# RCR National guideline of Bone health management in patients with prostate cancer

**Contents**



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## Key Messages

1. One in 5 men over the age of 50 suffer from a fracture because of osteoporosis.[1] The majority of prostate cancer patients are over 70 years old and have an increased risk of **primary osteoporosis** and **fragility fracture (FF).** This is often under recognised and undermanaged in the UK.[2]

2. Prostate cancer patients receiving androgen deprivation therapy (ADT) with or without other combination systemic treatment concurrently or sequentially have significantly accelerated bone mineral loss and **secondary osteoporosis** and fragility fracture risk, in addition to their baseline risk.

3. Advanced prostate cancer patients also have a high incidence of bone metastases, leading to **skeletal related events (SRE)** including factures. The terms “pathological fracture” and “fracture in a diseased bone” refer to both fragility (osteoporotic) fractures and those caused by malignancy.

4. Despite longer overall cancer specific survival thanks to advances in oncological therapeutic options, FFs and SREs in patients with prostate cancer result in significant premature mortality, morbidity, with an associated socioeconomic burden. “If Disability Adjusted Life Years (DALYs) are used to calculate the disability burden of different diseases, osteoporosis has a greater impact than most types of cancer, with the exception of lung cancer”. [3]

5. The goals of bone health management in prostate cancer patients include **prevention, reduction and delaying both FFs and SREs**, in order to retain and maintain independence and promote optimal cancer survivorship.

6. Until now, there has been no national or international consensus on how to optimise bone health in prostate cancer patients despite growing evidence about the increased risk of anticancer treatment-associated fragility fracture.

The RCR guideline focuses on early identification of fracture risk, proactive general health promotion, and pragmatic shared decision-making using risk stratification for pharmacological intervention.

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## Executive Summary

With the advent of more effective treatments for advanced or metastatic prostate cancer, for many men, prostate cancer becomes a chronic illness with significant improvements in overall survival seen. As we intensify the upfront treatment of our patients, we also place them more at risk of life limiting toxicity, and so it is paramount that we as a uro-oncology community pay much more attention to the side effects that we directly cause by our life extending treatments.

Bone health in men and people with prostate cancer historically has been very poorly understood, and managed, with even standard measurements of bone health underestimating the impact on patients. This consensus brings together stakeholders committed to ensuring that our patients' quality of life remains as good as possible, both because of, and despite our treatments.

"Do the best you can until you know better. Then when you know better, do better" Maya Angelou

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## Brief description of sections:

**Section 1** defines bone health in prostate cancer and why this guidance was written

**Section 2** describes the impact of oncological prostate cancer treatments on bone health including both systemic and localised treatments.

**Section 3** addresses the practicalities of fragility fracture risk (FFR) assessment, looking at **who** should be assessed**, how** and **when** this should be undertaken and **by whom**.

**Section 4** addresses how FFR should be managed with regards to lifestyle changes and pharmacological approaches.

**Section 5** summarises the key recommendations including in visual and tabular form to improve the management of bone health in men and people with prostate cancer.

**Section 6** highlights the important role of staff education, clinical research, audit and service development in supporting optimal management of bone health in this group.

**Section 7** appendices include detailed pharmacological advice. Useful patient resources and model letters to primary care settings.

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# 1. Introduction

*1.1 For whom is this guidance written?*

These guidelines aim to provide evidence-based recommendations to aid clinicians in the management of bone health in patients with prostate cancer. This is a bespoke guideline on prostate cancer treatment induced bone loss and SRE prevention and delaying.

*1.2 What is bone health in prostate cancer?*

Prostate cancer is the most common cancer [4] in the UK affecting 1 in 6-8 men and people with a prostate. Androgen deprivation therapy (ADT) is the mainstay of medical treatment for patients with high risk localised and metastatic prostate cancer as it significantly improves overall survival. Suppression of circulating androgens leads to disruption of bone remodelling resulting in loss of bone mineral density (BMD).[5,6] BMD loss and alterations in bone microarchitecture occur most rapidly within the first 6-12 months of commencing ADT (between 5-10%). This process continues throughout the duration of treatment contributing to an increased risk of **fragility fracture**.[7,8,9,10,11] In addition, bone is the most common metastatic site, with bone metastases present in approximately 80% of patients presenting with metastatic prostate cancer.[12] Patients with prostate cancer and bone metastases are at risk of pain, skeletal complications including pathological fractures (i.e. fracture at a site of metastatic disease), and spinal cord compression. These complications frequently significantly impact morbidity and decrease quality of life.[13] The term, **skeletal related event (SRE)**, encompasses pathological fractures as well as spinal cord compression, surgery to bone, radiation to bone or a change in systemic anti-cancer therapy due to bony pain. Data from the National Prostate Cancer Audit highlights the high cumulative incidence of clinical SREs at 5 years, which is around 44% for patients with metastatic disease.[14]

Osteoporosis is defined by low BMD and micro deterioration of bone tissue leading to fragile bone with an increased risk of fragility fractures.[15] The prevalence of osteoporosis increases with advancing age, affecting 10-25% of men and people with a prostate aged 60 and over, and 50% of men and people with a prostate in their eighties. Osteoporosis is usually asymptomatic until fractures occur. The most common site of osteoporotic fracture are the vertebrae, accounting for around 25% of fragility fractures.[16,17] Although osteoporosis is closely associated with fragility fractures, most patients who sustain a fracture do not have osteoporosis.[18] In the UK there are approximately half a million fragility fractures each year.[19] Fragility fractures, in particular hip fractures, are associated with increased mortality and can cause pain, disability, and reduced quality of life. In the UK the cost of fragility fractures to the National Health Service (NHS) exceeds £4.7 billion per annum.[20]

The last decade has seen significant improvements in overall survival through earlier treatment sequencing in patients with high risk non-metastatic and metastatic hormone sensitive prostate cancer. Doublet therapy including androgen receptor pathway inhibitor (ARPI) alongside ADT is now the standard of care first line treatment. Patients are therefore living longer on treatment with potential for greater exposure to the toxicities and side effects of treatment. Furthermore, patients with advanced prostate cancer prior to ADT have higher rates of osteoporosis and osteopenia than age-matched controls: 42% and 27%

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respectively.[21] A meta-analysis of adverse event data on fractures and falls from randomised clinical trials highlighted a significantly increased risk with the addition of ARPIs to ADT.[22] Second line therapies including the addition of Radium223 alongside ARPIs further increase the risk of fractures, but can be mitigated with use of appropriate bone protection.[23] [24] For the first time in prostate cancer studies, the PEACE-3 subgroup analysis also demonstrated OS benefit (of 17 month, HR 0.56, 95% CI 0.37-0.86) with BPAs compared without. This is the only data to date in prostate cancer trials demonstrating a survival advantage of bone protection agents. We note that this is from a subgroup analysis and is contrary to the results of the STAMPEDE study looking at docetaxel and zoledronic acid.[25]

*1.3 What is the current evidence / available Recommendations?*

There is widespread variation in assessment of bone health and use of bone protection with bone modifying agents (BMA).[26,27] In addition, fracture risk prediction using FRAX and other tools currently recommended within international guidelines were not developed in men and people with prostate cancer and may therefore have a limited role in this patient population.[28] BMAs (bisphosphonates and RANKL inhibitors such as denosumab) can be used to help preserve BMD in men and people with prostate cancer treated with ADT although no survival benefit or reduction in fracture risk had previously been demonstrated.[29,30]

Both the STAMPEDE and LATITUDE trials have, within recent years demonstrated a significant reduction fracture related hospitalisations with the addition of bone protection agents to those receiving ADT or ARPi respectively. [31] These studies support the need for bone protection the use of BMA in patients with newly diagnosed metastatic prostate cancer commencing lifelong ADT. The updated European Association of Urology (EAU) guideline (March 2025) has recommended "*offer bone protection to avoid fractures in patients receiving combination treatment. Offer Calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonate and monitor serum calcium*." [32]

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**Case Illustration:**
Fragility fracture in a patient receiving multimodality treatment for metastatic castration resistant prostate cancer (mCRPC)

Mr A was a 69-year-old man who had a clinical diagnosis of metastatic prostate cancer - T3 N0 M1 with a presenting PSA 194 ng/ml in 2016. He had a past medical of hypertension and COPD. His medications included amlodipine, atorvastatin and inhalers (salbutamol and beclomethasone). He lived with his wife in a house with stairs. He was an ex-smoker of 40 pack years. He drinks 2 pints of beer every night (4 units/day). Functionally he was fit and active - walking unaided. His clinical frailty scale 2 and performance status 1.

He started on lifelong ADT mono treatment in 2016. In 2019 he developed castration resistant disease with symptomatic disease progression in bone. He started on abiraterone 1 g daily and prednisolone 10 mg daily. He had an excellent durable biochemical response.
He received palliative radiotherapy to T11 single 8 Gy with good pain control in 2020. He had re-treatment at the same level of spine (T10-T12) 6 months later as he developed recurrent pain. Unfortunately, his pain worsened after radiotherapy this time with change in character compared with pre radiotherapy pain. It was a constant ache and worsened by movement. There were no neurological symptoms.

Examination showed significant new kyphosis, tender lower thoracic spine on percussion and reduced range of movement. MRI whole spine showed no spinal cord compression but new (since baseline before radiotherapy) compression fractures of vertebra body in T10 and T12 (levels above and below T11 which was the target vertebrae with bone metastases). See figure A.

Despite maximal analgesia, oral bone protection agents (BPAs) with Calcichew D3 Forte 2 tablets daily and alendronic acid 70 mg weekly and physiotherapy, Mr A was unable to recover to his baseline functional status. He became housebound and relies on a Zimmer frame for mobilisation. He died of chest infection a year later at home.
This is likely a case of fragility fracture with a multifactorial cause /pre-existing risk factors including:

- Age
- Smoking history
- Alcohol (> 3 units/day)
- Glucocorticoid treatment (inhaler and prednisolone) and
- Lifelong ADT
- Abiraterone
- Radiotherapy
- Bone metastasis

**Questions:**

1. Should he have a primary osteoporosis assessment at primary care e.g. Wellman clinic based on his multiple risk factors independent of his cancer diagnosis?
2. Should he have had bone health assessment when he was diagnosed with prostate cancer when starting ADT?
3. Would earlier bone protection agents on starting ADT prevent or delay his fracture?
4. Would parenteral bone strengthening agents be more effective in his case?

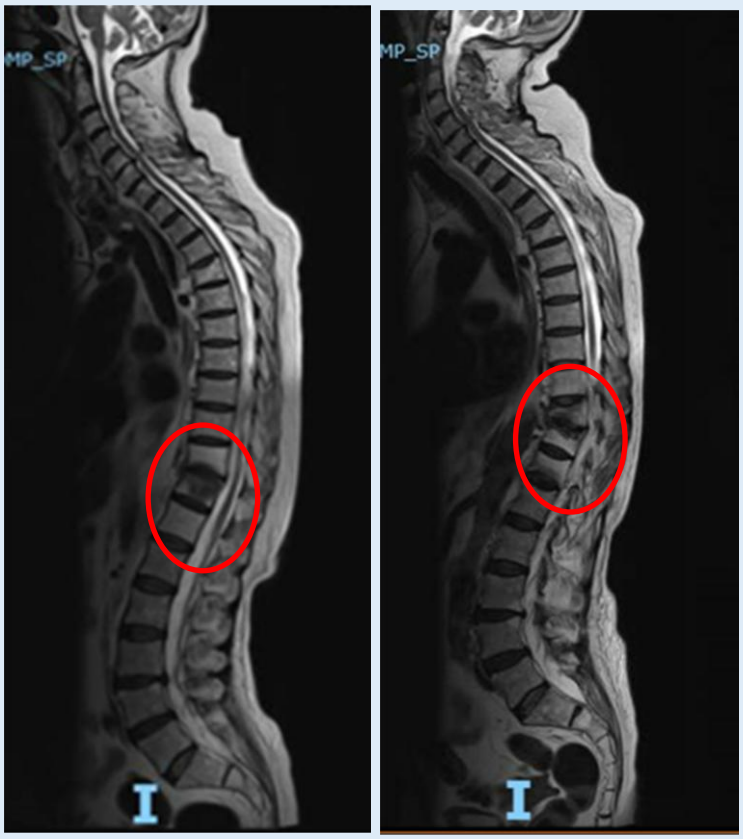


Figure A: MRI whole spine showing compression fractures at T10 and T12 (B) compared with baseline 3 months since palliative radiotherapy to T11 bone metastasis (which included T10 and T12 as standard margins).

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## 2. ADT, SACT and radiotherapy in prostate cancer and their impact on bone health

*2.1 Androgen Deprivation Therapy and Secondary Osteoporosis and Fragility Fracture*

The intended therapeutic effect of ADT is hypogonadism, which causes a rapid reduction in circulating androgens and oestrogens.[33] [34] Hypogonadism in turn causes a disruption in bone remodelling by increasing bone osteoclast activity, decreasing osteoclast apoptosis, and increasing osteoblast apoptosis, with a net increase in bone resorption. [33] [34] [35] [36]A retrospective large study by Shahinian et al. looking at claims data for more than 50,000 patients in the Surveillance, Epidemiology, and End Results (SEER)/Medicare, demonstrated that ADT for prostate cancer increases the risk of fracture).[37] In data from the Surveillance, Epidemiology, and End Results (SEER)/Medicare database, patients on ADT were 4 times more likely to suffer from significant bone mass loss, and for those surviving 5 years after prostate cancer diagnosis, fracture incidence rose from 12 to 19.4% (P<0.001). [34] [37]

Bone-health complications cause significant morbidity and all-cause mortality. Annual loss of bone mineral density (BMD) in older men ranges from 0.5% to 1% compared with 1% to 2% in women. [35] However, BMD in men receiving ADT rapidly declines within the first 12 months of therapy. The rates of bone loss in the lumbar spine ranges from 2-8% and 1.8-6.5% in the femoral neck. BMD continues to fall with ADT treatment beyond 12 months.

ADT also causes muscle loss, with changes in body composition from a substantial increase in adiposity and decrease in lean body mass within 3-12 months of initiation of ADT. This ADT-induced sarcopenia compounds the risk of falls, fractures, and loss of independence. [36]

*2.2 ARPI and Secondary Osteoporosis and fragility fracture*

ADT was the cornerstone treatment for prostate cancer for many decades. The last decade has seen significant improvements in overall survival in overall survival with the earlier use of ARPI alongside ADT in both the high risk non-metastatic and metastatic prostate cancer settings in both hormone sensitive and castrate resistant disease.[38] [39]

As discussed earlier, the addition of ARPI to standard ADT has showed an improvement in the survival outcomes in patients with advanced prostate cancer. A recent large systematic review and meta-analysis of randomised control trials from February 2024 A total of 23 randomised control trials were included in the meta-analysis, including many of the cornerstone trials. [40] [41] [42] [43] [44] [45] [46] [47] [48] **Error! Bookmark not defined.** [50] [51] [52] [53] [54] [55]

Abiraterone irreversibly inhibits androgen production in the tumour cells, testes, and adrenal glands. Abiraterone requires steroid use alongside treatment (usually Prednisolone 5 mg twice a day) to overcome secondary cortisol insufficiency and prevent overproduction of adrenocorticotrophic hormone (ACTH) and mineralocorticoids. Since 2015, the STAMPEDE and LATITUDE phase III trials have led to the widespread use of Abiraterone in combination with ADT in the UK, demonstrating survival advantage in comparison to ADT

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alone. Abiraterone can be used in newly diagnosed mHSPC and metastatic castration-resistant prostate cancer (mCRPC) as well as in the high-risk non-metastatic setting. [38 39]

Recent phase III trials have showed the efficacy of Enzalutamide [4948 50 51 52], Apalutamide [53 54] and Darolutamide[55] in combination with ADT, demonstrating survival advantage in comparison to ADT alone.

*2.3 Glucocorticoids and Bone Loss*

Glucocorticoids are commonly prescribed in prostate cancer treatment. They have an independent, negative effect on bone health and increase risk of fracture in patients with prostate cancer. They are often used long-term and is a well-established and common cause of iatrogenic and secondary osteoporosis. The risk of hip and vertebral fractures increases with docetaxel and abiraterone up to 7 and 17-fold, respectively, with doses as low as 10-12 mg Prednisolone given for as little as 3 months. [36]

*2.4 Radium 223 Radionuclides*

The ERA223 trial in 2019 concluded that the addition of Radium-223 to Abiraterone plus Prednisone or Prednisolone did not improve symptomatic skeletal event-free survival in patients with castration-resistant prostate cancer and bone metastases and was associated with an increased frequency of bone fractures compared with placebo. [56] Recent evidence from the PEACE 3 trial supports a new first line mCRPC treatment option of combining Radium-223 with Enzalutamide for some patients. [57]

Both trials have unequivocally demonstrated higher fracture rate in those receiving these combinations and the importance of mandatory bone protection in these patients. [48 50] The guideline group agrees that Radium 223 patients should be classified as the “very high risk “group for SRE and FF with parallel parenteral bone protection agents preferred if possible.

**Recommendation:**
The guideline group agrees that Radium 223 patients should be classified as the “very high risk “group for SRE and FF with parenteral bone protection agents preferred if feasible especially during the duration of Radium 223 treatment. For patients already established on oral agents, switch may not be required however escalation to parenteral agents (more potent) can be considered if SRE /FF occurred while on oral agents.

*2.5 Radiotherapy*

Radiotherapy has been shown in cell culture and animal models to affect osteoblasts and osteoclasts leading to reduced bone formation. [58] In clinical practice, pelvic radiotherapy increases risk of fractures. However, the association between pelvic radiotherapy and an increased risk of hip fractures has not been formally established as an independent contributing factor. It remains unclear whether pelvic radiotherapy causes any independent deterioration in BMD or increases the risk of clinically meaningful fractures.[59]

*2.6 The Impact of systemic prostate cancer therapy on frailty and fall.*

Patients with advanced prostate cancer have a higher incidence of osteoporosis with loss of BMD 10-fold higher than for patients without prostate cancer of the same age. 5%, compared to 0.5% for age-matched controls. [60]

A recent large meta-analysis looked at the risk of fractures and falls in patients with advanced or metastatic prostate cancer receiving ADT and ARPI. It demonstrated that the overall fracture incidence of any grade fracture was 8.3% with the addition of an ARPI in comparison to 3.2% in the control group. ARPI use was also associated with an increase in the overall incidence of any grade falls at 11.1% in comparison to the control group at 4.6%. [61]

STAMPEDE compared ADT ± Docetaxel ± Zoledronic acid (ZA). A recent post hoc analysis on falls and fracture rates of the trial population demonstrated that patients with advanced prostate cancer have a high incidence of clinical fractures. This was substantially reduced in participants allocated to ZA, with the 5-year fracture incidence in the ZA arm and the non-ZA arm being 4.5% and 12.9%, respectively. [62]

The LATITUDE trial compared Abiraterone (and Prednisolone) with ADT versus ADT (and dual placebos). A recent subgroup post hoc analysis in Japan demonstrated that bone-modifying agent use (Bisphosphonates or Denosumab) was associated with a longer time to skeletal-related events in patients with high-risk mCSPC treated with ADT, both with or without Abiraterone (and Prednisolone).[63]

**Recommendation:**
Given the significantly increased risk of both fractures and falls, it is important to appropriately consider and assess the frailty status and falls history in our patients. Please see the RCR frailty guidelines for further information including falls prevention strategies.[72]

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# 3. Fragility fracture (FF) risk assessment in patients with PC: who, how and when?

*3.1 Who should be assessed?*

Fragility fractures are preventable and are becoming more common in our aging population. One in 5 men over the age of 50 suffer from a fracture because of osteoporosis.[1]

Prostate cancer is predominantly a disease of older people, with more than 50% of cases are diagnosed in the UK in those aged 70 years and older[4]. The American Society of Clinical Oncology (ASCO) recommends that patients with prostate cancer and **any** risk factor in Table 1 be assessed for short- or long-term risk of osteoporotic fracture. [64] This therefore affects nearly ALL prostate cancer patients. Please see section 3.3 for information on how FFR should be assessed.

**Recommendation:**
Everyone with prostate cancer should have their bone health assessed.

The following criteria should be considered high risk for developing fractures (Table 1). It is important to remember that anti-cancer therapies in combination or sequence may have a cumulative or synergetic effects in increasing fracture risk in the short and the long term.

**Table 1: Factors that Increase Risk of Osteoporotic Fractures in patients with prostate cancer**

1. Advanced age (> 50 years)
2. Current cigarette smoking
3. Excessive alcohol consumption (> 20 units/week)
4. History of non-traumatic fractures in adulthood
5. Hypogonadism
6. Impaired mobility
7. Increased risk of falls
8. Long-term exposure to glucocorticoids
9. Low body weight <19
10. Parental history of hip fracture
11. Anti-cancer treatment

*Adapted from ASCO[64] and NOGG 2022 [65]*

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*3.2 Who should perform FFR assessments?*

Bone health management is everyone's business. Bone health can be assessed at any point in the prostate cancer pathway but should be assessed as early as possible. Performing fragility fracture risk assessments requires a fully multi-disciplinary approach.

Assessments should be documented and updated by any qualified member of the healthcare team, including GPs, specialist nurses, pharmacists, therapeutic radiographers, dietitians, physiotherapists, occupational therapists, and healthcare assistants as well as urologists and oncologists. The person assessing may differ depending on the service set up, training and the stage of the patient in the care pathway.

*3.3 How should FFR be assessed?*

A dynamic and systematic approach to FFR assessment should include the following:

1. **Medical history** –Assessment of specific risk factors, as per table 1
2. **Physical examination** – Height and weight measurement. Assessment of BMI and appropriate referral. Loss of height or changes in posture (kyphosis) may indicate clinical manifestations of fragility fractures
3. **Laboratory Testing** – (these as per NOGG guidelines) includes[65]:
    - Full blood cell count
    - Erythrocyte sedimentation rate or C-reactive protein
    - Renal function
    - Bone profile
    - Liver function
    - Serum 25-hydroxyvitamin D*
    - Thyroid function tests
4. **Bone Mineral Density Testing** – where available in a timely way** consider baseline Dual-Energy X-ray Absorptiometry (DEXA) in non-metastatic patients. DEXA scanning allows monitoring of bone mineral loss over time and the efficacy of interventions. FRAX or DEXA could be used as an optional risk stratification tool to aid treatment decision in addition to duration of ADT e.g. in Amber group[66]. FRAX score needs to be adjusted upward when there is recent fragility fracture (the last 2 years) depending on the type of fragility fracture and age of the patient in line with FRAX Plus software and most recent NOGG 2024 guidelines.[67]

* Mandatory when starting parenteral antiresorptive agents

**The guideline working group recognises that there is significant variation in access to DEXA across the UK. DEXA primarily focuses on BMD and does not provide qualitative information on other factors such as bone quality or microarchitecture. Therefore, we recommend empirical BPA treatment can be started based on clinical judgment (see section 5) and the use of DEXA is not mandated.

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### *3.4 When should FFR be assessed?*

Assessing FFR should be done proactively and opportunistically at the first opportunity. This could happen as early as at the time of diagnosis and should remain under review throughout the diagnostic and treatment pathway. This should be before, or at the start of ADT or any other systemic anticancer agents. This stratifying patients into low (green), medium(amber) and high (red) (fracture) risk categories (the traffic light system, see section 5) will guide ongoing management and timing of future assessment.

## 4. Management of FF risks in patients with advanced prostate cancer

### *4.1 Lifestyle Interventions*

There is good evidence for lifestyle interventions to improve or maintain BMD and reduce risk of fractures. However, lifestyle interventions alone are not enough in patients on ADT to maintain BMD and reduce fracture risk.

#### *4.1.1 Smoking and Alcohol*

Smoking, vaping and excessive alcohol intake are risk factors for fracture in older people. Moderate-to-heavy smoking (>20 pack years) with low body weight, especially, increases the risk of bone loss. Smoking cessation should therefore be advised in all patients and referral to local smoking cessation services made.

There is a dose-dependent relationship with bone loss and alcohol use. Increased bone loss is associated with heavy alcohol use, particularly having a significant effect on BMD in men and people with prostate cancer on ADT. [68], [69] The UK NOGG guideline [65] has indicated that in men with previous alcohol dependence, BMD is significantly lower than in controls but improves following 3–4 years of abstinence.

**Recommendation:**
Lifestyle modifications should be recommended to maximise active lifestyles, and to minimise or stop smoking and alcohol consumption.

#### *4.1.2 Diet, Calcium and Vitamin D Supplementation*

Meta-analyses have reported combined calcium and vitamin D supplements can reduce hip and non-vertebral fractures, and possibly also vertebral fractures. Overall, there is little evidence that vitamin D supplementation alone reduces fracture incidence, although it may reduce falls risk. It is however, important for patients taking antiresorptive and anabolic osteoporosis drug therapies to be vitamin D replete.[61] The Scientific Advisory Committee on Nutrition (SACN) recommends a reference nutrition intake (RNI) of 400 IU daily of vitamin D

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for adults of all ages, in the context of osteoporosis higher levels, specifically 800 IU to 2000 IU daily may be appropriate.[65] A healthy varied diet should be recommended in all patients initiating ADT. For patients who would only receive <= 6 months of androgen deprivation therapy, dietary modification to include foods high in calcium are recommended.

**Recommendation:**

Please see the flow chart in section 5 for a risk stratified pharmacological intervention approach.

*4.1.3 Exercise and falls prevention*

A combination of BMD reduction and sarcopenia increases the risk of fractures in men and patients with prostate cancer receiving ADT. The gradual loss of lean muscle mass or sarcopenia and muscle function, particularly in the lower extremities, leads to poor muscle strength and poor physical function, resulting in falls and fractures. ADT associated metabolic syndrome is also linked with increased cardiovascular morbidity.[70] [71] ADT with or without additional ARPI is also known to exacerbate cognitive impairment.[72] An active lifestyle and exercise, especially in the form of weight-bearing aerobic or resistance exercises, should be an essential component in the management of bone health. [65]

Combined exercise protocols including resistance training, balance challenging, aerobic exercise and impact exercise totalling at least 3 hours per week should be recommended in patients with high risk of falls who are initiating ADT as part of their holistic care and survivorship programme. Home safety interventions (best delivered by an occupational therapist) have been shown to reduce the risk of falls in people living in the community. [65]

The guideline group references the Royal Osteoporosis Society Strong, Steady and Straight Expert Consensus Statement, which offers advice on intensity and duration and linked patient information videos and factsheets [73]. Please see Table 2 for a summary of recommendations for non-pharmacological lifestyle interventions.

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**Table 2: The national osteoporosis guideline group (NOGG)[65] recommend the following**:

1. A healthy, nutrient-rich balanced diet **(Strong recommendation)**.
2. An adequate intake of calcium (minimum 700mg daily) preferably achieved through dietary intake or otherwise by supplementation **(Strong recommendation)**.
3. To consume vitamin D from foods or be prescribed vitamin D supplements of at least 800IU/day if they have identified vitamin D insufficiency or risk factors for vitamin D insufficiency. Those who are either housebound or living in residential or nursing care are more likely to require calcium and vitamin D supplementation to achieve recommended levels of intake **(Strong recommendation)**.
4. A combination of regular weight-bearing and muscle strengthening exercise, tailored according to the individual patient's needs and ability **(Strong recommendation)**.
5. Advice about smoking cessation if an individual is a smoker **(Strong recommendation)**.
6. Advice to restrict alcohol intake to ≤ 2 units/day **(Strong recommendation)**.
7. A falls assessment should be undertaken in all patients with osteoporosis and fragility fractures; those at risk should be offered exercise programmes to improve balance and/or that contain a combined exercise protocol **(Strong recommendation)**.

## 4.2 Pharmacological management

### *4.2.1 Anti-Resorptive Agents*

All patients should be risk stratified using the traffic light system below in section 5.

The significant increase in fracture risk in patients with prostate cancer in the 5 years following the initiation of ADT when compared to those not receiving ADT. Antiresorptive agents are effective drug treatments for preventing BMD loss in those on ADT; exercise programmes are insufficient in isolation. Upfront intervention with selected antiresorptive agents in combination with calcium/vit D are recommended (NOGG strong recommendation) and are referred as bone protection agents (BPAs) in this guideline. [65]

Oral or intravenous bisphosphonates are the most cost-effective interventions. Where these are not tolerated, denosumab is an approved option for the treatment of men with increased FFR. Denosumab is given as a subcutaneous injection of 60 mg every 6 months. The discontinuation of Denosumab is associated with profound increase in bone turnover ('rebound phenomenon'). Stopping Denosumab should be followed by 2 IV zoledronic acid 6 months apart and not one off IV zoledronic acid.

Adults who have been taking bisphosphonates for 5 years should have a review of the need for continuing treatment. Please see the Appendix for information on the toxicities of antiresorptive agents and their management (including GI and renal toxicity, hypocalcaemia, Medication Related Osteonecrosis of the Jaw (MRONJ), and atypical fracture).

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**Recommendation:**

The guideline recommends oral antiresorptive agents as the first line treatment for the amber group unless contraindicated. See section 5 for the traffic light system.

**Table 3: Summary of pharmacological Treatment Recommendation**s (Adapted from NOGG 2022 page 14/46) [65] please also se Appendix 7.1.3 for more details.

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1. Oral bisphosphonates (Alendronic acid 70 mg once weekly or Risedronate 35 mg once weekly by mouth) are recommended for at least 5 years and then re-assess fracture risk. Longer durations of treatment, for at least 10 years, are recommended for high-risk (Red group) patients (strong recommendation) (see Fig. c).

2. In patient without bone metastasis (Amber or Red group), Intravenous Zoledronic acid once yearly by intravenous infusion (5 mg over 15 minutes) for 3 years if oral bisphosphates contraindicated or poorly tolerated e.g. Barret's oesophagus, troublesome gastrointestinal symptoms and bowel disturbance.

3. Consider Zoledronic acid intravenous 4 mg every 3-4 weeks (as per STAMPEDE & PEACE-3 criteria- red group)[24 25] or 3 monthly (as per NOGG)[65] as a first-line treatment option following
    1) a hip fracture (strong recommendation) or
    2) SRE occurred while on oral bisphosphonate
    3) Or patients at very high risk:
        - Radium223 treatment (current or previous)
        - 1 Vertebral fracture within the last 2 years
        - ≥2 vertebral fractures at any time
        - BMD T-Score ≤-3.5
        - Treatment with high dose glucocorticoids (≥7.5 mg/day of prednisolone or equivalent over ≥3 months)
          Multiple clinical risk factors (e.g. Smoking, alcohol consumption etc), particularly with a recent fragility fracture.

4. Avoid unplanned cessation of denosumab because it can lead to increased vertebral fracture risk, hence it must not be stopped without considering an alternative therapy (strong recommendation).

5. Before starting subcutaneous denosumab, ensure that both the patient and the primary care practitioner are made aware that denosumab treatment should NOT be stopped or delayed without discussion with a specialist healthcare professional (strong recommendation).

6. If denosumab therapy is stopped, a consolidation dose of intravenous infusion of zoledronate is recommended 6 months after the last injection of denosumab and consider further dose 6 months after the first dose of zoledronate.

7. Offer calcium and/or vitamin D supplementation as an adjunct to anti-osteoporosis drug treatment, if dietary calcium is low and/or vitamin D insufficiency is a risk, respectively (strong recommendation).

8. Treat symptomatic vitamin D deficiency and insufficiency prior to initiation of parenteral anti-osteoporosis drug treatment, and alongside initiation of oral anti-osteoporosis drug treatment (strong recommendation).

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646 Figure C: Summary of Traffic light System for Treatment Decision Making[74]

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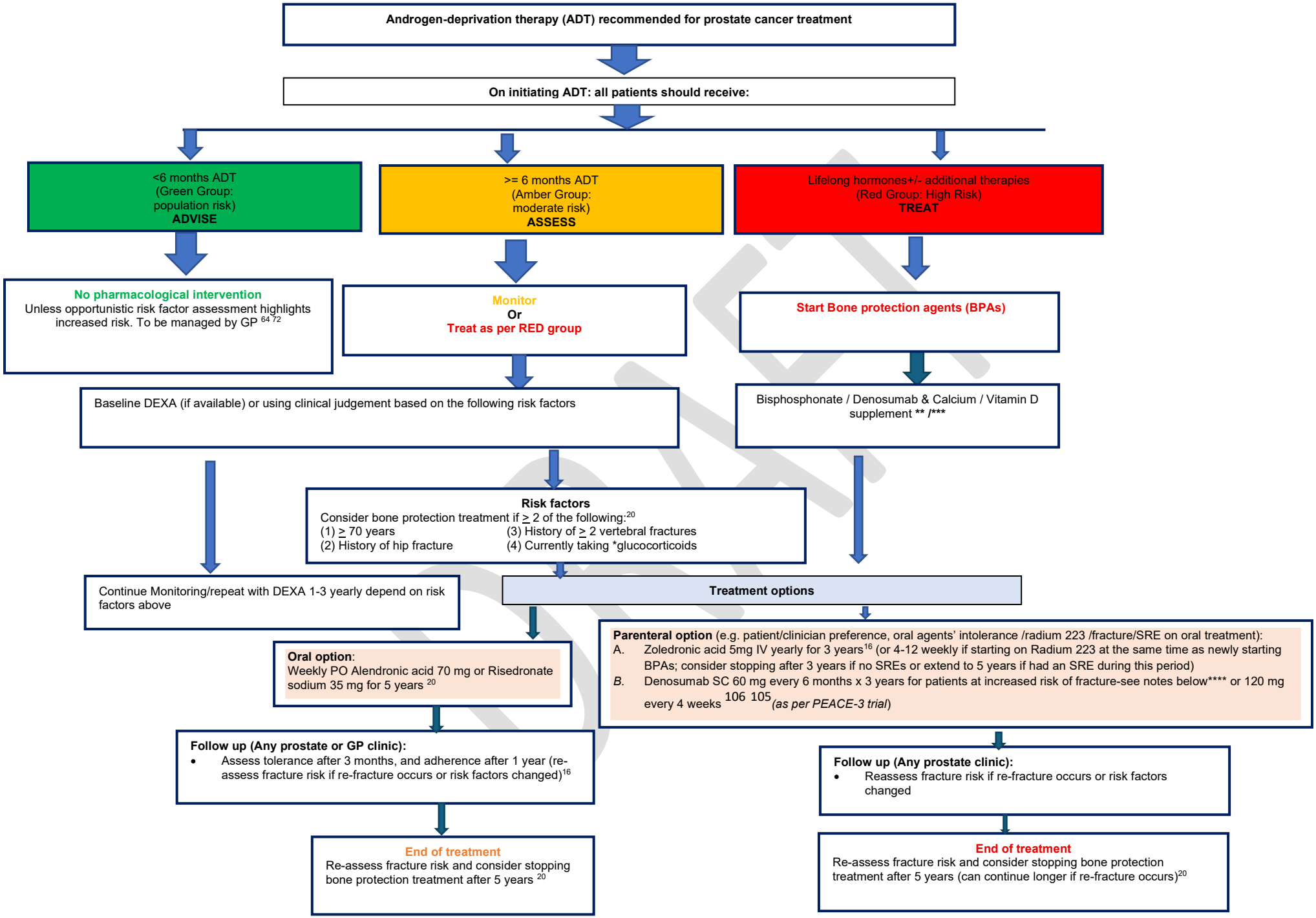
Androgen-deprivation therapy (ADT) recommended for prostate cancer treatment
On initiating ADT: all patients should receive:
<6 months ADT
(Green Group:
population risk)
ADVISE
>= 6 months ADT
(Amber Group:
moderate risk)
ASSESS
Lifelong hormones+/- additional therapies
(Red Group: High Risk)
TREAT
No pharmacological intervention
Unless opportunistic risk factor assessment highlights increased risk. To be managed by GP 64 72
Monitor
Or
Treat as per RED group
Start Bone protection agents (BPAs)
Baseline DEXA (if available) or using clinical judgement based on the following risk factors
Bisphosphonate / Denosumab & Calcium / Vitamin D supplement ** /***
Risk factors
Consider bone protection treatment if ≥ 2 of the following:20
(1) ≥ 70 years
(2) History of hip fracture
(3) History of ≥ 2 vertebral fractures
(4) Currently taking *glucocorticoids
Continue Monitoring/repeat with DEXA 1-3 yearly depend on risk factors above
Treatment options
Oral option:
Weekly PO Alendronic acid 70 mg or Risedronate sodium 35 mg for 5 years 20
Parenteral option (e.g. patient/clinician preference, oral agents' intolerance /radium 223 /fracture/SRE on oral treatment):
A. Zoledronic acid 5mg IV yearly for 3 years16 (or 4-12 weekly if starting on Radium 223 at the same time as newly starting BPAs; consider stopping after 3 years if no SREs or extend to 5 years if had an SRE during this period)
B. Denosumab SC 60 mg every 6 months x 3 years for patients at increased risk of fracture-see notes below**** or 120 mg every 4 weeks 106 105 (as per PEACE-3 trial)
Follow up (Any prostate or GP clinic):
• Assess tolerance after 3 months, and adherence after 1 year (re-assess fracture risk if re-fracture occurs or risk factors changed)16
Follow up (Any prostate clinic):
• Reassess fracture risk if re-fracture occurs or risk factors changed
End of treatment
Re-assess fracture risk and consider stopping bone protection treatment after 5 years 20
End of treatment
Re-assess fracture risk and consider stopping bone protection treatment after 5 years (can continue longer if re-fracture occurs)20

Notes for Figure C: Summary of Traffic light System for Treatment Decision Making:

**Oral prednisolone ≥ 7.5 mg/day or equivalent.*[20]

***Vitamin D level should be measured and deficiency (< 25 nmol/L) be corrected with loading regimen if patient is symptomatic (e.g. bone pain, lower back pain, muscle pain or weakness) or before starting IV Zoledronic acid or SC Denosumab.*[78] *Vitamin D level is not routinely required in asymptomatic patient starting oral bisphosphonates.* [78]

****Consider use concomitantly if receiving Radium 223 and step down to oral or continuous after completing radium 223 depending on patient fitness, preference and logistics on shared decision making.*

*****Increased risk of fracture is defined as > 70 years, or < 70 years with a BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 or a history of an osteoporotic fracture.) ref:*
*Prolia 60 mg solution for injection in pre-filled syringe - Summary of Product Characteristics (SmPC) - (emc) | 568*

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**Table 4**

*Summary of prostate cancer disease patient Groups, fracture risk stratification and treatment recommendation*

| | ***Green Group (Low Risk: M0, Stage I-II): ADVISE***<br>7 | ***AMBER Group (Moderate Risk: M0, Stage III-IV): ASSESS*** | **Red Group (High Risk: M1 or M0 Advanced Disease): *TREAT*** |
|---|---|---|---|
| **Patient Group** | Non-metastatic prostate cancer at general population risk. | Non-metastatic prostate cancer at risk-stratified level | 1. **M0:** Non-metastatic hormone-sensitive prostate cancer (nmHSPC) on upfront ARPI/ARPI.<br>2. Metastatic hormone-sensitive prostate cancer (mHSPC) on lifelong ADT +/- additional therapy.<br>3. **mCRPC/nmCRPC:** Castration-resistant prostate cancer on lifelong ADT +/- additional therapy. |
| **Oncological Treatment** | Surgery (radical or salvage) or radiotherapy with ≤ 6 months of ADT. | Radical or salvage radiotherapy with **≥ 6-36 months ADT** | Lifelong ADT with or without additional other treatment |
| **Bone Heath Management** | No additional intervention required unless opportunistic identification of multiple fracture risk factors.<br>• communicate to primary care for further management. | 1. Lifestyle advice and general health promotion<br>2. **Consider FRAX Score** and/or **baseline DEXA +/- follow-up (see flow chart-Amber group)**. | 1. Lifestyle advice and general health promotion<br>2. Upfront pharmacological intervention<br>**1) Calcium and Vitamin D (at least 1g elemental calcium + 800 IU Colecalciferol daily) AND**<br>**2) An Anti-resorptive agent** |

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| | | | |
|---|---|---|---|
| | | 3. **Thresholds for treatment based clinical judgement (see flow chart- Amber group +NOGG[72]**<br>4. If BMD ≤ -2.5 (osteoporotic) or clinically high risk (>= 2 risk factors)- treat as per red group (except denosumab not indicated in this group) | **A. Oral Alendronic Acid 70 mg weekly or Risendronate 35 mg weekly for 5 years OR**<br>**B. Parenteral options for** very High-Risk Group (**Radium 223 or NOGG definition** [72]<br>○ **Zoledronic Acid IV 5 mg annually or** 3-4 weekly or 3 monthly or<br>○ **Denosumab SC 60 mg every 6 months** or 120 mg 4 weekly<br>**3.** Monitor tolerability and risk of hypocalcemia with IV/SC therapies. |
| **Comments** | Managed as per general population risk (primary care-led) as per NICE[72] and NOGG guideline[75] | Pathways may vary (e.g., primary care-led or specialist-led based on local arrangements) | Consider referral of very high-risk patients to an osteoporosis specialist in secondary care, for assessment and consideration of parenteral treatment (some may need first-line anabolic drug treatment, especially those with multiple vertebral fractures). [71] |

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## 6. Education, research, audit and service improvement

*6.1 Education*

Patient education should begin with an understanding of how ADT affects bones and why fracture risk increases. Patients should be informed of symptoms such as bone pain, loss of height, or sudden fractures, which may indicate underlying osteoporosis or metastatic involvement. Preventive strategies (calcium and vitamin D supplementation, regular weight-bearing, resistance exercises), lifestyle changes (smoking cessation, moderation of alcohol intake) and fall prevention are endorsed by major guidelines. [76] [77]Interventions to increase BMD and reduce SRE (bisphosphonates, denosumab), particularly in patients with bone metastases[78] should be considered in men with high fracture risk or confirmed osteoporosis. Patients should have a conversation about the importance of evaluation of oral health prior to initiation and maintaining oral health to reduce the risk of osteonecrosis of the jaw.

The assessment of bone health should become second nature to healthcare professionals caring for patients with prostate cancer. Optimisation of bone health can and should start at the earliest possible opportunity. This requires good education about the assessment and management of bone health for teams. This guideline is a good starting point for current best practice, but it is crucial to keep knowledge among teams up to date to allow optimal bone health management. A collaborative approach with patients to manage their bone health, including discussions regarding the risks and benefits of treatment should be established to allow patients to take an active role in managing their own risk of fracture with regards to lifestyle and treatment compliance. Interdisciplinary collaboration across professions and specialties could potentially improve the effectiveness of bone health management.

Educational tools such as printed materials, videos, workshops, and digital apps can improve awareness and adherence to bone health guidelines. There should be particular emphasis on early intervention and continuous monitoring, which can significantly reduce SREs in patients with prostate cancer undergoing ADT.

*6.2 Audit*

The following audit aspects are designed to evaluate and improve clinical practice related to bone health in this patient population.

1. Baseline Evaluation

- DEXA Scan: Was a baseline bone mineral density (BMD) assessment performed prior to or within 6 months of starting ADT?
- Fracture Risk Assessment: Was a risk score tool (e.g., FRAX) used to stratify patients?
- Calcium & Vitamin D Levels: Were these checked before initiating therapy?

2. Risk Factor Identification

- Osteoporosis or Prior Fracture History: Documented evidence of past fragility fractures?

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- Patient Age: Older age as a documented risk factor?
- Bone Metastases: Was bone imaging done to identify skeletal involvement?

3. Preventive Measures

- Supplementation: Were calcium and vitamin D supplements prescribed?
- Lifestyle Counseling: Documented advice on smoking cessation, alcohol moderation, fall prevention, and exercise?
- Fall Risk Assessment: Especially in elderly or frail patients.

4. Pharmacologic Interventions

- Bone-Modifying Agents: Appropriately prescribed (e.g., bisphosphonates or denosumab) for high-risk patients?
- Dental Review: Prior to initiating antiresorptive therapy?
- Monitoring for Adverse Events: Was the patient monitored for side effects like jaw osteonecrosis or hypocalcemia?

5. Follow-Up and Monitoring

- Repeat DEXA Scans: Timely re-assessments (every 1–2 years)?
- Adherence Review: Ongoing documentation of adherence to supplements and medications?
- Fracture Surveillance: Were any new fractures identified and managed?

6. Documentation and Communication

- Multidisciplinary Involvement: Was there evidence of referrals (e.g., to endocrinology or geriatrics)?
- Patient Education: Were risks, benefits, and self-care strategies explained and documented?

7. Audit Metrics

- % of patients starting ADT with baseline DEXA scan
- % prescribed calcium/vitamin D
- % of high-risk patients receiving bone-sparing therapy
- Incidence of new fractures during follow-up
- Audit Checklist: Bone Health in Prostate Cancer

| Audit Criterion | Yes/No | Comments/Notes |
|---|---|---|
| DEXA scan performed before or shortly after starting ADT | | |
| FRAX score or other fracture risk tool used | | |
| Baseline calcium and vitamin D levels checked | | |
| Vitamin D deficiency corrected prior to ADT | | |
| History of fragility fracture documented | | |
| Age >70 or other risk factors identified | | |
| Imaging performed to check for bone metastases (if symptomatic/high risk) | | |

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| | | |
|---|---|---|
| Calcium (1000–1200 mg/day) and vitamin D (800–1000 IU/day) prescribed | | |
| Lifestyle advice given (smoking, alcohol, fall prevention, exercise) | | |
| Physical activity/exercise plan discussed | | |
| Antiresorptive therapy prescribed if high fracture risk (bisphosphonates/denosumab) | | |
| Indications for bone-sparing treatment clearly documented | | |
| Oral health assessment before bisphosphonate/denosumab | | |
| Follow-up DEXA scan within 12–24 months | | |
| Adherence to prescribed supplements and therapies assessed | | |
| Monitoring for medication side effects (e.g., jaw osteonecrosis, hypocalcemia) | | |
| Bone health risks discussed with patient | | |
| Interdisciplinary team involved where appropriate | | |

### *6.3 Research*

1. Is FRAX score appropriate for assessing BMD for pts with CaP on ADT?
2. Are oral bisphosphonates superior to intravenous bisphosphonates?
3. What is the optimal duration of bisphosphonates?

4. Projected health economic impact analysis of the intervention/guideline

5. Evaluation of compliance of oral BPAs –consider addressing some well-known reasons:
    - Lack of motivation: since osteoporosis is often asymptomatic many patients experience no obvious improvement
    - Adverse effects associated with some treatments
    - Safety concerns about treatments
    - Inconvenient dosing, such as daily dosing and/or the need for fasting
    - Simply forgetting to take medication as directed

6. Frequency of DEXA monitoring if used in patients on ADT+/- other agents

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Service Improvement: identifying and addressing some well-known challenges:

1) Under-treatment /over-treatment
2) Failure to implement recommendations
3) Poor co-ordination between primary and secondary care
4) Lack of public awareness about osteoporosis and fragility fracture
5) Lack of prostate cancer HCP awareness about osteoporosis and fragility fracture

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# 7 Appendix A

## 7.1 Bone Health Supplements and Medications

### *7.1.1 Calcium and Vitamin D Supplementation*

All patients should be screened for symptoms of vitamin D deficiency (e.g. generalised bone pain, lower back pain, muscle pain or weakness).[79] Serum vitamin D level is **not** routinely recommended in asymptomatic patients starting oral bisphosphonates.[80] If an oral antiresorptive agent is initiated - maintenance dosing of calcium and vitamin D supplements (refer to Table 5 ) should be co-prescribed.

**Table 5: The recommended vitamin D thresholds in the UK with respect to bone health are:** [79 80]

| Serum vitamin D level (nmol/L) | Threshold | Action required |
|---|---|---|
| < 25 | Deficient | **If symptomatic or starting IV zoledronic acid or SC denosumab:** Loading regimen (refer to Table 6), followed by regular maintenance doses (refer to Table 7) a month later. |
| 25 – 50 | Insufficient | Regular maintenance doses (refer to Table 7). |
| > 50 | Sufficient | No action required. |

**Table 6: Suggested Vitamin D loading regime in vit D deficiency:**

*The loading regimen should provide a total of approximately 300,000 IU of vitamin D, given either as separate weekly or daily doses over 6-10 weeks.

**Several vitamin D loading dose treatment regimens are available**:

- 50,000 IU once a week for 6 weeks (300,000 IU in total)
- 40,000 IU once a week for 7 weeks (280,000 IU in total)
- 1000 IU four times a day for 10 weeks (280,000 IU in total)
- 800 IU five times a day for 10 weeks (280,000 IU in total)

**Table 7 *Commonly used calcium/vitamin D supplements** (aiming for daily intake of ≥ 1000 mg calcium & ≥ 800 IU vitamin D)

| Brand | Formulation | Elemental calcium (mg) | Vitamin $D_3$ (IU) | Suggested dose | Notes |
|---|---|---|---|---|---|
| Accrete D3[81] | Tablets | 600 | 400 | 1 BD | - |
| Accrete D3 One a Day[82] | Chewable Tablets | 1000 | 880 | 1 OD | Suitable for vegetarians and safe in peanut/soya allergy |
| Adcal-D3 [83 84] | Caplets | 300 | 200 | 2 BD | Suitable for vegetarians and safe in peanut/soya allergy |
| Adcal-D3 [85] | Chewable Tablets | 600 | 400 | 1 BD | - |
| Adcal-D3 Dissolve [83 86] | Effervescent Tablets | 600 | 400 | 1 BD | Suitable for vegetarians and safe in peanut/soya allergy |
| Cacit D3 [83 87] | Sachet | 500 | 440 | 1 BD | Safe in peanut/soya allergy |
| Calceos [88] | Chewable Tablets | 500 | 400 | 1 BD | - |
| Calcichew-D3 Forte [83 89] | Chewable Tablets | 500 | 400 | 1 BD | Safe in peanut/soya allergy |
| Calcichew-D3 Once Daily [83 90] | Chewable Tablets | 1000 | 800 | 1 OD | Safe in peanut/soya allergy |
| Evacal D3 [8383 91] | Chewable Tablets | 600 | 400 | 1 BD | Suitable for vegetarians and safe in peanut/soya allergy |
| Natecal D3 [92] | Chewable Tablets | 600 | 400 | 1 BD | - |
| theiCal-D3 [83 93] | Chewable Tablets | 1000 | 880 | 1 OD | Suitable for vegetarians and safe in peanut/soya allergy |

**The above information might change over time. Please always check the latest summary of product characteristics (SPC) or with the manufacturer before treatment initiation. Licensed colecalciferol preparation is currently unavailable for vegans due to the involvement of lanolin in the production process. However, unlicensed products are available for vegans using colecalciferol that is produced from lichen. Please check with your pharmacy team for more advice.*

### *7.1.2 Oral Bisphosphonates*

Oral bisphosphonate is recommended as the first-line treatment option for patients in the amber or red groups, with the exception of patients receiving radium-223. They **should not be used in patients with** oesophageal disorders such as achalasia, esophageal stricture, oesophageal varices, or Barrett's oesophagus as they can increase the risk of esophageal irritation or damage due to the medication.[94 95]

There are two main oral bisphosphonates:

**Table 8**

| | Alendronic acid | Risedronate sodium |
|---|---|---|
| Recommended renal function | Creatinine clearance > 35 mL/min [96 97 98 99] | Creatinine clearance > 30 mL/min [100 101] |
| Dosing frequency | 70 mg once weekly (same day every week) [96 97 98 99] | 35 mg once weekly [100 97] (same day every week) |

| Available formulation | Tablet [96 97] effervescent tablet [96 98] liquid [96 99] | Tablet [100 101] |
|---|---|---|
| Administration method | 1. Take first thing in the morning when stomach is empty [at least half an hour before any food / drink (plain water is fine) / medications]. Take calcium and vitamin D supplements at least 2 hours later.[102 96 97 98 99]<br><br>**Tablet:**<br>2. Swallow the tablet whole (do not chew / suck / crush) with a full glass of water (≥ 200 mL). [102 96 97]<br><br>**Effervescent tablet:**<br>2. Dissolve tablet completely in half a glass of water (≥ 120 mL) before administration. Another ≥ 30 mL of water should be taken afterwards. [98]<br><br>**Liquid (70 mg / 100 mL):**<br>2. Take the 100 mL dose (1 bottle) as a single dose. Another ≥ 30 mL of water should be taken afterwards. [99]<br><br>3. Sit upright or stand for at least half an hour after taking alendronic acid. [102 96 97 98 99] | 1. Take when stomach is empty [at least half an hour before breakfast / drink (plain water is fine) / medications OR at least 2 hours before or after food / drink (plain water is fine) / medications if between meals OR at least 2 hours after evening meal / drink (plain water is fine) / medications]. Take calcium/vitamin D supplements at least 2 hours later. [102 96 97]<br><br>2. Swallow the tablet whole (do not chew / suck / crush) with a full glass of water (≥ 200 mL [102 96 97]<br><br>3. Sit upright or stand for at least half an hour after taking risedronate sodium. [102 96 97] |
| Missed dose | Can still take it when you remember (e.g. the following morning), then return to your usual day every week. Do not take two doses on the same day. [102 97 98 100 101] | |
| Common side effects | Upper gastrointestinal problems (e.g. heartburn or dyspepsia) – usually the first month and improve over time. [102] | |
| Red flag symptoms | New pain in the jaw, thigh, hip, groin, ear or when you are swallowing, discharge from ear, ear infection and swallowing difficulties. [102 96 97 98 99] | |

### *7.1.3 Parenteral anti-resorptive agents*

Parenteral anti-resorptive agents recommended in this guideline are zoledronic acid (bisphosphonate) and denosumab (fully human monoclonal antibody). They work differently in stopping the activity of osteoclasts but shares some risks and side effects. Table below summarises the key information for both agents.

832 **Table 9**
833

| | Zoledronic acid | Denosumab |
|---|---|---|
| **Dosing schedule** | **Option 1:** 5 mg IV infusion yearly[103]<br><br>OR<br><br>**Option 2 (with bone metastases):** 4 mg IV infusion every 3-4 weeks [104] [105] *(as per STAMPEDE & PEACE-3 trial) or 3 monthly as per NOGG recommendation for very high risk group (see table xx)* | **Option 1:** 60 mg SC injection 6-monthly[106]<br><br>OR<br><br>**Option 2 (with bone metastases):** 120 mg SC injection every 4 weeks [106] [105]*(as per PEACE-3 trial)* |
| **Renal function** | **Option 1:** Proceed if CrCl ≥ 35 mL/min; contraindicated if CrCl < 35 mL/min[107]<br><br>**Option 2 (with bone metastases):** Refer to the following table for starting dose based on renal function. Withhold treatment if serum creatinine increases by 44 µmol/L (baseline serum creatinine < 124 µmol/L) or 88 µmol/L (baseline serum creatinine > 124 µmol/L). Resume at the same dose when serum creatinine returned to within 10% of the baseline value.[108] | Higher risk of hypocalcaemia if CrCl < 30 mL/min or having dialysis[109] |
| **Supplements** [103] [106] [108] [107] [109] | Vitamin D deficiency must be treated with loading regimen (see Table 5 and 6) and hypocalcaemia must be corrected beforehand. Maintenance doses of calcium and vitamin D supplements (see Table 7) should be taken alongside treatment. | |
| **Monitoring** [103] [106] [108] [107] [109] | - Baseline dental assessment and maintain good oral hygiene<br>- Osteonecrosis of the jaw<br>- Atypical femoral fractures<br>- Osteonecrosis of the external auditory canal<br>- Urea and electrolytes (particularly hypocalcaemia) before each dose<br>- Serum creatinine and renal function (use Cockcroft-Gault equation) before each dose | |

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**Table 10**

| Baseline creatinine clearance (mL/min) | Zoledronic acid starting dose (mg) |
|---|---|
| > 60 | 4 |
| 50 – 60 | 3.5 |
| 40 – 49 | 3.3 |
| 30 – 39 | 3 |

## 7.2 Antiresorptive agent toxicities and management

### *7.2.1 Gastrointestinal Toxicity*

Oral bisphosphonates (Alendronic acid or Risedronic acid) and intravenous Zoledronic acid are recommended for use in prostate cancer patients.

- Alendronic acid is given 70 mg orally once weekly
- Risedronate 35mg orally once weekly.
- Zoledronic acid may be administered annually via intravenous infusion (5 mg over 15 minutes), particularly when oral bisphosphonates cause significant adverse effects, including upper gastrointestinal discomfort and bowel disturbances. [110]

Bisphosphonates may cause the following gastrointestinal adverse effects:

- Common: stomach pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer, dysphagia, abdominal distension, acid regurgitation. [111]
- Uncommon: nausea, vomiting, gastritis, oesophagitis, oesophageal erosions, melena.
- Rare: oesophageal stricture, oropharyngeal ulceration, upper gastrointestinal perforation, ulcers, haemorrhage. [111]

Use with caution when prescribing bisphosphonates to: [110]

- Individuals with upper gastrointestinal disorders, including dysphagia, oesophageal disease, gastritis, duodenitis, and peptic ulceration. [110]
- A recent history (within the past 12 months) of significant gastrointestinal disease or upper gastrointestinal tract issues. [110]
- Consider the pros as well as cons of treatment in patient with Barrett's oesophagus on a case-by-case basis. [110]

### *7.2.2 Hypocalcaemia*

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Anti resorptive agents may cause hypocalcaemia.

**Recommendation**

- Pre-existing hypocalcaemia must be addressed prior to initiating bisphosphonate therapy. Concurrent disorders of bone and mineral metabolism (e.g., parathyroid dysfunction, hypovitaminosis D) should be addressed upon initiation of bisphosphonate therapy. [112] [113] [114]Calcium supplements may be necessary to achieve 1000-1200 mg per day. [112]
- Vitamin D levels should be sustained with regular supplementation of vitamin D3, ranging from 800 to 2000 IU per day. A loading dose should be given if indicated as per Table 6

*7.2.4 Effects on renal toxicity*

Special consideration must be given to the possible renal damage associated with bisphosphonates.

**Recommendations**

- Oral bisphosphonates and Zoledronic acid are contraindicated in cases of severe renal impairment (creatinine clearance < 30 ml/min). Alendronic acid should be avoided where eGFR is <35ml/min [112]112 Stepwise dose reductions of zoledronic acid are recommended for patients with a baseline creatinine clearance of 30 - 60 ml/min, depending on the renal function. [112]
- Check renal function before each administration of Zoledronic acid.
    - In patients with bone metastases and mild to severe renal impairment (eGFR 30-60mls/min), it is advisable to dose reduce zoledronic acid at the start of treatment.
    - In patients who develop renal impairment during treatment, discontinue zoledronic acid. Zoledronic acid can be reinstated when serum creatinine levels revert to within 10% of baseline. Restart zoledronic acid at the dose used before the treatment break. [112]
    -

## 7.3 Medication Related Osteonecrosis of the Jaw (MRONJ)

MRONJ is a rare but significant side effect of antiresorptive and antiangiogenic agents. In patients with cancer, studies estimate incidence of around 5%. [115] The incidence of MRONJ in patients with prostate cancer appears to be higher than in other cancers, but this may be related to the longevity of prostate cancer follow up. Denosumab has been shown to increase the risk of MRONJ when compared to bisphosphonates. [116]An RCT in 2012 noted a 5% risk of MRONJ in patients with non-metastatic castrate resistant prostate cancer who had received 6 months of ADT and intravenous Denosumab. [117]

MRONJ is defined clinically as; (1) exposed bone, or bone that can be probed through an intra or extra oral fistulae in the maxillofacial region, (2) persisting for greater than 8 weeks,

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(3) in patients on anti-resorptive and antiangiogenic agents, (4) with no history of radiation therapy to the jaws or metastatic disease to the jaws.[117]

A key risk factor is dentoalveolar and mucosal trauma, typically extraction of teeth, however it can also occur spontaneously. Pathophysiology is not fully understood, but hypotheses suggest necrosis secondary to suppression of bone remodelling inhibition, angiogenesis inhibition, toxic effects of soft tissue inflammation or infection.[118]

Additional risk factors include cumulative drug dose (linked to duration,) and concurrent use of glucocorticoids. [118]

The type of antiresorptive agent used can affect the risk of MRONJ. The incidence of MRONJ in osteoporotic patients taking Denosumab has been reported as 0.3%. This is higher than those taking oral and IV bisphosphonates. In patients with cancer the literature for both Denosumab and IV zoledronate has reporting rates of <5% but with ranges of 0-6.9% and 0-18% respectively. [115] A Cochrane review in 2016 reported risk of MRONJ specifically with long term use and frequent IV dosing. [119]

To minimise the risk, dentoalveolar surgery (typically extraction of teeth with a poor prognosis,) should ideally be carried out before starting antiresorptive/antiangiogenic agents. Then prevention of dental disease is key, with oral health recommendations including brushing twice daily with a fluoride toothpaste, flossing teeth daily, dietary advice to prevent tooth decay and regular dental review.

If a significant delay to dental treatment is anticipated, starting a patient on oral bisphosphonates at the same time as dental referral, given the low risk of MRONJ, could be considered. However, patients considered for IV bisphosphonates or denosumab therapy should ideally have a dental assessment and complete treatment prior to starting the medication. [103] The MRONJ risk also increases with the duration of therapy, so early involvement of the dentist when prescribing these medications will reduce the risk. [115]

**Recommendation:**
Patients should ideally have a dental assessment before starting BMD. Where this is unavailable significant delay to dental treatment is anticipated, oral bisphosphonates can be started and a dental referral done at the same time.

Management of MRONJ is led by secondary care oral surgery / special care dentistry teams. Antibiotics in conjunction with antibacterial mouthwashes and regular follow up can be effective conservative management. However, in severe cases, debridement, extensive resection and reconstruction may be indicated, causing severe patient morbidity.

## 7.4 Atypical fractures / rebound bone resorption with denosumab withdrawal

**Atypical fractures**

Atypical fractures are rare, typically involving the lateral cortex of the proximal femoral shaft, and the subtrochanteric and diaphyseal regions of the neck of femur.[120]

Bisphosphonates prevent normal bone remodelling hence microscopic damage can accumulate resulting in brittle bones likely to fracture during low impact activity. [121]

Risk factors include longer duration of bisphosphonate treatment (particularly over 5 years) Asian ancestry, shorter height, higher weight and glucocorticoid use greater than one year. [122]

Patients present with groin, hip or thigh pain. Atypical fractures are typically seen bilaterally, and imaging of the contralateral side is recommended if suspected. [120]

Urgent assessment by orthopaedics is required. Stopping bisphosphonates results in a rapid decline in risk of atypical fracture but should be balanced against typical fracture risk. [122]

**Rebound bone resorption**

Discontinuing denosumab results in the rapid reversal of its inhibition of bone remodelling. The relative risk of major osteoporotic fracture, including vertebral fracture, hip and other fractures is significantly higher when denosumab is discontinued. Multiple vertebral fractures are more likely after stopping the medication, especially if the patient has a history of vertebral fracture prior to commencing therapy. [123]

Evidence suggests that vertebral fractures occur earlier and in higher number in longer durations of treatment or history of osteoporosis prior to treatment. [123]

Discontinuing denosumab treatment therefore comes with risks. Extending denosumab beyond 10 years should be on an individual basis, and, if discontinuing, starting an oral bisphosphonate towards the end of therapy may reduce the incidence of rebound resorption.[123] In metastatic prostate cancer continuing patients on denosumab for life seems sensible given their life expectancy and the risks of withdrawal.

## 7.5 Useful resources

At present there is no single resource addressing all aspects of bone health in this cohort of patients. Prostate Cancer UK have information on diet and physical activity for patients with prostate cancer. Macmillan produce generic information on bone health and cancer ranging from detailed booklets to simple factsheets. The Royal Osteoporosis Society (ROS) have produced good guidance on the risks of osteonecrosis of the jaw which can be provided to patients to facilitate discussions on dental care and hygiene while on bisphosphonates. The ROS have also produced a helpful guide to the “Strong, Steady and Straight” approach to physical exercise in the setting of osteoporosis which can be incorporated in local practice. It is recommended that patients are referred to local exercise classes where available.

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### *7.5.1 Dietary guidance*

A list of the calcium content of different foods can be found on the link below by the International Osteoporosis Foundation).

- Calcium Rich Food List 3007.pdf (osteoporosis. Foundation)

The national osteoporosis guideline group (NOGG) recommend the following:

- Recommend a healthy, balanced diet, moderation of alcohol consumption and avoidance of smoking.
- Ensure dietary calcium and vitamin D intake and supplement these as necessary.
- Encourage a combination of regular weight-bearing and muscle strengthening exercise.

### *7.5.2 Exercise guide*

Strong, Steady and Straight: Physical Activity and Exercise for Osteoporosis Quick guide: summary (for use in conjunction with full Expert Consensus Statement (Royal Osteoporosis Society)

- ros-strong-steady-straight-quick-guide-february-2019.pdf (theros.org.uk)

- Strong, steady and straight: UK consensus statement on physical activity and exercise for osteoporosis | British Journal of Sports Medicine (bmj.com)

## 7.6 Patient information leaflets –bisphosphonate)

Bisphosphonates-PIL-June-2018.pdf (scot.nhs.uk)

## 7.7 General information on osteoporosis

Information for patients and the public on the Prevention and Treatment of osteoporosis in the NOGG Clinical Guideline. [65]

Royal Osteoporosis Society - Better Bone Health for Everybody (theros.org.uk)

## 7.8 Dental letter: recommendations for patients

A rare side effect of some of the antiresorptive drugs used to manage your prostate cancer may cause osteonecrosis of the jaw (**or Medication Related Osteonecrosis of the Jaw (MRONJ) see 7.3).** This is where an area of bone around teeth /jaw becomes uncovered, which can be painful and become infected.

It is more likely to happen if you have poor dental health or after having a tooth removed. It is important to try to keep your mouth healthy throughout your treatment and maintain good mouth health in the future to minimize the risk of this occurring. **Tooth removal**

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**should be avoided where possible, but if unavoidable, will need careful follow-up by your dentist to ensure that you heal properly and do not require further treatment.**

*Keeping your mouth healthy*

Tooth decay only occurs due to sugar in your diet. The frequency of sugar intake should be limited to mealtimes to help minimise the risk of decay. Snack on sugar free food like cheese or vegetables and only drink water or tea/coffee without sugar between meals.
Tooth wear/erosion can occur from having acidic food and drink. Try to minimise your intake of fizzy drinks, smoothies and fruit juice, and keep them to mealtimes when taken.

Gum disease can occur from the build-up of tARPir and plaque around the edges of the teeth. Risk of this can be minimised by keeping the mouth clean, having regular cleaning at your dentist and avoiding smoking.

*How to keep the mouth clean*

- Brush your teeth twice a day, morning and night, with a fluoride containing toothpaste
- Brush your teeth for 2 – 3 minutes each time
- Use a medium bristled manual or electric toothbrush
- Interdental brushes or floss should be used to clean in between your teeth, where your toothbrush is unable to reach
- Mouthwashes can be used in addition to toothbrushing to minimize the risk of decay and gum disease

*Dental check-ups*

Ideally you should have your teeth checked by a dentist prior to starting your cancer treatment to minimise the risk of you developing a problem during your treatment. Sometimes you may need to start your cancer treatment urgently and should therefore see a dentist as soon as possible to ensure your mouth is healthy during your treatment. **If you do develop a dental problem during your treatment, then you should seek dental intervention urgently.** A sample letter is available within this document for consideration of use by your oncologist to communicate this need with your dentist.

## 8.0 Template Bone Health Management Letters

Letter 1 – Sample template letter to GP – Amber group

Dear Dr [GP's name],

Recommendation of Bone Protection Agents for Patient with Prostate Cancer

[Patient name; NHS number] has a diagnosis of prostate cancer and requires long-term androgen deprivation therapy (ADT). ADT is known to reduce bone mineral density over time. A bone health assessment has been performed to manage the high cumulative risk of secondary osteoporosis and fragility fracture, along with provision of lifestyle advice. We

recommend the following as per The Royal College of Radiologists National Guideline of Bone Health Management in Patients with Prostate Cancer:

Please prescribe bone protection agents including:

a) Weekly bisphosphonate (e.g. Alendronic acid 70mg or risedronate sodium 35mg); AND
b) Calcium and vitamin D3 supplement (e.g. Evacal D3 chewable tablets 1 BD; aiming for daily intake of at least 1000mg elemental calcium and 800 units vitamin D3).

We would be grateful if you could add these to their repeat prescriptions.

A dental check has been advised if there is a history of poor dentition prior to starting bisphosphate therapy. Patient has also been counselled with side effects of bisphosphonate therapy, including oesophagitis and osteonecrosis of the jaw.

In the event of intolerance to ALL types of oral treatment, please contact us to consider alternative route of administration.

Yours sincerely,

**Letter 2 – Sample template letter to GP – Red group**

Dear Dr [GP's name],

Recommendation of Bone Protection Agents for Patient with Prostate Cancer

[Patient name; NHS number] has a diagnosis of prostate cancer and requires long-term androgen deprivation therapy, and a new [additional system anticancer therapy] treatment. They are known to reduce bone mineral density over time. A bone health assessment has been performed to manage the high cumulative risk of secondary osteoporosis and fragility fracture, along with provision of lifestyle advice. We recommend the following as per The Royal College of Radiologists National Guideline of Bone Health Management in Patients with Prostate Cancer:

Please prescribe bone protection agents including:

a) Weekly bisphosphonate (e.g. Alendronic acid 70mg or risedronate sodium 35mg); AND
b) Calcium and vitamin D3 supplement (e.g. Evacal D3 chewable tablets 1 BD; aiming for daily intake of at least 1000mg elemental calcium and 800 units vitamin D3).

We would be grateful if you could add these to their repeat prescriptions.

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A dental check has been advised if there is a history of poor dentition prior to starting bisphosphate therapy. Patient has also been counselled with side effects of bisphosphonate therapy, including oesophagitis and osteonecrosis of the jaw.

In the event of intolerance to ALL types of oral treatment, please contact us to consider alternative route of administration.

Yours sincerely,

**Letter 3: Sample letter to dentist**

Re: Baseline dental assessment for risk of MRONJ

[Insert date]

Dear…,

I would be grateful if you could make arrangements to carry out a dental assessment of [insert patient name] to ensure they are dentally fit prior to starting anti-resorptive treatment as part of the management of their prostate cancer.

- Diagnosis:
- Proposed treatment and start date:
- Medical History:
- Medications:
- Allergies:

[insert patient name] is/is not aware of current dental problems. [Give details of any history of pain/infection from the mouth]. They do not have access to a primary care dental practitioner and due to the risk of them developing osteonecrosis of the jaw as a result of their treatment, I would be grateful if you could provide an urgent assessment to help to minimise this risk.

Thank you for your help with their care.

Yours sincerely,

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**Published July 27, 2017 N Engl J Med 2017;377:338-351 DOI: 10.1056/NEJMoa1702900**
**VOL. 377 NO. 4**

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Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol

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Prof Gerhardt Attard, PhD[a,b] g.attard@ucl.ac.uk · Laura Murphy, PhD[c] · Prof Noel W Clarke, ChM[d] · William Cross, FRCS[e] · Prof Robert J Jones, PhD[f] · Prof Christopher C Parker, MD[g] · et al. Show more

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Download Full Issue
Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design
Prof Karim Fizazi, MD[a] karim.fizazi@gustaveroussy.fr · Stéphanie Foulon, MD[b,c] · Prof Joan C arles, MD[e] · Guilhem Roubaud, MD[f] · Prof Ray McDermott, MD[g] · Aude Fléchon, MD[h] · et al. Show more

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## Section 9 : Glossary of Terms and Abbreviations

**A**

- **ADT (Androgen Deprivation Therapy)** – A hormone based treatment that reduces androgen levels to slow or stop the growth of prostate cancer.
- **AHP (Allied Health Professionals)** – Healthcare workers such as pharmacists or physiotherapists (not doctors or dentists), who provide system-wide care across a variety of healthcare and social settings.
- **Androgen** - a steroid hormone. For the purposes of this guideline, the us of androgen will refer specifically to Testosterone.
- **Androgen Receptor** – Proteins found on the external cell surface which bind testosterone. Once activated these receptors promote down-stream signalling essential for cell growth and survival. Prostate cancer cells are often dependent on androgens and are a common target in its treatment.
- **ARPI (androgen receptor pathway inhibitor)**
- **ARSI (Androgen Receptor Signalling Inhibitor)** – A class of drugs that block androgen receptors and prevent testosterone bonding. ARSIs disrupt signalling pathways which would otherwise promote cell growth and survival.
- **ARTA (Androgen Receptor Targeted Agent)** – Drugs that interfere with androgen receptor activation, inhibiting cell growth and survival. Examples include Enzalutamide or Darolutamide.

**B**

- **BMA (Bone Modifying Agent)** – Medications such as bisphosphonates and denosumab that alter normal bone metabolism to help protect bone health.
- **BMD (Bone Mineral Density)** – A measure of bone strength often helpful in assessing osteoporosis risk.
- **BPAs (Bone Protection Agents)** – A term referring to drugs that prevent bone loss in prostate cancer patients undergoing treatment. Examples include bisphosphonates and denosumab
- **Bisphosphonates** – A class of drugs that slow bone breakdown and reduce the risk of fractures or conditions like osteoporosis. Bisphosphonates work by reducing the activity of osteoclasts, cells responsible for the breakdown, or resorption of bone.

**C**

- **CRPC (Castration-Resistant Prostate Cancer)** – A form of prostate cancer that continues to progress despite low testosterone levels.

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- **CFS (Clinical Frailty Scale)** – A tool used to assess a patient's frailty level and risk of falls.
- **COPD (Chronic Obstructive Pulmonary Disease)** – A lung disease that may be a comorbidity in prostate cancer patients.

**D**

- **DEXA (Dual-Energy X-ray Absorptiometry)** – A scan used to measure bone mineral density, useful in assessing conditions such as osteoporosis and assessing risk of fragility fracture.
- **Denosumab** – A targeted drug (monoclonal antibody) treatment used to prevent bone loss and fractures in patients receiving hormone therapy.

**F**

- **FFR (Fragility Fracture Risk)** – A scoring system to assess the likelihood of a fracture due to weakened bones.
- **FRAX (Fracture Risk Assessment Tool)** – A tool used to estimate the 10-year probability of a major osteoporotic fracture.

**G**

- **GP (General Practitioner)** – A primary care physician responsible for managing general health and referrals.
- **Glucocorticoids** – A type of steroid medication that can contribute to bone loss when used long-term.

**H**

- **HSPC (Hormone-Sensitive Prostate Cancer)** – Prostate cancer that responds to hormone therapy.

**L**

- **LHRHa (Luteinizing Hormone-Releasing Hormone Agonist)** – A drug that works on the pituitary gland to reduce testosterone levels, commonly prescribed in the prostate cancer treatment.

**M**

- **mCRPC (Metastatic Castration-Resistant Prostate Cancer)** – A stage of prostate cancer that has spread beyond the prostate and does not respond to hormonal therapy.

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- **mHSPC (Metastatic Hormone-Sensitive Prostate Cancer)** – Prostate cancer that has spread beyond the prostate but still responds to hormone therapy.
- **MRONJ (Medication-Related Osteonecrosis of the Jaw)** – A rare but serious condition of the jawbone related to medication use and often characterised by pain, swelling or poor healing.
- **Metastasis** – The spread of cancer beyond the prostate to effect other parts of the body, such as bones.

**N**

- **NICE (National Institute for Health and Care Excellence)** – A UK body that provides guidelines for healthcare treatment and management.
- **NOGG (National Osteoporosis Guideline Group)** – A UK-based organization providing recommendations for osteoporosis prevention and management.

**O**

- **Osteoporosis** – A condition that weakens bones, making them more prone to fractures, often without other noticeable symptoms. For patients who receive DXA imaging osteoporosis is defined by a T-score of < -2.5. T-scores compare a patient's bone mineral density to that of a healthy young adult.
- **Osteopenia** – A condition where bone mineral density is lower than average, but not sufficient to be classified as osteoporosis or to significantly increase your risk of fracture. For patients who have received DXA imaging Osteopenia is described as a T-score between -1 and -2.5.

**P**

- **Prednisolone** – A corticosteroid often prescribed alongside prostate cancer treatments or to manage treatment side effects.

**R**

- **Radium 223** – A radiopharmaceutical used to treat bone metastases in prostate cancer.
- **Rebound Bone Resorption** – A condition where bone density rapidly declines after stopping certain osteoporosis treatments, such as denosumab.
- **RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand)** – A protein involved in bone metabolism, targeted by drugs like denosumab.

**S**

- **SACT (Systemic Anti-Cancer Therapy)** – Treatments such as chemotherapy or targeted therapy used to treat cancer throughout the body.

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- **SRE (Skeletal-Related Event)** – A complication such as a fracture, spinal cord compression, or bone pain caused by bone metastases.

**T**

- **Traffic Light System** – A risk stratification method categorizing patients into low (green), moderate (amber), and high (red) risk for bone fractures.

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