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ASSOCIATION BETWEEN WARFARIN ADHERENCE TRAJECTORIES, HOSPITALIZATION RISK, AND HEALTHCARE UTILIZATION AMONG MEDICARE PATIENTS WITH ATRIAL FIBRILLATION: A GROUP-BASED TRAJECTORY MODELLING APPROACH

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

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Dedication

To the memory of my dad, who always had faith in me, to my beloved mom, who always encourage me to work harder, to my dearest husband; I couldn't have done this without your great support, and to my beautiful children, who always cheer me up.

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Introduction: Warfarin is the most commonly prescribed drug for stroke prevention among Atrial Fibrillation (AF) patients, especially in older adult populations, but medication nonadherence reduces its effectiveness in clinical practice. Group Based Trajectory Models (GBTM) have been used to identify distinct patterns of adherence behavior related to various medications and understand the patient characteristics associated with each trajectory. The objectives of the study were: 1) Describe trajectories of warfarin adherence among Medicare AF patients, 2) Assess impact of adherence trajectories on AF-related hospitalization, 3) Estimate the AF-related direct costs for each adherence trajectory group.

Methods: We identified elderly AF patients initiating warfarin treatment during 2008-2010 using data from a random sample of Medicare beneficiaries. The study's first aim is to classify patients into different trajectory groups based on their monthly adherence patterns using a Group-Based Trajectory Model (GBTM). A multinomial regression model was used to assess associations between baseline characteristics and adherence trajectories. The second aim is to evaluate the association between adherence trajectories and time to first hospitalization related to stroke or bleeding event. Hospitalization events due to bleeding or stroke were identified using corresponding ICD-9 codes, and a Cox proportional hazard model was performed. The third aim of the study is to calculate AF-related direct medical costs associated with each trajectory group. SASv9.4 was used for analysis.

Results: Among 3,246 beneficiaries who met inclusion criteria, six adherence trajectories were identified: 1) rapid-decline non-adherence group (11.5%), 2) moderate non-adherence group (24%), 3) rapid-decline then increasing adherence group (6.8%), 4) moderate-decline non-adherence group (8.2%), 5) slow-decline non-adherence group (24.3%), and 6) perfect adherence group (25.3%). Even though no statistical significances were found in the hazard of hospitalization among the adherence groups, there were higher odds of hospitalization among the lower adherence groups compared to perfect adherence group. Outpatient and monitoring costs were significantly higher in the lower adherence trajectories compared to perfect adherence group.

Conclusion: The GBTM is considered an innovative methodological approach that can be applied to longitudinal medication adherence data and account for the dynamic nature of adherence behavior in a better way than traditional adherence measures.

Chapter 1: Introduction

1.1 Introduction

Medication non-adherence is a major obstacle to improving healthcare outcomes. Poor medication adherence is associated with numerous adverse health outcomes.[1] Older adults, patients with critical conditions, and those treated with medications with narrow therapeutic windows are at increased risk for non-adherence related adverse events.[2]

Atrial Fibrillation:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice.[3] The condition affects more than 3 million Americans, and this figure is projected to increase to 8 million by 2050.[4] Approximately 70% of AF patients are between the age of 65 and 85 years.[5] AF is a major risk factor for ischemic stroke (IS). Patients with AF are five times more likely to develop IS than those without AF.[3] Risk of IS increases in AF patients with advancing age and the presence of other cardiovascular diseases, including hypertension, heart failure, diabetes mellitus, and history of previous stroke or transient ischemic attack (TIA).[4]

Stroke contributes to substantial morbidity and mortality among the AF population. AF patients who experience a stroke have increased mortality rates relative to those who do not.[6] Moreover, strokes may cause an array of disabilities, such as vision impairment, inability to walk without assistance, cognitive deficits, and depression. Stroke complications are associated with a notable socioeconomic burden on both individuals and the healthcare system. In the

United States, the mean lifetime cost per patient with an IS has been estimated at $140,048.[6] Inpatient care is considered to be the main driver of stroke-related costs, accounting for 70% of costs in the first year after a stroke.[6] After the first year of survival, costs of lost productivity and rehabilitation can be significant. According to the U.S. Centers for Disease Control and Prevention (CDC), the stroke costs United States 34.6 billion dollars annually.[7]

Warfarin:

Warfarin, a vitamin K antagonist, has long been the most common treatment for preventing stroke in AF patients. Several clinical trials have shown warfarin to be effective in decreasing stroke by up to 64% compared to placebo, and it has been associated with reductions in mortality among AF patients.[8] Effective treatment with warfarin requires patients to be maintained within a narrow International Normalized Ratio (INR) range between 2 to 3. Maintenance of that range requires regular INR monitoring and potential dosing changes due to the pharmacokinetic properties of warfarin.[9] Specifically, a variety of drug-drug and drug-food interactions can significantly impact the pharmacokinetics of warfarin and patients' INR values. In 1996, Rosendaal reported that extensive anticoagulation monitoring in specialized clinics improves treatment effectiveness and reduces complications associated with warfarin therapy.[10]

Direct oral anticoagulants (DOAC):

In recent years, direct oral anticoagulants (DOACs) have been introduced into the US market with the potential to overcome limitations of warfarin treatment. Dabigatran was the first direct oral anticoagulation agent approved by the FDA in 2010, followed by rivaroxaban in 2011, apixaban in 2013, and edoxaban in 2015. The DOACs, which are administered with a fixed dose either once or twice daily, do not require the regular monitoring needed during warfarin

treatment. In several clinical trials, these agents have demonstrated similar or superior efficacy and safety compared to warfarin for the treatment of stroke prevention in AF patients.[9-12]

Use of Warfarin vs. DOAC:

Despite the favorable data on DOAC safety and efficacy, a number of barriers have limited widespread utilization of the DOACs. While warfarin has a long history of clinical use, little evidence currently exists surrounding the long-term safety and effectiveness of the DOACs. Moreover, the four major clinical trials that assessed safety and efficacy of the DOACs compared to warfarin took place under controlled conditions, and vulnerable populations like elderly (aged ≥75 years) patients and those with severe renal or hepatic impairment were underrepresented. Thus, these trials cannot determine conclusively that the overall safety and efficacy of DOACs is the same in these higher risk populations as in their lower risk counterparts.[13] Given the lack of real world evidence on effectiveness and safety, some clinicians still hesitate to prescribe DOACs in higher risk patient popluations.[14] Additionally, unlike warfarin, there is no antidote to reverse the anticoagulant effect of these agents in case of life threating bleeding,. Although a new antidote agent for DOACs has been approved recently, still there is a doubt about its effectiveness in reversing major bleeding events associated with DOACs. Furthermore, the acquisition costs of the DOACs, which are still under patent protection, are considerably higher than the cost of generically-available warfarin. Although multiple studies have found that the DOACs can be cost-effective compared to warfarin in AF patients, many of these studies reported that their results apply only when INR control with warfarin treatment was poor.[9,15] In other words, warfarin might be more economical in patients with excellent INR control, as is commonly the case in patients treated at anticoagulant clinics.[10,12]

For these reasons, the majority of AF patients in the US are still treated with warfarin.[13] According to a recent study by Desai et al., warfarin is the most commonly prescribed drug for AF patients with $CHADS_2$ scores ≥ 2.[16] It is likely that warfarin will remain the most commonly used anticoagulant in AF patients, especially among older adults, and switching to DOACs may not be necessary for patients who are well maintained on warfarin.[13]

Medication Non-adherence:

Poor adherence to warfarin therapy is associated with increased risks of hospitalization and mortality.[2] These risks are especially high among the elderly population due to age-related declines in mental and physical health.[16] In the US, almost one-third of annual emergency hospitalizations for adverse drug events have been attributed to warfarin, a finding that is even more pronounced in older adult patients.[17] These adverse drug events may be related to the difficulty of warfarin dosing, the need for regular monitoring, and the many drug-drug and drug-food interactions that impact the drug's pharmacodynamics. Proper adherence is essential to maintaining a therapeutic INR, as even one missed dose can significantly impact the INR.

Despite the documented importance of warfarin adherence, nonadherence to the medication is widespread. Kimmel et al. used the medication event monitoring system (MEMS) to assess adherence to warfarin treatment and reported that up to 40% of patients were poorly adherent.[18] Another study by Davis et al., using the Morisky Medication Adherence Scale (MMAS), found that adequate adherence was only reported in 50% of the participants, and it was significantly associated with anticoagulation control.[19] Based on the literature, patients with high adherence to warfarin (PDC>80%) are associated with reduction in costs and resources utilization compared to low adherent patients. It is estimated that well adherent patients are 28% less likely to be hospitalized compared to poorly adherent patients.[20]

The findings from the literature suggest that increased adherence to warfarin treatment in the management of AF results in improved health outcomes.[21] Despite these findings and an array of interventions to improve warfarin adherence among AF patients, nonadherence continues to be a significant problem in this population. Most of the existing interventions that target poor adherence to warfarin are based on crude measures of medication adherence that consider patients to have the same adherence patterns over time. Most adherence measures rely on defined cut point, leading them to collapse a broad spectrum of adherence behavior patterns into two groups, either adherent or non-adherent. Such a dichotomization can mask important differences among patients' adherence behavior, in turn having a great impact on the effectiveness of the intervention. For example, the optimal intervention for a patient that is highly adherent for short time and then discontinues the drug may differ from that of a patient who is consistently non-adherent throughout their treatment period. In order to better tailor interventions to improve warfarin adherence, there is a need for methods that can distinguish between different patterns of warfarin adherence, as medication adherence is a dynamic behavior that can change over time. In other words, there is a need for methods that not only measure medication adherence but are also able to accurately predict the degree and timing of a given patient's non-adherence. Moreover, the ability to classify patients into groups according to their adherence behavior over time may allow clinicians to develop targeted adherence interventions for different groups.

According to the World Health Organization (WHO), medication adherence is defined as, "the extent to which a person's behavior – taking medications, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider."[1] In administrative claims data, medication adherence is most commonly measured using the

proportion of days covered (PDC) or medication possession ratio (MPR).[21-23] Both measures are well-established and validated. However, in practice, these measures are frequently used to dichotomously classify patients as adherent or not relative to predetermined threshold (e.g., PDC > 80%). The use of the conventional adherence measures (e.g., PDC) can mask underlying differences in medication refill behavior. For example, a patient with a PDC of 0.6 may have (1) been highly adherent during the early follow-up but become increasingly less adherent as time went on, (2) been poorly adherent during the early follow-up but become increasingly more adherent over time, or (3) been intermittently adherent throughout follow-up period. All three patients are considered non-adherent, but each may require a different type of intervention at different times to improve their adherence behavior. Studies using these measures generally assume that patients with similar scores maintained similar adherence patterns over the study period and subsequently analyze those patients as a homogenous behavioral group. However, underlying differences in the refill patterns and patients' adherence behavior may play a crucial role in the effectiveness of their medications and subsequently health outcomes and healthcare utilization and associated costs.

Group Based Trajectory Model (GBTM):

Group-based trajectory models (GBTMs) are a new methodological approach that can help to summarize long-term medication adherence by taking into account the dynamics of medication adherence and changes in adherence behavior over time.[21] GBTM is a latent class analysis that provides an alternative method to capture adherence behavior over time.[21] Unlike PDC and other conventional adherence measures, GBTM is able to distinguish between different patterns of medication non-adherence. The model provides a framework through which to identify groups of individuals, termed trajectory groups, with similar behavioral patterns over a

period of time.[24,25] The GBTM is considered a person-centered approach, like cluster analysis, that take into account the relationship among individuals.[26] In GBTM, patients are grouped into different trajectories based on their prescription refill patterns over time and summarized with an average adherence in an easily interpretable graphical depiction. This approach allows patients to be classified into different groups according to their adherence behavior over time, and the characteristics of patients in each group can be identified and compared. By identifying key characteristics associated with poor adherence trajectories, this can facilitate designing targeted interventions more accurately.[27] Moreover, GBTMs enable measurement of both the intensity and the timing of medication adherence, thus capturing the dynamic nature of non-adherence behavior in a way that conventional measures of adherence do not.

The GBTM has been widely used in sociological and medical research for understanding disease progression and behavioral development patterns in children and adolescents.[24,25] In recent years, GBTMs have been applied to the study of medication adherence patterns and the associations between adherence and health outcomes.[21-23] Specifically, Franklin et al. used the trajectory model to examine statin adherence, and Lo-Ciganic et al.[22,23] applied GBTM to classify diabetic medication adherence patterns and their association with clinical outcomes. In both studies, the GBTM showed better predicative performance for clinical outcomes associated with each trajectory group compared to conventional methods (e.g., PDC). Moreover, this method has been shown to capture long-term medication adherence more accurately than conventional measures.[21]

The application of GBTMs to the classification of medication adherence patterns offers the potential to more comprehensively understand dynamic of adherence behavior and its associated consequences. Furthermore, the use of GBTMs in clinical practice provides a method

by which healthcare providers and payers can identify groups of patients, based on their refill behavior, and tailored interventions to improve their adherence. By understanding predictive characteristics of different adherence behaviors, this can better aid in customizing intervention programs to the right patient at the right time. Tailored interventions can then be administered with the most appropriate timing to better allocate resources and ultimately improve patient outcomes and healthcare costs.

1.2 Rationale

Atrial fibrillation (AF) is a growing health concern with significant complications that affects large numbers of US patients, especially older adults.[28] Warfarin is the most commonly used drug for the prevention of stroke in AF patients in the US.[29] Nearly two-thirds of AF patients on Medicare have been prescribed warfarin.[30] Due to the narrow therapeutic window of warfarin and the severity of both treatment failure and overdosing, medication adherence is critically important for patients on this anticoagulant. It is well established in the literature that poor adherence to warfarin among AF patients is associated with poor health outcomes and increased healthcare costs.[31] However, medication nonadherence is a major barrier to effective warfarin treatment and remains a significant problem despite numerous interventions to improve adherence.

Given the prevalence and consequences of poor adherence to warfarin, there is a need to better understand different patterns of adherence behavior and to more accurately identify patients likely to be poorly adherent for tailored adherence interventions. No study yet has assessed adherence to warfarin in AF patients by classifying patients according to their adherence patterns over time. This study aims to classify patients according to their different patterns of warfarin adherence over time and to identify predictors of adherence behavior. Moreover, this study investigated the impact of each trajectory adherence pattern on subsequent clinical outcomes and associated costs. Hence, this study is designed to enable healthcare providers and payers to better identify patients with high risk of warfarin nonadherence and its associated healthcare costs. Providers and payers will then be better equipped to implement interventions tailored to a patient's specific pattern of adherence. Furthermore, the results of this

study can be used to assess the most effective interventions to improve warfarin adherence for each trajectory group.

1.3 Specific Aims

The study aims to identify and describe warfarin adherence trajectory groups among AF patients and to identify predictors associated with membership in each trajectory group. It also aims to assess the impact of membership in each adherence trajectory group on clinical outcomes and associated healthcare costs. The specific aims of the study are:

Specific Aim 1:

A. Identify and describe the trajectory groups of warfarin adherence in patients with AF in Medicare population;
B. Estimate the likelihood of patients belonging to each adherence trajectory;
C. Identify patients' characteristics and factors associated with each adherence trajectory.

Specific Aim 2:

A. Estimate the rates of hospitalizations related to a stroke or bleeding event (clinical outcomes) associated with each adherence trajectory;
B. Evaluate the association between warfarin adherence trajectory group membership and the likelihood of hospitalization due to a stroke or bleeding event.

Specific Aim 3:

A. Estimate the AF-related costs for each adherence trajectory group.

Chapter 2: Literature Review

2.1 Summary of literature on the use of GBTM in medication adherence research

In order to describe the adherence trajectories of warfarin by using the Group Based Trajectory Model (GBTM) and to assess the impact of adherence trajectory groups on clinical outcomes and associated healthcare costs, we need to evaluate the literature relating to this topic. This was done in two steps. First, we looked at studies that use GBTM in describing medication adherence. Second, we evaluated studies that compared GBTM to PDC as an adherence measure. A literature review conducted on October 2017 using PubMed/MEDLINE and CINAHL used both Mesh terms and key words in appropriate combinations. The search terms were combinations of: (group based trajectory modeling OR group based trajectory models OR group based trajectory OR trajectory) AND (medication adherence OR "Medication Adherence"[Mesh]), (group based trajectory modeling OR group based trajectory models OR group based trajectory OR trajectory) AND (fill prescription), (group based trajectory modeling OR group based trajectory models OR group based trajectory OR trajectory) AND (medication compliance), (group based trajectory modeling OR group based trajectory models OR group based trajectory OR trajectory) AND (medication persistence). (Table 1)

Titles and abstracts from search result articles were screened using the following inclusion and exclusion criteria:

Inclusion criteria:

1. Assess medication adherence
2. Apply Group Based Trajectory Model (GBTM)
3. Published in English

Exclusion criteria:

1. Apply GBTM to describe trajectories of disease progression
2. Review paper, report, or proposal.

The search on PubMed and CINAHL revealed a total of 208 articles. After eliminating duplicates and applying inclusion and exclusion criteria, 23 research articles remained. Out of these 23 articles, 19 articles were chosen to be discussed as they assessed medication adherence specifically by performing GBTM. The four excluded studies used GBTM to describe patterns of disease progression or program intervention (Figure 1). The references of the selected studies were reviewed to identify additional studies that meet inclusion criteria. One additional study from the references was added to the literature review.

The total search resulted in 20 study articles that reported on the use of GBTM in describing medication adherence.

Table 1: Search term combinations used and resulting number of articles

Search term combinations	**Total number of articles**	**Articles Meeting Inclusion Criteria**
((group based trajectory modeling) OR (group based trajectory models) OR (group based trajectory) OR (trajectory)) AND (("Medication Adherence"[Mesh]) OR medication adherence)	72	22
((group based trajectory modeling) OR (group based trajectory models) OR (group based trajectory) OR (trajectory)) AND fill prescription	9	3
((group based trajectory modeling) OR (group based trajectory models) OR (group based trajectory) OR (trajectory)) AND medication compliance	69	20
((group based trajectory modeling) OR (group based trajectory models) OR (group based trajectory) OR (trajectory)) AND medication persistence	58	21

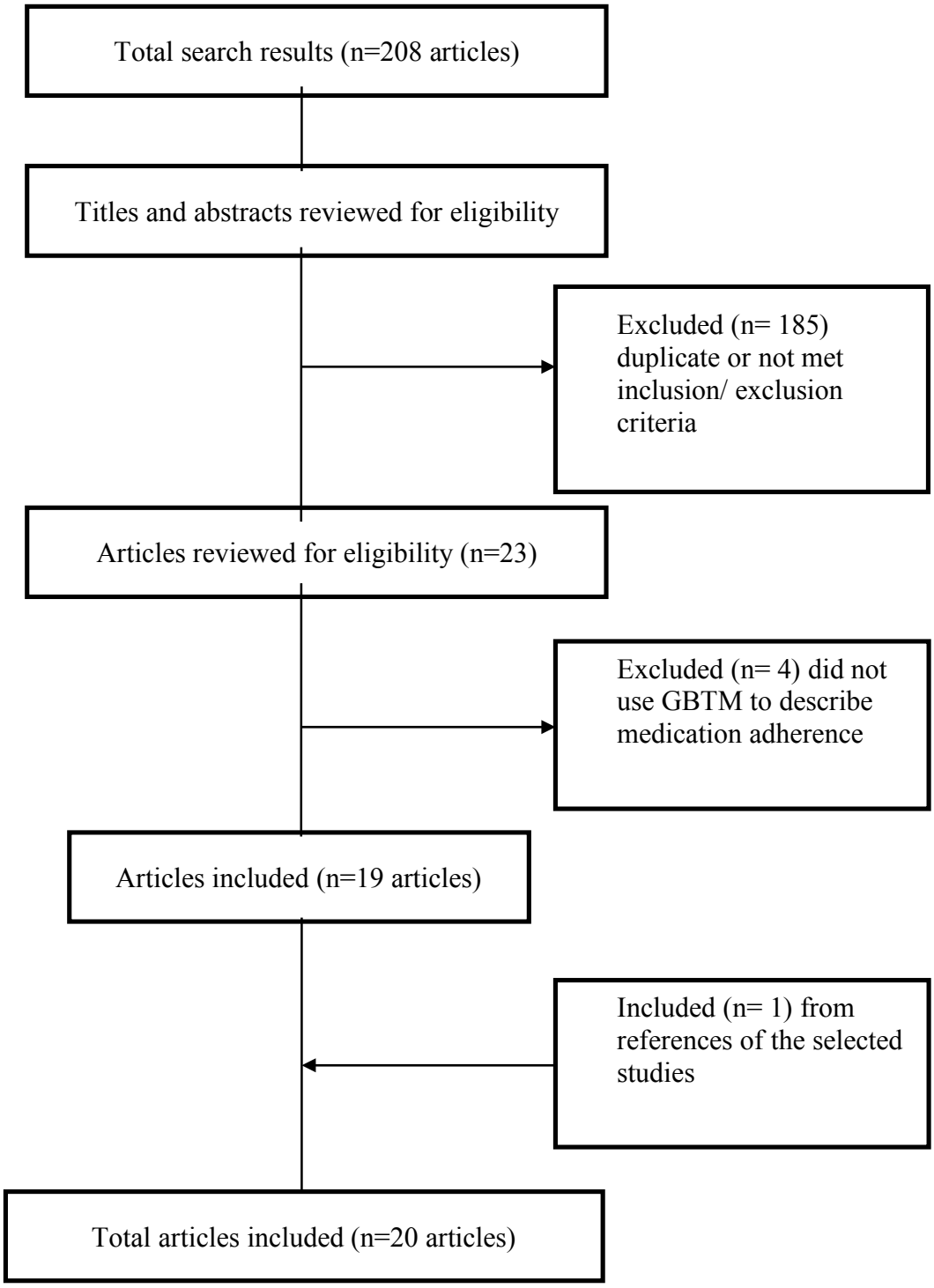

Figure 1: Selection process flow chart

Overall the search revealed a total of 20 relevant studies that applied GBTM to describe medication adherence patterns among different disease conditions and drug classes. All the identified papers were recently published (2010-2017). Six studies were conducted outside the United States (one in Taiwan, and five in Europe).[32-37] Study populations vary throughout the literature, as some studies examined only pediatrics patients,[38-40] others included all adult patients ≥ 18 years old, and some studies assessed adherence specifically for the elderly population. The selected studies assess medication adherence in different disease conditions, however, the majority of them focused on populations with cardiovascular diseases.[22,23,32,33,35,37,41-44] (Table 2)

Important criteria in comparing studies

There are several important criteria to consider when comparing between different studies that applied GBTM. These are the time period of the study, the number of trajectory groups resulting from the analysis, the types of trajectory groups identified, and the drug classes studied.

Time period of the study. First is the time of the outcome's measuring period, as it can influence the shape of the group trajectories. The time period to measure medication adherence varied across studies. Some captured adherence for a short period only (e.g., four months) while others extended over longer periods of time (e.g., six years).

Number of trajectory groups. Another important criterion to consider when comparing between the different trajectory models is the number of groups that resulted from the GBTM. The number of trajectory groups describes the level of diversity in the outcome's patterns (e.g. medication adherence patterns). As the number of groups increases, the model can better explain the heterogeneity in the outcome trajectories among the study population. On the other hand, a large number of groups can be difficult to interpret, so there is always a tradeoff between the

accuracy of capturing the underlying reality and the ease of interpreting the analysis. Throughout the literature, the number of trajectory groups identified varied between the studies. Overall, the optimum number of groups identified in most of the studies was four to six adherence groups. However, a study by Lo-Ciganic et al., for hypoglycemic drugs was able to classify patients' adherence patterns using seven trajectory groups.[23] At the other extreme, Greenley et al., found only two adherence trajectories for patients on thiopurine for Inflammatory Bowel Disease (IBD).[40] The identification of only two adherence groups may have been due to a small sample size (n= 96) which limited the ability to add more groups because group sizes were too small (i.e. the proportion of patients in each group should not be less than 5% of total sample).

Types of trajectory groups. The third criterion to consider when comparing between GBTMs across the literature relates to the types of the identified trajectory groups. The most common trajectory groups identified in the literature were: "perfect adherence", "non-adherence", and "slow-decline adherence". The perfect adherent group was described as a steady line plotted on a graph over time, where the patients belonging to this group have a persistently good adherence level to their medication over the study period. The average PDC value for the patients in this group is usually >90 %. Consistently throughout the literature, the highest proportion of patients falls in the "perfect adherence" trajectory. On the other hand, the "non-adherent" group was described in most of the studies as constant low or non-adherence over the study period, with less than two prescriptions filled, and can be described in a graph as a low steady line. Some of the studies reported that it was hard to distinguish whether the patients who belong to this group were truly non-adherent or just discontinued their medication and switched to another class.[23] The final commonly identified group was the trajectory in which patients

started with good adherence and became slowly non-adherent over time. The average PDC for this group was 50-60%.

Studies differed when describing the trajectory groups between perfect adherence and non-adherence groups. Few studies identified trajectory groups in which patients experienced a very rapid decline in their adherence pattern.[34,38,41,45-47] In these studies, they included new patients who filled at least one prescription of medication. So, a trajectory of very rapid decline can be related to the improvement in the disease condition to the point that patients do not require treatment any more, or that patients were on a one-time dose and then discontinue treatment. This is can be In contrast, a study by MacEwan identified trajectory where the adherence was good at first and then declined after a period of time (e.g. after 6 months or 9 months).[48] These differences in the identified trajectory groups among the studies can be due to several factors related to study population, disease characteristics, sample size, and the assigned duration for assessing medication adherence (study period). All of these factors can play a role in describing adherence trajectory patterns.

Drug classes studied. Most GBTM studies on patterns of medication adherence limited their analysis to a single therapeutic drug class over time which limited the ability to identify differences across medications in a single population. An exception was a study by Librero et al. that examined and compared adherence trajectories for four different drug classes: beta-blockers, ACEIs/ARBs, antiplatelet agents, and statins for discharged patients with congestive heart failure (CHF).[33] The GBTM showed three different patterns of trajectory for this population that varied depending on the drug class. There were five trajectories for the antiplatelet cohort, four trajectories for the beta-blocker and ACEI/ARB cohort, and three trajectories for patients on statins indicating that adherence trajectories were not homogeneous for CHF discharge patients

prescribed different medications. The authors concluded that the GBTM approach better captures the dynamic nature of the adherence behavior over time than other traditional measures (e.g., PDC).

Patient Characteristics Associated with Trajectories

The literature suggests that a deeper understanding of patients' characteristics associated with each trajectory group can help in identifying patients in poor adherent groups and in implementing more effective interventions to improve their adherence. Adherence groups may vary upon demographic characteristics and benefit differently from alternative intervention strategies. In addition, adherence trajectories may diverge based upon patients' characteristics.[33,48]

Different studies in the literature identified characteristics associated with poor and intermediate adherence trajectories which can serve as a signal for the clinicians to target those patients with a suitable intervention at the proper time. For example, Juarez et al., found that the white, Asian, and Pacific Islanders patients with CHF were more likely to have low adherence in the first year after discharge compared to black patients.[42] Such findings can aid in the targeting of patients with the right intervention at the early phase after discharge to ensure better adherence behavior. Thus, a useful application of the GBTM rests on its ability to identify patients with a high probability of having a poor adherence trajectory and thereby targeting them with proper intervention.[33]

Some studies examined the association between patients' demographic and clinical characteristics with different adherence trajectories. Age, gender, race, and educational level have been found to be associated significantly with adherence trajectories.[23,34-36,42,43,49] It has been reported that the patients in the lower adherent groups tend to be younger, non-white, males

with low educational level. Higher adherent trajectories are more common in older, white populations with higher educational level (bachelor's degree and above). Other studies have not found an association between these demographics factors and adherence trajectories.[39] This may be due to the different characteristics of the study design including: disease population, study's sample size, and study period.

Other population characteristics have been related to adherence trajectories. Low socioeconomic status is associated with lower adherent trajectories.[32,34,39,48] Higher copayment share is also associated with lower adherent trajectory groups.[33] The presence of comorbidities has been found to be a strong predictor of low adherence groups.[48,50] Many of these characteristics are also variables described in theoretical frameworks related to medication adherence, such as the Andersen Behavioral Model (ABM).[51]

Trajectories and Healthcare Utilization

Adherence trajectories have been associated with healthcare utilization. Six studies examined specifically at the impact of adherence trajectories on healthcare events (e.g., hospitalization events, ED visit, disease-related adverse events, or death).[22,23,38,48,52,53] They found that better adherent trajectories were associated with fewer hospitalization events and a lower mortality rate. Mac Ewan et al., used GBTM to stratify schizophrenic patients treated with oral Atypical Antipsychotics into groups based on their adherence behaviors.[48] They reported that patients in the perfect adherent group had fewer ED visits compared to low adherent groups. Lo-Ciganic et al., assessed the association between trajectories of hypoglycemic medication adherence and risk of ED visit and hospitalization.[23] They concluded that low and moderate adherent and non-adherent group membership was associated with higher risk of ED visits/ hospitalizations in contrast to perfect-adherent trajectory. A study by Winn et al., examined the

relationship between adherence trajectories of endocrine therapy and death in women with breast cancer.[53] They found that patients in rapidly and moderate decline adherence trajectories had significantly higher risk of death compared to perfect adherent trajectories. Furthermore, Franklin et al., studied the association between trajectories of statin adherence and cardiovascular events, and they concluded that lower adherent groups were associated with higher risk of cardiovascular events compared to perfect adherent trajectories.[22] A study by Modi et al., evaluated the relationship between adherence trajectories of antiepileptic drugs in a pediatric population with seizure outcomes, and they reported that patients with unstable adherence levels have a higher rate of seizures.[38] Similarly, a study by Gueorguieva et al., assessed the relationship between adherence trajectories of pharmacological treatment (naltrexone, acamprosate), behavioral interventions, and drinking outcomes and concluded that the perfect-adherent group experienced less drinking compared to non-adherent groups.[52]

Predictive Validity of GBTM

Several published studies in the literature have examined the predictive performance of GBTM compared to conventional measures (e.g. PDC). Six out of seven studies showed GBTM to be superior in capturing longitudinal adherence patterns than PDC.[22,23,32,44,50,53] A study by Hargrove et al., compared adherence trajectories identified by GBTM to conventional adherence measures (proportion days covered (PDC), medication possession ratio (MPR) and reported that a six group trajectory model better distinguished between adherent and non-adherent months than the PDC or PMC, especially for patients with inconsistent adherence patterns.[44] A study by Aarnio et al., examined the relationship between socioeconomic position (SEP) and statin adherence for men compared to women using GBTM and conventional measures (PDC<80%).[32] They found that GBTM provided a better description of adherence behavior and more

comprehensive details in differentiating between adherence groups. Winn et al., investigated the association between endocrine therapy adherence trajectories and mortality compared to the conventional PDC measure.[53] They found that both measures show significant association between adherence and mortality; however, the hazard of survival when using PDC was very small (hazard ratio (HR) 1.21) and did not distinguish between different adherence groups as seen when using GBTM. Lo Ciganic et al., examined the impact of adherence trajectories in predicting diabetes-related hospitalization and ED visits compared to conventional PDC measures.[23] They concluded that the adherence trajectories in the multi-variants model showed better prediction for the clinical outcomes compared to a dichotomous PDC measure. Similarly, Franklin et al., reported that the use of statin adherence trajectories predicts cardiovascular events better than the traditional PDC ≥ 80% threshold.[22] Finally, Li et al., compared biological treatment adherence patterns using GBTM and PDC in patients with psoriasis.[50] The GBTM identified four trajectory patterns. In order to compare the two measures, an equivalent number of groups were constructed from the same cohort of patients using the PDC measures in the following way: Group 4 (PDC≥ 75%), Group 3(50% <PDC <75%), Group 2 (25%< PDC< 50%), and Group 1 (PDC ≤25%). The authors reported that GBTM and PDCs were similar in categorizing patients in the extreme groups (perfect-adherent and non-adherent groups). However, for the patients in the intermediate groups, there was a difference in the longitudinal adherence patterns when using GBTM compared to PDC. The use of GBTM resulted in a better classification of adherence patterns compared to the traditional PDC measure.

Only one study has reported that GBTM might not accurately reflect adherence behavior.[37] In this study, the authors evaluated the predictive validity of GBTM in patients with hypertension. They identified four trajectories for hypertensive medication adherence for 905

patients. The predictive validity was measured by assessing relationships between trajectory groups and blood pressure (BP) measurements. They did not find association between adherence trajectories and BP measurements, although they offered several explanations for their results. First, the result could be related to the "white coat adherence effect", in which patients exhibit better adherence behavior in the day prior to the clinic visit. The theory posits that since patients already knew that they would undergo a BP measurement during their visit, they adhered to their medication before the visit. Second, blood pressure was only measured a single time, which might make it less reliable. Third, the small sample size restricted the generalizability of the study results.

Summary of Findings

Based on this literature review, there are important points to consider when applying GBTM. GBTM assumes that there are an infinite number of patterns that can model differences between the individuals in the real world.[54] Therefore, when starting to build a GBTM, there are an almost unlimited numbers of possible trajectory groups to describe the different adherence patterns seen with the real-world patients.[33]

Depending on the criteria used for fitting the final model, the number of trajectory groups is identified using the following methods: 1) model fit using Bayesian information criteria (BIC), where a lower value indicates better fit; 2) the proportion of patients in each group is not less than 5% of total sample; and 3) Nagin's criteria for model adequacy.[33] Then, after identifying the appropriate number of trajectory groups, the patients in the cohort are classified into these groups based on their membership probabilities (that is, group membership is determined by the highest likelihood of belonging to a certain trajectory group). Once classified, the GBTM assumes that patients in groups will have similar patterns of adherence over time.

The literature appears to show that trajectory group classification is most beneficial for patients who are somewhere between perfect adherence and non-adherence. GBTM is no better than PDC measures for these patients. The value of GBTM lies in understanding adherence patterns in intermediate groups (e.g., slowly declining and low adherence then rapid increase groups). PDC measures lump patients into single groups while GBTM identifies more adherence patterns. For instance, a study by Mardby et al., found PDC classified half of the study population as non-adherent.[34] In contrast, GBTM found one third of the study population non-adherent within the first few months after initiating the therapy because it differentiated non-adherence according to the time it occurred. The ability to more finely differentiate patient adherence over time is why the GBTM has the advantage over PDC measurement.

It is important to understand that the main goal of GBTM is to describe and summarize different patterns, and to simplify the complexity of the real-world situation in order to better understand differences between patients' behaviors.[54] Thus, the summarization of the real-world differences means that there must be some approximation for the simplicity of understanding and interpretations. The key point is that the individuals belonging to each trajectory group are not identical, rather similar in many aspects.

GBTM is an innovative approach that can be used to describe adherence patterns by taking into account the dynamics of medication adherence and changes in adherence behavior over time. GBTM can be clinically useful for healthcare providers and payers in tailoring adherence interventions to better allocate resources and enhance patients' outcomes and overall healthcare costs.

Table 2: Summary of identified studies

Authors	Objective	Population	Type of treatment	Length of study period	Country	Sample size	Trajectory group	Clinical outcomes	Conclusion
1. Dillon et al., 2017[37]	1.Characterize adherence to antihypertensive medication 2. Test predictive validity of GBTM against blood pressure measurement	Patients aged ≥ 65 years old	Antihypertensive	1-year	Republic of Ireland	905	1.Perfect adherence 2.High adherence 3.Moderate non-adherence	-	GBTM identified 3 trajectories. However, did not show predictive validity with BP measurement
2. Hargrove et al., 2017[44]	1.Use GBTM to identify antihypertensive adherence trajectories 2.Comapre adherence trajectories to traditional adherence measures 3. Identify patients characteristics associated with adherence trajectories	Medicare patients aged ≥ 65 years old	Antihypertensive	1-year	US	282,520	1.Perfect adherence 2. Rapid decline, then increase 3. Moderate decline, then increase 4. Moderate decline 5. Rapid decline 6. Very rapid decline	-	GBTM is an effective method to identify patterns of medication adherence compared to PDC
3.MacEwan et al., 2016[48]	1. Identify adherence trajectory for oral atypical antipsychotics (OAA) 2. Identify associated factors	Adult schizophrenia patients	Oral atypical antipsychotic	1-year	US	29,607	1. Perfect adherence 2. Decline after 3 months 3. Decline after 6 months 4. Decline after 9 months 5. Rapid decline, then increase after 6 months 6. Very rapid decline	Psychiatric inpatient admission and ED visit	-Adherence patterns identified by GBTM are more varied than research based on PDC -Lower adherence trajectories associated with higher ED visits
4.Aarnio et al.,2016[32]	1. Identify adherence trajectory of statin 2. Examine association between SEP and adherence trajectories	Patients aged 45 to 75 years	Statin	18-months	Finland	116,846	1. Perfect adherence 2. High adherence 3. Rapid decline, then increase 4. Moderate decline 5. Rapid decline 6. Very rapid decline	-	SEP is associated with low adherence groups. Overall, GBTM provide insight to dynamics of adherence behavior

Table 2: Continued

Authors	Objective	Population	Type of treatment	Length of the study period	Country	Sample size	Trajectory group	Clinical outcomes	Conclusion
5.Libero et al., 2016[33]	1. Identify adherence trajectory for ACEI, statin BB, and antiplatelet 2. Identify associated factors	Patients discharged with coronary heart disease (CHD)	ACEI, statin BB, and antiplatelet	9-months	Spain	7,462	1.Perfect adherence 2. Low adherence, then increase 3. Moderate decline, then increase 4. Moderate decline 5. Rapid decline	-	GBTM identified distinct adherence trajectories for difference preventive medication for CHD. It showed advantage over traditional measure
6.Mårdby et al., 2016[34]	1. Identify adherence trajectory of antidepressants 2. Identify associated factors	Patients aged 18–85 years	Citalopram	24-months	Sweden	54,248	1. Perfect adherence 2. Moderate decline 3. Rapid decline, then increase 4. Rapid decline 5. Very rapid decline	-	- GBTM identified 5 distinct patterns -low adherence trajectories associated with lower SEP
7. Lo-Ciganic et al., 2016[23]	1. Identify adherence trajectory of oral hypoglycemic 2. Identify associated factors 3. Examine association with clinical events	Patients aged 18–64 years with diabetes (DM)	Oral hypoglycemic medication	1-year	US	16,256	1. Perfect adherence 2. High adherence 3. Moderate decline 4. Moderate non-adherence 5. Rapid decline, then increase 6. Rapid decline 7. Very rapid decline	1. DM related ED visit/hospitalization 2. All cause ED visit/hospitalization	Lower adherence trajectories associated with higher ED/hospitalization events
8. Winn et al., 2016[53]	1. Identify adherence trajectory of ET 2. Identify associated factors 3. Examine association with mortality	Women with breast cancer	Endocrine therapy (ET)	1-year	US	9,492	1. Perfect adherence 2. Slow decline 3. Rapid decline, then increase 4. Moderate decline 5. Rapid decline	Mortality	Low adherence groups associated with higher mortality rate
9. Chen et al., 2016[35]	1. Identify adherence trajectory of hypoglycemic 2. Identify associated factors	Patients aged ≥ 18 years type 2 diabetes	Oral hypoglycemic medication	Six-years	Taiwan	12,123	1. Perfect adherence 2. Moderate adherence, then increase 3. Moderate decline 4. Low adherence, then increase	-	GBTM help in identifying heterogeneity of medication adherence

Table 2: Continued

Authors	Objective	Population	Type of treatment	Length of the study period	Country	Sample size	Trajectory group	Clinical outcomes	Conclusion
10. Franklin et al., 2015[41]	Identify adherence trajectory of statin	Patients aged ≥ 65 years old	Statin	1-year	US	77,703	1.Perfect adherence 2. Moderate adherence 3. Rapid decline, then increase 4. Moderate decline, then increase 5. Rapid decline 6. Very rapid decline	-	Initial adherence behavior associated with better future adherence
11.Newman-casey et al., 2015[49]	1. Identify adherence trajectory of glaucoma medication 2. Identify associated factors	Patients ≥40 years old treated for glaucoma	Glaucoma medication	4-years	US	1,234	1. Perfect adherence 2. Moderate non-adherence 3. Moderate decline 4. Low adherence, then increase 5. Rapid decline	-	Adherence patterns for first year, had great impact on future adherence behavior
12.Juarez et al., 2015[42]	1. Identify adherence trajectory of ACEI 2. Identify associated factors	Patients with Congestive Heart failure (CHF)	ACEI	1-year	US	10,986	1.Perfect adherence 2. Moderate decline 3. Low adherence, then increase 4. Rapid decline	-	Patients factors associated with low adherence trajectories can be used to target interventions
13. Franklin et al., 2015[22]	1. Identify adherence trajectory of statin 2. Examine association with clinical events	Patients in the UnitedHealth Optum Research Datamart, aged 35-64 years	Statin	1-year	US	519,842	1.Perfect adherence 2. Rapid decline then increase 3. Moderate decline 4. Moderate decline, then increase 5. Rapid decline 6. Very rapid decline	Hospitalization for an acute coronary event, revascularization, cerebrovascular event, or heart failure	Adherence trajectories predicts future clinical outcomes better than PDC

Table 2: Continued

Authors	Objective	Population	Type of medication	Length of the study period	Country	Sample size	Trajectory group	Clinical outcomes	Conclusion
14. Li et al., 2014[50]	1. compares GBTM and PDC 2. identify the clinical and demographic factors associated with adherence groups	Patients >18 years old with Psoriasis	Treated with at least one biologic: etanercept, adalimumab, ustekinumab, and infliximab	1-year	US	3,249	1.Perfect adherence 2.Moderate non-adherence 3.Moderate decline 4.Rapid decline	-	GBTM is better in capturing dynamic of adherence behavior than PDC
15. Modi AC et al., 2014[38]	1.Identify adherence trajectory of antiepileptic drugs 2.Examine association with seizure outcomes	Children diagnosed with epilepsy	Antiepileptic drugs	2-years	US	109	1. Perfect adherence 2. Slow decline 3. Rapid decline, then increase 4. Very rapid decline	Seizure outcomes	Low adherence trajectory associated with higher seizures
16. Greenley et al., 2014[40]	1. Identify adherence trajectory of thiopurine 2. Identify associated factors	Adolescents with Inflammatory Bowel Disease (IBD)	Thiopurine	6-months	US	96	1. Perfect adherence 2. Moderate non-adherence	-	Nearly 60% of participants are perfectly adherent
17.Franklin et al., 2013[43]	1. Identify adherence trajectory of statin 2. Identify associated factors	Patients initiating statin in CVS Caremark	Statin	15-months	US	264,789	1. Perfect adherence 2. Rapid decline then increase 3. Moderate decline 4. Moderate non-adherence 5. Rapid decline 6. Very rapid decline	-	GBTM summarized adherence patterns better than traditional measures

Table 2: Continued

Authors	Objective	Population	Type of treatment	Length of the study period	Country	Sample size	Trajectory group	Clinical outcomes	Conclusion
18.Gueorguieva et al., 2013[52]	1. Identify adherence trajectory of medication adherence and participation in Combined Behavioral Intervention 2.Estimate effects of adherence trajectories on drinking outcomes	Abstinent alcohol dependent patients enrolled in COMBINE study	Naltrexone, Acamprosate	4-months	US	1,174	1. Perfect adherence 2. Moderate non-adherence 3. Rapid decline	Percent days abstinent (PDA) and percent heavy drinking days (PHDD)	Lower adherence trajectories associated with worse drinking outcomes
19. Modi AC et al., 2011[39]	1. Identify adherence trajectory of antiepileptic drugs 2. Identify associated factors	Children diagnosed with epilepsy	Antiepileptic drugs	6-months	US	124 patients	1. Perfect adherence 2. slow decline 3. Moderate non-adherence 4. Moderate decline 5. Rapid decline	-	GBTM identified 5 patterns for antiepileptic medication adherence, and were significantly associated with SEP
20. Glass et al., 2010[36]	1. Identify adherence trajectory of combination antiretroviral therapy (cART) 2.Identify associated factors	HIV adult patients	Combination antiretroviral therapy (cART)	6-years	Switzerland	6,709 patients	1. Moderate non-adherence 2. Moderate decline 3 Low adherence, then increase 4. Low adherence	-	Substance and alcohol consumption, psychiatric treatment, and loss of social support were significantly associated with lower adherence trajectories

2.2 Gaps in the literature

This literature review found that GBTM is considered a better approach to capture longitudinal patterns of medication adherence compared to conventional measures. Moreover, the literature indicates that GBTM can provide more details on characteristics of patients who are likely to be non-adherent. Based on published results, the GBTM approach can better predict clinical outcomes compared to conventional measures.

No study has yet applied GBTM to capture long-term adherence trajectories of warfarin in AF patients. Moreover, no published study has used GBTM to describe key characteristics of different patterns of warfarin adherence. This study is the first to describe warfarin adherence patterns using GBTM and to assess relationships between adherence trajectories, hospitalization, and healthcare-related costs. The results of this study can help in identifying AF patients who are more likely to be non-adherent to warfarin therapy and to have higher healthcare utilization, allowing healthcare professionals to target them with suitable interventions.

2.3 Conceptual framework

In this study, the Andersen Behavioral Model (ABM) was used to evaluate the relationship between medication adherence and health outcomes. This model is useful in identifying factors related to warfarin adherence and explaining the association between adherence and health outcomes. The model was first developed to better predict utilization of health services and behaviors and has since been adapted to better understand medication adherence.[51,55,56] The ABM classifies the predictors of health behavior into 3 main components: predisposing factors, enabling factors, and need factors. The predisposing factors are those factors that explain an individual's tendency toward certain behavior and include demographic, social structure, and health belief variables. Enabling factors are the individual resources that promote or inhibit certain behaviors, including personal and community factors. Need factors relate to an individual's assessment of their need to adopt a health behavior and include perceived factors (e.g. perception of illness) and evaluated factors (e.g. illness severity). In the ABM, these three components affect health behavior which, in turn, impacts health outcomes. Moreover, in this model, the health outcomes also have an impact on the predisposing, enabling, and need factors as well as overall health behavior.

In this study, the ABM has been modified to fit medication adherence in older populations based on the published literature (Appendix A).[51,55] The predisposing factors in the adherence-specific ABM model include demographic characteristics (age, gender, and race), in addition to a social factor, educational level. Furthermore, two additional factors have been added to the original model: treatment characteristics (dosing, regimen complexity, INR monitoring) and disease characteristics (cognitive impairment and depression). These two factors were added as they have been found to significantly impact medication adherence behavior in older adults.[51,57]

The enabling factors in this model include personal-level factors, namely, insurance status and income, as well as a community-level factor, specifically, social support. The need factors are comorbidity, illness severity, and AF-specific symptoms. Additionally, anticoagulant clinic participation has been added to the original model given its importance in explaining warfarin adherence behavior. Each of these factors has previously been identified as a significant predictor for warfarin adherence in older adults.[57]

Chapter 3: Method

This chapter explains the methodology used to address specific aims 1, 2, and 3. It describes data sources, study design, study population, variables, outcomes measures, and statistical analyses.

Approvals

The proposal for this study was approved by the Virginia Commonwealth University institutional review board (IRB) under expedited review. In addition, the study was also approved by the Centers for Medicare and Medicaid Services (CMS).

Data Source:

The data employed for this study was obtained from the CMS. The study used 2008-2010 Chronic Condition Data Warehouse (CCW) Medicare files, which was provided via the Research Data Assistance Center (ResDAC). Medicare is a federal insurance program that is offered for people aged 65 years or older, end stage renal disease patients, and patients with disabilities.

The population of interest for this study was AF patients treated with warfarin. The majority of AF patients in the database are ≥65 years of age. According to the CCW sample size estimator, five percent of all the Medicare beneficiaries were diagnosed with AF, and almost two third of AF patients were being treated with warfarin.[58] Medicare data were used in this study as this resource is considered a good source for information on the elderly population. Moreover, claims data are known to be associated with lower recall bias and self-reporting bias compared to survey data.

In this study, a 5% random sample of all Medicare beneficiaries in 2008 to 2010 was used to provide information on health services and associated billings issued under Medicare Part A (inpatient), Medicare Part B (physician visits, outpatient care, ED visits) and Medicare Part D (pharmacy drug claims). A number of different Medicare files were employed to address the objectives of this study. The beneficiaries' information linked across files using a unique coded patient identifier to prevent patient identification (BENE_ID). The Master Beneficiary Summary file (MBSF) was used to obtain patients' demographic and enrollment information. The MBSF Chronic Condition and Other Chronic Condition files were used to identify different AF patients and different comorbid conditions. The beneficiary was flagged with a specific condition in the Chronic Condition and Other Chronic Condition files based on the existence of one inpatient or at least two outpatient claims. Files of Part A contain all claims related to hospital services and inpatient services and was used to identified all hospitalization events related to AF and to calculate associated costs. Files from Medicare Part B contain all hospital outpatient and anticoagulant clinic claims. Medicare Part D events file (PDE) and drug characteristics file contain information regarding prescription drug claims, including national drug code (NDC), date of prescription refill, quantity supply, days of supply. These claims were used to identify patients who are treated with warfarin and to assess adherence trajectories. The files and the variables that have been used are shown in the tables below.

Table 3: Master Beneficiary Summary File (MBSF)

SAS Variable Name	Description
BENE_ID	An unique encrypted beneficiary identification number that was used to link the beneficiaries across files
AGE	Beneficiary's age at the end of the year
SEX	Beneficiary's gender
RACE	Beneficiary's race was categorized as White, Black and Others
DEATH_DT	Beneficiary's date of death was used to identify patients who were alive from baseline through the measurement period
A_MO_CNT	Month counts of part A coverage, used to identify beneficiaries with continuous enrollment in part A
B_MO_CNT	Month counts of part B coverage, used to identify beneficiaries with continuous enrollment in part B
PTD_MO	Month counts of part D coverage, used to identify beneficiaries with continuous enrollment in part D
HMO_MO	Total number of months of HMO coverage, used to identify beneficiaries with fee-for–service versus HMO coverage
PTD_CNTRCT_ID (1-12)	A unique encrypted contract ID, used to identify patients with stand-alone prescription (i.e. no MA-PD beneficiary)
CST_SHR_GRP_CD(1-12)	Cost share group code, used to identify beneficiaries with low income subsidy as proxy for income variable

Table 4: Inpatient and outpatient files

SAS variable Name	Description
BENE_ID	An unique encrypted beneficiary identification number that was used to link the beneficiaries across files
CLM_ID	Unique encrypted identifier number for claims used to identify duplication of claims
CLM_THRU_DT	Claim date
PMT_AMT	Amount of payment made from the Medicare for the services covered by claim
UTIL_DAY	Number of days utilized by claims, used in calculating amount paid by Medicare not included in the claim payment amount
PER_DIEM	Pass through amount not included in the claim payment amount
PRPAYAMT	Amount paid by primary payer other than Medicare
DED_AMT	Beneficiary deductible amount for inpatient service
COIN_AMT	Beneficiary coinsurance amount for inpatient service
BLDDEDAMT	Beneficiary blood deductible liability amount
ADMTG_DGNS_CD	Beneficiary's initial diagnosis at admission ICD-9-CM code
PRNCPAL_DGNS_CD	Primary diagnosis ICD-9-CM code
ICD_DGNS_CD1-25	Claim diagnosis code
ADMSN_DT	Claim admission date
HCPCS_CD	The Health Care Common Procedure Coding System (HCPCS) is used to identify anticoagulant services
CLM_LINE_NUM	Claim line number, used to identify line outpatient claims

Table 5: Part D Event (PDE) File

SAS variable Name	Description
BENE_ID	An unique encrypted beneficiary identification number that was used to link the beneficiaries across files
PDE_ID	An unique encrypted Part D identification claim number used to identify duplicate claims
SRVC_DT	Prescription service date
BENEFIT_PHASE	Benefit phase of the part D event, used to identify beneficiary in the coverage gap
PTPAYAMT	Amount paid by patient for claim
CPP_	Amount paid by Medicare for claim
GNN / PRDSRVID	Product service ID by NDC
DAYSSPLY	Number of days' supply of the drug, used to measure warfarin adherence

Table 6: MBSF Chronic Condition and Other Chronic Condition Files

SAS variable Name	Description
BENE_ID	An unique encrypted beneficiary identification number that was used to link the beneficiaries across files
AMI	Acute Myocardial infarction
ALZ	Alzheimer's disease
ATRIAL_FIB	Atrial Fibrillation
COPD	Chronic Obstructive Pulmonary Disease
CHF	Congestive Heart Failure
DIABETES	Diabetes
RA_OA	Rheumatoid Arthritis
STRKETIA	Stroke /Transient Ischemic Attack (TIA)
CNCRBRST	Breast Cancer
CNCRCLRC	Colorectal Cancer
CNCRPRST	Prostate Cancer
CNCRLUNG	Lung Cancer
CNCRENDM	Endometrial Cancer
DEPRESSN	Depression
HYPERT	Hypertension
HIVAIDS_MEDICARE	HIV/AIDS
BIPL_MEDICARE	Bipolar disorder
LIVER_MEDICARE	Liver Disease/Cirrhosis and other liver conditions exclude Hepatitis
SCHIOT_MEDICARE	Schizophrenia and other psychotic disorders
PVD_MEIDCARE	Peripheral Vascular Disease

Study design:

This is a retrospective cohort study examining the adherence behaviors and healthcare utilization of AF patients treated with warfarin using Medicare claims data from 2008 to 2010. The index period defined for the study was July 1, 2008 – December 31, 2009 and the date of the first warfarin prescription claim received in the index period was assigned as the index date for warfarin users. A pre-index period was defined as the six months period prior to the index date. A pre-index period is important to identify baseline characteristics and incident warfarin users. The incident users were defined as those patients who did not have a prescription claim for warfarin in the six months prior to the index date. Patient prescription refill claims were followed for 12 months from the index date to assess warfarin adherence. Any additional period after the 12-month follow-up period was used to measure AF-related clinical outcomes (AF-related hospitalizations) and to calculate AF-associated costs (Figure 2).

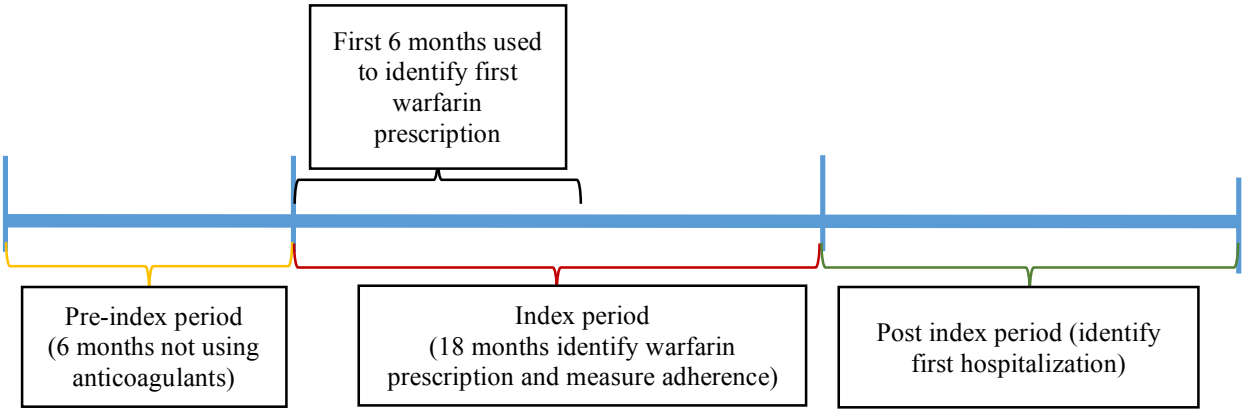

Figure 2: Study timeline

Population and setting:

From the Medicare 5% sample population, all patients ≥ 65 years old with Atrial Fibrillation (AF) and treated with warfarin between July 1, 2008 and December 31, 2010 were eligible for inclusion in this study. Patients with AF were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes from principle diagnosis, admitting diagnosis or any of the 25 ICD diagnosis variables in the inpatient (Part A), outpatient (Part B) claims, or the chronic condition file. Any patient who had at least one inpatient claim or two outpatient claims for AF in any of the claim fields was included in the study (ICD-9-CM codes 427.31 is associated with AF). The National Drug Codes (NDC) of warfarin were used to identify patients on warfarin treatment. Any AF patient who had at least two warfarin prescription claims from July 1st 2008 to December 31, 2009 in the claims data was included in the study. A minimum of two claims of warfarin was chosen to exclude patients who might be given one prescription of warfarin and then discontinued treatment.

Only the beneficiaries with fee-for-service benefits and continuous enrollment in the Medicare Parts A, B and D throughout the study period were included in the study. The continuous enrollment was defined as having 12 months of part A, B, and D access, as represented in the variables A_MO_CNT, B_MO_CNT and PTD_MO, for each year from January 1, 2008 to December 31, 2010. The beneficiaries with fee-for-service benefits were identified by using the HMO_MO and PTD_CNTRCT_ID variables from the MBSF files. The fee-for-service beneficiaries were defined as those with zero months of HMO coverage and who were enrolled in "Stand Alone Prescription Drug Plan" from January 1, 2008 to December 31, 2010. Patients were excluded: 1) their encounter was for palliative care, including end of life care, hospice care and terminal care (identified by ICD-9_CM V66.7) or 2) if they were

diagnosed with metastatic cancer as those beneficiaries have different drug utilization patterns which affect their adherence behavior (using ICD-9-CM code 196-199.1); or 3) patients enrolled in managed care plans.

Variables:

The relevant factors presented in the conceptual model were included as potential confounders in the different analyses in this study. As previously discussed, those factors have been shown to impact medication adherence and healthcare utilization in the elderly. Patient-related variables, including age, gender, and race, were identified from the Beneficiary summary file (MBSF) at the baseline period. The Medicare data used in this study does not contain information regarding a beneficiary's income. The low income subsidy (LIS) variable was used as a proxy for income. This Medicare program offers the medications at reduced cost for the beneficiaries who are eligible based on income, family size, and household resources. The LIS was used in different studies as proxy for the income variable.[44,59] The prescription-related variables, including number of unique medications, were identified from the PDE and drug characteristics file. The INR monitoring and anticoagulant clinic access were identified by using the corresponding Current Procedural Terminology (CPT) code in outpatient files. Disease characteristic variables, including Charlson Comorbidity Index (CCI), $CHADS_2$ (as an indicator of stroke risk), depression and presence of cognitive impairment during the baseline period (six months before the index date) were identified from Chronic Condition and Other Chronic Condition files, inpatient claims, or outpatient claims using corresponding ICD-9-CM codes. Due to limitations of Medicare dataset, the social support and health belief factors of the Andersen Behavioral Model were not assessed in this study.

Age:

The age variable was identified from the MBSF file and was coded as a continuous variable based on the age of the beneficiary in the baseline period.

Gender:

The gender variable was identified from the MBSF file and was categorized as male or female.

Race:

The race variable was identified from the MBSF file and was coded as "White", "Black", or "Others".

Income:

Eligibility for the low income subsidy (LIS) program (as a proxy for income of beneficiary) was identified using the cost share group variable (CST_SHR_GRP_CD) in the MBSF file. The cost share code variable indicates the beneficiary's part D low income subsidy cost sharing group for each month of the year (from January- December). The LIS program for the Medicare Part D provides subsidies that lower or eliminate Part D premiums and defines cost sharing for certain low income beneficiaries. The LIS variable was identified for each beneficiary in the study cohort in the baseline period and was coded as a categorical variable indicating whether or not the beneficiary was eligible for the LIS program or not.

Charlson Comorbidity Index (CCI):

The CCI has been used in many retrospective claims studies as an indicator of patient comorbid conditions, and mortality risk.[60] This variable was coded as a continuous variable and calculated for each beneficiary in the study based on the existence of 17 comorbid conditions.[61]

The conditions were identified based on the presence of corresponding ICD-9- CM codes in the inpatient claims, outpatient claims, the Chronic Conditions file, and the Other Chronic Conditions CCW files (Table 7). For each beneficiary, corresponding scores were summed based on the presence of comorbid conditions and assigned as a CCI score. For example, a patient with peptic ulcer (CCI score of 1) and Myocardial Infarction (CCI score of 1) would have been assigned a CCI score of 2.

Table 7:Conditions included in Charlson Comorbidity Index (CCI)

Condition	ICD-9-CM codes	Score
Myocardial infarction	410.x, 412.x	1
Congestive heart failure (CHF)	428.x	1
Peripheral vascular disease	441.x, 443.9, 785.4	1
Cerebrovascular disease	430-438	1
Dementia	290.x	1
Chronic obstructive pulmonary disorder	490-496, 500-505, 506.4	1
Rheumatologic disease	714.81, 725, 710.0, 710.1, 710.4, 714.0- 714.2	1
Peptic ulcer	531.0-531.7, 532.0-532.7, 533.0-533.7, 534.0-534.7 ,534.9	1
Mild liver disease and cirrhosis	571.2, 571.4x-571.6	1
Diabetes	250.0-250.3, 250.7	1
Paralysis	342.x, 344.1	1
Diabetes with chronic complications	250.4-250.6	2
Renal disease	582.x,585, 586, 588.x, 583.0-583.7	2
Any malignancy include leukemia or lymphoma	140-172.9, 174-195.8, 200-208.9	2
Moderate or severe liver disease	572.2-572.8, 456.0-456.21	3
AIDS	042-044	6
Metastatic solid tumor	196-199.1	6

$CHADS_2$-VASc score:

The $CHADS_2$-VASc score was used as an indicator of stroke risk. The $CHADS_2$-VASc score is a validated scheme for stratifying stroke risk in AF patients. It is a number from 0 to 9, where 0 is lowest risk and 9 is highest risk. Stroke risk is calculated depending on the presence of the following risk factors: Congestive Heart Failure (CHF), Hypertension, age ≥75, Diabetes Mellitus (DM), history of stroke or TIA symptoms, vascular disease, age 65-74, and being female. Presentation of each risk factor adds 1 point to the total the $CHADS_2$-VASc score with the exception of history of a previous stroke and age ≥75 which add 2 points (table 8). The conditions were identified using inpatient claims, outpatient claims, the Chronic Conditions file, and the Other Chronic Conditions CCW files using corresponding ICD-9- CM codes. The variable $CHADS_2$-VASc score was coded as a continuous variable.

Table 8: CHADS2-VASc score for stratifying stroke risk in AF patients

Criteria	ICD-9-CM codes	Value
History of Congestive Heart Failure (CHF)	428.x	+1
History of Hypertension	401.x-405.x	+1
Age ≥ 75	-	+2
History of Diabetes Mellitus (DM)	250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73	+1
Stroke or TIA* Symptoms Previously	433.x1, 434.x1, 435.x, or 436	+2
Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	410.x, 412.x, 441.x, 440.0, 440.1, 440.2, 440.20, 440.21, 440.22, 440.23, 440.29, 440.4, 443.80, 443.81, 443.82, 443.89, 443.9, 785.4	+1
Age 65–74 years	-	+1
Gender (female)	-	+1

Depression:

Depression was identified from the Chronic Condition and Other Chronic Condition files inpatient claims, outpatient claims using corresponding ICD-9- CM code (296.2, 296.3, 311.xx). This variable was coded as a dummy variable indicating whether or not the beneficiary had received a diagnosis of clinical depression. This is an important variable to include in the analysis as depression has been found to affect medication adherence behavior.[62,63]

Cognitive impairment and mental disorders:

This variable denotes the presence of different mental and cognitive conditions. It was coded as a dummy variable indicating whether or not the beneficiary had any of the following conditions: dementia (including Alzheimer's disease), bipolar disorder, or schizophrenia. These conditions were considered in the analysis as they have been shown to have an impact on patients' medication adherence behavior.[2,55] This variable was defined using inpatient claims, outpatient claims, the Chronic Conditions file, and the Other Chronic Conditions CCW files using corresponding ICD-9- CM codes (table 9).

Table 9: Cognitive impairment conditions and corresponding ICD-9-CM codes

Condition	ICD-9-CM codes
Dementia	290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40,290.41, 290.42, 290.43, 290.8, 290.9
Schizophrenia	295.xx
Bipolar disorder	296.0, 296.1, 296.4-296.9

Number of unique medications:

This variable was calculated by using prescription claims data in the PDE file. The unique medication for each beneficiary in the cohort was identified using the GNN variable (generic name of the drugs). The number of a unique medications was coded as a continuous variable indicating the number of different medications each beneficiary received in the baseline period. This is an important variable to consider since increased number of medications and polypharmacy impact medication adherence behavior.[64,65]

Anticoagulant access and INR monitoring:

Access to an anticoagulant clinic was identified by using Healthcare Common Procedure Coding System codes 85610 or 85730, which represent claims submitted for INR testing or the prothrombin test. This variable was coded as a continuous variable indicating number of anticoagulant clinic access or the INR monitoring throughout the index period (12 months after initiating warfarin therapy).

However, after analyzing the data, we found that almost two thirds of the study population (68.7%) had missing values for the "anticoagulant clinic access" variable. This is a limitation of the data source**.** The data used in this study only capture hospital outpatient claims. Thus, there was not sufficient information regarding access to an anticoagulant clinic for a large proportion of the study population. As a consequence, the number of INR monitoring for this variable could not be determined accurately. In other words, we were unable to capture access to anticoagulant clinic outside hospitals or clinics (i.e., a private clinic). To overcome this limitation, an indicator variable was created (0= missing value, 1= a value in the "number anticoagulant access" variable). The indicator variable was included in all the study models, and if the significance of the indicator variable was not statistically significant, this was interpreted as an indication that the missing values in the "anticoagulant clinic access" variable did not impact study outcomes.

Medicare coverage gap variable:

This variable was calculated using benefit phase variables from the PDE file. Medicare covers most drug-related costs until the beneficiary reaches a defined threshold each year. When the beneficiary exceeds that threshold, he/she enters into the coverage gap (i.e., "donut hole"), in which the Medicare no longer covers the medication expense. The coverage gap variable was

coded as a dummy variable indicting whether or not the beneficiary was in the coverage gap during the baseline period. This variable has also been found to impact patient's medication adherence behavior.[66]

3.1 Specific Aim 1

Specific Aim 1A Identify and describe the trajectory groups of warfarin adherence in patients with AF in a Medicare population

Specific Aim 1B: Estimate the likelihood of patients belonging to each adherence trajectory

Specific Aim 1C: Identify characteristics of trajectory members and factors associated with each adherence trajectory

Outcome measures:

The primary outcome measure was the trajectories of warfarin adherence over the time period. The Group Based Trajectory Model (GBTM) was used to identify different group patterns of adherence to warfarin in the study population over a one-year study period and to estimate likelihood of patients belonging to each adherence trajectory.

Adherence measures:

First, we assessed adherence by creating a supply diary for each patient in the cohort, indicating if the warfarin was available on each day for 12 months after the index date (first prescription of warfarin). The supply diary was created by linking all warfarin-related pharmacy claims based on days' supply and dispensing date variables in the PDE file. Then, the monthly proportion of days covered (PDC) was calculated for each patient in the cohort for a period of 12 months after the index date. Monthly PDC was calculated by dividing number of days "covered" for warfarin in a given month by 30 days:

$$\text{Monthly Proportion Days Covered (PDC)} = \frac{Number\ of\ days\ "covered"\ per\ month}{30\ days}$$

Each patient in the cohort would have 12 calculated PDC values for one year after initiating warfarin therapy. The PDC was adjusted when the next prescription was filled before the end of supply of the previous fill. For example, figure 3 shows the case in which the second claim, filled on Oct. 10, 2008, occurs before the end of supply of the first claim (Sept.15, 2008). In this case, the PDC was calculated by adjusting the overlapping days' supply and shifting the fill date of the second claim forward until the end of supply of the first claim (i.e., the new fill date of the second claim, thus becomes Oct.15, 2008).[67]

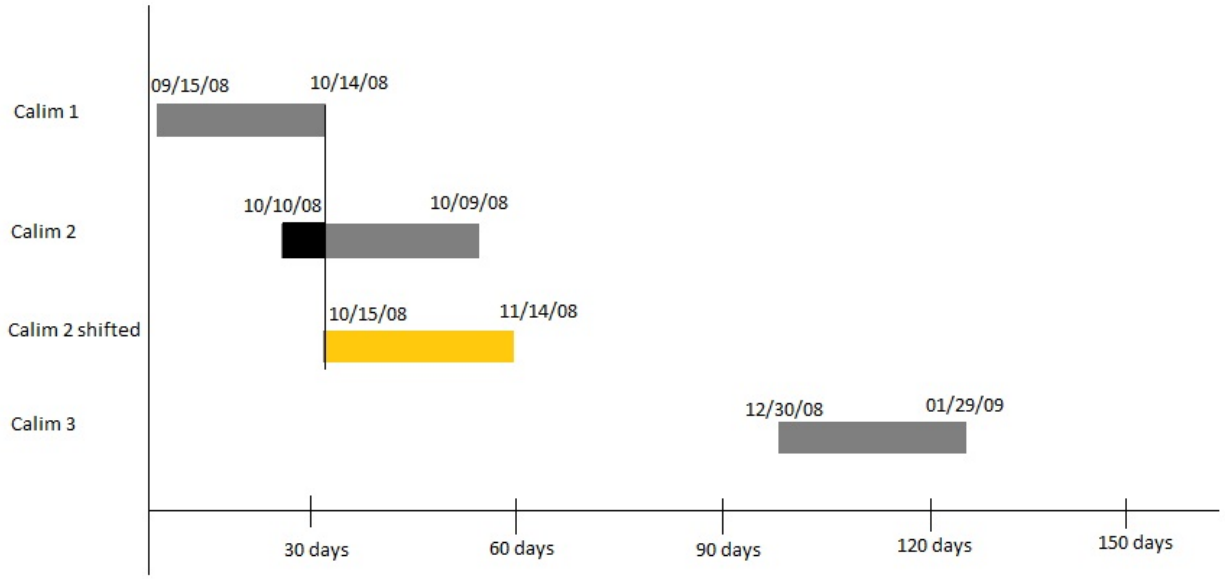

Figure 3: Example of adjusted PDC for overlapping days' supply

Group based trajectory model:

The 12 monthly measures for warfarin adherence for each patient in the cohort were modeled using GBTM. Each patient was classified into a trajectory group based on his/her adherence pattern over the one-year period. When running the trajectory model, several multiple regression models were estimated simultaneously, where the outcome was the probability of being adherent (monthly PDC) and the independent variable was time in months.

The GBTM is an application of finite mixture models and the estimation of model parameters is a product of the maximum likelihood function. These parameters determine the shape of the trajectories and the size of the groups. The GBTM estimates the posterior probabilities or the membership probabilities for each beneficiary in the cohort, which in turn determine the assignment of the beneficiaries to the trajectory groups according to the highest membership probability.[32]

The PROC TRAJ function of SAS 9.4® was used in this study to run the GBTM. The PROC TRAJ procedure is not part of the base SAS software, and was downloaded separately from B. Jones's website.[68]

The main inputs necessary to run the GBTM are:

1. Outcome variable: the 12 repeated measures of PDC for each patient in the cohort.
2. Independent variable: the 12 time variables (month1-month12), which patient's adherence were measured over.
3. Distribution of the outcome variable: as the PDC is proportion data (censored data), so the distribution was specified as censored normal distribution.
4. Number of groups.
5. Order of each equation that describes change over time for each group.

The model fitting process of the GBTM is iterative and required running the model several times, changing the number of groups and assigned order each time, in order to achieve the best fitted model for the data. The model fit process can be summarized in the following steps:

1. Determining the maximum number of groups.
2. Select the appropriate order for each group and run models, starting with one group model until maximum assigned number of groups is reached in a stepwise manner.
3. Select the the model with the appropriate number of groups that best fits the data.

In step one, the maximum number of groups can be determined based on the literature. In this study, the maximum number of groups was limited to six groups for simplicity of interpretations and to avoid small size of trajectory groups.[44,69]

In the second step, the shape of the trajectory for each group over time was determined based on the proper order of each equation. According to the recommendation by Nagin et al., each group should be assigned to second order (quadratic order) at the beginning of the analysis and then changing it until reaching an appropriate order for the best model. The PROC TRAJ function can model up to a fourth order polynomial. As a general rule, one group model with quadratic order is tested first. If the parameters of the single quadratic model are not significant, then another model is run by changing the order of the group from quadratic to linear or cubic until getting significant parameters. If the parameters of the single quadratic model are significant, then a two groups quadratic model is performed. This process is repeated with additional number of the trajectory groups until the six groups model (i.e., maximum number of groups). In this study, the parameters of the quadratic order for all six models were significant so there was no need to change the order of the groups to linear, cubic, or quartic.

After performing the second step, six models were produced with different number of groups and shapes of trajectories. The selection of the final model is based on three main criteria: 1) Bayesian information criteria (BIC); 2) the proportion of beneficiaries in each group is not less than 5% of total sample; and 3) Nagin's criteria.

The BIC values are estimated for each model and considered the fit index when comparing between models. To compare between competing models, the log Bayes factor was used and is calculated by subtracting the BIC of the simple model (model with fewest groups) from each successive, more complex model (model with more groups) and multiplying it by two:[70,71]

$$2\Delta BIC = 2 \times [\, BIC_{(complex)} - BIC_{(simple)}]$$

The interpretation of the log Bayes factor in terms of model fit is explained according to guidelines by Jones et al., (table 10)

Table 10: Interpretation of logged Bayes factor (2*ΔBIC) for model selection

2*ΔBIC	**Evidence against Ho**
0 to 2	Not worth mentioning
2 to 6	Positive
6 to 10	Strong
> 10	Very strong

According to this guideline, a logged Bayes factor value of 0 to 2, for example, indicates weak evidence that a more complex model has a better fit compared to the simple model. While a value of more than ten is interpreted as very strong evidence of better fit of the complex model. First, the model with two trajectory groups is compared to the single group model by calculating log Bayes factor. If the value is indicative of a better fit (i.e., $2*\Delta BIC > 2$), then the two groups

model is compared to three groups model. This process is continued, by comparing to each the increasingly complex model, until there is no more evidence for improvement in the model fit.

Once the number of trajectory groups was determined, the beneficiaries were classified into the groups based on the highest posterior probability (maximum-probability assignment rule).[27,34] An example for applying the maximum-probability assignment rule to assigned beneficiaries to groups is shown in table 11. This process is done automatically by the PROC TRAJ function in SAS.

Table 11: Example of assigning beneficiaries to trajectory groups based on the maximum-probability assignment rule

Beneficiary ID	Probability to group 1	Probability to group 2	Probability to group 3	Probability to group 4	Assigned group
1	0.21	**0.63**	0.02	0.14	2
2	0.24	0.02	0.07	**0.67**	4
3	**0.54**	0.11	0.33	0.02	1

After selecting the appropriate number of groups according the logged Bayes factor, the proportion of the beneficiaries in each group is evaluated. Ideally, the proportion of beneficiaries in each group should not be less than 5% of the total sample.

The third criteria for model selection is Nagin's criteria for model adequacy which indicates how well or precisely the beneficiaries are assigned to each trajectory group based on average posterior probability.[27,44] The average posterior probability is an indicator of the internal reliability of the model. It is calculated for each group and equals the average assigned posterior probabilities of the beneficiaries to trajectory using the maximum-probability assignment rule. An average posterior probability greater of 0.7 for all the groups is recommended.

The major outputs for the trajectory model are the appropriate trajectory groups of warfarin adherence, the membership probability for each beneficiary in each group, and graphical illustration of trajectory curves, with PDC values on the y-axis and time (months) on the x-axis.

Statistical analysis:

Baseline characteristics of the cohort, stratified by trajectory group, were described, with means and standard deviation calculated for continuous variables and percentages for categorical variables.

To describe associations between patients' characteristics, including confounders in the conceptual framework, and trajectory groups, a multinomial regression model was used:

Log $(P(groupA)/P(Ref\ group*)) = \beta_0 + \beta_1$ AGE + β_2 GENDER + β_3 RACE + β_4 LIS + β_5 COVERAGE_GAP + β_6 $CHADS_2$-VASc + β_7 CCI +β_8 DEPRESSION+β_9 COGNITIVE_IMPAIRMENT+ β_{10} NO_MEDICATION+ β_{11} INR_MONITORING

*Ref group: perfectly adherent

The outcome of interest was the odds of being in a given group compared to a perfectly adherent group. Odds ratios and 95% Confidence intervals (95% CI) from the multinomial regression model were reported. All statistical analyses were conducted using SAS 9.4® and a significance level of $\alpha \leq 0.05$ was assigned.

3.2 Specific Aim 2

Specific Aim 2A: Estimate the rates of hospitalizations related to a stroke or bleeding event (clinical outcomes) associated with each adherence trajectory

Specific Aim 2B: Evaluate the association between warfarin adherence trajectory group membership and the likelihood of hospitalization due to a stroke or bleeding event

Outcome measures:

For Specific Aim 2, the outcome of interest is time to first hospitalization related to AF or warfarin therapy. In this study, a hospitalization event is defined as the first admission due to a bleeding event or stroke in the follow-up period (one year after first warfarin fill). The follow-up was restricted to only one year to limit the assessment to hospitalization events occurring at the same time as the observed adherence patterns. The hospitalization events were identified from the corresponding ICD-9-CM codes as the primary discharge diagnosis for hospitalization or admitting diagnosis in the inpatient file. The defined ICD-9 codes are listed in table 12.

Table 12: ICD-9 codes and corresponding definitions for hospitalization events

Condition	ICD-9 codes
Major Bleeding	
Gastrointestinal bleeding	456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x
Non-traumatic intracranial hemorrhage	430, 431, 432.x
Traumatic intracranial hemorrhage	852.x, 853.x
Bleeding from other sites	423.0, 459.0, 596.7, 599.71, 719.1x, 784.8, 786.3
Stroke	
Ischemic stroke	433.x1, 434.x1, or 436
Transit ischemic attack (TIA)	435.X
Systemic embolism	444.x

Statistical analysis:

Baseline characteristics of the cohort were described between patients who experienced hospitalization events in the follow-up period and those that did not have an event, with means and standard deviation for continuous variables and percentages for categorical variables. In order to examine the association between trajectory groups and the first hospitalization event, while controlling for potential confounders, a multivariable Cox proportional hazards model was used:

$$\text{Log}\,[h(t|x)] = \beta_0 + \beta_1\,\text{TRAJ}^* + \beta_X\,X^{**}$$

[$h(t|x)$]: hazard ratio of hospitalization

*TRAJ: Warfarin adherence trajectory groups

**X: Confounders

The dependent variable in the model is time to first hospitalization event due to bleeding or stroke events in the follow-up period. Time units were coded as days starting after one year from the index date. Beneficiaries were followed until the first hospitalization event, death, or end of follow-up period. Cases were coded as censored if the hospitalization event had not occurred by the end of the follow up period, or if the beneficiary died. The proportion of patients who experienced events was presented by trajectory group. Results for the association between adherence trajectories and time to first hospitalization were reported as a hazard ratio (HR) and 95% CI. Statistical significance was defined as $\alpha \leq 0.05$.

3.3 Specific Aim 3

Specific Aim 3A: Estimate the AF-related costs for each adherence trajectory group

Outcome measures:

The primary outcome for this aim was AF-related costs associated with each trajectory adherence group through the follow-up period. In this study, the costs included were direct medical costs from the societal perspective. The direct medical costs associated with AF were calculated by including cost of 1) anticoagulant clinic services, 2) outpatient visits, and 3) inpatient visits related to bleeding or thromboembolic events. Use of anticoagulant clinic services was identified using corresponding CPT codes for INR testing (CPT codes '85610','85730'). AF-related inpatient and outpatient visits were identified using corresponding ICD-9-CM codes for AF, bleeding or thromboembolic events in the principal diagnosis, admitting diagnosis or the first three diagnosis variables in the inpatient and outpatient Medicare files (Table 8). Total cost was computed by summing the amount paid by Medicare, the beneficiary and other third-party payers, if any. The amount paid by Medicare, other third party payers, and beneficiary were obtained from the base inpatient and outpatient files, but the amount paid by the beneficiary for anticoagulant clinic was identified from the Revenue Center files and were linked to the base file by a unique claim identifier (CLM_ID). The different cost components were calculated as follows:

$Medicare\ share = Amount\ paid\ by\ Medicare + (Diem\ amount\ paid * Number\ of\ days\ in\ claim)$

$Beneficiary\ share = Deductible + Coinsurance + Blood\ deductible$

$Total\ amount\ paid = Medicare\ share + Beneficiary\ share + Third\ party\ payment$

All costs associated with emergency department visits (ED) were already captured in the inpatient or outpatient billing depending if the beneficiary was admitted (inpatient) or discharged (outpatient) after their ED visit.

All positive cost data were presented in $US and inflated to 2018 currency values by using the US Healthcare inflation rate from the Bureau of Labor Statistics (Appendix B).[72]

Statistical analysis:

Direct medical costs associated with each adherence trajectory were calculated. Cost components included in the analysis were costs related to inpatient visits, outpatient visits, and INR monitoring. The mean of total costs related to AF associated with each trajectory group were reported in addition to a breakdown of cost components stratified by adherence trajectory. An ANOVA analysis was performed to test for differences in total cost and cost components (inpatient visits, outpatient visits, and INR monitoring) between different trajectory groups. All analyses were performed using SAS 9.4 software. A P-values less than 0.05 denoted statistical significance.

3.4 Sensitivity Analysis

To confirm robustness of the study results, two sensitivity analyses were conducted. As medication adherence can have an impact on short-term clinical outcomes, a three months' follow-up period was examined in place of the one-year follow-up period used in the main analysis. Another sensitivity analysis was performed defining hospitalization events due to stroke or bleeding using corresponding ICD-9 codes in the secondary discharge diagnosis field instead of the primary diagnosis field.

Chapter 4: Results

In this section the final study population is described. This is followed by the description of the results for each individual aim.

4.1 Study Population

From the random sample of Medicare beneficiaries, 50,636 beneficiaries met the eligibility criteria, i.e., AF patients, age ≥65, with three years of continuous enrollment in Medicare Part A, B and D. Of those, 3,246 beneficiaries were identified as new users of warfarin with at least two prescriptions and were identified to be the population of interest (Figure 4). On average beneficiaries were 78 years old, 63% women, and 91% white (Table 13).

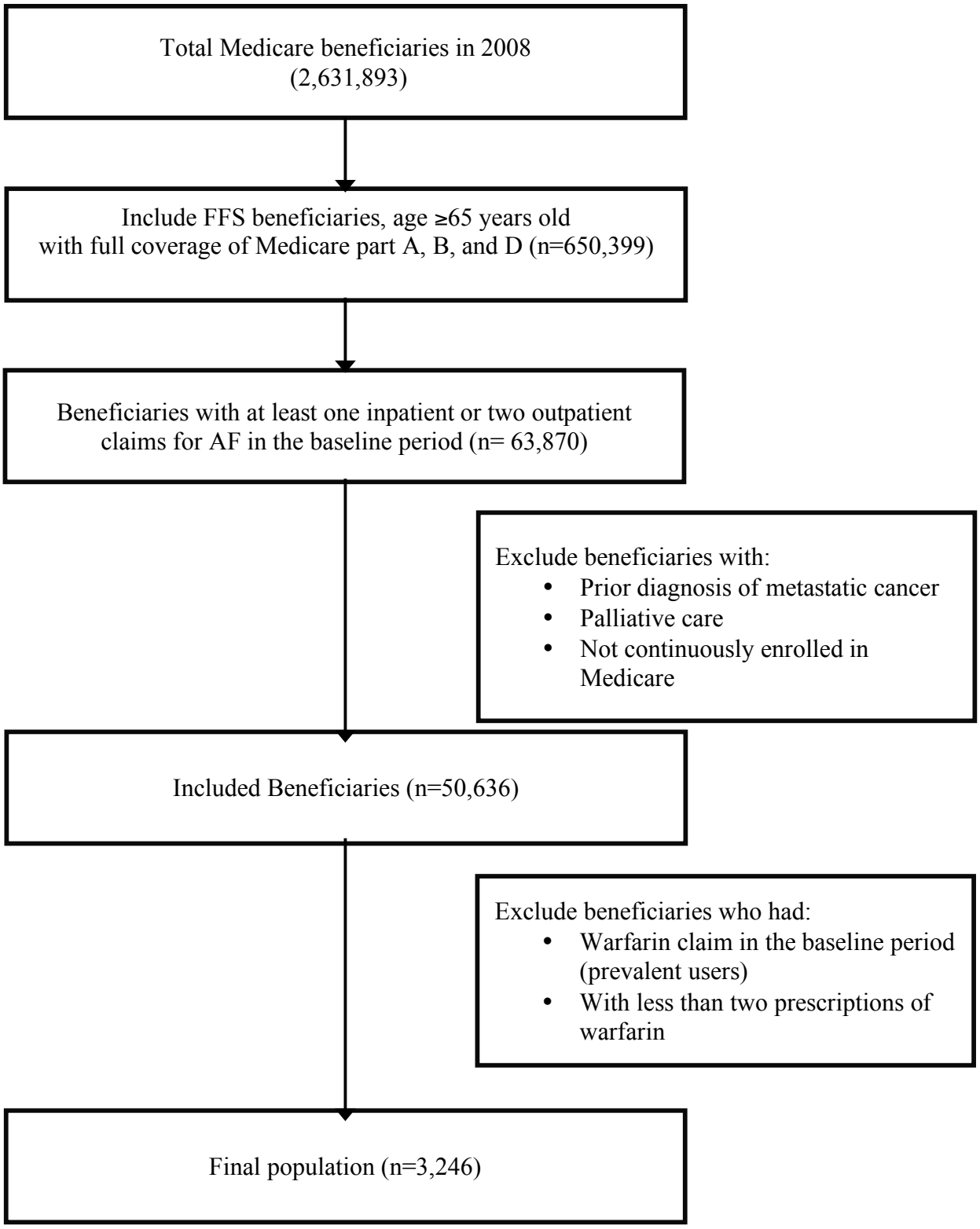

Figure 4: Eligibility flow chart for the study cohort

Table 13: Baseline characteristics for the study cohort

Characteristics	Total (3,246)
Age	
Mean (SD)	78.42 (7.02)
Gender (%)	
Male	37.34
Female	62.66
Race (%)	
White	91.74
Black	3.82
Others	4.44
LIS eligibility (%)	
No	72.64
Yes	27.36
CCI	
Mean (SD)	3.06 (2.28)
Median (min-max)	3.00 (0-13)
$CHADS_2$-VASc score	
Mean (SD)	5.10 (1.74)
Median (min-max)	5.00 (1-9)
Depression (%)	
No	80.62
Yes	19.38

*Abbreviation used: LIS eligibility: Low Income Subsidy eligibility, CCI: Charlson Comorbidity Index

Table 13: Continued

Characteristics	Total (3,246)
Cognitive impairment and mental disorders (%)	
No	91.25
Yes	8.75
Number of chronic medications	
Mean (SD)	13.41 (6.15)
Median (min-max)	12.50 (1-39)
Coverage Gap	
Yes	40.70
No	59.30
Anticoagulant access (%)	
Yes	32.10
No	67.90

4.2 Specific Aim 1

Specific Aim 1A: Describe the trajectory groups of warfarin adherence in patients with AF in Medicare population

Specific Aim 1B: Estimate the likelihood of patients belonging to each adherence trajectory

Six trajectory models were performed ranging from one group to six groups (figure 5). As the number of groups increased, there was an improvement in the statistical fit (i.e., the absolute BIC value getting lower indicating better fit). The Bayes factor and estimated group proportions were used to determine the best GBTM model (Table 14). The six groups model provided the best statistical fit based on the Bayes factor, and the estimated proportion of the beneficiaries in each group were more than 5% of the total study population. Thus, the six groups model was selected as the final model. The parameter estimates of the final model were all significant and are presented in Table 15.

Additionally, Nagin's criteria for assessing the final model adequacy in assigning the beneficiaries in each trajectory group was checked, and indicated that the six group model performed well in distinguishing between beneficiaries with different adherence patterns (i.e., average posterior probability for each trajectory group is ≥ 0.7) (Table 16).

Figure 6 illustrates six distinct adherence patterns for warfarin during the first year after initiating treatment. The six adherence trajectories were described and labeled based on the timing of discontinuation of warfarin and the level of the PDC: 1) Rapid decline non-adherence group (11.5%, mean PDC: 0.22), 2) moderate non-adherence group (24%, mean PDC: 0.56), 3) rapid decline then increasing adherence group (6.8%, mean PDC: 0.85), 4) moderate decline non-adherence group (8.2%, mean PDC: 0.51), 5) slow decline non-adherence group (24.3%,

mean PDC: 0.84), and 6) perfect adherence group (25.3%, mean PDC: 0.99) (table 16). Table 17 shows the baseline characteristics of beneficiaries stratified by trajectory groups. Relative to other adherence groups, the beneficiaries in the "rapid decline then increase adherence group" were more likely to be male. Overall, beneficiaries in the "perfect adherence group" were more likely to be eligible for the LIS program and to suffer from mental health conditions.

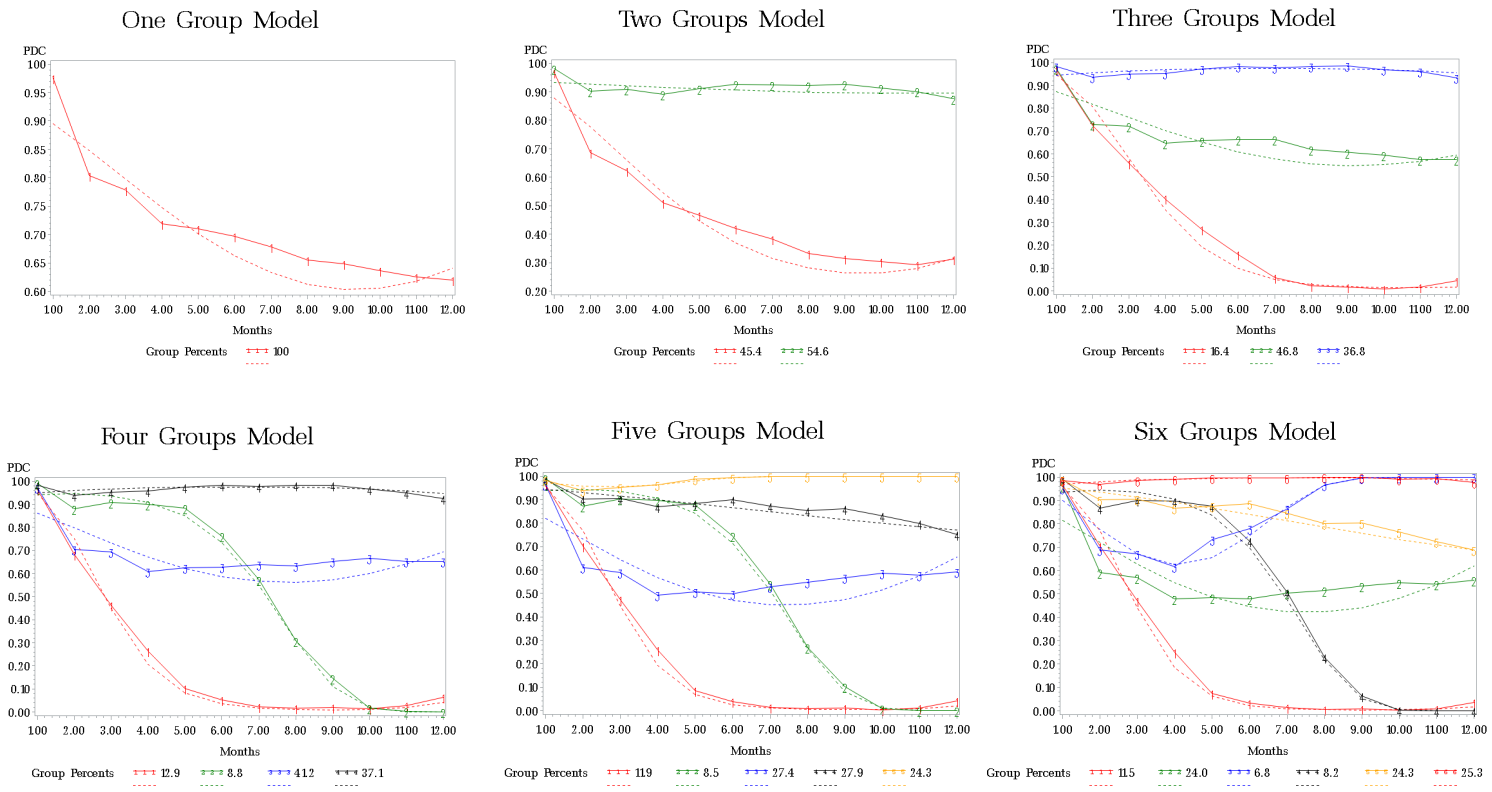

Figure 5: Trajectory models using one to six groups. In each plot, the solid lines represent the predicted probability of adherence in each group, and the dotted lines represent the observed proportion. The proportion of beneficiaries in each group is given under each graph

Table 14: Bayesian Information Criterion (BIC) values and percentage of patient in each group for the six models

Model	BIC	Bayes factor	Percentage of patients in each group					
			Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
1 group	-37,135.97	-	100%	-	-	-	-	-
2 groups	-30,902.02	12,467.9	45.37%	54.63%	-	-	-	-
3 groups	-28,608.53	4,586.98	16.42%	46.80%	36.78%	-	-	-
4 groups	-27,667.02	1,883.02	12.90%	8.77%	41.20%	37.13%	-	-
5 groups	-27,139.29	1,055.46	11.89%	8.50%	27.39%	27.88%	24.34%	-
6 groups	-26,778.85	720.88	11.53%	23.95%	6.79%	8.17%	24.28%	25.27%

Table 15: Parameter estimates of adherence trajectories for the six-groups model

Trajectory group	Parameter order	Estimate	P-value
1. Rapid decline non-adherence group	Intercept	2.59	<0.001
	Linear	-0.87	<0.001
	Quadratic	0.04	<0.001
2. Moderate non-adherence group	Intercept	1.40	<0.001
	Linear	-0.28	<0.001
	Quadratic	0.02	<0.001
3. Rapid decline then increasing adherence group	Intercept	1.93	<0.001
	Linear	-0.58	<0.001
	Quadratic	0.07	<0.001
4. **Moderate decline non-adherence group**	Intercept	1.46	<0.001
	Linear	0.18	<0.001
	Quadratic	-0.05	<0.001
5. **Slow decline non-adherence group**	Intercept	1.80	<0.001
	Linear	-0.12	<0.001
	Quadratic	0.01	0.009
6. **Perfect adherence group**	Intercept	1.64	<0.001
	Linear	0.20	<0.001
	Quadratic	-0.01	<0.001

Table 16: Model fit statistics for the six-groups model

Trajectory group	Group size		PDC		Average Posterior probability*	
	N	%	Mean	SD	Mean	SD
1. Rapid decline group	378	11.53%	0.22	0.08	0.97	0.09
2. Moderate non-adherence group	787	23.95%	0.56	0.14	0.91	0.14
3. Rapid decline then increasing adherence group	216	6.79%	0.85	0.09	0.87	0.16
4. Moderate decline group	262	8.17%	0.51	0.10	0.94	0.11
5. Slow decline group	760	24.28%	0.84	0.07	0.89	0.14
6.Perfect adherent group	843	25.27%	0.99	0.02	0.94	0.13

*Average posterior probability: represents how well beneficiaries are classified into trajectory groups. An average posterior probability greater than 0.7 indicates a good model fit

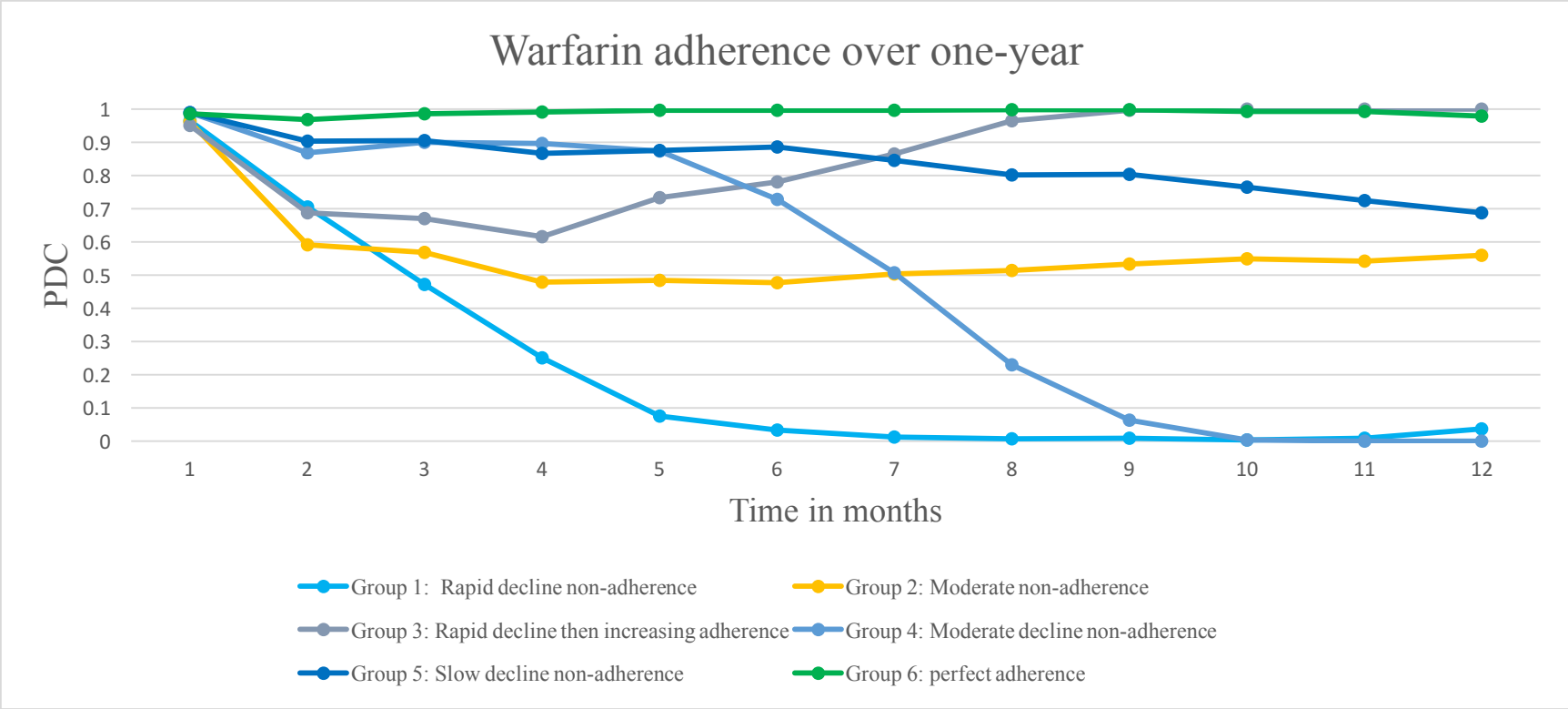

Figure 6:Warfarin adherence trajectories in the 12 months following initiation (Final model)

Table 17: Baseline characteristics of study population stratified by adherence trajectory groups

Characteristics	1. Rapid decline group (n= 378)	2. Moderate non-adherence group (n=787)	3. Rapid decline then increasing adherence group (n=216)	4. Moderate decline group (n=262)	5. Slow decline group (n=760)	6. perfect adherence group (n=843)	Total (3,246)
Age							
Mean (SD)	78.13 (7.10)	78.02 (6.57)	78.90 (7.24)	78.13 (7.35)	78.31 (6.90)	79.01 (7.32)	78.42 (7.02)
Gender (%)							
Male	38.10	37.23	43.98	37.40	39.61	33.33	37.34
Female	61.90	62.77	56.02	62.60	60.39	66.67	62.66
Race (%)							
White	90.48	93.14	93.98	89.69	91.18	91.58	91.74
Black	3.44	3.81	2.78	3.05	4.61	3.80	3.82
Others	6.08	3.05	3.24	7.25	4.21	4.63	4.44
LIS eligibility (%)							
No	74.60	77.51	73.61	73.28	73.68	65.84	72.64
Yes	25.40	22.49	26.39	26.72	26.32	34.16	27.36

*Abbreviation used: LIS eligibility: Low Income Subsidy eligibility

Table 17: Continued

Characteristics	1. Rapid decline group (n= 378)	2. Moderate non-adherence group (n=787)	3. Rapid decline then increasing adherence group (n=216)	4. Moderate decline group (n=262)	5. Slow decline group (n=760)	6. perfect adherence group (n=843)	Total (3,246)
CCI							
Mean (SD)	3.23 (2.19)	3.07 (2.32)	2.93 (2.23)	3.14 (2.33)	3.00 (2.32)	3.03 (2.26)	3.06 (2.28)
Median (min-max)	3.00 (0-10)	3.00 (0-12)	3.00 (0-10)	3.00 (0-11)	3.00 (0-13)	3.00 (0-11)	3.00 (0-13)
$CHADS_2$-VASc score							
Mean (SD)	5.04 (1.70)	5.11 (1.69)	4.98 (1.71)	4.95 (1.72)	5.06 (1.79)	5.23 (1.79)	5.10 (1.74)
Median (min-max)	5.00 (2-9)	5.00 (1-9)	5.00 (1-9)	5.00 (1-9)	5.00 (1-9)	5.00 (1-9)	5.00 (1-9)
Depression (%)							
No	80.69	82.97	80.09	77.10	81.97	78.41	80.62
Yes	19.31	17.03	19.91	22.90	18.03	21.59	19.38

*Abbreviation used: CCI: Charlson Comorbidity Index

Table 17: Continued

Characteristics	1. Rapid decline group (n= 378)	2. Moderate non-adherence group (n=787)	3. Rapid decline then increasing adherence group (n=216)	4. Moderate decline group (n=262)	5. Slow decline group (n=760)	6. perfect adherence group (n=843)	Total (3,246)
Cognitive impairment (%)							
No	91.27	94.28	91.67	90.08	92.24	87.78	91.25
Yes	8.73	5.72	8.33	9.92	7.76	12.22	8.75
Number of chronic medications							
Mean (SD)	13.68 (6.00)	13.27 (6.20)	12.69 (5.62)	13.90 (6.22)	13.11 (5.97)	13.70 (6.43)	13.41 (6.15)
Median (min-max)	13.00 (3-37)	13.00 (1-39)	12.00 (3-32)	13.00 (2-34)	12.00 (3-37)	13.00 (2-39)	12.50 (1-39)
Coverage Gap							
Yes	39.95	39.26	41.20	41.22	41.97	40.93	40.70
No	60.05	60.74	58.80	58.78	58.03	59.07	59.30

Table 17: Continued

Characteristics	1. Rapid decline group (n= 378)	2. Moderate non-adherence group (n=787)	3. Rapid decline then increasing adherence group (n=216)	4. Moderate decline group (n=262)	5. Slow decline group (n=760)	6. perfect adherence group (n=843)	Total (3,246)
Anticoagulant access (%)							
Yes	32.28	34.56	29.17	28.63	31.58	32.03	32.10
No	67.72	65.44	70.83	71.37	68.42	67.97	67.90

Specific Aim 1C: Identify patients' characteristics and factors associated with each adherence trajectory

The results of the multinomial logistic regression model for identifying predictors of adherence trajectory groups are presented in Table 18. No significant differences were found between adherence trajectories and demographic characteristics, presence of clinical depression, number of chronic medications, or access to an anticoagulant clinic. However, Hispanic, Asian, or North American natives together had twice the odds of being in the "moderate decline" group compared to the "perfect adherence" group (others vs. white OR: 2.01, 95% CI: 1.11-3.63). LIS eligibility was found to be a significant predictor of adherence trajectory groups. Specifically, being eligible for the LIS program was associated with higher odds of being in "perfect adherence" group compared to other groups. Having more cognitive conditions was associated with lower risk for being in the "moderate non-adherent" and "slow decline" groups relative to the "perfect adherence" group (OR: 0.51, 95%CI: 0.35-0.74, OR: 0.68 95%CI: 0.48-0.97, respectively). Keeping other covariates constant, with every unit increase in the CCI there were increased odds of being in the "rapid decline" and "moderate decline" group" relative to the "perfect adherent" group (OR:1.12, 95%CI: 1.04-1.2, OR: 1.11, 95%CI: 1.02-1.2, respectively). Moreover, with every unit increase in the stroke risk score ($CHADS_2$-VASc score), there was a 15% decrease in the odds of being in "moderate decline" group compared to being in the "perfect adherence" group (OR: 0.85, 95% CI: 0.76-0.96). The odds for being in the "slow decline" group compared to the "perfect adherence" group were 29% higher for beneficiaries who had been in the insurance gap (OR: 1.29, 95% CI: 1.02-1.63).

Table 18: Multinomial Logistic Regression: Predictors of Adherence Trajectory Group

Characteristics	1. Rapid decline group, OR (95%CI)	2. Moderate non-adherence group, OR (95%CI)	3. Rapid decline then increasing adherence group, OR (95%CI)	4. Moderate decline group, OR (95%CI)	5. Slow decline group, OR (95%CI)	6. perfect adherence group (Ref)
Age	0.99 (0.97-1.01)	0.98 (0.96-1.00)	1.01 (0.98-1.03)	1.00 (0.97-1.02)	0.99 (0.98-1.01)	1
Gender						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	1.03 (0.77-1.38)	0.98 (0.78-1.24)	0.70 (0.49-1.00)	1.09 (0.78-1.52)	0.86 (0.68-1.09)	1
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.11 (0.56-2.19)	1.52 (0.74-2.12)	0.98 (0.36-2.21)	1.01 (0.45-2.29)	1.50 (0.90-2.49)	1
Others	1.70 (0.98-2.95)	0.84 (0.49-1.43)	0.73 (0.33-1.77)	2.01 (1.11-3.63)	1.07 (0.65-1.76)	1
LIS eligibility	0.60 (0.44-0.82)	0.58 (0.45-0.73)	0.79 (0.54-1.14)	0.62 (0.44-0.88)	0.69 (0.54-0.88)	1
CCI	1.12 (1.04-1.2)	1.05 (0.99-1.11)	1.04(0.95-1.14)	1.11 (1.02-1.2)	1.03 (0.97-1.10)	1
$CHADS_2$-VASc score	0.91 (0.82-1.01)	1.01 (0.93-1.10)	0.96 (0.84-1.09)	0.85 (0.76-0.96)	0.99 (0.90-1.07)	1

*Abbreviation used: LIS eligibility: Low Income Subsidy eligibility, CCI: Charlson Comorbidity Index

Table 18: Continued

Characteristics	1. Rapid decline group, OR (95%CI)	2. Moderate non-adherence group, OR (95%CI)	3. Rapid decline then increasing adherence group, OR (95%CI)	4. Moderate decline group, OR (95%CI)	5. Slow decline group, OR (95%CI)	6. perfect adherence group (Ref)
Depression	0.91 (0.66-1.26)	0.83 (0.64-1.08)	1.11 (0.75-1.65)	1.13 (0.80-1.62)	0.91 (0.70-1.81)	1
History of cognitive impairment and mental disorders	0.79 (0.51-1.21)	0.51 (0.35-0.74)	0.70 (0.40-1.22)	0.90 (0.56-1.46)	0.68 (0.48-0.97)	1
Number of chronic medications	1.00 (0.97-1.03)	0.99 (0.97-1.01)	0.97 (0.94-1.00)	1.01 (0.98-1.03)	0.98 (0.96-1.00)	1
History of being in the insurance gap	1.03 (0.77-1.37)	1.10 (0.87-1.39)	1.38 (0.97-1.97)	1.05 (0.75-1.46)	1.29 (1.02-1.63)	1
Having access to anticoagulant clinic	0.95 (0.73-1.25)	1.11 (0.89-1.38)	0.88 (0.62-1.23)	0.81 (0.59-1.11)	0.97 (0.78-1.21)	1

4.3 Specific Aim 2

Specific Aim 2A: Estimate the rates of hospitalizations related to a stroke or bleeding event (clinical outcomes) associated with each adherence trajectory

Overall, 7.5% of the sample population had an AF-related hospitalization event (figure 7). As shown in table 19, beneficiaries who had AF-related hospitalization had slightly lower overall PDC (PDC for hospitalized: 0.68, non-hospitalized: 0.71). The AF-related hospitalization events in the 12-month period following therapy initiation was least frequent in the "rapid decline then increasing adherence", "slow decline", and "perfect adherent" groups (6.02%, 6.18%, and 7.35%, respectively) and highest in the "moderate decline" and "rapid decline" groups (9.54%, and 8.73%, respectively).

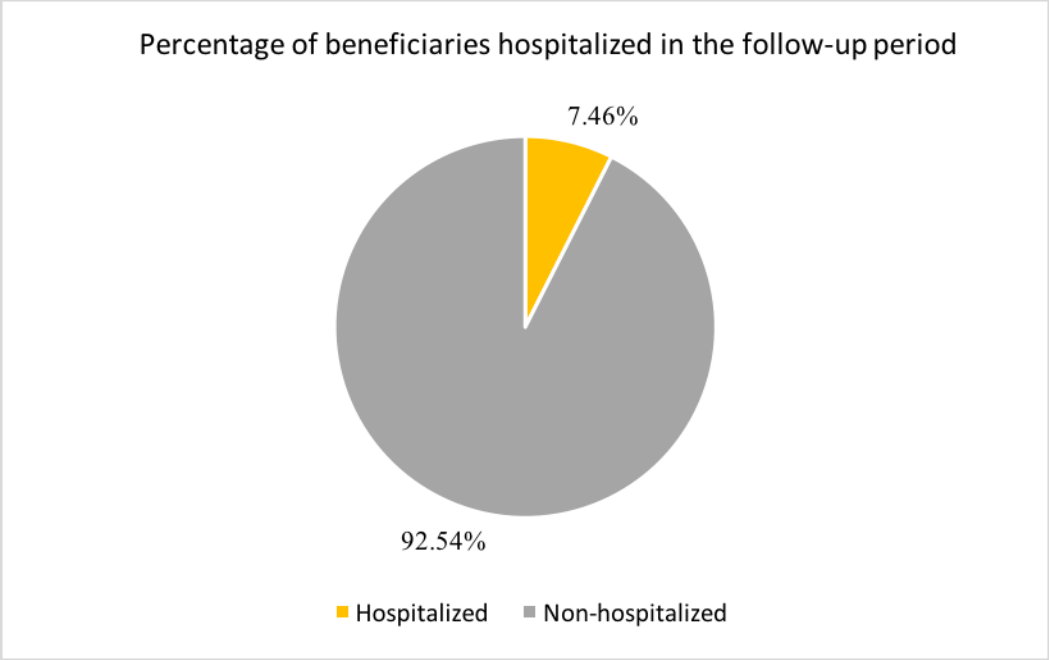

Figure 7: Percentage of AF-related hospitalization after one year of initiating warfarin therapy

Table 19: Baseline characteristics for hospitalized compared to non-hospitalized patients

Characteristics	Hospitalized (7.46%)	Non-hospitalized (92.54%)
Adherence trajectories (%)		
1. Rapid decline group	8.73%	91.27%
2. Moderate non-adherence group	7.88%	92.12%
3. Rapid decline then increasing adherence group	6.02%	93.98%
4. Moderate decline group	9.54%	90.46%
5. Slow decline group	6.18%	93.82%
6.Perfect adherent group	7.35%	92.65%
Overall PDC	0.68	0.71
Age		
Mean (SD)	78.95% (7.02)	78.38 (7.02)
Gender (%)		
Male	5.36%	94.64%
Female	8.70%	91.30%
Race (%)		
White	7.32%	92.68%
Black	7.26%	92.74%
Others	10.42%	89.58%
LIS eligibility (%)		
No	6.70%	93.30%
Yes	9.46%	90.54%

*Abbreviation used: LIS eligibility: Low Income Subsidy eligibility

Table 19: Continued

Characteristics	Hospitalized (7.46%)	Non-hospitalized (92.54%)
CCI		
Mean (SD)	4.04 (2.30)	2.98 (2.26)
Median (min-max)	4.00 (0.00-11.00)	3.00 (0.00-13.00)
$CHADS_2$-VASc score		
Mean (SD)	5.83 (1.67)	5.04 (1.74)
Median (min-max)	6.00 (2.00-9.00)	5.00 (1.00-9.00)
Depression (%)		
No	7.11%	92.89%
Yes	8.90%	91.10%
Cognitive impairment and mental disorders (%)		
No	7.53%	92.47%
Yes	6.69%	93.31%
Number of chronic medications		
Mean (SD)	14.50 (6.45)	13.32 (6.12)
Median (min-max)	13.00 (2.00-34.00)	12.00 (1.00-39.00)
Coverage Gap		
Yes	7.34%	92.66%
No	7.53%	92.47%
Anticoagulant access (%)		
Yes	7.77%	92.23%
No	7.30%	92.70%

*Abbreviation used: CCI: Charlson Comorbidity Index

Specific Aim 2B: Evaluate the association between warfarin adherence trajectory group membership and the likelihood of hospitalization due to a stoke or bleeding event

Results for the Cox proportional hazard model are presented in table 20. Even though no statistically significant differences were found in the hazard of hospitalization between the adherence groups, there were higher odds of hospitalization among the lower adherence groups (moderate adherence, moderate decline non-adherence and the rapid decline non-adherence), compared to perfect adherence group. Beneficiaries in the "rapid decline" and "moderate non-adherence" groups had 23% and 34% higher odds of being hospitalized in the year after initiating warfarin treatment compared to the "perfect adherence" group, respectively.

Other factors associated with an increased risk of AF-related hospitalization events were gender, Charlson comorbidity index, $CHADS_2$-VASc score, and being in the Medicare coverage gap. In the study population, females had 41% higher risk of being hospitalized compared to males (P-value = 0.03). After adjustment for all covariates, with every unit increase in the Comorbidity Index and the stroke risk score there is a 16% and 17%, respectively, higher odds of being hospitalized in the year after initiating warfarin treatment (P-values <0.0001, <0.005 respectively).

Finally, the proportionality assumption for the Cox proportional model was evaluated by examining the log minus log curve and the Schoenfeld residuals. Based on the graphs and the p-value for the Schoenfeld residuals, the proportionality assumption of the model was satisfied. (See Appendix C, D, and E)

Table 20: Multivariable Cox Proportional Hazard Models of Adherence Trajectories of warfarin and risk of AF-related hospitalization

Characteristics	**AF-related hospitalization**	
	HR (95%CI)	**P-value**
Trajectory group (ref= perfect adherent)	REF	REF
1. Rapid decline group	1.23 (0.80-1.88)	0.35
2. Moderate non-adherence group	1.10 (0.77-1.56)	0.62
3. Rapid decline then increasing adherence group	0.88 (0.48-1.61)	0.68
4. Moderate decline group	1.34 (0.84-2.14)	0.22
5. Slow decline group	0.87 (0.59-1.27)	0.47
Age	0.99 (0.97-1.04)	0.51
Gender (ref= Male)	1.41 (1.03-1.94)	0.03
Race (ref= White)	REF	REF
Black	0.65 (0.33-1.29)	0.22
Others	1.29 (0.75-2.23)	0.36
LIS eligibility	1.26 (0.94-1.69)	0.13
CCI	1.16 (1.08-1.24)	<0.0001
$CHADS_2$-VASc score	1.17 (1.05-1.30)	<0.005
Depression	1.02 (0.75-1.40)	0.89
Cognitive impairment and mental disorders	0.67 (0.41-1.08)	0.10
Number or chronic medications	1.00 (0.97-1.02)	0.77
Coverage gap	0.70 (0.52-0.95)	0.02
AC indicator	0.86 (0.65-1.14)	0.29

*Abbreviation used: LIS eligibility: Low Income Subsidy eligibility, CCI: Charlson Comorbidity Index

4.4 Specific Aim 3

Specific Aim 3A: Estimate the AF-related costs for each adherence trajectory group

Table 21 presents direct AF-related health care costs for Medicare beneficiaries treated with warfarin during the follow-up period stratified by adherence trajectory groups. Because the cost data were predictably extremely right-skewed (Figure 8) and there was a large number of zero values (67%-83%), the cost variables were log-transformed. By taking the log, the cost data become more standardized and demonstrate closer to a normal distribution This transformation leads to more reliable estimates and the variation in the means is reduced. Table 22 presents log direct AF-related health care costs for Medicare beneficiaries treated with warfarin stratified by adherence trajectory groups.

Table 22 presents log direct AF-related health care costs for Medicare beneficiaries treated with warfarin stratified by adherence trajectory groups.

The log of monitoring cost and outpatient cost were found to differ significantly among the trajectory groups (p-value<0.0001, 0.0013, respectively). Mean log monitoring costs were found to be highest among beneficiaries in the "perfect adherence" and "moderate non-adherence" groups, and lowest among the "moderate decline" group. The mean log outpatient cost was significantly higher among the "moderate non-adherence" group compared to other trajectory groups (table 22).

Beneficiaries in the "rapid decline" group were found to have the highest inpatient costs as compare to the other trajectory groups, but the differences were not statistically significant (p-value= 0.33). Similar to mean log outpatient cost, mean log total cost was higher among the "moderate non-adherence" group compared to other trajectory groups, but this difference was

not statistically significant (p-value = 0.23). Among all the trajectory groups, the majority of the costs were attributed to inpatient costs.

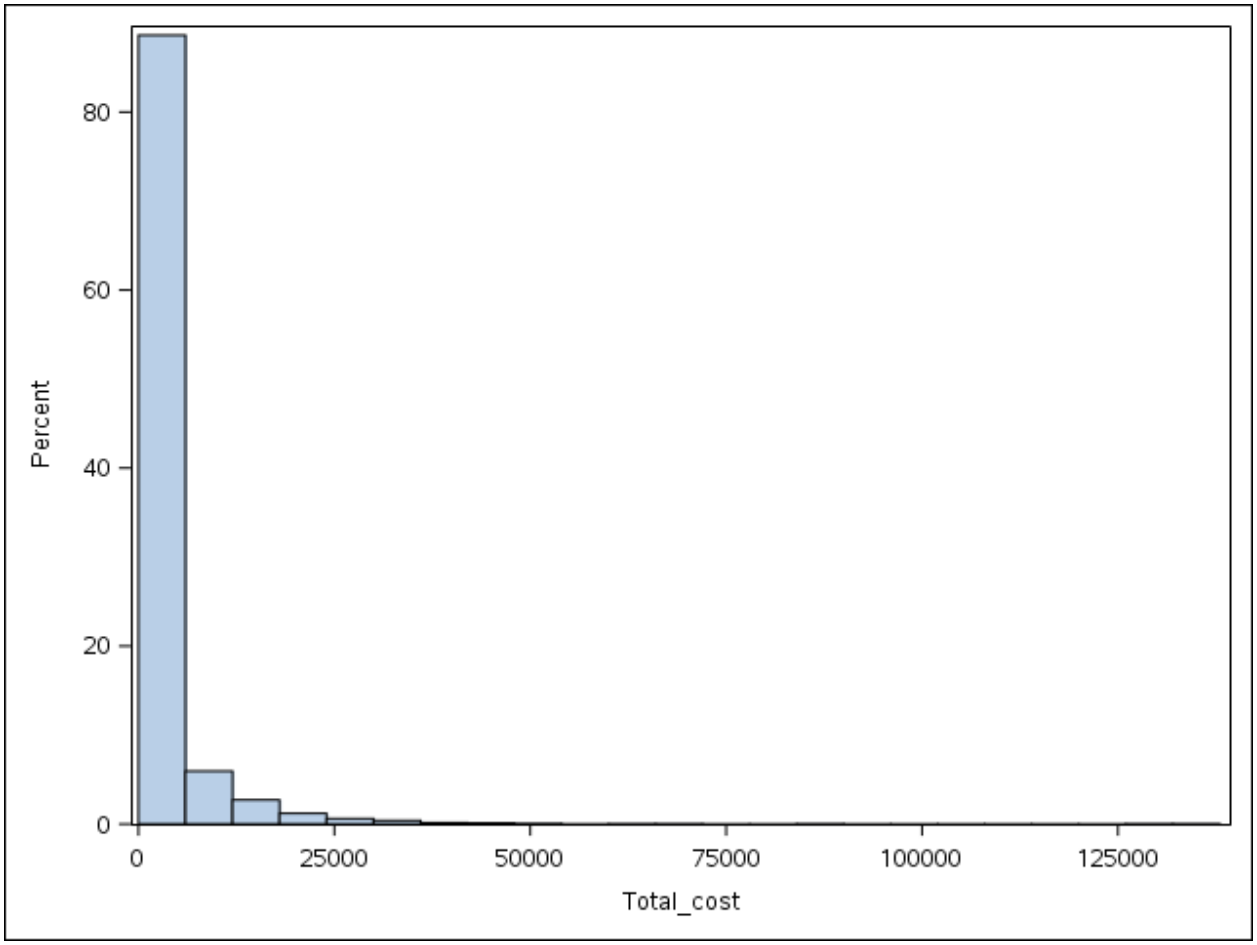

Figure 8: Distribution of total AF-related direct medical cost

Table 21: Mean AF-related costs stratified by trajectory groups

Variable	**1. Rapid decline group,** Mean (SD)	**2. Moderate non-adherence group,** Mean (SD)	**3. Rapid decline then increasing adherence group,** Mean (SD)	**4. Moderate decline group,** Mean (SD)	**5. Slow decline group,** Mean (SD)	**6. perfect adherence group,** Mean (SD)	**P-value**
Inpatient cost	2,756.61 (7,480.18)	2,686.93 (9,069.58)	1,676.31 (5,637.46)	2,400.38 (6,907.50)	2,239.20 (9,511.57)	2,555.00 (9,987.34)	0.6146
Outpatient cost	181.02 (977.28)	349.40 (2741.49)	135.53 (544.48)	102.30 (473.43)	172.83 (1,014.71)	264.18 (1,350.88)	0.1509
INR monitoring cost	7.57 (33.81)	19.14 (67.79)	14.86 (48.63)	4.85 (26.24)	19.98 (77.77)	20.76 (68.44)	**0.0003**
Total cost	2,945.2 (7,609.46)	3,055.47 (9,590.49)	1,826.7 (4,916.03)	2,507.53 (6,983.44)	2,432.01 (7,240.56)	2,839.94 (11,133.63)	0.4178

Table 22: Mean log AF-related log costs stratified by trajectory groups

Variable	**1. Rapid decline group,** Mean (SD)	**2. Moderate non-adherence group,** Mean (SD)	**3. Rapid decline then increasing adherence group,** Mean (SD)	**4. Moderate decline group,** Mean (SD)	**5. Slow decline group,** Mean (SD)	**6. perfect adherence group,** Mean (SD)	**P-value**
Inpatient cost	2.23 (4.64)	2.11 (4.53)	1.57 (4.00)	2.12 (4.52)	1.80 (4.24)	1.89 (4.33)	0.33
Outpatient cost	0.96 (2.61)	1.44 (3.12)	1.19 (2.79)	0.74 (2.33)	1.09 (2.70)	1.40 (3.05)	**0.0013**
INR monitoring cost	0.54 (1.48)	1.02 (2.06)	0.85 (1.93)	0.36 (1.24)	0.91 (1.98)	0.97 (2.07)	**<0.0001**
Total cost	3.02 (4.84)	3.40 (4.85)	2.76 (4.44)	2.70 (4.71)	2.99 (4.61)	3.17 (4.74)	0.23

4.5 Sensitivity analysis

1. Sensitivity Analysis One: Three month follow-up period instead of one year

   In the first sensitivity analysis, the follow-up period was defined as three months instead of one year (as in the main analysis) to capture the short-term impact of warfarin adherence on health outcomes. The number of beneficiaries who had been hospitalized in the first three months after initiating warfarin therapy was 74 (2.3%). Similar to the main analysis, the AF-related hospitalization events were most frequent in the "moderate decline" group (4.2%) and least frequent in the "rapid decline then increasing adherence" group (0.93%) (Table 23). The results for the Cox proportional hazards model for the three months follow up period were similar to the main analysis (Table 24). There was no statistical difference in the hazard ratio for AF-related hospitalization among the adherence groups. Only the comorbidity index and the coverage gap remained significant in this sensitivity analysis.

Table 23: Percentage of beneficiaries who had been hospitalization among adherence trajectories

Characteristics	Hospitalized (2.28%)	Non-hospitalized (97.72%)
Adherence trajectories (%)		
1. Rapid decline group	2.12%	97.88%
2. Moderate non-adherence group	2.16%	97.84%
3. Rapid decline then increasing adherence group	0.93%	99.07%
4. Moderate decline group	4.20%	95.80%
5. Slow decline group	1.71%	98.29%
6.Perfect adherent group	2.73%	97.27%

Table 24: Multivariable Cox proportional hazard models of adherence trajectories of warfarin and risk of AF-related hospitalization in three months follow up period

Characteristics	**AF-related hospitalization**	
	HR (95%CI)	**P-value**
Trajectory group (ref= perfect adherent)	REF	REF
1. Rapid decline group	0.76 (0.34-1.70)	0.50
2. Moderate non-adherence group	0.80 (0.43-1.52)	0.50
3. Rapid decline then increasing adherence group	0.37 (0.09-1.55)	0.17
4. Moderate decline group	1.56 (0.75-3.22)	0.23
5. Slow decline group	0.64 (0.33-1.28)	0.21
Age	0.99 (0.95-1.03)	0.57
Gender (ref= Male)	1.10 (0.64-1.90)	0.73
Race (ref= White)	REF	REF
Black	0.00 (0.00-.)	0.98
Others	1.91 (0.83- 4.38)	0.13
LIS eligibility	1.30 (0.76-2.22)	0.35
CCI	1.16 (1.03-1.32)	0.02
$CHADS_2$-VASc score	1.18 (0.98-1.43)	0.09
Depression	0.73 (0.39-1.35)	0.31
Cognitive impairment and mental disorders	0.69 (0.29-1.64)	0.40
Number or chronic medications	1.01 (0.97-1.06)	0.61
Coverage gap	0.53 (0.30-0.93)	0.03
AC indicator	1.07 (0.65-1.76)	0.78

2. Sensitivity Analysis Two: Identify hospitalization events due to stroke or bleeding in all diagnosis variables

   In the second sensitivity analysis, the AF-related hospitalization events were identified using all 25 diagnosis variables. The number of beneficiaries who had been hospitalized was 994 beneficiaries (30.62%). The AF-related hospitalization events were most frequent in the "moderate non-adherence" group (32.91%) and least frequent in the "rapid decline then increasing adherence" group (28.24%) (Table 25).

   Similar to the main analysis, there was no statistical difference in the hazard ratio for AF-related hospitalization among the adherence groups. The comorbidity index and the stroke risk index remained statistically significant in this sensitivity analysis. (Table 26)

Table 25: Percentage of beneficiaries who had been hospitalization among adherence trajectories

Characteristics	**Hospitalized (30.62%)**	**Non-hospitalized (69.38%)**
Adherence trajectories (%)		
1. Rapid decline group	30.69%	69.31%
2. Moderate non-adherence group	32.91%	67.09%
3. Rapid decline then increasing adherence group	28.24%	71.76%
4. Moderate decline group	29.01%	70.99%
5. Slow decline group	30.79%	69.21%
6.Perfect adherent group	29.42%	70.58%

Table 26: Multivariable Cox proportional hazard model of adherence trajectories of warfarin and risk of AF-related hospitalization-sensitivity analysis

Characteristics	**AF-related hospitalization**	
	HR (95%CI)	**P-value**
Trajectory group (ref= perfect adherent)	REF	REF
1. Rapid decline group	1.07 (0.86-1.33)	0.57
2. Moderate non-adherence group	1.16 (0.97-1.38)	0.10
3. Rapid decline then increasing adherence group	1.01 (0.76-1.34)	0.96
4. Moderate decline group	0.94 (0.72-1.22)	0.63
5. Slow decline group	1.08 (0.90-1.29)	0.43
Age	1.01 (1.00-1.02)	0.18
Gender (ref= Male)	1.07 (0.92-1.24)	0.36
Race (ref= White)	REF	REF
Black	1.03 (0.77-1.38)	0.83
Others	0.98 (0.72-1.34)	0.90
LIS eligibility	1.01 (0.87-1.17)	0.91
CCI	1.25 (1.21-1.29)	<0.0001
$CHADS_2$-VASc score	1.08 (1.03-1.14)	<0.01
Depression	1.14 (0.98-1.33)	0.10
Cognitive impairment and mental disorders	0.95 (0.77-1.18)	0.65
Number or chronic medications	0.99 (0.98-1.00)	0.26
Coverage gap	1.00 (0.86-1.15)	0.94
AC indicator	0.77 (0.67-0.88)	<0.01

Chapter 5: Discussion

This chapter discusses the results of the current study and addresses its strengths and limitations.

5.1 Specific aim 1

The current study applied the Group Based Trajectory Model (GBTM) to identify adherence patterns of warfarin in AF patients during the first year after initiating treatment. The study revealed that six trajectory groups best describe adherence patterns for warfarin therapy among Medicare beneficiaries with AF. Based on the timing of warfarin discontinuation, the identified groups are: 1) Rapid decline non-adherence group (11.5%, mean PDC: 0.22), 2) moderate non-adherence group (24%, mean PDC: 0.56), 3) rapid decline then increasing adherence group (6.8%, mean PDC: 0.85), 4) moderate decline non-adherence group (8.2%, mean PDC: 0.51), 5) slow decline non-adherence group (24.3%, mean PDC: 0.84), and 6) perfect adherence group (25.3%, mean PDC: 0.99).

In our study, GBTM shows an advantage over traditional adherence measures (i.e., PDC). For example, when using an arbitrary cut-point of 80%, beneficiaries in the "6- perfect adherence" group, "5- slow decline non-adherence" group, and "3- rapid decline then increasing adherence" groups would be collapsed into one group and classified as perfectly adherent. In other words, traditional measures such as PDC and MPR, would not differentiate between these three groups, although, the beneficiaries in two groups, "5- slow decline non-adherence", and "3- rapid decline then increasing adherence", would occasionally miss filling their warfarin prescriptions.

Moreover, this study provides some key information regarding patterns of warfarin adherence. First, almost one fourth of elderly AF patients remained perfectly adherent during the first year of warfarin treatment. On the other hand, almost 65% of new users of warfarin

discontinued treatment at some point in the first year, as most of the identified adherence trajectories show decline in their adherence behavior over time.

By running the GBTM, we were able to identify the time when patients are likely to be non-adherent, thereby detecting the best timing for delivery of appropriate interventions. For example, by exploring warfarin adherence trajectories we can recognize a clear separation between the adherence trajectories in the fifth or sixth month after initiating warfarin treatment. This separation between the adherence groups can provide insights for healthcare providers to target patients with adherence interventions. For instance, based on our model, in the six months follow-up visit for AF patients, the healthcare providers could focus on educating patients about the importance of adherence to warfarin, try to address potential adherence barriers, and/or identify any adverse events that may have caused them to discontinue warfarin. This is especially true since a large proportion of AF patients are likely to show decline in their adherence to warfarin after approximately six months of initiating treatment.

To our knowledge, this is the first study to utilize GBTM to identify the distinct patterns of warfarin adherence in an AF Medicare population. In the previously published literature, GBTM has been applied to classify adherence trajectories for different medications including statins, oral hypoglycemic, antipsychotics, antihypertensive, and glaucoma medications. Consistent with this literature, the current study showed that six trajectory groups best describe longitudinal adherence patterns.[32,44,45,48] The proportions of patients presented in our adherent groups were similar to those of previous studies, in which most of the population was classified in the "perfect adherence" group. However, Librero et. al, found that higher proportion of patients (almost 60%) fell in the perfect adherent group than our study. This discrepancy could be related to differences in the study population.[69] Specifically, Librero et.al, studied the

adherence trajectories for patients with Coronary Heart Disease (CHD) and included both the incident and prevalent medication users, while in our study we only included incident users of warfarin. Based on the literature, incident users are likely to be poorly adherent to their medications compared to established patients.[73,74]

Compared to previous studies, there are some similarities in the identified patterns of medication adherence. For example, "rapid decline non-adherence", "moderate decline non-adherence", and "perfect adherence" patterns were also identified in the previous studies.[32,34,44,47,48] In contrast, there were some differences in the intermediate trajectory groups. Only Lo-Ciganic et. al, and Modi et. al, have identified similar trajectories of "moderate non-adherence" and "slow decline non-adherence" groups that were presented by our model.[39,47] This divergent finding may be due to many factors related to differences in disease characteristics, study population, or study design.

In this study, we identified main characteristics and factors associated with the trajectory groups. The factors that were found to be significantly associated with poor or intermediate adherence patterns were race, CCI, $CHADS_2$-VASc score, LIS, and being in Medicare coverage gap. Compared to white patients, Hispanic, Asian, and North American Native patients were more likely to have a moderate decline in their warfarin adherence in the first year of therapy, which is consistent with other studies.[41,44] Also, our study reveals that patients in the "moderate" and "rapid decline non-adherence" groups had significantly higher comorbidities than patients in the "perfect adherence" group. Several studies have also concluded that comorbidity is associated highly with poor adherence.[2,48]

The characteristics identified in this study may guide healthcare providers and clinicians to target patients who are more likely to have poor adherence to warfarin in the year following

initiation. For example, for patients who are at higher risk of discontinuing warfarin, such as Hispanic, Asian, and North American Native, the clinicians may need to educate them more about the importance of adherence and facilitate their access to healthcare resources and system.

Moreover, by knowing characteristics of patients in each adherence trajectory we can identify the best timing to deliver an intervention. For example, if the patient is likely to be in the rapid decline group, as are patients with higher comorbidity, then clinicians may need to educate those patients at the beginning of the warfarin treatment and try to identify potential barriers of non-adherence such as cost, access to the healthcare system, or difficulty in managing disease conditions.

Furthermore, some of these predictive factors are considered modifiable and can be used to tailor appropriate interventions in order to improve patient adherence. For instance, in our study, we found that patients who were not eligible for the LIS program were significantly more likely to be in the rapidly and moderately declining groups compared to the perfect adherence group. The LIS variable was used in this study as a proxy for patient income; however, LIS does not reflect the exact socioeconomic status of the beneficiary. A Medicare beneficiary may not be eligible for the LIS program but may still have a low income (i.e., income that does not reach the Medicare threshold for LIS eligibility). This finding suggests that, although a patient's income may not be a modifiable factor, access to the healthcare system can be modifiable. Healthcare providers or payers may need to improve regulation to facilitate access to the healthcare system for the elderly population in order to enhance their medication adherence behavior and overall health outcomes.

5.2 Specific aim 2 and 3

In the current study, the effect of warfarin adherence trajectories on AF-related hospitalization was assessed. We found that the risk of hospitalization was higher for the beneficiaries in lower adherence groups compared to beneficiaries in the perfect adherence trajectory. Patients with declining adherence and constantly moderate adherence had higher odds of being hospitalized in the year following warfarin initiation compared to patients who were well adherent to warfarin therapy.

In previous studies, adherence trajectories have been shown to have a significant association with clinical outcomes for patients treated with statins, oral hypoglycemic medications, anti-epileptics, endocrine therapy, and antipsychotics. In contrast, in our study we did not observe any significant association between warfarin trajectory groups and AF-related hospitalization.[38,44,45,47-49] A number of reasons can explain this finding. First, this lack of an association may be due to the lower number of hospitalization events captured in our data compared to previous studies. Lo-Ciganic et. al. reported that the percentage of diabetes-related hospitalizations/ED visits among the trajectory groups ranged between 14% to 19.5%, a range sufficient to permit detection of significant differences between the trajectory groups.[47] Conversely, the percentage of hospitalization events in our adherence groups ranges between 6-9%. Hence, due to the small proportion of beneficiaries that had experienced hospitalization among the groups, we were not able to detect any significant differences. However, in the sensitivity analyses we redefined hospitalization by using all the diagnosis variables, and the number of hospitalization events increased, but we were still unable to observe a significant difference in the hospitalization risk among trajectory groups. Second, the clinical outcome measures in previous studies differ from those used in the current study. In our study we only

looked at the risk of AF-related hospitalization. However, in other studies, the clinical outcomes included ED visits with hospitalization events, and death. A study by MacEwan et. al, measured the impact of trajectory group membership on psychiatrics ED visits separately from psychiatrics hospitalization events and found significant differences in ED visits between trajectory groups. However, the authors did not report any significant association with hospitalization events between the trajectory groups.[48] The third reason can be related to statistical issues. Each parameter estimate has a standard error, which measures the variation of the sample parameter from the population value. In the current study, the standard errors of the parameter estimates for the hazard ratio, especially for the smaller size trajectory groups (group 3 and 4) were very large and caused the confidence intervals to be wide. Hence, the hazard ratios for hospitalization were not statistically significant. In other words, when we classified 3,246 beneficiaries into six trajectory groups and used Cox proportional hazards modelling to compare the risk of hospitalization among the groups, the variation associated with the parameter estimates of the trajectory groups was found to be very high.

Although we did not observe a significant association between warfarin adherence trajectories and AF-related hospitalization, we were still able to recognize the trend of hospitalization risk between the trajectory groups. Based on the results, we can see that the trajectory groups with declining adherence had a higher risk of being hospitalized in the year following warfarin initiating compared to adherent groups, which is consistent with other studies.[44,45,47]

Moreover, in this study we were able to quantify AF-related cost associated with each trajectory group. To our knowledge, no previous study has assessed the economic impact of adherence trajectory groups and compared between them. We found that there were significant

differences between the monitoring costs and the outpatient costs among the adherence trajectories. The beneficiaries in the "perfect adherence trajectory" had the highest INR monitoring cost, which reflect the high number of anticoagulant clinic visits. Conversely, the beneficiaries in the "rapidly decline" and "moderate decline" trajectories had the lowest INR monitoring cost, and lowest number of anticoagulant clinic visits. This finding emphasizes the important role of anticoagulant clinic access in improving patients' adherence to warfarin. This also is consistent with prior research.[75]

Although were not able to detect significant differences in the inpatient costs and the overall direct medical costs among the trajectory groups, we were able to evaluate the trend in the AF-related cost among different trajectory groups. Accordingly, we found that average overall AF-related costs were higher for the beneficiaries with constantly moderate adherence or rapidly declining adherence in their first year of warfarin treatment compared to beneficiaries in the perfect adherence group.

These findings provide insight for healthcare providers and payers on trajectory groups that are associated with higher cost and hence require more attention to improve their adherence and promote lower overall healthcare costs.

5.3 Strengths and limitations

To the best of our knowledge, this is the first study that has used GBTM to identify adherence patterns for warfarin patients. The strength of our study is the use of the GBTM approach in identifying the distinct adherence trajectories of warfarin in elderly AF patients. Unlike traditional adherence measures, the GBTM accounts for the dynamic nature of the adherence behavior over time, and can thus distinguish between different adherence patterns. In the current study, we were able to identify six adherence trajectories for warfarin, which the PDC and other traditional adherence measures cannot distinguish. For example, with the application of a dichotomous PDC measure, patients in the "rapid decline non-adherence", "moderate non-adherence" and "moderate decline non-adherence" groups will all be classified as non-adherent although each group has a clearly different trajectory over time. Furthermore, we were able to identify the predictive factors associated with each adherence trajectory. This can guide clinicians and healthcare providers in identifying patients that are more likely to have poor adherence to warfarin and target them with appropriate interventions. For example, a patient who has a sustained moderate adherence over a long period of time, similar to patients in the "moderate non-adherence" group, would benefit from a different intervention than a patient who has decline in his adherence over time, such as patients in "moderate decline non-adherence" group.

Moreover, in our study we used Medicare data, which is nationally representative and is a good source of health information, especially for the elderly population. Further, recall bias was reduced in our study as administrative data were used for warfarin refill information instead of

self-reported surveys.

On the other hand, the study has several limitations. First, the selection of study population depends on the accuracy of the reported ICD-9 codes in the Medicare dataset, which may be subject to miscoding and misclassification, and hence could lead to inaccurate, though conservative, results. We tried to address this limitation by requiring AF patients to have at least one inpatient claim or two outpatient claims for AF in any of the 25 diagnosis variables in the Medicare files. Second, we measured patients' monthly adherence based on the refill data, a method that may not capture actual consumption of warfarin. However, several studies have shown a high correlation between refill data and patient consumption.[76,77] Third, due to limitations related to the data source, we were not able to examine the impact of some important predictive factors, such as: social support, marital status, educational level, patients' belief, and medication-related adverse events. Also, Medicare data do not report the INR values and length of time within the therapeutic range (TTR), which are important factors when assessing the impact of warfarin therapy. The TTR reflect the quality of warfarin treatment, and hence can drive adherence behavior. The TTR can play big role in explain warfarin adherence trajectories and help in exploring reasons behind such trajectories. Moreover, we did not have information regarding beneficiary income level, which could have influenced adherence trajectories. However, we adjusted for this limitation, by using LIS eligibility as a proxy for low income, as recommended by other investigators.[44] Fourth, we were not able to capture prescriptions dispensed outside of Medicare data (e.g., samples from physicians or medications purchased out of pocket), especially as warfarin is available as a $4 generic and can be affordable. Fifth, as warfarin is considered a critical drug (i.e., requiring regular dosage adjustment based on the INR level, correlated with many drug/food interaction, and associated with higher risk of

bleeding/stroke), the patient is likely to discontinue the treatment due to adverse events. For example, if the patient's adherence level was initially good and then dropped, this could be related to unmeasured adverse events associated with warfarin use. However, in our study, we were unable to distinguish between treatment discontinuation and non-adherence. Sixth, due to the limited funding available for this study, we were only able to capture institutional resource utilization and associated costs. That is, we were not able to include the carrier file claims (non-institutional- physician office-based outpatient claims). Therefore, the resources utilized, including access to anticoagulant clinics and associated costs were only reflective of the institutional perspective (i.e., hospital outpatient claims).

Furthermore, some of the limitations of this study were related to the study's design. For example, it is likely that non-adherence behavior had an impact shortly after it occurred. However, due to the time interval between the adherence measuring period and the outcome period (one year follow up period) in the current study, we cannot affirm that AF-related hospitalization is caused by adherence trajectories. However, we tried to address this limitation in the sensitivity analysis, by testing a temporally closer three-months follow-up period, and the results were essentially unchanged from the main analysis. Moreover, we did not account for the hospitalization days when measuring monthly PDC. The hospitalization events occurring in the identification period may have an impact on adherence behaviors, and hence can paly role in describing adherence trajectories.

An important point to consider with the GBTM, is that there might be more than the six identified warfarin adherence trajectories in the "real world". However, as in the case with any statistical approach, the goal of the GBTM is provide simplification of the real-world situation in order to better understand the different adherence trajectories.

Finally, our study was restricted to the elderly Medicare population having no HMO coverage, so the results cannot be generalized to all AF patients treated with warfarin. Further research is needed to identify adherence trajectories in a wider, more generalizable population treated with warfarin.

5.4 Conclusion and future directions

GBTM is a novel methodological approach that can be used to identify different patterns of warfarin adherence in elderly AF patients. In our study, we were able to identify six distinct adherence trajectories for new warfarin users that traditional adherence measures would not have been able to detect. The application of the GBTM enabled us to visualize and better understand changes in adherence behavior over time.

In this study, we also identified several significant predictors associated with each trajectory group. These identified characteristics can enable healthcare providers to detect patients who are more likely to become non-adherent to warfarin soon after treatment initiation and determine the time when non-adherence may occur. Moreover, we evaluated the impact of each adherence trajectory on subsequent AF-hospitalization and calculated associated costs for each trajectory group. Hence, the findings of our study can help healthcare providers and payers to target those groups of patients who might be associated with higher resource utilization and healthcare costs.

The usefulness of applying GBTM in clinical practice is defined by its ability to identify patients who are more likely to be in the poor or intermediate adherence groups, allowing providers and health systems to target them with the suitable adherence interventions. Our findings suggest that patients in the poor adherence groups may express different patterns of adherence over time. This may indicate, hence, that such patients could benefit from different interventions at different time points. Additionally, GBTM allows us to determine the timing of onset of non-adherence, helping to identify the optimal times to deliver an intervention and prevent further decline in adherence. For example, for patients who are likely to have rapid decline in their adherence, it is better to target them with a suitable intervention at the beginning

of treatment; while patients who might have slow decline in their adherence can be targeted with a reminder intervention at later time (e.g., after six months). Overall, early identification of patients at higher risk of non–adherence, and customization of suitable interventions for each trajectory group of patients can help to better allocate resources and ultimately to improve patient adherence and outcomes.

Further research is needed to evaluate the most effective adherence intervention for each trajectory group. Moreover, there is increasing interest in the pharmacogenetics of warfarin therapy in clinical practice. The metabolism of warfarin and its therapeutic effectiveness are influenced by genetic variations. Pharmacogenetics can guide in estimating the appropriate dose of warfarin. Hence, future research should examine the impact of pharmacogenetics effects on warfarin adherence trajectories. Future research should also examine patterns of warfarin adherence for longer periods of time (e.g., a five year follow up measuring period). Given that warfarin is considered a life-long treatment for most AF patients, it would be of interest to examine the long-term adherence patterns of warfarin patients. Moreover, further research is needed to identify adherence patterns for warfarin in different populations and to compare between these.

In conclusion, the results of this study illuminate important changes in adherence behavior for the new warfarin users. GBTM is considered a promising methodological approach that can be applied to the study of longitudinal adherence data and account for the dynamic nature of adherence behavior in a better way than traditional adherence measures.

List of References

List of References

1. World Health Organization. Adherence to long-term therapies: Evidence for action. 2003.

2. Brown TM, Siu K, Walker D, Pladevall-Vila M, Sander S, Mordin M. Development of a conceptual model of adherence to oral anticoagulants to reduce risk of stroke in patients with atrial fibrillation. *J Manag Care Pharm*. 2012;18(5):351-362. doi: 2012(18)5: 351-362 [pii].

3. Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: Results from a population-based study. *Stroke*. 2005;36(6):1115-1119. doi: 01.STR.0000166053.83476.4a [pii].

4. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: A report from the american heart association. *Circulation*. 2014;129(3):e28-e292. doi: 10.1161/01.cir.0000441139.02102.80 [doi].

5. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the american college of cardiology/american heart association task force on practice guidelines and the heart rhythm society. *J Am Coll Cardiol*. 2014;64(21):e1-76. doi: 10.1016/j.jacc.2014.03.022 [doi].

6. Sanoski CA. Current approaches to anticoagulation for reducing risk of atrial fibrillation-related stroke. *J Pharm Pract*. 2013;26(3):204-213. doi: 10.1177/0897190012452309 [doi].

7. http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm#healthcare. Updated 2014. Accessed jan\22, 2015.

8. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857-867. doi: 146/12/857 [pii].

9. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151. doi: 10.1056/NEJMoa0905561 [doi].

10. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. doi: 10.1056/NEJMoa1009638 [doi].

11. Goette A, Merino JL, Ezekowitz MD, et al. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): A randomised, open-label, phase 3b trial. *Lancet*. 2016;388(10055):1995-2003. doi: S0140-6736(16)31474-X [pii].

12. Lopes RD, Al-Khatib SM, Wallentin L, et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: A secondary analysis of a randomised controlled trial. *Lancet*. 2012;380(9855):1749-1758. doi: 10.1016/S0140-6736(12)60986-6 [doi].

13. Hanley CM, Kowey PR. Are the novel anticoagulants better than warfarin for patients with atrial fibrillation? *J Thorac Dis*. 2015;7(2):165-171. doi: 10.3978/j.issn.2072-1439.2015.01.23 [doi].

14. Huang C, Siu M, Vu L, Wong S, Shin J. Factors influencing doctors' selection of dabigatran in non-valvular atrial fibrillation. *J Eval Clin Pract*. 2013;19(5):938-943. doi: 10.1111/j.1365-2753.2012.01886.x [doi].

15. Nutescu EA. Anticoagulation management services: Entering a new era. *Pharmacotherapy*. 2010;30(4):327-329. doi: 10.1592/phco.30.4.327 [doi].

16. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. 2003;289(9):1107-1116. doi: joc21714 [pii].

17. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older americans. *N Engl J Med*. 2011;365(21):2002-2012. doi: 10.1056/NEJMsa1103053 [doi].

18. Kimmel SE, Chen Z, Price M, et al. The influence of patient adherence on anticoagulation control with warfarin: Results from the international normalized ratio adherence and genetics (IN-RANGE) study. *Arch Intern Med*. 2007;167(3):229-235. doi: 167/3/229 [pii].

19. Davis NJ, Billett HH, Cohen HW, Arnsten JH. Impact of adherence, knowledge, and quality of life on anticoagulation control. *Ann Pharmacother*. 2005;39(4):632-636. doi: aph.1E464 [pii].

20. Socha T. UNDERUTILIZATION OF WARFARIN AND ASSOCIATED COSTS. 2012.

21. Franklin JM, Shrank WH, Pakes J, et al. Group-based trajectory models: A new approach to classifying and predicting long-term medication adherence. *Med Care*. 2013;51(9):789-796. doi: 10.1097/MLR.0b013e3182984c1f [doi].

22. Franklin JM, Krumme AA, Tong AY, et al. Association between trajectories of statin adherence and subsequent cardiovascular events. *Pharmacoepidemiol Drug Saf*. 2015;24(10):1105-1113. doi: 10.1002/pds.3787 [doi].

23. Lo-Ciganic WH, Donohue JM, Jones BL, et al. Trajectories of diabetes medication adherence and hospitalization risk: A retrospective cohort study in a large state medicaid program. *J Gen Intern Med*. 2016;31(9):1052-1060. doi: 10.1007/s11606-016-3747-6 [doi].

24. Nagin DS. Group-based trajectory modeling: An overview. *Ann Nutr Metab*. 2014;65(2-3):205-210. doi: 10.1159/000360229 [doi].

25. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol*. 2010;6:109-138. doi: 10.1146/annurev.clinpsy.121208.131413 [doi].

26. Muthen B, Muthen LK. Integrating person-centered and variable-centered analyses: Growth mixture modeling with latent trajectory classes. *Alcohol Clin Exp Res*. 2000;24(6):882-891.

27. Librero J, Sanfelix-Gimeno G, Peiro S. Medication adherence patterns after hospitalization for coronary heart disease. A population-based study using electronic records and group-based trajectory models. *PLoS One*. 2016;11(8):e0161381. doi: 10.1371/journal.pone.0161381 [doi].

28. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: A report of the american college of cardiology/american heart association task force on practice guidelines and the european society of cardiology committee for practice guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation). *Eur Heart J*. 2006;27(16):1979-2030. doi: 27/16/1979 [pii].

29. Desai NR, Krumme AA, Schneeweiss S, et al. Patterns of initiation of oral anticoagulants in patients with atrial fibrillation- quality and cost implications. *Am J Med*. 2014;127(11):1075-82.e1. doi: 10.1016/j.amjmed.2014.05.013 [doi].

30. National action plan for adverse drug prevention: Anticoagulants. https://health.gov/hcq/pdfs/ADE-Action-Plan-Anticoagulants.pdf. Updated 2016. Accessed Nov/15, 2016.

31. Obamiro KO, Chalmers L, Bereznicki LR. A summary of the literature evaluating adherence and persistence with oral anticoagulants in atrial fibrillation. *Am J Cardiovasc Drugs*. 2016;16(5):349-363. doi: 10.1007/s40256-016-0171-6 [doi].

32. Aarnio E, Martikainen J, Winn AN, Huupponen R, Vahtera J, Korhonen MJ. Socioeconomic inequalities in statin adherence under universal coverage: Does sex matter? *Circ Cardiovasc Qual Outcomes*. 2016. doi: CIRCOUTCOMES.116.002728 [pii].

33. Librero J, Sanfelix-Gimeno G, Peiro S. Medication adherence patterns after hospitalization for coronary heart disease. A population-based study using electronic records and group-based trajectory models. *PLoS One*. 2016;11(8):e0161381. doi: 10.1371/journal.pone.0161381 [doi].

34. Mardby AC, Schioler L, Sundell KA, Bjerkeli P, Lesen E, Jonsson AK. Adherence to antidepressants among women and men described with trajectory models: A swedish longitudinal study. *Eur J Clin Pharmacol*. 2016;72(11):1381-1389. doi: 10.1007/s00228-016-2106-1 [doi].

35. Chen CC, Cheng SH. Continuity of care and changes in medication adherence among patients with newly diagnosed diabetes. *Am J Manag Care*. 2016;22(2):136-142. doi: 86530 [pii].

36. Glass TR, Battegay M, Cavassini M, et al. Longitudinal analysis of patterns and predictors of changes in self-reported adherence to antiretroviral therapy: Swiss HIV cohort study. *J Acquir Immune Defic Syndr*. 2010;54(2):197-203. doi: 10.1097/QAI.0b013e3181ca48bf [doi].

37. Dillon P, Stewart D, Smith SM, Gallagher P, Cousins G. Group-based trajectory models: Assessing adherence to antihypertensive medication in older adults in a community pharmacy setting. *Clin Pharmacol Ther*. 2017. doi: 10.1002/cpt.865 [doi].

38. Modi AC, Wu YP, Rausch JR, Peugh JL, Glauser TA. Antiepileptic drug nonadherence predicts pediatric epilepsy seizure outcomes. *Neurology*. 2014;83(22):2085-2090. doi: 10.1212/WNL.0000000000001023 [doi].

39. Modi AC, Rausch JR, Glauser TA. Patterns of nonadherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. *JAMA*. 2011;305(16):1669-1676. doi: 10.1001/jama.2011.506 [doi].

40. Greenley RN, Karazsia B, Schurman JV, et al. Trajectories of oral medication adherence in youth with inflammatory bowel disease. *Health Psychol*. 2015;34(5):514-521. doi: 10.1037/hea0000149 [doi].

41. Franklin JM, Krumme AA, Shrank WH, Matlin OS, Brennan TA, Choudhry NK. Predicting adherence trajectory using initial patterns of medication filling. *Am J Manag Care*. 2015;21(9):e537-44. doi: 86318 [pii].

42. Juarez DT, Williams AE, Chen C, et al. Factors affecting medication adherence trajectories for patients with heart failure. *Am J Manag Care*. 2015;21(3):e197-205. doi: 86047 [pii].

43. Franklin JM, Shrank WH, Pakes J, et al. Group-based trajectory models: A new approach to classifying and predicting long-term medication adherence. *Med Care*. 2013;51(9):789-796. doi: 10.1097/MLR.0b013e3182984c1f [doi].

44. Hargrove JL, Pate V, Casteel CH, et al. Antihypertensive adherence trajectories among older adults in the first year after initiation of therapy. *Am J Hypertens*. 2017;30(10):1015-1023. doi: 10.1093/ajh/hpx086 [doi].

45. Franklin JM, Krumme AA, Tong AY, et al. Association between trajectories of statin adherence and subsequent cardiovascular events. *Pharmacoepidemiol Drug Saf*. 2015;24(10):1105-1113. doi: 10.1002/pds.3787 [doi].

46. Franklin JM, Shrank WH, Pakes J, et al. Group-based trajectory models: A new approach to classifying and predicting long-term medication adherence. *Med Care*. 2013;51(9):789-796. doi: 10.1097/MLR.0b013e3182984c1f [doi].

47. Lo-Ciganic WH, Donohue JM, Jones BL, et al. Trajectories of diabetes medication adherence and hospitalization risk: A retrospective cohort study in a large state medicaid program. *J Gen Intern Med*. 2016;31(9):1052-1060. doi: 10.1007/s11606-016-3747-6 [doi].

48. MacEwan JP, Forma FM, Shafrin J, Hatch A, Lakdawalla DN, Lindenmayer JP. Patterns of adherence to oral atypical antipsychotics among patients diagnosed with schizophrenia. *J Manag Care Spec Pharm*. 2016;22(11):1349-1361. doi: 10.18553/jmcp.2016.22.11.1349 [doi].

49. Newman-Casey PA, Blachley T, Lee PP, Heisler M, Farris KB, Stein JD. Patterns of glaucoma medication adherence over four years of follow-up. *Ophthalmology*. 2015;122(10):2010-2021. doi: 10.1016/j.ophtha.2015.06.039 [doi].

50. Li Y, Zhou H, Cai B, et al. Group-based trajectory modeling to assess adherence to biologics among patients with psoriasis. *Clinicoecon Outcomes Res*. 2014;6:197-208. doi: 10.2147/CEOR.S59339 [doi].

51. Murray MD, Morrow DG, Weiner M, et al. A conceptual framework to study medication adherence in older adults. *Am J Geriatr Pharmacother*. 2004;2(1):36-43. doi: S1543594604900050 [pii].

52. Gueorguieva R, Wu R, Krystal JH, Donovan D, O'Malley SS. Temporal patterns of adherence to medications and behavioral treatment and their relationship to patient characteristics and treatment response. *Addict Behav*. 2013;38(5):2119-2127. doi: 10.1016/j.addbeh.2013.01.024 [doi].

53. Winn AN, Dusetzina SB. The association between trajectories of endocrine therapy adherence and mortality among women with breast cancer. *Pharmacoepidemiol Drug Saf*. 2016;25(8):953-959. doi: 10.1002/pds.4012 [doi].

54. Nagin DS. Group-based trajectory modeling: An overview. *Ann Nutr Metab*. 2014;65(2-3):205-210. doi: 10.1159/000360229 [doi].

55. Josh Unni E. *Development of models to predict medication non-adherence based on a new typology* [Phd]. University of Iowa; 2008.

56. Carolyn B. ResearcConceptualizing researchh method for pharmaceutical practice and policy. In: Aparasu R, ed. *Research method for pharmaceutical practice and policy.* Pharmaceutical Press; 2011:17-36.

57. Brown TM, Siu K, Walker D, Pladevall-Vila M, Sander S, Mordin M. Development of a conceptual model of adherence to oral anticoagulants to reduce risk of stroke in patients with atrial fibrillation. *J Manag Care Pharm*. 2012;18(5):351-362. doi: 2012(18)5: 351-362 [pii].

58. Chronic condition data WarehouseEstimate study size. https://www.ccwdata.org/web/guest/pricing/estimate-study-size. Updated 2018. Accessed Jan/25, 2018.

59. Chronic Conditions Data Warehouse. CCW technical guidance: Options for determining which CMS medicare beneficiaries are dually eligible for medicare and medicaid benefits . . 2015.

60. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987;40(5):373-383.

61. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619. doi: 0895-4356(92)90133-8 [pii].

62. DiMatteo MR. Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. *Med Care*. 2004;42(3):200-209. doi: 00005650-200403000-00002 [pii].

63. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487-497. doi: 353/5/487 [pii].

64. Shaya FT, Du D, Gbarayor CM, Frech-Tamas F, Lau H, Weir MR. Predictors of compliance with antihypertensive therapy in a high-risk medicaid population. *J Natl Med Assoc*. 2009;101(1):34-39. doi: S0027-9684(15)30808-7 [pii].

65. Donnan PT, MacDonald TM, Morris AD. Adherence to prescribed oral hypoglycaemic medication in a population of patients with type 2 diabetes: A retrospective cohort study. *Diabet Med*. 2002;19(4):279-284. doi: 689 [pii].

66. Zhang Y, Lave JR, Donohue JM, Fischer MA, Chernew ME, Newhouse JP. The impact of medicare part D on medication adherence among older adults enrolled in medicare-advantage products. *Med Care*. 2010;48(5):409-417. doi: 10.1097/MLR.0b013e3181d68978 [doi].

67. Zhao B ea. Estimating patient adherence to medication with electronic health records data and pharmacy claims combined. 2013;167-2013.

68. https://www.andrew.cmu.edu/user/bjones/. Updated 2017. Accessed 03/29, 2018.

69. Librero J, Sanfelix-Gimeno G, Peiro S. Medication adherence patterns after hospitalization for coronary heart disease. A population-based study using electronic records and group-based trajectory models. *PLoS One*. 2016;11(8):e0161381. doi: 10.1371/journal.pone.0161381 [doi].

70. Arrandale V ea. How to use SAS® proc traj and SAS® proc glimmix in Respiratory epidemiology. 2006.

71. Andruff H ea. Latent class growth modelling: A tutorial *Tutorials in Quantitative Methods for Psychology*. 2009;Vol. 5(1):11-24.

72. https://ycharts.com/indicators/us_health_care_inflation_rate. Updated 2018. Accessed 05/20, 2018.

73. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. *CMAJ*. 1999;160(1):31-37.

74. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag*. 2008;4(1):269-286.

75. Chamberlain MA, Sageser NA, Ruiz D. Comparison of anticoagulation clinic patient outcomes with outcomes from traditional care in a family medicine clinic. *J Am Board Fam Pract*. 2001;14(1):16-21.

76. Grymonpre R, Cheang M, Fraser M, Metge C, Sitar DS. Validity of a prescription claims database to estimate medication adherence in older persons. *Med Care*. 2006;44(5):471-477. doi: 10.1097/01.mlr.0000207817.32496.cb [doi].

77. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: Methods, validity, and applications. *J Clin Epidemiol*. 1997;50(1):105-116. doi: S0895435696002685 [pii].

Appendix A

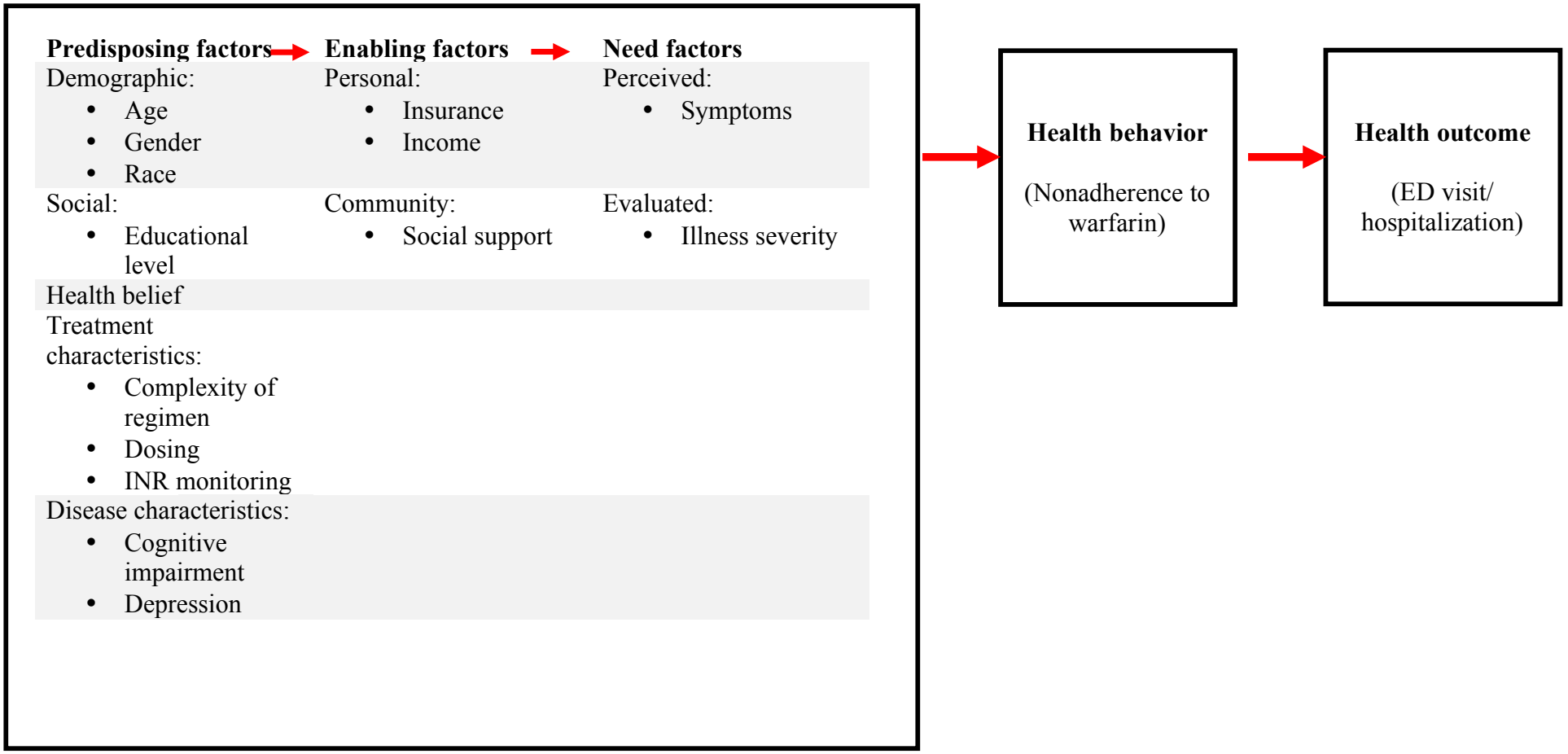

Figure A.1: Conceptual framework based on Andersen Behavioral model (ABM)

Appendix B

Table B.1: Percent change in Consumer price index (CPI) from 2009-2018

	2010	2011	2012	2013	2014	2015	2016	2017	2018
Medical care services	3.62%	2.87%	3.43%	2.75%	2.42%	2.90%	2.98%	2.95%	2.21%

Appendix C

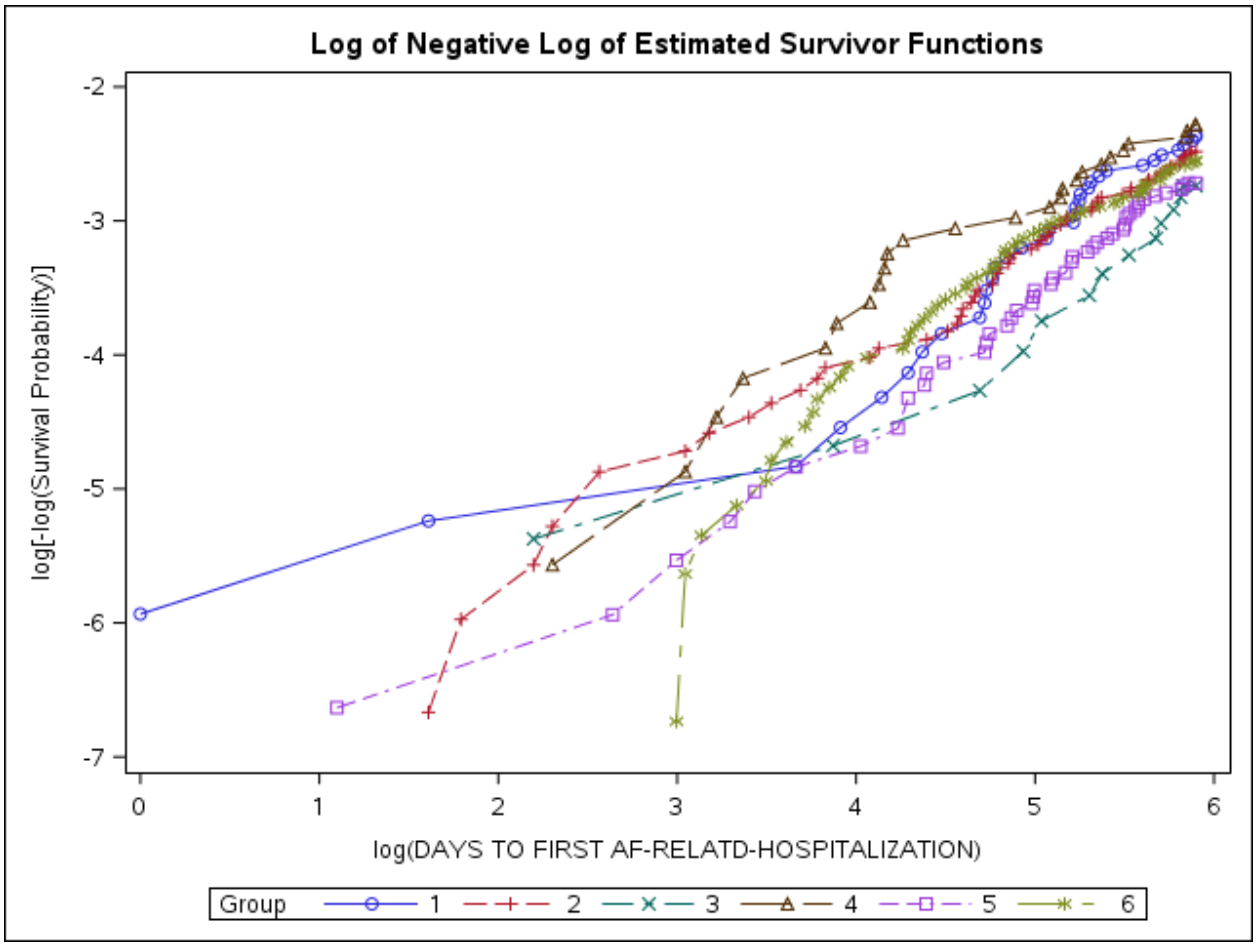

Figure C.1: Log minus log curve of the six trajectory groups and time to first hospitalization

Appendix D

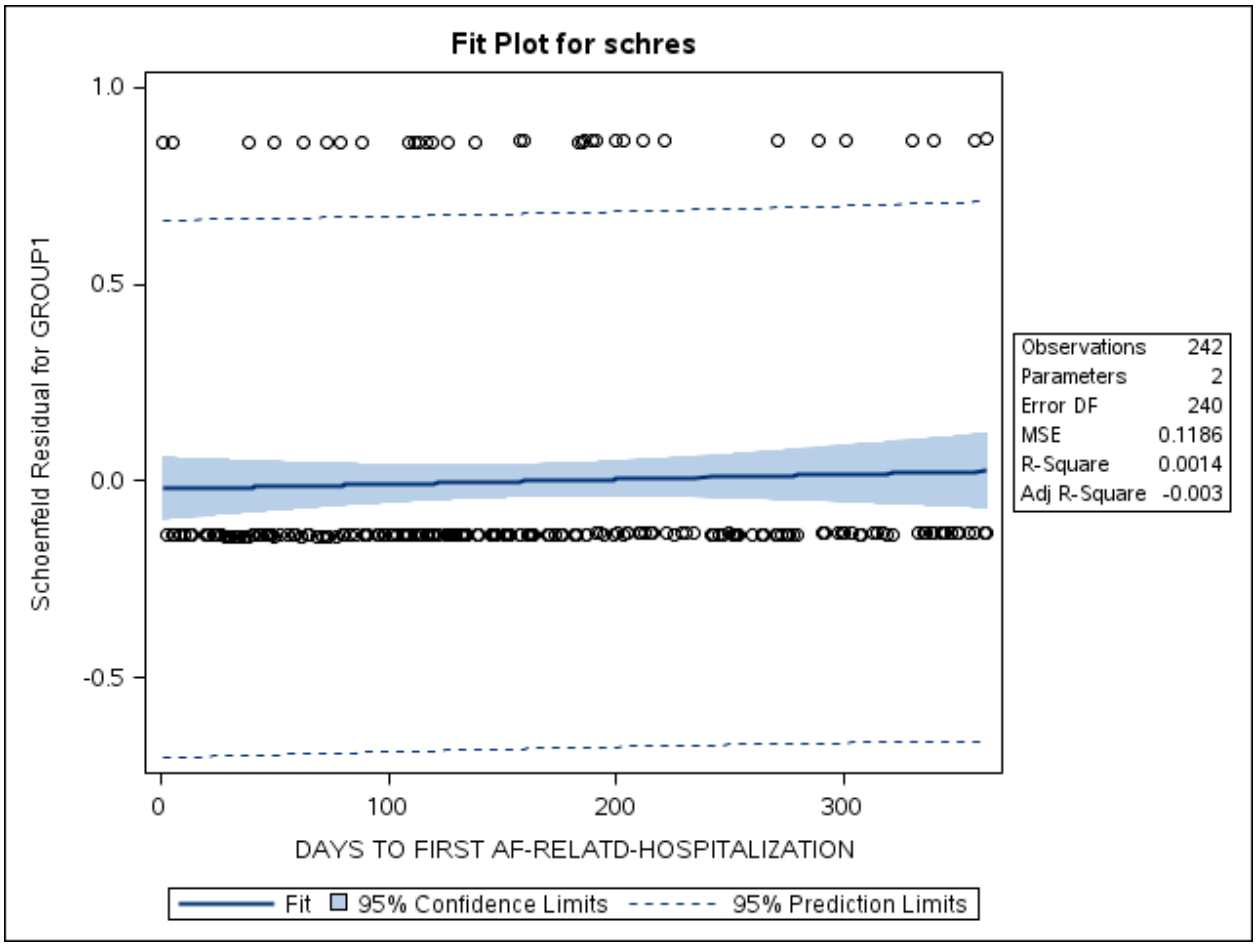

Figure D.1: Smoothed hazard ratio estimates using Schoenfeld residuals (Schres)

Appendix E

Table E.1: Smoothed hazard ratio estimates using Schoenfeld residuals

Variable	Parameter estimate	Standard error	P-value
Intercept	-0.02	0.04	0.63
Time to first hospitalization	0.0001	0.0002	0.57