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REVIEW ARTICLE

Management and mitigation of metabolic bone disease and cardiac adverse events throughout the prostate cancer pathway: clinical review and practical recommendations

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ABSTRACT

Some current prostate cancer (PCa) treatment regimens are known to have adverse effects on bone, for example androgen deprivation therapy (ADT), and on cardiovascular health, for example ADT and antiandrogen therapy. Strengthened recommendations for the practical assessment and management of bone and cardiovascular health in men with PCa are needed. This review aims to provide practical guidance for healthcare providers along the continuum of patient care on the management of bone and cardiovascular health in men with PCa undergoing ADT and antiandrogen therapy based on real-world evidence. Evidence was identified by searching PubMed for publications that reported the effects of PCa treatment on bone or cardiovascular health in a real-world setting and were published between January 2017 and August 2023. Review articles were excluded. The evidence identified indicates that ADT decreases bone mineral density (BMD) and increases the risk of osteoporosis and fractures. Bone-protecting agents (BPAs) are effective at improving bone health in patients undergoing ADT and antiandrogen therapy at all stages of the PCa pathway. Despite this, the use and timing of initiation of BPAs are variable. Furthermore, real-world studies have confirmed an association between ADT and cardiovascular risk. As survival outcomes improve, maintenance of bone and cardiovascular health is increasingly important in men with PCa. Risk is a continuous variable that must be assessed throughout the continuum of PCa treatment. Therefore, all men starting ADT should be assessed for bone and cardiovascular risk. Lifestyle adjustments, dietary supplementation and pharmacological intervention may be advised.

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Introduction

Androgen-deprivation therapy (ADT), whether through orchiectomy or the use of luteinizing hormone-releasing hormone (LHRH) agonists and antagonists or gonadotrophin-releasing hormone (GnRH) agonists and antagonists, forms the mainstay treatment for patients with locally advanced or hormone-sensitive, metastatic prostate cancer (PCa) and is continued, in combination with other treatments, after patients become castrate-resistant. Often, ADT is combined with other therapy such as the androgen receptor (AR) targeted therapies (antiandrogens) abiraterone acetate, enzalutamide, darolutamide or apalutamide, or with radiotherapy (RT). ADT is also recommended as adjuvant treatment for biochemical relapse after RT or surgery[1]. The low, castrate levels of testosterone induced by ADT impact bone and cardiovascular health[2]. AR-targeted therapies also impact bone and cardiovascular health[3,4]. With earlier diagnosis and improvement in treatment, patients diagnosed with PCa may live for many years and undergo longer durations of treatment; therefore, it is paramount to optimize patient health and minimize adverse treatment effects[5].

ADT is associated with a range of side effects, including fatigue, hot flushes, hyperlipidemia, flare effect, osteoporosis, insulin resistance, cardiovascular disease (CVD), anemia, and sexual dysfunction[6]. AR-targeted therapies are associated with overlapping as well as unique side effects including hypertension, arthralgia, hypothyroidism, and seizures[7–11]. Patients with comorbidities such as pre-existing CVD and diabetes, advanced age and prior fragility fractures fall into the highest risk categories for cardiovascular and bone complications[12]. Since CVD is a primary cause of death in patients with PCa[13,14], the proportion of this increased risk that is caused by ADT or antiandrogens is a cause for concern[15]. In

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addition, the prevalence of hypertension as a comorbidity in men with PCa means that the risk of hypertension with AR-targeted therapies needs to be considered[9]. Furthermore, as men survive longer with PCa, bone complications are becoming an increasing issue. The reductions in testosterone and estradiol levels caused by ADT result in a 4–4.6% annual increase in bone loss through increased bone turnover and bone damage (cancer treatment-induced bone loss [CTIBL]), which increase bone fragility and the risk of fractures[5,16]. These effects add to the negative impact on bone health of age and PCa-associated bone metastasis[5,16].

Despite recommendations by the National Comprehensive Cancer Network (NCCN)[17] and European guidelines[1,18], bone mineral density (BMD) testing and the use of bone-protecting agents (BPAs) in patients with PCa are infrequent in many countries[19–22]. However, evaluating and managing bone and cardiovascular health throughout the disease continuum, with appropriate intervention, can mitigate the detrimental effects of ADT in patients with PCa. In contrast, there are no definitive guidelines for monitoring and managing cardiotoxicity associated with therapy for PCa. A recent consensus statement provides guidance[23] and general guidelines for the management and prevention of cardiotoxicity in people who have undergone anticancer therapy are available[24–26]. Guidelines from the European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology make no recommendations specific for cardiovascular risk management in patients with PCa[24,26].

Due to their increasing impact for patients with PCa, this review aims to highlight practical guidance on the evaluation and management of bone and cardiovascular health in patients with PCa undergoing ADT for healthcare providers along the long-term continuum of patient care. Where relevant, data for AR-targeted therapies are included, although real-world evidence based on long-term follow-up is limited due to the relatively recent approval of these agents for clinical use. Current evidence regarding the effects of treatment on bone and cardiovascular health and the use of BPAs in the different stages of PCa is reviewed.

Evidence acquisition

The Population, Intervention, Comparison, Outcomes and Study (PICOS) approach was used to formulate the question that this review was designed to answer: "in men with prostate cancer (P), what is the effect of ADT (I) versus no ADT (C) on the incidence of bone and cardiac health (O) as observed in real-world and observational studies (S)?" Based on this question, a comprehensive literature search of PubMed was performed using combinations of keywords including prostate cancer, androgen deprivation therapy, bone health and cardiovascular health. Full search strategies are described in Supplementary Material Appendix A. The searches were limited to articles published between January 2017 and August 2023. This timeframe was selected to ensure that the most up-to-date data reflecting the bone and cardiovascular effects of hormonal therapies in patients treated long-term were included, although ADT has been in clinical use for >25 years. The initial search identified 340 publications, abstracts for which were screened by two independent reviewers to identify articles that reported: real-world evidence/observational studies or relevant meta-analyses; and data on the effects of PCa treatment on bone or cardiovascular health. Disagreements were resolved by discussion. The screening process identified 73 articles for inclusion in the review. These articles were reviewed by the authors and relevant data were identified. Due to the nature of the data, a narrative approach to the description of the data and implications was taken. Based on these findings, the authors developed recommendations for management of men with prostate cancer treated with ADT in clinical practice. The AGREE reporting checklist were used to guide development of this evidence-based review and the recommendations for patient management.

The prostate cancer pathway

The median age of PCa diagnosis is around 70 years and many patients have poor bone health, with high prevalence of osteoporosis (10%), osteopenia (58%) and fractures (46.5–63.9%) prior to treatment[27,28]. NCCN and European guidelines recommend ADT with or without AR-targeted therapies as standard of care in a number of disease stages (Figure 1)[1,17,18]; however, real-world studies have highlighted complications of current treatment regimens including CTIBL and cardiovascular risks[3,21,29–47]. As the disease progresses to the metastatic setting, further complications known as skeletal-related events (SREs), which include the need for radiotherapy or surgery, pathological fractures and spinal cord compression, can occur. Patients with metastatic PCa also experience fractures at non-metastatic sites due to the effects of long-term hormonal therapy; such fractures may be asymptomatic and therefore underdiagnosed[5]. Furthermore, PCa progression is associated with increased pain, decreased health-related quality of life (QoL) and increased health resource utilization[5,48]. While acknowledging the differences in side-effect profile associated with disease stage and the effects these have on patients as they progress, detailed consideration of this is beyond the scope of this review. We focus on the latest real-world evidence on the effect of current treatment regimens on bone and cardiovascular health in men with PCa, which is summarized below.

Bone health

A systematic review published in 2009 showed that ADT increased fracture risk in men with prostate cancer by 23% compared with men who were not treated with ADT[49]. Subsequent real-world and observational studies confirm this finding, showing that ADT decreases bone mineral density (BMD) and increases the risk of osteoporosis and fragility fractures in men with PCa compared with non-ADT and healthy controls (Table 1)[32,35,39,50–60]; both orchiectomy and AR-targeted therapy may also increase fracture risk compared to no therapy[39]. The reduction in testosterone and estradiol associated with ADT causes an increase in bone turnover, which results in loss of bone mass and microarchitectural

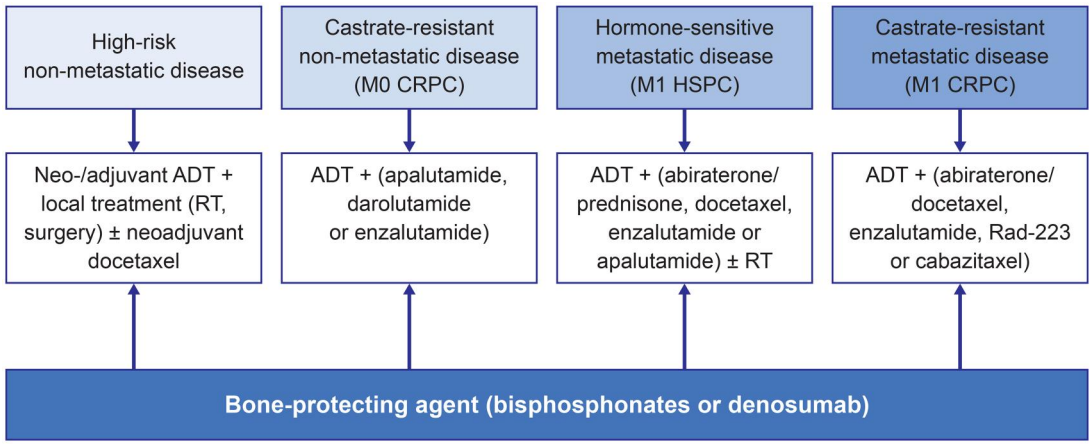

Figure 1. Summary of NCCN and European guideline recommendations for the treatment of patients along the PCa pathway[1,17,18]. if long-term ADT is started, a BPA should be administered[1]. ADT, androgen deprivation therapy; BPA, bone-protecting agent; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer; RT, radiotherapy.

damage and ultimately, bone fragility and osteoporotic fractures[5,57,58,60,61]. Frailty from ADT-induced loss of muscle mass increases the risk of falls, and the lack of bone-protective estrogens further increases the fracture risk in patients undergoing ADT[62]. It is hypothesized that follicle-stimulating hormone (FSH) signalling mediates bone loss and increased fracture risk in patients with PCa, because there is less testosterone available to convert estrogen, which is inversely related to osteoclast activity (Figure 2)[63]. Preclinical and *in vitro* studies show that FSH signalling stimulates the expression of several cytokines and other signalling molecules that are critical to the resorption process, including receptor activator of nuclear factor kappa B (RANK), tumor necrosis factor alpha (TNF-α) and interleukin-1β (IL-1β)[64,65]. RANK and TNF-α facilitate the transformation of osteoclast precursors to osteoclasts, increasing bone resorption, while IL-1β increases the survival time of mature osteoclasts, allowing them to participate in several rounds of resorption[64,65]. FSH-mediated osteoclast activity may also promote the growth and progression of bone metastasis[64].

Real-world studies show that ADT, AR-targeted therapy and surgical orchiectomy are associated with a higher risk of fractures than radical prostatectomy in men with newly diagnosed PCa[39]. A more recent study in a population of men with either non-metastatic or metastatic PCa showed numerically higher fracture rates with ADT and surgical orchiectomy than with medical castration[66]. Further studies in which data for men treated with GnRH antagonists or agonists were combined also showed an increased risk of fractures in this population[39,45]; however, the fracture risk with GnRH agonists appears to be lower than with GnRH antagonists[45]. Increasingly, antiandrogens (including abiraterone, which inhibits a cytochrome in androgen synthesis, and more recent androgen receptor blockers, such as enzalutamide, darolutamide and apalutamide) are used in combination with GnRH antagonists to improve survival in metastatic hormone-sensitive, castrate-resistant and, in some cases, higher-risk localized prostate cancer. These agents may have the potential to add to the bone loss caused by GnRH antagonists alone. For example, enzalutamide increased fracture risk from 6% to 18%[11] and apalutamide increased fracture risk from 6.5% to 11.7%[10] when added to ADT in men with non-metastatic PCa. In contrast, no increase in fracture risk was observed when darolutamide was added to luteinising hormone-releasing hormone (LHRH) agonist/antagonist therapy in this population[7]. Reversibility of ADT-induced bone loss and decreases in serum levels of bone metabolism markers were observed in men with non-metastatic PCa who discontinued ADT[56,57], due to the role of androgens in bone metabolism.

A study in men with metastatic PCa showed that gonadotrophin-releasing hormone (GnRH) antagonists were associated with a higher risk of fractures than orchiectomy[67]. Furthermore, in men with bone metastatic PCa, fracture risk is also increased when ADT is combined with a radiopharmaceutical. The ERA 223 trial showed that radium-223 in combination with abiraterone and prednisolone was associated with increased incidences of fracture and death and did not improve SRE-free survival; however, the majority of patients were not receiving BPA[68]. In agreement, a longitudinal study showed that radium-223 induced skeletal fragility with high risk of vertebral fractures, independently of ADT and abiraterone therapy, when patients were not receiving BPA[69]. Through mandating BPAs, fracture rate dramatically decreased in the EORTC 1333/PEACE III trial, which compared enzalutamide in combination with radium-223 to enzalutamide alone in patients with metastatic castrate-resistant PCa (mCRPC)[70].

Bone-protecting agents

Despite the known impact of ADT on bone health and CTIBL and advice based on a systematic review showing the magnitude of the increase fracture risk that preventive therapies be considered[49], rates of BMD testing in patients with non-metastatic PCa in the real world are low: in North America, BMD testing rates increased between 2000 and 2015, but remained <25% at the end of this period, although rates were higher in patients with non-metastatic PCa than those with metastatic PCa[21,22]. These studies showed that a history of osteoporosis or bisphosphonate use prior to ADT use or

Table 1. Summary of data from real-world and observational studies on the effect of PCa treatment on bone and cardiovascular health.

Study	Patient populations	Effect on bone health
Arévalo Ruales et al. 2023[61]	PCa (not otherwise specified) ($n = 83$) Treated with LHRH agonists with or without denosumab	• Patients who received denosumab had better evolution of BMD in femoral neck ($p = 0.048$), total hip ($p = 0.24$) and lumbar spine ($p = 0.039$) than those who did not
Chen et al. 2023[39]	PCa (not otherwise specified) ($n = 13,321$) Treated with ADT or AR-targeted therapy by injection vs orally vs orchiectomy vs radical prostatectomy	• Increased risk of fracture with GnRH agonists/antagonists administered by injection or orally and with orchiectomy (HR 1.55, $p < 0.001$; HR 1.37, $p < 0.001$; HR 1.95, $p < 0.001$, respectively) • Decreased risk of fracture with radical prostatectomy (HR 0.51, $p = 0.001$) and in patients receiving medication for osteoporosis (HR 0.26, $p < 0.001$)
Dalla Via et al. 2019[50]	PCa (not otherwise specified) ($n = 192$) ADT-treated vs PCa controls and healthy controls	• Lumbar spine aBMD: 7.2–7.8% lower than controls ($p = 0.037$) • Distal tibia, total vBMD: 8.4−8.7% lower than controls ($p < 0.01$); BSI: 10.8% lower than healthy controls ($p < 0.01$) • Distal radius, total and trabecular vBMD: 10.7–14.8% lower than controls ($p < 0.05$); BSI: 23.6–27.5 % lower than controls ($p < 0.001$)
Ilyas et al.[57]	Non-metastatic PCa ($n = 40$) Treated with ADT for <6 months, >6 months, ADT in the past and no ADT	• Decrease in ultra-distal forearm BMD with ADT for <6 months (4.05%, $p = 0.001$) and for >6 months (2.54%, $p = 0.016$) • BMD was increased in the femoral neck and lumbar spine of the past ADT group (1.60%, $p = 0.001$; 2.85%, $p = 0.0064$, respectively)
Kato et al. 2019[51]	Non-metastatic PCa ($n = 230$) Treated with prolonged ADT vs no ADT	With increasing duration of ADT (median 31 (IQR 13.5, 52.5) months): • Lumbar spine BMD decreased gradually ($p = 0.0005$) • Femoral neck BMD decreased gradually ($p = 0.0014$) • Prevalence of osteoporosis increased ($p = 0.0002$)
Kim et al. 2017[32]	Non-metastatic ($n = 240$) or metastatic ($n = 63$) PCa Treated with ADT with combined androgen block or GnRH agonist monotherapy	• BMD significantly decreased in both groups with no group wise differences • Proportion of osteopenia or osteoporosis was slightly increased 12 months post-ADT with no significant difference between the groups ($p > 0.05$) • Ten-year probability of hip fracture and major osteoporotic fracture was approximately 2% and 5%, respectively
Kim et al. 2021[52]	PCa (not otherwise specified) ($n = 144,670$) Treated with ADT vs no ADT	• Higher risk of osteoporosis (HR, 1.381; 95% CI, 1.305–1.461; $p < 0.0001$) • Higher risk of fractures (HR, 1.815; 95% CI, 1.703–1.935; $p < 0.0001$) • Risk of osteoporosis and fractures increased as the duration of ADT increased
Lee et al. 2017[53]	PCa (not otherwise specified) ($n = 741$) Treated with ADT vs no ADT	• Higher risk of incident fracture (HR, 3.60; 95% CI, 1.41–9.23; $p = 0.008$)
Mazziotti et al. 2020[69]	Metastatic CRPC with symptomatic bone metastases ($n = 49$) Treated with Radium-223	• Incident vertebral fractures occurred in 25% of patients in relationship with prevalent vertebral fractures (HR, 6.89) and change in serum total alkaline phosphatase (HR, 0.97)
Nguyen et al. 2018[119]	Non-metastatic or metastatic PCa ($n = 201,797$) Treated with ADT vs no ADT	• Higher risk of bone fractures (HR, 1.39, 95% CI, 1.35–1.43)
Poulsen et al. 2019[54]	PCa (not otherwise specified) ($n = 105$) Treated with ADT from baseline to 2-year follow up	• Prevalence of osteoporosis increased from 10% to 22% • Prevalence of normal BMD decreased from 32% to 8%
Sharma et al. 2021[59]	Non-metastatic ($n = 18$) or metastatic ($n = 65$) PCa Treated with ADT	• ADT caused duration-dependent worsening of FRAX and FACT-P score at 12 months, while improvements of FRAX were seen when patients received bone-directed therapy • ADT duration correlated with major osteoporotic fracture (R^2 0.148, $p < 0.001$) and hip fracture risk (R^2 0.164, $p < 0.001$)
Shin et al. 2020[55]	PCa (not otherwise specified) ($n = 48,298$) Treated with ADT vs matched non-cancer control group	• Higher risk of fracture (HR, 1.92; 95% CI, 1.82–2.02)
Trieu et al. 2022[76]	Metastatic castration-resistant PCa ($n = 177$) Treated with radium-223 with abiraterone or enzalutamide with a bone protective agent	• The fracture rate in patients who received combination therapy plus denosumab and zoledronic acid was 5.7%
Wallander et al. 2018[35]	PCa (not otherwise specified) ($n = 20,082$) Treated with ADT vs non-PCa control group	• Increased risk of any fracture (HR, 1.40; 95% CI, 1.28–1.53) • Increased risk of hip fracture (HR, 1.38; 95% CI, 1.20–1.58) • Increased risk of major osteoporotic fractures (HR, 1.44; 95% CI 1.28–1.61) • No increased risk of non-skeletal fall injury (HR, 1.01; 95% CI, 0.90–1.13)

(*continued*)

Table 1. Continued.

Study	Patient populations	Effect on bone health
Watanabe et al. 2020[60]	PCa (not otherwise specified) ($n = 65$) Treated with ADT	• Significant annual BMD changes were observed in the lumbar spine (-1.65%), femoral neck (-3.50%) and total hip (-3.14%) • Significant annual changes in cross-sectional area (-2.55%), cross-sectional moment of inertia (-3.50%) and section modulus (-3,14%) in narrow femoral neck • Femoral neck BMD decreased more in patients with visceral fat obesity than those without (-1.79% vs 0.28%)
Study	**Patient populations**	**Effect on cardiovascular health**
Bretagne et al. 2020[102]	PCa (not otherwise specified) (based on adverse drug reaction reports in French pharmacovigilance database) Treated with abiraterone or enzalutamide	• Atrial tachyarrhythmia: abiraterone vs enzalutamide (ROR, 5.7; 95% CI, 1.3–25.3); vs other ADTs (ROR, 36.5; 95% CI, 14.9–89.1); $p < 0.05$ for both • Heart failure: abiraterone vs enzalutamide (ROR, 4.3; 95% CI, 1.4–12.9); vs other ADTs (ROR, 21.9; 95% CI, 11.6–41.4); $p < 0.05$ for both
Bretagne et al. 2020[102]	PCa (not otherwise specified) (based on adverse drug reaction reports in European pharmacovigilance database) Treated with abiraterone or enzalutamide	• Atrial tachyarrhythmia: abiraterone vs enzalutamide (ROR, 3.9; 95% CI, 3–5.3); vs other ADTs (ROR, 3.8; 95% CI, 3–4.9); $p < 0.05$ for both • Heart failure: abiraterone vs enzalutamide (ROR, 2.7; 95% CI, 2.3–3.3); vs other ADTs (ROR, 2; 95% CI, 1.7–2.3); $p < 0.05$ for both
Bretagne et al. 2020[102]	PCa (not otherwise specified) (based on adverse drug reaction reports in Vigibase) Treated with abiraterone or enzalutamide	• Atrial tachyarrhythmia: abiraterone vs enzalutamide (ROR, 4.1; 95% CI, 3.1–5.3); vs other ADTs (ROR, 3.7; 95% CI, 3–4.5); vs all other drugs (ROR, 3.2; 95% CI, 2.7–3.7); $p < 0.0001$ for all • Heart failure: abiraterone vs enzalutamide (ROR, 2.5; 95% CI, 2–3); vs other ADTs (ROR, 1.5; 95% CI, 1.3–1.7); vs all other drugs (ROR, 2; 95% CI, 1.7–2.3); $p < 0.05$ for all
Cavo et al. 2018[120]	Metastatic castration-resistant PCa ($n = 105$) Treated with abiraterone acetate and prednisone	• Hypertension 17.1%; fluid retention 4.8%; cardiac disorders 8.6%; hypokalemia 16.2%
Chan et al. 2023[36]	PCa (not otherwise specified) ($n = 2,479$) Treated with >6 months of GnRH agonists or antagonists and followed for >6 months	With a median follow-up of 3 years • The incidence of MACE (all-cause mortality, stroke or MI) was 45% • The incidence of MACE(CVM) (CV mortality, stroke or MI) was 13.9% • The incidence of MACE and MACE(CVM) was lower in patients who received GnRH agonists versus antagonists ($p < 0.001$), but only with >1 year of treatment, and in those without CV risk factors at baseline who received GnRH agonists ($p < 0.001$)
Chan et al. 2023[37]	PCa (not otherwise specified) ($n = 13,537$) Treated with ADT	Patients receiving ADT more recently (2015–2021) compared to those treated less recently (1993–2000) had: • More CV risk factors and were receiving more CV medication • A higher risk of MACE (CV mortality, stroke, heart failure or MI) (HR 1.11, $p = 0.002$) but lower mortality (HR 0.76, $p < 0.001$) • 5-year risks of MACE and mortality for the most recent group (2015–2021) were 22.5% and 52.9%, respectively
Chen et al. 2017[85]	PCa (not otherwise specified) ($n = 3,578$) Undergone bilateral orchiectomy or treated with GnRH agonist	The risk of ischemic CV events was similar with bilateral orchiectomy and GnRH agonist therapy (HR 1.16, 95% CI 0.97–1.38) at median follow-up of 3.3 years, but was higher in the bilateral orchiectomy group in the first 1.5 years of follow-up (HR 1.40, 95% CI 1.04–1.88), particularly in patients with a history of hypertension, Charleson comorbidity index score ≥3, aged ≥65 years, or with a history of MI, ischemic stroke or coronary heart disease
Chen et al. 2021[38]	PCa (not otherwise specified) ($n = 1,998$) Treated with a GnRH antagonist versus propensity score-matched patients receiving a GnRH agonist	• With a median follow-up of 1.21 years, GnRH antagonists were associated with a lower risk of a composite endpoint of MI, ischemic stroke or CV death (HR 0.48, 95% CI 0.25–0.90) • A lower risk of CV death or all-cause mortality was also observed with GnRH antagonists versus GnRH agonists (HR 0.21, 95% CI 0.06–0.70 and 0.77, 95% CI 0.61–0.97, respectively)
Cone et al. 2021[3]	PCa (not otherwise specified) (based on adverse drug reaction reports in Vigibase) Treated with GnRH agonists, abiraterone or enzalutamide based on analysis of VigiBase	• Abiraterone had higher odds of overall cardiac events (ROR 1.59, 95% CI 1.48–1.71), myocardial infarction (1.35, 1.16–1.58), arrhythmia (2.04, 1.82–2.30), and heart failure (3.02, 2.60–3.51) • GnRH agonists also had increased risks of cardiac events (ROR 1.21, 95% CI 1.12–1.30), myocardial infarction (1.80, 1.61–2.03) and heart failure (2.06, 1.76–2.41)

(*continued*)

Table 1. Continued.

Study	Patient populations	Effect on cardiovascular health
Conover et al. 2023[103]	Castration-resistant PCa ($n = 5,159$) Treated with abiraterone or enzalutamide based on US claims data	• HRs for heart failure (2.56, 95% CI 1.32–4.94), acute MI (1.94, 0.90, 4.18) and ischemic stroke (1.25, 95% CI 0.54–2.85) were all increased with abiraterone compared to enzalutamide
Davey and Kirby. 2021[29]	Non-metastatic PCa ($n = 9,081$) Treated with GnRH agonist or antagonist	• Relative risk of cardiovascular events was lower with degarelix, a GnRH antagonist, compared with GnRH agonists (6.9% vs 17.7%; RR, 0.39; 95% CI 0.191–0.799; $p = 0.01$)
Forster et al. 2022[40]	Non-metastatic PCa ($n = 8,449$) Treated with ADT in the first year after diagnosis between 2008 and 2018 in Norway	• At mean follow-up of 2.9 years, ADT was associated with composite CVD (HR 1.13, 95% CI 1.05–1.21), MI (1.18, 1.05–1.32), stroke (1.21, 1.06–1.38), heart failure (1.23, 1.13–1.35), and all-cause mortality (1.49, 1.39–1.61) • Associations persisted in those with low and moderate CVD risk and ADT >7 months
Gagliano-Jucá et al. 2018[121]	PCa (not otherwise specified) ($n = 70$) Treated with ADT vs control group (no-ADT)	• Reduction in erythrocyte count (estimated mean difference, -0.2×10^6cells/μL; 95% CI, -0.3×10^6 to -0.1×10^6; $p < 0.001$) • Reduction in hematocrit (−1.9%, 95% CI, −2.7 to −1.1%; $p < 0.001$) • Reduction in hemoglobin (−0.6 g/dL, 95 %CI, −0.8 to −0.3 g/dL; $p < 0.001$)
Gagliano-Jucá et al. 2018[122]	Non-metastatic PCa ($n = 37$) Treated with ADT vs control group (no-ADT)	• Prolongation of QTc by 7.4 ms compared with the non-ADT group (95% CI, 0.08–14.7 ms; $p = 0.048$)
Gheorghe et al. 2021[123]	PCa (not otherwise specified) Treated with ADT	• ADT induced subclinical alterations in global left ventricular longitudinal strain (−16.93% ± 3.89 vs −14.43% ± 3.57, $p < 0.001$), mechanical dispersion (77.4 ± 21.4 ms vs 89 ± 27 ms, $p = 0.004$), electrocardiographic repolarization parameters (QTc: 458.8 ± 43.4 ms vs 485.6 ± 45.1 ms, $p = 0.01$), and high sensitivity cardiac troponin I (4.6 ± 5.4 ng/mL vs 5.4 ± 6.4 ng/mL, $p = .01$) during the first 6 months of treatment
Gong et al. 2020[41]	PCa (not otherwise specified) Treated with ADT and referred for exercise treadmill testing	• Prolonged ADT (>6 months) was associated with reduced cardiorespiratory fitness (CRF; odds ratio [OR] 2.71; 95% CI: 1.31–5.61, $p = 0.007$) and increased CV mortality (HR 3.87, 95% CI: 1.16–12.96, $p = 0.028$) • The association between short-term ADT (≤6 months) and reduced CRF was of borderline significance (OR: 1.71, 95% CI 1.00–2.94, $p = 0.052$) and there was no association with CV mortality (HR 1.60, 95% CI 0.51–5.01, $p = 0.420$)
Haque et al. 2017[30]	Non-metastatic PCa ($n = 7,637$) Treated with ADT or not	• ADT exposure increased risk of heart failure (adjusted HR, 1.81; 95% CI,1.40–2.32) in men without pre-existing CVD • Increased risks of arrhythmia (adjusted HR, 1.44; 95% CI 1.02–2.01) and conduction disorder (adjusted HR, 3.11; 95% CI, 1.22–7.91) observed only in patients with pre-existing CVD
Hong et al. 2022[87]	Non-metastatic or metastatic PCa ($n = 10,840$) Treated with GnRH agonists or antagonists and propensity score-matched with non-GnRH users	• At 5 years of follow-up, the venous thromboembolic event incidence among GnRH users was 1.13% compared with 0.98% among non-users. After adjusting for potential confounding factors, the risk showed borderline statistical significance for GnRH users compared to non-users • In subgroup analyses, patients receiving GnRH therapy who were <70 years or at an earlier stage (stage I/II) were at a higher risk of venous thromboembolic events
Jonušas et al. 2022[42]	Non-metastatic ($n = 8,936$), metastatic ($n = 387$) or unknown ($n = 4,020$) PCa Treated with ADT or not	• The risk of CV death was higher in patients treated with ADT than in those who did not receive ADT (HR 2.14, 95% CI 1.86–2.45, $p < 0.001$) • The risk of death from ischemic heart disease (HR 1.42, 95% CI 1.16–1.73) and stroke (1.70, 95% CI 1.18–2.45) was also increased in ADT users • The risk of CV-related mortality was highest in the 70–79 years of age group of ADT users (HR 4.78, 95% CI 3.79–6.04)
Kan et al.[124]	PCa (not otherwise specified) ($n = 10,559$) Underwent bilateral orchiectomy or treated with GnRH agonists/antagonists	• The crude incidences of 3-year mortality and major adverse cardiovascular and cerebrovascular events (MACCEs) were 19.90% vs 26.51% and 8.23% vs 8.65% in patients receiving GnRH therapies or bilateral orchiectomy • After adjusting for age, cancer stage, and comorbidities, there was no significant difference in MACCE, but a slight increase in the incidence of acute MI with bilateral orchiectomy; patients with stage IV disease showed the most significantly increased risk of acute MI • Mortality adjusted HRs of MACCEs and acute MI among patients undergoing bilateral orchiectomy were 1.11- and 1.8-fold higher than those receiving GnRH therapies

(*continued*)

Table 1. Continued.

Study	Patient populations	Effect on cardiovascular health
Kao et al. 2019[43]	PCa (not otherwise specified) ($n = 3,050$) Treated with ADT or not and followed for 1 year	• Heart failure incidence rates per 100 person-years were 4.00 (95% CI 2.95–5.30) and 1.89 (95% CI 1.30–2.66) for ADT users and non-users, respectively (HR 1.72, 95% CI 1.08–2.73) • In a propensity score-matched cohort study, the adjusted HR for heart failure among ADT users was 1.92 (95% CI 1.15–3.18) versus non-users
Lazzerini et al. 2020[125]	PCa (not otherwise specified) ($n = 66$) Treated with ADT	• Four patients were undergoing ADT for PCa when Torsades de Pointes occurred; two cases progressed to cardiac arrest. ADTs were the second most frequently administered QTc-prolonging medication (4/24, 17%)
Li et al. 2022[88]	Non-metastatic PCa ($n = 1,940$) Treated with radiotherapy and ADT or radiotherapy alone	After a median follow-up of 10 years (radiotherapy) and 7.2 years (radiotherapy + ADT) • The cumulative incidence of MACE at 1, 3, and 9 years was 1.2, 5, and 16.2% in the radiotherapy group, and 1.1, 5.2, and 17.6% in the radiotherapy + ADT group (HR 1.01, 95% CI 0.78–1.30, $p = 0.969$) • After propensity score adjustments, there remained no significant differences in MACE risk between the radiotherapy + ADT and radiotherapy groups on multivariate analysis
Liu et al. 2020[105]	PCa (not otherwise specified) ($n = 17,168$) Treated with ADT versus RT only and RP only	• Increased risk of subsequently developing hematologic disorders (ADT: adjusted HR, 1.60; 95% CI, 1.29–1.97; RT: adjusted HR, 1.98; 95% CI, 1.62–2.42) vs RP only
Liu et al. 2021[104]	Metastatic castration-resistant PCa ($n = 4,962$) Treated either first line with ADT or second-line with enzalutamide or abiraterone	• MACE event rates were 2.92% in the second-line hormonal therapy group and 2.22% in the first-line ADT group • Patients who received second-line hormonal therapy had a significantly increased risk of MACE (HR 3.15; 95% CI 2.03–4.89), acute coronary syndrome (HR 4.94; 95% CI 2.36–10.33), and heart failure (HR 2.83; 95% CI 1.53–5.25) compared with the first-line ADT group, but a similar risk for IS (HR 1.70; 95% CI 0.95–3.04)
Perrone et al. 2020[94]	PCa (not otherwise specified) ($n = 9,785$) Treated with GnRH agonist or antagonist	• Higher incidence of cardiovascular events in patients treated with GnRH agonists than antagonists (8.8 vs 6.2, $p = 0.002$) • Risk of cardiovascular events was lower in patients treated with GnRH antagonist than those treated with GnRH agonists (HR, 0.76; 95% CI, 0.60–0.95; $p = 0.018$)
Seong et al. 2020[89]	PCa (not otherwise specified) ($n = 2,413$) Treated with GnRH agonists or anti-androgens	• 5-year acute MI-free rates for patients treated with GnRH agonists or antiandrogens, and those who were ADT-naïve were 97.0%, 96.5%, and 98.3%, respectively, while 5-year ischemic heart disease-free rates were 93.2%, 92.3%, and 94.5%, respectively • 5-year ischemic stroke-free rates were 94.8%, 94.7%, and 95.5%, respectively, while 5-year CVD-free rates were 92.9%, 93.3%, and 94.6%, respectively • Cox proportional-hazards models showed no significant increase in risk with GnRH agonist or antiandrogen treatment
Shao et al. 2022[46]	Non-metastatic ($n = 10,011$) or metastatic ($n = 5,615$) PCa and pre-existing CVD Treated with GnRH agonists or antagonists	• Lower composite CV event risk with GnRH antagonist compared with GnRH agonists overall and in patients with metastasis at diagnosis (adjusted HR 0.16, 95% CI 0.04–0.38, $p = 0.013$) and those receiving ADT for >6 months (adjusted HR 0.30, 95% CI 0.16–0.54, $p < 0.0001$) • In patients with pre-existing CVD, the MACE risk was 33% lower (adjusted HR 0.67, 95% CI 0.46–0.96, $p = 0.0299$) and composite CV event risk was 84% lower (adjusted HR 0.16, 95% CI 0.05–0.50, $p = 0.0017$) in GnRH antagonist-treated than GnRH agonist-treated patients
Shim et al. 2020[47]	PCa (not otherwise specified) ($n = 4,707$) Treated or not with GnRH agonists	• GnRH agonist users had more comorbidities than nonusers (all $p < 0.050$) • GnRH agonist use was associated with an increased incidence of cerebrovascular attack and ischemic heart disease ($p = 0.013$ and 0.048, respectively) in univariate analysis, but not in multivariate analysis
Shin et al. 2020[86]	PCa (not otherwise specified) ($n = 48,298$) Treated with ADT vs matched non-cancer control group	• Overall, PCa patients had a slightly lower risk of ischemic heart disease (adjusted HR 0.89, 95% CI 0.83–0.96) or stroke (adjusted HR 0.90, 95% CI 0.87–0.95) • Patients who underwent surgery had lower risks of ischemic heart disease (adjusted HR 0.70, 95% CI 0.61–0.80) and stroke (adjusted HR 0.73, 95% CI 0.67–0.81), but patients who had ADT had a significantly greater risk of stroke (aHR 1.16, 95% CI 1.02–1.32) than an active surveillance/watchful waiting group

(*continued*)

Table 1. Continued.

Study	Patient populations	Effect on cardiovascular health
Tae et al. 2019[90]	PCa (not otherwise specified) ($n = 36,146$) Treated with ADT	• At mean follow-up of 4.1 years, the annual incidence of cerebral infarction differed between the ADT and non-ADT groups (22.8 vs 14.6 per 1000 person-years, respectively) in an unmatched cohort, but this difference was not seen for matched cohorts (14.9 vs 14.6 per 1000 person-years) (adjusted HR 1.045, 95% CI 0.943–1.159, $p = 0.401$) • Cumulative duration of ADT was not associated with an increased risk of cerebral infarction, whereas older age, hypertension, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, renal disease, dementia, and atrial fibrillation were associated with increased risk

ADT, androgen deprivation therapy; aBMD, areal bone mineral density; BMD, bone mineral density; CI, confidence interval; CVD, cardiovascular disease; GnRH, gonadotrophin releasing hormone; HR, hazard ratio; PCa, prostate cancer; ROR, reporting odds ratio; RP, radical prostatectomy; RR, relative risk; RT, radiotherapy; vBMD, volumetric BMD.

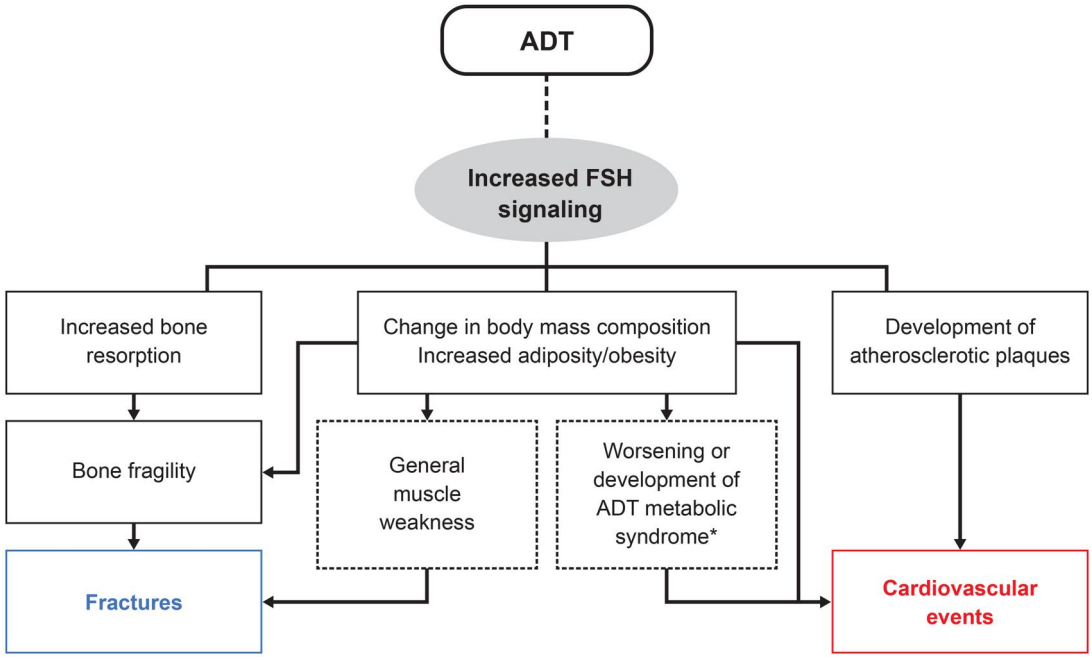

Figure 2. The role of FSH in ADT-induced bone and cardiovascular adverse events in patients with PCa[5,29,63]. ADT has been associated with increased FSH signalling, which indirectly results in increased bone resorption, change in body mass composition and increased adiposity and development of atherosclerotic plaques. Such bone and metabolic alterations contribute to bone fragility, general muscle weakness and worsening or development of ADT metabolic syndrome, which impact fracture risk and cardiovascular events.
*ADT metabolic syndrome is a syndrome induced by testosterone deficiency with some similarities to diabetes, but with additional features that may be imposed by FSH or GnRH mononuclear blood cell GnRH receptor stimulation. ADT, androgen deprivation therapy; FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; PCa, prostate cancer.

occurrence of osteoporosis or treatment with bisphosphonates while receiving ADT were associated with higher odds of BMD testing in both studies. In a similar study, Suarez-Almazor et al. showed that the rate of dual-energy x-ray absorptiometry (DXA) screening of older men with non-metastatic PCa initiating ADT treatment was 6.8% in 2005 and 8.4% in 2015, even though screening was associated with a decreased risk of major fractures[71].

Despite the low rates of BMD testing, evidence supports the use of BPAs in patients undergoing ADT treatment for PCa[2,5]. Dosing schedules for CTIBL are typically alendronic acid 70 mg or risedronate sodium 35 mg, once weekly, intravenous zoledronic acid (ZA) 5 mg once yearly, or subcutaneous denosumab 60 mg once every 6 months[72]. In the non-metastatic setting, all BPA schedules and doses that were tested were effective at reducing bone loss, although for all agents except denosumab, the studies were not designed to detect fracture reduction[5]. In a large randomized controlled trial (RCT), denosumab was found to significantly reduce the incidence of new vertebral fractures compared with placebo (1.5% versus 3.9% with placebo at 36 months; risk ratio [RR] 0.38, 95% CI 0.19 to 0.78; $p = 0.006$)[73]. Real-world evidence also supports the use of BPAs in patients receiving ADT treatment for non-metastatic PCa, with improved BMD, decreased fracture risk, and improved quality of life[59,61].

Similarly, administration of BPAs, which are now being used at higher doses than in patients with non-metastatic PCa to prevent/reduce SREs in metastatic disease, is inadequate and timing of initiation of BPAs is highly variable for

cancer-induced bone complications[19,20,74]. The cumulative incidence of BPA initiation after bone metastasis diagnosis was 34% at 30 days, 64% at 180 days and 88% at 2 years[74]. Factors for initiating treatment included diabetes, more bone lesions and history of ADT. In a study of BPA-treated patients with bone metastases from solid tumors, >50% initiated BPA only after experiencing a bone complication[20]. However, a study of ZA in patients with locally advanced and metastatic PCa reported a significant improvement in mean BMD post-ZA therapy at 12 months and a significant deterioration in mean BMD in patients who did not receive ZA[75]. Pain scores also significantly decreased in patients with after 12 months of ZA use (-2.92 ± 2.16, $p < 0.01$)[75]. Evidence suggests that BPAs are also critical in the management of bone health in patients with metastatic castration-resistant PCa (M1 CRPC). The ERA 223 trial demonstrated that the use of BPAs in patients with M1 CRPC halved the number of patients with osteoporotic fractures in both treatment arms (abiraterone acetate plus prednisone/prednisolone and randomized to receive Radium-223 or placebo) compared to without BPAs[68]. Real-world evidence also supports the use of BPAs in patients undergoing ADT treatment for metastatic PCa, with decreased fracture risk and improved quality of life[59,76].

It is important to note that BPAs have been associated with side effects such as nausea, vomiting, epigastric pain, bone, joint or muscle pain, renal failure and osteonecrosis of the jaw. The adverse events of the upper gastrointestinal tract have been linked to oral administration of BPAs while intravenous bisphosphonates have been associated with renal failure[77]. In a retrospective study of 191 Japanese patients with PCa treated with doses of ZA or denosumab used for prevention of metastatic SREs, 28 (14.7%) developed osteonecrosis of the jaw[78]. The incidence of osteonecrosis of the jaw is much lower in patients treated with BPAs for prevention or treatment of osteoporosis than those with metastatic disease, in which the doses used are higher (0.001–0.01% and 1–15%, respectively)[79]. With preventative measures such as carrying out essential dental work before starting BPAs and measures to improve dental hygiene, the incidence can be significantly reduced[80].

Cardiovascular health

The negative impact on the cardiovascular system associated with ADT has been reported in several observational studies and meta-analyses since 2006 (Table 2)[49,81–84]. More recent studies (Table 1) and meta-analyses[31,33] continue to demonstrate that ADT increases the risk of cardiovascular events, as well as showing that AR-targeted agents also increase the risk (Table 1). A meta-analysis showed that acute myocardial infarction (AMI) (8 studies, 316,590 patients) and CVD (13 studies, 542,220 patients) were increased in patients undergoing ADT compared with those who had not received ADT, but the cardiovascular events were not associated with duration of ADT[33]. Similarly, a review of meta-analyses of RCTs and observational studies reported that the AR-targeted agent abiraterone was associated with increased risk of cardiovascular events and hypertension[31].

Real-world evidence generally supports the conclusions of meta-analyses, with several large studies showing an increased risk of cardiac events with ADT compared to no ADT or compared to risk prior to the widespread use of ADT[37,40–43,47,85,86]. However, it has to be noted that other real-world studies have failed to identify an association[85,87–90], although duration of follow-up, baseline cardiovascular risk factors and treatment exposure need to be taken into account. Several real-world studies have suggested that risk is increased in patients with a history of CVD[85], duration of treatment[40], and older age[42,87]. Patients with established vascular disease have much higher rates of further vascular events than those without vascular disease[91]. It is therefore perhaps not surprising that any risk factor that increases vascular event rates affects those with established vascular disease to a greater extent. There also seems to be a difference in cardiovascular event rate between those treated with GnRH agonists and antagonists, as shown in pooled data analyses and systematic review[92,93]. Analysis of real-world data also suggests that GnRH antagonists are associated with a lower risk of experiencing cardiovascular events than GnRH agonists, both in patients with and without a history of cardiovascular events[29,36,38,46,94].

The Phase III HERO trial demonstrated a 54% lower cardiovascular risk in patients with advanced PCa treated with the oral GnRH antagonist relugolix compared with the injected GnRH agonist leuprolide[14], but the PRONOUNCE study, the first, international randomized clinical trial to prospectively compare the effects of GnRH antagonists and GnRH agonists on the occurrence of major adverse cardiovascular events (MACE) in patients with PCa, was terminated early due to low MACE rates in both arms and slow enrolment. Interestingly, while this study found no difference in MACE rates between therapies, all patients were required to be under the care of a cardiologist at study entry and throughout the study, which is not the case with real-world ADT treatment. The low MACE rates may reflect the efficacy of targeted modern cardiovascular therapy in preventing disease and may suggest that greater involvement of CVD specialists in the care of patients with PCa is justified[95].

While observational studies have usually found an association between ADT and cardiovascular events, RCTs have largely not shown these associations reproducibly. This may be a result of the specified inclusion and exclusion criteria[31,96], which often exclude men with pre-existing CVD from RCTs. However, a large systematic analysis of controlled studies reported in 2009 showed that ADT increased cardiovascular mortality by 17%, an absolute increase in mortality of approximately 1.5–1.7 deaths per 1000 person-years[49].

Studies have shown that ADT-targeting of GnRH/LHRH receptors with agonists increases the levels of FSH, which is involved in both vascular endothelial growth factor (VEGF)-mediated angiogenesis and vascular calcification[63,97–99]. Elevated FSH signalling has also been associated with increased adiposity and the development of atherosclerotic plaques[100]. The causes of any increased cardiovascular risk in patients undergoing ADT is unclear, and multiple possible mechanisms have been proposed, including induction of a form of metabolic syndrome, with increased adiposity and insulin resistance, GnRH receptor stimulation in peripheral blood monocytes, and increased FSH signalling

Table 2. Summary of historical landmark studies demonstrating the association between ADT and cardiovascular risk.

Study	Type of study	Patients, n	Effect on cardiovascular health
Keating et al. 2006[81]	Observational	73,196	• 16% increase in risk of coronary artery disease and of sudden cardiac death (both $p < 0.01$)
Saigal et al. 2007[82]	Observational	22,816	• Patients receiving ADT had a 20% higher risk of serious cardiovascular morbidity compared with those not receiving ADT
Tsai et al. 2007[83]	Observational	3,262	• ADT use was associated with a significantly increased risk of death from cardiovascular causes • (HR = 2.6; 95% CI, 1.4–4.7; $p = 0.002$)
Zhao et al. 2014[84]	Meta-analysis	295,407	• ADT use was associated with a higher risk of cardiovascular disease (HR = 1.10; 95% CI, 1.00–1.21; $p = 0.06$) and cardiovascular death (HR = 1.17; 95% CI, 1.04–1.32; $p = 0.01$)

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio.

found with agonist-based ADT[101]. The consequences of a loss of testosterone, and its atheroprotective properties, may also have a role[101].

For AR-targeted agents, a large pharmacovigilance study reported that abiraterone was associated with higher rates of atrial tachyarrhythmia, heart failure, hypokalemia, hypertension and edema than other testosterone-lowering therapies[102]. Other studies have reported similar results[3,103,104], while also showing differences in risk between abiraterone and enzalutamide[3,103]. However, as with studies of ADT, other studies have failed to find an association with increased risk of cardiovascular events with AR-targeted agents[89]. Data regarding any association are likely to evolve because AR-targeted agents have been available for widespread clinical use for considerably less time than ADT.

ADT and RT have been associated with an increased risk of developing hematologic disorders, including anemia, compared with radical prostatectomy only, which increased with duration of androgen deprivation[105]. Furthermore, higher 6-month mortality was observed in patients with pre-existing CVD, compared to those without, following treatment with the AR-targeted therapies abiraterone and enzalutamide[96]. Abiraterone was also associated with higher hospitalization rates in patients with pre-existing CVD and those on several classes of medications. Unfortunately, other treatment options for PCa also confer cardiovascular risks; chemotherapeutic agents such as docetaxel can cause heart failure and endothelial dysfunction[106,107]. This evidence highlights the importance of assessing patient cardiovascular risk, including CVD history and current medications, prior to treatment and throughout the continuum of care.

Finally, real-world evidence suggests that there is inadequate cardiovascular risk assessment of patients with PCa. A cross-sectional analysis of >90,000 US veterans with PCa reported that 68.1% received comprehensive cardiovascular risk factor assessment, 54.1% had uncontrolled cardiovascular risk factors and of these, 29.6% were not receiving cardiac risk-reducing medication. ADT initiation was not associated with substantial improvements in cardiovascular risk factor assessment or management[108].

Management of bone and cardiovascular health in patients with prostate cancer

The real-world data assessed have confirmed the importance of managing the recognized increased risk of bone and cardiovascular events in patients with PCa receiving ADT and AR-targeted therapy along the continuum of cancer treatment (Figure 3). However, management guidelines for such events have sometimes been adapted from those for other conditions, such as non-cancer related osteoporosis. While ongoing analysis of, e.g. the Fracture Risk Assessment Tool (FRAX) and linked hospital episode statistics for symptomatic fractures in thousands of patients in studies such as STAMPEDE, should provide further high-quality evidence, we break down the key steps for event management into 1) assess, 2) intervene and 3) monitor (Figure 4). As noted, the recent guidelines from the ESC developed in collaboration with the EHA, ESTRO and the IC-OS describe the risks associated with ADT, but do not make detailed recommendations specifically for the management of cardiovascular risk with ADT or AR-targeted therapy[25,109]. A previously reported systematic analysis of data on bone and cardiac health in men exposed to ADT suggested preventive treatment to manage fracture risk and encouraging lifestyle modifications to manage cardiovascular risk[49]. This was based on a limited number of comparative trials and data available in 2009, and did not provide guidance on how to assess baseline risk and decide on the appropriate management. We have based our recommendations on more recent real-world and observational data, thus reflecting the clinical practice setting.

Assess

Assessment of the risk to bone and cardiovascular health is critical; pre-existing risk factors should be evaluated prior to initiation of treatment and at regular intervals along the PCa pathway. Bone health in patients with PCa is heavily influenced by age, history of fractures, use of corticosteroids and duration of ADT[110]. The individual fracture risk should be calculated as a standard minimum baseline assessment. The FRAX score, which incorporates a relatively small number of clinical risk factors excluding anticancer treatments, calculates the 10-year fracture risk with or without BMD measurement[111]. FRAX does not require specialist knowledge and can be used in general practice or the outpatient setting. Alongside FRAX, a dual-energy X-ray absorptiometry (DEXA) scan should be performed where possible (Figure 3)[112]. The use of FRAX for all patients with PCa is recommended by a recent Spanish multidisciplinary consensus statement, which also recommends the use of DEXA in all patients scheduled for or on ADT[113]. However, evidence for the utility of FRAX in patients with bone metastases is limited.

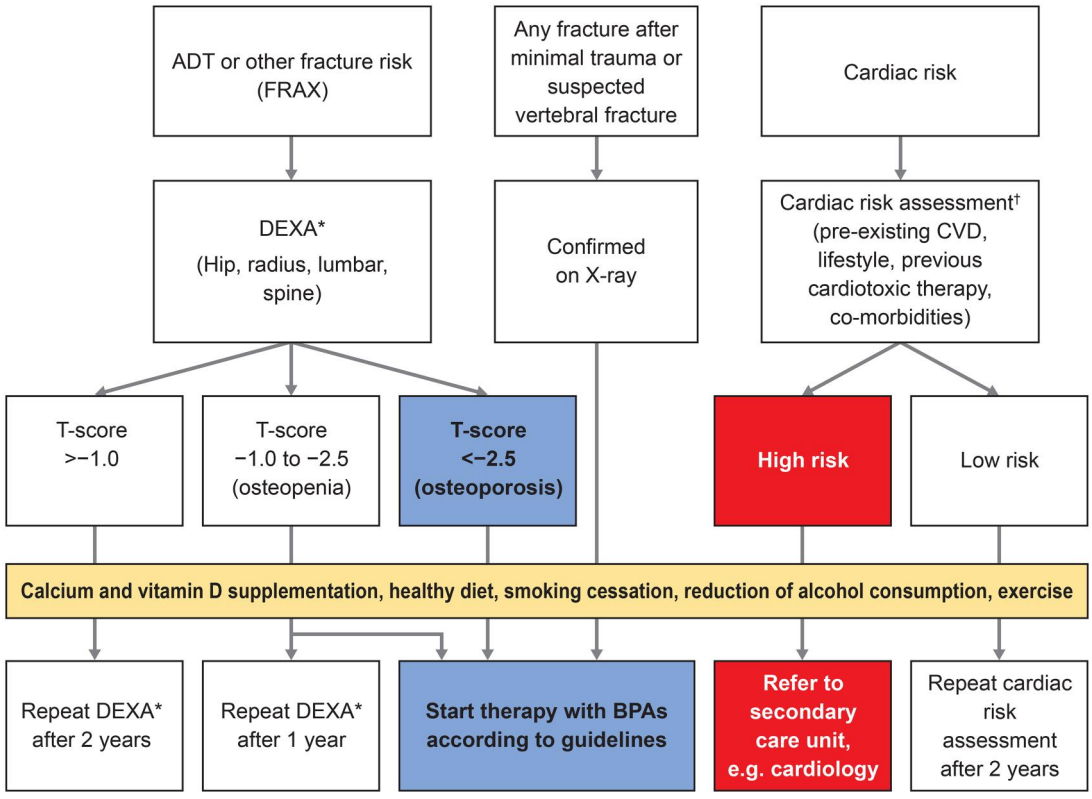

Figure 3. Treatment algorithm for assessing and managing bone and cardiovascular health in patients with PCa. Clinical presentation and baseline risk should be confirmed through DEXA, X-ray and cardiovascular risk assessment. Adequate daily intake of calcium and vitamin D should be recommended to all patients, coupled with lifestyle changes and supervised resistance and aerobic exercise. High-risk patients should be referred to specialist units and administered BPAs. All patients undergoing ADT should be monitored routinely or following changes to systemic therapy or patient risk profile.
*If DEXA scanning is unavailable, FRAX assessment can be used alone.
†The Joint Heart Failure Association and International Cardio-Oncology Society position statement recommends several established cardiovascular risk calculators that can be used for patients with PCa receiving ADT[109].

Cardiovascular risk, which is usually elevated in this patient population, is magnified by factors such as pre-existing CVD, lifestyle choices (smoking, alcohol consumption, obesity), previous cardiotoxic cancer therapy and co-morbidities such as diabetes and hypertension[109]. CVD includes previous stroke or transient ischemic attack, coronary artery disease, aortic disease and peripheral artery disease[102]. Baseline cardiovascular risk stratification should be calculated promptly according to the Joint Heart Failure Association and International Cardio-Oncology Society position statement on cardiovascular risk stratification for patients with cancer, also referred to in the recent ESC guidelines,[25,109] so as not to delay cancer treatment[109]. This takes into account previous CVD, cardiac biomarkers, demographic and cardiovascular risk factors, previous cardiotoxic cancer treatment, current anticancer therapy, and lifestyle risk factors to generate a risk score, which can be calculated using the tables included in the publication[109]. Patients may be classified as high risk if they have known pre-existing CVD or a CVD 10-year risk score $\geq$20%. Medium and low risk patients are those who have CVD 10-year risk scores of $\geq$10% to $<$20% and $<$10%, respectively[109]. A Canadian consensus statement recommends the use of a simple screening tool (STAMP) to identify patients referred for ADT with pre-existing CVD who may benefit from additional treatment and those who may benefit from referral to a cardio-oncology clinic[114]. Once cardiovascular risk is established, the full range of risk reduction measures should be undertaken, including lifestyle adjustment and pharmacology, as stated in recent guidelines[18,25].

Due to different healthcare systems and specialisms, there are differences in who is primarily responsible for the management of bone and cardiovascular health in patients with PCa. This may lead to undertreatment and inadequate care of patients[72]. Therefore, a multi-disciplinary team that includes representatives with expertise in PCa, bone pathology and cardiology needs to be involved in determining the patient care pathway; exact MDT membership can be determined based on institutional best practice[5,109]. The lack of clarity as to who is responsible for non-cancer health is often a critical weakness, and we suggest the single most important aspect of the management of patients with PCa is for the urologist/oncologist to establish unambiguously who is responsible. In our view, there is a key role for specialist nurses in the management of bone and cardiovascular health in patients with PCa. Specialist nurses should perform the baseline cardiac and bone health assessment of patients with PCa and identify risk factors, involving the MDT as needed. Specialist nurses should also provide information to patients on their treatment, including adverse effects, and direct patients to the support they may require while undergoing treatment, such as physiotherapy.

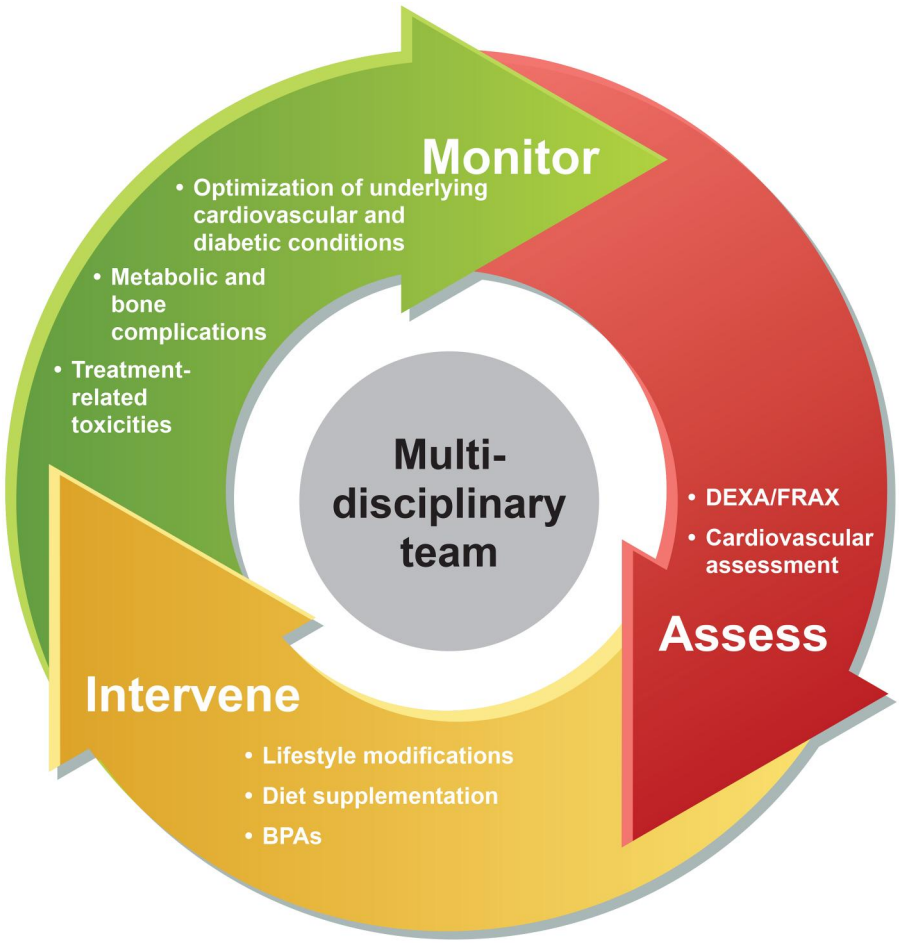

Figure 4. Continuous management of bone and cardiovascular health through repeated assessment, intervention and monitoring of patients throughout the PCa journey by a multidisciplinary team. BPA, bone-protecting agent; DEXA, dual-energy X-ray absorptiometry; FRAX, fracture risk assessment tool; PCa, prostate cancer.

Intervene

In patients receiving ADT and/or AR-targeted therapy, management of bone and cardiovascular health should include lifestyle adjustments. Basic lifestyle recommendations include smoking cessation, reduction of alcohol consumption, maintaining a healthy diet and weight-bearing and muscle-strengthening exercises[115]. Prevention of cardiovascular events in patients with PCa may require blood pressure and cholesterol control and diabetes management, which may involve pharmacological intervention[31]. Choice of treatment modality should be made taking into account pre-existing CVD where appropriate[2].

Specifically, for all men with PCa starting or on systemic therapy, NICE and European guidance recommends supervised resistance and aerobic exercise for 12 weeks[18,116]. For the management of CTIBL, dietary supplementation and BPAs is recommended[1,2,18]. Daily supplementation of calcium and vitamin D can moderately increase BMD and reduce fractures: calcium 700–1200 mg/day ideally by dietary intake with supplements added if this is insufficient, and vitamin D 800–2000 IU/day[5,72,113,117]. It is the responsibility of all healthcare providers, including GPs and pharmacists, to ensure that all patients undergoing ADT are prescribed vitamin D and calcium, if dietary calcium is insufficient (Supplementary Material Appendix B). These dietary measures alone are not proven in the prevention or treatment of bone loss in men receiving ADT for PCa. BPAs including oral (alendronate and risedronate) or intravenous (pamidronate and zoledronic acid) bisphosphonates and denosumab should be administered routinely alongside ADT or following DEXA test or FRAX calculations[5,18]. The threshold for use of BPAs for CTIBL is considered in detail in a recent consensus statement on bone health in PCa[72]. This statement states that in clinical practice, men often receive once-weekly oral bisphosphonates (alendronic acid 70 mg or risedronate sodium 35 mg), which can often be initiated by the patient's GP following assessment of fracture risk[72]. Furthermore, if oral bisphosphonates are not tolerated, it is stated that intravenous ZA (5 mg once yearly) or subcutaneous denosumab (60 mg once every 6 months) may be administered[72]. For M1 CRPC, dosing schedules are typically denosumab 120 mg or ZA 4 mg every 4 weeks[118]. Many patients with metastatic hormone-sensitive PCa currently receive no BPA treatment; for these patients, we recommend denosumab 60 mg once every 6 months as a minimum, increasing to 120 mg every 4 weeks if an SRE occurs or disease becomes castration resistant.

Monitor

Metabolic and bone complications relating to CTIBL should be monitored routinely[18]. For patients on BPAs, reassessment should be performed at 3 years for those receiving intravenous ZA and 5 years for oral bisphosphonate or denosumab use[72]. Patients should be closely monitored for the potential toxicities of BPAs such as osteonecrosis of the jaw, hypocalcemia and renal toxicity[18]. For patients not on BPAs, DEXA and FRAX as well as cardiovascular risk assessment should be repeated after 12–24 months, or if there is a change in treatment or risk factor profile (Figure 3). As patients are likely to be elderly with multiple comorbidities, an annual review and optimisation of any underlying medical conditions such as hypertension, diabetes, etc., should be performed. It is the joint responsibility of primary, secondary and tertiary care providers to monitor bone and cardiovascular health in patients with PCa and seek the advice of specialist units for high-risk patients. A draft letter to GP is attached in Supplementary Material Appendix B.

Conclusions

With improved survival rates and longer durations of treatment, maintenance of bone and cardiovascular health is increasingly important in patients with PCa. Risk is a continuous variable that must be assessed throughout the continuum of PCa treatment. The basic strategies of assessing, intervening and monitoring should be implemented by all healthcare providers with a responsibility for patient care.

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Authors' contributions

Study concept and design: LDC, PD, JB; acquisition of data: LDC, PD, ELG, JB; analysis and interpretation of data: LDC, PD, JM, ELG, JB; drafting of the manuscript: LDC, PD, JM, QH, ELG, JB; critical revision of the manuscript for important intellectual content: JB, LDC, PD, JM, ELG, QH; statistical analysis: LDC; obtaining funding: LDC, ELG, JB; administrative, technical, or material support: LDC, ELG; supervision: LDC, PD.

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