Comparative effectiveness of alendronate and risedronate in reducing the risk of hip fracture

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The authors declare the following disclosures:

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# List of abbreviations

ATC Anatomic Therapeutic Chemical

CYCLOPS Cyclic coordinate descent for logistic, Poisson and survival analysis

MedDRA Medical Dictionary for Regulatory Activities

OHDSI Observational Health Data Sciences and Informatics

OMOP Observational Medical Outcomes Partnership

PRR Proportional Reporting Ratio

PS Propensity Scores

BP Bisphosphonate

SERM Selective Estrogen Receptor Modulator

# Abstract

This study aims to compare the effectiveness in reducing the risk of hip fracture between alendronate(BP) and raloxifene(SERM) and to evaluate the adverse reactions of both medications. In this study, we will analyze data from a distributed network using the OHDSI CohortMethod package.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | 23 March 2017 | Yeesuk Kim | Initial draft |

# Milestones

|  |  |
| --- | --- |
| Milestone | Planned / Estimated Date |
| Start of analysis |  |
| End of analysis |  |
| Posting of results |  |
| Submission of manuscript |  |

# Rationale and Background

Osteoporosis is characterized by decreased bone mass and deterioration of bone tissue, resulting in reduced bone strength and increased fracture risk. Approved therapies for osteoporosis include bisphosphonates(BP), calcitonin, raloxifene(SERM), and teriparatide. Among them, alendronate and raloxifene are the most popular osteoporosis medication and a burden of prescription are performed annually.

A definitive study comparing the effectiveness of alendronate and raloxifene was limited. The EVA trial (Evista Alendronate Comparison trial) was designed to be the first double-blind, randomized comparison trial to compare osteoporosis therapies head-to-head for fracture risk reduction among 3,000 postmenopausal women. However, the study enrollment was stopped early due to difficulties with timely recruitment of treatment women. Foster et al. conducted a retrospective database study comparing the fracture rate and breast cancer rate between alendronate and raloxifene groups. However, the adverse outcomes associated with alendronate such as atypical fracture, esophageal cancer, osteonecrosis of jaw, and adverse outcome associated with raloxifene such as increased risk of venous thromboembolic event were not investigated.

Therefore, we thought that the evaluation of hip fracture rate in patients of taking osteoporosis medications (alendronate or raloxifene) and of adverse outcomes in using osteoporotic medication are necessary with a large population study.

In the study described here we will utilize the OHDSI CohortMethod package to compare the effectiveness in reducing the risk of hip fracture between alendronate and risedronate, and to evaluate the adverse reactions of both medications.

## Research Questions

**Alendronate** **and Raloxifene**

Alendronate and raloxifene are anti-resorptive therapies approved for the prevention and treatment of postmenopausal osteoporosis. Alendronate is incorporated into the bone matrix and acts to inhibit osteoclasts. Raloxifene binds to estrogen receptors and appears to act as an estrogen agonist in bone. Both drugs reduce bone turnover and increase bone mineral density, though alendronate has a stronger effect on these domains than raloxifene.

Primary hypothesis

* The study’s primary hypothesis is that there is no difference in incidence rate of osteoporotic hip fracture between alendronate and raloxifene.

Secondary hypothesis

* The study’s secondary hypothesis is that there is no difference in rate of adverse outcomes between alendronate and raloxifene.

## Objectives

Primary objective

* Assess the adjusted hazard ratio for use of alendronate vs raloxifene on risk of osteoporotic hip fracture.

Secondary objective

* Assess the adjusted hazard ratio for use of alendronate vs raloxifene on risk of adverse outcome.

# Research methods

## Study Design

### Overview

This study will be a retrospective, observational, new-user cohort study. By ‘retrospective’ we mean the study will use data already collected at the start of the study. By ‘observational’ we mean no intervention will take place in the course of this study. By ‘new-user’ we mean we will only analyze the first exposure of a subject to the drugs of interest. By ‘cohort study’ we mean two cohorts, a treatment and comparator cohort, will be followed from index date (start of first exposure) to some end date, and assessed for the occurrence of the outcomes of interest.

The treatment cohort will be new users of alendronate. The comparator cohort will be new users of raloxifene. For both groups we restrict to people with seizure disorder, one of the main indications for the drugs of interest. The outcome of is hip fracture. Proportional hazard models will be used to assess the hazard ratios between the two exposure cohorts.

Adjustment for baseline confounders will be done using propensity scores. First, a propensity model will be fitted and used to create propensity scores (PS). These PS will be used to match the treatment and comparator cohorts, and the proportional hazards outcome models will be conditioned on the matched sets of strata respectively.

The time of risk will be defined as all time on the drug (so-called per-protocol), and will end at the end of exposure or end of observation, whichever is first. Multiple prescriptions will be considered continuous exposure with a maximum gap of 30 days.

Negative control outcomes (outcomes not believed to be caused by either alendronate or raloxifene) will also be included. The hazard ratios computed for these negative controls will be used to evaluate residual bias and compute calibrated p-values for the outcomes of interest.

### Study population

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the first exposure to alendronate or raloxifene)

* Women over 45 years
* Exposure to alendronate or raloxifene
* At least 90 days of observation time prior to the index date
* A diagnose of hip fracture on or preceding the index date
* No diagnosis of the outcome of interest preceding the index date

### Additional analysis details

The propensity model will be fitted using L1 regularized logistic regression. The regularization hyperparameter will be selected by optimizing the likelihood in a 10-fold cross-validation.

Variable-ratio propensity score matching will be performed using greedy matching [1](#_ENREF_1). A caliper of 0.25 times the standard deviation of the propensity score distribution will be used.

The outcome model will be fitted using a Cox regression conditioned on the matched sets, with only the treatment variable as predictor.

### Analysis variations

The following variations of the analysis will be performed:

Primary analysis:

* Using a PS model to match treated and comparator. The outcome model will be condition on the matched sets.

Secondary analyses:

* No PS model, a simple outcome model with only the treatment as predictor.
* Using a PS model and perform 1-on-1 matching. The outcome model will be condition on the matched sets, but will only contain the treatment as predictor. This is included to allow plotting of the Kaplan-Meier curve, which is not possible when using variable ratio matching.
* Variable ratio matching on the PS. The outcome model will include all covariates that were also included in the propensity model, and will be fitted using a L1 regularized conditional Cox regression with prior. The regularization hyperparameter will be selected be selected by optimizing the likelihood in a 10-fold cross-validation. No regularization will be applied to the coefficient corresponding to the treatment variable (i.e. those representing the hazard ratio of interest).
* All analyses will be repeated using an intent-to-treat risk window definition, which starts on treatment initiation, and ends when observation ends.

## Variables

### Exposures

#### Alendronate

Index rule defining the index date:

* First exposure to any drug containing the RxNorm ingredient Alendronate

Inclusion rules based on the index date:

* At least 90 days of observation time prior to the index date
* A diagnosis of hip fracture on or preceding the index date
* No diagnose of hip fracture preceding the index date

#### Raloxifene

Index rule defining the index date:

* First exposure to a drug containing any Raloxifene

Inclusion rules based on the index date:

* At least 90 days of observation time prior to the index date
* A diagnosis of hip fracture on or preceding the index date
* No diagnosis of hip fracture preceding the index date

### Outcomes

#### Hip fracture

Index rule defining the index date:

* Any occurrence of a hip fracture diagnosis code

Inclusion rules based on the index date:

* Cannot have a hip fracture diagnosis code prior to the index date.

#### Atypical femora fracture

Index rule defining the index date:

* Any occurrence of subtrochanteric and midshaft femoral fracture diagnosis code

Inclusion rules based on the index date:

* Cannot have subtrochanteric and midshaft femoral fracture code prior to the index date.

#### Osteonecrosis of the jaw

Index rule defining the index date:

* Any occurrence of osteonecrosis diagnosis code

Inclusion rules based on the index date:

* Cannot have osteonecrosis diagnosis code prior to the index date.

#### Esophageal cancer

Index rule defining the index date:

* Any occurrence of esophageal cancer diagnosis code

Inclusion rules based on the index date:

* Cannot have esophageal cancer diagnosis code prior to the index date.

#### Deep vein thrombosis or pulmonary embolism

Index rule defining the index date:

* Any occurrence of deep vein thrombosis or pulmonary embolism diagnosis code

Inclusion rules based on the index date:

* Cannot have deep vein thrombosis or pulmonary embolism diagnosis code prior to the index date.

### Potential confounders

The following will be included as potential covariates: (note: most covariates are assessed on or in the 365 days prior to index date)

* Demographics (age in 5-year increments, gender, race, ethnicity, year of index date, month of index date)
* Condition occurrence (one or more variables per diagnosis code)
* Condition era (one or more variables per diagnosis code)
* Condition group (one or more variables per MedDRA group or SNOMED groups)
* Drug exposure (one or more variables per drug code)
* Drug era (one or more variables per RxNorm ingredient)
* Drug group (one or more variables per ATC group)
* Procedure occurrence (one or more variables per procedure code)
* Observations (one or more variables per observation concept ID)
* Measurements (one or more variables per measurement concept ID, including variables for within / above / below normal range)
* Risk scores (including Charleston, DCSI, CHADS2, CHADS2VASc

For the full details see the OHDSI CohortMethod package (<https://github.com/OHDSI/CohortMethod>).

Variables with less than 100 non-zero values are discarded. All covariates were used in both the propensity model and the outcome model.

### Negative controls

Negative controls were selected using the following criteria:

* No evidence found in literature on clinical trials using the method proposed by Avillach [2](#_ENREF_2).
* No evidence found in literature using the method used in SemMedDB [3](#_ENREF_3).
* No evidence found in the structured product label (US and EU) for the outcome or associated outcomes
* FAERS Proportional Reporting Ratio (PRR) needed to be less than 2.
* Sufficient exposure in a US healthcare database (Over 10,000 occurrence of the diagnoses code in the Truven CCAE database).

Negative controls were defined as any of the following diagnoses:

|  |
| --- |
| Acute renal failure syndrome |
| Anal finding |
| Aortic aneurysm |
| Aortic valve disorder |
| Appendicitis |
| Arthritis of elbow |
| Arthropathy associated with another disorder |
| Arthropathy of knee joint |
| Ascites |
| Aseptic necrosis of bone |
| Astigmatism |
| Atelectasis |
| Atopic dermatitis |
| Bacterial intestinal infectious disease |
| Barrett's esophagus |
| Benign neoplasm of endocrine gland |
| Blepharitis |
| Bronchopneumonia |
| Burn |
| Bursitis |
| Candidiasis of mouth |
| Candidiasis of urogenital site |
| Condyloma acuminatum |
| Coxsackie virus disease |
| Croup |
| Cystic disease of kidney |
| Cystitis |
| Deficiency of macronutrients |
| Dental caries |
| Duodenitis |
| Dyspareunia |
| Dysplasia of cervix |
| Dyspnea |
| Dysthymia |
| Dysuria |
| Effusion of joint |
| Endocarditis |
| Enthesopathy of elbow region |
| Fibrocystic disease of breast |
| Gastroesophageal reflux disease |
| Hemorrhoids |
| Hypermetropia |
| Hyperplasia of prostate |
| Hypokalemia |
| Impetigo |
| Infectious disorder of kidney |
| Infestation by Sarcoptes scabiei var hominis |
| Inflammatory disease of female pelvic organs AND/OR tissues |
| Inflammatory disease of the uterus |
| Inflammatory disorder of breast |
| Ingrowing nail |
| Injury of abdomen |
| Intervertebral disc disorder |
| Intracranial injury |
| Iridocyclitis |
| Irritable bowel syndrome |
| Late effects of cerebrovascular disease |
| Leukorrhea |
| Lipoma |
| Malignant neoplasm of thorax |
| Mitral valve disorder |
| Mononeuropathy of upper limb |
| Non-toxic uninodular goiter |
| Open-angle glaucoma |
| Osteomyelitis |
| Otitis externa |
| Otorrhea |
| Paraplegia |
| Paronychia |
| Paroxysmal tachycardia |
| Peripheral venous insufficiency |
| Plantar fasciitis |
| Pleurisy |
| Pneumococcal infectious disease |
| Pneumonia due to Gram negative bacteria |
| Pneumothorax |
| Presbyopia |
| Primary malignant neoplasm of respiratory tract |
| Prolapse of female genital organs |
| Prostatitis |
| Pyelonephritis |
| Respiratory arrest |
| Retinopathy |
| Rosacea |
| Sciatica |
| Seborrheic keratosis |
| Secondary malignant neoplastic disease |
| Sialoadenitis |
| Staphylococcal infectious disease |
| Symbolic dysfunction |
| Temporomandibular joint disorder |
| Tetraplegia |
| Thyrotoxicosis |
| Tietze's disease |
| Tinea pedis |
| Torticollis |
| Tricuspid valve disorder |
| Urge incontinence of urine |
| Viral hepatitis |
| Viral pneumonia |

### Other variables

Hip fracture will be identified using the concept for femur neck fracture, femur intertrochanteric fracture and any of its descendants in the OMOP Vocabulary.

## Data Sources

The analyses will be performed across a network of observational healthcare databases. All databases have been transformed into the OMOP Common Data Model, version 4 or OMOP Common Data Model, version 5. The complete specification for OMOP Common Data Model, version 4 is available at: <http://omop.org/cdm>. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>. The following databases will be included in this analysis:

* Truven MarketScan Commercial Claims and Encounters (CCAE)
* Truven MarketScan Medicare Supplemental Beneficiaries (MDCR)
* Truven MarketScan Multi-state Medicaid (MDCD)
* Optum ClinFormatics (Optum)
* Clinical Practice Research Datalink (CPRD)
* Indiana Network for Patient Care
* Columbia University Medical Center
* Others….

Truven MarketScan Commercial Claims and Encounters (CCAE)

CCAE is an administrative health claims database for active employees, early retirees, COBRA continues, and their dependents insured by employer-sponsored plans (individuals in plans or product lines with fee-for-service plans and fully capitated or partially capitated plans). As of 30November2014, CCAE contained 117m patients with patient-level observations from Jan2000 through Jul2014. Source codes used in CCAE include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming CCAE into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/truven_ccae/dashboard>.

Truven MarketScan Medicare Supplemental Beneficiaries (MDCR)

MDCR is an administrative health claims database for Medicare-eligible active and retired employees and their Medicare-eligible dependents from employer-sponsored supplemental plans (predominantly fee-for-service plans). Only plans where both the Medicare-paid amounts and the employer-paid amounts were available and evident on the claims were selected for this database.. As of 30November2014, MDCR contained 9m patients with patient-level observations from Jan2000 through Jul2014. Source codes used in MDCR include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming MDCR into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/truven_mdcr/dashboard>.

Truven MarketScan Multi-state Medicaid (MDCD)

MDCD is an administrative health claims database for the pooled healthcare experience of Medicaid enrollees from multiple states. As of 30November2014, MDCD contained 16m patients with patient-level observations from Jan2006 through Dec2012. Source codes used in MDCD include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming MDCD into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/truven_mdcd/dashboard>.

Optum ClinFormatics (Optum)

Optum is an administrative health claims database for members of United Healthcare, who enrolled in commercial plans (including ASO, 36.31M), Medicaid (prior to July 2010, 1.25M) and Legacy Medicare Choice (prior to January 2006, 0.36M) with both medical and prescription drug coverage. As of 30November2014, Optum contained 38m patients with patient-level observations from Oct2005 through Dec2013. Source codes used in Optum include: conditions- ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; lab: LOINC.

The ETL specification for transforming Optum into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/optum/dashboard>.

Clinical Practice Research Datalink (CPRD)

CPRD is an anonymized longitudinal electronic health records from primary care practices in UK. Patient management system with many aspects of patient care covered, including diagnoses, prescriptions, signs and symptoms, procedures, labs, lifestyle factors, clinical and administrative/social data. As of 30November2014, CPRD contained 11m patients with patient-level observations from Jan1988 through Nov2013. Source codes used in CPRD include: conditions- Read; drugs: Multilex; procedures: OPCS.

The ETL specification for transforming CPRD into the OMOP CDM is available at: <http://omop.org/cdm>.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Janssen at: <http://hix.jnj.com/achilles/#/cprd/dashboard>.

Indiana Network for Patient Care (INPC)

The INPC is a 22-year-old health information exchange operated in Indiana. The health information exchange data repository carries over 6 billion pieces of clinical data, including over 118 million text reports, for approximately 27.5 million different patient registrations, for approximately 13.4 million unique patients derived from over 100 hospitals. All clinical data is standardized, and laboratory test results are mapped to a set of common test codes (LOINC) with standard units of measure for patient care, public health, and research purposes.

ACHILLES has been used to characterize the database and provide a data quality assessment. The ACHILLES summary is available internally within Regenstrief at <https://nlp01.regenstrief.org/Achilles>

## Sample Size and Study Power

No power calculations have been performed.

## Quality control

We will evaluate the PS by

* Inspection of the fitted PS model for large coefficients (indicative of model-misspecification) and predictors that we cannot explain (post-hoc).
* Inspection of the PS distribution.
* Evaluation of covariate balance after matching using the standardized difference in means between treatment and comparator cohort before and after matching [4](#_ENREF_4). Standardized differences greater than 0.2 will be reported and investigated.

We will investigate the outcome model by

* Inspection of the fitted outcome model for large coefficients and predictors that we cannot explain (post-hoc).

The error distribution estimated using the negative controls will be used to estimate residual bias after adjustments.

The CohortMethod package itself, as well as other OHDSI packages on which CohortMethod depends, use unit tests for validation.

## Strengths and Limitations of the Research Methods

Strength

* Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.
* PS matching and full outcome models allow balancing on a large number of baseline potential confounders.
* Use of negative control outcomes allow for evaluating the study design as a whole in terms of residual bias.

Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or misspecified confounders.
* The outcome of interest, hip fracture, is rare and typically captured only in inpatient settings, so we may have insufficient numbers of patients to generate reliable evidence on this drug-outcome association.

# Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# Plans for Disseminating and Communicating Study Results

The study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

# References

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