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STATE-OF-THE-ART REVIEW

Cardiovascular Risk in Prostate Cancer

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

Cardiovascular disease is common in patients with prostate cancer and is a significant cause of death. Cardiovascular risk factors are frequent in this population and are often not addressed to thresholds recommended by cardiovascular practice guidelines. Androgen deprivation therapy reduces muscle strength and increases adiposity, increasing the risk for diabetes and hypertension, although its relationship with adverse cardiovascular events requires confirmation. Androgen receptor pathway inhibitors, including androgen receptor antagonists and cytochrome P450 17A1 inhibitors confer incremental risks for hypertension and cardiovascular events to androgen deprivation therapy. Lower cardiovascular risk with gonadotropin-releasing hormone antagonists compared with agonists requires confirmation in well-designed randomized trials. (JACC CardioOncol. 2024;6:835–846) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Prostate cancer (PC) is the most common cancer in men.[1] It is projected that worldwide, the number of new PC cases annually will double between 2020 and 2040, from 1.4 million per year to 2.9 million.[2] Cardiovascular disease (CVD) is an important comorbidity for patients with PC. In this state-of-the-art review, we provide a comprehensive, contemporary analysis of the epidemiology of CVD in the PC population; describe potential mechanisms that may explain the increased risk for CVD; examine cardiotoxicities associated with various PC treatment strategies; and discuss approaches to address CVD and its risk factors in patients with PC.

EPIDEMIOLOGY OF CVD IN PATIENTS WITH PC

CVD is a common comorbidity in patients with PC (**Table 1**), contributing significantly to morbidity and mortality in this population. Among more than 90,000 U.S. veterans with PC, 17% had established atherosclerotic CVD.[3] The prevalence of CVD was especially high (21%) among those treated with androgen deprivation therapy (ADT). We conducted a prospective study seeking to enroll an unbiased cohort of patients with PC.[4] Among 2,492 Canadian participants, 92% had newly diagnosed PC, of whom

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ABBREVIATIONS AND ACRONYMS

ADT = androgen deprivation therapy

ARPI = androgen receptor pathway inhibitor

CVD = cardiovascular disease

GnRH = gonadotropin-releasing hormone

PC = prostate cancer

SCORE2 = Systematic Coronary Risk Evaluation 2

SEER = Surveillance, Epidemiology, and End Results

9% had metastatic disease. In this cohort, 13% had coronary artery disease, 5% had established cerebrovascular disease, 2% had known peripheral arterial disease, 6% had atrial fibrillation, 2% had histories of heart failure, and 22% had at least 1 of these diseases. Rates of CVD among Chinese patients with PC may be even higher.[5]

In UK administrative data, compared with patients from the general population, individuals who survived at least 1 year after PC diagnosis exhibited an elevated risk for future coronary artery disease (adjusted HR: 1.09; 95% CI: 1.02-1.17), heart failure (HR: 1.12; 95% CI: 1.05-1.20), and venous thromboembolism (HR: 1.72; 95% CI: 1.57-1.89), but not stroke (HR: 1.06; 95% CI: 0.99-1.14) or peripheral arterial disease (HR: 0.94; 95% CI: 0.84-1.05).[6] Patients with PC accounted for the largest burden of CVD hospitalization among English patients with potentially curable cancers.[7] Among these individuals with PC, the prevalence of CVD using administrative data was estimated at 14% to 19%.

CVD is a major cause of death in patients with PC. Between 1973 and 2012, more cardiovascular deaths occurred among patients with PC than for any other cancer among patients in the Surveillance, Epidemiology, and End Results (SEER) program.[8] In patients with nonmetastatic PC in the United States, CVD was a more common cause of death than the cancer itself.[9] Even among those with metastatic disease, the standardized cardiovascular mortality ratio was 1.48 (95% CI: 1.41-1.54), indicating that these patients are at approximately 50% higher risk for cardiovascular death than expected for their age. Among Danish patients with PC, those treated with palliative intent (>90% of whom were treated with ADT) were twice as likely to experience ischemic stroke or heart failure compared with participants without PC.[10]

In summary, the available data, mostly from administrative sources, indicate that the burden of prevalent CVD and incident CVD, and especially coronary artery disease, among patients with PC is high. Importantly, however, data from middle- and low-income countries is scant, so further research is necessary to gain a global appreciation of the burden of CVD among patients with PC.

HIGHLIGHTS

- Patients with PC are at an elevated risk of CVD and cardiovascular mortality.
- Cardiovascular risk factors are worsened by ADT.
- ARPIs worsen hypertension and fluid retention incrementally to ADT.
- The relationship between GnRH antagonists and cardiovascular events is unclear.

SUMMARY

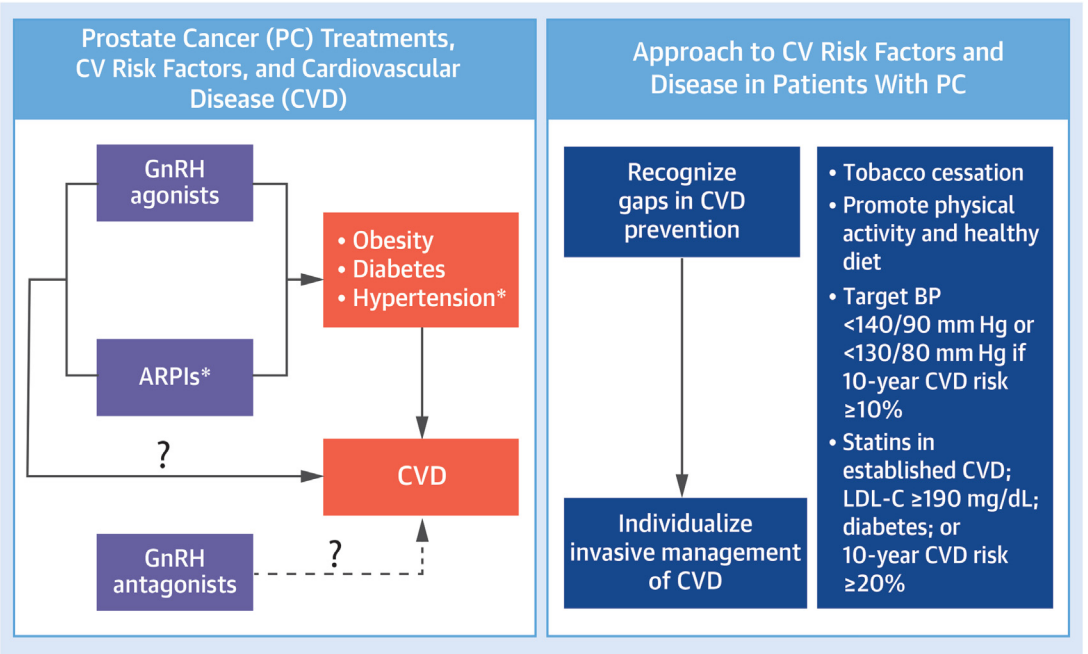
- Approximately 1 in 5 patients with PC have established CVD.
- Patients with PC have a higher risk for developing coronary artery disease, heart failure, and venous thromboembolism than the general population.

TABLE 1 Prevalence Rates of CVD in Prostate Cancer Populations From Different Geographic Regions

Region	Prostate Cancer Population	CVD Prevalence	Specific Conditions
North America (United States)	90,494 Veterans[3]	17%	Atherosclerotic CVD: coronary artery disease, stroke, peripheral vascular disease
North America (Canada)	2,492 (prospective cohort study)[4]	22%	Coronary artery disease (13%), cerebrovascular disease (5%), peripheral arterial disease (2%), atrial fibrillation (6%), heart failure (2%)
South America, Asia, Australia, Israel	1,065 (prospective cohort study)	24%	Coronary artery disease (14%), cerebrovascular disease (6%), peripheral arterial disease (4%), atrial fibrillation (6%), heart failure (5%)
United Kingdom	175,639 patients with nonmetastatic prostate cancer[5]	15%	Previous CVD hospitalization
China	4,253 (retrospective study)[5]	27%	43% had hypertension, poorly controlled in one-half
Saudi Arabia	Retrospective study[67]	16%	Stroke (2%), deep vein thrombosis (2%), peripheral vascular disease (0.5%), percutaneous coronary intervention (19%), other cardiac disease (4%)

CVD = cardiovascular disease.

CENTRAL ILLUSTRATION **The Relationship Between PC Treatments, Cardiovascular Risk Factors and Disease; and Strategies to Mitigate Cardiovascular Risk**



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GnRH agonists promote obesity, diabetes and hypertension; ARPIs promote hypertension. The relationship between GnRH antagonists and CVD is uncertain while the magnitude of cardiovascular risk directly attributable to GnRH agonists and ARPIs is to be defined. *ARPIs have been specifically been associated with the development of hypertension.

- CVD is the most common cause of death in patients with localized PC.

REASONS UNDERLYING THE HIGH CVD BURDEN AMONG PATIENTS WITH PC

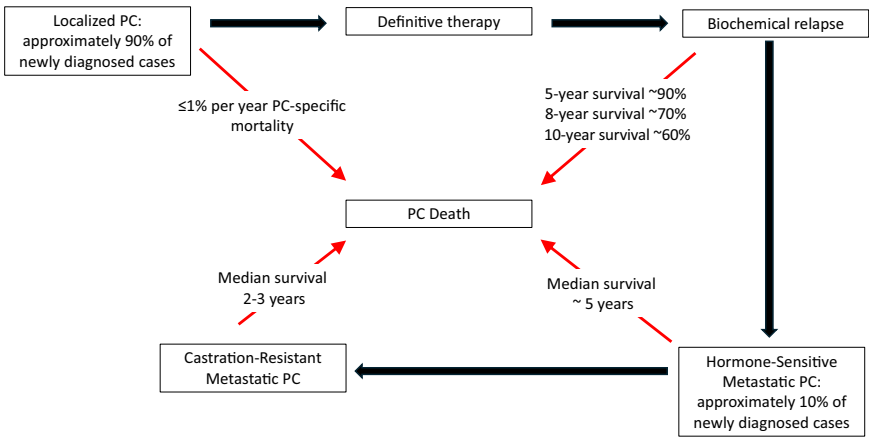
Several factors may account for the high risk for adverse cardiovascular outcomes observed among patients with PC (**Central Illustration**). These include 1) improving cancer-specific survival; 2) a high burden of conventional cardiovascular risk factors; 3) inflammation; and 4) ADT, although the relationship between ADT use and the risk for developing CVD is complex and incompletely understood.

PC SURVIVAL. PC survival varies by stage, with patients having localized disease showing excellent long-term outcomes (**Figure 1**). Among 94,934 patients diagnosed with localized PC between 1992 and 1997 in the SEER database, the average PC mortality rate was 1.5% per year.[11] In the ProtecT (Prostate Testing for Cancer and Treatment) trial in the United Kingdom, 1,643 patients diagnosed with localized PC found by prostate-specific antigen screening were randomly assigned to active surveillance (in which no disease-modifying therapy was initiated at the time of randomization) vs prostatectomy vs radiotherapy. That study demonstrated an overall mortality rate of 21.7%, and respective PC-specific mortality rates of 3.1%, 2.2%, and 2.9% at a median of 15 years.[12] 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 with localized disease.

The favorable PC-specific survival among patients with localized PC[12] leaves patients at risk for developing comorbid conditions for an extended time. Among such comorbidities, CVD is particularly relevant in the context of their high burden of cardiovascular risk factors, as will subsequently be discussed.

Survival decreases substantially with more advanced PC. Biochemical relapse refers to the increase in prostate-specific antigen after treatment with curative intent (including prostatectomy or

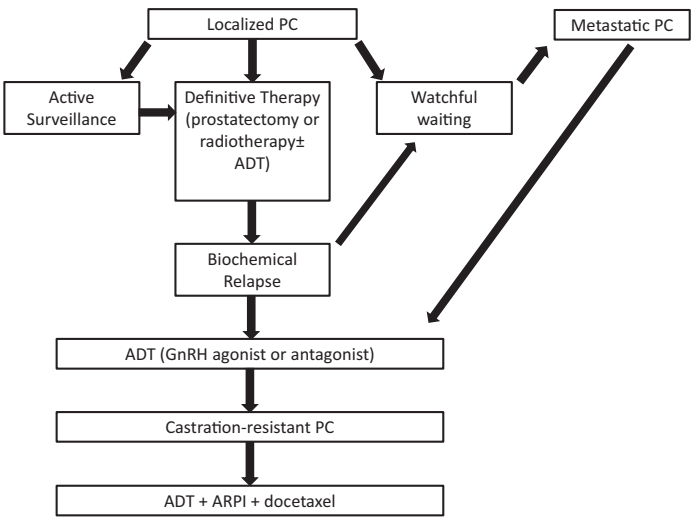
FIGURE 1 Prostate Cancer Mortality Rates at Different Disease Milestones



Understanding PC prognosis is important in weighing the risks and benefits of cardiovascular interventions in affected patients.

radiotherapy) but with no evidence of metastases using conventional imaging techniques (Figure 1). In data from the Swedish national cancer registry, 10-year PC-specific mortality rates following biochemical relapse in patients who had undergone prostatectomy between 2003 and 2019 were 4% (95% CI: 2%-6%) among those with low-risk features and 9% (95% CI: 5%-13%) among those with high-risk features.[13] Respective rates in patients with biochemical relapse following definitive radiotherapy were 24% (95% CI: 19%-29%) and 46% (95% CI: 40%-51%). In a systematic review of studies of biochemical relapse, 5-year survival rates of approximately 90%, 8-year survival rates of approximately 70% and 10-year survival rates of approximately 60% were reported.[14]

FIGURE 2 Prostate Cancer Treatment Strategies



ADT and ARPI affect cardiovascular risk factors and have been associated with increased cardiovascular events.

Metastatic PC remains largely incurable, although recent advances in treatment have improved survival rates typically to about 4 to 5 years.[15] Castration-resistant PC introduces further complexity, as the cancer develops resistance mechanisms requiring treatment beyond ADT alone to control the disease. Resistance mechanisms include amplification or mutation of androgen receptors to allow increased sensitivity to testosterone and its weaker androgenic precursors or constitutively active receptors, as well as intratumoral androgen synthesis. Among others, medications to treat castration-resistant PC include androgen receptor pathway inhibitors (ARPIs), which is an umbrella term representing androgen receptor signaling inhibitors (eg, enzalutamide, apalutamide, darolutamide) and cytochrome P450 (CYP) 17A1 inhibitors (eg, abiraterone). In addition, other therapies include radioligand therapy, taxane chemotherapies, poly(adenosine diphosphate ribose) polymerase inhibitors and immunotherapies in select patients.[16-19] In contemporary U.S. data, patients ≥65 years of age exhibited a median survival duration following diagnosis with metastatic castration-resistant disease of 25.6 months.[20]

CARDIOVASCULAR RISK FACTORS. The burden of cardiovascular risk factors is high even at the time of PC diagnosis. In a Canadian cohort of 2,492 patients with PC, 92% of whom were diagnosed within 12 months, 58% were current or former smokers, 45% had hypertension, 16% had diabetes, 31% were obese (body mass index ≥30 kg/m^2), 24% had low levels of physical activity, and 22% already had established CVD.[4] Consequently, 69% had Framingham cardiovascular risk scores associated with a high risk for future adverse cardiovascular outcomes. Similarly, among U.S. veterans diagnosed with PC between 2010 and 2017, approximately 65% were current or former smokers, 39% had body mass index >30 kg/m^2, and 17% had established atherosclerotic CVD.[3] Notably, several cardiometabolic risk factors can be exaggerated by the use of ADT.

INFLAMMATION. Evidence from epidemiologic, genetic, pathologic, and laboratory research suggests that inflammation may play a role in the development of PC and in its progression once established.[21] Inflammation has also been compellingly demonstrated to be a causal factor in the occurrence of cardiovascular events.[22,23] Therefore, chronic inflammation may be a shared determinant of PC and CVD, contributing to their coexistence.

ADT. ADT is a cornerstone in the treatment of advanced PC (**Figure 2**). Although the salutary effects of testosterone suppression in metastatic PC were first discovered through orchiectomy,[24] androgen deprivation is now administered mostly in the form of gonadotropin-releasing hormone (GnRH) agonists. These subcutaneous or depot GnRH agonist injections can be administered at 1-, 3-, 4-, or 6-month intervals. They continuously stimulate the anterior pituitary, resulting in an initial surge of luteinizing hormone and thus testosterone. However, continuous (rather than physiological pulsatile) anterior pituitary stimulation rapidly leads to marked reductions in luteinizing hormone and testicular testosterone synthesis.

ADT can be used as concurrent and adjuvant therapy with radiotherapy (with which it reduces metastasis-free survival [HR: 0.83; 95% CI: 0.77-0.89][25] as well as PC-specific and overall mortality, with respective relative risks of 0.69 [95% CI: 0.56-0.84] and 0.86 [95% CI: 0.80-0.93][26]) or in patients with evidence of high-risk biochemical relapse after previous definitive PC therapy. Combining ADT with ARPIs is standard of care for metastatic PC.

GnRH agonists and cardiovascular risk factors. To our knowledge, there are no published randomized controlled trial data to inform the cardiometabolic effects of GnRH agonists compared with the absence of a GnRH agonist. Given their established benefits in patients with advanced disease, such data are unlikely to be forthcoming.

In observational research, GnRH agonists lead to an increase in fat mass of approximately 11%.[27] In a large retrospective analysis, ADT use was also associated with a 60% increase in the risk for developing diabetes among patients with localized PC.[28] In another large, retrospective Taiwanese study, ADT use was associated with an 80% higher risk for developing hypertension.[29] GnRH agonists are also associated with loss of skeletal muscle strength.[30] Muscle strength is an underappreciated risk factor for adverse cardiovascular outcomes, including myocardial infarction, stroke, heart failure, and cardiovascular death.[31,32] We recently demonstrated in 3,967 patients with PC prospectively recruited in 7 countries, 44% of whom were receiving ADT, that ADT use was associated with a 2.2% increase in waist circumference and a 27.4% reduction in handgrip strength over 12 months.[33] Baseline waist circumference in the highest quartile (>110 cm) and handgrip strength in the lowest quartile (<29.5 kg) were respectively associated with adjusted HRs for adverse cardiovascular outcomes of 1.40 (95% CI: 1.03-1.90) and 1.59 (95% CI: 1.14-2.22).

GnRH agonists and incident CVD. A meta-analysis of retrospective studies in which cardiovascular outcomes in patients with PC treated with ADT were compared with those in patients with PC not treated with ADT demonstrated that ADT use was associated with higher CVD and cardiovascular mortality rates.[34] The respective HRs were 1.10 (95% CI: 1.00-1.21) and 1.17 (95% CI: 1.04-1.32). In another meta-analysis of retrospective studies, GnRH agonist use was associated with nonfatal cardiovascular events, with relative risk of 1.38 (95% CI: 1.29-1.48).[35] In a retrospective analysis of patients with localized PC, ADT was associated with an approximately 2-fold higher risk for cardiovascular death in men ≥65 years of age who had undergone prostatectomy, with 5-year cumulative incidence rates of 5.5% (95% CI: 1.2%-9.8%) compared with 2.0% (95% CI: 1.1%-3.0%) in those not receiving ADT.[36]

The existing retrospective data linking ADT use with adverse cardiovascular outcomes are limited. The range and accuracy of covariates are incomplete in these predominantly administrative data sets, and cardiovascular outcomes were not ascertained using standardized definitions. In contrast to findings from these retrospective studies, a meta-analysis of randomized trials in which up-front ADT was compared with a control arm of delayed or no ADT found no difference in the risk for cardiovascular death

between the groups.[26] However, a more recent long-term analysis of a trial in which patients receiving radiotherapy for PC were randomized to receive 4 months vs 28 months of ADT demonstrated that longer ADT exposure might be associated with an increased risk for death of myocardial infarction, especially in patients with known CVD.[37] Respective subdistribution HRs overall and in those with established CVD were 1.58 (95% CI: 1.00-2.50) and 2.54 (95% CI: 1.16-5.58).

Given the different findings from different studies, the magnitude of any effect of ADT on adverse cardiovascular outcomes remains uncertain. In the general population, treatments to mitigate the effects of hypertension, dyslipidemia, and diabetes have been shown in numerous randomized and nonrandomized studies to reduce cardiovascular event rates. To the extent that these approaches can decrease the deleterious cardiometabolic consequences of ADT, any effect of ADT on the risk for clinical cardiovascular outcomes may be modest. However, this hypothesis needs to be confirmed in further data. Currently, the U.S. Food and Drug Administration requires that GnRH agonists' product information include a warning about the increased risk for CVD.

GnRH agonists and the QT interval. GnRH agonists may lead to a modest prolongation in the corrected QT interval, by 7.4 ms (95% CI: 0.08-14.7 ms) compared with a control group.[38] However, the clinical relevance of any small effect on the QT interval is unclear.

GnRH antagonists and incident CVD. GnRH antagonists are another class of ADT. In contrast to GnRH agonists, these drugs lead to more rapid and complete suppression of luteinizing hormone release from the anterior pituitary and testosterone synthesis. Notably, they avoid the initial testosterone surge caused by GnRH agonists. The relationship between this drug class and cardiovascular outcomes is described subsequently, as there is promising but inconclusive evidence that GnRH antagonists may lead to fewer adverse cardiovascular events than GnRH agonists.

ARPIs. The development of castration-adjunctive therapies that block other androgen-related pathways through which PC can progress represents a major advance in the treatment options for advanced PC, improving overall survival (**Figure 2**).

The most robustly identified cardiovascular adverse effect observed with the ARPIs is hypertension. Compared with control groups, enzalutamide leads to an increased risk for hypertension, with a relative risk of 2.66 (95% CI: 1.93-3.66).[39] Abiraterone also leads to an increased risk for hypertension compared with control groups, with relative risk 1.46 (95% CI: 1.20-1.78). Abiraterone and enzalutamide appear to increase the risk for "fluid retention" and "edema" in randomized trials, as identified by safety reporting mechanisms.[40]

Adverse cardiovascular outcomes were not prespecified in registration trials of ARPIs, and these trials were not powered to detect differences in such events with the use of these drugs. Population-based research from Sweden demonstrated that abiraterone and enzalutamide are associated with a higher risk for incident CVD than their nonuse in patients with PC, with respective HRs for abiraterone and enzalutamide of 1.19 (95% CI: 1.03-1.38) and 1.10 (95% CI: 1.01-1.20).[41] Collectively, in a recent meta-analysis of randomized, controlled trials, ARPIs were associated with a 2-fold increased risk for cardiovascular death (relative risk: 2.02; 95% CI: 1.32-3.10).[42] Importantly, the increase in cardiovascular risk associated with ARPIs is incremental to GnRH agonists, with which these drugs are used in combination.

A further consideration is the potential for drug-drug interactions between these drugs and cardiovascular medications through CYP pathways. Abiraterone strongly inhibits CYP1A2, CYP2C8, and CYP2D6, while enzalutamide strongly induces CYP3A4 and apalutamide strongly induces CYP2B6, CYP2C19, and CYP3A4. These effects might lead to theoretical pharmacokinetic interactions with apixaban, rivaroxaban, and warfarin, which are strongly metabolized by CYP3A4, while the prodrug clopidogrel is a substrate of CYP2C19, requiring its metabolism to its pharmacologically active form. There is scant empirical evidence on the clinical consequences of these interactions,[43] so potential drug-drug interactions need to be anticipated on the basis of what is known about the drugs' pharmacokinetics and analogous interactions with other CYP inhibitors and inducers. Notably, the likelihood of a clinically relevant drug-drug interaction between darolutamide and edoxaban, dabigatran, or clopidogrel appears low.[43]

SUMMARY

- The burden of cardiovascular risk factors is high among patients with PC.
- ADT is associated with increased adiposity, an increased risk for diabetes and hypertension, and decreased muscle strength, which are cardiovascular risk factors.
- ARPIs increase the risk for hypertension and fluid retention over and above the effects of GnRH agonists.
- The relationship between GnRH agonist use and adverse cardiovascular events remains to be well

characterized, as the existing retrospective data linking ADT use with adverse cardiovascular outcomes are limited.

ADDRESSING CARDIOVASCULAR RISK IN PATIENTS WITH PC

Reducing cardiovascular risk in patients with PC requires that gaps in cardiovascular risk factor control be addressed and that strategies to treat established or emergent severe CVD in patients with advanced PC be developed. Some data suggest that compared with GnRH agonists, GnRH antagonists are associated with a reduced risk for cardiovascular events.[44] However, this research has important limitations, which are described subsequently.

GAPS IN CARDIOVASCULAR RISK FACTOR CONTROL. Cardiovascular risk factor control is often suboptimal in North American patients with PC. Among U.S. veterans with PC, 36% had blood pressure of ≥140/90 mm Hg, 22% had low-density lipoprotein cholesterol levels ≥130 mg/dL or total cholesterol levels ≥240 mg/dL, and 17% had glycated hemoglobin levels ≥7% or fasting glucose levels ≥126 mg/dL.[3] Guidelines recommend that more aggressive factor goals be set in those with established CVD or risk factors, such as diabetes. In a study of 2,811 patients with PC from 4 countries, 51% had suboptimal control of 3 or more modifiable cardiovascular risk factors when more stringent, guideline-driven targets were applied.[45] Specifically, 10% were current smokers, 20% were considered physically inactive, 51% had low-density lipoprotein cholesterol levels higher than target, 75% had suboptimal blood pressure, and 91% had elevated ratios of waist to hip circumference (>0.90). These findings highlight a significant care gap in this population that needs to be addressed, as these patients are already engaged in the health care system.

The optimal strategy to address this gap in care is unclear. Tools have been developed to help uro-oncologists identify CVD, address cardiovascular risk factors, and refer suitable patients to cardiologists or cardio-oncologists.[46] Guidelines recommend eliciting or requesting that a patient's primary care physician elicit a history of stroke, transient ischemic attack, aortic disease, myocardial infarction or other coronary artery disease, and peripheral arterial disease, along with physical examination and measurement of glycated hemoglobin, lipids, uric acid, electrolytes, renal function, complete blood count, and electrocardiography annually in patients receiving ADT.[46,47] The implementation of these recommendations and their effectiveness at reducing cardiovascular risk, especially in patients with advanced PC, is unknown. Many uro-oncologists and medical oncologists may not have the expertise or time during clinical visits to manage blood glucose and lipid levels. Although primary care is typically responsible for cardiovascular risk management, the data presented here indicate that risk factor targets are frequently unmet in patients with PC, despite most having had access to primary health care.[45]

Arterial calcification, which may be observed incidentally in staging pelvic imaging, is associated with an increased risk for adverse cardiovascular outcomes.[48] Specialists treating patients with PC should be vigilant for signs of atherosclerotic vascular disease. The presence of calcification, especially if extensive, may warrant referral to a cardiovascular physician for evaluation.

Cardiovascular risk scores may help identify patients with PC who are at high cardiovascular risk. The European Society of Cardiology cardio-oncology guidelines recommend applying the Systematic Coronary Risk Evaluation 2 (SCORE2) risk stratification score in patients treated with ADT.[47] However, despite the Class 1 recommendation of this approach, the validity of SCORE2 has not been demonstrated in patients with PC, particularly in those with advanced or metastatic disease, among whom the competing risk for PC death may limit the validity of the score. In contrast to SCORE2, the New Zealand cardiovascular risk prediction equation has been shown to predict 5-year cardiovascular event rates adequately in New Zealander patients with PC.[49] 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 are not known. Research is ongoing to develop cardiovascular risk scores that are validated in populations with PC.[50]

Physicians managing patients with PC should promote healthy lifestyle habits, including tobacco cessation. However, there is scant evidence as to what diets are optimal for cardiovascular health in patients with PC.[51] Both aerobic and strength training exercise programs have demonstrated short-term improvements in surrogate endpoints in populations with PC.[52,53] However, their sustainability and impact on clinical outcomes are incompletely defined. Optimal blood pressure, glucose, and cholesterol targets in patients with PC (especially in those with metastatic disease) are not known. Until they have been defined, we suggest applying current American College of Cardiology targets for most patients with PC unless risk factor surveillance and aggressive

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treatment are not part of an individual's goals of care. Current guidelines suggest that statins are indicated for those with established atherosclerotic CVD, adults 40 to 75 years of age with low-density lipoprotein cholesterol levels ≥190 mg/dL (≥4.9 mmol/L), those with diabetes, and those with ≥20% 10-year risk for atherosclerotic CVD, while decision making in adults >75 years of age should be invidividualized.[54] Patients with blood pressure ≥140/90 mm Hg and those with values of 130 to 139/80 to 89 mm Hg and 10-year risk for atherosclerotic CVD ≥10%, including those with established atherosclerotic CVD, should be treated with blood pressure-lowering medication.

THE UNCERTAIN ROLE OF GnRH ANTAGONISTS. Initial interest in the cardiovascular effects of degarelix, the first widely available GnRH antagonist, arose from post hoc analyses of early-phase trials suggesting fewer cardiovascular events with degarelix compared with GnRH agonists.[55] Animal studies supported this hypothesis by showing less atherosclerotic aortic disease in low-density lipoprotein receptor-knockout mice with degarelix compared with a GnRH agonist.[56]

The HERO (A Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer) trial, an open-label, randomized trial, compared the oral GnRH antagonist relugolix with the GnRH agonist leuprolide. A lower incidence of cardiovascular events with relugolix was found in a nonprespecified analysis.[57] A systematic review of randomized trials of GnRH antagonists, including HERO, showed that the pooled risk ratios for adverse cardiovascular events, cardiovascular death, and all-cause mortality were respectively 0.57 (95% CI: 0.39-0.81), 0.49 (95% CI: 0.25-0.96), and 0.48 (95% CI: 0.28-0.83) compared with GnRH agonists.[58] Importantly, the risk for bias in the trials identified was considered high, and confidence in these findings was moderate.

The PRONOUNCE (A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease) trial was the first prospective trial to compare a GnRH antagonist (degarelix) with a GnRH agonist (leuprolide) with respect to a prespecified primary cardiovascular endpoint.[59] There were some important methodological features to the trial. A high-risk population was targeted by including only patients with established coronary, cerebrovascular, or peripheral arterial disease. A cardiovascular physician optimized participants' cardiovascular medications. The sample size was calculated assuming a 10.2% incidence of death, myocardial infarction, or stroke at 12 months, 80% power, and an HR of 0.49 in the degarelix group.

The trial was terminated prematurely when only 545 of the planned 900 participants had been enrolled. Because of the reduced sample size, as well as a lower outcome event rate than anticipated (5.5% with degarelix vs 4.1% with leuprolide), the trial was not powered to be able to draw inferences about the cardiovascular effects of degarelix.[60] Some have interpreted the neutral findings as evidence that GnRH agonists have no increase in CVD risk compared with GnRH antagonists.[61] However, the trial duration was too short, the expected effect size was too large, the assumed power was too low, and the primary outcome rate was too low to draw any firm conclusions. The conflation of neutrality with lack of effect should be avoided in the absence of sufficient data, and overinterpretation of a single (underpowered) trial may incur the cost of discarding a potentially important avenue of research.

When the findings from PRONOUNCE were incorporated into an updated meta-analysis, the ORs for the composite of major adverse cardiovascular events and overall mortality were, respectively, 0.57 (95% credible interval: 0.37-0.86) and 0.58 (95% credible interval: 0.32-1.08).[44] However, as with the prior meta-analysis, confidence in these findings is not high, because of 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. Furthermore, 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, which can be administered less frequently. Relugolix is an oral agent, which requires adherence to a daily dosing regimen. Research is ongoing into teverelix, an injectable GnRH antagonist that can be administered every 6 weeks. Until more data are available, it is reasonable to discuss with patients the uncertainties surrounding the potential benefits of GnRH antagonists, especially in those with high cardiovascular risk.

SUMMARY

- Cardiovascular risk factors are frequently suboptimally controlled in patients with PC. Strategies should be developed to address this care gap.

- There are some data to suggest that GnRH antagonists may be associated with fewer adverse cardiovascular events than GnRH agonists, but confirmation is needed in appropriate prospective randomized, controlled trials. Until such trials have been performed, the use of GnRH antagonists should be individualized.

MANAGEMENT OF SEVERE CVD IN PATIENTS WITH METASTATIC PC

Administrative data suggest that survival with metastatic PC is increasing. Between 2008 and 2020, 5-year survival in patients with metastatic castration-sensitive disease in Sweden increased from 26% to 35%.[62] In the United States, from 2000-2004 to 2015-2019, 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.[63] In contemporary clinical trials in metastatic hormone-sensitive PC, survival times of approximately 5 years are reported.[15] The progressive improvement in overall survival in patients with metastatic PC exposes this population to the risk for developing severe CVD for a longer time, which is especially pertinent given the cardiovascular risks described previously.

Historically (and to some extent currently), a cancer diagnosis has been associated with less invasive treatment of coronary artery disease.[64] Given the improving survival and rapid advances in the treatment of metastatic PC, the role of invasive cardiovascular interventions in patients with metastatic disease needs to be carefully considered. Factors contributing to the decision-making process include characteristics of both the PC and the cardiovascular comorbidity; non-PC, non-cardiovascular comorbidities, including the risk for bleeding; and patient goals of care.[65] There are few randomized controlled trial data to inform the risks and benefits of invasive cardiovascular interventions in populations with current cancer. However, there is some relevant information from a randomized trial of invasive vs noninvasive management of non-ST-segment elevation myocardial infarction in frail adults.[66] The invasive approach was associated with worse survival at 1 year, although this difference was attenuated subsequently, potentially because of the depletion of susceptible patients. These data warn against extrapolation of findings from noncancer populations to patients with active cancer.

In general, cardiovascular interventions that confer substantial benefit (including symptomatic benefit) rapidly, such as primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, transcatheter aortic valve replacement, a routine invasive approach for non-ST-segment elevation myocardial infarction with ongoing symptoms, and cardiac resynchronization therapy for severe symptomatic heart failure, are compelling in many patients with metastatic PC.[65] In contrast, invasive strategies such as primary prevention implantable cardioverter-defibrillators that confer little symptomatic benefit and whose survival benefits are observed only after a longer lag are generally not indicated in those with metastatic cancer. The most challenging of decisions relate to the role of coronary revascularization (in particular coronary artery bypass surgery) for minimally symptomatic multivessel coronary disease because the survival advantage over medical therapy is more modest, there are front-loaded procedural risks, and the net benefit may only be apparent years after intervention.

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 levels recommended in cardiovascular practice guidelines. ADT reduces muscle strength and increases adiposity and is associated with an increased risk for diabetes and hypertension, although its relationship with adverse cardiovascular events requires confirmation. ARPIs may confer incremental risks for hypertension and cardiovascular events to ADT, while GnRH antagonists have been linked with lower cardiovascular risk with compared with GnRH agonists in some studies. However, this association has yet to be confirmed in a randomized clinical trial with a cardiovascular primary endpoint that has incorporated the necessary measures to fully mitigate bias.

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