EFFECT OF POLICY AND PRACTICE CHANGES ON ORAL ANTICOAGULATION USE IN NORTH CAROLINA

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ABSTRACT

CHRISTOPHER BEADLES: Effect of policy and practice changes on oral anticoagulation use in North Carolina
(Under the direction of Kristen Hassmiller Lich)

Despite a long history of proven effectiveness, oral anticoagulation therapy (OAT) has been underused in medical practice so the full potential for stroke risk reduction has yet to be realized in everyday clinical settings. Several policy changes intended to improve care quality and change care delivery were recently established, but the effect of these policy changes on OAT use is unknown. The overall objective of this proposal is to estimate the effect of policy and practice changes on OAT use in real world clinical settings. This work: investigates the impact of The Joint Commission's National Patient Safety Goals on the initiation of OAT in eligible AF patients (Aim 1); evaluates the effect of geographic, physician, facility and patient factors on OAT initiation and time to discontinuation for eligible AF patients (Aim 2); and investigates the effect of patient-centered medical homes (PCMH) on OAT initiation (Aim 3). The overall hypothesis of the work is that both National Patient Safety Goals and PCMHs are associated with increased use of OAT, but only PCMHs are associated with greater time to OAT discontinuation.

Claims data from the North Carolina State Health Plan are used to create cohorts of incident AF before and after policy changes. Difference in difference regression modeling is utilized to evaluate OAT initiation upon hospital discharge in the cohorts before and after The Joint Commission policy changes. A survival analysis approach is employed

using Cox proportional hazard regressions to evaluate time to OAT discontinuation before and after these policy changes. A difference in difference modeling approach is used to compare OAT initiation by PCMH exposure status.

This research is significant in several respects: 1) it examines an understudied area of health policy governing health care delivery safety and quality in a population with documented underuse of appropriate therapy; 2) it identifies and differentiates specific populations who have benefitted from policy and practice changes enabling targeted future interventions for maximum effect; and 3) it evaluates an innovation in the health care delivery model for primary care, the PCMH, by providing evidence of its impact on guideline adherence in receiving OAT.

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AF	Atrial Fibrillation
ARF	Area Resource File
CMS	Centers for Medicaid and Medicare Services
$CHADS_2$	Congestive Heart Failure, Hypertension, Age>75, Diabetes, TIA/Stroke
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
HPSA	Health Professional Shortage Area
ICD-9-CM	International Classification of Disease 9^{th} Edition Clinical Modification
IPTW	Inverse Probability of Treatment Weight
NCQA	National Committee on Quality Assurance
NCSHP	North Carolina State Health Plan
NPSGs	National Patient Safety Goals
OAT	Oral Anticoagulation Therapy
OSCAR	Online Survey, Certification and Reporting Database
PCMH	Patient-Centered Medical Home
TIA	Transient Ischemic Attack

CHAPTER 1

OVERALL BACKGROUND AND SIGNIFICANCE

The Burden of Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting between 2.7 and 6.1 million Americans, and a major independent risk factor for stroke [1]. The lifetime risk for developing AF is 1 in 4 for men and women age 40 years and older [2]. In observational cohort studies, documented AF clearly precedes stroke in patients with an initial stroke event [3]. Patients with AF have a five-fold greater risk of stroke even after adjusting for other stroke risk factors [1]. Moreover, strokes secondary to AF are nearly twice as likely to be fatal as non-AF caused stroke, more likely to recur within one year, and result in greater severity of functional deficits among survivors [4,5]. The increased severity is independent of advanced age and other stroke risk factors [6]. AF is often asymptomatic [7,8] and frequently clinically undetected [9], thus the true risk of stroke related to AF is likely underestimated [10].

Stroke is associated with substantial health care costs, long term disability and is the 4th leading cause of death in the US [1]. The annual direct cost of stroke in the United States in 2009 was an estimated $22.8 billion (total direct and indirect costs of $38.6 billion) [1] and the long-term cost of a single major ischemic event is an estimated $145,251 [11]. Following a first event stroke, one year mortality is approximately 25%, while 5-year mortality is greater than 50% [1]. While AF is directly responsible for 15-20% of strokes [12], direct annual costs of AF reflect more than just the cost of stroke care and are estimated at $6.6 billion [13]. Analysis of administrative claims data reveal that after an AF diagnosis, patient health care

costs are 3 times greater than before an AF diagnosis, and for those who experience a subsequent transient ischemic attack, ischemic stroke or major bleed, post-event total direct costs increase 4-8 times pre-AF costs [14].

While the overall prevalence of AF is roughly 1-2% among adults 20 years or older, it increases dramatically from 50 years of age (0.1%) to 80 years of age (10%) [15]. Applying the current prevalence of AF to US Census Bureau projections for the year 2050, the number of individuals with AF is expected to reach 12 million secondary to the larger proportion of elderly individuals [2].

Oral Anticoagulation Therapy Efficacy, Effectiveness and Utilization

Clinically, AF allows blood to pool in the small chambers of a patient's heart (atria). This pooling of blood fosters a favorable environment for the coagulation of blood and formation of blood clots. In time, the blood clots dislodge or fragment blocking the arteries that supply the brain, resulting in an ischemic stroke. Warfarin decreases the blood's ability to form clots and has been the primary anticoagulant in oral anticoagulation therapy (OAT) for nearly six decades. Beginning in the early 1990's multiple randomized controlled trials confirmed the efficacy of Warfarin in reducing stroke risk secondary to AF and its superior stroke risk reduction to the anti-platelet agent acetylsalicylic acid (ASA) or aspirin (Table 1). Multiple meta-analyses have confirmed the results of individual trials [16-18]. Oral anticoagulation with Warfarin reduces the relative risk of stroke secondary to AF by 64% compared to placebo, while ASA reduces the relative risk by 22% compared to placebo [18].

Table 1. Stroke Prevention Trials using Antithrombotics in Atrial Fibrillation			
Study	Year	Participants	Intervention Arms
AFASAK	1989	1007	Warfarin*, aspirin and placebo
BAATAF	1990	420	Warfarin* and control
SPAF I	1991	1330	Warfarin*, aspirin* and placebo
CAFA	1991	378	Warfarin and placebo
SPINAF	1992	571	Warfarin* and placebo
EAFT	1993	1007	Warfarin*, aspirin and placebo
SPAF II	1994	1100	Warfarin and aspirin
SPAF III	1996	1044	Warfarin* and low-dose Warfarin plus aspirin
ACTIVE-W	2006	6706	Warfarin* and clopidogrel plus aspirin

* Indicates a statistically significant result reported for efficacy
ACTIVE-W: Atrial Fibrillation Clopidogrel Trial with Warfarin AFASAK: Atrial Fibrillation, Aspirin, Anticoagulation BAATAF: Boston Area Anticoagulation Trial for Atrial Fibrillation CAFA: Canadian Atrial Fibrillation Anticoagulation EAFT: European Atrial Fibrillation Trial SPAF: Stroke Prevention in Atrial Fibrillation SPINAF: Stroke Prevention in Non-rheumatic Atrial Fibrillation

Observational studies confirm stroke risk reduction but at a smaller effect size. An early prospective observational study in two practice settings in Montreal followed 221 patients with documented AF for a mean of 27 months [19]. The study reported a relative risk reduction in stroke for patients in the Warfarin treatment arm that was equivalent to the randomized trials, despite having patients that were older and sicker than those included in the trials. Go and colleagues found a 51% relative risk reduction associated with Warfarin use for an assembled cohort of 11,526 AF patients (July 1996-Jan 1997) followed for 25,341 person-years in a large integrated health care system in Northern California [20]. Darkow and associates utilized a large claims database from a managed care organization to create a cohort of 12,539 patients with incident AF in the 2000 calendar year, of which approximately 40% received Warfarin while the remainder were Warfarin candidates [21]. After adjusting for age, gender and other stroke risk factors they observed a 22% relative risk reduction for patients receiving Warfarin during a maximum 720-day follow-up.

In contrast, a similarly designed study of a large commercial health plan with 6.4 million members identified a cohort of 6,764 incident AF patients from January 1998 to December 2000, in which 52% were exposed to Warfarin. Following adjustment for baseline characteristics, the study found no benefit of Warfarin in reducing intracranial ischemic

events [22]. Birman-Deych and associates studied a cohort of Medicare beneficiaries with AF who were hospitalized between March 1998 and April 1999 in all 50 states. After adjusting for comorbid conditions, Warfarin prescription was associated with a 35% relative risk reduction in ischemic strokes, but this effect was smaller in black and Hispanic beneficiaries [23]. A similar finding has been reported in Medicaid participants as well. Boulanger and associates created a retrospective cohort from administrative claims data in California Medicaid recipients aged 50 years and older. They identified 4,355 patients with incident AF between January 1998 and March 2002 in which 59% filled any prescription for Warfarin and Warfarin exposure occurred during only 37% of days following diagnosis. The relative risk reduction of stroke during periods of Warfarin exposure was 27% less than during periods of Warfarin non-exposure [24].

Effectiveness of OAT in reducing stroke risk in clinical practice is lower than that achieved in randomized clinical trials for several reasons. To achieve the same results as clinical trials, an equivalent level of anticoagulation is required [25,26]. However, observational studies of patients hospitalized for stroke as well as other reasons who are receiving OAT are often sub-therapeutic at the time of admission [27,28]. Clinical trials are designed and funded to have sufficient resources to provide a high level of supervision that leads to greater OAT control, while community practice in addition to lacking resources encounters multiple barriers to OAT initiation and persistence [29]. Poor management of OAT and patient non-adherence results in less time spent within therapeutic range [30,31]. Less time spent within therapeutic range translates into reduced stroke risk reduction associated with OAT [32]. Finally elderly individuals have a greater net benefit from receiving OAT, yet in clinical practice are less likely to receive OAT [33,34]. Fewer individuals, who receive the greatest benefit, initiating OAT in clinical practice further minimizes the observed effect of OAT on stroke risk reduction.

Despite heterogeneous estimates of Warfarin effectiveness in stroke risk reduction in practice, observational studies have demonstrated a significant and consistent reduction in overall medical costs associated with Warfarin exposure. A retrospective observational cohort study using claims data from a large managed care organization identified a cohort of 3,981 incident AF patients between January 2001 and June 2002 and followed them at least 6 months. The researchers found a 200% increase in total direct health care costs from pre- to post-AF diagnosis. Interestingly, regardless of stroke risk, exposure to Warfarin was associated with an 18-29% decrease in costs [14]. A similar finding was recently demonstrated in Medicare beneficiaries. Mercaldi and colleagues analyzed claims data from the Medicare 5% sample, identifying 119,764 incident AF patients from 2004 to 2005 and compared Warfarin users to non-users for an average of 2.1 years follow-up. Individually, use of Warfarin therapy among patients with AF was independently associated with lower medical costs, averaging $9,836 per patient per year [35].

The reported magnitude of benefit with Warfarin oral anticoagulation therapy in practice is generally favorable and recent cost studies also support OAT. One might expect utilization among eligible candidates to be high as well. However, many observational studies have found substantial underuse of OAT among eligible patients with AF [36]. Olgilvie and colleagues provide a systematic review of observational studies examining AF and stroke prevention therapy. They identified 78 studies, of which 56 met inclusion criteria containing data from 1980 to 2007. They report on data from 2000 to 2007 showing that among moderate and high risk stroke patients 4-48% (median 18%) received no therapy, 10-56% (median 30%) received antiplatelet therapy and 9-86% (median 52%) received Warfarin therapy [37]. In AF patients that are at moderate or high risk for stroke, Warfarin is the guideline recommended therapy. However, the data from studies reporting underuse of

OAT is becoming outdated and in all cases precedes the development of two major policy changes anticipated to meaningfully affect OAT use.

Policy and Practice Changes in Oral Anticoagulation: the establishment of anticoagulation National Patient Safety Goals

The Joint Commission is the nation's oldest and largest standards-setting and accrediting body in health care. Its primary purpose is to [38]: “continuously improve health care for the public, in collaboration with other stakeholders, by evaluating health care organizations and inspiring them to excel in providing safe and effective care of the highest quality and value.” To this end, the Joint Commission evaluates and accredits more than 19,000 health care organizations and programs in the United States. Joint Commission accreditation is required for reimbursement from Medicare and many private health insurance companies. The Joint Commission established its National Patient Safety Goals (NPSGs) program in 2002 to help accredited organizations address particular areas of concern in regards to patient safety [38]. The first set of NPSGs became effective January 1, 2003 [38]. The NPSGs concerning anticoagulation were added in 2007 and became effective January 1, 2008 [38]. These goals were intended to increase the rate of guideline concordant care concerning OAT among hospitals providing anticoagulation services. Presumably the goals improve OAT utilization through a direct effect on hospitals and an indirect effect on patient adherence to OAT. The direct effect is a result of a hospital implementing a policy, guidelines, or anticoagulation management services in response to establishment of the NPSGs. The indirect effect may be mediated through a greater availability of OAT management resources, once it has been initiated [29,39].

To my knowledge, the effect of The Joint Commission’s revision of the NPSGs has not been evaluated. However, literature examining the relationship between adoption of The

Joint Commission process of care guidelines and improved outcomes yields mixed results. For example, VanSuch and colleagues [40] found compliance with The Joint Commission guidelines for discharge instructions in heart failure patients was associated with decreased readmission rates and Kfoury and associates [41] reported a positive incremental relationship between degree of adherence to The Joint Commission core measures for heart failure and one-year survival. But Fonarow's group [42] reported no association with adherence to The Joint Commission heart failure core measures and 60-90 day mortality or readmission; and Patterson and colleagues [43] found compliance with The Joint Commission heart failure core measures had no association with one year mortality or readmission.

The contribution of this research is expected to provide a greater understanding of the effect of The Joint Commission NPSGs concerning anticoagulation on guideline concordant use of OAT with a specific focus on initiation and time to discontinuation. *This contribution is significant because it examines an understudied area of health policy, The Joint Commission NPSGs that govern health care delivery in a population with documented underutilization of appropriate therapy.* The study addresses a relevant policy intervention intended to modify organization of health care systems, delivery of health care services, and utilization with the intent to improve health care outcomes and cost-effectiveness. Understanding the effect of policy interventions such as The Joint Commission NPSGs on advancing health care safety, quality and efficiency will provide a baseline for evaluating future interventions aimed at improving America's healthcare system.

Policy and Practice Changes in Oral Anticoagulation: the emergence of the Patient Centered Medical Home

Although the concept of a medical home originated in the pediatric population for children with special health care needs in 1967, the patient-centered medical home (PCMH)

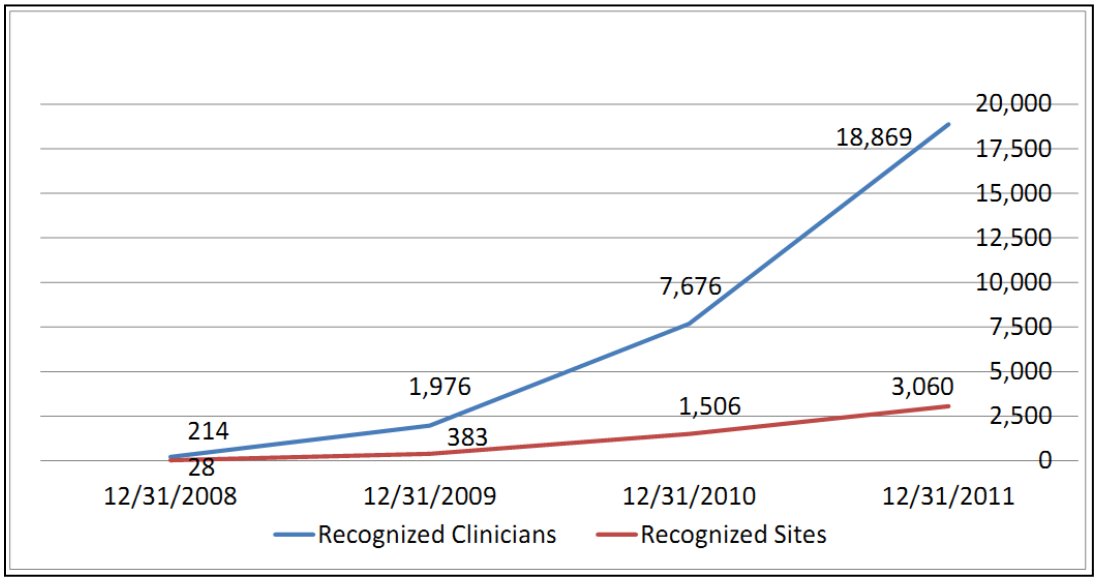
that adopts many aspects of Wagner's chronic care model [44] at first glance appears relatively novel [45]. Kilo and Wasson provide a brief yet remarkably clear summative history of forces that have lead to rapid and accelerating interest in PCMH model. They describe three phases of the PCMH development: 1) basic investigation (1970-1997) 2) model development (1997-mid-2000s) and 3) model dissemination (mid-2000s-present). A merging of various political and economic forces served to intensify attention on the PCMH model [45]. The current PCMH concept generally follows seven principles (see Text Box 1) outlined in the Joint Principles of the PCMH [46,47]. The PCMH is intended to re-center the US health care delivery system while improving quality and reducing health care costs [48-50].

Text Box 1. Joint Principles of the Patient Centered Medical Home

1. A personal physician
2. Physician directed medical practice
3. A whole-person orientation
4. Provides coordinated and/or integrated care
5. Committed to continuous evaluation/ improvement of care quality and patient safety
6. Provides enhanced access to care
7. Provides an enhanced payment structure

Since 2007 PCMHs have steadily increased in number nationally (Figure 1) [51]. This research effort represents a timely evaluation of a model of health care delivery that is being rapidly disseminated with substantial national policy ramifications.

Figure 1. Growth of NCQA Accredited PCMHs and Participating Clinicians in the United States



Substantial evidence exists supporting the effectiveness of several individual components of the PCMH. Rosenthal reviews much of the previous literature supporting these components [52]. For example, literature supporting the benefits of a personal physician includes: better patient health process measures and health outcomes for those with a continuous longitudinal relationship with a primary care provider; improved cancer screening; greater vaccination rates and reduced emergency department expenditures [52]. Rosenthal also reviews the literature supporting team directed practice, a whole-person patient orientation, coordinated care across all domains of a health care system, quality and safety, and finally enhanced access. Each individual component does appear to have solid grounding in the literature. However, little evidence exists today concerning the ability of PCMHs to improve quality, improve health outcomes and reduce costs [53,54]. Early evaluations of PCMHs typically included programs that adopted one or two components of the PCMH. An early review of the evidence on the PCMH model by Homer and colleagues found that that only 1 of the 33 studies reviewed was of an intervention modeled after the PCMH while the others tested only selected components [55]. Two other early papers

reviewed the literature on individual components of the medical home such as team-based care, rather than reviewing multi-component interventions that more closely resemble the PCMH model [56,57]. While several systematic reviews have been published providing support for the PCMH model, each has potentially troubling limitations. Three did not consider the rigor of the evidence in the studies reviewed [49,57,58]. Two reviews conducted a limited assessment selecting comparison group studies and peer-reviewed studies, respectively [55,59]. Neither of these considered the studies' strength of the analytical methods or excluded studies lacking rigorous methods from evidence synthesis steps.

Peikes et al. conducted a large systematic review of the evidence for the PCMH model through September 2010 [53]. They found that most interventions cited in the literature were actually precursors to the PCMH model and tested simply the addition of a care manager operating within a primary care practice. They also found that less than half of evaluations studied all three outcomes of cost, quality and access. Limiting the inclusion of studies to those that described interventions containing at least 3 of 5 principles of the PCMH model and utilized rigorous analytic methods generated 14 evaluations of 12 interventions. The evidence from these studies indicates; some favorable effects on quality, patient experience, and caregiver experience; a few unfavorable effects on costs; and mostly inconclusive results. The authors conclude that stronger well-designed, well - implemented evaluations of the full PCMH model are required to provide needed evidence and guide decisions regarding this promising but unproven model of care delivery. A more recent systematic review by Jackson et al. compared 19 studies of PCMH interventions and found a small positive effect on patient experience and small to moderate positive effects on the delivery of preventive care, but limited evidence in reduction of emergency room visits or

hospital admissions and no evidence for cost savings [54]. Jackson et al. have found essentially identical results in their more recent review as well [54].

PCMHs may have a beneficial effect on OAT initiation and persistence through several mechanisms which include: a stronger therapeutic relationship with a personal physician; enhanced access to care (ex: obtaining prescription refills, laboratory collections); greater follow-up and monitoring (ex: laboratory values, unfilled prescriptions); coordination of care with specialists (ex: cardiologists); and a practice commitment to improving quality and patient safety. As described above, these mechanisms are individually supported in the literature but have not been well demonstrated as part of a multi-component intervention. The specific barriers and principles of the PCMH that address these barriers are summarized in Table 2.

Table 2. Barriers to OAT Initiation Addressed by Principles of the PCMH

Barriers to OAT Initiation	Principles of PCMH That Address Barriers
Patient Level	
Percieved Stroke Risk	Personal relationship with physician
Perceived Adverse Event Risk	Personal relationship with physician
Difficulty with access	Enhanced Access
Difficulty with adherence	Personal relationship with physician
Physician Level	
Perceived Risk/Benefit Ratio	Coordinated care / Commitment to quality improvement
Lack of guideline awareness	Coordinated care / Commitment to quality improvement
Discrepancy between believed & actual practice patterns	Commitment to quality improvement (Audit-Feedback)
Guidelines inappropriate for patient	Commitment to quality improvement
Perceive patient will be non-adherent	Personal relationship with physician
Health Care System Level	
Access to laboratory facilities	Enhanced Access
Access to Provider	Enhanced Access
Follow-up of out of range lab values	Enhanced Access

Of particular interest to anticoagulation, some PCMHs accredited by the National Committee on Quality Assurance choose to also pursue a Heart Stroke Recognition Program. This program contains an audit of the practice's use of guideline appropriate antithrombotics as a criterion for the recognition. This raises awareness concerning practice

norms and performance in providing guideline concordant care in AF patients with moderate or high stroke risk. The audit-feedback intervention has been consistently shown to have an effect on provider behavior in health care delivery [60].

This research contributes to existing literature through examining processes of care and disease specific outcomes in a variety of independent PCMHs. This contribution is significant because it implements a rigorous evaluation of the PCMH model while providing much needed evidence concerning the effect of receiving care within an accredited PCMH on guideline concordant care in OAT initiation and time to OAT discontinuation.

Policy and Practice Changes in Oral Anticoagulation: Interactions with patient-, physician- , and facility-level factors

As alluded to above, several hypothesized types of factors serve as barriers to OAT initiation. Patient factors, physician factors and facility factors have each been reported as determinants of receiving OAT among AF patients [23,61-64,29,39]. However, these three categories of factors have not been studied since establishment of NPSGs or PCMHs and have not been studied in combination with each other. Studying patient, provider and system factors in combination following these policy changes reflects a more realistic clinical practice scenario. Additionally, while the role of these factors on prevalent use of OAT among AF patients has been reported, these factors have not been evaluated in the context of initiation and time to discontinuation of OAT among a cohort of incident AF patients. Existing work primarily emphasizes barriers to OAT initiation. However, for most patients with AF at moderate or high risk for ischemic stroke, the indication for OAT is long-term, or life-long. The risk of stroke, does not decline with time, rather it increases, and substantially. Thus, it is crucial to raise awareness concerning persistence, or time to discontinuation of OAT in clinical practice. I aim to expand current thinking in anticoagulation treatment beyond

prevalent OAT use among AF patients to a greater awareness of two distinct and equally important processes: initiation and time to discontinuation. These processes will more accurately define aspects of OAT use than has been done in prior research. A more precise understanding of factors influencing both OAT initiation and time to OAT discontinuation will assist in identifying additional specific intervention targets to increase OAT use and enhance effectiveness in clinical settings.

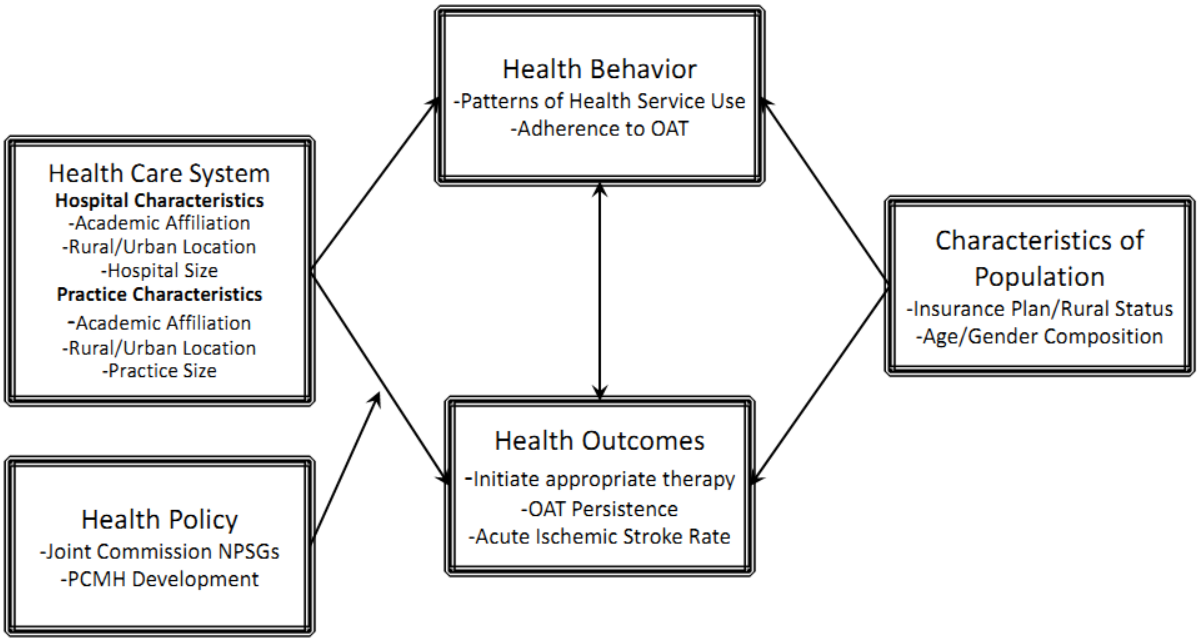
Evaluating the interplay of patient, physician and facility factors allows me to examine the degree of uniformity or lack of uniformity in the effect of policy changes on OAT initiation and time to OAT discontinuation. Population groups at highest risk for stroke or at highest risk for not receiving OAT may experience a disproportionately small increase in appropriate OAT initiation compared to other population groups. This research contributes to existing knowledge concerning variation in OAT initiation and time to discontinuation, and evaluates the impact of anticoagulation policy change as it relates to two specific aspects of OAT utilization. This contribution is significant because it identifies and differentiates specific populations who have benefitted from the policy change and thereby aids in targeting future interventions.

Conceptual Framework

The research questions and subsequent hypotheses in this proposal draw support from a conceptual framework that is an adaptation of Andersen's behavioral model of health services use and his subsequent revisions to the original framework [65]. As illustrated in Figure 2, the framework considers the two policy changes (National Patient Safety Goals and patient-centered medical homes) as part of the external environment. The external environment, which includes physical, political and economic components, such as a

healthcare system influence an individual's use of health services and subsequently their likelihood of receiving appropriate treatment and continuing treatment. While not explicitly shown below, dynamic feedback loops also affect the external environment and other predisposing factors, such as age, gender, and insurance status of the population.

Figure 2. External Environment Changes & Their Effects on OAT Use & Persistence



For instance a hospital with an academic affiliation may be more likely to provide onsite outpatient anticoagulation management services in a dedicated anticoagulation clinic. A hospital with an academic affiliation may also have greater capacity for patient follow-up via the use of an electronic health record and additional staff resources. This greater patient follow-up capacity translates into a more efficient system of monitoring and reinforcing adherence to prescribed treatment regimens. The hospital's urban or rural location influences both the level of patient access to hospital-provided outpatient services and the strength of association with academic institutions. While hospital size is not thought to

strongly influence patient access to services, it is associated with location, academic affiliation and overall capacity to provide requisite patient follow-up.

Similarly the effect of changes in the external environment would be anticipated to affect health care systems differently according to their inherent characteristics. A large academic hospital in an urban setting previously providing anticoagulation management services in an anticoagulation clinic might logically have a well developed anticoagulation policy when the NPSGs became effective. This hospital would be relatively unaffected by the change in the external environment. However, a small or medium size hospital without academic affiliation, and lacking well developed anticoagulation management services or internal anticoagulation policies, may be substantially affected by establishment of the NPSGs. Hospitals that are significantly affected by policy changes in the external environment are also more likely to modify or alter hospital practice norms.

Specific Aims

The work of this proposal is summarized in the following specific aims and tests hypotheses that follow from reflecting on the conceptual model in Figure 1 and evidence published in the peer-reviewed literature grounding the model in OAT initiation and time to discontinuation:

Aim 1: To investigate the effect of The Joint Commission National Patient Safety Goals on OAT initiation in eligible AF patients.

Hypothesis: Establishment of The Joint Commission National Patient Safety Goals has led to increased initiation of OAT among eligible patients.

I utilize claims data from the North Carolina State Health Plan to create a longitudinal cohort of individuals diagnosed with AF from 2006-2010; the cohort will be split into pre- (January 2006-December 2008) and post- (January 2009-December 2010) intervention periods.

Using novel control groups (e.g. mechanical heart valve patients with high stroke risk, and paroxysmal AF patients with minimal stroke risk) I use difference in difference regression models to compare OAT initiation following hospital discharge before and after policy changes.

Aim 2: To evaluate the effect of geographic, physician, facility and patient factors on OAT initiation and discontinuation.

Hypothesis: Rural status, health professional shortage areas, outpatient diagnosis, increasing number comorbid chronic conditions, and increasing patient age are negatively associated with initiation and long term persistence of OAT.

Using the previously defined cohort, difference in difference regression modeling is used to estimate the effect of these factors on OAT initiation. Survival analysis using Cox proportional hazards regressions is used to estimate the effect of these factors on time to OAT discontinuation.

Aim 3: To investigate the effect of exposure to a Patient-Centered Medical Home on OAT initiation.

Hypothesis: Receipt of care in a National Committee on Quality Assurance accredited Patient Centered Medical Home among eligible atrial fibrillation patients is directly associated with OAT initiation.

Inverse probability of treatment weights combined with generalized estimating equations are used to compare OAT initiation among those exposed to an accredited PCMH to those unexposed.

Chapter 2

THE EFFECT OF NATIONAL PATIENT SAFETY GOALS ON INITIATION OF ORAL ANTICOAGULATION THERAPY

Overview

To examine the effect of The Joint Commission's National Patient Safety Goals (NPSGs) on initiation of oral anticoagulation therapy for individuals with incident atrial fibrillation. Our data source is the North Carolina State Health Plan claims data from 944,500 individuals enrolled between January 1, 2006 and December 31, 2010, supplemented with data from the Area Resource File and Online Survey, Certification and Reporting data network. We utilize a retrospective cohort new user design with two control groups: guideline positive—patients at very high risk of thromboembolism (mechanical heart valve and pulmonary embolism); guideline negative—patients at very low risk of thromboembolism. We test for changes in oral anticoagulation therapy initiation following revision of NPSGs to include anticoagulation. We developed multivariate models using difference-in-difference estimates with control variables defined a priori. Effects were estimated with generalized estimating equations. Following revision of NPSGs to include anticoagulation, eligible individuals with incident atrial fibrillation exhibited an 11 percentage point increase in oral anticoagulation therapy initiation (SE=3.6; $p<.01$). NPSGs for anticoagulation resulted in greater initiation of guideline concordant oral anticoagulation therapy for eligible individuals with incident atrial fibrillation.

Introduction

Oral anticoagulation therapy (OAT) to reduce acute ischemic stroke risk in moderate or high risk atrial fibrillation (AF) patients, typically with Warfarin, has been recommended by guidelines from major organizations for nearly two decades [66]. However, despite its benefit, OAT is often underutilized among eligible AF patients [63,67,25,27,28,68,69,29,70,71,21-23,72,73,61,74-76]. Reasons for underutilization of this therapy are attributed to patients and physicians; however, health care systems also play a role [71,72,77-79,39,80].

The Joint Commission is the nation's oldest and largest standards-setting and accrediting body in health care. Its primary purpose is to [38]: “continuously improve health care for the public, in collaboration with other stakeholders, by evaluating health care organizations and inspiring them to excel in providing safe and effective care of the highest quality and value.” To this end, the Joint Commission evaluates and accredits more than 19,000 health care organizations and programs in the United States. Joint Commission accreditation is required for reimbursement from Medicare and many private health insurance companies. The Joint Commission established a National Patient Safety Goals (NPSGs) program in 2002 to help accredited organizations address specific concerns regarding patient safety. To this end, they established the Patient Safety Advisory Group, a panel of nurses, physicians, pharmacists, risk managers, clinical engineers and other professionals who have hands-on experience in addressing patient safety issues in a wide variety of health care settings. This panel continuously evaluates and updates NPSGs to identify, prioritize, and help address a broad range of emerging patient safety issues. In 2008, the NPSGs were updated to include goals regarding OAT.

The NPSGs concerning anticoagulation (NPSG 03.05.01) represent a change in the external environment intended to affect the health care system, most notably hospitals. They do not mandate that all eligible patients receive anticoagulation, but rather provide explicit

guidelines and expectations for hospitals that provide anticoagulant therapy and/or long-term anticoagulation prophylaxis to reduce the likelihood of patient harm associated with these therapies. Achieving compliance with NSPGs may be moderated by a hospital's preexisting resources and practice norms, as well as their willingness to invest in the infrastructure required to meet them. Hospitals with sufficient resources may be in compliance with regulatory requirements before or soon after they are established. Hospitals with fewer resources may take longer to become compliant with new regulatory requirements. In the case of OAT, hospitals may invest in resources to provide long term out-patient management and monitoring for patients receiving OAT, for example, anticoagulation clinics. Providing anti-coagulation clinics may have an indirect effect on hospital performance, as community physicians with admitting privileges in these hospitals may be more likely to initiate OAT for eligible patients because of both hospital regulatory requirements and additional resources to manage and monitor anti-coagulation [29,39].

Implementation of NPSGs, in general, was intended to substantially impact the health care quality (especially process-oriented measures) in organizations they accredit. However, results for various other Joint Commission initiatives have been mixed. For example, compliance with Joint Commission guidelines for discharge instructions in heart failure patients was associated with decreased readmission rates [40], and there was a positive relationship between adherence to The Joint Commission heart failure core measures and one-year survival [41]. However, other studies found no association between adherence to Joint Commission heart failure core measures and 60-90 day mortality or readmission [42] or with mortality or readmission at one year [43].

We sought to determine the effect of The Joint Commission's NPSGs for anticoagulation on OAT initiation. We hypothesized the NPSG were associated with increased initiation of OAT among eligible patients hospitalized with incident AF. Our

primary analysis examines a potential direct effect of the NPSGs while a set of sensitivity analyses examine potential indirect effects of the NPSGs.

Methods

Data Sources

We used data from January 1, 2006-Deceember 31, 2010 from the North Carolina State Health Plan (NCSHP), a large self-funded insurance plan for the study. The NCSHP, administered by Blue Cross and Blue Shield of North Carolina, includes almost 1 million state employees, teachers, retirees and their dependents. Approximately 10% of enrollees are retired non-Medicare participants, and 16% of enrollees are retired Medicare beneficiaries. This claims structured database contains inpatient, outpatient and pharmacy records. Enrollee descriptors include unique encrypted member identification numbers, basic demographic information including age, gender, county, and zip code of primary residence. Records include information about diagnoses, procedures, providers, charges and payments. The database also contains physician level characteristics which include provider zip code, type of provider and provider specialty if applicable. We linked hospital facility characteristics to the database, including accreditation as a primary stroke center, hospital bed size, and participation in a stroke quality improvement program. Finally we linked individual and facility counties with additional variables from the Area Resource File providing a unique opportunity to concurrently analyze health care delivery at multiple levels including: individual patient characteristics, provider characteristics, and hospital facility characteristics.

Study Sample

We created three cohorts of patients: (1) new onset AF patients; (2) guideline positive controls, which includes patients at very high risk of thromboembolism (mechanical

heart valve and pulmonary embolism); and (3) guideline negative controls, that is patients with a very low risk of thromboembolism (paroxysmal atrial fibrillation). For all three cohorts, patients needed to be continuously enrolled in the NCSHP a minimum of 6 months prior to the qualifying index claim and a minimum of 6 months following the qualifying index claim. Individuals with a prescription claim for Warfarin more than 30 days prior to an index claim for any of the three cohorts (i.e. AF, mechanical heart valve, paroxysmal AF) were excluded from the sample due to a high probability of representing prevalent rather than incident conditions. Figure one provides a summary of cohort identification and determination of eligibility. Eligibility criteria for each cohort are described below.

New onset AF patients: We used either one inpatient diagnosis or two outpatient diagnoses within 12 months (International Classification of Disease 9th edition-Clinical Modification (ICD-9-CM) code 427.31) to identify individuals with AF. We designated the first outpatient AF claim or the date of admission for an inpatient claim as the date of entry into the cohort. The American College of Cardiology, The American College of Chest Physicians and the American Heart Association endorse the use of a risk based score to identify individuals who will benefit from receiving OAT. $CHADS_2$ is a commonly employed scoring system [81]. Individuals receive 1 point for congestive heart failure, hypertension, age greater than 75 years, diabetes mellitus and receive 2 points for any prior stroke or stroke symptoms. It is recommended that an individual with a score of 2 or more should receive OAT. This score is readily generated using claims data and was used to identify individuals with new onset AF who should receive OAT (See Appendix Table 2.1 for ICD-9-CM codes for these diagnoses). We included all individuals meeting criteria for incident AF with a $CHADS_2$ score $\geq$ 2. While there are very few absolute contraindications to receiving OAT, numerous relative contraindications exist. To increase the precision of our estimates we excluded individuals with one or more relative contraindications to receiving OAT (identified using ICD-9-CM codes) from the incident AF or intervention cohort (See Appendix Table 2.2

for contraindications and ICD-9-CM codes). Finally, to reduce the probability of including individuals with prevalent AF rather than incident AF we excluded individuals with any AF related claim in the six months preceding the index claim.

Guideline positive controls: Individuals with either one inpatient diagnosis or two outpatient diagnoses within 12 months indicating a mechanical heart valve or significant thromboembolism with at least six months of continuous eligibility prior to and six months continuous eligibility following the index claim were included in the guideline positive cohort (See Appendix Table 2.3 for diagnoses and ICD-9-CM codes). The $CHADS_2$ score was not applied to this cohort, as it is only validated in patients with AF. Finally, to reduce the probability of including individuals with prevalent conditions rather than incident mechanical heart valves or significant thromboembolism we excluded individuals with any condition related claim in the six months preceding the index claim.

Guideline negative controls: Individuals with either one inpatient diagnosis or two outpatient diagnoses within 12 months for paroxysmal AF (ICD-9-CM code 427.21) with at least six months of continuous eligibility prior to and six months continuous eligibility following the index claim were included in the guideline negative cohort. Figure 2 provides a visual summary of the initial sample and final cohort size for each group.

Measures

The primary dependent variable is OAT initiation, a binary outcome defined as having a prescription drug claim for Warfarin within 30 days of the index claim. Index claims occurring in years 2006-2008 were assigned pre-NPSGs status while index claims occurring in 2009-2010 were assigned post-NPSGs status. The key explanatory variable is the interaction term between a binary indicator for pre/post status of The Joint Commission's NPSGs and a binary indicator variable for the incident AF cohort, which represents the difference in difference estimator.

Control variables were created at the patient level and facility level. All control variables were identified a priori and measured in the baseline period or immediately prior to the index AF claim to mitigate potential confounding. Patient level control variables include age, gender, Charlson Comorbidity Index, $CHADS_2$ score, rural/urban residence, and number of outpatient visits to a primary care provider in the 30 days prior to the index claim. Charlson Comorbidity Index was categorized as 0, 1-2, and 3 or more. $CHADS_2$ score was categorized as 2, 3-4, and 5 or more. Rural/Urban status was categorized as metropolitan, micropolitan or rural as defined by the Area Resource File [82].

Facility level control variables include a binary variable indicating hospital primary stroke center accreditation status (as defined by CMS) for each time period, a binary variable indicating participation in an acute stroke care quality improvement program (Get With the Guidelines Stroke or North Carolina Stroke Care Collaborative) for each time period, distance of hospital from enrollee residence, hospital bed size and rural/urban facility location. Get with the Guidelines Stroke participation was determined from the American Heart Association website (www.heart.org). Participation in the North Carolina Stroke Care Collaborative was provided by the organization. We calculated distance as a function of straight line distance from the centroid of patient and hospital zip codes using SAS 9.2. Hospital bed size was determined from the Online Survey, Certification and Reporting (OSCAR) data network maintained by the Centers for Medicare and Medicaid Services.

Statistical Analysis

We examined cohorts for differences in baseline covariates as well as differences within cohorts between pre and post time periods. Unadjusted rates of oat initiation for each cohort were also examined. We then estimated the relationship between NPSG and initiation of OAT among individuals with new onset AF using a difference in difference approach and multivariable regression equations. Differences in OAT initiation before and

after the policy change for the comparison group are attributed to a time effect. Subtracting this difference from the difference in the AF cohort yields an estimate that is more robust to external factors and time effects. In practice the difference in difference estimate is created by interacting the treatment (in this case time) variable with a dummy variable indicating the treatment cohort.

$$Pr(OATi_{ft}=1|X_{ift}) = X\beta \quad \text{where } f(E[Y]) = X\beta \text{ and } var(E[Y])=g(E[Y]) \qquad \text{(Eqn 1)}$$

$$\text{with } X\beta = \beta_0 + \beta_1 AF_i + \beta_2 Post_i + \beta_3(AF_i * Post_i) + \beta_4 X_i + e$$

where *i* indicates the individual. *OAT* is the outcome variable as defined above. *AF* represents the cohort and *Post* indicates whether the index claim occurred pre (Post=0) or post (Post=1) NPSG development. *X* is a vector of individual patient and facility control variables defined above. Facility level fixed effects are taken into account by clustering within facilities and specifying an exchangeable within-group correlation structure. The coefficient that identifies the effect of interest is β_3, which estimates the effect of NPSG on the probability of OAT initiation for patients with incident AF.

We utilized a generalized estimating equation model with a Poisson distribution, log link (denoted by f(E[Y]) above) and exchangeable within group correlation structure (denoted by var(E[Y]) above) to account for within hospital correlation. Robust standard errors were included to correct for underdispersion of the binary dependent variable in the context of a count distribution. While the exponentiated coefficients may be interpreted as risk ratios when using a log link, we converted the coefficients to average marginal effects as absolute risk differences for ease of interpretation. All models were estimated in Stata 11 (StataCorp, College Station, TX).

We conducted several sets of sensitivity analyses. The first assessed potential measurement error in the dependent variable, OAT initiation. The rise of many low-cost generic prescription drug programs administered through major retailers has caused concern regarding under identification of generic drugs within pharmacy claims data [83].

Warfarin has been generic for several decades, and multiple generic formulations exist. While a claim for Warfarin is specific for OAT initiation, it may be lacking somewhat in sensitivity. We created two additional definitions for OAT initiation using claims for laboratory blood tests associated with blood coagulation or anticoagulation management claims. (See Appendix Table 2.4 for CPT codes and ICD-9-CM codes employed) The laboratory blood tests were hypothesized to represent a sensitive measure of OAT initiation that might have less specificity for OAT initiation as it is associated with the monitoring of the effect of Warfarin, but is not specific to anticoagulation management alone. The first additional definition for OAT initiation combined either a pharmacy claim for Warfarin or a claim for associated laboratory blood tests or a claim for outpatient anticoagulation management. The second additional definition for OAT initiation excluded the pharmacy claim, utilizing only the laboratory blood test and outpatient anticoagulation management claims to define initiation. The next sensitivity analysis compared the effect of the policy on an inpatient only cohort, hypothesized to demonstrate the greatest effect, an outpatient only cohort, and a combined inpatient and outpatient cohort. The final set of sensitivity analyses involved an extensive evaluation of nonlinear effects of included model covariates and additional county level covariates that could be hypothesized to affect the observed relationship between the policy change and observed OAT initiation rates.

The study protocol was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

Results

Descriptive Findings

Baseline characteristics of the AF, guideline positive and guideline negative cohorts are presented in Table 3. While the cohorts differ from each other with respect to indication for OAT, they are relatively homogeneous between pre and post time periods. As expected,

OAT initiation was decidedly higher in the guideline positive cohort (67.5%) than in the intervention (26.8%) or guideline negative cohort (23.8%). Additionally, OAT initiation in the guideline negative cohort was higher than expected. OAT initiation in the intervention group (26.8%) was within range of previous observational studies [36]. Within specific indication cohorts, average age remained stable while number of diagnoses tended to increase in the post period. Overall number of relative contraindications for OAT did not change appreciably between pre and post periods. The number of outpatient claims from primary care physicians in the 30 days preceding entry into a cohort remained stable or marginally increased between the pre and post periods. Hospital characteristics are notable for a marked increase in the percentage of individuals treated in hospitals that were accredited primary stroke centers or participating in some form of quality improvement program for acute stroke care. This trend was observed in all cohorts. The percentage of individuals treated in rural and critical access hospitals increased marginally from the pre period to the post period. County level characteristics in general remained stable from the pre to post period. Two notable exceptions to this trend were average unemployment rate in the county and percent of persons in poverty in the county, which increased in all cohorts from the pre to post period. Consistent with unemployment rates and percent persons in poverty, median household income fell in the post period for all cohorts. The number of general practice providers and cardiovascular specialists remained stable or marginally increased in the post period for the intervention and guideline positive cohorts but decreased slightly for the guideline negative cohort. The county level race and ethnicity demographics remained stable across time for all cohorts.

Regression Results

The unadjusted bivariate results (top of Table 4) indicate that OAT initiation marginally decreased for the guideline positive and guideline negative cohorts while OAT initiation increased for the intervention cohort. The marginal effect for the interaction term

between the intervention cohort and the post period represents the difference in difference estimate. The OAT initiation rate increased on average 12 percentage points ($p<0.001$) for this cohort in the post period. This increase in OAT initiation dropped slightly, but remained significant (11 percentage point increase, $p<0.01$) in multivariable models controlling for additional patient and hospital facility characteristics. While the difference in difference estimate for the guideline negative cohort suggested a decrease in OAT initiation, the marginal effect was small and insignificant. Oldest individuals (71+ years) were less likely to initiate OAT as were individuals with the highest number of co-morbid conditions. Higher $CHADS_2$ scores, indicating greater risk of acute ischemic stroke were not associated with greater OAT initiation. Greater number of outpatient primary care physician claims preceding entry into the cohort was associated with increased OAT initiation. Finally, residential distance from the admitting hospital was negatively associated with OAT initiation.

Sensitivity Test Results

Results of sensitivity analyses are presented in Table 5. Overall, the difference in difference estimate for the intervention group was robust to alternate definitions of OAT initiation. The combined pharmacy claim, blood laboratory test, anticoagulation management definition of OAT initiation yielded a similar marginal effect of a 9 percentage point increase ($p<0.05$) in OAT initiation for the treatment group in the post period. The marginal effect was smaller and insignificant in the blood laboratory test and anticoagulation management only definition of OAT initiation. Other associations were similar to that observed in the primary analysis. We also found a strong marginal effect on OAT initiation for an outpatient only intervention cohort and the combined inpatient-outpatient cohort. Finally multiple model specifications with alternate functional form and additional control covariates resulted in similar findings as our primary analysis (See Appendix Table 2.5).

Discussion

This study assessed the effect of the Joint Commission updating NPSG to include OAT on OAT initiation within a large privately insured population across North Carolina with new onset AF. The study has several unique strengths. First, the use of guideline positive and guideline negative control groups allow for greater mitigation of potential time bias between the pre and post periods. This overcomes a traditional deficit in observational studies. Second, the nature of this statewide claims database allows for analysis of a relatively stable population of privately insured state workers, spouses, dependents and retirees in a population of approximately one million, providing support for generalizing to other privately insured populations. A third strength of the study is the data linkages with the Area Resource File to provide a rich array of county level control variables and survey information from the OSCAR database to provide hospital facility variables. A fourth strength of the study is inclusion of multiple controls for co-morbid conditions and relative contraindications to OAT. Finally, the clustering of individuals within the hospital in which they received treatment mitigates potential effects of outlier hospitals on the population averaged effect of the policy change.

We found a positive association between revision of NPSG by The Joint Commission to include OAT and OAT initiation for individuals with new onset AF, on average a 10 percentage point increase in the rate of OAT initiation. The strong positive association between NPSG and the outpatient cohort in our sensitivity analysis suggest an indirect effect of NPSG as well. While our results suggest that OAT initiation decreased for individuals in whom OAT is not indicated (the guideline negative cohort), the effect size is small and insignificant. The rate of OAT initiation in the guideline positive cohort was smaller than anticipated, but remained relatively constant in pre and post periods; this supports our choice as a positive control which was relatively unaffected by the policy change. The negative association between age and OAT initiation as well as number of comorbidities and

OAT initiation are consistent with what has been previously described in the literature [84]. The relative lack of association of increasing $CHADS_2$ scores and OAT initiation is also consistent with prior work [85].

The relatively low OAT initiation in the guideline positive cohort and the intervention cohort, as well as the higher than expected OAT initiation in the guideline negative cohort, are interesting. However this finding may reflect the nature of health insurance claims data that represent imperfect information collected for purposes other than the observational study. Our measured rates of OAT initiation in the AF cohort are consistent with prior work in this area [36]. We are not aware of published OAT initiation rates for individuals with mechanical heart valves or significant thromboembolism. Using this group as a benchmark sheds new light on previous observational studies. Underutilization of OAT should be reported with caution given the inherent limitations of using claims data. We view our results, not as an indictment suggesting poor quality of care for new onset AF, but rather as an examination of positive trends in guideline concordant care following policy change.

There are several limitations of our study. First, because we used claims data, we may have misclassified OAT initiation. This is especially true because the popularity of low-cost generic prescription drug programs may lead to patients filling prescriptions for OAT without billing the insurer[83]. We do not have reason to suspect a differential error in pharmacy claims for Warfarin with respect to the three cohorts regarding OAT initiation. Furthermore, this trend, if present, may increase with time, which would bias OAT initiation downwards in the post period and may explain the slight decrease in OAT initiation among the guideline positive cohort. Importantly, our sensitivity analyses suggested that findings were robust to alternative definitions of OAT initiation. Second, we could not control for individual level race, ethnicity or socioeconomic status. However, we controlled for county level indicators of race and socioeconomic status to mitigate these potential effects. Finally, our cohorts were predominantly individuals with employee sponsored group health

insurance and the results may not generalize to publicly insured populations. Notably, our cohorts included a large proportion of retired Medicare enrollees utilizing both their Medicare and NCSHP benefits, which serves to enhance generalizability to Medicare beneficiaries.

Despite the noted limitations, our findings suggest that NPSG concerning anticoagulation resulted in greater initiation of oral anticoagulation therapy for eligible individuals with incident atrial fibrillation, increasing guideline concordant care in this population. Finally we note that new medications for OAT were approved for reduction of stroke risk in patients with AF in late 2010. These agents do not require the same frequency of laboratory monitoring and titration of dosage as Warfarin. While more expensive than Warfarin, these new agents are anticipated to significantly reduce the burden of anticoagulation management for both patients and providers. OAT initiation may increase to a greater degree in years following 2010 that are unrelated to policy changes and rather determined by the availability of novel anticoagulation agents with less intensive monitoring requirements. Observational studies in the future may reveal OAT initiation practice patterns more concordant with guidelines in association with the availability of novel oral anticoagulants.

Figure 3. Selection of Incident AF, application of inclusion/exclusion criteria and identification of comorbid conditions

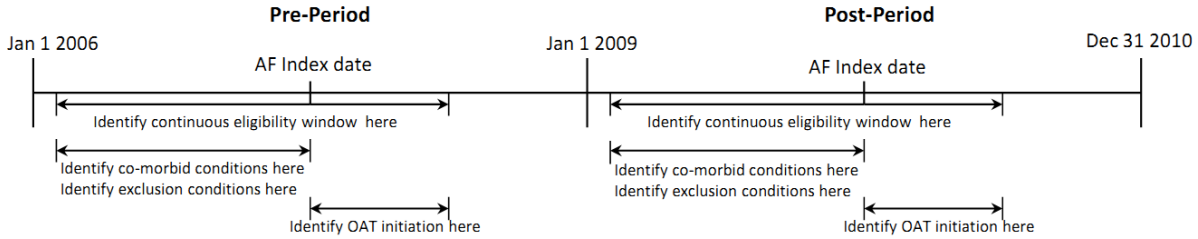


Figure 4. AF Cohort Sample Selection

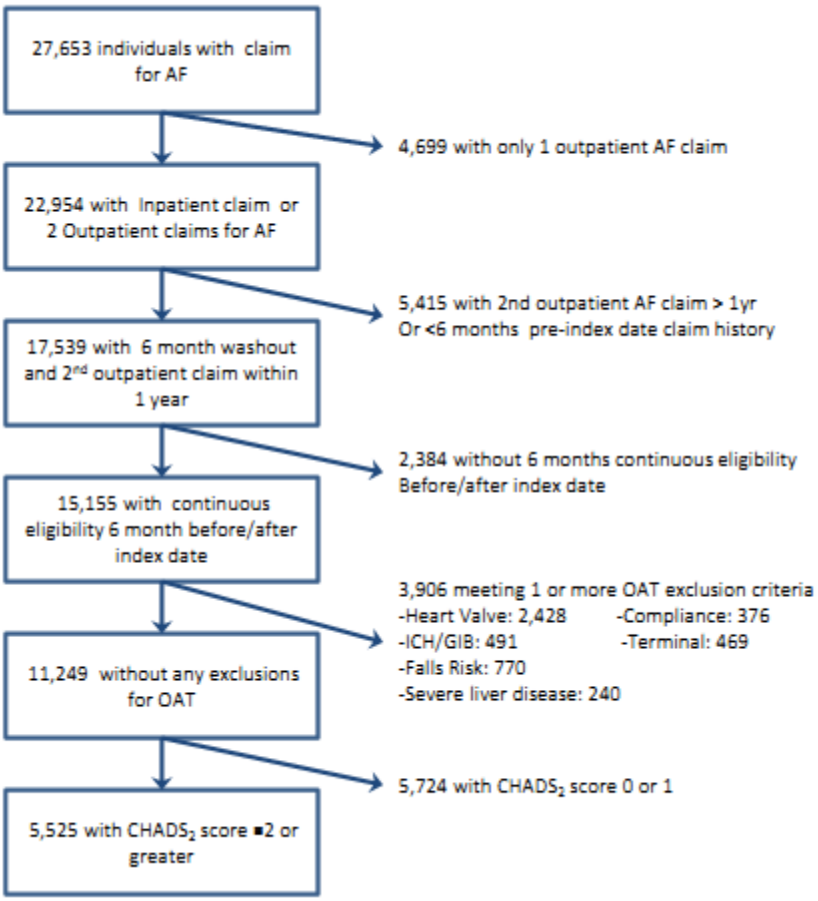


Table 3. Baseline Characteristics Among Intervention Group and Control Groups

Variable	Pre Period			Post Period		
	Eligible AF	Mechanical Heart Valve (+ Control)	Non-eligible AF (- Control)	Eligible AF	Mechanical Heart Valve (+ Control)	Non-eligible AF (- Control)
Sample Size	1,359	1,597	302	662	1,111	204
OAT initiation	26.8	67.5	23.8	31.7	62.0	20.6
Patient Characteristics						
Age	77.9 (11.2)	65.0 (15.7)	71.2 (12.9)	76.7 (11.3)	65.4 (15.3)	70.6 (12.6)
Male	40.5	41.3	53.3	38.7	40.8	57.4
Rural	9.7	10.2	9.3	12.3	10.5	11.8
CHF	29.7	18.8	32.5	23.0	27.1	34.3
Hypertension	94.7	68.1	82.8	96.2	76.8	85.8
Diabetes Mellitus	45.3	26.5	39.4	45.5	35.2	39.7
Ischemic Stroke	23.7	18.8	21.5	35.5	31.1	29.4
$CHADS_2$ Score	2.9 (1.0)	1.8 (1.5)	2.4 (1.5)	3.0 (1.1)	2.3 (1.7)	2.6 (1.6)
Charlson Index	2.0 (1.7)	1.4 (1.6)	2.3 (2.0)	2.1 (1.7)	1.9 (2.0)	2.7 (2.3)
Hemorrhagic stroke	0	1.8	0.7	0	1.6	2
GI bleed	0	4.1	2.0	0	8.5	5.4
Falls Risk	0	7.5	8.9	0	13.8	7.4
Cirrhosis	0	2.9	2	0	5.3	4.9
Dementia	0	1.8	2.3	0	2.3	2.5
Terminal Illness	0	7.4	6.3	0	7.5	6.9
Relative OAT Contraindications	0*	0.5 (0.7)	0.4 (0.7)	0*	0.7 (0.9)	0.6 (0.9)
Outpatient visits	3.1 (3.6)	4.1 (6.1)	4.0 (7.2)	3.5 (3.6)	4.8 (5.6)	4.0 (5.5)
Facility Characteristics						
Rural Hospital	4.7	4.4	2.4	5.8	6.0	3.1
Primary Stroke Center	19.2	21.7	31.1	45.8	43.8	50.5
Participates in GWTG	48.6	50.5	47.4	59.2	56.3	63.7
Hospital Bed Size	449 (311)	464 (309)	525 (322)	461 (307)	460 (310)	506 (324)
Distance residence-hospital (miles)	21.7 (82.2)	23.9 (76.7)	22.9 (57.9)	20.1 (48.0)	18.4 (53.4)	18.5 (28.7)
County Characteristics						
Percent White	68.9 (15.3)	68.3 (15.0)	68.5 (14.5)	68.5 (15.1)	68.7 (15.0)	67.6 (15.2)
Percent Black	21.4 (13.2)	21.8 (13.2)	21.6 (12.6)	22.0 (13.3)	21.4 (13.3)	22.5 (14.2)
Percent American Indian	1.4 (5.2)	1.5 (5.2)	1.4 (4.8)	1.3 (4.7)	1.5 (5.1)	1.2 (2.0)
Asian	2.0 (1.9)	2.2 (2.0)	2.2 (2.0)	1.9 (1.9)	2.1 (2.0)	2.2 (2.0)
Hispanic	7.9 (3.6)	8.0 (3.7)	8.0 (3.3)	8.0 (3.7)	8.1 (3.6)	8.3 (4.4)
General Practitioners	62.6 (67.8)	68.1 (72.1)	73.5 (76.1)	68.4 (79.8)	73.5 (87.0)	73.6 (80.9)
CV specialists	17.0 (21.6)	18.6 (22.9)	20.7 (24.2)	17.6 (23.2)	19.4 (24.8)	19.6 (23.7)
3 yr avg death CV dz	106.5 (90.0)	113.2 (96.8)	119.3 (101.3)	107.0 (91.7)	112.7 (105)	108.7 (93.7)
County Median Hhld income (1000's)	44.6 (9.4)	45.1 (9.6)	46.6 (10.2)	43.5 (9.6)	44.7 (10.0)	44.7 (10.5)
Unemployment rate	5.2 (1.4)	5.4 (1.5)	5.5 (1.7)	10.7 (2.1)	10.7 (2.1)	10.5 (2.3)

Notes: *****Inclusion in AF treatment group conditional on value of zero for this variable. ()=standard deviation

Table 4. Estimated Marginal Effects of Policy Changes, Patient Characteristics and Inpatient Facility Characteristics on OAT initiation

	Adjusted for Patient Characteristics		Adjusted for Patient and Facility Characteristics	
Unadjusted Results				
Guideline Positive	-0.05			
Guideline Negative	-0.02			
Intervention	0.05			
Adjusted Results				
Post Period	-0.04*	(-0.07,-0.01)	-0.03*	(-0.06,-0.00)
Treatment Group	-0.39***	(-0.43,-0.35)	-0.38***	(-0.42,-0.34)
Post*Treatment	0.10**	(0.04,0.17)	0.11**	(0.04,0.18)
Post*Gldln Negative	-0.03	(-0.19,0.13)	-0.03	(-0.19,0.13)
Patient Characteristics				
18-40yrs	0.03	(-0.03,0.09)	0.03	(-0.02,0.09)
61-70yrs	-0.01	(-0.04,0.02)	-0.01	(-0.04,0.02)
71+years	-0.10***	(-0.13,-0.07)	-0.10***	(-0.14,-0.07)
Gender (Male)	0.02*	(0.00,0.04)	0.03**	(0.01,0.05)
Charlson(0)	0.01	(-0.03,0.06)	0.01	(-0.03,0.05)
Charlson(2)	-0.04*	(-0.07,-0.00)	-0.04*	(-0.07,-0.00)
Charlson(3-4)	-0.02	(-0.06,0.03)	-0.01	(-0.06,0.03)
Charlson(5-11)	-0.13***	(-0.17,-0.09)	-0.12***	(-0.17,-0.08)
CHADS2(0-1)	-0.02	(-0.05,0.02)	-0.01	(-0.05,0.03)
CHADS2(3-4)	-0.05*	(-0.09,-0.01)	-0.04*	(-0.08,-0.00)
CHADS2(5-6)	-0.04	(-0.11,0.04)	-0.03	(-0.10,0.04)
Rural	0.02	(-0.03,0.06)	0.01	(-0.05,0.07)
Micropolitan	0.01	(-0.03,0.04)	-0.00	(-0.05,0.04)
0 Pre-Event Visits	-0.05*	(-0.09,-0.00)	-0.04	(-0.09,0.00)
2+ Pre-Event Visits	0.06***	(0.03,0.09)	0.05***	(0.02,0.08)
Facility Characteristics				
Primary Stroke Center			-0.01	(-0.06,0.04)
GWTG participation			-0.01	(-0.03,0.02)
4-99 beds			-0.04	(-0.09,0.00)
500+ beds			-0.04	(-0.08,0.00)
25+ miles			-0.10***	(-0.16,-0.05)
Rural provider			0.07	(-0.01,0.16)
Micropolitan Provider			0.04	(-0.01,0.09)
Observations	5235		5235	

95% confidence intervals in parenthesis * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 5. Estimated Marginal Effects of Sensitivity Analyses in Alternate Outcome Definitions, Outpatient Only Cohort and Combined Inpatient/Outpatient Cohorts

	OAT-RX & OAT-Labs		OAT-Labs		OAT-Outpatients		OAT-ALL	
18-40yrs	0.01	(-0.04,0.07)	0.01	(-0.03,0.06)	-0.02	(-0.07,0.03)	0.01	(-0.03,0.04)
61-70yrs	-0.02	(-0.04,0.01)	-0.18***	(-0.21,-0.14)	0.02	(-0.01,0.06)	0.01	(-0.02,0.04)
71+years	-0.12***	(-0.16,-0.09)	-0.38***	(-0.43,-0.34)	-0.05*	(-0.09,-0.01)	-0.09***	(-0.11,-0.06)
Gender (Male)	0.02	(-0.00,0.04)	0.01	(-0.01,0.03)	0.06***	(0.03,0.08)	0.04***	(0.02,0.06)
Charlson(0)	0.02	(-0.02,0.06)	0.03	(-0.00,0.05)	0.03	(-0.01,0.07)	0.01	(-0.01,0.04)
Charlson(2)	-0.03	(-0.06,0.01)	-0.02	(-0.05,0.01)	-0.04	(-0.08,0.01)	-0.05**	(-0.08,-0.01)
Charlson (3-4)	-0.00	(-0.05,0.04)	-0.04*	(-0.07,-0.00)	-0.05	(-0.09,0.00)	-0.05**	(-0.08,-0.01)
Charlson(5-11)	-0.12***	(-0.16,-0.07)	-0.07***	(-0.11,-0.03)	-0.11***	(-0.17,-0.05)	-0.13***	(-0.17,-0.09)
CHADS2(0-1)	-0.00	(-0.04,0.04)	0.02	(-0.01,0.05)	0.02	(-0.02,0.06)	0.00	(-0.03,0.03)
CHADS2(3-4)	-0.04*	(-0.08,-0.00)	-0.01	(-0.03,0.02)	-0.01	(-0.05,0.03)	-0.03*	(-0.05,-0.00)
CHADS2(5-6)	-0.02	(-0.08,0.04)	-0.04	(-0.10,0.02)	-0.04	(-0.10,0.03)	-0.04	(-0.09,0.01)
Rural	-0.00	(-0.07,0.06)	-0.04*	(-0.08,-0.01)	-0.05	(-0.11,0.01)	-0.03	(-0.07,0.01)
Micropolitan	-0.01	(-0.06,0.04)	-0.03**	(-0.05,-0.01)	0.00	(-0.05,0.05)	-0.01	(-0.04,0.02)
Post Period	-0.02	(-0.05,0.01)	0.03**	(0.01,0.05)	0.01	(-0.02,0.04)	-0.01	(-0.03,0.01)
Treatment Group	-0.38***	(-0.42,-0.34)	-0.14***	(-0.18,-0.10)	-0.44***	(-0.50,-0.39)	-0.42***	(-0.46,-0.38)
Post*Treatment	0.09*	(0.02,0.16)	0.03	(-0.03,0.09)	0.17***	(0.09,0.25)	0.14***	(0.08,0.19)
Guideline Negative	-0.44***	(-0.53,-0.36)	-0.21***	(-0.27,-0.15)	-0.49***	(-0.64,-0.34)	-0.49***	(-0.57,-0.40)
Post*Gldln Negative	-0.03	(-0.19,0.13)	-0.02	(-0.11,0.08)	0.09	(-0.10,0.29)	0.02	(-0.10,0.14)
0 Pre-diagnosis Visits	-0.05*	(-0.09,-0.00)	-0.06***	(-0.10,-0.03)	0.09**	(0.03,0.14)	0.02	(-0.01,0.06)
2+ Pre-diagnosis Visits	0.05***	(0.02,0.08)	0.04***	(0.02,0.07)	0.08***	(0.04,0.12)	0.06***	(0.03,0.08)
Primary Stroke Center	-0.01	(-0.06,0.04)	-0.02	(-0.05,0.00)				
GWTG participation	-0.01	(-0.04,0.01)	-0.00	(-0.03,0.02)				
4-99 beds	-0.04*	(-0.09,-0.00)	0.01	(-0.02,0.04)				
500+ beds	-0.03	(-0.07,0.01)	-0.01	(-0.05,0.03)				
25+ miles	-0.10***	(-0.15,-0.05)	-0.04***	(-0.06,-0.02)				
Rural provider	0.08	(-0.00,0.17)	0.05	(-0.01,0.10)	0.12**	(0.04,0.20)	0.11***	(0.05,0.17)
Micropolitan Provider	0.05*	(0.00,0.09)	0.04*	(0.00,0.08)	0.01	(-0.04,0.06)	0.04*	(0.01,0.07)
Inpt Index Claim							-0.03**	(-0.05,-0.01)
Observations	5235		5235		4694		9380	

95% confidence intervals in parentheses * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Chapter 3

THE EFFECT OF GEOGRAPHIC, PHYSICIAN, FACILITY, AND PATIENT FACTORS ON ORAL ANTICOAGULATION INITIATION AND DISCONTINUATION

Overview

Although some barriers to anticoagulation for patients with atrial fibrillation are known, little is known concerning their overlap with determinants of time to anticoagulation discontinuation or how initial inpatient versus outpatient diagnosis influences them. We identified a cohort of incident atrial fibrillation patients using five years of claims data. Based on this and other linkable data sources, we measured: patient, provider, and geographic characteristics; diagnosis setting; and anticoagulation therapy initiation and time to discontinuation in a prospective new-user design study. We implemented generalized linear models and survival analysis methods to examine barriers to initiation, determinants of time to discontinuation and overlap between them. We identified a total of 7,748 incident atrial fibrillation patients, of which 2,146 (28%) initiated anticoagulation therapy. Initial diagnosis setting was not associated with initiation or time to discontinuation. Older age at diagnosis was associated with lower initiation (0.7% per year 95% CI -0.8% to -0.6%) and a lower hazard of discontinuation (HR 0.66 95% CI 0.42-0.85). Men had greater initiation (OR=1.25 95% CI 1.08-1.35) and greater hazard of discontinuation (HR=1.09 95% CI 0.99-1.20). Greater number of comorbidities at diagnosis was associated with lower initiation and greater hazard of discontinuation. Within one year 1,167 (54%) patients discontinued therapy, and 63% of them did not restart during the observation period. Too few patients initiate OAT and among those that do, many discontinue therapy quickly. The potential

stroke risk reduction of anticoagulation therapy is mitigated by its underutilization and early discontinuation among eligible individuals.

Introduction

Oral anticoagulation therapy (OAT) to reduce acute ischemic stroke risk in moderate or high risk atrial fibrillation (AF) patients, typically with Warfarin, has been recommended by guidelines from major organizations for nearly two decades [66]. However, despite its benefit, OAT is often underutilized among eligible AF patients [86,87,75,76]. This underutilization may be secondary to low rates of OAT initiation or precipitous OAT discontinuation.

Barriers to OAT initiation exist at the level of patients, physicians and health care systems (see Table 6) [23,61,62,88,29,78,89,39,72,90,80]. In contrast, determinants of OAT discontinuation and the extent of their overlap with barriers to OAT initiation are not as well documented, with notable exceptions summarized in Table 6. Higher stroke risk and age >65 years at OAT initiation are inversely associated with OAT discontinuation [85,91]. Male gender [85,69] poor cognitive function [92], poverty [93], higher educational attainment [92], and homelessness [94] have been associated with OAT discontinuation.

Recent years demonstrate a growing trend of initial diagnosis and management for incident AF in the outpatient setting [95,96]. It is not known how this shift away from an inpatient initial diagnosis setting may influence barriers to OAT initiation or determinants of discontinuation. Additionally, changes in the healthcare system such as revision of The Joint Commission National Patient Safety Goals (NPSG) to include anticoagulation and the emergence of the patient centered medical home (PCMH) may increase or attenuate potential differences in OAT initiation by initial diagnosis setting (i.e., inpatient versus outpatient). We sought to: examine the influence of initial diagnosis setting on barriers to OAT initiation, corroborate and expand predictors of OAT discontinuation, and determine the degree of overlap, if any, with barriers to OAT initiation in patients with incident AF.

Methods

Data Source

Data came from the North Carolina State Health Plan (NCSHP), a large self-funded insurance plan. NCSHP includes almost 1 million state employees, teachers, retirees and their dependents. Retired non-Medicare participants and retired Medicare beneficiaries compose 10% and 15% of the plan respectively. This claims database contains inpatient, outpatient and pharmacy records. Fields include encrypted member identification numbers, age, gender, county, and zip code of member residence. Records include diagnoses, procedures, providers, charges and payments. The database also contains provider level characteristics which include zip code, type of provider and specialty if applicable. We linked individual and hospital/practice counties with additional variables from the Area Resource File which allowed us to examine patient, provider, and county characteristics.

Procedures

We used NCSHP data from January 1, 2006-December 31, 2010 to examine OAT initiation and persistence during two time periods -- before (January 2006-December 2008) and after (January 2009-December 2010) NPSG revisions. For both periods, patients needed to be continuously enrolled in the NCSHP a minimum of 6 months prior to and a minimum of 6 months following the qualifying index claim. Individuals with a prescription claim for Warfarin more than 30 days prior to an index claim were excluded due to a high probability of representing prevalent rather than incident AF.

We used either one inpatient diagnosis or two outpatient diagnoses within 12 months (ICD-9-CM code 427.31) to identify individuals with new onset AF. Cohort entry date was defined as either the first outpatient AF claim or the inpatient admission date. $CHADS_2$ is a commonly employed scoring system to evaluate stroke risk and benefit from OAT [81] that

can be generated from claims data (See Appendix Table A3.1 for ICD-9-CM codes). We included all individuals meeting criteria for incident AF with a $CHADS_2$ score $\geq$ 2. Finally, to reduce the probability of including individuals with prevalent AF we excluded individuals with any AF-related claim in the six months preceding the index claim.

Measures

Our key dependent variables were OAT initiation (a prescription claim for Warfarin within 30 days of index AF claim) and OAT discontinuation (greater than 60 days without Warfarin coverage by prescription claims).

Explanatory variables of interest were initial AF diagnosis setting (inpatient versus outpatient) and receipt of care in a PCMH (1 or more outpatient claims from a provider in a PCMH) in the 30 days preceding the index claim. We created control variables at the patient, provider, and county level. To mitigate potential confounding, all control variables were measured in the baseline period or immediately prior to the index AF claim [97]. Patient level control variables include age, gender, Charlson Comorbidity Index [98] (categorized as 0,1-2,3^+), $CHADS_2$ score [81] (categorized as 2,3-4,5^+), rural/urban residence, and number of outpatient visits to a primary care provider in the 30 days prior to the index claim. Rural/Urban status was categorized as metropolitan, micropolitan or rural as defined by the Area Resource File [82]. Median county household income, unemployment rate, number of office based general practitioners per county, health professional shortage area (HPSA), number of office based cardiovascular specialists per county and the 3 year average number of deaths from cerebrovascular disease were also from the Area Resource File.

Propensity Score Implementation

To reduce possible confounding with medical home enrollment, we used propensity scores to balance the two groups on pre-treatment covariates. We estimated, conditional on baseline covariates, an individual's probability of receiving care in a medical home in the 30 days before the index event. In our models we included variables associated with OAT initiation, based on theory or prior evidence, and potentially associated with medical home status [99]. To estimate the propensity score, we employed generalized boosted regression with an iterative algorithm that optimized covariate balance based on average standardized absolute mean difference (ASAMD) [100]. We then used stabilized inverse-probability-of-treatment weights (IPTW) to estimate the average treatment effect [101].

Statistical Analysis

We examined characteristics of eligible AF patients by OAT initiation status and then compared patient characteristics by the setting in which the initial diagnosis was made. In multivariable analysis, we used a generalized linear model with a log link, Poisson distribution and robust clustered standard errors. This model accounted for within-facility correlation among practices and hospitals. We then re-estimated the model for inpatients and outpatients separately, followed by a generalized Hausman test to compare effects. We present marginal effects (absolute risk differences) for ease of interpretation.

To examine discontinuation, we implemented a repeated events analysis using the Prentice, Williams, Peterson-Gap time approach to account for multiple periods of OAT initiation and persistence. We then performed non-parametric tests for differences in hazard of discontinuation by individual covariates. We created smoothed hazard functions for each covariate to visually assess for violations of the proportional hazards assumption. We then implemented a Cox proportional hazards model, clustered at the individual level to account

for multiple OAT use periods and stratified by AF diagnosis year. Following model specification and optimizing covariate functional form, we formally tested for violations to the proportional hazards assumption globally and for each covariate. All models were estimated in Stata 11. (StataCorp, College Station, TX)

Sensitivity Analysis

We conducted several sensitivity analyses to assess sensitivity to alternate definitions of OAT initiation, OAT discontinuation and PCMH engagement. To examine OAT initiation we used the ICD-9 CM code for anticoagulation management (V58.61) and procedure codes for corresponding blood tests (CPT codes: 99363, 99364, 85610, 85730 and, 85732) within 30 days of index event to create a non-pharmacy claims OAT initiation definition. To maximize sensitivity, a third OAT initiation definition combined the pharmacy claim and non-pharmacy claims definitions (positive if either of these two definitions were positive).

We then examined the length of time without Warfarin required to indicate OAT discontinuation. We used 30, 90, 120, 150 and 180 days without Warfarin by pharmacy claims to define OAT discontinuation in addition to our primary 60 day definition.

We examined variations in defining PCMH engagement based upon the percentage of all primary care visits to a PCMH 30 days preceding the index event. We used 30% and 50% thresholds for two additional definitions of PCMH engagement.

Finally, we performed the time to discontinuation analysis in a competing events, or cause specific framework, in which death was included as a competing event to discontinuation.

Results

Characteristics of Patients

OAT initiators were on average 3.5 years younger, slightly more likely male, and had marginally lower number of exclusions, Charlson comorbidity index, and $CHADS_2$ scores (Table 7). They were also slightly less likely to receive an initial AF diagnosis in an inpatient setting. OAT initiators had similar numbers of outpatient visits in the baseline period as non-initiators but resided a shorter distance from their provider. Although statistically different, the OAT initiators came from counties with approximately similar unemployment rates and median household incomes. Distribution of rural/urban and HPSA status was similar for both groups. Finally, the number of office based general internists and cardiovascular specialists practicing in the county was similar in both groups.

Patients with an initial inpatient diagnosis were on average 2.2 years older, slightly more likely female, and had a marginally higher Charlson comorbidity index (Table 8). Number of relative exclusions from OAT and $CHADS_2$ score was similar between the groups. Patients with an initial inpatient diagnosis were less likely to initiate OAT (26.1% vs. 29.2% $p<.003$). Initial inpatients had on average one less visit in the baseline period (3.5 vs. 4.4 $p<.001$) but were similar to initial outpatients in the distribution of rural/urban status HPSA status and numbers of office based general internists and cardiovascular specialists.

Associations with OAT Initiation and Discontinuation

Average marginal effects for OAT initiation are shown in Table 9. Column 1 displays the aggregate model, while column 2 and 3 represent models for initial inpatients only and initial outpatients only. Each additional year of age at initial diagnosis reduced the probability of OAT initiation by 0.69%. That is, a five year increase in age at time of diagnosis was associated with a 3.45% decrease in the probability of OAT initiation. Medical home enrollment and male gender were associated with an increase in the probability of OAT initiation, while an increasing number of relative exclusions to OAT, increasing Charlson

comorbidity score, and increasing $CHADS_2$ score were associated with a decreased probability of OAT initiation in the aggregate model. Median household income and unemployment rate of the patients' county were weakly positively associated with OAT initiation. Patients residing in metropolitan and micropolitan counties were slightly less likely to initiate OAT than patients residing in rural counties. HPSA status, initial inpatient status, and diagnosis in 2009-2010 were not associated with OAT initiation.

Average marginal effects for the inpatient and outpatient subsets were generally similar with two notable exceptions. Male patients were more likely to initiate OAT as outpatients than as inpatients (6.5%, 95% CI 2 to 11%). Increasing $CHADS_2$ score was associated with a lower probability of OAT initiation for outpatients (-2.7%, 95% CI -0.65% to -4.7%) but not for inpatients.

Median aggregate time to discontinuation was 289 days after index event. Times were similar for diagnosis setting (301 days vs. 275 days) and medical home engagement (287 days vs. 297 days). Results from the time to event analysis are displayed in Table 10. Older age at diagnosis was associated with a lower hazard for OAT discontinuation. Male gender was weakly associated with discontinuation. Increasing Charlson score and number of individual relative exclusions to receiving OAT were associated with a greater hazard for OAT discontinuation. However, $CHADS_2$ score was not associated with time to OAT discontinuation. Outpatient visits in the baseline period, initial inpatient diagnosis and PCMH engagement were also not associated with time to OAT discontinuation.

Sensitivity Analysis

Our multiple sensitivity analyses (see appendix material) were not qualitatively different from our primary analyses presented here. Changes in the definition of OAT initiation marginally increased the percentage of OAT initiators as expected, but did not change the average marginal effects substantially for our first analysis. Increasing the number of days without Warfarin required indicating discontinuation reduced the number of

OAT periods observed in our data but did not substantially influence our hazard ratio estimates for time to OAT discontinuation. Some estimates were less significant with the observed reduction in sample size. Changes in the definition of PCMH engagement decreased the number of patients with PCMH engagement, but did not substantially change the average marginal effects of our estimates. Finally, our competing events analysis was essentially identical to our cumulative incidence analysis. We observed only 34 competing events in comparison to 2,225 failures.

Discussion

The prevalence of AF in an aging US population is increasing. Availability of new anticoagulants and efforts to deliver more patient-centric coordinated care hold transformative potential but remain largely untested in clinical practice. These trends, combined with a shift towards greater outpatient diagnosis and management, provide rationale for reevaluating OAT initiation and discontinuation. Within this context we sought to examine the influence of initial diagnosis setting on OAT initiation and discontinuation while controlling for previously identified barriers to initiation and predictors of discontinuation. Among observational studies, our work exhibits several relative strengths which include: a large stable insured population across the state of North Carolina; a five year time period; analysis of only incident AF; the merged nature of our data; controlling for a number of relative exclusions to OAT; and analysis in a state with a robust PCMH movement.

Barriers to OAT initiation: Consistent with prior literature, we found increasing age, increasing number of relative OAT exclusions, and increasing Charlson score were associated with a lower probability of OAT initiation. For these individuals risks associated with OAT may outweigh potential benefits. Initial diagnosis setting was not associated with OAT initiation. While in some respects this finding is reassuring as more diagnosis happens in the outpatient setting, however overall rates of OAT initiation remained low (27.7%)

suggesting continued underuse among AF patients. Somewhat surprisingly in sub-analysis, increasing $CHADS_2$ score was not associated with OAT initiation for initial inpatients but was strongly negative for outpatients. Lower outpatient initiation for individuals with high $CHADS_2$ scores may reflect competing co-morbidities and risk of death, unobserved provider barriers or unobserved differences in treatment preferences among these patients.

Determinants of discontinuation: Consistent with prior work, we found increasing age associated with a reduced hazard of discontinuation. Thus age is a determinant for initiation and discontinuation, decreasing OAT initiation yet also decreasing discontinuation. Similarly male gender is associated with greater probability of initiation but greater OAT discontinuation.

Our 56% one year OAT discontinuation rate is substantially greater than that observed in trials (8-12%) [102-104] and reported in observational studies (26-30%) [85,91]. We did not attempt to determine whether this high discontinuation rate reflects: a rational clinical evaluation of ongoing risks and benefits associated continuing OAT; a change in patient preference concerning treatment; unobserved barriers; or clinical practice oversight. We believe at minimum it reflects the need for development of decision tools (similar to existing initiation decision tools) to evaluate persistence or discontinuation of OAT. They should incorporate new knowledge regarding severity of risks and benefits of OAT [105] as well as cumulative patient experience with OAT. We do not believe our observed rate of discontinuation can be wholly explained by adverse events such as intracranial hemorrhage and gastrointestinal bleeding associated with OAT. Annual rates of major bleeding in clinical trials are 3-4% per year [102-104]. If discontinuation is primarily a result of major bleeding, rates of major bleeding in our study would be 6.5 times that reported in trials or 19-26% per year. We find it unlikely that the level of discontinuation in our results is driven primarily by adverse events associated with OAT.

Our study has several limitations. First, we did not examine or adjust for reasons to discontinue therapy. However, we do not believe this introduces any substantial bias in our initiation results concerning our primary exposure of interest, diagnosis setting. Identification and adjusting for adverse events and patient preferences may allow for greater clarity in evaluating determinants of OAT persistence, but is difficult with only claims level data. Second, because we utilized claims data, we did not have access to the level of anticoagulation control during OAT. Some patients may have appropriately discontinued OAT (in exchange for an antiplatelet agent) secondary to poor anticoagulation level control. This question can only be answered with additional laboratory data not available in claims. A third limitation was our relative inability to control for race, ethnicity, education and socioeconomic status in this analysis. While we did control for these factors to some extent using county level variables, the presence of strong unmeasured confounders associated with our measures may over or underestimate their association with OAT initiation and time to discontinuation. A final limitation is that we analyzed data in a state located in the "stroke belt" within the southeastern United States [1]. Clinical practice patterns concerning OAT initiation and discontinuation may not generalize well to regional variations in clinical practice.

Our findings suggest OAT remains underutilized via both low OAT initiation and early discontinuation, providing a target for improved health care quality and a reduction in stroke associated mortality and morbidity. The availability of novel anticoagulants and new models of care delivery (e.g. the PCMH) provide opportunities for improvement, but their impact needs to be thoughtfully supported. For example, PCMHs seem to lead to slightly improved initiation rates, but can this impact be strengthened? Why aren't PCMHs associated with decreased discontinuation? If discontinuation of Warfarin is so high, will novel anticoagulants that require less ongoing contact with providers be wise? A greater attention to duration of pharmacotherapy is needed to manage chronic conditions, particularly when

long-term or life-long indications for pharmacotherapy exist. To facilitate increased awareness of risks and benefits associated with ongoing pharmacotherapy we encourage the development of decision support tools for clinical decision making for continuing or discontinuing current management.

Table 6. Factors Influencing OAT Initiation and Time to OAT Discontinuation

	OAT Initiation	OAT Discontinuation
Patient-Level	Age<50 or Age>85 (-)[23, 39, 63,67,68,69,70, 72, 80, 84, 85, 90]	Age<50 (+)[91, 94]; Age>65 (-)[85, 91,
	Male (+)[70, 72]	Male (+)[85,69, 94]
	Non-white race (-)[23, 61]	Non-white race (-/?)
	Poverty (-)[71]	Poverty (+)[93, 94]
	Rural Residence (-)[70]	Rural Residence (?)
	Higher educational attainment (-)[94]	Higher educational attainment (+)[92, 94]
	Prior Stroke, Heart Failure, Hypertension (+)[23, 63, 69, 71, 72]	Prior Stroke (-)[91]
	Bleed Risk: Frail, prior ICH, GIB, Falls, Renal or Hepatic Impairment (-)[23, 63, 64, 69, 71, 78, 84]	Bleed Risk (?)
	Compliance Concerns: Dementia, Severe Mental Illness, Alcoholism (-)[23, 71, 78, 84, 85]	Dementia(+)[92, 94]
	$CHADS_2$ (measure of stroke risk) (-)[23, 71, 72, 76]	$CHADS_2$ (measure of stroke risk) (-/+)[76, 85, 91, 94]
Provider-Level	Non-malficience (-)[80]	Non-malficience (?)
	Clinical Uncertainty (-)[23, 39, 80]	Clinical Uncertainty (?)
	Burden of monitoring (-)[23, 39, 80]	Burden of monitoring (?)
	Perceived benefit/risk ratio (-)[23, 39, 80, 90]	Perceived benefti/risk ratio (?)
	Higher % Medicaid (-)[80]	Higher % Medicaid (?)
	Greater level of experience (+)[63, 64, 80]	Greater level of experience (?)
	Number years in practice (+)[64, 80]	Number years in practice (?)
	Primary care vs. Cardiologist (+/-)[39, 61, 72, 88]	Primary care vs. Cardiologist (?)
	PCMH (?)	PCMH (?)
System-Level	Diagnosis Setting (?)	Diagnosis Setting (?)
	Lower Hospital Acuity Level (+)[64]	Hospital Acuity Level (?)
	Community practice vs. Coag clinic (?)	Community Practice vs. Coag clinic (?)
	South, West Regions (?)	South, West Regions (+)[94]
	Cost-sharing (?)[39]	Cost-sharing (+)[94]

Notes: (?) Represents unexplored or unknown. (+) = Positive Association in literature, (-)= Negative Association in literature.

Table 7. Patient Characteristics of OAT Initiators and Non-Initiators

	Overall (N= 7,748)	Non-Initiator (N= 5,602)	OAT Initiator (N= 2,146)	*P* value
	Mean (Standard Deviation) or %			
Mean Age	76.2 (11.3)	77.2 (11.4)	73.7 (10.6)	<0.001
Percent Male	43.3%	41.3%	48.6%	<0.001
Mean Number relative OAT exclusions	0.5 (0.7)	0.6 (0.8)	0.4 (0.7)	<0.001
Mean Charlson Score	2.2 (1.9)	2.3 (1.9)	2.0 (1.7)	<0.001
Mean $CHADS_2$ Score	3.1 (1.2)	3.2 (1.2)	2.9 (1.1)	<0.001
Percent Initial Inpatient Diagnosis	49%	50.1%	46.2%	0.003
Mean outpatient visits during baseline	4.0 (5.4)	4.0 (5.5)	3.9 (5.0)	0.53
Mean distance to outpatient provider (miles)	35.2 (135.9)	40.3 (156.7)	23.7 (68.6)	0.002
Mean County: Median Household Income (thousands)	45.1 (9.9)	45.2 (9.9)	45.1 (9.8)	0.64
Mean County: Unemployment Rate	7.5 (3.1)	7.4 (3.1)	7.8 (3.2)	<0.001
Percent Metropolitan Residence	65.4%	66.1%	63.6%	
Percent Micropolitan Residence	23.2%	23.1%	23.6%	0.03
Percent Rural Residence	11.4%	10.9%	12.8%	
Percent Entire County Health Professional Shortage Area	7.6%	7.8%	7.0%	
Percent Partial County Health Professional Shortage Area	58.5%	58.8%	57.8%	0.24
Percent County Not Health Professional Shortage Area	33.9%	33.4%	35.2%	
Mean County: Office based General Practice Internists	69.0 (76.2)	69.5 (76.3)	67.6 (75.8)	0.32
Mean County: Office based Cardiovascular Specialists	18.3 (23.7)	18.5 (23.7)	17.9 (23.6)	0.28
Mean County: 3 yr average deaths cerebrovascular disease	110.9 (100.6)	112.1 (101.7)	107.8 (97.8)	0.09

P-values by t-test for continuous variables and chi2 test for binary / categorical variables

Table 8. Characteristics of AF Patients by Initial Diagnosis Setting

	Overall (N= 7,748)	Initial Outpatient (N= 3,952)	Initial Inpatient (N= 3,796)	*P* value
	Mean (Standard Deviation) or %			
Mean Age	76.2 (11.3)	75.1 (11.1)	77.3 (11.4)	<0.001
Percent Male	43.3%	46.4%	40.1%	<0.001
Mean Number relative OAT exclusions	0.5 (0.7)	0.5 (0.8)	0.5 (0.7)	0.58
Mean Charlson Score	2.2 (1.9)	2.1 (1.9)	2.3 (1.9)	<0.001
Mean CHADS 2 Score	3.1 (1.2)	3.1 (1.2)	3.1 (1.2)	0.04
Percent Initiated Warfarin	27.7%	29.2%	26.1%	0.003
Mean outpatient visits during baseline	4.0 (5.4)	4.4 (6.1)	3.5 (4.5)	<0.001
Median Index Claim Year	2008	2008	2008	<0.001
Mean County: Median Household Income (thousands)	45.1 (9.9)	45.3 (9.9)	45.0 (9.9)	0.15
Mmbr Cnty unemployment rate	7.5 (3.1)	7.6 (3.1)	7.3 (3.1)	<0.001
Percent Metropolitan Residence(1)	65.1%	66.0%	64.8%	
Percent Micropolitan Residence (2)	23.2%	21.8%	24.7%	0.002
Percent Rural Residence (0)	11.4%	12.3%	10.5%	
Percent Entire County Health Professional Shortage Area	7.6%	7.3%	7.9%	
Percent Partial County Health Professional Shortage Area	58.5%	59.5%	57.5%	0.19
Percent County Not Health Professional Shortage Area	33.9%	33.2%	34.6%	
Mean County: Office based General Practice Internists	69.0 (76.2)	69.8 (76.9)	68.2 (75.4)	0.34
Mean County: Office based Cardiovascular Specialists	18.3 (23.7)	18.6 (23.7)	18.1 (23.7)	0.31
Mean County: 3 yr average deaths cerebrovascular disease	110.9 (100.6)	111.1 (101.7)	110.7 (99.5)	0.86

P-values by t-test for continuous variables and chi2 test for binary / categorical variables

Table 9. Average Marginal Effects for Oral Anticoagulation Therapy Initiation

	Aggregate Model		Initial Inpatients		Initial Outpatients	
Age	-0.0069***	(-0.0079,-0.0060)	-0.0088***	(-0.010,-0.0073)	-0.0050***	(-0.0065,-0.0035)
PCMH	0.071***	(0.045,0.097)	0.078***	(0.033,0.12)	0.065**	(0.020,0.11)
Male	0.031**	(0.0100,0.052)	-0.0052	(-0.039,0.029)	0.064***	(0.029,0.098)
Relative OAT Exclusions	-0.037***	(-0.053,-0.021)	-0.036**	(-0.062,-0.011)	-0.039**	(-0.065,-0.012)
Charlson Score	-0.014***	(-0.021,-0.0069)	-0.017**	(-0.028,-0.0057)	-0.010	(-0.022,0.0015)
$CHADS_2$ Score	-0.012*	(-0.023,-0.0011)	0.0017	(-0.016,0.020)	-0.027**	(-0.047,-0.0065)
Median Household Income	0.0016*	(0.00017,0.0031)	0.00042	(-0.0018,0.0027)	0.0026*	(0.00032,0.0049)
Unemployment Rate	0.0075*	(0.00071,0.014)	0.0068	(-0.0040,0.017)	0.0085	(-0.0023,0.019)
1 Outpatient Baseline Visit	0.00012	(-0.036,0.036)	0.0090	(-0.044,0.062)	-0.0066	(-0.061,0.048)
2^+ Outpatient Baseline Visits	0.032*	(0.0036,0.060)	0.027	(-0.016,0.070)	0.037	(-0.0070,0.081)
Metropolitan	-0.053*	(-0.094,-0.012)	-0.056	(-0.12,0.0092)	-0.053	(-0.12,0.012)
Micropolitan	-0.045*	(-0.089,-0.00087)	-0.049	(-0.12,0.018)	-0.045	(-0.11,0.023)
Whole County HPSA	-0.021	(-0.077,0.036)	-0.030	(-0.094,0.034)	-0.012	(-0.084,0.061)
Partial County HPSA	-0.019	(-0.041,0.0025)	-0.023	(-0.061,0.014)	-0.015	(-0.055,0.024)
Initial Inpatient	-0.0019	(-0.026,0.022)				
Diagnosed 2009-10	0.016	(-0.025,0.057)	-0.0049	(-0.071,0.061)	0.033	(-0.031,0.097)
N	7746		3796		3952	

95% confidence intervals in parentheses. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 10. Patient Characteristics and Hazard of OAT discontinuation		
	Hazard Ratio	95% Confidence Interval
Age 41-60 years	0.669*	(0.45,0.99)
Age 61-70 years	0.598**	(0.41,0.88)
Age 71+ years	0.647*	(0.44,0.95)
PCMH	0.929	(0.81,1.06)
Initial Inpatient	1.071	(0.98,1.17)
Male	1.089	(0.99,1.20)
Charlson Score	1.055**	(1.02,1.09)
Number relative exclusions	1.204***	(1.09,1.33)
CHADS2 Score	1.012	(0.96,1.06)
Median Household Income	1.005	(1.00,1.01)
1 Outpatient Visit Baseline	1.112	(0.95,1.30)
2+ Outpatient Visits Baseline	1.009	(0.90,1.13)
Rural	1.131	(0.97,1.32)
Micropolitan	1.002	(0.89,1.13)
County Not HPSA	0.954	(0.80,1.14)
Partial County HPSA	0.929	(0.78,1.11)
N	3087	

95% confidence intervals in parentheses. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Chapter 4

THE EFFECT OF PATIENT CENTERED MEDICAL HOMES ON INITIATION OF ORAL ANTICOAGULATION THERAPY

Overview

Multiple barriers to oral anticoagulation therapy (OAT) for eligible atrial fibrillation patients exist within the current healthcare system. Patient-centered medical homes (PCMHs) are intended to increase access, quality and value through coordinating more holistic patient-centered care, which may reduce these barriers and increase OAT initiation. Our objective was to estimate the effect of receiving care in an accredited PCMH on OAT initiation for newly diagnosed eligible atrial fibrillation patients compared to conventional care. We utilized a retrospective cohort new user design with two comparison groups (2006-2010). Our population studied was privately insured patients in North Carolina with incident atrial fibrillation, mechanical heart valve, significant venous embolism or paroxysmal atrial fibrillation. OAT initiation and PCMH exposure were our key dependent and independent variables. We developed propensity scores for PCMH exposure followed by inverse probability of treatment weighting and estimated effects with generalized estimating equations. We found a positive association between PCMH exposure and percentage of patients initiating OAT in both unadjusted (Average Marginal Effect 6.78% $p<.001$) and fully adjusted (6.25% $p<.001$) models that was robust to variation in defining both PCMH exposure and OAT initiation. Males (6.7% $p<.001$) and individuals with access to care (4.88% $p<.001$), operationalized as those with greater than 2 outpatient visits 90 days before the index event, were also associated with greater OAT initiation. PCMH exposure is associated with greater OAT initiation for eligible individuals with incident atrial fibrillation.

However, the effect size is modest and the specific mechanism or mechanisms contributing to this effect remain undetermined.

Introduction

Acute stroke is the 4th leading cause of death [106]. Patients with atrial fibrillation (AF) have an average 5-fold increase in ischemic stroke risk [12] that increases with age from 1.5% in individuals ages 50-59 to 23.5% for those ages 80-89 [107,108]. Moreover, severity, disability, mortality and frequency of stroke recurrence are greater with AF associated stroke [5,4,6]. Since the first randomized clinical trial found that Warfarin reduced stroke risk for patients with AF [109], guidelines from major organizations and professional societies have recommended oral anticoagulation therapy (OAT) for AF patients at moderate- and high-risk of ischemic stroke [66,110-112]. Yet studies repeatedly report OAT underutilization in eligible AF patients [63,67,25,27,28,68,69,29,70,71,21-23,72,73,61,74-76]. Physician and healthcare system factors contribute to OAT underutilization [71,72,77-79,39,80]. Physician-level barriers to OAT initiation include: (1) perceiving that the risks exceed benefits to patients [63,113-117] (despite physicians frequently underestimating the relative stroke risk reduction of OAT and overestimating the risk of adverse events such as major gastrointestinal bleeding or intracranial hemorrhage [114]); (2) being unfamiliar with guidelines recommending OAT for AF patients with moderate or high risk of ischemic stroke [114,115]; and (3) believing that patients will not adhere to OAT [63,114,115]. Healthcare system barriers to OAT initiation include poor access to appropriate laboratory facilities for necessary blood work, difficulty with provider schedule availability, and difficulty with follow-up on out of range laboratory values for OAT monitoring and dosage titration [115-117].

Physician and healthcare system barriers may be mitigated by patient centered medical homes (PCMH). The PCMH is intended to increase access, quality and value by

coordinating, patient-centered care to enhance population health [53]. Despite the potential of the PCMH, many decision makers and policy makers are awaiting empirical evidence supporting its effectiveness. Although there is empirical support for individual components of PCMH [52], there is little evidence concerning the ability of PCMH to improve quality and health outcomes while reducing costs [53,55-57]. Two recent large PCMH systematic reviews found some favorable effects on quality, patient experience, and caregiver experience; a few unfavorable effects on costs; and mostly inconclusive results [53,54].

PCMHs have the potential to address many barriers to OAT initiation including: strengthening the therapeutic relationship with a personal physician; enhancing access to care; increasing follow-up and monitoring; coordinating care with specialists; and emphasizing a commitment to improving quality and patient safety. The National Committee on Quality Assurance (NCQA) accredits practices that meet PCMH criteria. We examined whether exposure to an NCQA accredited PCMH is associated with increased OAT initiation compared to no PCMH exposure.

Methods

Data Source

We used data from January 1, 2006-December 31, 2010 from the North Carolina State Health Plan (NCSHP), a large self-funded insurance plan administered by Blue Cross and Blue Shield of North Carolina. NCSHP includes almost 1 million state employees, teachers, retirees and their dependents. Retired non-Medicare participants and retired Medicare beneficiaries compose 10% and 15% of the plan, respectively. This claims-structured database contains inpatient, outpatient and pharmacy records. Fields include unique encrypted member identification numbers, basic demographic information including age, gender, county, and zip code of primary residence. Records include diagnoses,

procedures, providers, charges and payments. The database also contains provider-level characteristics including zip code, type of provider and specialty. We also linked individual and facility counties with additional variables from the Area Resource File [82], which allowed us to consider patient, provider, and county characteristics concurrently.

Study Design

We created three cohorts of patients: (1) new onset AF patients; (2) guideline positive controls, i.e., patients at very high risk of thromboembolism (mechanical heart valve and pulmonary embolism); and (3) guideline negative controls, i.e., patients at very low risk of thromboembolism (paroxysmal AF). For all three cohorts, patients needed to be continuously enrolled in the NCSHP a minimum of 6 months prior to and a minimum of 6 months following the qualifying index claim. Individuals with a prescription claim for Warfarin more than 30 days prior to an index claim for any of the three cohorts were excluded due to a high probability of representing prevalent rather than incident conditions. Specific eligibility criteria for each cohort are described below.

New onset AF patients: We used either one inpatient diagnosis or two outpatient diagnoses within 12 months (International Classification of Disease- 9-Clinical Modification (ICD-9-CM) code 427.31) to identify individuals with AF. Cohort entry date was defined as either the first outpatient AF claim or the date of admission for an inpatient claim. $CHADS_2$ is a commonly-used risk-based score [81] that can identify individuals who are most likely to benefit from OAT that can be readily generated using claims data (See Appendix Table A3.2 for ICD-9-CM codes). We included all individuals meeting criteria for incident AF with a $CHADS_2$ score $\geq$ 2. To increase the appropriateness of this cohort, we excluded individuals with one or more relative contraindications to receiving OAT (identified using ICD-9-CM

codes) from the incident AF or intervention cohort (See Appendix Table A3.3 for contraindications and ICD-9-CM codes). Finally, to reduce the probability of including individuals with prevalent AF rather than incident AF we excluded individuals with any AF related claim in the six months preceding the index claim.

Guideline positive controls: We identified individuals with either one inpatient diagnosis or two outpatient diagnoses within 12 months indicating a mechanical heart valve or significant thromboembolism. Those with at least six months of continuous eligibility prior to and six months continuous eligibility following the index claim were included in the guideline positive cohort (See Appendix Table A3.4 for diagnoses and ICD-9-CM codes). The $CHADS_2$ score was not applied to this cohort, as it is only validated in patients with AF; however, individuals with one or more relative contraindications to receiving OAT were excluded to increase comparability between cohorts. Finally, to reduce the probability of including individuals with prevalent conditions rather than incident mechanical heart valves or significant thromboembolism, we excluded individuals with any condition-related claim in the six months preceding the index claim.

Guideline negative controls: We identified individuals with either one inpatient diagnosis or two outpatient diagnoses within 12 months for paroxysmal AF (ICD-9-CM code 427.21). Those with at least six months of continuous eligibility prior to and six months continuous eligibility following the index claim were included in the guideline negative cohort. Again we excluded individuals with one or more relative contraindications to receiving OAT to create cohorts similar in bleeding risk that differed only in their risk of acute ischemic stroke.

Measures

The dependent variable was OAT initiation, defined by a prescription claim for Warfarin within 30 days from AF date of onset. The exposure of interest was receipt of care

in an NCQA-accredited PCMH during the 30 days prior to the index event. We created control variables at the patient and provider level. To mitigate potential confounding, all control variables were measured in the baseline period or immediately prior to the index AF claim. Patient level control variables include age, gender, Charlson comorbidity Index (categorized as 0, 1-2, and ≥3), $CHADS_2$ score (categorized as 2, 3-4, and ≥ 5), rural/urban residence (metropolitan, micropolitan or rural [82]), and number of outpatient visits to a primary care provider in the 30 days prior to the index claim. Provider level control variables included Rural/Urban location and a binary variable indicating participation with the North Carolina Medicaid's medical home program [118].

Propensity Score Implementation

To reduce possible confounding with PCMH exposure, we used propensity scores to balance the two groups on pre-treatment covariates. We estimated, conditional on baseline covariates, an individual's probability of receiving care in a PCMH during the 30 days prior to the index event. In our propensity score models, we included variables that, based on prior theory or evidence, were associated with OAT initiation or OAT initiation and PCMH status [99]. To estimate the propensity score, we employed generalized boosted regression using the "twang" package in R (Version 2.15.1). This package uses an iterative algorithm to construct multiple classification and regression trees, leading to selection of a model that optimizes covariate balance based on the average standardized absolute mean difference across covariates [100]. We then used stabilized inverse-probability-of-treatment weights (IPTW) to estimate the average treatment effect [101].

Statistical Analysis

To estimate the association between PCMH exposure and OAT initiation within each cohort, we utilized a generalized estimating equation model with a Poisson distribution, log link, and exchangeable within-group correlation structure. We grouped at the practice level using practice identification fields in the database. This model accounted for within-practice correlation of outcomes among the accredited PCMH and non-PCMH practices across separate individuals. We estimated average marginal effects (absolute risk differences) for ease of interpretation. All models were estimated in Stata 11. (StataCorp, College Station, TX)

Sensitivity Analysis

We first examined variations in the definition of OAT initiation. To test and compare with our OAT initiation definition based on pharmacy claims, we created a second non-pharmacy claims definition of OAT initiation. The second definition used ICD-9 CM codes for anticoagulation management and procedures codes for corresponding blood tests within 30 days of index event (See Appendix Table A3.5). A third definition of OAT initiation was a combination of the first two; positive if either of the first two definitions were positive. Next, we examined variations in the definition of PCMH exposure based upon the percentage of all primary care visits in the 30 days prior to index event that were to a PCMH. We used 30% and 50% thresholds for these two additional definitions of PCMH exposure.

Results

Descriptive

Baseline characteristics of the AF (n=4,424), guideline positive (n=6,530) and guideline negative cohorts (n=618) following IPTW are presented in Table 11. Standardized differences between PCMH users and non-PCMH users for each cohort are also shown. Standardized difference was below the suggested threshold of 10% for all variables in both the AF and the guideline positive cohorts, indicating sufficient baseline covariate balance by PCMH status. However, the guideline negative cohort contained multiple baseline covariates that remained above the 10% threshold in absolute standardized mean difference following optimized generation of propensity scores and IPTW [119]. This cohort was also quite small in comparison to the other cohorts. Thus, although we report data for this cohort, we are cautious in interpreting the results. The AF cohort had a greater mean age and Charlson comorbidity index score than the guideline positive cohort. The proportion of males in the guideline negative cohort was greater than the AF and guideline positive cohorts. The number of pre-index outpatient visits was highest in the guideline positive cohort. The distribution of individuals by geographic residence, health professional shortage areas, generalist and specialist availability, and year of entry into the cohort was comparable among the three cohorts.

Multivariable Results

Multivariable adjusted results are consistent with unadjusted bivariate results (top of Table 12) for exposure to an NCQA PCMH. Model 1 for each cohort adjusts for patient characteristics, location of residence, use of health care in the baseline period, and year of cohort entry. Model 2 adjusts for the aforementioned characteristics and additional practice characteristics. Unadjusted and adjusted estimates for Model 1 and Model 2 of the effect of

PCMH use on OAT initiation are comparable for both the AF (6-7%) and guideline positive (14%) cohorts. In other words, patients exposed to an NCQA accredited PCMH were 6-7 percentage points more likely to initiate OAT than patients not exposed to an NCQA accredited PCMH.

Examining the adjusted results in more detail, men were more likely to initiate OAT in the AF cohort, but equally as likely to initiate OAT in the guideline positive cohort. Charlson comorbidity scores decreased the likelihood of initiating therapy only in the highest comorbidity category for the AF cohort, while the guideline positive cohort exhibited decreasing initiation in a stepwise fashion. Increasing $CHADS_2$ scores were unexpectedly associated with a lower likelihood of initiating OAT for the AF cohort, while increasing $CHADS_2$ scores had no effect on OAT initiation for the guideline positive cohort. Rural residence appeared to be associated with a slight increase in the likelihood of initiating OAT but this effect was mitigated when we controlled for practice location (rural, micropolitan, metropolitan). We also discovered a higher than anticipated positive association between rural practice location and OAT initiation in both the AF and guideline positive cohorts. More than two outpatient visits in the 90 days preceding the index event was also associated with an increased likelihood of OAT initiation. We found a strong positive time association with initiating OAT in the AF cohort that was not observed (as expected) in the guideline positive cohort. Finally practice participation in the North Carolina Medicaid medical home program was weakly suggestive of a positive association with OAT initiation in both AF and guideline positive cohorts.

Sensitivity Analysis

Results of sensitivity analyses are presented in Table 13. We implemented the fully adjusted models (Model 2) in these analyses, but report only the average marginal effect of

PCMH use on OAT initiation here. Generally, the average marginal effect of PCMH on OAT initiation was robust to alternative definitions of OAT initiation and PCMH status. Model 1 in each cohort reflects the first alternative definition of OAT initiation as defined by ICD-9-CM anticoagulation management codes and blood lab tests. The second model in each cohort reflects the second alternative definition of OAT initiation, either a positive original definition or a positive first alternative definition. Finally, after returning to the original OAT initiation definition the third and forth models represent the previously described 30 percent and 50 percent thresholds respectively. The magnitude of the association decreases with increasing sensitivity and decreasing specificity of the OAT initiation measure, but in all cases remains positive. Similarly varying the definition of PCMH user resulted in a smaller magnitude positive association of PCMH with OAT initiation.

Discussion

Despite evidence-based guidelines, OAT initiation rates are low for patients with AF. Along with the rise of Accountable Care Organizations, PCMHs hold potential for improving OAT initiation for AF patients. We examined the effect of receiving care in an NCQA accredited PCMH on OAT initiation among incident AF patients. The study and analysis have several notable strengths. The data represent a large, stable, insured population across the entire state of North Carolina during 5 years of observation, allowing us to implement a new user type study design with comparison groups. The merged aspect of the data including provider, practice, and county level variables also strengthens the analysis. Second, we perform this analysis in a state that has a well-documented and robust PCMH movement. During the observation period, North Carolina had more accredited PCMHs than any other state except New York. This critical mass of PCMHs resulted in an analysis that included more than 100 independent PCMHs, far more than any other analysis known to us.

This heterogeneity allows a greater generalizability to the PCMH experience as a whole rather than the selected experience of a few PCMHs.

We found a modest increase in OAT initiation associated with PCMH exposure for patients with incident AF as well as the guideline positive comparison cohort. The effect sizes are within plausible ranges for both cohorts, but are somewhat larger for the guideline positive comparison group. We hypothesize several possible explanations for these findings. First, as noted above, there are numerous provider and healthcare system barriers to OAT initiation. It may be that the PCMH only partially mitigated these barriers, and the effect of some barriers may have been less substantial for the younger guideline positive cohort. Second, our results may reflect greater use of OAT in PCMHs regardless of the indication. The practices that become accredited PCMHs may be more likely to prescribe OAT either because of geographic location, previous practice patterns or patient preference. In this case, PCMH accreditation status may serve as a proxy for practices inclined towards OAT use. Given the breadth of scope and principles of the PCMH model, we believe this explanation unlikely. Finally, practices with PCMH accreditation may reflect higher quality practices or practices that are more predisposed to practice pattern change at baseline. Ultimately we believe our findings represent a mixture of the first and third explanations. PCMH status does appear associated with modest increasing OAT initiation in eligible AF patients and the guideline positive comparison group that may result from PCMH status reflecting higher baseline quality or partial implementation of all components in the PCMH model.

The positive time trend associated with OAT initiation in only the AF cohort also merits discussion. We believe this finding represents, in part, an external trend towards increasing OAT initiation in eligible AF patients, which may reflect response to The Joint Commission's revised National Patient Safety Goals for anticoagulants [38]. However, the

trend begins before these revisions were publicly announced in 2008. A second reason for the observed positive time trend of OAT initiation in the AF cohort could relate to anticipated availability of novel anticoagulants that were not yet approved for use in AF. Knowledge of these novel oral anticoagulants poised to enter the market circulated among clinicians as early as 2006. The first of these agents did not ultimately reach the market for use in AF until late 2010, but this interest may have resulted in greater awareness and willingness to prescribe OAT for eligible AF patients. How the availability of these novel oral anticoagulants will influence OAT initiation in these patients and by PCMH practice status is an area of great interest to us.

There are several limitations of our study. First, because we used insurance claims data, we may have misclassified OAT initiation. This is especially true because the popularity of low-cost generic prescription drug programs may lead to patients filling prescriptions for OAT without billing the insurer [83]. If this were to occur, we would have underestimated the rate of OAT initiation in both cohorts regardless of PCMH status. However, we have no reason to suspect a differential error in pharmacy claims for Warfarin with respect to the cohorts or PCMH status regarding OAT initiation. Moreover, because we control for time in our models, we would have expected this trend, decreasing OAT initiation in later years, to appear in the year indicators. However, we find the opposite trend in our year indicators, suggesting this effect is small or non-existent. Importantly, our sensitivity analyses suggested that findings were robust to alternative definitions of OAT initiation. Second, we could not directly control for patient's race, ethnicity or socioeconomic status, though we did control for county level indicators of race and socioeconomic status. Finally, our cohorts were predominantly individuals with employee sponsored group health insurance and the results may not generalize to publicly insured populations. Notably, our

cohorts included a large proportion of retired Medicare enrollees utilizing both their Medicare and NCSHP benefits, which serves to enhance generalizability to Medicare beneficiaries.

Despite the noted limitations, our findings suggest that PCMH status is associated with greater OAT initiation among eligible AF patients. However, this effect may increase or decrease in time secondary to continued refinement of the PCMH model and the availability of novel oral anticoagulants. Future investigations of PCMHs and OAT initiation will be of great interest with respect to the changes in delivery of care and the real-world effectiveness of these agents.

Table 11. Baseline Characteristics Following Inverse Probability of Treatment Weighting For Each Cohort

Covariate	Atrial Fibrillation Cohort			Positive Comparison Group			Negative Comparison Group		
	Medical Home	Non-Medical Home	Std Difference	Medical Home	Non-Medical Home	Std Difference	Medical Home	Non-Medical Home	Std Difference
	(N=466)	(N=3,957)	%	(N=863)	(N=5,667)	%	(N=69)	(n=549)	%
Age	76.3	76.2	0.70%	63.2	64.4	7.10%	68.3	67.8	3.60%
Charlson	1.85	1.87	1.20%	1.47	1.61	7.80%	1.71	1.72	0.50%
$CHADS_2$ Score	2.83	2.87	3.30%	1.91	2.02	6.80%	2.06	1.96	7.50%
Male	0.42	0.45	4.80%	0.39	0.41	4.40%	0.59	0.63	7.10%
Pre Index Visits	3.52	3.45	1.40%	4.58	4.97	5.30%	3.6	3.59	0.10%
Metropolitan	66.90%	64.90%	6.70%	70.80%	66.30%	3.10%	63.77%	67.05%	13.20%
Micropoltan	24.10%	23.06%		22.50%	23.80%		27.39%	21.71%	
HPSA –No	32.60%	35.30%	6.40%	31.40%	33.90%	6.40%	30.14%	35.17%	10.70%
HPSA – Yes	6.90%	8.00%		6.40%	7.50%		7.67%	7.65%	
HPSA - Partial	60.39%	56.70%		62.20%	58.50%		62.75%	57.21%	
#GPs	70.3	65.5	6.20%	77.7	71.6	7%	79.74	71.2	10.70%
#CV Specialist	19	17.5	6.50%	21	19.1	7%	22.4	19.2	12.70%
Dth_CV_DZ	111.12	107.71	3.40%	118.9	114.4	3.90%	123.98	113.28	10.50%
2006	15.00%	18.40%	6.30%	12.60%	15.80%	8%	9.42%	13.33%	7.70%
2007	26.90%	25.40%		20.70%	21.00%		19.93%	25.66%	
2008	20.90%	21.10%		20.60%	20.90%		32.17%	20.46%	
2009	19.90%	19.10%		24.30%	21.50%		23.91%	23.59%	
2010	17.30%	16.00%		21.90%	20.80%		15.07%	16.99%	

Notes: Std=Standardized, HPSA = Health Professional Shortage Area, GPs = Number of office based general practitioners in county. CV Specialist = Number of office based cardiovascular specialists in county, Dth_CV_DZ = 3 year average number of cerebrovascular (stroke) deaths in county.

Table 12. Unadjusted Difference in Percent OAT Initiation & Average Marginal Effect of Explanatory Variables in Three Cohorts

Covariate	Atrial Fibrillation Cohort		Positive Comparison Group		Negative Comparison Group	
	Unadjusted Estimate	6.78%***	Unadjusted Estimate	14.4%***	Unadjusted Estimate	6.53%
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Medical Home User	7.04%***	6.25%***	14.71%***	13.95%***	11.67%**	9.98%**
Age 18-40 (referent group 41-60)	-3.89%	-1.75%	-1.67%	-2.21%	-14.51%*	-14.7%**
Age 61-70	3.15%	4.29%*	-2.04%	-2.01%	12.91%***	15.1%***
Age 71+	-1.68%	-1.41%	-7.69%***	-8.19%***	5.17%	5.53%
Male	6.67%***	6.70%***	1.63%	1.80%	15.48%***	15.33%**
Charlson 0 (referent group Charlson 1)	-0.55%	-0.02%	4.97%**	5.03%**	0.13%	-0.9%
Charlson 2	-1.05%	-0.82%	-6.07%***	-5.79%**	-4.84%	-4.5%
Charlson 3-4	-2.02%	-1.43%	-6.09%***	-5.87%**	-5.85%	-5.71%
Charlson 5-12	-8.63%***	-8.54%***	-14.59%***	-14.07%***	-11.04%**	-12.86%**
$CHADS_2$ 3-4 (referent group $CHADS_2$ 2)	-4.14%**	-4.26%**	0.74%	1.36%	-5.06%	-7.13%
$CHADS_2$ 5-6	-5.44%*	-5.31%*	-1.05%	-0.96%	4.73%	-7.49%
Rural (referent group Metropolitan)	4.17%*	-1.59%	4.23%**	-1.52%	-4.36%	-3.43%
Micropolitan	2.6%	-0.22%	2.05%	-3.73%**	4.83%	4.64%
Zero prior visits (referent group 1 prior visit)	1.53%	1.92%	-6.0%***	-5.15%**	7.28%	7.84%
2+ prior visits	5.19%***	4.88%***	6.73%***	7.17%***	12.36%**	12.14%**
Year=2007 (referent group 2006)	10.82%***	11.04%***	0.66%	1.21%	18.04%***	18.12%***
Year=2008	13.35%***	13.43%***	0.66%	0.52%	-1.4%	-1.81%
Year=2009	15.77%***	16.94%***	-2.42%	-2.25%	6.45%	7.18%
Year=2010	12.86%***	13.10%***	-0.91%	-0.84%	10.05%*	9.22%
Rural Practice (referent group Metropolitan)		10.98%***		12.4%***		-8.18%
Micropolitan Practice		4.3%		9.93%***		-0.87%
CCNC Practice		3.96%*		3.12%		5.78%
N	4,423	4,423	6,530	6,530	610	610

CCNC = Community Care North Carolina (Medicaid Medical Home member) * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 13. Sensitivity Analysis

	Atrial Fibrillation Cohort			Positive Comparison Group			Negative Comparison Group		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
MH30D	7.07%***	3.08%**		13.90%***	8.76%***		8.17%	10.87%***	
MH30P			4.05%**			4.55%**			11.51%***
MH50P			3.96%*			4.99%**			13.39%***

Notes: MH30D = PCMH visit within 30 days of index event; MH30P = 30% of primary care visits to PCMH in initial 90 days following index event; MH50P = 50% of primary care visits to PCMH in initial 90 days following index event. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Chapter 5

CONCLUSIONS

Summary of Findings

Each of these three studies provides unique opportunities for synthesis of new information, practice implications, policy implications and suggest additional research questions to be answered. The studies as a whole, however, provide a larger narrative than the sum of their individual parts. In general, we sought to: develop a greater understanding of barriers to OAT initiation, determinants of OAT discontinuation and areas of overlap between these two events; and to what extent observed policy and practice changes may have influenced the use of OAT via their influence on these two events. Here, I will discuss five over-arching strategic concepts that frame the broader meta-narrative of this research effort.

First, I found that policy and practice change levers do appear to create sufficient alterations in the external healthcare system that foster modest changes in the receipt and provision of care. These changes may be in the provision of guideline concordant care such as an increasing rate of OAT initiation among incident AF patients appearing eligible for OAT as indicated by claims data. The changes may also be a reduction in inappropriate care such as the reduction in the rate of OAT initiation among incident paroxysmal atrial fibrillation patients appearing ineligible for OAT as indicated by claims data. I saw these changes specifically in the revision of the NPSG by The Joint Commission in 2008 to include

standard safety practices and guidelines concerning the use of OAT as an example of a policy lever. This policy lever provided incentives for change in hospitals and other healthcare organizations via a potential loss of Medicare reimbursement in the event of non-compliance or failure to achieve Joint Commission accreditation. I presented the PCMH as an example of a practice change lever. Patients with incident AF who appeared eligible for OAT as indicated by claims and who received care in a PCMH accredited by the National Committee on Quality Assurance (NCQA) had a higher rate of OAT initiation than patients not receiving care in an accredited PCMH. I posit that the incentives to undergo the necessary accreditation by NCQA and the process changes required to become a PCMH are currently generally positive incentives (i.e. greater market share, greater reimbursement, etc). Thus it would appear that irrespective of the positive or negative incentives for modification, both polarities of incentives can provide sufficient motivation by participants to do so. Because the policy and practice levers are not directly comparable, I cannot speak to the relative magnitude of effect between policy and practice levers and the changes in provision of care. I do want to note that these observed changes were for relatively short-term measures usually requiring a point-in-time decision such as OAT initiation. However, I did not find strong evidence to support policy and practice levers' ability to generate changes in longer term measures typically requiring more sustained effort such as time to OAT discontinuation.

Second, I learned that the inclusion of positive and negative control groups or nonequivalent dependent variables is imperative in observational research using claims data. For example, I expected a 95% OAT initiation rate for individuals with newly implanted mechanical heart valves and serious systemic thromboembolism such as a pulmonary embolism. However I found a substantially lower "observed" rate of OAT initiation in this population. I believe this reflects a limitation in using claims data rather than the failure to

provide appropriate care. In other words, this observed level of OAT initiation for the strongest known indication for OAT was only 65%. I would not expect to find a greater rate of OAT initiation for a population with a "relatively weaker" indication for OAT, such as AF. This finding alone provides much needed context for many prior observational studies using claims involving OAT use among individuals with AF. More study is needed to validate an "appropriate" rate of observed OAT initiation among eligible incident AF individuals in claims data.

The third strategic concept that emerged as a result of this interrelated body of work reflects the measurement of provision and receipt of care for long-term or life-long indicated therapies. I gained a greater understanding of the complexity involved in measuring receipt of care for therapies that have long-term or life-long indications. Population health concerning chronic conditions requires more than an emphasis on initiation of appropriate therapy alone. It also includes a focus on the maintenance of that therapy for an extended period of time. This duration of therapy might be termed persistence, or as I refer to it in this work, time to discontinuation. In fact these concepts of initiation and duration of therapy (e.g. maintenance, persistence, time to discontinuation) appear to be two unique concepts. These concepts share some overlapping predictors or determinants that at times work in the same direction and at times in opposing directions (See Table 14 below). For example, a greater number of comorbidities at time of diagnosis and a greater number of relative OAT exclusions were associated with both a lower rate of OAT initiation and a greater hazard of OAT discontinuation. Initiation and duration of therapy may also have non-overlapping factors which we need to identify as well. Receipt of care in a PCMH and $CHADS_2$ score were both correlated with OAT initiation but not associated with time to OAT discontinuation. There is a need to sharpen the way we think about these concepts when we as health services researchers study these interventions and their outcomes.

Fourth, I was initially surprised by my findings that increased stroke risk, as indicated by a claims implemented $CHADS_2$ score at the time of AF diagnosis was paradoxically associated with a lower OAT initiation rate and a greater hazard of discontinuation. I can identify several distinct possible explanations for these findings. Despite a rigorous review of prior literature validating the $CHADS_2$ score as a measure of stroke risk among patients with AF, there may be problems with the implementation of this score using claims data [81,120]. Others have utilized the $CHADS_2$ score with claims data and have reported findings consistent with these findings [121,37]. Or perhaps the $CHADS_2$ score functions as a low hurdle to overcome for OAT initiation but at higher $CHADS_2$ scores, other comorbidities present serve to outweigh potential benefits of therapy. Despite sufficient risk of stroke secondary to AF, other concurrent disease processes with a high probability of death mitigate the potential benefits of receiving OAT. Finally, these findings do not account for patient preference or knowledge which is integral to studying both therapy initiation and time to therapy discontinuation [122].

The fifth and final strategic concept I wish to convey relates to study design. To be consistent with a new user study design, I constructed the PCMH engagement variable as a baseline measurement that occurred in a 30 day window immediately prior to the index event. This operationalization of PCMH engagement is equivalent to an intent-to-treat analysis in a randomized controlled trial. However, the real world is not a randomized controlled trial. People change treatment arms, or do not accept the treatment they are randomized to receive. Crossover in treatment arms within a randomized controlled trial can lead to an averaging of effects, which may also be considered a bias towards a null effect. It is possible that this occurred in this study as well. While the results are encouraging with respect to OAT initiation and PCMH engagement, I realize that in some aspects, an “as treated analysis” may give us more real world information. I was reminded that researchers

should always be mindful of the type of treatment effect they want to measure and to ask if it is appropriate for the research question they are trying to answer.

Limitations

As with any study or body of work, there are limitations, and this work is not an exception to that rule. I want to acknowledge and discuss the implications of these limitations. First I will review several general limitations that are common to all three aims. Then I will discuss and review several limitations specific to individual studies.

This study utilizes claims level data. While robust in nature, it does not perfectly convey the truth of what actually happened in any particular situation. Identification of AF, concurrent comorbid conditions, OAT initiation, and subsequent time to OAT discontinuation are subject to misclassification. I acknowledge that claims data does not reflect in all cases complete fidelity to the gold standard of a patient's medical record. However, I believe on the whole, it is a reasonable proxy for studying relative differences in OAT initiation over time.

Second, I did not have access to individual level race, ethnicity, income or, education data in this work. Prior literature has demonstrated that these are important factors in OAT initiation [23,61,29,78,89,39,72,123]. Similarly, poverty and educational attainment have been associated with OAT discontinuation [92,93]. I did however attempt to control for these factors to some degree with county level measures of race, ethnicity, and income. The inability to completely control for these factors at the individual level has several potential implications. While I do not believe the aggregate results are substantially influenced, I may overlook possible heterogeneity of treatment effect with respect to the key independent variables and specific subpopulations defined by race, ethnicity, income and, education

level. I was also unable to identify potential intervention targets with respect to these subpopulations.

The third broad limitation refers to the study sample. These studies examined a privately insured population in NC from 2006-2010. I acknowledge the regional variation inherently present in clinical practice and cannot claim that clinical practice by providers in North Carolina reflects the spectrum of clinical practice within the United States as a whole. I believe the study sample does generalize well to the population of North Carolina. However, attempts to generalize it to publicly insured populations such as Medicaid or Medicare or outside this state should be approached with caution. With this in mind, I observed a large number of Medicare eligible and Medicare receiving individuals in this study, and I don't have prima fascia reasons to believe this population would not generalize to other states.

There are several study specific limitations to mention as well.

Study 1

I know aggregate OAT initiation rate for the population of individuals diagnosed with incident AF both before and after a policy level was introduced. However, I do not know which hospitals had well developed OAT policies in place before the guidelines, or if (and when) they subsequently modified their policies to achieve compliance with the revised 2008 NPSG. Moreover, I do not know which hospitals created policies where none previously existed, and when they did so. This does not affect the overall estimates of effect of the policy, but does limit the ability to examine specific hospitals and the exact mechanism of change.

Study 2

I did not attempt to examine or adjust for clinical reasons to discontinue OAT. Because both risks and benefits exist with this therapy, from a clinical perspective there are several valid reasons for discontinuation. If a known adverse event of therapy such as severe bleeding (i.e. intracranial hemorrhage or gastrointestinal bleed) occurs with a patient, it may be appropriate to discontinue OAT either temporarily or permanently. Similarly, I did not adjust for the percentage of time a patient was within an optimal therapeutic level (e.g. INR=2-3) of anticoagulation while receiving OAT. Therefore, in the instance of an extremely small percent of time spent within optimal therapeutic level of anticoagulation, a provider may appropriately opt to discontinue OAT and switch to another less effective but also potentially less harmful therapy. I was not able to identify these individuals in our data. Thus the results may overestimate the percentage of people with AF who discontinue OAT and receive no stroke risk reduction therapy.

Study 3

As was briefly mentioned in the synthesis of findings, this study was an intent-to-treat analysis based upon PCMH exposure during the baseline period. I did not examine the amount of crossover between treatment assignment arms. It is possible that crossover between treatment arms is approximately equal in which crossover at worst biases results towards a null effect. However when unequal crossover between treatment groups occurs, it is more difficult to anticipate the expected direction and magnitude of the biases introduced. While I believe the results are robust in small to moderate amounts of crossover, I recognize the possibility that large degrees of unobserved treatment crossover may alter the findings. In the future I will repeat this study, quantify the magnitude of crossover and implement an as treated analysis to establish greater real world practice relevance.

Practice Implications, Policy Implications and Future Directions

The one year rate of OAT discontinuation was substantially higher in this study than has previously been reported both in trials and other observational studies. While I acknowledge that OAT discontinuation is somewhat sensitive to the definition of discontinuation, the underlying observation is substantial regardless. Because I utilize claims data rather than patient medical records, it is unclear if this high discontinuation rate reflects: a rational clinical evaluation of ongoing risks and benefits associated with continuing OAT; a change patient preference with respect to continuing OAT; unobserved barriers in receipt of medical care; or clinical practice oversight. Undeniably, the unobserved factors associated with OAT discontinuation require further elucidation. However, I believe at minimum the findings reflect the need for development of clinical decision support tools (similar to existing initiation clinical decision support tools) to facilitate a systematic clinical decision making process in the persistence or discontinuation of OAT. These tools should incorporate new knowledge regarding severity of risks and benefits of OAT [105] as wells as cumulative patient experience with OAT. To maximize clinical practice value, the tools should also incorporate additional concurrent but unrelated potential for morbidity and mortality secondary to the presence of multiple co-occurring chronic conditions.

In the post health care reform era, much of health care policy is centered upon quantifying, measuring and delivering high quality care. A current metric frequently utilized is the receipt of guideline concordant care. As health policy analysts and researchers attempt to define receipt of guideline concordant care across a multitude of conditions to measure care quality, we encourage consideration of duration of appropriate therapy in addition to initiation of appropriate therapy. This consideration is particularly germane when considering non-acute chronic conditions with long-term or life-long indications for treatment.

Summary

Policy and practice change in health care can improve the delivery of health care and subsequently the quality and length of human life. In this body of work, I utilized observational methods to gain a greater understanding of barriers to OAT initiation, determinants of OAT discontinuation, areas of overlap between them and to what extent observed policy and practice changes influenced the use of OAT via their influence on initiation and discontinuation. I then reviewed several strategic concepts that emerged as a result of the synthesis of three separate but related studies. I also discussed global and specific limitations of these studies and their implications concerning my primary findings. Finally, I briefly identified relevant implications of my findings for practice, policy and avenues of future research.

Table 14. Factors Influencing OAT Initiation and Time to OAT Discontinuation

	OAT Initiation	OAT Discontinuation
Patient-Level	**Increasing Age(-)**	**Age>40 (-)**
	Male (+)	**Male (+)**
	Non-white race (-)	Non-white race (-/?)
	Poverty (-)	Poverty (+)
	Rural Residence (+)	**Rural Residence (0/+)**
	Higher educational attainment (-)	Higher educational attainment (+)
	Prior Stroke, Heart Failure, Hypertension (+)	Prior Stroke (-)
	Bleed Risk: Frail, prior ICH, GIB, Falls, Renal or Hepatic Impairment (-)	**Bleed Risk: Frail, prior ICH, GIB, Falls, Renal or Hepatic Impairment (+)**
	Compliance Concerns: Dementia, Severe Mental Illness, Alcoholism (-)	Dementia(+)
	Increasing Comorbidities (-)	**Increasing Comorbidities (+)**
	$CHADS_2$ (measure of stroke risk) (-)	**$CHADS_2$ (measure of stroke risk) (0/+)**
Provider-Level	Non-malficience (-)	Non-malficience (?)
	Clinical Uncertainty (-)	Clinical Uncertainty (?)
	Burden of monitoring (-)	Burden of monitoring (?)
	Perceived benefit/risk ratio (-)	Perceived benefti/risk ratio (?)
	Higher % Medicaid (-)	Higher % Medicaid (?)
	Greater level of experience (+)	Greater level of experience (?)
	Number years in practice (+)	Number years in practice (?)
	Primary care vs. Cardiologist (?)	Primary care vs. Cardiologist (?)
	PCMH (+)	**PCMH (0/-)**
System-Level	**Inpatient Diagnosis Setting (0)**	**Inpatient Diagnosis Setting (0/+)**
	Rural Hospital (+)	Hospital Acuity Level (?)
	Community practice vs. Coag clinic (?)	Community Practice vs. Coag clinic (?)
	South, West Regions (?)	South, West Regions (+)
	Cost-sharing (?)	Cost-sharing (+)

Notes: Bolded factors represent factors and associated relationships between OAT initiation and discontinuation explored in this work. (?) Represents unexplored or unknown. (+) = Positive Association, (-)= Negative Association, (0)=No association in published literature

Appendix One: CHAPTER 2 SUPPLEMENTAL MATERIAL

Table 15. ICD-9-CM Codes and Drug Class Codes Employed to Assign $CHADS_2$ Stroke Risk Score

Condition	Classification	Codes used to identify condition
Congestive Heart Failure	ICD-9-CM	425.4, 428.x, 429.4
Hypertension	ICD-9-CM	362.11, 401.x-405.xx, 437.2
Diabetes Mellitis	ICD-9-CM	250.xx, 357.2, 362.0x, 366.41
Prior thromboembolism	ICD-9-CM	325, 362.3x, 410.xx, 411.1, 411.81, 415.1x, 433.xx-434.xx, 435.x 436, 437.1, 437.6, 444.xx, 451.xx 452, 453.x

ICD-9-CM = International classification of Diseases, Ninth Revision, Clinical Modification

Table 16. ICD-9CM Codes Utilized to Identify Relative Exclusions to OAT

Heart Valves	394.XX, 395.XX, 396.XX, 397.XX, 398.90 424.XX, 093.2X, V42.2, V43.3
Hemorrhagic Stroke	430.XX, 431.XX, 432.XX, 852.0X, 852.2X, 852.4X, 853.XX
Gastrointestinal or other major bleed	286.0X, 286.1X, 286.2X, 286.3X, 286.4X, 287.1X, 287.8X, 287.9X, 456.0X, 530.21, 530.7X, 530.82, 531.00, 531.01, 531.20, 531.40, 531.41, 531.60, 531.61, 532.00, 532.01, 532.20, 532.21, 532.40, 532.41, 532.60, 532.61, 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60, 533.61, 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 569.85, 569.86, 596.7X, 626.2X
Fall Risk	332.0X, 333.4X, 333.5X, 333.90, 333.99, 334.XX, 335.XX, 340.XX, 345.1X, 345.3X, 345.4X, 345.5X, 345.7X, 345.8X, 345.9X, V15.88 E880-E888
Cirrhosis	570.XX, 571.2X, 571.3X, 571.5X, 571.6X, 571.8X, 571.9X, 572.2X, 572.3X, 572.4X, 572.8X
Compliance	291.XX, 292.1X, 292.8X, 295.03, 295.04, 295.13, 295.14, 295.23, 295.24, 295.33, 295.34, 295.43, 295.44, 295.53, 295.54, 295.63, 295.73, 295.74, 295.83, 295.84, 295.93, 295.94, 297.XX, 298.XX, V15.81, V60.1, V60.2, V60.3, V60.4
Dementia	290.XX
Terminal	150.XX, 151.XX, 155.XX, 156.XX, 157.XX, 162.XX, 172.XX, 183.XX, 191.XX, V66.7

Table 17. ICD-9CM and CPT Codes Utilized to Identify Guideline Positive Cohort

Heart Valve Replacement	33405, 33406, 33407, 33408, 33409, 33410, 33411, 33412, 33413, 33430, 33465, 33475, V42.2, V43.3
Embolism	415.12, 415.13, 415.19, 416.2X, 425.11, 453.2X, 453.3X, 453.4X, 453.5X, 453.72, 453.73, 453.74, 453.75, 453.76, 453.77, 453.79, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87, 453.89, 453.9X

Table 18. ICD-9-CM / CPT codes to identify laboratory blood tests and anticoagulation management

ICD-9-CM Code	V58.61
CPT Code	99363, 99364, 85610, 85730, 85732

Table 19. Model Specification and Average Marginal Effect of Post_TrtGrp

	(1) LN	(2) Cat	(3) AGE	(4) Age_NoBed	(5) CatNoBed
Post* TrtGrp	0.11** [0.04,0.18]	0.11** [0.04,0.18]	0.11** [0.04,0.18]	0.11** [0.04,0.18]	0.11** [0.04,0.18]
N	5235	5235	5235	5235	5235

95% confidence intervals in brackets * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix Two: CHAPTER 3 SUPPLEMENTAL MATERIAL

Table 20. ICD-9-CM Codes and Drug Class Codes Employed to Assign $CHADS_2$ Stroke Risk Score

Condition	Classification	Codes used to identify condition
Congestive Heart Failure	ICD-9-CM	425.4, 428.x, 429.4
Hypertension	ICD-9-CM	362.11, 401.x-405.xx, 437.2
Diabetes Mellitus	ICD-9-CM	250.xx, 357.2, 362.0x, 366.41
Prior thromboembolism	ICD-9-CM	325, 362.3x, 410.xx, 411.1, 411.81, 415.1x, 433.xx-434.xx, 435.x 436, 437.1, 437.6, 444.xx, 451.xx 452, 453.x

ICD-9-CM = International classification of Diseases, Ninth Revision, Clinical Modification

Appendix Three: CHAPTER 4 SUPPLEMENTAL MATERIAL

Table 21. Baseline Characteristics (Unadjusted)

Covariate	Atrial Fibrillation Cohort			Positive Comparison Group			Negative Comparison Group		
	Medical Home	Non-Medical Home	Std Difference	Medical Home	Non-Medical Home	Std Difference	Medical Home	Non-Medical Home	Std Difference
	N=466	N=3,957	%	N=863	N=5,667	%	N=69	n=549	%
Age	75.2	76.3	9.00%	61.0	65.1	26.30%	69.6	67.7	14.40%
Charlson	1.91	1.87	2.70%	1.41	1.66	14.10%	1.75	1.72	2.00%
CHADS2 Score	2.88	2.87	1.20%	1.78	2.08	18.30%	2.16	1.95	15.90%
Male	0.41	0.45	8.30%	0.40	0.41	2.30%	0.55	0.63	16.90%
Pre Index Visits	4.6	3.32	27.00%	5.69	4.92	9.90%	4.37	3.43	18.00%
Metropolitan	75.00%	63.39%	7.40%	79.41%	63.86%	12.90%	75.27%	65.47%	6.70%
Micropolitan	16.35%	24.18%		14.46%	25.58%		19.35%	22.48%	
HPSA –No	26.28%	36.44%		21.65%	36.05%		22.58%	35.97%	
HPSA – Yes	2.72%	8.64%	28.80%	3.10%	8.33%	38.50%	5.38%	8.09%	33.10%
HPSA – Partial	70.99%	54.92%		75.25%	55.62%		72.04%	55.94%	
#GPs	95.9	61.3	45.00%	102.2	66.1	42.70%	96.3	68	36.90%
#CV Specialist	27	16	44.50%	28	17	42.10%	27	18	37.20%
Dth_CV_DZ	141.15	102.91	38.90%	146.32	108.45	32.30%	140.55	109.63	31.60%
2006	8.97%	19.61%		11.68%	16.51%		8.60%	13.85%	
2007	22.44%	25.65%		17.65%	21.52%		16.13%	26.26%	
2008	25.48%	20.73%	30.00%	22.71%	20.50%	15.70%	33.33%	19.78%	18.80%
2009	22.12%	18.63%		26.31%	20.76%		23.66%	23.02%	
2010	20.99%	15.38%		21.65%	20.69%		18.28%	17.09%	

Notes: Std=Standardized, HPSA = Health Professional Shortage Area, GPs = Number of office based general practitioners in county. CV Specialist = Number of office based cardiovascular specialists in county, Dth_CV_DZ = 3 year average number of cerebrovascular (stroke) deaths in county.

Table 22. ICD-9-CM Codes and Drug Class Codes Employed to Assign $CHADS_2$ Stroke Risk Score

Condition	Classification	Codes used to identify condition
Congestive Heart Failure	ICD-9-CM	425.4, 428.x, 429.4
Hypertension	ICD-9-CM	362.11, 401.x-405.xx, 437.2
Diabetes Mellitus	ICD-9-CM	250.xx, 357.2, 362.0x, 366.41
Prior thromboembolism	ICD-9-CM	325, 362.3x, 410.xx, 411.1, 411.81, 415.1x, 433.xx-434.xx, 435.x 436, 437.1, 437.6, 444.xx, 451.xx 452, 453.x

ICD-9-CM = International classification of Diseases, Ninth Revision, Clinical Modification

Table 23. ICD-9CM Codes Utilized to Identify Relative Exclusions to OAT

Heart Valves	394.XX, 395.XX, 396.XX, 397.XX, 398.90 424.XX, 093.2X, V42.2, V43.3
Hemorrhagic Stroke	430.XX, 431.XX, 432.XX, 852.0X, 852.2X, 852.4X, 853.XX
Gastrointestinal or other major bleed	286.0X, 286.1X, 286.2X, 286.3X, 286.4X, 287.1X, 287.8X, 287.9X, 456.0X, 530.21, 530.7X, 530.82, 531.00, 531.01, 531.20, 531.40, 531.41, 531.60, 531.61, 532.00, 532.01, 532.20, 532.21, 532.40, 532.41, 532.60, 532.61, 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60, 533.61, 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 569.85, 569.86, 596.7X, 626.2X
Fall Risk	332.0X, 333.4X, 333.5X, 333.90, 333.99, 334.XX, 335.XX, 340.XX, 345.1X, 345.3X, 345.4X, 345.5X, 345.7X, 345.8X, 345.9X, V15.88 E880-E888
Cirrhosis	570.XX, 571.2X, 571.3X, 571.5X, 571.6X, 571.8X, 571.9X, 572.2X, 572.3X, 572.4X, 572.8X
Compliance	291.XX, 292.1X, 292.8X, 295.03, 295.04, 295.13, 295.14, 295.23, 295.24, 295.33, 295.34, 295.43, 295.44, 295.53, 295.54, 295.63, 295.73, 295.74, 295.83, 295.84, 295.93, 295.94, 297.XX, 298.XX, V15.81, V60.1, V60.2, V60.3, V60.4
Dementia	290.XX
Terminal	150.XX, 151.XX, 155.XX, 156.XX, 157.XX, 162.XX, 172.XX, 183.XX, 191.XX, V66.7

Table 24. ICD-9CM and CPT Codes Utilized to Identify Guideline Positive Cohort

Heart Valve Replacement	33405, 33406, 33407, 33408, 33409, 33410, 33411, 33412, 33413, 33430, 33465, 33475, V42.2, V43.3
Embolism	415.12, 415.13, 415.19, 416.2X, 425.11, 453.2X, 453.3X, 453.4X, 453.5X, 453.72, 453.73, 453.74, 453.75, 453.76, 453.77, 453.79, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87, 453.89, 453.9X

Table 25. ICD-9-CM / CPT codes to identify laboratory blood tests and anticoagulation management

ICD-9-CM Code	V58.61
CPT Code	99363, 99364, 85610, 85730, 85732

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