Abstract 1 for Rheumatology Conference (Deadline: 28 October 2016, word limit: 450)

Title: Comparative fracture risk amongst users of different anti-osteoporosis therapies: meta-analysis of propensity-matched cohort studies using data from the Clinical Practice Research Datalink (UK) and SIDIAP (Spain).

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Background: Despite the existence of plentiful evidence on the efficacy of anti-osteoporosis drugs (AOD) to prevent fractures in randomized controlled trials [1-4], there is a need for data on their comparative effectiveness and safety in actual practice [5, 6].

Objectives: We aimed to compare the anti-fracture effectiveness of available AODs based on the observed risk of fracture while on treatment using 'real world' data from the UK NHS and Spanish healthcare records.

Methods: A cohort study was conducted including all users of anti-osteoporosis medications registered in the CPRD database and in the SIDIAP database in 1995-2014 and 2006-2014 respectively. The Clinical Practice Research Datalink (CPRD) and the SIDIAP database contain pseudonymised primary care records for a representative >10 million and >6 million UK NHS and Catalan healthcare system users respectively.

Exposure was use (as defined by GP prescriptions in CPRD and pharmacy dispensations in SIDIAP) of alendronate (reference group) compared to 1) other oral bisphosphonates, 2) strontium ranelate, and 3) SERMs. Users of denosumab and teriparatide were excluded due to low numbers (n =29 and n =7 respectively) in the CPRD database.

Major fractures (hip, spine, wrist, and proximal humerus) while on treatment were the main outcome, with secondary analyses of hip, and all (except digits and skull/face) non-hip fractures.

Statistics: Multiple imputation was used to handle missing data on co-variables, and propensity score matching (PSM) [7] was performed to minimise the effect of confounders (Table 1). A proportional sub-distribution hazards regression model was used to estimate relative risk of fracture (SHR) with a competing risk of death [8].

Results: Data for 163,950 patients and 145,236 was included in the analysis from the CPRD and SIDIAP datasets, respectively. Meta-analysis showed no significant association was found between fracture(s) and AOD use except for SERM users who appeared to have a reduced fracture risk (Table 1). In addition, a lower risk was seen amongst users of other bisphosphonates in the SIDIAP dataset (SHR 0.88 (95%CI 0.85 0.91)), which did not replicate in CPRD (SHR 1.15 (95%CI 0.95, 1.39)).

Discussion: We found no evidence of differential anti-fracture effectiveness of different AODs in actual practice. The finding of reduced fracture risk amongst SERM users is likely related to residual confounding due to lack of data on disease severity (i.e. bone mineral density). The relatively lower risk amongst other bisphosphonate users in the SIDIAP (but not replicated in the CPRD) dataset is likely due to differential conditions of use in both countries and related confounding by indication.

Table 1. Fracture incidence rate in person years (IR) and relative risk (SHR) amongst different drug users compared to comparable (propensity-matched) alendronate users. Confounders for PSM included age, gender, body mass index, smoking, drinking, fracture/s history, Charlson co-morbidity index, and concomitant medications (oral glucocorticoids, anti-coagulants, hormone replacement therapy and contraceptives, aromatase inhibitors, calcium, corticosteroids, heparin, anxiolytics and sedatives). Effect size = average effect size (from forest plot) of the meta-analysis.

		CPRD-90day		**SIDIAP**		**Effect Size**
Fracture	**Drug**	IR (100 py)	SHR (95% CI)	IR (100 py)	SHR (95% CI)	OR (95% CI)
Major osteoporotic	Alendronate	1.39 1.41	ref	3.01	ref	180-day:0.89 (0.86, 0.92) *90-day:0.92 [0.89 to 0.95]*
	Other bisphosphonates	1.63 1.64	1.15 (0.95, 1.39) 1.13 (1.05 1.21), 0.00062	2.52	0.88 (0.85, 0.91)	
	Alendronate	2.05 2.11	ref	2.93	ref	1.07 (1.02, 1.12) *[1.01 to 1.11]*
	Strontium ranelate	2.73 2.77	1.20 (0.99, 1.45) 1.1 (0.91, 1.34), 0.33	2.97	1.06 (1.01, 1.11)	
	Alendronate	0.79 0.89	ref	2.19	ref	0.71 (0.67, 0.75)
	SERMs	0.59 0.67	0.72 (0.50, 1.0) 0.76 (0.53,1.08), 0.12	1.50	0. 71 (0.67, 0.76)	
Hip	Alendronate	0.79 0.80	ref	0.51	ref	1.03 (0.97, 1.09)
	Other bisphosphonates	0.98 0.98	1.21 (1.11, 1.32) 1.21(1.11,1.32), 3e-05	0.43	0.89 (0.82, 0.97)	
	Alendronate	1.42 1.36	ref	0.49	ref	1.25 (1.14, 1.38)
	Strontium ranelate	1.92 1.91	1.14 (0.91, 1.43) 1.16 (0.93, 1.45),0.19	0.59	1.28 (1.15, 1.42)	
	Alendronate	0.31 0.35	ref	0.23	ref	0.65 (0.53, 0.80)
	SERMs	0.27 0.27	0.73 (0.43, 1.23) 0.73 (0.43, 1.23), 0.3	0.14	0.64 (0.51, 0.79)	
Non-hip	Alendronate	1.19 1.19	ref	2.55	ref	0.92 (0.88, 0.96)
	Other bisphosphonates	1.28 1.28	1.05 (0.97, 1.13)	2.14	0.88 (0.84, 0.91)	

			1.05 (0.97, 1.13), 0.2			
	Alendronate	1.39 1.54	ref	2.51	ref	1.01 (0.97, 1.05)
	Strontium ranelate	1.72 1.72	1.1 (0.87, 1.39) 0.99 (0.79, 1.26), 0.99	2.44	1.01 (0.97 1.07)	
	Alendronate	0.92 0.99	ref	1.94	ref	0.72 (0.68, 0.78)
	SERMs	0.74 0.74	0.81 (0.59, 1.11) 0.81 (0.59, 1.11), 0.074	1.35	0.72 (0.67 0.77)	

Disclosures/ Conflict of Interest

DPA has received research funding from Servier Laboratoires and Amgen.

SK is funded by the Nuffield Department of Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford.

ALL AUTHORS TO FILL IN PLEASE

Funding statement

This work was funded by a Programme Grant from the National Osteoporosis Society. DPA received partial support from the Oxford NIHR Musculoskeletal Biomedical Research Unit (BRU).

Ethics Approval

ISAC approval was obtained for access to CPRD data. Ethics approval from the local board (Comite d'Etica en Investigacio Clinica Idiap Jordi Gol, Barcelona, Spain) was obtained for the analysis of SIDIAP data.

References (Supplementary information, not to be submitted with the abstract)

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