A STUDY OF THE CONTEMPORARY ATRIAL FIBRILLATION EPIDEMIOLOGY AND ORAL ANTICOAGULATION IN BRITISH COLUMBIA: A POPULATION BASED STUDY

by

Patrick Daniele

B.Sc., Simon Fraser University, 2015

A THESIS SUBMITTED IN PARTIAL FULFULLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

The Faculty of Graduate and Postdoctoral Studies

(Population and Public Health)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

March 2020

The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis entitled:

A Study of the Contemporary Atrial Fibrillation Epidemiology and Oral Anticoagulation in British Columbia: A Population Based Study

submitted by Patrick Daniele in partial fulfillment of the requirements for

the degree of Master of Science

in Population and Public Health

Examining Committee:

Dr. Joel Singer, Professor, School of Population and Public Health, UBC
Supervisor

Dr. Karin Humphries, Associate Professor, Department of Medicine, UBC
Supervisory Committee Member

Dr. Jason Sutherland, Professor, School of Population and Public Health, UBC
Additional Examiner

Additional Supervisory Committee Members:

Dr. Nathaniel Hawkins, Assistant Professor, Department of Medicine, UBC
Supervisory Committee Member

Abstract

Background: Atrial fibrillation (AF) is the most common sustained arrhythmia with an estimated prevalence between 1-3%. There is a paucity of research studying the contemporary AF epidemiology and novel stroke prophylaxis pharmaceuticals for AF in Western Canada. Starting in 2011, the first direct oral anticoagulant (DOAC) drugs were approved in Canada. This thesis identifies and describes British Columbia's (BC) AF population then explores epidemiological trends and differences in AF including incidence, prevalence, treatment preferences, and outcomes. Furthermore, age and sex differences are investigated in each endpoint to identify potential health inequalities.

Methods: This study linked administrative healthcare databases to identify the AF population in BC from 2008 to 2016. Patient characteristics were defined at date of AF diagnosis. Clinical endpoints following AF diagnosis included hospital admission, use and type of oral anticoagulants (OAC), and adverse outcomes. Analyses were stratified by age and sex.

Results: The incidence of AF remains stable throughout the study window at approximately 0.43% per year (431/100,000 in 2016). The prevalence of AF grew from 2.2% in 2008 to 3.2% in 2016 with provincial demographics shifting towards an older population. The rate of OAC use following incident AF diagnosis was sub-optimal; among patients guideline indicated for OAC, 45.9% received OAC within 100 days of diagnosis. Temporal trends were observed in first OAC; DOACs grew to approximately 65% of all initial OAC prescriptions by 2016. Apixaban and rivaroxaban were associated with lower risk of composite events (mortality, stroke, and heart failure) than warfarin (adjusted hazard ratios 0.75 (0.66, 0.86) and 0.77 (0.70, 0.86), respectively). By 2016, the sex difference in OAC use had disappeared and outcomes were comparable. Rates of incidence, prevalence, OAC use, and outcomes are strongly associated with age.

Conclusions: The burden of AF is growing in BC; the population is shifting to an older, more at risk population. The broadened armamentarium of OAC agents available is being utilized and is associated with improved outcomes. The epidemiology of AF, the treatment, and outcomes of patients differ by age and sex; therefore, future research should account for age and sex differences through appropriate methodology.

Lay Summary

Atrial fibrillation (AF) is the most common arrhythmia and affects between 1-3% of the population. Oral anticoagulants (OAC) are essential to prevent strokes in patients with AF. Starting in 2011, novel pharmaceuticals novel drugs which are more convenient than warfarin, which requires regular blood testing, were approved. This study uses healthcare system data to identify and describe the AF population, and evaluate treatment, outcome, and potential health inequalities related to age and sex. The study found the burden of AF is increasing as the population grows older. New drugs are being prescribed and the outcomes of patients using them are better than warfarin. Women are older at time of diagnosis, but by 2016 equally likely to be treated, and have similar outcomes to men with comparable characteristics. Increasing age is associated with the development of AF, different treatment choices, and higher rates of adverse outcomes.

Preface

The study protocol and analyses presented henceforth were approved by the University of British Columbia's Research Ethics Board [certificate # H17-02216]

The study methodology was developed through collaboration of P. Daniele and the thesis supervisory committee. The ethics application was completed by Dr. Nathaniel Hawkins and the Data Access Request was completed by P. Daniele to access administrative databases stored at Population Data BC.

All analyses were performed by P. Daniele. The thesis was completed with the guidance of the thesis supervisory committee, Drs. Joel Singer, Karin Humphries, and Nathaniel Hawkins from the University of British Columbia.

Results presented in chapter 5 surrounding sex differences in emergency department presentations of atrial fibrillation were presented by P. Daniele at the European Society of Cardiology Congress, August 29th to September 4th, 2019 in Paris, France.

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Acknowledgements

First and foremost, I would like to thank my supervisors Drs. Joel Singer and Karin Humphries. Their patience, kindness, and mentorship have made this thesis possible. Second, I would like to thank my colleagues and friends at the BC Centre for Improved Cardiovascular Health. This wonderful group supported me throughout my studies. Finally, I would like to thank my family who have loved and inspired me during this challenging undertaking.

1. Introduction

Chapter 1 reviews the literature to identify key knowledge gaps which this study seeks to address. The literature review focused on epidemiology, clinical management, inequalities, and treatment setting. The summary is followed by detailed study objectives. Chapter 2 describes the methods used to address the study objectives followed by the results in Chapter 3. Chapter 4 summarizes the results within the greater context of the literature and includes key findings, limitations, and areas for future research.

1.1 Review of Atrial Fibrillation

Atrial fibrillation (AF) is a heart arrhythmia caused by chaotic electrical signals in the heart resulting in irregularly or rapidly beating atria. While most AF is asymptomatic, common symptoms include heart palpitations, fainting, lightheadedness, chest pain, fatigue, and shortness of breath. [1-7] Risk factors for AF include hypertension, diabetes, valve disease, heart failure, coronary artery disease, and cardiomyopathy. [8-11] However, approximately 50% of AF is unrelated to clinical risk factors and advancing age appears to be the primary explanation for AF development. [11] While many patients remain asymptomatic, there are significant complications associated with AF. Disorganized beating of the atria reduces the ability of the heart to pump blood which causes blood to pool in the atria and form blood clots leading to strokes. AF patients have up to a 5-fold higher risk of stroke and studies have estimated approximately 15% of all strokes are caused by AF. [12] Furthermore, strokes caused by AF are more severe than non-AF strokes; one study estimated ischemic strokes caused by AF are approximately twice as likely to be fatal compared to non-AF strokes. [13] In addition to increased stroke risk, AF is associated with a 1.5 to 1.9-fold increase rate of mortality, a 2-fold increase in the rate of myocardial infarction (MI), and a 3.4-fold increase in the rate of heart failure. [3, 14, 15]

AF is the most common sustained arrhythmia with an estimated global burden of 33.5 million people in 2010.[16] The prevalence varies markedly across countries with a prevalence of 1-2% in most European and North American countries, 0.1% in India, 1.1% in Taiwan, and 4% in Australia.[17-21] Higher prevalence in western countries is largely attributable to older populations.[22] AF development is strongly associated with advanced age; one study found ages of 60 to 69, 70 to 79, and 80 to 89 are associated with a 4.98, 7.35, and 9.33-fold increased risk

of AF compared with ages 50 to 59, respectively.[23] Similar associations between age and AF have been observed and reported around the world.[19, 24-34]

The association between age and AF development has caused the burden of AF to increase rapidly throughout the western world and is projected to continue rising.[16, 35, 36] Age adjusted incidence in the United States grew from 3.7 in 1958 to 13.37 in 2007 per 1000 person years.[23] In 2000, the estimated burden of AF in the United States was estimated to be 5.1 million and projected to increase to 12-15 million by 2050. [35] Similar models have projected a burden of 17.9 million people in the European Union by 2060 up from 8.8 million people in 2010. [36]

The Framingham Heart Study (FHS) estimated the lifetime risk of AF was 26% and 23% for men and women at age 40, respectively.[37] Similar results were observed in the Rotterdam study which reported a lifetime risk of AF for men and women of 23.8% and 22.2%, respectively.[38] Comparing the lifetime risk at age 40 of AF, 1 in 4, to that of breast cancer, 1 in 8, highlights the epidemic rate of AF and the necessity to thoroughly study and understand the management, outcomes, and inequalities. [37, 39]

Modern estimates of AF incidence and prevalence are not readily available for British Columbia (BC). The 2016 census showed that between 2011 and 2016, the number of seniors aged 65 and older in Canada increased by 20%. [40] The shift in demographics toward an older and more at-risk population may result in changes to the characteristics of AF patients and rates of AF. Therefore, it is essential to accurately describe the incident and prevalent AF populations, the rates of AF, and assess whether temporal trends exist in the incidence and prevalence of AF in BC. Addressing this knowledge gap would allow policy makers to properly plan and manage the AF population in BC.

1.2 Atrial Fibrillation Management

Management of AF centers around two main objectives: restoring the rate and/or rhythm of the heart and stroke prevention. Newly diagnosed AF patients are typically prescribed a rate control medication such as beta blockers or calcium channel blockers. Rate control medications lower the heart rate with a resting goal heart rate of <110 beats per minute. [41] Rhythm control medications, antiarrythmics, may be used alone or in conjunction with rate control medications.

Antiarrhythmics such as amiodarone, propafanone, and digoxin are prescribed to restore heart rhythm thereby controlling AF. Cardioversion or catheter ablation may be used to restore the heart rate and rhythm alone or in conjunction with medications. Finally, to manage risk of stroke, patients with elevated stroke risk are prescribed oral-anticoagulant (OAC) therapy which prevents the formation of blood clots and thereby reduces the risk of stroke. The medical requirement for OAC therapy depends on each patients' stroke risk.

1.2.1 Stroke Risk

The increased risk of stroke among AF patients motivates the use of OAC therapies for stroke prophylaxis. However, while OAC therapies reduce the risk of stroke, they also increase the risk of bleeding. [(42)] Therefore, several scores have been developed to identify patients with high risk of stroke and target therapies to the higher risk sub-group. In 2001, the $CHADS_2$ score was developed which assigns a score of 1 to each of: congestive heart failure, hypertension, diabetes, and age ≥ 75 years. [(43)] Additionally, the $CHADS_2$ score assigns prior stroke a score of 2 points, as the most important risk factor for future stroke. A $CHADS_2$ score is calculated for each AF patient by summing the weighted scores. This scoring algorithm stratifies stroke risk and each 1 point increase is associated with a 1.5 fold increase in the risk of stroke without OAC. [(43)] In 2010, the CHA_2DS_2-VASc score was developed, which incorporated additional risk factors into the stroke risk model. [(44)] In addition to the $CHADS_2$ components, the new score assigns a value of 1 point to each of female sex and history of vascular disease. The score for age ≥ 75 years increases to 2 points and 1 point is assigned for age between 65 and 74 years. The CHA_2DS_2-VASc more accurately identifies low and intermediate risk patients than the $CHADS_2$ score. [(44)]

The current European and American guidelines for OAC indication are based on the CHA_2DS_2-VASc score. Women and men with AF and a CHA_2DS_2-VASc score of ≥3 and ≥2, respectively, are indicated for OAC use to manage stroke risk. [(45)] The Canadian guidelines for OAC indication were updated in 2014 and use a modified $CHADS_2$ algorithm called CHADS65. [(46)] The CHADS65 algorithm recommends OAC if AF patients are either: 1) ≥ 65 years old or 2) < 65 years old with any of diabetes, congestive heart failure, hypertension, or prior stroke. This algorithm is not recognized elsewhere in the world.

1.2.2 Oral Anti-coagulation

OAC therapy is used in patients with AF for stroke prophylaxis by preventing the formation of blood clots in the heart which cause strokes. Randomized controlled trials comparing OAC therapy to no OAC therapy are not available as the use of OAC predates the requirement for evidence from randomized control trials. However, studies have compared OAC to 75mg and 325mg aspirin among both inpatients and out-patients with persistent AF in Denmark, Canada, and the United States and reported between 36-68% reductions in the annual stroke rate. [47-51] Regardless of the known therapeutic benefit associated with OAC in AF patients, a significant treatment gap remains. [52-54] For example, the GARFIELD study of AF patients across Australia, Brazil, Canada, East Asia, Mexico, and Western Europe showed 40.7% of patients with a CHA_2DS_2-VASc ≥ 2 were not prescribed OAC. [55] A potential cause of the treatment gap may be the increased risk of bleeding associated with OAC. The ATRIA study cohort reported patients receiving OAC had an annual rate of major haemorrhage of 1.1% and an annual rate of intracranial haemorrhage of 0.47%. [56] Patients experiencing a major haemorrhage had a 50% 30-day mortality rate. One explanation for the observed treatment gap is risk aversion among physicians who overemphasize bleeding prevention at the expense of increased stroke risk. Bleeding events caused by OAC are easily observed, whereas strokes prevented by OAC are not observable. The result may cause physicians to undertreat patients with AF. Another hypothesis to explain the treatment gap is the challenge of managing patients using warfarin. [57]

Warfarin for stroke prevention predates the requirement for evidence from randomized controlled trials. Until 2010, Warfarin was the only OAC available for stroke risk management in AF and remained the most prescribed OAC in Canada as of 2016. [58, 59] Warfarin is inexpensive and effective, but there are significant challenges in managing patients' dosages. Patients require routine monitoring to ensure their blood clotting rate, measured by international normalized ratio (INR), is within the proper therapeutic range. An INR that is too low results in reduced therapeutic benefit for stroke prevention and an INR that is too high is more likely to cause bleeding. Typically, INRs among the general population not receiving OAC is 0.8 to 1.2, and the target range for AF patients is 2-3, and any INR > 4.5 requires discontinuation due to bleeding risk. [60] One study has shown INRs greater than 3 are associated with a 20-fold increase in the risk of major bleeding compared with normal INRs. [61] Routine monitoring is required because the levels of warfarin in the blood fluctuate significantly for several reasons. First, the rate of

warfarin metabolism varies significantly between patients; meaning the rate at which warfarin is eliminated from the body is highly variable, therefore, doses are not consistent across patients. [62] Second, there are many food and drug interactions which alter the levels of warfarin the blood. Food and drug interactions may inhibit the ability of the warfarin to prevent clotting and therefore increase the risk of stroke or may enhance the effect of warfarin resulting in increased risk of bleeding. [62] For example, foods high in vitamin K, such as green tea, broccoli, or spinach may reverse the effects of warfarin and restore the bloods ability to clot.[62] Drugs such as acetaminophen or amiodarone may also interact with warfarin. [63, 64] Therefore any changes to diet or drug regimens may result in drastically different levels in the blood. The challenges associated with managing patients on warfarin led to the development of direct oral anti-coagulants (DOAC).

1.2.3 Direct Oral Anti-Coagulants

For decades, warfarin was the only OAC for stroke prevention among patients with non-valvular AF. However, its limitations, including increased bleeding risk and need for routine monitoring led to the development of DOACs specifically, dabigatran, rivaroxaban, apixaban, and edoxaban. DOAC use began in Canada with the approval of dabigatran in October 2010, followed by rivaroxaban in January 2012, apixaban in December 2012, and finally edoxaban in November 2016. The approval of these medications followed the results of large-scale randomized control trials, specifically: Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY; dabigatran), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), and the ENGAGE AF–TIMI 48 study (edoxaban). [65-68] The trials were designed as non-inferiority trials and each drug was compared against warfarin. Results of each randomized control trial are summarized below.

RE-LY compared dabigatran at two dosages, low (110mg) and high (150mg), to warfarin. Though the dose was determined randomly in the study, a lower dose, 75 mg, is now recommended in patients with poor kidney function. The primary endpoint for the study was stroke and systemic embolism and secondary outcomes included bleeding and all-cause mortality. To satisfy non-inferiority, the one-sided 97.5% confidence interval (CI) of the relative

risk (RR) for the primary endpoint could not exceed 1.46. The study showed non-inferiority of dabigatran compared to warfarin with respect to the primary outcome in low dose (RR, 0.91; 95% CI 0.74 to 1.11; P < 0.001 for non-inferiority) and superiority in high dose (RR 0.66; 95% CI 0.53 to 0.82; P<0.001 for superiority).[68] Additionally, rates of life-threatening bleeding (p <0.05), intracranial bleeding (p<0.001), and major and minor bleeding (p<0.002) were lower than warfarin at both dosages.

ROCKET-AF compared rivaroxaban at a single dosage to warfarin. The primary endpoint for the study was stroke and systemic embolism and secondary outcomes included bleeding and all-cause mortality. To satisfy non-inferiority, the one-sided 97.5% CI of the RR for the primary endpoint could not exceed 1.44. The study showed non-inferiority of rivaroxaban compared to warfarin with respect to stroke or systemic embolism (hazard ratio [HR] 0.79, 95% CI 0.65 to 0.95; P<0.001 for non-inferiority).[67] The study also found similar rates of bleeding between warfarin and rivaroxaban (HR 1.03, 95% CI 0.96 to 1.11).

ARISTOTLE compared apixaban at a single dosage to warfarin. The primary endpoint for the study was stroke and systemic embolism and secondary outcomes included bleeding and all-cause mortality. To satisfy non-inferiority, the one-sided 97.5% CI of the RR for the primary endpoint could not exceed 1.46. The study showed superiority with respect to stroke or systemic embolism (HR 0.79, 95% CI 0.66 to 0.95, P=0.01 for superiority) and lower all-cause mortality (HR 0.89, 95% CI 0.80 to 0.998).[66] The study also showed lower rates of bleeding (HR 0.69, 95% CI 0.60 to 0.80). Additionally, the rate of intracranial hemorrhage was 0.33% per year in the apixaban group and 0.80% per year in the warfarin group (HR 0.42, 95% CI, 0.30 to 0.58).

ENGAGE compared edoxaban at two dosages, high (60mg) and low (30mg), to warfarin with a primary endpoint of stroke or systemic embolism. A 60mg dose of edoxaban is now recommended for stroke prophylaxis in AF. To satisfy non-inferiority, the one-sided 97.5% confidence interval (CI) of the relative risk (RR) for the primary endpoint could not exceed 1.38. The study showed superiority to warfarin with respect to stroke or systemic embolism at high dose (HR 0.79; 97.5% CI 0.63 to 0.99; P=0.02 for superiority) and non-inferiority at low dose (HR 1.07; 97.5% CI 0.87 to 1.31; P=0.005 for non-inferiority).[65] The trial found edoxaban was superior to warfarin and had lower rates of major bleeding and all-cause mortality at both dosages.

A meta-analyses combined the results of RE:LY, ROCKET-AF, ARISTOTLE and ENGAGE to compare all DOACs vs. warfarin. The study found significant reductions in stroke or systemic embolism (RR 0.81, 95% CI 0.73 to 0.91), which was primarily driven by a reduction in hemorrhagic stroke (RR 0.49, 95% CI 0.38 to 0.64), intracranial hemorrhage (RR 0.48, 95% CI 0.39 to 0.59) and all-cause mortality (RR 0.90, 95% CI 0.85 to 0.95) in the DOAC group compared to warfarin. [69] However, the study found increased rates of gastro-intestinal bleeding in the DOAC group (RR 1.25, 95% CI 1.01 to 1.55). The analysis reported an I^2 statistic of 47% indicating moderate heterogeneity between the studies, though the heterogeneity was only borderline significant using the conventional $p<0.1$ criteria. [70] The heterogeneity may be attributable to the choice of population in the apixaban trial, which sampled a healthier population. [66]

Unlike warfarin, DOACs do not require regular monitoring of INRs. [71] Additionally, DOACS have fewer food and drug interactions than warfarin. [71] The convenience associated with DOAC use may be strong enough incentive for patients and physicians to elect to initiate on or switch to DOACs. However, there are two drawbacks to DOACs. First, warfarin is more easily reversed in the case of an emergent bleeding event. Application of prothrombin complex concentrate can completely restore clotting factors within 15 minutes. [72] Each DOAC has an FDA approved reversal agent as of 2019, however DOAC reversal agents are expensive and post-market studies are still underway with expected completion in 2023. [73] Second, the cost of each DOAC is approximately 40 to 50 times the price of warfarin; a one month supply of warfarin is $10 USD compared to $385 to $525 USD for DOACs. [74]

The development and approval of DOACs significantly expands the options available for stroke prophylaxis in AF patients. However, the increased cost versus warfarin motivates the need to thoroughly understand the prescription patterns and outcomes of patients prescribed DOACs. Several knowledge gaps remains with the recent approval of DOACs. First, there is limited knowledge as to whether preferences in OAC initiation are changing over time and whether the rate of initiation is increasing thereby reducing the observed treatment gap. Second, the results of clinical trials showed DOACs were non-inferior for most outcomes compared with warfarin, but each DOAC was not compared head-to-head. The choice of DOAC cannot, therefore, be informed by clinical trial evidence Furthermore, the generalizability of clinical

trials results are often limited. While observation studies may be susceptible to bias, they may answer questions which describe the real-world experiences and outcomes of patients. In this case, observations studies may be used to provide valuable insights as to whether DOACs have truly improved the rates of initiation and outcomes. Addressing these knowledge gaps will provide valuable insight into the experience of AF patients following the introduction of DOACs to Canada.

1.3 Health Inequalities

Health inequalities or disparities are differences in health and healthcare related to important demographic, social, or environmental factors including, but not limited to, age, sex, socioeconomic status, ethnicity, and rurality. [75, 76] Differences related to these factors often exist in access to healthcare, diagnosis, treatment, and outcomes. [75] Inequalities may exist for a variety of reasons including differences in presentation, etiology, or genetics or due to biases from healthcare practitioners, researchers, and the general population. [75] The Canadian Institute for Health Information (CIHI) has emphasized the need to study health inequalities in all research in order to identify actionable insights to addresses heterogeneity in the health of Canadians. [77] The study recognized that inequalities are often understudied and therefore differences are either unknown or considered normal. [77] For example, MI is typically considered a "man's disease", however, recent evidence has shown that young women are being underdiagnosed. [78] Young women may actually have similar rates of MI to young men, but are systematically under identified and undertreated and therefore experience worse outcomes than men following MI. In the context of AF, age and sex have been identified as two potential sources of health inequalities. [6] Age and sex differences have been observed in the diagnosis of incident AF and the treatment and outcomes following AF diagnosis. [2, 5, 6, 16, 23, 38, 56, 78-89]

1.3.1 Age Differences

Age differences have been observed in the epidemiology, treatment, and outcomes of AF. Age has been recognized as a strong predictor of AF development; the prevalence of AF is known to increase steadily with advancing age. [23] Ages of 60 to 69, 70 to 79, and 80 to 89 are associated with a 4.98, 7.35, and 9.33-fold increase risk of AF compared with ages 50 to 59, respectively. [23] Increasing age is also associated with higher burden of comorbidities such as hypertension, diabetes, obesity etc. all of which significantly increase stroke risk. [90, 91] Age

along with comorbidities compose the CHA_2DS_2-VASc score which stratifies stroke risk. [44] However, treatment with OAC is often inversely associated with age.

There is an apparent risk-treatment paradox for oral anticoagulation in AF, wherein the older and therefore higher risk population receives less or lower doses of appropriate OAC than the younger lower risk population. [89] The elderly patients (≥ 75 years of age) are more likely be prescribed anti-platelet agents which both Canadian and European guidelines indicate is not sufficient for managing stroke risk. [89] Treatment preferences surrounding optimal OAC agent are still being debated. Several studies have demonstrated the safety and efficacy of DOACs among the elderly. [92, 93] However, the same studies urge caution as seniors have a higher risk of bleeding events and renal complications.

Rates of mortality, stroke/TIA, and systemic thromboembolism are higher among elderly AF patients compared to their younger counter-parts. One study reported rates of mortality and a composite endpoint of death, stroke/TIA, and systemic embolism between elderly and non-elderly patients at 11.5% vs. 3.7% and 13.6% vs. 4.9% respectively. [89] The difference in risk of adverse events remained even after adjustment for confounders associated with age, indicating age is a strong independent predictor of adverse events.

The literature shows age is an important factor in the epidemiology, treatment, and outcomes of AF. Therefore, this study will consider age for all endpoints and assess whether age differences exist in any of the aforementioned areas.

1.3.2 Sex Differences

This section, and analyses throughout this study, explore sex differences. The study authors acknowledges the difference between biological sex and gender. However, sex differences in cardiology research are commonly described as comparisons between women and men. Therefore, this study will use the terms women and female, and men and males interchangeably.

The incidence and prevalence of AF are higher in men than women. The Framingham study reported an incidence of 1.6 per 1000 person years in women compared with a 3.8 in men. [37] The difference in AF development persists even after adjustment for age and differences in patient characteristics; men have 1.5-fold higher odds of developing AF than women. [23] The

prevalence of AF in the UK among residents > 35 years was estimated to be 3.9% in men and 2.7% in women. [94] However, in spite of the both lower incidence and prevalence, women make up a larger proportion of the total AF population due to increased longevity. [38] Sex differences in incidence and prevalence have been observed across studies and throughout European, North American, and Asian populations. [16, 22, 36-38]

Men and women differ in terms of clinical presentation; women present more often with hypertension and valvular disease, whereas men tend to present with coronary artery disease, MI, and abnormal left ventricular function. [79] Symptoms of AF also tend to differ between men and women; women experience palpitations less often, and experience weakness more often than men. [1] Women appear to be more impacted by AF diagnosis as they are less likely to be asymptomatic and as a result report lower quality of life. [95]

Sex differences have been reported in the management of patients with AF including differences in OAC strategy and agent. A risk treatment paradox has been observed in stroke prevention strategies, wherein women who are at higher risk of stroke receive less oral anti-coagulation or lower doses of OAC. [96] Instead of OAC, women are more likely to be prescribed anti-platelet agents; however, anti-platelets alone are not considered sufficient for stroke prevention by both Canadian and European guidelines. [44, 46, 96] In addition to receiving less oral-anticoagulation, sex differences have been reported in the choice of OAC agent. Women tend to be prescribed DOACs as the anticoagulant of choice more often than men. [97] One study reported a difference in the residual risk of stroke that was 1.28-fold higher in women than men on warfarin, which is hypothesized to motivate the observed treatment preference for DOACs in women. [84] Women also tend to have fewer major bleeding events on DOACs compared to men. [84] Treatment preferences may also differ by DOAC agent. Studies have observed women are more likely to be prescribed rivaroxaban and men were more likely to receive dabigatran. [97] Preferences in DOAC agent may be related to observed sex differences in the rates of bleeding between DOACs. Among women taking rivaroxaban, the risk of bleeding was observed to be 0.89 in women and 1.12 in men compared with warfarin. [84]

Rates of outcomes following AF diagnosis differ between men and women. A meta-analysis reported 12% higher risk of all-cause mortality among women compared to men. [98] The CHA_2DS_2-VASc score includes female sex as an important predictor of increased risk of

stroke. [44] However, recent evidence has shown that female sex is not an independent predictor of stroke. The study compared women with lone AF, CHA_2DS_2-VASc = 1, to men with lone AF, CHA_2DS_2-VASc = 0, and showed that men and women experience the same risk of stroke in the absence of other risk factors. [88] However, in the presence of other risk factors, the stroke risk is higher in women. [88] Strokes experienced by women also tend to be more severe. [2] Therefore, as women enter the high risk group, they are more likely to have a stroke than men and strokes are more likely to be debilitating.

The literature shows men and women with AF differ with respect four key areas: epidemiology, presentation, treatment, and outcomes. However, there is limited research into sex differences in each of these areas following the approval of DOACs to Canada. Therefore, this study will consider sex for all endpoints and assess whether sex differences exist in the epidemiology, clinical presentation, uptake, treatment preferences, and outcomes of AF patients in BC.

1.4 Atrial Fibrillation in the Emergency Department

AF is a sustained arrhythmia and optimal management requires regular healthcare interactions to ensure appropriate OAC selection/dosing and rhythm/rate management therapies. While patients may be managed entirely on an out-patient basis, a recent study estimated only 43% of Canadian could access their family physician the same day or next-day. [99] Given the observed barriers to seeing an out-patient physician and the symptoms of AF such as palpitations and shortness of breath, the emergency department (ED) may be the first point of contact for patients with incident AF. [7] Therefore, appropriate selection of cases for admission to hospital and OAC therapy following presentation to the ED with incident AF is imperative.

Studies often identify AF cohorts through hospitalization records alone, however one study reported fewer than 50% of patients were admitted to hospital following an ED visit with primary diagnosis of AF. [1] Therefore, the burden of AF and the OAC treatment gap may be significantly underestimated in part due to the high proportion of patients discharged home following index ED diagnosis. AF patients without proper OAC are at a significantly higher risk of stroke, therefore ensuring adequate care is provided in the ED is critical to minimizing long term adverse outcomes. One study reported that treatment setting is associated with differences

in diagnosis, treatment, and outcomes; heart failure patients in the ED had the highest rates of repeat ED visits, and future hospitalizations. [100]

Sex differences in the management and outcomes of AF patients diagnosed in the ED have not been studied extensively. A knowledge gap exists in examining sex differences in the rates of admission, OAC use, and outcomes following incident AF diagnosis in the ED.

1.5 Study Objectives

A review of the current literature surrounding the epidemiology, management, outcomes, and inequalities associated with AF identified several key knowledge gaps. First, demographics and clinical characteristics of the incidence and prevalent AF populations are changing over time. Therefore, accurately describing the AF population will provide valuable insight into the current landscape of AF patients in BC. Second, BC is lacking contemporary estimates of age- and sex-standardized incidence and prevalence rates of AF and trends over time are poorly described. Third, the sudden increase in pharmacological options available for stroke prophylaxis in AF patients results in a lack of knowledge surrounding temporal trends in uptake, and prescription patterns. Additionally, at this time DOACs have not been compared head to head, and there is limited data regarding the real world outcomes of patients taking DOACs vs. warfarin. AF patients are managed in a variety of settings with many exclusively in the out-patient setting. However, a key gap exists in understanding the experiences of patients who are diagnosed in the ED. Finally, age and sex are important factors in the AF development, management, and outcomes. Based on these knowledge gaps, this study was conducted with the following objectives:

1. Describe the incident AF populations with respect to demographics and comorbidities in BC overall, and by age and sex.
2. Estimate the rates of incidence and prevalence of AF in BC and assess whether rates vary by age and sex.
3. Describe temporal trends in OAC use for warfarin, apixaban, rivaroxaban and dabigatran in all newly diagnosed AF patients in BC. Furthermore, assess whether prescription trends vary by age and sex.
4. Examine and compare the rates of major adverse outcomes for warfarin and DOACs, and determine if rates of outcomes vary by age and sex.
5. Examine sex differences in the rates of hospital admission, OAC use, and major adverse outcomes following presentation to the emergency department with incident AF.

2. Methods

AF is the most common arrhythmia affecting up to 33.5 million people worldwide in 2010.[22] AF patients have up to a 5-fold increased risk of stroke and are at an increased risk of heart failure.[101] However, the approval of DOACs in Canada in 2011 has changed the treatment options available for the management of stroke risk in AF patients. There is an urgent need to study AF trends, treatments and outcomes as BC's shifts towards an older, more at-risk, population coupled with a sudden expansion in available pharmaceuticals for stroke prophylaxis. Understanding the modern epidemiology of AF in BC, differences in the management of stroke risk, and inequalities in the treatment and outcomes of AF patients will provide valuable insight into this condition. This chapter outlines the methods used to address these knowledge gaps.

2.1 Study Design

2.1.1 Data Sources

This study was a retrospective cohort study of AF patients using administrative health data. Administrative health databases offer an opportunity for health researchers to address research questions in a cost-effective and low-risk manner at the population level. Population Data BC maintains administrative data holdings for British Columbia and provides researchers with de-identified patient-level data that can be linked across datasets. Population Data BC's holdings include demographics, provincial medical services registration, as well as hospitalizations, and out-patient visits which result from interactions with the health care system. Many studies have used Population Data BC's administrative health data holdings to address a wide range of research questions. Population Data BC and PharmaNet holdings cover approximately 96% of all BC residents with the exception of those under federal health coverage such as status Indians, and members of the Canadian Armed forces and Royal Canadian Mounted Police.

Population Data BC holdings were accessed from January 1st, 2003 to December 31st, 2016 to identify patients diagnosed with AF. Population Data BC extracted all records for patients ≥ 20 years of age date of AF diagnosis, pharmacy dispensation, or procedure date meeting the following at least one of the following criteria:

a. AF diagnosis codes International Classification of Diseases, 9th Canadian Revision (ICD-9-CA) 427.3x or International Classification of Diseases, 10th Canadian Revision (ICD-10-CA) I48.x in any diagnosis position
b. AF specific medication: amiodarone, sotalol, flecainide, dronaderone, propafenone, or disopyramide
c. AF specific procedure: catheter ablation or cardioversion (Fee codes: 33084, 33025, Y33025)

After identifying patients with an AF diagnosis, the following databases were queried to provide detailed de-identified patient-level data during the study time frame to accurately define demographics, comorbidities, and outcomes:

1. Discharge abstracts database (DAD) containing hospitalization records [102]
2. Medical services plan (MSP) containing out-patient physician claims [103]
3. National ambulatory care reporting system (NACRS) containing emergency department visits [104]
4. Vital statistics containing mortality records [105]
5. Pharmanet holdings containing community pharmacy dispensation and claim records [106]
6. Consolidation file containing provincial medical services registration and demographics [107]

2.1.2 Cohort Definition

AF patients were identified by searching DAD, NACRS, and MSP from January 1st, 2008 to December 31st, 2016 for ICD-9-CA and ICD-10-CA codes of 427.3x and I48.x (AF/Flutter), respectively. The first encounter with an AF diagnosis code in DAD, NACRS, or MSP was considered the index AF diagnosis. The date of diagnosis was defined as admission date for DAD, registration date for NACRS, and service date for MSP. Patients were excluded if they met any of the following criteria:

1. Non-BC resident on diagnosis date
2. < 20 years of age on diagnosis date
3. Unknown sex
4. Transient AF defined as post-admit diagnosis of AF in hospital with cardiac surgery during admission (coronary artery bypass graft (CABG), valve replacement or repair, or pericardial procedure)

5. History of valve disease

BC residency at the time of diagnosis was required to ensure all other administrative health data records were available during the study. Patients <20 years of age on date diagnosis were excluded because the data extract does not include full patient records on residents under 20 years of age. Sex differences were a primary comparison of the study, therefore patients with unknown sex were excluded. AF diagnoses as indicated by post-admit diagnosis codes within a hospitalization including CABG, valve, or pericardial surgeries were excluded because the cases were more likely to be transient AF which is not a chronic condition and does require OAC treatment. Finally, patients with a history of valve disease were excluded because DOACs are not approved in the management of stroke risk among AF patients with mechanical valves.

The study tested a second cohort definition of any DAD, NACRS, or 2 MSP diagnoses within a year, but more than 30 days apart. The requirement for a second confirmatory out-patient diagnosis to confirm AF diagnosis has been used in several studies.[59, 108] This definition is less likely to capture transient AF cases which do not require OAC. However, this algorithm is more likely to misclassify true AF as non-AF particularly in patients managed through out-patient physician visits alone, which is common as the condition often does not require hospitalization. This definition would also require patients to survive long enough to receive a second diagnosis which may result in immortal time bias.

In addition to diagnosis codes, the study considered AF specific drugs such as amiodarone, sotalol, flecainide, dronaderone, propafenone, or disopyramide and AF specific procedures such as cardioversion and catheter ablation as sources to identify AF patients. However, most patients receiving AF specific drugs and/or procedures also have diagnosis codes of AF elsewhere, therefore these additional criteria did not significantly change the cohort size or AF identification dates. [109]

2.1.3 Incident vs. Prevalent AF

The study applied a five year washout period to determine incident vs. prevalent cases. AF patients identified after 2008 were considered incident cases if they did not have any AF diagnosis codes and were BC residents continuously in the previous five years. Continuous BC residency was required to ensure complete patient histories. Patients identified before 2008 were considered prevalent at the beginning of the study. Patients who entered the province during the

study window and had a diagnosis of AF before accumulating five years of history defaulted to prevalent AF. For example, a case identified in 2009, but whose registration in BC began in 2006 had at most three years of prior medical history and therefore defaulted to a prevalent case. The patients were considered prevalent for up to five years beyond diagnosis date. For example, a case identified in 2008 was considered prevalent until 2013 if no other diagnoses of AF were identified following index diagnosis. The five year prevalent period was selected to be consistent with the five year washout for incidence or prevalent AF.

2.1.4 Demographics, Comorbidities, and Medications

Age at time of diagnosis, sex, and BC residency were determined using the consolidation file. In addition to demographic data, the consolidation file indicates BC residency registration periods which may be used to determine BC residency status. To be considered a BC resident, a patient must have maintained continuous registration in the consolidation file with at most a 93 day gap in coverage. A 93 day gap has been used on other studies to allow for short lapses in registration unrelated to migration. Comorbidities were identified using ICD-9-CA codes in MSP and ICD-10-CA codes in NACRS and DAD. A five year lookback was used to determine baseline comorbidities at time of incident AF diagnosis. Comorbidities identified in DAD or NACRS required a single ICD-10-CA code within five years prior to index diagnosis date. For patients identified by hospitalizations records or ED visit resulting in hospitalization within 24 hours, comorbidities as indicated by a single ICD-10-CA code with a diagnosis type of pre-admit were also included. Comorbidities identified by out-patient physician billings required at minimum two ICD-9-CA codes in 2 year period prior at minimum 30 days apart within the previous 5 years. Two codes were required to limit the potential for misclassification due to queries with negative findings. Codes used for each comorbidity are listed in Table 1. [110, 111]

Table 1. Comorbidity ICD9, ICD10, and CCI Codes

Comorbidity	ICD-9-CA Codes	ICD-10-CA/CCI Codes
Prior Stroke/TIA	362.3, 431, 433.x1, 434.x1, 436, 435	H34.1, I61, I63, I64, G45
Prior MI	410, 412	I21, I22, I25.2
Prior CABG	Not applicable	Z95.1 CCI*:* 1.IJ.76.X
Prior PCI	Not applicable	CCI*:* 1.IJ.50.X
Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428	I25.5, I42.0, I42.6–I42.9, I43, I50
Hypertension	401–405	I10–I13, I15
Diabetes	250	E10-E14
PVD	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Liver Disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0–456.2, 570.x, 571.x, 572.2–572.8, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, I85.x, I86.4, I98.2, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4
Cancer	140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6, 196.x–199.x	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C85.x, C88.x,C90.x–C97.x, C77.x–
CKD	583, 584, 585, 586, 592, 593.9	N00-N23
COPD	490, 491, 492, 494, 496	J41, J42, J43, J44, J47
VTE (DVT/PE)	451, 453, 415	I26, I80.2, I80.3, I80.1, I82.8, I80.9, I82.9, I80.8, O22.3, O22.9, O87.1
Valvular Etiology		
Mitral or aortic valve disease	394, 395, 396, 424.0, 424.1	I05, I06, I08.0, I08.1, I085.2, I08.3, I34, I35
Tricuspid or pulmonary valve disease	397, 424.2, 424.3	I07, I08.1, I08.2, I08.8, I08.9, I36, I37
Valve surgery and procedures	Not applicable	CCI: 1.HS.80,1.HS.90, 1.HT.80, 1.HT.89,1.HT.90,1.HU.80,1.HU.90, 1.HV.80, 1.HV.90

.x includes all sublevels

Baseline medications were defined by searching PharmaNet for medications dispensed within 100 days prior to index AF diagnosis. Table 2 lists all medications defined and the Anatomical Therapeutic Chemical Classification System codes (ATC) used to identify each medication. OAC was defined as any of warfarin, apixaban, rivaroxaban, or dabigatran. Edoxaban was not included as the drug was not approved in Canada during the study timeframe. OAC naïve was defined as not filling a prescription for OAC in the previous 5 years.

Table 2. Medication ATC Codes

Category	Medication	ATC Codes
Oral Anticoagulants	Warfarin	B01AA03
	Apixaban	B01AF02
	Rivaroxaban	B01AF01, B01AX06
	Dabigatran	B01AE07
Other Medications	Beta-Blockers	C07x
	Digoxin	C01AA05
	Diltiazem/Verapamil	C08DB01, C08DA01, C09BB10
	Amiodarone	C01BD01
	Sotalol	C07AA07
	ACEI/ARB	C09Ax, C09Bx, C09Cx, C09Dx
	Statin	C10AA, C10BA, C10BX

x includes all sublevels.

First OAC prescription following incident AF diagnosis was defined by searching Pharmanet for any of warfarin, apixaban, rivaroxaban, or dabigatran within the 100 out-patient days following index diagnosis. A window of 100 out-patient days was used to allow sufficient time for patients to fill prescriptions following healthcare encounters and patients identified in hospital to deplete medications provided by hospital pharmacies. The start of out-patient follow-up began on the date of visit for cases identified by ED visits without subsequent hospitalization or MSP visits and on the date of discharge for AF cases identified through hospitalizations records or by ED visits which lead to a hospital admission. Limiting follow-up to out-patient days was necessary as medications dispensed in hospital are not captured by BC PharmaNet.

Guideline indication for OAC was defined following AF diagnosis using the CHA_2DS_2-VASc score. Women and men with AF and a CHA_2DS_2-VASc score of ≥3 and ≥2, respectively, are indicated for OAC use to manage stroke risk.[44, 45] The CHA_2DS_2-VASc score is calculated

by summing the weights assigned to each demographic and clinical factor as per the following table.

Table 3. CHA_2DS_2-VASc Score Components and Weights

Condition		Points
C	Congestive Heart Failure	1
H	Hypertension	1
A_2	Age ≥ 75	2
D	Diabetes Mellitus	1
S_2	Prior Stroke, TIA, or Thromboembolism	2
V	Vascular Disease (PAD, Prior MI)	1
A	Age 65-74 years	1
Sc	Sex category (Female)	1

Major adverse outcomes were defined as a composite endpoint of all-cause mortality, stroke, and heart failure. Additionally, bleeding events were evaluated separately as there is often a tradeoff of reduced risk of stroke with increased risk of bleed events. Therefore, including bleeding events in the composite endpoint would be inappropriate. Stroke, heart failure, and bleeding events were defined by searching hospitalization and ED records for visits with a primary diagnosis of stroke, heart failure, or bleeding. Codes used to define outcomes are listed table 4. All-cause mortality was determined by querying vital statistics for death dates.

Table 4. ICD-10-CA Outcome Codes

Outcome	ICD-10-CA Codes
Stroke/Systemic Embolism	H34.1, I61, I63, I64, I74
Heart Failure	I25.5, I42.0, I42.6–I42.9, I43, I50

2.2 Statistical Analyses

2.2.1 AF Population Characteristics

This analysis describes the incident AF population. The prevalent population consists of patients identified prior to 2008 and therefore prevalent at the beginning of the study. The incident population included any newly diagnosed AF patients identified throughout the study period. Demographics, comorbidities, and baseline medications were summarized at index

diagnosis date and stratified by age, sex, and prescribed OAC drug. Continuous variables were summarized using mean and standard deviation and compared using t-tests when normally distributed. In the presence of skewed data, continuous variables were summarized using median and inter-quartile range and compared using the Wilcoxon rank-sum test. Categorical variables were summarized by frequency and percentages and compared using a χ^2 test, Fisher's exact test, or Cochrane-Armitage test for ordinal variables.

2.2.2 Temporal Trends in AF Epidemiological

This analysis describes the burden of AF by estimating incidence and prevalence of AF and evaluating trends in BC. The incidence and prevalence of AF from 2008 to 2016 was estimated using both crude and age/sex standardized rates of AF in BC for each study year. The most recent census year, 2016, was used as the reference for standardization. Direct age standardization was used because a standard reference population of all British Columbians was available. Five year age intervals, i.e. 50-54, 55-60 etc., were used as the age categories because the BC government population estimate tables were already summarized to that level. Trends in AF incidence and prevalence were visualized graphically by age, and sex.

2.2.3 Trends in OAC Prescription

This analysis describes temporal changes in prescription trends by determining whether the rate of OAC use and initial treatment preferences following incident AF diagnosis changed over time. Furthermore, we assessed whether age or sex differences were present in the rates of OAC use and initial treatment preferences throughout the study period.

OAC rates were determined for incident AF cases between January 1st, 2008 and December 31st, 2016. Cumulative incidence functions were estimated to determine rates and 95% CIs of OAC use up to 100 days following index AF diagnosis treating death as a competing risk. Rates of OAC use were estimated for each OAC drug by treating death and other OAC as competing risks. Overall, sex, age, and OAC drug specific rates were estimated for each study year to visualize trends in OAC use. All descriptive analyses were repeated on a sub-group of guideline-indicated OAC patients to exclude patients not requiring OAC for stroke prophylaxis. Age and sex differences in the rate of OAC use were examined among guideline-indicated patients. Cox-proportional hazards (PH) models were fit with death as a competing risk to estimate unadjusted and adjusted HRs for age and sex on OAC use. Study year was included in

the model to test for time trends in the rate of OAC use. Two-way interaction effects between each of age, sex, and time were tested.

To test for age and sex differences in initial treatment preference, DOAC vs. Warfarin vs. No OAC, the cohort was restricted to OAC naïve patients who were guideline indicated for OAC from January 1st, 2011 to December 31st, 2016. To determine initial treatment preference a land-marking period of 100 days was required. Patients who died during the land-marking period were excluded. The change to the study period was required as DOACs became available in late 2010. A multinomial logistic regression model was fit with DOAC, Warfarin, or No OAC as the outcome to estimate unadjusted and adjusted ORs for age and sex.

2.2.4 Adverse Outcomes

This analysis compares adverse outcomes differ between warfarin, rivaroxaban, and apixaban. Differences by age and sex were evaluated in each analysis. The cohort was defined as guideline indicated OAC naïve incident AF patients who filled a prescription within 100 days of AF diagnosis from January 1st, 2013 to December 31st, 2016. Patients were required to be OAC naïve to ensure past treatment preferences or experiences with OAC did not impact treatment allocation. Patients were excluded if they experienced any of the components of the composite endpoint before filling a prescription for OAC. Patients were followed for up to 1 year after filling the first OAC prescription or until end of follow-up data on December 31st, 2016.

The Kaplan-Meier (KM) method was used to estimate and compare the rates of the composite endpoint and death up to 1 year. Cumulative incidence functions were used to estimate rates for each of stroke, and heart failure treating death as a competing risk. Rates were estimated for each OAC drug separately then reported overall and stratified by age and sex. Cox-PH models were fit to estimate unadjusted and adjusted HRs for age, sex, each DOAC vs. warfarin, and rivaroxaban vs. apixaban on the composite endpoint. Interaction effects between OAC drug type and sex/age were estimated to evaluated differences in OAC drug effectiveness by age and sex.

2.2.5 Sex Differences in Treatment and Outcomes of ED Presentations of AF

This analysis examined the sex differences in the rates of hospital admission, OAC use, and major adverse outcomes following presentation to the emergency department with incident AF. The cohort was restricted to patients identified using the NACRS database with incident AF

diagnosis during an ED visit from April 1st, 2012 to March 30th, 2016. Baseline characteristics were summarized by sex. ED discharge status, admitted to hospital or discharged home, was defined by searching DAD records for hospitalizations within 1 day following index ED visit. A logistic regression model was fit to estimate unadjusted and adjusted odds ratios (OR) for age and sex on admission to hospital following presentation to the ED.

OAC use following index ED visit was defined by querying BC Pharmanet records up to 1 year following index ED presentation among patients discharged home and up to 1 year following hospital discharge among patients admitted to hospital. Patients who died prior to hospital discharge were excluded. Cumulative incidence functions were used to estimate rates of OAC use at 90 days and Gray's test was used to compare rates up to one year. A Cox-PH model was fit to estimate HR for sex on OAC use up to one year following index ED visit or hospital discharge. Unadjusted and adjusted HRs for sex were reported with 95% CI for the overall cohort and the subgroup that was restricted to patients who were guideline–indicated for OAC. Death was treated as a competing risk among patients surviving to discharge.

Patients were followed for up to one year or until end of follow-up data on December 31, 2016 following index ED visit to obtain major adverse outcomes. The Kaplan-Meier method was used to estimate the rates of composite endpoint and mortality at 30 days and one year. Cumulative incidence functions were used to estimate rates of stroke and heart failure at 30 days and one year. Cox-PH models were fit to estimate unadjusted and adjusted HRs for age and sex on outcomes up to one year following index ED visit for each endpoint. Death was treated as a competing risk when examining individual endpoints of stroke and heart failure.

2.2.6 General Methods

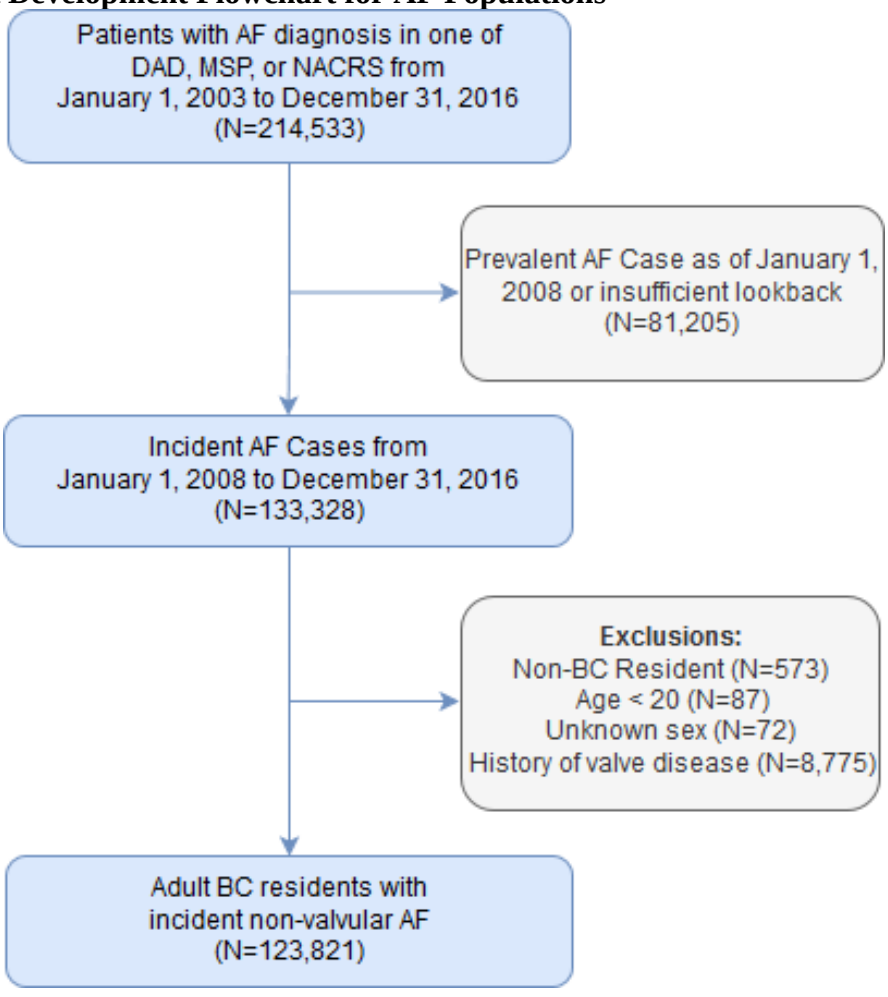
All adjusted models included diabetes, hypertension, heart failure, prior stroke/TIA, prior MI, PAD, COPD, and CKD as covariates. Adjustment factors were selected *a priori* based on clinical input. Given the large sample size and number of events, no variable selection was performed; therefore, all adjusted models included all adjustment factors. All ORs and HRs are reported for both unadjusted and adjusted models with 95% CIs. Time-to-event analyses censored patients at study end on December 31st, 2016 or out-of-province migration. Proportional hazards assumption was verified with Schoenfeld residuals and/or Kolmogorov supremum-type test as appropriate. All analyses were performed using SAS 9.4 (Cary, North Carolina).

3. Results

3.0 Cohort Overview

Figure 1 presents a flowchart describing the cohort definition process for incident and prevalent cases. The algorithm of AF diagnosis in any of DAD, MSP, or ED from January 1, 2003 to December 31st, 2016 identified 214,533 cases. Cases identified during the study washout period from 2003 to 2008 are classified as prevalent at the beginning of the study. Additionally, patients with < 5 years of BC registration at index diagnosis date are also classified as prevalent. Prior to exclusions, 81,778 patients are identified as prevalent cases and 123,821 as incident cases. In total, 9,507 patients are excluded due to non-BC residency, age < 20 years, unknown sex, and history of valve disease.

Figure 1. Cohort Development Flowchart for AF Populations



Tables 5 reports the number of incident cases identified from each of DAD, MSP, and NACRS records each study year. Overall, the number of cases each year identified increases 31% over the course of the study. This is largely attributable to an increase in patients identified through out-patient physician records and the availability of NACRS data in 2012; mandatory NACRS reporting for 29 EDs commenced in BC in 2012. Overall, MSP claims identify the largest proportion of AF cases (55.2%), while the number of cases identified by hospitalization records slowly decreases. The availability of NACRS data could result in cases being identified prior to hospitalization and therefore cause the reduction in cases identified through hospital records.

Table 5. Incident Cases Identified by Source and Year

Source	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
DAD	5,426	5,455	5,538	5,413	5,555	5,497	5,505	5,389	5,119	48,897
MSP	6,286	6,594	7,471	8,270	7,898	7,558	7,549	8,017	8,659	68,302
NACRS	N/A	N/A	N/A	N/A	689	1,067	1,589	1,745	1,532	6,622
Total	11,712	12,049	13,009	13,683	14,142	14,122	14,643	15,151	15,310	123,821

Age and sex are two main stratifying variables which are explored in each following analysis. Table 6 reports the age and sex frequencies among incident cases. Overall, women appear to be older than men, comprising a significantly larger portion of the age ≥ 75 group. Baseline characteristics including demographics, comorbidities, and baseline medications are further explored in objective 1.

Table 6. Incident Cases Age and Sex Summary

	Age < 65	65 - 74	Age ≥ 75	Total
Female	11,522 (36.7)	12,513 (40.4)	32,290 (52.6)	56,325
Male	19,908 (63.3)	18,436 (59.6)	29,152 (47.4)	67,496
Total	31,430	30,949	61,442	123,821

3.1 Patient Characteristics

Tables 7, 8, and 9 summarize baseline characteristics of incident AF cases by sex, age, and index diagnosis year. Though p-values are presented for completeness, large sample sizes may cause small and potentially clinically unimportant differences, to be statistically significant. The average age in the overall cohort is 72.5 years and 46% are female. Incident AF cases present with high rates of hypertension, heart failure, and diabetes, 60.0%, 18.1%, and 24.4%, respectively. Advanced age and high comorbid burden of the incident AF population is reflected in the median CHA_2DS_2-VASc score of 3 which indicates at a minimum 50% are guideline indicated for OAC therapy. Cardiac medications such as beta-blockers, calcium channel blockers (CCB), statins, and ACEi/ARBs are commonly prescribed prior to index diagnosis in this population.

Table 7 highlights several important sex differences. Women are older than men by 4.2 years on average and the ≥ 75 years old is much larger in women than in men, 57.3% vs. 43.2%, respectively Comorbidities differ between men and women; women present with more hypertension whereas men present with more vascular disease (PVD or MI) and diabetes. Higher rates of comorbidities observed in women may be related to age differences. Advanced age and higher rates of hypertension in women result in a median CHA_2DS_2-VASc score of 4 in women vs. 2 in men. The difference indicates that women with incident AF are at higher risk of stroke than men in excess of the single point allocated for female sex. With respect to baseline medications, women appear more likely to be prescribed CCBs while men are more likely to be prescribed statins.

Table 7. Baseline Characteristics by Sex

Baseline characteristic	Overall (n=123,821)	Female (n=56,325)	Male (n=67,496)	P-value
Age (Years), mean ± SD	72.5 ± 13.7	74.8 ± 13.7	70.6 ± 13.5	< 0.001
Age categories (Years)				< 0.001
<65	31430 (25.4)	11522 (20.5)	19908 (29.5)	
65-74	30949 (25.0)	12513 (22.2)	18436 (27.3)	
≥75	61442 (49.6)	32290 (57.3)	29152 (43.2)	
CHA_2DS_2-VASc	3.0 (2.0,4.0)	4.0 (3.0,5.0)	2.0 (1.0,4.0)	< 0.001
Heart Failure	22412 (18.1)	10476 (18.6)	11936 (17.7)	< 0.001
Hypertension	74314 (60.0)	35873 (63.7)	38441 (57)	< 0.001
Stroke/TIA	10129 (8.2)	4908 (8.7)	5221 (7.7)	< 0.001
PVD	6412 (5.2)	2287 (4.1)	4125 (6.1)	< 0.001
MI	10695 (8.6)	3617 (6.4)	7078 (10.5)	< 0.001
Diabetes	30180 (24.4)	12268 (21.8)	17912 (26.5)	< 0.001
CKD	18598 (15.0)	8289 (14.7)	10309 (15.3)	0.006
COPD	8731 (7.1)	4043 (7.2)	4688 (6.9)	0.11
Anemia	14746 (11.9)	7543 (13.4)	7203 (10.7)	< 0.001
Hyperthyroidism	762 (0.6)	558 (1)	204 (0.3)	< 0.001
Hypothyroidism	7464 (6.0)	5303 (9.4)	2161 (3.2)	< 0.001
History of Bleeding	9445 (7.6)	3889 (6.9)	5556 (8.2)	< 0.001
VTE	4610 (3.7)	2229 (4)	2381 (3.5)	< 0.001
Cancer	18638 (15.1)	7317 (13)	11321 (16.8)	< 0.001
Liver Disease	2266 (1.8)	841 (1.5)	1425 (2.1)	< 0.001
Medications				
OAC	10234 (8.3)	4172 (7.4)	6062 (9)	< 0.001
Beta Blockers	33894 (27.4)	15320 (27.2)	18574 (27.5)	0.21
CCB	26509 (21.4)	13327 (23.7)	13182 (19.5)	< 0.001
ACEi/ARB	50947 (41.1)	22998 (40.8)	27949 (41.4)	0.04
Anti-platelets	7870 (6.4)	3172 (5.6)	4698 (7)	< 0.001
Statin	36100 (29.2)	13978 (24.8)	22122 (32.8)	< 0.001
Digoxin	3175 (2.6)	1525 (2.7)	1650 (2.4)	0.004

Comorbidities and medications by age group are presented in table 8. As expected, comorbidities are strongly associated with increasing age. The proportion of patients with heart failure, hypertension, COPD, anemia, and cancer appear to increase in a stepwise fashion with age. Diabetes is higher among ages 65-74 and ≥75 than < 65 but similar between those groups.

Liver disease is the only comorbidity which decreases with advancing age. However, this result may be caused by a high mortality rate among patients with liver disease or higher rates of liver disease in men who comprise more of the < 65 age group. (112) A similar stepwise pattern is observed in baseline medications with the exception of statins which plateau after age 65.

Table 8. Baseline Characteristics by Age Category

Baseline characteristic	**Age < 65** (n=31,430)	**Age 65 - 74** (n=30,949)	**Age ≥ 75** (n=61,442)	**P-value**
Female Sex	11522 (36.7)	12513 (40.4)	32290 (52.6)	< 0.001
CHA_2DS_2-VASc	1.0 (0.0, 2.0)	3.0 (2.0, 3.0)	4.0 (3.0, 5.0)	< 0.001
Heart Failure	2874 (9.1)	4228 (13.7)	15310 (24.9)	< 0.001
Hypertension	11114 (35.4)	18725 (60.5)	44475 (72.4)	< 0.001
Stroke/TIA	1101 (3.5)	2063 (6.7)	6965 (11.3)	< 0.001
PVD	757 (2.4)	1689 (5.5)	3966 (6.5)	< 0.001
MI	1924 (6.1)	2735 (8.8)	6036 (9.8)	< 0.001
Diabetes	5287 (16.8)	8779 (28.4)	16114 (26.2)	< 0.001
CKD	2521 (8)	4025 (13)	12052 (19.6)	< 0.001
COPD	903 (2.9)	2111 (6.8)	5717 (9.3)	< 0.001
Anemia	2039 (6.5)	3001 (9.7)	9706 (15.8)	< 0.001
Hyperthyroidism	257 (0.8)	160 (0.5)	345 (0.6)	< 0.001
Hypothyroidism	1285 (4.1)	1700 (5.5)	4479 (7.3)	< 0.001
History of Bleeding	1640 (5.2)	2168 (7)	5637 (9.2)	< 0.001
VTE	1087 (3.5)	1171 (3.8)	2352 (3.8)	0.02
Cancer	2411 (7.7)	5030 (16.3)	11197 (18.2)	< 0.001
Liver Disease	943 (3)	731 (2.4)	592 (1)	< 0.001
Medications				
OAC	1953 (6.2)	2660 (8.6)	5621 (9.1)	< 0.001
Beta Blockers	6297 (20)	8930 (28.9)	18667 (30.4)	< 0.001
CCB	3347 (10.6)	6388 (20.6)	16774 (27.3)	< 0.001
ACEi/ARB	7887 (25.1)	13414 (43.3)	29646 (48.3)	< 0.001
Anti-platelets	1002 (3.2)	1781 (5.8)	5087 (8.3)	< 0.001
Statin	5693 (18.1)	10361 (33.5)	20046 (32.6)	< 0.001
Digoxin	403 (1.3)	590 (1.9)	2182 (3.6)	< 0.001

Trends in patient baseline characteristics and medications over the study window are summarized in table 9. The distribution of men and women appears to remain stable, remaining around 46% for the duration of the study window. Age at incident AF diagnosis appears to be

decreasing slowly from an average age of 73.2 in 2008 to 71.7 in 2016 years. The decrease in age was largely fueled by a decrease in the number of patients age ≥ 75 which dropped from 53.1% in 2008 to 46.1% in 2016. CHA_2DS_2-VASc score remained stable throughout along with anemia, cancer, and the use of ACEi/ARB, statins, and anti-platelets. A decrease is observed in heart failure, hypertension, PVD, and MI. The use of digoxin decreases significantly from 5.7% in 2008 to 0.6% in 2016. This is consistent with expectations as several studies have noted beta-blockers are preferable to digoxin. (113) Increases in the rates of CKD and liver disease were observed as well. Trends could be attributable to better coding, particularly in out-patient physician claims where the proportion of 4 digit codes, denoting more detailed diagnosis codes, is increasing with time.

Table 9. Baseline Characteristics by Index Diagnosis Year

Baseline characteristic	2008 (n=11,712)	2009 (n=12,049)	2010 (n=13,009)	2011 (n=13,683)	2012 (n=14,142)	2013 (n=14,122)	2014 (n=14,643)	2015 (n=15,151)	2016 (n=15,310)	P-value for trend
Age (Years), mean ± SD	73.2 ± 13.2	73.2 ± 13.3	72.9 ± 13.4	72.9 ± 13.6	72.7 ± 13.6	72.3 ± 13.8	72.3 ± 14.0	71.9 ± 14.1	71.7 ± 14.2	< .0001
Age categories (Years)										< .0001
<65	2774 (23.7)	2853 (23.7)	3203 (24.6)	3365 (24.6)	3560 (25.2)	3670 (26)	3778 (25.8)	4035 (26.6)	4192 (27.4)	
65-74	2719 (23.2)	2836 (23.5)	3096 (23.8)	3353 (24.5)	3535 (25)	3567 (25.3)	3757 (25.7)	4033 (26.6)	4053 (26.5)	
≥ 75	6219 (53.1)	6360 (52.8)	6710 (51.6)	6965 (50.9)	7047 (49.8)	6885 (48.8)	7108 (48.5)	7083 (46.7)	7065 (46.1)	
Female Sex	5366 (45.8)	5540 (46)	5955 (45.8)	6297 (46)	6515 (46.1)	6303 (44.6)	6611 (45.1)	6774 (44.7)	6964 (45.5)	0.0186
CHA_2DS_2-VASc	3.0 (2.0,4.0)	3.0 (2.0,4.0)	3.0 (2.0,4.0)	3.0 (2.0,4.0)	3.0 (2.0,4.0)	3.0 (2.0,4.0)	3.0 (2.0,4.0)	3.0 (2.0,4.0)	3.0 (2.0,4.0)	<.0001
Heart Failure	2253 (19.2)	2445 (20.3)	2528 (19.4)	2575 (18.8)	2580 (18.2)	2482 (17.6)	2565 (17.5)	2561 (16.9)	2423 (15.8)	<.0001
Hypertension	7095 (60.6)	7451 (61.8)	8004 (61.5)	8475 (61.9)	8702 (61.5)	8516 (60.3)	8678 (59.3)	8773 (57.9)	8620 (56.3)	<.0001
Stroke/TIA	980 (8.4)	1020 (8.5)	1073 (8.2)	1162 (8.5)	1164 (8.2)	1134 (8)	1193 (8.1)	1217 (8)	1186 (7.7)	0.01
PVD	706 (6)	716 (5.9)	704 (5.4)	753 (5.5)	713 (5)	705 (5)	727 (5)	724 (4.8)	664 (4.3)	<.0001
MI	1086 (9.3)	1134 (9.4)	1200 (9.2)	1165 (8.5)	1270 (9)	1221 (8.6)	1257 (8.6)	1220 (8.1)	1142 (7.5)	<.0001
Diabetes	2586 (22.1)	2794 (23.2)	3070 (23.6)	3337 (24.4)	3521 (24.9)	3555 (25.2)	3707 (25.3)	3899 (25.7)	3711 (24.2)	<.0001
CKD	1332 (11.4)	1555 (12.9)	1740 (13.4)	1951 (14.3)	2150 (15.2)	2233 (15.8)	2492 (17)	2546 (16.8)	2599 (17)	<.0001
COPD	941 (8)	938 (7.8)	933 (7.2)	1014 (7.4)	1004 (7.1)	1015 (7.2)	984 (6.7)	998 (6.6)	904 (5.9)	<.0001
Anemia	1392 (11.9)	1386 (11.5)	1485 (11.4)	1642 (12)	1729 (12.2)	1773 (12.6)	1809 (12.4)	1781 (11.8)	1749 (11.4)	0.66
Hyperthyroidism	65 (0.6)	66 (0.5)	80 (0.6)	99 (0.7)	92 (0.7)	83 (0.6)	99 (0.7)	89 (0.6)	89 (0.6)	0.79
Hypothyroidism	591 (5)	650 (5.4)	723 (5.6)	791 (5.8)	902 (6.4)	878 (6.2)	918 (6.3)	949 (6.3)	1062 (6.9)	<.0001
History of Bleeding	940 (8)	969 (8)	1025 (7.9)	1026 (7.5)	1214 (8.6)	1072 (7.6)	1115 (7.6)	1064 (7)	1020 (6.7)	<.0001
VTE	437 (3.7)	453 (3.8)	501 (3.9)	560 (4.1)	502 (3.5)	536 (3.8)	510 (3.5)	591 (3.9)	520 (3.4)	0.10
Cancer	1805 (15.4)	1776 (14.7)	1963 (15.1)	2081 (15.2)	2126 (15)	2175 (15.4)	2221 (15.2)	2226 (14.7)	2265 (14.8)	0.31
Liver Disease	167 (1.4)	161 (1.3)	184 (1.4)	209 (1.5)	233 (1.6)	279 (2)	316 (2.2)	318 (2.1)	399 (2.6)	<.0001
Baseline Medication										
OAC	1473 (12.6)	1413 (11.7)	1410 (10.8)	1411 (10.3)	1098 (7.8)	1004 (7.1)	859 (5.9)	862 (5.7)	704 (4.6)	<.0001
Beta Blockers	3422 (29.2)	3517 (29.2)	3782 (29.1)	3985 (29.1)	3942 (27.9)	3791 (26.8)	3905 (26.7)	3865 (25.5)	3685 (24.1)	<.0001
CCB	2656 (22.7)	2698 (22.4)	2956 (22.7)	3096 (22.6)	3014 (21.3)	3023 (21.4)	2966 (20.3)	3114 (20.6)	2986 (19.5)	<.0001
ACEi/ARB	4867 (41.6)	5156 (42.8)	5499 (42.3)	5882 (43)	6008 (42.5)	5864 (41.5)	5845 (39.9)	6002 (39.6)	5824 (38)	<.0001
Antiplatelets	671 (5.7)	763 (6.3)	824 (6.3)	932 (6.8)	994 (7)	892 (6.3)	878 (6)	972 (6.4)	944 (6.2)	0.84
Statin	3132 (26.7)	3461 (28.7)	3849 (29.6)	4135 (30.2)	4353 (30.8)	4227 (29.9)	4242 (29)	4488 (29.6)	4213 (27.5)	0.47
Digoxin	668 (5.7)	560 (4.6)	520 (4)	439 (3.2)	290 (2.1)	254 (1.8)	184 (1.3)	166 (1.1)	94 (0.6)	<.0001

3.2 Temporal Trends in AF Epidemiology

Table 10 presents the overall crude and age/sex standardized incidence and prevalence rates of AF in BC from 2008 to 2016. The crude incidence increases from 374.5/100,000 to 431/100,000, a 15% increase. However, the standardized incidence remains stable at 428.0 in 2008 and 431.0 in 2016 with significant overlap in confidence intervals. Figure 2 visualizes the trends in standardized incidence and prevalence throughout the study window. The prevalence of AF increases by 45% over the course of the study, or approximately 5.5% per year. As of 2016, the prevalence is estimated to be 3.2% (121,363/3,792,585) which is consistent with estimates reported in other developed countries with older populations. [16, 30, 31, 94]

Table 10. Overall Crude and Age/Sex Standardized Incidence and Prevalence (per 100,000)

Year	Crude Incidence	Std. Incidence	95% CI	Crude Prevalence	Std. Prevalence	95% CI
2008	374.50	427.96	(420.4, 435.5)	1930.85	2204.52	(2187.4, 2221.6)
2009	376.68	425.65	(418.3, 433.0)	2081.10	2354.04	(2336.7, 2371.4)
2010	400.79	447.08	(439.6, 454.5)	2262.78	2527.02	(2509.3, 2544.7)
2011	415.27	454.81	(447.4, 462.2)	2401.04	2629.18	(2611.4, 2647.0)
2012	420.32	451.61	(444.4, 458.8)	2544.45	2736.19	(2718.4, 2754.0)
2013	416.97	439.02	(432.0, 446.0)	2698.65	2843.96	(2826.1, 2861.8)
2014	423.42	437.93	(431.1, 444.8)	2853.36	2954.18	(2936.3, 2972.0)
2015	433.21	439.83	(433.0, 446.6)	3033.37	3082.09	(3064.1, 3100.0)
2016	431.00	431.00	(424.4, 437.6)	3194.42	3194.42	(3176.4, 3212.4)

Figure 2. Overall Age/Sex Standardized Incidence and Prevalence Curves

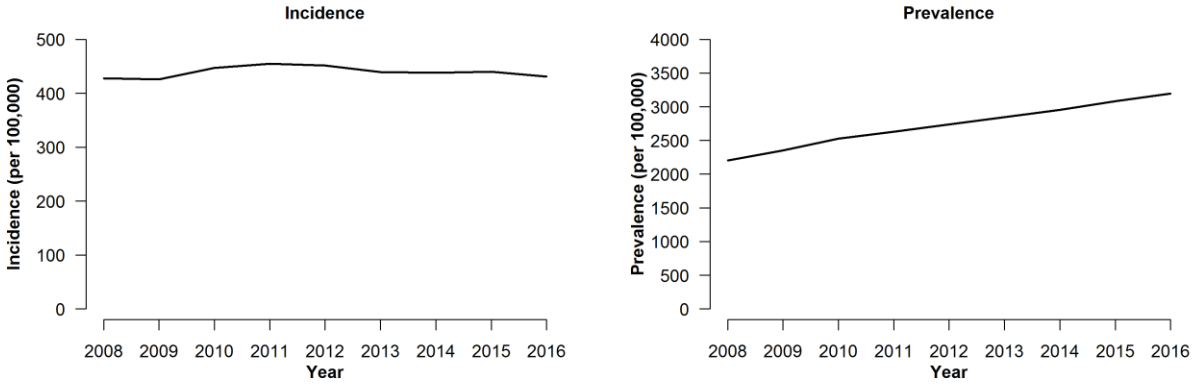


Figure 3 visualizes the trends in standardized incidence and prevalence throughout the study window by sex. The incidence remains unchanged in both men and women; however, the prevalence grows by 46% in men and 43% in women from 2008 to 2016. Table 11 presents the crude and age/sex standardized incidence and prevalence rates of AF in BC from 2008 to 2016 stratified by sex. Both incidence and prevalence are consistently higher in men than women; incidence rates were 482.1 vs. 381.7 and prevalence rates were 3684.2 vs. 2721.3 in men and women in 2016, respectively. The observed sex difference in AF incidence and prevalence grows slightly over the course of the study period.

Figure 3. Age/Sex Standardized Incidence and Prevalence Curves by Sex

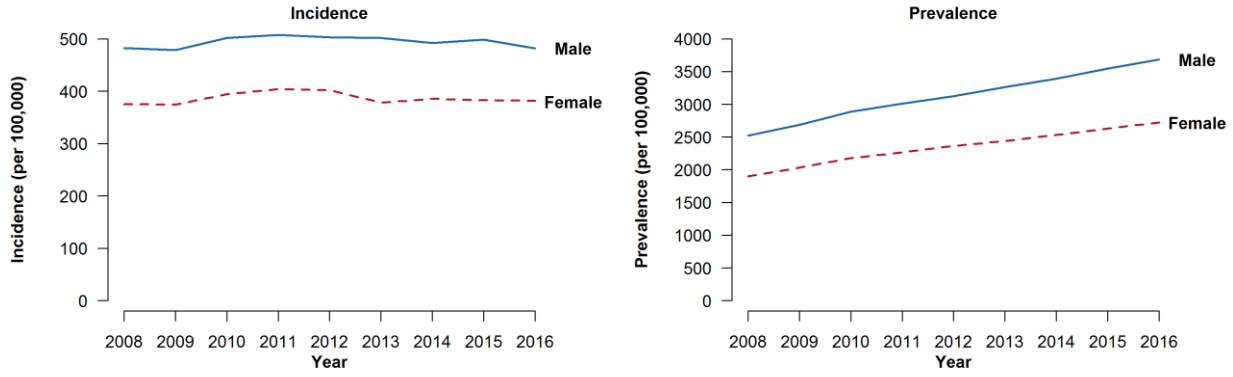


Table 11. Crude and Age/Sex Standardized Incidence and Prevalence by Sex (per 100,000)

Year	Sex	Crude Inc.	Std. Inc.	95% CI	Crude Prev.	Std. Prev.	95% CI
2008	**F**	335.22	375.13	(365.4, 384.9)	1703.13	1899.40	(1877.4, 1921.3)
2008	**M**	415.31	482.64	(471.1, 494.2)	2167.48	2520.39	(2494.1, 2546.7)
2009	**F**	338.19	374.61	(365.0, 384.2)	1835.38	2034.47	(2012.1, 2056.9)
2009	**M**	416.60	478.50	(467.2, 489.8)	2335.91	2684.86	(2658.2, 2711.6)
2010	**F**	359.04	394.45	(384.7, 404.2)	1985.31	2178.76	(2155.9, 2201.6)
2010	**M**	444.07	501.57	(490.2, 512.9)	2550.36	2887.55	(2860.3, 2914.8)
2011	**F**	373.08	403.99	(394.3, 413.7)	2095.21	2262.83	(2239.9, 2285.8)
2011	**M**	458.98	507.43	(496.2, 518.6)	2717.89	3008.44	(2981.2, 3035.7)
2012	**F**	377.29	402.06	(392.5, 411.6)	2217.98	2361.19	(2338.1, 2384.3)
2012	**M**	464.90	502.91	(492.0, 513.8)	2882.69	3124.41	(3097.1, 3151.7)
2013	**F**	361.05	378.18	(369.1, 387.3)	2330.18	2439.30	(2416.2, 2462.4)
2013	**M**	474.88	501.99	(491.3, 512.7)	3080.27	3262.88	(3235.5, 3290.2)
2014	**F**	374.08	385.63	(376.6, 394.7)	2457.82	2533.83	(2510.7, 2557.0)
2014	**M**	474.50	492.07	(481.7, 502.5)	3262.80	3389.35	(3362.0, 3416.7)
2015	**F**	377.64	382.97	(374.1, 391.8)	2595.02	2632.22	(2609.0, 2655.5)
2015	**M**	490.78	498.69	(488.4, 509.0)	3487.40	3547.81	(3520.3, 3575.3)
2016	**F**	381.67	381.67	(373.0, 390.4)	2721.33	2721.33	(2698.0, 2744.6)
2016	**M**	482.06	482.06	(472.1, 492.0)	3684.18	3684.18	(3656.6, 3711.7)

Table 12 presents the crude and age/sex standardized incidence and prevalence rates of AF in BC from 2008 to 2016 by age category. Both incidence and prevalence increase dramatically with advancing age. For example, in 2016 the standardized incidence rates among age groups 65 – 74 and ≥ 75 years compared with the age < 65 years group were 6- and 14-fold higher, respectively. Similarly, in 2016, the standardized incidence rates among age groups 65 – 74 and ≥ 75 years compared to the age < 65 years groups were 7- and 17-fold higher, respectively. Figure 4 visualizes the trends in standardized incidence and prevalence throughout the study window by age category. The incidence remains constant among the age < 65 years group, however the incidence appears to be decreasing slightly among the ≥ 75 years group. Consistent with the overall and sex stratified results, the prevalence is steadily increasing with

the most dramatic increase among the ≥ 75 years population. In 2016, the prevalence is estimated at 0.9%, 6.5%, and 17.2% in the <65, 65-74, and ≥ 75 year populations, respectively.

Table 12. Crude and Age/Sex Standardized Incidence and Prevalence by Age (per 100,000)

Year	Age Group	Crude Inc.	Std. Inc.	95% CI	Crude Prev.	Std. Prev.	95% CI
2008	**< 65**	108.42	115.62	(111.4, 119.8)	529.82	565.04	(555.8, 574.3)
	65-74	895.89	888.44	(856.5, 920.4)	4589.67	4546.79	(4474.5, 4619.1)
	≥ 75	2267.64	2332.99	(2276.5, 2389.4)	11996.43	12303.35	(12173.9, 12432.8)
2009	**< 65**	109.42	114.90	(110.8, 119.0)	577.82	608.10	(598.7, 617.5)
	65-74	889.41	883.98	(852.7, 915.3)	4851.95	4821.58	(4748.5, 4894.6)
	≥ 75	2272.02	2320.76	(2265.3, 2376.2)	12871.78	13144.23	(13012.2, 13276.2)
2010	**< 65**	120.79	125.23	(121.0, 129.4)	637.84	661.12	(651.5, 670.8)
	65-74	943.99	939.00	(907.3, 970.7)	5180.49	5155.01	(5080.8, 5229.3)
	≥ 75	2349.62	2387.05	(2331.7, 2442.4)	13845.01	14070.68	(13936.3, 14205.1)
2011	**< 65**	125.50	128.21	(124.0, 132.4)	681.90	695.97	(686.2, 705.8)
	65-74	969.93	964.61	(933.1, 996.1)	5341.08	5315.56	(5241.6, 5389.5)
	≥ 75	2380.11	2409.36	(2354.6, 2464.1)	14472.58	14637.51	(14502.7, 14772.4)
2012	**< 65**	130.88	133.21	(128.9, 137.5)	720.89	733.19	(723.2, 743.2)
	65-74	955.27	954.90	(924.5, 985.3)	5524.20	5523.07	(5449.9, 5596.3)
	≥ 75	2330.84	2348.74	(2295.6, 2401.9)	15059.89	15173.46	(15038.4, 15308.5)
2013	**< 65**	134.41	136.03	(131.7, 140.3)	765.74	774.73	(764.5, 785.0)
	65-74	917.66	918.09	(889.1, 947.1)	5715.30	5719.22	(5646.9, 5791.6)
	≥ 75	2230.82	2244.09	(2193.0, 2295.2)	15622.66	15697.44	(15562.3, 15832.6)
2014	**< 65**	136.60	137.60	(133.3, 141.9)	809.53	816.16	(805.7, 826.6)
	65-74	913.38	913.49	(885.3, 941.7)	5914.22	5915.43	(5843.8, 5987.1)
	≥ 75	2219.84	2226.21	(2176.2, 2276.3)	16210.40	16247.75	(16112.6, 16382.9)
2015	**< 65**	145.69	146.07	(141.7, 150.5)	864.83	867.10	(856.4, 877.8)
	65-74	930.05	930.85	(903.1, 958.6)	6212.01	6218.79	(6147.0, 6290.5)
	≥ 75	2152.81	2154.70	(2106.3, 2203.1)	16750.35	16762.84	(16627.8, 16897.9)
2016	**< 65**	148.74	148.74	(144.3, 153.1)	919.97	919.97	(909.0, 930.9)
	65-74	896.92	896.92	(870.3, 923.6)	6435.89	6435.89	(6364.5, 6507.3)
	≥ 75	2086.54	2086.54	(2039.7, 2133.4)	17215.10	17215.10	(17080.6, 17349.6)

Figure 4. Age/Sex Standardized Incidence and Prevalence Curves by Age Group

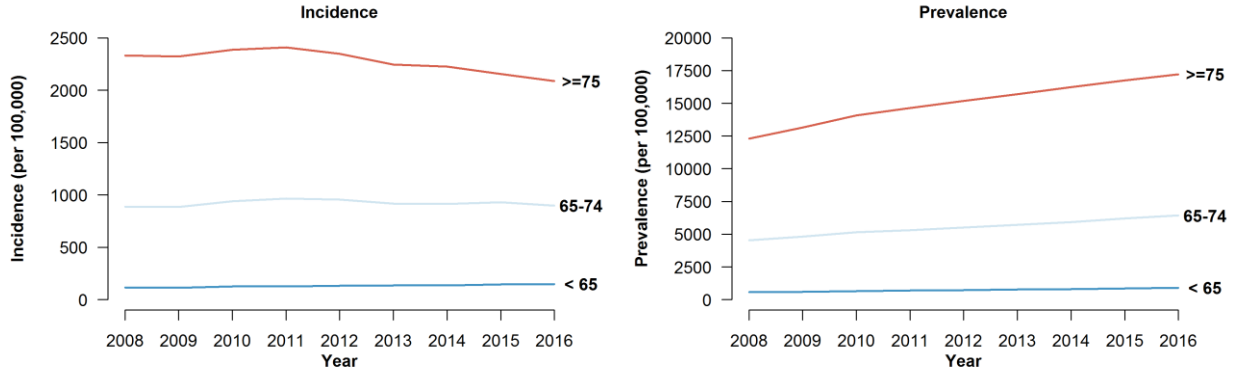
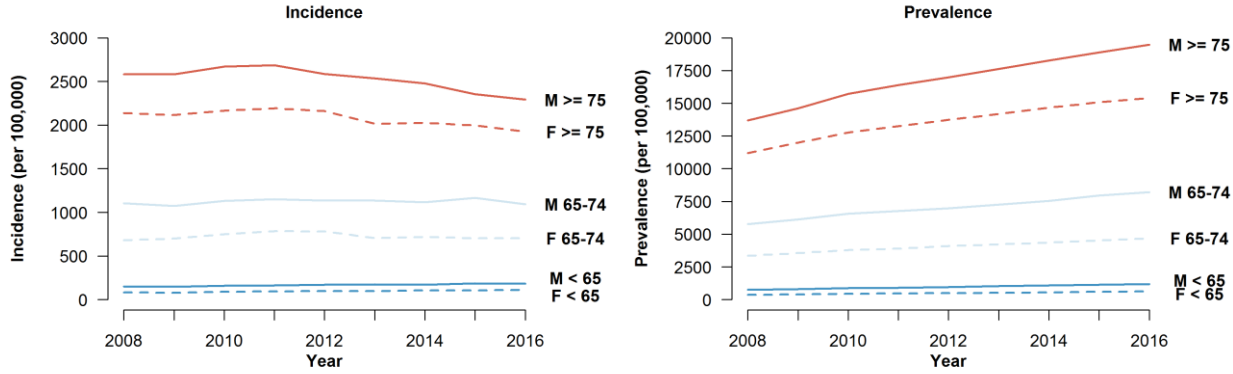


Figure 5 visualizes the trends in standardized incidence and prevalence throughout the study window by age category. The incidence and prevalence curves demonstrate three findings. First, the prevalence of AF is growing among men and women of all age groups. Second, the observed sex difference in rates is consistent across all age groups; men consistently have higher incidence and prevalence of AF regardless of age. Third, incidence and prevalence increased dramatically with age, and this effect is consistent across men and women. Crude and standardized incidence and prevalence rates by sex and age group are available in the appendix.

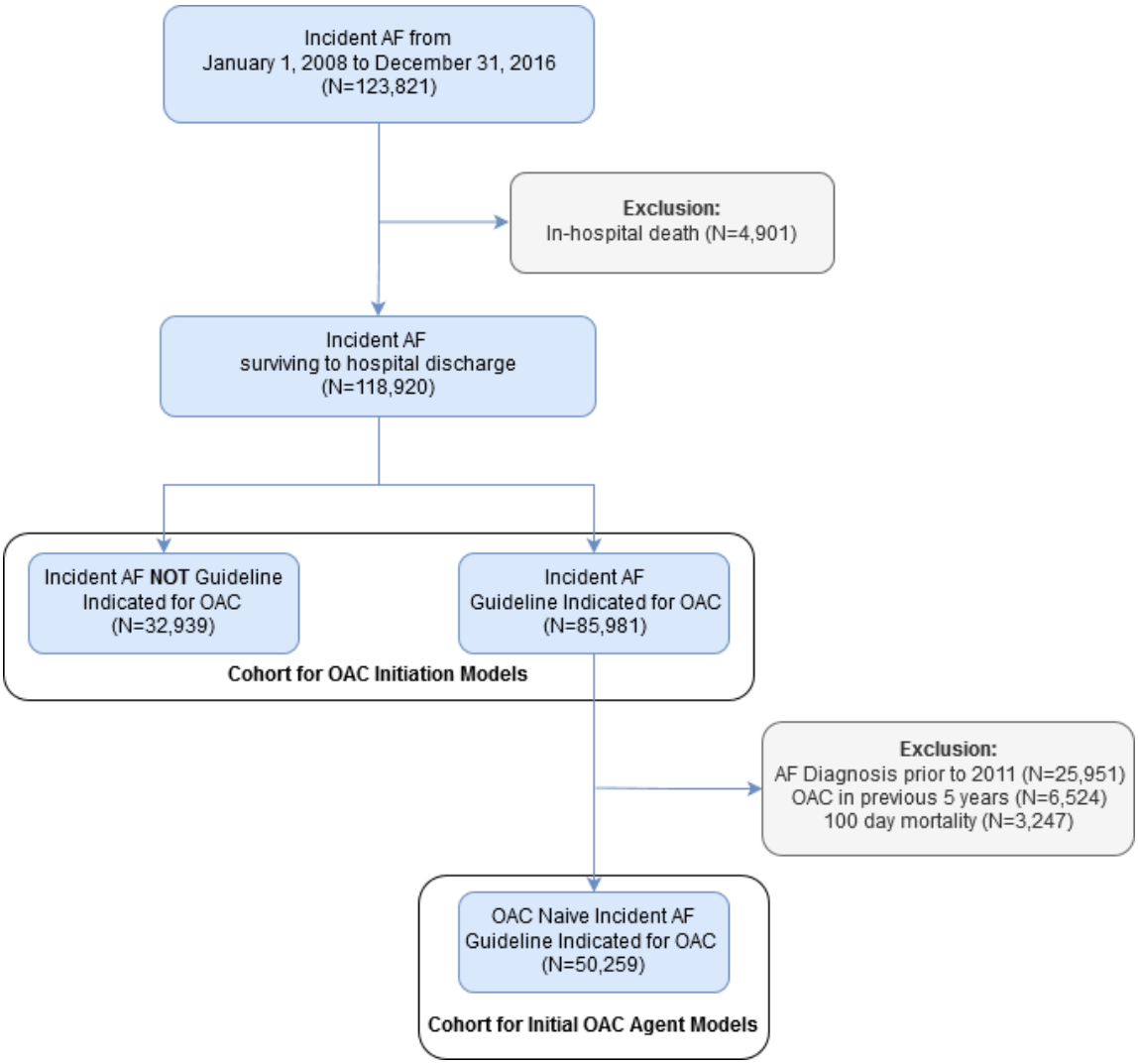
Figure 5. Age/Sex Standardized Incidence and Prevalence Curves by Sex and Age Group



3.3 OAC Initiation and Prescription Trends

Figure 6 is a flowchart describing the cohort selection process for the prescription trends cohorts. Incident AF patients from January 1st, 2008 to December 31st, 2016 who survived to hospital discharge were included in the OAC use analyses. Patients who died prior to hospital discharge were excluded because they were unable to fill prescriptions captured by PharmaNet records. OAC use analyses were performed on the overall cohort and repeated on the CHA_2DS_2-VASc guideline indicated subgroup. The cohort for initial choice of OAC agent analyses were restricted to OAC naïve patients identified after 2011 who survived at least 100 days following index AF diagnosis.

Figure 6. Cohort Development for OAC Initiation and Initial OAC Agent Cohorts



3.3.1 OAC Initiation Following Incident AF Diagnosis

Table 13 presents baseline characteristics by guideline indication for OAC. The cohort of patients with guideline indicated use of OAC results in an older population with higher rates of comorbidities and baseline medication use. Among the AF cohort, 60.5% of patients without guideline indicated use of OAC were mostly male and 76.2% were under the age of 65. Given comorbidities are strongly associated with age, the significantly lower rates observed in this group is consistent with expectations.

Table 13. Baseline Characteristics by Guideline Indication for OAC

Baseline characteristic	Guideline Indicated (n=85,981)	Not Indicated (n=32,939)	p-value
Age (Years), mean ± SD	78.0 ± 9.5	56.9 ± 11.1	< 0.001
Age categories (Years)			< 0.001
<65	5886 (6.8)	25109 (76.2)	
65-74	22322 (26)	7830 (23.8)	
≥75	57773 (67.2)	0 (0.0)	
Female Sex	40929 (47.6)	12998 (39.5)	< 0.001
CHA_2DS_2-VASc	4.0 (3.0,5.0)	1.0 (0.0,1.0)	< 0.001
Heart Failure	19614 (22.8)	841 (2.6)	< 0.001
Hypertension	65070 (75.7)	6032 (18.3)	< 0.001
Stroke/TIA	9315 (10.8)	0 (0.0)	< 0.001
PVD	5789 (6.7)	167 (0.5)	< 0.001
MI	9532 (11.1)	452 (1.4)	< 0.001
Diabetes	27170 (31.6)	1540 (4.7)	< 0.001
CKD	15213 (17.7)	1720 (5.2)	< 0.001
COPD	6993 (8.1)	759 (2.3)	< 0.001
Anemia	11816 (13.7)	1708 (5.2)	< 0.001
Hyperthyroidism	476 (0.6)	256 (0.8)	< 0.001
Hypothyroidism	5557 (6.5)	1611 (4.9)	< 0.001
History of Bleeding	7359 (8.6)	1394 (4.2)	< 0.001
VTE	3306 (3.8)	1033 (3.1)	< 0.001
Cancer	14166 (16.5)	3065 (9.3)	< 0.001
Liver Disease	1336 (1.6)	710 (2.2)	< 0.001
Medications			
OAC	8128 (9.5)	1807 (5.5)	< 0.001
Beta Blockers	27812 (32.3)	4688 (14.2)	< 0.001
CCB	23125 (26.9)	2178 (6.6)	< 0.001
ACEi/ARB	44314 (51.5)	4555 (13.8)	< 0.001
Antiplatelets	7093 (8.2)	423 (1.3)	< 0.001
Statin	31053 (36.1)	3754 (11.4)	< 0.001
Digoxin	2657 (3.1)	326 (1)	< 0.001

Table 14 presents rates of OAC use at 100 days following index AF diagnosis for the overall cohort and guideline indicated subgroup. During the study, the rate of OAC use was 45.9% and 27.8% in the guideline indicated and not guideline indicated groups, respectively. The observed OAC rate at 100 days is sub-optimal; however, significant treatment gaps have been noted by other studies. Additionally, rates reported by administrative database studies consistently report lower rates than chart review or registry studies. Underestimation of rates could be the function of three potential sources of bias. First, administrative database studies rely on identification of AF through diagnosis codes. Diagnosis codes could indicate the presence of AF or indicate a query which, may not confirmed as AF. The latter would result in non-AF being misclassified as AF. Second, some AF may be transient and does not require OAC. Lastly, administrative database studies rely on pharmacy records of prescriptions filled. While patients may be prescribed OAC, they may not fill the prescription.

Overall, men have higher rates of OAC use at 100 days than women regardless of guideline indication; however, the gap is significantly smaller in patients who are guideline-indicated. OAC rates increase with age among patients not meeting guideline criteria. However, among the guideline-indicated subgroup the difference is not clinically meaningful. Accounting for age and sex, men have consistently higher rates of OAC use regardless of age while women under <65 have the lowest rates.

Table 14. OAC Rates at 100 days following index AF diagnosis

Subgroup	Level	Guideline Indicated			Not Guideline Indicated		
		Rate	95% CI	p-value*	Rate	95% CI	p-value*
Overall	**-**	45.9	(45.5, 46.2)		27.8	(27.3, 28.3)	
Sex	**F**	44.4	(43.9, 44.8)	< 0.001	22.2	(21.5, 22.9)	<0.001
	M	47.2	(46.8, 47.7)		31.4	(30.8, 32.1)	
Age Group	**< 65**	45.8	(44.5, 47.1)	< 0.001	25.7	(25.1, 26.2)	<0.001
	65-74	46.6	(46.0, 47.3)		34.5	(33.4, 35.5)	
	≥ 75	45.6	(45.2, 46.0)				
Age/Sex	**F < 65**	41.7	(39.4, 44.0)	< 0.001	19.2	(18.4, 20.0)	<0.001
	M < 65	47.6	(46.0, 49.1)		29.7	(29.0, 30.5)	
	F 65-74	44.7	(43.7, 45.7)		30.8	(29.2, 32.3)	
	M 65-74	47.9	(47.0, 48.7)		37.3	(35.9, 38.8)	
	F ≥ 75	44.4	(43.9, 45.0)		N/A		
	M ≥ 75	46.8	(46.2, 47.4)		N/A		

*Gray's Test for difference in group cumulative incidence up to 1 year

Figure 7 presents graphical explorations of trends in OAC rates at 100 days following index AF diagnosis by age and sex. Panel A shows OAC rates increased throughout the study among the guideline indicated subgroup, 43.25% in 2008 vs. 47.0% in 2016. However, OAC rates decreased in patients who are not guideline indicated, 32.3% in 2008 vs. 26.3% in 2016. In Panel B, OAC rates are stratified by sex and demonstrates trends in the observed sex differences. Among both the not indicated and guideline indicated cohorts, the treatment gap between men and women narrowed and by 2016 OAC rates differ by less than 2% between men and women, 47.0% vs. 48.9%, respectively, in patients guideline-indicated for OAC. Panel C shows OAC rates stratified by age category. Age differences in the rates of OAC use in the guideline-indicated subgroup do not appear to be clinically meaningful. In contrast, OAC rates are dropping steadily in patients not guideline-indicated and age <65.

Figure 7. OAC Rates at 100 Days Overall, and by Age and Sex over Time

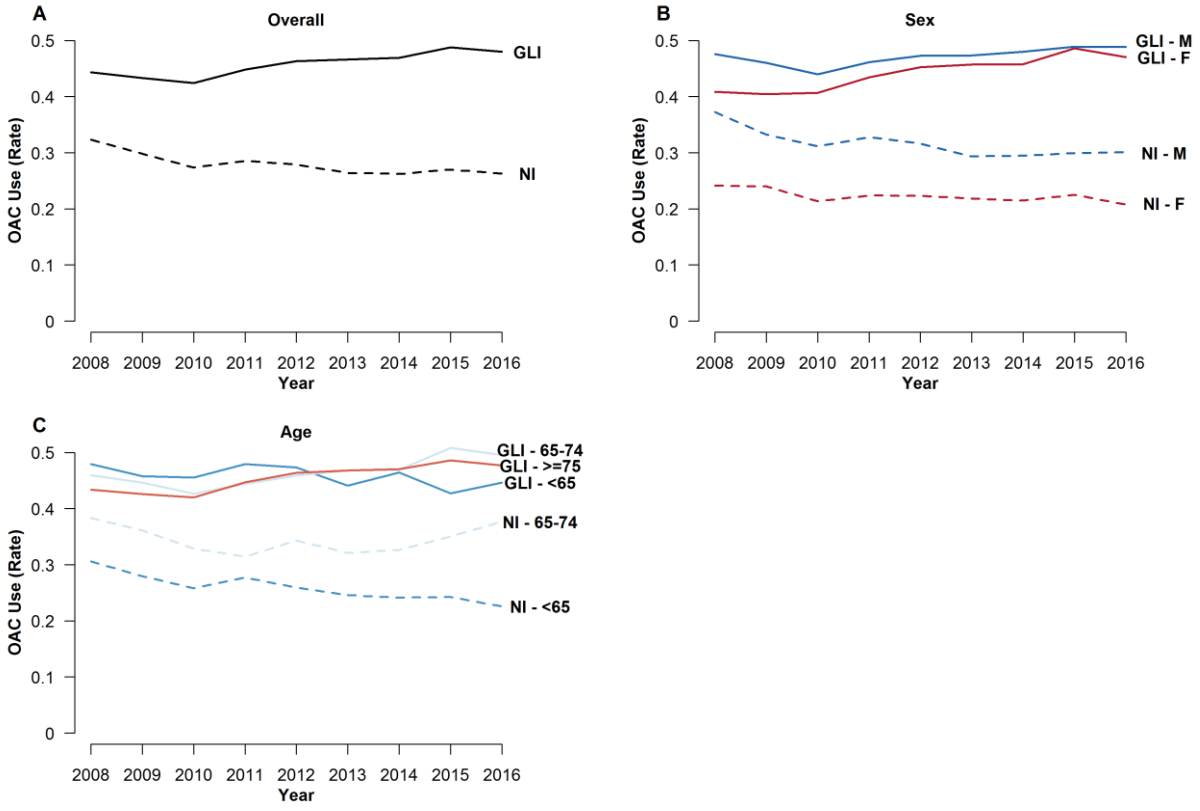


Table 15 presents the unadjusted and adjusted HRs for sex and age on OAC use up to 1 year. The unadjusted model includes categorical age, sex, study year, and sex by study year interaction. The interaction term for age and sex was statistically significant; however, the magnitude of the difference between the strata specific HRs and the pooled HRs was not clinically meaningful. In the overall cohort, age was strongly associated with OAC use in both the unadjusted and adjusted models. In the unadjusted model, patients ≥75 had significantly higher OAC use than both ages 65-74 and <65; however, after adjustment, the difference between patients ≥75 and those 65-74 was no longer significant. Consistent with the observations noted in figure 7, the sex difference in OAC use changed over time. In 2008, women received less OAC than men in both the not indicated, and guideline indicated subgroup. However, by 2016 the sex difference has narrowed significantly in the overall and disappeared in the guideline indicated subgroups.

Table 15. HRs for OAC Use Up to 1 year

Model	Factor	Guideline Indicated			Not Guideline Indicated		
		HR	95% CI	p-value	HR	95% CI	p-value
Unadjusted	**Age (65-74 vs. <65)**	1.02	(0.98, 1.07)	0.26	1.43	(1.37, 1.50)	<0.001
	Age (≥75 vs. <65)	1.01	(0.98, 1.05)	0.46	N/A		
	2008 Sex (F vs. M)	0.86	(0.83, 0.90)	<0.001†	0.62	(0.57, 0.68)	0.11†
	2016 Sex (F vs. M)	0.99	(0.96, 1.03)		0.70	(0.65, 0.75)	
Adjusted*	**Age (65-74 vs. <65)**	1.04	(1.00, 1.09)	<0.001	1.87	(1.78, 1.97)	<0.001
	Age (≥75 vs. <65)	1.02	(0.99, 1.07)		N/A		
	2008 Sex (F vs. M)	0.85	(0.82, 0.88)	<0.001†	0.63	(0.58, 0.69)	0.068†
	2016 Sex (F vs. M)	0.98	(0.94, 1.01)		0.72	(0.66, 0.77)	

*Adjusted for hypertension, diabetes, PVD, MI, stroke/TIA
† p-value for interaction

3.3.2 Choice of OAC Agent

To evaluate whether treatment preferences in terms of initial OAC type, DOAC vs. OAC, vary by age or sex, the cohort was restricted to patients who were guideline indicated for OAC, OAC naïve, and survived at least 100 days following index AF diagnosis. Table 16 summarizes the baseline characteristics of the initial OAC choice cohort, overall and by sex. After exclusions, the cohort was reduced to 50,259 patients, of which 47.6% were female. Notably, women were older than men on average and had higher rates of hypertension than males. Men used more medications, except CCBs, and had higher rates of PVD, MI, and diabetes.

Table 16. Baseline Characteristics of Initial OAC Type Cohort overall and by sex

Baseline characteristic	Overall (n=50,259)	Female (n=23,900)	Male (n=26,359)	P-value
Age (Years), mean ± SD	77.7 ± 9.5	79.6 ± 9.2	76.0 ± 9.5	< 0.001
Age categories (Years)				< 0.001
<65	3565 (7.1)	1065 (4.5)	2500 (9.5)	
65-74	13777 (27.4)	5448 (22.8)	8329 (31.6)	
≥75	32917 (65.5)	17387 (72.7)	15530 (58.9)	
CHA_2DS_2-VASc	4.0 (3.0,4.0)	4.0 (3.0,5.0)	3.0 (2.0,4.0)	< 0.001
Heart Failure	10318 (20.5)	4856 (20.3)	5462 (20.7)	0.26
Hypertension	38143 (75.9)	18616 (77.9)	19527 (74.1)	< 0.001
Stroke/TIA	5271 (10.5)	2510 (10.5)	2761 (10.5)	0.92
PVD	3054 (6.1)	1059 (4.4)	1995 (7.6)	< 0.001
MI	5374 (10.7)	1746 (7.3)	3628 (13.8)	< 0.001
Diabetes	16234 (32.3)	6646 (27.8)	9588 (36.4)	< 0.001
CKD	9181 (18.3)	4182 (17.5)	4999 (19)	< 0.001
COPD	3644 (7.3)	1752 (7.3)	1892 (7.2)	0.51
Anemia	6565 (13.1)	3340 (14)	3225 (12.2)	< 0.001
Hyperthyroidism	294 (0.6)	227 (0.9)	67 (0.3)	< 0.001
Hypothyroidism	3461 (6.9)	2421 (10.1)	1040 (3.9)	< 0.001
History of Bleeding	3980 (7.9)	1633 (6.8)	2347 (8.9)	< 0.001
VTE	818 (1.6)	453 (1.9)	365 (1.4)	< 0.001
Cancer	7853 (15.6)	3056 (12.8)	4797 (18.2)	< 0.001
Liver Disease	847 (1.7)	326 (1.4)	521 (2)	< 0.001
Medications				
Beta Blockers	15343 (30.5)	7005 (29.3)	8338 (31.6)	< 0.001
CCB	13297 (26.5)	6752 (28.3)	6545 (24.8)	< 0.001
ACEi/ARB	25758 (51.3)	11874 (49.7)	13884 (52.7)	< 0.001
Antiplatelets	4365 (8.7)	1750 (7.3)	2615 (9.9)	< 0.001
Statin	18368 (36.5)	7258 (30.4)	11110 (42.1)	< 0.001
Digoxin	686 (1.4)	370 (1.5)	316 (1.2)	< 0.001

Figure 8 describes temporal trends in the proportion of DOAC vs. Warfarin and specific OAC agent prescribed over time following incident AF diagnosis. Panel A shows the proportion of DOAC vs. Warfarin overall. In 2008, warfarin was the only available OAC and therefore accounted for all prescribed OACs. However, use of DOACs has been steadily increasing since their introduction in 2011. By 2014, DOACs and warfarin were being prescribed equally in incident AF patients and in 2016 DOACs accounted for over 65% of all initial OAC prescription in incident AF patient. Panel B breaks the overall prescription trends down by specific OAC agent. By 2016, the proportion of patients initiated on warfarin, rivaroxaban, apixaban and dabigatran were 34.9%, 30.8%, 30.2%, and 4.1%, respectively. Of note, while dabigatran was adopted rapidly following its approval to the Canadian market, its use peaked in 2012 and has

been steadily decreasing. This could be related to known side effects such as nausea which significantly impact patients' day to day lives. Panel C shows proportion of DOAC vs. warfarin stratified by sex. Graphically, differences appear to be minor between men and women; however, women may be slightly more likely to receive DOAC than males. This difference could be due to older average age among women. Panel D breaks down the sex specific prescription patterns by OAC agent. Sex differences appear to be minor and women and men appear equally likely to receive apixaban, rivaroxaban, or dabigatran. Panel E stratifies prescription trends by age group. Graphically, patients ≥65 appear to receive more DOACs than patients <65 with minimal differences between patients 65 to 74 and ≥75. Panel F further stratifies the DOACs by OAC agent. Graphically, older patients appear more likely to receive apixaban or rivaroxaban than younger patients.

Figure 8. Proportion of OAC Agents Initiated Overall, and by Age and Sex over Time

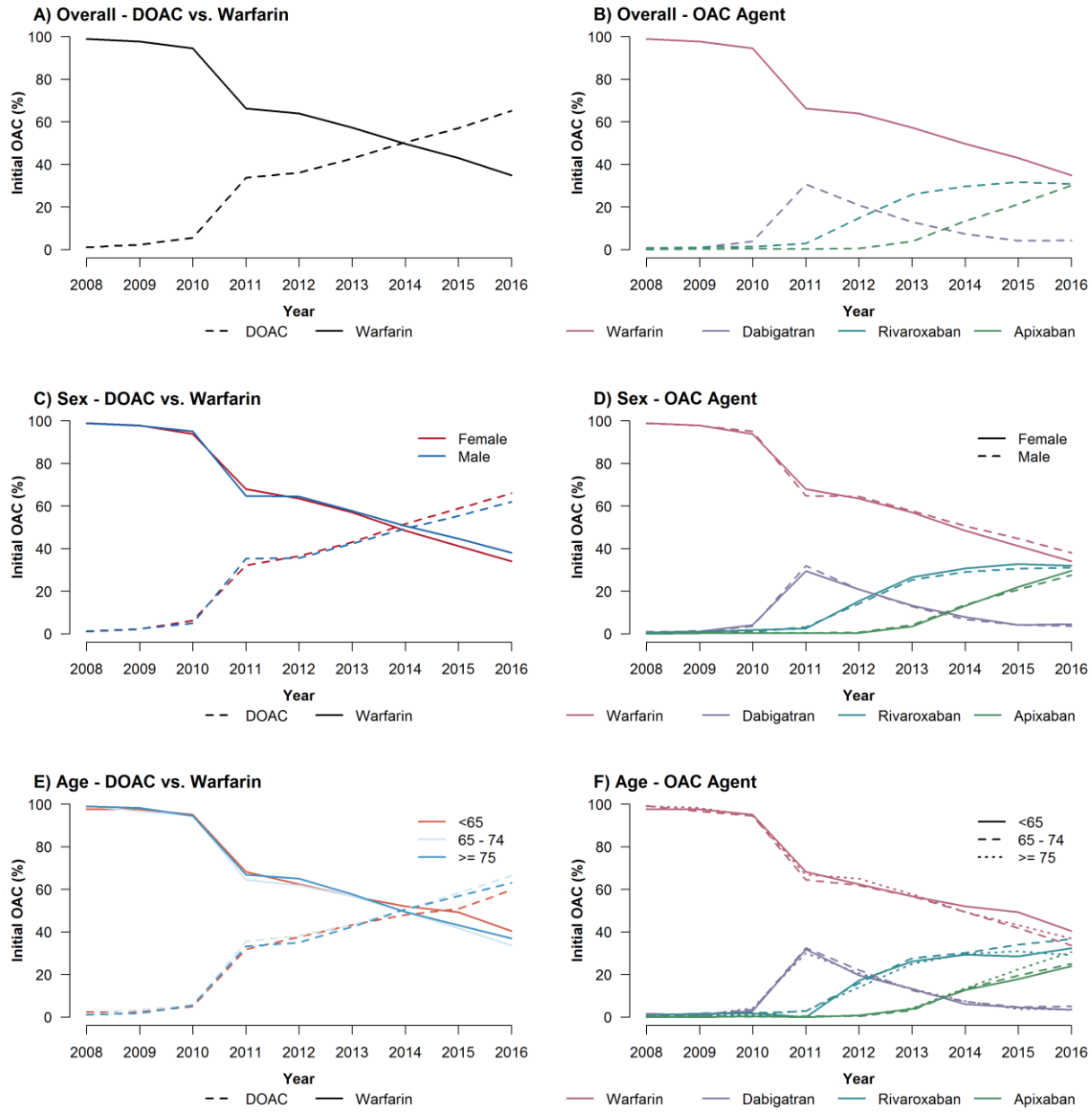


Table 12 presents the results of the multinomial logistic regression models for initial OAC drug. The unadjusted model includes age and sex as predictor variables, and the adjusted model adds hypertension, diabetes, PVD, MI, and stroke/TIA. The unadjusted ORs show women are less likely than men to receive any type of OAC, than no OAC. However, women are more likely than men to receive DOAC vs. warfarin. The results are consistent with the graphical explorations in Figure 7 and the OAC use models which showed women received more DOAC and less OAC, respectively. The unadjusted ORs for age show that OAC use is strongly associated with age; older patients are more likely to receive DOAC or warfarin than no OAC. Older patients are also more likely to be initiated on DOACs. Results of the adjusted models are largely consistent with the unadjusted models. Women remain less likely to receive OAC, regardless of type. However, after accounting for confounders, women are equally likely to receive DOAC vs. warfarin as men. The adjusted ORs show than age remains strongly associated with receiving any OAC. However, in contrast to the unadjusted models, patients ≥ 75 are less likely to receive DOACs after adjustment.

Table 12. ORs for Sex on Choice of Initial OAC Agent Type

Model	Factor	Outcome	OR	95% CI	p-value
Unadjusted	**Sex (F vs. M)**	Warfarin vs. No OAC	0.92	(0.88, 0.96)	0.0001
	Sex (F vs. M)	DOAC vs. No OAC	0.97	(0.93, 1.02)	0.22
	Sex (F vs. M)	DOAC vs. Warfarin	1.06	(1.00, 1.12)	0.04
	Age (65-74 vs. < 65)	Warfarin vs. No OAC	1.05	(0.95, 1.15)	0.35
	Age (≥75 vs. < 65)	Warfarin vs. No OAC	1.12	(1.03, 1.23)	0.01
	Age (65-74 vs. < 65)	DOAC vs. No OAC	1.25	(1.13, 1.37)	<0.0001
	Age (≥75 vs. < 65)	DOAC vs. No OAC	1.21	(1.11, 1.33)	<0.0001
	Age (65-74 vs. < 65)	DOAC vs. Warfarin	1.19	(1.07, 1.34)	0.002
	Age (≥75 vs. < 65)	DOAC vs. Warfarin	1.08	(0.97, 1.20)	0.17
Adjusted*	**Sex (F vs. M)**	Warfarin vs. No OAC	0.92	(0.88, 0.96)	<0.0001
	Sex (F vs. M)	DOAC vs. No OAC	0.92	(0.88, 0.96)	0.0004
	Sex (F vs. M)	DOAC vs. Warfarin	1.00	(0.95, 1.06)	0.80
	Age (65-74 vs. < 65)	Warfarin vs. No OAC	1.19	(1.09, 1.31)	0.0002
	Age (≥75 vs. < 65)	Warfarin vs. No OAC	1.28	(1.17, 1.40)	0.003
	Age (65-74 vs. < 65)	DOAC vs. No OAC	1.16	(1.05, 1.28)	<0.0001
	Age (≥75 vs. < 65)	DOAC vs. No OAC	1.11	(1.01, 1.22)	0.03
	Age (65-74 vs. < 65)	DOAC vs. Warfarin	0.96	(0.87, 1.10)	0.66
	Age (≥75 vs. < 65)	DOAC vs. Warfarin	0.87	(0.78, 0.97)	0.02

3.4 Adverse Outcomes by OAC Drug

Figure 9 is a flowchart describing the cohort definition process for the outcomes analyses. Patients with index incident AF diagnosis from January 1, 2013 to December 31, 2016 were included. Patients were excluded if they were not guideline indicated for OAC per CHA_2DS_2-VASc criteria, were not OAC naïve, did not fill a prescription for OAC within 100 days following index AF diagnosis, or filled a prescription for dabigatran. Dabigatran was excluded from comparisons as the results in section 3.3 demonstrated a rapid decline in initial prescriptions likely due to side effects of dyspepsia. Patients who experienced any of the composite endpoint within exposure definition window of 100 days were excluded. After exclusions, 14,609 patients were included in the cohort of which 18.9%, 31.6%, and 49.5% were initiated on apixaban, rivaroxaban, and warfarin, respectively.

Figure 9. Adverse Outcomes Cohort Flowchart

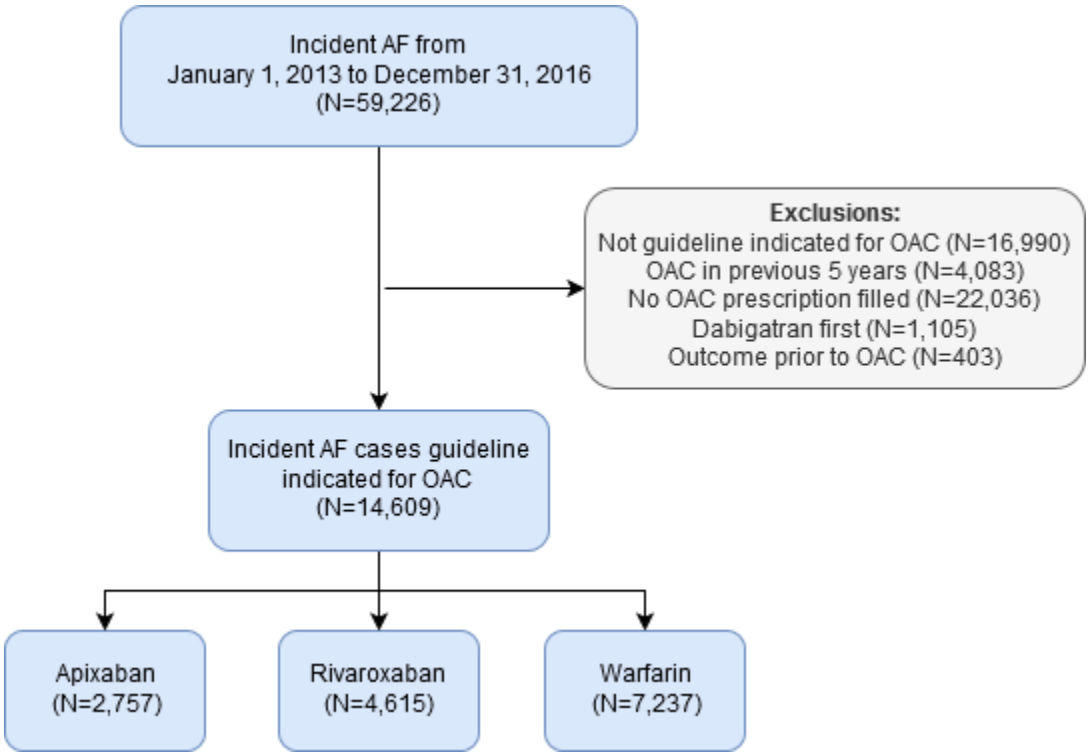


Table 17 summarizes baseline characteristics and medications by first OAC drug prescription filled. Mean age between each drug group was within 1.5 years and the proportion of women in each group was slightly lower in the warfarin group. Overall, patients filling a prescription for warfarin had higher rates of comorbidities including heart failure, diabetes,

hypertension, PVD, MI, CKD, COPD, anemia, and history of bleeding. Patients prescribed warfarin used more beta blockers, CCBs, and ACEi/ARBs at baseline.

Table 17. Baseline Characteristics by OAC Drug

Baseline characteristics	Apixaban (n=2,757)	Rivaroxaban (n=4,615)	Warfarin (n=7,237)	P-value
Age (Years), mean ± SD	78.6 ± 9.0	77.1 ± 8.5	77.7 ± 9.0	< 0.001
Age categories (Years)				< 0.001
<65	147 (5.3)	273 (5.9)	488 (6.7)	
65-74	705 (25.6)	1386 (30)	1942 (26.8)	
≥75	1905 (69.1)	2956 (64.1)	4807 (66.4)	
Female Sex	1314 (47.7)	2206 (47.8)	3262 (45.1)	0.005
CHA2DS2-VASc	4.0 (3.0,5.0)	3.0 (3.0,4.0)	4.0 (3.0,5.0)	< 0.001
Heart Failure	572 (20.7)	765 (16.6)	1946 (26.9)	< 0.001
Hypertension	2049 (74.3)	3510 (76.1)	5562 (76.9)	0.03
Stroke/TIA	405 (14.7)	417 (9)	873 (12.1)	< 0.001
PVD	116 (4.2)	187 (4.1)	506 (7)	< 0.001
MI	183 (6.6)	258 (5.6)	867 (12)	< 0.001
Diabetes	857 (31.1)	1428 (30.9)	2659 (36.7)	< 0.001
CKD	478 (17.3)	520 (11.3)	1674 (23.1)	< 0.001
COPD	150 (5.4)	233 (5)	671 (9.3)	< 0.001
Anemia	268 (9.7)	371 (8)	966 (13.3)	< 0.001
Hyperthyroidism	13 (0.5)	23 (0.5)	31 (0.4)	0.85
Hypothyroidism	189 (6.9)	294 (6.4)	447 (6.2)	0.46
History of Bleeding	146 (5.3)	226 (4.9)	520 (7.2)	< 0.001
Cancer	440 (16)	650 (14.1)	1105 (15.3)	0.07
Liver Disease	34 (1.2)	71 (1.5)	132 (1.8)	0.10
Baseline Medications				
Beta Blockers	815 (29.6)	1262 (27.3)	2420 (33.4)	< 0.001
CCBs	727 (26.4)	1231 (26.7)	2156 (29.8)	< 0.001
ACEi/ARB	1415 (51.3)	2441 (52.9)	4001 (55.3)	< 0.001
Antiplatelets	228 (8.3)	301 (6.5)	573 (7.9)	0.005
Statin	1019 (37)	1696 (36.7)	2805 (38.8)	0.05
Digoxin	12 (0.4)	30 (0.7)	65 (0.9)	0.04

Figure 10 presents cumulative incidence curves for the composite endpoint and each component up to 1 year with estimates and 95% CIs of one year rates. Panel A shows the rates of composite endpoint for each drug; the rate of composite endpoint was markedly higher in the warfarin group compared with the rivaroxaban and apixaban groups (P<0.0001). The observed difference between warfarin and the two DOACs was driven by differences in mortality and heart failure (panels B and D). Rivaroxaban had the lowest rate of composite outcome; however, the difference between apixaban and rivaroxaban was < 1% (Panel A). Panel C highlights the

rates of stroke in each drug; there are no statistically or clinically significant differences in the stroke rates between each OAC drug. The differences in observed mortality rate are noteworthy given the similar rates of stroke between the drugs. One explanation is mortality may be driven by out of hospital fatal strokes. Cause of death is poorly coded in BC vital statistics; therefore, the analysis is unable to determine whether the difference in mortality is due to out of hospital fatal stroke.

Figure 10. Cumulative Incidence Curves by OAC Drug for Adverse Outcomes

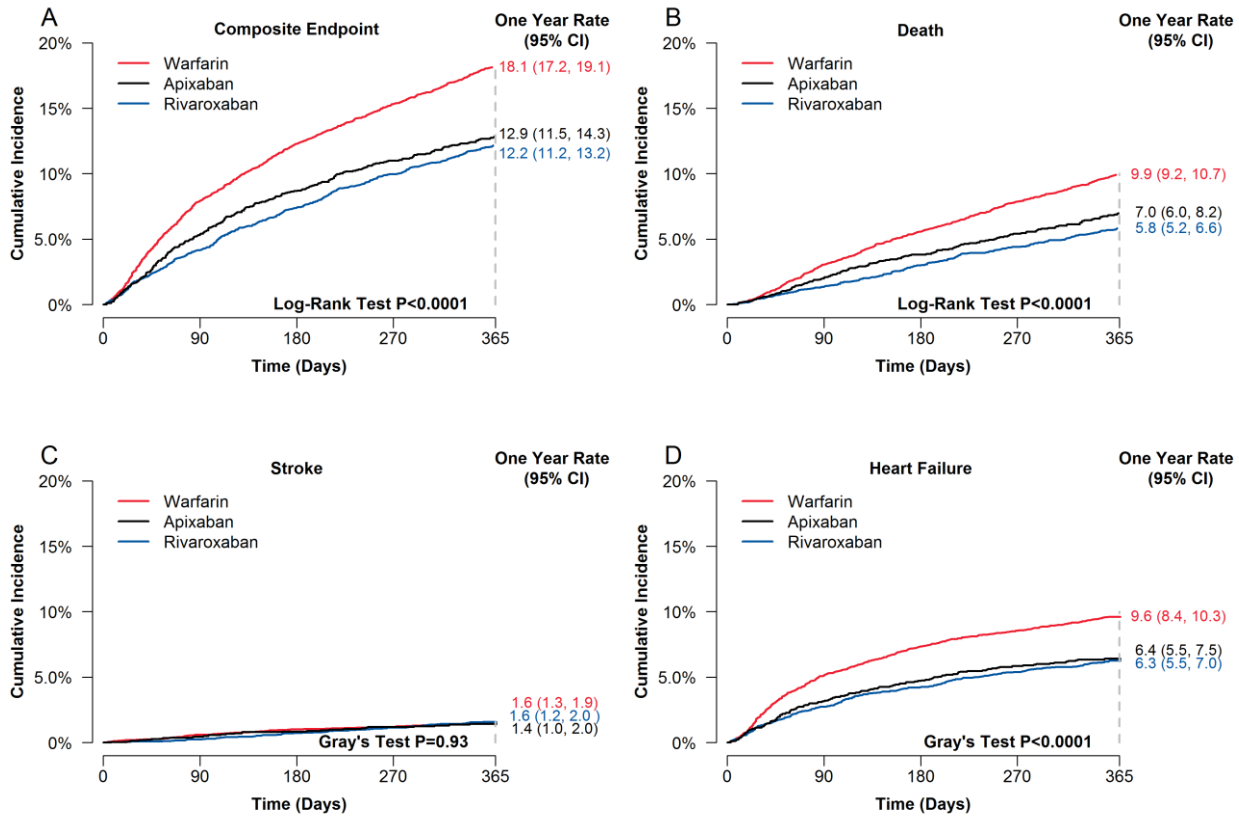
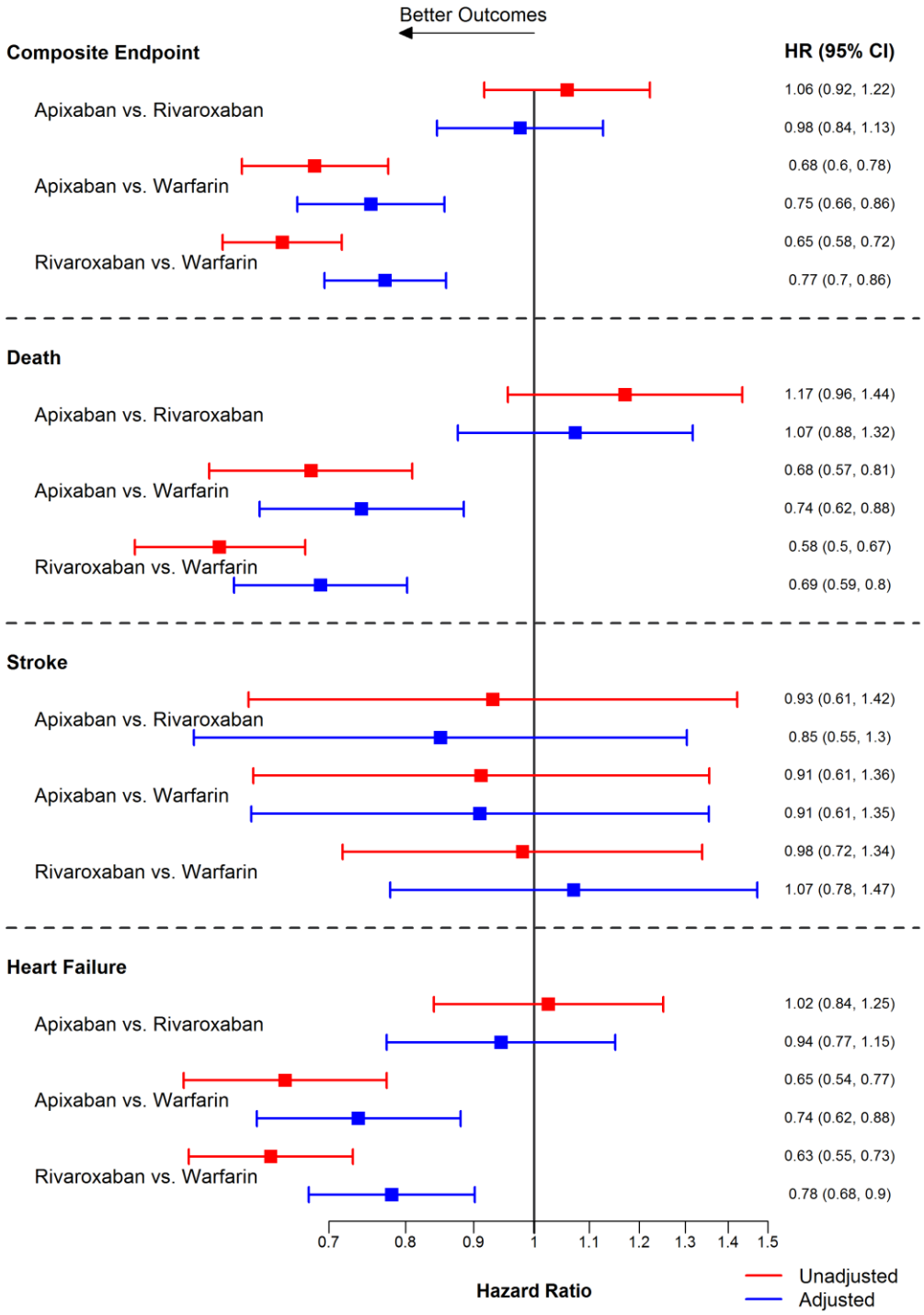


Figure 11 presents the unadjusted and adjusted cox-PH models for OAC drug on outcomes. Warfarin users experienced higher rates of composite, death, and heart failure than apixaban or rivaroxaban users. The HRs for warfarin vs. each DOAC were slightly attenuated after adjustment for baseline characteristics but remained significant. Outcome rates for patients prescribed rivaroxaban or apixaban were similar with respect to all outcomes. Rates of stroke did not vary significantly between each OAC drug.

Figure 11. Forest Plot of HRs of OAC Drug on Adverse Outcomes



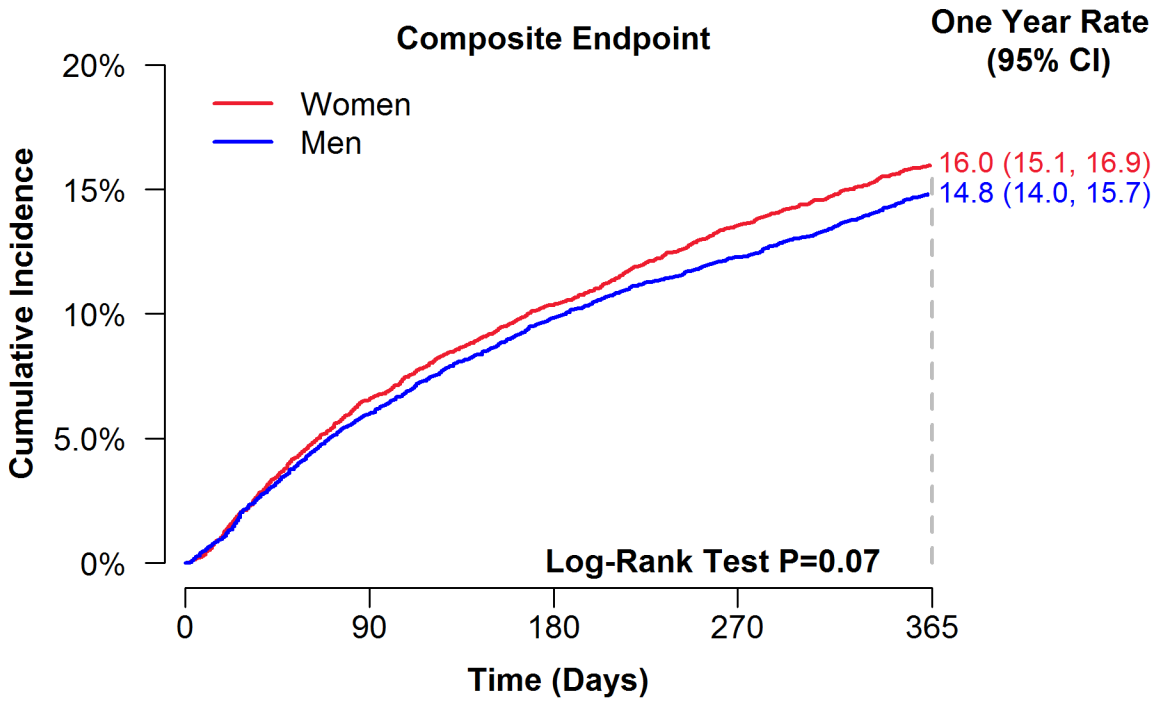
3.4.1 Sex Differences

Sex differences in the rates of outcomes were explored through interaction terms of sex and OAC drug and the main effect of sex. No significant interaction effects between sex and OAC drug were present in the composite endpoint either before or after adjustment for baseline characteristics (all interaction p-values > 0.3). Table 18 reports the unadjusted and adjusted HRs for sex on composite outcome up to 1 year with 95% confidence intervals; women and men have comparable rates of composite outcome in this cohort. Figure 12 presents the cumulative incidence curves for outcomes up to one year by sex; while rates are higher in women, the difference is not significant. Since no significant interaction or main effects were detected in the composite endpoint no additional testing was performed on components of composite to prevent problems arising from multiple comparisons.

Table 18. HRs for Sex on Adverse Outcomes

Model	HR (F vs. M)	95% CI	p-value
Unadjusted	1.02	(0.94, 1.12)	0.63
Adjusted	1.05	(0.96, 1.15)	0.25

Figure 12. Cumulative Incidence Curves for Adverse Outcomes by Sex



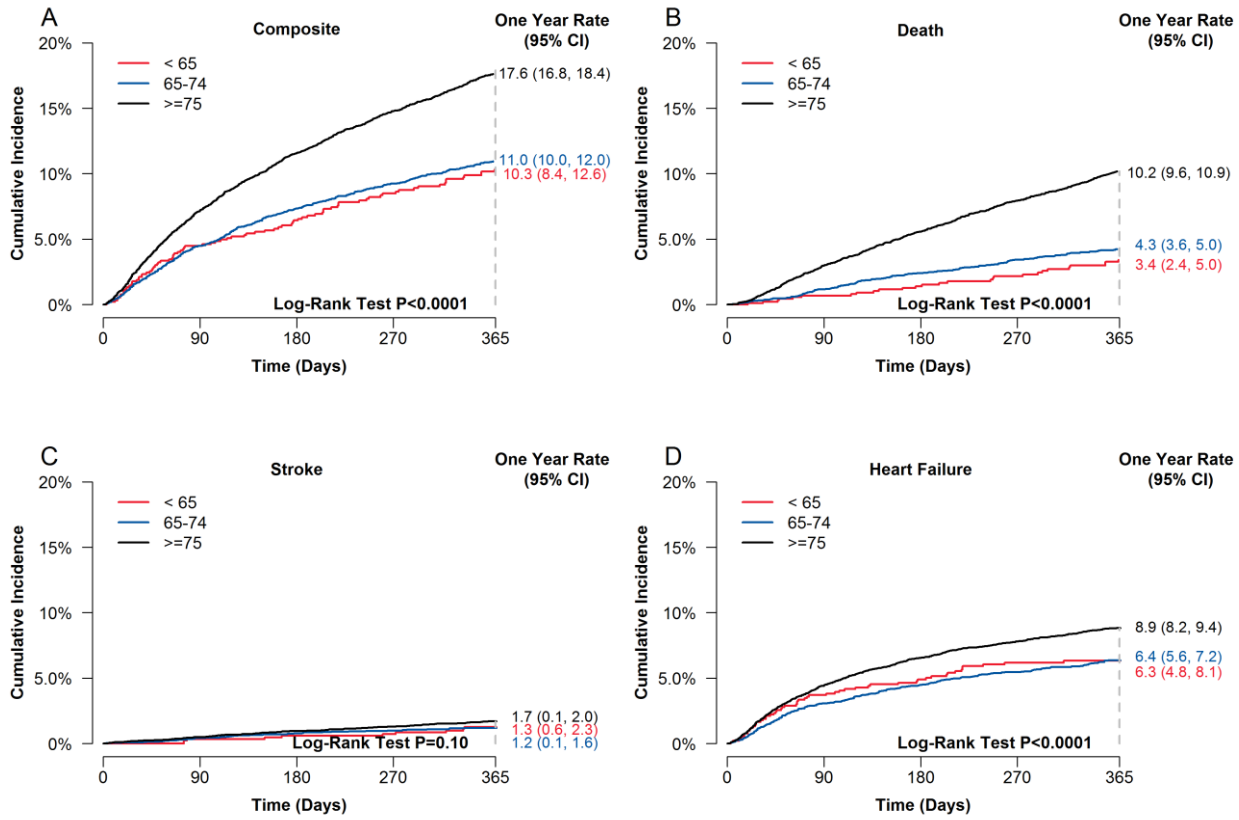
3.4.2 Age Differences

Age differences in the rates of outcomes were explored using similar methods to the sex differences analyses: interaction effects of age and OAC drug and main effect of categorical age. No significant interactions between age and OAC drug were present in the composite endpoint both before and after adjustment for baseline characteristics (all interaction $p > 0.11$). Figure 13 reports the cumulative incidence curves for the composite outcome and each component of the composite outcome. The rates of outcomes are significantly higher in the ≥ 75 group for each of composite, death, and heart failure up to 1 year, but are comparable among patients <75. The results of the unadjusted and adjusted models are reported in table 19. The unadjusted demonstrate a similar pattern to the cumulative incidence functions. However, after adjustment the HR for 65-74 vs. < 65 becomes significant, which indicates the relationship between age and outcomes increases in a stepwise fashion. This relationship is consistent with expectations. Typically, adjustment attenuates the relationship when factors that are strong predictors of outcomes are added to the model; however, the opposite is observed in this case. One possible explanation is that comorbid burden typically increases with age, however in this cohort patients <65 must present with ≥2 CHA_2DS_2-VASc risk factors. In contrast, patients 65-74 and ≥ 75 require 1 and 0 risk factors, respectively. This may result in similar crude event rates of outcomes, but HRs which are stronger after adjustment for baseline characteristics.

Table 19. HRs for Age on Adverse Outcomes

Model	Level	HR	95% CI	p-value
Unadjusted	65-74 vs. <65	1.09	(0.86, 1.38)	0.47
	≥ 75 vs. <65	1.79	(1.44, 2.24)	<0.0001
Adjusted	65-74 vs. <65	1.43	(1.13, 1.81)	0.003
	≥ 75 vs. <65	2.27	(1.81, 2.83)	<0.0001

Figure 13. Cumulative Incidence Curves by Age Group for Adverse Outcomes



3.5 Sex Differences in Treatment and Outcomes of ED Presentations of AF

3.5.1 Cohort Description and Patient Characteristics

Figure 14 is a flowchart describing the cohort development process for the ED AF cohort. Overall, 15,955 patients presented to the ED with an AF diagnosis at least once during the study period. Of those patients, 7,450 were excluded due to previous AF diagnoses, insufficient length of provincial registration, age <20, unknown sex, or history of valve disease. After exclusions, 8,505 incident non-valvular AF cases remained of which 4,071 (47.9%) were women and 4,434 (52.1%) were men.

Figure 14. Cohort Development for ED Presentations of AF

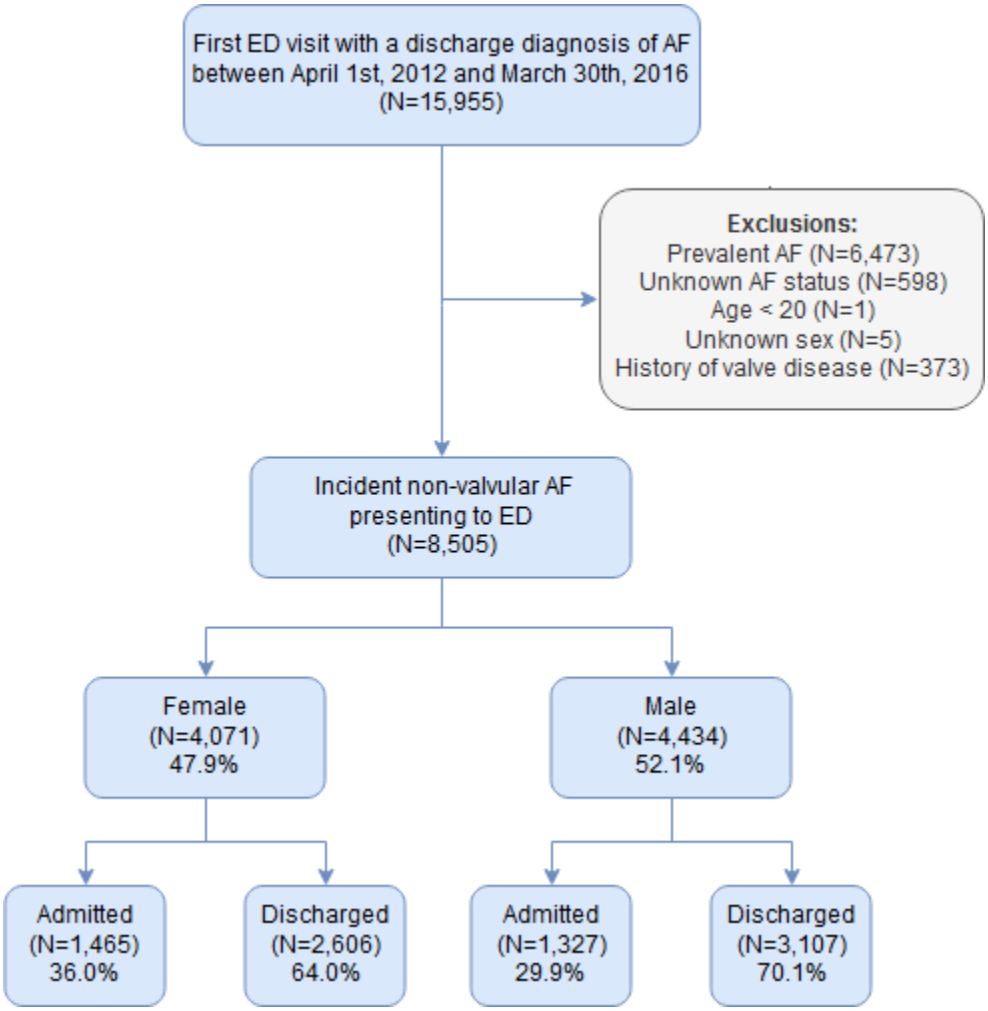


Table 20 presents baseline characteristics of the ED cohort by sex. Women were 8.0 years older on average and had higher rates of heart failure and hypertension. The combination of higher rates of CHA_2DS_2-VASC component comorbidities and advanced age resulted in a significantly larger portion of women being guideline indicated for OAC than males at 73.2% vs. 55.3%, respectively. Men presented with higher rates of PAD and prior MI.

Table 20. Baseline Characteristics by Sex

Baseline Characteristic	Female (N=4,071)	Male (N=4,434)	p-value
Age at diagnosis, mean ± SD	74.3 ± 13.2	66.3 ± 15.1	<0.001
Age Category, n (%)			<0.001
< 65	886 (21.8)	1859 (41.9)	
65-74	989 (24.3)	1166 (26.3)	
≥ 75	2196 (53.9)	1409 (31.8)	
CHA_2DS_2-VASc, median [IQR]	4.0 [2.0, 4.0]	2.0 [1.0, 3.0]	<0.001
CHA_2DS_2-VASc Components, n (%)			
Heart Failure	656 (16.1)	587 (13.2)	<0.001
Hypertension	2540 (62.4)	2182 (49.2)	<0.001
Diabetes	857 (21.1)	978 (22.0)	0.29
Stroke/TIA	216 (5.3)	179 (4.0)	0.005
Peripheral Arterial Disease	98 (2.4)	151 (3.4)	0.006
Prior Myocardial Infarction	150 (3.7)	238 (5.4)	<0.001
Guideline Indication for OAC	2980 (73.2)	2452 (55.3)	<0.001
Other comorbidities, n (%)			
COPD	488 (12.0)	178 (10.8)	0.08
Dementia	228 (5.6)	121 (2.7)	<0.001
Cancer	455 (11.2)	588 (13.3)	0.003
Renal Disease	510 (12.5)	499 (11.3)	0.07
Anemia	472 (11.6)	308 (6.9)	<0.001
Baseline Medications, n (%)			
OAC	332 (8.2)	332 (7.5)	0.25
ACEi/ARB	1594 (39.2)	1525 (34.4)	<0.001
Beta Blocker	967 (23.8)	944 (21.3)	0.007
Statins	991 (24.3)	1156 (26.1)	0.067
CCB - Dihydro	694 (17.0)	532 (12.0)	<0.001
CCB – Non-dihydro	214 (5.3)	158 (3.6)	<0.001
Digoxin	57 (1.4)	52 (1.2)	0.352

3.5.2 Admission to Hospital

Overall, the admission rate following index ED presentation was 32.8%. The admission rates varied significantly by sex; women were more frequently admitted to hospital, 36.0% vs. 29.0% ($p < 0.0001$). Table 21 presents the results of the unadjusted and adjusted logistic regression models for admission to hospital. The unadjusted OR of 1.32 reflects the difference observed in the univariate proportions of patients admitted to hospital. After adjustment for CHA_2DS_2-VASc components, anemia, dementia, COPD, renal disease, and cancer, the difference is largely attenuated and the OR is reduced to 1.12 which remains borderline significant. Ultimately, women are admitted to hospital more often than men following incident AF presentation to the ED.

Table 21. Odds ratios for sex on admission to hospital following index ED visit

Model	Odds Ratio (F vs. M)	95% CI	p-value
Unadjusted	1.32	(1.20, 1.44)	<0.0001
Adjusted	1.12	(1.01, 1.24)	0.04

3.5.3 OAC Use

The rate of OAC use at 90 days following index ED presentation was 49.2% (95% CI: 48.2, 50.3) overall. A significant proportion of patients (36.1%) were not guideline indicated for OAC per CHA_2DS_2-VASc criteria, therefore all OAC analyses are presented stratified by guideline indication. The rate of OAC use in guideline indicated patients was 60.2% (95% CI: 58.9%, 61.5%). While the rates of OAC use were substantially lower in patients not guideline indicated for OAC approximately 30% were using OAC after presentation to the ED with incident AF. Table 16 describe rates of OAC use at 90 days by sex and ED discharge status. The rates of OAC use at 90 days were similar between men and women in both cohorts.

Table 22. Rates of OAC use at 90 days

Indication	Overall		Discharged		Admitted	
	Female (N=2,980)	**Male** (N=2,452)	**Female** (N=1,711)	**Male** (N=1,482)	**Female** (N=1,269)	**Male** (N=970)
Guideline Indicated	60.4 (58.5, 62.1)	59.5 (57.5, 61.4)	58.1 (55.8, 60.5)	58.2 (55.6, 60.7)	62.8 (60.0, 65.5)	61.0 (57.8, 64.1)
	Female (N=1,091)	**Male** (N=1,982)	**Female** (N=895)	**Male** (N=1625)	**Female** (N=196)	**Male** (N=357)
Not Indicated	30.0 (27.3, 32.7)	30.3 (28.3, 32.4)	27.3 (24.5, 30.3)	27.1 (25.0, 29.3)	42.3 (35.2, 49.3)	45.0 (39.8, 50.1)

Figure 15 shows cumulative incidence curves for OAC use up to 1 year following index ED visit. The curves show that while rates of OAC use are comparable between men and women, there is a significant treatment gap up to 1 year in patients guideline indicated for OAC. At 1 year, the OAC rate for men and women is approximately 65%, therefore a treatment gap of 35% is observed in patients who should receive OAC.

Figure 15. Cumulative Incidence Curves for OAC use by Sex up to 1 Year

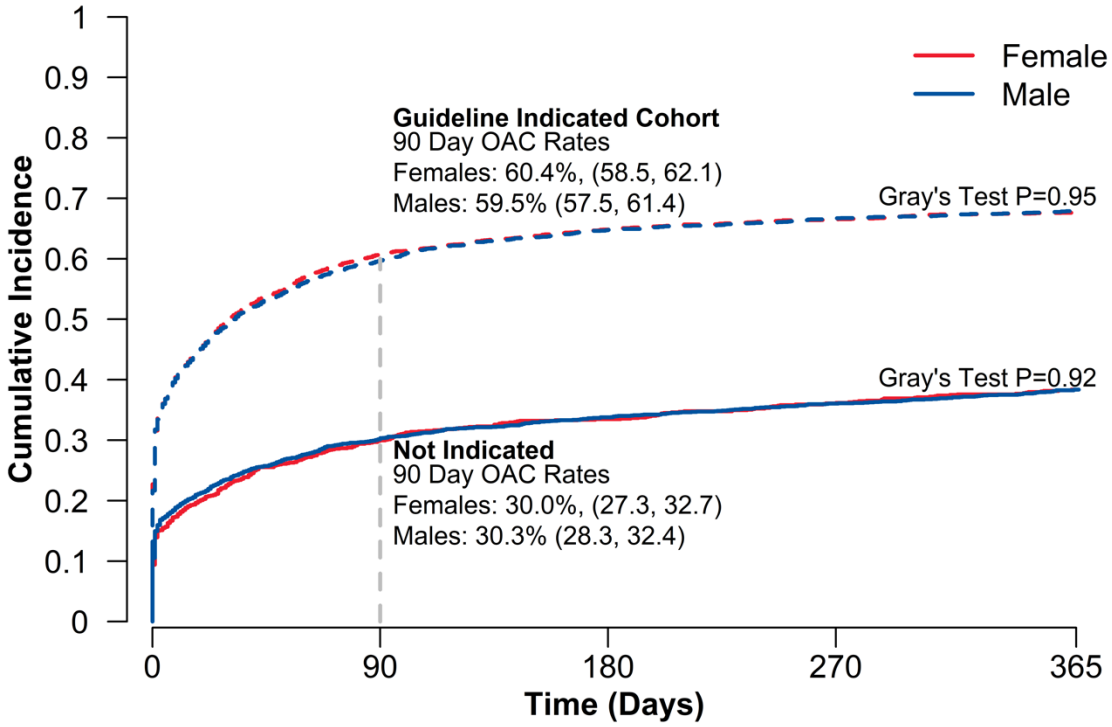
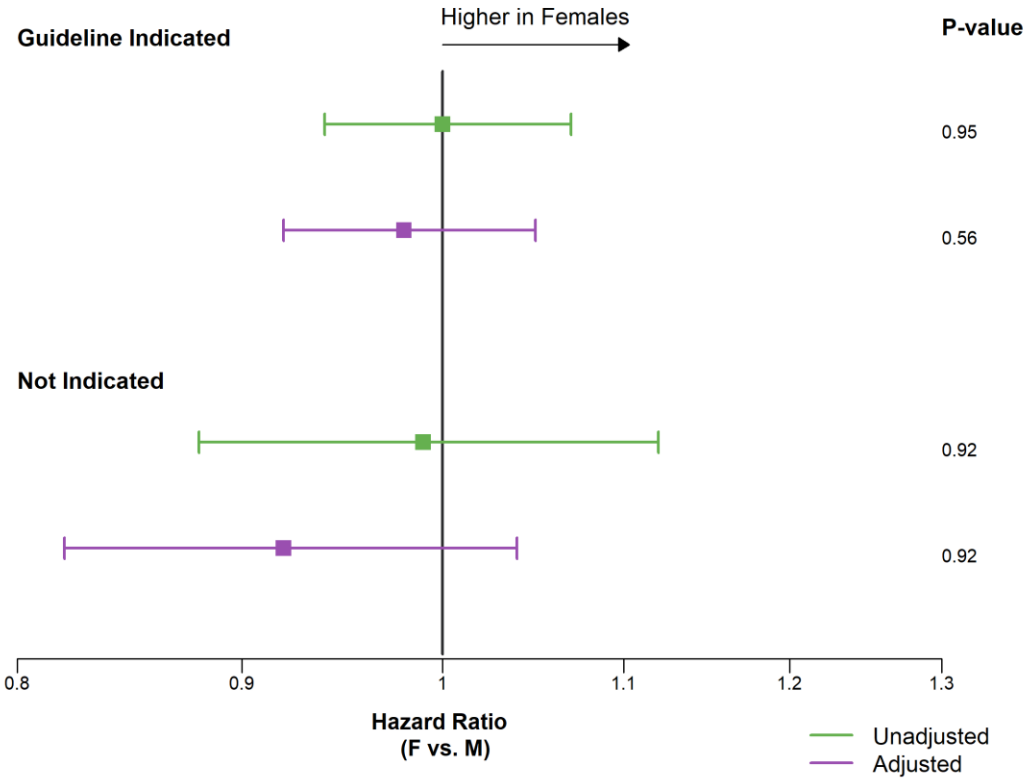


Figure 16 presents the results of the unadjusted and adjusted time to event models for sex on OAC use up to 1 year following index ED visit. The unadjusted HRs for sex were 1.00 (95% CI: (0.94, 1.07)) and 0.98 (95% CI: (0.92, 1.05)) for the guideline indicated and not indicated cohorts, respectively. The results did not change significantly after adjustment for baseline characteristics; adjusted HRs were 0.99 (95% CI: (0.88, 1.12)) and 0.92 (95% CI: (0.82, 1.04)) for the guideline indicated and not indicated cohorts, respectively. As noted in the crude rates presented in table 22 and figure 15, women and men were equally likely to be prescribed OAC in both cohorts even after adjustment for differences in baseline characteristics.

Figure 16. HRs for Sex on OAC use up to 1 Year



3.5.4 Adverse Outcomes

Figure 17 presents Kaplan-Meier (KM) curves for the composite endpoint of death, stroke, and heart failure up to 1 year following index ED AF diagnosis. The curves show women have higher rates of the composite endpoint up to 1 year (log-rank $p < 0.0001$). Table 23 presents crude rates of the composite endpoint and components at 30 days and 1 year overall and stratified by ED discharge status. Women have higher rates of all endpoints at both 30 days and 1 year. This trend is consistent among patients discharged home; however, among patients admitted to the hospital, males have similar or slightly higher rates at 30 days which is driven by higher rates of heart failure at 30 days. By 1 year, outcome rates in patients admitted to hospital show similar trends to the overall and discharged groups.

Figure 17. KM Curves Outcome of Death, Stroke, and Heart Failure

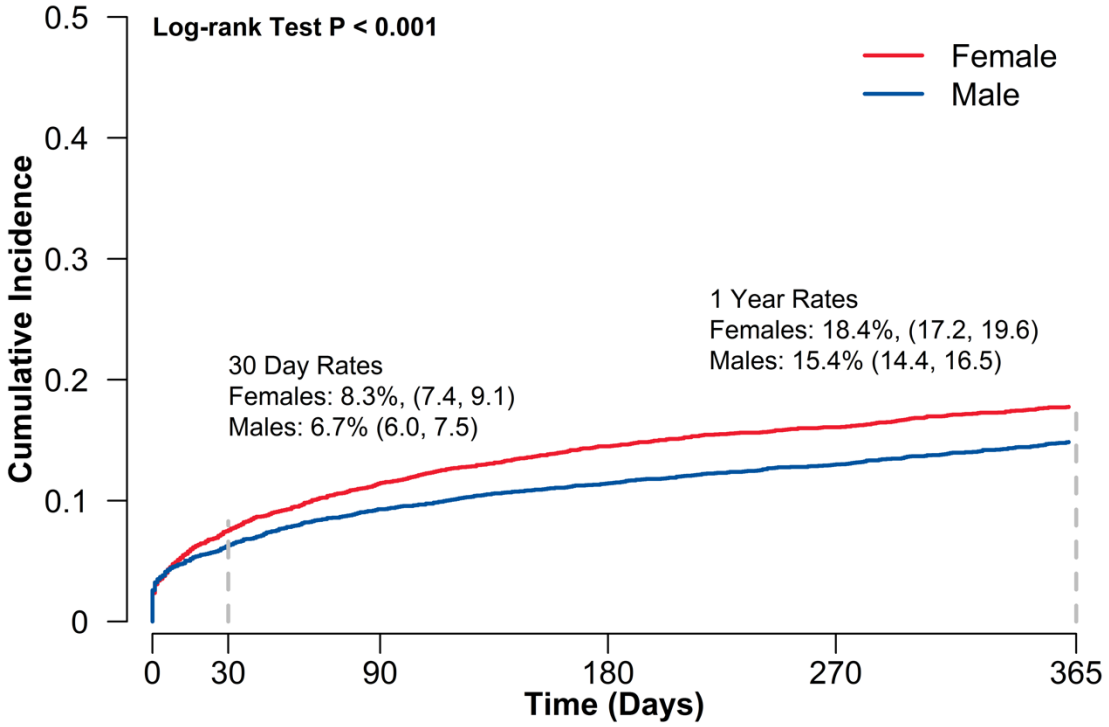
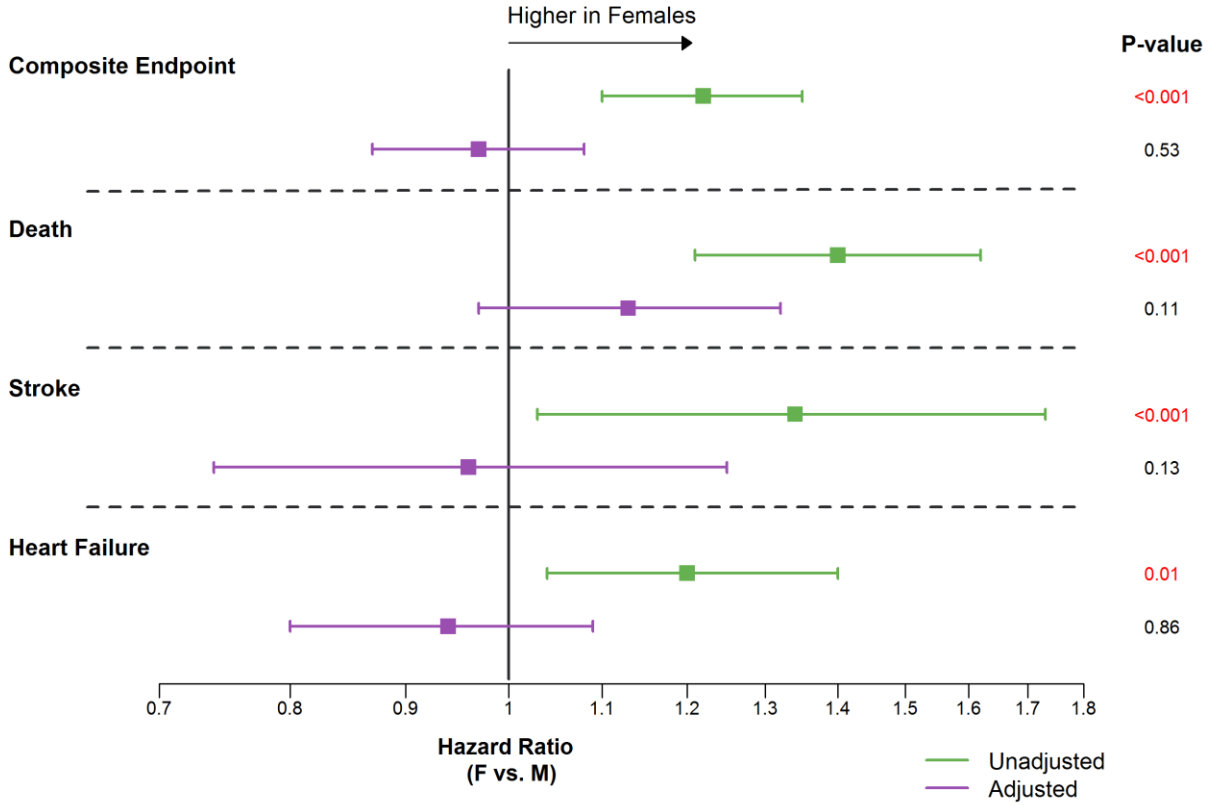


Table 23. Outcome rates (95% CIs) at 30 days and 1 Year by Sex and ED Discharge Status

	Outcome	Overall		Discharged		Admitted	
		Female (N=4,071)	**Male** (N=4.434)	**Female** (N=2,606)	**Male** (N=3,107)	**Female** (N=1,465)	**Male** (N=1,327)
30 Day	**Composite**	8.3 (7.4, 9.1)	6.7 (6.0, 7.5)	2.8 (2.3, 3.6)	1.6 (1.2, 2.1)	17.9 (16.0, 19.9)	18.7 (16.7, 20.9)
	Death	2.8 (2.4, 3.4)	1.9 (2.4, 3.4)	0.8 (0.6, 1.3)	0.4 (0.2, 0.7)	6.4 (5.3, 7.8)	5.4 (4.3, 6.8)
	Stroke	1.5 (1.1, 1.9)	1.2 (0.9, 1.5)	0.7 (0.4,1.1)	0.3 (0.1, 0.5)	2.7 (2.0, 3.6)	3.3 (2.5, 4.4)
	HF	4.5 (3.9, 5.2)	4.2 (3.6, 4.8)	1.4 (1.0, 1.9)	1.1 (0.7, 1.5)	10.0 (8.6, 11.6)	11.4 (9.7, 13.2)
1 Year	**Composite**	18.4 (17.2, 19.6)	15.4 (14.4, 16.5)	8.9 (7.8, 10.0)	7.8 (6.9, 8.8)	35.4 (33.0, 37.9)	33.2 (30.7, 35.8)
	Death	10.1 (9.3, 11.1)	7.4 (6.7, 8.2)	4.4 (3.7, 5.3)	3.3 (2.7, 4.0)	20.3 (18.3, 22.5)	17.0 (15.1, 19.2)
	Stroke	3.1 (2.3, 3.6)	2.3 (1.9, 2.8)	1.9 (1.4, 2.4)	1.2 (0.8, 1.6)	5.3 (4.3, 6.6)	5.1 (4.0, 6.4)
	HF	9.3 (8.4, 10.2)	7.8 (7.0, 8.6)	4.5 (3.8, 5.4)	4.1 (3.5, 4.8)	17.9 (15.9, 19.9)	16.4 (14.5, 18.5)

Figure 18 shows the results of the unadjusted and adjusted Cox-PH models for the composite endpoint of death, stroke, and heart failure up to 1 year and each of the components. The results of the unadjusted models show that women have a higher risk of all endpoints with HRs of 1.22, 1.40, 1.34 and 1.20 for composite, death, stroke, and heart failure, respectively. However, after adjustment for CHA_2DS_2-VASc components, anemia, dementia, COPD, renal disease, and cancer the sex differences are attenuated in all endpoints. The resulting adjusted HRs are 0.97 (95% CI: (0.87, 1.08)), 1.13 (95% CI: (0.97, 1.32)), 0.96 (95% CI: (0.74, 1.25)), and 0.94 (95% CI: (0.80, 1.09)) for composite, death, stroke, and heart failure, respectively. The adjusted models showing attenuation of the sex differences indicates that differences in the crude rates are driven by differences in baseline characteristics such as advanced age and high rates of comorbidities in women.

Figure 18. HRs for Sex on Outcomes of Death, Stroke, and Heart Failure



4. Discussion and Conclusion

4.1 Results Summaries

This population-based study used administrative healthcare databases to identify the AF population in BC from 2008 to 2016. At the beginning of the study, we identified 81,205 prevalent cases and an additional 123,821 incident cases during the study from 2008 to 2016. The majority of patients were identified from MSP records (55.2%). Cohorts of incident AF cases were analyzed to address important knowledge gaps in the epidemiology, treatment preferences, and outcomes of AF.

4.1.1 Patient Characteristics

Characteristics of patients with AF varied by sex and age, and over time. Women were 4.2 years older on average and as a result had higher median CHA_2DS_2-VASc scores, 4.0 vs. 2.0 for women and men, respectively. The observed difference in age of onset is consistent with other studies, which reported women initially present with AF approximately 5 years later than men on average. [1, 6] In this study, women presented with higher rates of heart failure (18.6% vs. 17.7%), hypertension (63.7% vs. 57.0%) and prior stroke (8.7% vs. 7.7%). In contrast, men presented with more diabetes (26.5% vs. 21.8%), prior MI (10.5% vs. 6.4%), PVD (6.1% vs. 4.1%), CKD (15.3% vs. 14.7%), and cancer (16.8 vs. 13.0%). Similar differences in the presentation and comorbid conditions of AF have been reported in other studies. [1, 6, 79] Intriguingly, despite presenting with higher rates of cardiac comorbidities than men, women were filled fewer cardiac medications preceding AF diagnosis. A risk treatment paradox for pharmaceutical under-treatment of cardiovascular disease in women has been noted and merits further research. [114]

Consistent with expectations and results reported in other studies, comorbid burden increases as a function of age; rates of all CHA_2DS_2-VASc components increase steadily with advancing age. [89] AF in the young may present as lone-AF, AF in the absence of other risk factors, or with fewer comorbidities. [115] In contrast, AF in an older population often presents with other underlying heart conditions. As a result, managing the stroke risk of elderly AF patients can be further complicated by the treatment requirements of comorbid conditions. Approximately 50% of incident AF patients were $\geq$ 75 years of age and presented with high rates

of comorbidities; 72.4%, 24.9%, and 26.2% for hypertension, heart failure, and diabetes, respectively.

Temporal trends were observed in the characteristics of patients with AF from 2008 to 2016. The average age of patients decreased by 1.5 from 2008 to 2016 and the number of patients < 65 grew from 23.7% to 27.4%. The trend towards younger patients has been noted in US hospital admissions for AF, where the proportion of admissions patients <60 grew from 19% in 1996 to 25.3% in 2010. [116] Rates of comorbidities such as heart failure and hypertension are decreasing, while rates of diabetes and CKD are increasing. Changes in the composition of patient characteristics could be related to earlier diagnoses of AF, before the development of other comorbidities. These findings further highlight the need to incorporate age into future research and considerations for treatment options.

4.1.2 Epidemiological Trends

This study reports contemporary estimates of the incidence and prevalence of AF in BC from 2008 to 2016. The estimated prevalence of AF was 3.2% in 2016, up from 2.2% in 2008. The crude and standardized incidences of AF were 374.5/100,000, and 428/100,000 in 2008 and crude and standardized incidences were 431/100,000 in 2016. Crude rates grew while standardized rates stagnated indicating the underlying population demographics are shifting towards an older and more at-risk population. This is reflected in the population changes from 2008 to 2016; the proportion of BC residents 65 or older grew from 14.2% 2008 to 18.2% in 2016, representing a 28.2% increase. [117] Increasing prevalence of AF is common to Western countries with growing elderly populations.[16, 22] These findings describe current trends in BC and highlight the need for the healthcare system to prepare for an increased burden of AF.

Incidence and prevalence of AF varied significantly by sex and age; women had both lower incidence and prevalence of AF than men in BC. In 2016, the incidence of AF in women was 381.7/100,000 compared to 482.1/100,000 in men. The prevalence in 2016 was 2.7% in men and 3.7% in women. The prevalence of AF is growing regardless of sex, but slightly more in men; 46% vs. 43% increase from 2008 to 2016 for men and women, respectively. Our findings are consistent with epidemiological trends reported in Western countries. [35, 108, 116] Studies including the Framingham and Rotterdam cohort studies have reported lower incidence and prevalence of AF in women and strong associations between age and AF development. [37, 38] The

prevalence of AF grows with increasing age; the estimated prevalence was 0.9%, 6.5%, and 17.2% in 2016 for <65, 65-74, and ≥75 age groups, respectively. This study provides further evidence that sex and age are strong explanatory variables in the epidemiology of atrial fibrillation, therefore future studies of trends in AF epidemiology should stratify by sex and age.

4.1.3 OAC Initiation and Prescription Trends

The use of OAC for stroke prophylaxis was sub-optimal; the study found only 45.9% of patients guideline-indicated for OAC were dispensed a prescription within 100 days following incident AF diagnosis. Significant treatment gaps in guideline-indicated OAC use have been reported previously; the RE-LY AF registry and administrative database studies in Ontario estimated 34.3% and 47% of guideline-indicated patients did not receive OAC, respectively. [108, 118] Rates of OAC use appear to be increasing slightly over time from 43.25% in 2008 to 47.0% in 2016; however, without a drastic change in the rate of increase, a significant treatment gap will remain for decades. By the end of the study, less than 5 years had elapsed since the approval of the first DOAC in Canada. In that time, the proportion of treated patients initiated on warfarin dropped from 100% in 2010 to 34.9% in 2016; physicians and patients are rapidly adopting DOACs for management of stroke risk. Nonetheless, the sudden increase in available pharmaceutical options has not translated into a significant improvement in OAC use. This study shows that barriers to OAC use are not solely caused by the challenges associated with warfarin.

The study investigated sex and age differences in the use and choice of OAC. While women received less OAC throughout the course of the study, by 2016 the difference is no longer significant (HR_{2016}= 0.98, (0.94, 1.01)). Preferences in OAC drug did not vary significantly by sex. Age was associated with higher rates of OAC use, and patients over 75 were less likely to be initiated on DOAC compared to warfarin (OR=0.87, (0.78, 0.97)).

4.1.4 Adverse Outcomes

Composite outcomes of death, stroke, and heart failure were compared between the three most commonly prescribed OACs as of 2016: rivaroxaban, apixaban, and warfarin. Apixaban and rivaroxaban were associated with better outcomes than warfarin (HR= 0.77, (0.7, 0.86), HR = 0.75, (0.66, 0.86), respectively), but were had similar outcomes when compared head-to-head (HR= 1.06, (0.92, 1.22)), for apixaban vs. rivaroxaban). Differences in the rates of composite endpoint up to 1 year were driven primarily by death (9.9% for warfarin, 7.0% for apixaban, and

5.6% for rivaroxaban) and heart failure (9.6% for warfarin, 6.4% for apixaban, and 6.3 for rivaroxaban). No significant differences were observed with respect to stroke rates (1.6% for warfarin, 1.6% for rivaroxaban, and 1.4% for apixaban). The results of the clinical trials comparing rivaroxaban and apixaban to warfarin reported hazard ratios for stroke of 0.79 (0.66, 0.95) and 0.79 (0.66, 0.96), respectively.[66, 67] Therefore, the lack of observed difference in stroke rates is unexpected. However, two possible mechanisms could drive the observed difference in mortality and underestimate stroke rates. First, as a result of using community pharmacy dispensation records, patients were required to fill prescriptions prior to having any outcomes. If warfarin users were more likely to have strokes prior to filling prescriptions the difference in stroke rate would be biased. Second, cause of death is poorly captured in BC vital statistics; as a result, out-of-hospital fatal strokes may be recorded as all-cause mortality. Therefore, if the increase in mortality is driven by out-of-hospital fatal strokes, the stroke rates will be underestimated.

Age and sex did not modify the effectiveness of OAC drug type. Rates of outcomes did not vary by sex, but were strongly associated with age. Patients ≥ 75 had a significantly higher risk of adverse outcome which was driven by a 10.2% risk of all-cause mortality up 1 year following diagnosis.

4.1.5 Sex Differences in ED Presentations of AF

This study reports sex differences in the clinical characteristics and rate of hospital admission, but not in the rates of OAC use and outcomes following initial AF diagnosis in the ED. Women were 8.0 years older on average than men and had higher rates of heart failure, hypertension, and prior stroke/TIA. In contrast, men presented with higher rates of diabetes, PAD, and prior MI. These results are consistent with the sex differences in clinical characteristics described by other studies. [1, 6] After adjustment for differences in clinical characteristics, women were more likely than men to be admitted to hospital (OR=1.12, (1.01, 1.24)). However, women were equally likely as men to receive OAC regardless of guideline indication (HR_{GLI}= 0.99, (0.88, 1.12) and HR_{NI}= 0.92, (0.82, 1.04)). Women had higher crude rates of events, but after adjustment for age and comorbidities, the effect was attenuated ($HR_{composite}$= 0.97, (0.87, 1.08)).

To the author's knowledge and to date, only a single additional study has investigated sex differences in ED presentations of AF. A retrospective chart review of 1,112 consecutive AF cases at two BC hospitals had similar findings; women presented with different clinical characteristics and had higher rates of admission, but treatment and outcomes were similar. [1] The chart review study had several limitations:

1) Underpowered for outcomes of stroke and death up to one year

2) Limited to two hospitals and therefore generalizability was limited

3) Lacked access to provincial hospitalization records for outcomes.

4) Did not utilize time to event analyses to account for censoring

Our study addresses each of the limitations of the chart review study and improves the generalizability of the conclusions. While OAC rates following initial AF diagnosis at the ED could be improved, this study reports no evidence of bias in AF treatment or outcomes related to sex in the ED.

4.2 Strengths and Limitations

Administrative health databases provide a powerful resource for conducting population-based research. Large research cohorts can be derived at a fraction of the cost of prospective registry or trial-based studies. The population-based nature of the study reduces the reliance on retrospective methods such as surveys which often suffer from recollection and selection biases. In addition, BC has universal health coverage, therefore all residents are covered and all routine interactions with the healthcare system generate records of the encounter. The datasets held at Population Data BC are made available to researchers on a study by study basis with appropriate ethics and data steward approval. While cost-effective, convenient, powerful, and accessible, several challenges are common to retrospective observational studies based on administrative data. First and foremost, the study is retrospective and non-randomized; therefore, observed differences may be attributed to unmeasured confounding or confounding by indication. Other limitations relate to the administrative purpose of the data.

Administrative datasets are designed primarily for billing and therefore do not capture all of the data required by researchers. The study defines comorbidities, medications, and outcomes

based on administrative billing records using diagnosis, pharmaceutical, and procedure codes which are susceptible to under-coding and misclassification. Physician mistakes and data entry errors in administrative databases have been noted at 8% and 22%, respectively. [119] Furthermore, MSP records require ICD-9 codes only up to 3 digits of detail; however, several health conditions, including AF, require 4 digits to be distinguished from related conditions. Provided data errors, misclassification, and under-coding are not systematically associated with a comparison group, (i.e. women more likely to be under-coded), the resulting bias would be towards the null hypothesis.

The cohort definition of AF patients relies on diagnosis codes primarily from hospital and out-patient physician records. There are two primary limitations to this definition. First, AF diagnosed during a hospitalization may be transient as a result of another condition or procedure such as sepsis or coronary artery bypass grafting (CABG) and therefore not require OAC. This may cause over-estimation of the OAC treatment gap. Second, diagnosis codes in MSP require only 3 digit ICD-9-CA codes, but this is not sufficient to differentiate between AF and other conditions. As a result, patients who are managed through out-patient physician billings may not be captured or the date of AF diagnosis defined by the study may be later than incident AF date. If a substantial portion of patients are not identified then the incidence and prevalence may be underestimated. Additionally, if patients are identified later than the actual AF incident diagnosis date then initial treatment preferences may be inaccurate.

The study defined baseline and discharge medications by pharmacy dispensation records in Pharmanet as opposed to physician prescription records. Therefore, the treatment gap in OAC prescriptions may be overestimated if a significant proportion of patients do not fill their prescriptions. While estimates based on community dispensation records will more accurately reflect the proportion of patients in compliance, the estimate will underestimate the proportion of patients receiving appropriate care from physicians. Second, over the counter medications such as ASA are not captured by Pharmanet; therefore, any patients managed on ASA alone will not be identified. However, both the Canadian and European guidelines are consistent that ASA alone is not sufficient for stroke prophylaxis in the AF population. [120] Finally, Pharmanet tracks dispensations from community pharmacies and does not capture hospital pharmacies. Therefore,

any patients who remain in an acute care facility for an extended period or die prior to discharge will not be accurately categorized.

4.3 Future Research

Observational studies and network meta-analyses have compared DOACs; however, all large-scale randomized controlled trials have only compared DOACs to warfarin, typically for non-inferiority. [65-68] While network meta-analyses are useful to provide indirect comparisons in the absence of head-to-head trials, these techniques assume homogenous populations and cannot account for unmeasured confounding. To determine which DOAC is preferable, a head-to-head trial including each DOAC is advisable. Randomization will ensure internal validity by balancing unmeasured confounders.

This study was unable to accurately define discontinuation and switching of OAC drugs. Future research could incorporate INR lab data to define OAC as a time-varying exposure which would account for discontinuation and switching between OAC drugs. This strategy would provide more accurate estimates of the differences in outcome rates between OAC drugs. Furthermore, INR could be used as a measure of bleeding risk and incorporated into adjustment models.

4.4 Research and Policy Implications

The results presented have important implications for patients, physicians, and policymakers. From a patient's perspective, the choice of available OACs is greater than ever before. Patients may opt for the convenience of DOACs over Warfarin regardless of the higher cost. Additionally, more OAC options provides second- and third-line alternatives when patients experience adverse events from an OAC agent and are required to discontinue. On the other hand, patients must determine, often with the help of their physician, which drug is most appropriate given their presentation, comorbid conditions, and resources available. The results of our study may help to inform patients about the most prescribed OACs and the outcomes associated with those medications. Further research incorporating quantitative and qualitative patient reported outcome measures is essential to provide patients with the evidence necessary to inform decisions regarding best available OAC treatment options.

Physicians are actively adopting new treatments as evidenced by the rapid uptake of DOACs observed in British Columbia. With the expansion of available treatment options comes an increased challenge of determining the most appropriate treatment with each patient. Physicians must balance stroke prevention and bleeding risk with patient convenience and resources. Furthermore, physicians must assess, with their patients, risk tolerance for bleeding events. This is complicated by factors such as urban versus rural location, which can impact the ability of the patient to access an emergency department or hospital in the event of a bleeding event. Further research to evaluate the risk benefit profile of each drug is necessary to inform clinicians and provide patients with the evidence necessary to make an informed decision surrounding choice of OAC.

The results of this study may most significantly impact policymakers. First and foremost, there is a concerning trend in the prevalence of AF in British Columbia; the prevalence of AF has grown up to 50% during the study period. The population of BC is shifting towards an older and more at-risk population; the number of seniors has grown significantly and based on the population pyramid, will continue to do so for the next decade. Additionally, according to the trends observed in incident AF patients, AF is being diagnosed at a younger age. As a result, the burden of AF on the healthcare system has grown drastically and will likely continue to grow. Policymakers should recognize the need for additional resources in order to manage the needs of this growing population. Novel therapeutics like DOACs may help to improve outcomes for patients and reduce the burden on testing, but at a significant increase in pharmaceutical costs. Further research is imperative to inform policymakers as to the cost-benefits of these novel therapeutics in the British Columbia healthcare system.

4.5 Conclusion

The burden of AF in BC is growing as the provincial demographics shift towards an older and more at-risk population. As a result, the characteristics of the incident AF population are changing and present a dynamic landscape for physicians and patients to navigate. Alongside the evolving AF population, the armamentarium has expanded for stroke prophylaxis in AF. Novel pharmaceuticals are being rapidly adopted and the outcomes associated are preferable to traditional pharmaceuticals. The epidemiology, clinical characteristics, treatment, and outcomes of AF may differ by age and sex.

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Appendix

Table 24 - Crude and Age/Sex Standardized Incidence and Prevalence Rates by Sex and Age Group (per 100,000)

Year	Sex	Age Group	Crude Incidence	Std. Incidence	95% CI	Crude Prevalence	Std. Prevalence	95% CI
2008	**F**	**< 65**	75.58	81.26	(76.3, 86.2)	345.50	371.36	(360.8, 382.0)
	F	**65-74**	686.69	679.19	(640.1, 718.2)	3409.86	3363.24	(3276.5, 3450.0)
	F	**≥ 75**	2085.25	2136.97	(2066.1, 2207.8)	10983.93	11201.57	(11039.7, 11363.4)
	M	**< 65**	141.52	150.33	(143.6, 157.1)	715.63	760.73	(745.6, 775.9)
	M	**65-74**	1114.42	1104.16	(1053.2, 1155.1)	5822.05	5766.84	(5650.5, 5883.2)
	M	**≥ 75**	2518.08	2581.48	(2490.3, 2672.6)	13386.69	13700.10	(13490.3, 13909.9)
2009	**F**	**< 65**	75.74	80.26	(75.4, 85.1)	382.39	405.99	(395.1, 416.9)
	F	**65-74**	707.28	699.93	(661.1, 738.8)	3595.94	3558.82	(3471.2, 3646.5)
	F	**≥ 75**	2088.15	2114.30	(2044.9, 2183.8)	11811.14	11991.18	(11825.5, 12156.8)
	M	**< 65**	143.34	149.90	(143.3, 156.5)	774.60	812.31	(796.9, 827.7)
	M	**65-74**	1079.46	1073.72	(1024.4, 1123.0)	6162.49	6123.27	(6005.6, 6240.9)
	M	**≥ 75**	2521.47	2582.49	(2492.6, 2672.4)	14310.76	14605.96	(14392.7, 14819.2)
2010	**F**	**< 65**	86.76	90.70	(85.6, 95.8)	428.53	448.68	(437.4, 460.0)
	F	**65-74**	757.02	751.06	(711.4, 790.7)	3817.97	3784.60	(3695.7, 3873.5)
	F	**≥ 75**	2145.43	2164.55	(2095.2, 2233.9)	12657.97	12773.05	(12604.6, 12941.6)
	M	**< 65**	155.07	160.12	(153.4, 166.8)	848.74	875.77	(860.0, 891.5)
	M	**65-74**	1138.68	1132.74	(1083.0, 1182.5)	6599.20	6567.68	(6447.9, 6687.4)
	M	**≥ 75**	2623.43	2669.11	(2579.6, 2758.7)	15436.79	15715.69	(15498.4, 15933.0)
2011	**F**	**< 65**	90.70	93.76	(88.6, 98.9)	457.83	473.03	(461.5, 484.5)
	F	**65-74**	792.58	784.35	(744.7, 824.0)	3939.70	3901.50	(3813.0, 3990.1)
	F	**≥ 75**	2180.16	2192.45	(2123.5, 2261.4)	13194.72	13249.97	(13080.7, 13419.2)
	M	**< 65**	160.59	163.02	(156.3, 169.7)	907.81	921.23	(905.3, 937.2)
	M	**65-74**	1154.11	1150.42	(1101.3, 1199.6)	6796.44	6773.22	(6654.0, 6892.4)
	M	**≥ 75**	2644.83	2684.34	(2596.2, 2772.5)	16164.33	16396.52	(16178.7, 16614.4)
2012	**F**	**< 65**	93.65	96.25	(91.1, 101.4)	484.61	498.25	(486.5, 510.0)
	F	**65-74**	780.96	778.83	(740.3, 817.3)	4115.32	4102.72	(4014.4, 4191.1)
	F	**≥ 75**	2159.22	2162.84	(2095.4, 2230.3)	13733.79	13754.14	(13584.0, 13924.3)

	M	**< 65**	168.44	170.55	(163.7, 177.4)	959.31	970.56	(954.3, 986.8)
	M	**65-74**	1135.88	1136.40	(1089.0, 1183.8)	6984.04	6987.23	(6869.7, 7104.8)
	M	**≥ 75**	2556.01	2584.40	(2499.5, 2669.3)	16799.80	16972.75	(16755.2, 17190.3)
2013	**F**	**< 65**	95.39	97.30	(92.2, 102.4)	511.41	521.76	(509.9, 533.7)
	F	**65-74**	709.56	708.78	(673.1, 744.5)	4224.55	4219.52	(4132.4, 4306.6)
	F	**≥ 75**	2009.81	2014.07	(1949.8, 2078.4)	14176.19	14181.04	(14010.6, 14351.5)
	M	**< 65**	173.80	175.16	(168.3, 182.0)	1022.47	1030.32	(1013.6, 1047.0)
	M	**65-74**	1132.68	1133.86	(1087.9, 1179.8)	7255.65	7265.17	(7148.8, 7381.5)
	M	**≥ 75**	2517.99	2535.67	(2453.2, 2618.1)	17502.08	17619.81	(17402.5, 17837.1)
2014	**F**	**< 65**	102.56	103.79	(98.5, 109.1)	550.38	557.64	(545.4, 569.9)
	F	**65-74**	717.95	717.13	(682.1, 752.1)	4352.60	4347.03	(4260.9, 4433.2)
	F	**≥ 75**	2026.49	2027.34	(1963.7, 2090.9)	14673.64	14660.56	(14489.7, 14831.5)
	M	**< 65**	170.97	171.77	(165.0, 178.5)	1071.12	1077.35	(1060.4, 1094.3)
	M	**65-74**	1115.26	1115.90	(1071.5, 1160.3)	7527.45	7532.20	(7416.9, 7647.5)
	M	**≥ 75**	2468.46	2478.32	(2398.4, 2558.2)	18186.55	18259.85	(18043.0, 18476.7)
2015	**F**	**< 65**	106.37	106.95	(101.6, 112.3)	592.73	595.84	(583.3, 608.4)
	F	**65-74**	703.06	703.13	(669.3, 737.0)	4533.44	4534.07	(4448.2, 4620.0)
	F	**≥ 75**	1997.51	1996.20	(1934.0, 2058.4)	15104.77	15087.98	(14917.0, 15259.0)
	M	**< 65**	185.42	185.61	(178.6, 192.6)	1139.82	1141.17	(1123.8, 1158.6)
	M	**65-74**	1164.61	1165.58	(1121.3, 1209.9)	7946.59	7955.46	(7839.7, 8071.2)
	M	**≥ 75**	2350.80	2355.63	(2279.2, 2432.0)	18848.23	18886.07	(18669.7, 19102.4)
2016	**F**	**< 65**	114.81	114.81	(109.4, 120.3)	637.96	637.96	(625.1, 650.8)
	F	**65-74**	705.01	705.01	(671.8, 738.2)	4700.90	4700.90	(4615.2, 4786.6)
	F	**≥ 75**	1924.73	1924.73	(1864.6, 1984.9)	15423.82	15423.82	(15253.5, 15594.1)
	M	**< 65**	183.02	183.02	(176.1, 190.0)	1204.92	1204.92	(1187.1, 1222.7)
	M	**65-74**	1094.74	1094.74	(1052.8, 1136.7)	8224.40	8224.40	(8109.3, 8339.5)
	M	**≥ 75**	2291.66	2291.66	(2217.7, 2365.6)	19485.93	19485.93	(19270.4, 19701.5)