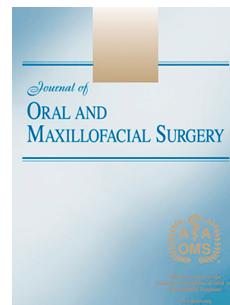


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The type of antiresorptive treatment influences the time to onset and the surgical outcome of medication-related osteonecrosis of the jaw

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## The type of antiresorptive treatment influences the time to onset and the surgical outcome of medication-related osteonecrosis of the jaw

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### Running title:

**Impact of antiresorptives on onset and outcome of jaw necrosis**

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The study has not been presented elsewhere before.

## ABSTRACT

**Objectives:** Few data exist focusing on differences in the time to disease onset and the success rates in patients suffering from medication-related osteonecrosis of the jaw (MRONJ) dependent on their different antiresorptive treatment. The purpose of this study was to analyse and compare these variables for patients treated with bisphosphonates (BP) or denosumab (DNO), and for patients who switched the antiresorptive drug (BP/DNO).

**Patients and Methods:** A retrospective single-center cohort study with patients suffering from MRONJ was conducted. The predictor variable was the antiresorptive treatment, the outcome variables were I) time to onset of MRONJ (time of antiresorptive treatment to MRONJ diagnosis) and II) treatment success (mucosal integrity 12 months postoperatively). The other variables include data on demographic, underlying disease, MRONJ stage, and trigger events. Cox and logistic regression, Phi-coefficient, Cramer's V, and Kruskal-Wallis tests were applied.

**Results:** One hundred thirty two patients were included and divided into three groups: group I (BP) n=45 patients, n=59 lesions; group II (BP/DNO) n=42 patients, n=71 lesions; group III (DNO) n=45 patients, n=62 MRONJ lesions. Treatment success and time to onset differed significantly between the groups: success rates in group I (84.7%) were significantly lower ( $p=0.04$ ) than in group II (91.5%, ( $p=0.12$ ), and group III (90.3%,  $p=0.35$ ). The onset was significantly earlier in group III DNO (median 2.0 years,  $Q_{0.25}$ : 1.49,  $Q_{0.75}$ : 2.98; CI95: 1.93 – 2.83) compared with group II BP/DNO (median 4.07 years,  $Q_{0.25}$ : 1.64,  $Q_{0.75}$ : 6.70; CI95: 3.55 – 5.68) and group I BP (median 3.86 years,  $Q_{0.25}$ : 1.69,  $Q_{0.75}$ : 6.46; CI95: 3.43 – 5.87).

**Conclusion:** The different antiresorptive drugs show distinctive characteristics of time to onset and treatment success with the lowest success rates in the bisphosphonates group and the earliest onset in the denosumab group. The switch of the antiresorptive therapy (bisphosphonate to denosumab) did not influence the outcome variables negatively.

**Keywords:** MRONJ; osteonecrosis of the jaw; success rate; time to onset; surgical therapy; drug holiday; bisphosphonate; denosumab; ONJ

## INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but severe adverse side-effect of an antiresorptive therapy with bisphosphonate and denosumab administration. Increasing tumor incidences, longer patient survival, adjuvant antiresorptive therapy strategies, and rising numbers of first line regimens for osteoporosis are turning MRONJ into a disease of increasing importance [1, 2].

General debates about treatment strategies have influenced the literature over the last decade. However, treatment success rates appear to be significantly higher for surgical therapy regimens, and so a broader acceptance for early surgical approaches by international guidelines can be observed [2]. Indeed, research groups report variable surgical success rates for surgical therapy ranging from 70 to 90% [3-7]. Surgical experience and techniques, timing of surgery, the extent or stage of the disease, the underlying disease, and co-morbidities are also known to have an impact on the treatment success [8, 9]. Of note, the success rates are also influenced by the definition of what is considered as success (mucosal integrity vs. no disease progression vs. reduction of clinical complaints). However, only a few studies have addressed the therapy outcome in relation to the antiresorptive treatment [10].

Both bisphosphonates and denosumab are potent inhibitors of osteoclast maturation and activity. However, their pharmacological effects and their pharmacokinetics are markedly different. Orally or intraveneously administered bisphosphonates selectively bind to hydroxyapatite and thus accumulate in the bone. When released from the bone and in the soluble phase, bisphosphonate molecules intracellularly interfere in the mevalonate pathway and inactivate osteoclasts, but also other cells [11]. Bisphosphonates have a high organ specificity and can remain in the bone for months and even years. This might be one reason why the possible effects of a bisphosphonate discontinuation (drug holiday) have not as yet been thoroughly investigated. In contrast, the subcutaneously administered human monoclonal antibody denosumab inhibits the RANK ligand, which is a key cytokine for the

differentiation, maturation, and activation of osteoclasts. Thus, denosumab has a high cell specificity. As is the fate of other allogeneic proteins, denosumab is inactivated by the immune system within weeks and does not accumulate in the body. The potential effect of a drug holiday of denosumab appears obvious.

Indeed, because of their pharmacological differences, disease onset and treatment success might be influenced by the type of antiresorptive therapy. An amplifying effect of two different antiresorptive therapies might occur, when patients have been sequentially treated with boths drugs (usually in the order of first bisphosphonates and second denosumab). To date, only limited data with small sample sizes are available focusing on time to onset of the disease and the therapy success of patients treated with the two antiresorptive drug classes [3, 10, 12].

Therefore, the purpose of this study was to find out whether different antiresorptive drugs have an impact on the time to the onset of MRONJ as well as on the treatment success.

The authors hypothesize that the type of antiresorptive therapy I) influences the time to MRONJ onset significantly, II) does not influence the therapy success rate, and III) that the combination of different antiresorptive drugs has an amplifying effect (earlier onset and worse success rate).

The specific aims of this study were to estimate I) the time to onset of MRONJ, II) the success rates of the surgical therapy, and III) to measure the association among BP, DNO, and BP/DNO and time to onset of MRONJ and success rates of treatment.

## PATIENTS AND METHODS

This study was approved by the local medical association authority (Bayerische Landesärztekammer) and was carried out according to the Declaration of Helsinki.

### Study sample

We designed and implemented a retrospective single-center cohort study and consecutively enrolled a sample derived from the population of subjects who had been given the working diagnosis of MRONJ [13], were treated at the Department for Medicine and Aesthetics, Clinic for Oral and Maxillofacial Surgery, Munich between 2011 und 2019, and fulfilled the following inclusion criteria: (1) indication for surgical treatment (stage I to III according to AAOMS [13]), (2) no evaluated preceding surgical approach to the lesion.

Patients were divided into three groups, dependent on their predictor variable antiresorptive drug-class history: group I with bisphosphonates (BP) only, group II with a therapeutic switch from bisphosphonates to denosumab (BP/DNO) over time, and group III with denosumab (DNO) only administration (figure 1).

The exclusion criteria were as follows: (1) patients refusing surgical therapy, (2) general medical condition of the patient did not allow surgical therapy, (3) history of head and neck radiation, (4) metastatic bone disease of the maxillofacial region, (5) missing follow-up examinations, (6) patients suffering from multiple myeloma. Patients suffering from multiple myeloma were excluded from this study because, in the present cohort, these patients were only treated with bisphosphonates. Neither in the group II BP/DNO nor in group III DNO had patients suffered from multiple myeloma, because denosumab was approved for multiple myeloma in the European Union only as of 2018. (7) Furthermore, patients that have been published in previous studies with the same outcome variables were excluded in order to avoid double publication (different studies using the same collective and the same outcome variables (success rate)).

### Study variables

The predictor variable was the type of the antiresorptive therapy and it was grouped into three levels, BP, DNO, and BP initiated and then discontinued and DNO initiated (BP/DNO). The outcome variables were I) the success one year after intervention (success was defined as complete mucosal recovery and absence of symptoms), and II) the time to onset to MRONJ (defined as time from first antiresorptive treatment to disease onset measured in years). Demographics and baseline characteristics, underlying diseases, MRONJ stages (stages 0 – 3 according to the classification of the AAOMS [13], and triggering events (events that led to the onset of MRONJ) were also collected (Table 1).

### Surgical protocol

All patients followed the same therapeutic standardized protocol. All surgical treatments were performed under general anesthesia by the same oral and maxillofacial surgery specialist (CP) using the established technique of fluorescence-guided bone resection as described previously [6, 7, 14]. If possible, a double-layer wound closure was performed as detailed elsewhere [15]. All patients remained in hospital for three days after surgery. Perioperatively, patients received antibiotic treatment either with ampicillin/sulbactam (3 times 2g +1g per day) or, in cases with penicillin allergy, clindamycin (3 times 600mg per day) for 7 days. Clinical follow-up investigations were performed by the same investigators who had been trained in MRONJ treatment (CP, AW, BHM, OR): at 12 days (removal of sutures) and at 4 weeks, followed by quarterly clinical investigations. Therapy was rated as success when complete mucosal integrity and absence of complaints (in particular, pain and infection) were present 12 months after surgery. As a secondary outcome, the time to onset defined as the first time of antiresorptive treatment to first diagnosis of the disease was evaluated for every group.

## Data analysis

Statistical analysis was performed with SPSS version Version 21 (SPSS Inc., Chicago, IL, USA).

The statistical differences between the treatment groups with regard to the outcome variable “time to onset” was evaluated using Cox regression. The differences with regard to outcome variable “treatment success” was tested applying a Kruskal Wallis test with post-hoc analysis and logistic regression.

Cox regression for time-to-event outcomes, logistic regression for continuous outcomes, and Kruskal-Wallis tests for binary outcomes were applied.

To detect statistical differences within the secondary variables (sex, age, underlying disease, MRONJ stage, antiresorptive drug, trigger events) the Phi-coefficient and Cramer’s V were applied. To evaluate the potential impact of these variables on the outcome variables “time to onset” and “treatment success” the Cox regression and logistic regression were applied and the secondary variables were included as covariates. Differences were considered statistically significant when the p-value was lower than 5% ( $p<0.05$ ).

## RESULTS

In total, 258 individuals were identified as fulfilling the criteria for MRONJ according to the AAOMS 2014. Sixty-two patients met one or more exclusion criteria and were excluded from this study. The remaining 196 patients were divided into three groups dependent on their antiresorptive medication: n=109 bisphosphonates (BP), n=42 bisphosphonates/denosumab (BP/DNO), and n=45 denosumab (DNO). Out of the 109 patients suffering from MRONJ attributable to bisphosphonates 40 patients were omitted because these patients have been published in previous studies using the same outcome variable (treatment success) [7, 16]. Out of the remaining 69 patients 45 were selected so that group I BP was most similar compared to group II and III concerning age, sex, and underlying disease (Figure 1):

- **group I BP:** n=45 patients with 59 MRONJ lesions, 16 males (35.6%) and 29 females (64.4%) with an average age of 74.4 years ( $\pm 10.41$ ). Three patients (6.6%) died during the period of data evaluation.
- **group II BP/DNO:** n=42 patients with 71 MRONJ lesions, 15 males (35.7%) and 27 females (64.3%) with an average age of 70.6 years ( $\pm 9.8$ ). Four patients (9.5%) died during the period of data evaluation.
- **group III DNO:** n=45 patients with 62 MRONJ lesions, 24 males (53.3%) and 21 females (46.7%) with an average age of 73.02 years ( $\pm 14.02$ ). Two patients (4.4%) died during the period of data evaluation.

The median follow-up on 31<sup>st</sup> December 2019 (end of data acquisition) of the study was 3.1 years (Q<sub>0.25</sub>: 1,7, Q<sub>0.75</sub>: 4,7) with a maximum follow-up time of 8.1 years and a minimum of one year (12 months). Most of the patients in this study suffered from breast cancer, followed by prostate cancer and osteoporosis. The proportion of patients suffering from cancer and osteoporosis was similar in all three groups. The distribution of MRONJ stages was similar in all groups.

The most frequently administered bisphosphonate derivative in group I (BP) and group II (BP/DNO) was zoledronate followed by ibandronate and alendronate. The most frequent trigger events associated with the onset of MRONJ were tooth extraction at 51.7%, followed by periodontitis at 19.3%, and dental implants (Table 1).

Statistical testing of secondary variables (sex, age, underlying disease, MRONJ stage, trigger events) impact on predictor variable (treatment group, applying Kruskall Wallis, Phi- and Cramer's V- tests, Table 1) as well as the outcome variables time to onset (applying cox regression, Table 2) and treatment success (applying logistic regression, Table 3) showed no statistical significance ( $p>0.05$ ).

### **Time to onset**

The median duration of the antiresorptive therapy was 6.6 years ( $Q_{0.25}$ : 5.2,  $Q_{0.75}$ : 8.5). The median time period from the beginning of the antiresorptive therapy until the onset of MRONJ was 3.98 years ( $Q_{0.25}$ : 1.98,  $Q_{0.75}$ : 8.70 ) (Figure 2). A significant difference was found between the three groups. The onset of MRONJ was significantly earlier in group III DNO (median 2.0 years,  $Q_{0.25}$ : 1.49,  $Q_{0.75}$ : 2.98; confidence interval 95% (CI95): 1.93 – 2.83) compared with group II BP/DNO (median 4.07 years,  $Q_{0.25}$ : 1.64,  $Q_{0.75}$ : 6.70; CI95: 3.55 – 5.68) and group I BP (median 3.86 years,  $Q_{0.25}$ : 1.69,  $Q_{0.75}$ : 6.46; CI95: 3.43 – 5.87) (Figure 3).

When computing the hazard ratio for the entire surveillance period no difference between groups I, II and III was discovered ( $HR=1$ ) as all patients that were included in this study would developed MRONJ over time. Limiting the surveillance period to the first 5 years of the antiresorptive therapy group III (DNO) presented an elevated risk to develop MRONJ within the first 5 years compared to group I (BP) ( $HR=1.57$ ; CI95: 1.32; 1.92) and group II (BP/DNO) and ( $HR=1.47$ ; CI95: 1.27; 1.89) (Table 4).

Between groups I (BP) and II (BP/DNO) no significant difference concerning the time to onset of MRONJ could be noticed ( $HR=0.96$ ; CI95: 0.90; 1.04). Cox regression analysis revealed that the time to onset of MRONJ was significantly longer in group I (BP) and group II (BP/DNO) compared to group III (DNO) (Table 5).

The subgroup analysis showed that patients in group II (BP/DNO) developed MRONJ after the switch from BP to DNO after 1.99 years and thus a little earlier than patients in group III with DNO only. However, this difference was statistically not significant. Notably, the temporal course of MRONJ onset of this subgroup group IIb (DNO) and group III (DNO) was almost identical (Figure 3). The 95% confidence intervals for the subgroups of group II BP/DNO were: group IIa BP 5.38 – 8.88, and group IIb 1.53 – 2.45, respectively. The subgroup analysis further revealed that patients in group II (BP/DNO) had a discontinuation of the bisphosphonate therapy of two years (under ongoing denosumab therapy) before the onset of MRONJ (Figure 4).

We found rising incidence rates for patients treated with bisphosphonate (both group I (BP) and group II (BP/DNO)) for the whole observation period. Patients treated with denosumab revealed rising incidences until year 5 followed by falling incidences for group II (BP/DNO) and group III (DNO) (Table 6).

### **Therapy success**

The overall treatment success of all three groups was 89.1% for the first surgical approach. The success rates of the single groups differed significantly with the highest success rate in group II BP/DNO (65/71 (91.5%)) followed by group III DNO (56/62 (90.3%)), with group I BP (50/59 (84.7%)) showing the lowest success rate (Table 7). To compare the therapy success of the three groups a Kruskal-Wallis test with post hoc analysis was performed. Treatment success differed significantly between group I (BP) and group II (BP/DNO) with  $p=0.01$  as well as between group I (BP) and group III (DNO) with  $p=0.001$ . Between groups II (BP/DNO) and group III (DNO) no significant difference with ( $p=0.45$ ) was found (Table 8).

The 95% confidence intervals for group I BP was 0.75 – 0.94, for group II BP/DNO 0.85 – 0.98, and for group III DNO 0.83 – 0.98, respectively.

Furthermore logistic regression was used to compare the treatment success between groups I, II and III (Table 7). It was revealed, that the success of group I (BP) differed significantly ( $p=0.04$ ) compared to groups II (BP/DNO) ( $p=0.35$ ) and III (DNO) ( $p=0.12$ ), resulting in a higher incidence of MRONJ recurrence/persistent MRONJ lesions (Table 9).

The overall treatment success rate after surgical revision was 95.3%. No statistically significant difference was found after revision surgery between the three groups (Table 6).

## DISCUSSION

The purpose of this study was to determine whether the antiresorptive drug class or their combination have an impact on the time to onset of medication-related osteonecrosis of the jaw (MRONJ) or on the results of the surgical treatment.

The fastest onset of the disease was found in patients in the denosumab only group after 2.0 years while the onset in the bisphosphonate only group (3.86 years) and the bisphosphonate/denosumab switch group (4.07 years) were similar and significantly later. These findings correlate well with those of other studies, however, in those studies MRONJ occurred even after a shorter denosumab therapy duration compared to the present study: 18.4 months [10], 19.1 months [12], 15.3 months [3]. A possible explanation for the earlier MRONJ onset under denosumab therapy compared to bisphosphonates might be that the osteoclast-suppressing effect of the antibody denosumab is immediate. The risk of MRONJ development is imminent after the first denosumab injection and increases under conditions in which osteoclast activity is essential, i.e., in bone infections or after tooth extractions. Interestingly, although denosumab is not known to accumulate in the body, MRONJ incidences increased up to year 5 during an ongoing denosumab therapy in this study as well as in other investigations (Table 5) [17, 18]. This phenomenon can be explained by the increasing probability of denosumab administrations closely associated with a triggering event such as tooth extraction or chronic infection like periodontitis.

Of note, the time to MRONJ onset did not differ significantly if patients were treated with bisphosphonates before. Indeed, the Kaplan-Meier curves of MRONJ onset in patients of group III DNO and the subgroup IIb (patients in group II BP/DNO after the switch to DNO) were almost congruent (Figure 3). These results are in agreement with those of Aljohani et al. who also did not find a difference in the time to onset of MRONJ between patients under denosumab only and denosumab after the switch from bisphosphonates [3]. In contrast, Yarom et al. discerned a shorter duration to the onset of MRONJ after a switch of

antiresorptive therapy [12]; however, the number of patients included in their study was very small.

Also, patients in groups I BP and group II BP/DNO revealed almost an identical MRONJ incidence time course. Although it appears plausible that two different antiresorptive therapies suppressing osteoclastic activity by two different modes of action would cause an overlapping or amplifying risk for an early MRONJ onset, this effect could not be confirmed in the present study. A possible explanation for these findings is that there is a fading antiresorptive effect after bisphosphonates discontinuation. At the time of MRONJ onset patients in group II BP/DNO had not received bisphosphonates for 24 months (notably, the antiresorptive therapy was not interrupted but switched to denosumab) (Figure 3). The fact that bisphosphonate is bone bound, only few investigations have been performed with focus on time to onset or MRONJ incidence dependent on a drug holiday [19].

The second outcome variable in the present study was the therapy success rate. Although the overall surgical success rates of 89.1% are encouraging, we found that the success rate in the bisphosphonate only group (84.7%) was significantly lower compared to the denosumab only group (90.3%) and the bisphosphonate/denosumab switch group (91.5%). The success rates of MRONJ attributable with bisphosphonates align with those of previous investigations [6, 7, 20] and other studies [21]. Recent studies have demonstrated that bisphosphonates do not suppress bone remodeling to a greater extent compared to denosumab (and neither are the jaw bones overly suppressed compared to other bones) [22, 23]. But contrary to denosumab, bisphosphonates are known to bind to bone and accumulate so that the risk of MRONJ manifestation is higher the longer the antiresorptive therapy lasts (table 5) [11, 24, 25]. The accumulation effect of bisphosphonates seems to be negatively correlated with the treatment success. Interestingly, the switch from bisphosphonates to denosumab did not negatively influence the treatment success. Indeed, the therapy success rates of the patients who first received bisphosphonates and that switched to denosumab was significantly higher compared with the bisphosphonate only group. Notably, there was no interruption of the antiresorptive therapy but at the time of MRONJ onset patients in group

II BP/DNO had a bisphosphonate discontinuation of 24 months. It is likely that a drug holiday and thus the fading pharmacologic effect of bisphosphonates probably positively influences the surgical therapy results. However, only a few studies have investigated the effect of a drug holiday for bisphosphonates on the treatment success of surgical therapy [19, 26-28]. Further studies are needed to address this proposal.

The surgical success rates of patients suffering from MRONJ attributable to denosumab were 90.3%. This is higher than previously reported in the literature [29]. Whether the technique of fluorescence-guided bone resection is beneficial for the success rates compared with the conventional surgical technique has not yet been thoroughly investigated [30]. In a recent multicenter study, the surgical success rates in MRONJ attributable to denosumab have also been reported to be higher using the fluorescence technique (77.2 vs. 71.7%) [3]. Nevertheless, further studies are needed to compare the fluorescence technique with conventional bone resection. Furthermore, patients under denosumab treatment are often advised by their oncologists to discontinuate the antiresorptive treatment at the time of MRONJ diagnosis. Consequently, patients have a short drug holiday from the time of diagnosis to time of intervention (usually 8 weeks), which might have a positive influence on the surgical success rates in both groups (group II BP/DNO and group III DNO).

Despite these results, a general debate continues about the recommended therapy strategies in MRONJ, and only few studies exist that directly compare surgical and conservative management [5]. Several societies of oral and maxillofacial surgeons strongly promote conservative therapy (wound cleaning, antibacterial rinsing, antibiotic therapy, superficial debridement, analgesia) in particular for stage 1 [13, 31, 32]. In this stage, the jaw bone is exposed to the oral cavity, but no sign of infection is present. Surgical therapy is recommended in stage 2 (exposed bone accompanied by infection signs). However, in most of the cases, the applied antibiotic treatment will reduce the infection so that a stage 2 MRONJ lesion can be redesignated as a stage 1 lesion for which no surgical therapy is recommended. This management will inevitably lead to a progression of the MRONJ lesions.

Interestingly, the size of the lesion is not considered in current MRONJ staging, but undoubtedly, an extended MRONJ lesion is more difficult to treat than a small lesion.

Although, in this study, we have investigated a large cohort of patients in order to compare the time to onset and the surgical therapy success between the two antiresorptive classes, some drawbacks arise because of the retrospective nature of this study. As a consequence, no profound analysis of the influence of co-medications in particular of different chemotherapeutics was possible. The heterogeneous study population, including various underlying diseases and, derived from this, the heterogeneous use of two different antiresorptive drugs, might be also considered as a limitation. The fact that the surgery was performed by the same surgeon might be contemplated as constraint of the study. On the other hand, a single surgeon using a standardized and reproducible procedure (fluorescence-guided surgery) reduces the variance of the influencing factor surgical experience and surgical technique. The application of multifactorial regression models (consideration of covariants as the risk group and medication type) might therefore be the aim of a subsequent prospective trial. Furthermore, the increasing number of patients exposed to additional anti-angiogenetic-targeted therapies or other immunomodulatory medication should be a focus of interest and should be considered as a major covariant in future study protocols.

In conclusion, the two different antiresorptive drugs show distinctive characteristics in terms of time to onset and treatment success with the lowest success rates in the bisphosphonates only group and the earliest onset in the denosumab only group. The switch of the antiresorptive therapy from bisphosphonates to denosumab did neither influence the time to onset nor the success rates negatively. Further studies are necessary to substantiate the differences and the possible role for a therapy discontinuation for both denosumab and bisphosphonates.

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**FIGURE LEGENDS AND TABLES**

**Figure 1:** Flowchart demonstrating the selection and inclusion of patients in the three groups.

**Figure 2:** Figure displaying the temporal course of the onset of MRONJ of all patients included in this study

**Figure 3:** Figure displaying the temporal course of the onset of MRONJ of the three groups as Kaplan-Meier curves als well es the subgroups of group II.

Legend figure 2: The time course between group III and the other groups was statistically significant ( $p=0.001$ ), while the curves of groups I and II are almost identical. The subgroup analysis of group II BP/DNO (dashed lines) revealed that the curves of group IIb DNO was almost congruent to group III DNO.

**Figure 4:** Detailed presentation of characteristics of patients in group II BP/DNO. The antiresorptive treatment (ART) switch in this group was from bisphosphonates to denosumab in all cases.

Legend figure 4: The detailed analysis of group II (BP/DNO) revealed that the median MRONJ onset (overall) of this group was 4.1 years ( $Q_{0.25}$ : 2.5,  $Q_{0.75}$ : 5.8) and 1.8 years ( $Q_{0.25}$ : 0.9,  $Q_{0.75}$ : 2.6) after the switch to denosumab. The median duration of the BP therapy before the switch to denosumab was 3.2 years ( $Q_{0.25}$ : 1.4,  $Q_{0.75}$ : 7.1) and the median denosumab therapy after switch of the drug clas was 5.7 years ( $Q_{0.25}$ : 3.7,  $Q_{0.75}$ : 6.9). Note that there was no interruption of the antiresorptive therapy.

**Table 1: Distribution of sex, age, underlying disease, MRONJ stage, antiresorptive drug and triggering events**

	Group I BP	Group II BP/DNO	Group III DNO		p
<b>Sex</b>					<b>p = 0.42</b>
Male	16	15	24	55 (41.7%)	
Female	29	27	21	77 (58.3%)	
Total	45	42	45	132 (100%)	
<b>Age (years)</b>	74.4 (±10.41)	70.6 (±9.8.)	73.02 (±14.02)	73.45 (±11.66)	<b>p = 0.98</b>
<b>Underlying disease</b>					<b>p = 0.63</b>
Breast cancer	21	16	11	48 (36.4%)	
Prostate cancer	9	11	16	36 (27.3%)	
Osteoporosis	12	13	13	38 (28.8%)	
Other	3	2	5	10 (7.5%)	
Total	45	42	45	132 (100%)	
<b>MRONJ stage</b>					<b>p = 0.12</b>
Stage I	10	19	15	44 (33.3%)	
Stage II	30	19	24	73 (53.3%)	
Stage III	5	4	6	15 (11.4%)	
Total	45	42	45	132 (100%)	
<b>Antiresorptive drug</b>					<b>p = 0.17</b>
Denosumab 120mg	0	29	32	61 (34.1%)	
Denosumab 60 mg	0	13	13	26 (24.5%)	
Zoledronate	35	20	0	55 (30.7%)	
Ibandronate	8	17	0	25 (13.9%)	
Alendronate	4	4	0	8 (4.4%)	
Risedronate	0	3	0	3 (1.6%)	
Pamidronate	0	1	0	1 (0.5%)	
Total	47	87	45	179 (100%)	
<b>Triggering event</b>					<b>p = 0.12</b>
Procedural (tooth extraction, dental implant, endodontic treatment, etc.)	30	25	34	89 (65.9%)	
Pathology (Periodontitis, Ulcer, etc.)	9	13	11	33 (24.4%)	
Unclear	6	4	3	13 (9.7%)	
Total	45	42	48	135 (100%)	

P = level of significance. In cases of the presence of two underlying diseases (e.g., cancer + osteoporosis), the assignment was made according to the antiresorptive therapy (oncologic or osteoporotic dosing). Note that, in group I BP and group II BP/DNO, a shift in the

bisphosphonate derivative took place in 2 and 3 cases, respectively, so that the total number of derivatives is higher than the number of patients. Note that, in group III DNO in three patients, the main trigger could not clearly be identified; hence, both potential triggers are listed. Consequently, the number of triggering events is higher than the number of patients.

**Table 2 - Cox Regression of all variables vs. primary outcome variable (time to onset of ONJ)**

	p	HR	CI95	
			lower	upper
Treatment success	0.28	1.271	0.826	1.956
Sex (ref. is male)	0.06	0.691	0.471	1.013
Age	0.60	0.996	0.979	1.013
underlying disease (ref. is no underlying disease)	0.82	1.021	0.852	1.223
Stage (ref. is stage 0)	0.38	1.135	0.855	1.506
Trigger (ref. is no trigger)	0.52	1.062	0.884	1.276

Cox regression for time to onset of ONJ with the variables = treatment success, sex, age, underlying, disease, MRONJ stage and trigger. P = Level of significance, CI95 = 95% confidence interval, HR = hazard ratio, ref. = reference. No significant correlation was found.

**Table 3 – Logistic regression of all variables vs. secondary outcome variable (treatment success)**

	p	HR	CI95	
			lower	upper
Time to onset of MRONJ	0.22	0.918	0.800	1.053
Sex (ref. is male)	0.42	0.709	0.305	1.645
Age	0.18	0.977	0.944	1.011
underlying disease (ref. is no underlying disease)	0.63	0.902	0.595	1.367
Stage (ref. is stage 0)	0.12	2.223	0.116	4.236
Trigger (ref. is no trigger)	0.12	0.672	0.407	1.108

Logistic regression for treatment success with the variables = time to onset of ONJ, sex, age, underlying disease, MRONJ stage and trigger. P = level of significance, CI95 = 95% confidence interval, HR = Hazard ratio, ref. = reference. No significant correlation was found.

**Table 4: Cox Hazard ratio of predictor variable (type of antiresorptive treatment) vs. primary outcome variable (time to onset) within first 5 years after initial antiresorptive treatment**

	HR	CI95	
		Lower	Upper
Group I (BP) vs. Group II (BP/DNO)	0.96	1.04	1.89
Group I (BP) vs. Group III (DNO)	<b>1.57</b>	1.32	1.92
Group II (BP/DNO) vs. Group III (DNO)	<b>1.47</b>	1.27	1.89

HR = hazard ratio, CI95 = 95% confidence interval. Compared to groups I (BP) and II (BP/DNO) group III (DNO) presents an elevated Hazard to develop MRONJ within the first 5 years after initial antiresorptive treatment.

**Table 5: Cox regression of predictor variable (type of antiresorptive treatment) vs. primary outcome variable (time to onset of ONJ)**

	p	HR	CI95	
			lower	upper
Group I (BP) vs. Group II (BP/DNO)	0.77	0.857	0.504	1.456
Group I (BP) vs. Group III (DNO)	0.001	1.783	1.124	2.512
Group II (DNO/BP) vs. Group III (DNO)	0.001	2.329	1.477	3.674

P = level of significance, CI95 = 95% confidence interval, HR = hazard ratio. The time to onset of MRONJ is significantly longer in group I (BP) and group II (BP/DNO) compared to group III (DNO).

**Table 6: Overview of relative incidence rates in relation to duration of antiresorptive treatment.**

Incidence	Group I BP	Group II (BP/DNO)		Group III DNO
		BP	DNO	
Year 1	6.7%	2.2%	28.6%	15.6%
Year 2	20%	4.4%	38.1%	37.8%
Year 3 – 5	20%	26.7%	28.6%	42.2%
Year >5	53.3%	48.9%	4.8%	4.4%

Note, that in all bisphosphonates groups a rising incidence of the the complete investigation period was observed while under denosumab therapie a rising incidence was only found until year 5.

**Table 7: Overview of success rates after initial and revision MRONJ surgery**

	Group I BP	Group II BP/DNO	Group III DNO	total
MRONJ lesions	59	71	62	192 (100%)
Therapy success	50 (84.7%)	65 (91.5%)	56 (90.3%)	171 (89.1%)
Recurrence	9 (15.3%)	6 (8.5%)	6 (9.7%)	22 (10.9%)
Therapy success including recurrence	56 (94.9%)	67 (94.4%)	60 (96.8%)	183 (95.3%)
MRONJ persistence	3 (5.1%)	4 (4.6%)	2 (3.2%)	9 (4.7%)

Note, that the therapy success between group I and the other groups was statistically significant. Neither the success rates between group II and III nor the success rates of all three groups after revision surgery differed statistically significantly.

**Table 8 – Kruskall Wallis Test, post-hoc analysis: comparison of treatment success between groups I, II and III**

	Ts	Se	Sts	p	Cor. p
Group I (BP) vs Group II (BP/DNO)	-23.850	9.305	-2.563	0.01	0.03
Group I (BP) vs. Group III (DNO)	-30.922	10.619	-2.912	0.004	0.01
Group II (BP/DNO) vs. Group III (DNO)	-7.072	9.305	-0.760	0.45	1.00

Ts = Teststatistics, Se = standard-error, Sts = Standard test statistics, p = significance level,

Cor. p = Adjusted p. The treatment success of group I (BP) differs significantly from groups II (BP/DNO) and III (DNO).

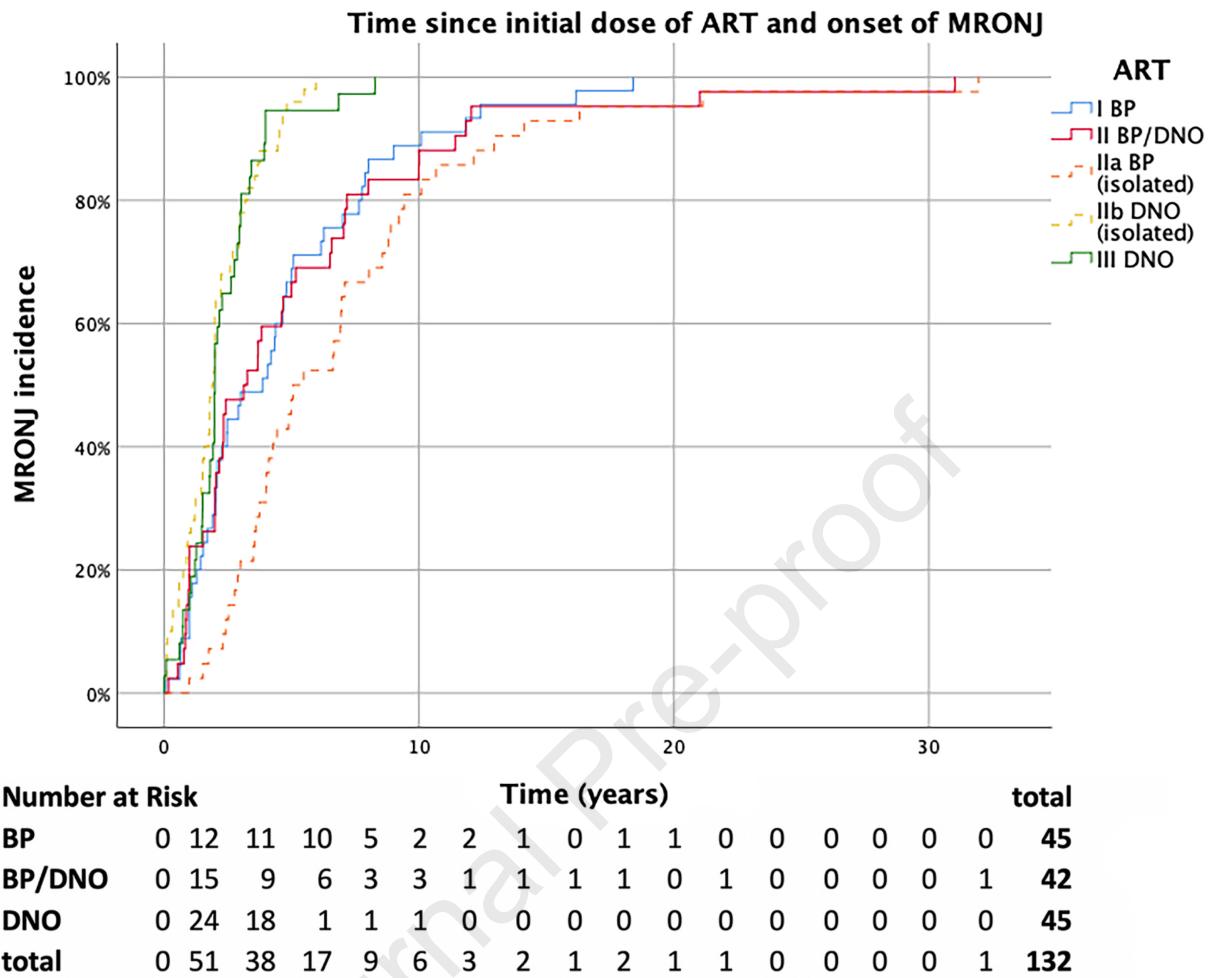
**Table 9 – Logistic regression of the predictor variable (type of antiresorptive treatment) vs. secondary outcome variable (treatment success).**

	p	HR	CI95	
			lower	upper
Group I (BP) vs. Group II (BP/DNO)	0.04	0.561	0.293	1.121
Group I (BP) vs. Group III (DNO)	0.003	0.486	0.196	1.203
Group II (DNO/BP) vs. Group III (DNO)	0.35	1.641	0.587	4.589

P = level of significance, CI95 = 95% confidence interval, HR = hazard ratio. The treatment

success of group I (BP) differs significantly compared to groups II (BP/DNO) and III (DNO).

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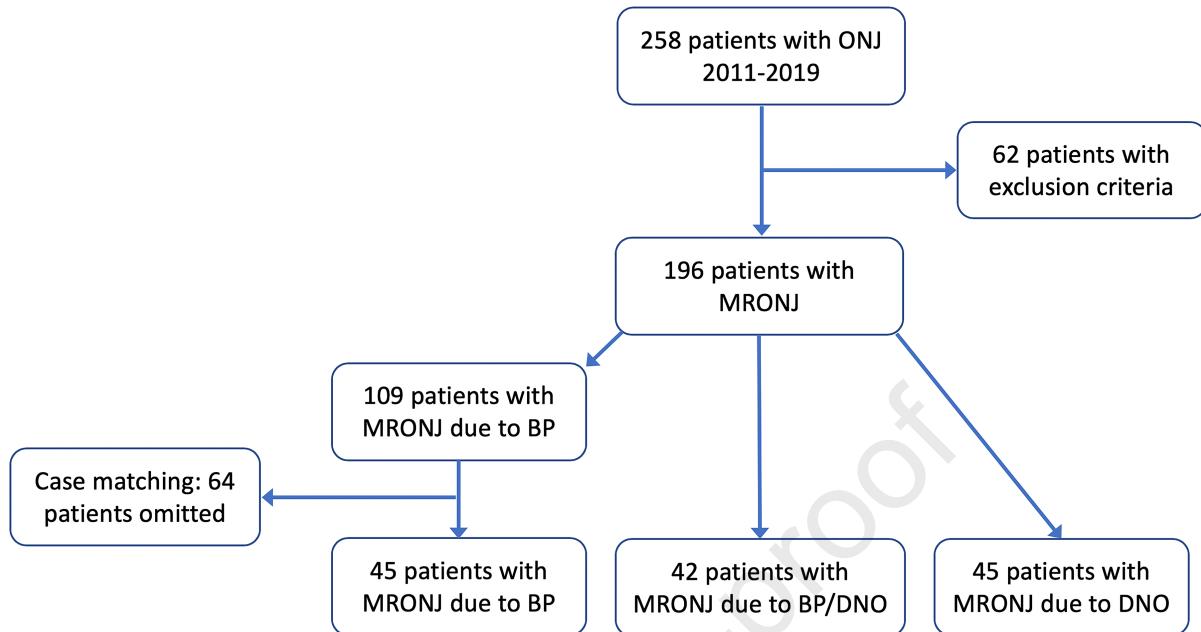
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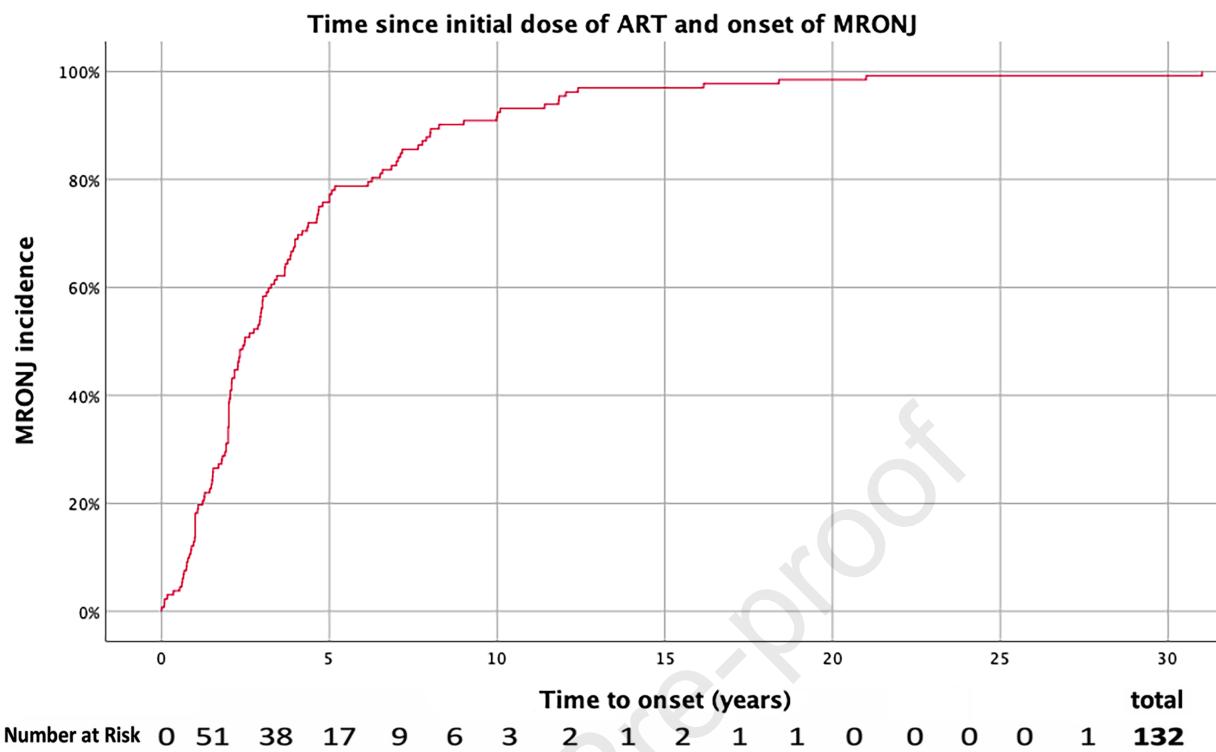
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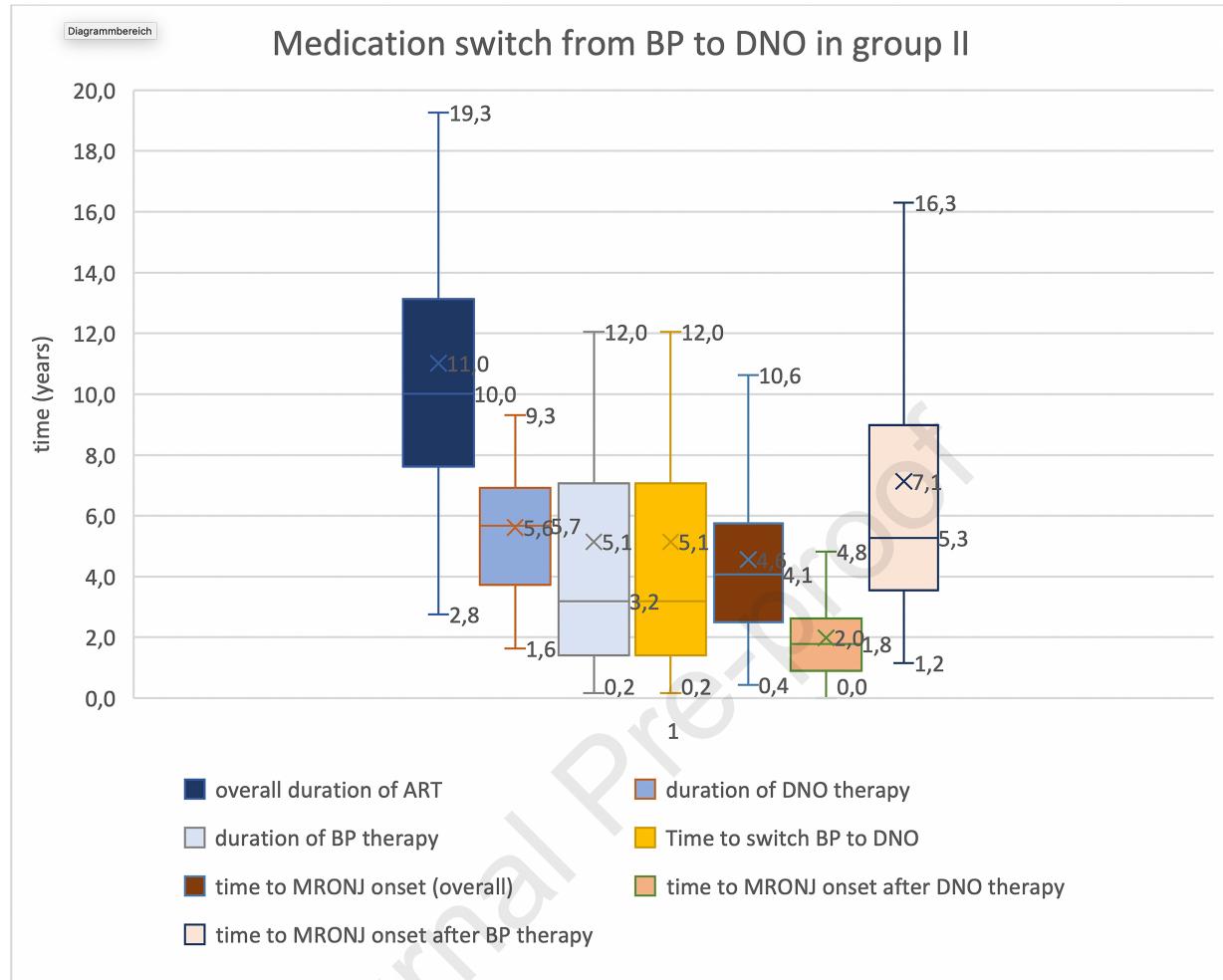
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**Answers to editor and reviewer comments**

(in italic below comments)

*We would like to thank the editor and the reviewers for their thoughtful comments to improve the quality of our manuscript. We addressed all comments as outlined below. All changes and amendments were highlighted blue in the manuscript.*

**Revision 6**

Managing editor's comments:

**Before we can finalize the acceptance of your manuscript, please cite all figures and tables in numerical order in the text of the manuscript.**

*All figures and tables are cited in numerical order in the text of the manuscript*