2011	TRA	PCI	Extra Back Up	6Fr	LCA
2011	TRA	PCI	Judkin's Left	6Fr	LCA
2012	TRA	PCI	Amplatz Left	6Fr	RCA
2015	TRA	PCI	Judkin's Right	5Fr	RCA
2017	TFA	PCI	Amplatz Left	6Fr	LCA
2019	TRA	PCI	Extra-Back Up	6Fr	LCA
2019	TFA	PCI	Judkin's Left	6Fr	LCA
2020	TRA	PCI	Amplatz Left	6Fr	RCA

LCA = left coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; TFA = transfemoral access; TRA = transradial access

4.8 Supporting material

Invited presentation:

Mar 2023 Cardiac Cath Conference Rounds
Association between access site and catheter induced coronary artery dissection
Medstar Washington Hospital Center, Washington, D.C., United States



Association Between the Access Site for Coronary Angiography and Q3 Catheter-induced Coronary Artery Dissection Summarize

BH Benjamin Hibbert

Reply Reply all Forward

To: Lowell Satler <satlerlowell@gmail.com>; Pietro DI SANTO

Sun 3/5/2023 8:35 AM

Thank you for the invitation - I am unavailable but would strongly suggest you consider Dr Pietro DiSanto - he is the lead author, an interventional cardiologist and is currently completing his critical care fellowship. He will be joining on staff in Ottawa after completion of this training and is also currently running a randomized trial of Rivaroxaban after transradial access to reduce RAO (CAPITAL RAPTOR trial).

I have cced him on this email and he is available/willing to present the findings.

Cheers,
B

From: Lowell Satler <satlerlowell@gmail.com>
Sent: Sunday, March 5, 2023 7:02 AM
To: Benjamin Hibbert <BHibbert@ottawaheart.ca>
Subject: Association Between the Access Site for Coronary Angiography and Q3 Catheter-induced Coronary Artery Dissection

*** CAUTION: This email originates from outside the UOHI. Do not click links or download and open attachments unless you trust the sender and know the content is safe. ***
*** MISE EN GARDE : Ce courriel provient de l'extérieur de l'ICUO. Ne cliquez sur aucun lien, ne téléchargez aucun fichier et n'ouvrez aucune pièce jointe à moins de connaître l'expéditeur et de savoir que le contenu est sûr. ***

Invitation to participate in the Medstar Washington Hospital Center Cardiac Cath Conference

Important series of observations.

Would you be interested in presenting this to the Medstar Washington Hospital Center Conference live via the web on Wednesday March 9 2023 at 7:30AM?

We connect securely with you via ZOOM. The PowerPoint presentation should be no longer than
be 10 minutes in duration.

Let me know.

Best
Lowell

Sent from Mail for Windows

CHAPTER 5: POCUS FOR DETECTION OF VASCULAR ACCESS COMPLICATIONS

5.1 Chapter overview

Chapter 5 addresses the research question: “Can point-of-care ultrasound (POCUS) improve the detection of clinically important vascular access complications following invasive cardiac procedures performed via the TRA or TFA approach?”

This chapter evaluates the role of POCUS as an adjunct to the physical examination for the detection of vascular access complications following invasive cardiovascular procedures. Although arterial access complications (e.g. pseudoaneurysm) are relatively infrequent, they are a frequent source of post-procedural morbidity, prolonged hospitalization, and increased healthcare costs. Current clinical practice relies primarily on physical examination, with formal diagnostic imaging used selectively when complications are suspected however this approach is limited by the known poor sensitivity of bedside examination alone.

The ULTRASITCOM study is a prospective diagnostic accuracy study which was conducted at a high-volume quaternary care cardiac centre, enrolling patients with clinical concern for access site complications following a range of invasive cardiac procedures. The primary objective was to compare the diagnostic performance of a combined clinical and POCUS assessment with the physical examination alone, using formal Doppler ultrasonography or computed tomography as the reference standard. In addition to evaluating diagnostic accuracy, this chapter explores feasibility, training requirements, and downstream management implications associated with POCUS integration into routine post-procedural care.

5.2 Importance of this study

First, the ULTRASITCOM study addresses a common yet under recognized clinical problem. Vascular access complications, particularly pseudoaneurysms, are among the most frequent adverse events following invasive cardiac procedures and are associated with increased morbidity, mortality, and healthcare resource utilization. Despite this, post-procedural assessment remains heavily reliant on physical examination, a modality with well documented limitations. Second, this study provides the first prospective evaluation of POCUS for the detection of post-procedural vascular access complications in the setting of interventional cardiology. By demonstrating that a combined clinical and POCUS assessment significantly improves diagnostic accuracy compared with physical examination alone, this work established POCUS as a viable bedside screening tool in this context. Third, the findings have important clinical implications for training and implementation. The ULTRASITCOM study demonstrates that cardiology trainees can acquire the skills required to perform high quality POCUS assessments after a brief, structured training session which further supports scalability and feasibility across diverse practice settings.

Finally, this chapter complements earlier thesis work focused on access site safety by shifting attention from prevention to early detection and management of complications. Together with preceding chapters evaluating access site selection and rare procedural harms, this study contributes to a comprehensive framework for optimizing patient safety across the entire continuum of interventional cardiology.

5.3 Manuscript status

This manuscript has been published:

> **Di Santo P**, Abdel-Razek O, Prosperi-Porta G, Motazedian P, Theriault-Lauzier P, Alhassani S, Sterling LH, Parlow S, Mathiew ME, Jung RG, Morgan B, Coyle D, Fergusson DA, Kyeremanteng K, Mathew R, Labinaz M, Froeschl M, Hibbert R, Simard T, Bird JG, Wells GA, Hibbert B. *Point-of-Care Ultrasound for the Detection of Vascular access complications—The ULTRASITCOM Study*. JSCAI (2025): 4(2):102516

5.4 Author roles/contributions

PDS, GAW, and BH conceived the study. PDS drafted the protocol, which was reviewed and approved by all authors. PDS, OAR, GPP, PM, PTL, SA, LHS, MEM, SP, RGJ, ML, MF, RH, TS, JGB, and BH provided clinical perspective. RH provided the POCUS training sessions. PDS analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors provided comments on the draft and approved the version of the manuscript submitted for publication.

5.5 Related thesis appendices

Appendix C – PDF of published manuscript – ULTRASITCOM study

5.6 Manuscript

Point-of-care Ultrasound for the Detection of Vascular access complications – the ULTRASITCOM study

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Running title: The ULTRASITCOM study

Disclosures: None to declare

Abstract

Background:

Recent technological advancements have expanded access to ultrasound technology. Invasive cardiac procedures come with risks of vascular access complications, necessitating efficient detection methods for dangerous complications such as pseudoaneurysms. Current clinical practice has relied on physical examination, and often require formal diagnostic imaging to diagnose these complications.

Aims:

The ULTRAsound Assessment of Access SITe COMplications (ULTRASITCOM) study assessed the diagnostic accuracy of point-of-care ultrasound (POCUS) as an adjunct to physical examination for the detection of vascular access complications following invasive cardiac procedures.

Methods:

We conducted a single centre study which enrolled patients who underwent invasive cardiovascular procedures with suspected access site complications. Cardiology fellows were trained on the use of POCUS by a radiologist with expertise in vascular imaging. The primary outcome focused on the diagnostic accuracy of combined clinical and POCUS assessments compared to Doppler ultrasound or computed tomography.

Results:

Among 111 participants, most were female (59.5%), with a mean age of 72.2 years, and with transfemoral access being most prevalent (67.6%). A total of 15 participants were found to have a pseudoaneurysm on formal diagnostic imaging. The combined clinical and POCUS assessments demonstrated superior sensitivity for detecting pseudoaneurysms compared to physical exam alone (93.3% [95% CI 80.7-100.0] vs. 80.0% [95% CI 59.8-100.0%], p=0.03).

Conclusions:

POCUS is a highly sensitive tool for detecting pseudoaneurysms following invasive cardiovascular procedures. These findings suggest the potential integration of POCUS into routine practice, which could result in timely complication identification and management, thereby improving patient outcomes and reducing healthcare costs.

Keywords

Point-of-care ultrasound (POCUS)

Vascular access complications

Cardiac catheterization

Diagnostic accuracy

Pseudoaneurysm

Abbreviations

POCUS – point-of-care ultrasound

Introduction

Ultrasound is a versatile tool used for diagnosing patients across diverse clinical environments. Its widespread use has been attributed to its notable diagnostic sensitivity, absence of ionizing radiation, minimal invasiveness, and cost-effectiveness.[1] Recent technological progress has led to the miniaturization of ultrasound components, substantial enhancements in battery longevity, and the creation of compact, high-resolution displays. These advancements have converged to give rise to handheld devices, and when coupled with declining costs, have broadened the accessibility of ultrasonography beyond the boundaries of formal diagnostic imaging departments.[2]

Diagnostic and interventional procedures encompassing coronary, electrophysiological, and valvular interventions are central to the contemporary management of cardiovascular disease. While radial artery access is associated with improved outcomes and a reduction in complications in patients undergoing percutaneous coronary intervention,[3,4] femoral access remains widely utilized, especially for procedures necessitating large-bore sheaths. Although infrequent, these procedures may result in vascular access complications, primarily pseudoaneurysms, hematomas, arteriovenous (AV) fistulas, dissections, and local stenoses or occlusions related to vascular closure devices. These access site complications have in turn been associated with an extended hospital length of stay, increased patient morbidity and mortality, and increased costs.[5,6] For many transcatheter procedures, vascular access complications remain the most common complication for affiliated procedures.

Post-procedure evaluation of access site complications is reliant on physical examination and secondarily on formal diagnostic studies in cases in which complications are suspected. The poor diagnostic accuracy of physical examination has been long recognized and has increased physician reliance on formal diagnostic investigations.[7,8] As such, routine use of point-of-care ultrasound (POCUS) at the bedside has become an established standard of care in other aspects of cardiovascular medicine. As a result of a growing body of literature suggesting possible advantages of ultrasonographic assessment as an adjunct to physical examination, we sought to evaluate the ability of POCUS to detect vascular access complications following invasive cardiac procedures.

Methods

Study design

The ULTRAsound Assessment of Access SITe COMplications (ULTRASITCOM) study is a prospective diagnostic accuracy study conducted a single quaternary care cardiac centre in Ottawa, Canada. Participants were recruited over an 18-month period from February 2022 until September 2023. The study was approved by the Ottawa Health Science Network Research Ethics Board and the study was conducted in accordance with the Helsinki Declaration.

Patient population

Patients who underwent invasive cardiac procedures which required radial, brachial, or femoral arterial and/or femoral venous access and in whom there was a clinical suspicion of an access site complication were considered eligible for the study. Patients were excluded if they had hemodynamic instability as defined by mean arterial pressure less than 65mmHg or requiring vasopressor support or if they had an urgent or emergent need for surgical intervention as determined by the treating physician. All study participants provided written informed consent.

POCUS training

General cardiology and interventional cardiology fellows underwent a 2-hour training session with a vascular radiologist which consisted of a didactic teaching session and a case-based review of common pathologies including hematoma, arteriovenous fistula, pseudoaneurysm, active extravasation/bleeding, venous and/or arterial thrombosis, edema and lymph nodes. Training sessions were provided every 6 months and fellows were required to attend at least 1 session prior to enrolling their first participant.

Index and Reference Tests

Study participants underwent a comprehensive physical examination by a general cardiology or interventional cardiology fellow followed by a POCUS assessment of the access site of concern. A standardized case report form to document the result of their clinical and POCUS assessments was then completed prior to obtaining formal imaging studies. The participant's electronic medical record was reviewed to obtain baseline demographics, procedural characteristics, the results of the formal diagnostic imaging study, and management of access site complications.

Study Outcomes

The primary outcome of the ULTRASITCOM study was the sensitivity of combined clinical and POCUS assessment as compared to formal diagnostic imaging (i.e. Doppler ultrasound or computed tomography) in the detection of pseudoaneurysm. Sensitivity was selected as the principal measure as a highly sensitive test means that there are few false negative results, and thus fewer cases of disease are missed. The implications of a false negative result when it comes to an access site complication, such as pseudoaneurysm, could be catastrophic for patients and therefore it was deemed to be most important in having a highly sensitive test which could 'rule out' disease.

Other measures of diagnostic accuracy including specificity, positive predictive value, negative predictive value, overall diagnostic accuracy, and diagnostic odds ratio (DOR) are also reported. The DOR is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease and can be

used as single indicator of test performance.[9] The value of a DOR ranges from 0 to infinity, with higher values indicating better discriminatory test performance. A DOR of 1 means that a test does not discriminate between patients with the disorder and those without it. The DOR does not depend on the prevalence of the disease that the test is used for. The diagnostic accuracy of the combined physical examination and POCUS assessment was also compared to physical examination alone.

Secondary outcome measures included post-procedure management strategies of post-procedure pseudoaneurysms.

Statistical Analysis

Categorical data are expressed as numbers and percentages and continuous variables are expressed as means and standard deviations. We analyzed the diagnostic accuracy of the combined clinical and POCUS assessment (i.e. index test) in the detection of pseudoaneurysm to formal diagnostic imaging (i.e. reference standard) using sensitivity as the primary measure of test performance. We also evaluated test performance using measures of specificity, positive predictive value, negative predictive value, overall diagnostic accuracy and DOR for the combined assessment as a secondary outcome. Other secondary outcomes evaluating the individual physical examination which were analyzed in the same manner as the combined clinical and POCUS assessment. Point estimates and 95% confidence intervals for each measure of diagnostic accuracy were calculated. The sensitivity of the combined clinical and POCUS assessment was also compared to the sensitivity of the physical exam only using a McNemar's test. Of note, if a 2 x 2 table contained zeroes, the DOR was undefined, and therefore 0.5 was

added to all counts in the table as this is a commonly used method to calculate an approximation of the DOR.[9]

A convenience sample was used without a formal sample size calculation. We planned to open recruitment for 18 months with recruitment of as many participants as possible during this timeframe acknowledging that consecutive patient recruitment was not feasible due to logistical constraints. All reported P-values are two-sided and a value less than 0.05 was considered statistically significant. Analyses were performed using SAS (version 9.4, SAS Institute, Cary, North Carolina, USA)

Results

There were 111 study participants enrolled during the study period (Figure 1). All participants underwent detailed clinical evaluation with both physical examination and POCUS assessments (i.e. index test). Formal diagnostic imaging with either Doppler ultrasonography or computer tomography (i.e. reference standard) was available in 108 study participants (97.3%).

Participant demographics and procedural characteristics

Most study participants were female (59.5%) with an average age of 72.2 ± 12.5 years, height of 166 ± 10 cm and weight of 77.3 ± 17.4 kg (Table 1). Cardiovascular risk factors were prevalent with nearly two-thirds of study participants having a known history of hypertension and half with a history of dyslipidemia. Most patients were taking aspirin, P2Y12 inhibitors, beta-blockers, and statins. With respect to procedural characteristics, nearly half of the study participants underwent percutaneous coronary intervention, followed by approximately 25% who had diagnostic coronary angiography alone and the remaining 25% had a structural heart procedure (e.g. transcatheter aortic valve intervention, transcatheter edge-to-edge repair, etc.). The most common access site of concern was transfemoral (67.6%) followed by transradial (31.5%). Maximum sheath size was most commonly 6-French (70.4%) followed by sheaths greater than 8-French (18.0%) and nearly half of study participants had a vascular closure device deployed at the end of the procedure (21.6% with collagen plug-based device and 22.5% with suture-based device).

Diagnostic accuracy of index test

95 study participants (88.0%) underwent Doppler ultrasound assessment while 13 participants (12.0%) had computed tomography as the reference standard. The diagnostic test accuracy of the

combined clinical and POCUS assessments, as well as the accuracy of physical examination alone can be found in Table 2 and Supplementary Tables 1-2.

Using the reference standard, a pseudoaneurysm was detected in 15 study participants (13.9%) (Figure 2). The sensitivity for pseudoaneurysm detection was greater using the combined physical exam and POCUS assessment, compared to physical exam alone (93.3% [95% CI 80.7-100.0%] vs. 80.0% [95% CI 59.8-100.0], p=0.03) The negative predictive value for pseudoaneurysm was similar between the two assessment methods (combined: 98.6% [95% CI 95.9-100.0%] vs. physical exam only: 96.1% [95% CI 91.8-100.0]). The DOR for the detection of pseudoaneurysm was greater with the combined clinical and POCUS assessment compared to physical exam only (42.6 [95% CI 34.6-50.6] vs, 15.6 [95% CI 11.7-19.5], p<0.01).

Management of access site complications

Most study participants with pseudoaneurysm required either a thrombin injection (20.0%) or underwent surgical arterial repair (40.0%) (Table 3). The remaining study participants with pseudoaneurysm were treated conservatively. Of note, the single participant in whom a pseudoaneurysm was missed by combined clinical and POCUS assessments did not require arterial repair or thrombin injection.

Discussion

The ULTRASITCOM study evaluated the utility of POCUS as an adjunct to clinical assessment in detecting vascular access complications, namely pseudoaneurysms, following invasive cardiac procedures. The study has three major findings. First, the sensitivity of a combined clinical and POCUS evaluation was high at 93.3% with a negative predictive value of 98.6% - suggesting that a negative study was reassuring to rule out pseudoaneurysm. Second, the diagnostic performance as reflected in a DOR of 42.6 for POCUS in this post procedure population suggests a strong overall performance. Third, the cardiology fellows had a 2 hour of didactic training with no further hands-on training suggesting a rapid acquisition of the skill set necessary to perform these assessments. Thus, while the performance of POCUS in this study is excellent, one would expect that with more experience and training interventional cardiologists and fellows could attain diagnostic accuracy approaching that of formal studies.

While many types of vascular access complications are possible, including hematoma, arteriovenous fistula, active extravasation/bleeding, and venous and/or arterial thrombosis, the focus of the ULTRASITCOM study was pseudoaneurysm. A pseudoaneurysm is a contained rupture of an artery that involves disruption in all 3 layers of the arterial wall and is usually a consequence of an arterial puncture that does not adequately seal.[10] This allows pulsatile blood to track into the perivascular space and a hematoma with surrounding tissue form the wall of the pseudoaneurysm. The incidence of this complication is reported to be 2-6% following percutaneous coronary intervention.[10] While some pseudoaneurysms may thrombose spontaneously, this complication could be life threatening should the pseudoaneurysm rupture. Nonetheless, there are many pseudoaneurysms which are small and managed conservatively. In

the current study, the only pseudoaneurysm that was not identified on POCUS was not clinically relevant and was managed conservatively. Thus, we are reassured that all clinically relevant pseudoaneurysms were identified with the combined clinical and POCUS assessment strategy.

The result of the ULTRASITCOM study has an important implication for clinical practice and training. Increasingly, POCUS for cardiac applications is being integrated into cardiology training and interventional fellows increasingly have vascular ultrasound skills for access.[11] While commonly used to evaluate cardiac pathology, this is – to the best of our knowledge – the first application for assessment of vascular access complications. Indeed, with relatively abbreviated training, learners were able to perform and diagnose pseudoaneurysms with a high degree of accuracy. Furthermore, there have been individual reports in which the addition of POCUS has resulted in point-of-care diagnosis.[12,13] As a result, one can envision POCUS for vascular complications becoming a standard part of interventional training to enable timely interventions, and potentially reduce morbidity and health care costs.

This study is not without limitations. First, a non-randomized, convenience sample size from a single centre was used, which may limit the external generalizability of the study results. All efforts were made to include patients in whom there was concern regarding an access site complication over the 18-month study period. Secondly, a variety of invasive procedures were performed, and some procedural factors are associated with an increased risk of pseudoaneurysm (e.g. sheath size, anticoagulation, simultaneous arterial and venous cannulation).[10] However, while various procedures were performed, we do not believe this impacted the ability of the POCUS scans to detect the presence of a pseudoaneurysm. Third, the general and interventional

cardiology fellows underwent a formal but unvalidated 2-hour training session with a radiologist and the impact this had on the ability to detect pseudoaneurysms remains unknown. Whether more optimized training is needed remains to be studied. Fourth, POCUS and physical exam evaluations were compared to two different reference modalities to confirm the diagnosis of a pseudoaneurysm. However, both doppler ultrasonography and CT angiography have demonstrated similar sensitivity and specificity in the detection of pseudoaneurysms. Lastly, the direct and indirect health care costs and possible adverse events associated with delays in obtaining formal imaging are not available.

Conclusion

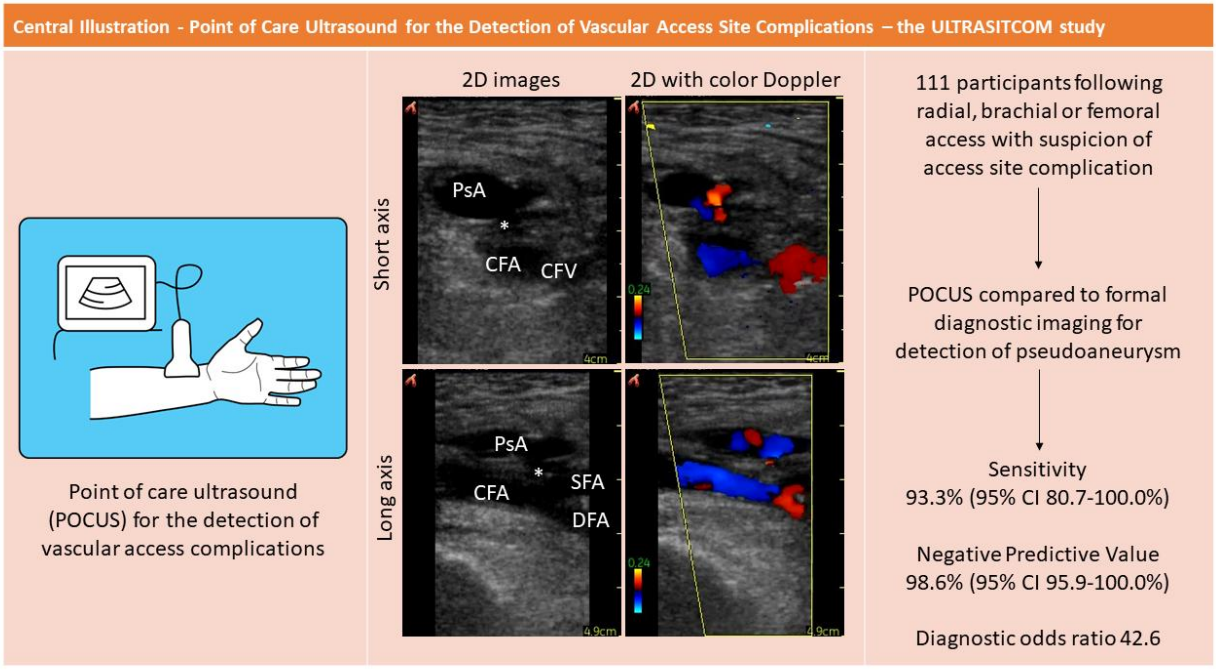
POCUS, when combined as an adjunct to clinical assessment, is a highly sensitive tool for detecting pseudoaneurysms following invasive cardiovascular procedures. These findings suggest the potential integration of POCUS into routine practice, which could result in timely complication identification and management, thereby improving patient outcomes and reducing healthcare costs.

Acknowledgements

None

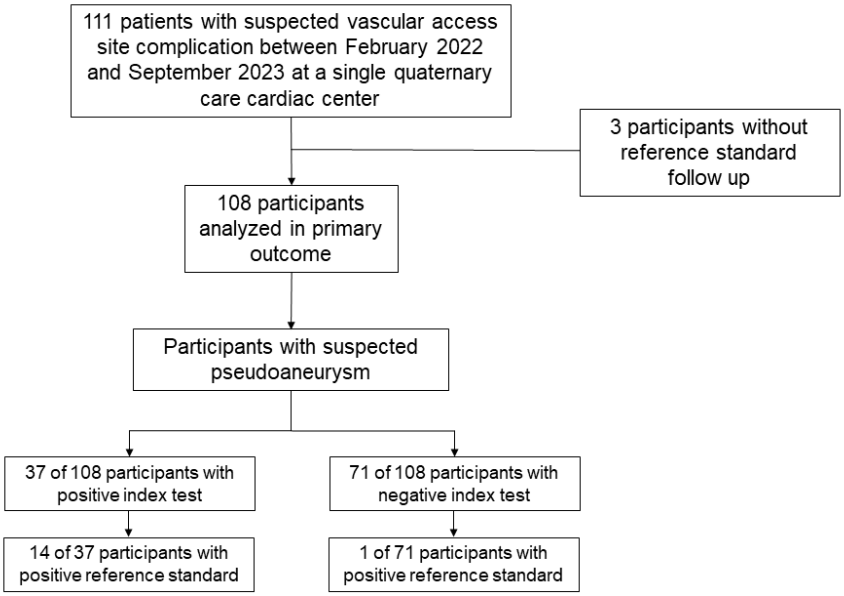
Figures

Central Illustration



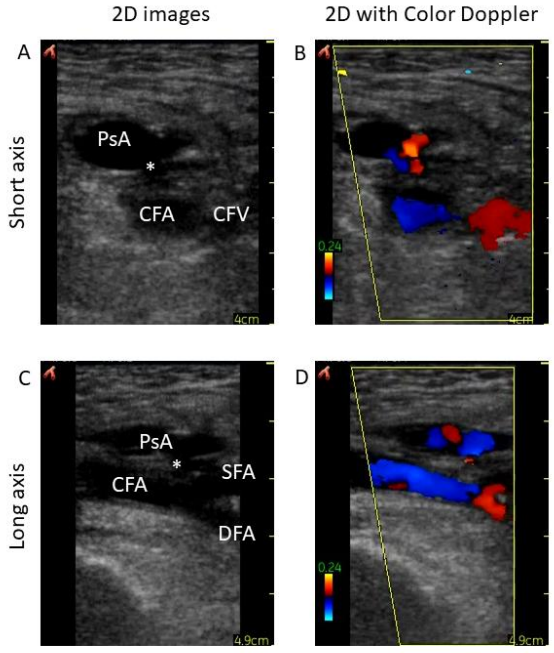
Performance characteristics of comprehensive physical exam plus POCUS assessment in the diagnosis of post-procedural pseudoaneurysm. In a cohort of 111 patients following radial, brachial or femoral access, combined physical exam and POCUS assessment had greater sensitivity (93.3%) and negative predictive value (98.6%) in the diagnosis of pseudoaneurysm compared to physical exam alone; POCUS skills were rapidly acquired after a single 2-hour training session with a vascular radiologist;

Figure 1 – Study Flow



Flow of participants through the ULTRASITCOM study

Figure 2 – Pseudoaneurysm identified on point-of-care ultrasound.



Pseudoaneurysm as visualized on point-of-care ultrasound with the neck of the pseudoaneurysm (*) just proximal to the femoral artery bifurcation in the (A) short axis without colour, (B) short axis with colour Doppler, (C) long axis without colour, and (D) long axis with colour Doppler. CFA = common femoral artery; DFA = deep femoral artery; PSA = pseudoaneurysm; SFA = superficial femoral artery

Tables

Table 1 – Baseline participant demographics and procedural characteristics

	Study participants (n=111)
Age (years) – mean (SD)	72.2 (12.5)
Female sex – no. (%)	66 (59.5%)
Height (cm) – mean (SD)	166 (10)
Weight (kg) – mean (SD)	77.3 (17.4)
Past medical history	
Hypertension – no. (%)	70 (63.1%)
Dyslipidemia – no. (%)	58 (52.7%)
Active smoking – no. (%)	16 (14.4%)
Diabetes – no. (%)	38 (34.2%)
Family history of premature CAD – no. (%)	11 (9.9%)
Medications	
Aspirin – no. (%)	79 (71.2%)
P2Y12 inhibitor – no. (%)	75 (67.6%)
Direct oral anticoagulant – no. (%)	12 (10.8%)
Warfarin – no. (%)	0 (0.0%)
ACEI/ARB/ARNI – no. (%)	50 (45.1%)
Beta-blocker – no. (%)	60 (54.1%)
Mineralocorticoid receptor antagonist – no. (%)	15 (13.5%)
SGLT2 inhibitor – no. (%)	16 (14.6%)
Statin – no. (%)	76 (68.5%)
Procedural characteristics	
Diagnostic coronary angiogram – no. (%)	26 (23.4%)
Percutaneous coronary intervention – no. (%)	54 (48.7%)
Transcatheter aortic valve intervention – no. (%)	20 (18.0%)
Transcatheter edge-to-edge repair – no. (%)	2 (1.8%)
Other structural heart intervention – no. (%)	9 (8.1%)
Access site of concern	
Femoral – no. (%)	75 (67.6%)
Radial – no. (%)	35 (31.5%)
Brachial – no. (%)	1 (0.9%)
Maximum sheath size	
6-French – no. (%)	76 (70.4%)
7-French – no. (%)	3 (2.8%)
8-French – no. (%)	9 (8.3%)
Greater than 8-French – no. (%)	20 (18.0%)
Closure device	
None/compression – no. (%)	62 (55.9%)
Angioseal – no. (%)	24 (21.6%)
Proglide – no. (%)	25 (22.5%)

Abbreviations: ACEI = Angiotensin-converting enzyme inhibitor, ARB = Angiotension Receptor Blocker, ARNI = angiotensin receptor/neprilysin inhibitor, CAD = Coronary Artery Disease, SD = standard deviation

Table 2 – Diagnostic accuracy of clinical and point-of-care ultrasound assessments for pseudoaneurysm detection

	Physical exam + POCUS	**Physical exam only**	**p-value**
Sensitivity	93.3% (95% CI 80.7-100.0%)	80.0% (95% CI 59.8-100.0%)	0.03
Negative predictive value	98.6% (95% CI 95.9-100.0%)	96.1% (95% CI 91.8-100.0%)	
Specificity	75.3% (95% CI 66.5-84.0%)	79.6% (95% CI 71.4-87.8%)	
Positive predictive value	37.8% (95% CI 22.2-53.5%)	38.7% (95% CI 21.6-55.9%)	
Overall accuracy	77.8% (95% CI 68.8-85.2%)	79.6% (95% CI 70.8-86.8%)	
Diagnostic odds ratio	42.6 (95% CI 34.6-50.6)	15.6 (95% CI 11.7-19.5)	<0.01

Table 3 – Management of access site complications

	Pseudoaneurysm (n=15)
Conservative/manual compression	6 (40.0%)
Thrombin injection	3 (20.0%)
Surgical repair	6 (40.0%)

References

1. Chawla TP, Cresswell M, Dhillon S, et al. Canadian Association of Radiologists Position Statement on Point-of-Care Ultrasound. *Can Assoc Radiol J*. Aug 2019;70(3):219-225. doi:10.1016/j.carj.2019.06.001
2. Díaz-Gómez JL, Mayo PH, Koenig SJ. Point-of-Care Ultrasonography. *New England Journal of Medicine*. 2021;385(17):1593-1602. doi:10.1056/NEJMra1916062
3. Di Santo P, Simard T, Wells GA, et al. Transradial Versus Transfemoral Access for Percutaneous Coronary Intervention in ST-Segment-Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Interv*. Mar 2021;14(3):e009994. doi:10.1161/circinterventions.120.009994
4. Amin AP, Rao SV, Seto AH, et al. Transradial Access for High-Risk Percutaneous Coronary Intervention: Implications of the Risk-Treatment Paradox. *Circulation: Cardiovascular Interventions*. 2021;14(7)doi:10.1161/circinterventions.120.009328
5. Jacobson KM, Hall Long K, McMurtry EK, Naessens JM, Rihal CS. The economic burden of complications during percutaneous coronary intervention. *Quality and Safety in Health Care*. 2007;16(2):154-159. doi:10.1136/qshc.2006.019331
6. Sugiharto F, Trisyani Y, Nuraeni A, Mirwanti R, Melati Putri A, Aghnia Armansyah N. Factors Associated with Increased Length of Stay in Post Primary Percutaneous Coronary Intervention Patients: A Scoping Review. *Vascular Health and Risk Management*. 2023;Volume 19:329-340. doi:10.2147/vhrm.s413899
7. Martindale JL, Wakai A, Collins SP, et al. Diagnosing Acute Heart Failure in the Emergency Department: A Systematic Review and Meta-analysis. 2016:n/a-n/a. doi:10.1111/acem.12878
8. Marbach JA, Almufleh A, Di Santo P, et al. Comparative accuracy of focused cardiac ultrasonography and clinical examination for left ventricular dysfunction and valvular heart disease: a systematic review and meta-analysis. *Annals of internal medicine*. 2019;171(4):264-272.
9. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *Journal of clinical epidemiology*. Nov 2003;56(11):1129-35. doi:10.1016/s0895-4356(03)00177-x
10. Webber GW, Jang J, Gustavson S, Olin JW. Contemporary Management of Postcatheterization Pseudoaneurysms. *Circulation*. 2007;115(20):2666-2674. doi:10.1161/circulationaha.106.681973
11. Jolly SS, AlRashidi S, d'Entremont M-A, et al. Routine Ultrasonography Guidance for Femoral Vascular Access for Cardiac Procedures: The UNIVERSAL Randomized Clinical Trial. *JAMA Cardiology*. 2022;7(11):1110-1118. doi:10.1001/jamacardio.2022.3399
12. Azzo C, Driver L, Clark KT, Shokoohi H. Ultrasound Assessment of Post-procedural Arterial Pseudoaneurysms: Techniques, Clinical Implications, and Emergency Department Integration. *Cureus*. 2023;doi:10.7759/cureus.43527
13. Bektas F, Soyuncu S. Pseudoaneurysm of the superficial femoral artery detected by emergency medicine bedside ultrasound. *International Journal of Emergency Medicine*. 2010;3(4):425-426. doi:10.1007/s12245-010-0186-8

5.7 Supplemental file – Supplementary tables

Supplemental Table S1 – Combined physical examination and point of care ultrasound assessment for the detection of pseudoaneurysm

	Reference test positive (i.e. pseudoaneurysm present)	**Reference test negative** (i.e. pseudoaneurysm absent)	
Combined assessment positive (i.e. pseudoaneurysm suspected)	14	23	**Positive predictive value** 37.8% (95% CI 22.2-53.5%)
Combined assessment negative (i.e. pseudoaneurysm not suspected)	1	70	**Negative predictive value** 98.6% (95% CI 95.9-100.0%)
	Sensitivity 93.3% (95% CI 80.7-100.0%)	**Specificity** 75.3% (95% CI 66.5-84.0%)	**Overall diagnostic accuracy** 77.8% (95% CI 68.8-85.2%)

Supplemental Table S2 - Physical examination only for detection of pseudoaneurysm (n=108)

	Reference test positive (i.e. pseudoaneurysm present)	**Reference test negative** (i.e. pseudoaneurysm absent)	
Clinical exam positive (i.e. pseudoaneurysm suspected)	12	19	**Positive predictive value** 38.7% (95% CI 21.6-55.9%)
Clinical exam negative (i.e. pseudoaneurysm not suspected)	3	74	**Negative predictive value** 96.1% (95% CI 91.8-100.0%)
	Sensitivity 80.0% (95% CI 59.8-100.0%)	**Specificity** 79.6% (95% CI 71.4-87.8%)	**Overall diagnostic accuracy** 79.6% (95% CI 70.8-86.8%)

5.8 Supporting material

Invited presentations:

Feb 2025 SCAI Conversations in Interventional Cardiology
Point-of-care Ultrasound for the Detection of Vascular access complications
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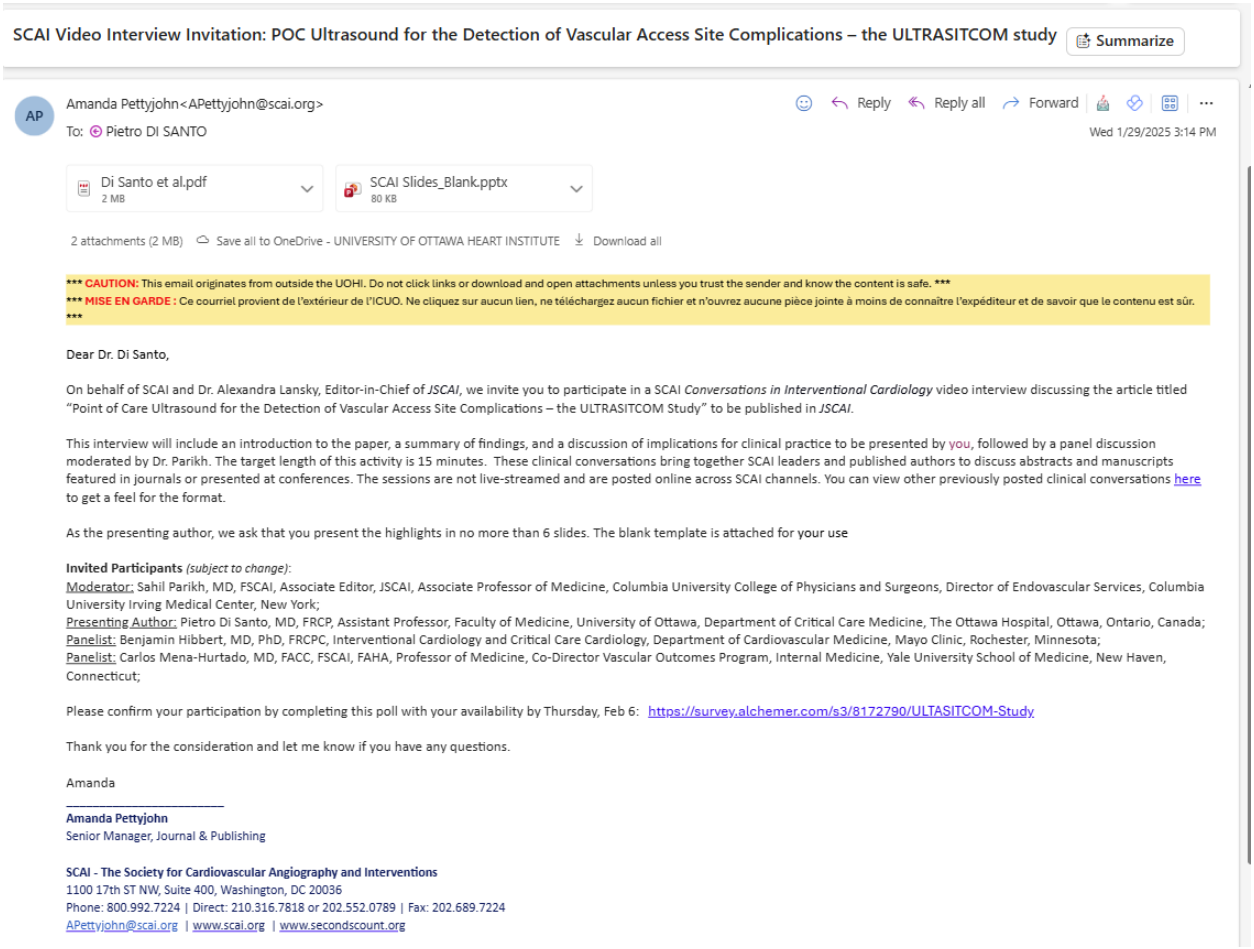

SCAI Video Interview Invitation: POC Ultrasound for the Detection of Vascular Access Site Complications – the ULTRASITCOM study Summarize

AP Amanda Pettyjohn<APettyjohn@scai.org>
To: Pietro DI SANTO
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Dear Dr. Di Santo,

On behalf of SCAI and Dr. Alexandra Lansky, Editor-in-Chief of *JSCAI*, we invite you to participate in a SCAI *Conversations in Interventional Cardiology* video interview discussing the article titled "Point of Care Ultrasound for the Detection of Vascular Access Site Complications – the ULTRASITCOM Study" to be published in *JSCAI*.

This interview will include an introduction to the paper, a summary of findings, and a discussion of implications for clinical practice to be presented by you, followed by a panel discussion moderated by Dr. Parikh. The target length of this activity is 15 minutes. These clinical conversations bring together SCAI leaders and published authors to discuss abstracts and manuscripts featured in journals or presented at conferences. The sessions are not live-streamed and are posted online across SCAI channels. You can view other previously posted clinical conversations here to get a feel for the format.

As the presenting author, we ask that you present the highlights in no more than 6 slides. The blank template is attached for your use

Invited Participants *(subject to change)*:
Moderator: Sahil Parikh, MD, FSCAI, Associate Editor, JSCAI, Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, Director of Endovascular Services, Columbia University Irving Medical Center, New York;
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Panelist: Carlos Mena-Hurtado, MD, FACC, FSCAI, FAHA, Professor of Medicine, Co-Director Vascular Outcomes Program, Internal Medicine, Yale University School of Medicine, New Haven, Connecticut;

Please confirm your participation by completing this poll with your availability by Thursday, Feb 6: https://survey.alchemer.com/s3/8172790/ULTASITCOM-Study

Thank you for the consideration and let me know if you have any questions.

Amanda

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CHAPTER 6: COST EFFECTIVENESS OF TRA VS. TFA IN THE CANADIAN HEALTH CARE SYSTEM

6.1 Chapter overview

Chapter 6 addresses the research question: "Is TRA a cost-effective strategy compared with TFA within a publicly funded healthcare system?"

This chapter evaluates the economic implications of TRA compared with TFA for invasive coronary angiography in patients presenting with acute myocardial infarction (AMI) within a publicly funded Canadian healthcare system. While randomized trials and meta-analyses have consistently demonstrated that TRA reduces bleeding, vascular complications, and mortality, the translation of these clinical benefits into economic value has not been well characterized in the Canadian context.

Using a decision analytic modeling framework, this study estimates cost, quality adjusted life years (QALYs), and incremental cost differences associated with TRA and TFA over a 6-month time horizon. The model integrates contemporary clinical event rates from randomized evidence with Canadian specific cost data and health utility estimates. Probabilistic sensitivity analysis was performed to assess the robustness of findings across parameter uncertainty. By focusing on a high-risk population with substantial procedural volume, this chapter evaluates whether access site selection influences not only patient outcomes but also system-level efficiency.

6.2 Importance of this study

This cost effectiveness analysis addresses a critical evidence gap at the intersection of clinical effectiveness and health system sustainability. Despite strong guideline recommendations favoring TRA, access site decisions are often influenced by perceptions of procedural complexity and occasionally, resource utilization within publicly funded health care systems. This study provides the first Canadian specific economic evaluation of TRA versus TFA in the setting of AMI. Secondly, the analysis demonstrates that TRA is economically dominant, achieving equivalent short term health outcomes at lower overall costs. Although per patient cost savings are modest, the findings are highly relevant given the large number of coronary angiograms performed annually in Canada, where small incremental savings can translate into a substantial aggregate health system impact. Finally, this chapter highlights the disconnect within clinical benefited measured utility gains. Despite reductions in bleeding and vascular complications with TRA, short term QALYs and life years were similar between strategies underscoring the challenge of capturing the value of rare but significant complications with limited time horizons. This insight is important for interpreting cost effectiveness analyses in interventional cardiology and for designing future models that incorporate longer term outcomes.

Within the broader thesis framework, this chapter extends the evaluation of access site selection beyond safety and complication rates to include economic value and policy relevance. Together with preceding chapters examining mortality, rare complications, and diagnostic strategies for complication detection, the study completes a comprehensive assessment of access site choice from patient, provider, and system-level perspectives.

6.3 Manuscript status

The manuscript has been submitted for peer review publication at the time of this submission:

> **Di Santo P**, Motazedian P, Coyle D, Abdel-Razek O, Kolobaric N, Barbour W, Mathieu ME, Jung RG, Hakimjavadi R, Almoosawy S, Fergusson DA, Kyeremanteng K, Labinaz M, Froeschl M, Simard T, Wells GA, Hibbert B. *Cost effectiveness of transradial access for percutaneous coronary intervention in ST-elevation myocardial infarction: a Canadian perspective.* Under review

6.4 Author roles/contributions

PDS, PM, DC, KK, GAW and BH conceived the study. PDS drafted the protocol, which was reviewed and approved by all authors. PDS, PM, OAR, KK, ML, MF, TS and BH provided clinical perspective. PDS and PM co-developed the decision tree under the supervision of DC. PDS analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors provided comments on the draft and approved the version of the manuscript submitted for publication.

6.5 Manuscript

Cost effectiveness of transradial access for percutaneous coronary intervention in acute myocardial infarction

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Short title: CEA of TRA in STEMI

Word count: 1529

Abbreviations

AMI – acute myocardial infarction

CIHI – Canadian Institute for Health Information

ICER – incremental cost-effectiveness ratio

PCI – percutaneous coronary intervention

QALY – quality-adjusted life years

STEMI – ST-segment myocardial infarction

TFA – transfemoral access

TRA – transradial access

Abstract

Background

Acute myocardial infarction (AMI) requires timely invasive coronary angiography. Evidence from randomized trials demonstrates that transradial access (TRA) reduces major bleeding, vascular complications, and mortality, leading to guideline recommendations favoring TRA over transfemoral access (TFA). However, the economic impact of TRA within the Canadian healthcare system remains unknown.

Objective

To evaluate the cost-effectiveness of TRA versus TFA for invasive coronary angiography in AMI patients from a Canadian healthcare perspective.

Methods

A decision-analytic model was developed using Canadian cost data and clinical outcomes from meta-analyses. Transition probabilities included major bleeding, vascular complications, stroke, recurrent AMI, and death. Quality-adjusted life years (QALYs) were derived from the VALsartan In Acute myocardial iNfarcTion (VALIANT) study. Costs were sourced from the Canadian Institute for Health Information and provincial case-cost databases. A six-month time horizon and probabilistic sensitivity analysis with 5,000 Monte Carlo simulations were applied.

Results

TRA and TFA yielded similar QALYs (0.37) and life-years (0.49) over six months. Mean costs were $6,688 for TRA and $6,826 for TFA, resulting in an incremental cost difference of $138 favoring TRA. Given equivalent outcomes and lower costs, TRA was economically dominant.

Conclusions

TRA offers modest cost savings compared to TFA without compromising outcomes, supporting its continued adoption as the preferred access strategy for coronary angiography in AMI within Canada. While short-term benefits are clear, future research should assess long-term economic and clinical impacts.

Introduction

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality in Canada, accounting for over 50,000 hospital admissions annually and a significant the cardiovascular disease burden in the country [1, 2]. The management of AMI requires timely diagnosis and intervention, as delays in revascularization are associated with increased mortality and adverse outcomes. Invasive coronary angiography remains the cornerstone of treatment, allowing for diagnoses and treatment of the culprit lesions[3, 4]. Traditionally, transfemoral access (TFA) was the standard approach for coronary procedures; however, growing evidence from randomized controlled trials and meta-analyses has demonstrated significant clinical advantages of transradial access (TRA)[5-9]. Compared to TFA, TRA is associated with lower rates of major bleeding, vascular complications, and all-cause mortality, prompting its inclusion as a Class 1A recommendation in contemporary Canadian and American guidelines[10, 11]. These benefits have driven a substantial shift in practice patterns over the past decade, with TRA now considered the preferred access site for coronary angiography and intervention[12].

Despite the well-established clinical benefits of TRA, its economic implications in publicly funded healthcare systems, namely Canada, has yet to be studied. As such, we conducted a cost-effectiveness analysis comparing TRA and TFA for invasive coronary angiography in patients presenting with AMI within the Canadian healthcare context. Using a decision-analytic model, our study's objective was to quantify costs, quality-adjusted life years (QALYs), and incremental cost differences to determine the impact access site in AMI.

Methods

Model

A decision tree model was developed following International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM) best modeling practices to estimate the incremental cost-effectiveness ratio (ICER) for TRA compared to TFA in invasive coronary angiography during acute myocardial infarction (AMI) (Figure 1)[13]. The analysis was completed from the perspective of the publicly funded Canadian healthcare system.

Population

The study population consisted of patients presenting to the hospital who underwent invasive coronary angiography for the treatment of AMI.

Transition Probabilities

Transition probabilities are summarized in Table 1. Patients undergoing TRA and TFA have different risks, which has been summarized in an individual patient data meta-analysis of randomized controlled trials[7]. We included complications that were statistically different between radial and femoral access, namely major bleeding, death, vascular complications, and those associated with a significant impact on quality of life, such as repeat AMI and disabling stroke[14]. In our model, patients could either have no complications or a combination of complications. We assumed the risks of complications were independent of one other.

Cost

Canadian sources were used for cost estimates, including the Canadian Institute for Health Information (CIHI) patient cost estimator and the Government of Alberta inpatient care case costs[15, 16]. The costs of the angiogram procedure and subsequent management of any complications were assumed to be the same between TRA and TFA. No measurements of variability were provided, and therefore standard error was assumed to be 25% of the deterministic value (Table 2).

Utilities

Table 2 includes the utilities used in our model. The Valsartan In Acute Myocardial Infarction (VALIANT) quality-of-life and utility substudy was used for our model. This is a primary data study which used the EQ-5D questionnaire to assess quality-adjusted life years (QALYs) after AMI. This study had separated their data by geography; given the similarities between U.S. and Canadian sociodemographic characteristics, U.S. QALY data (n=597) were preferentially used over U.K. data[14]. For post-procedure complications, a disutility was applied based on its occurrence[17, 18]. The impact of multiple complications was considered additive.

Analysis

Probabilistic sensitivity analysis was performed using a Monte Carlo simulation with 5,000 replications to estimate uncertainty around costs and outcomes. A six-month time horizon was applied, as complications or events occurring beyond this period are unlikely to be attributable to the procedure[19]. Our intent was to calculate an ICER for TRA, but given our findings, this was not calculated.

Reporting of the study findings was performed according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) recommendations.

Results

The findings of our probabilistic analysis are summarized in Table 3. In patients undergoing angiography for AMI, our analysis found that TRA access was economically dominant compared to TFA. Both strategies had similar QALYs (0.37) and life-years (0.49) over the six-month time horizon. However, TRA had a lower mean cost of $6,697 compared to $6,836 for femoral access, resulting in an incremental cost difference of $139 in favor of radial access. Given that TRA and TFA had similar clinical outcomes, the ICER was not calculated as the cost of TRA was lower.

Discussion

Our analysis demonstrates that radial artery access is economically dominant compared to femoral access in patients undergoing angiography for AMI within the Canadian healthcare context. Both strategies resulted with identical QALYs and life-years over a six-month horizon, but given the lower risks of complication, TRA was associated with lower costs.

Health economic analyses comparing TRA and TFA have been completed in other settings with mixed results. In a substudy of the OCEAN RACE trial, which compared TRA to TFA in 103 patients presenting with ST-segment elevation myocardial infarction (STEMI), the average per-patient cost was €2,740 for TRA and €2.686 for TFA[20]. These estimates were inclusive of hospital stay, complications, medical equipment, and pharmacotherapy. However, given the low incidence of complications following angiography, the small sample size represents a significant limitation to these findings. In contrast, registry data from Australia found that for every patient undergoing percutaneous coronary interventions (PCI) by TRA, there was net cost saving of $1,214.69 per patient [21]. Furthermore, in the cost-effectiveness analysis of the MATRIX trial, TRA was found to be superior to TFA, as a result of improvements in both QALYs and overall costs[22].

Our analysis demonstrated that while TRA was superior to TFA from a health economic perspective, the overall cost-saving benefits were relatively modest. For the many reasons already highlighted, TRA has become the recommended approach for coronary angiography, and its adoption has increased significantly over the past 10–15 years [10-12]. Considering that hundreds of thousands of coronary angiograms are performed annually in Canada, even modest per-patient economic gains translate into a substantial aggregate impact given the overall procedural burden [23].

Interestingly, despite the clinical benefits of TRA over TFA, the impact in patient utility and life-years was equivalent between both in our analysis. Although TRA is associated with a statistically significant reduction in major complications, the overall event rates for these complications are low, and the absolute difference is likely too small to meaningfully affect QALYs or life-years within a six-month horizon. Extending the model to a lifetime horizon could potentially reveal larger differences in QALYs and survival due to improved long-term outcomes; however, the lack of robust long-term data limits the feasibility of such modeling[7]. Moreover, while access site may influence outcomes beyond six months, other patient and procedural variables likely have a greater impact on long-term outcomes.

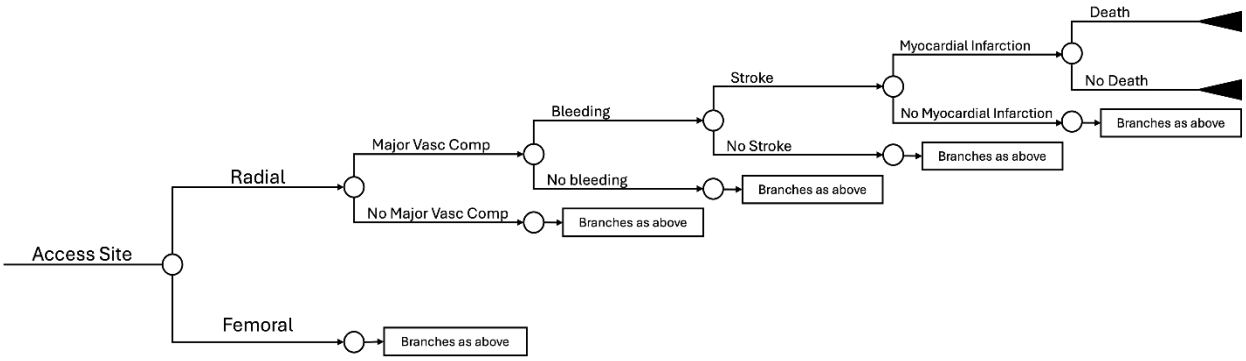
Our study has several limitations. First, as previously noted, we applied a six-month time horizon. While this duration minimizes confounding from other variables and aligns with available clinical trial data, the longer-term impacts remain uncertain. Similarly, the MATRIX trial substudy limited its analysis to two years to match the duration of follow-up. Second, utility values were derived from a U.S. population due to limited Canadian-specific data, which may introduce variability and reduce the precision of QALY estimates in the Canadian context. Third, procedural costs were assumed to be equivalent between access sites; however, real-world differences in resource utilization during TRA and TFA procedures, such as equipment and pharmacotherapy, may influence actual costs.

Conclusion

TRA is economically dominant over TFA for coronary angiography in AMI within Canada. While both approaches have similar short-term utility and life years, TRA offers modest cost savings due to fewer complications. Given the high procedural volume, these savings have the potential to create a meaningful impact at a systemic level.

Figure Titles

Figure 1. Decision tree for radial and femoral invasive coronary angiogram access site in patients presenting with myocardial infarction.



Tables

Table 1. Transition probabilities.

Variable	Input	Alpha/Beta	Probability Distribution	Reference
Transition Probabilities – Radial Artery Access				
Vascular complication	0.007	63/9574	Beta	[7]
Major Bleeding complication	0.015	162/10611	Beta	[7]
Stroke	0.005	52/9830	Beta	[7]
Post-revascularization myocardial infarction	0.04	169/10606	Beta	[7]
Death	0.016	398/9484	Beta	[7]
Transition Probabilities – Femoral Artery Access				
Vascular complication	0.017	163/9496	Beta	[7]
Major Bleeding complication	0.027	289/10526	Beta	[7]
Stroke	0.004	39/9892	Beta	[7]

Post-angiography myocardial infarction	0.043	218/10607	Beta	[7]
Death	0.021	429/9502	Beta	[7]

Table 2. Utility and costs.

Variable	Input	Standard Error	Probability Distribution	Reference
Utility				
Post-myocardial infarction – no complications	0.76	0.009	Lognormal	[14]
Vascular complication – disutility	0.06	0.029	Lognormal	[17]
Major bleeding complication – disutility	0.04	0.015	Lognormal	[18]
Stroke – disutility	0.15	0.038	Lognormal	[14]
Post-angiography myocardial infarction – disutility	0.06	0.020	Lognormal	[14]
Costs				
Cost of invasive coronary angiogram	$6,323	$1,580	Gamma	CIHI 176[16]
Vascular complication	$9,422	$2,355	Gamma	CMG +213[15]
Major bleeding complication	$2,638	$659	Gamma	CMG +782[15]
Stroke	$6,196	$1,549	Gamma	[24]

Post-angiography myocardial infarction	$6,323	$1,580	Gamma	CIHI 176[16]

Table 3. Monte Carlo simulation probabilistic results.

Probabilistic Result	**Radial artery access**	**Femoral artery access**	**Incremental Change**
Quality-adjusted life years	0.37	0.37	0
Costs	$6,697	$6,836	– $139
Life years	0.49	0.49	0

References

1. Rawson, N.S., et al., *The aging Canadian population and hospitalizations for acute myocardial infarction: projection to 2020*. BMC Cardiovasc Disord, 2012. **12**: p. 25.
2. Jung Richard, G., et al., *Prognostic Factors Associated with Mortality in Cardiogenic Shock — A Systematic Review and Meta-Analysis*. NEJM Evidence, 2024. **3**(11): p. EVIDoa2300323.
3. Simard, T., et al., *The Evolution of Coronary Stents: A Brief Review*. Canadian Journal of Cardiology, 2014. **30**(1): p. 35–45.
4. Simard, T., et al., *Modifiable Risk Factors and Residual Risk Following Coronary Revascularization: Insights From a Regionalized Dedicated Follow-Up Clinic*. Mayo Clinic Proceedings: Innovations, Quality & Outcomes, 2021. **5**(6): p. 1138–1152.
5. Di Santo, P., et al., *Association Between the Access Site for Coronary Angiography and Catheter-induced Coronary Artery Dissection*. Journal of the Society for Cardiovascular Angiography & Interventions, 2023. **2**(3): p. 100606.
6. Le May, M., et al., *Safety and Efficacy of Femoral Access vs Radial Access in ST-Segment Elevation Myocardial Infarction: The SAFARI-STEMI Randomized Clinical Trial*. JAMA Cardiol, 2020. **5**(2): p. 126–134.
7. Gargiulo, G., et al., *Effects on Mortality and Major Bleeding of Radial Versus Femoral Artery Access for Coronary Angiography or Percutaneous Coronary Intervention: Meta-Analysis of Individual Patient Data From 7 Multicenter Randomized Clinical Trials*. Circulation, 2022. **146**(18): p. 1329–1343.
8. Jolly, S.S., et al., *Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial*. Lancet, 2011. **377**(9775): p. 1409–20.
9. Valgimigli, M., et al., *Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial*. The Lancet, 2018. **392**(10150): p. 835–848.
10. Rao Sunil, V., et al., *2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes*. JACC, 2025. **85**(22): p. 2135–2237.
11. Fazel, R., et al., *Radial vs femoral access for percutaneous coronary intervention: temporal trends and outcomes in the USA*. Eur Heart J, 2025.
12. Bainey, K.R., et al., *Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology 2023 Focused Update of the Guidelines for the Use of Antiplatelet Therapy*. Canadian Journal of Cardiology, 2024. **40**(2): p. 160–181.
13. Siebert, U., et al., *State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3*. Value Health, 2012. **15**(6): p. 812–20.
14. Lewis, E.F., et al., *Impact of Cardiovascular Events on Change in Quality of Life and Utilities in Patients After Myocardial Infarction: A VALIANT Study (Valsartan In Acute Myocardial Infarction)*. JACC: Heart Failure, 2014. **2**(2): p. 159–165.

15. *Hospital Inpatient Care Case Costs—CMG/Plex—Open Government*. Government of Alberta.
16. *Patient Cost Estimator*. Canadian Institute for Health Information (CIHI).
17. Morgan, C.L., et al., *Characterization and comparison of health-related utility in people with diabetes with various single and multiple vascular complications*. Diabet Med, 2006. **23**(10): p. 1100–5.
18. Amin Amit, P., et al., *Impact of Bleeding on Quality of Life in Patients on DAPT*. JACC, 2016. **67**(1): p. 59–65.
19. Naidu, S.S., et al., *SCAI expert consensus update on best practices in the cardiac catheterization laboratory*. Catheterization and Cardiovascular Interventions, 2021. **98**(2): p. 255–276.
20. Kołtowski, Ł., et al., *Cost-effectiveness of radial vs. femoral approach in primary percutaneous coronary intervention in STEMI - Randomized, control trial*. Hellenic J Cardiol, 2016. **57**(3): p. 198–202.
21. Lee, P., et al., *The cost-effectiveness of radial access percutaneous coronary intervention: A propensity-score matched analysis of Victorian data*. Clinical Cardiology, 2022. **45**(4): p. 435–446.
22. Lee, P., et al., *Cost-effectiveness of Radial Access Percutaneous Coronary Intervention in Acute Coronary Syndrome*. American Journal of Cardiology, 2021. **156**: p. 44–51.
23. Faris, P.D., et al., *Diagnostic cardiac catheterization and revascularization rates for coronary heart disease*. Can J Cardiol, 2004. **20**(4): p. 391–7.
24. Motazedian, P., et al., *Cost-effectiveness of population screening for aortic stenosis*. Eur Heart J Qual Care Clin Outcomes, 2025. **11**(4): p. 378–387.

CHAPTER 7: RIVAROXABAN FOR THE PREVENTION OF RADIAL ARTERY OCCLUSION STUDY PROTOCOL AND SAP

7.1 Chapter overview

Chapter 7 addresses the research question: “Can post-procedural oral anticoagulation reduce the incidence of radial artery occlusion, the most common complication of TRA?”

This chapter describes the rationale, trial design, and prespecified Statistical Analysis Plan (SAP) for the Rivaroxaban Post-Transradial Access for the Prevention of Radial Artery Occlusion (RAPTOR) trial, a multicentre, international randomized clinical trial evaluating the safety and efficacy of short-term post-procedural anticoagulation following TRA for coronary angiography or PCI. Radial artery occlusion (RAO) is the most common complication of TRA and represents an important limitation of an otherwise preferred procedural strategy given its implications for future cardiovascular procedures, surgical conduit availability, and access for dialysis in chronic kidney disease patients.

The published study design and rationale manuscript details the biological rationale, eligibility criteria, intervention, outcome definitions, sample size justification, and operational aspects of the trial including Doppler ultrasound-based adjudication of RAI and blinded/centralized bleeding adjudication. Building on this foundation, the accompanying unpublished statistical analysis plan prespecifies all primary, secondary and subgroup analyses, interim monitoring strategies, and data handling procedures prior to unblinding of trial data. Together these documents defined the methodological framework governing trial conduct and analysis, ensuring transparency, reproducibility, and protection against analytic bias.

7.2 Importance of this study

The RAPTOR study will address a major unresolved limitation of TRA. While TRA is associated with reductions in bleeding and mortality, RAO remains a common and clinically meaningful complication of TRA. By targeting RAO prevention rather than access site bleeding, this trial shifts focus toward long-term vascular preservation. Secondly, this chapter represents a methodological contribution beyond clinical trial reporting. The publication of a detailed trial protocol coupled with the SAP completed prior to data unblinding reflects best practices in contemporary clinical trials and enhances the credibility and interpretability of the eventual trial results. Lastly, the SAP demonstrates advanced statistical and trial methodology expertise, including intention to treat principles, prespecified subgroup analyses, interim efficacy and futility monitoring using O'Brien-Fleming boundaries, and rigorous handling of missing data and treatment crossovers. These features strengthen internal validity and reduce the risk of data-driven inference.

Within the context of the thesis, this chapter represents a natural progression from observational and health economic analysis to prospective randomized evidence generation. It operationalizes insights gained from earlier chapters on access site complications and long-term vascular outcomes into a definitive interventional trial designed to inform clinical practice. As such it completes the thesis arc by translating epidemiological and mechanistic observations into a scalable, patient-centred therapeutic strategy

7.3 Manuscript status

This manuscript has been published:

Di Santo P, Abdel-Razek O, Jung RG, Parlow S, Poulin A, Bernick J, Morgan B, Robinson L, Feagan H, Wade J, Goh CY, Singh K, Froeschl M, Labinaz M, Fergusson D, Coyle D, Kyeremanteng K, Abunassar J, Wells GA, Simard T, Hibbert B. *Rationale and Design of the Rivaroxaban Post-Transradial Access for the Prevention of Radial Artery Occlusion Trial (CAPITAL-RAPTOR).* BMJ Open (2023). 13:e070720

The unpublished Statistical Analysis Plan can be found in Appendix E.

7.4 Author roles/contributions

PDS, OAR, RGJ, TS, and BH conceived the study. PDS drafted the protocol, which was reviewed and approved by all authors. PDS, OAR KS, MF, ML, JA, TS, and BH provided clinical perspective. PDS and GAW provided developed the statistical analysis plan, which was reviewed and approved by all authors. All authors provided comments on the draft and approved the version of the manuscript submitted for publication.

7.5 Related thesis appendices

Appendix D – PDF of published manuscript – RAPTOR study design and rationale
Appendix E – Statistical Analysis Plan for the RAPTOR study

7.6 Manuscript

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 as an important complication of TRA as it precludes future ipsilateral transradial procedures. While intraprocedural anticoagulation has been studied extensively, the definitive role of post-procedural anticoagulation has not yet been established.

Methods and Analysis:

The Rivaroxaban Post-Transradial Access for the Prevention of Radial Artery Occlusion (CAPITAL-RAPTOR) trial is a multicentre, prospective, randomized, open-label, blinded-endpoint (PROBE) design study investigating the efficacy and safety of rivaroxaban to reduce the incidence of RAO. Eligible patients will undergo randomization to receive either rivaroxaban 15mg once daily for 7 days or to no additional post-procedural 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 Research Ethics Board (approval number 20180319-01H). The study results will be disseminated via conference presentations and peer-reviewed publications.

Trial Registration Number: The study is registered with *ClinicalTrials.gov* (NCT03630055).

Strengths and Limitations of This Study:

- This will be the largest randomized trial to date assessing post-procedure 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 hemostasis, early ambulation after the procedure thereby improving patient comfort and experience and decrease length of stay.(2) There is also a reduction in all-cause mortality, major adverse cardiovascular events, major bleeding and vascular complications with TRA as compared to transfemoral access (TFA) (3, 4) which has led to a Class IA recommendation for TRA over TFA in patients presenting with an acute coronary syndrome.(5) However, radial artery occlusion (RAO) remains as an important complication of TRA as it precludes future ipsilateral transradial procedures, utilization of the vessel as a conduit for coronary artery bypass grafting (CABG) or for the creation of an arteriovenous fistula in patients requiring hemodialysis.(6, 7)

Reports of RAO following TRA varies between 1 to 10% in observational and randomized trials.(8-10) In the largest systematic review published to date, the overall rate of RAO was 5.2% amongst the 46,631 subjects across 92 studies between 1989 and 2016.(6) This study also noted that the rate of early RAO (i.e. within 7 days) was significantly higher than late RAO (i.e. after 7 days) which is suggestive of late recanalization in some patients. The factors which affect recanalization are not clear; however, current standard of care to reduce RAO involves administration of intraprocedural unfractionated anticoagulation and post-procedural patent hemostasis.(7)

Numerous trials have explored the role of intraprocedural anticoagulation during angiography to reduce RAO.(11, 12) A recent meta-analysis demonstrated high dose unfractionated heparin

(UFH) is associated with less incidence of RAO compared to low dose UFH(6). Additionally, there were higher rates of RAO with diagnostic CA compared to PCI purportedly as the latter involves higher doses of anticoagulation. Two randomized trials including the RESTORE(13) and the RIVARAD(14) trials examined short-term anticoagulation with rivaroxaban in patients following TRA and observed trends towards reduced rates of RAO with use of anticoagulation. Herein, we describe the rationale and design of the randomized Rivaroxaban Post-Transradial Access for the Prevention of Radial Artery Occlusion Trial (CAPITAL-RAPTOR) – the largest proposed study evaluating post-procedural anticoagulation following TRA.

Methods and Analysis

Trial design and methods

The CAPITAL-RAPTOR trial is a multicentre, international, prospective, randomized, open-label, blinded-endpoint (PROBE) design study investigating the efficacy and safety of rivaroxaban to reduce the incidence of RAO. Patients who have undergone CA or PCI via TRA will be screened for eligibility using pre-defined inclusion and exclusion criteria (Table 1). Patients who are eligible and agree to participate will provide written informed consent. All participants will receive the same intra-procedural standard of care which currently involves administration of 3000-5000 international units (IU) of unfractionated heparin during CA(15) and patent hemostasis following the procedure.(16)

Table 1 – Eligibility Criteria for the CAPITAL RAPTOR 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 hematoma or clinical concern of hemostasis at the transradial access site
Unsuccessful or abandoned attempt at a secondary arterial access site
Planned staged procedure, CABG or noncardiac surgery within 30-days
Contraindication or high risk of bleeding with anticoagulation, including any of the following: a. any bleeding requiring medical attention in the previous 6 months b. thrombocytopenia with platelets <50 x 10^9/L c. any prior intracranial hemorrhage d. use of IIb/IIIa during percutaneous coronary intervention e. administration of thrombolytic therapy in the preceding 24 hours f. use of non-steroidal anti-inflammatory medications, excluding aspirin g. ischemic stroke or transient ischemic attack diagnosed in the last 3 months
Cardiogenic shock
Ventricular arrhythmias refractory to treatment
Liver dysfunction (Child-Pugh class B or C)
Unexplained anemia with a hemoglobin less than 100 g/L
History of medication noncompliance or risk factor for noncompliance
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 30mL/min
History of antiphospholipid syndrome, in particular triple positive (lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies)

Randomization and study procedures

Randomization will take place following completion of the post-procedure patent hemostasis period to ensure only patients without concerns regarding hematoma or bleeding complications are enrolled. Eligible patients will undergo randomization in a 1:1 fashion using a centralized,

computer-generated sequence to receive either rivaroxaban 15mg once daily for 7 days or to no additional post-procedural anticoagulation (Figure 1). Stratification will be performed by study site only. The stratified randomization will be generated using varying block sizes to make the sequence difficult to predict without leading to 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 visualized and measured in both short and long axis views. Maximum lumen diameter, intimal thickness and color Doppler will be measured at 1 cm proximal to the styloid process of the radius.(17) 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(17); thus we will use the most extreme case (i.e. absence of flow) as our standard.

Study intervention

Participants in the treatment arm will receive rivaroxaban 15mg 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 15mg daily has demonstrated safety in conjunction with antiplatelet therapy(18) and remains guideline recommended for post-PCI patients in patients with atrial fibrillation.(19-21) Additionally, reduced dose rivaroxaban is recommended for atrial fibrillation patients with creatinine clearance

30-60mL/min thereby permitting the inclusion of patients with moderate renal dysfunction. As such, it was determined by the trial steering committee that rivaroxaban 15mg daily would provide the optimal balance between efficacy and safety while permitting maximal generalizability 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.(6) Doppler ultrasound will be performed at 30-days to avoid capturing early RAO which may resolve as late recanalization may be observed in some patients.(22, 23)

Data collection

Baseline demographics of the study participants will include age, sex, height and weight. The participant's ethnicity will be collected voluntarily. Past medical history regarding cardiovascular risk factors, previous myocardial infarction, previous PCI, previous coronary artery bypass graft surgery, or previous stroke/transient ischemic attack will also be collected. Renal function will be collected based on the study participant's pre-procedure 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 (e.g. CA or PCI), maximal sheath diameter, maximal catheter size, and dose of intra-procedural unfractionated heparin 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 of Thrombosis and Hemostasis (ISTH) 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 hemoglobin level of ≥2g/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 (ischemic or uncertain)
3. Stroke (hemorrhagic)
4. Fatal bleeding
5. Symptomatic bleeding in a critical area or organ
6. Bleeding requiring medical attention
7. Global Strategies for Opening Occluded Coronary Arteries (GUSTO) bleeding criteria
8. Thrombolysis In Myocardial Infarction (TIMI) bleeding criteria
9. Bleeding Academic Research Consortium (BARC) bleeding criteria
10. Myocardial infarction
11. Stent thrombosis as defined by the Academic Research Consortium criteria

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

Sample size and data analysis

Using a modified Delphi process, the minimal clinically important difference 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 pre-specified 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% loss to follow up, a total of 913 participants per study arm for a grand total of 1,826 participants will need to be recruited.

The statistical analysis plan will be reviewed by trial investigators and finalized 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 Chi-squared 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.

Pre-specified 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 to 75 years, and > 75 years
4. Weight > 70kg
5. Estimated glomerular filtration rate <50ml/min
6. Diabetes
7. Hypertension
8. Type of coronary disease (acute coronary syndrome or stable coronary artery disease)
9. Presence of dual antiplatelet therapy

Patient and Public Involvement

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

Current state of the trial

Enrollment 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 the Supplementary Material.

Discussion

RAO is the most common complication after TRA, with an estimated incidence of approximately 5%.(24) 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 arterio-venous fistula formation in patients requiring hemodialysis. 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 (OCT) and demonstrated 67% of radial arteries had intimal tears and 36% had medial dissections.(25) 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 hemostasis.(26) The process of

sheath insertion and instrumentation during TRA causes repeated endothelial damage, leading to vessel remodeling 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 catheterization.(27) 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.(28, 29) Procedural risk factors for RAO include repeated unsuccessful puncture attempt, larger sheath size, absence of pre-treatment aspirin and lack of peri-procedural intravascular coagulation.(30-32) Post-procedural variables that are associated with an increased risk of RAO include non-patent hemostasis(10, 33) and longer duration of compressive hemostasis.(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(18, 35-39) and venous thromboembolism.(40-43) Recently, low dose rivaroxaban in combination with aspirin has been shown to reduce cardiovascular outcomes compared to aspirin alone among patients with stable cardiovascular disease(44). Given emerging evidence suggestive of late RAO recanalization(6) and higher dose intraprocedural anticoagulation in preventing RAO(11), we hypothesized that a 7-day post-procedure 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 (i.e. 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 post-procedural anticoagulation in reducing RAO post TRA. The RESTORE trial randomized 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.(13) The RIVARAD trial randomized 521 patients to rivaroxaban 10mg daily vs. placebo and observed significant reduction in 1-month RAO with anticoagulation.(14) Our trial will utilize a unique dosing regimen of rivaroxaban in conjunction with standard of care practices including patent hemostasis and intra-procedural anticoagulation. Finally, as the largest study to date, RAPTOR will be the only study adequately powered to determine the definitive role of post-procedural 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 post-procedural 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.

Authors' contributions

PDS, OAR, RGJ, SP, TS, BH – Writing, editing, and revision of present manuscript.

PDS, OAR, RGJ, SP, JB, DF, DC, KK, JA, GAW, TS, BH – Critical trial design and statistical analysis plan, assistance with writing analysis section of present manuscript.

PDS, OAR, RGJ, SP, AP, BM, LR, HF, JW, CYG, KS, MF, ML, TS, 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.

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Competing interests statement: None of the authors have any competing interests to declare.

References

1. Volz S, Angeras O, Koul S, Haraldsson I, Sarno G, Venetsanos D, et al. Radial versus femoral access in patients with acute coronary syndrome undergoing invasive management: A prespecified subgroup analysis from VALIDATE-SWEDEHEART. Eur Heart J Acute Cardiovasc Care. 2019;8(6):510-9.
2. Schussler JM, Vasudevan A, von Bose LJ, Won JI, McCullough PA. Comparative Efficacy of Transradial Versus Transfemoral Approach for Coronary Angiography and Percutaneous Coronary Intervention. The American journal of cardiology. 2016;118(4):482-8.
3. Ferrante G, Rao SV, Juni P, Da Costa BR, Reimers B, Condorelli G, et al. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. JACC Cardiovasc Interv. 2016;9(14):1419-34.
4. Di Santo P, Simard T, Wells GA, Jung RG, Ramirez FD, Boland P, et al. Transradial Versus Transfemoral Access for Percutaneous Coronary Intervention in ST-Segment–Elevation Myocardial Infarction. Circulation: Cardiovascular Interventions. 2021;14(3).
5. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). European heart journal. 2016;37(3):267-315.
6. Hahalis G, Aznaouridis K, Tsigkas G, Davlouros P, Xanthopoulou I, Koutsogiannis N, et al. Radial Artery and Ulnar Artery Occlusions Following Coronary Procedures and the Impact of Anticoagulation: ARTEMIS (Radial and Ulnar ARTEry Occlusion Meta-AnalysIS) Systematic Review and Meta-Analysis. J Am Heart Assoc. 2017;6(8).
7. Bernat I, Aminian A, Pancholy S, Mamas M, Gaudino M, Nolan J, et al. Best Practices for the Prevention of Radial Artery Occlusion After Transradial Diagnostic Angiography and Intervention. JACC: Cardiovascular Interventions. 2019;12(22):2235-46.
8. Pancholy SB. Transradial access in an occluded radial artery: new technique. The Journal of invasive cardiology. 2007;19(12):541-4.
9. Sciahbasi A, Rigattieri S, Sarandrea A, Cera M, Di Russo C, Fedele S, et al. Radial artery occlusion and hand strength after percutaneous coronary procedures: Results of the HANGAR study. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2016;87(5):868-74.
10. Pancholy S, Coppola J, Patel T, Roke-Thomas M. Prevention of radial artery occlusion-patent hemostasis evaluation trial (PROPHET study): a randomized comparison of traditional versus patency documented hemostasis after transradial catheterization. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2008;72(3):335-40.
11. Hahalis GN, Leopoulou M, Tsigkas G, Xanthopoulou I, Patsilinakos S, Patsourakos NG, et al. Multicentre Randomized Evaluation of High Versus Standard Heparin Dose on Incident Radial Arterial Occlusion After Transradial Coronary Angiography: The SPIRIT OF ARTEMIS Study. JACC Cardiovasc Interv. 2018;11(22):2241-50.

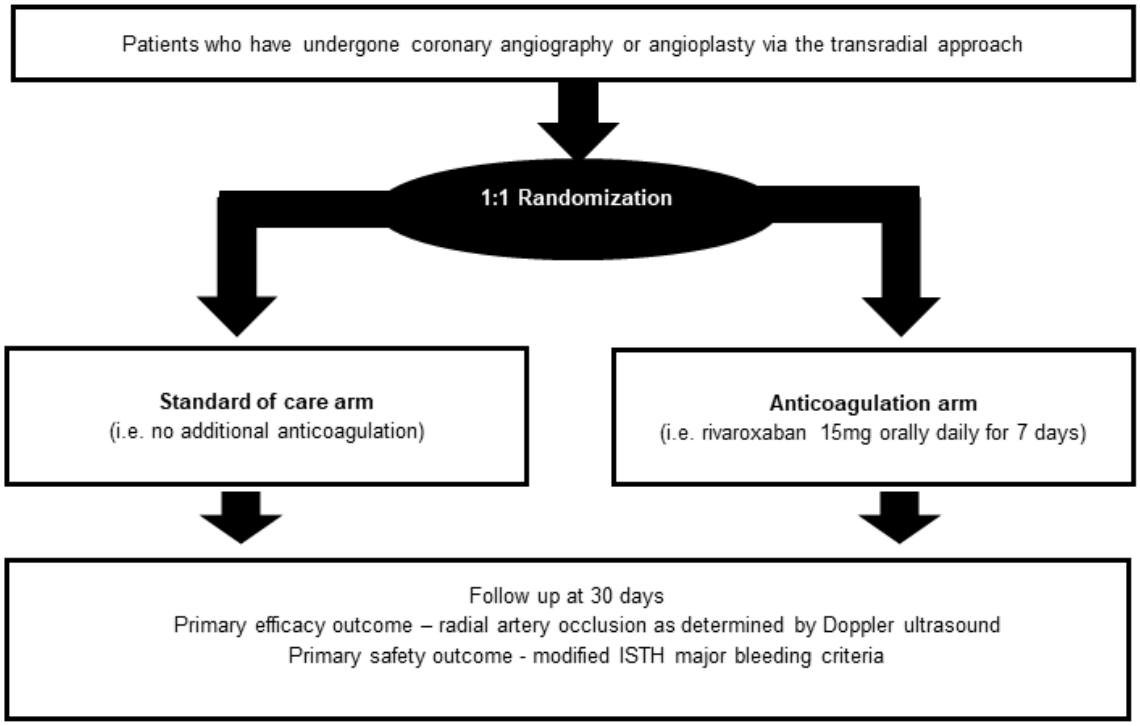
12. Pancholy SB. Comparison of the effect of intra-arterial versus intravenous heparin on radial artery occlusion after transradial catheterization. The American journal of cardiology. 2009;104(8):1083-5.
13. Liang D, Lin Q, Zhu Q, Zhou X, Fang Y, Wang L, et al. Short-Term Postoperative Use of Rivaroxaban to Prevent Radial Artery Occlusion After Transradial Coronary Procedure: The RESTORE Randomized Trial. Circ Cardiovasc Interv. 2022;15(4):e011555.
14. Bavry AA. Prevention of Radial Artery Occlusion With Rivaroxaban After Transradial Coronary Procedures: The RIVARAD Multicentric Randomized Trial. Transcatheter Cardiovascular Therapeutics; September 19, 2022; Boston, MA2022.
15. Mason Peter J, Shah B, Tamis-Holland Jacqueline E, Bittl John A, Cohen Mauricio G, Safirstein J, et al. An Update on Radial Artery Access and Best Practices for Transradial Coronary Angiography and Intervention in Acute Coronary Syndrome: A Scientific Statement From the American Heart Association. Circ Cardiovasc Interv. 2018;11(9):e000035.
16. Rao SV, Tremmel JA, Gilchrist IC, Shah PB, Gulati R, Shroff AR, et al. Best practices for transradial angiography and intervention: A consensus statement from the society for cardiovascular angiography and intervention's transradial working group. 2014;83(2):228-36.
17. Habib J, Baetz L, Satiani B. Assessment of collateral circulation to the hand prior to radial artery harvest. Vascular Medicine. 2012;17(5):352-61.
18. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med. 2016;375(25):2423-34.
19. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. Canadian Journal of Cardiology. 2020;36(12):1847-948.
20. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart R. Circulation. 2019;140(2).
21. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2021;42(5):373-498.
22. Sinha SK, Jha MJ, Mishra V, Thakur R, Goel A, Kumar A, et al. Radial Artery Occlusion – Incidence, Predictors and Long-term outcome after TRAnsradial Catheterization: clinico-Doppler ultrasound-based study (RAIL-TRAC study). Acta Cardiologica. 2017;72(3):318-27.
23. Garg N, Madan BK, Khanna R, Sinha A, Kapoor A, Tewari S, et al. Incidence and predictors of radial artery occlusion after transradial coronary angioplasty: Doppler-guided follow-up study. The Journal of invasive cardiology. 2015;27(2):106-12.
24. Kotowycz MA, Dzavik V. Radial artery patency after transradial catheterization. Circulation Cardiovascular interventions. 2012;5(1):127-33.

25. Yonetsu T, Kakuta T, Lee T, Takayama K, Kakita K, Iwamoto T, et al. Assessment of acute injuries and chronic intimal thickening of the radial artery after transradial coronary intervention by optical coherence tomography. European heart journal. 2010;31(13):1608-15.
26. Mamas MA, Fraser DG, Ratib K, Fath-Ordoubadi F, El-Omar M, Nolan J, et al. Minimising radial injury: prevention is better than cure. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2014;10(7):824-32.
27. Sakai H, Ikeda S, Harada T, Yonashiro S, Ozumi K, Ohe H, et al. Limitations of successive transradial approach in the same arm: the Japanese experience. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2001;54(2):204-8.
28. Abdelaal E, Molin P, Plourde G, Machaalany J, Bataille Y, Brousseau-Provencher C, et al. Successive transradial access for coronary procedures: experience of Quebec Heart-Lung Institute. American heart journal. 2013;165(3):325-31.
29. Kotowycz MA, Johnston KW, Ivanov J, Asif N, Almoghairi AM, Choudhury A, et al. Predictors of radial artery size in patients undergoing cardiac catheterization: insights from the Good Radial Artery Size Prediction (GRASP) study. The Canadian journal of cardiology. 2014;30(2):211-6.
30. Rashid M, Kwok CS, Pancholy S, Chugh S, Kedev SA, Bernat I, et al. Radial Artery Occlusion After Transradial Interventions: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2016;5(1).
31. Aminian A, Saito S, Takahashi A, Bernat I, Jobe RL, Kajiya T, et al. Comparison of a new slender 6 Fr sheath with a standard 5 Fr sheath for transradial coronary angiography and intervention: RAP and BEAT (Radial Artery Patency and Bleeding, Efficacy, Adverse evenT), a randomised multicentre trial. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2017;13(5):e549-e56.
32. Dahm JB, Vogelgesang D, Hummel A, Staudt A, Volzke H, Felix SB. A randomized trial of 5 vs. 6 French transradial percutaneous coronary interventions. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2002;57(2):172-6.
33. Sanmartin M, Gomez M, Rumoroso JR, Sadaba M, Martinez M, Baz JA, et al. Interruption of blood flow during compression and radial artery occlusion after transradial catheterization. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2007;70(2):185-9.
34. Pancholy SB, Patel TM. Effect of duration of hemostatic compression on radial artery occlusion after transradial access. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2012;79(1):78-81.
35. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med. 2017;377(16):1513-24.

36. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51.
37. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093-104.
38. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-92.
39. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-91.
40. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808.
41. Hokusai VTEI, Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369(15):1406-15.
42. Investigators E-P, Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287-97.
43. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-52.
44. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017;377(14):1319-30.

Figure Legend

Figure 1 – Flow of patient screening and enrolment



CHAPTER 8: DISCUSSION AND CONCLUSION

8.1 Overview of the chapter

This final chapter provides an integrated discussion and conclusion for the thesis as a whole. Each preceding chapter includes a study specific discussion therefore, the purpose of this chapter is to synthesize the findings across all studies, contextualize them within the existing literature, and consider their implications for clinical practice, health systems, and future research.

Specifically, this chapter aims to:

1. Revisit the rationale and objectives of the thesis
2. Synthesize findings across the individual studies in relation to the research questions outlined in Chapter 1
3. Discuss implications for clinical practice and healthcare policy
4. Highlight the novelty and strengths as well as limitations of this body of work
5. Identify priorities for future research related to access site selection

8.2 Summary of thesis rationale and objectives

Transradial access (TRA) has emerged as the preferred access site for coronary angiography and percutaneous coronary intervention (PCI), supported by randomized trials and meta-analyses demonstrating reductions in bleeding, vascular complications, and mortality compared to transfemoral access (TFA). These findings have driven strong guideline recommendations endorsing a “radial first” approach in contemporary interventional cardiology practice.[1-4]

Despite this evolution, access site selection remains nuanced. As TRA adoption has increased, important questions have emerged regarding detection and management of both common and rare access site complications, long term vascular access preservation, and healthcare system-level value. Prior to this thesis, these issues have largely been evaluated in isolation rather than within a unified conceptual framework.

The overarching objective of this thesis was therefore to comprehensively evaluate the consequences of arterial access site selection across the continuum of invasive cardiovascular care, extending beyond traditional bleeding outcomes to include rare complications, diagnostic strategies, long term vascular outcomes, and cost effectiveness.

8.3 Synthesis of findings across research questions

8.3.1 Clinical efficacy and safety

This systematic review and meta analysis presented in Chapter 3 demonstrates that TRA is associated with lower 30-day mortality, major bleeding, and vascular complications compared with TFA in patients undergoing PCI for ST-elevation myocardial infarction (STEMI).[5] These findings reinforce the evidence from broader acute coronary syndrome populations and provide high quality, STEMI specific data supporting guideline recommendations for a “radial first” strategy. [1-4]

Importantly, this analysis addresses lingering concerns that benefits observed in lower risk patient populations may not extend to acutely ill STEMI patients requiring urgent reperfusion and potent antithrombotic therapy.

8.3.2 Rare but catastrophic complications

Chapter 4 addresses catheter-induced coronary artery dissection, a rare but potentially fatal complication of coronary angiography. Concerns regarding a possible association between TRA and catheter dissection have persisted due to anatomical and mechanical considerations.[6] Using a large, contemporary cohort, this study demonstrated that access site was not independently associated with catheter-induced coronary artery dissection risk in modern practice, particularly after institutional transition to a predominant TRA strategy. These findings suggest that early signals of harm may reflect learning curve effects rather than intrinsic limitations of TRA, providing reassurance regarding TRA as the default vascular access.

8.3.3 Detection and management of access site complications

While prevention of access site complications is critical, early detection and management if they do occur remains essential. Chapter 5 demonstrated that point-of-care ultrasound (POCUS), when used as an adjunct to the physical examination, significantly improves diagnostic accuracy for detecting complications compared with clinical assessment alone.[7] This work highlights the limitations of traditional bedside examination and supports the integration of POCUS into routine post-procedural care. Importantly, the study demonstrated feasibility and scalability with cardiology trainees achieving adequate proficiency following brief structured training.

8.3.4 Economic and health system implications

Chapter 6 demonstrated that TRA is economically dominant compared with TFA within a publicly funded Canadian healthcare system, yielding similar short-term quality adjusted life years at lower overall costs. Although per patient cost differences were modest, the high volume

of coronary angiography procedures performed annually in Canada suggest substantial aggregate system-level impact. This finding reinforces the alignment between patient centred outcomes and health care sustainability supporting TRA adoption from both clinical and policy perspectives.

8.3.5 Long term vascular preservation and radial artery occlusion

Radial artery occlusion (RAO) remains the most common complication of TRA and has important implications for future access site selection, coronary artery bypass graft surgery, and dialysis access. Chapter 7 presented the rationale, design, and pre-specified statistical analysis plan of the RAPTOR randomized clinical trial. In this trial, short-term anticoagulation with rivaroxaban for RAO prevention will be studied.[8] By addressing RAO directly, this work shifts focus from short-term procedural success to long-term vascular preservation, an increasingly important consideration as TRA has become the default access site.

8.4 Implications for clinical practice and policy

Collectively, the findings of this thesis support a comprehensive “radial first” strategy that extends beyond procedural choice to include complication detection, vascular preservation, and system-level efficiency. Clinicians should consider access site selection a longitudinal decision with downstream consequences, rather than a purely technical preference.

From a policy perspective, these findings support institutional investment in TRA prioritization, POCUS education, and standardized RAO prevention strategies. Health systems may also consider incorporating access site related outcomes into quality metrics and procedural benchmarks.

8.5 Novelty, strengths, and limitations

This thesis makes several novel contributions to literature on arterial access site selection by extending evaluation beyond traditional procedural and bleeding outcomes and by integrating multiple methodological approaches within a single conceptual framework.

8.5.1 Novelty and contribution

A key novel aspect of this thesis is its comprehensive, continuum-based approach to access site selection. Rather than treating TRA versus TFA as a binary technical comparison, this thesis conceptualizes access site selection as a longitudinal determinant of patient outcomes, procedural safety, vascular access preservation, and health system value. This is the first body of work to systematically evaluate access site selection across short-term mortality, rare but potentially catastrophic complications, diagnostic strategies for complication detection, economic impact, and preventative interventional strategies within a single doctoral thesis.

The thesis also contributes new evidence in several underexplored domains. The STEMI specific meta-analysis provides the most contemporary and focused synthesis of randomized evidence examining mortality associated with access site selection in a high-risk PCI population. The catheter-induced coronary artery dissection analysis represents the largest access site specific evaluation of this rare complication to date and is the first to examine temporal trends in relation to institutional adoption of "radial first" strategies. The ULTRASITCOM study is the first prospective diagnostic accuracy study to evaluate POCUS for the detection of post-procedural vascular access complications in interventional cardiology practice. Finally, the design and prespecified statistical analysis plan of the RAPTOR randomized clinical trial represents an

important translational contribution, bridging observational mechanistic insights into a pragmatic interventional strategy aimed at preserving long term vascular access. The inclusion of a statistical analysis plan prior to unblinding reflects best practices in trial methodology and strengthens the interpretability of future trial results.

8.5.2 Methodological strengths

This thesis is strengthened by its methodological breadth and coherence. Each research question was addressed using a study design appropriate to the nature of the outcome under investigation. Randomized clinical trial data and meta-analysis were used where causal inference was paramount; large retrospective cohort analysis were employed to evaluate rare outcomes not amenable to randomized trials; prospective diagnostic accuracy methodology was used to assess bedside imaging strategies; decision analytic modeling was applied to evaluate health system implications; and rigorous clinical trial methodology was used to design a definitive randomized intervention.

The use of contemporary data across studies further strengthens the relevance of the findings. All analyses reflect modern interventional cardiology practice. This enhances the external validity of the results and their applicability to current clinical practice. In addition, several studies within this thesis emphasize pre-specification and transparency, including protocol publication, adherence to established reporting standards, and completion of a detail statistical analysis plan prior to data unblinding. These features reduce the risk of selective reporting and data-driven inference.

8.5.3 Limitations

Despite these strengths, several limitations warrant consideration. First, observational analyses included in this thesis are subject to residual confounding, despite adjustment for important covariates. This is particularly relevant for rare complications such as catheter-induced coronary artery dissection where event rates are low and unmeasured procedural factors may influence risk. While large sample sizes and temporal trend analyses mitigate this concern to some extent, causality cannot be established. Second, the evaluation of rare outcomes is inherently constrained by low absolute event rates, which limits statistical power and precision of effect estimates. Although the large cohorts used in this thesis represent some of the most comprehensive datasets available for studying such events, findings should be interpreted in the context of these limitations.

Next, the cost-effective analysis relies on model-based assumptions and a relatively short analytic time horizon. While this approach reflects available data and minimizes extrapolation, it underestimates the long term economic and quality of life benefits associated with vascular access site strategies. Future models incorporating patient reported outcomes may provide a more complete assessment of value.

Fourth, although the RAPTOR trial design and statistical analysis plan are robust, definitive conclusions regarding RAO prevention cannot be drawn until trial results are available. The inclusion of the trial design and SAP in this thesis reflects methodological and conceptual contribution rather than completed outcome evaluation.

Finally, this thesis focuses primarily on outcomes relevant to TRA and TFA in coronary angiography and PCI. Such findings may not be directly generalizable to other access sites, large bore interventions, or structural heart procedures, where different technical and risk considerations may apply.

8.5.4 Overall assessment

Taken together, the strengths of this thesis, including its integrative framework, methodological rigour, and focus on clinically meaningful outcomes, outweigh its limitations. The work provides a comprehensive and contemporary evaluation of arterial access site selection and advances understanding beyond isolated procedural endpoints. These contributions support informed clinical decision making, guide health system policy, and establish a foundation for future research aimed at optimizing invasive cardiovascular care.

8.6. Current state of evidence

Given that the studies included in the thesis were conducted and published over several years, it is important to contextualize their findings within the most current evidence base and evolving clinical practice. While the core conclusions of this work remained valid, their interpretation has become more nuanced over time as additional data and experience have accumulated.

8.6.1 Systematic review and meta analysis (Chapter 3)

The systematic review and meta analysis provided a focused synthesis of randomized evidence evaluating TRA versus TFA and patients with STEMI, demonstrating reductions in 30-day mortality, major bleeding, and vascular complications with TRA. These findings remain broadly

consistent with contemporary clinical guidelines which continue to support a radial first approach in acute coronary syndrome populations.

However, the interpretation of the mortality benefit has evolved. More recent high quality evidence, including an individual patient level data meta analysis of over 21,000 patients from multicenter randomized trials, has confirmed that TRA is associated with lower all-cause mortality and major bleeding at 30 days, with a relative reduction in mortality of 20 to 25%. [9] Importantly, this analysis also demonstrated that the mortality benefit is not uniform across all patients, but appears to be driven primarily by higher risk subgroups, particularly those with baseline anemia, and is only partially mediated by reductions in major bleeding.

Taken together with more contemporary evidence, the findings suggest that while a mortality reduction with TRA is biologically plausible, the magnitude and consistency of this effect are likely context dependent. Improvements in femoral access technique, pharmacotherapy, and bleeding avoidance strategies have narrowed outcome differences between access sites and modern practice. As such, the most robust and consistent advantages of TRA are now understood to be reductions in bleeding and vascular complications, while the mortality signal should be interpreted with greater nuance and in the context of patient risk profile.

8.6.2 Retrospective CICAD study (Chapter 4)

The retrospective cohort study evaluating CICAD remains one of the largest analyses of this rare complication and continues to provide clinically relevant insights. The principal finding, that access site is not independently associated with increased CICAD risk in contemporary practice, remains valid.

With the benefit of temporal analysis and evolving practice patterns, this finding is now best interpreted within the context of operator and institutional experience. The observed attenuation of apparent risk with TRA over time supports the interpretation that early signals of harm likely reflected a learning curve effect rather than intrinsic limitation of the radial approach. In current practice, where TRA is widely adopted and operator proficiency is high, access site alone appears to play a limited role in determining CICAD risk.

8.6.3 Propsective POCUS study (Chapter 5)

The ULTRASITCOM study demonstrated that point of care ultrasound, when used as an adjunct to physical examination, improves the sensitivity of detecting vascular access complications. These findings remain contemporary and relevant, especially given the increasing integration of POCUS into cardiovascular training and practice.

However, the interpretation of this work has also evolved. The study should be viewed as establishing diagnostic validity and feasibility rather than definitive evidence for routine implementation. While pocus improves detection, its impact on clinical outcomes, workflow efficiency, and resource utilization has not yet been established. Therefore, current evidence supports the selective integration of POCUS in appropriate clinical settings, with further research needed to evaluate its role within structured care pathways.

8.6.4 Health economic analysis (Chapter 6)

The cost effectiveness analysis demonstrated that TRA is economically dominant compared with TFA within the Canadian healthcare system, yielding similar quality-adjusted life years at lower overall cost. The primary direction of this finding remains consistent with contemporary evidence, particularly given that the primary drivers of cost effectiveness (i.e. reductions in bleeding, vascular complications, and length of stay) continue to favor TRA.

However, the absolute magnitude of cost savings is context specific and dependent on local cost structures, practice patterns, and healthcare system organization. Additionally the short term time horizon used in the model reflects the predominance of early procedural benefits and likely underestimates longer term patient centered outcomes. Therefore, while the conclusion that TRA is cost effective remains robust, its precise economic impact may vary across jurisdictions and modeling assumptions.

8.6.5 RAPTOR trial (Chapter 7)

At the time of initial thesis submission, Chapter 7 described the design and rationale of the RAPTOR randomized clinical trial evaluating short-term rivaroxaban for the prevention of radial artery occlusion. Since that time, the trial has been completed and was stopped early following a Data Safety Monitoring Board recommended futility analysis.

This outcome provides important and clinically meaningful information. It suggests that in contemporary radial first practice environments, where baseline RAO rates are relatively low and procedural techniques are optimized, the incremental benefit of routine post procedural

anticoagulation is likely limited. Rather than representing a negative or failed study, this finding reflects a rigorous evaluation of a clinically relevant intervention and contributes to refining best practices in radial artery preservation.

8.6.5 Overall current status of evidence

Taken together, the body of work presented in this thesis remains current and relevant; however, its interpretation has matured. The central message is that TRA is a safe, effective, and economically favorable strategy for coronary angiography and PCI. While this continues to be supported by contemporary evidence, the emphasis has shifted toward a more nuanced understanding of the context dependent nature of mortality benefits, the importance of operator experience and institutional practice patterns, the distinction between diagnostic performance and clinical utility, and the need to evaluate incremental interventions within already optimized care pathways. This evolution reflects the natural progression of evidence in the field where a once novel technique has become standard practice, and where the focus of research has appropriately shifted from establishing superiority to optimizing implementation and addressing residual uncertainties.

8.7 Future directions

The findings of this thesis identify several important directions for future research and implementation. First, completion and dissemination of results from randomized trials targeting RAO prevention, including the RAPTOR trial, will be essential to determine whether a post-procedural pharmacological strategy should be incorporated into routine transradial practice. Future studies should also evaluate the durability of radial artery patency over longer follow-up periods and better assess patient-reported outcomes.

Second, further research is needed to refine strategies for early detection and management of access site complications. Multicentre evaluations of POCUS-based post-procedural assessment protocols could help determine their generalizability, cost effectiveness, and impact on downstream imaging, length of stay, and overall patient experience. Standardized training pathways and competency frameworks for POCUS in interventional cardiology warrant formal evaluation.

Beyond additional research, effective knowledge translation will be critical to ensure that the findings of this thesis inform clinical practice and health system decision making. Several knowledge translation strategies may be considered. Dissemination of results through national and international cardiology conferences and guideline committees can support incorporation of these findings into consensus statements and best practice recommendations. Locally, integration of access site related metrics into quality improvement dashboards may facilitate sustained practice change.

Educational initiatives represent another important knowledge translation pathway. Incorporating evidence from this thesis to fellowship curricula, simulation-based training, and continuing medical education programs may further enhance operator proficiency and reinforce a longitudinal perspective on access site selection. Finally, collaboration with health system leaders and policy makers may further support adoption of “radial first” strategies, POCUS integration, and vascular access preservation initiatives by aligning clinical benefits, economic benefits and patient-centred outcomes. Together, these research and knowledge translation efforts

have the potential to move access site selection from an operator dependent technical choice to a standardized evidence informed component of high quality interventional cardiology care.

8.8 Conclusion

In conclusion, this thesis demonstrates that arterial access site selection is a multi-dimensional determinant of patient outcomes and health system performance. TRA is associated with improved safety, comparable or superior efficacy, and favorable economic value, without increased risk of rare complications when performed in contemporary interventional cardiology practice. By extending evaluation beyond traditional endpoints, this work provides a comprehensive framework to guide clinical decision making, policy development, and future research in interventional cardiology.

8.9 References

1. Bernat, I., et al., *Best Practices for the Prevention of Radial Artery Occlusion After Transradial Diagnostic Angiography and Intervention: An International Consensus Paper.* JACC Cardiovasc Interv, 2019. **12**(22): p. 2235–2246.
2. Lawton, J.S., et al., *2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.* J Am Coll Cardiol, 2022. **79**(2): p. e21–e129.
3. Rao, S.V., et al., *2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.* Circulation, 2025. **151**(13).
4. Rao, S.V., et al., *Best practices for transradial angiography and intervention: a consensus statement from the society for cardiovascular angiography and intervention's transradial working group.* Catheter Cardiovasc Interv, 2014. **83**(2): p. 228–36.
5. Di Santo, P., et al., *Transradial Versus Transfemoral Access for Percutaneous Coronary Intervention in ST-Segment–Elevation Myocardial Infarction.* Circulation: Cardiovascular Interventions, 2021. **14**(3).
6. Di Santo, P., et al., *Association Between the Access Site for Coronary Angiography and Catheter-induced Coronary Artery Dissection.* J Soc Cardiovasc Angiogr Interv, 2023. **2**(3): p. 100606.

7. Di Santo, P., et al., *Point-of-Care Ultrasound for the Detection of Vascular access complications—The ULTRASITCOM Study.* Journal of the Society for Cardiovascular Angiography & Interventions, 2025. **4**(2): p. 102516.

8. Di Santo, P., et al., *Rationale and Design of the Rivaroxaban Post-Transradial Access for the Prevention of Radial Artery Occlusion Trial (CAPITAL-RAPTOR).* BMJ Open, 2023. **13**(5): p. e070720.

9. Gargiulo G, et al. *Effects on Mortality and Major Bleeding of Radial Versus Femoral Artery Access for Coronary Angiography or Percutaneous Coronary Intervention: Meta-Analysis of Individual Patient Data From 7 Multicenter Randomized Clinical Trials.* Circulation. 2022;146(18):1329–43.

APPENDICES

Appendix A – PDF of published manuscript - systematic review/meta-analysis

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Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Transradial Versus Transfemoral Access for Percutaneous Coronary Intervention in ST-Segment–Elevation Myocardial Infarction

A Systematic Review and Meta-Analysis

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BACKGROUND: Transradial access (TRA) has emerged as the preferred vascular access site for coronary angiography and percutaneous coronary intervention. This systematic review and meta-analysis was performed to evaluate 30-day all-cause mortality comparing TRA with transfemoral access for percutaneous coronary intervention in patients with ST-segment–elevation myocardial infarction.

METHODS: We performed a systematic literature search and meta-analysis of randomized controlled studies published from inception until January 7, 2020, in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science Core Collection. Preferred Reported Items for Systematic Reviews and Meta-Analyses guidelines were used for abstracting data. The primary outcome was all-cause mortality at 30 days. Secondary outcomes included myocardial infarction, major bleeding, stroke, and access site complications.

RESULTS: A total of 14 studies representing 11 707 patients (5802 patients with TRA; 5905 patients with transfemoral access) were included in this systematic review. All-cause mortality (N=8 studies) was significantly reduced in the TRA group with an overall risk ratio (RR) of 0.72 (95% CI, 0.56–0.92) in the pooled analysis. Major bleeding (N=12 studies; RR, 0.60 [95% CI, 0.45–0.80]) and access site complications (N=9 studies; RR, 0.40 [95% CI, 0.30–0.53]) were significantly higher in the transfemoral access group. There was no statistical difference in reinfarction (N=10 studies; RR, 0.96 [95% CI, 0.75–1.25]) or stroke (N=8 studies; RR, 1.47 [95% CI, 0.87–2.50]).

CONCLUSIONS: TRA is associated with lower 30-day mortality, major bleeding, and access site complications when compared with transfemoral access in ST-segment–elevation myocardial infarction patients who undergo percutaneous coronary intervention.

REGISTRATION: URL: https://www.crd.york.ac.uk/PROSPERO/; Unique identifier: 127955.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: acute coronary syndrome ■ coronary angiography ■ glycoprotein ■ percutaneous coronary intervention ■ ST-segment–elevation myocardial infarction

See Editorial by Jolly and Nolan

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WHAT IS KNOWN

- Transradial access has emerged as the preferred access site for coronary angiography and percutaneous coronary intervention, including in patients with ST-segment–elevation myocardial infarction.

WHAT THE STUDY ADDS

- In this meta-analysis of 14 randomized controlled trials including 11 707 patients, transradial access was associated with reduced all-cause mortality when compared with transfemoral access.
- Transradial access was also associated with reductions in major bleeding and access site vascular complications.
- There was no difference in reinfarction or stroke between transradial and transfemoral access.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
BARC	Bleeding Academic Research Consortium
GPI	glycoprotein IIb/IIIa inhibitor
HORIZONS-AMI	Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction Trial
MATRIX	Minimizing Adverse Haemorrhagic Events by Transradial ACCESS Site and Systemic Implementation of Angiox
PCI	percutaneous coronary intervention
REPLACE-2	Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events 2
RIVAL	Radial Versus Femoral Access for Coronary Intervention
RR	risk ratio
SAFARI-STEMI	Safety and Efficacy of Femoral Access Versus Radial Access in ST-Elevation Myocardial Infarction
STEMI	ST-segment–elevation myocardial infarction
TFA	transfemoral access
TRA	transradial access

Coronary angiography and percutaneous coronary intervention (PCI) are the gold standard for the treatment of obstructive lesions in ST-segment–elevation myocardial infarction (STEMI).[1,2] Transradial access (TRA) has emerged as the preferred vascular access site over transfemoral access (TFA) for coronary angiography and PCI[3,4] with several international cardiology society guidelines now strongly recommending TRA over TFA in STEMI.[5,6] Despite several reported advantages to TRA in STEMI, including a reduction in major bleeding, access site complications and a signal towards a reduction in all-cause mortality in the setting of primary PCI,[7–9] there has been a slow adoption of TRA for patients with STEMI in the United States.[10]

Two of the largest studies to date evaluating the role of access site on the safety and efficacy of PCI are the MATRIX study (Minimizing Adverse Haemorrhagic Events by Transradial ACCESS Site and Systemic Implementation of Angiox)[11] and the RIVAL study (Radial Versus Femoral Access for Coronary Intervention).[12] Notably, both trials included patients with acute coronary syndromes (ACS) and were not limited solely to patients with STEMI. While the randomization in the MATRIX study was stratified by type of ACS, the RIVAL study only stratified by study center. Moreover, patients with STEMI in these trials encompassed both a cohort of patients undergoing primary PCI and those who had received fibrinolytic therapy before PCI. Most recently, the SAFARI-STEMI trial (Safety and Efficacy of Femoral Access Versus Radial Access in ST-Elevation Myocardial Infarction) has demonstrated no difference in 30-day all-cause mortality or major bleeding in a dedicated primary PCI STEMI population.[13] While previous systematic reviews in the field have been reported, they were not specific to patients with STEMI and did not include the SAFARI-STEMI study.[8,9] Additionally, the systematic review by Singh et al,[14] included 2 pseudo-randomized controlled studies and one nonrandomized cohort study which did not meet their own eligibility criteria. Therefore, we sought to perform an updated systematic review and meta-analysis of randomized controlled trials to provide the most contemporary and robust review of the data in this highly debated field. For this study, we hypothesized that 30-day all-cause mortality in patients with STEMI who underwent PCI via the TRA would not be significantly different compared with TFA.

METHODS

The data, methods used in the analysis, and materials used to conduct the research will be made available upon request from the authors. Institutional ethics board approval was not required for this study.

Search Strategy

This systematic review was conducted in accordance to the Preferred Reported Items for Systematic Reviews and Meta-Analyses guidelines (appendix A).[15] We performed a computerized literature search of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science Core Collection from inception until January 7, 2020. No restrictions were placed on date or language of publication.

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A combination of both free text words and Medical Subject Heading terms were used to identify studies which assess TRA versus TFA (appendix B). Additionally, a manual search of all eligible articles' reference lists, articles citing eligible articles, and relevant review articles was performed to identify additional literature. The resulting citations were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) with removed duplicates reviewed manually using the duplicate identification function.

Study Selection, Data Extraction, and Quality Assessment

The review was limited to randomized control trials examining TRA as compared with TFA for STEMI. All other study designs were excluded given the large volume of randomized control trials available on this subject. Titles, abstracts, and full texts were screened by 2 independent reviewers. Any discrepancies in the review stage were resolved by further discussion and consensus amongst these two reviewers. Reference lists of all eligible studies were then screened to identify any additional publications meeting inclusion criteria. Data from articles were independently extracted by 2 reviewers. The primary outcome of interest was all-cause mortality at 30 days. Secondary outcomes included in-hospital all-cause mortality, >30-day all-cause mortality, myocardial infarction, major bleeding as defined by each individual study, stroke (ischemic or hemorrhagic), and access site complications (eg, bleeding, hematoma, pseudoaneurysm, distal limb ischemia) as defined by each study. All studies included in the final analysis were assessed according to the Cochrane Handbook for Systematic Reviews of Intervention[16] criteria to determine their relevance, risk of bias, and methodological validity.

Statistical Analyses

The Mantel-Haenszel method was used to calculate the pooled risk ratio (RR) and 95% CIs associated with TRA versus TFA for all-cause mortality in PCI in patients with STEMI using a random effects model. RRs and 95% CIs were generated for our secondary outcomes. Additionally, prespecified subgroup analyses evaluating trials with only primary PCI and GPI (glycoprotein IIb/IIIa inhibitor) use >50% versus <50% were evaluated. An additional post hoc analysis was performed to further evaluate the impact of GPI use on mortality, bleeding, and access site complications by further stratifying the rates of usage into groups according to the proportion of GPI usage. This additional analysis was performed to further elucidate the impact of GPI given the degree of imbalance between the number of patients in the above and below 50% usage cutoff groups initially selected. Sensitivity analyses were performed excluding studies at high or unclear risk of bias and excluding studies with incomplete outcome data. Heterogeneity among eligible studies was visually assessed through inspection of the forest plots and statistically assessed using the I^2 statistic. Publication bias was assessed using Egger regression and visual inspection of funnel plots. Statistical analyses were conducted using Review Manager (RevMan version 5.3, Cochrane Collaboration, London, United Kingdom) and Meta-Essentials: Workbooks[17] for Egger regression. Two-sided P values <0.05 were considered statistically significant.

RESULTS

Study Selection and Characteristics

A total of 1214 records were identified in our search after duplicates were removed (Figure 1). Full-text review was performed on 89 articles, and a total of 14 studies were included in our meta-analysis (Tables I through III in the Data Supplement). Of the identified studies, 2 trials did not include only STEMI patients but rather included broader ACS populations which also included non-STEMI and unstable angina patients.[11,12] As both trials were of considerable sample size and subgroup analyses of patients with STEMI were reported,[18,19] they were included in this systematic review. All included studies were parallel-group randomized controlled trials. There were 9 multicenter studies[13,18–25] and 7 single-center studies[26–30] from various countries. Follow-up duration ranged from in-hospital outcomes in six studies, 30-day outcomes in eight studies, and more than 30-day outcomes in four studies as some studies reported outcomes at various time intervals. With respect to reperfusion strategies, six studies included isolated primary PCI strategies, 6 studies included both primary PCI and combination fibrinolytic/PCI therapies, and the reperfusion strategy was unknown in one trial.

Patient Population

Of the 11 707 patients included in this review, 5802 (49.6%) underwent PCI with TRA approach and 5905 (50.4%) with TFA (Table). The mean age of study participants across all studies was similar in both groups (60.5±4.1 years in the TRA group versus 61.0±4.1 years in the TFA group). Most patients were male (77.6% in TRA and 77.0% in TFA) and >80% of patients in both groups presented Killip class I. Ten percent of all patients had a history of a previous MI and previous PCI, and 1% had previous coronary artery bypass grafting. The reperfusion strategy was reported in only 50% of patients, of which 89.4% of patients in the TRA group underwent primary PCI as compared with 89.9% in the TFA group.

Mortality

All-cause mortality at 30 days was reported in seven of the included studies. One study reported only cardiac death, which was defined as any death due to cardiac cause, procedure-related death, and death of unknown cause.[24] As this study reported 30-day outcomes, it was included in the all-cause mortality outcome as part of this meta-analysis given their broad mortality definition. All-cause mortality at 30 days was low in both groups but was significantly reduced in the TRA group (RR, 0.72 [95% CI, 0.56–0.92; Figures 2 and 3). Overall, there was low heterogeneity based on visual interpretation of the forest plot as well as statistical testing (I^2=8%, P=0.37).

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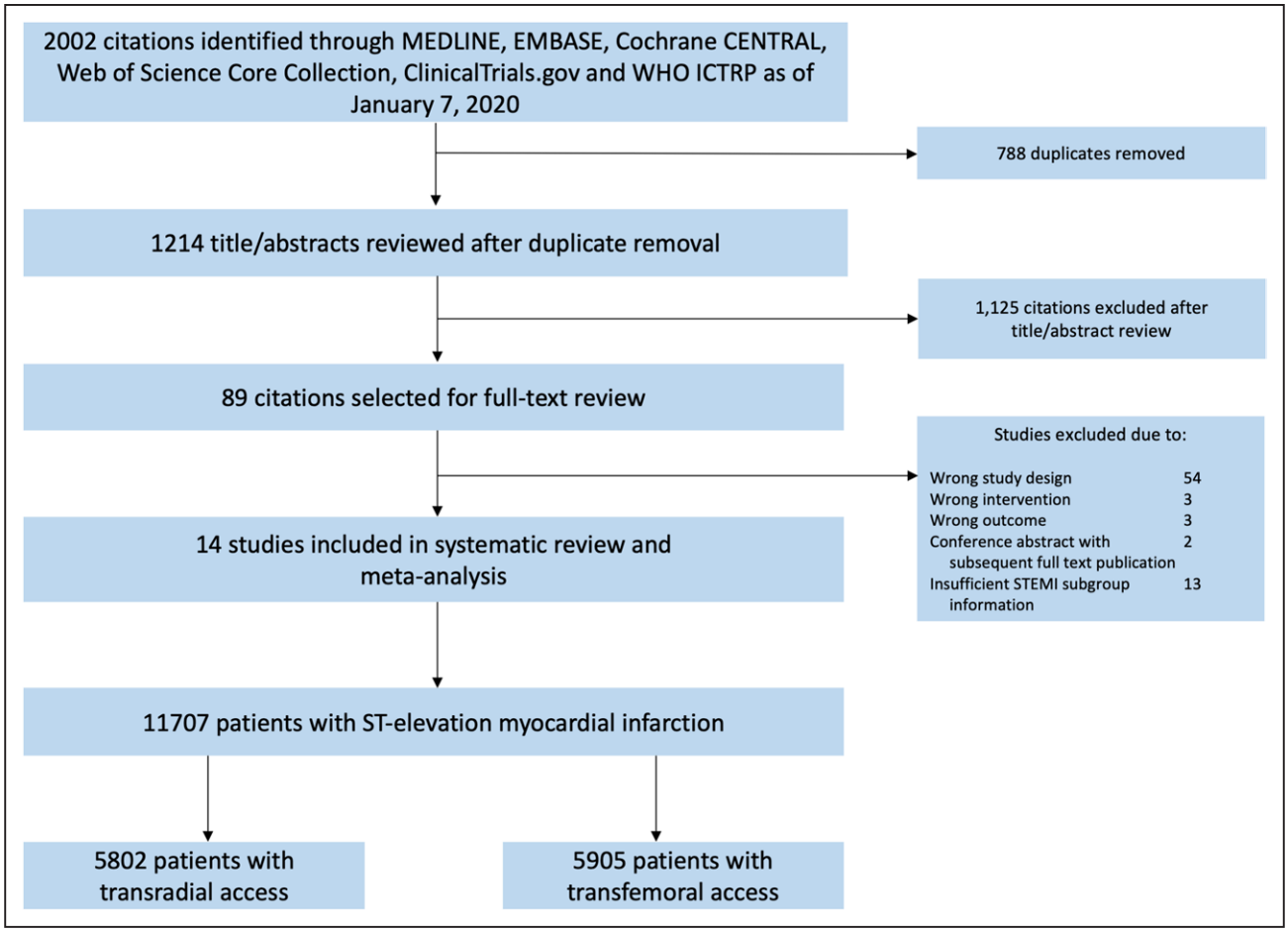

Figure 1. Flow diagram of the systematic review according to the Preferred Reported Items for Systematic Reviews and Meta-Analyses guidelines.
STEMI indicates ST-segment–elevation myocardial infarction.

No statistical difference was observed between TRA and TFA with respect to in-hospital mortality (RR, 0.78 [95% CI, 0.32–1.91]) or in mortality beyond 30 days (RR, 0.62 [95% CI, 0.35–1.10]; Figure I in the Data Supplement). With respect to differences in reperfusion strategies, all-cause mortality in the TRA and TFA groups was not different in the primary PCI population (RR, 0.83 [95% CI, 0.53–1.29]) nor in the not exclusively primary PCI population (RR, 0.73 [95% CI, 0.53–1.00]) when the longest time interval was considered in studies reporting outcomes at more than one follow-up duration (Figure II in the Data Supplement).

With respect to GPI usage above and below 50% in each trial, there was no difference in 30-day mortality in studies using <50% GPI (RR, 0.78 [95% CI, 0.58–1.06]); however, a significant difference was seen in the trials using >50% GPI (RR, 0.56 [95% CI, 0.35–0.89; Figure III in the Data Supplement). In the post hoc analysis of 30-day all-cause mortality stratified into groups according to the proportion of GPI usage in each trial (Figure IVA in the Data Supplement; Figure 3), there is a trend toward favoring TRA as the frequency of GPI use increased. In the 3 studies with the lowest GPI usage group, there was no difference between TRA and TFA (RR, 0.93 [95% CI, 0.67–1.28]). In the second and third groups, the RRs were 0.59 (95% CI, 0.35–1.00]) and 0.57 (95% CI, 0.36–0.90), respectively, in favor of TRA. In the highest usage group, no significant difference was seen between TRA and TFA (RR, 0.33 [95% CI, 0.01–7.81]); however, this highest group was only comprised of one small study with a total of 50 patients. Due to the single study in this highest usage group, we further stratified GPI usage into thirds (ie, usage between 0%–33%, 34%–66%, and 67%–100%). There were no differences in the lowest and second usage groups. In those studies with >66% GPI usage, the RR was 0.56 (95% CI, 0.35–0.89) in favor of TRA (Figure IVB in the Data Supplement).

Major Bleeding

Major bleeding was reported in 12 of the trials. The definition of major bleeding was variable and included the Thrombolysis in Myocardial Infarction,[31] HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction Trial),[32] REPLACE-2 (Randomized Evaluation in Percutaneous

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Table. Baseline Characteristics of Patients Included in Systematic Review and Meta-Analysis

	Total number of participants with available data	Transradial access	Transfemoral access
Total number of participants	11 707	5802	5905
Mean age, y	11 707	60.5±4.1	61.0±4.1
Males, n (%)	11 485	4416/5690 (77.6%)	4462/5795 (77.0%)
Mean body mass index, kg/m^2	6157	27.5±1.1	27.4±0.6
Hypertension	9630	2553/4787 (53.3%)	2569/4843 (53.1%)
Diabetes	11 588	1108/5742 (19.3%)	1084/5846 (18.5%)
Dyslipidemia	9630	1810/4787 (37.8%)	1880/4843 (38.8%)
Smoking	11 588	2496/5742 (43.5%)	2509/5846 (42.9%)
Previous myocardial infarction	10 854	543/5376 (10.1%)	562/5478 (10.3%)
Previous percutaneous coronary intervention	9406	419/4657 (9.0%)	480/4749 (10.1%)
Previous coronary artery bypass grafting	4717	30/2349 (1.3%)	28/2368 (1.2%)
Previous stroke	8598	161/4279 (3.8%)	180/4319 (4.2%)
Killip class			
I	6714	2805/3342 (83.9%)	2864/3372 (84.9%)
II	6714	362/3342 (10.8%)	366/3372 (10.9%)
III/IV	6714	175/3342 (5.2%)	142/3372 (4.2%)
Primary PCI	5768	2540/2840 (89.4%)	2632/2928 (89.9%)
Mean total procedure time, min	1735	45.3±9.2	44.9±9.9
Mean total contrast volume used, mL	5478	196.1±26.0	198.7±31.2

Weighted mean and SDs were calculated based on the sample size of the respective studies. Notably, the SD presented is of the study-level variable and not based on individual patient data. Where median and interquartile range were reported in an individual study, the mean was assumed to be equal to the median and the SD was calculated from interquartile range/1.3. PCI indicates percutaneous coronary intervention.

Coronary Intervention Linking Angiomax to Reduced Clinical Events 2),[33] BARC (Bleeding Academic Research Consortium),[34] and several trial-specific definitions (Table III in the Data Supplement). The overall incidence of major bleeding was low in both groups (2.0% in the TRA group and 3.4% in the TFA group), but significantly less bleeding was seen in the TRA group (RR, 0.60 [95% CI, 0.45–0.80], $P<0.001$). Similar reductions in major bleeding in the TRA group were observed irrespective of stratification by frequency of GPI use (Figure 4 and Figure V in the Data Supplement). Overall, there was low heterogeneity based on visual interpretation of the forest plot and statistical testing ($I^2=16\%$, $P=0.29$).

Vascular Access Complications

Vascular access complications were reported in 13 studies. There were significantly fewer vascular access complications in patients with TRA (1.4% versus 3.5% in the TFA group) with an overall RR of 0.40 (95% CI, 0.30–0.53), and TRA was favored irrespective of GPI use (Figure 4 and Figure VI in the Data Supplement). Radial artery occlusion, which is the most common vascular complication following TRA, was reported in 4 studies.[22,23,25,26] There was low heterogeneity based on visual interpretation of the forest plot as well as statistical testing ($I^2=0\%$, $P=0.86$).

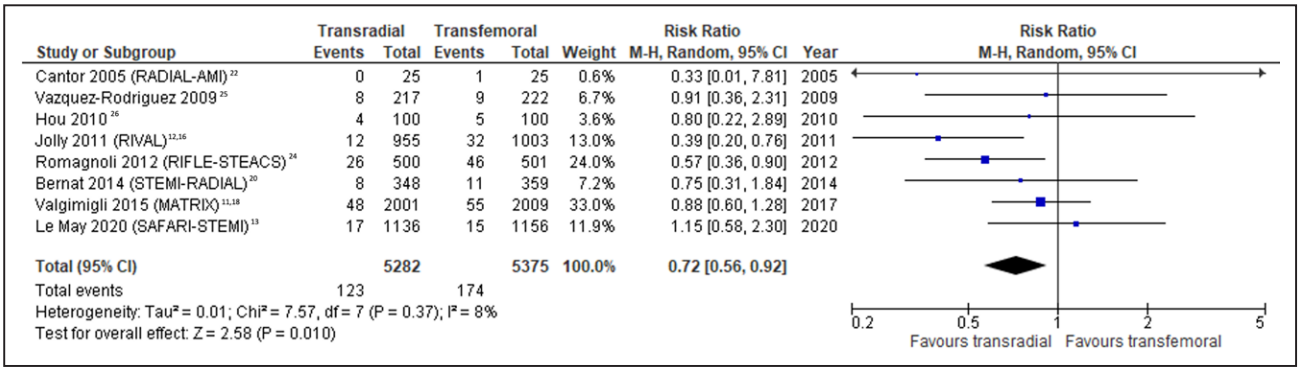

Figure 2. The association between access site for percutaneous coronary intervention in patients with ST-segment–elevation myocardial infarction (STEMI) and all-cause mortality at 30 d was assessed.
Transradial access (TRA) was associated with reduced morality (risk ratio, 0.72 [95% CI, 0.56–0.92]) over transfemoral access (TFA).

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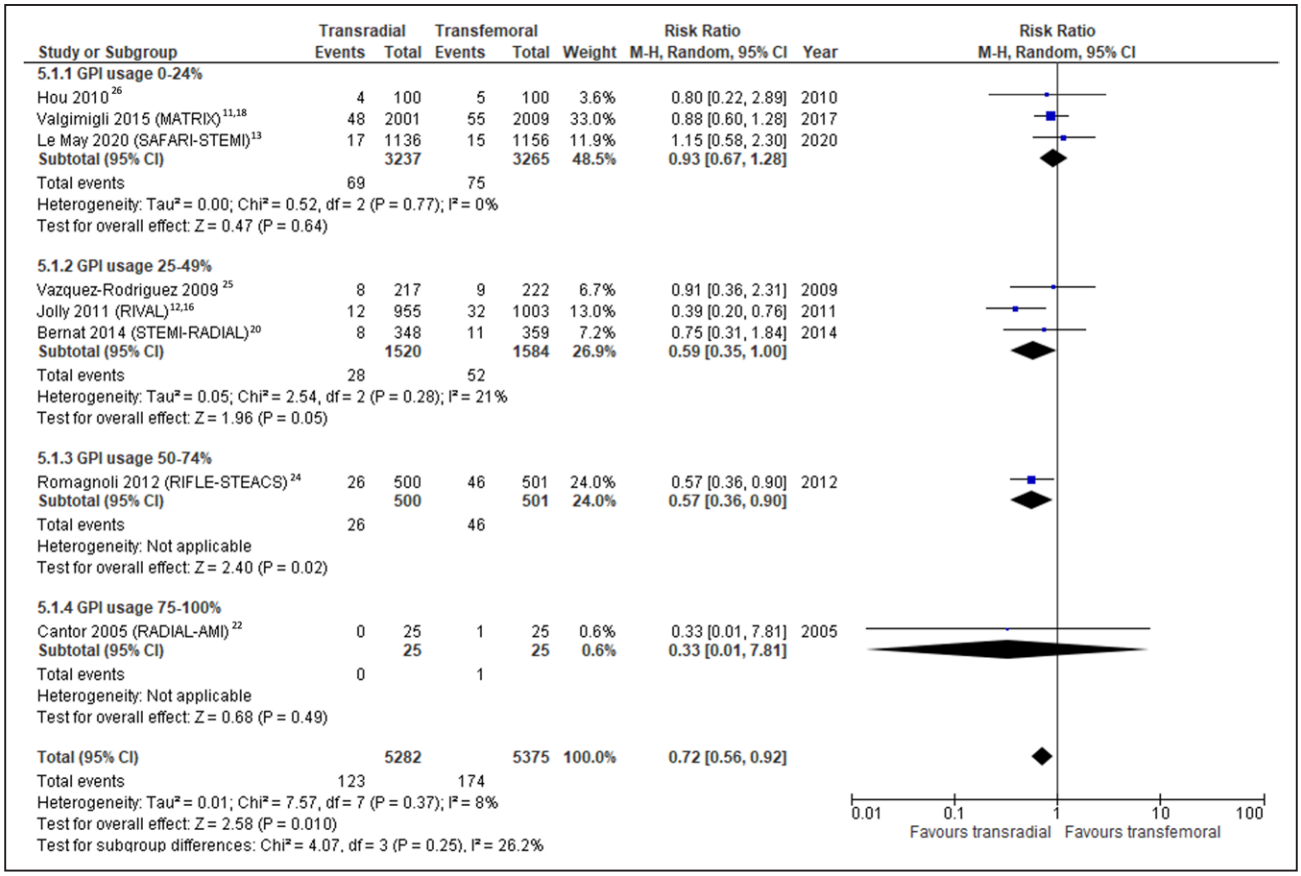

Figure 3. The association between access site for percutaneous coronary intervention in patients with ST-segment–elevation myocardial infarction and all-cause mortality at 30-d was assessed and stratified by frequency of GPI (glycoprotein) IIb/IIIa inhibitor frequency of use.

MI and Stroke

With respect to both reinfarction and stroke, there was no difference between TRA and TFA with an RR 0.96 (95% CI, 0.75–1.25) and 1.47 (95% CI, 0.87–2.50), respectively (Figure 4 and Figures VII and VIII in the Data Supplement). There was low heterogeneity based on visual interpretation of both forest plots as well as statistical testing for reinfarction (I^2=0%; P=0.95) and stroke (I^2=0%; P=0.97).

Risk of Bias

All studies were at low risk of performance bias and most studies were at low risk of attrition bias, reporting bias, and detection bias with respect to all objective outcomes included in this review (Figure IX in the Data Supplement). Only half of the included studies were at low risk of selection bias due to issues with random sequence generation and allocation concealment. Assessment of publication bias was performed through visual inspection of the funnel plot for all-cause mortality (Figure X in the Data Supplement). The funnel plot appeared symmetrical suggesting an absence of publication bias, which was further supported by formal testing with Egger regression (P=0.42).

Sensitivity Analyses

Sensitivity analyses were performed excluding studies with incomplete outcome data and excluding studies at high or unclear risk of bias (Figure XI in the Data Supplement). Six studies with complete study follow-up were included. Notably, these studies largely involved only in-hospital outcomes and had an overall RR of 0.63 (95% CI, 0.36–1.11; Figure XIA in the Data Supplement). Five studies were deemed to not be at high or unclear risk of bias, all of which reported 30-day outcomes. In this analysis, there was no difference between TRA and TFA (RR, 0.79 [95% CI, 0.62–1.02]; Figure XIB in the Data Supplement).

DISCUSSION

In our systematic review and meta-analysis examining the differences between TRA and TFA for PCI in STEMI, patients who underwent TRA had a significantly lower 30-day all-cause mortality and were less likely to experience major bleeding or vascular access site complications. Notably, radial artery occlusion was included as a vascular access complication in only 4 of the included trials. There were no statistical differences in the rates of stroke or MI between these 2 strategies.

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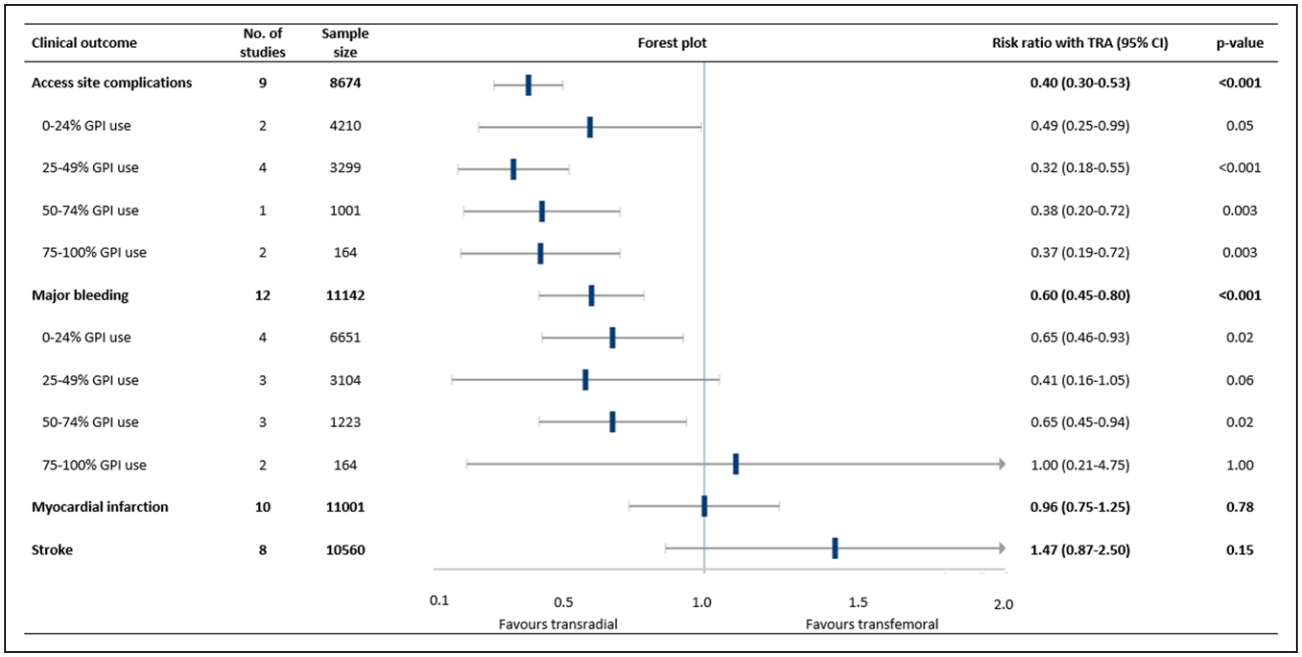

Figure 4. Secondary outcomes.
The association between access site for percutaneous coronary intervention in patients with ST-segment–elevation myocardial infarction and access site complications, major bleeding, myocardial infarction, and stroke were assessed. GPI indicates glycoprotein IIb/IIIa inhibitor; and TRA, transradial access.

In previously reported pooled analyses, a significant reduction in all-cause mortality has been reported with use of the TRA in the primary PCI population.[35,36] This mortality benefit is largely attributed to a reduction in both bleeding and vascular access complications.[37] As expected, our analysis demonstrates an increased risk of both complications with TFA, which may in part contribute to the lower 30-day all-cause mortality. Interestingly, despite the pooled analysis of eight studies reporting our primary outcome, the only trials that individually identified a mortality benefit were RIVAL[12,19] (RR, 0.39 [95% CI, 0.20–0.76]) and RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome Study)[24] (RR, 0.57 [95% CI, 0.36–0.93]). Importantly, the RIVAL study was not limited to patients with STEMI but rather included patients with any ACS. Furthermore, this trial did not stratify by type of ACS as was done in the MATRIX trial. Finally, the RIFLE-STEACS study reported cardiac death, which given the broad definition and brief study follow-up duration, was used as a surrogate for all-cause mortality, although these may not be equivalent.

In studies performed in the past decade, there has been a trend away from favoring the TRA approach with respect to all-cause mortality at 30 days (Figure 3). In our post hoc analysis, we demonstrated an increased trend in mortality with increasing GPI use (Figure IV in the Data Supplement; Figure 3). In further subgroup analyses stratified by GPI use, there was no difference in major bleeding or access site complications across the frequency of GPI use and TRA was consistently favored. Therefore, while the mechanism of increased mortality in TFA is thought to be attributable to higher rates of bleeding and access site complications, increased usage of GPI increased the risks of these complications in both groups. There was insufficient data provided to explore the relationship between vascular closure devices usage and access site sheath size usage with all-cause 30-day mortality (Table IV in the Data Supplement). Ongoing use of both pharmacological and technological bleeding avoiding strategies may continue to further mitigate the differences in outcomes between access sites.

With respect to the incidence of stroke, our analysis demonstrated a trend towards increased stroke with TRA which did not meet statistical significant but we would argue has important clinical significance. The vast majority of TRA cases are performed via the right radial artery.[4] When compared with the left radial artery, right radial artery is preferred due to operator comfort, less fluoroscopy time, and limitations of typical catheterization laboratory radiation safety equipment design.[38] However, with right radial artery for TRA there are anatomic variations which may require extensive catheter manipulation and possibly lead to embolization through the right carotid artery. Interestingly, the use of the left radial artery for TRA appears to have lower stroke risk than via the right radial artery purportedly due to these anatomic differences.[39] Overall, the event rate for stroke in both TRA (0.6%) and TFA (0.4%) for patients with STEMI is quite low; however, this remains an important consideration in the debate on access site selection.

Access site remains an important consideration in diagnostic coronary angiography and PCI with several

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international cardiology society guidelines now strongly recommending TRA over TFA in STEMI.[5,6] While this systematic review further supports the use of TRA through a reduction in all-cause mortality at 30 days, major bleeding and vascular complications, it is important to consider the implications of maintaining competency in both access site options. It has been established that experience and procedural volume are the most important factors in reducing radiation exposure from coronary procedures to both patients and operators, irrespective of access site.[40] Additionally, despite potential benefits to a radial first approach to coronary angiography and PCI in STEMI, it is important to recognize that there is a considerable rate of access site crossover in published trials (Table III in the Data Supplement), underscoring the importance of maintaining proficiency in both TRA and TFA, especially in centers using TRA as the default strategy for planned procedures. Last, there is a paucity of reported radial artery occlusion in these trials, potentially biasing comparisons between these 2 groups given that it is the most frequent postprocedure complication of TRA. This is an important complication of TRA as it restricts the use of the same radial artery for future procedures, including repeat angiography and coronary artery bypass grafting.[41]

Our analysis is not without limitations. First, the definitions of the 2 a priori secondary outcomes of interest (ie, major bleeding and vascular access site complications) varied between studies. However, there was low heterogeneity across the included studies with respect to these outcomes, suggesting a true association between access site and major bleeding or vascular access complications. Second, the analysis of the association of GPI usage and mortality was not prespecified and could be subject to confounding. Additionally, the indication for GPI as a routine strategy or as bail-out could not be evaluated in this systematic review which could impact outcomes. Third, patient-level data was not used for this meta-analysis—an analysis that could prove informative as it would allow for more robust statistical adjustments, given that patients with STEMI were not sub-randomized in many studies. Finally, over 75% of patients included in these studies were males, and due to varying eligibility criteria in the included studies (Tables I and III in the Data Supplement), patients who presented cardiogenic shock or required intraaortic balloon pumps were largely excluded, thereby limiting the generalizability of these results to these populations.

CONCLUSIONS

TRA is associated with lower 30-day mortality when compared with TFA in patients with STEMI who undergo PCI. Moreover, a significant reduction in major bleeding and vascular access site complications with TRA is observed without any differences in MI or stroke.

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REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003;361:13–20. doi: 10.1016/S0140-6736(03)12113-7
2. Simard T, Hibbert B, Ramirez FD, Froeschl M, Chen YX, O'Brien ER. The evolution of coronary stents: a brief review. *Can J Cardiol.* 2014;30:35–45. doi: 10.1016/j.cjca.2013.09.012
3. Shroff AR, Fernandez C, Vidovich MI, Rao SV, Cowley M, Bertrand OF, Patel TM, Pancholy SB. Contemporary transradial access practices: results of the second international survey. *Catheter Cardiovasc Interv.* 2019;93:1276–1287. doi: 10.1002/ccd.27989
4. Bertrand OF, Rao SV, Pancholy S, Jolly SS, Rodés-Cabau J, Larose E, Costerousse O, Hamon M, Mann T. Transradial approach for coronary angiography and interventions: results of the first international transradial practice survey. *JACC Cardiovasc Interv.* 2010;3:1022–1031. doi: 10.1016/j.jcin.2010.07.013
5. Wong GC, Welsford M, Ainsworth C, Abuzeid W, Fordyce CB, Greene J, Huynh T, Lambert L, Le May M, Lutchmedial S, et al; Members of the Secondary Panel. 2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Guidelines on the acute management of ST-elevation myocardial infarction: focused update on regionalization and reperfusion. *Can J Cardiol.* 2019;35:107–132. doi: 10.1016/j.cjca.2018.11.031
6. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39:119–177. doi: 10.1093/eurheartj/ehx393
7. Schussler JM, Vasudevan A, von Bose LJ, Won JI, McCullough PA. Comparative efficacy of transradial versus transfemoral approach for coronary angiography and percutaneous coronary intervention. *Am J Cardiol.* 2016;118:482–488. doi: 10.1016/j.amjcard.2016.05.038
8. Ferrante G, Rao SV, Jüni P, Da Costa BR, Reimers B, Condorelli G, Anzuini A, Jolly SS, Bertrand OF, Krucoff MW, et al. Radial versus femoral access for coronary interventions across the entire spectrum of patients with coronary artery disease: a meta-analysis of randomized trials. *JACC Cardiovasc Interv.* 2016;9:1419–1434. doi: 10.1016/j.jcin.2016.04.014
9. Kolkailah AA, Alreshq RS, Muhammed AM, Zahran ME, Anas El-Wegoud M, Nabhan AF. Transradial versus transfemoral approach for diagnostic coronary angiography and percutaneous coronary intervention in people with coronary artery disease. *Cochrane Database Syst Rev.* 2018;4:CD012318. doi: 10.1002/14651858.CD012318.pub2
10. Howe MJ, Seth M, Riba A, Hanzel G, Zainea M, Gurm HS. Underutilization of radial access in patients undergoing percutaneous coronary intervention for ST-segment-elevation myocardial infarction: insights from the blue cross blue shield of michigan cardiovascular consortium. *Circ Cardiovasc Interv.* 2015;8:e002036. doi: 10.1161/CIRCINTERVENTIONS.114.002036

11. Valgimigli M, Gagnor A, Calabró P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Andò G, Repetto A, et al; MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet*. 2015;385:2465–2476. doi: 10.1016/S0140-6736(15)60292-6
12. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, Budaj A, Niemelä M, Valentin V, Lewis BS, et al; RIVAL trial group. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet*. 2011;377:1409–1420. doi: 10.1016/S0140-6736(11)60404-2
13. Le May M, Wells G, So D, Chong AY, Dick A, Froeschl M, Glover C, Hibbert B, Marquis JF, Blondeau M, et al. Safety and efficacy of femoral access vs radial access in ST-segment elevation myocardial infarction: the SAFARI-STEMI Randomized Clinical Trial. *JAMA Cardiol*. 2020;5:126–134. doi: 10.1001/jamacardio.2019.4852
14. Singh S, Singh M, Grewal N, Khosla S. Transradial vs transfemoral percutaneous coronary intervention in ST-segment elevation myocardial infarction: a systemic review and meta-analysis. *Can J Cardiol*. 2016;32:777–790. doi: 10.1016/j.cjca.2015.08.019
15. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1. doi: 10.1186/2046-4053-4-1
16. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.1 (updated September 2020). Cochrane, 2020. www.training.cochrane.org/handbook.
17. Suurmond R, van Rhee H, Hak T. Introduction, comparison, and validation of Meta-Essentials: a free and simple tool for meta-analysis. *Res Synth Methods*. 2017;8:537–553. doi: 10.1002/jrsm.1260
18. Vranckx P, Frigoli E, Rothenbühler M, Tomassini F, Garducci S, Andò G, Picchi A, Sganzerla P, Paggi A, Ugo F, et al; MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes with or without ST-segment elevation. *Eur Heart J*. 2017;38:1069–1080. doi: 10.1093/eurheartj/ehx048
19. Mehta SR, Jolly SS, Cairns J, Niemela K, Rao SV, Cheema AN, Steg PG, Cantor WJ, Džavík V, Budaj A, et al; RIVAL Investigators. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *J Am Coll Cardiol*. 2012;60:2490–2499. doi: 10.1016/j.jacc.2012.07.050
20. Bernat I, Horak D, Stasek J, Mates M, Pesek J, Ostadal P, Hrabos V, Dusek J, Koza J, Sembera Z, et al. ST-segment elevation myocardial infarction treated by radial or femoral approach in a multicenter randomized clinical trial: the STEMI-RADIAL trial. *J Am Coll Cardiol*. 2014;63:964–972. doi: 10.1016/j.jacc.2013.08.1651
21. Brasselet C, Tassan S, Nazeyrollas P, Hamon M, Metz D. Randomised comparison of femoral versus radial approach for percutaneous coronary intervention using abciximab in acute myocardial infarction: results of the FARMI trial. *Heart*. 2007;93:1556–1561. doi: 10.1136/hrt.2007.117309
22. Cantor WJ, Puley G, Natarajan MK, Dzavik V, Madan M, Fry A, Kim HH, Velianou JL, Pirani N, Strauss BH, et al. Radial versus femoral access for emergent percutaneous coronary intervention with adjunct glycoprotein IIb/IIIa inhibition in acute myocardial infarction–the RADIAL-AMI pilot randomized trial. *Am Heart J*. 2005;150:543–549. doi: 10.1016/j.ahj.2004.10.043
23. Gan L, Lib Q, Liuc R, Zhaoc Y, Qiuc J, Liao Y. Effectiveness and feasibility of transradial approaches for primary percutaneous coronary intervention in patients with acute myocardial infarction. *J Nanjing Med Univ*. 2009;23:270–274.
24. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, Summaria F, Patrizi R, Borghi A, Di Russo C, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol*. 2012;60:2481–2489. doi: 10.1016/j.jacc.2012.06.017
25. Vazquez-Rodriguez J. *Comparacion del acceso radial frente al acceso femoral en la revascularizacion precutánea durante la fase aguda del infarto agudo de miocardio con elevacion del segment ST [Comparison of Radial Access from Access Femoral in Precutaneous Revascularization During the Acute Phase of Acute Myocardial Infarction ST Segment Elevation]*. Coruña, Spain: Universidade da Coruña; 2009.
26. Hou L, Wei YD, Li WM, Xu YW. Comparative study on transradial versus transfemoral approach for primary percutaneous coronary intervention in Chinese patients with acute myocardial infarction. *Saudi Med J*. 2010;31:158–162.
27. Kołtowski L, Filipiak KJ, Kochman J, Pietrasik A, Rdzanek A, Huczek Z, Scibisz A, Mazurek T, Opolski G. Access for percutaneous coronary intervention in ST segment elevation myocardial infarction: radial vs. femoral–a prospective, randomised clinical trial (OCEAN RACE). *Kardiol Pol*. 2014;72:604–611. doi: 10.5603/KP.a2014.0071
28. Li WM, Li Y, Zhao JY, Duan YN, Sheng L, Yang BF, Wang FL, Gong YT, Yang SS, Zhou LJ, et al. Safety and feasibility of emergent percutaneous coronary intervention with the transradial access in patients with acute myocardial infarction. *Chin Med J (Engl)*. 2007;120:598–600.
29. Saito S, Tanaka S, Hiroe Y, Miyashita Y, Takahashi S, Tanaka K, Satake S. Comparative study on transradial approach vs. transfemoral approach in primary stent implantation for patients with acute myocardial infarction: results of the test for myocardial infarction by prospective unicenter randomization for access sites (TEMPURA) trial. *Catheter Cardiovasc Interv*. 2003;59:26–33. doi: 10.1002/ccd.10493
30. Wang YB, Fu XH, Wang XC, Gu XS, Zhao YJ, Hao GZ, Jiang YF, Li SQ, Wu WL, Fan WZ. Randomized comparison of radial versus femoral approach for patients with STEMI undergoing early PCI following intravenous thrombolysis. *J Invasive Cardiol*. 2012;24:412–416.
31. TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial. Phase I findings. *N Engl J Med*. 1985;312:932–936. doi: 10.1056/NEJM198504043121437
32. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, et al; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358:2218–2230. doi: 10.1056/NEJMoa0708191
33. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, et al; REPLACE-2 Investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA*. 2003;289:853–863. doi: 10.1001/jama.289.7.853
34. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449
35. Joyal D, Bertrand OF, Rinfret S, Shimony A, Eisenberg MJ. Meta-analysis of ten trials on the effectiveness of the radial versus the femoral approach in primary percutaneous coronary intervention. *Am J Cardiol*. 2012;109:813–818. doi: 10.1016/j.amjcard.2011.11.007
36. Vorobcsuk A, Kónyi A, Aradi D, Horváth IG, Ungi I, Louvard Y, Komócsi A. Transradial versus transfemoral percutaneous coronary intervention in acute myocardial infarction Systematic overview and meta-analysis. *Am Heart J*. 2009;158:814–821. doi: 10.1016/j.ahj.2009.08.022
37. Mamas MA, Ratib K, Routledge H, Fath-Ordoubadi F, Neyses L, Louvard Y, Fraser DG, Nolan J. Influence of access site selection on PCI-related adverse events in patients with STEMI: meta-analysis of randomised controlled trials. *Heart*. 2012;98:303–311. doi: 10.1136/heartjnl-2011-300558
38. Kado H, Patel AM, Suryadevara S, Zenni MM, Box LC, Angiolillo DJ, Bass TA, Guzman LA. Operator radiation exposure and physical discomfort during a right versus left radial approach for coronary interventions: a randomized evaluation. *JACC Cardiovasc Interv*. 2014;7:810–816. doi: 10.1016/j.jcin.2013.11.026
39. Rashid M, Lawson C, Potts J, Kontopantelis E, Kwok CS, Bertrand OF, Shoaib A, Ludman P, Kinnaird T, de Belder M, et al. Incidence, determinants, and outcomes of left and right radial access use in patients undergoing percutaneous coronary intervention in the United Kingdom: a national perspective using the BCIS dataset. *JACC Cardiovasc Interv*. 2018;11:1021–1033. doi: 10.1016/j.jcin.2018.01.252
40. Jolly SS, Cairns J, Niemela K, Steg PG, Natarajan MK, Cheema AN, Rao SV, Cantor WJ, Džavík V, Budaj A, et al; RIVAL Investigators. Effect of radial versus femoral access on radiation dose and the importance of procedural volume: a substudy of the multicenter randomized RIVAL trial. *JACC Cardiovasc Interv*. 2013;6:258–266. doi: 10.1016/j.jcin.2012.10.016
41. Bernat I, Aminian A, Pancholy S, Mamas M, Gaudino M, Nolan J, Gilchrist IC, Saito S, Hahalis GN, Ziakas A, et al; RAO International Group. Best practices for the prevention of radial artery occlusion after transradial diagnostic angiography and intervention: an international consensus paper. *JACC Cardiovasc Interv*. 2019;12:2235–2246. doi: 10.1016/j.jcin.2019.07.043

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Appendix B – PDF of published manuscript – catheter-induced coronary artery dissection

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Original Research

Association Between the Access Site for Coronary Angiography and Catheter-induced Coronary Artery Dissection

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ABSTRACT

Background: Catheter-induced coronary artery dissection (CICAD) is a rare complication of coronary angiography. The association between access site and CICAD remains unclear; however, transradial access (TRA) may be associated with a higher incidence of CICAD due to access vessel tortuosity and the mechanical disadvantage of catheters designed for the transfemoral access (TFA) approach.

Methods: In this retrospective study, the reports of consecutive left heart catheterizations between April 2007, and December 2021 were reviewed for CICAD. Patients were excluded if the procedural report did not report an arterial access site. Identified CICAD cases were reviewed in detail.

Results: There were 142/89,876 (0.16%) identified cases of CICAD. The access site was not associated with an increased risk of CICAD (0.18% with TRA vs 0.15% with TFA; relative risk [RR], 1.18; 95% CI, 0.84-1.65; $P = .34$) over the entire study period. With respect to TRA-related CICAD, male sex was associated with a decreased risk of dissection (RR, 0.64; 95% CI, 0.41-0.99; $P = .04$), but ST-elevation myocardial infarction at presentation was associated with an increased risk (RR, 3.01; 95% CI, 1.86-4.85; $P < .01$). In the TFA-predominant era, TRA was associated with an increased risk of CICAD (0.48% TRA vs 0.11% TFA; RR, 3.42; 95% CI, 2.05-5.69; $P < .01$)—an association that was not present in the TRA-predominant era. In-hospital mortality in patients with CICAD was 8.5%.

Conclusions: CICAD is a rare complication of coronary angiography. Over a 15-year period, we did not demonstrate an association between access site and an increased risk of CICAD. There is substantial mortality associated with CICAD.

Introduction

Transradial access (TRA) has emerged over transfemoral access (TFA) as the preferred approach for coronary angiography. The advantages of TRA include lower access site complications, earlier patient ambulation, and improved patient comfort.[1] Several randomized control trials and meta-analyses comparing TRA to TFA in acute coronary syndrome have shown lower bleeding complications and reduced mortality favoring TRA.[2–6]

Although there are numerous advantages to TRA, there are disadvantages associated with this access site that must be considered. Patient factors include difficulty obtaining radial artery access, radial artery

Abbreviations: CABG, coronary artery bypass graft; CICAD, catheter-induced coronary artery dissection; NHLBI, National Heart, Lung, and Blood Institute; PCI, percutaneous coronary intervention; TFA, transfemoral access; TRA, transradial access.

Keywords: catheter-induced coronary artery dissection; coronary angiography; percutaneous coronary intervention; transfemoral approach; transradial approach.

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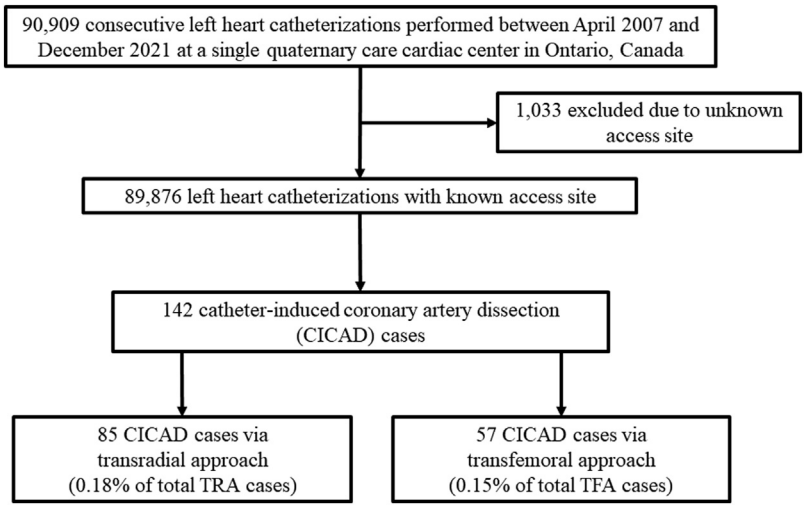


Figure 1.
Flow diagram of study patients.
CICAD, catheter-induced coronary artery dissection; TFA, transfemoral access; TRA, transradial access.

spasm, and difficulty with navigating tortuous upper extremity arterial anatomy. The catheters used for coronary angiography and percutaneous coronary angiography (PCI) were designed for use with TFA, contributing to increased difficulty with catheter manipulation and coronary intubation when utilized from a radial approach. Initial concerns about increased procedural failure, contrast use, and radiation exposure have been mitigated by studies showing that these parameters improve with operator experience.[7,8]

Catheter-induced coronary artery dissection (CICAD) is a rare complication of coronary angiography and PCI. The incidence of left main involvement was estimated between 0.03% and 0.07% in a large case series,[9–11] whereas the incidence of right coronary artery CICAD is estimated at 0.14%.[12] In a large contemporary series, the incidence of CICAD was 0.09% and most common with guide catheters.[13] Anecdotally, TRA is accompanied by an increased risk of CICAD, theoretically due to access vessel tortuosity and the mechanical disadvantage of catheters designed for TFA.

In the retrospective study herein, we aim to compare the risk of CICAD in TRA versus TFA, as well as describe the risk factors, management, and clinical outcomes of CICAD at a large academic cardiac care center.

Methods

Reports of consecutive cardiac catheterization procedures at a large quaternary care cardiac center between April 2007 and December 2021 were obtained. Patients could be included more than once if they had repeated catheterizations performed during the study period. Patients were excluded if the procedural report did not report an arterial access site. Reports with identified dissection were reviewed for the mechanism of dissection (eg, catheter-induced, spontaneous coronary artery dissection, postintervention stent edge dissection, etc.). Procedures involving transbrachial access were treated as TRA for the purpose of analysis. The study complied with the Declaration of Helsinki and was approved by the Ottawa Health Sciences Network Research Ethics Board. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

A "catheter-induced coronary artery dissection" was defined as an unplanned dissection of the left main, right coronary artery, left internal thoracic artery, right internal thoracic artery, or aortic dissection/hematoma for which the catheter was identified as the cause by the operator's procedural report. In cases where both TRA and TFA were reported as being accessed, CICAD cases were further reviewed to identify the arterial access resulting in the dissection. Procedural details, including equipment information such as catheter type, size, and shape, were obtained from the procedure log. Other key data, including age, height, weight, sex, procedure date, cardiovascular risk factors, operators, and presence of ST-elevation myocardial infarction were also collected from the catheterization reports and chart review.

All CICAD cases were further reviewed by 2 interventional cardiologists (P.D.S. and O.A.R.), and the coronary artery dissections were classified as types A to F based on the National Heart, Lung, and Blood Institute (NHLBI) system developed from the Coronary Angioplasty Registry.[14] The type of dissection was based on the angiographic appearances of the intimal disruption and contrast clearance:

1. Type A dissections represent radiolucent areas within the coronary lumen during contrast injection, with minimal or no persistence of contrast.
2. Type B dissections are parallel tracts or double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence.
3. Type C dissections appear as contrast outside the coronary lumen with persistence of contrast in the area after clearance of contrast from the coronary lumen.
4. Type D dissections represent spiral luminal filling defects, frequently with extensive contrast staining of the vessel.
5. Type E dissections appear as new, persistent filling defects.
6. Type F dissections represent those that lead to total occlusion of the coronary artery, without anterograde flow.

In cases where the angiographic images were not available for review, the detailed angiographic report was reviewed by 2 interventional cardiologists (P.D.S. and P.B.) to adjudicate if the dissection was felt to represent a catheter-induced dissection rather than by guide wires, intravascular imaging catheters, and/or postintervention complications (eg, postballoon dissection, distal stent edge dissection, etc.).

The primary outcome of this study was the incidence of CICAD by TRA vs TFA access sites. Secondary outcomes included evaluating risk factors for CICAD by access site. We also describe the management and clinical outcomes of patients with CICAD.

Outcomes were assessed using unadjusted χ^2 analyses to compare the CICAD and non-CICAD groups, and corresponding relative risks

(RRs) were generated along with 95% CIs. A sensitivity analysis was performed to evaluate the association between CICAD and access site stratified according to the most frequent access site utilized at our institution in a given year—a predominant TFA era (ie, prior to 2012) and a predominant TRA era (ie, 2012-2021; "radial first"). All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

Results

A total of 90,909 consecutive cardiac catheterizations were performed between April 2007 and December 2021. There were 1033 catheterizations without information on arterial access, which were excluded (Figure 1). The baseline characteristics of the entire study cohort as well as cases with and without CICAD are presented in Table 1. The mean age of the study patients was 66.1 ± 12.1 years, and most patients were males (68.2% across the entire study). Traditional cardiovascular risk factors were similar between the CICAD and non-CICAD groups.

A total of 142 cases were found to have CICAD (Table 2). The access site was not associated with an increased risk of CICAD (0.18% of all TRA cases vs 0.15% of all TFA cases; RR, 1.18; 95% CI, 0.84-1.65; $P = .34$). Of note, there was no difference in CICAD between right and left radial artery TRA procedures ($P = .52$). NHLBI classification was available for 54 cases of CICAD with type B and F dissections representing two-thirds of dissection cases (Supplemental Table 1). Age was not associated with TRA-related CICAD ($P = .86$) or TFA-related CICAD ($P = .30$). With respect to TRA-related CICAD, male sex was associated with a decreased risk of dissection (RR, 0.64; 95% CI, 0.41-0.99; $P = .04$), but not with TFA ($P = .84$). ST-elevation myocardial infarction was associated with an increased risk of dissection in TRA (RR, 3.01; 95% CI, 1.86-4.85; $P < .01$) but not with TFA (RR, 1.46; 95% CI, 0.72-2.97; $P = .30$). The right coronary artery was the most affected artery in both the TRA-related CICAD (54.1%) and TFA-related CICAD (43.9%). Guide catheters and 6F catheters were used in approximately 80% of CICAD cases across both access site groups. There were 947 procedures during which a catheter greater than 6F was used, corresponding to 1.1% of the total number of catheterizations. As reported in Table 2, there were 5 cases of CICAD in these patients with greater than 6F catheters used—an incidence of 0.53% in this group with larger catheters than 0.16% in the overall cohort.

Table 1. Baseline demographic characteristics of overall cohort as well as patients with and without catheter-induced coronary artery dissection.

	Left heart catheterization (N = 89,876)	CICAD (n = 142)	Non-CICAD (n = 89,734)
Age, y	66.1 ± 12.1	65.5 ± 12.9	65.9 ± 12.1
Male sex	60,956 (68.2%)	89 (63.1%)	60,867 (68.2%)
Height, m	1.70 ± 0.10	1.69 ± 0.11	1.70 ± 0.10
Weight, kg	83.8 ± 19.8	81.8 ± 17.9	83.4 ± 19.8
Medical history			
Hypertension	30,005 (33.4%)	43 (30.3%)	29,962 (33.4%)
Dyslipidemia	25,440 (28.3%)	30 (21.1%)	25,410 (28.3%)
Diabetes	23,047 (25.6%)	46 (32.4%)	23,001 (25.6%)
Active smoking	15,556 (17.3%)	24 (16.9%)	15,532 (17.3%)
Family history of premature CAD	4428 (4.9%)	3 (2.1%)	4425 (4.9%)
Procedural details			
STEMI at presentation	10,071 (11.2%)	32 (22.5%)	10,039 (11.2%)
Transradial access	47,826 (53.2%)	85 (59.9%)	47,741 (53.2%)
Transfemoral access	37,778 (42.0%)	57 (40.1%)	37,721 (42.0%)
Multiple access sites during procedure	4272 (4.8%)	30 (21.1%)	4272 (4.8%)
PCI during procedure	38,985 (43.4%)	115 (81.0%)	38,870 (43.3%)

Values are mean ± SD or n (%).
CAD, coronary artery disease; CICAD, catheter-induced coronary artery dissection; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

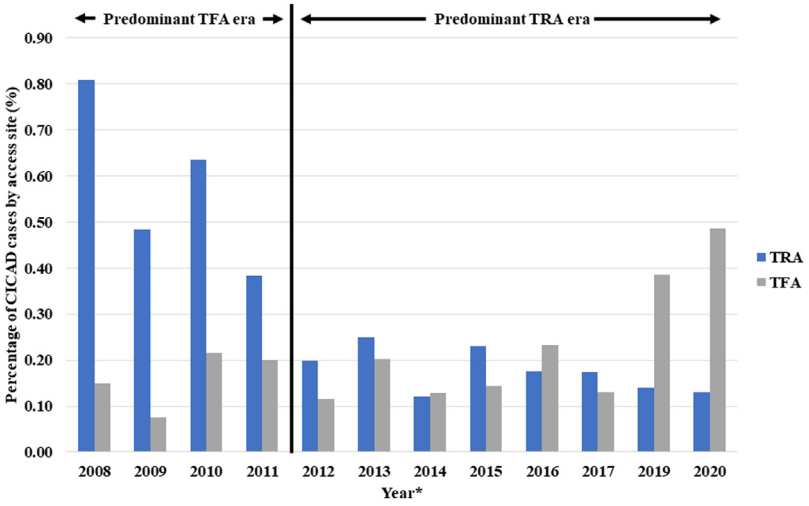
Table 2. Catheter-induced coronary artery dissection procedural details by access site.

	Total CICAD (N = 142)	Transradial access (n = 85)	Transfemoral access (n = 57)
Procedural characteristics			
STEMI at presentation	35 (24.6%)	23 (27.1%)	9 (15.8%)
Coronary artery involved in CICAD			
Left coronary artery dissection	52 (36.6%)	32 (37.7%)	20 (35.1%)
Right coronary artery dissection	71 (50%)	46 (54.1%)	25 (43.9%)
Isolated aortic dissection	10 (7.0%)	6 (7.1%)	4 (7.1%)
Left internal thoracic artery dissection	6 (4.2%)	1 (1.2%)	5 (8.8%)
Right internal thoracic artery dissection	3 (2.1%)	0 (0.0%)	3 (5.3%)
Catheter type			
Diagnostic	31 (21.8%)	15 (17.6%)	16 (28.1%)
Guide	110 (77.5%)	69 (81.2%)	41 (71.9%)
Unknown	1 (0.7%)	1 (1.2%)	0 (0.0%)
Catheter design			
Amplatz left	23 (16.2%)	11 (12.9%)	12 (21.1%)
Extra back-up	35 (24.6%)	22 (25.9%)	13 (22.8%)
Hockey stick	3 (2.1%)	0 (0.0%)	3 (5.3%)
Judkins left	15 (10.6%)	11 (12.9%)	4 (7.0%)
Judkins right	44 (31.0%)	27 (31.8%)	17 (29.8%)
Multiaortic curves	3 (2.1%)	3 (3.5%)	0 (0.0%)
Multipurpose	2 (1.4%)	1 (1.2%)	1 (1.8%)
Radial curve	1 (0.7%)	1 (1.2%)	0 (0.0%)
Special curve	7 (4.9%)	7 (8.2%)	0 (0.0%)
Internal mammary	7 (4.9%)	0 (0.0%)	7 (12.3%)
Ikari left	1 (0.7%)	1 (1.2%)	0 (0.0%)
Unknown	1 (0.7%)	1 (1.2%)	0 (0.0%)
Catheter size			
5F	13 (9.2%)	11 (12.9%)	2 (3.5%)
6F	123 (86.6%)	72 (84.7%)	51 (89.5%)
>6F	5 (3.5%)	1 (1.2%)	4 (7.0%)
Unknown	1 (0.7%)	1 (1.2%)	0 (0.0%)

Values are n (%).
CICAD, catheter-induced coronary artery dissection; STEMI, ST-elevation myocardial infarction.

In terms of absolute numbers, the extra back-up (15.0% usage in the overall cohort) and Judkins right (39.9% usage in overall cohort) were the 2 most common catheter designs associated with CICAD and comprised more than 50% of CICAD cases, followed by the Amplatz left (4.7% usage in overall cohort) and Judkins left (38.1% usage in overall cohort) (Table 2). The rate of CICAD per 10,000 uses of the most commonly utilized catheters was the greatest with the Amplatz left (126.1 cases of CICAD per 10,000 uses) followed by the extra back-up (21.0 cases of CICAD per 10,000 uses), Judkins left (9.9 cases of CICAD per 10,000 uses), and Judkins right (3.6 cases of CICAD per 10,000 uses).

In a sensitivity analysis, the association between access site and CICAD was evaluated from 2007-2011 (ie, TFA-predominant era) and 2012-2021 (ie, TRA-predominant era) (Central Illustration, Supplemental Table 2). In the TFA-predominant era, there were a total of 59 cases of CICAD, and TRA was associated with an increased risk of dissection (0.48% TRA vs 0.11% TFA; RR, 3.42; 95% CI, 2.05-5.69; $P < .01$). In the TRA-predominant era, there were 83 cases of CICAD, with 0.13% in the TRA group and 0.16% in the TFA group, and the association between access site and CICAD was no longer present ($P = .40$).



Central Illustration.
Percentage of catheter-induced coronary artery dissection cases over study period stratified by access site. In the TFA-predominant era, TRA was associated with an increased risk of dissection (0.48% TRA vs 0.11% TFA; RR 3.42, 95% CI 2.05-5.69, $P < .01$). In the TRA-predominant era, the association between access site and CICAD was no longer present ($P = .40$). *Only years in which there were more than 5 CICAD cases have been included in the figure
CICAD, catheter-induced coronary artery dissection; TFA, transfemoral access; TRA, transradial access.

The management of CICAD involved bailout stenting in 99 (69.7%) cases and emergency coronary artery bypass graft (CABG) surgery in 18 (12.7%) cases (Table 3). There were 21 patients (14.8%) in whom the CICAD was felt to be self-limited and improved during intraprocedural observation—notably, the majority of these were isolated aortic injury (n = 12). Two patients required emergent mechanical circulatory support with veno-arterial extracorporeal membrane oxygenation prior to revascularization. Two patients (1.4%) experienced immediate death at the time of CICAD with inability to achieve revascularization. Of the 18 patients who were referred to CABG, 3 (17%) died during the surgery. In total, 12 patients (8.5%) with CICAD died in the hospital (Supplemental Table 3). Of these 12 patients who died in the hospital, 7 (58%) had retrograde extension of the CICAD into the aorta noted during the index procedure.

Discussion

We report a series of 142 CICADs at our institution over a 15-year period. To the best of our knowledge, this represents the largest reported series of CICAD in the literature to date and the first to evaluate the incidence by vascular access site. CICAD remains a very rare complication of coronary angiography, with an incidence of 16 cases per 10,000 procedures in our series, similar to the incident rates previously reported in the literature.[9–13]

Table 3. Outcomes of patients with CICAD.

	Total CICAD (N = 142)
Management of CICAD	
Medical therapy	21 (14.8%)
Bailout stenting	99 (69.7%)
Coronary artery bypass graft surgery	18 (12.7%)
Extracorporeal membrane oxygenation prior to revascularization	2 (1.4%)
None–death prior to revascularization established	2 (1.4%)
Clinical outcomes	
Death during index procedure	2 (1.4%)
Death during coronary artery bypass graft surgery	3 (2.1%)
Death in-hospital	12 (8.5%)

Values are n (%).
CICAD, catheter-induced coronary artery dissection.

The TRA approach has a significant learning curve due to various factors including catheter manipulation, which is impeded by radial vasospasm, tortuous subclavian anatomy, and the use of catheters designed for TFA.[7] Anecdotally, it has been felt that these factors increased the probability of suboptimal catheter engagement in noncoaxial or deep-seated positions, predisposing to CICAD. Similarly, torque introduced by catheter manipulation can transfer significant potential energy to the interface between the catheter and coronary wall. Despite these theoretical possibilities, we did not demonstrate an association between access site and CICAD over a 15-year period. However, when stratified by "predominant femoral access" between the years 2007-2011, we found that the risk of CICAD with TRA was nearly 3.5 times greater than with femoral access; however, this association was no longer present once our center had transitioned to "predominant radial access" (ie, 2012 and onwards). Similar to the initial concerns about increased procedural failure, contrast use, and radiation exposure, which have been refuted by studies showing that these parameters improve with operator experience,[7,8] perhaps the risk of CICAD with radial access is also reduced as we progress along the learning curve of this approach. Of note, female sex was associated with an increased risk of CICAD in patients who underwent TRA. It has been hypothesized that hormonal imbalances may directly impact the coronary endothelium due to the presence of estrogen and progesterone receptors. This may result in decreased collagen production and ultimately weaken the arterial wall, culminating in increased susceptibility to dissection.[13,15,16] Although this may increase the risk of dissection among females in general, we suspect that the reason this association was observed only in the TRA group is likely spurious.

The most common catheter designs associated with CICAD were the extra back-up and Judkins right. The Amplatz left catheter has been postulated to cause a disproportionate number of iatrogenic dissections.[17] Our series corroborates this finding, with the Amplatz left design implicated in 16.2% of CICAD cases, although it was used in only 4.7% of all procedures. The special curve design was the CICAD culprit in 4.9% of cases, although it was used only in 0.3% of procedures (206 cases of CICAD per 10,000 uses of the catheter), suggesting it is a particularly risky catheter. Although the extra back-up was responsible for nearly a quarter of all CICAD, this likely represents its widespread use at our institution (15.0% of procedures). Similarly, while the Judkins catheters are responsible for a combined

42% of CICAD, they are used in nearly 80% of cases at our institution, suggesting they have a lower risk of CICAD. However, the Judkins catheters have both diagnostic and guide designs, which we were unable to differentiate in the "overall" group data, and the lower frequency of CICAD might simply be reflective of a lower risk with diagnostic catheters. Similarly, aggressive catheters such as the Amplatz left are used more frequently in complex diseases where more support is required, which may also increase the risk of CICAD.

Catheter-induced coronary artery dissection is a feared complication because of the perceived high morbidity and mortality.[11] Conservative management, bailout stenting, and emergency CABG have all been described as CICAD treatment strategies.[9–12,18–20] In our series, the treatment strategy of choice was bailout stenting (69.7%) followed by conservative management (14.8%). The use of emergency CABG was less common (12.7%). CICAD was associated with 8.5% in-hospital mortality, which is slightly greater than previously reported.[11,13] The reason for the discrepancy is unclear and may reflect differences in practice or reporting patterns at our institutions. In addition, of the 12 patients who died in the hospital, 7 (58%) had retrograde extension of the CICAD into the aorta noted during their procedure. Clinicians should maintain a high index of suspicion of aortic involvement with CICAD and have a low threshold to pursue imaging of the ascending aorta as this may be a potentially modifiable target for intervention following CICAD. Based on our data, the mortality of CICAD is substantial, and every step should be taken to mitigate the risk of this feared complication.

Our study is not without limitation. First, we relied on catheterization reports to identify cases of reported CICAD, which are likely underreported, and therefore, our work likely represents an underestimate of the incidence of this complication. Second, angiographic images were only available from 2014, thereby limiting our ability to grade the CICAD events according to the NHLBI system to ~40% of CICAD cases.[21] Similarly, we were unable to provide insight into the factors described by other authors that may contribute to the risk of dissection, including ascending aorta configuration, aberrant anatomy of the coronary ostium, presence of proximal atherosclerosis or plaque rupture or noncoaxial catheter engagement.[19,22,23] Importantly, there were few universal catheters that permit both left and right coronary artery angiography used during the study period and therefore, this study does not exclude the possibility of higher CICAD with TRA with these catheters. Finally, this retrospective, observational study is hypothesis generating, and conclusions are limited by unforeseen bias and variables left unaccounted for.

Conclusions

CICAD is a rare complication of coronary angiography and PCI. Over a 15-year period, we did not demonstrate an association between access site and the incidence of CICAD. There is considerable mortality associated with CICAD, and bailout stenting is the most common treatment, when possible. All operators must remain vigilant and mitigate the risk of CICAD whenever possible.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement and patient consent

The study complied with the Declaration of Helsinki and was approved by the Ottawa Health Sciences Network Research Ethics Board. Patient consent was not required for this study.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2023.100606.

References

1. Rao SV, Turi ZG, Wong SC, Brener SJ, Stone GW. Radial versus femoral access. *J Am Coll Cardiol*. 2013;62:S11–S20 (17)(suppl).
2. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol*. 2012;60(24):2481–2489.
3. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet*. 2011;377(9775):1409–1420.
4. Bernat I, Horak D, Stasek J, et al. ST-segment elevation myocardial infarction treated by radial or femoral approach in a multicenter randomized clinical trial: the STEMI-RADIAL trial. *J Am Coll Cardiol*. 2014;63(10):964–972.
5. Valgimigli M, Gagnor A, Calabró P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet*. 2015;385(9986):2465–2476.
6. Di Santo P, Simard T, Wells GA, et al. Transradial versus transfemoral access for percutaneous coronary intervention in ST-segment-elevation myocardial infarction: a systematic review and meta-analysis. *Circ Cardiovasc Interv*. 2021;14(3):e009994.
7. Simard T, Hibbert B, Natarajan MK, et al. Impact of center experience on patient radiation exposure during transradial coronary angiography and percutaneous intervention: a patient-level, international, collaborative, multi-center analysis. *J Am Heart Assoc*. 2016;5(6), e003333.
8. Hess CN, Peterson ED, Neely ML, et al. The learning curve for transradial percutaneous coronary intervention among operators in the United States: a study from the National Cardiovascular Data Registry. *Circulation*. 2014;129(22):2277–2286.
9. Cheng CI, Wu CJ, Hsieh YK, et al. Percutaneous coronary intervention for iatrogenic left main coronary artery dissection. *Int J Cardiol*. 2008;126(2):177–182.
10. Lee SW, Hong MK, Kim YH, et al. Bail-out stenting for left main coronary artery dissection during catheter-based procedure: acute and long-term results. *Clin Cardiol*. 2004;27(7):393–395.
11. Eshtehardi P, Adorjan P, Togni M, et al. Iatrogenic left main coronary artery dissection: incidence, classification, management, and long-term follow-up. *Am Heart J*. 2010;159(6):1147–1153.
12. Chai HT, Yang CH, Wu CJ, et al. Utilization of a double-wire technique to treat long extended spiral dissection of the right coronary artery. Evaluation of incidence and mechanisms. *Int Heart J*. 2005;46(1):35–44.
13. Ramasamy A, Bajaj R, Jones DA, et al. Iatrogenic catheter-induced ostial coronary artery dissections: prevalence, management, and mortality from a cohort of 55,968 patients over 10 years. *Catheter Cardiovasc Interv*. 2021;98(4):649–655.
14. Huber MS, Mooney JF, Madison J, Mooney MR. Use of a morphologic classification to predict clinical outcome after dissection from coronary angioplasty. *Am J Cardiol*. 1991;68(5):467–471.
15. Vijayaraghavan R, Verma S, Gupta N, Saw J. Pregnancy-related spontaneous coronary artery dissection. *Circulation*. 2014;130(21):1915–1920.
16. Tweet MS, Hayes SN, Codsi E, Gulati R, Rose CH, Best PJM. Spontaneous coronary artery dissection associated with pregnancy. *J Am Coll Cardiol*. 2017;70(4):426–435.
17. Dunning DW, Kahn JK, Hawkins ET, O'Neill WW. Iatrogenic coronary artery dissections extending into and involving the aortic root. *Catheter Cardiovasc Interv*. 2000;51(4):387–393.
18. Connors JP, Thanavaro S, Shaw RC, Sandza JG, Ludbrook PA, Krone RJ. Urgent myocardial revascularization for dissection of the left main coronary artery: a complication of coronary angiography. *J Thorac Cardiovasc Surg*. 1982;84(3):349–352.
19. Boyle AJ, Chan M, Dib J, Resar J. Catheter-induced coronary artery dissection: risk factors, prevention and management. *J Invasive Cardiol*. 2006;18(10):500–503.
20. Awadalla H, Sabet S, El Sebaie A, Rosales O, Smalling R. Catheter-induced left main dissection incidence, predisposition and therapeutic strategies experience from two sides of the hemisphere. *J Invasive Cardiol*. 2005;17(4):233–236.
21. Rogers JH, Lasala JM. Coronary artery dissection and perforation complicating percutaneous coronary intervention. *J Invasive Cardiol*. 2004;16(9):493–499.
22. Ammann P, Brunner-La Rocca HP, Angehrn W, Roelli H, Sagmeister M, Rickli H. Procedural complications following diagnostic coronary angiography are related to the operator's experience and the catheter size. *Catheter Cardiovasc Interv*. 2003;59(1):13–18.
23. Namazi MH, Rostami RT, Mohammadi A, et al. Iatrogenic left main artery dissection: a catastrophic complication. *Exp Clin Cardiol*. 2012;17(4):254–256.

Appendix C – PDF of published manuscript – ULTRASITCOM study

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Original Research

Point-of-Care Ultrasound for the Detection of Vascular Access Site Complications—The ULTRASITCOM Study

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ABSTRACT

Background: Recent technological advancements have expanded access to ultrasound technology. Invasive cardiac procedures come with risks of vascular access complications, necessitating efficient detection methods for dangerous complications such as pseudoaneurysms. Current clinical practice has relied on physical examination, and often requires formal diagnostic imaging to diagnose these complications. The ULTRAsound Assessment of Access SITe COMplications study assessed the diagnostic accuracy of point-of-care ultrasound (POCUS) as an adjunct to physical examination for the detection of pseudoaneurysms following invasive cardiac procedures.

Methods: We conducted a single-center study that enrolled patients who underwent invasive cardiovascular procedures with suspected access site complications. Cardiology fellows were trained on the use of POCUS by a radiologist with expertise in vascular imaging. The primary outcome focused on the diagnostic odds ratio (DOR) of combined clinical and POCUS assessments compared to Doppler ultrasound or computed tomography.

Results: Among 111 participants, most were female (59.5%), with a mean age of 72.2 years, and with transfemoral access being most prevalent (67.6%). A total of 15 participants were found to have a pseudoaneurysm on formal diagnostic imaging. The combined clinical and POCUS assessments were highly sensitive and demonstrated superior DOR for detecting pseudoaneurysms compared to the physical examination alone (DOR 42.6 [95% CI, 34.6-50.6] vs 15.6 [95% CI, 11.7-19.5]; $P < .01$).

Conclusions: Point-of-care ultrasound is a highly sensitive tool for detecting pseudoaneurysms following invasive cardiovascular procedures. These findings suggest the potential integration of POCUS into routine practice, which could result in timely complication identification and management, thereby improving patient outcomes and reducing health care costs.

Introduction

Ultrasound is a versatile tool used for diagnosing patients across diverse clinical environments. Its widespread use has been attributed to its notable diagnostic sensitivity, absence of ionizing radiation, minimal invasiveness, and cost-effectiveness.[1] Recent technological progress has led to the miniaturization of ultrasound components, substantial enhancements in battery longevity, and the creation of compact,

Abbreviations: DOR, diagnostic odds ratio; POCUS, point-of-care ultrasound.

Keywords: cardiac catheterization; diagnostic accuracy; point-of-care ultrasound; pseudoaneurysm; vascular access complications.

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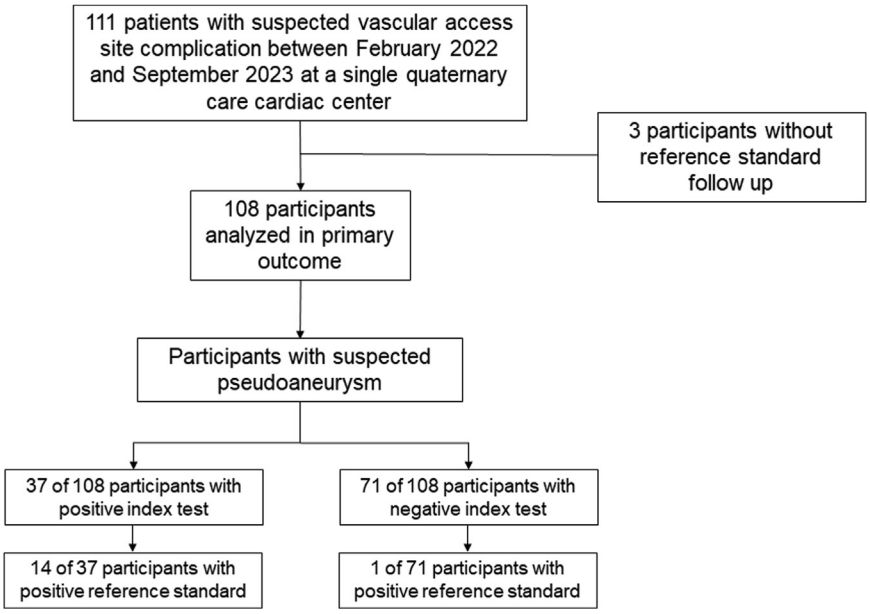


Figure 1.
Study flow. Flow of participants through the ULTRAsound Assessment of Access SITe COMplications study.

high-resolution displays. These advancements have converged to give rise to handheld devices, and when coupled with declining costs, have broadened the accessibility of ultrasonography beyond the boundaries of formal diagnostic imaging departments.[2]

Diagnostic and interventional procedures encompassing coronary, electrophysiological, and valvular interventions are central to the contemporary management of cardiovascular disease. Although radial artery access is associated with improved outcomes and a reduction in complications in patients undergoing percutaneous coronary intervention,[3,4] femoral access remains widely utilized, especially for procedures necessitating large-bore sheaths. Although infrequent, these procedures may result in vascular access site complications, primarily pseudoaneurysms, hematomas, arteriovenous (AV) fistulas, dissections, and local stenoses or occlusions related to vascular closure devices. These access site complications have in turn been associated with an extended hospital length of stay, increased patient morbidity and mortality, and increased costs.[5,6] Of particular concern, a pseudoaneurysm is a contained rupture of an artery that involves disruption in all 3 layers of the arterial wall and is usually a consequence of an arterial puncture that does not adequately seal.[7] This allows pulsatile blood to track into the perivascular space and a hematoma with surrounding tissue forms the wall of the pseudoaneurysm. The incidence of this complication is reported to be 2% to 6% following percutaneous coronary intervention.[7] Although some pseudoaneurysms may thrombose spontaneously, this complication could be life-threatening should the pseudoaneurysm rupture. For many transcatheter procedures, vascular access complications remain the most common complication for affiliated procedures.

Postprocedure evaluation of access site complications is reliant on physical examination and secondarily on formal diagnostic studies in cases in which complications are suspected. The poor diagnostic accuracy of physical examination has been long recognized and has increased physician reliance on formal diagnostic investigations.[8,9] Routine use of point-of-care ultrasound (POCUS) at the bedside has become an established standard of care in other aspects of cardiovascular medicine. As a result of a growing body of literature suggesting possible advantages of ultrasonographic assessment as an adjunct to physical examination, we sought to evaluate the ability of POCUS to detect vascular access site complications following invasive cardiac procedures.

Methods

Study design

The ULTRAsound Assessment of Access SITe COMplications (ULTRASITCOM) study is a prospective diagnostic accuracy study conducted at a single quaternary care cardiac center in Ottawa, Canada. Participants were recruited over an 18-month period from February 2022 until September 2023.

Ethical statement

The study was approved by the Ottawa Health Science Network Research Ethics Board and the study was conducted in accordance with the Helsinki Declaration. All study participants provided written informed consent.

Patient population

Patients who underwent invasive cardiac procedures that required radial, brachial, or femoral arterial and/or femoral venous access and in whom there was a clinical suspicion of an access site complication were considered eligible for the study. In patients with isolated venous access (eg, transcatheter edge-to-edge repair), patients could be included if there was a clinical concern regarding potential arterial injury—venous complications were not specifically addressed in this research study. Patients were excluded if they had hemodynamic instability as defined by mean arterial pressure less than 65 mm Hg or requiring vasopressor support or if they had an urgent or emergent need for surgical intervention as determined by the treating physician.

POCUS training

General cardiology and interventional cardiology fellows underwent a 2-hour training session with a vascular radiologist which consisted of a didactic teaching session and a case-based review of common pathologies including hematoma, AV fistula, pseudoaneurysm, active extravasation/bleeding, venous and/or arterial thrombosis, edema and

lymph nodes. Training sessions were provided every 6 months and fellows were required to attend at least 1 session prior to enrolling their first participant.

Index and reference tests

Study participants underwent a comprehensive physical examination by a general cardiology or interventional cardiology fellow followed by a POCUS assessment of the access site of concern. A standardized case report form to document the result of their clinical and POCUS assessments was then completed prior to obtaining formal imaging studies. The participant's electronic medical record was reviewed to obtain baseline demographics, procedural characteristics, the results of the formal diagnostic imaging study, and management of access site complications.

Study outcomes

The primary outcome of the ULTRASITCOM study was the diagnostic odds ratio (DOR) comparing combined clinical and POCUS assessment to the reference standard of formal diagnostic imaging. The DOR is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease and can be used as a single indicator of test performance.[10] The value of the DOR ranges from 0 to infinity, with higher values indicating better discriminatory test performance. A DOR of 1 means that a test does not discriminate between patients with the disorder and those without it. The DOR does not depend on the prevalence of the disease that the test is used for. The diagnostic accuracy of the combined physical examination and POCUS assessment was also compared to the physical examination alone by comparing the DOR of each test.

Other measures of diagnostic accuracy including sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy are also reported. Secondary outcome measures included postprocedure management strategies of postprocedure pseudoaneurysms.

Statistical analysis

Categorical data are expressed as number and percentage and continuous variables are expressed as mean and SD. We analyzed the diagnostic accuracy of the combined clinical and POCUS assessment (ie, index test) in the detection of pseudoaneurysm to formal diagnostic imaging (ie, reference standard) using DOR as the primary measure of test performance. We also evaluated test performance using measures of sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy for the combined assessment as a secondary outcome. Other secondary outcomes evaluating the individual physical examination were analyzed in the same manner as the combined clinical and POCUS assessment. Point estimates and 95% CI for each measure of diagnostic accuracy were calculated. Of note, if a 2 $\times$ 2 table contained zeroes, the DOR was undefined, and therefore 0.5 was added to all counts in the table as this is a commonly used method to calculate an approximation of the DOR.[10]

A convenience sample was used without a formal sample size calculation. Given the level of uncertainty regarding the pseudoaneurysm rate, it was not possible to accurately estimate the required sample size. We planned to open recruitment for 18 months with the recruitment of as many participants as possible during this timeframe acknowledging that consecutive patient recruitment was not feasible due to logistical constraints (eg, patients could be referred from the ward or as outpatients without informing the interventional cardiology team). All reported *P* values were 2-sided and a value less than .05 was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute).

Results

There were 111 study participants enrolled during the study period (Figure 1). All participants underwent detailed clinical evaluation with both physical examination and POCUS assessments (ie, index test). Formal diagnostic imaging with either Doppler ultrasonography or computer tomography (ie, reference standard) was available in 108 study participants (97.3%).

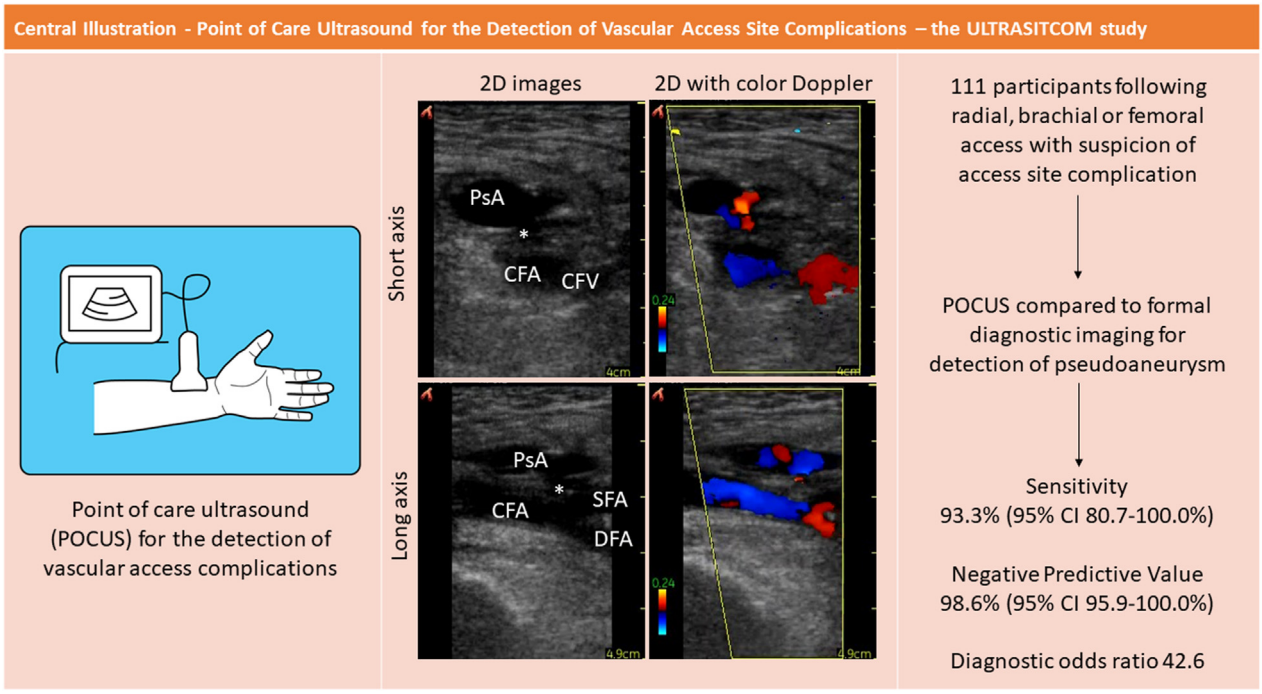
Participant demographics and procedural characteristics

Most study participants were female (59.5%) with an average age of 72.2 $\pm$ 12.5 years, height of 166 $\pm$ 10 cm, and weight of 77.3 $\pm$ 17.4 kg (Table 1). Cardiovascular risk factors were prevalent with nearly two-

Table 1. Baseline participant demographics and procedural characteristics.

	Study participants (N = 111)
Age, y	72.2 $\pm$ 12.5
Female sex	66 (59.5%)
Height, cm	166 $\pm$ 10
Weight, kg	77.3 $\pm$ 17.4
Past medical history	
Hypertension	70 (63.1%)
Dyslipidemia	58 (52.7%)
Active smoking	16 (14.4%)
Diabetes	38 (34.2%)
Family history of premature CAD	11 (9.9%)
Medications	
Aspirin	79 (71.2%)
P2Y12 inhibitor	75 (67.6%)
Direct oral anticoagulant	12 (10.8%)
Warfarin	0 (0.0%)
ACEI/ARB/ARNI	50 (45.1%)
Beta-blocker	60 (54.1%)
Mineralocorticoid receptor antagonist	15 (13.5%)
SGLT2 inhibitor	16 (14.6%)
Statin	76 (68.5%)
Procedural characteristics	
Diagnostic coronary angiogram	26 (23.4%)
Percutaneous coronary intervention	54 (48.7%)
Transcatheter aortic valve intervention	20 (18.0%)
Transcatheter edge-to-edge repair	2 (1.8%)
Other structural heart intervention	9 (8.1%)
Access site of concern	
Femoral	75 (67.6%)
Radial	35 (31.5%)
Brachial	1 (0.9%)
Maximum sheath size	
6F	76 (70.4%)
7F	3 (2.8%)
8F	9 (8.3%)
9F	14 (13.0%)
10F	0 (0.0%)
11F	2 (1.9%)
12F	4 (3.7%)
Closure device	
None/compression	62 (55.9%)
Angioseal	24 (21.6%)
Proglide	25 (22.5%)

Values are mean $\pm$ SD or n (%).
ACEI, angiotensin-converting enzyme inhibitor, ARB, angiotensin receptor blocker, ARNI, angiotensin receptor/neprilysin inhibitor; CAD, coronary artery disease.



Central Illustration.

Performance characteristics of the comprehensive physical examination plus point-of-care ultrasound (POCUS) assessment in the diagnosis of postprocedural pseudoaneurysm (PsA). In a cohort of 111 patients following radial, brachial, or femoral access, combined physical examination and POCUS assessment had greater sensitivity (93.3%) and negative predictive value (98.6%) in the diagnosis of PsA compared to physical examination alone; POCUS skills were rapidly acquired after a single 2-hour training session with a vascular radiologist. CFA, common femoral artery; DFA, deep femoral artery; SFA, superficial femoral artery.

thirds of study participants having a known history of hypertension and half with a history of dyslipidemia. Most patients were taking aspirin, P2Y12 inhibitors, beta-blockers, and statins. With respect to procedural characteristics, nearly half of the study participants underwent percutaneous coronary intervention, followed by approximately 25% who had diagnostic coronary angiography alone and the remaining 25% had a structural heart procedure (eg, transcatheter aortic valve intervention, transcatheter edge-to-edge repair, etc). The most common access site of concern was transfemoral (67.6%) followed by transradial (31.5%). Maximum sheath size was most commonly 6F (70.4%) followed by large-bore sheaths (ie, greater than 8F) (18.0%) and nearly half of the study participants had a vascular closure device deployed at the end of the procedure (21.6% with collagen plug-based device and 22.5% with suture-based device).

Table 2. Diagnostic accuracy of clinical and POCUS assessments for pseudoaneurysm detection.

	Physical examination + POCUS	Physical examination only
Diagnostic odds ratio[a]	42.6 (95% CI, 34.6-50.6)	15.6 (95% CI, 11.7-19.5)
Sensitivity	93.3% (95% CI, 80.7%-100.0%)	80.0% (95% CI, 59.8%-100.0%)
Negative predictive value	98.6% (95% CI, 95.9%-100.0%)	96.1% (95% CI, 91.8%-100.0%)
Specificity	75.3% (95% CI, 66.5%-84.0%)	79.6% (95% CI, 71.4%-87.8%)
Positive predictive value	37.8% (95% CI, 22.2%-53.5%)	38.7% (95% CI, 21.6%-55.9%)
Overall accuracy	77.8% (95% CI, 68.8%-85.2%)	79.6% (95% CI, 70.8%-86.8%)

POCUS, point-of-care ultrasound.

[a] *P* value comparing diagnostic odds ratio between combined physical examination + POCUS vs physical examination only is <.01.

Diagnostic accuracy of index test

Ninety-five study participants (88.0%) underwent Doppler ultrasound assessment whereas 13 participants (12.0%) had computed tomography as the reference standard. The diagnostic test accuracy of the combined clinical and POCUS assessments, as well as the accuracy of physical examination alone, can be found in the Central Illustration, Table 2, and Supplemental Tables S1 and S2.

Using the reference standard, a pseudoaneurysm was detected in 15 study participants (13.9%)—9 of which occurred following transfemoral access and 6 occurred after transradial access (Figure 2). There were no brachial artery pseudoaneurysms identified. Thirteen of the pseudoaneurysms occurred in patients in whom the maximal sheath size was 6F, and 2 of the pseudoaneurysms occurred in patients with 9F sheaths. The DOR for the detection of pseudoaneurysm was greater with the combined clinical and POCUS assessment compared to the physical examination only (42.6 [95% CI, 34.6-50.6] vs 15.6 [95% CI, 11.7-19.5]; $P < .01$). The sensitivity for pseudoaneurysm detection was greater using the combined physical examination and POCUS assessment, compared to physical examination alone (93.3% [95% CI, 80.7%-100.0%] vs 80.0% [95% CI, 59.8%-100.0%]) The negative predictive value for pseudoaneurysm was similar between the 2 assessment methods (combined: 98.6% [95% CI, 95.9%-100.0%] vs physical examination only: 96.1% [95% CI, 91.8%-100.0%]).

Management of access site complications

Most study participants with pseudoaneurysm required either a thrombin injection (20.0%) or underwent surgical arterial repair (40.0%) (Table 3). The remaining study participants with pseudoaneurysm were treated conservatively. Of note, the single participant in whom a pseudoaneurysm was missed by combined clinical and POCUS assessments did not require arterial repair or thrombin injection.

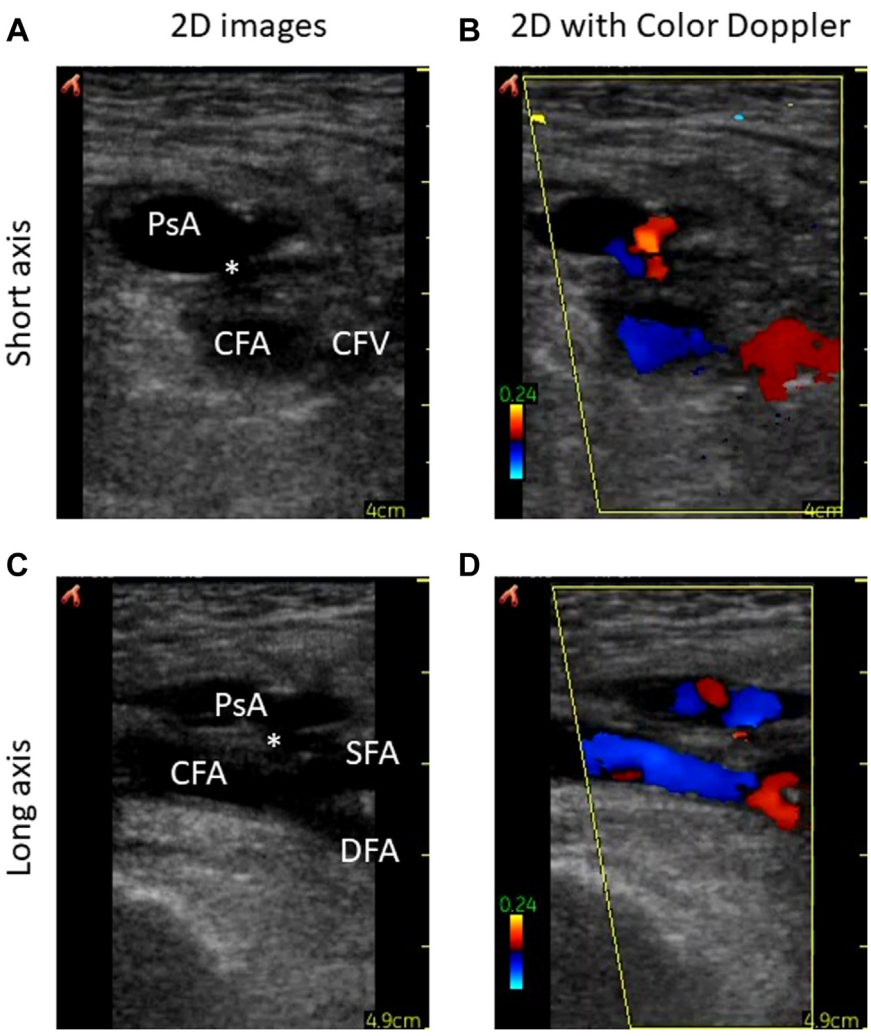


Figure 2.
Pseudoaneurysm (PsA) identified on point-of-care ultrasound. PsA as visualized on point-of-care ultrasound with the neck of the PsA (*) just proximal to the femoral artery bifurcation in the (**A**) short axis without color, (**B**) short axis with color Doppler, (**C**) long axis without color, and (**D**) long axis with color Doppler. CFA, common femoral artery; DFA, deep femoral artery; SFA, superficial femoral artery.

Discussion

The ULTRASITCOM study evaluated the utility of POCUS as an adjunct to clinical assessment in detecting vascular access site complications, namely pseudoaneurysms, following invasive cardiac procedures. The study has 3 major findings. First, the diagnostic performance as reflected in a DOR of 42.6 for POCUS in this post-procedure population suggests a strong overall performance. Second, the sensitivity of a combined clinical and POCUS evaluation was high at 93.3% with a negative predictive value of 98.6%—suggesting that a negative study was reassuring to rule out pseudoaneurysm. Third, the cardiology fellows had a 2 hour of didactic training with no further hands-on training suggesting a rapid acquisition of the skill set necessary to perform these assessments. Thus, although the performance of POCUS in this study is excellent, one would expect that with more experience and training, interventional cardiologists and fellows could attain diagnostic accuracy approaching that of formal studies.

Table 3. Management of access site complications.

	Pseudoaneurysm (n = 15)
Conservative/manual compression	6 (40.0%)
Thrombin injection	3 (20.0%)
Surgical repair	6 (40.0%)

Although many types of vascular access complications are possible, including hematoma, AV fistula, active extravasation/bleeding, and venous and/or arterial thrombosis, the focus of the ULTRASITCOM study was pseudoaneurysm. A pseudoaneurysm is a contained rupture of an artery that involves disruption in all 3 layers of the arterial wall and is usually a consequence of an arterial puncture that does not adequately seal.[7] This allows pulsatile blood to track into the perivascular space and a hematoma with surrounding tissue forms the wall of the pseudoaneurysm. The incidence of this complication is reported to be 2% to 6% following percutaneous coronary intervention.[7] Although some pseudoaneurysms may thrombose spontaneously, this complication could be life-threatening should the pseudoaneurysm rupture. Nonetheless, there are many pseudoaneurysms that are small and managed conservatively. In the current study, the only pseudoaneurysm that was not identified on POCUS was not clinically relevant and was managed conservatively. Thus, we are reassured that all clinically relevant pseudoaneurysms were identified with the combined clinical and POCUS assessment strategy.

The result of the ULTRASITCOM study has an important implication for clinical practice and training. Increasingly, POCUS for cardiac applications is being integrated into cardiology training and interventional

fellows increasingly have vascular ultrasound skills for access.[11] Although commonly used to evaluate cardiac pathology, this is—to the best of our knowledge—the first application for assessment of vascular access complications. Indeed, with relatively abbreviated training, learners were able to perform and diagnose pseudoaneurysms with a high degree of accuracy. Furthermore, there have been individual reports in which the addition of POCUS has resulted in point-of-care diagnosis.[12,13] As a result, one can envision POCUS for vascular complications becoming a standard part of interventional training to enable timely interventions, and potentially reduce morbidity and health care costs.

This study is not without limitations. First, a nonrandomized, convenience sample size from a single center was used, which may limit the external generalizability of the study results. All efforts were made to include patients in whom there was concern regarding an access site complication over the 18-month study period. Second, a variety of invasive procedures were performed, and some procedural factors are associated with an increased risk of pseudoaneurysm (eg, sheath size, anticoagulation, simultaneous arterial and venous cannulation).[7] However, although various procedures were performed, we do not believe this impacted the ability of the POCUS scans to detect the presence of a pseudoaneurysm. Third, the general and interventional cardiology fellows underwent a formal but unvalidated 2-hour training session with a radiologist and the impact this had on the ability to detect pseudoaneurysms remains unknown. Whether more optimized training is needed remains to be studied. Fourth, POCUS and physical examination evaluations were compared to 2 different reference modalities to confirm the diagnosis of a pseudoaneurysm. However, both Doppler ultrasonography and CT angiography have demonstrated similar sensitivity and specificity in the detection of pseudoaneurysms. Additionally, although the absolute number of large-bore access sheaths was small, the majority of pseudoaneurysms occurred following procedures requiring 6F access sheaths. Lastly, the direct and indirect health care costs and possible adverse events associated with delays in obtaining formal imaging are not available.

Conclusion

Point-of-care ultrasound when combined as an adjunct to clinical assessment, is a highly sensitive tool for detecting pseudoaneurysms following invasive cardiovascular procedures. These findings suggest the potential integration of POCUS into routine practice, which could result in timely complication identification and management, thereby improving patient outcomes and reducing health care costs. Further studies are needed to confirm whether POCUS identification of pseudoaneurysms can translate into improved clinical outcomes.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement and patient consent

The study was approved by the Ottawa Health Science Network Research Ethics Board and the study was conducted in accordance with the Helsinki Declaration. All study participants provided written informed consent.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2024.102516.

References

1. Chawla TP, Cresswell M, Dhillon S, et al. Canadian Association of Radiologists position statement on point-of-care ultrasound. *Can Assoc Radiol J*. 2019;70(3):219–225. https://doi.org/10.1016/j.carj.2019.06.001
2. Díaz-Gómez JL, Mayo PH, Koenig SJ. Point-of-care ultrasonography. *N Engl J Med*. 2021;385(17):1593–1602. https://doi.org/10.1056/NEJMra1916062
3. Di Santo P, Simard T, Wells GA, et al. Transradial versus transfemoral access for percutaneous coronary intervention in ST-segment-elevation myocardial infarction: a systematic review and meta-analysis. *Circ Cardiovasc Interv*. 2021;14(3):e009994. https://doi.org/10.1161/CIRCINTERVENTIONS.120.009994
4. Amin AP, Rao SV, Seto AH, et al. Transradial access for high-risk percutaneous coronary intervention: implications of the risk-treatment paradox. *Circ Cardiovasc Interv*. 2021;14(7):e009328. https://doi.org/10.1161/CIRCINTERVENTIONS.120.009328
5. Jacobson KM, Hall Long K, McMurtry EK, Naessens JM, Rihal CS. The economic burden of complications during percutaneous coronary intervention. *Qual Saf Health Care*. 2007;16(2):154–159. https://doi.org/10.1136/qshc.2006.019331
6. Sugiharto F, Trisyani Y, Nuraeni A, Mirwanti R, Melati Putri A, Aghnia Armansyah N. Factors associated with increased length of stay in post primary percutaneous coronary intervention patients: a scoping review. *Vasc Health Risk Manag*. 2023;19:329–340. https://doi.org/10.2147/VHRM.S413899
7. Webber GW, Jang J, Gustavson S, Olin JW. Contemporary management of postcatheterization pseudoaneurysms. *Circulation*. 2007;115(20):2666–2674. https://doi.org/10.1161/CIRCULATIONAHA.106.681973
8. Martindale JL, Wakai A, Collins SP, et al. Diagnosing acute heart failure in the emergency department: a systematic review and meta-analysis. *Acad Emerg Med*. 2016;23(3):223–242. https://doi.org/10.1111/acem.12878
9. Marbach JA, Almufleh A, Di Santo P, et al. Comparative accuracy of focused cardiac ultrasonography and clinical examination for left ventricular dysfunction and valvular heart disease: a systematic review and meta-analysis. *Ann Intern Med*. 2019;171(4):264–272. https://doi.org/10.7326/M19-1337
10. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PMM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol*. 2003;56(11):1129–1135. https://doi.org/10.1016/s0895-4356(03)00177-x
11. Jolly SS, AlRashidi S, d'Entremont MA, et al. Routine ultrasonography guidance for femoral vascular access for cardiac procedures: the UNIVERSAL randomized clinical trial. *JAMA Cardiol*. 2022;7(11):1110–1118. https://doi.org/10.1001/jamacardio.2022.3399
12. Azzo C, Driver L, Clark KT, Shokoohi H. Ultrasound assessment of postprocedural arterial pseudoaneurysms: techniques, clinical implications, and emergency department integration. *Cureus*. 2023;15(8):e43527. https://doi.org/10.7759/cureus.43527
13. Bektas F, Soyuncu S. Pseudoaneurysm of the superficial femoral artery detected by emergency medicine bedside ultrasound. *Int J Emerg Med*. 2010;3(4):425–426. https://doi.org/10.1007/s12245-010-0186-8

Appendix D - PDF of published manuscript – Study design and rationale of the RAPTOR trial

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BMJ Open

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 as 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 Research Ethics Board (approval number 20180319-01H). 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 procedure thereby improving patient comfort and experience and decrease length of stay.[2] There is also a reduction in all-cause mortality, major adverse cardiovascular events, major bleeding and vascular complications with TRA as compared with transfemoral access (TFA),[3 4] which has led to a class IA recommendation for TRA over TFA in patients presenting with an acute coronary syndrome.[5] However, radial artery occlusion (RAO) remains as 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.[8–10] In the largest systematic review published to date, the overall rate of RAO was 5.2% among the 46 631 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]

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Numerous trials have explored the role of intraprocedural anticoagulation during angiography to reduce RAO.[11 12] A recent meta-analysis demonstrated high-dose unfractionated heparin (UFH) is associated with less incidence of RAO compared with low-dose UFH.[6] 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)[13] and the Prevention of Radial Artery Occlusion With Rivaroxaban After Transradial Coronary Procedures (RIVARAD)[14] 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 Kington, 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[15] and patent haemostasis following the procedure.[16]

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.

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. Thrombocytopaenia with platelets $<50\times10^9$/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.
6. Use of non-steroidal anti-inflammatory medications, excluding aspirin.
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 30mL/min.
History of antiphospholipid syndrome, in particular triple positive (lupus anticoagulant, anticardiolipin antibodies and anti-beta 2-glycoprotein I antibodies).

Randomisation and study procedures

Randomisation will take place following completion of the postprocedure patent haemostasis period to ensure only patients without concerns regarding haematoma 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

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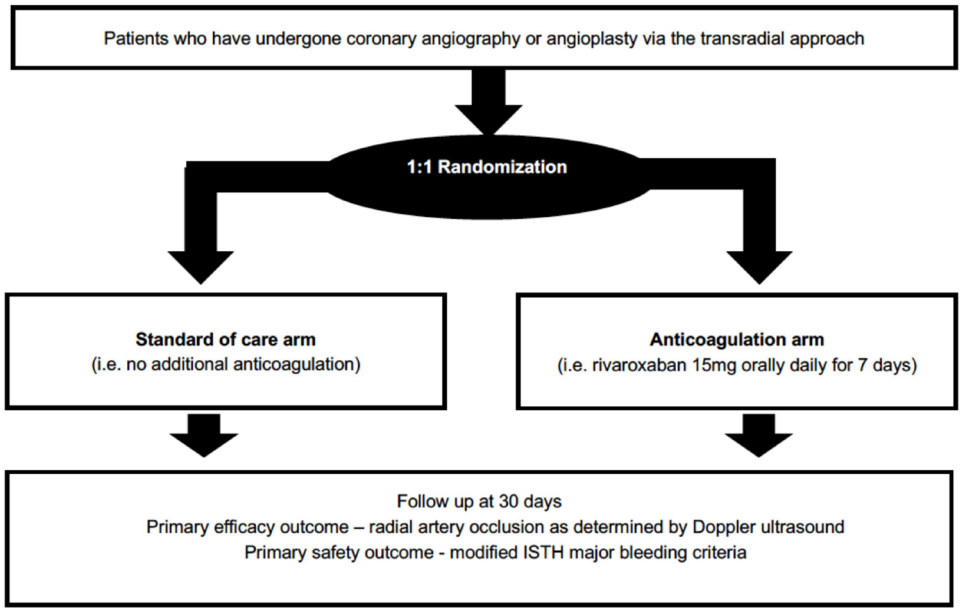

Figure 1 Flow of patient screening and enrolment. ISTH, International Society on Thrombosis and Haemostasis.

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.[17] 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[17]; 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[18] and remains guideline recommended for post-PCI patients in patients with atrial fibrillation.[19–21] 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.[6] 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.[22 23]

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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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).
3. Stroke (haemorrhagic).
4. Fatal bleeding.
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.
9. Bleeding Academic Research Consortium (BARC) 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 χ^2 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.
6. Diabetes.
7. Hypertension.
8. Type of coronary disease (acute coronary syndrome or stable coronary artery disease).
9. Presence of dual antiplatelet therapy.

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%.[24] 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.[25] 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.[26] The process of sheath insertion and instrumentation during TRA causes repeated

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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.[27] 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.[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.[30–32] Postprocedural variables that are associated with an increased risk of RAO include non-patent haemostasis[10 33] and longer duration of compressive haemostasis.[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[18 35–39] and venous thromboembolism.[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.[44] Given emerging evidence suggestive of late RAO recanalisation[6] and higher-dose intraprocedural anticoagulation in preventing RAO,[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 10 mg 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.[13] The Prevention of Radial Artery Occlusion With Rivaroxaban After Transradial Coronary Procedures (RIVARAD) trial randomised 521 patients to rivaroxaban 10 mg daily versus placebo and observed significant reduction in 1-month RAO with anticoagulation.[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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REFERENCES

1 Völz S, Angerås O, Koul S, *et al*. Radial versus femoral access in patients with acute coronary syndrome undergoing invasive management: a prespecified subgroup analysis from VALIDATE-SWEDEHEART. *Eur Heart J Acute Cardiovasc Care* 2019;8:510–9.
2 Schussler JM, Vasudevan A, von Bose LJ, *et al*. Comparative efficacy of transradial versus Transfemoral approach for coronary angiography and percutaneous coronary intervention. *Am J Cardiol* 2016;118:482–8.
3 Ferrante G, Rao SV, Jüni P, *et al*. Radial versus femoral access for coronary interventions across the entire spectrum of patients with coronary artery disease: a meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2016;9:1419–34.
4 Di Santo P, Simard T, Wells GA, *et al*. Transradial versus Transfemoral access for percutaneous coronary intervention in ST-segment-elevation myocardial infarction: a systematic review and meta-analysis. *Circ Cardiovasc Interv* 2021;14:e009994.
5 Roffi M, Patrono C, Collet J-P, *et al*. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of cardiology (ESC). *Eur Heart J* 2016;37:267–315.
6 Hahalis G, Aznaouridis K, Tsigkas G, *et al*. Radial artery and ulnar artery occlusions following coronary procedures and the impact of anticoagulation: ARTEMIS (radial and ulnar artery occlusion meta-analysis). *J Am Heart Assoc* 2017;6:8.
7 Bernat I, Aminian A, Pancholy S, *et al*. Best practices for the prevention of radial artery occlusion after transradial diagnostic angiography and intervention: an international consensus paper. *JACC Cardiovasc Interv* 2019;12:2235–46.
8 Pancholy SB. Transradial access in an occluded radial artery: new technique. *J Invasive Cardiol* 2007;19:541–4.
9 Sciahbasi A, Rigattieri S, Sarandrea A, *et al*. Radial artery occlusion and hand strength after percutaneous coronary procedures: results of the HANGAR study. *Cathet Cardiovasc Intervent* 2016;87:868–74.
10 Pancholy S, Coppola J, Patel T, *et al*. Prevention of radial artery occlusion-patent hemostasis evaluation trial (PROPHET study): a randomized comparison of traditional versus patency documented hemostasis after transradial catheterization. *Cathet Cardiovasc Intervent* 2008;72:335–40.
11 Hahalis GN, Leopoulou M, Tsigkas G, *et al*. Multicenter randomized evaluation of high versus standard heparin dose on incident radial arterial occlusion after transradial coronary angiography: the spirit of ARTEMIS study. *JACC Cardiovasc Interv* 2018;11:2241–50.
12 Pancholy SB. Comparison of the effect of intra-arterial versus intravenous heparin on radial artery occlusion after transradial catheterization. *Am J Cardiol* 2009;104:1083–5.
13 Liang D, Lin Q, Zhu Q, *et al*. Short-Term postoperative use of rivaroxaban to prevent radial artery occlusion after transradial coronary procedure: the restore randomized trial. *Circ Cardiovasc Interv* 2022;15:e011555.
14 Bavry AA. Prevention of radial artery occlusion with rivaroxaban after transradial coronary procedures: the RIVARAD multicentric randomized trial. *Transcatheter Cardiovascular Therapeutics* 2022.
15 Mason PJ, Shah B, Tamis-Holland JE, *et al*. An update on radial artery access and best practices for transradial coronary angiography and intervention in acute coronary syndrome: a scientific statement from the American heart association. *Circ Cardiovasc Interv* 2018;11:e000035.
16 Rao SV, Tremmel JA, Gilchrist IC, *et al*. Best practices for transradial angiography and intervention: a consensus statement from the Society for cardiovascular angiography and intervention's transradial Working group. *Cathet Cardiovasc Intervent* 2014;83:228–36.
17 Habib J, Baetz L, Satiani B. Assessment of collateral circulation to the hand prior to radial artery harvest. *Vasc Med* 2012;17:352–61.
18 Gibson CM, Mehran R, Bode C, *et al*. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;375:2423–34.
19 Andrade JG, Aguilar M, Atzema C, *et al*. The 2020 Canadian cardiovascular society/canadian heart rhythm Society comprehensive guidelines for the management of atrial fibrillation. *Canadian Journal of Cardiology* 2020;36:1847–948.
20 January CT, Wann LS, Calkins H, *et al*. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of cardiology/american heart association Task force on clinical practice guidelines and the heart rhythm society in collaboration with the Society of thoracic surgeons. *Circulation* 2019;140:e125–51.
21 Hindricks G, Potpara T, Dagres N, *et al*. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for cardio-thoracic surgery (EACTS). *Eur Heart J* 2021;42:373–498.
22 Sinha SK, Jha MJ, Mishra V, *et al*. Radial artery occlusion-incidence, predictors and long-term outcome after transradial catheterization: clinico-doppler ultrasound-based study (RAIL-TRAC study). *Acta Cardiol* 2017;72:318–27.
23 Garg N, Madan BK, Khanna R, *et al*. Incidence and predictors of radial artery occlusion after transradial coronary angioplasty: Doppler-guided follow-up study. *J Invasive Cardiol* 2015;27:106–12.
24 Kotowycz MA, Dzavík V. Radial artery patency after transradial catheterization. *Circ Cardiovasc Interv* 2012;5:127–33.
25 Yonetsu T, Kakuta T, Lee T, *et al*. Assessment of acute injuries and chronic intimal thickening of the radial artery after transradial coronary intervention by optical coherence tomography. *Eur Heart J* 2010;31:1608–15.
26 Mamas MA, Fraser DG, Ratib K, *et al*. Minimising radial injury: prevention is better than cure. *EuroIntervention* 2014;10:824–32.
27 Sakai H, Ikeda S, Harada T, *et al*. Limitations of successive transradial approach in the same arm: the Japanese experience. *Cathet Cardiovasc Intervent* 2001;54:204–8. 10.1002/ccd.1268 Available: http://doi.wiley.com/10.1002/ccd.v54:2
28 Abdelaal E, Molin P, Plourde G, *et al*. Successive transradial access for coronary procedures: experience of Quebec heart-lung Institute. *American Heart Journal* 2013;165:325–31.
29 Kotowycz MA, Johnston KW, Ivanov J, *et al*. Predictors of radial artery size in patients undergoing cardiac catheterization: insights from the good radial artery size prediction (GRASP) study. *Can J Cardiol* 2014;30:211–6.
30 Rashid M, Kwok CS, Pancholy S, *et al*. Radial artery occlusion after transradial interventions: a systematic review and meta-analysis. *J Am Heart Assoc* 2016;5:e002686.
31 Aminian A, Saito S, Takahashi A, *et al*. Comparison of a new slender 6 Fr sheath with a standard 5 Fr sheath for transradial coronary angiography and intervention: Rap and beat (radial artery patency and bleeding, efficacy, adverse event), a randomised multicentre trial. *EuroIntervention* 2017;13:e549–56.
32 Dahm JB, Vogelgesang D, Hummel A, *et al*. A randomized trial of 5 vs. 6 French transradial percutaneous coronary interventions. *Cathet Cardiovasc Intervent* 2002;57:172–6. 10.1002/ccd.10321 Available: http://doi.wiley.com/10.1002/ccd.v57%3A2
33 Sanmartin M, Gomez M, Rumoroso JR, *et al*. Interruption of blood flow during compression and radial artery occlusion after transradial catheterization. *Cathet Cardiovasc Intervent* 2007;70:185–9. 10.1002/ccd.21058 Available: http://doi.wiley.com/10.1002/ccd.v70:2
34 Pancholy SB, Patel TM. Effect of duration of hemostatic compression on radial artery occlusion after transradial access. *Cathet Cardiovasc Intervent* 2012;79:78–81.
35 Cannon CP, Bhatt DL, Oldgren J, *et al*. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;377:1513–24.
36 Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51.
37 Giugliano RP, Ruff CT, Braunwald E, *et al*. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–104.
38 Granger CB, Alexander JH, McMurray JJV, *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92.
39 Patel MR, Mahaffey KW, Garg J, *et al*. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–91.
40 Agnelli G, Buller HR, Cohen A, *et al*. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799–808.
41 Hokusai V, Buller HR, Decousus H, *et al*. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406–15.
42 Investigators E-P, Buller HR, Prins MH, *et al*. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287–97.
43 Schulman S, Kearon C, Kakkar AK, *et al*. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342–52.
44 Eikelboom JW, Connolly SJ, Bosch J, *et al*. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377:1319–30.

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Appendix E – Statistical Analysis Plan for the RAPTOR study

STATISTICAL ANALYSIS PLAN – Rivaroxaban Post-Transradial Access for the Prevention of Radial Artery Occlusion (CAPITAL-RAPTOR)

Health Canada Protocol Number: VBEML110318

OHSN-REB Protocol Number: 20180319-01H

Version: 2

Date: June 25, 2025

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Table of Contents

1. General Principles

For the purposes of data analysis, the study population will be defined by the intention to treat (ITT) population - all patients who are allocated to a study therapy, regardless of whether they received the therapy will be included. In all analyses, the patient therapy group will be categorized by their allocation, regardless of what therapy they have received.

SAS software will be used for all statistical analysis.

2. Baseline Analysis

Baseline clinical and demographic information will be summarized by (1) frequencies and percentages for categorical variables and (2) by mean and standard deviation (for normally distributed data) or median and interquartile range (for skewed data). Baseline information will include age, sex, height, weight, ethnicity (if available), body mass index, past medical history including traditional cardiovascular risk factors, baseline laboratory values and baseline medications.

SAS procedures	PROC FREQ
	PROC NPAR1WAY
	PROC MEANS
	PROC TTEST

3. Index Left Heart Catheterization

Index left heart catheterization procedural characteristics will be summarized by (1) frequencies and percentages for categorical variables and (2) by median and interquartile range (for skewed data). Procedural characteristics will include indication for the procedure, type of procedure (i.e. diagnostic coronary angiography vs. percutaneous coronary intervention), length and size of the sheath, left or right radial arterial access, maximum coronary catheter size, and type of anticoagulation used with total dose.

SAS procedures	PROC FREQ
	PROC MEANS

4. Primary Analysis

For this study, there will be both a primary efficacy and a primary safety outcome.

The primary efficacy outcome will be the presence of radial artery occlusion at 30 days post-transradial access as determined by Doppler ultrasound assessment.

The primary safety outcome will be a modified International Society on Thrombosis and Haemostasis definition of major bleeding:

a. Fatal bleeding and/or
b. Symptomatic bleeding in a critical area or organ and/or

    a. Intracranial, spinal, ocular, retroperitoneal, pericardial, articular, muscular with compartment syndrome
c. Bleeding causing a fall in hemoglobin level of ≥20g/L *or* transfusion of ≥2 units of packed red blood cells in a 48-hour period

For the primary efficacy and safety analyses, a Chi-square test will be used. Results will be presented as absolute and relative risks with 95% confidence intervals.

SAS procedures PROC FREQ

5. Secondary Analyses

Secondary analyses will be performed including:

a. All-cause mortality
b. Stroke (ischemic or uncertain)
c. Stroke (hemorrhagic)
d. Fatal bleeding
e. Symptomatic bleeding in a critical area or organ
f. Bleeding requiring medical attention
g. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) bleeding criteria
h. Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria
i. Bleeding Academic Research Consortium (BARC)bleeding criteria
j. Myocardial infarction
k. Stent thrombosis (Academic Research Consortium criteria)

These outcomes will be summarized descriptively. Frequencies and percentages will be reported for categorical variables. No formal hypothesis testing will be conducted for these endpoints, and the analyses will not be powered to account for multiplicity.

SAS procedures PROC FREQ

6. Prespecified Subgroup Analyses

As identified *a priori*, subgroup analysis will include:

a. Type of procedure (i.e. diagnostic coronary angiography vs. percutaneous coronary intervention)
b. Sex (i.e. male vs. female)
c. Age (i.e. less than 65 years old, 65 to 75 years old, and greater than 75 years old)
d. Weight (i.e. ≤70kg vs. > 70kg)
e. Baseline renal function (i.e. estimated glomerular filtration rate <50ml/min vs. ≥ 50ml/min)
f. Diabetes status (i.e. history of diabetes vs. no history of diabetes)
g. Hypertension status (i.e. history of hypertension vs. no history of hypertension)
h. Type of presentation (i.e. acute coronary syndrome vs. not acute coronary syndrome)
i. Dual antiplatelet therapy usage (i.e. participants also on dual antiplatelet therapy vs. not)

7. Frequency of Analyses

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.

At the request of the Data Safety Monitoring Board, an interim futility analysis was conducted.

8. Data Handling

8.1 Missing Data

Missingness will be considered to be missing at random (MAR) and multiple imputation (MI) techniques will be considered for handling missing data.

8.2 Cross-Overs

The primary analysis will be conducted using the intention to treat principle. A sensitivity analysis using per-protocol analysis may be performed as follows:

For participants randomized to receive rivaroxaban, patients who do not take any doses will be considered to crossover to the standard of care group.

For participants randomized to receive standard of care (i.e. no anticoagulation), patients who are started on oral anticoagulation for another indication in the first 7 days after the procedure will be considered to have crossover to the intervention arm (i.e. rivaroxaban).

9. Revisions to Statistical Analysis Plan

June 2025

- Only unadjusted Chi-square analysis will be performed for the primary analysis
- Secondary outcomes will not have formal hypothesis testing/Chi-square analyses performed.
- Addition of an interim futility analysis
- Sensitivity analysis using per-protocol definitions may be performed