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EDUCATION

2007-2016 Ph.D. (Pharmaceutical Health Services Research), University of Maryland, Baltimore, MD
2004-2006 M.B.A. (Pharmaceutical Business), University of the Sciences in Philadelphia, Philadelphia, PA
1999-2004 B.S. (Pharmacy), National Taiwan University, Taipei, Taiwan

POSITIONS

2015-Present Instructor, Department of Social, Behavioral and Administrative Sciences, Touro College of Pharmacy, New York, NY
2011-2015 Graduate Research Assistant, University of Maryland School of Pharmacy
Supervisor: Bruce Stuart, Ph.D.
2008-2011 Graduate Research Assistant, University of Maryland School of Pharmacy
Supervisor: Ebere Onukwugha, M.S., Ph.D.
Summer 2008 Intern, Department of Health Economics and Outcomes Research, Bristol-Myers Squibb
Supervisor: Edward Kim, M.D., M.B.A.
2007-2008 Graduate Teaching Assistant, University of Maryland School of Pharmacy
2005-2007 Research Fellow, Center for Pharmaceutical Health Services Research, Temple University
Supervisor: Albert Wertheimer, Ph.D., M.B.A.
2005 Graduate Research Assistant, University of the Sciences in Philadelphia
Supervisor: Harold Glass, Ph.D.

PEER REVIEWED JOURNAL PUBLICATION

1. Stuart B., Shen X., Quinn C., Brandt N., Roberto P., **Loh F.E.**, Hendrick F., Kim C., Huang X., Rajpathak S. "Proximal Predictors of Discontinuance with Oral Antidiabetic Agents among the Elderly." *Journal of Managed Care Pharmacy.* 2016;22(9):1019-27.

2. Tan E., Yang W., Pang B., Dai M., **Loh F.E.**, Hogan P. "Geographic Variation in Antidiabetic Agent Adherence and Glycemic Control among Patients with Type 2 Diabetes" *Journal of Managed Care Pharmacy.* 2015;21(12):1195-1202.

3. Stuart B., Dai M., Xu J., **Loh F.E.,** Shoemaker J.S. "Does Good Medication Adherence Really Save Payers Money?" *Medical Care.* 2015;53(6):517-23.

4. **Loh F.E.**, Stuart B., Zuckerman I.H. "Treatment Patterns for Osteoporosis in Elderly Women Residing in the Community and Long-Term Care Facilities Enrolled in Medicare." *Journal of Pharmaceutical Health Services Research.* 2015;6(1):19-26.

5. Stuart B., **Loh F.E.,** Roberto P.N., Miller L. "Incident User Cohorts to Assessing Medication Cost-Offsets." *Health Services Research.* 2014;49(4):1364-86.

6. Stuart B., **Loh F.E.,** Magder L., Shaffer T., Park J., Zacker C. "Anticipating Changes in Drug Coverage: How Elderly Heart Failure Patients Respond to Medicare Part D Benefit Phases." *Journal of Pharmaceutical Care and Health Systems.* 2014;1(1):104.

7. Stuart B., **Loh F.E.,** Miller L., Roberto P.N. "Should Eligibility for Medication Therapy Management Be Based on Drug Adherence?" *Journal of Managed Care Pharmacy.* 2014;20(1):66-75.

8. Stuart B., **Loh F.E.,** Roberto P.N., Miller L. "Increasing Medicare Part D Enrollment in Medication Therapy Management Could Improve Health and Lower Costs." *Health Affairs.* 2013;32(7):1212-20.

9. Onukwugha E., Saunders E., Mullins C.D. Pradel F.G., Zuckerman M., **Loh F.E.**, Weir M.R. "A Qualitative Study to Identify Reasons for Discharges against Medical Advice in the Cardiovascular Setting." *BMJ Open.* 2012;2(4):e000902.

10. Stuart B., **Loh F.E.** "Medicare Part D Enrollees' Use of Out-of-Plan Discounted Generic Drugs." *Journal of the American Geriatrics Society.* 2012;60(2):387-8.

11. Onukwugha E., Mullins C.D., **Loh F.E.**, Saunders E., Shaya F.T., Weir M.R. "Readmissions after Unauthorized Discharges in the Cardiovascular Setting." *Medical Care.* 2011;49(2):215-24.

12. Wertheimer A.I., **Loh E.F.** "Making Pharmaceuticals Affordable in Lesser Developed Countries: A Public Health Role for the Pharmacist." *Journal of Public Health Pharmacy.* 2008;1(1):3-15.

PEER-REVIEWED ABTRACT/PODIUM PRESENTATION

1. Stuart B., Brandt N., Quinn C., Shen X., Roberto P., **Loh F.E.**, Rajpathak S., Huang X. "Discontinuation of Oral Antidiabetic Drugs among Medicare Beneficiaries with Diabetes: Different Factors Predict Short Verses Long Periods Without Drug Therapy." *The American Public Health Association Annual Meeting*, Chicago, IL, Nov. 2015.

2. Feldman S., Truong H.A., **Loh F.E.** "Medication Therapy Management (MTM) in Pharmacy Practice." *The American Public Health Association Annual Meeting*, Chicago, IL, Nov. 2015.

PEER-REVIEWED ABSTRACT/POSTER PRESENTATION

1. Dym S., Kploanyi S., Barron S., Zino V., Jones S., Milan C., Jani R., Mahmood M., Bui M., Nguyen C., Askari B., **Loh F.E.** "Patient Knowledge of Over-The-Counter Pain Medication and Their Perception of Pharmacists: A Survey of the Harlem

Community." *The American Public Health Association Annual Meeting*, Denver, CO, Nov. 2016.

2. Chou J., **Loh F.E.**, Brandt N., Stuart B. "Differences among Antipsychotic Users Enrolled in Stand-Alone Prescription Drug Plans and Medicare Advantage Plans in 2008." *The American Society of Consultant Pharmacists Annual Meeting and Exhibition,* Las Vegas, NV, Oct. 2015.

3. Stuart B., Brandt N., Quinn C., Shen X., Roberto P., **Loh F.E.**, Rajpathak S., Huang X. "Proximal Predictors of Discontinuance with Oral Antidiabetic Agents among the Elderly." *The American Diabetes Association 75th Scientific Sessions*, Boston, MA, Jun. 2015.

4. Chou J., **Loh F.E.**, Brandt N., Stuart B. "Differences among Antipsychotic Users Enrolled in Stand-Alone Prescription Drug Plans and Medicare Advantage Plans in 2008." *The American Geriatric Society Annual Scientific Meeting,* National Harbor, MD, May 2015.

5. **Loh F.E.** "Use and Patterns of Osteoporosis Pharmacotherapy in Medicare Beneficiaries with Osteoporosis." *The Gerontological Society of America 67th Annual Scientific Meeting,* Washington, DC, Nov. 2014.

6. **Loh F.E.** "Use of Evidence-Based Medications in Treating Medicare Beneficiaries with Osteoporosis." *DIA 50th Annual Meeting,* San Diego, California, Jun. 2014.

7. **Loh F.E.** "Use and Patterns of Osteoporosis Pharmacotherapy on Community-Dwelling and Long-Term Care Facility-Residing Medicare Beneficiaries with Osteoporosis." *AcademyHealth 31th Annual Research Meeting,* San Diego, California, Jun. 2014.

8. Stuart B., Dai M., Xu J., **Loh F.E.**, Dougherty J.S. "Does Good Medication Adherence Really Save Payers Money?" *AcademyHealth 31th Annual Research Meeting,* San Diego, California, Jun. 2014.

9. Stuart B., **Loh F.E.**, Roberto P., Miller L. "Incident User Cohorts to Assessing Medication Cost-Offsets." *AcademyHealth 30th Annual Research Meeting,* Baltimore, Maryland, Jun. 2013.

10. Stuart B., **Loh F.E.**, Roberto P., Miller L. "Medication Adherence, Medicare Costs, and Targeting Medication Therapy Management Services." *AcademyHealth 30th Annual Research Meeting,* Baltimore, Maryland, Jun. 2013.

11. Stuart B., **Loh F.E.**, Miller L., Roberto P. "Longitudinal Patterns in Drug Utilization among Medicare Part D Enrollees with Chronic Disease: Lessons for Medication Therapy Management Programs." *AcademyHealth 29th Annual Research Meeting,* Orlando, Florida, Jun. 2012.

12. **Loh F.E.**, Stuart B. "Patterns of Treatment Utilization for Osteoporosis in Elderly Women Residing in the Community and in Long-Term Care Facilities." *ISPOR 16th Annual International Meeting,* Baltimore, MD, May 2011.

13. Onukwugha E., Saunders E., Mullins C.D. Pradel F.G., Zuckerman M., **Loh F.E.**, Weir M.R. "Reasons for Discharges Against Medical Advice in the Cardiovascular Setting: A Qualitative Analysis." *Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke,* Washington, D.C., May 2010.

14. Onukwugha E., Mullins C.D., **Loh F.E.**, Saunders E., Shaya F.T., Weir M.R. "Readmissions after Unauthorized Discharges in the Cardiovascular Setting." *ISPOR 15th Annual International Meeting,* Atlanta, GA, May 2010.

15. Onukwugha E., **Loh F.E.**, Weir M.R., Shaya F.T., Mullins C.D. "Costs Associated with Discharges against Medical Advice in a Cardiovascular Population." *ISPOR 15th Annual International Meeting*, Atlanta, GA, May 2010.

NON-PEER REVIEWED PUBLICATIONS

Book

1. Stuart B., **Loh F.E.,** Xu J., Roberto P.N., Shoemaker J.S. "Medication Utilization Patterns and Outcomes among Part D Enrollees with Common Chronic Diseases." PhRMA, Washington, DC, 2014. *http://www.pharmacy.umaryland.edu/media/SOP/wwwpharmacyumarylandedu/centers/lamy/pdf/Part_D_Chartbook_Final_2014.pdf*

Book Chapters

1. **Loh F.E.** "End-of-Lifecycle Management." In *Modern Pharmaceutical Industry.* 2nd Ed. Thomas M. Jacobsen and Albert I. Wertheimer. Kendall Hunt Publishing Company, Dubuque, IA. In press.

2. **Loh F.E.** "The Financial and Economic Aspects of Counterfeit Medicines." In *Counterfeit Medicines Volume 1: Policy, Economics and Countermeasures.* 1st Ed. Albert I. Wertheimer and Perry G. Wang. ILM Publications, Hertfordshire, UK, 2012.

Book Review

1. **Loh F.** Book Review of "Drugs for Less: The Complete Guide to Free and Discounted Prescription Drugs, Featuring More Than 600 of The Most Commonly Prescribed Medications", by Michael P. Cecil, MD. New York: Hatherleigh Press, 2005. *Journal of Pharmaceutical Finance, Economics and Policy.* 2007;15(2):121-23.

Letter to Editor

1. Stuart B., **Loh F.E.** "Response Letter to Jonathan Harding." *Journal of the American Geriatrics Society.* 2013;61(2):310.

Journal Articles

1. Wertheimer A.I., **Loh E.F.** "Getting Value from End-of-Life-Cycle Pharmaceuticals." *Pharmaceutical Commerce.* 2009;4(9).

2. Wertheimer A.I., **Loh E.F.,** Poli L.G. "Lifecycle: End Game." *Pharmaceutical Executive.* 2007;27(10).

3. Wertheimer A.I., **Loh F**. "Getting Better?" *Pharmaceutical Executive.* 2006;26(8):72-84.

Work in Progress

1. Stuart B., Brandt N., Quinn C., Shen X., Roberto P., **Loh F.E.**, Rajpathak S., Huang X. "Discontinuation of Oral Antidiabetic Drugs among Medicare Beneficiaries with Diabetes: Different Factors Predict Short Verses Long Periods Without Drug Therapy." Diabetes Research and Clinical Practice. Under Review.

2. Chou J., **Loh F.E.**, Brandt N., Stuart B. "Differences among Antipsychotic Users Enrolled in Stand-Alone Prescription Drug Plans and Medicare Advantage Plans in 2008." The Consultant Pharmacist. Under review.

3. **Loh F.E.,** Stuart B., Davidoff A., Sturpe D., Onukwugha E., Hochberg M. "Patterns of Evidence-Based Osteoporosis Medication Use: A Comparison of Elderly Female Long-Term Care Facility Residents to Community Dwellers Enrolled in Medicare Part D."

4. **Loh F.E.,** Stuart B., Davidoff A., Sturpe D., Onukwugha E., Hochberg M. "Differences in Evidence-Based Osteoporosis Medication Use between Elderly Men and Women Enrolled in Medicare Part D."

5. **Loh F.E.,** Stuart B., Davidoff A., Sturpe D., Onukwugha E., Hochberg M. "Effectiveness of Evidence-Based Osteoporosis Medications among Elderly Enrolled in Medicare Part D: Do Sex and Medication Adherence Cause a Difference?"

HONOR AND AWARDS

2014	Student Poster Fellowship, Drug Information Association (DIA) 50th Annual Meeting
2014	Travel Fellowship, Graduate Student Association, University of Maryland, Baltimore
2014	Travel Award, Department of Pharmaceutical Health Services Research, University of Maryland, Baltimore
2009-present	The Rho Chi Society

TRACHING EXPERIENCE

2016-present	Coordinator, Touro College of Pharmacy PHRM 530 Principles of Management, Pharmacoeconomics and Outcomes Research PHRM 510 Epidemiology and Biostatistics
2015-present	Lecturer, Touro College of Pharmacy Topics: Pharmacoepidemiology and Biostatistics in PHRM 570 *Drug Information, Pharmacoepidemiology and Biostatistics*
2014	Guest Lecturer, Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy Topic: The Affordable Care Act: What policies really matter and why, and how drugs are being covered (in PHSR 610 *Pharmacy, Drugs, and the Health Care System*)
2013	Guest Lecturer, Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy Topic: Policies Designed to Obtain Maximum Value from Pharmaceutical Products; Policy Issues in the Medicare Part D Program (in PHSR 610 *Pharmacy, Drugs, and the Health Care System*)
2009	Seminar Presenter, Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy Topics: Readmissions after Unauthorized Discharges in the Cardiovascular Setting; Treatment Patterns for Osteoporosis in Elderly Women Residing in the Community and in Long-Term Care Facilities.
2007-2008	Graduate Teaching Assistant, University of Maryland School of Pharmacy
1999-2004	Private Tutor, Taiwan

PROFESSIONAL MEMBERSHIP

2016	Academy of Managed Care Pharmacy
2015-present	The American Public Health Association
2014-2015	The American Geriatrics Society
2014-2015	The Gerontological Society of America
2011-present	AcademyHealth
2005-present	International Society of Pharmacoeconomics and Outcomes Research (ISPOR)

ADMINISTRATIVE SERVICES

Institutional Service

2015-present	Member, Research Council, Touro College of Pharmacy
2015-present	Member, Assessment Committee, Touro College of Pharmacy
2012-2013	Vice President, University of Maryland AcademyHealth Student Chapter
2009-2011	Treasurer, University of Maryland ISPOR Student Chapter
2005-2006	Treasurer, University of the Sciences in Philadelphia ISPOR Student Chapter

Departmental Service

2015-present Member, Research Committee, Department of Social, Behavioral and Administrative Sciences, Touro College of Pharmacy

2012-2013 Member, Seminar Committee, Department of Pharmaceutical Health Services Research, University of Maryland, Baltimore

Referee Activities

2015-present Health Affairs

2015-present American Journal of Managed Care

2014-present Medical Care

2013-present Journal of Managed Care Pharmacy

2013-present American Journal of Pharmacy Benefit

2010-present Journal of Pharmaceutical Health Services Research

CLINICAL EXPERIENCE

2004 Pharmacy Intern, Department of Pharmacy Administration, National Taiwan University Hospital
Principal responsibilities: Developed a patient satisfaction survey with team members, surveyed patients, analyzed results, and provided recommendations for improvement in quality of care based on the survey results.

2004 Pharmacy Intern, Department of Outpatient Pharmacy, National Taiwan University Hospital
Principal responsibilities: Educated patients on appropriate use, potential adverse effects, and drug-drug/food interactions of prescription medications.

2004 Pharmacy Intern, Department of Inpatient Pharmacy, National Taiwan University Hospital
Principal responsibilities: Monitored safety of patients on anticoagulant therapy, and reported medication adverse events to the Taiwanese FDA.

Abstract

Title of Dissertation: Osteoporosis Medication Use, Adherence, and Outcomes in Elderly Enrolled in Medicare Part D

Feng-Hua Loh, Doctor of Philosophy, 2016

Dissertation Directed by: Dr. Bruce C. Stuart, Professor and Director, The Peter Lamy Center on Drug Therapy and Aging, Department of Pharmaceutical Health Services Research, School of Pharmacy

Background

Osteoporosis affects an enormous number of people of both sexes, and osteoporosis-related fractures are costly to treat. Yet osteoporosis is poorly managed and managed differently by sex and residential setting. Therefore, this study aimed to assess the difference in medication use, adherence, and outcomes between men and women and among women, between long-term care (LTC) facility and community residents.

Methods

Using the 2006-2008 Chronic Condition Data Warehouse 5% national random sample of Medicare beneficiaries, this retrospective study identified elderly 70 years and older with osteoporosis enrolled in Medicare Part A, B, and D stand-alone prescription drug plans from January 1, 2006 through December 31, 2008, or death. Use of bisphosphonates, calcitonin, parathyroid hormone and selective estrogen receptor modulator was tracked over the 3-year period. Treatment effectiveness was measured as hazard of fracture after treatment initiation. Modified Poisson regression was used for analyzing the effect of sex and residential status on osteoporosis medication use. Cox proportional hazard model was used for analyzing the effect of medication use and adherence on fracture risk.

Results

The samples included 96,408 females, 8,465 males and 90,956 females, and 2,083 males and 10,262 females enrolled in Medicare Part D for aims 1, 2, 3, respectively. Utilization was lower among LTC residents (RR 0.89, 95% CI [0.87, 0.91]). Bisphosphonates were prescribed less often to LTC residents (RR 0.79, 95% CI [0.75, 0.83]) compared to among community residents. Prevalence of osteoporosis medication use in men was substantially lower than that in women (25.2% vs. 44.3% in 2006). Good adherence decreased the hazard of fracture in both sexes (HR 0.86, 95% CI [0.75, 0.99]). No difference in either treatment or adherence effect on fracture between men and women existed.

Conclusion

Prevalence of osteoporosis medication use is low in elderly women enrolled in Part D whether community dwelling or LTC residents. Elderly men are undertreated for osteoporosis compared to elderly women. There is strong confounding by indication in the effect of osteoporosis medications on the risk of fracture; however, good adherence reduces the risk of fracture. There is no evidence for heterogeneity in treatment response among men and women.

Osteoporosis Medication Use, Adherence and Outcomes in Elderly Enrolled in Medicare Part D

by
Feng-Hua Loh

Dissertation submitted to the faculty of the Graduate School
of the University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
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Acknowledgement

First of all, I would like to sincerely thank my advisor, Dr. Bruce Stuart. Thank you, Dr. Stuart, for being such a great advisor and role model. You always provide great advice and clear guidance to me. You have shown enormous patience to me. You set such a great example that nowadays when I face any issues with my students, I always ask myself, "What would Dr. Stuart do?"

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I would also like to express my appreciation to the faculty, staff and students at PHSR. You have made PHSR a rich environment to learn, an enjoyable place to work, and feel like home to me. Especially thank you, Colleen, for taking such a good care of us. You are a wonderful academic mom. I am also grateful to my colleagues, Candice, Abdulla, Ming, Sammy, and Mark for being a great support.

Besides, I would like to thank my dear friends Hsiuwen, Chun and Jui-Hua, for your precious friendship. Thank you for listening to me whining and always cheering me up. That means a lot to me.

Finally, thank you, grandpa and grandma, for providing me a stable environment and always supported me. You taught me the importance of knowledge and always encouraged me to pursue more. Therefore, I dedicate this dissertation to both of you.

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1 Introduction

1.1 Study Motivation

Osteoporosis is the most common bone disease in humans, and it represents a major public health problem.[1] Osteoporosis affects an enormous number of people of both genders and all races, and its prevalence will increase as the population ages. About half of Caucasian women will experience an osteoporosis-related fracture at some point in their lifetimes, as will approximately one-fifth of men.[1] Among nursing home residents, the prevalence of osteoporosis is up to 90%.[2-4]

There were over 2 million fractures in the US costing $17 billion to treat in 2005.[5] Of those who sustain a hip fracture, up to 75% require nursing home placement for rehabilitation or long-term care.[6] Many of the remainder receive home health care, resulting in over 2 million home health care visits for post-hospitalization fracture care annually.[1]

Although osteoporosis has such a huge impact on our lives, it has been poorly managed. Also, the poor management differs by gender and residential setting. To better manage osteoporosis with scarce health care resources, we need to develop tailored treatment strategies for patients with different gender in different settings. For this purpose, we need knowledge about the current state of osteoporosis management in men and women residing in LTC facilities and in the community. However, there is very little knowledge about the management of osteoporosis in men and in LTC facilities residents and no information about the differences in osteoporosis management in men vs. women, and residents in LTC facilities vs. in the community. Therefore, this study investigated

use of evidence-based osteoporosis medication and the effectiveness of osteoporosis medications on risk of future fractures among men and women, and among community-dwelling and LTC facility-residing elderly women. This study results are reported in chapter 5, 6 and 7. Following are the specific aims of this study:

1.2 Research Questions and Aims

Research question 1: What is the difference in use of pharmacologic treatment for osteoporosis after a diagnosis of osteoporosis or a hip fracture between community- and facility-residing elderly women?

Specific aim 1. To compare exposure to pharmacologic treatment for osteoporosis among elderly osteoporotic women residing in the community and in LTC facilities. I hypothesized that LTC facility residents would have higher exposure to pharmacologic treatment for osteoporosis than community dwellers. Clinical guidelines recommend utilization of pharmacologic treatment for osteoporosis for patients having known osteoporosis and for those having experienced fragility fractures to prevent future fractures. However, previous studies using different data sets have shown that use of pharmacologic treatment for osteoporosis is low, especially among LTC facility residents.[7-14] If findings of this study show low use of pharmacologic treatment for osteoporosis in current practice in either setting, tailored policies should be developed to promote higher utilization of pharmacologic treatments.

Research question 2: What is the difference in use of pharmacologic treatment between elderly male and female osteoporotic patients?

Specific aim 2. To compare use of pharmacologic treatment for osteoporosis among elderly female vs. male osteoporotic patients. I hypothesized that due to the level of awareness about osteoporosis, women would have higher use of pharmacologic treatment for osteoporosis than men. Previous literature has been focused on use of osteoporosis medications in women, and there is very little knowledge about use of osteoporosis medications in men. If this study finds use of osteoporosis medications in women is higher than use in men, tailored strategies should be developed to promote higher use of osteoporosis medication in men.

Research question 3: What is the impact of initiation of and adherence to pharmacologic treatment for osteoporosis on risk of subsequent fracture among elderly male vs. female osteoporotic patients?

Specific aim 3. To compare the risk of subsequent fracture between treated vs. untreated, and among those treated, to compare the risk of subsequent fracture between adherent vs. non-adherent elderly osteoporotic patients, stratified by gender. I hypothesized that initiation of and better adherence to pharmacologic treatment for osteoporosis would reduce risk of subsequent fracture regardless of gender. The ultimate goal of treatment for osteoporosis is to reduce risk of future fracture. Clinical research has shown that higher initiation rates of and better adherence to pharmacologic treatment for osteoporosis will reduce the risk of subsequent fracture. If this study finds that higher initiation rates of and better adherence to treatment are associated with lower risk of subsequent fractures, policies should be developed to incentivize higher initiation of and better adherence to treatment.

2 Background and Literature Review

2.1 Definition of Osteoporosis

According to the National Institutes of Health's consensus conference, osteoporosis is defined as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk for fracture."[2] Osteoporosis can be diagnosed either by the occurrence of fragility fracture or by low bone mineral density (BMD), which is especially applicable for patients without fragility fracture. The current gold standard test for diagnosing osteoporosis in people without an osteoporotic fracture is dual x-ray absorptiometry (DXA). Results of DXA are reported as T-scores, which are standard deviations (SDs) from a young healthy norm (usually female).[15] According to the international reference standard established by the World Health Organization (WHO) for description of osteoporosis in postmenopausal women and in men aged 50 years or older, osteoporosis is defined as a femoral neck bone mineral density of 2.5 SD or more below the young female adult mean, whereas osteopenia is defined as a femoral neck bone mineral density between 1.0 SD and 2.5 SD below the young female adult mean.[15]

2.2 Burden of Osteoporosis

Osteoporosis and low bone mass are major public health threats for an estimated 44 million Americans or 55% of the population aged 50 years and older.[16] These conditions are projected to impact approximately 61 million adults over the age of 50 by 2020.[16] Osteoporosis is of clinical and public health importance because it has been associated with millions of fractures annually. Osteoporosis-related fractures create a heavy economic burden, causing more than 432,000 hospital admissions, almost 2.5 million

medical office visits, and about 180,000 nursing home admissions annually in the US.[1] In 2005, there were over 2 million fractures costing $17 billion to treat.[5] The majority of costs were incurred by inpatient hospital care (57%), followed by LTC (30%) and outpatient care (13%).[5] By 2025, annual fractures and costs are projected to increase to 3 million and $25 billion, respectively.[5]

Among all types of fractures, hip fractures are the most serious consequences of osteoporosis and are strongly related to low BMD. About 24% of patients over 50 years of age die within a year of a hip fracture and approximately 20% of hip fracture patients require LTC.[1]

Long-term care facility residents are more likely to have osteoporosis than their counterparts in the community. Eighty-five percent of all nursing home residents are reported to have osteoporosis.[2] Moreover, the rate of fractures in nursing home residents is 2.5-10 times higher than their age-matched counterparts in the community.[17, 18]

2.3 Pharmacologic Treatment for Osteoporosis

Current available pharmacologic treatments for osteoporosis approved by the U.S. Food and Drug Administration (FDA) include bisphosphonates, calcitonin, teriparatide and selective estrogen receptor moderator (SERM). Teriparatide is an anabolic agent that stimulates new bone formation by activating osteoblasts.[19] Except for teriparatide, all of the treatments work as antiresorptive agents, which inhibit osteoclastic activity. Bisphosphonates are the first-line treatment in confirmed osteoporosis cases.[20] Bisphosphonates approved for osteoporosis treatment include alendronate, ibandronate, risedronate and zoledronic acid. However, they are not all the same in term of efficacy. Evidence shows that alendronate, ibandronate and risedronate decrease risk of vertebral

fractures.[20] Alendronate, risedronate and zoledronic acid have also been proven to be effective in reducing hip fracture and other nonvertebral fractures.[21, 22] Evidence indicates that calcitonin decreases risk of vertebral fractures,[23, 24] but is ineffective in reducing nonvertebral fractures.[25, 26] Teriparatide has been proven to be effective in reducing vertebral fractures,[27] but the evidence for teriparatide's effect on nonvertebral fractures is mixed.[27-29] Raloxifene has been proven effective for preventing vertebral fractures but not for hip fractures.[30, 31]

2.4 Predictors of Use of Pharmacologic Treatment for Osteoporosis

Clinical guidelines recommend that men and women who have known osteoporosis and those who have experienced fragility fractures should initiate pharmacologic treatment for osteoporosis.[20] However, many studies have found that osteoporosis is undertreated in this population.[7, 8, 32-34]

2.4.1 In Long-term Care Facilities

Osteoporosis is especially undertreated among LTC facility residents.[7-14] In the current literature, only eight studies of treatment use in the LTC facilities were found. [7-14] Among the eight studies, three reported rate of treatment initiation;[7, 36, 37] the others reported prevalence of treatment.[7, 13, 14] The three incidence studies assessed rate of treatment initiation for osteoporosis within a fixed period of time (i.e. 6 months[7] or 12 months [36, 37]) after diagnosis of osteoporosis or fractures among LTC facility residents.

Parikh and colleagues conducted a cohort study to examine the association of nursing home-level characteristics with osteoporosis treatment in elderly patients admitted to a nursing home after a fracture using claims data from the New Jersey Medicaid and Pharmaceutical Assistance for the Aged and Disabled (PAAD) programs.[14]

The study recruited 2,838 post-fracture patients admitted to 180 nursing homes in New Jersey. Among the post-fracture patients, only 5.5% were prescribed any osteoporosis medication during the 12 months post fracture. Patient characteristics associated with osteoporosis treatment included female gender (odds ratio (OR)=2.56, 95% confidence interval (CI)=[1.42, 4.61]), younger age (OR=0.98, 95%CI=[0.96, 0.99]), white race (OR=2.37, 95%CI=[1.23, 4.56]) and prior history of fracture (OR=4.41, 95%CI=[1.04, 18.73]).

Using Medicare data linked with pharmaceutical claims data from New Jersey Medicaid and PAAD, Parikh et al. studied the patterns and predictors of osteoporosis medication use in elderly patients who sustained a fracture and were admitted to a nursing home.[13] Of the 4,430 eligible post-fracture patients, only 11.5% were prescribed an osteoporosis medication. The rate of treatment initiation 12 months post fracture among these patients increased from 1.6% in 1995 to 18.7% in 2001 and remained constant through 2004. Calcitonin was the most commonly prescribed medication (56.1%), followed by bisphosphonates (35.1%), estrogen-containing hormone therapy (5.3%), and raloxifene (3.7%). Patient characteristics associated with osteoporosis medication use included a history of osteoporosis medication use in the prior 12 months (hazard ratio (HR) = 19.5, 95% confidence interval (CI) = [16.0, 23.7]) and female sex (HR=1.57, 95% CI = [1.13, 2.21]).

In 67 nursing facilities in North Carolina and Arizona with more than 10 residents with osteoporosis or recent hip fracture, Colón-Emeric and colleagues found that overall, 35.7% of residents aged 50 years or older with either a history of hip fracture or a diagnosis of osteoporosis received any bone protection (medication or hip protectors),

with wide variation among facilities (0-85%).[28] Within the 6 months after the first fracture or osteoporosis diagnosis was recorded in the MDS, calcium was prescribed for 69.2% of residents, vitamin D for 62.8%, bisphosphonates for 19.1%, calcitonin for 14.4%, raloxifene for 3.2%, hormone replacement therapy for 3.1%, and teriparatide for 0.1%. Positive predictors of any bone protection included female gender (OR=2.4, 95% CI=[1.5-3.7]) and nonurban/suburban location (OR=1.5, 95% CI=[1.1-2.2]), whereas negative predictors included esophagitis, peptic ulcer disease or dysphagia (OR=0.6, 95% CI=[0.4-0.9]) and alcohol abuse (OR=0.2, 95% CI=[0.0-0.9]).

Rates of treatment initiation found in the three incidence studies varied between 5.5%[14] and 11.5%[13]. The difference in reported rate of treatment initiation may result from different study periods and different sample inclusion criteria. Previous studies also found different rates of treatment initiation between different therapeutic classes, with bisphosphonates as the most frequently used and teriparatide as the least used.[7] Female gender was the common predictor of pharmacologic treatment for osteoporosis in all three studies. [7, 13, 14] However, these studies used data from only one or two states, making the generalizability of the study results questionable.

2.4.2 In the Community

Many studies have been conducted to investigate treatment initiation for osteoporosis in the community.[32, 33, 35-42] Rates of treatment initiation reported in these studies ranged from 2.8%[33] to 78%[42]. The wide range of treatment initiation rate is due to different study populations (both men and women[33, 40] vs. men only[38] vs. women only[32, 37, 39, 41, 42]), different inclusion criteria in terms of age (starting age from 45 to 70), different length of

follow-up (from several days during hospitalization[40] to 24 months[33, 38, 42]), and the existence of evidence of osteoporosis[32, 33, 38, 40].

Positive predictors of initiation of pharmacologic treatment for osteoporosis found in these studies included female gender, BMD testing, decreased T-scores, having a diagnosis of osteoporosis, having vertebral fracture, and use of glucocorticoids. Negative predictors of initiation of pharmacologic treatment for osteoporosis were found to be advanced age, low social status, African-American race, increased number of comorbid conditions, and increased number of non-osteoporosis medications. Advanced age was also found to be a positive predictor of initiation of non-HRT therapy. However, none of these studies used a nationally representative sample to study this issue, making it difficult to generalize study results to the elderly population nationwide.

Rates of treatment initiation found in the literature indicate underuse of pharmacologic treatment for osteoporosis both in LTC facilities and in the community. However, to my knowledge, no study has been conducted to compare rates of treatment initiation among elderly patients residing in LTC facilities and in the community. The proposed study will investigate overall rate of treatment initiation as well as rate of treatment initiation for each therapeutic class in the community and in LTC facilities. The proposed study will also examine predictors of treatment initiation for a nationally representative sample of elderly Medicare beneficiaries, thus assuring that the study results are generalizable to elderly population nationwide.

2.5 Predictors of Adherence to Pharmacologic Treatment for Osteoporosis

Once treatment is initiated, patients should be adherent to their pharmacologic treatment to achieve optimal treatment outcomes. Nonadherence to pharmacologic treatment for osteoporosis has been associated with increased risk of fracture.(AHRQ Report, 2007) However, like other chronic and asymptomatic diseases, adherence to osteoporosis medications tends to be suboptimal.[43-46]

2.5.1 In Long-term Care Facilities

To my knowledge, no prior studies have examined adherence to pharmacologic treatment for osteoporosis in LTC facilities. One study that was conducted to determine the prevalence and predictors of osteoporosis evaluation and treatment in nursing home residents with osteoporosis or recent hip fracture briefly looked at discontinuation rates of osteoporosis treatments .[7] The authors discovered that osteoporosis treatment was discontinued in 7% of residents in whom it was prescribed during the study period. Discontinuation rates by specific treatment were 14.3% for hormone replacement therapy, 7.5% for calcitonin, 5.4% for bisphosphonates and 1.3% for calcium. The reason for discontinuation were documented infrequently (14%); however, patient or family preference was documented in 8%, clinical status change in 3%, and adverse reaction in 3%. However, this study only included 895 residents in 67 nursing homes in 2 states (North Carolina and Arizona), which might not reflect the general situation in LTC facilities nationwide.

2.5.2 In the Community

Many studies have been conducted to assess adherence to pharmacologic treatment for osteoporosis in the community with widely varied findings.[47-59] It is somewhat difficult to compare findings from previous studies because of the different reporting styles – some studies reported mean medication possession ratio (MPR) whereas others reported percentage of study sample in different adherence categories (high, medium low, etc.), and the definition of adherence categories varied as well. The length of refill interval used for the denominator of MPR also varied widely (from 30 days to 5 years). The most commonly discussed barriers to adherence include age, prior history of fracture, dosing frequency, concomitant use of other medications and adverse effects of the osteoporosis medication.[79]

The majority of studies used medication possession ratio (MPR) to measure adherence. I have found only one study[51] that used proportion of days covered (PDC) instead of MPR to measure adherence. However, I propose to use PDC to measure adherence in this study. Compared to MPR, PDC has an advantage because when measured repeatedly and analyzed using appropriate statistical methods for within-subject repeated measures, the PDC simultaneously reflects both compliance and persistence.[60]

All prior studies found suboptimal adherence to pharmacologic treatment for osteoporosis in community settings. However, very little knowledge about adherence in the male population can be found in current literature, and no study has compared adherence to pharmacologic treatment for osteoporosis among elderly patients residing in LTC facilities and in the community. The proposed study will compare levels of

adherence to treatment among females and males residing in the community and LTC facilities.

2.6 Impact of Initiation of and Adherence to Pharmacologic Treatments for Osteoporosis on Risk of Future Bone Fractures

The primary goal of treating osteoporosis is to reduce risk of future fracture.[16] However, when assessing the effect of treatment for osteoporosis on the risk of future fractures, both initiation of and adherence to treatment should be taken into account.

2.6.1 In Long-term Care Facilities

To date, no study has been conducted to assess effectiveness of pharmacologic treatment among LTC facility residents. Several trials have been conducted to assess efficacy of treatment for osteoporosis on risk of fractures or on BMD among LTC facility patients.[61-67] However, most of these trials used vitamin D and/or calcium as intervention. The only trial that used a pharmacologic treatment as intervention was conducted by Greenspan et al.[67] and the study used BMD and biochemical markers of bone turnover instead of risk of fracture as the endpoint. The authors conducted a randomized, double-blind, placebo-controlled clinical trial to examine the efficacy and safety of alendronate for treatment of osteoporosis in elderly female residents of long-term care facilities. The study recruited 327 elderly women with osteoporosis in 25 long-term care facilities. Patients were randomly assigned to receive alendronate 10 mg/d or placebo. All patients received vitamin D 400 IU/d, and some received supplemental calcium for which total intake is approximately 1500 mg/d. They found that alendronate produced significantly greater increases in BMD of spine and hip that did placebo (4.4% [3.3%, 5.5%]) in spine and 3.4% [2.3%, 4.4%] in femoral neck for 24-month differences). Alendronate produced

greater decreases from baseline in biochemical markers of bone turnover than did placebo ($p<0.001$).he most recent guidelines on the evaluation of medicinal products in the treatment of primary osteoporosis issued by the European Medicines Agency's Committee for Medicinal Products in Human Use make it clear that reduction in fracture risk is the only endpoint that is acceptable in drug registration studies.[68] Bone mineral density is acceptable as the primary endpoint in bridging studies or as a secondary efficacy endpoint in pivotal trials, but it is not an appropriate surrogate for fracture reduction.

2.6.2 In the Community

Only four studies have been conducted to assess effectiveness of pharmacologic treatment for osteoporosis in the community setting.[69-72] The studies reported 0[69]-32%[70] of reduction in risk of fractures. None of the four studies took adherence to treatment into account when assessing effectiveness of pharmacologic treatment for osteoporosis.

Numerous studies have examined the relationship between adherence to pharmacologic treatment for osteoporosis and the risk of future fracture. The studies reported 0%[48] to 45%[54] reduction in the risk of future fractures for patients with high adherence. However, all these studies examined the relationship in the treated patient population, which means findings were conditional on initiation of treatment. No study has investigated the joint impact of initiation of and adherence to pharmacologic treatment for osteoporosis on the risk of future fractures.

When assessing the impact of initiation of and adherence to pharmacologic treatment for osteoporosis on the risk of future fractures, one has to consider the fact that the decision of initiating a treatment and being adherence to a treatment are two different

decisions. To deal with this issue, the proposed study will use two models to each assess the impact of initiation of and the impact of adherence to pharmacologic treatment on the risk of future fractures. Moreover, to my knowledge, there has not been a study focusing on the comparison of joint impact of initiation of and adherence to pharmacologic treatment for osteoporosis on risk of future fracture between community dwellers and LTC facility residents.

3 Preliminary Study

I have conducted a pooled cross-sectional study using the 2000-2003 Medicare Current Beneficiary Survey (MCBS) to compare patterns of treatment of osteoporosis and to identify predictors for osteoporosis treatment in elderly women residing in the community and in LTC facilities.[73] Drugs for osteoporosis treatment included in this study were bisphosphonates, calcitonin, estrogens, parathyroid hormone analog, and selective estrogen receptor modulator (SERM). Demographics, socio-economic factors, Medicare supplemental insurance coverage, clinical risk factors for osteoporosis, bone fractures, and falls were identified from MCBS survey data. A multivariable logistic regression was utilized to analyze the conditional likelihood of receiving osteoporosis treatment given the covariates. Results showed that the overall prevalence of treatment was 52.1% for community dwellers and 40.9% for facility residents. However, facility residents were more likely to be treated for osteoporosis with medications compared to community dwellers when controlling for other factors. Elderly women residing in the community and in LTC facilities differed substantially in baseline characteristics. Elderly women residing in LTC facilities tended to be older, non-Hispanic white, widowed, less educated, with poor health status, underweight, and they also tended to have less income, a prior history of hip fracture, and more limits in their daily activities. Findings of this study suggested that differences in baseline characteristics may cause differential prevalence of osteoporosis and incidence of bone fracture and subsequently contribute to differences in treatment utilization for osteoporosis between community dwellers and LTC facility residents.

4 Research Design and Methodology

4.1 Data Source and Study Design

This study used data from the 2006-2008 Chronic Condition Data Warehouse (CCW) 5% national random sample of Medicare beneficiaries. Following are the files and type of information contained in the CCW: (1) Beneficiary Summary File, which contains demographic, entitlement and enrollment data for beneficiaries who were part of the CCW 5% sample, were documented as being alive for some part of the reference year of the Beneficiary Summary File and were enrolled in the Medicare program during the file's reference year; (2) Chronic Condition Summary file, which is a selected summary of clinical information for all beneficiaries included in the CCW data back to 1999; it provides the date of first occurrence and occurrence in a given year of 21 chronic conditions including osteoporosis and hip fracture; (3) CMS 5% Denominator file, which combines Medicare beneficiary entitlement status information from administrative enrollment records for Part A, B, C and D; (4) Part A and B claims data in 7 SAF files: inpatient, outpatient, skilled nursing facility, home health agency, hospice, carrier, and durable medical equipment files; (5) Part D Prescription Drug Event (PDE) file, which contains Part D Prescription Drug Event data; (6) the Minimum Data Set (MDS), which records admission and discharge date of each nursing home stay that a beneficiary has as well as other information about nursing home residents as described in section 4.3.2. All the files can be linked by a unique CCW beneficiary identifier included in each data file.

4.2 Study Cohort

This study used a retrospective cohort design. The study cohort included Medicare beneficiaries aged 70 years and older with evidence of osteoporosis. Setting age at 70 years and older enabled the construction of a 5-year look-back window to check beneficiaries' history of osteoporosis in order to distinguish incident from prevalent cases. Evidence of osteoporosis was defined using the CCW algorithm as the presence of (1) at least one inpatient, outpatient or physician claim with relevant ICD-9 diagnosis codes for osteoporosis (Appendix Table 1), or (2) at least one inpatient claim with relevant ICD-9 diagnosis codes for hip/pelvic fracture (Appendix Table 1).

The study cohort was restricted to beneficiaries with continuous enrollment in Medicare Part A, B and a Part D stand-alone Prescription Drug Plan (PDP) from January 1, 2006 through December 31, 2008, or death. The cohort excluded (1) Medicare Advantage Prescription Drug (MAPD) plan enrollees, (2) beneficiaries not enrolled in Part D, and (3) LTC facility residents whose admission or discharge date cannot be identified. Medicare Advantage Prescription Drug (MAPD) plan enrollees were excluded because they lacked Part A and B claims files necessary to identify diagnosis and utilization of Medicare services. Non-Part D enrollees were excluded because they lacked prescription drug data. Long-term care facility residents whose admission or discharge date could not be identified were excluded because they lacked the data for cohort definition for aim 1.

Beneficiaries aged 70 years and older with evidence of osteoporosis and continuous enrollment in Medicare Part A, B and a Part D PDP in 2006 were categorized into 2 groups: (1) prevalent cases (first occurrence of diagnosis of osteoporosis before

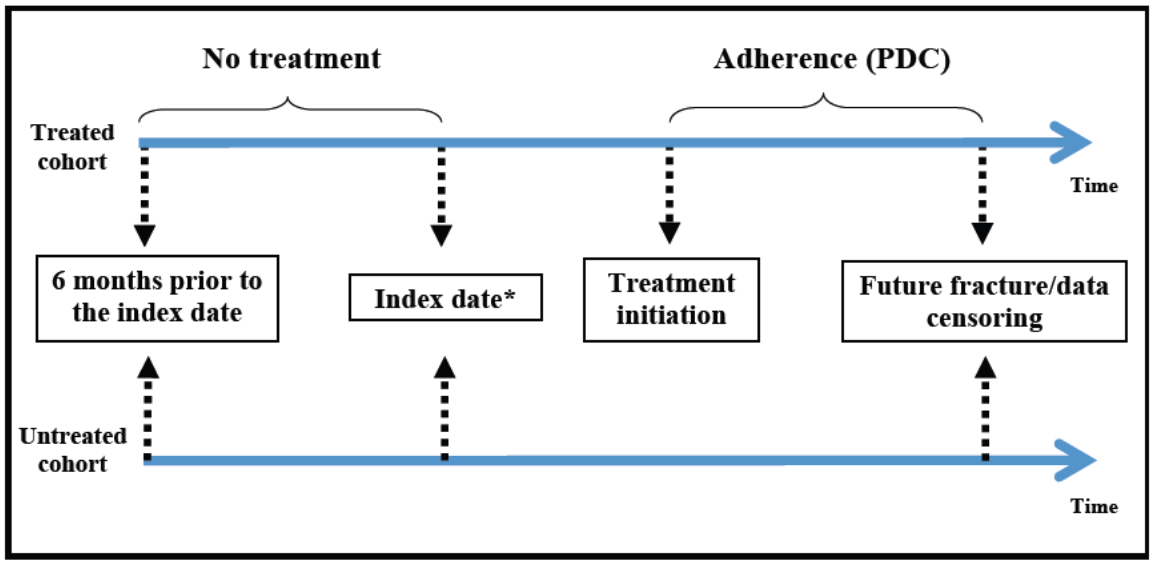
January 1, 2006) and (2) incident cases (first occurrence of diagnosis after January 1, 2006). Prevalent cases were included in the sample on January 1, 2006 and followed through December 31, 2008, or death. Incident cases were included in the sample on the date of diagnosis of osteoporosis and followed through December 31, 2008, or death. All prevalent cases were included in the analysis for aim 1 and 2, and only incident cases identified between July 1, 2006 and June 30, 2008 were included in the analysis for aim 3 (Figure 4.1). Setting starting date of inclusion on July 1, 2006 allowed a window of at least 6 months to look back beneficiaries' medication history to ensure no use of pharmacologic treatment for osteoporosis and therefore, true incident cases. Setting end date of inclusion on June 30, 2008 allowed a window of at least 6 months to look forward beneficiaries' development of subsequent fracture.

Both incident and prevalent cases were further categorized into 2 cohorts: LTC facility-resident and community-resident cohorts and the two cohorts are mutually exclusive. In the main analysis, LTC facility-resident cohort only included individuals who stayed in a LTC facility for the entire study period, community-resident cohort only included individuals who stayed in the community for the entire study period (Figure 4.2), and switchers included individuals who stayed in both the community and LTC facilities.

Figure 4.3 shows the sample sizes for the final study cohorts based on the inclusion and exclusion criteria described above. The CCW 5% sample included 2,860,348 Medicare beneficiaries in 2006 to 2008. There were 486,932 beneficiaries with continuous enrollment in Medicare Part A, B and a Part D PDP in 2006 to 2008, of which 282,460 beneficiaries aged 70 years and older. Of this latter sample 113,202 beneficiaries

had evidence of osteoporosis, of which 99,421 were prevalent cases and 13,781 were incident cases.

Figure 4.1. Schematic Study Design for Aim 3



*Date of diagnosis of osteoporosis or hip fracture between July 1, 2006 and June 30, 2008

Figure 4.2. Definition of LTC Facility and Community Residents

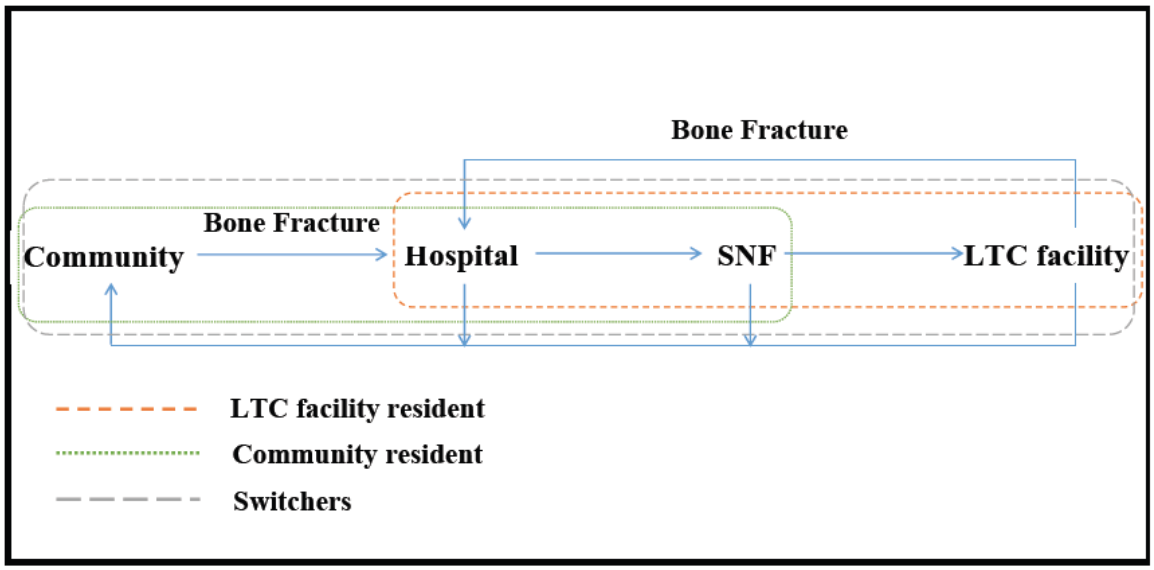
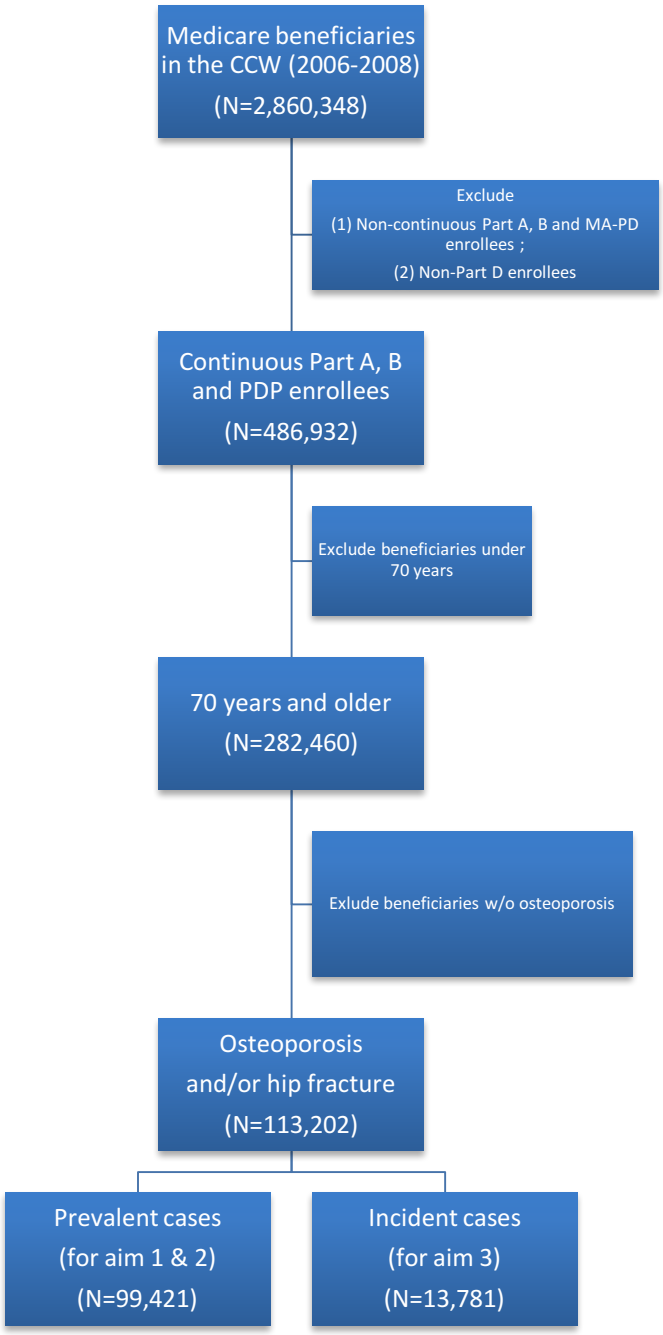


Figure 4.3. Schematic Showing Inclusion and Exclusion Criteria for Cohort Selection



4.3 Measurement of Key Variables

4.3.1 Measures of Drug Utilization

Pharmacologic treatment for osteoporosis included bisphosphonates, calcitonin, parathyroid hormone analogs and selective estrogen receptor modulators (SERM). Appendix Table 2 shows all the pharmacologic treatments for osteoporosis included in this study. Use of pharmacologic treatments for osteoporosis was identified by J codes (J0630 for calcitonin salmon up to 400 units injection, J1740 for ibandronate sodium 1 mg injection, J3110 for teriparatide 10 mcg injection, J3487 and J3488 for zoledronic acid 1 mg injection) in Part B claim records and by National Drug Codes (NDC) in the Part D PDE file using the FirstDataBank drug dictionary for non-Part B osteoporosis medications.

For aims 1 and 2, use of pharmacologic treatments was a dichotomized variable indicating the utilization of any pharmacologic treatment for osteoporosis following a diagnosis of osteoporosis during the study period. Use of pharmacologic treatment for osteoporosis was captured for both prevalent and incident cases.

For aim 3, adherence will be measured by proportion of days covered (PDC) during the period exposed to any pharmacologic treatment for osteoporosis and was further categorized into high (i.e. PDC$\geq$0.8) and low adherence (i.e. PDC<0.8). The PDC measure was calculated based on total number of days covered by all pharmacologic treatments for osteoporosis during the study period divided by total number of days within the study period, excluding days in a hospital, a SNF or a hospice from the denominator and the numerator.

4.3.2 Measure of Bone Fractures

For aim 3, risk of subsequent fracture was measured as time-to-first subsequent fracture from medication initiation date for treatment-initiated patients and from a randomly selected "potential initiation" date for non-users. Fractures on all sites excluding skull, nose, fingers and toes were identified and categorized as vertebral (spine and trunk) and non-vertebral (upper limb and lower limb) fractures (Appendix Table 1).

4.3.3 Measure of Residential Status

The primary independent variable of interest for aim 1 was an indicator of being a LTC facility or community resident. Figure 2 shows how LTC facility and community residents were defined. Long-term care facility residents were defined as individuals that stayed in a nursing home, a hospital and a skilled nursing facility (SNF) during the study period, but did not stay in the community. Community residents were defined as individuals that stayed in the community, a hospital and a SNF, but did not stay in a LTC facility (i.e. more than 100 days in a SNF). The rest were switchers, who stayed in both a LTC facility and the community. Long-term care facility residents, community residents and switchers were mutually exclusive. Long-term care facility residents were identified using the MDS. The MDS is part of the federally mandated process for clinical assessment of all residents in Medicare or Medicaid certified nursing homes. This process provides a comprehensive assessment of each resident's functional capabilities and helps nursing home staff identify health problems. Resident Assessment Protocols (RAPs) are part of this process and provide the foundation upon which a resident's individual care plan is formulated. MDS assessment forms are completed for all residents in certified nursing homes, regardless of source of payment for the individual resident. MDS

assessments are required for residents on admission to the nursing facility and then periodically, within specific guidelines and time frames. The MDS records residents' admission and discharge dates for each stay. Therefore, I used these dates to define nursing home residents and the length of their nursing home stays. Additionally, the Medicare inpatient and SNF claims data was used to identify days of Part A-covered hospitalization and SNF stays.

In all analyses, the indicator of residential status was dichotomized with1 indicating LTC facility residents and 0 indicating community residents for the entire study period.

4.3.4 Other Explanatory Variables

For all aims, model covariates included demographics (age, gender, race, geographic location), proxy socioeconomic status using indicators of Medicare/Medicaid dual eligibility, and receipt of low income subsidy (LIS) but no Medicare/Medicaid dual eligibility, clinical indicators of osteoporosis (history of hip fracture and receipt of BMD testing (ICD-9 code 88.98, CPT codes 76977, 77078, 77079, 77080, 77081, 77082, 77083, 78350, 78351 and HCPCS code G0130)), and total number of chronic medications used. Demographics were included in the model because they were common confounders. Socioeconomic status was included because it affected access to health services and thus affects exposure and adherence to treatment and the fracture outcome as well. Clinical indicators of osteoporosis were included because to some extent, they were proxies of severity of osteoporosis. The hypothesis is that the more severe the disease is, the more likely a patient would be exposed and adherent to treatment. The total number of chronic medications used was included for two reasons: the clinical effect is that the

more medications one takes, the less likely one would be exposed to and adherent to one more medication; the economic effect is that the more medications one takes, the more out-of-pocket expense on drugs one pays, the less likely one would be willing to pay for one more medication.

For aims 1 and 2, additional model covariates included relevant comorbidities (Appendix Table 3) and other relevant medication use (anticoagulants, anticonvulsants, aromatase inhibitors, barbiturates, cancer chemotherapeutic drugs, cyclosporine A and tacrolimus, depo-medroxyprogesterone, glucocorticoids, gonadotropin releasing hormone agonists and lithium).[74] These comorbidities and medications were included in the model as they may cause or contribute to osteoporosis and fractures. Therefore, individuals with these comorbidities or on these medications have a higher risk of having a fracture and thus should more likely be on pharmacologic treatment to treat their osteoporosis.

For aim 3, additional model covariates included relevant comorbidities (Appendix Table 3) and other relevant medication use (anticoagulants, anticonvulsants, aromatase inhibitors, barbiturates, cancer chemotherapeutic drugs, cyclosporine A and tacrolimus, depo-medroxyprogesterone, glucocorticoids, gonadotropin releasing hormone agonists and lithium).[74] The reason of including these comorbidities and medications in the model was that these comorbidities and medications cause or contribute to osteoporosis and future fractures.

4.4 Analytic Plan

4.4.1 Specific Aim 1

I first used univariate and bivariate statistics to describe characteristics of community dwellers, LTC residents and switchers. Then I described rates of use of any

pharmacologic treatment for osteoporosis, as well as for each therapeutic class, among community- and LTC facility-residing elderly female osteoporotic patients in 2006, 2007 and 2008.

I employed a multivariable modified Poisson regression to analyze factors affecting use of pharmacologic treatment for osteoporosis including residential status as well as other control variables guided by economic theory and clinical practice as described above. I also included interaction terms between residential status and year to test whether or not there was a difference in use between community dwellers and LTC facility residents over time.

Full model:

$$P(y = 1|x) = \mathrm{G}[\,\alpha_0 + \alpha_1 residential\ status + \alpha_2 residential\ status \times year + \alpha_3 x_3 + \cdots + \alpha_k x_k]$$

where G is log function.

4.4.2 Specific Aim 2

I first described baseline characteristics of female and male osteoporotic patients. Then I described rates of use of any pharmacologic treatment for osteoporosis, as well as for each therapeutic class, among male and female elderly osteoporotic patients in 2006, 2007 and 2008.

I performed a multivariable modified Poisson regression to analyze factors affecting use of pharmacologic treatment for osteoporosis including gender as well as other control variables guided by economic theory and clinical practice as described above. The reason for using adherence as a set of categorical variables instead of a

continuous variable is that it would be difficult to interpret the result if using adherence as a continuous variable.

Full model:

$$P(y = k|x) = G[\beta_0 + \beta_1\, gender + \beta_2 x_2 + \cdots + \beta_k x_k]$$

Stratified models:

$$P(y = k|gender) = G[\beta_{g,0} + \beta_{g,2} x_2 + \cdots + \beta_{g,k} x_k]$$

where G is log function, g=1 for men, g=2 for women.

4.4.3 Specific Aim 3

In descriptive analysis I first characterized elderly incident osteoporotic patients stratified by gender. Then I reported mean time-to-first subsequent fracture among elderly incident osteoporotic patients who initiated and did not initiate treatment, and among treatment initiators by different levels of adherence stratified by gender.

I used two multivariable models to analyze the effect of initiation of and adherence to pharmacologic treatment for osteoporosis on risk of first subsequent fracture. In the first model, I estimated effects of treatment initiation on the risk of subsequent fracture given the individual's gender and other covariates using a Cox proportional hazard (PH) model. In the second model, I estimated effects of different levels of adherence (i.e. PDC<0.8 and PDC≥0.8) to pharmacologic treatment for osteoporosis on the risk of subsequent fracture given the individual's gender and other covariates using a Cox PH model among those who initiated pharmacologic treatment for osteoporosis.

- 1st part – an equation estimating the effect of initiating a treatment on the risk of first subsequent fracture given a set of covariates

  Full model:

$$h_i(t|x) = \exp\left[\gamma_0(t) + \gamma_1 treatment\ initiation + \gamma_2 gender + \gamma_3 x_3 + \cdots + \gamma_k x_k\right]$$

Stratified models:

$$h_i(t|gender) = \exp\left[\gamma_{g,0}(t) + \gamma_{g,1} gender + \gamma_{g,3} x_3 + \cdots + \gamma_{g.k} x_k\right]$$

where $h_i(t|x)$ is hazard of first subsequent fracture, g=1 for men and g=2 for women.

- 2nd part – an equation estimating the effect of different level of adherence to a treatment on the risk of first subsequent fracture given a set of covariates conditional on that a treatment is initiated

  Full model:

$$h_i(t|x, treatment\ initiated) = exp[\lambda_0(t) + \lambda_1 adherence\ to\ therapy + \lambda_2 gender + \lambda_3 x_3 + \cdots + \lambda_k x_k]$$

  Stratified models:

$$h_i(t|gender, treatment\ initiated) = exp\left[\lambda_{g,0}(t) + \lambda_{g,1} adherence\ to\ therapy + \lambda_{g,3} x_3 + \cdots + \lambda_{g,k} x_k\right]$$

  where $h_i(t|x,$ treatment initiated) is hazard of first subsequent fracture given that pharmacologic treatment is initiated, g=1 for men and g=2 for women.

5 Patterns of Evidence-Based Osteoporosis Medication Use: A Comparison of Elderly Female Long-Term Care Facility Residents to Community Dwellers Enrolled in Medicare Part D

5.1 Introduction

Osteoporosis is the most common bone disease in humans[75] and a major threat to public health[76]. Along with low bone mass, osteoporosis affects an estimated 51 million Americans aged 50 years and older and is projected to affect approximately 65 million adults over the age of 50 by 2030[76]. Among Americans with osteoporosis, 80% are women. Osteoporosis is associated with millions of fractures annually at a cost of billions to treat, thus creating a heavy economic burden to the health care system[5]. The majority of costs are for inpatient hospital care (57%), followed by long-term care (LTC) (30%) and outpatient care (13%)[5]. Among all types of fractures, hip fractures are the most serious consequences of osteoporosis. About 24% of patients over 50 years of age die within a year of a hip fracture and approximately 20% of hip fracture patients require LTC[1]. Furthermore, patients who survive an osteoporotic fracture use more than twice the healthcare resources compared to similar patients without fractures for at least 3 years after their fractures[77]. Therefore, osteoporosis should be properly treated regardless of residential setting in order to prevent osteoporosis-related fractures and associated costs.

Clinical guidelines recommend pharmacologic therapy for men and women who have bone mineral density (BMD) T-scores ≤-2.5 at the femoral neck or spine by dual-energy x-ray absorptiometry (DXA) or have experienced fragility fractures[20, 78, 79]. The 2008 National Osteoporosis Foundation (NOF) clinical guidelines identified 4 classes of

evidence-based medications: bisphosphonates, calcitonin, parathyroid hormone analog (teriparatide) for both sexes, and a selective estrogen receptor modulator (raloxifene) for women. Bisphosphonates are recommended as first-line therapy[78]. However, because each class of drugs is associated with unique benefits and risks, the choice of therapy should be guided by physician judgment of the best option for each individual patient[20, 78]. Many studies have found that osteoporosis is undertreated in men and women who have known osteoporosis or have experienced fragility fractures [7, 8, 32-34] with prevalence of osteoporosis treatment ranging between 4.6%[33] and 50%[80]. Furthermore, studies have found that osteoporosis is much less likely to be treated in LTC settings[7-14] despite the fact that residents in these facilities are more likely to have osteoporosis[81] and bone fractures[17, 18] than their counterparts in the community. Around 85% of all nursing home residents have osteoporosis[81], and the rate of fractures in nursing home residents is 2.5-10 times higher than their age-matched counterparts in the community[17, 18]. Therefore, it is important to better understand why nursing home residents are undertreated.

Since osteoporosis is a disease of aging and Medicare covers over 95% of the elderly in the United States, the Medicare population is the population of choice for studying patterns of evidence-based osteoporosis medication use. It is estimated that between 7%[82] and 14.9%[83] of Medicare beneficiaries have osteoporosis, and Medicare pays for repair of 80% of bone fractures due to osteoporosis[84]. Yet, osteoporosis treatment in this population is understudied. Of particular note is the lack of data on differences in osteoporosis treatment by residential setting. Only one comparative study of osteoporosis treatments in female Medicare beneficiaries in the community and LTC facilities has been published, and that covered the period 1998 to 2003[80]. This study

found that LTC facility residents were more likely (prevalence ratio (PR) 1.31, 95% confidence interval (CI) [1.12,1.53]) to be treated for osteoporosis; however, they were less likely to use bisphosphonates when being treated compared to community dwellers. This study also found that Medicare beneficiaries with supplemental drug coverage were more likely (PR 1.22, 95% CI [1.13, 1.38]) to receive osteoporosis treatment compared to those without[80]. It is unknown whether trends in treatment reported in that study has persisted over time. Moreover, since 2006 Medicare beneficiaries have a new option for drug coverage (Part D) that significantly reduces cost barriers to needed medications. It is also unknown if the reduced cost barriers due to Medicare Part D helps increased use of osteoporosis medications.

This study was designed to address these unknowns. We tracked treatment patterns from 2006 through 2008 for a large nationally-representative sample of female Medicare beneficiaries previously diagnosed with osteoporosis. We identified the residential status of each study subject each year. This permitted us to determine not only whether there were persistent trends between community and LTC residents, but also whether treatments differed among beneficiaries who moved between the two settings. We conducted the analysis based on the following considerations. In the clinical decision-making process, a physician would normally first decide whether or not to prescribe any osteoporosis medication to a patient, then decide if the patient was a good candidate for bisphosphonates since bisphosphonates are the first-line medication recommended by clinical guidelines. The final clinical decision would be choice of specific bisphosphonate or selection of an alternative medication (calcitonin, teriparatide, or raloxifene) based on considerations of contraindications and/or side effects. However,

due to the relatively few non-bisphosphonate users in our sample, we were only able to model the first two steps in this clinical decision-making process. Based on the previous study[80], we hypothesized that LTC residents would be more likely to receive osteoporosis treatment than community dwellers with similar characteristics. We also hypothesized that residents in LTCs only would be less likely to receive bisphosphonates compared to community residents. The study results will provide baseline information of clinical practice in treatment of osteoporosis in the earlier years of Part D and to identify future direction and challenges for treatment of osteoporosis in the Medicare population.

5.2 Methods

5.2.1 Data and sample selection

Data for the study were obtained from the 2006-2008 Chronic Condition Data Warehouse (CCW) 5% national random sample of Medicare beneficiaries.[85] We used data from the Medicare enrollment files, Part A, B and D claims, and the Minimum Data Set (MDS), which contains information completed for all beneficiaries who admitted into a Medicare certified nursing home. MDS assessments are required for residents on admission to the nursing facility and then periodically, within specific guidelines and time frames, until discharge. Therefore, the MDS can provide admission and discharge dates to identify duration of each stay. The study sample included female Medicare beneficiaries aged 70 years and older with evidence of osteoporosis or hip fracture prior to January 1, 2006. Setting the minimum age at 70 enabled the construction of a 5-year look-back window to check beneficiaries' history of osteoporosis or hip fracture in order to guarantee that all subjects had prevalent disease. Evidence of osteoporosis was defined using the CCW algorithm of at least one inpatient, outpatient or physician claim with ICD-9 diagnosis

codes 733.0x and evidence of hip fracture was at least one inpatient or skilled nursing facility (SNF) claim with ICD-9 codes 733.14, 733.15, 733.96, 733.97, 733.98, 808.x, 820.x[86]. The study sample was also restricted to beneficiaries with continuous enrollment in Medicare Part A, B and a Part D stand-alone prescription drug plan (PDP) from January 1, 2006 through December 31, 2008, or death. The sample excluded (1) Medicare Advantage Prescription Drug (MAPD) plan enrollees, (2) beneficiaries not enrolled in Part D, and (3) LTCF residents whose admission or discharge date could not be identified. MAPD plan enrollees were excluded because they lacked Part A and B claims files necessary for identifying diagnosis and utilization of Medicare services. Non-Part D enrollees were excluded because they lacked prescription drug data. Long-term care facility residents whose admission or discharge date could not be identified were excluded because they lacked data necessary for sample definition.

5.2.2 Drug measures

The outcome variables are use of any osteoporosis medication among all beneficiaries with osteoporosis and use of non-bisphosphonates among osteoporosis medication users. Use of osteoporosis medications listed in the 2008 NOF guidelines was identified by National Drug Codes (NDCs) in the Part D prescription drug event (PDE) file using the FirstDataBank drug dictionary and by Current Procedural Terminology (CPT) codes in the Part B claims file for Part B covered osteoporosis drugs. The 2008 NOF guidelines were used because it was the most relevant guideline for the study period. Part B covers all injected drugs provided in the physician office setting. It should be noted that estrogen is sometimes used as treatment of osteoporosis; however, the Food and Drug Administration (FDA)-approved indication is only for prevention of osteoporosis, so use

of estrogens was not included in this study. In preliminary analyses, we found less than 1% of study subjects used Part B covered ibandronate sodium and zoledronic acid injections during the study period, so use of those two Part B covered drugs was not included in the final analysis. The unit of observation for osteoporosis medication use was person-year. One or more fills in a given year was considered as having any use in that year. Having at least one fill in a year over all 3 years was defined as having consistent use while having at least one fill in 2006 and 2008 with no fill in 2007 was defined as having significant gap in medication use. Osteoporosis drugs used during Medicare covered hospitalizations and SNF stays could not be observed as they are covered under Part A and were not included in the measures.

5.2.3 Residential Status

The main independent variable of interest is Part D enrollees' residential status, categorized as community only, LTC only, and both. Residential status was identified using the MDS together with inpatient and SNF claims. The MDS provided residents' admission and discharge dates for each stay in the nursing homes regardless of payment source while inpatient and SNF claims provided information on days of Part A covered hospitalizations and SNF stays. The unit of observation for residential status was person-year. We tracked subjects' location (categorized as community, hospital, Part A SNF, and non-Part A SNF) every day during the study period. We created indicators for any days in each setting for each year (2006-2008) and then assigned individuals to one of the three categories. In the assignment to the community only category we permitted exceptions for inpatient or Part A SNF stays.

5.2.4 Other measures

Other measures included in the statistical models described below included demographics (age, gender, race/ethnicity, and geographic region), indicators of Medicare-Medicaid dual eligibility and receipt of Part D low-income subsidy (LIS) as proxy variables of socioeconomic status. General health status was represented by counts of conditions from the Center for Medicare and Medicaid Services (CMS) prescription drug hierarchical condition categories (RxHCC) at baseline, and death at the end of each year. Indicators for conditions and medications that may cause or contribute to osteoporosis and bone fractures and risk factors for fall were selected based on the 2008 NOF guidelines[78]. Disease factors included prior hip fracture, diabetes mellitus, rheumatoid arthritis/osteoarthritis, congestive heart failure (CHF), depression, end stage renal disease, chronic obstructive lung disease (COPD), and breast cancer, all defined by CCW diagnostic algorithms[86]. Commonly used medications that may cause or contribute to osteoporosis and bone fractures included anticonvulsants, cancer chemotherapy and glucocorticoids. Risk factors for fall included Alzheimer's disease/dementia as a proxy of reduced problem solving or mental acuity and diminished cognitive skills, glaucoma as proxy of poor vision, and stroke as proxy of poor balance. FDA's medication guides were used to identify possible contraindications/medication side effects that may influence osteoporosis medications choices (see list in Appendix Table 4). The most common contraindication for osteoporosis medications is chronic kidney disease. The main side effect is GI problems. Other contraindications and side effects from the FDA guides were identified in Medicare claims and reported as summary dummy variables. We measured number of other chronic medication used per month as an indicator of pill

burden, as a high number of other chronic medication used per month may cause individuals unable to manage multiple medications, burden individuals with the cost of multiple medications, or cause physicians to prioritize other conditions over osteoporosis management. Finally, we captured receipt of bone mineral density (BMD) testing as an indicator of osteoporosis management. The unit of observation was person-year. We hypothesized that factors that increase risk of osteoporosis and/or falls would be positively associated with use of any osteoporosis medications, while contraindications for osteoporosis medications would be negatively associated with use of any osteoporosis. Among those receiving any osteoporosis medications, the choice of bisphosphonates vs. non-bisphosphonates would be affected mainly by contraindication or side effects of bisphosphonates.

5.2.5 Statistical analysis

We conducted both descriptive and multivariate regression analyses to identify trends and correlates of osteoporosis medication use. The descriptive analyses included, first, an examination of differences in characteristics among female Part D enrollees by residential status and year. For categorical variables, both Chi-square tests and t-tests were conducted but only the results of t-tests were reported to show where the difference between LTC residents/switchers and community dwellers occurred. For numerical variables, t-tests were conducted. Next we calculated use of any osteoporosis medication for each of the three study years including measures of initiation and persistency over time. Then, among drug users we calculated annual prevalence of use for bisphosphonates, calcitonin, teriparatide, and raloxifene by residential status. Finally, we

characterized annual differences between bisphosphonate and non-bisphosphonate users by residential status and year.

For multivariate analysis, we used modified Poisson regressions[87] with robust error variance to estimate factors associated with any osteoporosis medication use, and among users, use of bisphosphonates versus non-bisphosphonates. We used Poisson rather than logistic regression in order to derive accurate measures of relative risk. When the probability of an outcome is extremely low or high, the odds ratio approximates relative risk; however, when the probability of the outcome is common, odds ratio would be overestimated and conversion of an adjusted odds ratio to a relative risk produces an inconsistent estimate for the true risk. Both models included binary variables for residential status and year plus interaction terms for these variables to assess temporal change in patterns of medication use. All variable described in the measures section above were included as covariates. The analyses were conducted using SAS 9.3 with the REPEATED command to adjust the standard errors for multiple observations of the same individuals.

To test the sensitivity of patterns of osteoporosis medication use to remaining life expectancy, we conducted sensitivity analyses in a sample excluding decedents. It is suspected that physicians would be less likely to prescribe osteoporosis medications to elderly with shorter life expectancy. Therefore, we hypothesized that with a longer remaining life expectancy, the prevalence of osteoporosis medication use would be higher and non-bisphosphonate use would be lower in this survivor sample.

Because not all individuals in the sample with a diagnosis of hip fracture had osteoporosis and some may not have needed osteoporosis treatment, we conducted

sensitivity analyses in a sample including only those with diagnosis of osteoporosis. We hypothesized that by excluding those who may not need to be treated for osteoporosis, the prevalence of osteoporosis medication use would be higher in this subsample.

The study protocol was approved by the University of Maryland Baltimore Institutional Review Board.

5.3 Results

The final study sample included 96,408 female Medicare beneficiaries diagnosed with osteoporosis or hip fracture, representing 46% of women meeting the study inclusion criteria for Medicare enrollment and age (Figure 5.1). Of the 96,408 female Medicare beneficiaries, 12,236 had both a diagnosis of osteoporosis and hip fracture, 78,630 had a diagnosis of osteoporosis only, and 5,452 had a diagnosis of hip fracture only. Table 5.1 presents baseline characteristics of this sample. Subjects' residential status remained relatively stable over the study period. Compared to those with only community residence, LTC-only residents and those in both settings were older, more likely to be white (89.6% vs. 84.0%, $p<0.05$ for LTC-only residents vs. community-only residents; 88.3% vs. 84.0%, $p<0.05$ for those in both settings vs. community-only residents), Medicare-Medicaid dual eligible, in poorer health (i.e. higher RxHCC counts), and higher rates of prior hip fracture, diabetes, CHF, depression, COPD, Alzheimer's disease/dementia, and stroke. Having some LTC facility exposure was also associated with higher rates of anticonvulsant use, chronic kidney disease, more chronic medications per month, and higher rates of mortality. Subjects in LTC facilities were less likely to have BMD tests.

Figure 5.1. Sample Selection Flowchart Showing Residential Status by Year

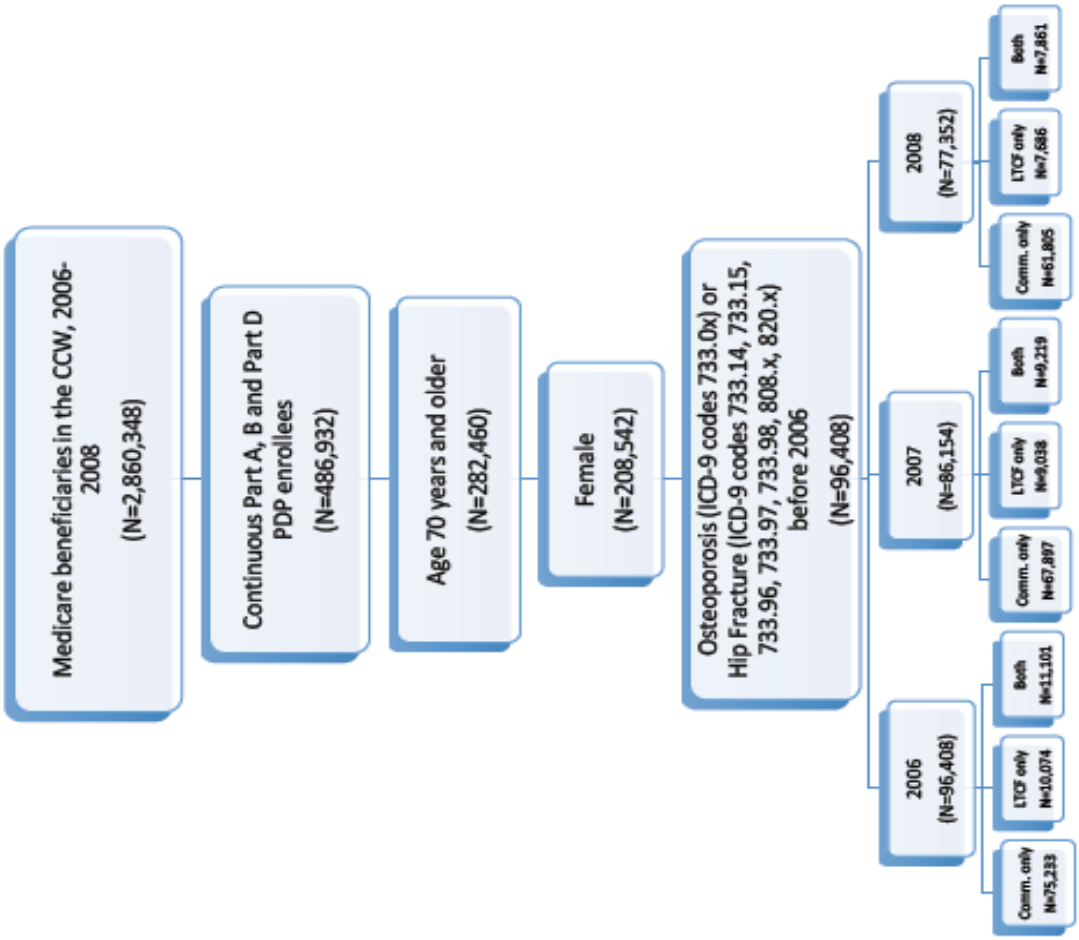


Table 5.1. Characteristics of Female Medicare Part D Enrollees with Osteoporosis or Prior Hip Fracture by Residential Status (N=96,408)

Beneficiary Characteristics	Residence in 2006		
	LTCF only (N=10,074)	Both (N=11,101)	Community only (N=75,233)
Residential status			
LTCF only			
2007	34.9*	22.2*	4.3
2008	25.5*	13.7*	5.0
Both			
2007	62.5*	23.1*	0.2
2008	43.9*	17.8*	1.7
Community only			
2007	0.4*	6.7*	89.2
2008	0.8*	5.3*	81.3
Demographic characteristics			
Age			
70-79	18.3*	20.8*	53.5
80-89	50.1*	49.2*	38.4
90+	31.5*	30.0*	8.1
Race/ethnicity			
White	89.6*	88.3*	84.0
Black	6.9*	7.1*	6.1
Hispanic	1.4*	2.2*	4.2
Other	2.1*	2.4*	5.7
Geographic region			
Northeast	25*	21.1	20.2
Midwest	27.7*	28.2*	22.5
South	37.3	38.9*	40.4
West	9.9*	11.9*	16.9
Socioeconomic status			
Non- Low income subsidy (LIS)	5.3*	14.1*	52.0
LIS recipient but non-dual	0.5*	2.0*	5.0
Medicare-Medicaid dual eligibility	94.2*	83.9*	43.0
Health Status			
RxHCC count (sd)	7.9* (3)	9.5* (3.9)	7.0 (3.5)
Comorbidities causing or contributing to osteoporosis and fractures			
Prior hip fracture	28.2*	25.2*	7.6
Diabetes mellitus	34.9*	38.3*	30.0
Rheumatoid arthritis/osteoarthritis	63.8	64.3	54.5
Congestive heart failure	55.2*	61.0*	33.2
Depression	63.6*	58.2*	29.1
End-stage renal disease	0.3*	1.4*	0.6

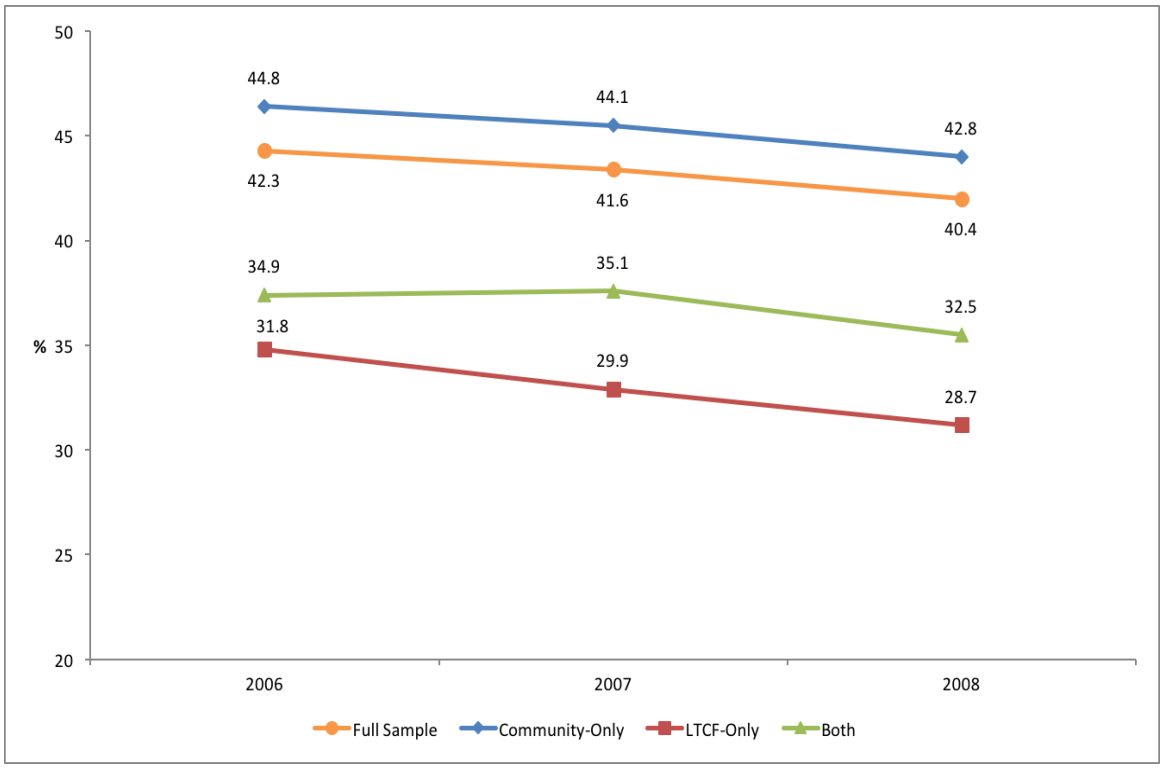
Table 5.1. ***Continued***

	Residence in 2006		
Beneficiary Characteristics	LTCF only (N=10,074)	Both (N=11,101)	Community only (N=75,233)
COPD	30.1*	37.4*	24.9
Breast cancer	4.8	5.3	6.8
Medications causing or contributing to osteoporosis and fractures			
Anticonvulsants	21.3*	25.4*	11.8
Cancer chemotherapy	7.5	12.5*	5.2
Glucocorticoids	14.9*	22.9	20.7
Risk factors for fall			
Alzheimer's/dementia	80.3*	67.5*	16.4
Glaucoma	19.6*	19.8*	23.9
Stroke	34.7*	35.1*	16.2
Contraindications of all osteoporosis medications			
Chronic kidney disease	18.5*	23.0*	12.7
Any other contraindications of all osteoporosis medications	8.1	4.1*	7.3
Side effects of all osteoporosis medications			
GI problems	21.7	30.0*	22.8
Any other side effects of all osteoporosis medications	43.9*	28.0*	48.2
Number of chronic medications used per month (sd)	5.1* (2.8)	4.5* (2.7)	3.2 (2.3)
Receipt of BMD testing	1.5*	2.3*	17.9
Death rate over study period	51.1*	73.1*	18.1

* Difference between cohort in LTCF only/both setting and cohort in community only are significant at α=0.05 level.

Prevalence of evidence-based osteoporosis medication use ranged from 42.3% in 2006 to 40.4% in 2008 among those diagnosed with osteoporosis or hip fracture, with a slight downward trend over time (Figure 5.2). Medication use was highest among subjects with only community exposure (44.8% in 2006 to 42.8% in 2008) and lowest among subjects with just LTC exposure (31.8% in 2006 to 28.7% in 2008).

Figure 5.2. Prevalence of Evidence-Based Osteoporosis Medication Use among Female Medicare Part D enrollees with Osteoporosis or Prior Hip Fracture by Year and Residential Status



As shown in Table 5.2, a plurality of individuals (49.3%) did not receive osteoporosis medications over the 3 years, while 28.1% had evidence of use in each of the years. A total of 7.2% initiated medication use in either 2007 or 2008, and around 16% exhibited significant gaps in use or discontinued use altogether. However, the distribution differed by residential status. The proportion of consistent users was the highest (31.4%) and that of non-users was the lowest (46.9%) among subjects with only community exposure.

Table 5.2. Temporal Patterns of Any Evidence-Based Osteoporosis Medication Use among Female Part D Enrollees with Osteoporosis by Residential Status

		Residence in 2006		
Patterns of Use, 2006-2008	Total (%)	LTC only (%)	Both (%)	Community only (%)
Any use	50.7	40.6	43.6	53.1
Consistent use	28.1	18.2	14.8	31.4
New initiation				
2007	3.6	3.8	4.1	3.5
2008	3.6	4.3	3.5	3.5
Inconsistent use				
Use only in 2007	1.3	0.7	1.2	1.4
Use in 2006 and 2008	1.0	0.4	1.0	1.1
Discontinuation				
2007	6.9	4.9	13.5	6.2
2008	6.3	8.7	5.5	6.1
No use	49.3	59.4	56.4	46.9

Among evidence-based osteoporosis medication users, bisphosphonates were the top prescribed medication (Table 5.3) representing 80.3% of subjects in 2006 and 82.0% in 2008. Prevalence of other osteoporosis medications was below 13% in every year. Prevalence of raloxifene was the second highest and remained stable over time. Prevalence of calcitonin was nearly as high as raloxifene in 2006 but decreased significantly over time (from 12.4% in 2006 to 9.5% in 2008, $p<0.05$). Teriparatide was the least prescribed osteoporosis medication during this period. Non-bisphosphonate users were more likely to be LTC residents than bisphosphonate users. Non-bisphosphonate users were older, more likely to be white, live in the South, have generally poorer health status, chronic kidney disease, and much higher mortality rates.

Table 5.3. Characteristics of Female Osteoporosis Medication Users by Year and Type of Drug Used

	Bisphosphonate Users			Non-Bisphosphonate Users		
Beneficiary Characteristics	2006 (N=32,747)	2007 (N=29,069)	2008 (N=25,621)	2006 (N=8,013)	2007 (N=6,783)	2008 (N=5,612)
Prevalence of use						
Bisphosphonates	80.3	81.1	82.0			
Calcitonin				12.4	10.9	9.5
Parathyroid hormone				1.9	2.2	2.0
Selective estrogen receptor modulator				12.5	12.6	12.4
Residential status in 2006						
Community only	85.3	88.3	91.0	73.0*	77.6*	82.3*
LTCF only	6.4	7.2	5.5	13.6*	15.3*	12.0 *
Both	8.5	4.5	3.5	13.4*	7.1*	5.7*
Demographic characteristics						
Age						
70-79	50.9	53.5	56.6	44.0*	47.4*	50.6*
80-89	39.8	38.8	37.3	41.2*	40.6*	39.9*
90+	9.2	7.7	6.0	14.8*	12.0*	9.5*
Race/ethnicity						
White	84.2	83.7	83.3	88.3*	88.0*	86.6*
Black	4.4	4.3	4.2	3.4*	3.2*	3.1*
Hispanic	4.4	4.4	4.4	2.3*	2.6*	3.3*
Other	6.9	7.7	8.1	5.9*	6.3*	7.0*
Geographic region						
Northeast	20.7	20.7	20.7	20.1	20.1	20.0
Midwest	24.1	23.9	24.1	24.6	24.6	23.5
South	37.4	37.1	36.7	40.5*	40.8*	41.5*
West	17.7	18.3	18.4	14.7*	14.5*	15.0*
Socioeconomic status						
Non- Low income subsidy (LIS)	48.4	50.0	51.8	42.9*	45.9*	47.6*
LIS recipient but non-dual	3.7	3.7	3.9	4.1*	3.8	4.1
Medicare/Medicaid dual eligibility	47.9	46.3	44.3	53.1*	50.2*	48.4*
Health Status						
RxHCC count (sd)	7.4 (3.5)	7.2 (3.4)	7.0 (3.3)	7.8* (3.5)	7.6* (3.4)	7.4* (3.4)
Comorbidities causing or contributing to osteoporosis and fractures						

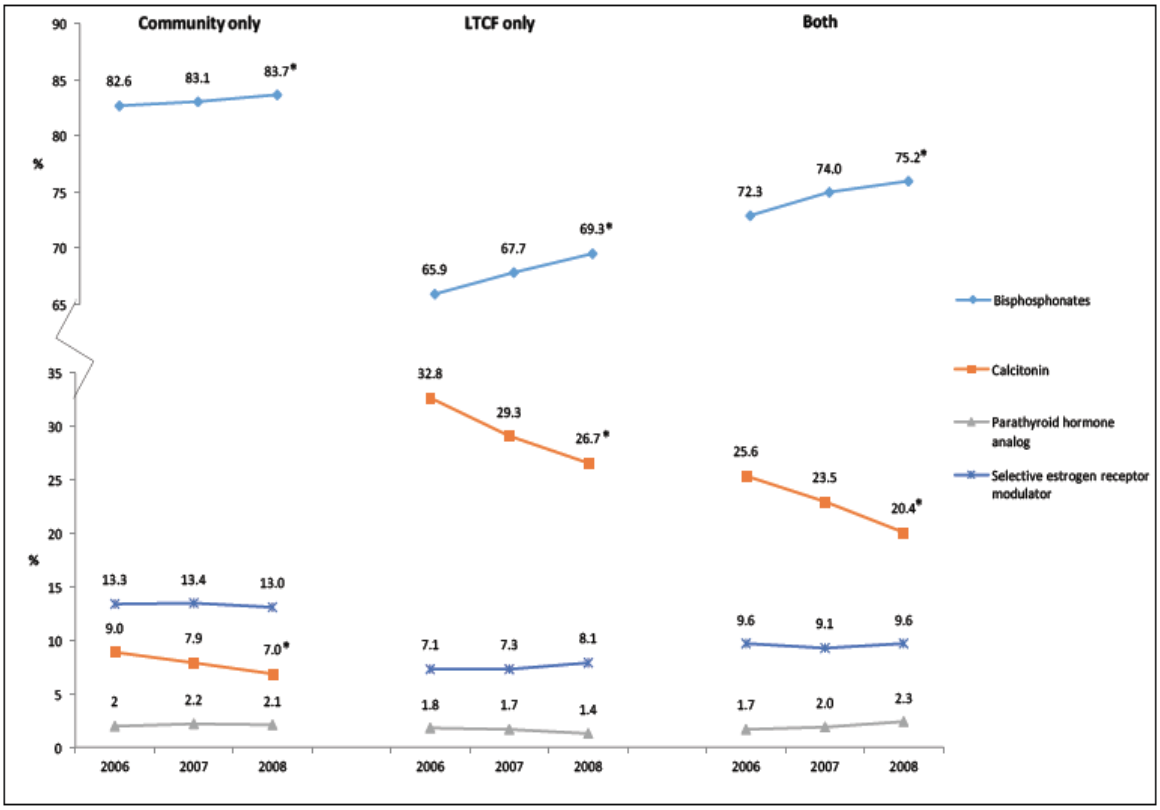
Table 5.3. ***Continued***

Prior hip fracture	8.8	7.6	6.6	18.2*	20.4*	21.1*
Diabetes mellitus	26.5	25.9	25.5	26.9	26.1	26.2
Rheumatoid arthritis/osteoarthritis	53.8	53.3	52.6	57.4*	56.3*	55.8*
Congestive heart failure	31.0	28.7	26.7	37.0*	34.0*	31.4*
Depression	30.4	29.0	27.2	37.9*	34.5*	32.8*
End-stage renal disease	0.3	0.2	0.1	0.6*	0.5*	0.3*
COPD	24.0	22.8	21.5	27.2*	26.3*	24.9*
Breast cancer	7.0	6.9	7.0	5.7*	5.9*	5.9*
Medications causing or contributing to osteoporosis and fractures						
Anticonvulsants	13.2	12.1	11.6	16.3*	14.4*	13.9*
Cancer chemotherapy	6.6	5.6	4.9	6.9	5.6	4.6
Glucocorticoids	22.1	21.0	20.2	22.5	21.9	20.5
Risk factors for fall						
Alzheimer's/dementia	21.9	19.2	16.5	30.4*	25.8*	22.5*
Glaucoma	23.5	23.9	23.9	22.2*	22.6*	22.5*
Stroke	16.1	15.0	14.0	19.3*	17.2*	16.0*
Contraindications of bisphosphonates						
Chronic kidney disease	11.0	9.9	9.1	13.5*	12.0*	11.3*
Any other contraindications of bisphosphonates	7.2	7.5	7.6	6.5	6.9	7.2
Side effects of bisphosphonates						
GI problems	21.8	21.4	21.0	29.5*	29.6*	29.4*
Any other side effects of bisphosphonates	48.8	50.3	50.9	48.6	48.3*	49.5
Number of chronic medications used per month (sd)	3.7 (2.4)	3.6 (2.4)	3.5 (2.3)	4.1* (2.6)	4.1* (2.6)	3.9* (2.6)
Receipt of BMD testing	23.9	24.6	25.2	26.9*	26.1*	26.2*
Death rate of the year	8.4	8.6	8.1	11.3*	11.6*	11.4*

*Difference between bisphosphonate users and non-bisphosphonate users are significant at α=0.05 level

Bisphosphonates were the most commonly prescribed medication for osteoporosis regardless of residential status (Figure 5.3). Bisphosphonate use was the highest among subjects with only community exposure (82.6% in 2006 to 83.7% in 2008), followed by those in both settings (72.3% in 2006 to 75.2% in 2008), and last among LTC residents (65.9% in 2006 to 69.3% in 2008). Calcitonin was much more likely to be prescribed to subjects with at least some LTC exposure (20.4% to 32.8%) compared to those with only community exposure (7% to 9%). Use of raloxifene was much higher among community-only residents (slightly more than 13%) compared to those in LTC only and in both settings (7.1% to 9.6%).

Figure 5.3. Patterns of Osteoporosis Medication Use Among Female Drug Users by Year, Residential Status, and Drug Class



Note: *Difference between 2006 and 2008 significant at α=0.05 level.

In adjusted analyses, having any LTC exposure significantly decreased the probability of receiving osteoporosis medications (Table 5.4). Compared to subjects with only community exposure, those in both settings were 4% less likely (95% CI [0.94, 0.99]) and those in LTC facilities were 11% less likely (95% CI [0.87, 0.91]) to receive any evidence-based osteoporosis medication. The interaction terms of residential status and year indicate declines over time for LTC-only residents compared to community-only residents. In addition, advanced age, being LIS recipients or Medicare-Medicaid dual eligible, having comorbidities that cause or contribute to osteoporosis and bone fractures besides prior hip fracture and breast cancer, chronic kidney disease and GI problems were all associated with lower probabilities of receiving osteoporosis medications.

Table 5.5 presents adjusted results for type of medication use (non-bisphosphonates versus bisphosphonates). Compared to osteoporosis medication users with only community exposure, those in both settings were 21% more likely (95% CI [1.15, 1.27]) and those with only LTC exposure were 26% more likely (95% CI [1.20, 1.33]) to receive non-bisphosphonates. Two of the interaction terms reached statistical significance indicating that non-bisphosphonate use declined more rapidly among subjects residing in both residential settings in 2008 (RR 0.92, 95% CI [0.87, 0.98]) and rose among subjects residing in LTCs in 2008 (RR 1.05, 95% CI [1.00, 1.09]) compared to community-only residents in 2006. In addition to residential status, being older was associated with increased probability of getting non-bisphosphonates whereas being non-white significantly reduced the likelihood of receiving these medications compared to bisphosphonates. Among the disease factors, having end-stage renal disease was a strong predictor of receiving non-bisphosphonates (RR 1.63, 95% CI [1.40, 1.91]).

Table 5.4. Estimated Effects of Residential Status and Other Potential Predictors on Use of Any Evidence-Based Osteoporosis Medication among Female Medicare Part D Enrollees with Osteoporosis or Prior Hip Fracture

	Test for Main Effects		Test for Temporal Effects	
	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Residential status				
Community only (ref)				
LTCF only	0.86	(0.84-0.88)*	0.89	(0.87-0.91)*
Both	0.97	(0.96-0.99)*	0.96	(0.94-0.99)*
Year				
2006 (ref)				
2007	1.01	(1.00-1.01)*	1.01	(1.00-1.01)*
2008	1.01	(1.01-1.02)*	1.02	(1.01-1.03)*
Residential status x year				
LTCF only x 2007	-	-	0.96	(0.94-0.98)*
LTCF only x 2008	-	-	0.93	(0.91-0.96)*
Both x 2007	-	-	1.03	(1.01-1.06)*
Both x 2008	-	-	0.99	(0.96-1.01)
Age				
70-79 (ref)				
80-89	1.00	(0.99-1.01)	1.00	(0.99-1.00)
90+	0.93	(0.91-0.94)*	0.93	(0.91-0.94)*
Race/ethnicity				
White (ref)				
Black	0.79	(0.76-0.81)*	0.79	(0.76-0.81)*
Hispanic	1.19	(1.16-1.23)*	1.19	(1.16-1.23)*
Other	1.45	(1.42-1.49)*	1.45	(1.42-1.49)*
Geographic region				
Northeast (ref)				
Midwest	1.02	(1.00-1.04)*	1.02	(1.00-1.04)*
South	0.96	(0.95-0.98)*	0.96	(0.95-0.98)*
West	1.06	(1.04-1.08)*	1.06	(1.04-1.08)*
Socioeconomic status				
Non-LIS recipient (ref)				
Low income subsidy (LIS) recipient but non-dual	0.91	(0.88-0.93)*	0.91	(0.88-0.93)*
Medicare/Medicaid dual eligibility	0.91	(0.90-0.92)*	0.91	(0.90-0.92)*
RxHCC count	1.02	(1.02-1.02)*	1.02	(1.02-1.02)*
Comorbidities causing or contributing to osteoporosis and fractures				
History of hip fracture	0.98	(0.97-1.00)	0.99	(0.97-1.00)
Diabetes mellitus	0.83	(0.82-0.84)*	0.83	(0.82-0.84)*
Rheumatoid arthritis/osteoarthritis	0.98	(0.97-0.99)*	0.98	(0.97-0.99)*

Table 5.4. ***Continued***

	Test for Main Effects		Test for Temporal Effects	
	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Congestive heart failure	0.84	(0.83-0.84)*	0.84	(0.83-0.85)*
Depression	0.90	(0.89-0.91)*	0.90	(0.89-0.91)*
End-stage renal disease	0.66	(0.61-0.72)*	0.66	(0.61-0.72)*
COPD	0.94	(0.93-0.95)	0.94	(0.93-0.95)
Breast cancer	1.00	(0.98-1.02)*	1.00	(0.98-1.02)*
Medications causing or contributing to osteoporosis and fractures				
Anticonvulsants	0.99	(0.97-1.00)*	0.99	(0.97-1.00)*
Cancer chemotherapy	1.06	(1.04-1.07)*	1.06	(1.04-1.07)*
Glucocorticoids	1.04	(1.03-1.05)*	1.04	(1.03-1.05)*
Risk factors for fall				
Alzheimer's/dementia	0.92	(0.91-0.93)*	0.92	(0.91-0.93)*
Glaucoma	0.99	(0.98-1.00)	0.99	(0.98-1.00)
Stroke	0.89	(0.88-0.90)*	0.89	(0.88-0.90)*
Contraindications of all osteoporosis medications				
Chronic kidney disease	0.90	(0.88-0.91)*	0.90	(0.89-0.91)*
Any other contraindications of all osteoporosis medications	1.00	(0.99-1.01)	1.00	(0.99-1.01)
Side effects of all osteoporosis medications				
GI problems	0.97	(0.97-0.98)*	0.97	(0.97-0.98)*
Any other side effects of all osteoporosis medications	1.03	(1.02-1.03)*	1.03	(1.02-1.03)*
Number of chronic medications used per month	1.08	(1.08-1.08)*	1.08	(1.08-1.08)*
Receipt of BMD testing	1.24	(1.23-1.25)*	1.24	(1.23-1.25)*
Death	1.21	(1.20-1.23)*	1.22	(1.20-1.24)*

*P<0.05

In the sensitivity analysis excluding decedents, we found results similar to that in our main analysis. Prevalence of osteoporosis medication use was slightly higher (from 46.8% in 2006 to 42.5% in 2008) than that in the sample with decedents (results not shown). Among evidence-based osteoporosis medication users, bisphosphonates were the top prescribed medications and the prevalence of bisphosphonate use was slightly higher (from 82.3% in 2006 to 82.6% in 2008) than that in the sample with decedents (results not shown). Compared to subjects with only community exposure, those in both settings

were equally likely (95% CI [0.95, 1.01]) and those only in LTC facilities were 11% less likely (95% CI [0.87, 0.91]) to receive any evidence-based osteoporosis medication (results not shown). Compared to osteoporosis medication users with only community exposure, those in both settings were 21% more likely (95% CI [1.14, 1.28]) and those with only LTC exposure were 33% less likely (95% CI [1.27, 1.40]) to receive non-bisphosphonates (results not shown).

Table 5.5. Estimated Effects of Residential Status and Other Potential Predictors on Use of Non-Bisphosphonates among Female Osteoporosis Medication Users

	Test for Main Effects		Test for Temporal Effects	
	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Residential status				
Community only (ref)				
LTCF only	1.32	(1.26-1.38)*	1.26	(1.20-1.33)*
Both	1.15	(1.10-1.20)*	1.21	(1.15-1.27)*
Year				
2006 (ref)				
2007	0.98	(0.97-0.99)*	0.98	(0.96-0.99)*
2008	0.94	(0.93-0.96)*	0.94	(0.92-0.96)*
Residential status x year				
LTCF only x 2007	-	-	1.00	(0.97-1.03)
LTCF only x 2008	-	-	1.05	(1.00-1.09)*
Both x 2007	-	-	0.96	(0.91-1.01)
Both x 2008	-	-	0.92	(0.87-0.98)*
Age				
70-79 (ref)				
80-89	1.03	(1.01-1.06)*	1.04	(1.02-1.07)*
90+	1.13	(1.08-1.17)*	1.13	(1.09-1.17)*
Race/ethnicity				
White (ref)				
Black	0.71	(0.64-0.78)*	0.74	(0.68-0.80)*
Hispanic	0.62	(0.56-0.69)*	0.63	(0.57-0.70)*
Other	0.92	(0.85-0.99)*	0.92	(0.85-1.00)*
Geographic region				
Northeast (ref)				
Midwest	1.02	(0.97-1.08)	1.02	(0.97-1.07)
South	1.15	(1.10-1.20)*	1.14	(1.09-1.19)*
West	0.90	(0.84-0.95)*	0.89	(0.84-0.94)*

Table 5.5. ***Continued***

	Test for Main Effects		Test for Temporal Effects	
	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Socioeconomic status				
Non-LIS recipient (ref)				
Low income subsidy (LIS) recipient but non-dual	1.02	(0.96-1.10)	1.04	(0.98-1.12)
Medicare/Medicaid dual eligibility	1.06	(1.02-1.10)*	1.05	(1.01-1.09)*
RxHCC count	1.00	(0.99-1.00)*	1.00	(0.99-1.00)*
Comorbidities causing or contributing to osteoporosis and fractures				
History of hip fracture	1.04	(0.99-1.09)	1.05	(1.01-1.09)*
Diabetes mellitus	1.00	(0.97-1.03)	0.99	(0.96-1.02)
Rheumatoid arthritis/osteoarthritis	1.03	(1.00-1.06)	1.03	(1.00-1.06)
Congestive heart failure	1.03	(1.00-1.06)	1.03	(1.01-1.06)*
Depression	1.08	(1.05-1.11)*	1.07	(1.04-1.10)
End-stage renal disease	1.82	(1.49-2.21)*	1.63	(1.40-1.91)*
COPD	1.06	(1.03-1.10)	1.05	(1.02-1.09)
Breast cancer	0.88	(0.83-0.94)	0.89	(0.84-0.94)
Medications causing or contributing to osteoporosis and fractures				
Anticonvulsants	1.00	(0.97-1.03)	0.99	(0.96-1.02)
Cancer chemotherapy	0.98	(0.93-1.02)	0.96	(0.92-1.01)
Glucocorticoids	0.99	(0.96-1.01)	0.98	(0.96-1.00)*
Risk factors for fall				
Alzheimer's/dementia	1.07	(1.03-1.10)*	1.07	(1.03-1.10)*
Glaucoma	0.98	(0.95-1.02)	0.99	(0.96-1.03)
Stroke	1.02	(0.98-1.05)	1.02	(0.99-1.06)
Contraindications of all osteoporosis medications				
Chronic kidney disease	1.04	(1.01-1.07)*	1.02	(0.99-1.05)
Any other contraindications of bisphosphonates	0.95	(0.87-1.02)	0.95	(0.89-1.03)
Side effects of bisphosphonates				
GI problems	1.02	(1.00-1.04)*	1.03	(1.01-1.05)*
Any other side effects of bisphosphonates	1.01	(0.99-1.03)	1.01	(0.99-1.02)
Number of chronic medications used per month	1.00	(1.00-1.01)	1.01	(1.00-1.01)*
Receipt of BMD testing	0.90	(0.89-0.91)*	0.90	(0.89-0.91)*
Death	0.98	(0.94-1.01)	0.98	(0.94-1.01)

*P<0.05

In the sensitivity analysis restricted to those with a diagnosis of osteoporosis, we found results somewhat different from that in our main analysis. Prevalence of osteoporosis medication use was slightly higher (from 44.3% in 2006 to 42.0% in 2008) than that in the sample with those who had a diagnosis of hip fracture (Appendix Figure 2). Among evidence-based osteoporosis medication users, bisphosphonates were the top prescribed medications and the prevalence of bisphosphonate use was similar (from 80.5% in 2006 to 82.1% in 2008) to that in the sample including those who had a diagnosis of hip fracture (Appendix Figure 3). Compared to subjects with only community exposure, those only in LTC facilities and those in both settings were more likely (RR 1.27, 95% CI [1.24, 1.31] for those only in LTC facilities and RR 1.26, 95% CI [1.22, 1.29] for those in both settings) to receive any evidence-based osteoporosis medication (Appendix Table 8). Compared to osteoporosis medication users with only community exposure, those only in LTC facilities and those in both settings were more likely (RR 1.27, 95% CI [1.21, 1.33] for those with only LTC exposure and RR 1.21, 95% CI [1.15, 1.27] for those in both settings) to receive non-bisphosphonates (Appendix Table 9).

5.4 Discussion

This is the first US national study to compare patterns of evidence-based osteoporosis medication use among elderly women residing in the community and LTC facilities under the auspices of the Medicare Part D program. We found that prevalence of osteoporosis medications was low (less than 50%) in both community dwellers and LTC residents, but was especially low among LTC residents (below 35%). By contrast, Loh et al.[80] found that in 2003, 52.1% of elderly community dwellers and 49.3% of LTC

residents with osteoporosis enrolled in the Medicare program received osteoporosis pharmacotherapy. By that standard, there has been a huge decline over time. This is the opposite of our expectation that Medicare Part D would improve access to necessary medications and thus increase use of osteoporosis medications. Furthermore, the gap in prevalence of evidence-based osteoporosis medication use by residence status has grown from about 3 percentage points in 2003 in the previous study to more than 14 percentage points in 2008 based on our findings. We found that community dwellers and LTC residents differed substantially in age, comorbidities, and contraindications of osteoporosis medications, especially chronic kidney disease. These factors may influence a physician's decision to prescribe an evidence-based osteoporosis medication to the elderly population. After adjusting for these factors at the baseline, we found that LTC residents were still less likely to receive osteoporosis medications. This finding suggests that the difference in osteoporosis medication use between LTC residents and community dwellers may be due to nursing home or physician-level factors that are unobservable in our data.

Cost, medication adverse effects, and competing patient comorbidities are the most commonly cited factors limiting osteoporosis treatment in the literature [88, 89]. Cost may be less of an issue for accessing necessary drug treatments in this population since it is covered by Part D. Among adverse effects, GI problems are common for bisphosphonate use. One study found that GI problems were more common among women with bisphosphonate use and were associated with treatment discontinuation[90]. In the current study, we found that GI problems only slightly decreased the probability of any treatment use and increased the probability of non-bisphosphonate use, regardless of

beneficiaries' residential status. Regarding competing patient comorbidities, we found that most of the comorbidities contributing to osteoporosis or bone fracture decreased the probability of receiving any osteoporosis treatment.

The especially low prevalence of osteoporosis medication use in LTC residents represents a missed opportunity for treatment of osteoporosis. Conventional thinking is that with their shorter life expectancy, it is not worthwhile to initiate osteoporosis medications in LTC residents. However, LTC residents were more likely to have osteoporosis[81] and fracture[17, 18] than their counterparts in the community. Even after taking the life expectancy into account, the results of our sensitivity analysis showed that the prevalence of osteoporosis medication use was not much higher among those who survived through our study period. A previous study found that reimbursement concerns, state oversight of the number of medications prescribed, and high nursing staff turnover were barriers to providing osteoporosis care in nursing facilities[91]. To the extent that remains true, policy makers should work to remove barriers to increase use of evidence-based osteoporosis medications among LTC residents. Physicians should also pay more attention to osteoporosis management for LTC residents and consultant pharmacists may be able to take advantage of the opportunity of periodic and complete medication review to facilitate osteoporosis medication use.

It is important to note that even within LTCs, the prevalence of osteoporosis treatment may differ substantially. One study found that with an average of 5.5% prevalence of treatment, wide variation existed between individual nursing facilities (0-40%)[14]. In this study, we only explored the impact of a limited set of LTC residents' characteristics on osteoporosis medication use. Future research is needed to investigate

the effect of other LTC residents' characteristics included in the MDS as well as characteristics of nursing home themselves (e.g. ownership status of LTC facilities).

Osteoporotic fractures are sustained through falls. Therefore, it is important to consider the factors that increase the risk for falling. In this study we captured Alzheimer's disease/dementia, glaucoma and stroke as risk factors for fall but only found small, mixed effects on osteoporosis treatment. The effects of these factors are small and mixed may be due to the different level of emphasis on fall put by physicians of community dwellers and LTC residents. Falling is an important quality measure of long stay residents in the current Medicare's 5-star rating for nursing homes. Therefore, LTC facilities may emphasize more on fall prevention than pharmacologic treatment when preventing osteoporotic fractures from happening on their residents. This effect may decrease the likelihood of medication use in LTC residents. CMS may consider also incorporating osteoporosis as one of the quality measures in the Medicare Nursing Home Compare to promote better osteoporosis management in LTC facilities.

Another important issue related to residential status is care transition. Treatment patterns may change during a movement from one healthcare setting to another or to home. Necessary treatment may be missed during this transition. In this study, we included switchers between community and LTC facilities but did not emphasize on the change during transition of residential status. We found that switchers behaved more like LTC residents than community dwellers in terms of osteoporosis medication use. Future research is necessary to investigate how treatment patterns change during the transition of residential status by focusing on the switchers.

In terms of choice of treatment, although we found that bisphosphonates were the top prescribed medication to women with osteoporosis, regardless of residential status, LTC residents were more likely to use non-bisphosphonates compared to community dwellers. Use of calcitonin was much higher among LTC residents. This is a concern given the lack of evidence that calcitonin is effective in reducing bone fractures. This lack of evidence was known before 2008 and may have been responsible for the relative declines in calcitonin use during our study period. Since that time a 2012 AHRQ review determined that calcitonin was not appropriate therapy for osteoporosis[92], and in 2013, a FDA panel voted that the risks of calcitonin salmon outweigh the benefits for the treatment of postmenopausal osteoporosis due to the higher rates of cancer among patients taking calcitonin[93]. These decisions are expected to affect the choice of osteoporosis medication of many osteoporotic patients, especially those in LTCs. Nonetheless, calcitonin has been shown to have an analgesic effect in acute vertebral fractures[94] and remains an alternative for patients with isolated spine osteoporosis or who have painful acute vertebral fracture and cannot tolerate other drugs. Future research will be needed to investigate change in patterns of evidence-based osteoporosis medication use after the FDA panel's decision.

Even though this study did not include ibandronate and zoledronic acid injections in the analyses due to the low rates of use during the study period, it is reasonable to suspect that the availability of those two injectable bisphosphonates may change patterns of osteoporosis therapy over time. Indeed, these two drugs may be good candidate for treating osteoporotic patients without contraindications of bisphosphonates but with difficulty taking oral medications. Moreover, with Part B coinsurance typically picked up

by Medicare supplements, these two drugs may be more affordable than some Part D covered drugs.

Other recent events are also likely to change future treatment patterns for osteoporosis. The first event is generic bisphosphonates coming to the market. The first FDA approved bisphosphonate, alendronate, lost its patent protection in 2008 and generic alendronate is now a staple on the market. Subsequently, risedronate's patent expired in 2012 and generic risedronate is now widely available. Availability of generic bisphosphonates significantly lowers the price of osteoporosis treatment which in turn may change patients' use and choice of osteoporosis medication. One study has found that 81% of branded alendronate users and 10% of risedronate users switched to generic alendronate in 2008[95].

The second event is the launch of a new class of osteoporosis drug- receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors in 2010. The first RANKL inhibitor, denosumab, is indicated of treatment of osteoporosis in postmenopausal women at higher risk for fracture and/or with breast cancer. Denosumab is a once every 6 months subcutaneous injection covered by Part B and is recommended as first-line therapy along with bisphosphonates by the 2010 American Association of Clinical Endocrinologist Medical guidelines[96]. Future research is necessary to establish how these events have changed osteoporosis treatment, and even more importantly, whether they are effective in reducing the burden of osteoporosis-related bone fractures on our health care system.

This study has several limitations. First, while the study only tracked osteoporosis treatment patterns through 2008, it provides important information about how

osteoporosis was treated during the formative years of the Medicare Part D program. Second, the CCW provides data on drug use only for Medicare Part D enrollees. Therefore, the study findings may not generalize to Medicare beneficiaries not enrolled in Part D. Also, MAPD enrollees were excluded because they did not generate Part A and B claims necessary for identifying evidence of osteoporosis. Use and choice of osteoporosis medication may differ between MAPD and PDP enrollees, and therefore, the findings of this study may not be generalizable to MAPD enrollees, either. Fourth, drug use during beneficiaries' Part A covered hospitalization and post-acute skilled nursing facility (SNF) stays was not observed due CMS reimbursement policy, and any osteoporosis treatments during these periods were not observed. Therefore, we may underestimate medication use because patients may initiate treatment during hospital stay but discontinue after discharge. This is especially likely to happen among community dwellers and thus bias our estimate of difference in drug use between community dwellers and LTC residents toward the null. Fifth, use of chronic kidney disease as a contraindication of bisphosphonates may have introduced bias. The exact contraindication of bisphosphonates is *Creatinine Clearance* (CrCl) < 30 mL/min. However, the actual CrCl value is not available in the CCW, thus we can only use diagnosis of chronic kidney disease as a proxy and the result of chronic kidney disease's impact on treatment use are biased toward the null. Perhaps most significant of all, while osteoporosis guidelines suggest initiating use of calcium and vitamin D for all institutionalized patients able to tolerate it[97], Part D does not cover over-the-counter medications and thus we have systematically underestimated the degree to which LTC residents (and community residents as well) received any osteoporosis treatment.

In conclusion, female Medicare Part D enrollees are undertreated for osteoporosis whether they reside in the community or LTC facilities, but long-term nursing home residents are more likely to be treated with non-bisphosphonates. Policy makers and clinicians should work together to reduce these differentials and the attendant clinical and economic burden of osteoporosis on these vulnerable populations.

6 Differences in Evidence-Based Osteoporosis Medication Use between Elderly Men and Women Enrolled in Medicare Part D

6.1 Introduction

Among all patients diagnosed with osteoporosis, approximately 20% are men and 80% are women.[76] Despite the huge difference in prevalence between men and women, men are treated less often than women even when diagnosed with osteoporosis. The prevalence of osteoporosis medication use ranges from 7.1% to 27% in men compared to 4.6% to 50% in women[33, 80] despite the fact that osteoporosis treatment guidelines recommend initiation of pharmacologic therapy in both men and women who have bone mineral density (BMD) T-scores ≤-2.5 at the femoral neck or spine by dual-energy x-ray absorptiometry (DXA) and those who have experienced fragility fractures.[20, 98] The lower medication use rate in men may be owing to the lack of awareness of osteoporosis and its consequences in men.[99] Osteoporosis is an asymptomatic disease and has long been seen as a women's disease; therefore, men may not be aware of osteoporosis and its related bone fractures and thus do not pursue care. Even if men pursue care, their physicians may lack awareness of osteoporosis in men and thus do not properly screen and diagnose the disease. Under-diagnosis of osteoporosis is an issue in men. But even when diagnosed with osteoporosis, there are fewer evidence-based medications available for men. Among all evidence-based osteoporosis medications, only 3 classes are indicated for men while 4 are indicated for women.

Men diagnosed with osteoporosis have a higher risk of bone fracture[100] compared to women and suffer more severe outcomes after having a bone fracture.[101, 102] Twenty-

eight percent of hip fractures in the United States occur in men[100], and mortality after hip fractures is doubled in men as compared to in women.[101, 102]

Besides disparities in osteoporosis care between men and women, there is also a gap in research addressing osteoporosis management in men and women. The vast majority of osteoporosis research to date has focused on women. Few studies have been conducted in men, one comparative study between men and women has been conducted and no comparative study between men and women in the Medicare population has been published.

In this study, we examined how use of evidence-based osteoporosis medications differed by sex in the Medicare Part D enrollees from 2006 through 2008. Based on the few comparative research studies on osteoporosis[103, 104], we hypothesized that men would be less likely to receive any osteoporosis treatment, and among men receiving osteoporosis treatment, more would receive bisphosphonates. The study results will provide baseline information of clinical differences in osteoporosis treatment use in men and women in the early years of the Medicare Part D drug benefit and to identify challenges and future direction for treatment of osteoporosis, especially in the male Medicare population.

6.2 Methods

6.2.1 Data and sample selection

Medicare enrollment and claims data for the study were obtained from the 2006-2008 Chronic Condition Data Warehouse (CCW) for a 5% national random sample of beneficiaries.[85] The study sample included Medicare beneficiaries aged 70 years and older with evidence of osteoporosis prior to January 1, 2006. Setting the minimum age at

70 enabled the construction of a 5-year look-back window to check beneficiaries' history of osteoporosis. Evidence of osteoporosis was defined using the CCW algorithm of at least one inpatient, outpatient or physician claim with ICD-9 diagnosis codes 733.00, 733.01, 733.02, 733.03, 733.09. The study sample was also restricted to beneficiaries with continuous enrollment in Medicare Part A, B and a Part D stand-alone prescription drug plan (PDP) from January 1, 2006 through December 31, 2008, or death. The sample excluded (1) Medicare Advantage Prescription Drug (MAPD) plan enrollees from 2006 to 2008, (2) beneficiaries not enrolled in Part D from 2006 to 2008, and (3) long-term care (LTC) facility residents whose admission or discharge date could not be identified. MAPD plan enrollees were excluded because they lacked Part A and B claims files necessary for identifying diagnosis and utilization of Medicare services. Non-Part D enrollees were excluded because they lacked prescription drug data. LTC residents with missing admission or discharge dates were excluded because they lacked data necessary for sample classification by residence.

6.2.2 Drug measures

Outcomes of interest were dichotomized variables indicating use of any osteoporosis medications among individuals diagnosed with osteoporosis and use of non-bisphosphonates among osteoporosis medication users. Use of osteoporosis medications listed in the 2008 National Osteoporosis Foundation (NOF) guidelines was identified by National Drug Codes (NDCs) in the Part D prescription drug event (PDE) file using the FirstDataBank drug dictionary and by the Healthcare Common Procedure coding System (HCPCS) codes in the Part B claims file for Part B covered osteoporosis drugs. The 2008 NOF guidelines were used because they were the most relevant guidelines for the study

period. It should be noted that estrogen is sometimes used as treatment of osteoporosis; however, the Food and Drug Administration (FDA)-approved indication is only for prevention of osteoporosis, so use of estrogens was not included in this study. In preliminary analyses, we found fewer than 1% of study subjects used Part B covered ibandronate sodium and zoledronic acid injections during the study period, so use of those two Part B covered drugs was not included in the final analysis. The unit of observation for osteoporosis medication use was person-year. One or more fills in a given year was considered as having any use in that specific year. Osteoporosis drugs used during Medicare covered hospitalizations and skilled nursing facility (SNF) stays could not be considered as they are covered under Part A and are thus not observable in the PDE file.

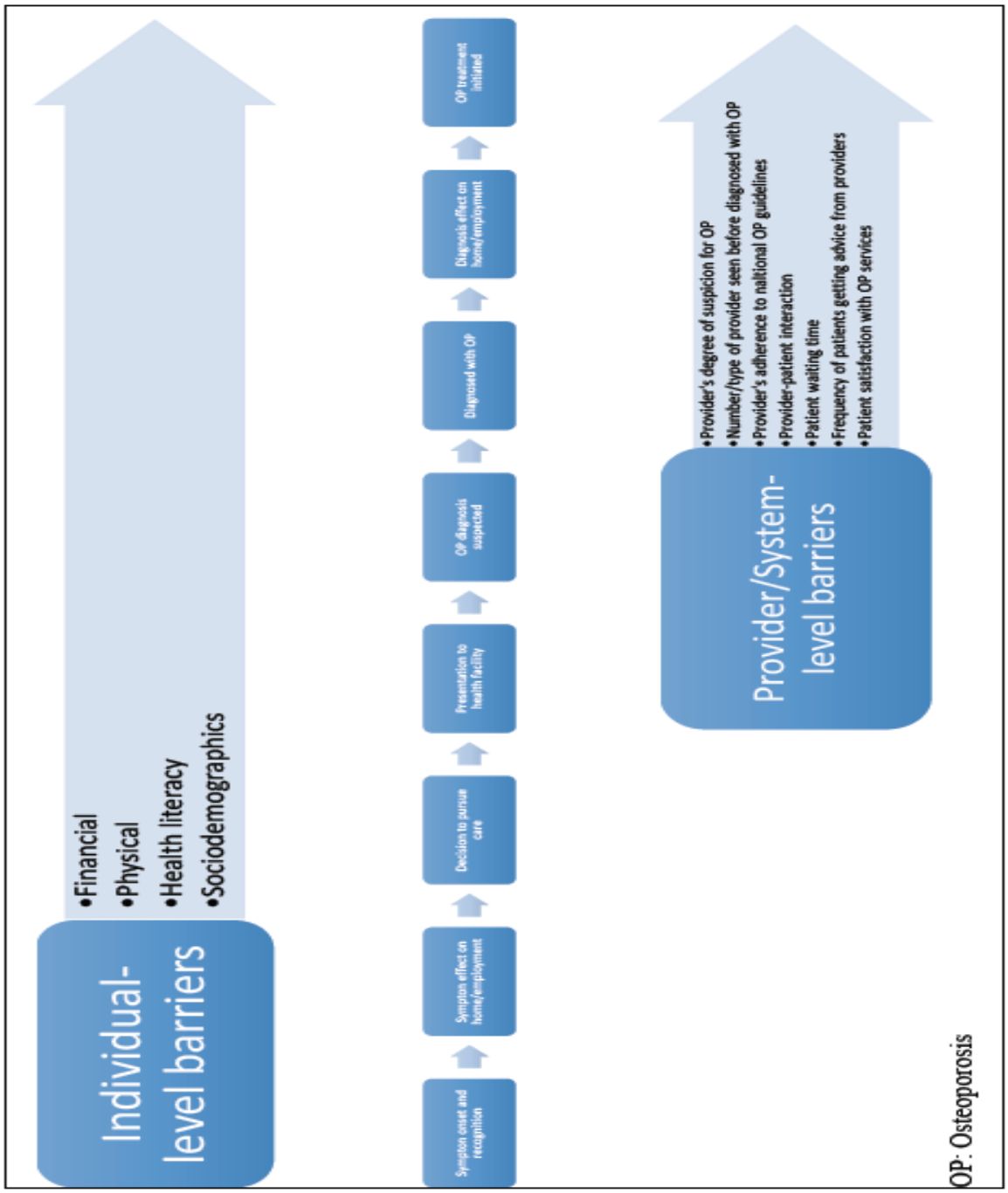
6.2.3 Other measures

The primary independent variable is sex. A conceptual framework for treatment of osteoporosis originally developed by Krishman et al. for tuberculosis treatment[105] was adapted to guide inclusion of other measures (see Figure 6.1). These measures included demographics (age, race/ethnicity, and geographic region), and residential status (categorized as community only, LTC only, and both using the minimum data set (MDS) together with inpatient and SNF claims). Socioeconomic status was captured via indicators of Medicare-Medicaid dual eligibility and receipt of Part D low-income subsidy (LIS). General health status was represented by counts of conditions from the prescription drug hierarchical condition categories (RxHCC) risk adjustment measure developed by the Center for Medicare and Medicaid Services (CMS). Indicators for conditions and medications that may cause or contribute to osteoporosis and bone

fractures and risk factors for fall were selected based on the 2008 NOF guidelines.[78] Disease factors included prior hip fracture, diabetes mellitus, rheumatoid arthritis/osteoarthritis, congestive heart failure (CHF), depression, end stage renal disease (ESRD), chronic obstructive lung disease (COPD), and breast cancer, all defined by CCW diagnostic algorithms.[86] Commonly used medications that may cause or contribute to osteoporosis and bone fractures included anticonvulsants, cancer chemotherapy and glucocorticoids. Risk factors for fall included Alzheimer's disease/dementia, glaucoma (as proxy for poor vision), and stroke (as proxy for poor balance). FDA approved package inserts were used to identify possible contraindications/medication side effects that may influence osteoporosis medication choices (list provided in Appendix Table 4). The most common contraindication for osteoporosis medications is chronic kidney disease. The main side effect is GI problems. Other contraindications and side effects from the FDA inserts were identified in Medicare claims and reported as summary dummy variables. We measured number of other chronic medications used per month as an indicator of pill burden, as a high number of other chronic medications used per month may cause individuals unable to manage multiple medications, burden individuals with the cost of multiple medications, or cause physicians to prioritize other conditions over osteoporosis management. Finally, we captured receipt of bone mineral density (BMD) testing as an indicator of osteoporosis management. We hypothesized that factors that increase risk of osteoporosis and/or falls would be positively associated with use of any osteoporosis medication, while contraindications for osteoporosis medications would be negatively associated with use of any pharmacologic treatment for osteoporosis. Among those receiving any osteoporosis medication, the choice of bisphosphonates vs. non-

bisphosphonates would be affected by contraindications or side effects of bisphosphonates.

Figure 6.1. Conceptual Framework Illustrating Barriers and Delays that Limit Osteoporosis Diagnosis and Treatment Services



Note: This conceptual framework was adapted from Krishnan et al. "Gender-Related Barriers and Delays in Accessing Tuberculosis Diagnostic and Treatment Services: A Systematic Review of Qualitative Studies."[105]

6.2.4 Statistical analysis

The descriptive analyses included, first, an examination of differences in characteristics between men and women among Part D enrollees with osteoporosis. For categorical variables, both Chi-square tests and t-tests were conducted but only the results of t-test were reported to show where the difference between men and women occurred. For numerical variables, t-tests were conducted. Next, we analyzed prevalence of any evidence-based osteoporosis medication use by sex and then by drug class (bisphosphonate, calcitonin, teriparatide, and raloxifene).

The multivariate analysis was driven by the following considerations. In the clinical decision-making process, a physician would normally first decide whether or not to prescribe any osteoporosis medication to a patient, then decide if the patient was a good candidate for bisphosphonates since bisphosphonates are the first-line medication recommended by clinical guidelines. The final clinical decision would be choice of specific bisphosphonate for good candidates for bisphosphonates or selection of an alternative medication (calcitonin, teriparatide, or raloxifene) based on considerations of contraindications and/or side effects. However, due to the relatively few non-bisphosphonate users in our sample, we were only able to model the first two steps in this clinical decision-making process.

We used modified Poisson regressions[87] with robust errors variance to estimate factors associated with any osteoporosis medication use, and among users, use of bisphosphonates versus non-bisphosphonates. We used Poisson rather than logistic regression in order to derive accurate measures of relative risk. When the probability of an outcome is extremely low or high, the odds ratio approximates relative risk; however,

when the probability of the outcome is common, conversion of an adjusted odds ratio to a relative risk produces inconsistent estimates of the true risk. All variables described in the measures section above were included as covariates. To understand the difference each factor had on drug use for men and women, we first conducted a full analysis with interaction terms between sex and age, race, and residential status. Significant coefficients on the interaction terms were justification for stratified analyses by sex, which were subsequently conducted. The analyses were conducted using SAS 9.3 with the REPEATED command to adjust the standard errors for multiple observations of the same individuals. The study protocol was approved by the University of Maryland Baltimore IRB.

6.3 Results

The final study sample included 99,421 Medicare beneficiaries aged 70 or older with a diagnosis of osteoporosis: 8,465 men and 90,956 women (Table 6.1). The overall prevalence of osteoporosis was 11% among men meeting the study inclusion criteria compared to 44% among women. Compared to women, men diagnosed with osteoporosis were younger, more likely to be Hispanic and Asian, in poorer health (i.e. higher RxHCC counts and higher rates of diabetes, CHF, end-stage renal disease, COPD, Alzheimer's disease/dementia, glaucoma, stroke, and chronic kidney disease), and at higher risk of death. Men were also more likely to use anticonvulsants, cancer chemotherapy, and glucocorticoids, but were less likely to have BMD tests.

Table 6.1. Baseline (2006 Characteristics of Medicare Part D Enrollees Aged 70+ Diagnosed of Osteoporosis, by Sex (N=99,421)

Beneficiary Characteristics	Women (N=90,956)	Men (N=8,465)
Demographic characteristics		
Age		
70-74	22.2	24.8*
75-79	25.1	28.1*
80-84	23.4	23.2
85-89	17.0	15.3*
90+	12.3	8.5*
Race/ethnicity		
White	84.9	77.3*
Black	6.2	5.0*
Hispanic	3.8	5.5*
Asian	3.5	9.5*
Other	1.6	2.6*
Geographic region		
Northeast	20.8	19.7*
Midwest	23.5	20.3*
South	39.9	34.5*
West	15.8	25.5*
Residential status		
Community only	79.3	80.2
LTCF only	9.9	8.2*
Both	10.8	11.7*
Socioeconomic status		
Non- Low income subsidy (LIS)	43.6	43.3
LIS recipient but non-dual	4.2	2.6*
Medicare/Medicaid dual eligibility	52.1	54.1*
Health Status		
RxHCC count (sd)	7.4 (3.6)	8.2* (3.9)
Comorbidities causing or contributing to osteoporosis and fractures		
Prior hip fracture	9.1	8.2*
Diabetes mellitus	31.1	41.3*
Rheumatoid arthritis/osteoarthritis	57.4	56.5
Congestive heart failure	38.2	49.2*
COPD	26.9	43.9*
Breast cancer	6.6	-
Prostate cancer	-	17.9*
Depression	35.7	32.5*
End-stage renal disease	0.6	1.3*

Table 6.1. ***Continued***

Beneficiary Characteristics	Women (N=90,956)	Men (N=8,465)
Medications causing or contributing to osteoporosis and fractures		
Anticonvulsants	14.2	17.5*
Cancer chemotherapy	6.2	11.7*
Glucocorticoids	20.7	24.7*
Risk factors for fall		
Alzheimer's/dementia	27.7	30.9*
Glaucoma	23.2	24.2*
Stroke	19.9	25.0*
Contraindications/side effects of all osteoporosis medications		
Chronic kidney disease	14.2	24.4*
Other contraindications of all osteoporosis medications	7.1	7.5
Side effects of all osteoporosis medications		
GI problems	23.8	22.9
Other side effects of all osteoporosis medications	45.7	38.2*
Number of chronic medications used per month (sd)	3.5 (2.5)	3.4* (2.6)
Receipt of BMD testing	15.2	9.9*
Died in 2006	10.1	14.2*
Died in 2007	10.0	12.9*
Died in 2008	9.8	11.9*

*Difference between men and women significant at α=0.05 level.

About three quarters of men and more than half the women with osteoporosis in our study sample received no osteoporosis drug treatment between 2006 and 2008 (Table 6.2). Treatment rates among women fell sharply with age from 47.7% (70-74) to 36.5% (90+), whereas the overall treatment rate for men differed little by age. There were marked differences in treatment rates by race/ethnicity. Among women, 64.4% of Asians were treated compared to 30.0% for blacks. Among men the rates were 37.9% treated for Asians and 15.5% among blacks. Women residing in nursing homes were less likely to be treated than those living in the community (34.9% vs 44.0%), but this relationship did not hold for men. For both sexes, the likelihood of receiving any osteoporosis treatment

and bisphosphonates in particular was much higher among Medicare beneficiaries with higher socioeconomic status (i.e., not receiving either Medicaid or LIS). As expected, given possible contraindications, Medicare beneficiaries with ESRD were least likely to be treated with bisphosphonates irrespective of sex, but there was no evidence that this led to a greater likelihood of treatment with non-bisphosphonates. Also as expected, osteoporosis medication rates were higher than average in both men and women receiving BMD testing, and bisphosphonate use was especially high in this group.

We also tracked changes in use of osteoporosis medications from 2006 to 2008 (see Figures 6.2 and 6.3). Overall, treatment rates ranged from 44.3% in 2006 to 42% in 2008 among women diagnosed with osteoporosis and from 25.2% in 2006 to 24.5% in 2008 among men (Figure A6.1). When stratified by drug class, bisphosphonates were the most commonly prescribed medication for osteoporosis for both men and women in all 3 years (Figure A6.2). Bisphosphonate use went up slightly (76.4% in 2006 to 78.3% in 2008 for women and from 91.3% in 2006 to 93.3% in 2008 for men. Calcitonin use went down slightly (11.6% in 2006 to 8.9% in 2008 for women and 10.4% in 2006 to 7.2% in 2008 for men). Use of raloxifene in women and parathyroid hormone in both men and women remained stable for all 3 years.

Table 6.2. Prevalence of Evidence-Based Osteoporosis Medication Use among Medicare Part D Enrollees Aged 70+ Diagnosed of Osteoporosis, By Sex and Drug Class Used in 2006

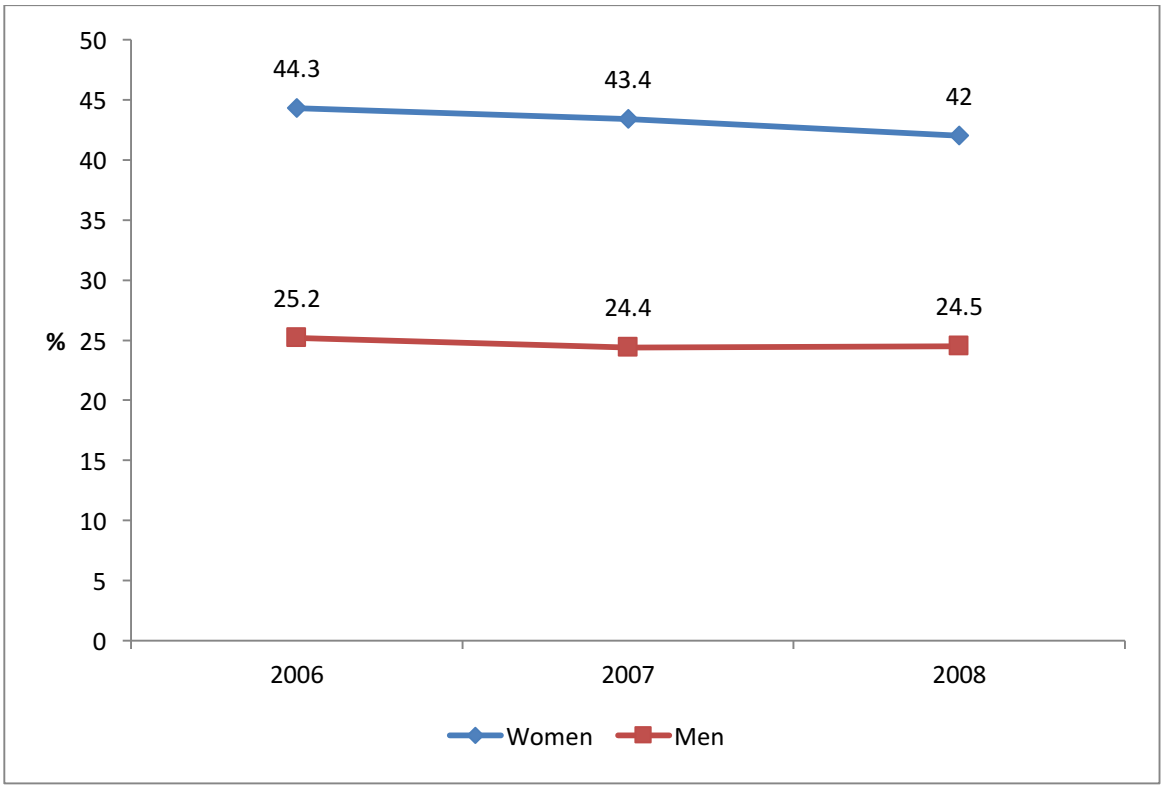
Beneficiary Characteristics	Women (N=90,956)			Men (N=8,465)		
	Any Treatment	Bisphosphonate Users	Non-Bisphosphonate Users	Any Treatment	Bisphosphonate Users	Non-Bisphosphonate Users
Overall prevalence	44.3	35.6	8.7	25.1	22.9	2.2
Demographic characteristics						
Age						
70-74	46.7	38.7	7.9	26.3	24.6	1.8
75-79	46.8	38.4	8.4	23.9	22.5	1.4
80-84	45.1	36.6	8.5	25.1	22.5	2.7
85-89	42.2	33.0	9.2	25.7	23.1	2.6
90+	36.5	26.3	10.2	24.6	20.2	4.5
Race/ethnicity						
White	44.4	35.4	9.0	24.5	21.9	2.6
Black	30.0	25.2	4.8	15.5	14.1	1.4
Hispanic	46.5	41.2	5.3	19.3	18.4	0.9
Asian	64.4	53.1	11.3	37.9	37.1	0.9
Other	52.0	43.8	8.2	27.9	26.9	1.0
Geographic region						
Northeast	44.0	35.6	8.4	25.5	22.5	3.1
Midwest	45.6	36.6	9.1	26.6	24.3	2.3
South	42.2	33.4	8.8	21.8	19.5	2.4
West	48.2	40.1	8.1	28.1	26.8	1.3
Residential status						
Community only	46.4	38.4	8.0	25.1	23.6	1.6
LTCF only	34.9	23.0	11.9	24.1	19.4	4.6
Both	37.5	27.1	10.4	25.7	20.4	5.3
Socioeconomic status						
Non- Low income subsidy (LIS)	48.3	39.7	8.6	25.6	24.0	1.6
LIS recipient but non-dual	39.3	30.9	8.5	19.5	18.1	1.4
Medicare/Medicaid dual eligibility	41.4	32.6	8.8	25.0	22.2	2.8
Comorbidities causing or contributing to osteoporosis and fractures						
Prior hip fracture	42.8	31.9	10.8	18.8	22.6	6.2
Diabetes mellitus	37.8	30.3	7.5	21.9	19.8	2.1

Table 6.2. ***Continued***

Rheumatoid arthritis/osteoarthritis	42.2	33.5	8.7	23.8	21.7	2.2
Congestive heart failure	37.1	28.8	8.4	22.2	19.8	2.4
Depression	39.3	30.2	9.1	24.1	20.7	3.5
End-stage renal disease	22.2	13.9	8.3	20.0	17.3	2.7
COPD	40.6	31.9	8.7	24.6	22.1	2.6
Breast cancer	45.5	38.0	7.5	-	-	-
Prostate cancer	-	-	-	26.1	24.4	1.7
Medications causing or contributing to osteoporosis and fractures						
Anticonvulsants	42.5	32.8	9.8	26.6	22.5	4.2
Cancer chemotherapy	47.1	37.6	9.5	29.1	27.3	1.8
Glucocorticoids	47.5	38.1	9.4	29.7	26.7	3.1
Risk factors for fall						
Alzheimer's/dementia	37.2	27.9	9.4	23.0	19.7	3.3
Glaucoma	44.5	36.2	8.4	24.9	22.9	2.0
Stroke	36.8	28.5	8.3	22.5	19.9	2.7
Contraindications of bisphosphonates						
Chronic kidney disease	35.4	27.2	8.2	22.3	20.0	2.3
Other contraindications of bisphosphonates	45.5	36.6	8.9	28.4	21.6	6.8
Side effects of bisphosphonates						
GI problems	43.5	32.7	10.9	26.0	22.7	3.3
Other side effects of bisphosphonates	51.8	41.6	10.1	31.8	29.1	2.7
Receipt of BMD testing	67.1	56.6	10.5	51.3	48.8	2.5
Died in 2006	37.5	28.2	9.3	29.6	25.1	4.5
Died in 2007	36.0	26.0	10.0	22.3	19.3	3.0
Died in 2008	38.0	28.1	9.9	23.3	19.9	3.4

Note: *Difference between men and women are significant at α=0.05 level

Figure 6.2. Prevalence of Evidence-Based Osteoporosis Medication Use among Medicare Part D Enrollees Aged 70+ Diagnosed of Osteoporosis, by Year and Sex

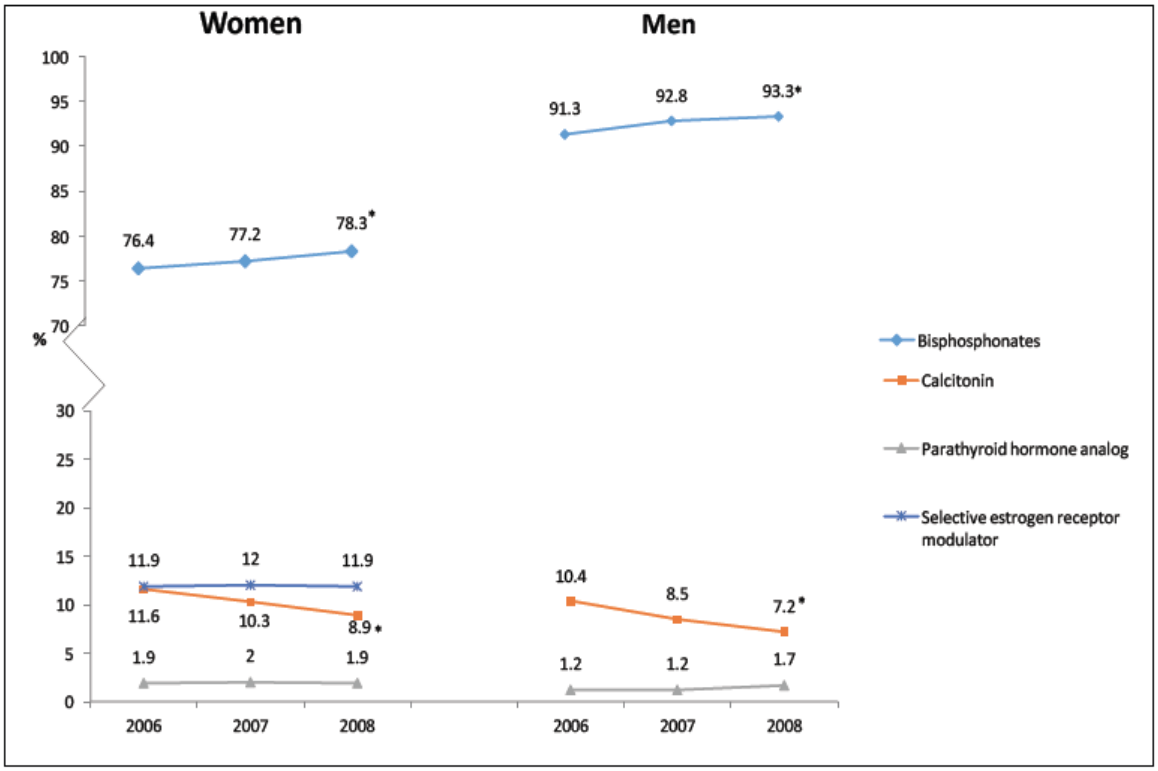


Note: *Difference between 2006 and 2008 significant at α=0.05 level.

In the initial adjusted analyses including both men and women, men had significantly lower probability of receiving osteoporosis medications (RR 0.20, 95% CI [0.19, 0.22]) (results not shown). Interaction terms between sex and age, race, and residential status were all statistically significant; therefore, justifying stratified analysis. Table 6.3 presents adjusted results of the stratified analysis for any osteoporosis medication use among women and men. The probability of receiving any evidence-based osteoporosis medication increased with age among men, but remained relatively constant among women except for those aged 90 or older when utilization rates dropped. Black men and women were much less likely (RR 0.76, 95% CI [0.68, 0.85] for men; RR 0.61, 95% CI [0.59, 0.63] for women) to be treated for osteoporosis compared to white men

and women. Hispanic men were equally likely (RR 0.95, 95% CI [0.83, 1.09]) to receive osteoporosis medications compared to white men, while Hispanic women were less likely (RR 1.36, 95% CI [1.32, 1.41]) to receive osteoporosis medication compared to white women. In contrast to the unadjusted results, nursing home residence actually increased the probability of treatment once all other factors are controlled (RR 1.65, 95% CI [1.44, 1.90] for men and RR 1.17, 95% CI [1.15, 1.20] for women). Having diabetes or chronic kidney disease reduced the likelihood of treatment in both sexes, whereas using anticonvulsants, cancer chemotherapy, and glucocorticoids had the opposite effect. Having BMD testing significantly increased the probability of receiving any evidence-based osteoporosis medication among both men and women, although the effect was much stronger in men.

Figure 6.3. Choice of Evidence-Based Osteoporosis Medication among Drug Users, by Drug Class, Sex and Year



Note: *Difference between 2006 and 2008 significant at α=0.05 level

Table 6.3. Estimated Effects of Predictors on Any Use of Evidence-Based Osteoporosis Medications among Medicare Part D Enrollees Diagnosed with Osteoporosis, Stratified by Sex

	Women		Men	
	Prevalence Ratio	95% Confidence Interval	Prevalence Ratio	95% Confidence Interval
Age				
70-74 (ref)				
75-79	1.03	(1.02-1.04)*	1.06	(1.00-1.12)*
80-84	1.05	(1.04-1.07)*	1.25	(1.17-1.34)*
85-89	1.02	(1.01-1.04)*	1.29	(1.20-1.40)*
90+	0.96	(0.94-0.98)*	1.39	(1.27-1.52)*
Race/ethnicity				
White (ref)				
Black	0.61	(0.59-0.63)*	0.76	(0.68-0.85)*
Hispanic	1.36	(1.32-1.41)*	0.95	(0.83-1.09)
Asian	1.96	(1.90-2.02)*	1.89	(1.70-2.10)*
Other	1.25	(1.19-1.31)*	1.25	(1.07-1.46)*
Geographic region				
Northeast (ref)				
Midwest	0.94	(0.92-0.96)*	0.97	(0.89-1.05)
South	0.95	(0.93-0.96)*	0.93	(0.86-1.00)*
West	1.04	(1.01-1.06)*	1.18	(1.09-1.28)*
Residential status				
Community only (ref)				
LTCF only	1.17	(1.15-1.20)*	1.65	(1.44-1.90)*
Both	1.12	(1.10-1.14)*	0.97	(0.89-1.06)
Socioeconomic status				
Non-LIS recipient (ref)				
Low income subsidy (LIS) recipient but non-dual	0.88	(0.86-0.91)*	1.01	(0.88-1.15)
Medicare/Medicaid dual eligibility	0.84	(0.82-0.85)*	1.07	(1.00-1.13)*
RxHCC count	1.02	(1.02-1.02)*	1.01	(1.01-1.02)*
Comorbidities causing or contributing to osteoporosis and fractures				
History of hip fracture	1.23	(1.20-1.26)*	1.14	(1.03-1.25)*
Diabetes mellitus	0.80	(0.79-0.81)*	0.89	(0.85-0.94)*
Rheumatoid arthritis/osteoarthritis	1.11	(1.10-1.12)*	1.11	(1.05-1.16)*
Congestive heart failure	0.85	(0.84-0.86)*	0.98	(0.92-1.03)
Depression	0.92	(0.91-0.93)*	1.03	(0.97-1.09)
End-stage renal disease	0.74	(0.68-0.80)*	0.96	(0.82-1.13)
COPD	0.97	(0.95-0.98)*	1.03	(0.98-1.08)
Breast cancer	1.04	(1.02-1.07)*	-	-
Prostate cancer	-	-	1.09	(1.02-1.16)*

Table 6.3. ***Continued***

	Women		Men	
	Prevalence Ratio	95% Confidence Interval	Prevalence Ratio	95% Confidence Interval
Medications causing or contributing to osteoporosis and fractures				
Anticonvulsants	1.17	(1.15-1.19)*	1.63	(1.51-1.77)*
Cancer chemotherapy	1.15	(1.13-1.18)*	1.36	(1.22-1.52)*
Glucocorticoids	1.22	(1.21-1.24)*	1.82	(1.69-1.96)*
Risk factors for fall				
Alzheimer's/dementia	0.90	(0.89-0.91)*	1.01	(0.95-1.07)
Glaucoma	1.04	(1.03-1.05)*	1.02	(0.97-1.09)
Stroke	0.90	(0.89-0.91)*	0.99	(0.93-1.04)
Contraindications/side effects of all osteoporosis medications				
Chronic kidney disease	0.90	(0.89-0.91)*	0.94	(0.89-0.99)*
Other contraindications of all osteoporosis medications	1.00	(0.98-1.01)	1.00	(0.93-1.08)
Side effects of all osteoporosis medications				
GI problems	0.98	(0.97-0.99)*	1.00	(0.95-1.04)
Other side effects of all osteoporosis medications	1.03	(1.02-1.04)*	1.08	(1.04-1.12)*
Number of chronic medications used per month	1.07	(1.06-1.07)*	1.04	(1.03-1.05)*
Receipt of BMD testing	1.33	(1.31-1.34)*	2.34	(2.11-2.58)*
Death	1.52	(1.50-1.54)*	4.20	(3.98-4.44)*
Year				
2006 (ref)				
2007	0.99	(0.99-1.00)*	1.01	(0.98-1.04)
2008	0.98	(0.97-0.99)*	1.00	(0.96-1.04)

Note: *P<0.05

When treated, men had significantly higher probability of receiving non-bisphosphonates in the combined analyses of men and women (RR 1.16, 95% CI [1.16, 1.17]) (results not shown). Interaction terms between sex and age, race, and residential status in this model were all statistically significant, thus justifying stratified analysis by sex. Table 6.4 presents adjusted results from the stratified analysis by type of medication use (non-bisphosphonates versus bisphosphonates) among the treated. For both men and women, the probability of receiving non-bisphosphonates increased with age. Asian men

were much less likely to receive non-bisphosphonates (RR 0.31, 95% CI [0.18, 0.52]) compared to white men; however, Asian women were equally likely (RR 0.97, 95% CI [0.89, 1.06]) to receive non-bisphosphonates compared to white women. Non-bisphosphonate use was much higher among men and women residing in nursing facilities (RR 1.27, 95% CI [1.21, 1.32] for women, and RR 1.43, 95% CI [1.14, 1.78] for men). Among disease factors, having end-stage renal disease was a strong predictor of receiving non-bisphosphonates in women (RR 1.52, 95% CI [1.32, 1.76]), but not in men.

Table 6.4. Estimated Effects of Predictors on Non-Bisphosphonate Use among Osteoporosis Medication Users, Stratified by Sex

	Women		Men	
	Prevalence Ratio	95% Confidence Interval	Prevalence Ratio	95% Confidence Interval
Age				
70-74 (ref)				
75-79	1.03	(1.00-1.06)*	0.97	(0.80-1.18)
80-84	1.05	(1.02-1.09)*	1.29	(1.05-1.59)*
85-89	1.15	(1.10-1.19)*	1.43	(1.14-1.80)*
90+	1.22	(1.17-1.28)*	1.44	(1.12-1.86)*
Race/ethnicity				
White (ref)				
Black	0.75	(0.69-0.81)*	0.71	(0.50-1.00)
Hispanic	0.62	(0.56-0.69)*	0.46	(0.28-0.76)*
Asian	0.97	(0.89-1.06)	0.31	(0.18-0.52)*
Other	0.82	(0.71-0.93)*	0.55	(0.30-1.02)
Geographic region				
Northeast (ref)				
Midwest	1.02	(0.97-1.07)	0.77	(0.62-0.97)*
South	1.14	(1.10-1.19)*	1.11	(0.91-1.35)
West	0.89	(0.84-0.94)*	0.66	(0.51-0.86)*
Residential status				
Community only (ref)				
LTCF only	1.27	(1.21-1.32)*	1.43	(1.14-1.78)*
Both	1.15	(1.11-1.19)*	1.31	(1.10-1.55)*
Socioeconomic status				
Non-LIS recipient (ref)				
Low income subsidy (LIS) recipient but non-dual	1.04	(0.98-1.11)	1.24	(0.85-1.81)

Table 6.4. ***Continued***

	Women		Men	
	Prevalence Ratio	95% Confidence Interval	Prevalence Ratio	95% Confidence Interval
Medicare/Medicaid dual eligibility	1.04	(1.01-1.08)*	1.28	(1.07-1.54)*
RxHCC count	1.00	(0.99-1.00)*	1.01	(0.99-1.03)
Comorbidities causing or contributing to osteoporosis and fractures				
History of hip fracture	1.04	(1.00-1.09)*	1.25	(1.03-1.53)*
Diabetes mellitus	1.00	(0.97-1.03)	0.92	(0.80-1.07)
Rheumatoid arthritis/osteoarthritis	1.02	(1.00-1.05)	0.94	(0.81-1.09)
Congestive heart failure	1.03	(1.00-1.06)*	1.16	(0.99-1.36)
Depression	1.07	(1.04-1.10)*	1.07	(0.91-1.24)
End-stage renal disease	1.52	(1.32-1.76)*	1.38	(0.85-2.22)
COPD	1.05	(1.02-1.09)*	0.96	(0.82-1.11)
Breast cancer	0.89	(0.84-0.94)*	-	-
Prostate cancer	-	-	0.96	(0.80-1.16)
Risk factors for fall				
Alzheimer's/dementia	1.06	(1.03-1.09)*	0.97	(0.83-1.13)
Glaucoma	0.99	(0.96-1.02)	0.94	(0.79-1.11)
Stroke	1.02	(0.99-1.05)	0.98	(0.83-1.14)
Medications causing or contributing to osteoporosis and fractures				
Anticonvulsants	0.99	(0.96-1.02)	1.20	(1.04-1.40)*
Cancer chemotherapy	0.96	(0.92-1.00)	0.95	(0.76-1.19)
Glucocorticoids	0.98	(0.96-1.00)*	0.95	(0.83-1.09)
Contraindications/side effects of bisphosphonates				
Chronic kidney disease	1.02	(0.99-1.05)	1.05	(0.91-1.22)
Other contraindications of bisphosphonates	0.95	(0.88-1.02)	1.23	(0.81-1.86)
Side effects of all bisphosphonates				
GI problems	1.03	(1.01-1.05)*	1.14	(1.01-1.28)*
Other side effects of bisphosphonates	1.01	(0.99-1.02)	1.05	(0.93-1.17)
Number of chronic medications used per month				
Receipt of BMD testing	0.90	(0.89-0.91)*	0.83	(0.75-0.93)*
Death	0.97	(0.94-1.00)	1.05	(0.90-1.22)
Year				
2006 (ref)				
2007	0.97	(0.96-0.98)*	0.89	(0.82-0.96)*
2008	0.93	(0.92-0.95)*	0.75	(0.67-0.84)*

Note: *P<0.05

6.4 Discussion

This is the first large national study to compare patterns of evidence-based osteoporosis medication use among elderly men and women in the Medicare program. We found low rates of osteoporosis medication use in both men and women diagnosed with osteoporosis, but it was especially low among men (around 25%). Even after adjusting for age and other characteristics, the probability of an elderly man with diagnosed osteoporosis being treated with evidence-based pharmacotherapy was just 20% of that in women. Although we found some factors associated with gender-related differences in treatment (e.g., higher prevalence of chronic kidney disease in men), most of the difference remains unexplained by the factors included in our model. This huge difference may be due to lack of awareness of the disease and its consequences in elderly men and their physicians.[99] Osteoporosis has traditionally been seen as a women's disease, so elderly men and their physicians may fail to manage it appropriately. This apparent lack of awareness was unobserved in our results. Why that is the case requires further study. It may be due to other provider/system level factors, such as number/type of providers seen before diagnosed with osteoporosis, provider's adherence to national osteoporosis guidelines, or provider-patient interaction, that were shown in our conceptual framework but not observable in our data.

When treated, elderly males with osteoporosis were much more likely to receive bisphosphonates compared to elderly females. Whether this is true today remains to be seen. In 2010, a new class of osteoporosis drug- RANKL inhibitors was approved by the FDA. The first RANKL inhibitor, denosumab, is indicated for treatment of osteoporosis in men and postmenopausal women at higher risk for fracture and/or with non-metastatic

prostate cancer or breast cancer. Denosumab is a once every 6 months subcutaneous injection covered by Part B and is recommended as first-line therapy along with bisphosphonates by the 2010 American Association of Clinical Endocrinologist Medical guidelines[96] and the 2014 NOF Clinicians' Guide.[106] Availability of RANKL inhibitors may increase men's likelihood of using evidence-based osteoporosis medications.

Besides low utilization rates, we also discovered important gender-related racial distinctions in osteoporosis treatment. Blacks had by far the lowest treatment rates (30% for women and 15.5% for men). Whites were in the middle (44.4% for women and 24.5% for men) with the highest rates for Asians (64.4% for women and 37.9% for men). Treatment rates among Hispanic women (46.5%) exceeded that of whites, but the rate for Hispanic men (19.3%) was significantly below that for white men. Such wide racial and ethnic differences raise important questions about osteoporosis education and access that deserve further research.

In particular, our finding that receipt of BMD testing significantly increases the probability of osteoporosis treatment use for both sexes, but more so for men is telling. This is consistent with the view that men receive BMD tests later in the course of their disease and thus are more likely to be treated as a result. This also suggests that BMD testing should be expanded particularly for men. Since Medicare Part B covers BMD tests once every 24 months for beneficiaries who are at risk of developing osteoporosis, physicians should make Medicare beneficiaries aware of and take better advantage of this coverage to help identify osteoporosis and initiate treatment early.

This study has several limitations. First, we only tracked osteoporosis treatment patterns through 2008. The study provides important information about how osteoporosis

was treated during the formative years of the Medicare Part D program, but clearly, analysis of more recent trends is warranted. Second, the CCW provides data on drug use only for Medicare Part D enrollees. Therefore, the study findings may not generalize to Medicare beneficiaries not enrolled in Part D. Also, MAPD enrollees were excluded because they did not generate Part A and B claims necessary for identifying evidence of osteoporosis. Use and choice of osteoporosis medication may differ between MAPD and PDP enrollees, and therefore, the findings of this study may not be generalizable to MAPD enrollees, either. Fourth, drug use during beneficiaries' Part A covered hospitalization and post-acute SNF stays was not observed due to CMS reimbursement policy. Fifth, use of chronic kidney disease as a contraindication of bisphosphonates may have introduced bias. The exact contraindication of bisphosphonates is creatinine clearance < 30 mL/min. However, the actual creatinine clearance value is not available in CCW data, thus we can only use diagnosis of chronic kidney disease as a proxy and the result of chronic kidney disease's impact on treatment use are likely biased toward the null. Perhaps most significant of all limitations is the fact that we were unable to capture use of over-the-counter calcium and vitamin D, both of which may be effective in reducing bone fractures, Part D does not cover over-the-counter medications and thus we have systematically underestimated the degree to which Medicare beneficiaries received any osteoporosis treatment.

6.5 Conclusion

Elderly men are undertreated for osteoporosis compared to elderly women, and this is particularly problematic among blacks. Policy makers should expand the focus of improving osteoporosis treatment to include men and clinicians should treat their male

patients with osteoporosis more appropriately in order to reduce the gender difference in osteoporosis treatment.

7 Effectiveness of Osteoporosis Medicare in Reducing Fracture Risk among Elderly Medicare Beneficiaries: Do Sex and Medication Adherence Make a Difference?

7.1 Introduction

Osteoporosis is the most common bone disease in humans[75] and is a major threat to public health[76]. Osteoporosis affects an estimated 7%[82] to 14.9%[83] of the Medicare population and repair of bone fractures due to osteoporosis represents a major cost to the program. These costs make osteoporosis a major illness among the highest cost Medicare beneficiaries.[84] Therefore, it is important to understand how to effectively treat osteoporosis using evidence-based medications and prevent costly bone fractures among Medicare beneficiaries.

Despite the impact of osteoporosis, few studies have assessed the effectiveness of evidence-based osteoporosis medications on reducing the risk of fractures in the Medicare population[107] including only one study among Part D enrollees[95]. Moreover, virtually all research has focused on women and the effectiveness of osteoporosis medications in men is lacking.[24, 28, 29, 108-111] Because men and women have different sex hormones that play an important role in bone health, it is unclear if the effectiveness of osteoporosis medications for men is the same as that for women. Therefore, it is important to assess the effectiveness in men and test for heterogeneity of effectiveness of osteoporosis treatment by sex.

Medication adherence generally improves treatment outcomes. Numerous studies have examined the relationship between adherence to osteoporosis medications and the

risk of future fracture,[107] reporting up to a 45%[54] reduction in the risk of future fractures for patients with high adherence. However, as noted, few studies have focused on Medicare beneficiaries and none on male beneficiaries. Therefore, we conducted this study to test for possible heterogeneous treatment effects associated with initiation and adherence with evidence-based osteoporosis medication in male and female Medicare Part D enrollees with osteoporosis. We hypothesized that treatment would be effective in preventing subsequent bone fracture but more effective in women than in men, and that better patient adherence would improve treatment effectiveness.

7.2 Methods

7.2.1 Data and sample selection

Data for the study were obtained from the 2006-2008 Chronic Condition Data Warehouse (CCW) 5% national random sample of Medicare beneficiaries.[85] The study sample included Medicare beneficiaries aged 70 years and older with first evidence of osteoporosis between July 1, 2006 and June 30, 2008 without use of osteoporosis medication prior to the first evidence of osteoporosis. Setting the minimum age at 70 enabled the construction of a 5-year look-back window to check beneficiaries' history of osteoporosis and ensure inclusion of true incident osteoporosis cases. Without the 5-year look-back window, individuals who had a diagnosis of osteoporosis prior to joining Medicare may be included in the sample, and these false incident osteoporosis cases may have use of osteoporosis medications prior to joining Medicare that is unobserved in the CCW, which may bias the estimate of treatment effect because bisphosphonates may have residual effects for an extended period of time. Setting the beginning of the inclusion period at July 1, 2006 allowed at least 6 months to ensure no osteoporosis

medication was used prior to the diagnosis of osteoporosis while setting the end of the inclusion period at June 30, 2008 allowed at least 6 months for follow-up to observe the treatment effect. Evidence of osteoporosis was defined using the CCW algorithm of at least one inpatient, outpatient or physician claim with ICD-9 diagnosis codes 733.00, 733.01, 733.02, 733.03, 733.09. Beneficiaries who had first evidence of osteoporosis between July 1, 2006 and June 30, 2008 but used any osteoporosis medications listed in the 2008 National Osteoporosis Foundation (NOF) clinician's guide (see Appendix Table 2) before the first diagnosis of osteoporosis were excluded to ensure unbiased estimate of treatment effect. The study sample was also restricted to beneficiaries with continuous enrollment in Medicare Part A, B and a Part D stand-alone prescription drug plan (PDP) from January 1, 2006 through December 31, 2008, or death.

The sample excluded Medicare Advantage Prescription Drug (MAPD) plan enrollees from 2006 to 2008, and beneficiaries not enrolled in Part D from 2006 to 2008. MAPD plan enrollees were excluded because they lacked Part A and B claims files necessary for identifying diagnosis and fractures. Non-Part D enrollees were excluded because they lacked prescription drug data.

7.2.2 Bone fracture measures

The outcome of interest was a dichotomized variable indicating the occurrence of osteoporotic bone fractures after the first evidence of osteoporosis using the ICD-9 diagnostic codes (see diagnostic codes in Appendix Table 1). If multiple osteoporotic bone fractures occurred during the study period, the first was used for the analysis.

7.2.3 Other measures

The main independent variables were any use of evidence-based osteoporosis medications and adherence to these medications among users. Use of osteoporosis medications listed in the 2008 NOF clinician's guide (see Appendix Table 2) was identified by National Drug Codes (NDCs) in the Part D prescription drug event (PDE) file using the FirstDataBank drug dictionary, and by the Healthcare Common Procedure Coding System (HCPCS) codes in the Part B claims file for Part B covered osteoporosis drugs. The 2008 NOF clinician's guide was used as it was the most relevant guideline for the study period. Beneficiaries who used any osteoporosis medications between the date of first diagnosis of osteoporosis and December 31, 2008 were categorized as users; otherwise as non-users. It should be noted that although estrogen is sometimes used as treatment of osteoporosis, the Food and Drug Administration (FDA)-approved indication (ref) is only for prevention of osteoporosis, so use of estrogens was not included in this study. In preliminary analyses, we found fewer than 1% of study subjects used Part B covered ibandronate sodium and zoledronic acid injections during the study period, so use of those two Part B covered drugs was not included in the final analysis. Osteoporosis drugs used during Medicare covered hospitalizations and skilled nursing facility (SNF) stays could not be considered as they are covered under Part A and are thus not observable in the PDE file.

In order to control for the survival bias associated with time-to-treatment initiation, we performed prescription time-distribution matching [112] after identifying users and nonusers. For users, we first calculated the number of days from the date of diagnosis of osteoporosis to the date of the first filled prescription for osteoporosis medication. We

then randomly selected a user's number of days from diagnosis to first prescription filled and assigned it to a nonuser. We subsequently calculated the date of "potential treatment initiation" by adding the assigned number of days from diagnosis to first prescription filled to the date of diagnosis for nonusers. After this matching process, anyone who initiated or potentially initiated treatment after June 30, 2008 was excluded due to insufficient follow-up time. Nonusers whose potential treatment initiation date fell after their date of death were also excluded.

Persons with one or more fills of any evidence-based osteoporosis drug following first diagnosis of osteoporosis up to June 30, 2008 were considered as receiving treatment. For users, adherence to osteoporosis medication was measured by proportion of days covered (PDC) from the date of the first prescription for osteoporosis medication filled to December 31, 2008 or death. Days spent in inpatient hospital, skilled nursing facility (SNF) or hospice stays were removed from both the numerator and denominator of the PDC ratio. Beneficiaries were then categorized as adherent (PDC$\geq$0.8) and non-adherent (PDC<0.8).[113]

Other measures included in the analyses described below included demographics (age, sex, race/ethnicity, and geographic region), residential status (categorized as community only, long-term care only, and both using the Minimum Data Set (MDS) together with inpatient and SNF claims), and indicators of Medicare-Medicaid dual eligibility and receipt of Part D low-income subsidy (LIS) as proxy variables for socioeconomic status. General health status was represented by counts of conditions from the prescription drug hierarchical condition categories (RxHCC) risk adjustment measure developed by the Center for Medicare and Medicaid Services (CMS). Indicators

for conditions and medications that may cause or contribute to osteoporosis and bone fractures and risk factors for fall were selected based on the 2008 NOF guidelines.[78] Disease factors included prior hip fracture, diabetes mellitus, rheumatoid arthritis/osteoarthritis, congestive heart failure (CHF), depression, end stage renal disease (ESRD), chronic obstructive pulmonary disease (COPD), and breast cancer, all defined by CCW diagnostic algorithms.[86] Commonly used medications that may cause or contribute to osteoporosis and bone fractures included anticonvulsants, cancer chemotherapy and glucocorticoids. Risk factors for fall included Alzheimer's disease/dementia, glaucoma (as proxy for poor vision), and stroke (as proxy for poor balance). Finally, we captured receipt of bone mineral density (BMD) testing as an indicator of osteoporosis management. We hypothesized that factors that increase risk of osteoporosis and/or falls would be positively associated with bone fracture.

7.2.4 Statistical analysis

The descriptive analyses included, first, an examination of differences in characteristics between men and women among Part D enrollees with osteoporosis stratified by treatment status (yes or no), and then among those receiving treatment stratified by adherence (PDC < 0.80 versus ≥ 0.80). Next, we analyzed time-to-first fracture for males and females by treatment status and adherence. As described above, the start point of time-to-first fracture was the actual treatment initiation date for users and the "potential treatment initiation" date for nonusers.

In the multivariate analysis, we first analyzed the effect of any osteoporosis medication use on subsequent bone fracture from the date of first osteoporosis prescription fill or potential treatment initiation date adjusting for other factors using a

standard Cox proportional hazard model. However, treatment was not randomly assigned to the patients in our study and could be correlated to factors such as age and disease severity. In order to adjust for potential selection bias, we then incorporated the inverse probability of treatment use as a weight in a second set of Cox proportional hazard models. Finally, to account for the fact that bone fracture is not a terminal outcome of osteoporosis and patients may die before the occurrence of subsequent bone fracture, we incorporated death as a competing risk in a final set of Cox models including inverse probability of treatment weighting.

We then used the same strategy to estimate the impact of adherence on subsequent fracture risk from the date of medication initiation. All variables described in the measures section above were included as covariates in every model. To determine if there was significant difference in subsequent bone fracture between men and women, we ran two sets of regressions for both analyses of treatment effect and adherence effect among the treated. The first set of regressions included a single binary variable for sex, and the second included an interaction term between treatment use or adherence and sex to determine whether or not the difference in outcomes between men and women was significant.

The analyses were conducted using SAS 9.3. The study protocol was approved by the University of Maryland Baltimore IRB.

7.3 Results

The final study sample included 12,344 Medicare beneficiaries aged 70 or older with an initial diagnosis of osteoporosis and the first prescription for osteoporosis medications filled between July 1, 2006 and June 30, 2008, among whom 2,083 were men and 10,262

were women (Table 7.1). Among men, the treated were more likely to be Asian, living in the West, community dwellers, and in better health (i.e. lower RxHCC counts and lower rates of diabetes, CHF, depression, Alzheimer's disease/dementia, and stroke) compared to the untreated. Treated men also had much higher utilization of BMD tests compared to the untreated men. Among women, the treated were younger, more likely to be Hispanic and Asian, living in the West, community dwellers, and in better health (i.e. lower RxHCC counts and lower rates of prior hip fracture, diabetes, rheumatoid arthritis, CHF, depression, end-stage renal disease, COPD, Alzheimer's disease/dementia, and stroke). Treated women were also much more likely to have BMD tests compared to the untreated women.

Among the treated, 32.5% of men and 30.0% of women were adherent to their osteoporosis medications (Table 7.2). Among men, the adherent were more likely to be 70-74 years old, living in the Midwest, non-LIS recipients, taking glucocorticoids and more likely to receive BMD tests compared to the non-adherent. Among women, adherent patients were more likely to be white or Asian, and in better health (i.e. lower RxHCC counts and lower rates of diabetes, rheumatoid arthritis, CHF, depression, and COPD). Adherent women were also more likely to have BMD tests.

Table 7.1. Baseline (Year of Diagnosis) Characteristics of Medicare Beneficiaries Newly Diagnosed of Osteoporosis, by Sex and Treatment Use (N=12,344)

	Women		Men	
Beneficiaries Characteristics	Treated (N=3,174)	Untreated (N=7,087)	Treated (N=495)	Untreated (N=1,588)
Age				
70-74	24.5	19.7*	25.3	25.1
75-79	30.1	24.6*	28.7	29.9
80-84	23.5	23.1	25.1	22.2
85-89	15.8	18.2*	14.9	14.7
90+	6.1	14.5*	6.1	8.1
Race/ethnicity				
White	78.7	82.6*	72.3	79.6*
Black	8.9	10.9*	4.2	6.4
Hispanic	5.6	3.4*	7.1	7.7
Asian	4.4	1.6*	13.7	4.0*
Other	2.3	1.6*	2.6	2.3
Census region				
Northeast	15.3	20.3*	15.2	20.5*
Midwest	25.0	25.1	17.0	19.8
South	40.4	40.8	36.6	39.4
West	19.2	13.9*	31.3	20.3*
Residential status				
Community only	93.2	82.7*	93.5	85.1*
Long-Term Care Facility only	3.0	9.9*	3.0	7.3*
Both	3.9	7.3*	3.4	7.6*
Socio-economic status				
Non-LIS recipient	42.5	41.7	47.9	47.9
LIS recipient but non-dual	5.9	4.3*	1.4	2.9
Dual eligible	51.7	54.0*	50.7	49.2
RxHCC count	8.2 (3.4)	8.9 (3.5)*	9.0 (3.3)	10.0 (3.8)*

Table 7.1. *Continued*

Diseases/conditions that contribute to osteoporosis/bone fracture				
History of hip fracture	6.0	8.0*	7.9	6.9
Diabetes mellitus	33.8	37.9*	37.2	43.5*
Rheumatoid arthritis	45.4	54.6*	47.9	49.6
Congestive heart failure	31.7	41.2*	43.2	47.3*
Depression	28.4	34.5*	23.6	31.3*
End-stage renal disease	0.6	1.0*	1.2	1.7
COPD	23.6	25.2*	37.4	42.1
Cancer (breast for women/prostate for men)	6.7	6.5	0	0.4
Medications that contribute to osteoporosis/bone fracture				
Anticonvulsants	13.7	16.6*	17.8	17.8
Cancer chemotherapy	4.8	6.3*	11.5	9.6
Glucocorticoids	23.0	20.0*	26.7	24.2
Risk factors for fall				
Alzheimer's disease	17.1	30.1*	20.8	30.4*
Glaucoma	22.9	22.8	24.8	26.0
Stroke	14.9	20.3*	21.4	24.2
Contraindications for any osteoporosis medication				
Chronic kidney disease	15.1	20.2*	22.2	28.7*
Other contraindication	6.3	6.1	7.3	7.4
Side effects of any osteoporosis medication				
GI problems	19.9	23.5*	22.4	22.0
Other side effects	49.1	46.5*	40.0	40.6
Number of chronic medication used per month	3.5 (2.3)	3.5 (2.4)	3.4 (2.4)	3.3 (2.5)
Receipt of BMD test	73.8	37.3*	74.7	38.1*
Died in 2006	0.3	0.8*	0.4	1.2
Died in 2007	3.3	6.9*	4.4	9.4*
Died in 2008	5.8	11.0*	10.9	12.5

Note: * Difference between treated and untreated significant at α=0.05 level

Table 7.2. Baseline (Year of Diagnosis) Characteristics of Medicare Beneficiaries Newly Diagnosed of Osteoporosis and Treated, by Sex and Adherence (N=3,669)

	Women		Men	
Beneficiary Characteristics	Adherent (N=952)	Non-Adherent (N=2,222)	Adherent (N=161)	Non-Adherent (N=334)
Age				
70-74	23.6	24.9	31.1	22.5*
75-79	31.1	29.6	24.8	30.5
80-84	24.2	23.2	26.7	24.3
85-89	15.5	15.9	11.8	16.5
90+	5.6	6.3	5.6	6.3
Race/ethnicity				
White	81.1	77.6*	76.4	70.4
Black	8.0	9.4	1.9	5.4
Hispanic	3.2	6.7*	5.6	7.8
Asian	5.7	3.9*	14.3	13.5
Other	2.1	2.4	1.9	3.0
Census region				
Northeast	16.5	14.9	13.0	16.2
Midwest	26.4	24.4	22.4	14.4*
South	38.2	41.4*	29.8	39.8*
West	18.9	19.4	34.8	29.6
Residential status				
Community only	93.4	93.1	92.5	94.0
Long-Term Care Facility	3.8	2.6	3.7	2.7
Both	2.8	4.3*	3.7	3.3
Socio-economic status				
Non-LIS recipient	44.6	41.5	56.5	43.7*
LIS recipient but non-dual	5.0	6.2	1.2	1.5
Dual eligible	50.3	52.3	42.2	54.8*
RxHCC count	7.6 (3.3)	8.5 (3.4)*	8.6 (3.4)	9.2 (3.3)

Table 7.2. *Continued*

Diseases/conditions that contribute to osteoporosis/bone fracture				
History of hip fracture	6.4	5.9	8.7	7.5
Diabetes mellitus	30.7	35.1*	32.9	39.2
Rheumatoid arthritis	42.4	46.7*	44.1	49.7
Congestive heart failure	27.9	33.3*	35.4	47.0*
Depression	25.6	29.6*	21.1	24.9
End-stage renal disease	0.4	0.7	1.2	1.2
COPD	19.5	25.4*	34.2	38.9
Cancer (breast for women/prostate for men)	7.4	6.5	0	0
Medications that contribute to osteoporosis/bone fracture				
Anticonvulsants	12.1	14.4	16.1	18.6
Cancer chemotherapy	3.9	5.1	13.0	10.8
Glucocorticoids	21.8	23.5	30.4	24.9
Risk factor for fall				
Alzheimer's disease	16.1	17.5	19.9	21.3
Glaucoma	22.3	23.2	24.8	24.9
Stroke	13.4	15.5	20.5	21.9
Contraindications for any osteoporosis medication				
Chronic kidney disease	13.9	15.6	19.9	23.4
Other contraindication	6.0	6.4	6.8	7.5
Side effects of any osteoporosis medication				
GI problems	18.3	20.6	20.5	23.4
Other side effects	45.3	50.7*	38.5	40.7
Number of chronic medication used per month	3.7 (2.5)	3.4 (2.2)*	3.7 (2.7)	3.2 (2.3)*
Receipt of BMD test	79.1	71.6*	83.2	70.7*
Died in 2006	0.2	0.4	0.6	0.3
Died in 2007	1.5	4.1*	3.1	5.1
Died in 2008	3.4	6.8*	9.3	11.7

Note: * Difference between adherent and nonadherent significant at α=0.05 level

Overall, the rate of bone fracture in the treated was similar to that among the untreated, regardless of sex (Figure 7.1). The mean time to fracture from the initiation of osteoporosis medication was 779 days for treated men and 729 days for untreated men (p=0.53). Among women, the mean time to fracture from the initiation of osteoporosis medication was 759 days for the treated and 778 days for the untreated (p=0.31). Among the treated, the rate of bone fracture in adherent patients was similar to that in the nonadherent (Figure 7.2). Among men, the mean time to fracture from the initiation of osteoporosis medication was 332 days for the adherent and 770 days for the nonadherent (p=0.12). For women the mean time to fracture from initiation of osteoporosis medication was 695 days for adherent women and 756 days for nonadherent women (p=0.14).

Table 7.3 presents adjusted results from the stratified analyses for risk of subsequent bone fracture among women and men based on medication utilization status. In the model estimating the main effect, use of any evidence-based osteoporosis medication was found to be associated with increased risk of subsequent bone fracture in men and women (hazard ratio (HR) 1.10, 95% confidence interval (CI) [1.02, 1.18]). In the standard Cox model, men were found to be less likely (HR 0.84 95% CI [0.72, 0.97]) to have subsequent bone fracture; however, after adjusting for selection bias in treatment and competing risk of death, men were found to be more likely (HR 1.15, 95% CI [1.11, 1.20]) to have subsequent bone fracture. Men and women who were non-white or Hispanic and living in LTC facilities were significantly less likely to have subsequent bone fracture. Moreover, men and women who received BMD tests were less likely (HR 0.56, 95% CI [0.53, 0.59]) to experience subsequent bone fracture. On the other hand,

Figure 7.1. Time to Fracture among Female and Male Medicare Beneficiaries Newly Diagnosed with Osteoporosis, by Treatment Use

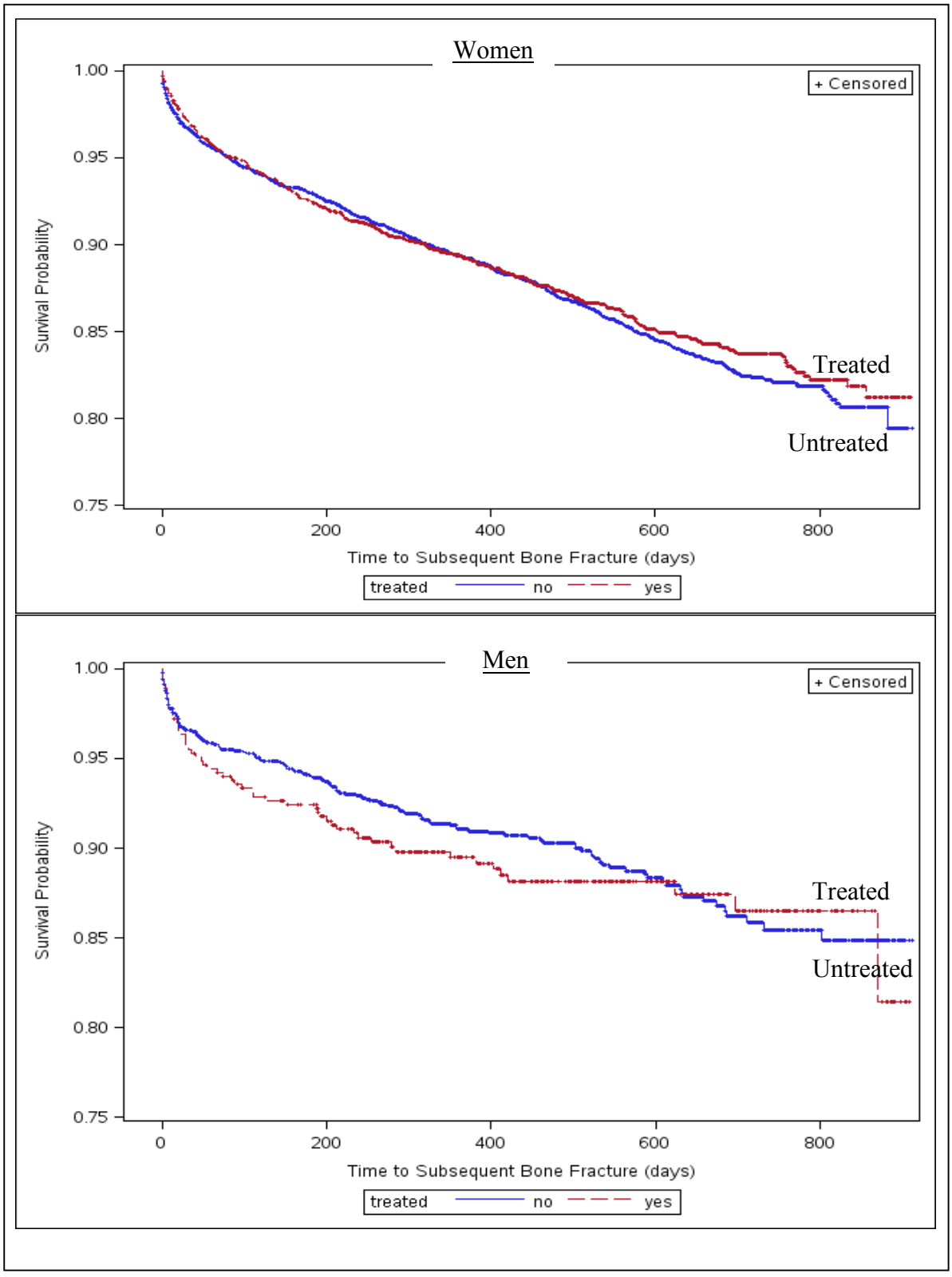
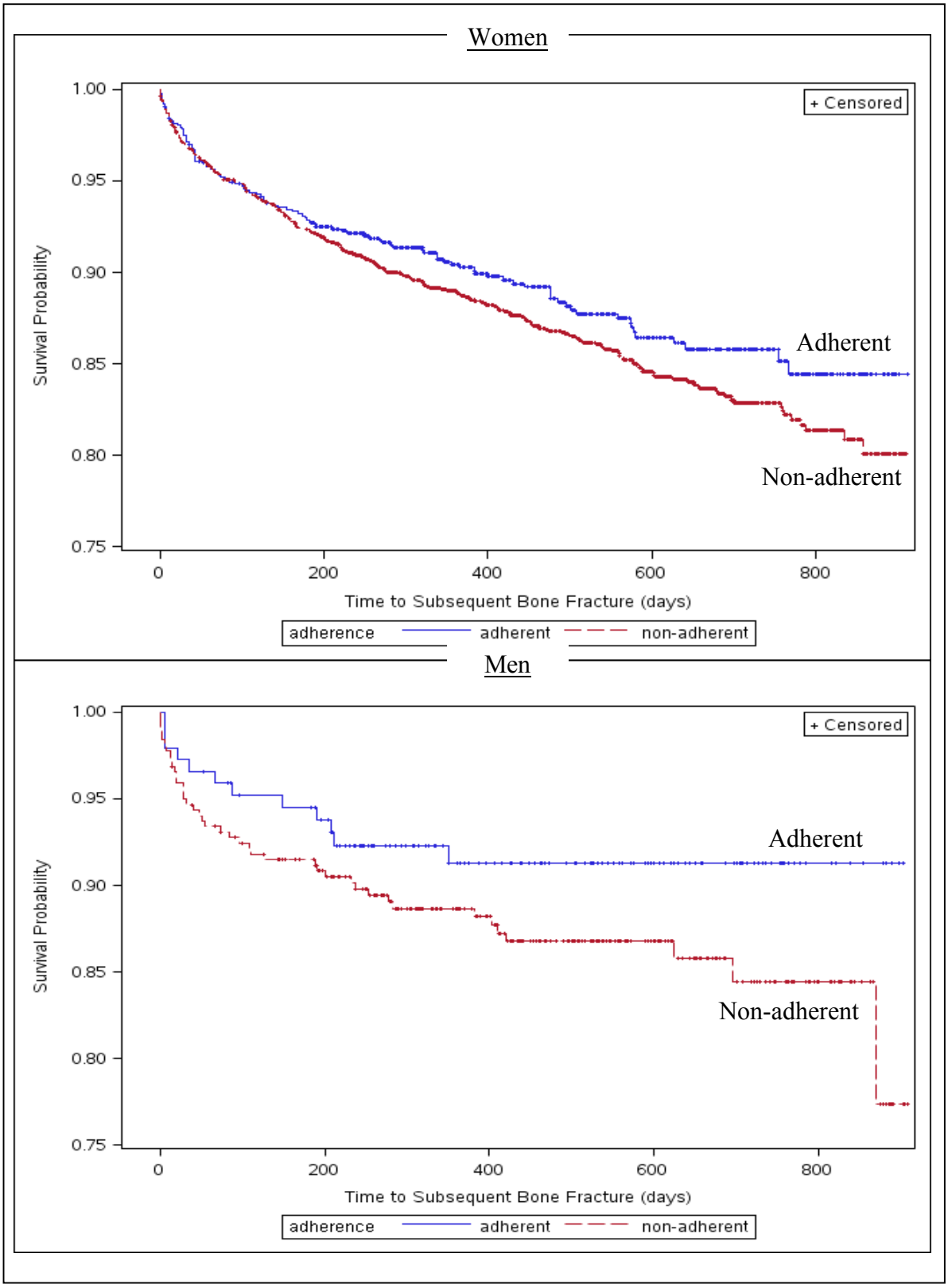


Figure 7.2. Time to Fracture among Female and Male Medicare Beneficiaries Newly Diagnosed of Osteoporosis and Treated, by Adherence Status



men and women with advanced age, transitioning between community and LCT facilities, with poorer socioeconomic status, prior hip fracture, diabetes, CHF, end-stage renal disease, COPD, Alzheimer's disease/dementia, stroke, and taking anticonvulsants, cancer chemotherapy and glucocorticoids were more likely to have subsequent bone fracture. In the model examining the differential effect between men and women, no significant difference (HR 1.06, 95% CI [0.90, 1.26]) was found. The effects of other factors in this model were similar to those in the model estimating main effects.

Table 7.4 presents adjusted results from the analyses by adherence level (PDC≥0.8 versus PDC<0.8) among the treated. In main effects model, high adherence was found to be associated with reduced risk of bone fracture (HR 0.86, 95% CI [0.75, 0.99]). Among the treated, men were equally likely to have subsequent bone fracture as women in the standard Cox model; however, after adjusting for selection bias of treatment utilization and competing risk of death, men were found to be more likely (HR 1.24, 95% CI [1.11, 1.38]) to experience subsequent bone fracture. Being Asian, Medicare-Medicaid dual eligible, having glaucoma were all negative predicators of having subsequent bone fracture for men and women with osteoporosis treated with any evidence-based osteoporosis medications. Receiving BMD tests was associated with lower risk (HR 0.59, 95% CI [0.55, 0.65]) of subsequent bone fracture. Advancing age, residence in both community and LTC facilities, LIS recipients, prior hip fracture, CHF, depression, end-stage renal disease, COPD and receiving cancer chemotherapy were all positive predictors of having subsequent bone fractures in both men and women. No significant differences were found in the models testing differential treatment effects between men and women.

Table 7.3. Estimated Effects of Potential Predictors on Subsequent Bone Fracture among Medicare Part D Enrollees Newly Diagnosed with Osteoporosis (N=12,344)

	Hazard Ratio					
	Tests for Main Effects			Tests for Differential Effects b/w Males and Females		
Beneficiary Characteristics	Cox PH Model	Cox PH Model w/ Inverse Probability of Treatment Weighting Adjustment	Cox PH Model w/ Inverse Probability of Treatment Weighting and Competing Risk Adjustment	Cox PH Model	Cox PH Model w/ Inverse Probability of Treatment Weighting Adjustment	Cox PH Model w/ Inverse Probability of Treatment Weighting and Competing Risk Adjustment
Use of any osteoporosis medication	**1.34* (1.18-1.51)**	**1.31* (1.20-1.44)**	**1.10* (1.02-1.18)**	**1.33* (1.17-1.51)**	**1.30* (1.19-1.43)**	**1.09* (1.01-1.17)**
Demographic characteristics						
Sex						
Female (ref)						
Male	0.84* (0.72-0.97)	0.84* (0.79-0.89)	1.15* (1.11-1.20)	0.83* (0.69-0.99)	0.83* (0.78-0.89)	1.15* (1.10-1.19)
Use*sex	-	-	-	1.05 (0.75-1.47)	1.08 (0.85-1.37)	1.06 (0.90-1.26)
Age						
70-74 (ref)						
75-79	1.36* (1.15-1.61)	1.49* (1.37-1.62)	1.41* (1.33-1.49)	1.36* (1.15-1.60)	1.49* (1.37-1.62)	1.41* (1.33-1.49)
80-84	1.62* (1.37-1.92)	1.70* (1.56-1.84)	1.46* (1.38-1.55)	1.62* (1.37-1.92)	1.70* (1.56-1.84)	1.46* (1.38-1.55)
85-89	1.60* (1.34-1.93)	1.67* (1.53-1.83)	1.85* (1.74-1.95)	1.60* (1.33-1.93)	1.67* (1.53-1.83)	1.85* (1.74-1.95)
90+	1.85* (1.50-2.27)	2.01* (1.83-2.20)	2.43* (2.29-2.57)	1.84* (1.50-2.27)	2.01* (1.83-2.19)	2.43* (2.29-2.57)

Table 7.3. *Continued*

Race/ethnicity						
White (ref)						
Black	0.61* (0.49-0.76)	0.57* (0.52-0.63)	0.69* (0.65-0.73)	0.61* (0.49-0.76)	0.57* (0.52-0.63)	0.69* (0.65-0.73)
Hispanic	0.71* (0.53-0.94)	0.67* (0.58-0.78)	0.63* (0.58-0.70)	0.71* (0.53-0.94)	0.67* (0.58-0.78)	0.64* (0.58-0.70)
Asian	0.63* (0.43-0.92)	0.57* (0.46-0.72)	0.56* (0.47-0.66)	0.63* (0.43-0.92)	0.57* (0.45-0.72)	0.55* (0.47-0.65)
Other	0.92 (0.61-1.37)	0.89 (0.72-1.11)	0.98 (0.85-1.12)	0.92 (0.61-1.38)	0.89 (0.72-1.11)	0.98 (0.85-1.12)
Geographic region						
Northeast (ref)						
Midwest	0.90 (0.77-1.05)	0.93* (0.87-1.00)	1.01 (0.96-1.05)	0.90 (0.77-1.05)	0.93* (0.87-1.00)	1.01 (0.96-1.05)
South	0.99 (0.86-1.14)	1.04 (0.98-1.11)	1.01 (0.97-1.05)	0.99 (0.86-1.14)	1.04 (0.98-1.11)	1.01 (0.97-1.05)
West	1.03 (0.86-1.23)	1.15* (1.06-1.25)	1.04 (0.98-1.10)	1.03 (0.86-1.23)	1.15* (1.06-1.25)	1.04 (0.98-1.10)
Residential status						
Community (ref)						
LTCF	0.86 (0.63-1.18)	0.87* (0.77-0.97)	0.43* (0.39-0.47)	0.86 (0.63-1.18)	0.87* (0.77-0.97)	0.43* (0.39-0.47)
Both	1.89* (1.64-2.18)	1.90* (1.79-2.03)	1.98* (1.90-2.06)	1.89* (1.64-2.18)	1.91* (1.79-2.03)	1.98* (1.90-2.06)
Socioeconomic status						
Non-LIS recipient (ref)						
Low income subsidy (LIS) recipient but non-dual	1.17 (0.91-1.50)	1.16* (1.02-1.31)	1.26* (1.15-1.38)	1.17 (0.92-1.50)	1.16* (1.02-1.31)	1.26* (1.15-1.38)
Medicare/Medicaid dual eligibility	0.97 (0.86-1.10)	0.95 (0.90-1.01)	1.21* (1.16-1.26)	0.97 (0.86-1.10)	0.95 (0.90-1.01)	1.21* (1.16-1.26)
RxHCC count	1.03* (1.01-1.04)	1.04* (1.03-1.04)	1.02* (1.02-1.03)	1.03* (1.01-1.04)	1.04* (1.03-1.04)	1.02* (1.02-1.03)

Table 7.3. *Continued*

Relevant comorbidities						
History of hip fracture	2.56* (2.20-2.98)	2.39* (2.23-2.56)	1.51* (1.44-1.59)	2.56* (2.20-2.98)	2.39* (2.23-2.56)	1.51* (1.44-1.59)
Diabetes mellitus	1.10 (0.98-1.23)	1.14* (1.08-1.20)	1.10* (1.06-1.14)	1.10 (0.98-1.23)	1.14* (1.08-1.20)	1.10* (1.06-1.14)
Rheumatoid arthritis	1.06 (0.95-1.18)	1.03 (0.98-1.08)	0.90* (0.87-0.92)	1.06 (0.95-1.18)	1.03 (0.98-1.08)	0.90* (0.87-0.92)
Congestive heart failure	1.01 (0.90-1.14)	0.99 (0.94-1.04)	1.18* (1.14-1.22)	1.01 (0.90-1.14)	0.99 (0.94-1.04)	1.18* (1.14-1.22)
Depression	1.08 (0.96-1.22)	1.04 (0.98-1.09)	1.00 (0.97-1.04)	1.08 (0.96-1.22)	1.04 (0.98-1.09)	1.00 (0.97-1.04)
End-stage renal failure	2.14* (1.44-3.19)	1.83* (1.56-2.15)	2.15* (1.95-2.37)	2.14* (1.44-3.19)	1.83* (1.56-2.15)	2.15* (1.95-2.37)
COPD	1.05 (0.93-1.19)	1.02 (0.97-1.08)	1.11* (1.07-1.15)	1.06 (0.93-1.19)	1.02 (0.97-1.08)	1.11* (1.07-1.15)
Other relevant medication use						
Anticonvulsants	1.27* (1.12-1.45)	1.28* (1.21-1.36)	1.15* (1.11-1.19)	1.27* (1.12-1.45)	1.28* (1.21-1.36)	1.15* (1.11-1.19)
Cancer chemotherapy	1.09 (0.89-1.34)	0.90* (0.82-0.99)	1.41* (1.34-1.48)	1.09 (0.89-1.34)	0.90* (0.82-0.99)	1.41* (1.34-1.48)
Glucocorticoids	1.05 (0.92-1.19)	1.02 (0.95-1.08)	1.20* (1.15-1.25)	1.05 (0.92-1.19)	1.02 (0.95-1.08)	1.20* (1.15-1.25)
Risk factor for fall						
Alzheimer's/dementia	0.86* (0.75-0.99)	0.84* (0.80-0.90)	1.17* (1.13-1.22)	0.86* (0.75-0.99)	0.84* (0.80-0.90)	1.18* (1.13-1.22)
Glaucoma	0.95 (0.84-1.07)	0.98 (0.92-1.03)	0.89* (0.86-0.93)	0.95 (0.84-1.07)	0.98 (0.92-1.03)	0.89* (0.86-0.93)
Stroke	0.94 (0.82-1.07)	0.91* (0.86-0.97)	1.04* (1.01-1.08)	0.94 (0.82-1.07)	0.91* (0.86-0.97)	1.04* (1.01-1.08)
Receipt of BMD testing	0.72* (0.63-0.81)	0.70* (0.65-0.76)	0.56* (0.53-0.59)	0.72* (0.63-0.81)	0.70* (0.65-0.76)	0.56* (0.53-0.59)

Note: * Significant at α=0.05 level

Table 7.4. Estimated Effects of Potential Predictors on Subsequent Bone Fracture among Medicare Part D Enrollees Newly Diagnosed of Osteoporosis and Treated (N=3,669)

	Hazard Ratio					
	Tests for Main Effects			Tests for Differential Effects b/w Males and Females		
Beneficiary Characteristics	Cox PH Model	Cox PH Model w/ Inverse Probability of Treatment Weighting Adjustment	Cox PH Model w/ Inverse Probability of Treatment Weighting and Competing Risk Adjustment	Cox PH Model	Cox PH Model w/ Inverse Probability of Treatment Weighting Adjustment	Cox PH Model w/ Inverse Probability of Treatment Weighting and Competing Risk Adjustment
Adherence to any osteoporosis medication	**0.92 (0.74-1.14)**	**0.89 (0.76-1.05)**	**0.86* (0.75-0.99)**	**0.95 (0.76-1.20)**	**0.94 (0.79-1.12)**	**0.91 (0.78-1.05)**
Demographic characteristics						
Sex						
Female (ref)						
Male	0.82 (0.61-1.10)	0.88 (0.75-1.04)	1.24* (1.11-1.38)	0.89 (0.63-1.24)	0.93 (0.78-1.10)	1.28* (1.13-1.43)
Adherence*sex	-	-	-	0.73 (0.37-1.45)	0.64 (0.39-1.07)	0.74 (0.51-1.07)
Age						
70-74 (ref)						
75-79	1.14 (0.86-1.50)	1.10 (0.94-1.27)	0.97 (0.86-1.09)	1.13 (0.86-1.50)	1.09 (0.94-1.27)	0.97 (0.86-1.08)
80-84	1.58* (1.19-2.08)	1.38* (1.18-1.60)	1.27* (1.13-1.43)	1.57* (1.19-2.08)	1.38* (1.18-1.60)	1.27* (1.13-1.43)
85-89	1.55* (1.14-2.10)	1.52* (1.30-1.78)	1.43* (1.27-1.61)	1.54* (1.13-2.09)	1.51* (1.29-1.78)	1.42* (1.26-1.61)
90+	1.42 (0.94-2.14)	1.29* (1.04-1.60)	1.41* (1.21-1.65)	1.42 (0.94-2.14)	1.29* (1.04-1.60)	1.41* (1.21-1.65)

Table 7.4. *Continued*

Race/ethnicity						
White (ref)						
Black	0.68 (0.46-1.02)	0.64* (0.52-0.78)	0.88 (0.77-1.01)	0.68 (0.46-1.02)	0.64* (0.52-0.78)	0.88 (0.77-1.01)
Hispanic	0.76 (0.47-1.24)	0.87 (0.71-1.06)	0.94 (0.81-1.10)	0.77 (0.47-1.24)	0.87 (0.71-1.07)	0.95 (0.81-1.10)
Asian	0.82 (0.50-1.36)	0.78 (0.58-1.06)	0.71* (0.55-0.90)	0.82 (0.50-1.36)	0.78 (0.58-1.06)	0.71* (0.56-0.91)
Other	0.99 (0.51-1.89)	1.00 (0.71-1.40)	0.89 (0.67-1.17)	0.98 (0.51-1.89)	1.00 (0.71-1.40)	0.89 (0.67-1.17)
Geographic region						
Northeast (ref)						
Midwest	0.86 (0.64-1.15)	0.77* (0.65-0.90)	1.05 (0.92-1.20)	0.86 (0.64-1.15)	0.77* (0.66-0.90)	1.05 (0.92-1.20)
South	0.85 (0.65-1.11)	0.83* (0.71-0.95)	1.04 (0.92-1.18)	0.85 (0.65-1.11)	0.83* (0.72-0.96)	1.04 (0.92-1.18)
West	0.86 (0.63-1.18)	0.83* (0.70-0.99)	1.07 (0.93-1.23)	0.86 (0.63-1.19)	0.83* (0.70-0.99)	1.07 (0.93-1.23)
Residential status						
Community (ref)						
LTCF	1.31 (0.67-2.56)	1.39 (0.89-2.16)	0.78 (0.52-1.17)	1.31 (0.67-2.56)	1.39 (0.89-2.16)	0.78 (0.52-1.17)
Both	2.21* (1.70-2.88)	2.13* (1.87-2.44)	2.32* (2.10-2.57)	2.22* (1.71-2.90)	2.14* (1.87-2.45)	2.33* (2.11-2.57)
Socioeconomic status						
Non-LIS recipient (ref)						
Low income subsidy (LIS) recipient but non-dual	1.18 (0.80-1.75)	1.31* (1.07-1.59)	1.36* (1.16-1.60)	1.18 (0.80-1.75)	1.31* (1.08-1.59)	1.36* (1.16-1.60)
Medicare/Medicaid dual eligibility	0.85 (0.68-1.06)	0.77* (0.68-0.87)	0.88* (0.80-0.97)	0.85 (0.67-1.06)	0.77* (0.68-0.87)	0.88* (0.80-0.97)
RxHCC count	1.01 (0.98-1.04)	1.00 (0.98-1.01)	1.03* (1.01-1.04)	1.01 (0.98-1.04)	1.00 (0.98-1.01)	1.03* (1.01-1.04)

Table 7.4. *Continued*

Relevant comorbidities						
History of hip fracture	2.76* (2.04-3.73)	2.81* (2.38-3.32)	2.07* (1.80-2.38)	2.76* (2.04-3.73)	2.81* (2.38-3.32)	2.07* (1.80-2.38)
Diabetes mellitus	1.09 (0.88-1.34)	1.12* (1.00-1.25)	1.08 (1.00-1.18)	1.09 (0.88-1.34)	1.12* (1.01-1.25)	1.09 (1.00-1.18)
Rheumatoid arthritis	1.04 (0.86-1.26)	1.12* (1.01-1.24)	0.96 (0.89-1.04)	1.04 (0.86-1.26)	1.12* (1.01-1.24)	0.96 (0.89-1.04)
Congestive heart failure	1.14 (0.92-1.40)	1.25* (1.11-1.39)	1.34* (1.23-1.46)	1.13 (0.99-1.40)	1.24* (1.11-1.39)	1.34* (1.23-1.46)
Depression	1.12 (0.90-1.39)	1.12 (1.00-1.25)	1.16* (1.07-1.27)	1.12 (0.90-1.39)	1.12 (1.00-1.25)	1.16* (1.07-1.27)
End-stage renal failure	2.28 (0.99-5.24)	2.12* (1.40-3.19)	3.27* (2.58-4.14)	2.28 (0.99-5.25)	2.11* (1.40-3.19)	3.26* (2.57-4.13)
COPD	1.14 (0.90-1.43)	1.08 (0.96-1.21)	1.10* (1.01-1.20)	1.13 (0.90-1.42)	1.08 (0.96-1.21)	1.10* (1.01-1.20)
Other relevant medication use						
Anticonvulsants	1.13 (0.88-1.46)	0.94 (0.82-1.08)	1.06 (0.96-1.17)	1.13 (0.87-1.46)	0.94 (0.82-1.08)	1.06 (0.96-1.17)
Cancer chemotherapy	1.51* (1.05-2.17)	1.58* (1.32-1.88)	1.60* (1.41-1.82)	1.52* (1.06-2.18)	1.59* (1.33-1.89)	1.61* (1.41-1.82)
Glucocorticoids	1.02 (0.81-1.28)	1.04 (0.92-1.17)	1.07 (0.98-1.17)	1.02 (0.82-1.29)	1.04 (0.92-1.18)	1.08 (0.98-1.18)
Risk factor for fall						
Alzheimer's/dementia	0.87 (0.67-1.14)	0.89 (0.77-1.02)	0.99 (0.90-1.09)	0.87 (0.67-1.14)	0.89 (0.77-1.02)	0.99 (0.89-1.09)
Glaucoma	0.95 (0.76-1.19)	0.79* (0.70-0.90)	0.84* (0.76-0.92)	0.95 (0.76-1.19)	0.79* (0.70-0.89)	0.84* (0.76-0.92)
Stroke	0.92 (0.71-1.19)	0.91 (0.79-1.04)	1.03 (0.93-1.13)	0.92 (0.71-1.19)	0.91 (0.79-1.04)	1.03 (0.93-1.13)
Receipt of BMD testing	0.71* (0.58-0.88)	0.71* (0.64-0.79)	0.59* (0.55-0.65)	0.72* (0.58-0.88)	0.71* (0.64-0.79)	0.60* (0.55-0.65)

Note: * Significant at α=0.05 level

7.4 Discussion

Most prior studies of the effectiveness of osteoporosis medications have been conducted among females, and there is little knowledge about the effectiveness of osteoporosis medications in males. Our study helped fill this knowledge gap. We found a small increase in fracture risk associated with treatment initiation, which may appear counter-intuitive. However, this should not be taken to mean that the medications are ineffective. Rather, it suggests that treatment initiation is primarily a measure of the prescribing physician's assessment of the patient's risk of bone fracture. It would appear that physicians delay initiation of drugs until there is an elevated risk of bone fracture.

We did not find any significant evidence for heterogeneity of treatment effectiveness between men and women. Despite fewer treatment choices for men (selective estrogen receptor modulator is not available for men), the combination of evidence-based osteoporosis medications taken by men and women appeared to have equal effectiveness.

Among users, we found that drug adherence was low, with less than a third of both women and men achieving the standard for good adherence of 80%. This finding is in line with the literature.[92] Higher adherence was found to be associated with lower fracture risk, which suggests that adherence is key to optimal treatment outcomes. The 2012 AHRQ comparative effectiveness review on treatment to prevent fractures in men and women with low bone density and osteoporosis identified age, prior history of fracture, dosing frequency, concomitant use of other medications, and adverse effects of the osteoporosis medications as the top five factors affecting adherence.[92] Future research is needed to identify ways to improve patients' medication adherence targeting these

factors and to determine whether there are differential effects on men and women. In the meantime, physicians may consider prescribing intravenous (IV) injectable bisphosphonates such as zoledronic acid and IV ibandronate to patients with osteoporosis, because treatment outcomes for these IV bisphosphonates are independent of patient adherence.

This study also demonstrated the importance of adjusting for selection bias for treatment and competing risk of death when assessing the effectiveness of osteoporosis medications on the risk of subsequent bone fracture. The adjustment for selection bias by incorporating the inverse probability of treatment had a small effect on the study results, possibly due to insufficient control for disease severity. However, the adjustment for competing risk of death reversed the effect of sex on the fracture risk. This finding has important implications when interpreting results from prior research studies which generally have not adjusted for selection bias and competing risks. Also, this finding reinforces the importance of treatment initiation in men. Fracture risk in men may seem lower than that in women in unadjusted results, and even in adjusted results without adjusting for competing risk of death. However, fracture risk in men is masked by the higher mortality rate; men actually have a higher risk of fracture than women and deserve to be treated more appropriately.

In other findings, this study indicated that age 90 year and older, having prior hip fracture, end-stage renal disease, and transition between community and LTC facilities were strong predictors of subsequent bone fracture. For patients aged 90 years and older, conventional thinking is that the limited longevity negates the worthiness of treatment initiation.[114] However, undertreatment of the oldest old represents a missed opportunity

for fracture prevention given that they are at higher risk of bone fracture and more likely to die of a fracture.[75]

Patients with prior hip fracture are known to be at a higher risk of subsequent fracture.[115] According to the NOF clinician's guide, medications should be initiated in these patients.[78] However, we found in chapter 6 that the likelihood of treatment did not much increase in these patients. This represents another missed opportunity for fracture prevention in the current osteoporosis management. Medications need to be initiated for patients with prior hip fracture.

For patients with end-stage renal disease, the increased risk of bone fracture may be due to the abnormalities of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D, abnormalities in bone turnover, mineralization, volume, linear growth, or strength, and/or vascular or other soft tissue calcification related to ESRD. It is challenging to treat these patients because renal impairment is a contraindication of bisphosphonates. Fortunately, with the availability of the new drug denosumab, these patients may be more appropriately treated today than during the time period of the current study.

The much higher than average rates of bone fracture we saw among patients transitioning between community and LTC facilities is alarming. There are many issues during care transition including not taking medications appropriately and unsafe environments conducive to falls. Special attention should be paid to patients with care transition, and pharmacists may be able to help with appropriate medication taking by providing medication reconciliation, patient education, and periodic follow-up.

Last but not least, we found that receiving BMD tests was negatively associated with subsequent bone fracture. This is encouraging and suggests that fracture rates might be further reduced with additional screening. Since Medicare Part B covers BMD tests once every 24 months for beneficiaries who are at risk of developing osteoporosis, physicians should make patients aware of and take better advantage of this coverage to help identify osteoporosis and initiate treatment early.

This study also has several limitations. First, the CCW provides data on drug use only for Medicare Part D enrollees. Therefore, the findings may not generalize to Medicare beneficiaries not enrolled in Part D. Also, MAPD enrollees were excluded because they did not generate Part A and B claims necessary for identifying evidence of osteoporosis. However, use and choice of osteoporosis medication may differ between MAPD and PDP enrollees given the different financial incentives faced by free-standing and managed care insurers. Third, drug use and adherence during beneficiaries' Part A covered hospitalization and post-acute SNF stays were not observed and could lead to underestimating the effectiveness of osteoporosis treatment. Fourth, the primary independent variable of this study was use of any osteoporosis medication as opposed to individual classes of medication. The four classes of osteoporosis medications—bisphosphonates, calcitonin, parathyroid hormone analog, and selective estrogen receptor modulator—have been shown to have different effectiveness on different fracture sites. Due to the small sample size of non-bisphosphonates users, we were unable to conduct an analysis of the effectiveness of osteoporosis medications stratified by therapeutic class. Future research for comparative effectiveness of osteoporosis medications in different therapeutic classes is needed. Fifth, the follow-up time in this study was relatively short

(from 6 months up to 2.5 year). The short follow-up time may bias the estimate of treatment effectiveness toward the null because it takes a few months for bisphosphonates to take effect. Future research with longer follow-up time is also needed. Last but not least, our sample of males, especially treated males, was small, which likely was responsible for the failure to find significant effects of osteoporosis medication adherence on reducing fractures risk.

7.5 Conclusion

We found no direct evidence that initiation of osteoporosis medication reduced subsequent bone fracture risk overall, most likely due to indication bias in treatment initiation. Noteworthy is that the apparent positive impact of treatment initiation on males in unadjusted and partially adjusted models was, in reality, an artifact of higher mortality among men with osteoporosis. Being adherent to medication significantly reduced the risk of fracture in both sexes with no evidence of heterogeneity in treatment response among men and women.

8 Discussion

Although osteoporosis has a huge impact on our lives, it has been poorly managed. In aim 1, I found that prevalence of osteoporosis medications use was low (less than 50%) in both female community dwellers and LTC residents, but was especially low among LTC residents (below 35%). I also found that community dwellers and LTC residents differed substantially in age, comorbidities, and contraindications of osteoporosis medications, especially in chronic kidney disease. These factors may influence physicians' decision to prescribe evidence-based osteoporosis medication to their elderly patients. After adjusting for these factors at baseline, I found that LTC residents were still less likely to receive osteoporosis medications.

Another important issue related to residential status is care transition. Treatment patterns may change during a move from one healthcare setting to another or to home. Necessary treatment may be missed during this transition. In this study, I included switchers between community and LTC facilities but did not emphasize on the change during transition of residential status. I found that switchers behaved more like LTC residents than community dwellers in terms of osteoporosis medication use. Future research is necessary to investigate how treatment patterns change during transitions in residential status.

In terms of choice of treatment, although I found that bisphosphonates were the top prescribed medication to women with osteoporosis, regardless of residential status, LTC residents were more likely to use non-bisphosphonates compared to community dwellers. Use of calcitonin was much higher among LTC residents. This is a concern

given the lack of evidence in calcitonin's effective in reducing bone fractures. This lack of evidence was known before 2008 and may have been responsible for the relative declines in calcitonin use during our study period. Since that time a 2012 AHRQ review determined that calcitonin was not appropriate therapy for osteoporosis[92], and in 2013, a FDA panel voted that the risks of calcitonin salmon outweighed the benefits for the treatment of postmenopausal osteoporosis due to the higher rates of cancer among patients taking calcitonin[93]. These decisions are expected to affect the choice of osteoporosis medication of many osteoporotic patients, especially those in LTCs. Nonetheless, calcitonin has been shown to have an analgesic effect in acute vertebral fractures[94] and remains an alternative for patients with isolated spine osteoporosis or who have painful acute vertebral fracture and cannot tolerate other drugs. Future research will be needed to investigate change in patterns of evidence-based osteoporosis medication use after the FDA panel's decision to ban calcitonin.

In aim 2, I found low rates of osteoporosis medication use in both men and women diagnosed with osteoporosis, but it was especially low among men (around 25%). Even after adjusting for age and other characteristics, the probability of an elderly man with diagnosed osteoporosis being treated with evidence-based pharmacologic treatment was just 20% of that of an elderly woman. Although I found some factors associated with gender-related differences in treatment (e.g., higher prevalence of chronic kidney disease in men), most of the difference remained unexplained by the factors included in our model. This huge difference may be due to lack of awareness of the disease and its consequences in elderly men and their physicians.[99] Osteoporosis has long been seen as a

women's disease, so elderly men and their physicians may fail to manage it appropriately. Unfortunately, this lack of awareness was unobserved in our model.

When treated, elderly males with osteoporosis were much more likely to receive bisphosphonates compared to elderly females. Whether this is true today remains to be seen. In 2010, a new class of osteoporosis drug- RANKL inhibitors was approved by the FDA. The first RANKL inhibitor, denosumab, is indicated for treatment of osteoporosis in men and postmenopausal women at higher risk for fracture and/or with nonmetastatic prostate cancer or breast cancer. Denosumab is a once every 6 months subcutaneous injection covered by Part B and is recommended as first-line therapy along with bisphosphonates by the 2010 American Association of Clinical Endocrinologist Medical guidelines[96] and the 2014 NOF Clinicians' Guide.[106] Availability of RANKL inhibitors may increase men's likelihood of using evidence-based osteoporosis medications.

Besides low utilization rates, I also discovered important gender-related racial distinctions in osteoporosis treatment. Blacks had by far the lowest treatment rates (30% for women and 15.5% for men). Whites were in the middle (44.4% for women and 24.5% for men) with the highest rates for Asians (64.4% for women and 37.9% for men). Treatment rates among Hispanic women (46.5%) exceeded that of whites, but the rate for Hispanic men (19.3%) was significantly below that for white men. Such wide racial and ethnic differences raise important questions about osteoporosis education and access that deserve further research.

In aim 3, I found that use of osteoporosis medications was associated with higher hazard of bone fracture. Although counter-intuitive, this should not be taken to mean that the medications are ineffective. Rather, it suggests that treatment initiation is primarily a

measure of the prescribing physician's assessment of the patient's risk of bone fracture. It would appear that physicians delay initiation of drugs until there is an elevated risk of bone fracture.

Among users, I found that drug adherence was low, with less than a third of both women and men achieving the standard for good adherence of 80%. This finding is in line with the literature.[92] Higher adherence was found to be associated with lower fracture risk, which suggests that adherence is key to optimal treatment outcomes. The 2012 AHRQ comparative effectiveness review on treatment to prevent fractures in men and women with low bone density and osteoporosis identified age, prior history of fracture, dosing frequency, concomitant use of other medications, and adverse effects of the osteoporosis medications as the top five factors that affects adherence.[92] Future research is needed to identify ways to improve patients' medication adherence targeting these five factors.

The study findings of aim 3 also demonstrated the importance of adjusting for selection bias for treatment and competing risk of death when assessing the effectiveness of osteoporosis medications on the risk of subsequent bone fracture. The adjustment for selection bias by incorporating the inverse probability of treatment had a small effect on the study results, possibly due to insufficient control for disease severity. However, the adjustment for competing risk of death reversed the effect of sex on the fracture risk. This finding has important implications when interpreting results from prior research studies which generally have not adjusted for selection bias and competing risks. Also, this finding reinforces the importance of treatment initiation in men. Fracture risk in men may seem lower than that in women in unadjusted results, and even in adjusted results without

adjusting for competing risk of death. However, fracture risk in men is masked by the higher mortality rate; men actually have a higher risk of fracture than women and deserve to be treated more appropriately.

Medicare covers 95% of the elderly population aged 65 and older in the US and the CCW consists of a random sample of 5% of Medicare beneficiaries in a given year. Thus the CCW may be considered representative of the elderly US population. In addition, the CCW provides complete information on utilization of inpatient services, outpatient services, and prescription drugs for beneficiaries who enrolled in fee-for-service Medicare and in Part D as well. However, there are limitations with the CCW. First, the CCW provides data on drug use for Medicare Part D enrollees only. Data on drug use for non-Part D enrollees will not be captured in the CCW and thus non-Part D enrollees are excluded from the analyses. Also, Medicare Advantage prescription drug plan (MA-PD) enrollees were excluded because they do not generate Part A and B claims necessary for identifying osteoporosis and bone fractures. Third, drug use during beneficiaries' Part A post-acute SNF stays was not captured in the CCW due to current Center for Medicare and Medicaid Services (CMS) reimbursement policy (drugs dispensed during SNF stays are covered by SNF per diem payments and are not separately reimbursed). Fourth, adherence to drugs during beneficiaries' hospitalizations and SNF stays was not captured in the PDC. Lastly, although I could track the first mention of osteoporosis diagnosis back 5 years using the CCW condition summary file, I could not observe drug use prior to 2006. For this reason, I could only identify treatment initiation for incident osteoporosis cases after January 1, 2006. Also, I could not rule out

the possibility that prevalent but currently untreated cases had unobserved treatment use before January 1, 2006.

In conclusion, osteoporosis is undertreated in the elderly population in general; however, it is especially undertreated in men and in women residing in LTC facilities. Given that in aim 3, osteoporosis medications found to be effective in reducing subsequent bone fracture in both men and women adherent to their osteoporosis medication, once an elderly individual is diagnosed of osteoporosis, clinicians should initiate treatment early and help the patient be adherent to the osteoporosis medication.

Appendix Table 1. ICD-9 Codes for Osteoporosis, Hip and Other Fractures

Disease/condition	ICD-9 codes
Osteoporosis **(CCW algorithm for identifying study cohort)**	733.0x – osteoporosis
Hip/pelvic fracture **(CCW algorithm for identifying study cohort)**	733.98 – stress fracture of pelvis 808.xx – fracture of pelvis 820.xx – fracture of neck of femur
Fracture of spine and trunk **(for identifying fracture outcome)**	805.xx – fracture of vertebral column without mention of spinal cord injury 806.xx – fracture of vertebral column with spinal cord injury 807.xx – fracture of rib(s) sternum larynx and trachea 808.xx – fracture of pelvis 809.xx – ill-defined fractures of bone of trunk
Fracture of upper limb **(for identifying fracture outcome)**	810.xx – fracture of clavicle 811.xx – fracture of scapula 812.xx – fracture of humerus 813.xx – fracture of radius and ulna 814.xx – fracture of carpal bone(s) 815.xx – fracture of metacarpal bone(s) 817.xx – multiple fractures of hand bones 818.xx – ill-defined fractures of upper limb 819.xx – multiple fractures involving both upper limbs and upper limb with rib(s) and sternum
Fracture of lower limb **(for identifying fracture outcome)**	733.93 – stress fracture of tibia or fibula 733.94 – stress fracture of the metatarsals 733.95 – stress fracture of other bone 733.96 – stress fracture of femoral neck 733.97 – stress fracture of shaft of femur 733.98 – stress fracture of pelvis 820.xx – fracture of neck of femur 821.xx – fracture of other and unspecified parts of femur 822.xx – fracture of patella 823.xx – fracture of tibia and fibula 824.xx – fracture of ankle 825.xx – fracture of one or more tarsal and metatarsal bones 827.xx – other multiple and ill-defined fractures of lower limb 828.xx – multiple fractures involving both lower limbs with upper limb and lower limb(s) with rib(s) and sternum 829.xx – fracture of unspecified bones

Appendix Table 2. Pharmacologic Treatments for Osteoporosis by Dose, Administration Route, Price and FDA Approved Indication and Date

Drug Name	Brand Name	Dose	Route	Price per Month		FDA Approved Indication and Date
				Generic	Brand	
Bisphosphonates						
Alendronate	Fosamax	10 mg daily 70 mg once weekly	Oral Oral	$90 $80	$95 $85	Prevention/ treatment, September 29, 1995
Ibandronate	Boniva	2.5 mg daily 150 mg once monthly 3 mg every 3 months	Oral Oral IV	NA	$100 $100 $485	Prevention/ treatment, May 16, 2003
Risedronate	Actonel	5 mg daily 35 mg once weekly 75 mg daily for 2 days each month 150 mg once monthly	Oral Oral Oral Oral	NA	$100 $90 $100 $100	Prevention/ treatment, March 27, 1998
Zoledronic acid	Reclast	5 mg once yearly	IV	NA	$105	Prevention/ treatment, April 16, 2007
Non-bisphosphonates						
Calcitonin	Miacalcin, Fortical	100 IU every other day 200 IU daily	SQ, IM IN	NA	$425 $115	Treatment, August 17, 1995
Teriparatide	Forteo	20 mcg daily	SQ	NA	$845	Treatment, December 2002
Raloxifene	Evista	60 mg daily	Oral	NA	$100	Prevention/ treatment, December 1997

Source: AHRQ. *Fracture Prevention Treatments for Postmenopausal Women with Osteoporosis*. June 2008. (http://www.effectivehealthcare.ahrq.gov/ehc/products/8/95/LowBoneDensityClinician.pdf)

Appendix Table 3. Conditions and Diseases that Cause or Contribute to Osteoporosis and Fractures

Cycstic fibrosis	Pancreatic disease
Ehlers-Danlos	Primary biliary cirrhosis
Gaucher's disease	Hemophilia
Glycogen storage diseases	Leukemia and lymphomas
Hemochromatosis	Multiple myeloma
Homocystinuria	Sickle cell disease
Hypophosphatasia	Systemic mastocytosis
Idiopathic hypercalciuria	Thalassemia
Marfan syndrome	Ankylosing spondylitis
Menkes steely hair syndrome	Lupus
Osteogenesis imperfect	Rheumatoid arthritis
Porphyria	Alcoholism
Riley-Day syndrome	Amyloidosis
Androgen insensitivity	Chronic metabolic acidosis
Anorexia nervosa and bulimia	Congestive heart failure
Athletic amenorrhea	Depression
Hyperprolactinemia	Emphysema
Panhypopituitarism	End-stage renal failure
Premature ovarian failure	Epilepsy
Turner's & Klinefelter's syndromes	Idiopathic scoliosis
Adrenal insufficiency	Multiple sclerosis
Cushing's syndrome	Muscular dystrophy
Diabetes mellitus	Parenteral nutrition
Hyperparathyroidism	Post-transplant bone disease
Thyrotoxicosis	Sarcoidosis
Celiac disease	COPD
Gastric bypass	Dialysis
GI surgery	Peptic ulcer disease
Inflammatory bowel disease	Gastroesophageal reflex disease
Malabsorption	

Souce: NOF. *Clinician's Guide to Prevention and Treatment of Osteoporosis.* January 2010.[74]

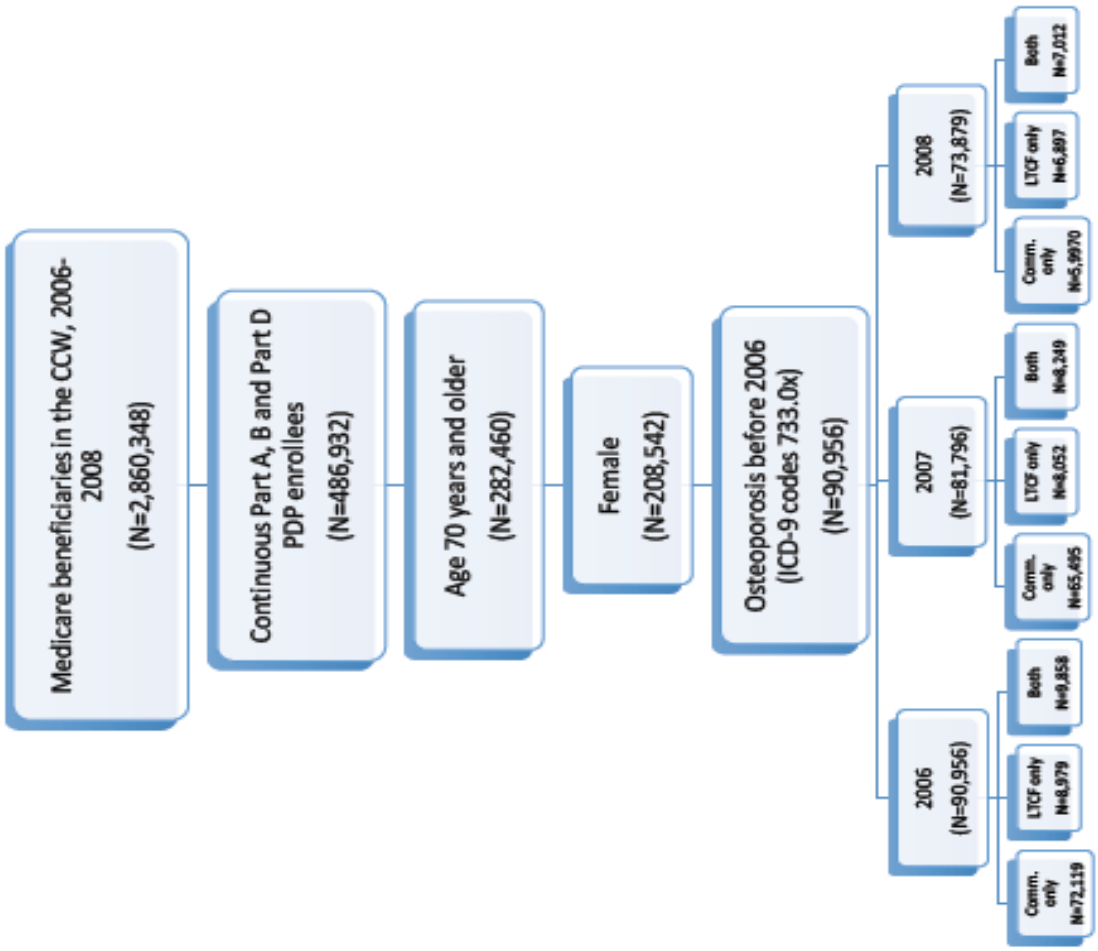
Appendix Table 4. Contraindications and Side Effects of Pharmacologic Treatments for Osteoporosis

Drug Class	Contraindications	Side Effects

Bisphosphonates	• CrCl<30 mL/min
	• Hypocalcemia
	• Esophagitis
	• Malabsorption syndrome
		• GI problems
		  ○ Heartburn
		  ○ Nausea
		  ○ Dysphagia
		  ○ Abdominal pain
		  ○ Constipation
		  ○ Diarrhea
		  ○ Gastric ulcer
		  ○ Acid reflux
		  ○ Dyspepsia
		• Osteonecrosis of the jaw
		• Osteomalacia
		• Subtrochanteric and diaphyseal femoral fracture
		• Bone, joint, muscle pain
		• Back pain

Non-bisphosphonates		
Calcitonin	•	• Nasal mucosa ulcer • Rhinitis • Epistaxis • Back pain • Joint pain • Headache
Parathyroid hormone	• Paget's disease • Kidney stone • Hypercalcemia • Bone metastases • Skeletal malignancy •	• Osteosarcoma • Positional hypotension • Hypercalcemia • Nausea • Leg cramps • Dizziness
Selective estrogen receptor modulator	• Breast cancer • Liver problem • Kidney problem • Hyperglyceridemia •	• Myocardial infarction • Pulmonary embolism • Deep vein thrombosis • Swelling in legs • Sudden change in vision • Hot flashes • Leg cramps

Appendix Figure 1. Sample Selection Flowchart showing Residential Status by Year (for Sensitivity Analysis only including Beneficiaries with Diagnosis of Osteoporosis)



Appendix Table 5. Characteristics of Female Medicare Part D Enrollees with Osteoporosis by Residential Status (for Sensitivity Analysis only including Beneficiaries with Diagnosis of Osteoporosis)

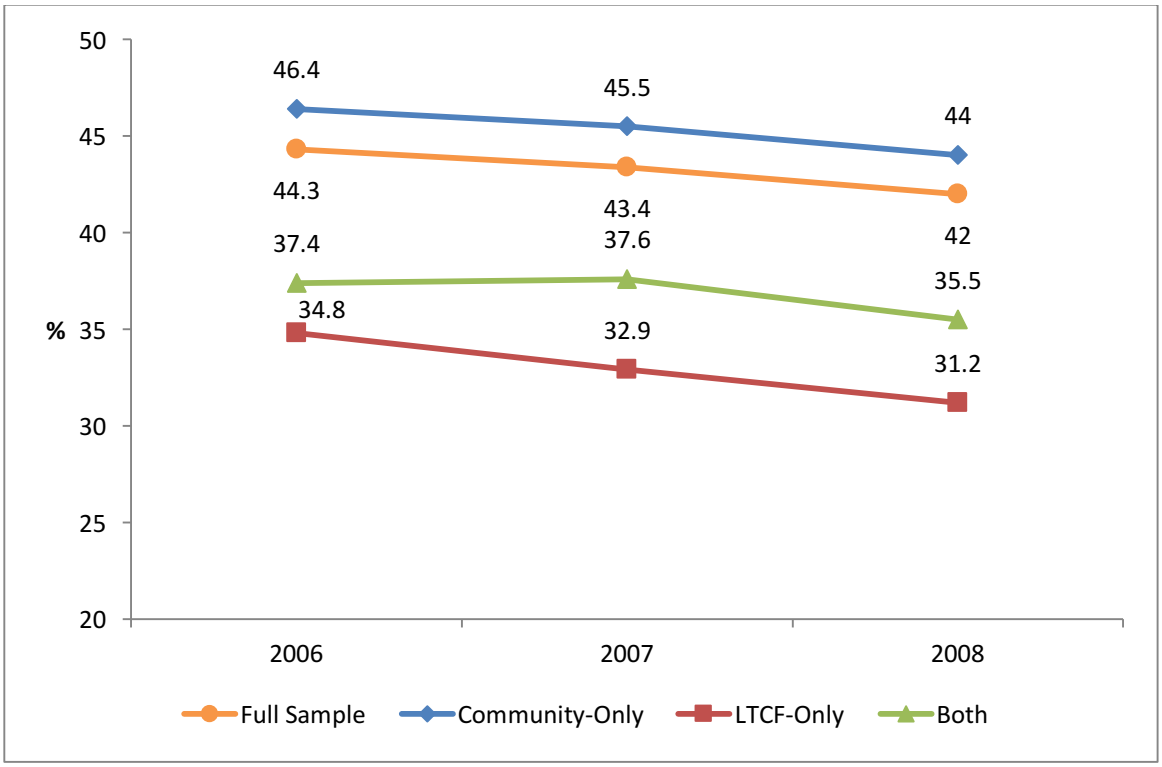
	Residence in 2006		
Beneficiary Characteristics	LTCF only (N=8,979)	Both (N=9,858)	Community only (N=72,119)
Residential status			
LTCF only			
2007	62.6	23.1	0.2
2008	44.4	17.8	1.6
Both			
2007	34.9	22.5	4.0
2008	25.2	13.8	4.7
Community only			
2007	0.4	6.7	89.8
2008	0.8	5.3	82.3
Demographic characteristics			
Age			
70-79	18.4*	20.8*	54.5
80-89	50.1*	49.5*	37.9
90+	31.5*	29.7*	7.5
Race/ethnicity			
White	89.6*	88.2*	83.8
Black	6.8*	7.0*	6.1
Hispanic	1.4*	2.3*	4.3
Other	2.1*	2.5*	5.8
Geographic region			
Northeast	24.8*	21.0	20.3
Midwest	27.7*	27.8*	22.3
South	37.5*	39.2*	40.4
West	10.0*	12.0*	17.0
Socioeconomic status			
Non- Low income subsidy (LIS)	5.2*	14.2*	52.5
LIS recipient but non-dual	0.6*	1.9*	5.0
Medicare-Medicaid dual eligibility	94.2*	83.9*	42.6
Health Status			
RxHCC count (sd)	7.9* (3.0)	9.6* (3.9)	7.0 (3.5)
Comorbidities causing or contributing to osteoporosis and fractures			
Prior hip fracture	22.3*	20.3*	6.0
Diabetes mellitus	34.5*	37.9*	29.7
Rheumatoid arthritis/osteoarthritis	65.8*	66.5*	55.1
Congestive heart failure	55.7*	61.5*	32.8
Depression	64.1*	58.7*	29.0

Appendix Table 5. ***Continued***

Beneficiary Characteristics	Residence in 2006		
	LTCF only (N=8,979)	Both (N=9,858)	Community only (N=72,119)
End-stage renal disease	0.3*	1.3*	0.5
COPD	30.5*	38.5*	24.8
Breast cancer	5.0*	5.4*	6.9
Medications causing or contributing to osteoporosis and fractures			
Anticonvulsants	21.6*	25.3*	11.8
Cancer chemotherapy	7.6*	12.4*	5.2
Glucocorticoids	15.3*	23.8*	20.9
Risk factors for fall			
Alzheimer's/dementia	79.7*	67.0*	15.8
Glaucoma	19.9*	20.0*	24.1
Stroke	35.1*	35.4*	15.9
Contraindications of all osteoporosis medications			
Chronic kidney disease	18.5*	23.0*	12.5
Any other contraindications of all osteoporosis medications	8.1	4.1*	7.3
Side effects of all osteoporosis medications			
GI problems	22.5	30.8*	23.0
Any other side effects of all osteoporosis medications	43.9*	28.0*	48.2
Number of chronic medications used per month (sd)	5.2* (2.8)	4.5* (2.7)	3.2 (2.3)
Receipt of BMD testing	1.7*	2.5*	18.6
Death rate over study period	50.5*	73.0*	17.2

Note: * Difference between cohort in LTCF only/both setting and those in community only are significant at α=0.05 level

Appendix Figure 2. Prevalence of Evidence-Based Osteoporosis Medication Use among Female Medicare Part D Enrollees with Osteoporosis by Year and Residential Status (for Sensitivity Analysis only including Beneficiaries with Diagnosis of Osteoporosis)



Note: *Difference between 2006 and 2008 significant at α=0.05 level.

Appendix Table 6. Temporal Patterns of Any Evidence-Based Osteoporosis Medication Use among Female Part D Enrollees with Osteoporosis by Residential Status (For Sensitivity Analysis only including Beneficiaries with Diagnosis of Osteoporosis)

		Residence in 2006		
Patterns of Use, 2006-2008	Total (%)	LTC only (%)	Both (%)	Community only (%)
Any use	53.1	43.8	47.2	55.0
Consistent use	29.7	20.1	16.2	32.7
New initiation				
2007	3.7	3.9	4.4	3.6
2008	3.7	4.4	4.2	3.6
Inconsistent use				
Use only in 2007	1.4	0.8	1.2	1.5
Use in 2006 and 2008	1.1	0.4	1.3	1.2
Discontinuation				
2007	7.1	4.9	14.2	6.3
2008	6.5	9.3	5.8	6.2
No use	46.9	56.2	52.8	45.0

Appendix Table 7. Characteristics of Female Osteoporosis Medication Users by Year and Type of Drug Used (for Sensitivity Analysis only including Beneficiaries with Diagnosis of Osteoporosis)

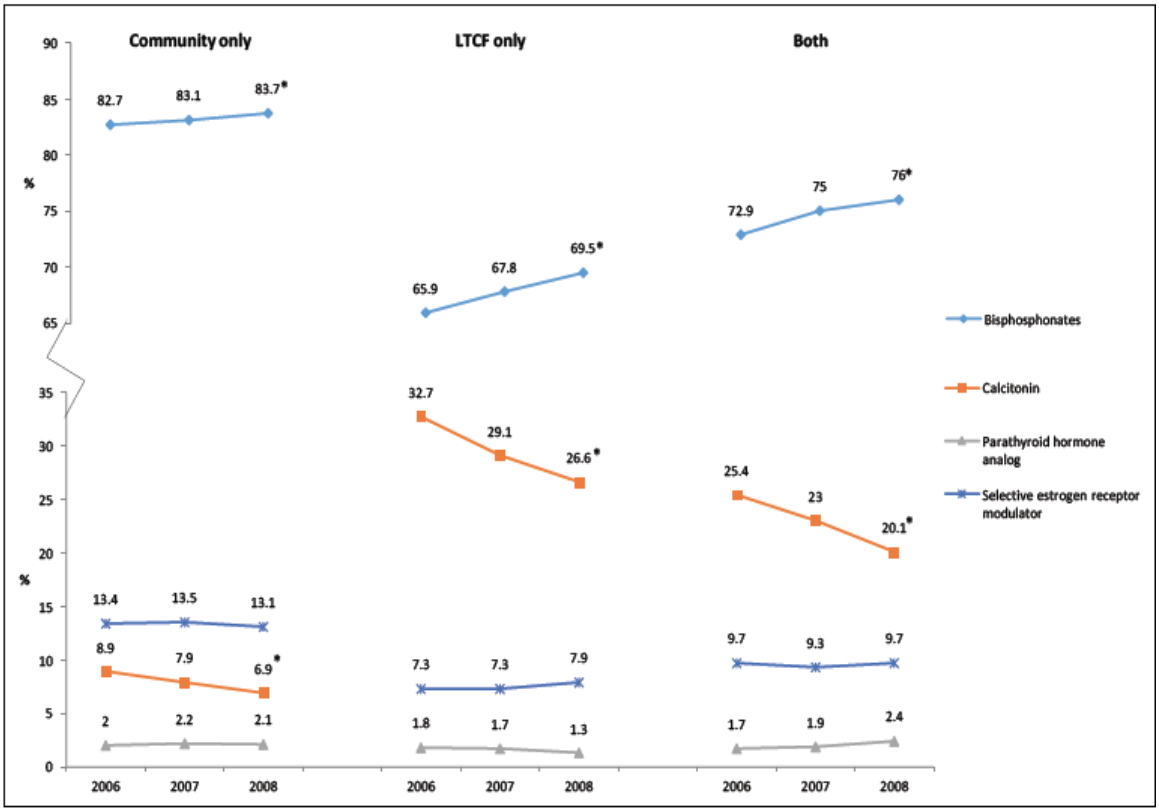
Beneficiary Characteristics	Bisphosphonate Users 2006 (N=32,408)	Bisphosphonate Users 2007 (N=28,867)	Bisphosphonate Users 2008 (N=25,466)	Non-Bisphosphonate Users 2006 (N=7,866)	Non-Bisphosphonate Users 2007 (N=6,671)	Non-Bisphosphonate Users 2008 (N=5,545)
Prevalence of use						
Bisphosphonates	80.5	81.2	82.1			
Calcitonin				12.3	10.8	9.3
Parathyroid hormone				1.9	2.1	2.0
Selective estrogen receptor modulator				12.6	12.7	12.5
Residential status in 2006						
Community only	85.3	88.5	91.2	73.7*	78.4*	82.6*
LTCF only	6.4	7.1	5.4	13.6*	14.8*	11.7*
Both	8.3	4.4	3.4	12.7*	6.8*	5.7*
Demographic characteristics						
Age						
70-79	51.3	53.7	56.9	44.6*	48.0*	51.0*
80-89	39.7	38.8	37.2	41.0*	40.4*	39.6*
90+	9.0	7.5	5.9	14.4*	11.5*	9.4*
Race/ethnicity						
White	84.2	83.6	83.2	88.2*	87.8*	86.4*
Black	4.4	4.3	4.2	3.4*	3.1*	3.1*
Hispanic	4.4	4.4	4.4	2.3*	2.7*	3.3*
Other	7.0	7.7	8.1	6.1*	6.4*	7.1*
Geographic region						
Northeast	20.7	20.7	20.7	19.9	20.3	20.1
Midwest	24.1	23.8	24	24.6	24.4	23.5
South	37.5	37.3	36.8	40.6*	40.5*	41.4*
West	17.8	18.3	18.6	15.0*	14.9*	15.0*
Socioeconomic status						
Non- Low income subsidy (LIS)	48.7	50.1	51.8	43.4*	46.5*	47.6*
LIS recipient but non-dual	3.7	3.7	3.9	4.2*	3.9	4.2
Medicare/Medicaid dual eligibility	47.7	46.2	44.3	52.5*	49.6*	48.1*
Health Status						
RxHCC count (sd)	7.4 (3.5)	7.2 (3.4)	7.0 (3.3)	7.7* (3.5)	7.6* (3.4)	7.5* (3.4)

Appendix Table 7. *Continued*

Comorbidities causing or contributing to osteoporosis and fractures						
Prior hip fracture	8.1	7.3	6.3	18.5*	20.7*	21.3*
Diabetes mellitus	26.4	25.9	25.6	26.7	25.9	26.0
Rheumatoid arthritis/osteoarthritis	53.9	53.5	52.7	57.5*	56.4*	55.8*
Congestive heart failure	30.7	28.7	26.6	36.5*	33.6*	31.4*
Depression	30.2	28.9	27.2	37.4*	34.2*	32.7*
End-stage renal disease	0.2	0.2	0.1	0.6*	0.4*	0.3*
COPD	24.0	22.8	21.5	27.1*	26.4*	24.7*
Breast cancer	7.0	7.0	7.0	5.6*	6.0*	6.0*
Risk factors for fall						
Alzheimer's/dementia	21.6	19.1	16.4	15.7*	14.2*	14.0*
Glaucoma	23.5	23.9	24.0	6.8	5.5	4.7
Stroke	15.9	15.0	13.9	22.4	21.9	20.5
Medications causing or contributing to osteoporosis and fractures						
Anticonvulsants	13.0	12.1	11.6	29.8*	25.3*	22.2*
Cancer chemotherapy	6.5	5.6	4.8	22.4*	22.7*	22.3*
Glucocorticoids	22.1	21.0	20.3	19.2*	17.0*	15.9*
Contraindications of bisphosphonates						
Chronic kidney disease	10.9	9.9	9.1	13.4*	12.0*	11.3*
Any other contraindications of bisphosphonates	7.2	7.5	7.6	6.5	6.9	7.2
Side effects of bisphosphonates						
GI problems	21.8	21.5	21.1	29.6*	29.8*	29.5*
Any other side effects of bisphosphonates	48.8	50.3	50.9	48.6	48.3*	49.5
Number of chronic medications used per month (sd)	3.7 (2.4)	3.6 (2.4)	3.4 (2.3)	4.1* (2.6)	4.0* (2.6)	3.9* (2.6)
Receipt of BMD testing	24.1	24.7	25.3	26.7*	25.9*	26.0*
Death rate of the year	7.9	8.5	7.9	10.5*	10.9*	11.0*

Note: *Difference between bisphosphonate users and non-bisphosphonate users are significant at α=0.05 level

Appendix Figure 3. Patterns of Osteoporosis Medication Use Among Female Drug Users by Year, Residential Status, and Drug Class (for Sensitivity Analysis only including Beneficiaries with Diagnosis of Osteoporosis)



Note: *Difference between 2006 and 2008 significant at α=0.05 level.

Appendix Table 8. Estimated Effects of Residential Status and Other Potential Predictors on Use of Any Evidence-Based Osteoporosis Medication among Female Medicare Part D Enrollees with Osteoporosis (for Sensitivity Analysis only including Beneficiaries with Diagnosis of Osteoporosis)

	Test for Main Effects		Test for Temporal Effects	
	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Residential status				
Community only (ref)				
LTCF only	1.16	(0.85-0.88)*	1.27	(1.24-1.31)*
Both	1.03	(0.96-0.99)*	1.26	(1.22-1.29)*
Year				
2006 (ref)				
2007	1.00	(1.00-1.01)	1.01	(1.00-1.01)*
2008	1.01	(1.00-1.01)	1.01	(1.00-1.01)
Residential status x year				
LTCF only x 2007	-	-	0.91	(0.89-0.93)*
LTCF only x 2008	-	-	0.86	(0.83-0.88)*
Both x 2007	-	-	0.89	(0.87-0.92)*
Both x 2008	-	-	0.80	(0.77-0.83)*
Age				
70-79 (ref)				
80-89	1.00	(0.99-1.01)	1.02	(1.00-1.03)*
90+	0.94	(0.92-0.95)*	0.94	(0.93-0.96)*
Race/ethnicity				
White (ref)				
Black	0.79	(0.76-0.81)*	0.61	(0.59-0.63)*
Hispanic	1.18	(1.14-1.21)*	1.37	(1.32-1.41)*
Other	1.44	(1.40-1.47)*	1.67	(1.63-1.72)*
Geographic region				
Northeast (ref)				
Midwest	1.02	(1.00-1.04)*	0.94	(0.92-0.96)*
South	0.96	(0.95-0.98)*	0.95	(0.93-0.96)*
West	1.05	(1.03-1.07)*	1.05	(1.02-1.07)*
Socioeconomic status				
Non-LIS recipient (ref)				
Low income subsidy (LIS) recipient but non-dual	0.91	(0.89-0.94)*	0.88	(0.86-0.91)*
Medicare/Medicaid dual eligibility	0.91	(0.90-0.93)*	0.84	(0.83-0.85)*
RxHCC count	1.02	(1.02-1.02)*	1.02	(1.02-1.02)*

Appendix Table 8. ***Continued***

	Test for Main Effects		Test for Temporal Effects	
	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Comorbidities causing or contributing to osteoporosis and fractures				
History of hip fracture	1.12	(1.10-1.14)*	1.23	(1.20-1.25)*
Diabetes mellitus	0.83	(0.82-0.84)*	0.80	(0.79-0.81)*
Rheumatoid arthritis/osteoarthritis	0.97	(0.96-0.98)*	1.11	(1.10-1.12)*
Congestive heart failure	0.84	(0.83-0.85)*	0.84	(0.83-0.86)*
Depression	0.90	(0.89-0.91)*	0.92	(0.91-0.93)*
End-stage renal disease	0.66	(0.61-0.72)*	0.74	(0.68-0.80)*
COPD	0.93	(0.92-0.94)	0.96	(0.95-0.98)
Breast cancer	0.99	(0.97-1.01)*	1.04	(1.02-1.06)*
Risk factors for fall				
Alzheimer's/dementia	0.93	(0.91-0.94)*	0.90	(0.88-0.91)*
Glaucoma	0.99	(0.98-1.00)	1.04	(1.03-1.06)*
Stroke	0.89	(0.88-0.90)*	0.90	(0.89-0.91)*
Medications causing or contributing to osteoporosis and fractures				
Anticonvulsants	0.98	(0.97-0.99)*	1.17	(1.15-1.19)*
Cancer chemotherapy	1.05	(1.03-1.07)*	1.15	(1.13-1.18)*
Glucocorticoids	1.04	(1.03-1.05)*	1.22	(1.20-1.23)*
Contraindications of all osteoporosis medications				
Chronic kidney disease	0.90	(0.89-0.91)*	0.90	(0.89-0.91)*
Any other contraindications of all osteoporosis medications	1.00	(0.99-1.02)	1.00	(0.98-1.01)
Side effects of all osteoporosis medications				
GI problems	0.97	(0.96-0.98)*	0.98	(0.97-0.99)*
Any other side effects of all osteoporosis medications	1.03	(1.02-1.03)*	1.03	(1.02-1.03)*
Number of chronic medications used per month	1.08	(1.08-1.08)*	1.07	(1.06-1.07)*
Receipt of BMD testing	1.23	(1.22-1.24)*	1.33	(1.31-1.34)*
Death	1.19	(1.17-1.20)*	1.54	(1.52-1.56)*

Note: *P<0.05

Appendix Table 9. Estimated Effects of Residential Status and Other Potential Predictors on Use of Non-Bisphosphonates among Female Osteoporosis Medication Users (for Sensitivity Analysis only including Beneficiaries with Diagnosis of Osteoporosis)

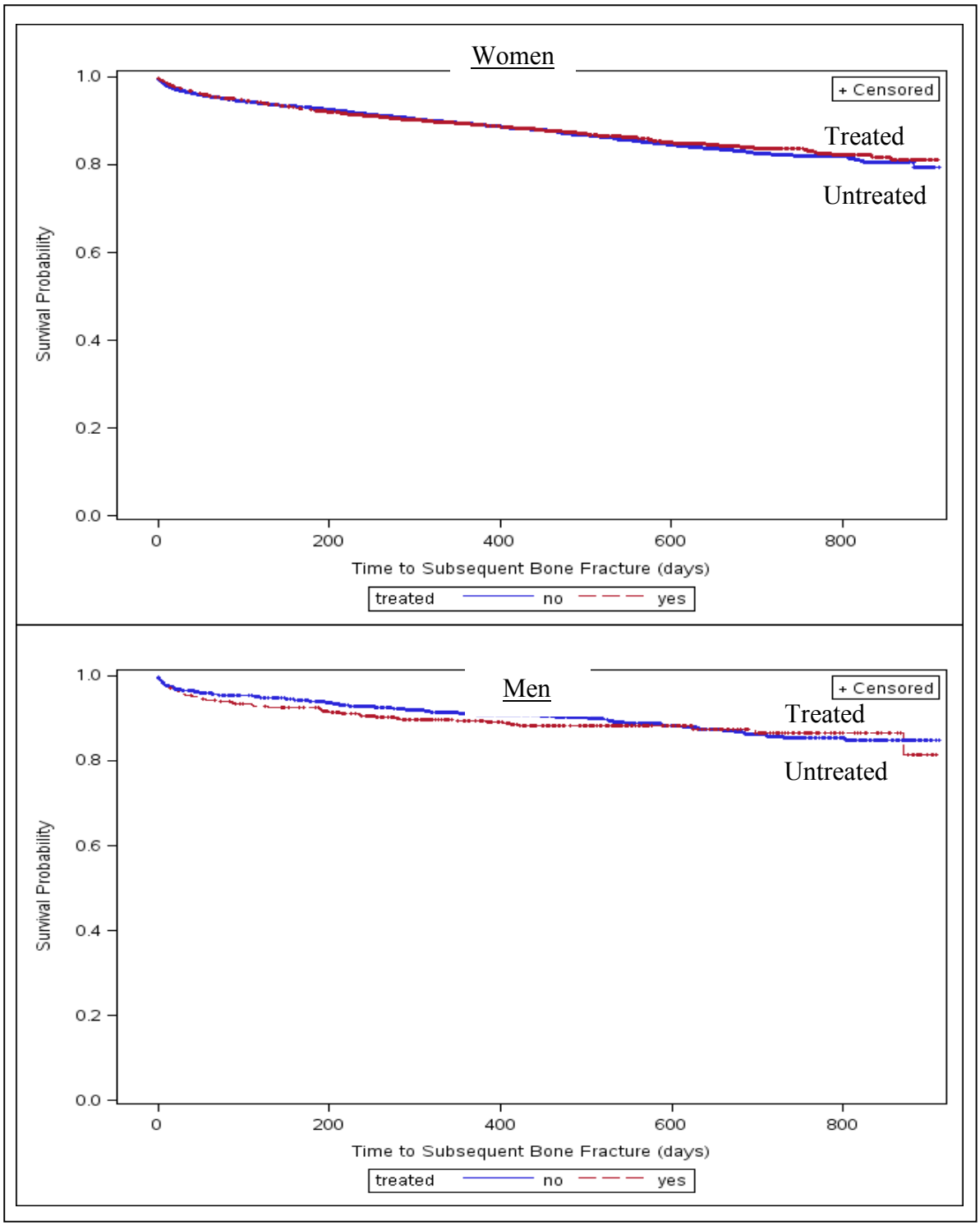
	Test for Main Effects		Tests for Temporal Effects	
	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Residential status				
Community only (ref)				
LTCF only	1.32	(1.26-1.38)*	1.27	(1.21-1.33)*
Both	1.15	(1.10-1.20)*	1.21	(1.15-1.27)*
Year				
2006 (ref)				
2007	0.98	(0.97-0.99)*	0.97	(0.96-0.99)*
2008	0.95	(0.93-0.96)*	0.94	(0.92-0.96)*
Residential status x year				
LTCF only x 2007	-	-	1.00	(0.97-1.04)
LTCF only x 2008	-	-	1.05	(1.00-1.09)*
Both x 2007	-	-	0.96	(0.91-1.01)
Both x 2008	-	-	0.92	(0.87-0.98)*
Age				
70-79 (ref)				
80-89	1.03	(1.01-1.06)*	1.04	(1.02-1.07)*
90+	1.12	(1.08-1.17)*	1.13	(1.09-1.17)*
Race/ethnicity				
White (ref)				
Black	0.71	(0.64-0.78)*	0.75	(0.69-0.81)*
Hispanic	0.62	(0.56-0.69)*	0.62	(0.56-0.69)*
Other	0.92	(0.85-0.99)*	0.92	(0.85-0.99)*
Geographic region				
Northeast (ref)				
Midwest	1.02	(0.97-1.08)	1.02	(0.97-1.06)
South	1.14	(1.09-1.20)*	1.14	(1.09-1.19)*
West	0.90	(0.84-0.95)*	0.90	(0.85-0.95)*
Socioeconomic status				
Non-LIS recipient (ref)				
Low income subsidy (LIS) recipient but non-dual	1.03	(0.96-1.10)	1.04	(0.98-1.12)
Medicare/Medicaid dual eligibility	1.05	(1.02-1.09)*	1.05	(1.01-1.08)*
RxHCC count	1.00	(0.99-1.00)*	1.00	(0.99-1.00)*

Appendix Table 9. ***Continued***

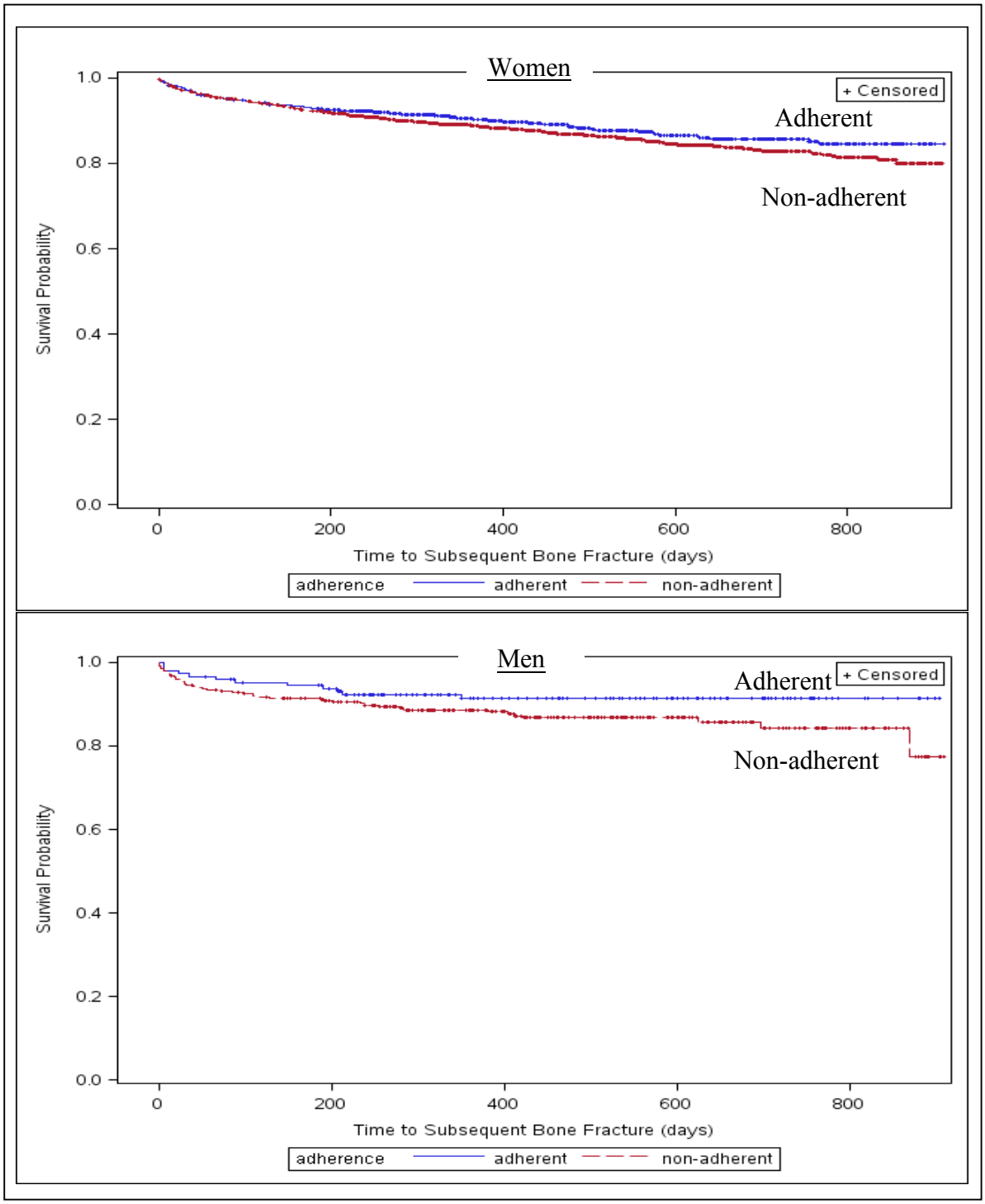
	Test for Main Effects		Tests for Temporal Effects	
	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Comorbidities causing or contributing to osteoporosis and fractures				
History of hip fracture	1.04	(0.99-1.09)	1.05	(1.01-1.09)*
Diabetes mellitus	1.00	(0.97-1.03)	1.00	(0.97-1.03)
Rheumatoid arthritis/osteoarthritis	1.03	(1.00-1.06)	1.02	(1.00-1.05)
Congestive heart failure	1.03	(1.00-1.06)	1.03	(1.01-1.06)*
Depression	1.08	(1.05-1.11)*	1.07	(1.04-1.10)
End-stage renal disease	1.81	(1.48-2.21)*	1.50	(1.30-1.74)*
COPD	1.06	(1.03-1.09)	1.05	(1.02-1.08)
Breast cancer	0.88	(0.83-0.93)	0.89	(0.84-0.94)
Risk factors for fall				
Alzheimer's/dementia	1.07	(1.03-1.10)*	1.06	(1.03-1.10)*
Glaucoma	0.98	(0.95-1.02)	0.99	(0.96-1.02)
Stroke	1.02	(0.98-1.06)	1.02	(0.99-1.06)
Medications causing or contributing to osteoporosis and fractures				
Anticonvulsants	1.00	(0.97-1.03)	0.99	(0.96-1.02)
Cancer chemotherapy	0.97	(0.93-1.02)	0.97	(0.93-1.01)
Glucocorticoids	0.99	(0.96-1.01)	0.98	(0.96-1.00)*
Contraindications of bisphosphonates				
Chronic kidney disease	1.04	(1.01-1.08)*	1.02	(0.99-1.05)
Any other contraindications of bisphosphonates	0.94	(0.87-1.02)	0.95	(0.88-1.02)
Side effects of all osteoporosis medications				
GI problems	1.02	(1.00-1.04)*	1.03	(1.01-1.05)*
Any other side effects of bisphosphonates	1.01	(0.99-1.02)	1.01	(0.99-1.02)
Number of chronic medications used per month	1.00	(1.00-1.01)	1.01	(1.00-1.01)*
Receipt of BMD testing	0.90	(0.88-0.91)*	0.90	(0.89-0.91)*
Death	0.98	(0.94-1.01)	0.98	(0.94-1.01)

Note: *P<0.05

Appendix Figure 4. Time to Fracture among Female and Male Medicare Beneficiaries Newly Diagnosed with Osteoporosis, by Treatment Use (Full Scale)



Appendix Figure 5. Time to Fracture among Female and Male Medicare Beneficiaries Newly Diagnosed of Osteoporosis and Treated, by Adherence (Full Scale)



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