Management of Stroke Risk in Patients on Hemodialysis with Non-Valvular Atrial Fibrillation: A Comparison of Cardiologists and Nephrologists in Canada

By

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Pharmaceutical Sciences
University of Toronto

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Abstract

Antithrombotic therapy for stroke prevention in atrial fibrillation (AF) is standard practice, but for hemodialysis (HD) patients, the benefits are unclear and risks are high. Our study objectives were to compare cardiologists’ and nephrologists’ stroke prevention practices in this population and their associated decisional certainty. A cross-sectional, online survey was distributed to members of three Canadian physician societies (Nephrology, Cardiovascular, Heart Rhythm), and to cardiologists at three Universities. The questionnaire included four scenarios of AF in HD patients with varying stroke and bleeding risks. Respondents selected from treatment options and rated their level of certainty. Cardiologists were 3 times more likely than nephrologists to choose anticoagulant therapy, regardless of stroke or bleeding risk. Level of certainty differed between specialties across scenarios; however, this finding is not conclusive. Due to the low response rate (9%), results must be considered tentative. Physicians in Canada are encouraged to consider these differences in prescribing.
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Abbreviations

AF – non-valvular atrial fibrillation

ANOVA – Analysis of Variance

CA – census agglomeration

CCS – Canadian Cardiovascular Society

CHA2DS2-VASc - a recent update to the CHADS2 tool

CHADS2 - risk stratification tool for predicting stroke in AF patients

CHRS – Canadian Heart Rhythm Society

CI – 95% confidence interval

CKD – chronic kidney disease

CMA – census metropolitan area

CSN – Canadian Society of Nephrology

DF – degrees of freedom

DOAC – direct acting oral anticoagulant

DOPPS – Dialysis Outcomes and Practice Patterns Study

GI – gastrointestinal

HAS-BLED – a bleeding risk stratification tool for AF patients

HD – hemodialysis

HR – hazard ratio

INR – international normalized ratio
IQR – interquartile ranges

OR – odds ratio

PD – peritoneal dialysis

PRU – Physicians’ Reactions to Uncertainty

RCT – randomized control trial

RR – relative risk

SD – standard deviation

TTR – time in therapeutic range

UofA – University of Alberta

UofC – University of Calgary

UofT – University of Toronto

US – United States
Chapter 1 Introduction

Background

Non-valvular atrial fibrillation (AF) increases the risk of stroke five-fold and mortality two-fold.\(^1,2\) Approximately 14% of hemodialysis (HD) patients have AF, a rate several times higher than that of the general population.\(^3\) The use of antithrombotic (anticoagulant or antiplatelet) therapy is a well-established standard of care for stroke prevention in AF in the general population. However, for HD patients with AF, the benefits of antithrombotic therapy for stroke prevention are unclear.\(^3-12\) There are no randomized control trials evaluating antithrombotic therapy for stroke prevention in this population and observational studies have shown mixed results.\(^6,7,13-15\) Some observational studies actually have shown an increased risk of stroke (both ischemic and hemorrhagic) with warfarin compared to no therapy.\(^7,13-15\)

Furthermore, HD patients have a 3 to 10 times higher risk of bleeding at baseline compared to the general population, and the serious adverse effects of antithrombotic therapy – such as intracranial hemorrhage and gastrointestinal (GI) bleeding – are more frequent in HD patients.\(^3-12,16\) Therefore, it is not surprising that evidence-based guidelines have conflicting recommendations about the optimal management of stroke risk (whether to use an antiplatelet agent, anticoagulant or no drug therapy) in HD patients with AF\(^2,16-20\) and that there is no consensus amongst clinicians globally.\(^3-12\) Notably, a 2010 study by Wizeman et al. found that prescribing of warfarin, an anticoagulant option for managing AF-related stroke risk in the HD population, to be highest in Canada, compared to most countries in the Western world.\(^8\)

Decisions about the use of antithrombotic therapy for the management of AF-related stroke risk in HD patients are complicated and involve a careful analysis of the risk-benefit profile for each treatment option in each patient. The clinicians involved in this decision-making
in Canada are most commonly nephrologists and cardiologists. Several studies have demonstrated that cardiologists prescribe antithrombotic therapy (particularly anticoagulant therapy) more frequently for AF than do other physician specialties, which may indicate that cardiologists place more importance on stroke risk than on bleeding risk. On the other hand, nephrologists may place more importance on bleeding risk than on stroke risk because they are likely cognizant of the exceptionally high bleeding risk in the HD population. However, no study has directly compared antithrombotic prescribing by cardiologists to that of nephrologists.

Because cardiologists and nephrologists focus on AF populations that have very different risks of stroke and bleeding and because there is research evidence that physicians’ prior direct experience with stroke and major bleeding events in the AF population has affected their prescribing of anticoagulation for AF, there is good reason to postulate that cardiologists and nephrologists differ in their prescribing of antithrombotic therapy for AF.

A 2013 survey by Juma et al. revealed that Canadian nephrologists were uncertain when managing HD patients with AF, especially patients that had bleeding risk factors. Juma et al. found that uncertainty about prescribing warfarin for stroke prevention was higher when hypothetical patients (with HD and AF) had a history of falls (a known bleeding risk factor) or a GI bleed (48% and 43% of nephrologists were uncertain, respectively) than when the hypothetical patient did not have those risk factors (20% of nephrologists were uncertain).

Physician uncertainty in decision-making is important because it has been shown to impact their treatment choices and result in variation in patterns of care. Gerrity and others developed the Physicians’ Reactions to Uncertainty (PRU) model in order to study how uncertainty may influence physician decision-making. The PRU model focuses on five major
elements of the physician decision-making process that are relevant to this research, including:
(1) the specific medical problem, (2) patient characteristics, (3) organizational characteristics, (4)
test and treatment characteristics, and (5) physician characteristics (Figure 2.1).

Statement of the Problem

Compared to most countries in the Western world, physicians practicing in Canada are
the highest prescribers of warfarin for AF in HD patients.\textsuperscript{8} However research evidence suggests
that antithrombotic therapy may be causing more harm than good for HD patients with AF,\textsuperscript{2-15}
making this an important clinical issue in Canada. Given the weak research evidence for a net
benefit of antithrombotic therapy, the lack of treatment consensus and the increased bleeding risk
in the HD population, stroke prevention practices are probably variable and physicians
understandably experience uncertainty when managing this population. Variation in medical
practice is thought to pose “serious questions about the quality, appropriateness and cost-
effectiveness of health care”.\textsuperscript{43}

To address variation in management of such high-risk patients (HD patients with AF)
among experts (cardiologists and nephrologists), it is important that prescribers’ rationale for
their antithrombotic therapy choice (weight put on stroke and bleeding risk) and associated
decisional certainty be understood by both physician specialties. Understanding physicians’
stroke prevention practices for HD patients with AF in Canada is an essential first step to
promote constructive discussion about this issue.
Study Aim

This study aims to identify whether there are systematic differences in drug therapy choices for AF in HD patients between cardiologists and nephrologists in Canada. In the event that such differences are found, the ultimate goal is to stimulate discussion of such differences and establish the need for rigorous prospective clinical research on the optimal management of AF-related stroke risk in HD patients.

Objectives and Hypotheses

Objective 1:

To compare the choice of stroke prevention therapy for HD patients with AF between cardiologists and nephrologists in Canada.

Hypothesis 1:

Cardiologists and nephrologists differ in their choice of drug therapy for stroke prevention in HD patients with AF.

Hypothesis 2:

The influence that level of stroke risk (high versus low) has on choice of drug therapy for stroke prevention in HD patients with AF differs between cardiologists and nephrologists.

Hypothesis 3:

The influence that level of bleeding risk (high versus low) has on choice of drug therapy for stroke prevention in HD patients with AF differs between cardiologists and nephrologists.
Rationale for Hypotheses 1-3

Due to their different experiences, cardiologists and nephrologists may weigh the risk of stroke and bleeding differently when considering antithrombotic therapy to prevent stroke in HD patients with AF. As per the prior discussion, cardiologists appear to place greater importance on stroke risk than do other specialties because they are known to have the highest anticoagulant prescribing rates for AF patients (compared to several other physician specialties). In contrast, nephrologists likely place greater importance on bleeding risk than cardiologists due to their heightened awareness of the high bleeding rates seen in the HD population.

Objective 2:

To compare the level of certainty between cardiologists and nephrologists in Canada for their choice of stroke prevention therapy for HD patients with AF.

Hypothesis 4:

Cardiologists and nephrologists differ in their level of certainty for their choice of drug therapy for stroke prevention in HD patients with AF.

Rationale for Hypothesis 4

Physician certainty is important because it has been associated with variability in medical practices and potentially needless exposure to risk.\textsuperscript{33,35,36,43} The study by Juma et al. was the first to assess the level of certainty among nephrologists in prescribing warfarin to the HD population with AF; it found that certainty was lower when patients had bleeding risk factors.\textsuperscript{27} They also
found that 72.2% of surveyed nephrologists agreed there is clinical equipoise (a state of genuine uncertainty within the expert medical community)\textsuperscript{44,45} about the use of warfarin in HD patients with AF.\textsuperscript{27} No study has measured cardiologists’ certainty regarding managing stroke risk in HD patients with AF even though both cardiologists and nephrologists prescribe antithrombotic therapy for HD patients with AF.

**Research Approach**

To address the above study objectives and hypotheses, an online survey of cardiologists and nephrologists practicing in Canada was undertaken. An adapted version of the PRU model was used as the conceptual framework to guide development of the survey instrument for our study and discussion of our results (Figure 2.2).

**Overview of Thesis**

This thesis is organized into five chapters. Chapter 1 provided background and rationale for this study, and stated the study objectives and hypotheses. Chapter 2 discusses related research and describes the conceptual framework for this study. Chapter 3 outlines the study methods and Chapter 4 presents the results. Finally, Chapter 5 discusses study findings, implications and limitations, and provides suggestions for future research.
Chapter 2 Literature Review

Overview of Chapter

In this chapter, the consequences and treatment options for patients with atrial fibrillation are reviewed with a focus on the HD population. This is followed by a discussion of physician prescribing patterns for the treatment of AF-related stroke risk in the general and HD population. Then, the conceptual framework used to guide this research is described and certainty in medical decision-making is reviewed. Lastly, options for administering surveys are reviewed.

Literature Search Methods

Relevant English-language articles were searched for using the electronic databases MEDLINE and Embase from the establishment of the database to June 2015. A list of keyword and MeSH terms can be found in Appendix A. In addition, the related research references cited by original articles were manually searched.

Atrial Fibrillation and Drug Therapy for Stroke Reduction in the General Population

AF is the most common sustained cardiac arrhythmia. Approximately 25% of individuals over 40 years old will develop AF in their lifetime.\(^2\) A diagnosis of AF is associated with serious health implications, including a five-fold increase in stroke risk.\(^2\) AF is a strong, independent predictor of stroke, with the rate estimated at 5% per year if not treated.\(^2\)

Antithrombotic therapy is frequently used for stroke prevention in patients with AF. Decisions regarding which antithrombotic agent to use for stroke prevention are aided by the CHA\(_2\)DS\(_2\)-VASc and HAS-BLED tools.\(^2,16-19\) CHA\(_2\)DS\(_2\)-VASc (a recent update to the CHADS\(_2\)
tool) is a widely used risk stratification tool for predicting stroke in AF patients based on expert consensus.\(^2\) One point is given for each of the following: congestive heart failure or left ventricular ejection fraction ≤ 40%, hypertension, age 65-74, diabetes, vascular disease and female sex. Two points are given for the following: history of stroke, transient ischemic attack or thromboembolism and age ≥ 75.\(^2\) Anticoagulant therapy (warfarin, rivaroxaban, apixaban or dabigatran) is the standard treatment in AF patients with a CHA\(_2\)DS\(_2\)-VASc score of 2 or greater, while aspirin (an antiplatelet agent) or anticoagulant therapy is indicated for CHA\(_2\)DS\(_2\)-VASc of 1 and aspirin or no therapy is usually recommended for patients with CHA\(_2\)DS\(_2\)-VASc of 0.\(^{2,16-19}\) Patients who cannot take anticoagulant therapy are sometimes recommended dual antiplatelet therapy with aspirin and clopidogrel.\(^2\)

HAS-BLED is a bleeding risk stratification score for AF patients. One point is given for each of the following: hypertension (uncontrolled, ≥ 160mmHg systolic), abnormal renal function, abnormal liver function, history of stroke, history of a bleeding event, labile International Normalized Ratio (INR) (Time in Therapeutic Range < 60%), elderly (≥ 65 years), drugs (use of antiplatelet or non-steroidal anti-inflammatory drugs) and alcohol use.\(^2\) A score of 3 or more indicates increased one-year bleeding risk on anticoagulation sufficient to justify caution or more regular review.\(^2\) A few risk factors are common to both the CHA\(_2\)DS\(_2\)-VASc and HAS-BLED tools (hypertension, age ≥65 years and history of stroke), indicating that these risk factors increase an AF patient’s risk for both stroke and bleeding.

A 2007 meta-analysis by Hart et al. demonstrated that compared to placebo, warfarin reduced AF-related stroke risk by 64% (6 trials) and antiplatelet agents reduce AF-related stroke risk by 22% (8 trials); however, warfarin doubled the risk for hemorrhagic stroke (12 trials).\(^{46}\)
Furthermore, warfarin caused more major bleeding than antiplatelet therapies (relative risk (RR) of 1.5 in trials of AF, but up to 2.5 in non-AF trials).\textsuperscript{16,17}

The new direct-acting oral anticoagulants (DOACs), rivaroxaban, apixaban and dabigatran, have all been evaluated in large, blinded, randomized control trials (RCTs) involving \textgreater 70,000 patients.\textsuperscript{49-51} Each of the DOACs have been found to be non-inferior or superior to warfarin for the outcome of stroke or systemic embolism.\textsuperscript{47-49} None of them caused more major bleeding than warfarin and all were superior for the outcome of hemorrhagic stroke.\textsuperscript{17}

Additionally, it is well established that bleeding risk increases as the intensity of antithrombotic therapy increases from aspirin (75mg-325mg/day) or clopidogrel (75mg/day) alone, to dual anti-platelet therapy (aspirin plus other anti-platelet agent), to the DOACs and finally warfarin therapy.\textsuperscript{17} Therefore, with the numerous RCTs and meta-analysis performed to date and the tools (CHA\textsubscript{2}DS\textsubscript{2}-VASc and HAS-BLED) for weighing the risks and benefits for each individual patient, clinicians and patients are able to make informed decisions about the management of AF-related stroke risk in the general population.

**Atrial Fibrillation and Drug Therapy for Stroke Reduction in the Hemodialysis Population**

The prevalence of AF in HD patients is several times higher than in the general population (14\% versus 2-4\%).\textsuperscript{3} In the HD population, AF is associated with a two-fold increased risk of mortality compared to patients without AF.\textsuperscript{1} Further, HD patients have 4 to 10 times higher rate of stroke and 3 to 10 times the risk of bleeding compared to the general population,\textsuperscript{1,5,6} making the use of antithrombotic therapy for stroke prevention in HD patients with AF a treatment dilemma.

HD patients have a higher baseline bleeding risk compared to the general population due
to a series of multifactorial alterations in the coagulation system, but primarily it is caused by defects in platelet function, which is thought to be due to uremia. The reported higher baseline stroke risk is owing to an acceleration of atherosclerotic processes, but no study has sub-classified ischemic stroke into thromboembolic (due to AF) or thrombotic (caused by atherosclerosis or other mechanisms). HD patients have higher rates of hypertension and diabetes mellitus than the general population. As such, it is possible that the majority of strokes are due to atherosclerosis and not related to AF, providing rationale that anticoagulation may not be the most effective strategy for stroke prevention.

To further complicate the issue, HD patients have more medications and comorbidities and altered pharmacokinetics, putting them at an increased risk of drug interactions and adverse events. There is also evidence that warfarin may increase the risk of vascular calcification in HD patients. Consequently, managing antithrombotic therapy can be difficult in HD patients and one must weigh the risks and benefits carefully.

There is a lack of literature to support the use of antithrombotic therapy for AF-related stroke prevention in HD patients. This is primarily because patients with severe chronic kidney disease (CKD) (glomerular filtration rate < 30ml/min) have been excluded from the RCTs evaluating antithrombotic therapy for stroke prevention in AF. Patients on HD were also excluded from the studies used to generate and validate the CHA2DS2-VASC and HAS-BLED tools, making it unclear if these risk stratification tools can be used in patients who require HD.

To date, there are no RCTs evaluating antithrombotic therapy for prevention of AF-related stroke in the HD population; however, several observational studies have been conducted. Overall, results for the effectiveness of antithrombotic agents are mixed and there are numerous
safety concerns.⁴-⁹,¹³,¹⁴,⁵⁴-⁵⁷ Results from some of these studies suggest that antithrombotic therapy in the HD population increases mortality or the incidence of both ischemic and hemorrhagic strokes (Table 2.1).⁷,⁸,⁵⁷,⁵⁸

**Evidence for use of Warfarin and Antiplatelet Therapies**

Most of the observational studies evaluated the effectiveness and safety of warfarin therapy alone, so there is limited evidence for the other antithrombotic agents (Table 2.1). A 2009 study in the United States (US) by Chan et al.⁷ found that among 1671 patients new on HD with pre-existing AF, warfarin was associated with an increased risk of stroke (combined endpoint of hemorrhagic and ischemic strokes), (hazard ratio (HR) 1.93, 95% confidence interval (CI) 1.29-2.90), but aspirin or clopidogrel use was not associated with stroke. Winkelmayer et al. published a US study comparing stroke rates with and without warfarin therapy for 2313 HD patients with a new AF diagnosis and found no difference in ischemic stroke (HR 0.92, CI 0.61-1.37), but an increase in hemorrhagic stroke (HR 2.38, CI 1.15-4.96).¹³ In contrast, in 2012 Olesen et al. showed that warfarin reduced risk of thromboembolism (combined endpoint of peripheral-artery embolism, ischemic stroke, and transient ischemic attack) (HR 0.44, CI 0.26-0.74), but aspirin did not (HR 0.88, CI 0.59-1.32) in a sub-group of 901 Danish patients on HD or peritoneal dialysis (PD) with AF.⁶ Lastly, a 2014 Canadian study, published by Shah et al., found that treatment with warfarin showed no difference in ischemic stroke or transient ischemic attack (HR 1.14, CI 0.78-1.67), but was associated with an increase in bleeding events (HR 1.44, CI 1.13-1.85) in a Canadian population of 1626 HD and PD patients with newly diagnosed AF.¹⁴

A meta-analysis of 6 observational studies (n=9816, HD and PD patients) comparing warfarin to no drug therapy was performed by Li et al. in 2015, which concluded that warfarin
does not provide a protective effect in dialysis patients with AF, although the heterogeneity of the study was high. This group reported that in dialysis (HD and PD) patients with AF there was no difference in stroke with warfarin (HR 1.23, CI 0.80-1.87, I^2=79.2%) and in HD patients alone, there was an increased risk of stroke (HR 1.57, CI 1.09-2.25, I^2=53.5%). Further, authors reported that warfarin increases the risk of bleeding (HR 1.20, CI 1.03-1.39, I^2=20.4%), and concluded that warfarin should not be routinely recommended to prevent AF-related stroke in dialysis patients. Lastly, a large retrospective study of 41,425 patients with incident HD but not necessarily AF, found that several therapies increase mortality: warfarin (RR 1.27, CI 1.18-1.37), clopidogrel (RR 1.24, CI 1.13-1.35) and aspirin (RR 1.06, CI 1.01-1.11).

While this review highlights the conflicting evidence for the use of antithrombotic therapy in HD patients, any inferences drawn are limited by possible confounding variables due to the observational study design and the fact that INR results (a routine measure of warfarin effectiveness) were not documented well in these studies.
Table 2.1 Observational studies evaluating warfarin in hemodialysis (HD) and peritoneal dialysis (PD) patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Hazard Ratio for Stroke HR (CI)</th>
<th>Hazard Ratio for Major Bleeding HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ischemic</td>
<td>Hemorrhagic</td>
</tr>
<tr>
<td>Chan et al. 2009 – United States⁷</td>
<td>Retrospective cohort n=1671, HD</td>
<td>1.81 (1.12-2.92)</td>
<td>2.22 (1.01-4.91)</td>
</tr>
<tr>
<td>Winkelmayer et al. 2011 – United States¹³</td>
<td>Prospective cohort n=2313, HD</td>
<td>0.92 (0.61-1.37)</td>
<td>2.38 (1.15-4.96)</td>
</tr>
<tr>
<td>Olesen et al. 2012 – Denmark⁶</td>
<td>Prospective cohort n=901, HD + PD</td>
<td>0.44 (0.26-0.74)</td>
<td>No data</td>
</tr>
<tr>
<td>Shah et al. 2014 – Canada¹⁴</td>
<td>Retrospective cohort n=1626, HD + PD</td>
<td>1.14 (0.78-1.67)</td>
<td>1.44 (1.13-1.85) (combined endpoint: hemorrhagic stroke and major bleeding)</td>
</tr>
<tr>
<td>Li et al. 2015¹⁵</td>
<td>Meta-analysis (6 observational studies) n=9816</td>
<td>HD+PD: 1.23 (0.80-1.87) I² = 79.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HD: 1.57 (1.09-2.25) I² = 53.5%</td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

Evidence for use of Direct Oral Anticoagulant Therapy

Aside from warfarin and antiplatelet therapy, the other options for antithrombotic therapy in AF are the DOACs (dabigatran, apixaban and rivaroxaban). These drugs all undergo renal metabolism and clearance to varying degrees and therefore require special consideration in patients with CKD. In the RCTs to date involving 11,169 patients with moderate CKD the DOACs had similar efficacy and safety profiles to warfarin in non-CKD patients. However, the DOACs are not considered safe or indicated for patients with severe CKD or patients on HD due
to the serious risk of drug accumulation. Nevertheless, a 2015 observational study by Chan et al. found that, among 29,977 HD patients with AF in the US, 3.1% and 2.8% were prescribed dabigatran and rivaroxaban, respectively.

Furthermore, the study revealed that, compared with warfarin, dabigatran (HR 1.48, CI 1.21-1.81) and rivaroxaban (HR 1.38, CI 1.03-1.83) were associated with a higher risk of hospitalization or death from bleeding, highlighting the important safety concerns with using the DOACs in the HD population.

**Guidelines for AF-related Stroke Risk Management in HD Patients**

Given the absence of RCT data, controversial observational data and the challenging risk-benefit profile, there is little consensus on initiation and management of antithrombotic therapy in HD patients amongst clinicians globally. This is reflected in the discordant recommendations from current guidelines. The Canadian Cardiovascular Society (CCS) updated its Atrial Fibrillation Guidelines in 2012 to recommend that AF patients with a creatinine clearance < 15ml/min (including patients on dialysis) should not routinely receive either anticoagulant or aspirin for stroke prevention in AF. Similarly, the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines provided this update in 2011: “until new data become available, routine anticoagulation of stage 5 CKD (HD patients fall in this category) patients with AF for primary prevention of stroke is not indicated”. Cardiovascular guidelines from the US provide a different recommendation on this issue. The 2014 American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society states that “for patients with nonvalvular AF with a CHA2DS2-VASc score of 2 or greater and who have end-stage CKD (creatinine clearance <15 mL/min) or are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation”. Lastly, the latest guidelines from
the American College of Chest Physicians (2012) and the European Society of Cardiology (2012) do not make any specific mention of how to manage AF-related stroke risk in patients with end-stage renal disease.\textsuperscript{15,18} The lack of agreement amongst evidence-based guidelines – and, in some cases, failure to even recognize the different risk profile of the HD population – leaves clinicians to make difficult decisions around the use of antithrombotic therapy with their HD patients.

**Prescribing Rates of Antithrombotic Therapy for AF**

**General population**

Numerous studies have demonstrated that antithrombotic therapy for AF in the general population has been underused or inadequate.\textsuperscript{21,60-64} Registries in the US have shown that about half of AF patients with risk factors for stroke are not treated.\textsuperscript{65,66} However, this may change with the introduction of the DOACs due to their improved safety profile compared to warfarin.\textsuperscript{46-49} Among 18,611 anticoagulant naive AF patients being started on anticoagulation in Denmark, warfarin initiation declined by about 40% between August 2011 and October 2013.\textsuperscript{67} This decline in warfarin use is explained by a steep concurrent uptake in dabigatran prescribing, which began just after its introduction to the market in 2011.\textsuperscript{67} Overall, the use of all three DOACs is increasing in the Danish AF population. Other European studies have shown comparable numbers for the uptake of the DOACs and it is expected that similar trends in prescribing are occurring in the US and Canada.\textsuperscript{67}

In fact, the most recent Canadian data on antithrombotic prescribing patterns for AF from a chart audit in the primary care setting (January to June 2013) reveals much higher rates of antithrombotic therapy prescribing than previously reported.\textsuperscript{68} In this study, 647 primary care
physicians provided data on 6,346 patients with AF: 58% were prescribed warfarin, 22% dabigatran, 14% rivaroxaban, 0.3% apixaban, and only 6.6% of patients were not treated with anticoagulant therapy. In terms of antiplatelet therapy, 20% of patients were prescribed aspirin, 2.1% clopidogrel, and 0.8% dual anti-platelet therapy. As this study suggests, an overall increase in anticoagulant prescribing for AF patients is expected to occur in the general population. This is likely due to the strong positive evidence from RCTs for the DOACs and support for their use from evidence based guidelines.

HD Population

The use of anticoagulants in HD patients with AF is low compared to their use in all AF patients: 2-45% in HD patients with AF versus 50% or more of the general population with AF. In 2012, Winkelmayer et al. linked Medicare and prescription claims from HD patients in the US and discovered that of 2,185 HD patients with a diagnosis of AF, only 24% were currently on warfarin (25% had been prescribed warfarin in the past; 51% had never been prescribed warfarin). Antiplatelet prescribing was not considered in this study.

Internationally, warfarin prescribing patterns for HD patients with AF vary widely. Wizemann et al. used data from the international Dialysis Outcomes and Practice Patterns Study (DOPPS) to determine warfarin and aspirin prescribing rates between 1996 and 2004 for HD patients with AF. Overall, in this study of HD patients, aspirin was the most frequently prescribed cardiac-related medication in patients with AF (31%), though it was also prescribed frequently to non-AF patients (23%). Warfarin was used three times more often in AF patients compared to non-AF patients (16% versus 5%). Warfarin use in HD patients with AF was quite variable between countries ranging from 2% in Germany to 37% in Canada.
Australia/New Zealand and the United Kingdom had the next highest warfarin prescribing rates for HD patients with AF at 26%, 25%, and 24%, respectively, and the overall prevalence of warfarin use for HD patients with AF in all European countries was only 9%.  

Considering the extent of warfarin prescribing in the Canadian HD population, the potential harm linked to using antithrombotic therapy in the HD population, along with the new recommendation from Canadian guidelines to avoid routine use of antithrombotic therapy for AF in HD patients, a better understanding of physicians’ stroke prevention practices for the Canadian HD population with AF is needed.

**Antithrombotic Prescribing for AF by Physician Specialty**

Several studies have documented variations in physicians’ prescribing patterns of antithrombotic therapy for stroke prophylaxis in AF by medical specialty. Cardiologists have been identified as the specialty most likely to prescribe anticoagulant therapy to their patients. Kowey et al. published data in 2010 revealing that cardiologists in the AFFECTS registry (a registry designed to assess the treatment patterns of AF among practicing cardiologists in the US who had received training with the 2001 or 2006 American College of Cardiology/American Heart Association/European Society of Cardiology AF guidelines) prescribed antithrombotic therapy to 83% of their patients with AF (64% warfarin and 32% aspirin). A 1996 survey of 88 cardiologists and 126 non-cardiologists in the United Kingdom found that 69% of cardiologists agreed they would prescribe an anticoagulant to new AF patients, compared to only 27% of non-cardiologists (p<0.0001). More recently, in 2013, among 4,845 patients admitted to cardiology or medicine units in Italy with a primary or secondary diagnosis of AF, cardiologists prescribed anticoagulant therapy more often than
internal medicine physicians (64.2% versus 46.3%, p<0.001), even though the stroke risk was
dlower in patients admitted to the cardiology service (mean CHADS<sub>2</sub> scores were 1.7 ± 1.2 versus
2.4 ± 1.3, p<0.0001).<sup>22</sup> In 2013, using the ORBIT-AF Registry (a US database of outpatients
with incident and prevalent AF), Fosbol et al. revealed that the prescribing of warfarin or
dabigatran in 10,097 AF patients was 73.6% for internal medicine/primary care physicians,
76.7% for cardiologists, and 76.8% for electrophysiologists (p=0.02).<sup>23</sup> In a 2013 US cohort of
141,642 patients with newly diagnosed AF, warfarin use was higher in cardiology-treated
patients than primary-care-treated patients (68.6% versus 48.9%, p<0.0001).<sup>24</sup> Finally, in a 2007
Dutch study, cardiologists prescribed anticoagulation more often than general practitioners and
internists (84% versus 76% and 70% respectively; p < 0.001), and less often antiplatelet drugs
(12% versus 20% and 18% respectively; p < 0.001) in a cohort of 1,596 AF patients.<sup>70</sup>

There are no data comparing cardiologist prescribing rates for AF to that of
nephrologists, nor are there data on prescribing rates of nephrologists exclusively. Overall, the
literature to date demonstrates variable rates of antithrombotic prescribing to AF patients
globally. However, cardiologists are consistently found to be higher prescribers of anticoagulant
therapy for AF compared to other specialties.

**Patient Factors Associated with Prescribing of Antithrombotic Therapy for AF**

**General Population**

Numerous studies have investigated factors that may explain the under prescribing of
antithrombotic therapy for AF. In 2011, Pugh et al. conducted a systematic review of 30 surveys
(5 of which were done in Canada) that addressed physicians’ attitudes around prescribing
anticoagulation for patients with AF.<sup>28</sup> Increasing age, bleeding risk, risk of falls, co-morbidities
alcoholism and cognitive impairment) and the patients’ ability to comply with treatment were all important barriers to anticoagulation for AF. Bleeding risk was the most cited reason for not prescribing anticoagulation, followed by risk of falls.

Findings from a 2015 study of physicians caring for French nursing home patients (n = 1,085) with AF, echo Pugh’s results; recurrent falls (odds ratio (OR) 4.9, CI 2.4–9.9), past history of bleeding (OR 3.62, CI 1.54–8.51) and advanced age (OR 1.1, CI 1.01–1.17) were significantly associated with not prescribing anticoagulants. Nicholls et al. published Canadian data on this issue in 2014; falls risk, bleeding risk and poor patient adherence were all highly cited reasons for not treating with warfarin among 335 physicians (46% family doctors, 38.5% internal medicine specialists, and 15.5% geriatricians).

HD Population

Research on factors that correlate with antithrombotic prescribing in the HD population is limited. One study published in 2014 collected data from 10 Italian HD centers on 1,529 HD patients with paroxysmal AF (self-terminating), persistent AF (required termination by cardioversion), or permanent AF (arrhythmias that could not be interrupted spontaneously or by cardioversion) to investigate nephrologists’ clinical approach to the prescribing of anticoagulants for HD patients with AF. It found that the presence of permanent AF (OR 4.28, p < 0.0001) (as opposed to persistent or paroxysmal) was the only clinical factor positively associated with anticoagulant prescribing, while previous major bleeding event (OR 0.35, p = 0.004) was inversely related. The CHADS 2 score was not associated with anticoagulant prescribing (OR 0.85, p = 0.08), meaning stroke risk did not influence prescribing of anticoagulation. Yet, a higher bleeding risk (measured by the HAS-BLED score) did result in lower anticoagulant
prescribing (OR 0.74, p = 0.03). Therefore, compared to predictive factors identified from studies in the general population (age, bleeding risk, falls risk and adherence to therapy), bleeding risk was the only common statistically significant barrier to prescribing anticoagulants in this HD population with AF. Bleeding risk is an important consideration when prescribing anticoagulation in any population, but given that the risk of bleeding in HD patients is elevated and exacerbated by anticoagulation, physicians have reason to be more conservative with therapy.

A 2013 Canadian study published by Juma et al. surveyed nephrologists practicing in Canada (n=56) to determine their opinions on the use of warfarin for AF in hypothetical HD patients with different stroke and bleeding risk factors, and to identify the degree of uncertainty involved. Nephrologists were most uncertain about warfarin use for AF when patients were at risk of falls or had a history of GI bleeding, which are two deterrents to anticoagulation reported in previous studies. Further, Juma et al. revealed that unlike the Genovesi study of nephrologists in Italy, Canadian nephrologists may be using the stroke risk stratification tools when prescribing because the likelihood of using warfarin increased from 50% to 77% (p = 0.006) as CHADS2 score increased from 2 to 5, as long as bleeding risk factors were absent.

Effect of Physician Experiences on Prescribing

Physicians’ prior direct experience with adverse events has been shown to impact their prescribing of anticoagulation for AF. In a 2014 survey of Canadian family doctors, geriatricians, and internal medicine specialists, Nicholls et al. investigated factors that may have an effect on warfarin prescribing for AF including prior experience with a patient who had a stroke or bleed. They reported that physician experience with a serious bleeding event was not
associated with warfarin prescribing; however, experience with a stroke in an AF patient not prescribed warfarin was a significant influence. In contrast, two studies, a 2008 survey of Australian family physicians and a 2006 retrospective cohort study of Canadian physicians (physician specialty unspecified), have found that physicians who had prior experience with AF patients that had suffered a major bleeding event were less likely to endorse anticoagulation (i.e. warfarin) in subsequent patients. However, in these studies, no association was found between anticoagulant prescribing and physician experience with AF patients who had experienced a stroke. The effect physician experience can have on prescribing has been argued to stem from the “availability heuristic”, a general psychological mechanism underlying many human judgments whereby the judgment of the probability of a particular outcome can be based on how easily one can recall previous similar outcomes. Vivid events are more easily remembered than everyday ones, so the memory of a single severe bleeding event while on warfarin might lead to a general overestimation of the bleeding risk for future patients, and consequently reduced warfarin use. A 2012 meta-analysis studying the predictors of warfarin use in AF, concluded that the influence that physician characteristics and experiences may have on prescribing patterns should be taken into consideration in understanding physician prescribing. If experience with a stroke or bleeding event influences anticoagulant prescribing (albeit not always in a similar manner for all physicians) there will likely be variation in drug therapy recommendations for AF between cardiologists and nephrologists because the patient populations that these specialties have experience with have very different stroke and bleeding event rates.
Uncertainty in Clinical Decision-Making

Uncertainty is ubiquitous in medical care and shapes many decisions made by clinicians everyday.\textsuperscript{33} It can cause considerable stress and anxiety for both patients and clinicians.\textsuperscript{34,40} Uncertainty can have multiple meanings and sources, and it has not been explicitly defined in the literature.\textsuperscript{75} Often it is thought of as a subjective awareness of one’s lack of knowledge. Medical uncertainty can arise from several sources: limited medical knowledge, unpredictability of disease and of a patients’ response to therapy, and variability in the physicians’ and patients’ attitudes toward risk.\textsuperscript{33,41,43,76-80}

There are numerous studies about the impact of uncertainty in medical care\textsuperscript{33,34,36,43,80-87} and several researchers have investigated the relationship between physician uncertainty and physician decision-making or behaviour.\textsuperscript{37-39,43,78,80,88-90} Both uncertainty and physicians’ reaction to it may result in unexplained variations in patterns of care.\textsuperscript{33,35,36,43} Clinicians must learn to tolerate uncertainty and develop strategies to deal with uncertainty if they are to provide quality care to patients with complex conditions.\textsuperscript{33-35,81,82}

Numerous scales have been developed for measuring physician uncertainty.\textsuperscript{40-42,77,78,85,91} The most reliable and commonly used scale is the Physicians’ Reactions to Uncertainty (PRU) scales developed by Gerrity and others.\textsuperscript{40-42} The PRU scales seek to isolate physicians’ reaction to uncertainty from other uncertainties present in the clinical encounter, such as patient uncertainty or uncertainty of the effectiveness of therapy.\textsuperscript{42} The PRU scales include: (1) “anxiety due to uncertainty”, (2) “concern about bad outcomes”, (3) “reluctance to disclose uncertainty to patients” and (4) “reluctance to disclose uncertainty to physicians”.\textsuperscript{40-42} The latest version of the PRU scales is a result of numerous iterations using factor analysis and they have good internal
consistency, with an alpha coefficient of approximately 0.75.\textsuperscript{42}

PRU (measured using the PRU scales) has been shown to impact decision-making, leading to excessive resource use or changes in test interpretation.\textsuperscript{37-39,92} Allison and others\textsuperscript{37} studied the relationship between PRU and resource use of general internists and found that higher PRU scores were associated with more test ordering and, subsequently, higher costs. In the 2007 study by Carney,\textsuperscript{39} it was found that radiologists with higher PRU scores had higher recall rates and lower specificity in diagnostic mammography interpretation.

Some degree of physician uncertainty is unavoidable in medicine, from making a diagnosis to selecting a test procedure or treatment to estimating outcomes for patients. Based on the literature reviewed above, how a physician deals with their uncertainty is an important factor in their decision-making process. Techniques have been developed to help physicians deal with uncertainty, which could reduce stress and anxiety and also decrease the variation in physician decision-making and use of resources.\textsuperscript{34} The rise of the evidence-based medicine movement, an approach of combining a physician’s clinical expertise with available high-quality scientific evidence and the patient’s values into clinical decision-making, has increased awareness of the limitations of scientific knowledge and is one approach that may help physicians deal with uncertainty.\textsuperscript{34,75} At the very least, acknowledgement and awareness of physician uncertainty is important to improving medical care.

Uncertainty in Decision-Making for HD Patients with AF in Canada

Findings from the survey by Juma et al. demonstrated that Canadian nephrologists were uncertain about the use of warfarin to manage stroke risk in HD patients with AF, particularly when patients had bleeding risk factors.\textsuperscript{27} Uncertainty about prescribing warfarin for stroke
prevention was higher when hypothetical patients (with HD and AF) had a history of falls or a GI bleed (48% and 43% of nephrologists were uncertain, respectively) compared to a patient without those risk factors (20% of nephrologists were uncertain). When a high stroke risk patient had both a history of falls and GI bleeding, only 4% of nephrologists were likely to prescribe warfarin and 29% were uncertain. Even without bleeding risk factors, uncertainty about starting warfarin treatment in an HD patient with AF was higher compared to in an AF patient not on HD (36% compared to 16%, p = 0.03). They also found that 72.2% of respondents agreed that there was clinical equipoise (a state of genuine uncertainty within the expert medical community) about the use of warfarin in HD patients with AF. The majority of respondents agreed that the results of an RCT of warfarin versus placebo in HD patients with AF would be relevant to their practice (98.2%) and the majority agreed that they would be willing to enroll their patients in such an RCT, whether the patient was (67%) or was not (82%) anticoagulated, demonstrating the desire for increased certainty in management of these patients. This group did not assess the level of certainty around the use of other drug therapy options for reducing stroke risk in this population – i.e., antiplatelet agents (aspirin, clopidogrel, dipyridamole) or the DOACs (rivaroxaban, apixaban, dabigatran) – nor did they investigate the level of certainty that cardiologists experience. It is the intent of this research to fill this gap in the literature.

**Conceptual Framework for the Study**

The conceptual framework for our survey was adapted from the PRU model, developed by Gerrity et al. The PRU model integrates internal processes (cognitive and affective) with external influences (sociological and cultural) that may be involved in physicians’ decision-making processes. The PRU model focuses on five major elements of the decision-making
process, including: (1) the specific medical problem, (2) patient characteristics, (3) organizational characteristics, (4) test and treatment characteristics, and (5) physician characteristics (Figure 2.1). This model was created by Gerrity et al. to guide their investigations of uncertainty in physician decision-making with the goal of creating a validated scale (PRU scales) to study the relationship between physicians’ emotions, their cognitive processes and their coping behaviors under conditions of uncertainty.

**Figure 2.1** The PRU Model: Conceptual model by Gerrity et al. of the factors influencing Physicians Reactions to Uncertainty (with permission)⁴⁰-⁴²
For our research, an adapted version of the PRU model was used to guide development of the survey instrument. The model was adapted to better reflect the clinical scenario under investigation and the scope of this research, so certain aspects of the Gerrity model were removed: patient past experiences and attitudes, test characteristics, source of payment for physician encounter, appointment schedule and time a physician spent with patient (Figure 2.2). In addition, a pathway connecting physician characteristics and physician behavior was added to our adapted model because it was hypothesized that cardiologists and nephrologists (i.e. the physician characteristic, specialty) would differ in their choice of drug therapy (physician behavior). The basis for this hypothesis was that cardiologists and nephrologists focus on AF populations that have very different risks of stroke and bleeding (general population and HD population, respectively). So, it is reasonable to postulate that cardiologists and nephrologists differ in their choice of drug therapy for AF because there is research evidence that physicians’ prior direct experience with stroke and major bleeding events in the AF population has affected their prescribing of anticoagulation for AF. Further, cardiologists are known to have higher anticoagulant prescribing rates for AF patients (compared to several other physician specialties) suggesting they may place greater importance on stroke risk than do other specialties. In contrast, nephrologists likely place greater importance on bleeding risk than cardiologists due to their longitudinal experience with the HD population, which have exceptionally high bleeding rates.

Our model began with the identification of the medical problem (i.e., preventing stroke in HD patients with AF) and then identified potential therapies and their characteristics (efficacy, safety, monitoring and costs). Associating the medical problem and treatment characteristics
with a patient’s characteristics (age, gender and medical history translated into stroke and bleeding risk scores: CHA$_2$DS$_2$-VASC and HAS-BLED) is the next step in the model and leads to the physician level of certainty. “Uncertainty inherent in the clinical encounter” from Gerrity’s model was changed to “physician level of certainty” in our model so that it could more easily be measured and interpreted. For some combinations of patient and treatment, the level of certainty may be low, while for others it may be high. Physicians bring to clinical encounters their own reactions to clinical uncertainty (i.e., PRU) and this may vary depending on their age, gender, years in practice and clinical specialty (physician characteristics). Along with physician characteristics, practice setting and location (organizational characteristics), as well as patient and treatment characteristics, are postulated to influence PRU. The primary outcome variable, choice of drug therapy for stroke risk management, is directly influenced by four variables: organizational characteristics, patient characteristics, PRU and physician characteristics. With the exception of PRU, these variables, and physician level of certainty, are translated into items in our survey instrument.
Figure 2.2 Conceptual model of the factors influencing choice for stroke risk management (adapted with permission from Gerrity’s Physicians’ Reactions to Uncertainty model)\(^{40-42}\)

The PRU scales were not incorporated into our survey instrument because the aim of this research was to first identify and compare the level of certainty for cardiologists and nephrologists in deciding between drug therapy options for AF-related stroke risk management of HD patients. Studying the relationship between PRU (using the PRU scales described above) and choice of drug therapy to reduce stroke in AF patients on HD would be best explored through qualitative methodology in order to better understand a physician’s thought process. For example, it would be difficult in a quantitative survey to understand how physician scores on the
PRU subscale, Concern About Bad Outcomes, may affect choice of drug therapy because it would not be clear which bad outcome (stroke, bleed or other) the physicians were concerned about when choosing that particular therapy. While PRU scales are central to Gerrity’s model, including them in our survey instrument would have made the questionnaire lengthy, would likely have impacted our response rate and was not a primary aim of this thesis. The impact of this limitation on study findings is described in Chapter 5.

Review of Survey Administration Methods

Common survey administration methods include electronic or online questionnaires, postal questionnaires, face-to-face interviews, and telephone interviews. Online questionnaire distribution is usually considered the most convenient and efficient way of connecting with potential participants.\(^9\) However, a disadvantage to online questionnaires is that they may produce a lower response rate than other survey distribution methods, such as postal questionnaires.\(^9\) In a survey of orthopedic surgeons, Leece et al. compared online (n=221) and postal (n=221) administration methods and found that online recipients had a lower response rate (45% versus 58%, p < 0.01).\(^9\) One method of maximizing response rate is to use follow up contacts with potential participants in the form of reminders or providing additional copies of the questionnaire. Kittleson et al. stated that a 25-30% response rate from an online survey can be expected with one contact and that repeated contact can approximately double the response rate.\(^9\) For postal surveys, each additional mailed reminder yields about 30-50% of initial responses\(^9\) and Dillman has proposed that 3 follow-up contacts is optimal.\(^9\)

There is variability in the range of response rates reported in online surveys of health professionals.\(^9\) For example, the response rate for 2 online surveys of health professionals
containing hypothetical patient cases was 18% (where the survey was distributed at 0, 1 and 3 months) and 67% (two distributions, but interval was not specified)\textsuperscript{99,100}. Identifying individuals using membership to a professional society or association for participation in a survey does not improve the predictability of response rates for health professionals, as shown in the following online physician surveys, but it is a convenient way of reaching a large sampling frame. A study published by Pharis et al. in 2011 surveyed 134 Canadian cardiologists specializing in congenital heart disease identified through professional membership lists and achieved a 70% response rate for their online survey.\textsuperscript{101} Non-responders were sent the questionnaire up to four times, with two-week intervals between each follow-up. In 2013, Juma et al. surveyed a random sample of one-third (n=90) of nephrologist members of the Canadian Society of Nephrology (CSN) and achieved a response rate of 62%.\textsuperscript{27} This group sent their online questionnaire three separate times at two-week intervals. In contrast, the response rate in a 2012 survey of Canadian Cardiovascular Society (CCS) members was poor: 9.3% of cardiac specialist members (n=765) completed the online questionnaire, even though a personalized approach with repeated contacts was used to optimize response rate (number of contacts or interval between contacts was not specified).\textsuperscript{102}

Online surveys using professional societies or associations may provide unpredictable response rates, yet studies by Juma and Pharis discussed above, demonstrate that high response rates are achievable (62% and 70%, respectively). Both Juma and Pharis used repeated contacts and a distribution interval of two-weeks. For our study, the sampling frame available to study investigators included cardiologist and nephrologist professional societies that provided means to conveniently connect with members electronically. Therefore, our questionnaire was distributed in electronic format with three repeated contacts at two-week intervals with the goal of achieving a response rate of 60% or greater.
Chapter 3 Methods

Overview of Chapter

This chapter first describes the process undertaken to develop the survey instrument. Then, the study design, sampling frame and survey procedures are outlined, followed by a description of the statistical analyses planned to address each study objective.

Survey Questionnaire

Questionnaire Development

The conceptual framework (described in Chapter 2) used to create the questionnaire was an adapted version of the PRU model (Figure 2.2). For this study, the PRU element, the medical problem, was preventing stroke in HD patients with AF; and the PRU element, physician behavior, was the physician’s choice of drug therapy. Development of questionnaire items drew upon the following PRU elements: physician, patient, treatment, and organizational characteristics, as well as uncertainty inherent in the clinical encounter (physician level of certainty in our model).

The PRU elements patient characteristics, treatment characteristics, and physician behavior (choice of drug therapy) were represented in seven patient scenarios in the initial version of the questionnaire. The comorbidities that described these patients were selected from comorbidities in the CHA²DS²-VASc and HAS-BLED tools or were known adverse reactions to warfarin.³,¹¹,¹³ The drug therapy options for each scenario were aspirin, other anti-platelet agent (clopidogrel, dipyridamole, etc.), warfarin, one of the DOACs (apixaban, rivaroxaban or dabigatran), no drug therapy or other.
Physician level of certainty was assessed using an 11-point rating scale anchored by very uncertain (score of 0) and very certain (score of 10) and it’s purpose was to measure the respondents’ level of certainty for their choice of drug therapy in each of the patient scenarios. A validated certainty scale could not be identified in the literature. However, several studies have used similar scales to our 11-point scale to assess decisional certainty. For example, Jeffrey et al. sought to determine the degree of certainty for medical students’ interpretation of chest radiographs using a five-point scale that ranged from 0 (uncertain), 1 (25% certain), 2 (50% certain) 3 (75% certain) and 4 (100% certain). An 11-point scale was chosen, as opposed to a shorter scale (less than 11 points) to ensure respondents could provide more precision to their certainty because investigators believed that certainty may vary substantially among cardiologists and nephrologists due to its subjective nature. Further, a scale with an odd number of values was used, so that a neutral score could be selected (score of 5).

The PRU elements physician and organizational characteristics were represented in the section on physician demographics. The response options in this section were adapted with permission from a recent survey study by Juma et al.

After the initial questionnaire development, four clinicians with expertise in nephrology or cardiology met on an iterative basis to assess the face and content validity of the questionnaire. This process resulted in changes to the wording of scenarios, minor changes to the structure of the questionnaire and removal of one item that sought to assess whether nephrologists and cardiologists routinely consult each other when making decisions around stroke prevention in HD patients with AF.

Discussion with my advisory committee led to a decision to limit the scenarios from seven to four, to reflect a 2 x 2 matrix of high and low levels of risk for each of stroke and
bleeding because, as discussed in Chapter 2, these patient characteristics are of great importance when making decisions about drug therapy for AF. Furthermore, this stroke and bleeding risk matrix created extremes of patient risk which allowed data analysis to be optimized (stroke and bleeding risk could be coded as high or low). The four scenarios that were included were the most clinically relevant and had CHA₂DS₂-VASc and HAS-BLED scores that fit into the following risk categories: (1) low risk of stroke and bleeding, (2) high risk of bleeding and low risk of stroke, (3) high risk of stroke and low risk of bleeding and (4) high risk of stroke and bleeding (Appendix B).

**Questionnaire Pretesting**

The questionnaire (Appendix B) was pretested with a convenience sample of four cardiologists and four nephrologists, each practicing in a university-affiliated hospital in Toronto. The eight physicians were provided with an overview of the study in an email and offered a brief in-person or telephone conversation with the primary investigator to obtain additional information about the study. They were then asked to review the questionnaire in electronic format, which was sent to them by email. In addition, they were asked to participate in a 20 to 30-minute telephone or in-person interview with the primary investigator a few days after they had completed the questionnaire to provide their recommendations for improving the questionnaire and to respond to several debriefing questions (Appendix C).

Pretesting was completed using iterative methods. The first phase involved two nephrologists and two cardiologists from the convenience sample. These pre-test participants had positive comments overall, but made the following suggestions: add “dual antiplatelet therapy” as a drug therapy choice, add the term “non-valvular” to AF (valvular AF, which is a less
common condition, requires different treatment considerations) and other minor modifications. These comments and suggestions were incorporated as revisions were made to the questionnaire. In the second phase, the revised questionnaire was distributed to the remaining four physicians (two cardiologists and two nephrologists) in the convenience sample. These participants had positive comments about the timeliness and importance of the survey. One suggested removing the drug therapy option “other” as it was unnecessary and might create confusion in data analysis. Two physicians suggested specific additions to the case descriptions, such as “bleed has resolved” in the scenario where a patient had a recent GI bleed. Another suggested that the statement “please choose one of the options provided for your management of stroke risk” be changed to “please choose one of the options provided that you would recommend for the management of stroke risk”. The physician’s rationale was that in practice there might be other factors that could not be expressed in this questionnaire that may influence how a physician actually manages a patient and therefore thought the use of the word “recommend” was superior. For example, the patient’s preference might change the physician’s recommended drug therapy. After incorporating these suggestions from the debriefing interviews in phase two and further discussion with co-investigators, a final version of the questionnaire was prepared (Appendix D).

Final Questionnaire Structure

A written introduction to the survey (Appendix E) preceded the questionnaire (Appendix D) in the electronic version that was distributed to respondents. Section one of the questionnaire consisted of four patient scenarios, which systematically presented all possible combinations of high and low risk of stroke and bleeding. Respondents were asked to select from drug therapy options for the management for AF-related stroke for each scenario. Drug therapy options were
aspirin, other anti-platelet agent (clopidogrel, dipyridamole, etc.), dual anti-platelet therapy (aspirin plus another agent), warfarin, one of the DOACs (apixaban, rivaroxaban or dabigatran) or no drug therapy. Participants then rated their level of certainty in their decision for that scenario on a scale of zero to ten (0 being very uncertain, 5 being neutral, 10 being very certain).

Example of a patient scenario from the questionnaire:

**Scenario 2:** A 50-year-old male on HD with non-valvular AF, hypertension, alcoholism and a history of gastrointestinal bleeding in the past 3 months (bleed has resolved).
  - Aspirin
  - Other anti-platelet agent (clopidogrel, dipyridamole, etc.)
  - Dual anti-platelet therapy (Aspirin plus other)
  - Warfarin
  - One of the new oral anticoagulant therapies (apixaban, rivaroxaban or dabigatran)
  - No drug therapy

Level of CERTAINTY (0 being very uncertain, 5 being neutral, 10 being very certain):
0 1 2 3 4 5 6 7 8 9 10

In section two, respondents were asked to provide information on their demographic characteristics: age, gender, years in practice, province of practice, and clinical specialty (Appendix D). The survey software, Survey Monkey®, was used to create an electronic version of the questionnaire.

**Study Design**

This study was a cross-sectional survey of nephrologists and cardiologists practicing in Canada in 2015. The Research Ethics Board at the University of Toronto approved the research protocol (REB #31274).
Sampling Frame

The survey sampling frame included members of the Canadian Society of Nephrology (CSN) and the Canadian Cardiovascular Society (CCS). At the time of survey distribution, in 2015, the CSN had 400 nephrologist members, which represented approximately 62% of the practicing nephrologists in Canada. The CCS had 900 cardiologist members, representing about 66% of the cardiologists practicing in Canada.

Due to low participation by cardiologist members of the CCS (only 5 completed questionnaires were returned) the sampling frame was expanded to include cardiologist members of the Canadian Heart Rhythm Society (CHRS) and cardiologists affiliated with the Divisions of Cardiology at the University of Toronto (UofT), the University of Calgary (UofC) and the University of Alberta (UofA). In 2015, the CHRS had 204 cardiologist members and the Cardiology Divisions at the UofT, UofC and UofA had 103, 60, and 30 affiliated cardiologists, respectively.

There may have been some overlap among the cardiology groups in the sampling frame. For example, some cardiologists in the CHRS may also have been members of the CCS or affiliated with one of the universities. Potential participants were told that, although the questionnaire had been distributed to several groups, we expected only one response from each individual.

Survey Eligibility Criteria

Study participants must have been cardiologists or nephrologists practicing in Canada and they must have managed or been consulted on stroke prevention for HD patients with AF. To exclude physicians that did not meet the latter inclusion criterion a screening question was
included at the beginning of the questionnaire: “Are you involved in decisions regarding the use of antithrombotic therapy to prevent stroke in hemodialysis patients with atrial fibrillation? (If you answer no, please disregard the rest of the survey).” Upon selecting “no”, the online questionnaire automatically ended.

**Survey Procedures**

The questionnaire and accompanying cover letter was distributed three times at two-week intervals to members of the CSN and CCS through their respective organizations (Appendix D and E). CSN members received a link to the questionnaire and cover letter in an email, forwarded by the CSN from the email account of a co-investigator, who was a member of the CSN (Appendix F). Investigators did not have access to the contact information of CSN members. The CCS did not offer direct email distribution of the questionnaire to individual members; instead, it offered to include a link to the questionnaire and cover letter in its bi-weekly electronic newsletter sent to their members. In the newsletter, the questionnaire website was hyperlinked to the phrase “Clinical Controversy in Atrial Fibrillation – CCS Members Need Your Help!” under the newsletter heading “In This Issue” and a message containing the questionnaire website was also included in the main content of the newsletter (Appendix G).

After initial distribution to the CSN and CCS, the questionnaire and cover letter were also distributed three times at two-week intervals to members of the CHRS via email from a co-investigator (a CHRS member), and to cardiologists affiliated with UofT, UofA, and UofC via email from the Director of Cardiology at UofT, the Division Chief of Cardiology at UofA and the Acting Director of Cardiology at UofC, respectively. Investigators did not have access to the contact information of CHRS members or cardiologists affiliated with any of the universities.
See Appendix F for content of the email forwarded to potential respondents from CSN, CHRS, UofT, UofA and UofC. The timeline for distribution of the questionnaire is outlined in Appendix H.

**Data Management and Analyses**

Data analysis was performed with the Statistical Program for Social Sciences (SPSS) software, version 23.0 and R software, version 3.2.3, package ‘multgee’ (2015).\textsuperscript{113,114} The \textit{a priori} level of statistical significance was $p \leq 0.05$ for all statistical tests.

**Data Management**

For purposes of the regression analyses, drug therapy choice responses for each patient scenario were recoded into “anticoagulant” and “antiplatelet” choices. Aspirin, other anti-platelet agent (clopidogrel, dipyridamole, etc.) and dual antiplatelet therapy were grouped in the “antiplatelet” choice category. Warfarin and the direct-acting oral anticoagulant therapies (apixaban, rivaroxaban or dabigatran) were grouped in the “anticoagulant” choice category. No drug therapy was in its own category.

Respondents who did not complete all items in the questionnaire were excluded from the data analysis. Exclusion of these responses (26 out of 188) was required for data analysis because the last item on the questionnaire was regarding physician specialty (a critical independent variable for each hypothesis in this study), and a respondent could not simply “skip” an item; they had to finish the questionnaire in order to reach the physician specialty item.
Data Analyses

Item responses were summarized in frequency distributions and means. Non-response bias was assessed by comparing the characteristics of physician respondents to 2015 Canadian physician demographic statistics from the Canadian Medical Association.115,116

Objective 1: Comparison of Cardiologists’ and Nephrologists’ Choice of Drug Therapy

First, a 2x3 chi-square test was performed on each of the four scenarios in the questionnaire to determine whether there was a statistically significant difference in drug therapy choice between cardiologists and nephrologists. Chi-square tests were performed first in order to confirm a difference in drug therapy choice between specialties before conducting the complex logistic regression model. The dependent variable, drug therapy choice had three levels (“anticoagulant”, “antiplatelet”, and “no drug therapy”) and the independent variable was physician specialty with two levels (cardiologist and nephrologist). Then, a mixed-effects multinomial logistic regression model was applied to evaluate the association between drug therapy choice and physician specialty, bleeding risk and stroke risk. The dependent variable was drug therapy choice and independent variables were as follows: physician specialty, stroke risk (high and low), and bleeding risk (high and low). Main effects of each independent variable and two-way interactions between physician specialty and stroke risk and between physician specialty and bleeding risk were evaluated.

Interaction terms in the model were not found to be statistically significant and they were subsequently removed from the model. For the remaining of the analysis only a main effects model was used. The main effects model was run twice, first with no drug therapy as the reference category, then with antiplatelet therapy as the reference category. Even though it is not
typical to run a model with multiple reference categories, it was done so that an OR and CI could be calculated for each drug therapy choice pair.

Hypothesis 1 (“cardiologists and nephrologists differ in their choice of drug therapy for stroke prevention in HD patients with AF”) was addressed through main effect of physician specialty. Hypothesis 2 (“the influence that level of stroke risk (high versus low) has on choice of drug therapy for stroke prevention in HD patients with AF differs for cardiologists compared to nephrologists”) was addressed through the interaction effect of physician specialty and stroke risk. Hypothesis 3 (“the influence that level of bleeding risk (high versus low) has on choice of drug therapy for stroke prevention in HD patients with AF differs for cardiologists compared to nephrologists”) was addressed through the interaction effect of physician specialty and bleeding risk. By providing one drug therapy choice for each of the four scenarios, each physician provided four correlated data points and therefore a mixed effects model was used to account for within-physician variability. See Appendix I for the model equation and variable coding.

Objective 2: Comparison of Cardiologists’ and Nephrologists’ Level of Certainty

To address hypothesis 4 (“cardiologists and nephrologists differ in their level of certainty for their choice of drug therapy for stroke prevention in HD patients with AF”) the relationship between physician specialty and level of certainty in drug therapy choice across four patient scenarios was evaluated using a mixed-design Analysis of Variance (ANOVA). By providing their level of certainty for each of the four scenarios, each physician provided four correlated data points and therefore a mixed effects model was used to account for within-physician variability. Data was first examined to ensure that assumptions for mixed-design ANOVA were met (normality was tested by the D’Agostino-Pearson normality test, homogeneity of variance
by Levene’s Test and sphericity by Mauchly’s test). The dependent variable was level of certainty (scale of 0-10), the within-subjects effect was scenario and the between-subjects effect was physician specialty (nephrologist and cardiologist).

\[ \text{i} \] The assumption of sphericity is unique to repeated measures and mixed-design ANOVA and it tests whether the population variance of difference scores computed between any two levels of a within-subjects factor is the same for all levels. In other words, if this assumption is met, it means that correlations between pairs of experimental conditions (scenarios in this study) are the same.\[^{117}\]
Chapter 4 Results

Overview of Chapter

This chapter begins by presenting the survey response rate and then describes the characteristics of the respondents as compared to the population of nephrologists and cardiologists in Canada. Descriptive statistics for responses to questionnaire items are then presented, followed by the results of the inferential analyses performed to address the study objectives and hypotheses.

Survey Response

Survey response rates are depicted in Figure 4.1. A total of 1697 questionnaires were distributed electronically to physicians in Canada, 400 to nephrologists and 1297 to cardiologists. Of these physicians, 188 responded to the survey (11% overall response rate). Eight physicians declared themselves ineligible to participate by stating that they were not involved in decisions regarding the use of antithrombotic therapy in HD patients with AF. Twenty-six physicians did not answer the question on physician specialty; therefore, their responses were excluded. One physician completed the questionnaire but claimed to no longer work in Canada and was therefore excluded. This left 153 usable responses (9% usable response rate), of which 103 were from nephrologists and 50 were from cardiologists. The usable response rates were 25.8% for nephrologists (103 out of 400 questionnaires returned complete) and 3.9% for cardiologists (50 out of 1297 questionnaires returned complete).

The CCS newsletter returned a response rate of 0.6% (5 out of 900 members returned completed questionnaires). Specific response rates for each of the four other cardiologist groups
(CHRS, UofT, UofA, and UofC) could not be determined because the questionnaire was
distributed to all groups during a similar timeframe and the questionnaire did not ask respondents
which group they were affiliated with (see Appendix H for the survey distribution timeline). Of
note, there may have been some overlap among cardiologist groups. For example, some
cardiologists in the CHRS may have been members of the CCS or affiliated with one of the three universities.

**Figure 4.1** Survey distribution and responses
CCS, Canadian Cardiovascular Society; CHRS, Canadian Heart Rhythm Society; UofT,
University of Toronto; UofC, University of Calgary; UofA, University of Alberta.
Respondent Characteristics

Respondent characteristics are reported in Table 4.1. This table also provides comparable statistics for all nephrologists and cardiologists practicing in Canada in 2015, although data on years in practice were not available. The majority of respondents (both cardiologists and nephrologists) were between the ages of 36 and 50; however, their reported years in practice were more variable and were not consistent with the distribution of age. Fifty-six percent of nephrologist respondents and 88% of the cardiologist respondents were male. Nephrologist respondents were more evenly distributed across Canada compared to cardiologists (88% of cardiologists were practicing in either Ontario or Alberta).

All respondents were working in hospital settings. The majority of nephrologists and cardiologists were working in university-affiliated hospitals (71.8% and 96.0%, respectively). All physicians that reported working in rural hospitals were nephrologists. In comparison, in 2015, Canadian specialists (all physicians excluding general practitioners and family physicians) worked primarily in hospital settings: 88% worked in a census metropolitan area (CMA) and 9.8% worked in a census agglomeration (CA) leaving 2.2% working outside CMA and CA areas (Table 4.1).

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ii Definitions of rural and urban were not provided to respondents; their responses were based on their perception of what they considered rural versus urban.

iii CMA: total population of at least 100,000 of which 50,000 or more live in the core.

iv CA: core population of at least 10,000.
Table 4.1 Survey respondent characteristics compared to the Canadian population of cardiologists and nephrologists

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Survey Respondents</th>
<th>Canadian Population^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiologists</td>
<td>Nephrologists</td>
</tr>
<tr>
<td></td>
<td>n = 50</td>
<td>n = 103</td>
</tr>
<tr>
<td>Age (years)^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 36</td>
<td>2 (4%)</td>
<td>30 (29%)</td>
</tr>
<tr>
<td>36-50</td>
<td>31 (62%)</td>
<td>57 (55%)</td>
</tr>
<tr>
<td>51-65</td>
<td>12 (24%)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>5 (10%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44 (88%)</td>
<td>58 (56%)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (12%)</td>
<td>45 (44%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Years in Practice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>8 (16%)</td>
<td>35 (34%)</td>
</tr>
<tr>
<td>6-10</td>
<td>13 (26%)</td>
<td>20 (19%)</td>
</tr>
<tr>
<td>11-15</td>
<td>9 (18%)</td>
<td>26 (25%)</td>
</tr>
<tr>
<td>16-20</td>
<td>6 (12%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>14 (28%)</td>
<td>17 (17%)</td>
</tr>
<tr>
<td>Province of Practice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alberta</td>
<td>18 (36%)</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>British Columbia</td>
<td>1 (2%)</td>
<td>13 (13%)</td>
</tr>
<tr>
<td>Manitoba</td>
<td>1 (2%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Newfoundland and</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Labrador</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>0 (0%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Ontario</td>
<td>26 (52%)</td>
<td>38 (37%)</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Quebec</td>
<td>4 (8%)</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Territories</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Location of Practice^c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University-affiliated</td>
<td>48 (96%)</td>
<td>74 (72%)</td>
</tr>
<tr>
<td>hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-university</td>
<td>2 (4%)</td>
<td>20 (19%)</td>
</tr>
<tr>
<td>affiliated urban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospital</td>
<td>0 (0%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Rural hospital</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

^a Source: Canadian Medical Association, January 2015; this data is for all specialists in Canada.115

^b Age categories differed for Canadian population compared to survey respondents. For the Canadian population the age categories were as follows: <35, 35-54, 55-64, >64, unknown. Age ranges for questionnaire were taken from survey study by Juma et al.27 Canadian Medical Association data was obtained after questionnaire creation.

^c For the Canadian Population location of practice was categorized as Census Metropolitan Area (CMA), Census Agglomeration (CA) and outside CMA/CA.

Definitions:
CMA: geographic area with a total population of at least 100,000 of which 50,000 or more live in the core.116
CA: geographic area with a core population of at least 10,000.116
Responses to Quantitative Questionnaire Items

Drug therapy choices for each scenario are reported by physician specialty in Tables 4.2-4.5. The three options, “other antiplatelet agent”, “dual anti-platelet therapy” and “one of the new oral anticoagulant therapies”, were chosen the least by both physician specialties. As planned a priori, all drug therapy options were collapsed into the categories “anticoagulant”, “antiplatelet” and “no drug therapy”. Overall, nephrologists chose no drug therapy or antiplatelet therapy options (i.e. more conservative options) over anticoagulant options more often than cardiologists (Figures 4.2-4.5). For both cardiologists and nephrologists, anticoagulant therapy options were chosen more often in scenarios with a low bleeding risk (scenarios 1 and 3) compared to scenarios with a high bleeding risk (scenarios 2 and 4). The highest rate of anticoagulant choice was in scenario 3 (high stroke and low bleed risk); 88% of cardiologists and 62% of nephrologists chose an anticoagulant (Figure 4.4) compared to 46% and 26% for scenario 1 (Figure 4.2), 16% and 4% for scenario 2 (Figure 4.3), and 26% and 8% for scenario 4 (Figure 4.5), respectively.
Table 4.2 Drug therapy choice for scenario 1 (low bleed, low stroke risk)

<table>
<thead>
<tr>
<th>Physician Specialty</th>
<th>Drug Therapy Choice, Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin</td>
</tr>
<tr>
<td>Cardiologist (n=50)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>Nephrologist (n=103)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>57 (55%)</td>
</tr>
</tbody>
</table>

DOAC, direct acting oral anticoagulant

Figure 4.2 Drug therapy choice (condensed into three categories) for scenario 1 (low bleed, low stroke risk)
**Table 4.3** Drug therapy choice for scenario 2 (high bleed, low stroke risk)

<table>
<thead>
<tr>
<th>Physician Specialty</th>
<th>Drug Therapy Choice, Frequency (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin</td>
<td>Other antiplatelet</td>
</tr>
<tr>
<td><strong>Cardiologist (n=50)</strong></td>
<td>13 (26%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td><strong>Nephrologist (n=103)</strong></td>
<td>40 (39%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

DOAC, direct acting oral anticoagulant

**Figure 4.3** Drug therapy choice (condensed into three categories) for scenario 2 (high bleed, low stroke risk)
Table 4.4 Drug therapy choice for scenario 3 (low bleed, high stroke risk)

<table>
<thead>
<tr>
<th>Physician Specialty</th>
<th>Drug Therapy Choice, Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin</td>
</tr>
<tr>
<td>Cardiologist (n=50)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Nephrologist (n=103)</td>
<td>28 (27%)</td>
</tr>
</tbody>
</table>

DOAC, direct acting oral anticoagulant

Figure 4.4 Drug therapy choice (condensed into three categories) for scenario 3 (low bleed, high stroke risk)
Table 4.5 Drug therapy choice for scenario 4 (high bleed, high stroke risk)

<table>
<thead>
<tr>
<th>Physician Specialty</th>
<th>Drug Therapy Choice, Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin</td>
</tr>
<tr>
<td>Cardiologist (n=50)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Nephrologist (n=103)</td>
<td>50 (48%)</td>
</tr>
</tbody>
</table>

DOAC, direct acting oral anticoagulant

---

**Drug therapy choice for scenario 4: high bleed, high stroke risk**

- Cardiologist
- Nephrologist

![Drug therapy choice for scenario 4: high bleed, high stroke risk](image)

**Figure 4.5** Drug therapy choice (condensed into three categories) for scenario 4 (high bleed, high stroke risk)
Descriptive statistics for certainty of drug therapy choice by cardiologists and nephrologists for each scenario are displayed in Table 4.6. Nephrologists’ certainty scores in scenario 1 and cardiologists’ certainty scores in scenario 3 were not normally distributed (according to the D’Agostino-Pearson normality test); therefore medians and interquartile ranges (IQR) are reported along with means and standard deviations (SD). See Appendix J for certainty score frequency distributions by physician specialty for each scenario.

Mean certainty scores for cardiologists were more variable across patient scenarios than were nephrologists’; mean certainty scores ranged from 5.26 to 7.10 across scenarios for cardiologists and 6.08 to 6.83 for nephrologists (Table 4.6). The highest mean certainty score for cardiologists was in scenario 3 (low bleed, high stroke risk) and in scenario 2 (high bleed, low stroke risk) for nephrologists. The lowest mean certainty score for cardiologists was in scenario 4 (high bleed, high stroke risk) and in scenario 3 for nephrologists. Overall, a change in bleeding risk from low to high, keeping stroke risk the same, resulted in a decrease in certainty for cardiologists, but an increase in certainty for nephrologists.
Table 4.6 Statistics for level of certainty\(^a\) for drug therapy choice by cardiologists and nephrologists for each scenario

<table>
<thead>
<tr>
<th>Physician Specialty</th>
<th>Scenario 1 (low bleed, low stroke risk)</th>
<th>Scenario 2 (high bleed, low stroke risk)</th>
<th>Scenario 3 (low bleed, high stroke risk)</th>
<th>Scenario 4 (high bleed, high stroke risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology (n=50)</td>
<td>Mean 6.54</td>
<td>5.62</td>
<td>7.10(^b)</td>
<td>5.26</td>
</tr>
<tr>
<td></td>
<td>SD 2.38</td>
<td>2.59</td>
<td>2.29</td>
<td>2.53</td>
</tr>
<tr>
<td></td>
<td>Median 7.0</td>
<td>6.0</td>
<td>7.0</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>IQR 5.0, 8.0</td>
<td>4.0, 7.0</td>
<td>6.0, 8.25</td>
<td>3.0, 7.0</td>
</tr>
<tr>
<td>Nephrology (n=103)</td>
<td>Mean 6.37(^b)</td>
<td>6.83</td>
<td>6.08</td>
<td>6.51</td>
</tr>
<tr>
<td></td>
<td>SD 2.17</td>
<td>2.31</td>
<td>2.05</td>
<td>2.40</td>
</tr>
<tr>
<td></td>
<td>Median 7.0</td>
<td>7.0</td>
<td>6.0</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>IQR 5.0, 8.0</td>
<td>5.0, 9.0</td>
<td>5.0, 7.0</td>
<td>5.0, 8.0</td>
</tr>
</tbody>
</table>

\(^a\) Certainty scores measured on an 11-point bipolar scale where 0 = very uncertain and 10 = very certain
\(^b\) Data not normally distributed (D’Agostino-Pearson test)
SD, standard deviation; IQR, interquartile range

Inferential Analyses

Objective 1: Comparison of Cardiologists’ and Nephrologists’ Choice of Drug Therapy

*Chi-Square Test*

A chi-square test was performed to determine whether cardiologists’ choice of drug therapy for each of the four scenarios differed significantly from those of the nephrologists. Drug therapy choice was grouped into three categories: anticoagulant, antiplatelet and no drug therapy (see Figures 4.2 to 4.5). A chi-square test showed that there was a statistically significant difference in drug therapy choice between cardiologists and nephrologists in each of the four scenarios (Table 4.7).
Table 4.7 Chi-Square Test for drug therapy choice (anticoagulant, antiplatelet, no drug therapy) in each scenario by physician specialty

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Pearson Chi-Square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: low bleed, low stroke risk</td>
<td>7.96</td>
<td>0.019</td>
</tr>
<tr>
<td>2: high bleed, low stroke risk</td>
<td>6.93</td>
<td>0.031</td>
</tr>
<tr>
<td>3: low bleed, high stroke risk</td>
<td>11.12</td>
<td>0.004</td>
</tr>
<tr>
<td>4: high bleed, high stroke risk</td>
<td>9.56</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*Mixed Effects Multinomial Logistic Regression Analysis*

A mixed effects multinomial logistic regression analysis was performed to determine the association between drug therapy choice and physician specialty, stroke risk, and bleeding risk while adjusting for within-physician clustering. Hypothesis 1 was addressed by testing the main effect of physician specialty, hypothesis 2 was addressed by testing the interaction effect of physician specialty and stroke risk, and hypothesis 3 was addressed by testing the interaction effect of physician specialty and bleeding risk. Model equations and variable coding are provided in Appendix I.

Interactions were investigated using no drug therapy as the reference category (Table 4.8). No statistically significant interactions (either double or triple) were found; therefore hypotheses 2 and 3 were rejected. A main effects analysis was then performed without interaction terms, first, using no drug therapy as the reference category (Table 4.9), and then using antiplatelet as the reference category (Table 4.10) in order to definitively compare each drug therapy choice pair. Significant main effects were found for each of physician specialty (supporting hypothesis 1), bleeding risk and stroke risk when comparing anticoagulant to no drug therapy and anticoagulant to antiplatelet therapy (Tables 4.9 and 4.10). However, when comparing antiplatelet to no drug therapy, there was only a significant main effect for bleeding risk (Table 4.9).
Table 4.8 Results from mixed effects (physician specialty, bleeding risk and stroke risk) multinomial logistic regression model of drug therapy choice (no drug therapy as reference category) with interactions

<table>
<thead>
<tr>
<th>Specialty (cardiologist vs. nephrologist)</th>
<th>Main Effects</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Specialty by bleeding risk</td>
<td>Specialty by stroke risk</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>Anticoagulant vs. no drug therapy</td>
<td>2.44 *</td>
<td>1.07</td>
</tr>
<tr>
<td>Antiplatelet vs. no drug therapy</td>
<td>1.91</td>
<td>1.06</td>
</tr>
</tbody>
</table>

p values: **<0.001; *<0.05
β, coefficient estimates; SE, standard error
Table 4.9 Results from mixed effects (physician specialty, bleeding risk and stroke risk) multinomial logistic regression model of drug therapy choice (no drug therapy as reference category) without interactions

<table>
<thead>
<tr>
<th>Specialty (cardiologist vs. nephrologist)</th>
<th>Bleeding risk (low vs. high)</th>
<th>Stroke risk (low vs. high)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>Anticoagulant vs. no drug therapy</td>
<td>1.14 *</td>
<td>0.32</td>
</tr>
<tr>
<td>Antiplatelet vs. no drug therapy</td>
<td>0.05</td>
<td>0.25</td>
</tr>
</tbody>
</table>

* p < 0.001

β, coefficient estimates; SE, standard error

Table 4.10 Results from mixed effects (physician specialty, bleeding risk and stroke risk) multinomial logistic regression model of drug therapy choice (antiplatelet as reference category) without interactions

<table>
<thead>
<tr>
<th>Specialty (cardiologist vs. nephrologist)</th>
<th>Bleeding risk (low vs. high)</th>
<th>Stroke risk (low vs. high)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>No drug therapy vs. Antiplatelet</td>
<td>-0.05</td>
<td>0.25</td>
</tr>
<tr>
<td>Anticoagulant vs. Antiplatelet</td>
<td>1.09 *</td>
<td>0.24</td>
</tr>
</tbody>
</table>

* p < 0.001

β, coefficient estimates; SE, standard error

For the main effects model, being a cardiologist increased the odds of choosing anticoagulant therapy over no drug therapy by 3.13 and choosing anticoagulant over antiplatelet therapy by 2.97 (Table 4.11) compared to being a nephrologist. There was no statistically
significant difference in odds of choosing antiplatelet therapy versus no drug therapy when cardiologists were compared to nephrologists (p=0.08).

Physicians were 5 times (1/0.20) more likely to choose anticoagulant over no drug therapy and 3.6 times (1/0.28) more likely to choose anticoagulant over antiplatelet therapy, when stroke risk was high (Table 4.11). Varying stroke risk did not result in a statistically significant difference between physicians’ choice for antiplatelet therapy over no drug therapy.

Lastly, a low bleeding risk increased the odds that physicians would choose anticoagulant therapy over no drug therapy by 50.40, choose anticoagulant over antiplatelet therapy by 7.17, and choose antiplatelet therapy over no drug therapy by 6.96 (Table 4.11).

**Table 4.11** Odds ratios and confidence intervals for the main effects model of physician specialty, bleeding risk and stroke risk on drug therapy choice

<table>
<thead>
<tr>
<th></th>
<th>Anticoagulant vs no drug therapy</th>
<th>Anticoagulant vs antiplatelet</th>
<th>Antiplatelet vs no drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specialty:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cardiologist vs nephrologist)</td>
<td>3.13 * 1.67-5.85</td>
<td>2.97 * 1.30-4.76</td>
<td>1.05 0.64-1.72</td>
</tr>
<tr>
<td><strong>Bleeding risk:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(low vs high)</td>
<td>50.40 * 26.92-94.37</td>
<td>7.17 * 4.48-11.48</td>
<td>6.96 * 4.10-11.81</td>
</tr>
<tr>
<td><strong>Stroke risk:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(low vs high)</td>
<td>0.20 * 0.11-0.36</td>
<td>0.28 * 0.17-0.45</td>
<td>0.71 0.48-1.05</td>
</tr>
</tbody>
</table>

* p < 0.001

OR, odds ratio; CI, confidence interval

In summary, study results supported hypothesis 1. Cardiologists were 3 times more likely to choose anticoagulant therapy over both antiplatelet therapy and no drug therapy compared to nephrologists. There were no interaction effects between physician specialty and stroke risk or
between physician specialty and bleeding risk; therefore hypotheses 2 and 3 were rejected. However, there were significant differences in drug therapy choice for the main effects of stroke risk and bleeding risk. Both cardiologists and nephrologists chose anticoagulant therapy less often when bleeding risk was high and more often when stroke risk was high. Further, both physician groups were less likely to choose antiplatelet therapy compared to no drug therapy when bleeding risk was high; however, a difference was not found for stroke risk.

Objective 2: Comparison of Cardiologists’ and Nephrologists’ Level of Certainty

A mixed-design ANOVA was conducted with scenario as a within-subjects effect, physician specialty as a between-subjects effect and level of certainty in drug therapy choice as the dependent variable. Certainty scores did not meet the assumption of normality required for ANOVA (normality was determined using the D’Agostino-Pearson test). While this may result in a reduction of power for the statistical analysis, with more than 15 cases per physician specialty group, our sample size should be large enough to obtain reasonably accurate p values. The homogeneity of variance assumption required for ANOVA was met (Levene’s Test); however Mauchly’s test revealed a violation of sphericity, therefore a correction (Huynh-Feldt) was applied to the results of the ANOVA (Table 4.12).
Table 4.12 Results from mixed-design ANOVA on level of certainty in drug therapy choice across four scenarios and physician specialties

<table>
<thead>
<tr>
<th>Factor</th>
<th>Type III Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>p value</th>
<th>Partial Eta Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>physician specialty</td>
<td>13.50</td>
<td>1</td>
<td>13.50</td>
<td>1.09</td>
<td>.299</td>
<td>.01</td>
</tr>
<tr>
<td>error (physician specialty)</td>
<td>1877.95</td>
<td>1</td>
<td>12.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>scenario(^a)</td>
<td>38.11</td>
<td>2.75</td>
<td>13.85</td>
<td>4.30</td>
<td>.007</td>
<td>.03</td>
</tr>
<tr>
<td>physician specialty by scenario(^a)</td>
<td>124.54</td>
<td>2.75</td>
<td>45.25</td>
<td>14.05</td>
<td>.000</td>
<td>.08</td>
</tr>
<tr>
<td>error (scenario)(^a)</td>
<td>1338.31</td>
<td>415.64</td>
<td>3.22</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Huynh-Feldt correction due to violation of the assumption of sphericity
df, degrees of freedom

The main effect of physician specialty was not significant (p=0.299); therefore hypothesis 4 was rejected. However, a significant interaction effect was found between physician specialty and scenario, Pillai’s Trace = 0.18 (F (3, 149) = 10.84, p=0.000). A post-hoc analysis was performed to investigate this interaction effect. Results are provided in Table 4.13 and Figure 4.6.

Figure 4.6 illustrates that the interaction between physician specialty and scenario on level of certainty was due to a “cross-over” type of interaction.\(^{114}\) Across each scenario, the changes in stroke and bleeding risk had opposite effects on the changes in level of certainty in drug therapy choice for cardiologists compared to nephrologists.
There were statistically significant differences in level of certainty between cardiologists and nephrologists for all scenarios with the exception of scenario 1, low stroke risk and low bleeding risk (p=0.659) (Table 4.13). In scenario 2 (a patient with low stroke risk and high bleeding risk) and scenario 4 (a patient with high risk of both stroke and bleeding) nephrologists had a higher level of certainty than cardiologists (6.83 versus 5.62, p = 0.004, and 6.51 versus 5.26, p = 0.003, respectively). In contrast, in scenario 3 where stroke risk was high and bleeding risk was low, cardiologists had a higher level of certainty than nephrologists (7.10 versus 6.08, p = 0.006).

**Figure 4.6** Interaction effect of physician specialty and scenario on decisional certainty when making a drug therapy choice in patient scenarios
Table 4.13 Post-hoc analysis of the interaction effect of physician specialty and scenario on level of certainty with drug therapy choice (cardiologists compared to nephrologists)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Difference in Cardiologists’ and Nephrologists’ Mean Certainty</th>
<th>Standard Error</th>
<th>p Value</th>
<th>95% Confidence Interval for Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 low stroke, low bleed</td>
<td>.17</td>
<td>.39</td>
<td>.659</td>
<td>-.59 - .93</td>
</tr>
<tr>
<td>2 low stroke, high bleed</td>
<td>-1.21</td>
<td>.41</td>
<td>.004</td>
<td>-2.02 - -.39</td>
</tr>
<tr>
<td>3 high stroke, low bleed</td>
<td>1.02</td>
<td>.37</td>
<td>.006</td>
<td>.30 - 1.75</td>
</tr>
<tr>
<td>4 high stroke, high bleed</td>
<td>-1.26</td>
<td>.42</td>
<td>.003</td>
<td>-2.09 - -.42</td>
</tr>
</tbody>
</table>

\[^a\] Certainty scores measured on an 11-point bipolar scale where 0 = very uncertain and 10 = very certain

In summary, cardiologists’ and nephrologists’ level of certainty for their drug therapy choice for stroke prevention was different in three of the four patient scenarios. Post-hoc analysis revealed that, in scenarios with a high bleeding risk (scenario 2 and 4), certainty was higher for nephrologists than cardiologists. In contrast, where stroke risk was high but bleeding risk was low (scenario 3), cardiologists had the higher certainty.

Qualitative Responses to Open-ended Questions

Eleven (7.2%) of 153 survey respondents provided a comment to the open-ended question soliciting additional comments at the end of the questionnaire (Table 4.14). Several physicians provided positive comments about the study. Others expressed their concern with the lack of evidence supporting the use of antithrombotic therapy in HD patients with AF (e.g. “there is no evidence to support a net benefit of anticoagulating patients with HD and AF: may be harm”). Three respondents provided comments on how to improve the survey or suggested a
future direction for research. A nephrologist stated that clinicians in their HD unit have disagreements with consultants from cardiology about the management of warfarin therapy and “therefore (their) unit takes charge of all anticoagulation in (their) patients” (Nephrologist 1). One cardiologist stated, “I may be involved with these decisions but ultimately, the nephrologists follow the patients more closely; they make the final decisions”. Comments from respondents were organized into themes, as shown in Table 4.14.
### Table 4.14 Additional comments offered by respondents (n=11)

<table>
<thead>
<tr>
<th>Theme</th>
<th>Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive comments about the study (n=4)</td>
<td>• “I look forward to seeing the results of the study!” (Cardiologist 1)</td>
</tr>
<tr>
<td></td>
<td>• “Please make the results public; it will be interesting!” (Cardiologist 2)</td>
</tr>
<tr>
<td></td>
<td>• “would love to hear the results of this survey” (Cardiologist 3)</td>
</tr>
<tr>
<td></td>
<td>• “great survey” (Cardiologist 4)</td>
</tr>
<tr>
<td>Concern regarding the use of antithrombotic therapy in HD patients with AF due to lack of evidence (n=4)</td>
<td>• “very contentious issue based on lack of randomized data to guide” (Cardiologist 4)</td>
</tr>
<tr>
<td></td>
<td>• “there is no evidence to support a net benefit of anticoagulating patients with HD and AF: may be harm” (Cardiologist 5)</td>
</tr>
<tr>
<td></td>
<td>• “We have reviewed this recently in context of several significant hemorrhages in patients on chronic Coumadin closely monitored in our unit. After a series of patients with: retroperitoneal bleed, abdominal wall hematoma, subdural hematoma, exsanguinating GI bleed, we reviewed all our patients on anticoagulation. This resulted in discontinuation of long term Coumadin in a number of patients whom we evaluated as being at high risk for falls, recurrent bleeding and uncontrolled hypertension. In those patients in whom Coumadin is absolutely necessary, we maintain the INR at the very lowest end of the recommended therapeutic range. This involves a constant battle with consultants from cardiology and thrombosis - therefore our unit takes charge of all anticoagulation in our patients.” (Nephrologist 1)</td>
</tr>
<tr>
<td></td>
<td>• “recent literature especially U. of Ottawa draws much of this therapy into question” (Nephrologist 2)</td>
</tr>
<tr>
<td>Parties involved in decision-making (n=2)</td>
<td>• “I may be involved with these decisions but ultimately, the nephrologists follow the patients more closely; they make the final decisions.” (Cardiologist 6)</td>
</tr>
<tr>
<td></td>
<td>• “Decision to withhold or withdraw Coumadin is explicitly discussed with patients and/or substitute decider.” (Nephrologist 1)</td>
</tr>
<tr>
<td>Thoughts on future direction for research (n=1)</td>
<td>• “RCT required to determine whether warfarin provides benefit or increased risk of ischemic stroke. Important to gauge willingness of nephrologists to enrol patients in a RCT.” (Nephrologist 3)</td>
</tr>
<tr>
<td>Thoughts on how questionnaire could have been improved (n=2)</td>
<td>• “kidney transplant eligibility would be important information” (Nephrologist 4)</td>
</tr>
<tr>
<td></td>
<td>• “The choice to use gastric protection with antiplatelet or anticoagulant therapy should have been given as it can mitigate some of the risks.” (Nephrologist 5)</td>
</tr>
</tbody>
</table>
Summary of Results

The response rate for this survey was 9% (26% for nephrologists and 4% for cardiologists). Respondent characteristics were similar to those of nephrologists and cardiologists in the Canadian Medical Association’s 2015 database, except that cardiologist respondents were predominantly working in university-affiliated hospitals in Ontario and Alberta.

Cardiologists were three times more likely than nephrologists to choose anticoagulant therapy (which has the highest bleeding risk, but is most effective at stroke risk reduction) across all levels of stroke and bleeding risk. Both cardiologists and nephrologists adjusted their drug therapy choice when stroke risk and bleeding risk varied; they chose anticoagulant therapy more when stroke risk was high and less when bleeding risk was high. Cardiologists’ and nephrologists’ decisional certainty differed across patient scenarios. In scenarios with a high bleeding risk nephrologists had a higher level of certainty in drug therapy choice than cardiologists, but in scenario 3 (where patient stroke risk was high and bleeding risk was low) nephrologists’ level of certainty was lower, however this effect was not hypothesized. Open-ended comments provided by respondents were few in number (n=11); the most common theme was concern regarding evidence for a net benefit for antithrombotic therapy in HD patients with AF (n=4).
Chapter 5 Discussion and Conclusions

Overview of Chapter

This chapter discusses the study’s findings and associations to relevant literature. First, the influence that the three factors studied (physician specialty, stroke risk and bleeding risk) had on physician choice of drug therapy for stroke prevention in HD patients with AF is discussed, then comments are offered on other study observations regarding drug therapy choice. Second, differences in certainty for drug therapy choice between the two physician specialties across the four patient scenarios are considered. Finally, limitations to this study are identified and recommendations for practice and future research are made.

Physician Choice of Drug Therapy

Effect of Physician Specialty on Drug Therapy Choice

Regression analyses demonstrated that overall cardiologists chose anticoagulant therapy over each of antiplatelet therapy and no drug therapy three times more often than nephrologists did. This difference in drug therapy choice cannot be explained by differences in the way cardiologists and nephrologists interpret patient stroke risk or bleeding risk because interactions between specialty and these risk factors were not significant. Therefore, it must be due to other unmeasured factors. Some possibilities are described below.

Studies have demonstrated that prior experience with stroke and bleeding events can affect physician prescribing.\textsuperscript{30,31} Therefore, we hypothesized that nephrologists who are more exposed than cardiologists to the exceptionally high stroke and bleeding event rates seen in the HD population,\textsuperscript{1,3-12} would make different drug therapy choices for AF than cardiologists. Yet,
our findings do not support this reasoning because no interactions were found between physician specialty and stroke or bleeding risk on drug therapy choice.

It may be that different training with antithrombotic prescribing within each specialty created different prescribing beliefs. Notably, one of the cardiologists who pretested the survey questionnaire stated that “cardiologists have been trained to put all AF patients on warfarin because prescribing rates are so low”. While this was just one cardiologist’s opinion, several studies performed in several Western countries have shown cardiologists to be the most frequent prescribers of anticoagulant therapy for AF compared to other types of physician specialists (nephrologists were not included in these studies).²²-²⁵,⁷⁰ It is also possible that cardiologists are less aware than nephrologists of the lack of evidence to support the efficacy and safety of antithrombotic therapy in the HD population since it makes up a smaller proportion of cardiologists’ patients.

Despite the differences choosing anticoagulant therapy, cardiologists and nephrologists did not differ significantly in their choice between antiplatelet therapy and no drug therapy. This may have been because the reduction in stroke risk from antiplatelet therapy is much less than from anticoagulant therapy (22% versus 64%).⁴⁶ Whereas the difference between antiplatelet therapy and no drug therapy is only 22%, which could make the choice between the latter two seem much less significant.

In summary, while this research cannot explain why cardiologists and nephrologists differ in their drug therapy choice for stroke prevention in HD patients with AF, it is postulated that differences in training and nephrologists’ presumed greater familiarity with the research evidence in the HD population account for the disparity. Explanations for the differences should be explored through qualitative research. Given that HD patients with AF are at a high risk for
morbidity and mortality, communication and collaboration (e.g. through joint continuing education programs) between cardiologists and nephrologists is important to ensure the two specialties have a shared understanding of the evidence of the risk-benefit and rationale for each drug therapy choice for this population.

Effect of Stroke and Bleeding Risk on Drug Therapy Choice

Although not hypothesized, it was not surprising to the investigators that the main effects of stroke risk and bleeding risk on drug therapy choice were statistically significant. The comorbidities in each scenario in the questionnaire were intentionally selected to create contrasts in stroke and bleeding risk, and respondents’ drug therapy choices reflected the expected pattern (described below) based on current evidence.\(^2,16-19\)

When patient scenarios included comorbidities that increased stroke risk, respondents chose drug therapy that was more effective for stroke risk reduction in spite of having a higher bleeding risk (anticoagulant therapy).\(^2,46\) In other words, they were willing to accept a higher bleeding risk if stroke risk could be reduced. Stroke risk did not however affect the choice between antiplatelet therapy and no drug therapy.

When patient scenarios included comorbidities that increased bleeding risk, respondents chose antiplatelet or no drug therapy over anticoagulant therapy. Therefore, they were willing to trade off reduction in stroke risk for a lesser exacerbation of bleeding risk. This is consistent with previous studies that have identified age, falls risk and prior bleeding events (all of them bleeding risk factors) to be barriers to anticoagulant prescribing.\(^32,28,29\)

Overall, results from regression analyses demonstrated that bleeding risk had a stronger influence on choice of drug therapy than did stroke risk, particularly for the comparison of
anticoagulant therapy versus no drug therapy, where bleeding risk had a 10-fold higher influence on choice than stroke risk (Table 4.11). Moreover, bleeding risk had a statistically significant influence on the choice within all three of the drug therapy pairs, whereas stroke risk only influenced choice of anticoagulant over no drug therapy and over antiplatelet therapy. This may be because physicians (particularly nephrologists) are cognizant of the high bleeding event rates\textsuperscript{3-5,10-12} and the lack of evidence supporting the efficacy of antithrombotic therapy for AF in the HD population.\textsuperscript{6,7,13-15} It could also be because of the credo: “Do no harm”. In other words, that an iatrogenic harm (error of commission) is viewed more unfavorably than an error of omission, i.e. undertreating a disease or condition.

**Other Observations Regarding Drug Therapy Choice**

Respondents selected warfarin, aspirin or no drug therapy more frequently than “other antiplatelet agent”, “dual anti-platelet therapy”, and “one of the new oral anticoagulant therapies (rivaroxaban, apixaban or dabigatran)”. This was expected since anticoagulant therapy (such as warfarin) is the recommended treatment in the general population of AF patients with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 2 or greater, while aspirin or anticoagulant therapy is indicated for CHA\textsubscript{2}DS\textsubscript{2}-VASc of 1, and aspirin (an antiplatelet agent) or no therapy is usually recommended for patients with CHA\textsubscript{2}DS\textsubscript{2}-VASc of 0.\textsuperscript{2,16-19} Rivaroxaban, apixaban and dabigatran (DOACs) are other anticoagulant options in the general population and are used by some physicians in the HD population, but HD patients are at risk of drug accumulation, which explains the low selection of the DOAC option by respondents. For patients who cannot take anticoagulant therapy safely (for example, due to an inability to access INR testing), guidelines recommend that they are prescribed dual antiplatelet therapy with aspirin and clopidogrel.\textsuperscript{2,16-19} However, the
questionnaire stated that hypothetical patients were capable of managing any of the drug therapy options presented, so it was expected that dual antiplatelet therapy would be chosen less than other options as this is considered a second-line option.²

Physicians in this survey chose anticoagulant therapy at rates as low as 4% (nephrologists in the low stroke risk/high bleeding risk scenario) to as high as 88% (cardiologists in the high stroke risk/low bleeding risk scenario). Anticoagulant therapy was chosen 32% of the time across all four patient scenarios (26% by nephrologists and 44% by cardiologists). Interestingly, this proportion is similar to DOPPS data from 1996 to 2004, which revealed that physicians in Canada were prescribing warfarin to 37% of HD patients with AF.⁸ As discussed in Chapter 2, the updated 2012 Canadian guidelines on AF recommended that HD patients not routinely receive either anticoagulant therapy or aspirin for stroke prevention (implying no drug therapy is recommended).¹⁶,¹⁷ Therefore, both physician specialties in this survey were not following Canadian guidelines. Also, the anticoagulant prescribing rate from our survey was not appreciably lower than that in the DOPPS, although the latter included all prescribers in Canada, not just nephrologists and cardiologists. Even for the low stroke risk/high bleeding risk scenario in our survey, only 55% of nephrologists and 46% of cardiologists chose no drug therapy. Perhaps because the 2012 guideline on treatment of HD patients with AF was a conditional recommendation based on low quality evidence,¹⁶,¹⁷ physicians felt free to deviate from it.

Importantly, in the high stroke risk/low bleeding risk scenario, 88% of cardiologists and 62% of nephrologists chose anticoagulant therapy despite the lack of evidence to support its efficacy in stroke risk reduction and the safety concerns demonstrated by a 2015 meta-analysis¹⁵ and several observational studies in HD patients.⁷,¹³,¹⁴ This anticoagulant prescribing rate is comparable to the findings from Juma et al. where 77% of nephrologists indicated that they were
“likely to prescribe” warfarin in a patient with a high stroke risk and low bleeding risk.\textsuperscript{27} However, physician respondents in this study did adjust their drug therapy choice when bleeding risk was high. In a patient with both high stroke and high bleeding risk, anticoagulant choice in this study was 26\% for cardiologists and only 8\% for nephrologists. Likewise, in a similar patient case, Juma et al. found that only 4\% of nephrologists were likely to prescribe warfarin.\textsuperscript{27} It seems that physician respondents, particularly cardiologists in this study, were basing their drug therapy choice on the positive results from RCTs on anticoagulant therapy in the general AF population, assuming that there might be comparable benefit in HD patients. This non-evidence based choice supports the need for a large RCT in the HD population with AF that compares the safety and efficacy of warfarin, aspirin, and no drug therapy in order to conclusively address the controversial issue of how to manage the AF-related stroke risk in HD patients.

**Level of Certainty for Choice of Drug Therapy**

A significant “cross-over” interaction effect,\textsuperscript{118} depicted in Figure 4.6, was found between physician specialty and patient scenario on physician certainty for drug therapy choice. In other words, differences in cardiologists’ and nephrologists’ certainty about their drug therapy choice depended on the scenario. When stroke risk and bleeding risk were both low (scenario 1), there was no difference in level of certainty between physician specialties; however, when scenarios described patients with high stroke or high bleeding risk (scenarios 2-4) a significant difference was found. What is interesting is that, this difference was not in the same direction across all three of these scenarios. Cardiologists had a lower level of certainty than nephrologists in
scenarios that had a high bleeding risk (scenarios 2 and 4). However, when bleeding risk was low (scenario 3) the opposite was true.

A plausible explanation for the interaction is that, as stated earlier, cardiologists are less aware than nephrologists of the lack of evidence to support the efficacy and safety of antithrombotic therapy for AF in the HD population. For instance, in this study, cardiologists were less certain about drug therapy choice when bleeding risk was high compared to nephrologists. This may be because cardiologists preferred to select an anticoagulant due to its superior effectiveness for stroke risk reduction (in the general population), but when presented with a patient with high bleeding risk they became less certain about that choice. In contrast, nephrologists were aware that anticoagulant therapy might not prevent stroke in the HD population, so they felt self-assured selecting drug therapy options with a lower bleeding risk (antiplatelet and no drug therapy).

Notably, when certainty for a high bleeding risk scenario versus a low risk scenario is compared it is lower for cardiologists and higher for nephrologists regardless of stroke risk (Figure 4.6). However this was not statistically significant for all scenario pairs. In the study by Juma et al., nephrologists’ certainty in prescribing warfarin to HD patients with AF seem counter to the above. They found that when bleeding risk factors were present nephrologists (also CSN members) had lesser certainty about prescribing warfarin than in cases without bleeding risk factors. However, because the measure of certainty differed from this study, one must be cautious when comparing results. Juma et al. asked respondents “How likely are you to recommend starting (or continuing in some cases) treatment with warfarin in this patient?” and certainty was measured on a 7-point scale from “definitely no” to “definitely yes”. Importantly, in the study by Juma et al. certainty was only measured for prescribing or not prescribing
warfarin, whereas this study looked at certainty for the respondent’s choice from several antithrombotic therapy options for AF. When the results from Juma et al. are combined with the results from this study it seems that nephrologists are less certain about prescribing to patients with bleeding risk factors when warfarin is the only option, but when other drug therapy options are available (such as antiplatelet therapy or no drug therapy) nephrologists are more certain.

In summary, certainty in drug therapy choice was different for cardiologists compared to nephrologists when evaluated across four patient scenarios that systematically varied in level of stroke and bleeding risk. Cardiologists’ certainty was higher than nephrologists’ when stroke risk was high and bleeding risk was low. In contrast, nephrologists’ certainty was higher than cardiologists’ when bleeding risk was high, regardless of stroke risk. Nephrologists’ presumed greater awareness of the evidence for antithrombotic therapy for AF in the HD population compared to cardiologists, may explain the above findings. Research on physician awareness of the research evidence on antithrombotic therapy in this patient population is required for confirmation.

Limitations

Non-Response Bias

The greatest limitation to this study is the low survey response rate (9%), particularly from cardiologists (4%). This increases the probability that respondents are different from physicians in the sampling frame, i.e., that non-response bias is present. Thus results from this research may not be generalizable to the Canadian population of cardiologists and nephrologists. A study by Kittleson reported that a 25-30% response rate can be expected from an email survey with one contact and that repeated contact (three being optimal) can approximately double the
response rate.\textsuperscript{95} Another recent survey of CSN members reported a response rate of 62% (compared to our 26%) using the same follow-up schedule.\textsuperscript{27}

The response rate from cardiologists in our survey was much lower than from nephrologists: 4% and 26%, respectively (Figure 4.1). The most likely explanation for this was that the first distribution of the questionnaire to cardiologists was through a web link in the CCS newsletter. The survey announcement and a link to the questionnaire was embedded amongst other information in the newsletter making it less noticeable, whereas nephrologists, and subsequently targeted cardiologist groups, were sent a link to the questionnaire in an email sent directly to them from their affiliated organization. This may have impacted the response rate from CCS cardiologists because the contents of the newsletter may have distracted respondents from the questionnaire. Nevertheless, the response rate from cardiologists affiliated with UofT, UofC, UofA and CHRS was still lower than that for the nephrologists: 11% (45 out of 397 questionnaires returned complete) compared to 26%. Another possible explanation for the difference may have been that nephrologists have a greater interest in the HD patient population. HD patients (patients with end stage kidney disease) make up a small proportion of cardiologists’ patients.

The Canadian Medical Association reported in January 2015 that there were a total of 1367 cardiologists and 647 nephrologists practicing in Canada in 2015.\textsuperscript{115} Our survey reached 4% of cardiologists (50 respondents) and 16% of nephrologists (103 respondents). Clearly, a large number of these physician specialists in Canada are not represented, and a low survey response rate makes drawing conclusions about the population difficult. However, the characteristics of nephrologist respondents were comparable to the Canadian Medical Association’s database of the characteristics of nephrologists practicing in Canada in 2015.\textsuperscript{115}
providing some reassurance that non-response bias for nephrologists may have had less influence on results.

**Sampling Bias**

Cardiologists from Ontario and Alberta were overrepresented in the survey (Table 4.1). This was likely due to the altered survey distribution methods after the CCS newsletter strategy failed; the new sampling frame included cardiologists from the CHRS, UofT, UofA and UofC and therefore was heavily weighted towards Ontario and Alberta. Regional variation in medical practice has been reported in numerous studies.\textsuperscript{119-122} Thus, it cannot be assumed that the cardiologist respondents in our survey reflect the practices of cardiologists working in other provinces in Canada.

Another factor limiting the generalizability of our study findings is that 96% of cardiologist respondents were working in university-affiliated hospitals compared to only 72% of nephrologists. Again, this was possibly caused by the altered survey distribution method after the CCS newsletter strategy failed. University-affiliated hospitals often facilitate peer-engagement rounds and are able to provide more learning opportunities for their staff compared to non-academic hospitals. This could create disparities in prescribing practices of physicians working in university-affiliated hospitals compared to those working in regular urban hospitals or rural hospitals.

An additional limitation to this study relating to sampling bias is that all nephrologists in the study were members of the CSN, their Canadian professional society, whereas an unknown number (possibly as low as 10%) of cardiologist respondents were known to be members of a
professional society, the CCS or CHRS. It is possible that physicians who are members of a professional society differ in their prescribing practices from those who are non-members.

Certainty Scale

A possible limitation of this study is that the 11-point rating scale measuring level of certainty was not validated. However, several studies have used similar scales to assess decisional certainty.\textsuperscript{103-106} For example, Jeffrey et al. sought to determine the degree of certainty for medical students’ interpretation of chest radiographs using a five-point scale that ranged from 0 (uncertain), 1 (25% certain), 2 (50% certain) 3 (75% certain) and 4 (100% certain).\textsuperscript{103}

As discussed in Chapter 2, uncertainty is important because it may result in unexplained variations in patterns of care\textsuperscript{33,35,36,43} and can cause stress and anxiety for both patients and clinicians.\textsuperscript{35,40} Measuring certainty, albeit with an unvalidated scale, allowed us to tentatively identify important relationships in our results that could provide a better understanding of nephrologists’ and cardiologists’ management of AF-related stroke risk in HD patients and that warrant further investigation using a validated instrument.

Use of Adapted Physicians’ Reactions to Uncertainty Model

The conceptual framework used to guide this study was an adapted version of the PRU model, developed by Gerrity and others (Figures 2.1 and 2.2).\textsuperscript{40-42} Two elements of the model, patient characteristics (bleeding risk and stroke risk) and physician characteristics (physician specialty) predicted choice of drug therapy for AF in HD patients (the medical problem). PRU, a central element of the model, was not measured by the questionnaire since understanding its influence on choice of drug therapy was not a primary aim of this study. Also, interviews and/or
focus groups using qualitative methodology would be needed to better understand the relationship between PRU and choice of drug therapy, which was beyond the scope of this thesis. Yet, because PRU is a central element of this study’s conceptual framework, not using the PRU scales has implications for the interpretation of study findings. The relationships between physician and patient characteristics and choice of drug therapy may not be direct, as we have depicted them; there may be intervening variables (such as PRU) that influence choice of drug therapy. Ultimately, it was thought that including the PRU scales in the questionnaire would unduly lengthen the questionnaire and greatly impact the response rate.

**Value of the Research and Recommendations for Practice**

Variations in physician practices may signify that the quality, appropriateness, and cost effectiveness of health care may be compromised. Publication of this research will increase awareness of the variation in prescribing practices for AF in the HD population among cardiologists and nephrologists in Canada. To address this prescribing diversity in practice, we suggest that cardiologists and nephrologists consult each other when making decisions about the stroke risk management of HD patients with AF. We also suggest that joint continuing education events are held for cardiologists and nephrologists so that these specialists could share insights about managing this population. Through communication and collaboration, physicians from both specialties could ensure that their risk-benefit analysis, rationale for choice of drug therapy and certainty for their choice are understood. Over time, this may lead to improved uniformity of treatment strategies. Furthermore, we recommend that physicians enroll their HD patients with AF in a future RCT (comparing drug therapy options for stroke risk reduction) so that better research evidence is gathered on the best drug therapy choice for this high-risk population.
Recommendations for Future Studies

This study focused on how physician specialty (cardiologist versus nephrologist), bleeding risk, and stroke risk affect the choice of drug therapy and accompanying level of certainty for managing AF-related stroke risk in HD patients. Future research is recommended on the influence that other elements of the PRU model (Figure 2.1) have on choice of drug therapy for the HD population with AF. In particular, it is important to understand how PRU and patients’ preferences, beliefs, or past experiences may influence a physician’s choice of drug therapy. A physician survey could elicit physician’s responses to PRU scales and drug therapy choice for HD patients with AF, then interviews and/or focus groups could be held to better understand the thought process behind their drug therapy choice. Understanding how patient preferences (as opposed to just their clinical attributes) influence a physician’s choice of drug therapy is even more important, as involving patients in decisions regarding their care and using an approach such as “shared decision-making” is becoming a focus among health care providers globally. Such a study would be best conducted qualitatively using focus groups with HD patients and physicians in order to invoke dialogue regarding drug therapy choices for AF that could resemble that of an office visit between a patient and a physician.

Given that the response rate in our study was so low, particularly from cardiologists (4%), future survey research should investigate other methods to connect with Canadian cardiologists and nephrologists. One possibility could be to mail the questionnaires to potential respondents, rather than use email, because postal questionnaires have been shown to result in higher response rates. However, one may have more success by finding a way to increase motivation for respondents to complete the questionnaire. This could be achieved by having the
survey endorsed by presidents of professional societies or by prominent leaders in the respondents' field. Further, considering the use social media as a way to facilitate endorsement of a survey and as a means to reach a larger sampling frame should be investigated (for example, Twitter or Facebook). Another valuable future study would be to survey physicians (and patients) about their willingness to and reasons why or why they would not enroll their patients (or themselves) in an RCT to determine efficacy and safety of warfarin versus aspirin versus placebo for AF-related stroke reduction in HD patients. Ultimately, determining the best drug therapy for the management of HD patients’ AF-related stroke risk is the most important research question left unanswered at this point in time and this can only be resolved conclusively by a large, multi-center RCT.

Conclusions

This survey of nephrologists and cardiologists practicing in Canada provides a better understanding of differences in physician management of AF-related stroke risk in the Canadian HD population. Cardiologists were three times more likely than nephrologists to choose anticoagulant therapy and patient stroke and bleeding risk did not have a significant influence on this difference.

Despite the lack of evidence to support the efficacy of anticoagulation in stroke risk reduction in HD patients, a high number of cardiologists and nephrologists recommended it in patient scenarios with comorbidities that increased stroke risk. And in spite of recently updated evidence-based guidelines suggesting that no drug therapy is appropriate for HD patients with AF, the anticoagulant prescribing rate from our survey was not appreciably lower than it was in
1996 to 2004. Physicians (particularly cardiologists) may be basing their drug therapy choice on the RCT evidence for antithrombotic therapy in the general population, even though observational evidence suggests antithrombotic therapy may actually increase morbidity and mortality in HD patients. This supports the need for a large RCT in the HD population with AF to determine best management.

Certainty for drug therapy choice differed between cardiologists and nephrologists across four patient scenarios that varied in risk profile. However, this finding cannot be considered conclusive, as it was not hypothesized *a priori*.

Because of sampling and response bias, particularly with regards to cardiologists, these findings are not generalizable to the Canadian population of cardiologists and nephrologists. Publication of this research may motivate physicians in Canada to collaborate on discovering the safest and most effective way to manage HD patients with AF.
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111. W. Tymchak, Acting Director, Division of Cardiology, University of Calgary. Email communication. September 9, 2015.

112. E. O’Bien, Division Chief, Division of Cardiology, University of Alberta. Email communication. September 9, 2015.


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Appendix A: Literature search methods

The databases MEDLINE (1946 to 2015 week 25) and Embase (1980 to 2015 week 25) were searched using the following keyword and MeSH terms:

A. Atrial fibrillation and considerations in the hemodialysis population

Keyword and MeSH terms:
1. exp warfarin/ OR exp anticoagulants/ OR exp apixaban/ OR exp rivaroxaban/ OR exp dabigatran/
2. exp renal dialysis/ OR hemodialysis.mp. OR exp renal insufficiency/
3. 1 AND 2
4. antithrombotic therapy.mp. AND 2
5. exp atrial fibrillation/
6. 5 AND 2
7. 5 AND 3
8. exp aspirin/ AND 6
9. exp stroke/ OR exp thromboembolism/
10. 3 AND 9
11. 6 AND 9
12. exp intracranial hemorrhage/ OR exp hemorrhage/
13. 3 AND 12
14. 6 AND 12
15. risk stratification.mp. AND 5
16. risk stratification.mp. AND 3

B. Physician prescribing patterns, rates and attitudes towards prescribing for AF

Keyword and MeSH terms:
1. attitude of health personnel.mp. OR exp attitude to health/
2. exp atrial fibrillation/
3. 1 AND 2
4. exp renal dialysis/ OR exp renal insufficiency/
5. 1 AND 4
6. exp warfarin/ OR exp anticoagulants/
7. 3 AND 6
8. 5 AND 6
9. exp practice patterns, physicians’/
10. 2 AND 9
11. 9 AND 4 AND 6
12. exp nephrology/
13. exp cardiology/
14. 10 AND 12
15. 10 AND 13
C. Uncertainty and risk in clinical decision-making

Keyword and MeSH terms:
1. exp uncertainty/ OR certainty.mp. OR physician uncertainty.mp. OR clinical uncertainty.mp.
2. exp decision making/
3. 1 AND 2
4. exp atrial fibrillation/
5. 1 AND 4
6. 2 AND 4
7. 3 AND 4
8. exp renal dialysis/ OR exp renal insufficiency/
9. 1 AND 8
10. 2 AND 8
11. 6 AND 8
12. exp warfarin/
13. 1 AND 12
14. 5 AND 12
15. measurement.mp.
16. 1 AND 14
17. 3 AND 14
18. exp risk factors/
19. 3 AND 17
20. 6 AND 17
21. patient risk.mp.
22. 3 AND 20
Appendix B: Pretest version of questionnaire

Part 1: Exclusion criterion

Do you manage or get consulted on stroke prevention in HD patients with chronic AF? (If you answer no, please disregard the rest of the survey).

- Yes
- No

Part 2: Patient Cases

All patients in the following cases receive HD 3 times weekly for 4 hours and have developed AF for which they are being considered for stroke prophylaxis. Assume in each scenario that this individual has been a patient of yours for 3 years and that they are competent to manage any of the therapies and are able to access INR testing.

Please choose one of the options provided for your management of stroke risk from AF in each patient. Please also indicate your level of certainty on the choice you made for each scenario.

REMINDER: All scenarios involve an HD patient with AF being considered for stroke prophylaxis.

Scenario 1: A 50-year-old male with HTN.

- Aspirin
- Other anti-platelet agent (clopidogrel, dipyridamole, etc.)
- Warfarin
- One of the new oral anticoagulant therapies (apixaban, rivaroxaban or dabigatran)
- No drug therapy
- Other (please explain)

Level of CERTAINTY (0 being very uncertain, 5 being neutral, 10 being very certain):
**Scenario 2:** A 50-year-old male with HTN, alcoholism and a history of GI bleeding in the past 3 months.

- Aspirin
- Other anti-platelet agent (clopidogrel, dipyridamole, etc.)
- Warfarin
- One of the new oral anticoagulant therapies (apixaban, rivaroxaban or dabigatran)
- No drug therapy
- Other (please explain)

Level of CERTAINTY (0 being very uncertain, 5 being neutral, 10 being very certain):

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**Scenario 3:** A 79-year-old female with previous ischemic stroke, HTN, type 2 diabetes and congestive heart failure (CHF).

- Aspirin
- Other anti-platelet agent (clopidogrel, dipyridamole, etc.)
- Warfarin
- One of the new oral anticoagulant therapies (apixaban, rivaroxaban or dabigatran)
- No drug therapy
- Other (please explain)

Level of CERTAINTY (0 being very uncertain, 5 being neutral, 10 being very certain):

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**Scenario 4:** A 79-year-old female with previous ischemic stroke, HTN, type 2 diabetes and CHF. She also is a high risk for falls, drinks alcohol (2 drinks/day) and has liver cirrhosis.

- Aspirin
- Other anti-platelet agent (clopidogrel, dipyridamole, etc.)
- Warfarin
- One of the new oral anticoagulant therapies (apixaban, rivaroxaban or dabigatran)
- No drug therapy
- Other (please explain)

Level of CERTAINTY (0 being very uncertain, 5 being neutral, 10 being very certain):

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Part 3: Physician Demographics

2.1. Age:
- 35 and under
- 36-55
- 56-65
- 66 and older

2.2 Gender:
- Male
- Female

2.3. How many years have you been in practice?
- 5 or less
- 6-10
- 11-15
- 16-20
- more than 20

2.4. Province of primary clinical practice (select one of the following):

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2.5. Where is your primary clinical practice?
- University-affiliated hospital
- Non-university affiliated metropolitan hospital
- Regional/rural hospital
- Private hospital
- Family Health team (FHT)
- Non-hospital or non-FHT or other

2.6. What is your primary clinical specialty?
- Nephrology
- Cardiology
- Other

Please provide any comments or feedback on the questionnaire or any additional information you would like us to know.
Appendix C: Debriefing questions for participants in questionnaire pretest

1) Is the information given about the study sufficient for you to understand the purpose of the questionnaire?
2) Can you comment on the clarity of the survey? Is the wording clear?
3) How do you feel about the length of the survey? Are there any sections that you would suggest we shorten or take out?
4) Do the questions asked reflect the purpose of this research?
5) Do you think the scenarios are realistic?
6) Please comment on the drug therapy choices for the patient cases. Are they compatible with your experience in this clinical scenario?
7) Do you think the structure of this questionnaire captures your opinion on the subject matter?
8) Do any of the items produce irritation, or confusion?
9) Do you think any of the questions generate response bias? If so, which ones?
10) Have any other important issues been overlooked?
11) What were your overall thoughts on the survey? Do you have any other comments or suggestions?
Appendix D: Final version of questionnaire

Are you involved in decisions regarding the use of antithrombotic therapy to prevent stroke in hemodialysis patients with atrial fibrillation? (If you answer no, the questionnaire will end and you can disregard the rest of the survey).

- Yes
- No

Section 1: Patient Scenarios

All patients in the following patients receive HD 3 times weekly for 4 hours and have developed AF for which they are being considered for stroke prophylaxis.

Assume in each scenario that this individual has been a patient of yours for 3 years and that they are competent to manage any of the therapies and are able to access INR testing.

Please choose one of the options provided that you would recommend for the management of stroke risk from non-valvular AF in each patient. Please also indicate your level of certainty on the choice you made for each scenario.

**Scenario 1**: A 50-year-old male on HD with non-valvular AF and hypertension.

- Aspirin
- Other anti-platelet agent (clopidogrel, dipyridamole, etc.)
- Dual anti-platelet therapy (Aspirin plus other)
- Warfarin
- One of the new oral anticoagulant therapies (apixaban, rivaroxaban or dabigatran)
- No drug therapy

Level of CERTAINTY (0 being very uncertain, 5 being neutral, 10 being very certain):

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**Scenario 2**: A 50-year-old male on HD with non-valvular AF, hypertension, alcoholism and a history of gastrointestinal bleeding in the past 3 months (bleed has resolved).

- Aspirin
- Other anti-platelet agent (clopidogrel, dipyridamole, etc.)
- Dual anti-platelet therapy (Aspirin plus other)
- Warfarin
- One of the new oral anticoagulant therapies (apixaban, rivaroxaban or dabigatran)
- No drug therapy
Scenario 3: A 79-year-old female on HD with non-valvular AF, previous ischemic stroke, hypertension, type 2 diabetes and congestive heart failure.

- Aspirin
- Other anti-platelet agent (clopidogrel, dipyridamole, etc.)
- Dual anti-platelet therapy (Aspirin plus other)
- Warfarin
- One of the new oral anticoagulant therapies (apixaban, rivaroxaban or dabigatran)
- No drug therapy

Section 2: Physician Demographics

2.1. Age:
- 35 and under
- 36-50
- 51-65
- 66 and older

2.2 Sex:
- Male
- Female
2.3. How many years have you been in practice?
   - 5 or less
   - 6-10
   - 11-15
   - 16-20
   - more than 20

2.4. Province of primary clinical practice (select one of the following):

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<td>Ontario</td>
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</table>

2.5. Where is your primary clinical practice?
   - University-affiliated hospital
   - Non-university affiliated metropolitan hospital (urban)
   - Rural hospital
   - Private hospital
   - Family Health team (FHT)
   - Non-hospital or non-FHT or other

2.6. What is your primary clinical specialty?
   - Nephrology
   - Cardiology
   - Other

Please provide any comments or feedback on the questionnaire or any additional information you would like us to know.

*End Questionnaire*
Appendix E: Survey cover letter

Investigation into the Stroke Prevention Management Practices for Hemodialysis Patients with Atrial Fibrillation among Nephrologists and Cardiologists in Canada

Laura Quinn Marcus (Masters Student)
Marisa Battistella (Supervisor)

The purpose of this survey is to gain a better understanding of the stroke prevention practices for hemodialysis (HD) patients with non-valvular atrial fibrillation (AF) among cardiologists and nephrologists in different practices settings in Canada. We recognize that each patient has individual needs and risk factors and thus one may not treat each patient the same. However, the following questions are intended to help us understand your recommendations for stroke prevention practices in the HD population. The survey will take about 5 minutes to complete.

This questionnaire is anonymous and all information obtained during the study will be held in strict confidence. Servers for Survey Monkey are located in the United States and are therefore subject to the Patriot Act. Representatives of the Research Ethics Board may look at the study records to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines. You will not be named in any reports, publication or presentations that may come from this study.

You will not receive any direct benefit from being in this study. Your participation in this study is voluntary. You have the right to refuse participation in this study or not complete the study in its entirety. Once you have completed the questionnaire, you will not be able to withdraw from the study because we are unable to link you to your responses.

If you have any questions, concerns or would like to speak to the study team for any reason, please call: Laura Quinn Marcus at 416-340-4800 x3781. If you have any questions about your rights as a research participant or have concerns about this study, you can contact the Research Ethics office number at 416-946-3273 or ethics.review@utoronto.ca.

By completing this questionnaire you are agreeing to participate in the study. If you wish to continue, click here.
Appendix F: Email distributed to potential respondents

Colleagues,

Please consider participating in our survey to improve our understanding of how nephrologists and cardiologists manage the stroke risk due to non-valvular atrial fibrillation in the hemodialysis population in Canada.

We present four patient cases and ask for your choice of drug therapy (or no drug therapy). The survey will take 5 minutes to complete.

Your opinion is greatly valued and we plan to publish this research in the near future so that you may benefit from insight into how your colleagues across Canada manage this controversial clinical issue. Please note that we have distributed this questionnaire to several groups and apologize for any duplication but appreciate one response from each individual.

Please use the link below to access the online questionnaire.

https://www.surveymonkey.com/r/AFtherapyinHD

Sincerely,

Laura Quinn Marcus, BScPhm, RPh,
ACPR
Clinical Pharmacist – Cardiovascular Surgery
Peter Munk Cardiac Centre
University Health Network
200 Elizabeth St.
Toronto, ON M5G 2C4
416-340-4800 ext. 3781
laura.quinn@uhn.ca

Marisa Battistella, BSc Phm, Pharm D,
ACPR
Pharmacy Clinician Scientist
Assistant Professor, Leslie Dan Faculty of Pharmacy, University of Toronto
Clinical Pharmacist-Nephrology
University Health Network
200 Elizabeth St EB 214
Toronto, ON M5G 2C4
416-340-4800 ext. 3207
marisa.battistella@uhn.ca
Appendix G: Survey-related notice in Canadian Cardiovascular Society newsletter

Clinical Controversy in Atrial Fibrillation – CCS Members Need Your Help!

Stroke prevention therapy in atrial fibrillation for patients with end-stage renal disease is controversial. For hemodialysis patients, the benefits of antithrombotic therapy are unclear and the risks may be increased. Canadian Cardiologists and Nephrologists are being surveyed to understand their current management of these patients.

Please take a 5-minute case-based survey.

Your participation in this research is greatly valued. The results will be made available in a publication to enhance our collective understanding of the current management of these patients across Canada.

Click here to participate: https://www.surveymonkey.com/r/AFtherapyinHD

Thank you!

Paul Dorian and Kori Leblanc
# Appendix H: Timeline of survey distribution

<table>
<thead>
<tr>
<th>Date</th>
<th>Step in Questionnaire Distribution</th>
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<tbody>
<tr>
<td>March 11, 2015</td>
<td>First email to CSN members</td>
</tr>
<tr>
<td>March 24, 2015</td>
<td>Second email to CSN members</td>
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<tr>
<td>April 9, 2015</td>
<td>Third email to CSN members</td>
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<td>First newsletter (with questionnaire link embedded) to CCS members</td>
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<td>May 4, 2015*</td>
<td>Second newsletter (with questionnaire link embedded) to CCS members</td>
</tr>
<tr>
<td>May 18, 2015</td>
<td>Third newsletter (with questionnaire link embedded) to CCS members</td>
</tr>
<tr>
<td>August 11, 2015</td>
<td>First email to cardiologists affiliated with UofT</td>
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<td>August 12, 2015</td>
<td>First email to cardiologists affiliated with UofA and UofC</td>
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<td>August 13, 2015</td>
<td>First email to CHRS members</td>
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<td>August 25, 2015</td>
<td>Second email to cardiologists affiliated with UofT</td>
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<td>August 26, 2015</td>
<td>Second email to cardiologists affiliated with UofA and UofC</td>
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<tr>
<td>August 27, 2015</td>
<td>Second email to CHRS members</td>
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<tr>
<td>September 8, 2015</td>
<td>Third email to cardiologists affiliated with UofT</td>
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<tr>
<td>September 10, 2015</td>
<td>Third email to CHRS members</td>
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<tr>
<td>September 15, 2015*</td>
<td>Third email to cardiologists affiliated with UofA and UofC</td>
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* Distribution was more than 2 weeks after the prior distribution due to undisclosed administration issues at the CCS, UofA and UofC.

CSN, Canadian Society of Nephrology; CCS, Canadian Cardiovascular Society; CHRS, Canadian Heart Rhythm Society; UofT, University of Toronto; UofA, University of Alberta; UofC, University of Calgary.
Appendix I: Mixed effects multinomial logistic regression model equation and variable coding

**Dependent Variable:**

1. drug therapy choice
   - 0 – no drug therapy
   - 1 – antiplatelet
   - 2 – anticoagulant

**Independent Variables:**

1. Between subjects: physician specialty
   - 0 – cardiologists
   - 1 – nephrologists
2. Within subjects: bleeding risk
   - 0 - low risk bleed
   - 1 - high risk bleed
3. Within subjects: stroke risk
   - 0 - low risk stroke
   - 1 - high risk stroke

**Model equation with interactions (with no drug therapy as reference therapy)**

\[
\ln\left(\frac{P(\text{anticoagulant or antiplatelet})}{P(\text{no drug therapy})}\right) = \beta_0(\text{intercept}) + \beta_1(\text{specialty: nephrologist vs. cardiologist}) + \beta_2(\text{bleeding risk: high vs. low}) + \beta_3(\text{stroke risk: high vs. low}) + \beta_4(\text{specialty x bleeding risk}) + \beta_5(\text{specialty x stroke risk}) + \beta_6(\text{bleeding risk x stroke risk}) + \beta_7(\text{specialty x bleeding risk x stroke risk})
\]

**Model equation without interactions (with no drug therapy as reference therapy)**

\[
\ln\left(\frac{P(\text{anticoagulant or antiplatelet})}{P(\text{no drug therapy})}\right) = \beta_0(\text{intercept}) + \beta_1(\text{specialty: nephrologist vs. cardiologist}) + \beta_2(\text{bleeding risk: high vs. low}) + \beta_3(\text{stroke risk: high vs. low})
\]

**Model equation without interactions (with antiplatelet as reference therapy)**

\[
\ln\left(\frac{P(\text{anticoagulant or no drug therapy})}{P(\text{antiplatelet})}\right) = \beta_0(\text{intercept}) + \beta_1(\text{specialty: nephrologist vs. cardiologist}) + \beta_2(\text{bleed risk: high vs. low}) + \beta_3(\text{stroke risk: high vs. low})
\]
Appendix J: Frequency distribution of certainty scores by physician specialty and patient scenario