8-28-2020 1:00 PM

Cost-effectiveness Analysis of Pharmacogenomics (PGx) based Warfarin, Apixaban and Rivaroxaban compared to Standard Warfarin for Atrial Fibrillation Patients in Canada

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics

Abstract

This study assessed cost-effectiveness of pharmacogenomics (PGx)-based warfarin, apixaban and rivaroxaban compared to standard warfarin therapy for atrial fibrillation (AF) patients in Canada. A decision-analytic Markov model was developed to compare lifetime costs and quality-adjusted life years (QALYs) from the public healthcare payer perspective. The parameters applied in the model were derived from published literature and some costs from the ICES databases. The results were summarized in terms of the incremental cost-effectiveness ratio (ICER). Compared to standard warfarin, PGx-based warfarin care had an ICER of 17,727/QALY and apixaban had an ICER of $64,853/QALY gained. Apixaban dominated rivaroxaban. The probabilistic sensitivity analysis showed that apixaban, rivaroxaban, PGx-based warfarin and standard warfarin were cost-effective at some willingness-to-pay (WTP) thresholds. Specifically, PGx-based warfarin therapy had a higher probability of being cost-effective than apixaban (51.5% vs 14.1%) at a WTP threshold of $50,000/QALY. At a WTP threshold of $150,000/QALY, apixaban had the highest probability of being cost-effective than PGx-based warfarin (70.1% vs 5.7%). We found that apixaban offers the best balance between efficacy and safety and has a high probability of being cost-effective for AF patients in Canada at a WTP threshold of $150,000/QALY.

Keywords

Anticoagulants, atrial fibrillation, warfarin, apixaban, rivaroxaban, pharmacogenomic, genotype-guided, cost-effectiveness, Ontario, Canada

Summary for Lay Audience

Atrial fibrillation (AF) is a condition defined by the presence of irregular rapid heartbeats. Patients with AF have been commonly treated by a blood thinner (anticoagulant) called warfarin to reduce the risk of stroke. However, rigorous monitoring of the blood thinning effect is required to avoid adverse events such as stroke and/or bleeding from inappropriate warfarin dosing. The trial and error approach of current clinical practice for warfarin dosing involves routine blood tests and poses an increased risk of adverse events during the initial dose adjustment period. Warfarin-related adverse events entail a substantial burden on patients' health and the healthcare system. In comparison, pharmacogenomic-based (PGx) warfarin therapy adjusts the drug dose according to the inherent genetic differences of AF patients and has been shown to reduce risk of adverse events. A new class of drugs for AF therapy are called direct oral anticoagulants (DOACs), and offer several advantages over warfarin. For example, apixaban and rivaroxaban are now funded by the Ontario Ministry of Health and long-term care (MOHLTC). DOACs have a predictable pharmacokinetic and dose response, do not require continuous monitoring, have increased effectiveness in reducing the risk of stroke and embolism and are associated with decreased risk of bleeding. However, PGx-based warfarin entails an upfront cost for genetic testing, while the medication cost for DOACs is more than twice than that of warfarin. This cost-effectiveness analysis compares the lifetime costs and benefits incurred under each treatment strategy from the MOHLTC perspective. We found that PGx-based warfarin care as well as apixaban and rivaroxaban improved the health of AF patients by reducing the risk of ischemic strokes and intracranial bleeding as compared to standard warfarin, yet these alternative treatments also increased lifetime costs when compared to standard warfarin. PGx-based warfarin led to a small increase in QALYs and large increase in costs. Among the DOACs, apixaban treatment resulted in the highest health benefit and dominated rivaroxaban. The results of this study were sensitive to treatment effectiveness and should be interpreted with caution.

Co-Authorship Statement

This work was compiled with collaborative efforts of a team. Briefly, Nivi Jeyakumar and Eric McArthur contributed to the dataset creation plan and data extraction from the ICES databases, respectively. Aneeka Hafeez was the principal contributor in designing the decision-analytic model framework, implementing research, analyzing results and drafting the manuscript. Dr. Sisira Sarma, Dr. Ute Schwarz and Dr. Lauren Cipriano provided valuable consultation, input and constructive feedback throughout research implementation and writing of the manuscript. Dr. Greg Zaric, Dr. George Dresser and Dr. Yun-Hee Choi provided valuable feedback and guidance in the development and execution of the research project.

Acknowledgments

I would like to acknowledge and show my gratitude to my research supervisors, Dr. Sisira Sarma and Dr. Ute Schwarz in guiding me through the study design and thesis writing process. With their constructive feedback and support, I learned to think critically and aim for producing high quality research. Under their mentorship, I also learned to integrate multidisciplinary point of views to produce knowledge translational deliverables.

I would also like to show my sincere gratitude to Dr. Lauren Cipriano, Dr. George Dresser and Dr. Ava John-Baptiste for their comments and suggestions that helped to improve modelling, choice of input parameters and produce this high-quality research.

I would also like to thank my supervisory committee members, Dr. Greg Zaric and Dr. Yun-Hee Choi, for their expert advice and support. I would like to acknowledge Dr. Richard Kim for his clinical insight. I am also in gratitude to the support staff at TreeAge Software Inc. for their swift responses to my inquiries about modelling.

Finally, I would like to thank my family, especially my parents, and close friends for their continuous support, encouragement, sound advice and belief in me, which gave me the strength to continue in times of doubt and frustration.

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). This study also received funding from: The Canadian Institute of Health Research (CIHR), Ontario Ministry of Research and Innovation, London Health Sciences Centre (LHSC) and Western University via the Western Graduate Research Scholarship. Parts of this material are based on data and information compiled and provided by: MOHLTC, CIHI and IMS Brogan Inc. We thank IMS Brogan Inc. for use of their Drug Information Database. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

AF: Atrial fibrillation

ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation

BID: Twice daily

CEA: Cost-effectiveness analysis

CRNMB: Clinically relevant non-major bleeding

DOAC: Direct oral anticoagulants

ECH: Extracranial hemorrhage

ICER: Incremental cost-effectiveness ratio

ICH: Intracranial hemorrhage

INR: International normalized ratio

IS: Ischemic stroke

LHSC: London Health Sciences Center

LY: Life-years

MI: Myocardial infarction

MOHLTC: Ontario Ministry of Health and Long-Term Care

mRS: Modified Rankin Score

NHS: National Health Services

ODB: Ontario Drug Benefit

PGx: Pharmacogenomics

PT/INR: Prothrombin time/international normalized ratio

QALY: Quality-adjusted life-years

QD: Once daily

RCT: Randomized clinical trial

ROCKET-AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

SD: Standard deviation

SEE: Systemic embolism

SEK: Swedish krona

SNP: Single nucleotide polymorphism

TIA: Transient ischemic attack

THB: Thai baht

UK: United Kingdom

US: United States

WRAPID: Warfarin Regimen using A Pharmacogenetics-guided Initiation Dosing

WTP: Willingness-to-pay

Chapter 1 - Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias among seniors, affecting approximately 300,000 Canadians (1). In Canada, AF accounted for about 2.6% of all acute hospital admissions and about 5.6% of all hospitalizations from 2007-2008 (2). In Ontario, about 193 per 100,000 hospitalizations and about 231 per 100,000 emergency visits were directly attributed to atrial fibrillation (2). Patients with AF experience high morbidity and mortality because the arrhythmia increases the risk of stroke and death by 3-5-fold and more than 3.5-fold respectively, when compared to the general population (3). In addition, nearly 50% of AF-related stroke patients are discharged with severe disability (modified Rankin Score, mRS=3-5)[1] and left with complications ranging from needing assistance with daily activities of living to requiring 24/7 nursing and long-term care (4,5). With an aging population, the prevalence of AF is expected to increase. The lifetime risk of AF is 1 in 4 at the age of 40 and the incidence doubles with each decade of life in both males and females (6).

1.1 Pathophysiology of atrial fibrillation

Atrial fibrillation is a condition of the heart. The human heart is divided into four chambers: two atria and two ventricles. In a healthy heart, cardiovascular contractions are coordinated by neural pacemaker cells within the sinoatrial node such that the ventricles contract after the atria finish contracting. However, in the case of AF, dysfunctional pacemaker cells produce uncoordinated cardiovascular contractions such that an irregular, and often rapid, heartrate develops. The term used to describe this type of arrhythmia is tachycardia. Patients displaying such an arrhythmic activity of the atria suffer from atrial fibrillation.

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[1] The modified Rankin Score is a standardized instrument that measures the degree of disability, dependence in function and stroke severity at hospital discharge (4).

1.2 Atrial fibrillation burden on patients and the healthcare system

If untreated, AF is often accompanied by symptoms such as rapid heart rate, palpitations, chest discomfort, shortness of breath and chest pain (7). In addition, stroke is a complication of untreated AF. The irregular atrial contractions decrease the efficiency with which blood can be pumped out of the heart. Blood begins to pool in the atria, which increases the risk of blood clot or thrombus formation. This can lead to stroke (if the thrombus clogs a blood vessel leading to the brain), systemic embolism (if the thrombus clogs a systemic blood vessel), myocardial infarction (if the thrombus clogs a coronary artery) and even death.

AF also imposes a huge financial strain on Canadian hospitals. From 2007-2008, the cost of AF-related hospital care was about $815 million in Ontario (2). About $710 million can be attributed to acute hospital care, $32 million to same-day operations and $73 million to emergency department visits (2). On average, AF patients stayed in the hospital for 5.7 days, costing the Canadian healthcare system $8,148 (2010 CAD) per hospitalization. However, hospitalizations for whom AF was listed as a comorbidity were even more costly. The overall cost for AF-related complications was found to be about $558 million (2010 CAD), constituting 69% of the total hospital care expenses. As noted earlier, stroke is a serious complication of AF. In Ontario, AF-related ischemic stroke or transient ischemic attack had the longest average length of hospital stay (20.2 days) with an average cost of $19,113 (2010 CAD) per admission. Thus, AF and AF-related complications entail substantial costs to Canadian hospitals. The high AF-related hospitalization risks and costs can be averted through several existing therapeutic interventions, such as long-term anticoagulation therapy. However, different anticoagulation treatments vary in terms of clinical effectiveness and costs.

1.3 Atrial fibrillation management strategies

Several oral anticoagulation therapies are available to mitigate the risks of atrial fibrillation complications (8). The $CHADS_2$ score is a validated and frequently used prognostic model that incorporates patient age (>75 years) and comorbidities such as

history of hypertension, congestive heart failure, diabetes and stroke or TIA and estimates patients' risk of thromboembolism without anticoagulation therapy. In general, anticoagulation therapy is recommended for patients with a $CHADS_2$ score ≥1 (9). Oral anticoagulants prevent formation of blood clots by inhibiting blood clotting factors in the clotting cascade (8). Until recently, warfarin (commercially known as Coumadin) was commonly prescribed drug to manage AF. However, achieving the drug's therapeutic anticoagulation effect is challenging because warfarin's pharmacological response is highly variable in patients due to clinical and genetic factors. As such, two strategies emerged to improve the clinical utility of the standard warfarin therapy: pharmacogenomics (PGx)-based warfarin care and direct oral anticoagulants (DOACs). PGx-based warfarin care sought to optimize warfarin therapy through a patient-centered genotype-guided drug dosing method (10). DOACs, such as apixaban and rivaroxaban, were developed to achieve safer and more efficacious anticoagulation compared to standard warfarin therapy without a need for routine monitoring (11). The advantages and disadvantages of each treatment strategy are described in the following subsections.

1.3.1 Standard warfarin care

Until recently, warfarin, commercially known as Coumadin, was one of the most commonly prescribed drugs to manage AF (12). Warfarin acts by indirectly inhibiting the vitamin K-dependent clotting mechanism (13). Under normal circumstances, blood clots when an enzyme called vitamin K epoxide reductase (VKORC1) generates a pool of reduced vitamin K, which in turn activates clotting factors II, VII, IX and X. Warfarin prevents this generation of reduced vitamin K by inhibiting VKORC1, and thus, impairing the activation of vitamin K-dependent blood clotting factors. For patients with AF, decreased blood clotting capacity was shown to reduce the risk of stroke (8). However, warfarin's mechanism of action also increases the risk of adverse drug reactions such as hemorrhages, particularly with higher drug doses (8). On the other hand, drug doses that are too low may not be effective in reducing the risk of ischemic stroke among patients with AF (8).

Consequently, warfarin dose requirements among patients are highly variable. A narrow therapeutic range must be achieved using regular blood monitoring and guided by an

international normalized ratio (INR)[2] of 2 to 3 to ensure the correct dose for each patient (8). This is a tedious trial-and-error process.

Anticoagulation therapy with warfarin has been shown to significantly reduce the risk of stroke among patients with AF as compared to no anticoagulation or antiplatelet therapy (14). Due to the high efficacy, warfarin anticoagulation had been the gold standard for AF treatment for decades. A meta-analysis by Hart *et al.* (2007) reported that dose-adjusted warfarin therapy can be as much as 64% effective in reducing the risk of stroke for patients with AF as compared to no anticoagulation therapy (14). Dose-adjusted warfarin therapy is superior in reducing the risk of stroke compared to antiplatelet therapy with aspirin alone (Relative Risk Reduction (RRR) 37%, 95% confidence interval (CI) = 23%, 48%) and combination therapy of aspirin and clopidogrel (RRR, 40%, 95% CI=18%, 56%). Not only is warfarin therapy effective in reducing the risk of ischemic stroke, it is also inexpensive as a monthly supply of warfarin costs anywhere between $5 and $8 (2011 CAD) (15).

Although standard warfarin therapy is effective compared to no treatment, it has several caveats. The standard trial and error approach to determine the therapeutic warfarin dose for each patient is clinically challenging. It requires routine patient monitoring, including reiterative blood testing with subsequent dose adjustments to achieve the narrow therapeutic window of an INR ranging from 2 to 3 (8). Moreover, the effectiveness of warfarin therapy in observational studies has been found to be much lower; a therapeutic range (INR 2-3) in patients has been only observed 58% of the time. In addition, during the initial dose adjustment period, there is an increased risk of adverse events; subtherapeutic dosing can lead to stroke and supratherapeutic dosing can cause hemorrhage. According to a meta-analysis, standard warfarin therapy has been shown to significantly increase the risk of major hemorrhages and nearly double the risk of intracranial hemorrhages as compared to antiplatelet therapy (14). In fact, annual

[2] The international normalized ratio (INR) is a standardized score obtained from the prothrombin time/international normalized ratio (PT/INR) test. The PT/INR test measures the effectiveness of warfarin by assessing the time taken for blood to clot (9).

incidences of about 0.6% for fatal bleeding, 3.0% for major bleeding, and 9.6% for minor bleeding cases have been estimated among patients on warfarin (8). Thus, achieving the drug's therapeutic anticoagulation effect is challenging and associated with a high risk of severe adverse events under standard warfarin therapy.

Warfarin-related adverse events are not only life threatening but they are also costly to treat. In Ontario, AF-related hospitalizations due to bleeding are the costliest hospital admissions, with an average cost of $22,051 (2010 CAD) per admission (2). Moreover, the need for routine INR monitoring with standard warfarin care incurs a substantial financial burden; about one third of direct medical costs incurred by AF patients can be attributed to anticoagulation management (16).

1.3.2 Pharmacogenomics (PGx) based warfarin care

The observed wide interpatient variability in warfarin dose requirements has been reported to depend on several demographic, clinical and pharmacogenetic factors. Specifically, about 30% of this variability can be attributed to single nucleotide polymorphisms (SNPs) in three pharmacogenes encoding the following enzymes involved in warfarin metabolism and response: (i) cytochrome P450 (CYP) 2C9 involved in S-warfarin metabolism (gene *CYP2C9*), (ii) vitamin K epoxide reductase (gene *VKORC1*), the pharmacological target, and (iii) *CYP4F2* (gene *CYP4F2*) involved in vitamin K metabolism (17). Common SNPs in *CYP2C9* cause impaired metabolism and thus reduced drug clearance leading to increased drug levels in blood. Common SNPs in *VKORC1* lead to increased sensitivity to the anticoagulation effect of warfarin. As such, a SNP in one or more of these pharmacogenes often results in lower dose requirement and higher risk of over-anticoagulation. In fact, the administration of a standard warfarin dose can result in severe bleeding complications in patients that are carriers of such SNPs in these pharmacogenes because of reduced drug clearance and/or increased warfarin sensitivity. Moreover, the prevalence of these SNPs can be high in certain populations. For example, about 41% of Caucasians are carriers of *CYP2C9* polymorphism, and thus, require a lower than standard warfarin dosage to reach the drug's therapeutic effect (18). Similarly, about 37% of Caucasians and 14% of Africans carry a SNP of the *VKORC1* gene, and thus, require a lower than standard warfarin dose to reach therapeutic INR.

Moreover, the frequency of the *CYP4F2* allele is about 30% among Caucasians and Asians, compared to 7% in African Americans. As such, the US Food and Drug Administration has revised warfarin dose recommendations to incorporate patient genotype information (17). The incorporation of patient genotype information during the initial warfarin dosing period has the potential to optimize warfarin use, to reduce risks of life-threatening adverse events and to decrease the financial burden of warfarin-related hospitalizations.

Pharmacogenomics (PGx) based warfarin therapy tailors the drug dose for each patient using his/her genotypic information in conjunction with demographic and clinical characteristics. Several genotype-guided warfarin dosing algorithms have been developed. An algorithm developed by Gage *et al*. (2008) has been widely used for warfarin dosing (19). This algorithm uses information on the *CYP2C9* and *VKORC1* genes, age, body surface area, amiodarone use, target INR, race and smoking status to determine warfarin dose for each patient. In 2009, the International Warfarin Pharmacogenetics Consortium reported another warfarin dosing algorithm (20). It was based on a diverse population and explained about 47% of the interpatient warfarin dose variation through genetic, clinical and demographic factors such as *CYP2C9*, *VKORC1*, age, height, weight, amiodarone use, race and number of CYP enzyme inducers (20). In addition, modified versions of these two and other dosing algorithms have been applied in different clinical settings to successfully predict the correct warfarin dose for patients before initiating treatment. For example, a prospective cohort study of outpatients conducted at the London Health Sciences Center (LHSC) and the Ottawa Hospital developed a novel pharmacogenetics-based treatment initiation protocol known as WRAPID (Warfarin Regimen using A Pharmacogenetics-guided Initiation Dosing) that predicts loading and maintenance doses based on genetics, clinical variables and patient response during the first 9 days of initiating warfarin therapy. The model aimed to provide a uniform response among all patients (21,22).

PGx-based warfarin care offers several benefits over standard warfarin care. PGx-based warfarin dosing has increased the efficiency with which the therapeutic anticoagulation effect is achieved among patients. Recent meta-analyses show that patients under PGx-

based care reach the first stable therapeutic dose 5 days earlier and the maintenance dose by about 10 days earlier compared to patients on standard warfarin therapy (23,24). Moreover, PGx-based warfarin dosing has been shown to decrease the risk of adverse events and associated hospitalizations during the initial dose adjustment period. In recent meta-analyses, the risk of major hemorrhage has been significantly reduced by 30-60% for patients who received PGx-based warfarin dosing as compared to patients who received standard warfarin dosing (23,24). No significant reduction in the risk of thromboembolism and all-cause mortality has been demonstrated by PGx-based warfarin dosing when compared to standard warfarin dosing (23,24). However, a prospective study that compared 896 patients receiving genotype-guided warfarin dosing with a matched historical control of 2688 patients in the US found that PGx-based warfarin care reduced all-cause hospitalizations by 31% and bleeding or thromboembolism-related hospitalizations by 28% when compared to standard warfarin care (25).

The increased safety associated with PGx-based warfarin dosing may translate into reduced financial burden posed by warfarin-related hemorrhagic hospitalizations. However, PGx-based warfarin care also entails an upfront cost of the genotyping test. In published cost-effectiveness analyses (CEAs), a genotyping test has been estimated to cost anywhere between $500 and $800 USD per patient in the US and Canada (studies range from 2009-2014) (10). In contrast, a more recent European CEA by Verhoef *et al*. (2016) reported a point-of-care genotyping test costing (in 2014 cost year) £35.03 (~$70 2017 CAD) or 440 SEK (~$68 2017 CAD) in the UK and Sweden, as estimated from the EU-PACT trial (26). At these genotyping test costs, PGx-based warfarin care was cost-effective compared to standard warfarin care in the UK, Sweden and some US studies. In contrast, Nshimyumukiza *et al*. (2013) found PGx-based warfarin care was not cost-effective compared to standard warfarin care at a genotyping test cost of $615 (2010 CAD) per patient in Canada (27). The per patient cost of a genotyping test for four SNPs in *CYP2C9* (rs1799853, rs1057910) *VKORC1* (rs9923231) and *CYP4F2* (rs2108622), was estimated to be less than $100 (2017 CAD) at the Personalized Medicine Clinic at LHSC in Ontario, Canada (unpublished data). Thus, in Canada, it is important to assess if the upfront cost of genotyping test outweighs the differences in lifetime costs between PGx-based and standard warfarin care.

1.3.3 Direct Oral Anticoagulants (DOACs): Apixaban and Rivaroxaban

Given the challenges associated with warfarin therapy, a new class of drugs called DOACs have been recently developed, including dabigatran, rivaroxaban and apixaban. Here we will focus on the two most frequently prescribed DOACs in Canada: rivaroxaban and apixaban (28). Rivaroxaban was approved for funding by the Ontario Ministry of Health and Long-Term Care (MOHLTC) for stroke prophylaxis among AF patients in July 2012, followed by apixaban in August 2013 (28). Apixaban and rivaroxaban offer several advantages over warfarin and exert their anticoagulation activity through direct inhibition of blood clotting factor Xa (11). In doing so, they prevent the conversion of prothrombin to thrombin and reversibly cease the coagulation cascade. As such, the DOACs have a more predictable therapeutic effect based on plasma concentrations, require no routine INR monitoring, and demonstrate lower potential for adverse events compared to warfarin. Consequently, DOACs offer several benefits over warfarin in terms of clinical utility.

In large clinical trials, the DOACs have demonstrated greater or similar efficacy in stroke prevention, and reduction in the risk of hemorrhagic events when compared to warfarin. In the ARISTOTLE trial (n=18,201), apixaban reduced the risk of stroke and systemic embolism by 21%, the risk of bleeding by 31%, and mortality by 11% when compared to warfarin (11). Similarly, rivaroxaban has been shown to be non-inferior to warfarin and reduced the risk of a composite outcome of stroke or systemic embolism in AF patients by 12% in the ROCKET-AF trial (n=14,264) (11). Moreover, patients on DOACs have lower drug discontinuation rates due to adverse events as compared to warfarin. In summary, DOACs have been associated with a lower risk of adverse events in large clinical trials, and hence, serve as a safer alternative to standard warfarin care.

The unit cost of DOACs is more than 20 times the cost of warfarin (29). In 2012, the Ontario Drug Benefit (ODB) formulary covered DOAC treatments for seniors (65+ years old) diagnosed with AF (28,30). Consequently, MOHLTC incurs a significantly higher drug cost from the administration of DOACs to seniors with AF. Therefore, it is important to carefully assess the cost-effectiveness of anticoagulation therapy with

DOACs such as apixaban and rivaroxaban when compared to warfarin therapy in Canada.

1.4 Rationale

Standard warfarin care has several drawbacks and poses a substantial burden on patient health and the Canadian healthcare system. At present, there are several alternatives to standard warfarin care. First, PGx-based warfarin dosing has been shown to be a safer alternative to conventional warfarin dosing by reducing the risk of hemorrhages (31). However, there remains considerable heterogeneity in the cost-effectiveness of PGx-based warfarin care as compared to standard warfarin care in the published literature. This heterogeneity, in part, depends on the institutional environment within which the CEA was conducted because of differences in cost of drugs and genotyping tests (10). With current advances in technology, genotyping test costs have significantly decreased compared to those estimated in published literature. As a result, there is a need to conduct an updated CEA of PGx-based warfarin care using the latest Canadian cost data. Another alternative is treatment with apixaban and rivaroxaban, a new class of drugs called DOACs. There is a consensus that DOACs entail improved clinical effectiveness and safety for AF patients as compared to standard warfarin care (11). However, the unit drug cost of DOACs is more than 20 times the unit drug cost of warfarin (29). The ODB formulary covered rivaroxaban and apixaban in 2012 for seniors (aged 65+) with AF in Ontario requiring anticoagulation therapy (28). Thus, there is a need to conduct a CEA of apixaban and rivaroxaban to understand whether the clinical advantages of DOACs justify their higher drug costs in the Canadian health care setting.

1.5 Research Question

The purpose of this study is to conduct a CEA of pharmacogenomics (PGx) based warfarin, apixaban and rivaroxaban care as compared to standard warfarin therapy among newly diagnosed atrial fibrillation (AF) patients aged 65 years and older. The CEA will estimate the incremental cost-effectiveness ratio (ICER) values of the three proposed alternative treatments as compared to standard warfarin therapy using Canadian costs, adverse event rates from the most recent clinical literature and meta-analyses and health

utilities to understand the cost-effectiveness of anticoagulation strategies for AF patients in Canada.

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Chapter 2

Literature review of cost-effectiveness analyses

Several cost-effectiveness analyses (CEAs) that compare standard warfarin therapy, pharmacogenomics (PGx) based warfarin therapy, apixaban and rivaroxaban have been conducted. Herein, a literature review of the relevant published CEAs is presented.

2.1 Cost-effectiveness analyses of PGx-based warfarin care with standard warfarin care

To date, published CEAs of PGx-based warfarin therapy as compared to standard warfarin therapy have produced conflicting results. In a recent systematic review of 12 CEA and cost-saving studies, three studies found PGx-guided warfarin therapy to be cost-effective, four were inconclusive, and five found that PGx-based warfarin therapy was not cost-effective at the country-specific willingness-to-pay (WTP) thresholds (1). More specifically, PGx-based warfarin therapy has been favoured over standard warfarin care in United Kingdom (UK) and Sweden (2). In Canada and the US, the clinical utility of PGx-based warfarin dosing was found to be very small and costs were higher when compared to standard warfarin dosing (3,4). Consequently, there is considerable variability in the cost-effectiveness of PGx-based warfarin therapy; the results seem to vary by country and the institutional environment. Key CEA studies comparing the cost-effectiveness of PGx-based warfarin care with standard care are described and gaps in the published literature are presented below.

Nshimyumukiza *et al*. (2013) investigated the cost-effectiveness of PGx-guided warfarin management and standard warfarin management for the prevention of stroke and systemic thromboembolism from the Quebec healthcare system perspective (3). This study compared direct medical care costs and quality-adjusted life-years (QALYs) incurred by a cohort of newly diagnosed atrial fibrillation (AF) patients aged 64 years and older with no previous history of stroke over the 5-year time horizon. The Markov model used INR specific risks of major hemorrhage (classified as intracranial and gastrointestinal hemorrhages) and major thromboembolism (a composite outcome of stroke, myocardial infarction, deep vein thrombosis and pulmonary embolism) using data

derived from a US-based randomized clinical trial (RCT) (3). Nshimyumukiza *et al*. (2013) found that genotype-guided warfarin management increased QALYs by 0.0085 units and costs by $460 (2010 CAD) as compared to standard warfarin therapy. This resulted in an incremental cost-effectiveness ratio (ICER) of ~$55,000/QALY, which was slightly above the willingness-to-pay (WTP) threshold of $50,000/QALY gained the authors had assumed in the study.[3] The base case results were robust to deterministic and probabilistic sensitivity analysis. According to the probability sensitivity analysis, there was ~10% chance of PGx-based warfarin care being cost-effective at the WTP threshold of $50,000/QALY.

Similarly, Patrick *et al*. (2009) found that PGx-based warfarin management was not cost-effective as compared to standard warfarin management from a US societal perspective (4). The CEA compared costs and QALYs incurred by a cohort of 70-year old newly diagnosed AF patients over the lifetime horizon. The Markov model used INR-specific risks of major hemorrhage (intracranial and extracranial) and ischemic stroke. The study concluded that genotyping could be cost-effective under an assumed WTP of $50,000/QALY if the time in therapeutic INR range was increased by more than 8.5%. Finally, the probabilistic sensitivity analysis showed that genotype-guided warfarin therapy was cost-effective ~42% of the time under this WTP threshold.

Although both Nshimyumukiza *et al*. (2013) and Patrick *et al*. (2009) found that PGx-based warfarin therapy was not cost-effective as compared to standard warfarin care in Canada and the US, respectively, there are several limitations concerning study conclusions. Firstly, Nshimyumukiza *et al*. (2013) and Patrick *et al*. (2009) modelled major hemorrhage events (further classified as intracranial and extracranial hemorrhages), but the authors excluded clinically relevant non-major (CRNM) bleeding events. In fact, there has been little attempt to capture differences in costs and risks of CRNMB events in much of the published CEAs to date. However, there is evidence that

[3] A willingness-to-pay (WTP) is an estimate of how much a decision maker is willing to pay to obtain a unit of health benefit (3).

PGx-based warfarin dosing reduces the risk of CRNMB events as compared to standard warfarin dosing (5). Moreover, CRNMB events are more common among warfarin users than initially understood; they increase short-term costs and decrease patients' quality of life (6). As such, existing CEAs do not capture the health benefit and cost differences between PGx-based and standard warfarin care.

Secondly, by modelling the distribution of INR ranges and INR-specific risks using a single clinical trial population, generalizability of the results was limited. For example, Nshimyumukiza *et al*. (2013) modelled the INR range distributions found in a cohort of 206 AF patients in the US because the INR data were not available on a Canadian population cohort (3). This approach is a limitation because data obtained from one RCT on a small sample size is less generalizable than evidence obtained from a systematic review and meta-analysis. The allele frequencies of variants determining warfarin dose requirement vary in different populations (7). As such, the use of evidence from a single RCT introduces a certain degree of uncertainty into the generalizability of the conclusions.

Finally, modelling INR-specific risks of adverse events applies an intermediate marker for hard endpoints such as major hemorrhages. There is evidence that improved time in therapeutic INR translates into decreased incidences of adverse events. However, not every INR above (supratherapeutic) or below (subtherapeutic) the therapeutic range of 2 to 3 will result in an adverse event. Moreover, health states must be mutually exclusive, but the transient nature of changing INR values applies strong assumptions among existing models. As such, there is a gap in published CEAs on evaluating the cost-effectiveness of PGx-based warfarin by modelling clinically relevant and hard outcomes.

Importantly, the cost-effectiveness of PGx-based warfarin therapy varies by country. For example, Patrick *et al*. (2009) and Nshimyumukiza *et al*. (2013) did not find PGx-based warfarin care to be cost-effective in the US and Canada. In contrast, Verhoef *et al*. (2016) found that PGx-based warfarin care was cost-effective as compared to standard warfarin care in the context of UK and Sweden (2). Verhoef *et al*. (2016) compared direct medical care costs and QALYs incurred by a cohort of AF patients aged on average 70.9 years in

the UK and 72.5 years in Sweden, from the healthcare payer perspective over the lifetime horizon. The Markov model modelled INR-specific risks of intracranial hemorrhage, extracranial hemorrhage, ischemic stroke and transient ischemic attacks (TIA) using the European Pharmacogenetics of Anticoagulant (EU-PACT) trial. The base case results showed that the lifetime costs (in 2014 cost year) increased by £26 in the UK and by 382 Swedish krona (SEK) in Sweden under PGx-guided warfarin care. The incremental QALYs were 0.0039 in the UK and 0.0015 in Sweden under PGx-guided warfarin. This resulted in an ICER of £6,702/QALY gained in the UK and 253,848 SEK/QALY gained in Sweden. Both ICER values were under the WTP of £20,000/QALY in the UK and 500,000 SEK/QALY in Sweden. The probabilistic sensitivity analysis showed that the PGx-guided warfarin therapy was cost-effective 93% of the times in the UK and 67% of the times in Sweden at these WTP thresholds. Verhoef *et al*. (2016) concluded that pharmacogenetic-guided dosing of warfarin is a cost-effective strategy as compared to standard warfarin dosing for AF patients in the UK and Sweden.

The observed heterogeneity among published CEAs by country indicate that region-specific cost parameters should be incorporated in future CEA studies. To date, Nshimyumukiza *et al*. (2013) is the only CEA study that compared PGx-based and standard warfarin care in the context of Canada (3). In this study, the authors obtained event-specific and ongoing unit costs from the Quebec health administrative data and the published literature. The unit costs were multiplied by the estimated healthcare resource use to estimate costs of genotype test, hemorrhagic and thromboembolic events and follow-up costs for long-term sequalae of adverse events. Although this costing methodology is sound in nature and the assumptions for estimated healthcare resource use are justifiable, there is a gap in the published literature to model costs pertaining to real-life consumption of healthcare resources in Canada.

In another CEA, Chong *et al*. (2014) assessed the cost-effectiveness of pharmacogenetic-guided warfarin for a hypothetical cohort of 45 years and older patients initiating warfarin therapy in Thailand (8). The CEA was conducted from both societal and health care system perspective over the lifetime horizon. The CEA constructed a two-part model; first, the patients were stratified by *CYP2C9* and *VKORC1* variants in a decision

tree; then, patients transitioned through a Markov model illustrating the consequences of two predominant warfarin-related adverse events (major bleeding and thromboembolism). The base case results showed that the incremental cost was 2,959 Thai baht (2013 costing year) and 2,953 THB from the healthcare system and societal perspective, respectively. PGx-based care increased QALYs by 0.002 units under both healthcare system and societal perspective. This resulted in ICERs of 1,477,042 THB per QALY gained and 1,473,851 THB per QALY gained under healthcare system and societal perspective, respectively. Both ICERs were above the WTP of 160,000 THB and the probabilistic sensitivity analysis showed that PGx-based care was cost-effective 41-42% of the time. Moreover, deterministic sensitivity analysis showed that results were most sensitive to the risk ratio (RR) of major bleeding among the VKORC1 variants. As such, the authors concluded that PGx-guided warfarin was unlikely to be cost-effective in Thailand.

Patrick *et al*. (2009), Nshimyumukiza *et al*. (2013) and Verhoef *et al*. (2016) modelled INR-specific risks of adverse events, while Chong *et al*. (2014) modelled allele frequencies of warfarin pharmacogenes and variant-specific risks of adverse events for the Thai population. Both methodologies have made assumptions by connecting intermediate outcomes such as INR ranges or allele frequencies with clinical outcomes such as major hemorrhage and ischemic stroke.

In summary, PGx-based warfarin therapy has been shown to be cost-effective in the UK and Sweden. In contrast, PGx-based warfarin care was not found to be cost-effective in Canada, US and Thailand. Thus, there is potential for further CEA research using data on adverse events and updated Canadian costs.

2.2 Cost-effectiveness analyses of apixaban and rivaroxaban

To date, several cost-effectiveness analyses comparing the direct oral anticoagulants (DOACs), such as apixaban and rivaroxaban, with standard warfarin care have been conducted. In general, studies conducted in the context of Canada, US, France and UK have found the DOACs to be cost-effective as compared to standard warfarin therapy. In

most of these studies, apixaban has been the recommended anticoagulation strategy in terms of cost-effectiveness. Moreover, rivaroxaban is usually ruled out by apixaban through the principle of strong dominance or extended dominance. In contrast, these DOACs were not cost-effective as compared to standard warfarin care in the context of Germany, Thailand and China. Key CEA studies on the cost-effectiveness of apixaban and rivaroxaban are described below and potential gaps in the published literature will be mentioned (see Table 2.2.1 for additional details).

To date, Coyle *et al*. (2013) is the only Canadian study that assessed the cost-effectiveness of DOACs, including apixaban, rivaroxaban and dabigatran, as compared to standard warfarin care in preventing stroke and other cardiovascular events (9). This CEA compared direct medical costs and QALYs incurred by a cohort of 72-year-old Canadians on average with nonvalvular AF from the Ministry of Health perspective over the lifetime horizon. The Markov model captured health states such as ischemic stroke, major hemorrhage, intracranial hemorrhage, minor bleeding, transient ischemic attack, myocardial infarction and pulmonary embolism. As compared to warfarin, apixaban, rivaroxaban and dabigatran (150 mg) increased costs by $3,346, $3,396 and $2,866 (2011 CAD) and QALYs by 0.137, 0.061 and 0.137, respectively. This resulted in estimated ICERs of $24,312/QALY, $55,757/QALY and $20,797/QALY gained for apixaban, rivaroxaban and dabigatran (150 mg), respectively. Thus, dabigatran (150 mg) dominated apixaban and rivaroxaban. However, as compared to warfarin alone, apixaban was found to be cost-effective and the ICER for rivaroxaban was slightly above the WTP of $50,000/QALY. The deterministic sensitivity analysis showed that estimated ICERs were sensitive to drug costs, time horizon and treatment discontinuation rates. Moreover, the probabilistic sensitivity analysis showed that apixaban, rivaroxaban and dabigatran were cost-effective in 44.1%, 2.1% and 50.8% of the simulations, respectively, at the $50,000/QALY WTP threshold. Coyle *et al*. (2013) concluded that dabigatran was the optimal anticoagulation treatment strategy but also showed that apixaban was cost-effective for AF patients in Canada.

At the time of the Coyle *et al*. (2013) study, the DOAC drug costs were not available from the Canadian public healthcare perspective. Thus, the US drug costs were applied to

the model and the drug cost for apixaban was assumed to be the same as dabigatran. Currently, all the DOACs are included in the Ontario Drug Benefit (ODB) formulary and the drug costs for DOACs are available from the Canadian public healthcare perspective. In 2012, dabigatran was the first DOAC to be covered by the ODB formulary, followed by apixaban and rivaroxaban shortly after (10). The inclusion of DOACs under the ODB formulary led to rapid changes in the physician prescribing behaviour. When dabigatran was first included in the formulary, there was a rapid increase in the total percent of dabigatran prescriptions among all oral anticoagulant prescriptions for AF patients. However, when rivaroxaban and apixaban were included in the formulary, there was a simultaneous decrease in the percent of dabigatran prescriptions and increase in the percent of apixaban and rivaroxaban prescriptions. A closer look at the clinical effectiveness of dabigatran revealed that the drug fared worse in terms of drug safety as compared to warfarin (11). Specifically, there has been a significant increase in the risk of gastrointestinal bleeding associated with high-dose dabigatran use as compared to warfarin, and a non-significant increase in the risk of myocardial infarction. Moreover, dyspepsia (indigestion) is a common adverse event exclusive to dabigatran use. Interestingly, physicians seemed to prefer prescribing apixaban and rivaroxaban over dabigatran for AF patients in Ontario (10). This directly contradicts the results of Coyle *et al*. (2013) who found that dabigatran was economically the optimal anticoagulation strategy in Canada. Thus, an updated cost-effectiveness evaluation of apixaban and rivaroxaban as compared to standard warfarin care is necessary from a Canadian healthcare payer perspective.

A more recent study by López-López *et al*. (2017) assessed the cost-effectiveness of oral anticoagulants, including apixaban, rivaroxaban and dabigatran, for the prevention of stroke in the UK (12). The CEA compared direct medical care costs and QALYs incurred by a cohort of 70-year old AF patients from the perspective of UK National Health Services (NHS) over the lifetime horizon. The Markov model simulated patients through health outcomes such as all ischemic stroke, systemic embolism, clinically relevant bleeding (including major hemorrhage, intracranial hemorrhage and minor bleeding) and myocardial infarction. As compared to warfarin, apixaban had the highest expected incremental net benefit of £7,533, followed by dabigatran with an expected incremental

net benefit of £6,365 and rivaroxaban with an expected incremental net benefit of £5,279 (cost year was not specified in source). The probabilistic sensitivity analysis showed that the probability of apixaban, dabigatran and rivaroxaban was cost-effective was close to 60%, 25% and 10% at a WTP threshold of £20,000/QALY.

Overall, apixaban has been found to be the recommended anticoagulation strategy with a high degree of certainty in various countries including the US, Taiwan, Italy, France, Portugal, Slovenia, Belgium, and Singapore (13–21) (Table 2.2.1). Among DOACs, apixaban produces the highest incremental health benefit at the lowest incremental cost. However, some studies found that the DOACs are not cost-effective in the context of Thailand, Germany and the US. For example, a CEA by Jarungsuccess *et al*. (2014) recommended dose-adjusted warfarin therapy for 65-year old AF patients in Thailand and found that DOACs could be cost-effective if the drug unit cost decreased by 85% (22). Similarly, Dilokthornsakul *et al*. (2019) found that DOACs were not cost-effective at the WTP of 160,000 THB/QALY for the Thai AF population and these results were sensitive to DOAC drug costs among other clinical factors (23). A CEA by Krejczy *et al*. (2014) also did not find the DOACs to be cost-effective at the current drug unit cost in the prevention of stroke among AF patients in Germany (24). Thus, the cost-effectiveness of DOACs seems to be very sensitive to drug costs, which varies by geographical region. Given the influence of drug costs and the shortcomings of the previous Canadian CEA study, there is the potential need for further research and evaluation of the cost-effectiveness of DOACs using updated Canadian cost data.

Although the cost-effectiveness of DOACs were sensitive to drug cost in the context of Thailand and Germany, You *et al*. (2013) found that the DOACs had the potential to be cost-effective in the US if the time in therapeutic range (TTR) under standard warfarin care was below 60% (25). In addition to drug costs, the authors found that the cost-effectiveness of DOACs was sensitive to quality of anticoagulation control with warfarin use and anticoagulation service cost in the US. PGx-based warfarin care optimizes warfarin dosing and TTR. However, You *et al*. (2013) did not include PGx-based warfarin care as an alternative OAC strategy in their CEA. This highlights a gap in the

published literature on the cost-effectiveness analysis of standard warfarin care, PGx-based warfarin care and DOACs for AF patients in a single study.

In summary, the DOACs have been consistently shown to be or have the potential to be cost-effective alternatives to standard warfarin care. Among apixaban and rivaroxaban, apixaban is often the recommended treatment when compared to standard warfarin care. However, it has been shown that the cost-effectiveness of DOACs is influenced by drug costs and anticoagulation control under warfarin care. The unit costs of DOACs vary by geographical region which highlights potential for research in Canada. Moreover, PGx-based warfarin care has been shown to improve the anticoagulation control of warfarin use. However, there are a limited number of studies that evaluate the cost-effectiveness of all four strategies; standard warfarin care, PGx-based warfarin care, apixaban and rivaroxaban, as described in the next section.

2.3 Cost-effectiveness analyses of PGx-based warfarin care, apixaban and rivaroxaban relative to standard warfarin care

A few published CEAs in the literature compared PGx-based warfarin care, standard warfarin care, apixaban and rivaroxaban for AF patients.

You *et al*. (2013) assessed the cost-effectiveness of pharmacogenetic-guided selection of warfarin and DOACs, including apixaban and rivaroxaban, as compared to standard warfarin for stroke prevention (26). The CEA compared direct medical costs and QALYs incurred by a cohort of 65-year-old newly diagnosed AF patients from the US public healthcare payer perspective using two treatment strategies. In the first strategy, all patients undergo standard warfarin care. In the second strategy, patients are genotyped for CYP2C9 and VKORC1 genes and then, wild-type patients are triaged into genotype-guided warfarin care and variant carriers are administered DOAC treatment. The Markov model captured the following adverse events: ischemic stroke, major hemorrhage (ICH and ECH) and myocardial infarction. The base-case analysis showed that pharmacogenetics-guided selection of warfarin increased QALYs by 0.191 units and costs by $543 (2013 USD). The pharmacogenetics-guided selection of warfarin was

found to have an ICER of $2,843/QALY (2013 USD) gained. The deterministic sensitivity analysis showed that the base case results were sensitive to the DOAC drug costs, relative risk of stroke, relative risk of hemorrhage and the time spent in therapeutic range under warfarin care. Moreover, the probabilistic sensitivity analysis showed that the probability of PGx-guided warfarin being cost-effective was 96.4% at WTP threshold of $50,000/QALY USD. Although this study modelled genotype-guided warfarin care, their research question assessed the cost-effectiveness of pharmacogenetics use to select between warfarin (included only patients lacking select *CYP2C9* and *VKORC*1 variants) and DOAC treatments. As such, there is still a gap in the published literature necessitating evaluation of the comparative cost-effectiveness of treatment strategies for AF patients receiving either standard warfarin dosing, PGx-guided warfarin dosing, apixaban or rivaroxaban treatment in current clinical practice.

In another study, Pink *et al*. (2014) assessed the cost-effectiveness of DOACs, pharmacogenetic-guided warfarin dosing and standard warfarin dosing in the UK (27). The authors used a discrete-event simulation model to compare direct medical costs and QALYs in AF patients (72.5-year-old on average) from the perspective of the UK public healthcare payer over the lifetime horizon. In their CEA, Pink *et al*. (2014) conducted a pharmacokinetic-pharmacodynamic simulation using clinical trials data to estimate the distribution of INR ranges under standard and PGx-based warfarin dosing. Then, INR-specific risks of adverse events were modelled using an updated meta-analysis. The study captured the following adverse events: stroke or systemic embolism, transient ischemic attack, major hemorrhage (including intracranial hemorrhage) and myocardial infarction. The base-case analysis showed that PGx-based warfarin care increased QALYs by 0.003 units and apixaban increased QALYs by 0.130 as compared to standard warfarin care. The discounted lifetime costs in 2011 cost-year were £8,437, £5,921, and £5,880 for apixaban, PGx-guided warfarin care and standard warfarin care, respectively. Both apixaban and PGx-based warfarin care improved health outcomes at an additional cost relative to standard warfarin care. The estimated ICER value was £13,226/QALY gained for PGx-guided warfarin care as compared to standard warfarin care. In comparison, the ICER was £19,858/QALY gained under apixaban treatment as compared to PGx-guided warfarin care. As compared to standard warfarin care, rivaroxaban increased QALYs and

costs. However, rivaroxaban was dominated by apixaban because it resulted in lower QALYs but higher costs. The probabilistic sensitivity analysis showed that PGx-guided warfarin had a high probability of being cost-effective as compared to standard warfarin care at the WTP threshold of £6,700/QALY and apixaban had a high probability of being cost-effective at the WTP threshold of £20,500/QALY when compared to PGx-guided warfarin. In summary, apixaban resulted in the largest gains in QALYs and had the highest probability of being cost-effective among all four strategies.

In another CEA, Janzic and Kos (2015) assessed the cost-effectiveness of DOACs, including apixaban and rivaroxaban, and PGx-based warfarin as compared to standard warfarin care for stroke prevention in a Markov cohort analysis (17). The CEA compared direct medical costs and QALYs in a cohort of 70-year-old AF patients from the Slovenian healthcare payer perspective over the lifetime horizon. All patients began from the event-free health state and could experience the following adverse events at monthly intervals: ischemic stroke (disabling, non-disabling or fatal), intracranial hemorrhage (disabling, non-disabling or fatal); extracranial hemorrhage (fatal or non-fatal), systematic embolism (no change in state); myocardial infarction (no change in state or death) and non-event death. The modelled health states comprised of well, non-disabled and on-treatment, disabled and on-treatment, disabled and off-treatment, and nondisabled and off-treatment. The authors modelled distribution of TTR using the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI trials and predicted hemorrhagic and thromboembolic rates as a function of TTR under standard warfarin care. The EU-PACT trial reported that PGx-based warfarin dosing increased the TTR by 8.8% in the first 4 weeks and then, by 10.2% in the subsequent 4 weeks. Janzic and Kos (2015) used this finding to model improved quality of warfarin anticoagulation control under PGx-based warfarin care for the first 6 months of treatment initiation. The base case analysis showed that, as compared to standard warfarin care, the incremental costs in 2014 cost year were about €16, €3,678 and €4,193 and the incremental QALYs were about 0.003, 0.235 and 0.064 for PGx-based warfarin care, apixaban and rivaroxaban, respectively. Thus, the corresponding estimated ICERs were €6,959/QALY, €15,679/QALY and €66,328/QALY. Apixaban was found to be a cost-effective alternative to standard warfarin care with a high degree of certainty at the WTP threshold of €20,000/QALY and

dominated rivaroxaban. Although PGx-based warfarin was found to be cost-effective, the absolute incremental benefit was small. Thus, the authors did not recommend PGx-based warfarin care as a "structural measure" to improve long-term anticoagulation control. Although both Pink *et al*. (2014) and Janzic and Kos (2015) provide valuable insights about the comparative cost-effectiveness of PGx-based warfarin care, apixaban and rivaroxaban, to date, no Canadian study has compared all four treatment strategies.

In summary, published CEAs comparing standard warfarin care, PGx-based warfarin, apixaban and rivaroxaban show that the DOACs and PGx-based warfarin therapy can be cost-effective strategies as compared to standard warfarin care. Moreover, apixaban is usually the recommended DOAC for AF patients. However, there is heterogeneity in the published literature and the results vary by population and geographical region. The estimated ICER values are sensitive to the DOAC drug costs and efficacy of anticoagulation managements under warfarin care. In addition, most of the published CEAs have overlooked to model the cost and risk differences associated with clinically relevant non-major bleeding events. Considering the emerging evidence that highlights the clinical importance of CRNMB events and latest meta-analyses that show a significant reduction in adverse events under alternative to warfarin treatments, there is potential for further research using latest effectiveness data and region-specific costs in the context of Canada.

Table 2.2.1: Summary of published cost-effectiveness analyses of DOACs, including apixaban and rivaroxaban, as compared to standard dose-adjusted warfarin care included in the literature review.

First Author (Reference)	Year	Setting	Target population	Interventions	Health Outcomes	Cycle length	Time frame	Perspective	Base Case Analysis Results
Canestaro (14)	2013	US	70-year-old warfarin eligible patients	Dabigatran 150 mg BID, Apixaban 5 mg BID, Rivaroxaban 20 mg QD	Ischemic stroke, non–central nervous system embolism, intracranial hemorrhage, gastrointestinal bleeds, extracranial non-gastrointestinal bleed, myocardial infarctions and death	1-month cycle	Lifetime	Societal perspective (all costs were included regardless of payer)	Compared with warfarin, dabigatran, rivaroxaban, and apixaban cost $140,557, $111,465, and $93,062 per additional QALY gained, respectively, in 2011 USD. When rank-ordered by costs, apixaban was found to be optimal.
Coyle (9)	2013	Canada	72-year-old AF patients	Dabigatran (150 mg twice daily or 110 mg twice daily) Rivaroxaban Apixaban Aspirin in case of therapy discontinuation	Ischemic stroke (fatal, major or minor), bleeding (fatal, intracranial hemorrhage, major non-ICH, and minor), TIA, myocardial infarction, pulmonary embolism (fatal or nonfatal) and death	3-month cycle	Lifetime	Third-party payer perspective of the provincial ministry of health	Dabigatran 150 mg was the recommended option and dominated all other treatment options.
Harrington (28)	2013	US	70-year-old AF patients	Apixaban (5 mg BID) Rivaroxaban (20 mg QD)	Ischemic stroke (minor or major), Intracranial hemorrhage (minor or	1-month cycle	30 years or until death	Societal	Apixaban was the recommended strategy, followed by dabigatran and then rivaroxaban.

				Dabigatran (150 mg)	major), myocardial infarction (MI), and death				
You (25)	2013	US	65-year-old newly diagnosed AF patients	DOACs (dabigatran 150mg twice daily, rivaroxaban 20mg daily, or apixaban 5mg twice daily)	Ischemic stroke (mild, moderate or severe), major bleeding (intra- or extracranial hemorrhage), myocardial infarction and death	1-month cycle	25 years	Healthcare payer	DOACs increased lifetime costs and QALYs as compared to standard warfarin care. At the WTP threshold of $50,000/QALY, the DOACs were cost-effective in ~80% of the time at the TTR <= 60% under warfarin therapy or at a monthly drug cost of $200 or less.
Jarungsuc-cess (22)	2014	Thailand	65-year-old newly diagnosed AF patients	Dabigatran (150mg BID or 110mg BID) Rivaroxaban 20mg/day QD Apixaban 5mg BID	Ischemic stroke (non-disabling [mRS=0–1], disabling [mRS=2–5]), major bleeding (non-disabling [mRS=0–2], disabling [mRS=3–5]), intracranial hemorrhage, extracranial hemorrhage, myocardial infarction (with/without	1-year cycle	30 years or until death	Both government and societal perspectives	Warfarin was the recommended option from both healthcare and societal perspective in Thailand. The DOACs had the potential to be cost-effective if the drug unit cost was reduced by at least 85%.

					complications) and death				
Kongnak-orn (18)	2014	Belgium	Belgium AF patients eligible for anticoagul-ation treatment	Apixaban 5mg twice daily, Rivaroxaban 20mg once daily, Dabigatran 110mg twice daily or 150mg twice daily	Ischemic stroke, hemorrhage (mild, moderate, severe and fatal), systemic embolism, intracranial hemorrhage, other major bleeding, clinically relevant non-major bleeding and myocardial infarction	6-week cycle	Lifetime	Belgian healthcare payer; the Belgian National Institute for Health and Disability Insurance (RIZIV/INAMI)	Apixaban was found to be a cost-effective strategy as compared to warfarin at an ICER of €7,212/QALY gained (2013 EUR). Apixaban dominated rivaroxaban.
Krejczy (24)	2014	Germany	65-year-old AF patients	Dabigatran (110 and 150mg BID), Rivaroxaban 20mg OD, Apixaban 5mg BID	Ischemic stroke (fatal, moderate to severe, mild), hemorrhage (fatal, moderate to severe intracranial, mild intracranial, major non-cerebral, minor non-cerebral), transient ischemic attack, myocardial infarction (MI), recurrent and combined events and death	1-year cycle	20 years	German public healthcare insurance	At the current drug prices, the DOACs were not found to be cost-effective from the German public health care insurance perspective.

Lanitis (13)	2014	France	French AF patients	Apixaban (5 mg BID) Rivaroxaban (20 mg QD) Dabigatran (150 mg or 110 mg BID) Aspirin	Ischemic stroke (mild, moderate, severe or fatal), hemorrhage (intracranial hemorrhage, major bleed or clinically relevant nonmajor bleeding), systemic embolism, myocardial infarction and death	6-week cycle	lifetime	French National Health Insurance (healthcare payer)	Apixaban was found to be the economically efficient alternative to warfarin and dominated all other treatment alternatives in AF patients eligible for stroke prevention in France.
Rognoni (29)	2014	Italy	71-year-old AF patients	Apixaban (5 mg BID) Rivaroxaban (20 mg QD) Dabigatran (150 mg or 110 mg BID)	Ischemic stroke (temporary, mild, moderate/severe or fatal), intracranial hemorrhage (mild, moderate–severe or fatal), minor and major extracranial bleedings, myocardial infarction and death	3-month cycle	Lifetime	Italian National Health System	Apixaban was the recommended strategy at the willingness-to-pay (WTP) threshold of €25,000/QALY gained (2013 EU).
Wisløff (15)	2014	Norway	75-year-old general Norwegian population with medium risk of stroke	Sequential Dabigatran (2x150 mg), Dabigatran (2x110mg), Apixaban (2x5mg), Rivaroxaban (1x20mg)	Ischemic stroke (IS), intracranial hemorrhage, major gastrointestinal bleeding, acute myocardial infarction and death	N/A	Lifetime	Norwegian publicly financed healthcare system	Sequential dabigatran (2x150 mg before the age of 80 and then, 2x110 mg at the age of 80) was the recommended alternative for AF patients, followed by apixaban. The cost-effectiveness of dabigatran was found to

									be dependent on the dose switching age.
Zheng (30)	2014	UK	71-year-old AF patients	Dabigatran 150mg or 110mg based on patient age, Rivaroxaban, Apixaban	Primary and recurrent IS, systemic embolism, acute myocardial infarction, transient ischemic attack, intracranial hemorrhage, major extracranial hemorrhage, minor bleeding and death	3-month cycle	Lifetime	UK payer perspective	Dabigatran was found to be economically dominant over rivaroxaban and apixaban in the UK setting.
Costa (16)	2015	Portugal	AF patients with a mean age of 70 years old	Apixaban 2.5-5mg twice daily, Dabigatran (150mg up to 80yrs and 110mg after 80 years), Rivaroxaban 15-20mg once a day	Ischemic stroke (mild, moderate, severe and fatal), bleeding (intracranial, other major bleeding and clinically relevant non-major bleeding), myocardial infarction and death	6-week cycle	Lifetime	Portuguese national healthcare system	Apixaban provided the most health gains at the lowest incremental cost and dominated rivaroxaban. As such, apixaban was found to be the optimal alternative to warfarin in AF patients from the perspective of the Portuguese national healthcare system.
Shah (20)	2016	US	AF patients with a CHADS2 score of ≥1	Apixaban (5mg BID), rivaroxaban (20mg QD), Dabigatran (150mg BID),	Ischemic stroke (transient ischemic attacks, reversible, major, minor, or fatal), intracranial hemorrhage (major,	1-month cycles	Lifetime	Private payer's perspective	Apixaban was the recommended strategy over standard warfarin care with an estimated ICER of $25,816/QALY

				Edoxaban (60mg QD)	minor or fatal), extracranial hemorrhage (ECH) and death				(2015 USD) and dominated rivaroxaban.
Zhao (21)	2016	Singapore	65-year-old AF patients	Apixaban 5mg twice daily, Rivaroxaban 20mg daily, Aspirin low dose (<100mg daily), Aspirin medium dose (100-300mg daily), Aspirin/clopidogrel (75mg once daily), Dabigatran 110mg twice daily or 150mg twice daily, Edoxaban 60mg daily	Ischemic stroke (minor, major or fatal), intracranial hemorrhage (minor, major or fatal), gastrointestinal bleeding (non-fatal or fatal), myocardial infarction (non-fatal or fatal) and non-event death	1-month cycles	Lifetime	Based on the info under cost source, it seems the perspective is that of a healthcare payer which could be the hospital or the public/government. The payer is not specified in the article.	All the DOACs (except dabigatran 110) were found to be cost-effective as compared to standard warfarin care at the WTP threshold of $49,700/QALY (2015 USD). Apixaban produced the highest number of QALYs (11.22) at the lowest ICER value (2015 USD 24,476/QALY gained).
Hernandez (19)	2017	US	65-year-old AF patients	Apixaban 5 mg, Rivaroxaban 20 mg, Dabigatran 150 mg or 110 mg, Edoxaban 60 mg	Severe stroke, other thromboembolic events including minor ischemic stroke, transient ischemic attack and systemic embolism, intracranial	1-year cycles	Until 90 years of age or death	US-based third-party payer	The DOACs increased QALYs at a higher cost as compared to standard warfarin care. Among the DOACs, apixaban was the recommended strategy at WTP

					bleeding, extracranial bleeding and death				thresholds above $84,129/QALY (2012 USD) and dominated rivaroxaban.
Liu (31)	2017	Taiwan	18+ year old AF patients enrolled in the national health insurance program	Apixaban (5 mg BID) Rivaroxaban (20 mg QD) Dabigatran (150 mg or 110 mg BID)	Ischemic stroke (mild, moderate or severe), hemorrhage (mild ICH, moderate ICH, severe ICH, major bleeding, clinically relevant non-major bleeding), myocardial infarction, systemic embolism and death	6-week cycle	Lifetime	Healthcare payer	Apixaban was the recommended OAC alternative to standard warfarin care.
López-López (12)	2017	UK	70-year-old AF patients	Antiplatelet (aspirin, <159 mg once daily; >= 150 mg once daily) Apixaban (5 mg twice daily) Rivaroxaban (20 mg once daily) Dabigatran (110 mg or 150 mg twice daily) Edoxaban (30	Ischemic stroke, intracranial hemorrhage, other-clinically relevant bleeding, transient ischemic attack, systemic embolism, myocardial infarction and death	3-month cycle	Lifetime	National Health Services (NHS)	Apixaban (5 mg twice daily) was the recommended anticoagulation strategy at the WTP of €20,000/QALY gained.

				mg and 60 mg twice daily)					
Hospoda (32)	2018	US	65-year-old AF patients	Apixaban 5mg, Edoxaban 60mg, Rivarixaban 20mg, Dabigatran (150mg or 110mg)	Ischemic stroke, other thromboembolic events (minor ischemic stroke, transient ischemic attack or systemic embolism), intracranial bleeding, extracranial bleeding and death	1-year cycles	until 90 years old or death	US third-party payer perspective	Warfarin with a time in therapeutic range (TTR) of 70% or less was a cost-effective strategy and dominated apixaban and rivaroxaban at the WTP threshold of $100,000/QALY USD.
Dilokthorn-sakul (23)	2019	Thailand	68-year-old AF patients	Apixaban 5 mg twice daily, Rivaroxaban 20 mg once daily, Dabigatran 150 mg or 110 mg twice daily, Edoxaban 60 mg and 30 mg once daily	Ischemic stroke, extracranial hemorrhage (fatal or non-fatal), intracranial hemorrhage (mild, moderate, severe or fatal), myocardial infarction (fatal or non-fatal) and death	1-year cycles	Lifetime	Societal perspective	In Thailand, all the DOACs were not found to be cost-effective for the AF population. The cost-effectiveness acceptability curve indicated that apixaban had the potential to be a cost-effective strategy at higher WTP thresholds as compared to other DOACs.

Note: Target population is the average age used for the modelled analysis. BID; two times a day. QD: once daily

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Chapter 3

Cost-effectiveness analysis of pharmacogenomics (PGx) based warfarin, apixaban and rivaroxaban compared to standard warfarin for atrial fibrillation patients in Canada

3.1 Introduction

Atrial fibrillation (AF) is a common cardiac arrythmia among seniors (aged 65 years and older) in Canada. The prevalence of AF is approximately 300,000 Canadians in Canada (1). AF patients suffer from high morbidity and mortality risk, increasing the risk of stroke 3-5 times and death by 3.5-fold as compared to the general population. In addition to posing a substantial burden on patients' health, AF entails a huge financial burden on the Canadian healthcare system. In the fiscal year of 2007-2008, the estimated cost of AF-related hospitalizations was $815 million (2010 CAD), representing some 4.6% of acute inpatient costs. In addition, AF-related ischemic stroke or transient ischemic attack complications were associated with the longest length of hospital stay of about 20.2 days with an average cost of $19,113 (2010 CAD) per hospitalization (1).

Warfarin, a relatively inexpensive oral anticoagulant, has been the cornerstone of AF therapy for decades to mitigate AF-related adverse events (2). Although warfarin has been shown to reduce the risk of stroke by up to 60%, the drug's optimal therapeutic effect, defined by an international normalized ratio (INR) of 2-3 (also therapeutic range), is difficult to achieve among patients due to highly variable dose requirements (3).[4] Warfarin's unpredictable pharmacological response is caused by interpatient genetic variability in drug metabolism and response (4). In practice, the therapeutic dose for each patient is typically determined by trial and error, an approach that often results in INRs above or below the therapeutic range. Consequently, patients under standard warfarin care require repetitive INR tests and frequent dose adjustments (3). Not only is this

[4] The international normalized ratio (INR) is a standardized score obtained from the prothrombin time/international normalized ratio (PT/INR) test, which measures the effectiveness of warfarin by assessing the time it takes for blood to clot (10).

inconvenient to patients, it also increases the risk of adverse events, particularly during the initial dose adjustment period. Due to its narrow therapeutic window, subtherapeutic warfarin doses can lead to stroke while supratherapeutic doses may cause hemorrhagic events. Annual incidences of 0.6% fatal bleeding, 3.0% major bleeding and 9.6% minor bleeding have been estimated for patients on warfarin therapy (3). As expected, these adverse events entail substantial financial strain on Canadian hospitals. In Ontario, bleeding complications are the costliest; AF-related hospitalizations cost an average of $26,746 (2010 CAD) per hospital admission (1).

About 18%, 30%, and 11% of the interpatient variability in therapeutic dose in patients of European ancestry can be attributed to common genetic polymorphisms in the *S*-warfarin-metabolizing enzyme cytochrome P450 (CYP) 2C9, the pharmacological target of warfarin vitamin K epoxide reductase complex 1 (VKORC1), and vitamin K_1 hydroxylase (CYP4F2), respectively (5). Pharmacogenomics (PGx)-based warfarin care tailors drug dose for each patient using his or her genotype information in conjunction with the relevant demographic and clinical variables such as age, sex, weight, height, and smoking status. Two recent meta-analyses have shown that PGx-based warfarin dosing increases the efficiency with which the therapeutic effect is achieved among patients while decreasing the risk of adverse events during the initial dose adjustment period (6,7). Thus, PGx-based warfarin care has the potential to optimize warfarin use and decrease the financial burden entailed by warfarin-related adverse events. However, there is an upfront cost of genotyping test incurred under PGx-based warfarin care.

Direct oral anticoagulants (DOACs) such as apixaban and rivaroxaban represent another treatment alternative available recently for patients with AF, which has confirmed non-inferiority to warfarin (8). DOACs have the added benefits, including more predictable dosing requirements, rapid onset of drug action, fewer drug-food interactions, and no need for routine monitoring (8). However, DOACs may not be suitable for patients with poor renal function and have substantially higher drug costs than warfarin. Over the last few years in Canada, there has been a shift in physician prescribing behaviour from warfarin to DOACs, such as apixaban and rivaroxaban (9). Since the inclusion of DOACs in the provincial formulary in 2012, apixaban and rivaroxaban represent a growing

segment of oral anticoagulant (OAC) prescriptions with a simultaneous decline in warfarin use. As DOAC treatments are adopted in current clinical practice, there is a need for an updated cost-effectiveness analysis (CEA) of existing OAC therapies for AF patients.

Existing CEAs have shown that the cost-effectiveness of OAC treatments is sensitive to drug costs and quality of anticoagulation control under warfarin care, which varies by geographical region and patient populations. In the context of Thailand, Germany and United States, the DOACs can be cost-effective conditional on reduced drug acquisition costs by almost 80% and time in therapeutic range (TTR) under warfarin care by almost 60% (10–12). In other studies, apixaban and PGx-based warfarin care have been found to be cost-effective compared to standard warfarin care in the context of Slovenia and the United Kingdom (13,14). As such, there is considerable between-study heterogeneity in the published literature that, in part, depending on the institutional environment within which the CEA was conducted. Thus, previous CEAs may not inform optimal AF treatment strategy in Canada from the resource allocation perspective.

In previous Canadian CEAs, dabigatran was found to be the most cost-effective strategy (15,16). However, latest clinical evidence shows that high dose dabigatran is associated with higher gastrointestinal bleeding than standard warfarin care. Moreover, dyspepsia (indigestion) is a common adverse event of dabigatran use and discourages prescription (4). Although dabigatran was the first DOAC to be publicly funded in Canada, apixaban and rivaroxaban were included in the Ontario Drug Benefit (ODB) formulary shortly after (9). Since then, there has been a simultaneous decrease in the percentage of dabigatran prescriptions and increase in the percentage of other DOAC prescriptions (9). Contrary to previous CEA recommendation, physicians in Canada prefer prescribing apixaban or rivaroxaban over dabigatran. Moreover, the evidence used to populate previous CEA models was limited. Most of the previous studies have not captured costs and risk differences associated with clinically relevant non-major bleeding. Considering the emerging evidence on the clinical effectiveness and safety of DOACs and heterogeneity in existing studies, there is a need for a comprehensive CEA using latest effectiveness data and region-specific updated costs in the context of Canada.

Since the current healthcare climate in Canada requires efficient allocation of resources, an updated CEA is critical for all stakeholders given the inclusion of DOACs in the ODB formulary and the changing treatment landscape in long-term OAC therapies for AF patients. Accordingly, we assessed the cost-effectiveness of PGx-based warfarin, apixaban and rivaroxaban as compared to standard warfarin care for AF patients in Canada using updated clinical evidence on effectiveness and costs.

3.2 Methods

3.2.1 Overview

We developed a Markov model to assess the cost-effectiveness of PGx-based warfarin, apixaban and rivaroxaban compared to standard warfarin care. The model was populated with parameters obtained from published literature and some costs obtained from the ICES (formerly known as the Institute of Clinical and Evaluative Sciences) and the London Health Sciences Centre (LHSC).

Cost effectiveness was evaluated using the incremental effectiveness ratio (ICER). Benefits were measured in discounted life-time quality-adjusted life-years (QALYs) and life-years (LYs) gained and the number of each type of acute event. QALYs were calculated by adjusting life years of survival by a health state utility value, which ranges from 0 to 1, with 0 representing death and 1 representing perfect health. The CEA adopted the Canadian public healthcare perspective and captured all direct medical care costs from the Ontario population, whenever available. When estimating literature-based model parameters, Canadian studies were prioritized. In case of limited Canadian data, US and European studies were selected. Deterministic and probabilistic sensitivity analyses were carried out to characterize uncertainty introduced by model parameters.

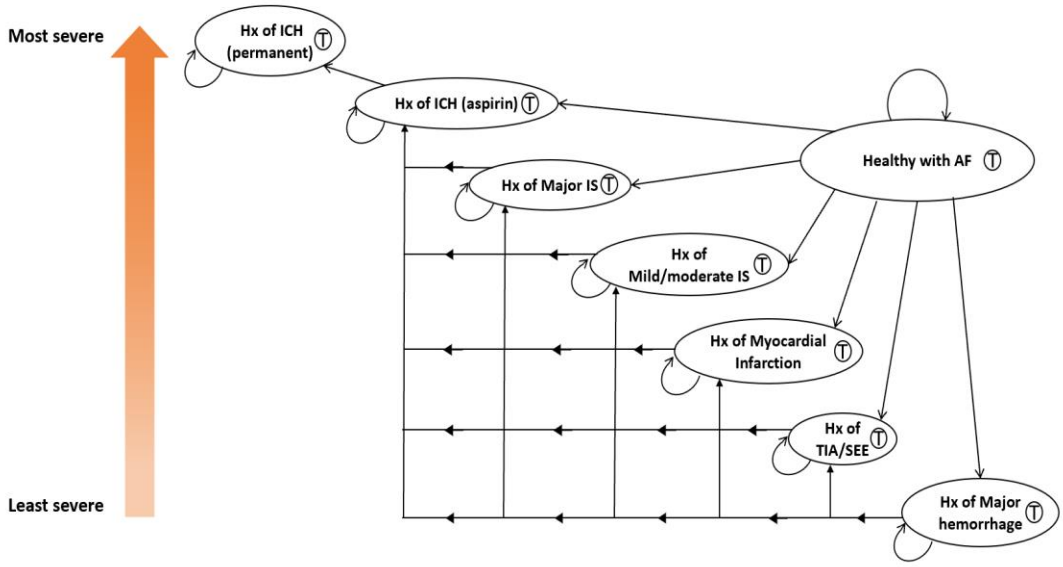
The target population was Canadian senior residents with an average age of 65 years or older who were diagnosed with nonvalvular AF and initiated long-term anticoagulation therapy for the first time. In the base case analysis, we considered a population with no history of stroke, myocardial infarction, or other cerebrovascular or cardiovascular event. In sensitivity analysis, we varied the characteristics of patients.

The following treatment strategies were compared: standard warfarin care, PGx-based warfarin care, apixaban, and rivaroxaban, with standard warfarin care as the reference treatment. It was assumed that all patients under PGx-based warfarin care were genotyped before initiating therapy, which is predicted to reduce the short-term risk of warfarin-related complications. We restricted our analysis to apixaban and rivaroxaban; dabigatran was excluded because of concerns about its safety and limited uptake in current clinical practice.

The expected costs, QALYs and LYs under each treatment strategy were compared over the lifetime horizon. The patients transitioned between health states at monthly intervals to adequately capture risk and cost differences between treatment strategies. PGx-based warfarin care has been shown to improve the TTR by about 6% as compared to standard warfarin (59.4% vs 53%; Mean Difference = 6.35 [95% Cl, 1.76 to 10.95]; P =0.007; I_2 =73%) (6). However, the benefits of PGx-based warfarin therapy are more evident after one month because the higher percent TTR translates into lower risks of major hemorrhage at more than 1 month of follow-up. As such, a monthly cycle length was considered appropriate for this CEA. Costs, QALYs and LYs were discounted at an annual rate of 1.5% as per the Canadian Agency for Drug and Technologies in Health (CADTH) guidelines (17).

3.2.2 Markov model

A.



B.

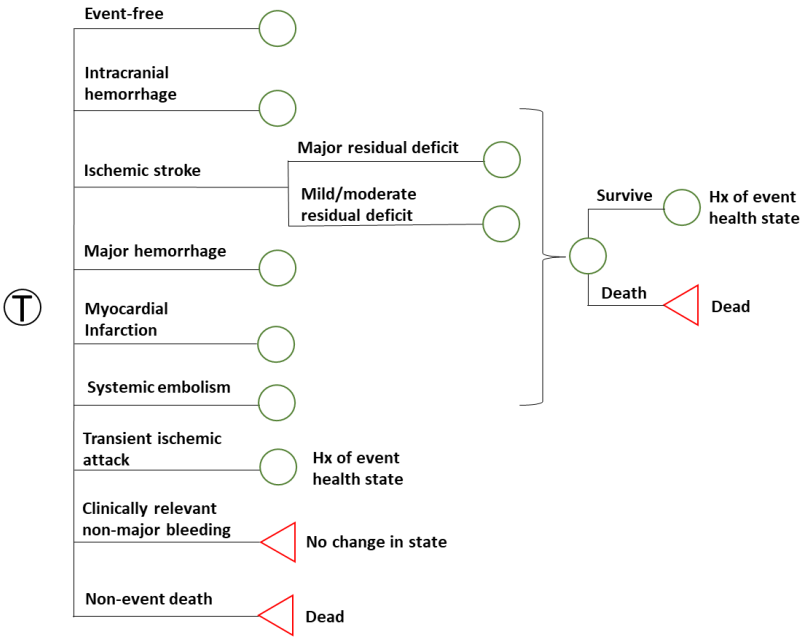


Figure 3.2.6.1: A, Markov model showing health states in order of severity. **B**, Tree diagram (T) showing adverse events in each health state. All patients begin from the "Healthy with AF" health state.
Hx, history; PGx, pharmacogenomics; ICH, intracranial hemorrhage; IS, ischemic stroke; TIA, transient ischemic attack; SEE, systemic embolic events

A decision-analytic Markov model was developed in TreeAge Pro (2020). The Markov model structure was based on recommendations from the Canadian stroke best practice guidelines, other peer-reviewed medical literature, and expert opinion (18–20). The Markov model consisted of the following health states (Figure 3.2.6.1): healthy-with-AF, history of intracranial hemorrhage (ICH)- temporary on aspirin, history of (ICH)-permanent on OAC, history of major ischemic stroke (IS), history of mild/moderate IS, history of major hemorrhage, history of myocardial infarction (MI), history of transient ischemic attack/systemic embolic events (TIA/SEE) and death. In the base-case analysis, all patients begin from the healthy-with-AF health state. In each health state, patients could experience one of the following adverse events: ICH, IS, major hemorrhage, MI, TIA, SEE, clinically relevant non-major bleeding (CRNMB), or death from other causes. Experiencing any of the acute event could also result in death within the month. Ischemic stroke was categorized into major (modified Rankin Score=3-5) and mild/moderate stroke (Figure 3.2.6.1). CRNMB was modelled as transient events after which an individual did not change health states because there is limited evidence of direct long-term health deficits and costs associated with this adverse event.

From the healthy-with-AF health state, patients who experience an adverse event transitioned to a health state defined by the sequelae of the event based on their most severe event to date. We ordered health states according to the seriousness of long-term consequences among survivors from most to least severe in the following way: ICH, major IS, mild/moderate IS, MI, TIA/SEE and major hemorrhage (19,21,22). For example, a patient with a history of major IS transitioned to the history of ICH health state upon surviving an ICH. However, if, some months later, this patient experienced a MI, the patient remained in the history of ICH health state. The patients remained in the most severe health state until death. Major adverse events increased the risk of future adverse events. As such, the risk of future events was adjusted for the history of most severe adverse event to date.

3.2.3 Treatment Effectiveness

The effectiveness of alternative treatments (PGx-based warfarin, apixaban and rivaroxaban) was implemented as hazard ratios (HRs) compared to warfarin for each

adverse event (major hemorrhage, ICH, stroke, MI and SEE) using previously published large randomized clinical trials and meta-analyses. The COAG trial (2014) is one of the largest double-blinded and multicenter randomized controlled trial (RCT) that compared pharmacogenetically based warfarin dosing with standard warfarin dosing in a cohort of 59+ year old US residents (n=1,015) (23). Findings from this trial represent the best available evidence for the effectiveness of PGx-based care in reducing the risk of major hemorrhage and CRNMB. The evidence of DOAC effectiveness was obtained from the 2017 National Health Services (NHS) competing risks network meta-analysis (24).

The risk of ischemic stroke was assumed to be the same under both standard and PGx-based warfarin care. Kimmel *et al.* (2014) did not find a significant difference in the risk of thromboembolism, which was defined as a composite of deep venous thrombosis, pulmonary embolism and embolic stroke (23). Similarly, Tse *et al.* (2018) did not find a statistically significant difference in the risk of thromboembolism in their meta-analysis (7). As such, the risks of IS, TIA, SE and MI were assumed to be the same under both PGx-based and standard warfarin care in our CEA. Due to limited published evidence on ICH, the risk of ICH was assumed to be the same under PGx-based and standard warfarin. To summarize, the benefit of PGx-based warfarin was to reduce risks for major hemorrhage and CRNMB by optimizing warfarin dosing using patient genotype information.

The hazard ratios of treatment effectiveness for apixaban and rivaroxaban relative to warfarin were mostly obtained from a NHS Health Technology Assessment 2017 study (24). We were unable to locate credible evidence to support DOAC effectiveness in reducing the risk of TIA; thus, we did not model treatment differences in the risk of TIAs.

The differences in the risk of major hemorrhage and CRNMB between PGx-based and standard warfarin care were allowed for 6 months based on findings in published literature. In a cohort study, Epstein *et al*. (2010) found that the reduced incidence of bleeding or thromboembolism-related hospitalizations among patients receiving PGx-based care as compared to a matched historical control group on standard warfarin persisted throughout the 6 months of follow-up (25). After 6 months, we assumed that the

effect of PGx-based warfarin therapy diminished; the availability of more INR measurements in the first 6 months led to appropriate dose adjustments under standard warfarin therapy (26). A treatment difference lasting 3 months to 1 year was explored in sensitivity analysis. In comparison, the risk differences between warfarin and DOACs (apixaban and rivaroxaban) were modelled over the lifetime horizon.

3.2.4 Transition probabilities

Rates of acute adverse events for elderly AF patients on warfarin, hazard ratios indicating treatment effectiveness and their sources are presented in Table 3.2.4.1, acute mortality probabilities and hazard ratios for long-term mortality in Table 3.2.4.2, and hazard ratios for the effect of previous events on future adverse events in Table 3.2.4.3.

Intracranial hemorrhage (ICH): The risk of adverse events decreases over time as warfarin dose is optimized for each patient through re-iterative prothrombin time/international normalized ratio (PT/INR) lab tests.[5] The rate of ICH among 65-year-old Ontario residents having AF and on warfarin decreased by half after the first month of initiating OAC treatment as compared to the rest of follow-up (27). Treatment effectiveness on adverse event rates was modelled using hazard ratios. We assumed the rate of ICH under standard warfarin care and PGx-based warfarin care were the same because of limited evidence on the effectiveness of PGx-based warfarin care in reducing the risk of ICH events. The surviving ICH patients discontinue anticoagulation and transition to aspiring therapy for three months. Aspirin is not as effective in reducing the risk of stroke as warfarin. As such, we increased the risk of stroke for these patients for three months. After this period, the surviving patients resumed OAC treatment with the same agent as they were on before the adverse event (19). Patients with an ICH incurred a cost of acute care, disutility in the month of the event, and a possibility of death within 30 days. Patients who survived longer than one month entered a health state in which

[5] The PT/INR test measures the effectiveness of warfarin in plasma by assessing time taken for blood to clot. Under standard practice, warfarin patients are monitored through routine laboratory PT/INR testing.

they incurred a long-term increase in costs and a reduction in utility. The surviving ICH patients faced higher risks of future adverse events.

Ischemic stroke (IS): The real-world rate of ischemic stroke found in a cohort of Ontario residents with AF and on warfarin decreased after the first month of OAC treatment and reflected temporal changes in risks (28). Some strokes were fatal. The surviving stroke cases were categorized into major and mild/moderate cases. In a Canadian-based study by Mittmann *et al.* (2012), about 48.7% of surviving ischemic stroke cases had a modified Rankin Score (mRS) between 3 to 5 at discharge and were classified as major strokes (29). We used this study to model the proportion of major strokes among the surviving cases and investigated the impact of varying this proportion in one-way sensitivity analysis. An acute treatment cost of fatal and non-fatal stroke was calculated using administrative databases at ICES Western site (Table 3.2.5.1). The surviving stroke patients incurred an immediate reduction in quality in life. Subsequently, these patients entered a health state in which they incurred a long-term increase in costs, reduction in utility, and higher risks of future adverse events. Major stroke patients incurred a greater reduction in utility and increase in long-term costs as compared to mild/moderate stroke.

Myocardial Infarction (MI): We estimated the baseline rate of MI among AF-patients on warfarin from a Canadian-based study (8). Patients with an MI accrued a cost of acute care, disutility, and a possibility of death in the month of the event. Patients who survived longer than one month had an increased risk of future adverse events and non-event death.

Transient ischemic attack/Systemic embolic events (TIA/SEE): The baseline rate of SEE and TIA among AF-patients on warfarin was obtained from the published literature (30,31). Patients with a TIA or SEE received a cost of acute care and disutility in the month of the event. SEE patients had a possibility of death within 30 days. Transient ischemic attacks are transient events and do not result in death as a direct outcome. However, these events are indicative of increased risk of future adverse events. As such, patients who survived a TIA/SEE experience an increased risk of future adverse events and non-event death.

Major hemorrhage: The real-world rate of major hemorrhage on warfarin was a weighted average rate of upper gastrointestinal, lower gastrointestinal and other hemorrhages rates (27). A higher rate of event was modelled in the first month of initiating OAC treatment as compared to the rest of time horizon. Patients who had a major hemorrhage received a one-time event cost of acute treatment, disutility in the month of the event and probability of death within 30 days. The surviving patients transitioned to the history of major hemorrhage health state and continued anticoagulation therapy with the same agent as they were on before the adverse event. Clinical evidence recommends that patients suffering a major hemorrhage should restart anticoagulation therapy within 4-14 weeks (19). Moreover, resuming anticoagulation therapy once the major hemorrhage event has been managed is associated with lower mortality as compared to not resuming any anticoagulation therapy. Thus, in our model, patients who survived major hemorrhages were assumed to have the adverse event managed within a month and resume anticoagulation therapy by the next month/cycle. Patients with a history of major hemorrhage had increased rates of future acute events and mortality. Moreover, the surviving patients in this health state incurred additional costs for one year but no long-term change in health utility.

Clinically relevant non-major bleeding (CRNMB): The baseline rate of CRNMB among AF-patients on warfarin was obtained from a published study, which estimated risks from the ARISTOTLE trial (32). We assumed that CRNMB could not be a fatal adverse event. Patients with a CRNMB received a cost of acute care and disutility at the time of the event. We assumed that a history of CRNMB did not increase the baseline age-specific mortality rate, increase long-term costs, affect long-term quality of life, or increase the rate of future adverse events and so individuals with a history of CRNMB did not transition out of their current health state.

Background mortality: The age-specific mortality rates for the Ontario population were obtained from Statistics Canada, Table 13-10-0114-01 (33). The influence of ischemic heart diseases and cerebrovascular diseases were removed from the all-cause mortality rates and the annual probabilities were modelled as non-event mortality in the Markov model. The influence of prior adverse events such as ICH, major hemorrhage, MI and

stroke were modelled by applying hazard ratios to the baseline age-specific mortality rates.

Calibration: A patient's age-specific mortality rate was adjusted for post-event mortality risk (history of ICH, major IS, mild/moderate IS, MI, TIA/SEE and major hemorrhage) using calibration to observed long-term mortality outcomes. Long-term all-cause mortality rates after an event were obtained from published literature and the model was calibrated to reach those targets. For example, Sennfält *et al.* (2019) found a cumulative mortality rate of 62.2% at 5-years among 30-day ICH survivors with an average cohort age of 73 years (34). We calculated the hazard ratio on baseline age-specific mortality after ICH that was able to achieve this 5-year mortality outcome, including the risk of death associated with the acute events that may occur within the 5-years to avoid overcounting deaths. In this case, we estimated that individuals with a history of ICH have a hazard ratio of 4.37 on age-specific mortality. Similarly, we performed step-wise calibration for the most to least severe health state. The model was calibrated to reach a cumulative 5-year death rate of 88% for patients with a history of major IS (35), cumulative 5-year death rate of 72.8% for patients with a history of mild/moderate IS (35), cumulative 6-year death rate of 50.3% for patients with a history of MI (36), cumulative 5-year death rate of 29.8% for patients with a history of TIA/SEE (37) and cumulative 2.5-year all-cause death rate of 7.5% (38).

Table 3.2.4.1: Base-case rates for adverse events and effectiveness of treatment.

Parameter		Base-case	Range		Distribution	Source
			Low value	High value		
Baseline event rates under standard warfarin therapy (% per person-year)						
Major hemorrhage	(<= 30 days)	13.3	12.9	13.7	Normal (0.133, 0.207)	Gomes *et al.* (2013) (27)
	(> 30 days)	3.4	3.33	3.47	Normal (0.034, 0.036)	
ICH	(<= 30 days)	0.4	0.35	0.45	Normal (0.004, 0.026)	Gomes *et al.* (2013) (27)
	(> 30 days)	0.2	0.16	0.24	Normal (0.002, 0.02)	
CRNMB		9.4	9.34	9.462	Normal (0.094, 0.003)	Bahit *et al.* (2017) (32)
Ischemic stroke	(<= 30 days)	6	5.55	6.45	Normal (0.06, 0.23)	Tung *et al.* (2015) (28)
	(> 30 days)	1.6	1.55	1.65	Normal (0.016, 0.03)	
MI		0.8	0.68	0.93	Normal (0.008, 0.06)	Yu *et al.* (2017) (8)
TIA		2.7	2.52	2.88	Normal (0.027, 0.09)	SPAF III Trial, 1996 (31)
SEE		0.1	0.09	0.11	Normal (0.001, 0.004)	Apixaban Monograph, 2016 (30)
Stroke severity: Proportion of non-fatal strokes that are major (vs. mild/moderate) (%)						
Major stroke (mRS=3-5)		48.71	42.31	55.13	Beta (113, 119)	Mittmann *et al.* (2012) (29)
Effectiveness of treatment (HR, with warfarin as comparator)						
Major hemorrhage						
	PGx-based warfarin	0.41	0.13	1.31	LogNormal (-0.89, 0.59)	Kimmel *et al.* (2014) (23)
	Apixaban	0.72	0.62	0.82	Normal (0.72, 0.05)	Sterne *et al.* (2017) (24)
	Rivaroxaban	1.02	0.89	1.18	Normal (1.02, 0.07)	
CRNMB						
	PGx-based warfarin	0.62	0.3	1.27	LogNormal (-0.48, 0.37)	Kimmel *et al.* (2014) (23)
	Apixaban	0.69	0.63	0.75	Normal (0.69, 0.03)	Bahit *et al.* (2017) (32)
	Rivaroxaban	1.04	0.96	1.13	Normal (1.04, 0.04)	Patel *et al.* (2011) (39)

ICH						
	Apixaban	0.46	0.36	0.58	Normal (0.46, 0.06)	Sterne *et al.* (2017) (24)
	Rivaroxaban	0.65	0.46	0.89	Normal (0.65, 0.11)	
Ischemic stroke						
	Apixaban	0.9	0.72	1.11	Normal (0.90, 0.10)	Sterne *et al.* (2017) (24)
	Rivaroxaban	0.92	0.73	1.13	Normal (0.92, 0.10)	
MI						
	Apixaban	0.86	0.65	1.1	Normal (0.86, 0.11)	Sterne *et al.* (2017) (24)
	Rivaroxaban	0.79	0.61	1.01	Normal (0.79, 0.10)	
SEE						
	Apixaban	0.65	0.33	1.18	LogNormal (-0.43, 0.33)	Sterne *et al.* (2017) (24)
	Rivaroxaban	0.95	0.79	1.13	Normal (0.95, 0.09)	
Ischemic stroke (HR, aspirin as comparator)						
	Warfarin	0.64	0.55	0.75	Normal (0.64, 0.05)	Vargas *et al.* (2018) (40)
	Apixaban	0.59	0.37	0.73	Normal (0.59, 0.09)	
	Rivaroxaban	0.6	0.41	0.88	Normal (0.6, 0.12)	

The differences in treatment effectiveness between PGx-based and standard warfarin care are allowed for 6 months.

There is no credible evidence of treatment impact on the risk of transient ischemic attack. As such, we did not model difference in treatment effectiveness for this outcome.

Hazard ratios are parametrized as Normal (mean, standard error), LogNormal as (ln(mean), ln(standard error)) and beta as Beta (alpha, beta).

PGx, pharmacogenomics; ICH, intracranial hemorrhage; CRNMB, clinically relevant non-major bleeding; MI, myocardial infarction; TIA, transient ischemic attack; SEE, systemic embolic embolism

Table 3.2.4.2: Base-case acute event mortality and mortality hazard ratios associated with a history of adverse event

Parameter	Base-case	Range		Distribution	Source
		Low Value	High Value		
Acute event mortality (%)					
Major hemorrhage	13.94	12.50	15.45	Beta (295, 1822)	Gomes *et al.* (2013) (27)
ICH	41.71	37.62	45.86	Beta (229, 320)	Gomes *et al.* (2013) (27)
Ischemic stroke	27.29	26.17	28.42	Beta (1639, 4367)	Tung *et al.* (2015) (28)
MI	28.40	27.58	29.23	Beta (3268.84, 8241.16)	Rathore *et al.* (2001) (41)
SEE	25.00	19.53	30.90	Beta (55.25, 165.75)	Bekwelem *et al.* (2015) (42)
Increased mortality (hazard ratios) for patients with a history of					
ICH	4.37	3.77	4.87	Normal (4.37, 0.28)	Sennfält *et al.* (2019) (34)*
Major IS	6.1	5.15	6.85	Normal (6.1, 0.43)	Fang *et al.* (2014) (35)*
Mild/moderate IS	2.76	2.1	3.48	Normal (2.76, 0.35)	
MI	2.23	1.17	3.44	Normal (2.23, 0.58)	Consuegra-Sanchez *et al.* (2016) (36)*
Major hemorrhage	1.2	0.87	1.6	Normal (1.2, 0.19)	(43)
TIA/SEE	1.48	1	2.33	LogNormal (0.39, 0.22)	Yousufuddin *et al.* (2018) (37)*
AF	1.15	1.02	1.33	Normal (1.15, 0.08)	Granger *et al.* (2011) (38)*

Beta distributions are parameterized as Beta (alpha, beta). Hazard ratios are parametrized as Normal (mean, standard error) or LogNormal as (ln(mean), ln(standard error)).

ICH, intracranial hemorrhage; IS, ischemic stroke; MI, myocardial infarction; TIA, transient ischemic attack; SEE, systemic embolic embolism

*Hazard ratios were calibrated to reach long-term mortality rates reported in sources.

The effects of history of previous events on future adverse events are presented in Table 3.2.4.3. Most of this data were obtained from a Swedish study on a cohort of 182,678 AF patients (44). The long-term risk of recurrent IS or MI among stroke or TIA survivals were obtained from a Canadian based study (45).

Table 3.2.4.3: Hazard ratios of effect of history of previous events on future adverse events. (95% Confidence interval) [(Reference)]

Risk Factor	ICH	Major hemorrhage	IS†	MI†	TIA/SEE
ICH	10.2 (8.59 to 12.2) [(44)]	2.95 (2.57 to 3.39) [(44)]	1.78 (1.56 to 2.03) [(44)]	0.85 (0.61 to 1.18) [(44)]	1.82 (1.62 to 2.04) [(44)]
Major hemorrhage	3.54 (3.02 to 4.17) [(44)]	3.32 (3.06 to 3.60) [(44)]	1.32 (1.21 to 1.44) [(44)]	1**	1.36 (1.26 to 1.46) [(44)]
IS (Major or mild/moderate)	1.64 (1.39 to 1.94) [(44)]	1.39 (1.27 to 1.52) [(44)]	8.2 (YR 1) (7.3 to 9.3) 5.9 (YR 2+) (5.4 to 6.4) [(45)]	1.8 (YR 1) (1.5 to 2.1) 1.6 (YR 2+) (1.5 to 1.8) [(45)]	3.61 (3.44 to 3.78) [(44)]
MI	0.94 (0.78 to 1.12) [(44)]	1.24 (1.15 to 1.35) [(44)]	1.24 (1.17 to 1.33) [(44)]	1.77 (1.15 to 2.39) [(46)]	1.29 (1.22 to 1.36) [(44)]
TIA/SEE	1.55 (1.2 to 2.0) [(44)]	1.27 (1.1 to 1.45) [(44)]	4.6 (YR 1) (3.9 to 5.4) 3.9 (YR 2+) (3.4 to 4.3) [(45)]	1.5(YR 1) (1.2 to 1.9) 1.6 (YR 2+) (1.4 to 1.8) [(45)]	2.34 (2.18 to 2.52) [(44)]

† Different rate ratios for Years 1 and 2+ are listed above

** Assumption because of limited evidence available in the published literature

Hazard ratios are parametrized as Normal (mean, standard error).

ICH, intracranial hemorrhage; IS, ischemic stroke; MI, myocardial infarction; TIA, transient ischemic attack; SEE, systemic embolic embolism

3.2.5 Cost inputs

Table 3.2.5.1 presented costs in 2017 CAD dollars using the Gross Domestic Product deflator. Treatment costs with drug and genotyping costs are presented in Table 3.2.5.2. Costs in foreign currency were adjusted to Canadian values using the Purchasing Power Parity (47,48).

Each month, the surviving individuals incurred the average age-specific baseline healthcare costs, which was obtained using the CIHI-Total Expenditure Per Capita data for the Ontario population (49). The baseline healthcare costs were not adjusted for potential double counting. But we do not expect double counting to have a significant impact because the proportion of average baseline healthcare costs attributable to AF and stroke is low since the prevalence of AF is relatively low in the general population.[6] We also varied baseline healthcare costs to investigate their impact on CEA results in one-way sensitivity analysis.

The average incremental cost attributable to AF was added to the baseline healthcare costs. This incremental cost included inpatient (hospitalization) and outpatient costs (emergency visit, physician visit, laboratory services and other outpatient services) related to causes other than modelled and non-cerebrovascular diseases in a cohort of AF patients (See Appendix A.6.2 for the details) (50). We did not include costs related to common cardiovascular outcomes that were modelled in our Markov model. Because this cost was obtained from a US-based study, we adjusted for percent inflation due to the US healthcare system. The percent US inflation was approximated by comparing the average healthcare expenditure accrued by a 71-year-old non-AF Canadian resident to 71-year-old non-AF US patients. The average annual cost of baseline health care was capped at $22,248.59 for patients who were 90 and older.

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[6] We investigated the proportion of baseline costs attributable to AF at age-specific prevalence of AF using prevalence data among 60+ year old participants in the Framingham study (75). The CIHI-Total Expenditure Per Capita is the sum of average non-AF and AF costs. In our sensitivity analysis, we found that AF-attributable costs made-up about only 1-5% of age-specific Total Expenditure Per Capita when we increased the AF-attributable costs by 40%.

3.2.5.1 Acute care costs

Patients who had an adverse event incurred a one-time treatment cost, including hospitalization and emergency visit costs, at the time of the event. The acute care costs for ICH and SEE was obtained from published studies and were estimated from the Ontario Case Costing Initiative (51,52). The hospitalization and ER visit costs for MI were obtained from published literature as well (53).

Acute care costs for major hemorrhage, major ischemic stroke and TIA were estimated using the ICES data (unpublished data). Using the ICES data, an Ontario population-based cohort of newly diagnosed AF patients >65 years of age initiating anticoagulation therapy with warfarin (n=794), apixaban (n=603) or rivaroxaban (n=534) for the first time between January 1st, 2012 to December 31st, 2017 were followed until March 31st, 2018, death, treatment discontinuation or treatment switch. Those patients who had hospitalization(s) or emergency room (ER) visit(s) for each adverse event were identified using the International Classification of Diseases and Disorders, 10th Revision (ICD-10), diagnostic codes from the Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD), and the National Ambulatory Care Reporting System (NACRS) database, respectively. Any repeated hospitalizations or ER visits within 30-days were included to obtain a comprehensive measure of healthcare resource use and event-specific treatment costs. We assumed that 30-day repeated admissions for the same diagnosis were related to the previous admission. The per patient acute hospitalization and ER visit costs were calculated by multiplying the year-specific resource intensity weights (RIW) with the cost per weighted case (CPWC) for DAD and NACRS, respectively, and adjusted for the consumer price index (CPI) for healthcare.[7] Fatal adverse events were identified as cases in which death occurred at ≤ 30 days. The average

[7] The RIWs are relative values that measure total patient resource use as compared to resource use during a typical hospitalization (1). The CPWC values include the inpatient portions of emergency, ambulatory and day surgical procedure costs as well as physician fees for admitting and discharging (1). The CPI values for healthcare were obtained from Statistics Canada (CANSIM Table No. 18-10-0005-01) (76).

per patient acute care cost for each adverse event and outcome at 30 days are presented in Table 3.2.5.1.

We assumed that the acute care cost of a mild/moderate ischemic stroke is the same as a non-fatal ischemic stroke. We also assumed that similar rehabilitative services (i.e., the number of appointments) will be accessed after a mild/moderate IS but for a shorter period. As such, we increased the acute care cost by a 3-month cost of ongoing care to adjust for the turning on and off of accrued costs for this acute event. This will slightly overcount the costs because all mild/moderate IS survivors will incur the rehabilitation cost at the time of the event.

In the face of limited published data on CRNMB costs, the acute care cost of CRNMB was estimated with expert input. At the time of a CRNMB, a patient may seek care from a family physician or a specialist. Since most patients have an ongoing relationship with their family physicians, a ratio of 3:1 was applied to reflect the interaction frequency with GP/FP to specialist. Using this information, the average fixed cost of an encounter with a healthcare professional was calculated. Based on published evidence, CRNMB events were divided into the following categories; hematuria (16.4%), epistaxis (14.8%) and non-major GI bleed (13.3%) (32). A low-end cost and high-end treatment cost for these different types of bleeds was developed using physician input on care services and the Ontario Schedule of Benefits for Physician Services (54). The base-case cost included the weighted average of low-end and high-end costs. In sensitivity analysis, we varied base-case costs by assuming all low-end costs or all high-end costs were accrued. The remaining proportion of CRNMB events, including haematoma and bruising/ecchymosis, consisted of the average fixed cost of an encounter with a healthcare professional. The cost components are presented in Appendix A – Table A.6.3.

3.2.5.2 Incremental care costs

The patients who survived an ICH, major hemorrhage, major ischemic stroke or MI incurred an incremental cost of ongoing care. The ongoing costs for IS and ICH were estimated from an Australian-based longitudinal study and included direct medical costs for aged facilities, community services, inpatient rehabilitation, general practitioner care,

hospitalizations for complications and other direct medical costs including specialist care, outpatient rehabilitation, emergency department care, private allied health, respite care, investigations, aids and modifications, ambulance transfers, and aged care assessment teams (55). The study reported the costs incurred in the first year of the event, 3-5 years after the event and 10-years after the event. We excluded the percent hospitalization cost from the modelled first-year cost. The study also reported an increase in the ongoing costs incurred from 3-5 years to 10-years but a closer look at cost components showed that aged care facilities primarily drove this increase. The aging costs were modelled using CIHI age-specific expenditure. As such, the 3-5 year average cost was modelled as the incremental cost for the IS and ICH health state from year 2 and onwards. Due to uncertainty introduced by differences in healthcare systems and time, we varied the incremental costs by 25% in sensitivity analysis.

The patients who survived a major hemorrhage incurred an incremental cost of long-term care for one year only. This cost was obtained from a Canadian-based study and included cost of transfer to a rehabilitation facility, transfer to an acute or chronic hospital care, hospitalization post discharge, long term care/nursing and home care, tests and procedures, outpatient visits, doctor visits/other health professionals and assistive devices or home renovations (56).[8]

We estimated the incremental cost associated with a history of MI based on a Canadian study reporting 3-year health care costs before and after MI (53). Medication costs as reported in source were excluded from all long-term costs and the cost of OAC treatment was added manually. Although, this removes the cost of non-OAC drugs, our analysis focuses on AF-related drug costs. We also removed any loss of productivity costs because our analysis captures only direct medical costs incurred by the public healthcare payer.

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[8] The source prospectively followed a cohort of patients in which 12% of participants were diagnosed with AF. The reported costs may include those related to ICH. However, most of the reported cost can be attributed to major hemorrhages other than ICH because ICH events are very rare (0.004%-0.002%) and have high case fatality (~42%).

Individuals who died from causes other than modelled incurred an average age-specific incremental cost of death. This cost was estimated as the difference between the average age-specific cost of living and cost in the year of death among a cohort of senior Ontario residents who died between 2010 and 2012 (57).

Table 3.2.5.1: Base-case estimates, ranges for sensitivity analysis and sources for cost inputs.

Parameter	Base-Case (2017 CAD)	Range		Distribution	Source
		Low Value	High Value		
Age-specific cost of death from other causes (annualized)					
65-69	63,345	56,377	81,082		(49,50,57)
70-74	62,041	55,217	79,413		
75-79	55,789	49,652	71,410		
80-84	53,211	47,358	68,110		
85-89	40,875	36,379	52,320		
90+	40,520	36,063	51,866		
Baseline age-specific health care expenditure for AF patients (annualized)					
65-69	9,869	8,783	12,632		CIHI-National Health Expenditure Trends (49)
70-74	11,173	9,944	14,301		
75-79	13,086	11,647	16,750		
80-84	15,664	13,941	20,050		
85-89	21,894	19,486	28,025		
90+	22,249	19,801	28,478		
Sensitivity analysis multiplier for baseline and non-event death costs					
	1	0.89	1.28	Gamma (2, 1)	
Incremental baseline health care costs (annual) associated with specific medical history					
ICH					
=<12 months	13,592	10,194	16,990	Normal (13,592, 1,734)	Gloede *et al.* (2014) (55)
>12 months	5,645	4,233	7,056	Normal (5,645, 720)	
Major IS					
=<12 months	19,702	14,776	24,627	Normal (19,702, 2,513)	Gloede *et al.* (2014) (55)

>12 months	4,282	3,211	5,352	Normal (4,282, 546)	
Major hemorrhage	6,712	5,034	8,390	Normal (6,712, 856)	Goeree *et al.* (2005) (56)
MI	242	213	271	Normal (242, 44)	Cohen *et al.* (2014) (53)
Acute adverse event costs (Fatal cases that result in death within 30 days of event)					
ICH	17651	8072	30914	Gamma (9, 1,961)	Micieli *et al.* (2016) (51)
CRNMB	164	144	183	Normal (164, 10)	Appendix A – Table A.6.3
SEE	11,605	7,510	16,576	Gamma (27, 430)	HQO-HTA Series (52)
MI					
Hospitalization	12,250	10,500	14,292	LogNormal (9.41, 0.08)	Cohen *et al.* (2014) (53)
Emergency visit	1,826	380	8,777	LogNormal (7.51, 0.80)	
Major hemorrhage					
Non-fatal	3,126	2,840	3,425	Gamma (439, 7)	Calculated from ICES databases
Fatal	4,424	2,770	6,457	Gamma (22, 202)	
Major IS					
Non-fatal	5,665	5,081	6,281	Gamma (343, 17)	Calculated from ICES databases
Fatal	7,683	6,199	9,323	Gamma (93, 83)	
TIA	1,412	1,175	1,671	Gamma (124, 11)	
Mild/moderate IS	10,591	5,629	15,552	Normal (10,591, 2,532)	*Calculated

*Sum of non-fatal Major IS and one-fourth of incremental cost after major IS

Gamma distributions are parameterized as Gamma (alpha, beta), normal distributions as Normal (mean, standard error) and lognormal distributions as LogNormal (ln(mean), ln(standard error)).

ICH, intracranial hemorrhage; IS, ischemic stroke; MI, myocardial infarction; CRNMB, clinically relevant non-major bleeding; TIA, transient ischemic attack; SEE, systemic embolic embolism; HQO-HTA, Health Quality Ontario Health Technology Assessment

The monthly medication costs included the cost of drug, pharmacy dispensing fee, physician fees and other relevant costs (Appendix A: Table A.6.4). The monthly drug costs of warfarin, apixaban and rivaroxaban were obtained from the ODB formulary by multiplying the unit costs with monthly dose regimes. The monthly therapy costs were calculated by multiplying the estimated healthcare resource use with unit costs. The healthcare resource use was quantified using clinical guidelines, published literature and expert opinion. The unit costs were obtained from the Ontario Schedule of Benefits for Physician Services, the Schedule of Benefits for Laboratory Services and the ODB formulary. Long-term drug therapy costs included the cost of general cardiologist consultation (billing code A605), general practitioner consultation (billing code A005) and drug supply. In addition, the cost of PT/INR lab testing (billing code L445), lab testing consultation fees (billing code G031) and long-term anticoagulation supervision via telephone (billing code G271) were included for warfarin therapy.[9]

The cost of genotyping test for four warfarin SNPs was obtained from the London Health Science Center – Personalized Medicine clinic. The cost estimate was the sum of fixed annualized cost of machinery (including DNA extraction equipment and software) and variable cost of technician and reagents. The base-case cost was estimated for the total number of patients tested at the clinic in one year (n=905). The estimated cost was varied with a minimum cost calculated under the maximally efficient scenario. Calculations for the number of patients tested in the maximally efficient scenario and for the hourly wage of the technician involved genotype testing over a period of fifty-two weeks, five full working days a week (n=13,000).

[9] The cost of INR monitoring is included for warfarin therapy. In comparison, the DOACs are direct inhibitors of the blood clot factor Xa and do not require INR/PT monitoring. As such, no INR/PT monitoring costs were included for DOAC therapies.

Table 3.2.5.2: Treatment costs (monthly)

Drug	Base-case	Range		Source
		Low	High	
Warfarin				
1st month	282	279	286	Appendix A – Table A.6.4
2-12 month	32	29	35	
>12 month	26	23	29	
Apixaban				
1st month	343	335	351	Appendix A – Table A.6.4
2-12 month	102	94	109	
>12 month	122	114	130	
Rivaroxaban				
1st month	331	325	337	Appendix A – Table A.6.4
2-12 month	82	77	88	
>12 month	110	104	116	
Aspirin	3			CADTH-HTA Series (58)
Genotyping test	84	24	500	Personalized Medicine Clinic-LHSC

LHSC, London Health Science Centre; CADTH-HTA, Canadian Agency for Drugs and Technologies in Health – Health Technology Assessment

3.2.6 Utilities

All quality-of-life inputs are presented in Table 3.2.6.1. Priority was given to Canadian studies using generic preference-based health utility measures from the literature. The utility values were weighted with the average time spent in corresponding health states to produce QALYs.

Each month, the surviving individuals incur the average age-specific health utility at baseline, which was estimated from the general Canadian population responding to the 2013-2014 Canadian Community Health Survey (CCHS) (59). The CCHS used the Health Utility Index III, a generic preference-based health utility measurement instrument, to examine 8 health attributes (i.e. vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain/discomfort) on 5 or 6 levels in the general population. The quality-of-life weights were lowered multiplicatively to account for long-term disability after an adverse event (ICH, IS and MI).

The health utility after a major IS and ICH was approximated to the 6-month utility reported for moderate stroke in the Oxford Vascular Study, a UK population-based study (60). The study assessed quality of life at one month, six months, 12 months and five years of follow-up using the EQ-5D (EuroQol-5 Dimensions) questionnaire among 73 to 75-year-old TIA or stroke patients. We chose to model the 6-month utility in our CEA because the value reflects the long-term disability after the event without reflecting the immediate severe effects. We assumed major IS utility for ICH patients because ICH patients have high case fatality. As such, the most severe ICH patients will result in immediate death and the lesser severe cases that survive will incur a utility close to major IS patients. We approximated the long-term decrement in quality of life to be the same for minor IS, MI and TIA patients.

At the time of an adverse event, patients experience an immediate and temporary decrement in health, which were captured as one-time disutility. The disutilities for non-fatal major IS or ICH and mild/moderate IS or MI were estimated as the difference in level of utility at three and six months after event (60). Disutilities are approximated as the area under the utility curve. In this case, we reduced the 3-month change in utility in half to approximate one-month disutility. Wang *et al.* (2017) reported change in EQ-5D utility after extracranial hemorrhage and CRNMB at event onset, 3 months, 6 months, 9 months and 12 months among patients with atrial fibrillation (61). We employed the same technique to estimate one-month disutility after a non-fatal major hemorrhage and CRNMB.

Table 3.2.6.1: Base-case estimates, ranges for sensitivity analysis and sources for quality-of-life inputs.

Parameter	Base-Case	Range		Distribution	Source
		Low	High		
Age-specific baseline health utilities (Annualized)					
60-64	0.842	0.674	1		Guertin *et al.* (2018) (59)
65-69	0.842	0.674	1		
70-74	0.835	0.668	1		
75-79	0.792	0.634	0.950		
80-84	0.741	0.593	0.889		
85+	0.640	0.512	0.768		
Health state utility weights for patients with history of					

ICH/Major IS	0.62	0.584	0.656		Luengo-Fernandez *et al.* (2013) (60)
Minor IS/MI	0.76	0.725	0.793		
Multiplier for sensitivity analysis					
	1	0.8	1.2	Normal (1, 0.10)	
Event-specific disutility (in the month it occurs)					
CRNMB	-0.005	-0.008	-0.002	Normal (-0.005, 0.0014)	Wang *et al.* (2017) (61)
Major Hemorrhage	-0.015	-0.022	-0.007	Normal (-0.0145, 0.0038)	
Stroke/ICH	-0.060	-0.065	-0.055	Normal (-0.06, 0.0026)	Luengo-Fernandez *et al.* (2013) (60)
Minor stroke/MI	-0.015	-0.020	-0.010	Normal (-0.015, 0.0026)	

3.2.7 Deterministic sensitivity Analysis

A deterministic sensitivity analysis (DSA) was performed to evaluate model sensitivity to input parameters. Ranges used in the DSA are listed in tables reporting base-case inputs. The ranges were derived from 95% confidence intervals reported in source material. In some cases, there were no 95% confidence intervals or standard errors reported. For rare-event count data, we estimated ranges by varying the number of events by assuming one more event or one less event. For rates, we estimated ranges by deriving a standard error around the mean (assuming a Poisson distribution). In other cases, we estimated ranges based on variation observed across published literature. For example, we estimated drug cost ranges by comparing ODB unit costs to the British Columbia formulary.

We varied baseline costs and non-event cost of death using a single multiplier in order to impose correlation between the values. The multiplier was parameterized using a gamma distribution with a mean of 1 (alpha=2, beta=1) and evaluated the area under the curve at 25^{th} and 97.5^{th} percentile to provide values for the deterministic sensitivity analysis.

3.2.8 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed using Monte Carlo simulation technique with 3000 replications. Distributions were specified using the reported means and 95% confidence intervals, standard errors or other distribution parameters obtained

from sources. When the statistical analysis used in the primary analysis assumed a Normal distribution around the estimated mean or the 95% confidence interval provided was relatively symmetric around the mean, we used normal distributions to capture uncertainty around the mean estimates. Uncertainty around the mean is often normally distributed by the Central Limit Theorem. If the confidence interval was not symmetric, we transformed data on the LogNormal scale to test if we satisfy the normality assumption and used a LogNormal distribution. We used beta and gamma distributions for proportions and skewed costs, respectively.

3.2.9 Model validation

Formal internal validation was conducted by testing the mathematical logic of the model, verifying equations for the first 10 stages in the full Markov trace and comparing extreme input values with expected results as a quality assurance measure of coding and model development. We confirmed the 5-year background mortality rate as predicted from the model (~11%) with expected mortality rate (~12%) from the Canadian life table.

Model validation was also conducted by populating model with data parameters found in published studies. When we populated our model with data parameters used by Shah *et al.* (2016), patients under apixaban lived an average of 9.96 QALYs (9.38 QALYs in the original study), 9.68 QALYs under rivaroxaban (9.24 QALYs in the original study) and 9.52 QALYs (9.02 QALYs in the original study) under standard warfarin care (62). The differences in results can be attributed to some structural differences between our model and published models. Shah *et al.* (2016) assumed death after 2 major events and transition to a severe health state after 2 minor neurological events. In contrast, our model predicts patients reach a worse-off health state upon experiencing an adverse event more severe than present history. Patients remain in the more severe health until death or the next event worse in magnitude. As such, patients in our model live slightly longer because we did not assume death for these patients after 2 major events.

The average LYs and QALYs accrued under warfarin care and apixaban in our model are similar to those reported in published literature. In our model, patients had an average life expectancy of 78.46 years under warfarin, 78.75 years under rivaroxaban and 78.93 years

under apixaban. When adjusted for quality of life, patients had an average life expectancy of 75.59 years under warfarin, 75.82 under rivaroxaban and 75.96 years under apixaban. Similarly, in the CEA by Dilokthornsakul *et al.* (2019), patients had an average life expectancy of 77.28 years under warfarin, 77.49 years under rivaroxaban and 77.75 years under apixaban for a cohort of 68-year-old Thai AF patients (and the study used most of the same effectiveness parameters as our model) (10). When adjusted for quality of life, patients had an average life expectancy of 74.98 years under warfarin, 75.20 years under rivaroxaban and 75.42 years under apixaban. Shah *et al.* (2016) also reported an average life expectancy of 78.02 QALYs for patients under warfarin, 78.24 QALYs under rivaroxaban and 78.38 years under apixaban for a cohort of 69-years-old AF US patients (unadjusted life expectancy not reported in study) (62).

3.3 Results

3.3.1 Base-case Analysis

In our model, the cohort of 65-year-old AF patients lived an additional 13.46 years under standard warfarin care, 13.50 years under PGx-based warfarin care, 13.75 years under rivaroxaban and 13.93 years under apixaban. When adjusted for quality of life, AF patients accrued an additional 10.59 QALYs under standard warfarin care, 10.63 QALYs under PGx-based warfarin care, 10.82 QALYs under rivaroxaban and 10.96 QALYs under apixaban (all discounted). Over the lifetime horizon, patients accrued about $217,977 under standard warfarin care, $218,560 under PGx-based warfarin care, $235,537 under rivaroxaban and $240,351 under apixaban (all discounted) (Table 3.3.1).

Two comparisons of the base-case results are reported. First, PGx-based warfarin care, apixaban and rivaroxaban, were compared to the reference treatment strategy of standard warfarin care. Second, all OAC treatment strategies were ranked in terms of increasing effectiveness and sequential comparisons were made. Standard warfarin care was ranked the lowest in effectiveness because it produced the least number of QALYs and life-years, while apixaban was ranked the highest in effectiveness because it produced the highest QALYs and life-years.

Table 3.3.1: Number of acute events per cohort of 10,000 patients aged 65 years accrued over 5 years, average life expectancy, average lifetime discounted costs and QALYs, and ICER for alternative oral anticoagulation treatments in AF patients from the public healthcare payer perspective.

Outcomes	Strategy			
	Standard warfarin	**PGx-based warfarin**	**Rivaroxaban**	**Apixaban**
Time horizon – 5 years				
IS, n	1,034	1,034	949	926
ICH, n	111	109	72	50
Major hemorrhage, n	916	752	937	650
CRNMB, n	2,890	2,722	3,016	2,010
MI, n	397	398	314	343
TIA, n	1,456	1,454	1,455	1,453
SEE, n	54	54	51	35
Time horizon – lifetime				
Average life expectancy, yrs	13.46	13.50	13.75	13.93
Average lifetime costs (discounted), $	217,977	218,560	235,537	240,351
Average lifetime QALYs (discounted)	10.59	10.63	10.82	10.96
Comparison to standard warfarin				
Incremental costs, $	Reference	583	17,560	22,373
Incremental QALYs, (months)	Reference	0.03 (0.36 months)	0.23 (2.76 months)	0.37 (4.44 months)
ICER ($/QALY gained)	Reference	$17,727	$78,020	$60,649
Excluding dominated				
Incremental costs, $	Reference	583	N/A	21,790
Incremental QALYs, units (months)	Reference	0.03 (0.36 months)	N/A	0.34 (4.08 months)
ICER ($/QALY gained)	Reference	17,727	Ext. Dominated	64,853

ICER, incremental cost-effectiveness ratio; PGx, Pharmacogenomics; Ext, Extended; ICH, intracranial hemorrhage; IS, ischemic stroke; MI, myocardial infarction; CRNMB, clinically relevant non-major bleeding; TIA, transient ischemic attack; SEE, systemic embolic embolism.

3.3.1.1 Comparison to standard warfarin care

Patients under standard warfarin care had the shortest life expectancy. In a cohort of 10,000 patients, there were approximately 1,034 ischemic strokes, 111 ICHs, 916 major hemorrhages and 2,890 CRNMB events within 5 years of initiating standard warfarin therapy (Table 3.3.1). PGx-based warfarin care was slightly more effective and costlier than standard warfarin. Patients accrued an additional 0.25 years (3 months), 0.03 QALYs (~11 days) and $583 under PGx-based warfarin care as compared to standard warfarin care. In a cohort of 10,000 patients, there were approximately 1,034 ischemic strokes, 109 ICHs, 752 major hemorrhages and 2,722 CRNMB events within 5 years of initiating PGx-based warfarin therapy. Overall, there were 2 fewer ICHs, 164 fewer major hemorrhages and 167 fewer CRNMB events under PGx-based warfarin care as compared to standard warfarin care. Over the lifetime horizon, the incremental cost per QALY gained under PGx-based warfarin was $17,727/QALY.

As compared to standard warfarin care, treatment with DOACs was more effective but also more expensive. Apixaban and rivaroxaban increased costs by about $22,373 and $17,560, respectively. In terms of effectiveness, apixaban and rivaroxaban increased QALYs by about 0.37 units (~4.44 months) and 0.23 units (~2.76 months), respectively. In a cohort of 10,000 patients, there were approximately 926 ischemic strokes, 50 ICHs, 650 major hemorrhages and 2,010 CRNMB events within 5 years under apixaban. As compared to standard warfarin, there were 108 fewer ischemic strokes, 61 fewer ICHs, 266 fewer major hemorrhages and 880 fewer CRNMB events under apixaban. If the cohort of 10,000 patients started treatment with rivaroxaban, there were 85 fewer strokes and 39 fewer ICHs as compared to standard warfarin. However, there were 20 additional major hemorrhages and 125 additional CRNMB events within 5 years of initiating rivaroxaban treatment as compared to standard warfarin. The incremental cost per QALY gained under apixaban and rivaroxaban was $60,649/QALY gained and $78,020/QALY, respectively.

3.3.1.2 Excluding dominated strategy

When treatments were ranked in order of increasing effectiveness, rivaroxaban was dominated by the principle of extended dominance (Figure 3.3.1).[10] The undominated strategies, in order of increasing effectiveness and costs, were standard warfarin care, PGx-based warfarin care and apixaban. Apixaban increased lifetime costs by $21,790 and QALYs by 0.34 units (~4.08 months) as compared to PGx-based warfarin care. It costed about $64,853 to gain one additional QALY under apixaban as compared to PGx-based warfarin.

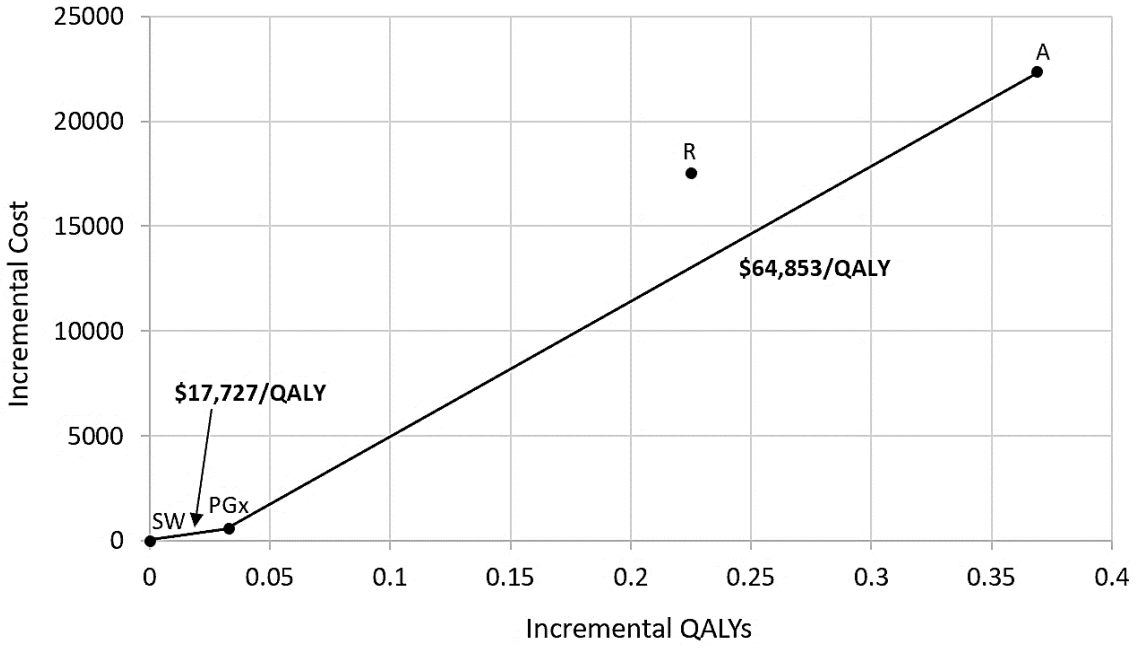

Figure 3.3.1: Cost-effectiveness plane. Incremental costs and QALYs comparing alternative oral anticoagulation treatments with standard warfarin care.
SW, standard warfarin; PGx, Pharmacogenomics (PGx)-based warfarin; R, rivaroxaban; A, apixaban; QALY, quality-adjusted life-years

[10] A strategy is dominated by the principle of extended dominance if it costs more and provides fewer QALYs than a linear combination of two other alternatives.

3.3.2 Deterministic Sensitivity Analysis Results

The results of the deterministic sensitivity analysis are presented in Table 3.3.2.

Table 3.3.2: Incremental cost-effectiveness ratio ($/QALY gained) of alternative oral anticoagulation strategies as compared to standard warfarin care.

	PGx-based warfarin	**Rivaroxaban**	**Apixaban**
Base-case	17,727	Ext. Dominated	64,853
Discounting			
0%	19,136	Ext. Dominated	62,829
3%	16,439	Ext. Dominated	67,214
Patient Characteristics			
Age (yrs) at initiating OAC treatment			
70	20,492	Ext. Dominated	76,547
75	24,343	Ext. Dominated	92,659
80	29,562	Ext. Dominated	114,187
85	35,614	Ext. Dominated	139,700
Baseline Health			
Substantially above-average health (Baseline utilities increased by 20%, costs decreased by 10%, event rates decreased by 50%*)	15,981	Ext. Dominated	98,024
Above-average health (Baseline utilities increased by 10%, costs decreased by 5%, below-average event rates**)	16,337	Ext. Dominated	72,946
Below-average health (Baseline utilities decreased by 10%, costs increased by 10%, above-average event rates**)	19,893	Ext. Dominated	55,287
Substantially below-average health (Baseline utilities decreased by 20%, costs increased by 28%, event rates doubled*)	24,872	Ext. Dominated	58,262
Medical history (History of an adverse event)			
Hx of ICH	34,316	Ext. Dominated	70,002
Hx of major ischemic stroke	37,994	Ext. Dominated	97,332
Hx of minor ischemic stroke	23,762	Ext. Dominated	59,103
Hx of myocardial infarction	22,696	Ext. Dominated	50,931
Hx of TIA/SEE	22,565	Ext. Dominated	80,541

Hx of major hemorrhage	15,430	Ext. Dominated	47,347
Risks and treatment effectiveness			
Treatment difference between PGx-based warfarin and standard warfarin (Base-case=6 months)			
3 months	19,057	Ext. Dominated	63,782
12 months	16,748	Ext. Dominated	67,084
Low OAC effectiveness (HRs=95% CI upper bounds)			
PGx-based warfarin	***	Ext. Dominated	46,257 (ICER- compared to Standard warfarin)
Rivaroxaban	17,727	Dominated by PGx-based warfarin	64,853
Apixaban	17,727	88,344	Dominated by PGx-based warfarin
High OAC effectiveness (HRs=95% CI lower bounds)			
PGx-based warfarin	16,949	Ext. Dominated	76,727
Rivaroxaban	17,727	42,210.38	Ext. Dominated
Apixaban	17,727	Ext. Dominated	41,240
Patient susceptibility to adverse events			
Higher than average (Upper ranges of event rates, future risks and non-event death)	17,694	Ext. Dominated	58,382
Lower than average (lower ranges of event rates, future risks and non-event death)	17,083	Ext. Dominated	74,933
Costs			
Baseline costs			
11% lower	15,557	Ext. Dominated	62,263
28% higher	23,250	Ext. Dominated	71,445
PGx test cost (Base-case=$84.00)			
24.05	15,812	Ext. Dominated	65,040
145	19,489	Ext. Dominated	64,680
200	21,161	Ext. Dominated	64,517
500	30,279	Ext. Dominated	63,623
1000	45,475	Ext. Dominated	62,136
PGx-test in patients with high baseline costs (increased by 28%)			
Low PGx test cost ($24)	21,335	Ext. Dominated	71,632
High PGx test cost ($145)	25,013	Ext. Dominated	71,272
Low apixaban cost (1st month=$335, 2nd – 12th month=$94, 12+ months=$114) vs. PGx test cost			
Low PGx test cost ($24)	15,812	Ext. Dominated	61,140
High PGx test cost ($145)	19,489	Ext. Dominated	60,780
High acute and ongoing costs (upper ranges) for patients with a medical history of			
ICH	37,200	Ext. Dominated	66,843
Major IS	40,379	Ext. Dominated	99,069

MI	22,850	Ext. Dominated	50,590
Utilities			
Baseline utilities			
10% lower	22,109	Ext. Dominated	80,865
20% lower	19,677	Ext. Dominated	71,979
Low health utilities (lower ranges) for patients with a medical history of			
Major hemorrhage	16,522	Ext. Dominated	51,924
Major IS	40,282	Ext. Dominated	104,878
MI	22,751	Ext. Dominated	50,758
PGx-test in patients with low baseline health utilities (decreased by 10%)			
Low PGx test cost ($24.05)	17,551	Ext. Dominated	72,187
High PGx test cost ($145.00)	21,633	Ext. Dominated	71,788

*The event rates were varied based on risks observed by patients on different $CHADS_2$ scores in the literature.[11]
**Above average event rates were the average of base rates and doubled rates. Below-average were the average of base rates and rates reduced in half.
***Standard warfarin accrues higher costs and QALYs than PGx-based warfarin at an ICER of $10,024/QALY.

The CEA results were sensitive to patient characteristics (Table 3.3.2). In particular, the results were highly sensitive to start age. As the OAC therapy starting age increased, the lifetime accrued costs and QALYs decreased across all OAC strategies and the differences between strategies decreased. As a result, the ICER values increased among the undominated strategies (standard warfarin, PGx-based warfarin and apixaban). The ICER values increased more sharply for apixaban as compared to PGx-based warfarin (Figure 3.3.2.1). Apixaban reached a maximum ICER of $139,700/QALY gained and PGx-based warfarin reached a maximum ICER of $35,614/QALY if start age of OAC therapy was 85 years.

There is heterogeneity in the baseline health of 65-year-old AF patients based on comorbidities that are not explicitly accounted for in the model. We explored the 'healthy' and 'less healthy' individuals by simultaneously varying their baseline

[11] The base-case rate of ischemic stroke was almost double the event rate reported for patients with a $CHADS_2$ score of 2 and half the event rate reported for patients with a $CHADS_2$ score of 4&6 (62). As such, we doubled or reduced in half the event rates to explore the impact of patients with substantially-below or -above average baseline health on ICERs in sensitivity analysis. Please note our analysis did not include $CHADS_2$ score directly in the Markov model.

healthcare costs, baseline utilities, and baseline event rates. For a cohort of healthier than average 65-year old patients, a group with lower than average baseline costs and event rates and higher than average baseline utilities, we found the ICER for PGx-based warfarin compared to standard warfarin decreased from $17,727/QALY to $16,337/QALY and the ICER of apixaban compared to PGx-guided warfarin increased from $64,853/QALY to $72,946/QALY. For slightly below-average healthy individuals, ICER for PGx-based warfarin compared to standard warfarin increased from $17,727/QALY to $19,893/QALY and the ICER of apixaban compared to PGx-guided warfarin decreased from $64,853/QALY to $55,287/QALY. When we considered a more extreme scenario in which baseline health care costs were increased by 28%, baseline utilities were decreased by 20%, and baseline risks of adverse events were doubled, we found that among substantially below-average healthy patients, the ICER of apixaban increased again. This scenario corroborates what was seen in the sensitivity analysis on starting age of OAC initiation. With higher rates of competing mortality, which results in smaller incremental benefits, more expensive treatment corresponds to higher ICERs.

We approximated higher patient susceptibility to adverse events by assuming higher event rates, risk of future adverse events and non-event death. In this scenario, the cost per QALY gained decreased to $58,382 under apixaban as compared to PGx-based warfarin. In contrast, when lower patient susceptibility was assumed, the cost per QALY increased to $74,933 under apixaban as compared to PGx-based warfarin. The ICER value for PGx-based warfarin was not very influenced by patient susceptibility and remained around $17,000/QALY gained.

The CEA results were sensitive to patient medical history of adverse events. The ICERs increased by a large magnitude for patients who had a history of major ischemic stroke, ICH and TIA/SEE. For these patients, it costed more to gain one additional QALY under PGx-based warfarin and apixaban as compared to the average person in base-case. For patients who had a history of minor ischemic stroke and myocardial infarction, the ICERs increased for PGx-based warfarin and decreased under apixaban treatment. For these patients, it costed more to gain one additional QALY under PGx-based warfarin and less to gain one additional QALY under apixaban as compared to base-case. For patients with

a history of major hemorrhage, it costed less to gain one additional QALY as compared to what it costed in the base-case under both PGx-based warfarin and apixaban.

The general trend was that ICERs increased with age for all medical histories. The ICERs increased sharply for older apixaban patients with a history of major IS, ICH and TIA/SEE as compared to PGx-based warfarin (Figure 3.3.2.3).

The results were very sensitive to treatment effectiveness of PGx-based warfarin care. When low effectiveness of PGx-based warfarin was assumed (i.e. it was less effective than standard warfarin care), patients under standard warfarin accrued higher costs and QALYs. It costed about $10,024 to gain one additional QALY under standard warfarin as compared to PGx-based warfarin. The lower effectiveness of PGx-based warfarin was due to increased risk of major hemorrhage and CRNMB events during the first six-months of OAC therapy. Assuming lower effectiveness of PGx-based warfarin also decreased the ICER for apixaban and it costed about $46,257 to gain one additional QALY under apixaban treatment as compared to standard warfarin. When high PGx-based warfarin effectiveness was assumed, patients under PGx-based accrued higher costs and QALYs than standard warfarin. It costed about $16,949 to gain one additional QALY under PGx-based warfarin as compared to standard warfarin care. The ICER for apixaban increased and it costed about $76,728 to gain one additional QALY under apixaban as compared to standard warfarin.

In the base-case analysis, rivaroxaban was ruled out through the principle of extended dominance. Although it decreased the risk of IS and ICH, patients experienced higher risks of major hemorrhage and CRNMB under rivaroxaban as compared to standard warfarin. When low rivaroxaban effectiveness was assumed and patients experienced increased risk of all adverse events, patients accrued higher costs and lower QALYs, and rivaroxaban was absolutely dominated by PGx-based warfarin. In contrast, when higher-than-average rivaroxaban effectiveness was assumed, rivaroxaban dominated apixaban through the principle of extended dominance and it costed about $42,210 to gain one additional QALY under rivaroxaban as compared to PGx-based warfarin.

When lower apixaban effectiveness was assumed, PGx-based warfarin dominated apixaban and rivaroxaban also became an undominated option. Under this scenario, it costed about $88,344 to gain one additional QALY under rivaroxaban as compared to PGx-based warfarin. In contrast, when high apixaban effectiveness was assumed, the cost to gain one additional QALY decreased to $41,240 under apixaban as compared to PGx-based warfarin.

In the base-case scenario, we assumed a six-month treatment difference between PGx-based warfarin and standard warfarin. We assumed that more INR measurements and dose adjustments under standard warfarin will diminish the added benefit of PGx-based warfarin care. We investigated the impact of this assumption on the CEA results. We found that the ICER value for PGx-based warfarin increased to $19,057/QALY gained if treatment difference was reduced to 3 months. Consequently, the ICER value for apixaban decreased to $63,782/QALY gained. On the other hand, the ICER value for PGx-based warfarin decreased to $16,748/QALY gained if treatment difference was increased to 12 months. Consequently, the ICER value for apixaban increased to $67,084/QALY gained.

The cost of PGx test influenced the ICER values for PGx-based warfarin. Under the assumption of maximally efficient scenario, we calculated a cost of $24.05 per PGx test at the Personalized Medicine Clinic at LHSC. In this scenario, the cost to gain one additional QALY decreased to $15,812 under PGx-based warfarin as compared to standard warfarin. However, the ICER values increased as PGx test cost increased. The cost to gain one additional QALY increased to $45,475 if PGx test cost was increased to $1,000 per patient. Rivaroxaban was ruled out by principle of dominance and the ICER for apixaban did not change by a large magnitude across all PGx-test costs. The general trend was that the ICER for PGx-based warfarin as compared to standard warfarin increased sharply and ICER for apixaban as compared to PGx-based warfarin decreased gradually as PGx test prices increased. The increasing PGx test prices did not affect the clinical effectiveness of treatments and therefore, the ranking of strategies. Patients under apixaban accrued higher QALYs than PGx-based warfarin and patients under PGx-based warfarin accrued higher QALYs than standard warfarin. Higher PGx-test prices increased

the lifetime costs, incremental costs and ICERs under PGx-based warfarin as compared to standard warfarin care. However, PGx test prices did not affect the lifetime costs accrued under apixaban as compared to PGx-based warfarin. As such, the ICERs for apixaban as compared to PGx-based warfarin gradually decreased as PGx test prices increased. The incremental cost per QALY gained under PGx-based warfarin as compared to standard warfarin surpassed the ICER under apixaban as compared to PGx-based warfarin at a genotype test price of $1,500/patient or higher (Figure 3.3.2.4).

We investigated the impact of baseline costs alone and found that the CEA results were sensitive to baseline costs. We found that the ICER for PGx-based therapy decreased to $15,557/QALY gained if we reduced baseline costs by 11% and increased to $23,250/QALY gained if we increased baseline costs by 28%. Similarly, the ICER for apixaban decreased to $62,263/QALY gained if we reduced baseline costs by 11% and increased to $71,445/QALY gained if we increased baseline costs by 28%.

We investigated the sensitivity of CEA results to PGx-test cost and baseline costs. In patients with higher baseline costs, the ICER values increased to $21,335/QALY gained if we assumed low PGx-test cost of $24 under the maximally efficient scenario and to $25,013/QALY gained if we assumed higher-end PGX-test cost of $145 per patient. Generally, the ICER values increased as baseline costs and PGx-test costs increased.

The CEA results were sensitive to acute and ongoing costs for patients with a medical history of ICH, major IS and MI. For these patients, the ICERs increased and it costed more to gain one additional QALY under both PGx-based warfarin and apixaban as compared to base case. However, for patients with a history of MI, it costed less to gain one additional QALY under apixaban as compared to base case.

The CEA results were sensitive to baseline utilities. It generally costed more to gain one additional QALY if baseline utilities were lowered. The ICER increased to $19,677/QALY if baseline utilities were lowered by 10% and $22,109/QALY if baseline utilities were lowered by 20% under PGx-based therapy. The ICER increased to $71,979/QALY if baseline utilities were lowered by 10% and $80,865/QALY if baseline utilities were lowered by 20% under apixaban. In patients with 10% lower baseline

health utility, the cost to gain one additional QALY decreased to $17,551 at low-end PGx test cost and increased to $21,633 at high-end PGx test cost.

The ICERs increased to $40,282/QALY gained under PGx-based warfarin and to $104,878/QALY gained under apixaban for patients with a major IS and accruing low-end health state utilities after an adverse event as compared to base case. In comparison, the ICERs decreased to $16,522/QALY gained under PGx-based warfarin and to $51,924/QALY gained under apixaban for patients with a history of major hemorrhage and accruing low-end health state utilities after an adverse event as compared to base case. For patients with a history of MI, the cost to gain one additional QALY increased to $22,751 under PGx-based warfarin and decreased to $50,758 under apixaban.

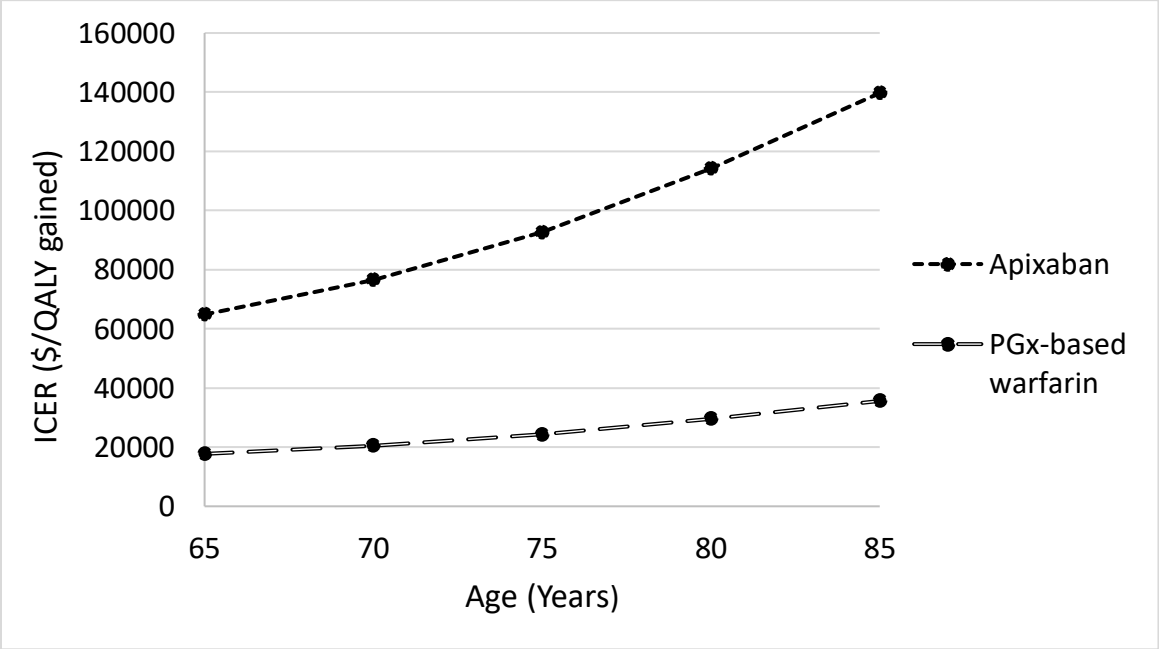

Figure 3.3.2.1: ICER indicates the cost to gain one additional QALY under apixaban as compared to PGx-based warfarin and under PGx-based warfarin as compared to standard warfarin care at different OAC therapy starting ages.
QALY, quality-adjusted life-years; PGx, Pharmacogenomics; OAC, oral anticoagulation

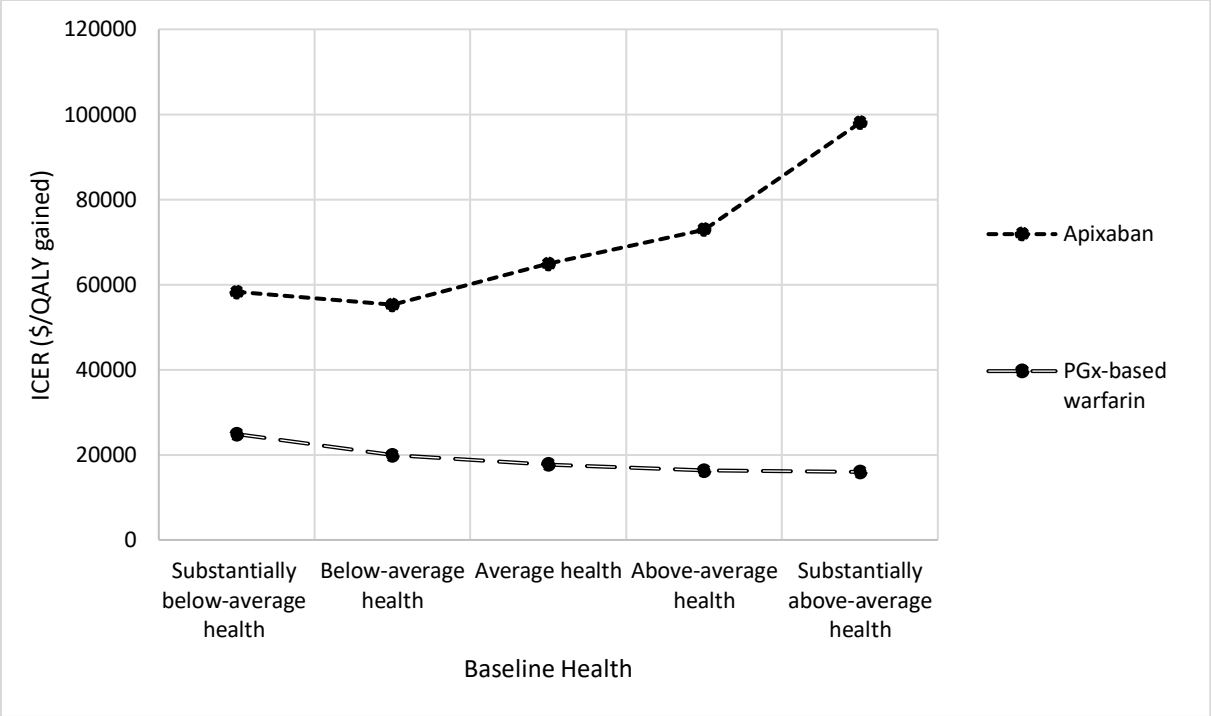

Figure 3.3.2.2: ICER indicates the cost to gain one additional QALY at different baseline health status under apixaban as compared to PGx-based warfarin and under PGx-based warfarin as compared to standard warfarin care.
QALY, quality-adjusted life-years; PGx, Pharmacogenomics

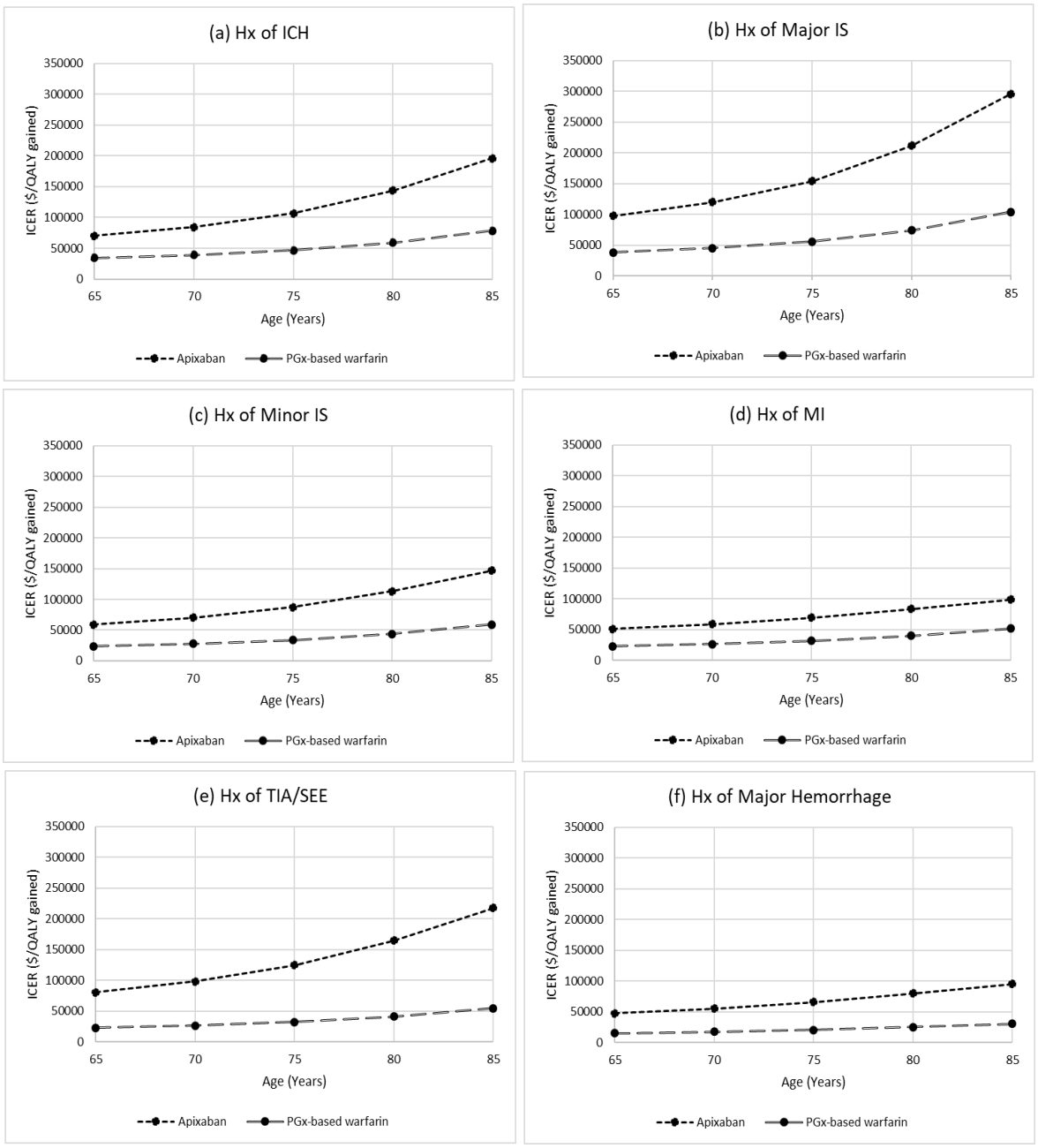

Figure 3.3.2.3: ICER indicates the cost to gain one additional QALY for patients with a history of adverse event and across different ages.
Dotted line represents ICERs under apixaban as compared to PGx-based warfarin and dashed line represents ICERs under PGx-based warfarin as compared to standard warfarin care.
Hx, history; ICH, intracranial hemorrhage; IS, ischemic stroke; MI, myocardial infarction; TIA, transient ischemic attack; SEE, systemic embolic events; QALY, quality-adjusted life-years; PGx, Pharmacogenomics

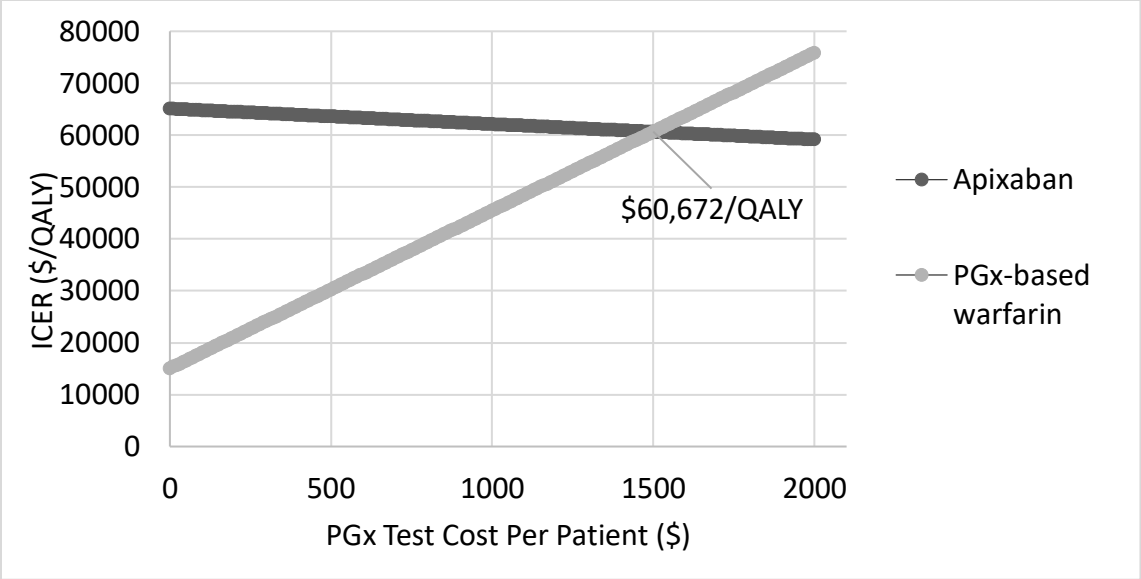

Figure 3.3.2.4: ICERs of apixaban as compared to PGx-based warfarin and ICERs of PGx-based warfarin as compared to standard warfarin care across increasing PGx test prices.
QALY, quality-adjusted life-years; PGx, Pharmacogenomics

3.3.3 Probabilistic Sensitivity Analysis Results

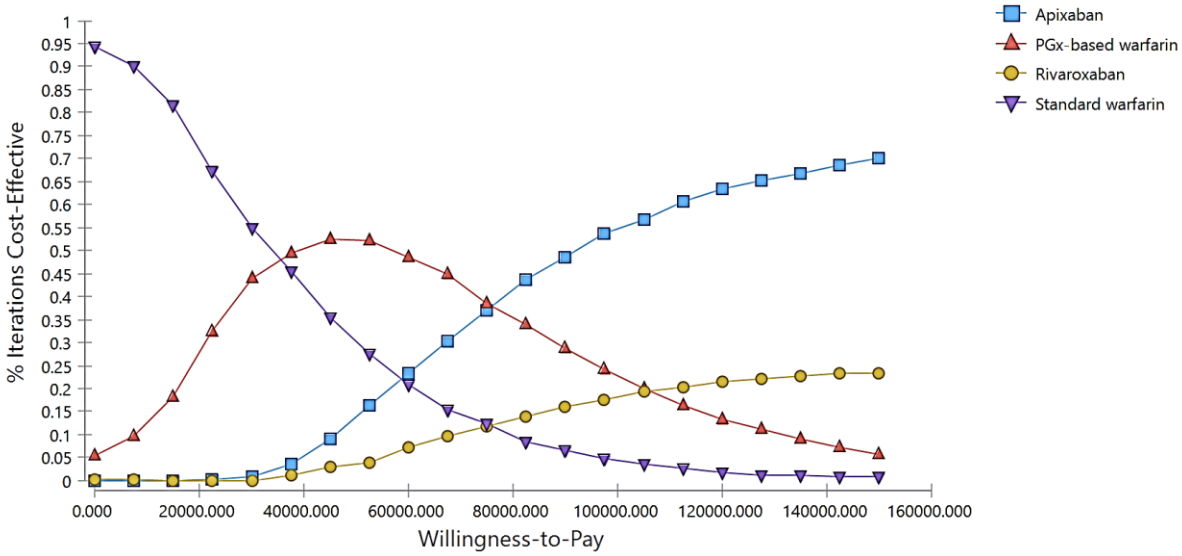

Figure 3.3.3.1: Cost-effectiveness acceptability curves (the percent of iterations in which each treatment strategy is a cost-effective option at various WTP) thresholds).

The probabilistic sensitivity analysis (PSA) results were summarized using cost-effectiveness acceptability curves in Figure 3.3.3.1. The results showed that all four treatment strategies were potentially cost-effective at some percentage of the time across the range of WTP values. At the WTP threshold of $50,000/QALY gained, PGx-based warfarin was the cost-effective treatment in 51.5% of the iterations, followed by standard warfarin in 30.7% of iterations, apixaban in 14.1% of iterations and rivaroxaban in about 3.7% of iterations. At the WTP threshold of $100,000/QALY gained, apixaban was the cost-effective treatment in 54.7% of the iterations, followed by PGx-based warfarin in 22.8% of iterations, rivaroxaban in 18% of iterations and standard warfarin in about 4.5% of iterations. At the WTP threshold of $150,000/QALY gained, apixaban was the cost-effective treatment in 70.1% of the replications, rivaroxaban in 23.3% of iterations, PGx-based warfarin care in 5.7% of iterations and standard warfarin care in only 0.9% of iterations.

We investigated the robustness of PSA results to patient age and medical histories. The ranking of OAC strategies at the WTP threshold of $150,000/QALY did not change when patients started OAC treatment at an older age or had a history of major IS, minor IS or TIA/SEE (Appendix B: Supplementary PSA Results).

3.4 Discussion

Our CEA results indicate that PGx-based warfarin care, apixaban and rivaroxaban improve the health of AF patients by reducing the risk of ischemic strokes and major or intracranial bleeding as compared to standard warfarin. However, alternative OAC strategies also increase lifetime costs when compared to standard warfarin. Both PGx-based warfarin and apixaban lie on the cost-effectiveness frontier and can be cost-effective at some willingness-to-pay (WTP) thresholds. However, rivaroxaban lies above the cost-effectiveness frontier. Clinical trial data have shown that rivaroxaban increases the risk of major and clinically relevant non-major bleeding as compared to standard warfarin. As such, rivaroxaban is dominated by apixaban through extended dominance.

3.4.1 Apixaban and rivaroxaban versus standard warfarin care

Our findings indicate that the DOACs are more effective and expensive than standard warfarin care. In the base-case analysis, 65-year old AF patients accrued an average of 10.59 QALYs under standard warfarin, 10.82 QALYs under rivaroxaban and 10.96 QALYs under apixaban. Rivaroxaban increased QALYs by 0.23 units (~2.76 months) and costs by $17,560. In comparison, apixaban increased QALYs by 0.37 units (~4.44 months) and costs by $22,374. It costed about $78,020 to gain one additional QALY if all AF patients in our hypothetical cohort were treated with rivaroxaban as compared to standard warfarin. In comparison, it costed about $60,649 to gain one additional QALY if all AF patients in our hypothetical cohort were treated with apixaban as compared to standard warfarin.

Our results on the cost-effectiveness of DOACs versus standard warfarin care are consistent with findings in the published literature. Several studies have found the DOACs to be more costly and more effective as compared to standard warfarin care in the context of Canada, US, France and UK (16,24,62–65). Coyle *et al*. (2013) found that AF patients in Canada accrued higher QALYs under the DOACs as compared to standard warfarin. In their study, patients had an average gain of 6.48 QALYs under standard warfarin, 6.62 QALYs under apixaban and 6.54 QALYs under rivaroxaban. The lower lifetime QALYs in their study as compared to our study can be explained by differences in the age of target population. As the starting age of OAC treatment increased, the lifetime and incremental QALYs decreased in our one-way sensitivity analysis. The target population in our CEA is younger than in most published CEAs, which may explain the higher QALYs accrued in our CEA. In the Coyle *et al*. (2013) study, the target population had an average age of 72 years. In comparison, the target population in our CEA had an average age of 65 years, which is the age at which OAC treatments are funded by the MOHLTC under the ODB formulary. On average, the AF patients had a life expectancy of 75 years in our CEA and 78 years in the Coyle *et al*. (2013) study. Among the DOACs, apixaban treatment led to highest QALYs when compared to standard warfarin both in our and published studies.

The lifetime costs and incremental cost estimates in our analysis are higher than previously reported estimates (15,16,62). Our CEA includes the average age-specific healthcare costs at baseline incurred by Ontario patients with AF and non-event death costs. Stroke prevention through OAC treatments shifts the cause of death from cardiovascular diseases (such as ischemic stroke) to other age-specific causes (40). Other studies understate the costs attributable to life-extending interventions by assuming low baseline healthcare costs and making non-event death free of cost. Our CEA captures the cost of extended life expectancy and death from causes other than modelled.

3.4.2 PGx-based warfarin versus standard warfarin care

To date, published studies on the cost-effectiveness of PGx-based warfarin therapy compared to standard warfarin have produced conflicting results; three studies found PGx-based warfarin care was cost-effective, five found PGx-based warfarin care was not cost-effective and four were inconclusive (66). Although PGx-based warfarin care has been found to be cost-effective in the context of Sweden and the UK, a previous Canadian study found that PGx-based warfarin care led to large increase in costs and small increase in QALYs (15,65). Nshimyumukiza *et al.* (2013) found that PGx-based warfarin increased costs by $460 and QALYs by only 0.0085 units (~3 days). With an ICER of $54,118/QALY gained, the authors concluded PGx-based warfarin was not cost-effective as compared to standard warfarin care at a WTP threshold of $50,000/QALY. In comparison, our study found that PGx-based warfarin increased costs by $583 and QALYs by 0.03 units (~11 days). It costed about $17,727/QALY gained under PGx-based warfarin as compared to standard warfarin therapy. Our CEA found that PGx-based warfarin increases QALYs by a larger magnitude and can be cost-effective at lower WTP thresholds than previously suggested. Nshimyumukiza *et al*. (2013) did not consider treatment effectiveness for clinically relevant minor thromboembolic and hemorrhagic events in their analysis. In contrast, we included the effectiveness of PGx-based warfarin in reducing the risk of CRNMB events, in addition to major hemorrhagic events in our analysis. As such, our CEA provides a more comprehensive approach by capturing the added benefit of PGx-based warfarin in reducing CRNMB events which are much more prevalent than major hemorrhage.

As compared to published CEAs that found PGx-based warfarin to be cost-effective at WTP thresholds higher than $20,000/QALY, we captured CRNMB events separately from major bleeding events because the treatment cost for each type of bleeding is very different. Major bleeding events are considered to lead to hospitalization and can cost between $10,819 to $22,355 (67). In comparison, CRNMB events do not require intensive treatment and typically cost approximately $100 per event (51). Including major hemorrhage and CRNMB events as one cluster would have produced biased cost estimates.

Previous CEAs have stratified the risk of adverse events by INR ranges in their analysis (65,68). For example, Patrick *et al*. (2009) first stratified patients into INR ranges and modelled INR-specific adverse event rates for the first 3-months (68). In comparison, we modelled the overall risk of adverse events using clinical trial evidence and avoided making assumptions about the time it takes for intermediate outcomes such as INR ranges to be translated into clinically relevant adverse events.

Finally, previous CEAs in the context of US and Canada have used a genotyping cost of about $500-$800 (15,65,68). In comparison, the cost for a genotyping test in our CEA was estimated to be $87 per patient, which was obtained from the LHSC-PM clinic. Using latest effectiveness and cost data, our CEA found that PGx-based warfarin care can be cost-effective at WTP thresholds of $20,000/QALY and higher as compared to standard warfarin.

3.4.3 PGx-based warfarin versus apixaban

Treatment with rivaroxaban resulted in lower incremental QALYs and higher incremental costs than apixaban. As such, rivaroxaban was ruled out by extended dominance because decision makers prefer the more effective intervention with a lower ICER. Among the undominated strategies, PGx-based warfarin was cost-effective at WTP thresholds of $20,000/QALY or higher and apixaban was cost-effective at WTP thresholds of $65,000/QALY gained or higher. Previous studies that compared PGx-based warfarin and DOACs with standard warfarin report similar findings. PGx-based warfarin and apixaban provide a net clinical benefit to patients, increasing quality-adjusted life

expectancy as compared with standard warfarin (13–16). Moreover, PGx-based warfarin results in small increase in QALYs and large increase in costs.

Two previous Canadian CEAs recommended dabigatran 150 mg as the optimal OAC strategy. Dyspepsia is a common adverse event associated with dabigatran use. These studies did not include the impact of dyspepsia on incremental costs and quality of life in their analyses. We excluded dabigatran from our CEA because of its limited uptake in current clinical practice (9). Nshimyumukiza *et al*. (2013) found PGx-based warfarin was not cost-effective at the WTP threshold of $50,000/QALY gained in Canada (15). In contrast, our CEA finds that PGx-based warfarin can be cost-effective at this threshold at a real-world genotyping test cost of $87 per patient. In a CEA of DOACs, Coyle *et al*. (2013) assumed the drug cost of apixaban to be the same as dabigatran because apixaban was not covered by the ODB formulary at the time of their study (16). Importantly, our CEA improves on the previous study by including the current drug costs incurred by the MOHLTC through the ODB formulary and treatment effectiveness in reducing the risk of clinically relevant non-major bleeding. As mentioned above, CRNMB events are more prevalent than major bleeding events. Moreover, there is a cost incurred by the Canadian health care system and time is consumed in the management of CRNMB event when a patient interaction occurs. Using latest effectiveness and Canadian cost data, our CEA found that PGx-based warfarin is cost-effective at a lower WTP threshold than previously reported and apixaban is the recommended DOAC in the treatment of AF patients.

Our CEA finds that apixaban is cost-effective at higher WTP thresholds than in most published US and Canadian studies. Our analysis included baseline cost of living and non-event death and reported higher lifetime accrued costs and incremental costs than previous estimates. Our model improves on previous models by capturing intended and unintended costs of introducing alternative OAC treatments that would be incurred by the Canadian public healthcare payer. Moreover, the cost to gain one additional QALY under apixaban increases from $60,649 when compared to standard warfarin to $64,853 when compared to PGx-based warfarin. As such, our CEA improves on previous studies by including all four OAC treatments in one analysis and allows decision makers to judge the frontrunner strategy.

3.4.4 Sensitivity Analyses

The deterministic analyses results show that there was high uncertainty around treatment effectiveness. If low treatment effectiveness was assumed under PGx-based warfarin, the risk of CRNMB and major hemorrhage increased, and standard warfarin offered a net clinical benefit over PGx-based warfarin. On the other hand, if low rivaroxaban or apixaban effectiveness was assumed, the DOACs were dominated by PGx-based warfarin. Under low treatment effectiveness, the risks of ischemic stroke, myocardial infarction and systemic embolism increased under DOAC treatment. The risk of CRNMB and major hemorrhage also increased under rivaroxaban. In our analysis, rivaroxaban was an undominated option only if low apixaban effectiveness was assumed or high rivaroxaban effectiveness was assumed. In other cases, PGx-based warfarin and apixaban were cost-effective at some willingness-to-pay thresholds.

In Canada, there is not one value set for willingness-to-pay threshold. In the past, a range of values has been used in specific disease areas. For non-oncology drugs, a threshold of $50,000/QALY has been considered a good value for money (69). Other expert opinion suggests that a threshold of $100,000/QALY is the informal standard. The new 2020 Patented Medicine Prices Review Board (PMPRB) guidelines mention a specific threshold of $150,000/QALY for pharmacoeconomic value assessments (70). When compared to this threshold, both PGx-based warfarin and apixaban are viable OAC strategies in Canada. Evidence strength and uncertainty also play a role in developing grades of recommendation for adopting new technologies (71). The PSA results showed that PGx-based warfarin had a higher probability of being cost-effective than apixaban (51.5% vs 14.1%) at a WTP threshold of $50,000/QALY. At a WTP threshold of $150,000/QALY, apixaban had a higher probability of being cost-effective than PGx-based warfarin (70.1% vs 5.7%).

3.5 Limitations

There are several limitations to our study. First, the estimated cost of the genotyping test at the LHSC assumed optimal use of healthcare resources and staff time. The per patient cost was calculated using the total number of tests conducted at the facility in 2018. The

genotyping cost per patient may vary under other scenarios. Moreover, the marginal cost of genotyping test did not include overhead costs such as the cost of facilities because the test cost was obtained from a publicly funded university-affiliated hospital setting. In addition, the lab manager fee to authorize test results and potential additional physician billings due to tests were not included in our genotype test cost calculation. We tested the sensitivity of our CEA results to varying PGx test costs in one-way sensitivity analysis and found that PGx ICER values were sensitive to PGx test prices (Figure 3.3.2.4).

Second, our CEA included only direct medical care costs that were relevant from the Canadian public healthcare payer perspective. A cost-utility analysis incorporating indirect costs may decrease the estimated ICER values. If the costs of lost productivity, absenteeism, presenteeism and unpaid care incurred by the patients are included, the lifetime costs under standard warfarin care may increase and make alternative treatment strategies more attractive.

Third, the relative effectiveness parameters of DOACs compared to standard warfarin care were obtained from a study on indirect comparisons using a competing risks network meta-analysis (24). PGx-based warfarin effectiveness parameters were obtained from a single large double-blinded North American RCT (the COAG trial) (23). This trial determined standard warfarin dosing using a clinical algorithm, which included body surface area, age, African-American race, target INR, amiodarone use, smoking status and a diagnosis of deep vein thrombosis/pulmonary embolism. However, current clinical practice may not follow this dosing algorithm for standard warfarin. The genotype-guided algorithm used these variables as well in addition to patient genotype. Accordingly, this trial was designed to show the added value of the genotype in addition to known clinical covariates, and may not represent standard warfarin care typically applied by health care providers.

Fourth, the hazard ratio of CRNMB events under apixaban, rivaroxaban and PGx-based warfarin were obtained from single RCTs (23,32,39). Several definitions of clinically relevant non-major bleeding events exist in the published literature. Bahit *et al*. (2017) identified CRNMB events as any acute or subacute clinically overt bleeding that did not

satisfy the criteria for major bleeding by the International Society on Thrombosis and Hemostasis (ISTH), the latter defined as a bleeding that led to a "hospital admission for bleeding, physician-guided medical or surgical treatment for bleeding or change in antithrombotic therapy (including study drug) due to bleeding" (32). The definition of minor bleeding in the literature is even more ambiguous, and was classified as any clinically overt bleeding that did not meet the criteria for either major or clinically relevant non-major bleeding. Bahit *et al.* (2017) assessed the incidence of non-major bleeding (including minor and CRNMB events) using patient-level data obtained from the ARISTOTLE trial (32). Similarly, patients were assessed by the Kimmel *et al.* (2014) and Patel *et al.* (2011) trial personnel to identify CRNMB events as per ISTH criteria (23,39). As such, we can be reasonably confident in their classification of these events. Despite these limitations, clinically relevant non-major bleeding events are important patient-centric outcomes and may influence the quality of life adversely (72). CRNMB events can lead to OAC discontinuation, which increases the risks of ischemic stroke and death. In the ARISTOTLE trial, about 4.4% of AF patients who had a non-major bleeding permanently discontinued anticoagulation therapy. As such, CRNMB events are important drivers of physician-prescribing behaviour. Thus, we incorporated treatment and cost differences in managing CRNMB events using best available evidence at this time. However, given the ambiguous and overlapping definitions of CRNMB in the literature, more data on the incidence and management of CRNMB for patients on different anticoagulation strategies would improve future CEAs.

Fifth, the acute care costs of adverse events included the average hospitalization and emergency costs. The acute care costs estimated from the ICES databases do not include physician billing because an appropriate algorithm to capture these costs was not available. However, we expect these costs will have a relatively small impact on the results because the number of adverse events across treatment strategies is not too high. We also did not capture downstream costs related to complications. For example, a gastrointestinal (GI) bleed may precipitate from a bowel cancer. In this case, a subsequent surgery care cost will be incurred by the healthcare system. However, colorectal cancer complicated by GI bleeding in anticoagulated patients with AF are rare. A recent study by Rasmussen *et al.* (2020) investigated the risk of colorectal cancer

among AF patients aged 66 years and older. They reported an absolute 1-year colorectal cancer risk of 4%-8% among patients with a lower GI bleed (73). The annual rate of lower GI bleed among AF patients on warfarin in Ontario ranged from 4.6% in the first month of anticoagulation to 1.2% for the rest of 5-years of follow-up in a population-based study (27). Because the prevalence of colorectal cancer among lower GI bleeding cases is relatively low, we assumed that the average cost of complications by colorectal cancer will not have a substantial impact on the average cost of GI bleeding across treatment strategies. Moreover, anticoagulation may lead to an earlier diagnosis of GI cancer, which may reduce costs for subsequent care, but it might also increase costs. Downstream costs may have an impact in tipping the scales in favour or against OAC treatments if the ICER values were close to the general WTP thresholds, which are not found to be the case here. Finally, our CEA focuses on cost differences driven by OAC treatments.

Sixth, our CEA attempted to capture average acute care costs incurred by the Canadian healthcare system using administrative databases, where feasible. We assumed that event-specific acute care costs will be the same. However, there might be differences in the severity of adverse events for patients on different OAC treatments. Our analysis does not adequately account for the reduced risk of mortality under the DOACs. Moreover, we removed non-OAC medication costs from ongoing care costs because our analysis focused on OAC-related drug costs. However, higher OAC effectiveness may decrease other medication costs. Cost data specific to OAC strategies may improve future CEAs. In the face of limited published data, our estimates for CRNMB quantified costs relied on healthcare resource use based on expert opinion. It is important to note that healthcare response and resource use may vary in other settings.

Seventh, the risks of intracranial hemorrhage, transient ischemic attack, systemic embolism and myocardial infarction were assumed to be the same for PGx-based and standard warfarin care. Existing RCTs comparing PGx-based and standard warfarin care have low event rates and are not powered to detect a significant difference for these adverse events.

Finally, this CEA makes long-term projections based on short-term clinical evidence and clinically informed assumptions about plausible treatment pathways and transitions between health states. Moreover, the patient profiles in clinical trials may not be the same as those observed in real world patients. Consequently, the treatment effectiveness is generally lower than efficacy. In routine-care, the plasma concentrations of DOACs among patients are highly variable as compared to the variation observed in clinical trials (74). The PSA acceptability curves showed that there was considerable parameter uncertainty in our model. Nonetheless, in this model, the highest quality of effectiveness data from meta-analysis of RCTs or single RCT with low confounding were used.

It is also important to note that our model is not designed for patients who switch or permanently discontinue therapy. Additionally, our model does not consider patient adherence or a no treatment option for patients with very low stroke risk or patients at high mortality risk due to comorbidities other than AF. Future research is warranted for these specific patient populations.

3.6 Strengths

Our findings add to the existing scientific knowledge in several ways. Contrary to current medical practice and physician prescribing behaviour, the last two Canadian studies recommended dabigatran 150 mg based on its cost-effectiveness. Since then, dabigatran at this dose has been shown to increase the risk of gastrointestinal bleeds and dyspepsia. Moreover, physicians prefer to prescribe apixaban or rivaroxaban over dabigatran for AF patients in Canada (9). We excluded dabigatran from our analysis because of its limited uptake in current clinical practice. Previous CEAs also estimated costs of apixaban and rivaroxaban using literature-based data and showed that base case results were sensitive to drug costs. Our CEA evaluated the cost-effectiveness of oral anticoagulation therapies using most costs obtained from the Ontario population. A notable strength of our CEA is that we included clinically relevant non-major bleeding events in addition to major hemorrhagic and thromboembolic events to capture more comprehensively all relevant risk and cost differences between treatment strategies. Our CEA improves on previous studies by establishing the cost components of CRNMB using trial data and expert opinion. Moreover, we incorporated clinically relevant adverse events without making

explicit assumptions between INR ranges and adverse events. Finally, by comparing standard warfarin care, PGx-based warfarin care, apixaban and rivaroxaban in one CEA, we made it easy for healthcare decision makers and stakeholders to judge the frontrunner anticoagulation strategy among all four treatments available for AF patients in Canada. Our study shows the importance of including all available treatment strategies in the CEA analysis. Our results show that excluding strategies can change the cost-effectiveness frontier, which may lead to decision-making based on incomplete information. As such, there must be strong justifications for excluding strategies in a cost-effectiveness analysis.

3.6.1 Excluded alternatives: Dabigatran etexilate and Edoxaban

Although dabigatran etexilate belongs to the same class of drugs as apixaban and rivaroxaban, dabigatran treatment is not being evaluated in this CEA because of lower prescription numbers and some safety concerns. Specifically, two standard doses of dabigatran are usually prescribed; 110 mg or 150 mg twice daily (4). Dabigatran 110 mg has been shown to be non-inferior to warfarin in reducing the risk of stroke and systemic embolism. However, dabigatran 110 mg has been found to be a safer alternative to warfarin because it reduces the risk of major bleeding by ~20%. In contrast, dabigatran 150 mg has been found to be superior to warfarin by reducing the risk of ischemic stroke, hemorrhage and systemic embolism by ~34%. However, although dabigatran 150 mg reduces the risk of intracranial hemorrhages, gastrointestinal hemorrhages are more common with high-dose dabigatran as compared to warfarin. Moreover, there is a non-significant increase in the risk of myocardial infarction with dabigatran as compared to warfarin. Furthermore, dyspepsia (indigestion) is another common adverse event associated with dabigatran use. In the RE-LY trial (n=18,113), about 11.8% of patients on dabigatran 110 mg and about 11.3% of patients on dabigatran 150 mg suffered dyspepsia as compared to 5.8% of patents on warfarin ($P<0.001$ for both comparisons) (4). Moreover, physicians do not seem to prefer prescribing dabigatran for AF patients. Since the approval of apixaban and rivaroxaban under the provincial formulary, a trend towards declining number of dabigatran prescriptions for stroke prevention among AF

patients is documented in Ontario (9). For these reasons, dabigatran is not considered as an oral anticoagulant alternative in this CEA.

Our CEA also does not evaluate edoxaban because there is limited data on its effectiveness and complications. Edoxaban is a relatively new anticoagulant that was approved by Health Canada in November 2016 and thus not yet widely prescribed in current clinical practice. Future studies should consider edoxaban if it becomes another alternative treatment strategy for patients with AF.

3.7 Conclusions

As compared to standard warfarin care, PGx-based warfarin, apixaban and rivaroxaban were more effective and expensive than standard warfarin care. However, PGx-based warfarin care improved health benefits by only a small margin. Moreover, rivaroxaban was not as effective in improving QALYs as apixaban and was associated with higher costs. Consequently, apixaban dominates rivaroxaban. The incremental cost incurred under apixaban therapy to gain one additional QALY is considered generally acceptable at the willingness-to-pay thresholds of $65,000/QALY gained or higher. On the other hand, the incremental cost to gain one additional QALY under PGx-based warfarin is cost-effective at WTP thresholds of $20,000/QALY gained or higher. Given the 2020 PMPRB guidelines (70) comparing incremental cost-utility ratio values to a threshold of $150,000/QALY, both PGx-based warfarin and apixaban may demonstrate two viable strategies for Canada. However, structural limitations need to be considered before incorporating PGx-based warfarin care into routine clinical practice and on a wider scale as it is currently limited to specialty clinics. Moreover, if one argues that the most cost-effective strategy is the one closest to the WTP threshold, then, apixaban maximizes average patient health gain given the public healthcare payer's willingness to pay in Canada. We found that apixaban offers the best balance between efficacy and safety and has a high probability of being cost-effective for AF patients in Canada at a WTP threshold of $150,000/QALY.

For AF patients who are eligible for DOAC treatment, apixaban remains a more feasible treatment option than PGx-based warfarin care. For patients who are ineligible for DOAC

treatment, such as those with mechanical heart valves or poor renal function, PGx-based warfarin care may be the only treatment option for anticoagulation. However, the results of our CEA are not applicable to this patient population and no conclusions can be made. Future CEA for this specific target population is needed before any conclusions can be drawn.

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Chapter 4 - Conclusions

Atrial fibrillation (AF) is a common cardiac arrhythmia among seniors (65+ years old) and is associated with high morbidity and mortality risks. AF increases the risk of stroke by 3-5 times and all-cause mortality by 3.5-fold (1). In addition, stroke complications can leave patients with physical disabilities, poor quality of life and in need of constant nursing and long-term care (2,3). Not only does AF entail substantial burden on patient health, it also imposes a huge financial strain on the Canadian healthcare system. In Ontario, hospitalizations due to AF-related ischemic stroke or transient ischemic attack cost about $19,113 per admission and have the longest in-hospital stay of 20.2 days (1). In addition, hospitalizations due to AF-related hemorrhages are the costliest hospital admissions, with an average cost of $26,746 per admission. Since AF risk increases with ageing, the prevalence and burden of AF is expected to increase with the ageing of the Canadian population in the foreseeable future and beyond (2).

Several oral anticoagulation therapies are available to mitigate the risks of AF. Warfarin, also commercially known as Coumadin, is a commonly prescribed anticoagulant drug to treat AF patients (4). It can reduce the risk of stroke by 66% if the drug's therapeutic effect is achieved, which is defined as having an International Normalized Ratio (INR) of 2-3 (4). Although warfarin has been widely prescribed in the past few decades, there are many challenges associated with standard warfarin therapy. Warfarin therapy is known to have a narrow therapeutic window, delayed pharmacodynamic response and interpatient genetic variability in drug metabolism and response (5,6). In current clinical practice, warfarin patients must initially undergo an adjustment period during which the optimal dose for the individual is determined through trial and error and guided by repeated blood tests (4). During this adjustment period, patients may experience a high risk of adverse events if inappropriate dose is prescribed.

There is a wide interpatient variability observed in warfarin dose requirements. About 30% of this variability can be attributed to single nucleotide polymorphisms (SNPs) in three pharmacogenes encoding the following enzymes: (i) cytochrome P450 (CYP) 2C9 involved in S-warfarin metabolism (gene *CYP2C9*), (ii) vitamin K epoxide reductase (gene *VKORC1*), the pharmacological target, and (iii) *CYP4F2* (gene *CYP4F2*) involved

in vitamin K metabolism (7). Individuals with one or all of these mutations experience a longer and riskier warfarin dose adjustment period (4). Pharmacogenomics (PGx) based warfarin therapy tailors the drug dose for each patient using his/her genotypic information in conjunction with demographic and clinical variables such as age, weight, height, smoking status and more (8). PGx-based warfarin care offers several benefits over standard warfarin care; it has been shown to increase the efficiency with which the therapeutic anticoagulation effect is achieved among patients and reduce risk of adverse events (9–11). Recent meta-analyses show that PGx-based warfarin dosing reduces the risk of major hemorrhage by 30-60% (9–11). However, PGx-based warfarin care requires an upfront cost of genotyping test. Thus, it is important to assess if the upfront cost of genotyping test outweighs the benefits.

To date, published studies on the cost-effectiveness of PGx-based warfarin therapy compared to standard warfarin therapy have produced conflicting results with 3 studies finding PGx cost-effective, 5 finding PGx not cost-effective and 4 being inconclusive (12). The published cost-effectiveness analyses (CEAs) have compared standard warfarin dosing with genotype guided warfarin dosing for a hypothetical cohort of senior AF patients between the ages of 45-75 years. Patrick *et al.* (2009) found that PGx-based warfarin care could be cost-effective in the US if the time in therapeutic range (TTR) was increased by 5-9% in the first 3 months of initiating therapy (13). In Canada, Nshimyumukiza *et al.* (2013) found PGx-based warfarin care was not cost-effective at the willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY) gained (14). In contrast, a more recent CEA by Verhoef *et al.* (2016) found that PGx-based warfarin care was cost-effective as compared to standard warfarin care in the UK and Sweden (15). There is considerable uncertainty about the cost-effectiveness of PGx-based warfarin care relative to standard warfarin care in the published literature; the results seem to vary by population and geographical region.

In Canada, direct oral anticoagulants (DOACs) such as apixaban and rivaroxaban were recently approved for funding for stroke prophylaxis among AF patients by the Ontario Ministry of Health and Long-Term Care (MOHLTC) (16). Studies have shown that DOACs offer several advantages over warfarin therapy such as a more predictable

therapeutic effect, require no routine INR monitoring, demonstrate increased effectiveness in stroke prevention and are associated with lower risks of hemorrhagic adverse events as compared to warfarin (17). The improved safety of DOACs may translate into reduced financial strain on the Canadian healthcare system. However, the unit cost of DOACs is more than 20 times the cost of warfarin (18). Thus, it is important to carefully assess the cost-effectiveness of anticoagulation therapy with DOACs such as apixaban and rivaroxaban as compared to warfarin therapy.

To date, published studies on the cost-effectiveness of DOACs such as apixaban and rivaroxaban compared to warfarin therapy in the US, Europe and Canada have generally produced conclusions in favour of DOACs (15,19–21). Among apixaban and rivaroxaban, apixaban is often found to be the most cost-effective DOAC when compared to standard warfarin care. However, it has also been shown that the cost-effectiveness of DOACs is sensitive to drug prices and anticoagulation control under warfarin care. For example, Jarungsuccess *et al*. (2014) found that dose-adjusted warfarin therapy could be cost-effective option in Thailand if the drug unit costs decreased by 85% (22). Similarly, You *et al*. (2013) concluded that the DOACs could be cost-effective in the US if the TTR under standard warfarin care was below 60% (20). Although, DOACs have been shown to be cost-effective alternative to warfarin care in Canada, Coyle *et al*. (2013) and Nshimyumukiza *et al*. (2013) found that dabigatran prescribed at 150 mg twice daily was the recommended DOAC based on its cost-effectiveness (14,21). However, latest clinical effectiveness data show that high-dose dabigatran is associated with increased risks of gastrointestinal hemorrhages and dyspepsia (17). These adverse events were not considered by Coyle *et al*. (2013) and Nshimyumukiza *et al.* (2013), thus requiring an updated cost-effectiveness evaluation of DOACs from a Canadian healthcare payer perspective.

This CEA investigated the cost-effectiveness of PGx-based warfarin, apixaban and rivaroxaban as compared to standard warfarin care from the Canadian public healthcare perspective using literature-based effectiveness data and most costs from the ICES data repository. A decision-analytic Markov model was developed to compare the lifetime costs and quality-adjusted life years (QALYs) or life-years (LYs) gained by a

hypothetical cohort of newly diagnosed AF patients aged 65 or older. Deterministic and probabilistic sensitivity analyses were undertaken to study the influence of uncertainty in model parameters on the incremental cost effectiveness ratio (ICER).

The base case results of this CEA indicate that the PGx-based warfarin and DOACs produce higher QALYs than standard warfarin care but at higher costs. Among undominated strategies, PGx-based warfarin increased QALYs by 0.03 units (~11 days) and costs by $583; it costed about $17,727/QALY gained. Apixaban increased QALYs by 0.34 units (~4.08 months) and costs by $21,790; it costed about $64,853/QALY gained. Rivaroxaban was dominated by apixaban. Deterministic sensitivity analysis showed high uncertainty associated with treatment effectiveness. The ICER value for PGx-based warfarin was also sensitive to PGx test price and age of OAC initiation. PGx-based warfarin had a higher probability of being cost-effective than apixaban (51.5% vs 14.1%) at a WTP threshold of $50,000/QALY. At a WTP threshold of $150,000/QALY, apixaban had a higher probability of being cost-effective as compared to PGx-based warfarin (70.1% vs 5.7%).

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Appendix A: Sample Calculations

To specify probability distributions for the probabilistic analysis, the uncertainty (95% confidence interval (CI)) around the mean estimate was investigated.

A.1 Parameterizing using Normal distribution

If the 95% CI was relatively symmetric around the mean estimate, we parameterized using normal distribution.

Table A.1: Calculations carried out to draw normal distribution around hazard ratios for effect of history of event on future adverse event (example).

Future adverse event	Hazard ratio	95% CI LB	95% CI UB	Difference between LB and Mean	Difference between UB and Mean	Standard error *	Distribution
Effect of ischemic stroke on future events							
Major hemorrhage	1.39	1.27	1.52	0.12	0.13	0.06	Normal
ICH	1.64	1.39	1.94	0.25	0.30	0.14	Normal

CI, confidence interval; LB, lower bound; UB, upper bound
*****Standard error was the average difference between mean and 95% CI divided by 1.96

A.2 Parameterizing using LogNormal distribution

In some cases, the 95% CI was not symmetric around the mean. In these cases, we investigated and confirmed normality assumption on the logarithmic scale and used a LogNormal distribution.

Table A.2.a: The 95% CIs around hazard ratios (HRs) of PGx-based warfarin effectiveness were not symmetric around the mean estimates (example).

Adverse event	Hazard ratio	95% CI LB	95% CI UB	Difference between LB and Mean	Difference between UB and Mean
Major hemorrhage	0.41	0.13	1.31	0.28	0.9
CRNMB	0.62	0.3	1.27	0.32	0.65

Table A.2.b: Calculations carried out on HRs and 95% CIs presented in Table A.2.a to confirm normality on logarithmic scale and parameterize using LogNormal distribution.

Adverse event	Mean of logs, μ	95% CI LB-log scale	95% CI UB-log scale	Difference from mean to LB	Difference from mean to UB	Standard error*	Distribution
Major hemorrhage	-0.89	-2.04	0.27	1.15	1.16	0.59	LogNormal
CRNMB	-0.48	-1.20	0.24	0.73	0.72	0.37	LogNormal

CI, confidence interval; LB, lower bound; UB, upper bound
*****Standard error was the average difference between mean and 95% CI divided by 1.96

A.3 Parameterizing using Beta distribution

To ensure the correct support for acute (30-day) mortality and proportions, we used beta distributions.

Table A.3: Calculations carried out to draw beta distribution around acute mortality after an ischemic stroke estimated from the Tung *et al.* (2015) study (1) (example).

No. of total ischemic stroke cases	No. of acute deaths	Acute death (%)	Distribution	alpha	beta	95% CI LB	95% CI UB
6006	1639	27.29	Beta	1639	4367	26.17%	28.42%

No., number; CI, confidence interval; LB, lower bound; UB, upper bound
alpha= No. of acute deaths; beta= No. of total ischemic stroke cases - No. of acute deaths

A.4 Parameterizing using Gamma distribution

To ensure the correct support for skewed costs, we used gamma distributions.

Table A.4: Calculations carried out to draw gamma distribution around acute care cost after major hemorrhage (example).

Adverse event	Sample size, N	Mean Cost	Standard deviation	Standard error	alpha	beta	95% CI LB	95% CI UB
Non-fatal major hemorrhage	947	3126	4593	149	438	7	2840	3425

CI, confidence interval; LB, lower bound; UB, upper bound
Standard error=Standard deviation/square- root(Sample size, N)
alpha=(mean cost^2/standard error^2); beta=(standard error^2/mean cost)

A.5 Major hemorrhage rates

Major hemorrhage was a weighted average of upper and lower gastrointestinal and other hemorrhages. In *Gomes et al.* (2013), Table 2, the 95% confidence intervals were nearly symmetric around the mean estimates (2). And so, we assumed normal distribution. The standard deviation of mean of rates is the sum of variances (assuming independent random variables).

Table A.3: Estimates of the rate of major hemorrhage during first month of therapy and distribution parameters (example).

Type of hemorrhage	**Annual rate (%/PY)**	**95% CI LB**	**95% CI UB**	**Difference between LB and Mean**	**Difference between UB and Mean**	**Standard deviation***	**Variance ****
<=30 days							
Upper gastrointestinal	4.00	3.80	4.20	0.20	0.20	0.10	0.0104
Lower gastrointestinal	4.60	4.40	4.90	0.20	0.30	0.13	0.0163
Other	4.70	4.50	5.00	0.20	0.30	0.13	0.0163
Mean rate (%/PY)	**13.30**						
Sum of variances							**0.0430**
Square root of sum of variance							**0.2072**

PY, person-years; CI, confidence interval; LB, lower bound; UB, upper bound
*****Standard deviation was the average difference between mean and 95% CI divided by 1.96
**Variance is the square of standard deviation

A.6 Costs

A.6.1 Estimating baseline age-specific health care expenditure

The 2017 Ontario expenditure per year for both sexes were obtained from CIHI website (Table E.1.20.2-Estimate of total per capita provincial/territorial government health expenditures) (3). The age-specific probability of dying was obtained from STATCAN website (Table: 13-10-0114-01) (4). Tanuseputro *et al.* (2015) reported the average age-

specific costs incurred by the Ontario population in the last year of death (5). We assumed the following formula in the calculation of CIHI-Expenditure per capita.

CIHI-Expenditure per capita =
(Baseline age-specific health care expenditure)*(1-Probability of dying) + (Cost in last year of death)*(Probability of dying)

Baseline age-specific health care expenditure =
[CIHI-Expenditure per capita - (Cost in last year of death)*(Probability of dying)]/(1-Probability of dying)

Then, we increased the baseline age-specific health care expenditure by an incremental cost of AF of $3,898.33 (2017 CAD).

A.6.2 Estimating incremental cost of AF

Kim *et al.* (2010) reported the incremental cost incurred by ~71-year-old AF patients using a matched US cohort (6). About 57% of patients in the AF cohort were on warfarin and only 5% of control non-AF patients were on warfarin, which is reasonable given we want the incremental costs incurred by AF patients as compared to general population.

We extracted the costs attributed to AF-related hospitalization (inpatient costs) and outpatient medical services (ER visits, physician visits, laboratory services and other outpatient services). In addition, we extracted the non-CVD costs for inpatient hospitalizations and outpatient services. We did not extract other CVD costs because those events were modelled separately in our Markov model. The US costs were converted to CAD costs using purchasing power parity of 0.8 (7). Costs were adjusted to 2017 using STATCAN website, CANSIM Table:18-10-0005-01 (8).

The CIHI-expenditure (Table E.1.20.2) shows that the total cost per 71-year-old is $8,335.14 (2017 CAD). Table 2 in Kim *et al.* (2010) reported that a 71-year-old non-AF patient costs about $11,965 (2008 USD). We compared the reported costs of non-AF US patient to Canadian patient and adjusted for percent inflation due to US healthcare system.

A.6.3 Acute care cost of CRNMB

Table A.6.3: Estimating acute care cost of CRNMB using Bahit *et al.* (2017) and expert opinion (9,10).

Cost components	Cost ($)	Sub-type Proportions	Notes
Fixed cost of consultation (A005, A135)	**97.15**		Each CRNMB encounter leads to a general consultation with a GP/FP or a specialist. Based on expert opinion, the ratio of GP/FP to specialist is 3:1. Using this information, the average fixed cost of an encounter with a healthcare professional is calculated.
Hematuria		0.164	Bahit *et al.* (2017) (9)
Common antibiotics	10.00		Based on expert opinion, the average cost of antibiotics is ~$10. (10)
Pharmacy dispensing fee	11.31		Average pharmacy dispensing fee across Ontario. (11)
Urology consultation (A355)	80.00		If patient is referred to a specialist.
Cystoscopy (Z606)	71.00		
Low end cost	**21.31**	**0.6**	Includes cost of antibiotics and pharmacy dispensing fee. The sub-type proportion was expert's opinion.
High end cost	**151.00**	**0.4**	Includes cost of urology consultation and cystoscopy. The sub-type proportion was expert's opinion.
Total sub-type cost	170.34		Weighted average of low- and high-end cost + fixed cost of consultation
Epitaxis		0.148	Bahit *et al.* (2017) (9)
Anterior packing (Z315)	15.35		
Cauterization (Z314)	11.50		
Posterior packing (Z316)	35.50		
ENT consult (A245)	80.00		
Low end cost	**26.85**	**0.8**	Includes cost of anterior packing and cauterization. The sub-type proportion was expert's opinion.
High end cost	**142.35**	**0.2**	Includes all cost components. The sub-type proportion was expert's opinion.
Total Sub-type cost	$147.10		Weighted average of low- and high-end cost + fixed cost of consultation

Non-major GI bleed		0.133	Bahit *et al.* (2017) (9)
Colonoscopy (Z496+E74O+E741+E747+E705)	197.21		
Gastroenterology consult (A415)	157.00		
Sum of Cost	**354.21**	**1**	All patients who come-in for a non-major GI bleed are administered a colonoscopy and have a GI consult.
Total Sub-type cost	451.36		Weighted average of low- and high-end cost + fixed cost of consultation
Non-major CRNMB	**97.15**	**0.555**	Only the fixed cost of consultation is accrued for all other non-major bleeding events.
Total Sub-type cost	97.15		
Total CRNMB cost	**$163.66**		**Weighted average cost per patient by proportions of CRNMB sub-types**

A.6.4 Anticoagulation drug therapy costs

Table A.6.4: Calculations carried out to estimate drug therapy costs.

Unit costs of resource utilization	**Mean Cost**	**Source**
Cardiologist consultation fee (billing code A605)	157.00	Schedule of Benefits for Physician Services (12)
Physician consultation fee (billing code A005)	77.20	
Consultation fee for Prothrombin time (PT/INR) lab test (billing code G031)	6.20	
Anticoagulant supervision fee - long-term management of warfarin via telephone advice (billing code G271)	12.75	
Prothrombin time (PT/INR) lab test (billing code L445)	2.66	Schedule of Benefits for Laboratory Services (13)
Average pharmacy dispensing fee	11.31	(11)
Monthly drug costs (Summary)		**Notes**
Monthly cost of warfarin drug (5mg qd)	2.03	Unit cost obtained from ODB Formulary (14) and multiplied with the monthly dose regime.
Monthly cost of apixaban drug (2.5-5 mg bid)	98.02	

Monthly cost of rivaroxaban (15-20 mg qd)	86.10	
Estimating monthly therapy costs		
Monthly cost of warfarin therapy (1st month)	**282.98**	
Cardiologist consultation fee (billing code A605)	157.00	*assumed one specialist visit based on expert opinion (15)
Physician consultation fee (billing code A005)	77.20	
Monthly cost of warfarin drug (5mg qd)	2.03	Unit cost obtained from ODB Formulary (14)
Prothrombin time (PT/INR) lab test (billing code L445)	10.64	*assumed one PT/INR test per week in the first month as per warfarin dosing protocol (16)
Consultation fee for Prothrombin time (PT/INR) lab test (billing code G031)	24.80	*assumed each PT/INR test elicited a PT/INR lab test consultation fee
Average pharmacy dispensing fee	11.31	(11)
Monthly cost of warfarin therapy (2-12th month)	**32.58**	
Total cost over 11-month period	358.42	The 11-month cost was calculated and divided into monthly costs to reduce bias in costs because the exact timing of visits, consultation and PT/INR tests is not known.
Physician consultation fee (billing code A005)	159.37	Schulman *et al*. (2010) reported a total of 235 healthcare contacts for 96 patients over 3-month period and 23% of these interactions were site visits with physician consultations at a community-based family physician. Thus, an average of ~2.06 physician consultations were assumed over the 11-month period. (17)
Anticoagulant supervision - long-term, telephone advice (billing code G271)	60.65	Schulman et al. (2010) reported a total of 235 healthcare contacts for 96 patients over 3-month period and 53% of these interactions occurred via telephone at a community-based family physician. Thus, an

		average of ~4.76 telephone interactions were assumed over the 11-month period. (17)
11- Month cost of warfarin drug (5mg qd)	22.28	Unit cost obtained from ODB Formulary (14)
Prothrombin time (PT/INR) lab test (billing code L445)	21.28	A total of 8 PT/NR tests were assumed; 1 PT/INR test/month for 2-6 months and then, 1 PT/INR test every other month for 7-12 months as recommended by the Warfarin Dosing Protocol. (16)
Consultation fee for Prothrombin time (PT/INR) lab test (billing code G031)	49.60	Each PT/INR test was assumed to incur a PT/INR test consultation fee (8 PT/INR consultations in total over 11-month period).
Average pharmacy dispensing fee	45.24	A total of 4 pharmacy claims left in one year after first month.
Monthly cost of warfarin therapy (>12th month)	**26.48**	
Total annual cost	317.71	The annual cost was calculated and then, divided into monthly cost because the timing of visits, consultations and PT/INR test is not known.
Cardiologist consultation fee (billing code A605)	157.00	*assumed one specialist visit based on expert opinion (15)
Physician consultation fee (billing code A005)	77.20	
12-Month cost of warfarin drug (5mg qd)	24.30	(14)
Prothrombin time (PT/INR) lab test (billing code L445)	2.66	*assumed one PT/INR test per year for event-free patients because warfarin therapy involves routine PT/INR monitoring
Average pharmacy dispensing fee	56.55	(11)
Monthly cost of apixaban therapy (1st month)	**343.53**	
Cardiologist consultation fee (billing code A605)	157.00	*assumed one specialist visit based on expert opinion (15)

Physician consultation fee (billing code A005)	77.20	
Monthly cost of apixaban drug (2.5-5 mg bid)	98.02	(14)
Average pharmacy dispensing fee	11.31	(11)
Monthly cost of apixaban therapy (2-12th month)	**102.13**	*includes the cost of drug only (14)
Total cost over 11-month period	1,123.42	
11- Month cost of apixaban drug (2.5-5 mg bid)	1,078.18	
Average pharmacy dispensing fee	45.24	(11)
Monthly cost of apixaban therapy (>12th month)	**122.25**	
Total annual cost	1,466.94	The annual cost was calculated and then, divided into monthly cost because the timing of visits, consultations is not known.
Cardiologist consultation fee (billing code A605)	157.00	*assumed one specialist visit based on expert opinion (15)
Physician consultation fee (billing code A005)	77.20	
12-Month cost of apixaban drug (2.5-5 mg bid)	1176.19	(14)
Average pharmacy dispensing fee	56.55	(11)
Monthly cost of rivaroxaban therapy (1st month)	**331.61**	
Cardiologist consultation fee (billing code A605)	157.00	*assumed one specialist visit based on expert opinion (15)
Physician consultation fee (billing code A005)	77.20	
Cost of rivaroxaban drug (10-20 mg qd)	86.10	(14)
Average pharmacy dispensing fee	11.31	(11)
Monthly cost of rivaroxaban therapy (2-12th month)	**82.70**	*includes the cost of drug only (14)
Total cost over 11-month period	992.34	
11- Month cost of rivaroxaban drug (10-20 mg qd)	947.10	

Average pharmacy dispensing fee	45.24	(11)
Monthly cost of rivaroxaban therapy (>12th month)	**110.33**	
Total annual cost	1,323.95	The annual cost was calculated and then, divided into monthly cost because the timing of visits, consultations is not known.
Cardiologist consultation fee (billing code A605)	157.00	*assumed one specialist visit based on expert opinion (15)
Physician consultation fee (billing code A005)	77.20	
12-Month cost of rivaroxaban drug (10-20 mg qd)	1033.20	(14)
Average pharmacy dispensing fee	56.55	

Note: Unit costs were multiplied with the respective estimated healthcare resource use to obtain costs.

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Appendix B: Supplementary PSA Results

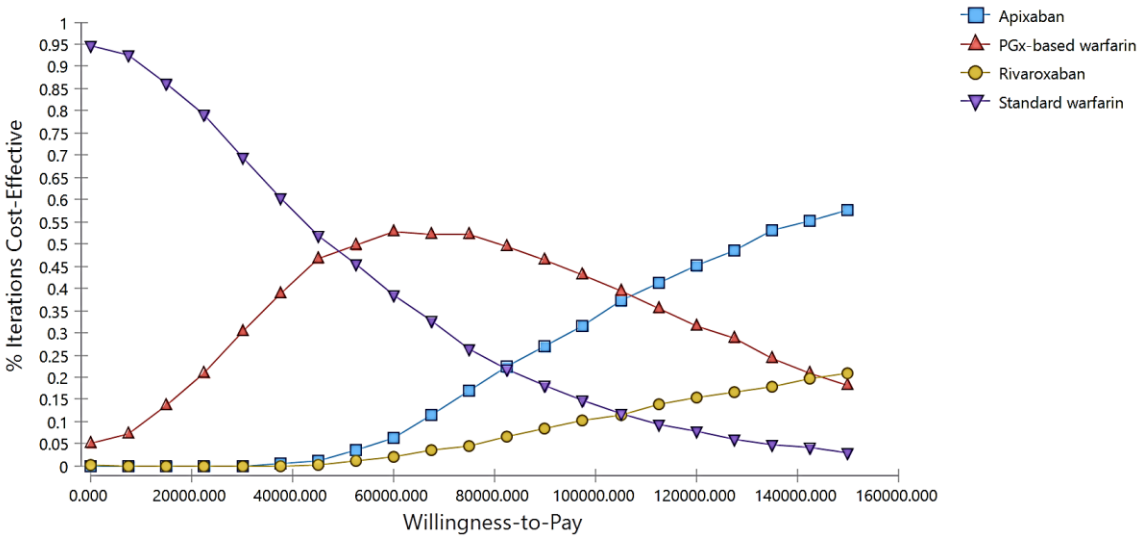

Figure B.1: Cost-effectiveness acceptability curves for patients initiating OAC treatment at the age of 75 years.

At the WTP threshold of $50,000/QALY gained, PGx-based warfarin was the cost-effective treatment in 49% of the iterations, followed by standard warfarin in 47.7% of iterations, apixaban in 2.6% of iterations and rivaroxaban in about 0.7% of iterations. At the WTP threshold of $100,000/QALY gained, PGx-based warfarin was cost-effective in 42.9% of the iterations, followed by apixaban in 33% of iterations, standard warfarin in 13.5% of iterations and rivaroxaban in 10.6% of iterations. At the WTP threshold of $150,000/QALY gained, apixaban was cost-effective in 57.7% of the replications, rivaroxaban in about 20.9% of iterations, PGx-based warfarin care in 18.3% of iterations and standard warfarin care in only 3.1% of iterations.

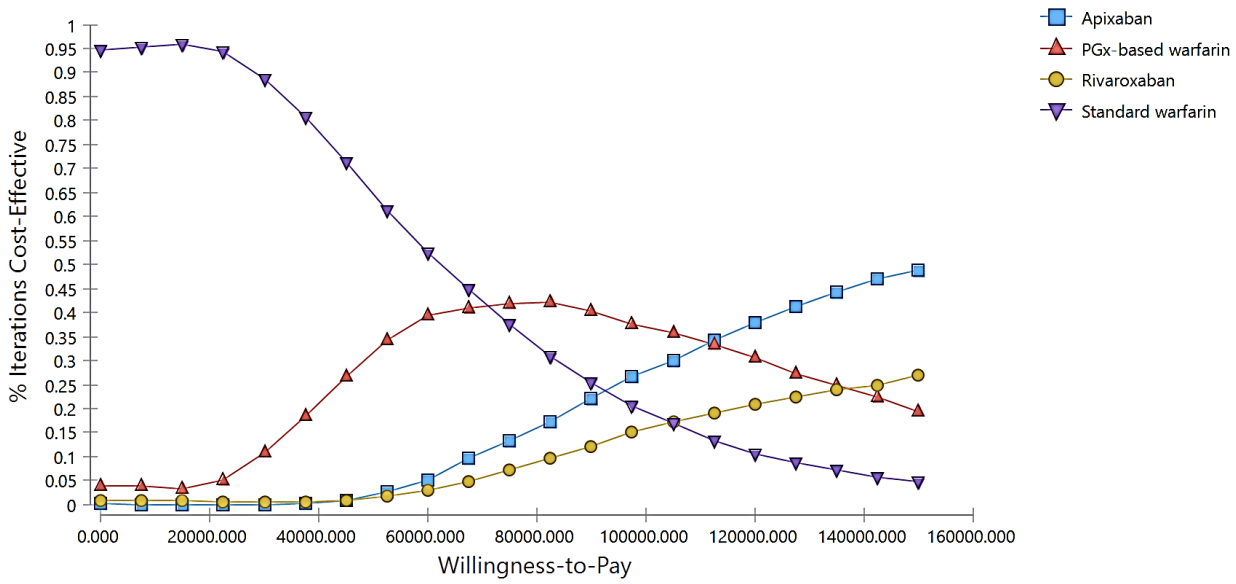

Figure B.2: Cost-effectiveness acceptability curves for patients with a history of Major IS.

At the WTP threshold of $50,000/QALY gained, standard warfarin was the cost-effective treatment in 64.3% of the iterations, followed by PGx-based warfarin in 32.2% of iterations, apixaban in 1.7% of iterations and rivaroxaban in about 1.8% of iterations. At the WTP threshold of $100,000/QALY gained, PGx-based warfarin was cost-effective in 36.6% of the iterations, followed by apixaban in 27.7% of iterations, standard warfarin in 19.8% of iterations and rivaroxaban in about 15.9% of iterations. At the WTP threshold of $150,000/QALY gained, apixaban was cost-effective in 48.7% of the replications, rivaroxaban in about 27.1% of iterations, PGx-based warfarin care in 19.5% of iterations and standard warfarin care in only 4.7% of iterations.

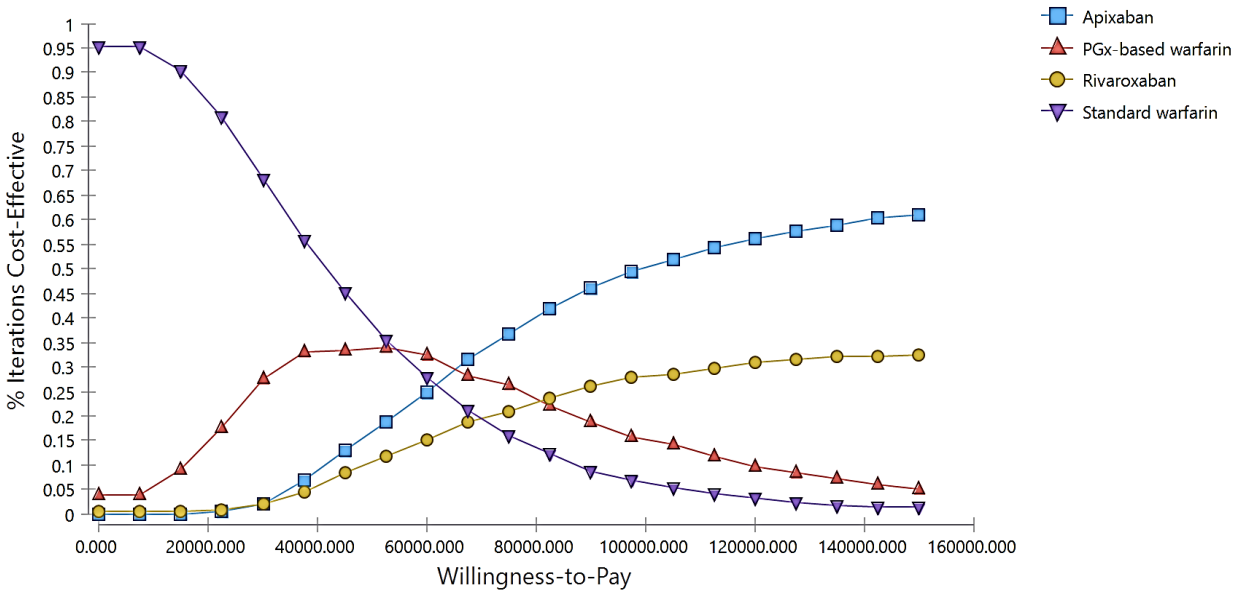

Figure B.3: Cost-effectiveness acceptability curves for patients with a history of Minor IS.

At the WTP threshold of $50,000/QALY gained, standard warfarin was the cost-effective treatment in 39.5% of the iterations, followed by PGx-based warfarin in 32.7% of iterations, apixaban in 17.1% of iterations and rivaroxaban in about 10.7% of iterations. At the WTP threshold of $100,000/QALY gained, apixaban was cost-effective in 50.5% of the iterations, followed by rivaroxaban in 28.2% of iterations, PGx-based warfarin in 15% of iterations and standard warfarin in about 6.3% of iterations. At the WTP threshold of $150,000/QALY gained, apixaban was cost-effective in 61.1% of the replications, rivaroxaban in about 32.5% of iterations, PGx-based warfarin care in only 5% of iterations and standard warfarin care in only 1.4% of iterations.

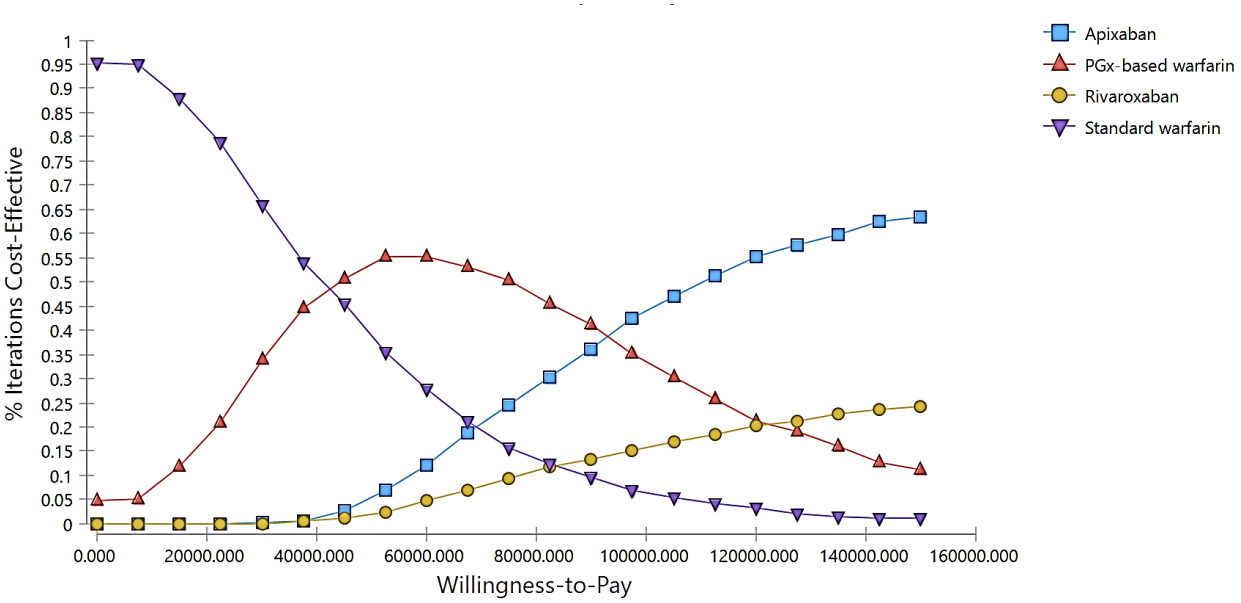

Figure B.4: Cost-effectiveness acceptability curves for patients with a history of TIA or SEE.

At the WTP threshold of $50,000/QALY gained, PGx-based warfarin was the cost-effective treatment in 54.5% of the iterations, followed by standard warfarin in 38% of iterations, apixaban in 5,4% of iterations and rivaroxaban in about 2.1% of iterations. At the WTP threshold of $100,000/QALY gained, apixaban was cost-effective in 44.1% of the iterations, followed by PGx-based warfarin in 33.9% of iterations, rivaroxaban in 15.6% of iterations and standard warfarin in only 6.4% of iterations. At the WTP threshold of $150,000/QALY gained, apixaban was cost-effective in 63.4% of the replications, rivaroxaban in about 24.3% of iterations, PGx-based warfarin care in only 11.1% of iterations and standard warfarin care in only 1.2% of iterations.

Curriculum Vitae

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