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Anticoagulant Use, Safety and Effectiveness for Ischemic Stroke Prevention in Nursing Home Residents with Atrial Fibrillation

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ANTICOAGULANT USE, SAFETY AND EFFECTIVENESS FOR ISCHEMIC STROKE PREVENTION IN NURSING HOME RESIDENTS WITH ATRIAL FIBRILLATION

A Dissertation Presented

By

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ABSTRACT

Background

Fewer than one-third of nursing home residents with atrial fibrillation were treated with the only available oral anticoagulant, warfarin, historically. Management of atrial fibrillation has transformed in recent years with the approval of 4 direct-acting oral anticoagulants (DOACs) since 2010.

Methods

Using the national Minimum Data Set 3.0 linked to Medicare Part A and D claims, we first described contemporary (2011-2016) warfarin and DOAC utilization in the nursing home population (Aim 1). In Aim 2, we linked residents to nursing home and county level data to study associations between resident, facility, county, and state characteristics and anticoagulant treatment. Using a new-user active comparator design, we then compared the incidence of safety (i.e., bleeding), effectiveness (i.e., ischemic stroke), and mortality outcomes between residents initiating DOACs versus warfarin (Aim 3).

Results

The proportion of residents with atrial fibrillation receiving treatment increased from 42.3% in 2011 to 47.8% as of December 31, 2016, at which time 48.2% of treated residents received DOACs. Demographic and clinical characteristics of residents using DOACs and warfarin were similar in 2016. Half of the 8,734 DOAC users received standard dosages and most were treated with apixaban (54.4%) or rivaroxaban (35.8%) in 2016.

Compared with warfarin, bleeding rates were lower and ischemic stroke rates were higher for apixaban users. Ischemic stroke and bleeding rates for dabigatran and rivaroxaban were comparable to warfarin. Mortality rates were lower versus warfarin for each DOAC.

Conclusions

In nursing homes, DOACs are being used commonly and with equal or greater benefit than warfarin.

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LIST OF ABBREVIATIONS

Acute myocardial infarction (AMI)

Area Health Resource File (AHRF)

Certification and Survey Provider Enhanced Reporting (CASPER)

Direct acting oral anticoagulant (DOAC)

Food and Drug Administration (FDA)

International Classification of Disease (ICD)

Minimum Data Set (MDS)

Skilled nursing facility (SNF)

Transient ischemic attack (TIA)

Venous thromboembolism (VTE)

PREFACE

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CHAPTER I

INTRODUCTION

Atrial Fibrillation in the United States

The number of people with atrial fibrillation is on the rise, driven by increases in the prevalence of certain atrial fibrillation risk factors (e.g., obesity, diabetes),[1–3] population growth, and the overall aging of the population.[4] For example, in the United States, ~ 6.1 million adults had diagnosed atrial fibrillation in 2010,[4] which is projected to increase to 12.1 million by 2050.[4] The age and sex-adjusted incidence of atrial fibrillation increased 21% from 1980 to 2000.[4] Ischemic stroke risk increases 5-fold in the presence of atrial fibrillation.[5] Ischemic strokes caused by atrial fibrillation are more severe on average than other etiologies.[6–8] In adults aged 80-89 years, atrial fibrillation is responsible for one in four strokes.[4,5] Ischemic stroke has devastating consequences for patients' functional independence, cognitive status, and quality of life,[9–11] effects which are more severe at older ages.[12] After a stroke, patients lose the equivalent of two activities of daily living[11] and quality of life is diminished.[10] Incident stroke is associated with an acute decline in measures of global cognition, new learning, and verbal memory, and a sustained increase in the rate of incident cognitive impairment.[9] Considering five out of six patients with atrial fibrillation are at least 65 years of age,[13] improving atrial fibrillation management among older adults is imperative to reduce the burden of ischemic stroke.

This introduction reviews information regarding the use of anticoagulants in nursing homes. We then review the importance of nursing homes as a segment of the healthcare industry. A summary of the evidence on anticoagulants is also provided. We then provide a review of what is known about anticoagulant use in nursing home settings. The information provided in this introduction highlights the "geriatric pharmacoparadox",

coined because the understudied population of nursing home residents are most likely to be in need of supportive clinical evidence regarding anticoagulation, but least likely to have risk/benefit information from trials. This introduction highlights research gaps regarding the contemporary use of anticoagulants in nursing home residents.

Nursing homes: an important segment in the healthcare industry

The United States, like so many countries, is experiencing a "silver tsunami" owing to the aging of the population. By 2060, it is estimated that almost 1 in 4 Americans will be at least 65 years of age (currently 15%).[14,15] During this time period, the number of Americans over 85 years of age is expected to triple to ~19.7 million, representing 4.7% of the total United States population (2.0% currently).[14] Given these shifts in the age distribution, the need for nursing home care is likely to increase. By 2040 nursing homes are expected to provide care for 7.3 million patients annually.[16]

Currently, in the United States, on any given day ~1.4 million residents live in one of the ~16,000 nursing homes.[17] By 2050, the demand for long-term care services is projected to nearly double. Among people aged at least 85 years, nursing home care accounts for the largest share of healthcare expenditures.[18] This is because people in this age group often have a high disability rate and need help in activities of daily living.[19,20] In the United States, Medicaid[21] bears the brunt of most nursing home costs (e.g., $60 billion in 2016).[22] With a staggering $92,000 median annual per-resident nursing home cost coupled with annual expenditure growth rates at 3.5%,[23] reducing acute and post-acute care expenditures, while striving for improved outcomes with pharmacotherapy, is imperative. Because most nursing home residents experience multimorbidity and have

advanced age, virtually all nursing home residents with atrial fibrillation have indications for anticoagulation (CHA_2DS_2-VASc score $\geq$2).[24] Given the severity of cognitive and/or functional deficits of nursing home residents, the net clinical benefit of anticoagulation is often less certain compared with independent community dwelling older adults.

Changing landscape of anticoagulant use

There has been a dramatic change in the landscape of anticoagulation in the past 8 years. Until 2010, vitamin K antagonists were the only marketed oral anticoagulants (i.e., only warfarin in the US). Meta-analysis of clinical trials supports a 64% risk reduction for stroke and a 0.3% increased risk for serious extracranial hemorrhage with warfarin versus placebo in patients with atrial fibrillation.[25] Anticoagulation is recommended for high risk patients ($CHADS_2$ or CHA_2DS_2-VASc $\geq$2) with atrial fibrillation,[24] but for warfarin users, concerns remain regarding time spent outside the therapeutic range. In 9 of 15 trials, the time in therapeutic range for warfarin was $\geq$65%.[26] Yet, in the "real world", treated patients[26] including nursing home residents[27] spent ~50% of time outside the therapeutic range, placing them at risk for adverse events.[26]

Alternatives to warfarin— direct acting oral anticoagulants (DOACs)— have entered the market since 2010. In the United States, dabigatran was the first to be approved by the Food and Drug Administration in the fall of 2010, followed by rivaroxaban (2011), apixaban (2012), and edoxaban (2015). These 4 medications were approved for patients with atrial fibrillation based upon head to head Phase III clinical trial comparisons versus warfarin.[28–31] Reviews of the trial and post-marketing observational evidence have indicated the DOACs are generally comparable in safety and effectiveness to warfarin,

with a potentially lower risk of intracranial hemorrhage.[32,33] Yet, clinicians caring for nursing home residents may be hesitant to extrapolate trial evidence to their patients. Unlike warfarin, the direct acting agents do not typically require strict monitoring.[34–37] For these reasons, it comes as no surprise that direct acting oral anticoagulant use rose rapidly in the United States,[38,39] initially displacing warfarin[38] and subsequently expanding the number of treated community dwelling atrial fibrillation patients.[40]

Before the widespread availability of the DOACs, low treatment rates were common in the United States and internationally.[40-43] In two large community based cohorts (enrolled 1996-97 and 2006-09) of high-risk older adults with atrial fibrillation, over 40% of patients hospitalized for ischemic stroke were discharged without an oral anticoagulant.[41] In Sweden, 73% of adults with atrial fibrillation 80 years and older were discharged without an oral anticoagulant after an ischemic stroke between 2006-2013.[42] In a large single-center cohort in France, hospitalized patients with atrial fibrillation over 75 years of age were untreated with oral anticoagulants in 59% of hospital stays between 2009-2013.[43] However, evidence suggests that the community dwelling Medicare Advantage population had a high (70%) prevalence of oral anticoagulant use for atrial fibrillation (although the study's methods may have inflated this estimate), which remained relatively stable over the period 2008-2014.[44]

In the general United States population, the prevalence of oral anticoagulant use at ambulatory care visits by patients with a diagnosis of atrial fibrillation increased from 52% to 67% over the period 2009 to 2014, and the number of visits with warfarin use was similar to the number with DOAC use.[40] Other single-center studies of hospitalized older adults in

Belgium[45] and Germany[46] have reported increased use of anticoagulants comparing periods after to before the availability of the DOACs. In a community based registry of US patients with newly diagnosed atrial fibrillation initiating oral anticoagulation between 2013-2016, 75% of patients initiated DOACs (40% rivaroxaban, 30% apixaban, and 6% dabigatran) while 25% initiated warfarin.[39] More than 70% of adults over age 75 years in this community based cohort initiated DOACs in this study.[39] Similar distributions of prevalent DOAC (80%) versus warfarin use (20%) were observed among commercially insured and Medicare Advantage members overall and among older adults as of the first quarter of 2017.[47] In the setting of secondary prevention for patients with atrial fibrillation discharged from Get With the Guidelines Stroke hospitals after an ischemic stroke, almost all (88%) patients were discharged on an oral anticoagulant, but only 18% were discharged on a DOAC as of 2012.[38]

Use of anticoagulants in nursing homes

Most nursing home residents with atrial fibrillation are high risk and qualify for anticoagulation.[48,49] Yet, historically, fewer than half of nursing home residents with atrial fibrillation were treated[48,49] owing to high perceived bleeding risk,[41,50] labile anticoagulation with warfarin in nursing homes (~50% of time outside of therapeutic range),[27,51,52] and a high burden of complicating clinical factors (i.e., polypharmacy, comorbidities, cognitive impairment, functional limitations).[17,53,54] Only one-third of residents newly initiating warfarin for atrial fibrillation remain on treatment at 1-year, suggesting improvements are needed in pharmacologic management of these patients.[55] Contemporary evidence remains scarce, as evaluations of anticoagulation practices in

nursing homes were regional in scope, and were based on data before direct acting oral anticoagulants were approved by the Food and Drug Administration.[27, 48-52,55-57]

The uptake of DOACs in nursing homes remains unknown. It is likely that the diffusion of DOACs to nursing home residents may be slower than in the community (which may be appropriate owing to the absence of evidence in a clinically complex population). There is a paucity of information regarding the safety and effectiveness of warfarin and DOACs in the oldest old, complicating the selection of a specific medication.[58] The Birmingham Atrial Fibrillation Treatment of the Aged randomized clinical trial comparing warfarin to aspirin in community dwelling patients over 75 years of age constitutes the strongest evidence in support of the anticoagulation of older adults.[59] The study reported a ~50% reduction in the rate of stroke and a comparable bleeding risk in those randomized to warfarin,[59] however the time in therapeutic range was higher (67%) than is typical in nursing home residents. Even with the availability of direct acting oral anticoagulants, appropriately managed warfarin in older adults is expected to be the preferred regimen for certain patients, especially where frequent monitoring is viewed as beneficial. Beyond the decision to initiate anticoagulation, the question of if and when to discontinue therapy in the context of changes in a resident's clinical and functional status is also important. In Veterans at least 65 years of age treated with warfarin for atrial fibrillation, 16% continued anticoagulation after an incident dementia diagnosis and the rates of stroke and death were lower (with no excess rates of gastrointestinal bleeding) in those who persisted with warfarin compared with those who discontinued.[60]

In the nursing home setting, concern about safe use of warfarin is warranted. Gurwitz et al documented that adverse events associated with warfarin therapy are common in the nursing home setting.[27] The authors noted that most of the warfarin-related adverse events were preventable with appropriate warfarin management at the prescribing and monitoring stages.[27] Recent research has cautioned that practical advice on handling of warfarin treatment and drug interactions is needed because electronic alerts embedded within electronic medical records appeared to be insufficient to change practice.[61]

Contemporary evidence for the treatment of atrial fibrillation is lacking in nursing homes. The frequency of warfarin use and the quality of monitoring may have changed since earlier evaluations were conducted. The availability of DOACs requiring less monitoring and having less potential for interactions may have increased the number of residents receiving oral anticoagulants. Moreover, shifts in anticoagulant utilization precipitated by the emergence of the direct acting agents may have improved outcomes for residents with atrial fibrillation.

Evidence from clinical trials should not be extrapolated to nursing home residents

Evidence on the safety and effectiveness of the direct acting oral anticoagulants specific to nursing home residents is needed. Decision-making in nursing homes is often complicated by the presence of cognitive impairment and functional limitations. Whether benefits of anticoagulation outweigh harms among residents with severe cognitive impairment and physical limitations is unknown. Advanced age, comorbid diseases, and polypharmacy increase risk for adverse events. Beyond the initial decision to treat,

maintenance of warfarin within a narrow therapeutic range is challenging in nursing homes. Nursing home residents have been excluded from recent evaluations of anticoagulation practices[38,39] and have not been identified in recently published trials.[28–31]

The 2016 Joint Scientific Statement from the American Heart Association, American College of Cardiology, and American Geriatrics Society[62] called for atrial fibrillation research on anticoagulant comparative effectiveness, adverse event risks by specific anticoagulant, consequences of non-adherence, and cessation of anticoagulation in older adults. One in three nursing home residents with atrial fibrillation have a history of stroke, placing them at increased risk of recurrent stroke.[52] Yet as few as 30% of nursing home residents with atrial fibrillation received anticoagulation historically.[48,49,51]

Evidence to inform anticoagulant treatment decisions among the ~240,000 American nursing home residents with atrial fibrillation is needed.[17,52] Clinical trials of direct acting oral anticoagulants will not likely be conducted in nursing homes despite the evidence needed to inform the difficult treatment decisions facing residents and their providers. In the absence of the "gold-standard" study design, observational research using large databases of real-world patients is well-suited to handle treatment effect heterogeneity and to inform decisions made for an individual patient. Evidence on key parameters (e.g., use, dosing, safety, effectiveness) of direct acting oral anticoagulants and contemporary evidence on warfarin specific to the nursing home setting are needed to identify changes in anticoagulant use patterns, to quantify their impact, and to improve resident-centered decision-making[63] regarding anticoagulation in nursing homes.

The quality of medication decisions in the nursing home environment depends upon the quality of communication between on-site clinicians (e.g., nurses, nurse practitioners), off-site physicians, consultant pharmacists, social workers, the patient and their family.[64,65] This introduction highlights the need for evidence to inform a shared decision-making process and address the dilemma facing all clinicians caring for very old, clinically complex patients: *Will initiating an anticoagulant cause harm without the potential for substantial benefit? Is withholding an anticoagulant (proven effective in younger, less frail patients) more judicious? Will this resident benefit from aggressive pharmacologic management of atrial fibrillation? If so, which specific anticoagulant will increase the probability of benefit while reducing risk?* The time has come to address the information needs for a growing segment of the population neglected by the evidence.

Specific Aims

This dissertation described the diffusion of DOACS, the factors associated with anticoagulant use, and evaluated the comparative effectiveness and safety of oral anticoagulants in the nursing home population. The specific aims of this dissertation were as follows.

Aim 1. To characterize contemporary and changing vitamin K antagonist and DOAC utilization rates in a nursing home population.

In this aim, the proportion of nursing home residents with atrial fibrillation treated with an oral anticoagulant was examined overall, by medication class, by medication and by dosage, over the period 2011 to 2016.

Aim 2. To quantify the magnitude of geographic variation in oral anticoagulant use and the contributions of resident, facility, and county characteristics to such variation.

In this aim, county and state level variation in oral anticoagulant use was described and multilevel models were fit to quantify the extent to which the variation was explained by resident, facility, and county characteristics.

Aim 3: To compare the incidence of safety (i.e., bleeding) and effectiveness (i.e., ischemic stroke) outcomes between vitamin K antagonist users versus DOAC users.

In this aim, DOAC users (apixaban, dabigatran, and rivaroxaban) were propensity matched to warfarin users. The safety and effectiveness of each DOAC was then compared to warfarin.

Data Source and Study Population

The following datasets (2011-2016) were used for this dissertation: 1.) Minimum Data Set (MDS) 3.0 for clinical information (e.g., comorbid diseases, physical and cognitive functioning), 2.) Medicare Master Beneficiary Summary File for eligibility and mortality, 3.) Medicare Part A for hospitalizations, skilled nursing facility (SNF) stays, and diagnoses, 4.) Medicare Part D claims for medications, 5.) the Certification and Survey Provider Enhanced Reporting (CASPER) files for nursing facility characteristics, and 6.) the Area Health Resource File (AHRF) for county characteristics.

MDS 3.0 assessments are mandatory for all residents of Medicare- and Medicaid-certified NHs, including SNFs and long-term care facilities. For long-term care residents, assessments are performed at admission, quarterly, annually, and upon a significant change in the resident's status. The MDS 3.0 provides reliable and valid information of

research quality.[65-67] The Master Beneficiary Summary File provides demographic information (age, sex, race, ZIP code), vital status (validated Social Security Administration date of death), and eligibility for Medicare and Medicaid. Medicare Part A claims via the MedPAR Research Identifiable File provided information on hospital and SNF claims (e.g., provider IDs, service dates, diagnosis and procedure codes, charges and/or Medicare payments). Medicare Part A claims contain International Classification of Disease (ICD-9 CM, ICD-10) diagnosis codes and Current Procedural Terminology, 4th edition codes. Medicare Part D claims document outpatient medication dispensings that are reimbursed by Medicare. The Part D Drug Event File contains dates of service, payment information, National Drug Codes, quantity dispensed, and days supply. The Drug Event File is linked to the Part D characteristics file which provides additional information on the brand and generic drug name, the strength, and the dosage form. Information on ownership, size, certification, special services, inspection results, facility-aggregated resident characteristics, and staffing hours derived from annual inspections of Medicare- and Medicaid-certified nursing facilities are included in the CASPER files. The AHRF is a publicly available database containing county-level data on the characteristics of the population (e.g., from the Census), as well as information on the supply of healthcare professionals and healthcare facilities in the county (e.g., from the American Medical Association Master File and the American Hospital Association database).

The study population for this dissertation included older non-SNF nursing home residents with atrial fibrillation residing in facilities throughout the United States. The

inclusion criteria were: 1) residence in one of the ~16,000 Medicare- or Medicaid-certified nursing homes; 2) age ≥65 years; 3) Medicare fee-for-service Part A and Part D beneficiary; 4) 180 days of Medicare fee-for-service Part A and Part D enrollment prior to the index date; and 4) a diagnosis of atrial fibrillation. Exclusion criteria were: 1) Medicare Advantage member; 2) comatose state at nursing home admission; and 3) SNF stay without long-term nursing home residence. Medicare Advantage members are excluded due to incomplete Medicare Part A and Part D claims information. The small number of residents in a comatose state at admission are also excluded because decision-making regarding potentially life-extending medications for these patients is distinct from the decision-making process for non-comatose patients. Community-dwelling patients admitted to a nursing home for a SNF stay that do not remain in or return to the nursing home beyond the SNF stay will be excluded because Medicare Part D does not reimburse for medications during SNF stays.

The study period for Aim 1 encompassed 2011 to 2016, and the study population included 250,092 residents. The study period for Aim 2 spanned 2014 to 2016, and the population for Aim 2 was a subset of those included in Aim 1 with a further inclusion requirement of residence in a county with at least 11 included residents. The study population for Aim 2 was 89,176 residents. The study population for Aim 3 was distinct from Aims 1 and 2 (which included prevalent users and non-users). In order to identify comparable groups of warfarin and DOAC users, only new users of warfarin or DOACs were included. The study population for Aim 3 was 21,346 new-users of warfarin or DOACs.

Analytic Methods

The primary goal of Aim 1 was to describe anticoagulant utilization patterns in nursing homes over time. Using a repeated cross-sectional design, we sought to estimate the proportion of residents known to be residing in a nursing home on a specific day that were receiving oral anticoagulants for atrial fibrillation. We examined prevalence because it reflects the current treatment for all United States nursing home residents with a diagnosis of atrial fibrillation, rather than only the subset who were newly initiating during a given time window. Furthermore, the decision to initiate may not be the most relevant decision for many residents, for whom the decision to discontinue, change dosages, or switch anticoagulants may be most important. For this reason, we examined dosing, switching, and discontinuation of oral anticoagulants, in addition to point prevalence. Each of these measures were defined using information on Part D claims (dispensing dates and days supply), adjusting for early refills and inpatient hospitalizations as needed and allowing for a grace period between fills. In addition to describing utilization patterns, nursing home resident characteristics were also described by anticoagulation status (i.e., treated and untreated) and by type of oral anticoagulant (vitamin K antagonist and DOAC) in both 2011 and 2016 (to describe changes in groups over time).

In Aim 2, data were aggregated to the county and state levels to describe variation in use across nursing homes and geographies. We used multilevel modeling as our data were inherently nested (residents within counties within states). We could not examine facility level variation due to insufficient sample size within facilities, however, we

evaluated the explanatory power of facility characteristics as fixed effects in multilevel models. Specifically, to evaluate the extent to which resident characteristics, facility characteristics, county characteristics, and state of residence explained variation in oral anticoagulant use among nursing home residents with atrial fibrillation, we fit a series of five multilevel models:

Model 1. Null two-level logistic model including a random intercept term for county level variation:

$$\text{logit}\left(P\left(Y_{ijs}=1\middle|b_{0j}\right)\right)=\ \beta_0+b_{0j}+\boldsymbol{\beta_t}$$

The outcome (Y_{ijs}) equaled 1 if resident *i* within county *j* in state s was exposed to an oral anticoagulant on the point prevalence date, and otherwise the outcome equaled 0; β_0 is the average log-odds of the proportion of exposed residents given the same level county effects, while b_{0j} is the county specific random intercept measuring variation in the proportion of residents exposed to oral anticoagulants on the log-odds scale, and $\boldsymbol{\beta_t}$ was a fixed effect for time (year). The variance in intercepts across counties is assumed to be normal with mean 0 and variance σ_c^2.

Model 2. A hierarchical two-level logistic model including random intercepts for counties and resident characteristics:

$$\text{logit}\left(P\left(Y_{ijs}=1\middle|b_{0j},\boldsymbol{X}_{ijs}^{r}\right)\right)=\beta_0+b_{0j}+\boldsymbol{\beta_r}\boldsymbol{X}_{ijs}^{\boldsymbol{r}}+\ \boldsymbol{\beta_t}$$

Model 2 additionally includes $\boldsymbol{\beta_r}\boldsymbol{X}_{ijs}^{\boldsymbol{r}}$, terms for a vector of resident characteristics included as fixed effects. The between-county variance estimate from this model is adjusted for resident characteristics.

Model 3. A hierarchical two-level logistic model including random intercepts for counties and adjusting for resident and facility level characteristics:

$$\text{logit}\left(P\left(Y_{ijs}=1\middle|b_{0j},\boldsymbol{X}_{ijs}^{r},\boldsymbol{X}_{ijs}^{f}\right)\right)=\beta_0+b_{0j}+\boldsymbol{\beta_r}\boldsymbol{X}_{ijs}^{r}+\boldsymbol{\beta_f}\boldsymbol{X}_{ijs}^{f}+\boldsymbol{\beta_t}$$

Model 3 also includes $\boldsymbol{\beta_f}\boldsymbol{X}_{ijs}^{f}$ (terms for a vector of facility characteristics included as fixed effects). The between-county variance estimate from this model is adjusted for both resident and facility characteristics.

Model 4. A hierarchical two-level logistic model including random intercepts of counties and adjusting for resident, facility, and county level characteristics:

$$\text{logit}\left(P\left(Y_{ijs}=1\middle|b_{0j},\boldsymbol{X}_{ijs}^{r},\boldsymbol{X}_{ijs}^{f}\right)\right)=\beta_0+b_{0j}+\boldsymbol{\beta_r}\boldsymbol{X}_{ijs}^{r}+\boldsymbol{\beta_f}\boldsymbol{X}_{ijs}^{f}+\boldsymbol{\beta_c}\boldsymbol{X}_{ijs}^{c}+\boldsymbol{\beta_t}$$

The term $\boldsymbol{\beta_c}\boldsymbol{X}_{ijs}^{c}$ represents terms for a vector of county characteristics included as fixed effects. The between-county variance estimate from this model is adjusted for resident, facility, and county characteristics.

Model 5. A hierarchical three-level logistic model including a random intercept term for county level variation, a second random intercept term for state level variation, and adjusting for resident, facility, and county level characteristics:

$$\text{logit}\left(P\left(Y_{ijs}=1\middle|b_{0j},b_{0s},\boldsymbol{X}_{ijs}^{r},\boldsymbol{X}_{ijs}^{f},\boldsymbol{X}_{ijs}^{c}\right)\right)=\beta_0+b_{0j}+b_{0s}+\boldsymbol{\beta_r}\boldsymbol{X}_{ijs}^{r}+\boldsymbol{\beta_f}\boldsymbol{X}_{ijs}^{f}+\boldsymbol{\beta_c}\boldsymbol{X}_{ijs}^{c}+\boldsymbol{\beta_t}$$

This model includes random intercepts of states variation in anticoagulant use, b_{0s} The between-county variance estimate from this model is adjusted for resident, facility, and county characteristics, as well as state of residence.

In addition to the five multilevel models, we also fit a single level logistic model with only resident characteristics and time to examine differences between each county's observed prevalence of anticoagulant use and the prevalence that would be expected based solely on the composition of its resident population (i.e., observed versus predicted).

Comparative Safety and Effectiveness

Observational pharmacoepidemiologic studies comparing outcomes of alternative treatment strategies must inevitably consider and address threats to internal validity from selection bias (e.g., confounding by indication), information bias (e.g., exposure and outcome misclassification), and confounding. Although observational studies generally cannot achieve the level of causal inference derived from clinical trials, the application of modern pharmacoepidemiologic methods can be applied to produce observational comparative effectiveness evidence that is valuable for informing clinical practice, particularly for populations for whom clinical trial evidence is sparse and unlikely to be generalizable. Therefore, in Aim 3, we implemented an active comparator new-user cohort design to mitigate confounding by indication.[68] Furthermore, we used validated outcome definitions to attenuate concerns of misclassification, and we applied propensity score matching to assemble balanced groups of warfarin and DOAC users. The propensity score estimates the probability of receiving a treatment using logistic regression, and once estimated is used to assemble groups with similar characteristics.[63,64] To maintain a clear temporal relationship between the exposure (anticoagulant use) and

the outcome, we applied an as-treated design and censored residents discontinuing or switching anticoagulants.

In recognition of the unique pharmacologic profiles of individual DOACs,[34-37] separate propensity matched comparisons were implemented for apixaban, dabigatran, and rivaroxaban versus warfarin. Due to a high prevalence of DOAC dosing that was not aligned with Food and Drug Administration (FDA) approved labeling, and earlier evidence suggesting misaligned dosing is associated with risk for adverse events, we performed analyses among subgroups defined by DOAC alignment or misalignment with labeled dosing recommendations. Separate competing risk Cox proportional hazards models were fit for effectiveness (i.e., ischemic stroke and transient ischemic attack (TIA)), safety (intracranial and extracranial bleeding), other ischemic events (i.e., systemic embolism, venous thromboembolism (VTE), acute myocardial infarction (AMI)), and all-cause mortality. To better understand the overall risk-benefit profile of each medication, a net clinical benefit composite outcome which included each of these outcomes was also evaluated.

CHAPTER II

CHANGES IN ANTICOAGULANT UTILIZATION AMONG UNITED STATES NURSING HOME RESIDENTS WITH ATRIAL FIBRILLATION FROM 2011 TO 2016

Abstract

Background

Nursing home residents with atrial fibrillation (AF) are at high risk for ischemic stroke and bleeding events. The most recent national estimate (2004) indicated less than one-third of this high-risk population was anticoagulated. Whether direct-acting oral anticoagulant (DOAC) use has disseminated into nursing homes and increased anticoagulant use is unknown.

Methods

A repeated cross-sectional design was used to estimate the point prevalence of oral anticoagulant use on July 1st and December 31st of calendar years 2011-2016 among Medicare fee-for-service beneficiaries with AF residing in long-stay nursing homes. Nursing home residence was determined using Minimum Data Set 3.0 records. Medicare Part D claims for apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin were identified and point prevalence was estimated by determining if the supply from the most recent dispensing covered each point prevalence date. A Cochran-Armitage test was performed for linear trend in prevalence.

Results

On December 31, 2011, 42.3% of 33,959 residents (median age: 85; Q1 79, Q3 90) were treated with an oral anticoagulant, of whom 8.6% used DOACs. The proportion receiving treatment increased to 47.8% of 37,787 residents as of December 31, 2016 ($p<0.01$); 48.2% of 18,054 treated residents received DOACs. Demographic and clinical characteristics of residents using DOACs and warfarin were similar in 2016. Half of the

8,734 DOAC users received standard dosages and most were treated with apixaban (54.4%) or rivaroxaban (35.8%) in 2016.

Conclusions

Increases in anticoagulant use among US nursing home residents with AF coincided with declining warfarin use and increasing DOAC use.

Introduction

The number of Americans with atrial fibrillation (AF) is projected to double to more than 12 million between 2010 and 2050, driven by increasing population size, aging, and a rising burden of risk factors such as obesity.[4] By 2050, more than half of Americans with AF are expected to be over 80 years of age.[13] As of 2010, approximately one in eight Americans over the age of 85 resided in an institutional setting.[65]

Anticoagulation decisions for older adults with AF at high risk for ischemic stroke are particularly challenging because most are also at high risk of bleeding. This leaves providers uncertain of the net benefit of treatment[41,50] and has contributed to low use of anticoagulants for high-risk older adults[72] despite evidence supporting their safety and effectiveness for older populations.[59] Nursing home residents with AF are at particularly high risk for ischemic stroke and bleeding events due to a high prevalence of risk factors, including frailty, advanced age, and comorbidities.[48-49, 73] Yet in the final wave of the National Nursing Home Study conducted in 2004, less than one-third of this high-risk population was anticoagulated.[49] Historically, nursing home residents commonly experienced high rates of adverse events related to warfarin therapy, many of which were considered preventable and associated with time spent outside of the therapeutic range.[27]

Among patients in the United States attending ambulatory care visits, the market entrance of direct-acting oral anticoagulants (DOACs) was followed by a shift in utilization from warfarin to DOACs, accompanied by an increase in the fraction of patients with AF receiving anticoagulation.[40] This shift extends to high-risk community dwelling older adults, as the large majority of high-risk patients initiating anticoagulants

during the period 2013-2016 were prescribed DOACs.[39] Nursing home residents have a high burden of cognitive impairment and shortened life expectancy,[74-75] which demands a complex multi-stakeholder shared decision-making process. Furthermore, extensive functional limitations[17] diminish residents' access to specialists outside of the institutional setting who have a greater propensity to prescribe anticoagulants overall and DOACs specifically.[76,77] It is uncertain the extent to which the use of DOACs has disseminated into the nursing home setting and increased anticoagulant use for this high-risk and vulnerable population.

Methods

Data

Medicare administrative files and the Minimum Data Set (MDS) 3.0 were linked to assemble a near-comprehensive data source encompassing enrollment and demographic characteristics from the Medicare Beneficiary Summary file, hospital and SNF claims (Medicare Part A), prescription claims (Medicare Part D), and clinical and functional assessment data (MDS 3.0). The MDS 3.0 is mandatory for all Medicare and Medicaid certified nursing facilities and the information collected through the MDS 3.0 has been previously validated.[65-67] Medicare administrative files and the MDS 3.0 were used through a data use agreement with the Centers for Medicare and Medicaid Services (CMS). Dr. Alcusky had full access to all study data and takes responsibility for data integrity and analysis. Due to the sensitive nature of the CMS research identifiable files, researchers interested in requesting files should consult the information available from the Research Data Assistance Center.[78] The University of Massachusetts Medical School

Institutional Review Board approved this study (H00015376); informed consent was not required.

Study Design

A repeated cross-sectional design was used to estimate the point prevalence of oral anticoagulant use overall, by anticoagulant class (i.e., warfarin or DOAC), and by specific medication on July 1st and December 31st of calendar years 2011-2016. A 12-month lookback period was used for all cross-sections with the exception of the first because Medicare and MDS 3.0 data were only available for 6 months and 9 months, respectively, prior to July 1, 2011.

Study Population

For each cross-section, Medicare fee-for-service beneficiaries with diagnosed AF residing in a long-stay nursing home on the point prevalence date and with at least six months of baseline Medicare enrollment were eligible to enter the study population. Included residents had at least one diagnosis of AF or flutter (Table 2.1) on a Medicare Part A claim and one diagnosis of AF, atrial flutter, or dysrhythmia on a MDS 3.0 assessment in the 12 months preceding the point prevalence date. Excluded residents were <65 years of age, without at least one Part D claim in the preceding 12 months, enrolled in hospice, or in a comatose state.

Anticoagulant Use

Oral anticoagulant use including apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin was measured using a daily approach, enabling a precise estimate of current anticoagulant use in a national population of residents who were known to be residing in

a nursing home on a specific date. The point prevalence of oral anticoagulant utilization was estimated on the first day of each half-year of the study (July 1st and December 31st of calendar years 2011-2016) by summing the number of eligible residents exposed to an anticoagulant on that date and dividing by the number of residents in the population. Exposure was estimated using fill dates and number of days supplied from Part D claims in the 12-months preceding the point prevalence date. Each day a resident was present in the study population was marked as exposed if the supply from the most recent dispensing was sufficient to cover that day, accounting for medication accumulation and inpatient/SNF stays. Residents with at least one dispensing for an oral anticoagulant who were not exposed on the point prevalence date were considered to have discontinued anticoagulant use. For analyses of switching at the level of the class (warfarin or DOAC), residents that made multiple switches during a cross-section were grouped according to the most recent switch. Among switchers, the proportion switching from one class to the other and back was also described.

Resident Characteristics

Resident characteristics were operationalized using information from the most recent long-stay MDS 3.0 assessment preceding the point prevalence date, diagnoses on Part A claims and medication information on Part D claims during the 12-months preceding the point prevalence date. Resident characteristics included demographics, hospital admissions (including for ischemic stroke,[79] extracranial bleeding,[80] or intracranial hemorrhage[80]), CHA_2DS_2-VASc risk score,[81] ATRIA risk score,[82] select comorbid conditions associated with increased ischemic stroke (i.e., components of the

CHA_2ADS_2-Vasc score) or bleeding risk[83] (fall history, chronic renal insufficiency[84]), select medication classes and total unique medications (as an indicator of polypharmacy) used, functional status, and cognitive impairment. Renal functioning was grouped in four categories using a combination of information from Medicare claims and MDS 3.0 items: 1) on dialysis (MDS item O0100J2), 2) end-stage renal disease (MDS item I1500) and not on dialysis, 3) chronic renal insufficiency (corresponding to an estimated glomerular filtration rate <60 ml/min)[84] without end-stage renal disease or dialysis, and 4) no evidence of chronic renal impairment. The select medication classes described were those associated with increased bleeding risk (non-steroidal anti-inflammatory drugs, antiplatelets) and chronic medications (statins, angiotensin converting enzyme inhibitors, angiotensin receptor blockers) used for the prevention of cardiovascular and cerebrovascular events. Use of selective serotonin reuptake inhibitors was also described due to a possible association with bleeding when combined with anticoagulant use.[85,86] A recent history of one or more falls since nursing home admission or the last assessment was ascertained from the MDS 3.0 (item J1800) and operationalized dichotomously. Functional status was operationalized as the four-item activities of daily living (ADL) score, which summarizes a resident's ability to perform four ADLs (personal hygiene, toileting, locomotion, and eating) and ranges from a score of 0 (independent in all four ADLs) to 16 (totally dependent in all four ADLs).[87] Cognitive impairment was scored using the MDS 3.0 Cognitive Function Scale.[74]

Statistical Analysis

Characteristics of the study population were described overall and by anticoagulant use for the residents included in the December 31st 2011 and 2016 point prevalence estimates. Among residents using oral anticoagulants as of December 31st 2011 and 2016, resident characteristics were summarized separately for users of DOACs and warfarin. Descriptive statistics included frequencies and percentages for categorical variables and medians with first and third quartiles for continuous variables.

The prevalence of anticoagulant use was plotted overall and by anticoagulant class for the twelve half-years comprising the study period. For each half-year, the prevalence of anticoagulant use was also described by specific medication. The prevalence of anticoagulant use overall and by medication class was also described within subgroups defined by renal function, cognition, and functional status for the December 31st 2011 and 2016 cross-sections. The prevalence of anticoagulant discontinuation and the prevalence of switching between medication classes were each plotted over the course of the study period. A Cochran-Armitage test with a 2-sided statistical significance level of <0.05 was performed for linear trend in prevalence of anticoagulant use. Data analyses were performed with SAS Version 9.4 (SAS Institute Inc.) and Microsoft Excel 2016 (Microsoft Corporation).

Results

Resident Characteristics

The number of residents included ranged from 17,895 for the July 1, 2011 cross-section to 37,787 for the December 31, 2016 cross-section. Resident age remained consistent between 2011 (median: 85; Q1 79, Q3 90) and 2016 (median: 84; Q1 78, Q3

90). In 2016, 34% of residents were men; with 29% men in 2011. The proportion of residents with CHA_2DS_2-Vasc scores $\geq$6 was 36% in 2011 and 30% in 2016; in each time period >99% of residents had scores of $\geq$2. The fraction with renal impairment (chronic renal insufficiency, end-stage renal disease, or using dialysis) was 51% in 2016 and 43% in 2011. Residents were substantially limited in ADLs in 2011 and 2016. The prevalence of moderate to severe cognitive impairment was 39% in 2011 and 34% in 2016. The median number of unique prescriptions among residents in 2011 was 17 and in 2016 was 18.

Table 2.2 displays characteristics of the resident population in 2011 and 2016 for both treated and untreated residents. In 2011 and 2016, the median CHA_2DS_2-Vasc score was 5 (Q1 4, Q3 6) and the median ATRIA risk score was 3 (Q1 3, Q3 6) among both treated and untreated residents. In 2011, moderate to severe cognitive impairment was present among 44% of untreated and 34% of treated residents, while in 2016 the prevalence was 40% and 30%, respectively. During the 2011 and 2016 cross-sections, 5% of untreated and 7% of treated residents had been hospitalized for ischemic stroke. Among untreated residents, 23% used antiplatelets in 2011 and 19% used antiplatelets in 2016; less than 10% of treated residents used antiplatelet medication during either time period. Table 2.3 displays characteristics of nursing home residents treated with DOACs and warfarin in 2011 and 2016.

Anticoagulant Use

The proportion of residents with AF treated with oral anticoagulants was 42.4% as of July 1st 2011, at which time the majority of treated residents were using warfarin.

Anticoagulant use remained stable through the close of 2013, at which time 42.8% of residents were treated, 35.2% with warfarin and 7.7% with DOACs (Figure 2.1). Beginning in the first half of 2014 the prevalence of anticoagulant use increased during each half-year through the end of the study (December 31st, 2016), at which time 47.8% of residents were treated (p-value for 2011-2016 trend <0.001). This period (2014-2016) of increasing anticoagulant use coincided with a decline in warfarin use and a rise in DOAC use such that by the end of 2016, the prevalence of warfarin use (24.7%) was nearly equal to DOAC use (23.1%).

Dabigatran use increased during the early study period and peaked in the first half of 2012 before stabilizing in the range of 2.2%-3.1% through 2016 (Table 2.4). In contrast, the prevalence of rivaroxaban and apixaban use continued to rise through the end of the study. Over the five full years (2012-2016) after market entry, rivaroxaban use increased from 0.4% to 8.3%. During the four full years after market entry (2013-2016), apixaban use grew from 0.1% to 12.6%. In contrast, edoxaban use remained rare after its approval in 2015.

In 2011, 36% of residents with moderate-to-severe cognitive impairment were treated with oral anticoagulants and 46.4% of cognitively intact or mildly impaired residents were treated (Table 2.5); the percentages treated in 2016 were 40.4% and 51.7%, respectively. The change in the prevalence of oral anticoagulant use between 2011 and 2016 was 5% among residents with and without chronic renal insufficiency (43% to 48%); the change among those with end-stage renal disease was 8% (39% to 47%) (Table 2.6). In 2016, use of low DOAC doses was common (44%) among residents

without a diagnosis of renal impairment, while standard DOAC doses were commonly used among those with chronic renal insufficiency (47%), end-stage renal disease (40%), and those on dialysis (31%). Among 2,676 apixaban users likely to have an indication for dosage reduction (at least two of: weight ≤60 kilograms, renal impairment, age ≥80 years), 26.2% received the standard dose. Among 3,122 apixaban users who likely did not have an indication for dose reduction, 36.0% received the low dose. As of the second half of 2016, 48.3% of white residents, 46.5% of black residents, 42.3% of Hispanic residents, and 36.7% of Asian/Pacific Islander residents were treated with oral anticoagulants (Table 2.7). No sex-based differences in anticoagulant use were observed.

Anticoagulant Switching and Discontinuation

The proportion of nursing home residents with AF discontinuing oral anticoagulants was in the range of 8.6% to 10.1% for each half-year of the study period (Figure 2.1). Among treated residents, the fraction switching from a DOAC to warfarin remained in a narrow range (1.8%-2.4%) from the second half of 2011 through the end of 2016 (Figure 2.2). Switchers from warfarin to a DOAC comprised 2.4% of treated residents in the first half of 2011 and 7.8% of treated residents in the second half of 2016. Among residents that switched between anticoagulant classes, the percentage of switchers that switched back to their original anticoagulant class ranged from 13% to 21% of all switchers during 2011 and 2012, and from 8% to 11% of all switchers during 2013-2016 (approximately 1% of the total treated population).

Discussion

The proportion of US nursing home residents with AF using oral anticoagulants was stable during the initial three-year period following the market release of the DOACs in the US, but then steadily increased from 2014 to 2016. Underlying this overall trend, the pace of gradual decline in warfarin use mirrored uptake in DOAC use during 2011-2013, with DOAC uptake consistently outpacing declines in warfarin use beginning in 2014. Utilization growth peaked for dabigatran in 2012 and slowed for rivaroxaban in 2015. Continued increases in DOAC use and anticoagulation overall were fueled by the rapid uptake of apixaban, which began approximately one year after its market entrance (2014) and was sustained through the end of 2016. By the end of 2016, approximately equal fractions of residents were treated with DOACs as were treated with warfarin.

Prior to DOAC availability, low use of oral anticoagulants among high-risk older adults with AF was reported in the US and internationally.[42,43,72,88,89] In two large US community-based AF cohorts (median CHA_2DS_2-Vasc: 5), over 40% of patients hospitalized for ischemic stroke were discharged without an anticoagulant.[41] Estimates of anticoagulant use among US nursing home residents with AF in the 1990s and early 2000s suggested approximately two-thirds of residents were not treated with warfarin.[49,52] At that time, reports of high rates of adverse events and labile international normalized ratios for nursing home residents[27,52] were accompanied by physician uncertainty regarding the relative benefits and risks of warfarin in the long-term care setting.[50] This uncertainty regarding the net benefit of treatment continues to affect anticoagulant prescribing decisions for high-risk older adults.[41]

Low use of anticoagulation was widespread despite evidence supporting clinical benefit. A meta-analysis of clinical trials comparing warfarin to control reported a 64% risk reduction for stroke and comparable risk for major extracranial hemorrhage in patients with AF.[25] Similar findings were reported for warfarin versus aspirin among older adults over 75 years.[59] Prominent reasons clinicians refrain from anticoagulation among high-risk older adults post-stroke include perceived fall risk, poor prognosis, and a history of bleeding.[41,50] Considering a history of falls is common among nursing home residents, coupled with a high burden of cognitive impairment[74] and short life expectancy,[75] it is reasonable to expect a lower prevalence of anticoagulation compared with community-dwelling populations. Interestingly, although the prevalence of bleeding risk factors was directionally consistent with greater provider caution in treating patients with higher bleeding risk, more than half of the untreated population had low bleeding risk (ATRIA<4) and more than three-quarters did not have a recent history of falls. This suggests a role for other factors beyond these commonly reported reasons for not prescribing oral anticoagulants. In this respect, our findings were similar to earlier studies in the nursing home setting which reported lower likelihood of preventative treatment for residents with cognitive impairment in addition to atrial fibrillation[52] or prior myocardial infarction.[90] However, existing functional limitations did not appear to deter anticoagulant use in our study population, as treated fractions were generally consistent across levels of functional limitation.

Even in the presence of bleeding risk factors, cognitive impairment, and/or functional limitations, clinicians should maintain a focus on the overall risk-benefit

profile, while incorporating patient and family input. Patients often place greater weight on the prevention of stroke than the risk of bleeding,[91] which may reflect recognition of stroke's long-term consequences for functioning and cognition.[9,11] However, patient aversion to bleeding risk as well as the need for additional blood testing and clinical evaluation, even with DOACs, may also contribute to lower treatment rates than would be expected if guidelines were strictly followed. Beyond the decision to treat, the selection of dosage may also be affected by resident factors associated with perceived bleeding and stroke risk, potentially leading to dosing that is inconsistent with product labeling. In a large US cohort of privately insured and Medicare Advantage enrollees with atrial fibrillation, 43% of DOAC users received standard doses in the presence of a renal indication for dose reduction while 13% received low doses despite no renal indication.[92] In the nursing home population, we estimated 44% of DOAC users without renal impairment (renal insufficiency, end-stage disease, or on dialysis) received low dosages and 44% with renal impairment received standard dosages. In the community dwelling population, overdosing was associated with a more than two-fold increased risk of bleeding and comparable stroke risk, while under dosing was associated with a more than four-fold higher stroke risk among apixaban (but not rivaroxaban or dabigatran) users.[92]

After DOACs became available, changes in anticoagulant utilization among US nursing home residents were delayed and smaller in magnitude compared with changes in the broader community-dwelling population. The prevalence of anticoagulant use among nursing home residents with AF had already increased from 30% in 2004[49] to 43% at the

start of our study (2011). In the early period of DOAC availability, the percentage of residents anticoagulated remained steady before increasing to 48% during 2014-2016. This contrasts with the ambulatory care population, where the percentage of office-based visits for AF with anticoagulant use increased from 52% in 2009 to 67% by the end of 2014.[40] The rate of diffusion of DOACs in the community was also faster than in the nursing home, as the number of office visits for AF with DOAC use equaled the number of visits with warfarin use by the close of 2013.[40] The proportion of nursing home residents using DOACs did not approach the proportion using warfarin until the end of 2016. However, increases in anticoagulant and DOAC use continued through the end of our study, suggesting these trends may have continued into 2017. The uptake of DOACs among Medicare Supplemental enrollees in the community was slower than the broader community-dwelling population and more closely resembled uptake among nursing home residents.[44]

Clinical trial evidence comparing DOACs to warfarin specific to older adults is limited. Meta-analysis of available trial data has suggested the DOACs have similar or improved efficacy and comparable or lower risk of major bleeding (except for dabigatran) compared with warfarin in adults 75 years and older.[93,94] Although time in therapeutic range was below target levels in the DOAC trials (55%-65%),[94] similar to studies of real-world populations,[26] inferences regarding comparative effectiveness among older adults maintained within warfarin's therapeutic range require additional evidence. In the absence of definitive evidence in older frail populations, and in light of highly similar resident characteristics for DOAC and warfarin users in 2016, the increase

in anticoagulant use during 2014-2016 may have been driven by several factors. American College of Cardiology/American Heart Association guidelines for AF management published in 2014 listed warfarin and DOACs as class one options for non-valvular AF.[24] Lack of monitoring requirements, fewer drug and dietary interactions, and less frequent need for dose adjustments may have contributed to subgroups of patients receiving treatment with DOACs that historically would not have received warfarin. Furthermore, superiority in safety and effectiveness of apixaban versus warfarin in the ARISTOTLE trial[29] may have tipped the balance of perceived risks and benefits in favor of treatment for certain residents, a possibility supported by the timing and magnitude of increases in apixaban use.

Limitations

In this first national study of anticoagulant use in nursing homes since 2004, we employed daily tracking of exposure and repeated point prevalence measurements to understand the evolution of anticoagulant use while accounting for switching and discontinuation. Limitations stem primarily from the use of diagnostic and medication utilization information derived observational data sources. Detailed clinical data on the type of AF, AF disease history, and renal functioning were not available. Use of over-the-counter medications such as aspirin was not observed unless there was a Part D claim. Anticoagulant exposure was estimated based on medication fill patterns and actual use may have differed, although nonadherence is less of a concern due to the nature of medication administration in nursing homes. Finally, this was a population-based study which used a repeated cross-sectional design to describe patterns of real-world

medication use over time among US nursing home residents with AF. Although we describe resident characteristics in 2011 and 2016, the contributions of within-resident correlation and changes in the characteristics of the US nursing home population over time to changes in anticoagulant utilization patterns were not evaluated statistically in the present study.

Conclusions

Even after a marked increase in anticoagulant use between 2004 and 2016, more than half of nursing home residents with AF remain untreated. The large majority of residents with AF are at high risk for stroke, evidenced by 85% of residents with a CHA_2DS_2-Vasc score of four or more. Recent estimates (2013-2016) of anticoagulant use in the community indicate a large majority (75%) of new-users are initiating DOACs, including older adults.[39] With recent availability of DOAC reversal agents[95] and emerging observational evidence reinforcing trial findings in real-world populations,[96,97] including the frail,[98] it is likely the gradual increase in anticoagulation of nursing home residents and ongoing shift from warfarin to DOACs will continue. The early plateau in dabigatran use suggests any further increase in DOAC use among nursing home residents is likely to be driven by the factor Xa inhibitors apixaban, and to a lesser extent, rivaroxaban. Comparative effectiveness research specific to this medically complex older adult population is warranted to determine the clinical implications of these shifts in anticoagulant prescribing.

Figure 2.1 Percentage of US Nursing Home Residents with Atrial Fibrillation Treated with Warfarin and Direct Acting Oral Anticoagulants (DOACs), 2011-2016 by Half (H) Year

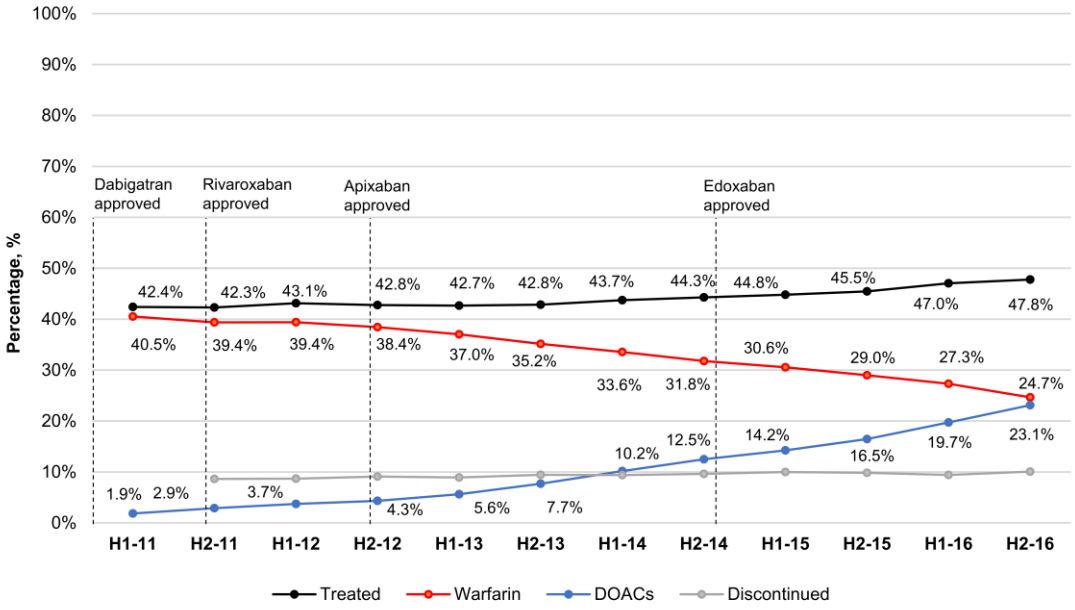

Figure 2.2. Percentage of Treated Residents that Switched Between Warfarin and Direct-Acting Oral Anticoagulants (DOACs),* 2011-2016 by Half (H) Year

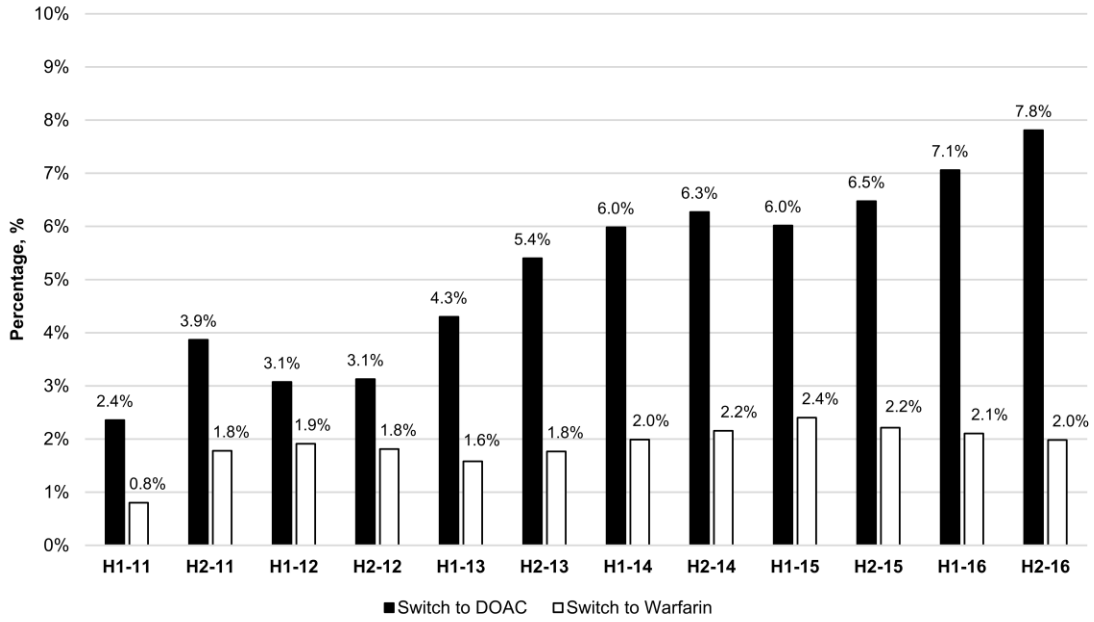

Table 2.1 ICD-9 and ICD-10 Code Based Definitions Applied to Medicare Part A Claims to Identify Specific Conditions		
Clinical Condition	**ICD-9 CM Codes***	**ICD-10 CM Codes***
Atrial fibrillation/flutter†	42731, 42732	I480, I481, I482, I483, I484, I4891, I4892
Ischemic stroke‡	43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, 43491, 436	I6302, I6312, I6322, I63239, I63232, I63231, I63139, I63132, I63131, I63039, I63032, I63031, I63011, I63012, I63019, I63111, I63112, I63119, I63211, I63212, I63219, I6359, I6319, I6309, I6329, I6320, I6310, I6300, I6330, I63311, I63312, I63319, I63321, I63322, I63329, I63331, I63332, I63339, I63341, I63342, I63349, I6339, I636, I6349, I63449, I63442, I63441, I63439, I69432, I69431, I63429, I63422, I63421, I63419, I63412, I63411, I63430, I6350, I63511, I63512, I63519, I63521, I63529, I63531, I63532, I63539, I63541, I63542, I63549, I6359, I638, I639, I6789
Intracranial hemorrhage§	430, 431, 4320, 4321, 4329	I609, I608, I607, I606, I6052, I6051, I6050, I604, I6032, I6031, I6030, I6022, I6021, I6020, I6012, I6011, I6010, I6002, I6001, I6000, I610, I611, I612, I613, I614, I615, I616, I618, I619, I621, I6200, I6201, I6202, I6203, I629
Extracranial bleeding§	In primary position alone: 5310, 5312, 5314, 5316, 5320, 5322, 5324, 5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 53501, 53511, 53521, 53531, 53541, 53551, 53561, 53783, 4560, 45620, 5307, 53082, 5780, 4552, 4555, 4558, 56202, 56203, 56212, 56213,	In primary position alone: K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K2931, K2941, K2951, K2961, K2921, K2971, K2981, K2991, K31811, I8501, I8511, K226, K228, K920, K648, K643, K642, K641 K640, K5711, K5751, K5753, K5741, K5713, K5701, K5791, K5731, K5793, K5781, K5733, K5721, K661, K625, K5521, K921, K922, N280, R310, R311, R312, R319, N898, N920, N921, I312, R58, M2500, M25011, M25012, M25019,

	56881, 5693, 56985, 5781, 5789, 59381, 5997, 6238, 6262, 6266, 4230, 4590, 56881, 7191, 7847, 7848, 7863 In primary position, with above code in secondary position: 5311, 5313, 5315, 5317, 5319, 5321, 5323, 5325, 5327, 5329, 5331, 5333, 5335, 5337, 5339, 5341, 5343, 5345, 5347, 5349, 53500, 53510, 53520, 53530, 53540, 53550, 53560, 455, 56200, 56201, 56210, 56211, 5301, 2800, 2851, 2859, 79092	M25021, M25022, M25029, M25031, M25032, M25039, M25041, M25042, M25049, M25051, M25052, M25059, M25061, M25062, M25069, M25071, M25072, M25073, M25074, M25075, M25076, M2508, R040, R041, R042, R0481, R0489, R049 In primary position, with above code in secondary position: K251, K253, K255, K257, K259, K261, K263, K265, K267, K269, K271, K273, K275, K277, K279, K281, K283, K285, K287, K289, K2900, K2930, K2960, K2920, K2930, K2970, K2980, K640, K641, K642, K643, K644, K645, K648, K649, K5750, K5710, K5752, K5740, K5712, K5700, K5730, K5790, K5792, K5780, K5732, K5720, K210, K209, K208, K200, D800, D62, D649, R791
Chronic renal insufficiency**	582, 583, 585, 586, 587	M3218, M3214, M3504, N050, N051, N052, N053, N054, N055, N056, N057, N058, N059, N060, N061, N062, N063, N064, N065, N066, N067, N068, N069, N070, N071, N072, N073, N074, N075, N076, N077, N078, N079, N08, N140, N142, N144, N150, N158, N159, N171, N16, N170, N172, N178, N179, N181, N182, N183, N184, N185, N186, N189, N19, N261, N269

*ICD-9 CM code based algorithms were converted to ICD-10 CM codes using the 2016 General Equivalence Mappings available from the Centers for Medicare and Medicaid Services at https://www.cms.gov/Medicare/Coding/ICD10/2016-ICD-10-CM-and-GEMs.html

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[§]Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. 2011;(March):560-566.
[**]Winkelmayer WC, Schneeweiss S, Mogun H, Patrick AR, Avorn J, Solomon DH. Identification of individuals with CKD from medicare claims data: A validation study. *Am J Kidney Dis*. 2005;46(2):225-232.

Table 2.2 Characteristics of Residents Treated or Not Treated with an Anticoagulant, by Time Point				
	December 31, 2011		December 31, 2016	
	Untreated (n=19,598)	Treated (n=14,361)	Untreated (n=19,733)	Treated (n=18,054)
Demographics				
Age in years, median (Q1, Q3)	86 (80, 91)	84 (78, 89)	86 (79, 91)	83 (77, 89)
Women, %	70.9	71.2	66.2	65.9
Hospital admissions in prior year, %				
Number of hospitalizations, %				
2-3	38.0	38.4	36.8	37.9
4+	13.7	14.1	12.1	13.1
Ischemic stroke	5.0	7.3	4.7	7.3
Extracranial bleed	7.9	5.3	7.2	4.5
Intracranial hemorrhage	1.0	0.4	1.2	0.5
Unique medications, median (Q1, Q3)	17 (12, 22)	19 (14, 24)	16 (12, 22)	18 (14, 24)
Select Medications,[*] %				
NSAID	18.3	15.8	17.7	16.9
Antiplatelet	22.5	9.5	18.5	8.6
Statin	42.4	51.0	51.1	60.6
SSRI	52.3	55.9	50.0	52.0
ACE inhibitor or ARB	49.8	54.0	45.3	50.1
Select Comorbidities,[†] %				
Diabetes	35.2	41.0	36.3	41.8
Heart failure	42.1	48.7	42.0	48.1
Hypertension	82.7	84.3	85.7	87.8
Coronary artery disease	33.4	31.2	31.3	29.3
Anemia	38.4	32.4	39.2	33.2
Fall since NH admission/last assessment	22.1	18.8	21.8	18.1
Stroke	19.6	24.3	12.5	16.2
CHA_2DS_2-Vasc Risk Score, %				
2-3	13.6	11.1	15.7	13.0
4	25.0	22.3	26.9	24.3
5	27.1	27.3	28.1	29.7
6	19.4	21.7	18.7	20.3
7+	14.5	17.4	10.1	12.4

ATRIA Bleeding Risk Score,[‡] %				
Low (0-3)	54.1	60.8	50.7	55.8
Intermediate (4)	3.6	4.6	5.8	6.5
High (5-10)	42.3	34.6	43.6	37.7
Cognitive skills, %				
Mildly impaired	25.4	26.2	26.1	26.5
Moderately to severely impaired	44.4	34.2	39.6	29.4
ADL score (0-16),[§] median (Q1, Q3)	9 (6, 12)	9 (6, 11)	10 (7, 11)	9 (7, 11)

[*]Any Part D claim during the 12-month period
[†]Resident characteristics exclude residents with missing values for fall history, heart failure, hypertension, diabetes, and stroke ($n \leq 10$ for all characteristics with missing values in 2011 and 2016).
[‡]Percentages may not total 100% due to rounding
[§]Higher scores indicate greater limitation in ADLs
Abbreviations: activities of daily living (ADLs), non-steroidal anti-inflammatory drugs (NSAID), selective serotonin reuptake inhibitor (SSRI), angiotensin converting enzyme (ACE), angiotensin receptor blocker (ARB)

Table 2.3 Characteristics of Residents using DOACs or Warfarin, by Time Point				
	December 31, 2011		December 31, 2016	
	Warfarin (n=13,375)	DOAC (n=986)	Warfarin (n=9,320)	DOAC (n=8,734)
Demographics				
Age in years, median (Q1, Q3)	84 (78, 89)	83 (77, 88)	84 (77, 89)	83 (76, 88)
Women, %	71.1	71.6	64.6	67.3
Hospital admissions in prior year, %				
Number of hospitalizations, %				
2-3	38.2	41.0	36.8	39.1
4+	13.9	15.7	12.5	13.8
Ischemic stroke	7.1	10.0	5.9	8.9
Extracranial bleed	5.0	6.5	5.0	4.0
Intracranial hemorrhage	0.4	Sup.	0.5	0.5
Medications				
Unique medications, median (Q1, Q3)	19 (14, 24)	20 (15, 26)	18 (14, 23)	19 (14, 24)
Less than standard anticoagulant dose, %	NA	36.0	NA	50.0
Select medications, * %				
NSAID	15.6	17.9	15.1	18.7
Antiplatelet	9.2	13.8	7.5	9.7
Statin	50.7	54.0	60.2	61.1
SSRI	55.5	62.0	51.0	53.1
ACE inhibitor or ARB	53.7	57.6	48.8	51.6
Select Comorbidities,† %				
Diabetes	41.0	41.3	41.8	41.9
Heart failure	49.0	45.0	50.3	45.7
Hypertension	84.2	85.5	87.4	88.1
Coronary artery disease	31.2	30.8	30.0	28.5
Anemia	32.4	32.5	33.9	32.5
Fall since NH admission/last assessment	18.6	20.5	17.6	18.6
Stroke	24.2	26.8	15.7	16.7
CHA_2DS_2-Vasc Risk Score, %				
2-3	11.2	12.6	12.7	13.9
4	22.6	19.5	23.8	24.8
5	27.3	27.0	30.2	29.9
6	21.7	22.4	20.9	19.7
7+	17.3	18.6	12.4	12.5
ATRIA Bleeding Risk Score, %				
Low (0-3)	60.6	62.6	54.1	57.6

Intermediate (4)	4.6	5.4	6.3	6.6
High (5-10)	34.8	32.0	39.6	35.8
Cognitive skills, %				
Mildly impaired	26.0	28.3	25.9	27.1
Moderately to severely impaired	34.3	33.7	28.7	30.1
ADL score (0-16),[‡] median (Q1, Q3)	9 (6, 11)	9 (6, 11)	9 (7, 11)	9 (7, 11)

[*]Any Part D claim during the 12-month period
[†]Resident characteristics exclude residents with missing values for fall history, heart failure, hypertension, diabetes, and stroke ($n \leq 10$ for all characteristics with missing values in 2011 and 2016).
[‡]Higher scores indicate greater limitation in ADLs
Abbreviations: activities of daily living (ADLs), non-steroidal anti-inflammatory drugs (NSAID), selective serotonin reuptake inhibitor (SSRI), angiotensin converting enzyme (ACE), angiotensin receptor blocker (ARB), suppressed (Sup.)

Table 2.4 Percentage of Treated Residents by Anticoagulant Class and Medication

	H1-2011	H2-2011	H1-2012	H2-2012	H1-2013	H2-2013	H1-2014	H2-2014	H1-2015	H2-2015	H1-2016	H2-2016
N, total	17,895	33,959	33,493	33,956	35,709	37,118	36,183	36,379	36,807	37,644	37,474	37,787
Treated, * %	42.4	42.3	43.1	42.8	42.7	42.8	43.7	44.3	44.8	45.5	47.0	47.8
Warf., %	40.5	39.4	39.4	38.4	37.0	35.2	33.6	31.8	30.6	29.0	27.3	24.7
DOAC, %	1.9	2.9	3.7	4.3	5.6	7.7	10.2	12.5	14.2	16.5	19.7	23.1
Dab.,†	1.9	2.9	3.3	3.1	2.7	2.6	2.7	2.6	Sup.	Sup.	Sup.	2.2
Riv.,	0.0	0.0	0.4	1.2	2.9	4.6	6.2	7.1	7.1	7.3	7.8	8.3
Apix.,	0.0	0.0	0.0	0.0	0.1	0.5	1.3	2.8	4.7	7.0	9.8	12.6
Edox.,†	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	Sup.	Sup.	Sup.	0.1

*Treated percentage may not equal the sum of warfarin and DOAC percentages due to rounding
†Cell values suppressed to prevent any individual cell size from being <11
Abbreviations: half (H), dab. (dabigatran), riv (rivaroxaban), apix (apixaban), edox (edoxaban), warf (warfarin), DOAC (direct-acting oral anticoagulant)

Table 2.5 Percentage of Nursing Home Residents with Atrial Fibrillation Treated with Oral Anticoagulants by Cognitive Status and Functioning in ADLs				
	December 31, 2011		December 31, 2016	
	Cognitively Intact or Mild Impairment	Moderate or Severe Cognitive Impairment	Cognitively Intact or Mild Impairment	Moderate or Severe Cognitive Impairment
n	20,338	13,621	24,660	13,127
Treated, (%)	46.4	36.1	51.7	40.4
ADL Score 0 to 4,* n	4,275	772	4,076	677
Treated, %	46.9	33.0	51.7	40.9
ADL Score 5 to 8,* n	6,401	2,470	7,714	2,349
Treated, %	45.5	35.7	51.5	43.1
ADL Score 9 to 12,* n	8,195	5,953	11,501	6,850
Treated, %	47.1	37.0	52.3	40.3
ADL Score 13 to 16,* n	1,467	4,426	1,369	3,251
Treated, %	45.5	35.7	48.1	38.7

*Higher scores indicate greater limitation in ADLs
Abbreviations: activities of daily living (ADLs)

Table 2.6 Anticoagulant Use by Renal Function among Nursing Home Residents with Atrial Fibrillation

	No Diagnosis of Renal Insufficiency	Chronic Renal Insufficiency*	End Stage Renal Disease†	On Dialysis‡
December 31, 2016				
n	18,606	10,956	7,014	1,211
Treated, (%)	47.8	48.5	47.1	44.2
Warfarin, (%)	24.0	24.2	25.8	33.1
Low dose DOAC, (%)	10.5	12.9	12.8	7.7
Standard dose DOAC, (%)	13.4	11.4	8.4	3.4
December 31, 2011				
n	19,319	9,116	4,713	811
Treated, (%)	43.1	42.8	38.5	39.7
Warfarin, (%)	40.0	39.8	36.1	39.7
Low dose DOAC, (%)	0.8	1.4	1.3	0.0
Standard dose DOAC, (%)	2.2	1.6	1.1	0.0

*Identified from inpatient diagnoses. Corresponds to an estimated glomerular filtration rate <60 ml/min. Residents with evidence of more severe disease (end stage renal disease or on dialysis) were assigned to the more severe category.
†Identified from the most recent MDS 3.0 assessment (item I1500: end stage renal disease). Residents with evidence of more severe disease (on dialysis) were assigned to the more severe category.
‡Identified from the most recent MDS 3.0 assessment (item O0100J2) which indicates whether the resident has received dialysis within the last 14 days while a resident of the nursing facility.
Abbreviations: direct-acting oral anticoagulant (DOAC)

Table 2.7 Percentage of Residents Treated with Oral Anticoagulants by Race/Ethnicity						
Time Period	**Overall**	**White**	**Black**	**Hispanic**	**API**	**Other/ Unknown**
First half 2011						
n	17,895	15,404	1,421	688	257	125
Treated, %	42.4	42.6	41.5	42.4	32.7	43.5
Second half 2011						
n	33,959	29,268	2,623	1,316	530	222
Treated, %	42.3	42.8	40.3	39.7	31.7	39.9
First half 2012						
n	33,493	28,766	2,690	1,297	507	233
Treated, %	43.1	43.4	43.1	40.2	35.7	44.6
Second half 2012						
n	33,956	29,062	2,724	1,357	554	269
Treated, %	42.8	43.2	42.0	39.9	32.9	37.8
First half 2013*						
n	35,709	30,532	2,836	1,371	571	283
Treated, %	42.7	43.2	40.6	40.8	31.4	40.7
Second half 2013*						
n	37,118	31,524	2,926	1,454	590	300
Treated, %	42.8	43.5	40.9	39.1	29.3	39.0
First half 2014						
n	36,183	30,808	3,041	1,425	587	322
Treated, %	43.7	44.4	42.3	39.4	30.7	41.3
Second half 2014						
n	36,379	31,013	3,035	1,407	585	339
Treated, %	44.3	44.8	43.0	40.9	32.3	41.3
First half 2015						
n	36,807	31,490	3,071	1,354	560	332
Treated, %	44.8	45.3	43.8	42.5	31.6	43.7
Second half 2015						
n	37,644	32,222	3,068	1,410	595	349
Treated, %	45.5	46.0	43.8	43.0	33.8	43.8
First half 2016						
n	37,474	31,801	3,228	1,489	601	355

Treated, %	47.0	47.4	47.7	42.9	37.6	43.7
Second half 2016						
n	37,787	31,985	3,255	1,578	608	361
Treated, %	47.8	48.3	46.5	42.3	36.7	54.3
*Race/ethnicity missing for 116 residents in the first half of 2013 and 324 residents in the second half of 2013 Abbreviations: Asian or Pacific Islander (API);						

CHAPTER III

GEOGRAPHIC VARIATION IN ANTICOAUGLANT USE AND RESIDENT, FACILITY, AND COUNTY CHARACTERISTICS ASSOCIATED WITH TREATMENT AMONG UNITED STATES NURSING HOME RESIDENTS

Abstract

Background

Anticoagulation decisions for older adults with atrial fibrillation residing in nursing homes are complicated by the presence of both vascular and bleeding risk factors. Our objective was to quantify geographic variation in anticoagulant use and explore what resident, facility, and county characteristics were associated with anticoagulant use in a clinically complex population.

Methods

Long-stay nursing home residents (≥65 years) with a diagnosis of atrial fibrillation and ≥6 months of Medicare fee-for-service enrollment preceding the point prevalence date were eligible. Medicare Parts A and D were linked to the Minimum Data Set 3.0, facility level files, and the Area Health Resources File. The point prevalence of oral anticoagulant use was estimated on December 31st 2014, 2015, and 2016 using a repeated cross-sectional design with a 12-month lookback period. Multilevel logistic models evaluated the extent to which variation in anticoagulant use between counties could be explained by resident, facility, and county characteristics, and state of residence. Proportional changes in cluster variation (PCV), intraclass correlation coefficients (ICC), and adjusted odds ratios (aOR) were calculated.

Results

Among 89,176 eligible nursing home residents from 12,159 facilities and 1,722 counties, 70.6% was ≥ 80 years, 50% had renal impairment, 63% had cognitive impairment, and 20% had a recent fall. Forty-five percent used oral anticoagulants, with odds of using oral

anticoagulants 20% higher in 2016 than 2014 (aOR: 1.21; 95% confidence interval: 1.17 – 1.25). Most states were composed of counties in the highest (48% to 58%) and lowest (31% to 41%) quintiles of anticoagulant use. Compared with the null model, adjustment for resident characteristics increased variation between counties (PCV: -24.4%). The full model explained 38.4% of the between-county variation. Within county correlation was a small proportion (ICC≤2.3%) of total variation in all models.

Conclusion

Adjustment for resident characteristics, including clinical risk factors that typically drive treatment decisions, did not explain and instead increased the variation in anticoagulant use between counties. Comparative evidence and refinement of predictive algorithms specific to the nursing home setting may be warranted to guide residents, family, and providers making difficult decisions regarding the use of anticoagulants.

Introduction

Anticoagulation is highly effective for ischemic stroke prevention for individuals with atrial fibrillation,[25] yet fewer than one in three nursing home residents with atrial fibrillation were treated with oral anticoagulants (i.e., warfarin) during the early 2000s.[49,51] The use of oral anticoagulants among nursing home residents with atrial fibrillation has since increased substantially, with nearly one-half of residents receiving treatment as of the end of 2016.[99] Circumstances likely contributing to this increase during the intervening period included broad-based quality improvement efforts in the United States healthcare system[100] (and targeting nursing homes specifically[99]), the release of trial results specific to an older adult population which convincingly demonstrated real-world safety and effectiveness of anticoagulation with warfarin,[59] and the availability of four direct acting oral anticoagulants (DOACs) which have expanded therapeutic options for patients and providers.

Despite a nearly 20% increase in anticoagulant use,[99] the fraction of nursing home residents with atrial fibrillation receiving anticoagulants remains lower than in community dwelling Medicare population.[44] This difference may be appropriate in light of limited life expectancy[75] and other factors that may alter patient and clinician judgements of the net benefit of treatment. Anticoagulation decisions for older adults with atrial fibrillation, particularly those residing in nursing homes, are complicated by the presence of both vascular and bleeding risk factors.[100] Shared-decision making, as is recommended by current practice guidelines,[24] is challenging for this population with a high burden of cognitive impairment[17,100] and for whom there is a dearth of evidence on

the absolute risk of ischemic stroke and bleeding (and the consequences of each outcome) under alternative treatment scenarios.

Recognizing the limited availability of evidence to guide anticoagulation decisions for older nursing home residents with atrial fibrillation, our objective was to explore what resident, facility, and county characteristics were associated with anticoagulant use for this clinically complex and vulnerable population. Fundamental to this objective is the goal of identifying sociodemographic, clinical, and health system factors that may be amenable to clinical and health policy interventions. Considering that absolute differences on clinical risk scores[81-83] predicting ischemic stroke and bleeding risk are small between treated and untreated residents,[99] we hypothesized that in addition to risk factors included in summary scores, multiple other sociodemographic (e.g., age, Medicaid enrollment), clinical (e.g., medication use), and functional characteristics of residents would be associated with anticoagulant use. Furthermore, because of the large role for patient preference and clinician judgement in current clinical practice for this population, we expected to observe concordance in treatment patterns within local areas (i.e., counties) with shared personal values and healthcare providers.

Data

Medicare beneficiary enrollment and vital status (Master Beneficiary Summary File), hospital and skilled nursing facility utilization (Medicare Part A), medication dispensing records (Medicare Part D), and nursing home assessments (Minimum Data Set (MDS) 3.0) were accessed through a data use agreement with the Centers for Medicare and Medicaid Services. The MDS 3.0 is a mandatory assessment performed at regular

intervals in Medicare/Medicaid certified nursing homes and the data collected using the MDS 3.0 has been previously validated.[67] Facility characteristics were obtained from the Nursing Home Compare and the Certification and Survey Provider Enhanced Reporting (CASPER) files. Sociodemographic and health resources at the county level were linked from the Area Health Resources File. The University of Massachusetts Medical School Institutional Review Board approved this study (H00015376).

Study Design

The point prevalence of oral anticoagulant use was estimated on December 31st 2014, 2015, and 2016 using a repeated cross-sectional design with a 12-month lookback period.

Study Population

Long-stay nursing home residents (≥65 years of age) with a diagnosis of atrial fibrillation and at least 6 months of Medicare fee-for-service enrollment preceding the point prevalence date were eligible. At least one diagnosis of atrial fibrillation[102] on a Medicare Part A claim and one diagnosis of atrial fibrillation, atrial flutter, or dysrhythmia on an MDS 3.0 assessment were required. For residents eligible at multiple point prevalence dates, a single cross-section was selected at random. Residents in a coma and those without a Part D claim in the 12-month lookback period were excluded. Residents on hospice, in a hospital, or in a skilled nursing facility on the point prevalence date were excluded because medications are not reimbursed by Medicare Part D in these settings. Counties with fewer than 11 residents (1,499 of 3,221 counties) were excluded, which excluded 5,772 (6.4%) of 94,948 eligible residents.

Anticoagulant Use

Current use of an oral anticoagulant (apixaban, dabigatran, edoxaban, rivaroxaban, warfarin) was measured on the point prevalence date as the number of residents with medication on hand divided by the number of residents in the eligible population. Using dispensing dates and number of days supply, exposure status was recorded for each day of the cross-section while accounting for early medication fills, hospitalizations, and skilled nursing facility stays.

Resident Characteristics

Characteristics of the resident population were summarized from Medicare claims from the 12 months preceding the point prevalence date and from information on the most recent MDS 3.0 assessment. These included sociodemographic characteristics (age, sex, race/ethnicity, marital status, dual Medicare-Medicaid enrollment), number of hospital admissions, hospitalizations for certain conditions identified using diagnoses on Part A claims (ischemic stroke,[79] extracranial bleeding,[80] intracranial hemorrhage,[80] myocardial infarction,[103] venous thromboembolism,[104] or transient ischemic attack), CHA_2DS_2-Vasc ischemic stroke risk score and its components,[81] ATRIA bleeding risk score and its components,[82] other conditions associated with risk or perceived risk of bleeding (fall history,[41,51] renal impairment[83,84]), total unique medications used (a proxy for polypharmacy), specific medication classes associated with stroke and/or bleeding risk (angiotensin converting enzyme inhibitors/angiotensin receptor blockers,[105] non-steroidal anti-inflammatory drugs,[106] antiplatelets,[107] selective serotonin reuptake

inhibitors,[85,86] statins[108]), functional status (activities of daily living score),[87] and cognitive impairment (the MDS 3.0 Cognitive Function Scale).[74]

Facility Characteristics

Nursing home facility characteristics were conceptually classified as either structural, resource, staffing, or quality of care. Structural characteristics included size (number of beds) and specialized service availability for on-site residents (specialized rehabilitation, pharmacy, laboratory, hospice). Larger facilities and those with rehabilitation services were expected to be associated with a larger volume of residents with atrial fibrillation, potentially developing internal expertise or attracting external expertise into the nursing home, while availability of laboratory services may make it easier to monitor therapy.

Characteristics representing resources available to the facility included occupancy, for-profit status, and status as an individual or corporate entity. Not-for-profit facilities[109] and those with greater resources have traditionally achieved better care quality.[110] Facilities with greater resources, and those with multisite facilities, may be more predisposed to having programs (e.g., quality improvement), infrastructure (e.g., clinical decision support) and protocols in place that are associated with guideline adherence. Higher staffing has also been found to be positively associated with quality of care.[111] Staffing was operationalized as quartiles of the minutes per resident-day of care from nurses and nursing assistants (i.e., all nursing care), registered nurses (RN), all prescribers (medical director, other physicians, physician extenders), medical directors, and pharmacists. Quartiles of the fraction of prescriber minutes per day contributed by

physician extenders was also included to evaluate if prescriber type was associated with prescribing decisions. Quality of care in the facility was operationalized using the overall 5-star nursing home compare rating, which has been found to be associated with medication safety.[112]

County Characteristics

Wide regional variation exists within the United States in adherence to guideline recommendations for primary and secondary prevention for atherothrombosis.[113] To understand the contribution of county-level factors to variation in anticoagulant use in the nursing home setting, we considered socioeconomic factors, health system supply factors, and cerebrovascular risk. Counties were grouped using the 2013 Rural/Urban Continuum Codes[114] as either metropolitan, urban and metropolitan adjacent, urban and not metropolitan adjacent, rural and metropolitan adjacent, and rural not metropolitan adjacent. Sociodemographic factors categorized as quartiles included the proportion of the older adult ($\geq$65 years) population on Medicaid and the proportion of older adults in deep poverty, the proportion of the Medicare eligible residents enrolled in Part D, the proportion of the overall population that was white, without a high-school education, and the proportion of single parents. Other socioeconomic factors included whether the county was classified as experiencing population loss and persistent poverty.

On the health system supply side, quartiles of the ratio of total physicians to the county population, the fraction of total physicians in primary care, and the ratio of cardiologists and neurologists to the population were considered because provider type has been found to be an important determinant of anticoagulation decisions for patients with atrial

fibrillation.[76,77] Because geriatricians are accustomed to the management of nursing home residents, the presence of ≥1 hospital with a geriatric service was also included as a potential predictor (community based supply was not available). The presence of at least one hospital with a medical school was included as a potential facilitator of the dissemination of best practices and new technologies, while quartiles of the ratio of hospitals to land area (square miles) was included as an indicator of access to tertiary care. Finally, cerebrovascular risk was operationalized as the number of deaths from cerebrovascular disease per resident in the population.

Geographic Variation

Variation in prescribing quality for Medicare beneficiaries has been documented across healthcare markets and states,[115] and variation in prescribing of opioids has been observed in the nursing home population.[117] To examine within and between state variation in prescribing of oral anticoagulants, we grouped residents into counties and states. We chose to use counties as the healthcare market to incorporate county-level characteristics describing local health system supply factors and sociodemographic information. Furthermore, because counties do not cross state lines, differences in state policies can be largely excluded as a potential source of variability in prescribing observed between counties within states. We also evaluated interstate variation because of the concentration of Medicare Part D plans within states, and the variability in features between plans.[117]

Statistical Analysis

Descriptive statistics first summarized the study population by anticoagulation status for resident, facility, and county level characteristics. Medians with first and third quartiles were calculated for continuous variables and frequencies with percentages were calculated for categorical variables.

Statistical tests were performed to test whether two level (versus one level) and three level (versus two level) variance components models were better fits for the data. Then, to evaluate the extent to which variation in anticoagulant use between counties could be explained by resident characteristics, facility characteristics, county characteristics, and state, we fit five multilevel logistic models: 1) an intercept only model with random intercepts of counties (null model), 2) resident characteristics only, 3) adding facility characteristics, 4) county characteristics, and 5) adding random intercepts for states. Time (year) was included in all models as a fixed effect. To compare county's observed prevalence of anticoagulant use with the prevalence that would be expected based the composition of its resident population (i.e., observed versus predited), we also fit a single level logistic model with only resident characteristics and time.

The proportional change in cluster variation (PVC)[118] was estimated across multilevel models to characterize the between-county variation attributable to the explanatory factors included in each model. Intraclass correlation coefficients (ICCs) were also calculated to quantify the magnitude of correlation between residents within counties (all models) and within states across counties (for the model with random intercepts for states).[118,119] To examine associations between specific resident, facility,

and county characteristics, adjusted odds ratios (aOR) and 95% confidence intervals (CI) were estimated from the full model with random intercepts for states.

Results

During the 2014, 2015, and 2016 cross-sections, 45% of the 89,176 long-stay nursing home residents diagnosed with atrial fibrillation were using oral anticoagulants. Residents were included from 12,159 facilities located in 1,722 counties (number of residents in median county: 27, Q1 17, Q3 50). More than two-thirds (70.6%) of the population was older than 80 years, 67.3% were women, and 79.3% were dual Medicare-Medicaid enrollees. Half of residents had renal impairment, 62.6% had at least mild cognitive impairment, and 20.0% had a recent fall. The median facility size was 108 beds and the median facility occupancy was 86.7%. Physician extenders contributed 26.1% of the prescriber minutes at the median facility (Q1 0.0, Q3 58.8). Most facilities were for-profit (74.1%) and most were part of a chain (62.0%). Most counties were metropolitan (50.9%) or urban (44.8%). The median county had a ratio of 13.2 physicians, 0.2 cardiologists, and 0.1 neurologists per 10,000 persons. The median county experienced 52.7 cerebrovascular deaths per 10,000 persons per year.

Resident, facility, and county characteristics of treated and untreated residents are presented in Table 3.1. Among treated residents, 9.1% had been hospitalized for an ischemic stroke and 5.4% for an extracranial bleed in the prior year, compared with 5.9% and 8.2% of untreated residents. The proportion of treated and untreated residents with CHA_2DS_2-Vasc scores $\geq$6 was 37.4% and 32.0%, while the proportion with ATRIA

scores indicating high bleeding risk were 37.4% and 43.0%, respectively. Cognitive impairment was present among 57.2% of treated and 67.0% of untreated residents.

The unadjusted estimates of anticoagulant use plotted by county (Figure 3.1.a.) convey variation between counties within states, between states, and across regions. There was a nearly twofold difference between the county with the lowest proportion of residents anticoagulated (McLennan, Texas: 31.6%) and the county with the highest proportion treated (Pottawattamie, Iowa: 58.3%). Most states were composed of counties in the highest (48.1% to 58.3%) and lowest (31.6% to 42.0%) quintiles of anticoagulant use, and it was common to observe adjacent counties in the lowest and highest quintiles. Regionally, rural counties with an insufficient number of residents for inclusion were concentrated in the mountain west and south. In Figure 3.1.b., predicted values for the proportion of treated residents in each county based on resident characteristics (without county intercepts) were plotted. When compared with values in Figure 3.1.a., these population average estimates suggest that clusters of counties in certain regions (e.g., the Northeast) appear to have higher treated fractions than would be expected based solely on the characteristics of their residents, while for other regions the inverse may apply (e.g., the Pacific Northwest).

The adjusted odds ratios for several resident characteristics underscore the relative importance of clinical factors for prescribing decisions relative to facility and county contextual effects (Table 3.2). Compared with residents younger than 80 years, those $\geq$90 had 40% lower odds of receiving anticoagulation. Recent hospitalization for intracranial hemorrhage (aOR: 0.28; 95% CI: 0.24-0.33), extracranial bleeding (aOR 0.62; 95% CI:

0.58-0.66), severe cognitive impairment (aOR: 0.45; 95% CI : 0.42-0.48), and antiplatelet use (aOR: 0.32; 95% CI: 0.30-0.33) each exhibited large negative associations with treatment. The associations of facility and county characteristics were modest with aORs in the range of 0.92 to 1.17. Non-profit facilities, rural counties, and the highest quartile of Medicare Part D plan participation were each associated with increased odds of anticoagulant use of 12% to 17%. The odds of using oral anticoagulants was 20% higher in 2016 compared with 2014.

Compared with the null model with only random intercepts for counties, resident characteristics (PCV: -24.4%) and resident plus facility characteristics (PCV: -12.4%) increased the variation between counties (Table 3.3). The model with resident, facility, and county characteristics explained 13.2% of the between-county variation (versus the null model) and the model with resident characteristics, facility characteristics, county characteristics and random state intercepts explained 38.4% of the between-county variation. Within county correlation was weak in each of the models with only county random intercepts (ICC_{county}: 0.016 to 0.023). In the fully adjusted model with random county and state intercepts the probability of prevalent oral anticoagulant use was more closely correlated for two residents in the same county (ICC_{county}: 0.011) than for two residents in different counties within the same state (ICC_{state}: 0.006).

Discussion

In this large national study of United States nursing home residents with atrial fibrillation, we found that much of the variation in prevalent oral anticoagulant use stemmed from resident level factors, rather than contextual factors. Several clinical risk

factors for ischemic stroke and bleeding outcomes were strongly associated with treatment. As hypothesized, we observed correlation within counties. The proportion of residents using oral anticoagulants was 48-58% in the top quintile of counties and 32-42% in the bottom quintile of counties. Providers in different areas were less similar in their prescribing practices after accounting for individual residents' factors. When facility and county characteristics were introduced into the model, the increase in between-county variation from the addition of resident characteristics was fully offset. In the context of clinically significant variation of 24% between the highest and lowest counties, the magnitude of variation between individuals was sufficiently large for this seemingly large county level variation to represent less than two percent of the total. We postulate that this highly individualized treatment paradigm is both a manifestation of provider uncertainty stemming from inadequate evidence to standardize clinical practice and, perhaps to a lesser extent, an encouraging signal of a resident-centered process of shared decision-making.

The clinical guideline from the American Heart Association, the Heart Rhythm Society, and the American College of Cardiology recommends anticoagulation for patients with atrial fibrillation and a CHA_2DS_2-Vasc risk score of at least two on the basis of Level A evidence.[24] Despite a clear recommendation for the use of anticoagulants, many individuals do not receive treatment, even among less medically complex community dwelling populations.[40,44] The prevalence of anticoagulant use has been estimated to be 70% among older adults enrolled in Medicare Supplemental coverage,[44] more than 20% higher than in our population. It is reasonable to expect that the

prevalence of anticoagulant use in nursing homes should be lower than in the community because of differences between these populations. However, resident, family, and provider perceptions of the role for resident factors such as advanced age and cognitive impairment, which we found to be strongly associated with anticoagulant use, has not been well established.

More than 60% of the nursing home population with atrial fibrillation had cognitive impairment, and only two percent were fully independent in performance of activities of daily living. Residents with cognitive impairment were substantially less likely to receive anticoagulants, consistent with prior nursing home literature.[52,90] Intuitively, the benefit of stroke prevention diminishes with declining function because of floor effects with a lower baseline, limiting the potential for further loss of function in the event of a stroke. Yet the large variability in prevalent use of anticoagulants for individuals and geographically suggests that the wealth of information on clinical conditions, medications used, cognitive impairment, and physical functioning available to providers in the nursing home setting may not be used in a systematic manner. While variation introduced through a resident-centered shared decision-making process is appropriate,[24] predictive information on the absolute probability and functional consequences of ischemic stroke and major bleeding events under alternative treatment scenarios is necessary, and presently unavailable, to inform such a process.

Facility characteristics explained approximately one-tenth of the variation in anticoagulant use between counties, after accounting for resident characteristics. The odds of anticoagulant use was lowest in government owned facilities and highest in non-

profit owned facilities, regardless of whether the non-profit was a chain. During our study period, two-thirds of Medicare eligible Veterans Affairs beneficiaries with atrial fibrillation were receiving anticoagulation,[120] which suggests substantially lower anticoagulant use in Veterans Affairs nursing facilities compared with the general Veterans Affairs population and may also reflect incomplete capture of anticoagulant use in Veterans Affairs nursing homes by Medicare Part D claims. Overall nursing home quality was modestly associated with a higher prevalence of anticoagulant use. Prescribing quality, as measured by rates of medication errors and serious medication errors, has been found to be correlated with the overall nursing home quality ratings.[112] Nursing home staffing was not associated anticoagulant prescribing, although detailed information on the frequency and type of provider-patient interactions is not available in the CASPER and Nursing Home Compare files. Contextual variables describing the supply of cardiology, neurology, and geriatrics at the county level were evaluated because of earlier findings of variability in prescribing patterns by provider type.[76,77] Although no strong associations were found, further investigation is needed to understand resident access to specialist providers in the nursing home setting.

Several sociodemographic factors were associated with anticoagulant use. Residents who were currently married, a form of social support and connectivity associated with more aggressive care at the end of life,[121] had slightly higher odds of anticoagulant use. The positive association of county level Medicare Part D participation with anticoagulant use may also be a product of better social support structures and health literacy in counties with greater uptake of the Part D benefit, as the complexity of the

program has been cited as a potential contributor to lower enrollment among several subgroups including those with low income, low educational attainment, and those of Hispanic ethnicity.[122,123] Variation in anticoagulant use was observed between individuals of different races/ethnicities and between counties with varying racial/ethnic composition. Compared with black/African American residents (among whom anticoagulant use was highest), Hispanic residents and Asian/Pacific Islanders were less likely to use anticoagulants. Counties with the highest proportion of white residents had 18% higher odds of anticoagulant use, consistent with earlier findings of better processes and outcomes in nursing homes with higher proportions of white residents[119] and better quality of care in nursing homes located in neighborhoods with fewer minority residents.[32]

This study used a repeated cross-sectional design and applied multilevel modeling to explore geographic variation in anticoagulant use and variation associated with specific factors. This study builds on earlier work demonstrating an increase in anticoagulant use during 2014-2016,[99] and confirms that this increase cannot be explained by changes in observed resident characteristics. The present study has limitations. Medication use was operationalized using information from Medicare Part D claims, which may not represent actual medication use. However, in the nursing home setting, adherence is typically not of concern as administration of medications are overseen by medical personnel. Over the counter medications including aspirin are typically not recorded in Part D. The results should not be generalized to sparsely populated rural areas (counties in white in Figure 3.1) because counties with fewer than

11 eligible residents during 2014-2016 were excluded. Finally, although we studied a large set of important resident, facility, and county factors, it is likely that other individual (e.g., number and proximity of children) and provider/facility (e.g., availability of specialist providers, targeted clinical programs and protocols) factors influence medication use.

Conclusion

Variation in anticoagulant use between counties among nursing home residents with atrial fibrillation ranged from a minimum of 32% to a maximum of 58%. Adjustment for resident characteristics, including clinical risk factors for ischemic stroke and major bleeding that typically drive treatment decisions, did not explain and instead increased the variation in prescribing between counties. Correlation in anticoagulant use within counties and states was small as a proportion of total variation. Comparative evidence and refinement of predictive algorithms specific to the nursing home setting may be warranted to inform residents, family, and providers making difficult decisions regarding the use of anticoagulants for atrial fibrillation.

Table 3.1. Characteristics of Residents Treated or Not Treated with an Anticoagulant, 2014 to 2016		
	Treated (n=40,126)	Untreated (n=49,050)
Demographics		
Age in years, median (Q1, Q3)	84 (77, 89)	86 (79, 91)
Women, %	67.2	67.4
Married, %	21.6	19.9
Medicaid eligible, %	79.0	78.7
Race/ethnicity, %		
White	88.0	86.4
Black	8.4	8.8
Hispanic	1.3	1.7
Asian/Pacific Islander	1.1	1.8
Other/Unknown	1.2	1.3
Time since first observed nursing home admission, median (Q1, Q3)	821 (330, 1471)	822 (330, 1463)
Hospital admissions in prior year, %		
1	46.7	48.9
2-3	37.2	36.0
4+	13.1	12.1
Ischemic stroke	9.1	5.9
Transient ischemic attack	1.7	1.2
Extracranial bleed	5.5	8.3
Intracranial hemorrhage	0.6	1.6
Venous thromboembolism	4.0	1.6
Acute myocardial infarction	3.6	4.6
Unique medications, median (Q1, Q3)	19 (14, 24)	16 (12, 22)
Select prescription medications,* %		
Nonsteroidal anti-inflammatory drug	16.1	17.5
Antiplatelet	8.5	19.1
Statin	59.7	50.0
Selective serotonin reuptake inhinitor	52.4	49.8
Angiotensin converting enzyme inhibitor or Angiotensin II receptor blocker	51.4	46.9
Select comorbidities, %		
Diabetes mellitus		35.2
Heart failure	48.1	41.4
Hypertension	87.6	85.7
Coronary artery disease	30.9	32.5
Peripheral vascular disease	15.4	13.4
Anemia	33.7	38.7

Fall history		
Fall with fracture in six months before last admission	1.1	1.1
Fall since admission	18.2	21.5
Hip fracture	2.5	2.9
Stroke	18.4	14.7
Aphasia	4.9	3.9
Hemiplegia	12.5	7.9
Renal impairment		
Chronic renal insufficiency	31.0	30.2
End-stage renal disease	16.1	16.7
Dialysis	3.0	3.3
CHA_2DS_2-Vasc Risk Score, %		
2-3	11.8	14.7
4	22.4	25.6
5	28.2	27.5
6+	37.6	32.2
ATRIA Bleeding Risk Score, %		
Low (0-3)	55.4	50.0
Intermediate (4)	7.0	6.8
High (5-10)	37.6	43.2
Level of cognitive impairment, %		
Mildly impaired	26.8	26.1
Moderately to severely impaired	30.4	41.0
Activities of daily living score (0-16), median (Q1, Q3)	9 (7, 11)	10 (7, 11)
Facility characteristics		
Number of beds, median (Q1, Q3)	120 (95, 161)	120 (97, 161)
Occupancy (percentage of beds), median (Q1, Q3)	88.4 (79.9, 94.0)	88.6 (80.0, 94.0)
Non government chain, %	76.4	76.4
For profit ownership, %	70.2	71.6
Nursing home compare overall rating, %		
1-2	33.6	34.4
3	19.7	19.5
4-5	46.7	46.1
Clinical lab available, %	81.2	81.3
Medical director, %	89.7	90.2
Physician and extender minutes/resident/day, median (Q1, Q3)	2.4 (0.9, 4.7)	2.5 (0.94, 4.8)
Percentage of minutes from physician extenders, median (Q1, Q3)	30.0 (0.0, 60.7)	30.6 (0.0, 60.8)

Nursing minutes per resident per day, median (Q1, Q3)	345.1 (303.5, 392.0)	346.5 (303.7, 393.6)
Percentage of minutes from registered nurses, median (Q1, Q3)	11.6 (7.7, 16.4)	11.3 (1.3, 16.0)
Pharmacist minutes per resident per day, median (Q1, Q3)	0.9 (0.0, 1.6)	0.9 (0.0, 1.6)
Hospice beds, %	1.0	1.1
Special rehabilitation services, %	3.0	3.0
County characteristics		
Area sociodemographics		
Proportion of adults ≥65 eligible for Medicaid, median (Q1, Q3)	12.0 (8.8, 16.6)	12.1 (8.8, 16.7)
Proportion of adults ≥25 years of age without high school diploma, median (Q1, Q3)	7.8 (6.2, 10.1	7.9 (6.2, 10.2)
Proportion white race/ethnicity, median (Q1, Q3)	81.2 (68.3, 90.8)	80.0 (66.3, 90.1)
Proportion ≥65 years in deep poverty, median (Q1, Q3)	2.5 (2.1, 3.1)	2.5 (2.1, 3.2)
Single parent households per 10,000 persons, median (Q1, Q3)	405.3 (342.2, 459.4)	407.3 (347.6, 462.2)
Population density (persons per square mile), median (Q1, Q3)	381.2 (103.9, 1,429.6)	405.8 (113.0, 1,433.7)
Urban-rural continuum, %		
Metro area	76.5	77.9
Urban area metro adjacent	15.1	14.3
Urban not adjacent to metro	7.1	6.7
Rural	1.3	1.0
County experiencing population loss, %	5.0	5.1
County experiencing persistent poverty, %	9.3	8.2
Proportion of eligible enrolled in Medicare Part D, median (Q1, Q3)	49.5 (40.3, 56.9)	48.5 (38.8, 55.9)
Area healthcare resources		
Facilities		
Hospitals per 100 square miles, median (Q1, Q3)	0.6 (0.2, 1.7)	0.6 (0.2, 1.8)
At least 1 hospital with geriatric services, %	68.1	69.1
At least 1 medical school affiliated hospital, %	60.9	62.1
Providers		
Physicians per 10,000 persons, median (Q1, Q3)	24.1 (13.8, 37.3)	25.5 (14.1, 37.7)

Cardiologists per 10,000 persons, median (Q1, Q3)	0.6 (0.3, 1.0)	0.6 (0.3, 1.0)
Neurologists per 10,000 persons, median (Q1, Q3)	0.4 (0.2, 0.7)	0.4 (0.2, 0.7)
Primary care as fraction of all physicians, median (Q1, Q3)	30.1 (23.6, 37.9)	29.6 (23.4, 37.2)
Pharmacists per 10,000 persons, median (Q1, Q3)	1.4 (0.8, 2.2)	1.4 (0.9, 2.2)
At least 1 hospice provider, %	83.7	85.1
Health		
Cerebrovascular deaths per 10,000 persons, median (Q1, Q3)	4.4 (3.5, 5.4)	4.4 (3.5, 5.4)
*At least one Part D claim during the year before the point prevalence date		

Table 3.2. Adjusted Odds of Receiving Treatment with an Oral Anticoagulant by Resident, Facility, and County Characteristics	
	Adjusted Odds Ratio
Year	
2014	Reference
2015	1.05 (1.02-1.09)
2016	1.21 (1.17-1.25)
Demographics	
Age in years	
<80 years	Reference
80-84 years	0.98 (0.93-1.02)
85-89 years	0.88 (0.85-0.92)
≥90 years	0.60 (0.59-0.63)
Men	0.99 (0.95-1.04)
Married	1.06 (1.02-1.10)
Medicaid eligible	0.97 (0.93-0.91)
Race/ethnicity	
Black/African American	Reference
Non-Hispanic White	0.95 (0.90-1.00)
Hispanic	0.85 (0.75-0.97)
Asian/Pacific Islander	0.70 (0.61-0.80)
Other/Unknown	0.91 (0.79-1.04)
Time since first observed nursing home admission	
Q1	Reference
Q2	0.94 (0.90-0.98)
Q3	0.92 (0.88-0.96)
Q4	0.92 (0.88-0.96)
Hospital admissions in prior year	
0	Reference
1	0.95 (0.87-1.03)
2	0.90 (0.82-0.98)
3	0.85 (0.77-0.93)
4+	0.78 (0.71-0.85)
Ischemic stroke	1.54 (1.44-1.64)
Transient ischemic attack	1.39 (1.23-1.58)
Extracranial bleed	0.62 (0.58-0.66)
Intracranial hemorrhage	0.28 (0.24-0.33)
Venous thromboembolism	2.88 (2.63-3.16)
Acute myocardial infarction	0.89 (0.82-0.95)
Unique medications (one-unit increase from the mean value)	

Q1	Reference
Q2	1.61 (1.55-1.68)
Q3	2.02 (1.93-2.11)
Q4	2.45 (2.33-2.58)
Select Medications,*	
Nonsteroidal anti-inflammatory drug	0.87 (0.84-0.91)
Antiplatelet	0.32 (0.30-0.33)
Statin	1.42 (1.38-1.47))
Selective serotonin reuptake inhinitor	1.02 (0.99-1.05)
Angiotensin converting enzyme inhibitor or Angiotensin II receptor blocker	1.11 (1.08-1.14)
Select comorbidities,	
Diabetes mellitus	0.97 (0.93-1.02)
Heart failure	1.21 (1.16-1.26)
Hypertension	1.02 (0.97-1.08)
Coronary artery disease	0.88 (0.85-0.92)
Peripheral vascular disease	1.19 (1.14-1.25)
Anemia	0.73 (0.69-0.78)
Fall history	
Fall with fracture in six months before last admission	0.98 (0.85-1.12)
Fall since admission	0.85 (0.82-0.88)
Hip fracture	1.03 (0.94-1.13)
Stroke	1.16 (1.08-1.23)
Aphasia	1.18 (1.09-1.27)
Hemiplegia	1.52 (1.44-1.61)
Renal impairment	0.85 (0.91-0.89)
No renal impairment	Reference
Chronic renal insufficiency	0.95 (0.91-0.98)
End-stage renal disease	0.84 (0.79-0.89)
Dialysis	0.76 (0.69-0.83)
CHA_2DS_2-Vasc Risk Score,† %	
2-3	Reference
4	1.13 (1.08-1.19)
5	1.26 (1.20-1.33)
6	1.36 (1.29-1.44)
7+	1.52 (1.43-1.61)
ATRIA Bleeding Risk Score,† %	
Low (0-3)	Reference
Intermediate (4)	0.77 (0.72-0.81)
High (5-10)	0.71 (0.68-0.73)
Level of cognitive impairment, %	

No impairment	Reference
Mildly impaired	0.88 (0.85-0.91)
Moderately impaired	0.71 (0.69-0.74)
Severely impaired	0.50 (0.47-0.54)
Activities of daily living score	
0-4	Reference
5-8	0.99 (0.94-1.04)
9-12	0.96 (0.91-1.01)
13-16	0.79 (0.74-0.85)
Facility Characteristics	
Number of beds	
Quartile 1	Reference
Quartile 2	0.95 (0.91-0.99)
Quartile 3	0.96 (0.91-1.00)
Quartile 4	0.96 (0.91-1.01)
Occupancy	
Quartile 1	Reference
Quartile 2	1.00 (0.95-1.04)
Quartile 3	1.00 (0.96-1.04)
Quartile 4	1.00 (0.95-1.05)
Ownership	
Government	Reference
For profit, individual/partner entity	1.05 (0.97-1.13)
For profit corporation	1.06 (0.99-1.13)
Non-profit church or other non-corporation	1.12 (1.03-1.22)
Non-profit corporation	1.15 (1.06-1.23)
Nursing home compare overall rating	
1	Reference
2	0.99 (0.94-1.04)
3	1.03 (0.98-1.08)
4	1.04 (0.99-1.10)
5	1.06 (1.01-1.12)
Clinical lab available	1.02 (0.98-1.06)
Medical director	1.02 (0.96-1.08)
Physician and extender minutes/resident/day	
Quartile 1	Reference
Quartile 2	0.97 (0.93-1.02)
Quartile 3	1.00 (0.94-1.05)
Quartile 4	0.96 (0.90-1.01)
Proportion of minutes from physician extenders	
Quartile 1	Reference

Quartile 2	0.98 (0.93-1.04)
Quartile 3	1.01 (0.97-1.06)
Quartile 4	1.00 (0.95-1.05)
Nursing minutes per resident per day	
Quartile 1	Reference
Quartile 2	1.02 (0.98-1.07)
Quartile 3	0.99 (0.95-1.04)
Quartile 4	0.98 (0.94-1.03)
Proportion of minutes from registered nurses	
Quartile 1	Reference
Quartile 2	0.99 (0.95-1.03)
Quartile 3	0.98 (0.93-1.02)
Quartile 4	0.99 (0.95-1.04)
Pharmacist minutes per resident per day	
Quartile 1	Reference
Quartile 2	1.02 (0.97-1.06)
Quartile 3	1.00 (0.96-1.04)
Quartile 4	0.99 (0.95-1.04)
Hospice beds	0.94 (0.81-1.09)
Special rehabilitation services	0.94 (0.86-1.03)
County characteristics	
Area sociodemographics	
Proportion of adults ≥65 eligible for Medicaid	
Quartile 1	Reference
Quartile 2	1.02 (0.96-1.08)
Quartile 3	1.02 (0.95-1.10)
Quartile 4	1.05 (0.96-1.15)
Proportion of adults ≥25 years of age without high school diploma	
Quartile 1	Reference
Quartile 2	1.04 (0.98-1.11)
Quartile 3	1.04 (0.97-1.10)
Quartile 4	1.06 (0.97-1.16)
White race/ethnicity	
Quartile 1	Reference
Quartile 2	1.04 (0.97-1.12)
Quartile 3	1.14 (1.05-1.24)
Quartile 4	1.18 (1.07-1.30)
Proportion of adults ≥65 years of age in deep poverty	
Quartile 1	Reference

Quartile 2	0.97 (0.92-1.03)
Quartile 3	1.00 (0.94-1.06)
Quartile 4	0.96 (0.89-1.02)
Single parent households per 10,000 persons	
Quartile 1	Reference
Quartile 2	1.04 (0.96-1.12)
Quartile 3	1.01 (0.90-1.13)
Quartile 4	1.08 (0.93-1.25)
Population density (persons per square mile)	
Quartile 1	Reference
Quartile 2	0.92 (0.85-0.99)
Quartile 3	0.93 (0.84-1.05)
Quartile 4	0.96 (0.83-1.12)
Urban-rural continuum	
Metro area	Reference
Urban area metro adjacent	1.00 (0.93-1.07)
Urban not adjacent to metro	1.00 (0.92-1.09)
Rural	1.18 (1.00-1.38)
County experiencing population loss	1.10 (1.02-1.19)
County experiencing persistent poverty	0.96 (0.96-1.06)
Proportion of eligible enrolled in Medicare Part D, median	
Quartile 1	Reference
Quartile 2	1.05 (0.99-1.12)
Quartile 3	1.10 (1.03-1.18)
Quartile 4	1.12 (1.04-1.20)
Area healthcare resources	
Facilities	
Hospitals per 100 square miles	
Quartile 1	Reference
Quartile 2	1.07 (1.01-1.13)
Quartile 3	1.13 (1.03-1.23)
Quartile 4	1.10 (0.96-1.25)
At least 1 hospital with geriatric services	0.99 (0.94-1.03)
Hospitals affiliated with a medical school	
One medical school affiliated hospital in the county	0.98 (0.92-1.03)
Two or more medical school affiliated hospitals in the county	1.00 (0.92-1.09)
Providers	
Physicians per 10,000 persons	

Quartile 1	Reference
Quartile 2	0.99 (0.92-1.07))
Quartile 3	1.00 (0.90-1.12)
Quartile 4	1.04 (0.90-1.19)
Primary care as fraction of all physicians	
Quartile 1	Reference
Quartile 2	1.06 (0.97-1.16)
Quartile 3	1.09 (0.97-1.16)
Quartile 4	1.07 (0.95-1.20)
Cardiologists per 10,000 persons	
Quartile 1	Reference
Quartile 2	1.02 (0.95-1.09)
Quartile 3	1.01 (0.93-1.11)
Quartile 4	1.00 (0.90-1.11)
Neurologists per 10,000 persons	
Quartile 1	Reference
Quartile 2	1.01 (0.95-1.07)
Quartile 3	1.00 (0.92-1.08)
Quartile 4	0.95 (0.85-1.07)
Pharmacists per 10,000 persons	
Quartile 1	Reference
Quartile 2	1.02 (0.97-1.08)
Quartile 3	1.02 (0.95-1.09)
Quartile 4	1.03 (0.95-1.12)
At least 1 hospice provider	0.94 (0.88-0.99)
Health	
Cerebrovascular deaths per 10,000 persons	
Quartile 1	Reference
Quartile 2	0.93 (0.87-0.99)
Quartile 3	0.93 (0.87-1.00)
Quartile 4	0.92 (0.85-0.99)
*Individual medication estimates derived from models omitting the number of unique medications. †CHA_2DS_2-Vasc Risk Score and ATRIA Bleeding Risk Score estimates derived from separate models omitting the variables included in the scores	

Table 3.3. The Proportional Change in Between-County Variation in Oral Anticoagulant Use Explained by Resident Characteristics, Facility Characteristics, County Characteristics, and State					
Characteristics Included in Multilevel Model					
	Null Model	**Resident**	**Resident & Facility**	**Resident, Facility, & County**	**Resident, Facility, County, & State**
PCV (%)	Reference	-24.4	-11.8	13.2	38.4
ICC_{County}	0.019	0.023	0.021	0.016	0.011
ICC_{State}	-	-	-	-	0.006

Figure 3.1.a.

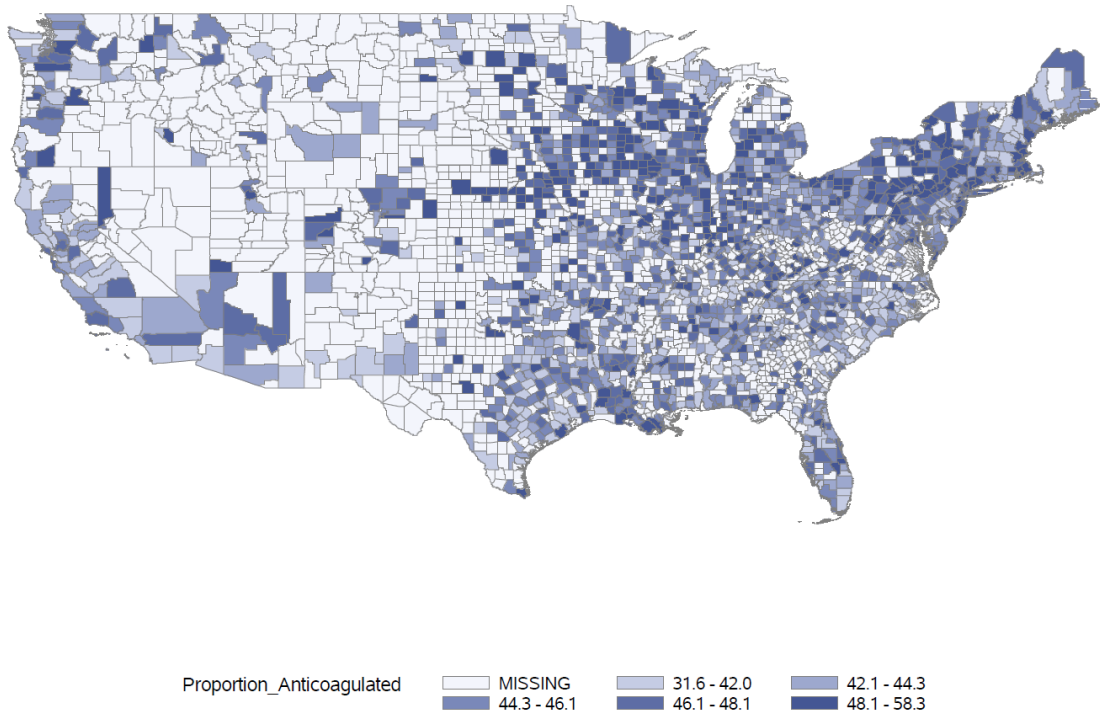

Figure 3.1.b.

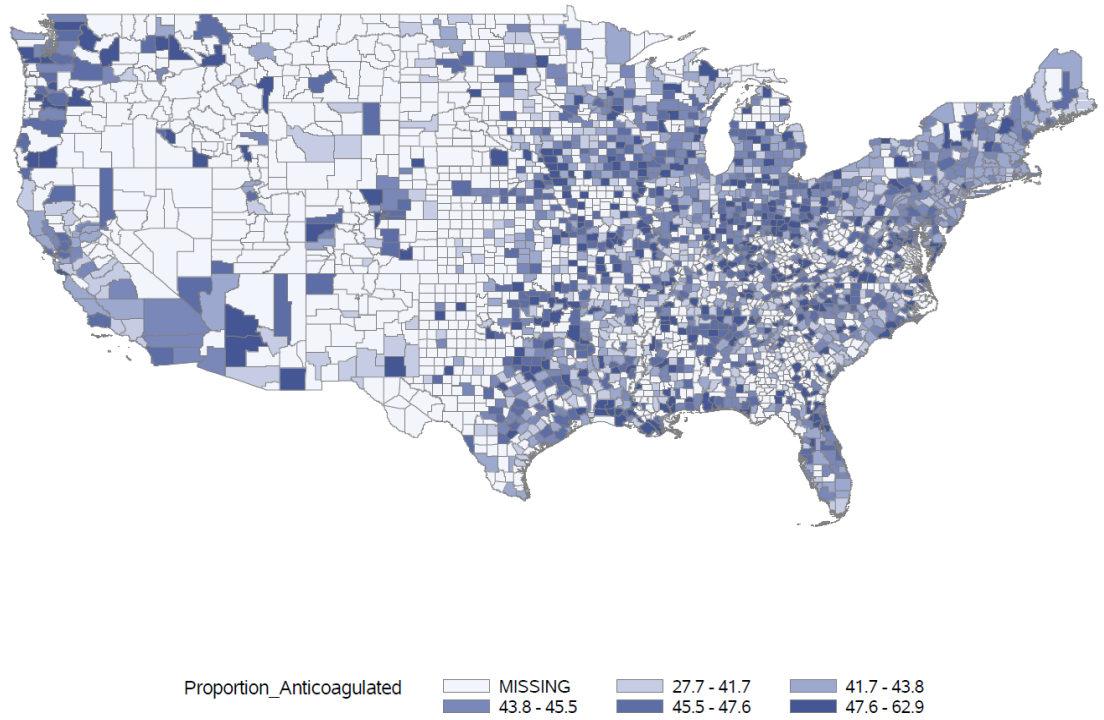

Figure 3.1a. Unadjusted Proportion* Receiving Treatment with Oral Anticoagulants Among Nursing Homes Residents with Atrial Fibrillation in the United States, by County (n=89,176 residents within 12,159 facilities within 1,722 counties in 2014-2016)

Figure 3.1.b. Adjusted Proportion† Receiving Treatment with Oral Anticoagulants Among Nursing Homes Residents with Atrial Fibrillation in the United States, by County (n=89,176 residents within 12,159 facilities within 1,722 counties in 2014-2016)

*Estimated from a null two-level logistic model including a random intercept term for county level variation. Counties with missing values were those with less than 11 residents.

†Estimated from a single-level logistic model adjusted for resident characteristics and time. Counties with missing values were those with less than 11 residents.

CHAPTER IV

DIRECT-ACTING ORAL ANTICOAGULANTS VERSUS WARFARIN FOR NONVALVULAR ATRIAL FIBRILLATION AMONG UNITED STATSE NURSING HOME RESIDENTS

Abstract

Background

Research comparing direct-acting oral anticoagulants (DOACs) to warfarin has excluded nursing home residents, a vulnerable population at high risk for vascular and bleeding events.

Objectives

To compare the safety and effectiveness of individual DOACS (rivaroxaban, apixaban, and dabigatran) versus warfarin among US nursing home residents.

Methods

Residents aged ≥65 years with non-valvular atrial fibrillation newly initiating oral anticoagulation and enrolled in fee-for-service Medicare for ≥6 months were studied. Nursing home residence was determined using Minimum Data Set 3.0 assessments. Outcomes included 1) ischemic stroke or transient ischemic attack (TIA); 2) bleeding (extracranial or intracranial); 3) other vascular events (myocardial infarction, venous thromboembolism, systemic embolism) 4) death; and 5) a composite of all outcomes. Follow-up continued until an outcome or 14-day treatment gap. DOAC initiators (2,881 apixaban, 1,289 dabigatran. 3,735 rivaroxaban) were 1:1 propensity matched to residents initiating warfarin in the same year. Cox proportional hazards models estimated cause-specific hazard ratios (HR).

Results

Median age (84 years), CHA_2DS_2-Vasc (5; Q1: 4, Q3: 6) and ATRIA risk scores (3; Q1: 3, Q3: 6) were similar across treatments and cohorts.

The incidence of ischemic stroke/TIA ranged from 0.94 to 1.84/100 person-years (PYs) and bleeding incidence ranged from 4.35 to 6.74/100 PYs across anticoagulants and cohorts. Outcomes differed by anticoagulant, with apixaban having lower bleeding rates (HR: 0.66; 95% Confidence Interval (CI): 0.49-0.88)) and higher ischemic stroke/TIA rates compared with warfarin (HR: 1.86; 95% CI: 1.00-3.45)). Dabigatran and rivaroxaban were comparable to warfarin for ischemic stroke/TIA and bleeding rates. Across all anticoagulants mortality rates ranged from 24-40 events/100 PYs. Mortality and composite rates were 14-32% lower for each DOAC versus warfarin.

Conclusions

In this national study of US nursing home residents, apixaban, rivaroxaban, and dabigatran were each associated with lower mortality and composite outcome rates compared with warfarin. Although specific DOACs had mixed results for safety and effectiveness endpoints, in aggregate, DOACs were being used with equal or greater benefit than warfarin.

Introduction

The RE-LY,[28] ROCKET-AF,[31] and ARISTOTLE[29] trials demonstrated superiority or non-inferiority in safety and effectiveness for each of the DOACs versus warfarin, but excluded nursing home residents. Observational evidence comparing the safety and effectiveness of warfarin and the DOACs for older adults has also been limited to community dwelling patients.[96-98] The generalizability of findings from community populations to the nursing home setting is complicated because residents have greater functional limitations, cognitive impairment, diminished life expectancy, polypharmacy, and the high burden of vascular and bleeding risk factors.[99]

Nursing homes are an important health care setting. If the fraction of older adults residing in nursing home remains at 2010 levels, the size of the nursing home population will increase 77% over the period 2016 to 2050, compared with a 20% increase in the size of the American population.[71,125] One in six US nursing home residents was diagnosed with atrial fibrillation and less than one-third of those with atrial fibrillation were treated with warfarin, although these estimates are dated (2004).[49] Among those treated, approximately half of the time on warfarin was estimated to be outside of the therapeutic range.[27,51] The prevalence of anticoagulant use has since increased to 48% and the mix of anticoagulants used has shifted considerably.[99] By 2016 nearly half of residents with atrial fibrillation receiving treatment were using direct-acting oral anticoagulants (DOACs),[99] despite limited evidence to inform anticoagulant and dosage selection in this population.

The choice of DOAC vs warfarin in the nursing home setting is unclear because the balance of risks and benefits is understudied. Clinician concerns regarding increased risk of adverse events[41,50] influence treatment patterns in nursing homes. However, resource inequity and other institutional characteristics introduce variability in treatment outcomes due to varied care quality delivered across facilities.[126,127] Further, recent efforts centered on improving quality of care in nursing homes,[101] may have contributed to changes in prescribing practices, the quality of warfarin therapy, and outcomes since earlier studies of warfarin were conducted.[27,48-51]

To address uncertainty regarding the relative safety and effectiveness of the DOACs and warfarin in the contemporary nursing home setting, we separately compared new-users of apixaban, rivaroxaban, and dabigatran to new-users of warfarin in a national cohort of nursing home residents with atrial fibrillation during 2011-2016. Motivated by earlier reports describing deviation from labeled dosing recommendations for the DOACs,[92,99] we also examined heterogeneity in comparative safety and effectiveness estimates by dosing alignment.

Methods

Data Sources

Data were obtained and linked through a data use agreement with the Centers for Medicare and Medicaid Services. The Master Beneficiary Summary File provided information on vital status and enrollment in Medicare and Medicaid. Inpatient and skilled nursing facility (SNF) records were drawn from Medicare Part A. Medication dispensing records and drug characteristics were sourced from the Medicare Part D Event

and Characteristics Files. The Minimum Data Set (MDS) 3.0, comprised of national data collected through mandatory assessments, provided information on SNF and long-stay nursing home residents in Medicare/Medicaid certified nursing homes. The MDS 3.0 data has been described in detail and validated previously.[65-67] The University of Massachusetts Medical School Institutional Review Board approved this study (H00015376).

Study Design

A retrospective cohort study with an active comparator new-user design compared nursing home residents initiating apixaban, rivaroxaban, or dabigatran to warfarin initiators during the period 07/01/2011 to 12/31/2016. Indexing of new DOAC users began in the month following marketing approval for apixaban (12/2012) and rivaroxaban (11/2011). Follow-up continued until occurrence of a study outcome, anticoagulant discontinuation (a treatment gap of >14 days), anticoagulant switch, end of Medicare Parts A, B, and D fee-for-service enrollment, or end of the study period (12/31/2016).

Source Population

The source population included residents of US nursing homes ≥65 years of age and diagnosed with non-valvular atrial fibrillation who newly initiated a DOAC or warfarin. Included residents had ≥6 months of pre-index Medicare fee-for-service enrollment and at least one diagnosis for atrial fibrillation, atrial flutter, or dysrhythmia on Part A or MDS 3.0 records during the pre-index year (Table 4.1). Because medications in hospitals or SNF settings or for those enrolled in hospice are not included

in Part D data, we excluded residents in a hospital, SNF, or on hospice on the index date. We also excluded residents with another indication for oral anticoagulant initiation based on an inpatient diagnosis of venous thromboembolism (VTE), valvular disease, or total hip/knee replacement during the baseline 6 months (Table 4.1). Residents with cancer or in a coma were also excluded due to distinct considerations regarding benefits and risks of treatment for these patients.

Anticoagulant Use

We operationally defined anticoagulant use to allow evaluation of specific anticoagulants initiated (warfarin, apixaban, dabigatran, rivaroxaban) because of differences in pharmacology and evidence suggesting safety and effectiveness may vary among the DOACs. Edoxaban was not studied due to low utilization. New users were defined as residents initiating one of these medications, without prior use of an oral anticoagulant in the preceding six months. The date of the first oral anticoagulant dispensing was established as the index date. Following the index dispensing, an as-treated approach was implemented using fill dates and number of days supplied from Part D claims to determine if residents remained exposed to the index medication on each day of follow-up. The end of treatment was assigned once the supply from the most recent medication fill was depleted and a gap in treatment of >14 days was observed, accounting for the potential for medication accumulation because of early fills and inpatient stays. Because DOACs are available in two dosages, we categorized residents as initiating standard doses versus those initiating reduced doses.

Outcomes

Primary time-to-event outcomes included ischemic cerebrovascular event ((ischemic stroke or transient ischemic attack (TIA)), intracranial or extracranial bleeding, and a composite net clinical benefit outcome comprised of ischemic stroke, TIA, intracranial bleeding, extracranial bleeding, venous thromboembolism (VTE), acute myocardial infarction (AMI), systemic embolism, and all-cause mortality. Each of the components of the net clinical benefit outcome, which was modeled after the net clinical benefit outcome from the RE-LY clinical trial,[28] were evaluated as secondary outcomes. Clinical outcomes were operationalized from diagnoses on hospitalization records using previously validated ICD-9 code-based algorithms (Table 4.1),[79,80,103,104] which were converted to ICD-10 using General Equivalence Mapping from the Centers for Medicare and Medicaid Services.[128] For each outcome, time-to-event was calculated as number of days from index until an outcome or censoring event. All outcomes were evaluated for the maximum duration of follow-up available with our data.

Covariates

Covariates included sociodemographics, the CHA_2DS_2-VASc[81] and ATRIA[82] risk scores and their components, hospitalizations, medication use, cognitive impairment, and functioning in activities of daily living (ADLs). Baseline hospitalizations for ischemic stroke or bleeding events were identified using the claims-based algorithms applied for outcome identification during the post-index period (Table 4.1).[79,80] The total number of hospitalizations and the number of unique medications used during the pre-index 6 months were summed. Polypharmacy has been linked to mortality risk.[129] Residents were classified as users of select medication classes (antiplatelets, non-steroidal anti-

inflammatory drugs, statins, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, selective serotonin reuptake inhibitors) associated with study outcomes[85-86,105-108] if at least one Part D claim was present during the pre-index 6 months.

Comorbid clinical conditions were operationalized using information from MDS 3.0 assessments with the exception of renal functioning, which was categorized as no impairment, chronic renal insufficiency without end-stage disease or dialysis,[84] end-stage renal disease (MDS item I1500) without dialysis, and dialysis (MDS item O0100J2). Cognitive status, a risk factor for mortality,[130] was categorized into no impairment, mild, moderate, and severe impairment using the MDS 3.0 Cognitive Function Scale.[74] Functional limitations in toileting, personal hygiene, locomotion, and eating were summarized using the ADL score (range 0-16 with higher scores indicating greater limitation).[87]

Statistical Analysis

We developed three separate cohorts for apixaban, dabigatran, rivaroxaban, respectively, using propensity score matching to develop comparable groups of DOAC and warfarin initiators. Each DOAC was matched separately because of differences in resident characteristics and temporal initiation patterns between DOACs.

Frequencies and percentages for categorical variables and medians with first and third quartiles were summarized by medication before and after matching for each of the three study cohorts. The propensity score estimation approach included the above described covariates selected because of associations with one or more study outcomes,

[85-86,105-108,129-130] avoiding bias from inclusion of variables only associated with the exposure.[131-133] Matching was performed within index year to account for secular trends. After matching, all characteristics with sufficient prevalence in the cohort (≥5%) to represent potential confounding threats were well balanced (standardized difference <0.10).[134]

Incidence rates were calculated for all primary and secondary outcomes. Cox proportional hazards models estimated cause-specific hazard ratios comparing each DOAC to warfarin. Dose was examined in combination with renal function as a source of potential heterogeneity. Prespecified analyses were performed within subgroups defined by DOAC dose alignment (or misalignment) with product labeling. Specifically, residents were classified as receiving supratherapeutic dosing (standard dose in the presence of an indication for dose reduction), aligned standard dosing, aligned low dosing, and subtherapeutic dosing (low dose in the absence of an indication for dose reduction). To evaluate potential selection bias in the early DOAC post-approval period, we conducted stratified analyses by time period (dichotomized as halves of the full study period). To examine the effects of the drug interaction between anticoagulants and antiplatelets, stratified analyses were performed among antiplatelet users and non-users. The proportional hazards assumption was evaluated graphically and satisfied for all models.

Sensitivity analyses

To examine residual confounding, hospitalizations for pneumonia and chronic obstructive pulmonary disease (COPD) were evaluated as falsification outcomes.[135,136]

Results

Among 3,422 apixaban, 3,758 rivaroxaban, and 1289 dabigatran initiators, 84%, 99%, and 100% were matched to warfarin initiators.

Resident Characteristics

Resident characteristics were summarized by treatment within matched cohorts (apixaban cohort n=5,762; dabigatran cohort n=2,578, and rivaroxaban cohort n=7,470; Table 4.2) and for the eligible population (n=21,346; Table 4.3). The median age was 83 years in the dabigatran cohort and 84 in the rivaroxaban and apixaban cohorts. In all cohorts more than two-thirds of residents were dual Medicare-Medicaid enrollees. Warfarin and DOAC users within each cohort had median CHA_2DS_2-Vasc risk scores of 5 (Q1 4, Q3 6) and ATRIA risk scores of 3 (Q1 3, Q3 6). The prevalence of renal impairment ranged from 29% in the dabigatran cohort to 40% in the apixaban cohort. Approximately one-eighth of DOAC users received standard dosages in the presence of an indication for dose reduction, while 34% of apixaban, 41% of dabigatran, and 56% of rivaroxaban users received low dosages without an indication for dose reduction.

Follow-up

The median duration of follow-up in the apixaban cohort was 137 days for apixaban and 124 days for warfarin users, during which time 663 events and 767 events occurred over 1,792 and 1,602 person-years, respectively. Median follow-up was 134 days for dabigatran and 212 days for matched warfarin users, during which time 372 and 571 events occurred during 1,153 and 1,384 person-years, respectively. Median follow-up in the rivaroxaban cohort was 139 days for rivaroxaban and 147 days for warfarin

users, during which time 1,049 and 1,223 events occurred over 2,710 and 2,722 person-years, respectively.

Apixaban versus Warfarin

The crude incidence of ischemic stroke and TIA was 1.67 events per 100 person-years among apixaban users and 0.94 events per 100 person-years among warfarin users (Table 4.4). Bleeding (intracranial and extracranial) rates were 4.35 and 6.74 events per 100 person-years among apixaban and warfarin users, respectively. The combined rate of AMI, VTE, and systemic embolism was 2.29 and 3.37 events per 100 person-years among apixaban and warfarin users.

Hazard ratios comparing apixaban to warfarin were 1.86 (95% CI: 1.00-3.45) for ischemic stroke/TIA and 0.66 (0.49-0.88) for bleeding (Table 4.5). Mortality was more than six times as numerous as any of the other outcomes and comprised more than 83% of the composite outcomes, and consequently, the mortality hazard ratio closely resembled the composite outcome hazard ratio (HR: 0.79; 95% CI: 0.71-0.88). Estimates for individual clinical components were directionally aligned with composite outcomes, with modest variation in the strength of associations (Table 4.6).

In analyses exploring heterogeneity by alignment of dosing with labeling recommendations, hazard ratios comparing bleeding rates between apixaban and warfarin consistently favored apixaban except in the subgroup receiving standard dose apixaban in the presence of an indication for dose reduction (HR: 1.87; 95% CI: 0.75-4.63) (Table 4.5). Although point estimates for ischemic stroke/TIA consistently favored warfarin, the number of events was small in each subgroup. Mortality (and composite) rates were

lower among aligned standard dose apixaban users (HR: 0.54; 0.44-0.65) and among low dose apixaban users without an indication for dose reduction (HR: 0.68; 0.53-0.86), but mortality rates were comparable to warfarin in the other dosing subgroups.

In analyses by index year (Table 4.7), point estimates favored apixaban for all study outcomes among those initiating anticoagulants in 2013-2014. Associations were attenuated, or in the case of ischemic stroke/TIA, reversed (2013-2014 HR: 0.89, 95% CI: 0.31-2.55; 2015-2016 HR: 2.71; 95% CI: 01.21-6.06) among those initiating during 2015-2016. Stratified analyses by antiplatelet use suggested heterogeneity may exist in the treatment-outcome association between those using and not using antiplatelets (Table 4.8). Associations between treatment and the falsification outcomes pneumonia and COPD were not indicative of strong residual cofounding (Table 4.9).

Dabigatran versus Warfarin

The crude incidence of ischemic stroke/TIA among dabigatran and warfarin users was 1.73 and 1.88 events per 100 person-years, respectively. Bleeding rates per 100 person-years were 6.07 (dabigatran) and 5.28 (warfarin). Hazard ratios did not suggest a meaningful difference in the rate of either outcome. As in the other DOAC cohorts, mortality was the most common outcome. Mortality (HR: 0.68; 95% CI: 0.59-0.79) and composite event rates (HR: 0.76; 95% CI: 0.67-0.87) were lower among dabigatran users.

Although confidence intervals were wide, point estimates for ischemic stroke/TIA favored dabigatran across dosing subgroups with the exception of those receiving less than standard dosing without an indication (HR: 2.50; 95% CI: 0.75-8.33). Bleeding rates were comparable for dabigatran and warfarin users across dosing subgroups with the

exception of the group receiving standard doses in the presence of an indication for dose reduction (HR: 1.80; 95% CI: 0.77-4.20). Mortality and composite rates were lower among dabigatran users in each dosing subgroup except for those receiving standard doses in the presence of an indication for dose reduction, among whom mortality and composite rates were similar for dabigatran and warfarin users.

Rivaroxaban versus Warfarin

The incidence of ischemic stroke/TIA was 1.84 events per 100 person-years among rivaroxaban and 1.69 events per 100 person-years among warfarin users. Bleeding rates were 6.46 (rivaroxaban) and 6.02 (warfarin) events per 100 person-years. Intracranial hemorrhage, (HR: 0.42; 95% CI: 0.19-0.90), mortality (HR: 0.79; 95% 0.72-0.87) and composite event rates (HR: 0.86; 95% CI: 0.79-0.94) were lower among rivaroxaban users. As in the apixaban cohort, heterogeneity in the incidence of ischemic and bleeding events were observed between warfarin initiators in the first (2011-2013 ischemic stroke/TIA: 2.46/100 PYs; bleeding: 4.39/100 PYs) and second (2014-2016 ischemic stroke/TIA: 1.29/100 PYs; bleeding: 6.88/100 PYs) halves of the study period (Table 4.7).

In subgroup analyses by dose and indication, mortality and composite event rates were lower among standard dose rivaroxaban users but not among low dose rivaroxaban users, regardless of indication. Bleeding rates were higher among low dose rivaroxaban users with an indication for dose reduction (HR: 1.77; 95% CI: 1.01-3.09), while ischemic stroke/TIA rates were higher among low dose rivaroxaban users without an indication for dose reduction (HR: 1.81; 95% CI: 0.96-3.36).

Discussion

In this national study of US nursing home residents, apixaban, rivaroxaban, and dabigatran were each associated with lower mortality and composite outcome rates compared with warfarin. Treatment-outcome associations for clinical endpoints varied between DOACs. Ischemic cerebrovascular event rates and bleeding rates among rivaroxaban and dabigatran users were comparable to event rates among warfarin users. Apixaban users experienced higher rates of ischemic cerebrovascular events and a lower rate of bleeding events compared with warfarin users. The interpretation of these findings was complicated by high mortality rates and heterogeneity in estimates across dosing subgroups and over the course of the study period. In aggregate, the results of this first investigation of the comparative effectiveness of the DOACs versus warfarin among nursing home residents suggested that DOACs are being used with equal or greater benefit than warfarin.

In the BAFTA trial,[59] ischemic or unknown stroke occurred at a rate of 1.2 events per 100 person-years among warfarin users compared with 3.0 events per 100 person-years among aspirin users, with no differences observed in major hemorrhage rates.[59] Despite the large burden of vascular risk factors in the nursing home population, we observed ischemic stroke incidence rates generally consistent with anticoagulants in BAFTA and the major DOAC clinical trials.[28-29,31,59] Rates of major bleeding, which carries a more stringent definition than our outcome of bleeding related hospitalization, ranged from 2.1 to 3.6 for the DOACs and 3.1 to 3.4 for warfarin across trials.[28-29,31] Unlike the generally similar safety and effectiveness outcome rates, mortality rates in

clinical trials[28-29,31,59] were one-fifth to one-third the mortality rates in the nursing home setting. Consistent with our findings, all-cause mortality rates were lower for the DOACs versus warfarin in the DOAC trial[28-29,31] and in the Medicare population.[97]

Utilization of low and misaligned DOAC dosages was more prevalent in the nursing home than in community-based cohorts.[92,137] Although some fraction of such dosing is potentially inappropriate, deviation from labeled dosing is also likely to occur as a consequence of shared decision-making between clinicians, caregivers, and patients who together consider the preferences and characteristics of an individual (as recommended in clinical guidelines[24]) alongside often inadequate information on the absolute and relative risks of alternative treatment strategies for a specific individual. Dose-specific evidence on the safety and effectiveness of low DOAC dosages is limited, particularly among high-risk older adults. The 75 mg dabigatran dose, which is only marketed in the US, was not studied in the RE-LY clinical trial.[28] Although the 15mg rivaroxaban dose was used for patients with a renal indication in the ROCKET-AF trial,[31] only pooled analyses were reported with the standard dose. In the ARISTOTLE trial, estimates for the 2.5mg apixaban dose were consistent with the standard 5 mg dose, although the sample size was small (n=831).[29]

Our findings were consistent with earlier research linking off-label dosing with ischemic stroke and bleeding risk. Among community-dwelling patients with private insurance or Medicare Advantage, ischemic stroke rates were higher among low dose apixaban users with and without a renal indication.[92] For apixaban users considered underdosed (i.e., 2.5mg without a renal indication), the ischemic stroke risk was nearly

five times greater than among apixaban 5 mg users, with similar bleeding rates.[92] In the same study, a pooled analysis of all 3 DOACs indicated that use of standard dosing in patients with a renal indication was associated with a more than twofold higher risk of major bleeding without a countervailing benefit for stroke risk.[92] Another study of community-dwelling ORBIT-AF registry members reported similar off-label dosing-outcome associations.[137] In our study, low dose apixaban and rivaroxaban users had higher rates of ischemic stroke/TIA with or without an indication for dose reduction, while underdosing (but not low dosing by indication) of dabigatran was associated with elevated ischemic stroke/TIA risk. The increased bleeding rate among aligned low dose rivaroxaban (15mg dose is 75% of the standard dose) but not under-dosed rivaroxaban users may stem from the 36% of under-dosed residents using the off-label rivaroxaban 10mg (50% of standard) dosage.

Although we applied a new-user active comparator design to mitigate selection biases often present in non-user or prevalent user comparisons, further research is needed to inform the decision to initiate, switch, or discontinue an anticoagulant, particularly for older adults with limited life expectancy. Differences in market entry dates for apixaban (12/2012), dabigatran (10/2010), and rivaroxaban (11/2011) meant that the warfarin comparator group varied between DOACs. The recency of DOAC approval also introduced the potential for channeling bias during the early post-approval period (i.e., a form of selection bias where the types of patients prescribed a newly marketed drug have a different prognosis than the types of patients prescribed an established drug with the same indication). By matching DOAC and warfarin users within the same calendar year,

we sought to identify a comparison group that reflected the prevailing real-world treatment conditions facing clinicians during a given time period. Cost is one potential mechanism through which channeling bias may operate. Multiple studies in community dwelling populations have found higher socioeconomic status to be associated with higher DOAC use after accounting for other factors (including prescriber specialty), suggesting the cost of newer (branded) DOACs may have deterred utilization for certain patients of lower socioeconomic status. The effects of cost on treatment selection was less of a concern in our study because more than two-thirds of our study population was dually Medicare-Medicaid enrolled (and had copay assistance), including similar proportions of residents in DOAC and warfarin treated groups.

Changes in ischemic and bleeding outcomes among residents initiating warfarin at different time points (i.e., before and after DOACs were commonly used in nursing homes)[99] suggests the quality of warfarin therapy, other delivery system factors, or patient characteristics may have been shifting during the study period. Although we lack laboratory values on renal functioning and time in therapeutic range, rather than bias our results, the observed changes over time represent the reality of changing treatment patterns with a highly individualized and oversight-intensive medication in the face of the entrance of alternative therapeutic options. The balance in observed characteristics within the matched cohorts and the absence of clear relationships between treatment group and falsification outcomes attenuates concerns of unmeasured confounding and lends support to the potential for contributions of health system factors such as warfarin dose titration and monitoring. The nursing home setting was the site of death for two-thirds of residents

who died during follow-up, introducing the potential for under-detection of fatal clinical events for those residents who experienced a study outcome and were not transported to the hospital. Consequently, incidence rates for clinical events were likely underestimated. Although deaths related to bleeding and embolic events comprised an unknown fraction of all deaths occurring in the nursing home, the consistent survival advantage for all 3 of the DOACs suggests the incidence of fatal clinical events among DOAC users may have been lower compared with warfarin users.

Conclusions

As the first study to investigate outcomes of anticoagulation in the nursing home setting in a contemporary post-DOAC period, our findings are foundational and provide initial guidance for clinical decision-makers caring for older, institutionalized populations. Ultimately, although comparative safety and effectiveness estimates varied by drug and dose, our findings of very low ischemic stroke rates without excessive bleeding reinforces the clinical utility of anticoagulation with either medication class for this older population at high risk of vascular and bleeding events.

Table 4.1. ICD-9 and ICD-10 Code Based Definitions Applied to Medicare Part A Claims to Identify Specific Conditions		
Clinical Condition	**ICD-9 CM Codes**	**ICD-10 CM Codes***
Atrial fibrillation/flutter†	42731, 42732	I480, I481, I482, I483, I484, I4891, I4892
Valvular disease‡	33400, 99602, 99661, V433, V422, 3979, 3971, 3970, 3969, 3968, 3963, 3962, 3961, 3960, 3959, 3952, 3951, 3950, 3949, 3942, 3941, 3940, 7467, 7466, 7465, 7464, 7463, 7462, 7461, 74609, 74602, 74601, 74600, 4243, 4242, 4241, 4240	I050, I051, I052, I058, I059, I069, I068, I062, I061, I060, I080, I088, I089, I0989, I091, I083, I082, I081, I079, I078, I072, I071, I070, A1884, I340. I341, I342, I348, I349, I350, I351, I352, I358, I359, I360, I361, I362, I368, I370, I371, I372, I378, I379, I38, I39, M3211, Q209, Q220 Q221, Q222, Q223, Q224, Q225, Q226, Q228, Q229, Q230, Q231, Q232, Q234, Z953, Z952, Z954, T8201XA, T8201XD, T8201XS, T8202XA, T8202XD, T8202XS, T8203XA, T8203XD, T8203XS, T8209XA, T8209XD, T8209XS, T826XXA, T826XXD, T826XXS,
Ischemic stroke§	43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, 43491, 436	I6302, I6312, I6322, I63239, I63232, I63231, I63139, I63132, I63131, I63039, I63032, I63031, I63011, I63012, I63019, I63111, I63112, I63119, I63211, I63212, I63219, I6359, I6319, I6309, I6329, I6320, I6310, I6300, I6330, I63311, I63312, I63319, I63321, I63322, I63329, I63331, I63332, I63339, I63341, I63342, I63349, I6339, I636, I6349, I63449, I63442, I63441, I63439, I69432, I69431, I63429, I63422, I63421, I63419, I63412, I63411, I63430, I6350, I63511, I63512, I63519, I63521, I63529, I63531, I63532, I63539, I63541, I63542, I63549, I6359, I638, I639, I6789

Intracranial hemorrhage**	430, 431, 4320, 4321, 4329	I609, I608, I607, I606, I6052, I6051, I6050, I604, I6032, I6031, I6030, I6022, I6021, I6020, I6012, I6011, I6010, I6002, I6001, I6000, I610, I611, I612, I613, I614, I615, I616, I618, I619, I621, I6200, I6201, I6202, I6203, I629
Extracranial bleeding**	In primary position alone: 5310, 5312, 5314, 5316, 5320, 5322, 5324, 5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 53501, 53511, 53521, 53531, 53541, 53551, 53561, 53783, 4560, 45620, 5307, 53082, 5780, 4552, 4555, 4558, 56202, 56203, 56212, 56213, 56881, 5693, 56985, 5781, 5789, 59381, 5997, 6238, 6262, 6266, 4230, 4590, 56881, 7191, 7847, 7848, 7863 In primary position, with above code in secondary position: 5311, 5313, 5315, 5317, 5319, 5321, 5323, 5325, 5327, 5329, 5331, 5333, 5335, 5337, 5339, 5341, 5343, 5345, 5347, 5349, 53500, 53510, 53520, 53530, 53540, 53550, 53560, 455, 56200, 56201, 56210, 56211, 5301,	In primary position alone: K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K2931, K2941, K2951, K2961, K2921, K2971, K2981, K2991, K31811, I8501, I8511, K226, K228, K920, K648, K643, K642, K641 K640, K5711, K5751, K5753, K5741, K5713, K5701, K5791, K5731, K5793, K5781, K5733, K5721, K661, K625, K5521, K921, K922, N280, R310, R311, R312, R319, N898, N920, N921, I312, R58, M2500, M25011, M25012, M25019, M25021, M25022, M25029, M25031, M25032, M25039, M25041, M25042, M25049, M25051, M25052, M25059, M25061, M25062, M25069, M25071, M25072, M25073, M25074, M25075, M25076, M2508, R040, R041, R042, R0481, R0489, R049 In primary position, with above code in secondary position: K251, K253, K255, K257, K259, K261, K263, K265, K267, K269, K271, K273, K275, K277, K279, K281, K283, K285, K287, K289, K2900, K2930, K2960, K2920, K2930, K2970, K2980, K640, K641, K642, K643, K644, K645, K648, K649, K5750, K5710,

	2800, 2851, 2859, 79092	K5752, K5740, K5712, K5700, K5730, K5790, K5792, K5780, K5732, K5720, K210, K209, K208, K200, D800, D62, D649, R791
Chronic renal insufficiency[††]	582, 583, 585, 586, 587	M3218, M3214, M3504, N050, N051, N052, N053, N054, N055, N056, N057, N058, N059, N060, N061, N062, N063, N064, N065, N066, N067, N068, N069, N070, N071, N072, N073, N074, N075, N076, N077, N078, N079, N08, N140, N142, N144, N150, N158, N159, N171, N16, N170, N172, N178, N179, N181, N182, N183, N184, N185, N186, N189, N19, N261, N269
Acute myocardial infarction[‡‡]	41001, 41011, 41021, 41031, 41041, 41051, 41061, 41071, 41081, 41091	I2109, I220, I2102, I2101, I2119, I221, I2111, I228, I2129, I214, I2121, I222, I229, I213
Venous thromboembolism[§§]	41511, 41519, 45111, 45119, 4512, 4519, 4531, 4532, 4534, 45341, 45342, 4538, 4539	I803, I809, I821, I82220, I82401, I82402, I82403, I82409, I84211, I82412, I82413, I82419, I82421, I82422, I82423, I82429, I82431, I82432, I82433, I82439, I82441, I82442, I82443, I82449, I82491, I82492, I82493, I82499, I824Y1, I824Y2, I824Y3, I824Y9, I824Z1, I824Z2, I824Z3, I824Z9, I82210, I82290, I82601, I82602, I82603, I82609, I82611, I82612, I82613, I82619, I82621, I82622, I82629, I82890, I82891, I8290, I82A11, I82A12, I82A13, I82A19, I82A21, I82A22, I82A23, I82A29, I82B11, I82B12, I82B13I82B13, I82B19, I82B21, I82B22, I82B23, I82B29, I82C11, I82C12, I82C13, I82C19
Systemic embolism[‡]	444, 445	I74
Pneumonia[***]	480, 481, 482, 485, 486, 4870	J120, J121, J122, J123, J1281, J1289, J129, J181, J13, J14,

		J150, J151, J152, J15211, J15212, J1529, J153, J154, J155, J156, J158, J159, J180, J188, J189, J129, J1108, J1100, J1008, J1001, J1000
Chronic obstructive pulmonary disease[†††]	In primary position alone: 49121, 49122, 4918, 4919 4928, 49320, 49321, 49322, 496 In primary position, with above code in secondary position: 51881, 51882, 51884, 7991	In primary position alone: J441J J440, J418, J42, J439, J438, J432, J431, J430, J449 In primary position, with above code in secondary position: J9600, J9601, J9602, J9690, J9691, J9692, J80, J9620, 9621, J9622, R092

*ICD-9 CM code based algorithms were converted to ICD-10 CM codes using the 2016 General Equivalence Mappings available from the Centers for Medicare and Medicaid Services at https://www.cms.gov/Medicare/Coding/ICD10/2016-ICD-10-CM-and-GEMs.html

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Table 4.2. Characteristics of Residents Treated with Apixaban, Dabigatran, Rivaroxaban, and Matched Warfarin Users						
	Apixaban Cohort		**Dabigatran Cohort**		**Rivaroxaban Cohort**	
	Apixaban n=2,881	**Warfarin n=2,881**	**Dabigatran n=1,289**	**Warfarin n=1,289**	**Rivaroxaban n=3,735**	**Warfarin n=3,735**
Demographics						
Age in years, median (Q1, Q3)	84 (77, 89)	84 (76, 89)	83 (77, 89)	83 (77, 89)	84 (77, 89)	84 (77, 89)
Women, %	68.5	67.8	67.2	69.7	69.3	68.2
Enrolled in Medicaid, %	68.5	70.3	74.9	72.2	72.1	71.8
Hospital admissions in prior year, %						
Number of hospitalizations, %						
1	36.8	37.9	33.4	31.3	36.1	36.4
2-3+	33.4	32.7	30.1	31.0	30.6	28.6
Ischemic stroke	12.7	12.8	12.6	11.4	10.6	10.6
Extracranial or intracranial bleed	1.8	1.8	1.5	1.8	1.3	1.5
Time since first observed nursing home entry, median (Q1, Q3)	588 (103, 1,319)	609 (114, 1287)	325 (108, 618)	302 (100, 617)	543 (118, 1073)	585 (120, 1103)
Unique medications, median (Q1, Q3)	21 (13, 31)	22 (13, 32)	17 (11, 25)	16 (10, 24)	21 (13, 30)	21 (13, 31)
DOAC dose, %						
Less than Standard	50.3	NA	42.1	NA	59.4	NA

Select Medications,* %						
NSAID	35.5	36.4	28.2	25.6	35.1	36.7
Antiplatelet	25.0	23.7	23.0	22.7	22.7	22.2
Statin	59.5	60.5	49.4	45.5	54.9	55.5
SSRI	47.2	48.2	45.6	46.2	48.9	49.3
ACE inhibitor or ARB	62.0	62.4	59.4	57.0	60.9	60.6
Select Comorbidities, %						
Diabetes	39.5	37.5	37.2	35.7	35.3	35.7
Heart failure	35.8	34.8	36.9	36.5	33.4	33.6
Hypertension	85.9	85.7	84.2	83.4	83.9	84.0
Coronary artery disease	29.9	27.5	29.3	28.1	16.4	25.6
Anemia	29.5	28.8	27.4	26.4	28.8	29.4
Fall history	16.4	17.8	17.1	15.4	19.0	19.7
Stroke	22.0	21.4	24.7	23.5	22.5	21.7
Renal impairment						
Chronic renal insufficiency	22.1	23.4	16.8	16.1	19.4	20.4
End-stage renal disease	13.7	13.8	11.5	12.7	11.5	12.5
Dialysis	3.1	3.7	Suppressed per DUA	Suppressed per DUA	0.5	0.6
History of pneumonia	6.0	7.2	5.5	5.8	7.0	6.0

Chronic lung disease	26.5	27.3	26.8	29.6	27.9	28.0
CHA_2DS_2-Vasc Risk Score, median (Q1,Q3)	5 (4, 6)	5 (4, 6)	5 (4, 6)	5 (4, 6)	5 (4, 6)	5 (4, 6)
ATRIA Bleeding Risk Score, %	3 (3, 6)	3 (3, 6)	3 (3, 6)	3 (3, 6)	3 (3, 6)	3 (3, 6)
Cognitive skills, %						
Mildly impaired	26.2	25.7	27.5	26.5	26.5	25.6
Moderately to severely impaired	32.8	33.0	33.1	34.7	37.0	37.0
ADL score (0-16),[†] median (Q1, Q3)	10 (7, 11)	10 (7, 11)	9 (6, 11)	9 (7, 11)	10 (7, 12)	10 (8,12)
Life expectancy >6months	99.5	99.7	>99.5	>99.5	>99.0	>99.0

[*]Any Part D claim during the 12-month period
[†]Higher scores indicate greater limitation in ADLs
Abbreviations: activities of daily living (ADLs), non-steroidal anti-inflammatory drugs (NSAID), selective serotonin reuptake inhibitor (SSRI), angiotensin converting enzyme (ACE), angiotensin receptor blocker (ARB), data use agreement (DUA), direct acting oral anticoagulant (DOAC)

Table 4.3. Characteristics of Residents Treated with Apixaban, Dabigatran, Rivaroxaban, and Warfarin Users (Pre-Matching)				
	Apixaban n=3,422	**Dabigatran n=1,289**	**Rivaroxaban n=3,760**	**Warfarin n=12,706**
Demographics				
Age in years, median (Q1, Q3)	84 (77, 89)	83 (77, 89)	84 (76, 89)	84 (77, 89)
Women, %	69.0	67.2	69.2	66.7
Non-Hispanic white	84.5	86.1	85.1	84.7
Enrolled in Medicaid, %	68.5	74.9	71.8	72.4
Hospital admissions in prior year, %				
Number of hospitalizations, %				
1	39.0	33.4	36.3	33.4
2-3+	34.2	30.1	30.6	30.4
Ischemic stroke	12.4	12.6	10.5	11.7
Extracranial or intracranial bleed	1.9	1.5	1.6	1.9
Time since nursing home entry, median (Q1, Q3)	619.5 (105, 1,339)	325 (108, 618)	547 (119, 1076)	378 (105, 794)
Unique medications, median (Q1, Q3)	22 (14, 33)	17 (11, 25)	21 (13, 30)	17 (11, 25)
DOAC dose, %				
Less than standard	50.0	42.0	59.3	NA
Select Medications,* %				
NSAID	38.8	28.2	35.4	26.0
Antiplatelet	27.1	23.1	22.7	19.2
Statin	61.8	49.3	54.9	49.3
SSRI	48.4	45.6	49.1	43.8
ACE inhibitor or ARB	64.7	59.5	61.0	53.9
Select Comorbidities, %				
Diabetes	39.1	37.1	35.2	38.3
Heart failure	35.8	36.8	33.2	35.7
Hypertension	86.3	84.2	83.9	83.6
Coronary artery disease	29.7	29.4	26.4	28.6
Anemia	27.9	27.5	28.9	32.3
Fall history	16.0	17.1	19.1	19.0

Stroke	20.7	24.8	22.4	24.4
Renal impairment				
Chronic renal insufficiency	23.7	16.8	19.4	18.5
End-stage renal disease	13.7	Suppressed per DUA	11.5	13.3
Dialysis	2.7	Suppressed per DUA	0.5	3.3
CHA_2DS_2-Vasc Risk Score, median (Q1,Q3)	5 (4, 6)	5 (4, 6)	5 (4, 6)	5 (4, 6)
ATRIA Bleeding Risk Score, %	3 (3, 6)	3 (3, 6)	3 (3, 6)	3 (3, 6)
Cognitive skills, %				
Mildly impaired	26.4	27.6	26.6	25.7
Moderately to severely impaired	31.5	33.1	36.8	36.0
ADL score (0-16),[†] median (Q1, Q3)	10 (7, 11)	9 (6, 11)	10 (7, 12)	10 (8, 12)

[*]Any Part D claim during the 12-month period
[†]Higher scores indicate greater limitation in ADLs
Abbreviations: activities of daily living (ADLs), non-steroidal anti-inflammatory drugs (NSAID), selective serotonin reuptake inhibitor (SSRI), angiotensin converting enzyme (ACE), angiotensin receptor blocker (ARB), data use agreement (DUA), direct acting oral anticoagulant (DOAC)

Table 4.4. Number of Events and Incidence Rates by Anticoagulant in Matched Cohorts of DOAC and Warfarin Users					
	# events	**Events/ 100 PYs**	**# events**	**Events/ 100 PYs**	**Rate Difference (95% CI)**
	Apixaban n=2,881		**Warfarin n=2,881**		**Apixaban vs. Warfarin**
Ischemic stroke/TIA	30	1.67	15	0.94	0.73 (-0.03 to 1.49)
Ischemic stroke	24	1.34	13	0.81	0.53 (-0.16 to 1.22)
Bleeding	78	4.35	108	6.74	-2.39 (-3.99 to -0.79)
AMI/VTE/SE	41	2.29	54	3.37	-1.08 (-2.22 to 0.06)
Mortality	554	30.7	645	40.0	-9.30 (-13.18 to -5.42)
Composite	669	37.0	767	47.9	-10.90 (-15.31 to -6.49)
	Dabigatran N=1,289		**Warfarin n=1,289**		**Dabigatran vs. Warfarin**
Ischemic stroke/TIA	20	1.73	26	1.88	-0.15 (-1.20 to 0.90)
Ischemic stroke	14	1.21	18	1.30	-0.09 (-0.96 to 0.78)
Bleeding	70	6.07	73	5.28	0.79 (-1.08 to 2.66)
AMI/VTE/SE	25	2.17	44	3.18	-1.01 (-2.27 to 0.25)
Mortality	283	24.3	496	35.09	-10.79 (-14.98 to -6.60)
Composite	372	32.25	571	41.27	-9.02 (-13.73 to -4.31)
	Rivaroxaban n=3,735		**Warfarin n=3,735**		**Rivaroxaban vs. Warfarin**
Ischemic stroke/TIA	50	1.84	46	1.69	0.15 (-0.56 to 0.86)
Ischemic stroke	37	1.36	36	1.32	0.04 (-0.58 to 0.66)
Bleeding	175	6.46	164	6.02	0.44 (-0.89 to 1.77)
AMI/VTE/SE	76	2.80	84	3.08	-0.28 (-1.19 to 0.63)
Mortality	824	30.15	1052	38.07	-8.92 (-12.01 to -5.83)
Composite	1049	38.70	1223	44.91	-6.21 (-9.65 to -2.77)
Abbreviations: transient ischemic attack (TIA), acute myocardial infarction (AMI), venous thromboembolism (VTE), systemic embolism (SE), direct acting oral anticoagulant (DOAC)					

Table 4.5. Results of Cox Proportional Hazards Models Comparing DOAC and Warfarin Groups Overall and in Subgroups Defined by Alignment with Recommended Dosing					
Apixaban versus Warfarin, HR (95% CI)					
	Overall n=5,762	**Overdosing[*] n=672**	**Aligned, std[†] n=2,192**	**Aligned, Low[‡] N=1,638**	**Underdosing[§] n=1,260**
Stroke/TIA	1.86 (1.00-3.45)	1.28 (0.29-5.70)	1.62 (0.60-4.39)	2.42 (0.85-6.86)	2.78 (0.29-26.71)
Bleeding	0.66 (0.49- 0.88)	1.87 (0.75-4.63)	0.70 (0.43-1.15)	0.55 (0.33-0.93)	0.45 (0.23-0.87)
AMI/VTE/SE	0.70 (0.46-1.05)	0.51 (0.15-1.76)	0.99 (0.51-1.90)	0.85 (0.43-1.71)	0.21 (0.06-0.75)
Mortality	0.78 (0.70-0.88)	1.01 (0.73-1.39)	0.54 (0.44-0.65)	1.19 (0.97-1.47)	0.68 (0.53-0.86)
Composite	0.79 (0.71-0.88)	1.08 (0.8-1.46)	0.59 (0.50-0.71)	1.09 (0.91-1.32)	0.66 (0.53-0.82)
Dabigatran versus Warfarin, HR (95% CI)					
	Overall n=2,578	**Overdosing*** n=354	**Aligned, std[†]** n=1,140	**Aligned, Low[‡]** n=384	**Underdosing[§]** n=700
Stroke/TIA	0.92 (0.51-1.65)	0.70 (0.13-3.84)	0.59 (0.24-1.48)	0.63 (0.15-2.63)	2.50 (0.75-8.33)
Bleeding	1.10 (0.80-1.53)	1.80 (0.77-4.2)	1.18 (0.71-1.95)	0.74 (0.32-1.73)	1.00 (0.53-1.89)
AMI/VTE/SE	0.66 (0.40-1.09)	1.79 (0.54-5.98)	0.57 (0.29-1.16)	4.24 (0.47-39.98)	0.25 (0.07-0.85)
Mortality	0.68 (0.59-0.79)	0.97 (0.67-1.41)	0.57 (0.45-0.71)	0.67 (0.46-0.97)	0.77 (0.59-1.01)
Composite	0.76 (0.67-0.87)	1.15 (0.82-1.60)	0.65 (0.53-0.80)	0.73 (0.53-1.02)	0.82 (0.64-1.05)
Rivaroxaban versus Warfarin, HR (95% CI)					
	Overall n=7,470	**Overdosing[*]** n=860	**Aligned, std[†]** n=2,176	**Aligned, Low[‡]** n=1,140	**Underdosing[§]** n=3,294
Stroke/TIA	1.09 (0.73-1.63)	0.87 (0.26-2.77)	0.44 (0.22-0.89)	6.97 (0.84-57.90)	1.81 (0.96-3.36)

Bleeding	1.07 (0.87-1.07)	1.08 (0.58-1.99)	0.95 (0.63-1.44)	1.77 (1.01-3.09)	0.99 (0.73-1.36)
AMI/VTE/SE	0.91 (0.67-1.24)	0.70 (0.25-1.98)	1.02 (0.56-1.85)	0.77 (0.34-1.74)	0.96 (0.62-1.50)
Mortality	0.79 (0.72-0.87)	0.75 (0.56-0.99)	0.63 (0.53-0.74)	1.04 (0.82-1.30)	0.87 (0.76-0.99)
Composite	0.86 (0.79-0.94)	0.82 (0.64-1.06)	0.70 (0.60-0.82)	1.10 (0.89-1.35)	0.93 (0.82-1.05)

[*]Receiving standard DOAC dosing in the presence of an indication for dose reduction.
[†]Receiving standard DOAC dosing in the absence of an indication for dose reduction.
[‡]Receiving an indicated renal dosage (apixaban 2.5 mg, dabigatran 75mg, rivaroxaban 15mg) in the presence of an indication for dose reduction.
[§]Receiving a less than standard dose in the absence of an indication for dose reduction. Rivaroxaban 10 mg was considered underdosing in the presence and in the absence of renal impairment.
Abbreviations: standard (std.), transient ischemic attack (TIA), acute myocardial infarction (AMI), venous thromboembolism (VTE), systemic embolism (SE), hazard ratio (HR), confidence interval (CI), direct acting oral anticoagulant (DOAC), standard (std)

Table 4.6. Results of Cox Proportional Hazards Models Comparing DOAC and Warfarin Groups on Component Endpoints of Composite Outcomes

	Apixaban	Warfarin	Apixaban vs. Warfarin	Dabigatran	Warfarin	Dabigatran vs. Warfarin	Rivaroxaban	Warfarin	Rivaroxaban vs. Warfarin
	# events (Rate per 100 PYs)		**HR (95% CI)**	**# events (Rate per 100 PYs)**		**HR (95% CI)**	**# events (Rate per 100 PYs)**		**HR (95% CI)**
Ischemic stroke	24 (1.34)	13 (0.81)	1.72 (0.87-3.37)	14 (1.21)	18 (1.30)	0.93 (0.47-1.88)	37 (1.36)	36 (1.32)	1.03 (0.65-1.64)
TIA*	Sup.	Sup.	Sup.	Sup.	Sup.	Sup.	Sup.	Sup.	Sup.
Extracranial bleeding	69 (3.85)	93 (5.80)	0.68 (0.50-0.92)	67 (5.81)	66 (4.77)	1.16 (0.83-1.63)	166 (6.12)	142 (5.21)	1.17 (0.94-1.47)
Intracranial hemorrhage*	Sup.	Sup.	0.55 (0.24 1.27)	Sup.	Sup.	0.54 (0.14-2.09)	Sup.	Sup.	0.42 (0.19-0.90)
Other vascular									
AMI	26 (1.45)	27 (1.68)	0.86 (0.50-1.48)	17 (1.47)	26 (1.88)	0.78 (0.42-1.44)	39 (1.44)	42 (1.54)	0.94 (0.61-1.45)
VTE*	14 (0.78)	25 (1.56)	0.53 (0.28-1.02)	Sup.	Sup.	0.45 (0.19-1.08)	31 (1.14)	37 (1.36)	0.84 (0.53-1.36)
SE[1]	Sup.	Sup.	Sup.	Sup.	Sup.	Sup.	Sup.	Sup.	Sup.

*Cell sizes suppressed so that no cell was <11 per data use agreement

Abbreviations: transient ischemic attack (TIA), acute myocardial infarction (AMI), venous thromboembolism (VTE), systemic embolism (SE), hazard ratio (HR), confidence interval (CI), direct acting oral anticoagulant (DOAC)

Table 4.7. Incidence Rates and Results of Cox Proportional Hazards Models Comparing DOAC and Warfarin Groups Overall and by Time Period

Apixaban versus Warfarin							
	2013-2016	**2015-2016**			**2013-2014**		
		Apixaban (n=2,333)	**Warfarin (n=2,333)**		**Apixaban (n=548)**	**Warfarin (n=548)**	
	HR (95% CI)	**# Events (rate per 100 PYs)**	**# Events (rate per 100 PYs)**	**HR (95% CI)**	**# Events (rate per 100 PYs)**	**# Events (rate per 100 PYs)**	**HR (95% CI)**
Stroke/TIA*	1.86 (1.00-3.45)	Sup.	Sup.	2.71 (1.21-6.06)	Sup.	Sup.	0.89 (0.31-2.55)
Bleeding	0.66 (0.49- 0.88)	61 (5.18)	78 (7.18)	0.73 (0.52-1.02)	2.77	5.81	0.49 (0.27-0.89)
AMI/VTE/SE*	0.70 (0.46-1.05)	33 (2.80)	35 (3.22)	0.89 (0.55-1.43)	Sup.	Sup.	0.36 (0.16-0.83)
Mortality	0.78 (0.70-0.88)	407 (37.29)	468 (39.60)	0.81 (0.71-0.93)	147 (23.70)	180 (34.52)	0.70 (0.57-0.88)
Composite	0.79 (0.71-0.88)	495 (27.58)	551 (30.70)	0.84 (0.74-0.95)	168 (27.38)	216 (41.86)	0.67 (0.55-0.82)
Dabigatran versus Warfarin							
	2011-2016	**2014-2016**			**2011-2013**		
		Dabigatran (n=378)	**Warfarin (n=378)**		**Dabigatran (n=911)**	**Warfarin (n=911)**	
	HR (95% CI)	**# Events (rate per 100 PYs)**	**# Events (rate per 100 PYs)**	**HR (95% CI)**	**# Events (rate per 100 PYs)**	**# Events (rate per 100 PYs)**	**HR (95% CI)**
Stroke/TIA*	0.92 (0.51-1.65)	Sup.	Sup.	NE	18 (2.01)	26 (2.30)	0.87 (0.47-1.58)

Bleeding	1.10 (0.80-1.53)	16 (6.19)	17 (6.66)	0.93 (0.47-1.84)	54 (6.04)	56 (4.96)	1.16 (0.80-1.69)
AMI/VTE/SE	0.66 (0.40-1.09)	16 (1.79)	31 (2.74)	0.69 (0.29-1.61)	130 (21.93)	160 (30.69)	0.65 (0.35-1.18)
Mortality	0.68 (0.59-0.79)	212 (23.48)	398 (34.42)	0.71 (0.53-0.97	71 (27.25)	98 (38.12)	0.67 (0.57-0.79)
Composite	0.76 (0.67-0.87)	280 (31.28)	454 (40.24)	0.78 (0.59-1.02)	92 (35.57)	117 (45.83)	0.76 (0.65-0.88)
Rivaroxaban versus Warfarin							
	2011-2016	**2014-2016**			**2011-2013**		
		Rivaroxaban (n=2832)	**Warfarin (n=2832)**		**Rivaroxaban (n=903)**	**Warfarin (n=903)**	
	HR (95% CI)	**# Events (rate per 100 PYs)**	**# Events (rate per 100 PYs)**	**HR (95% CI)**	**# Events (rate per 100 PYs)**	**# Events (rate per 100 PYs)**	**HR (95% CI)**
Stroke/TIA	1.09 (0.73-1.63)	34 (1.89)	23 (1.29)	1.48 (0.87-2.51)	16 (1.75)	23 (2.46)	0.71 (0.38-1.34)
Bleeding	1.07 (0.87-1.07)	118 (6.58)	123 (6.88)	0.96 (0.74-1.23)	57 (6.22)	41 (4.39)	1.42 (0.95-2.13)
AMI/VTE/SE	0.91 (0.67-1.24)	62 (3.46)	56 (3.13)	1.10 (0.77-1.58)	14 (1.53)	28 (3.00)	0.52 (0.27-0.98)
Mortality	0.79 (0.72-0.87)	563 (31.17)	709 (39.15)	0.80 (0.71-0.89)	261 (28.18)	343 (36.00)	0.78 (0.60-0.92)
Composite	0.86 (0.79-0.94)	725 (40.40)	830 (46.39)	0.87 (0.79-0.96)	324 (35.36)	393 (42.08)	0.84 (0.73-0.97)

*Cell sizes suppressed so that no cell was <11 per data use agreement

Abbreviations: transient ischemic attack (TIA), acute myocardial infarction (AMI), venous thromboembolism (VTE), systemic embolism (SE), not estimable (NE), hazard ratio (HR), confidence interval (CI), direct acting oral anticoagulant (DOAC)

Table 4.8. Results of Cox Proportional Hazards Models Comparing DOAC and Warfarin Groups Overall and within Strata of Antiplatelet Users and Non-Users

	Overall	Antiplatelet Use	No Antiplatelet Use
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Apixaban versus Warfarin			
Stroke/TIA	1.86 (1.00-3.45)	0.93 (0.31-2.76)	2.48 (1.15-5.37)
Bleeding	0.66 (0.49- 0.88)	0.30 (0.16-0.56)	0.85 (0.61-1.19)
AMI/VTE/SE	0.70 (0.46-1.05)	0.58 (0.28-1.18)	0.74 (0.45-1.22)
Mortality	0.78 (0.70-0.88)	0.85 (0.68-1.07)	0.75 (0.66-0.86)
Composite	0.79 (0.71-0.88)	0.75 (0.62-0.92)	0.80 (0.70-0.90)
Dabigatran versus Warfarin			
Stroke/TIA	0.92 (0.51-1.65)	0.74 (0.26-2.07)	1.01 (0.50-2.05)
Bleeding	1.10 (0.80-1.53)	1.24 (0.86-1.78)	0.67 (0.31-1.48)
AMI/VTE/SE	0.66 (0.40-1.09)	0.57 (0.24-1.33)	0.73 (0.40-1.33)
Mortality	0.68 (0.59-0.79)	0.63 (0.46-0.86)	0.70 (0.59-0.82)
Composite	0.76 (0.67-0.87)	0.68 (0.52-0.90)	0.79 (0.68-0.92)
Rivaroxaban versus Warfarin			
Stroke/TIA	1.09 (0.73-1.63)	0.94 (0.45-1.96)	1.15 (0.72-1.85)
Bleeding	1.07 (0.87-1.07)	0.96 (0.65-1.42)	1.11 (0.86-1.43)
AMI/VTE/SE	0.91 (0.67-1.24)	0.95 (0.56-1.62)	0.88 (0.60-1.29)
Mortality	0.79 (0.72-0.87)	0.83 (0.69-1.01)	0.78 (0.70-0.87)
Composite	0.86 (0.79-0.94)	0.89 (0.76-1.06)	0.85 (0.77-0.93)

Abbreviations: transient ischemic attack (TIA), acute myocardial infarction (AMI), venous thromboembolism (VTE), systemic embolism (SE), hazard ratio (HR), confidence interval (CI), direct acting oral anticoagulant (DOAC)

Table 4.9. Results of Cox Proportional Hazards Models Comparing DOAC and Warfarin Groups Overall on Falsification Outcomes: COPD and Pneumonia			
	Apixaban vs. Warfarin	Dabigatran vs. Warfarin	Rivaroxaban vs. Warfarin
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Pneumonia[1]	0.92 (0.70-1.22)	1.15 (0.84-1.56)	1.24 (0.99-1.54)
1st half of study period	1.02 (0.63-1.63)	1.18 (0.86 -1.63)	1.33 (1.01-1.74)
2nd half of study period	0.88 (0.62-1.23)	0.85 (0.28-2.51)	1.10 (0.76-1.58)
COPD[2]	0.88 (0.56-1.37)	0.97 (0.61-1.52	1.09 (0.78-1.52)
1st half of study period	0.69 (0.27-1.74)	1.12 (0.68-1.85)	0.72 (0.40-1.32)
2nd half of study period	0.95 (0.57-1.58)	0.54 (0.18-1.61)	1.32 (0.88-1.98)
Abbreviations: chronic obstructive pulmonary disease (COPD), hazard ratio (HR), confidence interval (CI), direct acting oral anticoagulant (DOAC)			

CHAPTER V

DISCUSSION AND CONCLUSIONS

Despite large randomized controlled trials demonstrating the effectiveness of available oral anticoagulants,[28-31,59] the generalizability of this evidence to the nursing home population is impeded by profound differences in patient characteristics and goals of care for those living independently in the community versus those residing in long-term care facilities. The historical warfarin centered treatment paradigm was ill-suited to the nursing home setting, particularly as it existed prior to modern quality improvement efforts.[27,50-52] Most residents with atrial fibrillation did not receive warfarin,[49] and those who were treated typically spent the majority of time outside of the therapeutic range,[27] increasing the risk for adverse events. Therefore, the objectives of this dissertation were to 1) modernize the clinical community's understanding of the atrial fibrillation treatment landscape in nursing homes, 2) explore what characteristics and potentially modifiable factors are associated with anticoagulant use in nursing homes, and 3) develop the comparative effectiveness evidence necessary to inform anticoagulant selection for this population.

In Aim 1, we established a contemporary understanding of anticoagulant utilization patterns by describing the prevalence of anticoagulant use, switching, and discontinuation. Analyses were performed in the full population, by medication class, and by medication. Simultaneously, we characterized the diffusion of a new class of oral anticoagulants into the nursing home setting longitudinally, a path that ultimately led to a new treatment paradigm in which the longtime mainstay of treatment (warfarin) continues to occupy a diminishing role in anticoagulation for nursing home residents with atrial fibrillation. The research conducted in Aim 1 was foundational for the analyses

subsequently conducted in Aims 2 and 3. In Aim 1, we identified the relevant time period during which an increase in anticoagulant utilization in the nursing home occurred after DOACs became available, which informed the selection of the study period for Aim 2, where we confirmed that the increase in anticoagulant use observed was not caused by changes in resident characteristics. In Aim 1, we also discovered that the use of DOAC doses that were not aligned with approved dosing recommendations was highly prevalent, which led to the inclusion of stratified analyses comparing medication safety and effectiveness by alignment of dosing with labeling recommendations in Aim 3.

The descriptive analyses in Aim 1 suggested resident factors such as cognitive impairment and recent clinical events (i.e., ischemic stroke, bleeding) were associated with anticoagulant use, but the multilevel multivariable modeling performed in Aim 2 was critical for understanding what resident, facility, and county characteristics were associated with prescribing in the nursing home setting, and whether anticoagulant use varied across the United States. As expected, well-recognized clinical risk factors comprising risk scoring algorithms were important predictors of treatment. Considerable variation in anticoagulant use was observed between counties, both within and between states. Most notably, this large variation in prescribing was not explained by resident factors as would be expected in situations where adequate evidence exists and best practices have been disseminated and standardized. Instead, after accounting for resident factors, the amount of variation in anticoagulant use between counties increased. The relative contributions of shared decision-making, as is recommended, versus other less desirable forces such as undertreatment of vulnerable residents (e.g., those without social

support) and minority populations, could not be disentangled with the available data. However, the magnitude of geographic variation and the disconnectedness from resident characteristics underscored the substantial need for safety and effectiveness information specific to anticoagulant use in the nursing home population.

In Aim 3, we began to address this prominent gap in the evidence, a gap that will become increasingly conspicuous as the size of the nursing home population continues to increase. This evidence gap was two-fold; 1) among residents with atrial fibrillation there is a need to distinguish which residents should be treated, and 2) among those for whom the net benefit of treatment is positive, there is a need to select the appropriate medication and dosage. A few factors influenced our decision to prioritize the second evidence gap for this dissertation. The characteristics of treated and untreated residents, as well as those receiving DOACs versus warfarin, were summarized in Aim 1. Similar distributions of stroke and bleeding risk factors among DOAC and warfarin users suggested clinical equipoise, an inference reinforced by the close to equivalent fractions of the population using each class of anticoagulants as of the end of 2016. Furthermore, one of the strongest pharmacoepidemiologic study designs (i.e., active-comparator new-user)[68] was well-suited to addressing the question of comparative safety and effectiveness between DOACs and warfarin. In contrast, a comparison of users versus non-users poses challenges associated with the construction of an unbiased comparison group that overcomes the prominent threat to validity posed by selection bias in such designs. Recognizing that clinical trials are very unlikely to be conducted in the nursing home setting, the results from Aim 3 (together with research in younger and community

dwelling populations) are positioned to serve as the backbone of the evidence to guide anticoagulant selection for this population.

Limitations and strengths

Although accepted pharmacoepidemiologic practices were applied throughout this dissertation, each of the studies involved observational research using secondary data sources, and as such, several limitations require acknowledgement. First, anticoagulant use was operationalized using dispensing dates and number of days supplied recorded in Medicare Part D claims. Actual medication use may deviate from observed dispensing patterns, although the issue of patient nonadherence is largely mitigated in nursing home settings by the nature of medication administration by facility staff. Deviations from dispensing patterns may occur due to transitions of care into and out of settings (e.g., hospitals, SNFs) where medications are dispensed and not reimbursed through Medicare Part D. To avoid prematurely censoring residents in hospital settings due to apparent discontinuation (depletion of their outpatient anticoagulant supply), we carried forward the supply available at the time of entry into the hospital/SNF until the end of the stay. Anticoagulant use may have also been misclassified if the medication was filled using health insurance (or cash) other than Medicare. All residents were required to be enrolled in Medicare Part D and to have had at least one medication dispensing, at least partially mitigating concerns of unobserved anticoagulant use. Finally, certain forms of non-standard medication taking behavior are typically not observable in Part D records (e.g., pill splitting), however these instances are expected to have been uncommon.

The study population for this dissertation included nursing home residents with diagnosed atrial fibrillation. To increase specificity, only residents with both a qualifying Medicare Part A diagnosis (atrial fibrillation or atrial flutter) and a qualifying MDS 3.0 diagnosis (dysrhythmia, atrial fibrillation, or atrial flutter) in the prior year were eligible for the study. As a consequence, only residents who had been discharged from a hospital or SNF in the prior year would be eligible for inclusion. Selection bias may have been introduced if long-term nursing home residents who did not recently contact acute or post-acute care differed in the prevalence of anticoagulant use from those residents who had a hospitalization or SNF stay. Our concerns regarding the inclusion of residents with only a hospital diagnosis centered on the potential for a diagnosis based on transient episode in the inpatient setting, while the majority of MDS diagnoses were non-specific (i.e., dysrhythmia). In practice our concerns were valid and the requirement for diagnoses in both settings justified, as only 27% of residents with a hospital diagnosis but no MDS diagnosis received oral anticoagulants, suggesting that a sizable fraction likely had a transient acute episode. However, it is also possible that residents did not have adequate follow-up for chronic atrial fibrillation after the transition in care back to the nursing home setting.

Outcome misclassification constituted a threat to validity for the comparative analyses performed in Aim 3. Validated algorithms relying on ICD-9 and ICD-10 codes from Medicare Part A claims were used to operationalize clinical outcomes. Although coding practices may change over time and most algorithms have not been validated since the transition from ICD-9 to ICD-10, we used federally issued General Equivalence

Mappings (GEMs)[128] to translate the ICD-9 based algorithms to ICD-10. Because of the close conceptual relationship between the ICD-9 and ICD-10 codes comprising our outcome definitions, and with the use of GEMs, positive predictive values of the algorithms were expected to be comparable to the original validation studies. Of potentially greater significance was under-detection of clinical outcomes which either were sufficiently minor to not precipitate a hospitalization or that were severe enough to cause death. In both cases, residents would not enter the hospital and generate a Medicare Part A claim from which the outcome could be identified. Our net clinical benefit composite outcome, which included all-cause mortality, shed some light on the possibility of differential incidence of severe clinical events resulting in death. The lower mortality and composite event rates with the DOACs versus warfarin suggested unobserved severe clinical events resulting in death may have been more common in the warfarin group. However, imbalance in unmeasured confounding variables associated with mortality could also explain this finding.

Unmeasured or residual confounding represents an additional threat to validity for the comparative effectiveness research conducted in Aim 3. Confounding by indication is typically most pronounced in comparisons across indications, between prevalent users, or between treated and untreated populations. Our new-user, active comparator design, was well-suited to dealing with confounding by indication.[68] Our analytic strategy, propensity score matching, was applied for the purpose of assembling balanced treatment and comparison groups to thwart confounding as a threat to validity.[69,70] Empirically, we achieved balance on a large set of potential confounders including the most important

clinical risk factors for the outcomes under investigation. Although unmeasured confounding cannot be entirely excluded as a possible explanation for the observed results, the results for falsification outcomes (pneumonia, COPD) not known to be associated with either of the classes of oral anticoagulants under study were not indicative of strong unmeasured confounding.

This dissertation had several strengths. By linking multiple the MDS 3.0 with Medicare files we were able to develop a near complete picture of a national population of residents' demographic, clinical, and functional characteristics and then follow residents longitudinally throughout transitions in care to acute, post-acute, and long-term care settings. The linkage to facility and county level files enabled multilevel modeling analyses which yielded insights into possible hot-spots for quality improvement (i.e., geographies with low anticoagulant utilization), while also providing important confirmation that widespread variation in prescribing is not systematic in nature and in doing so underscoring the need for best practice standards specific to the nursing home. Finally, the contemporary nature of the data used for this dissertation increases the potency of the findings for motivating clinical and policy changes.

Implications and future research

The output from the three specific aims of this dissertation have important clinical and research implications.

Clinical implications

The findings of this dissertation are expected to influence clinical practice and guide treatment protocols developed by health systems and guideline promulgating

committees. First, the prevalence of off-label DOAC dosing was higher in the nursing home than in the community. Individuals receiving DOAC doses that were not aligned with recommended dosing had higher rates of ischemic stroke in the case of underdosing and higher rates of hemorrhage in the case of overdosing. Targeted quality improvement activities by individual facilities, their corporate parents, and their clinical consultants (e.g., consultant pharmacists) may be warranted to address dosing alignment. Second, results of our comparative effectiveness research should reassure clinicians that DOACs can be confidently used with equal or greater benefit than warfarin. At the same time, our findings suggested that providers may be better selecting candidates for warfarin therapy and/or better managing warfarin users, as residents initiating warfarin after DOAC utilization was widespread achieved lower stroke rates than those initiating warfarin prior to the widespread utilization of DOACs. Individual comparisons of apixaban, rivaroxaban, and dabigatran versus warfarin by dose should be used to inform shared decision-making processes for drug and dose selection.

Research implications

This dissertation establishes a foundation for multiple avenues of future research. First, additional observational research is needed to inform the critical decision of whether or not to anticoagulate nursing home residents with atrial fibrillation. This will involve comparisons of users of anticoagulants, by medication, versus similar residents who are not receiving oral anticoagulants. To overcome the challenge of confounding by indication, researchers should consider the advantages of using antiplatelets as an active comparator group, or potentially leveraging variation in anticoagulant prescribing

preferences across nursing homes as an instrumental variable. Subgroup analyses will be important for identifying subgroups of residents with distinctly higher or lower risk of specific outcomes in the presence or absence of treatment. Beyond observational research, randomized clinical trials would provide gold standard level of evidence to guide treatment. Trials involving DOACs would be of highest value if multiple doses were evaluated separately for subgroups of residents with different levels of renal impairment. This level of trial-based research could be used to change the drug prescribing information approved by the FDA.

In addition to comparative effectiveness research, predictive modeling is an important next step for the purpose of developing risk scoring algorithms tailored to the nursing home population. If a parsimonious set of routinely available risk factors were to be assembled into a predictive algorithm with acceptable accuracy, opportunities for adapting the algorithm for clinical use should be explored with a goal of ultimately evaluating the utility within the context of resident-centered shared decision-making. Other important complimentary research efforts could improve the utility of the findings from this dissertation. Validation studies of ICD-10 code based outcome definitions for the nursing home population could illuminate the extent to which minor clinical events and fatal clinical events are under-detected by hospital-based ICD coding algorithms. Qualitative research is also needed to better understand resident, family member, and provider perceptions of and willingness to participate in a shared decision-making process for anticoagulation decisions.

Conclusions

In summary, the three studies comprising this dissertation updated and advanced the field's understanding of one of the most effective[25] and highest risk classes[138] of medications for a particularly vulnerable and challenging patient population. The proportion of nursing home residents with atrial fibrillation was found to have increased from 30% in 2004[49] to 48% by the end of our study period (2016). Simultaneously, the uptake of a novel class of medications (DOACs) was found to have displaced approximately half of the warfarin utilization in the nursing home setting, while also contributing to an increase in anticoagulant use of ~5% between 2014 and 2016. Our research demonstrated the absence of a systematic approach to anticoagulant use in United States nursing homes. We then began to address the glaring need for evidence to inform anticoagulant selection by evaluating the comparative safety and effectiveness of individual DOACs versus warfarin. Our findings suggested that overall, DOACs were being used with equal or greater benefit than warfarin, but that there is likely opportunity to improve outcomes with DOAC use by aligning dosing with FDA approved labeling. Future research should prioritize additional comparative effectiveness research and the development of predictive algorithms specific to the nursing home setting to identify subgroups of residents most likely to benefit from treatment and to package this information so that it is useful as part of a resident-centered shared decision-making process.

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