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Time since last intravenous bisphosphonate and risk of osteonecrosis of the jaw in osteoporotic patients

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Medication-related osteonecrosis of the jaw is a rare but serious condition in which the jawbone fails to heal and becomes necrotic, typically after dental surgery in patients treated with bisphosphonates. However, clear evidence guiding how long bisphosphonate treatment should be paused before dental surgery remains limited. Here we show that a longer time since the last dose of intravenous bisphosphonate is associated with a reduced risk of jawbone necrosis. Using a nationwide retrospective cohort of 152,299 older adults diagnosed with osteoporosis, we analyze the relationship between the duration of bisphosphonate discontinuation prior to dental extraction and the occurrence of osteonecrosis of the jaw. We find that the risk is substantially lower when treatment is paused for more than 90 days, and lowest when the pause exceeds one year. The risk reduction appears more consistent with ibandronate, whereas with zoledronate, only pauses longer than one year show a meaningful association. These findings underscore the potential value of personalized prevention strategies based on bisphosphonate type.

The prolonged use of bisphosphonates, which are widely used for treating and preventing osteoporosis due to their established effectiveness in inhibiting bone resorption, may lead to a complication known as medication-related osteonecrosis of the jaw (MRONJ)[1]. Of specific concern are the risks posed to individuals undergoing invasive dental procedures, particularly tooth extraction, as more than 60% of MRONJ patients were associated with tooth extraction, with reported increases ranging from 16.5 to 32.97-fold[2–5]. The significance of MRONJ lies in its potential to induce severe complications, including persistent pain, infection, and impaired oral function, significantly impacting the quality of life of affected individuals. Therefore, implementing proactive measures to prevent MRONJ is crucial, and temporarily discontinuing bisphosphonate therapy, often referred to as a drug holiday has been proposed as a potential preventive strategy[6,7]. However, since drug holiday can imply a deliberate or structured break, we hereafter refer to it more precisely as the time since the last dose (TSL), which better reflects the actual interval from the final intravenous (IV) bisphosphonate administration to the dental procedure.

However, in the updated 2022 American Association of Oral and Maxillofacial Surgery (AAOMS) position paper, the working group openly acknowledged the lack of consensus regarding the 'drug holiday' (i.e., TSL)[8]. Unlike previous recommendations, which suggested

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discontinuing oral bisphosphonates 2–3 months before undergoing an invasive dental procedure[6,9,10], the 2022 position paper highlights the ongoing controversy over TSL and refrains from specifying a discontinuation period. Their systematic review assessing the efficacy of the TSL in preventing MRONJ found varied reports with differing conclusions, indicating a lack of high-level evidence to support or refute TSL[8].

The challenges in assessing the effectiveness of an appropriate TSL between bisphosphonate and dental procedures arise from the rarity of MRONJ occurrences within the patient population, contributing to the scarcity of evidence in clinical studies. Due to the limited number of MRONJ events, randomized controlled trials offer insufficient data to develop reliable preventive protocols, especially for IV bisphosphonates in osteoporosis patients. Current clinical studies often involve mixed cohorts, including both osteoporosis patients and cancer patients[11], or those using various types of antiresorptive agents, such as oral and IV bisphosphonates, and denosumab[12], leading to ambiguity in clinical guidelines. Additionally, studies involving patients using oral bisphosphonates have increased ambiguity due to the inability to fully consider the variabilities in the possession rate and adherence of bisphosphonates[13].

The challenge of establishing definitive evidence for the optimal TSL between bisphosphonate and dental procedures emphasizes the necessity for large population-based studies, focusing solely on IV bisphosphonates to eliminate uncertainties associated with oral medications. Accordingly, we aimed to investigate whether a longer TSL could reduce the risk of MRONJ after dental procedures.

Here, we show that extending the interval between a dental procedure and the last dose of IV bisphosphonate, referred to as TSL, is associated with a reduced risk of MRONJ. Using a nationwide retrospective cohort of osteoporosis patients, we find that the risk significantly decreases once TSL exceeds 90 days, reaching its lowest level beyond 1 year. Notably, this reduction is more consistent with ibandronate, whereas for zoledronate, a meaningful benefit is observed only after TSL surpasses 1 year. These findings suggest that optimizing TSL according to the specific bisphosphonate may help tailor MRONJ prevention strategies.

Results

Baseline characteristics

The final cohort included 152,299 participants with a mean age of 72.9 ± 7.0 years, and 146,338 (96.1%) were female (Table 1). During a mean follow-up of 34.3 ± 24.6 months, 916 (0.6%) MRONJ patients were reported. Participants whose TSL was ≤90 days presented MRONJ development of 274 (1.3%) cases, which was significantly higher than the 341 (0.4%) cases in the group with TSL > 365 days ($p < 0.001$).

In the additional analysis of 785,256 osteoporosis patients who received IV bisphosphonates, after excluding those with malignancy, use of anabolic agents, or incomplete data, and including both patients who underwent tooth extraction and those who did not, 1644 MRONJ cases were identified, corresponding to an overall event rate of approximately 0.2% (Supplementary Table 1). Notably, participants who underwent tooth extraction after initiating IV bisphosphonates demonstrated a higher MRONJ incidence (0.6%) than those who did not. Additionally, zoledronate users exhibited a slightly higher MRONJ risk (0.25%) compared to ibandronate users (0.20%), suggesting potential differences in risk profiles between agents.

Among 152,299 patients who had received IV bisphosphonate and subsequently underwent tooth extraction, 23,062 (15.1%) restart bisphosphonate therapy, at a mean of 11.2 ± 15.5 months after tooth extraction. Across the TSL groups (≤90 days, 91–180 days, 181–365 days, and >365 days), the bisphosphonate restart rate ranged from approximately 14% to 15%, and the average time to bisphosphonate restart varied between about 10.1 and 13.2 months (Supplementary Table 2).

The risk of MRONJ according to time since last dose (TSL)

IV bisphosphonate users with longer TSL significantly reduced the risk of MRONJ, especially with TSL longer than 90 days, as assessed across various durations of the TSL (Fig. 1A). Compared to participants with TSL less than 90 days, the risk of MRONJ was significantly lower, with HRs of 0.57 (95% CI: 0.47–0.70), 0.45 (95% CI: 0.37–0.55), and 0.43 (95% CI: 0.36–0.50) for TSL of 91–180, 181–365, and >365 days, respectively (all $p < 0.001$), in the model adjusted for age, sex, economic status, Charlson comorbidity index, dose intensity of previous bisphosphonate use, and type of IV bisphosphonates (Table 2).

Subgroup analysis according to IV bisphosphonate type suggested that zoledronate possibly requires a longer TSL compared to ibandronate. Stratifying by the type of bisphosphonate used (see Supplementary Tables 3 and 4 for demographics), participants who were administered zoledronate and had TSL > 365 days exhibited a marked decreased risk, with an HR of 0.51 (95% CI: 0.33–0.79). In comparison, participants with TSL < 1 year had a similar risk as those with the TSL less than 90 days (Table 2 and Fig. 1B). In contrast, ibandronate users demonstrated a consistent reduction in risk across TSL > 90 days, with adjusted HRs of 0.47 (95% CI: 0.38–0.60), 0.42 (95% CI: 0.34–0.52), and 0.41 (95% CI: 0.35–0.49) for TSL of 91–180, 181–365, and >365 days, respectively (all $p < 0.001$) (Table 2 and Fig. 1C).

The nonlinear association of TSL with MRONJ risk

The nonlinear relationship between the TSL and the risk of MRONJ is shown in Fig. 2. The risk significantly decreases as the duration of the TSL increases. Notably, the HRs after 60 and 90 days were significantly decreased, signaling a reduced risk compared to shorter TSL (under 60 and 90 days, respectively). This trend was observed in both the unadjusted and adjusted models, with the unadjusted model showing an HR of 0.38 (95% CI: 0.32–0.45) for 60 days and 0.39 (95% CI: 0.34–0.45) for 90 days (Fig. 2A) and the adjusted model showing an HR of 0.45 (95% CI: 0.39–0.53) for 60 days and 0.46 (95% CI: 0.40–0.53) for 90 days (Fig. 2B). The TSL needed for the risk of MRONJ to be halved, which were 273 days in the unadjusted model and 329 days in the adjusted model for the total participant group.

A similar trend was observed in subgroup analyses by type of IV bisphosphonate, though with varying cutoff points. For IV zoledronate users, the risk reduction became noticeable only after extending the TSL beyond 90 days, with an HR of 0.78 (95% CI: 0.49–1.25) for 60 days and 0.69 (95% CI: 0.47–1.02) for 90 days (Fig. 2C). In contrast, for IV ibandronate users, a significant risk reduction was evident even at 60 and 90 days of TSL, with an HR of 0.41 (95% CI: 0.35–0.49) for 60 days and 0.43 (95% CI: 0.36–0.50) for 90 days (Fig. 2D). Furthermore, the respective TSL at which the risk of MRONJ is reduced by half are 520 days for IV zoledronate users and 292 days for IV ibandronate users.

Risk of major osteoporotic fractures according to TSL

The relationship between TSL and the risk of fractures was analyzed (Supplementary Table 5). Overall, the longer TSL was associated with progressively higher odds of fractures, with adjusted OR ranging from 1.96 to 5.32 compared to the reference group. This trend was particularly pronounced for vertebral fractures, where the >365 days group showed an adjusted OR of 4.04 (95% CI, 3.65–4.47). Hip fractures followed a similar pattern, with an adjusted OR of 8.47 (95% CI, 6.56–11.0) in the >365 days group, and distal radius fractures rose to an OR of 9.43 (95% CI, 7.34–12.12). Humerus fractures, though less common overall, also displayed a marked increase in risk (adjusted OR, 7.49; 95% CI, 4.68–12.00) for TSL exceeding 365 days.

Discussion

This longitudinal nationwide cohort study with 152,299 osteoporosis participants investigated the risk of MRONJ after tooth extraction

Table 1 | Baseline characteristics of patients stratified by the time since the last dose (TSL) of IV bisphosphonate before tooth extraction

Categories	Total (*n* = 152,299)	TSL of IV bisphosphonate before tooth extraction				
		≤90 days (*n* = 21,472)	91–180 days (*n* = 19,486)	181–365 days (*n* = 29,795)	>365 days (*n* = 81,546)	*p* value
Age, year	72.9 ± 7.0	73.8 ± 6.8	73.6 ± 6.8	73.6 ± 6.8	72.3 ± 7.1	<0.001
Female	146,338 (96.1%)	20,689 (96.4%)	18,772 (96.3%)	28,663 (96.2%)	78,214 (95.9%)	0.002
Resident area						<0.001
Urban area	90,422 (59.4%)	12,185 (56.8%)	11,523 (59.1%)	17,609 (59.1%)	49,105 (60.2%)	
Rural area	61,877 (40.6%)	9287 (43.3%)	7963 (40.9%)	12,186 (40.9%)	32,441 (39.8%)	
Economic status						<0.001
Others	138,786 (91.1%)	19,357 (90.2%)	17,669 (90.7%)	26,988 (90.6%)	74,772 (91.7%)	
Medical aid	13,513 (8.9%)	2115 (9.9%)	1817 (9.3%)	2807 (9.4%)	6774 (8.3%)	
Type of IV bisphosphonate						<0.001
Ibandronate	132,501 (87.0%)	18,770 (87.4%)	16,883 (86.6%)	25,461 (85.5%)	71,387 (87.5%)	
Zoledronate	19,798 (13.0%)	2702 (12.6%)	2603 (13.4%)	4334 (14.6%)	10,159 (12.5%)	
Dose intensity of previous bisphosphonate use						<0.001
DDD < 365	89,525 (58.8%)	10,795 (50.3%)	10,115 (51.9%)	16,050 (53.9%)	52,565 (64.5%)	
365 ≤ DDD < 730	34,645 (22.8%)	5238 (24.4%)	4688 (24.1%)	7326 (24.6%)	17,393 (21.3%)	
730 ≤ DDD < 1095	13,763 (9.0%)	2476 (11.5%)	2178 (11.2%)	3036 (10.2%)	6073 (7.5%)	
1095 ≤ DDD < 1460	7153 (4.7%)	1384 (6.5%)	1194 (6.1%)	1662 (5.6%)	2913 (3.6%)	
DDD ≥ 1460	7213 (4.7%)	1579 (7.4%)	1311 (6.7%)	1721 (5.8%)	2602 (3.2%)	
Comorbidities						
Hypertension	91,372 (60.0%)	13,104 (61.0%)	11,873 (60.9%)	18,028 (60.5%)	48,367 (59.3%)	<0.001
Diabetes mellitus	42,416 (27.9%)	6287 (29.3%)	5626 (28.9%)	8624 (28.9%)	21,879 (26.8%)	<0.001
Dyslipidemia	83,184 (54.6%)	12,473 (58.1%)	11,260 (57.8%)	16,801 (56.4%)	42,650 (52.3%)	<0.001
Anemia	15,545 (10.2%)	2340 (10.9%)	2062 (10.6%)	3102 (10.4%)	8041 (9.9%)	0.001
Cardiovascular diseases	20,161 (13.2%)	2906 (13.5%)	2647 (13.6%)	4087 (13.7%)	10,521 (12.9%)	<0.001
Rheumatoid arthritis	1657 (1.1%)	274 (1.3%)	249 (1.3%)	327 (1.1%)	807 (1.0%)	<0.001
Charlson comorbidity index						<0.001
≤1	134,692 (88.4%)	18,894 (88.0%)	17,173 (88.1%)	26,177 (87.9%)	72,448 (88.8%)	
2	11,249 (7.4%)	1672 (7.8%)	1472 (7.6%)	2320 (7.8%)	5785 (7.1%)	
≥3	6358 (4.2%)	906 (4.2%)	841 (4.3%)	1298 (4.4%)	3313 (4.1%)	
MRONJ events during follow-up	916 (0.6%)	274 (1.3%)	138 (0.7%)	163 (0.6%)	341 (0.4%)	<0.001

Continuous variables are presented as means ± standard deviations, and categorical variables are presented as counts with percentages in parentheses. Group comparisons were performed using one-way analysis of variance (ANOVA) for continuous variables and the Chi-square test for categorical variables. All statistical tests were two-sided, and *p* values < 0.05 were considered statistically significant.

IV intravenous, *DDD* defined daily doses, *MRONJ* medication-related osteonecrosis of the jaw.

according to the TSL. The study revealed that extended drug discontinuation significantly reduced the risk of developing MRONJ. The risk of MRONJ decreased progressively with longer TSL. This trend was similar across different IV bisphosphonate types, with the most substantial risk reduction for zoledronate users with TSL over 365 days and consistent risk reduction for ibandronate users with TSL over 90 days. However, our findings also indicate that extended discontinuation significantly increase the risk of fragility fractures, underscoring the importance of balancing MRONJ risk reduction with potential trade-offs in fracture prevention. These results are noteworthy as the first large-scale confirmation that discontinuing IV bisphosphonate treatment in osteoporosis patients can mitigate MRONJ risk—a topic that has remained controversial due to limited biological and clinical evidence. We hope our findings will contribute to shaping future guidelines aimed at minimizing this serious complication.

Clinical studies investigating the preventive effects of drug discontinuation before dental treatment in osteoporosis patients are limited. A retrospective study showed a lower incidence of MRONJ (2.9%) in patients with ~5-month drug discontinuation before dental procedures than in patients without drug discontinuation (10.9%), although the difference was not statistically significant[11]. In a multicenter retrospective study of 1175 patients undergoing oral bisphosphonate treatment, no significant difference in the incidence of MRONJ was reported, regardless of whether bisphosphonates were discontinued before tooth extraction[14]. In a prospective study assessing healing after tooth extraction in osteoporosis patients treated with bisphosphonate, the authors reported that MRONJ did not occur in all 36 patients who did not discontinue bisphosphonate and that proper healing after tooth extraction could be achieved without drug discontinuation[12]. However, the aforementioned studies involved cohorts including both osteoporosis and cancer patients[11], those treated with various antiresorptive agents[12], or those treated with oral bisphosphonate alone[14], leading to ambiguity in the clinical guidelines for IV bisphosphonates in osteoporosis patients. Additionally, our study is the first to demonstrate an increased risk of fragility fractures as the TSL lengthened, underscoring the need for careful clinical judgment when determining the optimal timing for dental interventions in patients on IV bisphosphonate therapy. Balancing the potential reduction in MRONJ risk against the increased likelihood of fractures is essential for achieving the best overall outcomes, and our findings may serve as a foundation for more refined guidelines in clinical practice.

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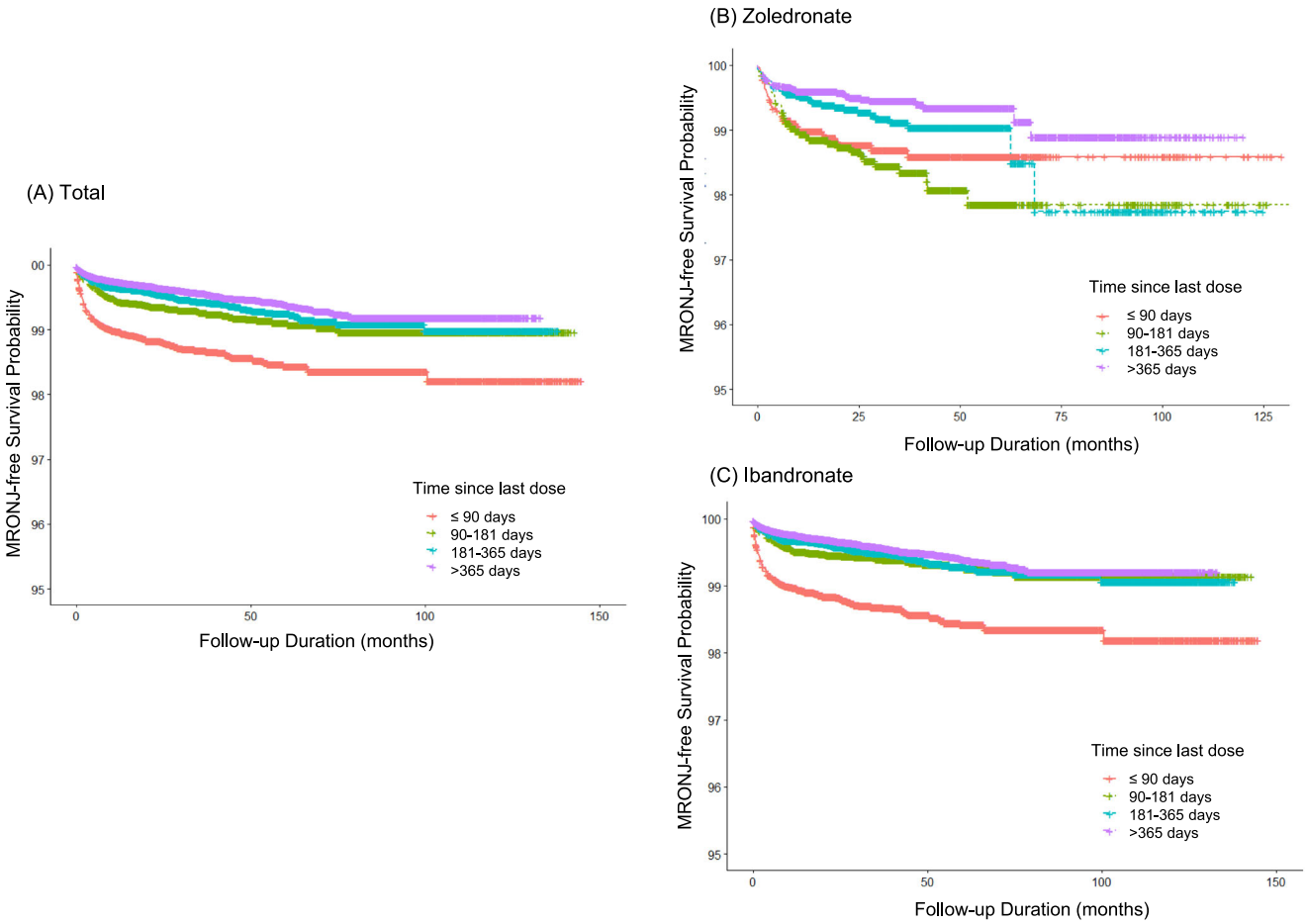

Fig. 1 | MRONJ-free survival according to the TSL between the last IV bisphosphonate and tooth extraction. A Total participants, **B** Zoledronate users, **C** Ibandronate users. *TSL* time since the last dose of IV bisphosphonate before tooth extraction.

Table 2 | Risk of MRONJ according to the time since the last dose (TSL) of IV bisphosphonate before tooth extraction

TSL of IV bisphosphonate before tooth extraction	MRONJ events/Total number of patients	Unadjusted HR (95% CI)	Model A HR (95% CI)	Model B HR (95% CI)	Model C HR (95% CI)
Total participants					
≤90 days	274/21,472	**Reference**	**Reference**	**Reference**	**Reference**
91–180 days	138/19,486	0.56 (0.45, 0.68)	0.56 (0.46, 0.69)	0.56 (0.46, 0.69)	0.57 (0.47, 0.70)
181–365 days	163/29,795	0.43 (0.35, 0.52)	0.43 (0.36, 0.53)	0.43 (0.36, 0.53)	0.45 (0.37, 0.55)
>365 days	341/81,546	0.33 (0.28, 0.39)	0.36 (0.31, 0.43)	0.37 (0.31, 0.43)	0.43 (0.36, 0.50)
Zoledronate users					
≤90 days	33/2702	**Reference**	**Reference**	**Reference**	**Reference**
91–180 days	39/2603	1.23 (0.77, 1.96)	1.23 (0.77, 1.96)	1.23 (0.77, 1.96)	1.26 (0.79, 2.00)
181–365 days	34/4334	0.65 (0.40, 1.05)	0.66 (0.41, 1.07)	0.66 (0.41, 1.07)	0.69 (0.43, 1.11)
>365 days	51/10,159	0.44 (0.28, 0.68)	0.46 (0.30, 0.72)	0.46 (0.30, 0.72)	0.51 (0.33, 0.79)
Ibandronate users					
≤90 days	241/18,770	**Reference**	**Reference**	**Reference**	**Reference**
91–180 days	99/16,883	0.46 (0.36, 0.58)	0.46 (0.37, 0.58)	0.46 (0.37, 0.59)	0.47 (0.38, 0.60)
181–365 days	129/25,461	0.39 (0.32, 0.49)	0.40 (0.32, 0.49)	0.40 (0.32, 0.49)	0.42 (0.34, 0.52)
>365 days	290/71,387	0.32 (0.27, 0.38)	0.35 (0.29, 0.42)	0.35 (0.30, 0.42)	0.41 (0.35, 0.49)

Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models. The reference group comprises patients whose tooth extraction occurred within ≤90 days after the last IV bisphosphonate dose. All statistical tests were two-sided, and p values < 0.05 were considered statistically significant. Model A was adjusted for age and sex. Model B was adjusted for age, sex, economic status, and Charlson comorbidity index. Model C was adjusted for age, sex, economic status, Charlson comorbidity index, dose intensity of previous bisphosphonate use, and type of IV bisphosphonate.

MRONJ medication-related osteonecrosis of the jaw, *IV* intravenous, *TSL* time since the last dose, *HR* hazard ratio, *CI* confidence interval.

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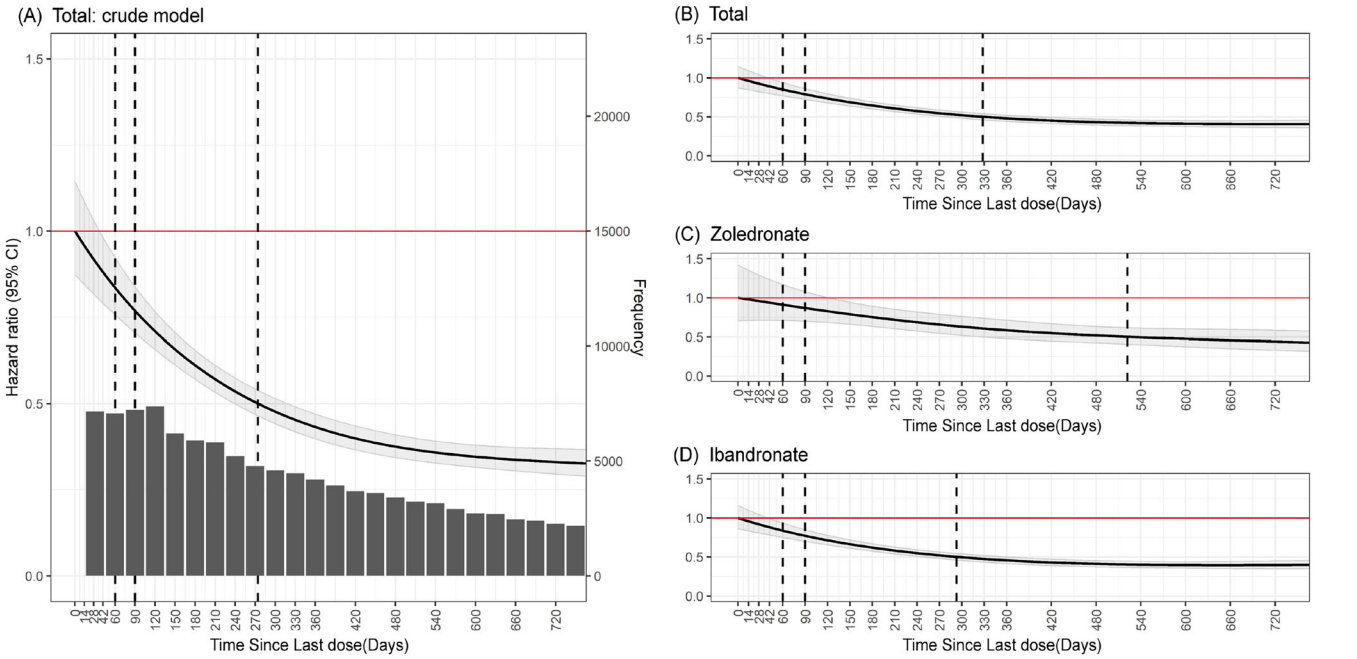

Fig. 2 | The nonlinear association of the TSL between the last IV bisphosphonate and tooth extraction with MRONJ risk. A Unadjusted model of total participants, **B** adjusted model of total participants, **C** zoledronate users, and (**D**) ibandronate users. *TSL* time since the last dose of IV bisphosphonate before tooth extraction. Gray error bands represent 95% confidence intervals around the estimated risk curves. In (**A**), the black bars indicate the frequency of MRONJ cases observed within each corresponding time interval. Cox proportional hazard model was used to estimated hazard ratio and 95% confidence intervals. Adjustments were done in (**B**–**D**) for age, sex, economic status, Charlson comorbidity index, dose intensity of previous bisphosphonate use, and type of IV bisphosphonate.

An additional challenge in existing research is the limited population size, compounded by the rarity of MRONJ. These constraints highlight the need for large-scale, population-based studies to achieve comprehensive insights into the effectiveness of prevention strategies. While a prior large-scale population-based study examined the pattern of drug discontinuation in patients with MRONJ, it concentrated on the cumulative incidence according to the duration of bisphosphonate discontinuation in patients who had already developed MRONJ[15]. However, to safely use IV bisphosphonates clinically, there is a need for insight into whether discontinuing bisphosphonates before dental treatment has a preventive effect on the occurrence of MRONJ. Therefore, we longitudinally tracked the occurrence of MRONJ after tooth extraction, which is considered the leading cause of MRONJ, according to the length of the TSL. This period was calculated from the date of the last IV bisphosphonate injection to the date of tooth extraction. Since our study focused exclusively on IV bisphosphonates, we could minimize compliance problems that may arise with oral bisphosphonates.

Interestingly, the study uncovered a notable disparity in the length of the TSL required to significantly reduce the risk of MRONJ between ibandronate and zoledronate users. For zoledronate users, a substantial reduction in MRONJ risk became evident after the TSL of more than a year. In contrast, ibandronate users displayed the same level of risk reduction after a much shorter TSL of just 90 days. This difference could be attributed to the varying antiresorptive potency and duration of action between these two IV bisphosphonates, with zoledronate typically being more potent and having a longer half-life than ibandronate. These findings suggest that the recommended drug discontinuation of IV bisphosphonate before dental intervention for MRONJ prevention might need to be tailored according to the specific IV bisphosphonate used, considering their pharmacokinetic profiles and half-lives.

The incidence of MRONJ in osteoporosis patients receiving bisphosphonates is generally reported to be around 0.1%[16]. In our study, however, the overall MRONJ incidence was approximately 0.21%, exceeding the previously noted incidence. This discrepancy may be attributed to broader inclusion criteria and the real-world design of our investigation, which encompassed older individuals with multiple comorbidities and relied on large-scale health insurance claims. Additionally, prior studies have shown that the risk of MRONJ increases significantly after tooth extractions, with reported rates of 0.9% to 3.4%[17–19], aligning with the higher incidence we observed in patients who underwent extractions. For instance, a recent study from Japan identified an MRONJ incidence of 0.9% among osteoporosis patients post–tooth extraction, consistent with our findings[17]. Moreover, because advanced age is a well-documented risk factor for ONJ, focusing on individuals aged 65 and older could further explain the increased incidence. Indeed, recent nationwide data indicate that MRONJ risk escalates markedly with age, rising from 6.5 per 100,000 person-years in those aged 50–59 to 26.4 per 100,000 person-years in those aged 80 or older[20]. Consequently, both the older population and the subset of patients undergoing extractions are likely contributors to the higher incidence noted in our study.

The validity of MRONJ case identification using ICD-10 codes presents an inherent limitation in studies utilizing claims-based databases. Prior studies have highlighted concerns regarding the specificity of ICD coding in capturing MRONJ cases, as misclassification can lead to overestimation of incidence[21]. In a validation study involving electronic medical records of over 2000 patients, the positive predictive value (PPV) of the K10.2 code was found to be 26.18%, raising concerns about potential overdiagnosis. However, when restricted to bisphosphonate users, the PPV increased significantly to 74.47%, suggesting that ICD codes in combination with bisphosphonate exposure history may serve as a reasonable surrogate for MRONJ case identification. To further enhance accuracy, our study adopted a stringent case definition, requiring at least two outpatient claims or at least one inpatient claim for MRONJ-related ICD-10 codes in conjunction with surgical procedure codes specific to MRONJ treatment. This approach was designed to mitigate false positives and improve case ascertainment. While the use of claims data inherently limits direct clinical confirmation, the integration of procedural data provides a refined operational definition, aligning with prior efforts to improve ICD-based case identification strategies. Nevertheless, future studies

incorporating direct clinical validation through medical record review remain essential to further optimize MRONJ classification accuracy in epidemiological research.

This study has several strengths. We utilized extensive, representative, longitudinal data on a national scale to elucidate the association of TSL with MRONJ incidence. This study is the first effort to investigate the preventive effect of the IV bisphosphonates discontinuation and dental intervention in patients with osteoporosis. Given the rarity of MRONJ, our study is noteworthy because significant results are often difficult to obtain, even in multicenter studies. Furthermore, we employed a robust multivariate model in which the variable of history of bisphosphonate use was calculated as the defined daily dose, ensuring proper adjustment for the effect of previous bisphosphonate accumulation. Additionally, by dividing the data by daily TSL of IV bisphosphonates, we were able to thoroughly assess the gradual reduction in risk as the TSL lengthened.

This study has several limitations. First, reliance on claims data inevitably restricts MRONJ case identification to ICD-10 codes and procedural records, preventing direct oral examinations and comprehensive assessment of disease severity. The absence of a blinded diagnostic process introduces the possibility of biased classification, as clinicians aware of a patient's bisphosphonate use may be more inclined to assign an MRONJ diagnosis. Although large-scale, blinded RCTs would theoretically mitigate such diagnostic bias, MRONJ is exceedingly rare in osteoporosis patients, as evidenced by prior trials reporting no or only isolated cases[22–25]. Consequently, conducting sufficiently powered studies to systematically evaluate MRONJ risk under blinded conditions remains impractical. To address this limitation, we employed a stricter case definition requiring both MRONJ-related diagnostic codes and corresponding surgical procedure codes, aiming to include only clinically significant cases and reduce false positives[26]. While this stringent definition may have reduced the total number of events and potentially affected model robustness, it enhances the specificity of our findings. Future investigations incorporating clinical record reviews or standardized severity assessments could further validate our approach and strengthen the evidence base regarding MRONJ risk in osteoporosis populations. Second, confounders not addressed in this study could influence MRONJ development. Due to the characteristics of the database used in this study, laboratory results such as bone turnover markers or participants' nutritional status could not be included. However, despite potential selection bias or unconsidered confounding factors, our results remained consistent across different adjusted models and subgroup analyses. Third, the inclusion criteria were limited to patients receiving two of IV bisphosphonates. Denosumab, another widely used antiresorptive agent known to induce MRONJ, could not be included due to limited access to the information of denosumab users due to NHIS policy. Therefore, additional research specifically focusing on denosumab is essential. Fourth, a comprehensive risk–benefit comparison is necessary to fully evaluate the implications of optimal timing since the last dose of IV bisphosphonates before dental intervention in the context of MRONJ development and potential fracture risk.

In conclusion, our study supports the efficacy of IV bisphosphonate discontinuation before tooth extraction in reducing MRONJ risk, showing that a longer TSL corresponds to a lower risk. Additionally, the TSL that can reduce MRONJ risk is different between IV ibandronate and zoledronate users, emphasizing the need to establish an appropriate TSL between tooth extraction and IV bisphosphonate for each antiresorptive agent according to their potencies and half-lives rather than adopting a uniform approach.

Methods

Data source

To evaluate the association between the temporary discontinuation of IV bisphosphonates and the occurrence of MRONJ, we used the National Health Information Database of the Korean National Health Insurance Service (NHIS). These data are nationwide retrospective cohort data based on health insurance information. All subjects were deidentified due to privacy concerns related to personal information protection.

South Korea enforces mandatory health insurance enrollment, and the NHIS is the sole insurance provider in South Korea, controlled and supported by the Korean government. It covers more than 97% of Koreans[27–29], and medical aid programs administered by the NHIS support the remaining 3% of the population. The NHIS database includes demographic and socioeconomic status information (e.g., age, birth year, residence, residential area, and economic status), as well as diagnoses (based on diagnostic codes), prescriptions, and treatments from 2002 to 2020.

Access to data from the NHIS database was granted to individuals diagnosed with osteoporosis who received IV bisphosphonates between 2009 and 2020 and were aged 65 years or older in 2020, comprising a total of 1,031,337 individuals (dataset number: NIHS-2023-1-011). IV bisphosphonates included zoledronate (M05BA08) and ibandronate (M05BA06) as classified by Anatomical Therapeutic Chemical (ATC) codes. The NHIS database distinguishes between oral and IV administration routes.

Study population

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (No. X-2108-705-901). All methods were carried out in accordance with the relevant guidelines and regulations of the Declaration of Helsinki. Informed consent was waived because retrospective anonymized data were used. This study complies fully with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Using the NHIS[27–29], the study included a total of 1,031,337 participants diagnosed with osteoporosis[26]. These participants received IV bisphosphonates (ibandronate and zoledronate) between 2009 and 2020 and were aged 65 years or older in 2020 (Fig. 3A). Among them, 193,697 individuals who underwent tooth extraction after their last administration of IV bisphosphonate before June 30, 2020, were included in the cohort. We excluded 2593 participants who had ever used anabolic agents (teriparatide) and 37,297 participants with a history of malignant neoplasms. Additionally, 1482 participants who were diagnosed with MRONJ before the index date—the day of the tooth extraction—were also excluded, as were 26 participants with incomplete data for variables of interest. Ultimately, the final analysis included 152,299 participants.

We defined the TSL—previously referred to as a 'drug holiday'—as the period (in days) from the final IV bisphosphonate injection to the date of tooth extraction (Fig. 3B). Based on this definition, participants were categorized into four groups: ≤90 days, 91–180 days, 181–365 days, and >365 days, comprising 21,472, 19,486, 29,795, and 81,546 individuals, respectively. The index date was determined as the date of the first tooth extraction following the last prescription of IV bisphosphonates.

Outcome assessment and definition of variables

The primary outcome of the study was the occurrence of MRONJ after tooth extraction. The follow-up duration (days) spanned from the index date to the earliest of the following events: the onset of MRONJ, patient death, or the end of the study period in December 2020. MRONJ was defined as at least one claim from inpatient admission or two or more claims from outpatient services of the 10th revision of International Classification of Diseases (ICD-10) codes M87.1 (osteonecrosis due to drugs) or K10.2 (inflammatory conditions of the jaw), including Current Procedural Terminology (CPT) codes of surgical interventions indicated for MRONJ treatment (Supplementary Table 6)[21]. The date

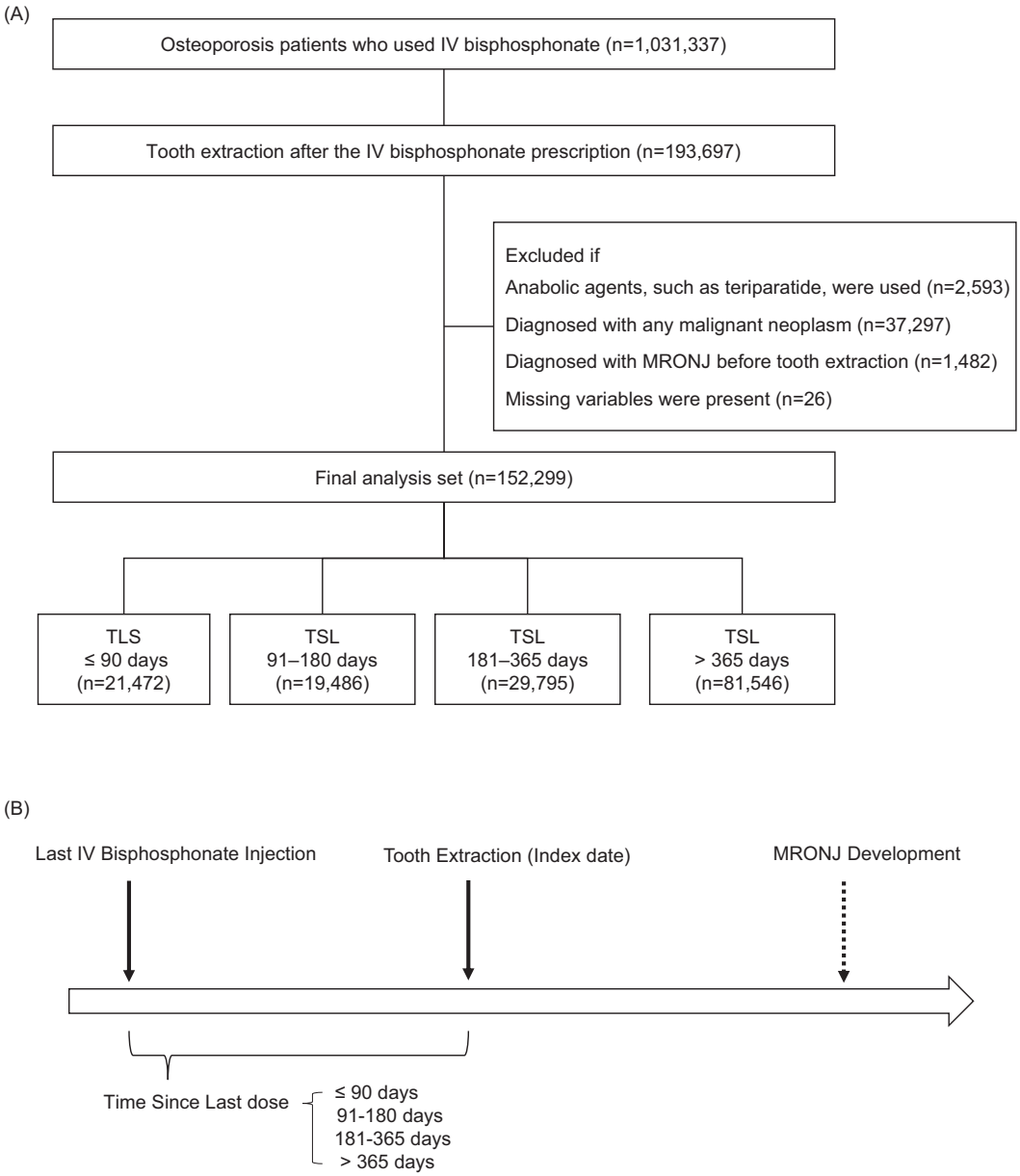

Fig. 3 | Overview of participant selection and study design. A Selection of participants, **B** graphical overview of the study design. TSL time since the last dose of IV bisphosphonate before tooth extraction.

of MRONJ diagnosis was established as the date of the first claim of an MRONJ diagnosis code.

Baseline demographic and socioeconomic data were collected as of the index date, with economic status classified according to NHIS records into medical aid beneficiaries and others based on insurance premium payment percentiles. Osteoporosis was defined using the 10th revision of the International Classification of Diseases (ICD-10) codes M80 (osteoporosis with pathological fracture), M81 (osteoporosis without pathological fracture), and M82 (osteoporosis in disease classified elsewhere)[26]. Tooth extraction procedures were identified by one or more claims of the specified procedure codes (Supplementary Table 7). Comorbid conditions were determined using ICD-10 codes, requiring a minimum of two diagnostic claims within the year prior to the index date to confirm a diagnosis: hypertension (I10, I15), diabetes mellitus (E10, E118, E119, E13, E149), dyslipidemia (E78), anemia (D46, D50–53, D55–64, D74), cardiovascular disease (I21, I22), and rheumatoid arthritis (M05). The Charlson comorbidity index was calculated based on established literature and stratified into three categories: ≤1, 2, and ≥3[30]. Malignant neoplasms were defined using ICD-10 codes C00-C97, and individuals with the codes from the entire period 2002–2020 were excluded from the cohort.

While only individuals whose last administration was IV bisphosphonate were included in the study cohort, both oral and IV forms were considered when calculating the dose intensity of previous bisphosphonate use, which was determined using defined daily doses (DDD)[26]. This calculation included alendronate, risedronate, ibandronate, and zoledronate in all dosage forms and formulations obtained from the prescription record prior to the index date. One DDD equals the usual dose a patient would receive daily for bisphosphonates. The dose intensity was calculated by multiplying the number of prescribed drugs by the amount of drugs divided by the DDD.

Secondary outcomes

First, to provide a broader epidemiological context for MRONJ risk among IV bisphosphonate users, we conducted an analysis that

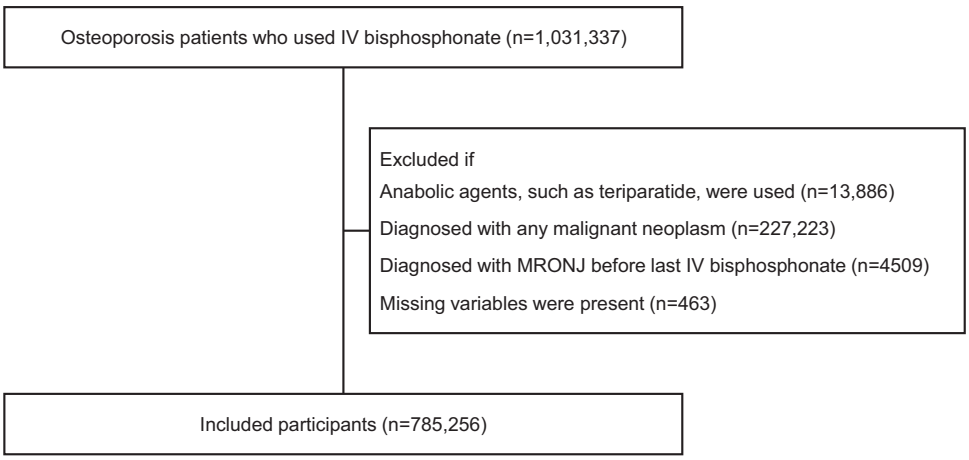

Fig. 4 | Flowchart of participant selection to evaluate MRONJ occurrence among IV bisphosphonate users, regardless of dental extration.

included all osteoporosis patients who had received IV bisphosphonates, regardless of whether they underwent a tooth extraction. Using the same NHIS dataset and selection criteria as the main cohort, we initially identified 1,031,337 osteoporosis patients treated with IV bisphosphonates between 2009 and 2020. After excluding patients who had used anabolic agents, had a history of malignant neoplasms, were diagnosed with MRONJ before the index date, or had missing data, a total of 785,256 patients remained (Fig. 4). MRONJ was defined based on ICD-10 diagnostic codes (M87.1, K10.2) and procedural codes for MRONJ-related surgical interventions (Table S1). The follow-up period was from the last administration of IV bisphosphonates until the earliest occurrence of MRONJ, death, or the end of the study period (December 2020). The MRONJ event rate was calculated as the number of MRONJ cases divided by the total number of participants, and event rates were further evaluated according to the type of the most recently prescribed IV bisphosphonate (ibandronate or zoledronate).

Second, we evaluated bisphosphonate restart patterns following tooth extraction to assess treatment continuity. Bisphosphonate restart was defined as the first recorded prescription of bisphosphonates after the tooth extraction date. For each TSL group, we determined the proportion of patients who restarted bisphosphonate therapy and the mean time (in month) from tooth extraction to restart.

Third, to assess the impact of the TSL on major osteoporotic fractures including vertebral, hip, distal radius, and humerus fractures, we observed these fractures from the last IV bisphosphonate administration until the date of tooth extraction, using operational definitions described in previous studies[31,32]. Vertebral fractures were identified as at least two claims for ICD-10 codes S22.0, S22.1, S32.0, S32.7, T08, M48.4, M48.5, or M49.5. Hip fractures were defined as at least one claim for ICD-10 codes S72.0 or S72.1 with one or more procedural codes, including N0601, N0611, N0305, N0981, N0641, N0652, N0654, N0711, or N0715. Distal radius fractures were identified as at least two claims for ICD-10 codes S52.5 or S52.6, and humerus fractures as at least two claims for ICD-10 codes S42.2 or S42.3.

Statistical analysis

The characteristics of the groups were compared using the chi-square test for categorical variables and analysis of variance for continuous variables. Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for MRONJ events. Participants who had TSL of 91–180, 181–365, and >365 days were compared to those with a TSL ≤ 90 days (reference). Multivariate HRs were adjusted for age and sex for model A, additionally adjusted for economic status, Charlson comorbidity index for model B, and additionally adjusted for dose intensity of previous bisphosphonate use and type of IV bisphosphonate for model C.

To assess the relationship between TSL and the risk of major osteoporotic fractures, odds ratios (ORs) with 95% CIs were calculated. Using the TSL ≤ 90 days as the reference, ORs were obtained for each group. Adjusted ORs were determined through multivariate logistic regression models adjusted for age and sex.

To visually assess the association between duration and the risk of MRONJ, we performed penalized splines to demonstrate the dose–response relationships. We partitioned the data into 'before' and 'after' periods based on daily intervals, assigning the 'before' period as the reference category. HRs were then calculated for the 'after' periods compared to their respective 'before' periods, and the results were depicted through graphical representation. We utilized R programming, specifically the *pspline* function, to find the optimal degrees of freedom for penalized splines for the models.

As a subgroup analysis, we analyzed the risk of MRONJ according to the TSL by dividing participants into subgroups: the ibandronate group for participants most recently treated with IV ibandronate, and the zoledronate group for those treated with IV zoledronate as their last therapy.

All analyses were performed using R version 4.3.2. (R Foundation for Statistical Computing, Vienna, Austria), SAS Enterprise Guide version 7.1 (SAS Institute, Inc., Cary, NC, USA). All values were considered statistically significant if the p value was <0.05.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data used in this study were obtained from the National Health Insurance Service (NHIS) database of Korea. The NHIS data are available under restricted access for legal and ethical reasons, including protection of personally identifiable health information. Access can be obtained by submitting a formal request through the NHIS Data Sharing Service (http://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do). Applicants must provide a study protocol, evidence of institutional review board (IRB) approval, and meet NHIS eligibility criteria. Requests are reviewed by the NHIS data access committee and, if approved, data are provided through a secure research environment for a limited project-specific period. The raw individual-level data are protected and are not available due to data privacy laws.

Code availability

All relevant statistical analysis code (R and SAS scripts) has been provided as a Supplementary data file for those wishing to replicate or extend our analyses.

References

1. Park, J. H. et al. Serum biomarkers for bisphosphonate-related osteonecrosis of the jaw: a prospective clinical study. *Osteoporos. Int.* **33**, 367–377 (2022).
2. Saad, F. et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Ann. Oncol.* **23**, 1341–1347 (2012).
3. Fehm, T. et al. Bisphosphonate-induced osteonecrosis of the jaw (ONJ): incidence and risk factors in patients with breast cancer and gynecological malignancies. *Gynecol. Oncol.* **112**, 605–609 (2009).
4. Kyrgidis, A. et al. Bisphosphonate-related osteonecrosis of the jaws: a case-control study of risk factors in breast cancer patients. *J. Clin. Oncol.* **26**, 4634–4638 (2008).
5. Vahtsevanos, K. et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. *J. Clin. Oncol.* **27**, 5356–5362 (2009).
6. Ruggiero, S. L. et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw–2014 update. *J. Oral. Maxillofac. Surg.* **72**, 1938–1956 (2014).
7. Khan, A. A. et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J. Bone Min. Res.* **30**, 3–23 (2015).
8. Ruggiero, S. L. et al. American Association of Oral and Maxillofacial Surgeons' position paper on medication-related osteonecrosis of the jaws-2022 update. *J. Oral. Maxillofac. Surg.* **80**, 920–943 (2022).
9. Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J. Oral. Maxillofac. Surg.* **65**, 369–376 (2007).
10. Ruggiero, S. L. et al. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws–2009 update. *J. Oral. Maxillofac. Surg.* **67**, 2–12 (2009).
11. Salgueiro, M. et al. Value of pre-operative CTX serum levels in the prediction of medication-related osteonecrosis of the jaw (MRONJ): a retrospective clinical study. *EPMA J.* **10**, 21–29 (2019).
12. Lesclous, P. et al. Alendronate or Zoledronic acid do not impair wound healing after tooth extraction in postmenopausal women with osteoporosis. *Bone* **137**, 115412 (2020).
13. Fatoye, F., Smith, P., Gebrye, T. & Yeowell, G. Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review. *BMJ Open* **9**, e027049 (2019).
14. Hasegawa, T. et al. A multicenter retrospective study of the risk factors associated with medication-related osteonecrosis of the jaw after tooth extraction in patients receiving oral bisphosphonate therapy: can primary wound closure and a drug holiday really prevent MRONJ? *Osteoporos. Int.* **28**, 2465–2473 (2017).
15. Jung, S. Y., Suh, H. S., Park, J. W. & Kwon, J. W. Drug holiday patterns and bisphosphonate-related osteonecrosis of the jaw. *Oral. Dis.* **25**, 471–480 (2019).
16. Woo, S.-B., Hellstein, J. W. & Kalmar, J. R. Systematic review: bisphosphonates and osteonecrosis of the jaws. *Ann. Intern. Med.* **144**, 753–761 (2006).
17. Fujieda, Y. et al. Incidence and risk of antiresorptive agent-related osteonecrosis of the jaw (ARONJ) after tooth extraction in patients with autoimmune disease. *J. Bone Miner. Metab.* **38**, 581–588 (2020).
18. Hansen, P. J., Knitschke, M., Draenert, F. G., Irle, S. & Neff, A. Incidence of bisphosphonate-related osteonecrosis of the jaws (BRONJ) in patients taking bisphosphonates for osteoporosis treatment—a grossly underestimated risk? *Clin. Oral. Investig.* **17**, 1829–1837 (2013).
19. Jeong, H.-G. et al. Risk factors of osteonecrosis of the jaw after tooth extraction in osteoporotic patients on oral bisphosphonates. *Imaging Sci. Dent.* **47**, 45 (2017).
20. Kim, S. H. et al. Incidence of and risk for osteonecrosis of the jaw in Korean osteoporosis patients treated with bisphosphonates: a nationwide cohort-study. *Bone* **143**, 115650 (2021).
21. Kim, H. Y., Kim, J. W., Kim, S. J., Lee, S. H. & Lee, H. S. Uncertainty of current algorithm for bisphosphonate-related osteonecrosis of the jaw in population-based studies: a systematic review. *J. Bone Miner. Res.* **32**, 584–591 (2017).
22. Black, D. M. et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N. Engl. J. Med.* **356**, 1809–1822 (2007).
23. Lyles, K. W. et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N. Engl. J. Med.* **357**, 1799–1809 (2007).
24. Black, D. M. et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J. Bone Miner. Res.* **27**, 243–254 (2012).
25. Boonen, S. et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. *N. Engl. J. Med.* **367**, 1714–1723 (2012).
26. Park, J. H. et al. Gradual, but not sudden, dose-dependent increase of ONJ risk with bisphosphonate exposure: a nationwide cohort study in women with osteoporosis. *Front. Endocrinol.* **12**, 774820 (2021).
27. Anabtawi, M., Tweedale, H. & Mahmood, H. The role, efficacy and outcome measures for teriparatide use in the management of medication-related osteonecrosis of the jaw. *Int. J. Oral. Maxillofac. Surg.* **50**, 501–510 (2021).
28. Park, J. H., Kim, J. W., Lee, H., Hong, I. & Song, T. J. Better oral hygiene is associated with a decreased risk of Meniere's disease: a nationwide cohort study. *J. Pers. Med.* **13**, 80 (2022).
29. Park, J. H., Lee, H., Kim, J. W. & Song, T. J. Better oral hygiene is associated with a reduced risk of cataract: a nationwide cohort study. *Front. Med.* **9**, 1036785 (2022).
30. Birim, O. et al. Validation of the Charlson comorbidity index in patients with operated primary non-small cell lung cancer. *Eur. J. Cardiothorac. Surg.* **23**, 30–34 (2003).
31. Ahn, S. H. et al. Risk of fractures in thyroid cancer patients with postoperative hypoparathyroidism: a nationwide cohort study in Korea. *J. Bone Miner. Res.* **38**, 1268–1277 (2023).
32. Park, H.-S. et al. Risk of fracture in patients with myasthenia gravis: a nationwide cohort study in Korea. *J. Bone Miner. Res.* **39**, 688–696 (2024).

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Author contributions

J.-H.P. and S.H.K. contributed to the study conception, design, and interpretation, and drafted the manuscript. J.L., J.O., and J.-R.L. contributed to data acquisition and analysis and critically revised the manuscript. H.-J.L. and J.-W.K. contributed to the study conception, design, data acquisition, and interpretation, and critically revised the manuscript. All authors reviewed the manuscript, gave final approval, and agreed to be accountable for all aspects of the work.

Competing interests

The authors declare no competing interests.

Additional information

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