

PREDICTION AND UTILITY OF A CLINICAL FRACTURE RISK SCORE IN
ADMINISTRATIVE CLAIMS

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ABSTRACT

ROBERT ALLEN OVERMAN: Prediction and Utility of a Clinical Fracture Risk Score in Administrative Claims
(Under the direction of Stacie B. Dusetzina)

The clinical manifestation of osteoporosis is osteoporotic fracture, which has been estimated to cost \$25.3 billion by 2025 within the US healthcare system. Osteoporotic fracture risk has been measured using various risk scores with the most prevalent being FRAX® from the World Health Organization. FRAX® scores are used clinically to guide treatment, but these scores and key inputs (such as bone mineral density and body mass index) cannot be measured in administrative claims. The objectives of this dissertation are 1) to create a claims-based fracture risk score to determine if administrative claims data can be used to predict FRAX® (interval validation); to evaluate how the risk score performs in a different population (external validity); and 3) to determine the best way to utilize the fracture risk score in a research study.

For this project, we linked registry data including clinical fracture risk factors from a multispecialty academic hospital with Medicare administrative claims for individuals receiving a dual energy x-ray absorptiometry scan (DXA) between 2009 and 2013. FRAX® has 4 different scores for 10-year fracture risk of hip and major osteoporotic fracture (MOF) with and without bone mineral density. We created the Calculated Fracture Risk Index (CFRI) to estimate these 4 scores. We found that we were able to predict a continuous FRAX® score with an adjusted R^2 that accounted for between 21 to 43% of variation in the estimates. We found these estimates to be internally valid.

Subsequently we used the linked dataset and a 20% random selection of fee-for-service Medicare beneficiaries to evaluate the external validity of our CFRI scores. We found no significant differences in CFRI and FRAX® ability to predict 1 year fractures. Additionally, we found CFRI and FRAX® to be similarly calibrated.

Lastly, we found that we were not able to sufficiently reduce confounding in a non-experimental comparative effectiveness study of alendronate users versus non-users to that of a randomized clinical trial using CFRI as a regression component or a restriction device. Although estimates including CFRI reduced confounding, residual confounding remained and estimates differed from those in the Fracture Intervention Trial (FIT); the gold standard in for our comparisons.

Overall CFRI appears to be internally and externally valid and a useful tool in reducing confounding compared to its non-use in osteoporosis research, though not to the level of an RCT. It also appears to be a reasonable proxy score for FRAX® when only administrative claims data are available. Therefore, CFRI when calculated in administrative claims should be useful for both researchers and policy makers to determine who is at risk for osteoporotic fracture.

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LIST OF ABBREVIATIONS

1se	One Standard Error
95% CI	95% Confidence Interval
ACR	American College of Rheumatology
ALN	Alendronate
AOM	Anti-osteoporosis medication
aR ²	Adjusted R ²
ASBMR	American Society for Bone and Mineral Research
AUC	Area Under the Curve
BMD	Bone mineral density
BMI	Body Mass Index
BP	Bisphosphonates
CCF	Cleveland Clinic Foundation
CFRI	Calculated Fracture Risk Index
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CPT	Common Procedure Terminology
df	Degrees of Freedom
DM	Diabetes mellitus (Type 1 & 2)
DXA	Dual Energy X-Ray Absorptiometry
EMR	Electronic Medical Record
Enet	Elastic Net

EVOS	European Vertebral Osteoporosis Study
FDA	Food and Drug Administration
FFS	Fee For Service
FIT	Fracture Intervention Trial
FNT	Femoral Neck T-Score
FRAX®	World Health Organization FRAX® 10-Year Fracture Risk Model
HCPCS	Healthcare Common Procedure Coding System
HD	High-Dimensional
HL	Hosmer-Lemeshow Test
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
ICD-9	International Classification of Diseases, Ninth Revision
IOF	International Osteoporosis Foundation
IQR	Inter-quartile Range
ISCD	International Society for Clinical Densitometry
JCAHO	Joint Commission on Accreditation of Healthcare Organization
LASSO	Least Absolute Shrinkage and Selection Operator
MAE	Mean Absolute Error
min	Minimum
MOF	Major Osteoporotic Fracture
MPAB	Medicare Part A & B
MPABD	Medicare Part A, B, & D

MPR	Medication Possession Ratio
MrOS	Osteoporotic Fractures in Men
MSE	Mean Squared Error
NIS	National Inpatient Sample
NOF	National Osteoporosis Foundation
NQF	National Quality Forum
OLS	Ordinary Least Squares
ONJ	Osteonecrosis of the Jaw
PCB	Placebo
PMW	Post-menopausal Women
PS	Propensity Score
PTH	Parathyroid Hormone
QM	Quality Measure
RCT	Randomized Clinical Trial
RMSE	Root Mean Square Error
ROC	Receiver Operating Curve
RR	Relative Risk
SD	Standard Deviation
SIPTW	Standardized Inverse Probability of Treatment Weights
SMRW	Standardized Mortality Rate Weights
SOF	Study of Osteoporotic Fracture
THIN	The Health Improvement Network

UAB	University of Alabama at Birmingham
UNC	University of North Carolina
US	United States
WHI	Women's Health Initiative
WHO	World Health Organization
ZA	Zoledronic Acid

CHAPTER 1: INTRODUCTION

1.1 Overview

Osteoporotic fractures are the clinical manifestation of osteoporosis and hip fractures and increase mortality, morbidity, future fracture risk, and health care costs while decreasing quality of life (1-4). The direct healthcare cost of osteoporotic fractures was estimated at \$18.7 billion US dollars in 2010 and expected to rise to \$25.3 billion by 2025 (5-7). Osteoporotic fracture risk increases with age and Medicare beneficiaries account for 80% of fracture-related costs (8).

Osteoporosis is defined as a bone mineral density (BMD) t-score of ≤ -2.5 standard deviations below the mean value for young healthy Caucasian women, measured using dual energy x-ray absorptiometry (DXA). However BMD alone does not predict all fracture; in fact, the majority of fractures occur in persons without osteoporosis (9-12). In 2010, 10.3 million US men and women ≥ 50 years of age were estimated to have osteoporosis, with a total of 43.1 million persons having low bone mass (5, 13, 14).

Decisions for treatment and prevention of osteoporosis and osteoporotic fracture utilize the osteoporotic BMD, prior fracture, and may use fracture risk tools to estimate future risk. FRAX® from the World Health Organization is a risk tool recommended by US guidelines, and is the most commonly used fracture risk tool (15). FRAX® estimates a patient's 10-year fracture risk and, if guidelines are used to make treatment decisions, is likely related to the therapy decision and may serve as a marker of future fracture risk. Research which fails to account for

fracture risk and its relation to treatment decisions may produce results that are counterintuitive and overestimate the effectiveness of specific anti-osteoporosis therapies (16, 17). In clinical practice FRAX® is a diagnostic risk tool and a potential confounder in research of comparative effectiveness or patterns of anti-osteoporosis medication use.

Although the variables used to calculate FRAX® should be available from a clinical interaction or from a medical records review, research using secondary data may not contain the variables necessary to calculate FRAX® or a recorded FRAX® score is generally not possible (18). For example, payers may be interested in evaluating the quality of care delivered to individuals they insure and basing reimbursement payments on that quality (19). Payers readily have access to administrative claims, which contain the reimbursed services a patient has received, but rarely contain any clinical variables. We are aware of only one claims-based algorithm for predicting fracture risk, however this score results in its own estimate of fracture risk, rather than producing an estimate of FRAX®, which is the fracture risk score clinicians use to make treatment decisions (20). Although useful in a research context, this administrative claims-based algorithm cannot be used directly for information at the clinical decision point, or as a measurement of guideline concordant care.

Rationale for the Calculated Fracture Risk Index (CFRI)

We propose to create a calculated fracture risk index (CFRI) to predict FRAX® using only administrative claims variables to provide payers and researchers with a proxy of the fracture risk score a clinician would have used to make a treatment decision. Although CFRI may not be the optimal tool to fully reduce epidemiologic confounding, whether it could be used as a proxy for FRAX for evaluations of care quality or to improve confounding control as a

disease risk in comparative effectiveness studies is unknown (21). Additionally, CFRI could be computed using existing data and made available to providers.

In non-experimental studies of treatment, it is challenging to validly contrast medication initiators to non-users due to baseline differences between the two groups, specifically due to confounding by indication (22-24). Approaches to making comparisons between these groups have included comparison groups of non-users (i.e., not using the medication of interest) or of groups using a different class of medication from the class of interest. Although non-users comparisons are generally not done, for our study we desire to compare effect estimates using CFRI to those which compared alendronate users to placebo users from the Fracture Intervention Trial (FIT) (25-27). The FIT trial represents the best estimate of the effectiveness of alendronate to non-users, because the placebo users are assumed to have similar medical histories and medication use as the alendronate users and change in fracture risk is attributed to the use of alendronate based on the theory of randomization. We will investigate ways that CFRI can balance baseline characteristics between alendronate users and a population of non-users by reducing confounding by indication in comparison to the FIT results.

The most promising technique where CFRI may be used is restriction, which can minimize confounding by creating more homogenous sub-populations (23). Which may be more likely to require treatment and medical care. This restricted population should be at a similar risk for fracture, with CFRI performing similarly across the entire population. FRAX® and by proxy CFRI are designed as tools to assist in making treatment decisions, therefore restricting the population to users and non-users with similar fracture risk based on the FIT trial will help to clarify the utility of these diagnostic risk tools to reduce confounding by indication for users versus non-users. Additionally, after restriction we will evaluate different

pharmacoepidemiologic methods for estimating osteoporosis treatment effects, including inverse probability of treatment weighting compared to unadjusted and multivariable-adjusted estimates. This analysis will evaluate the potential use of CFRI by payers to evaluate the utility of the current AOM treatment quality measures based on treatment guidelines.

1.2 Specific Aims

To address the influence of FRAX® on the treatment decision and subsequent fracture outcomes we will determine if it is possible to identify surrogates for FRAX® in administrative claims data. We are interested in the information a clinician had at the face-to-face interaction where a decision on initiation of treatment was made, which is most applicable to evaluation of the quality of care. This information (CFRI) will use claims-based encounters to approximate the risk score at the face-to-face interaction for female patients. The analysis is restricted to female patients only due to long-term risks of fracture differing between men and women as well as possible differences in the ability for FRAX® to identify long-term fractures by sex. The long-term goal of this work is to develop a proxy score for FRAX® which could be used to identify the quality of prescribing for individuals at risk for fracture and to reduce confounding in comparative effectiveness studies of AOMs. The objectives of this study are to develop and validate a claims-based algorithm for identifying FRAX® and to identify the best strategy for incorporating this measure into comparative effectiveness studies for optimal confounding control. To accomplish these goals, three specific aims have been crafted:

Aim 1: Develop and internally validate a claims-based fracture risk index (CFRI) to estimate FRAX® risk scores at clinical interaction (office visit) using clinical registry data linked to Medicare claims data.

Hypothesis 1: In the final model, there will be no significant difference in predicted (CFRI) to observed (FRAX®) scores based on aR^2 .

This aim will utilize clinical DXA registry data from the Cleveland Clinic Foundation that has been linked to Medicare Fee for Service (FFS) administrative claims. FRAX® scores are recorded during a DXA examination and include 10-year risks of major osteoporotic and hip fracture with and without BMD.

We will create CFRI by estimating FRAX® utilizing both content knowledge of variables associated with osteoporosis and fracture based on the 2004 US Surgeon General's report as well as identification of non-content variables associated with FRAX® using a high-dimensional variable selection method during the 365-days prior to DXA in only females (5, 17, 28). We will use an elastic net model to predict the independent variable (known FRAX®) using the factors associated with osteoporosis/ FRAX® as dependent variables (29-31). Validity of the estimates will be evaluated using calibration plots, R^2 , and mean-squared prediction error. This process will be repeated for all 4 types of FRAX® score; major osteoporotic fracture with and without BMD and hip fracture with and without BMD, with the internally validated model coefficients comprising the 4 CFRI algorithms.

Aim 2: Externally validate CFRI in a 20% random sample of Medicare beneficiaries by comparing the performance of CFRI and FRAX® to predict future fractures.

Hypothesis 2: There will be no significant difference between FRAX® and CFRI to predict future fractures as a continuous variable (calibration) between the linked and random sample.

Hypothesis 3: CFRI will identify fractures at a similar rate based on c-statistics in the random sample as FRAX® in the linked sample (discrimination).

This aim will utilize only females from the linked sample as well as a 20% random sample of Medicare fee-for-service beneficiaries. We will externally validate the CFRI algorithm using major osteoporotic fracture or hip fracture endpoints at 1-year, using hip fracture for hip risk scores, and major osteoporotic fracture for those scores. In the random sample a single randomly selected office visit with at least 365-days continuous enrollment prior to the visit will be used to calculate CFRI.

The data will be split into three groups, 1) linked sample FRAX®, 2) linked sample CFRI, 3) random sample CFRI. Calibration will be assessed using the Brier score and goodness-of-fit testing by use of the Hosmer-Lemeshow test. Discrimination will be measured using receiver operating curves (ROC) and area under the curve for the 3 populations. We will also examine the equivalency of calibration and discrimination between the populations (32).

Aim 3: Evaluate the utility of CFRI and restriction in a comparative effectiveness research study of alendronate users to non-users.

Hypothesis 4: Comparative effectiveness estimates will most closely approximate Fracture Intervention Trial results after restricting by trial inclusion criteria and incorporating CFRI, then estimates generated without CFRI.

Using the 20% sample of Medicare beneficiaries, we will compare estimates of fracture risk reduction in this sample for patients newly prescribed alendronate (users) versus patients with a new prescriptions for any drug other than medications prescribed to reduce fractures, including alendronate (non-users) to estimates generated from the randomized controlled Fracture Intervention Trial (FIT) which compared alendronate 10mg daily to placebo with up to 4 years follow-up (25-27). Three other approaches to define non-users, users of specific

medication classes, and anchoring on the receipt of a DXA. As a first step, we will restrict the candidate population to only those with CFRI values similar to patients in the FIT trial.

The goal of this aim is to present a likely way that payers would use CFRI to evaluate quality measures and reduce confounding in comparative effectiveness studies of AOMs. We will compare the effect estimates from our CFRI restricted population to those of the FIT trial to illustrate a user versus non-user application which may be applicable to payer quality measurement. To illustrate this we will present unadjusted, and multivariable adjusted estimates for the study population. The study population will be restricted to high-risk patients similar to FIT patients, and finally by all FIT inclusion/exclusion criteria with estimates created at each restriction. Lastly, we will fit a propensity score to model the receipt of alendronate using the content knowledge variables from Aim 1 (28, 33). This propensity score will be converted into a stabilized inverse probability of treatment weights, and weighted effect estimates will be produced. All analysis will utilize cox proportional hazards model and compare female new users of alendronate to new users of a non-AOM, with only the requirement of 365-days continuous enrollment in Medicare Parts A, B, and D prior to an office visit to calculate CFRI (22).

1.3 Importance of Proposed Research Plan

Benefits of Claims-based Algorithms for Defining Fracture Risk

The use of claims data to calculate FRAX® is important to payers and researchers for a number of reasons. FRAX® is the most widely recognized fracture risk score in current clinical practice and is a component of several US osteoporosis management guidelines. There are no methods to estimate FRAX® in administrative claims data wherein payers typically evaluate quality measures. Manual abstraction of FRAX® from medical records by payers would be

costly and time consuming as FRAX® scores and bone mineral density measurements are generally only available in unstructured data. The claims-based fracture risk index (CFRI) on the other hand is based solely in administrative claims and will allow payers to tie medical care to quality measures using data which they already collect. Additionally, CFRI can be used by payers to identify high-risk patients using readily available data without additional costs.

For researchers, collection of FRAX® from unstructured clinical data including the identification and collection of all patient-level FRAX® risk factors would be unfeasible on a population level. Calculating FRAX® using CFRI in administrative claims would provide the opportunity to account for FRAX® and treatment decisions related to FRAX® using available data. A clinician's decision based on National Osteoporosis Foundation (NOF) guidelines to initiate an anti-osteoporosis medication accounts for FRAX® risk, however without CFRI it cannot be measured or controlled for by researchers using administrative claims. Because FRAX® is a significant part of the US clinical osteoporosis guidelines with treatment decisions based on FRAX® risk, calculating FRAX® in administrative claims data available to payers and researchers will provide previously unavailable opportunities for the evaluation of care quality and effectiveness of therapies.

Payment Implications of Claims-based Fracture Risk Guidelines

Centers for Medicare and Medicaid Services (CMS) and commercial payers have increasingly moved towards reimbursement for medical care based on care quality. Quality measures generally are based on national guidelines and expert opinion. However, in osteoporosis, quality is assessed through diagnoses of osteoporosis, fracture, or AOM use. The rationale behind basing osteoporosis quality measures on these factors is related to the ability to capture these values in administrative claims (where most payers will evaluate care quality). As a

result, osteoporosis quality measures have only focused on specific groups at risk for fracture (AOM users, fracture patients, and patients with osteoporosis), rather than the general population as intended by the NOF guidelines. Payers reimbursing medical expenses, including CMS now linking reimbursement for hospital stays to quality may prompt both commercial payers and CMS to use quality measures based on NOF guidelines to increase clinician prescribing based on the guidelines, reduce preventable osteoporotic fractures, and not reduce their amount reimbursed for care administered (34).

CFRI may also be used to identify patients at high-risk for fractures and allow for intervention prior to a fracture, rather than after the patient has already had a fracture, been diagnosed with osteoporosis, or is prescribed an anti-osteoporosis medication. Up to thirty percent of patients with osteoporosis do not have a corresponding diagnostic code, and the majority of fractures occur in those without osteoporosis (35). Targeting patients based on fracture risk rather than prevalent fractures will allow payers to target primary prevention interventions rather than treatment of osteoporotic fractures, potentially reducing future costs.

Comparative Effectiveness Implications of Research

CFRI will be important in comparative effectiveness research (CER) as it may be used to create and evaluate “empirical equipoise” in osteoporosis research. Equipoise occurs in clinical practice when treatment options are considered interchangeable (no clear winner); for example, when a clinician chooses a therapy based on preference rather than on the merits of the specific therapy (21). For empirical equipoise to be valid, researchers need to be confident that a clinician views two patients at equal risk for fracture and make treatment decision based on preference.

In osteoporosis, fracture risk may be argued as the best proxy for empirical equipoise. Based on NOF guidelines, if two patients have equal fracture risks, it is a clinician’s choice as to

which medication to start rather than the guidelines. Ergo the clinician's preference should drive the choice of therapy for patients with similar fracture risks. In this way, propensity scores can be used to restrict or balance CFRI between the treated and the untreated and should serve as a proxy to control confounding by patient characteristics and create empirical equipoise. The results of these analyses should provide a basis to explain the difference in treatment decisions and effectiveness for the treatment of osteoporosis and osteoporotic fracture. Specifically, CFRI based restriction will be important for payers to determine optimal treatment groups, policy makers to evaluate the appropriateness of osteoporosis guidelines, and researchers to evaluate empirical equipoise in osteoporosis research.

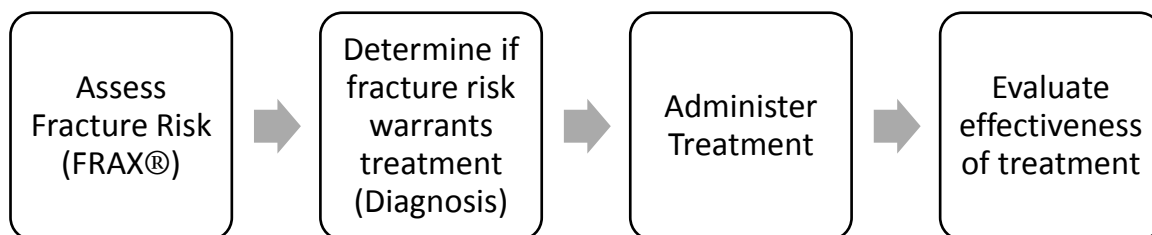
CFRI would be an essential tool for payers and those interested in the quality of care as well as a proxy for empirical equipoise. Although FRAX® itself is an imperfect estimate of a patient's future fracture risk, it is the most commonly used fracture risk tool in the US, has physician buy-in, and is currently used in national guidelines. Therefore, understanding patients' fracture risks retrospectively during clinical encounters will allow payers, policymakers, and researchers to assess appropriate care and identify ways to improve patient outcomes.

CHAPTER 2: BACKGROUND

2.1 Introduction

To help guide the reader through this project, an explanation of how each aim fits into the standard of care is warranted. Although standard of care is primarily a legal term, most authorities agree that a particular specialties standard of care is based on guidelines or consensus statements (36). In the US, the most common osteoporosis guidelines are those of the National Osteoporosis Foundation, and their Clinician's Guide. The 2014 Clinician's Guide describes the continuum of care as assessing fracture risk, diagnosing osteoporosis, administering treatment when appropriate, and measuring the effectiveness of treatment (Figure 2.1) (37).

Figure 2.1 Osteoporosis Standard of Care



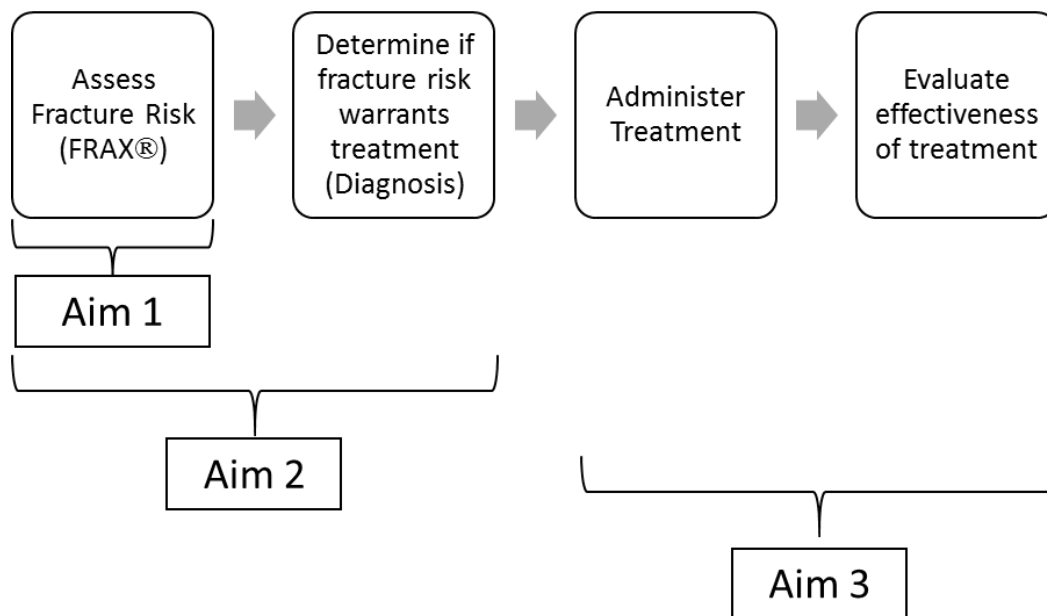
Revised from the Cosman et al, 2014 (37)

In brief FRAX®, DXA, and general health characteristics are first assessed by the clinician to assist in making a diagnosis. Once the patient has been assessed for osteoporosis by DXA bone density criteria, the clinician can then utilize the information gathered to determine if the patient meets the requirements for an osteoporosis diagnosis, or warrants treatment outside of

the osteoporosis diagnosis. For those patients who warrant treatment the next step is for treatment to be administered, and after a period of time for the effectiveness of therapy to be reevaluated. If a decision to treat is not made then the patients should be reassessed in the future to determine if a diagnosis or treatment are warranted.

The aims for this project are based on this standard of care model and follow along the continuum of care. We present where each of the Aims fall along the model in Figure 2.2. For this project, we are estimating FRAX® utilizing administrative claims data to create CFRI and evaluating its internal validity in Aim 1 which represents assessing fracture risk. Then in Aim 2 we are externally validating CFRI in a random population of Medicare beneficiaries and evaluating its ability to predict 1-year fracture rate, which requires both assessing fracture risk, and determining if the given fracture risk warrants treatment. Finally, in Aim 3 we are assessing the utility of CFRI to reduce confounding in the comparison of alendronate users to non-users, which spans both the administration of treatment and the evaluation of treatment effectiveness.

Figure 2.2 Aims role in Standard of Care



To understand why fracture risk and fractures in general are important, we felt it was first important to understand what type of fractures we were discussing. Therefore, we begin our background by discussing how fractures have been deemed to be osteoporotic, the relationship to osteoporosis, and the epidemiology of these fracture sites. Knowing the sites wherein osteoporotic fractures occur helps us to explore the costs, both economic and societal including morbidity and mortality of osteoporotic fracture, primarily in the US. Although these are the costs of fracture, there are ways to identify patients at risk prior to the fracture occurring, to this end we discuss the current fracture risk assessment tools, particularly focusing on FRAX®. To provide a context for building the claims-based fracture risk index (CFRI) we describe the data that FRAX® was built upon, including the patient characteristics and proprietary algorithm. With the discussion of FRAX® we also investigate its applicability to the US, including its use in the National Osteoporosis Foundation (NOF) guidelines and other risk tools that are currently being used in the US. Because AOM have been found to reduce fracture risk, and

recommendations are made for their use by the NOF guidelines we then describe the currently available Food and Drug Administration (FDA) approved therapies. We finish our background by discussing Andersen's model for Healthcare Utilization which provides a context for characteristics used to predict the use of AOMs in Aim 3.

2.2 Osteoporotic Fracture

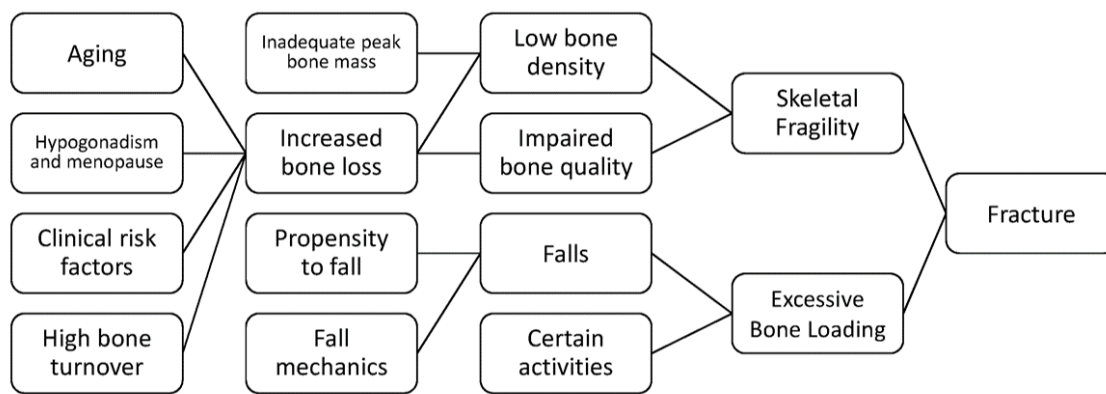
To better understand how osteoporotic fracture effects the population it is imperative to first understand what an osteoporotic fracture is. In this section, we discuss the different definitions of osteoporotic fracture including the definition currently favored by the FRAX® algorithm. The relationship between osteoporosis, bone mineral density, and fracture. The epidemiology of the fracture sites thought to be osteoporotic, and finally how these fracture sites have been identified in administrative claims-based analyses.

2.2.1 Definition

Although fracture is the clinical manifestation of osteoporosis, there is no universally agreed upon definition of osteoporotic fracture. The actual cause of a fracture is multi-factorial including heredity, fall mechanics, and bone density among other characteristics (Figure 2.3) (37-39). One common way to define osteoporotic or fragility fractures are those which occur in the presence of low bone mass with either no or a low-energy impact (40, 41). Low-energy impact fractures also commonly referred to as "fragility fractures" and are fractures which likely would have not occurred in healthy persons, particularly those that result from falls at a standing height or less (41, 42). When a person falls from a standing height the force exerted on the femur has been estimated to be at least 10 times the impact needed to fracture the femur (43). Only 10% of all falls result in serious injury and 5% in fracture (44). Cohort studies have found low bone mineral density, fall history, concomitant diagnoses, and how the patient falls are

associated with if a fall will cause a fracture (44-47). Studies of the addition of a hip protector for patients who have a fall history has not consistently shown fracture reduction, suggesting that only reducing the force on the femur at a fall is not sufficient to prevent fracture (48, 49). Fragility fractures were found to be responsible for the majority of hip and humeral fractures as well as 75% of vertebral fractures in a Swedish cohort (50). Though data from the Study of Osteoporotic Fracture (SOF) has suggested that only classifying fractures based on the amount of trauma needed to cause the fracture will lead to an under estimation of osteoporotic fractures (51).

Figure 2.3 Pathogenesis of osteoporosis-related fractures



From Cosman et al (37), adapted from Cooper and Melton (39), from Riggs (38)

SOF analyses also have demonstrated that all fractures, excluding those of the face, but including fractures caused by trauma are associated with low bone density measured at either the radius, hip or spine (51-53). For example, a one standard deviation decrease in BMD was associated with between 1.39 and 2.01 increase in the risk for hip fracture based on duration of follow-up and measurement site (51, 52). This increased risk also transfers to high-impact

fractures with patients having low bone mass at a greater risk of fracture after high-energy impact compared to those with normal bone mass (54, 55).

With the difficulties of quantifying the amount of trauma needed to cause the fracture, another definition based on fractures which are associated with low bone mass and increase after age 50 has been proposed (56, 57). Using this definition vertebral, rib, pelvic, humeral, forearm, hip, tibia and fibula in women, as well as fractures of the clavicle, scapula, and sternum are considered osteoporotic fractures (51, 53, 56, 58). In this definition, the only fracture sites which were not considered to be osteoporotic were skull and face, tibia and fibula in men, feet and toes, ankle, and patella fractures, though ankle fractures specifically have been found to be associated with low peak bone mass. One criticism of this definition is that it underestimates the burden of osteoporotic fracture for person under the age of 50 as the definition itself requires that fractures are at an increased rate after this period (40). Still another definition has been based on sites where reduced bone density has been associated with the fracture and consider fractures of the vertebrae (spine), proximal femur (hip), and distal forearm (wrist) as quintessential osteoporotic fractures (59).

Attempting to quantify osteoporotic fractures by bone mass or amount of trauma has not led to a concrete definition. However, to estimate the economic impact and societal burden of osteoporosis and osteoporotic fracture a common definition was sought. The first published report used discharges from the 1985 National Hospital Discharge Survey, National Nursing Home Survey, and National Ambulatory Medical Care Survey to determine what proportion of healthcare utilization with osteoporosis listed as a diagnosis were directly attributable to low bone mass (60). This report was the first to directly tie dollar amounts to osteoporosis and osteoporotic fracture using attribution rates for the contribution of osteoporosis to each medical

cost. Pathologic and non-pathologic fracture of vertebrae, pelvis, femoral neck, and humerus were the fracture sites most attributable to osteoporosis (70% attribution for patients aged ≥ 60) (60).

In 1995, the National Osteoporosis Foundation (NOF) convened an expert panel to assess the cost effectiveness of osteoporosis interventions. The expert panel viewed hip, spine, and forearm fractures as more than 50% attributable to osteoporosis, although the attribution did differ somewhat based on age and gender (42). The most attributable fractures were hip fractures (0.95 attribution probability) for all women aged 85 years or older. This panel for the first time addressed the differences in attribution of osteoporosis for men and non-white women. However, the only sites which were assessed were broadly defined as hip, spine, forearm, and other fractures which lack specificity for site specific probabilities and cost. The panel gave attribution weights which were designed to be utilized in cost analyses as the proportion of fracture costs which could be directly linked to osteoporosis and fracture in 1995 and are based solely on expert opinion.

With increasing use of administrative claims to evaluate osteoporosis, a 2011 meta-analysis and expert panel review provide likelihood estimates for fracture sites to be associated with osteoporosis. This working group for the first-time integrated ICD-9 codes for fractures into osteoporosis attribution to better estimate the burden and costs of osteoporosis and osteoporotic fracture. Femoral neck, pathologic vertebral fractures, lumbar, thoracic, closed distal forearm and radius/ulna (NOS), and pelvis were sites which had a median of rating of 9 (most likely because of osteoporosis) from the expert panel (61). Conversely open fractures of the proximal humerus and closed fractures of the skull and facial bones were viewed as least likely to be associated with osteoporosis (61).

In osteoporosis RCTs the difference in bone mineral density at the femoral neck or lumbar spine commonly are used as surrogate end points for treatment efficacy rather than differences in fracture rate. This is due to a very large population being needed to demonstrate a significant reduction in fracture rate between the treatment groups. Also, it has been suggested that it may be unethical to treat patients with established osteoporosis with placebo rather than active drug because we know that active drug can reduce fractures (62). In randomized clinical trials, all non-traumatic fractures other than those of the skull, fingers, and toes generally are used in endpoint definitions. In recent trials of osteoporotic medications, fractures at the femoral neck and vertebral spine commonly are specified as endpoints with other fractures combined into an omnibus category (63, 64). Trials of osteoporosis medications generally have separately analyzed hip and vertebral fractures with all fractures other than those of the skull, fingers, and toes also being assessed for treatment efficacy.

For epidemiologic studies the most commonly studied fracture definition is that of clinical spine, forearm, hip or shoulder which is defined by the WHO FRAX® tool as major osteoporotic fractures. This definition and specific sites are further discussed in section 2.5. In this proposal, we will utilize two osteoporotic fracture definitions. For aims 1 and 2 we will only use fracture sites included in FRAX® major osteoporotic fracture (spine, forearm, hip, or proximal humerus [shoulder]) with codes presented in Table 3.3 (65). While for aim 3 we will utilize a broader definition including all sites included in the MOF definition as well as pelvis tibia/fibula, clavicle, thoracic, and lumbar spine, because these were the sites from the Fracture Intervention Trial which corresponded to clinical fracture.

Osteoporotic fracture is the clinical manifestation of osteoporosis (low bone mass) or bone fragility. The first attempts to classify osteoporosis based on fracture risk found that the

90th percentile of 90% of all hip and vertebral fractures were approximately 2 standard deviations (SD) below the normal bone density distribution for both young men and women (66). This -2 SD threshold was found to hold for measurements at the hip, proximal femur, and distal radius in both men and women (66). When reporting on this topic Riggs et al were the first to provide support to the idea that if a patient decreased past a specific bone mineral density threshold then they were more likely to sustain a fracture.

In 1994 a specific threshold, that of -2.5 SD below the average value for a young healthy woman was proposed by the WHO for epidemiologic identification of osteoporosis using bone mineral density calculated by dual energy x-ray absorptiometry (DXA) (9, 67, 68). The reference value for defining osteoporosis among “young healthy women” were further clarified to the National Health and Nutrition Examination Survey (NHANES) III BMD values for 20-29-year-old Caucasian women (69, 70). Specifically, a femoral neck t-score is calculated as

$$\frac{(\text{BMD} - 0.858 [\text{reference mean}])}{0.120 [\text{reference SD}]}$$

with all other bone mineral density sites based on the same

population. The 1994 WHO definition also gives definitions for osteopenia (T-score -1.01 to -2.49), normal (T-score >-1.0), and severe osteoporosis (T-score ≤-2.5 and prevalent hip or vertebral fracture) (Table 2.1) (9). The WHO definition was clarified in 2008 to encourage use of the NHANES III reference values and measurement of BMD at the femoral neck for the diagnosis of osteoporosis (70).

Table 2.1: Osteoporosis Classifications

Bone Density T-Score	Diagnostic Category
Greater than or equal to -1.0	Normal
Less than -1.0 and greater than -2.50	Osteopenia
Less than or equal to -2.50	Osteoporosis
Less than or equal to -2.50 with one or more fragility fractures	Severe Osteoporosis

From WHO Technical Report, 1994 (9)

A position statement was presented in 2012 that argued that some of the under treatment and diagnosis of osteoporosis in the US may be due to a very limited definition of osteoporosis, which may need to be revised (71). To address insufficiencies of the current osteoporosis definition the Bone Health Alliance Working Group formalized a new definition in a 2014 position statement (72). The working group argues that patients who have experienced a low-trauma hip fracture and for those who have osteopenia by BMD who sustain a low-trauma vertebral, proximal humerus, pelvis, or, in some cases, distal forearm fracture, sites which are known to confer an increased future fracture risk, patients with a t-score ≤ -2.5 , as well as patients at an increased fracture risk based on fracture prediction tools should all be classified as having osteoporosis (72). This definition would include more persons in the US who previously had not been classified as osteoporotic and was intended to identify all persons at an increased fracture risk. At the present time, the new definition including fracture risk has not been formally accepted by payers as adequate for treatment reimbursement. If this new definition were to be adopted a formal process for assessing fracture risk based on data available to payers would need to be created and automated.

At the present time, BMD is important but not required in calculating fracture risk. Since 2006 the percentage of patients receiving DXA scans in the United States has diminished possibly due to a reduction in reimbursement in the outpatient setting (73-79) or a reduction in

serial scanning for patients where repeat scans are not warranted (76). However, King et al have suggested regardless of why fewer scans are being performed their decrease will lead to more osteoporotic fractures which will increase the cost of osteoporosis for the United States (74). Adding to the confusion is lack of consensus on when to start screening for osteoporosis, how often to screen, and whom to screen (80).

2.2.2 Epidemiology of Fracture

2.2.2.1 Hip Fracture

Hip fractures are fractures at the proximal femur either through the femoral cervix or through the trochanteric region (40). These fractures although only accounting for 20% of all osteoporotic fracture are the most readily captured and studied type of osteoporotic fracture as they typically require medical intervention (40, 81). It has been estimated that only 1% of all femoral fractures do not require medical intervention, possibly due to patients already lacking mobility and the risk of surgery outweighing the possible benefits of surgical fixation (82). Depending on location and severity of the fracture differing surgical interventions can be undertaken.

Incident hip fractures are associated with an increased risk of death within 1-year, with between an 8.4% and 36% of the risk of death attributed to hip fractures (83). Additionally, ~20% of patients require care at a long-term facility and only 40% regain the level of independence they had prior to the fracture. As such, hip fractures are responsible for much of the excess morbidity and healthcare cost associated with osteoporotic fracture. This has led to their use as a surrogate for the overall cost of osteoporosis and related care.

In the Rochester cohort increased between 1928 and 1982 before a decrease between 1983 and 1992, and a further decrease from 1992 to 2004 (84-86). Additionally, proximal femur

fractures decreased between 1989-1991 and 2009-2011 (87, 88). Results from the Framingham cohort suggest that when a person was born has as much to do with fracture rate as their age with more recent births having an increased fracture risk (89). Showing that hip fracture rates may differ based on US region. With only regional cohorts to base US hip fracture rates on, the National Hospital Discharge Survey for the years between 1970 and 1983 was used to make a nationally representative estimate. Between 1970 and 1983 hip fractures increased by 9.3% (90). A subsequent analysis of the National Hospital Discharge Survey (1965-1993) indicated a linear increase in hip fractures for men regardless of age group with a less sharp increase for women during the study period (91). This suggests that regional estimates alone may be insufficient to estimate hip fracture rates for the US.

The first estimate of hip fractures utilizing administrative data in the US utilized a 20% Medicare sample between 1985 and 2005 to estimate hip fracture in the United States. Using age adjusted rates hip fractures increased 9.0% in women between 1986 and 1995 before decreasing by 24.5% by 2005 (92). Men saw an increase of 16.4% between 1986 and 1995 before a decline of 19.2% by 2005 (92). These findings were echoed by an analysis of 1998 to 2007 rates of intracapsular hip fracture in a 5% sample of the Medicare population (93). In a non-Medicare commercially insured female population between 2000 and 2005 hip fractures increased (94). Which may suggest a continued increase in hip fracture for persons less than Medicare age (<65) with a decrease in hip fractures for older adults.

US and non-US hip fracture incidence rates were compared using the Rochester cohort between 1928 and 1982 and all other available estimates finding men to have similar fracture trajectories (84). While in women the US rates appear to stabilize in the 1950s, European and Oceanic estimates continued to rise (84). This was updated in 2011 finding that hip fractures

increased until the 1980s where they began to decline in the US, Canada, and Norway (95). In most other estimates hip fractures increased until the 1990s wherein they too began to stabilize or decline other than those from Japan. The study suggests that the secular trends are due to one of three rationales, 1) a change in the frequency of risk factors for fracture which act relatively late in the life course; 2) a change in the frequency of risk factors influencing bone strength and propensity to trauma in early life which feed through as altered fracture rates in successive birth cohorts; and 3) alterations in the demographic structure of the populations studied within age and sex strata (95).

2.2.2.2 Vertebral Fracture

Changes in the size and shape of the L1-L4 lumbar are typically considered vertebral deformities or fractures. It has been reported that less than 1/3 of all vertebral deformities noticed by radiologists necessitated medical attention with less than 1/10 necessitating hospital admission (96). Many patients complain of lower back pain or kyphosis (curvature of the spine) which prompts the discovery of vertebral fractures. Once a vertebral deformity is found it has been estimated that women have a four times higher risk of having an additional vertebral deformity without intervention (97, 98). Additionally, vertebral fractures were found to be associated with a 1.5 to 11.1 incidence rate increase in the Rochester cohort depending on site of future fracture (98). Though a study from European Vertebral Osteoporosis Study (EVOS) indicated that vertebral fractures were associated with an increase in hip but not forearm fractures (99). Vertebral deformities are typically augmented through balloon kyphoplasty or vertebroplasty which provide stability for the spine after the fracture. A recent randomized controlled trial has indicated that patients receiving either of these two treatments have similar long-term outcomes (100).

There are multiple definitions for vertebral fracture which make comparison across epidemiologic studies difficult. Some favor the idea of “you know one when you see one”, based on x-ray which is commonly referred to as expert opinion, however there have been recent attempts to create a more objective definition, these fractures are generally referred to as “clinical vertebral fractures” (101, 102). Clinical vertebral fractures generally are also based on if the patient sought medical attention care for their fracture. Morphometric vertebral fractures are diagnosed by vertebral measurements at the anterior, middle, or posterior heights of each vertebral column exceeded a pre-specified measurement (57, 101, 103). However, this technique has been found to underestimate the number of symptomatic and overall vertebral fractures (104). A second technique is based on a semi quantitative method proposed by Genant which summarizes the changes in shape as graded reductions in overall height and area (105). A further revision to a quantitative assessment has also been proposed (106). However, because all of the definitions differ at least slightly, they commonly disagree on the incidence and prevalence of vertebral fracture in the population (101, 107, 108).

In an EVOS study Leidig-Bruckner et al found that depending on age, sex, and definition of vertebral deformity prevalence ranged from 2% to 17% (estimated from figure) in men to 3% to 27% (estimated from figure) in women (109). The incidence of vertebral fracture has also been shown to increase after age 50. Based on data from the cohort in Rochester, Minnesota the incidence of vertebral fracture has increased from 659 per 100,000 persons to 968 per 100,000 persons in both sexes combined comparing 1989-1991 to 2009-2011 (88). The incidence of vertebral fracture increased by 280 for women (812 to 1092) and 338 (460 to 798) for men when comparing age adjusted rates from 1989-1991 to 2009-2011 (88).

In a study of patients (including men) admitted to an internal medicine service in Italy, 47.5% of all patients had at least one vertebral deformity. Of most interest was 79.7% of these vertebral fractures were found in persons without a previous diagnosis of osteoporosis. Although the rate of vertebral deformities is relatively high, with 32% (atraumatic vertebral fracture) or 25% (vertebral compression fracture) of women expected to have a measurable vertebral deformity in their lifetime (depending on definition), severe vertebral deformities representing ~10% of all vertebral deformities are responsible for substantial increases in back pain and disability (110-113). They also represent the majority of deformities which are symptomatic and require medical intervention (96, 114). Therefore, estimates based on report rather than measurement of vertebrae likely underestimate the prevalence of vertebral fracture.

2.2.2.3 Other Fractures

The most common fracture site after hip and vertebral are fractures of the wrist, typically classified as fractures of the ulna or radius. In an analysis of a commercially insured population between 2000 and 2005 Islam et al found the age adjusted incidence of wrist fractures to increase from 10.2 to 16.4 per 10,000 persons (94). Within this cohort, they also found an increase in rib and pelvis fractures between 2000 and 2005 (94). Based on the Rochester cohort, distal forearm fractures had increased by ~0.5% per year from 1945 to 1994 (115). While distal forearm fractures were reported to have decreased from 646 to 475 per 100,000 person years between 1989-1991 and 2009-2011 (88). Rib and pelvis fractures have also been noted to have decreased during this time period (88). However, the epidemiology of other fracture sites has not been well documented within the United States.

In a longitudinal study of the Geelong Osteoporosis Study 55.2% of the study population (females and males) had a fracture at some point in their lives. The study included all fracture

sites and did not discriminate based on age at fracture. First fractures more commonly occurred at young ages in men (<30 years of age), while females first fractures occurred mainly after age 50, possibly in a perimenopausal period (116).

2.2.3 Validated fracture sites

Hip fractures, as the mostly costly of osteoporotic fractures, have been the site most widely validated by medical record review (117). In the US only Ray et al have evaluated the validity of hip fracture codes in Medicare claims to have a sensitivity of 97% and a specificity of 98% comparing Medicare claims to hospital records (118). To our knowledge, the only other validation of hip fracture codes within the US was conducted comparing self-report of the Iowa Women's Health Study to Medicare claims with a sensitivity of 65% and specificity of 35% (119).

The group from Manitoba although not directly validating the codes for hip or other sites of fracture compared fracture prevalence based on a national cohort and those which they could validate within their own cohort. They found that in general ICD-9 codes generally underestimated the prevalence of hip fracture in females without a statistical significant difference in men (120). In the US only Curtis et al have validated the diagnostic codes for vertebral fracture finding a sensitivity of 56% (95% CI 43, 68%) and specificity of 69% (95% CI 58, 80%) comparing diagnoses and procedural codes to medical records (121).

2.2.4 Administrative claims-based definitions

Epidemiologic studies of fracture using administrative data typically include fractures of the hip, spine and humerus defined using International Classification of Disease, Ninth Edition (ICD-9) diagnoses of fracture and /or Common Procedure Terminology (CPT) or Healthcare Common Procedure Classification System (HCPCS) codes for repair of the fracture (Table 2.2).

Definitions may or may not take into account the duration of time between diagnoses and procedures, or how to differentiate between same site or multiple site fractures occurring around the same time. Most studies have defined osteoporotic fracture as hip and spine/vertebral fractures only, which underestimates osteoporotic fracture and has been shown to result in low power to detect a difference between AOMs (17). Because of this, including all fractures which can be logically attributed to osteoporosis (other than face, skull, fingers and toes) should increase the power to detect differences in effect size. However, in an analysis of GIO patients, the inclusion of all fracture sites increased the number of fractures, but reversed the directionality of the effect, suggesting that fracture locations outside of hip, vertebral, pelvis, humerus, or wrist may be poorly defined and may cause misclassification (17). When a fracture definition only including the hip, vertebral, pelvis, humerus, and wrist sites the expected directionality resumed, with most of these sites having administrative definitions which have been validated with medical records.

Many of these studies also use diagnosis codes for pathologic fractures (ICD-9 733.10-733.19) which are defined as fracture caused by disease other than those which are attributable to osteoporosis. In a review of pathologic fractures in Medicare claims, Curtis et al found that ~25% of patients with a pathologic vertebral fracture and ~66% of patients with a pathologic hip fracture had evidence of a possible cancer diagnosis associated with the fracture (122). However, the authors concluded that excluding pathologic fractures would result in a substantial underestimation of osteoporotic fracture (122).

Table 2.2 Administrative Claims Osteoporotic Fracture Definitions

First Author, Year	Sites Used
Halpern, 2011 (123)	Hip, vertebral, humerus, wrist, radius-ulna, femur, patella, tibia-fibula, ankle, pelvis, clavicle; Associated CPTs
Kim, 2010 (124)	Hip Pelvis, humerus, wrist; Accompanying CPTs
Liu, 2013 (125)	Hip, Radius, Humerus and Vertebral; Accompanying CPT codes
Lix, 2012 (120)	Hip (820-821.xx); Wrist (813.xx); Humerus (812.xx); Clinical Vertebral (805.xx) and accompanying CPTs
Looker, 2013 (126)	Hip, humerus, radius, spine
Martin, 2011 (127)	Hip, pelvis, femur, lower forearm, radius/ulna, humerus, vertebral, and other; Accompanying CPTs
Overman, 2015 (17)	Hip, pelvis, humerus, wrist, or spine; Accompanying CPTs
Patrick, 2011 (128)	Hip, distal forearm, spine, proximal forearm, humerus, non-hip femur, pelvis, clavicle/scapula, sternum, tibia/fibula; Accompanying CPT codes
Solomon, 2014 (129)	Hip Fracture (820.0x, 820.2x, 820.8, 733.14, 733.95) and accompanying CPTs
Taylor, 2011 (130)	Hip, pelvis, leg (other than hip), ankle, distal forearm, radius/ulna, humerus-closed, humerus, clavicle-closed, clavicle-other, spine, wrist

2.3 Burden of Osteoporosis and Osteoporotic Fracture

2.3.1 Prevalence

In the US estimates of osteoporosis prevalence have primarily been based on the National Health and Nutrition Examination Survey (NHANES) a cross sectional study of the non-institutionalized population of the United States (131). Based on femoral neck BMD from NHANES III (1988-1994), the NOF estimated that ~10 Million US adults aged 50 or older had osteoporosis with ~33 Million more US adults having osteopenia (14). This figure has been updated based on NHANES 2005-2010 to 10.3% (10.2 Million) of US adults aged 50 or older had osteoporosis and 43.9% (43.4 Million) US adults with low bone mass (osteopenia) (13). Estimates for European countries are similar to those of the US (40).

A 2014 analysis by Wade et al estimated the prevalence of osteoporosis in the US using total hip and lumbar spine BMD finding osteoporosis in 14% of females and 2% of US males 50 and older based on total hip BMD (8,237,129 persons) and 4% of males and 16% of females based on total hip and lumbar spine BMD (10,277,771) (132). Both of these figures are based on estimates combining weighted populations from NHANES III (1988-1994) and NHANES 2005-2008 and standardizing the population to 2010 US Census population (132). Prevalence estimates based on this methodology were significantly greater for European countries when lumbar spine was also used to estimate osteoporosis prevalence. The estimates by Wade et al for European countries however are lower than estimates by Hernlund et al basing osteoporosis prevalence for the European Union on population data extrapolated from NHANES III (133).

One estimate of osteoporosis prevalence has been made based on administrative claims data for the United States. Using the Medicare Fee-For-Service population from 1999-2005, and a definition both using a diagnosis, and an associated procedural code 29.7% (95% CI 29.6, 29.8%) of the population ≥ 65 were presumed to have osteoporosis. Specifically, 42.5% (95% CI 42.4, 42.6%) of women and 10.1% (95% CI 10.0, 10.2%) men in this age range were presumed to have osteoporosis (134). Age and sex specific estimates were similar in this analysis to those of Looker et al using the NHANES data (134, 135). However studies have found up to 30% of patients with osteoporosis on DXA did not have a corresponding diagnosis code within 1-year of DXA (35, 117, 136, 137).

Estimates of osteoporotic fracture within the US suggest that one out of every two Caucasian women and one in every five men in the US will experience an osteoporotic fracture at some point in their life (14).

2.3.2 Morbidity

Osteoporotic fracture particularly hip fractures are associated with a significant disability post-fracture. Between 20-60% of patients with hip fractures are reported to have needed long-term post-fracture care, including nursing home admission (14, 82). Additionally, in patients who survive to one year after fracture, between 40 and 49% of patients had returned to their pre-fracture state (14, 82).

A 2014 meta-analysis of studies providing health utility values (HUV), with a value of 0 being death and 1 being perfect health, for osteoporosis and osteoporotic fracture found a decrease of 0.19 for hip fractures and 0.17 for vertebral fractures at one year compared to pre-fracture value of 0.76 (138). Which indicates nearly 20% of a patient's health (quality of life) compared to perfect health is lost due to a hip or vertebral fracture. Immediately after the fracture the HUV values were 0.31 for hip fracture and 0.44 for vertebral fracture indicating that patients gain back a significant proportion of their expected health as time from fracture increases, but that a significant impairment is caused by fracture (138). A 2009 meta-analysis estimated the health of a patient after 1-year for vertebral fractures to be 0.30 and 0.24 for hip fractures (139). As meta-analyses are published it is important to note that osteoporosis and osteoporotic fracture are found to have a greater effect on health than previously thought (140). Overall osteoporosis and osteoporotic fracture cause a significant decline in patients' health in both the near and long-term, warranting early identification and intervention.

2.3.3 Mortality

Osteoporosis, regardless of osteoporotic fracture, is associated with an increased risk for mortality (4, 141, 142). This increased risk is typically due to associated complications (such as pneumonia due to lack of mobility) of the hip fracture, rather than the hip fracture itself. A 2010

meta-analysis reported a 5 to 8-fold increase in mortality risk in the 3 months after hip fracture (143). In the first year post-hip fracture mortality risk has been reported as high as ten times and as low as two times that of the general population (4, 144-146). The risk of death is greatest in the period immediately following the fracture, but continues to be elevated for the rest of a patient's life compared to the general populace (142, 143, 147). In an early analysis of the Rochester Cohort, 41% of patients with a hip fracture were deceased within one year after fracture (82). In women 60-69 an estimated 3,993 additional deaths per year could be attributed to osteoporotic fracture in the US, while an additional 9,303 deaths in men 60-69 based on data from a 1999 Australian study (4). Another study has estimated that 24% of all deaths after hip fracture are causally related to the fracture itself (148).

Following a vertebral fracture there also is an increased risk for death (4, 141, 142, 146, 147, 149-152). In one study women who had at least one morphometric vertebral fracture had a mortality rate 23% greater than that of women of a similar age (149). Clinical fractures however have a greater mortality risk with a hazard ratio of 4.4 reported in one study (151). Additionally, a prevalent vertebral fracture continues to be associated with an increased risk of fracture up to 22 years after the initial presentation of the fracture (152, 153).

Reports have indicated that there is no increase in mortality risk after wrist fracture (4, 142, 146, 150, 154, 155). However, in a 2002 study with 7 years of follow-up patients with a distal forearm fracture were found to be at increased risk for death, though this was most pronounced in patients with significant comorbidities (156). The increased risk was strengthened by a 2013 analysis of the Rochester cohort indicated that the risk of mortality is increased with fractures at the distal forearm at up to 22 years post-fracture, although this association was not previously documented in the same cohort with a shorter follow-up (146, 147). Numerous

studies have indicated an increased mortality risk following proximal humeral fracture (142, 147, 154, 155, 157-159).

The 2013 Rochester cohort study also indicated that mortality was increased at all skeletal sites other than hands/fingers, upper arm other than proximal humerus, and feet/toes (147). These results are similar to the fracture sites which were determined to be associated with osteoporosis by expert review (61). This may suggest that bone loss, and particularly osteoporosis is associated with an increased risk for fracture and death, therefore early identification of those at risk for fracture could reduce preventable deaths.

2.3.4 Economic

Osteoporotic fractures were estimated to cost the US healthcare system \$13.8 billion dollars in 1995, \$15.7 billion dollars in 2005 and are estimated to increase to \$25.3 billion by 2025 due to the aging population (7, 160). Hip fractures were responsible for nearly 65% of all osteoporotic fracture costs (160). Because the majority of fractures occur in older populations, in the US, Medicare is expected to be responsible for up to 80% of the fracture related costs (8).

Although AOMs are available for the treatment and prevention of osteoporosis, AOM treatment after hip and vertebral fracture has been reported to be as low as 15% in multi-national cohorts (161, 162). While the probability of treatment in a Medicare cohort was estimated at 28.5% in the year after hip fracture (129). An analysis of younger commercially insured patients indicated that only 9% of all osteoporotic fracture patients received an AOM within 1-year of the fracture (163). Additionally, non-adherence to AOM therapy is estimated to increase direct costs by 76% per month to the health system (164). As well as an increased risk of fracture for those who are non-adherent, which causes increased hospitalizations and associated costs (164, 165).

In patients currently receiving anti-osteoporosis medications the 6 months after a fracture were estimated to cost an additional \$10,000 compared to the period prior to the fracture (166).

2.4 FRAX® WHO Fracture Risk Assessment Tool

2.4.1 Background

In 1995, the National Osteoporosis Foundation (NOF) established a development committee to explore factors associated with and guidelines for treating osteoporosis (42). This committee examined and promoted the concept that fracture risk, rather than BMD alone, be used for establishing diagnostic and treatment thresholds. However, for this to occur a model of fracture risk would need to be created. The decision was made that intervention thresholds would be based on absolute probability of fracture (i.e. risk over a specific time period compared to the general population), derived from age, sex, life expectancy, and risk factors for fracture including bone mineral density (167-170).

To further investigate the relationship between clinical risk factors and fracture, the World Health Organization, with support from key osteoporosis-related organizations, established a group based at the WHO Collaborating Centre at Sheffield led by John A Kanis MD, FRCP, to evaluate and determine the relationship between clinical risk factors and fracture worldwide with and without the use of BMD (171). The risk tool which was created from this working group is property of the WHO rather than individual authors. This approach and goals were presented and endorsed by the IOF and NOF in year 2011(167).

Although osteoporosis is diagnosed based solely on a patient's BMD the ability to predict fracture based solely on BMD is no better than predicting heart disease based solely on LDL (9). This is due to a patient's risk for fracture also including other aspects including patient health, concomitant diagnoses, medications, likelihood to fall, and force of the fall among others.

Therefore, evaluations of risk should utilize information above and beyond BMD alone (170, 172). However, for a factor to make sense to be included in risk calculations it must present better accuracy for fracture risk above that found by BMD alone. Age is one example as it has been shown that an elderly patient with the same BMD is more likely to have a fracture than a young person (173).

The University of Sheffield group undertook a multitude of meta-analyses to quantify the risk of fracture associated with clinical risk factors and determine if the relationship between these factors were attenuated by age, sex or BMD. These meta-analyses assessed the relationship between BMI, BMD, alcohol intake, family history of fracture, smoking, glucocorticoid use, low milk intake, rheumatoid arthritis, and fracture risk (174-182). All of these factors other than milk intake were found to be associated with fracture risk irrespective of age, sex, and BMD (182).

Although absolute risk of fracture for the remainder of a patient's lifetime is generally greater than the 10-year risk, the WHO and IOF agreed that, for clinical practice, the risk of fracture was best expressed as the risk in the next 10-years. Using clinical practice as a model, 10-year probabilities of fracture were used as they would be easily understood in practice, AOMs had unknown efficacy past 5 years and the impact of risk factors may differ at longer time intervals (167). Specifically, studies have shown that the effect of BMD and associated risk factors on the long-term risk are varied due to differential changes in BMD over time as well as changes in lifestyle risk factors (183). For some AOMs, they have been shown to be no longer effective after cessation of use, this allows a 10-year risk to accommodate for treatment for 5 years with the risk returning to baseline in the next 5 years. Therefore FRAX® was designed to be based on 10-year risks rather than a different time period (167). Although FRAX® expresses 10-year risks, guidance on 1-year risks is espoused on their website "In young healthy

individuals (with a low mortality) the one year probability is approximately 10% of the 10-year probability. Thus, an individual with a 10-year fracture probability of 40% would have approximately a 1-year probability of 4%. Higher percentage figures are more readily understood by patients and clinicians.” This suggests that for patients who do not have a full 10-years of follow-up, fracture risk can be degraded by the amount of follow-up time they possess (65). Although this statement has been made for “young healthy individuals” this is the only advice given by FRAX® to reduce 10-year risks to a smaller fraction. It is likely that there will be lower fracture risk in the first years followed by a higher risk as the patient ages for many in a Medicare population, however without documentation we will use this method to calculate shorter risk periods.

2.4.2 Development of FRAX® Algorithm

The gradient of risk associated with different levels of BMD as well as the strength of association (beta-coefficients) from the meta-analyses were then evaluated in 9 primary prospective cohorts to create the FRAX® algorithm and externally validated in an additional 11 cohorts (18). The 9 sites were the Rotterdam Study, the European Vertebral Osteoporosis Study (later the European Prospective Osteoporosis Study (EVOS/EPOS), the Canadian Multicentre Osteoporosis Study (CaMos), Rochester, Sheffield, the Dubbo Osteoporosis Epidemiology Study (DOES), a cohort from Hiroshima and two cohorts from Gothenburg (184-198). The algorithms were then externally validated in an additional 7 international prospective cohorts including the Epidémiologie de l’ostéoporose (EPIDOS) study in France, the Study of Osteoporotic Fractures (SOF) in the United States, two cohorts from the Geelong study in Australia, the Osteoporosis Ultrasound Study (OPUS) drawn from five European countries, the Prospective Epidemiological Risk Factors Study (PERF) from Denmark, the York cohort in the United Kingdom, the Health

Improvement Network (THIN) research database from the United Kingdom, the Swiss Evaluation of Measurement of Osteoporotic Fracture Risk (SEMOF) study in Switzerland, the Women's Health Initiative (WHI) from the United States and the Miyama cohort from Japan (199-210). Of note, the US based cohorts were all female while the international cohorts included males and females. This may indicate that FRAX® is not well calibrated for US males.

The association between risk factors from the meta-analyses (presented as Table 2.3) and fracture risk were evaluated using Poisson regression. Four models (hip fracture and major osteoporotic fracture with and without BMD) evaluated the risk of fracture while accounting for the likelihood of death by the end of the 10-year period (144). This procedure rather than affixing death to every patient at the same age has been found to better represent the likelihood of fracture (144). Covariates used in the building of the models included age, time since start of follow-up, sex, continuous BMI, and with and without BMD (based on sex- and cohort-specific Z-scores). Significant interactions which had been identified during the meta-analyses based on the risk factor, age, sex, BMD, and time since cohort entry were entered into the model. If the interactions were subsequently not found to be significant they were removed from the model in a step-wise manner. The interactions that were used in the final model include age * sex, BMD * age, BMD*BMD, family history * age, prior fracture * age, BMI*BMI, and age*age (18, 171). Beta coefficients from these model variables are what are subsequently used to create the 10-year risks for major osteoporotic and hip fracture. The algorithm demonstrated an ability to better discriminate fracture risk using multiple risk factors than BMD alone (18).

Table 2.3: Risk Factors Included in the Fracture Risk Assessment Model (FRAX)

Clinical Risk Factors Included in the FRAX Tool	
Current age	Rheumatoid Arthritis
Gender	Secondary causes of osteoporosis: Type1 (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<40 years), chronic malnutrition or malabsorption and chronic liver disease
A prior osteoporotic fracture (including clinical and asymptomatic vertebral fractures)	Parental history of hip fracture
Femoral neck BMD	Current smoking
Low body mass index (BMI, kg/m²)	Alcohol intake (3 or more drinks/d)
Oral glucocorticoids ≥ 5 mg/d of prednisone for >3 months (ever)	

From: WHO Technical Report (171)

There are two fracture risk outputs from the FRAX algorithm, one for 10-year risk of hip fracture and a second for 10-year risk of major osteoporotic fracture. However, if a patient's femoral neck BMD is available, outputs (10-year risks) will be created that both use BMD and BMI alone, therefore creating 4 rather than 2 outputs. We provide the specific fracture sites used for calculation of the 10-year risks including the medical locations of these fractures in Table 2.4.

Table 2.4 FRAX® 10-year risk sites

FRAX® Output (10-year risk)*	Fracture sites (Medical Definition)
Hip fracture	Hip (Proximal Femur)
Major osteoporotic fracture	Hip (Proximal Femur), Spine (Clinical vertebral fractures [L1-T4]), shoulder (proximal humerus), or wrist (distal radius)
*: Can be calculated using femoral neck BMD (when available) or Body Mass Index (BMI) alone. Producing two outputs one with BMD and one without when BMD is available.	

FRAX® outputs the 10-year risk of hip fractures separately as this is the fracture site associated with the greatest disutility, mortality, and healthcare costs, as well as prompting the use of the femoral neck BMD value in the algorithm as it is a strong predictor of hip fracture.

FRAX defines major osteoporotic fractures as fracture of the hip, spine, shoulder (proximal humerus), or wrist (65). It has been suggested that these fractures were classified as osteoporotic due to their increased association with age and disability and were first used as osteoporotic fractures by Kanis et al in 2000 (211). Earlier publications had regarded other fracture sites including wrist, ankle, etc however these likely were used because epidemiologic data was available.

The calculation of FRAX® is based on weighted beta coefficients for each of the risk factors and risk factor interactions, however the model is based on 9 cohorts which may not actually be representative of fracture risk in a general population. To accommodate for this the WHO group has recalibrated the beta-coefficients from the model to the epidemiology of specific countries to create 10-year risk estimates for the general populace, with the first calibration being to the UK (212). FRAX is currently calibrated for 57 countries across Europe, North America, Asia, and Australia (65) and is available on the web (<http://www.shef.ac.uk/FRAX/>), however a batch program is also available. Research has found that expressing osteoporotic fracture risk as absolute rather than relative risk is better understood and accepted by both specialists and non-specialists (213). Based on clinical research and anecdotal evidence FRAX® is widely used in clinical practice.

Although FRAX® currently is the most widely used and validated osteoporotic fracture risk score it is not overly indicative of actual fracture risk. The c-statistics in the validation cohorts ranged from 0.78 (Hip fracture with BMD) to as low as 0.60 (Major osteoporotic without BMD) (18). Therefore, using FRAX® scores alone will not eliminate confounding by fracture risk, but offers the best estimate of the fracture risk a clinician could have accounted for when making a treatment decision. The FRAX® authors state that FRAX® is a "...technology

platform on which to build as new validated risk factors become available” and “...provides an aid to enhance patient assessment by integration of clinical risk factors and/or in combination with BMD” but that FRAX® itself is not a perfect measure of fracture risk (214). Although FRAX® itself may imperfectly predict fracture, its use in clinical practice make its results more applicable to practice than a perfect epidemiologic fracture score.

2.4.3 US-FRAX

The current FRAX® interface for the US-FRAX calculator is presented as Figure 2.4. The first iteration of the FRAX-US algorithm was calibrated to the Rochester cohort which consisted of hip and major osteoporotic fracture incidences from the inhabitants of Olmstead County, Minnesota between 1989 and 1991 and national mortality rates (87, 215). If the Olmstead County hip fracture rate was standardized to the 2000 US non-white population, similar incidence rates would be produced for both its (3.86 per 1,000) and an analysis of the 2001 National Inpatient Sample (NIS) (3.91 per 1,000) (7). However, the estimates of hip fracture incidence were greater in the NIS analysis due to a secular aging of the population, the hip fracture rates were updated to the NIS rates and revised to hip fracture based on a specific age rather than in 5-year groups to include updated mortality and incidence rates (215).

Figure 2.4 US-FRAX® web interface

FRAX® WHO Fracture Risk Assessment Tool

Home Calculation Tool Paper Charts FAQ References English

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: **US (Caucasian)** Name/ID: [About the risk factors](#)

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
Age: Date of Birth: Y: M: D:

2. Sex ☐ Male ☐ Female

3. Weight (kg)

4. Height (cm)

5. Previous Fracture ☒ No ☐ Yes

6. Parent Fractured Hip ☒ No ☐ Yes

7. Current Smoking ☒ No ☐ Yes

8. Glucocorticoids ☒ No ☐ Yes

9. Rheumatoid arthritis ☒ No ☐ Yes

10. Secondary osteoporosis ☒ No ☐ Yes

11. Alcohol 3 or more units/day ☒ No ☐ Yes

12. Femoral neck BMD (g/cm²)
Select BMD

Weight Conversion

Pounds kg

Height Conversion

Inches cm

03373252
Individuals with fracture risk assessed since 1st June 2011

From WHO FRAX® Website (<http://www.shef.ac.uk/FRAX/>) (65)

The comparison of major osteoporotic fractures from the NIS analysis to the Rochester cohort indicated a large discrepancy between rates. It was determined that this difference was primarily due to a high rate of vertebral fractures in the Rochester cohort that was not also shown in the NIS analysis. This was further supported by looking at data from the SOF cohort which gave similar vertebral fracture rates to those of the NIS. To account for this US-FRAX now uses a calculated ratio of vertebral fractures to hip fractures that was first established in Malmo, Sweden population (211, 212). The other fracture sites (shoulder and forearm) use updated epidemiologic estimates from the NIS analysis. Finally, mortality estimates were updated to 2004 figures from 2001 figures.

The last issue that was addressed in the updated US-FRAX version 3.0 algorithm was the overlap between each of the fracture sites, which if not accounted for would increase the rate of incident fracture. Based on the experience from the Malmo population and comparison of data to the SOF cohort, incident fracture was discounted by 10% for those under 65, 15% in 65-74 year olds, and 20% for person's ≥ 75 years of age (215).

The WHO group utilized these updated data points to complete the US-FRAX revision. In a publication which compared the calculated rates based on FRAX® 2.0 and 3.0, there was a significant reduction in the overall risk of major osteoporotic fracture and hip fracture based on the revised estimates (216). These revisions most affected the fracture probabilities for young men and women, with little change in estimates for older persons (216). No further US-FRAX revisions were made through the end of 2014. FRAX® estimates in the US are currently available for Caucasians, Blacks, Asians, and Hispanics (categories published by the WHO). These estimates were created by taking the ratio of fractures in these age groups compared to Caucasians based on epidemiologic data (59, 217).

2.4.4 Other Risk Scores

The goal of risk scores has primarily been to identify risk factors which are predictive of osteoporosis or fracture. However, the majority of these risk tools has only been internally validated and includes a significant number of variables that providers may or may not be able to access.

Other than FRAX® two risk scores, Garvan and QFracture have been validated in at least one independent cohort. Garvan is a risk score based on the Dubbo Osteoporosis Epidemiology study and includes data on 1,358 women and 858 men aged ≥ 60 years from Australia (218, 219). It outputs a 5 and 10-year risk of an osteoporotic fracture (hip, clinical vertebral, wrist,

metacarpal, humerus, scapula, clavicle, distal femur, proximal tibia, patella, pelvis and sternum). It includes fewer risk factors than FRAX®, though includes a fall history and requires either femoral neck BMD or weight. Garvan has been externally validated using the CaMos, GLOW, a calcium supplement trial, and a cohort of 600 Australian women (220-224). C-statistics for these cohorts ranged from 0.60 to 0.85 depending on cohort and type of fracture assessed (220).

Qfracture is a risk score developed based on data from the primary practice setting in the United Kingdom. They utilized data from 357 general practices in England and Wales for the creation of the risk score, and utilized an additional 178 practices to assess internal validation of the model (225, 226). The model outputs 1 to 10-year risk of hip fracture and includes significantly more risk factors for assessment than the other two risk scores. QFracture as well as Garvan includes a history of falls, which are highly correlated with hip fracture, but have been shown to not improve the FRAX® calculator's prediction of future fracture. There were two attempts to externally validate the prediction tool, one using 2.2 million adults from the THIN database in the UK and the other using 246 postmenopausal women with low-trauma fractures and 338 non-fracture controls. The AUC varied between 0.63 and 0.82 based on gender and cohort for these validation studies (227, 228).

2.4.5 National Osteoporosis Foundation (NOF)

In the United States, multiple clinical societies have produced guidelines for the treatment and prevention of osteoporosis. North American Menopause Society, USPTF, AACE, NOF, ACR for GIO, Guidelines for treatment and prevention of osteoporosis from the American Academy of Family Physicians were released in 1999 with treatment and prevention based on if a patient is likely to sustain an osteoporotic fracture because of low bone mineral density or an increased risk of falling, both based on clinician's opinions (229). However, the most commonly

utilized guideline is that of the National Osteoporosis Foundation, entitled the “Clinician’s Guide”.

Table 2.5 US Osteoporosis Guidelines

Organization	PMW	Men	AOM Treatment Decision
American Academy of Family Physicians, 1999 (229)	X		Is the patient likely to sustain an osteoporotic fracture because of low bone mineral density or an increased risk of falling?
US Preventive Services Task Force, 2011 (230)	X		No advice on use of AOM
American Association of Clinical Endocrinologists, 2003 (231)	X		1.) Women with postmenopausal osteoporosis, either by BMD or low-trauma fracture and low BMD 2.) Women with borderline-low BMD (t-score <-1.5) if risk factors are present 3.) Women in whom nonpharmacologic preventive measures are ineffective
North American Menopause Society, 2010 (232)	X		1.) Women who have had an osteoporotic vertebral or hip fracture 2.) Women who have osteoporosis (t-score \leq -2.5) at femoral neck, total hip, or lumbar spine 3.) Women with osteopenia (t-score -1.0 to -2.5) and a 10-year FRAX® risk of MOF \geq 20% or hip \geq 3%
ACR, 2010 (233)	X	X	Specifically, for patients being treated with glucocorticoids
National Osteoporosis Foundation, 2014 (37)	X	X	1.) Women who have had an osteoporotic vertebral or hip fracture 2.) Women who have osteoporosis (t-score \leq -2.5) at femoral neck, total hip, or lumbar spine 3.) Women with osteopenia (t-score -1.0 to -2.5) and a 10-year FRAX® risk of MOF \geq 20% or hip \geq 3%
PMW: Postmenopausal women			

Prior to 2008 the NOF began producing a yearly clinicians guide in 1999 basing their recommendations on a cost-effectiveness analysis of relevant diagnostic, evaluation, and treatment of osteoporosis from 1998 (234, 235). The 1999 guide specifically recommends treatment for women with BMD T-scores below -2.0 by central DXA with no risk factors, BMD T-scores below -1.5 by central DXA with one or more risk factors, or a prior vertebral or hip fracture. A 2003 update did not make any changes to treatment recommendations from the 1999 guide, though it anticipated changes once additional information was known about fracture risk

(236). The most significant change in the 2003 guide is the updated information on HRTs based on the WHI, which no longer recommend them as first line therapy for osteoporosis (236).

The Clinician's guide was revised in 2008 with substantial changes to evaluation of osteoporosis and treatment recommendations based on the updated US-FRAX algorithm (217, 237, 238). The 2008 guide was developed by the NOF in collaboration with the American Association of Clinical Endocrinologists, ACR, American Osteopathic Association, ASBMR, ISCD, and International Society for Physical Medicine and Rehabilitation. The guide was accompanied by an economic analysis which to determine FRAX® values wherein treatment was cost-effective (217, 238). For the first time the guide includes diagnostic and treatment recommendations for both postmenopausal women and men age ≥ 50 .

The new CEA calculated the cost effectiveness of AOM therapy based on 10-year risk of hip fracture based on US-FRAX 2.0 (217). The model used for the CEA was similar to the model used by the NOGG group to determine the intervention thresholds for Europe. A yearly cost of \$600 was used for treatment with sensitivity analyses also assessing the cost effectiveness at \$300 and \$900 (with \$300 being the estimated yearly cost once bisphosphonates were available as generics). The CEA estimated the effect of a first fracture without an increase in future fracture risk based on similar analyses done for the UK and Swedish population (239, 240). The CEA found that based on the expected decrease to \$300 for generic bisphosphonates, for all age groups and races a treatment threshold of 3% for females and 3.5% for males (217).

The 2008 guide used the results of the CEA as well as clinical judgment to amend their previous treatment recommendations and to expand the groups who recommendations were made to include men age 50 and older. AOM treatment was recommended for 3 groups, 1) those with hip or vertebral (clinical or morphometric) fractures; 2) those with osteoporosis at the

femoral neck, total hip, or lumbar spine; and 3) those with osteopenia who's FRAX® 10-year risk of major osteoporotic fracture is $\geq 20\%$ or hip fracture is $\geq 3\%$. The 3% hip fracture figure is representative of the results of the CEA for women and represents a woman 65 years of age with no risk factors which was determined to be cost effective (241). Based on nomograms (risk graphs) without fracture this patient has a 10-year risk of MOF of 14% but 26% with a fracture, which may represent how the 20% threshold was established (238). The new recommendations although based on different methodologies and included men ≥ 50 years of age, did not substantially increase the proportion of the population to be treated or screened (238). This was due to the FRAX® algorithm having similar risk factors to the 1999 guide, and two of the groups (prevalent fractures and current osteoporosis) are basically universally recommended treatment by clinical guidelines (238).

In 2010, the guide was updated to provide additional guidance on biochemical markers and update indications for medications, including the use of dinosaur (242). In 2013, the guide was updated 3 separate times for updated information on calcium, and vitamin D use, current knowledge about AOMs, additional guidance on the appropriate use of vertebral fracture assessment and the use of biochemical markers of bone turnover (11).

2.4.5.1 Current NOF Guidelines (2014)

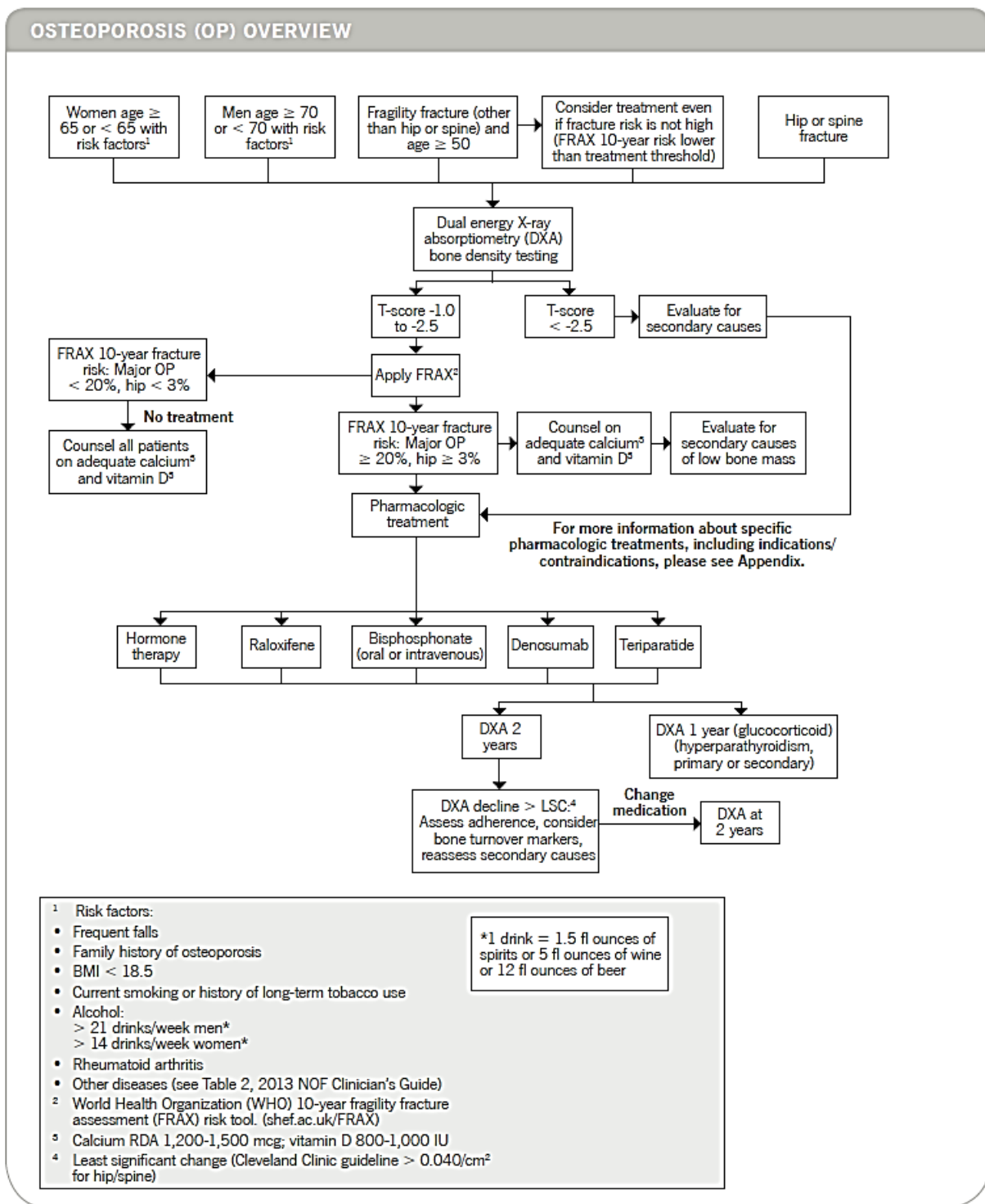
The clinician's guide was further updated in 2014 with additional information on calcium, vitamin D, AOM use including duration, use of vertebral fracture imaging, use of biochemical markers of bone turnover, and further evaluation of secondary causes of osteoporosis (8). The 2014 guide has been endorsed by the American Academy of Pain Medicine (AAPM), American Association of Clinical Endocrinologists (AACE), American Orthopaedic Association (AOA), American Osteopathic Association (AOA), American Society for Bone and

Mineral Research (ASBMR), and International Society for Clinical Densitometry (ISCD). Also for the first time the guide was published as a peer reviewed article in 2014 by Osteoporosis International (37).

2.4.5.1.1 Treatment Recommendations

To graphically illustrate the steps that a clinician must take to make a treatment decision we are presenting the Cleveland Clinic Foundation Carepath diagram as Figure 2.5. The guide includes information on all therapies currently FDA approved for treatment of osteoporosis in the US, including bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid), calcitonin, estrogen agonist/antagonist (raloxifene), estrogens and/or hormone therapy, tissue-selective estrogen complex (conjugated estrogens/bazedoxifene), parathyroid hormone 1–34 (teriparatide), and receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor (denosumab). However, the guide does not promote the use of any particular therapy leaving that decision up to the patient and the provider.

Figure 2.5 Carepath diagram¹



¹ Used with permission from Chad Deal, MD from the Cleveland Clinic Foundation

2.4.5.1.2 Applicability

There have been research efforts to determine how applicable the NOF guidelines are to the general US population and particularly the proportion of the population who would be recommended treatment. Two treatment estimates were made based on US cohort studies. Donaldson et al utilizing the SOF dataset found that based on the 2008 thresholds 72% of US Caucasian women ≥ 65 years of age would be recommended treatment, while 93% of women ≥ 75 would be recommended treatment, however these estimates were made prior to the US-FRAX update in 2008 (243). Berry et al utilized the Framingham Osteoporosis Study finding recommended treatment for 41.1% of all women based on the 2008 guidelines and 47.8% based on the 2003 guidelines. Additionally, 17.0% of all men were recommended treatment based on the 2008 guidelines (244). In comparison, when using estimates from a nationally-representative sample (NHANES from 2005-2008) for person of all races ≥ 50 years of age 30.8% for women and 19.3% for men were estimated to be eligible for treatment (245). For non-Hispanic whites aged ≥ 65 the proportion to be treated increased to 51.7% for women and 31.8% for men (245). This analysis also gave proportions of the population with t-scores between -1.0 and -2.5 for whom treatment is based on FRAX, finding 24.6% of women and 28.2% of men aged ≥ 50 would be recommended for treatment (245). An update using data through 2010 suggests that ~16 million persons in the US would qualify for osteoporosis treatment based on the current NOF guidelines (246).

Because there is no population based way to identify patients at risk for osteoporosis and treatment largely relies on events (diagnosis of osteoporosis or fracture) a sizeable portion of the population eligible for treatment remain untreated. As many as 25% of all women and 28% of men aged ≥ 65 are estimated to be eligible for but not receiving therapy (245). This highlights the

need for a population based fracture risk tool that identifies patients who would benefit from treatment prior to diagnosis of osteoporosis or occurrence of fractures.

2.5 Treatment

2.5.1 Pharmacologic Therapy

In 1979, the FDA published the first guidance document on therapies for osteoporosis. The effectiveness threshold in the 1979 guidance document stipulated that if a therapy could demonstrate an improvement in normal bone mass then fracture trials would not be required. However, more current guidance requires documented fracture reduction for approval of therapies (247). We present the therapies which are approved with their current dosing and their efficacy and list 4 therapies which have not been approved by the FDA in Table 2.6. Aim 3 of this dissertation is most interested in the comparison of alendronate to placebo, however we felt that a full review of Food and Drug Administration (FDA) approved AOMs was appropriate for this project.

Table 2.6 Anti-Osteoporosis Medications

Drug	Trade Name(s)	Label Indications	Dosing	Efficacy
<i>Bisphosphonates</i>				
Alendronate	Fosamax, Fosamax Plus D, Binosto	Indicated for treatment and prevention of osteoporosis in postmenopausal women; increasing bone mass in men with osteoporosis; treatment of glucocorticoid(GC)-induced osteoporosis in men and women with low bone mass	One 10mg tablet, once daily, or 70mg (as tablet, effervescent tablet, or oral solution) once weekly; 70mg (as tablet, effervescent tablet, or oral solution) once weekly or one 10mg tablet daily; One 35mg tablet weekly or one 5mg tablet daily; One 5mg table daily	In meta-analyses compared to placebo alendronate has been shown to decrease the incidence of vertebral fractures, as well as non-vertebral fractures (248-253). It has also been shown to decrease hip fractures, particularly in patients with osteoporosis or prior vertebral fractures (248-250, 254). Alendronate also has demonstrated the ability to reduce the loss of BMD compared to placebo (249, 255).
Ibandronate	Boniva	Indicated for the treatment and prevention of osteoporosis in postmenopausal women	One 150mg tablet once monthly or one 2.5mg tablet once daily or 3mg injectable every 3 months	In meta-analyses compared to placebo oral ibandronate has been shown to reduce the incidence of vertebral fractures (252). However meta-analyses have not been able to clarify if ibandronate reduces non-vertebral fractures (247, 256, 257). In RCTs both the oral and IV forms of ibandronate have been shown to increase BMD compared to placebo (258, 259).
Risedronate	Actonel, Actonel with calcium, Atelvia	Indicated for the treatment and prevention of osteoporosis in postmenopausal women and glucocorticoid-induced osteoporosis; Treatment to increase bone mass in men with osteoporosis	Treatment of postmenopausal women: 5 mg daily; 35 mg, weekly; 75 mg taken on two consecutive days each month; or 150 mg once monthly; Actonel with calcium is packaged as the once weekly 35mg with 1,250 mg calcium carbonate tablets to be taken daily; Atelvia is taken once weekly after breakfast	In meta-analyses compared to placebo risedronate has been shown to decrease the incidence of vertebral fractures, as well as non-vertebral fractures (248, 251, 260-263). It has also been shown to decrease hip fractures, particularly in patients with osteoporosis (248, 260). Risedronate also has demonstrated the ability to reduce the loss of BMD compared to placebo (261, 264-266).

Drug	Trade Name(s)	Label Indications	Dosing	Efficacy
Zoledronic Acid	Reclast	Indicated for treatment and prevention of osteoporosis in postmenopausal women and glucocorticoid-induced osteoporosis; Treatment to increase bone mass in men with osteoporosis	Treatment of postmenopausal women: 5mg infusion annually; prevention in postmenopausal women: 5 mg infusion biennially	Currently there are no meta-analyses of zoledronic acids efficacy. RCTs of ZA compared to placebo at a 5mg dose have shown decreases in all clinical fractures, vertebral fractures, and non-vertebral fractures based on the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trials (64, 267). Also, there is some evidence to suggest that ZA also is associated with a decrease in hip fractures (64). Zoledronic acid also has demonstrated the ability to reduce the loss of BMD compared to placebo (64, 268). Recent research has also suggested that a single dose of zoledronic acid may be as effective in reducing fractures as a consecutive series of three yearly infusions (269).
<i>Peptide Hormones</i>				
Teriparatide	Forteo	Indicated for treatment of osteoporosis in postmenopausal women at high risk for fracture	20 mcg subcutaneously once daily, maximum of two years use	In meta-analyses compared to placebo teriparatide at a 20µg/d has been shown to decrease the incidence of vertebral fractures, as well as non-vertebral fractures (248, 270). There are no meta-analyses which have shown a decrease in hip fractures, however RCTs have indicated a statistically significant reduction. Teriparatide also has demonstrated the ability to reduce the loss of BMD compared to placebo (270-273).
<i>Biologics</i>				

Drug	Trade Name(s)	Label Indications	Dosing	Efficacy
Denosumab	Prolia™	Indicated for treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.	60 mg injected subcutaneously every six months	Denosumab has been shown to decrease the likelihood of vertebral, non-vertebral, and hip fractures in women treated for postmenopausal osteoporosis at 36 months (63). However, there was not a statistically significant reduction at any of these sites in another RCT at two years (274). Additionally, denosumab has been shown to reduce bone loss compared to placebo (63, 274). Denosumab has been reported to have a treatment efficacy of ~6 months, which requires re-administration of therapy for continued effectiveness (275, 276). Though recent reports suggest that the effective period may be >6 months (276).
<i>Selective Estrogen Receptor Modulators</i>				
Raloxifene	Evista	Indicated for treatment and prevention of osteoporosis in postmenopausal women	60 mg tablet once daily	Subsequent trials and results from meta-analyses after FDA approval have shown a decrease in vertebral fractures with raloxifene compared to placebo (248, 277-279). AHRQ CERs have deemed the evidence for the reduction of vertebral fractures to be strong but have concluded that there is no evidence of a reduction in non-vertebral fractures (247, 280-282). Recent clinical guidelines have recommended raloxifene as a second line therapy due to other therapies demonstrating better fracture reduction. Based on not being a first line therapy, raloxifene will not be used as a primary AOM in this study.
<i>Steroid Hormones</i>				
Conjugated equine estrogen	Premarin	Indicated for prevention of postmenopausal osteoporosis	0.3mg tablet daily	Meta-analyses comparing estrogen and placebo represent good evidence of a decreased rate of vertebral, non-vertebral,

Drug	Trade Name(s)	Label Indications	Dosing	Efficacy
Conjugated estrogen (CEE)/Medroxyprogesterone (MPA)	Prempro	Indicated for prevention of postmenopausal osteoporosis	0.3 mg CEE/1.5 mg MPA daily;0.45 CEE/1.5 mg MPA; 0.625 mg CE/2.5 mg MPA; 0.625 CEE/5 mg MPA	and hip fractures for women on estrogen (283-286). The results from three pooled meta-analyses have shown a decrease in overall fracture risk, no significant difference, and were unable to assess the difference based on sample size (248, 283, 287).
Estradiol(E)/norgestimate(NE)	Prefest	Indicated for prevention of postmenopausal osteoporosis	1.0 mg E daily for 3 consecutive days; 1.0 mg E/ 0.09 mg NE daily for next 3 consecutive days	
17β Estradiol/norethindrone acetate	Activella, femhrt	Indicated for prevention of postmenopausal osteoporosis	Activella: 1.0mg E.0.5mg NE or 0.5 mg E/0.1 mg NE daily Femhrt: 1/0.5 mg or 0.5/0.25 mg daily	
17β Estradiol/levonorgestrel	ClimaraPro	Indicated for prevention of postmenopausal osteoporosis	0.045mg estradiol/ 0.015 mg levonorgestrel delivered daily	
Estradiol oral	Estrace Oral	Indicated for prevention of postmenopausal osteoporosis	0.5, 1, or 2mg daily	
Estradiol transdermal	Vivelle, Climara, menostar	Indicated for prevention of postmenopausal osteoporosis	Variable	
Calcitonin				
Salmon Calcitonin	Miacalcin	Treatment of postmenopausal osteoporosis, hypercalcemia, Paget's disease	Nasal - 200IU, Injectable - Variable	RCTs showed reduced bone turnover and increased BMD when compared to placebo in post-menopausal women prompting its FDA approval in 1995 (288-291). The 2007 ARHQ CER of treatments to prevent fracture indicated that based on meta-analyses calcitonin was effective in reducing vertebral fractures, created no change in the likelihood of non-vertebral fractures, and was not evaluated for its effect on hip fractures (281, 282). However calcitonin was not included in the 2013 AHRQ CER based on subject matter expert’s requests because calcitonin is

Drug	Trade Name(s)	Label Indications	Dosing	Efficacy
				thought to no longer represent appropriate treatment for osteoporosis (247).
<i>Not FDA Approved</i>				
Sodium Flouride, Etidronate, Pamidronate, Stromium Ralocate				

2.5.1.1 Alendronate v Placebo (PCB) Randomized Controlled Trials (RCT)

Bisphosphonates are classified as antiresorptive medications due to their affinity to slow bone breakdown. This is done by inhibiting reabsorption by osteoclasts before effecting bone formation (8). This causes more bone to be created than is broken down, increasing bone density. Although after a period of time formation may normalize there is an increase in bone density, improved bone mineralization, and reduced fracture risk.

Alendronate was the first bisphosphonate to receive FDA approval in 1995 and has been available in a generic formulation since 2008 (292). Based on its first in class designation and its availability as a generic it is the most utilized anti-osteoporosis medication. Although alendronate was originally approved at a 10mg QD indication the most common formulation currently being used is a 70-mg dosage once weekly, and is the only formulation still available from Merck (the alendronate patent holder) with a half-life of ~10 years (292).

Early bisphosphonate trials demonstrated a reduction in fractures, however to detect this difference a significant sample size was required (20,000 patients for 5 years). Further, following alendronate's approval, it was thought to be unethical to withhold active therapy from the control arm of future studies. This resulted in use of surrogate endpoints of change in BMD and bone turnover markers rather than actual fracture reduction for subsequent studies (51, 62). Recently superiority and non-inferiority trials have been undertaken to compare a new drug or formulation to previously-approved products (63).

In Aim 3 we are comparing alendronate users to non-users. We chose this comparison based on a bevy of published work on Alendronate and a large portion of this work comparing alendronate to placebo. After the initial bisphosphonate trials, ethical concerns have reduced the number of placebo controlled trials in osteoporosis with alendronate representing the largest

number. Aim 3 will directly compare estimate of fracture reduction in alendronate users to non-users using CFRI as a variable in regression models to the effect estimates from the published RCTs. We provide a summary of the placebo controlled RCTs with alendronate compared to placebo including all inclusion and exclusion criteria as well as a meta-analysis summary of the relative risks of fracture based on the placebo controlled trials in this section. Although these results primarily use patients who are adherent to their therapy they provide a benchmark for comparison to non-users. Based on a 2008 Cochrane review by Wells et al we identified 11 trials which either had published fracture rates or were available in the meta-analysis and an additional 3 trials based ARHQ Comparative Effectiveness Reviews in 2012 and 2014 by Crandall et al (247, 280, 293). We provide a brief synopsis and exclusion criteria for these 14 studies in Table 2.7.

Table 2.7 Alendronate v Placebo Randomized Control Trials with Fracture as an Outcome

RCT (Author, Year)	ALN Dose^	Population	Inclusion/Exclusion Criteria	Outcomes
Ascott Evans, 2003(294)	10 mg ALN (95), PCB (49)	≥3 yr PMW, <80 yo, used HRT >1yr and d/c HRT <3mo before enrollment	Inclusion: LST -3.5 to -1.5; Exclusion: other metabolic bone disease or osteoporotic fracture, recently received BP or GC	Bone Turnover, BMD
Black, 1996(25) Fracture Intervention Trial (FIT) with vertebral fracture	5-10mg ALN (1022), PCB (1005)	≥2 yr PMW age 55-81, prevalent vertebral fracture	Inclusion: FN BMD <0.68 g/cm ² ; Exclusion: peptic-ulcer disease (a single hospital admission for uppergastrointestinal bleeding or two or more documented ulcers within the preceding 5 years), dyspepsia requiring daily treatment, abnormal renal function (serum creatinine >144 µmol/L), major medical problems that would be likely to preclude participation for 3 years, severe malabsorption syndrome, uncontrolled hypertension (blood pressure >210 mm Hg systolic or >105 mm Hg diastolic), myocardial infarction during the previous 6 months, unstable angina, or evidence of disturbed thyroid or parathyroid function. Use of oestrogen or SCT within the preceding 6 months or BP or sodium fluoride (>1 mg daily for 2 weeks or longer) at any time	Bone Turnover, BMD, clinical vertebral, hip, or wrist fracture with ~3yr FU HR for any clinical fracture: 0.72 (0.58, 0.90)
Bone, 1997(295)	1 mg ALN (81), 2.5mg (85), 5mg (85), PCB (90)	Women 60-85	Inclusion: LST <-2.0; Exclusion: 1 or more lumbar crush fractures, recent major gastrointestinal disease, such as peptic ulcer, esophageal disorder, or malabsorption, or had recently used a drug to inhibit gastric acid secretion for more than 2 weeks. In addition, patients receiving chronic nonsteroidal antiinflammatory therapy or agents known to affect bone metabolism (such as etidronate, estrogen, glucocorticoids, fluoride, or calcitonin) were excluded.	Bone Turnover, BMD Fractures: 9/93 16/91 0.55 (0.26,1.18)

RCT (Author, Year)	ALN Dose^	Population	Inclusion/Exclusion Criteria	Outcomes
			Subjects receiving thyroid hormone replacement were required to have been on a stable dosage for at least 6 months before entry into the study and euthyroid by ultrasensitive TSH assay. Clinically significant vitamin D deficiency was similarly excluded or corrected.	
Chesnut, 1995(296)	5, 10, 40mg ALN (157), PCB (31)	≥5 yr PMW 42-75	Inclusion: LS BMD <0.68 g/cm ² ; Exclusion: any disease or drug therapy potentially affecting bone metabolism. Prevalent hip or spine fractures due to osteoporosis	Bone Turnover and BMD, 2-yr fractures
Cummings, 1998(26) FIT without vertebral fracture	5-10 mg ALN (2214), PCB (2218)	≥2 yr PMW 55-80 without vertebral fracture	Inclusion: LS BMD <0.68 g/cm ² ; Exclusion: peptic-ulcer disease (a single hospital admission for uppergastrointestinal bleeding or two or more documented ulcers within the preceding 5 years), dyspepsia requiring daily treatment, abnormal renal function (serum creatinine >144 μmol/L), major medical problems that would be likely to preclude participation for 3 years, severe malabsorption syndrome, uncontrolled hypertension (blood pressure >210 mm Hg systolic or >105 mm Hg diastolic), myocardial infarction during the previous 6 months, unstable angina, or evidence of disturbed thyroid or parathyroid function. Use of oestrogen or SCT within the preceding 6 months or BP or sodium fluoride (>1 mg daily for 2 weeks or longer) at any time	Bone turnover, BMD, clinical vertebral, hip, or wrist with ~4 yr FU HR for any clinical fracture: 0.86 (0.73, 1.01)
Dursun, 2001(297)	10mg ALN and calcium 1000mg (51), 1000mg calcium (50)	PMW no age range given	Inclusion: LS BMD <-2.0 SD at either LS or FN; Exclusion: Documented history of drug or alcohol abuse, any bone metabolism disorder, active gastrointestinal or liver disease, renal	Vertebral fractures at 1-year HR 0.84 (0.43, 1.63)

RCT (Author, Year)	ALN Dose^	Population	Inclusion/Exclusion Criteria	Outcomes
			failure, renal calculi, treatment with specific therapy for osteoporosis, treatment with systemic corticosteroid therapy, malignancy, disorder of calcium metabolism, and lumbar vertebrae abnormalities preventing evaluation of BMD.	
Greenspan, 1998(298)	ALN 5mg (60), PCB (60)	Women 65+	Inclusion: None; Exclusion: history of any illness affecting bone and mineral metabolism, currently taking medication known to affect bone metabolism, or had been treated for osteoporosis with BP, HRT, or calcitonin within 1-year of study entry	Non-vertebral at 3-yr 3/60 ALN, 1/60 PCB 3.00 (0.32, 28.03) Hip at 3-yr 0/60; 1/60 Wrist 3/60; 0/60 18.93 (0.99, 361.25)
Greenspan, 2002(299)	ALN 10mg (163), PCB (164)	Women 65+	Inclusion: Currently residing in a long-term facility, LS or TH T-score <-2.0; Exclusion: disorders of bone mineralization, 25-hydroxycholecalciferol level less than 25 mol/L, untreated hyperthyroidism, recent major upper gastrointestinal mucosal erosive disease, or use of bone-active agents	Hip fractures at 2yr 2/163; 4/164 0.50 (0.0069, 2.71)
Hosking, 1998 (300)	ALN 5mg (498), PCB (501)	≥ 6mo PMW 45-59	Inclusion: Only 10% of women at each center could have LS BMD <0.8 g/cm ² ; Exclusion: abnormal renal function (serum creatinine, >1.5 mg per deciliter, a history of cancer, peptic ulcer or esophageal disease requiring prescription medication within the previous five years, previous treatment with a bisphosphonate or fluoride, regular therapy with a phosphate binding antacid, estrogen-replacement therapy within the previous three months, and therapy with any other drug that affects the skeleton	Bone Turnover and BMD All fractures 22/498 ALN v 14/501 PCB 1.58 (0.82, 3.05)

RCT (Author, Year)	ALN Dose^	Population	Inclusion/Exclusion Criteria	Outcomes
Liberman, 1995 (255)	ALN (526), PCB (355); 3 groups of ALN (5, 10, 20mg not well defined as how many in each)	≥5 yr PMW 45-80	Inclusion: LST <-2.5; Exclusion: other causes of osteoporosis (e.g., treatment with glucocorticoids) or other disorders of bone and mineral metabolism (e.g., vitamin D deficiency, Paget's disease, or hyperparathyroidism); active peptic ulcer disease, abnormal renal function (serum creatinine level, >1.5 mg per deciliter, or abnormal hepatic function; abnormalities of the lumbar spine precluding the assessment of bone mineral density at a minimum of three lumbar vertebrae or a history of hip fracture; or any prior treatment with bisphosphonates or treatment within the preceding 12 months with estrogen, progestin, calcitonin, fluoride, or an anabolic steroid.	Vertebral fractures 0.52 (0.28, 0.95)
Orwoll, 2000(301)	ALN 10mg (146), PCB (95)	Men 31-87 yo	Inclusion: (FNT <-2.0 and LST <-1.0) OR (FNT <-1.0 and prior osteoporotic fracture or vertebral deformity); Exclusion: secondary causes of osteoporosis other than low serum free testosterone concentrations were ineligible, including those who were taking medications or who had medical conditions associated with bone loss, as were those with other bone diseases, vitamin D deficiency, renal disease (indicated by a serum creatinine concentration of more than 1.6 mg per deciliter), severe cardiac disease, a history of cancer other than basal-cell carcinoma of the skin, a recent history (within the previous year) of peptic ulcer or esophageal disease, or esophageal abnormalities that delayed esophageal emptying. We also excluded men who were unable to follow the	Bone Turnover, BMD, and fractures Using semi quantitative methods, we found that vertebral fractures occurred in 8.1 percent of men in the placebo group and 3.1 percent of men in the alendronate group (P=0.12). However, quantitative methods revealed that the incidence of vertebral fractures was 7.1 percent in the placebo group and 0.8 percent in the alendronate group (P=0.02). Four men had painful vertebral fractures: three (3.2 percent) in the placebo group and 1 (0.7 percent) in the alendronate group (P=0.3). Nonvertebral fractures

RCT (Author, Year)	ALN Dose^	Population	Inclusion/Exclusion Criteria	Outcomes
			instructions for taking the study drug and those with a history of treatment for osteoporosis	occurred in five men (5.3 percent) in the placebo group and six men (4.1 percent) in the alendronate group (P=0.8).
Pols, 1999(302)	ALN 10mg (950), PCB (958)	≥3 yr PMW and <85 yo	Inclusion: LST <-2.0, otherwise in good health and between 20% below and 50% above ideal weight; Exclusion: women with metabolic bone disease other than postmenopausal osteoporosis; disturbed parathyroid or thyroid function; major gastrointestinal disease (for example, peptic ulcer or malabsorption) within the year before enrollment or use of a drug to inhibit gastric acid secretion for >2 weeks within 3 months of study entry; myocardial infarction within the year prior to enrollment; uncontrolled hypertension or untreated angina; significantly impaired renal function (serum creatinine >150 mmol/l); or evidence of significant end organ disease. Also excluded were women who had received a bisphosphonate or fluoride (>8 mg/day) during the previous 6 months; estrogen (except vaginal 43 times/week), ipriflavone or calcitonin during the previous 4 months; or any anabolic steroid, glucocorticoid or progestin for >2 weeks within the previous 6 months. Participants could not be receiving any medications that might alter bone or mineral metabolism, including vitamin A in excess of 10 000 U/day, vitamin D in excess of 1000 U/day, anticonvulsants or phosphate-binding antacids. Finally, at least three vertebrae from L1 to L4 had to be	BMD, Bone Turnover, fractures at 1 yr FU HR: 0.53 (0.30, 0.90) for non-vertebral fracture (ankle/lower leg, foot, hand, hip/femur, rib, shoulder, wrist/arm, other), most difference for wrist/arm ~1.60% v 0.6%

RCT (Author, Year)	ALN Dose [^]	Population	Inclusion/Exclusion Criteria	Outcomes
			evaluable by DXA to determine BMD in this region.	
Quandt, 2005(27) FIT Trial	5-10 mg ALN (2214), PCB (2218)	Same as FIT, ie FIT subgroup analysis	Inclusion: T-score -1.6 to -2.49; Exclusion: Same as FIT	3-yr clinical vertebral 0.40 (0.19, 0.76),
Sato, 2006(303)	5mg ALN (144), PCB (144) both receiving 1,000 IU of ergocalciferol	Women ≥65	Inclusion: Parkinson Disease; Exclusion: Patients with impairment of renal, hepatic, cardiac, or thyroid function or those who had known causes of osteoporosis, such as primary hyperparathyroidism or renal osteodystrophy, were excluded from this study. Patients were excluded if they had been treated with corticosteroids, estrogens, calcitonin, bisphosphonate, calcium, or vitamins D and K for 3 months or more during the 12 months preceding the study; and those who had been administered these agents for even a brief period during the preceding 2 months were also excluded. PD patients at stage 5 in Hoehn and Yahr stage 16 were excluded, because their total disability virtually predicted minimum chance of a fracture. Patients with a previous history of non-vertebral fractures were also excluded.	Hip fracture 0.29 (0.10, 0.85) @ 2yrs
#: or any associated health problems that could affect their participation in the study or interfere with interpretation of the data; BP: Bisphosphonate; PMW: Postmenopausal Woman; ^: Dose per day unless otherwise specified; FN: Femoral Neck; TH: Total Hip; LS: Lumbar Spine; FNT: Femoral Neck T-score; THT: Total Hip T-score; LST: Lumbar Spine T-score; PCB: Placebo; ALN; Alendronate				

Generally trial inclusion criteria were based on postmenopausal status and specific lumbar spine or femoral neck BMD. Three of the trials highlighted were from the same parent trial (Fracture Intervention Trial [FIT]). Although there were additional trials of alendronate and placebo, the 14 trials reported here were the only to capture fracture outcomes.

Estimates of the risk ratio for vertebral and non-vertebral fractures are reproduced from Wells et al in Table 2.6. At 4 years Wells reports a weighted RR for ALN 10mg of 0.56 (95% CI 0.39, 0.80) for vertebral fractures and 0.89 (95% CI 0.76, 1.04) for non-vertebral fractures (293). The individual studies RR varies from 0.55 to 0.84 for vertebral fractures and 0.52 to 3.00 for non-vertebral fractures (293). Overall this demonstrates that alendronate is associated with a decreased risk for future fracture. The meta-analysis of dosages and time is particularly helpful to compare against any results of claims-based analysis, as risk changes over time. However these estimates may not be reachable due to patients likely being more adherent to their alendronate than patients in the real world.

Figure 2.6 Weighted Relative Risks

Fracture Site	Primary / Secondary Prevention	Dose (mg)	Weighted Relative Risk (95%CI) of Fracture			
			Year 1	Year 2	Year 3	Year 4
Vertebral	Overall	5 mg	NA	0.39 (0.28; 0.55)	0.46 (0.18; 1.20)	NA
		10 mg	0.79 (0.42; 1.47)	0.38 (0.27; 0.54)	0.52 (0.41; 0.67)	0.56 (0.39; 0.80)
	Primary	5 mg	NA	NA	NA	NA
		10 mg	NE	NA	NA	0.56 (0.39; 0.80)
	Secondary	5 mg	NA	0.39 (0.28; 0.55)	0.46 (0.18; 1.20)	NA
		10 mg	0.79 (0.42; 1.47)	0.38 (0.09; 2.71)	0.52 (0.41; 0.67)	NA
Non-Vertebral	Overall	5 mg	NA	0.96 (0.33; 2.78) [*]	NA	NA
		10 mg	0.55 (0.32; 0.94)	NA	0.82 (0.67; 0.99)	0.89 (0.76; 1.04)
	Primary	5 mg	NA	NA	NA	NA
		10 mg	NE	NA	NA	0.89 (0.76; 1.04)
	Secondary	5 mg	NA	NA	NA	NA
		10 mg	0.55 (0.32; 0.94)	NA	0.82 (0.67; 0.99)	NA
Hip	Overall	5 mg	NA	NA	NA	NA
		10 mg	0.71 (0.12; 4.23)	0.50 (0.09; 2.71)	0.45 (0.23; 0.87)	0.79 (0.44; 1.44)
	Primary	5 mg	NA	NA	NA	NA
		10 mg	NE	NA	NA	0.79 (0.44; 1.44)
	Secondary	5 mg	NA	NA	NA	NA
		10 mg	0.71 (0.12; 4.23)	0.50 (0.09; 2.71)	0.45 (0.23; 0.87)	NA
Wrist	Overall	5 mg	NA	NA	NA	NA
		10 mg	0.42 (0.17; 1.09)	NA	0.52 (0.34; 0.79)	1.19 (0.87; 1.62)
	Primary	5 mg	NA	NA	NA	NA
		10 mg	NE	NA	NA	1.19 (0.87; 1.62)
	Secondary	5 mg	NA	NA	NA	NA
		10 mg	0.42 (0.17; 1.09)	NA	0.52 (0.34; 0.79)	NA

^{*}Relative risk estimate based on random effects model; CI=Confidence Interval; NA=Not available; NE=Not Estimable

From: Wells et al, 2012 (293)

2.5.1.2 Fracture Intervention Trial

Of particular focus in the alendronate placebo RCTs are 3 reports of the same trial, the Fracture Intervention Trial (FIT) (25-27). The three reports were authored by Black in 1996, Cummings in 1998, and Quandt in 2005 and represent the largest participant numbers for any of the placebo-controlled alendronate fracture trials (25-27). FIT had a primary aim of testing “if alendronate reduces the risk of fracture in postmenopausal women with low bone mineral density” (304). The trial began recruiting in May 1992 and finished recruitment in May 1993 with follow-up continuing for up to 4 years through May 1997. Women aged 55 to 80 were recruited to two different arms, those with prevalent vertebral fractures (n=2023) and those without (n=4434) called the clinical fracture arm, with various inclusion criteria specified in Figure 2.8 (304). The primary endpoint for the vertebral fracture trial was new vertebral deformities while the primary endpoint for the clinical fractures arm were new clinical fractures. Clinical fractures were defined as any non-pathologic, non-traumatic fractures other than skull and facial fractures (26). Both trials also collected new occurrences of the other type of fracture as well as change in BMD, change in height, and bone turnover markers (304).

Figure 2.7 Inclusion and Exclusion Criteria for the Fracture Intervention Trial (FIT)

Inclusion Criteria:

1. Female, 55-80 years old
2. BMD at the femoral neck ≤ 0.68 g/cm² (Hologic QDR 2000)
3. Understands procedures of study

Exclusion Criteria:

1. Unable to give informed consent
2. Participating in another trial
3. Intends to move within 4 years
4. Alcohol Abuse
5. Major illnesses, including severe malabsorption, severe hypertension, myocardial infarction (within 6 months), unstable angina, serum creatinine > 1.6 mg/dl
6. Erosive gastrointestinal disease within 5 years. Dyspepsia requiring daily treatment
7. History of cancer (except: resected superficial skin cancer and treated malignancies, except breast, without recurrence in 10 years)
8. Metabolic bone disease (e.g. hyper- or hypoparathyroidism, Paget's disease, osteomalacia)
9. Treatment affecting bone turnover:
 - a. Estrogen, anabolic steroids, calcitonin, or progestins, within 6 months
 - b. A change in thyroid hormone dosage within the last 6 weeks
 - c. >2 weeks fluoride treatment (>1 mg/day) at any time
 - d. Glucocorticoid within 6 months
 - e. Bisphosphonate for more than 2 weeks
10. Unexplained weight loss $> 10\%$ of ideal body weight within last 12 months
11. Unsuitable anatomy on spinal radiographs
12. BMD at the femoral neck >3 SD below age-specific mean
13. Noncompliance with pre-randomization study procedures
14. Not ambulatory
15. History of bilateral hip replacements

The original intention of the FIT trial was to assess women with low bone mass, or a t-score of <-2.0 . However the femoral neck BMD of $\leq 0.68 \text{ g/cm}^2$ was found to correspond to a t-score of -1.6 based on NHANES III (26, 69). Treatment in both arms was initially initiated at 5mg per day but increased to 10mg based on other trial results at the second annual visit. The vertebral fracture arm was adequately powered to detect a 40% decrease in cumulative incidence of new vertebral fractures but underpowered to detect a change in clinical fractures and the clinical fracture arm was adequately powered to detect a 25% reduction in clinical fractures (304).

The vertebral fracture data was published in 1996 and categorized fractures into clinical vertebral, clinical fractures (composite of clinical vertebral, hip, wrist), hip, and wrist fractures with 4 years of follow-up. At 4 years there was a significant reduction in clinical vertebral fractures RR 0.45 (95% CI 0.27, 0.72). Also they found a significant reduction in any clinical fracture (RR 0.72, 95% CI [0.58, 0.90]) which included clinical vertebral fracture, hip fractures (RR 0.49, 95% CI [0.23, 0.99]), and wrist fractures (RR 0.52, 95% CI [0.31, 0.87]). However summing all non-vertebral fractures did not produce a significant reduction (RR 0.80, 95% CI [0.63, 1.01]) based largely on the non-significant reduction for all non-vertebral, hip, or wrist fractures (RR 0.99, 95% CI [0.75, 1.31]).

The clinical fracture arm study categorized their results up into clinical fractures, vertebral, hip, and wrist fractures as well as separating their results based on baseline t-score. With 4 years of follow-up the clinical fracture arm of the study found a non-significant relative risk of 0.86 (95% CI 0.73, 1.01) for clinical fractures in all study participants, but a significant RR of 0.64 (95% 0.50, 0.82) in women who had osteoporosis (t-score <-2.5) at baseline. There was no significant reduction in RR for hip fractures overall 0.79 (95% CI 0.43, 1.44), but again a

reduction in osteoporotic women 0.44 (95% CI 0.18, 0.97). Wrist fractures also varied based on baseline t-score (overall RR 1.19, 95% CI [0.87, 1.64]; osteoporosis RR 0.88, 95% CI [0.55, 1.40]) with neither reaching statistical significance. Vertebral fractures were reduced by alendronate use RR 0.56 (95% CI 0.39, 0.80) overall and RR 0.50 (95% CI 0.31, 0.82) in those with osteoporosis.

The third report was based solely on those women who had non-osteoporotic t-scores (t-score between -2.5 and -1.6). This reanalysis contained 484/456 (ALN/PCB) from the vertebral fracture arm and 1394/1403 from the clinical fracture arm. Combined there were 3737 women with non-osteoporotic t-scores, 1878 received alendronate and 1859 who received placebo. They report that regardless of baseline vertebral fracture, ALN is associated with a RR 0.40 (95% CI 0.19, 0.76) with 3.0 to 4.5 years of follow-up. This study only assessed vertebral fractures.

Overall these three studies found that alendronate was efficacious at reducing future fractures in comparison to placebo and were the basis of the FDA approval in 1995. Additionally a 70 mg once weekly dose was approved by the FDA in 2001 and it has been found to be as efficacious as the 10-mg dose once daily (305).

2.5.2 AOM Safety

Although commonly used in real-world practice and generally considered to be a safe and effective treatment, several significant safety concerns have been raised related to the use of AOMs. These include atypical femoral fractures, osteonecrosis of the jaw (ONJ), cardiovascular complications, and risk of cancer. Case reports of atypical femoral fractures began appearing in the late 2000s, these fractures occur in the subtrochanteric or diaphyseal femur rather than the femoral neck. An initial analysis of three AOM RCTs suggested that the incidence of atypical fractures was rare, even in women using AOMs for up to 10 years (306). A 2010 task force from

the American Society for Bone and Mineral Research (ASBMR) concluded that the incidence of atypical fractures appears to be rare, though it may be associated with long-term bisphosphonate use (307). This report was updated in 2014 and further suggested that these fractures be given a different procedural code as an increased awareness may help to further clarify an association between bisphosphonates and atypical femoral fractures (308).

Osteonecrosis of the jaw (ONJ) is defined by the 2007 ASBMR task force as “as the presence of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider” (309). Estimates of the prevalence of ONJ in osteoporosis have been <1 in 100,000 person years in the US (309-311), with an increase in ONJ with intravenous bisphosphonates, treatment for >5 years, and among patients with concomitant malignancies (309). Recent analyses have suggested that treatment for malignancy may be a greater contributor to ONJ than osteoporosis (312).

As osteoporosis is a disease which primarily affects older adults, determination of an association between the use of AOM and cancer has been an important area of study. Oral bisphosphonates have been shown to increase esophageal irritation if they become lodged during swallowing prompting the recommendation of a prone position for the 30 minutes after ingestion. This esophageal irritation has given rise to the question regarding potential increased risk of esophageal cancer. To date there are conflicting results as to the association between bisphosphonates and cancer (313-316). In cases of breast cancer and bone metastases due to cancer, bisphosphonates have been investigated as possible treatment options and - in the case of zoledronic acid - are currently approved (317).

2.5.3 Comparative Effectiveness and Epidemiology of AOM use

RCTs have been performed comparing therapies which have been approved for osteoporosis. We will only discuss those trials, meta-analyses, and systematic reviews which compare two therapies which are considered AOMs in this analysis. Additionally we only discuss studies which compare two different agents rather than comparison of different formulations of the same agent. A comprehensive review of all trials comparing all therapies has been compiled by MacLean et al and Crandall et al (247, 282). In RCTs alendronate was found to not have a significant difference in clinical fractures at 2 years, or composite fractures at 1 year (318-321). No difference was found in non-vertebral fracture at 14 or 36 months or hip fracture at 36 months (322, 323).

Observational studies have found no significant difference in the risk of non-vertebral fracture between alendronate, risedronate, and raloxifene (324). In British Columbia an increased risk for hip fracture in women who used risedronate compared to alendronate was found (325). Alendronate users had lower non-vertebral and hip fracture rates after hip or vertebral fracture in Taiwan (326). In a managed care cohort a reduction in non-vertebral fractures for risedronate users compared to alendronate or calcitonin was found, but no difference in non-vertebral fracture risk between alendronate and calcitonin users (327). In women aged ≥ 65 a reduction in incident fracture rates for risedronate compared to alendronate users was found (328). In adherent commercially insured women aged ≥ 65 who were weekly users of risedronate were at a greater risk of hip fracture than alendronate users, but no greater risk for clinical vertebral or non-vertebral fractures compared to weekly alendronate users (329). Alendronate has been found to be more effective at reducing fractures (vertebral and non-vertebral) compared to ibandronate

users, while risedronate was no more effective (330). In summary alendronate is an effective therapy for reduction of fractures even when compared to other AOMs.

Although osteoporosis must be defined by BMD, clinical guidelines and US quality measures encourage AOM treatment after fragility fracture (hip or vertebral) (331-333). Research has found that women are more likely to be treated than men, however less than 35% of patients typically receive an AOM within 6 months of fracture (125, 129, 163, 334). Although AOM treatment after fracture shows a decrease in future fracture a large portion of the population who are known to be at risk for future fracture are not utilizing AOMs (267).

Estimates of AOM utilization by the population at risk for osteoporosis is difficult owing to the under diagnosis of osteoporosis. After diagnosis of osteoporosis less than 50% of patients have been reported as receiving an AOM (334, 335). In patients known to be at risk for glucocorticoid-induced osteoporosis, less than 40% of patients are reported as treated with AOMs (16, 336-341). It appears that in cases where patients and clinicians are aware that a patient is at risk for fracture, therapy is somewhat utilized. However AOMs cannot be effective in reducing fractures if they are not used by patients. At an adherence (Medication Possession Ratio [MPR]) of $\geq 80\%$ fewer fractures occur (342, 343). Also 50% compliance is thought to be necessary for fracture reduction (344). However meta-analyses and systematic reviews have found one-year MPRs for daily oral bisphosphonates to be $\sim 50\%$ with even lower compliance at 24 months and $\sim 60\%$ in weekly bisphosphonates (345, 346). Patients who are at least 70% compliant with AOM therapy have been found to incur 9% less osteoporosis related costs and 7% less overall costs within 2 years (347). There are multiple rationales for low compliance to AOMs including patient side effects and questions regarding the efficacy of treatments (348,

349). However it is difficult to completely define who is at risk for fracture and should be treated or how effective treatment will be if medication isn't properly used.

2.5.4 Universal Supplement Recommendations

In all patients an adequate dietary intake of calcium and Vitamin D are recommended. In early life calcium plays a major role in increasing peak bone mass which plays a role in the development of osteoporosis. Vitamin D is involved in calcium absorption, bone health, muscle performance, balance, and the risk of falls. Although supplements are an important part of treating osteoporosis and osteoporotic therapy, their use alone is not sufficient to reduce future fractures. However in an attempt to increase Vitamin D intake some AOMs have begun including it in the capsule, ie Fosamax plus D, though it may cause osteomalacia in patients who are Vitamin D deficient (350).

2.6 Quality Measures and Evaluation of Guidelines

With diminishing resources for healthcare, payers and providers are increasingly looking for ways to measure quality patient care and improve outcomes. Quality measures (QM), which are derived from evidence-based medicine and expert opinion, are used to evaluate the care that patients receive. Commonly these quality measures are then used to incentivize reimbursement based on specific care measures in a process known as pay-for-performance (P4P). Although P4P has not convincingly been shown to improve outcomes many payers, including Medicare, have begun tying reimbursement to both processes and outcomes of care (351-353).

To our knowledge there are no P4P measures currently in use by Medicare for osteoporosis however establishment of reliable quality measures is necessary to tie reimbursement to quality. In osteoporosis, QMs are currently in place through the Joint Commission on Accreditation of Healthcare Organization (JCAHO), National Quality Forum

(NQF), and the National Committee for Quality Assurance. Current QMs for osteoporosis are listed in Table 2.8. The presented QMs measure process of care or treat-to-target measures likely due to the relative ease of assessment based on physician ordering or prescribing of therapy rather than the effect of the therapy on clinical outcomes (354).

Table 2.8 Quality Measures by Steward

Measure Title	Description	Number	Steward
Osteoporosis Management in Women Who Had a Fracture†§	The percentage of women 67 years of age and older who suffered a fracture and who had either a bone mineral density (BMD) test or prescription for a drug to treat or prevent osteoporosis in the six months after the date of fracture.	NQF #0053	NCQA
Osteoporosis testing in older women†§	Percentage of female patients aged 65 and older who reported receiving a bone density test (BMD) to check for osteoporosis	NQF #0037	NCQA
Osteoporosis: Communication with the Physician Managing On-going Care Post Fracture of Hip, Spine or Distal Radius for Men and Women Aged 50 Years and Older§	The percentage of patients aged 50 years and older treated for a hip, spine or distal radial fracture with documentation of communication with the physician managing the patient's ongoing care that a fracture occurred and that the patient was or should be tested or treated for osteoporosis.	NQF #0045	NCQA
Osteoporosis: Management Following Fracture of Hip, Spine or Distal Radius for Men and Women Aged 50 Years and Older§	Percentage of patients aged 50 years or older with fracture of the hip, spine or distal radius that had a central DXA measurement ordered or performed or pharmacologic therapy prescribed	NQF #0048	NCQA
Osteoporosis: Pharmacologic Therapy for Men and Women Aged 50 Years and Older§	Percentage of patients aged 50 years and older with a diagnosis of osteoporosis who were prescribed pharmacologic therapy within 12 months	NQF #0049	NCQA
Osteoporosis: Screening or Therapy for Women Aged 65 Years and Older§	Percentage of female patients aged 65 years and older who had a central dual-energy X-ray absorptiometry (DXA) measurement ordered or performed at least once since age 60 or pharmacologic therapy prescribed within 12 months.	NQF #0046	NCQA
Steroid Use - Osteoporosis Screening§	The percentage of patients aged 18 years and older who have been on chronic steroids for at least 180 days and had a bone density evaluation or were taking osteoporosis treatment	NQF #0614	ActiveHealth Management
Osteopenia and Chronic Steroid Use - Treatment to Prevent Osteoporosis	The percentage of women aged 55 years and older, or men, aged 50 years and older, who are taking chronic steroids (≥ 3 months), and are taking drugs to prevent osteoporosis	NQF #0633	ActiveHealth Management
Osteoporosis - Use of Pharmacological Treatment	The percentage of women, aged 55 and older, or men, aged 50 and older, with a diagnosis of osteoporosis who are taking osteoporosis therapy.	NQF #0634	ActiveHealth Management
Risk assessment/treatment after fracture- Inpatient	The percentage of all patients who had had a CBC, kidney and liver function tests, serum calcium, and 25 (OH)vitamin D level prior to discharge with a diagnosis of osteoporosis or fragility fracture of the hip, spine or other fracture	7	JCAHO
Risk assessment/treatment after fracture-Emergency Department	The percentage of all patients who had had a CBC, kidney and liver function tests, serum calcium, and 25 (OH)vitamin D level prior to discharge with a diagnosis of osteoporosis or fragility fracture of the hip, spine or other fracture	7a	JCAHO
NCQA: National Committee for Quality Assurance, NQF: National Quality Forum, JCAHO: Joint Commission on Accreditation of Hospital Organizations; HEDIS: Healthcare Effectiveness Data and Information Set; †: Use in HEDIS 2014; §: NQF Endorsed			

At the present time there are no QMs which measure the receipt of an AOM based on NOF guidelines, as there is no agreed-upon proxy for measuring FRAX® in most data sources (35, 136, 137). This leaves potentially a large proportion of the population at risk for osteoporotic fracture not having the quality of their care measured or administered in a systematic way.

In osteoporosis, the prevention of fracture is the primary measurable QM outcome as there is no target level for BMD wherein fractures will not occur (355-357). The creation of treatment guidelines and the measurement of quality care in osteoporosis is an ongoing process, and although numerous measures have been proposed, only process measures are currently in use (331, 358, 359). Of note, three NQF measures lost their approval due to an inability to accurately assess the effectiveness of the QM because of a lack of pharmacy, bone density, and fracture risk information.

The use of process measures also generally prevents researchers from determining if the receipt of a quality measure improves the patient's clinical outcome as evidenced by the conflicting results of two studies of AOM use in glucocorticoid-induced osteoporosis (16, 17). Although clinicians would generally agree that the use of an AOM should reduce the risk of fracture, if other factors including baseline fracture risk are not properly accounted for, spurious conclusions can be reached.

Current QMs based on receipt of an osteoporosis medication for patients with osteoporosis or prevalent fractures and/or the receipt of a DXA for women over age 65 both have shown less than optimal receipt of care. In patients with new fractures between 9.4% and 40.2% of patients treated for hip or vertebral fracture also received an AOM with the inclusion criteria for these populations varying widely (125, 129, 163, 334). Additionally only 41.6% of patients

with a diagnosis of osteoporosis received an osteoporosis medication within 90 days of their initial diagnosis (334). In a study of 25 million Medicare patients (5% Medicare sample), less than 30% of women aged 65 and older received a DXA between 1999 and 2005 (78). Other researchers have reported that less than 20% of Medicare patients received an AOM after diagnosis of osteoporosis (336, 360) and AOM use has been found to be even less among patients at risk for secondary osteoporosis (340, 361). A study by Antonelli et al found that fewer than 20% of patients with incident hip or vertebral fracture were screened for osteoporosis or provided with an AOM (362). Although these studies were not intended to measure the real-world effect of QM, they demonstrated that preventative care measures are not being utilized in actual practice for osteoporosis.

Attempting to evaluate QM based on real world practice is likely to be highly confounded by variables not available in most current datasets available to payers – specifically BMD and FRAX® 10-year risks for major osteoporotic or hip fracture. BMD is important to measure as this is currently the only accepted way to diagnosis osteoporosis and up to 30% of patients with osteoporosis by BMD do not have a corresponding diagnosis recorded (9, 35, 70, 137). FRAX® 10-year risk of fracture on the other hand is based on clinical characteristics that are generally unavailable in administrative claims which can be calculated with or without patients' BMD and provide a diagnostic threshold for treatment (65, 363).

2.7 Framework for variable selection

The purpose of this project is to estimate a fracture risk score based on characteristics which can be obtained through administrative claims. Primarily we are concerned with factors and patient characteristics which are associated with a patient's future fracture risk, including bone strength (decrease due to disease as well as possible increase due to the use of calcitonin,

HRT, or raloxifene), propensity to fall, as well as factors included in the FRAX® model (5, 8, 18, 46, 280). The patient characteristics listed in this section have been chosen based on their known relationships to bone strength, osteoporosis, falls, or propensity to fracture (364-370). Additionally we have included health system variables which have been shown to be associated with osteoporosis and osteoporotic fracture (including DXA utilization) (20, 80, 369, 371). Because CFRI is an estimation of FRAX®, the variables used in FRAX® which can be captured in administrative claims, age, gender, prior osteoporotic fracture, rheumatoid arthritis, secondary causes of osteoporosis, and current use of oral glucocorticoids will also be utilized (17).

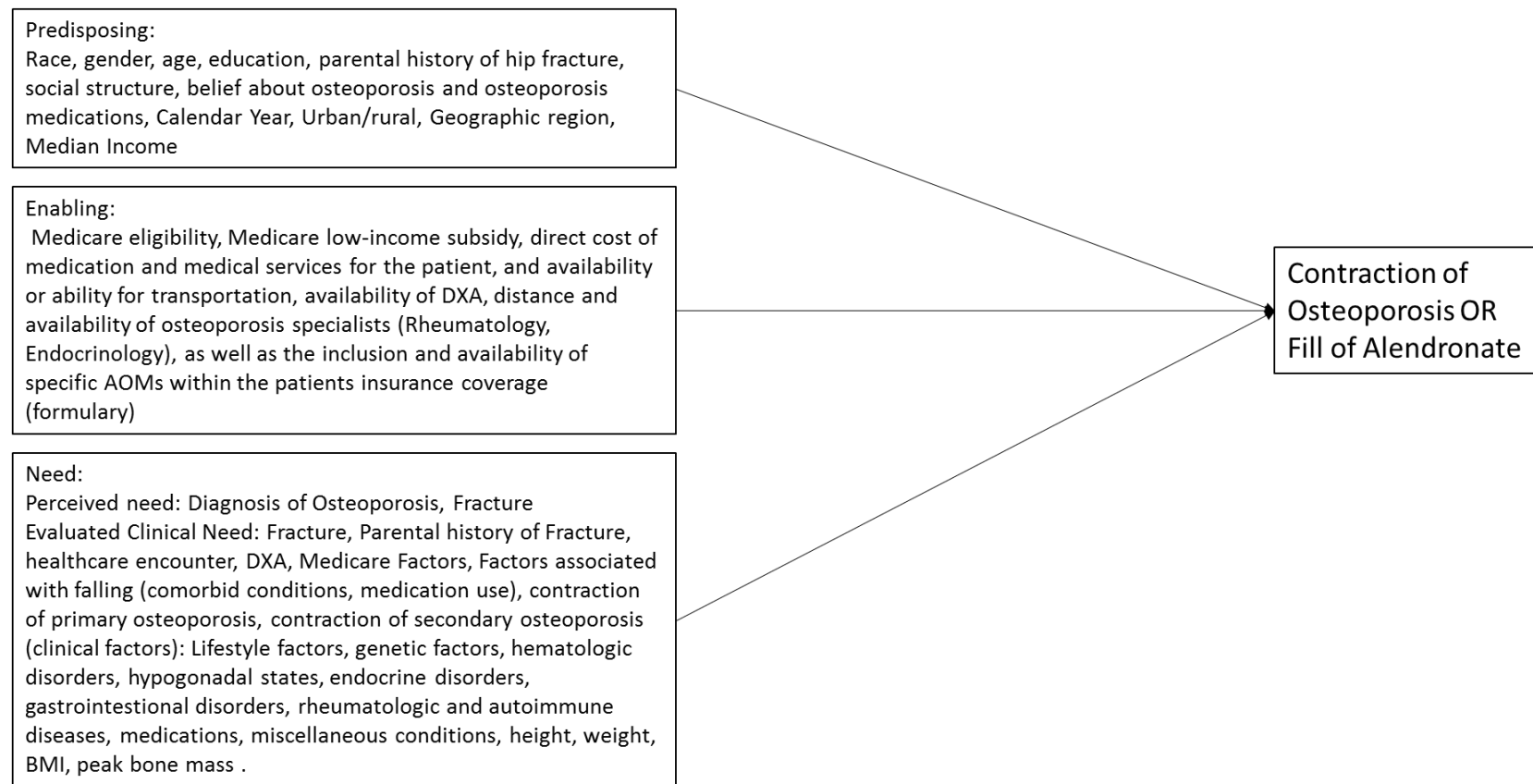
2.7.1 Andersen's Behavioral Model of Health Services Use

Within the project Aim 3 is used to demonstrate how CFRI could be used in actual practice. The intention is to create groups which are best representative of both users and non-users of alendronate and determine if the use of CFRI improves effect estimates. Although not intended for this purpose, Andersen's Behavioral Model of Health Services Use may be applicable to categorize the characteristics used in this analysis. Briefly Andersen posits that there are predisposing, enabling, and need factors which predict a patient's use of health services (372, 373). We previously have discussed the content variables which we expect to be associated with osteoporosis and possibly associated with the receipt of an AOM. We have taken the content variables in addition to health system variables and divided them into predisposing, enabling, and need factors based on Andersen's Model (Figure 2.8) (364-369).

The three facets of the model are predisposing, enabling, and need characteristics which explain why a person does or does not utilize healthcare. In Andersen's model predisposing variables are both biological imperatives, ie age, gender; social factors including education and race; as well as health beliefs, in our context the patient's ideas about osteoporosis and treatment.

Enabling characteristics generally can be split into financing and organizational factors. The financial factors can include those a patient's ability to pay for health care as well as the overall cost of healthcare, while the organizational factors include if a patient has a regular source of healthcare and what type care that is. Organizational factors also can include things like transportation or parking costs and the amount of time it takes for a patient to be seen. Lastly are need characteristics which have been split into perceived and evaluated need for healthcare. In the model perceived need are how the patient themselves views their health, ie do they think of themselves as sick, while evaluated need is moreso objective measures of the patients health (364-369, 372). When a researcher fills in each of the categories they are better able to understand the barriers which patients may face to receiving care, as well as possible intervention points to improve the patients care. Although much of this project is focused on predicting an actual clinical event, rather than use of medical services around the event, a better understanding of why a patient may or may not have sought help for the condition allows our research team to contextualize factors which are associated with either event.

Figure 2.8 Modified Andersen's Behavioral Model of Health Services Use



2.7.1.1 Study Variable Framework

Based on Andersen's model, predisposing characteristics fall into three groups. First are those characteristics which represent biological imperatives which will cause the patient to need the health service (372). Second are those characteristics which are associated with a patients' social structure, including their status within the community, and coping responses (372). Third are patients' health beliefs which are their attitudes, values, and knowledge the patient has about their health condition and the treatment of the health condition which influence if a patient uses the healthcare resource (372).

For this study race, gender, and age can be considered as biological imperatives; age, race, gender, education, parental history of hip fracture, and social structure are variables which could be considered as social structure; as well as a patients belief about osteoporosis and osteoporosis medications could be considered beliefs all of which can be labeled as predisposing variables (5, 8, 13, 69, 366, 374, 375). We would also include calendar year, urban/rural, geographic region, median income which were variables found to be associated with osteoporotic fracture in previous studies of Medicare data, as predisposing variables (20, 130). During creation of CFRI we found little to no variation in geographic region, urban/rural, or median income due to all patients being treated in Northeast Ohio. Additionally we removed calendar year from the algorithm as not all years ended up being significant covariates and if the algorithm was to be used with any other time period than it was created in the calendar year variable would not be informative or useful. Important but unmeasured variables include: education, social structure, or patient's beliefs about osteoporosis or osteoporosis medications. As BMI and parental hip fracture are part of the FRAX® calculator we will not directly be using these variables in this analysis. All factors expressed as predisposing variables have been

empirically shown to be associated with the development of osteoporosis, osteoporotic fracture, or the use of an anti-osteoporosis medication.

The model describes enabling resources as being in one of two main groupings, either personal/family or community. Andersen states that “Both community and personal enabling resources must be present for use to take place. First health personnel and facilities must be available where people live and work [community]. Then people must have the means and know-how to get to those services and make use of them [personal/family]” (372). For this analysis the personal/family predisposing variables are thought to be Medicare eligibility, Medicare low-income subsidy, direct cost of medication and medical services for the patient, and availability or ability for transportation, though based on the exposure of an office visit for Aim 3, these variables were not measured in the analysis. The community enabling variables are thought to include availability of DXA, distance and availability of osteoporosis specialists (Rheumatology, Endocrinology), as well as the inclusion and availability of specific AOMs within the patients insurance coverage (formulary), however for this analysis they were not measured (364-369).

Within the model, Andersen states that there are also need factors which are the immediate reason for health care utilization to take place, both realized and perceived (372). First are the diagnosis of osteoporosis or the actualization of a fracture. For our study many of the evaluative need factors are conditions (diseases) associated with osteoporosis, low bone mass, or falling based on prior research and meta-analyses including: fracture, parental history of fracture, healthcare encounter, DXA, Medicare factors (listed previously), factors associated with falling (comorbid conditions, medication use listed in Table 2.10), diagnosis of primary osteoporosis, diagnosis of secondary osteoporosis (clinical factors listed in Table 2.9): Lifestyle factors,

genetic factors, hematologic disorders, hypogonadal states, endocrine disorders, gastrointestinal disorders, rheumatologic and autoimmune diseases, medications, and miscellaneous conditions (5, 8, 17, 124, 130, 148, 175-180, 376, 377). The specific diseases which fall within these groups are listed in Table 2.9, the different diseases and disease groups have varying specific mechanisms for low bone mass and increased fracture risk with basic mechanism groupings provided in Table 2.10, including changes in bone resorption and formation, low peak bone mass, decreased sex hormones, malabsorption including Vitamin D and Calcium, use or excess production of glucocorticoids, excess parathyroid hormone, inflammation, decreased mobility, physical exercise, and balance, as well as an increase in falls and lower bone mass due to conditions which effect muscle strength and overall bone loss (5, 378-380).

Many of the conditions listed as content variables in Table 2.10, particularly the gastrointestinal, rheumatologic, and immunologic diseases necessitate the use of specific medications including glucocorticoids and proton pump inhibitors which have been shown to be associated with decreases in bone mass and increased risk for fracture (5, 37, 176, 381-384). The nine groups listed in Table 2.10 are decreased BMD, malabsorption, glucocorticoid use or production, falling, decreased sex hormones, low peak bone mass, changes in parathyroid hormone (PTH), immobilization, and inflammation. In many cases the conditions within a given group increase fracture risk by more than one of these categories. Broadly a decreased BMD either at or after peak means the patient has less bone to lose to before they are at risk for fracture due to a low BMD, the groups which have been checked in the table either reduce a patient's bone mass at a later point or are known to not allow a patient to achieve the highest possible bone mass prior to adulthood (385). Malabsorption is an issue in osteoporosis due to nutrients

including calcium not being absorbed in the gut preventing the body from having the necessary building blocks for bone formation (386-388).

Glucocorticoid use has been shown to be ~1.2% in the US, with glucocorticoids continuing to be a drug which is commonly prescribed for conditions that fall under endocrine disorders, rheumatic conditions, as well as in central nervous system disorders (particularly multiple sclerosis) (361, 389-391). Glucocorticoids both in the medication form as well as the body's own production effect bone remodeling and when used at high doses or prolonged periods of time put patients at an increased risk for osteoporosis (glucocorticoid-induced osteoporosis) as well as fracture (392). Decreased estrogen has been found to be associated with osteoporosis, as such hypogonadal states including premature ovarian failure, alter a patients estrogen levels and effect their bone (393-396).

Parathyroid hormone is an essential part of bone resorption by changing the absorption and expression of calcium in the bone (397, 398). Studies have shown that patients who are at a higher BMI are associated with stronger bones, under the hypothesis that their bones are being made to work more due to the increased weight, this is the same rationale as to why immobilization causes weak bone (399). If you are not putting weight onto and utilizing your bones they will become brittle and at a higher risk for fracture (400, 401). The last broad category was inflammation which has been shown to be associated with changes in bone turnover which can cause weakening of the bone (402, 403).

The specific conditions and medications which have been shown with at least moderate evidence to be associated with falls are checked in Table 2.10 and described in more detail in Table 2.11, and are arthritis, stroke, Alzheimer's, Parkinson's, Dementia, incontinence, postural hypotension, sedatives, antidepressants, cardiovascular drugs, and polypharmacy (370, 404).

Lastly are height, weight, BMI, peak bone mass which are biological determinants which predispose a patient to weak bones. Height, weight, and BMI are all interconnected and it has been found that persons with a higher BMI or greater weight have better BMD and are less likely to fracture. The thinking is that the extra weight stimulates the bone, thereby making it stronger (399). Peak bone mass effects the long-term fracture risk because if a patient had a low peak bone mass, then they do not have much to lose before they become osteoporotic thereby putting themselves at a greater risk for fracture (385). Peak bone mass although interesting and potentially important cannot be measured at the point of our study and therefore will be an unmeasured variable.

In general a face to face healthcare encounter is necessary for a patient to be diagnosed with osteoporosis, have their fracture risk evaluated, or receive a DXA, or have FRAX® calculated. Because the NOF guidelines use FRAX® to guide treatment decisions, the presence of osteoporosis or specific FRAX® score is a need variable to initiate treatment, but has little association with the independent development of osteoporosis (37).

Although not all of these risk factors can accurately be measured in administrative claims, when possible, measurement will be based on previously published algorithms. We previously measured the majority of the need variables in a study of glucocorticoid-induced osteoporosis (17). The variables used in this study grouped by type of disease, medication, or demographic characteristic are presented as Table 2.9. Variables both based on content knowledge and high-dimensional methods will be utilized in Aim 3 to control for confounding and include factors related to both the exposure and outcome (405-407). Failure to adjust for these confounders cause biased treatment estimates (407). Although the factors specified will be

used to create CFRI they also will be introduced into the model when CFRI is utilized as a disease risk score.

We are estimating a clinical fracture risk score (FRAX®) with our tool CFRI in this study. The intended purpose of CFRI is to inform researchers and policy makers of the information that a clinician had at the time of treatment decision. The clinical model which we have proposed allows our projects to address critical points in the decision-making process for treatment and evaluation of treatment for osteoporosis.

Table 2.9 Variables associated with Osteoporosis or Osteoporotic Fracture

Lifestyle Factors	Hypogonadal states	Medication Classes
Alcohol Abuse	Androgen insensitivity	Cyclosporine A and tacrolimus
Falling	Anorexia nervosa and bulimia	Proton pump inhibitors
Vitamin D insufficiency	Hyperprolactinemia	Anticoagulants
Excess Vitamin A	Premature ovarian failure	Selective serotonin reuptake inhibitors
Genetic factors	Athletic amenorrhea	Anticonvulsants
Cystic fibrosis	Turner and Klinefelters's syndromes	Glucocorticoids
Homocystinuria	Panhypopituitarism	Aromatase inhibitors
Osteogenesis imperfect	Endocrine disorders	GnRH (Gonadotropin releasing hormone) antagonists and agonists
Ehlers-Danos	Adrenal insufficiency	Thiazolidinediones
Hypophosphatasia	Diabetes mellitus (Type 1)	Barbiturates
Gaucher's disease	Cushing's syndrome	Lithium
Idiopathic hypercalciuria	Hyperparathyroidism	Methotrexate
Porphyria	Central Adiposity	Calcitonin
Glycogen storage diseases	Thyrotoxicosis	Hormone Replacement Therapy
Marfan syndrome	Gastrointestinal disorders	Raloxifene
Riley-Day syndrome	Celiac disease	Miscellaneous conditions and diseases
Hemochromatosis	Gastric bypass	AIDS/HIV
Menkes steely hair syndrome	Inflammatory Bowel Disease	Congestive Heart Failure
Hematologic disorders	Malabsorption	Muscular dystrophy
Hemophilia	Pancreatic disease	Depression
Thalassemia	Primary biliary cirrhosis	Amyloidosis
Sickle cell disease	Rheumatologic and autoimmune diseases	End stage renal disease
Systemic mastocytosis	Ankylosing spondylitis	Sarcoidosis
Multiple Myeloma	Lupus	Chronic metabolic acidosis
Leukemia's and Lymphomas	Rheumatoid arthritis	Hypercalciuria
Central nervous system disorders	Medicare Factors	Asthma/Chronic obstructive lung disease
Epilepsy	Gender	Idiopathic scoliosis
Parkinson's disease	Race	Kyphosis
Stroke	Age by 5 year increments	Immobilization
Multiple sclerosis	Calendar Year	Emphysema
Spinal cord injury	Urban/rural	
	Geographic region	
	Median Income	

From: US Surgeon General, 2004 (5), Taylor et al 2011 (130)

Table 2.10 Mechanism of Action for Conditions and Medications Associated with Osteoporosis and Osteoporotic Fracture

Factor group associated with osteoporosis and osteoporotic fracture	Decreased BMD (5, 37, 176, 381-384)	Malabsorption (386-388)	Glucocorticoid Use or production (361, 389-391)	Falling (370, 404)	Decreased Sex Hormones (393-396)	Low Peak Bone Mass (392)	PTH (397, 398)	Immobilization (400, 401)	Inflammation (402, 403)
Lifestyle Factors	X	X		X					
Genetic Factors	X								
Hematologic Factors									
Hypogonadal States					X	X			
Endocrine Disorders			X				X		
Gastrointestinal Disorders		X	X						
Rheumatologic and autoimmune diseases			X			X			X
Medications	X	X	X			X			X
Miscellaneous Conditions	X	X				X	X		X
Central Nervous System Disorders	X	X	X	X				X	

PTH: Parathyroid Hormone

Table 2.11 Conditions and Medications associated with Falling

Arthritis	Stroke
Alzheimer's	Parkinson's
Dementia	Incontinence
Postural Hypotension	Sedatives
Antidepressants	Cardiovascular Drugs
Polypharmacy	

From citations (370, 404)

2.8 Summary

Osteoporosis and osteoporotic-fracture are common and result in significant morbidity and mortality. Evidence suggests that a large proportion of patients who may benefit from therapy are not treated due largely to an inability to accurately and easily identify patients who may be eligible for treatment. Identifying patients who will go on to have a fracture isn't precise and the risk tools currently available generally rely on a patient's bone mineral density which isn't readily accessible to providers or payers. By developing a claims-based algorithm for accurately measuring FRAX we hope to provide a tool for identifying patients who might benefit from treatment and that could be used to improve the rigor of comparative effectiveness research studies comparing treatments for osteoporosis.

CHAPTER 3: METHODS

3.1 Data Sources

For this project two different data sources will be used, a clinical registry which has been linked to Medicare Claims referred to as the “linked sample” and a 20% random sample of Medicare administrative claims for fee-for-service beneficiaries. We describe how the linked sample is created, the inclusion and exclusion criteria of the linked sample, and the data which was linked in this section. Additionally we describe the data contained in the 20% random sample of Medicare beneficiaries.

3.1.1 Cleveland Clinic (CCF)

The Cleveland Clinic DXA Registry (CCF DXA) began prospectively collecting patient information in 2009 in an attempt to better measure the quality of their osteoporosis care (408). Patients administered DXAs at one of 9 sites within the CCF health system were consented to include their information in the registry. The information gathered includes all variables needed to calculate FRAX, current and past use of AOM, and basic demographic characteristics. Data is entered into the registry by DXA technologists or directly imported from the medical record. FRAX® is retrospectively calculated for all patients in the first quarter of the following year using either the batch utility tool or the current web version (65).

Through the end of 2014, 45,000 patients have had their data entered into the registry. Periodic quality checks of measures which are entered by hand such as height, weight, and BMD are conducted with changes made as needed. CCF DXA patients have successfully been linked

to their electronic medical record (EMR) (99.1% of cases) based on medical record number. This linkage allows analysis and collection of all discrete data elements contained within the patients EMR including all visit diagnoses, clinic notes, labs, procedure reports, and prescribed medications. Due to its registry status and linkage to the patients EMR the CCF, DXA is approved by the CCF Institutional Review Board (IRB).

3.1.2 University of Alabama at Birmingham (UAB)

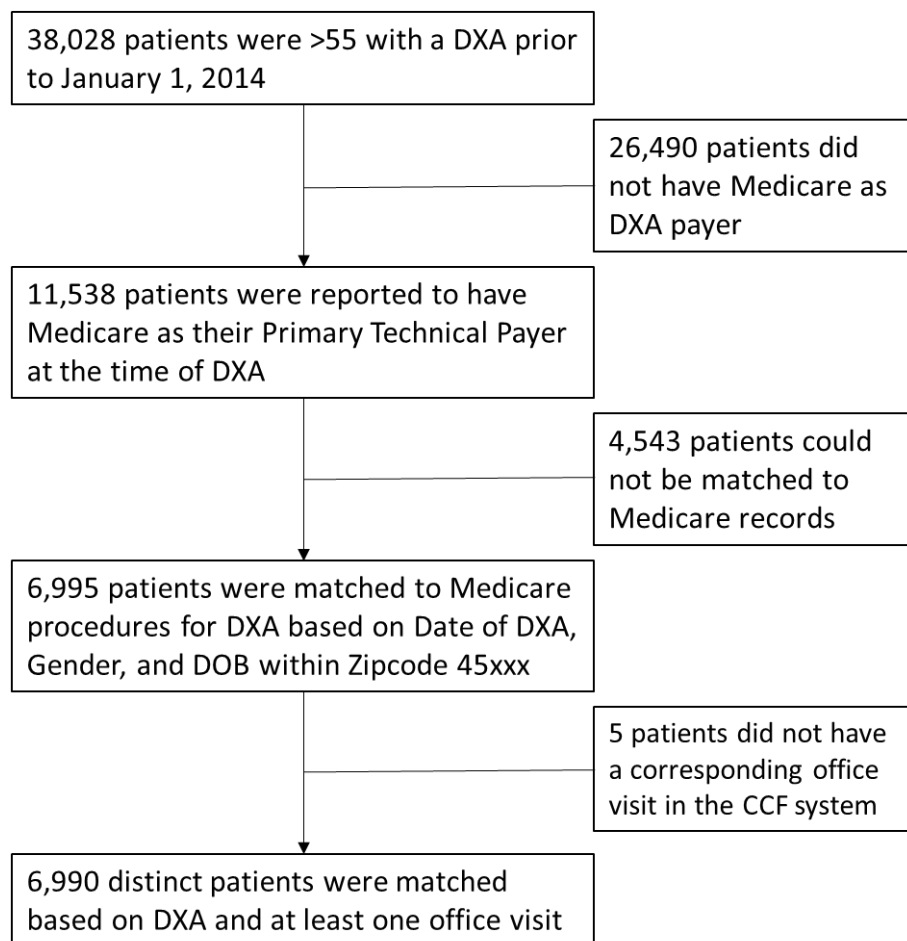
Utilizing a collection of multiple stakeholders the University of Alabama at Birmingham (UAB) under the direction of Jeffrey Curtis, MD, MPH, MS have gathered Medicare fee-for-service claims for patients at increased risk for fracture. This includes a 5% sample of all Medicare beneficiaries from 2006 to 2013, as well as 100% of women with a diagnosis of osteoporosis, claim for a fracture, or claim for an osteoporosis therapy between 2010 and 2013. The UAB FFS data includes the beneficiary annual summary file, Medicare claims file, and prescription drug claims file for the specified time periods. These files include demographic information including region of residence and date of death, inpatient and outpatient encounter based diagnosis and procedures, as well as all filled medications under Medicare Part B. Files can be linked based on a de-identified beneficiary id variable. Medicare FFS files have been used extensively in pharmacoepidemiologic research (20, 75).

3.1.3 CCF/Medicare Linkage (Linked Sample)

CCF patients aged 55 years or older with Medicare Part A/B as the primary payer for the service on the date of their CCF DXA were identified. Specifics of the matched population are presented as Figure 3.1. Patients available for linkage from the Medicare data were enrolled in Medicare Part A/B at the time of their DXA. This method identified a candidate 11,538 CCF patients matched to Medicare enrollment data. Variables used for linking between the CCF

registry and the Medicare claims were birth date, sex, and date of DXA. Before attempting to link the CCF patients, the CMS data was restricted to only DXAs (CPT 76499, 76977, 77080, 77081, 77082, 77083, 78399, 76075, 76076, 76078, 77078, 77079, 8898) with the service occurring within a zip code served by CCF centers. This restriction – called blocking - is intended to increase matching efficiency between the CCF registry and Medicare claims.

Figure 3.1 CCF/Medicare Linkage Flow Diagram



Based on exact matches to birth date, date of DXA, and gender 6,995 patients (60.6%) were matched between the CCF and UAB data. In cases where patients were not uniquely matched (n=55), service dates were compared to uniquely identify the patient from multiple

claims. In 5 cases no corresponding dates could be identified leaving a final cohort of 6,990 matched patients.

For those patients whose data were successfully linked, we identified, height, weight, BMD, FRAX® 10-year risks of major osteoporotic and hip fracture with and without BMD (when available), as well as responses to all FRAX® variables. A comparison of patient characteristics across each phase of data linkage - the full DXA registry (pre-linkage), individuals in the DXA registry with Medicare as the payer on record, and the linked population are presented as table 3.1. Although a small number of men are included in the linked sample we exclude them for our analyses based the small n and we do not know if FRAX® is able to predict fracture as well in men and women which could skew our predictions.

Table 3.1 Linked Population Characteristics

	Whole Registry	With Medicare	Linked
N	38028	11,538	6990
Male	5411 (14.2)	1653 (14.3)	101 (1.4)
Female	32,617 (85.8)	9885 (85.7)	6,889 (98.6)
Mean Age	67.2 (8.4)	72.3 (7.4)	73.3 (7.1)
2009	2872 (7.6)	1094 (9.5)	468 (6.7)
2010	8247 (21.7)	2724 (23.6)	1378 (19.7)
2011	10716 (28.2)	3567 (30.9)	2211 (31.6)
2012	8654 (22.8)	2431 (21.1)	1766 (25.3)
2013	7539 (19.8)	1722 (14.9)	1167 (16.7)

3.1.4 Medicare 20% Random Sample (Random Sample)

We utilized a 20% random sample of all Medicare FFS beneficiaries between 2007 and 2013 for evaluating the performance of CFRI in administrative data. The data is housed at the UNC Cecil B. Sheps Center for Health Services Research. The 20% random sample includes the beneficiary annual summary file, Medicare claims file, and prescription drug claims file for a

20% random sample of Medicare FFS beneficiaries. As in the linked sample, we exclude men from the claims for consistency between the linked and random sample.

3.2 Aim 1

Aim 1: Develop and evaluate a claims-based algorithm (CFRI) to estimate FRAX® risk scores using clinical registry data linked to Medicare claims data.

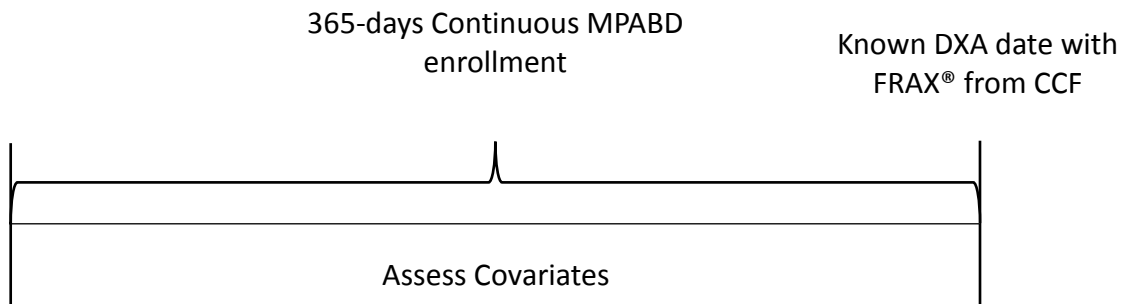
Hypothesis 1: In the final model there will be no significant difference in predicted (CFRI) to observed (FRAX®) scores based on R^2 .

Aim 1 will utilize the registry-claims linked dataset to create a linear model estimating the known values of FRAX® 10-year risk for 1) major osteoporotic fracture without BMD, 2) hip fracture without BMD, 3) major osteoporotic fracture with BMD, and 4) hip fracture with BMD. These four scores will be listed as continuous numeric variables as calculated using the FRAX® website and linked to the patient's claims data.

For aim 1, we required all women in the linked dataset to have at least 365-days continuous enrollment in Medicare Part A, B, and D prior to the date of DXA in the linked dataset (Figure 3.2). Although Part D enrollment could not be explicitly determined within the linked data, we required a fill of at least one medication in the 365-day look back period. The length of the look-back period allows us to collect the variables which are based both on content knowledge and selected using a high-dimensional method to estimate CFRI. Additionally patients were required to be anti-osteoporosis medication (bisphosphonates, Raloxifene, calcitonin, Denosumab, and Teriparatide) naïve as well as not have an ICD-9 diagnosis code associated with a major osteoporosis fracture during the look-back period. If a patient has more than one DXA, we will randomly select one of the dates for the parameter estimates. The

primary outcome for this aim is the known FRAX® score; we describe how we will chose the covariates, and the correct combination of the covariates will yield CFRI.

Figure 3.2 Aim 1 Study Schematic



MPABD: Medicare Part A, B and D enrollment

Aim 1 is a classic prediction model of an observed continuous variable. To describe the methods of how we are predicting FRAX® we have broken this aim into 3 specific steps (listed below).

STEP 1: Select covariates

STEP 2: Determine model type and outcome

STEP 3: Determine optimal model parameters for penalization values, stability, and coefficients using 10-fold cross validation

Further we will discuss how we will accomplish each of these steps in the following sections. This will include what information will be passed forward from each step, the diagnostics of each step, and the expected result of each step.

For this aim, we separated the cohort into a test and a training dataset. The training data set comprised 70% of the population and all models were created in this dataset. Once the models were fit, it was used to predict CFRI in the test dataset. Because some patients did not have a femoral neck BMD recorded at the time of their DXA the study population was subset by

BMD presence or absence. The same population was used for both models in each group (with/without BMD) and all patients are eligible for inclusion in the test and training sample regardless of their status in the other cohort.

3.2.1 Step 1: Select covariates

The model covariates are being chosen in one of two ways, 1) through content knowledge based on the Andersen's conceptual framework of factors known to be associated with osteoporosis, and 2) through a high-dimensional variable selection approach (described in detail below) to identify utilization and unknown healthcare characteristics associated with FRAX®. All model covariates will be based solely on diagnosis, procedure, medication, and utilization codes primarily found in administrative claims. Covariates based on content knowledge are those which were likely associated with osteoporosis or fracture in the 2004 Surgeon General's Report and identified in prior work (5, 17), (Table 2.9). For those conditions which are identifiable in administrative claims data utilizing The International Classification of Diseases, Ninth Revision (ICD-9), Current Procedural Terminology (CPT), or Healthcare Common Procedure Coding System (HCPCS) codes we present coding algorithms in Table 3.2. All factors in table 2.9 will be recorded as 0=absent, 1=present based on the 365-days prior to FRAX®. Based on the 2004 Surgeon General's report we have deemed the following characteristics as associated with osteoporosis, but it is unknown if many of these factors would also be associated with treatment. As CFRI is designed to estimate fracture risk, we are only concerned with factors which affect patients' bones, rather than those associated with AOM use. Lastly, we captured the use of hormone replacement therapy because this is a medication which improves patients bone mass, so although it doesn't demonstrate a decrease or increase in fracture risk, it does alter it.

Table 3.2 Content Variables Associated with Osteoporosis (Coding Algorithms)

Variable	ICD-9 Code unless specified
Osteoporosis	733.0x
Dual Energy X-ray absorptiometry (DXA) scan	CPT Codes: 76075, 76076, 77079, 76499, 77080, 77081, 77082, 77083
Lifestyle Factors	
Alcohol Abuse	303.xx, 305.0x
Falling	E880-E888.xx
Vitamin D insufficiency	268.xx
Excess Vitamin A	278.2
Genetic factors	
Cystic fibrosis	277.0x
Homocystinuria	270.4
Osteogenesis imperfecta	756.51
Ehlers-Danos	756.83
Hypophosphatasia	275.3
Gaucher's disease	272.7
Idiopathic hypercalciuria	275.4
Porphyria	277.1
Glycogen storage diseases	271.0
Marfan syndrome	759.82
Riley-Day syndrome	742.8
Hemochromatosis	275.03
Menkes steely hair syndrome	759.89
Hypogonadal states	
Androgen insensitivity	259.5x
Anorexia nervosa and bulimia	307.1, 783.0, 307.51
Hyperprolactinemia	253.1
Premature ovarian failure	256.31
Athletic amenorrhea	626.0
Turner and Klinefelters's syndromes	758.6, 758.7
Panhypopituitarism	253.7
Endocrine disorders	
Adrenal insufficiency	255.4
Diabetes mellitus (Type 1 & 2)	250.xx
Cushing's syndrome	255.0
Hyperparathyroidism	252.0x
Central Adiposity	278.xx
Thyrotoxicosis	242.xx

Variable	ICD-9 Code unless specified
Gastrointestinal disorders	
Celiac disease	579.0
Gastric bypass	CPT Codes: 43644, 43645, 43770, 43771, 43772, 43773, 43774, 43842, 43843, 43845, 43846, 43847, 43848, 43886, 43887, 43888
Inflammatory Bowel Disease	555-556.xx
Malabsorption	579.xx
Pancreatic disease	751.7, 577.xx
Primary biliary cirrhosis	571.6
Hematologic disorders	
Hemophilia	286.xx
Thalassemia	282.4x
Sickle cell disease	282.6x
Systemic mastocytosis	757.33, 202.6
Rheumatologic and autoimmune diseases	
Ankylosing spondylitis	720.xx
Lupus	710.0
Rheumatoid arthritis	714.xx
Central nervous system disorders	
Epilepsy	345.xx
Parkinson's disease	332.xx
Stroke	430-438.xx
Multiple sclerosis	340.xx
Spinal cord injury	806.xx, 952.xx
Alzheimer's*	290.xx, 294.xx, 330-331.xx
Miscellaneous conditions and diseases	
AIDS/HIV	042-044.xx
Congestive Heart Failure	428.xx, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91
Muscular dystrophy	359.0-359.1x
Depression	311.xx, 295-298.xx
Amyloidosis	277.3x
End stage renal disease	585.6
Sarcoidosis	135.xx
Chronic metabolic acidosis	276.2
Hypercalciuria	245.40
Asthma/Chronic obstructive lung disease	496.xx, 491-493.xx, 514.xx, 511.9, 518.0, 793.1, 786.09, 491.21
Idiopathic scoliosis	737.xx

Variable	ICD-9 Code unless specified
Cataracts*	366.1-366.9, 366.02, 366.03, 366.04, 366.09, 366.20, 379.31, V43.1
Glaucoma*	365.xx
Kyphosis*	737.1x, 737.41, 737.3x
Medications Classes†	
Cyclosporine A and tacrolimus	
Proton pump inhibitors	
Anticoagulants	
Selective serotonin reuptake inhibitors	
Anticonvulsants	
Glucocorticoids	
Aromatase inhibitors	
GnRH (Gonadotropin releasing hormone) antagonists and agonists	
Thiazolidinediones	
Barbiturates	
Lithium	
Methotrexate	
Hormone Replacement Therapy#	
ICD-9: International Classification of Disease Version 9; CPT: Common Procedure Terminology; †Medication Classes were based on National Drug Code (NDC) codes within each drug class; *: Conditions associated with falling; #: These are therapies which can be used to treat osteoporosis, however are less effective than bisphosphonates. We have included them because they effect (lessen) the patient's risk of osteoporosis.	

From Overman et al (17)

Additionally variables for age², age³, and age*osteoporosis were fit to the data based on their interactions.

The second variable identification method utilized a high-dimensional variable selection method of aggregating all procedures, diagnoses and drug classes within the baseline period. We used an adapted method for the variable selection as the Harvard HD-PS uses a JavaScript applet which requires connection to the Harvard server to give titles to the diagnoses, procedures, and medications (personal communication with Brookhart, MA). The Medicare DUA required that the data be housed on a server which did not have internet access, which made the connection by the applet impossible. Therefore we used coding which defined each of these groups without the

need to connect to the applet based on adapted code from M. Alan Brookhart, PhD. It is unknown how the method we used differs from the HD-PS approach, although all diagnoses and procedure codes were grouped based on Healthcare Cost and Utilization Project Clinical Classification Software and the medication classes were based on classes from the First Data Bank. All diagnosis or procedure codes, or medication classes present in >1% of the study population were included as candidate variables for the models. The HD models used both the >1% variables and the content variable previously discussed.

3.2.2 Step 2: Determine model type and outcome

The principle interest of this aim is creating a score which is a proxy of FRAX® and can effectively be used to identify patients at high risk for fracture or to control for confounding in comparative effectiveness studies. The outcome of interest is the FRAX® score available in the CCF registry. We have chosen to estimate a continuous FRAX® score (henceforth called CFRI) using linear regression models. Four different estimates will be derived for this project; 1) Major osteoporotic fracture (MOF) 10-year risk without BMD, 2) MOF 10-year risk of fracture with BMD, 3) Hip fracture 10-year risk without BMD, and 4) Hip fracture 10-year risk with BMD. The processes described henceforth will be reapplied for each of the 4 specified outcomes.

In this analysis we evaluated multiple ways that the predictive model could be constructed. After evaluating the distribution of FRAX® scores, we log transformed the outcome variable. All analysis was done with both an untransformed and log-transformed FRAX® score. Analysis were split into three different groups, basic, least absolute shrinkage and selection operator (LASSO), and elastic net. The basic models were constructed to determine how well standard multivariate and automated regression procedures would do predicting the outcome. Additionally the basic models could be used to demonstrate the improvement in prediction using

the more sophisticated models. Both the LASSO and elastic net models are penalized models which would be assumed to outperform the basic models. The elastic net model is a slight variation on the LASSO model which generally produces more accurate estimates, however the LASSO will occasionally outperform elastic net. Because we did not know if this would be one of the cases where LASSO would outperform the elastic net we chose to do both analyses. The optimal model from each group was then directly compared using density plots as well as all error terms. The best available model (highest aR^2) was also evaluated using a categorical outcome of treatment or no treatment based on the NOF guidelines (hip \geq or $< 3\%$ and MOF \geq or $< 20\%$). Finally the elastic net models for each outcome were fit using the HD approach to determine if the inclusion of additional prevalent variables improved model prediction.

The basic linear models were, 1) a null model where there were no covariates, 2) linear model with all available covariates, and 3) linear model using backwards stepwise regression based on improvement in AIC. The LASSO model was fit by specifying $\alpha=1$ in the glmnet model. The elastic net models did not specify an α thereby allowing the model to determine the optimal α value based on the data.

Ordinary least squares (OLS) is the most common method used in linear regression, as it creates estimates which minimize the sum of squared residuals. One of the most common measures of how well the model fits the data is the sum of squared error (SSE), which is a measure of the total vertical distance between the regression line and the predicted points. The mean squared error (MSE) is an estimate of how well the model fits to the data by expressing the average of the squared error which is the difference between the expected and estimated values which is calculated as SSE divided by 1 minus the degrees of freedom, but is composed of squared random error, squared model bias, and the model variance (409). This can further be

reduced to the root mean squared error or RMSE which is the square root of the MSE. All three of these error statistics are useful in determining how well the model predicts future data based on observed values. For many situations OLS is sufficient as it will fit the best line to the data available without bias, however in the setting of highly correlated variables, other models may be able to reduce the MSE and produced better predictions by altering the bias in the model.

Penalized Models

Since MSE is composed of random error, bias and variance, and random error cannot be changed, steps to reduce MSE must alter the bias and variance in the model. Models which alter the amount of allowable bias to reduce the overall error are commonly referred to as penalized models, in that they reduce the coefficient values to meet a pre-specified change in MSE. The basic delineation of penalized models is those that allow coefficients to be set equal to 0 and those that do not. Due to the correlated nature of variables within the proposed model, coefficients can become overly inflated and controlling or regularizing these values can reduce the out-of-sample MSE. We will be using an elastic net model which takes the advantages of the two other penalized models (ridge regression and LASSO) to reduce the MSE of the estimates.

Recent methodologic developments have permitted the use of both penalized methods to reduce the MSE for the model and provide more harmonious estimates under the umbrella of elastic net models (29-31, 409-411). This model shrinks the model coefficients towards 0, but does not eliminate coefficients unless their exclusion would correspond to a pre-specified change in the MSE. Using both of these methods at the same time allows the model to both determine which model inputs are most influential and combine these two penalized methods into one in the elastic net model. In this model, coefficients are regularized by reducing their values towards

0 and using feature selection to reduce the number of highly correlated estimates in the model (409).

For this study we will utilize the glmnet package for R statistical software (30, 31). This specific package was designed to reduce the computational time of computing the entire regularization pathway for the lasso model and allowing for the use of ridge regression penalties. The authors of the glmnet package have rewritten the naïve elastic net model to account for the packages ability to utilize not only linear, but logistic, and time to event models (30).

To perform various model diagnostic tests and to optimize the penalization and stability selection process for the final model we will also utilize the c060 package which has reduced computational time compared to glmnet alone and allows for bootstrapping model parameters (412). The glmnet package allows for 4 different penalization shrinkage settings, λ minimum of mean absolute error (MAE) and mean squared error (MSE) as well as shrinkage at one standard error from the λ minimum (1se). Because we did not assume that any of these parameters were superior to another we fit all 4 outcomes with all shrinkage parameters in both untransformed and log transformed models. For posterity all models were fit using both elastic net and LASSO, and all model results are presented. Additionally the λ value is variable, therefore we bootstrapped the output λ 100 times for a more stable result. In this situation λ is the penalization value.

3.2.3 Step 3: Evaluate Model Parameters

Each model was evaluated using five different measures. We present the number of variables which stayed in the model as well as the root mean squared error (RMSE), mean absolute error (MAE), R^2 , adjusted R^2 (aR^2), and calibration slope. Each of these measures were

calculated in the test sample based on the predicted CFRI using the parameters of the training sample. The optimal model was chosen based on the highest aR^2 .

Root mean squared error is the squared variance of the difference between the observed and predicted values. It is calculated by squaring the difference between the observed and predicted values for each observation, taking the mean of all of these values, and then taking the square root. The mean absolute error is calculated by taking the absolute difference between observed and predicted values and taking the mean of the sample. The MAE is useful for evaluating how far from the truth predictions are regardless of being high or low. The next measure is R^2 which can be calculated as 1- the residual sum of squares divided by the total sum of squares. The R^2 informs the percentage of variance in the outcome which can be explained by the predictors. The R^2 is generally used as the outcome of how well a model fits the outcome, however the R^2 increases as covariates are added. Because we are evaluating the optimal model to predict FRAX® and our basic models include >80 predictors, accounting for the number of variables in the model is necessary. Therefore, we will use the adjusted R^2 as our measure of the best model, which takes into account the number of variables the model retains in producing a statistic for the variance explained. The aR^2 is calculated as $((1-R^2)*(1- \text{sample N}))/ (1-\text{sample N}- \text{number of variables})$. Lastly, we present the calibration slope which is coefficient of a basic linear model of the outcome = prediction. In the setting of calibration, a perfectly calibrated model would have an intercept of 0 and a slope of 1 (413). The best model from each of the 4 outcomes will be plotted as observed compared to predicted values with the regression line superimposed to better evaluate how well the model predicts the outcome. Lastly, we will present the optimal model coefficients for each of the three types of models.

The HD variables along with the content variables will be evaluated using all four types of elastic net model. These models will produce similar outcomes to the basic models, and when superior to the basic models will be presented in full. If they are inferior to the basic models then the variables which were retained will be discussed. Additionally if the HD variable based models do not produce greater aR^2 no variables from the HD selection will be included in future models.

To determine if the models are informative based on treatment cut points from the NOF guidelines a planned sensitivity analysis will be undertaken. The linear outcome of CFRI will be transformed to a binary outcome based on if it is above or below the NOF threshold, as will the FRAX® scores. We will use receiver operating curves (ROC) and the area under the curve (AUC) to evaluate how well CFRI predicted above or below the threshold based on the gold standard (FRAX®). The cut points of 20% 10-year risk of major osteoporotic fracture and/or 3% 10-year risk of hip fracture will be analyzed separately for both with and without BMD CFRI.

For Aim 1 we are using variables based on content knowledge, however we are using automated regression procedures which supersede inclusion of variables based on known associations. For the variables which are not included in the final models one can view these are not influential, whereas variables with larger coefficients can be viewed as more significant or influential. We will not be presenting p-values for the coefficients in the final models as the difference from null is a better determinant of their influence in the model. Although it would be interesting to evaluate how variables are included and excluded in the models as they iterate, this information will not change the final models and would only be valuable for future hypothesis generation. Therefore we will only be presenting the coefficients for the best models from the basic, LASSO, and elastic net groups to evaluate which variables were retained. We are aware

that these are essentially black-box methods, however they offer the opportunity to create the best models to predict FRAX®.

3.3 Aim 2

Aim 2: Externally validate CFRI in a 20% random sample of Medicare beneficiaries by comparing the performance of CFRI and FRAX® to predict future fractures.

Hypothesis 2: There will be no significant difference between FRAX® and CFRI to predict future fractures as a continuous variable (calibration) between the linked and random sample.

Hypothesis 3: CFRI will identify fractures at a similar rate based on c-statistics in the random sample as FRAX® in the linked sample (discrimination).

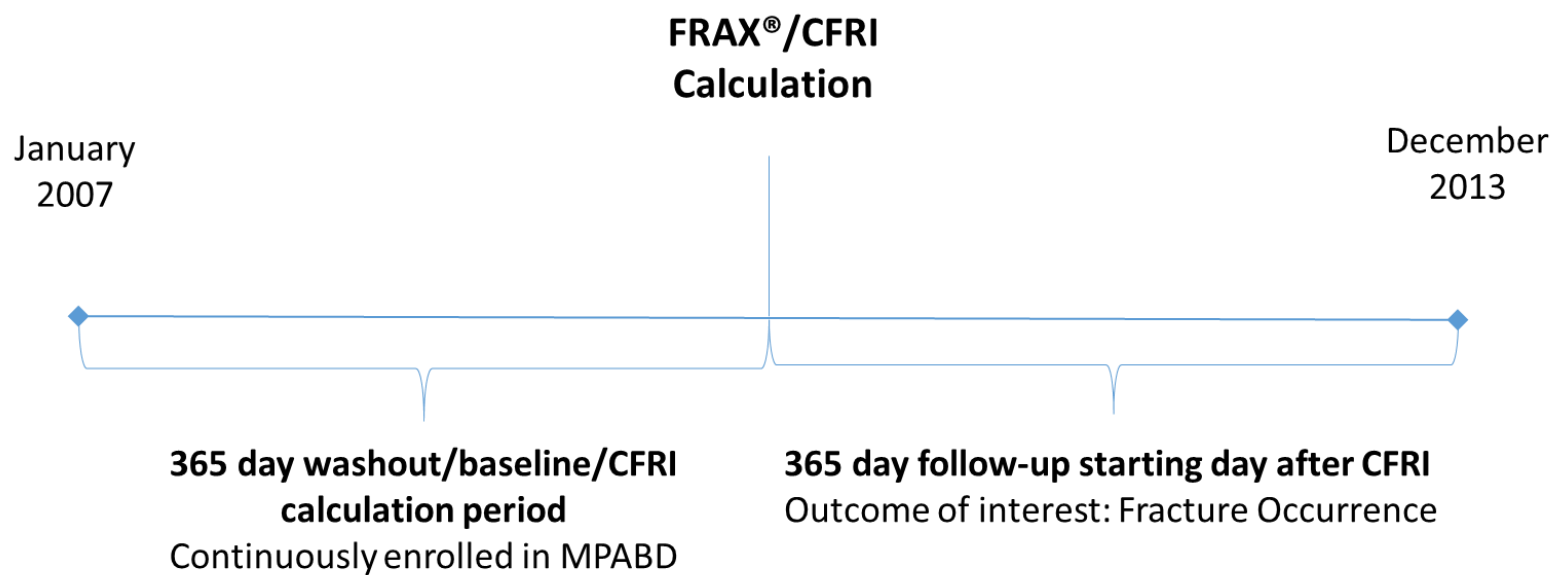
This aim will utilize the registry-claims linked data as well as the 20% random sample of Medicare beneficiaries. Calibration in Aim 1 was centered on how well CFRI predicted FRAX®. In the second aim we will evaluate how well FRAX® and CFRI predict actual fractures. If CFRI has a similar calibration and discriminatory ability in the random sample as the linked then an argument can be made that it is accurately predicting FRAX® in a situation where FRAX® is unknown. This is based on the external validity of the model and assumptions used to create CFRI.

For this Aim, fracture risk will be assessed among three distinct subgroups: 1) individuals with FRAX® risk scores in the linked population, 2) individuals with CFRI scores in the linked population (whose FRAX® scores are known), and 3) individuals with CFRI scores calculated in the 20% random population (whose FRAX® scores are unknown). In the linked dataset the population consists of all patients who have at least 365-days continuous enrollment prior to a DXA. In the 20% random sample the only inclusion criteria is that a patient has an office visit

after 365-days continuous enrollment. A secondary analysis will replace the office visit requirement with that of a DXA. The study schematic for Aim 2 is presented as Figure 3.3. Aim 2 is broken into two separate steps 1) evaluate the calibration and 2) evaluate the discrimination of CFRI.

Data will be collected from both samples based on Figure 3.3. In the linked sample the “FRAX®/CFRI Calculation” will be the date of DXA. In the random population “FRAX®/CFRI Calculation” will represent any office visit after the patient has been continuously enrolled in Medicare Part A, B, and D for 365-days. For the random population we will have multiple records for patients. However we will randomly select an available office visit of all candidate visits for the main analysis. In both the linked and random population, covariates used to calculate CFRI will be collected in the 365-day look back period prior to “FRAX®/CFRI Calculation”. Once the “FRAX®/CFRI Calculation” or index date has been determined patients will be followed until occurrence of fracture, 365-days from FRAX®, loss of continuous enrollment, death, or the end of the study period (December 31, 2012). A sensitivity analysis will be undertaken using only DXA visits (CPT codes 70675 or 77080) from the random population. This will help to determine if CFRI is more valid in a similar population to that which it was created (patients with DXA).

Figure 3.3 Aim 2 Study Schematic



In Aim 2 we will be capturing actual fractures which fit the FRAX® model. As previously discussed there are two types of fracture estimated by FRAX® - hip fracture and major osteoporotic fracture. We present the algorithms that will be used to capture each of the fracture sites in Table 3.3. The occurrence of either a hip or major osteoporotic fracture are the main outcomes of Aim 2. The primary predictors are the risk scores (CFRI and/or FRAX®). Although the death rate may be high in those patients who have hip fractures, we will not use death as a competing risk for this analysis.

Table 3.3 FRAX® Major Osteoporotic Fracture Site Codes

<i>Fracture Site</i>	<i>ICD-9 and CPT Definition</i>
<i>Hip*</i>	Hip fracture diagnosis (ICD-9 code: 820.xx, 733.14) during hospitalization AND procedure code during hospitalization (ICD-9: 78.55, 79.05, 79.15, 79.25, 79.35, 79.65; CPT-4: 27230-27248)
<i>Humerus</i>	Humerus fracture diagnosis (ICD-9: 812.xx, 733.11) AND procedure within 30-days of fracture date (ICD-9: 78.52, 79.01, 79.11, 79.21, 79.31, 79.61; CPT-4: 23600, 23605, 23610, 23615, 23620, 23625, 23630, 23665, 23670, 23680, 24500, 24505, 24506, 24510, 24515, 24530, 24531, 24535, 24536, 24538, 24540, 24542, 24545, 24560, 24565, 24570, 24575, 24581, 24583, 24585-8, 24516)
<i>Wrist</i>	Radius/ulna fracture diagnosis (ICD-9: 813.xx, 733.12) AND procedure within 30-days of fracture date (ICD-9: 78.53, 79.02, 79.12, 79.22, 79.32, 79.62; CPT-4: 24620, 24625, 24635, 24650, 24655, 24660, 24665-6, 24670, 24680, 24685, 25500, 25505, 25510, 25515, 25530, 25535, 25540, 25545, 25560, 25565, 25570, 25575, 25600, 25605, 25610-1, 25615, 25620, 25650)
<i>Vertebral</i>	(ICD-9: 805.8, 805.9, 806.8, 806.9, 733.13)
<i>*Hip Fractures are part of major osteoporotic fracture but are also a separate category</i>	

3.3.1 Calibration

In a binary setting, calibration is the rate of agreement between the predicted and observed outcomes for how well CFRI predicts future fractures. A model can be thought of as well calibrated if the mean prediction is equal to the number of outcomes (414). Based on observed 1-year fractures we will assess the calibration of the FRAX® and CFRI estimates in the linked data and compare these estimates to the 20% random sample. Calibration in this context is the ability to predict the risk level compared to observed outcomes (415). Calibration is primarily

evaluated in a binary outcome setting using the brier score and the Hosmer-Lemeshow goodness of fit test (415).

In many cases, we do not expect participants to have at least 1-year, let alone 10-years, follow-up after their FRAX® or office visit, due to the possibility of the first useable visit occurring in the last year of the data. To address this in the main comparison we will utilize the first office visit (CPT 99201-99205, 99211-99215) in any given year as the index date of CFRI calculation. For a woman to be eligible for inclusion in this aim the only requirement is at least 365-days continuous fee-for-service Medicare Parts A, B, &D enrollment prior to index. To better mimic aim 1, patients with prior AOM use or fracture will be excluded, even though prior AOM use has not been shown to significantly influence FRAX® scores (416). We will also conduct a sensitivity analysis only including patients who have a DXA, which will be then utilized as the index date.

CFRI will be calculated utilizing the available covariates in the 365-days prior to index and will be followed for a maximum of 365-days after index. The primary outcomes will be fracture (defined by type of CFRI evaluated) and patients will be censored at death, loss of continuous enrollment, or the end of the study period. CFRI and FRAX® will be degraded by the maximum length of follow-up (10 years) regardless of event type ie, $((365/36500)*\text{Risk score})$. This is based on recommendations that the FRAX® 1-year risk is essentially 1/10 of a 10-year risk (65). We will also conduct a sensitivity analysis varying the proportion of risk from 8% to 12% to evaluate if this may be a truer representation of a 1-year risk.

FRAX® major osteoporotic fracture risk is based on fractures of the hip, spine (vertebral), shoulder (humerus), or wrist, while hip fracture risk is limited to only hip (65). Therefore we will only use fractures at these sites to evaluate the calibration of CFRI to FRAX®.

We will use both the applicable CPT codes based on fractures from the Rochester cohort which were used to specify the FRAX® model as well as accepted claims-based algorithms using both ICD-9 and CPT codes (17, 61, 124).

Goodness of fit of the model will be assessed using the Hosmer-Lemeshow test which splits the study population in k samples, with k typically = 10. The observed number of events is calculated as the sum of the events in the sample, and the expected number is the sum of the predicted probabilities for the sample. These two values then are assessed using a chi-square test with k-1 degrees of freedom (df) in new datasets, but k-2 df in the dataset used to create the predictive model as 1 df is lost defining the groups. A p-value of ≤ 0.05 has typically been used to denote an acceptable goodness of fit for the model using the Hosmer-Lemeshow test. We can visually inspect a Hosmer-Lemeshow test using a calibration plot with an identity line with slope = 1. The calibration plot will break the study population into the same sample populations and plot the mean observed and mean predicted values for each of the groups.

Calibration and its predictive ability will be assessed using the brier score. This score is a measure of the accuracy of predicted probabilities. The brier score ranges from 0 (the best score) to 1 (the worst score).

Because we will be using all of the available information for the main analysis, we will be conducting a planned sensitivity analysis using only those patients in the random population who have DXAs. We will evaluate how the different parameters (FRAX with BMD compared to without BMD) behave within the random population. We hypothesize that CFRI without BMD will better predict fracture in general, but CFRI with BMD will better predict fracture for patients with a DXA. This will be evaluated using the same measures as in the full population.

3.3.2 Discrimination

We will be comparing the 3 risk-scores in the two populations (FRAX® in linked, CFRI in linked, CFRI in random) to evaluate discrimination (or ability to predict) actual fractures. Discrimination of a model seeks to correctly differentiate between those with and without the outcome. Simply, determining whether people with higher CFRI/FRAX® scores have fractures more often. Typically receiver operating characteristic curves (ROC) are used to visually inspect the discrimination of a model. ROC curves plot the true positive rate (sensitivity) with 1-false positive rate (specificity). These curves serve as a graphical representation of the discrimination of the model, however they themselves cannot give evidence as to the how well the model discriminates.

Commonly the measure used in tandem with ROC is the area-under-the-curve (AUC). This value is equal to the probability that a randomly chosen positive case will be ranked above a randomly chosen negative case. The AUC in the setting of binary outcomes (0/1) is mathematically equivalent to the concordance statistic or c-statistic (417). The c statistic is a rank-order statistic for evaluation of predictions against true outcomes. Because the c-statistic is meant to rank-order observations rather than evaluate model fit, it has been shown to be a poor judge of a badly fitting model (418). We will model the optimal c-statistic of FRAX® in the linked population by setting the half of the population with the highest CFRI score to a fracture outcome, and the other half to a non-fracture outcome regardless of their true outcome. This will provide a baseline for the c-statistic to be compared against.

We will create ROC curves for all 3 populations (FRAX in linked, CFRI in linked, and CFRI in random) and will directly compare the curves using a direct comparison of ROC curves as proposed by DeLong in 1988 (32). DeLong proposed a non-parametric method to compare

ROC curves when their predictions cross even if they have the same AUC. In this manner the test can give a permutation test statistic for the amount of variation between the two ROC curves as well as a non-parametric area estimate which is reported as the Mann-Whitney statistic (419). Both the permutation test and the area estimate are under the null hypothesis that there is no difference between the two ROC curves, and will be evaluated with a $p \leq 0.05$ indicating statistical significance. The discrimination analysis will be conducted using the R-statistical software package pROC (420).

The rationale behind comparing the ROC curves directly rather than visual inspection is that two populations can have the same c-statistic but different ability to predict over the whole population. Assessing the ROC curve will provide additional information as to how well CFRI fits the random population in proportion to FRAX®. If the ROC curves are not statistically significantly different in the three populations, we can conclude that CFRI is externally valid. Plots will be made of outcomes at 1, 2, and 3 years' post-index to determine if the main analysis cut point of 1 year is too conservative.

3.4 Aim 3

Aim 3: Evaluate the utility of CFRI and restriction in a comparative effectiveness research study of alendronate users to non-users.

Hypothesis 4: Comparative effectiveness estimates will most closely approximate Fracture Intervention Trial results after restricting by trial inclusion criteria and incorporating CFRI, then estimates generated without CFRI.

The goal of Aim 3 is to demonstrate the utility of restricting a study or patient population by CFRI values. For quality evaluations by payers, the use of CFRI in this manner would assist payers in identifying those patients at highest risk for fracture and those most likely to benefit

from pharmaceutical intervention. To evaluate CFRI-based restriction to identify a suitable candidate population we will compare effect estimates of the full population, restriction based on CFRI, and finally all inclusion/exclusion criteria specified in the FIT study.

The analysis utilizes 1) a null hazard model, 2) a hazard model with only MOF CFRI both with and without BMD, 3) a multivariable-adjusted hazard model with all content variables, and two propensity score based models 4) a stabilized inverse probability of treatment weighted (SIPTW) and 5) standardized mortality rate (SMRW) hazard model. We will measure the effect of alendronate use compared to non-use in the 20% Medicare Random sample, and compare these results to those from the FIT studies. Even if CFRI is not able to sufficiently discriminate continuous values of FRAX® the evaluation of restriction based on CFRI may provide a context wherein it may be useful to payers.

3.4.1 Study Design

Aim 3 is a retrospective cohort study using the 20% random sample. We will utilize a similar structure to that of Aim 2 with all office visits eligible for inclusion after 365-days of continuous enrollment in Medicare Part A, B, and D for females. We will be identifying patients with new alendronate use as the “alendronate users” and the new use of any drug, in any class other than AOMs as the “non-users”. The decision to use the new-use of any drug rather than of a specific class is based on the idea that the decision to initiate alendronate follows a clinician’s determination that a patient has sufficient fracture risk to warrant treatment, in the same way that the new use of a drug would be initiated because the clinician determined that the patient’s ailment warranted treatment. In this situation a full patient evaluation may have prompted alendronate initiation. One of the major drawbacks to the use of “any new user” as the non-user group is that depending on the drug, the patients who initiate them may be very different from

new users of alendronate, making the non-user group heterogeneous. If the use of “any new drug” is found to be too broad a category, we will employ one of the following approaches as an alternative approach for this analysis. Alternative approach #1: Schneeweiss et al articulated an approach for selecting non-users by taking all persons not initiating the drug of interest (alendronate) and taking a random date as their index (23). This theory of taking a random index date was the impetus of the any new use categorization as any new use would give a better random indexing point to choose from, and would satisfy the need for a similar experience within the healthcare system. However, these patients likely will be different from new alendronate users because they aren’t starting a medication. Alternative #2 would include all new users aside from those initiating medications in the classes which have been listed in Table 3.2 which are known to affect fracture risk.

There are two other approaches which were suggested by Schneeweiss et al, the first is to compare the new users of a different drug class to Alendronate users (23). For this approach to work the different drug class should not be associated with changes in the outcome under study. Statin, diabetes, and hypertension medication classes will be evaluated for use as the comparison group for this analysis. Drugs within the class will be defined based on Anatomical Therapeutic Chemical (ATC) Classification System codes. Some of the drawbacks to this approach are these patients were prescribed the new drug class for a different reason than osteoporosis which may create a heterogeneous population (421).

The third approach will be to take office visits and the 30-days after as the window for initiation of alendronate. If alendronate is not initiated during this 30-day window then the patient will be considered a non-user for the analysis. This approach eliminates the reliance on filling a medication other than Alendronate, but the office visit may have been a routine

examination where no disease was readily evaluated (23, 422). Also by not requiring the fill of a medication in the 30-days post office visit these patients may not be comparable to the Alendronate users. However this will allow the patients to at least have had a similar encounter within the healthcare system, wherein a medication could have been prescribed. A variation on the office visit approach will be to only use patients who receive DXAs (CPT codes 70675 or 77080) as the index event.

After evaluation within the 20% random sample the use of a random selection of office visits per patient yielded >1.5M patients, making modeling of outcomes computationally infeasible. When the same procedures were attempted in the 1% random sample of claims, no events were observed in the population after CFRI restriction. Because of this, our third approach was modified to include only patients with DXA visits, with patients who used an alendronate within 30-days as the alendronate users.

Knowing the strengths and limitations of each of the three methods, we will utilize the “any new drug use” approach as the primary analysis, and the comparison medication classes or inclusion based on office visits/DXAs as secondary analyses. We will utilize a new user design with a 365-days washout period for this aim (22). For a patient to be eligible for this study they must have had continuous enrollment for at least 365-days prior to an office visit and fill a new medication within 30-days of that visit. The new user design differentiates between incident and prevalent users of a medication as there are systematic differences between these two types of use in evaluating short-term outcomes (423). Prevalent users typically have exceeded the period of adverse event and continue to tolerate the therapy, therefore including them with incident users may cause adverse events to appear less frequently and make the medication appear less

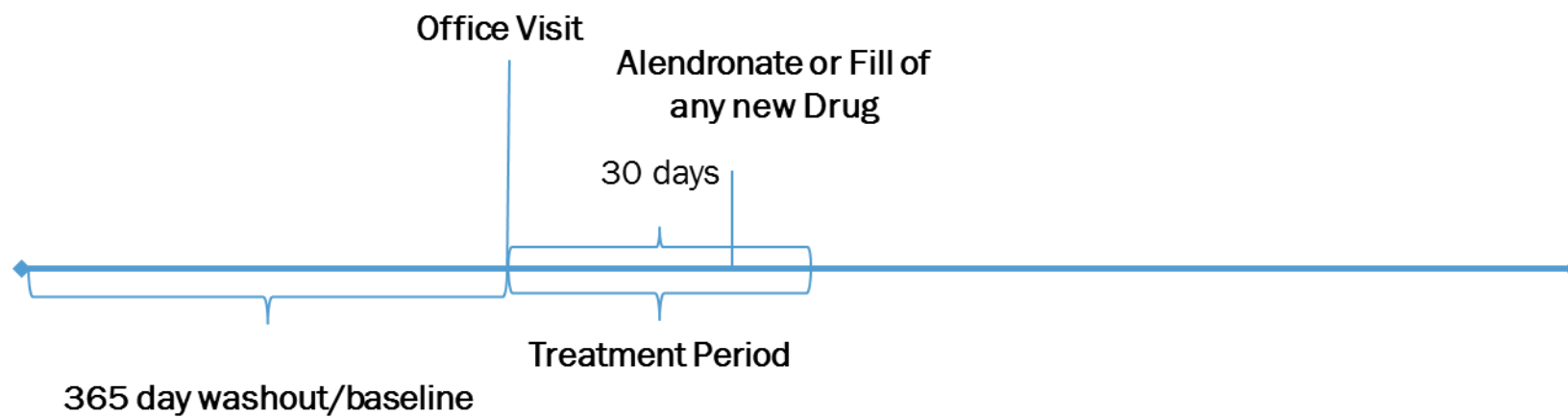
hazardous. Incident users on the other hand can be assumed to have a similar risk of the event of interest (421).

Patients with use of any bisphosphonate (alendronate, ibandronate, risedronate, or zoledronic acid), teriparatide, or denosumab during the washout period will be excluded from the analysis. We are choosing to exclude patients with any use of these therapies during the washout period due to their known effect on bone strength and fracture risk. The use of any formulation of alendronate (10mg QD, 70mg QWk, 10mg Effervescent) will be identified using national drug codes (NDC). Patients using other AOMs will be identified and excluded using NDC codes as well. In the comparison class analysis, patients who use one of the comparison medication during the washout period will also be excluded.

3.4.1.1 Inclusion/Exclusion Criteria

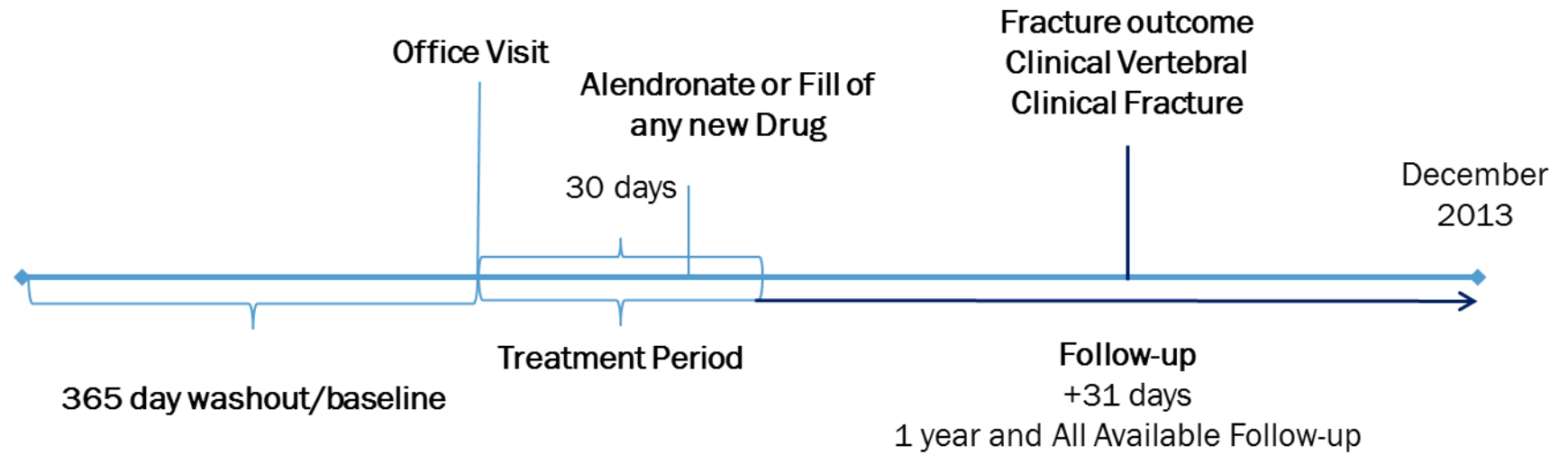
To begin this aim we will identify all office visits based on CPT codes (CPT codes 99201-99205 or 99211-99215) and collect continuous enrollment information prior to the first office visit which had at least 365-days continuous enrollment and where patients are aged ≥ 65 (Figure 3.4). Patients will also be required to have the fill of at least 1 medication in the 365-day washout period to ensure that they were using their Part D coverage. A sensitivity analysis will be performed using the date of a DXA as the index date rather than an office visit to determine if this is a more accurate use of CFRI.

Figure 3.4 Aim 3 Schematic Part 1



We will utilize the office visit that is chronologically prior to and closest to the new fill of a drug as the index date with 30-days being the maximum time period allowable between office visit and medication fill (Figure 3.5). The medication fill itself however will be the index date, as the office visit in the 30-days prior is an exposure event. For the main analysis patients who fill alendronate will herein be referred to as users and those who fill another drug will be herein referred to as non-users. Any patient who experiences a fracture between their office visit and index will be excluded. In the second approach, statins, hypertensives, and diabetes drugs will be used as the comparison group, all procedures will be the same, substituting any new drug with new statin/hypertensive/diabetes. For the third approach there will be no requirement of a fill of any medication in the treatment period for inclusion in the non-users and the users will have had an office visit less than 30-days prior to the alendronate fill and the non-users will be identified following a visit where a DXA is performed.

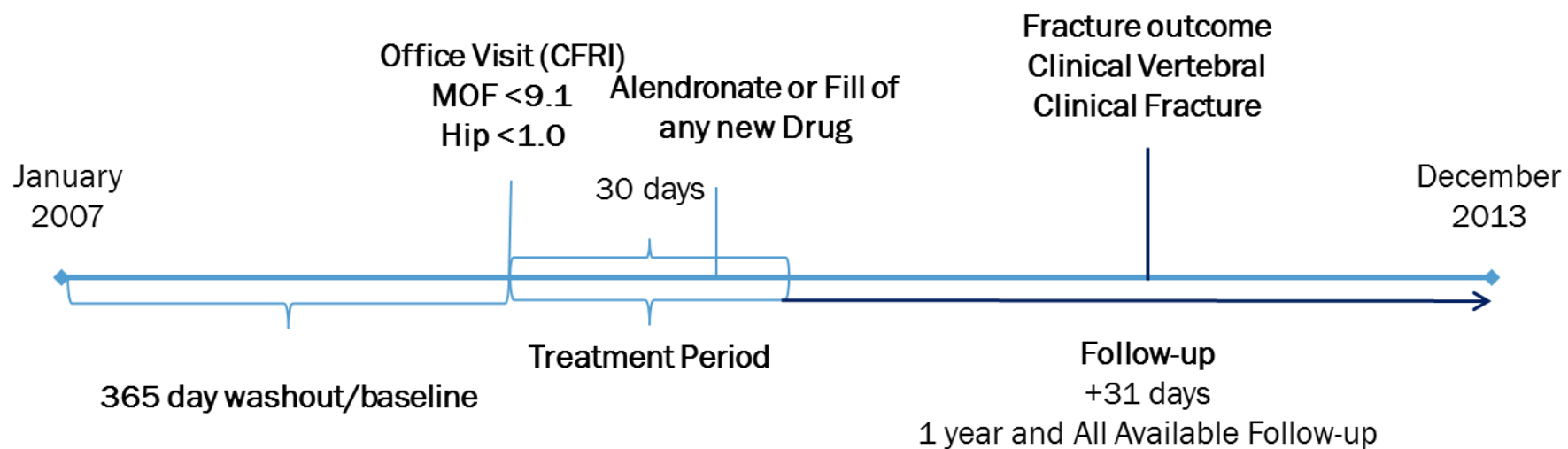
Figure 3.5 Aim 3 Schematic Part 2



Follow-up will begin on day +1 from the medication fill, as the inclusion criteria includes the office visit in the 30-days prior, which then allows follow-up to immediately begin. Patients will be followed until the occurrence of a fracture, death, loss of continuous enrollment, end of study period, or use of a non-alendronate AOM. Censoring for use of an AOM after the treatment period is based on a change in fracture risk at the time of treatment initiation (17). Lastly, we will investigate censoring at specific cut-points (i.e., 1 and 4 years) to make our results more directly comparable to those of the FIT trial. After evaluation with data 1 year follow-up was used as well as all available time. The schematic including these specifications is presented as Figure 3.6.

Although figure 3.5 is representative of how we will select patients for inclusion in the population for Aim 3, we will be introducing further restrictions for the majority of the analysis. The schematic including the restrictions are presented as Figure 3.6 and further details regarding the specific restrictions are presented in Section 3.4.2.3.

Figure 3.6 Aim 3 Restriction Study Schematic



3.4.1.2 Outcomes

The FIT Trial grouped fractures into six different fracture outcomes based on study type, 1) clinical vertebral fracture, 2) radiographic vertebral fracture, 3) clinical fracture (humerus, vertebrae, pelvis, wrist, ribs, legs, hand, feet, toes, and clavicle), 4) nonvertebral fractures, 5) hip fracture, 6) wrist fracture, and in women without pre-existing vertebral fractures 7) nonvertebral osteoporotic fractures (clavicle, humerus, wrist, pelvis, hip, and leg) (25, 26, 304).

Because alendronate has been shown to significantly reduce vertebral fractures compared to placebo, a vertebral only definition would be optimal, however there is a low prevalence of these fractures in administrative claims, likely under powering any estimates. Although the clinical fracture definition would seem to be the best for our study, the codes used to identify the fracture types are largely non-specific and when used this omnibus definition provided a significantly different estimate to all others in our glucocorticoid-induced osteoporosis study (17). Therefore, we will use the “nonvertebral osteoporotic fracture” and vertebral fracture outcomes as the main outcomes for Aim 3. Because the vertebral fracture outcome alone is unlikely to have enough events, we will create a third outcome which combines the two definitions. Coding algorithms used to define the three fracture outcomes for this study are in Table 3.4.

Table 3.4 Aim 3 Fracture Definitions

Fracture	Definition	Vert	Non-Vert
Hip	Hip fracture diagnosis (ICD-9 code: 820.xx,733.14) during hospitalization AND procedure code during hospitalization (ICD-9: 78.55, 79.05, 79.15, 79.25, 79.35, 79.65; CPT-4: 27230-27248)		X
Wrist	Radius/ulna fracture diagnosis (ICD-9: 813.xx, 733.12) AND procedure within 30-days of fracture date (ICD-9: 78.53, 79.02, 79.12, 79.22, 79.32, 79.62; CPT-4: 24620, 24625, 24635, 24650, 24655, 24660, 24665-6, 24670, 24680, 24685, 25500, 25505, 25510, 25515, 25530, 25535, 25540, 25545, 25560, 25565, 25570, 25575, 25600, 25605, 25610-1, 25615, 25620, 25650)		X
Humerus	Humerus fracture diagnosis (ICD-9: 812.xx, 733.11) AND procedure within 30-days of fracture date (ICD-9: 78.52, 79.01, 79.11, 79.21, 79.31, 79.61; CPT-4: 23600, 23605, 23610, 23615, 23620, 23625, 23630, 23665, 23670, 23680, 24500, 24505, 24506, 24510, 24515, 24530, 24531, 24535, 24536, 24538, 24540, 24542, 24545, 24560, 24565, 24570, 24575, 24581, 24583, 24585-8, 24516)		X
Pelvis	Pelvis fracture diagnosis (ICD-9: 808.xx)		X
Tibia/Fibula	(ICD-9: 823.xx, 733.16)		X
Femur	(ICD-9: 821.xx, 733.15)		X
Clavicle	(ICD-9: 810.xx)		X
Radius/Ulna	(ICD-9: 813.xx, 733.12)		X
Vertebral	(ICD-9: 805.8, 805.9, 806.8, 806.9, 733.13)	X	X
Thoracic spine	(ICD-9: 805.2, 805.3, 806.20 - 806.39)	X	X
Lumbar spine	(ICD-9: 805.4, 805.5, 806.4, 806.5)	X	X

Vert: Vertebral Fractures Only; Non-Vert: All specified fractures other than vertebral; All Specified fracture sites will be used in the combined outcome

3.4.2 Analysis Plan

3.4.2.1 Power Calculation

To calculate if our study would have sufficient power to detect a significant difference between alendronate users and non-users we calculated the minimum sample sizes needed for specific hazard ratios. These were performed using Proc Power TWOSAMPLESURVIVAL at 0.8 power with a two-tailed alpha of 0.05, one year accrual time, and one year follow-up time with the specified baseline hazards. Baseline hazards were calculated based on 1-year fracture rates in placebo users from Wells et al (250). The smallest sample size needed is 15,854 which

would represent 7,927 each of alendronate users and non-users, as such our study should be sufficiently powered. The specifics of the power calculation are presented as Table 3.5.

Table 3.5 Power Calculation Table

Outcome	Baseline Hazard (250)	Hazard Ratio				
		0.6	0.7	0.8	0.9	0.95
Vertebral Fracture	0.1	182	356	876	3808	15854
Hip Fracture	0.002979	172	338	834	3636	15154
Wrist Fracture	0.014896	174	340	838	3654	15230
Nonvertebral Fracture	0.036743	176	344	848	3690	15378

3.4.2.2 No Restrictions

For this analysis we will identify all patients who meet the new use of either alendronate or another drug classification. We will use all patients in this analysis and will use a naïve hazard model. This first analysis is designed to demonstrate what the study population and results would look like without any modifications or restrictions.

3.4.2.3 Restriction

Restriction is a technique whereby an estimate cannot be confounded by a factor after stratification or restriction. The rationale behind this is any confounding which would have been present for the different levels of the restricted variable will be eliminated by only analyzing that specific level of the variable (406). In pharmacoepidemiology studies Schneeweiss et al demonstrated that restricting a study population based on inclusion/exclusion criteria used in the RCT can create effect estimates of a similar value and magnitude as those from the RCT (23).

Although the FIT trial used inclusion/exclusion criteria based on BMD we will restrict the study population using CFRI values based on FRAX® which correspond to the minimum allowable BMD. Inclusion in FIT was based on a femoral neck t-score of ≤ -1.6 . Therefore we

input the average weight (75.39kg) and height (164.1 cm) of an American woman with an age of 65 and no risk factors into the FRAX® calculator which correspond to a 10-year risk of 9.1% for a major osteoporotic fracture and 1.0% for a hip fracture. To mimic FIT we will restrict inclusion in the study population to patients with an office visit corresponding to a CFRI major osteoporotic fracture score of $\geq 9.1\%$ or CFI hip fracture score $\geq 1\%$.

Further we will restrict the study population by the other inclusion/exclusion criteria specified by the FIT trial. In Table 3.6 we describe each of the FIT inclusion/exclusion criteria and how we will evaluate the criterion in the Medicare data. We will describe where the patients based on FIT restrictions are lost, and differences for samples with and without BMD CFRI scores (424). This restricted population will be used as the main analytic cohort for Aim 3. Although FIT included women aged 55-65 whom we cannot include due to the 365-day washout period and Medicare only including patients ≥ 65 years of age, we would speculate that our estimate should be similar or further from the null to those of FIT.

In creating the FIT restricted population we encountered some problems which made it impossible to use it as the main analysis population. First, only African-American's were not excluded in the with BMD analysis based on the age coefficient in the CFRI score. Second, in the without BMD population analysis not all patients with osteoporosis were excluded, which was a primary exclusion in FIT. Finally, the n's for the with BMD analysis particularly were underpowered, with few events causing the confidence intervals to be very wide.

Table 3.6 FIT Claims-based Restrictions

FIT Criterion	Claims-based Identification Method
<i>Inclusion</i>	
Female, 55-80 years old	Based on age at initiation
BMD at the femoral neck ≤ 0.68 g/cm ² (Hologic QDR 2000)	Corresponds to a t-score of -1.6 and MOF of 9.1 and hip fracture of 1.0

Understands procedures of study	Not possible to identify
<i>Exclusion*</i>	
Unable to give informed consent	Not possible to identify
Participating in another trial	Not possible to identify
Intends to move within 4 years	Not possible to identify
Alcohol Abuse	Not possible to identify
Major illnesses, including severe malabsorption, severe hypertension, myocardial infarction (within 6 months), unstable angina, serum creatinine > 1.6 mg/dl	2 options, any hospitalization within 6 months prior to alendronate, or just these conditions, serum creat will be assessed with ESRD code.
Erosive gastrointestinal disease within 5 years. Dyspepsia requiring daily treatment	530-539.xx or 531-539.xx?, GERD is 530.81, so possibly exclude for H2 or PPI use
History of cancer (except: resected superficial skin cancer and treated malignancies, except breast, without recurrence in 10 years)	140-208.81 except 173.xx
Metabolic bone disease (e.g. hyper- or hypoparathyroidism, Paget's disease, osteomalacia)	Parathyroid (hypo and hyper) 252.xx, Paget's disease 731.0, Osteomalacia 268.2
Treatment affecting bone turnover:	
Estrogen, anabolic steroids, calcitonin, or progestins, within 6 months	NDC
A change in thyroid hormone dosage within the last 6 weeks	NDC
>2 weeks fluoride treatment (>1 mg/day) at any time	Not possible to identify
Glucocorticoid within 6 months	NDC
Bisphosphonate for more than 2 weeks	NDC
Unexplained weight loss > 10% of ideal body weight within last 12 months	Not possible to identify
Unsuitable anatomy on spinal radiographs	Not possible to identify
BMD at the femoral neck >3 SD below age-specific mean	Corresponds to a BMD value of 0.324 g/cm2 or t-score of -4.45. FRAX values of 35 MOF and 21 Hip
Noncompliance with pre-randomization study procedures	Not possible to identify
Not ambulatory	Not possible to identify
History of bilateral hip replacements	Applicable CPT are (27090, 27091, 27125, 27130, 27132, 27134, 27236, 27137, 27138)

*:Additionally Vertebral fracture was a requirement for one arm of the FIT trial, and an exclusion for the clinical fracture population. We exclude all of these patients based on our overall inclusion exclusion criteria

3.4.2.4 Descriptive Statistics

All patient characteristics will be presented and compared between alendronate users and non-users for each analysis. Categorical characteristics will be assessed using Chi-square tests, while continuous characteristics will be assessed using student t-tests or ANOVA depending on the number of comparison groups. Any covariate which does not appear in either group

(alendronate users and referent) will be excluded from the final adjusted model due to it not presenting any influence on the final estimates.

We will describe characteristics of patients excluded in the treatment period due to fracture within the 30-days after their visit, as this is a relevant patient group. However they will not be included in the main analysis due to the event of interest occurring before the end of the treatment exposure window. Similarly, we will describe characteristics of patients who fill a non-alendronate AOM at index, but exclude them from the analysis due to the likelihood of fracture reduction by use of another AOM.

3.4.2.5 Cox Proportional Hazards Model

All analyses in Aim 3 will produce hazard ratios of alendronate users compared to non-users using cox proportional hazards models. A multivariable cox proportional hazard model takes the form $\lambda(t|x) = \lambda_0(t)\exp\{x\beta'\}$. Where λ_0 is the baseline hazard for a non-user and $x\beta'$ is the vector of specified covariates including treatment effect. The naïve model would be written as $\lambda(t|x) = \lambda_0(t)\exp(\beta_1x_1)$ where β_1x_1 is the incremental change in the hazard ratio for alendronate users compared to non-users. We will report hazard ratios and associated 95% confidence intervals (95% CI) for all analyses.

Cox proportional hazards models (PH) employ marginal likelihood estimates to produce a baseline hazard function based on covariate vector β' rather than requiring one to be specified. The model produces estimates which treat β' the same at t_0 as at any other time and give the difference in hazard for the active versus referent group. As with most models, Cox proportional hazards assumes that all observations are independent of another observation.

We will utilize a Cox model based on both a naïve model and a multivariable model. In the naïve model the outcome of interest will be the time to outcome or censoring and the only

predictor will be a dichotomous variable of alendronate use (alendronate user = 1, non-user = 0). The multivariable model will include the dichotomous alendronate use variable as well as all of the content variables specified in Table 2.7 and Table 3.1. Because we are basing our selection of factors on content knowledge, we will not be independently assessing model fit, but will present statistics such as AIC which give an estimate of model fit.

3.4.2.6 Multivariable Regression

After the initial restriction to a high-risk population based on CFRI we will utilize all content variables from Andersen's model in a multivariable regression. This will allow our estimates to be statistically adjusted for all measured covariates. All effect estimates which have been analyzed with multivariable regression will be referred to as "adjusted estimates" in the results.

In a planned sensitivity analysis we will utilize the continuous CFRI score as a disease risk score in the multivariable regression. Disease risk scores are summary scores which are meant to include all relevant factors of disease to predict the likelihood or rate of disease in the cohort as a function of the measured covariates (425). For interpretable results we will mean center the CFRI before including it in the multivariable regression models.

3.4.2.7 Propensity Score

In the presence of confounding by indication or unmeasured confounding, multivariable adjustment has been shown to not sufficiently reduce confounding (33). Propensity scores (PS) are a summary score of the measured covariates on the likelihood of receipt of a medication or medical procedure. Because persons who do and do not receive a particular treatment are generally dissimilar, the PS is a single score which can be used to balance the distribution of covariates between the two groups (426).

To control confounding by the specified characteristics, we will estimate a propensity score for alendronate use, using logistic regression models including all measured covariates from Table 2.7 (33, 427). Because we will restrict the study population based on CFRI values, we will not use CFRI as a covariate in the propensity score for the main analysis, but will for a sensitivity analysis. The predicted value or PS resulting from the logistic regression equation is the probability of alendronate use based on all the measured covariates. Although PS can be used in a variety of ways including matching, use in a regression term and weighting, we will only focus on weighting in this analysis.

Propensity score weighting can take a variety of approaches based on the desired treatment effect. For this project we are interested in estimating the average treatment effect, which will produce the difference in fracture rates for those treated with Alendronate compared to those who did not receive alendronate. We chose to estimate the overall average treatment effect rather than the average treatment effect in the treated for generalizability of our findings (428, 429). We utilize Stabilized Inverse Probability of treatment weights (SIPTW) which when used produce a pseudo-population where outcomes will not be associated with measured covariates provided the model is correctly specified. Stabilized IPTW use the marginal probability of treatment to help reduce weights variance which can improve precision of treatment estimates, but will not reduce bias (430-432). To calculate IPTW weights one calculates the marginal probability of treatment (PS) for the entire cohort and transforms the individual weights based on exposure prevalence in the cohort (33).

Although stabilizing the weights will reduce extreme weights, to some extent these extreme weights can still have a large effect on treatment estimates (433). To investigate their

effect we will plan to undertake sensitivity analysis investigating trimming at specified intervals, quartiles, and based on caliper distance (434, 435).

We will present propensity score distributions for each of the study populations (restricted only with CFRI and restricted with all FIT criterion). We will present IPTW weighted estimates compared to unweighted estimates from the study population. The estimates which utilize IPTW weighting will be presented as “Weighted Estimates” in the results.

CHAPTER 4: AIM 1 RESULTS

Aim 1: Develop and evaluate a claims-based algorithm (CFRI) to estimate FRAX® risk scores using clinical registry data linked to Medicare claims data.

Hypothesis 1: In the final model there will be no significant difference in predicted (CFRI) to observed (FRAX®) scores based on aR^2 .

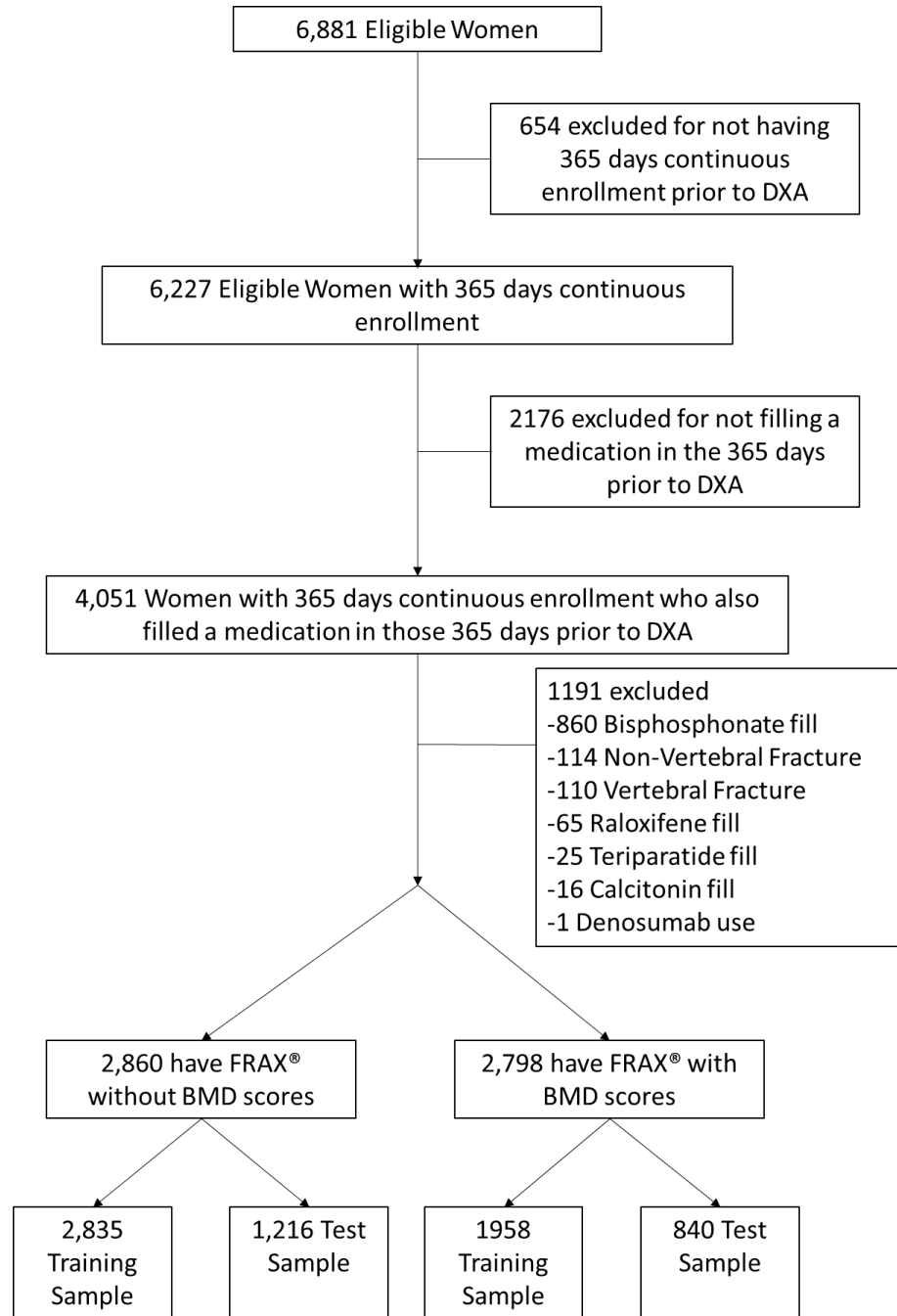
4.1 Cohort Selection

The Aim 1 population is comprised of women aged ≥ 65 from the CCF DXA registry with DXA scans between 2009 and 2013 who were able to be matched to their Medicare claims. For all of aim 1 patients had to have at least 365-days continuous enrollment prior to their FRAX® score as recoded in the registry, as well as fill at least one medication during the 365-days prior. Details of participant inclusion and exclusion are presented as Figure 4.1. Overall there were 7,885 DXAs scans linked to Medicare claims. There were 925 patients who had >1 DXA matched to their Medicare data, comprising 1869 distinct scans. Using a random selection method only one scan per patient was chosen yielding 6,881 patients eligible for inclusion in the study population. We excluded 654 patients who did not have 365-days continuous enrollment in Medicare Parts A, B and 2,176 patients who did not have a medication fill in Part D in the 365-days prior to DXA. This resulted in 4,051 women eligible for analysis.

The cohort is further separated based on if the patient did or did not have a score with bone mineral density (BMD). FRAX® can be calculated based on a patient's femoral neck BMD, or when this is not available, based on their body mass index (BMI). All 4,051 patients

had a score without BMD, however only 3,950 had a score with BMD. Further these cohorts were split 70/30 into training and test samples. The without BMD cohort is comprised of 2,835 patients in the training sample, 1,216 in the test sample while the “with BMD” cohort is comprised of 1,958 in the training sample and 840 in the test sample.

Figure 4.1 Aim 1 Patient Flowchart



4.2 Prediction

4.2.1 With BMD Cohort

The characteristics of patients with calculated FRAX scores with BMD are presented in Table 4.1. When comparing the training and test samples, the mean ages were similar 74.0 in the training and 74.2 in the test with similar distributions of DXAs across the study years (2009-2013). As each of these patients had a DXA it was interesting to note overall 51.8% of the population had a diagnosis of osteoporosis in the year preceding the DXA. Because the vast majority of these patients had been treated by a rheumatologist it was surprising that only 7.7% had a diagnosis of rheumatoid arthritis, but 96.5% had a diagnosis for kyphosis (back curvature), and 43.4% were diagnosed with osteoarthritis. Using the same coding algorithm, we found 18.1% of the with-BMD population to have kyphosis in an analysis of patients with glucocorticoid-induced osteoporosis, while a review of the published studies prior to 2009 speculated a prevalence of between 20 and 40% (436). As the 20 to 40% estimate was made for the general public it is possible that more of these patients had kyphosis as a diagnosis either as a consequence or attributable to their use of DXA. Only 3.8% of the population were reported as having a vertebral fracture in the preceding year, while 4.1% had a non-vertebral fracture (hip, humerus, wrist), and 12.3% fractured at a different site, with 7.1% having been reported as falling in the year preceding. Approximately 28.4% of the sample had a diagnosis corresponding to Vitamin D insufficiency, possibly related to geographic location (Northeast Ohio, where sunshine is not abundant). Other common comorbidities include prior stroke (14.2%), depression (16.8%), and COPD/Asthma (21.5%) and diabetes (20.2%), consistent with national trends based on Centers for Disease Control and Prevention statistics (<http://www.cdc.gov/datastatistics/>). Medications that were filled in the preceding year were most commonly glucocorticoids (22.5%),

proton pump inhibitors (28.8%) and SSRIs (17.6%). This is a higher proportion of glucocorticoid use than the general population, however that may have been the reason that they received the DXA in the first place. Characteristics were similar between the test and training sets except Parkinson's disease, stroke, anti-coagulant use, and the use of barbiturates.

Table 4.1 Basic Demographics of with BMD population

Attribute	Test	Train	Total
N	840	1958	2798
Mean Age	74.0	74.2	74.2
Year of DXA			
2009	45 (5.4)	116 (5.9)	161 (5.8)
2010	159 (18.9)	296 (15.1)	455 (16.3)
2011	227 (27.0)	567 (29.0)	794 (28.4)
2012	193 (23.0)	493 (25.2)	686 (24.5)
2013	216 (25.7)	486 (24.8)	702 (25.1)
In 365-days prior to index			
Osteoporosis, N (%)	363 (43.2)	857 (43.8)	1220 (43.6)
Lifestyle Factors, N (%)			
Alcohol Abuse	<11	<11	<11
Falling	40 (4.8)	103 (5.3)	143 (5.1)
Vitamin D insufficiency	242 (28.8)	550 (28.1)	792 (28.3)
Genetic factors, N (%)			
Homocystinuria	<11	<11	<11
Hypophosphatasia	<11	12 (0.6)	14 (0.5)
Gaucher's disease	<11	<11	<11
Porphyria	<11	<11	<11
Hemochromatosis	<11	<11	<11
Hypogonadal states, N (%)			
Anorexia nervosa and bulimia	<11	18 (0.9)	23 (0.8)
Hyperprolactinemia	<11	<11	<11
Premature ovarian failure	<11	<11	<11
Athletic amenorrhea	<11	<11	<11
Endocrine disorders, N (%)			
Diabetes mellitus (Type 1 & 2)	184 (21.9)	387 (19.8)	571 (20.4)
Cushing's syndrome	<11	<11	<11
Hyperparathyroidism	37 (4.4)	93 (4.7)	130 (4.6)
Central Adiposity	64 (7.6)	133 (6.8)	197 (7.0)
Thyrotoxicosis	13 (1.5)	33 (1.7)	46 (1.6)
Gastrointestinal disorders, N (%)			

Celiac disease	<11	16 (0.8)	20 (0.7)
Gastric bypass	<11	<11	<11
Inflammatory Bowel Disease	15 (1.8)	36 (1.8)	51 (1.8)
Malabsorption	<11	35 (1.8)	44 (1.6)
Pancreatic disease	<11	28 (1.4)	38 (1.4)
Primary biliary cirrhosis	<11	<11	13 (0.5)
Crohn's Disease	37 (4.4)	96 (4.9)	133 (4.8)
Hematologic disorders, N (%)			
Hemophilia	19 (2.3)	31 (1.6)	50 (1.8)
Thalassemia	<11	<11	<11
Systemic mastocytosis	<11	<11	<11
Rheumatologic and autoimmune diseases, N (%)			
Ankylosing spondylitis	<11	32 (1.6)	40 (1.4)
Lupus	<11	24 (1.2)	34 (1.2)
Rheumatoid arthritis	61 (7.3)	129 (6.6)	190 (6.8)
Gout	19 (2.3)	60 (3.1)	79 (2.8)
Polymyalgia Rheumatica	28 (3.3)	51 (2.6)	79 (2.8)
Central nervous system disorders, N (%)			
Epilepsy	<11	32 (1.6)	42 (1.5)
Parkinson's disease	<11	11 (0.6)	21 (0.8)
Stroke	67 (8.0)	201 (10.3)	268 (9.6)
Multiple sclerosis	<11	16 (0.8)	23 (0.8)
Spinal cord injury	<11	<11	<11
Alzheimer's	41 (4.9)	106 (5.4)	147 (5.3)
Miscellaneous conditions and diseases, N (%)			
Congestive Heart Failure	59 (7.0)	139 (7.1)	198 (7.1)
Liver Disease	34 (4.0)	97 (5.0)	131 (4.7)
Depression	136 (16.2)	308 (15.7)	444 (15.9)
Amyloidosis	<11	<11	<11
End stage renal disease	<11	17 (0.9)	21 (0.8)
Sarcoidosis	<11	<11	17 (0.6)
Chronic metabolic acidosis	<11	20 (1.0)	26 (0.9)
Asthma/Chronic obstructive lung disease	169 (20.1)	424 (21.7)	593 (21.2)
Idiopathic scoliosis	28 (3.3)	90 (4.6)	118 (4.2)
Cataracts	383 (45.6)	943 (48.2)	1326 (47.4)
Glaucoma	103 (12.3)	312 (15.9)	415 (14.8)
Kyphosis	796 (94.8)	1878 (95.9)	2674 (95.6)
Obesity	64 (7.6)	133 (6.8)	197 (7.0)
Disorders of the eye*	515 (61.3)	1278 (65.3)	1793 (64.1)
Osteoarthritis	331 (39.4)	859 (43.9)	1190 (42.5)
Renaulds	34 (4.0)	73 (3.7)	107 (3.8)
Medications, N (%)			
Cyclosporine A and tacrolimus	<11	13 (0.7)	15 (0.5)

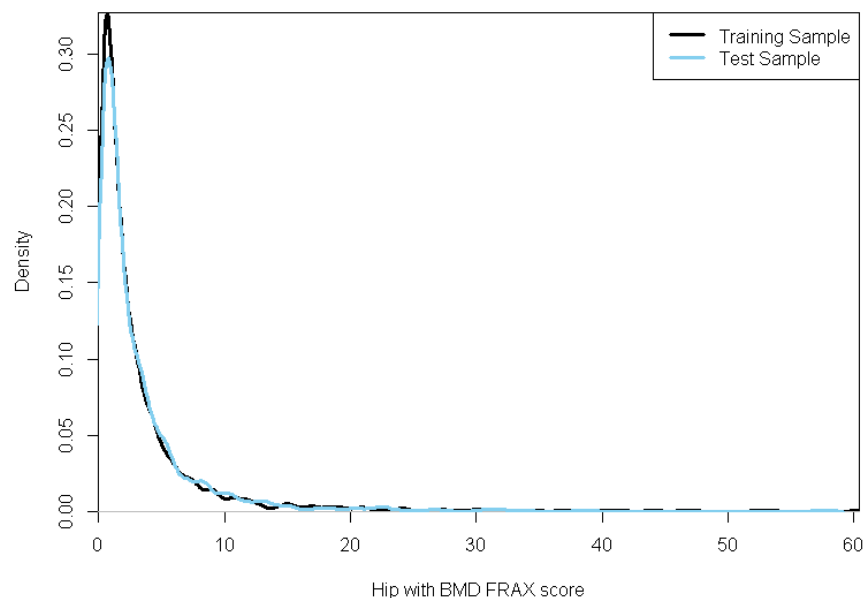
Proton pump inhibitors	236 (28.1)	575 (29.4)	811 (29.0)
Anticoagulants	77 (9.2)	167 (8.5)	244 (8.7)
Selective serotonin reuptake inhibitors	139 (16.5)	330 (16.9)	469 (16.8)
Anticonvulsants	112 (13.3)	260 (13.3)	372 (13.3)
Aromatase inhibitors	25 (3.0)	61 (3.1)	86 (3.1)
Thiazolidinediones	<11	25 (1.3)	31 (1.1)
Barbiturates	<11	<11	<11
Lithium	<11	<11	<11
Methotrexate	34 (4.0)	51 (2.6)	85 (3.0)
Glucocorticoids	184 (21.9)	428 (21.9)	612 (21.9)
Hormone Replacement Therapy	98 (11.7)	234 (12.0)	332 (11.9)
Fractures			
Non-MOF Sites	45 (5.4)	109 (5.6)	154 (5.5)
Race			
White	714 (85.0)	1694 (86.5)	2408 (86.1)
African-American	105 (12.5)	221 (11.3)	326 (11.7)
Hispanic	<11	<11	12 (0.4)
Asian	11 (1.3)	11 (0.6)	22 (0.8)
Other	<11	17 (0.9)	21 (0.8)
All Cells with a total of 0 were suppressed; *: Includes Cataracts and Glaucoma. <11: CMS does not allow cells with less than 11 patients to be presented			

4.2.1.1 Continuous Prediction of Hip with BMD Fracture Risk

Models were built for the prediction of the Hip with BMD FRAX® score. In both the training and test samples the distribution of the hip score was skewed due to extreme values. The mean score in the training sample is 3.12 (SD 4.80) median 2.70 (IQR 1.30, 5.40) while it is 3.10 (SD 4.46) median 2.60 (IQR 1.20, 5.10) in the test sample. A kernel density plot is presented as Figure 4.2 to demonstrate the wide spread of FRAX® values spanning from 0.1 to 60.43, which reflects the wide variation of possible FRAX® scores. As the figure demonstrates the majority of the scores are less than 10 and primarily grouped closer to 1. Based on a 3% threshold which is the National Osteoporosis Foundation (NOF) treatment threshold, 51.2% would have been recommended AOM treatment based on their hip FRAX® risk alone (>3%). Indicating a relatively balanced population for those who should and should not be treated based on

guidelines alone. Because some of these values were very extreme a hand check of the 5 most extreme values was done in the CCF data, and based on the patient's responses and femoral neck BMD these were the correct scores. To address the skewed nature of the data, a natural log of the outcome was taken and evaluated as well as the untransformed value to determine the best model. To describe the models we present the type of model, the number of covariates, the mean squared error, the mean absolute error, R^2 , adjusted R^2 , and the slope of the regression line.

Figure 4.2 Density Plot of FRAX(R) Hip with BMD



4.2.1.1.1 Basic Linear Regression Models for Hip with BMD

Basic linear regression models were used to predict the FRAX® hip with BMD score. All FRAX® scores were modeled on both untransformed and log transformed scales. A null model was calculated taking the mean of the FRAX® scores – the individual FRAX® scores to determine which models were more informative than a random guess. Multivariable regression utilizing all available covariates including interactions for age*age, age³, and age*osteoporosis were fit. Additionally backward stepwise regression was used to model both the untransformed

and log normal (LN) transformed outcome. The stepwise models were used to determine the most influential variables, and create a more parsimonious model. The best model was determined by the largest adjusted R^2 (aR^2), which can be interpreted as the amount of variation that can be accounted for by the model, accounting for the number of covariates in the model. Model results including error terms are presented as Table 4.2. Additionally if the only variable in the model is continuous age, the aR^2 was 0.12 and log transformed it was 0.03, which shows that although age was important, it alone could not be used to predict FRAX®.

Table 4.2 Hip Linear Model Error Terms

Analysis	# var	RMSE	MAE	R2	aR2	Slope
Null Model	-	5.81	3.52	-	-	-
Linear Model	80	5.00	2.77	0.17	0.09	0.75
LN Linear Model	80	4.88	2.33	0.21	0.12	1.17
Backwards Stepwise	20	4.97	2.76	0.18	0.16	0.77
LN Backwards Stepwise	26	4.85	2.32	0.22	0.19	1.22

var: Number of variables used in the model

RMSE: Root Mean Squared Error

MAE: Mean Absolute Error

aR2: Adjusted R^2

The root mean square error (RMSE) of the best guess model is 5.81 and mean absolute error (MAE) is 3.52. Any decrease from these values represents an improved model. Based on the criterion of the best aR^2 , the log-transformed backwards stepwise model is chosen as the optimal basic linear model for Hip with BMD with an aR^2 of 0.19. Although the linear log-transformed model had a higher R^2 its use of all 80 covariates lowers its aR^2 below the backwards stepwise model. A slope of 1.21 for the LN backwards stepwise model indicates extreme predictions, as a slope of 1 is perfect calibration.

4.2.1.1.2 LASSO Models for Hip with BMD

The LASSO model is created using the r package glmnet and a specified alpha value of 1 (31). Within linear glmnet model's shrinkage terms can be specified as MAE (mean absolute error) or MSE (mean squared error), and the LASSO penalty can be chosen as either the minimum penalty (λ minimum) or one standard error from the λ minimum (1se). To determine the best model all four variations were used with both untransformed and LN hip with BMD scores and 10-fold cross validation. For the 1se models, 100 bootstrap samples of the 1se value were taken with the mean of these estimates used as the value due to each cross-validation in glmnet creating different cross-validation cut points (30).

Table 4.3 LASSO Hip with BMD Model Results

Analysis	# var	RMSE	MAE	R2	aR2	Slope
LASSO MSE 1se	3	5.04	3.06	0.16	0.15	2.58
LASSO MSE λ minimum	15	4.85	2.68	0.22	0.20	0.96
LASSO MAE 1se	4	4.85	2.79	0.22	0.212883	1.43
LASSO MAE λ minimum	11	4.84	2.68	0.22	0.211979	1.02
LN LASSO MSE 1se	7	4.99	2.34	0.17	0.17	1.50
LN LASSO MSE minimum λ	75	4.87	2.32	0.21	0.13	1.15
LN LASSO mae 1se	7	4.99	2.34	0.17	0.17	1.49
LN LASSO mae λ min	27	4.90	2.32	0.20	0.17	1.17

Compared to the best guess model, all of the LASSO models, both untransformed and LN transformed represent a decrease in RMSE and MAE. The number of variables chosen in the optimal model range from 3 to 75. However based on aR^2 the best fitting model is MAE 1se with an aR^2 of 0.212. The smallest RMSE was found in the untransformed MAE λ minimum model which represented a decrease of 1.2, while the smallest MAE was found in the LN MAE λ minimum model which represented a decrease of 1.3. The untransformed model with the greatest aR^2 was MAE 1se with 0.212, while the LN MAE λ minimum had an aR^2 of 0.175. The untransformed model has fewer variables (4 versus 27) compared to the log-transformed model,

as well as a smaller RMSE and calibration slope closer to 0. Therefore the best LASSO model is the untransformed MAE 1se.

4.2.1.1.3 Elastic Net Models for Hip with BMD

The elastic net model is created using the glmnet R package without a specified alpha value but otherwise the same commands as the LASSO model, with the program allowed to determine the optimal alpha value between 0 (ridge regression penalty) and 1 (LASSO regression penalty). The methods to determine the optimal elastic net (Enet) model were identical to those of the LASSO model. Model error results are presented as Table 4.4.

Table 4.4 Elastic Net Hip with BMD Model Results

Analysis	# var	RMSE	MAE	R2	aR2	Slope
Enet MSE 1se	3	5.05	3.07	0.15	0.15	2.65
Enet MSE λ minimum	15	4.85	2.68	0.22	0.20	0.96
Enet MAE 1se	4	4.85	2.78	0.22	0.213636	1.41
Enet MAE λ minimum	11	4.84	2.68	0.22	0.211918	1.02
LN Enet MSE 1se	7	4.99	2.34	0.17	0.17	1.50
LN Enet MSE Lambda min	73	4.87	2.32	0.21	0.14	1.14
LN Enet MAE 1se	7	4.98	2.34	0.18	0.17	1.48
LN Enet MAE Lambda min	27	4.90	2.32	0.20	0.17	1.17

The elastic net models all represent a decrease in RMSE and MAE from the best guess model. The MAE 1se model represents the greatest predictive ability based on an aR^2 of 0.213, which exceeds the LASSO model of the same type. The slope of this model is 1.4 which indicates that it may have some extremely high predictions. No log-transformed model exceeded an aR^2 of 0.20.

4.2.1.1.4 Comparison of the best linear hip with BMD models

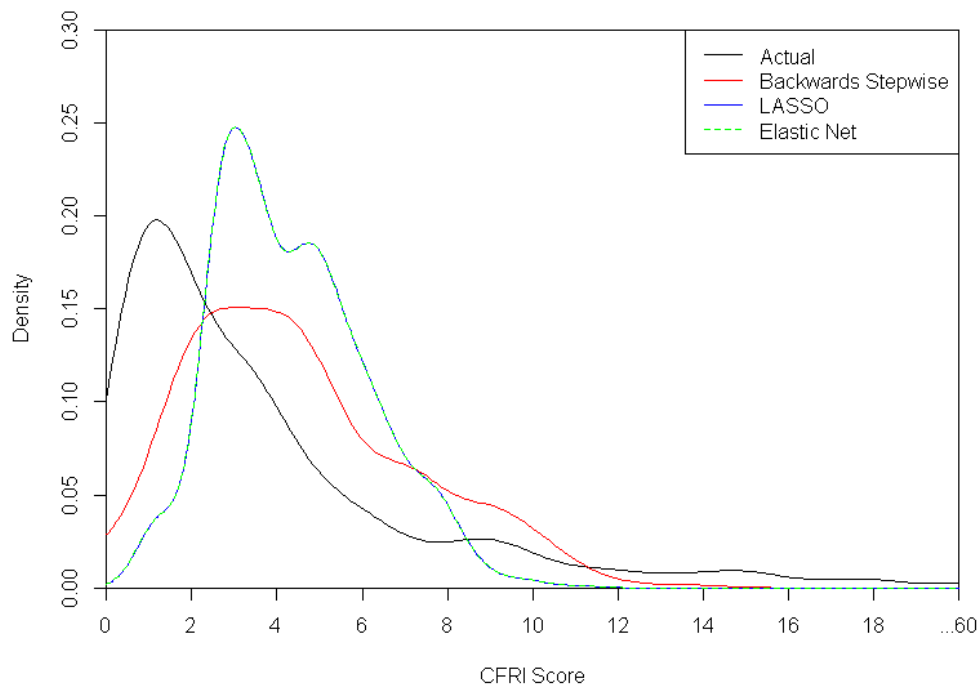
Three optimal basic linear, LASSO, and elastic net models have been chosen and constructed. In the basic linear models the backwards stepwise, the LASSO model was the MAE 1se, and the elastic net was MAE 1se as well. The model results are presented as Table 4.5.

Using our criterion of the highest aR^2 the LASSO model would be chosen over the basic linear and elastic net models. Of note both the LASSO and elastic net models would produce more extreme estimates (slope >1), while the backwards stepwise model would have produced more conservative estimates. The density plots for all three models are presented as Figure 4.3. The LASSO and Elastic Net estimates look very similar, both with bimodal distributions. The elastic net model appears to have the largest spread of all of the predicted models as evidence by a green line persisting to the end of the figure, whereas the red and blue lines stop, which indicates that their highest predictions were <10 .

Table 4.5 Best Linear hip with BMD models

Analysis	#	RMSE	MAE	R2	aR2	Slope
LN Backwards Stepwise	26	4.85	2.32	0.22	0.19	1.22
LASSO MAE 1se	4	4.85	2.79	0.22	0.212883	1.43
Enet MAE 1se	4	4.85	2.78	0.22	0.213636	1.41

Figure 4.3 Density Plot of Best 3 Hip with BMD models



The model coefficients for the three best models are presented as Table 4.6. Only variables which appeared in one model are included in the table. All three models include an intercept as well as a linear age term and age*osteoporosis. Cushing's syndrome was the variable which was most predictive of the FRAX® score based on this analysis, other than the intercept and linear age. Cushing's syndrome produces excess cortisol which has a similar effect on bone as glucocorticoid use, which would explain greater FRAX® scores based on lower BMD (233). The only other variable chosen by the elastic net model was African-American race which when present lowered a patient's risk.

Table 4.6 Model coefficients for best linear hip with BMD

Attribute	Backwards Stepwise	LASSO	Elastic Net
Intercept	153.4667957	-7.781649239	-7.78430299
Linear Age	-6.852048321	0.15458841	0.154623293
Age*Age	0.098895373	-	-
Age*Age*Age	-0.000455398	-	-
Age*Osteoporosis	0.041867044	0.03202327	0.032028816
In 365-days prior to index			
Endocrine disorders			
Diabetes mellitus (Type 1 & 2)	-0.445006777	-	-
Cushing's syndrome	46.29397364	21.47675009	21.48856957
Hyperparathyroidism	1.54388651	-	-
Gastrointestinal disorders			
Inflammatory Bowel Disease	1.701265774	-	-
Rheumatologic and autoimmune diseases			
Rheumatoid arthritis	1.302509408	-	-
Central nervous system disorders			
Spinal cord injury	5.562983558	-	-
Miscellaneous conditions and diseases			
Liver Disease	-0.912907042	-	-
Chronic metabolic acidosis	1.976389464	-	-
Idiopathic scoliosis	1.128290996	-	-
Renaulds	1.149202584	-	-
Medications			
Anticonvulsants	-0.489347769	-	-
Glucocorticoids	0.701835939	-	-
Hormone Replacement Therapy	0.548990432	-	-
Race			
African-American	-3.256347127	-1.36527375	-1.366183288
Hispanic	2.715173157	-	-

Describing how well the elastic net model predicts FRAX® is graphically shown as Figure 4.4. The intercept is -1.96 which indicates that the CFRI estimates are systematically too low, however the slope of 1.40 indicates that there are extreme estimates which accounts for the decent fit based on a low intercept. Although there were 18 patients who had a hip 10-year risk of >20% no characteristics identifiable in administrative claims that were more prevalent in this

group than in the population as a whole. This group primarily had at least one FRAX® risk factor, only 6 (4.4%) did not have a single FRAX® risk factor, and a t-score <-2.5.

The model has difficulty predicting larger values, and overall seems to do a relatively poor job of continuously predicting the 10-year hip risk, which wouldn't have been expected with an aR^2 of less than 0.2. In a clinical sense, a 3% threshold is important due to its inclusion in the NOF guidelines as the threshold for treatment of a FRAX® 10-year hip risk. Although the model may not be sufficiently calibrated to predict the continuous score, it may sufficiently discriminate between those who should and should not be treated. This is examined in Figure 4.5.

Figure 4.4 Scatterplot of Best Hip compared to FRAX

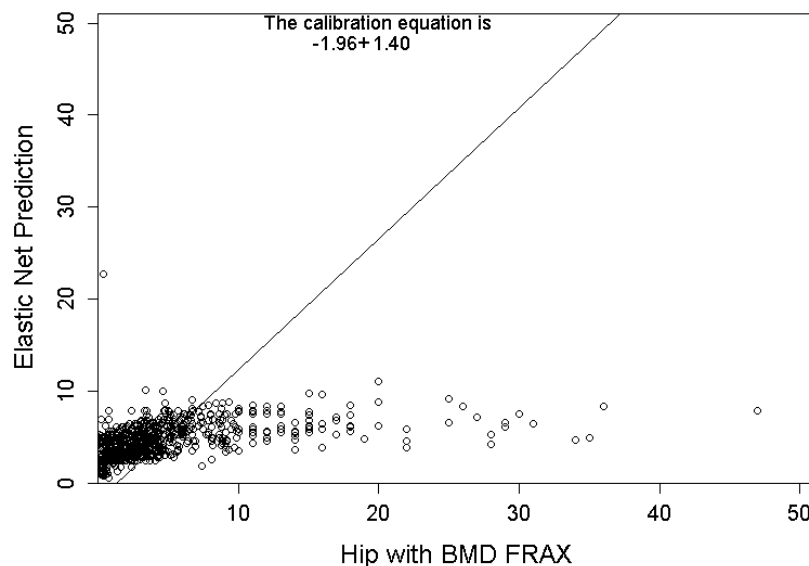
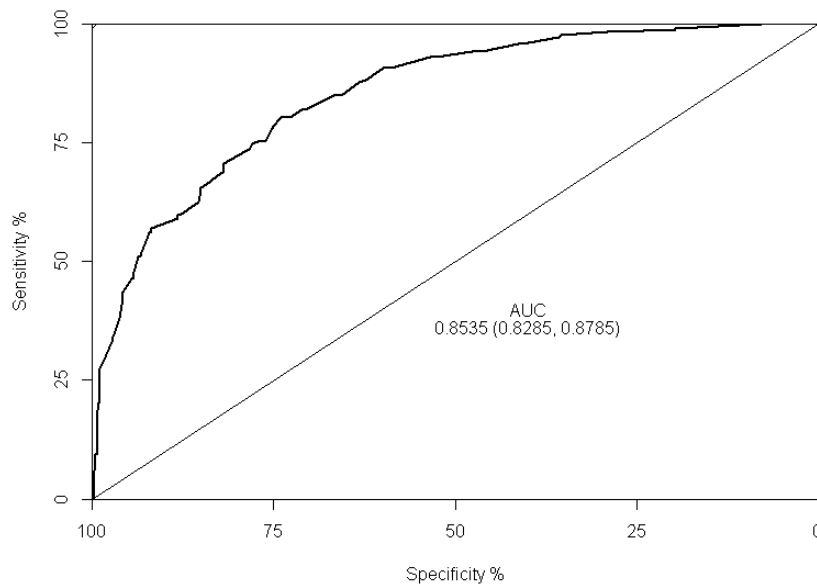


Figure 4.5 Receiver Operating Curve CFRI compared to 3% treatment threshold



Based on the ROC curve it appears that CFRI hip does a reasonable job of discriminating between those who are high and low risk (3% threshold). The area under the curve for CFRI hip is 85.4% (95% CI 82.3, 87.9). The AUC indicates that if you were to randomly draw one patient from the predicted dataset, 85% of the time they would correctly be identified as high-risk. In terms of the ability to predict above and below the NOF threshold of 3%, the test sample had 383 (45.6%) patients with a score >3 , while the predicted score placed 635 (75.6%) patients above the 3% threshold. Additionally 556 (66.2%) of patients were classified correctly of <3 or $\geq 3\%$ by CFRI compared to their FRAX[®] score. It appears that in terms of utility the CFRI hip score may be useable both as a continuous and categorical response. However the majority of the CFRI predictions themselves are below the 3% threshold.

4.2.1.1.5 High-Dimensional Variable Selection

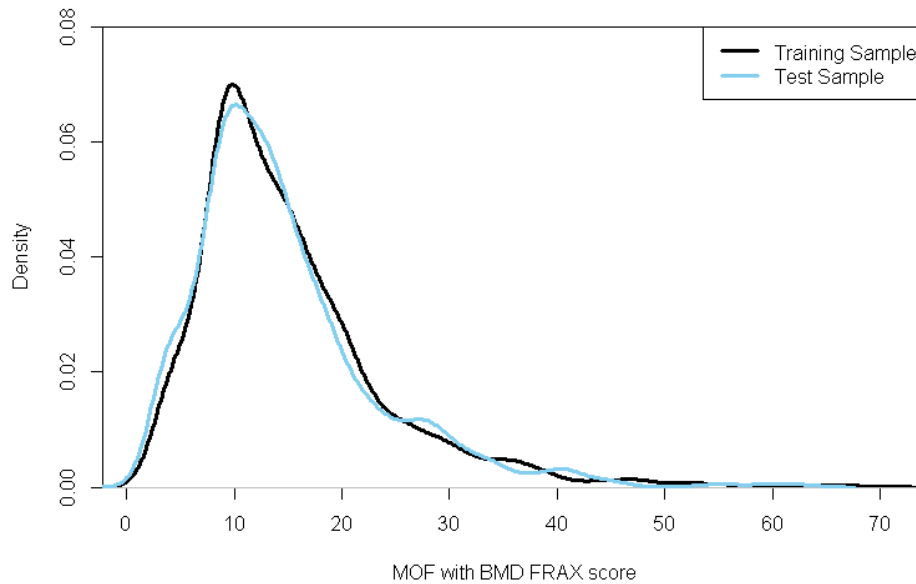
To evaluate the value of adding additional variables through a high-dimensional selection process of all variables with a prevalence of $\geq 1\%$, all four elastic net models were re-fit with the

additional covariates. For Hip with BMD, the high-dimensional variable selection approach included 135 medication classes, 129 different diagnoses, and 713 procedural classes. When these were added to the 87 content variables there were 1,063 different variables for the elastic net model to evaluate. After evaluation, the MAE λ minimum model was found to be the superior elastic net model, selecting 7 variables with no medication classes, no diagnosis codes, and 3 procedure codes (primarily associated with office visits). However the aR^2 for this model was 0.2125 which was less than the chosen elastic net model, suggesting that the high-dimensional approach did not improve model performance.

4.2.1.2 Continuous Prediction of Major Osteoporotic Fracture with BMD Fracture Risk

Models were built for the prediction of the MOF with BMD FRAX® score. In both the training and test samples the distribution of the MOF score was approximately normal, but highly skewed with a small number of extreme values. The mean score in the training sample is 12.8 (SD 7.7) median 13.0 (IQR 9.10, 18.00) while it is 12.8 (SD 7.6) median 13.00 (IQR 9.10, 18.00) in the test sample. A kernel density plot is presented as Figure 4.6 which shows that the spread of values is similar to that of the hip score (range 1.62 to 68.7), however the cluster of scores are much less spread as evidenced by the maximum density only reaching 0.08. As was presented in the Hip with BMD section, all analyses were done with both the untransformed and log transformed scores.

Figure 4.6 Density Plots of Test and Training Sample for MOF with BMD



4.2.1.2.1 Basic Linear Regression Models for MOF with BMD

The same methods including the interaction terms as the hip with BMD model (Section 4.2.1.1.1) were used for the MOF with BMD models. A null model was created taking the mean actual value subtracted by the actual value for the MAE and RMSE of the null model.

Multivariable, as well as backwards stepwise models were fit for both the untransformed and log-transformed outcome. Models results including aR^2 are presented as Table 4.7. The model with only age at DXA produced an aR^2 of 0.09 and when log transformed an aR^2 of 0.04 indicating poorer performance than the other models (Table 4.7). The model with only age at DXA produced an aR^2 of 0.09 and when log transformed an aR^2 of 0.04 indicating a poorer performance than the other models.

Table 4.7 MOF with BMD Linear Model Error Terms

Analysis	# var	RMSE	MAE	R2	aR2	Slope
Best Guess	-	8.88	6.44	-	-	-
Linear Model	80	7.07	4.89	0.34	0.27	0.93
LN Linear Model	80	6.99	4.54	0.35	0.29	1.09
Backwards Stepwise	28	7.03	4.89	0.35	0.32	0.94
LN Backwards Stepwise	32	6.96	4.51	0.36	0.33	1.10

var: Number of variables used in the model

RMSE: Root Mean Squared Error

MAE: Mean Absolute Error

aR2: Adjusted R²

As was done in the hip models a best guess scenario was undertaken to determine what minimum RMSE and MAE were for improvement. The RMSE of the best guess model is 8.9 and MAE is 6.4, indicating that for a model to be viewed as useful their RMSE and MAE must be less than these values. The RMSE and MAE for the MOF model are nearly double that of the hip model. With all 80 variables used (including dummy variables for race and year of DXA) the linear (aR²: 0.27) and log-linear (aR²: 0.29) models had a better predictive ability than the optimal hip model. The backwards stepwise regression procedures produced better fitting models, linear aR² 0.32, and log-linear aR² 0.33 while taking 52 and 48 fewer variables respectively. The backwards stepwise models also reduced RMSE and MAE compared to the best guess model. Based on the highest aR² value, the optimal model from the basic linear models would be the backwards stepwise model, with greater than 30% of the variation in the FRAX® 10-year risk of MOF with BMD explained by the model.

4.2.1.2.2 LASSO Models for MOF with BMD

The error terms of the LASSO models predicting the MOF with BMD FRAX® score are presented as Table 4.8.

Table 4.8 LASSO MOF with BMD Model Results

Analysis	# var	RMSE	MAE	R2	aR2	Slope
LASSO MSE 1se	7	7.19	5.16	0.32	0.309737	1.54
LASSO MSE λ minimum	34	6.93	4.84	0.37	0.338342	1.09
LASSO MAE 1se	8	7.05	5.02	0.34	0.33591	1.39
LASSO MAE λ minimum	27	6.93	4.85	0.36	0.3432393	1.12
LN LASSO MSE 1se	10	7.09	4.63	0.33	0.326905	1.39
LN LASSO MSE λ min	44	6.90	4.50	0.37	0.335453	1.20
LN LASSO MAE 1se	10	7.04	4.59	0.34	0.336219	1.36
LN LASSO MAE λ min	46	6.90	4.50	0.37	0.333775	1.20

Compared to the best guess model, all of the LASSO models represent a decrease in RMSE and MAE. However based on aR^2 the best fitting model is MAE λ minimum with an aR^2 of 0.282. All RMSE and MAE for the non-transformed models are within 0.3 of each other. In this model the 25 additional variables chosen from the MAE λ minimum are more useful in explaining the model, compared to the 1se model, as evidenced by aR^2 being the greatest in the MAE λ minimum model, even after taking account for the additional variables. The MAE λ minimum model would be chosen as the best of the 8 models based on the optimal aR^2 .

Compared to the best guess model, all of the log-transformed LASSO models represent decreases in RMSE and MAE. However based on aR^2 the best fitting model is MAE 1se with an aR^2 of 0.268. This model appears to have performed the best based on a small number of included variables and a lower error than the MSE 1se. The two λ minimum models suffer from the inclusion of too many variables, which causes their aR^2 to decrease past the MAE 1se. However if not for the penalization of selecting too many variables the log-transformed MAE λ actually represented the best R^2 of all 8 models with 0.306.

4.2.1.2.3 Elastic Net MOF with BMD

The error terms of the elastic net models predicting MOF with BMD FRAX® score are presented as Table 4.9.

Table 4.9 Elastic Net MOF with BMD untransformed model results

Analysis	# var	RMSE	MAE	R2	aR2	Intercept
Enet MSE 1se	7	7.19	5.16	0.32	0.311228	1.54
Enet MSE λ min	29	6.93	4.84	0.37	0.34235	1.10
Enet MAE 1se	8	7.05	5.02	0.34	0.336134	1.39
Enet MAE λ min	27	6.93	4.85	0.36	0.3432784	1.12
LN Enet MSE 1se	10	7.09	4.63	0.34	0.327023	1.39
LN Enet MSE λ min	46	6.90	4.50	0.37	0.333782	1.20
LN Enet MAE 1se	10	7.05	4.60	0.34	0.334553	1.37
LN Enet MAE λ min	46	6.90	4.50	0.37	0.333775	1.20

The elastic net untransformed model results all represent a decrease in RMSE and MAE to the best guess model. The error terms are very similar to that of the LASSO model, with each of these models increasing the aR^2 by a marginal amount. The MAE λ minimum model is the optimal model with an aR^2 of 0.282 indicating an ability to account for ~28% of all of the variability in the FRAX® 10-year MOF.

The elastic net log-transformed model results all represent a decrease in RMSE and MAE to the best guess model. Similar to the LASSO model, the MAE 1se model was the best model with an aR^2 of 0.269. This model has 23 variables, and had high RMSE and MAE compared to the λ minimum models. The results of the elastic net log transformed model are very similar to the LASSO model, as well as the density plot (not presented). In the log-transformed Elastic net model, the third hump of the distribution again appears to be smoothed. With the aR^2 used as the criteria for selecting the best model, we would view the MAE 1se as the best fitting of the log-transformed elastic net models.

The best elastic net model without transformation is the MAE 1se model with an aR^2 of 0.282, while the best log-transformed model is the MAE 1se model with an aR^2 of 0.269. These are the same models which were found to be the best LASSO models. Based on the criterion of largest aR^2 , we will accept the untransformed MAE 1se model as the optimal elastic-net model.

4.2.1.2.4 Comparison of the best linear MOF with BMD models

The three types of model which produced the best MOF with BMD estimates are presented as Table 4.10. The best performing models for MOF with BMD were the same as the Hip with BMD, except for the log-transformed chosen over the untransformed backwards stepwise model. The models are backwards stepwise regression, LASSO with MAE λ minimum, and Elastic net with MAE λ minimum. The model which represents the highest aR^2 is the elastic net model and based on our methodology it would be accepted as the best model. Based on the density plot (Figure 4.7), none of these models are able to accurately predict the maximum observed scores. The elastic net model only classified 322 patients as having an MOF of $\geq 20\%$ while the backwards stepwise model predicted 235 patients with that score which is the NOF threshold for treatment. The test model in total has 310 patients who have a MOF of $\geq 20\%$. A scatter plot of the predicted values compared to the actual values is presented as Figure 4.8. The intercept is -5.31 indicating that systematically the estimates are much lower than they should be. However with a slope of 1.33 the predictions had a tendency to be higher than expected. The other thing that the scatter plot shows us is that the majority of the predictions fall between 10 and 20 with the model not doing a good job of identifying extreme scores. Those patients at the highest MOF values, similar to the hip estimates didn't have any characteristics that were significantly different than the general population, other than FRAX® risk factors and BMD scores.

Table 4.10 Best linear MOF with BMD models

Analysis	# var	RMSE	MAE	R2	aR2	Slope
Backwards Stepwise	32	6.96	4.51	0.36	0.3340581	1.10
LASSO MAE λ minimum	27	6.93	4.85	0.36	0.3432393	1.12
Enet MAE λ minimum	27	6.93	4.85	0.36	0.3432784	1.12

Figure 4.7 Density Plot of Best 3 Linear MOF with BMD models

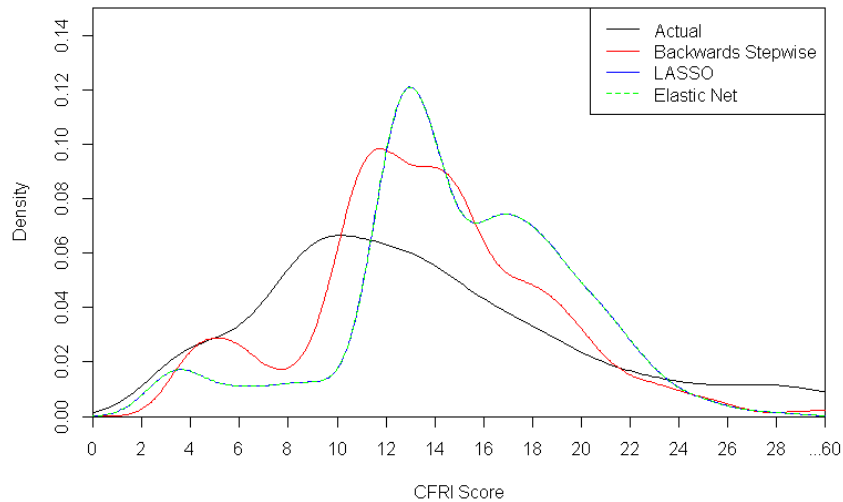
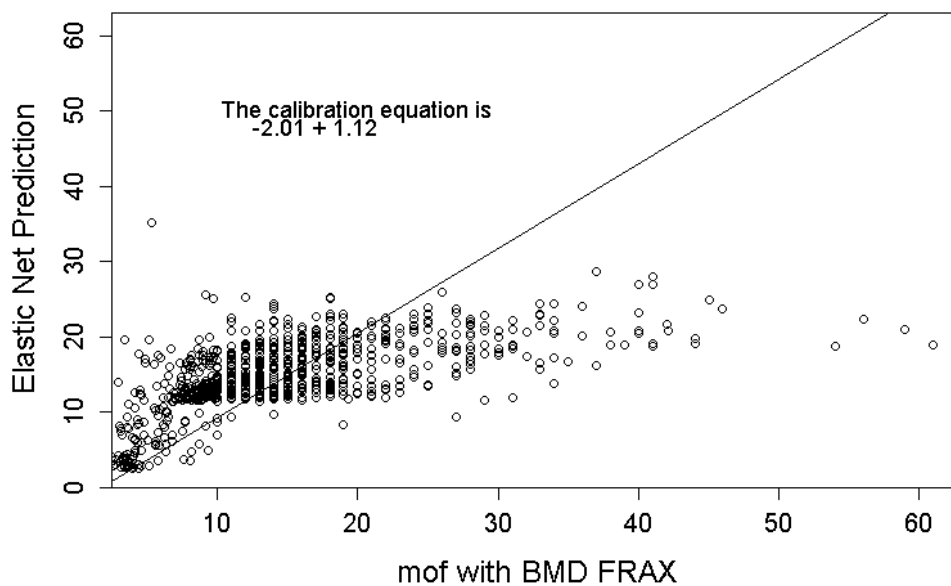


Figure 4.8 Scatterplot of best MOF with BMD model



The model coefficients for the 3 best models are presented as Table 4.10. All 3 models included the intercept and linear age. Similar to the hip with BMD model, Cushing's syndrome was the strongest predictor in the model. The next most influential variable was cystic fibrosis

and Hispanic race, each of these increasing the risk by >5%. As neither of these are FRAX® variables the most influential variable which is measured in the FRAX® algorithm was glucocorticoid use, but it (as well as rheumatoid arthritis diagnosis) increased a score by less than 2%. The models also all included race. Differently from the Hip with BMD estimates, all 3 include rheumatoid arthritis as predictor. Vertebral fracture is the variable with the largest effect on the CFRI estimate other than variables including age (linear age and osteoporosis*age) based on their multiplicative effects.

Table 4.11 Model coefficients for the best 3 linear MOF with BMD models

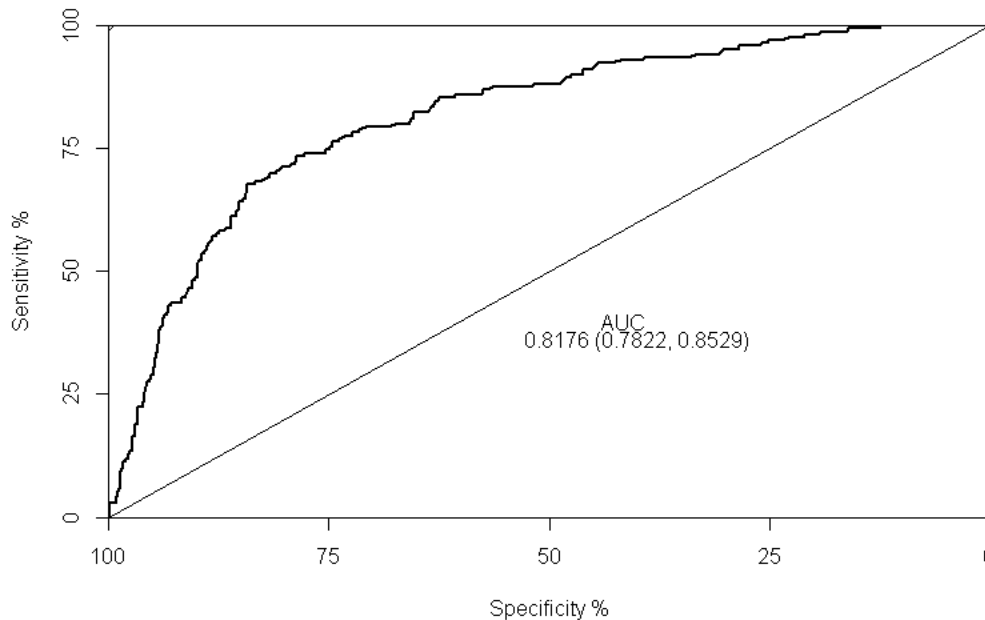
Attribute	Backwards Stepwise	LASSO	Elastic Net
Intercept	656107.4739	-4.793618214	-4.825318605
Linear Age	0.597352024	0.213689987	0.213882754
Age*Age	1.007664994	-	-
Age*Age*Age	0.999964141	-	-
Age*Osteoporosis	-	0.065007596	0.06501777
In 365-days prior to index			
Osteoporosis	1.32712879	-	-
<i>Lifestyle Factors</i>			
Vitamin D insufficiency	0.963579158	-0.011273041	-0.013289971
<i>Genetic factors</i>			
Hypophosphatasia	-	0.008092342	0.009540193
<i>Hypogonadal states</i>			
<i>Endocrine disorders</i>			
Diabetes mellitus (Type 1 & 2)	0.96018752	-0.009055322	-0.010675466
Cushing's syndrome	2.532662798	29.94834646	30.00819577
Hyperparathyroidism	1.095685332	0.492861044	0.498923702
Central Adiposity	0.948061336	-	-
<i>Gastrointestinal disorders</i>			
Inflammatory Bowel Disease	1.187847198	1.546359531	1.554882759
<i>Hematologic disorders</i>			
Hemophilia	0.883463892	-	-
<i>Rheumatologic and autoimmune diseases</i>			
Ankylosing spondylitis	1.106222719	-	-
Lupus	-	0.717620602	0.726900325
Rheumatoid arthritis	1.207422619	2.811289734	2.813412897
Polymyalgia Rheumatica	1.176553885	1.443967256	1.449502678
<i>Central nervous system disorders</i>			
Epilepsy	1.120652167	-	-
Spinal cord injury	1.48000584	1.053226296	1.093297267
<i>Miscellaneous conditions and diseases</i>			
Depression	-	0.018531661	0.021357651
End stage renal disease	1.173995164	-	-
Sarcoidosis	1.212139726	0.463805842	0.481572939
Chronic metabolic acidosis	1.310222847	1.657934364	1.667854978
Idiopathic scoliosis	1.075165666	0.993030423	0.996848535
Kyphosis	1.195302682	0.082614896	0.090356929
Renaulds	1.087214457	1.234849999	1.239561619
<i>Medications</i>			
Proton pump inhibitors	1.028449649	0.054361967	0.056608238
Anticonvulsants	0.95012885	-	-
Methotrexate	1.126143755	0.834020516	0.841853825
Glucocorticoids	1.068881586	0.965086179	0.965996066
Hormone Replacement Therapy	-	0.203410172	0.208072152
Non-MOF Fractures	1.17657041	2.164282235	2.169086603

<i>Race</i>			
White	0.838004021	2.259054019	2.266392607
African-American	0.321281092	-6.778268151	-6.775158983
Hispanic	-	2.631780414	2.662589671
Asian	0.598366463	-	-
Other	0.553936103	-0.003499407	-0.004125508

In a clinical sense it is important for models to be able to differentiate between high and low risk patients. For MOF we will use the 20% threshold as this is the value at which all patients are recommended treatment based on the NOF guidelines. A receiver operating curve has been created investigating the elastic net MAE 1se CFRI predictions ability to discriminate between high and low risk patients (Figure 4.9). The model is able to discriminate well between low risk and high risk patients, with a c-statistic of 0.81 (95% CI 0.78, 0.85), indicating that patients with a higher CFRI are more likely to have had a FRAX® MOF with BMD $\geq 20\%$. However CFRI does a poorer job of predicting treatable patients based on MOF than hip 10-year risks.

Based on raw statistics, 899 (76.9%) of patients were correctly classified using CFRI into above or below the 20% threshold. There were 334 patients who were listed as $\geq 20\%$ based on their FRAX® score, while CFRI listed 288 patients at this level. Based on these findings the MOF with BMD CFRI score should be valid in the general population.

Figure 4.9 Receiver Operating Curve for MOF with BMD 20% Threshold



4.2.1.2.5 High-Dimensional Variable Selection

Using the high-dimensional variable selection approach for MOF with BMD there were 135 medication classes, 129 different diagnoses, and 713 procedural classes added to the model. When these were added to the 87 content variables there were 1,063 different variables for the elastic net model to evaluate. After evaluation the MAE λ minimum model was found to be the superior elastic net model, selecting 40 variables with 4 medication classes (glipizide, methylprednisone, metronidazole, and motelukast), 8 diagnosis codes (goiter, bronchitis, blindness, intestinal obstruction, intestinal malabsorption, renal failure, and uterine disorders), and 16 procedure codes (primarily associated with office visits). However the aR^2 for this model was 0.3431 which was less than the chosen elastic net model. Therefore the choice of the best model does not change the choice of model for MOF with BMD.

4.2.2 Without BMD Cohort

There were 2,860 patients who met all entrance criteria for the study. Basic demographics of the overall population as well as the test and training samples are presented as Table 4.12. Based on a 70/30 split there were 2,001 patients in the training sample and 859 in the test sample. The demographics are similar to those of the with BMD population (Section 1.2.1). The only covariates out of balance between the test and training sample were lupus and SSRI use.

Table 4.12 Basic Demographics of the without BMD population

Characteristic	Test	Train	All
N	859	2001	2860
Mean Age	74.0	74.2	74.2
Year of DXA			
2009	49 (5.7)	115 (5.7)	164 (5.7)
2010	147 (17.1)	318 (15.9)	465 (16.3)
2011	216 (25.1)	595 (29.7)	811 (28.4)
2012	224 (26.1)	479 (23.9)	703 (24.6)
2013	223 (26.0)	494 (24.7)	717 (25.1)
In 365-days prior to index			
Osteoporosis, N (%)	364 (42.4)	888 (44.4)	1252 (43.8)
Non-MOF Fracture	56 (6.5)	102 (5.1)	158 (5.5)
Lifestyle Factors, N (%)			
Alcohol Abuse	<11	<11	<11
Falling	47 (5.5)	104 (5.2)	151 (5.3)
Vitamin D insufficiency	258 (30.0)	557 (27.8)	815 (28.5)
Genetic factors, N (%)			
Homocystinuria	<11	<11	<11
Hypophosphatasia	<11	11 (0.5)	14 (0.5)
Gaucher's disease	<11	<11	<11
Porphyria	<11	<11	<11
Hemochromatosis	<11	<11	<11
Hypogonadal states, N (%)			
Anorexia nervosa and bulimia	<11	17 (0.8)	25 (0.9)
Hyperprolactinemia	<11	<11	<11
Premature ovarian failure	<11	<11	<11
Athletic amenorrhea	<11	<11	<11
Endocrine disorders, N (%)			
Adrenal insufficiency	<11	<11	<11
Diabetes mellitus (Type 1 & 2)	186 (21.7)	398 (19.9)	584 (20.4)
Cushing's syndrome	<11	<11	<11
Hyperparathyroidism	41 (4.8)	93 (4.6)	134 (4.7)
Central Adiposity	60 (7.0)	146 (7.3)	206 (7.2)
Thyrotoxicosis	15 (1.7)	31 (1.5)	46 (1.6)
Gastrointestinal disorders, N (%)			
Celiac disease	<11	14 (0.7)	21 (0.7)
Gastric bypass	<11	<11	<11
Inflammatory Bowel Disease	17 (2.0)	38 (1.9)	55 (1.9)
Malabsorption	12 (1.4)	34 (1.7)	46 (1.6)
Pancreatic disease	<11	29 (1.4)	38 (1.3)
Primary biliary cirrhosis	<11	<11	13 (0.5)

Characteristic	Test	Train	All
Crohn's Disease	45 (5.2)	94 (4.7)	139 (4.9)
Hematologic disorders, N (%)			
Hemophilia	17 (2.0)	33 (1.6)	50 (1.7)
Thalassemia	<11	<11	<11
Systemic mastocytosis	<11	<11	<11
Rheumatologic and autoimmune diseases, N (%)			
Ankylosing spondylitis	<11	37 (1.8)	40 (1.4)
Lupus	16 (1.9)	18 (0.9)	34 (1.2)
Rheumatoid arthritis	53 (6.2)	148 (7.4)	201 (7.0)
Gout	30 (3.5)	52 (2.6)	82 (2.9)
Polymyalgia Rheumatica	26 (3.0)	55 (2.7)	81 (2.8)
Central nervous system disorders, N (%)			
Epilepsy	<11	36 (1.8)	45 (1.6)
Parkinson's disease	13 (1.5)	<11	22 (0.8)
Stroke	87 (10.1)	186 (9.3)	273 (9.5)
Multiple sclerosis	<11	14 (0.7)	23 (0.8)
Spinal cord injury	<11	<11	<11
Alzheimer's disease	52 (6.1)	101 (5.0)	153 (5.3)
Miscellaneous conditions and diseases, N (%)			
Congestive Heart Failure	64 (7.5)	140 (7.0)	204 (7.1)
Liver Disease	49 (5.7)	90 (4.5)	139 (4.9)
Depression	134 (15.6)	324 (16.2)	458 (16.0)
Amyloidosis	<11	<11	<11
End stage renal disease	<11	11 (0.5)	21 (0.7)
Sarcoidosis	<11	<11	17 (0.6)
Chronic metabolic acidosis	<11	22 (1.1)	28 (1.0)
Asthma/Chronic obstructive lung disease	191 (22.2)	427 (21.3)	618 (21.6)
Idiopathic scoliosis	48 (5.6)	74 (3.7)	122 (4.3)
Cataracts	401 (46.7)	958 (47.9)	1359 (47.5)
Glaucoma	136 (15.8)	291 (14.5)	427 (14.9)
Kyphosis	815 (94.9)	1914 (95.7)	2729 (95.4)
Obesity	60 (7.0)	146 (7.3)	206 (7.2)
Disorders of the eye*	549 (63.9)	1284 (64.2)	1833 (64.1)
Osteoarthritis	363 (42.3)	866 (43.3)	1229 (43.0)
Renauld's syndrome	37 (4.3)	75 (3.7)	112 (3.9)
Medications, N (%)			
Cyclosporine A and tacrolimus	<11	<11	16 (0.6)
Proton pump inhibitors	263 (30.6)	567 (28.3)	830 (29.0)
Anticoagulants	81 (9.4)	169 (8.4)	250 (8.7)
Selective serotonin reuptake inhibitors	151 (17.6)	330 (16.5)	481 (16.8)
Anticonvulsants	121 (14.1)	266 (13.3)	387 (13.5)

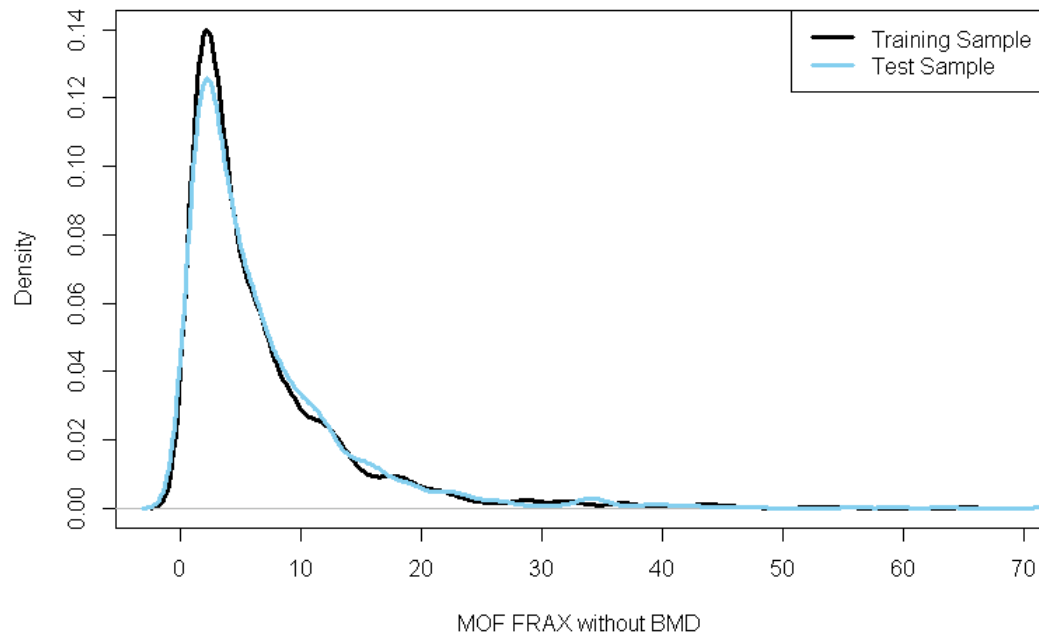
Characteristic	Test	Train	All
Aromatase inhibitors	27 (3.1)	61 (3.0)	88 (3.1)
Thiazolidinediones	13 (1.5)	19 (0.9)	32 (1.1)
Barbiturates	<11	<11	<11
Lithium	<11	<11	<11
Methotrexate	27 (3.1)	61 (3.0)	88 (3.1)
Glucocorticoids	182 (21.2)	450 (22.5)	632 (22.1)
Hormone Replacement Therapy	93 (10.8)	249 (12.4)	342 (12.0)
Race			
White	743 (86.5)	1718 (85.9)	2461 (86.0)
African-American	93 (10.8)	240 (12.0)	333 (11.6)
Hispanic	<11	<11	13 (0.5)
Asian	<11	12 (0.6)	22 (0.8)
Other	<11	16 (0.8)	21 (0.7)
All Cells with a total of 0 were suppressed; *: Includes Cataracts and Glaucoma <11: CMS does not allow cells with less than 11 patients to be presented			

4.2.2.1 Continuous Prediction of Hip without BMD Fracture Risk

Models were built for the prediction of hip without BMD FRAX® score. All patients were utilized for this prediction as everyone had all FRAX® risk factors, even if they didn't have a femoral neck BMD. The mean score of the training sample was 6.7 (SD 7.4) median 3.73 (IQR 1.90, 7.44), while the mean of the test sample was 7.0 (SD 7.8) median 3.79 (IQR 2.11, 7.44). A kernel density plot of the distribution of hip without BMD FRAX® for the training and test sample is presented as Figure 4.10. The hip without BMD scores range from 0.04 to 74.37 with both of the extremes being present in the test sample. Once again, a hand check was made of the most extreme values and they were found to be valid. Models will be built for basic linear models, LASSO, and elastic net models with the best models from each of the categories compared. The best model will be defined as the one with the greatest adjusted R-squared (aR^2). Additionally we will present the number of covariates, RMSE, MAE, R^2 , aR^2 , and calibration slope for each model. We will present the model coefficient values for best model in each of the

three categories. Finally, we will investigate the utility of the best model to predict a 3% FRAX® threshold based on the actual FRAX® without BMD score.

Figure 4.10 Density Plot of FRAX® Hip without BMD



4.2.2.1.1 Basic Linear Regression Models

A null model was fit to the data by taking the mean of the actual FRAX® scores and comparing it to the actual values to calculate the RMSE and MAE. A linear regression model using both an untransformed outcome as well as a log-transformed (LN) outcome were fit, as well as backwards stepwise regression models for both the untransformed and log-transformed outcomes. The model error terms are presented as Table 4.13. Additionally we tested only age in the model which produced an aR^2 of 0.29 with an untransformed FRAX® score and a aR^2 of 0.09 when log transformed. The null model produced a RMSE of 7.38 and a MAE of 4.94 which means that for a model to be more informative than a random guess they must have a lower error term than these values. The linear and LN linear models have very similar RMSE, but the LN

model has a much lower MAE. These correspond to very similar R^2 and aR^2 values with the LN model having a superior aR^2 . The untransformed model has a better calibration slope, but the LN model is only 0.17 away from a perfect slope. The backwards stepwise models are similar to the basic models in that the untransformed and LN have very similar results. Echoing the basic models, it is LN model which achieves the best aR^2 , with a value of 0.3736 the largest aR^2 , however this model includes 7 more variables than the untransformed model, which may indicate a need for a more intensive evaluation if this model is found to be better than the LASSO and elastic net models.

Table 4.13 Hip without BMD Linear Model Error Terms

Analysis	# var	RMSE	MAE	R2	aR2	Slope
Null Model	-	7.05	4.52	-	-	-
Linear Model	71	4.64	2.97	0.37	0.32	0.86
LN Linear Model	71	4.41	2.41	0.43	0.38	0.98
Backwards Stepwise	28	4.66	2.95	0.37	0.34	0.86
LN Backwards Stepwise	31	4.44	2.40	0.42	0.40	1.00

var: Number of variables used in the model

RMSE: Root Mean Squared Error

MAE: Mean Absolute Error

aR2: Adjusted R^2

4.2.2.1.2 LASSO Models for Hip without BMD

The error terms for the LASSO models predicting hip without BMD both untransformed and LN are presented as Table 4.14

Table 4.14 LASSO Hip without BMD Model Results

Analysis	# var	RMSE	MAE	R ²	aR ²	Slope
LASSO MSE 1se	5	4.82	3.06	0.32	0.319713	1.26
LASSO MSE λ minimum	26	4.60	2.87	0.38	0.363651	0.95
LASSO MAE 1se	5	4.69	2.95	0.36	0.353706	1.17
LASSO MAE λ minimum	19	4.59	2.86	0.39	0.37312	0.98
LN LASSO MSE 1se	59	4.76	2.52	0.34	0.291101	0.82
LN LASSO MSE λ min	70	4.45	2.41	0.42	0.372676	0.99
LN LASSO MAE 1se	56	4.67	2.49	0.36	0.318562	0.86
LN LASSO MAE λ min	71	4.44	2.41	0.43	0.373555	0.99

Compared to the null model all 8 LASSO models represent a decrease in RMSE and MAE. The models with the least number of variables are the untransformed 1se models (6 variables in both), while the LN λ minimum models retain the most variables (75 and 81). The LN MAE λ minimum model represents the smallest RMSE and the smallest MAE. This model also represents the largest R², but the use of 81 variables allows the untransformed MSE λ minimum model to produce a superior aR² (0.362 compared to 0.360). In the LN models it appears that overfitting did occur as the models with the most variables did produce the largest R² values. As opposed to both with BMD models, for the first time a λ minimum has been chosen as the optimal model, but the use of MAE shrinkage parameter has held constant. Based on the optimal aR², the untransformed λ minimum MAE model is the optimal LASSO model.

4.2.2.1.3 Elastic Net Hip without BMD

The error terms for the elastic net models predicting hip without BMD are presented as Table 4.15. The best model is chosen by a maximum aR².

Table 4.15 Elastic Net Hip without BMD Model Results

Analysis	# var	RMSE	MAE	R ²	aR ²	Intercept
Enet MSE 1se	4	4.84	3.09	0.32	0.312698	1.27
Enet MSE λ min	28	4.60	2.88	0.38	0.36154	0.94
Enet MAE 1se	5	4.69	2.94	0.36	0.355607	1.17
Enet MAE λ min	19	4.59	2.86	0.39	0.373274	0.98
LN Enet MSE 1se	59	4.81	2.53	0.33	0.275869	0.80
LN Enet MSE λ min	70	4.45	2.41	0.42	0.372893	0.99
LN Enet MAE 1se	56	4.70	2.50	0.35	0.309951	0.85
LN Enet MAE λ min	71	4.44	2.41	0.42	0.37312	0.99

All 8 elastic net models represent a decrease in RMSE and MAE compared to the null model. The number of variables retained by the models range from 6 to 81 with an optimal choice of 21 variables in the MAE λ minimum model. The smallest RMSE and MAE were found in the LN λ minimum models. The largest R² was found in the same models, however their retention of 40 more variables than the MAE λ minimum model reduced their aR². The best elastic net model would be the LN MAES λ minimum with an aR² of 0.37380.

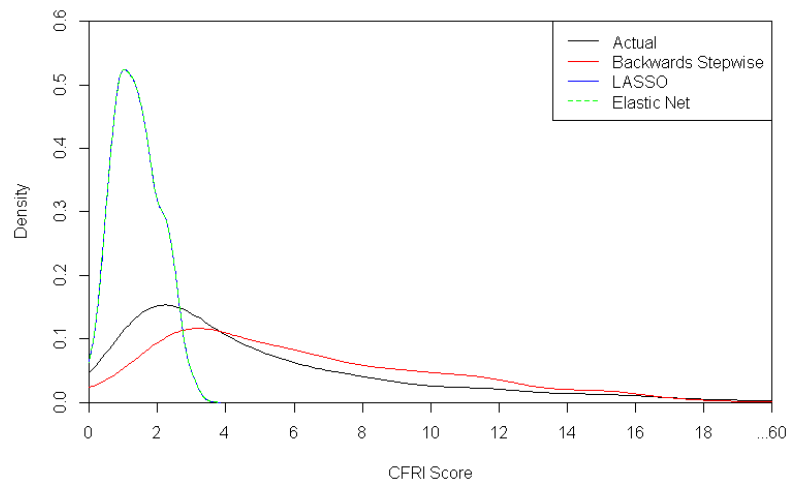
4.2.2.1.4 Comparison of the best linear hip without BMD models

The three models with the best aR², log transformed backwards stepwise, LASSO MAE λ minimum, and Elastic Net MAE λ minimum are compared in this section. The model error results are presented as Table 4.16. Additionally a kernel density plot of the predicted values compared to the actual values is presented as Figure 4.11.

Table 4.16 Comparison of the best linear hip without BMD models

Analysis	# var	RMSE	MAE	R ²	aR ²	Slope
LN Backwards Stepwise	31	4.44	2.40	0.42	0.40	1.00
LN LASSO MAE λ min	71	4.4460	2.414.3	0.43	0.373555	0.99
LN Enet MAE λ min	71	4.44	2.41	0.42	0.37312	0.99

Figure 4.11 Kernel Density plot of best 3 linear hip without BMD models



Based on the optimal aR^2 the LN backwards stepwise model would be chosen as the optimal model. This model also results in a smaller RMSE and MAE compared to the LASSO and Elastic Net models, but a larger slope. The inclusion of 42 variables may make this model more difficult to implement than the LASSO and Elastic Net models which include 21 variables. A scatter plot comparing CFRI values to FRAX® values for the LN backwards stepwise model are presented as Figure 4.12. Much like the with BMD models, this model does a poor job of predicting larger values. However, there are more values >20% predicted by the without BMD model than the with BMD model. The calibration equation is an intercept of 0.18 indicating systematic over prediction, and a slope of 1.18 indicating more extremely high predictions.

The model coefficients for the three optimal models are presented as Table 4.17. The LASSO and Elastic Net models produce very similar model coefficients, while the LN backwards model chose a much larger proportion of variables. The LN backwards model has a very small intercept and does not choose the basic linear age variable, only choosing the interaction terms. Osteoporosis was only chosen by the LN backwards model; however other

rheumatologic conditions were chosen by all 3 models. Both RA and glucocorticoid use were retained by the backwards stepwise model, important as both of these are FRAX variables.

Vertebral fractures were not chosen by the LN Backwards model which is surprising as this has been a covariate with a lot of importance in the other models.

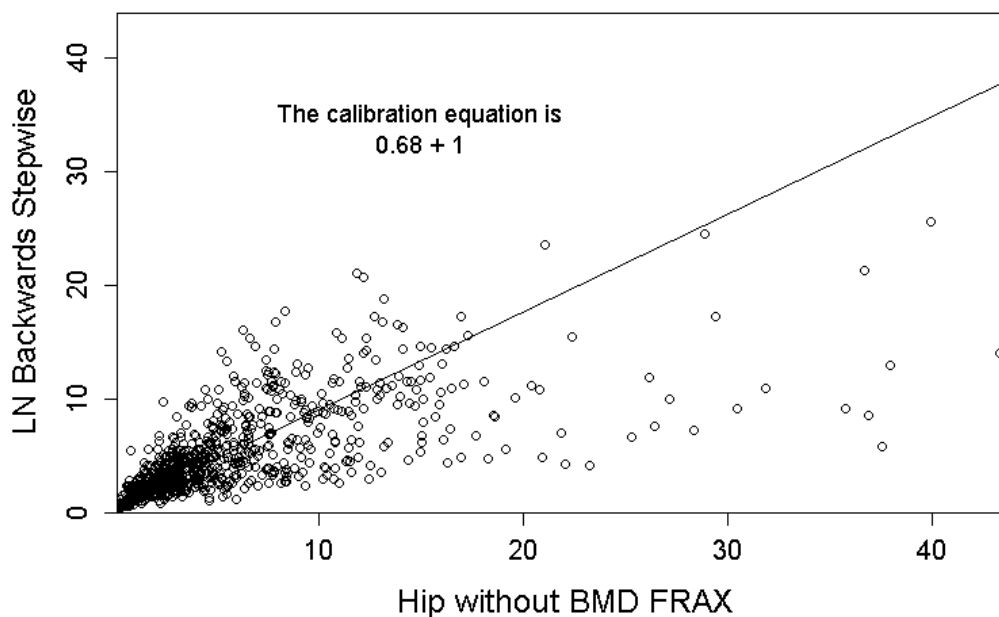
Table 4.17 Model Coefficients for Best Linear Hip without BMD

Attribute	LN Backwards	LASSO	Elastic Net
Intercept	13.17578348	-14.64248951	-14.66588037
Linear Age	-0.866260403	0.27164329	0.272105604
Age*Age	0.015398691	-	-
Age*Age*Age	-7.90E-05	-1.01E-05	-1.01E-05
Osteoporosis, N (%)	0.229939204	0.222514387	0.222569808
Lifestyle Factors, N (%)			
Alcohol Abuse	-	0.122297091	0.122448237
Falling	-	-0.026516442	-0.026598521
Vitamin D insufficiency	-	-0.014849375	-0.014874305
Genetic factors, N (%)			
Hypophosphatasia	0.524734704	0.537278564	0.537600674
Porphyria	-	0.237003518	0.237474064
Hemochromatosis	-	-0.383729672	-0.384098864
Hypogonadal states, N (%)			
Anorexia nervosa and bulimia	-	0.036913963	0.037275547
Premature ovarian failure	-0.290420231	-0.283755078	-0.283977476
Endocrine disorders, N (%)			
Diabetes mellitus (Type 1 & 2)	-0.159199428	-0.151566746	-0.151581912
Cushing's syndrome	-	0.555982822	0.557516197
Hyperparathyroidism	-	0.023518619	0.023590833
Central Adiposity	-0.264133914	-0.247525444	-0.247545026
Thyrotoxicosis	-	-0.002949795	-0.002960049
Gastrointestinal disorders, N (%)			
Celiac disease	-	-0.047753991	-0.048415943
Inflammatory Bowel Disease	-	-0.130820793	-0.131246614
Malabsorption	0.201816013	0.214086422	0.214472907
Pancreatic disease	0.18872779	0.114123204	0.114351762
Primary biliary cirrhosis	-	-0.064469809	-0.06495293
Crohn's Disease	0.168869922	0.230157155	0.230508762
Hematologic disorders, N (%)			
Hemophilia	-0.200298838	-0.165713083	-0.165919394

Attribute	LN Backwards	LASSO	Elastic Net
Thalassemia	-	-0.194978508	-0.195106538
Rheumatologic and autoimmune diseases, N (%)			
Ankylosing spondylitis	-	-0.041700591	-0.041807668
Lupus	0.207871113	0.21903413	0.219306833
Rheumatoid arthritis	0.342872904	0.35306675	0.353169056
Gout	-	0.033198394	0.033256117
Polymyalgia Rheumatica	0.141430641	0.145797399	0.145918519
Central nervous system disorders, N (%)			
Epilepsy	0.192915433	0.23073996	0.230959668
Parkinson's disease	-	0.145371534	0.145546936
Stroke	-0.079886673	-0.068076657	-0.068175056
Multiple sclerosis	-	-0.146151049	-0.146393999
Spinal cord injury	-	0.29836054	0.298972168
Alzheimer's disease	-	0.005265918	0.005484316
Miscellaneous conditions and diseases, N (%)			
Congestive Heart Failure	-	-0.004329417	-0.004410815
Liver Disease	0.105682215	0.089888081	0.089980881
Depression	-	0.006727432	0.006786355
Amyloidosis	0.630966755	0.476481045	0.476922038
End stage renal disease	-	-0.011448349	-0.011725172
Sarcoidosis	-	0.175679785	0.17580929
Chronic metabolic acidosis	0.347989776	0.335727973	0.335885424
Asthma/Chronic obstructive lung disease	-	0.000365177	0.000465412
Idiopathic scoliosis	-	0.059342503	0.059460451
Cataracts	-	0.040081371	0.040034303
Glaucoma	-	-0.002327282	-0.002430932
Kyphosis	0.093857352	0.088096049	0.088190437
Disorders of the eye	-	0.002000466	0.002046483
Osteoarthritis	-	-	-
Renauld's syndrome	-	-0.050327517	-0.05058248
Medications, N (%)			
Cyclosporine A and tacrolimus	-	0.019318383	0.019777256
Proton pump inhibitors	-0.045768346	-0.041372602	-0.04140867
Anticoagulants	-	0.01146825	0.011518812
Selective serotonin reuptake inhibitors	-	0.00331476	0.003358391
Aromatase inhibitors	-	-0.077371264	-0.077473724
Thiazolidinediones	-	-0.130218783	-0.130354479
Barbiturates	-	-0.274449874	-0.275247521
Lithium	-	-0.335272217	-0.335507472
Methotrexate	0.272679731	0.262703651	0.262745281

Attribute	LN Backwards	LASSO	Elastic Net
Glucocorticoids	0.103682447	0.106835672	0.10679937
Hormone Replacement Therapy	0.169297399	0.158392457	0.158442204
Fractures			
Other Sites	0.255680069	0.235075732	0.235262231
Race			
African-American	-0.926065479	-0.904729485	-0.904716208
Hispanic	-0.622755009	-0.573563018	-0.574002918
Asian	-0.431379367	-0.410321297	-0.410296945
Other	-0.538443005	-0.501412749	-0.501542105

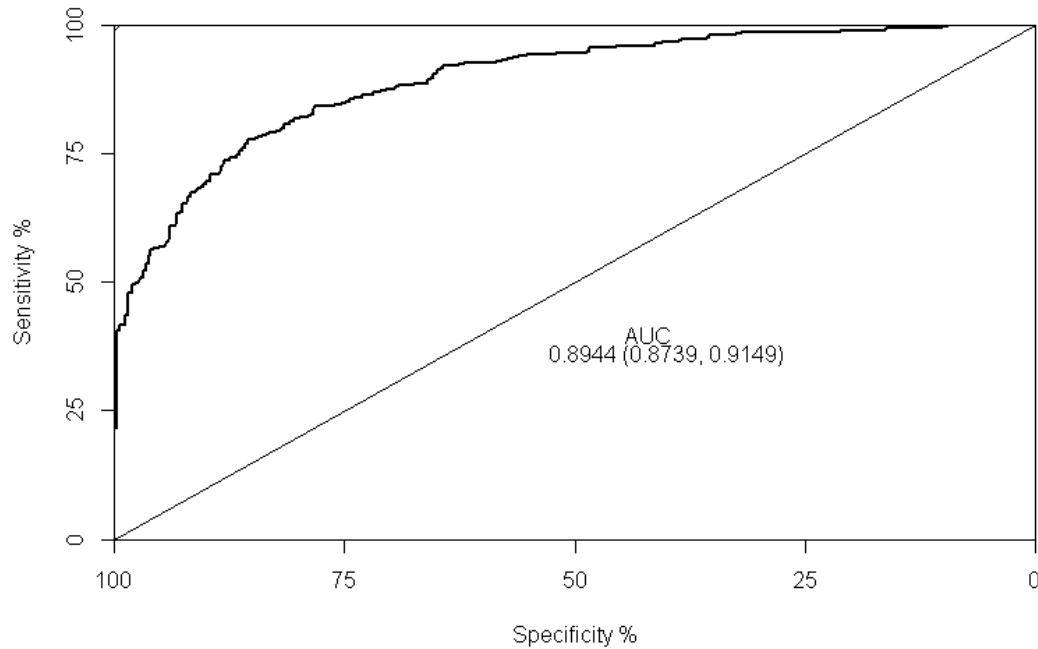
Figure 4.12 Best Hip without BMD model scatterplot



To determine the model's ability to determine the patients who truly should be treated (Hip $\geq 3\%$) based on the NOF guidelines we calculated a receiver operating curve and area under the curve (Figure 4.13). Overall the model seems to do a very good job of predicting who had a FRAX® hip without BMD score of $\geq 3\%$ as evidenced by an AUC of 0.912 (95% 0.896, 0.927).

Although the model requires 42 variables, 91% of the time it is able to correctly identify patients who had a treatment level Hip without BMD FRAX® score.

Figure 4.13 Receiver Operating Curve for Hip without BMD



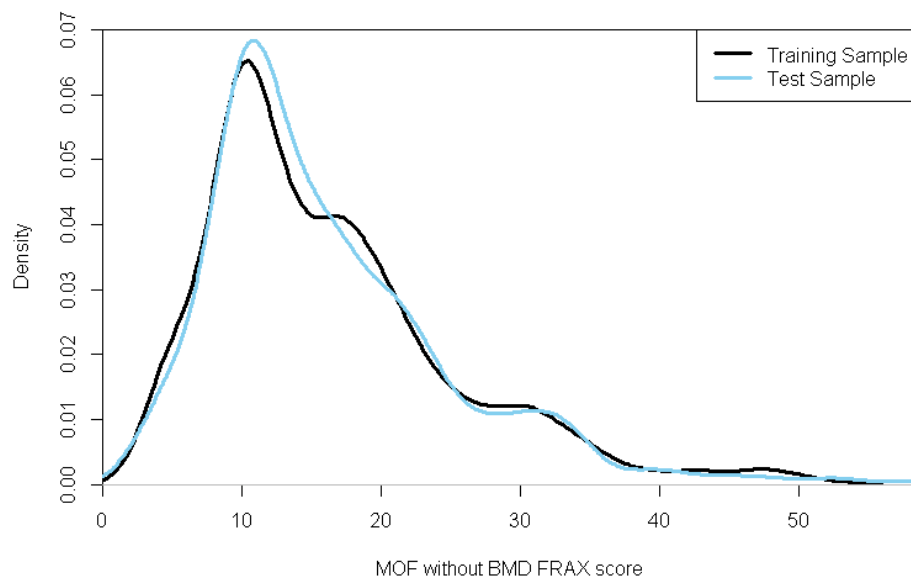
4.2.2.1.5 High-Dimensional Variable Selection

For hip without BMD the high-dimensional variable selection added 134 medication classes, 145 different diagnoses, and 702 procedural classes. When combined with the 87 content variables, there were 1,068 different variables for the elastic net model to evaluate. After evaluation the MAE λ minimum model was found to be the superior elastic net model, selecting 44 variables with 7 medication classes, 8 diagnosis codes, and 15 procedure codes. However the aR^2 for this model was 0.338 which was less than the LN backwards stepwise model. Therefore the choice of the best model does not change the choice of model for Hip without BMD.

4.2.2.2 Continuous Prediction of Major Osteoporotic Fracture without BMD

Models were built for the prediction of MOF without BMD FRAX® score. All patients were utilized for this prediction as everyone had all FRAX® risk factors, even if they didn't have a femoral neck BMD. The mean score of the training sample was 16.5 (SD 9.7) median 14.19 (IQR 9.98, 20.64), while the mean of the test sample was 16.2 (SD 8.8) median 13.82 (IQR 10.22, 20.40). A kernel density plot of the distribution of hip without BMD FRAX® for the training and test sample is presented as Figure 4.14. The hip without BMD scores range from 0.96 to 58.48 with both of the extremes being present in the test sample. Similar methods were used to evaluate model fit for the continuous score. We also evaluate model performance for predicting a 20% FRAX® threshold based on the actual FRAX® without BMD score.

Figure 4.14 Density Plot of FRAX® MOF without BMD



4.2.2.2.1 Basic Linear Regression Models

A null model was fit to the data by taking the mean of the actual FRAX® scores and comparing it to the actual values to calculate the RMSE and MAE. A linear regression model using both an untransformed outcome as well as a log-transformed (LN) outcome were fit, as well as backwards stepwise regression models for both the untransformed and log-transformed outcomes. The model error terms are presented as Table 4.18. When only age is introduced into the model an aR^2 of 0.20 is produced for the untransformed and 0.16 for the log-transformed model. The null model produced a RMSE of 10.2 and a MAE of 7.8. The linear and untransformed backwards stepwise model have very similar results for all error terms other than the backwards stepwise model using 46 less variables and producing a marginally better aR^2 . The LN models have less error and a greater aR^2 compared to their untransformed counterparts. The backwards stepwise model out performs the linear LN model producing an aR^2 of 0.44, the best basic linear model. The slopes for all 4 models are nearly 1 with the untransformed less than 1, and the LN slightly more than 1.

Table 4.18 MOF without BMD Basic Linear Model Error Terms

Analysis	# var	RMSE	MAE	R2	aR2	Slope
Null Model	NA	9.66	7.21	NA	NA	NA
Linear Model	71	6.62	4.99	0.43	0.38	0.93
LN Linear Model	71	6.51	4.52	0.45	0.40	0.96
Backwards Stepwise	26	6.64	4.97	0.43	0.41	0.93
LN Backwards Stepwise	28	6.56	4.54	0.44	0.43	0.97

var: Number of variables used in the model

RMSE: Root Mean Squared Error

MAE: Mean Absolute Error

aR2: Adjusted R^2

4.2.2.2.2 LASSO Models for MOF without BMD

The error terms for the LASSO models predicting hip without BMD both untransformed and LN are presented as Table 4.19.

Table 4.19 LASSO MOF without BMD Model Results

Analysis	# var	RMSE	MAE	R2	aR2	Slope
LASSO MSE 1se	9	6.85	5.15	0.39	0.387622	1.22
LASSO MSE λ minimum	30	6.64	4.97	0.43	0.411414	1.02
LASSO MAE 1se	12	6.73	5.04	0.42	0.406755	1.13
LASSO MAE λ minimum	35	6.63	4.96	0.43	0.40825	1.01
LN LASSO MSE 1se	16	6.80	4.64	0.40	0.39167	1.07
LN LASSO MSE λ min	57	6.66	4.59	0.43	0.386494	0.96
LN LASSO MAE 1se	26	6.74	4.61	0.41	0.395688	1.03
LN LASSO MAE λ min	70	6.52	4.54	0.45	0.40339	0.98

Compared to the null model, all 8 LASSO models represent a decrease in RMSE and MAE. The models with the least number of variables was the MSE 1se model with 9 variables, while the LN λ minimum models both nearly retained all variables. The LN λ minimum models represent the smallest error terms, but their high number of variables retained cause their aR^2 to be less than untransformed MAE 1se. Based on MAE, and slope the MAE 1se model only outperforms the MSE 1se model, however its retention of 15 variables seems to be the factor which is most associated with a superior aR^2 .

4.2.2.2.3 Elastic Net Hip without BMD

The error terms for the elastic net models predicting MOF without BMD are presented as Table 4.20. The best model is chosen by a maximum aR^2 .

Table 4.20 Elastic Net MOF without BMD Model Results

Analysis	# var	RMSE	MAE	R ²	aR ²	Intercept
Enet MSE 1se	9	6.86	5.16	0.39	0.386481	1.22
Enet MSE λ min	30	6.64	4.97	0.43	0.411434	1.02
Enet MAE 1se	12	6.73	5.04	0.42	0.407091	1.13
Enet MAE λ min	37	6.63	4.96	0.43	0.406835	1.01
LN Enet MSE 1se	16	6.81	4.64	0.40	0.391296	1.07
LN Enet MSE λ min	59	6.66	4.59	0.43	0.385339	0.96
LN Enet MAE 1se	26	6.74	4.61	0.41	0.395865	1.03
LN Enet MAE λ min	70	6.52	4.54	0.45	0.403456	0.98

All 8 elastic net models represent a decrease in RMSE and MAE compared to the null model. The number of variables retained by the models range from 11 to 84 with an optimal choice of 15 variables in the MAE 1se model. The smallest RMSE and MAE were found in the LN λ minimum models. The largest R² was found in the same models, however their retention of 40 more variables than the MAE λ minimum model reduced their aR². The best elastic net model would be the MAE λ minimum with an aR² of 0.42. It appears that the penalization can create models with a better fit, however the retention of a large number of variables causes the predictive ability to suffer.

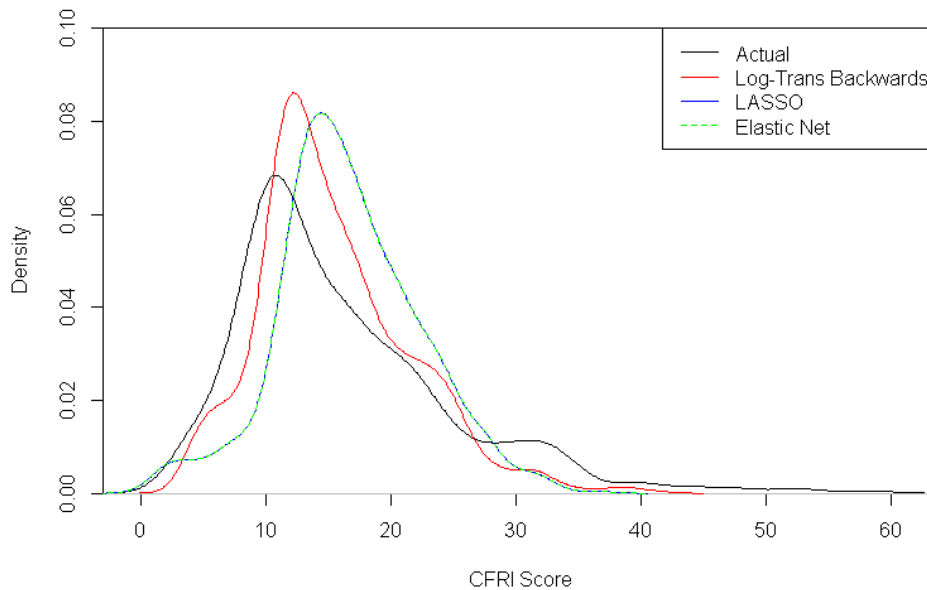
4.2.2.2.4 Comparison of the best linear MOF without BMD models

The three models with the best aR², log transformed backwards stepwise, LASSO MAE 1se, and Elastic Net MAE 1se are compared in this section. The model error results are presented as Table 4.21. Additionally a kernel density plot of the predicted values compared to the actual values is presented as Figure 4.15.

Table 4.21 Comparison of the best linear MOF without BMD models

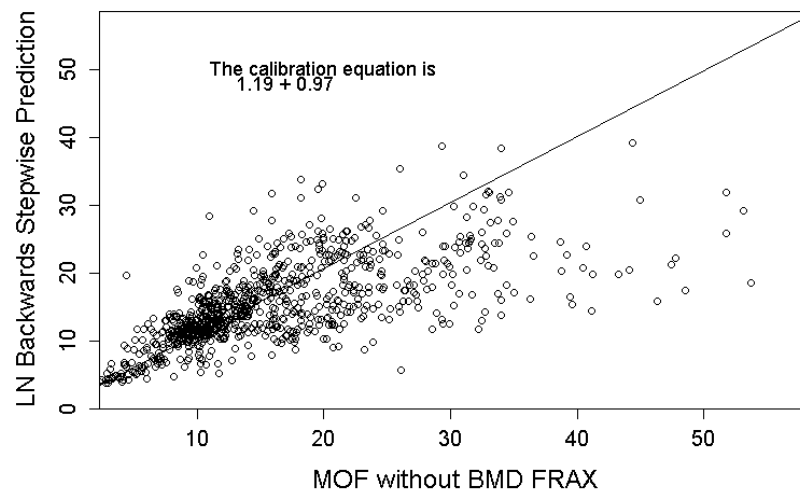
Analysis	# var	RMSE	MAE	R ²	aR ²	Slope
LN Backwards Stepwise	28	6.56	4.54	0.44	0.43	0.97
LASSO MSE λ minimum	30	6.64	4.97	0.43	0.41	1.02
Enet MSE λ min	30	6.64	4.97	0.43	0.41	1.02

Figure 4.15 Kernel Density plot of best 3 linear MOF without BMD models



Based on the optimal aR^2 the LN backwards stepwise model would be chosen as the optimal model. The LN backwards stepwise model outperforms the LASSO and elastic net models in all aspects. Similar to the Hip without BMD model, 42 variables are necessary to calculate the model. A scatter plot comparing CFRI values to FRAX® values for the LN backwards stepwise model are presented as Figure 4.16. This model seems to do the best job in predicting larger values, however with an intercept of 0.73 and slope of 1.03 the estimates are likely to be higher than expected. This is evident in the lower value predictions, which account for the model under predicting the larger values.

Figure 4.16 Best MOF without BMD model scatterplot



The coefficients for the three optimal linear models are presented as Table 4.22. Unlike the Hip without BMD, the intercept in the LN backwards model is large, and it retains age as well as age² and age³. In the MOF with BMD model's osteoporosis was only retained by the LN backwards stepwise model, however RA and glucocorticoids were retained by all 3 models. Fractures again were important variables, although the LN backwards model did not retain vertebral fractures. Overall within the LN backwards model most coefficients were very close to 1, while the LASSO and elastic net gave large weights to certain variables. In the end retaining more variables created a more harmonious model.

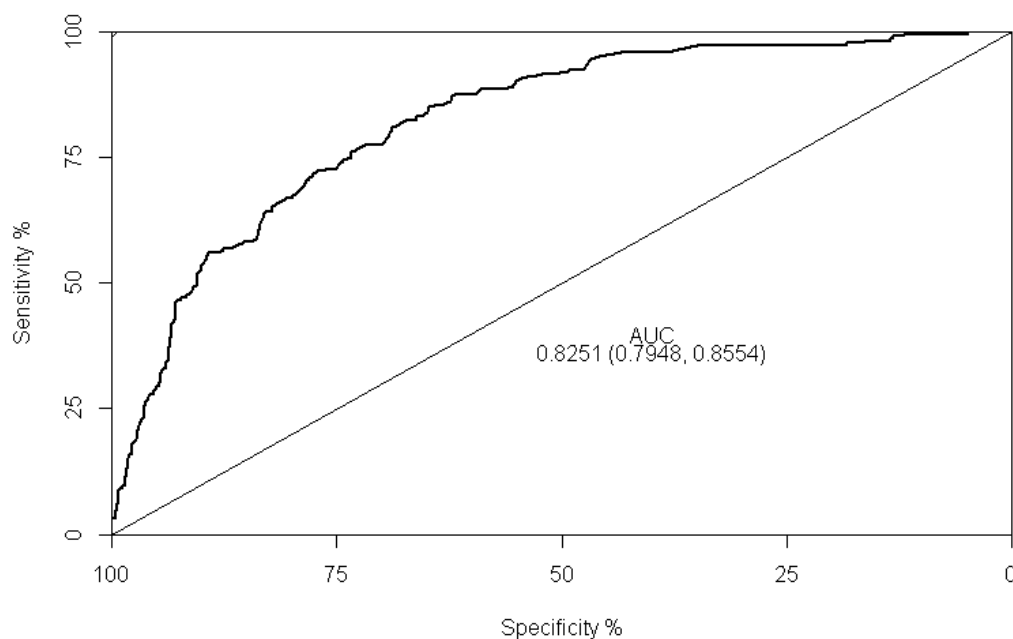
Table 4.22 Model Coefficients for Linear MOF without BMD

Attribute	LN Backwards	LASSO	Elastic Net
Intercept	22.25687045	-34.75496345	-34.79540886
Linear Age	-0.914502808	0.631668782	0.632320338
Age*Age	0.013336948	-	-
Age*Age*Age	-6.15E-05	-	-
Age*Osteoporosis	0.001681857	0.031372562	0.031419748
In 365-days prior to index			
Genetic factors			
Hypophosphatasia	0.281333375	2.471804805	2.518598059
Endocrine disorders			
Diabetes mellitus (Type 1 & 2)	-0.075335158	-0.538547956	-0.550364407
Central Adiposity	-0.109487081	-0.630311366	-0.649100307
Gastrointestinal disorders			
Inflammatory Bowel Disease	-0.108489108	-	-
Malabsorption	0.126877713	-	0.018374218
Crohn's Disease	0.142616646	0.969026877	0.985987218
Hematologic disorders			
Hemophilia	-0.119944794	-	-
Rheumatologic and autoimmune diseases			
Lupus	0.183524351	4.224023436	4.273632872
Rheumatoid arthritis	0.205507803	3.678520605	3.682881305
Gout	-	0.131721248	0.160127861
Polymyalgia Rheumatica	0.107395123	1.921607036	1.940065485
Central nervous system disorders			
Epilepsy	0.105167629	0.262548636	0.29712851
Stroke	-0.064792173	-0.621698485	-0.643372224
Miscellaneous conditions and diseases			
Liver Disease	0.077038137	0.77347816	0.791006586
Amyloidosis	0.532356113	7.206598946	7.340628687
Chronic metabolic acidosis	0.269888216	2.361874215	2.387891671
Idiopathic scoliosis	-	0.215785508	0.233170932
Obesity	-	-0.017332243	-0.017848227
Disorders of the eye	-	0.055497184	0.063399475
Osteoarthritis	-	0.032683451	0.037207593
Medications			
Selective serotonin reuptake inhibitors	-	0.199330688	0.211959154
Anticonvulsants	-	0.032115648	0.040350409
Methotrexate	0.208599974	2.954033763	2.975039838
Glucocorticoids	0.063924749	1.223561653	1.224988434
Hormone Replacement Therapy	0.098549558	1.341015845	1.353681926

Attribute	LN Backwards	LASSO	Elastic Net
Fractures			
Non-MOF	0.210669732	2.777596	2.794245798
Race			
White	-	4.045799614	4.023977424
African-American	-0.852807121	-5.353985077	-5.382784744
Hispanic	-0.491561947	-0.198996407	-0.299415187
Asian	-0.438087007	-	-
Other	-0.497591055	-	-0.030258459

To determine the model's ability to identify patients who truly should be treated (MOF $\geq 20\%$) based on the NOF guidelines we calculated a receiver operating curve and area under the curve (Figure 4.17). Overall the model seems to do a very good job of predicting who had a FRAX® MOF without BMD score of $\geq 20\%$ as evidenced by an AUC 0.825 (0.794, 0.855). However the without BMD model increases the AUC over the with BMD model by only 0.03 indicating a similar fit for both.

Figure 4.17 Receiver Operating Curve for MOF without BMD



4.2.2.2.5 High-Dimensional Variable Selection

For MOF without BMD there were 134 medication classes, 145 different diagnoses, and 702 procedural classes. When these were added to the 87 content variables there were 1,068 different variables for the elastic net model to evaluate. After evaluation the MAE 1se model was found to be the superior elastic net model, selecting 20 variables, however the aR^2 for this model was 0.397 which was less than the LN backwards stepwise model. Therefore the choice of the best model does not change the choice of model for MOF without BMD.

4.3 Summary

Overall the regression techniques were able to predict FRAX® at a fair rate. The with BMD models produced much lower aR^2 with fewer variables than the without BMD models. Age was the variable which was most influential in each of the models, which confirms other studies findings of the influence of age on fracture. In the without BMD cohorts as well as the without BMD MOF cohort age, RA, and glucocorticoids which are all FRAX® variables were also variables in CFRI. However in the with BMD hip prediction only age was similar between FRAX® and CFRI. Age was the most influential variable overall, and the variables which could reliably be identified in claims which also appeared in FRAX® were included in 3/4 models. It is likely that the small variation in hip with BMD score caused the non-inclusion of any additional variables including the FRAX® variables which the other models expressed. More descriptive summaries of each of the models follow this section.

All four models appear to do a similar job at predicting the appropriate FRAX® threshold (3% in hip and 20% for MOF). It could be argued that due to the models high c-statistics in predicting the thresholds, they should only be used for this purpose, however this is greatly reduces the utility of the score. Therefore in Aim 2 we will determine how well CFRI actually

predicts fractures which will provide us with a better context of if it should be limited to only thresholds.

4.3.1 Hip with BMD

The model which produced the best hip with BMD CFRI score was elastic net model based on the 1se penalty. This model marginally outperformed the LASSO model of the same penalization method, and was able to account for 21% of all variation in the FRAX® score after adjustment for the number of variables included in the final model (aR^2). The final scores had a similar density distribution to the actual FRAX® scores, if only increased by a score of 3. Based on the scatterplot it appears that when the FRAX® score was low, the model did a good job of predicting, but was unable to predict extremely large scores. We are unaware of any models which this performance can be compared to.

When we evaluated the predictive ability of the CFRI score based on a 3% threshold (which is the Hip FRAX® treatment threshold from the NOF), a c-statistic of 0.85 was produced. This demonstrates that 85% of the time a CFRI score of 3% would have predicted a high or low risk patient in the same risk group as their actual FRAX® score. These findings suggest that a 3% threshold may be the appropriate threshold in a policy context to identify patients who should receive anti-osteoporosis medication.

4.3.2 MOF with BMD

When predicting MOF with BMD the same model, the elastic net model with the 1se penalty produced the best predictive model. MOF has a much wider spread of predictable values, however the model chosen only had 27 variables, so there could be much less variation in the estimates than in the real values. This is particularly evident by looking at the scatterplot of the predicted compared to actual scores, where the data points repeat themselves frequently in the

10-20% range. The small number of variables also prevents the model from making extreme predictions in the same range as the actual values, as other than Cushing's syndrome there are no variables which if present would be able to drive an estimate to an extreme value.

The MOF with BMD score based on the NOF threshold of 20% was associated with a c-statistic of 0.81 which indicates that 81% of the time patients were correctly identified as above or below the 20% threshold in CFRI compared to FRAX®. This suggests that the threshold of 20% can be used based on CFRI to identify high and low-risk patients based on NOF treatment thresholds.

4.3.3 Hip without BMD

The model which produced the best hip without BMD CFRI score was backwards stepwise model which was log transformed. Although this model wasn't able to deal with extreme predictions, its calibration slope of ~1 indicates that with enough data points it should be able to give good predictions. The aR^2 of 0.40 indicates that 40% of the variation in FRAX® hip without BMD could be accounted for by the predictive model, which was only 0.02 less than the without BMD MOF CFRI which was the highest aR^2 . The rationale behind better prediction for the without BMD compared to the with-BMD is first the spread of the data, although the means were similar the distribution of hip without BMD scores was much wider than with BMD. Second the increased n because we were able to use all women who were in the dataset rather than just the selection who had a femoral neck BMD. Lastly, this model included more variables 31 compared to 4 in the with BMD model, which allowed for more variation in scores, increasing the predictive ability. In some regards it says something about how few variables are really needed to predict FRAX®, but when used appropriately the increase in predictive ability is substantial.

When we evaluated the predictive ability of the CFRI score based on a 3% threshold (which is the Hip FRAX® treatment threshold from the NOF), a c-statistic of 0.89 was produced. This demonstrates that 89% of the time a CFRI score of 3% would have predicted a high or low risk patient in the same risk group as their actual FRAX® score. These findings suggest that a 3% threshold may be the appropriate threshold in a policy context to identify patients who should receive anti-osteoporosis medication. This c-statistic is better than the with BMD statistic of 0.84, based on these findings the without BMD score should be preferred over the with BMD score.

4.3.4 MOF with BMD

When predicting MOF without BMD the log-transformed backwards stepwise model produced the best aR^2 of 0.43 which incidentally was the best predictive ability for any of the four variations. The model used 28 variables which was one more than the hip without BMD model, and had a similar predictive ability. The spread of MOF without was similar to the hip without in that it was larger than the with BMD estimates. This offers some explanation for better predictions. Based on visual inspection the density distribution is more similar for these predictions than for any other variation.

Although the aR^2 is greater for the MOF without BMD, the hip without BMD had the best c-statistic, as the MOF without only produced a score of 0.83. This was 2% better than the with BMD estimate, so based on the increased aR^2 and c-statistic, the MOF without BMD CFRI score would be preferred to the with-BMD.

CHAPTER 5: AIM 2 RESULTS

Aim 2: Externally validate CFRI in a 20% random sample of Medicare beneficiaries by comparing the performance of CFRI and FRAX® to predict incident fractures.

Hypothesis 2: There will be no significant difference between FRAX® and CFRI to predict incident fractures as a continuous variable (calibration) between the linked and random sample.

Hypothesis 3: CFRI will identify fractures at a similar rate based on c-statistics in the random sample as FRAX® in the linked sample (discrimination).

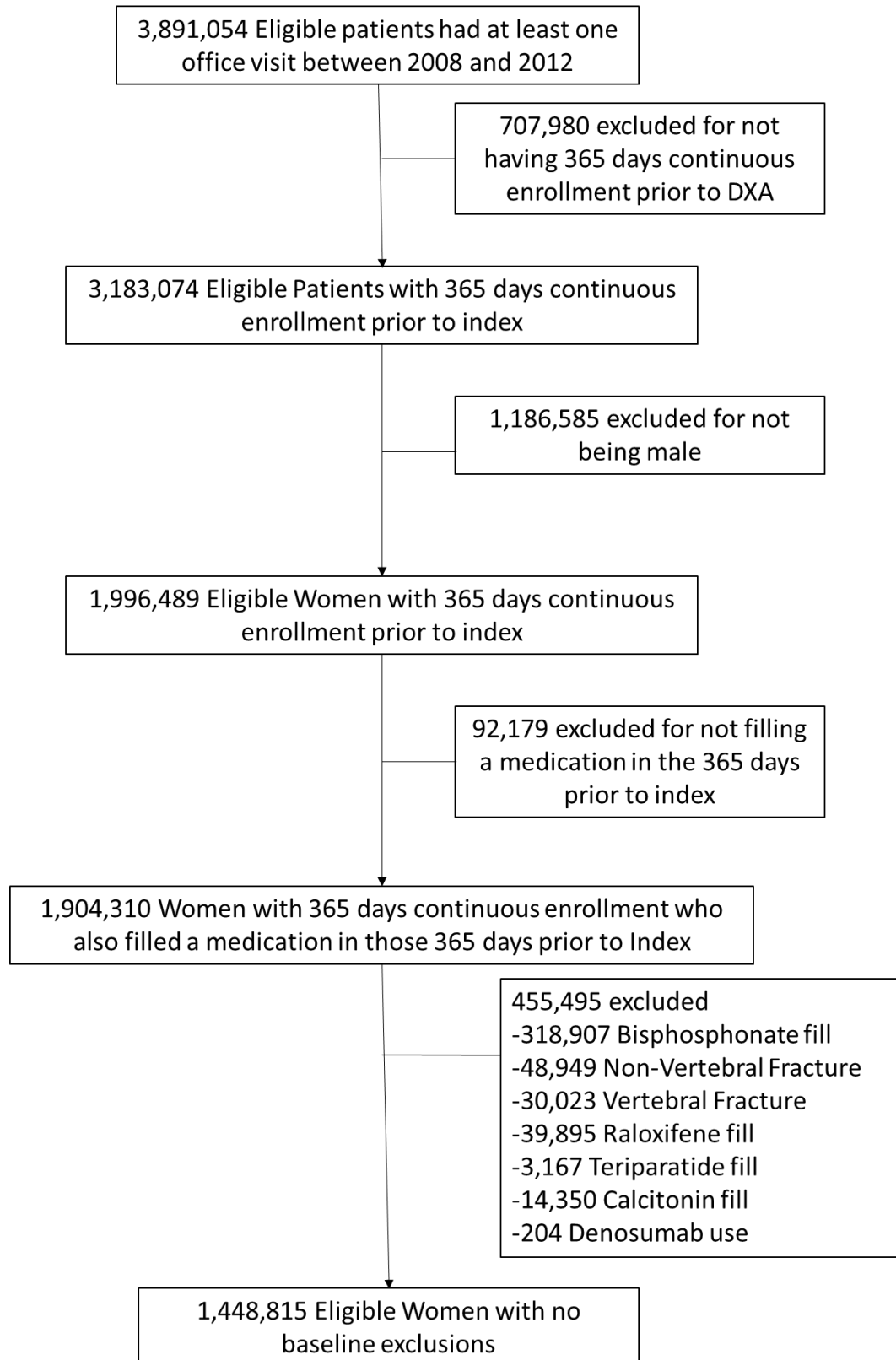
5.1 Study Population

The Aim 2 population is comprised of two separate cohorts from two different data sources, herein referred to as the linked and random populations. The linked population is the same cohort used from Aim 1. Specific details on this population and methods for linkage can be found in Section 3.1.3.

The random population is comprised of Medicare eligible females (age ≥ 65) who had at least 365-days continuous Medicare Parts A, B, and D enrollment prior to an office visit between 2008 and 2012. When an office visit met this criterion it was kept as an eligible date, however only the first office visit of any given calendar year could then be used to define the index date. If a woman had multiple years which met the enrollment criterion we randomly chose one year for the analysis. Additionally we required patients to be AOM naïve (bisphosphonate,

Raloxifene, Teriparatide, Calcitonin) and no inpatient or outpatient claims for a MOF in the 365-day wash-out period. A flowchart detailing exclusions is presented as Figure 5.1. Overall there were 1,448,815 women who met all inclusion criteria.

Figure 5.1 Aim 2 Random Population Selection Flowchart



For the comparison of the linked population, the model coefficients from the four optimal models from Aim 1, were culled and predicted values were created for everyone in the linked cohort, thereby dissolving the test and training samples. However the with (n=2,798) and without BMD (n=2,860) populations were preserved.

In the random population, all available patients were used to create the ROC curves for CFRI both with and without BMD. Model coefficients from the 4 relevant models from the Aim 1 results were used to calculate the CFRI score (Table 4.6, Table 4.10, Table 4.17, Table 4.22). The outcomes of interest were hip fracture or MOF within 1 year of the index date (index date = DXA for the linked population and an office visit for the random population). The algorithms used to evaluate the fractures are presented in Table 3.3. Patients were followed up to one year after their index office visit until occurrence of fracture, death, or loss continuous enrollment. If death, loss of continuous enrollment, or 365-days from index occurred prior to a fracture then the patient was administratively censored.

5.1.1 Characteristics of the Random Population

There were 1,444,815 women who met all inclusion criteria previously specified. Specifics of the random population are presented as Table 5.1. The mean age of the population was 76.0 (SD 8.2). The population was predominantly white (83.6%), and the index dates were relatively evenly spread between 2008 and 2012 with 16.9% in 2010 representing the smallest number and 26.2% in 2012 the highest. The most prevalent characteristic in the random population was disorders of the eye (53.5%), cataracts (36.4%), diabetes (32.1%), osteoarthritis (29.8%), use of a proton pump inhibitor (27.3%), kyphosis (24.4%), and asthma/COPD (21.3%).

Table 5.1. Population Characteristics of the Random Population

Attribute	Random Population (n=1,444,815)	Linked without BMD Population (n=2,860)
Mean Age	76.0 (8.2)	75.4 (7.7)
Year of DXA		
2008	300,076 (20.7)	-
2009	250,133 (17.3)	164 (5.7)
2010	245,034 (16.9)	465 (16.3)
2011	274,074 (18.9)	811 (28.4)
2012	379,498 (26.2)	703 (24.6)
In 365-days prior to index		
Osteoporosis, N (%)	164772 (11.4)	1252 (43.8)
Lifestyle Factors, N (%)		
Alcohol Abuse	4589 (0.3)	9 (0.3)
Falling	67499 (4.7)	151 (5.3)
Vitamin D insufficiency	112862 (7.8)	815 (28.5)
Excess Vitamin A	67 (<0.1)	<11
Genetic factors, N (%)		
Cystic fibrosis	360 (<0.1)	<11
Homocystinuria	1580 (0.1)	<11
Osteogenesis imperfecta	106 (<0.1)	<11
Hypophosphatasia	4803 (0.3)	14 (0.5)
Gaucher's disease	2200 (0.2)	<11
Idiopathic hypercalciuria	4 (<0.1)	<11
Porphyria	228 (<0.1)	<11
Glycogen storage diseases	128 (<0.1)	<11
Marfan syndrome	47 (<0.1)	<11
Riley-Day syndrome	37 (<0.1)	<11
Hemochromatosis	390 (<0.1)	<11
Hypogonadal states, N (%)		
Androgen insensitivity	40 (<0.1)	<11
Anorexia nervosa and bulimia	15901 (1.1)	25 (0.9)
Hyperprolactinemia	292 (<0.1)	<11
Premature ovarian failure	807 (0.1)	<11
Athletic amenorrhea	853 (0.1)	<11
Turner and Klinefelters's syndromes	30 (<0.1)	<11
Panhypopituitarism	92 (<0.1)	<11
Endocrine disorders, N (%)		
Adrenal insufficiency	525 (<0.1)	<11
Diabetes mellitus (Type 1 & 2)	465292 (32.1)	584 (20.4)
Cushing's syndrome	617 (<0.1)	<11
Hyperparathyroidism	13700 (0.9)	134 (4.7)
Central Adiposity	82981 (5.7)	206 (7.2)

Thyrotoxicosis	29324 (2.0)	46 (1.6)
Gastrointestinal disorders, N (%)		
Celiac disease	2244 (0.2)	21 (0.7)
Gastric bypass	0 (<0.1)	<11
Inflammatory Bowel Disease	11925 (0.8)	55 (1.9)
Malabsorption	6224 (0.4)	46 (1.6)
Pancreatic disease	15713 (1.1)	38 (1.3)
Primary biliary cirrhosis	1355 (0.1)	13 (0.5)
Crohn's Disease	54925 (3.8)	139 (4.9)
Hematologic disorders, N (%)		
Hemophilia	31298 (2.2)	50 (1.7)
Thalassemia	734 (0.1)	<11
Sickle cell anemia	290 (<0.1)	<11
Systemic mastocytosis	150 (<0.1)	<11
Rheumatologic and autoimmune diseases, N (%)		
Ankylosing spondylitis	16064 (1.1)	40 (1.4)
Lupus	6706 (0.5)	34 (1.2)
Rheumatoid arthritis	51970 (3.6)	201 (7.0)
Gout	45961 (3.2)	82 (2.9)
Polymyalgia Rheumatica	11961 (0.8)	81 (2.8)
Central nervous system disorders, N (%)		
Epilepsy	17014 (1.2)	45 (1.6)
Parkinson's disease	21173 (1.5)	22 (0.8)
Stroke	162004 (11.2)	273 (9.5)
Multiple sclerosis	4263 (0.3)	23 (0.8)
Spinal cord injury	1157 (0.1)	<11
Alzheimer's disease	159783 (11.0)	153 (5.3)
Miscellaneous conditions and diseases, N (%)		
AIDS/HIV	927 (0.1)	<11
Congestive Heart Failure	203151 (14.0)	204 (7.1)
Muscular dystrophy	408 (<0.1)	<11
Liver Disease	57151 (3.9)	139 (4.9)
Depression	206798 (14.3)	458 (16.0)
Amyloidosis	422 (<0.1)	<11
End stage renal disease	17938 (1.2)	21 (0.7)
Sarcoidosis	2647 (0.2)	17 (0.6)
Chronic metabolic acidosis	8682 (0.6)	28 (1.0)
Asthma/Chronic obstructive lung disease	307970 (21.3)	618 (21.6)
Idiopathic scoliosis	27901 (1.9)	122 (4.3)
Cataracts	527811 (36.4)	1359 (47.5)
Glaucoma	216032 (14.9)	427 (14.9)
Kyphosis	353679 (24.4)	2729 (95.4)

Obesity	82981 (5.7)	206 (7.2)
Disorders of the eye	774859 (53.5)	1833 (64.1)
Osteoarthritis	431348 (29.8)	1229 (43.0)
Renauld's syndrome	71213 (4.9)	112 (3.9)
Medications, N (%)		
Cyclosporine A and tacrolimus	1759 (0.1)	16 (0.6)
Proton pump inhibitors	395799 (27.3)	830 (29.0)
Anticoagulants	159834 (11.0)	250 (8.7)
Selective serotonin reuptake inhibitors	275156 (19.0)	481 (16.8)
Anticonvulsants	181120 (12.5)	387 (13.5)
Aromatase inhibitors	21560 (1.5)	88 (3.1)
GnRH (Gonadotropin releasing hormone) antagonists and agonists	1 (<0.1)	<11
Thiazolidinediones	52990 (3.7)	32 (1.1)
Barbiturates	184 (<0.1)	<11
Lithium	3105 (0.2)	<11
Methotrexate	14478 (1.0)	88 (3.1)
Glucocorticoids	209563 (14.5)	632 (22.1)
Hormone Replacement Therapy	129708 (9.0)	342 (12.0)
Calcium	1 (<0.1)	<11
Vitamin D	11 (<0.1)	<11
Non-MOF, N (%)	53076 (3.7)	158 (5.5)
Race, N (%)		
White	1211099 (83.6)	2461 (86.0)
African-American	152101 (10.5)	333 (11.6)
Hispanic	34128 (2.4)	13 (0.5)
Asian	25397 (1.8)	22 (0.8)
Other	17051 (1.2)	21 (0.7)
All Cells with a total of 0 were suppressed; *: Includes Cataracts and Glaucoma <11: CMS does not allow cells with less than 11 patients to be presented		

Comparing the random population to the linked population reveals that the linked population had characteristics typically associated with fracture in greater quantities than the general (random) population. The largest difference was in kyphosis where 95.4% of the linked and only 24.4% of the random population had a claim. Next was osteoporosis, where 43.8% of the linked and only 11.4% of the random population had a claim, vitamin D insufficiently was 28.5% in the linked and only 7.8% in the random population, osteoarthritis was 43.0% in the

linked and only 29.8% in the random, and glucocorticoid use was 22.1% in the linked and 14.5% in the random. These conditions are all common in the population seen by CCF Rheumatologists, but not necessarily for the population as a whole. This may suggest that the random population is healthier in regards to bone health compared to the linked population.

However if evaluating general health, the random population was older (76.0 compared to 73.5 years of age), had more prevalent cases of diabetes (32.1% compared to 20.4%), Alzheimer's disease (11.0% compared to 5.3%), as well as CHF (14.0% compared to 7.1%). The majority of the other attributes were very similar between the random and linked populations. With a greater age and more diabetes, it may be that the random population was at a greater risk for death in the 365-days following index, compared to the linked population being at a greater risk for fracture.

5.2 Analysis

5.2.1 Hip with BMD CFRI score

The table of coefficients used to calculate CFRI Hip with BMD is presented as Table 5.2. If a researcher was interested in using the CFRI score they would need to multiply the dummy variable (0/1) for absence/presence of the covariate in the data and sum the score.

Table 5.2 Hip with BMD CFRI Model Coefficients

Attribute	Hip with BMD CFRI
Intercept	-7.78430299
Linear Age	0.154623293
Age*Osteoporosis	0.032028816
Cushing's syndrome	21.48856957
African-American	-1.366183288

5.2.1.1 Comparison in Linked Population

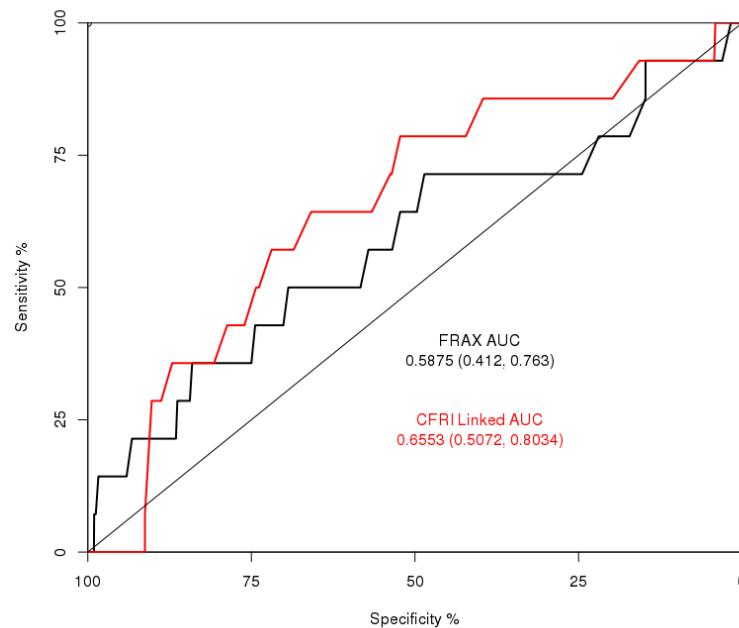
The hip with BMD CFRI score was calculated based on the presence of the covariates used in the model multiplied by their coefficient. The table used for the calculation was Table 4.6, column 4, Elastic Net. There were 14/2,798 (0.5%) women who had a femoral neck BMD value, and a hip fracture in the linked population within 1 year of their DXA (index date). The FRAX® and CFRI scores are relative to the 10-year risk of hip fracture for the individual. The mean hip with BMD FRAX® score was 4.4 (SD 5.7) and the mean hip with BMD CFRI score was 4.5 (SD 1.9).

Calibration was assessed using the Hosmer-Lemeshow test which is a variation on the chi-square by testing deciles of the risk score to determine if observed and expected event rates match each other (where a higher p-value indicates a better fit). In the linked population the FRAX® 10-year risk of hip fracture produces a p-value of 0.97 while the CFRI hip with BMD produces a p-value of 0.67. These both indicate a relatively good fit of prediction to fracture. We also evaluated calibration using the brier score, which is a measure of the accuracy of predicted probabilities. The brier score ranges from 0 (the best score) to 1 (the worst score). FRAX® had a brier score of 0.005 while CFRI also had a brier score of 0.005, both of these scores indicate nearly optimal predictive ability.

A paired De-Long test for equality of ROC curves was calculated with a $p \leq 0.05$ indicating a statistically significant difference between the two ROC curves (32, 420). The AUC for the FRAX® ROC was 58.75 (95% CI 41.20, 81.19), while for the CFRI curve the AUC was 65.53 (95% CI 50.72, 80.34). The paired De-Long test had a p-value of 0.33 indicating a lack of statistically significant difference between the two ROC curves (32, 420) (Figure 5.2).

Comparing the calibration of the two predictions based on HL and brier without much difference, hypothesis 2 would be confirmed. Hypothesis 2 in brief stated that there would be no significant difference in calibration between CFRI and FRAX®. The equality of the De-Long test supports hypothesis 3 for hip with BMD, as there is no statistically significant difference in the ability to predict fractures between FRAX® and CFRI in the linked population.

Figure 5.2 ROC Comparison for Hip with BMD in Linked Population



After visual inspection of Figure 5.2 the ROC curves for CFRI does not move from a sensitivity of 0% until the specificity is nearly 90%. The CFRI values which were associated with fractures were at lowest 2.1 and a highest 8.8, while the FRAX® values ranged from 0.2 to 29. There was no discernable difference in the ages of the patients who had fractures than those who did not (i.e., performance did not vary by age group); instead patients with a very low CFRI score did not fracture. This also is likely compounded by the small sample size, with only 14 hip

fractures, it may be that CFRI did poorly at finding those in the linked group who were most likely to fracture.

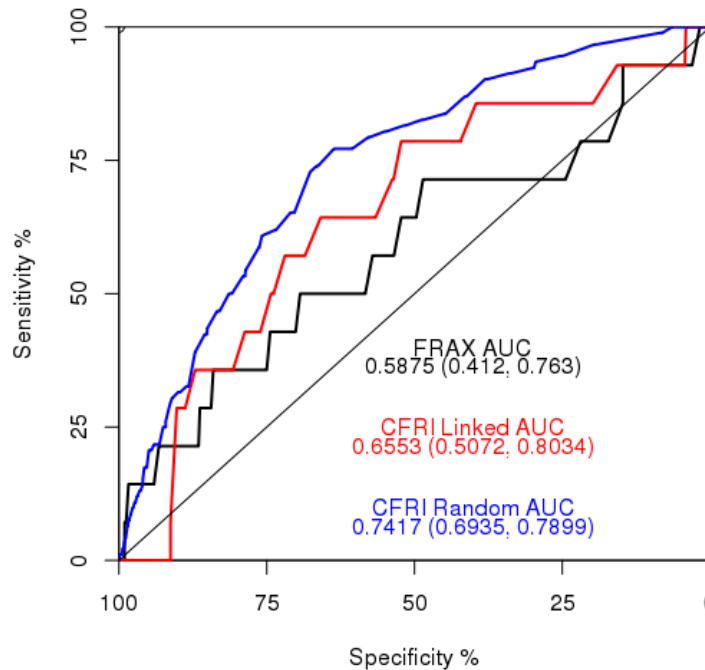
5.2.1.2 Comparison among the Linked FRAX®, Linked CFRI, and Random CFRI

There were 12,801/1,448,815 (0.9%) women who had a hip fracture by 365 days after index in the 20% random population. The mean hip with BMD CFRI score was 4.1 (SD 1.7). This score is lower and with a smaller standard deviation than in the linked population and likely represents a healthier population. The HL for the random population was <0.001 indicating that it was a very poor fit for the hip fracture outcome. However the brier score was 0.009 which although less predictive than the linked population demonstrates good predictive performance.

The AUC for the random population was 0.74 (95% CI 0.68, 0.79). Using a two sample DeLong test for equality, the difference between the FRAX® estimate and CFRI estimate was not statistically significant (Random AUC 74.2, FRAX® AUC 58.7, $p=0.10$). Additionally the two sample De-Long test did not show a statistically significant difference between the CFRI in the random and linked populations (Random 74.2, Linked 65.5, $p=0.28$). Graphical representation of the three curves is presented as Figure 5.3.

Hypothesis 2 was concerned with if there was a significant difference in calibration between CFRI and FRAX®. Although the HL test is vastly different for the linked and random population, the brier scores are very similar which would support the acceptance of the null hypothesis from hypothesis 2 of a similar calibration between estimates. Based on the statistical significance of the De-Long test, there is no difference between FRAX® in the linked and CFRI in the random populations ability to predict fractures at one year, this finding does not reject the null hypothesis of hypothesis 3.

Figure 5.3 ROC Comparison for Hip with BMD in Linked and Random Populations



The mean CFRI score for hip fractures in the random population was 5.4% (SD 1.6%), which is statistically significantly greater than those who did not have fractures 4.1% (SD 1.7%), $p < 0.001$, but follows what we would expect with a higher score being more indicative of a higher chance of fracture. The age of those with fractures in the random population was 83.3 (SD 8.0), which when compared to that of those who didn't have a fracture 75.9 (SD 8.2) ($p < 0.001$). Although fractures increased with age, the algorithm did not only assign high scores to older persons. Overall CFRI was able to better identify those persons who would have hip fractures in the random population than in the linked population. This was found even though patient characteristics in the linked population suggested that they were at a greater risk for fracture than the general population.

5.2.2 Major Osteoporotic Fracture with BMD CFRI Score

The table of coefficients used to calculate CFRI Hip with BMD is presented as Table 5.3.

If a researcher was interested in using the CFRI score they would need to multiply the dummy variable (0/1) for absence/presence of the covariate in the data and sum the score.

Table 5.3 MOF with BMD CFRI Model Coefficients

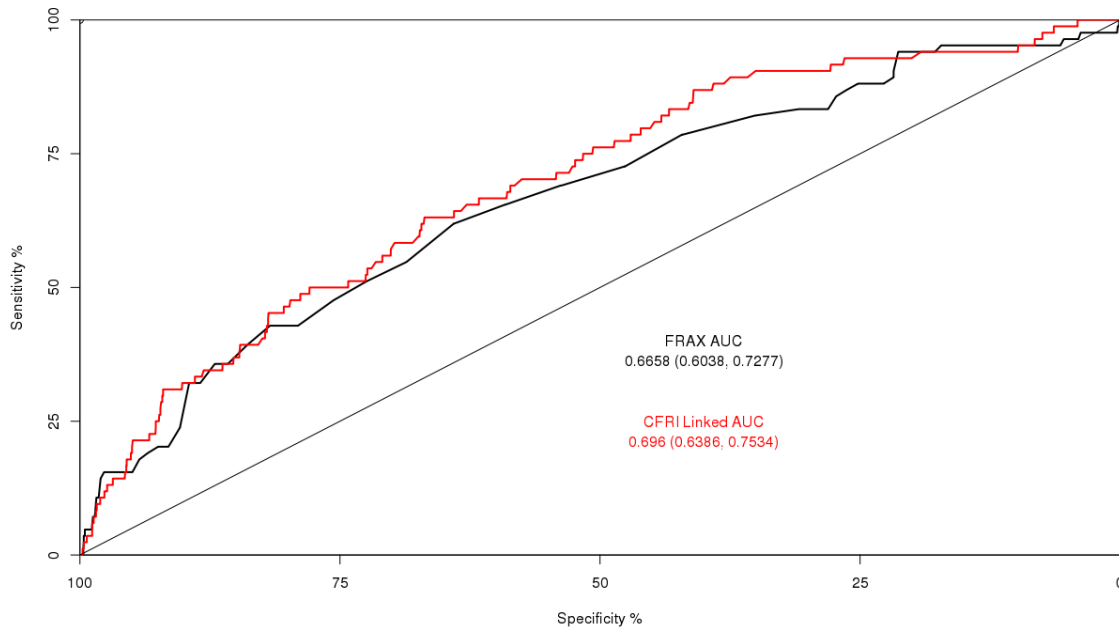
Variable	MOF with BMD CFRI
Intercept	-4.825318605
Linear Age	0.213882754
Age*Osteoporosis	0.06501777
Vitamin D insufficiency	-0.013289971
Hypophosphatasia	0.009540193
Diabetes mellitus (Type 1 & 2)	-0.010675466
Cushing's syndrome	30.00819577
Hyperparathyroidism	0.498923702
Inflammatory Bowel Disease	1.554882759
Lupus	0.726900325
Rheumatoid arthritis	2.813412897
Polymyalgia Rheumatica	1.449502678
Spinal cord injury	1.093297267
Depression	0.021357651
Sarcoidosis	0.481572939
Chronic metabolic acidosis	1.667854978
Idiopathic scoliosis	0.996848535
Kyphosis	0.090356929
Renaulds	1.239561619
Proton pump inhibitors	0.056608238
Methotrexate	0.841853825
Glucocorticoids	0.965996066
Hormone Replacement Therapy	0.208072152
Non-MOF Fractures	2.169086603
White	2.266392607
African-American	-6.775158983
Hispanic	2.662589671
Other	-0.004125508

5.2.2.1 Comparison in Linked Population

The MOF with BMD CFRI score was calculated based on the presence of the covariates used in the model multiplied by their coefficient. The table used for the calculation was Table 4.10, column 4, Elastic Net. There were 84/2798 (3.0%) MOF in the linked population with BMD within 1 year of their DXA. The mean MOF with BMD FRAX® score was 15.0 (SD 8.8) and the mean MOF with BMD CFRI score was 15.1 (SD 4.6). The HL for FRAX® MOF was 0.11, while CFRI produced a p-value of 0.08 indicating similar predictive abilities based on deciles of expected to observed fracture rate. The brier score was 0.0287 for FRAX® and 0.0289 for CFRI indicating very good predictive performance for both risk scores.

A paired De-Long test for equality of ROC curves was calculated with a $p \leq 0.05$ indicating a statistically significant difference between the two ROC curves. The AUC for the FRAX® ROC was 0.6658 (95% CI 0.6038, 0.7277), while for the CFRI curve the AUC was 0.6960 (95% CI 0.6386, 0.7534) (Figure 5.4). The paired De-Long test had a p-value of 0.26 indicating no significant difference between the two ROC curves. The equivalence of the De-Long test supports that there is no significant difference in the ability to predict fractures between FRAX® and CFRI in the linked population, using the MOF without BMD CFRI score.

Figure 5.4 ROC Comparison for MOF with BMD in Linked Population



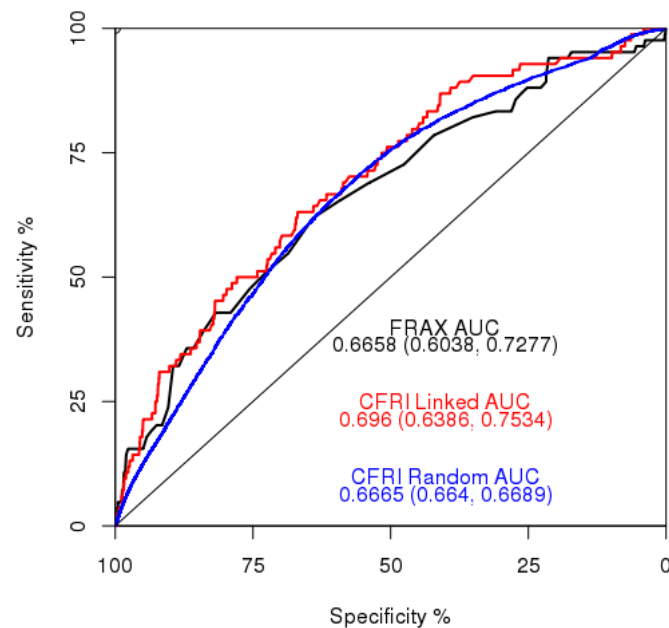
5.2.2.2 Comparison between the Linked FRAX®, Linked CFRI, and Random CFRI population

There were 45,414/1,448,815 (3.1%) women in the random population who had a MOF within 365-days of their index date. The mean MOF without BMD CFRI score was 13.8 (SD 4.0). The HL for MOF with BMD was <0.001 indicating a poor fit for expected to observed fracture rate. The brier score was 0.03, indicating in the random population CFRI was a better predictor than FRAX® or CFRI in the linked population. A De-Long test for equality of ROC curves was calculated with a $p \leq 0.05$ indicating a statistically significant difference between the two ROC curves. The AUC for CFRI in the random population was 0.667 (95% CI 0.664, 0.669). Comparing the random AUC to the FRAX® AUC indicated no significant differences

($p=0.98$), while the comparison to the linked CFRI also did not show a statistically significant difference ($p=0.31$). Graphical representation of the three curves is presented as Figure 5.5.

Although the HL test is vastly different for the linked and random population, the brier scores are very similar which would support the acceptance of the null hypothesis from hypothesis 2 of a similar calibration between estimates. The non-statically significant differences between the ROC curves using the De-Long test, supports the null of hypothesis 3 for MOF with BMD, of no difference between the three curves.

Figure 5.5 ROC Comparison for MOF with BMD in Linked and Random Populations



In women who had a MOF, the mean CFRI was 15.8% (SD 3.8) while those without a fracture had a mean CFRI of 13.7% (SD 4.0). These are smaller differences than fractures compared to non-fractures using the hip with BMD CFRI score. Women who had fractures were only slightly older than those who did not, 80.4 years (SD 8.6) compared to 75.9 years (SD 8.2). This is much less of a variation than in hip fractures, and may be an artifact of the covariate for

age being smaller in MOF algorithm than in the hip. It should be noted how closely the FRAX and random CFRI values are, although the linked have fewer fractures overall, the c-statistics are nearly identical.

5.2.3 Hip without BMD

The table of coefficients used to calculate CFRI Hip with BMD is presented as Table 5.4. If a researcher was interested in using the CFRI score they would need to multiply the dummy variable (0/1) for absence/presence of the covariate in the data and sum the score.

Table 5.4 Hip without BMD CFRI Coefficients

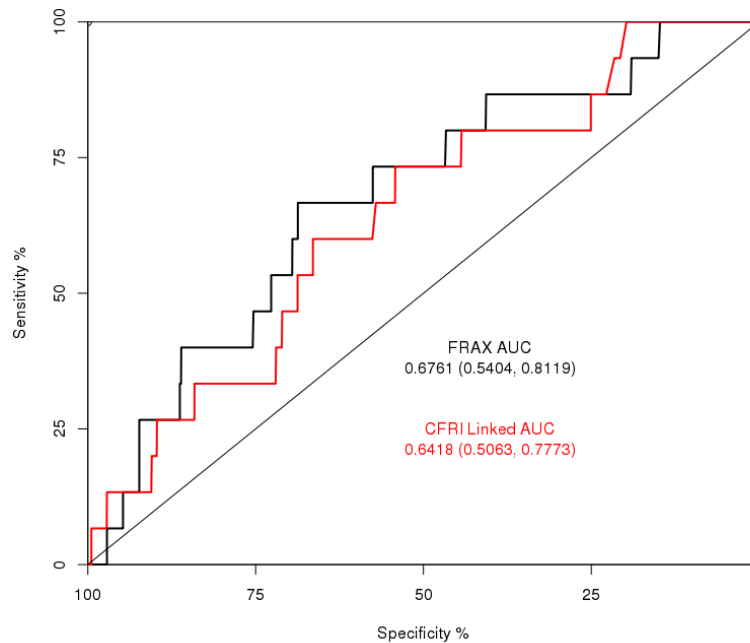
Attribute	Hip without BMD CFRI
Intercept	13.17578348
Linear Age	-0.866260403
Age*Age	0.015398691
Age*Age*Age	-7.90E-05
Osteoporosis	0.229939204
Hypophosphatasia	0.524734704
Premature ovarian failure	-0.290420231
Diabetes mellitus (Type 1 & 2)	-0.159199428
Central Adiposity	-0.264133914
Malabsorption	0.201816013
Pancreatic disease	0.18872779
Crohn's Disease	0.168869922
Hemophilia	-0.200298838
Lupus	0.207871113
Rheumatoid arthritis	0.342872904
Polymyalgia Rheumatica	0.141430641
Epilepsy	0.192915433
Stroke	-0.079886673
Liver Disease	0.105682215
Amyloidosis	0.630966755
Chronic metabolic acidosis	0.347989776
Kyphosis	0.093857352
Proton pump inhibitors	-0.045768346
Methotrexate	0.272679731
Glucocorticoids	0.103682447
Hormone Replacement Therapy	0.169297399

Non-MOF Fracture	0.255680069
African-American	-0.926065479
Hispanic	-0.622755009
Asian	-0.431379367
Other	-0.538443005

5.2.3.1 Comparison in the Linked Population

The hip without BMD CFRI score was calculated based on the presence of the covariates used in the model multiplied by their coefficient. The table used for the calculation was Table 4.17, column 2, LN Backwards. There were 15/2860 (0.5%) women who had a hip fracture in the linked population within 1 year of their DXA. The mean hip without BMD FRAX® score was 5.1 (SD 4.0) and the mean hip without BMD CFRI score was 5.9 (SD 6.7). The HL for FRAX® 10-year risk of hip fracture without BMD had a p-value of 0.67 and a brier score of 0.005, while CFRI's HL had a p-value of 0.86 and a brier score of 0.005. These calibration tests demonstrate that both risk scores are good predictors of future fracture, but CFRI has a greater predictive ability based on a higher HL p-value. A paired De-Long test for equality of ROC curves was calculated with a $p \leq 0.05$ indicating a statistically significant difference between the two ROC curves. The AUC for the FRAX® ROC was 0.6761 (95% CI 0.5404, 0.8119), while for the CFRI curve the AUC was 0.6418 (95% CI 0.5063, 0.7773). The paired De-Long test had a p-value of 0.49 indicating no statistically significant difference between the two ROC curves (Figure 5.6). The equality of the De-Long test supports hypothesis 3 for hip without BMD, as there is no difference in the ability to predict fractures between FRAX® and CFRI in the linked population.

Figure 5.6 ROC Comparison for Hip without BMD in Linked Population



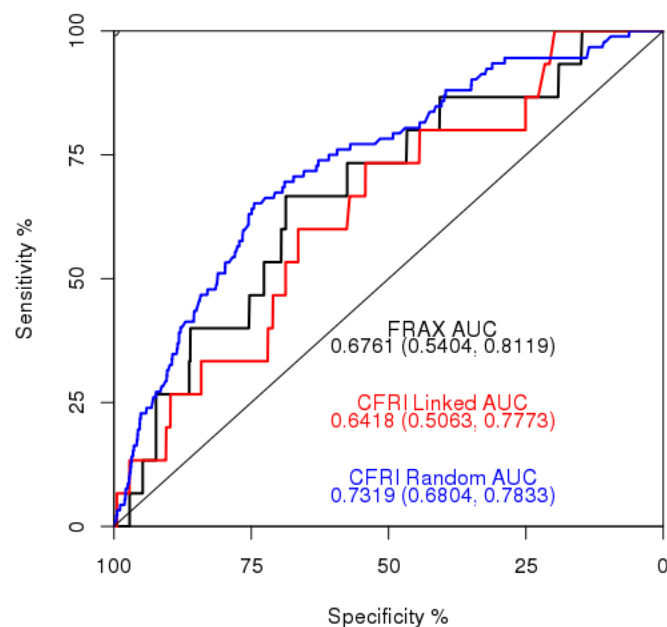
5.2.3.2 Comparison between the Linked FRAX®, Linked CFRI, and Random CFRI population

There were 12,801/1,448,815 (0.9%) women who had hip fractures by 365-days after index in the 20% random population. The mean hip without BMD CFRI score was 4.1 (SD 1.7). This score is lower and with a smaller standard deviation than in the linked population and likely represents a healthier population. The HL for the random population is associated with a p-value <0.001 indicating poor predictive ability, however the brier score is 0.009 which indicates the opposite. Based on the HL doing poorly with large sample sizes, we will defer to the brier score (437, 438). The AUC for the random population was 0.742 (95% CI 0.694, 0.790). Using a two sample DeLong test for equality, the difference between the FRAX® estimate and CFRI estimate was not statistically significant (Random AUC 0.742, FRAX® AUC 0.587, $p = 0.09677$), likely due to the small number of patients and events in the linked sample. Additionally the two sample

De-Long test did not show a statistically significant difference between the CFRI in the random and linked populations (Random 0.742, Linked 0.655, $p = 0.2769$) (Figure 5.7).

Although the HL test is vastly different for the linked and random population, the brier scores are very similar which would support the acceptance of the null hypothesis from hypothesis 2 of a similar calibration between estimates. Based on the statistical significance of the De-Long test, there is no difference in FRAX® ability to predict fractures in the linked population, as CFRI in the random population, this finding does not reject the null hypothesis of hypothesis 3.

Figure 5.7 ROC Comparison for Hip without BMD in Linked and Random Populations



5.2.4 MOF without BMD

The table of coefficients used to calculate CFRI Hip with BMD is presented as Table 5.5.

If a researcher was interested in using the CFRI score they would need to multiply a dummy variable (0/1) for absence/presence of the covariate in the data and sum the score.

Table 5.5 MOF without BMD CFRI Model Coefficients

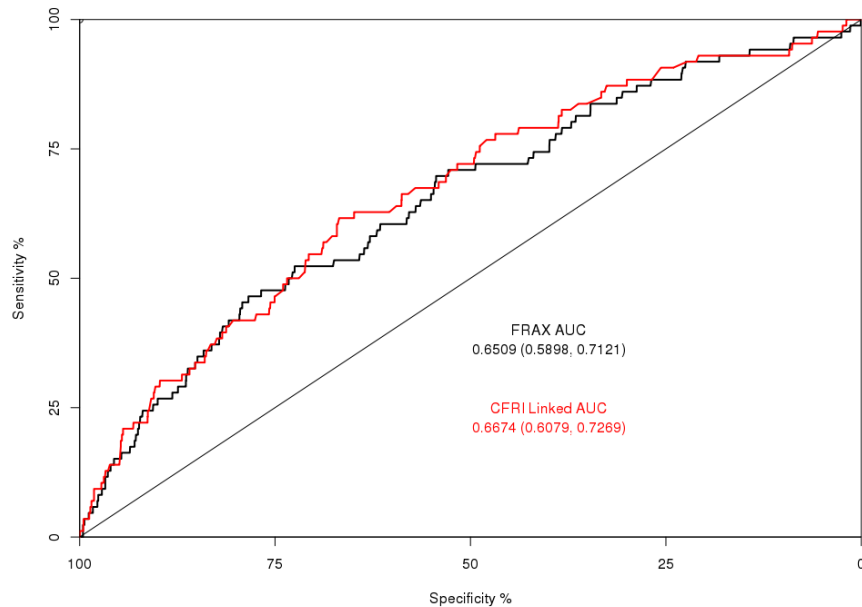
Attribute	MOF without BMD CFRI
Intercept	22.25687045
Linear Age	-0.914502808
Age*Age	0.013336948
Age*Age*Age	-6.15E-05
Age*Osteoporosis	0.001681857
Hypophosphatasia	0.281333375
Diabetes mellitus (Type 1 & 2)	-0.075335158
Central Adiposity	-0.109487081
Inflammatory Bowel Disease	-0.108489108
Malabsorption	0.126877713
Crohn's Disease	0.142616646
Hemophilia	-0.119944794
Lupus	0.183524351
Rheumatoid arthritis	0.205507803
Polymyalgia Rheumatica	0.107395123
Epilepsy	0.105167629
Stroke	-0.064792173
Liver Disease	0.077038137
Amyloidosis	0.532356113
Chronic metabolic acidosis	0.269888216
Methotrexate	0.208599974
Glucocorticoids	0.063924749
Hormone Replacement Therapy	0.098549558
Non-MOF	0.210669732
African-American	-0.852807121
Hispanic	-0.491561947
Asian	-0.438087007
Other	-0.497591055

5.2.4.1 Comparison in the Linked Population

The hip without BMD CFRI score was calculated based on the presence of the covariates used in the model multiplied by their coefficient. The table used for the calculation was Table 4.22, column 2, LN Backwards. There were 86/2860 (3.0%) MOF in the linked population within 1 year of their DXA. The mean MOF without BMD FRAX® score was 16.5 (SD 9.4) and the mean MOF without BMD CFRI score was 15.5 (SD 6.3). The calibration of FRAX® based on HL was p-value 0.41 and brier score of 0.028, while CFRI produced a HL of 0.48 and brier score of 0.027. Both of the calibration scores indicate a superior predictive ability of CFRI compared to FRAX® in the linked sample.

A paired De-Long test for equality of ROC curves was calculated with a $p \leq 0.05$ indicating a statistically significant difference between the two ROC curves. The AUC for the FRAX® ROC was 0.6509 (95% CI 0.5898, 0.7121), while for the CFRI curve the AUC was 0.6674 (95% CI 0.6079, 0.7269) (Figure 5.8). The paired De-Long test had a p-value of 0.49 indicating no statistically significant difference between the two ROC curves. The equality of the De-Long test supports hypothesis 3 for MOF without BMD, as there is no significant difference in the ability to predict fractures between FRAX® and CFRI in the linked population.

Figure 5.8 ROC Comparison for MOF without BMD in Linked Population



5.2.4.2 Comparison between the Linked FRAX®, Linked CFRI, and Random CFRI population

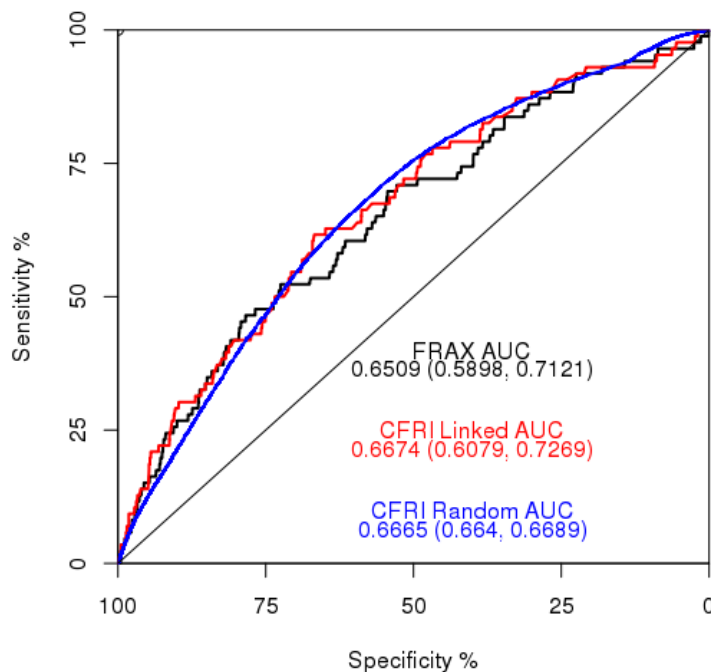
There were 45,414/1,448,815 (3.1%) women who had a MOF within 365-days of their index date. The mean MOF without BMD CFRI score was 15.4 (SD 6.1). The calibration of CFRI in the random population as measured by HL was <0.001 while the brier score was 0.03. Although the HL test indicates a poor fit and a worse fit than either risk score in the linked population, the brier score is similar to the linked sample, and indicates that based on one of two measures CFRI has a similar calibration.

A two sample De-Long test for equality of ROC curves was calculated with a $p \leq 0.05$ indicating a statistically significant difference between the two ROC curves. The AUC for CFRI in the random population was 0.666 (95% CI 0.663, 0.668). Comparing the random AUC to the FRAX® AUC indicated no significant differences ($p=0.6341$), while the comparison to the

linked CFRI also did not show a statistically significant difference ($p=0.958$). Graphical representation of the three curves are presented as Figure 5.9.

Although the HL test is vastly different for the linked and random population, the brier scores are very similar which would support the acceptance of the null hypothesis from hypothesis 2 of a similar calibration between estimates. The non-statically significant differences between the ROC curves using the De-Long test, supports the null of hypothesis 3 for MOF with BMD, of no difference between the three curves.

Figure 5.9 ROC Comparison for MOF without BMD in Linked and Random Populations



In women who had a MOF, the mean CFRI was 19.0% (SD 6.3) while those who did not have a fracture had a mean CFRI of 15.3% (SD 6.1). This represents a much larger difference in CFRI than for the with BMD score. As the fractures are the same as the with BMD population, there was a small variation in age (4.5 years) between those with and without fractures. Because

the patients who had fractures were the same population and it is only the covariates in the algorithm which changed, it appears that for MOF the log-normal backwards stepwise model was better able to predict a comparable score than the elastic net model. With all of the c-statistics being very similar for this score, it would be reasonable to extrapolate that they are predicting similar outcomes with their scores. However a higher CFRI score would be necessary to have the same dichotomous split as the NOF guidelines recommended FRAX® score of 20%.

5.3 Sensitivity Analysis

The planned sensitivity analyses for this aim involve identifying patients based on the receipt of DXA, rather than on an office visit to more closely resemble the linked population. Women were identified as receiving a DXA by CPT codes 76075 or 77080, the date of the DXA was then used as the index date. The same requirements of 365-days continuous enrollment prior to index in Medicare Parts A, B, and D were used. The patients were also required to be naïve to AOMs and be without a diagnosis of MOF during the 365-days prior to index.

There were 502,965 women who met the entrance criterion. The mean age was 74.2 (SD 6.6), with a similar distribution of patients in each year to the office visit cohort. The sensitivity population had a much lower percentage of patients with osteoporosis 5.8% compared to 11.4% in the full random population. All other characteristics are similar to the full population.

5.3.1 CFRI with BMD

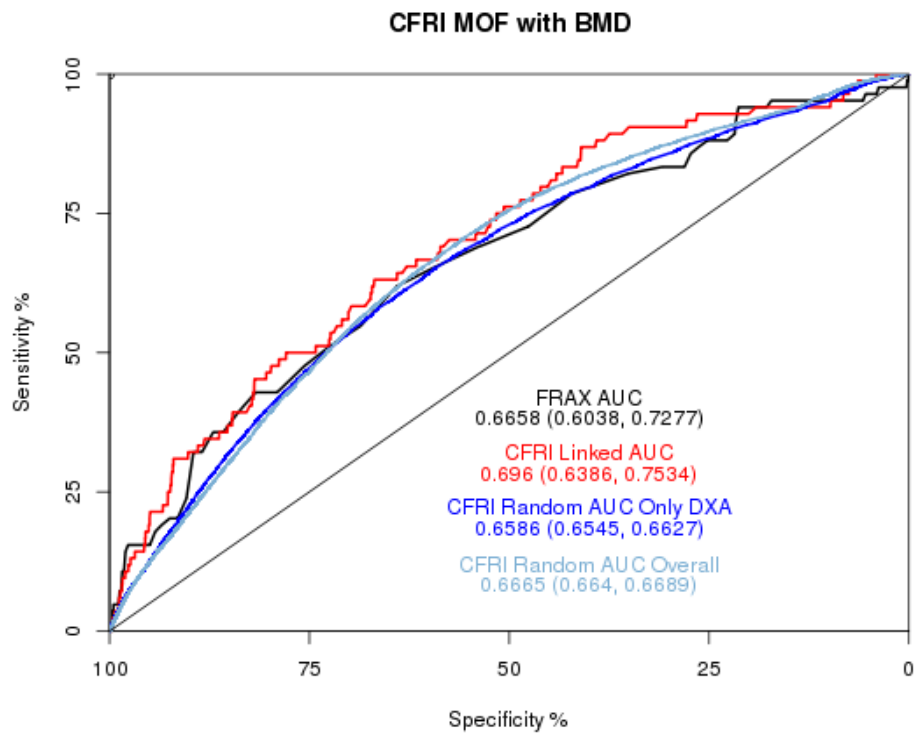
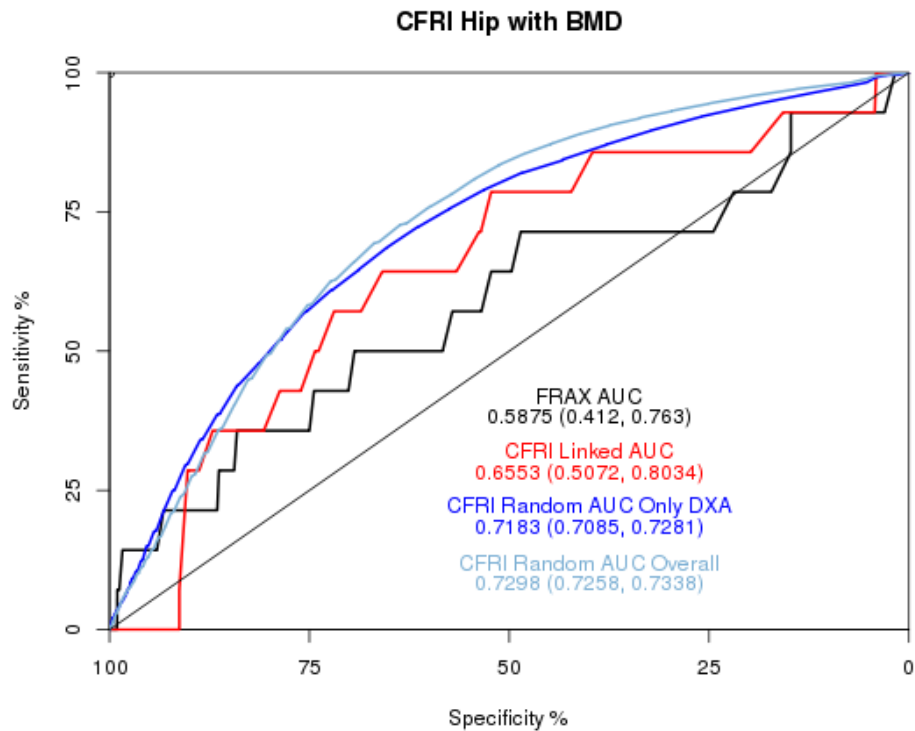
The hip and MOF results will be present simultaneously. Using DXA as the index date there were 2572/502,965 (0.5%) women who had hip fractures within 1 year and 17,533/502,965 (3.5%) women who had a MOF within 1 year of index. The ROC curves for the two outcomes are presented as Figure 5.10. The HL for hip with BMD was <0.001, however its chi-square was closer to the null than in the main analysis indicating a better fit. The brier score was 0.005

which is the same score as the linked population indicating a good predictive ability. The HL for MOF with BMD also was <0.001 indicating a poor fit, but the test statistic in the sensitivity analysis indicated a better fit than in the full analysis.

For the CFRI Hip with BMD analysis, the sensitivity cohort underperformed compared to the full population as evidenced by a c-statistic of 0.722 (95% CI 0.712, 0.732) compared to the full cohort c-statistic 0.732 (95% CI 0.728, 0.736). This is with both cohorts having 0.5% of the population with a hip fracture. There is more of a difference between those with and without a hip fracture 4.4% compared to 7.2% than in the full population where hip fractures had a mean CFRI of 5.4%. There was no significant difference between the c-statistic for the full population and the sensitivity population, suggesting that CFRI is as effective in the population with DXA as in those who only had an office visit.

For the CFRI MOF with BMD analysis, the sensitivity cohort had a lower c-statistic than the full population, although the difference was not statistically significantly different. The sensitivity cohort had a c-statistic of 0.659 (95% CI 0.654, 0.663) compared to the full population with a c-statistic of 0.667 (95% CI 0.664, 0.669). There was a smaller difference between the CFRI score for those who had an MOF and those who did not, 14.8% compared to 13.3% in the sensitivity cohort and 15.8% compared to 13.7% in the full cohort. This indicates that there isn't large difference between those patients who have fractures and who do not. With no significant difference between the sensitivity analysis and the full cohort, CFRI appears valid for use without mandating a DXA.

Figure 5.10 Sensitivity Analysis with BMD



5.3.2 CFRI without BMD

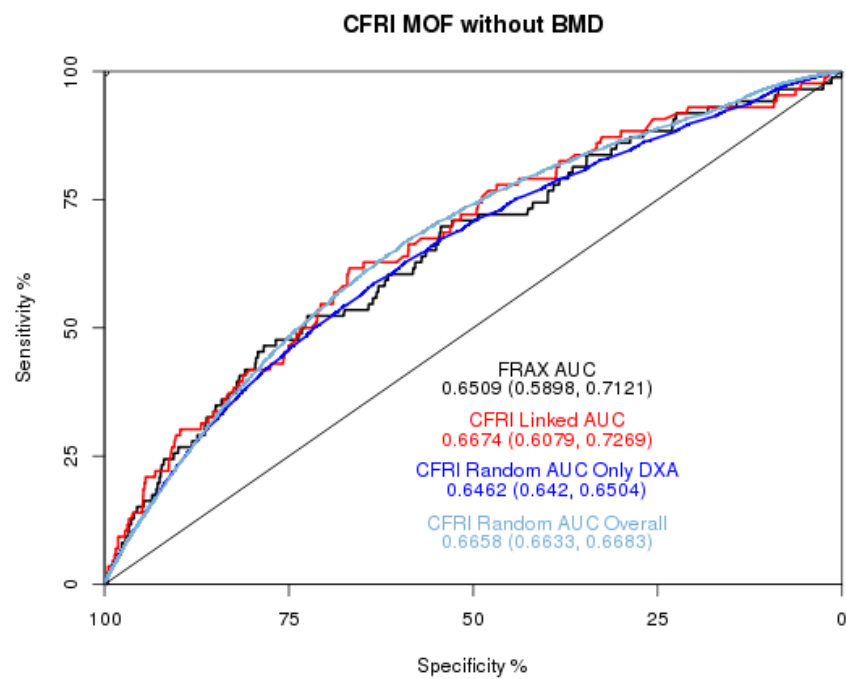
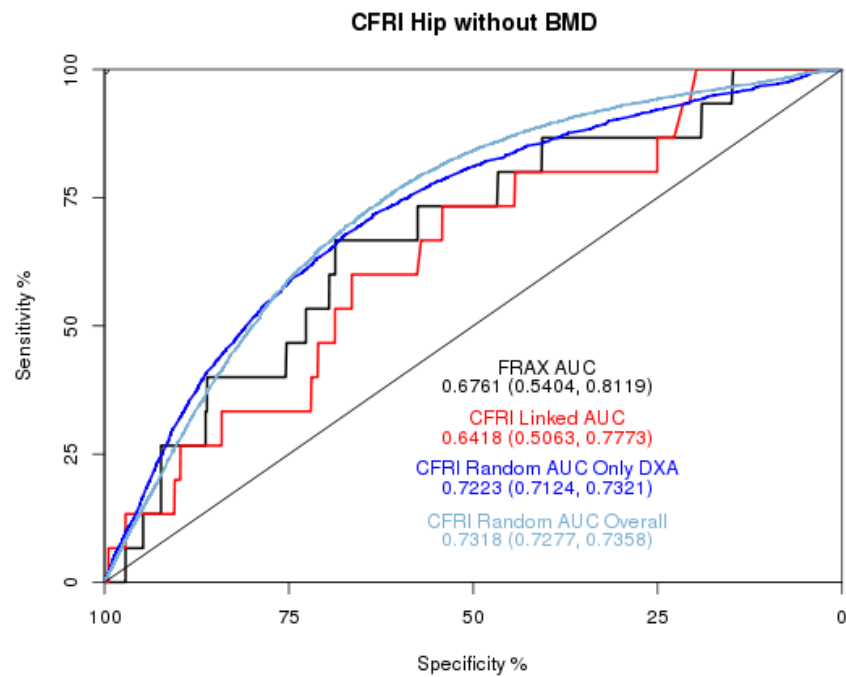
There was no difference in the percentage or number of fractures in sensitivity cohort regardless of if the with or without BMD CFRI score was used. CFRI hip without BMD population had 0.5% fractures while 3.5% of the sensitivity analysis population had an MOF within 1 year of their DXA. ROC for the without BMD population are presented as Figure 5.11. For both the hip and MOF CFRI scores, the full population outperformed the DXA population. The calibration of hip without BMD HL had a p-value <0.001 but an X^2 closer to the null than the full population, indicative of a better predictive ability. The brier score was 0.005 which was less than the full population also indicating a superior predictive ability. The calibration of MOF without BMD is as follows, HL p-value <0.001 and brier score 0.03, which are both marginally better than the main population.

Specifically the CFRI Hip without BMD score in the DXA population was 0.722 (95% CI 0.712, 0.732) while in the full population the c-statistic was 0.732 (95% CI 0.728, 0.736), the difference between the two curves was not statistically significantly different. The actual CFRI scores had a similar difference in the without population as in the with BMD population, 0.5% of women had a fracture with a mean CFRI of 7.2% and those without a fracture had a mean score of 4.4%. The women who had fractures were older 79.9 years to 74.2 years, and had osteoporosis more often 10.4% compared to 7.2% which were similar to the overall population. Based on the similar ROC and characteristics it appears that CFRI may be better used in the full population than in a subset of patients with DXAs.

In the CFRI MOF without BMD analysis no significant differences were found in ROC when the full and sensitivity analysis were compared. As with all of the other analyses there were no striking differences between the sensitivity analysis results and those of the main

analysis. The difference in CFRI scores 17.8% compared to 14.9% for those with and without a MOF is similar to the main analysis as is the difference in age, 77.4 compared to 74.1 years of age. With the sensitivity results being so similar to the main analysis, the CFRI for MOF without BMD appears to be calibrated for both any office visit or tying it specifically to a DXA.

Figure 5.11 Sensitivity Analysis without BMD



5.4 Summary

Overall CFRI performed as well as FRAX® in both the linked and random population for all four outcomes. The goal of Aim 2 was to externally validate CFRI based on one year fracture rates between the linked and random populations. Calibration was intended to be assessed by both the Hosmer-Lemeshow test and the Brier score, however the HL was found to not be valid in this population. Discrimination was evaluated using the AUC (c-statistic). Lastly AUCs were compared using a De-Long test. Broadly we found that CFRI in the random population was as well calibrated and had a similar ability to discriminate between those who would and would not have a fracture.

The AUCs for the random population ranged from 74.2 in hip with BMD, to 66.7 in MOF with BMD, to 73.2 in hip without BMD, and finally to 0.667 in MOF without BMD. It was odd that MOF with and without BMD essentially had identical discriminatory abilities, even though they had different mean scores. Additionally discrimination for the hip scores were only different by 1.0. This supports the idea from Kanis that in a general population the with and without BMD scores should be similar, as although the variables used to calculate the scores were different they were as able to determine who would go on to have a fracture (170).

The two hypotheses in this aim were concerned with the calibration (hypothesis 2) and discrimination (hypothesis 3). For each of the four outcomes confirmed both hypothesis 2 and hypothesis 3 that there were no significant differences in calibration or discrimination between the FRAX® linked sample and CFRI in the random population. Our sensitivity analysis demonstrated that not only when we used office visits, but when the index date was DXAs the

hypotheses were still confirmed. This not only demonstrates that there is little to no difference in FRAX® and CFRI in their ability to predict one year fractures, but that even though the linked population was created based on DXAs, in the general population CFRI behaves similarly.

CHAPTER 6: AIM 3 RESULTS

Aim 3: Evaluate the utility of CFRI and restriction in a comparative effectiveness research study of alendronate users to non-users.

Hypothesis: Comparative effectiveness estimates will most closely approximate Fracture Intervention Trial results after restricting by trial inclusion criteria and incorporating CFRI, then estimates generated without CFRI.

6.1 Overview

6.1.1 Study Population

The study population for Aim 3 is a collection of three different study populations based on how a non-user is defined (described in detail in Chapter 3). Approach 1 defines new users as a woman with new use of any drug within 30-days of an office visit, after 365-days continuous enrollment in Medicare Parts A, B, and D. Approach 2 uses the same idea as approach 1, but restricts new non-users to those starting a drug within the diabetes or hypertension classes or a statin. Approach 3 does not require any drug use, and index dates are chosen based on any office visit after the 365-days continuous enrollment requirement has been met. These three approaches allow our study to investigate how using CFRI in practical analysis can reduce confounding. For all three approaches we will be comparing alendronate users to non-users using CFRI, the composite fracture risk score created in Aim 1, and tested in Aim 2.

Additionally we will restrict the study populations to resemble to inclusion/exclusion criterion from the FIT trial. In brief the FIT trial was the only large scale alendronate versus

placebo randomized controlled trial (RCT) for post-menopausal women. The characteristics which can be measured in claims from the FIT trial include age, CFRI scores less than 9.1% MOF and/or 1.0% hip fracture, hip replacement, GERD, major illnesses, and specific medication classes. The algorithms for restriction are presented as Table 3.6.

The goal of Aim 3 is to determine if CFRI and restriction can reduce confounding in an observational comparative effectiveness study of alendronate versus non-users and produce effect estimates similar to those achieved in the FIT trial. While the unrestricted population is likely to suffer from confounding by indication, including CFRI as a fracture risk score should reduce some of this confounding. However CFRI alone may not completely reduce this bias when selecting non-users. However once the population is restricted to look the same as the RCT population we will better be able to determine if this technique and population are comparable and in fact reduce confounding. FIT had a clinical fracture HR of 0.72 at three years.

6.1.2 Use of CFRI

CFRI for this aim will be used as a covariate in regression as well as part of the restriction to the FIT trial. We will use both the with and without BMD MOF CFRI in the analysis, and will specify which score has been used. The primary outcome of the aim is vertebral fracture as this was the outcome which showed a protective effect in the FIT trial, and a secondary outcome of MOF. The two CFRI score are hip and MOF, but we will only use the MOF in this aim as vertebral fracture and MOF are to be predicted based on the score.

6.1.3 Outcomes

The primary outcome of Aim 3 is an incident vertebral fracture with a secondary outcome of major osteoporotic fracture (MOF). The Aim 3 analysis will use these sites as well as the pelvis tibia/fibula, clavicle, thoracic, and lumbar spine. The algorithm and applicable ICD-9, and

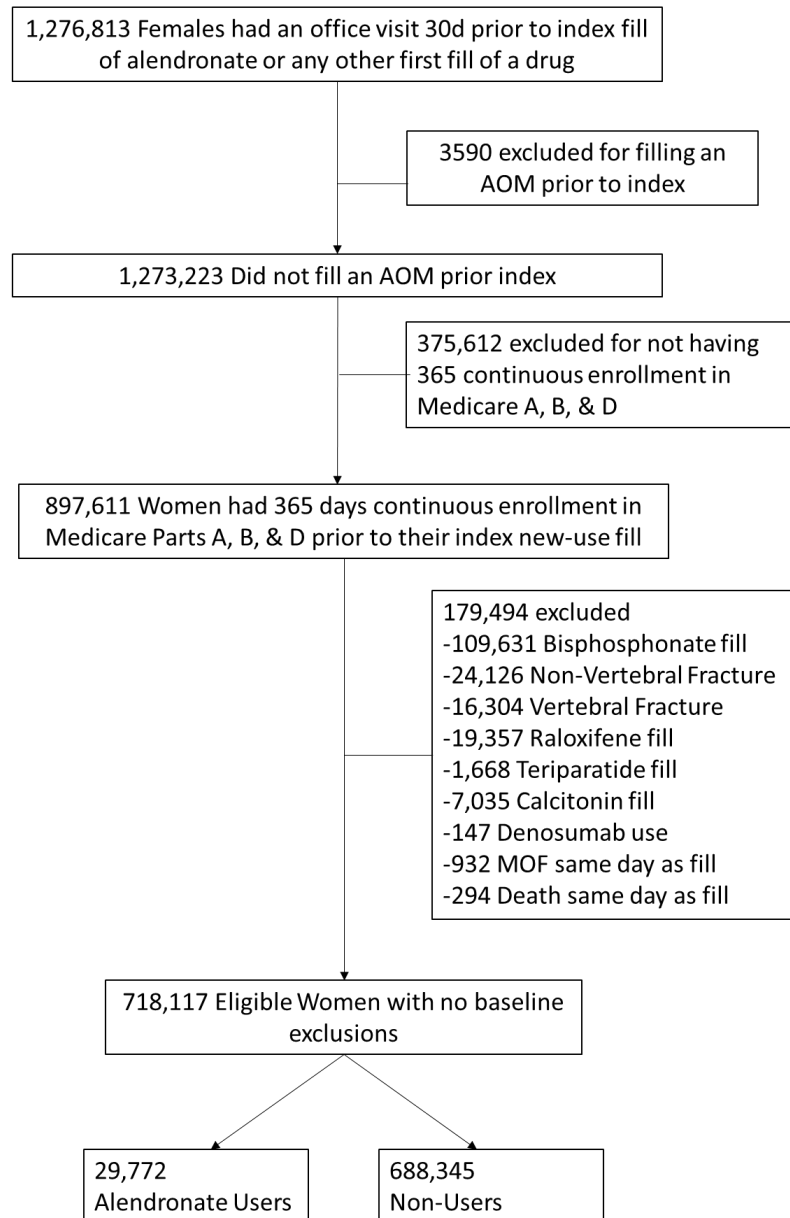
CPT codes for this definition are presented as Table 3.4. Follow-up will begin 30-days after index to allow all patients the same amount of time to fill a medication. Outcomes will be measured at one and three years' post-index, prior to the outcome patients can be administratively censored for losing Medicare A, B, D coverage, death, or initiation of an AOM.

6.2 Approach 1

6.2.1 Study Population

Two groups are compared in this analysis: alendronate users and non-users. For approach 1, non-users were required to have new use of any non-AOM drug (without prior use of the same drug in the preceding 365-days). Specific inclusion exclusion criterion for the population are presented as Figure 6.1. Overall 1,276,813 women filled any drug including alendronate with an office visit within 30-days prior to the fill. Of these women, 897,611 were continuous enrolled for at least 365-days prior to the office visit in Medicare Parts A, B, and D. Additional exclusions resulted in a final sample size of 718,117 women, of whom 29,772 were alendronate users, and 688,345 were classified as non-users.

Figure 6.1 Approach 1 (All New Users) Study Population Flowchart



From this cohort, when restricting further based on the FIT criteria, 149,570 were excluded for an inpatient stay in the 180 days prior to index. An additional 123,265 were excluded for medical diagnoses (77,437 for GERD, 51,969 for cancer diagnosis, and 5,233 for metabolic bone disease). Next, we excluded 114,922 for being outside of the trial age range, 38,627 for glucocorticoid use, 34,800 for HRT use, and 2,610 for history of a total hip

arthroplasty. This left 254,869 patients as eligible prior to exclusions based on CFRI score. The without BMD CFRI cohort resulted in 20,734 patients; 1,203 alendronate users and 19,504 non-users, while the with-BMD cohort had 3,951 patients with 268 alendronate users and 3,683 non-users.

The characteristics of the unrestricted study population are presented as Table 6.1. A second analysis will be performed with a population after FIT exclusions. In the unrestricted population there was a significant difference between users and non-users in regard to osteoporosis diagnosis with alendronate users having a greater proportion of the population with osteoporosis (37.2% compared to 10.7%) and kyphosis (55% compared to 24%). There were many more diabetics in the non-users than in the alendronate users (53.9% compared to 23.9%). The non-user population had a larger percentage of anti-convulsant, and SSRI fills in the 365-days prior to index. Otherwise the characteristics appear to be reasonably similar although some differences did reach statistical significance which can be attributed to the large sample size.

Table 6.1 Approach 1 (All New Users), Characteristics of the Study Population before Restricting to FIT Criteria

Attribute	Non-Users (n=688,345)	Users (n=29,772)	Total (n=718,117)
Mean Age	75.8 (8.1)	74.3 (7.5)	75.7 (8.1)
In 365-days prior to index			
Osteoporosis, N (%)	4873 (10.7)	7621 (37.2)	12494 (19.0)
Lifestyle Factors, N (%)			
Alcohol Abuse	143 (0.3)	78 (0.4)	221 (0.3)
Falling	2246 (4.9)	802 (3.9)	3048 (4.6)
Vitamin D insufficiency	4010 (8.8)	964 (4.7)	4974 (7.5)
Excess Vitamin A	<11	<11	<11
Genetic factors, N (%)			
Cystic fibrosis	15 (<0.1)	<11	22 (<0.1)
Homocystinuria	73 (0.2)	25 (0.1)	98 (0.1)
Osteogenesis imperfecta	<11	<11	<11
Hypophosphatasia	311 (0.7)	52 (0.3)	363 (0.6)
Gaucher's disease	77 (0.2)	39 (0.2)	116 (0.2)
Porphyria	<11	<11	<11
Glycogen storage diseases	<11	<11	<11
Marfan syndrome	<11	<11	<11
Riley-Day syndrome	<11	<11	<11
Hemochromatosis	<11	<11	<11
Hypogonadal states, N (%)			
Androgen insensitivity	<11	<11	<11
Anorexia nervosa and bulimia	582 (1.3)	175 (0.9)	757 (1.1)
Hyperprolactinemia	12 (<0.1)	<11	15 (<0.1)
Premature ovarian failure	30 (0.1)	34 (0.2)	64 (0.1)
Athletic amenorrhea	17 (<0.1)	19 (0.1)	36 (0.1)
Turner and Klinefelters's syndromes	<11	<11	<11
Panhypopituitarism	<11	<11	<11
Endocrine disorders, N (%)			
Adrenal insufficiency	<11	11 (0.1)	18 (<0.1)
Diabetes mellitus (Type 1 & 2)	24476 (53.9)	6739 (32.9)	31215 (47.4)
Cushing's syndrome	29 (0.1)	13 (0.1)	42 (0.1)
Hyperparathyroidism	528 (1.2)	290 (1.4)	818 (1.2)
Central Adiposity	4606 (10.1)	1015 (5.0)	5621 (8.5)
Thyrotoxicosis	1001 (2.2)	538 (2.6)	1539 (2.3)
Gastrointestinal disorders, N (%)			
Celiac disease	55 (0.1)	39 (0.2)	94 (0.1)
Gastric bypass	<11	<11	<11
Inflammatory Bowel Disease	302 (0.7)	127 (0.6)	429 (0.7)
Malabsorption	182 (0.4)	81 (0.4)	263 (0.4)

Pancreatic disease	593 (1.3)	167 (0.8)	760 (1.2)
Primary biliary cirrhosis	21 (<0.1)	<11	30 (<0.1)
Crohn's Disease	1786 (3.9)	685 (3.3)	2471 (3.7)
Hematologic disorders, N (%)			
Hemophilia	979 (2.2)	337 (1.6)	1316 (2.0)
Thalassemia	28 (0.1)	12 (0.1)	40 (0.1)
Sickle cell anemia	<11	<11	<11
Systemic mastocytosis	<11	<11	<11
Rheumatologic and autoimmune diseases, N (%)			
Ankylosing spondylitis	459 (1.0)	211 (1.0)	670 (1.0)
Lupus	203 (0.4)	118 (0.6)	321 (0.5)
Rheumatoid arthritis	1670 (3.7)	1003 (4.9)	2673 (4.1)
Gout	1792 (3.9)	480 (2.3)	2272 (3.4)
Polymyalgia Rheumatica	341 (0.8)	297 (1.4)	638 (1.0)
Central nervous system disorders, N (%)			
Epilepsy	639 (1.4)	212 (1.0)	851 (1.3)
Parkinson's disease	550 (1.2)	206 (1.0)	756 (1.1)
Stroke	6873 (15.1)	2166 (10.6)	9039 (13.7)
Multiple sclerosis	119 (0.3)	61 (0.3)	180 (0.3)
Spinal cord injury	44 (0.1)	20 (0.1)	64 (0.1)
Alzheimer's disease	5004 (11.0)	1424 (6.9)	6428 (9.8)
Miscellaneous conditions and diseases, N (%)			
AIDS/HIV	38 (0.1)	20 (0.1)	58 (0.1)
Congestive Heart Failure	7732 (17.0)	1902 (9.3)	9634 (14.6)
Muscular dystrophy	15 (<0.1)	<11	18 (<0.1)
Liver Disease	2121 (4.7)	757 (3.7)	2878 (4.4)
Depression	6932 (15.3)	2620 (12.8)	9552 (14.5)
Amyloidosis	16 (<0.1)	<11	20 (<0.1)
End stage renal disease	902 (2.0)	96 (0.5)	998 (1.5)
Sarcoidosis	86 (0.2)	44 (0.2)	130 (0.2)
Chronic metabolic acidosis	700 (1.5)	107 (0.5)	807 (1.2)
Asthma/Chronic obstructive lung disease	10039 (22.1)	4120 (20.1)	14159 (21.5)
Idiopathic scoliosis	760 (1.7)	492 (2.4)	1252 (1.9)
Cataracts	15769 (34.7)	7537 (36.8)	23306 (35.4)
Glaucoma	6390 (14.1)	2949 (14.4)	9339 (14.2)
Kyphosis	10677 (23.5)	11172 (54.5)	21849 (33.2)
Obesity	4606 (10.1)	1015 (5.0)	5621 (8.5)
Disorders of the eye*	23517 (51.8)	10705 (52.2)	34222 (51.9)
Osteoarthritis	13725 (30.2)	6238 (30.4)	19963 (30.3)
Renault's syndrome	4583 (10.1)	801 (3.9)	5384 (8.2)
Medications, N (%)			
Cyclosporine A and tacrolimus	51 (0.1)	21 (0.1)	72 (0.1)
Proton pump inhibitors	11868 (26.1)	5146 (25.1)	17014 (25.8)

Anticoagulants	4300 (9.5)	1619 (7.9)	5919 (9.0)
Selective serotonin reuptake inhibitors	7664 (16.9)	3407 (16.6)	11071 (16.8)
Anticonvulsants	5660 (12.5)	2225 (10.9)	7885 (12.0)
Aromatase inhibitors	563 (1.2)	448 (2.2)	1011 (1.5)
GnRH antagonists and agonists	<11	<11	<11
Thiazolidinediones	3420 (7.5)	1105 (5.4)	4525 (6.9)
Barbiturates	<11	<11	<11
Lithium	58 (0.1)	35 (0.2)	93 (0.1)
Methotrexate	379 (0.8)	327 (1.6)	706 (1.1)
Glucocorticoids	6163 (13.6)	2875 (14.0)	9038 (13.7)
Hormone Replacement Therapy	2745 (6.0)	1181 (5.8)	3926 (6.0)
Fractures			
Other Sites	1726 (3.8)	988 (4.8)	2714 (4.1)
Race			
White	34911 (76.9)	15821 (77.2)	50732 (77.0)
African-American	6426 (14.2)	1855 (9.1)	8281 (12.6)
Hispanic	1793 (3.9)	1170 (5.7)	2963 (4.5)
Asian	1177 (2.6)	1057 (5.2)	2234 (3.4)
Other	767 (1.7)	459 (2.2)	1226 (1.9)
<i>Non-users are defined as any new-use of any drug in any class</i>			
All Cells with a total of 0 were suppressed; *: Includes Cataracts and Glaucoma <11: CMS does not allow cells with less than 11 patients to be presented			

6.2.2 Unrestricted Population Results

The primary outcome of this aim is vertebral fracture, since the MOF includes these fractures, the CFRI score which is most applicable is the MOF rather than hip score. However there are two different ways to account for the score, both with and without BMD. The results for the unrestricted population using both with and without BMD MOF CFRI at 365-days post-index are presented in Table 6.2.

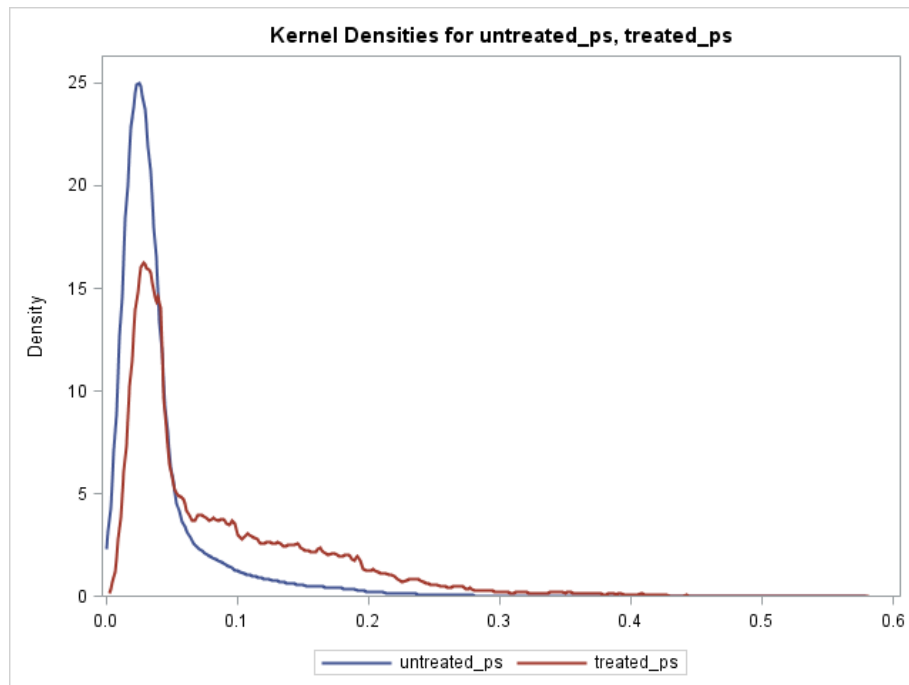
Table 6.2 Unrestricted Population for Approach 1 (All New Users), Hazard Ratio for MOF at 365-days comparing alendronate use to non-use

Type of Analysis	MOF Hazard Ratio	Vertebral Hazard Ratio
Null	1.26 (1.18,1.34)	1.33 (1.23,1.43)
Only MOF CFRI without BMD	1.23 (1.15,1.30)	1.30 (1.21,1.40)
Only MOF CFRI with BMD	1.08 (1.02,1.15)	1.14 (1.06,1.23)
Fully Adjusted	1.25 (1.17,1.32)	1.26 (1.17,1.36)
SIPTW	1.57 (1.49,1.66)	0.63 (0.17,2.41)
SMRW	1.29 (1.17,1.41)	0.58 (0.10,3.25)

For reference in the FIT trial any clinical fracture hazard ratio at three years was (HR 0.72, 95% CI [0.58, 0.90]). At one year 1,068 (3.6%) of alendronate users and 18,678 (2.7%) of non-users had a major osteoporotic fracture, while 732 (2.5%) of alendronate users and 12,091 (1.8%) of non-users had vertebral fractures. The naïve model produced a hazard ratio of 1.26 which was similar to the fully-adjusted model (HR 1.25). The propensity score inverse probability of treatment weights (SIPTW) model produced a HR of 1.57. The most conservative estimate was when the model only included CFRI MOF with BMD (HR 1.08) which was non-significant and 0.13 less than the without BMD estimate (1.23). The vertebral estimates followed a similar pattern with the estimate only including the with BMD CFRI score being closest to the null. However the fully adjusted model was closer to the null than the without BMD naïve estimate which may suggest that for vertebral fracture outcomes the with-BMD score is most appropriate.

In regards to the propensity score based approaches neither produced estimates which were less than the simple model with CFRI. The overlap of the propensity scores are presented as Figure 6.2. The propensity score for both the treated and untreated follow similar distributions with approximately four spikes, however there is very little similar overlap in the distribution other than approximately between 0.05 and 0.1 propensity for use of alendronate. The covariates appeared to be balanced between the two groups (results not shown), and the addition of the CFRI score did not improve the hazard ratios or the distribution of the propensity score.

Figure 6.2 Kernel Density Plot for Propensity Scores in Approach 1 (All New Users)



The results for the unrestricted population using both with and without BMD MOF CFRI with all available time are presented in Table 6.3.

Table 6.3 Unrestricted Population for Approach 1 (All New Users), Hazard Ratio for MOF using all available time

Type of Analysis	MOF Hazard Ratio	Vertebral Hazard Ratio
Null	1.44 (1.39,1.49)	1.36 (1.30,1.42)
Only MOF CFRI without BMD	1.38 (1.33,1.43)	1.31 (1.25,1.36)
Only MOF CFRI with BMD	1.23 (1.19,1.27)	1.16 (1.11,1.21)
Fully Adjusted	1.38 (1.33,1.43)	1.26 (1.20,1.31)
SIPTW	1.89 (1.40,2.54)	0.63 (0.17,2.41)
SMRW	1.66 (1.02,2.69)	0.58 (0.10,3.25)

Using all available time, alendronate users had a mean of 1286.6 (SD 646.5), median 1402 (IQR 737, 1863) days and non-users were followed for a mean of 909.2 (SD 597.0), median 810 (IQR 442, 1364) days. During this time period 3,632 (12.2%) MOF and 2,308

(7.8%) vertebral fractures in alendronate users and 43,347 (6.3%) MOF and 28,358 (4.1%) vertebral fractures for non-users had a major osteoporotic fracture. The naïve model which only includes the grouping indicator produced a hazard ratio of 1.44 which is more than the when the model used all of the content variables (HR 1.38), but smaller than the propensity score inverse probability of treatment weights (SIPTW) model which produced a HR of 1.89. The most conservative estimate was when the model only included CFRI MOF with BMD (HR 1.23) which was significant showing an increased fracture risk for alendronate users, but was 0.15 less than the without BMD estimate (1.38). Additionally the propensity score methods (SIPTW and SMRW) again produced increased hazard ratios compared to the regression based approaches. For the vertebral fracture outcome, the with BMD estimate and the fully adjusted estimate were closest to the null, however neither crossed 1 as such demonstrated a statistically significant increase in fracture risk for alendronate users.

Our estimates do not reach those of the FIT trial at 3 years (HR 0.72, 95% CI [0.58, 0.90]) even with the alendronate and non-user group were followed for around 3 years. Our results indicate that CFRI in the general population is not able to reduce confounding by indication of a sufficient amount.

6.2.3 FIT restricted population results

The population characteristics generally were very different within the FIT restricted population compared to the unrestricted population. The largest difference was in the with BMD population where there were only Black patients included. The reason for only including black patients was the combination of the with-BMD intercept and age coefficient. Unless a patient was <57 they had to have Black race to have a MOF <9.1% There are no patients in the with BMD population who had a diagnosis of osteoporosis, this is due to the inclusion of the age *

osteoporosis variable in CFRI hip with BMD which similar to the age variable increases the hip CFRI score to >1 , which excludes the patient from the analysis. Both of these factors make the with BMD population very different from the unrestricted population and question the generalizability of their results. In the end there were 20,734 patients in the without BMD CFRI population, 1,230 (5.9%) alendronate users and 19,504 (94.1%) who were non-users, while there were 3,951 patients in the with-BMD CFRI restricted population and 268 (6.8%) of these were alendronate users and the other 3683 (93.2%) were classified as non-users.

The distribution of characteristics seems to be reasonably well balanced between users and non-users, other than osteoporosis in the without BMD CFRI group. There were significant differences in some population characteristics, however many of these were due to sample size rather than a clinical difference. Central adiposity, COPD, and the use of anticonvulsants differed by >1 -2% between the users and non-users. Particularly in the with BMD CFRI population and for the most part in the without BMD population these population characteristics are not representative of the general population. This makes it difficult to claim any generalizability to the general population from these results. However these characteristics may be similar to those of the highly restricted RCT population.

Table 6.4 Population Characteristics of Restricted Population in Approach 1 (All New Users)

Attribute	Non-User BMD (n=3683)	User BMD (n=268)	Total BMD (n=3951)	Non-User No BMD (n=19504)	User No BMD (n=1230)	Total No BMD (n=20734)
Mean Age	64.4 (0.5)	64.2 (0.4)	64.4 (0.5)	66.6 (2.0)	65.7 (1.8)	66.6 (2.0)
In 365-days prior to index						
Osteoporosis, N (%)	<11	<11	<11	267 (1.4)	105 (8.5)	372 (1.8)
Lifestyle Factors, N (%)						
Alcohol Abuse	<11	<11	<11	37 (0.2)	<11	39 (0.2)
Falling	23 (0.6)	<11	24 (0.6)	224 (1.1)	<11	233 (1.1)
Vitamin D insufficiency	64 (1.7)	<11	65 (1.6)	579 (3.0)	29 (2.4)	608 (2.9)
Excess Vitamin A	<11	<11	<11	<11	<11	<11
Genetic factors, N (%)						
Cystic fibrosis	<11	<11	<11	<11	<11	<11
Homocystinuria	<11	<11	<11	<11	<11	<11
Hypophosphatasia	<11	<11	<11	15 (0.1)	<11	16 (0.1)
Gaucher's disease	<11	<11	<11	19 (0.1)	<11	20 (0.1)
Glycogen storage diseases	<11	<11	<11	<11	<11	<11
Riley-Day syndrome	<11	<11	<11	<11	<11	<11
Hemochromatosis	<11	<11	<11	<11	<11	<11
Hypogonadal states, N (%)						
Anorexia nervosa and bulimia	<11	<11	<11	46 (0.2)	<11	48 (0.2)
Hyperprolactinemia	<11	<11	<11	<11	<11	<11
Premature ovarian failure	<11	<11	<11	<11	<11	<11
Athletic amenorrhea	<11	<11	<11	<11	<11	<11
Panhypopituitarism	<11	<11	<11	<11	<11	<11
Endocrine disorders, N (%)						
Adrenal insufficiency	<11	<11	<11	<11	<11	<11
Diabetes mellitus (Type 1 & 2)	856 (23.2)	27 (10.1)	883 (22.3)	7949 (40.8)	391 (31.8)	8340 (40.2)
Cushing's syndrome	<11	<11	<11	<11	<11	<11
Central Adiposity	178 (4.8)	3 (1.1)	181 (4.6)	2414 (12.4)	90 (7.3)	2504 (12.1)
Thyrotoxicosis	22 (0.6)	<11	23 (0.6)	227 (1.2)	20 (1.6)	247 (1.2)
Gastrointestinal disorders, N (%)						
Celiac disease	<11	<11	<11	<11	<11	<11
Inflammatory Bowel Disease	<11	<11	<11	24 (0.1)	<11	26 (0.1)
Malabsorption	<11	<11	<11	18 (0.1)	<11	20 (0.1)
Pancreatic disease	<11	<11	11 (0.3)	57 (0.3)	<11	59 (0.3)
Primary biliary cirrhosis	<11	<11	<11	<11	<11	<11
Crohn's Disease	19 (0.5)	1 (0.4)	20 (0.5)	158 (0.8)	<11	163 (0.8)
Hematologic disorders, N (%)						

Hemophilia	17 (0.5)	<11	17 (0.4)	181 (0.9)	<11	189 (0.9)
Thalassemia	<11	<11	<11	14 (0.1)	<11	14 (0.1)
Sickle cell anemia	<11	<11	<11	<11	<11	<11
Systemic mastocytosis	<11	<11	<11	<11	<11	<11
Rheumatologic and autoimmune diseases, N (%)						
Ankylosing spondylitis	<11	<11	12 (0.3)	62 (0.3)	<11	67 (0.3)
Lupus	20 (0.5)	<11	21 (0.5)	47 (0.2)	<11	51 (0.2)
Rheumatoid arthritis	40 (1.1)	<11	44 (1.1)	150 (0.8)	<11	158 (0.8)
Gout	48 (1.3)	<11	48 (1.2)	428 (2.2)	11 (0.9)	439 (2.1)
Polymyalgia Rheumatica	<11	<11	<11	<11	<11	<11
Central nervous system disorders, N (%)						
Epilepsy	38 (1.0)	<11	41 (1.0)	109 (0.6)	<11	117 (0.6)
Parkinson's disease	<11	<11	<11	56 (0.3)	<11	60 (0.3)
Stroke	76 (2.1)	<11	76 (1.9)	852 (4.4)	38 (3.1)	890 (4.3)
Multiple sclerosis	6 (0.2)	<11	7 (0.2)	36 (0.2)	3 (0.2)	39 (0.2)
Spinal cord injury	<11	<11	<11	<11	<11	<11
Alzheimer's disease	42 (1.1)	<11	43 (1.1)	405 (2.1)	<11	415 (2.0)
Miscellaneous conditions and diseases, N (%)						
AIDS/HIV	22 (0.6)	<11	24 (0.6)	67 (0.3)	<11	71 (0.3)
Congestive Heart Failure	132 (3.6)	<11	140 (3.5)	1106 (5.7)	38 (3.1)	1144 (5.5)
Liver Disease	47 (1.3)	<11	49 (1.2)	359 (1.8)	25 (2.0)	384 (1.9)
Depression	180 (4.9)	<11	189 (4.8)	1290 (6.6)	91 (7.4)	1381 (6.7)
End stage renal disease	145 (3.9)	<11	150 (3.8)	394 (2.0)	13 (1.1)	407 (2.0)
Sarcoidosis	<11	<11	<11	54 (0.3)	<11	58 (0.3)
Chronic metabolic acidosis	<11	<11	<11	22 (0.1)	<11	22 (0.1)
Asthma/Chronic obstructive lung disease	221 (6.0)	<11	231 (5.8)	1932 (9.9)	87 (7.1)	2019 (9.7)
Idiopathic scoliosis	11 (0.3)	<11	11 (0.3)	76 (0.4)	<11	78 (0.4)
Cataracts	153 (4.2)	<11	161 (4.1)	2418 (12.4)	132 (10.7)	2550 (12.3)
Glaucoma	111 (3.0)	<11	118 (3.0)	1440 (7.4)	70 (5.7)	1510 (7.3)
Kyphosis	90 (2.4)	<11	100 (2.5)	1177 (6.0)	212 (17.2)	1389 (6.7)
Obesity	178 (4.8)	<11	181 (4.6)	2414 (12.4)	90 (7.3)	2504 (12.1)
Disorders of the eye*	309 (8.4)	12 (4.5)	321 (8.1)	4012 (20.6)	220 (17.9)	4232 (20.4)
Osteoarthritis	315 (8.6)	11 (4.1)	326 (8.3)	2908 (14.9)	161 (13.1)	3069 (14.8)
Renauld's syndrome	147 (4.0)	<11	150 (3.8)	927 (4.8)	30 (2.4)	957 (4.6)
Medications, N (%)						
Cyclosporine A and tacrolimus	<11	<11	<11	15 (0.1)	<11	16 (0.1)
Proton pump inhibitors	670 (18.2)	40 (14.9)	710 (18.0)	3956 (20.3)	217 (17.6)	4173 (20.1)
Anticoagulants	154 (4.2)	<11	164 (4.2)	850 (4.4)	34 (2.8)	884 (4.3)
Selective serotonin reuptake inhibitors	333 (9.0)	20 (7.5)	353 (8.9)	2058 (10.6)	127 (10.3)	2185 (10.5)
Anticonvulsants	467 (12.7)	30 (11.2)	497 (12.6)	2377 (12.2)	133 (10.8)	2510 (12.1)
Aromatase inhibitors	<11	<11	13 (0.3)	50 (0.3)	<11	55 (0.3)
Thiazolidinediones	122 (3.3)	<11	126 (3.2)	1264 (6.5)	59 (4.8)	1323 (6.4)

Lithium	<11	<11	<11	31 (0.2)	<11	32 (0.2)
Methotrexate	23 (0.6)	<11	29 (0.7)	52 (0.3)	11 (0.9)	63 (0.3)
Glucocorticoids	<11	<11	<11	<11	<11	<11
Calcitonin	<11	<11	<11	<11	<11	<11
Hormone Replacement Therapy	<11	<11	<11	<11	<11	<11
Raloxifene	<11	<11	<11	<11	<11	<11
Calcium	<11	<11	<11	<11	<11	<11
Vitamin D	<11	<11	<11	<11	<11	<11
Fractures						
Vertebral	<11	<11	<11	<11	<11	<11
Non-Vertebral	<11	<11	<11	<11	<11	<11
Other Sites	17 (0.5)	<11	17 (0.4)	139 (0.7)	<11	141 (0.7)
Race						
White	<11	<11	<11	1579 (8.1)	115 (9.3)	1694 (8.2)
African-American	3683 (100)	268 (100)	3951 (100)	13661 (70.0)	603 (49.0)	14264 (68.8)
Hispanic	<11	<11	<11	2337 (12.0)	276 (22.4)	2613 (12.6)
Asian	<11	<11	<11	854 (4.4)	148 (12.0)	1002 (4.8)
Other	<11	<11	<11	1040 (5.3)	85 (6.9)	1125 (5.4)
All Cells with a total of 0 were suppressed; *: Includes Cataracts and Glaucoma <11: CMS does not allow cells with less than 11 patients to be presented						

After restriction to only the FIT population based on with BMD CFRI the study population was significantly smaller with only 3951 patients in. At 365-days of follow-up there were <11 patients who had a MOF fracture in the alendronate group and 29/3683 (0.8%) patients who had a MOF in the non-users, as well as <11 vertebral fracture in the alendronate and 22 (0.6%) vertebral fractures in the non-users group. The results of the with and without BMD CFRI restricted analyses are presented as Table 6.5. While FIT restricted hazard ratios were lower than estimates from the full population, the model including only CFRI continued to produce the lowest HR.

When the CFRI population is restricted based on the without BMD CFRI population, the study population (n=20,734) is larger than the with BMD population. In this population at 365-days there were 13 (1.1%) MOF fractures and 11 (0.9%) vertebral fractures in the alendronate

group and 148 (0.8%) MOF fractures as well as 99 (0.5%) vertebral fractures in the non-user group (0 spine fractures in either group). Incidentally the naïve estimates in this population are only ~0.1 greater than those of the general population, and a similar amount greater than the without BMD population, which may be due to the small sample size and event count observed.

The results suggest that although the population can be restricted to mimic the FIT trial, the claims-based sample ultimately does not reflect the trial population. This is particularly evident by the protective estimates for the with BMD cohort, as they did not have enough events for a realistic result. Based simply on the hazard ratios produced by these analyses, none showed the expected direction of statistically significantly less than 1.

Table 6.5 FIT-restricted population using CFRI at one year, Approach 1 (All New Users)

Analysis Type	MOF Hazard Ratio	Vertebral Hazard Ratio
With BMD		
FIT Null	0.52 (0.07,3.87)	0.68 (0.09,5.08)
FIT with only CFRI	0.55 (0.08,4.09)	0.72 (0.10,5.39)
Fully Adjusted	0.50 (0.06,4.00)	0.84 (0.11,6.43)
FIT SIPTW	1.09 (0.26,4.54)	1.41 (0.33,5.96)
SMRW	0.49 (0.04,5.34)	0.61 (0.05,7.39)
Without BMD		
FIT Null	1.25 (0.68,2.31)	1.64 (0.86,3.15)
FIT with only CFRI	1.14 (0.62,2.11)	1.48 (0.77,2.85)
Fully Adjusted	1.02 (0.54,1.93)	1.25 (0.63,2.50)
FIT SIPTW	1.02 (0.53,1.99)	1.23 (0.59,2.56)
SMRW	0.97 (0.42,2.23)	1.23 (0.49,3.09)

Using all available time for follow-up the tables for the without and with BMD estimates have been combined in Table 6.6. There were 25 (1.6%) patients with a MOF and <11 vertebral fractures in the alendronate group and 180 (0.7%) MOF and 61 (1.7%) vertebral fractures in the non-user group based on with BMD CFRI, and the mean follow-up times for the alendronate group was 1082.8 (SD 659.0) days and 909.9 (SD 567.3) days in the non-users. There were 48

(3.9%) MOF and 36 (2.9%) vertebral fractures in the alendronate group and 347 (1.8%) MOF and 230 (1.2%) vertebral fractures in the non-user group based on without BMD CFRI, and the mean follow-up times for the alendronate group was 1043.9 (SD 652.2), median 1009.5 (IQR 460, 1628) days and mean of 889.4 (SD 555.9), median 760 (IQR 474, 1273) days in the non-users.

Compared to the full populations the FIT restricted populations either saw their estimates increase (for the without BMD population) or become non-significant due to small event counts in the with-BMD population. In both cases the estimates did not get close to the protective effect of alendronate found in the FIT trial. This suggests that any new user is too broad of a non-user comparison group. Also the restricted populations are not similar to the general population which makes it difficult to claim with any certainty that these results should be generalizable to a larger population, or are interpretable in the broader context. These results were similar to the results at one year and indicate that there may be a decrease in hazard when you restrict based on the with-BMD score, but none of the estimates reached statistical significance.

Table 6.6 FIT-Restricted Population All Available time, Approach 1 (All New Users)

Analysis Type	Hazard Ratio	Spine Hazard Ratio
With BMD		
FIT naïve	0.96 (0.35,2.65)	0.59 (0.14,2.41)
FIT with only CFRI	0.98 (0.36,2.71)	0.60 (0.15,2.47)
Fully Adjusted	1.04 (0.36,2.95)	0.58 (0.14,2.43)
FIT SIPTW	2.73 (1.43,5.20)	0.65 (0.17,2.50)
SMRW	1.03 (0.26,4.08)	0.58 (0.10,3.31)
Without BMD		
FIT naïve	1.91 (1.40,2.60)	2.17 (1.52,3.10)
FIT with only CFRI	1.73 (1.27,2.36)	2.00 (1.40,2.87)
Fully Adjusted	1.61 (1.16,2.23)	1.79 (1.22,2.61)
FIT SIPTW	1.93 (1.43,2.60)	2.15 (1.51,3.04)
SMRW	1.62 (0.99,2.65)	1.85 (1.03,3.35)

6.2.4 Conclusions

Evaluating the results of the approach 1 results, we find that classifying non-users as any new-use of a drug is not sufficient to reduce confounding to the level of a placebo compared to alendronate trial. When the population is restricted based on the with CFRI score the study population becomes very small and with a small number of events which create very large confidence intervals. Even when the without BMD CFRI score is used, the number of events are very small, which indicates that the analysis is underpowered and restriction of the study population based on CFRI may not be an appropriate use in a research context.

In general it appears that the any new-use categorization provides a large non-user base for evaluation. However the patients within this population aren't very similar to the users, and when propensity score weighting is used the estimates prior to CFRI exclusions do not follow the normal direction of towards the null. With the populations being so different, propensity scores may not be enough to create similar populations. As CFRI was created using advanced selection methods with the ability to increase error terms to improve prediction ability, it appears that CFRI may do a better job of reducing confounding between users and non-users than propensity

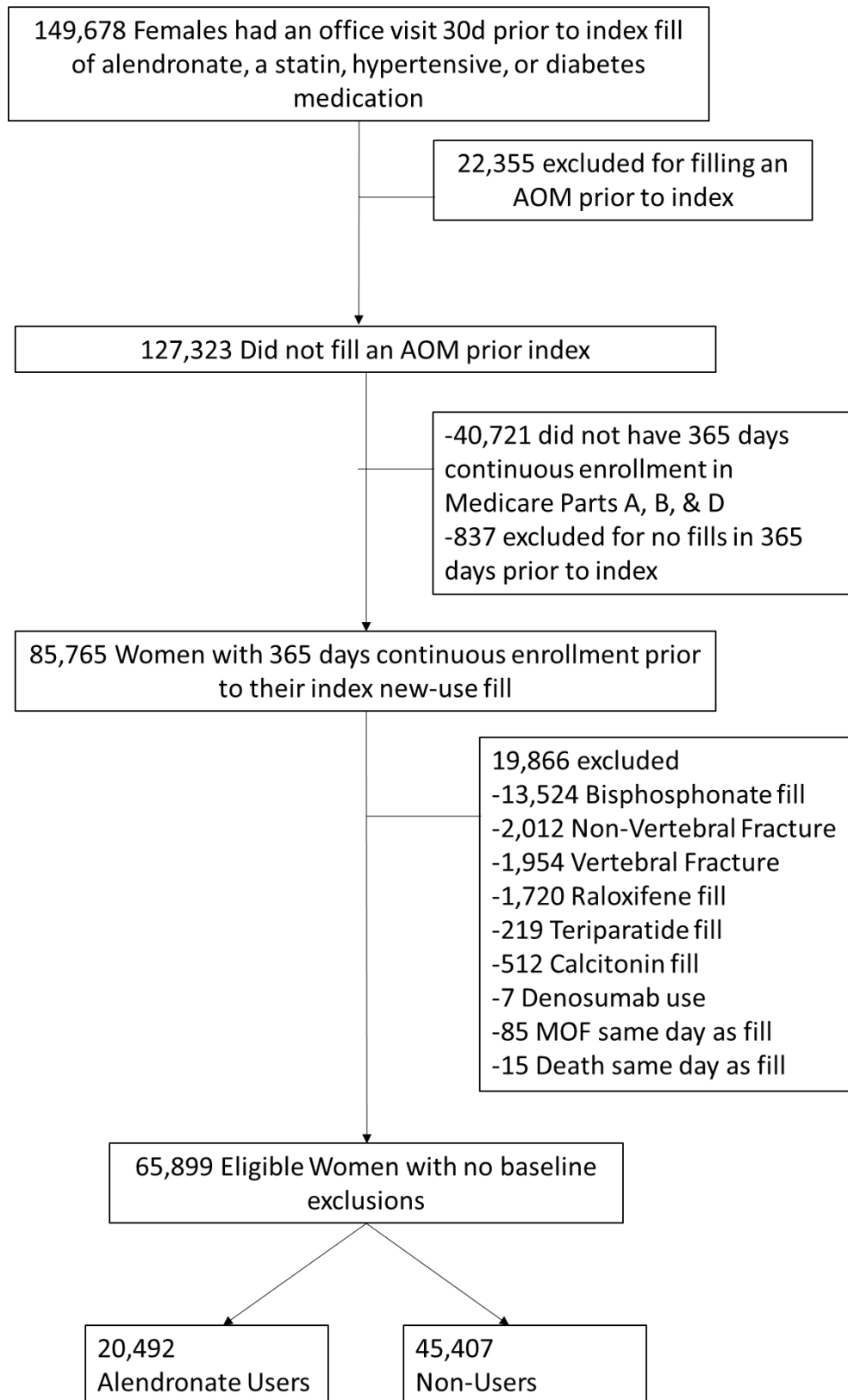
scores. Approach 2 will investigate if restricting the non-users to specific groups will increase CFRIs ability to reduce confounding.

6.3 Approach 2: Non-Users are New Initiators of Statins, Hypertensives and Diabetes Drugs

6.3.1 Study Population

The approach 2 non-user population was restricted to only patients who had either a new use of alendronate or a statin, hypertensive, or diabetes related drug. Specific inclusion and exclusion criterion are presented as Figure 6.3. Overall 149,678 women filled either alendronate or one of the non-use drug categories (statin, hypertension, or diabetes drug) with an office visit within 30-days prior to the fill. Of these women, 85,765 were continuous enrolled for at least 365-days prior to the office visit. Additional exclusions including use of an AOM (prior to index), or a diagnosis code relating to a MOF resulted in the inclusion of 63,882 women, of whom 20,492 were alendronate users, and 45,407 were classified as non-users.

Figure 6.3 Approach 2 Study Population Flowchart



Using the FIT criteria, 12,151 were excluded for an inpatient stay in the 180 days prior to index. An additional 12,604 were excluded for medical diagnoses (8,199 for GERD, 4,732 for cancer, and 766 for metabolic bone disease). Next, we excluded 8,210 for being >80 years old, 3,053 for glucocorticoid use, 2,012 for HRT use, and 210 for history of a total hip arthroplasty. This left 27,661 patients as eligible prior to exclusions based on CFRI score. The without BMD CFRI cohort resulted in 3,221 patients; 859 alendronate users and 2,362 non-users, while the with-BMD cohort had 585 patients with 160 alendronate users and 425 non-users.

Characteristics of the unrestricted study population are presented as Table 6.7. A second analysis will be performed after applying FIT exclusions. In the unrestricted population there was a significant difference between users and non-users in regard to osteoporosis diagnosis with alendronate users having a greater proportion of the population with osteoporosis and kyphosis. Non-users (those initiating statins, antihypertensive or antidiabetic agents) had a larger percentage of diabetes, and congestive heart failure. Otherwise the characteristics appear to be reasonably similar although some differences did reach statistical significance.

Table 6.7 Unrestricted-population Characteristics of Approach 2, Alendronate Users and Diabetes, Hypertension, and Statin Users (Non-Users)

Attribute	Non-Users (n=45,407)	Users (n=20,492)	Total (n=65,899)
Mean Age	74.6 (7.6)	74.4 (7.2)	74.5 (7.5)
In 365-days prior to index			
Osteoporosis, N (%)	4873 (10.7)	7621 (37.2)	12494 (19.0)
Lifestyle Factors, N (%)			
Alcohol Abuse	143 (0.3)	78 (0.4)	221 (0.3)
Falling	2246 (4.9)	802 (3.9)	3048 (4.6)
Vitamin D insufficiency	4010 (8.8)	964 (4.7)	4974 (7.5)
Excess Vitamin A	<11	<11	<11
Genetic factors, N (%)			
Cystic fibrosis	15 (<0.1)	<11	22 (<0.1)
Homocystinuria	73 (0.2)	25 (0.1)	98 (0.1)
Osteogenesis imperfecta	<11	<11	<11
Hypophosphatasia	311 (0.7)	52 (0.3)	363 (0.6)
Gaucher's disease	77 (0.2)	39 (0.2)	116 (0.2)
Idiopathic hypercalciuria	<11	<11	<11
Porphyria	<11	<11	<11
Glycogen storage diseases	<11	<11	<11
Marfan syndrome	<11	<11	<11
Riley-Day syndrome	<11	<11	<11
Hemochromatosis	<11	<11	<11
Hypogonadal states, N (%)			
Androgen insensitivity	<11	<11	<11
Anorexia nervosa and bulimia	582 (1.3)	175 (0.9)	757 (1.1)
Hyperprolactinemia	12 (<0.1)	<11	15 (<0.1)
Premature ovarian failure	30 (0.1)	34 (0.2)	64 (0.1)
Athletic amenorrhea	17 (<0.1)	19 (0.1)	36 (0.1)
Turner and Klinefelters's syndromes	<11	<11	<11
Panhypopituitarism	<11	<11	<11
Endocrine disorders, N (%)			
Adrenal insufficiency	<11	11 (0.1)	18 (<0.1)
Diabetes mellitus (Type 1 & 2)	24476 (53.9)	6739 (32.9)	31215 (47.4)
Cushing's syndrome	29 (0.1)	13 (0.1)	42 (0.1)
Hyperparathyroidism	528 (1.2)	290 (1.4)	818 (1.2)
Central Adiposity	4606 (10.1)	1015 (5.0)	5621 (8.5)
Thyrotoxicosis	1001 (2.2)	538 (2.6)	1539 (2.3)
Gastrointestinal disorders, N (%)			
Celiac disease	55 (0.1)	39 (0.2)	94 (0.1)
Inflammatory Bowel Disease	302 (0.7)	127 (0.6)	429 (0.7)
Malabsorption	182 (0.4)	81 (0.4)	263 (0.4)

Pancreatic disease	593 (1.3)	167 (0.8)	760 (1.2)
Primary biliary cirrhosis	21 (<0.1)	<11	30 (<0.1)
Crohn's Disease	1786 (3.9)	685 (3.3)	2471 (3.7)
Hematologic disorders, N (%)			
Hemophilia	979 (2.2)	337 (1.6)	1316 (2.0)
Thalassemia	28 (0.1)	12 (0.1)	40 (0.1)
Sickle cell anemia	<11	<11	<11
Systemic mastocytosis	<11	<11	<11
Rheumatologic and autoimmune diseases, N (%)			
Ankylosing spondylitis	459 (1.0)	211 (1.0)	670 (1.0)
Lupus	203 (0.4)	118 (0.6)	321 (0.5)
Rheumatoid arthritis	1670 (3.7)	1003 (4.9)	2673 (4.1)
Gout	1792 (3.9)	480 (2.3)	2272 (3.4)
Polymyalgia Rheumatica	341 (0.8)	297 (1.4)	638 (1.0)
Central nervous system disorders, N (%)			
Epilepsy	639 (1.4)	212 (1.0)	851 (1.3)
Parkinson's disease	550 (1.2)	206 (1.0)	756 (1.1)
Stroke	6873 (15.1)	2166 (10.6)	9039 (13.7)
Multiple sclerosis	119 (0.3)	61 (0.3)	180 (0.3)
Spinal cord injury	44 (0.1)	20 (0.1)	64 (0.1)
Alzheimer's disease	5004 (11.0)	1424 (6.9)	6428 (9.8)
Miscellaneous conditions and diseases, N (%)			
AIDS/HIV	38 (0.1)	20 (0.1)	58 (0.1)
Congestive Heart Failure	7732 (17.0)	1902 (9.3)	9634 (14.6)
Muscular dystrophy	15 (<0.1)	<11	18 (<0.1)
Liver Disease	2121 (4.7)	757 (3.7)	2878 (4.4)
Depression	6932 (15.3)	2620 (12.8)	9552 (14.5)
Amyloidosis	16 (<0.1)	<11	20 (<0.1)
End stage renal disease	902 (2.0)	96 (0.5)	998 (1.5)
Sarcoidosis	86 (0.2)	44 (0.2)	130 (0.2)
Chronic metabolic acidosis	700 (1.5)	107 (0.5)	807 (1.2)
Asthma/Chronic obstructive lung disease	10039 (22.1)	4120 (20.1)	14159 (21.5)
Idiopathic scoliosis	760 (1.7)	492 (2.4)	1252 (1.9)
Cataracts	15769 (34.7)	7537 (36.8)	23306 (35.4)
Glaucoma	6390 (14.1)	2949 (14.4)	9339 (14.2)
Kyphosis	10677 (23.5)	11172 (54.5)	21849 (33.2)
Obesity	4606 (10.1)	1015 (5.0)	5621 (8.5)
Disorders of the eye	23517 (51.8)	10705 (52.2)	34222 (51.9)
Osteoarthritis	13725 (30.2)	6238 (30.4)	19963 (30.3)
Renauld's syndrome	4583 (10.1)	801 (3.9)	5384 (8.2)
Medications, N (%)			
Cyclosporine A and tacrolimus	51 (0.1)	21 (0.1)	72 (0.1)
Proton pump inhibitors	11868 (26.1)	5146 (25.1)	17014 (25.8)

Anticoagulants	4300 (9.5)	1619 (7.9)	5919 (9.0)
Selective serotonin reuptake inhibitors	7664 (16.9)	3407 (16.6)	11071 (16.8)
Anticonvulsants	5660 (12.5)	2225 (10.9)	7885 (12.0)
Aromatase inhibitors	563 (1.2)	448 (2.2)	1011 (1.5)
GnRH (Gonadotropin releasing hormone) antagonists and agonists	<11	<11	<11
Thiazolidinediones	3420 (7.5)	1105 (5.4)	4525 (6.9)
Barbiturates	<11	<11	<11
Lithium	58 (0.1)	35 (0.2)	93 (0.1)
Methotrexate	379 (0.8)	327 (1.6)	706 (1.1)
Glucocorticoids	6163 (13.6)	2875 (14.0)	9038 (13.7)
Hormone Replacement Therapy	2745 (6.0)	1181 (5.8)	3926 (6.0)
Fractures			
Other Sites	1726 (3.8)	988 (4.8)	2714 (4.1)
Race			
White	34911 (76.9)	15821 (77.2)	50732 (77.0)
African-American	6426 (14.2)	1855 (9.1)	8281 (12.6)
Hispanic	1793 (3.9)	1170 (5.7)	2963 (4.5)
Asian	1177 (2.6)	1057 (5.2)	2234 (3.4)
Other	767 (1.7)	459 (2.2)	1226 (1.9)
All Cells with a total of 0 were suppressed; *: Includes Cataracts and Glaucoma <11: CMS does not allow cells with less than 11 patients to be presented			

6.3.2 Unrestricted Population Results

The primary outcome of this aim is major osteoporotic fracture, as such the CFRI score which is most applicable is the MOF rather than hip score. However there are two different ways to account for the score, both with and without BMD. The results for the unrestricted population using both with and without BMD MOF CFRI at 365-days post-index are presented in Table 6.8.

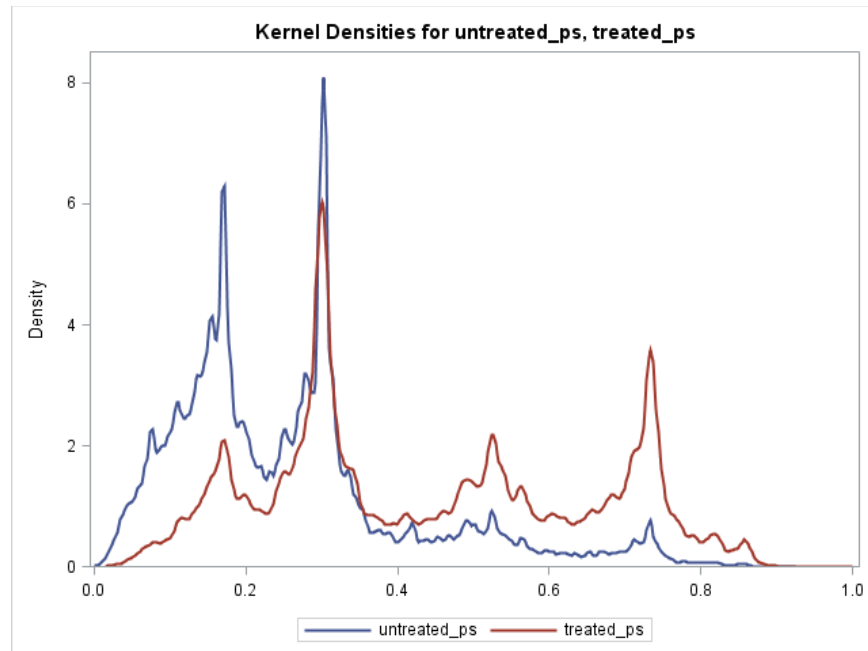
Table 6.8 Hazard Ratios of the Unrestricted Population at 365-days comparing Alendronate Users to Non-Users, Approach 2 (Diabetes, Hypertension, and Statin Users)

Type of Analysis	MOF Hazard Ratio	Vertebral Hazard Ratio
Null	1.41 (1.28,1.55)	1.84 (1.61,2.09)
Only MOF CFRI without BMD	1.28 (1.16,1.41)	1.68 (1.48,1.91)
Only MOF CFRI with BMD	1.20 (1.09,1.32)	1.57 (1.38,1.79)
Fully Adjusted	1.45 (1.30,1.61)	1.84 (1.60,2.12)
SIPTW	1.51 (1.37,1.65)	1.95 (1.72,2.20)
SMRW	1.35 (1.20,1.51)	1.54 (1.32,1.79)

At one year 721 (3.5%) alendronate users and 1,059 (2.3%) non-users had a major osteoporotic fracture. While 437 (2.1%) of alendronate users and 492 (1.1%) of non-users had a vertebral fracture. The null model produced a hazard ratio of 1.4. This was similar and slightly lower than the fully adjusted model using all of the content variables (HR 1.44), as well as the SIPTW model (HR 1.49). The most conservative estimate was the model of CFRI MOF with BMD (HR 1.198).

In regards to the propensity score based approaches neither produced estimates which were less than the simple model with CFRI. The overlap of the propensity scores are presented as Figure 6.4. The propensity score for both the treated and untreated follow similar distributions with approximately four spikes, however there is very little similar overlap in the distribution other than at ~0.3 score. The covariates appeared to be relatively well balanced between the two groups (results not shown), and the addition of the CFRI score did not improve the hazard ratios or the distribution of the propensity score.

Figure 6.4 Density Plot of the Unrestricted-populations Propensity Scores Approach 2 (Diabetes, Hypertension, and Statin Users)



When all available time was used there were 2,517 (12.3%) MOF and 1,439 (7.0%) vertebral fractures in the alendronate users and 2,648 (5.8%) MOF and 1,271 (2.8%) vertebral fractures in the non-users. The mean follow-up time in the alendronate users was 1350.8 (SD 625.3), median 1478 (IQR 864, 1901) days and in the non-users was 919.2 (SD 581.2), median 872 (IQR 456, 1373) days; a nearly 3-year follow-up period for non-users and a 4-year follow-up period for alendronate users. The results of the all available time analysis are presented as Table 6.9. All estimates using all available follow-up demonstrate increases over the one year estimate. The estimates for vertebral fracture continued to be greater than those for MOF with all available time, possibly due to fewer events.

Table 6.9 Hazard Ratios of the Unrestricted Population using all available time comparing Alendronate Users to Non-Users, Approach 2 (Diabetes, Hypertension, and Statin Users)

Type of Analysis	MOF Hazard Ratio	Vertebral Hazard Ratio
Null	1.44 (1.36,1.52)	1.71 (1.58,1.85)
Only MOF CFRI without BMD	1.30 (1.23,1.38)	1.55 (1.43,1.67)
Only MOF CFRI with BMD	1.23 (1.16,1.30)	1.45 (1.34,1.57)
Fully Adjusted	1.43 (1.34,1.52)	1.62 (1.49,1.77)
SIPTW	1.49 (1.41,1.57)	1.70 (1.58,1.83)
SMRW	1.33 (1.24,1.42)	1.40 (1.28,1.54)

6.3.3 FIT restricted population results

The population characteristics generally were very different within the FIT restricted population compared to the unrestricted population, as both of these populations comprised less than 10% of the unrestricted cohort. The distribution of population characteristics was also very different from the unrestricted including the proportion of patients with osteoporosis, though you wouldn't have expected any of these patients to have osteoporosis based on the FIT inclusion criteria only including osteopenic woman. There was a large proportion of patients with diabetes and hypertension in the FIT restricted population, however with these conditions being associated with the non-user drug classes, this is logical. Overall it does not appear that the restricted population either using the with or without BMD CFRI score is really representative of the general population who are using alendronate, which makes it difficult to generalize the results of this analysis to the overall alendronate-using population.

Table 6.10 Population Characteristics of Restricted Population in Approach 2 (Diabetes, Hypertension, and Statin Users)

Attribute	Non-User BMD (n=425)	User BMD (n=160)	Total BMD (n=585)	Non-User No BMD (n=2362)	User No BMD (n=859)	Total No BMD (n=3221)
Mean Age	64.4 (0.5)	64.2 (0.4)	64.3 (0.5)	66.5 (2.1)	65.8 (1.9)	66.3 (2.1)
In 365-days prior to index						
Lifestyle Factors, N (%)						
Alcohol Abuse	<11	<11	<11	<11	<11	<11
Falling	23 (0.6)	<11	24 (0.6)	23 (0.6)	<11	24 (0.6)
Vitamin D insufficiency	64 (1.7)	<11	65 (1.6)	64 (1.7)	<11	65 (1.6)
Excess Vitamin A	<11	<11	<11	<11	<11	<11
Genetic factors, N (%)						
Hypophosphatasia	<11	<11	<11	<11	<11	<11
Gaucher's disease	<11	<11	<11	<11	<11	<11
Riley-Day syndrome	<11	<11	<11	<11	<11	<11
Hemochromatosis	<11	<11	<11	<11	<11	<11
Hypogonadal states, N (%)						
Anorexia nervosa / bulimia	<11	<11	<11	<11	<11	<11
Endocrine disorders, N (%)						
Diabetes mellitus (Type 1 & 2)	856 (23.2)	27 (10.1)	883 (22.3)	856 (23.2)	27 (10.1)	883 (22.3)
Central Adiposity	178 (4.8)	<11	181 (4.6)	178 (4.8)	<11	181 (4.6)
Thyrotoxicosis	22 (0.6)	<11	23 (0.6)	22 (0.6)	<11	23 (0.6)
Gastrointestinal disorders, N (%)						
Celiac disease	<11	<11	<11	<11	<11	<11
Inflammatory Bowel Disease	<11	<11	<11	<11	<11	<11
Malabsorption	<11	<11	<11	<11	<11	<11
Pancreatic disease	<11	<11	11 (0.3)	<11	<11	11 (0.3)
Crohn's Disease	19 (0.5)	<11	20 (0.5)	19 (0.5)	<11	20 (0.5)
Hematologic disorders, N (%)						
Hemophilia	17 (0.5)	<11	17 (0.4)	17 (0.5)	<11	17 (0.4)
Thalassemia	<11	<11	<11	<11	<11	<11
Sickle cell anemia	<11	<11	<11	<11	<11	<11
Rheumatologic and autoimmune diseases, N (%)						
Ankylosing spondylitis	<11	<11	12 (0.3)	<11	<11	12 (0.3)
Lupus	20 (0.5)	<11	21 (0.5)	20 (0.5)	<11	21 (0.5)
Rheumatoid arthritis	40 (1.1)	<11	44 (1.1)	40 (1.1)	<11	44 (1.1)
Gout	48 (1.3)	<11	48 (1.2)	48 (1.3)	<11	48 (1.2)
Polymyalgia Rheumatica	<11	<11	<11	<11	<11	<11
Central nervous system disorders, N (%)						
Epilepsy	38 (1.0)	<11	41 (1.0)	38 (1.0)	<11	41 (1.0)

Parkinson's disease	<11	<11	<11	<11	<11	<11
Stroke	76 (2.1)	<11	76 (1.9)	76 (2.1)	<11	76 (1.9)
Multiple sclerosis	<11	<11	<11	<11	<11	<11
Spinal cord injury	<11	<11	<11	<11	<11	<11
Alzheimer's disease	42 (1.1)	<11	43 (1.1)	42 (1.1)	<11	43 (1.1)
Miscellaneous conditions and diseases, N (%)						
AIDS/HIV	22 (0.6)	<11	24 (0.6)	22 (0.6)	<11	24 (0.6)
Congestive Heart Failure	132 (3.6)	<11	140 (3.5)	132 (3.6)	<11	140 (3.5)
Liver Disease	47 (1.3)	<11	49 (1.2)	47 (1.3)	<11	49 (1.2)
Depression	180 (4.9)	<11	189 (4.8)	180 (4.9)	<11	189 (4.8)
End stage renal disease	145 (3.9)	<11	150 (3.8)	145 (3.9)	<11	150 (3.8)
Sarcoidosis	<11	<11	<11	<11	<11	<11
Chronic metabolic acidosis	<11	<11	<11	<11	<11	<11
Asthma/Chronic obstructive lung disease	221 (6.0)	<11	231 (5.8)	221 (6.0)	<11	231 (5.8)
Idiopathic scoliosis	11 (0.3)	<11	11 (0.3)	11 (0.3)	<11	11 (0.3)
Cataracts	153 (4.2)	<11	161 (4.1)	153 (4.2)	<11	161 (4.1)
Glaucoma	111 (3.0)	<11	118 (3.0)	111 (3.0)	<11	118 (3.0)
Kyphosis	90 (2.4)	<11	100 (2.5)	90 (2.4)	<11	100 (2.5)
Obesity	178 (4.8)	<11	181 (4.6)	178 (4.8)	<11	181 (4.6)
Disorders of the eye	309 (8.4)	12 (4.5)	321 (8.1)	309 (8.4)	12 (4.5)	321 (8.1)
Osteoarthritis	315 (8.6)	11 (4.1)	326 (8.3)	315 (8.6)	11 (4.1)	326 (8.3)
Renault's syndrome	147 (4.0)	<11	150 (3.8)	147 (4.0)	<11	150 (3.8)
Medications, N (%)						
Cyclosporine A and tacrolimus	<11	<11	<11	<11	<11	<11
Proton pump inhibitors	670 (18.2)	40 (14.9)	710 (18.0)	670 (18.2)	40 (14.9)	710 (18.0)
Anticoagulants	154 (4.2)	<11	164 (4.2)	154 (4.2)	<11	164 (4.2)
Selective serotonin reuptake inhibitors	333 (9.0)	20 (7.5)	353 (8.9)	333 (9.0)	20 (7.5)	353 (8.9)
Anticonvulsants	467 (12.7)	30 (11.2)	497 (12.6)	467 (12.7)	30 (11.2)	497 (12.6)
Aromatase inhibitors	<11	<11	13 (0.3)	<11	<11	13 (0.3)
Thiazolidinediones	122 (3.3)	<11	126 (3.2)	122 (3.3)	<11	126 (3.2)
Lithium	<11	<11	<11	<11	<11	<11
Methotrexate	23 (0.6)	<11	29 (0.7)	23 (0.6)	<11	29 (0.7)
Fractures						
Other Sites	17 (0.5)	<11	17 (0.4)	17 (0.5)	<11	17 (0.4)
Race						
African-American	3683 (100)	268 (100)	3951 (100)	3683 (100)	268 (100)	3951 (100)
All Cells with a total of 0 were suppressed; *: Includes Cataracts and Glaucoma <11: CMS does not allow cells with less than 11 patients to be presented						

There are 585 women who are eligible for inclusion based on their with BMD CFRI score. Within this population at one year there were 0 spine fractures and 0 MOF for alendronate users, and <11 MOF and <11 spine fractures for non-users. Based on 0 events for the alendronate group, hazard ratios cannot be estimated. When the restricted population uses the without BMD CFRI score there are 3,221 eligible women. There were <11 MOF and <11 vertebral fractures in the alendronate users as well as 22 (0.9%) MOF and <11 vertebral fractures in the non-users (Table 6.11).

Table 6.11 Hazard Ratios for FIT-restricted population using MOF without BMD CFRI at one year, Approach 2 (Diabetes, Hypertension, and Statin Users)

Analysis Type	MOF Hazard Ratio	Vertebral Hazard Ratio
Without BMD		
FIT Null	1.07 (0.49,2.31)	2.28 (0.82,6.29)
FIT with only CFRI	1.01 (0.47,2.20)	2.11 (0.77,5.82)
Fully Adjusted	0.75 (0.30,1.89)	1.52 (0.45,5.18)
FIT SIPTW	0.81 (0.35,1.87)	1.66 (0.58,4.76)
SMRW	0.83 (0.34,2.04)	1.58 (0.47,5.26)

Since there are no events in the with BMD group it is impossible to compare their estimates to the without BMD group. However the without BMD group produced MOF HR near one, with the fully adjusted models resulting in the lowest HR (this was true for both MOF and vertebral). The estimates for the without BMD CFRI group are ~0.5 lower than in the full population which suggests that if there were more events and these HR would hold, it may be possible to get to the same estimates as FIT for the MOF. However this does not hold true for the vertebral, as these estimates have increased compared to the general population. These results suggest that the selected population may not be generalizable to the groups of interest. Also CFRI reduced, but did not eliminate the confounding inherent in alendronate compared to non-users analyses.

Using all available time for follow-up the tables for the without and with BMD estimates have been combined in Table 6.12. In the with-BMD group there were <11 MOF and <11 vertebral fractures in the alendronate group as well as <11 MOF and <11 vertebral fractures in non-users by the end of follow-up. The mean follow-up time for the alendronate group was 994.6 (SD 585.6), median 988 (IQR 587, 1418.5) days and mean 796.4 (SD 554.2), median 698 (IQR 423, 1068) days in the non-users. In the without-BMD group there were 36 (4.2%) patients with a MOF and 24 (2.8%) vertebral fractures in the alendronate group and 36 (1.5%) MOF and 14 (0.6%) vertebral fractures for non-users using all available follow-up time. The mean follow-up time for the alendronate group was 1190.9 (SD 626.4), median 1126 (IQR 694, 1764) days and 867.9 (SD 556.3), median 743 (IQR 456, 1270) days in the non-users. Full results of the with and without BMD CFRI restricted analysis for MOF and vertebral fracture utilizing all available time are presented as Table 6.12.

Table 6.12 FIT-Restricted Population All Available time, Approach 2 (Diabetes, Hypertension, and Statin Users)

Analysis Type	MOF Hazard Ratio	Vertebral Hazard Ratio
With BMD		
FIT Null	0.90 (0.17,4.65)	1.07 (0.10,11.95)
FIT with only CFRI	0.85 (0.16,4.44)	1.03 (0.09,11.51)
Fully Adjusted	0.71 (0.07,7.32)	7.51 (0.000,9999.99)
FIT SIPTW	0.74 (0.11,4.88)	0.34 (0.01,18.74)
SMRW	1.23 (0.14,11.06)	1.65 (0.06,48.65)
Without BMD		
FIT Null	2.075 (1.301,3.310)	3.49 (1.79,6.80)
FIT with only CFRI	1.934 (1.212,3.087)	3.24 (1.66,6.31)
Fully Adjusted	1.381 (0.801,2.382)	2.15 (0.96,4.78)
FIT SIPTW	1.759 (1.096,2.823)	2.86 (1.48,5.52)
SMRW	1.636 (0.906,2.956)	2.44 (1.05,5.66)

Similar to the estimates at one year, the with-BMD estimates are unstable due to such small event counts. HRs increased in the without BMD CFRI restricted population compared to the one year estimates. The difference between fracture counts caused the majority of the without BMD estimates to be statistically significant indicating that alendronate is associated with an increase in fractures, which demonstrates that we were unable to sufficiently reduce confounding. The takeaway from the restricted analysis is that once this population is restricted, it is not generalizable, and there are so few events that any estimate is highly unstable. Therefore any generalizability based on these findings should be questioned. This indicates that the aim hypothesis was wrong, although in some cases the CFRI restricted estimates are closer to the null, they are unstable and should not be used as applicable to the general population.

6.3.4 Conclusions

Evaluating the approach 2 results, we find that classifying non-users as users of statins, diabetes, and hypertension drugs does not sufficiently reduce confounding to comparable levels of the FIT RCT (HR 0.72). When restriction is used, rather than following the hypothesis of creating the most harmonious estimates, the hazard ratios created are unstable due to small n's and event counts. This suggests that restriction based on all of the FIT criterion is likely not appropriate in this context. The most common reason women were excluded from this analysis were CFRI scores which corresponded to the BMD values from FIT, ergo if the acceptable CFRI scores are expanded restriction may still be a useful research tool, though in its current context the FIT restricted analyses are underpowered.

Overall it appears that the three medication classes may be appropriate comparison groups, if additional steps are taken. This is more apparent in this analysis compared to approach 1 where there were large discrepancies between the users and non-users. The user and non-user

groups appeared relatively well matched based on population characteristics, however propensity score methods increased HR compared to more standard methods. This likely is a result of imbalanced covariates, as evidenced by little to no overlap in the propensity score distributions. But in the case of the CFRI score, its simple inclusion in a regression equation was shown to bring the hazard ratios closer to the null which was the anticipated goal, as these were the findings from the FIT trial.

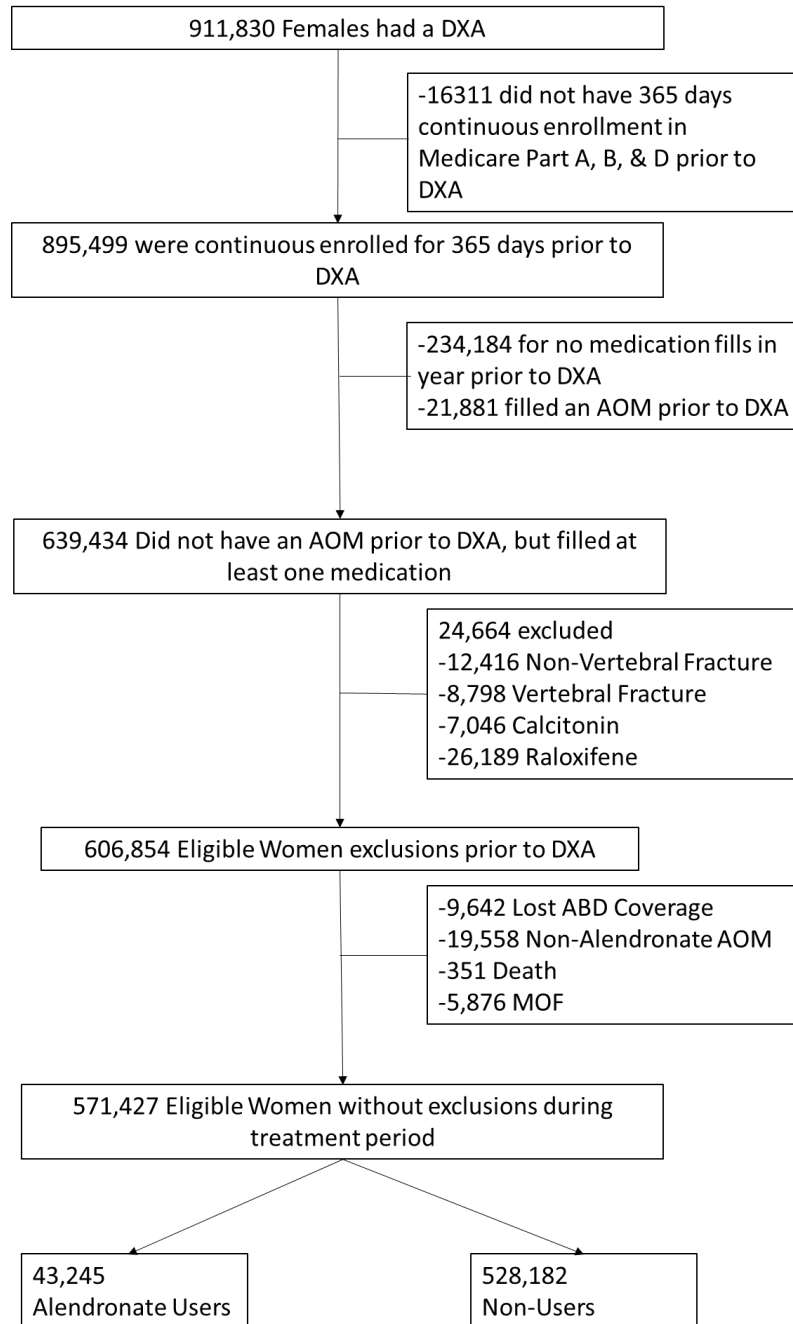
Based on these findings, non-users cannot be classified based on drug use alone in the context of alendronate compared to non-users. Approach 3 will investigate if the use of a DXA as the index event will improve estimates, rather than including individuals based on non-alendronate drug use.

6.4 Approach 3

6.4.1 Study Population

The approach 3 non-user population is defined as women who had a DXA (CPT 70675, 777080, 77081), and the alendronate users are those who were fully eligible in approach 1. The specific inclusion and exclusion criterion are specified in Figure 6.5, however these exclusions only include the non-user population. Overall 911,830 women had a DXA between 2008 and 2013. Of these 894,857 were continuous enrolled in Medicare Parts A, B, & D for at least 365-days before the DXA. Women were excluded for not filling a medication in the 365-days prior to DXA, as well as filling an AOM (bisphosphonate, calcitonin, Raloxifene, or Denosumab) during the same time period resulting in 623,391. Further exclusions included vertebral and non-vertebral fracture, as well as death, resulting in 597,827 non-users and 29,772 alendronate users for this analysis.

Figure 6.5 Approach 3 (DXA visit as non-user) Study Population Flowchart



*: AOM-Bisphosphonate, teriapatide or denosumab

Using the FIT criteria, 45,085 were excluded for an inpatient stay in the 180 days prior to index. An additional 78,041 were excluded for medical diagnoses (44,155 for GERD, 35,946 for cancer, and 3,835 for metabolic bone disease). Next, we excluded 74,892 for being >80 years of age, 45,270 for glucocorticoid use, 50,149 for HRT use, and 3,740 for history of a total hip arthroplasty. This left 273,793 patients as eligible prior to exclusions based on CFRI score. The without BMD CFRI cohort resulted in 16,531 patients; 1,401 alendronate users and 15,130 non-users, while the with-BMD cohort had 1,459 patients with 293 alendronate users and 1,166 non-users.

The characteristics of the unrestricted study population are presented in Table 6.13. A second analysis will be performed with a population after FIT exclusions. In the unrestricted population the population characteristics were largely similar. There were slight imbalances in asthma/COPD as well as HRT use, but generally very similar.

Table 6.13 Approach 3 (DXA visit as non-user) Characteristics of the Study Population

Attribute	Non-Users (n=527,254)	Users (n=43,716)	Total (n=570,970)
Mean Age	73.6 (6.5)	74.9 (6.9)	73.7 (6.5)
Osteoporosis, N (%)	26631 (5.1)	2338 (5.3)	28969 (5.1)
Lifestyle Factors, N (%)			
Alcohol Abuse	876 (0.2)	109 (0.2)	985 (0.2)
Falling	6436 (1.2)	770 (1.8)	7206 (1.3)
Vitamin D insufficiency	21348 (4.0)	1297 (3.0)	22645 (4.0)
Excess Vitamin A	11 (<0.1)	<11	11 (<0.1)
Genetic factors, N (%)			
Cystic fibrosis	39 (<0.1)	<11	45 (<0.1)
Homocystinuria	215 (<0.1)	<11	223 (<0.1)
Osteogenesis imperfecta	11 (<0.1)	<11	11 (<0.1)
Hypophosphatasia	773 (0.1)	62 (0.1)	835 (0.1)
Gaucher's disease	169 (<0.1)	11 (<0.1)	180 (<0.1)
Porphyria	50 (<0.1)	<11	55 (<0.1)
Glycogen storage diseases	22 (<0.1)	<11	22 (<0.1)
Marfan syndrome	13 (<0.1)	<11	13 (<0.1)
Riley-Day syndrome	<11	<11	<11
Hemochromatosis	117 (<0.1)	<11	125 (<0.1)
Hypogonadal states, N (%)			
Androgen insensitivity	<11	<11	<11
Anorexia nervosa and bulimia	1468 (0.3)	172 (0.4)	1640 (0.3)
Hyperprolactinemia	41 (<0.1)	<11	41 (<0.1)
Premature ovarian failure	40 (<0.1)	<11	44 (<0.1)
Athletic amenorrhea	86 (<0.1)	13 (<0.1)	99 (<0.1)
Turner and Klinefelters's syndromes	<11	<11	<11
Panhypopituitarism	21 (<0.1)	<11	22 (<0.1)
Endocrine disorders, N (%)			
Adrenal insufficiency	77 (<0.1)	<11	80 (<0.1)
Diabetes mellitus (Type 1 & 2)	84245 (16.0)	7006 (16.0)	91251 (16.0)
Cushing's syndrome	138 (<0.1)	11 (<0.1)	149 (<0.1)
Hyperparathyroidism	3405 (0.6)	225 (0.5)	3630 (0.6)
Central Adiposity	19086 (3.6)	1271 (2.9)	20357 (3.6)
Thyrotoxicosis	4738 (0.9)	424 (1.0)	5162 (0.9)
Gastrointestinal disorders, N (%)			
Celiac disease	522 (0.1)	26 (0.1)	548 (0.1)
Inflammatory Bowel Disease	2161 (0.4)	171 (0.4)	2332 (0.4)
Malabsorption	1182 (0.2)	76 (0.2)	1258 (0.2)
Pancreatic disease	3171 (0.6)	265 (0.6)	3436 (0.6)
Primary biliary cirrhosis	372 (0.1)	20 (<0.1)	392 (0.1)

Crohn's Disease	8523 (1.6)	805 (1.8)	9328 (1.6)
Hematologic disorders, N (%)			
Hemophilia	2643 (0.5)	242 (0.6)	2885 (0.5)
Thalassemia	210 (<0.1)	13 (<0.1)	223 (<0.1)
Sickle cell anemia	40 (<0.1)	<11	44 (<0.1)
Systemic mastocytosis	17 (<0.1)	<11	17 (<0.1)
Rheumatologic and autoimmune diseases, N (%)			
Ankylosing spondylitis	1375 (0.3)	102 (0.2)	1477 (0.3)
Lupus	1866 (0.4)	107 (0.2)	1973 (0.3)
Rheumatoid arthritis	11594 (2.2)	982 (2.2)	12576 (2.2)
Gout	7256 (1.4)	568 (1.3)	7824 (1.4)
Polymyalgia Rheumatica	2859 (0.5)	295 (0.7)	3154 (0.6)
Central nervous system disorders, N (%)			
Epilepsy	2632 (0.5)	288 (0.7)	2920 (0.5)
Parkinson's disease	2279 (0.4)	272 (0.6)	2551 (0.4)
Stroke	14961 (2.8)	1460 (3.3)	16421 (2.9)
Multiple sclerosis	846 (0.2)	82 (0.2)	928 (0.2)
Spinal cord injury	79 (<0.1)	12 (<0.1)	91 (<0.1)
Alzheimer's disease	11359 (2.2)	1474 (3.4)	12833 (2.2)
Miscellaneous conditions and diseases, N (%)			
AIDS/HIV	142 (<0.1)	<11	150 (<0.1)
Congestive Heart Failure	21716 (4.1)	2337 (5.3)	24053 (4.2)
Muscular dystrophy	64 (<0.1)	<11	68 (<0.1)
Liver Disease	10165 (1.9)	793 (1.8)	10958 (1.9)
Depression	29086 (5.5)	2830 (6.5)	31916 (5.6)
Amyloidosis	102 (<0.1)	<11	107 (<0.1)
End stage renal disease	2358 (0.4)	160 (0.4)	2518 (0.4)
Sarcoidosis	768 (0.1)	64 (0.1)	832 (0.1)
Chronic metabolic acidosis	1606 (0.3)	160 (0.4)	1766 (0.3)
Asthma/Chronic obstructive lung disease	51315 (9.7)	5446 (12.5)	56761 (9.9)
Idiopathic scoliosis	6012 (1.1)	579 (1.3)	6591 (1.2)
Cataracts	17777 (3.4)	1608 (3.7)	19385 (3.4)
Glaucoma	7916 (1.5)	676 (1.5)	8592 (1.5)
Kyphosis	56392 (10.7)	4755 (10.9)	61147 (10.7)
Obesity	19086 (3.6)	1271 (2.9)	20357 (3.6)
Disorders of the eye	36397 (6.9)	3242 (7.4)	39639 (6.9)
Osteoarthritis	61725 (11.7)	5192 (11.9)	66917 (11.7)
Renault's syndrome	14154 (2.7)	1196 (2.7)	15350 (2.7)
Medications, N (%)			
Cyclosporine A and tacrolimus	817 (0.2)	46 (0.1)	863 (0.2)
Proton pump inhibitors	140874 (26.7)	11984 (27.4)	152858 (26.8)
Anticoagulants	44817 (8.5)	4067 (9.3)	48884 (8.6)
Selective serotonin reuptake inhibitors	87327 (16.6)	7704 (17.6)	95031 (16.6)

Anticonvulsants	62458 (11.8)	5512 (12.6)	67970 (11.9)
Aromatase inhibitors	15584 (3.0)	994 (2.3)	16578 (2.9)
Thiazolidinediones	14383 (2.7)	1502 (3.4)	15885 (2.8)
Barbiturates	137 (<0.1)	11 (<0.1)	148 (<0.1)
Lithium	1085 (0.2)	81 (0.2)	1166 (0.2)
Methotrexate	8495 (1.6)	660 (1.5)	9155 (1.6)
Glucocorticoids	86617 (16.4)	7560 (17.3)	94177 (16.5)
Hormone Replacement Therapy	66397 (12.6)	2983 (6.8)	69380 (12.2)
Vitamin D	<11	<11	<11
Fractures			
Other Sites	10045 (1.9)	1197 (2.7)	11242 (2.0)
Race			
White	460912 (87.4)	36131 (82.7)	497043 (87.1)
African-American	38938 (7.4)	3222 (7.4)	42160 (7.4)
Hispanic	10541 (2.0)	1864 (4.3)	12405 (2.2)
Asian	7705 (1.5)	1500 (3.4)	9205 (1.6)
Other	6602 (1.3)	706 (1.6)	7308 (1.3)
<i>Non-users are defined as any new-use of any drug in any class</i>			
All Cells with a total of 0 were suppressed; *: Includes Cataracts and Glaucoma			

6.4.2 Unrestricted Population Results

The primary outcome of this aim is vertebral fracture, and the MOF score includes vertebral fractures, therefore the MOF CFRI scores will be used in adjustments for this analysis. The results for the unrestricted population using both with and without BMD MOF CFRI at 365-days post-index are presented in Table 6.14.

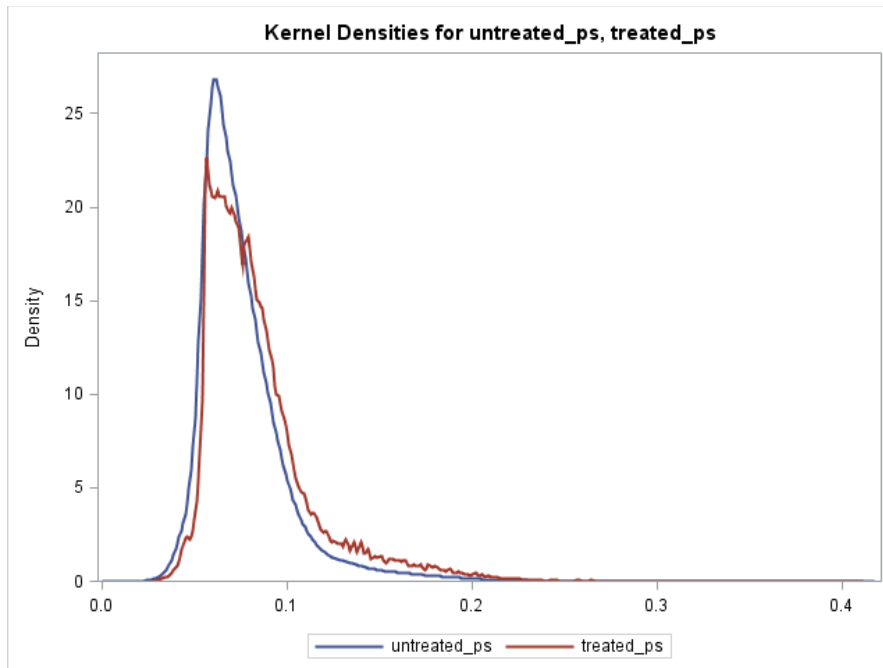
Table 6.14 Unrestricted Population for Approach 3 (DXA visit as non-user), Hazard Ratio for MOF at 365-days comparing Alendronate Users to Non-Users

Type of Analysis	MOF Hazard Ratio	Vertebral Hazard Ratio
Null	1.39 (1.31,1.47)	1.34 (1.26,1.46)
Only MOF CFRI without BMD	1.31 (1.24,1.38)	1.28 (1.18,1.37)
Only MOF CFRI with BMD	1.34 (1.27,1.42)	1.31 (1.21,1.41)
Fully Adjusted	1.24 (1.17,1.31)	1.20 (1.11,1.29)
SIPTW	1.26 (1.19,1.34)	1.23 (1.14,1.33)
SMRW	1.22 (1.12,1.32)	1.18 (1.06,1.31)

At one year 1,360 (3.1%) alendronate users and 11,520 (2.2%) non-users had a major osteoporotic fracture while 782 (1.8%) alendronate and 6,757 (1.3%) non-users had a vertebral fracture. The null model produced a hazard ratio of 1.4 for both MOF and vertebral fractures which represented the highest estimate in both groups. The most conservative estimate was the SMRW models followed by fully adjusted model for both groups, which was different than the other two approaches where this estimate was greater than when only the CFRI variable was included in the model. None of the estimates were less than 1 or crossed 1. Therefore at one year DXA users are not a sufficient comparison group.

In regards to the propensity score based approaches, for the first time in this analysis produced realistic estimates. The kernel density plot of the propensity scores is presented as Figure 6.6. These two distributions are very similar with the user group having a lower peak and less smooth distribution, however they nearly cover each other entirely. When the groups were compared after weighting the characteristics for the most part were not similar which is surprising based on the estimates being similar to those of the standard regression approaches.

Figure 6.6 Kernel Density Plot for Propensity Scores in Approach 3 (DXA visit as non-user)



The results for the unrestricted population using both with and without BMD MOF CFRI using all available time post-index are presented in Table 6.15.

Table 6.15 Unrestricted Population for Approach 3 (DXA visit as non-user), Hazard Ratio for MOF using all available time

Type of Analysis	MOF Hazard Ratio	Vertebral Hazard Ratio
Null	1.41 (1.37,1.46)	1.39 (1.34,1.45)
Only MOF CFRI without BMD	1.35 (1.31,1.40)	1.33 (1.28,1.39)
Only MOF CFRI with BMD	1.37 (1.33,1.42)	1.35 (1.30,1.41)
Fully Adjusted	1.30 (1.26,1.34)	1.27 (1.22,1.32)
SIPTW	1.29 (1.25,1.34)	1.27 (1.22,1.33)
SMRW	1.26 (1.21,1.32)	1.24 (1.17,1.31)

Using all available time, alendronate users had a mean of 1078.9 (SD 697.3), median 1024 (IQR 464, 1648) days and non-users were followed for a mean of 979.0 (SD 696.5), median 851 (IQR 375, 1525) days. During this time period 4,697 (10.7%) of alendronate users and 36,375 (6.9%) of non-users had a major osteoporotic fracture and 2664 (6.1%) of

alendronate users and 20,741 (3.9%) of non-users had a vertebral fracture. The null model which only includes the grouping indicator produced a MOF and vertebral hazard ratio of 1.4, which was similar to at 365-days. The most conservative estimates were the SMRW estimates, which is the same as at 365-days. The with-BMD estimates were greater than the without BMD estimates in approach 3 which was different than the first two approaches.

Comparing these estimate to the FIT trial clinical fracture hazard ratio at three years shows that even the lowest estimate at one year is greater than the FIT estimate. Both the alendronate and non-user group were followed for around 3 years, and our results indicate that CFRI in the general population is not able to reduce confounding by indication by a sufficient amount.

6.4.3 FIT restricted population results

The population characteristics generally were very different within the FIT restricted population compared to the unrestricted population. The characteristics of the population are presented as Table 6.16. The largest difference was in the with BMD population where there were only Black patients who were included. This was due to the Hip with BMD intercept being -7.8 and for most patients the only other variable which would be used in the algorithm was age, which to have a score <1.0 a patient would have needed to have had to have been under the age of 57, all of whom would have not been included in the population based on the Medicare age population being ≥ 65 . There are no patients in the with BMD population who had a diagnosis of osteoporosis, this is due to the inclusion of the age * osteoporosis variable in CFRI hip with BMD which similar to the age variable increases the hip CFRI score to >1 , which excludes the patient from the analysis.

The distribution of characteristics seems to be reasonably well balanced between users and non-users, other than osteoporosis in the without BMD CFRI group. There were significant differences in some population characteristics, however many of these were due to sample size rather than a clinical difference. Diabetes had an interesting spread across the groups with the alendronate users having a substantially lower percentage of patients with diabetes than non-users in the with-BMD, but the inverse in the without-BMD. The miscellaneous conditions all seemed to have large discrepancies in proportions between the with and without-BMD population which additionally leads credence to these populations not being sufficiently similar to the general population. This makes it difficult to claim any generalizability to the general population from these results. However these characteristics may be similar to those of the highly restricted RCT population.

Table 6.16 Population Characteristics of Restricted Population in Approach 3 (DXA visit as non-user)

Attribute	Non-User BMD (n=1043)	User BMD (n=84)	Total BMD (n=1127)	Non-User No BMD (n=13332)	User No BMD (n=1110)	Total No BMD (n=14442)
Mean Age	64.6 (0.5)	64.6 (0.5)	64.6 (0.5)	67.2 (1.8)	67.0 (1.6)	67.2 (1.8)
Osteoporosis, N (%)	<11	<11	<11	121 (0.9)	17 (1.5)	138 (1.0)
Lifestyle Factors, N (%)						
Alcohol Abuse	<11	<11	<11	14 (0.1)	<11	18 (0.1)
Falling	<11	<11	<11	80 (0.6)	<11	87 (0.6)
Vitamin D insufficiency	33 (3.2)	2 (2.4)	35 (3.1)	516 (3.9)	24 (2.2)	540 (3.7)
Excess Vitamin A	<11	<11	<11	<11	<11	<11
Genetic factors, N (%)						
Cystic fibrosis	<11	<11	<11	<11	<11	<11
Homocystinuria	<11	<11	<11	<11	<11	<11
Hypophosphatasia	<11	<11	<11	<11	<11	<11
Gaucher's disease	<11	<11	<11	11 (0.1)	<11	13 (0.1)
Hypogonadal states, N (%)						
Anorexia nervosa and bulimia	<11	<11	<11	25 (0.2)	<11	28 (0.2)
Hyperprolactinemia	<11	<11	<11	<11	<11	<11
Premature ovarian failure	<11	<11	<11	<11	<11	<11
Athletic amenorrhea	<11	<11	<11	<11	<11	<11
Endocrine disorders, N (%)						
Adrenal insufficiency	<11	<11	<11	<11	<11	<11
Diabetes mellitus (Type 1 & 2)	295 (28.3)	16 (19.0)	311 (27.6)	4068 (30.5)	278 (25.0)	4346 (30.1)
Cushing's syndrome	<11	<11	<11	<11	<11	<11
Central Adiposity	65 (6.2)	<11	67 (5.9)	1253 (9.4)	71 (6.4)	1324 (9.2)
Thyrototoxicosis	12 (1.2)	<11	12 (1.1)	142 (1.1)	13 (1.2)	155 (1.1)
Gastrointestinal disorders, N (%)						
Celiac disease	<11	<11	<11	<11	<11	<11
Inflammatory Bowel Disease	<11	<11	<11	13 (0.1)	<11	14 (0.1)
Malabsorption	<11	<11	<11	<11	<11	<11
Pancreatic disease	<11	<11	<11	21 (0.2)	<11	26 (0.2)
Primary biliary cirrhosis	<11	<11	<11	<11	<11	<11
Crohn's Disease	<11	<11	<11	65 (0.5)	<11	73 (0.5)
Hematologic disorders, N (%)						
Hemophilia	<11	<11	<11	57 (0.4)	<11	63 (0.4)
Thalassemia	<11	<11	<11	<11	<11	<11
Sickle cell anemia	<11	<11	<11	<11	<11	<11
Systemic mastocytosis	<11	<11	<11	<11	<11	<11
Rheumatologic and autoimmune diseases, N (%)						

Ankylosing spondylitis	<11	<11	<11	13 (0.1)	<11	14 (0.1)
Lupus	<11	<11	<11	30 (0.2)	<11	30 (0.2)
Rheumatoid arthritis	15 (1.4)	<11	16 (1.4)	64 (0.5)	<11	67 (0.5)
Gout	11 (1.1)	<11	13 (1.2)	181 (1.4)	<11	190 (1.3)
Polymyalgia Rheumatica	<11	<11	<11	<11	<11	<11
Central nervous system disorders, N (%)						
Epilepsy	<11	<11	<11	41 (0.3)	<11	47 (0.3)
Parkinson's disease	<11	<11	<11	20 (0.2)	<11	22 (0.2)
Stroke	21 (2.0)	<11	23 (2.0)	266 (2.0)	18 (1.6)	284 (2.0)
Multiple sclerosis	<11	<11	<11	20 (0.2)	<11	23 (0.2)
Spinal cord injury	<11	<11	<11	<11	<11	<11
Alzheimer's disease	<11	<11	<11	120 (0.9)	11 (1.0)	131 (0.9)
Miscellaneous conditions and diseases, N (%)						
AIDS/HIV	<11	<11	<11	28 (0.2)	<11	31 (0.2)
Congestive Heart Failure	35 (3.4)	<11	39 (3.5)	407 (3.1)	29 (2.6)	436 (3.0)
Muscular dystrophy	<11	<11	<11	<11	<11	<11
Liver Disease	<11	<11	<11	190 (1.4)	17 (1.5)	207 (1.4)
Depression	62 (5.9)	6 (7.1)	68 (6.0)	640 (4.8)	61 (5.5)	701 (4.9)
Amyloidosis	<11	<11	<11	<11	<11	<11
End stage renal disease	40 (3.8)	<11	43 (3.8)	187 (1.4)	<11	197 (1.4)
Sarcoidosis	<11	<11	<11	28 (0.2)	<11	28 (0.2)
Chronic metabolic acidosis	<11	<11	<11	11 (0.1)	<11	14 (0.1)
Asthma/Chronic obstructive lung disease	68 (6.5)	<11	78 (6.9)	819 (6.1)	72 (6.5)	891 (6.2)
Idiopathic scoliosis	<11	<11	<11	40 (0.3)	<11	44 (0.3)
Cataracts	33 (3.2)	<11	35 (3.1)	519 (3.9)	37 (3.3)	556 (3.8)
Glaucoma	28 (2.7)	<11	29 (2.6)	314 (2.4)	19 (1.7)	333 (2.3)
Kyphosis	31 (3.0)	<11	33 (2.9)	539 (4.0)	45 (4.1)	584 (4.0)
Obesity	65 (6.2)	<11	67 (5.9)	1253 (9.4)	71 (6.4)	1324 (9.2)
Disorders of the eye	75 (7.2)	<11	78 (6.9)	1050 (7.9)	79 (7.1)	1129 (7.8)
Osteoarthritis	93 (8.9)	<11	97 (8.6)	1294 (9.7)	88 (7.9)	1382 (9.6)
Renault's syndrome	43 (4.1)	<11	45 (4.0)	440 (3.3)	25 (2.3)	465 (3.2)
Medications, N (%)						
Cyclosporine A and tacrolimus	<11	<11	<11	20 (0.2)	<11	21 (0.1)
Proton pump inhibitors	269 (25.8)	14 (16.7)	283 (25.1)	3241 (24.3)	303 (27.3)	3544 (24.5)
Anticoagulants	53 (5.1)	6 (7.1)	59 (5.2)	578 (4.3)	39 (3.5)	617 (4.3)
Selective serotonin reuptake inhibitors	145 (13.9)	14 (16.7)	159 (14.1)	1406 (10.5)	137 (12.3)	1543 (10.7)
Anticonvulsants	178 (17.1)	15 (17.9)	193 (17.1)	1673 (12.5)	136 (12.3)	1809 (12.5)
Aromatase inhibitors	13 (1.2)	<11	16 (1.4)	138 (1.0)	<11	145 (1.0)
Thiazolidinediones	56 (5.4)	<11	61 (5.4)	793 (5.9)	75 (6.8)	868 (6.0)
Barbiturates	<11	<11	<11	<11	<11	<11

Lithium	<11	<11	<11	22 (0.2)	<11	23 (0.2)
Methotrexate	11 (1.1)	<11	13 (1.2)	57 (0.4)	<11	61 (0.4)
Fractures, N (%)						
Other Sites	<11	<11	<11	95 (0.7)	<11	104 (0.7)
Race, N (%)						
White	<11	<11	<11	613 (4.6)	38 (3.4)	651 (4.5)
African-American	1043 (100)	84 (100)	1127 (100)	9584 (71.9)	599 (54.0)	10183 (70.5)
Hispanic	<11	<11	<11	1590 (11.9)	272 (24.5)	1862 (12.9)
Asian	<11	<11	<11	606 (4.5)	118 (10.6)	724 (5.0)
Other	<11	<11	<11	930 (7.0)	82 (7.4)	1012 (7.0)
Cells with 0 persons were suppressed. <11: CMS does not allow cells with less than 11 patients to be presented						

After restriction to only the CFRI population based on with BMD CFRI, the study population was significantly smaller with only 1127 patients. At 365-days of follow-up there were 0 (0.0%) patients who had an MOF fracture in the alendronate group and <11 patients who had a MOF in the non-users, as well as 0 (0.0%) vertebral fracture in the alendronate and <11 vertebral fractures in the non-users group. Because there were no fractures in the alendronate group, the with-BMD hazard ratios could not be estimated. The results of the with and without-BMD CFRI restricted analyses are presented as Table 6.17. All of the FIT restricted estimates are less than those of the full population, though the same finding of the only inclusion of CFRI in the model producing the lowest HR also held true in this population.

When the CFRI population is restricted based on the without BMD CFRI population, the study population (n=16,531) is larger than the with BMD population. In this population at 365 days there were 22 (1.6%) MOF fractures and 17 (1.2%) vertebral fractures in the alendronate group and 63 (0.4%) MOF fractures as well as 38 (0.3%) vertebral fractures in the non-user group. Incidentally the null estimates in this population are only ~0.1 greater than greater than

those of the general population, and a similar amount greater than the without BMD population as well which may be due to the small sample size and event count for this population.

The results from both populations suggest that the selected population are not generalizable to the larger population. This is particularly evident by the protective estimates for the with BMD cohort, as they did not have enough events for a realistic result. Based simply on the hazard ratios produced by these analyses, none showed the expected direction of an estimate which was statistically significantly less than 1.

Table 6.17 FIT-restricted population at one year, Approach 3 (DXA visit as non-user)

Analysis Type	MOF Hazard Ratio	Vertebral Hazard Ratio
Without BMD		
FIT Null	2.25 (1.21,4.17)	2.32 (1.03,5.23)
FIT with only CFRI	2.06 (1.11,3.83)	2.14 (0.95,4.82)
Fully Adjusted	2.07 (1.09,3.93)	2.22 (0.95,5.20)
FIT SIPTW	2.48 (1.37,4.50)	2.43 (1.09,5.40)
SMRW	2.08 (0.76,5.67)	2.16 (0.57,8.17)

Using all available time for follow-up the tables for the without and with BMD estimates have been combined in Table 6.18. There were 0 (0.0%) MOF and 0 (0.0%) vertebral fractures in the alendronate group and <11 MOF and 3 <11 vertebral fractures in the non-user group based on with BMD CFRI, and the mean follow-up times for the alendronate group was 911.3 (SD 662.6), median 654 (IQR 385, 1417.5) days and mean of 899.1 (SD 671.6), median 727 (IQR 298, 1362) days in the non-users. There were 12 (1.1%) MOF and <11 vertebral fractures in the alendronate group and 62 (0.5%) MOF and 35 (0.3%) in the non-user group based on without BMD CFRI, and the mean follow-up times for the alendronate group was 1025.6 (SD 713.2), median 890 (IQR 412, 1607) days and 897.2 (SD 692.1), median 733 (IQR 299, 1382) days in the non-users.

Compared to the full populations the FIT restricted populations either saw their estimates increase (for the without BMD population) or become non-significant due to small event counts in the with-BMD population. In both cases the estimates did not get close to the protective effect of alendronate found in the FIT trial. This suggests that any new user is too broad of a non-user comparison group. Also the restricted populations are not similar to the general population which makes it difficult to claim with any certainty that these results should be generalizable to a larger population, or are interpretable in the broader context. These results were similar to the results at one year and indicate that there may be a decrease in hazard when you restrict based on the with-BMD score, but none of the estimates reached statistical significance.

Table 6.18 FIT-Restricted Population All Available time, Approach 3 (DXA visit as non-user)

Analysis Type	Hazard Ratio	Spine Hazard Ratio
With BMD		
FIT null	1.62 (0.37,7.08)	2.04 (0.46,9.11)
FIT with only CFRI	1.65 (0.38,7.22)	2.04 (0.46,9.10)
Fully Adjusted	2.20 (0.41,11.86)	3.42 (0.67,17.35)
FIT SIPTW	2.68 (0.71,10.07)	3.35 (0.87,12.93)
SMRW	1.89 (0.18,19.80)	2.44 (0.19,31.47)
Without BMD		
FIT null	1.56 (1.11,2.19)	1.77 (1.16,2.70)
FIT with only CFRI	1.45 (1.03,2.04)	1.66 (1.09,2.55)
Fully Adjusted	1.41 (0.99,2.00)	1.66 (1.07,2.56)
FIT SIPTW	1.46 (1.03,2.08)	1.55 (0.99,2.44)
SMRW	1.41 (0.84,2.35)	1.62 (0.83,3.14)

6.4.4 Conclusions

Evaluating the results of the approach 3 results, we find that classifying non-users based solely on if they did or did not have a DXA is not sufficient to reduce confounding to the level of a placebo compared to alendronate trial. When the population is restricted based on the with

CFRI score the study population becomes very small and with a small number of events which create very large confidence intervals. This corresponds to the FIT restricted analyses being underpowered to detect the appropriate effect sizes. Even when the without CFRI score is used the number of events are very small, which indicates that the restriction of the study population based on CFRI may not be an appropriate use in a research context. The idea of using DXA as the non-use event of interest was to create a population which was comparable to our original cohort (ie had a DXA in Aim 1), however it appears that these patients are in many ways still dissimilar. Restricting the study population based on CFRI for the first time created populations which had a reasonable number of events, but the estimates continued to not reach those of the FIT trial. From a research standpoint CFRI cannot be used alone to control for confounding in osteoporosis research, however it appears useful to reduce confounding based on fracture risk.

CHAPTER 7: **DISCUSSION**

Our goals for this project were to develop a claims-based algorithm to accurately measure FRAX® 10-year risks of fracture. To this end we have created the claims-based fracture risk index (CFRI) which we have shown is in many ways a comparable score. CFRI was shown to be as calibrated as FRAX® and of a similarly discriminatory ability for one-year fractures. Although the tool was not able to reduce confounding to the levels which we hoped for in a comparison of alendronate to non-users, CFRI should have merit as a tool in osteoporosis comparative effectiveness research going forward.

To our knowledge this project is the first US based dataset which has combined both administrative claims and clinical data necessary to calculate FRAX®. We are aware of one Canadian dataset in Manitoba and a second project which may soon yield a similar data source in Quebec (220, 439). Data of this kind is necessary to evaluate fracture risk models on a population rather than cohort based population.

Policy decisions continue to be made based on expert opinion as to the minimum fracture risk for which pharmaceutical therapy should be introduced without sufficient long-term evidence to demonstrate the thresholds effectiveness (37, 359). However one ongoing RCT the SCOOP trial in the United Kingdom aims to determine the effectiveness and cost-effective of a community based screening program utilizing FRAX® as a component (440). If the SCOOP trial finds a specific threshold to be optimal for screening or intervention it will increase the need for patients at or above this threshold to be identified and treated. CFRI would allow for retrospective in most cases, but possibly prospective identification of at-risk patients based on

claims data which would negate the need for collection of a baseline questionnaire as is currently being done in the SCOOP trial.

One future direction from this project was to determine if a fracture risk score based on administrative claims data could be created to approximate FRAX® so these guidelines could be evaluated. We feel that these three aims demonstrate that CFRI offers a sufficient alternative to FRAX® when only administrative claims data is available from a policy context. However, CFRI alone cannot be used to eliminate non-user confounding in a research context, though its use along with other variables and methods may continue to elucidate the comparative effectiveness of anti-osteoporosis medications.

The overall implications of this research study are that broadly it is possible to predict FRAX® using administrative claims. You may not be able to predict the linear value all that well, but that doesn't mean that what you can predict isn't useful and similar enough to FRAX® for it to be a reasonable claim based proxy. Broadly our results suggest that if FRAX® is available, then use FRAX® however if it is not and administrative claims are available then CFRI is a useful proxy. In the end CFRI will be useful for academic researchers as well as policy makers within insurance and healthcare environments where claims are readily available, but clinical data is not. CFRI is not a score which makes sense to calculate prior to a patient's visit to alter a treatment decision, this should be done with FRAX®, however when accounting for possible decisions made based on FRAX® but without the FRAX® score itself CFRI appears to have utility.

This study produced four models two for both with and without BMD estimating the FRAX® 10-year risk of fracture for both hip and major osteoporotic fracture. The with BMD models resulted in models with fewer variables and generally performed as well if not better than

the without BMD models. However the with BMD models had much lower statistics indicating their ability to account for variability in the associated FRAX® score. The without BMD models accounted for more of the variability which we have speculated is due to a wider variation in without compared to with BMD scores. Though when used in practice the with BMD scores tended to produce effect estimates closer to the null, which was the desired result. Broadly the models contained similar variables including race and age, with all but the with BMD hip model also containing other FRAX® variables previous fracture, rheumatoid arthritis, and glucocorticoid use. Although CFRI did not contain the same variables as FRAX® it did a passable job of predicting the continuous score, and did a far better job of discriminating between high and low risk patients.

One may question if we pursued the wrong use of the CFRI score after the high rate of discrimination for the categorization of high v low risk patients based on NOF thresholds. In a random pull, CFRI would correctly identify between 81 and 89 out of 100 (based on CFRI type) patients as either high or low risk. Although one of the interests in this study was to be able to evaluate the NOF guidelines, we found it important to predict the continuous score rather than just dichotomizing it, particularly because if it could be used as a continuous score it would be more useful than as a single measure of high v low risk. That being said, most of the stakeholders who are likely to use this score going forward, particularly payers would be most interested in the dichotomous rather than the continuous.

The ROC created in our study produced a small proportion of false positive and false negatives. If a prediction tool has a large proportion of false positives then it is likely that too many people would be screened/treated who would not benefit from it, however the inverse would be true if a large proportion of false negatives were present. The difficult part with the

ROC from Aim 1, is that the outcome that we are looking at isn't actual fracture, but the FRAX® score, which could theoretically be a bad representation of a patient's true fracture risk. However CFRI did not have a large proportion of false positives or false negatives, therefore should be a good proxy for FRAX® based on NOF thresholds. Since the continuous score performs well in Aim 2 in its ability to correctly predict fractures, this strengthens the idea that the categorical score would be useful in a context where identifying patients at high-risk would be important.

We have produced tables of model coefficients which can be used to calculate CFRI in research outside of this project. The SAS code to accomplish this is available upon request, however it can be implemented by using the same ICD-9 codes listed in the methods for each of the variables listed in the four best models. We would speculate that the researcher should use a 365-day lookback period for collection of covariates, as this would follow our method. The researcher then can multiply each of these 0/1 variable by the model coefficients from Aim 1 and sum all of the values to create CFRI in the four different variations. It was always a goal of this project to produce a model which could easily be reproduced by other researchers and if possible improved upon.

Overall, we would view this project as a success. Although our models did not predict the continuous FRAX® score very well, the continuous scores were externally valid and reduced the effect size estimates in Aim 3 towards the null. Our models generally included the FRAX® variables which were measureable in administrative claims and although they are significantly more complex than the FRAX® score due to many more variable included, the discrimination of our 4 models generally was better than the FRAX® validation cohorts. For a research in administrative claims we have now produced a fracture risk score which is largely similar to FRAX® and likely can be used in the same way. We would view this as confirmation that you

can predict a continuous fracture risk score using only administrative claims data. In the following sections we discuss the broader implications of the findings from each of our aims.

7.1 Aim 1

There are two different populations for whom predictive models were created in this aim. When a patient receives a DXA there are times where a femoral neck BMD score is either not recorded or not valid. For a small proportion of our population (62 patients) no femoral neck BMD value was recorded in the CCF DXA registry, so these patients could only have their FRAX® calculated without BMD. Largely the characteristics between the with and without-BMD cohorts were similar as they were comprised of the same patients. However the distribution of the FRAX® scores varied more widely in the without rather than with-BMD cohort. This is likely due to the fact that most of the patients who were getting DXAs were already viewed to be at risk for an osteoporosis related event, and likely had similar BMD values, which caused their FRAX® scores to be similar. Conversely because FRAX® without BMD is based on BMI rather than BMD a much wider spread of values was available for prediction which in turn created more predictive models.

Overall it was surprising that the elastic net models only produced the best predictive models for the with BMD cohorts. Based on the known methodology it was expected that they would outperform a backwards stepwise model, as they would be able to modify the amount of error given to each coefficient (441, 442). To our knowledge there are no studies which have demonstrated in a similar context a backwards stepwise model outperforming either a LASSO or elastic net model in prediction of a continuous outcome.

Also it was surprising that the inclusion of prevalence based HD covariates, rather than improving predictive ability, actually decreased the models predictive ability (31, 441, 443, 444).

Elastic net models are of a similar ilk to stepwise models, in that neither require any knowledge of the topic area, only the ability to measure and capture covariates and outcomes. The model performance based on content variables defined using theory (set in the framework of Andersen's Model of Healthcare Utilization) increases the justification for the inclusion of these variables in the model. Although it would have been useful to find additional variables which could have improved the model's predictive ability, it is reassuring that the variables chosen a priori as content variables and included in all subsequent aims were able to produce the most predictive parsimonious models. Although the elastic net models were supposed to be able to evaluate all of the variables and only choose those which were the best predictors, it may have been with ~1000 variables the models were overly saturated.

In the four models deemed to be most predictive based on aR^2 the only variables which were common across all 4 models were linear age and African-American race. This was largely due to the with-BMD hip model only including 4 variables. In the two with BMD models age*osteoporosis also remained in the model which is a variable which can be thought of a proxy for BMD in the FRAX® score. Both of these variables make sense for broad inclusion in the model as age is largely predictive of fracture risk and African-Americans have been shown to have better bone density than other races (445). For the without-BMD model's rheumatologic conditions were common including rheumatoid arthritis (RA), lupus, and polymyalgia rheumatica all three of these conditions are commonly treated with glucocorticoids which have a deleterious effect on the bone and RA particularly has an effect on bone strength outside of glucocorticoid use, meriting RA and glucocorticoids its inclusion in the FRAX® calculation (176, 376). There were no other FRAX® factors which could be well measured in administrative claims, though non-MOF fractures did appear as a variable which increased risk in all but the hip

with-BMD model. In terms of medications which were predictive of FRAX® it is odd that hormone replacement therapy in the three non-Hip with-BMD model had a positive coefficient as normally it would have been assumed that the use of HRT would lessen a person's fracture risk rather than raise it (283-286). However this may be indicative of women who already at a greater risk for fracture regardless of their HRT use. Outside of the one very small model at least one factor from each of the variable groups from Table 2.9 were included in the final predictive models. Some of the factors which were listed in Table 2.9 didn't have a large enough n to be effectively utilized in the model, as such there may be variables which should have remained in the models but were excluded.

Due to the inability to accurately measure most variables in FRAX® including BMD, parent fractured hip, smoking, alcohol use, and BMI our final CFRI model represents a departure from the variables which were included in their model. Broadly CFRI chose similar variables across the different outcomes, barring hip with BMD. The variables chosen by the models were factors which would be generally agreed upon to be associated with either fracture or osteoporosis. Though broadly there were very few conditions and medications which were associated with falling which were included in the model, only stroke appeared in both of the without-BMD models.

Lastly, Kanis et al suggest that for a study population to be broadly representative of the general population their with and without BMD FRAX® scores should be similar (170). Broadly he states that the distributions for the study population should be equivalent with the extremes balancing each other out when the with and without BMD scores are compared. For both the hip and MOF with and without BMD scores, the means were similar, though the standard deviations were slightly different. Additionally all of the CFRI scores (comparison of with BMD to without

BMD) were similar. This suggests that although the study population in Aim 1 was highly specialized (only patients at one regional healthcare center who had DXAs), the results of the predictive model should be representative for the general population.

The overall takeaway from the with BMD analyses is that although some of the predictive statistics, particularly aR^2 are relatively low for CFRI, the models are able to differentiate high and low risk patients. This may be more relevant from a policy perspective where the interest would be identifying treatment eligible patients, rather than determining a precise risk-level for a patient.

However the purpose of this project was to evaluate if a continuous score could be predicted, which we have demonstrated is possible. But none of the four models were able to do a very good job at predicting the extreme values, which seems to be more indicative of a lack of a specific condition or medication which was largely associated with those values. Although we couldn't have expected that one variable would stick out as predictive of a very large score, overall, we our collection of variables is able to relatively accurately predict the majority of the scores. We also tested if only the inclusion of age would produce models similar to the best models, and in all four outcomes the age only model produced aR^2 which were much less than even the best linear models.

The elastic net models produced the best fitting models based on aR^2 for the with BMD groups, while a log-transformed backwards stepwise model produced the best models for the without BMD groups. No model was able to explain more than 40% of the variation in the FRAX® scores. Likely due to the low number of events and small spread of actual FRAX® scores, notably when the scores were wider spread (MOF without BMD) the predictive power of CFRI was increased. However when NOF thresholds were applied to both FRAX® and CFRI,

our models were able to predict high or low risk FRAX® scores. There were very few variables which had a large effect on model building with the most important being age. Overall, we were able to predict FRAX® using CFRI for all four outcomes with moderate accuracy. Subsequent aims will address how well CFRI and FRAX® predict actual fractures, however based on aim 1, it is possible to predict a continuous FRAX® score using only administrative claims data.

7.2 Aim 2

The primary purpose of Aim 2 was to perform external validation of CFRI in a similar but separate population. To this end we used a 20% random sample of Medicare beneficiaries and compared calibration and discrimination between the CFRI and FRAX®. As a generalization we found that CFRI performed as well if not better than FRAX® in terms of discrimination, and predictive performance, but generally had a poor goodness of fit, due to an incorrect test (HL) being chosen. Based on these findings it can be argued that CFRI is able to similarly identify patients at risk for fracture using only data from administrative claims. Therefore the proxy score (CFRI) can be used to evaluate guideline concordant care in a policy context.

We were also concerned with how well the models were calibrated to predict future fracture. Because there is evidence that the Hosmer-Lemeshow is not informative for large datasets when it was created using a small dataset (437, 438), we use of the brier score to determine the model calibration. The brier scores for all of the models were adequate to demonstrate predictive accuracy. Based on the limitations of the Hosmer-Lemeshow test as well as adequate brier scores, we would conclude that there is no statistically significant difference in calibration between the linked and random population in any of the 4 outcomes. Broadly CFRI was able to predict fractures as well as FRAX® for all four outcomes. Therefore we would accept the null hypothesis of no difference in calibration between CFRI and FRAX®.

Finally, we investigated the discrimination between the linked and random population. We evaluated discrimination using the AUC or c-statistic which is graphically represented as the sensitivity (correctly identified true positive cases) compared to 1-specificity (correctly identified true negative cases). The basic definition of an AUC is the likelihood that a uniformly drawn positive is of a higher rank than a uniformly drawn negative. In aim 2 this would be explained as the likelihood that a patient would be correctly identified as high risk or low risk. In all 4 populations there were no significant differences in discrimination as measured by AUC and compared using De-Long test for ROC equality. Therefore we would accept the null hypothesis from of no difference in discriminatory ability between CFRI in the linked and random populations. Because we are not able to calculate FRAX® in any population other than the linked population, we are basing the interchangeability of the scores on a similar discriminatory ability for CFRI in both populations and lack of difference between discrimination between CFRI and FRAX in the linked population (446). Because we could not calculate FRAX® in the random population, we are basing the exchangeability of the risk scores on similar abilities to predict one year fracture rate.

Both the Yun et al model and the FRAX® model have evaluated their discrimination based on real fractures (18, 20). In both of the algorithms hip and major osteoporotic fracture were separately assessed. The hip model with the best AUC from Yun et al included demographic, fracture history, comorbidity and lifestyle questions, as well as a second model with included FRAX® hip finding similar predictive ability to CFRI. There was no designation for hip with or without BMD in the Yun et al model. In validation FRAX® gave AUC for each of the different validation cohorts, as well as an aggregate of the cohort used to create the model. Our AUC for hip with BMD CFRI in the random population was similar to the Yun et al model,

but less than the FRAX® AUC in their validation cohort. Our random population and the FRAX® validation cohort were not the same, therefore one could not expect that the AUC would be the same. Having a similar AUC in the linked population and a lack of statistically significant difference between the linked and random AUCs suggest that in similar cohorts CFRI is able to predict one year fractures at a similar rate to FRAX®. Ergo CFRI with BMD should be a reasonable proxy for FRAX® with BMD using administrative claims data.

The FRAX® without hip BMD model from the original cohort produced an AUC lower than CFRI, but in the validation cohort a higher AUC was produced. Although our AUCs for the linked cohort were comparatively low, they increased by nearly .1 in the random cohort and were comparable to the FRAX® and Yun et al AUCs. It is interesting that for our study hip without BMDs AUC is increased over hip with BMD. We would speculate that this is due to more variables in the without-BMD model therefore allowing better distribution of the risk score, whereas FRAX® used BMD as a primary variable for its calculation. When BMD was removed from any of the FRAX® models their predictive ability was decreased, but CFRI selected more variables and increased its predictive power. It appears that CFRI is able to predict one year fracture as well as FRAX® was able predict fractures at 5 years using the hip without BMD score. Although the models with more variables in the without BMD categories were better able to predict fracture, we set out to create more parsimonious models, so including additional variables would not be feasible.

In regards to MOF with BMD, all of the AUCs from both our study and from Yun et al outperformed the original cohort AUC from FRAX®, which suggests that in many ways FRAX® MOF with BMD is not an optimal model for predicting future fractures. However CFRI outperformed the original FRAX® and had the same performance as FRAX® in the linked

population. This suggests that CFRI should be relatively interchangeable with FRAX® based on its discriminatory ability to predict major osteoporotic fractures at one year.

The last model assessed MOF without BMD, where we found that CFRI in both the linked and random populations outperformed FRAX® in the linked and in their original cohort. It is important to remember that FRAX® was based on 5-year fracture risk and our model is based on 1-year fracture risk which would likely change our AUC at a longer time interval. However with CFRI having a superior discriminatory ability based on the same data, we would encourage its use as a proxy for FRAX® when only administrative claims data is available.

The external validation of the CFRI algorithm demonstrates the ability to predict fractures in a similar manner to the current gold standard of FRAX® using the same data, and subsequently in a population from a similar type data source. The populations for whom CFRI was tested in were largely similar which strengthens the claims that CFRI can be used as a proxy for FRAX® when only administrative claims data is available. Based on the internal validation from Aim 1, and the subsequent external validation in Aim 2, CFRI has demonstrated that it is a useful fracture risk prediction tool, and in many ways, may be interchanged with FRAX®.

The AUC for all three variations of the models in Aim 2 were generally within 0.1 of each other. In terms of osteoporotic fracture it is unlikely that these are large enough differences to suggest that one risk score be used over another. However the argument could be made that because CFRI generally outperformed FRAX® that the small increase in precision if enough patients would be treated/evaluated a transition to CFRI could be warranted. But CFRI has been designed in this case as an alternative to FRAX® only when FRAX® cannot be calculated. It will be important in the future when other risk scores are available to determine how well CFRI performs compared to those, not only in the population where the other scores were created, but

in a truly random population as well. A small increase in discrimination can be important when all scores are similar as this may allow more patients to be correctly identified.

7.3 Aim 3

The primary purpose of Aim 3 was to evaluate the utility of CFRI in clinical research by evaluating if using CFRI we could find effect estimates similar to the placebo versus alendronate trial, the Fracture Intervention Trial (FIT). Soon after FIT's publication, due to the benefits observed for alendronate over no treatment, it was judged to be unethical to not provide postmenopausal women with an active therapy when evaluating fracture risk (51, 62). To attempt to create similar effect sizes we employed CFRI in regression, in propensity score approaches, and finally through restriction to characteristics of patients included in the original FIT trial. We did not find that any of these techniques or the different ways that we defined new users were able to reduce our effect estimates to a similar level as those from the FIT trial.

Our study, against expert guidance, used a non-user group comprised of patients based on any new use of a non-alendronate therapy as well as based solely on having a DXA (447-451). Approach 2 was the only approach which used an advised variation on the active comparator with 3 drug classes not associated with the outcome of interest. Approach 1, although using active users, was a very broad net to encompass all new users regardless of their possible association with fracture (447, 448). Approach 3 on the other hand didn't require use of any drug, only use of the healthcare system which may suffer from bias (447-452).

In our study we based the measurement of CFRI on when the physician would have had the opportunity to evaluate fracture risk (422), but began follow-up at the fill of the medication as the patient could only have a fracture after this point. Although not against methodologic guidance this may have had an effect on our results as some patients may have had a shorter time

period between their office visit and the fill of a medication. Another approach would have been to have used the entire period of 30-days after the office visit as an exposure period, and then began follow-up at that point, this is what was done with approach 3. In the first two approaches because they required a medication fill we began follow-up the day after the fill.

Restriction of the administrative claims data by the characteristics of FIT trial participants was the a priori hypothesis for generating results that converge with trial estimates. This use of restriction, along with other methodologic techniques, have been identified as ways to emulate trial results (453, 454). Schneeweiss et al found that by restricting a study population in a similar manner to the RCT was sufficient to recreate RCT results (23). A second study of statin users was able to find similar protective results on par with the RCT as well, but when a true non-user group (ie no active comparator) was used the results were not to the level as the active comparators (455). Restriction has been used in other contexts and produced effect sizes similar to trial estimates (456).

In each of these prior studies the variables necessary to correctly restrict the population were available including appropriate diagnoses, procedures, lab tests, and medications, unlike ours and many other possible studies. For example, because BMD is not measured in administrative claims, we restricted or sample based on CFRI, rather than BMD (the restriction criteria for the FIT trial). By doing this, we likely introduced selection bias because we were not able to correctly select patients based on BMD which may account for the difference between our results and those of the FIT trial. This also would account for the small number of patients (between 0.01% and 3% of the unrestricted populations) who could be used in the restricted analysis, which resulted in small event numbers which prevented the creation of useable effect estimates. The variables that were

When comparative effectiveness studies have included “non-users” (i.e., those who are not using an active comparator product) results have been mixed (455, 457). Expert opinion is that alendronate is superior to placebo in reduction of vertebral fracture, however meta-analyses are used to substantiate non-vertebral fracture reduction (247, 280, 293). Unfortunately, the confounding by indication could not be adjusted away in this study, regardless of our inclusion of CFRI. Disease risk scores are composite scores of conditions which approximate the severity of a condition. In approach 1 and 2, CFRI behaved in a similar manner to a traditional disease risk score by reducing confounding and reducing the variability of the estimate. Therefore we would suggest that CFRI could be used in a similar manner to a disease risk score by including it as a variable in regression or propensity score analyses (425). The score itself is a combination of the variables in the best models multiplied by their coefficients, this should be produced in a research context not a patient care context.

In approach 1, we investigated if any new user could be an appropriate non-user group for alendronate. In both the 365-day and all available time estimate the inclusion of the with-BMD CFRI score was responsible for the most conservative hazard ratio. However even the most conservative estimates were >0.3 and hazardous rather than protective compared to the FIT estimates. Also interestingly as the time increased (comparing 365-days to all available time) hazard ratios increased rather than decreased. In a clinical trial you would expect the fracture rate to improve over time because the patient would continue to take active therapy. However in a real-world analysis we did not have this same assumption and the women were unlikely taking alendronate throughout the entire study. After stopping alendronate the protective effects likely wore off, which is why the estimates increased with all available time. These findings were similar to those of approach 2, however when statins, anti-hypertension, and anti-diabetes drugs

were used as the referent group the hazard ratios were greater than the any new user referent group. Based on the increased hazard ratios, away from the FIT results, the any new user group is a better referent group when comparing alendronate to placebo.

In approach 3 we intended to use any office visit as our non-user group, however that approach was found to be computationally and server space intensive, therefore we used the DXA which was listed as our sensitivity analysis as our primary analysis. At one year and using all available based on DXA, the SMRW estimate for the first time was the most conservative while the analyses only including the CFRI scores were greater than the fully adjusted analysis. Once the population was FIT restricted the n's and fracture counts became too small in the with-BMD population for accurate measurement. However the without BMD estimates were similar to the unrestricted population, if only farther from the null. As time increased the estimate generally increased rather than decreased. This is likely due to the study only requiring the fill of alendronate once, which was unlikely to confer a benefit if not consistently used.

For all three approaches we can reject hypothesis 4 of the restricted population creating estimates which more closely resembled the FIT trial. Before the study we were unaware of how many women FIT would restrict out of the population, and how this would affect our estimates. Although no unrestricted estimate was close to the FIT estimates the unstable nature of the restricted estimates supports the rejection of the hypothesis.

7.4 Strengths and Limitations

Our study has several important limitations. First, this is an observational study and unmeasured confounding may bias our results, however we have presented an approach to attempt to address unmeasured confounding related to fracture risk. We only used women in our analysis, however men can also suffer from osteoporosis and osteoporotic fracture. Our project

uses a linked population which is restricted to a subset of all patients who had a DXA through the Cleveland Clinic Foundation sites. Most notably, individuals who were linked were those with fee-for-service Medicare excluding those who were insured by Medicare Advantage or other payers and the patient had to be using their Medicare benefits. Additionally we had a large proportion of the population which was of Medicare age, but we could not link to their Medicare claims. As such, our results may not be entirely generalizable to females in the general population. The linked sample only has FRAX® scores recorded for patients who receive DXAs within the Cleveland Clinic Health System, therefore our method to calculate CFRI may not be generalizable to office visits, but only applicable for DXA visits. Though our results in Aim 2 suggest that CFRI does not have to be measured only at DXA, as the comparability in fracture prediction was similar for office visits as it was for DXA. Because this is an analysis of Medicare eligible patients, we did not include anyone under the age of 65.

In aim 1 we predict FRAX®, an imperfect measure of fracture risk. As such, our proxy for FRAX® (CFRI) is likely to be an imperfect estimation of future fracture risk. However FRAX® is the current gold standard for fracture risk prediction, making it useful for policy and quality measure applications. Although we were not able to predict fracture with high accuracy (as evidenced by low aR^2) CFRI was similar in its discrimination and calibration to FRAX®.

The linked population from Aim 1 is likely not broadly generalizable outside of its own population. However it is the only population which we had available to externally validate our model. The fact that the linked and random populations had similar calibration and discrimination statistics suggests that the population may be largely similar, or at least CFRI's ability to predict fracture is largely similar. The one concerning factor about generalizability is the 95% kyphosis in the linked sample. This is likely a coding artifact; however this abnormality

alone doesn't invalidate the method to determine external validity. Another concern to external validation was the small number of events in the linked sample, which likely under power the hip fracture estimates. However the fact that the predictive ability is similar to that of the random population lessens the worry that because this analysis was underpowered it is invalid.

There is no accepted method for comparing users to non-users and generally this practice has been discouraged. The most common suggestion for researchers attempting to incorporate a non-user treatment arm is to do so by selecting users of a drug class thought to have no relationship to the outcome under study. We tested three different approaches to define non-users and found that anchoring our population based on a DXA with a 30-day treatment window produced the estimates most closely resembling the RCT. These likely were more similar patients than the other approaches as although AOM use other than alendronate was excluded, simply having a DXA may indicate a similar health profile.

Our hazard ratios were never very similar to those of the FIT trial (FIT clinical fracture 0.72 our lowest estimate ~1.1), however the difference between hazard and risk ratios would not be interpreted differently at this magnitude making our results directly comparable to FIT (458). Particularly, all of our FIT restricted population analyses were underpowered due to the extreme restrictions, this makes any conclusions based on the FIT restricted populations of questionable validity. Because adherence to therapy is a realistic explanation of the longer-term outcomes worsening compared to the one-year estimates, controlling for adherence to medication would have been a possibility. Noting this limitation we chose to leave the analysis as an intent to treat as this was the same model as the RCT. Also on the adherence piece we did not define alendronate populations based on their dosage, ie 10mg daily or 70 mg weekly as these two formulations were found to be of the same efficacy by Merck. Stratifying by dosage could have

provided some guidance on this, however due to small n's this wasn't feasible, though the different formulations may have affected our results

Our study has some strengths that are unique to this project. First, we are the first research team to utilize this linked dataset of clinical and administrative data to evaluate osteoporosis care in the US. Second, we created an algorithm that only uses administrative claims data to predict a clinical risk score. Other attempts at calculating fracture risk scores in administrative claims have largely been focused on creating a separate measure rather than trying to recreate a current score. Although a new score could be useful within the data where it was created, they generally are not validated outside of that population. Our study performs the appropriate internal and external validation measures to establish the transferability of CFRI outside of our linked Medicare population.

An additional strength of our analysis was the three different ways that we defined and measured new users. Methodologic guidance has largely stated that non-users should not be patients who do not use the medication of interest, but patients who are similar based on other characteristics. We found that defining non-users as any new user of a medication produced the best active comparator estimates but defining non-users based on DXAs produced estimates more closely resembling those from the FIT trial. Because we tested three different techniques and all three had results in a similar direction and magnitude this strengthens the validity of our findings that CFRI alone cannot be used to completely reduce confounding in osteoporosis research.

7.5 Future Directions

Osteoporotic fracture continues to demand a substantial amount of healthcare resources within the US. Therefore any strategies to reduce the occurrence and cost of fracture are likely to

be advisable from a public health standpoint. One of the main strategies to improve long term outcomes in medicine have been the introduction and enforcement of care based on quality measures. However in most medical disciplines, including osteoporosis, these measures are based on expert opinion rather than empirical evidence of their utility. Being able to use CFRI in claims-based research would allow an analysis of the longer-term effect of treatment based on these guidelines and better inform the threshold for treatment effectiveness. The intention of quality measures is to improve long term outcomes and patient care, hopefully CFRI will be useful improving these. This could be brought about by payers and policy makers helping to identify patients to be treated and monitoring if those patients actually receive an AOM.

In this way if treatment based on a 10%, 30%, 40%, 50%, etc... threshold for major osteoporotic fracture or 6%, 9%, 12%, 20%, etc... hip fracture is actually found to be associated with a decrease in fracture, but the current thresholds are not, then either money could be saved by reducing over use of medications in a population for whom the benefit is less substantiated, or increase the use of medication in a population where its use will do the most good. Health care is a largely personal endeavor and with the increase in the want for “personalized medicine”, techniques and methods which are able to better drill down to the population which will most benefit from an intervention will continue to be desired by decision makers.

Our study only evaluated alendronate compared to placebo. However most comparative effectiveness research is conducted with two active comparators. Since we excluded all non-alendronate AOM users, future work should evaluate CFRI among other AOM users. Studies in glucocorticoid-induced osteoporosis have found contradictory results in the effect of AOMs in preventing future fracture, CFRI would likely be useful in reducing the inherent confounding in these studies (16, 17). Also future researchers may find that CFRI is more beneficial in reducing

confounding in one of these other populations, or in direct comparison to other osteoporosis medications rather than compared to new-users.

Our study was restricted to women aged 65 years and older, however osteoporosis and osteoporotic fracture also effect men and younger women. Using our methodology for the creation of CFRI other researchers will either be able to create similar fracture risk scores in these populations or measure the utility of CFRI. In this way confounding in osteoporosis comparative effectiveness research can be moved forward to determine the best care for patients of all ages and genders.

Our methods are reproducible as the codes used to measure the diseases and procedures of interest are presented within the methods section of this document. Additionally we provide model coefficients to 9 decimal places which will allow researchers and policy makers to produce CFRI in their own databases. Lastly the precise code used to measure the covariates and calculate CFRI including the model coefficients are available upon request.

Overall, we found that we were able to sufficiently predict FRAX® using the CFRI score based on administrative claims. This will allow clinical researchers, policy makers, and payers to approximate a patient's fracture risk score at the time of healthcare intervention to improve patient care and outcomes. We hope that CFRI will be a useful tool for others in this endeavor.

APPENDIX

Table A1 Approach 1, MOF 365 no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.21907	0.0323	45.9977	<.0001	1.245
Cystic Fibrosis	1	-0.12085	0.448	0.0728	0.7873	0.886
Congestive Heart Failure	1	-0.12071	0.02066	34.1348	<.0001	0.886
Ehlers-Danlos	1	8.34417	83.07385	0.0101	0.92	4205.593
Epilepsy	1	-0.02086	0.05854	0.127	0.7216	0.979
Osteogenesis Imperfecta	1	-0.59066	0.70787	0.6962	0.404	0.554
Parkinson's Disease	1	-0.0732	0.05147	2.0223	0.155	0.929
Stroke	1	-0.07312	0.02269	10.3874	0.0013	0.929
Adrenal insufficiency	1	0.1135	0.37852	0.0899	0.7643	1.12
AIDS/HIV	1	0.02803	0.35392	0.0063	0.9369	1.028
Alcoholism	1	-0.40196	0.09491	17.9378	<.0001	0.669
Alzheimer's	1	-0.09755	0.02225	19.2215	<.0001	0.907
Amyloidosis	1	-0.33598	0.28906	1.351	0.2451	0.715
Androgen insensitivity	1	-0.94235	1.00023	0.8876	0.3461	0.39
Anorexia	1	-0.23454	0.05303	19.5579	<.0001	0.791
Ankylosing spondylitis	1	-0.2856	0.06168	21.4389	<.0001	0.752
COPD	1	-0.31892	0.01703	350.8698	<.0001	0.727
Athletic amenorrhea	1	0.6195	0.44736	1.9176	0.1661	1.858
Cataracts	1	0.06349	0.02254	7.937	0.0048	1.066
Celiac	1	-0.32291	0.20856	2.3973	0.1215	0.724
Central Adiposity	1	0.18779	0.03413	30.2764	<.0001	1.207
Chronic metabolic acidosis	1	-0.1019	0.06208	2.6939	0.1007	0.903
Crohn's Disease	1	-0.11454	0.03736	9.4015	0.0022	0.892
Cushing's	1	-0.58855	0.23623	6.2075	0.0127	0.555
Depression	1	-0.054	0.02176	6.1588	0.0131	0.947
DM	1	0.01508	0.01748	0.7443	0.3883	1.015
ESRD	1	-0.44731	0.06257	51.1057	<.0001	0.639
Disorders of the Eye	1	0.01661	0.02163	0.5892	0.4427	1.017
Falling	1	-0.23655	0.0296	63.8714	<.0001	0.789
Gaucher's Disease	1	-0.14397	0.18595	0.5995	0.4388	0.866
Glaucoma	1	-0.01085	0.0257	0.1781	0.673	0.989
Gout	1	0.12752	0.04252	8.9932	0.0027	1.136
Glycogen storage diseases	1	0.70055	1.00016	0.4906	0.4837	2.015
Hemochromatosis	1	1.12572	1.00007	1.2671	0.2603	3.082
Hemophilia	1	-0.03609	0.04751	0.5771	0.4474	0.965
Homocystinuria	1	-0.23237	0.18934	1.5063	0.2197	0.793

Hyperprolactinemia	1	-0.52384	0.40861	1.6435	0.1998	0.592
Hyperparathyroidism	1	0.08646	0.07697	1.2617	0.2613	1.09
Hyperthyroid	1	-0.00133	0.0519	0.0007	0.9795	0.999
Hypophosphatasia	1	-0.31344	0.08782	12.7383	0.0004	0.731
IBD	1	0.04219	0.0829	0.259	0.6108	1.043
Idiopathic scoliosis	1	-0.23672	0.04221	31.4517	<.0001	0.789
Idiopathic hypercalciuria	1	8.30935	147.06175	0.0032	0.9549	4061.69
Kyphosis	1	-0.0133	0.02441	0.2968	0.5859	0.987
Liver Disease	1	-0.168	0.03579	22.0283	<.0001	0.845
Malabsorption	1	0.06413	0.14064	0.2079	0.6484	1.066
Marfan syndrome	1	-0.42044	1.00084	0.1765	0.6744	0.657
MS	1	-0.24893	0.12551	3.9334	0.0473	0.78
Muscular dystrophy	1	-0.11688	0.40884	0.0817	0.775	0.89
Obesity	0	0
Osteoarthritis	1	-0.01392	0.01651	0.7105	0.3993	0.986
Osteoporosis	1	-1.5223	0.1859	67.0598	<.0001	0.218
Other Fx	1	-0.24365	0.0317	59.058	<.0001	0.784
Panhypopituitarism	1	-0.28356	0.70778	0.1605	0.6887	0.753
Pancreatic Disease	1	-0.15854	0.05731	7.6535	0.0057	0.853
Poly Rheumatica	1	-0.1932	0.06043	10.2223	0.0014	0.824
Porphyria	1	8.15499	33.59426	0.0589	0.8082	3480.691
Premature ovarian failure	1	2.1593	1.0001	4.6616	0.0308	8.665
Primary biliary cirrhosis	1	-0.52893	0.18592	8.094	0.0044	0.589
Riley-Day	1	7.82208	78.17641	0.01	0.9203	2495.088
Renauld Disease	1	-0.01226	0.03035	0.1631	0.6863	0.988
RA	1	-0.17666	0.03772	21.9383	<.0001	0.838
Saccoidosis	1	-0.0717	0.1694	0.1791	0.6721	0.931
Sickle Cell Anemia	1	0.01845	0.57782	0.001	0.9745	1.019
Lupus	1	-0.44432	0.08312	28.5732	<.0001	0.641
Spinal cord injury	1	-0.29998	0.18981	2.4976	0.114	0.741
Systemic mastocytosis	1	0.40889	1.00009	0.1672	0.6826	1.505
Turner's & Klinefelter's syndromes	1	8.14346	92.1482	0.0078	0.9296	3440.814
Thalassemia	1	0.10773	0.30173	0.1275	0.7211	1.114
Thyrotoxicosis	0	0
Vitamin A	1	8.12421	54.81031	0.022	0.8822	3375.196
Vitamin D	1	0.05726	0.03498	2.6803	0.1016	1.059
barb	1	-0.67316	0.37848	3.1633	0.0753	0.51
lithium	1	0.42015	0.20067	4.3837	0.0363	1.522
thiaz	1	-0.2459	0.0383	41.2142	<.0001	0.782
gnrh	1	8.861	375.41413	0.0006	0.9812	7051.534

arom	1	-0.14618	0.05505	7.0511	0.0079	0.864
convulsants	1	-0.1783	0.02012	78.5478	<.0001	0.837
ssri	1	-0.21355	0.01806	139.8291	<.0001	0.808
ppi	1	-0.1486	0.01565	90.2035	<.0001	0.862
mtx	1	-0.30327	0.06155	24.2745	<.0001	0.738
csa	1	-0.15734	0.18283	0.7406	0.3895	0.854
coag	1	-0.1332	0.02207	36.4282	<.0001	0.875
white	1	-0.2652	0.18592	2.0347	0.1537	0.767
black	1	0.64993	0.18921	11.7985	0.0006	1.915
other_race	1	-0.01643	0.20075	0.0067	0.9348	0.984
asian	1	-0.01912	0.19453	0.0097	0.9217	0.981
hispanic	1	0.05828	0.19167	0.0925	0.7611	1.06
amnative	1	-0.35701	0.20774	2.9534	0.0857	0.7
Age	1	-2.36703	0.19549	146.6019	<.0001	0.094
Age*Age	1	0.03049	0.00244	156.3793	<.0001	1.031
Age*Age*Age	1	-0.0001268	0.0000101	158.5881	<.0001	1
Age*Osteoporosis	1	-0.01463	0.0023	40.5782	<.0001	0.985

Table A2 Approach 1, MOF All available, no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.31973	0.01791	318.5363	<.0001	1.377
Cystic Fibrosis	1	-0.30773	0.25037	1.5107	0.219	0.735
Congestive Heart Failure	1	-0.11555	0.01377	70.4137	<.0001	0.891
Ehlers-Danlos	1	-0.06718	1.0001	0.0045	0.9464	0.935
Epilepsy	1	-0.05014	0.03952	1.6096	0.2045	0.951
Osteogenesis Imperfecta	1	-0.40276	0.57805	0.4855	0.4859	0.668
Parkinson's Disease	1	-0.13851	0.03454	16.0769	<.0001	0.871
Stroke	1	-0.07927	0.01447	29.9926	<.0001	0.924
Adrenal insufficiency	1	-0.02193	0.22402	0.0096	0.922	0.978
AIDS/HIV	1	0.32397	0.26747	1.4671	0.2258	1.383
Alcoholism	1	-0.49186	0.06065	65.7726	<.0001	0.611
Alzheimer's	1	-0.04354	0.01548	7.9163	0.0049	0.957
Amyloidosis	1	-0.37475	0.20027	3.5014	0.0613	0.687
Androgen insensitivity	1	-0.08814	1.00007	0.0078	0.9298	0.916
Anorexia	1	-0.1872	0.03787	24.4408	<.0001	0.829
Ankylosing spondylitis	1	-0.26809	0.0372	51.9256	<.0001	0.765
COPD	1	-0.29428	0.01103	712.312	<.0001	0.745
Athletic amenorrhea	1	0.457	0.23581	3.756	0.0526	1.579

Cataracts	1	0.02214	0.01352	2.6809	0.1016	1.022
Celiac	1	-0.04725	0.13616	0.1204	0.7286	0.954
Central Adiposity	1	0.16259	0.02171	56.0639	<.0001	1.177
Chronic metabolic acidosis	1	-0.08598	0.04515	3.6274	0.0568	0.918
Crohn's Disease	1	-0.07678	0.02434	9.9476	0.0016	0.926
Cushing's	1	-0.43907	0.16261	7.2906	0.0069	0.645
Depression	1	-0.05662	0.01442	15.4235	<.0001	0.945
DM	1	0.02425	0.01126	4.6389	0.0313	1.025
ESRD	1	-0.46274	0.04485	106.4566	<.0001	0.63
Disorders of the Eye	1	-0.05735	0.01356	17.8797	<.0001	0.944
Falling	1	-0.21456	0.01974	118.1112	<.0001	0.807
Gaucher's Disease	1	0.01641	0.12055	0.0185	0.8917	1.017
Glaucoma	1	0.01692	0.01526	1.2297	0.2675	1.017
Gout	1	0.05983	0.02691	4.9437	0.0262	1.062
Glycogen storage diseases	1	-0.12271	0.40841	0.0903	0.7638	0.885
Hemochromatosis	1	1.61726	1.00003	2.6154	0.1058	5.039
Hemophilia	1	-0.04363	0.03022	2.0849	0.1488	0.957
Homocystinuria	1	0.19196	0.14161	1.8377	0.1752	1.212
Hyperprolactinemia	1	-0.21522	0.3017	0.5089	0.4756	0.806
Hyperparathyroidism	1	0.01205	0.0477	0.0638	0.8006	1.012
Hyperthyroid	1	0.017	0.03272	0.27	0.6034	1.017
Hypophosphatasia	1	-0.1835	0.06594	7.7457	0.0054	0.832
IBD	1	-0.05112	0.05181	0.9733	0.3239	0.95
Idiopathic scoliosis	1	-0.18381	0.02781	43.6913	<.0001	0.832
Idiopathic hypercalciuria	1	6.30083	26.25653	0.0576	0.8104	545.026
Kyphosis	1	-0.00875	0.01515	0.3336	0.5635	0.991
Liver Disease	1	-0.12473	0.02319	28.9199	<.0001	0.883
Malabsorption	1	-0.00794	0.08709	0.0083	0.9274	0.992
Marfan syndrome	1	0.34461	1.00029	0.1187	0.7305	1.411
MS	1	-0.17833	0.08606	4.2937	0.0383	0.837
Muscular dystrophy	1	0.39845	0.35371	1.2689	0.26	1.49
Obesity	0	0
Osteoarthritis	1	-0.01698	0.01047	2.6288	0.1049	0.983
Osteoporosis	1	-1.19985	0.12261	95.7678	<.0001	0.301
Other Fx	1	-0.27674	0.02069	178.9283	<.0001	0.758
Panhypopituitarism	1	-0.73735	0.35395	4.3397	0.0372	0.478
Pancreatic Disease	1	-0.14908	0.03827	15.1787	<.0001	0.862
Poly Rheumatica	1	-0.15984	0.03863	17.1193	<.0001	0.852
Porphyria	1	0.35662	0.40834	0.7627	0.3825	1.428
Premature ovarian failure	1	0.5873	0.25836	5.1675	0.023	1.799
Primary biliary cirrhosis	1	-0.48783	0.12517	15.1899	<.0001	0.614

Riley-Day	1	5.8241	20.36127	0.0818	0.7748	338.355
Renauld Disease	1	-0.01843	0.02078	0.7871	0.375	0.982
RA	1	-0.15129	0.0242	39.0842	<.0001	0.86
Saccoidosis	1	-0.06055	0.10685	0.3212	0.5709	0.941
Sickle Cell Anemia	1	0.27143	0.44759	0.3677	0.5442	1.312
Lupus	1	-0.39125	0.05399	52.5184	<.0001	0.676
Spinal cord injury	1	-0.25806	0.12749	4.0971	0.043	0.773
Systemic mastocytosis	1	0.28805	0.57741	0.2489	0.6179	1.334
Turner's & Klinefelter's syndromes	1	-0.49704	0.70724	0.4939	0.4822	0.608
Thalassemia	1	0.07424	0.19262	0.1486	0.6999	1.077
Thyrotoxicosis	0	0
Vitamin A	1	1.12958	1.00027	1.2753	0.2588	3.094
Vitamin D	1	0.0399	0.02313	2.9744	0.0846	1.041
barb	1	-0.39285	0.27759	2.0029	0.157	0.675
lithium	1	0.29612	0.12092	5.9967	0.0143	1.345
thiaz	1	-0.23351	0.02434	92.0717	<.0001	0.792
gnrh	1	6.88978	64.38509	0.0115	0.9148	982.188
arom	1	-0.13155	0.03595	13.3893	0.0003	0.877
convulsants	1	-0.18733	0.01334	197.3425	<.0001	0.829
ssri	1	-0.1923	0.01209	252.8766	<.0001	0.825
ppi	1	-0.11419	0.01027	123.7055	<.0001	0.892
mtx	1	-0.28953	0.04017	51.9543	<.0001	0.749
csa	1	-0.21938	0.11129	3.8861	0.0487	0.803
coag	1	-0.18764	0.01422	174.0544	<.0001	0.829
white	1	-0.30793	0.1326	5.393	0.0202	0.735
black	1	0.61511	0.13459	20.8883	<.0001	1.85
other_race	1	-0.03575	0.14127	0.064	0.8002	0.965
asian	1	-0.09508	0.13731	0.4795	0.4887	0.909
hispanic	1	-0.00771	0.13594	0.0032	0.9548	0.992
amnative	1	-0.38616	0.14585	7.0095	0.0081	0.68
Age	1	-2.14582	0.13538	251.2509	<.0001	0.117
Age*Age	1	0.02783	0.0017	269.2314	<.0001	1.028
Age*Age*Age	1	-0.0001164	7.04E-06	273.2939	<.0001	1
Age*Osteoporosis	1	-0.01116	0.00153	53.1422	<.0001	0.989

Table A3 Approach 1, MOF 365 days, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.01524	0.32681	0.0022	0.9628	1.015
Cystic Fibrosis	1	12.68328	9522	0	0.9989	322314.2
Congestive Heart Failure	1	0.07362	0.33977	0.0469	0.8285	1.076
Epilepsy	1	-0.07802	1.05209	0.0055	0.9409	0.925
Parkinson's Disease	1	-0.53803	1.01391	0.2816	0.5957	0.584
Stroke	1	-0.03809	0.35769	0.0113	0.9152	0.963
Adrenal insufficiency	1	13.26799	8955	0	0.9988	578380.5
AIDS/HIV	1	12.93149	1036	0.0002	0.99	413117.1
Alcoholism	1	13.53055	1614	0.0001	0.9933	752045.9
Alzheimers	1	0.24001	0.62351	0.1482	0.7003	1.271
Anorexia	1	-1.47149	0.75414	3.8072	0.051	0.23
Ankylosing spondylitis	1	-0.79749	1.01333	0.6194	0.4313	0.45
COPD	1	-0.09248	0.26807	0.119	0.7301	0.912
Athletic amenorrhea	1	13.9656	6579	0	0.9983	1161934
Cataracts	1	0.68341	0.41784	2.6751	0.1019	1.981
Celiac	1	-1.4186	5470	0	0.9998	0.242
Central Adiposity	1	0.82906	0.30788	7.2514	0.0071	2.291
Chronic metabolic acidosis	1	13.85803	1809	0.0001	0.9939	1043436
Crohn's Disease	1	-0.1068	1.01168	0.0111	0.9159	0.899
Cushing's	1	13.54194	4636	0	0.9977	760657.8
Depression	1	-0.31955	0.27893	1.3125	0.252	0.726
DM	1	-0.15384	0.20075	0.5872	0.4435	0.857
ESRD	1	-0.29634	0.4929	0.3615	0.5477	0.744
Disorders of the Eye	1	-0.09609	0.31501	0.093	0.7603	0.908
Falling	1	-1.46812	0.41029	12.8038	0.0003	0.23
Gaucher's Disease	1	13.5664	2184	0	0.995	779494.8
Glaucoma	1	0.63359	0.50769	1.5575	0.212	1.884
Gout	1	-0.62975	0.43674	2.0792	0.1493	0.533
Glycogen storage diseases	1	10.88815	7653	0	0.9989	53538.41
Hemochromatosis	1	14.25968	5333	0	0.9979	1559192
Hemophilia	1	-0.22839	0.57388	0.1584	0.6906	0.796
Homocystinuria	1	13.39097	3872	0	0.9972	654069.3
Hyperprolactinemia	1	13.99742	6429	0	0.9983	1199501
Hyperthyroid	1	-0.6956	0.52513	1.7546	0.1853	0.499
Hypophosphatasia	1	-2.27852	1.10243	4.2717	0.0388	0.102

IBD	1	13.50667	2291	0	0.9953	734299.5
Idopathic scoliosis	1	12.62684	807.98255	0.0002	0.9875	304626.3
Kyphosis	1	0.8155	0.5905	1.9072	0.1673	2.26
Liver Disease	1	1.08168	1.00837	1.1507	0.2834	2.95
Malabsorption	1	13.80847	1917	0.0001	0.9943	992982.8
MS	1	13.541	1780	0.0001	0.9939	759945.1
Obesity	0	0
Osteoarthritis	1	-0.16806	0.23294	0.5205	0.4706	0.845
Osteoporosis	1	-35.22601	26.6008	1.7536	0.1854	0
Other Fx	1	0.41494	1.02256	0.1647	0.6849	1.514
Panhypopituitarism	1	12.98192	12344	0	0.9992	434487.5
Pancreatic Disease	1	13.84892	1238	0.0001	0.9911	1033976
Poly Rheumatica	1	13.85454	3627	0	0.997	1039799
Premature ovarian failure	1	12.9975	4914	0	0.9979	441309.6
Primary biliary cirrhosis	1	11.82731	7166	0	0.9987	136941.8
Riley-Day	1	15.07286	8827	0	0.9986	3516091
Renault Disease	1	-0.27144	0.36504	0.5529	0.4571	0.762
RA	1	-0.76547	0.63854	1.4371	0.2306	0.465
Sarcoidosis	1	-0.68743	1.04717	0.4309	0.5115	0.503
Sickle Cell Anemia	1	13.07443	3980	0	0.9974	476596.3
Lupus	1	-0.78643	1.0317	0.5811	0.4459	0.455
Spinal cord injury	1	11.6896	7599	0	0.9988	119324.1
Systemic mastocytosis	1	13.21174	13174	0	0.9992	546748.2
Thalassemia	1	13.29856	3018	0	0.9965	596337.1
Thyrotoxicosis	0	0
Vitamin A	1	13.57887	10477	0	0.999	789278.5
Vitamin D	1	-0.85789	0.33588	6.5236	0.0106	0.424
barb	1	14.31906	9214	0	0.9988	1654578
lithium	1	14.02703	1726	0.0001	0.9935	1235557
thiaz	1	-0.17605	0.30317	0.3372	0.5614	0.839
arom	1	-0.67787	1.01121	0.4494	0.5026	0.508
convulsants	1	-0.10094	0.23121	0.1906	0.6624	0.904
ssri	1	-0.22882	0.23387	0.9573	0.3279	0.795
ppi	1	-0.227	0.18806	1.4571	0.2274	0.797
mtx	1	-0.546	1.03769	0.2769	0.5988	0.579
csa	1	13.26812	2503	0	0.9958	578457.7
coag	1	-0.63657	0.30907	4.242	0.0394	0.529
white	1	-13.39172	4695	0	0.9977	0
black	1	-12.54397	4695	0	0.9979	0
other_race	1	-12.49572	4695	0	0.9979	0

asian	1	-12.65013	4695	0	0.9979	0
hispanic	1	-13.40192	4695	0	0.9977	0
amnative	1	-15.23315	4695	0	0.9974	0
Age	1	70.03146	82.01864	0.7291	0.3932	2.60E+30
Age*Age	1	-1.05795	1.21036	0.764	0.3821	0.347
Age*Age*Age	1	0.00532	0.00595	0.7993	0.3713	1.005
Age*Osteoporosis	1	-0.51582	0.4064	1.611	0.2044	0.597

Table A4 Approach 1, MOF All available, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.47697	0.16655	8.2018	0.0042	1.611
Cystic Fibrosis	1	12.62001	3164	0	0.9968	302552
Congestive Heart Failure	1	0.15682	0.2201	0.5077	0.4761	1.17
Epilepsy	1	-0.84314	0.47622	3.1347	0.0766	0.43
Parkinson's Disease	1	-0.34856	0.72149	0.2334	0.629	0.706
Stroke	1	0.03851	0.22668	0.0289	0.8651	1.039
Adrenal insufficiency	1	13.51705	3268	0	0.9967	741959.6
AIDS/HIV	1	12.49987	505.10168	0.0006	0.9803	268301.2
Alcoholism	1	-1.18529	0.71992	2.7107	0.0997	0.306
Alzheimers	1	-0.07966	0.35065	0.0516	0.8203	0.923
Anorexia	1	-1.78924	0.47293	14.3136	0.0002	0.167
Ankylosing spondylitis	1	-0.41667	0.71629	0.3384	0.5608	0.659
COPD	1	-0.06055	0.16663	0.132	0.7163	0.941
Athletic amenorrhea	1	13.40077	2639	0	0.9959	660512.9
Cataracts	1	0.2761	0.20748	1.7709	0.1833	1.318
Celiac	1	12.60472	1828	0	0.9945	297961.3
Central Adiposity	1	0.66137	0.1893	12.206	0.0005	1.937
Chronic metabolic acidosis	1	12.57209	569.27227	0.0005	0.9824	288397.2
Crohn's Disease	1	0.19611	0.71325	0.0756	0.7834	1.217
Cushing's	1	12.57818	2019	0	0.995	290158.9
Depression	1	0.02415	0.1902	0.0161	0.899	1.024
DM	1	-0.25355	0.12672	4.0037	0.0454	0.776
ESRD	1	-1.08624	0.26688	16.566	<.0001	0.337
Disorders of the Eye	1	-0.16339	0.18073	0.8173	0.366	0.849
Falling	1	-1.15038	0.27528	17.4631	<.0001	0.317
Gaucher's Disease	1	12.75282	871.39009	0.0002	0.9883	345526.3

Glaucoma	1	0.24419	0.23017	1.1255	0.2887	1.277
Gout	1	-0.62186	0.27317	5.1823	0.0228	0.537
Glycogen storage diseases	1	9.69309	3724	0	0.9979	16205.21
Hemochromatosis	1	13.7444	2807	0	0.9961	931357.8
Hemophilia	1	-0.10927	0.39	0.0785	0.7793	0.896
Homocystinuria	1	12.60252	1530	0.0001	0.9934	297306.1
Hyperprolactinemia	1	13.23109	4955	0	0.9979	557429.2
Hyperthyrois	1	-0.16746	0.38826	0.186	0.6662	0.846
Hypophosphatasia	1	-1.15365	1.03107	1.2519	0.2632	0.315
IBD	1	-0.92513	1.23839	0.5581	0.455	0.396
Idopathic scoliosis	1	12.03616	355.87643	0.0011	0.973	168748.3
Kyphosis	1	0.48015	0.28849	2.7702	0.096	1.616
Liver Disease	1	0.80683	0.5071	2.5315	0.1116	2.241
Malabsorption	1	-0.3638	1.04871	0.1203	0.7287	0.695
MS	1	12.91374	732.01321	0.0003	0.9859	405848.9
Obseity	0	0
Osteoarthritis	1	-0.20227	0.1392	2.1114	0.1462	0.817
Osteoporosis	1	-23.88161	16.34535	2.1347	0.144	0
Other Fx	1	0.33841	0.59562	0.3228	0.5699	1.403
Panhypopituitarism	1	12.43877	4588	0	0.9978	252398.6
Pancreatic Disease	1	0.43381	1.01185	0.1838	0.6681	1.543
Poly Rheumatica	1	13.18055	1617	0.0001	0.9935	529956.9
Premature ovarian failure	1	12.08439	1787	0	0.9946	177086.3
Primary bilary cirrhosis	1	10.81919	3676	0	0.9977	49970.64
Riley-Day	1	13.60338	7631	0	0.9986	808855.6
Renauld Disease	1	-0.10611	0.23349	0.2065	0.6495	0.899
RA	1	0.45967	0.62363	0.5433	0.4611	1.584
Saccoidosis	1	0.06525	1.00767	0.0042	0.9484	1.067
Sickle Cell Anemia	1	12.44513	1654	0.0001	0.994	254009.2
Lupus	1	-1.28444	0.60366	4.5274	0.0334	0.277
Spinal cord injury	1	11.2201	2817	0	0.9968	74615.03
Systemic mastocytosis	1	12.68331	4612	0	0.9978	322323.7
Thalassemia	1	12.49705	1125	0.0001	0.9911	267547.1
Thyrotoxicosis	0	0
Vitamin A	1	12.87641	5870	0	0.9982	390979.4
Vitamin D	1	-0.51289	0.25926	3.9137	0.0479	0.599
barb	1	13.78925	3251	0	0.9966	974078
lithium	1	13.17088	800.76413	0.0003	0.9869	524858.7
thiaz	1	-0.31773	0.17599	3.2594	0.071	0.728
arom	1	-0.98352	0.58717	2.8057	0.0939	0.374

convulsants	1	-0.0639	0.15377	0.1727	0.6777	0.938
ssri	1	-0.33227	0.15074	4.8585	0.0275	0.717
ppi	1	0.02785	0.12752	0.0477	0.8271	1.028
mtx	1	-0.65945	0.7414	0.7912	0.3738	0.517
csa	1	12.42367	1026	0.0001	0.9903	248617.6
coag	1	-0.48836	0.20848	5.4874	0.0192	0.614
white	1	-12.48704	1953	0	0.9949	0
black	1	-11.60629	1953	0	0.9953	0
other_race	1	-12.00552	1953	0	0.9951	0
asian	1	-12.00845	1953	0	0.9951	0
hispanic	1	-12.46	1953	0	0.9949	0
amnative	1	-13.42879	1953	0	0.9945	0
Age	1	-6.97485	62.3686	0.0125	0.911	0.001
Age*Age	1	0.08722	0.92385	0.0089	0.9248	1.091
Age*Age*Age	1	-0.0003518	0.00456	0.006	0.9385	1
Age*Osteoporosis	1	-0.35107	0.24866	1.9933	0.158	0.704

Table A5 Approach 1, MOF 365 days, CFRI With BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	-0.69356	1.06123	0.4271	0.5134	0.5
Congestive Heart Failure	1	19.92888	1834	0.0001	0.9913	4.52E+08
Epilepsy	1	15.18062	2648	0	0.9954	3916154
Parkinson's Disease	1	17.08062	11056	0	0.9988	26183002
Stroke	1	-0.45959	1.12696	0.1663	0.6834	0.632
AIDS/HIV	1	16.0586	7375	0	0.9983	9422441
Alcoholism	1	20.78257	10035	0	0.9983	1.06E+09
Alzheimers	1	-1.84643	1.10724	2.7809	0.0954	0.158
Anorexia	1	16.99477	64062	0	0.9998	24028909
Ankylosing spondylitis	1	15.82383	14577	0	0.9991	7450811
COPD	1	-0.88173	0.68756	1.6445	0.1997	0.414
Cataracts	1	-15.39971	1978	0.0001	0.9938	0
Celiac	1	-50.16522	101892	0	0.9996	0
Central Adiposity	1	16.07604	2863	0	0.9955	9588140
Chronic metabolic acidosis	1	-13.23647	68371	0	0.9998	0
Crohn's Disease	1	16.22309	10061	0	0.9987	11107057
Depression	1	-0.21414	1.07345	0.0398	0.8419	0.807

DM	1	0.2845	0.53087	0.2872	0.592	1.329
ESRD	1	0.32259	1.04361	0.0955	0.7572	1.381
Disorders of the Eye	1	16.73025	1978	0.0001	0.9932	18444027
Falling	1	-2.02602	1.18467	2.9248	0.0872	0.132
Gaucher's Disease	1	16.01104	39579	0	0.9997	8984741
Glaucoma	1	13.56844	2965	0	0.9963	781086.2
Gout	1	14.9232	4291	0	0.9972	3027359
Hemochromatosis	1	0.80805	79409	0	1	2.244
Hemophilia	1	-2.9439	1.07878	7.4469	0.0064	0.053
Hyperthyroid	1	-2.4697	1.07785	5.2501	0.0219	0.085
Hypophosphatasia	1	-4.12193	1.40145	8.6506	0.0033	0.016
IBD	1	1.16656	35196	0	1	3.211
Idopathic scoliosis	1	0.75409	7521	0	0.9999	2.126
Kyphosis	1	15.83765	4026	0	0.9969	7554451
Liver Disease	1	15.81574	4450	0	0.9972	7390727
Malabsorption	1	1.93971	57086	0	1	6.957
MS	1	16.79441	16369	0	0.9992	19666191
Obesity	0	0
Osteoarthritis	1	-0.03336	0.72196	0.0021	0.9631	0.967
Other Fx	1	15.96891	6276	0	0.998	8614060
Pancreatic Disease	1	16.45632	13661	0	0.999	14024573
Poly Rheumatica	1	17.75901	40432	0	0.9996	51598891
Riley-Day	1	-12.2099	49063	0	0.9998	0
Renault Disease	1	-1.43126	0.887	2.6037	0.1066	0.239
RA	1	-2.48144	0.83109	8.9148	0.0028	0.084
Sacroiliitis	1	-3.45605	1.21108	8.1436	0.0043	0.032
Sickle Cell Anemia	1	16.27301	26050	0	0.9995	11675619
Lupus	1	16.17047	5588	0	0.9977	10537712
Spinal cord injury	0	0
Thalassemia	1	-12.40982	70178	0	0.9999	0
Thyrotoxicosis	0	0
Vitamin D	1	16.11881	4762	0	0.9973	10007111
lithium	1	17.13334	14464	0	0.9991	27600327
thiaz	1	-0.80602	0.80882	0.9931	0.319	0.447
arom	1	16.4601	16317	0	0.9992	14077640
convulsants	1	-0.49201	0.52994	0.862	0.3532	0.611
ssri	1	0.45869	0.77397	0.3512	0.5534	1.582
ppi	1	-0.82485	0.4409	3.5	0.0614	0.438
mtx	1	-0.72015	1.1953	0.363	0.5469	0.487
csa	1	16.32758	30697	0	0.9996	12330392
coag	1	-1.0694	0.64758	2.727	0.0987	0.343

Age	1	0.33078	0.42428	0.6078	0.4356	1.392
Age*Age	0	0
Age*Age*Age	0	0
Age*Osteoporosis	0	0

Table A6 Approach 1, MOF All Available, CFRI With BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.03677	0.53327	0.0048	0.945	1.037
Congestive Heart Failure	1	16.36058	936.23249	0.0003	0.9861	12744055
Epilepsy	1	15.21591	2375	0	0.9949	4056805
Parkinson's Disease	1	14.7651	3519	0	0.9967	2584639
Stroke	1	0.09488	0.90131	0.0111	0.9162	1.1
AIDS/HIV	1	15.15211	2993	0	0.996	3806097
Alcoholism	1	-0.28601	1.4678	0.038	0.8455	0.751
Alzheimers	1	-1.88413	0.7666	6.0407	0.014	0.152
Anorexia	1	1.23932	13202	0	0.9999	3.453
Ankylosing spondylitis	1	15.47151	5428	0	0.9977	5238338
COPD	1	-0.89941	0.45631	3.885	0.0487	0.407
Cataracts	1	1.0122	1.78174	0.3227	0.57	2.752
Celiac	1	-28.88026	24893	0	0.9991	0
Central Adiposity	1	-0.25547	0.62831	0.1653	0.6843	0.775
Chronic metabolic acidosis	1	0.15048	15810	0	1	1.162
Crohn's Disease	1	14.76468	3352	0	0.9965	2583555
Depression	1	1.19356	1.06284	1.2611	0.2614	3.299
DM	1	-0.28767	0.33035	0.7583	0.3839	0.75
ESRD	1	-1.03773	0.50646	4.1983	0.0405	0.354
Disorders of the Eye	1	1.04524	1.04638	0.9978	0.3178	2.844
Falling	1	-2.38019	0.68143	12.2007	0.0005	0.093
Gaucher's Disease	1	15.17937	12563	0	0.999	3911241
Glaucoma	1	14.42614	1527	0.0001	0.9925	1841587
Gout	1	15.17013	2151	0	0.9944	3875288
Hemochromatosis	1	-2.21412	41483	0	1	0.109
Hemophilia	1	-1.12177	1.31315	0.7297	0.393	0.326
Hyperthyroid	1	-1.575	1.0363	2.3099	0.1286	0.207
Hypophosphatasia	1	-3.08298	1.41277	4.7621	0.0291	0.046
IBD	1	1.86628	12680	0	0.9999	6.464

Idopathic scoliosis	1	-0.63508	3079	0	0.9998	0.53
Kyphosis	1	15.1517	1582	0.0001	0.9924	3804533
Liver Disease	1	14.95126	1838	0.0001	0.9935	3113519
Malabsorption	1	13.94973	9286	0	0.9988	1143641
MS	1	15.15946	7168	0	0.9983	3834159
Obesity	0	0
Osteoarthritis	1	-0.33851	0.45132	0.5626	0.4532	0.713
Other Fx	1	14.50604	2186	0	0.9947	1994779
Pancreatic Disease	1	15.42138	5800	0	0.9979	4982192
Poly Rheumatica	1	16.08604	11074	0	0.9988	9684540
Riley-Day	1	1.88542	23441	0	0.9999	6.589
Renauld Disease	1	-0.42566	0.61794	0.4745	0.4909	0.653
RA	1	-0.53012	0.89966	0.3472	0.5557	0.589
Sacroiliitis	1	-2.0071	1.12153	3.2027	0.0735	0.134
Sickle Cell Anemia	1	14.96295	8905	0	0.9987	3150111
Lupus	1	-1.70915	1.07869	2.5105	0.1131	0.181
Spinal cord injury	0	0
Thalassemia	1	1.12718	19285	0	1	3.087
Thyrotoxicosis	0	0
Vitamin D	1	15.23514	2010	0.0001	0.994	4135606
lithium	1	15.2486	6727	0	0.9982	4191615
thiaz	1	0.24455	0.75187	0.1058	0.745	1.277
arom	1	-2.08823	1.02754	4.13	0.0421	0.124
convulsants	1	-0.04753	0.40142	0.014	0.9057	0.954
ssri	1	0.21171	0.54058	0.1534	0.6953	1.236
ppi	1	-0.21495	0.32543	0.4363	0.5089	0.807
mtx	1	-0.54634	1.12669	0.2351	0.6277	0.579
csa	1	15.84067	9286	0	0.9986	7577337
coag	1	-0.38896	0.55644	0.4886	0.4845	0.678
Age	1	0.0102	0.294	0.0012	0.9723	1.01
Age*Age	0	0
Age*Age*Age	0	0
Age*Osteoporosis	0	0

Table A7 Approach 1 Vertebral Fracture 365 days, no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.23059	0.03911	34.7657	<.0001	1.259
Cystic Fibrosis	1	-0.01793	0.57812	0.001	0.9753	0.982
Congestive Heart Failure	1	-0.10348	0.02589	15.977	<.0001	0.902
Ehlers-Danlos	1	9.42058	172.16383	0.003	0.9564	12339.73
Epilepsy	1	0.11701	0.07735	2.2885	0.1303	1.124
Osteogenesis Imperfecta	1	-0.30079	1.00122	0.0903	0.7639	0.74
Parkinson's Disease	1	-0.09147	0.06508	1.9754	0.1599	0.913
Stroke	1	-0.06715	0.02838	5.5991	0.018	0.935
Adrenal insufficiency	1	0.01201	0.44786	0.0007	0.9786	1.012
AIDS/HIV	1	-0.40009	0.35412	1.2765	0.2586	0.67
Alcoholism	1	-0.47057	0.11289	17.3769	<.0001	0.625
Alzheimers	1	0.08334	0.02926	8.1105	0.0044	1.087
Amyloidosis	1	-0.63421	0.3168	4.0077	0.0453	0.53
Androgen insensitivity	1	8.96563	166.74087	0.0029	0.9571	7829.341
Anorexia	1	-0.27027	0.0656	16.9763	<.0001	0.763
Ankylosing spondylitis	1	-0.37177	0.07177	26.833	<.0001	0.69
COPD	1	-0.40223	0.0208	374.1083	<.0001	0.669
Athletic amenorrhea	1	0.22207	0.44743	0.2463	0.6197	1.249
Cataracts	1	0.04372	0.02789	2.4579	0.1169	1.045
Celiac	1	-0.35186	0.26818	1.7214	0.1895	0.703
Central Adiposity	1	0.15257	0.04161	13.4457	0.0002	1.165
Chronic metabolic acidosis	1	-0.07713	0.07909	0.951	0.3295	0.926
Crohn's Disease	1	-0.13887	0.04575	9.216	0.0024	0.87
Cushing's	1	-0.80611	0.25888	9.6961	0.0018	0.447
Depression	1	-0.04152	0.02729	2.3142	0.1282	0.959
DM	1	0.08842	0.02199	16.1708	<.0001	1.092
ESRD	1	-0.3078	0.08303	13.743	0.0002	0.735
Disorders of the Eye	1	0.00491	0.02692	0.0333	0.8552	1.005
Falling	1	-0.22278	0.03748	35.3398	<.0001	0.8
Gaucher's Disease	1	0.23198	0.27761	0.6983	0.4034	1.261
Glaucoma	1	-0.00502	0.0318	0.0249	0.8746	0.995
Gout	1	0.16713	0.05395	9.596	0.0019	1.182
Glycogen storage diseases	1	9.21742	89.80673	0.0105	0.9183	10071.03
Hemochromatosis	1	9.09615	65.56946	0.0192	0.8897	8920.887
Hemophilia	1	-0.07097	0.05763	1.5165	0.2181	0.931
Homocystinuria	1	-0.28669	0.22987	1.5554	0.2123	0.751
Hyperprolactinemia	1	-0.24516	0.57777	0.1801	0.6713	0.783
Hyperparathyroidism	1	0.13334	0.09809	1.8479	0.174	1.143

Hyperthyrois	1	0.03525	0.06531	0.2913	0.5894	1.036
Hypophosphatasia	1	-0.40828	0.10777	14.3515	0.0002	0.665
IBD	1	0.05588	0.10117	0.305	0.5807	1.057
Idopathic scoliosis	1	-0.28909	0.05023	33.1247	<.0001	0.749
Idiopathic hypercalciuria	1	9.34013	303.66494	0.0009	0.9755	11385.86
Kyphosis	1	-0.03348	0.03019	1.2301	0.2674	0.967
Liver Disease	1	-0.19932	0.04338	21.107	<.0001	0.819
Malabsorption	1	0.18316	0.18333	0.9982	0.3178	1.201
Marfan syndrome	1	-0.75561	1.00156	0.5692	0.4506	0.47
MS	1	-0.16716	0.16076	1.0812	0.2984	0.846
Muscular dystrophy	1	-0.14145	0.50062	0.0798	0.7775	0.868
Obseity	0	0
Osteoarthritis	1	-0.00628	0.02051	0.0937	0.7596	0.994
Osteoporosis	1	-0.91282	0.22662	16.2245	<.0001	0.401
Other Fx	1	-0.24942	0.03948	39.9085	<.0001	0.779
Panhypopituitarism	1	0.06828	1.00073	0.0047	0.9456	1.071
Pancreatic Disease	1	-0.15344	0.07094	4.6787	0.0305	0.858
Poly Rheumatica	1	-0.29932	0.07029	18.1337	<.0001	0.741
Porphyria	1	9.1852	69.11667	0.0177	0.8943	9751.696
Premature ovarian failure	1	1.78368	1.00015	3.1806	0.0745	5.952
Primary biliary cirrhosis	1	-0.54118	0.22232	5.9257	0.0149	0.582
Riley-Day	1	8.88134	172.62493	0.0026	0.959	7196.409
Renauld Disease	1	0.03027	0.03872	0.6112	0.4343	1.031
RA	1	-0.19308	0.04569	17.8567	<.0001	0.824
Saccoidosis	1	-0.08144	0.20459	0.1585	0.6906	0.922
Sickle Cell Anemia	1	-0.36523	0.57808	0.3992	0.5275	0.694
Lupus	1	-0.45374	0.0996	20.7521	<.0001	0.635
Spinal cord injury	1	-0.45368	0.21933	4.2786	0.0386	0.635
Systemic mastocytosis	1	-0.01382	1.00015	0.0002	0.989	0.986
Turner's & Klinefelter's syndromes	1	9.23187	191.56562	0.0023	0.9616	10217.67
Thalassemia	1	0.48943	0.44745	1.1964	0.274	1.631
Thyrotoxicosis	0	0
Vitamin A	1	9.11912	111.705	0.0067	0.9349	9128.152
Vitamin D	1	0.04929	0.04306	1.3105	0.2523	1.051
barb	1	-0.23222	0.5779	0.1615	0.6878	0.793
lithium	1	0.21459	0.22454	0.9134	0.3392	1.239
thiaz	1	-0.16883	0.04987	11.4592	0.0007	0.845
gnrh	1	9.69473	773.04082	0.0002	0.99	16231.76
arom	1	-0.05324	0.07087	0.5644	0.4525	0.948
convulsants	1	-0.23104	0.0246	88.235	<.0001	0.794

ssri	1	-0.18967	0.02258	70.5868	<.0001	0.827
ppi	1	-0.18092	0.01933	87.6412	<.0001	0.835
mtx	1	-0.33785	0.07307	21.3807	<.0001	0.713
csa	1	0.06626	0.25028	0.0701	0.7912	1.069
coag	1	-0.18359	0.02708	45.9736	<.0001	0.832
white	1	-0.11377	0.21851	0.2711	0.6026	0.892
black	1	0.79639	0.22299	12.7546	0.0004	2.218
other_race	1	-0.00436	0.23556	0.0003	0.9852	0.996
asian	1	-0.0032	0.22851	0.0002	0.9888	0.997
hispanic	1	0.19854	0.22611	0.771	0.3799	1.22
amnative	1	-0.15429	0.24856	0.3853	0.5348	0.857
Age	1	-2.58707	0.25038	106.7601	<.0001	0.075
Age*Age	1	0.03341	0.00313	113.696	<.0001	1.034
Age*Age*Age	1	-0.0001399	0.000013	116.0796	<.0001	1
Age*Osteoporosis	1	-0.0062	0.0028	4.8985	0.0269	0.994

Table A8 Approach 1 Vertebral Fracture All Available, no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.22861	0.02243	103.8331	<.0001	1.257
Cystic Fibrosis	1	-0.34424	0.30193	1.2999	0.2542	0.709
Congestive Heart Failure	1	-0.10813	0.01718	39.6297	<.0001	0.898
Ehlers-Danlos	1	-0.42674	1.00014	0.1821	0.6696	0.653
Epilepsy	1	0.05186	0.05101	1.0339	0.3093	1.053
Osteogenesis Imperfecta	1	-0.4026	0.70814	0.3232	0.5697	0.669
Parkinson's Disease	1	-0.14475	0.04368	10.9795	0.0009	0.865
Stroke	1	-0.06034	0.01812	11.0899	0.0009	0.941
Adrenal insufficiency	1	0.04235	0.28912	0.0215	0.8835	1.043
AIDS/HIV	1	0.23433	0.31651	0.5481	0.4591	1.264
Alcoholism	1	-0.57307	0.07162	64.018	<.0001	0.564
Alzheimers	1	0.1317	0.02036	41.8577	<.0001	1.141
Amyloidosis	1	-0.57096	0.22981	6.1726	0.013	0.565
Androgen insensitivity	1	7.89933	65.85558	0.0144	0.9045	2695.468
Anorexia	1	-0.14514	0.04831	9.0264	0.0027	0.865
Ankylosing spondylitis	1	-0.2935	0.04455	43.3948	<.0001	0.746
COPD	1	-0.34656	0.01349	660.3969	<.0001	0.707
Athletic amenorrhea	1	0.557	0.30164	3.4099	0.0648	1.745
Cataracts	1	0.03154	0.01684	3.5076	0.0611	1.032
Celiac	1	-0.1638	0.16766	0.9544	0.3286	0.849

Central Adiposity	1	0.12018	0.02641	20.7137	<.0001	1.128
Chronic metabolic acidosis	1	-0.07819	0.05685	1.8916	0.169	0.925
Crohn's Disease	1	-0.08397	0.02993	7.8701	0.005	0.919
Cushing's	1	-0.56927	0.18624	9.3432	0.0022	0.566
Depression	1	-0.04585	0.01797	6.5132	0.0107	0.955
DM	1	0.10164	0.01414	51.6819	<.0001	1.107
ESRD	1	-0.36031	0.05879	37.5649	<.0001	0.697
Disorders of the Eye	1	-0.0348	0.01684	4.2673	0.0389	0.966
Falling	1	-0.21605	0.02477	76.0685	<.0001	0.806
Gaucher's Disease	1	0.34432	0.17425	3.9046	0.0482	1.411
Glaucoma	1	0.04858	0.01916	6.4251	0.0113	1.05
Gout	1	0.08774	0.03393	6.6878	0.0097	1.092
Glycogen storage diseases	1	0.1757	0.57751	0.0926	0.7609	1.192
Hemochromatosis	1	8.06807	30.83918	0.0684	0.7936	3190.932
Hemophilia	1	-0.06299	0.03677	2.9342	0.0867	0.939
Homocystinuria	1	0.2639	0.18279	2.0842	0.1488	1.302
Hyperprolactinemia	1	-0.18333	0.37823	0.2349	0.6279	0.832
Hyperparathyroidism	1	0.08183	0.06109	1.7942	0.1804	1.085
Hyperthyroid	1	0.01673	0.04046	0.1709	0.6793	1.017
Hypophosphatasia	1	-0.26922	0.08084	11.0916	0.0009	0.764
IBD	1	-0.0691	0.06272	1.2138	0.2706	0.933
Idiopathic scoliosis	1	-0.20155	0.03357	36.0396	<.0001	0.817
Idiopathic hypercalciuria	1	8.30128	87.75497	0.0089	0.9246	4029.023
Kyphosis	1	-0.03338	0.01872	3.1794	0.0746	0.967
Liver Disease	1	-0.14157	0.02823	25.1523	<.0001	0.868
Malabsorption	1	0.07446	0.11089	0.4509	0.5019	1.077
Marfan syndrome	1	0.01958	1.00051	0.0004	0.9844	1.02
MS	1	-0.16384	0.10581	2.3979	0.1215	0.849
Muscular dystrophy	1	0.24875	0.40846	0.3709	0.5425	1.282
Obesity	0	0
Osteoarthritis	1	-0.00117	0.01298	0.0081	0.9285	0.999
Osteoporosis	1	-0.84085	0.14917	31.7743	<.0001	0.431
Other Fx	1	-0.27271	0.02568	112.8012	<.0001	0.761
Panhypopituitarism	1	-0.96119	0.3785	6.4489	0.0111	0.382
Pancreatic Disease	1	-0.15964	0.04697	11.554	0.0007	0.852
Poly Rheumatica	1	-0.28486	0.04462	40.7582	<.0001	0.752
Porphyria	1	0.63902	0.57745	1.2246	0.2685	1.895
Premature ovarian failure	1	0.84548	0.35374	5.7127	0.0168	2.329
Primary biliary cirrhosis	1	-0.43125	0.15497	7.7441	0.0054	0.65
Riley-Day	1	7.84587	72.11101	0.0118	0.9134	2555.15
Renault Disease	1	0.03377	0.02657	1.6148	0.2038	1.034

RA	1	-0.1564	0.02936	28.3736	<.0001	0.855
Saccoidosis	1	-0.12186	0.12631	0.9308	0.3347	0.885
Sickle Cell Anemia	1	0.08713	0.50052	0.0303	0.8618	1.091
Lupus	1	-0.49144	0.06186	63.1063	<.0001	0.612
Spinal cord injury	1	-0.31859	0.15314	4.328	0.0375	0.727
Systemic mastocytosis	1	0.25696	0.70719	0.132	0.7163	1.293
Turner's & Klinefelter's syndromes	1	8.20592	67.39314	0.0148	0.9031	3662.57
Thalassemia	1	0.1192	0.24274	0.2412	0.6234	1.127
Thyrotoxicosis	0	0
Vitamin A	1	8.13582	40.47546	0.0404	0.8407	3414.619
Vitamin D	1	0.01034	0.0282	0.1344	0.7139	1.01
barb	1	-0.40453	0.33362	1.4702	0.2253	0.667
lithium	1	0.21482	0.14354	2.2397	0.1345	1.24
thiaz	1	-0.15449	0.03162	23.8641	<.0001	0.857
gnrh	1	8.70604	213.12861	0.0017	0.9674	6039.264
arom	1	-0.06067	0.04576	1.7576	0.1849	0.941
convulsants	1	-0.24006	0.01625	218.2315	<.0001	0.787
ssri	1	-0.18893	0.01499	158.9214	<.0001	0.828
ppi	1	-0.15827	0.01262	157.3921	<.0001	0.854
mtx	1	-0.38201	0.04675	66.7679	<.0001	0.682
csa	1	-0.08861	0.14454	0.3758	0.5399	0.915
coag	1	-0.24102	0.01738	192.318	<.0001	0.786
white	1	-0.18415	0.15829	1.3533	0.2447	0.832
black	1	0.72948	0.16098	20.5356	<.0001	2.074
other_race	1	-0.02414	0.16844	0.0205	0.8861	0.976
asian	1	-0.14955	0.16352	0.8364	0.3604	0.861
hispanic	1	0.07922	0.16256	0.2375	0.626	1.082
amnative	1	-0.18767	0.17678	1.127	0.2884	0.829
Age	1	-2.21617	0.17231	165.4213	<.0001	0.109
Age*Age	1	0.02885	0.00216	177.6266	<.0001	1.029
Age*Age*Age	1	-0.0001215	9.01E-06	181.8347	<.0001	1
Age*Osteoporosis	1	-0.00583	0.00187	9.7636	0.0018	0.994

Table A9 Approach 1 Vertebral Fracture 365 days, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.22446	0.35235	0.4058	0.5241	1.252
Cystic Fibrosis	1	13.42767	17275	0	0.9994	678517.3
Congestive Heart Failure	1	0.12393	0.41981	0.0872	0.7678	1.132
Epilepsy	1	-0.51644	1.10019	0.2203	0.6388	0.597
Parkinson's Disease	1	14.68519	2457	0	0.9952	2386134
Stroke	1	-0.33824	0.4044	0.6996	0.4029	0.713
Adrenal insufficiency	1	13.66081	15601	0	0.9993	856671.1
AIDS/HIV	1	12.86624	1266	0.0001	0.9919	387024.9
Alcoholism	1	14.54208	2690	0	0.9957	2067980
Alzheimers	1	0.28062	0.76328	0.1352	0.7131	1.324
Anorexia	1	13.89782	1491	0.0001	0.9926	1085787
Ankylosing spondylitis	1	-1.0717	1.01858	1.107	0.2927	0.342
COPD	1	-0.207	0.3111	0.4427	0.5058	0.813
Athletic amenorrhea	1	14.24561	13000	0	0.9991	1537413
Cataracts	1	0.3977	0.50328	0.6245	0.4294	1.488
Celiac	1	-1.51083	7640	0	0.9998	0.221
Central Adiposity	1	0.69789	0.3661	3.6338	0.0566	2.009
Chronic metabolic acidosis	1	14.49818	3776	0	0.9969	1979163
Crohn's Disease	1	-0.34102	1.02154	0.1114	0.7385	0.711
Cushing's	1	14.34642	7991	0	0.9986	1700479
Depression	1	-0.46031	0.32024	2.0661	0.1506	0.631
DM	1	-0.04013	0.24097	0.0277	0.8677	0.961
ESRD	1	0.09545	0.68909	0.0192	0.8898	1.1
Disorders of the Eye	1	-0.09068	0.39145	0.0537	0.8168	0.913
Falling	1	-1.31709	0.53732	6.0085	0.0142	0.268
Gaucher's Disease	1	14.29963	4347	0	0.9974	1622746
Glaucoma	1	1.15724	0.76036	2.3163	0.128	3.181
Gout	1	-0.24202	0.62898	0.1481	0.7004	0.785
Glycogen storage diseases	1	12.30165	14117	0	0.9993	220058.7
Hemochromatosis	1	15.29951	9154	0	0.9987	4410563
Hemophilia	1	-0.67672	0.57178	1.4007	0.2366	0.508
Homocystinuria	1	14.29415	6662	0	0.9983	1613884
Hyperprolactinemia	1	14.77715	11547	0	0.999	2615976
Hyperthyroid	1	0.19781	1.01806	0.0378	0.8459	1.219
Hypophosphatasia	1	-2.82277	1.16098	5.9115	0.015	0.059

IBD	1	14.51044	3957	0	0.9971	2003572
Idopathic scoliosis	1	11.82032	946.36057	0.0002	0.99	135987.1
Kyphosis	1	1.59959	1.01221	2.4973	0.114	4.951
Liver Disease	1	14.3819	909.34937	0.0003	0.9874	1761893
Malabsorption	1	14.08019	3964	0	0.9972	1303014
MS	1	14.26417	2998	0	0.9962	1566213
Obesity	0	0
Osteoarthritis	1	-0.2533	0.27661	0.8386	0.3598	0.776
Osteoporosis	1	-50.969	30.67919	2.7601	0.0966	0
Other Fx	1	14.43621	1482	0.0001	0.9922	1860229
Panhypopituitarism	1	1.17679	22938	0	1	3.244
Pancreatic Disease	1	14.52086	2321	0	0.995	2024545
Poly Rheumatica	1	14.62233	6380	0	0.9982	2240775
Premature ovarian failure	1	13.81262	8582	0	0.9987	997109.3
Primary biliary cirrhosis	1	-0.71842	13092	0	1	0.488
Riley-Day	1	15.2713	19064	0	0.9994	4287849
Renault Disease	1	-0.24643	0.46724	0.2782	0.5979	0.782
RA	1	-1.26908	0.65794	3.7206	0.0537	0.281
Saccoidosis	1	13.47593	1300	0.0001	0.9917	712069.7
Sickle Cell Anemia	1	13.76344	7365	0	0.9985	949259.2
Lupus	1	-0.91683	1.04849	0.7646	0.3819	0.4
Spinal cord injury	1	12.05186	15211	0	0.9994	171418.1
Systemic mastocytosis	1	14.31059	24828	0	0.9995	1640624
Thalassemia	1	13.80997	5440	0	0.998	994472.4
Thyrotoxicosis	0	0
Vitamin A	1	14.75374	18181	0	0.9994	2555445
Vitamin D	1	-0.69882	0.43003	2.6408	0.1041	0.497
barb	1	16.05006	14618	0	0.9991	9342300
lithium	1	14.87818	3128	0	0.9962	2894081
thiaz	1	-0.24538	0.36434	0.4536	0.5006	0.782
arom	1	14.72058	2561	0	0.9954	2472099
convulsants	1	0.10049	0.28962	0.1204	0.7286	1.106
ssri	1	-0.36843	0.26735	1.8991	0.1682	0.692
ppi	1	-0.31592	0.22093	2.0449	0.1527	0.729
mtx	1	-0.72748	1.05793	0.4729	0.4917	0.483
csa	1	13.92998	4444	0	0.9975	1121280
coag	1	-0.74166	0.35329	4.4071	0.0358	0.476
white	1	-14.09551	8816	0	0.9987	0
black	1	-13.20542	8816	0	0.9988	0
other_race	1	-13.39167	8816	0	0.9988	0

asian	1	-13.52236	8816	0	0.9988	0
hispanic	1	-14.02925	8816	0	0.9987	0
amnative	1	-15.01976	8816	0	0.9986	0
Age	1	-395.61366	229.81153	2.9635	0.0852	0
Age*Age	1	5.90163	3.43732	2.9478	0.086	365.634
Age*Age*Age	1	-0.02934	0.01713	2.9329	0.0868	0.971
Age*Osteoporosis	1	-0.74453	0.47139	2.4946	0.1142	0.475

Table A10 Approach 1 Vertebral Fracture All Available, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.57988	0.19416	8.92	0.0028	1.786
Cystic Fibrosis	1	13.77302	8025	0	0.9986	958400
Congestive Heart Failure	1	0.322	0.28472	1.279	0.2581	1.38
Epilepsy	1	-0.69812	0.61049	1.3077	0.2528	0.498
Parkinson's Disease	1	-0.09159	1.01117	0.0082	0.9278	0.912
Stroke	1	-0.07097	0.27162	0.0683	0.7939	0.931
Adrenal insufficiency	1	14.92822	9625	0	0.9988	3042594
AIDS/HIV	1	12.70566	667.12417	0.0004	0.9848	329609.6
Alcoholism	1	-1.43645	0.73086	3.863	0.0494	0.238
Alzheimers	1	0.13917	0.46677	0.0889	0.7656	1.149
Anorexia	1	-1.02042	0.74143	1.8941	0.1687	0.36
Ankylosing spondylitis	1	-0.81662	0.7215	1.281	0.2577	0.442
COPD	1	-0.10356	0.20102	0.2654	0.6064	0.902
Athletic amenorrhea	1	14.47326	7238	0	0.9984	1930437
Cataracts	1	0.25683	0.26025	0.9739	0.3237	1.293
Celiac	1	14.38651	4446	0	0.9974	1770033
Central Adiposity	1	0.62553	0.23325	7.1919	0.0073	1.869
Chronic metabolic acidosis	1	14.23514	1582	0.0001	0.9928	1521395
Crohn's Disease	1	-0.17965	0.7159	0.063	0.8019	0.836
Cushing's	1	13.68044	4101	0	0.9973	873656.8
Depression	1	-0.07717	0.22851	0.114	0.7356	0.926
DM	1	-0.0794	0.15296	0.2695	0.6037	0.924
ESRD	1	-0.85634	0.3337	6.5856	0.0103	0.425
Disorders of the Eye	1	-0.11594	0.22718	0.2604	0.6098	0.891
Falling	1	-0.84601	0.37891	4.9852	0.0256	0.429

Gaucher's Disease	1	14.06614	2195	0	0.9949	1284832
Glaucoma	1	0.22657	0.28943	0.6128	0.4337	1.254
Gout	1	-0.49721	0.35197	1.9955	0.1578	0.608
Glycogen storage diseases	1	10.9326	8340	0	0.999	55971.39
Hemochromatosis	1	15.30407	8015	0	0.9985	4430697
Hemophilia	1	-0.51466	0.40061	1.6504	0.1989	0.598
Homocystinuria	1	13.99656	3891	0	0.9971	1198475
Hyperprolactinemia	1	14.83818	13802	0	0.9991	2780614
Hyperthyrois	1	0.19977	0.58813	0.1154	0.7341	1.221
Hypophosphatasia	1	-1.46908	1.05153	1.9518	0.1624	0.23
IBD	1	-0.90919	1.24288	0.5351	0.4645	0.403
Idopathic scoliosis	1	12.39725	503.65227	0.0006	0.9804	242135.4
Kyphosis	1	0.3845	0.33072	1.3517	0.245	1.469
Liver Disease	1	0.78111	0.58852	1.7615	0.1844	2.184
Malabsorption	1	-0.62731	1.06077	0.3497	0.5543	0.534
MS	1	14.40555	1815	0.0001	0.9937	1804066
Obseity	0	0
Osteoarthritis	1	-0.34313	0.16581	4.2827	0.0385	0.71
Osteoporosis	1	-37.28609	20.01037	3.472	0.0624	0
Other Fx	1	-0.18211	0.60613	0.0903	0.7638	0.834
Panhypopituitarism	1	14.1877	11522	0	0.999	1450913
Pancreatic Disease	1	0.06647	1.01667	0.0043	0.9479	1.069
Poly Rheumatica	1	14.69933	4116	0	0.9972	2420126
Premature ovarian failure	1	13.51051	4240	0	0.9975	737125.5
Primary biliary cirrhosis	1	12.5511	8368	0	0.9988	282407
Riley-Day	1	15.13239	19545	0	0.9994	3731773
Renauld Disease	1	-0.39547	0.27305	2.0977	0.1475	0.673
RA	1	0.16025	0.63281	0.0641	0.8001	1.174
Saccoidosis	1	13.09963	763.46147	0.0003	0.9863	488762.1
Sickle Cell Anemia	1	13.83732	4287	0	0.9974	1022052
Lupus	1	-1.45402	0.61379	5.6118	0.0178	0.234
Spinal cord injury	1	12.41521	6152	0	0.9984	246522.1
Systemic mastocytosis	1	14.02618	11791	0	0.9991	1234508
Thalassemia	1	13.74806	2686	0	0.9959	934771.6
Thyrotoxicosis	0	0
Vitamin A	1	14.46003	14906	0	0.9992	1905063
Vitamin D	1	-0.60147	0.30053	4.0054	0.0454	0.548
barb	1	15.72874	9151	0	0.9986	6774942
lithium	1	14.12055	1654	0.0001	0.9932	1356685
thiaz	1	-0.18957	0.22971	0.681	0.4092	0.827

arom	1	-0.34961	1.00738	0.1204	0.7286	0.705
convulsants	1	0.10552	0.19628	0.289	0.5909	1.111
ssri	1	-0.38524	0.18272	4.4452	0.035	0.68
ppi	1	-0.06393	0.1519	0.1771	0.6739	0.938
mtx	1	-0.89479	0.74592	1.439	0.2303	0.409
csa	1	13.02466	1690	0.0001	0.9939	453459.7
coag	1	-0.69275	0.23935	8.3766	0.0038	0.5
white	1	-13.62097	4990	0	0.9978	0
black	1	-12.95524	4990	0	0.9979	0
other_race	1	-13.38614	4990	0	0.9979	0
asian	1	-13.34897	4990	0	0.9979	0
hispanic	1	-13.74245	4990	0	0.9978	0
amnative	1	-14.34573	4990	0	0.9977	0
Age	1	-134.51749	109.77553	1.5016	0.2204	0
Age*Age	1	2.00064	1.63581	1.4958	0.2213	7.394
Age*Age*Age	1	-0.00992	0.00812	1.4912	0.222	0.99
Age*Osteoporosis	1	-0.55782	0.30592	3.3248	0.0682	0.572

Table A11 Approach 1 Vertebral Fracture 365 days, CFRI With BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	-0.17052	1.03674	0.0271	0.8694	0.843
Congestive Heart Failure	1	16.20557	2234	0.0001	0.9942	10914130
Epilepsy	1	15.20043	3346	0	0.9964	3994498
Parkinson's Disease	1	16.65143	9809	0	0.9986	17046073
Stroke	1	-0.24846	1.27293	0.0381	0.8452	0.78
AIDS/HIV	1	15.88307	4784	0	0.9974	7905482
Alcoholism	1	20.7782	8194	0	0.998	1.06E+09
Alzheimers	1	-2.29952	1.11288	4.2695	0.0388	0.1
Anorexia	1	4.21676	40887	0	0.9999	67.813
Ankylosing spondylitis	1	14.98169	13659	0	0.9991	3209697
COPD	1	-1.2873	0.68288	3.5536	0.0594	0.276
Cataracts	1	0.04853	3545	0	1	1.05
Celiac	1	-30.28138	93028	0	0.9997	0
Central Adiposity	1	16.16266	2705	0	0.9952	10455676
Chronic metabolic acidosis	1	-1.2787	49097	0	1	0.278
Crohn's Disease	1	16.27383	10813	0	0.9988	11685190

Depression	1	-0.73551	1.05581	0.4853	0.486	0.479
DM	1	-0.00619	0.58524	0.0001	0.9916	0.994
ESRD	1	0.57447	1.29428	0.197	0.6571	1.776
Disorders of the Eye	1	17.63102	2880	0	0.9951	45399941
Falling	1	15.64558	5044	0	0.9975	6234310
Gaucher's Disease	1	15.5225	39462	0	0.9997	5512357
Glaucoma	1	-1.09212	4517	0	0.9998	0.336
Gout	1	15.1723	5162	0	0.9977	3883719
Hemochromatosis	1	-15.75932	90002	0	0.9999	0
Hemophilia	1	-3.21122	1.10077	8.5103	0.0035	0.04
Hyperthyrois	1	-2.73334	1.10651	6.102	0.0135	0.065
Hypophosphatasia	1	-5.42681	1.15052	22.2487	<.0001	0.004
IBD	1	1.05406	32005	0	1	2.869
Idopathic scoliosis	1	-2.19341	7096	0	0.9998	0.112
Kyphosis	1	15.8881	3880	0	0.9967	7945368
Liver Disease	1	15.42408	4388	0	0.9972	4995679
Malabsorption	1	0.14435	33734	0	1	1.155
MS	1	16.41043	11017	0	0.9988	13395520
Obseity	0	0
Osteoarthritis	1	-0.28861	0.79977	0.1302	0.7182	0.749
Other Fx	1	14.07632	5156	0	0.9978	1297977
Pancreatic Disease	1	16.31273	11686	0	0.9989	12148671
Poly Rheumatica	1	17.33398	42340	0	0.9997	33732592
Riley-Day	1	-12.25841	46491	0	0.9998	0
Renauld Disease	1	-1.50847	1.01222	2.2209	0.1362	0.221
RA	1	-2.48256	0.89345	7.7207	0.0055	0.084
Saccoidosis	1	14.31583	6899	0	0.9983	1649252
Sickle Cell Anemia	1	15.66724	24203	0	0.9995	6370846
Lupus	1	16.00335	6950	0	0.9982	8915919
Spinal cord injury	0	0
Thalassemia	1	0.86751	78764	0	1	2.381
Thyrotoxicosis	0	0
Vitamin D	1	15.57106	3964	0	0.9969	5786625
lithium	1	17.33315	10261	0	0.9987	33704894
thiaz	1	-1.38213	0.79955	2.9882	0.0839	0.251
arom	1	16.23052	14476	0	0.9991	11189916
convulsants	1	0.43168	0.7858	0.3018	0.5828	1.54
ssri	1	0.1987	0.78806	0.0636	0.8009	1.22
ppi	1	-0.79525	0.51951	2.3432	0.1258	0.451
mtx	1	-1.47218	1.22569	1.4427	0.2297	0.229
csa	1	15.83201	30953	0	0.9996	7511998

coag	1	-1.32302	0.6802	3.7832	0.0518	0.266
Age	1	0.1539	0.48779	0.0995	0.7524	1.166
Age*Age	0	0
Age*Age*Age	0	0
Age*Osteoporosis	0	0

Table A12 Approach 1 Vert All Available, CFRI With BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	-0.55119	0.73395	0.564	0.4527	0.576
Congestive Heart Failure	1	16.16851	2146	0.0001	0.994	10517120
Epilepsy	1	16.2782	4258	0	0.9969	11736350
Parkinson's Disease	1	15.94851	8710	0	0.9985	8440174
Stroke	1	1.31702	1.51536	0.7554	0.3848	3.732
AIDS/HIV	1	16.35833	4326	0	0.997	12715427
Alcoholism	1	-1.12005	1.64462	0.4638	0.4958	0.326
Alzheimers	1	-2.27915	0.7693	8.7773	0.0031	0.102
Anorexia	1	1.28527	23387	0	1	3.616
Ankylosing spondylitis	1	15.88333	10121	0	0.9987	7907541
COPD	1	-0.63061	0.58868	1.1475	0.2841	0.532
Cataracts	1	1.03069	3375	0	0.9998	2.803
Celiac	1	-14.70279	48884	0	0.9998	0
Central Adiposity	1	0.55479	1.04148	0.2838	0.5942	1.742
Chronic metabolic acidosis	1	-0.22353	28521	0	1	0.8
Crohn's Disease	1	15.43021	8808	0	0.9986	5026357
Depression	1	0.76406	1.11365	0.4707	0.4927	2.147
DM	1	-0.38731	0.38136	1.0314	0.3098	0.679
ESRD	1	-0.854	0.62441	1.8705	0.1714	0.426
Disorders of the Eye	1	16.87932	3024	0	0.9955	21408896
Falling	1	-1.4954	1.14131	1.7168	0.1901	0.224
Gaucher's Disease	1	15.26351	19951	0	0.9994	4254609
Glaucoma	1	-0.14981	3852	0	1	0.861
Gout	1	16.30049	3476	0	0.9963	12000870
Hemochromatosis	1	-17.92489	78568	0	0.9998	0
Hemophilia	1	-1.32241	1.4252	0.861	0.3535	0.266
Hyperthyrois	1	-1.85091	1.04589	3.1318	0.0768	0.157
Hypophosphatasia	1	-4.40281	1.02593	18.4171	<.0001	0.012

IBD	1	2.40582	21012	0	0.9999	11.088
Idopathic scoliosis	1	-2.46875	5363	0	0.9996	0.085
Kyphosis	1	16.1634	3239	0	0.996	10463471
Liver Disease	1	16.00158	4116	0	0.9969	8900179
Malabsorption	1	-0.49843	20136	0	1	0.607
MS	1	16.05675	12682	0	0.999	9404968
Obesity	0	0
Osteoarthritis	1	-0.19586	0.56908	0.1185	0.7307	0.822
Other Fx	1	15.51281	6492	0	0.9981	5459179
Pancreatic Disease	1	16.30309	9396	0	0.9986	12032090
Poly Rheumatica	1	16.86626	22913	0	0.9994	21131278
Riley-Day	1	-13.96877	44995	0	0.9998	0
Renault Disease	1	-0.48476	0.7533	0.4141	0.5199	0.616
RA	1	-0.74841	0.97584	0.5882	0.4431	0.473
Sarcoidosis	1	14.8353	4645	0	0.9975	2772621
Sickle Cell Anemia	1	16.15505	17148	0	0.9992	10376405
Lupus	1	-1.98142	1.06697	3.4487	0.0633	0.138
Spinal cord injury	0	0
Thalassemia	1	0.54758	40211	0	1	1.729
Thyrotoxicosis	0	0
Vitamin D	1	15.99408	3648	0	0.9965	8833669
lithium	1	16.6642	10373	0	0.9987	17265185
thiaz	1	-0.1615	0.76087	0.0451	0.8319	0.851
arom	1	-2.31785	1.03968	4.9702	0.0258	0.098
convulsants	1	0.42034	0.54561	0.5935	0.4411	1.522
ssri	1	0.19961	0.61934	0.1039	0.7472	1.221
ppi	1	0.03313	0.407	0.0066	0.9351	1.034
mtx	1	-1.21201	1.16639	1.0797	0.2988	0.298
csa	1	16.6874	17050	0	0.9992	17670335
coag	1	-0.68439	0.56845	1.4495	0.2286	0.504
Age	1	-0.08383	0.338	0.0615	0.8041	0.92
Age*Age	0	0
Age*Age*Age	0	0
Age*Osteoporosis	0	0

Table A13 Approach 2 MOF 365 days, no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.36858	0.05452	45.6999	<.0001	1.446
Cystic Fibrosis	1	-0.73017	1.0011	0.532	0.4658	0.482
Congestive Heart Failure	1	-0.11012	0.06887	2.5567	0.1098	0.896
Ehlers-Danlos	1	10.99121	1910	0	0.9954	59350
Epilepsy	1	-0.04321	0.18858	0.0525	0.8188	0.958
Osteogenesis Imperfecta	1	11.60901	670.10401	0.0003	0.9862	110085.3
Parkinson's Disease	1	-0.13996	0.17909	0.6108	0.4345	0.869
Stroke	1	-0.01486	0.0674	0.0486	0.8255	0.985
Adrenal insufficiency	1	-1.05216	0.71064	2.1921	0.1387	0.349
AIDS/HIV	1	-0.58311	0.70919	0.6761	0.4109	0.558
Alcoholism	1	-0.45331	0.32007	2.0059	0.1567	0.636
Alzheimers	1	-0.16758	0.07566	4.9061	0.0268	0.846
Amyloidosis	1	11.43135	445.87077	0.0007	0.9795	92165.97
Androgen insensitivity	1	11.03792	1972	0	0.9955	62188.06
Anorexia	1	-0.34179	0.16561	4.2592	0.039	0.711
Ankylosing spondylitis	1	-0.50236	0.17268	8.4638	0.0036	0.605
COPD	1	-0.22254	0.05712	15.1774	<.0001	0.8
Athletic amenorrhea	1	11.58101	279.92818	0.0017	0.967	107045.2
Cataracts	1	0.01072	0.0659	0.0265	0.8707	1.011
Celiac	1	-0.23374	0.76528	0.0933	0.76	0.792
Central Adiposity	1	0.18675	0.09882	3.5711	0.0588	1.205
Chronic metabolic acidosis	1	0.13537	0.20802	0.4235	0.5152	1.145
Crohn's Disease	1	0.06131	0.12871	0.2269	0.6339	1.063
Cushing's	1	-1.22122	0.50434	5.8632	0.0155	0.295
Depression	1	0.04555	0.07248	0.3948	0.5298	1.047
DM	1	-0.07089	0.05407	1.7188	0.1899	0.932
ESRD	1	-0.59384	0.17573	11.4197	0.0007	0.552
Disorders of the Eye	1	0.08188	0.06753	1.47	0.2253	1.085
Falling	1	-0.37963	0.09074	17.5036	<.0001	0.684
Gaucher's Disease	1	-0.1596	0.50153	0.1013	0.7503	0.852
Glaucoma	1	0.09046	0.07648	1.3989	0.2369	1.095
Gout	1	0.19117	0.13702	1.9464	0.163	1.211
Glycogen storage diseases	1	11.45826	595.26769	0.0004	0.9846	94680.48
Hemochromatosis	1	11.38766	593.94541	0.0004	0.9847	88226.28
Hemophilia	1	-0.2411	0.13924	2.998	0.0834	0.786
Homocystinuria	1	-0.61417	0.41388	2.2021	0.1378	0.541
Hyperprolactinemia	1	-0.79095	1.01667	0.6053	0.4366	0.453
Hyperparathyroidism	1	0.03077	0.20938	0.0216	0.8832	1.031

Hyperthyrois	1	0.03282	0.15527	0.0447	0.8326	1.033
Hypophosphatasia	1	-0.05217	0.29201	0.0319	0.8582	0.949
IBD	1	-0.01308	0.30493	0.0018	0.9658	0.987
Idopathic scoliosis	1	-0.2845	0.14032	4.1105	0.0426	0.752
Idiopathic hypercalciuria	1	11.72908	1673	0	0.9944	124129.7
Kyphosis	1	0.12881	0.07493	2.9553	0.0856	1.137
Liver Disease	1	0.06364	0.12076	0.2777	0.5982	1.066
Malabsorption	1	0.22376	0.5021	0.1986	0.6559	1.251
Marfan syndrome	1	11.74442	1475	0.0001	0.9936	126047.8
MS	1	-0.21493	0.38111	0.318	0.5728	0.807
Muscular dystrophy	1	11.70761	382.74851	0.0009	0.9756	121492.2
Obseity	0	0
Osteoarthritis	1	-0.03661	0.05336	0.4706	0.4927	0.964
Osteoporosis	1	-0.79851	0.55557	2.0658	0.1506	0.45
Other Fx	1	-0.09201	0.10358	0.7892	0.3744	0.912
Panhypopituitarism	1	11.48238	743.72735	0.0002	0.9877	96991.2
Pancreatic Disease	1	-0.21986	0.18699	1.3824	0.2397	0.803
Poly Rheumatica	1	0.14623	0.22221	0.4331	0.5105	1.157
Porphyria	1	11.48693	662.38782	0.0003	0.9862	97434.16
Premature ovarian failure	1	11.46338	225.91756	0.0026	0.9595	95166.27
Primary biliary cirrhosis	1	-1.55742	0.59054	6.9553	0.0084	0.211
Riley-Day	1	12.44159	1262	0.0001	0.9921	253113.3
Renauld Disease	1	-0.23464	0.08732	7.2209	0.0072	0.791
RA	1	0.00494	0.12729	0.0015	0.969	1.005
Saccoidosis	1	-0.23609	0.50187	0.2213	0.6381	0.79
Sickle Cell Anemia	1	11.07343	597.89352	0.0003	0.9852	64436.39
Lupus	1	-0.76273	0.23501	10.5332	0.0012	0.466
Spinal cord injury	1	-0.8781	0.41263	4.5286	0.0333	0.416
Systemic mastocytosis	1	11.32435	662.88186	0.0003	0.9864	82814.2
Turner's & Klinefelter's syndromes	1	12.03053	1361	0.0001	0.9929	167801.1
Thalassemia	1	0.12751	1.0017	0.0162	0.8987	1.136
Thyrotoxicosis	0	0
Vitamin A	1	11.3577	866.57779	0.0002	0.9895	85622.01
Vitamin D	1	0.0426	0.09467	0.2025	0.6527	1.044
barb	1	-2.11873	0.71907	8.6819	0.0032	0.12
lithium	1	0.21051	0.7099	0.0879	0.7668	1.234
thiaz	1	-0.13955	0.09517	2.1498	0.1426	0.87
gnrh	1	11.7211	1583	0.0001	0.9941	123143.3
arom	1	-0.25813	0.1714	2.268	0.1321	0.772
convulsants	1	-0.2672	0.06875	15.1041	0.0001	0.766

ssri	1	-0.26154	0.06369	16.8656	<.0001	0.77
ppi	1	-0.25684	0.05394	22.6767	<.0001	0.773
mtx	1	-0.60638	0.19906	9.2796	0.0023	0.545
csa	1	11.46811	206.24759	0.0031	0.9557	95616.95
coag	1	-0.19316	0.07641	6.3897	0.0115	0.824
white	1	-1.28427	1.00084	1.6466	0.1994	0.277
black	1	-0.47536	1.00546	0.2235	0.6364	0.622
other_race	1	-1.14693	1.01964	1.2653	0.2607	0.318
asian	1	-1.07859	1.01059	1.1391	0.2858	0.34
hispanic	1	-1.15994	1.00683	1.3273	0.2493	0.314
amnative	1	-0.84505	1.08088	0.6112	0.4343	0.43
Age	1	-2.8391	0.71308	15.8519	<.0001	0.058
Age*Age	1	0.03576	0.00904	15.6445	<.0001	1.036
Age*Age*Age	1	-0.0001463	0.000038	14.846	0.0001	1
Age*Osteoporosis	1	-0.00789	0.00705	1.2519	0.2632	0.992

Table A14 Approach 2 MOF All Available, no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.35524	0.03118	129.7853	<.0001	1.427
Cystic Fibrosis	1	0.35528	1.0004	0.1261	0.7225	1.427
Congestive Heart Failure	1	-0.08714	0.04161	4.3861	0.0362	0.917
Ehlers-Danlos	1	8.70506	368.92716	0.0006	0.9812	6033.377
Epilepsy	1	0.0465	0.12567	0.1369	0.7114	1.048
Osteogenesis Imperfecta	1	9.20262	174.08619	0.0028	0.9578	9923.048
Parkinson's Disease	1	-0.24674	0.10762	5.2559	0.0219	0.781
Stroke	1	-0.02343	0.03969	0.3485	0.555	0.977
Adrenal insufficiency	1	-0.65177	0.44942	2.1032	0.147	0.521
AIDS/HIV	1	0.57141	0.70962	0.6484	0.4207	1.771
Alcoholism	1	-0.36787	0.20236	3.3048	0.0691	0.692
Alzheimers	1	-0.05559	0.04775	1.3555	0.2443	0.946
Amyloidosis	1	0.02465	1.00093	0.0006	0.9804	1.025
Androgen insensitivity	1	8.7391	310.61133	0.0008	0.9776	6242.291
Anorexia	1	-0.15569	0.11657	1.7838	0.1817	0.856
Ankylosing spondylitis	1	-0.26661	0.10803	6.0912	0.0136	0.766
COPD	1	-0.27332	0.03315	67.9864	<.0001	0.761
Athletic amenorrhea	1	0.45844	0.57828	0.6285	0.4279	1.582
Cataracts	1	-0.01404	0.03731	0.1417	0.7066	0.986
Celiac	1	0.10813	0.36652	0.087	0.768	1.114

Central Adiposity	1	0.24223	0.06131	15.6077	<.0001	1.274
Chronic metabolic acidosis	1	0.14796	0.14299	1.0706	0.3008	1.159
Crohn's Disease	1	-0.00527	0.07414	0.005	0.9434	0.995
Cushing's	1	-0.83998	0.35579	5.5738	0.0182	0.432
Depression	1	-0.05473	0.04307	1.6144	0.2039	0.947
DM	1	-0.04402	0.03129	1.9791	0.1595	0.957
ESRD	1	-0.59862	0.12118	24.4023	<.0001	0.55
Disorders of the Eye	1	0.05434	0.03929	1.913	0.1666	1.056
Falling	1	-0.32267	0.05588	33.3422	<.0001	0.724
Gaucher's Disease	1	0.92459	0.44778	4.2635	0.0389	2.521
Glaucoma	1	-0.00986	0.04178	0.0557	0.8135	0.99
Gout	1	-0.00504	0.07609	0.0044	0.9472	0.995
Glycogen storage diseases	1	-1.40616	0.71047	3.9172	0.0478	0.245
Hemochromatosis	1	9.09928	123.72466	0.0054	0.9414	8948.861
Hemophilia	1	-0.08271	0.0905	0.8353	0.3608	0.921
Homocystinuria	1	0.25871	0.35483	0.5316	0.4659	1.295
Hyperprolactinemia	1	-0.89801	0.71393	1.5822	0.2085	0.407
Hyperparathyroidism	1	0.111	0.12485	0.7904	0.374	1.117
Hyperthyroid	1	0.01572	0.08873	0.0314	0.8593	1.016
Hypophosphatasia	1	-0.1633	0.1907	0.7333	0.3918	0.849
IBD	1	-0.00812	0.17598	0.0021	0.9632	0.992
Idopathic scoliosis	1	-0.27078	0.08064	11.2751	0.0008	0.763
Idiopathic hypercalciuria	1	9.6526	251.6257	0.0015	0.9694	15562.25
Kyphosis	1	0.12698	0.04258	8.8944	0.0029	1.135
Liver Disease	1	-0.00786	0.06941	0.0128	0.9098	0.992
Malabsorption	1	-0.25668	0.22553	1.2954	0.2551	0.774
Marfan syndrome	1	9.97842	301.28879	0.0011	0.9736	21556.33
MS	1	0.00599	0.26001	0.0005	0.9816	1.006
Muscular dystrophy	1	9.77599	96.24069	0.0103	0.9191	17605.96
Obesity	0	0
Osteoarthritis	1	-0.02031	0.03073	0.4368	0.5087	0.98
Osteoporosis	1	-0.58701	0.32817	3.1996	0.0737	0.556
Other Fx	1	-0.28766	0.05709	25.3853	<.0001	0.75
Panhypopituitarism	1	-0.57668	1.00252	0.3309	0.5651	0.562
Pancreatic Disease	1	-0.08663	0.12105	0.5122	0.4742	0.917
Poly Rheumatica	1	-0.14121	0.10951	1.6626	0.1972	0.868
Porphyria	1	-0.55807	1.00319	0.3095	0.578	0.572
Premature ovarian failure	1	0.42263	0.50062	0.7127	0.3985	1.526
Primary biliary cirrhosis	1	-1.05	0.45332	5.3651	0.0205	0.35
Riley-Day	1	10.59561	493.44141	0.0005	0.9829	39959.15
Renault Disease	1	-0.15927	0.05536	8.2784	0.004	0.853

RA	1	-0.08967	0.07142	1.5765	0.2093	0.914
Saccoidosis	1	0.0007375	0.31748	0	0.9981	1.001
Sickle Cell Anemia	1	8.74962	113.28504	0.006	0.9384	6308.265
Lupus	1	-0.32269	0.16733	3.719	0.0538	0.724
Spinal cord injury	1	-0.66122	0.2696	6.0152	0.0142	0.516
Systemic mastocytosis	1	8.98237	121.23387	0.0055	0.9409	7961.44
Turner's & Klinefelter's syndromes	1	10.10154	311.43824	0.0011	0.9741	24380.54
Thalassemia	1	-1.0865	0.33526	10.5022	0.0012	0.337
Thyrotoxicosis	0	0
Vitamin A	1	-1.33217	1.00365	1.7618	0.1844	0.264
Vitamin D	1	0.00579	0.05915	0.0096	0.922	1.006
barb	1	-1.90778	0.58203	10.7438	0.001	0.148
lithium	1	-0.1087	0.35569	0.0934	0.7599	0.897
thiaz	1	-0.15881	0.05574	8.118	0.0044	0.853
gnrh	1	9.86582	246.05715	0.0016	0.968	19260.67
arom	1	-0.15032	0.10045	2.2394	0.1345	0.86
convulsants	1	-0.24199	0.04129	34.3411	<.0001	0.785
ssri	1	-0.20236	0.03811	28.1931	<.0001	0.817
ppi	1	-0.09271	0.03217	8.3053	0.004	0.911
mtx	1	-0.36606	0.11944	9.393	0.0022	0.693
csa	1	0.78561	0.57823	1.8459	0.1743	2.194
coag	1	-0.20879	0.04453	21.9822	<.0001	0.812
white	1	-0.92521	0.50057	3.4163	0.0646	0.396
black	1	-0.05625	0.50412	0.0124	0.9112	0.945
other_race	1	-0.45408	0.51737	0.7703	0.3801	0.635
asian	1	-0.5883	0.50751	1.3437	0.2464	0.555
hispanic	1	-0.68	0.50525	1.8113	0.1783	0.507
amnative	1	-0.79001	0.54073	2.1345	0.144	0.454
Age	1	-3.64426	0.47551	58.736	<.0001	0.026
Age*Age	1	0.04666	0.00607	59.1568	<.0001	1.048
Age*Age*Age	1	-0.0001949	0.0000257	57.687	<.0001	1
Age*Osteoporosis	1	-0.00545	0.00417	1.7065	0.1914	0.995

Table A15 Approach 2 MOF 365 days, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	-0.28368	0.46857	0.3665	0.5449	0.753
Cystic Fibrosis	1	16.12064	412857	0	1	10025433
Congestive Heart Failure	1	-1.60372	0.59356	7.3001	0.0069	0.201
Epilepsy	1	16.91242	7150	0	0.9981	22129501
Parkinson's Disease	1	16.42408	12688	0	0.999	13579549
Stroke	1	0.71451	1.05987	0.4545	0.5002	2.043
AIDS/HIV	1	17.33938	11938	0	0.9988	33915559
Alcoholism	1	15.67864	13345	0	0.9991	6443870
Alzheimers	1	14.27532	2143	0	0.9947	1583770
Anorexia	1	15.9626	16821	0	0.9992	8559916
Ankylosing spondylitis	1	16.52575	9533	0	0.9986	15032879
COPD	1	0.93074	0.78797	1.3952	0.2375	2.536
Cataracts	1	0.1135	0.7571	0.0225	0.8808	1.12
Central Adiposity	1	1.12081	0.79139	2.0058	0.1567	3.067
Chronic metabolic acidosis	1	16.02547	28929	0	0.9996	9115367
Crohn's Disease	1	15.76529	15939	0	0.9992	7027105
Depression	1	0.74972	0.79546	0.8883	0.3459	2.116
DM	1	-0.18855	0.47807	0.1556	0.6933	0.828
ESRD	1	-0.21237	1.31065	0.0263	0.8713	0.809
Disorders of the Eye	1	0.29768	0.67413	0.195	0.6588	1.347
Falling	1	-1.69707	1.08592	2.4423	0.1181	0.183
Gaucher's Disease	1	16.03658	13012	0	0.999	9217152
Glaucoma	1	0.11751	0.8539	0.0189	0.8905	1.125
Gout	1	-1.18307	1.07777	1.2049	0.2723	0.306
Hemophilia	1	-1.76349	0.90087	3.832	0.0503	0.171
Homocystinuria	1	16.52705	18487	0	0.9993	15052487
Hyperprolactinemia	1	16.03455	31683	0	0.9996	9198491
Hyperthyrois	1	-0.67518	1.04257	0.4194	0.5172	0.509
Hypophosphatasia	1	15.07996	14331	0	0.9992	3541160
IBD	1	0.37235	31302	0	1	1.451
Idopathic scoliosis	1	16.6427	6597	0	0.998	16897928
Kyphosis	1	1.02858	1.05763	0.9458	0.3308	2.797
Liver Disease	1	14.64156	1325	0.0001	0.9912	2284266
Malabsorption	1	15.53505	38961	0	0.9997	5581942
MS	1	-2.12777	1.39964	2.3111	0.1285	0.119
Obseity	0	0

Osteoarthritis	1	-0.30568	0.49084	0.3878	0.5334	0.737
Osteoporosis	1	-89.75277	57.35969	2.4484	0.1176	0
Other Fx	1	12.05379	1225	0.0001	0.9922	171748.5
Panhypopituitarism	1	16.84994	52848	0	0.9997	20789192
Pancreatic Disease	1	15.87426	17830	0	0.9993	7836149
Premature ovarian failure	1	16.4424	18204	0	0.9993	13830737
Renauld Disease	1	0.11501	0.93248	0.0152	0.9018	1.122
RA	1	16.72904	5746	0	0.9977	18421739
Saccoidosis	1	15.81459	17674	0	0.9993	7382290
Lupus	1	15.84586	5471	0	0.9977	7616777
Thalassemia	1	17.12619	30811	0	0.9996	27403615
Thyrotoxicosis	0	0
Vitamin D	1	-0.44756	0.75754	0.3491	0.5546	0.639
lithium	1	16.84089	12567	0	0.9989	20601726
thiaz	1	-0.46093	0.64346	0.5131	0.4738	0.631
arom	1	16.91942	39375	0	0.9997	22284984
convulsants	1	-0.64841	0.52749	1.511	0.219	0.523
ssri	1	-0.29111	0.58302	0.2493	0.6176	0.747
ppi	1	-0.48027	0.45395	1.1193	0.2901	0.619
mtx	1	15.54662	11071	0	0.9989	5646898
csa	1	16.27488	27897	0	0.9995	11697467
coag	1	0.77276	1.10446	0.4895	0.4841	2.166
white	1	-17.57485	21770	0	0.9994	0
black	1	-17.04869	21770	0	0.9994	0
other_race	1	-18.40695	21770	0	0.9993	0
asian	1	-17.06322	21770	0	0.9994	0
hispanic	1	-18.81	21770	0	0.9993	0
amnative	1	-19.95987	21770	0	0.9993	0
Age	1	-900.82493	803.44941	1.2571	0.2622	0
Age*Age	1	13.57082	12.09682	1.2585	0.2619	782943.2
Age*Age*Age	1	-0.06813	0.06069	1.2602	0.2616	0.934
Age*Osteoporosis	1	-1.35438	0.88521	2.3409	0.126	0.258

Table A16 Approach 2 MOF All Available, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.32303	0.27804	1.3498	0.2453	1.381
Cystic Fibrosis	1	13.74046	147206	0	0.9999	927693.5
Congestive Heart Failure	1	-0.63038	0.48205	1.7101	0.191	0.532
Epilepsy	1	-1.54791	1.15964	1.7818	0.1819	0.213
Parkinson's Disease	1	15.50091	1762	0.0001	0.993	5394603
Stroke	1	0.3265	0.57205	0.3258	0.5682	1.386
AIDS/HIV	1	14.08168	2636	0	0.9957	1304956
Alcoholism	1	14.00927	3377	0	0.9967	1213806
Alzheimers	1	0.03536	1.04572	0.0011	0.973	1.036
Anorexia	1	14.40483	5261	0	0.9978	1802766
Ankylosing spondylitis	1	13.80979	2950	0	0.9963	994295.2
COPD	1	-0.14988	0.3892	0.1483	0.7002	0.861
Cataracts	1	-0.54796	0.5298	1.0697	0.301	0.578
Central Adiposity	1	1.54823	0.57881	7.155	0.0075	4.703
Chronic metabolic acidosis	1	14.98971	6404	0	0.9981	3235561
Crohn's Disease	1	14.34443	3191	0	0.9964	1697103
Depression	1	-0.00596	0.41864	0.0002	0.9886	0.994
DM	1	-0.10394	0.32167	0.1044	0.7466	0.901
ESRD	1	0.31514	1.14959	0.0752	0.784	1.37
Disorders of the Eye	1	0.72026	0.51737	1.9381	0.1639	2.055
Falling	1	-1.40288	0.76433	3.3688	0.0664	0.246
Gaucher's Disease	1	14.56715	5841	0	0.998	2120481
Glaucoma	1	-0.09522	0.55587	0.0293	0.864	0.909
Gout	1	-1.85853	0.64405	8.3272	0.0039	0.156
Hemophilia	1	-1.9291	0.80154	5.7924	0.0161	0.145
Homocystinuria	1	15.21075	5334	0	0.9977	4035941
Hyperprolactinemia	1	14.99699	13808	0	0.9991	3259204
Hyperthyrois	1	-0.5923	0.73684	0.6462	0.4215	0.553
Hypophosphatasia	1	13.01116	4850	0	0.9979	447379.3
IBD	1	-0.5539	6634	0	0.9999	0.575
Idopathic scoliosis	1	-0.84768	1.43322	0.3498	0.5542	0.428
Kyphosis	1	1.26055	0.74909	2.8317	0.0924	3.527
Liver Disease	1	14.51888	947.20809	0.0002	0.9878	2020545
Malabsorption	1	12.91515	6697	0	0.9985	406424
MS	1	-0.29133	1.23919	0.0553	0.8141	0.747
Obseity	0	0

Osteoarthritis	1	-0.25734	0.33174	0.6018	0.4379	0.773
Osteoporosis	1	-56.37792	28.447	3.9278	0.0475	0
Other Fx	1	13.78157	1983	0	0.9945	966633.2
Panhypopituitarism	1	15.03757	14879	0	0.9992	3394167
Pancreatic Disease	1	14.02736	4508	0	0.9975	1235962
Premature ovarian failure	1	14.69674	4076	0	0.9971	2413860
Renauld Disease	1	-0.07913	0.60326	0.0172	0.8956	0.924
RA	1	14.67354	1087	0.0002	0.9892	2358507
Saccoidosis	1	13.69693	3444	0	0.9968	888176.1
Lupus	1	-1.20133	1.15125	1.0889	0.2967	0.301
Thalassemia	1	15.22605	9623	0	0.9987	4098161
Thyrotoxicosis	0	0
Vitamin D	1	0.28931	0.73043	0.1569	0.692	1.336
lithium	1	15.33033	4406	0	0.9972	4548590
thiaz	1	-0.2983	0.4482	0.4429	0.5057	0.742
arom	1	-3.33219	1.08761	9.3867	0.0022	0.036
convulsants	1	-0.74182	0.33738	4.8345	0.0279	0.476
ssri	1	-0.35919	0.37342	0.9252	0.3361	0.698
ppi	1	0.06593	0.34	0.0376	0.8463	1.068
mtx	1	-1.37102	1.11302	1.5173	0.218	0.254
csa	1	14.76422	5510	0	0.9979	2582382
coag	1	2.49805	1.13918	4.8086	0.0283	12.159
white	1	-15.53144	7884	0	0.9984	0
black	1	-14.38395	7884	0	0.9985	0
other_race	1	-15.14385	7884	0	0.9985	0
asian	1	-14.32086	7884	0	0.9986	0
hispanic	1	-15.66853	7884	0	0.9984	0
amnative	1	-16.97756	7884	0	0.9983	0
Age	1	-423.55269	419.21729	1.0208	0.3123	0
Age*Age	1	6.39307	6.29242	1.0322	0.3096	597.69
Age*Age*Age	1	-0.03216	0.03147	1.0444	0.3068	0.968
Age*Osteoporosis	1	-0.83541	0.43528	3.6835	0.055	0.434

Table A17 Approach 2 MOF 365 days, CFRI With BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	-18.80791	8021	0	0.9981	0
Congestive Heart Failure	1	13.10758	5565	0	0.9981	492662
Epilepsy	1	0.53908	457476	0	1	1.714
Parkinson's Disease	1	18.52079	47805	0	0.9997	1.11E+08
Stroke	1	20.5641	120081	0	0.9999	8.53E+08
AIDS/HIV	1	20.97013	668206	0	1	1.28E+09
Alcoholism	1	-32.03022	15400647	0	1	0
Alzheimers	1	21.86311	620417	0	1	3.13E+09
Anorexia	1	4.15658	8340429	0	1	63.853
Ankylosing spondylitis	1	-14.57984	14931778	0	1	0
COPD	1	14.95477	7522	0	0.9984	3124445
Cataracts	1	-0.12984	2.00626	0.0042	0.9484	0.878
Central Adiposity	1	22.09024	50065	0	0.9996	3.92E+09
Chronic metabolic acidosis	1	-5.42191	18966444	0	1	0.004
Crohn's Disease	1	-0.83807	3477073	0	1	0.433
Depression	1	22.76158	77339	0	0.9998	7.68E+09
DM	1	0.31862	1.47767	0.0465	0.8293	1.375
ESRD	1	21.31495	216797	0	0.9999	1.81E+09
Disorders of the Eye	1	-2.10283	1.60487	1.7168	0.1901	0.122
Falling	1	3.51056	712887	0	1	33.467
Gaucher's Disease	1	1.76246	23902434	0	1	5.827
Glaucoma	1	-0.59487	1.75183	0.1153	0.7342	0.552
Gout	1	18.7954	347157	0	1	1.45E+08
Hemophilia	1	4.26968	1789414	0	1	71.499
Hyperthyrois	1	2.2108	1834972	0	1	9.123
Hypophosphatasia	1	-12.88784	5230623	0	1	0
Idopathic scoliosis	1	-112.56166	323644682	0	1	0
Kyphosis	1	21.00894	73168	0	0.9998	1.33E+09
Liver Disease	1	2.41283	674246	0	1	11.166
Malabsorption	1	-14.19792	4009633	0	1	0
MS	1	-47.83553	58819289	0	1	0
Obesity	0	0
Osteoarthritis	1	21.35183	43810	0	0.9996	1.87E+09
Other Fx	1	22.86861	694132	0	1	8.55E+09
Pancreatic Disease	1	-13.16066	13723930	0	1	0
Renauld Disease	1	22.00549	69866	0	0.9997	3.60E+09

RA	1	2.18327	261487	0	1	8.875
Saccoidosis	1	1.61984	1267216	0	1	5.052
Lupus	1	20.1815	592006	0	1	5.82E+08
Thyrototoxicosis	0	0
Vitamin D	1	17.33169	22571	0	0.9994	33655627
lithium	1	-31.58284	18107120	0	1	0
thiaz	1	-1.46474	1.50155	0.9516	0.3293	0.231
arom	1	6.41079	1941730	0	1	608.372
convulsants	1	-2.58918	1.61945	2.5562	0.1099	0.075
ssri	1	19.74867	51955	0	0.9997	3.77E+08
ppi	1	-0.12358	1.38725	0.0079	0.929	0.884
mtx	1	22.2083	758071	0	1	4.42E+09
coag	1	18.65417	22419	0	0.9993	1.26E+08
Age	1	1.58787	1.50278	1.1165	0.2907	4.893
Age*Age	0	0
Age*Age*Age	0	0
Age*Osteoporosis	0	0

Table A18 Approach 2 MOF All Available, CFRI With BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	-0.34216	1.19022	0.0826	0.7737	0.71
Congestive Heart Failure	1	17.82317	8215	0	0.9983	55017836
Epilepsy	1	17.81151	39323	0	0.9996	54379934
Parkinson's Disease	1	18.32201	36146	0	0.9996	90603832
Stroke	1	14.24532	5626	0	0.998	1536964
AIDS/HIV	1	17.83429	69111	0	0.9998	55632991
Alcoholism	1	-25.53775	173905	0	0.9999	0
Alzheimers	1	13.80414	17738	0	0.9994	988697.6
Anorexia	1	0.39927	285644	0	1	1.491
Ankylosing spondylitis	1	1.51609	187740	0	1	4.554
COPD	1	-1.12955	1.57093	0.517	0.4721	0.323
Cataracts	1	-0.02912	1.84546	0.0002	0.9874	0.971
Central Adiposity	1	17.7537	9632	0	0.9985	51325344
Chronic metabolic acidosis	1	-28.87295	115118	0	0.9998	0
Crohn's Disease	1	2.88154	80308	0	1	17.842
Depression	1	29.84991	8000	0	0.997	9.20E+12

DM	1	-0.4323	1.05301	0.1685	0.6814	0.649
ESRD	1	18.74658	21428	0	0.9993	1.39E+08
Disorders of the Eye	1	-0.96714	1.29865	0.5546	0.4564	0.38
Falling	1	-18.31916	4240	0	0.9966	0
Gaucher's Disease	1	18.38577	294096	0	1	96568708
Glaucoma	1	-0.0791	1.72241	0.0021	0.9634	0.924
Gout	1	14.89705	27423	0	0.9996	2949208
Hemophilia	1	0.2718	70564	0	1	1.312
Hyperthyroid	1	4.48908	82627	0	1	89.04
Hypophosphatasia	1	0.85861	212541	0	1	2.36
Idopathic scoliosis	1	-97.79431	392621	0	0.9998	0
Kyphosis	1	17.38027	9060	0	0.9985	35331124
Liver Disease	1	0.88275	63889	0	1	2.418
Malabsorption	1	-14.37341	80778	0	0.9999	0
MS	1	-12.47286	174906	0	0.9999	0
Obesity	0	0
Osteoarthritis	1	16.39664	4240	0	0.9969	13212020
Other Fx	1	19.54016	48440	0	0.9997	3.06E+08
Pancreatic Disease	1	1.28946	179831	0	1	3.631
Renault Disease	1	17.02273	8414	0	0.9984	24710357
RA	1	14.84109	18593	0	0.9994	2788703
Sarcoidosis	1	0.77014	55927	0	1	2.16
Lupus	1	15.81039	34782	0	0.9996	7351325
Thyrotoxicosis	0	0
Vitamin D	1	16.4555	10326	0	0.9987	14013017
lithium	1	-27.60796	36941	0	0.9994	0
thiaz	1	-1.43116	1.55803	0.8438	0.3583	0.239
arom	1	-2.81434	1.66151	2.8691	0.0903	0.06
convulsants	1	-2.58737	1.00678	6.6046	0.0102	0.075
ssri	1	16.95838	7231	0	0.9981	23170345
ppi	1	-0.10395	1.32095	0.0062	0.9373	0.901
mtx	1	12.90646	26234	0	0.9996	402906.4
coag	1	15.39962	7704	0	0.9984	4874952
Age	1	-0.14032	1.09398	0.0165	0.8979	0.869
Age*Age	0	0
Age*Age*Age	0	0
Age*Osteoporosis	0	0

Table A19 Approach 2 Vertebral Fracture 365 days, no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.60981	0.07285	70.0757	<.0001	1.84
Cystic Fibrosis	1	-1.37604	1.00193	1.8862	0.1696	0.253
Congestive Heart Failure	1	-0.11085	0.09416	1.3861	0.2391	0.895
Ehlers-Danlos	1	11.54069	3600	0	0.9974	102815.2
Epilepsy	1	0.11192	0.2696	0.1723	0.6781	1.118
Osteogenesis Imperfecta	1	12.285	1419	0.0001	0.9931	216425
Parkinson's Disease	1	-0.39593	0.22078	3.2161	0.0729	0.673
Stroke	1	-0.00731	0.09256	0.0062	0.9371	0.993
Adrenal insufficiency	1	-0.99731	1.00491	0.9849	0.321	0.369
AIDS/HIV	1	-1.15326	0.71102	2.6308	0.1048	0.316
Alcoholism	1	-0.6345	0.38368	2.7348	0.0982	0.53
Alzheimers	1	-0.03338	0.1069	0.0975	0.7549	0.967
Amyloidosis	1	11.97897	837.47275	0.0002	0.9886	159367.7
Androgen insensitivity	1	11.32153	3910	0	0.9977	82580.56
Anorexia	1	-0.28013	0.23087	1.4722	0.225	0.756
Ankylosing spondylitis	1	-0.47053	0.2289	4.2254	0.0398	0.625
COPD	1	-0.32803	0.07605	18.6039	<.0001	0.72
Athletic amenorrhea	1	12.18837	501.86246	0.0006	0.9806	196490.8
Cataracts	1	-0.01058	0.08912	0.0141	0.9055	0.989
Celiac	1	-0.89515	0.91527	0.9565	0.3281	0.409
Central Adiposity	1	0.14214	0.13394	1.1262	0.2886	1.153
Chronic metabolic acidosis	1	0.27722	0.31163	0.7914	0.3737	1.319
Crohn's Disease	1	0.02904	0.17096	0.0289	0.8651	1.029
Cushing's	1	-1.09048	0.71175	2.3474	0.1255	0.336
Depression	1	0.06269	0.0991	0.4002	0.527	1.065
DM	1	0.00821	0.07395	0.0123	0.9116	1.008
ESRD	1	-0.29767	0.27504	1.1713	0.2791	0.743
Disorders of the Eye	1	0.04625	0.092	0.2528	0.6151	1.047
Falling	1	-0.42026	0.1207	12.1243	0.0005	0.657
Gaucher's Disease	1	0.64355	1.00141	0.413	0.5205	1.903
Glaucoma	1	0.10439	0.10338	1.0196	0.3126	1.11
Gout	1	0.35864	0.20196	3.1536	0.0758	1.431
Glycogen storage diseases	1	11.92805	1082	0.0001	0.9912	151455.6
Hemochromatosis	1	11.99174	1061	0.0001	0.991	161415.5
Hemophilia	1	-0.36201	0.18309	3.9094	0.048	0.696
Homocystinuria	1	-0.21143	0.7092	0.0889	0.7656	0.809
Hyperprolactinemia	1	11.74529	838.3193	0.0002	0.9888	126158.5
Hyperparathyroidism	1	0.58937	0.38313	2.3663	0.124	1.803

Hyperthyrois	1	0.25579	0.23281	1.2072	0.2719	1.291
Hypophosphatasia	1	-0.41959	0.37591	1.2459	0.2643	0.657
IBD	1	0.06681	0.41361	0.0261	0.8717	1.069
Idopathic scoliosis	1	-0.47906	0.1704	7.9042	0.0049	0.619
Idiopathic hypercalciuria	1	12.20653	3577	0	0.9973	200090.6
Kyphosis	1	0.13766	0.10115	1.8522	0.1735	1.148
Liver Disease	1	-0.06923	0.15486	0.1998	0.6549	0.933
Malabsorption	1	0.32334	0.70982	0.2075	0.6487	1.382
Marfan syndrome	1	12.8828	2773	0	0.9963	393484.4
MS	1	-0.40645	0.45455	0.7995	0.3712	0.666
Muscular dystrophy	1	11.79884	515.05537	0.0005	0.9817	133098.1
Obseity	0	0
Osteoarthritis	1	-0.09748	0.07192	1.8374	0.1753	0.907
Osteoporosis	1	0.03233	0.73934	0.0019	0.9651	1.033
Other Fx	1	-0.25315	0.13104	3.7322	0.0534	0.776
Panhypopituitarism	1	12.18312	1379	0.0001	0.993	195461.4
Pancreatic Disease	1	-0.28093	0.24901	1.2728	0.2592	0.755
Poly Rheumatica	1	0.00718	0.27326	0.0007	0.979	1.007
Porphyria	1	12.21953	1112	0.0001	0.9912	202710
Premature ovarian failure	1	12.12752	403.86823	0.0009	0.976	184890.6
Primary biliary cirrhosis	1	-2.05436	0.59894	11.7647	0.0006	0.128
Riley-Day	1	13.19721	2929	0	0.9964	538861.9
Renauld Disease	1	-0.18441	0.12329	2.2372	0.1347	0.832
RA	1	-0.02502	0.16469	0.0231	0.8792	0.975
Saccoidosis	1	-0.08119	0.70967	0.0131	0.9089	0.922
Sickle Cell Anemia	1	11.65146	1161	0.0001	0.992	114859.4
Lupus	1	-0.96688	0.27611	12.2623	0.0005	0.38
Spinal cord injury	1	-1.17826	0.45602	6.6758	0.0098	0.308
Systemic mastocytosis	1	11.88555	1318	0.0001	0.9928	145153.9
Turner's & Klinefelter's syndromes	1	12.76621	2401	0	0.9958	350181.9
Thalassemia	1	-0.44507	1.00311	0.1969	0.6573	0.641
Thyrotoxicosis	0	0
Vitamin A	1	12.00132	1705	0	0.9944	162970.5
Vitamin D	1	0.04748	0.1323	0.1288	0.7197	1.049
barb	1	-2.02045	1.01408	3.9697	0.0463	0.133
lithium	1	11.95049	342.56761	0.0012	0.9722	154893.2
thiaz	1	-0.10653	0.1335	0.6367	0.4249	0.899
gnrh	1	12.44447	3287	0	0.997	253843.6
arom	1	0.24349	0.29135	0.6984	0.4033	1.276
convulsants	1	-0.34251	0.09116	14.1169	0.0002	0.71

ssri	1	-0.20991	0.08717	5.7984	0.016	0.811
ppi	1	-0.32942	0.0724	20.6999	<.0001	0.719
mtx	1	-0.68403	0.2492	7.5344	0.0061	0.505
csa	1	11.27586	248.71516	0.0021	0.9638	78893.8
coag	1	-0.16268	0.10477	2.4107	0.1205	0.85
white	1	-0.56516	1.00149	0.3185	0.5725	0.568
black	1	0.19753	1.01036	0.0382	0.845	1.218
other_race	1	-0.89417	1.02349	0.7633	0.3823	0.409
asian	1	-0.56001	1.01614	0.3037	0.5816	0.571
hispanic	1	-0.40616	1.01289	0.1608	0.6884	0.666
amnative	1	1.04611	1.41535	0.5463	0.4598	2.847
Age	1	-2.83512	0.98463	8.2908	0.004	0.059
Age*Age	1	0.03561	0.01251	8.1048	0.0044	1.036
Age*Age*Age	1	-0.0001455	0.0000526	7.6419	0.0057	1
Age*Osteoporosis	1	0.00262	0.00938	0.0778	0.7803	1.003

Table A20 Approach 2 Vertebral Fracture All Available, no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.48367	0.04309	125.9881	<.0001	1.622
Cystic Fibrosis	1	-0.35775	1.00074	0.1278	0.7207	0.699
Congestive Heart Failure	1	-0.08887	0.05747	2.3912	0.122	0.915
Ehlers-Danlos	1	9.38269	749.36844	0.0002	0.99	11880.87
Epilepsy	1	0.16864	0.17658	0.9121	0.3396	1.184
Osteogenesis Imperfecta	1	9.72898	332.77068	0.0009	0.9767	16797.46
Parkinson's Disease	1	-0.45651	0.13652	11.1812	0.0008	0.633
Stroke	1	-0.02932	0.05484	0.2859	0.5929	0.971
Adrenal insufficiency	1	-0.80106	0.58037	1.9051	0.1675	0.449
AIDS/HIV	1	-0.01949	0.71207	0.0007	0.9782	0.981
Alcoholism	1	-0.60099	0.23941	6.3015	0.0121	0.548
Alzheimers	1	0.11034	0.06861	2.586	0.1078	1.117
Amyloidosis	1	-0.65624	1.00184	0.4291	0.5124	0.519
Androgen insensitivity	1	9.52044	627.80872	0.0002	0.9879	13635.63
Anorexia	1	-0.21883	0.15293	2.0474	0.1525	0.803
Ankylosing spondylitis	1	-0.36056	0.13683	6.9437	0.0084	0.697
COPD	1	-0.37341	0.04465	69.9501	<.0001	0.688
Athletic amenorrhea	1	0.26355	0.70856	0.1383	0.7099	1.302
Cataracts	1	0.00268	0.05108	0.0028	0.9582	1.003
Celiac	1	-0.34426	0.41972	0.6727	0.4121	0.709

Central Adiposity	1	0.23576	0.0851	7.6749	0.0056	1.266
Chronic metabolic acidosis	1	0.25766	0.206	1.5644	0.211	1.294
Crohn's Disease	1	0.02594	0.10139	0.0654	0.7981	1.026
Cushing's	1	-0.73661	0.50163	2.1563	0.142	0.479
Depression	1	-0.10268	0.05853	3.0774	0.0794	0.902
DM	1	0.04237	0.04357	0.9457	0.3308	1.043
ESRD	1	-0.51835	0.17291	8.9866	0.0027	0.596
Disorders of the Eye	1	-0.03886	0.05391	0.5195	0.471	0.962
Falling	1	-0.33857	0.07563	20.0416	<.0001	0.713
Gaucher's Disease	1	1.91252	1.0005	3.6541	0.0559	6.77
Glaucoma	1	0.09139	0.05827	2.4601	0.1168	1.096
Gout	1	-0.06827	0.10259	0.4428	0.5058	0.934
Glycogen storage diseases	1	-1.41154	1.00461	1.9742	0.16	0.244
Hemochromatosis	1	9.88555	245.33346	0.0016	0.9679	19644.53
Hemophilia	1	-0.09183	0.12403	0.5482	0.4591	0.912
Homocystinuria	1	0.99759	0.70819	1.9843	0.1589	2.712
Hyperprolactinemia	1	9.51323	191.21187	0.0025	0.9603	13537.7
Hyperparathyroidism	1	0.24468	0.18667	1.7181	0.1899	1.277
Hyperthyroid	1	0.0368	0.12269	0.0899	0.7642	1.037
Hypophosphatasia	1	-0.44768	0.24168	3.4312	0.064	0.639
IBD	1	-0.10372	0.23098	0.2016	0.6534	0.901
Idopathic scoliosis	1	-0.34364	0.10496	10.719	0.0011	0.709
Idiopathic hypercalciuria	1	10.1778	485.70985	0.0004	0.9833	26312.56
Kyphosis	1	0.13629	0.05911	5.3163	0.0211	1.146
Liver Disease	1	-0.03768	0.09298	0.1643	0.6853	0.963
Malabsorption	1	-0.34712	0.29141	1.4188	0.2336	0.707
Marfan syndrome	1	10.71209	481.49676	0.0005	0.9823	44895.33
MS	1	-0.17067	0.31967	0.285	0.5934	0.843
Muscular dystrophy	1	10.32737	168.91635	0.0037	0.9512	30557.67
Obesity	0	0
Osteoarthritis	1	-0.04119	0.04221	0.9523	0.3291	0.96
Osteoporosis	1	-0.20367	0.44242	0.2119	0.6453	0.816
Other Fx	1	-0.40505	0.07437	29.6663	<.0001	0.667
Panhypopituitarism	1	-1.14018	1.00461	1.2881	0.2564	0.32
Pancreatic Disease	1	-0.28267	0.15257	3.4324	0.0639	0.754
Poly Rheumatica	1	-0.31155	0.13499	5.3264	0.021	0.732
Porphyria	1	-1.04669	1.00626	1.082	0.2983	0.351
Premature ovarian failure	1	0.1364	0.57841	0.0556	0.8136	1.146
Primary biliary cirrhosis	1	-1.46948	0.50973	8.311	0.0039	0.23
Riley-Day	1	10.59055	841.464	0.0002	0.99	39757.38
Renault Disease	1	-0.13662	0.07837	3.0386	0.0813	0.872

RA	1	-0.17294	0.09202	3.532	0.0602	0.841
Saccoidosis	1	0.10481	0.44907	0.0545	0.8154	1.111
Sickle Cell Anemia	1	9.41011	229.69518	0.0017	0.9673	12211.16
Lupus	1	-0.50899	0.20088	6.4199	0.0113	0.601
Spinal cord injury	1	-0.7726	0.33694	5.258	0.0218	0.462
Systemic mastocytosis	1	9.60743	250.96746	0.0015	0.9695	14874.94
Turner's & Klinefelter's syndromes	1	10.5837	563.80589	0.0004	0.985	39486.05
Thalassemia	1	-0.96987	0.45006	4.6439	0.0312	0.379
Thyrotoxicosis	0	0
Vitamin A	1	-2.03039	1.00683	4.0668	0.0437	0.131
Vitamin D	1	0.16586	0.08828	3.53	0.0603	1.18
barb	1	-2.00293	0.71345	7.8815	0.005	0.135
lithium	1	0.63902	0.70901	0.8123	0.3674	1.895
thiaz	1	-0.08729	0.0804	1.1786	0.2776	0.916
gnrh	1	10.35542	450.6778	0.0005	0.9817	31427.04
arom	1	0.08193	0.15264	0.2881	0.5915	1.085
convulsants	1	-0.28703	0.05578	26.4766	<.0001	0.75
ssri	1	-0.18213	0.05242	12.0725	0.0005	0.833
ppi	1	-0.12701	0.04393	8.36	0.0038	0.881
mtx	1	-0.37498	0.15258	6.0397	0.014	0.687
csa	1	1.29262	1.00104	1.6674	0.1966	3.642
coag	1	-0.19331	0.06158	9.8555	0.0017	0.824
white	1	-0.88339	0.70789	1.5573	0.2121	0.413
black	1	-0.00103	0.71319	0	0.9988	0.999
other_race	1	-0.64404	0.72656	0.7857	0.3754	0.525
asian	1	-0.85285	0.71501	1.4227	0.233	0.426
hispanic	1	-0.72706	0.71378	1.0375	0.3084	0.483
amnative	1	-0.56026	0.77555	0.5219	0.47	0.571
Age	1	-3.15406	0.65743	23.0166	<.0001	0.043
Age*Age	1	0.04034	0.00839	23.1149	<.0001	1.041
Age*Age*Age	1	-0.0001682	0.0000355	22.4401	<.0001	1
Age*Osteoporosis	1	0.0001064	0.00563	0.0004	0.9849	1

Table A21 Approach 2 Vertebral Fracture 365 days, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.41921	0.625	0.4499	0.5024	1.521
Cystic Fibrosis	0	0
Congestive Heart Failure	1	-1.34929	0.94158	2.0535	0.1519	0.259
Epilepsy	1	10.30987	2733	0	0.997	30027.61
Parkinson's Disease	1	16.67073	22788	0	0.9994	17378272
Stroke	1	0.00659	1.09989	0	0.9952	1.007
AIDS/HIV	1	18.964	48162	0	0.9997	1.72E+08
Alcoholism	1	17.63052	31028	0	0.9995	45377252
Alzheimers	1	16.47216	9701	0	0.9986	14248432
Anorexia	1	17.2557	66809	0	0.9998	31192818
Ankylosing spondylitis	1	18.49681	24987	0	0.9994	1.08E+08
COPD	1	0.28083	0.94949	0.0875	0.7674	1.324
Cataracts	1	-0.20578	0.94644	0.0473	0.8279	0.814
Central Adiposity	1	1.61226	1.07202	2.2619	0.1326	5.014
Chronic metabolic acidosis	1	16.71124	86001	0	0.9998	18096677
Crohn's Disease	1	18.09184	38756	0	0.9996	71975814
Depression	1	0.54272	1.02391	0.2809	0.5961	1.721
DM	1	0.6147	0.76739	0.6416	0.4231	1.849
ESRD	1	14.78519	9502	0	0.9988	2637107
Disorders of the Eye	1	-0.39225	0.87196	0.2024	0.6528	0.676
Falling	1	-2.16692	1.13057	3.6736	0.0553	0.115
Gaucher's Disease	1	17.28224	37672	0	0.9996	32031744
Glaucoma	1	0.58929	1.17222	0.2527	0.6152	1.803
Gout	1	-1.93755	1.49429	1.6813	0.1948	0.144
Hemophilia	1	-2.01114	1.20946	2.7651	0.0963	0.134
Homocystinuria	1	18.7614	102535	0	0.9999	1.41E+08
Hyperprolactinemia	1	20.15119	132831	0	0.9999	5.64E+08
Hyperthyroid	1	18.13789	17944	0	0.9992	75367918
Hypophosphatasia	1	16.79765	50473	0	0.9997	19729910
IBD	1	-1.8744	102851	0	1	0.153
Idopathic scoliosis	1	19.93594	8527	0	0.9981	4.55E+08
Kyphosis	1	17.31603	2961	0	0.9953	33132605
Liver Disease	1	16.99293	7939	0	0.9983	23984781
Malabsorption	1	13.56798	82820	0	0.9999	780728.9
MS	1	-2.19092	1.75212	1.5636	0.2111	0.112
Obesity	0	0

Osteoarthritis	1	-1.17627	0.60986	3.7202	0.0538	0.308
Osteoporosis	1	-107.8273	2962	0.0013	0.971	0
Other Fx	1	14.2905	7656	0	0.9985	1607995
Panhypopituitarism	1	3.51203	251592	0	1	33.516
Pancreatic Disease	1	17.35964	71313	0	0.9998	34609625
Premature ovarian failure	1	18.76865	98803	0	0.9998	1.42E+08
Renauld Disease	1	15.64731	3682	0	0.9966	6245111
RA	1	17.57874	14868	0	0.9991	43087387
Saccoidosis	1	15.34089	37180	0	0.9997	4596879
Lupus	1	17.92022	18841	0	0.9992	60624938
Thalassemia	1	7.12439	150992	0	1	1241.896
Thyrotoxicosis	0	0
Vitamin D	1	-0.69386	1.08172	0.4114	0.5212	0.5
lithium	1	17.24014	56522	0	0.9998	30711382
thiaz	1	-1.36926	0.86732	2.4924	0.1144	0.254
arom	1	18.49956	183777	0	0.9999	1.08E+08
convulsants	1	-0.88545	0.72672	1.4845	0.2231	0.413
ssri	1	-0.63653	0.79018	0.6489	0.4205	0.529
ppi	1	0.17138	0.74161	0.0534	0.8172	1.187
mtx	1	17.43913	25427	0	0.9995	37473109
csa	1	2.81256	99149	0	1	16.652
coag	1	16.39138	2707	0	0.9952	13142783
white	1	-20.76686	131646	0	0.9999	0
black	1	-17.74349	131646	0	0.9999	0
other_race	1	-20.55535	131646	0	0.9999	0
asian	1	-1.49437	131912	0	1	0.224
hispanic	1	-20.43646	131646	0	0.9999	0
amnative	1	-1.3943	139673	0	1	0.248
Age	1	-1280	1696	0.5693	0.4505	0
Age*Age	1	19.35246	25.617	0.5707	0.45	2.54E+08
Age*Age*Age	1	-0.09753	0.12895	0.5721	0.4494	0.907
Age*Osteoporosis	1	-1.37491	0.98924	1.9317	0.1646	0.253

Table A22 Approach 2 Vertebral Fracture All Available, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.76387	0.40801	3.5051	0.0612	2.147
Cystic Fibrosis	0	0
Congestive Heart Failure	1	-1.13098	0.62346	3.2907	0.0697	0.323
Epilepsy	1	13.96177	5720	0	0.9981	1157497
Parkinson's Disease	1	13.8274	5362	0	0.9979	1011960
Stroke	1	-0.21638	0.6608	0.1072	0.7433	0.805
AIDS/HIV	1	15.13739	7181	0	0.9983	3750461
Alcoholism	1	15.0151	9707	0	0.9988	3318755
Alzheimers	1	14.96662	2716	0	0.9956	3161694
Anorexia	1	15.35077	13536	0	0.9991	4642527
Ankylosing spondylitis	1	14.56175	7979	0	0.9985	2109054
COPD	1	-0.66151	0.49047	1.8191	0.1774	0.516
Cataracts	1	-0.84162	0.72697	1.3403	0.247	0.431
Central Adiposity	1	1.34695	0.71589	3.5401	0.0599	3.846
Chronic metabolic acidosis	1	14.86413	19813	0	0.9994	2853713
Crohn's Disease	1	15.34409	7354	0	0.9983	4611623
Depression	1	-0.24319	0.54278	0.2007	0.6541	0.784
DM	1	0.75453	0.46679	2.6128	0.106	2.127
ESRD	1	16.30582	3429	0	0.9962	12064996
Disorders of the Eye	1	0.64128	0.72257	0.7876	0.3748	1.899
Falling	1	-0.87574	1.13556	0.5947	0.4406	0.417
Gaucher's Disease	1	15.8881	14645	0	0.9991	7945406
Glaucoma	1	0.08604	0.74084	0.0135	0.9075	1.09
Gout	1	-2.00106	0.87776	5.1972	0.0226	0.135
Hemophilia	1	-1.43897	1.13436	1.6092	0.2046	0.237
Homocystinuria	1	16.42181	12578	0	0.999	13548769
Hyperprolactinemia	1	17.22808	34227	0	0.9996	30343176
Hyperthyrois	1	-0.65925	1.04941	0.3946	0.5299	0.517
Hypophosphatasia	1	14.1518	11315	0	0.999	1399745
IBD	1	-1.02585	16354	0	0.9999	0.358
Idopathic scoliosis	1	0.50882	1.80202	0.0797	0.7777	1.663
Kyphosis	1	1.60088	1.10346	2.1048	0.1468	4.957
Liver Disease	1	16.59812	1991	0.0001	0.9933	16161178
Malabsorption	1	12.42078	15901	0	0.9994	247900.3
MS	1	-0.29956	1.48573	0.0407	0.8402	0.741

Obesity	0	0
Osteoarthritis	1	-0.48333	0.43638	1.2267	0.268	0.617
Osteoporosis	1	-63.6157	30.9486	4.2252	0.0398	0
Other Fx	1	14.2027	4226	0	0.9973	1472836
Panhypopituitarism	1	16.29293	44068	0	0.9997	11910483
Pancreatic Disease	1	15.12411	12479	0	0.999	3700995
Premature ovarian failure	1	16.33855	10665	0	0.9988	12466431
Renault Disease	1	-0.56996	0.78578	0.5261	0.4682	0.566
RA	1	16.03262	2473	0	0.9948	9180777
Sarcoidosis	1	13.94207	6191	0	0.9982	1134919
Lupus	1	-1.41418	1.35355	1.0916	0.2961	0.243
Thalassemia	1	16.73552	28620	0	0.9995	18541437
Thyrotoxicosis	0	0
Vitamin D	1	0.38292	1.05022	0.1329	0.7154	1.467
lithium	1	16.31406	10266	0	0.9987	12164857
thiaz	1	-0.96507	0.58599	2.7123	0.0996	0.381
arom	1	-4.5724	1.19905	14.5416	0.0001	0.01
convulsants	1	-0.47512	0.51836	0.8401	0.3594	0.622
ssri	1	-0.33962	0.53662	0.4005	0.5268	0.712
ppi	1	-0.05379	0.46889	0.0132	0.9087	0.948
mtx	1	-2.16794	1.23366	3.0882	0.0789	0.114
csa	1	15.73749	13847	0	0.9991	6834495
coag	1	16.19736	1513	0.0001	0.9915	10824870
white	1	-17.12683	25476	0	0.9995	0
black	1	-14.98353	25476	0	0.9995	0
other_race	1	-15.75829	25476	0	0.9995	0
asian	1	-14.57665	25476	0	0.9995	0
hispanic	1	-16.54522	25476	0	0.9995	0
american	1	-0.33222	26869	0	1	0.717
Age	1	-1999	1129	3.1391	0.0764	0
Age*Age	1	30.26741	17.04205	3.1543	0.0757	1.40E+13
Age*Age*Age	1	-0.15267	0.08576	3.169	0.075	0.858
Age*Osteoporosis	1	-0.92969	0.4721	3.878	0.0489	0.395

Table A23 Approach 2 Vertebral Fracture 365 days, CFRI With BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	0	-14.67275
Congestive Heart Failure	0	10.83239
Epilepsy	0	-44.16991
Parkinson's Disease	0	-20.64949
Stroke	0	27.26695
AIDS/HIV	0	-20.91575
Alcoholism	0	-9.34805
Alzheimers	0	-17.53555
Anorexia	0	0.19984
Ankylosing spondylitis	0	272.54957
COPD	0	26.42629
Cataracts	0	0.53638
Central Adiposity	0	9.59947
Chronic metabolic acidosis	0	54.58757
Crohn's Disease	0	-4.13548
Depression	0	10.65813
DM	0	-1.66942
ESRD	0	-17.23292
Disorders of the Eye	0	17.40843
Falling	0	18.25968
Gaucher's Disease	0	-10.7636
Glaucoma	0	-43.72316
Gout	0	12.55679
Hemophilia	0	5.83458
Hyperthyrois	0	34.72215
Hypophosphatasia	0	7.19154
Idopathic scoliosis	0	-3.78129
Kyphosis	0	16.85857
Liver Disease	0	5.69325
Malabsorption	0	6.38849
MS	0	-17.24928
Obseity	0	0
Osteoarthritis	0	-15.83894
Other Fx	0	-1.42016
Pancreatic Disease	0	5.19293
Renauld Disease	0	5.05151

RA	0	49.94904
Saccoidosis	0	-8.81972
Lupus	0	-25.74728
Thyrototoxicosis	0	0
Vitamin D	1	-4.48074	34558004	0	1	0.011
lithium	0	-10.06346
thiaz	0	-37.92258
arom	0	-1.947
convulsants	0	10.46405
ssri	0	15.64561
ppi	0	9.50334
mtx	0	-19.86823
coag	0	-6.62971
Age	1	18.41333	1153543	0	1	99268098
Age*Age	0	0
Age*Age*Age	0	0
Age*Osteoporosis	0	0

Table A24 Approach 2 Vertebral Fracture All Available, CFRI With BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	2.01615	160402	0	1	7.509
Congestive Heart Failure	1	174.65858	4367621	0	1	7.13E+75
Epilepsy	1	56.11989	7134271	0	1	2.36E+24
Parkinson's Disease	1	-76.16294	5538680	0	1	0
Stroke	1	-30.39157	4084802	0	1	0
AIDS/HIV	1	-122.05827	114890285	0	1	0
Alcoholism	1	-145.99136	443437919	0	1	0
Alzheimers	1	-119.76494	10439068	0	1	0
Anorexia	1	370.19929	1.74E+10	0	1	5.96E+160
Ankylosing spondylitis	1	-162.85208	421495224	0	1	0
COPD	1	-134.05357	697401	0	0.9998	0
Cataracts	1	-12.24814	3647130	0	1	0
Central Adiposity	1	45.39841	7780555	0	1	5.20E+19
Chronic metabolic acidosis	1	-255.46199	665324885	0	1	0
Crohn's Disease	1	-87.98374	1313874502	0	1	0
Depression	1	-52.95248	3543682	0	1	0

DM	1	-4.3601	46120	0	0.9999	0.013
ESRD	1	-0.12682	305603	0	1	0.881
Disorders of the Eye	1	48.78054	5485488	0	1	1.53E+21
Falling	1	-38.29993	3487709	0	1	0
Gaucher's Disease	1	135.21054	566759921	0	1	5.26E+58
Glaucoma	1	-75.33456	4121875	0	1	0
Gout	1	-54.75707	26189145	0	1	0
Hemophilia	1	-137.42218	188422408	0	1	0
Hyperthyroid	1	-100.09263	6889757	0	1	0
Hypophosphatasia	1	-95.10568	427781577	0	1	0
Idopathic scoliosis	1	191.49709	1073638808	0	1	1.47E+83
Kyphosis	1	4.4891	151255548	0	1	89.041
Liver Disease	1	-114.79502	87066432	0	1	0
Malabsorption	1	-133.33852	261920112	0	1	0
MS	1	216.22443	465610060	0	1	8.04E+93
Obesity	0	0
Osteoarthritis	1	49.32677	3517439	0	1	2.65E+21
Other Fx	1	-127.22382	77307607	0	1	0
Pancreatic Disease	1	-160.00767	500081197	0	1	0
Renault Disease	1	-45.16715	3640520	0	1	0
RA	1	-78.24089	7135778	0	1	0
Sarcoidosis	1	-168.86541	116574792	0	1	0
Lupus	1	-127.97522	24177620	0	1	0
Thyrotoxicosis	0	0
Vitamin D	1	47.14258	4226531	0	1	2.98E+20
lithium	1	-104.91797	916912	0	0.9999	0
thiaz	1	-141.38471	684855	0	0.9998	0
arom	1	-161.53417	700287	0	0.9998	0
convulsants	1	25.61996	365857	0	0.9999	1.34E+11
ssri	1	51.61049	3587043	0	1	2.60E+22
ppi	1	47.29894	551103	0	0.9999	3.48E+20
mtx	1	43.2768	7148669	0	1	6.24E+18
coag	1	60.13062	3584770	0	1	1.30E+26
Age	1	2.50468	155185	0	1	12.24
Age*Age	0	0
Age*Age*Age	0	0
Age*Osteoporosis	0	0

Table A25 Approach 3 MOF 365 days, no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.21107	0.02895	53.1574	<.0001	1.235
Cystic Fibrosis	1	9.12079	79.88164	0.013	0.9091	9143.403
Congestive Heart Failure	1	-0.19431	0.03511	30.6283	<.0001	0.823
Ehlers-Danlos	1	-1.09372	1.0005	1.195	0.2743	0.335
Epilepsy	1	-0.00174	0.10054	0.0003	0.9862	0.998
Osteogenesis Imperfecta	1	9.45425	179.99448	0.0028	0.9581	12762.25
Parkinson's Disease	1	-0.46581	0.08274	31.6957	<.0001	0.628
Stroke	1	-0.03044	0.04482	0.4612	0.497	0.97
Adrenal insufficiency	1	-0.81009	0.37897	4.5693	0.0325	0.445
AIDS/HIV	1	-1.28954	0.379	11.577	0.0007	0.275
Alcoholism	1	-0.44915	0.15023	8.9383	0.0028	0.638
Alzheimers	1	-0.16994	0.04347	15.2845	<.0001	0.844
Amyloidosis	1	0.02783	0.5776	0.0023	0.9616	1.028
Androgen insensitivity	1	9.47107	250.99625	0.0014	0.9699	12978.79
Anorexia	1	-0.24693	0.11443	4.6568	0.0309	0.781
Ankylosing spondylitis	1	-0.37724	0.12881	8.5773	0.0034	0.686
COPD	1	-0.27807	0.02617	112.8662	<.0001	0.757
Athletic amenorrhea	1	-0.57412	0.50019	1.3174	0.2511	0.563
Cataracts	1	0.02486	0.06134	0.1643	0.6852	1.025
Celiac	1	-0.50003	0.32646	2.346	0.1256	0.607
Central Adiposity	1	0.06125	0.04972	1.5177	0.218	1.063
Chronic metabolic acidosis	1	-0.10167	0.11966	0.7218	0.3955	0.903
Crohn's Disease	1	-0.20543	0.06345	10.4823	0.0012	0.814
Cushing's	1	-0.79076	0.31707	6.2198	0.0126	0.453
Depression	1	-0.09861	0.03466	8.0927	0.0044	0.906
DM	1	-0.02831	0.02501	1.2806	0.2578	0.972
ESRD	1	-0.64217	0.10522	37.2485	<.0001	0.526
Disorders of the Eye	1	-0.03736	0.04693	0.6338	0.426	0.963
Falling	1	-0.3455	0.05453	40.1448	<.0001	0.708
Gaucher's Disease	1	-0.16085	0.44742	0.1292	0.7192	0.851
Glaucoma	1	0.07215	0.07556	0.9119	0.3396	1.075
Gout	1	0.07936	0.06955	1.302	0.2538	1.083
Glycogen storage diseases	1	9.3876	161.93676	0.0034	0.9538	11939.38
Hemochromatosis	1	-0.41132	0.50028	0.676	0.411	0.663
Hemophilia	1	-0.08279	0.09451	0.7674	0.381	0.921
Homocystinuria	1	0.0932	0.40858	0.052	0.8196	1.098

Hyperprolactinemia	1	8.90496	81.74789	0.0119	0.9133	7368.395
Hyperparathyroidism	1	-0.0377	0.102	0.1366	0.7117	0.963
Hyperthyrois	1	-0.10177	0.08191	1.5436	0.2141	0.903
Hypophosphatasia	1	-0.2189	0.17025	1.6531	0.1985	0.803
IBD	1	-0.11286	0.12466	0.8197	0.3653	0.893
Idopathic scoliosis	1	-0.30763	0.0641	23.0319	<.0001	0.735
Kyphosis	1	-0.0768	0.0391	3.8574	0.0495	0.926
Liver Disease	1	-0.15342	0.06021	6.4925	0.0108	0.858
Malabsorption	1	0.16589	0.24331	0.4649	0.4954	1.18
Marfan syndrome	1	-1.0255	1.00071	1.0501	0.3055	0.359
MS	1	-0.04979	0.21401	0.0541	0.816	0.951
Muscular dystrophy	1	-0.12119	0.708	0.0293	0.8641	0.886
Obesity	0	0
Osteoarthritis	1	0.03364	0.02636	1.6284	0.2019	1.034
Osteoporosis	1	-1.49878	0.3126	22.9875	<.0001	0.223
Other Fx	1	-0.23699	0.04875	23.6362	<.0001	0.789
Panhypopituitarism	1	9.12389	124.16241	0.0054	0.9414	9171.841
Pancreatic Disease	1	-0.17711	0.09081	3.804	0.0511	0.838
Poly Rheumatica	1	-0.23995	0.08366	8.2252	0.0041	0.787
Porphyria	1	0.24181	1.00036	0.0584	0.809	1.274
Premature ovarian failure	1	8.53389	74.19095	0.0132	0.9084	5084.21
Primary biliary cirrhosis	1	-0.38735	0.27387	2.0003	0.1573	0.679
Riley-Day	1	9.86822	343.98611	0.0008	0.9771	19307
Renault Disease	1	-0.00508	0.05005	0.0103	0.9192	0.995
RA	1	-0.17013	0.0545	9.7432	0.0018	0.844
Sacrocodosis	1	0.13526	0.24302	0.3098	0.5778	1.145
Sickle Cell Anemia	1	-0.23357	1.0019	0.0544	0.8157	0.792
Lupus	1	-0.58389	0.10571	30.5073	<.0001	0.558
Spinal cord injury	1	-1.05573	0.33457	9.9573	0.0016	0.348
Systemic mastocytosis	1	8.895	166.53875	0.0029	0.9574	7295.433
Turner's & Klinefelter's syndromes	1	9.50802	484.15546	0.0004	0.9843	13467.3
Thalassemia	1	0.11724	0.44746	0.0687	0.7933	1.124
Thyrotoxicosis	0	0
Vitamin A	1	8.82345	207.70356	0.0018	0.9661	6791.625
Vitamin D	1	0.15349	0.04793	10.2547	0.0014	1.166
barb	1	-0.61044	0.40903	2.2273	0.1356	0.543
lithium	1	0.20745	0.21427	0.9373	0.333	1.231
thiaz	1	-0.24948	0.04867	26.273	<.0001	0.779
arom	1	-0.0004823	0.05325	0.0001	0.9928	1
convulsants	1	-0.33425	0.02447	186.5565	<.0001	0.716

ssri	1	-0.29322	0.02226	173.4605	<.0001	0.746
ppi	1	-0.15232	0.01957	60.5746	<.0001	0.859
mtx	1	-0.42294	0.06274	45.4456	<.0001	0.655
csa	1	-0.18767	0.21864	0.7368	0.3907	0.829
coag	1	-0.23607	0.02676	77.8041	<.0001	0.79
white	1	-0.20037	0.24284	0.6808	0.4093	0.818
black	1	0.82986	0.24836	11.1652	0.0008	2.293
other_race	1	0.36676	0.2672	1.8841	0.1699	1.443
asian	1	-0.06365	0.25434	0.0626	0.8024	0.938
hispanic	1	0.07049	0.25046	0.0792	0.7784	1.073
amnative	1	0.00833	0.29721	0.0008	0.9776	1.008
Age	1	-1.83513	0.3409	28.9792	<.0001	0.16
Age*Age	1	0.02425	0.00433	31.318	<.0001	1.025
Age*Age*Age	1	-0.0001024	0.0000183	31.4318	<.0001	1
Age*Osteoporosis	1	-0.01422	0.00395	12.9541	0.0003	0.986

Table A26 Approach 3 MOF All Available Time, no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.25813	0.01559	274.1333	<.0001	1.295
Cystic Fibrosis	1	8.11697	27.3571	0.088	0.7667	3350.837
Congestive Heart Failure	1	-0.1421	0.02151	43.6545	<.0001	0.868
Ehlers-Danlos	1	-0.91205	0.70728	1.6629	0.1972	0.402
Epilepsy	1	-0.05247	0.0624	0.7072	0.4004	0.949
Osteogenesis Imperfecta	1	8.48581	69.49969	0.0149	0.9028	4845.512
Parkinson's Disease	1	-0.38137	0.05227	53.2308	<.0001	0.683
Stroke	1	-0.02167	0.0265	0.6685	0.4136	0.979
Adrenal insufficiency	1	-0.5769	0.24303	5.6347	0.0176	0.562
AIDS/HIV	1	-0.89733	0.27797	10.4208	0.0012	0.408
Alcoholism	1	-0.48983	0.08768	31.2091	<.0001	0.613
Alzheimers	1	-0.14181	0.02694	27.7084	<.0001	0.868
Amyloidosis	1	-0.10881	0.33347	0.1065	0.7442	0.897
Androgen insensitivity	1	8.37925	82.41239	0.0103	0.919	4355.724
Anorexia	1	-0.23411	0.07174	10.6485	0.0011	0.791
Ankylosing spondylitis	1	-0.3212	0.08173	15.4432	<.0001	0.725
COPD	1	-0.2759	0.01547	317.8852	<.0001	0.759
Athletic amenorrhea	1	0.10752	0.40834	0.0693	0.7923	1.114
Cataracts	1	0.07487	0.03622	4.2733	0.0387	1.078
Celiac	1	0.26799	0.19839	1.8247	0.1768	1.307

Central Adiposity	1	0.13969	0.03157	19.5852	<.0001	1.15
Chronic metabolic acidosis	1	-0.1311	0.07642	2.9428	0.0863	0.877
Crohn's Disease	1	-0.0927	0.03943	5.5276	0.0187	0.911
Cushing's	1	-0.5405	0.224	5.8226	0.0158	0.582
Depression	1	-0.10954	0.021	27.2206	<.0001	0.896
DM	1	-0.02952	0.01447	4.1639	0.0413	0.971
ESRD	1	-0.61645	0.06643	86.1042	<.0001	0.54
Disorders of the Eye	1	-0.03648	0.02774	1.7296	0.1885	0.964
Falling	1	-0.22205	0.03404	42.5481	<.0001	0.801
Gaucher's Disease	1	0.1673	0.30162	0.3077	0.5791	1.182
Glaucoma	1	0.11378	0.04526	6.3185	0.0119	1.121
Gout	1	0.05451	0.04172	1.707	0.1914	1.056
Glycogen storage diseases	1	8.32746	53.77194	0.024	0.8769	4135.895
Hemochromatosis	1	-0.11516	0.44735	0.0663	0.7968	0.891
Hemophilia	1	-0.12916	0.05494	5.5264	0.0187	0.879
Homocystinuria	1	-0.05677	0.2184	0.0676	0.7949	0.945
Hyperprolactinemia	1	7.89711	30.82837	0.0656	0.7978	2689.486
Hyperparathyroidism	1	-0.03401	0.06195	0.3015	0.5829	0.967
Hyperthyroid	1	0.01432	0.05035	0.0809	0.776	1.014
Hypophosphatasia	1	-0.03693	0.12421	0.0884	0.7662	0.964
IBD	1	-0.1279	0.07854	2.6519	0.1034	0.88
Idopathic scoliosis	1	-0.21223	0.04032	27.7125	<.0001	0.809
Kyphosis	1	-0.02216	0.02359	0.8825	0.3475	0.978
Liver Disease	1	-0.13917	0.03609	14.8699	0.0001	0.87
Malabsorption	1	-0.31319	0.12264	6.5215	0.0107	0.731
Marfan syndrome	1	-0.1607	1.00031	0.0258	0.8724	0.852
MS	1	-0.04198	0.13062	0.1033	0.7479	0.959
Muscular dystrophy	1	-0.31356	0.37864	0.6858	0.4076	0.731
Obesity	0	0
Osteoarthritis	1	0.06299	0.01547	16.5899	<.0001	1.065
Osteoporosis	1	-1.39359	0.19376	51.7278	<.0001	0.248
Other Fx	1	-0.31914	0.0285	125.3768	<.0001	0.727
Panhypopituitarism	1	0.46299	1.00032	0.2142	0.6435	1.589
Pancreatic Disease	1	-0.07295	0.05651	1.6669	0.1967	0.93
Poly Rheumatica	1	-0.18258	0.05119	12.7206	0.0004	0.833
Porphyria	1	-0.14801	0.50015	0.0876	0.7673	0.862
Premature ovarian failure	1	0.26729	0.70722	0.1428	0.7055	1.306
Primary biliary cirrhosis	1	-0.11896	0.18912	0.3956	0.5294	0.888
Riley-Day	1	8.90994	202.16984	0.0019	0.9648	7405.21
Reynolds Disease	1	-0.05454	0.0308	3.1361	0.0766	0.947
RA	1	-0.24356	0.0323	56.8775	<.0001	0.784

Saccoidosis	1	0.14954	0.14459	1.0697	0.301	1.161
Sickle Cell Anemia	1	0.61193	1.00088	0.3738	0.5409	1.844
Lupus	1	-0.36458	0.07197	25.663	<.0001	0.694
Spinal cord injury	1	-0.77074	0.22992	11.2374	0.0008	0.463
Systemic mastocytosis	1	-0.48038	1.00016	0.2307	0.631	0.619
Turner's & Klinefelter's syndromes	1	8.37182	142.35415	0.0035	0.9531	4323.506
Thalassemia	1	-0.32367	0.21838	2.1968	0.1383	0.723
Thyrotoxicosis	0	0
Vitamin A	1	-0.92627	1.00054	0.8571	0.3546	0.396
Vitamin D	1	0.13017	0.03202	16.5203	<.0001	1.139
barb	1	-0.37835	0.27764	1.857	0.173	0.685
lithium	1	-0.06853	0.10676	0.4121	0.5209	0.934
thiaz	1	-0.23814	0.02613	83.0815	<.0001	0.788
arom	1	-0.06531	0.02987	4.7801	0.0288	0.937
convulsants	1	-0.27388	0.01458	353.094	<.0001	0.76
ssri	1	-0.26621	0.01281	431.5627	<.0001	0.766
ppi	1	-0.14587	0.01115	171.2685	<.0001	0.864
mtx	1	-0.3155	0.03784	69.5002	<.0001	0.729
csa	1	-0.23846	0.12333	3.7383	0.0532	0.788
coag	1	-0.23862	0.01546	238.0762	<.0001	0.788
white	1	-0.17305	0.1476	1.3745	0.241	0.841
black	1	0.73157	0.15022	23.7165	<.0001	2.078
other_race	1	0.19498	0.15802	1.5224	0.2173	1.215
asian	1	0.11243	0.15408	0.5325	0.4656	1.119
hispanic	1	0.08082	0.15149	0.2846	0.5937	1.084
amnative	1	-0.15619	0.17236	0.8212	0.3648	0.855
Age	1	-1.52219	0.2005	57.6407	<.0001	0.218
Age*Age	1	0.02046	0.00255	64.2584	<.0001	1.021
Age*Age*Age	1	-0.0000872	0.0000108	65.5271	<.0001	1
Age*Osteoporosis	1	-0.01277	0.00245	27.1417	<.0001	0.987

Table A27 Approach 3 MOF 365 days, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.72897	0.32683	4.9749	0.0257	2.073
Cystic Fibrosis	1	-14.41108	50920	0	0.9998	0
Congestive Heart Failure	1	0.06347	0.63806	0.0099	0.9208	1.066
Epilepsy	1	15.56033	4200	0	0.997	5724850
Parkinson's Disease	1	15.39725	6573	0	0.9981	4863388

Stroke	1	0.59113	1.02503	0.3326	0.5641	1.806
Adrenal insufficiency	1	14.68664	18043	0	0.9994	2389609
AIDS/HIV	1	-2.43472	1.02331	5.6609	0.0173	0.088
Alcoholism	1	-2.46884	1.05905	5.4345	0.0197	0.085
Alzheimers	1	15.05086	2057	0.0001	0.9942	3439592
Amyloidosis	1	-0.6469	38162	0	1	0.524
Anorexia	1	15.78787	6133	0	0.9979	7187630
Ankylosing spondylitis	1	15.73893	7597	0	0.9983	6844316
COPD	1	-0.01489	0.44751	0.0011	0.9735	0.985
Athletic amenorrhea	1	16.18802	26599	0	0.9995	10724256
Cataracts	1	0.3779	0.68779	0.3019	0.5827	1.459
Celiac	1	-14.28856	43780	0	0.9997	0
Central Adiposity	1	-0.56434	0.36924	2.3359	0.1264	0.569
Chronic metabolic acidosis	1	15.36887	7039	0	0.9983	4727326
Crohn's Disease	1	-1.24321	1.03201	1.4512	0.2283	0.288
Cushing's	1	14.94257	38833	0	0.9997	3086568
Depression	1	-0.59736	0.41933	2.0294	0.1543	0.55
DM	1	-0.22043	0.2812	0.6145	0.4331	0.802
ESRD	1	-1.25296	0.78658	2.5374	0.1112	0.286
Disorders of the Eye	1	-0.89643	0.47952	3.4948	0.0616	0.408
Falling	1	15.44987	2950	0	0.9958	5126149
Gaucher's Disease	1	14.68729	8122	0	0.9986	2391171
Glaucoma	1	15.98105	1544	0.0001	0.9917	8719261
Gout	1	-0.90835	0.74228	1.4975	0.2211	0.403
Hemophilia	1	14.70156	2213	0	0.9947	2425539
Homocystinuria	1	14.58446	19300	0	0.9994	2157489
Hyperprolactinemia	1	15.40618	27610	0	0.9996	4907051
Hyperthyroid	1	-0.13588	1.02065	0.0177	0.8941	0.873
Hypophosphatasia	1	15.7805	8974	0	0.9986	7134853
IBD	1	-1.63769	1.47912	1.2259	0.2682	0.194
Idopathic scoliosis	1	13.57227	3502	0	0.9969	784083.2
Kyphosis	1	15.17617	1346	0.0001	0.991	3898774
Liver Disease	1	15.29997	1923	0.0001	0.9937	4412563
Malabsorption	1	15.35701	11880	0	0.999	4671580
MS	1	15.95402	6839	0	0.9981	8486792
Muscular dystrophy	1	15.81172	23149	0	0.9995	7361111
Obesity	0	0
Osteoarthritis	1	-0.23343	0.34586	0.4555	0.4997	0.792
Osteoporosis	1	-805.00724	50042	0.0003	0.9872	0
Other Fx	1	-0.88563	1.02728	0.7432	0.3886	0.412

Pancreatic Disease	1	14.82909	3479	0	0.9966	2755451
Poly Rheumatica	1	14.91041	22679	0	0.9995	2988886
Premature ovarian failure	1	15.52736	20138	0	0.9994	5539175
Primary biliary cirrhosis	1	0.25527	14076	0	1	1.291
Renauld Disease	1	1.80247	1.10336	2.6687	0.1023	6.065
RA	1	-1.4604	1.03152	2.0044	0.1568	0.232
Saccoidosis	1	15.45237	6351	0	0.9981	5139011
Sickle Cell Anemia	1	13.53032	16488	0	0.9993	751869.2
Lupus	1	-2.0513	1.03314	3.9422	0.0471	0.129
Spinal cord injury	1	19.04181	29201	0	0.9995	1.86E+08
Systemic mastocytosis	1	2.23657	29084	0	0.9999	9.361
Thalassemia	1	16.00787	14992	0	0.9991	8956340
Thyrotoxicosis	0	0
Vitamin A	1	16.20872	16749	0	0.9992	10948530
Vitamin D	1	0.2098	0.7255	0.0836	0.7724	1.233
barb	1	16.34358	46462	0	0.9997	12529255
lithium	1	16.1129	6549	0	0.998	9948131
thiaz	1	-0.47551	0.37577	1.6014	0.2057	0.622
arom	1	-0.32092	1.01477	0.1	0.7518	0.725
convulsants	1	-0.44327	0.30254	2.1467	0.1429	0.642
ssri	1	0.12728	0.35912	0.1256	0.723	1.136
ppi	1	-0.01021	0.26878	0.0014	0.9697	0.99
mtx	1	15.83101	3226	0	0.9961	7504483
csa	1	14.79994	5889	0	0.998	2676285
coag	1	0.84568	0.74555	1.2866	0.2567	2.33
white	1	-16.57497	34071	0	0.9996	0
black	1	-16.10006	34071	0	0.9996	0
other_race	1	-16.72236	34071	0	0.9996	0
asian	1	-16.31158	34071	0	0.9996	0
hispanic	1	-16.69329	34071	0	0.9996	0
amnative	1	-19.15879	34071	0	0.9996	0
Age	1	-120.84015	116.12891	1.0828	0.2981	0
Age*Age	1	1.71115	1.71198	0.999	0.3175	5.535
Age*Age*Age	1	-0.00806	0.00841	0.918	0.338	0.992
Age*Osteoporosis	1	-12.31983	781.6282	0.0002	0.9874	0

Table A28 Approach 3 MOF All Available, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.34124	0.17884	3.641	0.0564	1.407
Cystic Fibrosis	1	-13.72707	14203	0	0.9992	0
Congestive Heart Failure	1	-0.24602	0.29395	0.7005	0.4026	0.782
Epilepsy	1	13.52436	482.17152	0.0008	0.9776	747399.4
Parkinson's Disease	1	13.21722	1130	0.0001	0.9907	549749.6
Stroke	1	0.66437	0.5132	1.6759	0.1955	1.943
Adrenal insufficiency	1	-3.10564	1.02818	9.1236	0.0025	0.045
AIDS/HIV	1	-1.64362	0.72275	5.1716	0.023	0.193
Alcoholism	1	-1.22986	1.01382	1.4716	0.2251	0.292
Alzheimers	1	0.4449	0.72476	0.3768	0.5393	1.56
Amyloidosis	1	0.45565	8414	0	1	1.577
Anorexia	1	13.43929	1008	0.0002	0.9894	686448.3
Ankylosing spondylitis	1	-1.39304	1.01911	1.8684	0.1717	0.248
COPD	1	-0.0315	0.23895	0.0174	0.8951	0.969
Athletic amenorrhea	1	13.15359	4845	0	0.9978	515857.3
Cataracts	1	-0.19558	0.33425	0.3424	0.5585	0.822
Celiac	1	-0.52122	10365	0	1	0.594
Central Adiposity	1	0.10909	0.23847	0.2093	0.6473	1.115
Chronic metabolic acidosis	1	12.97857	1330	0.0001	0.9922	433032.9
Crohn's Disease	1	-0.80705	0.59796	1.8216	0.1771	0.446
Cushing's	1	13.30528	5049	0	0.9979	600354.6
Depression	1	-0.42929	0.23532	3.3279	0.0681	0.651
DM	1	0.1012	0.1497	0.457	0.499	1.107
ESRD	1	-0.66716	0.4006	2.7736	0.0958	0.513
Disorders of the Eye	1	-0.51962	0.26861	3.7421	0.0531	0.595
Falling	1	0.09942	0.72033	0.019	0.8902	1.105
Gaucher's Disease	1	13.49569	1440	0.0001	0.9925	726278.2
Glaucoma	1	0.43458	0.42827	1.0297	0.3102	1.544
Gout	1	-0.22864	0.47093	0.2357	0.6273	0.796
Hemophilia	1	-0.92864	0.49067	3.5819	0.0584	0.395
Homocystinuria	1	12.99414	4283	0	0.9976	439826.9
Hyperprolactinemia	1	12.88717	3056	0	0.9966	395210.9
Hyperthyrois	1	0.39857	0.71312	0.3124	0.5762	1.49
Hypophosphatasia	1	-1.70864	1.06166	2.5902	0.1075	0.181
IBD	1	0.04517	1.20233	0.0014	0.97	1.046
Idopathic scoliosis	1	0.31327	1.04638	0.0896	0.7646	1.368

Kyphosis	1	-0.30011	0.32803	0.837	0.3602	0.741
Liver Disease	1	0.30907	0.59766	0.2674	0.6051	1.362
Malabsorption	1	13.2118	1930	0	0.9945	546779.1
MS	1	13.52665	1144	0.0001	0.9906	749118.9
Muscular dystrophy	1	-2.38724	1.03889	5.2803	0.0216	0.092
Obesity	0	0
Osteoarthritis	1	-0.03852	0.19401	0.0394	0.8426	0.962
Osteoporosis	1	-32.07708	23.60046	1.8473	0.1741	0
Other Fx	1	0.19387	0.72445	0.0716	0.789	1.214
Pancreatic Disease	1	12.72077	1021	0.0002	0.9901	334625.6
Poly Rheumatica	1	12.88873	4016	0	0.9974	395824.3
Premature ovarian failure	1	-2.80817	1.02446	7.5138	0.0061	0.06
Primary biliary cirrhosis	1	13.11218	3001	0	0.9965	494933.7
Renault Disease	1	0.0814	0.33563	0.0588	0.8084	1.085
RA	1	-0.80838	0.72107	1.2569	0.2622	0.446
Sarcoidosis	1	13.01672	1074	0.0001	0.9903	449873.3
Sickle Cell Anemia	1	12.82174	4478	0	0.9977	370180.1
Lupus	1	-1.32807	0.71832	3.4183	0.0645	0.265
Spinal cord injury	1	13.50122	4227	0	0.9975	730308.9
Systemic mastocytosis	1	10.69274	5676	0	0.9985	44034.94
Thalassemia	1	13.18354	1971	0	0.9947	531540.8
Thyrotoxicosis	0	0
Vitamin A	1	12.82543	3415	0	0.997	371546
Vitamin D	1	-0.12039	0.3686	0.1067	0.744	0.887
barb	1	14.27867	12603	0	0.9991	1589083
lithium	1	13.46455	841.52627	0.0003	0.9872	704012.4
thiaz	1	-0.39526	0.18924	4.3626	0.0367	0.674
arom	1	-0.17869	0.58249	0.0941	0.759	0.836
convulsants	1	-0.26568	0.16647	2.547	0.1105	0.767
ssri	1	-0.14595	0.17663	0.6828	0.4086	0.864
ppi	1	-0.05877	0.13499	0.1895	0.6633	0.943
mtx	1	13.13631	682.56811	0.0004	0.9846	507024.2
csa	1	13.10293	1347	0.0001	0.9922	490375.8
coag	1	-0.3649	0.23452	2.4211	0.1197	0.694
white	1	-13.52158	9372	0	0.9988	0
black	1	-12.76091	9372	0	0.9989	0
other_race	1	-13.14185	9372	0	0.9989	0
asian	1	-12.9572	9372	0	0.9989	0
hispanic	1	-13.42598	9372	0	0.9989	0
amnative	1	-15.46398	9372	0	0.9987	0

Age	1	-67.38977	82.67381	0.6644	0.415	0
Age*Age	1	0.97795	1.22451	0.6378	0.4245	2.659
Age*Age*Age	1	-0.00473	0.00604	0.6116	0.4342	0.995
Age*Osteoporosis	1	-0.48042	0.36154	1.7657	0.1839	0.619

Table A29 Approach 3 MOF 365 days, CFRI With BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	-18.62545	40798	0	0.9996	0
Cystic Fibrosis	1	-8.39431	481008	0	1	0
Congestive Heart Failure	1	14.72638	10975	0	0.9989	2486481
Epilepsy	1	13.0683	17434	0	0.9994	473687
Parkinson's Disease	1	-5.67966	1836524	0	1	0.003
Stroke	1	14.12195	32994	0	0.9997	1358573
AIDS/HIV	1	-0.80424	1015627	0	1	0.447
Alcoholism	1	20.31555	143115	0	0.9999	6.65E+08
Alzheimers	1	14.59562	174162	0	0.9999	2181707
Amyloidosis	1	-54.77667	11400943	0	1	0
Anorexia	1	-28.7664	5055631	0	1	0
Ankylosing spondylitis	1	21.85591	524217	0	1	3.10E+09
COPD	1	14.99373	11039	0	0.9989	3248590
Cataracts	1	1.83327	59699	0	1	6.254
Central Adiposity	1	13.68178	10228	0	0.9989	874822.6
Crohn's Disease	1	65.91109	65160156	0	1	4.22E+28
Depression	1	-5.30127	2.37653	4.9759	0.0257	0.005
DM	1	0.71043	1.37688	0.2662	0.6059	2.035
ESRD	1	-5.63026	2.35952	5.6939	0.017	0.004
Disorders of the Eye	1	17.36631	52774	0	0.9997	34841303
Falling	1	12.88048	18354	0	0.9994	392572.3
Gaucher's Disease	1	19.34989	1527793	0	1	2.53E+08
Glaucoma	1	2.41809	102187	0	1	11.224
Gout	1	18.45507	58113	0	0.9997	1.04E+08
Hemophilia	1	4.9776	224468	0	1	145.126
Hyperthyrois	1	15.3115	59200	0	0.9998	4463763
Hypophosphatasia	1	22.71562	479169	0	1	7.33E+09
Idopathic scoliosis	1	-12.53474	921771	0	1	0
Kyphosis	1	16.99021	8571	0	0.9984	23919559
Liver Disease	1	15.37602	18704	0	0.9993	4761223
Malabsorption	1	5.15212	1592579	0	1	172.797
MS	1	17.06398	474072	0	1	25750835

Muscular dystrophy	1	19.77781	1086252	0	1	3.89E+08
Obesity	0	0
Osteoarthritis	1	1.76326	2.07177	0.7243	0.3947	5.831
Other Fx	1	-7.69724	3.2207	5.7118	0.0169	0
Pancreatic Disease	1	18.95434	630091	0	1	1.71E+08
Premature ovarian failure	0	0
Renauld Disease	1	21.50862	35402	0	0.9995	2.19E+09
RA	1	17.21887	147804	0	0.9999	30064991
Saccoidosis	1	-74.32117	65069052	0	1	0
Lupus	1	10.42657	17636	0	0.9995	33744.35
Thalassemia	1	19.57649	1665059	0	1	3.18E+08
Thyrotoxicosis	0	0
Vitamin D	1	18.25388	43110	0	0.9997	84636809
lithium	1	23.18492	135774	0	0.9999	1.17E+10
thiaz	1	-4.48532	2.2754	3.8857	0.0487	0.011
arom	1	19.58351	280055	0	0.9999	3.20E+08
convulsants	1	-1.05558	1.32778	0.632	0.4266	0.348
ssri	1	18.83648	5006	0	0.997	1.52E+08
ppi	1	-2.31936	1.37667	2.8384	0.092	0.098
mtx	1	19.15476	267886	0	0.9999	2.08E+08
csa	1	4.16659	3005966	0	1	64.495
coag	1	17.13922	13304	0	0.999	27763026
Age	1	-0.05453	1.5625	0.0012	0.9722	0.947
Age*Age	0	0
Age*Age*Age	0	0
Age*Osteoporosis	0	0

Table A30 Approach 3 MOF, All Available, CFRI With BMD, regression coefficients

Label	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	0.78769	0.85978	0.8393	0.3596	2.198
Cystic Fibrosis	-15.61625	30424	0	0.9996	0
Congestive Heart Failure	-0.40583	1.30555	0.0966	0.7559	0.666
Epilepsy	17.39171	3740	0	0.9963	35737340
Parkinson's Disease	-1.86551	40920	0	1	0.155
Stroke	15.01715	3626	0	0.9967	3325558
AIDS/HIV	16.17611	8509	0	0.9985	10597287
Alcoholism	15.16029	10585	0	0.9989	3837330

Alzheimers	12.99491	5474	0	0.9981	440167.6
Amyloidosis	-0.83412	48312	0	1	0.434
Anorexia	-16.01437	85947	0	0.9999	0
Ankylosing spondylitis	15.64887	22401	0	0.9994	6254883
COPD	-0.22261	1.21798	0.0334	0.855	0.8
Cataracts	0.40762	1.45246	0.0788	0.779	1.503
Central Adiposity	0.42558	1.50777	0.0797	0.7777	1.53
Crohn's Disease	29.25709	80559	0	0.9997	5.08E+12
Depression	-1.21798	1.17909	1.0671	0.3016	0.296
DM	1.18236	0.82337	2.0621	0.151	3.262
ESRD	-2.075	1.03273	4.0371	0.0445	0.126
Disorders of the Eye	-2.08999	1.12829	3.4312	0.064	0.124
Falling	15.28744	4500	0	0.9973	4357623
Gaucher's Disease	15.70676	46121	0	0.9997	6627649
Glaucoma	0.47315	1.46104	0.1049	0.7461	1.605
Gout	-2.41852	1.74058	1.9307	0.1647	0.089
Hemophilia	13.75073	17843	0	0.9994	937272.7
Hyperthyrosis	15.11004	4984	0	0.9976	3649292
Hypophosphatasia	16.26318	8373	0	0.9985	11561414
Idopathic scoliosis	16.12249	9941	0	0.9987	10044009
Kyphosis	-0.25243	1.42127	0.0315	0.859	0.777
Liver Disease	-1.50738	1.34252	1.2607	0.2615	0.221
Malabsorption	14.79454	12057	0	0.999	2661878
MS	16.4326	10091	0	0.9987	13695812
Muscular dystrophy	-2.6517	1.41415	3.5161	0.0608	0.071
Obesity	0
Osteoarthritis	0.46456	1.06864	0.189	0.6638	1.591
Other Fx	-3.68769	1.27427	8.375	0.0038	0.025
Pancreatic Disease	15.78466	12143	0	0.999	7164588
Premature ovarian failure	0
Renauld Disease	1.35981	1.36564	0.9915	0.3194	3.895
RA	16.03491	4945	0	0.9974	9201758
Saccoidosis	-15.07126	78864	0	0.9998	0
Lupus	14.10817	8150	0	0.9986	1339989
Thalassemia	15.74842	30756	0	0.9996	6909597
Thyrotoxicosis	0
Vitamin D	15.20159	2900	0	0.9958	3999141
lithium	16.40757	6621	0	0.998	13357216
thiaz	-1.48729	0.76117	3.818	0.0507	0.226
arom	15.9346	6869	0	0.9981	8323521
convulsants	-0.43065	0.72984	0.3482	0.5552	0.65

ssri	0.98809	1.08069	0.836	0.3606	2.686
ppi	-0.34558	0.59786	0.3341	0.5633	0.708
mtx	15.4625	6200	0	0.998	5191323
csa	16.32858	63418	0	0.9998	12342733
coag	-0.2055	1.08895	0.0356	0.8503	0.814
Age	-0.15312	0.60787	0.0634	0.8011	0.858
Age*Age	0
Age*Age*Age	0
Age*Osteoporosis	0

Table A31 Approach 3 Vertebral Fracture 365 Days, no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.17914	0.03828	21.8942	<.0001	1.196
Cystic Fibrosis	1	9.09259	98.04542	0.0086	0.9261	8889.151
Congestive Heart Failure	1	-0.14697	0.04624	10.101	0.0015	0.863
Ehlers-Danlos	1	-1.56592	1.00102	2.4471	0.1177	0.209
Epilepsy	1	0.23446	0.14158	2.7424	0.0977	1.264
Osteogenesis Imperfecta	1	9.54645	253.01735	0.0014	0.9699	13994.88
Parkinson's Disease	1	-0.47032	0.1075	19.1424	<.0001	0.625
Stroke	1	-0.0585	0.05776	1.0257	0.3112	0.943
Adrenal insufficiency	1	-0.94405	0.44868	4.4272	0.0354	0.389
AIDS/HIV	1	-1.65297	0.41011	16.2456	<.0001	0.191
Alcoholism	1	-0.55226	0.1842	8.9889	0.0027	0.576
Alzheimers	1	-0.09296	0.05852	2.5231	0.1122	0.911
Amyloidosis	1	-0.53193	0.57776	0.8476	0.3572	0.587
Androgen insensitivity	1	9.50966	332.77993	0.0008	0.9772	13489.39
Anorexia	1	-0.08825	0.1596	0.3058	0.5803	0.916
Ankylosing spondylitis	1	-0.44139	0.15921	7.6856	0.0056	0.643
COPD	1	-0.37249	0.03324	125.6093	<.0001	0.689
Athletic amenorrhea	1	0.29903	1.00017	0.0894	0.765	1.349
Cataracts	1	0.0613	0.08011	0.5856	0.4441	1.063
Celiac	1	-0.59871	0.46495	1.6581	0.1979	0.55
Central Adiposity	1	0.08827	0.06566	1.8075	0.1788	1.092
Chronic metabolic acidosis	1	-0.01511	0.16329	0.0086	0.9263	0.985
Crohn's Disease	1	-0.27165	0.07986	11.5707	0.0007	0.762
Cushing's	1	-0.91916	0.37934	5.8712	0.0154	0.399
Depression	1	-0.11346	0.04506	6.3391	0.0118	0.893
DM	1	0.02819	0.03312	0.7243	0.3947	1.029
ESRD	1	-0.37456	0.15586	5.7757	0.0162	0.688

Disorders of the Eye	1	-0.05251	0.0609	0.7434	0.3886	0.949
Falling	1	-0.36726	0.07039	27.2249	<.0001	0.693
Gaucher's Disease	1	-0.48831	0.50031	0.9526	0.3291	0.614
Glaucoma	1	0.08058	0.09859	0.668	0.4138	1.084
Gout	1	0.11942	0.09282	1.6553	0.1982	1.127
Glycogen storage diseases	1	9.44522	206.91843	0.0021	0.9636	12647.6
Hemochromatosis	1	-0.64243	0.57779	1.2363	0.2662	0.526
Hemophilia	1	-0.26063	0.11268	5.3498	0.0207	0.771
Homocystinuria	1	0.67761	0.70745	0.9174	0.3382	1.969
Hyperprolactinemia	1	8.97511	110.34085	0.0066	0.9352	7903.919
Hyperparathyroidism	1	0.12879	0.14601	0.7781	0.3777	1.137
Hyperthyroid	1	0.01063	0.11278	0.0089	0.9249	1.011
Hypophosphatasia	1	-0.3935	0.21294	3.4148	0.0646	0.675
IBD	1	-0.04863	0.15941	0.093	0.7603	0.953
Idopathic scoliosis	1	-0.3737	0.07957	22.0566	<.0001	0.688
Kyphosis	1	-0.09953	0.05076	3.8446	0.0499	0.905
Liver Disease	1	-0.25046	0.07462	11.2666	0.0008	0.778
Malabsorption	1	0.42081	0.3545	1.4092	0.2352	1.523
Marfan syndrome	1	9.57792	259.81308	0.0014	0.9706	14442.38
MS	1	0.04032	0.2895	0.0194	0.8892	1.041
Muscular dystrophy	1	9.25403	99.05132	0.0087	0.9256	10446.6
Obesity	0	0
Osteoarthritis	1	0.067	0.03447	3.7782	0.0519	1.069
Osteoporosis	1	-1.63254	0.39753	16.8652	<.0001	0.195
Other Fx	1	-0.27824	0.06227	19.9653	<.0001	0.757
Panhypopituitarism	1	9.08085	155.99908	0.0034	0.9536	8785.388
Pancreatic Disease	1	-0.20563	0.11575	3.1557	0.0757	0.814
Poly Rheumatica	1	-0.33269	0.1027	10.4933	0.0012	0.717
Porphyria	1	-0.27004	1.0006	0.0728	0.7873	0.763
Premature ovarian failure	1	8.53209	95.70322	0.0079	0.929	5075.031
Primary biliary cirrhosis	1	-0.45455	0.32484	1.9581	0.1617	0.635
Riley-Day	1	9.95695	449.82625	0.0005	0.9823	21098.44
Reynolds Disease	1	0.05625	0.06735	0.6974	0.4037	1.058
RA	1	-0.26745	0.06729	15.7954	<.0001	0.765
Sacroiliitis	1	0.16796	0.31694	0.2808	0.5961	1.183
Sickle Cell Anemia	1	-0.7624	1.00339	0.5773	0.4474	0.467
Lupus	1	-0.67574	0.12814	27.8087	<.0001	0.509
Spinal cord injury	1	-1.48676	0.33557	19.6297	<.0001	0.226
Systemic mastocytosis	1	8.83735	207.18547	0.0018	0.966	6886.695
Turner's & Klinefelter's syndromes	1	9.42311	629.5518	0.0002	0.9881	12371

Thalassemia	1	-0.1946	0.5004	0.1512	0.6974	0.823
Thyrotoxicosis	0	0
Vitamin A	1	8.80783	277.096	0.001	0.9746	6686.394
Vitamin D	1	0.25611	0.0653	15.3812	<.0001	1.292
barb	1	-0.92564	0.44829	4.2635	0.0389	0.396
lithium	1	0.57921	0.3345	2.9984	0.0833	1.785
thiaz	1	-0.14228	0.06739	4.4571	0.0348	0.867
arom	1	0.07911	0.07266	1.1856	0.2762	1.082
convulsants	1	-0.41943	0.03118	180.9537	<.0001	0.657
ssri	1	-0.23614	0.02945	64.2833	<.0001	0.79
ppi	1	-0.21389	0.02538	71.0389	<.0001	0.807
mtx	1	-0.45177	0.0785	33.121	<.0001	0.636
csa	1	-0.24411	0.2779	0.7716	0.3797	0.783
coag	1	-0.27675	0.03459	64.0316	<.0001	0.758
white	1	-0.15118	0.31662	0.228	0.633	0.86
black	1	0.88838	0.32427	7.5055	0.0062	2.431
other_race	1	0.2428	0.34444	0.4969	0.4809	1.275
asian	1	-0.26223	0.32885	0.6359	0.4252	0.769
hispanic	1	-0.0174	0.32559	0.0029	0.9574	0.983
amnative	1	-0.05719	0.38163	0.0225	0.8809	0.944
Age	1	-2.45921	0.47394	26.9237	<.0001	0.086
Age*Age	1	0.03282	0.00604	29.4877	<.0001	1.033
Age*Age*Age	1	-0.0001413	0.0000256	30.5623	<.0001	1
Age*Osteoporosis	1	-0.01481	0.00504	8.6481	0.0033	0.985

Table A32 Approach 3 Vertebral Fracture All Available, no restriction, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.24011	0.02072	134.2844	<.0001	1.271
Cystic Fibrosis	1	8.14466	36.19567	0.0506	0.822	3444.948
Congestive Heart Failure	1	-0.12191	0.02835	18.4901	<.0001	0.885
Ehlers-Danlos	1	-1.42861	0.7074	4.0785	0.0434	0.24
Epilepsy	1	0.07463	0.08542	0.7634	0.3823	1.077
Osteogenesis Imperfecta	1	8.63225	102.07437	0.0072	0.9326	5609.673
Parkinson's Disease	1	-0.35485	0.06941	26.1394	<.0001	0.701
Stroke	1	-0.02714	0.03487	0.6057	0.4364	0.973
Adrenal insufficiency	1	-0.6962	0.28934	5.7895	0.0161	0.498
AIDS/HIV	1	-1.07115	0.3343	10.2664	0.0014	0.343
Alcoholism	1	-0.56668	0.11002	26.5312	<.0001	0.567

Alzheimers	1	-0.00361	0.03743	0.0093	0.9232	0.996
Amyloidosis	1	-0.27787	0.40844	0.4628	0.4963	0.757
Androgen insensitivity	1	8.38833	112.52141	0.0056	0.9406	4395.452
Anorexia	1	-0.16671	0.09666	2.975	0.0846	0.846
Ankylosing spondylitis	1	-0.43251	0.09954	18.8811	<.0001	0.649
COPD	1	-0.35358	0.01988	316.4659	<.0001	0.702
Athletic amenorrhea	1	0.24369	0.57747	0.1781	0.673	1.276
Cataracts	1	0.11153	0.04802	5.3937	0.0202	1.118
Celiac	1	0.13651	0.27178	0.2523	0.6155	1.146
Central Adiposity	1	0.14255	0.04167	11.7059	0.0006	1.153
Chronic metabolic acidosis	1	0.00273	0.10714	0.0007	0.9796	1.003
Crohn's Disease	1	-0.11073	0.05104	4.7066	0.03	0.895
Cushing's	1	-0.51781	0.28922	3.2053	0.0734	0.596
Depression	1	-0.13918	0.02738	25.8333	<.0001	0.87
DM	1	0.03258	0.01942	2.8148	0.0934	1.033
ESRD	1	-0.38879	0.09799	15.7423	<.0001	0.678
Disorders of the Eye	1	-0.03941	0.03653	1.1641	0.2806	0.961
Falling	1	-0.22647	0.04468	25.6885	<.0001	0.797
Gaucher's Disease	1	0.03265	0.37812	0.0075	0.9312	1.033
Glaucoma	1	0.11708	0.05983	3.8294	0.0504	1.124
Gout	1	0.15323	0.05755	7.0895	0.0078	1.166
Glycogen storage diseases	1	8.35405	70.90078	0.0139	0.9062	4247.354
Hemochromatosis	1	-0.43725	0.50021	0.7641	0.382	0.646
Hemophilia	1	-0.18001	0.0695	6.7084	0.0096	0.835
Homocystinuria	1	0.24505	0.33354	0.5398	0.4625	1.278
Hyperprolactinemia	1	7.98169	43.36403	0.0339	0.854	2926.87
Hyperparathyroidism	1	0.11656	0.08835	1.7405	0.1871	1.124
Hyperthyroid	1	0.02735	0.06647	0.1693	0.6808	1.028
Hypophosphatasia	1	-0.04129	0.16904	0.0597	0.807	0.96
IBD	1	-0.09951	0.10205	0.9508	0.3295	0.905
Idopathic scoliosis	1	-0.27118	0.05096	28.3153	<.0001	0.762
Kyphosis	1	-0.01824	0.03123	0.3413	0.5591	0.982
Liver Disease	1	-0.16854	0.04663	13.0653	0.0003	0.845
Malabsorption	1	-0.11848	0.17468	0.4601	0.4976	0.888
Marfan syndrome	1	8.34046	91.86795	0.0082	0.9277	4190.001
MS	1	-0.05203	0.1696	0.0941	0.759	0.949
Muscular dystrophy	1	-0.27696	0.50092	0.3057	0.5803	0.758
Obesity	0	0
Osteoarthritis	1	0.05668	0.02022	7.853	0.0051	1.058
Osteoporosis	1	-1.26232	0.24623	26.2812	<.0001	0.283
Other Fx	1	-0.33519	0.03707	81.7789	<.0001	0.715

Panhypopituitarism	1	-0.0976	1.00055	0.0095	0.9223	0.907
Pancreatic Disease	1	-0.13976	0.07181	3.7878	0.0516	0.87
Poly Rheumatica	1	-0.31607	0.0621	25.9017	<.0001	0.729
Porphyria	1	-0.38924	0.57763	0.4541	0.5004	0.678
Premature ovarian failure	1	0.40599	1.00016	0.1648	0.6848	1.501
Primary biliary cirrhosis	1	-0.26752	0.22835	1.3725	0.2414	0.765
Riley-Day	1	9.02865	281.20821	0.001	0.9744	8338.634
Renauld Disease	1	-0.00471	0.04176	0.0127	0.9103	0.995
RA	1	-0.33196	0.0401	68.5198	<.0001	0.718
Saccoidosis	1	0.16217	0.18934	0.7335	0.3917	1.176
Sickle Cell Anemia	1	0.06021	1.00164	0.0036	0.9521	1.062
Lupus	1	-0.48158	0.08712	30.5578	<.0001	0.618
Spinal cord injury	1	-1.15471	0.24341	22.5038	<.0001	0.315
Systemic mastocytosis	1	7.88444	85.75752	0.0085	0.9267	2655.635
Turner's & Klinefelter's syndromes	1	8.45738	196.53977	0.0019	0.9657	4709.689
Thalassemia	1	-0.53934	0.25844	4.355	0.0369	0.583
Thyrotoxicosis	0	0
Vitamin A	1	-1.50791	1.00094	2.2695	0.1319	0.221
Vitamin D	1	0.18265	0.04314	17.9241	<.0001	1.2
barb	1	-0.54481	0.33374	2.6648	0.1026	0.58
lithium	1	0.05137	0.14837	0.1199	0.7292	1.053
thiaz	1	-0.15506	0.03613	18.4224	<.0001	0.856
arom	1	0.03161	0.04154	0.5791	0.4466	1.032
convulsants	1	-0.31196	0.01896	270.6494	<.0001	0.732
ssri	1	-0.22969	0.01704	181.701	<.0001	0.795
ppi	1	-0.22011	0.01456	228.6088	<.0001	0.802
mtx	1	-0.41373	0.04659	78.8497	<.0001	0.661
csa	1	-0.3457	0.15462	4.9991	0.0254	0.708
coag	1	-0.29386	0.02007	214.399	<.0001	0.745
white	1	-0.17621	0.2002	0.7747	0.3788	0.838
black	1	0.73931	0.20382	13.1575	0.0003	2.094
other_race	1	0.01476	0.21195	0.0049	0.9445	1.015
asian	1	-0.13575	0.20703	0.4299	0.512	0.873
hispanic	1	-0.00717	0.20494	0.0012	0.9721	0.993
amnative	1	-0.11834	0.234	0.2557	0.6131	0.888
Age	1	-1.6171	0.27519	34.5314	<.0001	0.198
Age*Age	1	0.02208	0.00351	39.5647	<.0001	1.022
Age*Age*Age	1	-0.000096	0.0000149	41.8096	<.0001	1
Age*Osteoporosis	1	-0.00962	0.00311	9.5457	0.002	0.99

Table A33 Approach 3 Vertebral Fracture 365 Days, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.79975	0.43348	3.4038	0.065	2.225
Cystic Fibrosis	1	-30.63815	92868	0	0.9997	0
Congestive Heart Failure	1	0.02981	0.79818	0.0014	0.9702	1.03
Epilepsy	1	16.03403	6119	0	0.9979	9193681
Parkinson's Disease	1	15.47026	9523	0	0.9987	5231757
Stroke	1	0.01473	1.04008	0.0002	0.9887	1.015
Adrenal insufficiency	1	15.25963	28242	0	0.9996	4238130
AIDS/HIV	1	15.31237	10048	0	0.9988	4467650
Alcoholism	1	-2.88182	1.11378	6.6948	0.0097	0.056
Alzheimers	1	14.98305	2553	0	0.9953	3214069
Amyloidosis	1	0.2712	52805	0	1	1.312
Anorexia	1	15.91434	8526	0	0.9985	8156615
Ankylosing spondylitis	1	16.06285	10694	0	0.9988	9462494
COPD	1	-0.2104	0.55665	0.1429	0.7055	0.81
Athletic amenorrhea	1	16.21254	41883	0	0.9997	10990435
Cataracts	1	1.13584	1.18305	0.9218	0.337	3.114
Celiac	1	-29.10185	80019	0	0.9997	0
Central Adiposity	1	-0.46251	0.50417	0.8416	0.359	0.63
Chronic metabolic acidosis	1	16.30068	10271	0	0.9987	12003170
Crohn's Disease	1	-1.67533	1.06517	2.4738	0.1158	0.187
Cushing's	1	16.04969	51993	0	0.9998	9338807
Depression	1	-0.78342	0.50852	2.3734	0.1234	0.457
DM	1	-0.29034	0.37145	0.6109	0.4344	0.748
ESRD	1	-0.65686	1.13087	0.3374	0.5613	0.518
Disorders of the Eye	1	-0.8232	0.64138	1.6473	0.1993	0.439
Falling	1	15.49304	3689	0	0.9966	5352297
Gaucher's Disease	1	14.99006	12553	0	0.999	3236683
Glaucoma	1	16.0154	2173	0.0001	0.9941	9024007
Gout	1	-0.86614	1.03822	0.696	0.4041	0.421
Hemophilia	1	15.44611	2707	0	0.9954	5106945
Homocystinuria	1	15.40877	33016	0	0.9996	4919741
Hyperprolactinemia	1	15.81201	39038	0	0.9997	7363272
Hyperthyroid	1	-0.71269	1.04803	0.4624	0.4965	0.49
Hypophosphatasia	1	16.02008	14887	0	0.9991	9066353
IBD	1	-1.56275	1.54329	1.0254	0.3112	0.21
Idopathic scoliosis	1	13.56312	5660	0	0.9981	776940.3

Kyphosis	1	15.21857	1840	0.0001	0.9934	4067610
Liver Disease	1	15.51007	2802	0	0.9956	5444226
Malabsorption	1	14.88152	14654	0	0.9992	2903775
MS	1	16.20915	8757	0	0.9985	10953320
Muscular dystrophy	1	16.17629	32066	0	0.9996	10599247
Obesity	0	0
Osteoarthritis	1	0.35137	0.55523	0.4005	0.5268	1.421
Osteoporosis	1	-850.23432	58432	0.0002	0.9884	0
Other Fx	1	15.50041	4182	0	0.997	5391908
Pancreatic Disease	1	16.35724	6812	0	0.9981	12701571
Poly Rheumatica	1	15.7202	30994	0	0.9996	6717302
Premature ovarian failure	1	15.68312	32312	0	0.9996	6472794
Primary biliary cirrhosis	1	0.5312	20960	0	1	1.701
Renault Disease	1	0.93922	1.14733	0.6701	0.413	2.558
RA	1	-1.85513	1.05933	3.0668	0.0799	0.156
Sacroiliitis	1	15.85688	9134	0	0.9986	7701112
Sickle Cell Anemia	1	13.7788	24475	0	0.9996	963956
Lupus	1	-2.5625	1.04406	6.0239	0.0141	0.077
Spinal cord injury	1	2.93232	41856	0	0.9999	18.771
Systemic mastocytosis	1	1.83335	35028	0	1	6.255
Thalassemia	1	16.14933	22467	0	0.9994	10317260
Thyrotoxicosis	0	0
Vitamin A	1	16.20928	29695	0	0.9996	10954733
Vitamin D	1	0.28887	1.02105	0.08	0.7772	1.335
barb	1	16.30723	51875	0	0.9997	12082021
lithium	1	16.29604	8250	0	0.9984	11947609
thiaz	1	0.1278	0.62018	0.0425	0.8367	1.136
arom	1	15.67845	4016	0	0.9969	6442672
convulsants	1	-0.55846	0.38338	2.1219	0.1452	0.572
ssri	1	-0.06866	0.43996	0.0244	0.876	0.934
ppi	1	-0.37388	0.33666	1.2333	0.2668	0.688
mtx	1	16.35972	4658	0	0.9972	12733129
csa	1	15.31082	10306	0	0.9988	4460716
coag	1	0.24639	0.76989	0.1024	0.7489	1.279
white	1	-16.38061	41712	0	0.9997	0
black	1	-16.07785	41712	0	0.9997	0
other_race	1	-16.69215	41712	0	0.9997	0
asian	1	-16.32919	41712	0	0.9997	0
hispanic	1	-16.28262	41712	0	0.9997	0
amnative	1	0.36688	46192	0	1	1.443

Age	1	-102.39872	158.88923	0.4153	0.5193	0
Age*Age	1	1.43345	2.34535	0.3736	0.5411	4.193
Age*Age*Age	1	-0.00667	0.01153	0.3343	0.5631	0.993
Age*Osteoporosis	1	-13.01796	912.54594	0.0002	0.9886	0

Table A34 Approach 3 Vertebral Fracture All Available, CFRI Without BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	0.50515	0.22214	5.1709	0.023	1.657
Cystic Fibrosis	1	-14.41815	19750	0	0.9994	0
Congestive Heart Failure	1	-0.36744	0.35553	1.0681	0.3014	0.693
Epilepsy	1	14.13946	680.36975	0.0004	0.9834	1382580
Parkinson's Disease	1	13.23065	1563	0.0001	0.9932	557184.5
Stroke	1	0.0606	0.52114	0.0135	0.9074	1.062
Adrenal insufficiency	1	-3.60292	1.04637	11.856	0.0006	0.027
AIDS/HIV	1	-1.41497	1.02369	1.9105	0.1669	0.243
Alcoholism	1	-1.5965	1.03248	2.391	0.122	0.203
Alzheimers	1	-0.11219	0.7363	0.0232	0.8789	0.894
Amyloidosis	1	0.81559	11637	0	0.9999	2.261
Anorexia	1	13.46841	1434	0.0001	0.9925	706731.6
Ankylosing spondylitis	1	-2.05399	1.03044	3.9733	0.0462	0.128
COPD	1	-0.1305	0.29913	0.1903	0.6626	0.878
Athletic amenorrhea	1	13.39539	7084	0	0.9985	656965.8
Cataracts	1	0.25275	0.46814	0.2915	0.5893	1.288
Celiac	1	-0.64031	14824	0	1	0.527
Central Adiposity	1	0.01296	0.31574	0.0017	0.9672	1.013
Chronic metabolic acidosis	1	13.07401	1725	0.0001	0.994	476400.8
Crohn's Disease	1	-1.36465	0.61375	4.9438	0.0262	0.255
Cushing's	1	13.60222	6897	0	0.9984	807921
Depression	1	-0.18709	0.33243	0.3167	0.5736	0.829
DM	1	0.14596	0.19627	0.553	0.4571	1.157
ESRD	1	-0.41799	0.56837	0.5408	0.4621	0.658
Disorders of the Eye	1	-0.54715	0.34853	2.4646	0.1164	0.579
Falling	1	0.09401	1.01833	0.0085	0.9264	1.099
Gaucher's Disease	1	13.0736	2063	0	0.9949	476203.7

Glaucoma	1	0.10553	0.53534	0.0389	0.8437	1.111
Gout	1	-0.49598	0.54283	0.8348	0.3609	0.609
Hemophilia	1	-1.16462	0.56622	4.2306	0.0397	0.312
Homocystinuria	1	13.33371	6495	0	0.9984	617670.6
Hyperprolactinemia	1	12.97114	4205	0	0.9975	429825.8
Hyperthyrois	1	-0.2201	0.71767	0.0941	0.7591	0.802
Hypophosphatasia	1	13.44478	2319	0	0.9954	690228.4
IBD	1	0.25439	1.25329	0.0412	0.8392	1.29
Idopathic scoliosis	1	-0.52376	1.09561	0.2285	0.6326	0.592
Kyphosis	1	0.2033	0.50713	0.1607	0.6885	1.225
Liver Disease	1	0.16859	0.73081	0.0532	0.8176	1.184
Malabsorption	1	13.2355	2502	0	0.9958	559892.4
MS	1	13.51432	1525	0.0001	0.9929	739936.8
Muscular dystrophy	1	-2.86495	1.05862	7.3241	0.0068	0.057
Obseity	0	0
Osteoarthritis	1	-0.03414	0.2554	0.0179	0.8937	0.966
Osteoporosis	1	-31.32001	23.48582	1.7784	0.1823	0
Other Fx	1	0.46073	1.02345	0.2027	0.6526	1.585
Pancreatic Disease	1	12.85983	1430	0.0001	0.9928	384549.7
Poly Rheumatica	1	13.02795	5705	0	0.9982	454952.6
Premature ovarian failure	1	13.56857	4534	0	0.9976	781187
Primary biliary cirrhosis	1	13.25328	4351	0	0.9976	569938
Renauld Disease	1	0.04158	0.42996	0.0094	0.923	1.042
RA	1	-0.62849	1.01569	0.3829	0.5361	0.533
Saccoidosis	1	13.2138	1429	0.0001	0.9926	547874.3
Sickle Cell Anemia	1	12.87381	6171	0	0.9983	389963
Lupus	1	-1.81965	0.7284	6.2407	0.0125	0.162
Spinal cord injury	1	14.16103	5700	0	0.998	1412718
Systemic mastocytosis	1	10.00681	7071	0	0.9989	22177.03
Thalassemia	1	13.30288	2675	0	0.996	598919.1
Thyrotoxicosis	0	0
Vitamin A	1	13.09577	4712	0	0.9978	486878.3
Vitamin D	1	-0.35756	0.43364	0.6799	0.4096	0.699
barb	1	14.09933	16472	0	0.9993	1328192
lithium	1	13.40253	1085	0.0002	0.9901	661676.1
thiaz	1	-0.02316	0.28326	0.0067	0.9348	0.977
arom	1	-0.32193	0.71416	0.2032	0.6521	0.725
convulsants	1	-0.27188	0.21555	1.5909	0.2072	0.762
ssri	1	-0.18118	0.22935	0.624	0.4296	0.834
ppi	1	-0.14871	0.17473	0.7244	0.3947	0.862

mtx	1	13.26722	947.48806	0.0002	0.9888	577935.6
csa	1	13.13592	1868	0	0.9944	506823.1
coag	1	-0.614	0.28331	4.6969	0.0302	0.541
white	1	-13.32041	12981	0	0.9992	0
black	1	-13.00333	12981	0	0.9992	0
other_race	1	-13.46292	12981	0	0.9992	0
asian	1	-13.40495	12981	0	0.9992	0
hispanic	1	-13.48089	12981	0	0.9992	0
amnative	1	0.38176	13282	0	1	1.465
Age	1	-136.63286	118.77701	1.3233	0.25	0
Age*Age	1	1.9988	1.76294	1.2855	0.2569	7.38
Age*Age*Age	1	-0.00974	0.00872	1.2488	0.2638	0.99
Age*Osteoporosis	1	-0.45465	0.35961	1.5984	0.2061	0.635

Table A35 Approach 3 Vertebral Fracture 365 days, CFRI With BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	-18.53473	31721	0	0.9995	0
Cystic Fibrosis	1	1.58472	14332319	0	1	4.878
Congestive Heart Failure	1	19.6868	99815	0	0.9998	3.55E+08
Epilepsy	1	2.80638	141349	0	1	16.55
Parkinson's Disease	1	-11.90702	5447458	0	1	0
Stroke	1	1.237	107136	0	1	3.445
AIDS/HIV	1	-16.19229	756745	0	1	0
Alcoholism	1	20.48625	108957	0	0.9998	7.89E+08
Alzheimers	1	1.06987	190427	0	1	2.915
Amyloidosis	1	-45.49631	86947041	0	1	0
Anorexia	1	-62.06101	16962722	0	1	0
Ankylosing spondylitis	1	23.5922	682069	0	1	1.76E+10
COPD	1	17.68133	32307	0	0.9996	47742262
Cataracts	1	1.61924	55529	0	1	5.049
Central Adiposity	1	0.2491	32031	0	1	1.283
Crohn's Disease	1	74.67985	203513342	0	1	2.71E+32
Depression	1	-21.0892	5458	0	0.9969	0
DM	1	0.55534	1.29761	0.1832	0.6687	1.743
ESRD	1	-20.95346	5458	0	0.9969	0
Disorders of the Eye	1	17.54286	39793	0	0.9996	41568943
Falling	1	1.70748	146480	0	1	5.515

Gaucher's Disease	1	5.51945	2804446	0	1	249.498
Glaucoma	1	3.81352	121900	0	1	45.309
Gout	1	16.56229	37140	0	0.9996	15592265
Hemophilia	1	0.76951	207022	0	1	2.159
Hyperthyrois	1	2.99441	250956	0	1	19.974
Hypophosphatasia	1	25.47689	1418950	0	1	1.16E+11
Idopathic scoliosis	1	-34.92226	253366	0	0.9999	0
Kyphosis	1	18.85663	21846	0	0.9993	1.55E+08
Liver Disease	1	21.43191	299070	0	0.9999	2.03E+09
Malabsorption	1	-27.57887	5451409	0	1	0
MS	1	2.98279	656804	0	1	19.743
Muscular dystrophy	1	5.49478	1740904	0	1	243.419
Obseity	0	0
Osteoarthritis	1	34.99556	9846	0	0.9972	1.58E+15
Other Fx	1	1.481	372352	0	1	4.397
Pancreatic Disease	1	4.89266	1102600	0	1	133.307
Premature ovarian failure	0	0
Renauld Disease	1	38.04764	40708	0	0.9993	3.34E+16
RA	1	3.44589	241518	0	1	31.371
Saccoidosis	1	-85.64362	203370461	0	1	0
Lupus	1	2.34432	573318	0	1	10.426
Thalassemia	1	5.81667	2708899	0	1	335.853
Thyrotoxicosis	0	0
Vitamin D	1	16.30444	19670	0	0.9993	12048414
lithium	1	22.40185	108947	0	0.9998	5.36E+09
thiaz	1	-20.24671	5458	0	0.997	0
arom	1	5.01584	467642	0	1	150.783
convulsants	1	-0.56239	1.34623	0.1745	0.6761	0.57
ssri	1	35.37991	8557	0	0.9967	2.32E+15
ppi	1	-1.72701	1.29565	1.7767	0.1826	0.178
mtx	1	4.99487	471933	0	1	147.654
csa	1	-10.7067	6167317	0	1	0
coag	1	17.87794	21105	0	0.9993	58115268
Age	1	-0.36655	1.41501	0.0671	0.7956	0.693
Age*Age	0	0
Age*Age*Age	0	0
Age*Osteoporosis	0	0

Table A36 Approach 3 Vertebral Fracture All Available, CFRI With BMD, regression coefficients

Label	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Alendronate	1	1.2293	0.82864	2.2008	0.1379	3.419
Cystic Fibrosis	1	-33.19787	80625	0	0.9997	0
Congestive Heart Failure	1	-0.75775	1.41677	0.2861	0.5928	0.469
Epilepsy	1	18.62315	3604	0	0.9959	1.22E+08
Parkinson's Disease	1	-2.85721	38839	0	0.9999	0.057
Stroke	1	14.86032	3584	0	0.9967	2842868
AIDS/HIV	1	12.81816	9194	0	0.9989	368855.5
Alcoholism	1	14.15385	9864	0	0.9989	1402619
Alzheimers	1	11.75539	5403	0	0.9983	127438.1
Amyloidosis	1	-2.21341	44416	0	1	0.109
Anorexia	1	-16.99787	72364	0	0.9998	0
Ankylosing spondylitis	1	15.27267	19846	0	0.9994	4293757
COPD	1	-0.88796	1.18928	0.5575	0.4553	0.411
Cataracts	1	1.06603	1.64351	0.4207	0.5166	2.904
Central Adiposity	1	0.59233	1.77288	0.1116	0.7383	1.808
Crohn's Disease	1	27.14337	60510	0	0.9996	6.14E+11
Depression	1	-1.24775	1.27837	0.9527	0.329	0.287
DM	1	1.27133	1.03541	1.5076	0.2195	3.566
ESRD	1	-0.63197	1.52439	0.1719	0.6785	0.532
Disorders of the Eye	1	-2.54422	1.23342	4.2549	0.0391	0.079
Falling	1	15.98108	5369	0	0.9976	8719576
Gaucher's Disease	1	15.37863	42731	0	0.9997	4773673
Glaucoma	1	0.58455	1.52336	0.1472	0.7012	1.794
Gout	1	-4.23213	2.00876	4.4388	0.0351	0.015
Hemophilia	1	13.84087	17528	0	0.9994	1025684
Hyperthyroid	1	14.92506	6874	0	0.9983	3032986
Hypophosphatasia	1	14.00401	8040	0	0.9986	1207434
Idopathic scoliosis	1	17.11756	9528	0	0.9986	27168306
Kyphosis	1	-1.04056	1.60221	0.4218	0.516	0.353
Liver Disease	1	14.66245	4173	0	0.9972	2332502
Malabsorption	1	13.04945	13059	0	0.9992	464838.9
MS	1	16.3843	9530	0	0.9986	13050020
Muscular dystrophy	1	-2.35726	1.67665	1.9767	0.1597	0.095
Obesity	0	0
Osteoarthritis	1	1.63476	1.63965	0.994	0.3188	5.128
Other Fx	1	13.99555	7007	0	0.9984	1197270
Pancreatic Disease	1	15.96706	11800	0	0.9989	8598167

Premature ovarian failure	0	0
Renauld Disease	1	0.8523	1.68516	0.2558	0.613	2.345
RA	1	15.72298	4775	0	0.9974	6736021
Saccoidosis	1	-12.79544	58326	0	0.9998	0
Lupus	1	15.32885	13991	0	0.9991	4541891
Thalassemia	1	15.69047	28512	0	0.9996	6520584
Thyrotoxicosis	0	0
Vitamin D	1	15.53802	2393	0	0.9948	5598582
lithium	1	16.32624	6361	0	0.998	12313952
thiaz	1	-0.74402	1.01038	0.5423	0.4615	0.475
arom	1	16.04261	6352	0	0.998	9272930
convulsants	1	-0.01631	0.86452	0.0004	0.9849	0.984
ssri	1	0.7949	1.10136	0.5209	0.4705	2.214
ppi	1	-0.674	0.66947	1.0136	0.314	0.51
mtx	1	15.7304	6043	0	0.9979	6786190
csa	1	15.79084	63906	0	0.9998	7208960
coag	1	-0.42669	1.11556	0.1463	0.7021	0.653
Age	1	-0.3461	0.6434	0.2894	0.5906	0.707
Age*Age	0	0
Age*Age*Age	0	0
Age*Osteoporosis	0	0

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