Curriculum Vitae

Name: Christine Susan Gill (formerly Christine Susan Franey)

Contact information: csfraney@gmail.com

Degree and Date to be Conferred: Ph.D., 2018

Collegiate Institutions Attended:

University of Maryland, Baltimore, MD 2011-2018
Ph.D., Epidemiology
Mentor: Mona Baumgarten

University of Michigan School of Public Health, Ann Arbor 2006-2008
M.P.H. in Epidemiology, Reproductive and Women's Health Interdepartmental Concentration

Simmons College, Boston, MA 2002-2006
B.S. in Chemistry and Mathematics
Completed the Honors Program. Inducted into the Sigma Xi national honors society. Received the American Chemical Society award in Chemistry in 2006.

Professional Publications:

Franey C, Rattinger GB, Schneider M, Zuckerman IH. Osteoporosis treatment patterns and fracture risk among older women: when are women treated in conventional practice? Poster presented at the Women's Health 2010: The 18th Annual Congress, Washington, DC, March 26-28, 2010.

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Professional Positions Held:

Index Analytics, LLC
3700 Koppers Street, Baltimore, MD 21227
Research Scientist — November 2018 – present

IMPAQ International, LLC
10420 Little Patuxent Pkwy Suite 300, Columbia, MD 21044
Research Associate — June 2016 – October 2018

University of Maryland, Baltimore
220 North Arch Street, Baltimore, MD 21201
Assistant Project Director — January 2011 – June 2016
Research Information Specialist — April 2010 – January 2011
Research Analyst — June 2008 – April 2010

Abstract

Title: Oral Anticoagulation Medication Usage in Older Adults with Atrial Fibrillation Residing in Long-term Care Facilities

Christine Gill, Doctor of Philosophy, 2018

Dissertation Directed by: Mona Baumgarten

Statement of the problem: Oral anticoagulants (AC) reduce the risk of ischemic stroke (IS) in older adults with atrial fibrillation (AF) but increase the risk of major hemorrhage. Treatment with ACs requires prescribers and patients to weigh benefits against risks. Many older adults with AF residing in long-term care (LTC) facilities may not be using ACs, even in the absence of absolute contraindications. This study (1) examined the prevalence of AC use, (2) assessed which factors were associated with AC use, and (3) estimated the net effect of ACs weighing the benefit (IS prevention) against the risk (intracranial hemorrhage [ICH]) in older adults with AF residing in LTC facilities.

Methods: An observational cohort study was performed using a 5% random sample of older adults with AF residing in LTC facilities for at least 101 days from 2007 to 2013 using a Medicare administrative claims database linked to the Minimum Dataset assessments.

Results: Of the 21,877 Medicare beneficiaries meeting the study eligibility criteria, over half (54.6%) were 85 years or older, most were female (75.9%) and white (88.1%). The prevalence of AC use was 36.2% (95% confidence interval [CI]: 35.6%-36.8%). History of stroke or transient ischemic attack and history of thromboembolism were associated with an increased likelihood of AC use, while history of internal bleed was associated with a decreased likelihood of AC use. The net effect of AC use was 1.07 per 100 person-years, 95% CI: 0.31-3.01; this is the difference between, on the one hand, the difference in the estimated rate of IS while not using ACs and using ACs and, on the other hand, the difference between the estimated rate of ICH while using ACs and not using ACs .

Conclusions: The majority of older adults with AF residing in LTC facilities are not being managed with ACs. While this study provides evidence suggestive of a net benefit of AC use in older adults with AF residing in LTC facilities, health status and the burden of medication monitoring are among the other factors that patients, their caregivers and providers should consider when making the decision about initiating ACs.

Oral Anticoagulation Medication Usage in Older Adults with Atrial Fibrillation Residing in Long-term Care Facilities

by
Christine Gill

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
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List of Abbreviations

Abbreviation	**Description**
AC	Anticoagulant
AF	Atrial fibrillation
CI	Confidence interval
CCW	Chronic Condition Warehouse
CMS	Centers for Medicare and Medicaid Services
GEE	Generalized estimating equation
ICH	Intracranial hemorrhage
IPW	Inverse probability of exposure and censoring weight
IS	Ischemic stroke
LTC	Long-term care
MDS	Minimum Data Set
MSM	Marginal structural models
OR	Odds ratio

Chapter 1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Having AF increases a person's risk of ischemic stroke (IS) five-fold (Wolf 1991, Atrial Fibrillation Investigators 1994, Roger 2011). IS is the fifth leading cause of death in the nation (Kochanek 2013, Mozzafarian 2015) and if survived, can lead to permanent disability. Advancing age is also a potent risk factor for IS (Feinberg 1995). Therefore, older adults with AF are at particularly high risk for IS. The prevalence of AF is increasing (Naccarelli 2009), which is likely due to the aging population. In 2013, there were more than 2.3 million Medicare beneficiaries living with AF (CCW 2015).

Treatments are available to mitigate the risk of IS in people with AF. Guidelines for IS prevention in AF have been published by national and international committees and have been updated as recently as 2017 (Fuster 2006, Camm 2010, Kirchhof 2016, Singer 2008, You 2012, Frost 2017). All the guidelines recommend antithrombotic therapy for patients with AF to prevent emboli that could impede blood flow to the brain and lead to an IS. Two types of antithrombotic therapy are ACs and antiplatelet agents, which act in different ways within the human body. ACs "lengthen the time it takes to form a blood clot" while antiplatelet agents "prevent blood cells called platelets from clumping together to form a clot" (U.S. National Library of Medicine). The guidelines vary in their exact recommendations, but there is a clear message: ACs are recommended for those with moderate to high IS risk while aspirin, an antiplatelet medication, can be used for those with low IS risk or for those who cannot tolerate ACs (Fuster 2011, Anderson 2013).

Despite the benefits of AC treatment in terms of IS prevention, AC use increases the risk of hemorrhage including hemorrhagic stroke. Stroke from either etiology (ischemic or hemorrhagic) can lead to permanent disability, decline in quality of life, or sudden death. The most recent guidelines for the management of IS in people with AF recommend the use of IS and major hemorrhage risk scores to inform the AC treatment decision (Frost 2017). The IS risk score evaluates an individual's IS risk on a scale (low, medium, high) so that clinicians and patients can make informed, individualized treatment decisions. Similarly, recent guidelines recommend using a hemorrhage risk score (Frost 2017). Treatment decisions require balancing these two competing outcomes – IS prevention and major hemorrhage risk.

The AF management guidelines apply to people of all ages with AF and are based on expert consensus and review of the available literature. Many of these reviews are based on data from clinical trials. Most clinical trials establishing the efficacy and safety of ACs included younger and healthier older adults living in the community as compared to those residing in LTC facilities. Additionally, most of the clinical trials had a fairly short duration of AC exposure. For example, the Stroke Prevention in Atrial Fibrillation Study (SPAF) had a mean follow-up of 1.3 years (Stroke Prevention in Atrial Fibrillation Investigators, 1991), and the Boston Area Anticoagulation Trial had a mean follow-up of 2.2 years (Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990). These studies provided evidence for the efficacy of warfarin, the most commonly used AC, in the prevention of IS but because of the short duration of follow-up, these studies cannot support specific recommendations on the risks and benefits of treatment for people who have been using the medication for a longer duration. As people age, they may develop comorbid conditions and require treatment of these conditions with medications other than ACs, which adds complexity to the management of their increased IS risk due to AF. The guidelines do not provide recommendations specific to frail, medically complex older adults, including those residing in LTC facilities (Neidecker 2012).

Chapter 2 Critical Literature Review and Study Aims

Treatment decisions for IS prevention among people with AF require balancing the two competing consequences of AC treatment – IS and major hemorrhage. The guidelines recommend using a risk score to evaluate IS risk when deciding whether to prescribe anticoagulants (Lip 2010). A complicating factor is that the guidelines also recommend considering factors that increase hemorrhage risk when making a decision about prescribing anticoagulants. Some of the IS risk factors (e.g., uncontrolled hypertension, prior IS, and advanced age) are also associated with increased risk of hemorrhage. This overlap in risk factors for hemorrhage and IS leads to a clinical dilemma as to which patients will benefit from AC treatment.

The recommended IS risk score is referred to as the CHA_2DS_2-VASc risk score, which stands for Congestive heart failure/left ventricular dysfunction, Hypertension, Age >= 75 years, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism, Vascular disease, Age 65-74 years, Sex category (female gender). The motivation for developing the CHA_2DS_2-VASc score was that the prior stroke and thromboembolism scores were developed using data collected in clinical trials. Since clinical trial populations are highly selected, earlier risk scores were not considered accurate in predicting IS risk in more representative populations. The CHA_2DS_2-VASc risk score was developed to predict IS and thromboembolism in patients with AF in a 'real-world' setting. Each of the components is given a score of 1, with the exception of age >=75 years and stroke/transient ischemic attack/thromboembolism, which are given a score of 2. Low risk is defined as a score of zero, intermediate risk is defined as a score of 1, and high risk is defined as a score of 2 or greater.

In addition to IS risk, risk of major hemorrhage should be considered when deciding to prescribe – or to continue to prescribe – ACs. To evaluate hemorrhage risk, a number of risk scores have been developed, but the guidelines do not endorse one scoring tool over the others. The HASBLED is a tool that was developed to predict the one-year risk of major bleeding in people with AF. Major bleeding included intracranial bleeding, hospitalization for bleeding, hemoglobin decrease of more than two grams per liter, or blood transfusion. The score includes the following factors: Hypertension, Abnormal renal or liver function, prior Stroke, Bleeding history, Labile international normalized ratios, Elderly ($\geq$65 years), and concomitant Drug and alcohol use (Pisters 2010). The HASBLED tool and the CHA_2DS_2-VASc risk score include common factors that are predictive of both outcomes (i.e., IS and hemorrhage). Because of the overlap between the IS and hemorrhage risk factors, prescribers must weigh the risks of both ischemic IS and hemorrhage.

Despite the existence of IS and hemorrhage risk scores that can inform whether a patient may benefit from antithrombotic therapy for IS prevention, there are many older adults who are not being managed with ACs. Observational studies of older adults with AF without absolute contraindications to AC use, including studies examining LTC facility residing populations, report a frequency of AC use that ranges from 17% to 60% (Abdel-Latif 2005, Gurwitz 1997, Lackner 1995, Lau 2004, McCormick 2001), suggesting possible underutilization of AC in this population (Gurwitz 1997). However, there is a large variation in the estimated rates of AC use in LTC facility residents possibly due to the heterogeneity in the study samples and time periods of the studies.

Some early studies found lower warfarin utilization rates than more recent studies. For example, Lackner and colleagues (1995) found that only 20% of LTC facility residents with AF who lacked contraindications to warfarin were treated with warfarin in nursing homes in Minnesota. Another study performed by Gurwitz et al. (1997) measured AC use in 30 LTC facilities in New England, Quebec and Ontario and found that 32% of patients with AF were being treated with warfarin. Treatment with warfarin was defined as at least 10 days with warfarin treatment in a 12-month period. Another study by McCormick et al. (2001) found that 53% of ideal candidates for AC treatment were receiving warfarin treatment in a medical record review of residents with AF from a convenience sample of 21 LTC facilities in Connecticut. This study defined treatment with warfarin as at least two weeks with warfarin treatment during the 12-month study period. Both the Gurwitz and McCormick studies were based on medical chart abstraction. Lau and colleagues (2004) examined the rates of AC use in 17 LTC facilities in Alberta, Canada, and they found that 50% of AF residents with high IS risk were using ACs. In this study, 22% of residents with AF were using aspirin and 8% were using aspirin and AC. Similar rates of AC use and aspirin use were reported by Oo and colleagues (2015) among LTC facility residents with AF in one facility near New York City using retrospective chart review.

In a cross-sectional study, Reardon et al. (2013) found that 34% of LTC facility residents with AF were using ACs based on data from the 2004 National Nursing Home Survey (NNHS), a national survey implemented by the U.S. Center for Disease Control and Prevention. They also found that 45% of residents with AF were using ACs based on 2007-2009 data from AnalytiCare databases, which is derived from the Minimum Data

Set (MDS) and pharmacy dispensing records. A study by Ghaswalla and colleagues (2012) found a similar AC utilization rate of 30% in the 2004 NNHS. This estimate included those with AF and no known contraindication to warfarin use. They found that an additional 23% were receiving aspirin or clopidogrel, both antiplatelet agents. Thus, over 50% of LTC facility residents were not receiving any medication for IS prevention.

These studies examining AC utilization report heterogeneous estimates. The studies are primarily cross-sectional in design and define warfarin use based on a single point in time or as at least 10 days of use within a fairly long time period (e.g., over the course of 12 months). The variation observed in the proportion of AC users could be due to the point in time when the measurements in each study were taken. The characteristics of people with AF in LTC facilities could vary based on location or the time when the measure was taken, which could explain the differences in AC utilization found. The variation in these numbers supports the need for a current, national estimate of AC use in the LTC facility residing population stratified by demographic characteristics, as we propose to provide in Aim 1.

To understand what is responsible for low AC utilization rates, studies have examined physician prescribing of ACs for older adults. There is evidence that physicians err on the side of not prescribing AC medication when faced with complex patients. The most common reasons for not prescribing AC are recurrent falls, past history of bleeding, advanced age, frailty and cognitive impairment (Bahri 2015, Dharmarajan 2006, Monette 1997). In one study of 182 physicians who were actively providing care to older adults in 30 LTC facilities in New England, Quebec and Ontario, nearly 50% of the physicians agreed that “the benefits of warfarin therapy ‘greatly outweigh the risks’ in this setting”

(Monette 1997). Even after Monette's study was published in 1997, the low utilization patterns persisted. A study using data from nursing home residents in France in 2012 reported that physicians were not prescribing ACs for similar reasons – recurrent falls, past bleeding history, advanced age, frailty and cognitive impairment – even when managing residents with a high IS risk (Bahri 2015). Although a review of the literature found that fall risk alone should not be a contraindication for AC use (Garwood 2008), results from these other studies suggest that fall risk influences prescribing.

One study found that nearly 40% of LTC facility residents with AF discontinued warfarin within 90 days of starting and 65% discontinued by 365 days (Patel 2013). Advanced age and dementia were among the strongest predictors of discontinuation in that study. The factors leading to warfarin discontinuation in LTC facility residents are similar to the factors preventing people from receiving warfarin in the first place. The literature lacks a definitive answer to what factors or combination of factors prescribers should weigh most when deciding what treatment course to pursue with medically complex, older adults residing in LTC facilities. Therefore, there is a need to examine (1) which factors influence AC prescribing (Aim 2) and (2) whether or not there is a positive net effect of AC use (Aim 3).

Until recently, warfarin was the only AC medication available for IS prevention in people with AF. More recently, newer oral anticoagulants have been approved for IS prevention in AF. However, warfarin is still the most commonly used AC. Patients using warfarin require close monitoring of the international normalized ratio (INR), a measure of the blood's coagulation time (Kuruvilla 2001). Warfarin, unlike the newer ACs, interacts with diet, alcohol and other medications, which can make dosing more challenging due to the need for frequent INR monitoring. Warfarin is one of the most common causes of adverse drug events in the elderly. One study examining adverse events due to warfarin in 25 nursing homes in Connecticut found a rate of 2.49 adverse events per 100 resident months (Gurwitz 2007). The authors considered that 57% of the events (which they defined as “serious, life-threatening, or fatal”) were potentially preventable. Serious events were defined as those that required treatment or medical evaluation (like surgical intervention to stop bleeding), an IS or any two of the following: transfusion, hypotension, critical anemia or acute bleeding. The authors defined “potentially preventable” as events that were due to an error and were preventable by available means. These results support physician and resident concerns over the risks of warfarin use and reinforce the importance of careful monitoring.

Physicians may put more weight on the potential hemorrhage risk than on the potential for IS prevention. The effects of warfarin are reversible, meaning that its ability to reduce blood coagulation can be blocked with an antidote. The effects of the newer oral ACs are not reversible, but they have fewer side effects, making them more desirable to some people. This becomes clinically relevant when a person falls or sustains another trauma. If a person is on warfarin and begins to bleed, treatments can stop the bleeding, whereas a person on a new oral AC will not be able to control the bleeding as readily. Before the new oral ACs were on the market, physician preference for considering hemorrhage risk more than IS risk was one explanation for low AC utilization even in populations where there is a high prevalence of moderate to high IS risk. Studies have not examined physician preference in relation to use of the newer ACs.

Although there are validated measures of IS risk, like the CHA_2DS_2-VASc score described above, and risk assessment scales for major hemorrhage that are recommended in guidelines, there are still people with high IS risk and low to moderate hemorrhage risk who are not receiving AC treatment for IS prevention. The explanation for the potential underutilization of ACs may be that physicians rely on clinical judgement to determine the importance of bleeding risk relative to IS risk. Aim 2 will examine which individual IS risk factors, hemorrhage risk factors and other patient characteristics influence AC use.

While clinical trials have shown that there are significant benefits associated with AC use, there is still uncertainty about the relative risks and benefits in subgroups of the AF patient population, especially for those residing in LTC facilities. In addition studies have shown that while there has been an increased use of warfarin, the incidence of ischemic IS in Medicare beneficiaries declined both in those who were and who were not treated with warfarin from the early 1990s to 2009 (Shroff 2013, Shroff 2014). The uncertainty of whether the benefits outweigh the risks in older adults with AF residing in LTC facilities motivates Aim 3 of this study, which is to estimate the net effect associated with AC use considering both IS and ICH in people with AF residing in LTC facilities. The analytic approach for estimating net effect has been applied to data from a general adult population with non-valvular AF using data from an integrated health care system (Singer 2009). Singer and colleagues (2009) found a positive net effect of warfarin use, with the greatest benefit experienced by those with the highest IS risk. Our study applied similar methods to examine if there was a net benefit of AC treatment in the LTC facility residing population with AF. The results of our study will help providers and LTC facility residents make evidence-based choices when they face the dilemma of whether to prescribe and use ACs.

Research Questions: This study aimed to answer the following research questions:

1. What is the prevalence of oral AC medication use in older adults with AF residing in LTC facilities overall and by beneficiary characteristics?
2. What factors are associated with oral AC medication use in older adults with AF residing in LTC facilities?
3. Is there a net benefit associated with oral AC medication use considering risk of major hemorrhage and IS prevention among older adults with AF residing in LTC facilities?

Specific Aims:

1. To estimate AC medication use by year, type of medication, geographic region, age, race, and sex, among LTC facility residents with AF

2. To identify factors associated with AC medication use, including risk factors for IS, risk factors for major hemorrhage, and factors that may influence physician prescribing, among older adults with AF residing in LTC facilities

    a. Hypothesis: Characteristics known to be risk factors for major hemorrhage will be associated with a lower frequency of AC use.

    b. Hypothesis: Characteristics known to be risk factors for IS will be associated with a higher frequency of AC use.

c. Hypothesis: Malignancy, anemia, falls, frailty, cognitive impairment, Parkinson’s disease, and trauma will be associated with a lower frequency of AC use.

3. To measure the net effect of AC use considering the risk of ICH and the benefit of IS prevention, among LTC residents with AF

   a. Hypothesis: There will be a net benefit of AC use in LTC facility residents with AF.

Chapter 3 Methods

Study Design

This study was a retrospective cohort study using a Medicare administrative claims database.

Participant Selection

The target population was older adults with prevalent, non-valvular AF residing in LTC facilities.

The study population was identified using a 5% random sample of Medicare beneficiaries. Patients meeting all of the following criteria were included:

- Fee-for-service (FFS) Medicare beneficiaries during at least the one year prior to index date (defined below) and the first month of follow-up (the 30-day period including the index date plus 29 days): FFS enrollees have complete information on health services reimbursed by the Centers for Medicare and Medicaid Services (Centers for Medicare and Medicaid Services). This criterion excluded Medicare Advantage enrollees, who have incomplete information on health services.

- Enrolled in standalone Part D Prescription Drug Plans (PDP) during at least the one year prior to index date (defined below) and the first month of follow-up (the 30-day period including the index date plus 29 days): These people have information on all prescriptions filled using Part D. This is the type of drug plan available for FFS Medicare beneficiaries.

- Age 66 years and older: This allowed for inclusion of participants qualifying for Medicare based on age and excluded those qualifying for Medicare due to disability or end-stage renal disease alone.

- Non-valvular AF: This criterion was defined in administrative claims by the presence of an AF diagnosis code (ICD-9-CM 427.31) in a patient without any evidence of prosthetic valve replacement (ICD-9-CM diagnosis code: V43.3, ICD-9-CM procedure code 35.05, 35.07, 35.2, 35.20, 35.21, 35.22, 35.23, 35.24, 35.25, 35.26, 35.27, 35.28, or CPT code 33361, 33362, 33363, 33364, 33365, 33366, 33367, 33368, 33369, 33405, 33406, 33410, 33411, 33412, 33413, 33430, 33465, 33468, 33477, 33496). All codes and their descriptions are included in Appendix A. Those with a prosthetic valve were not included because having a prosthetic valve is an absolute indication for anticoagulant use.

- Resident of a CMS-certified LTC facility for at least 101 days: CMS-certified facilities provide short- and long-term care for people who need 24-hour nursing care and who cannot be cared for at home. This care setting does not include assisted living facilities, home- or community-based care (CMS, 2018). The 101-day requirement was selected for two reasons: (1) to exclude those with short stays who are not part of the target LTC population, and (2) because drug use is unobservable during the first 100 days due to the bundling of drug costs under the facility charge to Medicare.

- Non-missing demographic characteristics: This criterion excluded people with missing race or region so that all participants in the sample could be included in multivariable analyses. Also, results for some of the groups with missing values for demographic characteristics could not have been reported because the data use agreement prohibited reporting results for groups with fewer than 11 people.

Data Source

We used the Chronic Condition Warehouse (CCW) 5% Medicare sample data from 2006 to 2013. This data source contained a 5% random sample of Medicare beneficiaries who were followed from year to year. This allowed continued observation of these beneficiaries over the time the data were available (2006 to 2013). The random sample was designed by CMS's data vendor and was based on the presence of certain selected digits (unknown to researchers) in the last two positions of the unique beneficiary identifier. A unique, encrypted identifier was assigned to the beneficiary in the research-ready datasets. The same beneficiaries were included over time if they remained in Medicare. Over time, some beneficiaries left the sample due to death and others joined the sample as they qualified for Medicare. The CCW files that were requested for this study under the data use agreement with CMS were the Master Beneficiary Summary File (MBSF), all institutional and non-institutional claims, Part D Prescription Drug Events (PDE) and the Minimum Data Set (MDS) assessments.

The MBSF was used to capture demographic information (age, sex, race, and geographic location), monthly Medicare Part A and B coverage, monthly Part D PDP enrollment, and date of death. The MBSF – Chronic Condition Segment is another data file within the CCW database that provided annual indicators and first-ever dates of diagnosis for 27 chronic conditions, including atrial fibrillation. The AF first-ever date was used to identify people with prevalent atrial fibrillation. This date is defined as the earliest claim observed with the atrial fibrillation diagnosis code (427.31) on one inpatient or two outpatient or physician services claims.

The claims were used to capture information on diagnoses, procedures and health care utilization (e.g., hospitalizations). Claims included those for inpatient care, outpatient care, skilled nursing facility care, hospice care, home health care, physician services and durable medical equipment.

PDEs were used to capture information on filled prescriptions using the National Drug Code for ACs and antiplatelets (National Drug Code Directory 2017). The National Drug Code is a unique product identifier for medications and medical devices. The National Drug Codes were identified by searching the First Databank drug dictionary for the records that had a generic name that matched a drug of interest. We included warfarin and two newer ACs, dabigatran and rivaroxaban, approved in 2010 and 2011, respectively. We included clopidogrel and ticagrelor antiplatelet medications. The PDEs also included the prescription fill date, quantity dispensed and days' supply for each prescription.

The MDS was used to define LTC episodes and to capture information on falls, cognitive status, medically relevant conditions, and frailty. The MDS comprised data on federally-mandated clinical assessments that were completed on residents in Medicare- and Medicaid-certified nursing homes at semi-regular intervals (at least quarterly). The MDS included the type of assessment, and the admission and discharge dates from the facility. Because MDS version 3.0 was implemented in 2010, which was during the study period, both MDS versions 2.0 and 3.0 were included in this study. Information from both versions of the assessments was combined for study participants to capture information during their entire time residing in LTC facilities. The assessments are completed by medical staff (e.g., nurses) within the facility using a standardized form. Each of the assessments captures a number of conditions based on direct observation of the beneficiary, medical chart abstraction and, in some cases, interview of the beneficiary or his or her caregiver as, for example, in the case of cognitive impairment. The conditions captured are part of the “active diagnoses” section, which captures conditions that have a direct relationship with the resident’s current status and medical treatments (DHHS, 2015).

Observation Period

Since Medicare does not pay for LTC services, there were no claims that could identify a LTC stay. Therefore, all of the MDS assessments for each beneficiary were combined and sorted from earliest to latest during the study period to identify when a person was residing in a LTC facility. Study participants were considered to be residing in the facility from their earliest assessment date to their last assessment or the end of the study period, whichever came first. Since assessments are completed at least quarterly, per regulatory requirements, if a gap of more than a quarter was observed without an assessment, the study participant was censored as of the latest observed assessment.

After the LTC stays for each beneficiary were established using the MDS assessment, the study participant was assigned an index date that marked the start of follow-up. The index date was the date at which the study participant was both a LTC resident and diagnosed with AF. The start of LTC residence was defined as the 101st consecutive day after admission to a LTC facility. If a study participant was diagnosed with AF before the

101st day, then the 101st day was assigned as their index date. If a study participant was diagnosed with AF on or after the 101st day, then their index date was the date when they were diagnosed with AF. The same index date was used for all three study aims.

For Aim 1, the end of follow-up was defined as the date of the earliest of the following events: death, end of FFS Medicare coverage (Part A or B), end of Medicare Part D coverage, or discharge from the LTC facility. Aims 2 and 3 included an additional criterion to truncate the end of observation, which is described with each aim's methods.

Some characteristics were evaluated in the year prior to the index date. This time period was referred to as the baseline period.

Characterization of the Cohort

The following characteristics of the cohort were examined: (1) the distribution of the length of follow-up by reason for ending observation, (2) the distribution of the number of people entering and exiting the cohort in each calendar year, and (3) a comparison between the demographic characteristics of the cohort and of those people who met the cohort inclusion criteria up through being a resident in a CMS-certified LTC facility, but were excluded from the cohort based on a subsequent eligibility criterion.

Methods Specific to Aim 1

The first aim was to estimate the prevalence of AC medication use, among LTC residents with AF, by geographic region, age, race, sex, and year from 2007 to 2013**.** While the Part D prescription drug plan began in 2006, we began examining drug utilization in 2007 to allow time for the resolution of any administrative issues related to the implementation of the new program.

Variables for Aim 1

Two outcomes were measured. The first outcome was the period prevalence of AC use, where use was defined as having at least one prescription fill with a National Drug Code for warfarin, dabigatran, or rivaroxaban. A fill appeared in the data when a prescription or a refill was dispensed by a pharmacist.

The second outcome was the degree of medication use as measured by proportion of days covered (PDC) for prescriptions with a National Drug Code for warfarin, dabigatran, or rivaroxaban. All three anticoagulants were combined because the frequency of utilization of the new ACs, dabigatran and rivaroxaban, was too low to examine them separately from warfarin. The numerator of PDC was the number of days in a period with the drug available to be taken. The amount of drug available was calculated from the prescription fills by adding the days' supply reported on the claim to the fill date. The days' supply was the number of days the dispensed medication would cover if taken as prescribed. For example, a person with a drug claim with a fill date of January 1, 2007 and a prescription for a 30-day supply of the drug was considered to be taking the drug of interest from January 1, 2007 through January 30, 2007. The denominator of the PDC was the number of days within the period of interest. The denominator was restricted to days during which the person was in a LTC facility. PDC values of 80% or higher indicate a high level of adherence, according to the Pharmacy Quality Alliance, a group that makes recommendations to CMS on quality metrics derived from administrative claims data (Nau 2015).

The stratifying variables were geographic region, age group, race, sex, and year.

Analysis for Aim 1

For the first outcome, the period prevalence with 95% confidence interval was estimated. The period prevalence was defined as the number of study participants with at least one day of AC use during the time period divided by the number of study participants observed during the period. We defined the outcome as at least one day of AC use because our interest for this aim was any use of medication, regardless of duration. The time period was defined in two ways. First, the period prevalence was calculated per year (and per year by characteristic), and second, the period prevalence was calculated across all years. To generate the estimate of the overall prevalence and its 95% confidence interval across all years or across all years by characteristic (age group, sex, race and region), a regression model was used for each characteristic. We used a repeated measures logistic regression model using generalized estimating equations (GEE) with exchangeable correlation matrix to account for multiple observations per person.

For the second outcome, the distribution of PDC was reported using the following statistics: median, minimum, maximum, and cutoff for the lower quartile. The same time periods were used as for the first outcome. The PDC was calculated overall and by characteristic for all years combined, and separately for each year and characteristic.

Methods Specific to Aim 2

The second aim was to identify factors associated with AC medication use, including IS risk factors, risk factors for major hemorrhage, and factors that may influence physician prescribing among older adults with AF residing in LTC.

Observation Period for Aim 2

Follow-up time was divided into 30-day periods. Although these periods are referred to as “months” in this study, they do not correspond to calendar months and could cross calendar years.

The observation period was from entry into a LTC facility to the earliest of discharge from the facility, death, the end of the study period (12/31/2013), or the end of the first 24 months (30-day periods of follow-up) in LTC. The first three criteria were similar to those used for Aim 1. Because the study participants were followed for a variable amount of time, the sample size in later months became too small to generate reliable estimates. As a result, a follow-up duration of up to 24 months was used because it fell between the median follow-up time of 16 months and the upper quartile of follow-up time (30 months).

Variables for Aim 2

The outcome for this aim was AC medication use (yes/no indicator) in each month following entry into LTC. For a given study participant and a given month, AC use was considered to be present if there was a prescription fill with at least 15 days’ supply in the month. The reason for selecting the 15-day cut point was that warfarin’s half-life is one week, according to its package insert. If the study participant had at least 15 days of medication use, the study participant experienced the therapeutic effects for the majority of the month.

The potential predictors included were those that have been found to be associated with AC use in AF nursing home populations in prior studies (Abdel-Latif 2005, Gurwitz

1997, Lackner 1995, Lau 2004, McCormick 2001, Bahri 2015, Dharmarajan 2006, Monette 1997). These included IS risk factors, hemorrhage risk factors, and resident characteristics thought to influence physician prescribing of ACs. Some of these variables were static (measured at baseline) while others were time-varying. All were inherently categorical with the exception of frailty and age.

All factors (with the exception of age, sex, and antiplatelet use) were defined using the Minimum Dataset (MDS) assessments. The information contained in the MDS assessments was used to identify the presence of the following conditions: congestive heart failure, hypertension, diabetes mellitus, stroke or transient ischemic attack, thromboembolism, peripheral vascular disease, end stage renal disease (as a proxy for abnormal renal function), internal bleeding (as a proxy for hemorrhage history or predisposition), malignancy, anemia, fall, dementia or cognitive impairment, Parkinson's disease, and trauma history. Because there was no specific item on the MDS assessments for trauma, recent trauma history was defined as having at least one of the following: traumatic brain injury, hip fracture or other non-pathological fracture.

A study participant was considered to have a given condition during the baseline period if he or she had at least one MDS assessment indicating that the condition was present. The baseline conditions were identified using the assessment performed at entry into LTC. CMS mandates that all beneficiaries receive a set of assessments upon admission to the facility and within the first few weeks of the LTC stay. The initial set of assessments captures information on each beneficiary's health status upon admission. During follow-up, a study participant was considered to have a given chronic condition starting from the first MDS assessment on which he or she was reported as having the condition. The assumption was that these conditions are chronic and would continue to be present throughout the study participant's follow-up time. One exception was fall. Fall was defined in two ways, one as a history of fall and the second as a recent fall.

Frailty was evaluated using a modified version of the Changes in Health, End-stage disease and Signs and Symptoms (CHESS) scale. This scale was developed using information captured in the MDS assessment for nursing home residents to predict hospitalization (Mor 2011) and mortality (Hirdes 2003), and has been used as a measure of frailty (Hirdes, 2003, Tjam 2012). The score is constructed from MDS assessment elements within four domains: health status, decline in cognition, decline in activities of daily living, and having end stage disease. In this study, the cognition and activities of daily living components could not be included because information on these items was only available in the MDS 2.0 which was only used through the third quarter of 2010.

The health status component was based on the following five items from the MDS:

- Vomiting was a problem within the past 7 days
- Dehydration (output exceeds input) was a problem within the past 7 days
- Insufficient fluid intake – did not consume all or most of liquids provided during the past 3 days
- Unintentional weight loss of more than 5% in the past 30 days or more than 10% in the past 180 days
- Shortness of breath was a problem within the past 7 days

The score for this component could have a value of 0 or 1. A score of 0 was assigned when none of the items was present and a score of 1 point was assigned when one or more of the five items was present. Edema was part of the health status component of the original CHESS score, but was not included in the scale calculation for these analyses because information on edema was only available in the MDS 2.0 which was only available through the third quarter of 2010.

The presence of end stage disease added one additional point to the score, if present. Thus, the modified CHESS score was 0 if the participant had none of the five conditions listed above and did not have end stage disease. The score was 1 if the participant had at least one of the five conditions and/or end stage disease. Information on frailty was captured during the baseline period (the year prior to the index date) and throughout follow-up. If there was more than one assessment of frailty during the baseline period and the assessments were different, frailty was defined using the most severe frailty score. During follow-up, frailty was defined as an absorbing state variable meaning that once a person met the definition of being frail, the frailty value did not change in subsequent periods.

The remaining potential predictors of AC use were defined using sources other than the MDS assessments. Age was calculated based on date of birth and was categorized into 66-74 years, 75-84 years, and 85 years and older. Date of birth and sex were extracted from the Medicare administrative information that was populated with information from the Social Security Administration. Antiplatelet use was defined as a prescription with at least 15 days' supply within a given month for either clopidogrel or ticagrelor.

Race, region and month were also included in the analyses. Race was extracted from the Medicare administrative information, and was categorized into white, black and all other races. Region was categorized as West, Midwest, South and North East based on zip code reported in the Medicare administrative information. Month relative to entry to the LTC facility was defined as the number of 30-day periods since the index date.

Table 1 lists the potential predictors of AC use. The table classifies each factor as static, absorbing state, or time-varying. The static variables are permanent characteristics of an individual and do not change with time. For absorbing state variables, once a study participant was observed to have the condition in a given month, the variable was set to 1 to indicate having the condition, and this value of 1 was carried forward in all future follow-up months; otherwise, the value of the variable remained at 0. (In the Results section, these variables are referred to as having a history of the condition in question.) The values of the time-varying variables could vary month to month based on the information observed within the month. The table also identifies which factors are 1) IS risk factors, 2) hemorrhage risk factors, and 3) factors affecting physician prescribing of ACs. Some potential predictors of AC use fell into more than one of these categories.

Table 1. Predictors Potentially Influencing Anticoagulant Use in Older Adults Residing in Long-term Care Facilities

Potential Predictor	Variable Type (static, absorbing state, time-varying)	Stroke Risk Factor	Hemorrhage Risk Factor	Factor Affecting Physician Prescribing
Congestive heart failure	Absorbing state	X		
Hypertension as a proxy for uncontrolled hypertension	Absorbing state	X	X	
Diabetes mellitus	Absorbing state	X		
Stroke or transient ischemic attack	Absorbing state	X	X	
Thromboembolism	Absorbing state	X		
Peripheral vascular disease as a proxy for vascular disease	Absorbing state	X		
Advanced age (75 years and older)	Static	X	X	
Female gender	Static	X		
End stage renal disease	Absorbing state		X	
Internal bleeding	Absorbing state		X	
Antiplatelet (clopidogrel or ticagrelor) use	Time-varying		X	
Malignancy	Absorbing state			X
Anemia	Absorbing state			X
Fall history	Absorbing state			X
Fall in prior month	Time-varying			X
Dementia or cognitive impairment	Absorbing state			X
Parkinson's disease	Absorbing state			X
Frailty	Absorbing state			X
Trauma	Absorbing state			X

Analysis for Aim 2

Main model for Aim 2

The main model for aim 2 was fit to examine the relationship between each potential predictor and AC use using a repeated measures analysis with generalized estimating equations (GEE). Unadjusted odds ratios between each potential predictor and AC use were generated from GEE models with only the potential predictor included in the model. For the adjusted odds ratios, all potential predictors listed in Table 1 were included in the model along with the study participant's region (Midwest, North East, South, and West), an indicator for the month relative to entry into LTC, race (white, black and all other races), and calendar year. Month relative to entry into LTC was included as a continuous variable. Calendar year was included as a categorical variable with one indicator for each calendar year and 2007 as the reference. An autoregressive correlation matrix was used in the unadjusted and adjusted analyses to account for the correlation among repeated observations for the same study participant. Up to 24 months were included. For study participants residing in LTC for longer than 24 months, the additional months were dropped from the analysis.

Methods for Aim 3

The third aim was to measure the net effect of AC use considering IS prevention and the risk of ICH, among LTC residents with AF, using the net benefit approach proposed by Singer et al. (2009) except using marginal structural models (MSM) to account for time-dependent confounding.

Observation Period for Aim 3

The observation period was from entry into LTC to the earliest of discharge from LTC, death, the end of the study period (12/31/2013), or the end of the first 8 months in LTC. The first three criteria were similar to those used to define the observation period for Aim 1. Because the study participants were followed for a variable amount of time, the sample size in later months became too small to generate reliable estimates, in particular for the MSM analyses. As a result, a follow-up of up to 8 months was selected because the MSM weights started to have an unreasonable distribution after that month. A reasonable distribution is one in which the weights calculated for the MSM analysis (described in more detail below) have a mean of 1 and the standard deviation is less than 1.

Variables for Aim 3

Outcome variables

The outcome variables for this aim were IS and ICH. Each variable was operationalized using two definitions.

ICH was defined as a hospitalization with at least one of the following ICD-9-CM diagnosis codes for ICH: 430, 431, 432, 432.0, 432.1, and 432.9. In one study, among Medicare beneficiaries with AF who had one of these diagnosis codes on an administrative claim, 77% had an ICH documented in the medical chart (Birman-Deych 2005). IS was defined as a hospitalization with at least one diagnosis code for IS (433.x1, 434.x1, 436, 437.1, and 437.9), excluding transient ischemic attack (Birman-Deych 2005). The same study found that among those with a hospital claim for IS, 96% also has an IS documented in their medical chart (Birman-Deych 2005). Requiring a claim for a hospitalization ensured that only clinically relevant events were captured. The diagnosis codes and their descriptions are listed in Appendix A.

In a secondary analysis for this aim, we included only severe events, using hospital length of stay and death as indicators of severity. To define an IS or ICH, we required at least one of the following criteria in addition to the primary outcome definition: (1) length of stay of three days or longer or (2) length of stay less than three days and death (Wahl 2010). Events with length of stay less than three days without evidence of death were not included in the definition of the severe outcomes. The reason for focusing on severe events was to determine if the net effect was similar when considering only more disabling events.

Predictor variable

The predictor of interest was AC medication use, operationalized as a time-varying variable. AC use was defined as at least 15 days with medication available within a month and no AC use was defined as 0-14 days with medication available.

Confounding variables

Potential confounders included in the analysis for this aim were age group (<75 years, 75-84 years, and 85 years and older), sex, calendar year (2007-2012 vs 2013), month relative to entry into a LTC facility (2 vs 3-8), baseline stroke or transient ischemic attack, baseline internal bleed, history of hypertension, history of CHF, history of diabetes, and prior outcomes (i.e., time-varying IS and time-varying ICH). Calendar year was included in the model to account for variation in trends over time. Calendar year was dichotomized because the relationship between calendar year and AC use was similar for all years between 2007 and 2012. Month relative to entry into a LTC facility was included to capture variation in trends related to the duration of time in a LTC facility.

Month was dichotomized to minimize the number of variables in the regression models. The absorbing state variables were included in a previous study in community-dwelling older adults with AF when examining the relationship between AC use and IS and ICH (Singer 2009). We included prior outcomes at different points in time as potential time-varying confounders or mediators of the relationship between prior AC use and the current outcomes. For example, prior IS could be a confounder if it influences both future IS and future AC use. Prior IS could be a mediator if it influences future AC use, which then influences future IS.

Analysis for Aim 3

Unadjusted IS and ICH rates were reported, along with the differences in the rates of these events while using and not using AC.

The net clinical effect was calculated using a difference-in-differences approach as follows:

Formula 1:

$$\text{Net clinical effect} = (\text{IS rate not using AC} - \text{IS rate using AC}) - (\text{ICH rate using AC} - \text{ICH rate not using AC})$$

The first rate difference compared the rates of IS occurring during months when people were not using ACs and when people were using ACs. The second rate difference compared the rates of ICH comparing months when people were using ACs and when people were not using ACs. These rates were annualized. We hypothesized that AC decreases IS risk (the benefit) and increases ICH risk (the harm). Because we expected the IS rate to be higher when not using AC, the rate difference for IS was calculated as the rate while not using AC minus the rate while using AC. This number was interpreted as the average rate of IS occurring per year due to the lack of AC use. Because the ICH rate was expected to be higher while using AC, the rate difference for ICH was calculated as the rate using AC minus the rate not using AC. This number was interpreted as the average rate of ICH per year due to AC use. The difference of these two differences was the rate of IS prevented by AC use minus the rate of ICH due to AC use or the net number of events per 100 person-years. A positive value indicated a benefit of ACs in terms of these two outcomes, while a negative value indicated a benefit of not using ACs.

The main analysis used the equation above. The secondary analysis that included only severe events used the same approach but with different outcome events to generate the rates. Both analyses weighted the IS events equally to the ICH events.

MSMs were used for this analysis. The analysis was performed using GEE to account for the correlation of the repeated measures within person. Logistic regression was selected to generate probabilities to approximate rates. While the number of events per time period was low, making Poisson regression an appropriate choice, logistic regression was used because there were other variables measured on a monthly basis. In addition to the number of events per month being low, the number of months in which a person had more than one event was also low.

There was one record per person per month. In each month, the exposure (AC use) and potential confounders (age, sex, month relative to entry into LTC, calendar year, baseline internal bleed, baseline stroke or transient ischemic attack, hypertension absorbing state, diabetes absorbing state, congestive heart failure absorbing state, prior outcomes [IS, ICH]) were used to predict the outcome – either IS or ICH.

MSMs were used because there was the possibility of time-varying confounding of the relationship between AC use and the outcomes (ICH and IS), where a confounder is also predictive of future treatment by ACs.

A GEE logistic regression with MSM using a weighting method (inverse probability of exposure and censoring weights) was performed to estimate the four rates described in Formula 1. MSM was used because the relationship between time-varying treatment (AC use) and the outcomes (ICH, IS) may be biased if traditional regression techniques are used – that is, when the outcome is modeled as a function of past treatment. According to Hernan (2002), this bias may be present when the following two conditions are met:

1. "There exists a time-dependent covariate that is both a risk factor for the outcome, and also predicts subsequent exposure."
2. "Past exposure history predicts the risk factor"

These two criteria are plausible for prior outcomes (IS and ICH). Using IS to illustrate: for the first condition, past IS could be a risk factor for future IS, and past IS could predict subsequent AC use. For the second condition, past AC use could predict future IS. One time-varying variable with a one-month lag for hospitalization for IS and a second for hospitalization for ICH were included. The other factors (age, sex, month relative to entry into LTC, calendar year, baseline stroke or transient ischemic attack, baseline internal bleed, hypertension absorbing state, diabetes absorbing state, and congestive heart failure absorbing state) were included because they may be confounders of the relationship between AC use and the outcomes.

The estimation of the four rates in Formula 1 was accomplished by fitting six logistic regression models. The first two models were used to generate the inverse probability of exposure weights. The second two models were used to generate the inverse probability of censoring weights. These four models were used to calculate the inverse probability of exposure and censoring weights (IPW). The fifth and sixth models were regression models for ICH and IS, respectively, weighted by the IPW. The time-varying exposures are lagged by one month in each model, meaning the time-varying variables were included using information from the month prior to the outcome. To illustrate the lagging of exposures and outcome, when the outcome is assessed in a month, for example from January 15, 2008 to February 14, 2008, the exposure was evaluated up to and including the prior month, in this example, from December 16, 2007 to January 14, 2008.

Inverse Probability of Exposure and Censoring Weight Calculation

Stabilized IPWs were used in this analysis. The unstabilized inverse probability of exposure weight is “proportional to the inverse (or reciprocal) of the probability of having her own observed exposure…history through that visit” (Cole 2008), adjusting for baseline and time-varying factors. The IPWs can be unstabilized (as described in the prior sentence) or stabilized by redefining the numerator of the weight. The numerator of the stabilized weight is the probability of having his/her own observed exposure and censoring history through the month in question, adjusting only for baseline characteristics (i.e., those that do not vary with time) – as opposed to 1, the numerator of the unstabilized weight. The reason for stabilizing the weights is to mitigate the undue influence of extreme weights from a small number of observations (Robins 2000).

Stabilized IPW weights were calculated. Using models 1 and 2 (for exposure, defined below) and models 3 and 4 (for censoring, defined below), the predicted probability of the outcome was calculated for each person-month of observation. If the outcome was observed within the month, then the probability was the observed predicted probability. If the outcome was not observed within the month, then one minus the observed predicted probability was used. These probabilities for each month were the product of the predicted probability (or one minus the predicted probabilities) from the first month up to and including the current month. The inverse probability of exposure weights were generated by dividing the numerator by the denominator of accumulated predicted probabilities up to and including the person-month. The process was repeated for the censoring weights. Then, these two weights were multiplied together for each person-month of observation.

Here are the models that were fit for IPW:

<u>Model 1</u>, for numerator of the exposure weight:

$$logit(Y(t-1)) = \beta 0 + \beta 1 * age7584 + \beta 2 * Age \geq 85 + \beta 3 * Male + \beta 4 * Month2 + \beta 5 * Month3-8 + \beta 6 * CY2013 + \beta 7 * stroke + \beta 8 * bleed$$

Where Y = AC use at time, CY is calendar year, stroke is baseline stroke or transient ischemic attack, and bleed is baseline internal bleed

Model 2, for denominator of the exposure weight:

$$logit(Y(t-1)) = \beta 0 + \beta 1 * age7584 + \beta 2 * Age \geq 85 + \beta 3 * Male + \beta 4 * Month2 + \beta 5 * Month3 - 8 + \beta 6 * CY2013 + \beta 7 * stroke + \beta 8 * bleed + \beta 9 * HTN(t-2) + \beta 10 * CHF(t-2) + \beta 11 * DM(t-2) + \beta 12 * HospIS(t-2) + \beta 13 * HospICH(t-2)$$

Where Y = AC use at time, t-1, CY is calendar year, stroke is baseline stroke or transient ischemic attack, bleed is baseline internal bleed, HTN is hypertension absorbing state, CHF is congestive heart failure absorbing state, DM is diabetes mellitus absorbing state, HospIS is hospitalization for IS, and HospICH is hospitalization for ICH

Model 3, for numerator of the censoring weight:

$$logit(C(t-1)) = \beta 0 + \beta 1 * age7584 + \beta 2 * Age \geq 85 + \beta 3 * Male + \beta 4 * Month2 + \beta 5 * Month3 - 8 + \beta 6 * CY2013 + \beta 7 * stroke + \beta 8 * bleed$$

Where C = censoring at time, t-1, and CY is calendar year, stroke is baseline stroke or transient ischemic attack, and bleed is baseline internal bleed

Model 4, for the denominator of the censoring weight:

$$logit(C(t-1)) = \beta 0 + \beta 1 * age7584 + \beta 2 * Age \geq 85 + \beta 3 * Male + \beta 4 * Month2 + \beta 5 * Month3 - 8 + \beta 6 * CY2013 + \beta 7 * stroke + \beta 8 * bleed + \beta 9 * HTN(t-2) + \beta 10 * CHF(t-2) + \beta 11 * DM(t-2) + \beta 12 * HospIS(t-2) + \beta 13 * HospICH(t-2)$$

Where C = censoring at time, t-1, CY is calendar year, stroke is baseline stroke or transient ischemic attack, bleed is baseline internal bleed, HTN is hypertension absorbing state, CHF is congestive heart failure absorbing state, DM is diabetes mellitus absorbing state, HospIS is hospitalization for IS, and HospICH is hospitalization for ICH

Models 5 and 6 (defined below) were run using the generated weights in a weighted regression, including AC use as the exposure and adjusting for the baseline characteristics. The baseline characteristics were included in the weighted models because there can be residual confounding of the association between the exposure and outcome if they are not included (Cole 2008).

<u>Model 5,</u> weighted ICH model:

$$logit(ICH(t)) = \beta 0 + \beta 1 * age7584 + \beta 2 * Age \geq 85 + \beta 3 * Male + \beta 4 * Month2 + \beta 5 * Month3 - 8 + \beta 6 * CY2013 + \beta 7 * stroke + \beta 8 * bleed + \beta 9 * AC\ use(t-1)$$

Where ICH = intracranial hemorrhage at time, t, CY is calendar year, stroke is baseline stroke or transient ischemic attack, and bleed is baseline internal bleed

<u>Model 6,</u> weighted IS model:

$$logit(IS(t)) = \beta 0 + \beta 1 * age7584 + \beta 2 * Age \geq 85 + \beta 3 * Male + \beta 4 * Month2 + \beta 5 * Month3-8 + \beta 6 * CY2013 + \beta 7 * stroke + \beta 8 * bleed + \beta 9 * AC\ use(t-1)$$

Where IS = ischemic stroke at time, t, CY is calendar year, stroke is baseline stroke or transient ischemic attack, and bleed is baseline internal bleed

Assumptions Examined for Marginal Structural Model Implementation

The results from MSM are valid under four assumptions: consistency, positivity, exchangeability (no unmeasured confounding), and correct specification of the models used to generate the weights (Cole 2008). Some of these assumptions can be tested, while others cannot.

<u>Consistency</u> is the assumption that the observed outcome is the same as the counterfactual outcome, given the exposure history. This assumption cannot be tested empirically, but is likely to be valid in studies of medical treatment (Cole 2008). This is because the exposure, for example, AC use, is a medication administered to a person. The medication is likely to have a similar impact on all people receiving the medication, and the outcome being measured is a clinical condition, resulting from the treatment that would act in the same causal pathway between the exposure and outcome. An extension of the consistency assumption is that the exposure is defined unambiguously (Cole 2009). For AC use, the exposure is reasonably unambiguous. A person could be treated with ACs or not whereas for other exposures, like obesity defined using BMI, there is no ethical way to 'assign' someone to a BMI indicative of obesity. There could be different

causal relationships with the outcome depending on how a BMI is assigned, if that were possible.

Positivity is the assumption that the effect can be estimated in each subset of the population defined by the confounders included. There cannot be any combination of confounder, exposure and outcome that does not have observations; if there was, the positivity assumption would be violated. “Positivity is the condition that there are both exposed and unexposed individuals at every level of the confounders” (Cole 2008).

One possible reason for a positivity violation is due to structural zeroes. These would occur when a particular combination of characteristics could not be observed. This is common in occupational epidemiology studies – for example, if an exposure occurred on a day when an employee was not working. In this case, this person could not be exposed. These structural zeroes are unlikely in this analysis because there are no medical conditions included that would preclude someone from having another condition. The other concern is random zeroes, which could occur because the study cohort may not include at least one person with all possible combinations of the characteristics (exposures and outcomes in each month) included in the analysis. This is more likely for this study. Since month was included in the analysis, it was possible that a particular combination of characteristics was not observed in a particular month.

Possible methods for handling violations of the positivity assumption include collapsing categories of variables, reducing the number of covariates included in the analysis, or reducing the number of time points. Violations of positivity can result in extreme weights that do not have a mean close to 1 or have large standard deviations. The weight distribution by month was examined, and 8 months of observation was selected for this analysis because the mean was close to 1 and the standard deviation was no larger than the mean. Beyond 8 months, the standard deviation became larger than the mean.

Exchangeability is the assumption of no unmeasured confounding. This cannot be tested empirically, but sensitivity analyses can be performed that determine if the results are robust to different variables being included. There are tradeoffs. If all potential confounders are included, then there could be issues with positivity and sparseness in some strata – where some strata do not have people who were exposed and unexposed. Conversely, if too few confounders are included, then there may be inadequate adjustment and levels within strata (e.g., if age were collapsed into fewer categories that no longer reflected differences in outcome by age) may not be exchangeable because they are heterogeneous. For example, for race, all non-white and non-black participants were categorized as "all other races". This was done because of the small number of non-white and non-black participants. However, it is possible that there were differences between the different categories of race that were combined.

The model used to generate the weights was correctly specified. We cannot be sure that the weight models were correctly specified (i.e., match the "true" population model), but we took steps to make this assumption more likely. For example, we partitioned the follow-up period into months so that the exposure and outcome could be lagged, ensuring that the exposure was measured before the outcome. Partitioning the follow-up into 30-day periods was also appropriate because medication use can change over time and because chronic medications tend to be prescribed in 30-day prescription fills. We chose a GEE logistic regression model to account for the repeated measures within person. The chronic conditions were defined in terms of having a history of the condition rather than having the condition at one point in time because the patient's full medical history is more likely to influence prescribing than conditions at one point in time. The conditions included were motivated by prior research. Some static characteristics were included (age group, sex, race, and region) which have been used in prior research. The majority of the variables were dichotomous and a few were categorical (age group, race, and region). Because of the categorical nature of the variables, we did not need to test linear relationships between the variables.

The IPW distribution by month, along with the estimates from the denominator weight models, are included in Appendix B.

Rate Calculation using Average Marginal Effect Approach

An average marginal effect (AME) analysis was used to generate each of the four rates needed for Formula 1. The AME approach was used, as opposed to estimation at the mean or modes, because AME estimates can be generalized to the entire population rather than to a subset of the population or a population that does not exist. For example, the means approach produces estimates using the mean values of the covariates observed in the sample. When using the means approach, the proportion of males at a time point would be used to calculate the probability of the outcome at that time point. Since being male is a dichotomous variable, a proportion could not be observed in actuality. The AME was calculated using the following steps based on the process described by Muller et al. (2014):

1. Extract the coefficients from the weighted regression model (from models 5 and 6 above).
2. Combine the regression coefficients with the person-month observations used in the analysis.
3. Calculate the predicted probability at each time point under two situations:
    a. For AC use: use observed values for all covariates with the exception of AC use, and set AC use to 1 for all observations.
    b. For no AC use: use observed values for all covariates with the exception of AC use, and set AC use to 0 for all observations.
4. The formula used for the predicted probabilities of the outcome was:

$$\frac{e^{est}}{1 + e^{est}}$$

Where 'est' is short for the beta coefficients from the regression model multiplied by the observed value, with the exception of AC use, which was set to either "1" or "0" for each run

5. Average the predicted probabilities generated under each assumption – all AC use and all non-AC use

The model for each outcome with AME was used to generate two probabilities – one for the outcome while using ACs and a second for the outcome while not using ACs. The net effect was calculated using the four probabilities generated from these models, as described in Formula 1. The probabilities per person-month were assumed to be rates per person-month because probabilities can approximate rates when the rates are low. The rates per person-month were converted to per 100 person-years to present fewer decimal places. A 95% confidence interval for the net effect was generated using a percentile bootstrapping approach based on 2,000 samples of the study participants sampled with replacement. Each sample included 21,877 people (the number of people in the cohort) and all of their person-months of observation. The net effect was reported as the number of IS prevented after subtracting the number of ICH, reported per 100 person-years.

A sensitivity analysis was performed for the primary and secondary outcome definitions by adding a weighting factor of 1.5 to the ICH outcome. This model is referred to as the weighted net effect. The reason for adding the weight was that some clinicians and patients view an ICH (or any bleeding within the skull) as an event with more negative consequences (e.g., death) than IS (Singer 2009). Using the weighting factor allowed us to compare our findings in the LTC population to those reported in the literature for the community-dwelling AF population. The weight was applied as follows:

Formula 2:

$$\begin{aligned} &Net\ clinical\ effect \\ &\quad = (IS\ rate\ not\ using\ AC\ -\ IS\ rate\ using\ AC) - 1.5 \\ &\quad * (ICH\ rate\ using\ AC\ -\ ICH\ rate\ not\ using\ AC) \end{aligned}$$

The net effect was selected as the most appropriate analytic approach for this aim because it combined the risk and benefit associated with the treatment, AC use. We considered a competing risk analysis, in which time to IS would be the outcome and the competing risk would be ICH. Because having ICH does not prevent someone from having a subsequent IS, this approach did not fit the research question. Another approach considered was to use a composite outcome – ICH or IS. This was considered because many clinical trials for ACs use this approach. The concern was that because AC use increases risk of major hemorrhage and decreases IS risk, the exposure would act in opposite directions to the events combined in the outcome. This approach was dismissed because the analysis could not disentangle the relationship between AC use and the two events. Since both the risk and benefit need to be considered, the net effect approach was chosen.

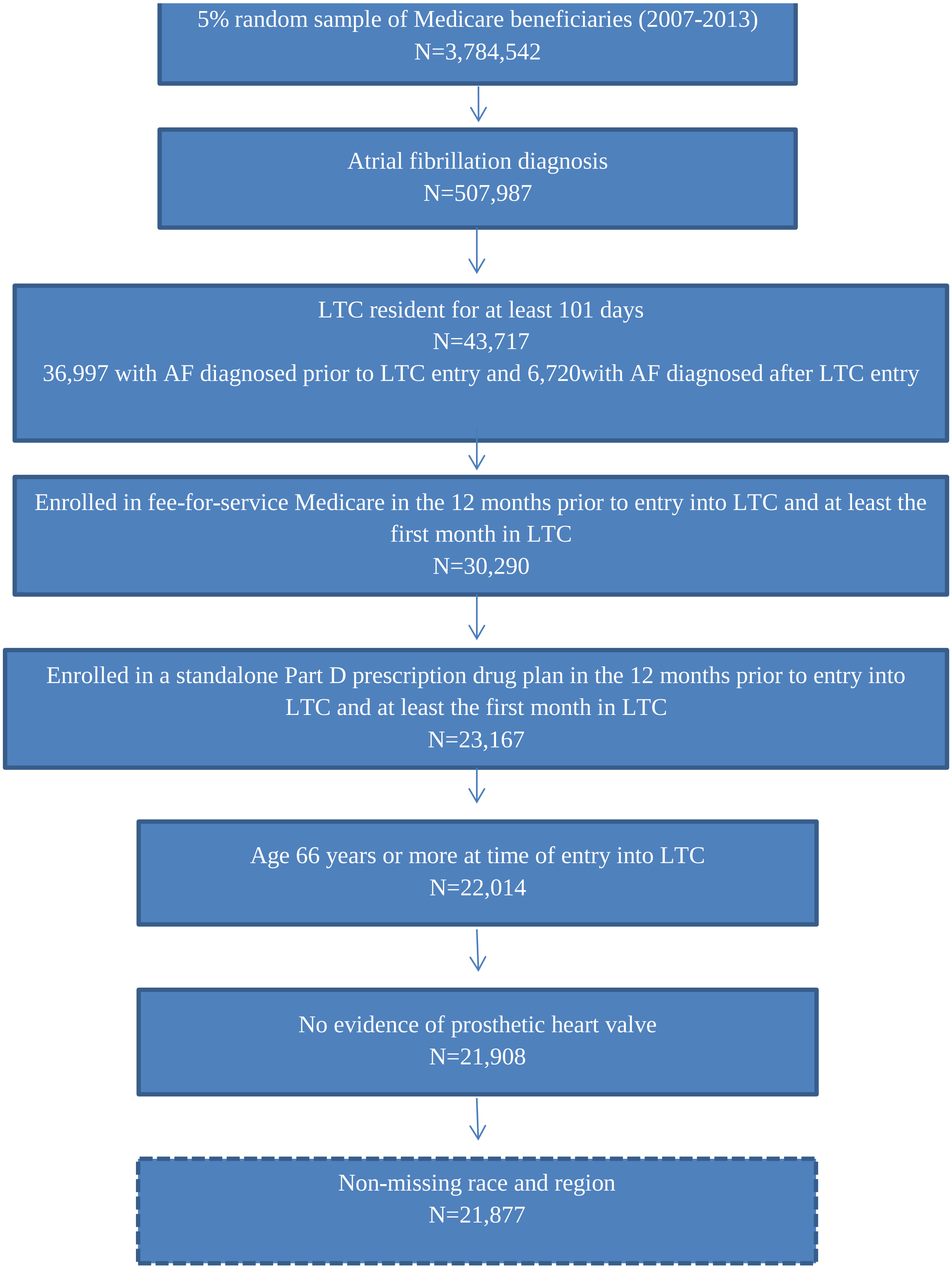
If there was a period at the end of follow-up that was less than 30 days, the partial month was excluded from the analysis.

Chapter 4 Results

Description of the Study Cohort

The target population for this study was older adults with prevalent, non-valvular AF residing in LTC facilities. As shown in Figure 1, there were 3,784,542 Medicare beneficiaries in the 5% random sample during 2007-2013, 507,987 (13.4%) of whom had a diagnosis of AF. Among those with AF, there were 43,717 (8.6%) who resided in a CMS-certified LTC facility for at least 101 days, 36,997 who had AF diagnosed prior to entry to a LTC facility and 6,720 who had AF diagnosed after entry to a LTC facility. Among those with AF residing in LTC for at least 101 days, 30,290 (69.3%) were enrolled in FFS Medicare in the 12 months prior to entry into LTC and during at least the first month following admission to LTC. Of these, 23,167 (76.4%) were enrolled in a standalone Part D prescription drug plan in the 12 months prior to entry into LTC and during at least the first month following admission to LTC. Among LTC residents with AF, FFS Medicare, and Part D coverage, 22,014 (95.0%) were at least 66 years old at the time they entered LTC. Within this group, 21,908 people (99.5%) did not have evidence of a prosthetic heart valve during the baseline period. Within this group, 21,877 people (99.9%) had non-missing values for race and region.

Figure 1. Cohort Selection



Characteristics of the Cohort

In Table 2, the characteristics of the study cohort are compared to the characteristics of beneficiaries who resided in a LTC facility and who were excluded from the study cohort because of their Medicare enrollment status, age, prosthetic heart valve status, or missing information on race or region. Information on 90 excluded residents could not be displayed in the table because the resident had missing race or region, and the data use agreement precluded reporting on groups with very small numbers. This comparison was performed in order to assess the representativeness of the study cohort as compared to all residents of a LTC facility with AF.

In the study cohort, the largest age group was 85 years old or older at entry into LTC (54.6%); 33.8% were 75-84, 11.6% were 66-74 years old (Table 2). The majority of the cohort was white (88.1%), followed by black (8.1%), and other races (3.9%). The study population was mostly female (75.9%). Almost all members of the cohort (99.6%) qualified for Medicare based on age. The largest proportion of study participants (36.7%) was from the southern region, and the west had the fewest (11.2%). The proportion of study participants entering the cohort was highest in 2009 (15.6%), and declined from 2009 through 2013 (11.9%).

Compared to the excluded group, the study cohort had a higher percentage of older people, a lower percentage of people qualifying for Medicare based on disability, and a higher percentage of females. The race and region distributions were similar in the two groups. The distribution of calendar year of entry into LTC was similar, except that the study cohort had fewer people entering in 2007 than those in the excluded group.

Table 2. Characteristics of the Study Cohort and of LTC Residents Who Were Excluded from the Cohort

Characteristic	Study Cohort		LTC Residents with AF Excluded from the Study Cohort	
	N=21,877		N=21,750*	
	N	%	N	%
Age at entry into LTC (years)				
<66	0	0.0	1,727	7.9
66-74	2,532	11.6	1,860	8.6
75-84	7,397	33.8	7,012	32.2
≥85	11,948	54.6	11,151	51.3
Race				
White	19,271	88.1	19,565	90.0
Black	1,763	8.1	1,655	7.6
Other	843	3.9	530	2.4
Sex				
Male	5,281	24.1	7,926	36.4
Female	16,596	75.9	13,824	63.6
Reason for Medicare entitlement				
Age	21,791	99.6	20,212	92.9
Disability with or without end-stage renal disease	33	0.2	1,443	6.6
End-stage renal Disease only	53	0.2	95	0.4
Region				
Midwest	6,235	28.5	6,189	28.5
Northeast	5,178	23.7	5,566	25.6
South	8,017	36.7	7,429	34.2
West	2,447	11.2	2,566	11.8
Calendar year of entry into LTC				
2007	2,920	13.4	3,622	16.7
2008	3,317	15.2	3,366	15.5
2009	3,409	15.6	3,199	14.7
2010	3,282	15.0	3,151	14,5
2011	3,290	15.0	3,168	14.6
2012	3,048	13.4	2,887	13.3
2013	2,611	11.9	2,357	10.8

*Ninety people were dropped from this group because of one or more missing values for age, race, sex or the reason for Medicare entitlement.

Table 3 shows additional characteristics of the study cohort. At baseline (i.e., in the year prior to the index date), the most common characteristics were fall (79.1%), hypertension (77.9%), frailty (43.2%), dementia or other cognitive impairment (41.4%), congestive heart failure (38.6%) and diabetes mellitus (35.3%). The prevalence of history of stroke or transient ischemic attack was 23.2%, and the prevalence of history of internal bleeding was 2.4%.

Table 3. Clinical Conditions at Baseline for the Study Cohort, N=21,877

Clinical Conditions at Baseline	N	%
Anemia	6,679	30.5
Congestive heart failure	8,437	38.6
Hypertension	17,045	77.9
Diabetes mellitus	7,714	35.3
Stroke or transient ischemic attack	4,067	23.2
Thromboembolism	820	3.8
Peripheral vascular disease	2,528	11.6
End stage renal disease	2,806	12.8
Internal bleeding	528	2.4
Antiplatelet use	3,449	15.8
Malignancy	1,636	7.5
Fall	17,299	79.1
Dementia or cognitive impairment	9,066	41.4
Parkinson’s disease	1,062	4.9
Trauma	3,838	17.5
Frailty		
Yes (score=1-4)	9,447	43.2
No (score=0)	12,430	56.8

Duration of Follow-Up

The median duration of follow-up was 339 days (interquartile range [IQR]: 131-747) (Table 4). Death was the most common reason for ending follow-up (42.5%), and the least common reason was a change in coverage (3.8%) (e.g., if the study participant switched from the Medicare Part A or B benefit under the FFS program to a Medicare

Advantage policy or if the study participant opted out of the Part D benefit). Those discharged from LTC had the shortest median follow-up (209 days, IQR: 86-515), while those who were followed until the end of the study had the longest median follow-up of (601 days, IQR: 258-1,084).

Table 4. Length of Follow-up, by Reason for Ending Follow-Up

Reason for Ending Follow-Up	Number of People	%	Length of Follow-up (Days)				
			Minimum	Cutoff for Lower Quartile	Median	Cutoff for Upper Quartile	Maximum
Change in coverage	832	3.8	32	160	386	775	2,314
End of study period	5,039	23.0	31	258	601	1,084	2,554
Discharge from LTC	6,719	30.7	32	86	209	515	2,521
Death	9,287	42.5	30	135	336	705	2,446
All reasons	21,877	100.0	30	131	339	747	2,554

For all years of entry into LTC, the percentage of people ending follow-up was highest in the year after entry and declined with each subsequent year, with the exception of 2013 because that was the last year of the study (Table 5).

Table 5. Year of Entry into LTC, by Year of End of Follow-up

	Year of End of Follow-up							
Year of Entry into LTC	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**Total**
	N	**N**	**N**	**N**	**N**	**N**	**N**	**N**
	%	**%**	**%**	**%**	**%**	**%**	**%**	%
2007	739	892	447	322	191	115	214	2,920
	25.3	30.5	15.3	11.0	6.5	3.9	7.3	100.0
2008		805	1,022	540	323	239	388	3,317
		24.3	30.8	16.3	9.7	7.2	11.7	100.0
2009			864	1,071	527	338	609	3,409
			25.3	31.4	15.5	9.9	17.9	100.0
2010				819	1,007	550	906	3,282
				25.0	30.7	16.8	27.6	100.0
2011					879	977	1,434	3,290
					26.7	29.7	43.6	100.0
2012						844	2,204	3,048
						27.7	72.3	100.0
2013							2,611	2,611
							100.0	100.0
Total	739	1,697	2,333	2,752	2,927	3,063	8,366	21,877

Aim 1 Results: Prevalence of Anticoagulant Use

Based on the regression-based summary estimate, the prevalence of AC use across all study years combined was 36.2% (95% confidence interval [CI]: 35.6%-36.8%). The prevalence ranged from a low of 35.7% in 2010 to a high of 36.9% in 2011 (Table 6). There was no clear pattern of variation across study years. The total number of people in the study cohort (i.e., those residing in LTC with AF, with FFS Medicare, with a Part D plan, at least 66 years old without evidence of a prosthetic heart value and non-missing demographic characteristics) at any point during the year increased from 2,920 in 2007 to 8,818 in 2012, and then decreased to 8,366 people in 2013.

Table 6. Prevalence of Anticoagulant Use, by Year

Year*	Number of People	Number of AC Users	Prevalence of AC Use (%)	95% Confidence Interval (%)
2007	2,920	1,070	36.6	34.9-38.4
2008	5,498	2,012	36.6	35.3-37.9
2009	7,210	2,582	35.8	34.7-36.9
2010	8,159	2,916	35.7	34.7-36.8
2011	8,697	3,213	36.9	35.9-38.0
2012	8,818	3,232	36.7	35.7-37.7
2013	8,366	3,076	36.8	35.7-37.8

*For each year, results are shown for people with any follow-up during that calendar year. A person could be included in more than one year.

Based on the regression-based summary estimates across all study years combined, those age 66-70 years had a prevalence of AC use of 43.2% (95% CI: 40.5%-46.0%). Those age 71-75 years had a prevalence of 42.3% (95% CI: 40.5%-44.1%). Those age 76-80 years had a prevalence of 39.6% (95% CI: 38.3%-40.9%). Those 81-85 age years had a prevalence of 37.5% (95% CI: 36.5%-38.0%). Those age 86 years and older had a prevalence of 33.5% (95% CI: 32.7%-34.2%).

In most study years, the observed prevalence of AC use was higher among those age 71-75 years than among those age 66-70 years (Table 7). The observed prevalence of AC use decreased with increasing age among those aged 76 and higher except in 2007 and 2008, when the prevalence increased for those 81-85 and then decreased in those 86 year and older.

Table 7. Prevalence of Anticoagulant Use, by Age Group

Year*	Age Group (Years)	Total Number of People†	Number of AC Users	Prevalence of AC Use (%)	95% Confidence Interval
2007	**66-70**	114	52	45.6	36.3-55.2
	71-75	260	114	43.9	37.7-50.1
	76-80	425	156	36.7	32.1-41.5
	81-85	726	299	41.2	37.6-44.9
	≥86	1,395	449	32.2	29.7-34.7
2008	**66-70**	208	79	38.0	31.4-45.0
	71-75	439	200	45.6	40.8-50.4
	76-80	762	299	39.2	35.8-42.8
	81-85	1,267	509	40.2	37.5-42.9
	≥86	2,822	925	32.8	31.1-34.5
2009	**66-70**	271	99	36.5	30.8-42.6
	71-75	522	211	40.4	36.2-44.8
	76-80	956	378	39.5	36.4-42.7
	81-85	1,610	623	38.7	36.3-41.1
	≥86	3,851	1,271	33.0	31.5-34.5
2010	**66-70**	310	122	39.4	33.9-45.0
	71-75	582	253	43.5	39.4-47.6
	76-80	1,039	431	41.5	38.5-44.6
	81-85	1,756	671	38.2	35.9-40.5
	≥86	4,472	1,439	32.2	30.8-33.6
2011	**66-70**	296	127	42.9	37.2-48.8
	71-75	654	294	45.0	41.1-48.9
	76-80	1,090	477	43.8	40.8-46.8
	81-85	1,842	750	40.7	38.5-43.0
	≥86	4,815	1,565	32.5	31.2-33.9
2012	**66-70**	322	143	44.4	38.9-50.0
	71-75	622	286	46.0	42.0-50.0
	76-80	1,128	470	41.7	38.8-44.6
	81-85	1,820	733	40.3	38.0-42.6
	≥86	4,926	1,600	32.5	31.2-33.8
2013	**66-70**	306	146	47.7	42.0-53.5
	71-75	617	284	46.0	42.0-50.1
	76-80	993	427	43.0	39.9-46.2
	81-85	1,655	651	39.3	37.0-41.7
	≥86	4,795	1,568	32.7	31.4-34.1

* For each year, results are shown for people with any follow-up during that calendar year. A person could be included in more than one year.

Based on the regression-based summary estimates across all study years combined, the prevalence of AC use was 36.9% (95% CI: 36.3%-37.6%) among those of white race, 31.5% (95% CI: 29.5%-33.6%) among those of black race, and 30.1% (95% CI: 27.2%-33.1%) among those of other race. In each study year, the observed prevalence of AC use was highest in those of white race followed by black race and all other races combined (Table 8).

Table 8. Prevalence of Anticoagulant Use, by Race

Year*	**Race**	**Total Number of People†**	**Number of AC Users**	**Prevalence of AC Use (%)**	**95% Confidence Interval**
2007	**White**	2,573	968	37.6	35.8-39.5
	Black	239	71	29.7	24.0-35.9
	Other	108	31	28.7	20.4-38.2
2008	**White**	4,874	1,815	37.2	35.9-38.6
	Black	435	135	31.0	26.7-35.6
	Other	189	62	32.8	26.2-40.0
2009	**White**	6,417	2,361	36.8	35.6-38.0
	Black	538	151	28.1	24.3-32.1
	Other	255	70	27.5	22.1-33.4
2010	**White**	7,233	2,627	36.3	35.2-37.4
	Black	625	197	31.5	27.9-35.3
	Other	301	92	30.6	25.4-36.1
2011	**White**	7,660	2,881	37.6	36.5-38.7
	Black	718	232	32.3	28.9-35.9
	Other	319	100	31.4	26.3-36.8
2012	**White**	7,739	2,894	37.4	36.3-38.5
	Black	720	228	31.7	28.3-35.2
	Other	359	110	30.6	25.9-35.7
2013	**White**	7,296	2,728	37.4	36.3-38.5
	Black	732	246	33.6	30.2-37.2
	Other	338	102	30.2	25.3-35.4

* For each year, results are shown for people with any follow-up during that calendar year. A person could be included in more than one year.

†The people in the study cohort, which includes those residing in LTC with AF, residing in FFS Medicare with a Part D plan at least 66-year-old without evidence of a prosthetic heart value and non-missing race and region.

Based on the regression-based summary estimates across all study years combined, the prevalence of AC use for females was 36.6% (95% CI: 35.9%-37.3%) and for males was 35.1% (95% CI: 33.9%-36.4%).

Females had a higher observed prevalence of AC use than males in all years except 2013, although the differences were not large (Table 9). The difference between females and males in the prevalence of AC use did not vary much across years.

Table 9. Prevalence of Anticoagulant Use, by Sex

Year*	Sex	Total Number of People†	Number of AC Users	AC Prevalence	95% Confidence Interval
2007	**Male**	672	243	36.2	32.5-39.9
	Female	2,248	827	36.8	34.8-38.8
2008	**Male**	1,253	432	34.5	31.8-37.2
	Female	4,245	1,580	37.2	35.8-38.7
2009	**Male**	1,587	534	33.7	31.3-36.0
	Female	5,623	2,048	36.4	35.2-37.7
2010	**Male**	1,793	596	33.2	31.1-35.5
	Female	6,366	2,320	36.4	35.3-37.6
2011	**Male**	1,929	683	35.4	33.3-37.6
	Female	6,768	2,530	37.4	36.2-38.6
2012	**Male**	1,996	714	35.8	33.7-37.9
	Female	6,822	2,518	36.9	35.8-38.1
2013	**Male**	1,879	692	36.8	34.6-39.1
	Female	6,487	2,384	36.8	35.6-37.9

* For each year, results are shown for people with any follow-up during that calendar year. A person could be included in more than one year.
†The people in the study cohort, which includes those residing in LTC with AF, residing in FFS Medicare with a Part D plan at least 66-year-old without evidence of a prosthetic heart value and non-missing race and region.

Based on the regression-based summary estimates for all study years combined, the prevalence of AC use was 40.1% (95% CI: 39.0%-41.3%) among study participants in the Midwest region, 36.7% (95% CI: 35.5%-38.0%) in the North East region, 33.8%

(95% CI: 32.8%-34.8%) in the South region, and 33.1% (95% CI: 31.3%-34.9%) in the West.

In each study year, the pattern of the observed prevalence of AC use within regions was similar.

Table 10. Prevalence of Anticoagulant Use by Region

Year*	Region	Total Number of People†	Number of AC Users	Prevalence of AC Use (%)	95% Confidence Interval
2007	**Midwest**	835	351	42.0	38.7-45.5
	North East	639	245	38.3	34.6-42.2
	South	1,113	358	32.2	29.4-35.0
	West	333	116	34.8	29.7-40.2
2008	**Midwest**	1,592	636	40.0	37.5-42.4
	North East	1,273	486	38.2	35.5-40.9
	South	2,015	688	34.1	32.1-36.3
	West	618	202	32.7	29.0-36.5
2009	**Midwest**	2,105	853	40.5	38.4-42.7
	North East	1,670	631	37.8	35.5-40.2
	South	2,622	826	31.5	29.7-33.3
	West	813	272	33.5	30.2-36.8
2010	**Midwest**	2,337	942	40.3	38.3-42.3
	North East	1,959	686	35.0	32.9-37.2
	South	2,998	1,004	33.5	31.8-35.2
	West	865	284	32.8	29.7-36.1
2011	**Midwest**	2,410	987	41.0	39.0-43.0
	North East	2,119	793	37.4	35.4-39.5
	South	3,221	1,114	34.6	32.9-36.3
	West	947	319	33.7	30.7-36.8
2012	**Midwest**	2,467	1,005	40.7	38.8-42.7
	North East	2,092	763	36.5	34.4-38.6
	South	3,293	1,148	34.9	33.2-36.5
	West	966	316	32.7	29.8-35.8
2013	**Midwest**	2,317	944	40.7	38.7-42.8
	North East	1,994	705	35.4	33.3-37.5
	South	3,168	1,124	35.5	33.8-37.2
	West	887	303	34.2	31.0-37.4

*For each year, results are shown for people with any follow-up during that calendar year. A person could be included in more than one year.

†The people in the study cohort, which includes those residing in LTC with AF, residing in FFS Medicare with a Part D plan at least 66-year-old without evidence of a prosthetic heart value and non-missing race and region.

Extent of Anticoagulant Use Among Users

Median PDC was close to 100% for all study participants regardless of year of entry, age group, race, sex or region (Tables 11 to 15).

Table 11. Proportion of Days Covered with Anticoagulant Medications, by Year

Year*	Number of People With Any AC Use in the Year†	Median PDC (%)	Minimum PDC (%)	Maximum PDC (%)	Cutoff for Lower Quartile (%)
2007	1,070	97.6	0.4	100.0	75.9
2008	2,012	99.5	0.3	100.0	81.3
2009	2,582	100.0	0.3	100.0	82.3
2010	2,916	100.0	0.3	100.0	83.3
2011	3,213	100.0	0.3	100.0	80.1
2012	3,232	100.0	0.3	100.0	83.2
2013	3,076	100.0	0.3	100.0	83.3

* For each year, results are shown for people with any follow-up during that calendar year. A person could be included in more than one year.

†The people in the study cohort, which includes those residing in LTC with AF, residing in FFS Medicare with a Part D plan at least 66-year-old without evidence of a prosthetic heart value and non-missing race and region, who used ACs.

Table 12. Proportion of Days Covered with Anticoagulant Medications, by Age Group

Year*	Age Group (Years)	Number of People With Any AC Use in the Year†	Median (%)	Minimum (%)	Maximum (%)	Lower Quartile (%)
2007	**66-70**	52	98.0	8.6	100.0	84.8
	71-75	114	98.6	15.6	100.0	68.0
	76-80	156	90.1	0.4	100.0	61.3
	81-85	299	97.3	1.4	100.0	76.2
	≥86	449	98.3	1.8	100.0	81.7
2008	**66-70**	79	97.6	8.2	100.0	66.0
	71-75	200	99.3	4.7	100.0	84.2
	76-80	299	99.2	1.0	100.0	72.3
	81-85	509	99.2	0.8	100.0	81.1
	≥86	925	100.0	0.3	100.0	84.2
2009	**66-70**	99	98.3	4.1	100.0	74.2
	71-75	211	100.0	0.3	100.0	80.7
	76-80	378	99.9	0.7	100.0	79.5
	81-85	623	100.0	0.9	100.0	81.3
	≥86	1,271	100.0	0.3	100.0	84.8
2010	**66-70**	122	99.9	0.5	100.0	72.0
	71-75	253	99.7	0.5	100.0	82.7
	76-80	431	100.0	0.4	100.0	78.6
	81-85	671	100.0	0.3	100.0	86.5
	≥86	1,439	100.0	0.3	100.0	83.8
2011	**66-70**	127	99.3	2.2	100.0	73.2
	71-75	294	100.0	2.7	100.0	84.3
	76-80	477	100.0	1.8	100.0	76.9
	81-85	750	100.0	0.3	100.0	79.7
	≥86	1,565	100.0	0.3	100.0	81.1
2012	**66-70**	143	100.0	2.8	100.0	84.6
	71-75	286	100.0	1.0	100.0	79.0
	76-80	470	100.0	0.3	100.0	80.6
	81-85	733	100.0	0.5	100.0	82.2
	≥86	1,600	100.0	0.3	100.0	84.5
2013	**66-70**	146	100.0	5.6	100.0	83.1
	71-75	284	99.5	0.3	100.0	74.7
	76-80	427	100.0	1.4	100.0	80.6
	81-85	651	100.0	0.3	100.0	86.0
	≥86	1,568	100.0	0.3	100.0	84.7

*For each year, results are shown for people with any follow-up during that calendar year. A person could be included in more than one year.
†The people in the study cohort, which includes those residing in LTC with AF, residing in FFS Medicare with a Part D plan at least 66-year-old without evidence of a prosthetic heart value and non-missing race and region, who used ACs.

Table 13. Proportion of Days Covered with Anticoagulant Medications, by Race

Year*	Race	Number of People With Any AC Use in the Year†	Median (%)	Minimum (%)	Maximum (%)	Lower Quartile (%)
2007	**White**	71	95.6	3.7	100.0	65.4
	Black	31	99.0	4.1	100.0	73.7
	Other	968	97.6	0.4	100.0	76.3
2008	**White**	135	98.0	0.8	100.0	73.3
	Black	62	97.1	3.6	100.0	82.4
	Other	1,815	99.6	0.3	100.0	81.8
2009	**White**	151	99.6	0.7	100.0	81.6
	Black	70	99.5	1.4	100.0	81.6
	Other	2,361	100.0	0.3	100.0	82.5
2010	**White**	197	99.1	0.3	100.0	64.9
	Black	92	99.9	2.1	100.0	70.6
	Other	2,627	100.0	0.3	100.0	84.8
2011	**White**	232	100.0	0.5	100.0	71.3
	Black	100	100.0	1.1	100.0	72.0
	Other	2,881	100.0	0.3	100.0	81.1
2012	**White**	228	100.0	0.3	100.0	74.0
	Black	110	97.9	3.6	100.0	78.9
	Other	2,894	100.0	0.3	100.0	84.2
2013	**White**	246	99.7	0.6	100.0	64.4
	Black	102	98.0	3.0	100.0	70.7
	Other	2,728	100.0	0.3	100.0	85.8

*For each year, results are shown for people with any follow up during that calendar year. A person could be included in more than one year.
†The people in the study cohort, which includes those residing in LTC with AF, residing in FFS Medicare with a Part D plan at least 66-year-old without evidence of a prosthetic heart value and non-missing race and region, who used ACs.

Table 14. Proportion of Days Covered with Anticoagulant Medications, by Sex

Year*	Sex	Number of People With Any AC Use in the Year†	Median (%)	Minimum (%)	Maximum (%)	Lower Quartile (%)
2007	**Male**	243	1.4	100.0	97.4	76.9
	Female	827	0.4	100.0	97.6	75.0
2008	**Male**	432	0.3	100.0	98.7	77.7
	Female	1,580	0.8	100.0	99.6	81.7
2009	**Male**	534	0.3	100.0	100.0	80.7
	Female	2,048	0.3	100.0	100.0	82.6
2010	**Male**	596	0.5	100.0	100.0	80.0
	Female	2,320	0.3	100.0	100.0	84.1
2011	**Male**	683	0.5	100.0	100.0	77.0
	Female	2,530	0.3	100.0	100.0	81.3
2012	**Male**	714	0.3	100.0	100.0	77.3
	Female	2,518	0.3	100.0	100.0	84.9
2013	**Male**	692	0.3	100.0	100.0	80.1
	Female	2,384	0.3	100.0	100.0	84.2

*For each year, results are shown for people with any follow up during that calendar year. A person could be included in more than one year.

†The people in the study cohort, which includes those residing in LTC with AF, residing in FFS Medicare with a Part D plan at least 66-year-old without evidence of a prosthetic heart value and non-missing race and region, who used ACs.

Table 15. Proportion of Days Covered with Anticoagulant Medications, by Region

Year*	Region	Number of People With Any AC Use in the Year†	Median (%)	Minimum (%)	Maximum (%)	Lower Quartile (%)
2007	**Midwest**	351	98.1	2.7	100.0	76.9
	North East	245	98.8	1.4	100.0	71.7
	South	358	96.3	0.4	100.0	76.2
	West	116	95.3	1.7	100.0	78.0
2008	**Midwest**	636	99.7	0.3	100.0	83.3
	North East	486	99.5	1.3	100.0	79.3
	South	688	99.2	0.8	100.0	78.9
	West	202	99.5	1.0	100.0	81.8
2009	**Midwest**	853	100.0	0.3	100.0	87.0
	North East	631	100.0	1.0	100.0	75.4
	South	826	100.0	0.3	100.0	82.5
	West	272	100.0	1.4	100.0	78.7
2010	**Midwest**	942	100.0	0.3	100.0	89.6
	North East	686	100.0	0.5	100.0	81.6
	South	1,004	100.0	0.3	100.0	78.9
	West	284	100.0	2.1	100.0	82.1
2011	**Midwest**	987	100.0	1.8	100.0	86.4
	North East	793	100.0	0.3	100.0	77.4
	South	1,114	100.0	0.3	100.0	79.5
	West	319	100.0	1.1	100.0	71.2
2012	**Midwest**	1,005	100.0	0.5	100.0	90.3
	North East	763	100.0	0.3	100.0	78.7
	South	1,148	100.0	0.3	100.0	82.3
	West	316	100.0	0.3	100.0	80.7
2013	**Midwest**	944	100.0	0.3	100.0	91.4
	North East	705	100.0	0.3	100.0	77.3
	South	1,124	100.0	0.6	100.0	82.4
	West	303	99.7	0.3	100.0	73.1

* For each year, results are shown for people with any follow up during that calendar year. A person could be included in more than one year.

†The people in the study cohort, which includes those residing in LTC with AF, residing in FFS Medicare with a Part D plan at least 66-year-old without evidence of a prosthetic heart value and non-missing race and region, who used ACs.

Aim 2 Results: Potential Predictors of AC use

Table 16 displays the results from the main model with all potential predictors included. As the number of months a person remained in LTC increased, there was no change in the likelihood of using ACs (odds ratio [OR]: 1.00, 95% confidence interval [CI]: 1.00-1.00). Non-whites had a lower likelihood of AC use compared to whites. Those in the Midwest and North East were more likely to be using ACs than those in the West, while those in the South were as likely as those in the West to be using ACs.

Some of the potential risk factors were included in the analysis because they are IS risk factors in LTC residents according to the literature. Of these, hypertension, diabetes mellitus, and peripheral vascular disease had no association with AC use. Congestive heart failure, stroke or transient ischemic attack and thromboembolism were associated with a greater likelihood of AC use. Those aged 75-85 were equally as likely to be using ACs as those 66-74 years, while those 85 and older were less likely than those 66-74 years to be using ACs. Males were less likely than females to be using ACs.

Some of the potential predictors were included because they are hemorrhage risk factors in LTC residents according to the literature. End stage renal disease was not associated with AC use. Internal bleeding and antiplatelet use were associated with a lower likelihood of AC use.

Some of the potential predictors were included because they are factors associated with physician prescribing in LTC residents according to the literature. Malignancy, trauma and fall history were not associated with AC use. Anemia, fall in prior month, dementia or cognitive impairment, Parkinson’s disease, and frailty were associated with a lower likelihood of AC use.

Table 16. Results of Logistic Regression Examining Predictors of Anticoagulant Medication Use, in the First 24 Months of Observation

Potential Predictor of AC Use		Person-months with No AC Use	Person-months with AC Use	Unadjusted* Odds Ratio (95% Confidence Interval)	Adjusted* Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio p-value
Month relative to LTC entry		183,983	88,616	1.00 (1.00-1.00)	1.00 (1.00-1.01)	<0.001
Calendar year	2007	9,751	4,606	Reference	Reference	-
	2008	25,002	12,131	1.01 (0.98-1.05)	1.01 (0.98-1.05)	0.503
	2009	31,864	15,032	1.04 (0.99-1.08)	1.03 (0.99-1.08)	0.124
	2010	31,884	14,535	1.02 (0.98-1.07)	1.02 (0.97-1.07)	0.394
	2011	31,018	15,256	1.04 (0.99-1.09)	1.04 (0.99-1.09)	0.155
	2012	29,853	14,783	1.04 (0.98-1.09)	1.04 (0.98-1.10)	0.169
	2013	24,611	12,273	1.04 (0.99-1.10)	1.05 (0.99-1.11)	0.139
Age (years)	66-74	17,144	11,158	Reference	Reference	-
	75-84	58,842	32,595	0.96 (0.90-1.02)	0.95 (0.89-1.00)	0.069
	≥85	107,997	44,863	0.87 (0.81-0.93)	0.85 (0.79-0.90)	<0.001
Race	White	160,739	80,036	Reference	Reference	-
	Other	7,707	2,600	0.70 (0.60-0.81)	0.73 (0.62-0.85)	<0.001
	Black	15,537	5,980	0.75 (0.68-0.84)	0.73 (0.66-0.81)	<0.001
Sex	Female	143,003	70,028	Reference	Reference	-
	Male	40,980	18,588	0.92 (0.87-0.98)	0.91 (0.86-0.97)	0.005
Region	West	20,703	8,508	Reference	Reference	-
	Midwest	49,061	28,530	1.37 (1.25-1.52)	1.33 (1.21-1.47)	<0.001
	North East	43,803	20,890	1.12 (1.02-1.24)	1.10 (0.99-1.22)	0.065
	South	70,416	30,688	1.03 (0.94-1.14)	1.02 (0.92-1.12)	0.751
Frailty score	0	114,998	54,582	Reference	Reference	-
	1	68,985	54,582	0.97 (0.94-0.99)	0.96 (0.93-0.98)	0.002
Anemia	No	108,611	56,441	Reference	Reference	-
	Yes	75,372	32,175	0.90 (0.88-0.93)	0.90 (0.87-0.93)	<0.001
Dementia	No	79,703	45,235	Reference	Reference	-
	Yes	104,280	43,381	0.92 (0.90-0.96)	0.93 (0.90-0.97)	<0.001
Malignancy	No	168,541	80,577	Reference	Reference	-
	Yes	15,442	8,039	0.96 (0.90-1.03)	0.96 (0.90-1.03)	0.275
Congestive heart failure	No	102,762	45,380	Reference	Reference	-
	Yes	81,221	43,236	1.03 (0.99-1.07)	1.04 (1.00-1.08)	0.038
Stroke or transient ischemic attack	No	135,580	58,992	Reference	Reference	-
	Yes	48,403	29,624	1.17 (1.12-1.22)	1.20 (1.15-1.25)	<0.001
Diabetes mellitus	No	117,697	53,993	Reference	Reference	-
	Yes	66,286	34,623	1.05 (1.01-1.10)	1.05 (1.00-1.10)	0.052
Thromboembolism	No	177,672	79,605	Reference	Reference	-
	Yes	6,311	9,011	1.50 (1.35-1.66)	1.55 (1.40-1.72)	<0.001
End stage renal disease	No	155,718	75,813	Reference	Reference	-
	Yes	28,265	12,803	1.00 (0.95-1.05)	1.01 (0.96-1.06)	0.761

Table 16. Results of Logistic Regression Examining Predictors of Anticoagulant Medication Use, in the First 24 Months of Observation, continued

Potential Predictor of AC Use		**Person-months with No AC Use**	**Person-months with AC Use**	**Unadjusted* Odds Ratio (95% Confidence Interval)**	**Adjusted* Odds Ratio (95% Confidence Interval)**	**Adjusted Odds Ratio p-value**
Hypertension	No	28,749	13,061	Reference	Reference	-
	Yes	155,234	75,555	0.96 (0.92-1.01)	0.98 (0.94-1.02)	0.300
Internal bleed	No	176,074	85,200	Reference	Reference	-
	Yes	7,909	3,416	0.90 (0.83-0.98)	0.91(0.83-0.99)	0.024
Parkinson's disease	No	171,839	83,486	Reference	Reference	-
	Yes	12,144	5,130	0.92 (0.85-0.99)	0.93(0.86-1.00)	0.045
Peripheral vascular disease	No	156,012	73,602	Reference	Reference	-
	Yes	27,971	15,014	1.02 (0.97-1.06)	1.02 (0.97-1.06)	0.475
Trauma	No	141,443	68,157	Reference	Reference	-
	Yes	42,540	20,459	1.00 (0.95-1.05)	1.00 (0.96-1.05)	0.877
Antiplatelet use	No	158,109	85,537	Reference	Reference	-
	Yes	25,874	3,079	1.00 (0.99-1.00)	1.00 (0.99-1.00)	<0.001
Fall history	No	22,968	11,240	Reference	Reference	-
	Yes	161,015	77,376	0.98 (0.94-1.02)	1.00(0.96-1.04)	0.850
Fall in prior month	No	168,223	81,473	Reference	Reference	-
	Yes	15,760	7,143	0.98 (0.98-0.99)	0.98(0.98-0.99)	<0.001

*Unadjusted results were generated from a series of generalized estimating equation models each of which included a single predictor and accounted for correlation among repeated measures on the same individual.
*Adjusted odds ratios were generated from one generalized estimating equation that included all of the potential predictors.

Aim 3 Results: Ischemic stroke and intracranial hemorrhage rates and net effect of AC use

Table 17 shows the number of months with one or more IS and ICH, the amount of follow-up and the unadjusted event rates per 100 person-years for cohort members while using ACs and while not using ACs. There were more person-years while not using ACs than while using ACs (3,469 versus 7,708). The observed event rates per 100 person-years were higher for ICH when not using ACs compared to using ACs (0.63 and 0.70 events per 100 person-years, respectively, using the primary outcome definition; 0.63 and 0.68, respectively, using the severe outcome definition), although these are not statistical differences. The observed IS rates were higher when not using ACs (4.10 and 2.94, respectively, using the primary outcome definition; 3.98 and 2.71, respectively, using the severe outcome definition).

Table 17. Unadjusted Rates of Ischemic Stroke and Intracranial Hemorrhage during the First 8 Months of Observation, by AC Use

	While Using AC (3,469 Person-years)		While Not Using AC (7,708 Person-years)	
Event	**Number of Events***	**Event Rate per 100 Person-years**	**Number of Events***	**Event Rate per 100 Person-years**
Ischemic stroke	102	2.94	324	4.10
Severe ischemic stroke	94	2.71	315	3.98
Intracranial hemorrhage	22	0.63	55	0.70
Severe intracranial hemorrhage	22	0.63	54	0.68

*Multiple events occurring in the same person-month were counted as a single event.

Table 18 reports the adjusted IS and ICH rates while using and not using ACs, along with the rate differences. The ICH rate per 100 person-years was higher in the presence of AC use (0.71, 95% CI: 0.29-2.15) than in the absence of ACs (0.65, 95% CI: 0.29-1.93) (rate difference 0.06, 95% CI: -0.32-0.54). The IS rate per 100 person-years was higher in the absence of AC use (3.95, 95% CI: 2.85-10.08) than in the presence of AC use (2.84, 95% CI: 1.98-7.25) (rate difference 1.11, 95% CI: 0.45-3.05). The unweighted and weighted net effects were positive and statistically significantly different from zero, supporting a net benefit of AC use (unweighted net effect: 1.07, 95% CI: 0.31-3.01 and weighted net effect: 1.05, 95% CI: 0.18-3.03). The results for the model that included only severe events had similar values for the rates, rate differences and net effects.

Table 18. Adjusted Net Effects for Ischemic Stroke and Intracranial Hemorrhage per 100 Person-Years

Ischemic Stroke*			
Model Outcomes†	**Rate with AC Use (95% CI)**	**Rate with No AC Use (95% CI)**	**Rate Difference (No AC-With AC) (95% CI)**
Ischemic stroke	2.84 (1.98, 7.25)	3.95 (2.85, 10.08)	1.11 (0.45, 3.05)
Severe ischemic stroke	2.71 (1.84, 6.69)	3.89 (2.75, 9.56)	1.28 (0.52, 3.13)
Intracranial Hemorrhage*			
Model Outcomes†	**Rate with AC Use (95% CI)**	**Rate with No AC Use (95% CI)**	**Rate Difference (AC-No AC) (95% CI)**
Intracranial hemorrhage	0.71 (0.29, 2.15)	0.65 (0.29, 1.93)	0.06 (-0.32, 0.54)
Severe intracranial hemorrhage	0.70 (0.28, 2.18)	0.64 (0.28, 1.93)	0.06 (-0.30, 0.56)
Net Clinical Effect			
Model Outcomes†	**Unweighted†** (95% CI)	**Weighted†‡§ (95% CI)**	
Intracranial hemorrhage and ischemic stroke	1.07 (0.31, 3.01)	1.05 (0.18, 3.03)	
Severe intracranial hemorrhage and severe ischemic stroke	1.14 (0.38, 3.07)	1.19 (0.25, 3.09)	

*The models were adjusted for month (1-2 vs 3-8), calendar year (2007-2012 vs 2013), age (<75, 75-84, ≥85 years), sex, baseline ischemic stroke or transient ischemic attack, baseline internal bleed, hypertension absorbing state, congestive heart failure absorbing state, diabetes absorbing state, hospitalization for IS in the prior month, and hospitalization for ICH in the prior month. All models used weighted MSM.

†The net effect is the difference between the IS and ICH rate differences. A value >0 supports a potential benefit of AC use, a value of 0 suggests no benefit and no harm, and a value <0 suggests potential harm from AC use.

‡The unweighted net effect calculation used the following formula: Net effect = (IS rate not using AC - IS rate using AC) – (ICH rate using AC - ICH rate not using AC).

§The weighted net effect was obtained by multiplying the ICH estimates by a factor of 1.5, as indicated in the following formula: Net effect = (IS rate not using AC - IS rate using AC) – 1.5*(ICH rate using AC - ICH rate not using AC).

Chapter 5 Discussion

To our knowledge, this is the first study to examine the net effect of AC use in a nationally representative sample of LTC residents with AF. The cohort included predominantly older, white, females from across the country. Despite many people having an indication for its use, only 36.2% of the LTC residents were using ACs. A net effect favoring AC use was observed.

Summary of Study Findings and Comparison with the Existing Literature

Study Cohort

Study inclusion criteria were applied to potential study participants in the administrative data source to ensure that sufficient information was available on the selected study participants. LTC facility residence was defined as having spent at least 101 days within the facility. This criterion excludes people who resided within the facility for short stays only. These people would likely be either much sicker residents, who died before reaching the long-stay definition, or perhaps healthier than those who were included in the cohort. These potentially healthier people may have been in the facility for a shorter rehabilitation and then discharged to home. This group may have suffered from a hip fracture or a stroke that may not have been severe or disabling enough to require longer-term care. The factors associated with AC use and the net effect could have been different in the group of people excluded for this reason. However, the long-term care population was the target population for this study.

Two additional study inclusion criteria were fee-for-service Medicare enrollment and Part D prescription drug coverage enrollment during the 13-month period comprised of the

12-month baseline period prior to study entry and the first month of follow-up. Of the 43,717 potential study participants who were LTC residents for at least 101 days, 30,290 (31%) were also enrolled in fee-for-service Medicare in the 13-month period comprised of the 12 months prior to entry into LTC and the first month in LTC. The LTC residents who were excluded could have been Medicare Advantage enrollees for some or all of the time, or they could be younger Medicare beneficiaries who qualified for Medicare less than 12 months prior to entry into LTC. Medicare beneficiaries qualifying for coverage based on age (as opposed to disability or end-stage renal disease) enrolled in Medicare Advantage plans tend to be younger and healthier than other beneficiaries (Centers for Medicare and Medicaid Services 2012, Avalere Health 2018). Of the 30,290 fee-for-service Medicare beneficiaries, 23,167 (24%) were not enrolled in a Part D prescription drug plan for the 13-month period comprised of the 12 months prior to entry into LTC and the first month of follow-up in LTC. These potential study participants could have lacked Part D coverage for a number of reasons. It is possible that they did not choose to enroll in a Part D plan because they did not want to pay the premium associated with the coverage, or they received their drug coverage through some other mechanism, e.g., an employer-sponsored prescription drug plan. This group may be healthier and elect not to enroll in drug coverage or have their prescription drugs covered by another source. People with a low enough income to qualify for the low-income subsidy would have been more likely to participate in this study because they would have Part D coverage offered through Medicare. This may make the study cohort more likely to include sicker LTC facility residents, compared with all LTC facility residents. As a result, the study cohort may have had a lower prevalence of AC use than if the healthier people had been included in the cohort, although it is not clear what impact this would have on the net benefit associated with AC use.

The number of study participants with AF entering LTC increased from 2007 to 2009 and then decreased each year from 2009 to the end of the study, with the exception of 2010. The number may have been slightly lower in 2007 because Medicare Part D prescription drug coverage only became available in 2006. The decrease in the number of people entering LTC from 2009 onward was likely due to a national declining trend. The CMS Nursing Home Data Compendium published in 2015 reported that "the number of nursing homes has gradually declined over the past 10 years" (Centers for Medicare and Medicaid Services 2015). The report also stated that "nursing home occupancy has declined very gradually but steadily from 85.5% in 2005 to 82.4% in 2014" (Centers for Medicare and Medicaid Services 2015). The number of people entering LTC in the study cohort decreased from 3,094 in 2007 to 2,641 in 2012 – a 14% decrease. We used the year 2012 to calculate the percent decrease because 2012 was the latest year in which study participants could enter the cohort throughout the year. The decline in the number of study participants residing in LTC between 2012 and 2013 was likely due to the LTC cohort inclusion criteria. Because a study participant must have resided in LTC for at least 101 days and must have had at least one month of follow-up, many study participants who entered the nursing home after August 23, 2013 did not have the opportunity to be included in the study. This study had a steeper percent decrease in nursing home occupancy than that reported by CMS; however, this study had stringent entry criteria whereas the report by CMS included all people who had a stay in a nursing home – including younger adults, those with short stays, and those with conditions other than AF. Even though slightly fewer study participants entered LTC each year than the preceding year, the absolute number of study participants residing in LTC increased across the study years, with the exception of the last year, because the median LTC stay was over one year.

Aim 1

This study found that 36.2% of study participants were using ACs. In other words, although the study participants were at high risk for IS because of the AF diagnosis and their advanced age, less than half of them were using ACs. This low frequency of AC utilization is consistent with some other studies in people with AF residing in LTC. For example, Gurwitz and coauthors found that 32% of nursing home residents with AF were using ACs (Gurwitz 1997). The frequency of AC use in the current study was higher than the 20% point prevalence observed by Lackner and coauthors in nursing home residents in Minnesota with AF (Lackner 1995). However, the frequency of AC use in the current study was lower than in the study by Lau and coauthors (49%) observed in nursing home residents in Alberta (Lau 2004) and in the study by Abdel-Latif and coauthors (47%) observed in six LTC facilities in one metropolitan area (Abdel-Latif 2005), both of which included nursing home residents with AF.

In this study, the prevalence of AC use was higher in younger than older age groups. A 1997 study by Gurwitz and coauthors in people with AF residing in LTC facilities also found a higher prevalence in younger age groups (Gurwitz 1997). Similarly, a 2004 study in nursing homes in six states found that older residents were less likely to initiate and more likely to discontinue antithrombotic therapy for secondary IS prevention in IS survivors (Hughes 2004). Lau and coauthors found that age was not statistically significantly associated with warfarin use among LTC residents with AF (Lau 2004).

White study participants had a higher prevalence of AC use than either black study participants or study participants of other races. This was consistent with other studies. For example, Quilliam and coauthors found that black LTC residents were less likely to be treated with drug therapy for secondary IS prevention than white LTC residents (Quilliam 2001). Hughes and coauthors found that black LTC residents were less likely than white LTC residents to initiate warfarin therapy for secondary IS prevention in their study using Minimum Dataset assessments (Hughes 2004). Christian and coauthors performed a study of nursing home residents with recent hospitalization for IS in which they found that black people received warfarin for secondary IS prevention less often than white people (Christian 2003). Abdel-Latif and colleagues in a study examining predictors of AC use for IS prevention in LTC residents with AF found that non-white people were less likely to receive ACs than white people (Abdel-Latif 2005). The findings from this study suggest that there may be some racial inequity in treatment for IS prophylaxis.

Females had a slightly higher prevalence of AC use than males. Gurwitz and colleagues did not find an association between female sex and warfarin use in a study of elderly LTC residents with AF (Gurwitz 1997).

Prevalence of AC use varied by geographic region. Study participants residing in the Midwest and North East regions had a higher frequency of utilization than those in the South and West. Similarly, a recent study of Medicare beneficiaries diagnosed with AF in

2013 and 2014 found that beneficiaries in the Midwest and North East had a higher probability of initiating ACs compared to those in the South (Hernandez 2017).

The median PDC was close to 100% among AC users for nearly all subgroups examined. This suggests that the majority of people who used ACs were receiving the medication consistently. A high PDC and consistent medication receipt in the LTC setting is expected because nursing home staff place a high priority on timely prescription medication administration (Barnes 2006). Furthermore, the high PDC suggests that there were few people who discontinued or started the medication in each year and that the decision to prescribe and use ACs for IS prevention in people with AF remains fairly stable. This may be because prescribers do not frequently reevaluate LTC residents' risk-benefit profile (the potential benefit for IS prevention and potential risks of major hemorrhage). An alternative explanation is that beneficiaries do not develop new conditions that change the risk-benefit ratio related to AC use.

Aim 2

Because of the large sample size and the repeated measures within study participant, some of the odds ratios for this aim were statistically significant although they were very close to the null value of 1. Some small effect sizes may not be clinically meaningful. For example, history of congestive heart failure, antiplatelet use and fall in prior month were all statistically significant, but had one confidence limit that rounded to 1.0.

Ischemic stroke risk factors

This study found that the longer a study participant resided in LTC, the more likely the study participant was to be using ACs after adjusting for age and chronic conditions.

However, the effect was so small (OR: 0.98, 95% CI: 0.98-0.98) that it is not likely to be clinically relevant.

The following IS risk factors were associated with a higher frequency of AC use: having a history of stroke or transient ischemic attack, thromboembolism, congestive heart failure, female sex and being age 85 years and older. The following potential IS risk factors were not associated with AC use in this study: hypertension, diabetes mellitus, and peripheral vascular disease. This suggests that stroke or transient ischemic attack, thromboembolism, female sex and advanced age may be the factors that prescribers do consider when prescribing ACs in LTC residents with AF.

A possible explanation for the lack of association (i.e., hypertension, peripheral vascular disease, congestive heart failure) with AC use could be that the definitions used to define many of these conditions were based on the MDS assessments for conditions actively affecting the care of patients. For example, because uncontrolled hypertension could not be measured in this study, hypertension was used as a proxy. Some people classified as having hypertension may have been receiving treatment for the condition. This study definition may not have been sensitive enough to capture those at higher risk for IS. Similarly, peripheral vascular disease was not associated with AC use. Peripheral vascular disease was used in this study as a proxy for vascular disease, an established IS risk factor and indication for the use of ACs. Peripheral vascular disease as a proxy for vascular disease may not have captured all of the increased IS risk that may lead to AC use. As a result, study participants with peripheral vascular disease were no more or less likely to be using ACs.

Major hemorrhage risk factors

Internal bleeding and antiplatelet use were statistically significantly associated with a lower frequency of AC use. Because of the statistically significant associations, these may be the most important factors considered when prescribing ACs in this population.

End stage renal disease was not associated with AC use. End stage renal disease was used as a proxy for chronic kidney disease, which is more encompassing than end stage renal disease. Perhaps this factor, a risk factor for major hemorrhage, is less important when considering AC use for IS prophylaxis. Alternatively, it may be other aspects of chronic kidney disease that influence AC use.

Factors influencing physician prescribing

Anemia, fall in prior month, dementia or cognitive impairment, Parkinson's disease, and frailty were associated with a lower frequency of AC use. Fall history, malignancy and trauma were not associated with AC use.

A few studies have been performed on groups of physicians to understand what motivates physician prescribing of ACs in older adults with AF residing in LTC. These studies, most of which had small sample sizes, have typically presented a clinical scenario of a medically complex older adult to see if physicians agreed on whether or not AC treatment is warranted, and what factors were most important when making the decision to treat. In one study of physicians providing care to older patients in LTC facilities responding to a questionnaire with two clinical scenarios, the physicians cited excessive risk of falls, history of gastrointestinal bleeding, history of other non-central nervous system bleeding and history of cerebrovascular hemorrhage as contraindications to warfarin use (Monette

1997). In this same study, 47% of physicians reported that the benefits of warfarin therapy greatly outweigh the risks. In another study in which physicians examined a case scenario of patients in the nursing home, the most common reasons cited for not prescribing ACs was the risk of falls, dementia and short life expectancy, even in patients for whom ACs were indicated for at least short-term use (Dharmarajan 2006). In this study, physicians were much more likely to provide antiplatelet therapy, like aspirin. In a more recent study of physician prescribing, physicians cited fall risk, bleeding risk and poor patient adherence as barriers to prescribing warfarin (Nicholls 2014). In this study, having treated a patient with an IS while not using warfarin increased the likelihood of prescribing ACs (Nicholls 2014). These studies all suggest that there is uncertainty around warfarin prescribing for IS prophylaxis in people with AF. In these studies, there seems to be additional complexity in deciding when to prescribe in older, frailer LTC facility residents which may partially explain the findings of our study.

Aim 3

The estimated rate of IS was lower for study participants while using ACs (2.84 per 100-person years, 95% CI: 1.98-7.25) compared to while not using ACs (3.95 per 100 person-years, 95% CI: 2.85-10.08), although the confidence intervals overlap meaning that these rates are not statistically different from each other. These rates are similar to the IS rates observed in other studies among people with low to moderate IS risk. In a cohort that included all people in Sweden with AF who were hospitalized, the rates of IS among those with moderate IS risk were reported by IS risk score, and they were higher in those not treated with ACs (3 per 100 person-years) than those who were treated with ACs (2 per 100 person-years), among those with moderate IS risk (Friberg 2012). While Friberg

(2012) reported IS rates for each IS risk level, we compare to those with a CHA_2DS_2-VASc score of 3, indicating moderate risk, which is similar to many of the participants in this study – 2 points for age 75 years and older and 1 point for female sex.

The rate of ICH was higher while using ACs (0.71 per 100 person-years, 95% CI: 0.29-2.15) compared to while not using ACs (0.65 per 100 person-years, 95% CI: 0.29-1.93). The opposite relationship was observed in the unadjusted ICH rates, suggesting that there is some confounding between lower bleeding risk and receiving ACs. The adjusted findings are consistent with other studies (Petersen 1989, Landefeld 1993). These adjusted estimates were very close to each other and the confidence intervals overlap meaning that they are not statistically different from each other. These rates are similar to those obtained in other studies (Singer 2009, Friberg 2012, Siu 2014, Allan 2017). For example, Friberg observed an annual incidence of 0.6 per 100 person-years for ICH in a cohort of adults with AF regardless of whether or not they were using warfarin (2012). The rates observed in this study were slightly lower than the annual incidence of 1-2% per year observed in the moderate bleeding risk group in the Euro Heart Study (Pisters 2010). The rates in this study in people while using ACs was similar to the 0.6% annualized rate observed in the Siu (2014) study, but the rates in this study while not using ACs was lower than the 1.1% annualized rate observed by Siu. Everyone in our study is age 65 and older and would therefore be classified as being at moderate risk or greater. An alternative explanation for the similarities in these two rates of ICH is that the study participants with lower bleeding risk were more likely to be AC users. If there was some unmeasured confounding, then the adjusted estimates may be biased. As a result, the increased risk of ICH in those using ACs may have been offset by their overall lower risk of bleeding compared to the nonusers of ACs.

Anticoagulant use was associated with a net benefit in older adults residing in LTC (net effect 1.07 per 100 person-years, 95% CI: 0.31-3.01). There are two ways to interpret the net effect. The net effect is the rate per 100 person-years of IS attributable to AC use after removing the rate of ICH attributable to AC use. This number can be reported as an annualized percentage, i.e., the net percent of prevented adverse events due to AC use is 1.07% per year. This finding is consistent with studies that examined the net benefit in community-dwelling older adults with AF. For example, Singer et al. found an overall net benefit of 0.68% per year for warfarin use in older adults with AF in an integrated health care delivery system.

Singer et al. and other studies published later using Singer's methodology stratified the analysis using an IS risk algorithm – most commonly the CHADS2 or CHA_2DS_2-VASc. These studies which included community-dwelling older adults with AF or both community-dwelling and institutionalized patients with AF (Friberg 2012, Allan 2016, Siu 2014), found a net benefit of AC use for people with moderate to high IS risk (Singer 2009, Friberg 2012, Siu 2014, Allan 2016, Kooistra 2016). Friberg found a net benefit of AC use when considering IS prevention and ICH for those with moderate to high IS risk (based on a CHA_2DS_2-VASc score of at least 2), and no benefit for those with a low IS risk. Friberg observed a net benefit of 3.9 events per 100 person-years overall, and a benefit ranging from of 1.7 to 12.2 events per 100 person-years, from moderate to highest IS risk. Siu found a net benefit of 5 to 8 events avoided per 100 person-years. The Siu study cohort included Chinese adults with AF who were at least 80 years old, and all study participants were at high risk for IS. Allan performed a study in England and found a net benefit of 0.5 events per 100 person-years for men and 1.5 for women (Allan 2016). Most of the participants in this study would likely have at least moderate stroke risk, due to being of advanced age, one of the components of the two risk scores mentioned above. The net benefit from our study is on the lower end of the ranges of the net benefit found in other studies, but still in the same direction. This suggests that AC use favors improved outcomes, even in LTC facility residents who are mostly of advanced age and have IS and major hemorrhage risk factors.

Strengths of the study

This study had a number of strengths including the ability to study medication utilization in older adults residing in LTC over a seven-year period. There was complete capture of all prescription drug fills covered by the Medicare Part D benefit. This allowed for the generation of national estimates of the annual prevalence of AC use from 2007 to 2013. Also, duration of follow-up was fairly long (median 339 days). The data source included information on a large, nationally representative sample of the target population of interest: older adults with AF residing in LTC. The large sample size allowed us to obtain precise prevalence estimates.

Information on medication use and risk factors was captured over time, enabling stronger conclusions to be drawn compared to a cross-sectional design. Linking the administrative data to the MDS assessments allowed for repeated measures on variables that are not available in claims data and that are relevant to this study, including falls and frailty.

Limitations of the study

Selection Bias

Selection bias was unlikely to be present in Aim 1. The study utilized retrospective data collected for billing (i.e., administrative claims) and routine regulatory (i.e., MDS assessments) purposes. These data were collected for all Medicare beneficiaries who resided in LTC during the study period. Information on all of the descriptive characteristics examined is collected routinely by the Medicare program, and all the conditions affecting the study participants' health status are part of the MDS assessments completed routinely on all beneficiaries while residing in CMS-certified nursing homes.

One hundred and six beneficiaries were excluded because of evidence of prosthetic heart valve. The number with prosthetic heart valves observed in this study was lower than expected. In the U.S. in 1988 (the most recent estimate available), the prevalence of heart valve replacement with prosthetic valves was 5.3 per 1,000 people for those 75 years of age and older (Garver 1995). Based on this prevalence, we would expect that there would be 117 beneficiaries with prosthetic heart valves (5.3/1,000*22,014). Since the 106 people identified is lower than the 117 people expected, it is possible that some beneficiaries with prosthetic heart valves were not excluded. People with an undetected prosthetic heart valve were overwhelmingly likely to be AC users because this condition is a nearly absolute indication for AC use. Because the number of study participants included erroneously was likely small, the prevalence estimates in Aim 1 were most likely not affected. Potentially including these additional people with a prosthetic heart valve was not likely to have major implications for Aims 2 and 3, again because the number of people affected was so small.

One concern was selection bias related to loss to follow-up for the Aim 2 and 3 analyses. The observation period was from entry into LTC to the earliest of the end of the study, death, discharge from LTC, or 24 months for Aim 2 or 8 months for Aim 3. There was no reason to believe that reaching the end of the study would be influenced differently by the values of any of the potential predictors. For Aim 3, if a person has an IS or ICH that leads to sudden death that is not reported in the administrative claims data (e.g., during a hospitalization), this most likely occurs irrespective of AC treatment status. For Aim 2, if a person leaves the facility for another reason (e.g., to go live with a caregiver), it is unlikely that that is related to AC treatment. Truncating the observation period at 24 months for Aim 2 or 8 months for Aim 3 would not be affected by the potential predictors of AC use (Aim 2) or AC use (Aim 3).

Months with fewer than 30 days were dropped from the analysis. Months with fewer than 30 days would only occur in the last month the study participant was observed. Excluding the last month could have led to bias, in particular for aim 3. This is because IS or ICH events occurring during the last month leading to death (and no longer being observed) would likely have occurred before the 30th day. IS and ICH would likely have been associated with AC use. Study participants using ACs would have been less likely to have IS and more likely to have ICH than study participants not using ACs during this month. This may have biased the net effect estimate towards the null. However, this exclusion was applied because, if a study participant was observed for fewer than 30 days in their last month for a reason unrelated to the outcomes, then there could have been an insufficient amount of observation during that last month.

Information Bias

The data source for this study contained a lot of information on LTC residents that was recorded consistently over time (administrative information, Part D events and administrative claims). However, these data are not collected specifically for research purposes. These data are collected for administration of the Medicare program, for billing purposes in the case of administrative claims, and for tracking the quality of nursing home care in the case of the MDS assessments. The MDS has been used by others to identify the nursing home length of stay (Wei 2016) and has been shown to be a valid source of information for this (Doupe 2018).Additionally, authors have reported that the MDS contains reliable and valid information (Hawes 1997, Mor 2004, Poss 2008), while other authors have reported some concerns with specific information that can be extracted from the MDS (Mor 2011). The validity of the definitions used is discussed in more detail below.

Aim 1 Misclassification of Exposure: Demographic Characteristics

The demographic characteristics were unlikely to be inaccurate because the information came from Medicare administrative data sources. A small number of beneficiaries were dropped from some analyses because of missing values for race and region. Because the numbers were so small, 30 and one beneficiary, respectively, it was unlikely that excluding these beneficiaries altered the observed prevalence estimates.

Aim 1 Misclassification of Outcome: AC Use

AC use was captured using prescription drug fills as a proxy for actual medication use. Study participants may have begun taking the medication after the prescription's fill date.

In this case, the AC use may have been attributed to the incorrect month. Alternatively, study participants who filled the prescription may not have taken the medication at all. Not taking the medication would have misclassified a non-AC user as an AC user. However, since study participants were residing in LTC, and their medication use was managed by the facility, it was unlikely that the medication would have been continually filled if the study participant refused the AC medication. It seems unlikely that misclassification of AC use influenced estimates of the frequency of AC use in Aim 1 because of the monitoring of the medication administration of LTC facility residents.

Study participants may have received AC medication from other sources – e.g., by paying out of pocket or through supplemental insurance. Receiving the medication from other sources was unlikely to occur, but would have misclassified a user as a nonuser. In this LTC population, many residents qualify for Medicare-Medicaid dual eligibility and the Medicaid Part D benefit covers the AC drugs of interest. Therefore, their prescription medications for these chronic medications were very likely to be covered by the Part D benefit.

Aim 2 Misclassification of Exposure: Potential Predictors of AC Use

The potential predictors of AC use were defined using MDS assessments. Studies have shown reasonable agreement on the diagnoses in the MDS and on hospital claims (Del Rio 2006, Mor 2011). The conditions that were included were from the section of the MDS assessment that captured conditions actively affecting the resident's care. While the MDS assessment is a standard form, it is completed by health care professionals in facilities across the country. There could be inconsistencies in the completeness of the conditions reported. In addition, not all of the potential predictors of AC use were included in the MDS assessment. For example, the MDS includes congestive heart failure and not left ventricular systolic dysfunction. There are also some differences in how information was collected on the two MDS assessment versions used during the study period. The most relevant difference was for stroke and transient ischemic attack. These two conditions are combined into one variable in the MDS 3.0, while stroke and transient ischemic are separate variables in the MDS 2.0. For comparability across time, stroke and transient ischemic attack were combined into one variable in the analysis. Additionally, the stroke variable from the MDS did not include the etiology (ischemic or hemorrhagic); therefore, all etiologies were included in the variable. Because IS could be prevented by AC use and hemorrhagic stroke could be caused by AC use, combining these could have led to differential misclassification of this exposure. Depending upon the prevalence of each stroke type, this could have led to an increase or decrease in the likelihood of being on an AC. Since hemorrhagic stroke is less common than IS, and this variable was aiming to capture IS, it is likely that the inclusion of hemorrhagic stroke would have biased the relationship between stroke or transient ischemic attack in the opposite direction (i.e., reducing the likelihood of AC use). Because regular evaluation of LTC residents using the MDS was mandated, the underreporting of conditions was less likely than it would be for the community-dwelling population. The conditions included in the analyses were serious enough that they would likely be reported on the assessment because they required ongoing management.

When constructing the variables for the conditions using the MDS, the prevalence was compared, when available, to other sources, including the Chronic Condition Warehouse. This was done as a check on face validity to ensure that using the information in the

MDS did not under- or overestimate the prevalence of the conditions on average. Because the numbers were similar, we had confidence in the validity of the information on the conditions from this data source.

The approach of using the MDS to define conditions, while reasonable for chronic conditions, may have led to some measurement error for other conditions, like fall and frailty. Studies have found that the MDS underreports falls (Hill-Westmoreland 2005, Marier 2016). Not including administrative data may have missed some falls, and these may have been the more severe falls. Using the MDS only may have biased the relationship between falls and AC use towards the null. Frailty was defined using an adapted version of the CHESS score. This score had to be adapted because not all of the necessary elements were available in the MDS 3.0. Furthermore, frailty was dichotomized into frail or not frail. This was necessary because the sample size was small for some of the levels. By dichotomizing the frailty score, information on all the levels could not be examined. This dichotomization could have obscured the relationship between frailty and AC use, if the frailer group had more AC use than the less frail people.

There is also a potential concern about whether all MDS assessments were completed and are available in the data during the follow-up period. When there was no evidence of discharge from the LTC facility, the study participant was censored when there was a gap of more than one calendar quarter between MDS assessment dates. One study examined the MDS and found that the MDS is a valid data source to capture time in a nursing home (i.e., admission, transfer from the facility and death) (Doupe 2018). It is unlikely that study participants were missing MDS assessments in a way that would have been associated with the exposure or the outcome for this aim.

Aim 2 Misclassification of Outcome: AC Use

The measurement issues related to capturing AC use described under Aim 1 also apply to AC use as the outcome for Aim 2. It is unlikely that the AC prescriptions filled were not received and taken by the beneficiary, or that the AC prescriptions were covered by another insurance provider or paid for out of pocket. As a result, it is likely that the outcome of AC use in this aim was accurately measured and it is unlikely that AC use was measured differentially for any of the potential predictors included in this aim's analysis.

Aim 3 Misclassification of Exposure: AC Use

The measurement issues of capturing AC use described under Aim 1 also apply to AC use as the exposure for Aim 3. It is unlikely that AC use would have been captured differently for study participants with and without either of the outcomes (IS or ICH) especially since any medication use would have occurred before the outcome was known. It is possible that study participants classified as AC users may not have been receiving the therapeutic benefits of the treatment. The therapeutic benefit of warfarin is measured by the INR level. When INR is too high, the risk of major hemorrhage increases. When INR is too low, the IS risk increases. INR values are not available in this data source. Evidence suggests that physicians may put more weight on hemorrhage risk than on IS risk (Charneski 2014). Because of this, it is more likely that people will have an INR below the therapeutic range than above the therapeutic range, putting them at increased risk for IS. The AC users who are sub-optimally managed may have IS outcomes that are more similar to those of the non-AC users than the AC users. This differential misclassification of exposure would bias the results towards the null, making it more difficult to detect differences, if they exist.

Aim 3 Misclassification of Outcome: Hospitalization for Ischemic Stroke or Intracranial Hemorrhage

For Aim 3, the IS and hemorrhage outcomes were defined based on a hospitalization for the event. The source of data for these outcomes was inpatient claims. Because administrative claims are used for billing purposes and not research purposes, only IS and ICH that required seeking medical care other than that which could be provided by the LTC facility were included in this definition. This seems reasonable because studies have used hospitalizations based on claims as the gold standard, and these studies do not recommend using the MDS assessments for defining health care utilization (Del Rio 2006, Rahman 2014). In additional, claims have a limited number of diagnosis codes to capture the conditions relevant to the claim. In the case of IS and ICH, these are likely to have been included in the list of relevant diagnoses because they are conditions that require care and affect cost.

Another concern with using claims is if there is no claim at all for an IS or ICH event. This could occur if a major IS or ICH leads to sudden death in the LTC facility and the person is not hospitalized. If this were to occur, the outcome would be missed. If AC users were more or less likely than non-users to die suddenly in the facility, this would bias the estimate of the net effect of AC use, but this differential rate of sudden death seems unlikely.

Confounding

Confounding was a threat to the validity of the Aim 2 and Aim 3 analyses. None of the potential risk factors for AC use was randomly assigned. This lack of randomization could lead to spurious observed relationships with AC use (Aim 2) or between AC use and hospitalizations for IS or major hemorrhage (Aim 3). Although we stratified by year and demographic characteristics in Aim 1, we adjusted for potential predictors of AC use in Aim 2, and we adjusted for potential confounders in Aim 3, some unmeasured confounding could remain. For example, we did not have information on smoking, alcohol abuse, and liver disease which are factors included in prior studies because they could increase the risk of IS (smoking) or major hemorrhage (alcohol abuse and liver disease). Smoking and alcohol use are probably rare in the LTC setting because residents are unlikely to be allowed to smoke or use alcohol in the facility. Therefore, missing information on smoking and alcohol abuse should not have a large impact on this study's findings for Aim 2 or 3.

Because the data source only captured prescription medication use, and aspirin is an over-the-counter medication, some of the study participants who were classified as nonusers of ACs may have been using aspirin. This may have been appropriate, since aspirin is not recommended as the first line treatment for IS prevention in AF. However, aspirin also increases bleeding risk. Not being able to measure aspirin use may have led to some unmeasured confounding when examining the predictors of AC use in Aim 2 and when examining the relationship between AC use and ICH in Aim 3.

Since medication use was not randomized, confounding by indication could have occurred in Aim 3 (i.e., patient characteristics that influence AC use also predict IS or

ICH). To address this, all measured confounders were incorporated into the statistical models for Aim 3, and MSMs were used to address the potential for time-varying confounding. However, some unmeasured confounding could have remained. The unadjusted rates of ICH are higher when not using ACs, whereas the adjusted rates are in the opposite direction. The differences between the adjusted and unadjusted rates suggest that there was confounding present.

Time-dependent confounding may also have occurred in Aim 2 for stroke or transient ischemic attack, thromboembolism, and internal bleed, where prior AC use could confound the relationship between these three factors and future AC use. The analysis performed for Aim 2 should be interpreted as an examination of the associations, but not a causal analysis.

Statistical Issues

The marginal structural model approach used in the Aim 2 sensitivity analysis and the Aim 3 analysis produces unbiased estimates under the assumption that all confounding has been accounted for in the statistical model (Hernan 2000). Because this study used administrative data and not data collected in a prospective design, it is unlikely that all confounders were measured perfectly. As a result, there was likely some residual confounding. Additionally, the assumptions required for the method, in particular the positivity assumption, required truncating the data to eight months of follow-up. Additional months were available, but the IPW began to have non-ideal properties (i.e., mean deviating from 1 and increase in the standard deviation relative to the mean) with increasing follow-up that led to the decision to truncate the follow-up.

Implications

This study found that many older adults with AF residing in LTC were not receiving ACs, even though they have a high risk of IS. This observation was fairly consistent throughout the duration of this study from 2007 through 2013, and was consistent with other literature published over the past 20 years examining older adults residing in LTC. These findings suggest that AC use may be lower than is clinically optimal for IS prevention in this population.

People age 85 year old and older, compared with younger residents, and minority residents (black and other races), compared with white residents, were less likely to be using ACs, even after adjusting for IS and hemorrhage risk factors and factors that have been shown to affect physician prescribing of ACs. These are groups that may warrant additional consideration when prescribing ACs to ensure that they are not denied the benefits of treatment.

A history of congestive heart failure, stroke or transient ischemic attack, and thromboembolism were the only factors associated with an increased likelihood of AC use. The other potential predictors of AC use hypothesized to be associated with an increase in AC use (hypertension, diabetes mellitus, and peripheral vascular disease) did not show this relationship. Internal bleed and antiplatelet use were two risk factors for major hemorrhage that decreased the likelihood of AC use, while end stage renal disease had no association with AC use. This suggests that risk factors for major hemorrhage influence physicians not to prescribe ACs. Anemia, recent falls, dementia or cognitive impairment, Parkinson’s disease, and frailty were associated with a lower likelihood of AC use, while trauma and malignancy had no association. While recent falls (those in the past month) was associated with a lower likelihood of AC use, a fall history (absorbing state version of fall) was not.

History of stroke or transient ischemic attack and history of thromboembolism were the strongest predictors of AC use, and history of internal bleed and advanced age were the strongest predictors of not using ACs, where strong predictors were defined as those that had odds ratios with the largest magnitude. These appear to be the factors that have the strongest influence on physician prescribing of ACs.

Anticoagulant use was found to confer a net benefit in older adults with AF residing in LTC when considering IS and ICH, the most severe possible outcomes related to treatment with ACs. These findings add to the growing literature suggesting that even the oldest of the older adults would benefit from AC use (Singer 2009, Friberg 2012, Siu 2014, Allan 2016, Kooistra 2016). If the net benefit observed (1.07 IS prevented per 100 person-years) were applied to all of the person-time when study participants were not using ACs during the follow-up (7,708 person-year), then 83 IS would have been prevented. While some of those people may have high bleeding risk that prevented them from using ACs, this estimate provides some context for the number of IS prevented.

Our study did not include other potential benefits of AC treatment (systemic thromboembolism prevention) or harms, such as hemorrhage occurring outside of the brain, like gastrointestinal bleeds, which could also influence resident quality of life. While the intention of this study was to focus on the most severe sequelae of treatment or lack of treatment, the findings need to be interpreted with that in mind. The inclusion of these additional benefits and risks could change the net effect. This examination could be the focus of additional research in older adults with AF residing in LTC facilities.

There are no guidelines for IS prophylaxis in LTC residents with AF, although there are treatment guidelines for IS prophylaxis in adults with AF. A recent guideline published in 2017 (Frost) strongly recommends using ACs in those with moderate IS risk, which includes the majority of LTC facility residents. However, these guidelines do point out that the contraindications to AC use should be considered along with the IS risk, but the guidelines do not provide a list of contraindications to consider or a specific bleeding risk score assessment tool to make the determination. These guidelines also state that studies have not examined the net benefit of ACs in specific subpopulations, like those with multiple chronic conditions or end-stage renal disease, which can make dosing more complicated. Evaluation of the net effect within specific subpopulations of particular concern (e.g., residents with multiple comorbidities) or that are prevalent within LTC facilities (e.g., residents with dementia or cognitive impairment) could be the focus of future research.

Despite the guideline recommendations for AC use, there is still some uncertainty as to how to evaluate the risks, most notably the risk of hemorrhage. There are safety concerns with using ACs, including drug interactions, food interactions and monitoring, that make the management of AC use complex (Holbrook 2005). While the LTC resident population is cared for in a facility with medical supervision, there are studies in this setting that found that residents using warfarin are in the therapeutic range between half and three-quarters of the time (Aspinall 2010, McCormick 2001, Verhovsek 2008). One study in LTC residents found that residents were in the therapeutic range as much as 70%

of the time (Sargent 2016). In two of these studies, the majority of the time outside of the therapeutic range was in the subtherapeutic range, which does not provide sufficient protection against IS, but does increase the bleeding risk (Aspinall 2010, McCormick 2001). The time outside of the therapeutic range is occurring in these settings even though these studies found sufficient monitoring of AC use in these residents. These studies point to variation in the quality of AC management in the LTC facility setting, although studies have also reported that there is poor quality of AC use in the community-dwelling population (Gottlieb 1994, Matchar 2002, Samsa 2000).

While it is likely that the quality of AC management is better, overall, for facility-dwelling residents, there is likely variation within each setting. In our study, we found a high (nearly 100%) proportion of days covered across all strata of AC users. While we were unable to capture the time within the therapeutic range, the high proportion of days covered suggests that the residents are consistently receiving their medications. This is across facilities throughout the nation with different characteristics and case-mix of residents. The LTC facility residents with moderate to high IS risk may benefit from additional AC use, even with moderate hemorrhage risk; but these same residents should continue to be monitored carefully to ensure they are receiving the benefits of the treatment.

To address these safety concerns associated with AC use, studies have been performed to understand and to propose strategies to improve the quality of medication management. For example, one study suggested that nursing homes having fewer residents to care for may improve the quality of care in LTC facilities, and another study proposed a tool to improve medication monitoring that could help with these safety concerns in regard to

ACs and other drugs (Papaioannou 2010). Most of the studies on medication safety have been in people using warfarin, the oldest AC, but more recently with the new oral ACs on the market, the safety of the newer medications has been examined and compared to warfarin. Warfarin has different considerations (i.e., interactions with food or other medications, the need for INR monitoring) from the new oral ACs. Warfarin is reversible in the case of bleeding, whereas the new oral ACs do not have an antidote to manage excess bleeding. Interventions for each of these medications may require different attention. With regards to safety, the new oral ACs have been shown to be non-inferior to warfarin with regards to IS and thromboembolism prevention, and have been shown to be associated with fewer ICH, but slightly higher rates of other bleeds (i.e., gastrointestinal bleeds) (Miller 2012, Capodanno 2013, Dogliotti 2013, Ruff 2014). Due to when the new oral ACs came onto the market and the data available for this study, we found very few people were using the new oral ACs. Examining if there is a different net effect for warfarin compared to the new oral ACs is a topic for future research. Also, examining the net effect within different groups of residents (i.e., those with congestive heart failure, diabetes mellitus, hypertension, age group, end-stage renal disease) would also be beneficial to understand which characteristics would enable a resident to benefit the most from the treatment.

This study did not examine variation in the net effect by LTC facility or physician characteristics. Studies have shown that the quality of AC use varies by physician within the same facility (Verhovsek 2008), and studies have shown that residents' quality of care varies by nursing home (Abt Associates 2014). This could be another area for future research.

In conclusion, older adults residing in LTC with AF may be undertreated with ACs for IS prevention, in particular minority races and those 85 years and older. History of stroke or transient ischemic attack, history of thromboembolism and history of internal bleed had the strongest association with likelihood of AC use, suggesting that physicians consider both IS and hemorrhage risk factors when prescribing ACs. There was a net benefit associated with AC use when considering the most severe consequences of ACs. While the net benefit was small, there is the potential for IS prevention in this population.

Appendices

Appendix A. Diagnosis and Procedure Codes Used to Define Variables

Definition	Code	Code Type	Description
Atrial fibrillation	427.31	ICD-9 diagnosis	Atrial fibrillation
Intracranial hemorrhage	430	ICD-9 diagnosis	Nontraumatic subarachnoid hemorrhage, unspecified.
	431	ICD-9 diagnosis	Intracerebral hemorrhage
	432	ICD-9 diagnosis	Other and unspecified intracranial hemorrhage
	432.0	ICD-9 diagnosis	Nontraumatic extradural hemorrhage convert
	432.1	ICD-9 diagnosis	Subdural hemorrhage
	432.9	ICD-9 diagnosis	Unspecified intracranial hemorrhage
Ischemic stroke	433.x1	ICD-9 diagnosis	Occlusion and stenosis of precerebral arteries with cerebral infarction
	434.x1	ICD-9 diagnosis	Occlusion of cerebral arteries with cerebral infarction
	436	ICD-9 diagnosis	Acute, but Ill-defined Cerebrovascular Disease
	437.1	ICD-9 diagnosis	Other generalized ischemic cerebrovascular disease
	437.9	ICD-9 diagnosis	Unspecified cerebrovascular disease
Prosthetic heart valve	V43.3	ICD-9-CM diagnosis code	Heart valve replacement NEC
	35.05	ICD-9-CM procedure code	Operations on valves and septa of heart - endovascular replacement of aortic valve
	35.07	ICD-9-CM procedure code	Operations on valves and septa of heart - endovascular replacement of pulmonary valve
	35.2	ICD-9-CM procedure code	Operations on valves and septa of heart - replacement of heart valve
	35.20	ICD-9-CM procedure code	Operations on valves and septa of heart - replacement of unspecified heart valve
	35.21	ICD-9-CM procedure code	Operations on valves and septa of heart - replacement of aortic valve with tissue graft
	35.22	ICD-9-CM procedure code	Operations on valves and septa of heart - other replacement of aortic valve
	35.23	ICD-9-CM procedure code	Operations on valves and septa of heart - replacement of mitral valve with tissue graft
	35.24	ICD-9-CM	Operations on valves and septa of heart - other replacement of

Definition	Code	Code Type	Description
Atrial fibrillation	427.31	ICD-9 diagnosis	Atrial fibrillation
		procedure code	mitral valve
	35.25	ICD-9-CM procedure code	Operations on valves and septa of heart - replacement of pulmonary valve with tissue graft
	35.26	ICD-9-CM procedure code	Operations on valves and septa of heart - replacement of tricuspid valve with tissue graft
	35.27	ICD-9-CM procedure code	Operations on valves and septa of heart - open and other replacement of tricuspid valve with tissue graft
	35.28	ICD-9-CM procedure code	Operations on valves and septa of heart - other replacement of tricuspid valve
	33361	CPT	Aortic valve procedures - Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach
	33362	CPT	Aortic valve procedures - Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open femoral artery approach
	33363	CPT	Aortic valve procedures - Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open axillary artery approach
	33364	CPT	Aortic valve procedures - Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open iliac artery approach
	33365	CPT	Aortic valve procedures - Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transaortic approach (eg, median sternotomy, mediastinotomy)
	33366	CPT	Aortic valve procedures - Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transapical exposure (eg, left thoracotomy)
	33367	CPT	Aortic valve procedures - Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (eg femoral vessels) (List separately in addition to code for primary procedure)
	33368	CPT	Aortic valve procedures - Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with open peripheral arterial and venous cannulation (eg, femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure)
	33369	CPT	Aortic valve procedures - Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with central arterial and venous cannulation (eg, aorta, right atrium, pulmonary artery)
	33405	CPT	Aortic valve procedures - Replacement, aortic valve, with cardiopulmonary bypass; with prosthetic valve other than homograft or stentless valve
	33406	CPT	Aortic valve procedures - Replacement, aortic valve, with cardiopulmonary bypass; with allograft valve (freehand)

Definition	Code	Code Type	Description
Atrial fibrillation	427.31	ICD-9 diagnosis	Atrial fibrillation
	33410	CPT	Aortic valve procedures - Replacement, aortic valve, with cardiopulmonary bypass; with stentless tissue valve
	33411	CPT	Aortic valve procedures - Replacement, aortic valve; with aortic annulus enlargement, noncoronary cusp
	33412	CPT	Aortic valve procedures - Replacement, aortic valve; with transventricular aortic annulus enlargement (Konno procedure)
	33413	CPT	Aortic valve procedures - Replacement, aortic valve; by translocation of autologous pulmonary valve with allograft replacement of pulmonary valve (Ross procedure)
	33430	CPT	Mitral valve procedures - Replacement, mitral valve, with cardiopulmonary bypass
	33465	CPT	Tricuspid valve procedures - Replacement, tricuspid valve, with cardiopulmonary bypass
	33468	CPT	Tricuspid valve procedures - Tricuspid valve repositioning and plication for Ebstein anomaly
	33475	CPT	Pulmonary valve procedures - Replacement, pulmonary valve
	33477	CPT	Pulmonary valve procedures - Transcatheter pulmonary valve implantation, percutaneous approach, including pre-stenting of the valve delivery site, when performed
	33496	CPT	Other valve procedures -Repair of non-structural prosthetic valve dysfunction with cardiopulmonary bypass (separate procedure)

Appendix B. Aim 3 MSM Supporting Tables

Distribution of the stabilized inverse probability of exposure and censoring weights

Month	Number of Observations	Mean (Standard Deviation)	Minimum-Maximum	Sum
1	21,877	1.00 (0.06)	0.73-1.31	21,881
2	19,829	1.00 (0.08)	0.70-1.35	21,903
3	18,183	1.00 (0.11)	0.75-1.88	19,805
4	16,882	1.01 (0.14)	0.68-1.97	18,279
5	15,748	1.01 (0.18)	0.62-2.10	16,989
6	14,761	1.02 (0.22)	0.57-2.23	15,965
7	13,883	1.03 (0.26)	0.52-2.30	15,101
8	13,122	1.04 (0.30)	0.47-2.25	14,367

Odds ratios for the exposure denominator weight-generating model for one replicate

Potential Predictor of AC Use		**Adjusted Odds Ratio (95% Confidence Interval)**
Intercept		0.34 (0.32, 0.36)
Month relative to LTC entry	1	Reference
	2	1.48 (1.42, 1.54)
	3-8	1.73 (1.67, 1.79)
Calendar year	2007-2012	Reference
	2013	1.03 (1.00, 1.07)
Sex	Female	Reference
	Male	0.85 (0.83, 0.88)
Age	66-74	Reference
	75-84	0.86 (0.82, 0.89)
	≥85	0.67 (0.65, 0.7)
Baseline stroke or transient ischemic attack	No	Reference
	Yes	1.34 (1.31, 1.38)
Baseline internal bleed	No	Reference
	Yes	0.86 (0.80, 0.93)
Hypertension absorbing state	No	Reference
	Yes	0.98 (0.95, 1.01)
Congestive heart failure absorbing state	No	Reference
	Yes	1.19 (1.16, 1.22)
Diabetes mellitus absorbing state	No	Reference
	Yes	1.01 (0.99, 1.04)
Hospitalization for ischemic stroke in the prior month	No	Reference
	Yes	0.87 (0.68, 1.13)
Hospitalization for intracranial hemorrhage in the prior month	No	Reference
	Yes	0.55 (0.26, 1.16)

Odds ratios for the censoring denominator weight-generating model for one replicate

Potential Predictor of AC use		**Adjusted Odds Ratio (95% Confidence Interval)**
Intercept		0.07 (0.07, 0.08)
Month relative to LTC entry	1	Reference
	2	1.88 (1.77, 1.99)
	3-8	1.32 (1.26, 1.39)
Calendar year	2007-2012	Reference
	2013	2.59 (2.48, 2.69)
Sex	Female	Reference
	Male	1.31 (1.26, 1.36)
Age	66-74	Reference
	75-84	0.92 (0.87, 0.97)
	≥85	0.99 (0.94, 1.04)
Baseline stroke or transient ischemic attack	No	Reference
	Yes	0.96 (0.92, 1.00)
Baseline internal bleed	No	Reference
	Yes	1.04 (0.93, 1.15)
Hypertension absorbing state	No	Reference
	Yes	1.08 (1.03, 1.13)
Congestive heart failure absorbing state	No	Reference
	Yes	1.35 (1.30, 1.39)
Diabetes mellitus absorbing state	No	Reference
	Yes	1.09 (1.06, 1.13)
Hospitalization for ischemic stroke in the prior month	No	Reference
	Yes	1.77 (1.29, 2.42)
Hospitalization for intracranial hemorrhage in the prior month	No	Reference
	Yes	1.64 (0.73, 3.66)

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