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CORRESPONDENCE

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Addressing cardiovascular risks with a goal to prevent cardiovascular complications in patients undergoing antihormonal therapy for prostate cancer

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Abstract

Over 1 million cases of prostate cancer are reported every year, and it is the second most common cancer in men. Androgen deprivation therapy (ADT) is a hallmark treatment for prostate cancer but is associated with the development or exacerbation of cardiovascular disease. The most common cause of non-cancer death in patients with prostate cancer is cardiovascular disease. Thus, a better understanding of the prevalence of cardiovascular toxicity across all therapies, management of potential cardiovascular complications, and prevention of cardiovascular events is essential as treatments continue to evolve. In this article, the first in a 2-part series, we provide a review of the current landscape of ADT therapy and its association with cardiovascular disease, summarize recent clinical trial data evaluating cardiovascular outcomes, and provide insights on the management of cardiovascular risk factors and adverse events for clinicians managing this high-risk population of men undergoing potentially cardiotoxic treatment for prostate cancer.

Keywords Androgen deprivation therapy, Cardiovascular diseases, Heart disease risk factors, Prostate cancer

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Introduction

Prostate cancer remains the second most common cancer in men, with over 1 million reported cases every year [1]. However, among patients with prostate cancer, the most common cause of non-cancer related death is atherosclerotic cardiovascular disease (ASCVD) [1]. Cardiovascular events have also been linked to the use of androgen deprivation therapy (ADT), a cornerstone treatment for advanced prostate cancer that may be prescribed for up to half of patients during their disease course [2]. Understanding the prevalence of cardiovascular risk factors, cardiovascular toxicities related to prostate cancer therapy, management of cardiovascular complications, and prevention of cardiovascular events is of utmost importance to improve outcomes in prostate cancer.

Prostate cancer, although serious, has an excellent prognosis overall, with more than 97% of patients surviving more than 5 years after diagnosis. However, there are currently an estimated 3.1 million prostate cancer survivors today with a high rate of pre-existing cardiovascular disease or cardiovascular risk factors (hypertension, type 2 diabetes, and hyperlipidemia) when compared with patients with other cancers [3]. Thus, the optimal management of these patients requires close coordination among cardiologists, oncologists, urologists, and primary care providers. Recognizing this need, in 2010, the American Heart Association (AHA), American Cancer Society (ACS), and American Urological Association (AUA) issued a science advisory; nonetheless, significant further efforts are required [4].

In an effort to raise awareness and make practical suggestions about how practitioners can effectively collaborate, the International Cardio-Oncology Society (IC-OS), in conjunction with the European Association of Urology (EAU) and the Canadian Urology Association (CUA), developed a webinar series in 2022 to review and develop strategies to anticipate cardiovascular toxicities related to prostate cancer treatment with the hope that early recognition and optimal management strategies would allow the most effective cancer therapy to be delivered to the largest number of men with prostate cancer. This review will concisely summarize the presentations and data discussed throughout.

Review

Prevalence of cardiovascular disease in patients with prostate cancer

Patients with advanced prostate cancer typically have a higher-than-expected rate of cardiovascular disease when compared with the general population [2, 5]. For instance, a population-based observational study of 185,106 men with local/regional prostate cancer examined preexisting cardiovascular risk factors or a prior cardiovascular event and found that about 4% had prior myocardial infarction, 31% had hypertension, 20% had congestive heart failure, and 17% had some form of stroke [6]. Furthermore, those undergoing ADT were at higher risk of myocardial infarction (adjusted hazard ratio (HR) 1.09; 95% confidence interval (CI) 1.02–1.16) and diabetes (adjusted HR 1.33; 95% CI 1.27–1.39) [6]. In another study of 37,443 men with localized prostate cancer from the Veterans Healthcare Administration, investigators found increased incidences of diabetes (adjusted HR 1.28; 95% CI 1.19–1.38), coronary heart disease (adjusted HR 1.19; 95% CI 1.10–1.28), myocardial infarction (adjusted HR 1.28; 95% CI 1.08–1.52), sudden cardiac death (adjusted HR 1.35; 95% CI 1.18–1.54), and stroke (adjusted HR 1.27; 95% CI 1.10–1.36) in patients on ADT compared with those not on ADT [7]. In a retrospective study of 354 patients with prostate cancer, incidental coronary calcification on PET/CT was associated with a significant incidence of MACE (21%) [8]. In a cross-sectional analysis of over 90,000 US veterans with prostate cancer from 2010 to 2017, the rates of incomplete cardiovascular risk factor assessments remained high. The study revealed significant gaps in comprehensive cardiovascular risk assessment, with more than 1 in 5 veterans not receiving complete evaluations. There were notable deficiencies in lipid screening, diabetes assessment, and obesity evaluation [9]. These studies highlight the importance of assessing cardiovascular risk in patients being considered for ADT.

How androgen deprivation therapy impacts the cardiovascular system

ADT, which suppresses testosterone synthesis, has been a cornerstone of management of metastatic prostate cancer since its landmark discovery by Charles Huggins and Clarence Hodges in 1941, and it has been increasingly used as neoadjuvant therapy for radiation therapy. As androgens are the major stimulus of prostate cancer growth, ADT impedes the progression of advanced prostate cancer (Fig. 1). While ADT may be delivered by bilateral orchiectomy, surgical castration has largely been supplanted by pharmacologic castration using gonadotropin-releasing hormone (GnRH) agonists or GnRH antagonists [10]. GnRH agonists stimulate the anterior pituitary gland on a continuous basis. While this initially leads to a surge in luteinizing hormone, follicle-stimulating hormone, and testosterone, the continuous stimulation of the pituitary (as distinct from pulsatile physiologic stimulation) leads to the suppression of luteinizing hormone, follicle-stimulating hormone, and testosterone within days to weeks [10]. To mitigate the initial testosterone surge observed with GnRH agonist use, antiandrogens are often administered with GnRH agonists early in the treatment course. In contrast to GnRH agonists,

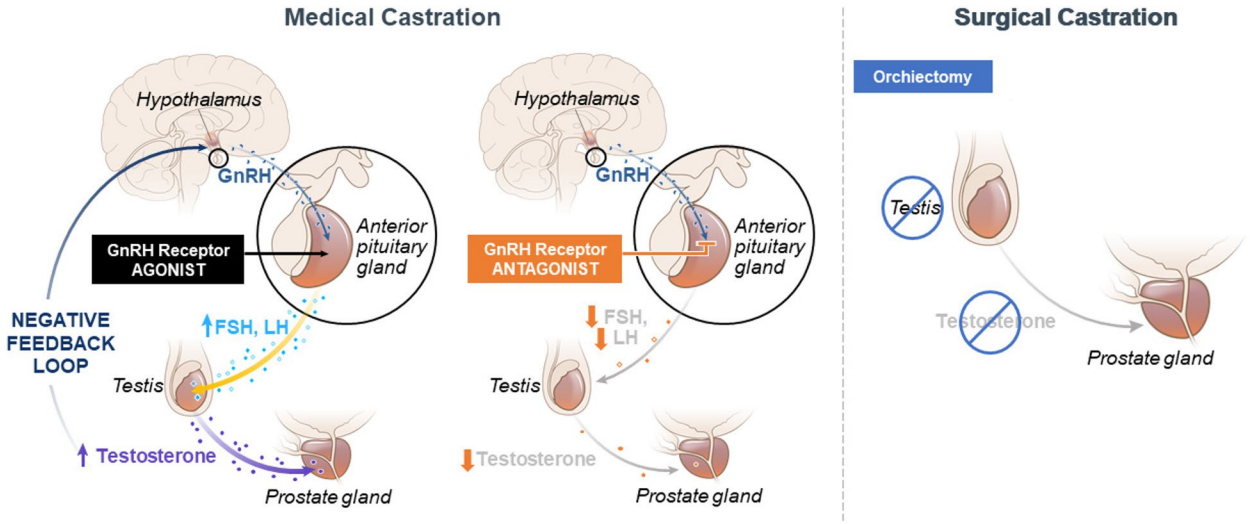

Fig. 1 Androgen deprivation therapy and mechanisms of testosterone suppression

GnRH antagonists directly inhibit the effects of GnRH on the anterior pituitary, leading to immediate suppression of luteinizing hormone, follicle-stimulating hormone, and testosterone [10, 11].

Despite the effectiveness of the above therapies in treating prostate cancer, they also physiologically increase cardiovascular risk. For instance, ADT is linked to a diminution in lean body mass with an increase in fat mass [12, 13]. ADT also increases total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides [13, 14]. Furthermore, ADT can increase insulin resistance, a mechanism thought to explain the high incidence of type 2 diabetes in patients on therapy [15, 16]. Additionally, low levels of testosterone have been associated with decreased arterial compliance and increased arterial stiffness leading to hypertension [17, 18]. All together these therapies can lead to the destabilization of atherosclerotic plaque [19].

There have been a few studies comparing types of ADT such as GnRH agonists, antiandrogens, orchiectomy, combined androgen blockage, and GnRH antagonist. One study found GnRH agonists to have higher cardiovascular risk than orchiectomy (HR 1.21; 95% CI 1.18–1.25 vs HR 1.16; 95% CI 1.08–1.25) [2]. A French observational study showed a higher risk of ischemic stroke and myocardial infarction in patients who received combination androgen blockade (adjusted HR 1.61; 95% CI 1.27–2.03) and decreased risk in those with antiandrogen monotherapy (adjusted HR 0.61; 95% CI 0.43–0.88) [20]. Table 1 shows a list of cardiovascular complications associated with various types of therapies.

Clinical trial data comparing the cardiovascular outcomes of various types of ADT remain scarce. A meta-analysis of phase III randomized clinical trial data of the GnRH antagonist degarelix compared with a GnRH agonist reported fewer adverse effects with GnRH antagonist [21]. Novel agents such as the androgen biosynthesis inhibitor abiraterone and the androgen

Table 1 Antihormone therapies for prostate cancer and their associated cardiovascular complications

Medication	Cardiovascular Complications
Androgen Deprivation Therapy	
GnRH antagonist	No significant cardiovascular complication
GnRH agonist	Hypertension
First-generation antiandrogens	Heart failure
	Atrial fibrillation
	QT interval prolongation
Second-Generation Androgen Receptor Blockers	
Enzalutamide	Hypertension[a] Ischemic heart disease
Darolutamide	Heart Failure
Apalutamide	Hypertension[a] QT interval prolongation
	Heart failure
	Ischemic heart disease
Androgen Metabolism Inhibitor	
Abiraterone acetate	Hypertension
	Atrial fibrillation
	QT interval prolongation Ischemic heart disease

GnRH Gonadotropin-releasing hormone

[a] High risk (> 10% incidence) adverse event. Other medications either lack sufficient surveillance data or exhibit a low incidence of cardiovascular events

receptor signaling inhibitor enzalutamide were found to have higher rates of hypertension and a 36% increased risk of cardiovascular events compared with placebo [22]. Furthermore, a randomized clinical trial comparing continuous ADT with intermittent ADT showed similar rates of adverse cardiovascular events, suggesting that timing of the initial ADT use correlated most with cardiovascular risk [23].

Insights from PRONOUNCE

More recently, the PRONOUNCE study compared the GnRH antagonist degarelix with the GnRH agonist leuprolide in patients with prostate cancer and established atherosclerotic cardiovascular disease [24]. PRONOUNCE was the first international, multicenter, prospective, randomized open-label trial in which participants were randomly assigned 1:1 to receive degarelix or leuprolide for 12 months. The primary outcome was time to first major adverse cardiovascular event (composite of death, myocardial infarction, or stroke). A total of 545 patients across 12 counties were enrolled. The median age was 73 years; about 50% had localized prostate cancer, 26% had locally advanced disease, and 20% had metastatic disease [24]. Due to slower-than-expected enrollment and fewer-than-projected primary outcome events, enrollment in the trial was stopped before the 900 planned participants accrued. In this setting, adverse cardiovascular events occurred in 5.5% of patients assigned to degarelix and 4.1% assigned to leuprolide (HR 1.28; 95% CI 0.59–2.79; $p=0.53$) [24]. Despite there being no difference in the primary outcome at one year, the question of the relative cardiovascular safety of a GnRH antagonist compared with a GnRH agonist remains unresolved given the early discontinuation of enrollment. Furthermore, there was no difference in oncologic outcomes such as time to death, radiographic disease progression, introduction of additional prostate cancer therapies, prostate-specific antigen (PSA) test failure, or testosterone levels [24]. There is a need for rigorously conducted cardio-oncology trials to better define the cardiovascular risk of new cancer agents. PRONOUNCE provides a model for interdisciplinary collaboration among urologists, oncologists, and cardiologists with a shared goal of evaluating the impact of cancer therapies on cardiovascular outcomes.

Benefits of ADT and ADT adjuncts in oncologic outcomes

Despite the cardiovascular risks associated with ADT, there are very clear oncologic benefits in prostate cancer, with novel agents on the horizon. For locally advanced disease, ADT can serve as adjuvant therapy with radiation (for high-risk disease) or post-operative adjuvant therapy if there are positive lymph nodes. ADT has also been shown to be helpful in patients with biochemical recurrence or PSA elevation who are otherwise asymptomatic but have a prior history of prostate cancer. Furthermore, ADT can be used in metastatic disease as palliative therapy to prevent severe complications and prolong life [25]. Therapies also need to be tailored to individual patient's needs, risk, and benefits, as real world populations differ from participants in clinical trials, which often exclude individuals with visceral metastatic disease or other poor prognostic factors [26, 27].

Many ADT adjuncts or antiandrogens have also shown survival benefits across a spectrum of patients with prostate cancer. For instance, the multicenter, international, randomized clinical trial LATTITUDE compared abiraterone acetate (an androgen biosynthesis inhibitor) plus prednisone with placebo in combination with ADT in patients with metastatic, castration-sensitive prostate cancer. The investigators found a significant benefit in survival in the intervention arm compared with the control (HR 0.62; 95% CI 0.51–0.76) [28]. The androgen receptor inhibitor enzalutamide also showed benefit compared with standard nonsteroidal antiandrogen therapy in patients with metastatic hormone-sensitive prostate cancer who underwent testosterone suppression. Specifically, there was improved overall survival (HR 0.67 l; 95% CI 0.52–0.86), PSA progression-free survival (HR 0.39; 95% CI 0.33–0.47), and clinical progression-free survival (HR 0.40; 95% CI 0.33–0.49) [29]. Additionally, the androgen receptor inhibitor apalutamide also showed a survival benefit compared with placebo in patients on ADT therapy with metastatic, castration-sensitive prostate cancer (HR 0.67; 95 CI 0.51–0.89) [30]. These therapies for prostate cancer have also shown a survival benefit for patients in advanced prostate cancer disease states such as non-metastatic castration-resistant and metastatic castration-resistant prostate cancer [31–37].

The appropriate length of time for combining ADT with high-dose radiotherapy for prostate cancer is a topic of ongoing debate. Recent studies such as DART and SPPORT offer valuable insights, suggesting that restricting the duration of ADT to 18 months might be the most favorable approach [38, 39]. Further, the utilization of molecular imaging for guiding decisions and planning treatments in prostate cancer is on the rise [40].

Management and prevention of cardiovascular disease

The American College of Cardiology (ACC) and AHA have released guidelines on the prevention of cardiovascular disease that may be helpful for clinicians [41]. Furthermore, the AHA has many patient-level educational resources available online (www.heart.org) that can help patients remain engaged in their overall health. To help

patients and providers remember some of the cornerstone concepts in maintaining heart health, the AHA has introduced "Life's Essential 8," which include having a healthy diet, maintaining physical activity, avoiding nicotine, having good sleep habits, maintaining a healthy weight, controlling cholesterol, controlling blood glucose, and controlling blood pressure [42]. Addressing these components in a patient-centered, team-based and shared decision making capacity can help optimize cardiovascular health. A summary of Life's Essential 8 and cardiovascular prevention strategies are presented in Table 2.

Heart healthy diet and nutrition

Current ACC/AHA guidelines recommend a diet that emphasizes the intake of vegetables, fruits, legumes, nuts, whole grains, and fish [41]. Furthermore, the replacement of saturated fats and trans fats with monounsaturated or polyunsaturated fats is recommended. Minimizing intake of processed meats, refined carbohydrates, sweetened beverages, cholesterol, and sodium can also reduce ASCVD risk [41]. Plant-based and Mediterranean diets have been shown in observational studies to reduce cardiovascular events [43, 44]. A recent systematic review that analyzed 32 publications including 5 interventional and 11 observational studies demonstrated short-term improvements in prostate cancer progression with a plant-based diet [45]. The PREDIMED (Prevencion con Dieta Mediterranea) trial compared a Mediterranean diet (supplemented with extra virgin olive oil or nuts) with low-fat diet in patients at high cardiovascular risk. The investigators found a reduction (30% with extra virgin olive oil and 28% with nuts) in the combined endpoint of myocardial infarction, stroke, and cardiovascular mortality [46]. Another analysis showed that more vegetable consumption compared with animal protein was associated with a higher mortality reduction [47]. The relationship between dairy consumption and the risk of prostate cancer has been subject to conflicting evidence. A prospective study from 2001 found that men who drank more than two glasses of milk daily had a higher risk of advanced prostate cancer compared with those who consumed less milk [48]. However, more recent systematic reviews indicate that the evidence is inconclusive [49], and no definitive conclusions can be drawn at this time.

Physical activity

There continues to be a rise in sedentary behaviors in Western societies. Life stresses, sedentary jobs, remote workplaces, unwalkable neighborhoods, and limited access to gyms are some of the many reasons to consider

Table 2 AHA's Life's Essential 8 and ACC/AHA guideline-based recommendations [40] for cardiovascular health

Life's Essential 8	Guideline-based Recommendations
Heart healthy nutrition	• Increase intake of vegetables, fruits, legumes, nuts, whole grains, and fish • Replace saturated fats and trans fats with monounsaturated or polyunsaturated fats • Minimize intake of processed meats, refined carbohydrates, sweetened beverages, cholesterol, and sodium • Follow a Mediterranean or plant-based diet, which have shown to reduce risk of heart disease
Physical activity	• Engage in 150 min per week of moderate intensity (3–5.9 METs) or 75 min per week of vigorous intensity (≥ 6 METs) exercise to reduce ASCVD risk • Minimize sedentary behaviors
Tobacco cessation	• Quit tobacco products, e-cigarettes, and vaping • Participate in early interventions with either behavioral therapies or pharmacotherapy to maximize quit rates
Healthy sleep	• Ensure good sleep hygiene: have consistent sleep and wake times; avoid electronics and screens; keep room dark and at a comfortable temperature; limit stimulants, exercise, and alcohol before bed
Management of weight	• Participate in comprehensive lifestyle programs that promote weight loss, assist in caloric restriction (800–1500 kcal/day, if safe), and promote physical activity with frequent follow-ups or check-ins
Control of cholesterol	• Receive statin therapy for those with established ASCVD, diabetes, extremely elevated LDL-C (≥ 190 mg/dL), and high (≥ 20%) 10-year ASCVD risk • Consider statins in those without ASCVD but with elevated 10-year ASCVD risk • Consider non-statin therapies if LDL-C is not at goal with statins alone or if statin intolerant • Aim for an ideal of LDL-C < 100 mg/dL for primary prevention and < 70 mg/dL for secondary prevention
Control of blood glucose	• Aim for an ideal HbA1C of < 7% • Consider lifestyle modifications and pharmacotherapy to achieve goals
Control of blood pressure	• Consider combination of non-pharmacologic and pharmacologic therapy may for those with elevated blood pressure or high 10-year ASCVD risk • Understand that office blood pressures may not reflect real-world value, and engage in home blood pressure monitoring if unsure • Aim for a goal blood pressure of < 130/ < 80 mm Hg

ASCVD Atherosclerotic cardiovascular disease, *HbA1c* Hemoglobin A1c, *LDL-C* Low-density lipoprotein cholesterol, *MET* Metabolic equivalent

when determining ways patients can get more exercise. To make matters worse, patients on ADT are at high risk of loss of muscle mass, osteoporosis, metabolic syndrome, and diabetes [50]. In a prospective study involving 1455 men diagnosed with localized prostate cancer, men who walked briskly for ≥ 3 h per week had a 57% lower rate of progression than men who walked at an easy pace for < 3 h per week (HR 0.43; 95% CI 0.21–0.91; $p = 0.03$) [51]. Current guidelines recommend at least 150 min per week of moderate-intensity exercise (achieving 3–5.9 metabolic equivalents [METs]) or 75 min per week of vigorous-intensity exercise (≥ 6 METs) to reduce ASCVD risk [41]. Unfortunately, about half of adults in the United States do not meet the minimum physical activity recommendations [52]. There are currently no specific recommendations with regard to minimum physical activity in patients diagnosed with prostate cancer.

Treatment of tobacco use

Smoking has been shown to have a significant impact on prostate cancer outcomes. Smoking at the time of diagnosis is associated with higher rates of disease recurrence, increased prostate cancer-specific mortality, and overall mortality [53]. Tobacco cessation is of upmost importance in reducing both cardiovascular and oncologic risk. The ACC/AHA recommend that all adults who smoke should be firmly advised to quit [41]. Early interventions with either behavioral therapies or pharmacotherapy are recommended to maximize quit rates [54, 55]. Furthermore, secondhand smoke is shown to increase ASCVD risk, and exposure should be avoided. E-cigarettes and vaping also share similar risks [56, 57].

Many institutions have smoking cessation programs that can be very helpful and often feature personalized strategies to help patients quit. In addition, there are a variety of nicotine replacement therapies including patches, gums, lozenges, nasal sprays, and inhalers. Other pharmacologic therapies include bupropion and varenicline [41].

Healthy sleep habits

Patients undergoing ADT frequently experience fatigue and sleep disturbances, which can negatively impact their quality of life and lead to reduced adherence to treatment [58]. There is increasing evidence to indicate that poor sleep can contribute to adverse cardiovascular outcomes [59]. Inadequate sleep (< 7 h) or interrupted sleep has been associated with diabetes, obesity, and hypertension [59, 60]. Patients with established cardiovascular disease were found to have high cardiovascular mortality with poor sleep patterns [61]. Poor sleep patterns can often be modified by practicing better sleep hygiene, including going to bed and waking up at the same time every day of the week, avoiding exposure to screens before going to bed, ensuring a comfortable temperature in the bedroom, making sure the room is dark, and avoiding stimulants or alcohol right before bedtime [59]. Poor sleep patterns may also be a sign of undiagnosed sleep apnea. Thus, providers should inquire about patient's sleep habits, as these could be another way to help improve overall cardiovascular risk.

Management of weight and obesity

There is a growing body of research that suggests that weight loss after a diagnosis of prostate cancer may be beneficial for both overall survival and prostate cancer-specific survival. One ACS study that followed nearly 12,000 men for an average of 11 years found that men who gained more than 5% of their body weight or more than 10 pounds after a diagnosis of localized prostate cancer were more likely to die of prostate cancer and all causes than men who maintained their weight [62].

There are not enough data to suggest that weight loss after prostate cancer diagnosis improves mortality. It is thought that weight loss may help reduce inflammation, improve insulin sensitivity, and decrease the production of testosterone, all of which may play a role in the development and progression of prostate cancer; however, weight loss can improve cardiovascular outcomes.

The ACC/AHA as well as several other obesity management societies recommend early enrollment in comprehensive lifestyle programs that promote weight loss, assist in caloric restriction (800–1500 kcal/day, if safe), and promote physical activity with frequent follow-up or check-ins [41]. The recommended physical activity level for weight loss is between 200–300 min a week if able. Many pharmaceutical therapies can also assist with weight loss, particularly glucagon-like peptide 1 receptor agonists (GLP1-RA) in patients who also have type 2 diabetes [63]. It is important to remember that even ≥ 5% of initial weight loss can result in moderate improvement of blood pressure, cholesterol, and blood glucose [41]. The importance of having a nutritionist can also not be understated.

Adults with elevated cholesterol

When a person is diagnosed with cancer, their focus often shifts from long-term health management to more acute management of the cancer. As a result, other chronic conditions, such as atherosclerotic disease, may be deprioritized. There is mixed evidence on the impact of statins on cancer-specific mortality. Most meta-analyses suggest either no effect or minimal effect on cancer-specific mortality [64–66]. However, it is important to recognize that patients diagnosed with cancer are more likely to be overweight or obese and have a history of smoking,

which increases their risk of cardiovascular disease. To make matters worse, ADT is associated with metabolic syndrome and increased cardiovascular mortality [67]. According to expert consensus, continued monitoring of lipid profiles per ACC/AHA guidelines and the continuation of lipid-lowering agents are recommended. The ACC/AHA guidelines recommend that cancer survivors have their lipid levels checked at least every year [68].

Adults with type 2 diabetes mellitus

Type 2 diabetes is a major risk factor for ASCVD and widely prevalent in the United States. Approximately 12% of adults in the United States have diabetes, primarily type 2 diabetes, and more than one-third of the population has pre-diabetes [41]. ADT has also been shown to be associated with the development of diabetes, making the identification and management of diabetes very important in reducing cardiovascular risk. Type 2 diabetes is defined by a hemoglobin A1c level of ≥ 6.5%, with the general goal being to maintain it below 7% for optimal glycemic control. However, specific recommendations for managing diabetes in patients with prostate cancer are lacking [41]. In addition to counseling patients to follow a heart healthy diet and recommending guideline-based physical activity requirements, patients may benefit from the addition of pharmacotherapy. The first treatment is typically metformin to improve glycemic control; however, in patients with heart failure, established ASCVD, or obesity, the use of sodium glucose cotransporter 2 (SGLT2) inhibitors or GLP1-RA has proven to be of significant benefit in reducing cardiac events [69–71]. Not all providers are familiar with the myriad pharmacotherapies for diabetes; therefore, collaboration with a cardiometabolic and/or endocrine specialist is encouraged.

Adults with elevated blood pressure

Chemotherapy is an independent risk factor for hypertension due to the direct effects on endothelial function, sympathetic activity, and renin-angiotensin system activity. Additionally, some chemotherapeutic agents can be nephrotoxic, which can also lead to hypertension. Adequate blood pressure management often requires a combination of nonpharmacologic and pharmacologic therapies [41]. Nonpharmacologic therapies include weight loss, following a heart healthy diet, sodium restriction, dietary potassium supplementation, increased physical activity, and limiting alcohol consumption. Pharmacologic therapy is also recommended in addition to nonpharmacologic therapy if blood pressure is ≥ 140/90 mmHg or ≥ 130/ ≥ 80 mmHg with a 10-year ASCVD risk calculated at ≥ 10% [41]. In general, a reasonable blood pressure goal according to the ACC/AHA guidelines is < 130/ < 80 mm Hg [41]. Blood pressure taken in clinic may not be accurate either due to "white coat hypertension" (possibly due to anxiety about the visit) or "masked" hypertension (values in the clinic setting are normal but are elevated in home environments). In these cases, home blood pressure monitoring can be helpful to determine how aggressively high blood pressure should be treated. This is especially true for patients on ADT or antiandrogen therapy, whose risk of developing elevated blood pressure is already high.

Conclusion

Patients diagnosed with prostate cancer often have significant baseline cardiovascular risk factors that are frequently overlooked during cancer diagnosis. Additionally, cancer therapies can be associated with cardiovascular toxicity. There are many ways providers can manage and prevent cardiovascular complications in men undergoing potentially cardiotoxic treatment for prostate cancer. Close collaboration with cardiometabolic and cardio-oncology specialists will be key to ensure cardiovascular health is optimized. The risks and benefits of prostate cancer treatment must always be considered, especially if patients are at high-risk for cardiovascular events. Despite great insights from the PRONOUNCE trial, more research, particularly randomized clinical trial data focused on cardiovascular outcomes, is certainly warranted as therapeutics for prostate cancer continue to evolve. Including cardiovascular specialists in tumor board discussions will also be important to investigate in the future. In the meantime, remembering the AHA's Life's Essential 8 and referring to the current ACC/AHA prevention guidelines will help both providers and patients promote heart-healthy living.

Abbreviations

ACC	American College of Cardiology
ACS	American Cancer Society
ADT	Androgen deprivation therapy
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
AUA	American Urological Association
CI	Confidence interval
CUA	Canadian Urology Association
EAU	European Association of Urology
GnRH	Gonadotropin-releasing hormone
HR	Hazard ratio
IC-OS	International Cardio-Oncology Society
LDL-C	Low-density lipoprotein cholesterol
MET	Metabolic equivalent
PSA	Prostate-specific antigen
SGLT2	Sodium glucose cotransporter 2

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References

1. Rawla P. Epidemiology of Prostate Cancer. World J Oncol. 2019;10(2):63-89. https://doi.org/10.14740/wjon1191.
2. O'Farrell S, Garmo H, Holmberg L, Adolfsson J, Stattin P, Van Hemelrijck M. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. J Clin Oncol. 2015;33. https://doi.org/10.1200/JCO.2014.59.1792.
3. An Interactive Website for SEER Cancer Statistics, Surveillance Research Program, National Cancer Institute. Accessed May 2, 2023. https://seer.cancer.gov/statistics-network/.
4. Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL, Milani RV, Sagalowsky AI, Smith MR, Zakai N. Androgen-deprivation therapy in prostate cancer and cardiovascular risk. Circulation. 2010;121(6):833–40. https://doi.org/10.1161/CIRCULATIONAHA.109.192695.
5. Rosario DJ, Bourke L. Cardiovascular disease and the androgen receptor: here we go again? Eur Urol. 2020;77(2). https://doi.org/10.1016/j.eururo.2019.08.017.
6. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Does comorbidity influence the risk of myocardial infarction or diabetes during androgen-deprivation therapy for prostate cancer? Eur Urol. 2013;64(1). https://doi.org/10.1016/j.eururo.2012.04.035.
7. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst. 2010;102(1). https://doi.org/10.1093/jnci/djp404.
8. Shaikh PA, Som A, Deych E, Deng AJ, Reimers MA, Baumann BC, Kim EH, Lenihan DJ, Zhang KW. Incidental coronary arterial calcification for cardiovascular risk assessment in men with prostate cancer undergoing PET/CT imaging. Clin Genitourin Cancer. 2024;22(2):586–92. https://doi.org/10.1016/j.clgc.2024.01.014.
9. Sun L, Parikh RB, Hubbard RA, Cashy J, Takvorian SU, Vaughn DJ, Robinson KW, Narayan V, Ky B. Assessment and management of cardiovascular risk factors among US veterans with prostate cancer. JAMA Netw Open. 2021;4(2):1–13. https://doi.org/10.1001/jamanetworkopen.2021.0070.
10. Gupta D, Chuy KL, Yang JC, Bates M, Lombardo M, Steingart RM. Cardiovascular and metabolic effects of androgen-deprivation therapy for prostate cancer. J Oncol Pract. 2018;14(10). https://doi.org/10.1200/JOP.18.00178.
11. Sayegh N, Swami U, Agarwal N. Recent advances in the management of metastatic prostate cancer. JCO Oncol Pract. 2022;18(1):45–55. https://doi.org/10.1200/OP.21.00206.
12. Smith JC, Bennett S, Evans LM, Kynaston HG, Parmar M, Mason MD, Cockcroft JR, Scanlon MF, Davies JS. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab. 2001;86(9). https://doi.org/10.1210/jcem.86.9.7851.
13. Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, Kantoff PW. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab. 2002;87(2). https://doi.org/10.1210/jcem.87.2.8299.
14. Levine GN, D'Aamico A V., Berger P, Clark PE, Eckel RH, Keating NL, Milani R V., Sagalowsky AI, Smith MR, Zakai N. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American heart association, American cancer society, and American urological association. Circulation. 2010;121(6). https://doi.org/10.1161/CIRCULATIONAHA.109.192695.
15. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006;24(27). https://doi.org/10.1200/JCO.2006.06.2497.
16. Tzortzis V, Samarinas M, Zachos I, Oeconomou A, Pisters LL, Bargiota A. Adverse effects of androgen deprivation therapy in patients with prostate cancer: focus on metabolic complications. Hormones. 2017;16(2). https://doi.org/10.14310/horm.2002.1727.
17. Zareba P, Duivenvoorden W, Leong DP, Pinthus JH. Androgen deprivation therapy and cardiovascular disease: what is the linking mechanism? Ther Adv Urol. 2016;8(2). https://doi.org/10.1177/1756287215617872.
18. Gupta D, Salmane C, Slovin S, Steingart RM. Cardiovascular complications of androgen deprivation therapy for prostate cancer. Curr Treat Options Cardiovasc Med. 2017;19(8). https://doi.org/10.1007/s11936-017-0563-1.
19. Cirne F, Aghel N, Petropoulos JA, Klotz L, Lenihan DJ, Saad F, Pinthus J, Leong DP. The cardiovascular effects of gonadotropin-releasing hormone antagonists in men with prostate cancer. Eur Hear J - Cardiovasc Pharmacother. 2022;8(3). https://doi.org/10.1093/ehjcvp/pvab005.
20. Scailteux LM, Vincendeau S, Balusson F, Leclercq C, Happe A, Le Nautout B, Polard E, Nowak E, Oger E. Androgen deprivation therapy and cardiovascular risk: no meaningful difference between GnRH antagonist and agonists—a nationwide population-based cohort study based on 2010–2013 French Health Insurance data. Eur J Cancer. 2017;77. https://doi.org/10.1016/j.ejca.2017.03.002.
21. Sciarra A, Fasulo A, Ciardi A, Petrangeli E, Gentilucci A, Maggi M, Innocenzi M, Pierella F, Gentile V, Salciccia S, Cattarino S. A meta-analysis and systematic review of randomized controlled trials with degarelix versus gonadotropin-releasing hormone agonists for advanced prostate cancer. Med (United States). 2016;95(27). https://doi.org/10.1097/MD.0000000000003845.
22. Iacovelli R, Ciccarese C, Bria E, Romano M, Fantinel E, Bimbatti D, Muraglia A, Porcaro AB, Siracusano S, Brunelli M, Mazzarotto R, Artibani W, Tortora G. The cardiovascular toxicity of abiraterone and enzalutamide in prostate cancer. Clin Genitourin Cancer. 2018;16(3). https://doi.org/10.1016/j.clgc.2017.12.007.
23. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, Wilding G, Prescott S, Kanaga Sundaram S, Small EJ, Dawson NA, Donnelly BJ, Venner PM, Vaishampayan UN, Schellhammer PF, Quinn DI, Raghavan D, Ely B, Moinpour CM, Vogelzang NJ, Thompson IM. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med. 2013;368(14). https://doi.org/10.1056/nejmoa1212299.
24. Lopes RD, Higano CS, Slovin SF, Nelson AJ, Bigelow R, Sørensen PS, Melloni C, Goodman SG, Evans CP, Nilsson J, Bhatt DL, Clarke NW, Olesen TK, Doyle-Olsen BT, Kristensen H, Arney L, Roe MT, Alexander JH. Cardiovascular safety of degarelix versus leuprolide in patients with prostate cancer: the primary results of the PRONOUNCE randomized trial. Circulation. 2021;144(16). https://doi.org/10.1161/CIRCULATIONAHA.121.056810.
25. Messing EM, Manola J, Yao J, Kiernan M, Crawford D, Wilding G, di'SantAgnese PA, Trump D. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol. 2006;7(6). https://doi.org/10.1016/S1470-2045(06)70700-8.
26. Boegemann M, Khaksar S, Bera G, Birtle A, Dopchie C, Dourthe LM, Everaert E, Hatzinger M, Hercher D, Hilgers W, Matus G, Alvarez LG, Antoni L, Lukac M, Pissart G, Robinson P, Elliott T. Abiraterone acetate plus prednisone for the Management of Metastatic Castration-Resistant Prostate Cancer (mCRPC) without prior use of chemotherapy: report from a large, international, real-world retrospective cohort study. BMC Cancer. 2019;19(1). https://doi.org/10.1186/s12885-019-5280-6.
27. Shore ND, Saad F, Cookson MS, George DJ, Saltzstein DR, Tutrone R, Akaza H, Bossi A, van Veenhuyzen DF, Selby B, Fan X, Kang V, Walling J, Tombal B. Oral relugolix for androgen-deprivation therapy in advanced prostate

cancer. N Engl J Med. 2020;382(23). https://doi.org/10.1056/nejmoa2004325.
28. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Özgüroğlu M, Ye D, Feyerabend S, Protheroe A, De Porre P, Kheoh T, Park YC, Todd MB, Chi KN. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med. 2017;377(4). https://doi.org/10.1056/nejmoa1704174.
29. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, Coskinas X, Frydenberg M, Hague WE, Horvath LG, Joshua AM, Lawrence NJ, Marx G, McCaffrey J, McDermott R, McJannett M, North SA, Parnis F, Parulekar W, Pook DW, Reaume MN, Sandhu SK, Tan A, Tan TH, Thomson A, Tu E, Vera-Badillo F, Williams SG, Yip S, Zhang AY, Zielinski RR, Sweeney CJ. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med. 2019;381(2). https://doi.org/10.1056/nejmoa1903835.
30. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez Soto, Merseburger AS, Özguroglu M, Uemura H, Ye D, Deprince K, Naini V, Li J, Cheng S, Yu MK, Zhang K, Larsen JS, McCarthy S, Chowdhury S. Re: Apalutamide for metastatic, castration-sensitive prostate cancer. J Urol. 2019;202(4):661. https://doi.org/10.1056/NEJMoa1903307.
31. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S, Davis ID, de Bono JS, Evans CP, Fizazi K, Joshua AM, Kim CS, Kimura G, Mainwaring P, Mansbach H, Miller K, Noonberg SB, Perabo F, Phung D, Saad F, Scher HI, Taplin ME, Venner PM, Tombal B. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. N Engl J Med. 2014;371(5). https://doi.org/10.1056/nejmoa1405095.
32. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. N Engl J Med. 2012;367(13). https://doi.org/10.1056/nejmoa1207506.
33. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PFA, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttmann H, Gerritsen WR, Flaig TW, George DJ, Yu EY, Efstathiou E, Pantuck A, Winquist E, Higano CS, Taplin ME, Park Y, Kheoh T, Griffin T, Scher HI, Rathkopf DE. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368(2). https://doi.org/10.1056/nejmoa1209096.
34. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21). https://doi.org/10.1056/nejmoa1014618.
35. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, Jievaltas M, Luz M, Alekseev B, Kuss I, Le Berre MA, Petrenciuc O, Snapir A, Sarapohja T, Smith MR. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. N Engl J Med. 2020;383(11). https://doi.org/10.1056/nejmoa2001342.
36. Sternberg CN, Fizazi K, Saad F, Shore ND, De Giorgi U, Penson DF, Ferreira U, Efstathiou E, Madziarska K, Kolinsky MP, Cubero DIG, Noerby B, Zohren F, Lin X, Modelska K, Sugg J, Steinberg J, Hussain M. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2020;382(23). https://doi.org/10.1056/nejmoa2003892.
37. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, Olmos D, Mainwaring PN, Lee JY, Uemura H, De Porre P, Smith AA, Brookman-May SD, Li S, Zhang K, Rooney B, Lopez-Gitlitz A, Small EJ. Apalutamide and overall survival in prostate cancer. Eur Urol. 2021;79(1). https://doi.org/10.1016/j.eururo.2020.08.011.
38. Pollack A, Karrison TG, Balogh AG, Gomella LG, Low DA, Bruner DW, Wefel JS, Martin AG, Michalski JM, Angyalfi SJ, Lukka H, Faria SL, Rodrigues GB, Beauchemin MC, Lee RJ, Seaward SA, Allen AM, Monitto DC, Seiferheld W, Sartor O, Feng F, Sandler HM. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. Lancet. 2022;399(10338). https://doi.org/10.1016/S0140-6736(21)01790-6.
39. Zapatero A, Guerrero A, Maldonado X, Álvarez A, San-Segundo CG, Rodríguez MÁC, Solé JM, Olivé AP, Casas F, Boladeras A, de Vidales CM, de la Torre MLV, Vara S, Sanz JL, Calvo FA. High-dose radiotherapy and risk-adapted androgen deprivation in localised prostate cancer (DART 01/05): 10-year results of a phase 3 randomised, controlled trial. Lancet Oncol. 2022;23(5). https://doi.org/10.1016/S1470-2045(22)00190-5.
40. Jani AB, Schreibmann E, Goyal S, Halkar R, Hershatter B, Rossi PJ, Shelton JW, Patel PR, Xu KM, Goodman M, Master VA, Joshi SS, Kucuk O, Carthon BC, Bilen MA, Abiodun-Ojo OA, Akintayo AA, Dhere VR, Schuster DM. 18F-fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial. Lancet. 2021;397(10288). https://doi.org/10.1016/S0140-6736(21)00581-X.
41. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC, Virani SS, Williams KA, Yeboah J, Ziaeian B. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. J Am Coll Cardiol. 2019;74(10):e177–232. https://doi.org/10.1016/j.jacc.2019.03.010.
42. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, Rosamond W. Life's essential 8: updating and enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory from the American Heart Association. Circulation. 2022;146(5):E18–43. https://doi.org/10.1161/CIR.0000000000001078.
43. Kim H, Caulfield LE, Rebholz CM. Healthy plant-based diets are associated with lower risk of all-cause mortality in US Adults. J Nutr. 2018;148(4). https://doi.org/10.1093/jn/nxy019.
44. AWhalen K, Judd S, McCullough ML, Flanders WD, Hartman TJ, Bostick RM. Paleolithic and mediterranean diet pattern scores are inversely associated with all-cause and cause-specific mortality in adults. J Nutr. 2017;147(4). https://doi.org/10.3945/jn.116.241919.
45. Gupta N, Patel HD, Taylor J, Borin JF, Jacobsohn K, Kenfield SA, Eggener SE, Price C, Davuluri M, Byrne N, Bivalacqua TJ, Loeb S. Systematic review of the impact of a plant-based diet on prostate cancer incidence and outcomes. Prostate Cancer Prostatic Dis. 2022;25(3). https://doi.org/10.1038/s41391-022-00553-2.
46. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí J V., Martínez JA, Fitó M, Gea A, Hernán MA, Martínez-González MA. Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med. 2018;378(25). https://doi.org/10.1056/nejmoa1800389.
47. Martínez-González MA, Sánchez-Tainta A, Corella D, Salas-Salvadó J, Ros E, Arós F, Gómez-Gracia E, Fiol M, Lamuela-Raventós RM, Schröder H, Lapetra J, Serra-Majem L, Pinto X, Ruiz-Gutierrez V. A provegetarian food pattern and reduction in total mortality in the Prevención con Dieta Mediterránea (PREDIMED) study. Am J Clin Nutr. 2014;100(suppl_1):320S-328S. https://doi.org/10.3945/ajcn.113.071431.
48. Chan JM, Stampfer MJ, Ma J, Gann PH, Gaziano JM, Giovannucci EL. Dairy products, calcium, and prostate cancer risk in the physicians' health study. Am J Clin Nutr. 2001;74(4):549–54. https://doi.org/10.1093/ajcn/74.4.549.
49. Sargsyan A, Dubasi HB. Milk consumption and prostate cancer: a systematic review. World J Mens Health. 2021;39(3):419. https://doi.org/10.5534/wjmh.200051.
50. Nguyen PL, Alibhai SMH, Basaria S, D'Amico A V., Kantoff PW, Keating NL, Penson DF, Rosario DJ, Tombal B, Smith MR. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol. 2015;67(5). https://doi.org/10.1016/j.eururo.2014.07.010.
51. Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, Chan JM. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. Cancer Res. 2011;71(11). https://doi.org/10.1158/0008-5472.CAN-10-3932.
52. 2018 Physical Activity Guidelines AdvisoryCommittee. 2018 Physical Activity Guidelines AdvisoryCommittee Scientific Report. Published 2018. https://health.gov/paguidelines/second-edition/report.
53. Nuru F, Osei E, Kassim R. A review of the effects of tobacco smoking on the treatment of prostate cancer. J Radiother Pract. 2022;21(1):109–16. https://doi.org/10.1017/S1460396920000552.

54. Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M, De Groot L, Freedman ND, Jansen E, Kee F, Kromhout D, Kuulasmaa K, Tiina L, O'Doherty MG, Bas BDM, Orfanos P, Peters A, Van Der Schouw YT, Wilsgaard T, Wolk A, Trichopoulou A, Boffetta P, Brenner H, Baceviciene M, Boer JMA, Drygas W, Eriksson S, Feskens E, Gafarov V, Gardiner J, Håkansson N, Jansson JH, Jousilahti P, Kampman E, Kontto J, Kubinova R, Leenders M, Linneberg A, Løchen ML, Lorbeer R, Malyutina S, Mathiesen EB, Melhus H, Michaëlsson K, Njølstad I, Orsini N, Pająk A, Pikhart H, Pisinger C, Salomaa V, Sánchez MJ, Sans S, Schaan B, Schneider A, Siganos G, Söderberg S, Streppel M, Tamošiunas A, Veronesi G, Waterham E, Wennberg P. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of Individual participant data from prospective cohort studies of the CHANCES consortium. BMJ. 2015;350. https://doi.org/10.1136/bmj.h1551.
55. Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev. 2016;2016(3). https://doi.org/10.1002/14651858.CD008286.pub3.
56. Moheimani RS, Bhetraratana M, Yin F, Peters KM, Gornbein J, Araujo JA, Middlekauff HR. Increased cardiac sympathetic activity and oxidative stress in habitual electronic cigarette users: implications for cardiovascular risk. JAMA Cardiol. 2017;2(3). https://doi.org/10.1001/jamacardio.2016.5303.
57. Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, Robertson RM, McAuley T, Goff D, Benowitz N. Electronic cigarettes: a policy statement from the American Heart Association. Circulation. 2014;130(16). https://doi.org/10.1161/CIR.0000000000000107.
58. Mangar S, Abbadasari M, Carollo A, Esposito G, Ahmed H, Shah T, Dimitriou D. Understanding sleep disturbances in prostate cancer—a scientometric analysis of sleep assessment, aetiology, and its impact on quality of life. Cancers (Basel). 2023;15(13):1–19. https://doi.org/10.3390/cancers15133485.
59. Kuehn BM. Sleep duration linked to cardiovascular disease. Circulation. 2019;139(21). https://doi.org/10.1161/CIRCULATIONAHA.119.041278.
60. Lee S, Mu CX, Wallace ML, Andel R, Almeida DM, Buxton OM, Patel SR. Sleep health composites are associated with the risk of heart disease across sex and race. Sci Rep. 2022;12(1). https://doi.org/10.1038/s41598-022-05203-0.
61. Kim JH, Hayek SS, Ko YA, Liu C, Samman Tahhan A, Ali S, Alkhoder A, Gafeer MM, Choudhary F, Bhimani R, Delawalla S, Choudhary M, Hartsfield DJ, Bliwise DL, Quyyumi AA. Sleep duration and mortality in patients with coronary artery disease. Am J Cardiol. 2019;123(6). https://doi.org/10.1016/j.amjcard.2018.11.057.
62. Troeschel AN, Hartman TJ, Jacobs EJ, Stevens VL, Gansler T, Flanders WD, McCullough LE, Wang Y. Postdiagnosis body mass index, weight change, and mortality from prostate cancer, cardiovascular disease, and all causes among survivors of nonmetastatic prostate cancer. J Clin Oncol. 2020;38(18). https://doi.org/10.1200/JCO.19.02185.
63. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989–1002. https://doi.org/10.1056/NEJMoa2032183.
64. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med. 2012;367(19). https://doi.org/10.1056/nejmoa1201735.
65. Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, Bhala N, Holland L, Peto R, Keech A, Collins R, Simes J, Baigent C, De Lemos J, Braunwald E, Blazing M, Murphy S, Downs JR, Gotto A, Clearfield M, Holdaas H, Gordon D, Davis B, Koren M, Dahlof B, Poulter N, Sever P, Knopp RH, Fellström B, Jardine A, Schmieder R, Zannad F, Goldbourt U, Kaplinsky E, Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Fuller J, Neil A, Wanner C, Krane V, Sacks F, Moyé L, Pfeffer M, Hawkins CM, Kjekshus J, Wedel H, Wikstrand J, Tavazzi L, Maggioni A, Marchioli R, Tognoni G, Franzosi MG, Armitage J, Parish S, Sleight P, Pedersen TR, Ridker PM, MacMahon S, Marschner I, Tonkin A, Shaw J, Serruys PW, Nakamura H, Knatterud G, Furberg C, Byington R, Macfarlane P, Cobbe S, Ford I, Murphy M, Blauw GJ, Packard C, Shepherd J, Wilhelmsen L, Cannon C, Bowman L, La Rosa J, Flather M, Kastelein J, Shear C, Tobert J, Varigos J, White H, Yusuf S, Baxter A, Barnes EH, Buck G, Herrington WG, Kirby A, Lewis DA, Mellies M, McGovern M, Barclay J, Belder R, Mitchell Y, Musliner T, Ansquer JC, et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One. 2012;7(1). https://doi.org/10.1371/journal.pone.0029849.
66. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA. 2006;295(1). https://doi.org/10.1001/jama.295.1.74.
67. Redig AJ, Munshi HG. Care of the cancer survivor: metabolic syndrome after hormone-modifying therapy. Am J Med. 2010;123(1). https://doi.org/10.1016/j.amjmed.2009.06.022.
68. Zullig LL, Sung AD, Khouri MG, Jazowski S, Shah NP, Sitlinger A, Blalock DV, Whitney C, Kikuchi R, Bosworth HB, Crowley MJ, Goldstein KM, Klem I, Oeffinger KC, Dent S. Cardiometabolic comorbidities in cancer survivors: JACC: cardiooncology state-of-the-art review. JACC CardioOncology. 2022;4(2):149–65. https://doi.org/10.1016/j.jaccao.2022.03.005.
69. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311–22. https://doi.org/10.1056/NEJMoa1603827.
70. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–44. https://doi.org/10.1056/NEJMoa1607141.
71. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28. https://doi.org/10.1056/NEJMoa1504720.

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