ORIGINAL ARTICLE

Use of bisphosphonates and the risk of osteonecrosis among cancer patients: a systemic review and meta-analysis of the observational studies

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Abstract

Purpose This study aims to systematically review observational studies evaluating the use of bisphosphonates (BPs) and risk of osteonecrosis of the jaw (ONJ) among cancer patients.

Methods PubMed, Embase, and Cochrane Library were screened from database inception to Aug 2012. Two reviewers independently identified cohort and case–control studies evaluating the use of oral or intravenous (IV) BPs and the risk of ONJ and extracted the characteristics of the studies and risk estimates. Pooled estimates of odds ratios and 95 % confidence intervals were derived by random effects meta-analysis. Subgroup analyses were carried out according to patients' characteristics and route of BP use.

Results We identified eight studies, including 1,389 cases and 569,620 controls. Use of BPs was associated with a significantly increased risk of ONJ (odds ratio (OR) 4.25; 95 % confidence interval (CI) 3.67–5.36; $I^2=0$ %). The summary OR was 4.22 (95 % CI 3.21–5.54; $I^2=0$ %) for adjusted studies. IV BPs were associated with higher risk (OR 4.27; 95 % CI 3.38–5.40; $I^2=0$ %) than oral BPs (OR 1.18; 95 % CI 0.89–1.56; $I^2=0$ %). Hospital-based studies were associated with higher risk estimates than population-based studies.

Conclusion The available evidence suggests that use of BPs in cancer patients is associated with a substantial risk for ONJ. Patients receiving IV BP are at the highest risk. It is important to assess oral health before initiating therapy and to avoid dental procedures during the active phase of intravenous BP therapy.

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Introduction

Bisphosphonates (BPs) are synthetic analogs of a naturally
occurring pyrophosphate that makes bone less susceptible to
bone resorption by reducing the survival of osteoclasts and
modulating the signaling from osteoblasts to osteoclasts [1].
Clinically, BPs are indicated for the management of metastatic
cancer in bone, prevention of osteoporosis and related
fracture, treatment of Paget's disease of bone, and acute
management of hypercalcemia. Since 2003, case reports and
case series of osteonecrosis of jaw (ONJ) have emerged, and
these cases have been linked to the use of BP treatment in
patients with cancer or osteoporosis [2, 3].

ONJ is an uncommon clinical entity defined as the
presence of exposed bone that fails to heal after an appropriate
intervention over a period of 6 or 8 weeks. ONJ was initially
associated with the use of intravenous zoledronic acid, the
most potent BP, but occurrences after the use of pamidronate
and other oral BPs (alendronate, etidronate, ibandronate,
risedronate, tiludronate) have also been reported. These
reports were mostly case reports or case series without
appropriate controls. More rigorous research design is clearly
needed to confirm and estimate the size of the risk.
Randomized clinical trial represents the highest level of
evidence for causal relationship in clinical research. However,
limited by the small sample size and short follow-up duration
for a rare adverse event that requires long-term BP exposure, it
is not easily identified. Restricted membership may further
exclude some patients that are prone to develop such rare
complications. Therefore, the risk of BP use on ONJ is better
studied in a large population-based well-controlled
observational study. Up to date, there are only a few such
studies with inconsistent findings [4–17], warranting a
systemic summary of current evidence and quantification the
risk of ON or ONJ associated with the use of BPs.

Methods

Search strategy

We searched the following sources for the use of
bisphosphonate and osteonecrosis: MEDLINE via PubMed
was searched between 1975 and Aug 2012, and Embase was
searched between 1992 and Aug 2012. We did not set
restrictions on publication date, country, or language. Two
authors conducted the database searches independently.
Studies published in the MEDLINE database were identified
by combining two separate queries composed of medical
subject heading (MeSH) and text word (tw) keywords for
exposure and outcome of interest. The exposure query was
searched using the following exploded headings and
independent terms: ["diphosphonates" (MeSH terms) OR
"alendronate" (MeSH terms) OR bisphosphonate (tw) OR
zoledronate (tw) OR pamidronate (tw) OR alendronate (tw)
OR neridronate (tw) OR olpadronate (tw) OR ibandronate
(tw) OR risedronate (tw) OR Aredia (tw) OR Zometa (tw)
OR Boniva (tw) OR Actonel (tw) OR Aclasta (tw) OR
Fosamax (tw)]. The outcome query was searched using
exploded headings and independent terms for osteonecrosis:
["osteonecrosis" (MeSH terms) OR osteonecrosis (tw) OR
Kienbock disease (tw) OR aseptic necrosis of bone (tw)].
We used manual restrictions by study type, the advanced
automated methods in PubMed, to avoid unnecessary
elimination of articles relevant to the search. We used a similar
search strategy and search terms when searching in Embase.
In addition, we searched reference lists of relevant articles
manually for additional articles.

Inclusion and exclusion criteria

Two reviewers independently identified articles eligible for in-
depth examination by using the following inclusion and
exclusion criteria. Observational studies were included if
osteonecrosis was analyzed as an outcome of the study. The
diagnosis of osteonecrosis was based on the physician
diagnosis regarding medical records, clinical findings of
exposed necrotic bone of jaw with compatible radiographic
findings, or ICD-9 code or other diagnostic code for ON in a
health claim database. Relevant exposures were defined as
oral or intravenous use of bisphosphonates. We included
studies on human subjects who were 15 years or older. The
study types included were cohort and case–control studies.
Case reports, case series, review articles, editorials, meta-
analysis, clinical guidelines, and randomized controlled trials
were excluded. We included studies on cancer patient
populations; studies on osteoporosis or postsurgery patients
were excluded. For those studies that reported the same cohort
in multiple articles, we included only the most recent
publication that met the inclusion criteria. Any discrepancies
between reviewers on articles meriting inclusion were
resolved by a consensus meeting of three authors. The study
selection is summarized in Appendix 1 in Electronic
supplementary material (ESM).

Data extraction and synthesis

We extracted data for study location, setting (e.g., population
based, hospital based), population characteristics such as age
range or underlying diseases, number of participants, type of
BPs used in the study and route of administration, diagnosis of
outcome, crude and adjusted effect sizes as available, and

corresponding confidence intervals. We also recorded quality indicators of the study design, including the presence of appropriate controls and covariates adjusted for multivariate analysis. When studies were identified as containing pertinent data not included in the published article, we attempted to contact the authors to procure the missing data. When the authors did not respond and raw data were provided in the article, manual calculations of unadjusted effect estimates [odds ratio (OR)] were performed for inclusion in our meta-analysis. Otherwise, such analyses were excluded.

Statistical analysis

We conducted the meta-analysis of observational studies in our data extraction, analyses, and report according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [18]. We used the odds ratio as the measurement estimate for risk; when raw data or odds ratios were not available, we used the hazard ratio or risk ratio for analysis. Pooled ORs were computed as the Mantel–Haenszel-weighted average of the ORs for all included studies. Heterogeneity was measured by the Cochran Q statistic ($p < 0.05$) and quantified with the I^2 statistic [19]. The I^2 statistic describes the variation in the effect estimate that is attributable to heterogeneity across studies. The value of the I^2 statistic was used to select the appropriate pooling method as follows: fixed effects models were used for I^2 values less than 50 % and for I^2 values greater than 50 %; random effects models were used [20]. Galbraith plots were used to visualize the impact of individual studies on the overall homogeneity test statistic [21]. Meta-regression was used to evaluate the amount of heterogeneity in the subgroup analysis. Publication bias was assessed by utilizing two methods. Begg and Egger tests were used to quantify the publication bias, and funnel plots were used to visualize the potential publication bias. Asymmetry of funnel plot indicated the reveal of publication bias [22]. To examine the potential effects of different methodological quality factors and adjustment for covariates, subgroup and sensitivity analyses were conducted. The metan, metabias, heterogi, and metareg macros were performed using Stata 11.0 (StataCorp, College Station, TX) as meta-analytic procedures. p values of <0.05 were considered statistically significant.

Results

Search results and study characteristics

The flow of inclusion and exclusion are summarized in Appendix 1 in ESM. Using our search criteria, we identified 1,722 studies, of which 761 were from PubMed, and 961 from Embase. We excluded 1,377 citations based on screening titles

and abstracts using predefined criteria mentioned in the method section. Five additional citations were identified from the reference lists. A total of 350 articles were retrieved from full-text review, and 342 were excluded due to various reasons, and these are detailed in Appendix 1 in ESM. Notably, the majority of studies were excluded due to a lack of appropriate controls. Finally, eight studies met the inclusion criteria. The eight included studies were comprised of 1,389 cases and 569,620 controls [4–17]. Of the included studies, two were case–control studies, and the remaining six were cohort studies. Details of the studies are summarized in Table 1. The studies varied with their settings, study populations, sample sizes, exposure and outcome definitions, and covariates adjusted in multivariate analysis. Breast cancer, lung cancer, prostate cancer, and multiple myeloma consisted of the largest part of study population. These are the four types of cancer with highest propensity for bone metastasis. The types of BPs and route of administration also varied with studies. Five studies reported effect estimate on oral BPs, and six reported effect estimates on intravenous (IV) BPs. Six of eight studies reported the predisposing factors for developing ONJ and ON. Dental extractions or trauma, poor oral hygiene, concurrent use of chemotherapeutic or antiangiogenic agents, or undergoing radiotherapy is the most commonly reported risk factors.

Use of BPs and risk of ON

When the results from all eight studies were combined, use of BPs was associated with an increased risk of ON (pooled OR 4.25; 95 % confidence interval (CI) 3.67–5.36; $I^2 = 0$ %, Fig. 1a). Four studies reported only crude effect estimate without multivariate adjustment. Of the remaining four studies providing adjusted effect estimates, the pooled OR was slightly attenuated (4.22; 95 % CI 3.21–5.54; $I^2 = 0$ %, Fig. 2).

Use of BPs and risk of ONs in study design subgroups

Five studies used the population-based claim databases or cancer registry, while three studies used medical records from the hospitals. Among the five population-based studies, the pooled OR is attenuated with an increased degree of homogeneity (2.15; 95 % CI 1.77–2.60; $I^2 = 44.8$ %). The pooled OR is higher in the three studies using hospital records with a more rigid definition on the ONJ outcome (pooled OR 3.62; 95 % CI 1.18–11.1; $I^2 = 0$ %) (Table 2).

Use of BPs and risk of ONs in different exposure subgroups

Use of oral BPs in cancer patients was associated with a small and nonsignificant risk for ONJ (pooled OR 1.18; 95 % CI 0.89–1.56; $I^2 = 0$ %). Use of IV BPs was associated with a
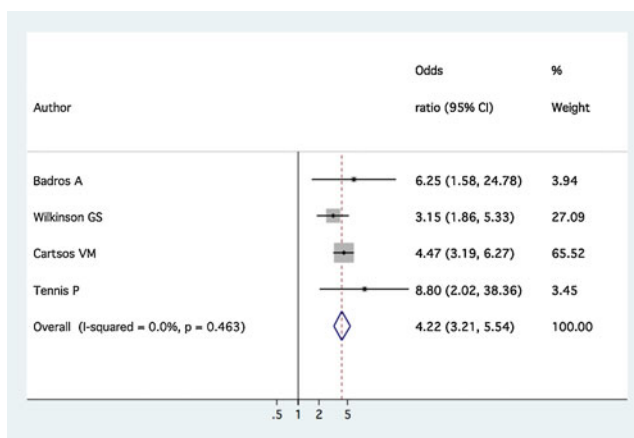
Table 1 Summary of studies on the association between use of bisphosphonates and risk of osteonecrosis of jaw

Author (location, year)	Design	Setting and study population	Sample size	Exposure	Predisposing factor	Outcome definition and case ascertainment	Adjustment in multivariate analysis
Badros et al. [4] (USA, 2006)	Retrospective cohort	Multiple myeloma patients	90	Sequential IV pamidronate/ zoledronate	Dental extraction, age	ONJ by complete dental and medical data	Age, time from diagnosis, dental extraction
Zavras and Zhu [17] (USA, 2006)	Retrospective cohort	Breast cancer, lung cancer, prostate cancer, multiple myeloma	255,757	IV and oral BP (oral alendronate, risedronate, IV pamidronate, and/or zoledronic acid)	Chemotherapy, radiotherapy	Surgical procedure to the mandible or the maxilla	Breast cancer, oral BPs
Wilkinson et al. [16] (USA, 2007)	Retrospective case–control	SEER*–Medicare linked database	16,073	IV pamidronate and/or zoledronic acid	DM, alcoholism, cigarette smoking, obesity, hyperlipemia, pancreatitis, or chemotherapy with L-asparaginase	ICD-9 or CPT codes	Month and year, cancer type, age, sex, diabetes, alcoholism, cigarette smoking, obesity, hyperlipemia, pancreatitis, or chemotherapy with L-asparaginase, bone metastasis, and SEER program geographic region
Wessel et al. [15] (USA, 2008)	Retrospective case–control	Cancer patients	180	Oral or IV BP, IV zoledronic acid, pamidronate	Dental extractions, age, thalidomide	new ONJ	Zoledronate per mg/month/infusion, smoking, obesity, metastasis
Cartsos et al. [7] (USA, 2008)	Retrospective cohort	Breast cancer, lung cancer, prostate cancer, multiple myeloma, osteoporosis	714,217	Oral alendronate, etidronate, ibandronate, risedronate or tiludronate, IV pamidronate, and/or zoledronic acid	Dental extractions, inflammation and poor oral hygiene, steroids, antiangiogenics and chemotherapeutics	ICD-9-coded inflammatory conditions of the jaws, including osteonecrosis	Inflammatory necrosis of jaw; surgery, necrotic process; surgery, cancer process
Guarneri et al. [11] (Italy, 2010)	Prospective study in three RCT cohorts	Local recurrent/ metastatic breast cancer	1,959	Oral BP, concurrent antiangiogenic agents	Dental extraction, dental trauma, use of dentures	New ONJ	Age, chemotherapy, with or without BP, other relevant medical history, interval from the start of bevacizumab to the onset of ON, grade of ONJ
Pavkovic et al. [13] (Macedonia, 2010)	Retrospective cohort	Multiple myeloma	247	Oral or IV BP (except for zoledronate)	N/A	ONJ, 3-month nonhealing defect in the jaw	Median time of exposure
Tennis et al. [14] (USA, 2012)	Retrospective cohort	HealthCore Integrated Research Database (≥40 years) with breast or prostate cancer or multiple myeloma	46,542	IV or oral BP	N/A	ONJ, screened ICD-9 or CPT codes and validated using a chart review	Breast cancer, multiple myeloma, prostate cancer, sex, use of corticosteroid, age
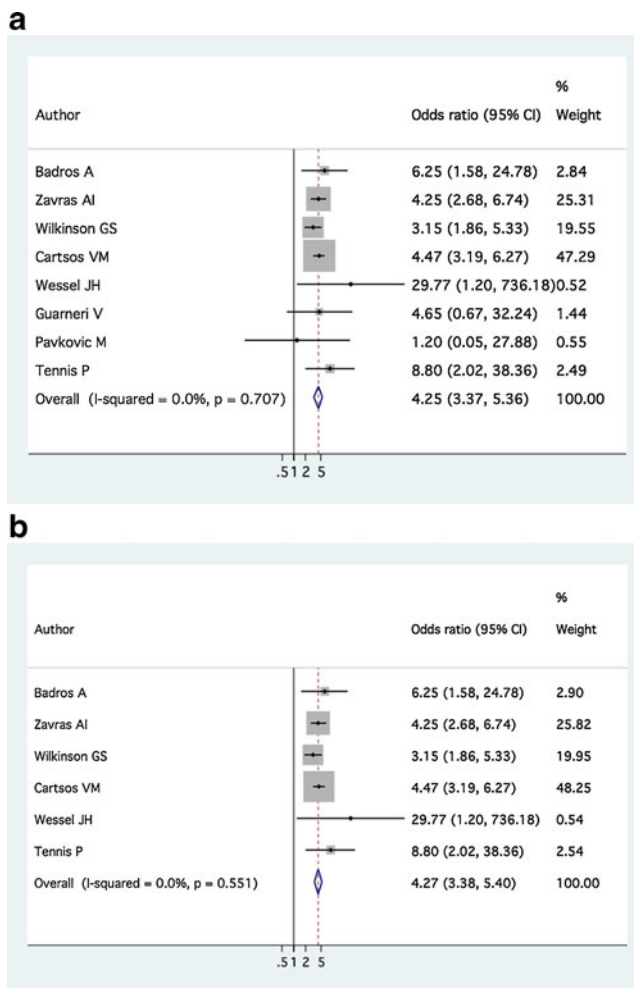
Fig. 1 Forest plot of the diagnostic odds ratios of studies using both oral and IV BPs (a) and IV BPs (b) for the detection an increased risk of ONJ

higher risk for ONJ (pooled OR 4.27; 95 % CI 3.38–5.40; I^2=0 % Fig. 1b) (Table 2).

Fig. 2 Forest plot of the diagnostic odds ratios of studies using adjusted effect estimates for the detection an increased risk of ON among BP users

Table 2 Summary of subgroup analysis of studies of the association of BPs and risk of ONJ

Category	Number of studies	Summary estimate (95 % CI)	I^2 (95 % CI)
All studies	8	4.25 (3.37–5.36)	00.0 (0.0–56.3)
Adjusted studies	4	4.22 (3.21–5.54)	00.0 (0.0–67.9)
Population-based studies	5	2.15 (1.77–2.60)	44.8 (0.0–78.3)
Hospital-based studies	3	3.62 (1.18–11.13)	00.0 (0.0–72.9)
IV BPs	6	4.27 (3.38–5.40)	00.0 (0.0–61.0)
Oral BPs	5	1.18 (0.89–1.56)	00.0 (0.0–64.1)

Publication bias

There is no compelling evidence of publication bias in the overall analysis and subgroup analysis. Table 3 shows the results of statistical tests for publication bias.

Meta-regression analysis

A meta-regression analysis was performed to help explain the variation even after subgroup analysis. Table 4 shows the relative diagnostic odds ratio estimates from the meta-regression analysis. Hospital-based studies and intravenous route of administration tend to increase the risk of ONJ, while adjusted studies were negatively associated with the risk estimate. None of the other covariates in the model reached a statistical significance.

Discussion

BPs are one of the most frequently prescribed drugs to treat cancer-related bone resorption. The use of BPs is consistently growing since its approval by the FDA. Unlike most medications, BPs are not totally excreted by the kidneys but are deposited within the bones. Accumulated literature has suggested a possible link between the use of BPs and a rare adverse effect, ONJ [19]. Due to the rarity of the ONJ, most published studies were isolated single case or retrospective case series reports without appropriate controls [19, 23]. The true impact of BPs on the incidence of ONJ at the population level has not been determined. Related literature has not been systemically reviewed and quantitatively summarized. In our

Table 3 Tests for publication bias and trim-and-fill ORs

Exposure	Begg p value	Egger p value
Overall	0.536	0.424
Adjusted	0.734	0.523

Table 4 Exploration of heterogeneity in studies evaluating a risk of osteonecrosis among uses of bisphosphonates

Comparison	Model coefficient	Relative diagnostic odds ratio	p value
Adjusted studies vs. unadjusted studies	−0.05 (0.29)	0.95 (0.43–2.10)	0.86
Hospital-based studies vs. population-based studies	0.18 (0.71)	1.20 (0.17–8.51)	0.81
Intravenous vs. oral route of administration	0.34 (0.95)	1.40 (0.10–19.60)	0.74

study of 0.5 million people in eight observational studies, we showed a statistically significant strong association between the use of BPs and the risk of ONJ in patients with cancer. The weighted summary OR for developing ON was 4.25 (3.37–5.36) for the use of BPs among cancer patients. Specifically, for cancer patients who received IV BPs, the odds ratio summary was 4.27 (95 % CI 3.38–5.40), and the incidence of ONJ may increase by 327 % with IV BP prescription. The number needed to harm (NNH) was estimated as being 305. The subgroup in which we could not find significant associations was in cancer patients receiving oral BPs.

The pathogenesis of ONJ remains to be elucidated [23–25]. Although animal studies have demonstrated some antiangiogenic properties of BPs, histological examination of most ONJ specimen did show adequate and patent blood vessels without evidence of ischemic necrosis of the bone [23, 24, 26]. Direct toxicity with induced apoptosis of osteocyte has also been suggested [23, 24, 26]. Histomorphometric studies showed defects in bone mineralization might also be a risk factor or BP-related ONJ [26, 27]. Recently, a specific polymorphism of RBMS3, a protein involved in the regulation of collagen type I in fibroblasts, has been suggested to associate with BP-related ONJ in a genome-wide association study [28]. In addition, infection was commonly observed in cases of ONJ and has been suggested to play a synergistic or triggering role for the pathogenesis of ONJ [29–31].

Several preexisting risk factors influencing the normal bone metabolism have been reported in the included studies. Increasing age, infection, dental extractions or trauma, or concurrent use of chemotherapeutic or antiangiogenic agents are the most common risk factors. Of note, dental trauma such as dental extraction, dentures, or dental trauma during intubation procedure has been clearly shown as the strongest precipitating factor for BP-related ONJ. Before starting BP therapy, a comprehensive dental examination should be arranged. The goal of the dental care would be to eliminate of all potential sites of infection and to attain a state of good oral and dental health during the course of IV BP therapy. For patients who already received bisphosphonate therapy, avoiding dental extraction is important since the most common history of BP-related ONJ is delayed or absent of

healing after dental extraction. For those dental procedures that are unavoidable, some experts recommend withdrawal of BP therapy for at least 3 months before dental surgery, although the optimal duration for BP withdrawal remains unknown. Discontinuation of BP therapy may not affect the BP already incorporated into the bone but may avoid the antiangiogenic effect of BP which is harmful for the healing of traumatized oral tissue. In the early stages of ONJ, radiographic manifestations can be vague. Severe jaw pain is usually the earliest symptoms, when necrotic bone has become infected. Therefore, early dental consultation is necessary for patients with dental symptoms during IV BP therapy. For those who consider starting the use of BP either for therapeutic or preventive purpose, the aforementioned conditions should be considered as relative contraindications, and good oral hygiene along with regular dental care is the best way to lower risk.

Five population-based studies used medical claims database and were associated with an attenuated risk estimate with increased heterogeneity. Some characteristics of medical claims database study may help explain the phenomenon. First, there is no ICD-9 code for ONJ. Investigators have to use operations on the jaw or facial bones or inflammatory conditions of the jaw as surrogate outcomes, and misclassification was likely. In the case of random misclassification, the risk estimates tend to be biased toward the null. In addition, different outcome definitions used may have increased the heterogeneity of the risk estimates. Secondly, patients with ONJ may have been treated by either dentists or oral surgeons. Unless both treatments were covered in a medical insurance plan, either a dental plan claims database or a medical plan claims database would not capture the full spectrum of the ONJ events. This could lead to the underestimation of the number of ONJ cases among both BP users and nonusers.

Despite the physiological plausibility and statistically significant and homogeneous results in this large sample size meta-analysis, several limitations to this study should be considered before a firm conclusion can be drawn. Firstly, the induction period of ONJ after BP exposure is unknown. However, the diagnosis of ONJ, by definition, requires a minimum of 6 weeks of exposed bone. Most of the included studies did not take this induction period into consideration for exposure classification, and there is a possibility of exposure misclassification. Random misclassification may attenuate the risk, and nonrandom misclassification may have biased the results in an unpredictable direction. Secondly, the modality and criteria of diagnosis of ONJ varied across included studies. Hospital-based studies used clinical records for outcome ascertainment; therefore, the diagnosis of ONJ may be more reliable. Population-based studies were based on health claim data that used a set of ICD-9 codes to capture ONJ events. We found the risk estimate for population-based studies (pooled OR 2.15; 95 % CI 1.77–2.60) which was

lower than that (pooled OR 3.62; 95 % CI 1.18–11.1) of hospital-based studies. Therefore, there is a tendency that ICD-9 codes may underestimate the incidence of ONJ. Lastly, the duration and dosage of BP use are important determinant factors for ONJ but have not been investigated in most of these studies. The reported median/mean duration of BP exposure in the included studies ranged from 10 months to 6 years. Unless patient-level data are available, analysis of dose–response relationship, defining a specific BPs with higher risk or defining safety range for BP use, is not possible.

In conclusion, our meta-analysis of more than 0.5 million patients indicated that the use of IV BPs among cancer patients is associated with four times risk of developing ONJ. Given the low baseline incidence, the absolute risk for those who received IV BP in cancer patients is low. For the majority of people considering the use of BPs for prevention of cancer-related fractures, these results should reassure them of the importance of weighing the benefits of BPs against this rare but severe complication. For those whose use of BPs is unavoidable, our results emphasize the importance of assessing oral health before initiating therapy and avoid dental procedures during the active phase of intravenous BP therapy.

Conflict of interest None declared.

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