BONE MODIFYING AGENTS AND OTHER RISK FACTORS FOR MORTALITY IN THE BRAZILIAN POPULATION WITH OSTEOPOROSIS: A SURVIVAL STUDY

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RESUMO

Context: Many real-world effectiveness studies have analyzed the effects of bone modifying agents (BMA) on overall survival in various populations with osteoporosis worldwide. However, there are no large-scale studies for the Brazilian population yet. **Objective**: To investigate the effect of BMA and other associated covariates on the outcome of overall survival in the Brazilian population with osteoporosis treated within the Brazilian Public Health System (BPHS). **Methods**: Non-concurrent cohort of the Brazilian population treated with BMA in the BPHS from 2000 to 2015. Global survival analysis was conducted, using Kaplan-Meier method and Cox proportional hazards model, with sensitivity analyses addressing additional risk factors. **Results**: 312,098 patients were included, most being female, aged 56 or older, residing in the southeast or northeast regions of Brazil, and persisting in BMA treatment for less than 12 months. Cox regression analysis identified that calcitriol had a higher risk of death than the anti-resorptive medications (ARM). All other covariates were associated with any cause death risk. Sensitivity analyses corroborated the main findings and showed that black individuals or those with low body weight had a higher risk of death. **Conclusion**: Monotherapy or polytherapy of ARM, when compared to calcitriol, appear to be protective factors for death risk from any cause in the Brazilian population with osteoporosis. The ARM did significantly differ from each other in the risk of death, whit alendronate and raloxifene showing the lowest risk when compared to other ARM.

KEYWORDS: Osteoporosis; Bone Density Conservation Agents; Treatment Outcome; Cohort Studies; Survival Analysis.

INTRODUCTION

Osteoporosis is a multifactorial condition, clinically asymptomatic, characterized by decreased bone density and structural deterioration of bone tissue, resulting from imbalances in the physiological dynamics of bone remodeling. This condition predisposes individuals to fractures caused by minor traumas, due to bone fragility. The osteoporotic fractures are classified into four categories: 1) hip fractures; 2) vertebral fractures; 3) major fractures (pelvis, distal femur, proximal tibia, humerus, and more than three ribs); 4) minor fractures (fractures in other locations).[1,2] In the Brazilian population aged 40 and above, in the year 2006, the prevalence of osteoporotic fractures was estimated be15.1% in women and 12.8% in men.[3]

There is no direct association between the risk of death and osteoporosis in the literature; however, there is an increased mortality associated with the occurrence of osteoporotic fractures.[1] The mortality in the first year after an osteoporotic vertebral fracture ranges from 6.7% to 28%, and after a hip fracture, it ranges from 10.1% to 31.5%.[4] The risk of death after an osteoporotic fracture varies according to age (2-4 times higher risk in the age group of 80 years or older), gender (2 times higher in men), the type of fracture (higher risk in hip fractures, prevalent vertebral fractures, and multiple concurrent fractures), the recurrence of osteoporotic fractures, and the time after the fracture (mortality is higher in the first months after the event).[1]

The etiology behind increased mortality following osteoporotic fracture remains uncertain. Reduced bone mineral density serves as a mortality risk factor and is presumed to be linked to comorbidities in affected patients. The increase in mortality immediately following the fracture arises from complications related to it (thromboembolism, infections, etc.), and in the long term, it is largely due to associated comorbidities. Based on this premise, it has been estimated that around 23% of hip fracture-related deaths may be directly attributed to the fracture itself.[1,5]

Osteoporotic fractures have various complications, including chronic pain, deformities, mobility restrictions, reduced motor control, reduced quality of life, and an increased risk of death. The primary therapeutic goal of bone modifying agents (BMA) use is to prevent fractures and their health consequences in individuals with osteoporosis. Increased bone mineral density is a secondary therapeutic outcome.[6,7]

There are several treatments available to prevent fractures in patients with osteoporosis, which can be categorized into non-pharmacological and pharmacological measures. Pharmacological agents include: antiresorptive medications (ARM), such as bisphosphonates (sodium alendronate or sodium risedronate), salmon calcitonin and selective estrogen receptor modulators (raloxifene); bone anabolic therapy medication (BATM), such as teriparatide and romosozumab; and nutritional supplements, such as vitamins D and K, magnesium, and calcium. Additionally, non-pharmacological measures involve lifestyle changes, such as a diet rich in vitamins and minerals, regular physical exercise, adequate sleep, and cessation of smoking and alcohol consumption.[6–8]

Brazil has a public health system with nationwide coverage. In the Brazilian Public Health System (BPHS), the first-line treatment for osteoporosis was an oral bisphosphonate medication, usually combined with calcitriol (a nutritional supplement of vitamin D analogue). For some cases of osteoporosis with low fracture risk, only calcitriol is used. Until 2021, the second-line treatment was raloxifene, salmon calcitonin, or disodium pamidronate (injectable bisphosphonate) as an alternative for cases of therapeutic failure, gastrointestinal intolerance, or contraindication to oral bisphosphonates.[7]

There are several real-world effectiveness studies that have analyzed the effects of BMA on overall mortality and fracture prevention in different osteoporotic populations around the world, including Japan[9], Taiwan[10–12], Taiwan and Hong Kong[13], Korea[14], the United States of America[15], Canada[16], Germany[17], Austria[18], Norway[19], Denmark[20], Sweden[21], Spain[22] and Italy[23]. However, there are no large studies for the Brazilian population yet.

This prior research has demonstrated the significant value that administrative databases hold for informed decision-making in healthcare. The BPHS operates a range of information systems that track the dispensation of medications, reportable diseases, hospital admissions, and mortalities. The efforts to merge this information have resulted in the development of a dataset that offers insights into the use of medications and health outcomes for the entire population of Brazil. This dataset, known as the National Database of Health Centered on the Individual (NDHCI), tracks the adoption, usage trends and effects of government subsidized medications in Brazil. The findings from this dataset can greatly impact practices and influence national health guidelines[24].

The NDHCI contains information on healthcare and mortality for nearly 159.7 million Brazilians over a 16-year period from 2000 to 2015[24], representing 77.8% of the Brazilian population, about 205.2 million in 2015[25]. Therefore, the NDHCI has significant statistical power and is representative of the Brazilian population and, thus, it is one of the most exhaustive healthcare databases in the world[24].

The NDHCI was created through deterministic-probabilistic linkage of records from four databases of the BPHS: The Outpatient Information System (SIA), the Hospital Information System (SIH), the Information System on Diseases of Compulsory Declaration (SINAN), and the Information System of Mortality (SIM). The construction and the validation of the NDHCI were described in the study by Guerra and collaborators[24] and it has already been used in many studies by a research group at the Federal University of Minas Gerais.[26,27]

In this this scenario, our objective was to investigate the effect of (BMA and other associated covariates on the outcome of overall survival in the Brazilian population with osteoporosis treated within the BPHS, identifying treatments and regimens that yield the most favorable outcomes for this demographic, for which, until now, only regional data were available in Brazil.

METHODS

This is a non-concurrent cohort study of the Brazilian population treated with osteoporosis medications in the BPHS. The cohort was established from a database with information collected from 2000 to 2015. The database was extracted from the NDHCI[24].

Participants were included in the cohort of this study if they met the following criteria: were over 18 years old; and received a prescription for BMA treatment (sodium alendronate, sodium risedronate, disodium pamidronate, raloxifene, salmon calcitonin, or calcitriol). The index date was defined as the date of the first prescription of these medications within the observation window, including their respective diagnosis. The exclusion criteria were patients with an index date after December 31, 2014, and participants using medications for four months or less. These exclusion criteria ensured a more accurate analysis of treatment effects because only patients who persisted in treatment for longer periods were included.

The event of interest for the survival analysis was death from any cause. All patients were followed from the index date until death or until December 2015 (right-censoring). Loss to follow-up was defined as informative censoring.

Baseline characteristics were reported in a descriptive analysis of all variables according to the data recorded on the index date. Explanatory variables were: sex; age at baseline; self-declared skin color at baseline; Body Mass Index (BMI) at baseline, calculated according to WHO parameters[28]; cohort entry period; residence region at baseline; diagnosis of osteoporosis according to ICD-10; time of illness (osteoporosis) before baseline; Charlson Comorbidity Index at baseline, which was the number and type of comorbidities, it predicts 10-year survival in patients with multiple comorbidities[29]; frailty index at baseline, which was the number of days of hospitalization for any cause during the two years preceding the index date[30]; coefficient of time of hospitalization after baseline, which was the result of the time of hospitalization divided by the time of total follow-up; type of fracture occurring after baseline; medication used in the first prescription at baseline and the therapeutic regimens during the follow-up, which could be either a single-drug treatment throughout the follow-up period (monotherapy) or polytherapy (changing the drug or using two or more drugs at the same time); persistence of medication use at 12 months of follow-up, where medication persistence refers to the continuity of medication use as prescribed over time, without unjustified interruptions[31]; and persistence at 24 months of follow-up. The first dispensed medication did not represent first-line treatment, as the data were not exclusive to treatment-naïve patients.

Statistical analysis was conducted using the R statistical software version 4.2.2[32] and R-Studio[33], considering a significance level of 5%. Overall survival was assessed using the Kaplan-Meier method, and the log-rank test was used to compare the patients' therapeutic regimens. Factors influencing survival rates were initially evaluated through univariate analysis. Variables with a p-value < 0.20 in univariate analysis were included in the multivariate Cox proportional hazards model. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated in the multivariate model, and their adequacy was assessed through residual analysis.

We performed two sensitivity analyses. In the first one, we conducted a multivariate analysis including self-declared skin color at baseline as a risk factor. In the second sensitivity analysis, we included BMI at baseline as a risk factor. The self-declared skin color and BMI at baseline, as explanatory variables, were excluded from the main multivariate analysis because they had 64% to 82% of missing data. It is important to clarify that, according to Brazilian laws, users of the public health system are not required to declare their skin color. Also, not all high-cost medication dispensing services have scales and stadiometers to measure body mass and height. These facts explain the high values of missing data for these covariates in the dataset.

The research followed national and international research ethics guidelines and was approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE number: 44121315.2.0000.5149).

RESULTS

This study included 312,098 individuals who were treated with a BMA in the BPHS from 2000 to 2015. The main demographic and clinical characteristics of the cohort are presented in Table 1. Most of the Brazilian osteoporotic population was female, it was aged 56 years or older, self-declared white or mixed-race, resident in the southeast or northeast regions from Brazil, had normal or pre-obese body mass, it was diagnosed with osteoporosis without pathological fractures (ICD-10 M81), it had no comorbidities, it had initiated osteoporosis medication treatment between the years 2004 and 2011, and persisted in osteoporosis medication treatment for less than 12 months. The average follow-up time in the cohort was 61,3 months, which is nearly 5 years, with a total of 1,594,301 persons-years of observation. During the follow-up, approximately 13% of the studied population experienced death from any cause, and 3.4% experienced fractures, with minor fractures and hip fractures being more common.

Table 1. Demographic and clinical characteristics of the patients at cohort entry.

Variável	**Distribuição**
Variable	**Distribution**
Sex	*n*= 312,098
Female	*n(%)*= 296,919 (95%)
Male	*n(%)*= 15,179 (4.9%)
Age at baseline (years)	$\bar{x}(s)$= 64 (11)
Age range at baseline	*n*= 312,098
> 65 years	*n(%)*= 142,027 (46%)
56 - 65 years	*n(%)*= 107,658 (34%)
46 - 55 years	*n(%)*= 51,064 (16%)
36 - 45 years	*n(%)*= 7,402 (2.4%)

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Table 1. Continues from the previous page.

26 - 35 years	*n(%)*= 2,771 (0.9%)
18 - 25 years	*n(%)*= 1,176 (0.4%)
Self-declared skin color at baseline	*n*= 112,420
White	*n(%)*= 64,929 (58%)
Mixed (brown, dark-skinned)	*n(%)*= 33,783 (30%)
Yellow	*n(%)*= 9,302 (8.3%)
Black	*n(%)*= 4,341 (3.9%)
Indigenous	*n(%)*= 65 (<0.1%)
Region of residence in Brazil at baseline	*n*= 312,098
Southeast	*n(%)*= 146,794 (47%)
Northeast	*n(%)*= 95,974 (31%)
Midwest	*n(%)*= 29,301 (9.4%)
South	*n(%)*= 26,083 (8.4%)
North	*n(%)*= 13,946 (4.5%)
Diagnosis of osteoporosis according to ICD-10 at baseline	*n*= 312,098
M80 Osteoporosis with pathological fracture	*n(%)*= 43,348 (14%)
M800 Postmenopausal osteoporosis with pathological fracture	*n(%)*= 61,896 (20%)
M805 Idiopathic osteoporosis with pathological fracture	*n(%)*= 10,780 (3.5%)
M810 Postmenopausal osteoporosis without pathological fracture	*n(%)*= 108,344 (35%)
M811 Post oophorectomy osteoporosis without pathological fracture	*n(%)*= 6,839 (2.2%)
M815 Idiopathic osteoporosis without pathological fracture	*n(%)*= 36,844 (12%)
M818 Other osteoporosis without pathological fracture	*n(%)*= 12,880 (4.1%)
M828 Osteoporosis in other diseases classified elsewhere	*n(%)*= 16,428 (5.3%)
Other bone diseases	*n(%)*= 14,739 (4.7%)
BMI class at baseline	*n*= 55,767
Normal weight (18.5 kg/m^2 |– 25 kg/m^2)	*n(%)*= 29,270 (52%)
Overweight (25 kg/m^2 |– 30 kg/m^2)	*n(%)*= 17,151 (31%)
Obesity class I (30 kg/m^2 |– 35 kg/m^2)	*n(%)*= 5,366 (9.6%)
Underweight (16 kg/m^2 |– 18.5 kg/m^2)	*n(%)*= 1,467 (2.6%)
Obesity class II (35 kg/m^2 |– 40 kg/m^2)	*n(%)*= 1,242 (2.2%)
Obesity class III (BMI≥ 40 kg/m^2)	*n(%)*= 696 (1.2%)
Severely underweight (BMI<16 kg/m^2)	*n(%)*= 575 (1.0%)
Cohort entry period	*n*= 312,098
From 2004 to 2007	*n(%)*= 112,802 (36%)
From 2008 to 2011	*n(%)*= 107,155 (34%)
From 2000 to 2003	*n(%)*= 62,429 (20%)
From 2012 to 2015	*n(%)*= 29,712 (9.5%)
Medication at baseline	*n*= 312,098
Alendronate	*n(%)*= 128,565 (41%)
Raloxifene	*n(%)*= 72,932 (23%)
Calcitonin	*n(%)*= 35,723 (11%)
Risedronate	*n(%)*= 34,653 (11%)
Calcitriol	*n(%)*= 21,682 (6.9%)
Polytherapy	*n(%)*= 18,378 (5.9%)
Pamidronate	*n(%)*= 165 (<0.1%)
Scheme of polytherapy at baseline	*n*= 18,378
Bisphosphonate + Calcitonin	n(%)= 898 (0.3%)
Bisphosphonate + Calcitriol	*n(%)*= 10,690 (3.4%)
Bisphosphonate + Raloxifene	*n(%)*= 1,332 (0.4%)
Calcitonin + Calcitriol	*n(%)*= 1,350 (0.4%)
Calcitonin + Raloxifene	*n(%)*= 346 (0.1%)

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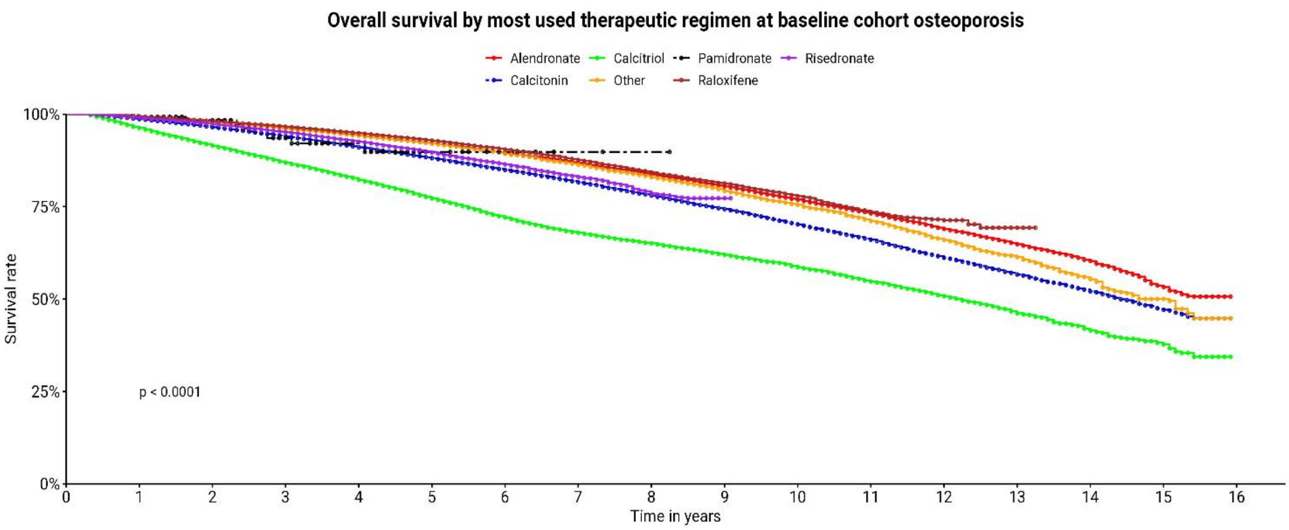
Table 1. Continues from the previous page.

Raloxifene + Calcitriol	*n(%)*= 3,093 (1.0%)
3 or 4 medications	*n(%)*= 661 (0.2%)
Level of Comorbidity in the Charlson Index at baseline	*n*= 312,098
No comorbidities	*n(%)*= 283,049 (91%)
1-2 comorbidities	*n(%)*= 25,846 (8.3%)
3-4 comorbidities	*n(%)*= 2,263 (0.7%)
5 or more comorbidities	*n(%)*= 940 (0.3%)
Frailty index at baseline (*n*= 312,098)	$\bar{x}(s)$= 1 (8)
Persistence of medication use at 12 months (*n*= 312,098)	*n(%)*= 119,441 (38%)
Persistence of medication use at 24 months (*n*= 312,098)	*n(%)*= 50,773 (16%)
Time of illness before baseline (*n*= 312,098)	$\bar{x}(s)$= -12 (40)
Coefficient of time of hospitalization after baseline (*n*= 312,098)	$\bar{x}(s)$= 0.0023 (0.0153)
Fracture after baseline	*n*= 312,098
No occurrence of fracture	*n(%)*= 301,449 (96.6%)
Occurrence of fracture	*n(%)*= 10,649 (3.4%)
Type of fracture after baseline	*n*= 10,649
Minor fracture	*n(%)*= 4,590 (43%)
Hip fracture	*n(%)*= 2,796 (26%)
Major fracture	*n(%)*= 2,777 (26%)
Vertebral fracture	*n(%)*= 486 (4.6%)
Event type	*n*= 312,098
Censored	*n(%)*= 271,184 (87%)
Death	*n(%)*= 40,914 (13%)

n: Absolute frequency.
n(%): Absolute frequency (percentual relative frequency).
$\bar{x}(s)$: mean (standard deviation).
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Figure 1 shows the Kaplan-Meier graph with the overall survival curves for each medication used in osteoporosis treatment. The curves suggest that the ARM had a lower mortality rate than calcitriol, and calcitonin and risedronate had a higher mortality rate than alendronate, pamidronate and raloxifene.

Figure 1. Kaplan–Meier survival curves of mortality of each BMA.



Other: Polytherapy.

Table 2 presents the univariate analysis of the Cox regression model. All covariates were associated with the risk of death from any cause (p-value≤ 0.20); therefore, they were potential risk factors for mortality and candidate covariates for the multivariate analysis of the Cox regression model. It is observed that when calcitriol was used as the reference in the univariate analysis, all ARM had a lower risk of death compared to calcitriol. When alendronate was used as the reference, risedronate, calcitonin, and polytherapy medications had a higher risk of death than alendronate. Raloxifene had a lower risk of death than alendronate, and pamidronate had a similar risk to alendronate.

Table 2. Univariate Cox Regression Analysis for risk factors for mortality in the study population.

Characteristic	HR	95% CI	p-value
Sex*			
Female (reference)	—	—	—
Male	3.08	2.99, 3.18	**<0.001**
Age at baseline (years)*	1.08	1.08, 1.08	**<0.001**
Age range at baseline*			
> 65 years (reference)	—	—	—
56 - 65 years	0.53	0.44, 0.63	**<0.001**
46 - 55 years	0.42	0.37, 0.48	**<0.001**
36 - 45 years	0.35	0.33, 0.38	**<0.001**
26 - 35 years	0.22	0.21, 0.23	**<0.001**
18 - 25 years	0.30	0.30, 0.31	**<0.001**
Self-declared skin color at baseline†			
Black (reference)	—	—	—
Yellow	0.29	0.26, 0.33	**<0.001**
White	0.70	0.64, 0.76	**<0.001**
Indigenous	1.07	0.59, 1.59	0.820
Mixed (brown, dark-skinned)	0.50	0.46, 0.54	**<0.001**
Region of residence in Brazil at baseline*			
Southeast (reference)	—	—	—
Northeast	0.76	0.73, 0.78	**<0.001**
Midwest	0.91	0.86, 0.97	**0.002**
South	1.08	1.04, 1.11	**<0.001**
North	1.16	1.11, 1.21	**<0.001**
Diagnosis of osteoporosis according to ICD-10 at baseline*			
M80 Osteoporosis with pathological fracture (reference)	—	—	—
M800 Postmenopausal osteoporosis with pathological fracture	0.61	0.59, 0.62	**<0.001**
M805 Idiopathic osteoporosis with pathological fracture	0.77	0.74, 0.81	**<0.001**
M810 Postmenopausal osteoporosis without pathological fracture	0.59	0.57, 0.60	**<0.001**
M811 Post oophorectomy osteoporosis without pathological fracture	0.76	0.70, 0.81	**<0.001**
M815 Idiopathic osteoporosis without pathological fracture	0.67	0.64, 0.70	**<0.001**
M818 Other osteoporosis without pathological fracture	0.87	0.82, 0.92	**<0.001**
M828 Osteoporosis in other diseases classified elsewhere	0.51	0.49, 0.53	**<0.001**
Other bone diseases	0.72	0.69, 0.76	**<0.001**
BMI class at baseline‡			
Normal weight (IMC= 18.5 |– 25 kg/m^2) (reference)	—	—	—
Obesity class I (IMC= 30 |– 35 kg/m^2)	0.89	0.78, 1.02	**0.091**
Obesity class II (IMC= 35 |– 40 kg/m^2)	1.05	0.82, 1.35	0.700
Obesity class III (IMC≥ 40 kg/m^2)	1.13	0.83, 1.53	0.450
Overweight (IMC= 25 |– 30 kg/m^2)	0.82	0.75, 0.90	**<0.001**
Severely underweight (IMC<16 kg/m^2)	2.34	1.85, 2.95	**<0.001**
Underweight (IMC= 16 |– 18.5 kg/m^2)	1.49	1.23, 1.80	**<0.001**
Cohort entry period*			
From 2004 to 2007 (reference)	—	—	—
From 2008 to 2011	1.37	1.34, 1.41	**<0.001**

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Table 2. Continues from the previous page.

From 2000 to 2003	1.13	1.10, 1.17	**<0.001**
From 2012 to 2015	0.92	0.85, 1.00	**0.060**
Medication at baseline*			
Alendronate (reference)	—	—	—
Calcitonin	1.38	1.35, 1.42	**<0.001**
Calcitriol	2.42	2.34, 2.49	**<0.001**
Polytherapy	1.05	1.01, 1.10	**0.023**
Pamidronate	1.21	0.60, 2.42	0.590
Raloxifene	0.90	0.87, 0.93	**<0.001**
Risedronate	1.25	1.19, 1.30	**<0.001**
Medication at baseline*			
Calcitriol (reference)	—	—	—
Raloxifene	0.37	0.36, 0.39	**<0.001**
Alendronate	0.41	0.40, 0.43	**<0.001**
Risedronate	0.51	0.49, 0.54	**<0.001**
Calcitonin	0.57	0.55, 0.59	**<0.001**
Pamidronate	0.50	0.25, 1.00	**0.050**
Polytherapy	0.44	0.41, 0.46	**<0.001**
Level of Comorbidity Charlson at baseline*			
No comorbidities (reference)	—	—	—
1-2 comorbidities	2.40	2.33, 2.47	**<0.001**
3-4 comorbidities	4.72	4.40, 5.05	**<0.001**
5 or more comorbidities	3.79	3.38, 4.25	**<0.001**
Frailty index at baseline*	<1.01	<1.01, <1.01	**<0.001**
Type of Fracture Description after baseline§			
Without fracture (reference)	—	—	—
Hip fracture	1.72	1.62, 1.83	**<0.001**
Vertebral fracture	0.85	0.69, 1.05	**0.130**
Major fracture	0.83	0.76, 0.91	**<0.001**
Minor fracture	0.56	0.52, 0.61	**<0.001**
Persistence of medication use at 12 months*	0.81	0.79, 0.82	**<0.001**
Persistence of medication use at 24 months*	0.67	0.65, 0.69	**<0.001**
Time of illness before baseline*	<1.01	<1.01, <1.01	**<0.001**
Coefficient of time of hospitalization after baseline*	224.00	199.00, 252.00	**<0.001**

95% CI: Confidence interval of 95%.
BMI: Body mass index.
HR: Hazards ratio.
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.
Significant p-values are in bold.
* Sample number= 312,098; number of events= 40,914.
† Sample number= 112,420; number of events= 11,475.
‡ Sample number = 55,767; number of events= 2,864.
§ Sample number = 10,649; number of events= 2,111.

In the multivariate analysis of the Cox regression model (table 3), most of the covariates were associated with the risk of death from any cause in the Brazilian osteoporotic population. The following characteristics were associated with a higher risk of death in the Brazilian osteoporotic population: The male sex; older age; residence in the South and the Midwest region from Brazil; cohort entry period between 2004 and 2011 (the middle cohort entry period); diagnosis of osteoporosis with pathological fracture (ICD-10 M80), and post oophorectomy osteoporosis without pathological fracture (ICD-10 M81.1); occurrence of hip fracture, and no occurrence of fracture; highest value of Charlson Comorbidity Index at baseline; highest value of frailty index at baseline; highest value of coefficient of hospitalization after baseline; and highest value of time of osteoporosis before baseline. These other characteristics had lower risk of death: residence in the Northeast, the North and the Southeast region from Brazil; persistence of medication use at 12 months of follow-up, and at 24 months of follow-up; cohort entry period between 2012 and 2015 (the latest cohort entry period).

Table 3. Multivariate Cox Regression Analysis for risk factors for mortality in the study population.

Characteristic*	HR	95% CI	p-value
Sex			
Female (reference)	—	—	—
Male	2.25	2.18, 2.33	**<0.001**
Age at baseline (years)	1.08	1.08, 1.08	**<0.001**
Region of residence in Brazil at baseline			
Midwest (reference)	—	—	—
Northeast	0.73	0.70, 0.76	**<0.001**
North	0.91	0.86, 0.96	**<0.001**
Southeast	0.95	0.92, 0.98	**0.002**
South	0.98	0.94, 1.02	0.352
Diagnosis of osteoporosis according to ICD-10 at baseline			
M80 Osteoporosis with pathological fracture (reference)	—	—	—
M800 Postmenopausal osteoporosis with pathological fracture	0.85	0.82, 0.89	**<0.001**
M805 Idiopathic osteoporosis with pathological fracture	0.69	0.65, 0.73	**<0.001**
M810 Postmenopausal osteoporosis without pathological fracture	0.84	0.81, 0.87	**<0.001**
M811 Post oophorectomy osteoporosis without pathological fracture	0.96	0.89, 1.04	0.293
M815 Idiopathic osteoporosis without pathological fracture	0.67	0.64, 0.70	**<0.001**
M818 Other osteoporosis without pathological fracture	0.86	0.81, 0.91	**<0.001**
M828 Osteoporosis in other diseases classified elsewhere	0.88	0.83, 0.93	**<0.001**
Other bone diseases	0.87	0.83, 0.93	**<0.001**
Cohort entry period			
From 2004 to 2007 (reference)	—	—	—
From 2008 to 2011	1.33	1.29, 1.38	**<0.001**
From 2012 to 2015	1.17	1.13, 1.21	**<0.001**
From 2004 to 2007	0.90	0.83, 0.99	**0.022**
Medication at baseline			
Alendronate (reference)	—	—	—
Calcitonin	1.20	1.16, 1.23	**<0.001**
Calcitriol	2.44	2.35, 2.53	**<0.001**
Polytherapy	1.12	1.07, 1.17	**<0.001**
Pamidronate	1.21	0.61, 2.43	0.584
Raloxifene	0.99	0.96, 1.03	0.674
Risedronate	1.20	1.15, 1.26	**<0.001**
Medication at baseline			
Calcitriol (reference)	—	—	—
Raloxifene	0.41	0.39, 0.43	**<0.001**
Alendronate	0.41	0.39, 0.43	**<0.001**
Risedronate	0.49	0.47, 0.52	**<0.001**
Calcitonin	0.49	0.47, 0.51	**<0.001**
Pamidronate	0.50	0.25, 0.99	**0.049**
Polytherapy	0.46	0.43, 0.48	**<0.001**
Charlson Comorbidity Index at baseline	1.27	1.26, 1.28	**<0.001**
Frailty index at baseline	<1.01	<1.01, <1.01	**<0.001**
Type of Fracture Description after baseline			
Without fracture (reference)	—	—	—
Hip fracture	0.95	0.90, 1.02	0.142
Vertebral fracture	0.77	0.63, 0.95	**0.014**
Major fracture	0.71	0.65, 0.78	**<0.001**
Minor fracture	0.56	0.52, 0.62	**<0.001**

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Table 3. Continues from the previous page.

Persistence of medication use at 12 months	0.91	0.89, 0.93	**<0.001**
Persistence of medication use at 24 months	0.68	0.66, 0.70	**<0.001**
Time of illness before baseline	<1.01	<1.01, <1.01	**<0.001**
Coefficient of time of hospitalization after baseline	68.03	59.26, 78.11	**<0.001**

Concordance= 0.762 (se = 0.001), Likelihood ratio test= 36,104 on 33 df, p<0.001
Wald test= 44,185 on 33 df, p<0.001, Score (logrank) test = 54,833 on 33 df, p<0.001

95% CI: Confidence interval of 95%.
HR: Hazards ratio.
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.
Significant p-values are in bold.
* Sample number= 312,098; number of events= 40,914.

In the main multivariate analysis, after adjusting for all confounding variables, all ARM had a lower risk of death than calcitriol. Alendronate, the first line medication for osteoporosis treatment, had a lower risk of death than risedronate, calcitonin, and polytherapy, but alendronate had the same risk as pamidronate, and raloxifene.

The table 4 and 5 shows the results of the sensitivity analyses. Sensitivity analyses present similar results to the main analysis. In the first sensitivity analysis (table 4), the self-declared skin color was a significant risk factor death. Self-declared black people had the higher risk of death and yellow people had the lower risk of death, with statistically significant differences. Risk data on indigenous people is not reliable, because there is possible high beta error due to the small indigenous population. The difference of risk of death from BMA remains in the same situation: calcitriol had higher risk than all ARM; alendronate had lower risk than risedronate, calcitonin, and polytherapy; and alendronate had similar risk to pamidronate and raloxifene.

Table 4. Sensitivity analysis by multivariate Cox Regression Analysis with additional risk factor: self-declared skin color at baseline.

Characteristic*	**HR**	**95% CI**	**p-value**
Sex			
Female (reference)	—	—	—
Male	2.34	2.21, 2.49	**<0.001**
Age at baseline (years)	1.06	1.06, 1.07	**<0.001**
Self-declared skin color			
Black (reference)	—	—	—
Yellow	0.37	0.33, 0.43	**<0.001**
White	0.73	0.67, 0.79	**<0.001**
Indigenous	0.97	0.53, 1.76	0.922
Mixed (brown, dark-skinned)	0.70	0.64, 0.77	**<0.001**
Region of residence in Brazil at baseline			
Midwest (reference)	—	—	—
Northeast	0.80	0.74, 0.87	**<0.001**
North	0.90	0.80, 1.01	0.066
Southeast	1.12	1.05, 1.20	**<0.001**
South	1.09	0.99, 1.21	0.068
Diagnosis of osteoporosis according to ICD-10 at baseline			
M80 Osteoporosis with pathological fracture (reference)	—	—	—
M800 Postmenopausal osteoporosis with pathological fracture	0.83	0.77, 0.90	**<0.001**
M805 Idiopathic osteoporosis with pathological fracture	0.64	0.58, 0.73	**<0.001**
M810 Postmenopausal osteoporosis without pathological fracture	0.81	0.76, 0.87	**<0.001**
M811 Post oophorectomy osteoporosis without pathological fracture	0.80	0.67, 0.95	**0.01**
M815 Idiopathic osteoporosis without pathological fracture	0.61	0.56, 0.67	**<0.001**
M818 Other osteoporosis without pathological fracture	0.78	0.69, 0.87	**<0.001**
M828 Osteoporosis in other diseases classified elsewhere	0.95	0.85, 1.06	0.386
Other bone diseases	0.91	0.82, 1.00	0.051
Cohort entry period			
From 2004 to 2007 (reference)	—	—	—

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Table 4. Continues from the previous page.

From 2008 to 2011	2.50	2.33, 2.69	**<0.001**
From 2012 to 2015	3.14	2.91, 3.39	**<0.001**
From 2004 to 2007	3.48	3.01, 4.01	**<0.001**
Medication at baseline			
Alendronate (reference)	—	—	—
Calcitonin	1.08	1.02, 1.15	**0.013**
Calcitriol	3.06	2.86, 3.28	**<0.001**
Polytherapy	1.11	1.01, 1.22	**0.028**
Pamidronate	0.97	0.36, 2.60	0.955
Raloxifene	0.93	0.87, 0.99	**0.014**
Risedronate	1.21	1.13, 1.30	**<0.001**
Medication at baseline			
Calcitriol (reference)	—	—	—
Raloxifene	0.30	0.28, 0.33	**<0.001**
Alendronate	0.32	0.30, 0.35	**<0.001**
Risedronate	0.40	0.36, 0.43	**<0.001**
Calcitonin	0.35	0.32, 0.38	**<0.001**
Pamidronate	0.32	0.12, 0.85	**0.022**
Polytherapy	0.36	0.33, 0.40	**<0.001**
Charlson Comorbidity Index at baseline	1.23	1.22, 1.25	**<0.001**
Frailty index at baseline	1.00	1.00, 1.00	0.227
Type of Fracture Description after baseline			
Without fracture (reference)	—	—	—
Hip fracture	1.21	1.08, 1.36	**<0.001**
Vertebral fracture	0.91	0.66, 1.25	0.549
Major fracture	0.84	0.72, 0.96	**0.014**
Minor fracture	0.76	0.67, 0.86	**<0.001**
Persistence of medication use at 12 months	0.94	0.89, 0.98	**0.006**
Persistence of medication use at 24 months	0.75	0.70, 0.80	**<0.001**
Time of illness before baseline	1.00	1.00, 1.00	0.249
Coefficient of time of hospitalization after baseline	110.32	82.23, 148.01	**<0.001**
Concordance= 0.783 (se = 0.002), Likelihood ratio test= 11,851 on 37 df, p<0.001 Wald test= 15,150 on 37 df, p<0.001, Score (log rank) test = 19,341 on 37 df, p<0.001			

95% CI: Confidence interval of 95%.
df: Degree of freedom.
HR: Hazards ratio.
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.
se: Standard error.
Significant p-values are in bold.
**Sample number= 112,420; number of events= 11,475.*

In the second sensitivity analysis (table 5), severely underweight and underweight people had the higher risk of death, and overweight people had the lower risk of death. The risk of death of all BMA are slightly different from the main analysis: calcitriol had lower risk than calcitonin alone but had similar risk to all other ARM; alendronate had lower risk than risedronate and calcitonin, but had similar risk to pamidronate, raloxifene and polytherapy. It is possible that a high beta error occurred to some comparisons, because the sample size of this sensitivity analysis is much smaller than that of the main analysis.

Table 5. Sensitivity analysis by multivariate Cox Regression Analysis with additional risk factor: BMI class at baseline.

Characteristic*	HR	95% CI	p-value
Sex			
Female (reference)	—	—	—
Male	1.70	1.48, 1.96	**<0.001**

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Table 5. Continues from the previous page.

Age at baseline (years)	1.08	1.08, 1.09	**<0.001**
BMI class at baseline			
Normal weight (IMC= 18.5 |– 25 kg/m^2) (reference)	—	—	—
Obesity class I (IMC= 30 |– 35 kg/m^2)	0.97	0.85, 1.11	0.655
Obesity class II (IMC= 35 |– 40 kg/m^2)	1.21	0.94, 1.56	0.141
Obesity class III (IMC≥ 40 kg/m^2)	1.10	0.80, 1.50	0.557
Overweight (IMC= 25 |– 30 kg/m^2)	0.86	0.79, 0.94	**<0.001**
Severely underweight (IMC<16 kg/m^2)	1.92	1.52, 2.42	**<0.001**
Underweight (IMC= 16 |– 18.5 kg/m^2)	1.36	1.12, 1.65	**0.002**
Region of residence in Brazil at baseline			
Midwest (reference)	—	—	—
Northeast	0.87	0.76, 1.03	0.055
North	0.90	0.75, 1.08	0.251
Southeast	1.03	0.91, 1.17	0.624
South	1.27	1.07, 1.50	**0.006**
Diagnosis of osteoporosis according to ICD-10 at baseline			
M80 Osteoporosis with pathological fracture (reference)	—	—	—
M800 Postmenopausal osteoporosis with pathological fracture	1.33x10^{4}	<0.01, 6.49x10^{295}	0.978
M805 Idiopathic osteoporosis with pathological fracture	1.33x10^{4}	<0.01, 6.45x10^{295}	0.978
M810 Postmenopausal osteoporosis without pathological fracture	1.15x10^{4}	<0.01, 5.58x10^{295}	0.978
M811 Post oophorectomy osteoporosis without pathological fracture	668.00	<0.01, 3.25x10^{295}	0.979
M815 Idiopathic osteoporosis without pathological fracture	1.20x10^{4}	<0.01, 5.83x10^{295}	0.978
M818 Other osteoporosis without pathological fracture	1.20x10^{4}	<0.01, 5.84x10^{295}	0.978
M828 Osteoporosis in other diseases classified elsewhere	1.25x10^{4}	<0.01, 6.09x10^{295}	0.978
Other bone diseases	1.32x10^{4}	<0.01, 6.41x10^{295}	0.978
Cohort entry period			
From 2004 to 2007 (reference)	—	—	—
From 2008 to 2011	—	—	—
From 2012 to 2015	0.73	0.61, 0.88	**<0.001**
From 2004 to 2007	0.75	0.60, 0.93	**0.008**
Medication at baseline			
Alendronate (reference)	—	—	—
Calcitonin	1.46	1.26, 1.68	**<0.001**
Calcitriol	1.05	0.88, 1.26	0.591
Polytherapy	0.92	0.79, 1.07	0.278
Pamidronate	0.58	0.14, 2.34	0.445
Raloxifene	1.05	0.94, 1.18	0.391
Risedronate	1.22	1.08, 1.38	**0.001**
Medication at baseline			
Calcitriol (reference)	—	—	—
Raloxifene	1.00	0.82, 1.21	0.992
Alendronate	0.95	0.79, 1.14	0.591
Risedronate	1.16	0.95, 1.42	0.136
Calcitonin	1.39	1.12, 1.71	**0.002**
Pamidronate	0.55	0.14, 2.24	0.406
Polytherapy	0.87	0.73, 1.05	0.148
Charlson Comorbidity Index at baseline	1.19	1.15, 1.24	**<0.001**
Frailty index at baseline	1.00	1.00, 1.00	0.691
Type of Fracture Description after baseline			
Without fracture (reference)	—	—	—
Hip fracture	1.02	0.78, 1.35	0.876

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Table 5. Continues from the previous page.

Vertebral fracture	1.19	0.44, 3.17	0.734
Major fracture	0.98	0.72, 1.33	0.896
Minor fracture	0.69	0.51, 0.92	**0.013**
Persistence of medication use at 12 months	0.79	0.73, 0.87	**<0.001**
Persistence of medication use at 24 months	0.43	0.38, 0.50	**<0.001**
Time of illness before baseline	1.00	1.00, 1.00	**<0.001**
Coefficient of time of hospitalization after baseline	91.03	48.47, 170.90	**<0.001**
Concordance= 0.778 (se = 0.005), Likelihood ratio test= 2,977 on 38 df, p<0.001 Wald test = 3,569 on 38 df, p<0.001, Score (log rank) test = 5,533 on 38 df, p<0.001			

95% CI: Confidence interval of 95%.
BMI: Body mass index.
df: Degree of freedom.
HR: Hazards ratio.
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.
se: Standard error.
Significant p-values are in bold.
**Sample number= 55,767; number of events= 2,864.*

DISCUSSION

As in our results, a review of several studies has reported on the association between demographic and clinical factors and mortality in osteoporotic populations. There is a heightened risk of death observed in males, black and older individuals, who underscored the gender, self-declared skin color and age differentials in osteoporosis-related mortality. Body composition, comorbidities and health status before fracture seem to have a substantial role in the increased mortality in patients with osteoporotic fractures, mainly hip fractures, but this finding was not consistent in other studies.[34]

The Dubbo Osteoporosis Epidemiology Study[35], a prospective longitudinal study on the aged population living in Dubbo, Australia, found a high risk of mortality in fractured females who were older, smoker, had lower bone mass density, had weaker quadriceps, and had higher sway (postural balance deficit). In fractured males, the study identified a higher risk of mortality in those who were older, had subsequent fractures, had weaker quadriceps, and had decreased physical activity. Unlike our results, comorbidities had no association with mortality risk in The Dubbo Study. Lower BMI had higher risk for death in univariate analysis, but not in multivariate cox regression in The Dubbo Study.[35]

As in the Brazilian population, the increased risk of mortality is associated with demographic and clinical factors in people with osteoporosis or with previous hip fractures in other nations. In a Spanish retrospective study[36], the higher risk of mortality in hip fractured people was associated with male sex, older age, comorbidities (mainly Parkinson Disease, dementia, ischemic heart disease, neoplasia, cirrhosis, pressure ulcer, diabetes, COPD, and chronic kidney disease), previous hospitalization, and underweight BMI class. The osteoporosis treatment and overweight BMI class had lower risk of death.[36] Also, in a Korean retrospective study[37], male sex, older age, underweight BMI class, but not comorbidities number and dementia, were associated with increased mortality risk in elderly patients with hip fracture.[37] In a Canadian prospective cohort of 23,178 individuals, male sex, older age, and higher Charlson Comorbidity Index, but no Vitamin D use, were associated with higher mortality risk and hip fracture risk.[29] In a Japanese cohort of osteoporotic men, older age, lower BMI, worst physical performance tests, presence of malignant disease, lower serum levels of albumin, of LDL-C (low-density lipoprotein cholesterol), and of total cholesterol, and higher serum of creatinine were associated with increased risk of death, but history of comorbidities and physical activity were not.[38]

Among the clinical risk factors found to be associated with mortality, treatment with various types of bone-modifying agents stands out. The results of the main multivariate analysis suggest that, compared to treatment with a vitamin supplement (calcitriol), monotherapy or polytherapy with ARM is a protective factor associated with a reduced risk of death from any cause. Among ARM, alendronate and raloxifene had the lower risk of death. This fact suggests that alendronate and raloxifene may be more effective in reducing mortality than other anti-resorptive medications, but this is not in accordance with the evidence from a recent meta-analysis of clinical trials[39], which reports there are no difference between bisphosphonates, denosumab, calcitonin, romosozumab, raloxifene and placebo (Vitamin D supplementation or no medication treatment) in the all-cause mortality risk. Otherwise, another meta-analysis[40] suggests that vitamin D supplementation treatment is no different from placebo or no treatment in the risk of death from any cause[40]; and a second meta-analysis[41] indicates that vitamin D treatment had no significant effect on reducing the incidence of total fracture, non-vertebral fracture, hip fracture and vertebral fracture[41]. These last two types of fracture have high risk of death[1].

In line with our findings, the results of several real-world effectiveness studies also suggest that treatment with ARM is associated with a lower risk of death in osteoporotic population, when compared to no ARM treatment[4,16,18,22,42–46], mainly the protective effect of the bisphosphonates for death risk[43–46]. Also, two old meta-analyses of clinical trials[47,48] support these findings. On the contrary, other two recent meta-analysis of clinical trials[39,49] has shown no difference of death risk between no treatment (or placebo) and ARM treatment. It is important to emphasize that in the most of clinical trial the placebo treatment is Vitamin D supplementation, and the evidence derived from meta-analyses of clinical trials is contradictory regarding the equality or superiority of MRA over Vitamin D in preventing deaths from any reason, sometimes reinforcing[47,48] and sometimes refuting[39,49] the findings of our study.

A Swedish study found that bisphosphonate use was associated with lower mortality within days of treatment initiation, and the authors state that this finding is consistent with confounding, although an early treatment effect cannot be ruled out[21]. On the other hand, for other authors[4,16], the decrease in the risk of death from bisphosphonate treatment likely involves many factors. This includes lowering the chances of fractures, which can lead to an increased risk of death in the two years following a fracture. Bisphosphonates also help reduce bone loss, which is a sign of health and higher mortality rates in individuals with or without fractures. Additionally, bisphosphonates may have inflammatory and anticancer properties.[16] Studies suggest that bisphosphonates could impact health by preventing plaque formation, showing statin-like effects, reducing arterial calcification, and decreasing the occurrence of heart rhythm issues and cardiovascular-related deaths. These discoveries highlight the mix of factors influencing mortality risk in people with osteoporosis, offering insights for interventions and improving treatments.[4]

The results of an Austrian retrospective cohort study[18] suggests that denosumab, injectable bisphosphonates, or oral bisphosphonates, despite they are associated with a lower risk of overall mortality when compared to treatment without medications, they do not significantly differ from each other in terms of the risk of death in the population with secondary osteoporosis and previous hip fracture. These findings align with the results of the present study, where alendronate (an oral bisphosphonate) does not statistically differ from pamidronate (an injectable bisphosphonate).[18] However, the lack of a significant risk difference between pamidronate and all other ARM in our results may be due to low statistical power (beta error value above the acceptable range), because the size of population using pamidronate was very small, and pamidronate has a paradoxical survival curve in the Kaplan-Meier graph, sometimes aligned with calcitonin, risedronate and polytherapy, and sometimes surpassing alendronate and raloxifene.

The findings of our investigation underscore the intricate interplay of various factors contributing to mortality risk in the osteoporotic population, providing insights into potential strategies for targeted interventions and optimization of treatments. One of the significant strengths of our study is the utilization of real-world data, encompassing nearly all individuals aged 18 and above in Brazil who had osteoporosis from 2000 to 2015, because we used a database that covered approximately 78% of the total Brazilian population. With access to personalized data utilizing unique anonymized codes, we were able to eliminate the possibility of multiple registrations, ensuring that all fracture events could be unequivocally linked to the study subjects. This approach allowed us to mitigate selection bias. Our analysis of osteoporosis medication effects was grounded in clinical practice, reflecting real-world practices, which can make the outcomes more relevant to policymakers.

However, there are some limitations to consider. Firstly, this study is observational. Cannot prove causation. Secondly, the data comes from individuals with osteoporosis in Brazil so it may not apply broadly to populations. Lastly, lifestyle factors like smoking habits, alcohol consumption levels, physical performance, during testing and activity levels were not accounted for in this study; these factors could also impact mortality rates significantly.

While there are constraints to consider, our research offers perspectives on the elements linked to a higher mortality risk among individuals, with osteoporosis, in Brazil. Our findings can be used to inform future research and to improve the care of patients with osteoporosis.

CONCLUSION

All other covariates were associated with any cause death risk in Brazilian population. Male, elderly, black, severely underweight, and underweight patients residing in the South and Midwest regions of Brazil, who experienced a hip fracture, exhibited higher comorbidity rates and longer hospitalization periods, had the highest risk of death. Monotherapy or polytherapy of ARM, when compared to calcitriol, appear to be protective factors for death from any cause risk in the Brazilian population with osteoporosis. ARM did significantly differ from each other in the risk of death: alendronate and raloxifene appear to be the most beneficial medications because they had the lowest risk of death when compared to other anti-resorptive medication.

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COMPETING INTERESTS, FUNDING AND GENERATIVE AI IN THE WRITING PROCESS

The authors declare that they have no conflict of interests.

This study was supported by the SUS Collaborating Centre Technology Assessment & Excellence in Health and of the Federal University of Minas Gerais. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

During the preparation of this work the authors used GPT-4 in order to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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