UNDERSTANDING ORAL ANTICOAGULATION ACROSS CLINICAL SETTINGS

By Pablo Mendoza, BSc

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Degree

Master of Science

DESCRIPTIVE NOTE

Master of Science (2020)

Department of Health Research Methods, Evidence, and Impact

McMaster University

Hamilton, Ontario

Title:	Understanding Oral Anticoagulation Across Clinical Settings
Author:	Pablo Mendoza, BSc (McMaster University)
Supervisor and Committee:	Richard Whitlock, MD, PhD, FRCSC (Supervisor) Emilie Belley-Côté, MD, PhD, FRCPC (Committee) Jeff Healey, MD, MSc, FRCPC (Committee) John Eikelboom, MBBS, MSc, FRCPC (Committee) Pablo Lamelas, MD, MSc, FRCPC (External Reader)
Number of Pages:	95

ABSTRACT

Oral anticoagulation (OAC) remains the cornerstone of stroke prevention in patients with atrial fibrillation (AF). Some areas of OAC management are well supported, while other areas require further research to inform clinical practise and support guidelines. My thesis focuses on generating knowledge about OAC use in 2 understudied settings: a) the emergency department (ED), and b) after cardiac surgery.

Chapter 1 is a preface that provides the rationale for conducting each of the following three chapters. In the ED, physicians are in a unique position to initiate OAC; however, prescription remains low. In the early period after open-heart surgery, initiating OAC is not the main issue, but rather, what class of OAC is the most safe and efficacious.

Chapter 2 uses a global registry dataset to explore the clinical patterns that lead to initiating OAC in the ED, along with the factors associated with patients' long-term use of OAC.

Chapter 3 reviews the current literature around the safety and efficacy of direct oral anticoagulants (DOACs) compared to vitamin K antagonists (VKAs) in the early period after cardiac surgery.

Subsequently, chapter 4 provides the rationale and design for the Direct Oral Anticoagulation versus Warfarin after Cardiac Surgery (DANCE) noninferiority, open-label vanguard trial.

In chapter 5, I present the main conclusions of this thesis and areas for further research.

ACKNOWLEDGEMENTS

I am sincerely grateful for the numerous people who have supported my academic and personal growth during the last two years.

Thank you, mom, for passing on your mission to improve people's lives.

A special thank you to the dream team, Drs. Richard Whitlock, Emilie Belley-Côté and William McIntyre, for providing careful instruction, advice and opportunities to me in the last two years. Dr. Whitlock, your commitment to pushing boundaries sets a tone that I plan to carry throughout my career. Dr. Belley-Côté, your attention and care for each of your students has been exemplary. Dr. McIntyre, thank you for sharing your humour, and your joy for learning with me daily. I am grateful for the many teaching moments you have provided as a mentor and friend.

Thank you to the rest of my committee, Drs. Jeff Healey and John Eikelboom, for providing careful insight and optimism in my research. Your effort and time do not go without my gratitude.

To my colleagues and friends at PHRI, in HRM and the MiNION-CIA research group, thank you for collaborating with me and providing guidance along the way. I will echo the same constructive working and learning environment wherever I go.

To each of you, I will stay in touch!

CONTRIBUTORSHIP STATEMENT

I prepared, wrote and revised all chapters. Several others contributed significantly to this thesis. The following is a summary of their contributions:

1. RICHARD WHITLOCK
    - Thesis – helped conceive idea and plan.
    - Chapter 2, 3 & 4 – contributed significantly to the manuscript design, interpretation of data, provided critical revisions, and approved of the final manuscript.
2. EMILIE BELLEY-CÔTÉ
    - Thesis – helped conceive idea and plan.
    - Chapter 2, 3 & 4 – contributed significantly to the manuscript design, interpretation of data, provided critical revisions, and approved of the final manuscript.
3. WILLIAM MCINTYRE
    - Thesis – helped conceive idea and plan.
    - Chapter 2, 3 & 4 – contributed significantly to the manuscript design, interpretation of data, provided critical revisions, and approved of the final manuscript.
4. JEFF HEALEY
    - Thesis – helped plan.
    - Chapter 2 – contributed significantly to the manuscript design, interpretation of data, provided critical revisions, and approved of the final manuscript.

- Chapter 3 & 4 – provided edits and approved of the final manuscript.

5. JOHN EIKELBOOM
    - Thesis – helped plan.
    - Chapter 3 & 4 – contributed to manuscript design, provided critical revisions and approved of the final manuscript.
6. JIA WANG
    - Chapter 2 – contributed to manuscript design, statistical analyses, provided critical revisions and approved of the final manuscript.
7. RATIKA PARKASH
    - Chapter 2 – provided critical revisions and approved of the final manuscript.
8. CLARE ATZEMA
    - Chapter 2 – provided critical revisions and approved of the final manuscript.
9. ALEXANDER BENZ
    - Chapter 2 – provided critical revisions and approved of the final manuscript.
10. JONAS OLDGREN
    - Chapter 2 – contributed to manuscript design and approved of the final manuscript.
11. HATIM ALRADDADI
    - Chapter 3 – contributed to manuscript analyses, provided critical revisions and approved of the final manuscript.
12. SAM SCHULMAN
    - Chapter 3 – provided critical revisions and approved of the final manuscript.
13. VIVEK RAO

- Chapter 3 – provided critical revisions and approved of the final manuscript.

14. RENATO LOPES

- Chapter 3 – provided critical revisions and approved of the final manuscript.

15. MICHAEL FARKOUH

- Chapter 3 – provided critical revisions and approved of the final manuscript.

16. PABLO LAMELAS

- Chapter 1-4 – provided critical revisions and approved of the final manuscript.

TABLE OF CONTENTS

CHAPTER 1: PREFACE

Background

Atrial fibrillation (AF) is an arrhythmia that affects an estimated 33 million people across the globe.(1) AF increases the risk of atrial thrombus formation;(2) patients with AF have a 5-fold increased risk of ischemic stroke and a 2-fold increased risk of death compared to a patient without AF.(3)

There are three main approaches to stroke prevention in AF: 1) eliminating AF, 2) occluding the left atrial appendage (LAA), or 3) anticoagulating to reduce thrombus formation.(4) Research has explored methods of eliminating AF including antiarrhythmic medication, electrical cardioversion, and catheter or surgical ablation.(5) However, complete elimination of AF is often not attainable and, therefore, this approach is generally not favoured for stroke prophylaxis. LAA occlusion has shown some promise in previous trials; however, these studies were small and underpowered.(6, 7) The Left Atrial Appendage Occlusion Study (LAAOS III), a multinational randomized controlled trial of 4,700 patients undergoing cardiac surgery with or without LAA occlusion will definitively inform on the efficacy of LAA occlusion .(4) Until then, anticoagulation will remain the cornerstone of stroke prevention in AF.

Anticoagulation therapy for stroke prevention: the golden bullet?

Oral anticoagulation (OAC) attenuates the risk of stroke in patients with AF, and improves their quality of life.(5, 8, 9) However, OAC also carries an increased risk for bleeding. In Canada and the United States, guidelines suggest the CHADS-65 and CHA_2DS_2-VASc stroke risk algorithms, respectively, and the HASBLED bleeding algorithm to predict the risk-benefit ratio for taking OAC.(5, 9)

Two major OAC classes are used in clinical practice: vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs). Warfarin, a VKA, has been the dominant agent since the 1950s. It inhibits the synthesis of clotting factors II, VII, IX, and X in the coagulation cascade.(10) For stroke prevention, it is superior to placebo and antiplatelet therapy in most patients with AF, except for patients with very low risk for stroke.(8, 11-13) However, VKAs have several adverse drug and food interactions, and require frequent laboratory tests to maintain the international normalized ratio (INR) in the therapeutic anticoagulation range.(14) Consequently, VKAs are underused and can lead to suboptimal stroke prevention.(15) In the last decade, DOACs have become an alternative. The direct thrombin inhibitor dabigatran, and the factor Xa inhibitors apixaban, rivaroxaban and edoxaban, have few interactions with food and other drugs, have a rapid onset of effect, and a fixed dosage that negates the need for regular monitoring.(16) Most importantly, DOACs are superior to warfarin in reducing stroke, systemic embolism and all-cause death in patients requiring long-term OAC. In general, they also have a superior safety profile for bleeding.(17)

Some areas of OAC management are supported by strong evidence from large randomized controlled trials. Other areas require further research to inform clinical practice and support guidelines. My thesis focuses on generating knowledge about OAC use in 2 understudied settings: a) the emergency department, and b) after cardiac surgery.

Initiating oral anticoagulation in the emergency department

OAC reduces thromboembolic events; nevertheless, studies continue to show under-prescription of guideline-directed OAC in general practice, and markedly, in the emergency department (ED).(18, 19) Clinicians who see AF patients in the ED are in a unique position to

initiate OAC in the ED; however, their decision process is complex. Clinicians must treat underlying comorbidities, stratify patients for OAC and explain the risks and benefits to the patient during the brief visit.(20) While long-term preventative treatments are often not initiated in the ED, a short-term prescription with coordinated follow-up care has been suggested. (20-22) In chapter 2, I explore the clinical patterns that lead to initiating OAC in the ED, along with the factors associated with patients' long-term use of OAC using a global registry dataset. We found that early initiation of OAC is associated with increased long-term use and reduced rates of stroke and death. This information may facilitate targeted education and evidence-based interventions to enhance stroke prevention strategies starting in the ED.

Current evidence for direct oral anticoagulation versus vitamin k antagonists after cardiac surgery

For the next two chapters, I move into the cardiac perioperative setting. AF is the most frequent complication after cardiac surgery and carries a significant risk of stroke and mortality.(23) Open heart surgery increases the risk of major bleeding early after surgery. Therefore, patients with AF after cardiac surgery require OAC that both minimizes the risk of stroke and bleeding. During long-term follow-up in the non-surgical population (e.g. patients with AF requiring stroke prevention, patients requiring venous thromboembolism prophylaxis), DOACs offer better stroke prevention and a lower risk of intracranial bleeding when compared to VKAs.(24) However, previous large trials comparing the two classes of OAC have excluded patients planned for cardiac surgery, providing no guidance for anticoagulation practice in this setting. In chapter 3, I review the current literature around the efficacy and safety of DOACs compared to VKAs in the post-operative cardiac surgery period. The results demonstrate the

clinical equipoise required to justify a randomized controlled trial comparing DOACs and VKAs in this setting. In chapter 4, I provide the rationale and design for the Direct Oral Anticoagulation versus Warfarin after Cardiac Surgery (DANCE) vanguard trial.

Conclusion and final remarks

In chapter 5, I present the conclusions based on this thesis work, describe areas for further research, and provide final remarks.

REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129(8):837-47.
2. Long B, Robertson J, Koyfman A, Maliel K, Warix JR. Emergency medicine considerations in atrial fibrillation. The American journal of emergency medicine. 2018;36(6):1070-8.
3. Wolf Pa Fau - Abbott RD, Abbott Rd Fau - Kannel WB, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. (0003-9926 (Print)).
4. Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A, et al. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. Ann Cardiothorac Surg. 2014;3(1):45-54.
5. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al. 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 Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1-76.
6. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. The Lancet. 2009;374(9689):534-42.
7. Holmes DR, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. Journal of the American College of Cardiology. 2014;64(1):1-12.
8. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European journal of cardio-thoracic surgery. 2016;50(5):e1-e88.
9. Verma A, Cairns JA, Mitchell LB, Macle L, Stiell IG, Gladstone D, et al. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol. 2014;30(10):1114-30.
10. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2):e44S-e88S.
11. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine. 2007;146(12):857-67.
12. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2007(3):Cd006186.
13. Saxena R, Koudstaal PJ. Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischaemic attack. Cochrane Database of Systematic Reviews. 2004(2).
14. Chang T-Y, Liao J-N, Chao T-F, Vicera JJ, Lin C-Y, Tuan T-C, et al. Oral anticoagulant use for stroke prevention in atrial fibrillation patients with difficult scenarios. IJC heart & vasculature. 2018;20:56-62.

15. Seliverstov I. Practical management approaches to anticoagulation non-compliance, health literacy, and limited English proficiency in the outpatient clinic setting. Journal of thrombosis and thrombolysis. 2011;31(3):321-5.
16. Hanley CM, Kowey PR. Are the novel anticoagulants better than warfarin for patients with atrial fibrillation? Journal of thoracic disease. 2015;7(2):165.
17. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. The Lancet. 2014;383(9921):955-62.
18. Dlott JS, George RA, Huang X, Odeh M, Kaufman HW, Ansell J, et al. National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation. Circulation. 2014;129(13):1407-14.
19. Atzema CL, Jackevicius CA, Chong A, Dorian P, Ivers NM, Parkash R, et al. Prescribing of oral anticoagulants in the emergency department and subsequent long-term use by older adults with atrial fibrillation. CMAJ. 2019;191(49):E1345-E54.
20. Atzema CL. Stroke Prevention for High-Risk Atrial Fibrillation in the Emergency Setting: The Emergency Physician Perspective. Can J Cardiol. 2018;34(2):125-31.
21. Atzema CL, Austin PC, Chong AS, Dorian P, Jackevicius CA. The Long-Term Use of Warfarin Among Atrial Fibrillation Patients Discharged From an Emergency Department With a Warfarin Prescription. Ann Emerg Med. 2015;66(4):347-54.e2.
22. TW B, KA M. Anticoagulation for emergency department patients with atrial fibrillation: is our duty to inform or prescribe? Ann Emerg Med. 2013;62(6):566-8.
23. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. European journal of cardio-thoracic surgery. 2010;37(6):1353-9.
24. Nazha B, Pandya B, Cohen J, Zhang M, Lopes RD, Garcia DA, et al. Periprocedural Outcomes of Direct Oral Anticoagulants Versus Warfarin in Nonvalvular Atrial Fibrillation. Circulation. 2018;138(14):1402-11.

CHAPTER 2: INITIATING OAC IN THE EMERGENCY DEPARTMENT

Oral Anticoagulation for Patients with Atrial Fibrillation in the ED: RE-LY AF Registry Analysis

Pablo A. Mendoza, BSc;[1,2] William F. McIntyre, MD;[1,2,3] Emilie P. Belley-Côté, MD, PhD;[2,3] Jia Wang, MSc;[2] Ratika Parkash, MD, MSc;[5] Clare L. Atzema MD, MSc;[6] Alexander P. Benz MD; [2] Jonas Oldgren MD, PhD;[7] Richard P. Whitlock MD, PhD;[1,2,4] and Jeff S. Healey, MD, MSc[1,2,3] on behalf of the RE-LY AF Registry Investigators

Affiliations:

1. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
2. Population Health Research Institute, Hamilton, Ontario, Canada
3. Department of Medicine, McMaster University, Hamilton, Ontario, Canada
4. Department of Surgery, McMaster University, Hamilton, Ontario, Canada
5. Department of Medicine, Dalhousie University, Halifax, Nova Scotia
6. Sunnybrook Health Sciences Centre, Toronto, Ontario
7. Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Uppsala, Sweden

2905 words, 5 tables, 2 supplementary tables, 39 references

ABSTRACT

Study Objective: Oral anticoagulation (OAC) reduces stroke risk in patients with atrial fibrillation (AF).We sought to determine predictors of OAC initiation in AF patients presenting to the emergency department (ED).

Methods: Secondary analysis of the RE-LY AF registry which enrolled individuals from 47 countries who presented to an ED with AF and followed them for 1 year.

Results: A total of 4149 patients with AF as their primary diagnosis who were not already taking OAC and had a CHA_2DS_2-VASc ≥1 for men or ≥2 for women were included in this analysis. Of these individuals, 26.8% were started on OAC in the ED and 29.8% were using OAC one year later. Factors associated with initiating OAC in the ED included: specialist consultation (relative risk [RR] 1.84, 95%CI 1.44-2.36), rheumatic heart disease (RR 1.60, 95%CI 1.29-1.99), persistence of AF at ED discharge (RR 1.33, 95%CI 1.18-1.50), diabetes mellitus (RR 1.32, 95%CI 1.19-1.47), and hospital admission (RR 1.30, 95%CI 1.14-1.47). Heart failure (RR 0.83, 95%CI 0.74-0.94), antiplatelet agents (RR 0.77, 95%CI 0.69-0.84), and dementia (RR 0.61, 95%CI 0.40-0.94) were inversely associated with OAC initiation. Patients taking OAC when they left the ED were more likely to be using OAC at 1-year (RR 2.81, 95%CI 2.55-3.09) and had lower rates of death (RR 0.55, 95%CI 0.38-0.79) and stroke (RR 0.59, 95%CI 0.37-0.96).

Conclusion: In patients with AF presenting to the ED, prompt initiation of OAC and specialist involvement are associated with a greater use of OAC one year later and may result in improved clinical outcomes.

INTRODUCTION

Background

Atrial fibrillation (AF) is the most common arrhythmia treated in the emergency department (ED) and is associated with a substantial risk for ischemic stroke and mortality.(1, 2) Oral anticoagulation (OAC) therapy is proven to reduce the risk of thromboembolism in patients with AF and is recommended by practice guidelines across the globe.(3-5) Nevertheless, studies continue to show the under-prescription of guideline-directed OAC in general practice, (6-8) and in the ED setting.(9-19) Although barriers exist, the ED may be a unique opportunity to improve stroke prevention for patients with AF eligible for OAC. (9-19)

Importance

Clinicians who see AF patients in the ED are in a position to initiate OAC in the ED; however, their decision process is complex. Clinicians must balance the benefit of OAC with the patient's bleeding risk and consider comorbidities, some of which may not be identified during this single episode of care (20). Additionally, time may be insufficient to discuss risks and benefits with the patient in the ED and follow-up of OAC management is not guaranteed. To address these issues, a short-term prescription has been suggested. (20-22) We need to further understand the clinical patterns that lead to initiating OAC in the ED, along with the factors associated with patient's long-term use of OAC. This information can facilitate targeted education and evidence-based interventions to enhance stroke prevention strategies.

Goals of This Investigation

We used the RE-LY AF (Risk Factors, Treatments and Outcomes for Emergency Department Patients with Atrial Fibrillation in Multiple Regions of the World) registry to determine the rate and predictors of OAC initiation in the ED, and the predictors of OAC use 1

year later. Given previous findings, we postulated that patients who were taking OAC when they left the ED will increase patient's use of OAC at 1-year follow up and impact patient outcomes.(9)

METHODS

Data Source

The RE-LY AF registry was an international prospective registry that enrolled patients who presented to an ED with a diagnosis of AF or atrial flutter. Its design and primary results have previously been described.(23, 24) Ethical committees approved the study at participating centers in 47 countries, and sites collected clinical data through interviews with patients, review of medical records and contact with the treating physician. At 1-year following enrollment, medication use and outcomes were collected either in person or via phone, with supplementary information acquired through medical records. Countries were divided into 8 geographic regions based on 2011 World Bank definitions.(23, 25) These included: Southeast Asia, China, India, Africa, Middle East, Eastern Europe, South America, and a composite of North America, Western Europe and Australia.

Study Population

Between December 2007 and October 2011, the RE-LY AF registry enrolled 15 400 patients. In this pre-planned sub-study, we excluded individuals who were on OAC at baseline. At enrolment, the site investigator registered the AF diagnoses as either being their primary reason or a secondary reason for the visit. We only included patients with a primary diagnosis of AF and an indication for OAC (i.e. CHA_2DS_2-VASc ≥ 1 for men or ≥ 2 for women). We included both patients with pre-existing and newly diagnosed AF. Patients were included in the

study regardless of whether they left the ED to go home or were subsequently admitted to the hospital for continued care.

Study Outcomes

We determined the proportion of patients who were taking OAC when they left the ED, regardless of prescriber specialty, for stroke prophylaxis. We also recorded OAC use at 1-year follow-up. Secondary outcomes included stroke, major bleeding, and death at 1 year. In this study, stroke was captured as ischemic or hemorrhagic stroke. Major bleeding was captured as a fatal bleed, and/or symptomatic bleed in a critical area, and/or bleeding causing a fall in hemoglobin level of 20g/L or more or leading to transfusion of two or more unites of whole blood or red cells.(23, 24)

Predictors of OAC Prescription after the ED visit

We did two analyses, first to determine the factors associated with initiating OAC in the ED (i.e. measured as taking OAC when they left the ED), and second, to determine the factors associated with OAC use at 1-year follow-up. *A priori*, we selected potential factors associated with OAC prescription based on the literature and factors perceived to influence physicians' decision making to prescribe OAC. These variables included the individual components of the CHA_2DS_2-VASc score, a history of major bleeding prior to ED visit, taking concomitant antiplatelet therapy prior to ED visit, body mass index (BMI), sleep apnea, tobacco use, history of dementia or cognitive dysfunction, presence of rheumatic heart disease, previous valve surgery or percutaneous valvuloplasty, significant valvular heart disease, attempted cardioversion in ED, patient still in AF/flutter at the time they left the ED, consultation with a specialist (e.g. consultation or referral with an internist, cardiologist, hematologist) for AF

management in the ED or in hospital shortly after, and patient outcome from ED visit (i.e. admission to hospital versus discharged).

Data Analysis

We summarized patient characteristics with mean and standard deviation for continuous variables, and with frequency and percentages for categorical variables. We used multivariable Poisson regression models with robust error variance to identify independent predictors of OAC initiation in the ED and usage at 1-year follow-up. We reported effect size via relative risk (RR) and their associated 95% confidence intervals (CI). All models were adjusted for region as a fixed effect. We forced prior stroke or transient ischemic attack (TIA), prior major bleeding and outcome from ED visit (admitted to hospital vs. discharged home) into the model given their clinical relevance. Other potential predictors with p-value < 0.2 in univariate analysis were tested for inclusion based on their influence on overall model fit and confounding effects. We used a backward elimination approach to sequentially remove baseline factors with p-values > 0.05, starting with the ones that had the highest p-value. To identify potential confounders, we added previously dropped factors back to the model and kept them in the model if the effect size of any existing predictors changed by >10%. Given that the patients admitted to hospital vs. discharged home may have very different risk profiles, we evaluated its interaction effect with each of the selected predictors and those interaction terms with p value<0.05 were kept in the multivariable models.

We assessed the effects of initiating OAC in the ED on the risk of stroke, major bleeding and death at 1-year follow-up. Given the small event number for some clinical outcomes, we adopted a propensity score matching approach to control for potential confounding effects. We estimated propensity scores for OAC prescription in the ED by a logistic regression model with

region as a fixed effect, including the following variables: age, sex, heart failure, hypertension, stroke or TIA, diabetes, significant valvular heart disease, rheumatic heart disease, dementia/cognitive defects, concomitant antiplatelet agents, patient still in AF/flutter at the time of discharge from the ED, consultation with a specialist for AF management, outcome from ED visit (i.e. hospitalization versus ED discharge), history of major bleeding and falls. One patient initiated on OAC in the ED was matched to up to two patients not prescribed OAC in the ED by logit of propensity score. Caliper width was set to 0.2 of pooled standard deviation of logit of propensity score.(26) We evaluated the quality of matching by standardized difference.(27) Conditional Poisson regression with robust error variance was conducted to account for the matched nature of the data. We performed statistical analyses using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

A total of 4149 patients with AF as their primary diagnosis were included in this analysis. Among these 4149 patients, patients had a mean age of 67, had a mean CHA_2DS_2-VASc score of 3.2, were attempted for cardioversion one third of the time, and frequently were still in AF at the time of leaving the ED. Table 1 summarizes full characteristics at baseline.

Rates of OAC Initiation

Upon leaving the ED, 1113 (26.8%) patients were initiated on OAC and 1232 (29.8%) were receiving OAC therapy at 1-year follow-up. The composite region of North America, Western Europe and Australia had the highest rate of initiating OAC in the ED and at 1-year follow up; while China had the lowest rate of OAC use (Table 2). After an ED visit, 34.0% of patients admitted to the hospital were initiated on OAC, and 32.5% were receiving OAC at 1

year. In contrast, among patients who were discharged from the ED, 16.2% of patients were initiated on OAC and 25.6% were receiving OAC at 1 year.

Predictors for Anticoagulation Use

Table 3 shows factors associated with OAC prescription in the ED. We also included the univariate analysis in Supplementary Table 1. Predictors of OAC prescription identified by multivariable analysis included: specialist consultation for AF management, having AF or atrial flutter status at the time of leaving the ED, admission to the hospital subsequently after the ED visit, history of rheumatic heart disease, and diabetes mellitus. Factors inversely associated with OAC initiation in the ED included patient having dementia or cognitive defects, taking antiplatelet agents prior to ED visit, and history of heart failure. We did not detect significant interaction effects between above-mentioned factors and outcome from ED visit.

Table 4 details the multivariable analysis of factors associated with OAC use at 1-year follow-up. Predictors of OAC use at 1year included: taking OAC at the time of leaving the ED and history of stroke or TIA. Factors inversely associated with OAC use by 1 year included male gender and cardioversion during the ED visit. Significant interaction effects with outcome from ED visit (i.e. hospital admission or discharge from ED) were detected for history of heart failure and specialist consultation for AF management. Among patients who were discharged home, both history of heart failure and specialist consultation for AF management were independent predictors of OAC use at 1-year visit (RR 1.43, 95%CI 1.22-1.68 and RR 3.10, 95%CI 2.31-4.16, respectively). Among patients who were admitted to hospital, however, neither of the factors were associated with OAC use at 1-year visit (RR 0.98, 95%CI 0.87-1.11 and RR 1.05 95%CI 0.81-1.37, respectively).

Outcomes at 1 Year

In Table 5, we summarized clinical outcomes at 1 year. In our analysis, 953 patients who left the ED on OAC were matched to 1576 patients not taking OAC using propensity scoring. Standardized differences for all the baseline variables and region factors included in the propensity score model between the matched groups were less than 0.1, suggesting sufficient balance (Supplemental Table 2). After matching, patients initiated on OAC in the ED had significantly lower rates of death (RR 0.55, 95%CI 0.38-0.79) and stroke (RR 0.59, 95%CI 0.37-0.96) at 1-year follow-up. The crude rate of major bleeding events was higher in patients started promptly on OAC (1.99% vs. 1.59%), but the difference was not statistically significant (RR 1.26, 95%CI 0.72-2.19).

DISCUSSION

In this global registry of patients presenting to an ED with a diagnosis of AF, we found that only one quarter of at-risk patients according to the CHA_2DS_2-VASC score were started on OAC. The rate of OAC use 1 year following an ED visit was approximately 3 times higher among patients who were started on OAC in the ED; and, initiating OAC was associated with a lower risk of stroke and death. Our results suggest that increasing the rate of OAC initiation promptly in the ED and including access to timely specialist care for AF management are needed to optimize stroke prevention strategies in this patient population.

Across the world, initiating OAC use during the ED visit varied extensively, from as low as 7% in low-income countries to 42% in North America, Europe and Australia. These low rates of OAC prescription in the ED are consistent with other studies and leave substantial room for improvement.(9-18) In this study, patients who had returned to sinus rhythm before ED discharge were less likely to be started on OAC. These results are consistent with other studies,

including the PINNACLE registry.(9, 19, 28) While paroxysmal AF is associated with a lower risk of stroke compared to persistent or permanent AF, this lower risk may not be sufficient to withhold OAC.(3, 19, 29-31)

Physicians were more likely to start OAC in patients with diabetes mellitus and rheumatic heart disease. This is expected as these patients are believed to be at higher risk; although, this paradigm for rheumatic heart disease has been challenged recently.(32-34) In contrast, OAC prescription during an ED visit was lower in patients with heart failure. Age, prior stroke or TIA showed no significant relationship with prescribing OAC in the ED. Hospital admission was associated with increased OAC use which may be expected as patients will have more opportunities to discuss AF management over the course of their stay. Similarly, coordinating AF management with a specialist resulted in higher rates of OAC prescription during an ED visit.

Typically, the ED is not the setting for primary prevention, as physicians must manage the whole department, and understand the potential consequences of increased wait times.(35) Instead, patients are frequently admitted to the hospital or referred to outpatient care for further discussion on AF management. In our study, we found that patients who were discharged home from the ED were three times as likely to be using OAC long term when a specialist (e.g. cardiologist, hematologist) was involved in evaluating AF management. A study by Atzema et al. suggested that patients referred to a primary care provider for AF management may also significantly reduce their hazard of death.(36) While most patients are seen within 30 days after their ED visit, (36) growing evidence suggests the initial encounter in the ED as a vital opportunity to introduce OAC for long-term stroke prevention.(20) Patients who were initiated on guideline recommended OAC in the ED were also 3 times more likely to be receiving OAC a

year later. Our findings are consistent with previous studies. In a retrospective study of 24 Canadian EDs with 137 patients, a prescription for warfarin by ED discharge had 76% of eligible patients still using warfarin at 1 year compared to 36% of patients for whom OAC was not initiated in the ED.(21) In a separate study of 2132 patients, patients initiated on OAC by ED discharge were more likely to fill a prescription a year later than those not started (63.7% vs 40.5%).(9) Although we did not account for all potential confounding variables, we found a reduction in deaths and strokes when initiating OAC early. Similarly, the EMERG-AF study of 1162 patients in 62 Spanish EDs found a reduction in mortality, and reported no increase in 1-year bleeding rates.(14) Our global registry adds evidence to a growing movement for early OAC in the ED to improve long-term stroke prevention.

Physicians working in the ED are in a unique position to introduce OAC and connect individuals with AF to outpatient care. For example, Rezazadeh et al. attached a reminder statement and a decision support package containing a guideline algorithm into charts of patients with a 12-lead-ECG showing AF.(15) This intervention increased rates of appropriate OAC use by 8.5%. In a prospective study of 301 patients, Barbic et al. found a 21.6% increase in appropriate OAC with an electronic clinical care pathway for patients with uncomplicated AF.(37) Moreover, in the C-CUSP ED study, Parkash et al. found a greater than 30% increase in OAC prescription when using their ED OAC prescription tool and referral plan.(38) Considering our findings, evidence-based clinical pathways that support initiation of short-term ED OAC prescriptions combined with coordination of outpatient follow-up by a specialist or primary care provider may be the optimal pathway to maximize long-term OAC use and to optimize patient outcomes. As these strategies continue to develop, it is important to explore how they function in other healthcare systems around the world. Ultimately, physicians who work in the ED will

consider the evidence, feasibility and patient interests when deciding whether to initiate guideline directed OAC in patients with AF.

LIMITATIONS

Our results may be subject to confounding by indication. Despite careful adjustment and matching for critical covariates and potential confounders, we cannot exclude residual confounding. While the CHA_2DS_2-VASc score is currently used to stratify stroke risk in patients with AF, only its predecessor, the $CHADS_2$ score was used in the first few years that patients were enrolled. We captured OAC use only at baseline and at 1-year follow-up. The main limitation of this study is that the RE-LY AF registry data are from an era where virtually all OAC treatment was with vitamin K anticoagulants.(9, 39) Although this registry is over five years old, it is one of the largest prospective registry studies of AF, with a significant number of patients from medium and low-income countries across all inhabited continents, and it is unlikely for a study of its size and scope to be repeated anytime soon. In addition, DOAC uptake may have increased OAC use; however, recent studies suggest similar issues remain present.

CONCLUSION

In this global registry of patients attending the ED with a primary diagnosis of AF, only one quarter of high-risk patients, according to the CHA_2DS_2-VASc score, was started on OAC. At 1-year, overall rates of OAC use remained low; however, rates were significantly higher in patients who had been started on OAC in the ED visit or who had seen a specialist for their AF management. System-wide initiatives are needed to support OAC prescribing from the ED and to coordinate subsequent follow-up.

TABLES

Table 1: Baseline characterisitics of primary AF patients started on OAC in the ED or not

Characteristics	OAC (N=1113)	No OAC (N=3036)	P value †
CHA_2DS_2-VASc score, mean ± SD	3.3±1.6	3.2±1.6	0.3
Age (years), mean ± SD	67.1±12.3	67.0±12.8	0.935
Age category:			0.773
<65, n (%)	398 (35.8)	1101 (36.3)	
65-74, n (%)	376 (33.8)	1045 (34.4)	
≥75, n (%)	339 (30.5)	890 (29.3)	
BMI (kg/m^2), mean ± SD	28.3±6.2	26.1±5.3	<0.001
BMI category:			<0.001
<20, n (%)	47 (4.2)	241 (7.9)	
20-30, n (%)	705 (63.3)	2172 (71.5)	
>30, n (%)	340 (30.5)	549 (18.1)	
Gender(male), n (%)	569 (51.1)	1556 (51.3)	0.941
MI or CAD, n (%)	310 (27.9)	1056 (34.8)	<0.001
Heart failure, n (%)	324 (29.1)	853 (28.1)	0.521
Rheumatic heart disease, n (%)	59 (5.3)	152 (5.0)	0.702
Permanent pacemaker, n (%)	35 (3.1)	79 (2.6)	0.344
Cardiac surgery <30 days ago, n (%)	9 (0.8)	29 (1.0)	0.661
Hypertension, n (%)	853 (76.6)	2189 (72.1)	0.003
Hemorrhagic stroke, n (%)	4 (0.4)	16 (0.5)	0.49
Ischemic stroke, n (%)	55 (4.9)	163 (5.4)	0.585
Unknown stroke, n (%)	7 (0.6)	25 (0.8)	0.526
TIA, n (%)	31 (2.8)	57 (1.9)	0.072
Sleep Apnea, n (%)	45 (4.0)	103 (3.4)	0.317
Tobacco use, n (%)	189 (17.0)	459 (15.1)	0.143
Dementia or cognitive defects, n (%)	16 (1.4)	66 (2.2)	0.131
Pericarditis, n (%)	7 (0.6)	14 (0.5)	0.5

Emphysema/COPD, n (%)	133 (11.9)	261 (8.6)	0.001
Diabetes mellitus, n (%)	278 (25.0)	555 (18.3)	<0.001
Hyperthyroidism, n (%)	50 (4.5)	110 (3.6)	0.198
Significant valvular heart disease, n (%)	128 (11.5)	508 (16.7)	<0.001
Valve Surgery, n (%)	30 (2.7)	67 (2.2)	0.356
Patient has had major bleeding before, n (%)	22 (2.0)	68 (2.2)	0.606
Diuretic, n (%)	372 (33.4)	1036 (34.1)	0.673
Calcium Channel Blockers, n (%)	295 (26.5)	641 (21.1)	<0.001
Beta-Blocker, n (%)	447 (40.2)	1190 (39.2)	0.573
ARB, n (%)	182 (16.4)	459 (15.1)	0.33
ACE Inhibitor, n (%)	392 (35.2)	888 (29.2)	<0.001
Digoxin, n (%)	84 (7.5)	523 (17.2)	<0.001
Anti-Platelet Agents, n (%)	475 (42.7)	1517 (50.0)	<0.001
Lipid Lowering Agents, n (%)	394 (35.4)	767 (25.3)	<0.001
Anti-arrhythmic, n (%)	166 (14.9)	511 (16.8)	0.139
Attempted cardioversion in ED, n (%)	373 (33.5)	1116 (36.8)	0.053
Patient leaving ED still in AF/flutter, n (%)	852 (76.5)	2146 (70.7)	<0.001
Consultation with a specialist for AF management, n (%)	1052 (94.5)	2404 (79.2)	<0.001
Admitted to hospital after ED visit, n (%)	844 (75.8)	1638 (54.0)	<0.001

Legend: BMI, body mass index; MI, myocardial infarction; CAD, coronary artery disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ARB, angiotensin II receptor blockers; ACE, angiotensin converting enzyme;
† P value is from Fisher's exact test or Chi-square test for categorical variables, depending on the expected cell counts, and two-sample t-test for continuous variables

Table 2: OAC initiation in the ED and use at 1-year follow up

	In the ED n/N (%)	**Use at 1-Year n/N (%)**
Overall	1113/4149 (26.8)	1232/4141 (29.8)
By Region		
N. Am/ W. Eur/ Aus.	386/918 (42.0)	432/918 (47.1)
Eastern Europe	356/898 (39.6)	304/898 (33.9)
Middle East	67/181 (37.0)	66/176 (37.5)
Africa	55/180 (30.6)	33/180 (18.3)
South America	78/365 (21.4)	106/364 (29.1)
Southeast Asia	41/199 (20.6)	47/197 (23.9)
India	89/782 (11.4)	212/782 (27.1)
China	41/626 (6.5)	32/626 (5.1)
By Patient Outcome from ED visit		
Admitted to Hospital	844/2482 (34.0)	806/2477 (32.5)
Discharged Home	269/1667 (16.2)	426/1664 (25.6)

Legend: N. Am, North America; W. Eur, Western Europe; Aus, Australia

Table 3: Multivariable analysis of factors associated with OAC initiation in the ED

Predictor	In the ED Relative Risk (95% CI)	P value
ED Management		
Consultation with a specialist for AF management*	1.84 (1.44-2.36)	<0.001
Patient still in AF/flutter	1.33 (1.18-1.50)	<0.001
Outcome from ED visit (admitted to hospital vs. discharged home)	1.30 (1.14-1.47)	<0.001
Demographics and Prior Medical History		
Rheumatic heart disease	1.60 (1.29-1.99)	<0.001
Diabetes mellitus	1.32 (1.19-1.47)	<0.001
Stroke/TIA	1.15 (0.97-1.37)	0.101
Heart failure	0.83 (0.74-0.94)	0.003
Anti-Platelet Agents	0.77 (0.69-0.84)	<0.001
Patient has had major bleeding before	0.77 (0.53-1.11)	0.162
Dementia or cognitive defects	0.61 (0.40-0.94)	0.025
Region (ref: N. Am/W. Eur/Aus.)		<0.001
Eastern Europe	0.93 (0.83-1.05)	
Middle East	0.76 (0.62-0.93)	
Africa	0.68 (0.54-0.87)	
South America	0.51 (0.41-0.62)	
Southeast Asia	0.50 (0.38-0.66)	
India	0.27 (0.22-0.34)	
China	0.18 (0.13-0.25)	

Legend: TIA, transient ischemic attack; N. Am, North America; W. Eur, Western Europe; Aus, Australia; CI, confidence interval

*Consultation or referral with a specialist (e.g. internist, cardiologist, hematologist) for AF management

Table 4: Multivariable analysis of factors associated with OAC use at 1-year follow up

Predictor	Use at 1-Year Relative Risk (95% CI)	P value
ED Management		
Consultation with a specialist for AF management*	3.10 (2.31-4.16)	<0.001
Initiating OAC use in the ED	2.81 (2.55-3.09)	<0.001
Outcome from ED visit (admitted to hospital vs. discharged home)	2.46 (1.69-3.59)	0.091
Cardioversion in the ED	0.84 (0.77-0.92)	<0.001
Demographics and Prior Medical History		
Heart failure	1.43 (1.22-1.68)	0.001
Stroke/TIA	1.25 (1.09-1.42)	0.001
Patient has had major bleeding before	1.11 (0.84-1.46)	0.459
Sex (male)	0.91 (0.83-0.98)	0.02
Interaction Effects of Predictors with Outcome from ED Visit		
Admitted to hospital × specialist consultation for AF management	0.34 (0.23-0.50)	<0.001
Admitted to hospital × heart failure	0.69 (0.57-0.84)	<0.001
Region (ref: N. Am/W. Eur/Aus.)		<0.001
Eastern Europe	0.71 (0.64-0.80)	
Middle East	0.87 (0.74-1.03)	
Africa	0.42 (0.32-0.56)	
South America	0.73 (0.61-0.87)	
Southeast Asia	0.64 (0.50-0.82)	
India	0.96 (0.84-1.10)	
China	0.19 (0.13-0.26)	

Legend: TIA, transient ischemic attack; N. Am, North America; W. Eur, Western Europe; Aus, Australia; CI, confidence interval

*Consultation or referral with a specialist (e.g. internist, cardiologist, hematologist) for AF management

Table 5: Effect of initiating OAC in the ED on clinical outcomes at 1-year follow-up in the unmatched and propensity score matched population

	Unmatched Population				**Matched Population***			
	OAC N = 1111	**No OAC N =3030**	**RR (95%CI)**	**P value**	**OAC N = 953**	**No OAC N = 1576**	**RR (95%CI)**	**P value**
Death	47 (4.2%)	232 (7.7%)	0.55 (0.41-0.75)	<0.001	36 (3.8%)	109 (6.9%)	0.55 (0.38-0.79)	0.001
Stroke	27 (2.4%)	109 (3.6%)	0.68 (0.45-1.02)	0.06	23 (2.4%)	64 (4.1%)	0.59 (0.37-0.96)	0.03
Major Bleeding	23 (2.1%)	35 (1.2%)	1.79 (1.06-3.02)	0.03	19 (2.0%)	25 (1.6%)	1.26 (0.72-2.19)	0.42

Legend: RR (95%CI), relative risk (95% confidence interval)
*Patients taking OAC in the ED visit were matched to up to two patients who were not started on OAC using propensity scoring.

Supplementary Material

Supplementary Table 1: Univariate analysis of factors associated with OAC initiation in the ED and use at 1-year follow up

Predictor	In the ED Relative Risk (95% CI)	P value	Use at 1-Year Relative Risk (95% CI)	P value
Age (years) (ref: <65)		0.524		0.229
65-74	0.99 (0.88-1.11)		1.09 (0.98-1.22)	
≥75	1.05 (0.93-1.18)		1.02 (0.91-1.15)	
BMI (kg/m^2) (ref: <20)		0.017		0.002
20~30	1.09 (0.83-1.42)		0.98 (0.79-1.22)	
>30	1.26 (0.95-1.65)		1.18 (0.94-1.48)	
Gender (male)	0.97 (0.88-1.07)	0.512	0.90 (0.82-0.99)	0.022
Heart failure	0.91 (0.81-1.02)	0.103	1.12 (1.00-1.25)	0.041
Rheumatic heart disease	1.64 (1.32-2.05)	<0.001	1.33 (1.08-1.63)	0.007
Hypertension	1.03 (0.92-1.16)	0.595	1.11 (1.00-1.24)	0.061
Stroke/TIA	1.10 (0.93-1.30)	0.278	1.32 (1.14-1.52)	<0.001
Sleep Apnea	0.92 (0.73-1.16)	0.484	0.99 (0.79-1.24)	0.94
Tobacco use	1.04 (0.92-1.18)	0.545	1.00 (0.88-1.13)	0.989
Dementia or cognitive defects	0.59 (0.38-0.91)	0.017	0.89 (0.62-1.27)	0.509
Diabetes mellitus	1.31 (1.18-1.46)	<0.001	1.05 (0.94-1.17)	0.378
Significant valvular heart disease	0.94 (0.80-1.10)	0.429	1.06 (0.93-1.21)	0.388
Valve Surgery	1.21 (0.88-1.65)	0.239	1.26 (0.98-1.61)	0.067

Patient has had major bleeding before	0.75 (0.52-1.08)	0.123	1.03 (0.79-1.34)	0.83
Anti-Platelet Agents	0.76 (0.69-0.84)	<0.001	0.90 (0.83-0.99)	0.029
Cardioversion in ED	0.87 (0.78-0.97)	0.009	0.81 (0.74-0.90)	<0.001
Patient still in AF/flutter	1.40 (1.24-1.57)	<0.001	1.34 (1.20-1.50)	<0.001
Consultation with a specialist for AF management*	2.08 (1.62-2.67)	<0.001	2.32 (1.86-2.90)	<0.001
Outcome from ED visit (admitted to hospital vs. discharged home)	1.53 (1.35-1.74)	<0.001	1.04 (0.94-1.15)	0.409
Initiating OAC use in the ED	N/A	-	2.89 (2.63-3.17)	<0.001

Legend: BMI, body mass index; TIA, transient ischemic attack; CI, confidence interval
*Consultation or referral with a specialist (e.g. internist, cardiologist, hematologist) for AF management

Supplementary Table 2: Evaluation of balance of baseline covariates in the unmatched and matched populations using propensity score matching*

	Unmatched Population			Matched Population		
	OAC in ED (N=1111)	**No OAC in ED (N=3030)**	**Standardized difference †**	**OAC in ED (N=953)**	**No OAC in ED (N=1576)**	**Standardized difference †**
Age (years), mean ± SD	67 ±12.3	67.0 ±12.8	0.0009	67.0 ±12.2	67 ±12.5	-0.0114
Gender(male), n(%)	568 (51.1)	1551 (51.2)	-0.0013	490 (51.4)	792 (50.3)	0.0233
Heart failure, n(%)	323 (29.1)	853 (28.2)	0.0204	285 (29.9)	473 (30.0)	-0.0023
Hypertension, n(%)	851 (76.6)	2185 (72.1)	0.1029	717 (75.2)	1201 (76.2)	-0.0226
Stroke/TIA, n(%)	97 (8.7)	261 (8.6)	0.0042	85 (8.9)	139 (8.8)	0.0035
Diabetes mellitus, n(%)	276 (24.6)	554 (18.3)	0.1600	215 (22.6)	348 (22.1)	0.0115
Significant valvular heart disease, n(%)	128 (11.5)	507 (16.7)	-0.1500	109 (11.4)	187 (11.9)	-0.0133
Rheumatic heart disease, n(%)	59 (5.3)	151 (5.0)	0.0148	50 (5.2)	76 (4.8)	0.0194
Dementia or cognitive defects, n(%)	16 (1.4)	66 (2.2)	-0.0554	15 (1.6)	30 (1.9)	-0.0252
Anti-Platelet Agents, n(%)	473 (42.6)	1515 (50.0)	-0.1493	411 (43.1)	744 (47.2)	-0.0821
Patient still in AF/flutter, n(%)	851 (76.6)	2143 (70.7)	0.1336	721 (75.7)	1145 (72.7)	0.0686

Referred to specialist for AF, n(%)	1050 (94.5)	2398 (79.1)	0.4653	892 (93.6)	1460 (92.6)	0.0379
History of major bleeding, n(%)	22 (2.0)	68 (2.2)	-0.0184	19 (2.0)	39 (2.5)	-0.0325
History of falls, n(%)	82 (7.4)	199 (6.6)	0.0320	75 (7.9)	128 (8.1)	-0.0093
Outcomes from ED visit (admitted)	842 (75.8)	1635 (54.0)	0.4689	705 (74.0)	1137 (72.1)	0.0413
Regions						
North America/Western Europe/Australia, n(%)	386 (34.7)	532 (17.6)	0.3988	311 (32.6)	474 (30.1)	0.0552
South America, n(%)	78 (7.0)	286 (9.4)	-0.0881	70 (7.3)	134 (8.5)	-0.0429
Eastern Europe, n(%)	356 (32.0)	542 (17.9)	0.3315	303 (31.8)	472 (29.9)	0.0399
Middle East, n(%)	65 (5.9)	111 (3.7)	0.1029	57 (6.0)	91 (5.8)	0.0088
Africa, n(%)	55 (5.0)	125 (4.1)	0.0396	43 (4.5)	76 (4.8)	-0.0147
India, n(%)	89 (8.0)	693 (22.9)	-0.4202	87 (9.1)	165 (10.5)	-0.0451
China, n(%)	41 (3.7)	585 (19.3)	-0.5049	41 (4.3)	82 (5.2)	-0.0423
Southeast Asia, n(%)	41 (3.7)	156 (5.1)	-0.0710	41 (4.3)	82 (5.2)	-0.0423

Legend: TIA, transient ischemic attack

* Caliper width for propensity score matching was set to 0.2 of pooled standard deviation of logit of propensity score. Each patient with OAC after ED visit was matched to up to 2 patients without OAC after ED visit

† A standardized difference <0.1 was considered as a negligible difference between groups

REFERENCES

1. Stiell IG, Macle L. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: management of recent-onset atrial fibrillation and flutter in the emergency department. Can J Cardiol. 2011;27(1):38-46.
2. Wakai A, O'Neill JO. Emergency management of atrial fibrillation. Postgrad Med J. 2003;79(932):313-9.
3. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al. 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 Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1-76.
4. Macle L, Cairns J, Leblanc K, Tsang T, Skanes A, Cox JL, et al. 2016 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Canadian Journal of Cardiology. 2016;32(10):1170-85.
5. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European journal of cardio-thoracic surgery. 2016;50(5):e1-e88.
6. Xian Y, O'Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC, et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. Jama. 2017;317(10):1057-67.
7. Dlott JS, George RA, Huang X, Odeh M, Kaufman HW, Ansell J, et al. National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation. Circulation. 2014;129(13):1407-14.
8. Cowan C, Healicon R, Robson I, Long WR, Barrett J, Fay M, et al. The use of anticoagulants in the management of atrial fibrillation among general practices in England. Heart. 2013;99(16):1166-72.
9. Atzema CL, Jackevicius CA, Chong A, Dorian P, Ivers NM, Parkash R, et al. Prescribing of oral anticoagulants in the emergency department and subsequent long-term use by older adults with atrial fibrillation. CMAJ. 2019;191(49):E1345-E54.
10. Laguna P, Martn A, del Arco C, Gargantilla P, Investigators in the Spanish Atrial Fibrillation in Emergency Medicine Study G. Risk Factors for Stroke and Thromboprophylaxis in Atrial Fibrillation: What Happens in Daily Clinical Practice? The GEFAUR-1 Study. Ann Emerg Med. 2004;44(1):3-11.
11. Scheuermeyer FX, Innes G, Pourvali R, Dewitt C, Grafstein E, Heslop C, et al. Missed opportunities for appropriate anticoagulation among emergency department patients with uncomplicated atrial fibrillation or flutter. Ann Emerg Med. 2013;62(6):557-65.e2.
12. Coll-Vinent B, Martin A, Malagon F, Suero C, Sanchez J, Varona M, et al. Stroke prophylaxis in atrial fibrillation: searching for management improvement opportunities in the emergency department: the HERMES-AF study. Ann Emerg Med. 2015;65(1):1-12.
13. Scott-Herridge JA, Seifer CM, Steigerwald R, Drobot G, McIntyre WF. A multi-hospital analysis of predictors of oral anticoagulation prescriptions for patients with actionable atrial fibrillation who attend the emergency department. Acute Card Care. 2016;18(4):71-8.
14. Coll-Vinent B, Martín A, Sánchez J, Tamargo J, Suero C, Malagón F, et al. Benefits of emergency departments' contribution to stroke prophylaxis in atrial fibrillation: the EMERG-AF study (Emergency Department Stroke Prophylaxis and Guidelines Implementation in Atrial Fibrillation). Stroke. 2017;48(5):1344-52.

15. Rezazadeh S, Chew DS, Miller RJH, Klassen S, Pournazari P, Bennett G, et al. Effects of a reminder to initiate oral anticoagulation in patients with atrial fibrillation/atrial flutter discharged from the emergency department: REMINDER study. Cjem. 2018;20(6):841-9.
16. Miller RJH, Chew DS, Rezazadeh S, Klassen S, Pournazari P, Lang E, et al. Factors Influencing Oral Anticoagulation Prescription for
Patients Presenting to Emergency Departments With Atrial
Fibrillation and Flutter. *Can J Cardiol*. 2018;34(6):804–7.
17. Stiell IG, Clement CM, Rowe BH, Brison RJ, Wyse DG, Birnie D, et al. Outcomes for emergency department patients with recent-onset atrial fibrillation and flutter treated in Canadian hospitals. Annals of emergency medicine. 2017;69(5):562-71. e2.
18. Misra P, Lang E, Clement CM, Brison RJ, Rowe BH, Borgundvaag B, et al. Emergency physician patterns related to anticoagulation of patients with recent-onset atrial fibrillation and flutter. Journal of atrial fibrillation. 2013;5(6).
19. Vinson DR, Warton EM, Mark DG, Ballard DW, Reed ME, Chettipally UK, et al. Thromboprophylaxis for patients with high-risk atrial fibrillation and flutter discharged from the emergency department. Western Journal of Emergency Medicine. 2018;19(2):346.
20. Atzema CL. Stroke Prevention for High-Risk Atrial Fibrillation in the Emergency Setting: The Emergency Physician Perspective. Can J Cardiol. 2018;34(2):125-31.
21. Atzema CL, Austin PC, Chong AS, Dorian P, Jackevicius CA. The Long-Term Use of Warfarin Among Atrial Fibrillation Patients Discharged From an Emergency Department With a Warfarin Prescription. Ann Emerg Med. 2015;66(4):347-54.e2.
22. TW B, KA M. Anticoagulation for emergency department patients with atrial fibrillation: is our duty to inform or prescribe? Ann Emerg Med. 2013;62(6):566-8.
23. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. Lancet (London, England). 2016;388(10050):1161-9.
24. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, et al. Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. Circulation. 2014;129(15):1568-76.
25. Bank W. World Bank list of economies 2011 2011 [Available from: https://openknowledge.worldbank.org/handle/10986/2124.
26. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharmaceutical statistics. 2011;10(2):150-61.
27. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine. 2009;28(25):3083-107.
28. Hsu JC, Chan PS, Tang F, Maddox TM, Marcus GM. Oral anticoagulant prescription in patients with atrial fibrillation and a low risk of thromboembolism: insights from the NCDR PINNACLE Registry. JAMA internal medicine. 2015;175(6):1062-5.
29. Stiell IG, Scheuermeyer FX, Vadeboncoeur A, Angaran P, Eagles D, Graham ID, et al. CAEP acute atrial fibrillation/flutter best practices checklist. Canadian Journal of Emergency Medicine. 2018;20(3):334-42.

30. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, et al. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. European heart journal. 2015;36(5):281-8.
31. Lilli A, Di Cori A, Zaca V. Thromboembolic risk and effect of oral anticoagulation according to atrial fibrillation patterns: A systematic review and meta-analysis. Clinical cardiology. 2017;40(9):641-7.
32. Wolf PA, Dawber TR, Thomas HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The fiamingham Study. Neurology. 1978;28(10):973-.
33. Wang D, Liu M, Lin S, Hao Z, Tao W, Chen X, et al. Stroke and rheumatic heart disease: a systematic review of observational studies. Clinical neurology and neurosurgery. 2013;115(9):1575-82.
34. Benz A, Healey J, Marsden T, Karthikeyan G, Hohnloser S, Oldgren J, et al. STROKE RISK PREDICTION IN PATIENTS WITH ATRIAL FIBRILLATION AND RHEUMATIC HEART DISEASE: RESULTS FROM THE RE-LY AF REGISTRY. Canadian Journal of Cardiology. 2019;35(10):S5.
35. Kelen GD. Public health initiatives in the emergency department: not so good for the public health? Academic emergency medicine: official journal of the Society for Academic Emergency Medicine. 2008;15(2):194.
36. Angaran P, Mariano Z, Dragan V, Zou L, Atzema CL, Mangat I, et al. The atrial fibrillation therapies after ER visit: outpatient care for patients with acute AF-The AFTER3 Study. Journal of atrial fibrillation. 2015;7(5).
37. Barbic D, DeWitt C, Harris D, Stenstrom R, Grafstein E, Wu C, et al. Implementation of an emergency department atrial fibrillation and flutter pathway improves rates of appropriate anticoagulation, reduces length of stay and thirty-day revisit rates for congestive heart failure. Canadian Journal of Emergency Medicine. 2018;20(3):392-400.
38. Parkash R, Magee K, McMullen M, Clory M, D'Astous M, Robichaud M, et al. The Canadian Community Utilization of Stroke Prevention study in atrial fibrillation in the emergency department (C-CUSP ED). Annals of emergency medicine. 2019;73(4):382-92.
39. Hawkins NM, Scheuermeyer FX, Youngson E, Sandhu RK, Ezekowitz JA, Kaul P, et al. Impact of cardiology follow-up care on treatment and outcomes of patients with new atrial fibrillation discharged from the emergency department. EP Europace. 2020;22(5):695-703.

CHAPTER 3: COMPARING THE SAFETY AND EFFICACY OF DOACS VERSUS VKA AFTER CARDIAC SURGERY

Direct oral anticoagulation versus vitamin K antagonists for atrial fibrillation following cardiac surgery: a systematic review and meta-analysis

Pablo A. Mendoza,[1,2] Hatim Alraddadi,[1,2,6] William F. McIntyre,[1,2,3] John Eikelboom,[2,4] Jeff S. Healey,[1,2,3] Sam Schulman,[1,4,5] Vivek Rao,[6] Renato D. Lopes,[8] Michael E. Farkouh,[6] Richard P. Whitlock,[1,2,7] Emilie P. Belley-Côté[2,3]

Affiliations:

1. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada
2. Population Health Research Institute, McMaster University, Hamilton, Canada
3. Division of Cardiology, Department of Medicine, McMaster University, Hamilton, Canada
4. Division of Hematology & Thromboembolism, Department of Medicine, McMaster University, Hamilton, Canada
5. Department of Obstetrics and Gynecology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia
6. Peter Munk Cardiac Centre , Heart and Stroke Richard Lewar Centre, University of Toronto, Toronto, Ontario
7. Division of Cardiac Surgery, Department of Surgery, McMaster University, Hamilton, Canada
8. Division of Cardiology, Department of Medicine, Duke University Medical Center and Duke Clinical Research Institute

2243 words, 3 tables, 4 figures, 4 supplemental tables and figures, 31 references

ABSTRACT

Aims: To assess the safety and efficacy of direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) in patients requiring anticoagulation after recent cardiac surgery.

Methods: We searched MEDLINE, EMBASE and CENTRAL until June 2020 and included studies that compared outcomes for patients given DOACs or VKAs for any indication after cardiac surgery. We excluded studies if >5% of patients were undergoing a mechanical valve replacement or had antiphospholipid syndrome. Independently and in duplicate, reviewers screened titles, abstracts, and full text of potentially eligible studies. We pooled observational studies using a random effects model and assessed quality of evidence using GRADE.

Results: Eight observational studies met eligibility criteria, representing 38 345 patients: 13 180 (34%) patients received DOACs and 25 165 (66%) patients received VKAs. No randomized controlled trials met eligibility criteria. In the first 30 days after surgery, DOACs were associated with a significant reduction in major bleeding events (risk ratio [RR] 0.75; 95% confidence interval [CI] 0.59-0.94, $I^2 = 0\%$). We found no significant difference in risk of stroke (RR 0.76; 95% CI 0.55-1.05, $I^2 = 0\%$), or death (RR 1.20; 95% CI 0.98-1.47, $I^2 = 0\%$). Quality of evidence was very low due to risk of bias, indirectness and imprecision.

Conclusions: DOACs may be an alternative to VKAs in the initial weeks after cardiac surgery. Given the very low confidence in the current data, a randomized trial is needed to determine whether DOACs are a safe alternative to VKAs early after cardiac surgery.

INTRODUCTION

Of patients undergoing cardiac surgery, 7% require anticoagulation pre-operatively. By the time of discharge after surgery, 32% have an indication for oral anticoagulation (PJ Devereaux, Principal Investigator of VISION Cardiac Surgery, unpublished data, 2019). Optimal antithrombotic strategies after cardiac surgery remain uncertain.

Until 2008, vitamin K antagonists (VKAs) were the only oral anticoagulants (OAC) available. Although effective, their use is limited by a narrow therapeutic index requiring frequent international normalized ratio (INR) measurements to ensure appropriate levels of anticoagulation,(1) leading to underuse, non-compliance and discontinuation.(2, 3)

In the last decade, direct oral anticoagulants (DOACs) – inhibitors of factor Xa or thrombin – have become broadly used.(4) In patients with AF requiring long term stroke prevention, DOACs yield lower rates of thromboembolism, and a lower risk of intracranial bleeding when compared to VKAs during long-term follow-up.(5-8) Moreover, DOACs have a rapid onset of effect, fixed dosage that obviates the need for regular monitoring, and few interactions with food and other medications.(9)

The safety of DOACs in the early weeks after cardiac surgery remains uncertain. Caution around DOACs after cardiac surgery stems from the Randomized, Phase II Study to Ev2aluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE- ALIGN) trial.(10) The RE-ALIGN trial compared the safety of dabigatran to warfarin after mechanical valve replacement. Patients on dabigatran had a significantly higher rate of major bleeding (hazard ratio [HR] 2.45; 95% confidence interval [CI], 1.23 to 4.86; P = 0.01) early after surgery. In addition, 7 patients experienced a pericardial bleeding in the dabigatran arm as compared to 2 patients in the warfarin arm. Although the difference did not

reach statistical significance (HR 1.76; 95% CI 0.36-8.45; p=0.48), these results have led some clinicians to avoid DOACs in the early period after cardiac surgery.(10, 11)

Despite the lack of high quality evidence, resumption or initiation of DOACs early after cardiac surgery is becoming more common.(11, 12) To address this, we performed a systematic review of studies comparing the safety and efficacy of DOACs compared to VKAs in patients requiring anticoagulation after cardiac surgery.

RESEARCH QUESTION

In adults requiring anticoagulation after cardiac surgery, does treatment with DOAC compared with VKA impact the incidence of major bleeding, stroke events and mortality after surgery?

METHODS

Prior to beginning our study, we registered our protocol with PROSPERO (CRD42019141097).

Search Strategy

We searched EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) from 2009 to June 2020 using a search strategy designed with the support of a research librarian (Supplementary Tables 1, 2 and 3). We started our search from 2009 because this is when the first indication-seeking DOAC trial was published.(7) We also searched Clinicaltrials.gov, the World Health Organization (WHO) International Clinical Trial Registry Platform (ICTRP), and the International Standard Registered Clinical/Social Study Number (ISRCTN) registry for relevant ongoing or unpublished studies. Along with searching the

references of included studies, we reviewed the conference proceedings for the last 2 years of the European Society of Cardiology, European Association for Cardio-Thoracic Surgery. American College of Cardiology, American Heart Association, and the Society of Thoracic Surgeons. We also inquired with topic experts about unidentified studies.

Study Selection

In duplicate, two reviewers (PM and HA) independently screened titles and abstracts of identified references using Covidence online.(13) If a reviewer deemed a study potentially relevant, its full text was reviewed independently and in duplicate. A third investigator resolved conflicts regarding eligibility.

Eligibility Criteria

The population of interest was adults requiring OAC for any indication following cardiac surgery. Studies were included if they compared DOACs (i.e. apixaban, dabigatran, rivaroxaban, edoxaban), with VKAs. We excluded studies if >5% of patients were undergoing a mechanical valve surgery or had antiphospholipid syndrome. Outcomes of interest included major bleeding, stroke, arterial systemic embolism, mortality, length of hospital stay, patient satisfaction, and quality of life measured in the 30 days and 90 days after cardiac surgery. We included randomized controlled trials (RCTs) and comparative observational studies with no language restrictions.

Data Abstraction and Management

For included studies, two reviewers independently abstracted data using Covidence online software. (13) Abstracted data included author name and institution, study design, population demographics per group (DOAC and VKA), indication for anticoagulation, length

and dosage of interventions, outcome definitions and outcome data. We contacted the corresponding authors when data of interest were missing in the primary report.

Risk of Bias Assessment

For observational studies, we used tools designed by the Clinical Advances Through Research and Information Translation (CLARITY) research group at McMaster University.(14) These tools contained eight questions: 1) Were patients in the exposed and non-exposed cohorts drawn from the same population? 2) Can we be confident in the assessment of exposure? 3) Can we be confident that the outcome of interest was not present at start of study? 4) Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? 5) Can we be confident in the assessment of the presence or absence of prognostic factors? 6) Can we be confident in the assessment of outcome? 7) Was the follow up of cohorts adequate? 8) Were co-interventions similar between groups? The tool uses the terminology of 'definitely yes/ probably yes/ probably no/ definitely no' in response to each question. If any of the questions were answered with 'definitely no' then we considered the study to have a high risk of bias. If one or more questions were answered 'probably yes or probably no,' then we considered the study to have unclear risk of bias. If all questions were answered as 'definitely yes,' then we considered the study to have low risk of bias. We resolved disagreement in risk of bias evaluation through discussion.

For randomized controlled trials, we planned to use the Revised Cochrane risk of bias tool and the accompanying users guide.(15)

Statistical Analyses

We performed analyses using Review Manager 5.4 software (Cochrane

Collaboration). Where multiple studies were sufficiently homogenous in describing an outcome, we used a random effects model to generate a pooled estimate of effect. Our pooled estimates are presented as a risk ratio (RR) with 95% CI. We assessed heterogeneity by inspecting the forest plots in conjunction with the I^2 statistic and a χ^2 test (statistical significance set at $p<0.10$).(16) In the presence of 10 or more studies addressing the same outcome, we planned to use a funnel plot to visually assess for publication bias.

Subgroup Analyses

We prespecified three exploratory subgroup analyses: low risk of bias versus high/unclear, type of DOAC, and type of cardiac surgery. However, data were insufficient to perform these analyses.

Quality of Evidence Assessment

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess quality of evidence. GRADE appraises the certainty of evidence per outcome by considering within study risk of bias, inconsistency, indirectness, imprecision, and potential publication bias.

RESULTS

We screened 2697 citations, reviewed 49 full-text report, and ultimately included 8 comparative observational studies (Figure 1). No published RCTs to date has answered this question. The 8 retrospective observational studies meeting eligibility criteria included a total of 38 345 patients, of which 13 180 (34%) received a DOAC and 25 165 (66%) received a VKA after cardiac surgery.(12, 17-24) Characteristics of included studies are presented in Table 1.

Major bleeding

Eight studies reported on major bleeding within 30 days after surgery (Figure 2). Pooled data from 38 247 patients with 381 events demonstrated a significant reduction in major bleeding with DOACs compared to VKAs (RR 0.75; 95% CI 0.59-0.94). Event rates were 0.7% (range: 0-10.2%) with DOACs, and 1.1% (range:0-21.9%) with VKAs. We rated the overall evidence for this outcome at 30 days as very low quality due to risk of bias and indirectness (Supplementary Table 4). In contrast, at 90 days after surgery pooled data showed no significant difference in major bleeding events with DOACs compared to VKA (RR 0.97; 95% CI 0.61-1.55) (Supplementary Figure 1).

Stroke

Six studies reported stroke events within 30 days after cardiac surgery (Figure 3). Stroke rates were 0.4% (range: 0-6.1%) with DOACs, and 0.6% (range: 0-2.1%) with VKAs. Pooled data of 37 953 patients with 213 events showed no significant difference in stroke events with DOACs compared to VKAs (RR 0.76; 95% CI 0.55-1.05). We rated the overall evidence for this outcome at 30 days as very low quality due to risk of bias, indirectness and imprecision (Supplementary Table 4). Moreover, at 90 days after surgery pooled data showed no significant difference in stroke events with DOACs compared to VKA (RR 0.75; 95% CI 0.55-1.03) (Supplementary Figure 2).

Mortality

Three studies reported deaths within 30 days after cardiac surgery (Figure 4). Pooled data from 37 671 patients with 398 vents showed no significant difference in death rates with DOACs compared to VKAs (RR 1.20; 95% CI 0.98-1.47) Patients on DOACs had a mortality rate of 1.2% (range: 0.9-4.1), while patients on VKAs had a 1% mortality rate (range: 0.6-3.1%). We rated the overall evidence for this outcome at 30 days as very low quality due to

risk of bias and imprecision (Supplementary Table 4). Similarly, at 90 days after surgery pooled data showed no significant difference in death events with DOACs compared to VKA (RR 1.18; 95% CI 0.97-1.44) (Supplementary Figure 3).

Post-operative length of stay

Patients given DOAC had a shorter length of hospital stay after surgery. Detailed results are presented in Table 2.

DISCUSSION

Key Findings

In this systematic review and meta-analysis of comparative observational studies, DOACs, as compared to VKAs, were associated with a reduction in major bleeding within 30 days post cardiac surgery. DOACs were not associated with differences in the risk of stroke or death. However, post-operative length of stay was shorter in patients who received DOACs. At 90 days post cardiac surgery, there was no significant difference in rates of major bleeding, strokes or death rates between OAC type. The confidence in the estimates of effect is diminished by the very low quality of the data.

Context within the literature

To our knowledge, this is the first systematic review and meta-analysis to compare DOACs to VKAs in patients requiring anticoagulation after cardiac surgery. Other, indirect evidence suggests that using DOACs after noncardiac surgery may be safe. A recent systematic review pooled 4 sub-studies of the landmark DOAC trials, comparing DOACs to warfarin in the periprocedural setting in 16,253 patients (25). This analysis found no significant difference

between DOACs and VKA with respect to major bleeding (2.1% versus 2.0%; RR 1.05; 95% CI 0.85-1.30) or stroke/systemic embolism (0.4% versus 0.5%; pooled RR 0.95; 95% CI 0.59-1.55) at 30 days post-surgery when OAC therapy was interrupted and resumed after surgery. While this was a sizeable meta-analysis, very few patients (n ~157, ≤2%) underwent cardiac surgery in these trials. One other study informs on the safety of DOACs after cardiac surgery. The Cardiovascular Outcomes for People Using Anticoagulation Strategies – Coronary Artery Bypass Grafting (COMPASS – CABG) sub-study, evaluating low-dose rivaroxaban among 1448 participants, found no increase in major bleeding in the first 30 post-operative days when started on rivaroxaban within 4 and 14 days after surgery.(26) Major bleeding in the first 30 days after (CABG) occurred in 2 (0.4%) participants who received rivaroxaban (2.5 mg BID) plus aspirin, 1 (0.2%) who received rivaroxaban alone (5 mg BID), and 5 (1.1%) who received aspirin alone.(26) Although this study are re-assuring, they represent indirect evidence as the risk of pericardial bleeding after noncardiac surgery is almost non-existent and the doses of rivaroxaban studied in COMPASS were lower than the atrial fibrillation (AF) doses.

Interpretation of findings

Our results suggest that DOACs may be a safe alternative to VKAs in patients who have recently undergone cardiac surgery. However, given the very low quality of the current body of evidence, these results have to be interpreted with caution. Randomized studies are required to determine if DOACs are a safe and effective alternative to VKAs in this patient population.

Our confidence in these data is further weakened because of the divergence in outcomes: DOACs were associated with a non-significant increase in mortality, a non-significant reduction in stroke and a reduction in bleeding. While the associations with stroke and bleeding are aligned

with the results of large DOAC trials, the non-significant increase in mortality raises the question of confounding.

The European Heart Rhythm Association (EHRA) completed a survey among 16 centres in 14 countries to assess current practice related to OAC use in patients with AF after cardiac surgery.(27) One quarter of respondents reported that they did not use DOACs in this setting. Respondent reported rates of post-operative pericardial bleeding ranging from 0 to 6.5%, and one third of the respondents perceived the use of DOACs in this setting to increase the risk of bleeding, compared to VKAs. While studies suggest an increase in DOAC use after cardiac surgery, VKAs continue to be the predominant choice of OAC.(12) The authors of the survey concluded by calling for more data to uniform practice guidelines. The need for further data is also highlighted in an American College of Cardiology (ACC) Clinical Expert Document Taskforce.(11)

Four ongoing randomized controlled trials are exploring this question (Table 3). Dyke and colleagues are performing a 56-participant pilot trial comparing apixaban to warfarin for the management of AF after CABG.(28) Voisine and colleagues are enrolling in a 206-participant RCT comparing DOAC to warfarin in patients with AF after cardiac surgery. (29) Osho and colleagues are undertaking a 300-participant RCT comparing rivaroxaban to warfarin for patients with AF after cardiac surgery.(30) Our group is beginning the vanguard phase of the Direct oral AnticoagulatioN versus warfarin after Cardiac surgEry (DANCE) international randomized controlled trial (NCT04284839), where we will recruit 400 patients with AF requiring OAC to determine feasibility of the a definitive trial enrolling approximately 6000 patients from 30 countries.

Strengths and limitations

Our systematic review has several strengths including a pre-registered protocol, a well-designed search strategy, and rigorous methods. In addition, we included unpublished subgroup data from the RE-LY trial, and, created a comprehensive summary of all present evidence around this topic. Our work is limited by the quality of the included studies - none presented adjusted analyses, limited information in studies published as abstracts only, and heterogenous outcome definitions.

Conclusions

DOACs may be an alternative to VKAs in the initial weeks after cardiac surgery. Given the very low confidence in the current data and indirect external evidence suggesting an increased risk of pericardial bleeding, a rigorous trial is needed to determine whether DOACs are a safe alternative to VKAs early after cardiac surgery.

FIGURES

Figure 1: PRISMA systematic review flow diagram for searching and selecting studies

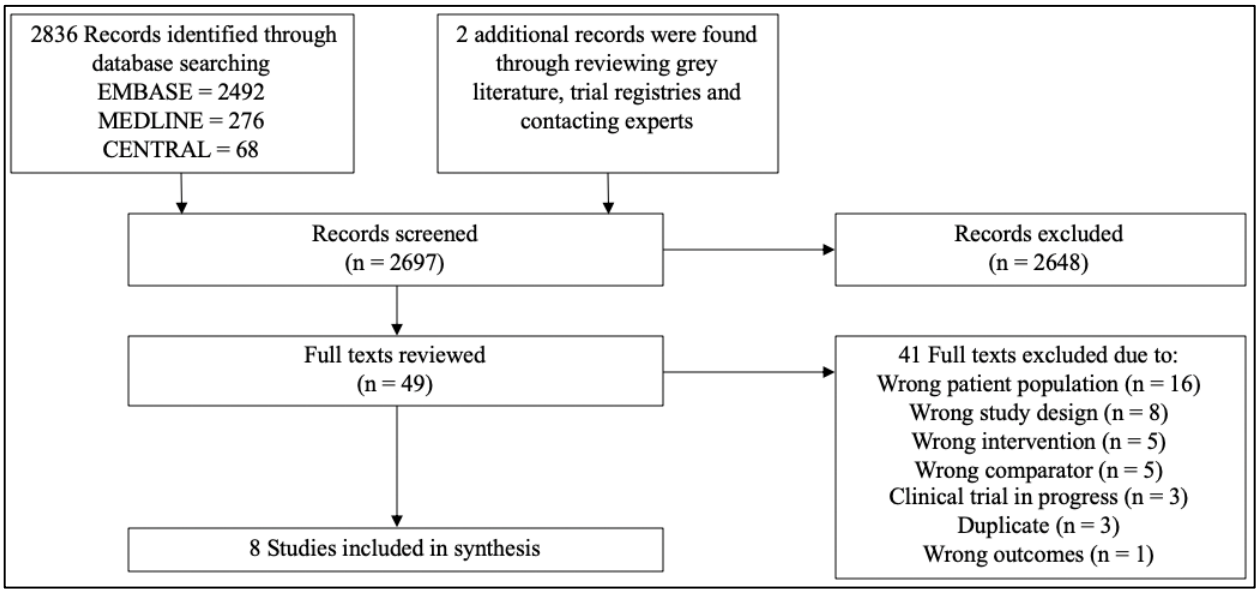


Figure 2: Forest plot of major bleeding events within 30 days post-surgery

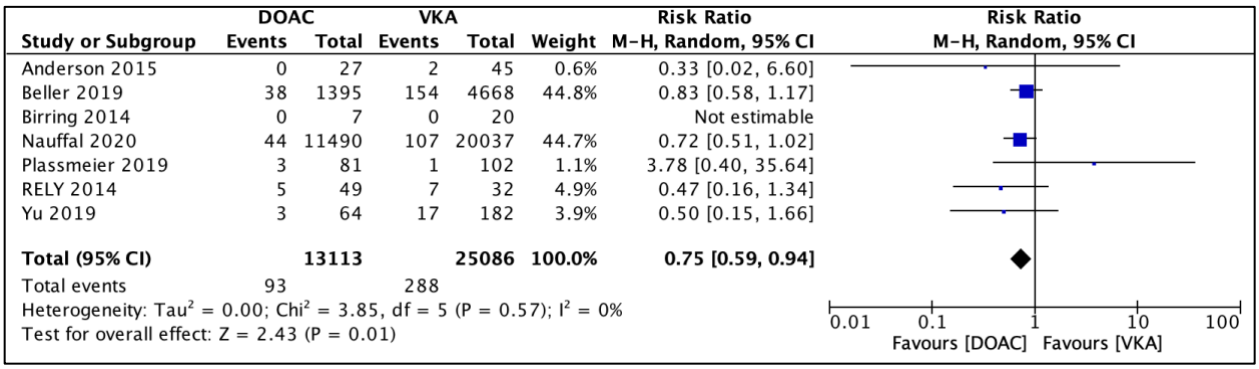


Figure 3: Forest plot of stroke events within 30 days post-surgery

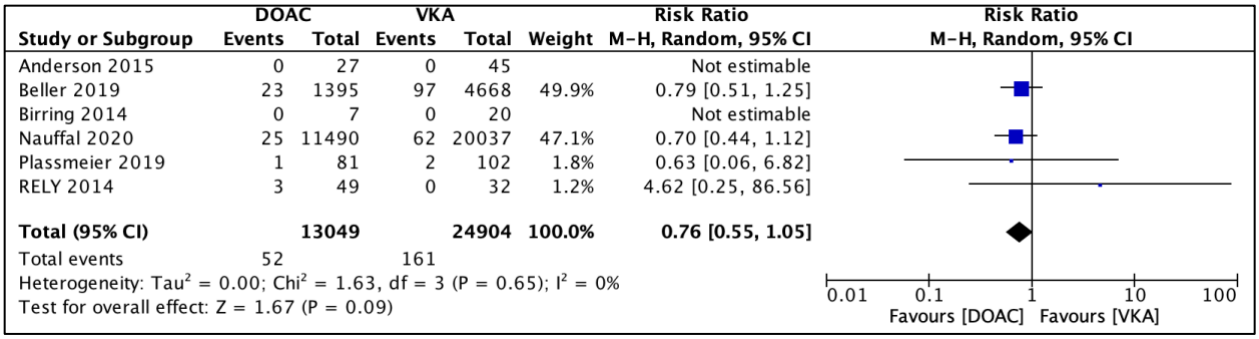
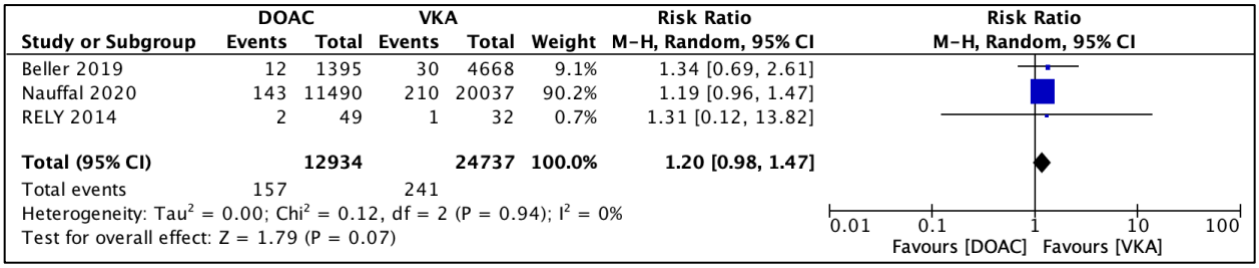


Figure 4: Forest plot of death within 30 days post-surgery



TABLES

Table 1: Characteristics included studies

Study	Data Source	Population	Intervention		Outcomes	Follow Up
Anderson 2015	Retrospective analysis at 1 large tertiary centre (2013-2015) *Full paper	Patients with new-onset AF following an isolated CABG	27 DOAC (apixaban, dabigatran, rivaroxaban)	45 warfarin (62% bridged)	Major bleed Minor bleed Stroke Mortality	4 weeks after surgery
Yu 2019	Retrospective analysis (2014-2017) *Full paper	Patients undergoing isolated CABG with any indication requiring anticoagulation	64 DOAC (apixaban, dabigatran, rivaroxaban)	182 warfarin (57% bridged)	Major bleed (pericardial and pleural effusion requiring invasive intervention) Post-operative length of stay	During index hospital stay & 3 months after discharge
RELY 2014	Retrospective analysis (2005-2009) *Unpublished data	Patients with pre-existing AF undergoing isolated CABG	49 DOAC (dabigatran)	32 warfarin (bridging unreported)	Major bleed Minor bleed Stroke Mortality Post-operative length of stay	30 & 90 days after surgery
Birring 2014	Retrospective analysis from the National Adult Cardiac Surgery Database in UK (2014) *Abstract	Patients with new-onset AF following cardiac surgery (unspecified)	7 DOAC (dabigatran)	20 warfarin (bridging unreported)	Major bleed† Stroke† Post-operative length of stay	Until hospital discharge

Study	Data Source	Population	Intervention		Outcomes	Follow Up
Patel 2018	Retrospective analysis at 1 centre (2014-2017) *Abstract	Patients with new-onset AF following isolated CABG	67 DOAC (apixaban, dabigatran, rivaroxaban)	79 warfarin (bridging unreported)	Major bleed Minor bleed Stroke Post-operative length of stay	Not reported
Beller 2019	Retrospective analysis from the Virginia Cardiac Services Quality Initiative (2011-2018) *Full paper	Patients undergoing bioprosthetic valve replacement or CABG with any indication requiring anticoagulation	1395 DOAC	4668 warfarin (bridging unreported)	Reoperation for bleeding complications Permanent stroke VTE Mortality Post-operative length of stay	30 days after surgery
Nauffal 2020	Retrospective analysis from the Society of Thoracic Surgery National Database (2017-2018) *Abstract	Patients with new-onset AF following cardiac surgery	11490 DOAC	20037 warfarin (bridging unreported)	Readmission for bleeding complications Stroke/TIA Mortality	30 days after surgery
Plassmeier 2019	Retrospective analysis from patients within the Indiana University Heath System (2014-2018) *Abstract	Patients with AF (onset unspecified) undergoing bioprosthetic valve replacement	81 DOAC	102 Warfarin (bridging unreported)	Major bleeding Stroke or systemic embolism	30 & 90 days after surgery

Table 2: Post-operative length of stay

Study	Mean/ median	Intervention	
		DOAC	VKA
Anderson 2015	Mean	6.6 days (SD not reported)	7.3 days (SD not reported)
Yu 2019	Median	8 days (IQR 6-9 days)	9 days (IQR 7-13 days)
RE-LY 2014	Median	9 days (IQR 7-13 days)	8 days (IQR 7-13 days)
Birring 2014	Mean	2.7 (SD not reported)	3.5 days (SD not reported)
Patel 2018	Median	8.5 days (rivaroxaban), 9 days (apixaban), and 12 days (dabigatran) (IQR not reported)	11 days (IQR not reported)
Beller 2019	Median	7 days (IQR 5-10 days)	8 days (IQR6-12 days)

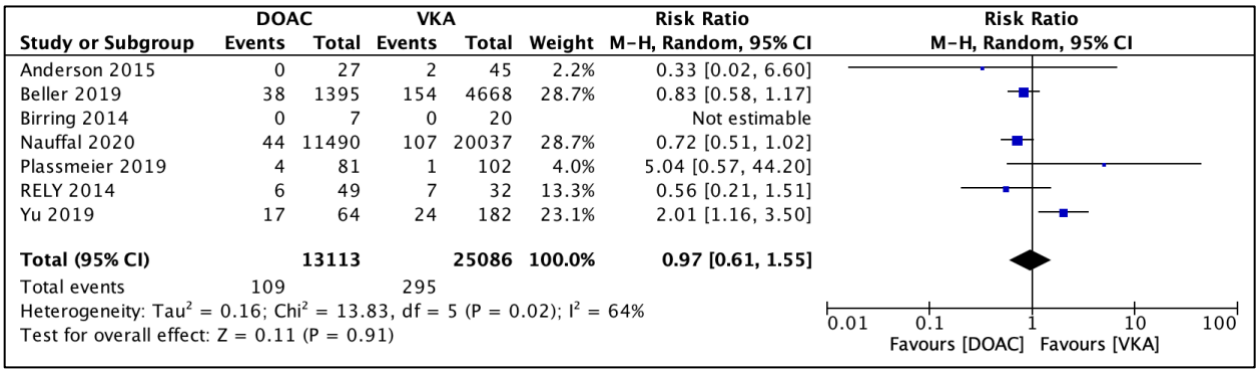
IQR, interquartile range; SD, standard deviation

Table 3: Ongoing RCTs exploring the optimal OAC therapy for AF post cardiac surgery

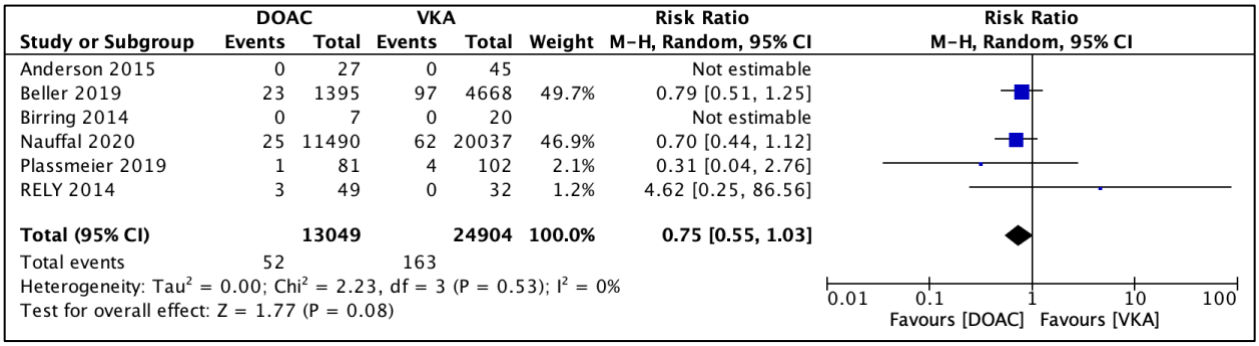
Trial	Interventions	Sample Size	Primary Outcome	Follow Up
Dyke et al. (NCT02889562)	Apixaban vs warfarin (open label)	~ 56	Freedom from thromboembolism	30 days
Voisine et al. (NCT04002011)	DOAC vs warfarin (open label)	~ 206	Hemorrhage, ischemia, death, QoL, and satisfaction	90 days
Oshno et al. (NCT03702582)	Rivaroxaban vs warfarin (open label)	~ 300	Postoperative length of stay	6 months
DANCE trial	DOAC vs warfarin (open label)	~ 400 & 6000 per phase	Vanguard phase: feasibility Full trial: Major bleeding	30 & 90 days

SUPPLEMENTARY FIGURES AND TABLES

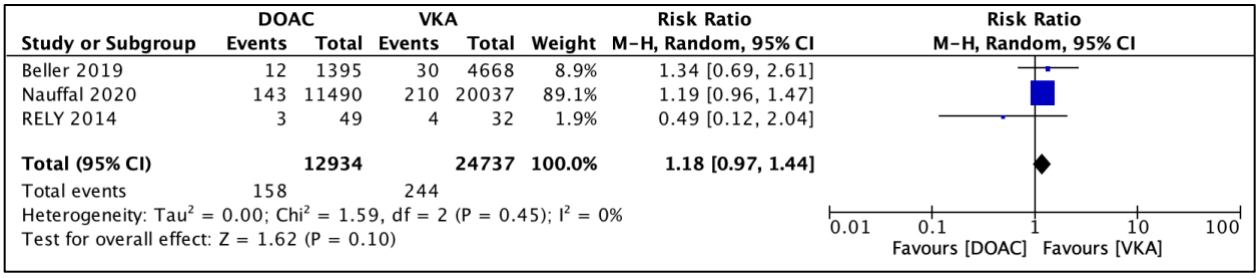
Supplementary Figure 1: Forest plot of major bleeding events within 90 days post-surgery



Supplementary Figure 2: Forest plot of stroke events within 90 days post-surgery



Supplementary Figure 3: Forest plot of death within 90 days post-surgery



Supplementary Table 1: MEDLINE (R) 1946 to present search strategy

1	exp atrial fibrillation/ (54642)
2	(atrial adj3 fibrillat*).ti,ab. (69274)
3	((auricular adj3 fibrillat*) or (supraventricul* adj3 arrhythmi*)).ti,ab. (3601)
4	thoracic surgery.mp. or exp Thoracic Surgery/ (27856)
5	cardiac surgery.mp. (40941)
6	preoperative period.mp. or exp Preoperative Period/ (9838)
7	perioperative care.mp. or exp Perioperative Care/ (151662)
8	intraoperative care.mp. or exp Intraoperative Care/ (17011)
9	postoperative care.mp. or exp Postoperative Care/ (63751)
10	cabg.mp. or exp Coronary Artery Bypass/ (57643)
11	exp Heart Valve Prosthesis Implantation/ (26625)
12	exp Cardiac Surgical Procedures/ (216306)
13	exp Postoperative Complications/ (542533)
14	blood coagulation factor inhibitors.mp. or exp Blood Coagulation Factor Inhibitors/ (17143)
15	antithrombins.mp. or exp Antithrombins/ (22865)
16	factor xa inhibitors.mp. or exp Factor Xa Inhibitors/ (7698)
17	direct thrombin inhibitor.mp. (1556)
18	exp Anticoagulants/ or oral anticoagulant.mp. (221619)
19	direct oral anticoagulant.mp. (817)
20	novel oral anticoagulant.mp. (315)
21	non vitamin k oral anticoagulant.mp. (60)
22	(doac* or noac*).tw. (3998)
23	dabigatran.mp. or exp Dabigatran/ (5377)
24	pradaxa.mp. (147)
25	edoxaban.mp. (1500)
26	Savaysa.mp. (23)
27	rivaroxaban.mp. or exp Rivaroxaban/ (5722)
28	xarelto.mp. (142)
29	apixaban.mp. (3629)
30	eliquis.mp. (66)
31	lixiana.mp. (19)
32	warfarin.mp. or exp Warfarin/ (30161)
33	coumadin.mp. (1063)
34	1 or 2 or 3 (82948)
35	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (871690)
36	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (226554)
37	32 or 33 (30612)
38	34 and 35 and 36 and 37 (405)
39	limit 38 to yr="2009 -Current" (276)

Supplementary Table 2: EMBASE 1974 to present search strategy

1 exp atrial fibrillation/ (68773)
2 (atrial adj3 fibrillat*).ti,ab. (123932)
3 ((auricular adj3 fibrillat*) or (supraventricul* adj3 arrhythmi*)).ti,ab. (4161)
4 blood coagulation factor inhibitors.mp. or exp blood clotting inhibitor/ (114689)
5 antithrombin.mp. or exp antithrombin/ (29763)
6 factor xa inhibitor.mp. or exp blood clotting factor 10a inhibitor/ (29412)
7 direct thrombin inhibitor.mp. or exp thrombin inhibitor/ (50841)
8 oral anticoagulant.mp. or exp anticoagulant agent/ (653242)
9 (direct oral anticoagulant or novel oral anticoagulant or non vitamin k oral anticoagulant).mp. (2174)
10 (doac* or noac*).tw. (8537)
11 exp dabigatran etexilate/ or exp dabigatran/ or dabigatran.mp. (16071)
12 edoxaban.mp. or exp edoxaban/ (4619)
13 rivaroxaban.mp. or exp rivaroxaban/ (17947)
14 apixaban.mp. or exp apixaban/ (12301)
15 pradaxa.mp. (1116)
16 savaysa.mp. (134)
17 lixiana.mp. (115)
18 xarelto.mp. (1164)
19 eliquis.mp. (617)
20 warfarin.mp. or exp warfarin/ (95168)
21 (coumadin or jantoven).mp. (4797)
22 vitamin k antagonist.mp. or exp antivitamin K/ (16158)
23 thoracic surgery.mp. or exp thorax surgery/ (592973)
24 cardiac surgery.mp. or exp heart surgery/ (375126)
25 Cardiothoracic surgery.mp. (4632)
26 perioperative period.mp. or exp perioperative period/ (54565)
27 perioperative care.mp. (5888)
28 intraoperative care.mp. or exp peroperative care/ (12988)
29 postoperative care.mp. or exp postoperative care/ (89742)
30 exp coronary artery bypass surgery/ or cabg.mp. or coronary bypass surgery.mp. (48690)
31 heart valve surgery.mp. or exp heart valve surgery/ (97646)
32 exp heart valve replacement/ or heart valve procedure.mp. (53438)
33 cardiac surgical procedure.mp. or exp heart surgery/ (363496)
34 1 or 2 or 3 (143638)
35 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (657440)
36 20 or 21 or 22 (105588)
37 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (739476)
38 34 and 35 and 36 and 37 (2929)
39 limit 38 to yr="2009 -Current" (2492)

Supplementary Table 3: CENTRAL Inception to Present search strategy

#1	atrial fibrillation	12436
#2	MeSH descriptor: [Atrial Fibrillation] explode all trees	4496
#3	cardiac surgery	20354
#4	MeSH descriptor: [Thoracic Surgery] explode all trees	160
#5	MeSH descriptor: [Coronary Artery Bypass] explode all trees	5384
#6	postoperative	114783
#7	MeSH descriptor: [Perioperative Period] explode all trees	8382
#8	MeSH descriptor: [Cardiac Valve Annuloplasty] explode all trees	46
#9	blood coagulation factor inhibitors	547
#10	[mh "blood coagulation factor inhibitors"]	728
#11	antithrombin	1879
#12	[mh "antithrombins"]	851
#13	factor xa inhibitor	691
#14	[mh "factor xa inhibitors"]	517
#15	direct oral anticoagul*	875
#16	novel oral anticoagul*	308
#17	non-vitamin k antagonist	145
#18	(doac* or noac*):ti,ab,kw	574
#19	dabigatran	1029
#20	pradaxa	61
#21	edoxaban	554
#22	savaysa	7
#23	lixiana	27
#24	rivaroxaban	1589
#25	xarelto	79
#26	apixaban	885
#27	eliquis	42
#28	warfarin	4974
#29	coumadin	213
#30	vitamin k antagonist	669
#31	#1 or #2	12436
#32	#3 or #4 or #5 or #6 or #7 or #8	129655
#33	#9 or #10 or #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 or #26 or #27	6492
#34	#28 or #29 or #30	5432
#35	#31 and #32 and #33 and #34	**68**

Supplementary Table 4: GRADE Summary of Findings. Safety of DOACs versus VKA after recent cardiac surgery

Patient or population: patients undergoing cardiac surgery requiring anticoagulation
Intervention: DOAC
Comparison: VKA
Follow up: 30 days

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA strategy	Risk difference with DOAC strategy
Major Bleeding	38199 (7 Observational studies)	⊕◯◯◯ VERY LOW[a]	**RR 0.75** (0.59 to 0.94)	11 per 1,000	3 fewer per 1,000 (5 fewer to 1 fewer)
Strokes	37953 (6 Observational studies)	⊕◯◯◯ VERY LOW[b]	**RR 0.76** (0.55 to 1.05)	6 per 1,000	2 fewer per 1,000 (3 fewer to 0 fewer)
Mortality	37671 (3 Observational studies)	⊕◯◯◯ VERY LOW[c]	**RR 1.20** (0.98 to 1.47)	10 per 1,000	2 more per 1,000 (0 fewer to 5 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: True effect may be substantially different from estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] Down-graded for *risk of bias and indirectness*
[b] Down-graded for *risk of bias, indirectness and imprecision*
[c] Down-graded for *risk of bias and imprecision*

REFERENCES

1. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. The Lancet. 2014;383(9921):955-62.
2. Spivey CA, Qiao Y, Liu X, Mardekian J, Parker RB, Phatak H, et al. Discontinuation/interruption of warfarin therapy in patients with nonvalvular atrial fibrillation. Journal of managed care & specialty pharmacy. 2015;21(7):596-606.
3. Seliverstov I. Practical management approaches to anticoagulation non-compliance, health literacy, and limited English proficiency in the outpatient clinic setting. Journal of thrombosis and thrombolysis. 2011;31(3):321-5.
4. Mazurek M, Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener H-C, et al. Regional differences in antithrombotic treatment for atrial fibrillation: insights from the GLORIA-AF Phase II Registry. Thrombosis and Haemostasis. 2017;117(12):2376-88.
5. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2011;365(11):981-92.
6. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine. 2011;365(10):883-91.
7. Connolly SJ, Ezekowitz Md Fau - Yusuf S, Yusuf S Fau - Eikelboom J, Eikelboom J Fau - Oldgren J, Oldgren J Fau - Parekh A, Parekh A Fau - Pogue J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. (1533-4406 (Electronic)).
8. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2013;369(22):2093-104.
9. Hanley CM, Kowey PR. Are the novel anticoagulants better than warfarin for patients with atrial fibrillation? Journal of thoracic disease. 2015;7(2):165.
10. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369:1206-14.
11. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. Journal of the American College of Cardiology. 2017;69(7):871-98.
12. Beller JP, Krebs ED, Hawkins RB, Mehaffey JH, Quader MA, Speir AM, et al. Non–vitamin K oral anticoagulant use after cardiac surgery is rapidly increasing. The Journal of Thoracic and Cardiovascular Surgery. 2019.
13. Covidence systematic review software VHI, Melbourne, Australia. Available at www.covidence.org.
14. Tool to Assess Risk of Bias in Cohort Studies The Clarity Review Group. [Available from: http://help.magicapp.org/knowledgebase/articles/327941-tool-to-assess-risk-of-bias-in-cohort-studies.

15. Higgins J, Sterne J, Savović J, Page M, Hróbjartsson A, Boutron I, et al. A revised tool to assess risk of bias in randomized trials (RoB 2). Cochrane Methods: Cochrane Database of Systematic Reviews; 2016.
16. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 ed: The Cochrane Collaboration; 2011.
17. Anderson E, Johnke K, Leedahl D, Glogoza M, Newman R, Dyke C. Novel oral anticoagulants vs warfarin for the management of postoperative atrial fibrillation: clinical outcomes and cost analysis. Am J Surg. 2015;210(6):1095-102; discussion 102-3.
18. Yu PJ, Lin D, Catalano M, Cassiere H, Manetta F, Kohn N, et al. Impact of novel oral anticoagulants vs warfarin on effusions after coronary artery bypass grafting. J Card Surg. 2019;34(6):419-23.
19. R. PARAPGKMD. Direct Oral Anticoagulants in Post-Operative Atrial Fibrillation Following Coronary Artery Bypass Graft Surgery. Thrombosis and Hemostasis Societies of North America (THSNA): American Journal of Hematology; 2018.
20. Birring A, Dark J. Hospital stays post cardiac surgery: Warfarin vs dabigatran. International Journal of Surgery. 2014;12:S20.
21. Connolly S, Mendoza P, Whitlock R, Belley-Côté E. Comparing the safety of Dabigatran to Warfarin after cardiac surgery: Substudy of the RELY Trial. 2020.
22. Nauffal V, Trinquart L, Osho A, Sundt TM, Lubitz S, Ellinor PT. DIRECT ORAL ANTICOAGULANTS VS. WARFARIN FOR NEW ONSET POST-CARDIAC SURGERY NON-VALVULAR ATRIAL FIBRILLATION. Journal of the American College of Cardiology. 2020;75(11 Supplement 1):370.
23. Plassmeier M, Czosnowski L. Non - vitamin K oral anticoagulants compared to warfarin for early anticoagulation of atrial fibrillation with bioprosthetic valves. Journal of the American College of Clinical Pharmacology. 2019;3(1).
24. Berenji N, Sheikh O, Kendall G, Al-Qaysi M, Roy D, Vinas A, et al. Safety of Direct Oral Anti-Coagulation Agents in Patients With Bio-Prosthetic Valves. Circulation. 2019;140(Suppl_1):A13926-A.
25. Nazha B, Pandya B, Cohen J, Zhang M, Lopes RD, Garcia DA, et al. Periprocedural Outcomes of Direct Oral Anticoagulants Versus Warfarin in Nonvalvular Atrial Fibrillation. Circulation. 2018;138(14):1402-11.
26. Lamy A, Eikelboom J, Sheth T, Connolly S, Bosch J, Fox KA, et al. Rivaroxaban, aspirin, or both to prevent early coronary bypass graft occlusion: the COMPASS-CABG study. Journal of the American College of Cardiology. 2019;73(2):121-30.
27. Vranckx P, Potpara T, Dagres N, Heidbuchel H. Non-vitamin K oral anticoagulants in patients with atrial fibrillation after cardiac surgery: the results of the European Heart Rhythm Association Survey. Europace. 2016;18(7):1113-6.
28. Apixaban Versus Warfarin for the Management of Post-operative Atrial Fibrillation. https://ClinicalTrials.gov/show/NCT02889562.
29. DOAC Versus VKA After Cardiac Surgery. https://ClinicalTrials.gov/show/NCT04002011.
30. Rivaroxaban vs. Warfarin for Post Cardiac Surgery Atrial Fibrillation. https://ClinicalTrials.gov/show/NCT03702582.

CHAPTER 4: RATIONALE AND DESIGN OF THE DANCE VANGUARD TRIAL

Design and Rationale for the Direct Oral Anticoagulation Versus Warfarin After Cardiac Surgery (DANCE) Vanguard Trial

Pablo A. Mendoza,[1,2] William F. McIntyre,[1,2,3] John Eikelboom,[2,4] Jeff S. Healey,[1,2,3] Sam Schulman,[1,4] Vivek Rao,[5] Renato D. Lopes,[7] Michael E. Farkouh,[5] Richard P. Whitlock,[1,2,6] Emilie P. Belley-Côté[2,3]

Affiliations:

1. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada
2. Population Health Research Institute, McMaster University, Hamilton, Canada
3. Division of Cardiology, Department of Medicine, McMaster University, Hamilton, Canada
4. Division of Hematology & Thromboembolism, Department of Medicine, McMaster University, Hamilton, Canada
5. Peter Munk Cardiac Centre, Heart and Stroke Richard Lewar Centre, University of Toronto, Toronto, Canada
6. Division of Cardiac Surgery, Department of Surgery, McMaster University, Hamilton, Canada
7. Division of Cardiology, Department of Medicine, Duke University Medical Center and Duke Clinical Research Institute

3113 words, 2 tables, 0 figures, 2 supplemental tables and figures, 36 references

ABSTRACT

Objective: Anticoagulation prevents embolic complications in patients with AF and direct oral anticoagulants (DOACs) are generally the treatment of choice. However, in the cardiac surgical population, a small phase II trial suggested a higher risk of complications with DOACs. The existing evidence to guide oral anticoagulation (OAC) after cardiac surgery is of very low quality. We herein describe the rationale and design of the Direct oral Anticoagulation versus warfariN after Cardiac surgEry (DANCE) vanguard trial in patients requiring anticoagulation for AF after cardiac surgery.

Methods and Results: DANCE is an open-label, blinded endpoint, multicentre, noninferiority randomized controlled trial comparing DOACs and vitamin K antagonists (VKA) in patients with pre-existing or new post-operative AF after cardiac surgery. The 400-patient vanguard phase aims to assess the feasibility of the definitive DANCE trial protocol. It will evaluate recruitment rate per centre, the proportion of participants that crossover OAC arms, and the ability to achieve follow-up at 30 days. The primary outcome of the definitive DANCE trial is major bleeding. Other outcomes include thromboembolism, mortality, hospital length of stay, and quality of life. We expect to start recruitment fall 2020 in 10 centres.

Conclusion: The DANCE trial will be the largest trial to explore the safety of DOACs versus VKAs in patients requiring anticoagulation for AF early after cardiac surgery. Its results will lead to better understanding of optimal anticoagulation management early after cardiac surgery.

RATIONALE

About 10% of patients undergoing cardiac surgery have a prior history of atrial fibrillation (AF).(1) Additionally, 20-50% of patients will develop AF early after cardiac surgery. AF, whether it is pre-existing or new after surgery, carries a significant risk for stroke and mortality in the perioperative setting.(2-8) While physicians will respond with rate and rhythm interventions to control AF, oral anticoagulation (OAC) therapy remains the preferred method for thromboembolic prevention.(9, 10) For over half a century, warfarin, a vitamin k antagonist (VKA), has been the primary OAC for treating AF; however, a new class of OAC has been approved for use. Direct oral anticoagulants (DOAC) - inhibitors of factor Xa or thrombin – have demonstrated similar efficacy and a lower risk of intracranial bleeding when compared to VKAs outside the perioperative setting.(11-14) Moreover, DOACs are more convenient for both patients and clinicians. They have a rapid onset of effect, fixed dosage that obviates the need for regular monitoring, and few interactions with food and other medications.(15) For these reasons, guidelines suggest DOACs as the preferred alternative to VKAs for stroke prevention.(9, 10)

Safety concerns remain with the use of DOACs after cardiac surgery. Previous large trials have excluded patients planned for cardiac surgery, leaving few studies to guide anticoagulation practice in this setting. (11-14) The main concerns for DOAC use post cardiac surgery stem from the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) trial published in 2013.(16) RE-ALIGN compared the safety of dabigatran to VKA after mechanical valve replacement in patients with low and high thromboembolic risk. In the trial, the risk of any bleeding and thromboembolic events was increased with dabigatran, a DOAC, when compared to VKA. However, it is important to keep in mind that, in RE-ALIGN, dabigatran doses were

adjusted to achieve minimum blood levels of 50 ng/mL. In consequence, many RE-ALIGN patients were taking dabigatran doses higher than those recommended for patients with AF. This led to contraindication of DOAC in patients undergoing a mechanical heart valve surgery.(9, 10) Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, the evidence from this trial is of very low quality due to severe imprecision and risk of bias (the RE-ALIGN trial was stopped early for harm).(17) In contrast, the Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS-CABG) trial, evaluating low dose rivaroxaban (2.5 mg BID), a DOAC, found no increase in major bleeding in the first 30 days post coronary artery bypass grafting (CABG).(18) We further reviewed the literature for studies comparing DOACs with VKA in the early period after cardiac surgery and found 8 observational studies representing 38,393 patients.(Chapter 3) In our meta-analysis, we found DOACs were associated with a significant reduction in major bleeding (RR 0.75; 95% CI 0.59-0.94), but we found no significant difference in stroke (RR 0.76; 95% CI 0.55-1.05), or mortality (RR 1.20; 95% CI 0.98-1.47). While this is, to our knowledge, the only meta-analysis comparing DOACs to VKAs early after non-mechanical valve cardiac surgery, we recognize the evidence is of very low quality due to high risk of bias, indirectness, and imprecision. In a separate analysis, we explored the incidence of major bleeding within 30 days post-operatively in the ongoing Left Atrial Appendage Occlusion (LAAOS) III trial.(1) LAAOS III evaluated the efficacy of concomitant left atrial appendage occlusion in patients with AF undergoing cardiac surgery. After adjustment for $CHADS_2$ score, the incidence of major bleeding between 48 hours and 30 days did not differ significantly when DOACs were compared with VKA (adjusted odds ratio [aOR] 1.05, 95% confidence interval [CI] 0.55-2.03, p=0.88, Richard Whitlock, unpublished data, 2019). The risk of stroke and systemic embolism between 48 hours and 30 days was also

similar: aOR 1.03, 95% CI 0.50-2.10, p=0.94). This large prospective observational cohort represents the highest quality evidence in this area but has several limitations due to the observational design.

Despite limited data informing the safety of this practice, resumption or initiation of DOAC therapy after cardiac surgery is becoming more frequent.(19, 20) From clinicians' and patients' perspectives, DOACs are a more practical option and are as effective as VKAs. However, the safety of this approach remains unclear, especially in light of the concern about an increased risk of major bleeding in the only randomized controlled trial performed in a similar population. Available observational studies do not provide the certainty of evidence required to definitively answer this important question. Accordingly, an expert panel from the American College of Cardiology has called for further study of this practice.(19)

We describe The Direct Oral Anticoagulation versus Warfarin after Cardiac Surgery (DANCE) vanguard randomized controlled trial to evaluate the *feasibility* of a large, multicenter randomized controlled trial comparing the safety of DOAC versus VKA therapy in patients with AF requiring anticoagulation after cardiac surgery. We also briefly outline the full trial; we may modify details of the full trial based on experience gained in the vanguard phase.

DESIGN

Specific Objectives

Vanguard Phase

To assess the feasibility of conducting a large randomized controlled trial evaluating the safety of DOACs versus VKAs after cardiac surgery in patients with AF requiring anticoagulation.

Full Trial

To evaluate the safety of DOACs versus VKAs after cardiac surgery in patients with AF requiring anticoagulation.

Study Design

Vanguard Phase

The DANCE Vanguard phase (NCT04284839) will be a 2-year, 400-patient, multicentre, randomized controlled vanguard trial evaluating whether the DANCE protocol is feasible to proceed to a full, international, multicentre RCT.

Full Trial

The DANCE trial will be a randomized, prospective, open-label, blinded end-point (PROBE), multicentre, non-inferiority clinical trial.(21) After cardiac surgery, patients who have AF and require anticoagulation will receive either a DOAC or VKA for 90 days. For patients allocated to the DOAC arm, the choice of DOAC will be at the discretion of the ordering physician. For patients allocated to the VKA arm, international normalised ratio (INR) monitoring and VKA dosing will be as per local practice. The sample size is expected to be approximately 6100 patients for the full trial.

Participant selection, recruitment and consent

We will enroll participants who meet the eligibility criteria outlined in Table 1. For the vanguard phase, participants will be recruited from approximately 10 sites; while, the full trial will recruit from approximately 30 sites across the world. Adults who have had open heart surgery in the last seven days and have AF (pre-existing AF or post-operative AF) requiring anticoagulation will be approached for the DANCE trial prior to hospital discharge. Patients eligible for participation will be identified and approached for consent prior to (or at the time of)

resuming or initiating OAC after the surgery. The clinical team will briefly introduce the trial, and, if the patient expresses interest, trained research personnel will provide a full explanation. The research personnel will then obtain informed consent.

Randomization and Allocation

Randomization will occur once the patient is deemed eligible and informed consent is obtained. Research personnel will randomize participants using a central Interactive Web Randomization System (IWRS), in randomly permuted blocks of various sizes. Randomization sequence and block sizes will be concealed. Participants will be randomly allocated in a 1:1 ratio to DOAC or to VKA. Randomization will be stratified by centre to account for potential differences in the patient population and co-interventions, and by whether they had an indication for OAC prior to surgery (e.g., history of AF) or have a new indication after surgery (e.g. post-operative AF).

After randomization, treatment allocation will not be concealed to the patient, medical team, data collectors, or investigators. Since INR has to be closely monitored, an open-label design is necessary to ensure feasibility with regard to cost and workload. Because blinding is impractical and expensive, DANCE will be conducted using a PROBE design with clear and objective outcome definitions.(21) A blinded panel of clinicians will adjudicate bleeding and thromboembolic outcomes.

Intervention

Patients in the DOAC group will receive a DOAC at recommended doses adjusting when necessary for their renal function, age and weight (Table 2). The choice of DOAC will be at the discretion of the treating physician. Treatment in the DOAC group will start on postoperative day 5 (if the patient is stable from a bleeding perspective) or at discharge, whichever occurs first.

Patients in the VKA group will receive a VKA once daily; the individual dose will be titrated to achieve a guideline-recommended INR range. VKA dosage and INR monitoring frequency will be as per local practice in the participating centre. Given the delay before achieving a therapeutic INR, the first dose of VKA can be resumed or initiated as soon as post-operative day 1.

Co-interventions

Antiplatelet therapy may be used at the discretion of the investigator and is expected to be common. The local centre will direct recommendations on diet and lifestyle related to VKA therapy.

Outcomes

Vanguard Phase

The vanguard phase will evaluate key parameters for the feasibility of the full trial including: i) the ability to recruit an average enrolment rate of 5 patients per centre per month, ii) the proportion of participants that crossover OAC arms is ≤ 5%, iii) the ability to achieve follow-up at 30 days in ≥ 95% of enrolled patients. The outcomes of the full trial will also be collected.

Full Trial

The primary outcome for the full trial is major bleeding at 30 days defined as bleeding that results in death and/or symptomatic bleeding in a critical area or organ and/or bleeding that causes a drop in the hemoglobin level of 20 g/L or more or that which requires the transfusion of ≥2 units of packed red blood cells (as defined by the International Society of Thrombosis and Hemostasis).(22)

Secondary outcomes include pleural effusion requiring drainage, pericardial effusion requiring drainage, systemic thromboembolism, ischemic stroke, deep vein thrombosis, pulmonary embolism, and length of postoperative hospital stay (Supplementary Table 2).

Tertiary outcomes will include minor bleeding, all bleeding (major plus minor), myocardial infarction, mortality, valve thrombosis, hemorrhagic stroke, all stroke, all arterial thrombosis/thromboembolism (e.g. ischemic stroke, systemic thromboembolism, myocardial infarction, valve thrombosis), quality of life measured by the EQ-5D-5L questionnaire, patient satisfaction measured by the PACT-Q2 questionnaire, and aggregate costs for both groups.

Patient Follow Up

At baseline (post-surgery and prior to randomization), research personnel will record patient demographics and medical history (e.g., age, sex, co-morbidities, thromboembolic risk factors, medications, most recent hemoglobin, most recent creatinine, presence of coronary disease or coronary bypasses) and administer the EQ-5D-5L and PACT-Q2 questionnaires.

Recruited patients will be followed up until 90-days post-randomization. We will collect all INR values measured during the study for patients in the VKA group. Follow-up evaluation for study outcomes can be performed in person, at hospital discharge, and during a clinic visit or by telephone at 30-days and 90-days post-randomization. The EQ-5D-5L and PACT-Q2 questionnaires will be administered at the 30-day and 90-day visits.

Study Organization

The Population Health Research Institute (PHRI) is the central coordinating centre for this trial and is responsible for the development of the protocol, development of the randomization scheme, trial database, data consistency checks, data analyses, coordination of the trial centres, and conducting the trial. The study team consists of a steering committee,

adjudication committee, and data safety and monitoring board (DSMB).

Statistical Analysis

Vanguard Phase

The feasibility objectives of the vanguard trial will be analyzed using descriptive statistics and 95% confidence intervals. We will enroll approximately 400 patients in the vanguard phase to generate precise feasibility estimates.

Full Trial

We will use a time-to-event analysis and present Kaplan-Meier survival curves with comparison between groups using a log rank test. We will present treatment effect estimated using a hazard ratio and 95% confidence interval derived by the Cox proportional hazards model. We will assess for differences between subgroups and interaction between subgroup factors and treatment effect using additional adjusted Cox models. Although time-to-event analysis may not be required given the short follow-up, it will allow us to evaluate the timing of the bleeding events after cardiac surgery. The primary analysis will be a per protocol analysis, with a secondary analysis following the intention to treat principle. This is because intention to treat analyses generally result in a smaller treatment effect which favours non-inferiority. If non-inferiority is established, we will perform an analysis for superiority.

We will evaluate secondary outcomes using the same approach as the primary outcome. Secondary outcome analyses will be adjusted for stratifying variables. We will conduct a sensitivity analysis to assess the effect of missing data using plausible worst-case scenario analysis as it is unlikely that patients will be lost to follow-up at random. In our cost-effectiveness analysis, we will use the perspective of the Canadian public healthcare system payer/Ministry of Health and Long-term Care. Our methods will follow the Canadian Agency for

Drugs and Technologies in Health (CADTH) guideline for economic evaluation in Canada as well as guidelines for economic evaluation alongside clinical trials (23, 24).

A blinded statistician, who will not be involved in the trial, will independently perform all statistical analyses. Baseline patient characteristics will be reported using counts and proportions, means and standard deviations (SDs), or medians with interquartile ranges (IQRs) as appropriate, based on variable distribution. For all non-primary analyses, we will consider a two-sided alpha < 0.05 significant.

Sample Size Calculation

Based on current estimates from the LAAOS III trial (1), we expect the incidence of major bleeding to be 1.3% at 30 days with VKAs and 1.4% with DOACs.The power calculation for the binary (non-inferior) outcome used the formula, $[n = f(\alpha/2, \beta) \times [p_1 \times (100 - p_1) + p_2 \times (100 - p_2)] / (p_1 - p_2 - d)^2]$ which was computed using online statistical software. Based on the current estimates (major bleeding incidence of 1.3% at 30 days with VKA and 1.4% with DOACs), a total sample size of 6100 patients would provide 85% power to ensure that a one-sided 97.5% confidence interval (alpha=0.025) will exclude an absolute difference in favour of the VKA arm of more than 1% (non-inferiority margin).(25)

Subgroup Analyses

We plan 6 main pre-specified subgroup analyses based on 1) OAC therapy resumption vs. initiation, 2) CABG vs. other procedure, 3) sex, 4) age, 5) renal function category, and 6) antiplatelet use. We will use stratified Cox proportional hazard regression models to assess for differences between subgroups and interactions between subgroup factors and the treatment effect.

DISCUSSION

The results of the DANCE vanguard trial will inform the feasibility and design of a large definitive trial. The results of the definitive DANCE trial will inform on the optimal OAC treatment for patients in the early postoperative period after cardiac surgery, impacting guidelines.

To assess safety concerns, major bleeding is the primary outcome of the DANCE trial. Bleeding is associated with poor prognosis.(26) The belief that stroke and myocardial infarction cause damage but patients recover from major bleeding without consequences is not supported by available evidence. For example, the ORBIT-AF II study showed that bleeding in patients on VKA was associated with a 17% incidence of mortality, 47% incidence of hospitalization, and a 7% incidence of recurrent major bleeding.(27) For patients on anticoagulation, a secondary analysis of the ACTIVE-Warfarin and RELY trials suggested that the risk of death was increased 7-fold after a myocardial infarction and 8-fold after an ischemic stroke, but 27-fold after a hemorrhagic stroke, and 5-fold after an extracranial bleeding event.(28) In addition, trials such as OASIS 5, HORIZONS-AMI, and ENGAGE-AF have demonstrated that reducing major bleeding reduces mortality.(14, 29, 30) Because it is already known that DOACs are either superior or noninferior to VKAs for thromboembolic protection, thromboembolism should not be the primary outcome of the definitive DANCE trial.(11-14)

Impact

Approximately 400,000 American and 36,000 Canadian adults undergo cardiac surgery annually (31, 32). Of these, over 10% have a history of AF and 20-50% will develop post-operative AF.(1-8) Establishing whether DOACs are non-inferior to warfarin for bleeding in the

early period after cardiac surgery will impact the clinical management of hundreds of thousands of patients in North America every year.

CONCLUSION

The existing evidence to guide OAC after cardiac surgery is of very low quality. Thus, a large, randomized controlled trial is required to definitively determine whether DOACs are safe in patients early after cardiac surgery. The Direct oral Anticoagulation versus warfariN after Cardiac surgEry (DANCE) vanguard randomized controlled trial will evaluate the *feasibility* of a large, multicenter randomized controlled trial comparing the safety of DOAC versus VKA therapy in patients with an indication for anticoagulation after cardiac surgery.

TABLES

Table 1: Inclusion and exclusion criteria for study participation

Inclusion Criteria
• Age ≥18 years at the time of enrolment, • Open heart surgery in the last 7 days, • AF requiring anticoagulation (including pre-existing AF or Post-operative AF), • Written informed consent from either the patient or a substitute decision-maker.
Exclusion Criteria
• Undergoing a mechanical valve replacement, • Antiphospholipid syndrome (triple positive), • Severe renal failure (Cockcroft Gault equation; creatinine clearance <30 ml/min), • Known significant liver disease (Child-Pugh classification B and C), • Ongoing bleeding, hemorrhagic disorders, or bleeding diathesis, • Known contraindication for any DOAC or VKA, • Women who are pregnant, breastfeeding, or of childbearing potential, • Previously enrolled in this trial, • Follow-up not possible.

Table 2: Recommended dosing schedule for patients taking DOAC

DOAC	Recommended dose
Apixaban	5 mg twice daily Dose reduction to 2.5mg twice daily if two or more of the following criteria are present: creatinine ≥133μmol/L, weight ≤60kg, age ≥80 years
Dabigatran	150 mg twice daily Dose reduction to 110 mg twice daily if concerns about the risk of bleeding
Edoxaban	Edoxaban 60 mg daily Dose reduction to 30mg daily if one of the following criteria are present: creatinine clearance 30-50 ml/min, weight ≤60kg, or concomitant treatment with a potent P-glycoprotein inhibitor (e.g. cyclosporin, dronedaron, erythromycin, ketoconazol, or quinidine);
Rivaroxaban	20 mg daily Dose reduction to 15 mg daily if creatinine clearance 30-50 ml/min

SUPPLEMENTARY INFORMATION

Supplementary Table 1: Full Trial Outcome Definitions

Major bleeding (ISTH definition):
1. Death and/or, 2. Symptomatic bleeding in critical area or organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome) and/or, 3. Bleeding that causes drop of hemoglobin level by ≥ 2g/dL, or that requires the transfusion of ≥ 2 units of packed red blood cells or whole blood
Minor bleeding: (ISTH definition):
1. Clinically relevant bleeding that does not meet major bleeding criteria and lead to at least one of the following: a. Hospital admission b. Require medical or surgical management c. Require interruption or discontinuation of study drug
Myocardial infarction
The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values. **Criteria for acute myocardial infarction (types 1, 2 and 3 MI).** The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following: 1. Symptoms of myocardial ischaemia; 2. New ischaemic ECG changes; 3. Development of pathological Q waves; 4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology; 5. Identification of a coronary thrombus by angiography or autopsy (not for type 2 or 3 MIs). Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for type 2 MI. Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI.
Systemic thromboembolism:
Systemic thromboembolism is defined as abrupt vascular insufficiency associated with evidence of arterial occlusion in the absence of other likely mechanisms. Clinical signs

and symptoms must be consistent with embolic arterial occlusion, there must be clear evidence of abrupt occlusion of a systemic artery, with at least one type of supporting evidence, such as surgical report indicating evidence of arterial embolism, pathological specimens related to embolism removal, imaging evidence consistent with arterial embolism, or autopsy report.
NOTE: Excluded from the definition are pulmonary embolism and non-embolic arterial occlusions.

Valve thrombosis (VARC definition):

Any thrombus related to the mechanical valve that affect the function of the valve or partly occludes blood flow or require medical or surgical intervention.

Pulmonary embolism:

Criteria for the objective diagnosis of pulmonary embolism include:
i) A high probability ventilation/perfusion lung scan
ii) An intraluminal filling defect of segmental or larger artery on helical CT scan
iii) An intraluminal filling defect on pulmonary angiography
iv) A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following: • non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan • non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan
v) evidence of pulmonary embolism in a segmental or larger artery on autopsy

Deep Vein Thrombosis:

Criteria for the objective confirmation of deep vein thrombosis include:
i) A persistent filling defect on contrast venography in the deep venous system
ii) Non-compressibility of one or more venous segments in the deep venous system on compression ultrasonography and/or thrombus visualized with Doppler.
iii) A clearly defined intraluminal filling defect on contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) in the deep venous system

Stroke

Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death. Stroke will be sub-classified into hemorrhagic and non-hemorrhagic stroke. Non-hemorrhagic stroke will sub-classified into ischemic, ischemic with secondary transformation, or stroke of uncertain classification. Hemorrhagic stroke will be sub-classified into primary intracerebral hemorrhage and primary subarachnoid hemorrhage.

1. Ischemic stroke: focal brain infarction caused by an arterial (or rarely venous) obstruction and as documented by CT/MRI that is normal or shows an infarct in the clinically expected area.

2. Secondary hemorrhagic transformation of ischemic stroke: hemorrhagic transformation of ischemic stroke may be symptomatic or asymptomatic.
   A. Symptomatic transformation of ischemic stroke is defined as a hematoma occupying 30% or more of the infarcted tissue associated with a significant neurologic deterioration (consistent with a decrease of 4 points in the NIHSS) compared to immediately before the worsening and an absence of an alternative explanation for deterioration.

B. Asymptomatic transformation of ischemic stroke is defined as a hemorrhagic transformation not meeting the criteria for symptomatic transformation. 3. Undetermined stroke: definite stroke that does not meet the criteria for ischemic or hemorrhagic stroke because CT scan or MRI are not done and there are no autopsy data. Rarely it cannot be determined with confidence whether the stroke was ischemic vs. hemorrhagic, even after review of CT/MRI images (e.g., primary intracerebral hemorrhage vs. severe hemorrhagic transformation); these stroke events will be classified as undetermined. 4. Hemorrhagic stroke: hemorrhagic stroke requires neuroimaging or autopsy confirmation and includes two subcategories: primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage. Intracranial bleeding caused by head trauma, bleeding associated with tumors, hemorrhagic transformation of ischemic stroke and subdural/epidural hematomas are not considered as hemorrhagic strokes (but these will be counted separately as major hemorrhages). Microbleeds are not considered intracranial hemorrhage. A. Primary intracerebral hemorrhage: These are symptomatic hemorrhagic strokes with CT/MRI or autopsy evidence of bleeding into the substance of the brain or ventricular spaces. Large or superficial intracerebral hemorrhages often are associated with minor amounts of subarachnoid hemorrhage, but these should be classified as intracerebral hemorrhages. Does not include secondary hemorrhage into cerebral infarct (i.e. hemorrhagic transformation which is defined separately), or intracerebral bleeding (i.e. contusions) due to trauma, or microbleeds detected by MRI. Primary subarachnoid hemorrhage: Typical clinical syndrome of sudden onset headache, with or without focal signs (subarachnoid hemorrhage may not have focal deficits), and CT or cerebrospinal fluid evidence of bleeding primarily into the subarachnoid space. Subarachnoid bleeding due to ruptured intracranial aneurysms and vascular malformation are counted as hemorrhagic strokes, but traumatic subarachnoid hemorrhage is not.
Pleural effusion requiring drainage
Pleural effusion requiring drainage with either: needle, selginder-technique percutaneous chest tube, surgical chest tube
Pericardial effusion requiring drainage
Pericardial effusion requiring drainage with either: needle, seldinger-technique percutaneous pericardial drain, pericardial window

Supplementary Table 2: Summary of Guidelines for the Management of Post-Operative Atrial Fibrillation after Cardiac Surgery

Scientific Association	Recommendations
American Heart Association/ American College of Cardiology/ Heart Rhythm Society (2014) (3)	It is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as advised for nonsurgical patients (Class of recommendation: 2a, Level of Evidence: B)
Society of Thoracic Surgeons (2011) (6)	Class IIa recommendation: For patients with two or more risk factors for stroke (age >75 years, hypertension, impaired left ventricular function, prior stroke or transient ischemic attack) who have postoperative AF that recurs or persists for more than 48 hours, anticoagulation therapy is reasonable if not otherwise contraindicated. (Level of evidence A) Class IIa recommendation: For patients with fewer than two risk factors for stroke and patients considered not suitable for warfarin who have postoperative AF that recurs or persists for more than 48 hours, aspirin, 325 mg daily, is reasonable if not otherwise contraindicated. (Level of evidence A) Class IIa recommendation: A target international normalized ratio (INR) of 2.0 to 2.5 is reasonable when using warfarin for AF in postoperative general thoracic surgical patients. (Level of evidence B) Class IIa recommendation: It is reasonable to continue anticoagulation therapy for 4 weeks after the return of
Canadian Cardiovascular Society (2010 & 2016) (1) (2)	We suggest that consideration be given to anticoagulation therapy if postoperative continuous AF persists for >72 hours. This consideration will include individualized assessment of the risks of a thromboembolic event and the risk of postoperative bleeding (Conditional Recommendation, Low Quality Evidence).(1) We recommend that, when anticoagulation therapy, rate-control therapy, and/or rhythm control has been prescribed for postoperative AF, formal reconsideration of the ongoing need for such therapy should be undertaken 6-12 weeks later (Strong Recommendation, Moderate Quality Evidence). (2)

European Association for Cardio-Thoracic Surgery (2017)(4)	Anticoagulation should be considered within 12-48 hours of AF in patients with POAF, balancing the risks for stroke and surgical bleeding (Class of recommendation: 2a, Level of evidence: B). (4) In patients with POAF at discharge, it is recommended to initiate OAC therapy and continue for at least 4 weeks (or longer), depending on the CHAsDSs-VASc risk score. (4) Note: Most of the evidence for anticoagulation of POAF has been obtained with VKAs. There is evidence supporting a greater benefit of NOACs over VKA in non-valvular POAF, including patients with a bioprosthetic valve (4).
European Society of Cardiology (2016) (5)	Long-term anticoagulation should be considered in patients with AF after cardiac surgery at risk for stroke, considering individual stroke and bleeding risk (Class of recommendation: 2a, Level of evidence: B) (5).

REFERENCES

1. Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A, et al. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. Ann Cardiothorac Surg. 2014;3(1):45-54.
2. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. Journal of the American College of Cardiology. 2008;51(8):793-801.
3. Bessissow A, Khan J, Devereaux P, Alvarez-Garcia J, Alonso-Coello P. Postoperative atrial fibrillation in non-cardiac and cardiac surgery: an overview. Journal of thrombosis and haemostasis. 2015;13:S304-S12.
4. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. European journal of cardio-thoracic surgery. 2010;37(6):1353-9.
5. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. Jama. 2004;291(14):1720-9.
6. Greenberg JW, Lancaster TS, Schuessler RB, Melby SJ. Postoperative atrial fibrillation following cardiac surgery: a persistent complication. European Journal of Cardio-Thoracic Surgery. 2017;52(4):665-72.
7. Saxena A, Dinh DT, Smith JA, Shardey GC, Reid CM, Newcomb AE. Usefulness of postoperative atrial fibrillation as an independent predictor for worse early and late outcomes after isolated coronary artery bypass grafting (multicenter Australian study of 19,497 patients). The American journal of cardiology. 2012;109(2):219-25.
8. Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, et al. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database of Systematic Reviews. 2013(1).
9. Macle L, Cairns J, Leblanc K, Tsang T, Skanes A, Cox JL, et al. 2016 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Canadian Journal of Cardiology. 2016;32(10):1170-85.
10. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al. 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 Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1-76.
11. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2011;365(11):981-92.
12. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine. 2011;365(10):883-91.
13. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2009;361(12):1139-51.
14. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2013;369(22):2093-104.
15. Hanley CM, Kowey PR. Are the novel anticoagulants better than warfarin for patients with atrial fibrillation? (2072-1439 (Print)).

16. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369:1206-14.
17. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.
18. Lamy A, Eikelboom J, Sheth T, Connolly S, Bosch J, Fox KA, et al. Rivaroxaban, aspirin, or both to prevent early coronary bypass graft occlusion: the COMPASS-CABG study. Journal of the American College of Cardiology. 2019;73(2):121-30.
19. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. Journal of the American College of Cardiology. 2017;69(7):871-98.
20. Beller JP, Krebs ED, Hawkins RB, Mehaffey JH, Quader MA, Speir AM, et al. Non–vitamin K oral anticoagulant use after cardiac surgery is rapidly increasing. The Journal of Thoracic and Cardiovascular Surgery. 2019.
21. Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Blood pressure. 1992;1(2):113-9.
22. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen M, Fisher W, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. Journal of Thrombosis and Haemostasis. 2010;8(1):202-4.
23. Raftery J, Young A, Stanton L, Milne R, Cook A, Turner D, et al. Clinical trial metadata: defining and extracting metadata on the design, conduct, results and costs of 125 randomised clinical trials funded by the National Institute for Health Research Health Technology Assessment programme. Health Technol Assess. 2015;19(11):1-138.
24. CADTH. Guidelines for the Economic Evaluation of Health Technologies: Canada 2017 [4:[Available from: https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.
25. Blackwelder WC. "Proving the null hypothesis" in clinical trials. Controlled clinical trials. 1982;3(4):345-53.
26. Connolly SJ. Anticoagulant-related bleeding and mortality. Journal of the American College of Cardiology. 2016;68(23):2522-4.
27. Steinberg BA, Simon DN, Thomas L, Ansell J, Fonarow GC, Gersh BJ, et al. Management of major bleeding in patients with atrial fibrillation treated with non–vitamin K antagonist oral anticoagulants compared with warfarin in clinical practice (from phase II of the outcomes registry for better informed treatment of atrial fibrillation [ORBIT-AF II]). The American journal of cardiology. 2017;119(10):1590-5.
28. Eikelboom JW, Connolly SJ, Hart RG, Wallentin L, Reilly P, Oldgren J, et al. Balancing the benefits and risks of 2 doses of dabigatran compared with warfarin in atrial fibrillation. Journal of the American College of Cardiology. 2013;62(10):900-8.
29. Investigators FOtASiAIS. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. New England Journal of Medicine. 2006;354(14):1464-76.

30. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. Bivalirudin during primary PCI in acute myocardial infarction. New England Journal of Medicine. 2008;358(21):2218-30.
31. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation. 2012;125(1):e2-e220.
32. Feindel CM. The current status of cardiac surgery workforce in Canada. http://www.royalcollege.ca/portal/page/portal/rc/common/documents/advocacy/hhr_attachment6_e.pdf 2010 [Available from: http://www.royalcollege.ca/portal/page/portal/rc/common/documents/advocacy/hhr_attachment6_e.pdf.

CHAPTER 5: CONCLUSION AND FINAL REMARKS

This thesis explored the management of oral anticoagulation (OAC) for stroke prevention in patients with atrial fibrillation (AF) in two clinical settings: a) the emergency department (ED), and b) after cardiac surgery.

OAC in the Emergency Department

In the ED, physicians are in a unique position to initiate OAC; however, prescription remains low. Using the global RE-LY AF registry, I retrospectively evaluated the clinical factors associated with new OAC prescription in the ED and with long term OAC use. Factors associated with initiating OAC in the ED included: specialist consultation for AF management, persistence of AF at ED discharge, rheumatic heart disease, diabetes mellitus, and admission to the hospital. As hypothesized, patients discharged from ED on OAC were nearly three times more likely to be using OAC a year later and had significantly lower rates of death and stroke. These findings support a growing momentum for early OAC in the ED to improve long-term stroke prevention.(1, 2)

While the findings were robust, there were some limitations. In particular, the RE-LY AF registry enrolled patients in an era where the only available OAC agents were vitamin K antagonists. With the uptake and convenience of DOACs, initiating OAC in the ED may become more frequent. Beyond this analysis, it might have been informative to perform a subgroup analysis of patients who were discharged from the ED, as this patient population likely has a different risk profile compared to patients who required hospital admission. Additionally, a subgroup analysis focused on patients who were diagnosed with AF but presented with another chief complaint in the ED (e.g. AF as a secondary diagnosis to pneumonia) may provide information on an understudied patient population. I suspect clinical patterns may differ in this

patient population due to the belief that AF occurring in the setting of an acute illness may convert once the illness resolves.(3)

OAC after cardiac surgery

AF is the most common complication after cardiac surgery. These patients are often prescribed OAC. In the post-operative setting, OAC prescription should aim to reduce the thromboembolic risk, but also to minimize the risk of major bleeding, which is higher in this population. Although uncertainty remains as to which patients with post-operative AF benefit from OAC, the focus in the third and fourth chapters of my thesis is on the choice of OAC agent. I performed a systematic review and meta-analysis that compared DOACs to VKAs in patients requiring OAC early after cardiac surgery. From eight observational studies of patients with AF, pre-existing or new-onset, after cardiac surgery (excluding mechanical valve replacement/repair) I found an association between DOACs and a reduction in major bleeding in the 30-days after surgery when compared to VKAs. However, the risks of stroke and mortality were similar. Given the observational nature of the data and the absence of well-adjusted analyses, I have very low confidence in these results. Accordingly, an expert panel from the American College of Cardiology has called for further study of DOACs in the post cardiac surgery period this practice.(4) Thus, I propose the Direct oral Anticoagulants versus warfariN after Cardiac surgEry (DANCE), a multicenter, open label, vanguard trial with blinded adjudication of outcomes to minimize risk of bias. The trial will have a noninferiority design and its primary outcome will be major bleeding as DOACs' efficacy at preventing thromboembolic outcomes in patients with AF is well established. If the multicentre vanguard phase demonstrates feasibility without major changes to the protocol, we will roll the vanguard participants in the full definitive trial.

To finalize the design of this trial, some areas require further information. For instance, the choice of the margin of noninferiority needs to be evaluated. This will involve collaborating with clinical experts and surgical patients to understand their perspective on an acceptable non-inferiority margin. Successfully implementing this trial will require a collaborative effort from medical and surgical healthcare providers, statisticians and researchers. I will remain deeply involved in the management and coordination of DANCE as a project officer.

Final Remarks

The Health Research Methodology program's experiential learning approach has provided me with the fundamental knowledge to design, analyze and appraise a variety of research studies. The ongoing support of my mentors and colleagues at McMaster University and the Population Health Research Institute have been paramount in my development as a young clinical researcher. I will continue to cultivate these research skills as I build my career as a clinician-scientist.

REFERENCES

1. Atzema CL, Jackevicius CA, Chong A, Dorian P, Ivers NM, Parkash R, et al. Prescribing of oral anticoagulants in the emergency department and subsequent long-term use by older adults with atrial fibrillation. CMAJ. 2019;191(49):E1345-E54.
2. TW B, KA M. Anticoagulation for emergency department patients with atrial fibrillation: is our duty to inform or prescribe? Ann Emerg Med. 2013;62(6):566-8.
3. McIntyre WF, Healey J. Stroke Prevention for Patients with Atrial Fibrillation: Beyond the Guidelines. J Atr Fibrillation. 2017;9(6):1475.
4. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. Journal of the American College of Cardiology. 2017;69(7):871-98.