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Associations between osteoporosis and drug exposure: a post-marketing study of the World Health Organization pharmacovigilance database (VigiBase®)

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- Osteoporosis
- Drug
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- Pharmacovigilance

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27 **HIGHLIGHTS**

28

29 *What is already known about the subject?*

- 30 • Several drugs are known to induce osteoporosis and/or increase the fracture risk.
- 31 • Pharmacovigilance and pharmacoepidemiologic studies are crucial for the safety assessment of
- 32 marketed drugs.

33

34 *What this study adds?*

- 35 • New disproportionality signals with a pharmacologically plausible mechanism in bone fragility
- 36 were found for drugs used in the fields of neurology (selective 5-HT₁ agonists, levodopa and
- 37 memantine), hematology (romiplostim), pulmonology (macitentan), ophthalmology (ranibizumab),
- 38 and rheumatology (tofacitinib).

ABSTRACT

Background: Bone remodeling is a complex process, and many conditions (including drug exposure) lead to osteoporosis. Here, we sought to detect new disproportionality signals for drugs associated with osteoporosis.

Methods: We performed a disproportionality analysis of the World Health Organization's VigiBase® pharmacovigilance database through April 12, 2020. The frequency of reports on osteoporosis for all identified drug classes was compared with that for all other drugs and quoted as the reporting odds ratio (ROR) [95% confidence interval (CI)].

Results: Of the 7,594,968 cases spontaneously recorded to VigiBase®, 4,758 concerned osteoporosis. New disproportionality signals with a pharmacologically plausible mechanism were found for drugs used in neurology (levodopa (ROR [95%CI]: 10.18 [4.33–25.10]), selective serotonin agonists (4.22 [2.34–7.00]) and memantine (4.10 [1.56–8.93])), hematology (romiplostim (4.93 [1.15–21.10])), pulmonology (macitentan (3.02 [1.84–4.90])), ophthalmology (ranibizumab (3.31 [1.00–10.51])) and rheumatology (tofacitinib (3.65 [3.00–4.40])). The robustness of these new results is supported by the significant RORs for the vast majority of drugs already known to induce osteoporosis and/or increase the fracture risk, namely glucocorticoids, gonadotropin-releasing hormone analogs, anti-aromatases, androgen receptor blockers, thyroid hormones, proton pump inhibitors, thiazolidinediones, vitamin K antagonists, loop diuretics, protease inhibitors, nucleoside and nucleotide reverse transcriptase inhibitors, and enzyme-inducing antiepileptics including barbiturates and derivatives, hydantoin derivatives, carboxamide derivatives and fatty acid derivatives.

Conclusion: We established up a comprehensive list of drugs potentially associated with osteoporosis and highlighted those with pharmacologically plausible mechanisms leading to bone fragility. Our results might pave the way for additional exploration of these mechanisms.

62 **ABBREVIATIONS**

63	5-HT	5-hydroxytryptamine (serotonin)
64	ADR	adverse drug reaction
65	AI	aromatase inhibitor
66	ATC	Anatomical Therapeutic Chemical
67	BMD	bone mineral density
68	CI	confidence interval
69	COX	cyclooxygenase
70	DMARD	disease modifying anti-rheumatic drug
71	ET-1	endothelin-1
72	GnRH	gonadotropin-releasing hormone
73	HCQ	hydroxychloroquine
74	ICSR	individual case safety report
75	IL	interleukin
76	IRD	inflammatory rheumatic disease
77	JAK	Janus kinase
78	MedDRA	Medical Dictionary for Regulatory Activities
79	Mpl	myeloproliferative leukemia virus oncogene
80	MS	multiple sclerosis
81	MTX	methotrexate
82	NFκB	nuclear factor-kappa B
83	NMDA	N-methyl-D-aspartate
84	NNRT	nucleoside and nucleotide reverse transcriptase
85	OB	osteoblast
86	OC	osteoclast
87	PDE-5	phosphodiesterase-5

88	PG	prostaglandin
89	PI	protease inhibitor
90	PPI	proton pump inhibitor
91	RA	rheumatoid arthritis
92	RANKL	receptor activator of nuclear factor-kappa B ligand
93	ROR	reporting odds ratio
94	SD	standard deviation
95	sGC	soluble guanylate cyclase
96	SMQ	standardized MedDRA query
97	SSRI	selective serotonin reuptake inhibitor
98	STAT	signal transducers and activators of transcription
99	TPO	thrombopoietin
100	TTR	transthyretin
101	VEGF	endothelial growth factor
102	VKA	vitamin K antagonist
103	WHO	World Health Organization

INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD), microarchitectural deterioration of the bone tissue, and a consequential increase in bone fragility [1].

Bone fractures (the main complication of osteoporosis) have a major impact on health and quality of life and constitute a significant economic burden [2].

The conditions or factors that lead to osteoporosis and/or an elevated fracture risk include age, sex, race, smoking, alcohol consumption, body weight, poor nutrition or any cause of malabsorption, low calcium and vitamin D intakes, chronic inflammatory rheumatic diseases (IRDs, particularly rheumatoid arthritis (RA)), other inflammatory diseases, endocrine disorders, bone marrow disorders, immobilization, a history of fractures, and the fall risk [3].

Furthermore, several drugs are known to induce osteoporosis and/or increase the fracture risk: systemic, inhaled and topical glucocorticoids [4], some hormone preparations (gonadotropin-releasing hormone (GnRH) analogs [5], aromatase inhibitors (AIs) [6], androgen receptor blockers [7], and thyroid hormones [8]), proton pump inhibitors (PPIs) [9], thiazolidinediones [10], vitamin K antagonists (VKAs) [11], loop diuretics [12], protease inhibitors (PIs), nucleoside and nucleotide reverse transcriptase (NNRT) inhibitors [13,14], opioids [15,16], antiepileptics [17], antipsychotics [18,19], benzodiazepines [20], antidepressants (mainly selective serotonin reuptake inhibitors (SSRIs)) [21], vitamin A [22], and heparin during pregnancy [23].

Although phase III studies are very robust tools for assess drug effectiveness, they are less able to evaluate adverse drug reactions (ADRs) because of the small sample sizes, highly selected populations, and short follow-up periods [24]. Hence, post-marketing pharmacoepidemiologic studies are important for detecting rare or long-term ADRs, such as osteoporosis in long-term users of PPIs [9] or VKAs [11]. Disproportionality analysis lies at the interface between pharmacovigilance and pharmacoepidemiology. It is usually based on the assessment of spontaneous individual case safety reports (ICSRs) and can detect early disproportionality signals for specific ADRs, which must then be confirmed by more specific pharmacoepidemiologic studies [25]. For example, a

disproportionality signal (defined as reports of events that are significantly disproportionate, i.e. an observed/expected ratio exceeding a specific threshold [26]) was detected for rofecoxib and thrombotic ADRs as early as the end of 2001 [27]. The drug was withdrawn from the market for this reason in September 2004.

Pharmacovigilance and pharmacoepidemiologic studies have identified a broad range of drug classes associated with an osteoporotic risk. The safety of recently marketed drugs must be assessed regularly. Dardonville et al. recently analyzed drug-induced osteoporosis in the French and Spanish pharmacovigilance databases but did not perform a disproportionality analysis that might have detected new disproportionality signals [28].

Consequently, we analyzed a global pharmacovigilance database in order to (i) provide an overview of drugs already known to induce osteoporosis and/or increase the fracture risk, and (ii) detect new disproportionality signals for osteoporosis and discuss potential mechanisms underlying bone fragility.

METHODS

2.1. Data source

ICSRs were collected from VigiBase® – the world’s largest pharmacovigilance database, curated by the World Health Organization (WHO) [29]. Each ICSR includes anonymous administrative data (the country, and the reporter’s qualification), patient information (age and sex), drug information (the international non-proprietary name or the trade name, Anatomical Therapeutic Chemical (ATC) classification, indication, start date, withdrawal date, dosage, and administration route), and information on the suspected ADR (coded according to the Medical Dictionary for Regulatory Activities (MedDRA)) [30]. There are five levels in the MedDRA hierarchy, ranging from very general to very specific. MedDRA also includes standardized MedDRA queries (SMQs), which are collections of MedDRA terms consistent with a description of a clinical syndrome associated with an ADR and

drug exposure [31]. As such, SMQs are useful for wide-ranging searches. There are two types of SMQ: the narrow SMQ contains fewer MedDRA terms than the broad SMQ and is therefore more specific. If a drug is considered to be at least probably responsible for the ADR, it is defined as “suspect” or “interacting” in the ICSR. If not, it is defined as “concomitant.” Probability scales are based on a variety of temporal, semiologic, and/or bibliographic criteria [32]. Full information on ICSRs is given on the Uppsala Monitoring Centre’s website [26].

2.2. Study design

Using the narrow SMQ “Osteoporosis/osteopenia” (including the MedDRA preferred terms “Bone density decreased”, “Bone formation decreased”, “Bone loss”, “Bone marrow oedema syndrome”, “Osteopenia”, “Osteoporosis”, “Osteoporosis postmenopausal”, “Osteoporotic fracture”, “Resorption bone increased”, “Senile osteoporosis”), we selected ICSRs recorded in Vigibase between January 1, 1967, and April 12, 2020. In order to analyze only the best-documented ICSRs (particular with regard to the nature of adverse drug reactions and the suspected or concomitant medications), we selected ICSRs filed by physicians, pharmacists, or other health professionals. Lastly, we analyzed only ICSRs for which the sex and age (18 or over) were reported. We then analyzed drugs reported as being “suspect” in least in three ICSRs [33]. Given the large number of suspect drugs at the 5th level of the ATC classification, we pooled the active substances at the 3rd level (the pharmacological subgroup) or the 4th level (the chemical subgroup) corresponding to the mechanism of action. In order to avoid the question of poor drug effectiveness, we excluded ICSRs for which the suspected, interacting, or concomitant drugs were indicated in osteoporosis, i.e. bisphosphonates (ATC M05BA and M05BB), denosumab (ATC M05BX04), burosumab (ATC M05BX05), romosozumab (ATC M05BX06), teriparatide (ATC H05AA02), abaloparatide (ATC H05AA04), strontium renalate (ATC M05BX03 and M05BX53), selective estrogen receptor modulators (ATC GX03XC), estrogen replacement therapy (ATC G03AA, G03AB, G03C, G03EA, G03EB,

G03F, L02AA), calcitonin preparations (ATC H05BA), calcium (ATC A12A), and vitamin D and its analogs (ATC A11CC).

2.3. Statistical analysis

In our descriptive analysis, categorical variables were expressed as the number (percentage), and continuous variables were expressed as the mean \pm standard deviation (SD) or, as appropriate, the median (range).

Several types of disproportionality analysis are available in the literature. Here, we chose to calculate reporting odds ratio (ROR) and its 95% confidence interval (CI) as a gauge of the association between a suspected drug and osteoporosis in the ICSRs filtered over the study period. This case/non-case approach is the best way to deal with the limitations of a database of spontaneous reports and to interpret the results optimally [34]. The ROR calculation method has been described elsewhere [25]. Briefly, $ROR = (a/c)/(b/d)$, where (a) is the number of osteoporosis ADRs with the suspected drug, (b) is the number of osteoporosis ADRs with all other drugs, (c) is the number of ADRs other than osteoporosis with the suspected drug, and (d) is the number of ADRs other than osteoporosis with all other drugs. If the ROR and the lower boundary of its 95%CI are above than 1, the ADR of interest is reported more frequently with the drug of interest than with all other drugs. It has been suggested that an ROR above 4 corresponds to a “large” effect size [25].

Given that many conditions can lead to osteoporosis, we expected to see false-positive RORs confounded by the disease itself and “disease spill-over” (i.e. aspects of the treated disease coded as an ADR, namely osteoporosis). In this case, the disproportionality signal would reflect the risk associated with the indication and not with the drug itself. Thus, we minimized this indication bias by stratifying the RORs by therapeutic area; we defined the comparator as the suspected drug’s therapeutic or pharmacological class, rather than all other drugs [35]. The therapeutic areas

considered in the analyses are summarized in **Supplementary Table S1**. The RORs were adjusted for age and sex, using logistic regressions.

Bias due to competition between events might mask interesting RORs and can be observed when the suspected drug is strongly associated with another ADR [36,37]. This bias can be minimized by removing the competitor event [37]. We therefore performed sensitivity analyses when RORs were not significant for drugs already known to be associated with osteoporosis by removing the most frequently reported ADR for each drug concerned from the analysis. Overall, this case was encountered only for antithrombotic agents, where the SMQ “Haemorrhages” was removed from the analysis for this drug class.

We performed sensitivity analyses by applying the above-mentioned method to (i) the broad SMQ “osteoporosis/osteopenia”, which includes ADRs related to fractures, a decrease in BMD, and changes in markers of bone turnover (such as elevated urine levels of collagen cross-linked N-telopeptide and elevated serum levels of collagen C-telopeptide), and (ii) the MedDRA terms related to fractures. The MedDRA terms related to the broad and narrow SMQs and to fractures are given in **Supplementary Table S2**.

All analyses were performed using R software (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

3.1. Study population

After the exclusion of drugs indicated in osteoporosis, 4,758 of the 7,594,968 ICSRs in adult patients of known age and sex reported by physicians, pharmacists or other health professionals to Vigibase® between January 1, 1967, and April 12, 2020, matched the narrow SMQ “osteoporosis/osteopenia”. There was a single suspect drug in 2,798 (58.8%) of the ICSRs. The mean \pm SD age was 57.1 ± 15.6 . The cases predominantly occurred in females (65.9%). The characteristics of the study population are summarized in **Table 1**.

3.2. Disproportionality analysis

3.2.1. Drugs already known to induce osteoporosis and/or increase the fracture risk

The adjusted RORs (aRORs) [95%CI] were significant for PPIs (12.12 [6.79–24.21]), thiazolidinediones (1.80 [1.11–2.82]), heparins (3.69 [2.75–4.92]), high-ceiling diuretics (2.37 [1.19–4.84]), systemic, inhaled and topical corticosteroids (14.14 [13.17–15.18], 2.55 [2.02–3.24] and 13.06 [12.17–14.00], respectively), antiandrogens (7.76 [3.78–14.84]), thyroid hormones (2.44 [1.64–3.46]), PIs (1.75 [1.38–2.18]), NNRT inhibitors (2.78 [2.37–3.25]), GnRH analogs (4.21 [3.25–5.45]), AIs (4.21 [3.25–4.45]), and enzyme-inducing antiepileptics, including barbiturates and derivatives (7.35 [5.05–10.43]), hydantoin derivatives (7.89 [1.32–2.64]), carboxamide derivatives (1.93 [1.42–2.59]) and fatty acid derivatives (2.06 [1.50–2.79]). The RORs are represented graphically in **Figures 1** and **2**.

These results were consistent with sensitivity analyses (**Supplementary Figures S1-S42**), with the exception of the following drugs. The aROR for heparin was not significant in the broad SMQ (0.69 [0.58–0.81], **Supplementary Figure S5**) but was significant in the fractures subset (3.69 [2.72–5.00], **Supplementary Figure S6**)). The aROR for thyroid hormones was not significant in the broad SMQ (0.83 [0.62–1.08], **Supplementary Figure S17**) but was significant in the fractures subset (2.65 [1.75–3.81], **Supplementary Figure S18**)). The aROR for opioids was significant in the broad SMQ (1.67 [1.47–1.89], **Supplementary Figure S29**) and not in the fractures subset (1.21 [0.83–1.71], **Supplementary Figure S30**)). The aROR for benzodiazepine-related hypnotics and sedatives was significant in the broad SMQ (1.34 [1.12–1.60], **Supplementary Figure S29**) but not in the fractures subset (0.55 [0.22–1.14], **Supplementary Figure S30**)). The aROR for retinoids in treatment of psoriasis was significant in the fractures subset (6.16 [1.44–42.22], **Supplementary Figure S12**).

For VKAs, the aROR was significant after removing the SMQ “Haemorrhages” from the analysis (1.68 [1.52–1.86], **Figure 3**) but not before (0.37 [0.31–0.44]; **Supplementary Figures S4-S6**). The RORs were not significant for platelet aggregation inhibitors, even the SMQ “Haemorrhages” had been removed from the analysis.

259

260 *3.2.2. New disproportionality signals*

261 In group A of the ATC classification, the aROR [95%CI] was significant for imiglucerase (4.87 [1.24–

262 20.33], **Figure 1**).

263 In group B of the ATC classification, the aRORs was significant for romiplostim (4.93 [1.15–21.10]),

264 **Figure 1**).

265 In group C of the ATC classification, the aRORs were significant for antihypertensives for pulmonary

266 arterial hypertension (particularly macitentan (3.02 [1.84–4.90]) and riociguat (2.83 [1.25–5.59],

267 **Figure 1**).

268 In group G of the ATC classification, the aROR was significant for sildenafil (2.84 [1.29–5.63]), **Figure**

269 **1**).

270 In group L of the ATC classification, the aRORs were significant for interferon beta-1a (9.49 [6.66–

271 13.73], **Figure 1**), mycophenolic acid (2.53 [1.99–3.16]), sirolimus (2.12 [1.02–3.85]), leflunomide

272 (4.84 [3.84–6.03]), abatacept (5.06 [4.08–6.20]), belimumab (3.17 [1.25–6.46]), tofacitinib (3.65

273 [3.00–4.40]), tocilizumab (6.16 [5.08–7.41]), calcineurin inhibitors (1.43 [1.11–1.80]), and

274 azathioprine (2.26 [1.69–2.96]), **Figure 2**).

275 In group M of the ATC classification system, the aRORs were significant for nonsteroidal anti-

276 inflammatory drugs (1.25 [1.11–1.40]), particularly for cyclooxygenase inhibitors (coxibs: 10.28 [8.06–

277 13.19], **Figure 2**).

278 In group N of the ATC classification, the aRORs were significant for selective serotonin (5-HT) agonists

279 (4.22 [2.34–7.00]), dopaminergic agents particularly dopa and its derivatives (10.18 [4.33–25.10]),

280 memantine (4.10 [1.56–8.93]), sodium oxybate (4.79 [2.75–7.66]) and amifampridine (43.60 [13.51–

281 104.15], **Figure 2**).

282 In group P of the ATC classification, the aROR was significant for hydroxychloroquine (7.91 [6.70–

283 9.26], **Figure 2**).

In group R of the ATC classification system, the aRORs were significant for omalizumab (2.38 [1.67–3.29]) and mepolizumab (2.94 [1.51–5.12], **Figure 2**).

In group S of the ATC classification, the aROR was significant for ranizumab (3.31 [1.00–10.51], **Figure 2**).

In group V of the ATC classification, the RORs were significant for iron-chelating agents (4.20 [2.58–6.39]) and radium Ra 223 dichloride (5.13 [1.27–13.36], **Figure 2**).

All these results were consistent with those of the sensitivity analyses, with the exception of imiglucerase (3.75 [0.86–16.24], **Supplementary Figure S3**), romiplostim (2.43 [0.33–12.68], **Supplementary Figure S6**), and radium Ra 223 dichloride (4.05 [0.67–12.55], **Supplementary Figure S42**) in the fractures subset, and for riociguat (1.09 [0.82–1.42], **Supplementary Figure S8**), mycophenolic acid (0.67 [0.57–0.78], **Supplementary Figure S23**), sirolimus (0.87 [0.58–1.24], **Supplementary Figure S23**), belimumab (1.59 [0.95–2.49], **Supplementary Figure S23**), calcineurin inhibitors (0.57 [0.49–0.65], **Supplementary Figure S23**), azathioprine (0.80 [0.66–0.92], **Supplementary Figure S23**), and nonsteroidal anti-inflammatory drugs (0.72 [0.67–0.77], **Supplementary Figure S26**) in the broad SMQ.

DISCUSSION

Our results are in line with the literature data and provide a comprehensive overview of drugs associated with osteoporosis and the risk of fracture. Furthermore, we report on new disproportionality signals for (i) drugs previously linked via clinical studies to a lower BMD and/or a higher fracture risk, (ii) drugs whose pharmacological properties provide a rationale for a potential effect on bone metabolism, and (iii) drugs that do not belong to either of the previous categories.

4.1. Drugs with previously published clinical data on a potential association with osteoporosis

The aRORs were significant for the vast majority of drugs already known to induce osteoporosis and/or increase the fracture risk, namely systemic, inhaled and topical glucocorticoids, GnRH

analogs, AIs, androgen receptor blockers, thyroid hormones, PPIs, thiazolidinediones, VKAs, loop diuretics, PIs, NNRT inhibitors and enzyme-inducing antiepileptics; however, the aRORs were also significant for opioids and benzodiazepines in the broad SMQ [4–21]. When considering vitamin A and its derivatives, the aROR was significant only for retinoids for the treatment of psoriasis in the fractures subset but not in the broad or narrow SMQs. Their use in clinical studies is associated with a lower BMD and a higher fracture risk [22,38] through osteoblast (OB) inhibition, osteoclast (OC) differentiation, and an antagonism of vitamin D's action [39–41]. Vitamin A and its derivatives are scattered across the ATC classification system (with vitamin A [A11CA01], retinoids for treatment of psoriasis [D05BB], topical retinoids for acne [D10AD], systemic retinoids for acne [D10BA], retinoids for cancer treatment [L01XF], and retinol eye drops [S01XA02]); this prevented us from calculating the overall ROR for this drug class.

We found a significant ROR for radium 223 dichloride, which is indicated in metastatic prostate cancer. This calcium-mimetic radioisotope was recently shown to induce osteoporosis with a high risk of vertebral fractures, independently of androgen deprivation therapy and abiraterone therapy [42]. This radioisotope binds selectively to hydroxyapatite in areas of increased bone remodeling; the short-range emission of high-energy alpha particles probably leads to bone fragility [43].

Testosterone-5-alpha reductase inhibitors (used in prostate cancer) prevent the conversion of testosterone to dihydrotestosterone. Low concentrations of dihydrotestosterone predispose men to a risk of osteoporosis [44] because this hormone is approximately ten times more potent than its precursor testosterone, and is the preferred ligand for androgen receptor transactivation [45]. Nevertheless, observational studies have yielded inconsistent findings [46–48].

Methotrexate (MTX, indicated in several chronic IRDs at low doses but also used to treat cancer at very high doses) appears to induce osteoporosis and increase the fracture risk in a dose-dependent manner. At high doses, MTX induces osteoporosis and fractures regardless of corticosteroid use [49–51] in a way that has not yet been fully elucidated – possibly through increased urinary calcium

excretion [52]. At low doses in IRDs, MTX use is not associated with lower BMD or a higher fracture risk [53–57].

In vivo, calcineurin inhibitors (indicated in patients undergoing organ transplantation) cause bone loss and increase the fracture risk [58] due to increased bone resorption - notably because of changes in T-cell cytokine production and altered vitamin D metabolism, with secondary hyperparathyroidism [59].

Azathioprine inhibits purine synthesis and also leads to autophagy [60]. A recent *in vivo* study found that the use of this drug is associated with a deterioration in the bone's trabecular microarchitecture, which might induce the autophagy pathway [60]. Azathioprine's detrimental effects on bone have already been described *in vivo* [61], and the results of an observational study showed an elevated fracture risk [62].

The involvement of non-steroidal anti-inflammatory drugs in bone remodeling appears to be complex and depends on the type of cyclooxygenase (COX) inhibited, sex, and hormone status. Prostaglandin (PG)E₂ and prostacyclin have complex roles in bone remodeling cycle; they may stimulate bone resorption (particularly PGE₂) as well as bone formation [63–65]. The literature data are contradictory. In a systematic review, aspirin (which inhibits COX-1 at low doses and both COX-1 and COX-2 at high doses) is associated with a decrease in the fracture risk and an increase in BMD in both men and women [66]. In a multicenter cohort study, COX-2-specific inhibitors are associated with a lower BMD in men and with a higher BMD in postmenopausal women not using estrogen replacement therapy [67]. In a large cohort study, the combination of coxibs with low-dose aspirin was associated with an increase in BMD in both men and women [68]. Nevertheless, we found a significant aROR only for coxibs.

4.2. Drugs with a pharmacological rationale for a potential bone effect but that have not yet been investigated in clinical studies

Romiplostim – indicated in immune thrombocytopenia – activates c- myeloproliferative leukemia virus oncogene (c-Mpl); this is the receptor for thrombopoietin (TPO) present in megakaryocytes and OCs, which are derived from the same hematopoietic precursor [69]. *In vitro*, TPO increases OC formation and differentiation through the mitogen-activated protein kinases, Janus kinases (JAKs)/signal transducers and activators of transcription (STAT), and nuclear factor-kappa B (NFκB) signaling pathways by activating c-Mpl [70]; this mechanism might explain our results.

We found a significant aRORs for macitentan - an endothelin-1 (ET-1) receptor antagonist indicated in pulmonary arterial hypertension. This finding is consistent with *in vitro* studies showing that exogenous ET-1 stimulates OB proliferation/differentiation and type I collagen production and inhibits osteoclastic resorption [71–73]. Moreover, ET-1 levels in a clinical study were positively correlated with BMD at the lumbar spine in non-osteoporotic women [74]. However, the drug class's possible direct effect on bone was not evaluated.

It is well known that Parkinson's disease is associated with bone loss through immobilization or hypokinesia. However, dopaminergic depression alters the sympathetic innervation of bone, which is fundamental for bone homeostasis [75,76]. Furthermore, the breakdown of L-dopa by catechol-O-methyltransferase results in greater homocysteine formation [77]. In turn, high level of homocysteine lead to osteoporosis and fractures - possibly through impaired collagen cross-linking [78]. This has been confirmed in mice but not in humans, where dopamine replacement treatment with levodopa further reduces the bone mass and raises the serum level of homocysteine [76].

The use of SSRIs appears to be associated with a reduction in BMD and an elevated risk of fracture [79]. SSRIs increase serum serotonin concentrations, and it has been suggested that serum 5-HT downregulates osteoblast proliferation, bone formation, and bone mass via the 5-HT_{1B} receptor [80–82]. On the same lines, selective 5-HT₁ agonists (some of which are indicated in migraine) bind to 5-HT_{1B/D} receptors, which might impair bone formation. Nevertheless, no clinical data on this topic have been published.

The N-methyl-D-aspartate (NMDA) receptor antagonist memantine is indicated in dementia. Mechanical loading (which contributes to the normal bone remodeling process [83]) increases the expression of NMDA receptors on OBs and OCs [84]. Accordingly, experiments *in vitro* and in an animal model showed that the downregulation of NMDA receptor expression decreased osteogenesis [85].

Ranibizumab – indicated in age-related macular degeneration – is a vascular endothelial growth factor (VEGF)-A inhibitor that has an important role in angiogenesis and osteogenesis [86]. A recent study showed that enhancing VEGF-A expression promotes osteogenesis in the context of postmenopausal osteoporosis [87]. Hence, ranibizumab might impair bone homeostasis.

Tofacitinib – indicated in RA – is a JAK1/JAK3 inhibitor. *In vivo*, JAK1 inhibition can lead to an osteoporotic bone phenotype [88] and JAK3 inhibition *via* the inactivation of signal transducers and activation of transcription 3 (STAT3) in OBs [89]. Moreover, STAT3 deficiency activates osteoclastogenesis [90]. Nevertheless, no clinical data on this topic are available.

The drugs with a pharmacologically plausible mechanism of osteoporosis induction are summarized in **Table 2**.

4.3. Drugs with disproportionality signals identified in the present study but that are not in line with the literature data

It is well known that Gaucher's disease (glycosphingolipidase deficiency) induces osteoporosis through the accumulation of glucosylceramide. The enzyme replacement therapy imiglucerase is associated with dose-related, long-term increases in BMD [91]. The significant ROR for imiglucerase might be related to drug ineffectiveness, rather than a direct effect on bone.

For certain vasodilator agents (namely the phosphodiesterase-5 (PDE-5) inhibitors sildenafil and tadalafil and the soluble guanylate cyclase (sGC) agonist riociguat, we also found significant RORs – a finding that contrasts with the literature data. In animal models, PDE-5 inhibitors prevent cGMP degradation and thus stimulate cGMP-dependent protein kinase (PKG) 1/2, leading to an increase in

411 BMD via OB proliferation and differentiation [92]. The sGCs (Gucy1a2 and Gucy1a3) are expressed in
412 mouse skeletal tissue, and the sGC agonists' effects appear to be driven by osteoblasts. *In vivo*, the
413 sGC agonist cinaciguat enhanced osteoblast proliferation and differentiation and reversed trabecular
414 bone loss in ovariectomized mice [92].

415 We found significant RORs for disease-modifying antirheumatic drugs (DMARDs) used to treat
416 chronic IRDs: leflunomide, TNF inhibitors, tocilizumab, abatacept, rituximab, and
417 hydroxychloroquine. In the present study population, the use of co-medications (e.g. glucocorticoids)
418 not addressed in the analysis or an indication bias (despite stratification by therapeutic area) might
419 explain these discrepancies. All these DMARDs are known to be associated with a reduction in the
420 osteoporosis risk through a decrease in systemic inflammation. *In vitro* and in an animal model,
421 leflunomide suppresses receptor activator of NFκB ligand (RANKL)-activated intracellular signaling
422 and OC differentiation, and this effect is independent of its suppressive effect on T cells [93].
423 However, a clinical study found that patients with RA exposed to leflunomide for an average of 2.4
424 years did not have a significant change in BMD [94]. It is well known that interleukin (IL)-6 induces
425 osteoporosis by activating osteoclastogenesis [95]. Biologic DMARDs targeting TNF and IL-6 inhibit
426 the expression of RANKL on synovial cells and T cells, which leads to the subsequent suppression of
427 osteoclast maturation and bone damage through RANKL; however, biologic DMARDs are not known
428 to affect bone metabolism and osteoporosis [96]. The use of the IL-6 inhibitor tocilizumab is
429 associated with lower levels of bone-resorbing markers and higher levels of bone formation markers
430 [97,98]. Nevertheless, the use of tocilizumab in RA patients appears to be associated with a bone
431 mass gain only in individuals who are positive for anti-citrullinated protein antibodies [99]. Abatacept
432 (a fusion protein containing the FC region of IgG1 and the extracellular domain of cytotoxic T-
433 lymphocyte-associated protein-4) inhibits the differentiation and maturation of OCs [100]. A clinical
434 study found that patients treated with abatacept had a greater BMD at the lumbar spine than
435 patients treated with tumor necrosis factor inhibitors or tocilizumab [101]. Few literature data on the
436 anti-B-cell (anti-CD20) rituximab are available. The use of this agent appears to be associated with a

reduction in levels of the bone resorption marker deoxypyridinoline [102], although the results of a clinical study were not conclusive [103]. Hydroxychloroquine (HCQ) was shown to reduce OC differentiation *in vitro* and levels of β -carboxy-terminal collagen *in vivo* [104]. One clinical study confirmed these preclinical results: HCQ use was associated with higher BMD in patients with systemic lupus erythematosus [105]. However, a recent study did not show an association between HCQ and the fracture risk in postmenopausal women with RA [106].

In mice, interferon beta – indicated in multiple sclerosis (MS) – appears to have beneficial effects on bone by interfering with the RANKL-induced expression of c-Fos and thus inhibition of osteoclastogenesis [107]. In one clinical study, the use of interferon beta by patients with MS was associated with lower osteoclastogenesis in response to RANKL [108]. In another clinical study, however, its use was associated with lower BMD in men with MS and no change in BMD in women with MS [109].

Omalizumab – indicated in allergic asthma, sinonasal polyposis, and chronic spontaneous urticaria – binds IgE specifically, whereas mepolizumab – indicated in severe eosinophilic refractory asthma – binds IL-5 specifically. These actions results in lower histamine levels and lower leukotriene and proinflammatory mediator levels *via* inhibition of mast cell degranulation and eosinophils, respectively [110,111]. In theory, these mechanisms of action should prevent bone loss [112]; again, no clinical data are available.

As mentioned above, iron accumulation harms bone [113,114]. Accordingly, a clinical study found that iron-chelating agents can restore iron-induced bone damage [115].

4.4. Drugs with neither clinical data or nor a pharmacological rationale for a potential association with osteoporosis

Mycophenolic acid and sirolimus inhibit inosine-5'-monophosphate dehydrogenase and IL-2 and other cytokine receptor-dependent signal transduction mechanisms *via* an action on mTOR. The two

drugs inhibit T and B lymphocyte proliferation and do not appear to harm bone in kidney transplant patients [116].

Amifampridine – indicated in MS and Lambert-Eaton myasthenic syndrome, respectively – are broad-spectrum voltage-dependent potassium channel blockers that enhance synaptic transmission. No clinical or preclinical data are available.

Tafamidis – indicated in transthyretin (TTR) amyloidosis – binds the TTR tetramer and prevents it from dissociating into monomers. Only one clinical study has shown that TTR levels were positively correlated with BMD but only in patients without amyloidosis; in this context, TTR is a nutritional marker [117]. Bone effects of TTR accumulation in the subset of patients with amyloidosis were not investigated.

The mechanism of action of sodium oxybate – indicated in narcolepsy with cataplexy or excessive daytime sleepiness – is not well understood [118]. Hence, no hypothesis can be made as to its possible harmful bone effects.

4.5. Study limitations and strengths

Our study had several limitations, most of which are inherent to all pharmacovigilance and case/non-case designs [25]. Firstly, we were not able to provide the absolute frequency of drugs associated with osteoporosis – notably because of underreporting. However, widespread underreporting would not affect the results of a disproportionality analysis [25]. Secondly, we did not have information on the severity of the diseases for which the studied drugs were administered; this might have created false positives in the ROR calculation. As a result, several RORs might be falsely significant even after stratification by therapeutic area: certain drugs used to treat IRDs, the imiglucerase used in Gaucher's disease. The significant ROR in this example probably reflects certain aspects of the disease itself. Nevertheless, many of the contrasting literature data comes from preclinical studies and have not always been confirmed in clinical studies. On the same lines, our analyses did not address the concomitant use of certain medications (e.g. glucocorticoids in patients with IRDs) or

previous medication use that was not documented in the database, which could have led to falsely significant RORs. Thirdly, our analyses took account of age and sex but not other conditions leading to osteoporosis (due to lack of data), which could result in confounding bias. Fourthly, event competition bias (as seen with VKAs) might have prevented us from detecting other disproportionality signals masked by other ADRs strongly associated with the drugs of interest. Fifthly, we cannot assert that fracture events in ICSRs are all low-energy osteoporotic fractures. In contrast, our study has several major strengths, due to its case/non-case design [25]. We studied the world's largest pharmacovigilance database, which reflects routine medication use. The case/non-case design is a validated means of investigating disproportionality between reports and drugs [25]. A recent study showed that in most cases, the ADR risk obtained in meta-analyses is correlated with the ROR from the disproportionality analysis [119]. In the present study, the RORs for the vast majority of drugs already known to induce osteoporosis or increase the fracture risk were significant, which testifies to the robustness of our results.

CONCLUSION

Our results are consistent with the literature data on drugs already known to induce osteoporosis or increase the fracture risk: glucocorticoids, GnRH analogs, AIs, androgen receptor blockers, thyroid hormones, PPIs, thiazolidinediones, VKAs, loop diuretics, PIs, NNRT inhibitors, opioids, enzyme-inducing antiepileptics, benzodiazepines, heparin, radium 223 dichloride, and high-dose MTX. We found new disproportionality signals with a pharmacologically plausible mechanism (requiring confirmation in clinical studies) in the fields of neurology (selective 5-HT₁ agonists, levodopa and memantine), hematology (romiplostim), pulmonology (macitentan), ophthalmology (ranibizumab), and rheumatology (tofacitinib).

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515 **Conflict of interest disclosure**

516 The authors declare that they have no competing interests.

517 **Ethics approval statement**

518 Not applicable

519 **Patient consent statement**

520 Not applicable

521 **Data availability statement**

522 The data that support the findings of this study are available on request from the corresponding
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528 **Authors' contributions**

529 BB and SL were the major contributors to the study conception and design and acquisition, analysis,
530 and interpretation of the data; they drafted the article and revised it critically for important
531 intellectual content. VGC, KM, SB, ASHL, SK and YB were major contributors to the analysis and
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534 **Disclaimer**

535 The interpretation of data in the present study represents the opinions of the authors only and not
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968 **FIGURE LEGENDS**

969 **Figure 1:** Significant RORs for osteoporosis (narrow SMQ) with drugs in the ATC groups A, B, C, D, G,
970 H, J and L.

971 *ROR calculation performed for the corresponding therapeutic area

972 ** ROR calculation not stratified by therapeutic area (the corresponding drugs are almost the only
973 ones in their therapeutic area)

974 *ATC, Anatomical Therapeutic Chemical; CI, confidence interval; ROR, reporting odds ratio.*

975 **Figure 2:** Significant RORs for osteoporosis (narrow SMQ) with drugs in the ATC groups L, M, N, P, R, S
976 and V

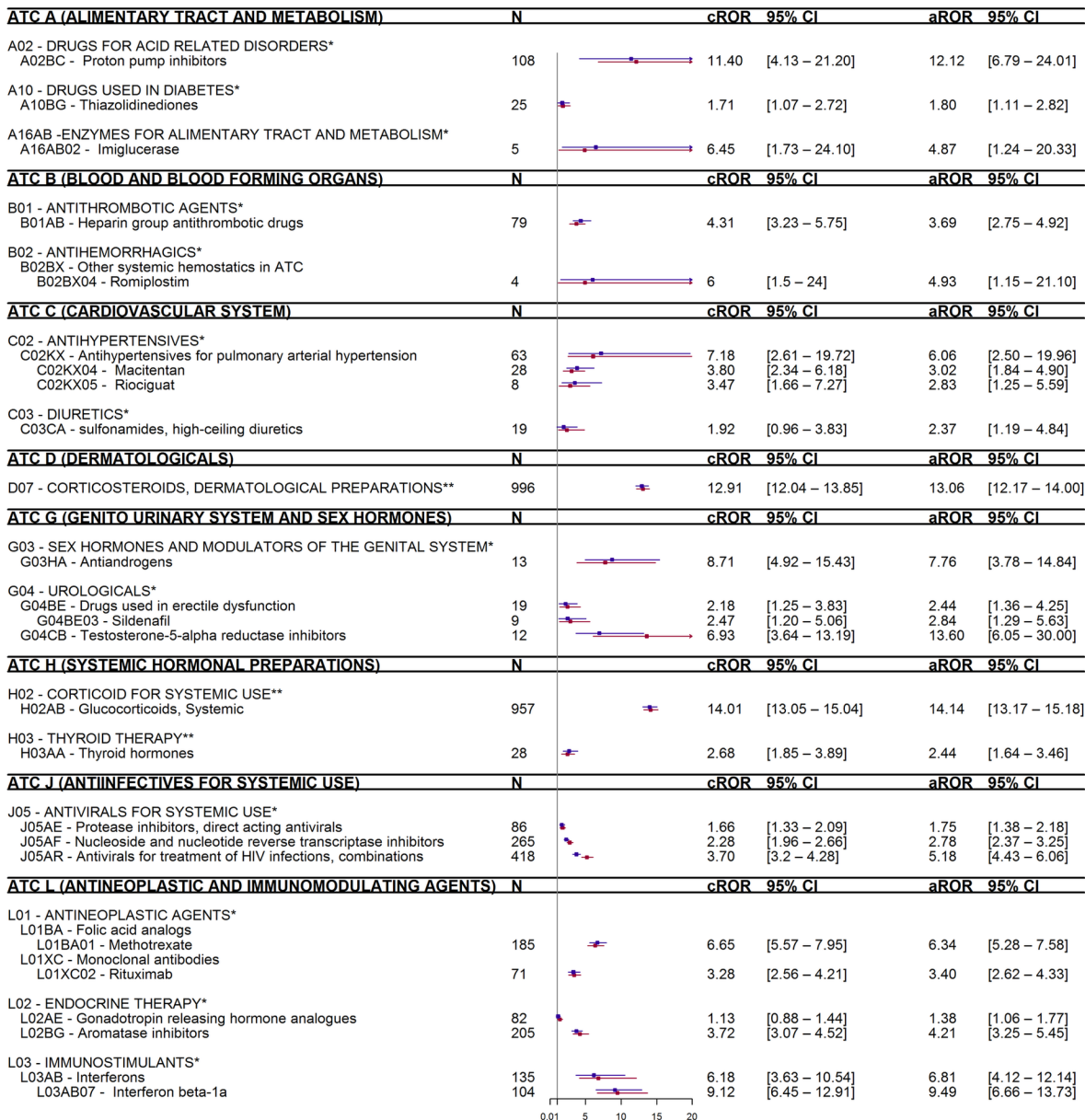
977 *ROR calculation performed in the corresponding therapeutic area

978 ** ROR calculation not stratified by therapeutic area (the corresponding drugs are almost the only
979 ones in their therapeutic area)

980 *ATC, Anatomical Therapeutic Chemical; CI, confidence interval; ROR, reporting odds ratio.*

981 **Figure 3:** RORs for osteoporosis (narrow SMQ) with antithrombotic agents after exclusion of the SMQ
982 “Haemorrhages”

983 *ATC, Anatomical Therapeutic Chemical; CI, confidence interval; MAO, monoamine oxidase; ROR,*
984 *reporting odds ratio; SMQ, standardized MedDRA query;*



■ crude ROR ■ adjusted ROR

ATC L (ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS)	N	cROR	95% CI	aROR	95% CI
L04 - IMMUNOSUPPRESSANTS*					
L04AA - Selective immunosuppressants					
L04AA06 - Mycophenolic acid	80	1.94	[1.55 – 2.44]	2.53	[1.99 – 3.16]
L04AA10 - Sirolimus	9	1.64	[0.85 – 3.17]	2.12	[1.02 – 3.85]
L04AA13 - Leflunomide	82	5.49	[4.38 – 6.87]	4.84	[3.84 – 6.03]
L04AA24 - Abatacept	118	6.20	[5.04 – 7.64]	5.06	[4.08 – 6.20]
L04AA26 - Belimumab	6	3.10	[1.38 – 6.88]	3.17	[1.25 – 6.46]
L04AA29 - Tofacitinib	119	4.35	[3.60 – 5.27]	3.65	[3.00 – 4.40]
L04AB - Tumor necrosis factor alpha (TNF-) inhibitors	586	1.50	[1.30 – 1.68]	1.53	[1.36 – 1.72]
L04AC - Interleukin inhibitors					
L04AC07 - Tocilizumab	124	7.07	[5.86 – 8.52]	6.16	[5.08 – 7.41]
L04AD - Calcineurin inhibitors	72	1.13	[0.89 – 1.44]	1.43	[1.11 – 1.80]
L04AX - Other immunosuppressants in ATC					
L04AX01 - Azathioprine	52	1.81	[1.37 – 2.40]	2.26	[1.69 – 2.96]
ATC M (MUSCULO-SKELETAL SYSTEM)	N	cROR	95% CI	aROR	95% CI
M01A - ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STERIODS**	307	1.25	[1.11 – 1.40]	1.25	[1.11 – 1.40]
M01AH - Coxibs*	209	12.42	[9.77 – 15.8]	10.28	[8.06 – 13.19]
ATC N (NERVOUS SYSTEM)	N	cROR	95% CI	aROR	95% CI
N02 - ANALGESICS*					
N02C - ANTIMIGRAINE PREPARATIONS					
N02CC - Selective serotonin (5HT1) agonists, antimigraine drugs	14	4.39	[2.57 – 7.53]	4.22	[2.34 – 7.00]
N03 - ANTIEPILEPTICS*					
N03AA - Barbiturates and derivatives	34	7.28	[5.06 – 10.48]	7.35	[5.05 – 10.43]
N03AB - Hydantoin derivatives	39	1.84	[1.30 – 2.59]	1.89	[1.32 – 2.64]
N03AF - Carboxamide derivatives	56	1.93	[1.43 – 2.60]	1.93	[1.42 – 2.59]
N03AG - Fatty acid derivatives	52	2.00	[1.48 – 2.73]	2.06	[1.50 – 2.79]
N03AX - Other antiepileptics in ATC					
N03AX16 - Pregabalin	43	1.40	[1.00 – 1.94]	1.41	[1.00 – 1.96]
N04 - ANTI-PARKINSON DRUGS*					
N04BA - Dopa and dopa derivatives	20	4.82	[2.36 – 9.86]	10.18	[4.33 – 25.10]
N06 - PSYCHOANALEPTICS*					
N06D - ANTI-DEMENTIA DRUGS					
N06DX - Other anti-dementia drugs in ATC					
N06DX01 - Memantine	6	3.81	[1.68 – 8.68]	4.10	[1.56 – 8.93]
N07X - OTHER NERVOUS SYSTEM DRUGS**					
N07XX - Other nervous system drugs in ATC					
N07XX04 - Oxybate sodium	15	4.56	[2.74 – 7.57]	4.79	[2.75 – 7.66]
N07XX05 - Amifampridine	4	44.66	[16.53 – 120.67]	43.60	[13.51 – 104.15]
ATC P (ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS)	N	cROR	95% CI	aROR	95% CI
P01B - ANTIMALARIALS**					
P01BA02 - Hydroxychloroquine	153	8.46	[7.20 – 9.95]	7.91	[6.70 – 9.26]
ATC R (RESPIRATORY SYSTEM)	N	cROR	95% CI	aROR	95% CI
R03 - DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES*					
R03BA - Glucocorticoid inhalants for obstructive airway disease	167	2.55	[2.01 – 3.22]	2.55	[2.02 – 3.24]
R03DX - Other systemic drugs for obstructive airway diseases in ATC					
R03DX05 - Omalizumab	41	2.42	[1.74 – 3.37]	2.38	[1.67 – 3.29]
R03DX06 - Mepolizumab	11	2.98	[1.63 – 5.46]	2.94	[1.51 – 5.12]
ATC S (SENSORY ORGANS)	N	cROR	95% CI	aROR	95% CI
S01L - OCULAR VASCULAR DISORDER AGENTS*					
S01LA04 - Ranibizumab	6	3.97	[1.38 – 11.45]	3.31	[1.00 – 10.51]
ATC V (VARIOUS)	N	cROR	95% CI	aROR	95% CI
V03AC - Iron chelating agents**	19	4.10	[2.61 – 6.44]	4.20	[2.58 – 6.39]
V10XX - Various therapeutic radiopharmaceuticals					
V10XX03 - Radium Ra 223 dichloride**	3	4.59	[1.48 – 14.26]	5.13	[1.27 – 13.36]

0.01 5 10 15 20

■ crude ROR ■ adjusted ROR

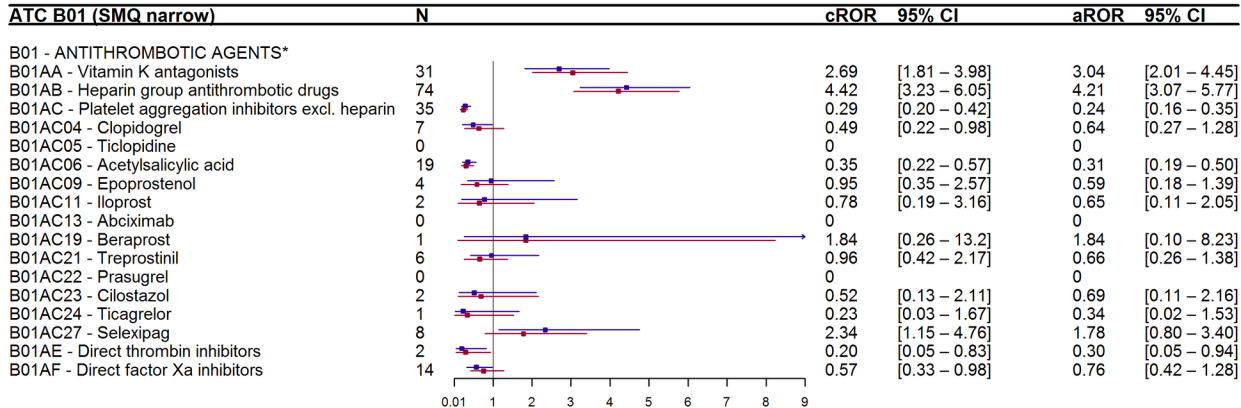


Table 1: Characteristics of ICSRs

Characteristics	Broad SMQ « Osteoporosis » n = 4,758
Age (years) \pm SD	51.1 \pm 15.6
Sex, n (%)	
Male	1,621 (34.1)
Female	3,137 (65.9)
Reporter qualification, n (%)	
Physicians	2,933 (61.6)
Pharmacists	383 (8.0)
Other health professionals	1,059 (30.4)
Continent, n (%)	
North America	2,184 (45.9)
Europe	1,785 (37.5)
Asia	645 (13.6)
Other regions ¹	144 (3.0)
Seriousness of ADRs ² , n (%)	
Death	157 (3.3)
Life-threatening event	62 (1.3)
Disability/incapacity	542 (11.4)
Hospitalization (caused or prolonged)	2,679 (56.3)
Others	2,684 (56.4)

¹including Oceania, Africa and South America

²ADRs of a unique ICSR can have a different seriousness

ADR, adverse drug reaction; ICSRs, individual case safety reports; SMQ, standardized medical dictionary for regulatory activities queries;

Table 2: Indications and mechanisms of action of molecules having a pharmacological plausibility to induce osteoporosis

Molecules	Indications	Mechanisms of action	Pharmacological plausibility
Selective 5-HT₁ agonists	Migraine	Selective 5-HT ₁ agonists	Binding to 5-HT _{1B} OB receptors → ↓ OB proliferation [80–82]
L-dopa	Parkinson disease	Dopamine substitution	Breakdown of L-dopa by COMT → ↑ Hcy → ↓ collagen cross-linking [78]
Memantine	Dementia	NMDA receptor antagonist	Down-regulation of NMDA receptors → ↓ osteogenesis [85]
Romiplostim	ITP	TPO receptor activation (c-Mpl)	Activation of MAPK, JAK/STAT and NFκB → ↑ OC formation and differentiation [70]
Macitentan	Pulmonary arterial hypertension	ET-1 receptors antagonists	ET-1 antagonism → ↓ OB proliferation and differentiation → ↓ type I collagen production → ↑ OC resorption [71–73]
Ranibizumab	Age-related macular degeneration	VEGF-A inhibitor	↓ VEGF-A → ↓ osteogenesis [86,87]
Tofacitinib	Rheumatoid arthritis	JAK1/JAK3 inhibitor	JAK1 inhibition → osteoporotic bone phenotype [88] JAK1/JAK3 inhibition → ↓ STAT3 → osteoclastogenesis [90]

c-Mpl, myeloproliferative leukemia virus oncogene; COMT, catechol-O-methyltransferase; CRBN, cereblon; ET-1, endothelin-1; Hcy, homocystein; ITP, immune thrombocytopenic purpura; JAK, Janus kinases; MAPK, mitogen-activated protein kinases; NFκB, nuclear factor-kappa B; NMDA, N-methyl-D-aspartate; OB, osteoblast; OC, osteoclast; sGC, soluble guanylate cyclase; VEGF, vascular endothelial growth factor;