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Bone health management in the continuum of prostate cancer disease: a review of the evidence with an expert panel opinion

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ABSTRACT

Bone health impairment is a frequent detrimental consequence of the high bone tropism of prostate cancer (PCa) cells. It is further worsened by administration of androgen-deprivation therapy (ADT), the current standard of care in the management of advanced PCa, through a rapid and dramatic increase in bone turnover and body mass changes. As a result, patients may experience substantial pain and poor quality of life (QoL) and have an increased risk of death. Notwithstanding the importance of this issue, however, bone health preservation is not yet a widespread clinical goal in daily practice.

To address this urgent unmet need, following a thorough discussion of available data and sharing of their clinical practice experience, a panel of Italian experts in the field of bone health and metabolism formulated a number of practical advices for optimising the monitoring and treatment of bone health in men undergoing ADT during all phases of the disease. The rationale behind the venture was to raise awareness on the importance of bone preservation in this complex setting, while providing an instrument to support physicians and facilitate the management of bone health.

Current evidence regarding the effects on bone health of ADT, of novel hormone therapies (which improve progression delay, pain control and QoL while consistently carrying the risk of non-pathological fractures in both non-metastatic and metastatic PCa) and of bone turnover inhibitors (whose use is frequently suboptimal) is reviewed. Finally, the expert opinion to optimise bone health preservation is given.

INTRODUCTION

Prostate cancer (PCa) remains the most frequent male cancer in Italy (1 in 9 men; 19% of all cancer diagnoses), with 37 000 new cases estimated in 2019, and represents the third leading cause of death in the population, the mortality rate being 2.4% among those diagnosed with PCa.[1] However, registry data indicate that incidence is decreasing and survival improving, with a 5-year survival rate of 92% and a 10-year survival rate of 90%.[1]

Advanced PCa exhibits a high bone tropism, which is responsible for the skeletal involvement observed in up to 90% of the cases.[2] For this reason, bone must be a target of clinical management throughout the course of the disease.

Androgen-deprivation therapy (ADT) represents a standard of care in the management of advanced PCa.[3] Despite the potential benefits associated to its use, however, ADT causes a number of side effects, including a detrimental effect on bone health[4–7]; this is even more concerning considering the longer life expectancy achieved in these patients, and the possible changes on the bone fostered also by ageing and comorbidities. Due to the sequelae of bone health impairment on the individual's quality of life (QoL) and health status, together with the considerable burden imposed on healthcare resources, preserving bone health in PCa men on ADT must be a clinical goal across the disease continuum. Notwithstanding the importance of this issue, however, several aspects of bone health are not yet supported by strong evidence. Consequently, they are not completely accounted for in many important international guidelines.[8]

Here, the available evidence on bone health during ADT and the effects of novel hormone therapies (NHTs) and bone turnover inhibitors (BTTs) on the bone are reviewed; in addition, the advices of a panel of Italian experts are provided to optimise bone health monitoring and treatment in advanced PCa.

BONE HEALTH DURING ADT

Effects of ADT on bone loss and fragility

In patients with PCa, bone health is frequently suboptimal already before commencing ADT: indeed, the prevalence of osteoporosis/osteopenia among ADT-naive patients ranges between 35% and 58%, with similar rates between localised and disseminated disease; still, this condition remains undiagnosed in

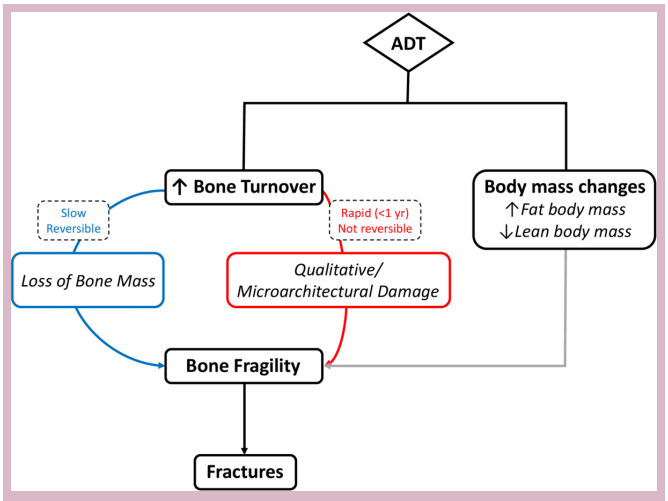

Figure 1 ADT-induced bone impairment. ADT augments bone fragility, and thus the risk of fracture, through two mechanisms: (1) bone turnover increase, which leads to bone mass loss via a slow, reversible process, and to qualitative/microarchitectural alterations via a rapid, non-reversible mechanism; (2) body mass changes, namely increased fat body mass and decreased lean body mass. ADT, androgen-deprivation therapy.

the majority of cases,[9] and approximately 30% of patients displaying ≥1 grade-2 fracture before starting ADT have normal bone mineral density (BMD).[10] Moreover, PCa itself is associated to a high risk of fractures (OR (95% CI) for all fractures: 1.8 (1.6 to 2.1) in PCa vs age-matched control men), which is further increased by the use of ADT (OR 1.7 (1.2 to 2.5), p<0.01).[11]

In men, bone remodelling and microstructure are directly affected by testosterone (T) levels, whereas the development and maintenance of the skeleton are predominantly regulated by estradiol (E2), acting as the main inhibitor of bone resorption. By reducing serum T levels to a castration range of values (<5% of the normal range) and serum E2 levels to <20% of the normal range,[12] ADT causes a rapid and dramatic increase of bone turnover that results in bone loss (generally slow and reversible) and in qualitative/microarchitectural damage (often rapid and not reversible)[13] (figure 1, left). Accordingly, the rate of bone loss recorded immediately after the start of ADT is 4%–4.6% per year, higher than the normal rate of approximately 0.5%–2% per year.[14–16] Of interest, among the ADT regimens tested, addition of bicalutamide to gonadotropin-releasing hormone (GnRH) agonists did not worsen BMD loss compared with GnRH agonists alone.[17]

Both mechanisms (ie, bone loss and qualitative/microarchitectural damage) increase bone fragility that may ultimately cause fractures.[7 13 18–21] A large population-based study demonstrated that, of men surviving at least 5 years after diagnosis, a significantly higher proportion of those treated with ADT versus without experienced a fracture (19.4% vs 12.6%, p<0.001), and the fracture risk increased with the number of ADT doses administered during the first year after diagnosis.[20] In this regard, however, it is worth noting that the use of intermittent versus continuous ADT in older men did not yield a significant reduction in bone events (26% vs 31%, respectively, p=0.15).[22 23]

In men affected by PCa on ADT, similarly to women with breast cancer treated with aromatase inhibitors (AIs), fractures (especially vertebral[21]) typically occur during the first year of therapy[19 20 24 25] as a consequence of the rapid qualitative damage determined by elevated bone turnover. Other risk factors for fractures are older age, a history of fracture, osteoporosis and the rate of bone loss during treatment.[26 27] Yet, it must be pointed out that the risk of fracture is often independent of BMD[13] and it is frequently misclassified when based only on dual-energy X-ray absorptiometry (DEXA) measurements (see section 5)[18 28]; this observation reinforces the fact that skeletal fragility is prominently dependent on the poor quality of bone microarchitecture rather than on the low bone mass.

In patients with PCa with bone disease (both hormone-sensitive *PCa* (HSPC) and *castration-resistant PCa* (CRPC)), the rate of pathological fractures ranges between 5% and 48%.[29–32] They are associated with increased risk of QoL impairment and death in men with malignant bone disease.[33 34] Regardless of the setting (HS or CR), however, men with metastatic (M1) disease may also experience fractures in non-metastatic sites as a consequence of long-term ADT: yet, since these fractures can be asymptomatic,[30] they are often overlooked and underdiagnosed. Furthermore, bone fragility may predispose patients with bone metastases to skeletal-related events (SREs). Therefore, preventing fragility fractures is an important goal also in patients with bone metastases considered at risk for skeletal complications. In this regard, it is likely that bone health is more preserved in men with M1 CRPC and bone metastases compared with those with non-metastatic (M0) PCa, due to the frequent concomitant administration of BTTs, which may protect also from fragility fractures (see section 4).

Besides the quantitative and qualitative alterations of bone that increase the fracture risk, ADT is associated with consistent changes in body composition, namely increased fat body mass and decreased lean body mass,[35 36] that may impair bone health (figure 1, right). Indeed, obesity may negatively affect bone quality via several mechanisms, including alteration of bone-regulating hormones, increased oxidative stress and inflammation. In healthy subjects, the negative effect of adiposity on bone health is blunted by the higher oestrogen levels (due to enhanced aromatase activity) that increase BMD (the so-called 'obesity paradox'). Obese men on ADT may be at higher risk of bone fractures because of the loss of the protection associated with oestrogens and to the detrimental changes in bone quality associated with adiposity. In a large single institution cross-sectional study recently published,[37] fat body mass assessed by DEXA scan had a protective effect on morphometric vertebral fractures in

patients with breast cancer not undergoing AIs, whereas it was associated with an increased risk of fragility fractures in women on AIs. Evidence supports the obesity paradox even in advanced PCa,[38] where early increase in fat body mass has recently been shown to predict a higher risk of SRE (HR 3.024, 95% CI 1.004 to 10.353, p<0.02), a higher risk of death (HR 2.373, 95% CI 1.012 to 5.567, p=0.04) and a non-significant higher risk of disease recurrence (HR 2.219, 95% CI 0.956 to 5.150, p=0.13).[39] As for ADT-associated sarcopenia,[40] it further increases the risk of fractures through falls and directs effects on the skeleton geometry and microstructure. When decreased muscle mass, strength and function occur concomitantly to BMD reduction, osteosarcopenia is diagnosed.[40]

In clinical practice, since bone fragility may be present already before the start of ADT and throughout the disease continuum, close attention should be paid to bone health. The early onset of fractures should be taken into account when managing the fracture risk and treatment timing. Moreover, it is important to plan strategies to prevent, assess and treat both osteoporosis and sarcopenia, to reduce the associated risk of falls, fractures and consequent disability.[40]

Skeletal effects of ADT

SREs (ie, pathological fractures, radiotherapy to bone, bone surgery and spinal cord compression) are associated with worse outcomes, including increased pain, poorer QoL, morbidity and shorter survival, and may occur throughout the entire course of the disease.

Fragility fractures are associated to increased mortality both in the general population[41] and in patients with PCa on ADT.[6 42–44] Van Hemelrijck *et al* demonstrated that men with a hip fracture were 2.4 times more likely to die than the control cohort of all PCa men (95% CI 2.29 to 2.60), and the risk was higher especially in the first month after the fracture (HR 5.64 (95% CI 4.16 to 7.48)).[45] In another study, men who developed a fracture within 48 months of cancer diagnosis had a significantly lower survival than men who did not (log-rank test: p<0.001), and the mortality risk increased by 40% after experiencing a fracture.[42] Moreover, ADT has been associated with a significantly increased risk of any fracture and hip fracture requiring hospitalisation: the excess risk was partly driven by pathological fractures and spinal cord compression, which are associated with decreased survival in ADT users.[6]

In clinical practice, accounting for patient risk before prescribing ADT for long-term use together with the close monitoring of bone health during ADT may reduce the risk of fracture and improve QoL and survival.[6 42]

BONE HEALTH DURING NHT

As already mentioned, the propensity of PCa cells to metastasise to the bone increases the risk of SREs, which, in turn, increase mortality and substantial pain, and reduce patient QoL.

Table 1 New hormone therapies currently approved by EMA in the different settings of PCA

Drug	Setting	Phase III trial	Year of EMA approval
M0 disease			
Enza	CRPC at high risk of metastases*	PROSPER[48]	2018
Apa	CRPC at high risk of metastases*	SPARTAN[49]	2019
M1 disease			
AAP	Post-CT CRPC	COU-AA-301[99]	2011
AAP	CT-naive CRPC	COU-AA-302[67]	2012
AAP	Newly diagnosed high-risk HSPC	LATITUDE[57 58]	2017
Enza	Post-CT CRPC	AFFIRM[59]	2012
Enza	CT-naive CRPC	PREVAIL[60]	2014

*Baseline PSA level of 2 ng per millilitre or greater, and a PSA doubling time of 10 months or less.
AAP, abiraterone acetate plus prednisone; Apa, apalutamide; CRPC, castration-resistant prostate cancer; CT, chemotherapy; EMA, European Medicines Agency; Enza, enzalutamide; HSPC, hormone-sensitive prostate cancer; M0, non-metastatic; M1, metastatic; PSA, prostate-specific antigen.

In the last decade, NHTs have been approved for the treatment of advanced PCa based on the survival benefit demonstrated in pivotal phase III randomised controlled trials (RCTs). Table 1 summarises the agents currently available in Europe. Moreover, the European Medicines Agency has recently received a marketing authorisation application for the selective AR antagonist darolutamide.[46 47]

Registration trials included bone-related efficacy endpoints, namely radiographic progression-free survival (rPFS) or metastasis-free survival (MFS), time to first skeletal-related event (tSRE), pain control and QoL deterioration, and the rate of non-pathological fractures for safety. In particular, MFS has been used as primary endpoint in alternative to overall survival (OS) in recent trials conducted in the setting of CRPC without overt metastatic disease detected by instrumental staging.[48–50] Indeed, in some diseases and treatment settings in which patients have a long life expectancy, post-progression survival (PPS) increases and, consequently, the likelihood that an advantage in terms of progression-free survival (PFS) translates into a significant prolongation of OS (defined as the sum of PFS and PPS) over an acceptable time frame decreases substantially.[51] Therefore, in practice, the use of surrogate endpoints may overcome the need for a much larger sample size and longer follow-up (thus expediting trial completion), as well as the 'dilution' effect determined by subsequent post-progression treatments that may confound the measurement of OS. Notably, a high correlation between MFS and OS has been demonstrated both at trial and patient level in a meta-analysis based on individual patient data from 12 712 men

Table 2 Bone-related efficacy endpoints

Drug	Trial	Endpoint	NHT vs placebo
M0 CRPC at high risk for metastases			
Enzalutamide	PROSPER[48]	MFS PROs	36.3 vs 14.7 months (HR for metastasis or death 0.29, 95% CI 0.24 to 0.35, p<0.001) Similar clinically meaningful deterioration of HRQoL
Apalutamide	SPARTAN[49 56]	MFS PFS2 Median time to symptomatic progression PROs	40.5 vs 16.2 months (HR for metastasis or death 0.28, 95% CI 0.23 to 0.35, p<0.001) 55.6 vs 43.8 months (HR 0.55, 95% CI 0.45 to 0.68, p<0.0001) NR vs NR (HR 0.45, 95% CI 0.32 to 0.63, p<0.001) Stable overall HRQoL over time, similar between groups
Darolutamide	ARAMIS[46]	Median MFS	40.4 vs 18.4 months (HR for metastasis or death 0.41, 95% CI 0.34 to 0.50, p<0.001)
		Median time to pain progression	40.3 vs 25.4 months (HR 0.65, 95% CI 0.53 to 0.79, p<0.001)
		Median time to first symptomatic SRE	NR in either group (16 vs 18 events, HR 0.43, 95% CI 0.22 to 0.84, p=0.01)
M1 HSPC			
AAP	LATITUDE[57 58 61 62 100]	Median rPFS Median time until pain progression Median time to next symptomatic skeletal events PROs	33.0 vs 14.8 months (HR 0.47, 95% CI 0.39 to 0.55, p<0.001) 47.4 vs 16.6 months (HR 0.72, 95% CI 0.61 to 0.86, p=0.0002) NR vs NR (HR 0.75, 95% CI 0.60 to 0.95, p=0.0181) Clinical benefit in pain progression, PCa symptoms, fatigue, functional decline and overall HRQoL
Apalutamide	TITAN[101]	Median rPFS 2-year OS rate	NR vs 22.1 months (HR 0.48, 95% CI 0.39 to 0.60, p<0.0001) 82% vs 73%
M1 CRPC			
AAP	COU-AA-301[99 102]	Median rPFS Median time to the first SRE Pain	5.6 vs 3.6 months (HR 0.67, 95% CI 0.58 to 0.78, p<0.001) 25.0 vs 20.3 months (HR 0.62, 95% CI 0.48 to 0.80, p=0.0001) Significant improvement in pain relief and delay of pain progression
AAP	COU-AA-302[67 103 104]	Median rPFS Median time to opiate use for cancer-related pain PROs	16.5 vs 8.2 months (HR 0.52, 95% CI 0.45 to 0.61, p<0.0001) NR vs 23.7 months (HR 0.71, 95% CI 0.59 to 0.85, p=0.0002) Consistent pattern of delays in pain progression and significant delayed degradation in FACT-P total scores (p=0.005)
Enzalutamide	AFFIRM[59]	rPFS Time to the first SRE QoL response rate	8.3 vs 2.9 months (HR 0.40, 95% CI 0.35 to 0.47, p<0.001) 16.7 vs 13.3 months (HR 0.69, 95% CI 0.57 to 0.84, p<0.001) 43% vs 18%, p<0.001
Enzalutamide	PREVAIL[60]	Median rPFS First SRE occurrence Median time to QoL deterioration	NR vs 3.9 months (HR 0.19, 95% CI 0.15 to 0.23, p<0.001) 32% vs 37% at 31 months, (HR 0.72, p<0.001) 11.3 vs 5.6 months (HR 0.63, 95% CI 0.54 to 0.73, p<0.001)

AAP, abiraterone acetate plus prednisone; CRPC, castration-resistant prostate cancer; FACT-P, Functional Assessment of Cancer Therapy–Prostate; HRQoL, health-related quality of life; HSPC, hormone-sensitive prostate cancer; M0, non-metastatic; M1, metastatic; MFS, metastasis-free survival; NHT, novel hormone therapy; NR, not reached; OS, overall survival; PCa, prostate cancer; PFS2, progression-free survival on next-line therapy; PRO, patient-reported outcome; QoL, quality of life; rPFS, radiographic progression-free survival; SRE, skeletal-related event.

included in 19 studies.[52] However, as acknowledged also by the Food and Drug Administration (FDA), the benefit yielded by alternative endpoints must go beyond statistical significance and be clinically meaningful.[53] In the case of MFS, for example, the magnitude of the benefit provided by denosumab (DNB) was not deemed as valid for FDA approval of a new indication,[50 54] while it was in the case of apalutamide and enzalutamide: in these cases, in fact, median MFS was dramatically higher than the few-month difference yielded by DNB in the same clinical setting (table 2).[48 49] However, some caution must be taken when interpreting MFS results, as occurrence of a bone metastasis (the main contributor to MFS in PCa) per se is not always a clinically meaningful event.[55] Due to the psychological implications of being diagnosed with metastatic disease, it is important to use patient-reported outcomes to match the instrumental data of MFS with the actual benefit in terms of both the delay of time to symptom worsening and global QoL. It is worth noting that in the most recent trials on PCa, the advantage in

MFS is well supported by evidence of clinical benefit in terms of improvement in PFS on next-line therapy (PFS2),[49 56] symptom delay and pain progression[46 49] and QoL.[48 49 57–63]

Hereinafter, the main clinical trial results are summarised, together with the real-world evidence available.

Bone-related efficacy endpoints during NHT

In all, the available data demonstrate that patients with CRPC or with M1 HSPC and overt bone disease may benefit from the use of NHT as for progression delay, pain control and QoL improvement (table 2). With regard to the combined use of radiopharmaceuticals and NHT, caution must be taken, as demonstrated by the recent ERA 223 study in which men with chemotherapy (CT)-naive asymptomatic or mildly symptomatic M1 CRPC treated with abiraterone acetate plus prednisone/prednisolone had a median symptomatic skeletal event-free survival of 26.0 months (95% CI 21.8 to 28.3).[30] However, adding the bone-seeking calcium mimetic radium 223 (Rad-223) increased fractures (29% vs 11%) and deaths (39% vs 36%), while it did not improve skeletal event-free survival (22.3 months (95% CI 20.4 to 24.8)), so that the combination is not recommended.[30]

In the setting of M1 CRPC, no direct comparison exists between abiraterone and enzalutamide; yet, a recent meta-analysis of registration trials demonstrated no significant difference in terms of rPFS and of tSRE.[64] In the real-world setting, a retrospective study on 1516 M1 CRPC men reported that those who had initiated on abiraterone acetate first had better SRE outcomes than those who had initiated on enzalutamide, who had a higher incidence rate (1.86 with enzalutamide vs 1.47 with abiraterone acetate; incidence rate ratio 1.27, p=0.044) and a higher hazard of SREs (HR 1.34 (95% CI 1.06 to 1.69); p=0.015).[65] The effectiveness of abiraterone acetate plus prednisone was investigated in the large Italian multicentre, prospective observational study ABITUDE[66]: in patients with CT-naive M1 CRPC, the 1-year probability of no radiographic progression was 73.9%, and a reduction in pain intensity and worst pain perception together with improvement in daily activity interference was observed, in line with the findings from COU-AA-302.[67]

As for the effects of NHT on the levels of bone biomarkers, few data are available and are mostly limited to abiraterone acetate. Treatment with this agent plus prednisone significantly reduced the levels of serum C-terminal cross-linked telopeptide of type I collagen (CTX) and bone-specific alkaline phosphatase (BALP) after 6 and 12 months from the start of therapy, likely because of the decrease of bone turnover activity and of bone tumour burden, respectively (unpublished data from ABITUDE). It is worth noting that preclinical data have suggested a direct effect of abiraterone acetate on bone microenvironment: indeed, in an in vitro model of human primary osteoclasts (OCLs)/osteoblasts (OBLs), non-cytotoxic doses of abiraterone acetate inhibited OCL differentiation and activity and stimulated OBL differentiation and bone matrix deposition.[68]

Bone safety of NHT: rate of non-pathological fractures

Despite the clinical benefit provided by NHT, evaluation of bone health in terms of non-pathological fracture rate in both M0 and M1 settings has unveiled that these consistently represent a common adverse event during treatment with all drugs tested. The rates recorded in the phase III trials are presented in table 3.

Overall, results from SPARTAN[49] and PROSPER suggest that treatment with new-generation HT further increases the fracture risk in men with M0 CRPC receiving long-term ADT. The rate of non-pathological fractures was higher on NHT, compared with placebo, also in men with M1 CRPC in both pre-CT and post-CT settings. Although the mechanisms causing non-pathological fractures remain unclear, it is possible that a more potent inhibition of testosterone activity may enhance bone turnover, ultimately causing fragility. It is also possible that patients receiving NHT were exposed to prolonged treatment, and therefore observed for a longer period compared with those given placebo.

EFFECTS OF DIFFERENT BONE TURNOVER INHIBITORS

Cancer treatment–induced bone loss (CTIBL) is generally more rapid and severe than bone loss associated with ageing in men and women or menopause.[15] Among the agents tested for their ability to attenuate CTIBL in patients with PCa, there are oral (alendronate and risedronate) or intravenous (pamidronate and zoledronic acid (ZA)) bisphosphonates (BPs) and DNB.

M0 HS disease

In the setting of M0 HS disease on ADT, all BTTs at all schedules and doses used were able to prevent bone loss and/or improve BMD compared with placebo.[69–74] However, whether this translates into reduced fractures remains unclear, as no RCTs were designed with fracture risk reduction as primary endpoint. Furthermore, the majority of RCTs include a relatively small number of patients and short follow-up periods, underpowered to detect evidence of any fracture reduction.[75–77] The only agent that demonstrated effective in reducing the incidence of new vertebral fractures is DNB (1.5% vs 3.9% with placebo at 36 months; RR 0.38, 95% CI 0.19 to 0.78; p=0.006), in a large RCT where this was a secondary endpoint.[25] Therefore, more trials are needed in this population to evaluate the effects of BTTs on fracture outcomes as well as on other outcomes relevant to patients, such as QoL, pain and disability.[69 75]

M1 HSPC disease

In men with M1 HSPC and bone metastases, early treatment with ZA in the CALGB 90202 study yielded no benefit, compared with placebo, in terms of time to first SRE and OS.[78] In the same setting, no benefit with regard to the time of treatment failure, tSRE and OS was

Table 3 Rate of non-pathological fractures in phase III trials of NHT by setting, grade (all and 3–4) and treatment arm (NHT vs placebo)

	Non-pathological fractures			
	All grade (%)		Grades 3–4 (%)	
Trial	NHT	Placebo	NHT	Placebo
M0 CRPC				
SPARTAN (Apa, n=806; placebo, n=401)[49]	11.7	6.5	2.7	0.8
PROSPER (Enza, n=933; placebo, n=468)[105]	11.0	4.1	1.3	0.6
M1 CRPC				
Post-CT				
COU-AA-301 (AAP, n=791; placebo, n=394)[106]	5.9	2.3	1.4	0.0
AFFIRM (Enza, n=800; placebo, n=399)[105]	4.0	0.8	1.4	0.3
Pre-CT				
PREVAIL (Enza, n=871; placebo, n=844)[105]	8.8	3.0	2.1	1.1
EORTC 1333/PEACE III (Enza+Rad-223, n=38; Enza, n=38)[82]	*12.4			
ERA-223 (AAP+Rad-223, n=401; vs AAP+placebo, n=405)[30]†	11			

Only currently approved agents are reported.
*IThe rate reported refers to the 1-year cumulative incidence of non-pathological fractures in the Enza arm.
†The rate reported refers to the rate of non-pathological fracures in the AAP+placebo arm.
AAP, abiraterone acetate plus prednisone; Apa, apalutamide; M0 CRPC, non-metastatic castration-resistant prostate cancer; M1 CRPC, metastatic castration-resistant prostate cancer; CT, chemotherapy; Enza, enzalutamide; NHT, novel hormone therapy.

provided by ZA in the ZAPCA trial, except for a significant delay of treatment failure in patients with baseline prostate-specific antigen <200 ng/mL.[79] Accordingly, current guidelines do not recommend the use of ZA or DNB in patients with M1 HSPC.[3 80] As ZA 4 mg monthly is no more suggested in SRE prevention in M1 HSPC and DNB 120 mg monthly has not been studied, it is likely that these patients, who are exposed to the risk of CTIBL at a similar or higher extent than those with M0 disease, do not receive any protection from fragility fracture risk.

M1 CRPC disease

As for patients with M1 CRPC and bone metastases, a post hoc analysis of the COU-AA-302 trial demonstrated that, in CT-naive men, the concomitant use of BTTs, compared with no BTT use, further increased the clinical advantage observed on abiraterone acetate plus prednisone compared with prednisone alone in terms of OS, time to ECOG deterioration and time to opiate use for cancer-related pain.[81] Moreover, the recent ERA-223 trial demonstrated that, in patients with CT-naive asymptomatic or paucisymptomatic M1 CRPC on abiraterone acetate plus prednisone/prednisolone and randomised to receive Rad-223 or placebo, the use of BPs or DNB halved the number of patients with osteoporotic fractures in both arms (from 37% in the Rad-223 arm and 15% in the placebo arm without BTTs, to 15% and 7%, respectively, with BTTs).[30] Similarly, early data from the EORTC 1333/PEACE III trial comparing enzalutamide and Rad-223 versus enzalutamide alone show that the risk of fractures is very well controlled in both arms, the cumulative 1-year risk of fracture being 37.4% and 12.4%, respectively, without BTTs, and 0% in both arms with BTTs.[82]

Moreover, in patients with M1 CRPC with bone metastases, ZA proved inferior to DNB in delaying occurrence of the first SRE,[83] and it ameliorated PFS, skeletal pain and SRE only in men with a Gleason score ≥8.[84] Yet, in the setting of M1 disease, no other data on prevention of fragility fractures are available, and those regarding prevention of BMD loss and the effects on pathological fractures versus fragility fractures among SREs are completely lacking.

In clinical practice, all patients with M1 CRPC and bone metastases should be given supportive treatment to preserve bone health. Yet, data regarding the real-world patterns of use of BTTs in subjects with bone metastases have unveiled that there is a considerable proportion of patients who do not receive adequate treatment to prevent SREs or manage pain. For example, in the Italian observational study ABITUDE, only approximately 14% of patients were given ZA.[66] Moreover, a recent multinational European study reported that 26% of patients with bone metastases did not receive a bone-targeting agent (BTA), and only 53% received treatment within 3 months of bone metastasis (BM) diagnosis.[85] Interestingly, oncologists more than urologists prescribed BTAs (78% vs 60%) and initiated treatment within 3 months of BM diagnosis (56% vs 43%). Bone pain was common and undertreated, as demonstrated by the fact that although most patients with BMs (97%) were on analgesics, with 30% receiving strong opioids, 70% were experiencing bone pain, which was moderate to severe in 28%.[85] In another recent retrospective study of 2559 men with M1 CRPC, overall, 34% of patients did not use bone health agents at any time. Notably, DNB was used more frequently than ZA (48%

vs 24%, respectively[86]); 58.2% vs 41.8% in another study including 3816 men with PCa and bone metastases.[87]

Altogether, these data suggest that awareness must be raised on the importance of using BTTs in the management of patients with M1 CRPC to improve care.[85] Importantly, to avoid underuse or misuse, BTTs should be employed in selected cases taking into consideration that the effects on bone fragility (ie, prevention) and SRE prevention in metastatic disease depend on the dose given.

OPTIMISING BONE HEALTH MANAGEMENT: AN EXPERT OPINION

Bone health preservation throughout the continuum of PCa disease represents a prerequisite for acceptable QoL and optimal disease outcome. However, in clinical practice, this is not yet a widespread clinical goal.[8]

With this in mind, in April 2019, a panel of Italian experts (all authors of the present document) in the field of bone health and metabolism at the national and international level gathered in an advisory board meeting to address this urgent unmet need. The rationale behind the venture was to raise awareness on the importance of bone preservation in this complex setting while providing an instrument to support physicians and facilitate the management of bone heath. Following a thorough discussion of available data and sharing of their clinical practice experience, the experts formulated a number of advices for optimising the monitoring and treatment of patients with PCa on ADT to preserve bone health. Importantly, bone health preservation was addressed in all the phases of the disease, that is, M0 HSPC, M0 CRPC, M1 HSCP and M1 CRPC. The opinions for which the experts reached a 100% agreement are reported hereinafter and the advices are summarised in tables 4 and 5. As they pointed out, the implementation of the experts' suggestions depends on the reimbursement policy adopted by each country.

In general, the experts advise, whenever possible and regardless of the setting, to evaluate bone health in a multidisciplinary context including other 'bone specialists' (rheumatologists, endocrinologists, geriatrics, orthopaedics) besides oncologists, radiotherapists and urologists. Importantly, the collaboration with a 'bone specialist' does not spare oncologists and urologists from monitoring and treating bone health.

Monitoring of bone health

Androgen and oestrogen deprivation increase bone loss, which is currently measured by BMD through DEXA scan. Indeed, BMD is considered a valid surrogate parameter of fracture risk in osteoporotic but otherwise healthy women and men, and current guidelines recommend the use of BMD as a parameter in the assessment of fracture risk among men on ADT and early breast cancer women on aromatase inhibitor therapy. In particular, international guidelines recommend that patients with PCa eligible for ADT should undergo basal and follow-up evaluation of BMD, as well as assessment of the 10-year fracture risk through the FRAX score. The latter takes into consideration the following risk factors, besides BMD: age, sex, weight, height, previous fracture, parent fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis and alcohol (≥3 units/day). Moreover, many guidelines have adopted a DEXA T-score threshold <−2.5 for treatment.[15 76 88–90] It should be noted, however, that in patients with PCa undergoing ADT, the increased risk of fracture is often independent of BMD[13] and, as fractures occur even with BMD T-score ranging between normal to osteopenic values, calculating the fracture risk based only on DEXA measurements can be misleading.[18 28] Therefore, it is not surprising that the FRAX algorithm[91] for fracture risk prediction underestimates the risk in patients with PCa on ADT when BMD is used, and it performs better when used without imputing BMD. Recently, a dedicated algorithm for the assessment of bone microarchitecture at the lumbar spine (LS), the trabecular bone score (TBS), has been introduced. TBS is a textural index based on the evaluation of the pixel grey-level variations in the LS DEXA image, and, thus, represents an indirect index of bone architecture that can assess bone quality and provide information about the fracture risk independently of BMD.[92] Therefore, TBS seems to be a better measure of bone fragility in individuals who are obese/overweight, and useful in assessing the osteoporotic fracture risk, with lower TBS values associated to a higher risk. Also, it could be suitable to improve the fracture risk definition in patients with CTIBL and could be usefully combined with FRAX and BMD to optimise the identification of patients with breast cancer and elevated risk.[93] However, it has not been validated in PCa, and, therefore, no recommendation for its routine use can be made. Finally, the experts underlined that, in case of metastatic HS disease, no study has demonstrated the efficacy of DNB and BTT in pathological SRE reduction. For this reason, in the setting of M1 HS disease, the goal of bone health preservation (bone fragility protection) can be achieved using the same strategy as in M0 HS disease.

In light of these data, the experts formulated the following advices, valid regardless of the setting and hormonal therapy:

- The use of the WHO risk assessment tool FRAX[91] as the most frequently used tool in clinical practice to evaluate the 10-year probability of osteoporotic fractures is discouraged, as it was not specifically designed for men receiving ADT and, indeed, it does not account for important clinical factors unique for this vulnerable population (eg, hormonal therapy); besides, it does not allow an adequate risk stratification.[90] The FRAX score should integrate the following.
- Evaluate the following independent factors of fracture risk:
  - BMD.
  - Familiarity for fragility fractures.
  - Corticosteroid therapy (>5 mg/prednisone equivalent in the past for more than 3 months consecutively or ongoing).

- Metabolic bone diseases or fragilising disease/treatment.
- Disability or high risk of fall.
- Age.
- Anamnesis for low-energy trauma fractures.

Non-metastatic disease

- Early management of bone health is mandatory from the start of hormonal therapy and at least throughout its course, regardless of the blockade scheme.
- When feasible, it is advised to perform the following evaluations at baseline and every 12–18 months afterwards:
  - Bone turnover markers (bone ALP).
  - Vitamin D, serum calcium and parathyroid hormone (PTH) (the latter in combination with calcium and vitamin D to differentiate between primary or secondary hyperparathyroidism).
  - DEXA scan (for BMD and if available vertebral morphometry (MXA)).
  - Height, weight and body mass index (BMI).
  - If feasible, evaluate body composition (by DEXA, bioelectrical impedance or plicometry) besides BMI.
- Do not overlook back pain.
- In case of back pain or height loss (as a reduction by ≥1 cm/year predicts a 98% probability of vertebral

Table 4 Experts' advices on monitoring modalities by setting

Non-metastatic disease	Metastatic disease
Early management of bone health is mandatory from the start of hormonal therapy and at least throughout its course, regardless of the blockade scheme	Monitor metastases by scintigraphy, NMR or any other evaluation at physician's discretion and pay closer attention to bone health
Assess the risk of fracture	Assess the risk of fracture
► FRAX score only discouraged; it should integrate the following	Same as for non-metastatic disease
► Independent factors: – BMD – Familiarity for fragility fractures – Corticosteroid therapy (>5 mg/prednisone equivalent in the past for >3 months consecutively or ongoing) – Metabolic bone diseases or fragilising disease/treatment – Disability or high risk of fall – Age – Anamnesis for low-energy trauma fractures	
When feasible, perform the following evaluations at baseline and every 12–18 months afterwards	When feasible, perform the following evaluations at baseline and every 12–18 months afterwards
► Bone turnover markers (bone ALP) ► Vitamin D, serum calcium and PTH ► DEXA scan (for BMD and if available vertebral morphometry (MXA)) ► Height, weight and BMI ► If feasible, evaluate body composition (by DEXA, bioelectrical impedance or plicometry) besides BMI	Same as for non-metastatic disease However, when assessing vitamin D, serum calcium and PTH, pay closer attention to the serum levels of these prognostic markers since ongoing administration of BPs or DNB therapies (at the dose for SRE prevention) may cause hypocalcemia
Do not overlook pain	Do not overlook pain
► In case of back pain or height loss, perform a spine radiography	Same as for non-metastatic disease
In the adjuvant setting of *M0 HSPC*, reassess the fracture risk at the end of hormonal therapy: if the patient experienced no fracture during treatment, no particular monitoring will be necessary; otherwise, monitoring should be continued; if the patient presents any additional risk factor (eg, new fracture), monitoring and therapy must be carried on	
In case of *M0 CRPC*, it is strongly advised to continue with the same monitoring scheme adopted in case of M0 HS disease, but with closer attention to bone health	

Unless specified, advices are valid for both settings. For detailed explanation, see the text.
HSPC hormone-sensitive prostate cancer; ALP, alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; BP, bisphosphonate; CRPC, castration-resistant prostate cancer; CTX, C-terminal cross-linked telopeptide of type I collagen; DEXA, dual-energy X-ray absorptiometry; DNB, denosumab; M0, non-metastatic; MXA, morphometric X-ray absorptiometry; NMR, nuclear magnetic resonance; P1NP, procollagen type 1 N-terminal propeptide; PTH, parathyroid hormone; SRE, skeletal-related event.

fracture),[94] perform a spine radiography for early identification of prevalent vertebral fractures.
  - In the adjuvant setting of M0 HSPC, it is suggested to reassess the fracture risk at the end of hormonal therapy: if the patient experienced no fracture during treatment, no particular monitoring will be necessary; otherwise, monitoring should be continued if the patient present any additional risk factor (eg, new fracture) and therapy must be carried on.
  - In case of M0 CRPC, it is strongly advised to continue with the same monitoring scheme adopted in case of M0 HS disease, but with closer attention to bone health, as the longer duration of hormonal therapy exposes patients to a higher risk of bone impairment.

Metastatic disease

- It is advised to pay close attention to bone health also in the metastatic setting.
- Besides monitoring metastases (by scintigraphy, NMR or any other evaluation at physician's discretion), the monitoring strategy for bone health is the same as for M0 PCa, but with closer attention when evaluating the serum levels of vitamin D, serum calcium and PTH as prognostic markers, since ongoing administration of BPs or DNB therapies (at the dose for SRE prevention) may cause hypocalcemia.
- In case of back pain or height loss, perform a spine radiography with the aim to early identify morphometric fractures.

Options of treatment for bone health

Available therapies in the different settings have been described above. As for BTTs, in Italy they are used, in the M0 setting, also in primary prevention and reimbursement is higher than abroad. The use of such agents is mandatory in case of T-score <2.5, but it can be suggested even with normal T-score in patients on ADT, based on the relevance of hormonotherapy as a risk factor for fractures, independently from basal T-score levels. As summarised in section 4, the use of BTTs in M1 CRPC disease may help preserve bone health in terms of fragility fracture prevention.

Non-metastatic disease

- Therapeutic thresholds and modalities are the same for M0 HS and M0 CR disease.
- Before starting any therapy specifically targeting the bone, evaluate and normalise the levels of vitamin D

Table 5 Experts' advices on treatment modalities by setting

Non-metastatic disease	Metastatic disease
Therapeutic thresholds and modalities are the same for M0 HSPC and M0 CRPC	In the setting of *M1 HSPC*, the therapeutic schedule of BTTs is that used for osteoporosis (the same of M0 CRPC), not for metastases
Before starting any therapy specifically targeting the bone, evaluate and normalise the levels of vitamin D (≥30 ng/mL) during hormonal therapy, regardless of the bone-modifying agent	Intervention for metastatic disease in *M1 CRPC* is indicated at the time of diagnosis of the first metastasis as per all guidelines, and it is aimed at reducing SREs; the regimen employed both for ZA and DNB will widely cover also the possibility to reduce the risk of fragility fractures (benign fractures)
Vitamin D supplementation during bone-modifying agents is mandatory	In case of *M1 CRPC*, consider the opportunity to continue therapy with bone-modifying agents adjusting the dosages for bone health in case of discontinuation of SRE-specific treatment. In particular, caution must be paid when using DNB
Do not consider vitamin D and calcium supplementation as sufficient to maintain bone health or prevent fragility fractures	
Physical activity and an adequate calcium intake are advised to avoid weight gain, reduce the risk of fall and for the likely positive impact on bone health	
The posology used for DNB is the same used in case of osteoporosis in both men and women; for a BP, a wide spectrum of doses has been proposed, sometimes even higher than those used for osteoporosis	
Start treatment with bone-modifying agents as soon as possible regardless of BMD even in M0 HSPC (no strict recommendations exist on PCa)	

Unless specified, advices are valid for both settings. For detailed explanation, see the text.
BMD, bone mineral density; BP, bisphosphonate; BTT, bone turnover inhibitor; CRPC, castration-resistant prostate cancer; DNB, denosumab; HSPC, hormone-sensitive prostate cancer; M0, non-metastatic; M1, metastatic; PCa, prostate cancer; SRE, skeletal-related event; ZA, zoledronic acid.

(≥30 ng/mL) during hormonal therapy, regardless of the bone-modifying agent.

- Vitamin D supplementation during bone-modifying agents is mandatory. Regardless of the threshold to be reached, it is difficult to suggest simple rules to follow that can be adapted to all individuals. The Italian Society of Osteoporosis and Mineral and Skeletal Metabolism, in line with the Endocrine Society, suggests the administration of a daily dose of 1500–2000 IU, to reach and maintain the value of 30 ng/mL (75 nmol/L).[95 96] A rapid correction of hypovitaminosis D is indicated in candidates for potent anti-resorptive therapy (ie, with a rapid effect), such as BPPs and DNB. The initial loading dose could be calculated on the basis of the half-life of the drug multiplied by the maintenance dose.[97]
- Do not consider vitamin D and calcium supplementation alone as sufficient to maintain bone health or prevent fragility fractures.
- Due to the initial evidence of detrimental effect of sarcopenic obesity on bone health, physical activity and an adequate calcium intake are advised to avoid weight gain, reduce the risk of fall and for the likely positive impact on bone health.
- BPs and DNB prevent bone loss and increase bone mass, but only DNB has been shown to decrease the fracture risk independently of bone mass effects. The posology used for DNB is the same used in case of osteoporosis in both men and women; for a BP, a wide spectrum of doses has been proposed, sometimes even higher than those used for osteoporosis.[76]
- It is advised to start treatment with bone-modifying agents, as primary prevention, as soon as possible regardless of BMD even in this setting (no strict recommendations exist on PCa).

Metastatic disease

- Due to the current paucity of evidence in the setting of M1 HSPC, the therapeutic schedule of BTTs is not the same used for metastases, but it is that for osteoporosis (the same of M0 CR). In fact, in M1 HS disease, the schedule used for BTT in M1 CRPC setting was not effective in reducing SREs and for DNB there are no data in support.
- Intervention for metastatic disease in M1 CRPC is indicated at the time of diagnosis of the first metastasis as per all guidelines, and it is aimed at reducing SREs; the regimen employed both for ZA and DNB will widely cover also the possibility to reduce the risk of fragility fractures (benign fractures).
- In case of M1 CRPC, consider the opportunity to continue therapy with bone-modifying agents adjusting the dosages for bone health in case of discontinuation of SRE-specific treatment. In particular, caution must be paid when using DNB, as, unlike for BPS, rapid bone loss occurs following treatment interruption, along with a potential rebound in the risk of vertebral fractures (pathological and osteoporotic fractures).[98]

CONCLUSION

Bone health preservation in PCa men undergoing ADT must be a clinical goal across the whole disease continuum because of the sequelae of bone health impairment on the individual's QoL and health status, as well as the considerable burden imposed on healthcare resources. Yet, it remains an urgent unmet need not yet given adequate attention from the scientific community. For this reason, it is crucial to raise awareness on the importance of bone preservation in this complex setting and optimise the management of bone health possibly through a multidisciplinary approach. This document is intended to be a tool to support physicians when managing bone health in their daily practice; still, the applicability of the advices formulated depends on the reimbursement policy of each individual country and region.

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