Comparative effectiveness of alendronate and raloxifene in reducing the risk of hip fracture in women with osteoporosis

**Version:** 0.2

**Authors:**

Yeesuk Kim, MD PhD, Hanyang University

Patrick B. Ryan, PhD, Janssen Research and Development

Martijn J. Schuemie, PhD, Janssen Research and Development

Jon Duke, MD, Georgia Tech

George Hripcsak, MD, Columbia University

Marc A. Suchard, MD PhD, University of California, Los Angeles

**Date:** 27 March 2017

**Acknowledgment:** The analysis is based in part on work from the Observational Health Sciences and Informatics collaborative. OHDSI (<http://ohdsi.org>) is a multi-stakeholder, interdisciplinary collaborative to create open-source solutions that bring out the value of observational health data through large-scale analytics.

The authors declare the following disclosures: Drs. Ryan and Schuemie are employees of Janssen Research & Development.

1. **Table of contents**

[2](#_gjdgxs) List of abbreviations 3

[3](#_30j0zll) Abstract 3

[4](#_1fob9te) Amendments and Updates 3

[Milestones 3](#_3znysh7)

[5](#_2et92p0) Rationale and Background 3

[5.1](#_tyjcwt) Research Questions 4

[5.2](#_3dy6vkm) Objectives 4

[6](#_1t3h5sf) Research methods 5

[6.1](#_4d34og8) Study Design 5

[6.1.1](#_2s8eyo1) Overview 5

[6.1.2](#_17dp8vu) Study population 5

[6.1.3](#_26in1rg) Additional analysis details 5

[6.1.4](#_lnxbz9) Analysis variations 6

[6.2](#_35nkun2) Variables 6

[6.2.1](#_1ksv4uv) Exposures 6

[6.2.2](#_44sinio) Outcomes 7

[6.2.3](#_2jxsxqh) Potential confounders 8

[6.2.4](#_z337ya) Negative controls 8

[6.2.5](#_3j2qqm3) Other variables 11

[6.3](#_1y810tw) Data Sources 11

[6.4](#_4i7ojhp) Sample Size and Study Power 13

[6.5](#_2xcytpi) Quality control 13

[6.6](#_1ci93xb) Strengths and Limitations of the Research Methods 14

[7](#_3whwml4) Protection of Human Subjects 14

[8](#_2bn6wsx) Plans for Disseminating and Communicating Study Results 15

[9](#_qsh70q) References 15

# 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 and raloxifene 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 framework to perform this comparative effectiveness study.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | 23 March 2017 | Yeesuk Kim | Initial draft |
| 0.2 | 27 March 2017 | Marc Suchard | Outcome definitions and intent-to-treat |

# 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) such as alendronate, calcitonin, raloxifene (SERM) and teriparatide. Among these drugs, alendronate and raloxifene are the most popular osteoporosis medications and a burden of prescription are performed annually.

A definitive study comparing the effectiveness of alendronate and raloxifene was limited. The Evista alendronate comparison (EVA) 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 hypotheses

* There is no difference in rate of vertebral fractures between alendronate and raloxifene.
* There is no difference in rate of atypical femural fractures between alendronate and raloxifene.
* There is no difference in rate of osteonecrosis of the jaw between alendronate and raloxifene.
* There is no difference in rate of esophageal cancer between alendronate and raloxifene.

## Objectives

Primary objective

* To compare the risk of **OHDSI Sisyphus O: new cases of hip fracture** between **OHDSI Sisyphus T: new users of alendronate in patients with osteoporosis** and **OHDSI Sisyphus C: new users of raloxifene in patients with osteoporosis**, we will estimate the population-level effect of exposure on the hazards of the outcome during the period from 90 days from cohort start date to 9999 days from cohort end date.

# Research methods

## Study Design

### Overview

This study will follow a retrospective, observational, comparative cohort design. We define ‘retrospective’ to mean the study will be conducted using data already collected prior to the start of the study. We define ‘observational’ to mean there is no intervention or treatment assignment imposed by the study. We define 'cohort' to mean a set of patients satisfying a one or more inclusion criteria for a duration of time. We define ‘comparative cohort design’ to mean the formal comparison between two cohorts, a target cohort and comparator cohort, for the risk of an outcome during a defined time period after cohort entry.

In this study, we compare **OHDSI Sisyphus T: new users of alendronate in patients with osteoporosis** with **OHDSI Sisyphus C: new users of raloxifene in patients with osteoporosis** for the hazards of **OHDSI Sisyphus O: new cases of hip fracture** from 90 days from cohort start date to 9999 days from cohort end date.

For both cohorts, we impose a requirement that patients must have at least 365 days of continuous observation prior to cohort entry.

The overall study population could be considered to be patients who entered either the target cohort or comparator cohort. Patients were excluded from consideration is they qualified for both the target cohort and comparator cohort at any time in their record.

The time-to-event of outcome among patients in the target and comparator cohorts is determined by calculating the number of days from the start of the time-at-risk window, 90 days from cohort start date until the earliest event among 1) the first occurrence of the outcome, **OHDSI Sisyphus O: new cases of hip fracture** before 9999 days from cohort end date, 2) the end of the time-at-risk window, 9999 days from cohort end date, and 3) the end of the observation period that spans the time-at-risk start.

Patients with **OHDSI Sisyphus O: new cases of hip fracture** prior to target or comparator cohort entry were excluded from consideration.

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates. In this study, the propensity score is estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross validation, using a starting variance of 0.01 and a tolerance of 2e-7.

The types of baseline covariates used to fit the propensity score model will be:

* Demographics
  + Gender
  + Age group (5-year bands)
  + Index year
  + Index month
* Conditions
  + In prior 30d
  + In prior 365d
* Condition aggregation
  + SNOMED
* Drugs
  + In prior 365d
* Drug aggregation
  + Ingredient
  + ATC Class
* Procedures
  + In prior 365d
* Measurement
  + Existence in prior 365d
* Risk scores
  + Charlson
* Concept counts (count of distinct conditions/procedures/visits in history)

Specific covariates to be excluded from the propensity score model are labelled **Sisyphus challenge: drugs to exclude** as detailed in Appendix 2.

All covariates that occur in fewer than 10 persons between the target and comparator cohorts combined will be excluded prior to model fitting.

The propensity score estimates are used to restrict the cohorts through patient trimming. Patients are excluded if their predicted probability is less than 10% or greater than 90% of the preference score.

The target cohort and comparator cohorts will be stratified into 5 quantiles of the propensity score distribution.

### Output and evaluation

Covariate balance will be summarized in tabular form by showing the mean value for all baseline covariates in the target and comparator cohort, with the associated standardized mean difference computed for each covariate.

Once the propensity score model is fit, we will plot the propensity score distribution of the target and comparator cohorts to evaluate the comparability of the two cohorts. The plot will be scaled to the preference score, normalizing for any imbalance in cohort size. The area under the Receiver Operating Characteric (ROC) curve (AUC) will be reported. The covariates selected within the propensity score model, with associated coefficients will also be reported.

A plot showing the propensity score distributions for both cohorts after stratification will be provided, with each quantile cutpoint shown as a vertical line.

An attrition diagram will be provided to detail the loss of patients from the original target cohort, **OHDSI Sisyphus T: new users of alendronate in patients with osteoporosis**, and comparator cohort **OHDSI Sisyphus C: new users of raloxifene in patients with osteoporosis** to the subpopulations that remain after all design considerations have been applied.

The final outcome model, a conditional Cox proportional hazards model, will be summarized by providing the hazards ratio and associated 95% confidence interval. The number of persons, amount of time-at-risk, and number of outcomes in each cohort will also be reported.

A Kaplan-Meier plot will be generated to characterize the contour of risk over time for the outcome of interest.

Negative control outcomes will be used to evaluate the potential impact of residual systematic error in the study design, and to facilitate empirical calibration of the p-value for the outcomes of interest. Negative control outcomes are concepts known not to be associated with either the target or comparator group, such that we can assume the true relative risk should equal 1. The negative control outcomes used in this study are labelled **Sisyphus challenge: negative controls for alendronate and raloxifene** as detailed in Appendix 2. For each negative control outcome, the study design described above will be implemented and the effect estimate will be recorded. The distribution of effect estimates across all negative control outcomes will be used to fit an empirical null distribution which models the observed residual systematic error. The empirical null distribution will then be applied to the target outcome of interest to calibrate the p-value. Empirical calibration serves as an important diagnostic tool to evaluate if the residual systematic error is sufficient to cast doubt on the accuracy of the unknown effect estimate. The calibration effect plot and calibration probability plots will be generated for review. We will report the traditional p-value and empirically calibrated p-value for each negative control, as well as the unknown outcomes of interest

### Study population

The study population is comprised of patients in a target cohort T or comparator cohort C.

Target cohort T: new users of alendronate, is formally defined here: <http://www.ohdsi.org/web/atlas/#/cohortdefinition/99321>

Comparator cohort C: new users of ralofixene, is formally defined here: <http://www.ohdsi.org/web/atlas/#/cohortdefinition/99322>

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 365 days of observation time prior to the index date
* At least 90 days of observation time after to the index date
* No prior hip fracture on or preceding the index date
* No prior hip replacement on or preceding the index date
* No other bisphosphonates or SERMs preceding the index date
* no prior disease related to pathological fractures including Pagets disease
* no prior high energy trauma fractures

## Variables

### Exposures

#### OHDSI Sisyphus T: new users of alendronate in patients with osteoporosis

http://www.ohdsi.org/web/atlas/#/cohortdefinition/99321

Initial Event Cohort

People having any of the following:

* a drug exposure of alendronate1
  + for the first time in the person's history
  + occurrence start is before 2012-02-01

with continuous observation of at least 365 days prior and 90 days after event index date, and limit initial events to: earliest event per person.

Inclusion Criteria #1: is woman >45 yo

Having all of the following criteria:

* with the following event criteria:
  + with age > 45
  + gender is any of: FEMALE

Inclusion Criteria #2: has osteoporosis diagnosis in 365d prior to index date

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of osteoporosis6
* starting between 365 days Before and 0 days After event index date

Inclusion Criteria #3: has no prior raloxifene exposure

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of raloxifene7
* starting between all days Before and 0 days After event index date

Inclusion Criteria #4: has no prior hip fractures

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of hip fracture4
* starting between all days Before and 0 days After event index date

Inclusion Criteria #5: has no prior hip replacement

Having all of the following criteria:

* exactly 0 occurrences of a procedure of Hip replacement5
* starting between all days Before and 0 days After event index date

Inclusion Criteria #6: has no prior drugs that should be excluded

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of Sisyphus challenge: drugs to exclude8
* starting between all days Before and 1 days Before event index date

Inclusion Criteria #7: no prior disease related to pathological fractures including Pagets disease

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of diseases related to pathological fractures2
* starting between all days Before and 0 days After event index date

#### OHDSI Sisyphus C: new users of raloxifene in patients with osteoporosis

http://www.ohdsi.org/web/atlas/#/cohortdefinition/99322

Initial Event Cohort

People having any of the following:

* a drug exposure of raloxifene5
  + for the first time in the person's history
  + occurrence start is before 2012-02-01

with continuous observation of at least 365 days prior and 90 days after event index date, and limit initial events to: earliest event per person.

Inclusion Criteria #1: is woman >45 yo

Having all of the following criteria:

* with the following event criteria:
  + with age > 45
  + gender is any of: FEMALE

Inclusion Criteria #2: has osteoporosis diagnosis in 365d prior to index date

Having all of the following criteria:

* at least 1 occurrences of a condition occurrence of osteoporosis4
* starting between 365 days Before and 0 days After event index date

Inclusion Criteria #3: has no prior alendronate exposure

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of alendronate1
* starting between all days Before and 0 days After event index date

Inclusion Criteria #4: has no prior hip fractures

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of hip fracture2
* starting between all days Before and 0 days After event index date

Inclusion Criteria #5: has no prior hip replacement

Having all of the following criteria:

* exactly 0 occurrences of a procedure of Hip replacement3
* starting between all days Before and all days After event index date

Inclusion Criteria #6: has no prior drugs that should be excluded

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of Sisyphus challenge: drugs to exclude6
* starting between all days Before and 1 days Before event index date

Limit qualifying cohort to: earliest event per person.

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of raloxifene5

* allowing 30 days between exposures
* adding 0 days after exposure end

Appendix 1: Concept Set Definitions

1. alendronate

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1557272 | Alendronate | Drug | RxNorm | NO | YES | NO |

2. hip fracture

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 4300192 | Fracture of pelvis | Condition | SNOMED | NO | YES | NO |
| 433856 | Fracture of neck of femur | Condition | SNOMED | NO | YES | NO |

3. Hip replacement

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 2104836 | Arthroplasty, acetabular and proximal femoral prosthetic replacement (total hip arthroplasty), with or without autograft or allograft | Procedure | CPT4 | NO | YES | NO |
| 4142076 | Primary cemented total hip replacement | Procedure | SNOMED | NO | YES | NO |
| 4079259 | Primary uncemented total hip replacement | Procedure | SNOMED | NO | YES | NO |
| 2005891 | Total hip replacement | Procedure | ICD9Proc | NO | YES | NO |
| 4001859 | Hip joint implantation | Procedure | SNOMED | NO | YES | NO |
| 4162099 | Prosthetic arthroplasty of the hip | Procedure | SNOMED | NO | YES | NO |
| 4010119 | Revision of hip replacement | Procedure | SNOMED | NO | YES | NO |
| 4203771 | Total replacement of hip | Procedure | SNOMED | NO | YES | NO |
| 4207955 | Insertion of hip prosthesis, total | Procedure | SNOMED | NO | YES | NO |
| 4297365 | Partial hip replacement by prosthesis | Procedure | SNOMED | NO | YES | NO |
| 2005902 | Partial hip replacement | Procedure | ICD9Proc | NO | YES | NO |
| 4266062 | Revision of total hip replacement | Procedure | SNOMED | NO | YES | NO |
| 4197231 | Removal of prosthesis of joint structures of hip | Procedure | SNOMED | NO | YES | NO |

4. osteoporosis

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 80502 | Osteoporosis | Condition | SNOMED | NO | YES | NO |

5. raloxifene

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1513103 | Raloxifene | Drug | RxNorm | NO | YES | NO |

6. Sisyphus challenge: drugs to exclude

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1557272 | Alendronate | Drug | RxNorm | NO | YES | NO |
| 44506794 | bazedoxifene | Drug | RxNorm | NO | YES | NO |
| 21604148 | Bisphosphonates | Drug | ATC | NO | YES | NO |
| 1513103 | Raloxifene | Drug | RxNorm | NO | YES | NO |

### Outcomes

#### Hip fracture : <http://www.ohdsi.org/web/atlas/#/cohortdefinition/99323>

Initial Event Cohort

People having any of the following:

* a condition occurrence of hip fracture1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. hip fracture

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 4230399 | Closed fracture of hip | Condition | SNOMED | NO | YES | NO |

#### Vertebral fracture: http://www.ohdsi.org/web/atlas/#/cohortdefinition/100791

Initial Event Cohort

People having any of the following:

* a condition occurrence of closed vertebral fracture1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of closed vertebral fracture1

* allowing 90 days between exposures
* adding 0 days after exposure end

Appendix 1: Concept Set Definitions

1. closed vertebral fracture

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 4170742 | Closed fracture of vertebral column | Condition | SNOMED | NO | YES | NO |

#### Non-Hip Non-Vertebral fracture: http://www.ohdsi.org/web/atlas/#/cohortdefinition/100792

Initial Event Cohort

People having any of the following:

* a condition occurrence of non-hip non-vertebral closed fracture1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. non-hip non-vertebral closed fracture

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 4307254 | Closed fracture | Condition | SNOMED | NO | YES | NO |
| 4230399 | Closed fracture of hip | Condition | SNOMED | YES | YES | NO |
| 4170742 | Closed fracture of vertebral column | Condition | SNOMED | YES | YES | NO |

#### osteonecrosis of jaw: <http://www.ohdsi.org/web/atlas/#/cohortdefinition/100793>

Initial Event Cohort

People having any of the following:

* a condition occurrence of Osteonecrosis of jaw1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Osteonecrosis of jaw

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 40480852 | Aseptic necrosis of bone of jaw | Condition | SNOMED | NO | YES | NO |
| 46270478 | Osteonecrosis of jaw caused by drug | Condition | SNOMED | NO | YES | NO |

#### esophageal cancer: <http://www.ohdsi.org/web/atlas/#/cohortdefinition/100794>

Initial Event Cohort

People having any of the following:

* a condition occurrence of esophageal cancer1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. esophageal cancer

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 4181343 | Malignant tumor of esophagus | Condition | SNOMED | NO | YES | NO |

#### atypical femural fracture : <http://www.ohdsi.org/web/atlas/#/cohortdefinition/100795>

Initial Event Cohort

People having any of the following:

* a condition occurrence of atypical femural fractures1
  + for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

Inclusion Criteria #1: no high energy trauma fractures around atypical fracture event

Having all of the following criteria:

* exactly 0 occurrences of a condition occurrence of high energy trauma fractures2
* starting between 7 days Before and 7 days After event index date

Limit qualifying cohort to: earliest event per person.

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. atypical femural fractures

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 438887 | Closed fracture of shaft of femur | Condition | SNOMED | NO | YES | NO |
| 4009610 | Closed fracture proximal femur, subtrochanteric | Condition | SNOMED | NO | YES | NO |

2. high energy trauma fractures

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 4300192 | Fracture of pelvis | Condition | SNOMED | NO | YES | NO |
| 4264281 | Open fracture | Condition | SNOMED | NO | YES | NO |

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

### 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](#_1pxezwc).
* No evidence found in the structured product label 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 at least database).

Negative controls are listed below, and available as a conceptset here: <http://www.ohdsi.org/web/atlas/#/conceptset/100603/details>

|  |  |
| --- | --- |
| Id | Name |
| 4305080 | Abnormal breathing |
| 45765647 | Acquired brain injury |
| 4217633 | Acrodermatitis |
| 198809 | Acute cholecystitis |
| 4133026 | Acute skin disorder |
| 440083 | Acute stress disorder |
| 376981 | Amblyopia |
| 4207240 | Anemia due to intrinsic red cell abnormality |
| 4312008 | Anemia due to substance |
| 4080321 | Animal-induced dermatosis |
| 4145825 | Anorectal disorder |
| 4081007 | Anterior chamber finding |
| 314054 | Aortic valve disorder |
| 137829 | Aplastic anemia |
| 440448 | Appendicitis |
| 261880 | Atelectasis |
| 4281109 | Autoimmune thyroiditis |
| 4193166 | Bacterial gastrointestinal infectious disease |
| 4224118 | Bladder dysfunction |
| 378425 | Blepharitis |
| 256722 | Bronchopneumonia |
| 442013 | Burn |
| 197028 | Calculus of lower urinary tract |
| 314658 | Cardiomegaly |
| 374384 | Cerebral ischemia |
| 4189855 | Chronic arthropathy |
| 4134586 | Chronic heart disease |
| 140057 | Chronic leukemia |
| 4304484 | Chronic myeloproliferative disorder |
| 440704 | Chronic pain syndrome |
| 4104204 | Complete bilateral paralysis |
| 312723 | Congenital heart disease |
| 4080664 | Corneal endothelium finding |
| 193016 | Cystic disease of kidney |
| 441267 | Cystic fibrosis |
| 432590 | Delusional disorder |
| 375801 | Demyelinating disease of central nervous system |
| 443767 | Diabetic oculopathy |
| 436641 | Disease due to Arthropod |
| 4225726 | Disease due to Gammaherpesvirinae |
| 4023319 | Disease due to Paramyxoviridae |
| 433694 | Disease due to Retroviridae |
| 22350 | Edema of larynx |
| 4157036 | Encephalomyelopathy |
| 4101350 | Finding of bowel continence |
| 4029295 | Folliculitis |
| 196456 | Gallstone |
| 4007453 | Gammopathy |
| 4295370 | Gastrointestinal fistula |
| 4055361 | Generalized epilepsy |
| 4263367 | Glomerulonephritis |
| 4195003 | Heart valve stenosis |
| 4163735 | Hemochromatosis |
| 432868 | Hemoglobinopathy |
| 195562 | Hemorrhoids |
| 444429 | Herpes simplex |
| 4038835 | Hodgkin's disease |
| 4214376 | Hyperglycemia |
| 438134 | Hypersomnia |
| 4124693 | Hypertrophic cardiomyopathy |
| 436375 | Hypovolemia |
| 4120621 | Immune thrombocytopenic purpura |
| 433752 | Impulse control disorder |
| 4080305 | Infection of nail |
| 192964 | Infectious disorder of kidney |
| 4208784 | Infective otitis media |
| 4074815 | Inflammatory bowel disease |
| 139099 | Ingrowing nail |
| 4092885 | Inguinal canal finding |
| 200588 | Injury of abdomen |
| 4152163 | Injury of eye region |
| 437409 | Intracranial injury |
| 436659 | Iron deficiency anemia |
| 75576 | Irritable bowel syndrome |
| 4004352 | Irritant contact dermatitis |
| 380397 | Keratoconjunctivitis |
| 4209145 | Ketoacidosis |
| 197676 | Large liver |
| 4199395 | Lesion of bronchus |
| 4103995 | Lesion of rectum |
| 4175297 | Lower respiratory tract infection |
| 316084 | Lymphadenitis |
| 4308125 | Macrocytic anemia |
| 4177067 | Mass of urinary bladder |
| 439045 | Mediastinitis |
| 435785 | Meningitis |
| 440389 | Mental retardation |
| 4271024 | Musculoskeletal fibromatosis |
| 440631 | Mycobacteriosis |
| 4129886 | Neoplasm of pancreas |
| 4130375 | Neoplasm of tongue |
| 40304526 | Nocturia |
| 4038838 | Non-Hodgkin's lymphoma |
| 198802 | Occlusion of ureter |
| 442274 | Oligomenorrhea |
| 372914 | Optic atrophy |
| 43531000 | Paralytic syndrome of all four limbs |
| 43531638 | Paralytic syndrome of both lower limbs |
| 43531639 | Paralytic syndrome on one side of the body |
| 440087 | Parasomnia |
| 313792 | Paroxysmal tachycardia |
| 4106574 | Partial seizure |
| 317309 | Peripheral arterial occlusive disease |
| 441838 | Personality disorder |
| 4304010 | Phobic disorder |
| 134870 | Pityriasis versicolor |
| 44783617 | Precapillary pulmonary hypertension |
| 4324261 | Pulmonary necrosis |
| 4114158 | Pulmonary valve finding |
| 198199 | Pyelonephritis |
| 133547 | Pyoderma |
| 4256228 | Respiratory failure |
| 73754 | Restless legs |
| 80809 | Rheumatoid arthritis |
| 4286201 | Schizoaffective disorder |
| 435783 | Schizophrenia |
| 319826 | Secondary hypertension |
| 196236 | Septic shock |
| 4021907 | Seventh cranial nerve finding |
| 433967 | Spirochetal infection |
| 4329707 | Strabismus |
| 437779 | Streptococcal infectious disease |
| 4279309 | Substance abuse |
| 4077081 | Superficial mycosis |
| 432436 | Symbolic dysfunction |
| 4227653 | T-cell AND/OR NK-cell neoplasm |
| 4344040 | Tendon injury |
| 4280071 | Thrombocytosis |
| 4207615 | Thrombosis of vein of trunk |
| 138387 | Thyrotoxicosis |
| 381839 | Tic disorder |
| 4234533 | Tonsillitis |
| 43021132 | Toxic metabolic encephalopathy |
| 4119796 | Toxic pneumonitis |
| 4002659 | Traumatic hemorrhage |
| 379801 | Trigeminal neuralgia |
| 201254 | Type 1 diabetes mellitus |
| 4281232 | Type B viral hepatitis |
| 4032424 | Upper urinary tract dilatation and obstruction |
| 195862 | Urethritis |
| 4082798 | Urinary tract pain |
| 443605 | Vascular dementia |
| 312935 | Venous hypertension |
| 40457757 | Ventricular septal abnormality |
| 197036 | Vesicoureteric reflux |
| 4193875 | Viral infection of the digestive tract |
| 439981 | Wound dehiscence |

## Data Sources

The analyses will be performed across a network of observational healthcare databases within the OHDSI community. 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 5 is available at: <https://github.com/OHDSI/CommonDataModel>.

Data sources expected to participate to include:

* Clinical Practice Research Datalink (UK EHR)
* IMS Disease Analyzer Germany (Germany EHR)
* Japan Medical Data Center (JMDC)
* Optum (US claims)
* Optum (US EHR)
* Truven MarketScan Commercial Claims and Encounters (US claims)
* Truven MarketScan Multi-state Medicaid (US claims)
* Truven MarketScan Medicare Supplemental Beneficiaries (US claims)
* Columbia University (US EHR)
* Stanford University (US EHR)
* <<OHDSI community members to add as they agree to participate>>

## 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](#_2p2csry). 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

2. Avillach P, Dufour JC, Diallo G, et al. Design and validation of an automated method to detect known adverse drug reactions in MEDLINE: a contribution from the EU-ADR project. *Journal of the American Medical Informatics Association : JAMIA* 2013;20(3):446-52. doi: 10.1136/amiajnl-2012-001083 [published Online First: 2012/12/01]

4. Austin PC. Assessing balance in measured baseline covariates when using many-to-one matching on the propensity-score. *Pharmacoepidemiology and drug safety* 2008;17(12):1218-25. doi: 10.1002/pds.1674 [published Online First: 2008/10/31]