Cardiovascular Risk in Prostate Cancer

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KEYWORDS

• Cardio-oncology • Risk factors • Prostate cancer • Cardiovascular disease
• Androgen deprivation therapy

KEY POINTS

- Patients with prostate cancer have a high burden of cardiovascular risk factors, which are often suboptimally controlled. The best strategy for stratifying and addressing cardiovascular risk in patients with prostate cancer has not been defined.
- Androgen deprivation therapy (ADT), most frequently administered in the form of a gonadotropin-releasing hormone (GnRH) agonist, is a cornerstone of prostate cancer therapy. It leads to increased adiposity and loss of skeletal muscle strength and has been associated with an increase in the risk of developing hypertension and diabetes. ADT has been weakly associated with an increase in the risk of adverse cardiovascular outcomes. However, these data are methodologically limited and the association needs confirmation in prospective studies.
- Androgen receptor signaling inhibitors (eg, enzalutamide, apalutamide, darolutamide) and cytochrome p450 17A1 (CYP17A1) inhibitors (eg, abiraterone) are used in addition to GnRH agonists for metastatic prostate cancer and increasingly for high-risk nonmetastatic disease. They increase hypertension over and above GnRH agonists and have been associated with incremental cardiovascular risk.
- GnRH antagonists have been associated with less adverse cardiovascular outcomes than GnRH agonists. However, this observation has yet to be proven in a prespecified randomized, controlled trial. While GnRH antagonists can be considered in patients at high cardiovascular risk, there is insufficient high-quality evidence to support its routine use in this population for the reduction of cardiovascular events.

INTRODUCTION

Patients with diverse cancers, including prostate cancer (PC), are experiencing progressive improvements in survival owing to advances in cancer therapeutics. This shift alone will leave populations of patients treated for cancer susceptible to the competing risk of cardiovascular disease (CVD). Coupled with the cardiotoxicity of some cancer treatments, many patients with cancer might be at high risk of developing CVD, and their management complicated by specific treatment and prognostic considerations of both morbidities. These issues have led to the rapid growth of the field of cardio-oncology.

Worldwide, PC is the most common cancer in men.[1] It is projected that the number of new PC cases annually will double between 2020 and 2040, from 1.4 million per year to 2.9 million.[2] It is estimated that over 3.5 million men in the United

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Cardiol Clin 43 (2025) 83–91
https://doi.org/10.1016/j.ccl.2024.09.003

States have been diagnosed with PC[3] and there are approximately 300,000 new cases annually.[4] Importantly, at least 90% of patients with newly diagnosed PC in contemporary cohorts will have localized disease, and PC mortality in these individuals is infrequent, occurring in less than 1.5% of patients per year.[5,6] Even in those with de novo metastatic disease, survival rates are generally 4 to 5 years.[7] Therefore, many patients with PC will be at risk of cardiovascular events for an extended time and the burden of cardio-oncology morbidity in patients treated for PC is large and will likely increase. The purpose of this article is to discuss what is known about the epidemiology of cardiovascular risk factors and disease in the PC population; the role of specific PC treatments in promoting cardiovascular risk factors and disease; strategies to address these challenges; and considerations in the management of severe CVD in patients with PC.

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN PATIENTS WITH PROSTATE CANCER

Most patients with localized disease have excellent long-term cancer-specific survival and for contemporary patients who are diagnosed with metastatic disease, cancer-specific survival is usually over 4 years.[8,9] The widespread use of screening, especially in high-income countries and settings, has led to increases in PC incidence, including the identification of many patients in the indolent phase. The favorable life-expectancy among these patients with early-stage PC[5] leaves them at risk of developing comorbid conditions for an extended time. Among such comorbidities, cardiovascular risk factors and disease are particularly relevant if only because of their frequency in men of the same demographic typically affected by PC.

In the subgroup of patients with PC who will develop advanced disease, hormonal therapy represents the cornerstone of cancer control. However, these treatments are well recognized as leading to worsening cardiometabolic complications. Such complications enhance the importance of cardiovascular risk factors and disease in patients with PC.

Among men with nonmetastatic PC in the United States, CVD is a more frequent cause of death than the cancer itself, while even in those with metastatic disease, the standardized cardiovascular mortality ratio is 1.48 (95% confidence interval [CI]: 1.41–1.54), indicating that these patients are at approximately 50% higher risk of cardiovascular death than expected for their age.[10] These data indicate that CVD may be very important comorbidity in patients with PC.

MECHANISMS UNDERLYING CARDIOVASCULAR DISEASE IN PROSTATE CANCER

Patients with PC may develop CVD frequently because of several potential reasons. These include demographic factors, shared risk factors, and the effects of androgen deprivation therapy (ADT; **Fig. 1**).

Demographics and Cardiovascular Risk Factors in Patients with Prostate Cancer

PC most frequently affects older men, a demographic that is inherently characterized by elevated CVD risk. Patients with PC exhibit a high burden of cardiovascular risk factors even at the time of PC diagnosis. In a large Canadian cohort, 58% of individuals with PC were current or former smokers, 45% had hypertension, 16% diabetes, 31% were obese (with body mass index $\geq$30 kg/m^2), 24% had low levels of physical activity, and 22% already had established CVD.[11] For these reasons, 69% had a Framingham cardiovascular risk score associated with a high risk for future adverse cardiovascular outcomes. While these risk factors are clearly associated with a high burden of CVD,[12,13] some may also be risk factors for PC (especially more aggressive PC), although epidemiologic patterns are inconsistent. Some prospective cohort data suggest that there is no relationship between cardiovascular risk factors and the incidence of PC.[14] However, other data suggest that every 5 kg/m^2 increase in body mass index has been associated with a relative risk of advanced PC of 1.12 (95% CI: 1.01–1.23).[15] This contrasts with evidence that diabetes has been associated with a lower incidence of PC,[16] while vigorous physical activity, which is typically associated with a lower risk of diabetes, has been linked with a lower risk of advanced PC.[17] *In summary, while the burden of cardiovascular risk factors in patients with PC is high, it is unclear whether they play a role in promoting the development or progression of PC.*

Androgen Deprivation Therapy

ADT is a fundamental part of the therapeutic armamentarium against advanced PC (**Fig. 2**). Ever since the seminal discovery of the effects of orchiectomy in patients with metastatic PC,[18] ADT, now more frequently administered in the form of gonadotropin-releasing hormone (GnRH)

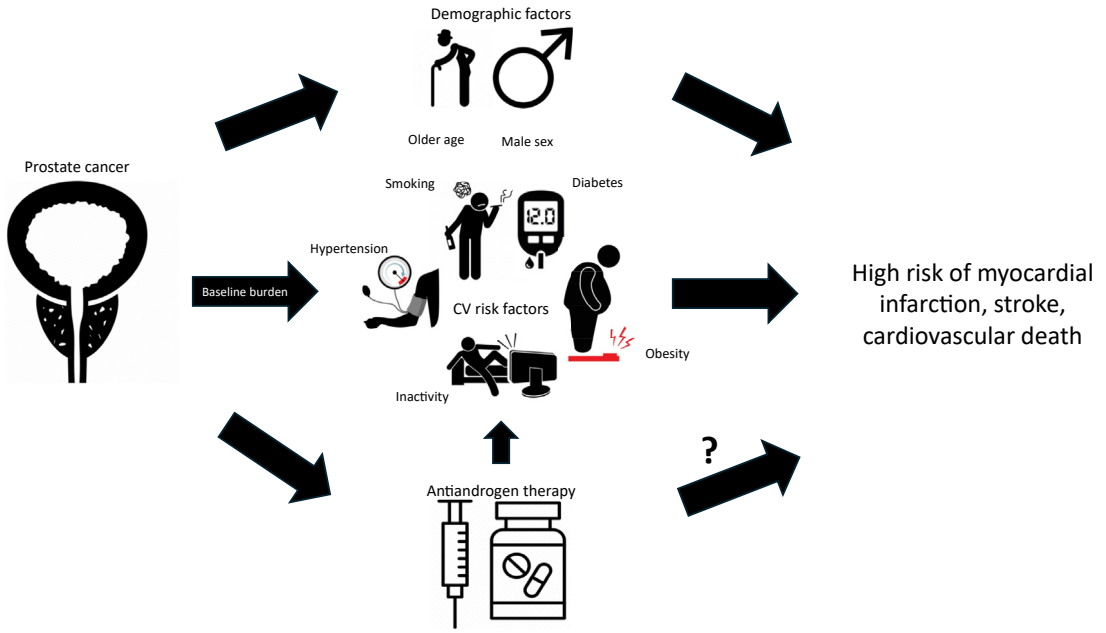

Fig. 1. Factors that may account for high cardiovascular risk in patients with prostate cancer. These include age and a high burden of conventional cardiovascular risk actors, which may be exacerbated by androgen deprivation therapy.

agonists together with new generation androgen receptor axis inhibitors, is standard-of-care for metastatic disease. ADT is also often used as adjuvant therapy with radiotherapy or in patients with evidence of biochemical relapse after previous definitive PC therapy. In this population, ADT reduces PC-specific mortality and overall mortality, with respective relative risks (95% CIs) of 0.69 (0.56–0.84) and 0.86 (0.80–0.93).[19]

The most common contemporary means of delivering ADT is as subcutaneous or depot GnRH agonist injection, which can be administered at intervals of 1, 3, 4, or 6 months. These drugs continuously stimulate the anterior pituitary, resulting in an initial surge of luteinizing hormone, and thus, testosterone. However, continuous (rather than physiologic pulsatile) stimulation of the anterior pituitary rapidly leads to marked reductions in luteinizing hormone, and thus testicular testosterone synthesis.

Gonadotropin-releasing hormone agonists and cardiovascular risk

GnRH agonists lead to weight gain, mostly through inducing an increase in fat mass, which increases by approximately 11%[20] (**Table 1**). Given the close relationship among adiposity, diabetes, and hypertension, it is an unsurprising consequence of weight gain that GnRH agonist use has been associated with an increased risk of diabetes and hypertension. In a large retrospective analysis, ADT use was associated with a 60% increase in the risk of developing diabetes among patients with localized PC.[21] In another large, retrospective Taiwanese study, ADT use was associated with an 80% higher risk of developing hypertension.[22]

GnRH agonists are also well known to cause loss of skeletal muscle strength.[23] Muscle strength is an underappreciated risk factor for adverse cardiovascular outcomes, including myocardial infarction, stroke, heart failure, and cardiovascular death.[13,24]

A meta-analysis of retrospective studies found that GnRH agonist use was associated with nonfatal cardiovascular events, with relative risk (95% CI) 1.38 (1.29–1.48).[25] In a retrospective analysis of patients with localized PC, ADT was associated with an approximately 2 fold higher risk of cardiovascular death in men aged 65 years or more who had undergone prostatectomy, with 5 year cumulative incidence rates of 5.5% (95% CI 1.2%–9.8%) as compared with 2.0% (95% CI 1.1%–3.0%) in those not receiving ADT.[26] This finding contrasts with those of a meta-analysis of randomized trials in which up-front ADT was compared with a control arm of delayed or no ADT.[19] In this study, no difference in the risk of cardiovascular death was observed.

Given the metabolic effects of ADT, it is plausible that ADT is a risk factor for subsequent CVD. However, the association between ADT and adverse cardiovascular events has been poorly characterized because most data are from

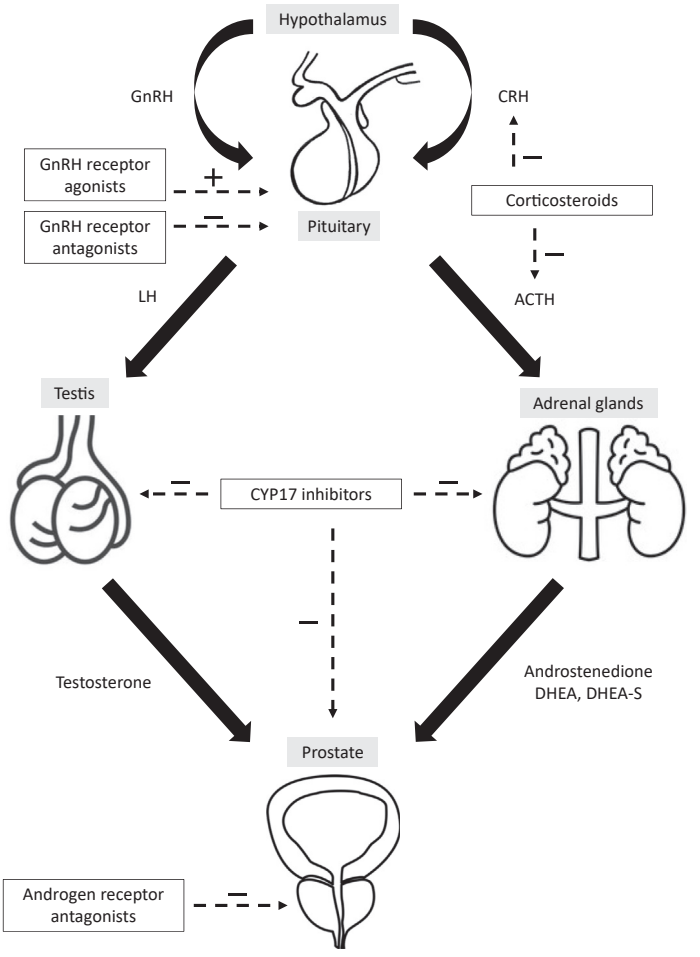

Fig. 2. Mechanisms of action of pharmacologic approaches to inhibiting androgen effects on prostate cancer. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

retrospective studies—mostly using administrative sources—where the ability to account for confounding factors is limited.

GnRH antagonists represent another means of inhibiting anterior pituitary gland stimulation of testicular testosterone synthesis. The relationship between this drug class and cardiovascular outcomes is described subsequently, given the promising but inconclusive evidence that GnRH antagonists may lead to fewer adverse cardiovascular events than GnRH agonists.

Table 1
Likely effects of androgen deprivation therapy on cardiovascular risk factors

Cardiovascular Risk Factor	ADT Effect
Adiposity	
Weight	↑
Waist Circumference	↑
Waist–hip Ratio	↔
Hypertension/Blood Pressure	↑
Diabetes/Blood Glucose	↑
Muscle Strength	↓
Lipids	
Triglycerides	↑

Other androgen pathways inhibitors

Castrate-resistant PC develops when the cancer acquires mutations that enable disease progression despite castrate levels of testosterone. It is recognized, however, that castrate-resistant PC is still frequently driven by androgens, but that the responsible mutations enhance the tumor's ability to proliferate under conditions of low-circulating testosterone and de novo intra-tumoral synthesis of androgens. Mechanisms include amplification or augmented sensitivity of androgen receptors, and responsiveness to non-testosterone androgens. Understanding of these pathophysiologic pathways has led to the development of classes of drugs, such as androgen receptor signaling

inhibitors (eg, enzalutamide, apalutamide, darolutamide) and CYP17A1 inhibitors (eg, abiraterone), which inhibit adrenal synthesis of androgen precursors, such dehydroepiandrosterone. Importantly, abiraterone, enzalutamide, darolutamide, and apalutamide prolong overall survival in patients with metastatic PC.[9,27–29]

As compared to placebo, abiraterone and, to a greater extent, enzalutamide are associated with an increased risk of hypertension, with respective relative risks (95% CI): 1.46 (1.20–1.78) and 2.66 (1.93–3.66).[30] Population-based research from Sweden demonstrated that these 2 drugs are associated with a higher risk of incident CVD than their nonuse, with respective hazard ratios (95% CI) for abiraterone and enzalutamide of 1.19 (1.03–1.38) and 1.10 (1.01–1.20).[31] Importantly, the increase in cardiovascular risk associated with these newer androgen pathway inhibitors is incremental to GnRH agonists, with which these drugs are used in combination. A further consideration is a potential for drug–drug interactions between these drugs and cardiovascular medications through cytochrome P450 and p-glycoprotein inhibition.

ADDRESSING CARDIOVASCULAR RISK IN PATIENTS WITH PROSTATE CANCER

Gaps in Cardiovascular Risk Factor Control

Data from both administrative sources and a prospective cohort study suggest that cardiovascular risk factor control is suboptimal in patients with PC. Among US veterans with PC, 36% did not have blood pressure below a threshold of 140/90 mm Hg, 22% had elevated cholesterol levels as identified by low-density lipoprotein cholesterol of 130 mg/dL or greater or total cholesterol 240 mg/dL or greater, and 17% had glycated hemoglobin (HbA1c) 7% or greater or fasting glucose levels 126 mg/dL or greater.[32] The thresholds referenced in this analysis were not refined according to patient's past history of CVD or cardiovascular risk. However, general cardiology guidelines recommend risk factor targets that vary, with more aggressive goals in those with established CVD or risk factors, such as diabetes. In 2811 patients with PC from 4 countries, risk factor targets were specified according to these participant characteristics. With these more stringent thresholds, 51% had suboptimal control of 3 of 5 or greater modifiable cardiovascular risk factors.[33] Ten percent were current smokers, 20% were considered physically inactive, 51% had low-density lipoprotein cholesterol levels above target, 75% had suboptimal blood pressure, and 91% had an elevated waist–hip ratio (>0.90). These data indicate that many patients with PC have suboptimal control of cardiovascular risk factors, highlighting an important care gap.

The optimal strategy to address this gap in care is unclear. Many uro-oncologists scope of practice may not extend to requesting and interpreting blood glucose and lipid results. While primary care may be considered the appropriate setting for managing cardiovascular risk factors, especially in patients receiving ADT, the data presented earlier indicate that risk factor targets are frequently unmet in these cohorts, despite most having had access to primary health care. Tools have been developed to help uro-oncologists identify patients with CVD, address cardiovascular risk factors, and refer suitable patients to a cardio-oncologist.[34] However, the extent to which clinicians will have the capacity to implement these recommendations, and their effectiveness at reducing cardiovascular risk, is unknown.

The implementation of cardiovascular risk scores may represent one way of identifying patients with PC who are at high cardiovascular risk. There are limited data about the validity of risk scores in PC populations that have been developed in the general population. The New Zealand cardiovascular risk prediction equation predicts 5 year cardiovascular event rates in New Zealand patients with PC.[35] The generalizability of this finding to other countries, and whether the inclusion of ADT use or PC characteristics in the risk score would add incremental information, is not known.

The Speculative Role of Gonadotropin-Releasing Hormone Antagonists

Unlike GnRH agonists, which achieve testosterone suppression by continual stimulation of the anterior pituitary, GnRH antagonists block the effects of GnRH on the pituitary. This leads to a more rapid and persistent suppression of luteinizing hormone, as well as testosterone release.

Degarelix was the first GnRH antagonist to achieve widespread availability. A post hoc analysis of early-phase randomized, controlled trials demonstrated that degarelix may be associated with fewer cardiovascular events than a GnRH agonist.[36] In addition, there are complementary data from animal models that raise the hypothesis that GnRH antagonists might differ from GnRH agonists with respect to their atherogenic effects. In in vivo studies in low-density lipoprotein (LDL) receptor (LDLR) knockout mice, the GnRH receptor antagonist, degarelix, led to less atherosclerotic aortic disease than a GnRH agonist.[37] In a more

recent in vivo study using a double-knockout (LDLR-/follicle-stimulating hormone [FSH]-) mouse model,[38] we demonstrated that FSH facilitates the atherogenic effects of testosterone deprivation. Specifically, FSHβ$^{-/-}$: LDLR$^{-/-}$ mice, untreated or castrated (orchiectomy, GnRH agonist, or antagonist), demonstrated significantly less atherogenesis compared with similarly treated LDLR$^{-/-}$ mice. Delivery of exogenous FSH in FSHβ$^{-/-}$;LDLR$^{-/-}$ mice restored the significant atherosclerotic changes seen in untreated LDLR$^{-/-}$ mice. Smaller plaque burden in LDLR$^{-/-}$ mice receiving GnRH antagonists versus agonists was nullified in FSHβ$^{-/-}$:LDLR$^{-/-}$ mice. Importantly, these data should be considered hypothesis generating only because they relate to atherogenesis and characteristics of atherosclerotic plaque vulnerability in a murine model and not to clinical cardiovascular events.

Interest in this potential protective effect of GnRH antagonists was renewed when the HERO trial found a lower incidence of cardiovascular events in patients randomized to receive the oral GnRH antagonist, relugolix, as compared with the GnRH agonist, leuprolide.[39] When these data were included in a systematic review of randomized trials of GnRH antagonists, the pooled risk ratios (95% CIs) for adverse cardiovascular events, cardiovascular death, and all-cause mortality were respectively 0.57 (0.39–0.81), 0.49 (0.25–0.96), and 0.48 (0.28–0.83) as compared with GnRH agonists.[40] However, an important caveat to these data was the high risk of bias in the trials identified.

The PRONOUNCE trial was the first prospective trial to compare a GnRH antagonist (degarelix) with a GnRH agonist (leuprolide) with respect to a primary cardiovascular endpoint.[41] However, the trial was terminated prematurely by the sponsor when only 545 of the planned 900 participants had been enrolled. Owing to the reduced sample size, as well as a lower outcome event rate than anticipated (which may have been partly related to the requirement that all participants be managed by a cardiologist), the trial was not powered to be able to draw inference about the cardiovascular effects of degarelix.[42] When the findings from this trial were incorporated into an updated meta-analysis, the odds ratios (95% credible interval) for the composite of major adverse cardiovascular events and overall mortality were respectively 0.57 (0.37–0.86) and 0.58 (0.32–1.08).[43] However, as with the prior meta-analysis, confidence in these findings is low owing to the open-label nature of the trials and other potential biases and methodological limitations. Currently, it remains unclear whether GnRH antagonists offer cardiovascular benefits over GnRH agonists. Further, there are clinical limitations to the current commercially available GnRH antagonists. Degarelix, which requires monthly injections, leads to a higher rate of skin adverse effects than GnRH agonists that can be administered less frequently. Relugolix is an oral agent, which requires adherence to a daily-dosing regimen. Research is ongoing into teverelix, a GnRH antagonist that can be administered every 6 weeks.

MANAGEMENT OF SEVERE CARDIOVASCULAR DISEASE IN PATIENTS WITH METASTATIC PROSTATE CANCER

Administrative data suggest that survival with metastatic PC is increasing. Between 2008 and 2020, 5 year survival in patients with metastatic castrate-sensitive disease in Sweden increased from 26% to 35%.[44] In the United States, from the years 2000 to 2004 to 2015 to 2019, among patients with de novo metastatic PC, median survival increased from 23 months to 30 months in the SEER registry and from 26 months to 31 months in the Veterans Health Administration registry.[45] The progressive improvement in overall survival in patients with metastatic PC exposes this population to the risk of developing severe CVD for a longer time, which is especially pertinent given the cardiovascular risks described previously.

There are numerous ongoing developments in the treatment of advanced PC, including the addition of androgen receptor signaling inhibitors to a GnRH agonist; PARP inhibitors; the promise of prolonged disease control with the use of radiotherapy for oligometastases; and prostate-specific membrane antigen-targeted therapies. These strategies have delivered or are expected to deliver even longer survival for patients with metastatic PC.

Historically (and to some extent currently), a cancer diagnosis has been associated with less invasive treatment of coronary artery disease.[46] Given the improving survival and rapid advances in metastatic PC treatment, the role of invasive cardiovascular interventions in patients with metastatic disease needs to be carefully considered. Factors that contribute to the decision-making process include characteristics of both the PC and the cardiovascular comorbidity; non-PC, non-cardiovascular comorbidities, including the risk of bleeding; and patient goals-of-care.[47] In general, cardiovascular interventions that confer substantial benefit (including symptomatic benefit) rapidly, such as primary percutaneous coronary intervention for ST-elevation myocardial infarction, transcatheter aortic valve implantation (TAVI), a routine invasive approach for non-ST elevation myocardial

infarction with ongoing symptoms, and cardiac resynchronization therapy for severe symptomatic heart failure, are compelling in many patients with metastatic PC. In contrast, invasive strategies like primary prevention implantable cardioverter-defibrillators that confer little symptomatic benefit and whose survival benefits are only observed after a longer lag are generally not indicated in those with metastatic cancer. The most challenging of decisions relates to the role of coronary revascularization (and in particular coronary artery bypass surgery) for minimally symptomatic multivessel coronary disease because the survival advantage over medical therapy is more modest, because of the front-loaded procedural risks and because net benefit may only be apparent years after intervention.

As localized PC has a low risk of 10 year PC-specific mortality, most invasive cardiovascular interventions that are otherwise indicated should be adopted in these patients. Among cardiac interventions, cardiac transplantation arguably demands the largest commitment on the part of the patient, health care providers, and health systems. At present, cardiac transplantation in patients with localized PC is only considered in a minority of intuitions in the United States.[48] Further research on outcomes in patients with localized PC may inform cardiac transplantation policies given their generally favorable cancer prognosis.

In some instances, PC may be diagnosed during the work-up of patients for invasive cardiac interventions. In one series of 414 German patients who underwent imaging in preparation for TAVI, 36 (9%) had incidental findings consistent with malignancy with a potential impact on life expectancy, including 3 (0.7%) with advanced PC.[49] While this research is methodologically limited, there was no evidence that such findings changed patient management or outcomes in these patients with an indication for TAVI.

In summary, the decision to undertake an invasive cardiovascular intervention in a patient with metastatic PC should be informed by a multidisciplinary team, with the patient and their caregivers at the center of the decision-making process, so that their goals-of-care are prioritized.

SUMMARY

CVD is common in patients with PC and is an important cause of death. Cardiovascular risk factors are frequent in this population and are often not addressed to thresholds recommended by cardiovascular practice guidelines. Further research is needed to understand the reasons for these treatment gaps and to examine the role of low education, racial inequities, disparities in access to care, patient perceptions of health priorities, and the impact of anxiety and depression.

ADT reduces muscle strength and increases adiposity, thereby increasing the risk of diabetes and hypertension, although its relationship with adverse cardiovascular events requires confirmation. Androgen receptor signaling inhibitors and CYP17A1 inhibitors may confer incremental risks of hypertension and cardiovascular events to ADT, so these patients may require particularly close clinical attention.

GnRH antagonists have been linked with a lower cardiovascular risk as compared with GnRH agonists. However, this association has yet to be confirmed in a randomized clinical trial that has implemented the appropriate measures to mitigate bias. Until such data are available, it is reasonable to consider GnRH antagonists in individuals at high cardiovascular risk who are likely to comply with GnRH antagonist regimens.

CLINICS CARE POINTS

- Clinicians should be aware that patients with prostate cancer frequently have a high burden of cardiovascular risk factors and disease, which may be undertreated.
- Androgen deprivation therapy increases adiposity and decreases muscle strength. Strategies for monitoring blood pressure, blood glucose levels and lipid levels should be developed.
- Prescribers should be aware of the potential for pharmacokinetic drug-drug interactions related to androgen receptor signaling inhibitors and abiraterone. These drugs also increase the risk of hypertension and fluid retention.
- It is uncertain whether GnRH antagonists, such as degarelix and relugolix, offer cardiovascular benefits over GnRH agonist androgen deprivation therapy regimens.

DISCLOSURE

D.P. Leong reports consultancy fees or advisory boards from Abbvie, Ipsen, Janssen, Jazz Pharmaceuticals, Myovant, Novartis, Sanofi, Antev, Bayer, Boston Scientific; speaker fees from Ferring, Pfizer, AstraZeneca; and research grants from Tolmar and Novartis. J.H. Pinthus reports consultancy fees or advisory boards from Ferring, Myovant and Antev; speaker fees from Ferring and research grants from Ferring. F. Cirne has no disclosures.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209–49.
2. James ND, Tannock I, N'Dow J, et al. The Lancet Commission on prostate cancer: planning for the surge in cases. Lancet 2024. https://doi.org/10.1016/S0140-6736(24)00651-2.
3. Miller KD, Nogueira L, Devasia T, et al. Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin 2022;72(5):409–36.
4. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74(1):12–49.
5. Hamdy FC, Donovan JL, Lane JA, et al. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2023;388(17):1547–58.
6. Clark R, Vesprini D, Narod SA. The effect of age on prostate cancer survival. Cancers 2022;14(17). https://doi.org/10.3390/cancers14174149.
7. Hamid AA, Sayegh N, Tombal B, et al. Metastatic hormone-sensitive prostate cancer: toward an era of adaptive and personalized treatment. Am Soc Clin Oncol Educ Book 2023;43:e390166.
8. Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. Lancet 2022;399(10336):1695–707.
9. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med 2022;386(12):1132–42.
10. Weiner AB, Li EV, Desai AS, et al. Cause of death during prostate cancer survivorship: a contemporary, US population-based analysis. Cancer 2021;127(16):2895–904.
11. Leong DP, Fradet V, Shayegan B, et al. Cardiovascular risk in men with prostate cancer: insights from the RADICAL PC study. J Urol 2020;203(6):1109–16.
12. Global Cardiovascular Risk C, Magnussen C, Ojeda FM, et al. Global effect of modifiable risk factors on cardiovascular disease and mortality. N Engl J Med 2023;389(14):1273–85.
13. Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet 2020;395(10226):795–808.
14. Lau ES, Paniagua SM, Liu E, et al. Cardiovascular risk factors are associated with future cancer. JACC CardioOncol 2021;3(1):48–58.
15. MacInnis RJ, English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. Cancer Causes Control 2006;17(8):989–1003.
16. Feng X, Song M, Preston MA, et al. The association of diabetes with risk of prostate cancer defined by clinical and molecular features. Br J Cancer 2020;123(4):657–65.
17. Pernar CH, Ebot EM, Pettersson A, et al. A prospective study of the association between physical activity and risk of prostate cancer defined by clinical features and TMPRSS2:ERG. Eur Urol 2019;76(1):33–40.
18. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. J Urol 2002;168(1):9–12.
19. Nguyen PL, Je Y, Schutz FA, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. Meta-Analysis Research Support, Non-U.S. Gov't. JAMA 2011;306(21):2359–66.
20. Smith MR, Lee H, McGovern F, et al. Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer: differences from the classic metabolic syndrome. Cancer 2008;112(10):2188–94.
21. Tsai HT, Keating NL, Van Den Eeden SK, et al. Risk of diabetes among patients receiving primary androgen deprivation therapy for clinically localized prostate cancer. J Urol 2015;193(6):1956–62.
22. Wu YH, Jhan JH, Ke HL, et al. Risk of developing hypertension after hormone therapy for prostate cancer: a nationwide propensity score-matched longitudinal cohort study. Int J Clin Pharm 2020;42(6):1433–9.
23. Gonzalez BD, Jim HSL, Small BJ, et al. Changes in physical functioning and muscle strength in men receiving androgen deprivation therapy for prostate cancer: a controlled comparison. Support Care Cancer 2016;24(5):2201–7.
24. Leong DP, Teo KK, Rangarajan S, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. Lancet 2015;386(9990):266–73.
25. Bosco C, Bosnyak Z, Malmberg A, et al. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol 2015;68(3):386–96.
26. Tsai HK, D'Amico AV, Sadetsky N, et al. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. Research Support, Non-U.S. Gov't. J Natl Cancer Inst 2007;99(20):1516–24.
27. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of

a randomised, double-blind, phase 3 trial. Lancet Oncol 2019;20(5):686–700.
28. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371(5):424–33.
29. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381(1):13–24.
30. Lee HY, Chen HL, Teoh JY, et al. Abiraterone and enzalutamide had different adverse effects on the cardiovascular system: a systematic review with pairwise and network meta-analyses. Prostate Cancer Prostatic Dis 2021;24(1):244–52.
31. George G, Vikman H, Gedeborg R, et al. Risk of cardiovascular events in men on abiraterone or enzalutamide combined with GnRH agonists: nation-wide, population-based cohort study in Sweden. Acta Oncol 2021;60(4):459–65.
32. Sun L, Parikh RB, Hubbard RA, et al. Assessment and management of cardiovascular risk factors among US veterans with prostate cancer. JAMA Netw Open 2021;4(2):e210070.
33. Klimis H, Pinthus JH, Aghel N, et al. The burden of Uncontrolled cardiovascular risk factors in men with prostate cancer: a RADICAL-PC analysis. JACC CardioOncol 2023;5(1):70–81.
34. Kenk M, Gregoire JC, Cote MA, et al. Optimizing screening and management of cardiovascular health in prostate cancer: a review. Can Urol Assoc J 2020;14(9):E458–64.
35. Tawfiq E, Selak V, Elwood JM, et al. Performance of cardiovascular disease risk prediction equations in more than 14 000 survivors of cancer in New Zealand primary care: a validation study. Lancet 2023; 401(10374):357–65.
36. Albertsen PC, Klotz L, Tombal B, et al. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Research Support, Non-U.S. Gov't. Eur Urol 2014;65(3):565–73.
37. Hopmans SN, Duivenvoorden WC, Werstuck GH, et al. GnRH antagonist associates with less adiposity and reduced characteristics of metabolic syndrome and atherosclerosis compared with orchiectomy and GnRH agonist in a preclinical mouse model. Urol Oncol 2014. https://doi.org/10.1016/j.urolonc.2014.06.018.
38. Duivenvoorden WCM, Margel D, Subramony Gayathri V, et al. Follicle-stimulating hormone exacerbates cardiovascular disease in the presence of low or castrate testosterone levels. JACC Basic Transl Sci 2024;9(3):364–79.
39. Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. N Engl J Med 2020;382(23):2187–96.
40. Cirne F, Aghel N, Petropoulos JA, et al. The cardiovascular effects of Gnrh antagonists in men with prostate cancer. Eur Heart J Cardiovasc Pharmacother 2021. https://doi.org/10.1093/ehjcvp/pvab005.
41. Melloni C, Slovin SF, Blemings A, et al. Cardiovascular safety of degarelix versus leuprolide for advanced prostate cancer. JACC CardioOncol 2020;2(1):70–81.
42. Lopes RD, Higano CS, Slovin SF, et al. Cardiovascular safety of degarelix versus leuprolide in patients with prostate cancer: the primary results of the PRONOUNCE randomized trial. Circulation 2021;144(16): 1295–307.
43. Nelson AJ, Lopes RD, Hong H, et al. Cardiovascular effects of GnRH antagonists compared with agonists in prostate cancer: a systematic review. JACC CardioOncol 2023;5(5):613–24.
44. Corsini C, Garmo H, Orrason AW, et al. Survival trend in individuals with de novo metastatic prostate cancer after the introduction of doublet therapy. JAMA Netw Open 2023;6(10):e2336604.
45. Schoen MW, Montgomery RB, Owens L, et al. Survival in patients with de novo metastatic prostate cancer. JAMA Netw Open 2024;7(3):e241970.
46. Bharadwaj A, Potts J, Mohamed MO, et al. Acute myocardial infarction treatments and outcomes in 6.5 million patients with a current or historical diagnosis of cancer in the USA. Eur Heart J 2020; 41(23):2183–93.
47. Leong DP, Cirne F, Aghel N, et al. Cardiac interventions in patients with active, advanced solid and hematologic malignancies: JACC: CardioOncology state-of-the-art review. JACC CardioOncol 2023; 5(4):415–30.
48. Raikhelkar J, Pham M, Lourenco L, et al. Heart transplantation in patients with localized prostate cancer-Are we denying a life-saving therapy due to an indolent tumor? Clin Transplant 2020;34(11):e14080.
49. Stachon P, Kaier K, Milde S, et al. Two-year survival of patients screened for transcatheter aortic valve replacement with potentially malignant incidental findings in initial body computed tomography. Eur Heart J Cardiovasc Imaging 2015;16(7):731–7.