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Managing the Care of Patients Receiving Antiresorptive Therapy for Prevention and Treatment of Osteoporosis

Recommendations from the American Dental Association Council on Scientific Affairs

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1.0 INTRODUCTION

1.1 Goals and rationale

This report is a narrative review on the subject of osteonecrosis of the jaw in low bone mass patients taking antiresorptive agents. It is based on an appraisal of the available literature identified using a systematic computer-aided search by an advisory committee of the American Dental Association (ADA) Council on Scientific Affairs. This review demonstrates where there is evidence, where evidence is lacking, and what topics future research should target in order to improve the dental management of patients on antiresorptive therapy.

The purpose of this report is to help dentists make treatment decisions based on the current best evidence when available, and expert opinion when necessary, for patients taking antiresorptive agents. In an effort to improve the quality and efficiency of oral health care, this report is intended as an educational tool to assist dentists when discussing oral health with patients on antiresorptive therapy, and when treating these patients. The report focuses on patients on antiresorptive therapy for low bone mass rather than patients on antiresorptive therapy for cancer management. This focus was chosen because patients with low bone mass are routinely seen by the general dentist, and, dosing, apparent risk and patient management are different for patients on antiresorptive therapy for cancer management.

The clinical recommendations in this report, which are based on critical evaluation of relevant scientific evidence, do not represent a standard of care. The clinical recommendations should be integrated with the practitioner's professional judgment and individual patient's needs and preferences. Treatments and procedures appropriate to the individual patient rely on mutual communication between patient, dentist and other healthcare practitioners. This report updates the 2008 advisory statement from the ADA Council on Scientific Affairs.[1]

1.2 Nomenclature

Osteonecrosis is defined by Dorland's Medical Dictionary[2] as "necrosis of bone due to obstruction of its blood supply". Osteonecrosis of the jaw (ONJ) can result from radiation therapy of the head and neck, chronic corticosteroids therapy, herpes zoster virus infection

in immunocompromised patients, anti-angiogenesis medications,[3] uncontrolled infections and major trauma.[4] By convention, the etiologic agents serve as a modifier for a specific case of osteonecrosis (e.g. radiation osteonecrosis) although spontaneous or idiopathic examples are recognized.

Osteonecrosis of the jaw (ONJ) associated with antiresorptive therapy deserves distinction from other causes and diseases/medications associated with the development of osteonecrosis. Various terminologies have been applied to ONJ secondary to bisphosphonates, including: “bisphosphonate-related osteonecrosis of the jaw” (BRONJ), “bisphosphonate-induced osteonecrosis of the jaw” (BIONJ), and “bisphosphonate-associated osteonecrosis of the jaw” (BONJ). Bisphosphonate-associated osteonecrosis (BON) originated in a paper published in the Journal of the American Dental Association, but nomenclature of the condition has continued to evolve.[5]

Non-bisphosphonate antiresorptive agents are now available. Denosumab (Prolia™) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of women with postmenopausal osteoporosis. Denosumab reduces bone resorption by inhibiting osteoclast function. The osteoclast targeting and end result is similar to bisphosphonates.[6] ONJ has been reported in a cancer patient taking denosumab.[7] Other antiresorptive agents, including cathepsin K inhibitors (discussed later), could also prove to be associated with ONJ. Therefore, we propose that all cases of ONJ related to the administration of antiresorptive therapeutic agents be termed ‘‘antiresorptive agent-induced ONJ” (ARONJ). This term will encompass bisphosphonate associated/induced cases as well as cases associated with the use of other antiresorptive agents. The term ARONJ will be used preferentially throughout this manuscript unless denoting a specific antiresorptive agent is more appropriate. The panel acknowledges that this condition has a history of variable and confusing terminology. The panel also acknowledges that there is limited information about denosumab and cathepsin K inhibitors. In addition, to our knowledge no cases of ONJ have been reported in patients taking the antiresorptive medications known as SERMS, selective estrogen receptor modulators, now called estrogen agonists/antagonists.

2.0 OSTEOPOROSIS

Increasingly prevalent in older adults, osteoporosis is responsible for considerable morbidity and mortality.[8-13] The characteristic bone fragility of osteoporosis often results in skeletal fractures, including wrist, spine and extremity fractures, of which hip fracture is the most serious. A woman is more likely to suffer an osteoporotic fracture than she is to suffer a heart attack, stroke or breast cancer.[14] Osteoporotic fractures have been associated with functional decline leading to disability, increased subsequent vertebral and hip fractures and increased mortality.[12, 15-17]

There are approximately 10 million Americans over the age of 50 with osteoporosis and an additional 34 million with low bone mass or "osteopenia," which puts them at risk for osteoporosis.[18] The bone health status of Americans will deteriorate due primarily to aging of the US population. By 2020, there will be 14 million cases of osteoporosis and 47 million cases of low bone mass. It is expected that the number of hip fractures in the US will double or triple by 2040.[19]

Fractures are common and have become a chronic and costly burden on individuals and society. An estimated 1.8 million individuals suffer a bone disease-related fracture each year.[20, 21] In the US, four out of every 10 white women age 50 or older will experience a hip, spine, or wrist fracture in their lifetime; at least 13 percent of white men will suffer a similar fate.[22] The risk of sustaining a fracture increases exponentially after menopause. Wrist fractures often occur in relatively independent women during the sixth decade of life, vertebral fractures during the seventh decade and hip fractures during the eighth decade of life. In men, osteoporotic fractures occur at a more advanced age but have worse prognosis with a mortality of 30% within a short time after fracture.[22-25] While the lifetime risk for men and non-white women is decreasing, it is rising in certain populations, such as Hispanic women.[26]

2.1 Therapies for osteoporosis

Therapy for osteoporosis has been shown to reduce the risk of fracture. Medications may be considered antiresorptive or anabolic. Antiresorptives, e.g., bisphosphonates, exert their effect by reducing bone resorption while anabolic agents, e.g. teriparatide, promote bone formation. The most commonly used medications for osteoporosis are the antiresorptive

bisphosphonates, which reduce bone resorption by inhibiting osteoclast function. Bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid) are effective in reducing vertebral and non vertebral fractures.[27-30] Alendronate, the first modern bisphosphonate was FDA-approved in 1995, and all drugs in this class are considered generally safe and effective. Therapy is continued for at least 5 years, and some patients need treatment for longer periods.[31] Bisphosphonates remain in bone and their effect to decrease bone resorption markers can be detected many months later.[32, 33]

The only available anabolic agent, teriparatide enhances osteoblast (bone-forming cell) activity and has not been associated with ARONJ. Clinical trials have shown efficacy in reducing vertebral and non-vertebral fractures.[34] Teriparatide appears to be a superior medication in glucocorticoid-induced osteoporosis.[35] Teriparatide, however, is FDA-approved only for up to 2 years of treatment and thus must be followed by another agent after 2 years.

2.2 New agents

Denosumab. Denosumab is a human monoclonal antibody that targets the receptor activator of nuclear factor-kappa B ligand (RANKL). RANKL is a cytokine member of the tumor necrosis factor family that is the principal final mediator of osteoclastic bone resorption. It plays a major role in the pathogenesis of postmenopausal osteoporosis, as well as bone loss associated with rheumatoid arthritis, metastatic cancer, multiple myeloma, aromatase inhibitor therapy and androgen deprivation therapy.[36] Denosumab prevents RANKL from binding to its receptor on the surface of osteoclasts and their precursors.[37] This inhibits osteoclast formation, function, and survival leading to a decrease in bone resorption and an increase in mass and strength of both cortical and trabecular bone. Clinical trials have also shown great clinical efficacy reducing fracture risk.[38] Denosumab increases bone mass and prevents fractures in women with postmenopausal osteoporosis[39-42] and in men on androgen deprivation therapy for prostate cancer.[43] It is administered as a subcutaneous injection twice yearly. Randomized controlled trials in postmenopausal women show a 68% and 20% reduction in spine and hip fractures, with no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia. Longer term surveillance of this medication is needed to confirm general safety. In the trials, there was one reported case of osteonecrosis of the jaw.[7] Denosumab has been tested to

prevent bone events in patients with cancer. Using higher doses, given more often than in osteoporosis, investigators have identified more cases of osteonecrosis of the jaw.[7, 44] Denosumab is FDA-approved for postmenopausal osteoporosis, and in Europe is also approved for men on androgen deprivation therapy. Unlike bisphosphonates, denosumab does not become incorporated into bone, and bone resorption markers return to baseline six months after the last injection.[45]

Other antiresorptive drugs. Cathepsin K, a cysteine protease expressed in osteoclasts, degrades type 1 collagen. Inhibition of cathepsin K (CatK) is a potential new treatment approach for osteoporosis. Odanacatib selectively and reversibly inhibited cathepsin K and rapidly decreased bone resorption in preclinical and phase I studies. Pharmacokinetic analysis revealed a long half-life ($t_{1/2}$ = 66-93 hours) consistent with once-weekly dosing. Odanacatib exhibits robust and sustained suppression of bone resorption biomarkers C-terminal telopeptide (CTx) and N-terminal telopeptide (NTx) at weekly doses above 25 mg.[46] A 1-year dose-finding trial with a 1-year extension on the same treatment assignment was performed in postmenopausal women with low bone mineral density (BMD). Women with BMD T scores of -2.0 or less at lumbar spine or femoral sites were randomly assigned to receive placebo or one of four doses of odanacatib. With a 50-mg dose of odanacatib, lumbar spine and total-hip BMD increased 5.5% and 3.2%. The safety and tolerability of odanacatib generally were similar to placebo.[47] Unlike bisphosphonates, odanacatib appears to have less effect on bone formation markers. The influence on side effects of this new drug is unknown at this time. The drug is undergoing further phase 3 studies.

Anabolic agents. A monoclonal antibody to sclerostin (AMG 785) has been evaluated in healthy men and postmenopausal women. Sclerostin is a bone morphogenetic protein (BMP) antagonist that decreases osteoblast activity and suppresses the differentiation of osteoprogenitors.[48] The mechanism of action of sclerostin is expressed in modeling and remodeling. In remodeling, sclerostin produced and secreted by newly embedded osteocytes may be transported to the bone surface where it inhibits osteoblastic bone formation and prevents overfilling of the bone modeling unit (BMU). In modeling, sclerostin may serve two actions. First, it may keep bone lining cells in a state of quiescence and prevent, consequent initiation of de novo bone formation. In addition, sclerostin produced and secreted by newly embedded osteocytes may inhibit osteoblastic bone formation, as in

a BMU.[49] The sclerostin antibody AMG 785 induces dose-related increases in the bone formation markers procollagen-1 N-peptide (PINP), bone alkaline phosphatase (BAP), and osteocalcin, along with a dose-related decrease in the bone resorption marker serum CTx (sCTx), resulting in a large anabolic window. AMG 785 has been reported to increase bone mineral density up to 5.3% at the lumbar spine and 2.8% at the total hip compared with placebo.[50, 51] This drug is still in development.

Strontium ranelate is an orally active treatment able to decrease the risk of vertebral and hip fractures in osteoporotic postmenopausal women. Strontium 2 g/day treatment for 3 years decreased the risk of both vertebral and nonvertebral fractures. The decrease in risk of vertebral fractures was 37% in women <70 years, 42% for those 70-80 years of age, and 32% for those ≥ 80 years.[52] The mechanism of action of strontium ranelate is unclear at this time, but there is some evidence of an anabolic effect.[53] This agent is not available in the United States.

3.0 REVIEW OF ARONJ LITERATURE

A search of Medline was conducted using PubMed for literature published between May 2008 (the end date of the last advisory statement search) and February 2011. The following search strategy was employed: ("Osteonecrosis"[Mesh] OR osteonecrosis) AND ("Diphosphonates"[Mesh] OR “bisphosphonate*” OR “denosumab”) AND ("Jaw"[Mesh] OR “jaw”) NOT "Addresses"[Publication Type] NOT "News"[Publication Type] NOT "Newspaper Article"[Publication Type] AND (English[lang]). The Cochrane Central Register of Controlled Trials was also searched using the following strategy: (Osteonecrosis OR “avascular necrosis” OR chemonecrosis) AND (Diphosphonate* OR bisphosphonate* OR denosumab) AND (jaw).

Since 2003, reports of ARONJ related to antiresorptive agents in the bisphosphonate drug class (initially associated with use of zoledronic acid, (Zometa™), and pamidronate, (Aredia™) have appeared in the literature.[54,55] Zoledronic acid and pamidronate are bisphosphonates administered intravenously as often as every three to four weeks to treat skeletal metastasis or hypercalcemia of malignancy, and yearly to treat Paget’s disease of bone. Other uses include treatment of children and young adults with osteogenesis

imperfecta, although cases of ARONJ have yet to be reported in children.[56, 57] More recently, annual and quarterly intravenous infusions have been used for the treatment of osteoporosis Regardless of the route of administration, or underlying disease, ONJ has primarily occurred in patients taking nitrogen-containing bisphosphonates. Nitrogen-containing bisphosphonates are significantly more potent than the first generation of bisphosphonates such as etidronate. Information about available bisphosphonates and other antiresorptive agents is presented in Table 1.

While the non-nitrogen-containing bisphosphonates are associated with a much lower risk for ONJ compared to the nitrogen-containing bisphosphonates, the former cannot be considered risk-free. On the other hand, the vast majority of low bone density and cancer patients in the U.S. are using nitrogen-containing bisphosphonates. As a result, most studies referenced in this report primarily involve the nitrogen-containing bisphosphonates. In general, the panel concluded that some level of ARONJ risk may be associated with any antiresorptive agent, and varies by type, delivery method, dose, dosing protocol and duration of therapy. Despite uncertainty regarding absolute risk for each agent with a given patient, this report will generally consider all antiresorptive medication for low bone mass as a single group.

TABLE 1. ANTIRESORPTIVE AGENTS

BRAND NAME, DOSAGE	DISTRIBUTOR	GENERIC	APPROVED	INDICATIONS*
ORAL FORMULATIONS				
Actonel 5, 35, 75, 150 mg tablets	Warner Chilcott	Risedronate	Worldwide	• To prevent and treat osteoporosis in postmenopausal women • To increase bone mass in men with osteoporosis • To prevent and treat osteoporosis in men and women that is caused by treatment with steroid medicines such as prednisone • To treat Paget's disease of bone in men and women
Atelvia 35 mg tablet once-weekly	Warner Chilcott	Risedronate	Worldwide	To treat osteoporosis in postmenopausal women

TABLE 1. ANTIRESORPTIVE AGENTS, cont'd.

Bonefos 400 mg capsules (Canada) 800 mg tablets (Europe)	Aventis Pasteur, Inc. (Canada) Bayer Schering (Europe)	Clodronate (not commercially available in the U.S.)	Canada (400 mg. capsules) Europe (800 mg. tablets)	• To treat and prevent osteoporosis in women after menopause • To treat hypercalcemia and osteolysis due to malignancy • To reduce occurrence of bone metastases in primary breast cancer
Boniva 2.5 tablet once-daily, 150 mg tablet once-monthly	Genentech USA	Ibandronate	United States	To treat and prevent osteoporosis in women after menopause
Bonviva 150 mg tablet once-monthly	Genentech USA	Ibandronate	Europe	To treat and prevent osteoporosis in women after menopause
Didronel 400 mg tablet	Warner Chilcott	Etidronate	United States, Europe	• To treat Paget's disease of bone • To prevent and treat heterotopic ossification in people who have had total hip replacement surgery (surgery to replace the hip joint with an artificial joint) or in people who have had an injury to the spinal cord **Note:** Off-label usage: to treat and prevent osteoporosis (condition in which the bones become thin and weak and may break easily) caused by corticosteroids. In addition, this medication may be used to treat a high level of calcium in the blood that may occur with some cancers.
Generic: Etidronate 200, 400 mg tablet	Mylan Pharmaceuticals	Etidronate	United States, Europe	
Fosamax, 5, 10, 35, 40 and 70 mg tablets	Merck & Co.	Alendronate	United States, Europe	• To treat or prevent osteoporosis (thinning of bone) in women after menopause • To increase bone mass in men with osteoporosis • To treat osteoporosis in either men or women who are taking corticosteroid medicines • To treat Paget's disease of bone
Fosamax Plus D 70 mg. tablet or 70 mg oral solution	Merck & Co.	Alendronate, cholecalciferol	United States, Europe	• To treat osteoporosis in postmenopausal women • To increase bone mass in men with osteoporosis
Generic: Alendronate 5, 10, 35, 40, 70 mg tablets	Various	Alendronate	Worldwide	• To treat or prevent osteoporosis (thinning of bone) in women after menopause • To increase bone mass in men with osteoporosis • To treat osteoporosis in either men or women who are taking corticosteroid medicines • To treat Paget's disease of bone
Skelid 240 mg tablets (equivalent to 200 mg base)	Sanofi-Aventis, United States	Tiludronate		To treat Paget's disease of bone

TABLE 1. ANTIRESORPTIVE AGENTS, cont'd

PARENTERAL FORMULATIONS				
Aredia 30, 90 mg vials	Novartis	Pamidronate	Worldwide	• To treat moderate or severe hypercalcemia with malignancy, with or without bone metastases • To treat in conjunction with standard antineoplastic therapy, osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma • To treat Paget's disease of bone
Bonefos 60 mg/1 ml, 1500 single-dose	Bayer	Clodronate	Canada Europe	• To treat Paget's disease of bone • To treat hypercalcemia due to metastatic bone disease, multiple myeloma and parathyroid carcinoma
Boniva IV 3 mg/3 ml single-use	Genentech, USA	Ibandronate	United States, Europe	To treat osteoporosis in postmenopausal women
Prolia 60 mg sub-cutaneous injection every 6 months	Amgen	Denosumab	United States, Europe, Norway, Iceland and Liechtenstein	To treat postmenopausal women with osteoporosis at high risk for fracture
XGEVA 120 mg in 1.7 ml subcutaneous injection every 4 weeks	Amgen	Denosumab	United States	To prevent skeletal-related events in patients with bone metastases from solid tumors
Reclast (United States)**, Aclasta** (Europe) 5 mg in a 100 ml ready-to-infuse solution	Novartis	Zoledronic acid	United States (**Reclast**) Worldwide (**Aclasta**)	• To treat osteoporosis in postmenopausal women • To prevent osteoporosis in postmenopausal women • To increase bone mass in men with osteoporosis • To treat and prevent glucocorticoid-induced osteoporosis in patients expected to be on glucocorticoids for at least 12 months • To treat Paget's disease of bone in men and women
Zometa 4 mg/5 ml single-dose vials	Novartis	Zoledronic acid	Worldwide	• To treat hypercalcemia of malignancy • To reduce and delay bone complications due to multiple myeloma and bone metastases from solid tumors, in conjunction with anti-cancer medications

*According to manufacturer product information. Because of the effect that therapeutics like the bisphosphonates have on bone remodeling, antiresorptive drugs are now being used off-label to treat patients with several pathologic bone processes other than osteoporosis, such as giant cell lesions, giant cell tumor of bone, osteogenesis imperfecta, fibrous dysplasia, Gaucher's disease, and osteomyelitis.[58]

3.1 Estimates of ARONJ risk

The risk for developing ARONJ remains unknown despite attempts at quantification. Study limitations such as small sample size, retrospective design, inadequate study duration, and issues associated with voluntary reporting of cases have hindered accurate estimation of incidence and prevalence in the general population. The studies that have attempted to estimate the risk for ARONJ are summarized in Table 2. Several potential risk factors and comorbidities have been reported in the literature, including: diabetes mellitus,[59] clinically and radiographically apparent periodontitis,[60] tooth extractions,[61] denture wearing[62, 63] and smoking.[64] Corticosteroid use was not consistently found to be a risk factor.[61, 65-67] Median duration of exposure to oral nitrogen-containing bisphosphonates in individuals who developed ARONJ was reported in two survey studies to be 24 months (range 3 to 87)[68] and 42 months (interquartile range 30 to 56).[69] The results of studies performed by three Dental Practice-based Research Networks found that for all ONJ cases identified (excluding cancer), bisphosphonate use for less than two years, two to five years, and more than five years was associated with odds ratios of 5.2 (1.2 – 22.5), 11.4 (3.2 – 40.2, and 26.6 (5.3 – 133.6), respectively.[67] While many cases of ARONJ have been associated with an invasive dental procedure such as tooth extraction, ARONJ also occurs spontaneously or in patients with minor mucosal irritation such as those who wear dentures. It may take many years to develop a thorough understanding of ARONJ, its risk factors and possible co-factors. At present, the best available data come from health databases. Earlier reports did not have the benefit of utilizing the American Association of Oral and Maxillofacial Surgeons (AAOMS) or American Society for Bone and Mineral Research (ASBMR) definitions; and, therefore, were not able to rigorously identify true cases of ARONJ.

The authors of a Canadian study used a risk ratio to describe the probability of what they termed aseptic osteonecrosis (AON) occurring in patients taking oral bisphosphonates as compared with patients not taking oral bisphosphonates.[70] The study utilized the administrative health databases of 87,837 patients and reported a risk ratio of 2.87 (95 percent confidence interval 1.17-5.05) for AON in past or present users of alendronate, etidronate and risedronate. Another study, which analyzed the United States medical claims data of 714,217 patients, found a four-fold increased risk of inflammatory conditions and surgical procedures of the jaw for users of intravenous bisphosphonates related to cancer

therapy, but not for users of oral bisphosphonates.[71] Both these studies are limited by their use of medical claims information, which can pose methodological challenges for accurate data reporting.

In an earlier report, Mavrokokki and colleagues reported on the frequency of ARONJ in Australia.[68] The authors utilized a mail survey of Australian oral and maxillofacial surgeons and other specialists as well as data from the Australia Adverse Drug Reaction Committee. One hundred and fifty eight cases of ARONJ were reported with nearly three-quarters occurring in cancer patients. A dental extraction was considered the precipitating factor in 73% of the cases. When investigating patients receiving bisphosphonate therapy for the treatment of osteoporosis, the frequency of ARONJ was observed to range from 1 in 2,260 (0.04%) to 1 in 8,470 (0.01%). However, when focusing on the population that underwent a dental extraction, the frequency of ARONJ was observed to range from 1 in 1,130 (0.09%) to 1 in 296 (0.34%).

More recently, Lo and colleagues investigated the prevalence of ARONJ, using the AAOMS definition, in patients with a history of chronic oral bisphosphonate use treated within a large US health care delivery system.[69] Of the 8,572 survey respondents, 2,159 reported pertinent dental symptoms and of these 2,159, 1,005 received a dental examination and 536 permitted review of their dental records. Nine cases of ARONJ were identified with a dental extraction reported to be a common initiating event in four of the nine cases. Overall, the data indicate a prevalence of ARONJ in this population of 1 in 952 bisphosphonate users, or approximately 0.10%. Because previous estimates[68, 72] had ranged from 0.001% to 0.01% among oral bisphosphonate users, these data represent the highest current estimate of ARONJ in a population of oral bisphosphonate users. In the study by Sedghizadeh et al.,[73] nine of 208 patients taking oral bisphosphonates for low bone density and being treated in dental school clinics, had active ONJ. A corresponding prevalence of over four percent ARONJ has not been duplicated by other investigators and may, in part, be attributable to a relatively small sample size.

A Dental Practice-based Research Network study[74] estimated ONJ incidence and odds ratios for bisphosphonate exposure of all individuals in two large health-care organizations

by searching the electronic records and charts. Fellows and colleagues reported an ONJ incidence of 0.63 per 100,000 person-years for all individuals. Individuals taking oral bisphosphonates were 15.5 (confidence interval, 6.0 – 38.7) times more likely to have ONJ than individuals who were not exposed to bisphosphonates.

Novartis sponsored a randomized controlled trial that studied the effect of once yearly zoledronate administered intravenously for treatment of osteoporosis in 7,714 postmenopausal subjects. Study results demonstrated clinical efficacy in preventing vertebral and hip fractures. In the three-year study, no ARONJ cases were reported. However, patients were not evaluated for jaw problems. A retrospective search of the adverse events database identified two possible cases of ONJ (defined as the presence of exposed bone for more than six weeks), one case in the treatment and one incidence in the placebo group.[75] Currently, there are insufficient data to determine the risk for ARONJ associated with yearly zoledronic acid infusion for treating osteoporosis.

The prevalence of ARONJ is higher in cancer patients. A 2010 systematic review in cancer patients revealed that the prevalence of ARONJ varies depending on the type and quality of studies. Analysis of 22 studies examining data from 39,124 individuals resulted in a mean weighted prevalence of 6.1% cases of ARONJ. However, when selecting studies with comprehensive and well-documented follow-up, the total sample included 927 individuals and the mean weighted prevalence was 13.3%. Other studies that reviewed medical records of 8,829 individuals showed a mean weighted prevalence of 0.7% and epidemiological studies that included 29,386 individuals showed a mean weighted prevalence of 1.2%.[76] Therefore, prospective, well-controlled studies are needed to better determine the true prevalence of ARONJ worldwide.

TABLE 2. SUMMARY OF PUBLISHED STUDIES ESTIMATING RISK FOR ARONJ IN PATIENTS ON ANTIRESORPTIVE THERAPY FOR TREATMENT OF OSTEOPOROSIS

Study	Data collection	Findings	Estimates of ARONJ
Felsenberg D, Hoffmeister B, Amling M. Bisphosphonattherapie assoziierte. Kiefernekrosen Deutsches Arzteblatt 2006;46:A3078-A3080.	Reports to the German Central Register of Necrosis of the Jaw to the Charité Hospital.	3 reports of ONJ out of 780,000 patients taking oral bisphosphonates	1 out of 263,158 (0.00038%)
Mavrokokki T Cheng A, Stein B et al. Nature and Frequency of Bisphosphonate-Associated Osteonecrosis of the Jaws in Australia. J Oral Maxillofac Surg 2007;65:415-23.[PubMed]	Survey sent to all members of the Australian and New Zealand Association of Oral and Maxillofacial Surgeons Case definition – area of exposed bone in the jaw area that fails to heal in 6 weeks in patients on a bisphosphonate for bone disease Total number of prescriptions was obtained from Medicare Australia	1 case of ONJ in every 8,470 to 2,260 patients on oral alendronate If extractions were carried out the frequency increased to 1 in 1,130 to 296	**No tooth extraction** 1 out of 8,470 to 2,260 (0.01% to 0.04%) **Tooth extraction** 1 out of 1,130 to 296 (0.09% to 0.34%)
Black DM, Delmas PD, Eastell R et al. HORIZON Pivotal Fracture Trial. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. N Engl J Med 2007;356(18):1809-22.[PubMed]	Randomized controlled trial with once yearly infusion of zoledronate for osteoporosis therapy	No spontaneous reports of ONJ during the study	0
Grbic JT, Landesberg R, Lin SQ, et al. Incidence of Osteonecrosis of the Jaw in Women with Postmenopausal Osteoporosis in the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial. J Am Dent Assoc 2008;139:32-40.[PubMed]	Three year follow-up of 7,714 women who received either 5 mg intravenous zoledronate or placebo in HORIZON Pivotal Fracture Trial	A retrospective review of the database identified 2 possible cases of ONJ. One in the zoledronate group and one in the control group	0

TABLE 2. SUMMARY OF PUBLISHED STUDIES ESTIMATING RISK FOR ARONJ IN PATIENTS ON ANTIRESORPTIVE THERAPY FOR TREATMENT OF OSTEOPOROSIS, cont'd

Etminan M, Aminzadeh K, Matthew IR et al. Use of Oral Bisphosphonates and the Risk of Aseptic Osteonecrosis: A Nested Case-Control Study. J Rheumatol 2008;35:1-5.[PubMed]	Administrative health database of 87,837 patients Includes all cases of aseptic osteonecrosis	267 cases per million person-years exposure Risk ratio equals 2.87 (95% confidence interval 1.17 – 5.05)	1 out of 3,745
Cartsos VM, Zhu S, Zavras AI. Bisphosphonate Use and the Risk of Adverse Jaw Outcomes. J Am Dent Assoc 2008;139;23-40.[PubMed]	U.S. medical claims data of 714,217 patients	Increased risk of inflammatory conditions and surgical procedures of the jaw for users of intravenous bisphosphonates, but no increased risk for users of oral bisphosphonates	0
Sedghizadeh PP, Stanley K, Caligiuri M, et al. Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw: an institutional inquiry. J Am Dent Assoc 2009;140(1):61-6.[PubMed]	Retrospective review of electronic medical record system at the University of Southern California School of Dentistry identifying 208 patients with a history of alendronate use.	Of the 208 patients, nine had active ONJ and were being treated in the clinics. The nine patients represent one in 23 of the patients receiving alendronate, or approximately 4 percent of the population.	4%
Lo JC, O'Ryan FS, Gordon NP, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg 2010;68(2):243-53.[PubMed]	Survey mailed to 13,946 members of a large integrated health care delivery system in Northern California who had received chronic oral bisphosphonate therapy as of 2006. Respondents who reported ONJ or certain symptoms were invited for examination or to have their dental records reviewed. ONJ was defined as exposed bone (of >8 weeks' duration) in the maxillofacial region in the absence of previous radiotherapy.	Of the 8,572 survey respondents (71 +/- 9 years, 93% women), 2,159 (25%) reported pertinent dental symptoms. Of these 2,159 patients, 1,005 were examined and an additional 536 provided dental records. Nine ONJ cases were identified among the survey respondents.	0.10% (95% confidence interval 0.05% to 0.20%)

TABLE 2. SUMMARY OF PUBLISHED STUDIES ESTIMATING RISK FOR ARONJ IN PATIENTS ON ANTIRESORPTIVE THERAPY FOR TREATMENT OF OSTEOPOROSIS, cont'd

Fellows JL, Rindal DB, Barasch A, et al. ONJ in Two Dental Practice-Based Research Network Regions. J Dent Res 2011;90(4):433-438. Feb 11 [PubMed]	Two health maintenance organizations records were searched and charts were reviewed for 572,606 cohort members.	23 cases were identified. 20 (87%) had at least one risk factor and six (26% had received oral bisphosphonates.	0.63 per 100,000 person-years. Odds ratio for oral bisphosphonate users versus non-users = 15.5 (confidence interval, 6.0 – 38.7).

New antiresorptive agents and ARONJ risk. Denosumab, a new non-bisphosphonate antiresorptive agent, was recently approved by the FDA for the treatment of women with postmenopausal osteoporosis and for the prevention of skeletal-related events in patients with bone metastasis. Denosumab inhibits bone resorption by binding to receptor activator of nuclear factor kappa-B ligand (RANKL), a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Following a single subcutaneous dose, the median time to maximum denosumab serum concentration was 10 days (range: 3 to 21 days). Denosumab concentrations declined over a period of 4 to 5 months with a mean half-life of 25.4 days (SD = 8.5 days; n = 46).[77] No residual effect on bone was noted after six months, and markers of bone turnover rose to normal postmenopausal levels.

In completed osteoporosis clinical trials representing 16,348 patient-years of follow-up, using 60 mg of denosumab every six months, no potential cases of ONJ were positively adjudicated. A total of five years of follow-up has been completed for all subjects who initially participated in the three-year pivotal fracture study[39] and are now participating in the seven-year open-label extension. ONJ was positively adjudicated in two subjects during the first two years of the extension study (H. Varav, Amgen, personal communication, September 2010). This represents a prevalence of ARONJ of 0.061%. For comparison in cancer patients, a study examining denosumab versus zoledronic acid for the treatment of bone metastases, found no significant difference in the occurrence of ARONJ (2.0%, denosumab; 1.4%, zoledronic acid; P=0.39).[78]

3.2 Pharmacology

In 2005, Novartis and the FDA issued drug precautions regarding ARONJ, a condition observed in cancer patients receiving intravenous bisphosphonate treatment.[79] The

precautions also raised concerns about patients who receive invasive dental treatment while taking oral bisphosphonates for other conditions.

Zometa ™ (zoledronic acid) is used for cancer therapy, while Reclast™ (zoledronic acid) is used for osteoporosis and metabolic bone disease. Intravenous infusion is used for both therapies, however the dose used for cancer therapy is approximately 48 mg per year as compared to 5 mg per year for osteoporosis therapy. It is believed that the higher concentration of zoledronic acid, skeletal issues associated with cancer therapy and steroid use, as well as intravenous route with greater bioavailability contribute to a higher incidence of ARONJ. In general, less than one percent of the dose of an oral bisphosphonate is absorbed by the gastrointestinal tract, whereas more than 50 percent of the dose of an intravenous bisphosphonate is available for incorporation into the bone matrix.[80]

Though it is early in the investigative stage, the relationship between bisphosphonate exposure and the occurrence of ONJ appears to be consistent with Bradford Hill's criteria for causality as shown in the Table 3.[81]

Bisphosphonates have shown benefit in the short-term treatment (fewer than six months) of periodontal disease and avascular necrosis of the hip.[88, 89, 94, 95] However, the median time to onset of ARONJ in patients taking alendronate is reportedly more than two years.[68] Also, two of the studies reporting a benefit used topical rather than systemic bisphosphonate administration. Recent animal studies (rodent models) have provided preliminary evidence that alendronate and zoledronic acid impair angiogenesis and delay bone formation, resulting in reduced healing after dental extraction.[96, 97] Prolonged bisphosphonate use in humans (more than three years) may result in poorly functional, highly multinucleated osteoclasts with nuclear condensation and poor adhesion to bone surface.[98] A recent study in dogs found that three years of daily oral bisphosphonate treatment significantly reduced bone turnover and increased the incidence of matrix necrosis in the mandible.[99]

TABLE 3. ANTIRESORPTIVE THERAPY AND OSTEONECROSIS OF THE JAW – ASSOCIATION OR CAUSATION?

Bradford Hill Criteria for Causation	Antiresorptive Therapy and ONJ
Strength of association	Individuals on antiresorptive therapy appear to present a higher incidence of ARONJ than nonusers.
Temporal association	Antiresorptive therapy precedes the occurrence of ARONJ.
Biological gradient (or dose response)	Higher doses and longer duration of treatment with antiresorptive agents result in more rapid and advanced presentations of ARONJ. Greater drug bio-availability resulting from intravenous bisphosphonate delivery in cancer patients associated with more advanced presentations of ARONJ compared to oral bisphosphonate delivery. Higher total drug accumulation (dose x dosing frequency x duration of drug therapy) associated with increasing risk of ARONJ.[82-84]
Consistency	ARONJ has been observed by several investigators, and in different regions of the world.[55, 60, 62, 65, 85, 86]
Strength	There is approximately a four-fold increased risk for ARONJ in patients treated with intravenous bisphosphonates used for cancer treatment.[71]
Specificity	ARONJ is seen in patients with cancer and metabolic bone disease (i.e. osteoporosis and Paget's disease of the bone). ARONJ is seen in patients taking bisphosphonates and denosumab.
Biologic plausibility	Although bisphosphonates have been used for prevention of progression of periodontal disease[87, 88] and avascular necrosis of the hip[89] paradoxical negative effects are being infrequently identified in the jaw and thigh bones.[90, 91] Denosumab, a non-bisphosphonate that inhibits bone resorption, is also associated with ARONJ.
Experiment	Animal studies have confirmed that high dose bisphosphonates result in abnormal osteoclasts and impaired angiogenesis.[92, 93]

To date, studies have consistently shown that the risk for developing ARONJ is higher for cancer patients on intravenous bisphosphonate therapy than for patients on oral bisphosphonate therapy for low bone density. Therefore, clinical recommendations are specific to the type of bisphosphonate therapy administered. Recommendations for cancer patients on intravenous therapy were initially developed by an expert panel and were published in 2006.[100] The American Academy of Oral Medicine and the American Association of Oral and Maxillofacial Surgeons have also published position papers on managing the care of patients with ARONJ.[5, 101] Readers should refer to these documents to obtain recommendations for the management of cancer patients on intravenous bisphosphonate therapy and patients with ARONJ. The American Dental Association, the American Academy of Oral and Maxillofacial Pathology, the American Association of Oral and Maxillofacial Surgeons and the American Society for Bone and Mineral Research also have published papers on ARONJ.[1, 102-104] The National Osteoporosis Foundation,[105] the American Association of Endodontists[106] and the American College of Rheumatology[107] among others, also have addressed these issues.

3.3 Clinical presentation of ARONJ

AAOMS uses the following case definition to describe bisphosphonate-related osteonecrosis of the jaw: exposed bone in the maxillofacial region persisting for more than eight weeks in a patient who is taking, or has taken, a bisphosphonate and has not had radiation therapy to the head and neck.[101]

This advisory committee also accepts the 2009 AAOMS staging criteria described in Table 4, but extends the criteria to patients taking any antiresorptive agent, rather than being restricted to a bisphosphonate.

Table 4. AAOMS Staging Criteria

Category	Criteria
At Risk	Clinically normal, asymptomatic patients who have received antiresorptive therapy
Stage 0	No clinical evidence of exposed bone, but presence of non-specific symptoms or clinical and/or radiographic abnormalities
Stage 1	Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed and necrotic bone associated with pain and/or signs of infection in the region of bone exposure with or without purulent drainage
Stage 3	Exposed and necrotic bone in patients with pain, infection, and at least one of the following: exposure and necrosis extending beyond the local alveolar tissues; radiographic evidence of osteolysis extending to the inferior mandibular border or the maxillary sinus floor; pathologic fracture; oro-antral, oro-nasal or oro-cutaneous communication

Clinical signs and symptoms of ARONJ typically include variable reports of pain, soft-tissue swelling and infection, loosening of teeth, halitosis, drainage, and exposed bone. Symptoms spontaneously may occur in the bone; or, more commonly, at a non-healing site following tooth extraction. In some cases, clinical features of osteonecrosis may not be obvious or even clinically detectable. In other cases, patients may present with pain, clinical swelling and/or purulent drainage in the absence of visible exposed necrotic bone.[108]

An asymptomatic patient can have ARONJ for weeks or months before exposed alveolar bone is detected by routine examination. Some patients may seek care because of oral pain or other non-specific symptoms but in the absence of signs of infection or bone exposure. In other patients, symptoms of ARONJ can mimic dental or periodontal disease; however, these symptoms do not typically resolve following routine dental and periodontal treatment. In challenging presentations such as these, involving a patient known to be receiving or to have previously received bisphosphonate therapy, stage 0 ARONJ should be considered in

the differential diagnosis. If a practitioner suspects a patient to have ARONJ, they should contact the FDA's MedWatch program at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm or 800-FDA-1088 .

4.0 PANEL CONCLUSIONS

Based on a review of the available scientific literature and expert opinion, the panel reached the following conclusions:

A non-cancer patient's risk of developing ARONJ appears to be low with the highest prevalence estimate in a large sample of about 0.10%.[69] At present there are no studies that adequately address incidence. The few studies to date use a wide range of methods, all with potential shortcomings, and come to varied estimates. Without good information on the incidence of ARONJ, it is difficult to predict risk in general, and impossible to predict an individual patient's risk.

ARONJ can occur spontaneously, but is more commonly associated with specific medical and dental conditions, including dental procedures or conditions that increase the risk for bone trauma. Most commonly, ARONJ is associated with invasive bone procedures such as dental extractions.[55] Older age (over 65 years), periodontitis, prolonged use of bisphosphonates (more than two years), smoking, denture wearing and diabetes have been associated with an increased risk for ARONJ.[59, 62-64, 109] Corticosteroid use was not consistently found to be a risk factor.[61, 65-67] One study (that controlled for the effects of several known or potential confounders) found that smoking and obesity were risk factors for developing ARONJ in cancer patients receiving intravenous zoledronic acid.[110]

If a physician prescribes or is planning to prescribe an antiresorptive agent, it is important for the patient and the patient's dentist to be informed. The panel advises that clinicians ask questions about osteoporosis, osteopenia and the use of one of the various antiresorptive agents, during the health history interview process. Both medical and dental communities continue to study ways to prevent and treat ARONJ to ensure the safest possible result for dental patients taking antiresorptive agents. The physician serves as the best source of information regarding the need for antiresorptive therapeutic agents. Given the significant benefits of these medications, and the significant skeletal and psychosocial complications of

osteoporosis, a physician will likely recommend continued antiresorptive treatment despite the slight risk of developing ARONJ. While neither the physician nor the dentist can eliminate the possibility of ARONJ development, regular dental visits and maintaining excellent oral hygiene are essential parts of risk management for the patient. Open communication regarding treatment options is a fundamental requirement for all members of the healthcare team, but particularly in patients with significant dental concerns or active ARONJ.

5.0 PANEL RECOMMENDATIONS FOR THE DENTAL MANAGEMENT OF NON-CANCER PATIENTS RECEIVING ANTIRESORPTIVE THERAPY

These recommendations focus on conservative surgical procedures, proper infection control technique, appropriate use of oral antimicrobials and the principle of effective antibiotic therapy when indicated. Because of a paucity of clinical data on the dental management of patients on antiresorptive therapy, these recommendations primarily are based on expert opinion. They are intended to help dentists make clinical decisions and should be considered with the practitioner's professional judgment and the patient's preferences. Dentists are encouraged to visit http://www.ada.org/2594.aspx?currentTab=2 before treating patients taking antiresorptive agents. As new information becomes available, these recommendations will be updated, as appropriate.

5.1 General treatment recommendations

Routine dental treatment generally should not be modified solely due to use of antiresorptive agents.

All patients should receive routine dental examinations. Patients who are prescribed antiresorptive agents and are not receiving regular dental care would likely benefit from a comprehensive oral examination before or early in their treatment.

Informing patients prior to dental care. A discussion of the risks and benefits of dental care with patients on antiresorptive therapy is appropriate. When informing a patient about the risk of ARONJ, the dental care provider must keep in mind that the patient may not be aware of this risk.[111] This may raise patient concerns about the continuation of dental treatment.

Points that could be discussed with the patient when informing about risks of bisphosphonate therapy include:

- Antiresorptive therapy for low bone mass use places them at low risk for developing ARONJ (the highest prevalence estimate in a large sample is 0.10%).
- The low risk for developing ARONJ can be minimized but not eliminated.
- An oral health program consisting of sound oral hygiene practices and regular dental care may be the optimal approach for lowering the risk for developing ARONJ.
- There is no validated diagnostic technique currently available to determine which patients are at increased risk for developing ARONJ.
- Discontinuing bisphosphonate therapy may not eliminate any risk for developing ARONJ. However, discontinuation of bisphosphonate therapy may have a negative impact on the outcomes of low bone mass treatment. Therefore, significant dental risks need to be present to consider cessation of antiresorptive therapy for low bone mass, cancer or other off-label therapies. Discussion with all members of the healthcare team is recommended prior to discontinuing therapy.

The patient should be informed of the dental treatment needed, alternative treatments, how any treatment relates to the risk of ARONJ, other risks associated with various treatment options, and the risk of foregoing treatment, even temporarily. The patient should be encouraged to consult with his/her physician about health risks associated with discontinuation of antiresorptive therapy. All decisions with respect to utilization of drugs prescribed for medical conditions should be discussed with the prescribing physician. Misinformation and misunderstandings can lead to severe and preventable adverse events. Therefore, efforts should be made to present to the patient a balanced assessment of the current information.[112] Patients taking antiresorptive agents should be instructed to contact their dentist if any problem develops in the oral cavity.

Making treatment decisions. The dental provider may face the decision of whether or not to treat a patient who has been exposed to antiresorptive agents. As discussed above, the risk for ARONJ is lower for a patient who is not taking these drugs for cancer therapy. The panel recommends that a patient with active dental or periodontal disease should be treated in spite of the risk for ARONJ because the risks and consequences of no treatment likely

outweigh the risks of developing ARONJ. Leaving active dental pathology (caries, periodontal disease, extensive periapical abscesses or granulomas) untreated can lead to future complications that may require more extensive and risky treatments.

Prior to starting therapy, patients should be informed to the fullest extent possible. The dentist should consider documenting the discussion of risks, benefits and treatment options with the patient (see discussion above) and obtaining the patient's written acknowledgment of that discussion and consent for the chosen course of treatment. The dentist should retain in the patient's record the acknowledgment and consent for treatment. Dentists are advised to review the above discussion on the risks associated with low-bone density so that an appropriate informed consent is obtained.

Prevention and treatment planning. Strategies for managing the oral health of patients on antiresorptive therapy in an effort to prevent ARONJ are described in Table 5. A major goal in the prevention of ARONJ is to limit the possibility of extensive or multifocal involvement. Despite limited supporting evidence, a localized clinical approach to dentoalveolar surgery in patients on antiresorptive therapy for low bone density may help the practitioner to assess risks on an individual basis and before putting multiple quadrants at risk. Common scenarios include, but are not limited to, a patient needing full mouth extractions for dentures or a patient needing full mouth periodontal surgery. For example, a single tooth extraction or one sextant of alveolar surgery could be performed initially while treating the patient with chlorhexidine, or another topical antiseptic.[113] Patient healing response may be assumed to be adequate once normal healing of the surgical site(s) is observed. Antiseptic agents may be used longer if the area remains inflamed, irritated or erythematous. After establishing the patient's apparent adequate healing response a more accelerated surgical treatment plan involving multiple (or all) sextants at a single appointment could be considered.

Because periapical pathoses, sinus tracts, purulent periodontal pockets, severe periodontitis and active abscesses that already involve the medullary bone, may exacerbate osteonecrosis and are themselves risk factors for ARONJ, they should be treated expeditiously. When dental pathoses are not evident, the trial sextant approach may be applicable. The sextant by sextant approach does not apply to emergency cases, even if multiple quadrants are involved.

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TABLE 5. PREVENTION STRATEGIES FOR PATIENTS ON ANTIRESORPTIVE THERAPY* (ABSENT EVIDENCE OF STAGE 1, 2 OR 3 ARONJ)**

Duration of antiresorptive therapy	Considerations for managing oral health
Prior to therapy	• Optimal time to establish a lifetime oral health awareness as the long-term nature of antiresorptive therapy is associated with ever increasing ARONJ risk • Optimal period to remove unsalvageable teeth and perform invasive dento-alveolar procedures, although a less stringent requirement than with patients using these drugs as part of cancer therapy • With assessment of overall caries risk, periodontal disease risk and "dental IQ" of the patient, the dentist is best qualified to establish an appropriate treatment plan in coordination with the patient and the patient's physician
Therapy < 2 years	• The discussions and assessments mentioned above are often NOT performed or even possible prior to the start of antiresorptive therapy, but all remain applicable after treatment has begun • Risk in this time period is very low, however, a few such cases of ARONJ have been reported • With the possible exception of orthognathic surgery, even dento-alveolar procedures involving periosteal penetration or intramedullary bone exposure (e.g. extractions, apicoectomies, periodontal surgeries, implants or biopsies) seem to carry a minimal risk for ARONJ • Chlorhexidine rinses are advised whenever periosteal or medullary bone exposure is anticipated or observed • - In patients with multiple surgical needs, a trial segmental approach may be helpful in assessing individual patient risk for osteonecrosis and reducing the likelihood of multifocal ARONJ
Therapy ≥ 2years	Continue as above while advising patient and prescribing physician that risk for ARONJ continues to increase with extended drug use
Any length of therapy	• It is appropriate for the dentist to discuss antiresorptive therapy as related to the patient's oral health with the patient's physician • Discontinuation of antiresorptive therapy should be a medical decision based primarily upon the risk for skeletally related events (e.g. fractures) secondary to low bone density, NOT the potential risk of ARONJ • As above, no oral and maxillofacial surgical procedures are strictly contraindicated although treatment plans that minimize periosteal and/or intrabony exposure or disruption are preferred

TABLE 5. PREVENTION STRATEGIES FOR PATIENTS ON ANTIRESORPTIVE THERAPY* (ABSENT EVIDENCE OF STAGE 1, 2 OR 3 ARONJ), cont'd.**

Risk assessment	• Serum CTx levels have not shown reliability or accuracy in predicting risk for ARONJ. Therefore, serum testing is not recommended to predict risk. • Though the trial segmental or sextant approach to surgical procedures described above has not been studied in a prospective fashion, it should help limit the extent of ARONJ in a given patient
Emergency dental therapy	All extractions or dento-alveolar surgeries required on the basis of dental or medical emergency are appropriate, regardless of number and multifocality
Routine dental care	Good oral health and routine dental care are always recommended

* Given limited data that suggests similar levels of risk for patients using oral bisphosphonates, intravenous bisphosphonates and subcutaneous denosumab in the treatment of low bone density; similar prevention strategies appear appropriate for each of these modalities with comparable modification by length of drug use. This does not mean that there are no differences between these treatment modalities and further studies are needed.
** Stage 0 disease may be difficult to separate from an odontogenic or sinonasal etiology. If these possibilities can be eliminated, refer to Table 7 regarding ARONJ.

5.2 Treatment recommendations for specific conditions

Management of periodontal diseases. Individuals on antiresorptive therapy who have active chronic periodontal diseases should generally receive appropriate forms of non-surgical therapy, which should be combined with the commonly recommended reevaluation at four to six weeks. This is not to say that surgical procedures are contraindicated in these patients, only that minimization of dento-alveolar manipulation is generally preferred. Because dental extractions constitute a risk factor for ARONJ, patients should be regularly monitored and treated with the goal of preventing progression of periodontal disease to the point where dental extractions are necessary. The goal of surgical periodontal treatment should be to obtain access to root surfaces, and preference should be placed on the use of atraumatic techniques when possible.

There are no published studies that evaluate the risk of ARONJ or the success of implant treatment following periodontal procedures such as guided tissue regeneration or bone replacement grafts. Use of such techniques should be judiciously considered based on patient need. Primary soft tissue closure following periodontal surgical procedures is desirable, when feasible, though extended periosteal bone exposure for the sake of primary closure may increase, rather than decrease, the risk of ARONJ. Patients without periodontal disease should receive preventive therapy or instruction for prevention of periodontal disease.

Implant placement and maintenance. The risk of ARONJ and/or implant failure in female patients with a history of bisphosphonate use has been examined in several relatively small, short-term studies. Although there are case reports of ARONJ at implant osteotomy sites, the relative scarcity of ARONJ and dental implant failure in bisphosphonate users despite the large number of these patients receiving dental implants is reassuring. Indeed, Fugazzotto and colleagues noted no ARONJ post-operatively in 61 patients with an average duration of bisphosphonate use of 3.3 years.[114] None of the implants failed in this population. In a population of 101 implants placed in 42 bisphosphonate users (range 6 months to 11 years duration of use prior to implant placement), Bell and Bell observed no ARONJ and a 95% implant success rate.[115] Using phone and e-mail surveys, Grant and colleagues noted no ARONJ associated with 468 implants placed in 115 bisphosphonate users with a 99.6% success rate.[116] Koka and colleagues compared 121 implants placed in 55 bisphosphonate users (approximately one third over 5 years of use) with 166 implants placed in 82 non-users.[117] No ARONJ was observed in either group and the implants in the two groups showed similar profiles with a 99.2% success rate in bisphosphonate users and a 98.2% in non-users.

Taken together, these data are encouraging. Patients may be informed that the risk of ARONJ as a result of antiresorptive therapy is low, and that the success rates of implants placed in bisphosphonate users appears to be no different than the success rates of implants placed in patients without a history of bisphosphonate use in the short-term. Presently, antiresorptive therapy does not appear to be a contraindication for dental implant placement. However, larger and longer-term studies are needed to determine if implants do as well in patients exposed to antiresorptive agents in comparison to those who have not been exposed to these agents.

Oral and maxillofacial surgery. When treatment of dental and/or periodontal diseases has failed, surgical intervention may be the best alternative. Patients receiving antiresorptive therapy who are undergoing invasive surgical procedures should be informed of the risk, albeit small, of developing ARONJ. Alternative treatment plans should be discussed with the patient, which include: endodontics (including endodontic treatment followed by removal of the clinical crown), allowing the roots to exfoliate (instead of extraction), and use of fixed and removable partial dentures.

If extractions or bone surgery are necessary, conservative surgical technique with primary tissue closure, when feasible, should be considered. Placement of semipermeable membranes over extraction sites may also be appropriate if primary closure is not possible. In addition, before and after any surgical procedures involving bone, the patient should gently rinse with a chlorhexidine-containing rinse until healed. The regimen may be extended based on the patient's healing progress but use twice daily for 4-8 weeks would be a common regimen. There is some evidence that antibiotic prophylaxis starting one day before and extending 3 to 7 days after dental procedures may be effective in preventing ARONJ.[118] In addition, use of chlorhexidine and systemic antibiotics pre and post tooth extraction appeared to reduce the risk of ARONJ in a small study of 23 patients undergoing tooth extraction.[119]

In patients who already have ARONJ, there is limited evidence that teriparatide, a recombinant form of parathyroid hormone, may be helpful in the treatment of ARONJ.[120, 121]

Endodontics. In patients with elevated risk of ARONJ, endodontic treatment is preferable to surgical manipulation if a tooth is salvageable. Routine endodontic technique should be used and manipulation beyond the apex is not recommended. There is limited evidence that periapical healing after endodontic therapy is similar regardless of whether a patient has a history of bisphosphonate use.[122] Endodontic surgical procedures should be guided by the same recommendation as is used for any oral and maxillofacial surgical procedure described above.

Restorative dentistry and prosthodontics. There is no evidence that malocclusion or masticatory forces increase the risk for ARONJ. All routine restorative procedures should be performed with the goal to minimize the impact on bone, so as not to increase the risk of infection. Prosthodontic appliances in patients should be promptly adjusted for fit in order to avoid ulceration and possible bone exposure.

Orthodontics. There are no published studies examining the effect of bisphosphonates on orthodontia. Case reports have recounted inhibited tooth movement in patients taking bisphosphonates.[123, 124] Patients should be advised of this potential complication.

Orthodontics is unique in the dental specialties in that its very existence is based on the delicate balance between osteoclast and osteoblast function. While orthodontic treatment occurs predominantly in children and early adolescent patients, one in five orthodontic patients in the US is an adult.[125] There have been sporadic reports in the orthodontic literature on the differences of treating post-menopausal patients. The orthodontic literature concerning bisphosphonates concentrates primarily in the ability of these drugs to stabilize teeth post-treatment or with focal topical application to a localized area during therapy.[126] But now with the advent of antiresorptive bone agents there are potentially 44 million Americans where orthodontic movement may be compromised by the medication. The potential problem of ARONJ and the alteration of the bone physiology caused by antiresorptive therapy need to be recognized by orthodontists.[95, 124, 127] The orthodontist should remain vigilant that the tooth movement is proportional to the amount of force being applied. It is possible that orthodontic treatment duration will be longer in bisphosphonate users.

6.0 CTX TESTING AND DRUG HOLIDAYS

Serum-based bone turnover markers are biochemical markers of bone remodeling. Two such markers are CTx and NTx. These markers together represent each end of the three strands of type 1 collagen and each is used in tests that monitor bone turnover. Some studies advocate the use of sCTx for predicting the risk of developing ARONJ,[101, 128-132] while others question its utility.[133-137] Because some recommendations address the use of sCTx, this section will examine the limitations of sCTx as a risk predictor for ARONJ; and will discuss why the panel does not recommend the use of sCTx for ARONJ risk assessment.

First, the wide variability of sCTx (values vary throughout any give 24-hour period) and the wide range of reference values makes individual test results unreliable and difficult to extrapolate from a given study population or test group.[129, 130, 133] In addition, a general lack of baseline sCTx levels in patients prior to beginning antiresorptive therapy makes it difficult to assess the significance of values obtained following the start of treatment.

Total sCTx is a mixture of four distinct forms of the molecule. The forms represent a maturation of bone ages: αL reflects the youngest bone, followed by βL, βD and, finally, αD, which reflects the oldest bone. Assays may detect one, two, three or four of these age-

related CTx isoforms. But most often, either only one form or an unknown combination of these forms is assayed. The interested reader of CTx literature is warned that most studies fail to identify the CTx form being assayed. Also comparisons between papers are difficult if the assayed form(s) is not identified, and the reference ranges by age and gender are unknown.[133, 138-146]

Only one laboratory performs sCTx analyses for patient samples in the United States (Quest Diagnostics, Nichols Institute, San Juan Capistrano, CA). The laboratory analyzes specimens for type 1 collagen by conducting assays for the βL subtype, the second youngest bone (M. Caufield, Quest Diagnostics, personal communication, September 2010). The reference ranges of the laboratory's test results vary widely as shown in Table 6.

Table 6. Adult Reference Ranges for Serum C- Terminal Telopeptide βL Subtype

Age (years)	Male	Female
18 - 29 years	87 - 1200 pg/ml	64 - 640 pg/ml
30 - 39 years	70 - 780 pg/ml	60 - 650 pg/ml
40 - 49 years	60 - 700 pg/ml	40 - 465 pg/ml
50 - 68 years	87 - 345 pg/ml	NA

Type 1 collagen is found in soft tissues and cartilage, as well as in bone. Therefore, sCTx laboratory results are not solely representative of bone. More than one sCTx measurement is needed to assess what, if any, of the sCTx level is related to bone. Consideration should also be given to baseline values, antiresorptive agent accumulation, and dosing patterns.

In one of the first articles to recommend the use of sCTx for predicting patient risk for the development of ARONJ by Marx et al,[128] the study population was small (n=30) and all of the study subjects had ARONJ. At the time initial laboratory values obtained, roughly half of the subjects were on bisphosphonate therapy and the other half were not. Furthermore, the picogram level selected as the predictive level for patient risk (150 picograms) was within the reference ranges (as indicated above). It is noteworthy that there is no reference range for women aged 50 years or older nor for men or women over 68. A 2009 study[131] found that

in individuals with a history of receiving bisphosphonate therapy, sCTx values varied from 100 pg/ml to more than 300 pg/ml. In addition, based on the results of a small study comparing radiographic markers to CTX, Fleisher et al. reported that the radiographic findings of sclerotic change may be a more sensitive predictor of ARONJ risk compared to sCTx levels.[135] The wide ranging values of these data and the lack of reference values in significant patient segments suggest that sCTx levels would have limited use for assessing risk for ARONJ in the individual patient or guiding treatment decisions.

Marx et al.[128] noted that sCTx levels rose in patients with ARONJ after their oral bisphosphonate therapy was discontinued. In a 2009 position paper,[101] the AAOMS recommended a drug "holiday" three months before and after surgical intervention, concluding that the Marx paper showed that the drug holiday invariably raised sCTx levels. In the Marx study all subjects had ARONJ. There are no published studies that demonstrate that either drug holidays or higher sCTx levels reduce the incidence of ARONJ. It is also unclear how drug holidays will affect the risk for fracture. There has been a study on fracture risk that compared discontinuing alendronate after five years to continuing alendronate for ten years.[147, 148] The results suggest that for women not at high risk of clinical vertebral fractures, discontinuation of alendronate after five years does not significantly increase fracture risk. However, there is no data on the effect of discontinuing antiresorptive therapy before five years, ARONJ can occur in patients on antiresorptive therapy for less than five years, and studies on whether alendronate findings can be extrapolated to other bisphosphonates have yet to be performed.

The panel believes the following concerns should be addressed before recommendations can be made:

1. The release/expression of CTx/NTx relies on bone turnover[129, 130] and osteoclast function is specifically inhibited by increased deposition of bisphosphonate in the bone.[149, 150]
2. CTx/NTx serum levels measure total body expression/release, and, therefore, do not measure the release from the alveolar processes of the jaws specifically.
3. Bisphosphonates are not equally deposited (throughout the skeleton). Due to the high bone turnover rate in the jaws, bisphosphonates are particularly

concentrated within the alveolar processes due to the 'homing in" effect of bisphosphonates.[150]

4. How osteoclasts function (and therefore how CTx/NTx is released from jaw) with the above mentioned local increases in antiresorptive agent levels, has yet to be studied.
5. Systemic measurements may identify localized release of CTx in cancer patients.[151] Such measurement, however, does not differentiate the site of bone turnover (i.e. not jaw specific).
6. The rate of bone turnover in the alveolar process in the jaw is several times higher than skeletal sites such as the femur and vertebral column; but with the concentration effect of bisphosphonates noted above (point 3) local CTx/NTx release may be different due to higher bisphosphonate concentrations in the jaw.
7. The jaw bones are at most risk of developing ARONJ, and they may have been affected by antiresorptive agents for a long duration. Measuring βL form, the second youngest of the type 1 collagen breakdown products, as is done in the currently available commercial test may, therefore, not be adequate or appropriate for risk assessment.[150]

For an excellent review of CTx and the many limitations associated with its use as a predictive test, the article by Baim and Miller may provide additional information.[133] The article reviews many of the points above and provides a detailed look at sCTx use in a clinical setting. Notably, the authors state that the process of mailing samples to a central laboratory invites a host of uncontrolled variables involved with specimen collection, handling, temperature and storage.

While there have been limited studies on stopping antiresorptive drugs (drug holidays) for treatment of ARONJ, currently there have yet to be studies to confirm drug holidays are effective in prevention of ARONJ without increasing the skeletally related risks of low bone mass. At present, there is insufficient evidence to recommend serum tests, such as sCTX as a predictor of ARONJ risk. In addition, there is insufficient evidence to recommend an antiresorptive "drug holiday" or waiting periods for prevention of ARONJ.

7.0 ARONJ STAGING AND TREATMENT STRATEGIES

Using the AAOMS staging criteria, Table 7 presents treatment strategies for patients at risk for, and who present with, different stages of ARONJ. This report does not provide guidance on specific treatment strategies for managing patients with ARONJ. Treatment should be generally conservative while at the same time realizing that some severe cases will need large segments of necrotic bone removed and will leave large defects. Treatment will vary by individual case with secondary infection, necrosis and fracture often being difficult, but necessary, to address. There is limited evidence that conservative surgical intervention with the ER:YAG laser leads to clinical improvement.[152-154] There is weak evidence to support discontinuation of antiresorptive therapy to promote healing when ARONJ is present.[128, 155-157] The decision to stop antiresorptive therapy must be weighed with the risks associated with the underlying systemic disease for which the antiresorptive agent is prescribed.

Several studies have postulated a role of actinomyces spp. in ARONJ as well as in osteoradionecrosis (ORN).[158, 159] The actinomyces are anaerobic gram-positive microorganisms considered to be early colonizers of the oral cavity and occasionally reported as the principal infectious agent of ARONJ lesions.[160] In a histopathological study, 42/45 patients with the diagnosis of actinomycosis were found to have ARONJ (58.7%) and ORN (35.6%) of the oral cavity. These findings have led to speculation that actinomyces are opportunistic microorganisms that can infect bone already altered by medications or radiotherapy. [158, 161] Nevertheless, a pathogenic role for actinomyces as a single-organism in the pathobiology of ARONJ remains controversial. This can be further disputed because authors have demonstrated that the formation of a multiorganism biofilm in ARONJ lesions could participate in the pathogenesis of this type of osteonecrosis.[162, 163] Because of difficulties related to isolating actinomyces, it is not always clear if their presence is due to surface colonization or a deep infection that contributes to the pathogenesis of osteonecrosis.[159] In a case report of a patient with an advanced case of Actinomyces-infected ARONJ, the lesion was treated with intravenous penicillin G (18 MU/day) in combination with intravenous metronidazole (1.5 g/day) for 6 weeks, followed by oral administration of oral amoxicillin (1.5 g/day) for 6 months. The aggressive treatment controlled infection and purulent drainage, but did not affect the necrotic bone area that continued to be exposed to the oral cavity.[160] At this point, the panel suggests that intravenous therapy should be reserved for advanced stages (stage 3 OMFS) where there is

supportive evidence (culture plus clinical evidence of purulence) for active actinomycotic infection of ARONJ lesions. It has been recently shown that chlorhexidine has a positive effect in controlling surface based actinomycotic colonizations such as are seen in oral biofilms.[164] For the more common lower stage cases where only actinomycotic surface colonization is suspected, chlorhexidine mouth rinses can be used with oral amoxicillin/penicillin added if indicated.

Table 7. ARONJ Staging and Treatment Strategies

ARONJ† Staging	Treatment Strategies‡,†††
At Risk Clinically normal, asymptomatic patients who have received antiresorptive therapy.	• No treatment beyond routine dental care • Patient education¥,†† (See section 3.1.2)
Stage 0 No clinical evidence of exposed bone, but presence of non-specific symptoms or clinical and/or radiographic abnormalities.	• Conservative local treatment measures • Analgesics and antibiotics as indicated • Communication with prescribing physician¥ ,†††
Stage 1 Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection.	• Antimicrobial mouth rinse • Smooth sharp bone to relieve soft tissue irritation, remove loose sequestra • Analgesics and antibiotics as indicated • Clinical follow-up every 3-6 months • Review indications for continued anti-resorptive therapy with prescribing physician
Stage 2 Exposed and necrotic bone associated with pain and/or signs of infection in the region of bone exposure with or without purulent drainage.	• **Stage 1 measures plus:** ○ Consider more frequent clinical follow-up visits customized to patient
Stage 3 Exposed and necrotic bone in patients with pain, infection, and at least one of the following: exposure and necrosis extending beyond the local alveolar tissues; radiographic evidence of osteolysis extending to the inferior mandibular border or the maxillary sinus floor; pathologic fracture; oro-antral, oro-nasal or oro-cutaneous communication.	• **Stage 2 measures plus:** ○ Surgical debridement/resection as needed for control of pain or at sites of persistent active infection

† Exposed bone in the maxillofacial region without resolution in 8-12 weeks in persons treated with antiresorptive medications who have not received radiation therapy to the jaws.

‡ Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process. Discontinuation of intravenous bisphosphonates in cancer patients has not been associated with short-term benefits.[128, 157]

¥ Should systemic conditions permit, however, long-term discontinuation *may* be beneficial in stabilizing sites of osteonecrosis, reducing the risk of new site development, and reducing clinical symptoms.[128] Decisions regarding antiresorptive therapy should only be made only by the treating physician in

consultation with the patient and patient's dentist or dental specialist. Discontinuation of antiresorptive therapy for low bone density in patients with ARONJ has been associated with gradual improvement in clinical disease. Discontinuation of these agents for 6-12 months may permit gradual resolution of areas of bone exposure or spontaneous sequestration of necrotic bone. In patients with modestly reduced bone density, therefore, modification or cessation of antiresorptive therapy by the prescribing physician may be warranted in consultation with the patient's dentist or dental specialist and with full understanding of the patient.

††Patient education is an essential part of treatment for all patients using antiresorptive therapy

†††Communication with the patient's prescribing physician is appropriate for all Stages of ARONJ

8.0 RECOMMENDATIONS FOR RESEARCH

Based on the current literature on ARONJ pathophysiology, and based on the lack of knowledge of the factors that place patients at risk for developing ARONJ, the panel recommends that research be conducted on a number of topics identified below.

8.1 Basic research

Researchers should investigate the molecular mechanisms that lead to development of ARONJ, the role of antiresorptive drugs in altering bone remodeling, and its effects on ARONJ. Research on pharmacogenetic factors that place patients at risk for ARONJ may be helpful for identifying patients at increased risk.

8.2 Clinical research

Researchers should continue or initiate adequately designed studies that:

- better define risks associated with routine dental therapy, placing dental implants and bone augmentation, orthodontic treatment, and tooth extraction in patients on antiresorptive therapy
- concomitant risk factors (e.g. oral and systemic disease)
- address the dental management of patients with ARONJ
- collaborate with bone specialists in order to establish whether ARONJ is a localized or systemic condition. Bone biopsy and histomorphometric assessment will provide insights into the underlying bone pathology
- evaluate the effect of discontinuing antiresorptive therapy and relevance to healing
- evaluate the use of surrogate bone markers relative to risk for, and treatment of, ARONJ
- evaluate screening and diagnostic tests

In addition, it would be desirable to have a national registry that would allow systematic study of cases of ARONJ related to antiresorptive therapy and the effect of co-morbidities and concurrent therapies.

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