Save our Sisyphus Challenge:

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

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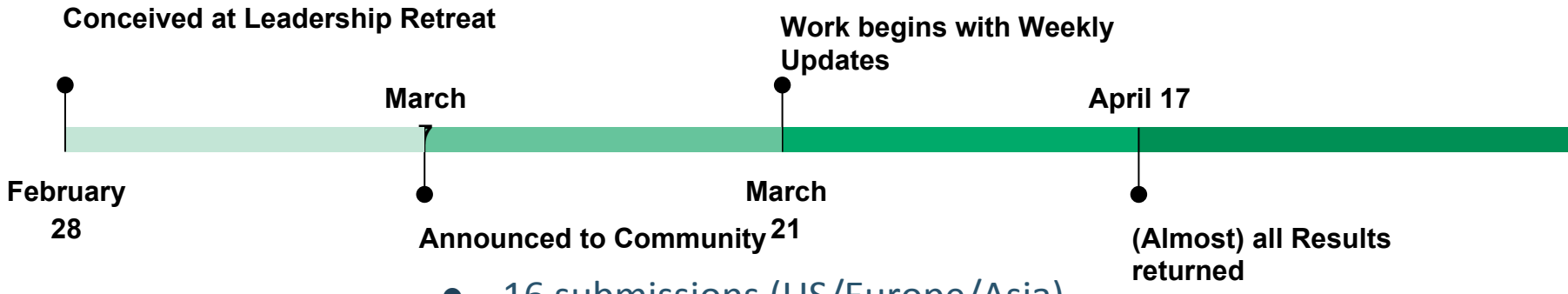
OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Save our Sisyphus challenge

- To demonstrate ***community*** capacity to address clinical questions from **design** through **execution** through **answers**
- A daunting, trans-disciplinary task

by Titan, 1548-9



- 16 submissions (US/Europe/Asia)

19 community partners

Design and analysis:

Vojtech Huser, NIH

Yuxi Tian, UCLA

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Design and leadership:

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Data partners:

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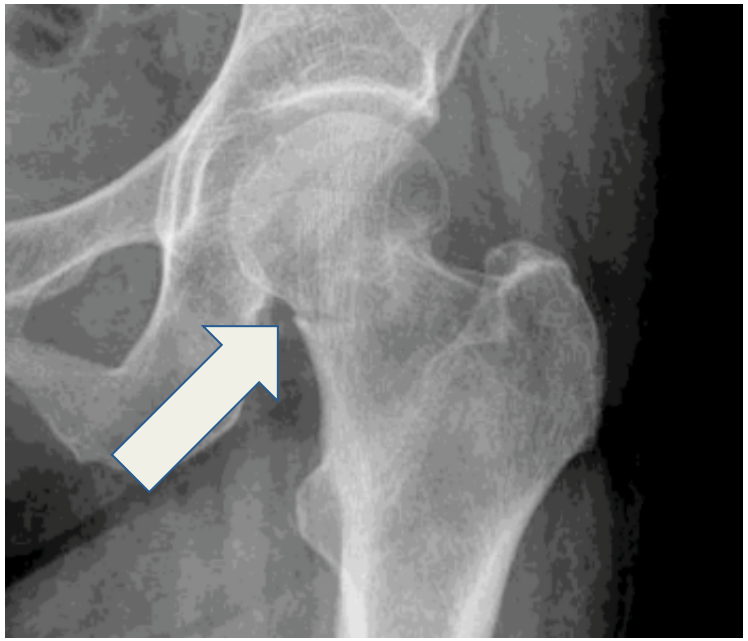
Yonghui Wu, University of Texas Health Sciences

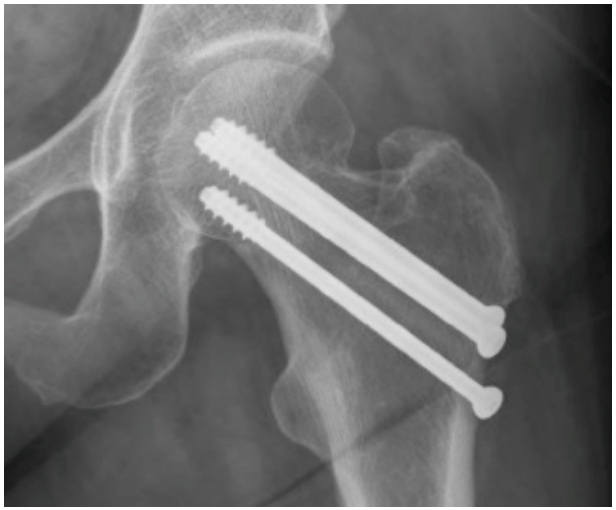
Mui Van Zandt, Quintiles-IMS

Clinical consult

60 y.o. female: playfully pushed by grandson and fell



- Left hip fracture (fx)
- Urgent surgery at 2AM
- T score: -2.6 → osteoporosis
- No previous treatment



On which osteoporosis drug do I start her, ***alendronate*** or ***raloxifene***?

Effectiveness and safety

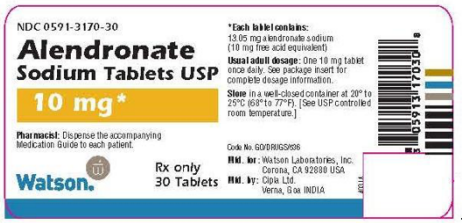
Osteoporosis: chronic ↑ bone resorption → fx's

Alendronate

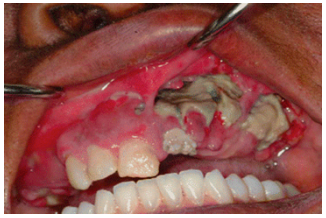
- Bisphosphonate (BP)
- ↓ risk (vs placebo, RCT) of vertebral and hip fx's
- Adverse effects:
  - Atypical femoral fx
  - Esophageal cancer
  - Osteonecrosis of the jaw

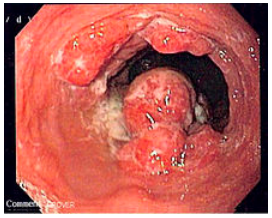
Raloxifene

- Selective estrogen receptor modulator (SERM)
- **No** ↓ risk (vs placebo, RCT) of hip fx's
- Fewer adverse effects
- Alendronate vs raloxifene RCT of limited size



NEJM 1995; 333:1437-1444





JAMA1999; 282:637-645
Bone 2007; 40:843-85

New-user cohort study design

Population:

- Women, > 45, with prior dx of osteoporosis, 2001 - 2012
- No prior BP, SERM, outcome, hip replacement, traumatic or pathological fx
- Min observation: - 365 → +90 days

Outcomes:

- Hip fx — Primary
- Vertebral fx
- Atypical femoral fx
- Esophageal cancer
- Jaw osteonecrosis

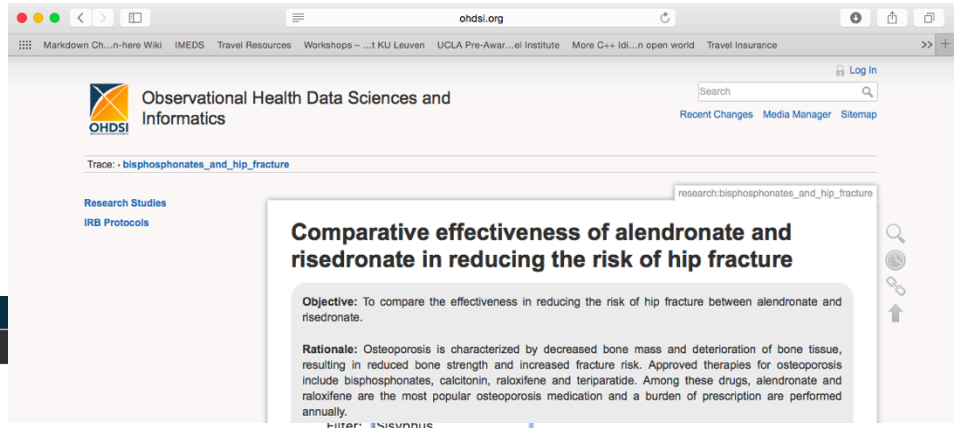
Approach:

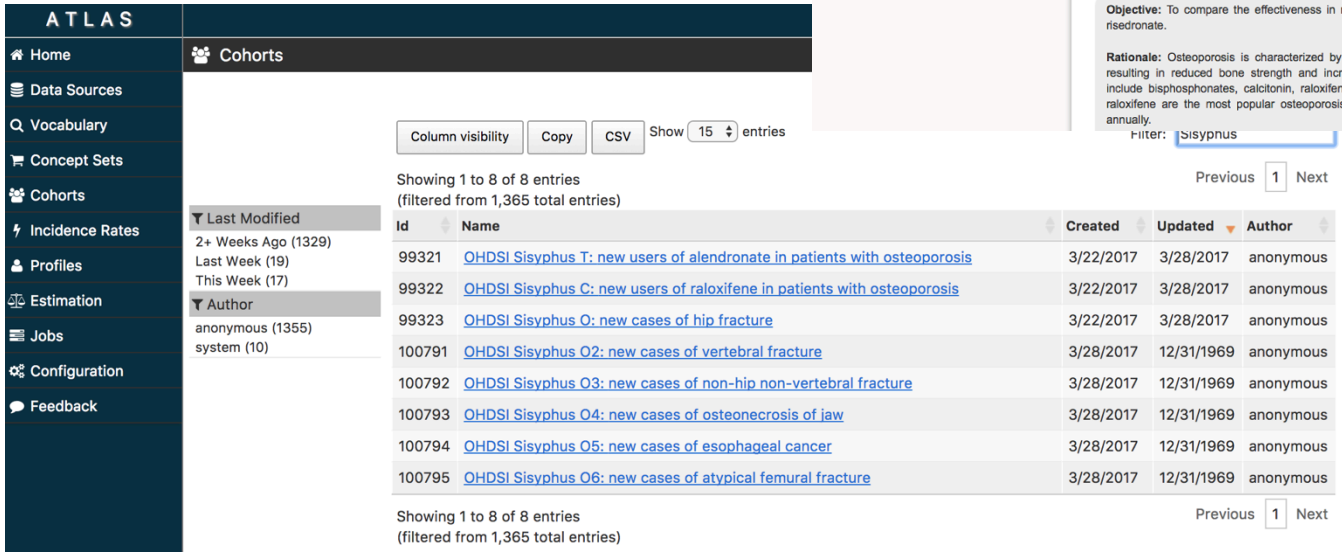
- Estimate exposure effect in outcome-free survival
- Risk window: +90 days → end of observation — Primary
- Propensity score stratified, full diagnostics and negative controls

Open-source study: ATLAS / Cyclops / CohortMethod

To foster community participation, everything was open:

Online protocol with community feedback





Full specified cohorts and open-source analysis

Data sources and unadjusted rates

Claims:

- IMS P-Plus
- Optum CEDM
- Truven CCAE
- Truven MDCR
- Truven MDCD

EHR:

- Cerner UT
- Columbia
- Stanford

	Alendronate				Raloxifene			
Outcome	Patients	Years	Events	Rate	Patients	Years	Events	Rate
Hip fracture (fx)	265,820	982,458	7,738	7.88	39,149	148,257	1,007	6.79
Vertebal fracture	261,731	963,932	8,628	8.95	38,736	146,147	1,131	7.74
Atypical femoral fx	266,141	999,462	1,160	1.16	39,187	150,841	104	0.70
Esophageal cancer	266,222	1,002,196	220	0.22	39,166	150,970	34	0.23
Jaw osteonecrosis	266,301	1,002,578	101	0.10	39,195	151,080	9	0.06

Rate: incidence per 1,000 person-years

> 1 million person-years of observation

Hip fractures by database

	Alendronate			Raloxifene		
Data source	Patients	Years	Events	Patients	Years	Events
IMS PPlus	78,155	245,336	1,216	10,742	34,711	117
Optum CEDM	67,100	262,467	2,495	10,167	40,528	323
Truven CCAE	64,003	228,085	432	10,534	38,655	63
Truven MDCR	47,576	210,908	3,247	6,459	29,840	457
Truven MDCD	4,570	16,454	209	369	1,340	19
Cerner EHR	2,644	8,867	100	787	2,740	23
Columbia EHR	1,131	7,696	24	49	298	<6
Stanford Stride	641	2,645	15	42	145	<6
Total	265,820	982,458	7,738	39,149	148,257	1,007

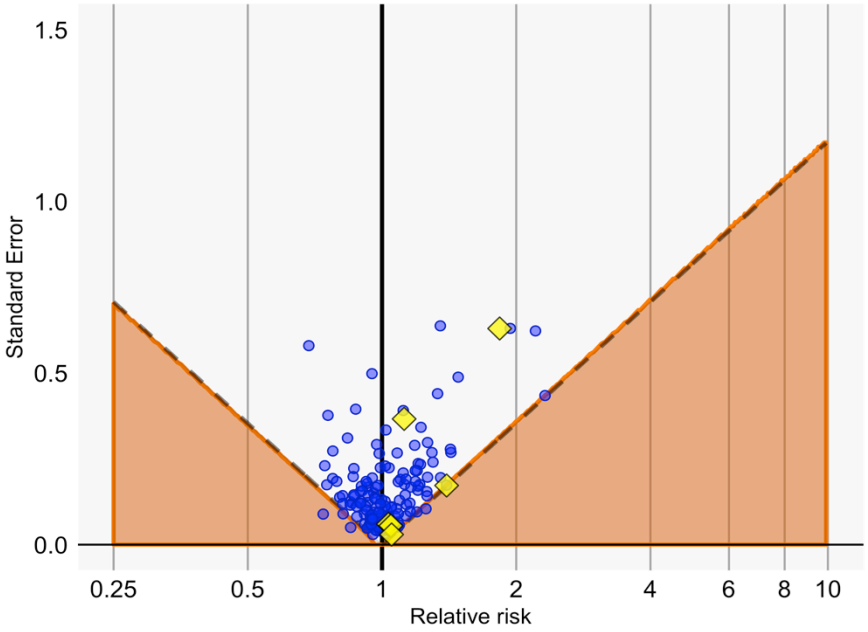
97% of patients from claims databases

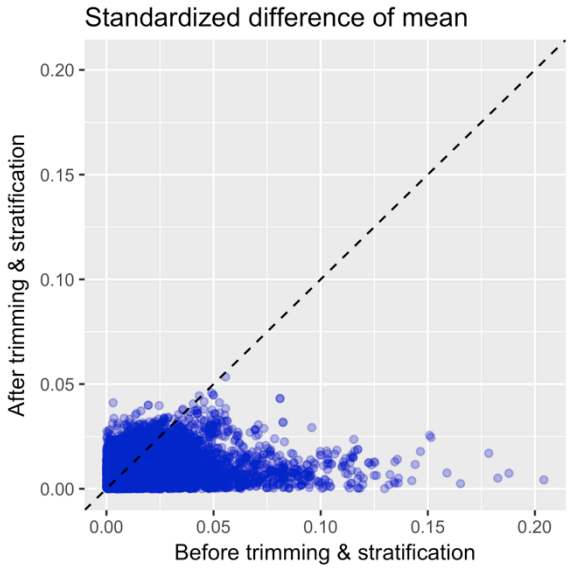
Propensity scores / diagnostics

Optum CEDM

- Cohorts are well-balanced after stratification
  - PS raloxifene predictors:
    Recent gyn exam, GERD, younger

- Negative controls show ***minimal bias***



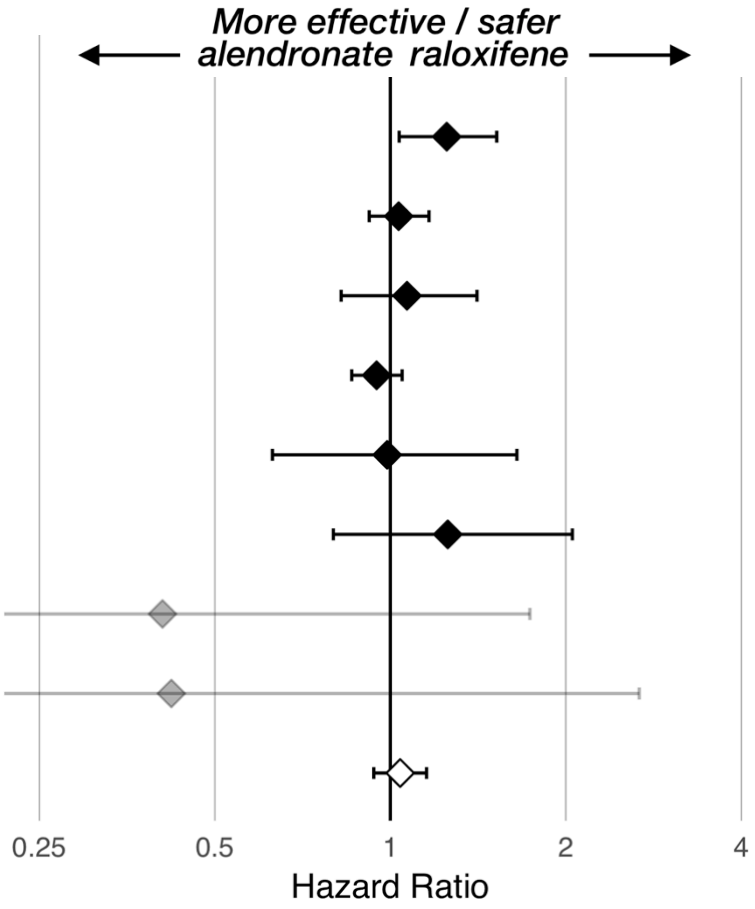


Achieved balance across databases

Data source	Before	After
IMS PPlus	0.23	0.04
Optum CEDM	0.20	0.05
Truven CCAE	0.16	0.05
Truven MDCR	0.20	0.06
Truven MDCD	0.32	0.21
Cerner EHR	0.46	0.13
Columbia EHR	0.73	0.44
Stanford Stride	0.45	0.44

Hip fracture hazard ratio

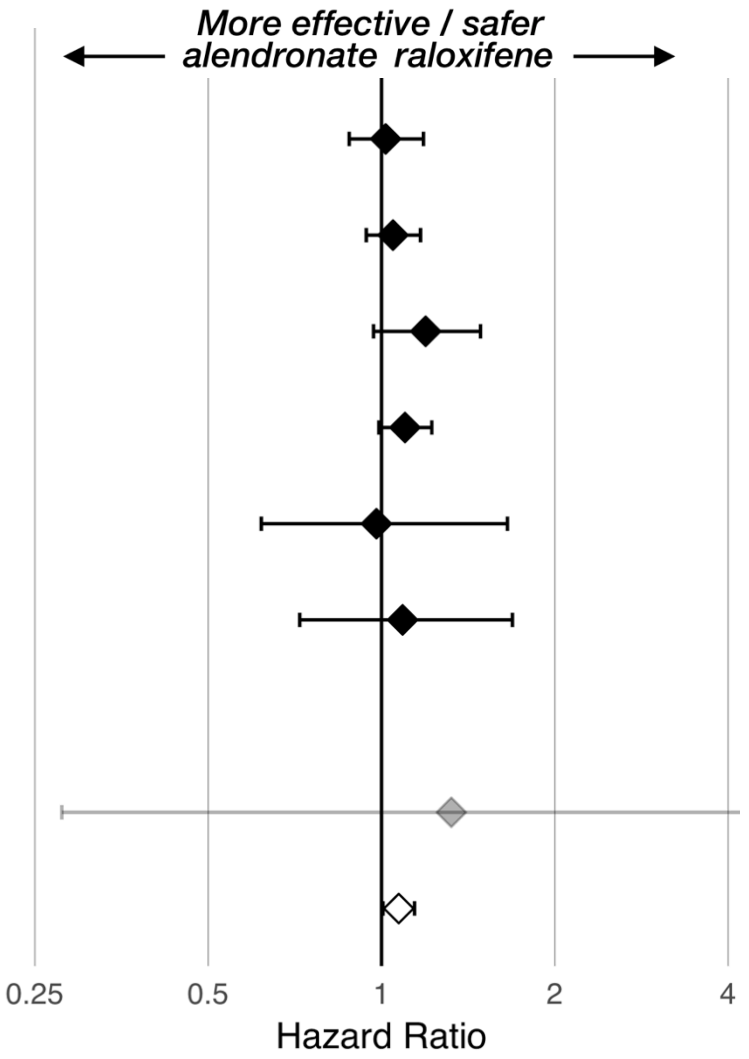
	Hazard Ratio (95% CI)
IMS PPlus	1.25 (1.04–1.52)
Optum CEDM	1.03 (0.92–1.16)
Truven CCAE	1.07 (0.82–1.41)
Truven MDCR	0.95 (0.86–1.05)
Truven MDCD	0.99 (0.63–1.65)
Cerner EHR	1.25 (0.80–2.05)
Columbia EHR	0.41 (0.14–1.74)
Stanford Stride	0.42 (0.12–2.67)
Summary	1.04 (0.94–1.15)



No significant difference in hip fracture risk

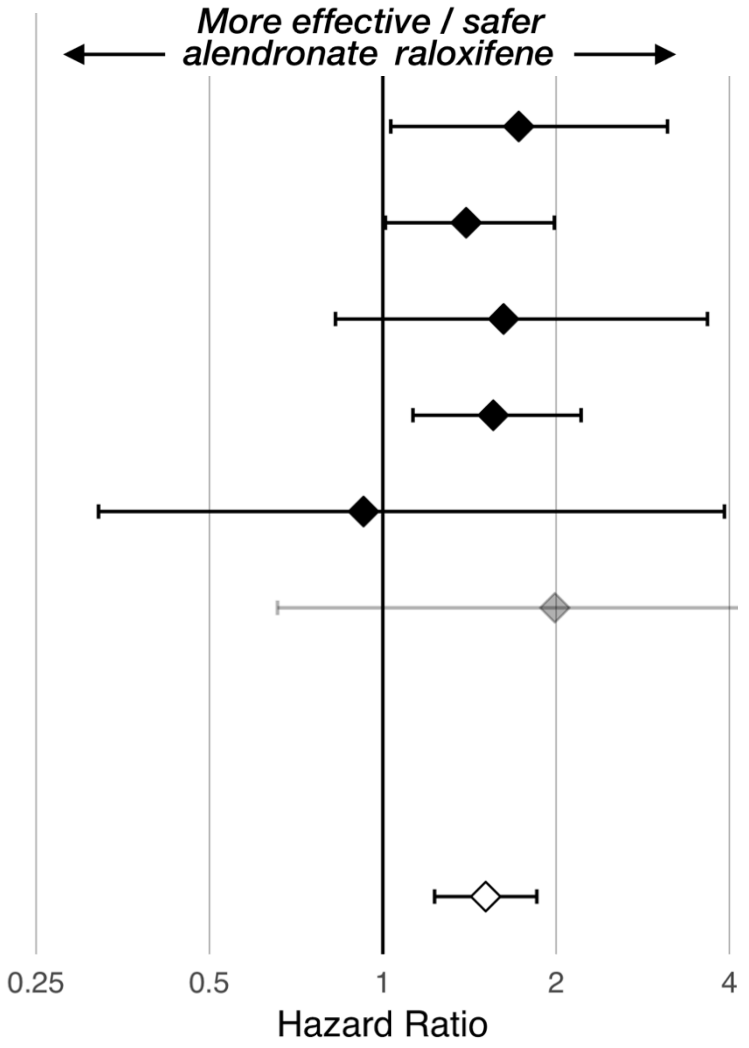
Vertebral fracture hazard ratio

	Hazard Ratio (95% CI)
IMS PPlus	1.02 (0.88–1.18)
Optum CEDM	1.05 (0.94–1.17)
Truven CCAE	1.19 (0.97–1.49)
Truven MDCR	1.10 (0.99–1.22)
Truven MDCD	0.98 (0.62–1.65)
Cerner EHR	1.09 (0.72–1.69)
Columbia EHR	––
Stanford Stride	1.32 (0.28–23.7)
Summary	1.07 (1.01–1.14)



Atypical femoral fracture hazard ratio

	Hazard Ratio (95% CI)
IMS PPlus	1.72 (1.03–3.12)
Optum CEDM	1.40 (1.01–1.99)
Truven CCAE	1.62 (0.83–3.66)
Truven MDCR	1.56 (1.13–2.21)
Truven MDCD	0.93 (0.32–3.92)
Cerner EHR	1.99 (0.66–8.64)
Columbia EHR	––
Stanford Stride	––
Summary	1.51 (1.23–1.85)



Evidence-based clinical pearls

- No significant difference between alendronate and raloxifene in risk of hip fracture
- Potentially lower risk of vertebral and atypical femoral fracture risk on raloxifene
- The OHDSI community is eager and able to engage in studies to improve health care
- My patient should continue to play with her grandson

One must imagine Sisyphus happy - Camus