ANTIHYPERTENSIVE ADHERENCE TRAJECTORIES AND THE ASSOCIATION BETWEEN ANTIHYPERTENSIVE MEDICATIONS AND FRACTURES AMONG OLDER ADULTS INITIATING THERAPY

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ABSTRACT

Jennifer Lee Jones: Antihypertensives Adherence Trajectories and the Association Between Antihypertensive Medications and Fractures Among Older Adults Initiating Therapy
(Under the direction of Til Stürmer)

Antihypertensive medications reduce the risk of cardiovascular diseases among hypertensive patients. Yet, few older adults are adherent to their antihypertensive therapy. Failure to remain adherent can lead to increased risk of cardiovascular disease, hospitalizations, and mortality. Prior studies have relied on adherence measures that fail to distinguish between medication adherence and persistence.

Furthermore, research suggests that antihypertensives are associated with fractures among older adults. However, prior research has found inconsistent results regarding the strength and direction of the association between antihypertensives and fractures. Few studies have examined the initial increased risk of fractures associated with starting antihypertensive therapy, and how the association between antihypertensive and fractures may change over time.

We used a 20% random sample of 2007-2013 Medicare Fee-For-Service data to identify beneficiaries initiating antihypertensive therapy between 2008 and 2011. Our primary objectives were: 1) examine whether group based trajectory models (GBTMs) could be used to identify antihypertensive adherence trajectories among older adults initiating therapy, and 2) examine the association between antihypertensive initiation and fractures according to antihypertensive class, duration of use, and fracture type.

In our first aim we found that antihypertensive adherence trajectories vary among Medicare beneficiaries and that GBTMs are an effective tool for capturing antihypertensive adherence. We identified six adherence trajectories ranging from beneficiaries who were fully adherent to beneficiaries who never returned after their first prescription. Compared to traditional adherence measures, GBTMs were better at identifying beneficiaries with fluctuating patterns of use. The strongest predictors of non-

adherence included initiation with a single antihypertensive class, non-White race, and no prior history of cardiovascular disease.

In our second aim we found that the association between antihypertensives and fractures varied according to antihypertensive class, time since initiation, and outcome definition (e.g., falls vs. fractures). Overall, beneficiaries who initiated with angiotensin-receptor blockers had the lowest rate of fractures in the year following initiation. Thiazides were associated with an initial increased rate of falls and fractures, but this association decreased over time. Results suggest clinicians may want to consider different fracture risks when choosing between antihypertensive drug classes, particularly for older adults with a history of falls or fractures.

I dedicate this dissertation research to my mother, Terry Bridges, who is my role model and who has always provided me with love, support, and confidence in all my life choices; and to my husband, Bo Hargrove, who has provided me with unconditional support, encouragement, and laughter throughout the dissertation process.

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LIST OF ABBREVIATIONS

ACE =	Angiotensin-Converting Enzyme Inhibitor
ARB =	Angiotensin-Receptor Blockers
BB =	Beta Blocker
BMD =	Bone Mineral Density
CCB =	Calcium Channel Blocker
CI =	Confidence Interval
CPT =	Current Procedural Terminology
GBTM =	Group Based Trajectory Model
HR =	Hazard Ratio
HT =	Hypertension
ICD9 =	International Classification of Diseases, 9th Edition
OR =	Odds Ratio
PDC =	Proportion Days Covered
PMC =	Proportion Months Covered
SMR =	Standardized Mortality Ratio

CHAPTER 1: INTRODUCTION

Hypertension is one of the most commonly diagnosed chronic health conditions in the United States.[1] Older adults are susceptible to developing hypertension due to changing metabolic and vascular functioning associated with age.[2] Antihypertensive medication can reduce the risk of cardiovascular disease[3] and mortality among older adults.[2] However, few older adults remain adherent to their antihypertensive therapy. It is estimated that only half of older adults remain adherent to their antihypertensive medications after one year of use.[4]

Older adults are at higher risk of being non-adherent due to an increased number of comorbidities and increased medication use.[2] Prior studies have relied on overall measures of adherence such as proportion of days covered (PDC) and the medication possession ratio (MPR), which quantify the number of days covered with medications over a defined period of time.[5,6] However, these measures cannot differentiate between adherence and persistence (i.e., changing patterns of medication use over time).[6,7] Recently, group based trajectory models (GBTM) have been used in place of traditional adherence measures to better capture natural changing patterns of medication use.[7-9] No prior study has used GBTMs to examine antihypertensive adherence among older adults initiating therapy.

Medication-related adverse events, such as fractures or falls, could impact antihypertensive adherence among older adults. Recent research suggests that antihypertensive medications are associated with falls and fractures.[10,11] However, the exact mechanism between antihypertensives and fractures is not known, and inconsistent results have been found in regards to specific classes of antihypertensives and fracture risk.[11,12] Prior research studies were subject to residual confounding, were limited to hip fractures, and few accounted for duration of antihypertensive use.

In this study, we examined whether GBTMs could be used to identify antihypertensive adherence trajectories in the first year following initiation, and if certain patient characteristics are associated with

better adherence. Additionally, we examined the association between antihypertensives and fractures according to antihypertensive class, time since initiation, and fracture type. In sub-analyses, we examined whether the association between antihypertensives and fractures varied according to antihypertensive adherence and if the outcome definition (falls vs. fractures) varied the results.

CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Hypertension in the U.S.

Hypertension is one of the most commonly diagnosed chronic health conditions in the United States.[13] An estimated 65% of older adults are taking antihypertensive medications or have elevated blood pressure according to the 2011-2014 National Health and Nutrition Examination Survey.[1] Hypertension is typically defined as having systolic blood pressure equal to or above 140 mm Hg and diastolic blood pressure equal to or above 90 mm Hg.[14] However, new recommendations suggest modifying the systolic blood pressure criteria for adults over the age of 60 to 150 mm Hg.[13] Hypertension is associated with a negative health outcomes (such as myocardial infarction, stroke, and kidney disease), and can lead to death if left untreated.[2,14]

2.2 Risk Factors for Hypertension

Previous research has identified certain factors can increase one's risk of developing hypertension. Health-related risk factors include elevated body mass index, hypercholesterolemia, chronic kidney disease, and diabetes.[2,15] Prevalence of hypertension tends to vary according to race and gender. Non-White populations had a higher prevalence of hypertension than White populations (41% vs. 28%, respectively)[1], and females over the age of 65 have higher rates compared to males.[14,16,17] See Figure 1 for the distribution of hypertension in the U.S.

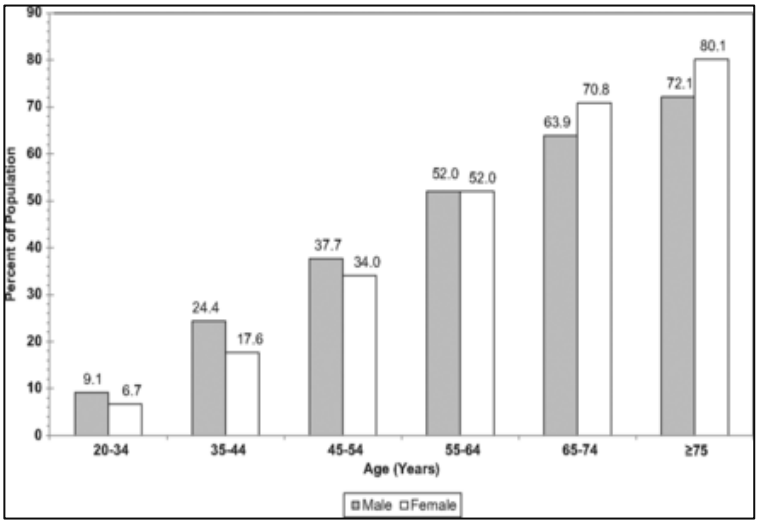

Figure 1: Prevalence of HT according to age and sex in the U.S (2007-2012)[14]

by age and gender according to the National Health and Nutrition Examination Survey (2007-2010).[14] Genetics, diet, and lifestyle factors such as alcohol consumption and smoking can also impact one's risk of developing hypertension.[2,14]

Advancing age is one of the strongest risk factors for developing hypertension.[2] The prevalence of hypertension among U.S. adults over 80 years of age was estimated to be 76% in 2010.[18] Older adults are at greater risk for developing hypertension due to changes in metabolic and vascular functioning associated with advancing age.[2,19] Additionally, increased presence of comorbidities, the potential for medication-related adverse events, and changing drug metabolism rates make it difficult to manage hypertension in older adults.[2,19,20] Finally, recommendations for hypertension treatment among older adults are often based on clinical trials of younger, healthier populations making hypertension management in older adults more challenging.[2,18,21]

2.3 Hypertension Management

Several treatment options are available for the management of hypertension. The primary goal of hypertension treatment is to reduce the risk of negative cardiovascular outcomes associated with high blood pressure.[22] Mild cases of hypertension can sometimes be managed by lifestyle changes such as increased exercise and diet modifications.[13,22] Although non-invasive, lifestyle changes alone are not effective forms of treatment for many hypertensive patients. In addition to lifestyle changes, many patients require medications for hypertension control.

Several classes of medications are available for the management of hypertension. See Table 1 for a listing of antihypertensive medication classes recommended as first line therapy treatment for older adults.[13] Antihypertensive medications act by lowering blood pressure and have been found to reduce the risk of adverse cardiovascular events and mortality among older adults.[13,23,24] Choice of antihypertensive medication class is dependent on a patients' age, race, and whether a patient has diabetes or chronic kidney disease.[2,13] See Figure 9 in the appendix for the 2014

Table 1: Recommended classes of antihypertensives medications for older adults
Diuretics
Thiazide diuretics
β-blockers (BBs)
Calcium Channel Blockers (CCBs)
Angiotensin-converting enzyme inhibitors (ACEs)
Angiotensin receptor blockers (ARBs)

Hypertension Guideline Management Algorithm developed by the Eighth Joint National Committee (JNC 8) appointed by the National Heart Lung and Blood Institute (NHLBI).[13]

The first class of antihypertensive medication recommended for hypertension management among older adults without diabetes or chronic kidney disease are thiazide diuretics.[2,13] Thiazides are low cost and have been found to successfully lower the risk of negative cardiovascular events among hypertensive patients.[25] However, if a patient has other chronic comorbidities, such as chronic kidney disease or heart failure, loop diuretics may be recommended in place or in conjunction with thiazides. [25,26] Older adults prescribed loop diuretics often have a higher number of comorbidities and are at greater risk of mortality compared to older adults prescribed other classes of antihypertensive drugs.[27] In terms of adverse events, use of any diuretic can cause electrolyte imbalance due to water loss, unwanted weight loss[28], orthostatic hypotension, and impotence.[2,25] Additionally, loop diuretics have been found to be associated with negative side effects such as headaches and anemia.[2]

β-blockers (BBs) are prescribed as first-line treatment of hypertension in patients with a history of cardiovascular disease, however evidence of their effectiveness in older adults in limited.[2,29] Therefore, they are often prescribed in combination with other classes of antihypertensive medications.[2] BBs are often given as first-line treatment to older adults with migraines, tremors, or other cardiovascular diseases (e.g., heart failure, arrhythmia, and coronary artery disease).[2] BBs have been found to be associated with an increased risk of orthostatic hypotension.[30] Another class of antihypertensive medication prescribed to older adults with a history of cardiovascular disease are calcium channel blockers (CCBs). However, CCBs have been found to be associated with negative side effects such as swelling, headache, dizziness, nausea, and orthostatic hypotension.[2,31]

In patients with chronic kidney disease or diabetes, angiotensin-converting enzyme inhibitors (ACEs) or angiotensin-receptor blockers (ARBs) are recommended as the first-line treatment of hypertension. ACEs and ARBs regulate blood pressure through modulation of the renin-angiotensin-aldosterone system (RAAS).[2,32,33] ACEs have been found to be associated with side effects including: hypotension, cough, and rash.[2] Additionally, ACEs have been found to be associated with balance

impairment among older adults.[28] ARBs are the newest class of antihypertensives recommended for first-line treatment.[33] Compared to other classes of antihypertensive medications, ARBs appear to be associated with fewer unwanted side effects and have higher levels of adherence.[6,33,34]

Several other forms of antihypertensive medications exist, however these medications are not commonly recommended as first-line treatment or are prescribed in combination with other classes of antihypertensive medications. Hypertensive older adults are normally prescribed one class of medication initially, but older adults may be prescribed a combination of antihypertensive medications if blood pressure is not controlled with the one class alone or among severe cases of hypertension.[13]

2.4 Antihypertensive Medication Adherence

In order for antihypertensive medications to be effective, it requires that patients follow their medication schedule as prescribed by their health care professional. However, prior research has found that many hypertensive patients do not take their medications as prescribed.[35] In a recent meta-analysis of antihypertensive adherence, Lemstra and Alsabbagh found that antihypertensive adherence ranges from 48%-49% after one year of follow-up.[4] Medication adherence is typically defined as taking one's medication as prescribed by a healthcare provider. Failure to remain adherent can lead to increased risk of hospitalizations, loss of independence, and higher medical costs.[35,36] Antihypertensive adherence tends to vary according to duration of use and has been found to be vary by patient demographics, type of medication class, and personal health characteristics.[5,34]

Factors that place individuals at higher risk of being non-adherent include increased age, presence of comorbidities, mental health disorders, cognitive impairment, treatment regimen (e.g., number of pills, strength, and schedule), medication cost, and adverse side effects.[2,5,34,36,37] Hypertension is asymptomatic making it difficult to assure adherence to treatment. Patients stopping therapy early may not feel any direct effects. Therefore, one of the main reasons for poor adherence to antihypertensive therapy are adverse side effects from the medications.[34,35,37]

Given the importance of antihypertensive adherence for clinical benefits, previous studies have been conducted to identify measures to quantify medication adherence. Both direct and indirect measures

of medication adherence exist. Direct measures involve clinical laboratory tests and are often costly and time-consuming for researchers.[5,34] Indirect measures of medication adherence are evaluated using pharmaceutical claims data or self-reported medication data.[5,34] Compared to direct measures, indirect measures are lower in time and cost.[5] Currently, no established standard exists for defining adequate medication adherence. However, 80% adherence is often used as the cut-point for classifying patients as adherent versus non-adherent.[5,38] Previous research has found the 80% threshold to have a high sensitivity and specificity for defining adherence to antihypertensive medications.[39] Additionally, the 80% threshold is associated with improved cardiovascular outcomes among hypertensive patients.[40]

Patterns of medication use change with time, therefore it is important that methods for quantifying medication adherence take into account changing patterns of use according to time.[34] Traditional measures of medication adherence, such as proportion days covered (PDC) and medication possession ratio (MPR), fail to account for changing patterns of use with time (Table 2).[41,42] Therefore, to better capture the natural changing patterns of medication use over time, Franklin et al. used group based trajectory models (GBTM) to assess statin adherence with claims data.[7,41] Franklin et al. used prescription claims to quantify medication adherence to statins. The authors found that statin users fell into six adherence trajectory groups ranging from individuals that were always adherent to individuals that had no refills during the study period. When compared to traditional measures of adherence, GBTMs were the best at distinguishing between adherent and non-adherent statin initiators.[7]

More recently, Franklin et al. used GBTMs to predict cardiovascular events among statin users and found similar results. [41] GBTMs were better than traditional adherence measures at predicting negative cardiovascular events following initiation.[41] However, these studies were limited to younger statin users and it is unknown if these same adherence trajectories would hold true for older adults initiating with other chronic medications. As mentioned above, older age is a strong predictor of poor adherence due to increased presence of comorbidities and polypharmacy. Therefore, it is important to adequately capture patterns of medication use among this age group to identify individuals that are at

greater risk of stopping therapy early in treatment. This is the first study to used GBTMs to identify antihypertensive adherence trajectories among older adults initiating therapy.

Table 2: Common measures of medication adherence using claims data

Term	Definition	Limitations[41]
Proportion of days covered (PDC)	$\frac{\#\ days\ medication\ is\ available\ to\ pt}{Total\ \#\ days\ in\ study}$	Fail to account to varying adherence patterns over time. Persons with different adherence patterns can be given the same adherence value.
Medication Possession Ratio (MPR)	$\frac{Total\ \#\ days\ supply}{Total\ \#\ days\ between\ first\ and\ last\ prescription}$	MPR can overestimate adherence. Does not take into account overlaps in prescriptions

2.5 Fractures Among Older Adults

Fractures are a major public health concern for older adults due to an increased risk of complications resulting from a fracture. Fractures are associated with an increased risk of mortality and loss of independence.[43,44] For instance, one meta-analysis conducted by Haentjens et al. found that hip fractures among older adults were associated with a 3% increased risk of death in women and a 7% increased risk of death in men in the one year following the injury.[45] Hip fractures are especially dangerous for older adults and are the primary reason older adults are hospitalized following a fracture.[46,47] Despite a decrease in hip fractures in the last decade, it is estimated that 289,000 older adults will have a hip fracture by 2030.[48] Furthermore, any fracture among older adults is associated with high medical care costs. One study found that fractures made up 80% of all hospitalization costs among older adults with fall-related injuries.[49]

Fractures among older adults are often the result of a fall. It is estimated that one out of every three older adults fall each year, and that 38% of the falls result in some form of injury.[50] Older adults are at greater risk of sustaining a fall-related injury due to an increased risk of osteoporosis.[51,52] Osteoporosis is a chronic health condition characterized by low bone mineral density (BMD) and greatly increases the risk of fractures resulting from falls.[53] Risk of osteoporosis increases in parallel with age and is common among post-menopausal women.[54] Osteoporotic fractures typically occur at the hip, vertebrae, or wrist.[53,54] In addition to osteoporosis, previous research has found that certain characteristics place older

adults at greater risk of a fracture. One of the strongest predictors of fractures is having a previous fracture. Once an older adult sustains a fracture, the risk for a subsequent fracture nearly doubles.[55] Additional risk factors for fractures include: advanced age, female gender, and White race.[52,56]

2.6 Antihypertensive Medications and Fractures

Use of psychotropic medications and taking multiple medications can increase the risk of both falls and fractures among older adults.[57-59] Recent evidence suggests that antihypertensive medications may increase the risk of falls and fractures among older adults.[60,61] Tinetti et al. found that among community-dwelling hypertensive older adults, use of antihypertensive medications was associated with an 11% increased risk of serious fall-related injuries. The authors found that the association between antihypertensives and injury was not significant when stratified according to antihypertensive class.[60] However, this study was limited to prevalent users of antihypertensives and was unable to capture falls that occurred early in treatment. In another study, Marcum et al. found that any use of antihypertensives were not associated with recurrent falls among non-frail older adults 70 years of age and older (odds ratio (OR): 1.13, 95% confidence interval (CI): 0.88-1.46). However, when stratified by antihypertensive class, loop diuretic users had higher odds of two or more falls.[62]

Previous research has found inconsistent results regarding the strength and direction of the association between antihypertensives and subsequent falls and fractures among older adults (Appendix Table 16). Some studies have found antihypertensives increase the risk of falls or fractures[60,61,63], while others have found no association[62,64-66], or a protective association for fractures or falls.[67] Choi et al. examined the risk of fractures associated with antihypertensive initiation among newly diagnosed hypertensive adults over the age of 50.[61] The authors' found that the risk of fractures varied according to antihypertensive class. Specifically, ARBs, BBs, and CCBs were not associated with an increased rate of fractures.[61] However, this study failed to examine fractures in the first six months following initiation, and only included antihypertensive users that were at least 80% adherent. In another study of hypertensive adults over 70 years of age, Lipsitz et al. found that the odds of self-reported injury falls

were lower among older adults taking ACEs or CCBs. However, the study was limited to 598 older adults and was reliant on self-reported falls and medication history.[64]

In 2008, Wiens et al. conducted a meta-analysis of previous studies examining the association between antihypertensives and fractures. The authors found that overall, thiazide diuretics and BBs reduced the risk of fractures by 14% using pooled risk ratios across studies.[10] However, the authors were not able to examine the risk of fractures associated with the other classes of antihypertensive given the low number of studies available to examine these effects.

In 2015, Butt and Harvey conducted an updated literature review of previous studies examining the association between antihypertensives and adverse events, including falls and fractures. [11] The authors found that in general, thiazides are associated with an initial increased risk of falls and fractures in the first few weeks after starting antihypertensive therapy.[11] However, few studies have examined the fracture or fall risk in the immediate period after initiation of therapy. Additionally, previous studies have been limited to hip fractures only. The authors found that chronic use of antihypertensives appears to be associated with an overall decreased risk of falls and fractures, however results have been inconsistent in regards to drug class.[11] No prior study has examined the effect outcome definition (falls vs. fractures) has on the association between antihypertensives and subsequent adverse events.

Antihypertensive medications are believed to impact fracture risk through two possible mechanisms. First, initial use or changing doses of antihypertensives can result in orthostatic hypotension which can increase the risk of falls and subsequent fractures.[12] Orthostatic hypotension is caused by a drop in blood pressure upon standing and is associated with an increased risk of falls among older adults.[68] Second, chronic use of antihypertensives can impact fracture risk through biologic interactions with BMD.[12] Much of the prior literature on fractures and antihypertensives have been limited to diuretics or BBs, and it is still not clear which mechanism or antihypertensive drug class poses the greatest risk of injury for older adults.[10]

One of the possible mechanisms antihypertensives can increase the risk of fractures is by interactions with BMD. Prior research has found that antihypertensives may have direct effects on

BMD.[32] For instance, thiazide diuretics decrease urinary calcium excretion and have been found to stimulate the formation of osteoblasts, or bone cells. BBs are thought to impact BMD by preventing bone loss through regulation of the sympathetic nervous system. Additionally, studies have found that ARBs and ACEs can impact BMD and subsequent fracture risk by inhibiting bone turnover caused by the renin-angiotensin-aldosterone system (RAAS).[32] However, the time it takes for antihypertensives to have BMD effects is not known. No prior study has examined the impact pattern of antihypertensive adherence has on fracture risk. This is the first study to examine the association between antihypertensive adherence and fractures among older adults. See Table 3 for a summary of antihypertensive medication classes and their potential associated impact on BMD.[32]

Table 3: Antihypertensive medications and their impact on bone health and fractures

Class	Impact on bone health	Effect on BMD	Effect on fracture risk	Comments
Thiazide Diuretics	Reduce calcium urinary loss and stimulate osteoblasts and bone formation	Strengthen	Decrease	Highly researched in observational and experimental settings.
BBs	Decrease bone loss by regulating the sympathetic nervous system	Strengthen	Decrease	Based on animal and observational studies. No randomized controlled trials.
ACEs/ ARBSs	Inhibit bone resorption by angiotensin-I	Strengthen	Decrease	Researched in animal studies. Mixed results found in observational studies.
CCBs	Inhibit bone resorption, increase calcium concentration in bone	Possibly strengthen	Unknown	Limited experimental and observational studies. Mixed results found in clinical studies.

Table is based off the manuscript published by Ghosh[32]

CHAPTER 3: SPECIFIC AIMS

In our first aim we used GBTMs to model patterns of antihypertensive adherence among older adults initiating antihypertensive therapy. Our second dissertation aim examined the association between starting antihypertensive therapy and incident fractures among older adults. Results can be used to identify older adults at greater risk of being non-adherent to their antihypertensive therapy and whether certain subclasses of antihypertensives are associated with higher risk of fractures after initiation. This research was conducted through the two aims listed below.

3.1 Aim 1: Examine Patterns of Antihypertensive Adherence Among New-Users of Antihypertensive Medications.

Aim 1.1 Identify patterns of antihypertensive adherence among new users of antihypertensive medications using GBTMs

Aim 1.2 Determine factors associated with patterns of antihypertensive use by comparing the distribution of covariates across adherence trajectory groups

Aim 1.3 Compare GBTMs to traditional methods of quantifying medication adherence (eg., proportion months covered and proportion of days covered), using the actual number of prescribed days as the gold standard

Hypotheses**:**

1) Patterns of antihypertensive adherence vary among older adults.
2) Older adults with poor antihypertensive adherence will be older, take multiple medications, and be in overall poorer health compared to adherent older adults.
3) GBTMs will be better at capturing patterns of antihypertensive adherence compared to traditional measures of quantifying medication adherence using claims data

Rationale: Antihypertensive medication reduce the risk of cardiovascular disease[3] and mortality among older adults.[2] However, few older adults remain adherent to their antihypertensive therapy. It is estimated that only half of older adults remain adherent to their antihypertensive medications after one year of use.[4] Older adults are at higher risk of being non-adherent due to an increased number of comorbidities and increased medication use.[2] Prior studies examining predictors of antihypertensive adherence have relied on overall measures of adherence such as proportion of days covered (PDC) and medication possession ratio (MPR), which quantify the number of days covered with medications over a defined period of time.[5,6] However, these measures cannot differentiate between adherence and persistence (i.e., changing patterns of medication use over time).[6,7] The benefit of using GBTMs over traditional methods is that we will be able to capture the time-varying nature associated with medication use. No prior study has used GBTMs to identify antihypertensive adherence among older adults initiating antihypertensive therapy. Results can be used by clinicians or public health researchers to begin to identify sub-populations of older adults at risk of being non-adherent to antihypertensive therapy.

Data: 20% random nationwide sample of Fee-For-Service Medicare data including parts A, B, and D.

Journal: Results from this aim are under review at *The American Journal of Hypertension.*

3.2 Aim 2: Examine the Association Between Antihypertensive Use and Fractures Among New Users of Antihypertensives.

Aim 2.1: Estimate the rate of fractures according to antihypertensive adherence trajectories identified in Aim 1

Aim 2.2: Estimate the rate of fractures according to antihypertensive class and time since initiation

Aim 2.3: Examine the association between antihypertensives and type of fracture outcome (probable low BMD vs. normal BMD) according to antihypertensive class

Aim 2.4: Examine the impact of using falls versus fractures as the primary outcome on the results of aim 2.2

Hypotheses:

1) The rate of fractures will be lowest among new users of ARBs compared to other classes of antihypertensive medications.
2) The rate of fractures will vary by antihypertensive class depending on the time since initiation. For instance, thiazide diuretics will initially be associated with an increased risk of fractures due to orthostatic hypotension. However, at the end of one year of use, thiazide diuretics will have a lower rate of fractures due to potentially protective effects from interactions with BMD.
3) Types of fracture will vary depending on the antihypertensive class. For instance, thiazide users will have a lower rate of probable low BMD fractures due to potentially protective effects of thiazides on BMD.
4) Outcome definition (falls vs. fracture) will impact the associations between antihypertensive class and adverse events. Given that only one third of falls result in a fracture, the results when using falls as the outcome may not be the same as the results when using fractures as the primary outcome.

Rationale: Fractures and falls are a major public health concern for older adults. Recent evidence suggests that antihypertensive medications may increase the risk of serious falls and fractures among older adults.[60,61] However, previous studies have found inconsistent results regarding the strength and direction of the association. Some studies have found antihypertensives increase the risk of falls or fractures[60,61,63], while others have found no association[62,64-66], or a protective association.[67] Few studies have examined the immediate fracture or fall in the first few weeks after initiation of therapy. Additionally, the majority of previous studies have been limited to hip fractures only or self-reported falls. This is the first study to examine the effect outcome definition (falls vs. fractures) has on the association between antihypertensives and subsequent adverse events. Additionally, no prior study has examined the association between antihypertensive adherence trajectories and subsequent fractures. Results from this aim can be used to identify if certain classes of antihypertensives are associated with greater risk of

adverse events among older adults. If certain antihypertensives increase the risk of adverse events, clinicians need to be aware of these risks when prescribing to older adults.

Data: 20% random nationwide sample of Fee-For-Service Medicare data including parts A, B, and D.

Journal: Results from Aim 2.2 and 2.3 are to be submitted to the journal of *Injury Epidemiology*.

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CHAPTER 4: ANTIHYPERTENSIVE ADHERENCE TRAJECTORIES AMONG OLDER ADULTS IN THE FIRST YEAR AFTER INITIATION OF THERAPY

4.1 Introduction

Hypertension is one of the most common chronic health conditions among older adults. An estimated 65% of older adults are taking antihypertensive medications or have elevated blood pressure.[1] The prevalence of hypertension increases with age due to changes in metabolic and vascular functioning.[2,19] Hypertension increases the risk for cardiovascular diseases (e.g., stroke, myocardial infraction), kidney disease, and death.[69]

Antihypertensive medications reduce the risk of cardiovascular disease among hypertensive patients.[13,23,24] Yet, few older adults are adherent to their antihypertensive medication.[6] A meta-analysis found that antihypertensive adherence was approximately 49% after one year of follow-up.[4] Failure to remain adherent can lead to increased risk of cardiovascular disease, hospitalizations, and mortality.[23,40,70,71] Older adults are at greater risk of nonadherence due to polypharmacy and increased comorbidities.[2] Female gender, low income, presence of comorbidities, mental health disorders, non-White race, and cognitive impairment are associated with non-adherence. [2,4,5,34]

Prior studies have used overall measures of adherence, such as proportion days covered (PDC) and medication possession ratio (MPR), which quantify the number of days covered with medications over a defined period of time.[5,6] However, these measures cannot quantify the time-varying nature of medication adherence.[6,42] Good control of the time-dependent nature of medication adherence may be critically important in studies of factors that strongly depend on age.

Group based trajectory models (GBTM) quantify time-varying patterns in medication adherence.[8,9,41] In a study of adults initiating statins, GBTMs were better at distinguishing between

adherent and non-adherent users than time-static adherence measures.[42] GBTMs account for dynamic patterns of medication use and thus do not make assumptions about the trajectory shape.[42,72]

Despite these advantages, no prior study has used GBTMs to model antihypertensive adherence trajectories among older adults initiating therapy. Our objectives were to 1) use GBTMs to identify antihypertensive adherence trajectories in the first year following initiation, 2) compare adherence trajectories to traditional adherence measures, and 3) examine whether patient characteristics predict adherence trajectories.

4.2 Methods

Data

We used a 20% nationwide, random sample of fee-for-service Medicare beneficiaries who were enrolled at least one month in Medicare parts A (inpatient care), B (outpatient care), and D (prescription drug) coverage between 2007 and 2011. Medicare is the federally provided health insurance available to all U.S. residents over the age of 65 and fee-for-service is the part of Medicare where individual insurance claims are sent directly to the Centers for Medicare and Medicaid Services (CMS). Data were obtained under a data use agreement established between CMS and the University of North Carolina at Chapel Hill (UNC). The study protocol was approved by the UNC's Non-Biomedical Institutional Review Board (#15-1704).

Cohort

The study cohort consisted of all new users of antihypertensive medications initiating therapy during 2008-2011 who were continuously enrolled in Medicare Parts A, B, and D for at least 12 months prior to initiation of therapy (index date). New use was defined as not having a prior prescription of the following antihypertensive medications in the last 12 months: angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB), or thiazide diuretics (THZ) (Appendix Table 18).

We limited the cohort to first time new users of antihypertensives (beneficiaries potentially could qualify as new users more than once). We required beneficiaries to be at least 66 years of age to ensure one full year of Medicare enrollment prior to initiation. Beneficiaries with nursing home stays and those with metastatic cancer claims in the last 12 months were excluded since these factors could affect medication adherence. Finally, we required beneficiaries to remain enrolled in Medicare for at least one year following initiation to capture patterns of antihypertensive use (Figure 2).

Antihypertensive Adherence

Patterns of antihypertensive use were defined using date of dispensing and days supply data. Starting on the index date, we counted the number of days each month a beneficiary was covered by any of the following antihypertensive drug classes: ACEs, ARBs, BBs, CCBs, or THZs. We choose these classes based on recommendations for hypertension treatment in older adults.[2] Months were defined in 30-day intervals. If a new prescription was filled prior to the end of the last days' supply, the day of the new prescription began the day after the prior prescription would have ended.

After counting the number of days covered each month, binary indicator variables were used to specify whether an individual was covered by an antihypertensive for at least 24 out of 30 days (e.g., 80% days covered). The 80% threshold is considered to have high sensitivity (92%) and specificity (89%) for distinguishing between adherent and non-adherent antihypertensive patients[73] and is associated with improved cardiovascular health.[40] We also calculated two common adherence measures: proportion months covered (PMC) and proportion days covered (PDC). PMC was defined as the number of months a beneficiary had at least 80% days covered divided by 12 (total months of follow-up). PDC was defined as the number of days covered with an antihypertensive medication divided by 360 (total days of follow-up).

Predictors of Adherence Trajectories

We selected predictors of antihypertensive adherence trajectories based on previous literature.[2-5,74] Potential predictors were defined based on claims during the 12 months prior to initiation. Demographics (age, gender, and race) were identified using the Medicare Denominator File. We categorized

antihypertensive medication initiated on the index date as combination therapy (more than one class of antihypertensive) or monotherapy. Concurrent medication use was defined as the number of distinct drugs prescribed in the 14 days prior to the index date. Also, we identified whether beneficiaries were in the Medicare coverage gap during the baseline period. Medicare will cover most drug-related expenses until a beneficiary reaches a threshold amount in drug-related costs each year, at which time Medicare will no longer cover these expenses unless the costs exceed another threshold amount. [75] As a proxy for sociodemographic status, we identified whether beneficiaries were eligible for the Medicare low-income subsidy (LIS) program. LIS offers medication at a reduced cost for beneficiaries that are eligible due to income, family size, and household resources. Finally, we identified whether beneficiaries had prescriptions for the following medications: loop diuretics, antiarrhythmics, antidepressants (includes: selective serotonin reuptake inhibitors, tricyclics, monoamine oxidase inhibitors, serotonin and norepinephrine reuptake inhibitors), antiepileptics, anxiolytics, benzodiazepines, opioids, and hypnotics.

Using the International Classification of Diseases 9th revision diagnostic codes (ICD-9, Appendix Table 19), chronic health predictors included: diabetes, chronic kidney disease, Parkinson's disease, Alzheimer's disease, chronic obstructive pulmonary disease (COPD), congestive heart failure, arrhythmia, osteoarthritis, rheumatoid arthritis, stroke, myocardial infarction, hypertension, obesity, and fractures.

We used the frailty index score (FIS) as a proxy measure of frailty.[76] FIS was developed using Medicare data to predict limitations in activities of daily living based on factors associated with frailty including: demographics, chronic health conditions, geriatric syndromes, medical equipment use, and health screenings. Additionally, we examined the prevalence of variables that were positively (ambulance transfer, wheelchair/walker use, home oxygen use, hospital bed, difficulty walking, and vertigo) and inversely (cancer screenings) associated with limitations in activities of daily living.[76]

Finally, we assessed history of hospitalizations by examining hospital admissions, long-term hospital stays, and short-term hospital stays in the year prior to the index date.

Analysis

Trajectory Models

We used group based trajectory models (GBTMs) to group beneficiaries by patterns of antihypertensive use. GBTMs are a type of mixed models originally developed to model changes in behavior.[72,77] We chose to use GBTMs over other modeling techniques, such as growth mixed modeling, because GBTMs do not require prior assumptions about trajectory shapes.[72]

GBTMs were estimated using logistic regression models. Dependent variables were the monthly binary indicators of antihypertensive use, and the independent variables were months since initiation. GBTMs were not adjusted for baseline covariates. Time was modeled using linear and cubic terms. In order to identify the best fitting model, we started with a two-group model and subsequently added up to seven groups. The maximum of seven groups was imposed to avoid small group sizes. We used Bayesian Information Criterion (BIC), group size, and the average posterior probability to identify the optimal number of groups. BIC is a measure of model fit with lower scores signifying better fit. The average posterior probability signifies how well beneficiaries fit within the trajectory group they are assigned. The typical threshold used to define good model fit is 0.7.[72]

We examined spaghetti plots (i.e., stacked individual line plots of the number of days covered with antihypertensives each month) for a random sample of 500 beneficiaries to verify that the average trends of use aligned with the trajectories identified with the best-fitting GBTM (results not shown). As a sensitivity analysis, we repeated the GBTM analyses removing beneficiaries who were in the Medicare insurance gap during the follow-up period to verify that the GBTM results were not driven by these individuals. Trajectories were defined using "Proc Traj".[78]

Comparison of Adherence Measures

We compared the GBTM results to traditional adherence measures, PDC and PMC, using the monthly binary indicators as the gold standard. We separated months into adherent versus non-adherent months and assigned adherence measures to each month (e.g., PDC, PMC, and trajectory measures). GBTM values varied across months, but PDC and PMC did not since these measures are static. Area

under the receiving operating characteristic curves (AUC) compared adherence measures ability to discriminate between adherent versus non-adherent months, with a value of one corresponding to perfect discrimination.[79-81]

Predictors of Adherence

We evaluated predictors of adherence by first examining the distribution of covariates across trajectory groups. Next, we used multivariable logistic models to examine associations between baseline covariates and trajectory groups. Adjusting for all baseline covariates, we calculated odds ratios (ORs) and 95% confidence intervals (95% CIs). The outcome of interest was being in a specific trajectory group versus the most adherent group. Strength of the ORs were determined by examining the distance from the null value (OR=1) and by examining their precision (width of the 95% CIs). AUC statistics quantified the ability of the predictors to discriminate between trajectory groups.

Since previous medication persistence is predictive of future use[82,83], we examined whether prior statin persistence improved prediction of antihypertensive trajectories in a subgroup of beneficiaries who had any statin filled at least 180 days prior to the index date. We chose to examine statins since these medications are frequently prescribed to older adults. We defined statin persistence as having at least 180 days continuously covered by a statin, allowing for a 30-day grace period between prescription fills.

4.3 Results

We identified 282,520 Medicare beneficiaries initiating antihypertensive therapy during 2008-2011. On average beneficiaries were 75 years old, 60% were women, and the majority were White (84%). Most beneficiaries initiated therapy with one antihypertensive class (86%) and the mean days supplied on the index date was 32.

Antihypertensive Adherence Trajectories

After fitting GBTMs with different groupings, we identified the six-group trajectory model as the best fit (Figure 3, Appendix Table 20). Beneficiaries were grouped as adherent (40%, mean adherence: 0.97); early drop-off then rebound to almost full adherence (10%, mean adherence: 0.73); partial drop-off (10%, mean adherence: 0.35); gradual drop-off (14%, mean adherence: 0.63); rapid drop-off (8%, mean

adherence: 0.27); and immediate drop-off (18%, mean adherence: 0.10). All trajectory groups had an average posterior probability greater than 0.8 (Table 4). When we removed beneficiaries in the insurance gap period during follow-up (n=43,595, 15%), the six-group model remained the best fitting model and the trajectories were similar to those identified using the full cohort (Appendix Figure 9).

Comparison of GBTMs to Traditional Adherence Measures

Compared to PDC and PMC, the 6-group trajectory model was better at discriminating between adherent and non-adherent months, with an AUC of 95%, compared to 91% for PDC and 92% for PMC (Table 4). In results stratified according to trajectory group, the trajectory model outperformed PDC and PMC for all groups except the adherent group (Appendix Table 21; *AUC*-statistics for the adherent group: PDC: 87%, PMC: 89%, GBTM: 66%).

Predictors of Adherence Trajectories

Individual factors that varied between trajectory groups were race, initiation with combination therapy, days supply on the index date, opioid use, history of COPD or cardiovascular disease (e.g., arrhythmia, hypertension, or myocardial infarction), vertigo, prior cancer screenings, and hospital utilization (Table 5).

In the adjusted, multivariable analysis, initiation with monotherapy, non-White race, and having no prior history of cardiovascular disease were most predictive of being non-adherent (OR>1.0 indicates non-adherence). Non-White beneficiaries (aOR: 2.05, 95%CI: 1.99-2.12) and those initiating with one class of antihypertensive drug (aOR: 2.08, 95%CI: 2.00-2.13) were approximately twice as likely to be in the immediate drop-off group compared to the adherent group. Other factors strongly predictive of non-adherence were having a high probability of being frail, Parkinson's disease, opioid use, no prior history of being in the Medicare insurance gap, vertigo, COPD, polypharmacy, and no prior history of having hospital admissions during baseline (Table 6, Appendix Table 22).

Prior Statin Persistence and Adherence Trajectories

Statins were dispensed at least 180 days prior to the start of antihypertensive use for 25% of beneficiaries (n=69,668). Of those, 68% (n=47,668) were persistent for at least 180 days. Prior statin persistence was predictive of being more adherent (Table 7). After adjustment, prior statin persistence was strongly associated with not being in the partial drop-off group versus adherent (aOR: 0.40, 95% CI 0.37-0.42).

4.4 Discussion

Overall, GBTMs are effective for identifying patterns of antihypertensive adherence among Medicare beneficiaries initiating therapy. We identified six distinct adherence trajectories ranging from fully adherent to those beneficiaries that never returned after their first prescription. Nearly half of beneficiaries remained adherent in the year following initiation. Compared to traditional adherence measures, GBTMs were better at distinguishing between fluctuating adherence patterns. Individual factors predictive of adherence included initiation with combination therapy, White race, and history of cardiovascular disease.

To our knowledge, no previous study has used GBTMs to identify antihypertensive adherence trajectories among older adults. The six trajectories identified are approximately similar to previous studies that have used GBTMs to model medication adherence to other drugs.[8,42,83,84] Similar to other studies [42,84], we found that GBTMs were better than PMC and PDC at distinguishing between adherent and non-adherent patients, especially for patients with fluctuating adherence. Factors such as physician visits, health screenings, and hospitalizations can influence patients stopping and re-initiating with statins[85], however, research is needed to examine if the same results hold true for other chronic medications. Future research could use GBTMs to identify time-dependent factors influencing fluctuations in medication behavior.

Similar to past studies, we found that beneficiaries with cardiovascular diseases and those who initiated therapy with more than one class of antihypertensive were more likely to be adherent.[3,74] These older adults may be more aware of the importance of being adherent due to more severe hypertension and

poor cardiovascular health. However, a large proportion of beneficiaries with cardiovascular disease were not adherent. For instance, 21% of beneficiaries in the immediate drop-off group had a history of arrhythmia and 10% had congestive heart failure. Our results suggest physicians should encourage older adults to remain adherent to antihypertensives, particularly among those with poor cardiovascular health.

Our results confirm previous studies that noted past medication behavior is predictive of future medication adherence.[82,83] Bushnell et al. found that prior persistence to chronic medication was associated with improved antidepressant persistence among adults.[82] Similarly, Franklin et al. found that the addition of initial statin adherence improved the prediction of future statin adherence trajectories.[83] We found that prior statin persistence was predictive of antihypertensive adherence. Since statins are commonly prescribed to older adults, results suggest that clinicians can consider prior persistence to other chronic medications to identify patients who are more or less likely to remain adherent to antihypertensives therapy.

This study has limitations. An antihypertensive prescription dispensed does not guarantee that the beneficiary is taking the medication as prescribed. However, since a co-payment is required for most dispensed prescriptions, it is reasonable to assume that patients actually take their antihypertensives after the first refill. Antihypertensive medications obtained outside of Part D (e.g., medication purchased out-of-pocket, through private insurance, or samples provided by physicians) were not captured. Fortunately, most antihypertensives are generic and sample use is less likely.[86,87]

Our results may be subject to residual confounding related to uncontrolled frailty measures and time-varying factors affecting medication adherence. Physician visits, frailty, and medication-related adverse events, such as orthostatic hypotension and fractures, are time-varying factors that likely affect antihypertensive adherence. For instance, we found that history of fractures was weakly associated with being non-adherent. This finding could potentially be due to individuals with a history of fractures stopping use of antihypertensive medication because of unwanted side effects that increased their risk of additional fractures. Older adults who experienced adverse events may have stopped therapy during the

initial period of use. Further research is needed to examine the impact time-varying covariates, including those affected by prior treatment, have on antihypertensive adherence trajectories.

Similar to the 2012 U.S. older adult population as a whole[88], the majority of our cohort was White (84% vs. 86%) and women (60% vs. 57%). It is unknown if these trajectories would hold true for non-White populations. Research featuring large non-White populations is needed to identify underlying factors that contribute to non-adherence among various race/ethnicity sub-populations.

Lastly, results of our comparison of traditional adherence measures to GBTMs should be interpreted with caution. We included PDC and PMC in our analysis to highlight one of the inherent disadvantages of using these static adherence measures in that they fall short of separating adherence from persistence. Further research is needed using external indicators, such as mortality outcomes or cardiovascular events, to validate the use of GBTMs over traditional adherence measures.

Our finding that nearly half of Medicare beneficiaries were adherent to their antihypertensive medication in the year following initiation is encouraging. GBTMs are an effective tool for visualizing and capturing patterns of antihypertensive use among older adult populations. Future studies can use GBTMs to identify factors influencing patients to return to being adherent after an initial decline and to assess if adherence trajectories are associated with improved clinical outcomes. Researchers and clinicians may find these results helpful in identifying target populations for interventions designed to increase adherence among older adults.

Table 4: Antihypertensive adherence trajectories in the 12 months following initiation according to adherence measures

	Group Size		Average Probability of Adherence[a]		Proportion Days Covered (PDC)		Proportion Months Covered (PMC)		Average Posterior Probability[b]	
Trajectory Group	N	%	Mean	Std	Mean	Std	Mean	Std	Mean	Std
Immediate Drop-off	50,797	18.0	0.095	0.257	0.136	0.092	0.099	0.050	0.887	0.174
Rapid Drop-off	22,404	7.9	0.267	0.385	0.318	0.093	0.281	0.064	0.856	0.177
Gradual Drop-off	39,953	14.1	0.629	0.258	0.708	0.137	0.636	0.135	0.855	0.169
Partial Drop-off	29,429	10.4	0.346	0.226	0.465	0.147	0.352	0.118	0.865	0.161
Early Drop-off then Rebound	28,304	10.0	0.733	0.196	0.789	0.100	0.720	0.100	0.818	0.151
Adherent	111,633	39.5	0.973	0.016	0.979	0.031	0.975	0.043	0.956	0.086

Comparison of Adherence Measures Ability to Distinguish between Adherent and Non-Adherent Months

Adherence Measure	AUC[c]	95% Confidence Interval (CI)
PDC	0.914	0.914, 0.914
PMC	0.918	0.918, 0.919
Trajectory Model	0.954	0.954, 0.955

[a] Average probability of being at least 80% adherent over 12 months of follow-up.

[b] Indicates how well beneficiaries fit in their assigned group. 0.70 is typically used as a threshold to signify good model fit.

[c] Area under the curve (AUC) statistics are used to quantify the ability of the measures to discriminate between adherent and non-adherent months. Values of 1 symbolize perfect discrimination.

Overall model BIC for 6-group trajectory model: -1300277.

BIC= Bayesian information criterion. BIC is used as a measure of model fit. Lower BIC values signify better model fit.

Logistic regression models were used to identify trajectory groups. The dependent variables were the monthly binary indicators of antihypertensive use and months since start of antihypertensive therapy were the independent variables. Time was modeled using cubic terms.

Table 5: Distribution of baseline characteristics according to adherence trajectory among Medicare beneficiaries initiating antihypertensives

Covariates	Trajectory Group, n %					
	Immediate Dropoff	Rapid Dropoff	Gradual Dropoff	Partial Dropoff	Early Dropoff then Rebound	Adherent
	n= 50,797	n=22,404	n=39,953	n=29,429	n=28,304	n=111,633
Female Gender	59.9	57.3	58.9	59.8	61.1	60.8
Mean Age (std)	75.3 (7.1)	75.0 (7.0)	75.0 (7.0)	75.1 (7.0)	75.2 (7.1)	75.0 (7.1)
White Race	80.8	82.2	83.6	77.9	83.4	88.6
Initiated with Combination Therapy	8.7	12.1	13.6	11.8	13.5	17.7
Average Days Supply on Index Date (std)	27.3 (9.0)	40.6 (25.9)	35.1 (21.9)	29.6 (15.1)	30.6 (17.5)	32.6 (19.7)
Medication Use 14 Days Prior to Index Date						
1-2 Meds	55.0	56.0	55.6	57.0	55.3	53.5
3-4 Meds	30.1	29.3	28.9	29.1	29.1	29.1
5 or More Meds	15.0	14.7	15.5	13.9	15.5	17.3
Insurance Gap During Baseline	16.0	15.7	16.4	14.5	16.5	16.7
Eligible for Low-Income Subsidy	5.6	5.3	5.6	6.1	5.7	5.6
Loop Diuretic	9.5	9.6	10.4	9.4	10.7	11.1
Antiarrhythmic	5.2	4.5	4.5	4.7	4.8	4.6
Antidepressant[a]	17.4	17.1	17.7	16.5	17.8	16.8
Antiepileptic	10.5	10.1	9.6	9.2	10.2	9.1
Anxiolytic	4.9	4.4	4.2	4.4	4.1	3.7
Benzodiazepine	1.5	1.3	1.3	1.2	1.2	1.2
Opioid	37.1	33.2	33.0	34.2	34.0	30.2
Hypnotic	8.5	8.0	7.3	7.5	7.7	6.7
Diabetes	24.8	28.3	27.6	28.3	28.6	25.5
Chronic Kidney Disease	11.9	11.8	12.0	11.8	12.4	11.5
Parkinson's Disease	2.0	1.7	1.7	1.5	1.7	1.5
Alzheimer’s Disease	3.3	2.8	3.3	2.7	3.3	3.5
COPD	19.5	17.3	17.5	17.3	17.7	16.4
Congestive Heart Failure	10.1	9.8	10.7	9.9	10.6	11.5
Arrhythmia	20.9	20.5	20.9	18.3	20.4	23.4
Osteoarthritis	18.7	18.0	17.5	18.5	18.2	16.1

Rheumatoid Arthritis	3.8	3.5	3.5	3.8	3.5	3.1
Stroke	16.1	15.9	16.1	15.2	16.8	16.6
Myocardial Infarction	1.8	2.0	2.4	1.5	2.1	3.8
Hypertension	66.4	73.2	77.8	74.6	79.1	79.6
Obesity	4.6	4.8	5.0	4.8	5.3	5.0
Fracture History	9.8	8.2	8.4	8.8	8.7	7.9
Average Frailty Predictor Index (std)[b]	0.11 (0.1)	0.10 (0.1)	0.10 (0.1)	0.10 (0.1)	0.11 (0.1)	0.10 (0.1)
Home Oxygen Use	5.1	4.5	4.2	4.3	4.4	4.1
Walker or wheelchair use	4.5	4.0	3.9	4.2	4.2	3.8
Hospital Bed	1.2	0.8	1.0	1.0	1.0	0.9
Difficulty Walking	11.4	10.6	10.5	10.4	11.0	10.3
Vertigo	15.9	14.6	13.7	14.5	14.0	12.7
Ambulance Transport	14.8	11.8	12.6	11.7	12.9	13.7
Cancer Screenings	34.6	35.5	37.3	34.8	37.7	39.5
Hospital Admissions	25.2	21.2	21.5	19.6	21.7	23.8
Long Stay Admissions	2.1	1.5	1.6	1.5	1.8	1.8
Short Term Hospital Stays	24.3	20.6	20.8	18.8	20.8	23.0

[a] Antidepressants include selective serotonin reuptake inhibitors, tricyclics, monoamine oxidase inhibitors, serotonin and norepinephrine inhibitors

[b] Higher scores denote a higher probability of being frail

std=standard deviation

Index date= start of antihypertensive therapy

Table 6: Strongest predictors of antihypertensive non-adherence trajectories among Medicare beneficiaries initiating antihypertensive therapy

	Patterns of Adherence Odds Ratios (ORs) and 95% Confidence Intervals (CIs)					
	Immediate Drop-off	Rapid Drop-off	Gradual Drop-off	Partial Drop-off	Early Drop-off then Rebound	Adherent
Initiation with Monotherapy[a]	2.08 (2.00, 2.13)	1.49 (1.43, 1.56)	1.33 (1.28, 1.37)	1.52 (1.45, 1.59)	1.32 (1.25, 1.35)	1
Non-White Race	2.05 (1.99, 2.12)	1.85 (1.78, 1.93)	1.59 (1.54, 1.64)	2.26 (2.19, 2.34)	1.58 (1.52, 1.64)	1
Hypertension	2.04 (2.00, 2.08)	1.49 (1.45, 1.56)	1.15 (1.12, 1.19)	1.41 (1.37, 1.45)	1.08 (1.04, 1.11)	1
No History of Myocardial Infarction	2.00 (1.85, 2.17)	1.52 (0.60, 0.74)	1.28 (1.19, 1.39)	1.92 (1.72, 2.13)	1.49 (1.35, 1.64)	1
Frailty Predictor Index	1.47 (1.32, 1.64)	1.37 (1.18, 1.61)	1.18 (1.04, 1.33)	1.72 (1.49, 2.00)	1.37 (1.19, 1.56)	1
Parkinson's Disease	1.40 (1.29, 1.53)	1.31 (1.16, 1.48)	1.20 (1.09, 1.32)	1.19 (1.07, 1.34)	1.21 (1.08, 1.35)	1
No History of Arrhythmia	1.30 (1.25, 1.33)	1.15 (1.10, 1.19)	1.14 (1.10, 1.16)	1.32 (1.27, 1.35)	1.18 (1.14, 1.22)	1
Opioid Use	1.33 (1.30, 1.36)	1.18 (1.14, 1.22)	1.16 (1.13, 1.19)	1.26 (1.22, 1.29)	1.19 (1.15, 1.22)	1
No History of Being In The Insurance Gap	1.25 (1.22, 1.30)	1.14 (1.09, 1.19)	1.09 (1.04, 1.12)	1.27 (1.22, 1.32)	1.12 (1.08, 1.16)	1
Vertigo	1.25 (1.21, 1.29)	1.20 (1.15. 1.26)	1.10 (1.06, 1.14)	1.17 (1.12, 1.21)	1.08 (1.04, 1.12)	1
COPD	1.24 (1.20, 1.28)	1.15 (1.10, 1.20)	1.15 (1.11, 1.19)	1.17 (1.13, 1.22)	1.14 (1.10, 1.18)	1
Prior Medication Use						
1-2 Meds	ref	ref	ref	ref	ref	ref
3-4 meds	1.04 (1.01, 1.06)	1.03 (1.00, 1.08)	1.06 (1.03, 1.09)	1.08 (1.05, 1.11)	1.06 (1.03, 1.10)	1
≥ 5 meds	1.23 (1.19, 1.28)	1.15 (1.10, 1.20)	1.16 (1.11, 1.20)	1.30 (1.23, 1.35)	1.19 (1.14, 1.25)	1
No History of Hospital Admissions	1.23 (1.05, 1.45)	1.45 (1.14, 1.85)	1.22 (1.02, 1.47)	1.19 (0.96, 1.47)	1.20 (0.98, 1.47)	1

[a] Initiated with one class of antihypertensive drug vs. more than one class of antihypertensive drugs. We did not distinguish between single pill combination therapy medications.

Odds Ratios and 95% CIs are adjusted for all baseline covariates. ORs > 1 are predictive of non-adherence.

AUC-statistic for fully adjusted model: 0.525

Only the strongest predictors of non-adherence are shown, see Table 23 in the Appendix for full listing of baseline covariates. Prevalence of baseline characteristics were assessed in the 12 months prior to initiation.

Table 7: Influence of prior statin persistence on antihypertensive adherence trajectories following initiation of antihypertensive therapy

	Trajectory Group (n, %)											
Statin Persist Sub-Cohort (n=69,668)	Immediate Drop-off		Rapid Drop-off		Gradual Drop-off		Partial Drop-off		Early Drop-off then Rebound		Adherent	
Persistent ≥ 180 days (n=47,668)	6,727	14.1	3,295	6.9	6,517	13.7	3,781	7.9	4,759	10.0	22,589	47.4
Not persistent at least 180 days (n=22,000)	4,215	19.2	2,003	9.1	3,501	15.9	2,973	13.5	2,454	11.2	6,854	31.2
Baseline Prediction Model + Prior Statin Persistence												
Odds Ratio (95% CI)[a]	0.48 (0.46, 0.50)		0.49 (0.46, 0.53)		0.56 (0.54, 0.59)		0.40 (0.37, 0.42)		0.60 (0.57, 0.64)		Referent	

AUC-statistic adjusted for all covariates and prior statin persistence: 0.531

[a] Odds ratio comparing prior statin persistence and the odds of belonging to the no drop-off group. Adjusted for all baseline covariates. ORs < 1 are predictive of being more adherent.

CI= confidence interval

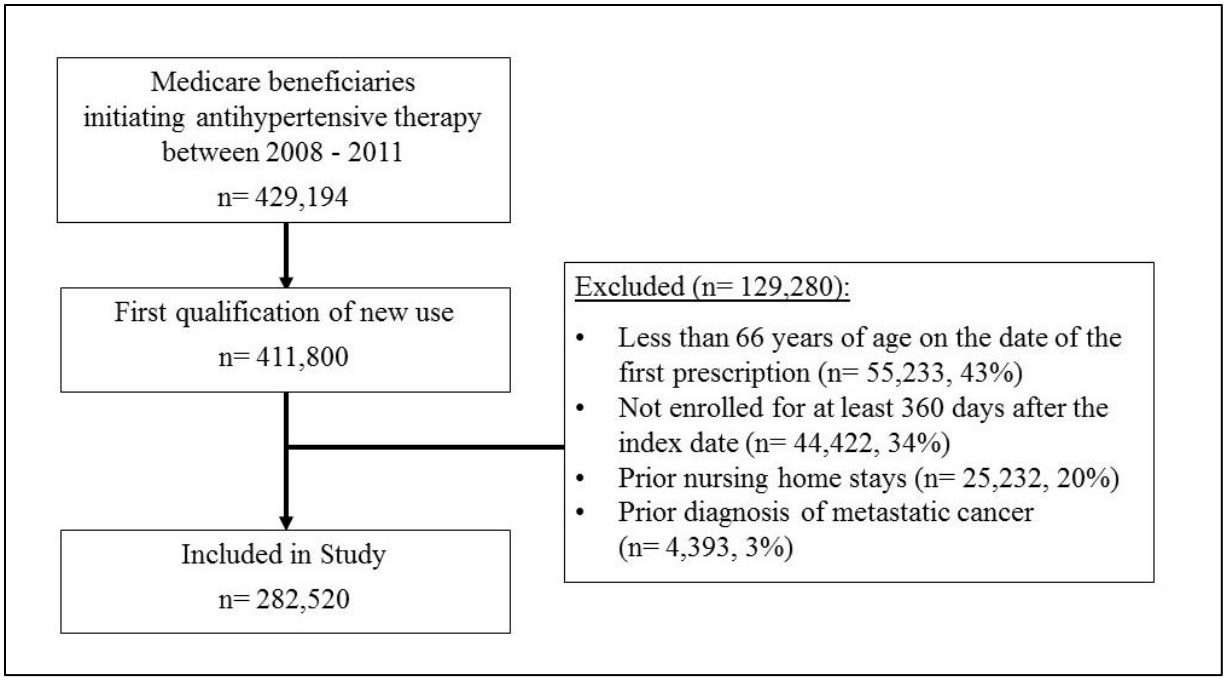

Figure 2: Eligibility flow chart for the study cohort

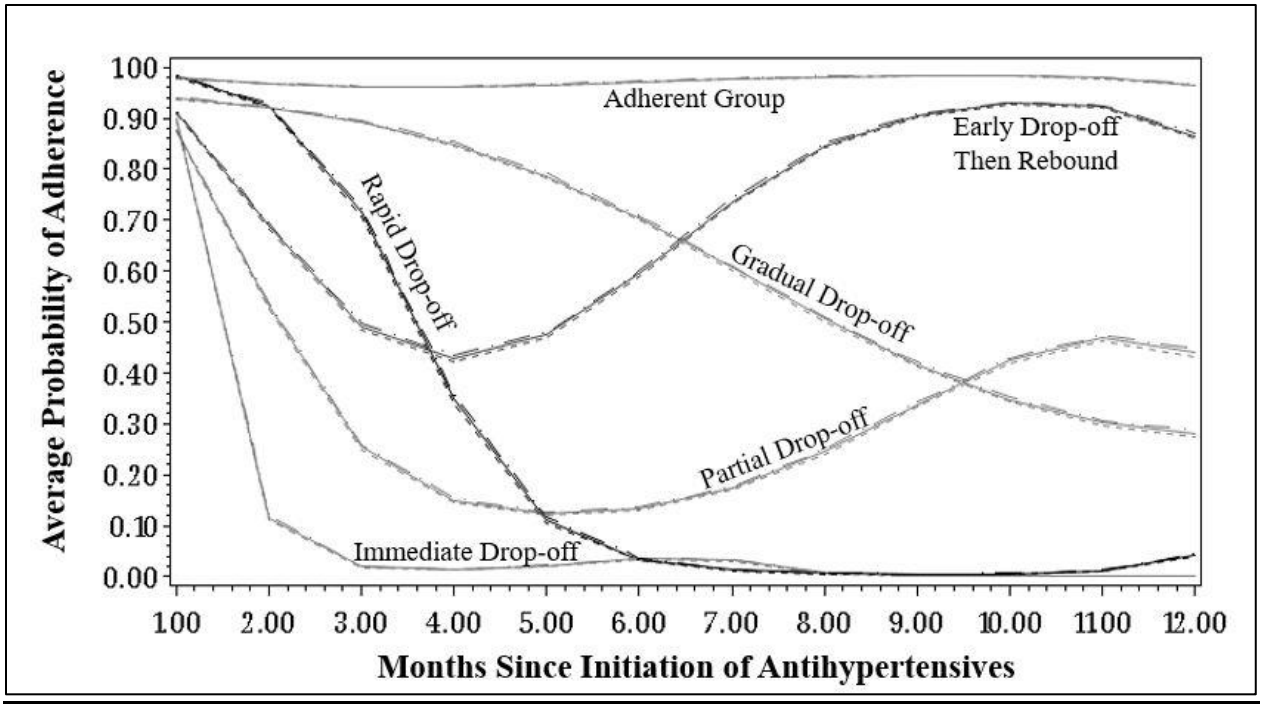

Figure 3: Antihypertensive adherence trajectories in the 12 months following initiation

CHAPTER 5: INITIATION OF ANTIHYPERTENSIVE MONOTHERAPY AND INCIDENT FRACTURES AMONG MEDICARE BENEFICIARIES

5.1 Introduction

Fractures are one of the most common fall-related injuries for adults over the age of 65.[89] In older adults, fractures are associated with high medical costs, loss of independence, and an increased risk of mortality.[43-45,90] Older adults are at greater risk of fractures due to decreased bone mineral density (BMD), increased comorbidities, and increased medication use.[30,91] Comorbidities such as cardiovascular disease, osteoporosis, Parkinson's disease, and diabetes can increase fracture risk.[30,52,92] Medications increasing the risk of fractures include opioids, benzodiazepines, antidepressants, antiepileptics, and skeletal muscle relaxants.[65,93,94] Recently, research suggests antihypertensives may increase the risk of fall-related injury by as much as 11% among older adults.[11,60]

Antihypertensives are associated with fractures through medication-related adverse events and by interactions with BMD.[12] First, antihypertensives can increase the risk of falls and subsequent fractures upon initiation due to orthostatic hypotension.[11,30] Orthostatic hypotension is defined as a decrease in blood pressure upon standing,[68] and is associated with an elevated risk of falls and fractures among hypertensive adults.[95] Second, antihypertensives have been suggested to impact BMD in observational and clinical studies. For instance, thiazide diuretics reduce urinary calcium secretion and can stimulate osteoblasts potentially providing a protective effect for fractures.[32,67,96] Angiotensin receptor blockers and angiotensin converting enzyme inhibitors are believed to impact BMD by inhibiting bone turnover caused by the renin-angiotensin-aldosterone system.[32]

Prior research has found inconsistent results regarding the strength and direction of the association between antihypertensives and fractures.[11,66] Some studies have found antihypertensives increase the risk of fractures[60,61,97], while others have found no association[65], or a protective association

for fractures.[67,96,98] Few studies have examined the initial increased risk of fractures associated with starting antihypertensive therapy, and how the association between antihypertensives and fractures varies time. Therefore, we sought to examine the association between antihypertensives and incident non-vertebral fractures within the first year of initiation among Medicare beneficiaries. We hypothesized that the association between antihypertensives and fractures would vary over time due to different time-dependent drug effects.

5.2 Methods

Data Source

We used a 20% nationwide, random sample of fee-for-service Medicare beneficiaries who were enrolled at least one month in Medicare Parts A (inpatient care), B (outpatient care), and D (prescription drugs) coverage between 2007 and 2011. Data were obtained under a data use agreement established with the Centers for Medicaid and Medicare Services (CMS) and the University of North Carolina at Chapel Hill (UNC-CH). The study protocol was approved by UNC's Non-Biomedical Institutional Review Board.

New Users of Antihypertensive Monotherapy

The study cohort consisted of all new users of antihypertensive medication initiating during 2008-2011 who were continuously enrolled in Medicare Parts A, B, and D for at least twelve months prior to initiation. New use was defined as not having a prior prescription of the following antihypertensive medications in the last twelve months: angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB), or thiazide diuretics (THZ). We limited the cohort to beneficiaries initiating with monotherapy (e.g., one class of antihypertensive drug) since we were interested in examining differences in effect by drug class.

We excluded beneficiaries who were originally eligible for Medicare due to end stage renal disease or disability and those beneficiaries with prior nursing home stays. Additionally, we excluded beneficiaries who had a previous diagnoses for tremor disorder or congestive heart failure since these health conditions could result in being prescribed antihypertensives. Since we were interested in

capturing incident fractures, we excluded beneficiaries who had prior falls or fractures. Finally, we required a second antihypertensive fill within 30 days of the end of the index drug's days supply to exclude those beneficiaries who filled the first prescription and never returned (Appendix Figure 10). We did not exclude beneficiaries with chronic kidney disease or diabetes, despite these being indications for certain antihypertensive drug classes, however we did conduct sub-analysis excluding these beneficiaries (see Statistical Analysis).

Initiation of Antihypertensive Therapy

Prescription medication data were identified using Medicare Part D. Using fill dates, we identified the date of the initial prescription for antihypertensive therapy (index date). Antihypertensive medications were identified using National Drug Codes (NDC) and generic drug names (Appendix Table 18). These specific drug classes were chosen based on the current recommendations for hypertension treatment in older adults.[13]

Incident Non-Vertebral Fractures

Incident non-vertebral fractures within twelve months of initiating antihypertensive monotherapy were our primary outcome. Starting the day after the index date, we followed beneficiaries until the first fracture event. Fractures were identified using validated diagnostic and procedure codes in Medicare Parts A and B (Appendix Table 23).[99] We chose to examine fractures instead of falls since the accuracy of fall reporting varies by state and has low specificity in claims data.[100] We excluded fractures that had a corresponding external cause-of-injury relating to motor vehicle crashes (E810-E825) and those that occurred on the index date.

In sub-analyses, we grouped fractures according to the anatomical location to distinguish between fractures that were likely related to low BMD. Low BMD fractures, or osteoporotic fractures, are typically defined as fractures occurring at the hip, radius, or vertebrae.[53] Since incident vertebral fractures are not well captured in claims data[101], we defined probable low BMD fractures as any fracture event involving the hip or radius.[53] All other non-vertebral fracture were classified as probable normal BMD fractures.

Risk Factors for Fractures

Covariates were selected based on the previous literature [30,92,93,102-104] and were defined based on claims during the twelve months prior to initiation (Appendix Table 24). Covariates included: demographics (age, gender, and race), concurrent medication use and prior use of medications associated with fractures (loop diuretics, antiarrhythmics, antidepressants, antiepileptics, anxiolytics, benzodiazepines, bisphosphonates, antipsychotics, skeletal muscle relaxants, opioids, and hypnotics), codes for chronic comorbidities associated with fracture risk (diabetes, chronic kidney disease, Parkinson's disease, Alzheimer's disease, osteoporosis, arrhythmia, osteoarthritis, rheumatoid arthritis, stroke, myocardial infarction, hypertension, orthostatic hypotension, syncope, dementia, urinary incontinence, dyslipidemia, and obesity), frailty predictors, and prior hospital utilizations (hospital admissions). Concurrent medication use was defined as the number of distinct drug prescriptions filled in the 14 days prior to antihypertensive initiation. As a proxy for sociodemographic status, we identified whether beneficiaries were eligible for the Medicare low-income subsidy (LIS) program. LIS offers medication at a reduced cost for beneficiaries that are eligible due to income, family size, and household resources. We included the frailty index score (FIS) as a proxy measure of frailty.[76] Additionally, we examined the prevalence of factors positively (ambulance transfer, wheelchair/walker use, home oxygen use, hospital bed, difficulty walking, and vertigo) and inversely (cancer screenings) associated with limitations in activities of daily living.[76]

Statistical Analysis

Descriptive statistics were used to compare baseline covariates according to antihypertensive class initiated on the index date. We estimated propensity scores using multinomial logistic regression models to adjust for differences in the distribution of baseline covariates across antihypertensive drug classes. Standardized mortality ratio (SMR) weighting was used to weight beneficiaries of each drug class to achieve the same baseline covariate distribution as beneficiaries receiving an ACE. Therefore, beneficiaries initiating with ACEs were assigned a weight of one and all others were assigned a weight that was the ratio of the propensity score to one minus the propensity score.[105] ACEs were used as the

referent since they were the most commonly prescribed drug class.[106] To assess the effectiveness of the propensity scores, we examined the distribution of baseline covariates after SMR weighting.

Incident fracture rates and corresponding 95% confidence intervals (CIs) were defined as the total number of incident fractures by the total person-years at risk. Person-years was defined as the total number of days at risk for fractures divided by 365.25. We used SMR-weighted Cox proportional hazard models to estimate hazard ratios (HRs) and 95% CIs of incident fractures for each drug class initiated on the index date versus receiving an ACE according to days since initiation of therapy, 1-14 days and 15-365 days. CIs were calculated using robust standard errors to account for SMR weights. We used a 'first-treatment-carried-forward' analysis to avoid introducing confounding by indication since antihypertensive adherence varies, and beneficiaries who remain adherent may differ from the majority of hypertensive patients.[107] Using this analysis, beneficiaries contributed person-time at risk until they had an incident fracture or until the end of the follow-up (death, disenrollment from Medicare, or December 31, 2012), whichever came first. SMR weighted Kaplan-Meier curves were used to graph the proportion of beneficiaries without fracture events according to time since initiation. For our secondary analysis when we classified fractures according to probable low vs. normal BMD fractures, if a beneficiary had a fracture event before the event of interest (e.g., normal BMD fracture before a low BMD fracture), beneficiaries were censored at the date of the first fracture event.

Sensitivity Analyses

To assess the robustness of our analysis decisions, we performed four separate sensitivity analyses. First, we repeated the analysis using an 'As-treated' design. In the 'As-treated' analysis, follow-up additionally ended when beneficiaries switched antihypertensive therapy (e.g., switched to another antihypertensive class or started combination therapy), or discontinued use (e.g., failed to fill another prescription 30 days after the end of the last drugs' days supply). Second, we repeated the analysis extending the first follow-up period to 30 days since the time it takes for blood pressure to stabilize after antihypertensive initiation is not known. Third, we repeated the primary analysis excluding beneficiaries who initiated therapy using a brand antihypertensive medication versus a generic

antihypertensive medication. Generic medications are less prone to sample use and are thus less prone to have started antihypertensive therapy before the first dispensed prescription.[87] Lastly, since chronic kidney disease and diabetes can impact physicians' choice of antihypertensive class prescribed, we repeated the analysis removing any beneficiaries with these chronic conditions.

5.3 Results

Between 2008 and 2011, 122,629 Medicare beneficiaries initiated antihypertensive monotherapy. On average beneficiaries were 75 years old, 61% were women, and the majority were White (86%). The most common classes of antihypertensives prescribed were ACEs (33%), BBs (30%), and CCBs (15%). Before SMR weighting, demographics, diabetes, chronic kidney disease, cardiovascular disease (e.g., arrhythmia, stroke, hypertension, and dyslipidemia), ambulance transfers, cancer screenings, and prior hospitalizations differed across beneficiaries according to antihypertensive class. After SMR weighting, there was little difference between baseline characteristics according to antihypertensive class (Table 8).

During the first year after initiation of antihypertensive monotherapy, beneficiaries experienced 4,430 incident non-vertebral fractures over 115,991 person-years (rate = 382 per 10,000 person-years, 95%CI: 371-393). Fractures most commonly occurred at the hip (79%), foot (17%), radius (15%), and hand (14%). Just over one-third of the fractures resulted in a single-bone break (77%).

Rates of incident fracture varied according to antihypertensive class and by time since initiation (Table 9, Appendix Figure 11). During the first 14 days, beneficiaries who initiated with THZs (438 per 10,000 person-years, 95%CI: 294-628) and BBs (410 per 10,000 person-years, 95%CI: 314-526) had the highest rate of fractures. Beneficiaries initiating with CCBs had the highest rate of fractures during the 15-365 days after initiation (435 per 10,000 person-years, 95%CI: 404-468), but a low rate in the first 14 days (383 per 10,000 person-years, 95%CI: 258-550). Initiators of ARBs had the lowest rate of fractures during the initial 14 days (333 per 10,000 person-years, 95%CI: 190-546) and during the 15-365 days after initiation (321 per 10,000 person-years, 95%CI: 287-358).

After controlling for differences in baseline characteristics, beneficiaries who initiated with THZs had the highest rate of fractures in the first 14 days after initiation compared to beneficiaries who initiated

with ACEs (SMR-HR: 1.40, 95%CI: 0.78-2.52). After the first 14 days, beneficiaries who initiated with CCBs (SMR-HR: 1.11, 95%CI: 1.00-1.24) and BBs (SMR-HR: 1.09, 95% CI: 1.00-1.19) had slightly higher fractures rates compared to the beneficiaries who initiated with ACEs.

When we compared the rates of incident probable low BMD fractures and normal BMD fractures, results were similar for all the antihypertensive classes except THZs. During the one year following initiation, beneficiaries who initiated with THZs had a lower hazard ratio of probable low BMD fractures (SMR-HR: 0.85, 95%CI: 0.68-1.06), but a slightly higher hazard ratio of normal BMD fractures (SMR-HR: 1.12, 95%CI: 0.98-1.29) compared to beneficiaries who initiated with ACEs (Table 10).

In sensitivity analyses, results were similar when we 1) used an 'as-treated' analysis, 2) excluded beneficiaries with a previous diagnosis of chronic kidney disease or diabetes, and 3) excluded beneficiaries who initiated with brand antihypertensive drugs (Figure 4, Appendix Table 25). When we extended the initial follow-up period to 30 days, beneficiaries who initiated with THZs (SMR-HR: 1.15, 95%CI: 0.75-1.76) and BBs (SMR-HR: 1.36, 95%CI: 1.01-1.83) still had the highest rate of fractures compared to beneficiaries who initiated with other antihypertensive classes (results not shown).

5.4 Discussion

We found incident fracture rates in the year following initiation of antihypertensive therapy differ depending on antihypertensive class, and these patterns were affected by the time since initiation. Medicare beneficiaries who initiated with THZs or BBs had higher fracture rates during the first two weeks compared to beneficiaries who initiated with other antihypertensives. However, during the first year beneficiaries who initiated with CCBs had the highest fracture rate. Similar to previous research, we found beneficiaries who initiated with ACEs or ARBs had the lowest rate of fractures.[11,61,108]

We found older adults initiating with THZs or BBs had the highest fracture rates during the first two weeks following initiation. Similar to our results, Berry et al. found that THZs initiators had an increased odds of hip fracture in the first days following initiation compared to periods of no use.[109] Butt et al. found that the use of any antihypertensive was associated with an increased risk of hip fracture in the first 45 days following initiation, and that this risk was most elevated for older adults initiating with

ACEs.[63] However, Ruths et al. found that only loop diuretics were associated with an initial increased risk of hip fractures during the first two weeks of use when comparing the initial fracture risk among antihypertensive classes.[67] The initial increase in fracture rates may be due to orthostatic hypotension. Among the classes of antihypertensives, THZs and BBs are most strongly associated with orthostatic hypotension.[30] Given that orthostatic hypotension can be asymptomatic,[11,110] results suggest that clinicians and older adults need to be aware of the potential increased risk of orthostatic hypotension and subsequent fractures upon initiation, especially when starting with THZs or BBs.

Gangavati et al. found that the risk of falls associated with orthostatic hypotension was lower among older adults with controlled hypertension compared to older adults with uncontrolled hypertension.[95] This suggests that increases in fracture rates once hypertension is controlled are due to other mechanisms besides orthostatic hypotension. One mechanism that may influence the association between antihypertensives and fractures could be antihypertensives interactions with BMD.[12,32] We found older adults initiating with THZs had a decreased rate of hip and radius fractures in the year following initiation. THZs can impact the risk of low BMD fractures by promoting osteoblast activity and reducing calcium urinary excretion.[32,111] A 2011 Cochrane review found that THZs were associated with as much as a 24% reduction in hip fractures when comparing THZ users vs. non-users.[111] Results suggest that older adults at elevated risk of fractures may potentially benefit from receiving THZs compared to other classes of antihypertensives. However, we were unable to clinically measure BMD. More research is needed featuring clinical BMD measurements to see if these results hold in clinical settings.

Older adults initiating with CCBs had higher fracture rates compared with ACE initiators. Previous studies have found inconsistent results regarding the association between CCBs and fractures. Ruths et al. found that CCBs were associated with a decreased risk of hip fractures when comparing periods of use and non-use.[67] However, this study was limited to hip fractures and results were unadjusted for comorbidities associated with fractures.[67] In another study, Choi et al. found that compared to non-users of antihypertensives, adults prescribed CCBs had a slightly elevated rate of non-

vertebral fractures.[61] In our study, beneficiaries who initiated with CCBs were frailer than beneficiaries who initiated with other antihypertensives. Although we included frailty predictors in the propensity scores, we cannot eliminate the possibility that residual confounding remained after adjustment, given that frailty is multi-dimensional and is difficult to capture with claims data alone.[112]

Despite conducting sensitivity analyses, this study does have limitations. First, results may be subject to residual confounding. We used SMR weights to limit confounding by indication but were unable to control for physical activity, visual impairment, baseline BMD, and alcohol use. Some research suggests removing outlier SMR weights to better control for residual confounding. We did not exclude outlier weights since excluding these observations resulted in little difference in the results, suggesting that variations in weights were most likely random. Second, our study population was predominantly White. It is unknown if these results would hold true for non-White populations. Third, our results are limited to the one year period following initiation. The time it takes for antihypertensives to have clinically relevant BMD affects are not known. One year may not have been long enough to identify all possible BMD affects. Lastly, our results did not take into account antihypertensive dose. Previous research suggests that the relationship between antihypertensives and fractures is linearly associated with increasing dose.[11,64] Results may be underestimated for older adults on higher doses of antihypertensives.

It is important that researchers and clinicians identify modifiable factors that can reduce the risk of fractures among older adults. We found certain classes of antihypertensive medications may impact the rate of fractures in older adults. Specifically, THZs and BBs were associated with increased fracture rates in the first two weeks after initiation. Older adults taking these medications should be aware of this possible increased risk of fractures, particularly in the first few weeks after starting therapy. Also, we found that ACEs and ARBs are associated with lower fracture rates after initiation. When deciding upon antihypertensive therapy, clinicians may want to consider different fracture risks when choosing between antihypertensive drug classes, especially in frail older adults or those with a history of falls or fractures.

Table 8: Characteristics of Medicare beneficiaries initiating antihypertensive monotherapy between 2008-2011 (n=122,629)

	ACE n=40,186	ARB n=10,954		BB n=36,972		CCB n=18,411		THZ n=16,106	
	Cohort	Cohort	SMRW	Cohort	SMRW	Cohort	SMRW	Cohort	SMRW
Mean Age, std (years)	74, 6.7	75, 6.7	74, 12.9	75, 7.0	74, 7.1	76, 7.4	75, 10.0	75, 7.0	75, 10.8
Mean Frailty Index, std	0.1, 0.1	0.1, 0.1	0.1, 0.2	0.1, 0.1	0.1, 0.1	0.1, 0.2	0.1, 0.2	0.1, 0.1	0.1, 0.2
Male, %	42.0	36.6	41.5	41.7	42.2	37.8	42.1	29.3	42.4
White Race, %	87.1	79.1	87.3	89.0	86.9	81.9	86.9	86.5	87.1
Low-Income Subsidy, %	5.3	5.5	5.5	4.6	5.4	5.8	5.4	5.1	5.2
Medication History, %									
1-2 Meds Filled[a]	61.3	62.4	61.8	58.6	61.4	59.8	62.5	66.9	62.5
3-4 Meds Filled[a]	27.7	26.5	27.4	28.7	27.2	27.1	26.3	24.7	26.5
5 + Meds Filled[a]	11.1	11.2	10.8	12.7	11.4	13.0	11.3	8.5	11.1
Loop Diuretic	5.8	5.9	5.9	7.0	6.1	6.4	6.0	3.7	6.4
Antiarrhythmic	2.6	4.2	2.5	5.4	2.8	4.5	2.7	2.7	3.0
Antidepressant[b]	15.2	14.9	15.2	16.0	15.6	15.9	15.6	15.4	15.5
Antipileptic[b]	7.4	7.3	7.3	8.0	7.5	8.2	7.6	7.7	7.4
Anxiolytic	3.4	3.4	3.5	4.0	3.6	4.1	3.6	3.7	3.5
Benzodiazpene[b]	1.1	1.0	1.1	1.5	1.2	1.3	1.2	1.3	1.1
Bisphosphonate	10.6	12.4	10.6	11.2	10.4	11.6	10.7	13.0	10.8
Antipsychotic[b]	3.5	2.8	3.5	4.2	3.7	4.9	3.7	3.8	3.7
Skeletal Muscle Relaxant[b]	6.2	6.2	6.2	6.5	6.5	6.3	6.4	6.5	6.4
Opioid	27.0	26.2	27.4	30.2	27.2	29.5	27.5	28.0	28.2
Hypnotic[b]	6.1	7.9	6.0	7.5	6.1	7.14	6.2	6.7	6.2
Chronic Conditions, %									
Diabetes	31.6	30.6	31.0	19.0	32.8	18.3	31.4	13.5	32.9
Chronic Kidney Disease	8.7	10.5	8.8	10.6	9.4	13.1	9.3	6.3	9.8
Parkinson's Disease	1.2	1.1	1.2	1.5	1.2	1.5	1.2	1.3	1.2
Alzheimer's Disease	3.2	2.4	3.1	3.0	3.4	4.4	3.3	3.1	3.6
Osteoporosis	14.1	17.3	14.2	16.0	14.1	17.4	14.4	16.9	14.6
Arrhythmia	10.5	10.9	10.4	32.9	10.6	25.4	10.6	8.5	11.6
Osteoarthritis	14.4	17.8	14.3	16.1	14.7	15.5	14.9	15.7	15.1
Rheumatoid Arthritis	2.5	3.4	2.5	3.2	2.6	3.0	2.7	2.5	2.6

Stroke	13.7	13.5	13.5	16.6	15.0	16.4	15.1	10.3	14.9
Myocardial Infarction	0.6	0.2	0.6	4.0	0.6	0.6	0.7	0.1	0.7
Hypertension	83.3	88.2	83.5	63.3	84.3	78.6	85.3	76.8	85.0
Orthostatic Hypotension	0.6	0.6	0.7	1.1	0.7	0.9	0.8	0.5	0.6
Syncope	3.8	4.2	3.7	7.4	4.0	6.1	4.2	3.0	4.3
Dementia	5.8	4.2	5.6	5.9	6.1	8.2	6.1	5.6	6.1
Urinary Incontinence	4.7	4.8	4.7	4.9	4.8	5.5	4.9	4.5	4.9
Dyslipidemia	64.8	70.2	64.2	64.0	65.7	58.2	65.3	57.2	65.3
Obesity	4.4	4.2	4.5	3.7	4.6	3.3	4.4	4.1	4.4
Frailty Indicators, %									
Home Oxygen Use	2.4	2.5	2.4	2.5	2.6	5.3	2.3	2.7	2.6
Walker/Wheelchair Use	2.2	2.4	2.2	2.8	2.3	3.3	2.3	2.4	2.5
Hospital Bed Use	0.5	0.5	0.5	0.5	0.5	0.9	0.5	0.5	0.6
Difficulty Walking	7.7	7.5	7.6	8.9	8.2	9.5	8.4	8.2	8.3
Vertigo	11.5	12.4	11.3	14.5	12.1	14.1	12.4	12.4	12.1
Ambulance Transport	6.9	4.8	6.8	12.4	7.3	12.6	7.3	5.4	7.5
Cancer Screenings	41.0	39.2	40.9	39.3	40.4	35.5	40.6	43.7	40.1
Hospital Utilization, %									
Hospital Admissions	13.2	10.1	13.2	25.5	13.6	23.8	13.3	10.1	14.3

[a] Number of number of distinct drug prescriptions filled in the 14 days prior to antihypertensive initiation

[b] Medication indicated to be associated with fracture risk according to the 2015 Beers Medication Guideline.[93]

Prevalence of baseline characteristics was identified 12 months prior to initiation of antihypertensive monotherapy.

Race was missing for a total of 147 beneficiaries and these were excluded from the SMR weighted analysis

SMRW= standardized mortality ratio weighting (ACE was the referent). Angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB), or thiazide diuretics (THZ)

Table 9: Rates and adjusted hazard ratios (HRs) of incident non-vertebral fractures within the first year of initiation among Medicare beneficiaries starting antihypertensive monotherapy

	1-14 days after initiation				15-365 days after initiation			
Drug Class	# Fractures	P-Yrs	Rate Per 10,000 P-Yrs (95% CI)	SMRW HR (95% CI)	# Fractures	P-Yrs	Rate Per 10,000 P-Yrs (95% CI)	SMRW HR (95% CI)
ACE	54	1,539	351 (266, 454)	ref	1,271	36,618	347 (328, 367)	ref
ARB	14	420	333 (190, 546)	0.92 (0.49, 1.75)	322	10,032	321 (287, 358)	0.96 (0.84, 1.09)
BB	58	1,416	410 (314, 526)	1.00 (0.65, 1.54)	1,375	33,449	411 (390, 433)	1.09 (1.00, 1.19)
CCB	27	705	383 (258, 550)	0.82 (0.50, 1.36)	720	16,540	435 (404, 468)	1.11 (1.00, 1.24)
THZ	27	617	438 (294, 628)	1.40 (0.78, 2.52)	562	14,656	384 (353, 416)	1.02 (0.90, 1.15)

P-Yrs= person-years (calculated by dividing the total number of follow-up days by 365.25)
SMRW= Standardized mortality ratio weight, calculated adjusting for all baseline covariates.
HRs and 95% confidence intervals (CIs) are adjusted for SMRWs.
Angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB), or thiazide diuretics (THZ)

Table 10: Rates and hazard ratios (HRs) of incident probable low and normal bone mineral density (BMD) fractures within the first year of initiation among Medicare beneficiaries starting antihypertensive monotherapy

	Probable Low BMD Fractures				**Normal BMD Fractures**			
Drug Class	# Fractures	P-Yrs	Rate Per 10,000 P-Yrs (95% CI)	SMRW HR (95% CI)	# Fractures	P-Yrs	Rate Per 10,000 P-Yrs (95% CI)	SMRW HR (95% CI)
ACE	424	38,157	111 (101, 122)	ref	901	38,157	236 (221, 252)	ref
ARB	99	10,452	95 (77, 115)	0.93 (0.74, 1.17)	237	10,452	227 (199, 257)	0.97 (0.84, 1.13)
BB	464	34,864	133 (121, 146)	1.08 (0.93, 1.26)	969	34,864	278 (261, 296)	1.09 (0.98, 1.21)
CCB	280	17,245	162 (144, 182)	1.13 (0.95, 1.35)	467	17,245	271 (274, 296)	1.09 (0.96, 1.24)
THZ	171	15,273	112 (96, 130)	0.85 (0.68, 1.06)	418	15,273	274 (248, 301)	1.12 (0.98, 1.29)

P-Yrs= person-years (calculated by dividing the total number of follow-up days by 365.25).
SMRW= Standardized mortality ratio weight, calculated adjusting for all baseline covariates.
HRs and 95% confidence intervals (CIs) are adjusted for SMRWs.
Probable low BMD fractures included hip and radius fractures. All other non-vertebral fractures were defined as normal BMD fractures.
Angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB), or thiazide diuretics (THZ).

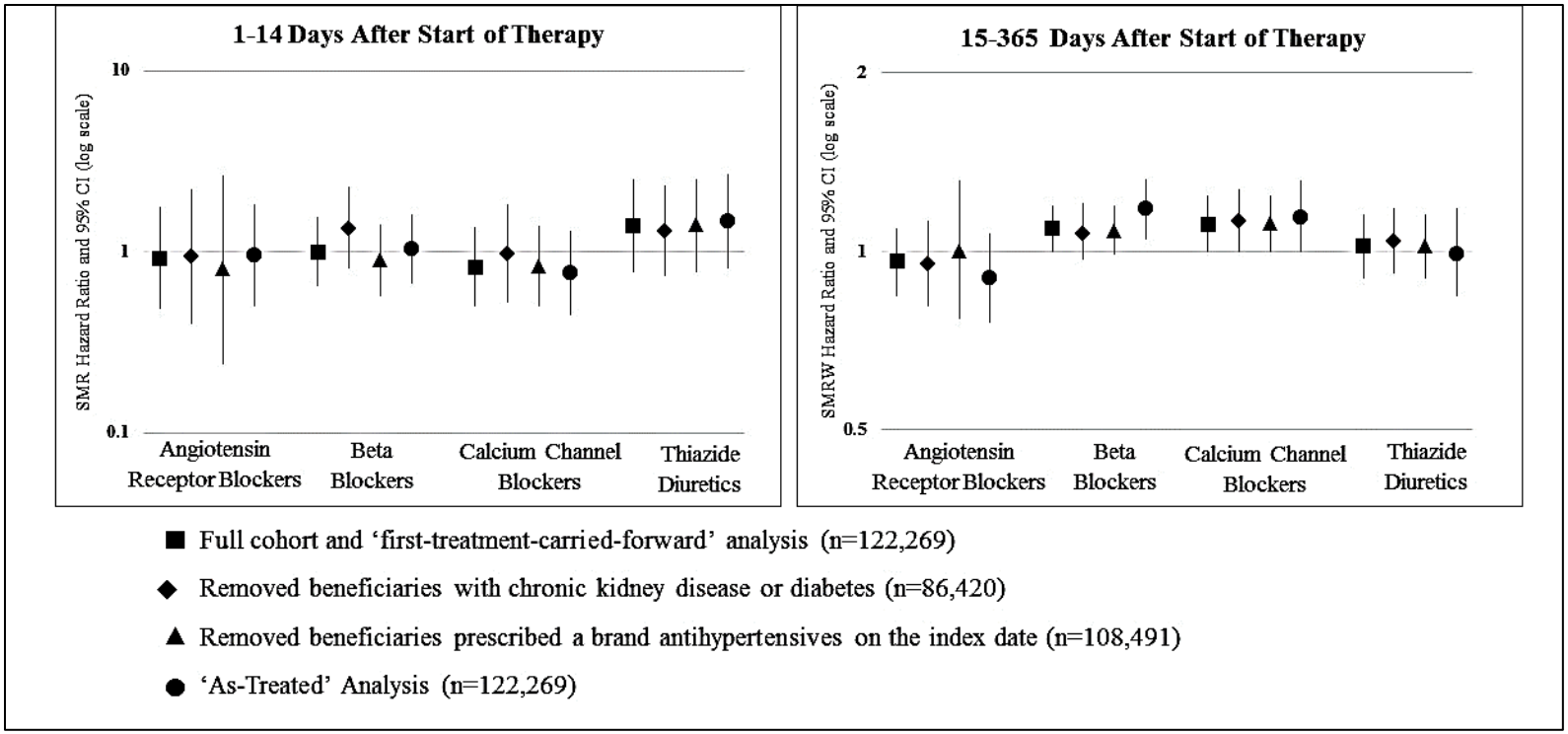

Figure 4: Sensitivity analysis results for the adjusted hazard ratios comparing the rate of incident fractures after initiation of antihypertensive monotherapy according to criteria used to identify the Medicare cohort. The reference group for the SMR weights were Medicare beneficiaries initiating with angiotensin converting enzyme inhibitors.

CHAPTER 6: ANTIHYPERTENSIVE ADHERENCE TRAJECTORIES AND SUBSEQUENT FRACTURES

6.1 Introduction

Previous research has suggested antihypertensive medications are associated with fractures due to interactions with bone mineral density (BMD).[11,32] For instance, thiazide diuretics reduce urinary calcium secretion and stimulate osteoblasts, or bone cells, potentially providing a protective effect for fractures.[32,67,96] Angiotensin-receptor blockers (ARB) and angiotensin-converting-enzyme inhibitors (ACE) are believed to impact BMD and subsequent fracture risk by inhibiting bone turnover caused by the renin-angiotensin-aldosterone system (RAAS).[32] However, prior research has found inconsistent results regarding the association between antihypertensives and fractures.[11,66] Some studies have found antihypertensives increase fracture risk[60,61,97], while others have found no association[65], or a protective association for fractures.[67,96,98]

One reason for the inconsistent results may be due to confounding introduced by antihypertensive adherence. Prior studies have found that antihypertensive adherence trajectories vary in the first year after initiation.[107] Approximately half of older adults remain adherent to their antihypertensive medication in the year following initation.[4] Failure to remain adherent can lead to an increased risk of cardiovascular disease, hospitalization, and mortality.[23,40,70,71] Older adults are at greater risk of nonadherence due to polypharmacy and increased comorbidities.[2] Female gender, low income, mental health disorders, non-White race and cognitive impairment are associated with non-adherence. [2,4,5,34]

No prior study has examined the impact antihypertensive adherence has on the association between antihypertensives and fractures. If antihypertensives have protective effects on BMD, then older adults who are more adherent to their antihypertensive medication would most benefit by these

interactions. In this study, we sought to examine the association between antihypertensive adherence and subsequent fractures among Medicare beneficiaries initiating antihypertensive therapy.

6.2 Methods

Data Source

We used a 20% nationwide, random sample of fee-for-service Medicare beneficiaries with at least one month of combined parts A (inpatient care), B (outpatient care), and D (prescription drugs) coverage between 2007 and 2011. Data were obtained under a data use agreement established with the Centers for Medicaid and Medicare Services (CMS) and the University of North Carolina at Chapel Hill (UNC-CH). The study protocol was approved by UNC's Non-Biomedical Institutional Review Board.

Medicare beneficiaries initiating antihypertensive therapy

The study cohort consisted of Medicare beneficiaries initiating therapy with antihypertensive medications during 2008-2011 who were enrolled in Medicare Parts A, B, and D for at least 12 months prior to initiation. New use was defined as not having a prior prescription for any of the following antihypertensive medications in the last 12 months: angiotensin-converting-enzyme inhibitors (ACE), angiotensin-receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB), or thiazide diuretics (THZ). Given the four-year window used for identifying new use, beneficiaries potentially could qualify as new users more than once, but we limited the cohort to first time qualification of new use.

Beneficiaries who were originally eligible for Medicare due to end stage renal disease or disability and those who were less than 66 years of age at the start of therapy were excluded. We excluded beneficiaries with prior nursing home stays and those with a diagnosis of metastatic cancer in the year prior to starting therapy since these factors could impact adherence to chronic medication. Additionally, we excluded beneficiaries who had previous diagnoses for tremors or congestive heart failure since these health conditions could result in being prescribed antihypertensives. Since prior fractures and falls increase your risk of future fractures, we excluded beneficiaries who had any falls or fractures in the 12 months prior to starting therapy. Finally, we required beneficiaries to remain enrolled in Medicare for at least 360 days following initiation to capture patterns of antihypertensive use (Figure 5).

Antihypertensive Adherence Trajectories

Antihypertensive adherence trajectories in the one year following initiation of therapy were the primary exposure. Adherence trajectories use were defined using date of dispensing and days supply data (assuming constant daily dose). Starting on the index date, we counted the number of days each month a beneficiary was covered by any of the following antihypertensive drug classes: ACEs, ARBs, BBs, CCBs, or THZ. We choose these classes based on recommendations for hypertension treatment in older adults.[2] Months were defined in 30-day intervals. If a new prescription was filled prior to the end of the last days' supply, the day of the new prescription began the day after the prior prescription would have ended.

After counting the number of days covered each month, binary indicator variables were used to specify whether an individual was covered by an antihypertensive medication for at least 24 out of 30 days (e.g., 80% days covered). The 80% threshold is considered to have high sensitivity (92%) and specificity (89%) for distinguishing between adherent and non-adherent antihypertensive patients[73] and is associated with improved cardiovascular health.[40]

Non-Vertebral Fracture Outcomes

After identifying the one-year antihypertensive adherence trajectories, we began following beneficiaries for non-vertebral fractures (Figure 6). We chose to focus on non-vertebral fractures since incident vertebral fractures are not well captured in claims data.[101] Therefore, follow-up for fractures began 361 days after the date of the initial antihypertensive prescription. Fractures were identified using validated diagnostic and procedure codes found in Medicare Parts A and B (Appendix Table 23).[99] We excluded fractures that had a corresponding external cause-of-injury code (E-code) relating to motor vehicle crashes (E810-E825).

Covariates

Covariates were selected based on the previous literature [30,57,91,92,102] and were defined based on claims during the 12 months prior to initiation. Covariates included: demographics (age, gender, and race), concurrent medication use and previous use of medications associated with fractures (loop

diuretics, antiarrhythmics, antidepressants, antiepileptics, anxiolytics, benzodiazepines, opioids, hypnotics, skeletal muscle relaxants, and antipsychotics), codes for chronic comorbidities associated with fracture risk (diabetes, chronic kidney disease, Parkinson's disease, Alzheimer's disease, osteoporosis, BMD testing, arrhythmia, osteoarthritis, rheumatoid arthritis, stroke, myocardial infraction, hypertension, orthostatic hypotension, obesity, dementia, dyslipidemia, and urinary incontinence), frailty predictors, and prior hospital admissions. Type of antihypertensive medication initiated on the index date was defined as combination therapy (e.g., more than one class of antihypertensive) vs. monotherapy. Concurrent medication use was defined as the number of distinct drugs prescribed in the 14 days prior to the index date. As a proxy for sociodemographic status, we identified whether beneficiaries were eligible for the Medicare low-income subsidy (LIS) program. LIS offers medication at a reduced cost for beneficiaries that are eligible due to income, family size, and household resources. We used the frailty index score (FIS), which was developed to predict limitations in activities of daily living, as a proxy measure of frailty among Medicare beneficiaries.[76] Additionally, we examined the prevalence of several variables that were found to be positively (ambulance transfer, wheelchair/walker use, home oxygen use, hospital bed, difficulty walking, and vertigo) and inversely (cancer screenings) associated with limitations in activities of daily living.[76]

Analysis

We used group based trajectory models (GBTMs) to classify beneficiaries by patterns of antihypertensive adherence in the first year following initiation. GBTMs were defined using logistic regression models. Dependent variables were monthly binary indicators of antihypertensive use, and months since index date were the independent variables. Time was modeled using cubic terms. In order to identify the best fitting model, we started with a two-group model and subsequently added up to seven groups. We used Bayesian Information Criterion (BIC), trajectory group size, and the average posterior probability of membership to identify the optimal number of groups. BIC is a statistical measure of model fit with lower scores signifying better overall fit. The average posterior probability of group membership

signifies how well beneficiaries fit within the group that they were assigned. Trajectories were defined using "Proc Traj".[78]

Descriptive statistics were used to compare the prevalence of baseline covariates according to antihypertensive adherence trajectory. Incident fracture rates and corresponding 95% confidence intervals (CIs) were defined as the total number of incident fracture events divided by the total person-time at risk for fractures. Person-years was defined as the total number of days at risk for fractures divided by 365.25. We used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% CIs for incident fractures for each antihypertensive adherence trajectory versus the most adherent trajectory group. Starting the day after the exposure period (Day 361) we followed beneficiaries until they had a fracture or until the end of the follow-up (death, disenrollment from Medicare, or December 31, 2013), whichever came first.

As a sensitivity analysis, we examined whether shortening the follow-up period to 6 months altered the results. Additionally, to assess possible bias associated with overall health, we calculated the rate of mortality or disenrollment from Medicare during the follow-up period according to trajectory groups. Finally, we examined the rate of incident fractures during the one year period used to define antihypertensive adherence trajectories (Day 1- Day 360).

6.3 Results

We identified 209,007 Medicare beneficiaries initiating antihypertensive therapy during 2008-2011. On average beneficiaries were 75 years of age (standard deviation [std]: 6.8), 60% were women, and the majority were White (85%). Most beneficiaries initiated antihypertensive therapy with one antihypertensive medication (87%). Of those that initiated with one antihypertensive class, the most frequently prescribed drug classes were BBs (32%) and ACEs (30%).

After fitting GBTMs with different groupings, we identified the five-group trajectory model as the best fit for our data (Figure 7, Appendix Table 26). Using the model, beneficiaries were grouped into the following adherence trajectories: immediate drop-off (15%, mean adherence: 0.10); gradual drop-off (17%, mean adherence: 0.28); partial drop-off (11%, mean adherence: 0.69); early drop-off then rebound

to almost full adherence (14%, mean adherence: 0.58); and adherent (43% of the population, mean adherence: 0.97) (Table 11).

When comparing the prevalence of baseline covariates across trajectory groups, the prevalence of the following baseline covariates differed across trajectory groups: gender, race, initiation with combination therapy, opioid use, diabetes, cardiovascular disease (e.g., arrhythmia, hypertension, and dyslipidemia), vertigo, cancer screenings, and prior hospitalizations (Table 12).

During the one year follow-up period, beneficiaries had a total of 8,678 non-vertebral fracture events over 209,007 person-years of follow-up (rate= 442 fractures per 10,000 person-years, 95% CI: 433-452). Most of the fractures resulted in single bone breaks (76%, n=6,682), and fractures most commonly occurred at the hip (23%), foot (16%), radius (16%), and hand (13%).

When examining fracture rates during the second year after initiation of therapy according to antihypertensive adherence trajectory, beneficiaries belonging to the adherent trajectory had the lowest rate of fractures (416 fractures per 10,000 person-years, 95% CI: 402-430), and beneficiaries belonging to the partial drop-off trajectory had the highest fracture rate (491 per 10,000 person-years, 95% CI:462-522). After adjusting for baseline covariates, beneficiaries belonging to the partial drop-off trajectory had the highest rate of fractures compared to beneficiaries who were adherent (Adjusted HR: 1.20, 95% CI: 1.12-1.29). The results were similar when we limited the fracture follow-up time to six months (Table 13).

In the sensitivity analysis, the one year mortality or disenrollment rate was lowest among beneficiaries belonging to the adherent trajectory group (702 per 10,000 person-years, 95% CI: 684-719). Rates of death or disenrollment were highest among beneficiaries belonging to the immediate drop-off trajectory group (925 per 10,000 person-years, 95% CI: 891, 960). The elevated rate of mortality or disenrollment in the immediate drop-off trajectory group remained after controlling for baseline covariates (adjusted HR: 1.32, 95% CI: 1.26, 1.38) (Appendix Table 27). Additionally, the results were similar when we examined the rates of incident fracture during the initial 360 days following initiation of therapy (Table 14).

6.4 Discussion

Among Medicare beneficiaries initiating antihypertensive therapy, we found that antihypertensive adherence trajectories differ in the year following initiation. We identified five adherence trajectories ranging from beneficiaries who were fully adherent to beneficiaries who never returned after the initial prescription. Medicare beneficiaries who were more adherent to their antihypertensive medication had lower fracture rates during the follow-up period.

In the year following initiation, we identified five different antihypertensive adherence trajectories. This number of adherence trajectories is lower than our previous study which identified six antihypertensive adherence trajectories.[107] However, the six group trajectory model failed to converge in the current study and resulted in small group sizes. The smaller number of trajectory groups identified is most likely due to the smaller sample size included in this study. In the current study we included additional exclusion criteria that reduced the sample size by nearly 80,000 beneficiaries compared to our first study. Results suggest that GBTMs are largely dependent on sample size. Future studies using GBTMs to quantify medication adherence need to be aware of the potential impact group size has the results.

Overall, we found that the rates of non-vertebral fractures were lowest among older adults who were adherent to their antihypertensive therapy. This result may be due to a protective effect from antihypertensives or it could be due to residual confounding related to the healthy user bias. In our sensitivity analysis, we found that older adults in the adherent group also had the lowest rate of mortality or disenrollment compared to older adults in other trajectory groups. Older adults who are in better health may be at lower risk of both falling and sustaining injuries from falls due to increased exercise or improved bone health. More research is needed featuring clinical BMD measurements or physical activity measures to better control for confounding caused by the healthy user bias.

Medicare beneficiaries belonging to the partial drop-off adherence trajectory had the highest rate of fractures compared to beneficiaries in other trajectory groups. This result may be due to changes in overall health during the exposure period. Although we tried to control for various risk factors for

fractures prior to antihypertensive initiation, our GBTM results are not adjusted for time-varying confounders. Older adults experiencing adverse medication events or cardiovascular events during the exposure period may be at higher risk of having a subsequent fall or fracture during the follow-up period. Future research studies using adherence trajectories as exposures for future events should include time-varying covariates in the model to allow for changing health status over the exposure period.

This was the first study to use GBTMs to examine the association between antihypertensive adherence and subsequent fractures among older adults initiating therapy. Given the substantial impact fractures can have on older adults, it is important to identify ways to reduce the risk of fractures among this population. Our results suggest that better antihypertensive adherence may be associated with fewer fractures among older adults. However, our results were not adjusted for changes in overall health during the exposure period and subject to residual confounding. More research is needed taking into account changes in overall health to further examine the association between antihypertensive adherence and fractures.

Table 11: Antihypertensive adherence trajectories in the 12 months following initiation according to adherence measures (n=209,007)

	Group Size		Average Probability of Adherence[a]		Average Posterior Probability[b]	
Adherence Trajectory	N	%	Mean	Std	Mean	Std
Immediate Drop-off	31,482	15.1	0.10	0.25	0.95	0.07
Gradual Drop-off	36,231	17.3	0.28	0.31	0.85	0.17
Partial Drop-off	22,510	10.8	0.69	0.26	0.84	0.16
Early Drop-off then Rebound	29,197	14.0	0.58	0.20	0.87	0.16
Adherent	89,587	42.9	0.97	0.02	0.96	0.10

[a] Average probability of being at least 80% adherent over 12 months of follow-up.
[b] Indicates how well beneficiaries fit in their assigned group. 0.70 is typically used as a threshold to signify good model fit.
Std= standard deviation.
BIC= Bayesian information criterion. BIC is used as a measure of model fit. Lower BIC values signify better model fit.
Logistic regression models were used to identify trajectory groups. The dependent variables were the monthly binary indicators of antihypertensive use and months since start of antihypertensive therapy were the independent variables. Time was modeled using cubic terms.

Table 12: Characteristics of Medicare beneficiaries initiating antihypertensive therapy between 2008-2011 according to one year adherence trajectory (n=209,007)					
	Immediate Dropoff n=31,482	Gradual Dropoff n=36,231	Partial Dropoff n=22,510	Early Dropoff then Rebound n=29,197	Adherent n=89,587
Mean Age, std (years)	75.1 (6.9)	74.9 (6.8)	74.7 (6.8)	74.9 (6.9)	74.6 (6.8)
Mean Frailty Index, std	0.09 (0.1)	0.08 (0.1)	0.08 (0.1)	0.08 (0.1)	0.08 (0.1)
Male, %	39.0	41.5	41.1	38.9	38.9
White Race, %	81.1	80.4	84.8	81.5	88.9
Low-Income Subsidy, %	5.2	5.3	5.0	5.2	5.1
Medication History, %					
1-2 Meds Filled[a]	59.5	60.6	60.5	61.1	59.3
3-4 Meds Filled[a]	29.1	28.1	27.6	27.9	28.1
5 + Meds Filled[a]	11.4	11.3	11.9	11.0	12.6
Combo Initiation[b]	8.1	11.5	13.4	12.1	16.4
Loop Diuretic	5.2	5.3	5.4	5.5	5.7
Antiarrhythmic	4.2	3.7	3.5	3.5	3.3
Antidepressant[c]	15.0	14.6	15.0	14.8	14.2
Antipileptic[c]	7.9	7.8	7.3	7.5	6.9
Anxiolytic	4.5	3.9	3.6	3.6	3.3
Benzodiazpene[c]	1.5	1.2	1.2	1.2	1.2
Bisphosphonate	10.7	10.4	10.8	10.7	11.3
Antipsychotics[c]	3.2	2.7	2.8	2.8	3.0
Skeletal Muscle Relaxant[c]	7.3	6.9	6.1	6.9	5.7
Opioid	32.1	28.9	28.0	29.4	25.8
Hypnotic[c]	7.7	7.1	6.8	7.2	6.2
Chronic Conditions, %					
Diabetes	22.3	25.1	24.8	26.0	23.1
Chronic Kidney Disease	9.5	9.1	9.3	9.8	9.0
Parkinson's Disease	1.4	1.2	1.3	1.1	1.0
Alzheimer's Disease	2.4	2.3	2.6	2.3	2.6
Osteoporosis	16.1	15.4	15.4	15.5	15.1
Arrhythmia	17.1	16.5	17.3	15.6	18.8
Osteoarthritis	17.1	16.1	15.6	16.3	14.8
Rheumatoid Arthritis	3.2	3.1	2.8	3.0	2.6
Stroke	13.4	13.1	13.7	13.4	14.1
Myocardial Infarction	1.0	1.3	1.8	1.2	2.7
Hypertension	63.7	71.7	77.5	76.9	79.5
Orthostatic Hypertension	0.9	0.8	0.8	0.7	0.6
Syncope	5.1	4.8	4.7	4.5	4.8

Dementia	4.7	4.4	5.1	4.7	5.0
Urinary Incontinence	5.1	4.6	4.8	4.5	4.4
Dyslipidemia	59.7	62.8	65.1	64.4	64.8
Obesity	3.7	4.0	4.2	4.1	4.2
Frailty Indicators, %					
Home Oxygen Use	3.3	2.8	2.4	2.5	2.3
Walker Use	1.9	1.7	1.6	1.8	1.6
Wheelchair Use	0.9	0.8	0.8	0.9	0.7
Hospital Bed	0.5	0.4	0.5	0.4	0.4
Difficulty Walking	8.2	7.6	7.6	7.8	7.5
Vertigo	14.7	13.5	12.6	13.1	11.8
Ambulance Transport	8.9	7.7	7.9	7.5	8.6
Cancer Screenings	36.7	37.0	39.9	38.7	41.9
Hospital Utilization, %					
Hospital Admissions	18.8	15.7	16.0	15.1	17.3

[a] Number of distinct medications filled 14 days prior to the index date (initiation of therapy)

[b] Combination therapy was defined as having more than one class of antihypertensive prescribed on the index date. Includes both single pill combination therapy and multiple pill combination therapy.

[c] Medication indicated to be associated with elevated risk of fractures according to the 2015 Beers Medication Guideline released by the American Geriatrics Society

Race was missing for a total of 246 beneficiaries and these were excluded from the analysis

Table 13: Rates and adjusted hazard ratios (HRs) of fractures in the second year of initiating antihypertensive therapy according to one year antihypertensive adherence trajectories

	1-182 Day Period				365 Day Period			
Drug Class	# Fractures	P-Yrs	Rate Per 10,000 p-yrs (95% CI)	Adjusted HR (95% CI)	# Fractures	P-Yrs	Rate Per 10,000 p-yrs (95% CI)	Adjusted HR (95% CI)
Immediate Drop-off	784	15,102	519 (484-556)	1.13 (1.04, 1.22)	1,374	29,320	469 (444-494)	1.11 (1.04, 1.18)
Gradual Drop-off	843	17,425	484 (452-517)	1.09 (1.01, 1.18)	1,454	33,881	429 (408-452)	1.06 (1.00, 1.13)
Partial Drop-off	614	10,801	569 (525-614)	1.27 (1.16, 1.39)	1,031	20,999	491 (462-522)	1.20 (1.12, 1.29)
Early Drop-off then Rebound	759	14,042	541 (503-580)	1.20 (1.10, 1.30)	1,297	27,286	475 (450-502)	1.15 (1.08, 1.23)
Adherent	1,986	43,339	458 (438-479)	ref	3,552	84,662	416 (402-430)	ref

HR's are adjusted for all baseline covariates, CI= Confidence Interval

P-Yrs= person-years of follow

Follow-up for fractures began after the one year exposure period used to define the trajectory groups (e.g., started on day 361 after initiation of antihypertensive therapy).

Table 14: Sensitivity analysis examining the rates of incident fracture in the first year following initiation of antihypertensive therapy according to antihypertensive adherence trajectories				
Drug Class	# Fractures	P-Yrs	Rate Per 10,000 p-yrs (95% CI)	Adjusted HR (95% CI)
Immediate Drop-off	1,174	30,450	386 (364-408)	1.23 (1.14, 1.31)
Gradual Drop-off	1,289	35,078	368 (348-388)	1.22 (1.14, 1.30)
Partial Drop-off	928	21,760	427 (400-455)	1.40 (1.30, 1.51)
Early Drop-off then Rebound	1,131	28,176	401 (379-425)	1.31 (1.23, 1.41)
Adherent	2,694	87,000	310 (298-322)	ref

HR's are adjusted for all baseline covariates
P-Yrs= person-years of follow

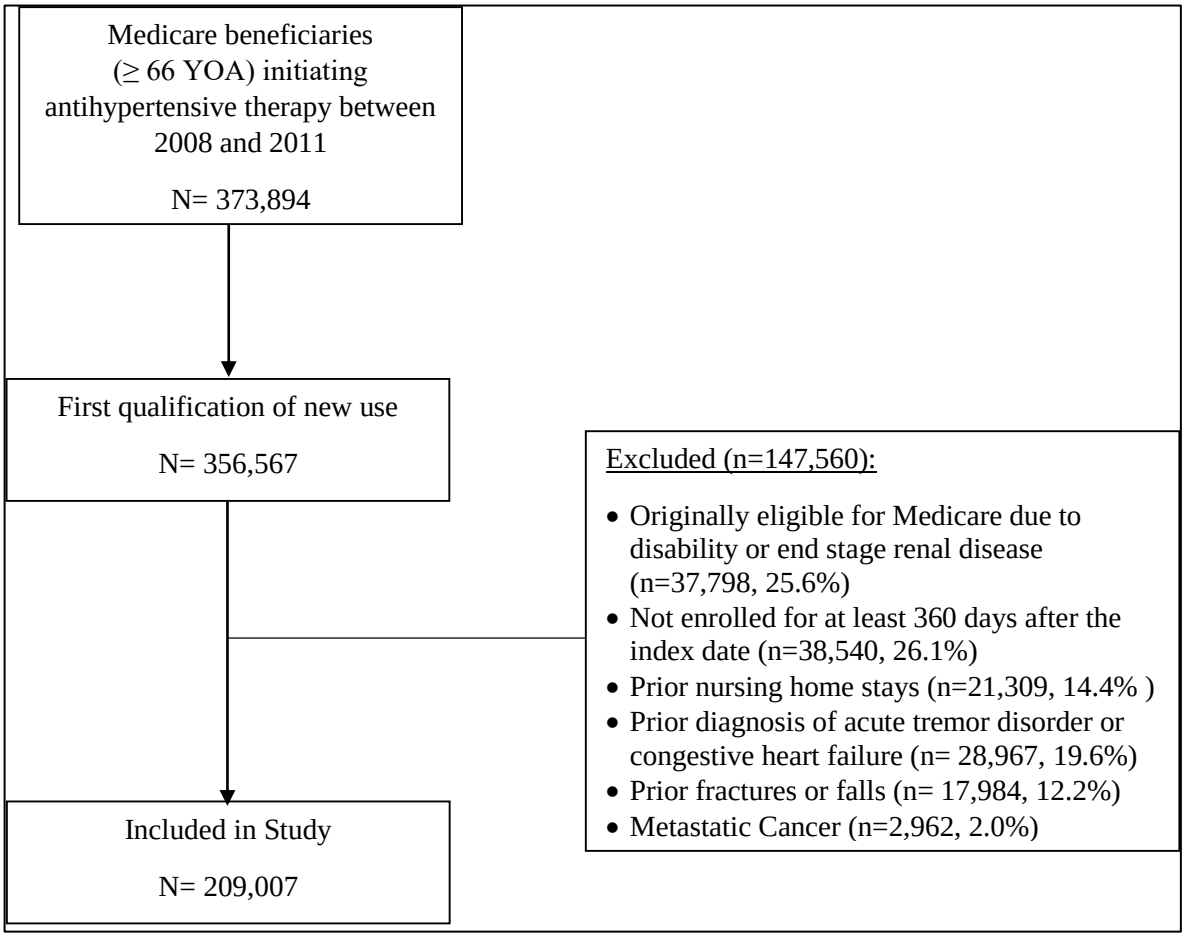

Figure 5: Flowchart of eligibility criteria for identifying Medicare beneficiaries initiating antihypertensive therapy between 2008 and 2011.

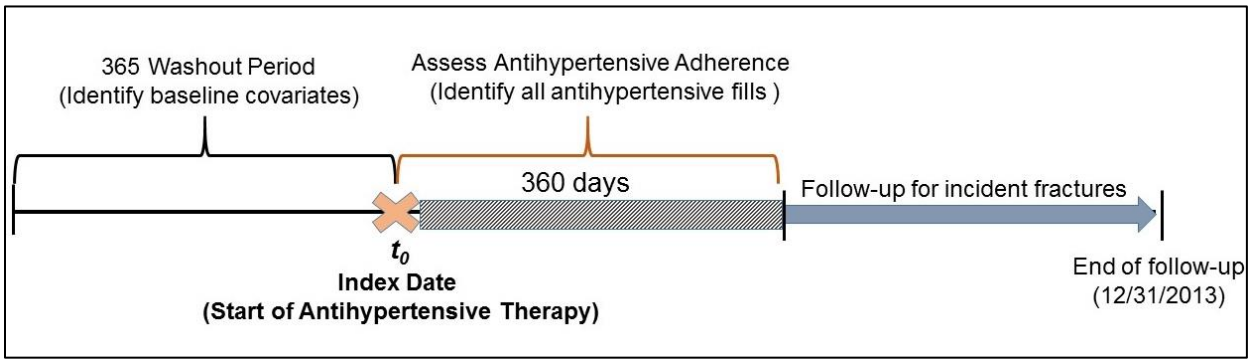

Figure 6: Study design used to assess antihypertensive adherence trajectories and fractures

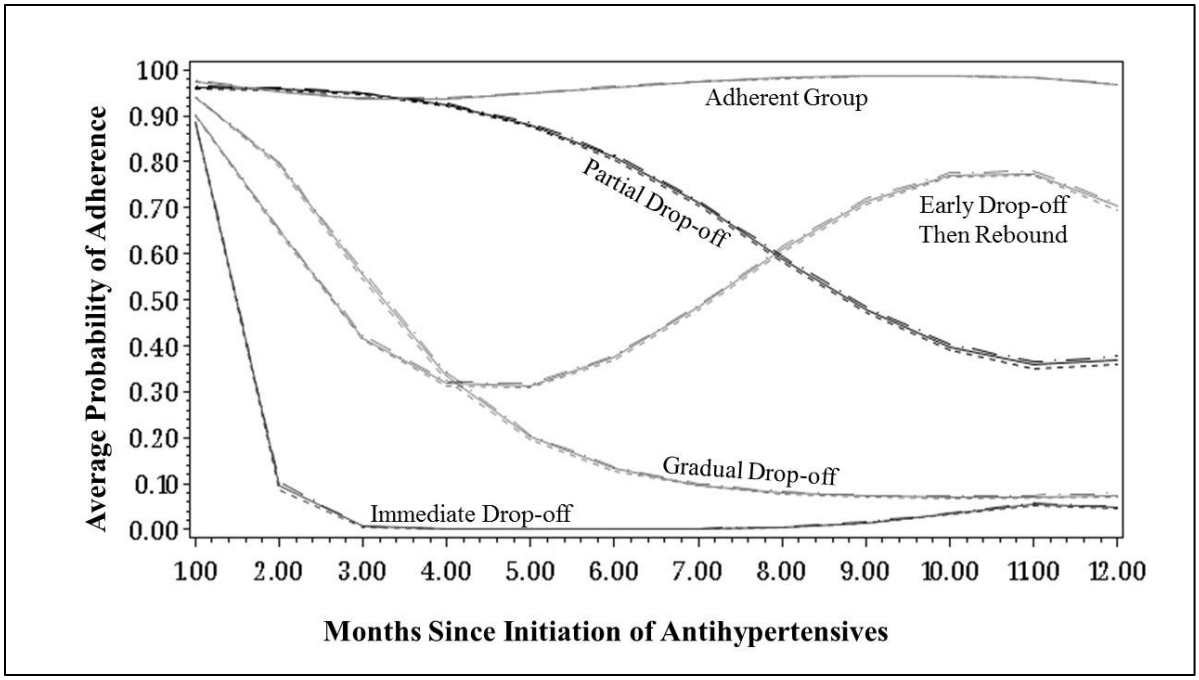

Figure 7: Antihypertensive adherence trajectories among Medicare beneficiaries initiating antihypertensive therapy between 2008 and 2011

CHAPTER 7: FALLS VS FRACTURES: THE IMPACT OUTCOME DEFINITION HAS ON THE ASSOCIATION BETWEEN ANTIHYPERTENSIVES MEDICATION AND ADVERSE EVENTS

7.1 Introduction

Falls are the leading cause of fatal and non-fatal injury among older adults, and an estimated one out of three older adults fall each year.[50] Fractures are one of the most common fall-related injuries.[89] In older adults, falls and fractures are associated with high medical costs, loss of independence, and an increased risk of mortality.[43,44,90] Older adults are at a greater risk of falls due to impaired balance or gait, increased presence of comorbidities, and increased medication use.[30,91,113]

Recently, evidence suggests that antihypertensive medications can increase the risk of falls and fractures among older adults.[11,63,114] Antihypertensive medications can increase the risk of falls by causing orthostatic hypotension. Orthostatic hypotension is defined as a drop in blood pressure upon standing and is a risk factor for falls among older adults.[68] Orthostatic hypotension is a possible adverse-medication related event reported with thiazide diuretics (THZs) and beta blockers (BBs).[2,30] Antihypertensives can also impact the risk of whether a fracture occurs as a result of a fall through interactions with BMD. For instance, thiazide diuretics have been found to stimulate the formation of osteoblasts potentially providing a protective effect for fractures.[32] Angiotensin-receptor blockers (ARBs) and angiotensin-converting-enzyme inhibitors (ACEs) are believed to impact BMD by inhibiting bone turnover caused by the renin-angiotensin-aldosterone system (RAAS),[32] and have been found to be associated with a lower risk of falls and fractures. [67,115]

Despite falls being the primary cause of fractures among older adults, no prior study has examined the impact of outcome definition (falls vs. fractures) has on the association between antihypertensives and these adverse events. Prior research has found that THZs are associated with a lower risk of both falls and fractures in the first few weeks following initiation.[10,11] However, previous

research examining the association between antihypertensives and adverse events is less consistent after longer periods of use.[11]

In this study we sought to examine the association between antihypertensives and incident falls according to antihypertensive class and time since initiation. As a secondary analysis, we examined how using fractures as the outcome altered the results.

7.2 Methods

We used a 20% nationwide, random sample of fee-for-service Medicare beneficiaries with at least one month of combined parts A (inpatient care), B (outpatient care), and D (prescription drugs) coverage between 2007 and 2011. Data were obtained under a data use agreement established with the Centers for Medicaid and Medicare Services (CMS) and the University of North Carolina (UNC) at Chapel Hill. The study protocol was approved by the UNC Institutional Review Board.

Study Population

The study cohort consisted of Medicare beneficiaries initiating therapy with antihypertensive medications during 2008-2011 who were enrolled in Medicare Parts A, B, and D for at least 12 months prior to initiation. New use was defined as not having a prior prescription for any of the following antihypertensive medications in the last 12 months: angiotensin-converting-enzyme inhibitors (ACE), angiotensin-receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB), or thiazide diuretics (THZ). The eligibility and exclusion criteria for the study population has previously been described (see Chapter 5, Appendix Figure 11).

Exposure

The primary exposure was initiation of antihypertensive therapy with one of the following drug classes: ACEs, ARBs, BBs, CCB, or THZ. These specific drug classes were chosen based on the current recommendations for hypertension treatment in older adults.[2,13] Loop diuretics were not included as a primary exposure since these medications are typically given to older adults with a higher number of comorbidities and at greater risk of mortality.[27] Prescription medication data were identified using

Medicare Part D (Appendix Table 18). Using fill dates, we identified the date of the initial prescription for antihypertensive therapy.

Outcome

Incident falls within 12 months of initiating antihypertensive monotherapy were our primary outcome. Starting the day after the initial antihypertensive prescription, we followed beneficiaries until the first fall event. Falls were identified using external-cause-of-injury (E-codes) in Medicare Parts A and B (E880-E888).

As a secondary outcome, we identified incident non-vertebral fractures. Fractures were identified using validated diagnostic and procedure codes found in Medicare Parts A and B.[99] Only fractures that had both a fracture diagnosis and a corresponding procedure code within seven days of the fracture diagnosis were included (Appendix Table 23). We excluded fractures that were due to motor vehicle crashes (E810-E825) and those that occurred on the index date.

Covariates

Covariates were selected based on previous literature [30,57,91,92,102] and were identified using claims in the 12 months prior to initiation (Appendix Table 24). Covariates included: demographics, concurrent medication use (e.g., number of distinct drugs prescribed in the 14 days prior to the index date) and use of medications associated with falls and fractures (loop diuretics, antiarrhythmics, antidepressants, antiepileptics, anxiolytics, benzodiazepines, opioids, hypnotics, skeletal muscle relaxants, and antipsychotics), chronic comorbidities associated with fall risk (diabetes, chronic kidney disease, Parkinson's disease, Alzheimer's disease, osteoporosis, BMD testing, arrhythmia, osteoarthritis, rheumatoid arthritis, stroke, myocardial infraction, hypertension, orthostatic hypotension, obesity, dementia, dyslipidemia, and urinary incontinence), frailty predictors, and previous hospital admissions. As a proxy for sociodemographic status, we identified whether beneficiaries were eligible for the Medicare low-income subsidy (LIS) program. LIS offers medication at a reduced cost for beneficiaries that are eligible due to income, family size, and household resources. We used the frailty index score (FIS) as a proxy measure of frailty among Medicare beneficiaries.[76] Additionally, we examined the

prevalence of several variables that were found to be positively (ambulance transfer, wheelchair/walker use, home oxygen use, hospital bed, difficulty walking, and vertigo) and inversely (cancer screenings) associated with limitations in activities of daily living.[76]

Analysis

Descriptive statistics were used to compare the prevalence of baseline covariates according to antihypertensive class initiated on the index date. We estimated propensity scores using multinomial logistic regression models to adjust for differences in the distribution of baseline covariates. Standardized mortality ratio (SMR) weighting was used to weight beneficiaries of each drug class to achieve the same baseline covariate distribution as the one observed in beneficiaries receiving an ACE.[105] ACEs were used as the referent since they were the most commonly prescribed drug class.[106] To assess the effectiveness of the SMR weights, we examined the distribution of baseline covariates after SMR weighting and examined the distribution of the SMR weights according to drug class. After identifying outlier SMR weights, we removed the 0.1% tail ends.

Incident fall rates and corresponding 95% confidence intervals (CIs) were defined as the total number of falls divided by the total person-time at risk. Person-time at risk was defined as the total days at risk divided by 365.25. We used SMR-weighted Cox proportional hazard models to estimate hazard ratios (HRs) and 95% CIs of incident falls for each drug class initiated on the index date versus receiving an ACE according to days since initiation of therapy, 1-14 days and 15-365 days. CIs were calculated using robust standard errors to account for SMR weights. We used an 'first-treatment-carried-forward' analysis to avoid introducing confounding by indication since antihypertensive adherence patterns vary over time and beneficiaries who remain adherent may differ from the majority of hypertensive patients.[107] Beneficiaries contributed person-time at risk until they had an incident event or until the end of the follow-up (death, disenrollment from Medicare, or December 31, 2012), whichever came first. To examine the impact outcome definition has on the results, we repeated the primary analysis using incident fractures as the outcome.

As a sensitivity analysis, we repeated the primary analysis removing beneficiaries with chronic kidney disease or diabetes since these chronic conditions could impact a physicians' choice in which antihypertensive class is prescribed.

7.3 Results

Between 2008 and 2011, 122,629 Medicare beneficiaries initiated monotherapy with antihypertensive medications. Beneficiaries were on average 75 years of age, 61% were women, and 86% were White. The most common classes of antihypertensives prescribed were ACEs (33%), BBs (30%), and CCBs (15%). Before SMR weighting, demographics, diabetes, chronic kidney disease, cardiovascular disease (e.g., arrhythmia, stroke, hypertension, and dyslipidemia), ambulance transfers, cancer screenings, and prior hospitalizations differed across beneficiaries according to antihypertensive class. After SMR weighting, there was little difference between baseline characteristics according to antihypertensive class (Table 8).

During the first year after initiating antihypertensive monotherapy, beneficiaries experienced 6,893 incident falls over a period of 114,843 person-years (rate = 600 per 10,000 person-years, 95% CI: 586-615). Twenty-eight percent of falls resulted in fractures (n=1,981). Fractures most commonly occurred at the hip (29%), radius (18%), humerus (13%), and rib (10%).

Rates of incident falls varied according to antihypertensive class (Table 15). Beneficiaries who initiated with CCBs had the highest rate of falls in the first 14 days (709 per 10,000 person-years, 95% CI: 532-928) and during the 15-365 days after initiation (701 per 10,000 person-years, 95% CI: 661-742). Beneficiaries who initiated with ACEs had the lowest rate of falls during the initial 1-14 days (526 per 10,000 person-years, 95% CI: 421-651). However, beneficiaries who initiated with ARBs had the lowest rate of falls during the 15-365 days after initiation (534 per 10,000 person-years, 95% CI: 490-581). After controlling for differences in baseline characteristics, beneficiaries who initiated with BBs had the highest rate of falls in the first 14 days compared to beneficiaries who initiated with ACEs (SMR HR: 1.13, 95% CI: 0.75-1.70). After the first 14 days, beneficiaries who initiated with THZs had the lowest rate of falls compared to beneficiaries who initiated with ACEs (SMR HR: 0.96, 95% CI: 0.87-1.07).

When we repeated the analysis using fractures as the outcome, the association between antihypertensive class and incident fractures varied according to time since initiation of therapy (Table 15). During the first 14 days, beneficiaries who initiated with THZs (438 per 10,000 person-years, 95% CI: 294-628) and BBs (410 per 10,000 person-years, 95% CI: 314-526) had the highest fracture rates. However, beneficiaries who initiated therapy with CCBs had the highest fracture rate during the 15-365 days after initiation (435 per 10,000 person-years, 95% CI: 404-468). Beneficiaries who initiated with ARBs had the lowest fracture rate during the initial 1-14 days (333 per 100 person-years, 95% CI: 190-546) and during the 15-365 days after initiation (321 per 100 person-years, 95% CI: 287-358).

After controlling for differences in baseline characteristics, beneficiaries who initiated with THZs had the highest fracture rate in the first 14 days compared to beneficiaries who initiated with ACEs (SMR HR: 1.42, 95% CI: 0.79-2.57). After the first 14 days, beneficiaries who initiated with CCBs (SMR HR: 1.09, 95% CI: 0.97-1.22) and BBs (SMR HR: 1.04, 95% CI: 0.93-1.15) had slightly higher fracture rates compared to the beneficiaries who initiated with ACEs.

In the sensitivity analysis when we removed beneficiaries with chronic kidney disease or diabetes, beneficiaries who initiated with ARBs had the lowest rate of falls and fractures in the first two weeks and during the 15-365 days after initiation compared to beneficiaries who initiated with ACEs (Table 16).

7.4 Discussion

Among Medicare beneficiaries initiating antihypertensive monotherapy, the association between antihypertensives and adverse events in the year following initiation differed according to antihypertensive class and by outcome definition (falls vs. fractures). When using falls as the primary outcome, initiating with CCBs was associated with an elevated rate of falls in the year after initiation. However, when using incident fractures as the primary outcome, results varied according to time since initiation. In the first two weeks, beneficiaries who initiated therapy with THZs had the highest rate of fractures. After the first two weeks, initiating with CCBs was associated with the highest rate of fractures. Initiating with ARBs was associated with the lowest rates of both falls and fractures.

Overall, Medicare beneficiaries initiating with ARBs had the lowest rate of both falls and fractures in the 15-365 days following initiation. ARBs lower blood pressure by regulating of the renin-angiotensin-aldosterone system (RAAS), and have been suggested to provide protective effects for fractures by preventing bone loss induced by RAAS.[32,67,115] This potential protective effect of BMD may explain the lower rate of fractures we found in our study, but the time it takes to achieve clinically relevant BMD effects is not known. Our results suggest that more research is needed to examine the potentially protective effect ARBs have on preventing fractures by inhibiting bone turnover caused by the renin-angiotensin-aldosterone system.[32] The lower rate of falls we observed among ARB users may be due to a lower risk of adverse medication events, such as orthostatic hypotension or urinary incontinence. Compared to other classes of antihypertensives, ARBs are associated with fewer side effects and have higher levels of adherence.[33,34] If given the choice between antihypertensive classes, clinicians may want to consider prescribing ARBs to older adults as first line treatment for hypertension.

Despite the similar results for beneficiaries initiating with ARBs, overall we found that the association between antihypertensives and adverse events differed depending on the outcome. One of the main reasons for the differences in results may be related to the accuracy of reporting falls and fractures in claims data. Falls are captured in claims data using E-codes, however E-code reporting is not required by every state.[100] Additionally, few studies have reported the accuracy of E-code reporting in clinical data.[116] Fractures, on the other hand, are identified using validated diagnostic and procedure codes in claims data. The sensitivity and specificity of fracture codes vary by fracture type, ranging from 97% sensitivity for hip fractures to 25% for thorax fractures.[99,117] Additionally, unlike E-codes, hospitals are incentivized to report fractures diagnostic and procedure codes for reimbursement purposes.[100] Results suggests that when examining the association between adverse events and antihypertensives, researchers should keep in mind the impact outcome definition can have on the results.

Despite this being the first study to examine the impact of outcome definition has on the association between antihypertensives and adverse events, this study does have limitations. First, our results may be subject to residual confounding. We used SMR weights to limit confounding by indication

but were unable to control for physical activity, baseline BMI levels, visual impairment, and alcohol use. Second, our study population was predominantly White Medicare beneficiaries. It is unknown if these results would hold true for non-White older populations. Third, our results are limited to the one year period following initiation. One year may not have been long enough to identify all the possible BMD effects. Lastly, results did not take into account antihypertensive dose. Previous research has found that the relationship between antihypertensives and fractures is linearly associated with increasing dose.[11,64] Results from our study may be underestimated for older adults on higher doses of antihypertensive drugs.

Overall, we found that ARBs were associated with fewer adverse events compared to the other antihypertensive drug classes. However, for other classes of antihypertensive drugs, the association between antihypertensives and subsequent injury differs depending on whether falls or fractures is used as the outcome. These results suggest that it is important to keep in mind the impact outcome definition can have on the results. Additionally, our results suggest that clinicians may want to consider different risks of adverse events when choosing between antihypertensive drug classes.

Table 15: Rates of incident falls and fractures in the first year after initiation among Medicare beneficiaries starting antihypertensive monotherapy between 2008-2011 (n=122,629)								
	1-14 Days After Initiation				15-365 Days After Initiation			
Drug Class	# Falls	P-Yrs	Rate Per 10,000 P-yrs (95% CI)	SMRW Adj HR (95% CI)	# Falls	P-Yrs	Rate Per 10,000 P-Yrs (95% CI)	SMRW Adj HR (95% CI)
ACE	81	1,539	526 (421, 651)	ref	1,986	36,253	548 (524, 572)	ref
ARB	25	419	597 (395, 868)	1.12 (0.67, 1.85)	530	9,932	534 (490, 581)	0.99 (0.89, 1.09)
BB	94	1,415	664 (540, 809)	1.13 (0.75, 1.70)	2,144	33,088	648 (621, 676)	0.99 (0.91, 1.08)
CCB	50	705	709 (532, 928)	1.04 (0.67, 1.62)	1,144	16,328	701 (661, 742)	1.05 (0.96, 1.15)
THZ	34	617	551 (388, 761)	1.06 (0.65, 1.71)	805	14,547	553 (516, 593)	0.96 (0.87, 1.07)
Results when using incident fractures as the outcome								
Drug Class	# Fractures	P-Yrs	Rate Per 10,000 P-Yrs (95% CI)	SMRW Adj HR (95% CI)	# Fractures	P-Yrs	Rate Per 10,000 P-Yrs (95% CI)	SMRW Adj HR (95% CI)
ACE	54	1,539	351 (266, 454)	ref	1,271	36,618	347 (328, 367)	ref
ARB	14	420	333 (190, 546)	0.91 (0.48, 1.74)	322	10,032	321 (287, 358)	0.96 (0.85, 1.09)
BB	58	1,416	410 (314, 526)	0.95 (0.57, 1.58)	1,375	33,449	411 (390, 433)	1.04 (0.93, 1.15)
CCB	27	705	383 (258, 550)	0.79 (0.46, 1.35)	720	16,540	435 (404, 468)	1.09 (0.97, 1.22)
THZ	27	617	438 (294, 628)	1.42 (0.79, 2.57)	562	14,656	384 (353, 416)	1.00 (0.89, 1.13)

We removed 0.1% of the outlier SMR weights when calculating the adjusted SMR HRs. Adjusted 95% confidence intervals were calculated using robust standard errors.

P-Yrs= person-years of follow (calculated by dividing the total number of follow-up days by 365.25)

SMRW= Standardized mortality ratio weighted

CI= confidence interval

HRs and 95% CIs are adjusted for SMRWs that were calculated using all the baseline covariates

Angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB), or thiazide diuretics (THZ)

Table 16: Rates of incident falls and fractures in the first year after initiation among Medicare beneficiaries *without chronic kidney disease or diabetes* starting antihypertensive monotherapy between 2008-2011 (n=86,420)

	1-14 Days After Initiation				15-365 Days After Initiation			
Drug Class	# Falls	P-Yrs	Rate Per 10,000 P-Yrs (95% CI)	SMRW Adj HR (95% CI)	# Falls	P-Yrs	Rate Per 10,000 P-Yrs (95% CI)	SMRW Adj HR (95% CI)
ACE	52	979	531 (401-691)	ref	1,213	23,156	524 (495-554)	ref
ARB	12	267	449 (244-761)	0.84 (0.41, 1.73)	324	6,340	511 (458-569)	0.98 (0.86, 1.11)
BB	62	1,045	593 (459-756)	1.08 (0.66, 1.78)	1,506	24,560	613 (583-645)	0.99 (0.89, 1.10)
CCB	37	513	721(515-984)	1.01 (0.62, 1.64)	767	11,984	640 (596-687)	0.98 (0.88, 1.09)
THZ	28	505	554 (376-791)	1.11 (0.68, 1.81)	638	11,952	534 (494-577)	0.94 (0.85, 1.05)
Results when using incident fractures as the outcome								
Drug Class	# Fractures	P-Yrs	Rate Per 10,000 P-Yrs (95% CI)	SMRW Adj HR (95% CI)	# Fractures	P-Yrs	Rate Per 10,000 P-Yrs (95% CI)	SMRW Adj HR (95% CI)
ACE	32	979	327 (227-456)	ref	774	23,373	331 (308-355)	ref
ARB	<11	NR	300 (139-569)	0.94 (0.39, 2.25)	196	6,398	306 (266-352)	0.97 (0.82, 1.14)
BB	45	1,045	431 (318-571)	1.41 (0.79, 2.52)	994	24,799	401 (377-426)	1.01 (0.89, 1.15)
CCB	19	513	370 (230-568)	0.95 (0.49, 1.84)	517	12,116	427 (391-465)	1.08 (0.95, 1.23)
THZ	22	505	436 (280-649)	1.29 (0.72, 2.32)	456	12,031	379 (345-415)	1.02 (0.90, 1.16)

We removed 0.1% of the outlier SMR weights when calculating the adjusted SMR HRs (n=65,358). 95% confidence intervals were calculated using robust standard errors.
P-Yrs= person-years of follow (calculated by dividing the total number of follow-up days by 365.25)
SMRW= Standardized mortality ratio weighted, CI= confidence interval
HRs and 95% CIs are adjusted for SMRWs that were calculated using all the baseline covariates
Angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB), or thiazide diuretics (THZ)
NR= non-reportable

CHAPTER 8: DISCUSSION

8.1 Overall Summary of Findings

The primary objectives of our first aim were to 1) use GBTMs to identify antihypertensive adherence trajectories in the first year following initiation; 2) compare adherence trajectories to traditional adherence measures; and 3) examine whether patient characteristics can predict adherence trajectories. We found that antihypertensive adherence patterns vary among older adults initiating therapy. Using GBTMs, we identified six different antihypertensive adherence trajectories ranging from older adults that were always adherent to those who stopped therapy after the first prescription. Nearly half of older adults initiating antihypertensive therapy remained adherent in the year following initiation. Compared to traditional adherence measures, GBTMs were better at distinguishing between adherent and non-adherent older adults. We found that certain patient characteristics were predictive of belonging to a less adherent trajectory group. Individual characteristics predictive of non-adherence include: non-White race, initiation with one class of antihypertensive drug, no history of cardiovascular disease, higher probability of being frail, Parkinson's disease, opioid use, and no history of being in the Medicare insurance gap period. Poor persistence to other chronic medication was also predictive of being non-adherent.

The primary objectives of our second aim were to 1) estimate the rate of fractures according to antihypertensive adherence trajectories; 2) estimate the rate of fractures according to duration of use; 3) examine the association between antihypertensives and type of fracture outcomes; and 4) examine the impact of using falls versus fractures as the primary outcome between antihypertensive and adverse events. Overall, we found that the rate of incident fractures in the year following initiation of antihypertensive therapy differs by antihypertensive class. During the first two weeks following initiation of therapy, older adults who initiated with THZs or BBs had an initial elevated rate of fractures compared to older adults who initiated with other classes of antihypertensive drugs. Older adults who initiated with

ARBs had the lowest rates of both falls and fractures in the one year following initiation. Better antihypertensive adherence in the year following initiation was associated with fewer fractures. Lastly, although fractures are often the result of a fall, we found that the association between most antihypertensive classes and adverse events differs depending on whether falls or fractures are used as the outcome.

8.2 Public Health Implications

Antihypertensive medications can reduce the risk of cardiovascular disease among hypertensive patients. We found that nearly half of older adults were adherent to their antihypertensive medication in the year following initiation. However, a large proportion of older adults with cardiovascular disease were not adherent. We found that initiation with monotherapy, no prior history of cardiovascular disease, and a low probability of being frail are strong predictors of non-adherence. Since hypertension is an asymptomatic disease, older adults who perceive they are in overall good health (e.g., those with no prior cardiovascular disease, or those with mild cases of hypertension) may be less likely to remain adherent compared to older adults who perceive their health to be poor.[2] Our results suggest that older adults should be made aware of the importance of being adherent. Specifically, older adults need to be aware of the potential health consequences of being non-adherent to their antihypertensive medications. Previous research has found that a better understanding of the value of taking antihypertensives by both patients and/or caregivers, is associated with improved adherence among hypertensive patients.[118] Results from this study can be used to identify sub-populations of older adults at greater risk of being non-adherent to their antihypertensive medication. Future research studies may want to consider targeting antihypertensive adherence interventions, such as setting reminders to encourage older adults to take their medication,[119,120] for these sub-populations at greater risk of non-adherence.

Given that hypertension is asymptomatic, some instances of non-adherence are likely to due to medication adverse-events. Fractures are an example of one unwanted side effect caused by initiation with antihypertensive medications. In older adults, fractures are associated with high medical costs, loss of independence, and an increased risk of mortality.[43,44,90] In Aim 2, we found that certain sub-classes of

antihypertensive medication are associated with elevated rates of fractures and falls among older adults. As the older adult population increases, it is important that researchers and clinicians identify modifiable factors that can reduce the risk of fractures and falls among this population. Our results suggest that the choice of antihypertensive medication prescribed may be one way clinicians can help prevent falls and fractures among older adults. Specifically, we found that THZs and BBs are associated with an elevated rate of fractures in the first few weeks after initiation compared to the other classes of antihypertensives. These specific medications may be associated with an increased risk of adverse medication events, such as orthostatic hypotension or urinary incontinence, causing an increase in falls and subsequent fractures after initiation. Older adults initiating with these medications should be made aware of this potential risk which may not only help prevent fractures, but also increase overall medication adherence. We found the newer classes of antihypertensive medications, ACEs and ARBs, are associated with lower fracture rates after initiation. Clinicians, caregivers, and older adults need to be aware of the potential interactions antihypertensives can have with fractures when initiating therapy. When deciding upon antihypertensive therapy, clinicians may want to consider the possibility of different drug side effects when choosing between antihypertensive drug classes.

8.3 Future Research

This was the first study to use GBTMs to identify antihypertensive adherence trajectories among older adults initiating therapy. Our results suggest that GBTMs may be a better alternative than traditional measures for capturing medication adherence using claims data. One of the inherent disadvantages of standard adherence measures (e.g., PDC and PMC) is that they fall short of separating adherence from persistence. Our results highlight that one of the benefits of using GBTMs is that they are able to better capture changing patterns of use over time. However, our results were not a true comparative analysis of adherence measures. Given the novelty of the method, we were interested in examining if the results of previous studies would hold true for antihypertensive users in an older adult population. More research is needed using external indicators, such as mortality or cardiovascular events, to validate the benefit of using GBTMs over traditional adherence measures. Additionally, future research studies could use

GBTMs to identify whether external factors, such as physician visits or adverse medication-related events, are influencing fluctuations in medication behavior for intervention purposes.

We also found that certain patient characteristics are predictive of being non-adherent. Non-White race was one of the strongest predictors of being non-adherent. This finding is clinically relevant given that hypertension is more prevalent among African Americans older adults.[2] However, we were unable to conduct separate analysis stratified by race given the small proportion of non-White older adults included in our study. More research is needed featuring large non-White populations to identify the causes of non-adherence among various race/ethnicity sub-populations.

Our results from aim 2 suggest that certain classes of antihypertensive medication may be associated with fewer rates of fractures and falls after initiation. However, our study did have some limitations. First, our cohort consisted primarily of White older adults. More research is needed using different ethnic/racial sub-populations to see if the same findings hold true among these sub-populations. Second, we were unable to control for known risk factors of falls and fractures such as: alcohol use, baseline BMD, and physical activity. Future research studies combining both clinical and survey data are needed to better control for these risk factors. Third, more research is needed to identify the time it takes for antihypertensives to have possible BMD effects. Our results suggest that the use of THZs may offer protective BMD benefits, but we were unable to clinically measure BMD effects using claims data. More research studies are needed featuring clinical BMD measurements to confirm our results. Additionally, future research studies with longer follow-up periods are needed to see if the same results hold true over longer periods of use.

APPENDIX

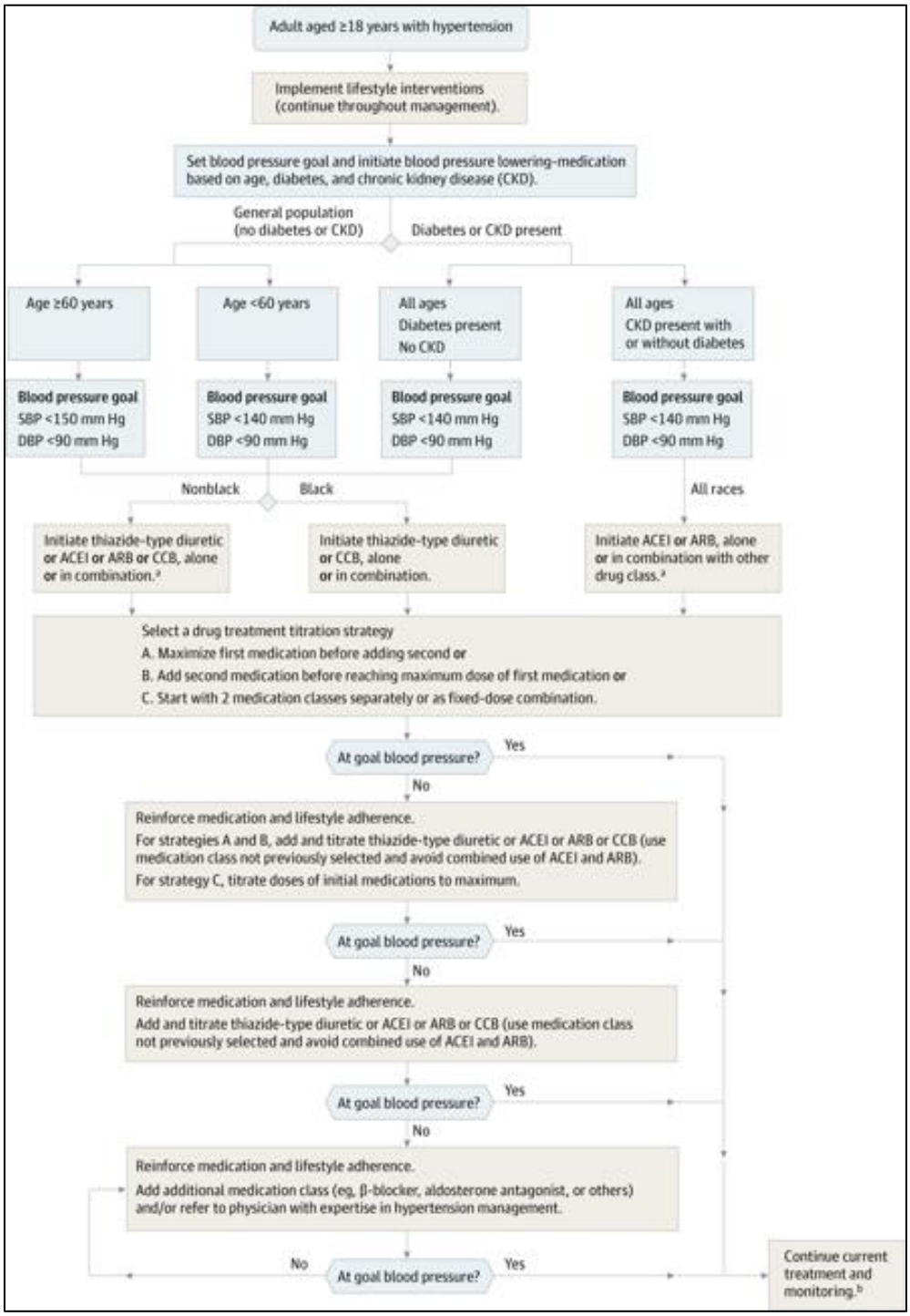

Figure 8: Guidelines for hypertension management among older adults (JNC8)

Table 17: Summary of previous research examining the association of antihypertensives and fractures or falls						
Authors	**Exposure**	**Outcome**	**Covariates**	**Study Design**	**Population/Data**	**Results**
Ruths et al., 2015 [67]	THZ, loop diuretics, CCBs, ACEs, ARBs, BBs, combination drugs	Incident Hip Fractures (identified by surgical records)	Year of birth, and sex	Cohort	Norwegian Prescription Database, Norwegian Hip Fracture Registry, and the Central Population Registry. Study cohort was all people aged 60 or older living in Norway on Jan. 1, 2005.	Loop diuretics associated with an elevated risk of fractures within the 14 days of use. Most antihypertensives were associated with a decreased risk of fracture. Lowest risk was for ARB/thiazide combination users. Association varied with age.
Choi et al., 2015 [61]	ARBs, ACRs, ABs*, BBs, CCBs, diuretics	Any fracture occurring 6 months after the index date	Age, gender, diabetes, osteoporosis, osteoporosis medication, osteoporosis diseases, Charlson index	New User Cohort	Health Insurance Review and Assessment service of South Korea which includes patients aged 50 or older with an antihypertensive prescription and hypertension diagnosis	ABs were associated with increased fracture rates. Results differed by gender. Females: ARBs associated with lowest fracture rate. Males: BBs were associated with the lowest fracture rate.
Zia et al., 2015 [30]	Self-reported use of ACEs, ARBs, BBs, CCBs, THZ diuretics, alpha-blockers, vasodilators (included combination therapy)	Self-reported falls and orthostatic hypotension diagnosed at fall clinics	Age, self-reported number of comorbidities	Case-Control Study	Older adults (65+) who went to the emergency department or clinic due to a fall and who enrolled in the Malaysian Falls Assessment and Intervention Trial. Cases were older adults with two or more falls or one injury-fall in the last year. Controls were sampled from population surrounding the clinics.	Alpha blockers and ARBs associated with recurrent or injury-falls in univariate analysis, but not significant after adjustment for age and comorbidity. Older adults with orthostatic hypotension had higher odds of taking THZs after adjustment for age and comorbidity. OH was not associated with recurrent or injury-falls.

Marcum, et al., 2015 [62]	BBs, alpha blockers, potassium-sparing diuretics, loop diuretics, THZ diuretics, CCBs, ACEs, ARBs (self-reported)	Number of self-reported falls in the year following med assessment. Primary outcome was recurrent falls (2 or more)	Demographics, health behavior/status, and access to care factors	Cohort	Community-dwelling older adults (70-79) who at baseline reported no difficulty walking ¼ mile and climbing 10 steps who were enrolled in the Health, Aging, and Body Composition study	After adjustment for confounders, older adults with a history of having a loop diuretic filled had higher odds of having two or more falls. Non-significant, 13% increased risk of recurrent falls with any antihypertensive use. No association according to dose and duration of use.
Lipsitz, et al., 2015 [64]	Alpha blockers, ACEs, ARBS, BBs, diuretics, and CCBs. (assessed at baseline at interviews). Dose was classified as : high, low/standard, and none	Self-reported recurrent falls. Classified by location and injury. Primary outcome was more than 1 fall.	Baseline blood pressure, # of comorbidities, education, race, body mass index, psychotropic medication use, time spent in outdoor activities	Cohort	598 hypertensive older adults (70-97) enrolled in the MOBILIZE Boston Study	Fallers were more likely to be white, higher educated, higher # of comorbidities, prior falls, lower cognition, and more depressed. During the one year follow-up, no class of antihypertensive was associated with increased risk of falls. CCBs were associated with a reduced fall risk and ACEs were associated with a reduced risk of injury falls
Fraser et al., 2014 [65]	Any anticholinergic medication use (included loop diuretic-Furosemide)	Falls and non-traumatic fractures	Gender, previous fracture, diabetes, age, femoral neck T-score, COPD, osteoarthritis, Parkinson's Disease, multiple sclerosis, bisphosphonate use	Cohort	Adults 50 years of age or older enrolled in the Canadian Multicentre Osteoporosis Study (CaMos).	After adjustment for covariates, there was no association between ACH use and falls or fractures.
Tinetti et al., 2014 [114]	ACEs, ARBs, BBs, CCBs, centrally acting antiadrenergic	Serious fall injuries resulting in fracture, brain injury, or	Demographics, education, perceived health, smoker, BMI, insurance, blood pressure,	Cohort	Community dwelling Medicare beneficiaries, 70+ YOA enrolled from 2004-2007 in the Medicare Current	Any antihypertensive use was associated with an increased risk of having a serious fall injury. When stratified by class, no class was associated

	agents, and other (peripheral acting antiadrenergic agents and vasodilators)	dislocations. Did not require a fall e-code.	BADLs, IADLs, mobility, social activity, urinary incontinence, cognitive incontinence, depression, prior fall injury, use assistive device, osteoporosis, prior MI, heart failure, diabetes, prior stroke, cardiac arrhythmia, valvular disease, a.fib, ESRD, blood loss anemia, weight loss, PVD, psychosis, elixhauser comorbidity score, statin use, medications history		Beneficiary Survey who had a claim-based diagnosis for hypertension	with an increased risk of injury. A past fall injury greatly increased the risk of a fall. Age and gender did not impact the association.
Berry et al., 2013 [109]	New use of loop or thiazide diuretic (new used defined using 180 day washout)	Hip Fracture identified with diagnostic and procedural codes	Demographics, BMI, smoking status, fracture history, use of osteoporosis medications	Case-crossover	THIN primary care database in the UK. 28,703 persons with hip fractures between 1987-2010.	Odds of hip fracture were increased in the 7 days following loop diuretic initiation compared to times of no use. THZs were associated with an increased odds of fractures in the 8-14 days following use.
Butt et al., 2013 [63]	ACEs, ARBs, CCBs, BBs, thiazide diuretics	Hip fracture	None	Self-controlled case series	Ontario Drug Benefit Program hypertensive new users of antihypertensives (mean age:81)	Antihypertensive initiation associated with a 43% increased risk of hip fracture in 45 days after initiation. ACE and BB significantly increased risk of hip fracture.

Berry et al., 2012 [121]	New or changing dose of diuretics (manly loop)	Incident Fall Reported on Nursing Reports	None	Case-crossover	1,785 long-term care nursing home residents with a fall history (mean age: 86)	New prescriptions *or* dose increases in loop diuretics were associated with increased risk of falls.
Gribbin et al., 2011 [122]	THZs, BBs, ACEs, ARBs, CCBs	Fall	None	Self-controlled case series	The Health Improvement Network (THIN). Patients who had a fall and had antihypertensives filled during the follow-up period.	THZs increase the rate of falls in the first 3 weeks following a prescription. BBs associated with a slightly elevated risk during the first 3 weeks. CCBs associated with a decreased risk of falls in first 3 weeks following use
Solomon et al., 2011 [96]	ACEs, CCBs, Loop diuretics, THZs	Fracture: hip, distal forearm, humerus, and pelvis	Demographics Charlson, hospital utilization, med history, osteoporosis diagnosis or meds, prior fractures, BMD testing, use of meds associated with fractures, prior fall, Parkinson disease and Alzheimer disease.	New User Cohort	Medicare beneficiaries enrolled in state-run drug benefit for low-income older adults with hypertension, no prior antihypertensive fill in the last 30 days, and had health care use during the study period.	No age or gender effects. THZs and ARBs associated with reduced risk compared to CCBs. Examined dose and duration effects. Similar to main effects.
Gribbin et al., 2010 [123]	ACEs, ARBs, BBs, CCBs, THZs (ever, current, recent, and never prescribed)	Falls	Coronary heart disease, heart failure, Afib, diabetes, Charlson index, or prescribing of other antihypertensives or antipsychotics	Case control	The Health Improvement Network (THIN). Cases had a fall and controls had no prior falls. Matched on age, sex, and primary care practice.	When comparing never prescribed patients to currently patients, THZs, BBs, and ACEs were associated with falls. Association was strongest for THZs- risk decreased with time. No age effect
Rejnmark et al., 2006 [124]	BBs, ACEs and ARBs, CCBs prescribed	Any fracture, hip fracture, spine fracture,	Charlson index, hospital utilization, fracture history, other meds use:	Case control	National Hospital Danish Register. Cases: all subjects who had a fracture in 2000.	BBs: decreased the risk of fractures. Dose effect present. CCBs: decreased risk of fracture. Dose effect was

	within 5 years of the fracture	and forearm fracture	diuretics, antiresorptive drugs, antiepileptic drugs, anxiolytics, sedatives, neuroleptics, antidepressants, systemic and topical corticosteroids, thyroid hormones, and antithyroid drugs. Income, social status, employment, demographics		Controls:: Civil registration system mated on gender and year of birth.	found. ACEs were associated with a decreased risk of fracture. No effect caused by age or gender.
*ABs= adrenergic blockers						

Table 18: List of antihypertensive drugs included in study according to antihypertensive class

Class	Generic Drug Names
ARBs	Azilsartan, Candesartan, Eprosartan, Fimasartan, Irbesartan, Losartan, Olmesartan, Tasosartan, Telmisartan, Valsartan
ACEs	Benazepril, Captopril, Cilazapril, Delapril, Enalapril, Fosinopril, Imidapril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Spirapril, Temocapril, Trandolapril, Zofenopril
CCBs	Amlodipine, Barnidipine, Benidipine, Bepridil, Clinidipine, Clevidipine, Diltiazem, Felodipine, Fendiline, Gallopamil, Isradipine, Lacidipine, Lercanidipine, Lidoflazine, Manidipine, Nicardipine, Nifedipine, Nilvadipine, Nimodipine, Nisoldipine, Nitrendipine, Perhexiline, Verapamil
BBs	Acebutolol, Alprenolol, Atenolol, Betaxolol, Bevantolol, Bisoprolol, Bopindolol, Bupranolol, Carteolol, Carvedilol, Celiprolol, Cloranolol, Epanolol, Esmolol, Labetalol, Mepindolol, Metipranolol, Metoprolol, Nadolol, Nebivolol, Netoprolol, Oxprenolol, Penbutolol, Pindolol, Practolol, Propranolol, Sotalol, Talinolol, Tertatolol, Timolol
THZs	Bendroflumethiazide, Chlorothiazide, Cyclopenthiazide, Cyclothiazide, Hydrochlorothiazide, Hydroflumethiazide, Mebutizide, Methyclothiazide, Polythiazide, Thiazide, Trichlormethiazide

Drugs were identified by generic drug name and National Drug Codes (NDC) in Medicare Part D data. Angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB), or thiazide diuretics (THZ)

Table 19: List of covariate definitions identified using ICD-9 or CPT Codes	
Covariate	**Code (includes ICD-9 and CPT Codes)**
Alzheimer's Disease	3310
Arrhythmia	4270, 4271, 4272, 42731, 42732, 42741, 42742, 4275, 42760, 42761, 42769, 42781, 42789, 4279
Cancer Screen	V760, V761, V7610, V7611, V7612, V7619, V762, V763, V7641, V7642. V7644, V7645, V7646, V7647, V7649, V7650, V7651, V7652, V768, V7681, V7689, V769
Congestive Heart Failure	428, 4280, 4281, 4282, 42820, 42821, 42822, 42823, 4283, 42830, 42831, 42832, 42833, 4284, 42840, 42841, 42842, 42843, 4289, 40201, 40211, 40291, 40401, 40403, 40411, 40413, 40491
Chronic Kidney Disease	2504, 25040, 25041, 25042, 25043, 27410, 403, 4039, 40390, 404, 4040, 40400, 40401, 40402, 40403, 4041, 40410, 40411, 40412, 40413, 4049, 40490, 40491, 40492, 40493, 4401, 4421, 5724, 580, 5800, 5804, 5808, 58081, 58089, 5809, 581, 5810, 5811, 5812, 5813, 5818, 58181, 58189, 5819, 582, 5820, 5821, 5822, 5824, 5828, 58281, 58289, 5829, 583, 5830, 5831, 5832, 5834, 5836, 5837, 5838, 58381, 58389, 5839, 584, 5845, 5846, 5847, 5848, 5849, 585, 5851, 5852, 5853, 5854, 5855, 5856, 586, 587, 5930 ,5931, 5932, 5933, 5934, 5935, 5936, 5937, 59370, 59371, 59372, 59373, 5938, 59381, 59382, 59389, 5939, 753, 7530 ,7533, 7912, 7913, 86600, 86601, 8661, 86610, 86611, 86612, 86613
COPD	491, 4912, 49120, 49121 ,49122, 492, 4928, 4932, 4940, 4941, 496,
Difficulty Walking	7197, 71970, 71975, 71976, 71977, 71978, 71979, 7812, 7813
Diabetes	2500, 25000, 25002, 25010 ,25012, 2502, 25020, 25022, 2503, 25030, 25032, 2504, 25040, 25042, 2505, 25050, 25052, 2506, 25060, 25062, 2507, 25070, 25072, 2508, 25080, 2509, 25090, 25092
Fracture	820xx, 813xx, 812xx, 8070, 8071, 8072, 8073, 8074, 8056, 8057, 8066, 8067, 808xx, 824xx, 821xx, 814xx, 815xx, 816xx, 817xx, 823xx, 800xx, 801xx, 802xx, 803xx, 804xx, 825xx, 826xx, 810xx, 811xx, 822xx
Hypertension	4010, 4011, 4019
Myocardial Infarction	410, 4100 ,41001, 4101, 41011, 4102, 41021, 4103, 41031, 4104, 41041, 4105, 41051, 4106, 41061, 4107, 41071, 4108, 41081, 4109, 41091
Obesity	27800, 27801, 27803
Osteoarthritis	71500, 71504, 71409, 71510, 71511, 71512, 71513, 71514, 71515, 71516, 71517, 71518, 71520, 71521, 71522, 71523, 71524, 71525, 71526, 71527, 71528, 71530 71531, 71532, 71533, 71534, 71535, 71536, 71537, 71538, 71580, 71589
Osteoporosis	73300, 73301, 73302, 73303, 73309
Parkinson's Disease	332, 3320 ,3321
Rheumatoid Arthritis	7140, 7142, 71430, 71431, 71432
Stroke	430, 431, 432, 4320, 4321, 4329, 4330, 43300, 43301, 4331, 43310, 43311, 4332, 43320, 43321, 4333, 43330, 43331, 4338, 43380, 43381, 4339, 43390, 43391, 4340, 43400, 43401, 4341, 43410, 43411, 4349, 43490, 43491, 435, 4350, 4351, 4352, 4353, 4358, 4359, 436, 4370, 4371, 4372, 4373, 4374, 4375, 4376, 4377, 4378, 4379, 438, 4380, 43810, 43811, 43812, 43813, 43814, 43819, 43820, 43821, 43822, 43830, 43831, 43832, 43840, 43841, 43842, 43850, 43851, 43852, 43853, 4386, 4387, 43881, 43882, 43883, 43884, 43885, 43889, 4389
Ambulance Transfer	A0426, A0427, A0428, A0429, A0999

Hospital Bed Use	E0250, E0251, E0255, E0256, E0260, E0261, E0265, E0266, E0270, E0290, E0291, E0292, E0293, E0294, E0295, E0296, E0297, E0301, E0302, E0303, E0304, E0316
Home Oxygen Use	E0431, E0433, E0434, E0435, E0439, E0441, E0442, E0443, E1390, E1391, E1392
Walker or Wheelchair Use	E0130, E0135, E0140, E0141, E0143, E0144, E0147, E0148. E0149, E0154, E0155, E0156, E0157, E0158, E1050, E1060, E1070, E1083, E1084, E1085, E1086, E1087, E1088, E1089, E1090, E1091, E1092, E1093, E1100, E1140, E1150, E1160, E1161, E1170, K0001, K0002, K0003, K0004, K0005, K0006, K0007, K0008, K0009
Vertigo	3860, 38600, 38601, 38602, 38603, 38604, 3861, 38610, 38611, 38612, 38619, 3862, 3863, 38630, 38631, 38632, 38633, 38634, 38635, 3864, 38640, 38641, 38642, 38643, 38648, 3865, 38650, 38651, 38652, 38653, 38654, 38655, 38656, 38658, 3868, 3869, 43885, 7804

Covariates were identified using Medicare Parts A and B data using International Classification of Diseases, Ninth Revision (ICD-9) and Current Procedural Terminology Codes (CPT).

Table 20: Trajectory model building results for Medicare beneficiaries initiating antihypertensives therapy between 2008-2011

	% Population in Each Group							
# Groups	Group1	Group2	Group3	Group4	Group5	Group6	Group 7	BIC
2	43.2	56.8	---	---	---	---	---	-1459845
3	28.5	28.1	43.4	---	---	---	---	-1367868
4	13.2	28.9	14.2	43.7	---	---	---	-1330199
5	13.6	15.2	17.2	11.1	42.9	---	---	-1311312
6	10.4	10.0	18.0	7.9	14.1	39.5	---	-1300277
7	10.1	5.6	17.4	8.3	7.7	12.1	38.8	-1293649

BIC= Bayesian information criterion. Lower values signify better model fit.
Logistic regression models were used to identify trajectory groups. The dependent variables were the monthly binary indicators of antihypertensive use and months since start of antihypertensive therapy were the independent variables. Time was modeled using cubic terms.

Table 21: Comparison of adherence measures ability to distinguish between adherent months according to antihypertensive trajectory group

	Adherence Measure (AUC)		
Trajectory Groups	PDC	PMC	Traj Model
Immediate Drop-off	0.609	0.633	0.960
Rapid Drop-off	0.563	0.581	0.969
Gradual Drop-off	0.646	0.665	0.789
Partial Drop-off	0.613	0.646	0.750
Early Drop-off then Rebound	0.615	0.636	0.797
Adherent	0.869	0.885	0.660

Area under the curve (AUC) statistics are used to quantify the ability of the measures to discriminate between adherent and non-adherent months. Values of 1 symbolize perfect discrimination.

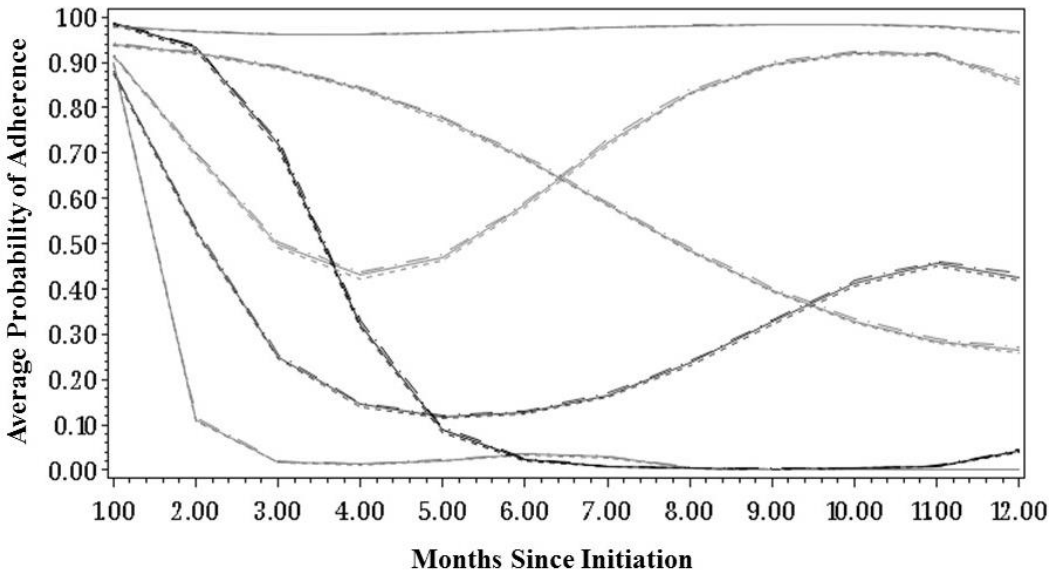

Figure 9: Six-group trajectory model excluding those Medicare beneficiaries that were in the insurance gap period during follow-up (n=238,925)

Table 22: Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for predictors of antihypertensive trajectories

Covariates	Immediate Dropoff	Rapid Dropoff	Gradual Dropoff	Partial Dropoff	Early Dropoff then Rebound
Male Gender	1.08 (1.06, 1.11)	1.12 (1.08, 1.15)	1.08 (1.06, 1.11)	1.07 (1.04, 1.10)	1.02 (0.99, 1.05)
Age					
66-74	ref	ref	ref	ref	ref
75-84	1.08 (1.05, 1.11)	1.09 (1.05, 1.12)	1.04 (1.01, 1.06)	1.07 (1.04, 1.11)	1.07 (1.04, 1.10)
85+	1.09 (1.04, 1.13)	1.13 (1.07, 1.20)	1.04 (1.00, 1.09)	1.12 (1.06, 1.17)	1.16 (1.11, 1.22)
Non-White Race	2.05 (1.99, 2.12)	1.85 (1.78, 1.93)	1.59 (1.54, 1.64)	2.26 (2.19, 2.34)	1.58 (1.52, 1.64)
Combination Therapy	0.48 (0.47, 0.50)	0.67 (0.64, 0.70)	0.75 (0.73, 0.78)	0.66 (0.63, 0.69)	0.76 (0.74, 0.80)
Days supply on Index Date	0.98 (0.98, 0.98)	1.02 (1.02, 1.02)	1.01 (1.01, 1.01)	0.99 (0.99, 0.99)	0.99 (0.99, 0.99)
Medication Use 14 Days Prior					
1-2 meds	ref	ref	ref	ref	ref
3-4 meds	0.96 (0.94, 0.99)	0.97 (0.93, 1.00)	0.94 (0.92, 0.97)	0.93 (0.90, 0.95)	0.94 (0.91, 0.97)
≥ 5 meds	0.81 (0.78, 0.84)	0.87 (0.83, 0.91)	0.86 (0.83, 0.90)	0.77 (0.74, 0.81)	0.84 (0.80, 0.88)
Insurance Gap During Baseline	0.80 (0.77, 0.82)	0.88 (0.84, 0.92)	0.92 (0.89, 0.96)	0.79 (0.76, 0.82)	0.89 (0.86, 0.93)
Eligible for Low-Income Subsidy	0.95 (0.91, 1.00)	0.96 (0.90, 1.02)	0.98 (0.94, 1.04)	1.00 (0.95, 1.06)	0.98 (0.93, 1.04)
Loop Diuretic	0.86 (0.83, 0.89)	0.93 (0.88, 0.98)	0.98 (0.94, 1.03)	0.91 (0.87, 0.96)	0.98 (0.93, 1.03)
Antiarrhythmic	1.12 (1.07, 1.18)	1.05 (0.98, 1.13)	1.03 (0.97, 1.09)	1.12 (1.05, 1.20)	1.07 (1.01, 1.14)
Antidepressant[a]	1.01 (0.98, 1.04)	1.08 (1.04, 1.13)	1.10 (1.07, 1.14)	1.05 (1.02, 1.10)	1.07 (1.03, 1.11)
Antiepileptic	1.07 (1.03, 1.11)	1.12 (1.07, 1.18)	1.03 (0.99, 1.08)	0.99 (0.95, 1.04)	1.07 (1.03, 1.12)
Anxiolytic	1.21 (1.14, 1.29)	1.22 (1.12, 1.33)	1.12 (1.04, 1.20)	1.21 (1.12, 1.30)	1.07 (0.99, 1.16)
Benzodiazepine	1.01 (0.91, 1.13)	0.88 (0.75, 1.03)	0.94 (0.83, 1.07)	0.88 (0.76, 1.01)	0.95 (0.83, 1.10)
Opioid	1.33 (1.30, 1.36)	1.18 (1.14, 1.22)	1.16 (1.13, 1.19)	1.26 (1.22, 1.29)	1.19 (1.15, 1.22)
Hypnotic	1.22 (1.17, 1.27)	1.21 (1.14, 1.28)	1.09 (1.04, 1.14)	1.15 (1.09, 1.21)	1.13 (1.07, 1.19)
Diabetes	1.01 (0.98, 1.03)	1.13 (1.09, 1.17)	1.09 (1.06, 1.12)	1.16 (1.13, 1.20)	1.16 (1.13, 1.20)
Chronic Kidney Disease	1.03 (0.99, 1.06)	1.05 (1.00, 1.10)	1.06 (1.02, 1.10)	1.08 (1.03, 1.13)	1.09 (1.04, 1.14)
Parkinson's Disease	1.40 (1.29, 1.53)	1.31 (1.16, 1.48)	1.20 (1.09, 1.32)	1.19 (1.07, 1.34)	1.21 (1.08, 1.35)
Alzheimer's	0.87 (0.82, 0.93)	0.92 (0.84, 1.01)	0.99 (0.93, 1.07)	0.83 (0.77, 0.91)	0.94 (0.87, 1.02)
COPD	1.24 (1.20, 1.28)	1.15 (1.10, 1.20)	1.15 (1.11, 1.19)	1.17 (1.13, 1.22)	1.14 (1.10, 1.18)
Congestive Heart Failure	0.90 (0.87, 0.94)	0.93 (0.88, 0.98)	0.99 (0.95, 1.03)	0.98 (0.93, 1.03)	0.95 (0.91, 1.00)
Arrhythmia	0.77 (0.75, 0.80)	0.87 (0.84, 0.91)	0.88 (0.86, 0.91)	0.76 (0.74, 0.79)	0.85 (0.82, 0.88)
Osteoarthritis	1.13 (1.09, 1.16)	1.12 (1.08, 1.17)	1.07 (1.04, 1.11)	1.15 (1.11, 1.19)	1.10 (1.06, 1.14)
Rheumatoid Arthritis	1.13 (1.06, 1.20)	1.09 (1.01, 1.18)	1.08 (1.02, 1.16)	1.15 (1.07, 1.24)	1.08 (1.00, 1.16)
Stroke	0.94 (0.91, 0.97)	1.00 (0.96, 1.04)	0.99 (0.95, 1.02)	0.97 (0.93, 1.01)	1.03 (0.99, 1.07)
Myocardial Infraction	0.50 (0.46, 0.54)	0.66 (0.60, 0.74)	0.78 (0.72, 0.84)	0.52 (0.47, 0.58)	0.67 (0.61, 0.74)
Hypertension	0.49 (0.48, 0.50)	0.67 (0.64, 0.69)	0.87 (0.84, 0.89)	0.71 (0.69, 0.73)	0.93 (0.90, 0.96)
Obesity	0.98 (0.93, 1.03)	0.98 (0.92, 1.05)	1.00 (0.95, 1.06)	1.01 (0.95, 1.07)	1.05 (0.99, 1.11)
Fracture	1.16 (1.12, 1.21)	1.07 (1.01, 1.13)	1.08 (1.04, 1.13)	1.15 (1.10, 1.21)	1.07 (1.02, 1.13)
Frailty Predictor Index[b]	0.68 (0.61, 0.76)	0.73 (0.62, 0.85)	0.85 (0.75, 0.96)	0.58 (0.50, 0.67)	0.73 (0.64, 0.84)

Home Oxygen Use	1.16 (1.09, 1.22)	1.13 (1.04, 1.22)	1.00 (0.94, 1.07)	1.10 (1.03, 1.18)	1.05 (0.98, 1.13)
Walker or wheelchair use	1.01 (0.95, 1.07)	1.05 (0.97, 1.14)	1.00 (0.94, 1.07)	1.12 (1.04, 1.20)	1.05 (0.98, 1.13)
Hospital Bed	1.21 (1.08, 1.34)	0.91 (0.77, 1.07)	1.06 (0.94, 1.20)	1.12 (0.98, 1.28)	0.97 (0.85, 1.12)
Difficulty Walking	0.99 (0.95, 1.03)	1.03 (0.98, 1.09)	1.00 (0.96, 1.04)	1.00 (0.95, 1.05)	1.00 (0.95, 1.05)
Vertigo	1.25 (1.21, 1.29)	1.20 (1.15. 1.26)	1.10 (1.06, 1.14)	1.17 (1.12, 1.21)	1.08 (1.04, 1.12)
Ambulance Transport	1.06 (1.02, 1.10)	0.97 (0.92, 1.02)	1.00 (0.96, 1.04)	0.98 (0.93, 1.02)	0.98 (0.94, 1.03)
Cancer Screenings	0.84 (0.82, 0.86)	0.81 (0.79, 0.84)	0.90 (0.88, 0.92)	0.83 (0.80, 0.85)	0.93 (0.91, 0.96)
Hospital Admissions	0.81 (0.69, 0.95)	0.69 (0.54, 0.88)	0.82 (0.68, 0.98)	0.84 (0.68, 1.04)	0.83 (0.68, 1.02)
Long Stay Admissions	1.23 (1.11, 1.37)	1.12 (0.96, 1.32)	1.04 (0.92, 1.18)	1.00 (0.86, 1.17)	1.16 (1.01, 1.33)
Short Term Hospital Stays	1.47 (1.26, 1.72)	1.48 (1.16, 1.88)	1.16 (0.97, 1.39)	1.06 (0.86, 1.31)	1.11 (0.91, 1.35)

[a] Antidepressants include selective serotonin reuptake inhibitors, tricyclics, monoamine oxidase inhibitors, serotonin and norepinephrine reuptake inhibitors

[b] Higher scores denote a higher probability of being frail.

Odds Ratios (ORs) and 95% CI (confidence intervals) are adjusted for all covariates in table. We presented the inverse of the ORs < 1 in the manuscript for consistency relating to non-adherence.

AUC-statistic for fully adjusted model: 0.525

Reference group is the adherent trajectory group. 330 observations were removed from the analysis due to missing race.

Table 23: Definitions of fractures identified in Medicare Claims

Fracture Type	ICD-9 Diagnosis Codes	ICD-9 Procedure Codes	Current Procedure Terminology (CPT) Codes
Hip	820.x,	7855, 7905, 7915, 7925, 7935, 7965, 8161, 8162	27125-27127, 27230, 27232, 27234-27236, 27238, 27240, 27242, 27244, 27246, 27248, 27130-27131, 29010, 29015, 29020, 29025, 29035, 29040, 29044, 29046, 29035, 29325, 29345, 29355, 29358, 29365, 29505, 29520, 29799, 73500, 73510, 73520, 73530, 73550
Radius	813.x,	7853, 7902, 7912, 7922, 7932, 7962	24620, 24625, 24635, 24650, 24655, 24660, 24665-24666, 24670, 24675, 24680, 24685, 25500, 25505, 25510, 25515, 25530, 25535, 25540, 25545, 25560, 25565, 25570, 25575, 25600, 25605, 25610. 25611, 25615, 25620, 25650, 24580-24581, 24583, 24585-24588, 29065, 29075, 29085, 29105, 29125-29126, 29799, 73070, 73080, 73080, 73090, 73100, 73110
Humerus	812.x,	7852, 7901, 7911, 7921, 7931, 7961	23600, 23605, 23610, 23615, 23620, 23625, 23630, 23665, 23670, 23675, 23680, 24500, 24505-24506, 24510, 24515, 24530-24531, 24535-24536, 24538, 24540, 24542, 24545, 24560, 24565, 24570, 24575-24581, 24583, 24585-24588, 29035, 29040, 29044, 29046, 29065, 29105, 29799, 73020, 73030, 73050, 73060, 73070, 73080
Rib	8070, 8071, 8072, 8073, 8074		21800, 21805, 21810, 21820, 21825, 29010, 29015, 29020, 29025, 29035, 29040, 29044, 29046, 29200, 71100, 71101, 71110, 71111, 71120, 71130
Pelvis	8056, 8057, 8066, 8067, 808.x		27190-27192, 27200, 27202, 27210-27212, 27214, 27220, 27222, 27224, 27225, 27120, 27122, 27130, 27131-27132, 72010, 72020, 72100, 72110, 72114, 72120, 72170, 72170, 72190, 72200, 72202, 72220, 73500, 73510, 73520, 73530
Ankle	824.x		27760, 27762, 27764, 27766, 27786, 27788, 27790, 27792, 27808, 27810, 27812, 27814, 27816, 27818, 27820, 27822, 27823, 29010, 29015, 29020, 29025, 29345, 29355, 29358, 29365, 29405, 29425, 29505, 29515, 29540, 29799, 703328, 70330, 73590, 73600, 73620, 73630
Femoral Shaft	821.x		27500, 27502, 27504, 27506, 27508, 27510, 27512, 27514, 29010, 29015, 29020, 29025, 29035, 29040, 29044, 29046, 29305, 29325, 29345, 29355, 29348, 29365, 29505, 29520, 29799, 73500, 73510, 73520, 73530, 73550
Hand	814.x-817.x,	7854, 7903, 7904, 7913, 7914, 7923, 7924, 7933, 7934, 7963, 7964	25622, 25624, 25626, 25628, 25630, 25635, 25640, 25645, 25680, 25685, 26600, 26605, 26607, 26610, 26615, 26645, 26650, 26655, 26660, 26665, 26720, 26725, 26727, 26730, 26735, 26740, 26742, 26743-26744, 26746, 26750, 26755-26756, 26760, 26765, 25600, 25605, 25610, 25611, 25615, 25620, 25650, 29035, 29075, 29085, 29105, 29125, 29126, 29130, 29131, 29799, 73100, 73110, 73120, 73130, 73140

Tibia	823.x,	7857, 7906, 7916, 7926, 7936, 7966	27530, 27532, 27534, 27536-27538, 27540, 27750, 27752, 27754, 27756, 27758, 27780, 27781-27782, 27784, 27800, 27802, 27804, 27806, 29010, 29015, 29020, 29025, 29345, 29355, 29358, 29365, 29405, 29425, 29505, 29515, 29799, 73560, 73562, 73564, 73590, 73600, 73610
Skull/Face	800-804.x	767	21300, 21310, 21315, 21320, 21325, 21330, 21335, 21334-21340, 21345-21347, 21350, 21355, 21360, 21365, 21380, 21385-21387, 21390, 21395-21400, 21401, 21406-21407, 21420-21422, 21431, 21432-21433, 21435, 21440, 21445, 21450, 21451-21455, 21461, 21462, 21465, 24170, 21495, 70230, 70231, 70250, 70260,
Foot	825.x-826.x,	7858, 7907, 7908, 7917, 7918, 7927, 7928, 7938, 7967, 7968	28400, 28405-28406, 28410, 28415, 28420, 28430, 28415, 28450, 28430, 28435-28436, 28440, 28445, 28450, 28470, 28475-28476, 28480, 28485, 28 490, 28495-28496, 28500, 28505, 28510, 28515, 28520, 28525, 29405, 29425, 29505, 29515, 29550, 29580, 73600, 73620, 73630, 73650, 73660
Clavicle	810.x-811.x		23500, 23505, 23510, 23515, 23570, 23575, 23585, 29010, 29015, 29020, 29025, 29035, 29040, 29044, 29046, 29049, 29055, 29058, 29065, 29105, 29240, 7300, 73010, 73020, 73030, 73050, 73060
Patella	822.x	7856	27520, 27522, 27534, 29010, 29015, 29020, 29025, 29035, 29040, 29044, 29046, 29345, 29355, 29358, 29365, 29355, 29358, 29365, 29435, 29505, 29530, 73550, 73560, 73562, 73564, 73590

Fractures were identified using validated diagnosis codes and procedure codes found in Medicare Parts A and B [99]. Fractures included in the study had an incident diagnosis code with a corresponding procedure code within 7 days of the diagnosis.

Table 24: List of covariate definitions identified using ICD-9 or CPT Codes	
Covariate	**Code (includes ICD-9 and CPT Codes)**
Ambulance Transfer	A0426, A0427, A0428, A0429, A0999
Alzheimer's Disease	3310
Arrhythmia	4270, 4271, 4272, 42731, 42732, 42741, 42742, 4275, 42760, 42761, 42769, 42781, 42789, 4279
Cancer Screen	V760, V761, V7610, V7611, V7612, V7619, V762, V763, V7641, V7642. V7644, V7645, V7646, V7647, V7649, V7650, V7651, V7652, V768, V7681, V7689, V769
Chronic Kidney Disease	2504, 25040, 25041, 25042, 25043, 27410, 403, 4039, 40390, 404, 4040, 40400, 40401, 40402, 40403, 4041, 40410-40413, 4049, 40490, 40491, 40492, 40493, 4401, 4421, 5724, 580, 5800, 5804, 5808, 58081, 58089, 5809, 581, 5810-5813, 5818, 58181, 58189, 5819, 582, 5820, 5821, 5822, 5824, 5828, 58281, 58289, 5829, 583, 5830, 5831, 5832, 5834, 5836, 5837, 5838, 58381, 58389, 5839, 584, 5845-5849, 585, 5851-5856, 586, 587, 5930-5937, 59370-59373, 5938, 59381, 59382, 59389, 5939, 753, 7530 ,7533, 7912, 7913, 86600, 86601, 8661, 86610-86613
Dementia	290, 294
Difficulty Walking	7197, 71970, 71975, 71976, 71977, 71978, 71979, 7812, 7813
Diabetes	2500, 25000, 25002, 25010 ,25012, 2502, 25020, 25022, 2503, 25030, 25032, 2504, 25040, 25042, 2505, 25050, 25052, 2506, 25060, 25062, 2507, 25070, 25072, 2508, 25080, 2509, 25090, 25092
Dyslipidemia	272-272.5
Hospital Bed Use	E0250, E0251, E0255, E0256, E0260, E0261, E0265, E0266, E0270, E0290, E0291, E0292, E0293, E0294, E0295, E0296, E0297, E0301, E0302, E0303, E0304, E0316
Home Oxygen Use	E0431, E0433, E0434, E0435, E0439, E0441, E0442, E0443, E1390, E1391, E1392
Hypertension	4010, 4011, 4019
Myocardial Infarction	410, 4100 ,41001, 4101, 41011, 4102, 41021, 4103, 41031, 4104, 41041, 4105, 41051, 4106, 41061, 4107, 41071, 4108, 41081, 4109, 41091
Obesity	27800, 27801, 27803
Orthostatic Hypotension	4580
Osteoarthritis	71500, 71504, 71409, 71510-71518, 71520-71528, 71530-71538, 71580, 71589
Osteoporosis	73300, 73301, 73302, 73303, 73309
Parkinson's Disease	332, 3320 ,3321
Rheumatoid Arthritis	7140, 7142, 71430, 71431, 71432
Stroke	430, 431, 432, 4320, 4321, 4329, 4330, 43300, 43301, 4331, 43310, 43311, 4332, 43320, 43321, 4333, 43330, 43331, 4338, 43380, 43381, 4339, 43390, 43391, 4340, 43400, 43401, 4341, 43410, 43411, 4349, 43490, 43491, 435, 4350, 4351, 4352, 4353, 4358, 4359, 436, 4370-4379, 438, 4380, 43810, 43811-43814, 43819, 43820, 43821, 43822, 43830, 43831, 43832, 43840, 43841, 43842, 43850, 43851, 43852, 43853, 4386, 4387, 43881-43885, 43889, 4389
Syncope	7802
Urinary Incontinence	7883
Walker or Wheelchair Use	E0130, E0135, E0140, E0141, E0143, E0144, E0147, E0148. E0149, E0154, E0155, E0156, E0157, E0158, E1050, E1060, E1070, E1083, E1084, E1085, E1086, E1087, E1088, E1089, E1090, E1091, E1092, E1093, E1100, E1140, E1150, E1160, E1161, E1170, K0001, K0002, K0003, K0004, K0005, K0006, K0007, K0008, K0009

Vertigo	3860, 38600, 38601, 38602, 38603, 38604, 3861, 38610, 38611, 38612, 38619, 3862, 3863, 38630, 38631, 38632, 38633, 38634, 38635, 3864, 38640, 38641, 38642, 38643, 38648, 3865, 38650, 38651, 38652, 38653, 38654, 38655, 38656, 38658, 3868, 3869, 43885, 7804

Covariates were identified using Medicare Parts A and B data using International Classification of Diseases, Ninth Revision (ICD-9) and Current Procedural Terminology Codes (CPT).

Table 25: Sensitivity analysis results examining the rates of incident non-vertebral fractures in the first year after initiation among Medicare beneficiaries initiating antihypertensive monotherapy from 2008-2011 according to duration of use

	0-14 days after initiation				15-365 days after initiation			
Drug Class	# Fractures	P-Yrs	Rate Per 10,000 p-yrs (95% CI)	SMRW HR (95% CI)	# Fractures	P-Yrs	Rate per 10,000 p-yrs (95% CI)	SMRW HR (95% CI)
Results when using an 'As-Treated' study design (n=122,629)								
ACE	52	1,502	346 (261-451)	ref	735	21,726	338 (315-363)	ref
ARB	14	410	342 (194-559)	0.96 (0.50, 1.82)	177	5,973	299 (255-343)	0.90 (0.76, 1.07)
BB	55	1,373	401 (302-521)	1.04 (0.67, 1.60)	842	19,802	425 (397-455)	1.18 (1.05, 1.33)
CCB	24	679	354 (232-518)	0.76 (0.45, 1.28)	432	9,534	453 (412-497)	1.14 (1.00, 1.31)
THZ	27	595	454 (305-651)	1.48 (0.82, 2.67)	277	7,932	349 (310-392)	0.99 (0.84, 1.18)
Results when excluding beneficiaries with chronic kidney disease or diabetes (n=86,420)								
ACE	32	979	327 (227-456)	ref	781	23,373	334 (211-358)	ref
ARB	<11	NR	300 (139-569)	0.94 (0.40, 2.22)	199	6,398	211 (270-357)	0.95 (0.81, 1.12)
BB	45	1,045	431 (318-571)	1.35 (0.81, 2.26)	1000	24,799	403 (330-488)	1.07 (0.96, 1.19)
CCB	19	513	370 (230-568)	0.97 (0.53, 1.81)	522	12,116	431 (395-469)	1.13 (1.00, 1.27)
THZ	22	505	436 (280-649)	1.30 (0.74, 2.30)	459	12,031	382 (348-418)	1.04 (0.92, 1.18)
Results when excluding beneficiaries that initiated with brand antihypertensive medications on the index date (n=108,491)								
ACE	54	1,529	353 (268-457)	ref	1,277	37,716	339 (320-358)	ref
ARB	<11	NR	370 (94-1,008)	0.80 (0.24, 2.63)	67	1,997	336 (262-423)	0.99 (0.76, 1.30)
BB	51	1,294	394 (297-514)	0.90 (0.58, 1.42)	1,267	31,800	398 (377-421)	1.08 (0.99, 1.19)
CCB	25	637	393 (260-571)	0.82 (0.49, 1.37)	659	15,648	421 (390-454)	1.11 (1.00, 1.24)
THZ	27	614	441 (296-632)	1.40 (0.78, 2.51)	563	15,105	373 (343-405)	1.02 (0.90, 1.15)

P-Yrs= person-years of follow (calculated by dividing the total number of follow-up days by 365.25)
SMRW= Standardized mortality ratio weight
Hazard ratios are adjusted for SMRWs that were calculated using all the baseline covariates.
NR= non-reportable
CI=confidence interval
Angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB), or thiazide diuretics (THZ)

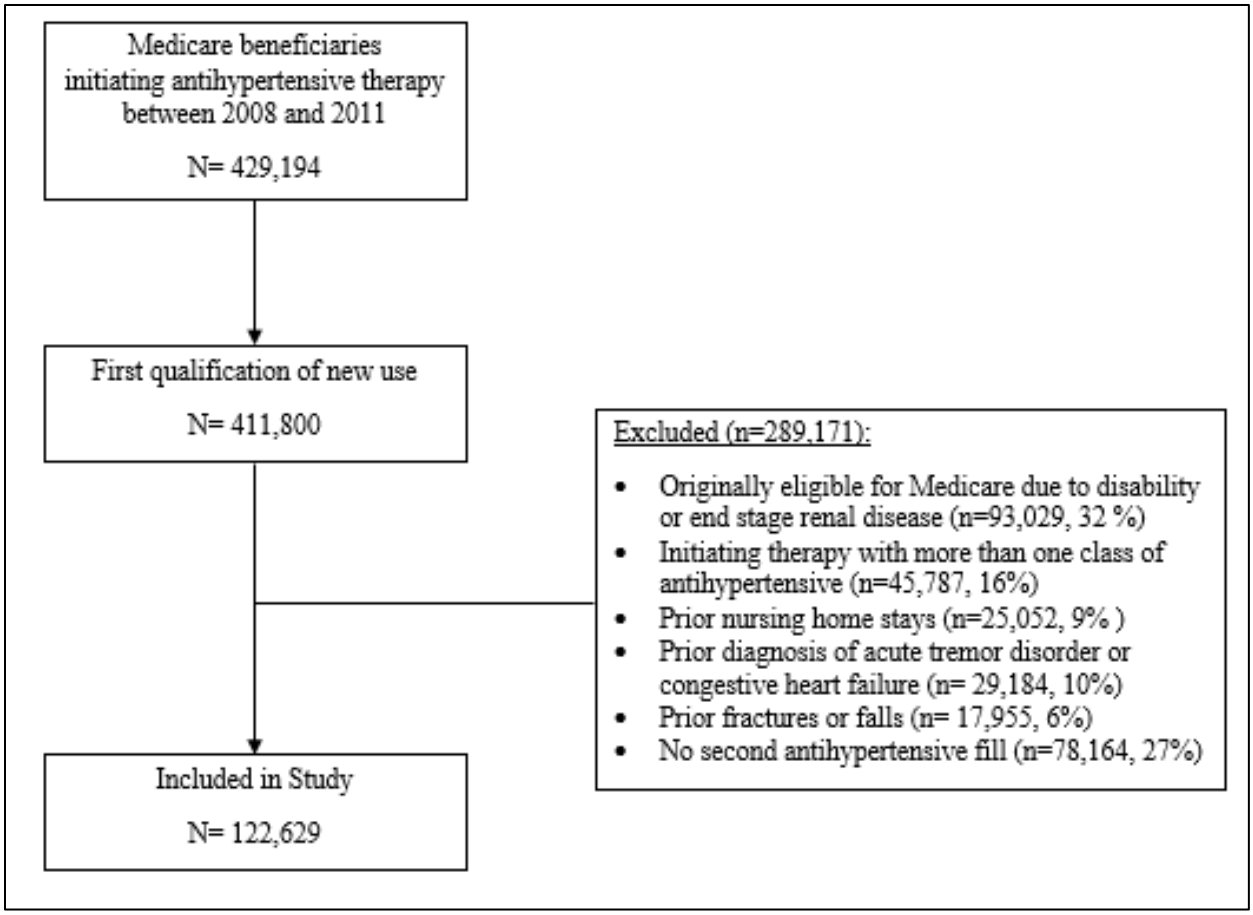

Figure 10: Eligibility flow chart of Medicare beneficiaries starting antihypertensive monotherapy between 2008-2011

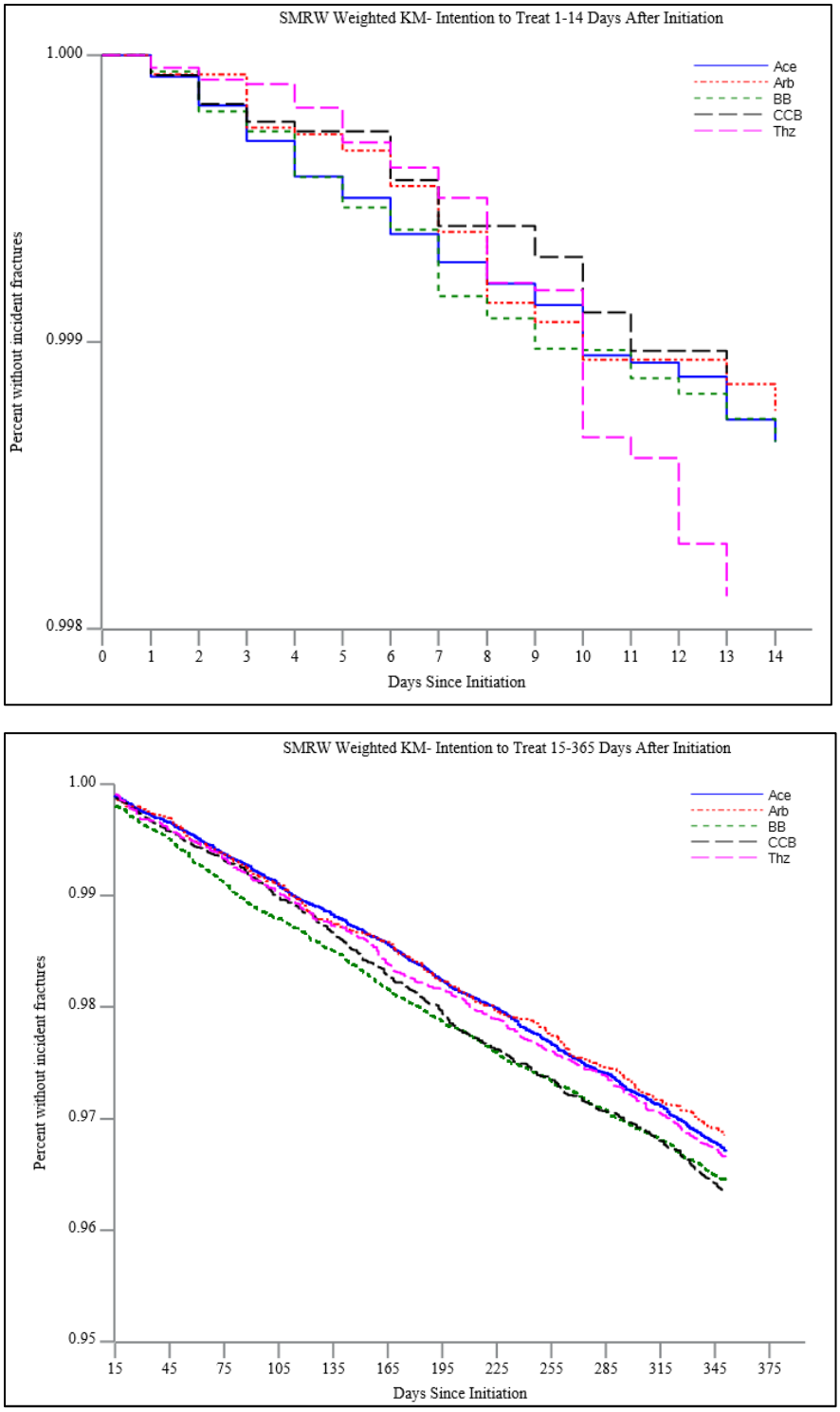

Figure 11: Adjusted SMR Kaplan-Meier curves for incident fractures according duration of use (1-14 days after initiation and 15-365 days after initiation) according to antihypertensive drug class among Medicare beneficiaries starting antihypertensive monotherapy. Top figure=1-14 days after initiation. Bottom figure=15-365 days after initiation.

Table 26: Antihypertensive adherence trajectory model building results (Chapter 6)								
	% Population in Each Group							
# Groups	Group1	Group2	Group3	Group4	Group5	Group6	Group 7	BIC
2	42.89	57.11	---	---	---	---	---	-1078223
3	28.08	28.14	43.78	---	---	---	---	-1010901
4	13.46	28.61	13.83	44.10	---	---	---	-983827
5	13.97	15.06	17.33	10.77	42.86	---	---	-970453
6	15.67	20.26	5.36	6.49	9.04	43.19	---	-963983

BIC= Bayesian information criterion. Lower values signify better model fit.
Logistic regression models were used to identify trajectory groups. The dependent variables were the monthly binary indicators of antihypertensive use and months since start of antihypertensive therapy were the independent variables. Time was modeled using cubic terms.
6 group failed to converge and had small group sizes

Table 27: Rates of death and disenrollment from Medicare according to one year antihypertensive adherence trajectories following initiation of therapy

	182 Day Period				365 Day Period			
Drug Class	# Deaths /Disenroll	Person-Years (p-yrs)	Rate Per 10,000 p-yrs (95% CI)	Adjusted HR (95% CI)	# Deaths /Disenroll	Person-Years (p-yrs)	Rate per 10,000 p-yrs (95% CI)	Adjusted HR (95% CI)
Immediate Drop-off	1,418	46,351	306 (290, 322)	1.30 (1.22, 1.39)	2,778	61,066	455 (438, 472)	1.25 (1.20, 1.31)
Gradual Drop-off	1,561	53,364	293 (278, 307)	1.27 (1.19, 1.35)	3,060	70,356	435 (420, 451)	1.22 (1.67, 1.27)
Partial Drop-off	954	33,157	288 (270, 306)	1.28 (1.19, 1.37)	1,859	43,735	425 (406, 445)	1.22 (1.53, 1.28)
Early Drop-off then Rebound	1,170	43,026	272 (257, 288)	1.19 (1.11, 1.28)	2,444	56,749	431 (414, 448)	1.22 (1.16, 1.28)
Adherent	2,952	132,187	223 (215, 232)	ref	6,069	174,808	347 (339, 356)	ref

Hazard Ratios (HRs) are adjusted for all baseline covariates. CI= Confidence Interval

REFERENCES

1. Yoon SS, Carroll MD, Fryar CD. Hypertension prevalence and control among adults: United states, 2011-2014. *NCHS Data Brief*. 2015;(220)(220):1-8.

2. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: A report of the american college of cardiology foundation task force on clinical expert consensus documents developed in collaboration with the american academy of neurology, american geriatrics society, american society for preventive cardiology, american society of hypertension, american society of nephrology, association of black cardiologists, and european society of hypertension. *J Am Coll Cardiol*. 2011;57(20):2037-2114.

3. Mazzaglia G, Ambrosioni E, Alacqua M, et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation*. 2009;120(16):1598-1605. doi: 10.1161/CIRCULATIONAHA.108.830299 [doi].

4. Lemstra M, Alsabbagh MW. Proportion and risk indicators of nonadherence to antihypertensive therapy: A meta-analysis. *Patient Prefer Adherence*. 2014;8:211-218. doi: 10.2147/PPA.S55382 [doi].

5. Lehmann A, Aslani P, Ahmed R, et al. Assessing medication adherence: Options to consider. *International journal of clinical pharmacy*. 2014;36(1):55-69.

6. Kronish IM, Ye S. Adherence to cardiovascular medications: Lessons learned and future directions. *Prog Cardiovasc Dis*. 2013;55(6):590-600.

7. 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; 10.1097/MLR.0b013e3182984c1f.

8. Bateman BT, Franklin JM, Bykov K, et al. Persistent opioid use following cesarean delivery: Patterns and predictors among opioid-naïve women. *Obstet Gynecol*. 2016.

9. 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.

10. Wiens M, Etminan M, Gill S, Takkouche B. Effects of antihypertensive drug treatments on fracture outcomes: A meta-analysis of observational studies. *J Intern Med*. 2006;260(4):350-362.

11. Butt D, Harvey P. Benefits and risks of antihypertensive medications in the elderly. *J Intern Med*. 2015;278(6):599-626.

12. Berry SD, Kiel DP. Treating hypertension in the elderly: Should the risk of falls be part of the equation? *JAMA internal medicine*. 2014;174(4):596-597.

13. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (JNC 8). *JAMA*. 2014;311(5):507-520.

14. Go A, Mozaffarian D, Roger V, et al. On behalf of the american heart association statistics committee and stroke statistics subcommittee. *Heart disease and stroke statistics—2013 update: a report from the American Heart Association.Circulation*. 2013;127(1):e1-e240.

15. Selby JV, Friedman GD, Quesenberry CP,Jr. Precursors of essential hypertension: Pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. *Am J Epidemiol*. 1990;131(6):1017-1027.

16. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among united states adults 1999-2004. *Hypertension*. 2007;49(1):69-75. doi: 01.HYP.0000252676.46043.18 [pii].

17. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the united states, 1988-2000. *JAMA*. 2003;290(2):199-206.

18. Bromfield SG, Bowling CB, Tanner RM, et al. Trends in hypertension prevalence, awareness, treatment, and control among US adults 80 years and older, 1988–2010. *The Journal of Clinical Hypertension*. 2014;16(4):270-276.

19. Rosenthal T, Nussinovitch N. Managing hypertension in the elderly in light of the changes during aging. *Blood Press*. 2008;17(4):186-194.

20. Hilmer SN, McLachlan AJ, Le Couteur DG. Clinical pharmacology in the geriatric patient. *Fundam Clin Pharmacol*. 2007;21(3):217-230.

21. Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. *Eur J Clin Pharmacol*. 2013;69(3):319-326.

22. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. *JAMA*. 2003;289(19):2560-2571.

23. Corrao G, Rea F, Ghirardi A, Soranna D, Merlino L, Mancia G. Adherence with antihypertensive drug therapy and the risk of heart failure in clinical practice. *Hypertension*. 2015;66(4):742-749. doi: 10.1161/HYPERTENSIONAHA.115.05463 [doi].

24. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665. doi: 10.1136/bmj.b1665 [doi].

25. Sica DA, Carter B, Cushman W, Hamm L. Thiazide and loop diuretics. *The Journal of Clinical Hypertension*. 2011;13(9):639-643.

26. Brater DC. Update in diuretic therapy: Clinical pharmacology. . 2011;31(6):483-494.

27. Glynn RJ, Knight EL, Levin R, Avorn J. Paradoxical relations of drug treatment with mortality in older persons. *Epidemiology*. 2001;12(6):682-689.

28. Agostini JV, Han L, Tinetti ME. The relationship between number of medications and weight loss or impaired balance in older adults. *J Am Geriatr Soc*. 2004;52(10):1719-1723.

29. Messerli FH, Grossman E, Goldbourt U. Are β-blockers efficacious as first-line therapy for hypertension in the elderly?: A systematic review. *JAMA*. 1998;279(23):1903-1907.

30. Weiss RJ, Saunders E, Greathouse M. Efficacy and tolerability of nebivolol in stage I–II hypertension: A pooled analysis of data from three randomized, placebo-controlled monotherapy trials. *Clin Ther*. 2011;33(9):1150-1161.

31. Zia A, Kamaruzzaman SB, Myint PK, Tan MP. The association of antihypertensives with postural blood pressure and falls among seniors residing in the community: A case–control study. *Eur J Clin Invest*. 2015;45(10):1069-1076.

32. Elliott WJ, Ram CVS. Calcium channel blockers. *The Journal of Clinical Hypertension*. 2011;13(9):687-689.

33. Ghosh M, Majumdar SR. Antihypertensive medications, bone mineral density, and fractures: A review of old cardiac drugs that provides new insights into osteoporosis. *Endocrine*. 2014;46(3):397-405.

34. Thomas GN, Chan P, Tomlinson B. The role of angiotensin II type 1 receptor antagonists in elderly patients with hypertension. *Drugs Aging*. 2006;23(2):131-155.

35. Burnier M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. *Am J Hypertens*. 2006;19(11):1190-1196. doi: S0895-7061(06)00277-9 [pii].

36. Frishman WH. Importance of medication adherence in cardiovascular disease and the value of once-daily treatment regimens. *Cardiol Rev*. 2007;15(5):257-263. doi: 10.1097/CRD.0b013e3180cabbe7 [doi].

37. MacLaughlin EJ, Raehl CL, Treadway AK, Sterling TL, Zoller DP, Bond CA. Assessing medication adherence in the elderly. *Drugs Aging*. 2005;22(3):231-255.

38. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487-497.

39. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15(8):565-574.

40. Hansen RA, Kim MM, Song L, Tu W, Wu J, Murray MD. Comparison of methods to assess medication adherence and classify nonadherence. *Ann Pharmacother*. 2009;43(3):413-422. doi: 10.1345/aph.1L496 [doi].

41. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: Its importance in cardiovascular outcomes. *Circulation*. 2009;119(23):3028-3035. doi: 10.1161/CIRCULATIONAHA.108.768986; 10.1161/CIRCULATIONAHA.108.768986.

42. Franklin JM, Krumme AA, Tong AY, et al. Association between trajectories of statin adherence and subsequent cardiovascular events. *Pharmacoepidemiol Drug Saf*. 2015.

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. Leibson CL, Tosteson AN, Gabriel SE, Ransom JE, Melton LJ. Mortality, disability, and nursing home use for persons with and without hip fracture: A population-based study. *J Am Geriatr Soc*. 2002;50(10):1644-1650.

45. Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. *N Engl J Med*. 1997;337(18):1279-1284. doi: 10.1056/NEJM199710303371806.

46. Haentjens P, Magaziner J, Colón-Emeric CS, et al. Meta-analysis: Excess mortality after hip fracture among older women and men. *Ann Intern Med*. 2010;152(6):380-390.

47. Marks R, Allegrante JP, MacKenzie CR, Lane JM. Hip fractures among the elderly: Causes, consequences and control. *Ageing research reviews*. 2003;2(1):57-93.

48. Desai MM, Zhang P, Hennessy CH. Surveillance for morbidity and mortality among older adults—United states, 1995–1996. *MMWR CDC Surveill Summ*. 1999;48(8):7-25.

49. Stevens J, Rudd R. The impact of decreasing US hip fracture rates on future hip fracture estimates. *Osteoporosis Int*. 2013;24(10):2725-2728.

50. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. *Injury prevention*. 2006;12(5):290-295.

51. Bergen G. Falls and fall injuries among adults aged≥ 65 years—United states, 2014. *MMWR.Morbidity and Mortality Weekly Report*. 2016;65.

52. Cumming RG. Epidemiology of medication-related falls and fractures in the elderly. *Drugs Aging*. 1998;12(1):43-53.

53. Woolf AD, Åkesson K. Preventing fractures in elderly people. *Br Med J*. 2003;327(7406):89-95.

54. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. *Osteoporosis Int*. 2005;16(2):S3-S7.

55. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *The Lancet*. 2002;359(9319):1761-1767.

56. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, Berger M. Patients with prior fractures have an increased risk of future fractures: A summary of the literature and statistical synthesis. *Journal of bone and mineral research*. 2000;15(4):721-739.

57. Ross PD. Osteoporosis: Frequency, consequences, and risk factors. *Arch Intern Med*. 1996;156(13):1399-1411.

58. Bloch F, Thibaud M, Dugue B, Breque C, Rigaud AS, Kemoun G. Psychotropic drugs and falls in the elderly people: Updated literature review and meta-analysis. *J Aging Health*. 2011;23(2):329-346. doi: 10.1177/0898264310381277; 10.1177/0898264310381277.

59. Cumming RG. Epidemiology of medication-related falls and fractures in the elderly. *Drugs Aging*. 1998;12(1):43-53.

60. Hilmer S, Gnjidic D. The effects of polypharmacy in older adults. *Clinical Pharmacology & Therapeutics*. 2009;85(1):86-88.

61. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA internal medicine*. 2014;174(4):588-595.

62. Choi HJ, Park C, Lee Y, Ha Y, Jang S, Shin CS. Risk of fractures in subjects with antihypertensive medications: A nationwide claim study. *Int J Cardiol*. 2015;184:62-67.

63. Marcum ZA, Perera S, Newman AB, et al. Antihypertensive use and recurrent falls in community-dwelling older adults: Findings from the health ABC study. *J Gerontol A Biol Sci Med Sci*. 2015;70(12):1562-1568. doi: 10.1093/gerona/glv095 [doi].

64. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of falls on initiation of antihypertensive drugs in the elderly. *Osteoporos Int*. 2013;24(10):2649-2657. doi: 10.1007/s00198-013-2369-7; 10.1007/s00198-013-2369-7.

65. Lipsitz LA, Habtemariam D, Gagnon M, et al. Reexamining the effect of antihypertensive medications on falls in old age. *Hypertension*. 2015;66(1):183-189. doi: 10.1161/HYPERTENSIONAHA.115.05513 [doi].

66. Fraser LA, Adachi JD, Leslie WD, et al. Effect of anticholinergic medications on falls, fracture risk, and bone mineral density over a 10-year period. *Ann Pharmacother*. 2014;48(8):954-961. doi: 1060028014535363 [pii].

67. Zang G. Antihypertensive drugs and the risk of fall injuries: A systematic review and meta-analysis. *J Int Med Res*. 2013;41(5):1408-1417. doi: 10.1177/0300060513497562 [doi].

68. Ruths S, Bakken MS, Ranhoff AH, Hunskaar S, Engesæter LB, Engeland A. Risk of hip fracture among older people using antihypertensive drugs: A nationwide cohort study. *BMC geriatrics*. 2015;15(1):1.

69. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: Diagnosis and treatment. *Am J Med*. 2007;120(10):841-847.

70. Go AS, Bauman MA, King SMC, et al. An effective approach to high blood pressure control: A science advisory from the american heart association, the american college of cardiology, and the centers for disease control and prevention. *J Am Coll Cardiol*. 2014;63(12):1230-1238.

71. Kim S, Shin DW, Yun JM, et al. Medication adherence and the risk of cardiovascular mortality and hospitalization among patients with newly prescribed antihypertensive medications. *Hypertension*. 2016;67(3):506-512. doi: 10.1161/HYPERTENSIONAHA.115.06731 [doi].

72. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: A meta-analysis of prevalence and clinical consequences. *Eur Heart J*. 2013;34(38):2940-2948. doi: 10.1093/eurheartj/eht295 [doi].

73. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annual Review of Clinical Psychology*. 2010;6:109-138.

74. Hansen RA, Kim MM, Song L, Tu W, Wu J, Murray MD. Comparison of methods to assess medication adherence and classify nonadherence. *Ann Pharmacother*. 2009;43(3):413-422. doi: 10.1345/aph.1L496 [doi].

75. Chapman RH, Petrilla AA, Benner JS, Schwartz JS, Tang SS. Predictors of adherence to concomitant antihypertensive and lipid-lowering medications in older adults. *Drugs Aging*. 2008;25(10):885-892.

76. Centers for Medicare and Medicaid Services. Costs in the coverage gap. Medicare.gov Web site. https://www.medicare.gov/part-d/costs/coverage-gap/part-d-coverage-gap.html. Updated 2016. Accessed June 24, 2016.

77. Faurot KR, Jonsson Funk M, Pate V, et al. Using claims data to predict dependency in activities of daily living as a proxy for frailty. *Pharmacoepidemiol Drug Saf*. 2015;24(1):59-66.

78. Muthén B, Shedden K. Finite mixture modeling with mixture outcomes using the EM algorithm. *Biometrics*. 1999;55(2):463-469. doi: 10.1111/j.0006-341X.1999.00463.x.

79. Jones BL, Nagin DS, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. *Sociological Methods & Research*. 2001;29(3):374-393.

80. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics*. 1988:837-845.

81. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143(1):29-36. doi: 10.1148/radiology.143.1.7063747 [doi].

82. Harrell FE, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA*. 1982;247(18):2543-2546.

83. Bushnell GA, Stürmer T, White A, et al. Predicting persistence to antidepressant treatment in administrative claims data: Considering the influence of refill delays and prior persistence on other medications. *J Affect Disord*. 2016;196:138-147.

84. 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].

85. 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].

86. Brookhart MA, Patrick AR, Schneeweiss S, et al. Physician follow-up and provider continuity are associated with long-term medication adherence: A study of the dynamics of statin use. *Arch Intern Med*. 2007;167(8):847-852.

87. Li X, Camelo Castillo W, Stürmer T, et al. Use of combination antihypertensive therapy initiation in older americans without prevalent cardiovascular disease. *J Am Geriatr Soc*. 2014;62(9):1729-1735.

88. Hampp C, Greene P, Pinheiro SP. Use of prescription drug samples in the USA: A descriptive study with considerations for pharmacoepidemiology. *Drug safety*. 2016;39(3):261-270.

89. U.S. Census Bureau, Population Division. Annual estimates of the resident population by sex, race, and hispanic origin for the united states, states, and counties: April 1, 2010 to july 1, 2015. http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk. Updated June 2016. Accessed 10/25/2016, 2016.

90. DeGrauw X, Annest JL, Stevens JA, Xu L, Coronado V. Unintentional injuries treated in hospital emergency departments among persons aged 65 years and older, united states, 2006–2011. *J Saf Res*. 2016;56:105-109.

91. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. *Inj Prev*. 2006;12(5):290-295. doi: 10.1136/ip.2005.011015.

92. Huang AR, Mallet L, Rochefort CM, Eguale T, Buckeridge DL, Tamblyn R. Medication-related falls in the elderly: Causative factors and preventive strategies. *Drugs Aging*. 2012;29(5):359-376. doi: 10.2165/11599460-000000000-00000; 10.2165/11599460-000000000-00000.

93. Lee RH, Pieper CF, Colón-Emeric C. Functional impairments mediate association between clinical fracture risk and type 2 diabetes mellitus in older women. *J Am Geriatr Soc*. 2015;63(8):1546-1551.

94. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American geriatrics society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63(11):2227-2246. doi: 10.1111/jgs.13702 [doi].

95. Takkouche B, Montes-Martinez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: A meta-analysis. *Drug Saf*. 2007;30(2):171-184.

96. Gangavati A, Hajjar I, Quach L, et al. Hypertension, orthostatic hypotension, and the risk of falls in a Community-Dwelling elderly population: The maintenance of balance, independent living, intellect, and zest in the elderly of boston study. *J Am Geriatr Soc*. 2011;59(3):383-389.

97. Solomon DH, Mogun H, Garneau K, Fischer MA. Risk of fractures in older adults using antihypertensive medications. *Journal of Bone and Mineral Research*. 2011;26(7):1561-1567.

98. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of hip fracture after initiating antihypertensive drugs in the elderly. *Arch Intern Med*. 2012;172(22):1739-1744.

99. Rejnmark L, Vestergaard P, Mosekilde L. Treatment with beta-blockers, ACE inhibitors, and calcium-channel blockers is associated with a reduced fracture risk: A nationwide case-control study. *J Hypertens*. 2006;24(3):581-589. doi: 10.1097/01.hjh.0000203845.26690.cb [doi].

100. Ray WA, Griffin MR, Fought RL, Adams ML. Identification of fractures from computerized medicare files. *J Clin Epidemiol*. 1992;45(7):703-714.

101. Annest JL, Fingerhut LA, Gallagher SS, et al. *Strategies to improve external cause-of-injury coding in state-based hospital discharge and emergency department data systems: Recommendations of the CDC*

workgroup for improvement of external cause-of-injury coding. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention; 2008.

102. Curtis JR, Mudano AS, Solomon DH, Xi J, Melton ME, Saag KG. Identification and validation of vertebral compression fractures using administrative claims data. *Med Care*. 2009;47(1):69-72. doi: 10.1097/MLR.0b013e3181808c05 [doi].

103. Woolf AD, Åkesson K. Preventing fractures in elderly people. *Br Med J*. 2003;327(7406):89-95.

104. Marks R. Hip fracture epidemiological trends, outcomes, and risk factors, 1970-2009. *Int J Gen Med*. 2010;3:1-17.

105. Nurminen J, Puustinen J, Piirtola M, Vahlberg T, Lyles A, Kivela SL. Opioids, antiepileptic and anticholinergic drugs and the risk of fractures in patients 65 years of age and older: A prospective population-based study. *Age Ageing*. 2013;42(3):318-324. doi: 10.1093/ageing/afs178; 10.1093/ageing/afs178.

106. Stürmer T, Rothman KJ, Glynn RJ. Insights into different results from different causal contrasts in the presence of effect-measure modification. *Pharmacoepidemiol Drug Saf*. 2006;15(10):698-709.

107. Li X, Camelo Castillo W, Stürmer T, et al. Use of combination antihypertensive therapy initiation in older americans without prevalent cardiovascular disease. *J Am Geriatr Soc*. 2014;62(9):1729-1735.

108. J. Jones, C. Casteel, Y. Golightly, et al. 62. determinants of antihypertensive adherence trajectories among older US adults in the first year after initiation. *Pharmacoepidemiol Drug Saf*. 2016;25(Supplement S3).

109. Wong AK, Lord SR, Sturnieks DL, Delbaere K, Trollor JN, Close JC. Angiotensin System–Blocking medications are associated with fewer falls over 12 months in Community-Dwelling older people. *J Am Geriatr Soc*. 2013;61(5):776-781.

110. Berry SD, Zhu Y, Choi H, Kiel DP, Zhang Y. Diuretic initiation and the acute risk of hip fracture. *Osteoporosis Int*. 2013;24(2):689-695.

111. Gupta A. Medical management of hip fractures and the role of the orthogeriatrician. *Rev Clin Gerontol*. 2012;22(4):261-273.

112. Aung K, Htay T. Thiazide diuretics and the risk of hip fracture. *The Cochrane Library*. 2011.

113. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*. 2004;59(3):255-263.

114. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med*. 1988;319(26):1701-1707. doi: 10.1056/NEJM198812293192604.

115. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA internal medicine*. 2014;174(4):588-595.

116. Kwok T, Leung J, Barrett-Connor E, Osteoporotic Fractures in Men (MrOS) Research Group. ARB users exhibit a lower fracture incidence than ACE inhibitor users among older hypertensive men. *Age Ageing*. 2016. doi: afw150 [pii].

117. McKenzie K, Enraght-Moony EL, Walker SM, McClure RJ, Harrison JE. Accuracy of external cause-of-injury coding in hospital records. *Inj Prev*. 2009;15(1):60-64. doi: 10.1136/ip.2008.019935 [doi].

118. Tamblyn R, Reid T, Mayo N, McLeod P, Churchill-Smith M. Using medical services claims to assess injuries in the elderly: Sensitivity of diagnostic and procedure codes for injury ascertainment. *J Clin Epidemiol*. 2000;53(2):183-194.

119. Gwadry-Sridhar FH, Manias E, Lal L, et al. Impact of interventions on medication adherence and blood pressure control in patients with essential hypertension: A systematic review by the ISPOR medication adherence and persistence special interest group. *Value in Health*. 2013;16(5):863-871.

120. Takiya LN, Peterson AM, Finley RS. Meta-analysis of interventions for medication adherence to antihypertensives. *Ann Pharmacother*. 2004;38(10):1617-1624.

121. Conn VS, Ruppar TM, Enriquez M, Cooper P. Medication adherence interventions that target subjects with adherence problems: Systematic review and meta-analysis. *Research in Social and Administrative Pharmacy*. 2016;12(2):218-246.

122. Berry SD, Mittleman MA, Zhang Y, et al. New loop diuretic prescriptions may be an acute risk factor for falls in the nursing home. *Pharmacoepidemiol Drug Saf*. 2012;21(5):560-563.

123. Gribbin J, Hubbard R, Gladman J, Smith C, Lewis S. Risk of falls associated with antihypertensive medication: Self-controlled case series. *Pharmacoepidemiol Drug Saf*. 2011;20(8):879-884.

124. Gribbin J, Hubbard R, Gladman JR, Smith C, Lewis S. Risk of falls associated with antihypertensive medication: Population-based case–control study. *Age Ageing*. 2010:afq092.

125. Rejnmark L, Vestergaard P, Mosekilde L. Fracture risk in patients treated with loop diuretics. *J Intern Med*. 2006;259(1):117-124.