Optimizing screening and management of cardiovascular health in prostate cancer: A review

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Abstract

In clinical practice, cancer management does not consistently encompass screening and identification of cardiovascular (CV) risk. The use of androgen deprivation therapy (ADT) in prostate cancer has been associated with increased CV risk and development of metabolic syndrome, necessitating identification of patients at risk in this population (e.g., those with pre-existing CV disease). A multidisciplinary team of Canadian physicians was assembled to develop a series of recommendations intended to identify patients who may benefit from optimal management of their CV disease and/or modification of cardiac risk factors. A key goal was the development of a simple screening tool for identification of patients with pre-existing CV disease. This simple and inclusive set of recommendations are intended for use within urology clinics to facilitate holistic approaches and simplify the management of patients.

Prostate cancer and cardiovascular disease

Prostate cancer is the most common form of cancer in men. Approximately one out of every nine men will be diagnosed with the disease during their lifetime.[1,2] The average age at diagnosis in North America is 66 years. Prevalence in North America is approximately 3 million, with approximately 200 000 new cases diagnosed each year. Due to the relatively indolent nature of this form of cancer, only one in 41 men die of prostate cancer itself.[1]

In contrast, cardiovascular (CV) disease is a far more prevalent condition, with approximately 100 million men and women in North America either directly affected or considered to be at risk of the disease.[3] It is the leading global cause of death, accounting for nearly 20 million deaths each year worldwide and approximately 1 million deaths per year in North America.[3]

Given the high prevalence of both conditions, the coexistence of prostate cancer and CV disease is inevitable. Furthermore, these two clinical conditions share a number of common risk factors, such as advanced age, metabolic syndrome, visceral adiposity, and physical inactivity.

Important advances in the understanding of cancer biology have led to breakthrough treatments and a growing number of cancer survivors. However, both traditional and novel cancer treatments are associated with CV and metabolic complications. The adverse effects of these treatments increase the short- and long-term risk of CV events above and beyond the already elevated risk present in patients with cancer. The use of androgen deprivation therapy (ADT) in the management of prostate cancer serves as an example. ADT has been used to treat this hormone-sensitive malignancy for decades and is accepted as front-line therapy for a large number of patients; however, ADT increases blood concentrations of total cholesterol and low-density lipoprotein cholesterol (LDL-C), and has been associated with a significantly increased risk of incident diabetes mellitus, coronary artery disease (CAD, including myocardial infarction [MI]), and sudden cardiac death. Furthermore, data from randomized oncology clinical trials have demonstrated that ADT increases mortality in patients with underlying CAD or heart failure (HF). Thus, optimal care of patients with cancer is best realized through a multidisciplinary approach whereby oncology and CV specialists partner (cardio-oncology) in order to assess CV risk, minimize vascular and metabolic toxicity, and manage long-term adverse effects.[4] This combined approach forms the basis for the emerging discipline of cardio-oncology.

Metabolic syndrome, prostate cancer, and CV disease

Metabolic syndrome has been proposed as a link between prostate cancer and CV complications. It is also, of itself, a risk factor for prostate cancer incidence, as well as for progression to higher-risk disease.[5] Metabolic syndrome comprises multiple interconnected factors (biochemical, metabolic, physiological, and clinical) that increase the risk of type 2 diabetes and heart disease, resulting in early mortality. The current term metabolic syndrome was proposed in 1998 by the World Health Organization.[6,7] In the ensuing decades, subspecialty societies have adopted their own modified definitions and criteria of this condition (Table 1).

A high prevalence of metabolic syndrome (51–55%) was reported among ADT-treated patients.[8-10] A meta-analysis demonstrated a 75% higher risk of metabolic syndrome and a 36% higher risk of diabetes in patients on ADT compared to controls.[11] Castration therapy among older men with prostate cancer can induce metabolic syndrome,[12,13] and is associated with an elevated risk of CV disease and type 2 diabetes.[14,15]

With the prolonged survival of patients on modern ADT, consideration of metabolic syndrome and its associated CV risks is becoming increasingly important in the management of prostate cancer, particularly in the context of the potential impact on quality of life and health resource utilization. Awareness of the importance of metabolic syndrome has led to recent efforts to reduce the impact of ADT through exercise regimens,[16] which are limited by suboptimal adherence.[17]

In addition to the well-recognized association of metabolic syndrome with elevated risk of CV disease, stroke, and diabetes, there is increasing awareness of its other potential interactions. Recent studies suggest that cancers with high incidence in the developed countries (such as colorectal and breast cancers) may be linked to metabolic syndrome.[18-22] Additionally, urological conditions are highly prevalent in aging men with metabolic syndrome. It is, therefore, crucial for urologists to be aware of metabolic syndrome and its constituent conditions, in terms of counselling and diagnosis.

The processes underlying metabolic syndrome are currently incompletely understood, with the associated physiological alterations not fully elucidated. The key characteristic is an energy imbalance, resulting from the interactions of genetic risk factors with environmental and lifestyle exposure (inactivity, tobacco smoking, excess caloric intake, pharmacological treatments, and psychological stress). Resulting adiposity is associated with abnormal fatty acid metabolism and stimulation of adipokines release. The resulting physiological abnormalities include endothelial dysfunction, insulin resistance, atherogenic dyslipidemia, hypertension, hypercoagulability, and a chronic low-grade inflammatory state.

At the vascular level, metabolic syndrome is characterized by impairments in endothelium-dependent vasodilatation and arterial compliance, as well as atherosclerosis.[23] These physiological abnormalities are mediated by factors including elevated levels of oxidative stress reactive species, hyperglycemia, adipokines, glycation products, free fatty acids, and inflammatory cytokines. Metabolic syndrome induces a chronic proinflammatory state, with elevated circulating levels of cytokines and acute-phase reactants. Coagulation anomalies, including alterations in the procoagulant factors fibrinogen, factor VII, factor VIII, and the plasminogen activator inhibitor-1, suggest that pro-thrombotic and pro-inflammatory states may be metabolically linked.

Table 1. Metabolic syndrome definitions and criteria

Clinical parameter	WHO (1998)	EGIR (1999)	ATP III (2001)	AACE (2003)	IDF (2005)
Obesity/body fat distribution	Waist/hip ratio >0.90 in men, >0.85 in women; or BMI >30 kg/m^2	Waist circumference ≥94 cm in men, ≥80 cm in women	Waist circumference >102 cm in men, >88 cm in women.	BMI ≥25 kg/m^2	Waist circumference ≥94 cm in men, ≥80 cm in women
Insulin resistance/ hyperglycemia	IGT, IFG, T2DM, or other evidence of insulin resistance	Hyperinsulinemia (plasma insulin >75th percentile)	Fasting glucose ≥110 mg/dL (6.1 mmol/L)	Fasting glucose ≥110 mg/dL (6.1 mmol/L)	Fasting glucose ≥100 mg/dL (5.5 mmol/L), T2DM
Triglyceridemia	≥150 mg/dL (1.7 mmol/L)	≥ 177 mg/dL (2.0 mmol/L)	≥ 150 mg/dL (1.7 mmol/L)	> 150 mg/dL (1.7 mmol/L)	> 150 mg/dL (1.7 mmol/L) or on treatment
Cholesterol	HDL-C <35 mg/dL (0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) in women	HDL-C <39 mg/dL (1.0 mmol/L)	HDL-C <40 mg/dL in men (1.0 mmol/L); <50 mg/dL (1.3 mmol/L) in women	HDL-C <40 mg/dL (1.0 mmol/L) in men; <50 mg/dL (1.3 mmol/L) in women	HDL-C <40 mg/dL (1.0 mmol/L) in men; <50 mg/dL (1.3 mmol/L) in women; or on treatment
Blood pressure	≥140/90 mmHg	≥140/90 mmHg or on treatment	>130/85 mmHg	≥130/85 mmHg	>130/85 mmHg or on treatment
Other	Microalbuminuria[a]			Other features of insulin resistance[b]	

[a]Microalbuminuria defined as urinary albumin excretion ≥70 µg/min or albumin/creatine ratio ≥30 mg/g. [b]Family history of T2DM, hypertension, or CVD; polycystic ovary syndrome; sedentary lifestyle; advancing age; ethnic groups having high risk for T2DM or CVD. AACE: American Association of Clinical Endocrinologists; ATP III: National Cholesterol Education Program Adult Treatment Panel III Report; BMI: body mass index; EGIR: European Group for the Study of Insulin Resistance; HDL-C: high-density lipoprotein cholesterol; IDF: International Diabetes Federation; IGT: impaired glucose tolerance; IFG: impaired fasting glucose; T2DM: type II diabetes mellitus; WHO: World Health Organization.

Targeting metabolic syndrome as a novel strategy in disease etiology

With growing recognition of the associations between metabolic syndrome and prostate cancer, the potential interventions that would reverse the constituent features (e.g., obesity, insulin resistance) via lifestyle modifications or pharmacotherapy are a topic of intense study.

Diet and exercise

Physiological studies evaluating the effects of exercise on the androgen axis found increased blood concentrations of both testosterone and cortisol following physical exertion. While testosterone levels increase immediately following exercise, cortisol response tends to be slightly delayed. An exercise protocol needs to be of sufficient intensity and duration to induce these endocrine changes, with obese men requiring more vigorous exercise.[24]

Statins

HMG-CoA inhibitors are used for the management of hypercholesterolemia and for the primary and secondary prevention of CV events in men. Epidemiological association studies suggest a protective effect of statins against the progression of prostate cancer,[25] warranting randomized trials.[26]

Metformin

Metformin is a biguanide drug used for treatment of type 2 diabetes. Metformin is believed to modify metabolism by inhibiting oxidative phosphorylation and generating energetic stress in the liver.[27] Since early-stage prostate cancer predominantly relies on the oxidative phosphorylation pathway for energy generation, this effect may be potentially useful in management of early disease. Men receiving metformin for diabetes treatment were shown to have a lower risk of incidence and risk of death from prostate[28] and other cancers, potentially including bladder carcinoma.[29] Current understanding of the effects of metformin is limited by the retrospective nature of the published association studies. One small-scale intervention trial in which metformin was administered to non-diabetic men prior to radical prostatectomy has shown a reduction in the proliferation of cancer cells and alterations in the PTEN/PI3K-AKT signaling pathway involved in disease progression.[30] A number of studies are currently in progress to address the lack of prospective data, including the MAST trial,[31] a Canadian study aiming to randomize 408 patients with prostate cancer managed by active surveillance to receive metformin or placebo under an investigational protocol modeled after the REDEEM trial.[32]

Treatment recommendations for patients with pre-existing CV disease

Despite being widely viewed as separate diseases, there is a remarkable overlap in risk factors common to both CV disease and cancer.[33] Hypertension, type 2 diabetes, tobacco use, and obesity are all highly prevalent in the aging population. A particularly high incidence is observed in individuals with prostate cancer, which remains the most common non-cutaneous malignancy in men. Recent data from an unselected population of 100 patients referred for ADT to a clinic at The University of British Columbia[34] demonstrated that 39% of patients had a CV condition (including items such as arrhythmia, pericarditis, coronary vasospasm), 25% had pre-existing heart disease, and 50% had elevated CV risk, as determined by the Framingham risk score. Notably, only one-third of patients at elevated CV risk were taking evidence-based therapies as recommended by the Canadian Cardiovascular Society (CCS)[35] and Diabetes Canada.[36,37] Additionally, a number of other studies suggest that approximately one-third of patients starting ADT have pre-existing CVD.[37,38]

A considerable amount of evidence supports the hypothesis that ADT is associated with a further increase in the risk of adverse CV events, including MI and CV death. The majority of these data are derived from large, observational studies involving patients receiving gonadotropin-releasing hormone (GnRH) agonist therapy.[37] However, it should be noted that randomized trial data do not support an association between ADT and CV events.[39] A number of factors may explain this discrepancy, including a lack of rigorous adjudication of CV events in cancer trials, highly selected clinical trial populations with low background prevalence of CV disease and risk factors, competing risks in high-risk prostate cancer patients, and unmeasured bias in observational studies. While further prospective studies with prespecified CV safety endpoints are needed to fully inform this issue, the safety signal identified in studies to date has already led the American Heart Association, American Cancer Society, and American Urological Association to jointly issue a warning on CV consequences of prostate cancer treatments.[40]

It is well-established that ADT is associated with adverse metabolic effects, including metabolic syndrome and its components.[41,42] Men treated with ADT have a 60% increased risk of incident diabetes,[43] while higher HbA1C values were observed in prostate cancer patients with pre-existing diabetes receiving ADT. Decreased lean body mass, increased visceral fat, and higher LDL concentration are also associated with ADT use. These metabolic risk factors, in turn, are associated with increased risk of atherosclerosis and vascular disease in the long-term.[41] However, it is difficult to explain the early risk of acute vascular events in patients receiving ADT on the basis of accelerated atherosclerosis alone. Importantly, the greatest risk has been observed in

patients with pre-existing CV disease.[42] While some of this risk may be due to the long-term adverse metabolic effects of ADT, the early separation of event curves (within one year of treatment initiation) suggests a more immediate effect, possibly mediated by accelerated plaque rupture in patients with pre-existing atherosclerotic disease.[44]

The transition from stable atherosclerotic plaque to vulnerable plaque is mediated, in large part, by the inflammatory system.[45] LDL accumulating in the arterial intima undergo oxidation, leading to the recruitment of circulating monocytes in response to endothelial cell expression of adhesion molecules. Monocytes differentiate into tissue macrophages in response to cytokines. Tissue macrophages then engulf trapped LDL, becoming foam cells, and eventually dying to form the central necrotic core of atherosclerotic plaque. This central core is isolated from the circulation by a fibrous cap. In the presence of a thin fibrous cap, a large necrotic core, and ongoing inflammation, plaque may rupture, leading to acute vascular events. Animal studies have demonstrated that GnRH receptors colocalize with CD3+ T-lymphocytes at the sites of atherosclerotic plaques.[46] In mouse models of atherosclerosis, treatment with GnRH agonists has been associated with increased numbers of tissue macrophages and increased plaque necrosis.[46,47] It has, therefore, been hypothesized that GnRH agonists may upregulate immune system activity at the level of pre-existing atherosclerosis, leading to plaque destabilization and rupture.

CV risks have also been associated with other forms of hormonal therapy. Enzalutamide is associated with a nearly three-fold increase in the risk of hypertension, placing patients at risk for both long-term and short-term vascular events.[48] Abiraterone is also associated with an increased risk of hypertension, as well as an increased risk of cardiac events, including heart failure.[48-50] Androgen suppression, in general, is associated with a prolongation of the QT interval and, therefore, theoretically increased risk of arrhythmia.[51] Patient selection In view of the CV risks associated with ADT, it is essential that the use of these therapies be limited to patients who are likely to derive a net clinical benefit.[52] Evidence clearly supports a net benefit among patients with metastatic or locally advanced prostate cancer.[53] Conversely, these benefits have not been reliably demonstrated in patients with low-risk prostate cancer. The importance of careful patient selection is illustrated by the results of the bicalutamide early prostate cancer program.[54] In three trials (with trial inclusion based on geographic region), progression-free survival (PFS) and overall survival (OS) were compared in patients with non-metastatic prostate cancer randomized to bicalutamide 150 mg daily or placebo, in addition to standard care. In the Scandinavian trial, bicalutamide was associated with increased survival among patients with locally advanced disease but decreased survival among those with localized disease.[55] In a review of the entire global program, there was a trend towards reduced survival with bicalutamide among patients managed with a watchful waiting approach, underscoring the lack of benefit in low-risk patients.

Early data suggest that the risk of CV events may be lower in patients receiving GnRH antagonists compared to GnRH agonists. A pooled analysis of patients enrolled in six randomized trials of degarelix vs. GnRH agonists demonstrated a 56% relative reduction in the risk of CV events or death among those randomized to degarelix in the subgroup of patients with pre-existing CV disease.[44] Additionally, a study comparing cardiac events in 80 patients randomized to one year of treatment with GnRH agonist or antagonist reported a higher number of patients experiencing a major cardiac event in the agonist-treated group compared to the antagonist-treated patients (20% vs. 3 %).[56] It has been proposed that this risk difference may be due to the fact that GnRH antagonists suppress both luteinizing hormone (LH) and follicle-stimulating hormone (FSH), while GnRH agonists primarily suppress LH. Alternatively, relative risk may be mediated by GnRH receptors on the surface of T lymphocytes localized to sites of atherosclerotic plaque. Ongoing randomized studies, such as PRONOUNCE (*ClinicalTrials.gov* Identifier: NCT02663908),[57] will provide additional insight into whether GnRH antagonists should be preferentially used instead of GnRH agonists in patients with established CV disease, in whom the risk of CV events is greatest.[58]

Recommendations for patient management

To aid the practitioner in diagnosing and treating patients with prostate cancer referred for ADT therapy, we recommend the following at the present time:

1) For every patient, collect routine medical history; perform a physical examination; determine the lipid profile; measure HbA1c, uric acid, serum electrolytes, and creatinine; and complete blood count (CBC) and electrocardiogram (ECG).
2) Identify patients with pre-existing CV disease using the suggested "STAMP" questions (Table 2). If a person has any of these conditions, he should be considered for acetylsalicylic acid (ASA; Aspirin®) and possibly additional anti-platelet or low-dose anti-coagulant therapy for higher-risk patients, lipid-lowering therapy

Table 2. STAMP – Identification of patients with cardiovascular disease

S	Stroke
T	Transient ischemic attack
A	Abdominal aortic aneurysm or other aortic disease
M	Myocardial infarction, angina, or previous coronary revascularization
P	Peripheral arterial disease

(preferably a statin), and a renin-angiotensin system antagonist, as per CCS guidelines (Table 3), unless contraindicated or not tolerated.

3) Identify patients who may benefit from referral to a cardio-oncology clinic for additional evaluation or therapy (Table 4).
4) In patients **without** pre-existing CV disease (as described in #2 and #3 above), calculate a Framingham or equivalent risk score and treat accordingly. Recommendation are the same as those for any patients concerned with keeping healthy: active lifestyle, physical activity, no smoking, good BP control, and body mass index (BMI) less than 30 (ideally, less than 25).

While assessments listed in #1 above can be performed by the healthcare practitioner treating the patient's prostate cancer, family doctors can be involved as well. Similarly, family physicians can help in calculating risk scores and working with the patients to reduce CVD risks by encouraging a healthier lifestyle and addressing risk factor management.

In managing patients who meet the criteria in #2 above, the physician should look for the following optimal conditions:

- Blood pressure below 140/90; for a diabetic patient, less than 130/80;
- LDL less than 2.0 mmol/L;
- HbA1c less than 7%;
- Smoking cessation;
- Exercise and active lifestyle;
- Good compliance with medication.

Patients who would benefit from a referral to a cardiologist or an internist (#3 above) are those who exhibit:

- Angina or dyspnea on a low level of activity or any significant functional class deterioration;
- Non-optimal treatment, as described in Table 3;
- MI or coronary revascularization in the last year;
- Cardiac patients without regular followup in cardiology or with the family physician.

Recommended procedures listed above should be done in conjunction with the "ABCDEs" of management (Table 5) in order to reduce CV risk. A multifactorial approach addressing healthy lifestyle, glycemic control, blood pressure control, dyslipidemia management, and other CV protective measures was shown to effectively lower the risk of serious complications and mortality and may prolong life expectancy in individuals with prostate cancer.[59]

Conclusions

Epidemiological studies increasingly support the interconnections between cancer and CV health (including risk factors such as diabetes mellitus). Use of ADT in prostate cancer has been associated with development of metabolic syndrome and increased CV risk. Patients with pre-existing CV disease who initiate ADT are at higher risk of a subsequent cardiac event.

Physicians treating prostate cancer, such as urologists and radiation oncologists, are increasingly required to consider the patient's CV health in making treatment decisions. In this review, we propose an inclusive set of recommendations for identifying and managing patients with prostate cancer who have concomitant CV disease or risk factors. Included with these recommendations is a simple screening tool (STAMP) that physicians can use to readily identify the patients at highest risk and implement multidisciplinary management.

Applying the presented recommendations within urology clinics should reduce the rate of potentially devastating CV

Table 3. Management of prostate cancer patients with established cardiovascular disease

Category	Population	Recommendation
Antithrombotic therapy	MI in past 12 months PCI with DES in past 3–12 months (or BMS in past 1 month)	ASA 81 mg daily AND P2Y12 inhibitor (ticagrelor or clopidogrel)
	All others	ASA 81 mg daily; consider either rivaroxaban 2.5 mg BID or ticagrelor 60 mg BID (or clopidogrel 75 mg daily) for higher risk patients
Lipid-lowering therapy	All	Statin therapy to target a decrease in LDL of ≥50% or LDL <2.0 Additional lipid-lowering therapy if unable to reach target with maximal tolerated statin dose (as per CCS lipid guidelines)
ACE or ARB	All	ACE inhibitor ARB if ACE-intolerant
β blocker	Angina	Target HR 55-60 bpm
	LVEF ≤40%	Metoprolol succinate, bisoprolol, or carvedilol at maximally tolerated HF doses
Anti-hyperglycemic therapy	Diabetes	HbA1C <7% Consider SGLT2 inhibitor or GLP1RA as per DC guidelines
Smoking cessation	All	Benefits of nicotine replacement or pharmacologic therapy outweigh risks in stable patients
Physical activity and dietary modification	All	Consider cardiac rehab referral

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; ASA: acetylsalicylic acid; BID: twice daily; BMS: bare metal stents; CCS: Canadian Cardiovascular Society; DES: drug-eluting stents; HF: heart failure; LDL: low-density lipoprotein; LHR: heart rate; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Table 4. Comorbidities that may benefit from cardio-oncology clinic referral

Condition	Additional treatment that may be indicated
Heart failure or impaired LV or RV function	Diuresis LV enhancement therapy (β blocker, ACE/ARB/ARNI, MRA, ivabradine) Device therapy as per CCS HF guidelines
Atrial fibrillation/ flutter	Stroke prevention therapy as per CCS AF guidelines Rate or rhythm control (including ablation)
Uncontrolled hypertension	Antihypertensive therapy as per Canadian Hypertension Education Program (CHEP) guidelines
Uncontrolled diabetes	Anti-hyperglycemic therapy as per Diabetes Canada (DC) guidelines

ACE: angiotensin-converting enzyme; AF: atrial fibrillation; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor II blocker - neprilysin inhibitor; CCS: Canadian Cardiovascular Society; HF: heart failure; LV: left ventricular; MRA: magnetic resonance angiogram; RV: right ventricular.

events in patients with prostate cancer, decrease mortality, and improve the quality of life of patients.

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Table 5. ABCDE of management of CVD risk

A	Assessment of risk Antiplatelet therapy
B	Blood pressure
C	Cholesterol Cigarette/tobacco cessation
D	Diet and weight management Diabetes prevention and treatment
E	Exercise

From Hsu et al, 2013. CVD: cardiovascular disease.

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