UPDATE – Canadian Urological Association guideline on androgen deprivation therapy: Adverse events and management strategies

Andrea Kokorovic[1], Alan I. So[2], Hosam Serag[2], Christopher French[3], Robert J. Hamilton[4], Jason P. Izard[5], Jasmir G. Nayak[6], Frédéric Pouliot[7], Fred Saad[1], Bobby Shayegan[8], Armen Aprikian[9], Ricardo A. Rendon[10]

[1]Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; [2]Department of Urological Sciences, University of British Columbia, Vancouver, BC, Canada; [3]Department of Surgery, Division of Urology, Memorial University, St. John's, NL, Canada; [4]Division of Urology, Department of Surgery, Princess Margaret Cancer Centre, Toronto, ON, Canada; [5]Department of Urology, Queen's University, Kingston, ON, Canada; [6]Section of Urology, Department of Surgery, University of Manitoba, Winnipeg, MB, Canada; [7]CHU de Quebec, Université Laval, Quebec City, QC, Canada; [8]Department of Surgery (Urology) and Oncology, McMaster University, Hamilton, ON, Canada; [9]McGill University Health Centre, Montreal, QC, Canada; [10]Department of Urology, Dalhousie, University, Halifax, NS, Canada

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Topics:

1. Introduction
2. Methods
3. Complications of ADT
3.1 Cardiometabolic health
3.1.1. Cardiovascular complications
– Cardiac complications
– Venous thromboembolism and cerebrovascular events
3.1.2. Body composition
3.1.3. Metabolic changes
3.1.4 Management of cardiovascular complications, body composition and metabolic changes
– Screening and treatment
– Exercise therapy
3.2 Bone health
3.2.1. Effects of ADT on bone health
3.2.2. Assessment of bone health and fracture risk
3.2.3. Management of bone complications
3.3 Hot flashes
3.4 Breast events
3.5 Cognitive function
3.6 Fatigue and anemia
3.7 Sexual function and body image
3.8 Health related quality of life (HRQOL)
3.8.1. Impact of ADT on HRQOL
3.8.2. Exercise therapy for improving HRQOL
3.8.3. Intermittent ADT
4. Conclusions and future directions

1. Introduction

Prostate cancer (PCa) is the most common type of malignancy in Canadian men. It is expected that 23 300 new cases of PCa were diagnosed in 2020, resulting in 4200 deaths.[1] Advanced PCa describes several disease states, including locally advanced or de novo metastatic disease (approximately 25% of newly diagnosed cases[2]), recurrent disease following primary treatment, and castrate-resistant prostate cancer (CRPC). Despite significant advances in the management of advanced PCa over the past several years, androgen deprivation therapy (ADT) remains the backbone of treatment. Additionally, ADT is used in localized disease among patients treated with radiation therapy (RT). Hence, ADT plays an important role in the contemporary management of PCa across various stages of the disease.

While ADT remains a highly effective treatment for PCa, it is not curative, and its use is associated with important adverse events that have the potential to cause significant morbidity. Recent therapeutic advancements have significantly improved outcomes and prolonged survival in patients with advanced disease. As such, the management and mitigation of ADT-related adverse events becomes a critical aspect of medical care for these men. The purpose of this guideline is to summarize the major adverse events associated with conventional ADT and provide evidence-based strategies to mitigate them. A summary of currently available agents is listed in Table 1.

Table 1. Summary of hormonal therapies

1.1	Surgical orchiectomy
1.2	Medical castration
1.2.1	Gonadal androgen ablation
1.2.1.1	Leutenizing hormone releasing hormone (LHRH) agonists: leuprolide, goserelin, and triptorelin
1.2.1.2	LHRH antagonists: degarelix, relugolix
1.2.2	Androgen receptor antagonists (AA)
1.2.2.1	First-generation: bicalutamide
1.2.2.2	Second-generation: enzalutamide, apalutamide, and darolutamide
1.2.3	Androgen synthesis inhibitors (CYP17 adrenal inhibitors): abiraterone acetate, ketoconazole

2. Methods

EmBASE and Medline databases were accessed to identify all relevant articles focused on adverse events related to ADT from inception to December 2020. The following key-word search strategy was used: "prostate cancer," "androgen deprivation therapy," "complications," "adverse events," "side effects." Reference lists of review articles were searched for any missing articles not captured by our search strategy. Evidence-based guidelines on side effects of ADT were retrieved and considered for additional source data. A complete bibliographic review of these guidelines was performed, and studies related to side effects of ADT were reviewed in full.

An expert panel comprised of urologists with significant experience prescribing and managing adverse events related to ADT was used to develop the recommendations. Guideline statements have been assigned a level of evidence (LE) using criteria from the Oxford Center for Evidence-based Medicine.[3] Each statement is also given a strong, moderate, or weak recommendation that was made based on subjective consensus recommendation using best available evidence.[3,4] "Strong" recommendations have been assigned if the statement is supported by high-quality and consistent evidence or in situations where unanimous expert consensus is present. In these cases, additional research has low likelihood of changing the strength of the recommendation. "Weak" recommendations are supported by low-quality evidence and there is a large amount of uncertainty regarding the statement. "Expert opinion" statements are not supported by explicit evidence, however, have sufficient biological plausibility to warrant a recommendation.

3. Complications of ADT

The castrate levels of testosterone induced by ADT result in adverse effects that span across various organ systems. These untoward side effects have the potential to cause significant morbidity and may alter health-related quality of life (HRQOL) in men living with PCa. Fortunately, most of these complications are not dose-limiting and can be managed through pharmacological or other interventions. Another important consideration is the testosterone flare associated with initiation of luteinizing hormone-releasing hormone (LHRH) agonists, which can be mitigated by the addition of a first-generation anti-androgen (AA) for the first 2–4 weeks of treatment.[5,6] In partnership with a multidisciplinary team, the overall goal of the urologist is to optimize oncological outcomes while maintaining acceptable HRQOL. For this, an in-depth understanding of treatment-related adverse events is required to offer appropriate patient counselling and to manage complications. For the purpose of this guideline, we focus only on adverse effects as a result of the use of LHRH agonists and antagonists. The ADT-related complication is listed, then followed by: a summary of the evidence, a summary of recommendations, and subsequently, a review of the data used to formulate the guideline statements.

3.1. Cardiometabolic health

The term cardiometabolic health collectively refers to the effects of ADT on cardiovascular disease (CVD), body composition, and metabolic parameters (including lipid profiles, insulin resistance, and glucose homeostasis).

Summary of evidence

- Cardiac complications:
  - ADT may increase the risk of cardiac complications, especially in patients with pre-existing CVD or a history of major adverse cardiac events (MACE).
- Thromboembolic and cerebrovascular events:
  - ADT may increase the risk of venous thromboembolism (VTE) and stroke.
- Body composition:
  - ADT is associated with changes in body composition, including increased body weight and fat mass, decreased lean body mass, and decreased muscle mass.
- Metabolic parameters:
  - The metabolic complications of ADT include insulin resistance, glucose intolerance, and changes in lipid profile.
  - ADT is associated with increased risk of incident diabetes and may worsen glycemic control in men with a pre-existing diagnosis.
  - Men receiving ADT may be at risk for developing metabolic syndrome.

Recommendations

- **The patient's primary care provider should be informed that the patient has been initiated on ADT and that there may be adverse events associated with this therapy** *(Expert opinion)*.
- **Lifestyle modifications (smoking cessation, dietary modifications, exercise) should be strongly encouraged** *(Expert opinion)*.
- **Providers should obtain a comprehensive baseline physical examination prior to ADT initiation that includes blood pressure, weight, waist circumference, and calculation of body mass index (BMI)** (*Expert opinion)*.
- **Patients should have their blood pressure monitored and hypertension should be treated** *(Expert opinion)*.
- **Providers should order baseline laboratory investigations, including fasting plasma glucose and lipid profile (triglycerides, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and total cholesterol)** *(Expert opinion)*.
- **Patients should be screened for diabetes with fasting plasma glucose, oral glucose tolerance test, or Hgb A1c level** *(Expert opinion)*.
- **Dyslipidemia should be treated according to current best practice guidelines** *(Expert opinion)*.
- **The above metabolic assessments should be continued at 6–12 month-intervals throughout treatment duration** *(Expert opinion)*.
- **Patients should be encouraged to attend supervised exercise programs using a combination of resistance and aerobic training** *(LE 2, strong recommendation)*.
- **Patients with a history of myocardial infarction (MI) or stroke should be referred to a cardiologist or cardio-oncologist for assessment and medical optimization at the time of initiating ADT** *(Expert opinion)*.
- **All patients receiving ADT should undergo a baseline cardiovascular risk assessment and be monitored for cardiovascular complications while receiving therapy** *(Expert opinion)*.

3.1.1. Cardiac complications

The leading cause of death in men with PCa not dying of the disease itself is CVD.[7] Initial reports describing this potential link emerged more than a decade ago and led to an advisory statement from the American Heart Association, American Cancer Society, and American Urological Association in 2010.[8] Subsequently, the U.S. Food and Drug Administration and Health Canada updated the safety warning label on GnRH agonist products to include the risk of CVD.[9,10] The product monograph for firmagon also suggests screening and intervention for CVD.

Large, observational cohort studies describe a strong link between ADT and CVD, including CAD, MI, and sudden cardiac death.[11-15] However, ad-hoc analyses from randomized control trials (RCTs) in the RT literature have failed to consistently demonstrate this association.[16-19] Several meta-analyses have attempted to address these discrepant findings. Zhao et al performed a meta-analysis of population-based, observational studies addressing the association of cardiovascular morbidity or mortality with use of ADT in over 119 000 PCa patients.[20] The authors concluded that use of ADT was associated with a significant risk of cardiovascular mortality (hazard ratio [HR] 1.17, 95% confidence interval [CI] 1.04–1.32, p= 0.01). Another meta-analysis that included eight observational studies found a 38% increase in nonfatal CVD for men treated with a GnRH agonist compared to those without (relative risk [RR] 1.38, 95% CI 1.29–1.48).[21] In contrast, Nguyen et al found no association between use of a GnRH agonist and cardiovascular death in a pooled analysis of eight RCTs that included over 4000 men.[22] The authors concluded that use of ADT lowers prostate cancer-specific and all-cause mortality without increasing risk of cardiovascular death.

There appears to be discrepancy between results of population-based, observational studies compared to those of RCTs from the RT literature on the association between ADT use and CVD. It is plausible that there are confounding factors not accounted for in database studies that may contribute to the higher CV event rates that were not, in general, observed in RCTs. On the other hand, the RCTs were not designed with MACE as a primary outcome measure, and therefore, would likely be underpowered to detect a difference given the low event rate. It is also important to note that the RCT data does not stratify results based on CVD history in individual patients, and therefore, the conclusions need to be interpreted with caution. Overall, the large, population-based, observational data provides sufficient evidence to suggest a link between use of ADT and CVD.

The presence of pre-existing heart disease appears to be a major risk factor for development of MACE in men receiving ADT. MACE is a cumulative term for adverse CV events and is defined as MI, coronary revascularization, stroke, and hospitalization because of heart failure. In one study, men who experienced two or more MACE before initiation of ADT were at highest risk for developing CVD during the first six months of therapy (HR 1.91, 95% CI 1.66–2.20 for GnRH agonist vs. no treatment) compared to an age-matched cohort from the general population.[23] Ziehr et al found no association between ADT and cardiac-specific mortality in men without any cardiac risk factors (defined as congestive heart failure [CHF] or prior MI).[24] However, men with a history of these risk factors treated with ADT had a significantly higher risk of cardiac mortality compared to those without treatment at five years (HR 3.28, 95% CI 1.01–10.64, p=0.048). A similar association was also reported by Nanda et al using similar cardiac risk stratification.[25] Importantly, even short durations of ADT (i.e., 3–6 months)

appear to increase CVD risk.[19] Together, the data suggests that men with pre-existing cardiac disease are at highest risk for developing MACE.

An important area of debate is whether treatment with a GnRH agonist vs. antagonist results in a different risk profile with respect to CVD and development of MACE. Studies in animal models suggest that GnRH agonists, but not antagonists, may induce plaque instability and rupture;[26,27] however, whether this translates to clinical practice remains unknown. A pooled analysis of six RCTs including 2328 men found that those with pre-existing CVD treated with a GnRH antagonist were 56% less likely to have a cardiovascular event within one year of beginning ADT compared to men treated with a GnRH agonist (HR 0.44, 95% CI 0.26–0.74, p=0.002).[28] However, this data is limited by results obtained from post-hoc analysis, short followup less than one year, and exclusion of patients with certain pre-existing cardiac risk factors. The results of this study are supported by a recent phase 2 trial in which patients using a GnRH antagonist were 18% less likely to experience a MACE (95% CI 4.6–31.2).[29] However, a large, population-based study from France did not identify a difference between the two treatment modalities.[30]

Recently, the efficacy and safety of the oral GnRH antagonist, relugolix, compared with leuprolide was investigated in the pivotal phase 3 HERO clinical trial.[31] Men with advanced PCa were randomized to receive relugolix or leuprolide for 48 weeks. The primary outcome was sustained castrate levels of testosterone (<50 ng/dl) throughout trial duration. Relugolix was non-inferior and superior to leuprolide in achieving castrate testosterone levels through 48 weeks, as well as at days 4 and 15. Development of MACEs was studied as part of a prespecified safety analysis. MACE was defined as non-fatal MI, non-fatal stroke, and death from any cause. Men treated with relugolix had a 2.9% incidence of MACE (exact 95% CI 1.7–4.5) compared with 6.2% in the leuprolide arm (exact 95% CI 3.8–9.5) at 48 weeks, which represented a 54% decrease in risk (HR 0.46, 95% CI 0.24–0.88). In men with a prior medical history of MACE (as defined in the trial), the incidence of new MACE appeared to be more pronounced (3.6 vs. 17.8% in the relugolix and leuprolide arms, respectively). Overall, the data suggest that men with prior history of MACE receiving leuprolide are 4.8 times more likely to experience MACE than those on relugolix.

PRONOUNCE is a multi-institutional, international, prospective, randomized control trial whose primary endpoint was to compare the effect of degarelix with leuprolide on MACE in patients with prostate cancer and a prior history of atherosclerotic cardiovascular disease (ASCVD).[32] Patients due to receive ADT for a minimum duration of 12 months were randomized to receive degarelix or leuprolide in standard doses. The primary endpoint of the study was the time from randomization to first occurrence of centrally adjudicated MACE, a composite of all-cause death, MI, or stroke through 12 months.

The primary outcome of first MACE occurrence (all cause-death, MI, or stroke) occurred in 15 (5.5%) patients receiving degarelix and 11 (4.1%) patients receiving leuprolide (HR 1.28, 95% CI 0.59–2.79, p=0.53). Additional prespecified sensitivity analyses and secondary endpoints were analyzed, none of which yielded a difference in event rate between the groups. Importantly, using the HERO trial definitions for MACE,[31] there were 18 events in the degarelix group compared to 21 events in the leuprolide group (HR 0.81, 95% CI 0.43–1.53).

The results of PRONOUNCE suggest that there is no added cardiovascular risk in men receiving a GnRH agonist compared to an antagonist. Limitations of the trial include a low accrual rate (60% of the targeted number of patients) and a lower than anticipated event rate (4.8% actual vs. 7.5% anticipated). The study is, therefore, underpowered to demonstrate a significant difference in the primary event rate.

Notably, the overall event rate was low in both groups at 4.8% and was, in fact, much lower than what was observed in the HERO trial, where 17.8% of patients with prior MACE receiving leuprolide experienced an additional MACE on trial. The lower event rate in PRONOUNCE can likely be attributed to the fact that all enrolled participants were followed by a cardiologist and underwent cardiac optimization for secondary prevention of cardiac events. This strongly suggests that routine monitoring of adverse events and optimization of cardiac risk factors throughout ADT treatment may reduce cardiac morbidity associated with ADT.

Additional insight will come from the RAndomizeD Intervention for Cardiovascular and Lifestyle Risk Factors in Prostate Cancer Patients (RADICAL-PC) trial. This trial is designed to assess the impact of systematic lifestyle and cardiovascular risk factor modification in men with prostate cancer, with a focus on ADT (ClinicalTrials.gov Identifier: NCT03127631). The primary outcome measure is a composite occurrence of cardiovascular death, MI, stroke, heart failure, or arterial revascularization.

Venous thromboembolism and cerebrovascular events

The outcome definitions for cardiovascular complications vary across studies, and some have included stroke and/or VTE. The pathophysiology behind ADT and cerebrovascular events is not fully understood, but one explanation is that GnRH agonists may destabilize atherosclerotic plaques.[26-28] The association between estrogen-containing compounds and thromboembolic events is well-characterized, however, the risk incurred with non-estrogen-containing ADT requires further study.

Using the Surveillance, Epidemiology, and End Results (SEER) database, an analysis including 59 000 men by Ehdaie et al found that ADT was associated with increased risk of deep vein thrombosis (DVT), pulmonary embolus (PE),

or arterial embolism.[32] Similarly, Kili-Drori et al found an association between ADT use and VTE-related hospitalization.[33] Men receiving ADT were 84% more likely to be hospitalized with DVT, PE, or both. Two recent meta-analyses demonstrated an increased risk of DVT and PE in men with PCa receiving ADT in the absence of estrogen.[34,35] Currently, there is insufficient evidence to recommend routine use of VTE prophylaxis in men receiving ADT.

Similar associations have been found for cerebrovascular events. A large observational study of over 37 000 men with local or regional PCa receiving GnRH agonist experienced a significantly increased risk of stroke compared to the no treatment group (HR 1.22, 95% CI 1.10–1.36).[13] Longer durations of ADT were associated with an increased number of these events. A meta-analysis of eight observational studies found a 51% increase in relative risk of stroke for men treated with a GnRH agonist compared to those without (RR 1.51, 95% CI 1.24–1.84).[21]

3.1.2. Body composition

Androgens are well-known moderators of body habitus in men. Patients treated with ADT experience an increase in body weight and percentage fat mass, which is largely due to an accumulation of subcutaneous fat, rather than intraabdominal adipose tissue.[36-38] A meta-analysis examining the effect of ADT on body composition that included 16 longitudinal studies found an increase in percentage body fat by 7.7% (95% CI 4.3–11.2, p<0.0001).[39] The authors also found a significant increase in body weight and BMI. These changes are thought to occur soon after initiating therapy, sometimes as early as one month following treatment.[39] Longer duration of therapy appears to increase weight gain and percentage fat mass,[39] and these changes may persist up to two years beyond treatment cessation.[40] ADT also causes a loss of muscle mass, with a resultant decrease in percentage lean mass.[31,36,41] In their meta-analysis on the effect of ADT on body composition, Haseen et al demonstrated an overall decrease in percentage lean body mass by 2.8% (95% CI -3.6 to -2.0, p<0.0001).[39]

The loss of lean body mass and accumulation of fat mass is collectively termed *sarcopenic obesity* and has important implications. A decrease in muscle mass causes a decrease in grip strength, absolute muscular strength, and gait speed.[42] ADT also results in detrimental changes to multiple other physical parameters, including aerobic fitness and overall physical function.[42,43] Together, these changes may contribute to morbidity in this patient population by increasing falls and fracture risk.[44]

Population-based studies suggest that an elevated BMI may be associated with PCa progression and death.[45-47] There may also be an association between obesity and development of CRPC and metastases in men treated with early ADT.[48] The mechanistic links and causal relationship between obesity and PCa remain unclear. Nonetheless, these findings, in addition to multiple metabolic and cardiovascular complications resulting from obesity, hold important implications for men with PCa treated with ADT.

3.1.3. Metabolic changes

The metabolic consequences of ADT include insulin resistance, glucose intolerance, and changes to lipid profile.[49,50] In a study of over 70 000 men, Keating et al demonstrated that men receiving ADT were more likely to develop incident diabetes compared to non-ADT controls.[12] Two additional population-based studies also demonstrated similar findings, with an increased association of ADT and incident diabetes by 16–28%.[13,51] In addition, use of ADT may worsen glycemic control in men with pre-existing insulin-dependent diabetes.[52] ADT also appears to change the lipid profile, although results describing these changes are conflicting.[53-58] Overall, most studies have consistently found an increase in triglyceride and total cholesterol levels, however, the cause of this rise (i.e., whether due to HDL or LDL cholesterol) remains to be determined.

This constellation of findings overlaps with the metabolic syndrome, which is defined in slightly different ways by different organizations. As an example, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) defines metabolic syndrome as meeting three of the following criteria[59]: waist circumference ≥102 cm in men, serum triglycerides ≥1.7 mmol/L, serum HDL cholesterol <1 mmol/L in men, blood pressure ≥130/85 mmHg, fasting plasma glucose ≥5.6 mmol/L, or requirement for medications to treat criteria 2–5 listed above. In one study, ADT was associated with higher risk of metabolic syndrome compared to controls, with more than 50% of men on ADT meeting criteria for metabolic syndrome.[58] The diagnosis of metabolic syndrome was attributable to an elevation of triglycerides, hyperglycemia, and abdominal obesity. This is an important finding, as patients with a diagnosis of metabolic syndrome are more likely to develop type 2 diabetes and CVD. These men require early identification and intervention to mitigate this risk.

Metformin has been investigated as a potential treatment for ADT-induced metabolic changes. In a small study of 40 men, six months of metformin combined with exercise resulted in decreased abdominal girth, BMI, and blood pressure.[60] There is currently insufficient evidence to recommend metformin prophylactically in men receiving ADT. The PRIME trial (ClinicalTrials.gov identifier: NCT03031821) is designed to specifically address this question and may provide further guidance in the future.

3.1.4. Management of cardiovascular complications, body composition, and metabolic changes

Current Canadian guidelines for prevention and management of CVD and dyslipidemia do not specifically address men receiving ADT. The Canadian Cardiovascular Harmonized

National Guidelines Endeavour (C-CHANGE) for prevention and management of CVD is aimed at identifying and managing patients who are at risk for developing CVD, including those with or at risk for diabetes and dyslipidemia.[61] Hence, a reasonable approach to the management of men on ADT is to adopt these guidelines for both a screening and management strategy. Accordingly, men should be encouraged to moderate their caloric intake and adapt healthy dietary patterns to decrease their risk of CVD. Smoking cessation should be strongly encouraged, and blood pressure should be regulated to a target level of <130/80. Diabetes screening with a fasting plasma glucose level, hemoglobin A1c, or oral glucose tolerance test should be performed at the time of ADT initiation, and at 6–12-month intervals following initiation of treatment. Baseline lipid profiles (triglycerides, LDL cholesterol, HDL cholesterol, and total cholesterol) should be obtained at the start of ADT and monitored throughout treatment duration. Management of dyslipidemia and lipid targets should be carried out according to 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult.[62] For patients at high risk for CVD, referral to cardiology or cardio-oncology should be considered for further assessment of risk event profile.

Pharmacological therapy should be considered as per current best practice in high-risk individuals according to the C-CHANGE guidelines.[61] This includes statins, aspirin, and angiotensin-converting enzyme inhibitors for primary and secondary prevention. The effect of these interventions in reducing cardiovascular morbidity in men with PCa receiving ADT requires further validation with randomized, prospective trials, such as RADICAL-PC, as described earlier.

It is evident that exercise has multiple beneficial effects in PCa patients receiving ADT. Specifically, muscle loss and the resultant decline in lean body mass may be prevented with resistance training.[63-65] A prospective study found significant improvements in lean mass, appendicular skeletal muscle mass, muscle strength, and physical function in men undergoing three or six months of supervised, resistance-based, multimodal training.[66] Other benefits of exercise include decreases in BMI, fat mass and glucose levels, as well as improvements in lipid profiles and insulin sensitivity.[43,63] In addition to improving metabolic indices and body composition, exercise therapy may ameliorate cardiovascular outcomes. For example, a 3–6-month supervised exercise program consisting of resistance and aerobic training in men receiving ADT improves peak oxygen consumption and a 400-meter walk test.[67,68] Other authors have demonstrated an improvement in endothelial function in men on long-term ADT in response to supervised exercise and dietary intervention.[69]

Together, these data support the use of a supervised exercise regimen using a combination of resistance and aerobic training to improve body composition and metabolic profiles of men receiving ADT, as well as overall physical and mental well-being. The 2018 American College of Sports and Medicine Roundtable recommendations provide detailed evidence-based guidance for exercise training in cancer survivors to improve fatigue, anxiety, depression, function, and quality of life.[70] Furthermore, the Exercise for People with Cancer Guideline Development Group, organized through Cancer Care Ontario, recommends 150 minutes of moderate intensity aerobic exercise spread over 3–5 days in addition to resistance training 2–3 times per week.[71] Resistance training should engage 8–10 muscle groups and include 8–10 repetitions with two sets. These interventions should be continued on an ongoing basis, and patients should be assessed for appropriateness to engage in rigorous physical activity prior to and during therapy. Studies suggest that supervised exercise therapy in men with PCa is superior to self-implemented exercise regimens.[43]

Given the complexities of exercise oncology, the ideal management would be referral to a professional (i.e., exercise physiologist, certified exercise instructor, community program, etc.) who can deliver supervised intervention tailored to men with PCa. We encourage physicians prescribing ADT to become familiar with regional resources that are available to patients. A summary of the benefits of exercise therapy is found in Table 2.

3.2. Bone health

Summary of evidence

Use of ADT in men with PCa has detrimental effects on bone health, including decreased bone mineral density (BMD), osteoporosis, and increased risk for clinical fractures.

Table 2. Benefits of exercise therapy in men receiving androgen deprivation therapy

Physical domains
Prevention of muscle loss and resultant decline in lean body mass
Decreased body mass index
Improved muscle strength
Improvements in peak oxygen consumption and endothelial function
Improved overall physical function
Functional domains
Lower levels of fatigue
Decreased risk of falls and fractures
Endocrine domains
Improved insulin and glucose homeostasis
Improved in lipid profile
Multiple health-related quality of life domains

Recommendations

- **A comprehensive history and physical examination to include falls risk and height measurement should be performed prior to initiating ADT** *(Expert opinion)*.
- **Patients should be counselled regarding smoking and alcohol cessation** *(Expert opinion)*.
- **Patients should be encouraged to participate in exercise therapy using a combination of resistance and aerobic training, preferably in a supervised setting** *(LE 2, strong recommendation)*.
- **Providers should obtain baseline calcium and 25-hydroxyvitamin D levels at the start of ADT** *(Expert opinion)*.
- **Men should maintain adequate calcium intake (1200 mg PO daily from dietary sources and supplements)** *(Expert opinion)*.
- **Vitamin D supplementation (800–2000 IU PO daily) should be initiated at the start of ADT** *(Expert opinion)*.
- **Providers should screen men initiating long-term ADT for osteoporosis using BMD testing with dual energy x-ray absorptiometry (DXA) (as per the 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada)** *(Expert opinion)*.
- **A 10-year major osteoporotic fracture risk using a validated tool should be calculated** *(Expert opinion)*.
- **Men diagnosed with osteoporosis, those with history of fragility fractures in the hip or spine, those with a history of multiple fragility fractures, or those with a moderate or high 10-year fracture risk should be treated with a bisphosphonate or denosumab at doses recommended for the general population** *(LE 1, strong recommendation)*.
- **DXA should be repeated every 2–3 years in men at low risk for fractures receiving ADT. In men with osteopenia or those at moderate or high risk for fractures, DXA should be repeated every 1–2 years until treatment cessation. Patients started on pharmacological therapy should have followup DXA to assess for treatment response** *(Expert opinion)*.

3.2.1. Effects of ADT on bone health

Men with PCa comprise mostly an older population that has an increased risk for osteoporosis, even in the absence of ADT.[72,73] In addition, ADT has been shown to decrease BMD, resulting in osteoporosis and an increased risk for clinical fractures.[74-77] A large, prospective cohort study demonstrated that use of ADT resulted in a 2.5% decrease in BMD at the femoral neck and 4.0% at the lumbar spine at 12 months of therapy, compared to no significant change in healthy age-matched controls and men with PCa not receiving ADT.[78] BMD loss occurs at a maximum rate during the first year of therapy, however, continues to decline with prolonged use of ADT.[74,79,80]

Men receiving ADT are at increased risk for fractures.[77,80,81] In a large, observational study of over 50 000 men, those receiving ADT had a fracture incidence of 19% within five years of PCa diagnosis compared to 13% in the non-ADT group.[77] The number needed to harm (i.e., cause one fracture) was 28 for men receiving a GnRH agonist.[77] These results are supported by a systematic review, which demonstrated that men receiving ADT had a 23% increased risk of fracture (RR 1.23, 95% CI 1.10–1.38) compared to non-ADT controls.[82]

3.2.2. Assessment of bone health

All men initiating ADT should be screened for osteoporosis as per the 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada.[83] They should undergo a comprehensive history and physical examination, with a focus on falls risk and height measurements. Basic laboratory investigations include calcium and 25-hydroxyvitamin D measurements.

All men initiating ADT should have initial BMD testing using DXA. Osteoporosis is defined as BMD of 2.5 or more standard deviations below the peak bone mass for young adults (i.e., T-score ≤-2.5). Osteopenia (low bone mass) is defined as BMD more than 1.0 but less than 2.5 standard deviations below the peak bone mass for young adults (i.e., T-score <-1 and >-2.5). Results of BMD testing, in addition to other clinical variables, should be used to calculate a patient's 10-year risk of a major osteoporotic fracture. The recommended tools for calculating fracture risk are: the Canadian Association of Radiologists and Osteoporosis Canada (CAROC; *www.osteoporosis.ca*)[84] and the Fracture Risk Assessment tool (FRAX) of the World Health Organization (WHO), specific for Canada (*www.sheffield.ac.uk/FRAX/tool.jsp?country=19*).[85] Using these tools, patients are stratified into low- (<10%), moderate- (10–20%) or high-risk (>20%) for fractures, which allows risk stratification for consideration of pharmacological therapy.[86] DXA scans should be repeated every 1–2 years or sooner for men with osteoporosis or osteopenia.

3.2.3. Management of adverse bone effects

All men receiving ADT should be encouraged to maintain basic bone health standards, as outlined by the Osteoporosis Canada guidelines.[83] This includes adequate calcium intake (1200 mg daily total from diet and supplements) and vitamin D supplementation (800–2000 IU daily). Of note, these strategies have not been proven to decrease risk of BMD loss or fractures in men receiving ADT but have been shown to prevent fractures in the general population over the age of 50.[87] Lifestyle modifications include smoking cessation and limited alcohol consumption, as both smoking and alcohol use are associated with bone loss and fractures.[88] Exercise therapy improves multiple physical domains in men with PCa receiving ADT, including preservation of muscle mass

and strength, which may decrease risk of fractures (see section 3.1.4 on exercise therapy). In addition, exercise appears to preserve BMD in men receiving ADT.[89,90]

The effect of various pharmacological therapies on BMD in men receiving ADT have been studied. Bisphosphonates (pamidronate, alendronate, risedronate, and zoledronic acid) act by inhibiting osteoclast activity, which decreases bone resorption. Smith et al evaluated the role of pamidronate on bone loss in men with advanced or recurrent PCa without bony metastases receiving leuprolide.[91] The study found that pamidronate (60 mg intravenously every 12 weeks) significantly improved BMD in the hip and lumbar spine at 48 weeks following initiation of therapy. Similar findings were obtained for zoledronic acid, alendronate, and risedronate in men with non-metastatic PCa.[92-94] However, the impact of bisphosphonates in reducing fracture risk in men with non-metastatic PCa receiving ADT has not yet been investigated in clinical trials. Therefore, routine use of bisphosphonates in these men without other risk factors is currently not recommended. Denosumab is a human monoclonal antibody against the receptor activator of nuclear factor κB (RANK) ligand, which mediates osteoclast differentiation and activation. It has been shown to improve BMD and decrease risk of vertebral fractures in men with non-metastatic PCa receiving ADT at high risk of fracture.[95]

Both zoledronic acid and denosumab have proven to be effective in reducing skeletal-related events (SREs) in men with CRPC. The role of bone-targeted agents in men with CRPC is beyond the scope of this guideline and described elsewhere.[96] *(Editor's note: A CUA guideline specifically on bone heath in prostate cancer is forthcoming and should be available by mid-2021.)*

Based on current guideline recommendations from Osteoporosis Canada, Cancer Care Ontario, and the American Society of Clinical Oncology,[83,97,98] combined with the above clinical trial results, the guideline committee has made recommendations on management of bone health in men receiving ADT. A summary of available pharmacological agents is listed in Table 3.

Table 3. Common pharmacological agents used for management of adverse bone events in men on androgen deprivation therapy

Name of agent	Mechanism of action	Doses (select one option)
Alendronate (Fosamax)	Bisphosphonate	– 10 mg orally daily – 70 mg orally weekly
Risedronate (Actonel)	Bisphosphonate	– 5 mg orally daily – 35 mg orally weekly – 150 mg orally monthly
Zoledronic acid (Aclasta)	Bisphosphonate	– 5 mg intravenously annually
Denosumab (Prolia)	RANK ligand inhibitor	– 60 mg subcutaneously every 6 months

3.3. Hot flashes

Summary of evidence

Hot flashes are a common and bothersome side effect of ADT.

Recommendations

- **Patients should be counselled on identification and avoidance of potential triggers** *(Expert opinion)*.
- **The best pharmacological therapy to treat hot flashes remains unclear, however, several agents have shown to be effective and may be considered for use** *(LE 2, weak recommendation)*.
- **Use of intermittent ADT improves hot flashes and should be considered in appropriately selected patients** *(LE 2, strong recommendation)*.
- **Acupuncture may have a beneficial effect and can be considered in patients unwilling or unable to use pharmacotherapy** *(LE 3, weak recommendation)*.

Vasomotor flushing or "hot flashes" occur in most men receiving ADT and are described as a sudden onset of facial sweating and discomfort. If bothersome, they can lead to a deterioration in HRQOL and may decrease compliance to ADT. Lifestyle modifications may be recommended, including avoidance of potential patient-identified triggers, commonly heat or spicy foods.[99]

Several pharmacological agents have been assessed in the treatment of hot flashes.[100,101] Gabapentin at a dose of

Table 4. Common pharmacological agents used to treat hot flashes in men receiving androgen deprivation therapy

Name of agent	Dose	Mechanism of action	Health Canada-approved for hot flashes
Medroxyprogesterone acetate (Provera)	20 mg orally daily	Synthetic derivative of progesterone	No
Megestrol acetate (Megace)	20 mg orally twice daily	Synthetic derivative of progesterone	No
Cyproterone acetate (Androcur)	50–100 mg orally daily	Antiandrogen	No (approved for palliative treatment of patients with advanced prostate adenocarcinoma)
Gabapentin (Neurontin)	900 mg orally daily	Antiepileptic agent	No
Venlafaxine (Effexor)	75 mg orally daily	Selective serotonin reuptake inhibitor	No

900 mg daily reduces hot flashes compared to placebo.[101] The role of venlafaxine (75 mg daily), medroxyprogesterone acetate (20 mg daily), or cyproterone acetate (100 mg daily) for reducing hot flashes in men receiving ADT was assessed in a RCT of 311 men.[100] The authors found a significant decrease in frequency of hot flashes using all therapies (-47.2% for venlafaxine, -94.5% for cyproterone, -83.7% for medroxyprogesterone; all p<0.001 from baseline), however, medroxyprogesterone and cyproterone appeared to be more effective than venlafaxine. Megestrol acetate has also proven to be of benefit in reducing the frequency of hot flashes in men receiving ADT.[102] Common pharmacological agents used for the treatment of hot flashes are listed in Table 4.

The role of complementary medicine has been investigated for treatment of hot flashes. Of these, the most widely studied is acupuncture therapy. Acupuncture has been shown to decrease hot flash symptoms by 89–95%,[103,104] however, these results are not based on RCT data. In men who do not wish to receive pharmacological therapy, acupuncture may be a reasonable option, albeit based on low-quality evidence.

In a RCT of continuous ADT vs. intermittent ADT, men receiving intermittent therapy experienced significantly better scores for hot flashes (p<0.001).[105] Use of intermittent ADT is discussed in further detail in the HRQOL section of this guideline.

3.4. Breast events

Summary of evidence

ADT-related breast events include gynecomastia and mastodynia. Gynecomastia occurs most commonly with AA monotherapy and is a rare complication of LHRH monotherapy or combined androgen blockade.

Recommendations

- **Prophylaxis for the prevention of gynecomastia in men receiving ADT is not currently recommended** *(Expert opinion)*.
- **Tamoxifen or RT may be used for treatment of breast events in men receiving bicalutamide monotherapy; tamoxifen is more effective than RT** *(LE 1, strong recommendation)*.

Gynecomastia (increased amount of breast tissue) and mastodynia (breast tenderness), collectively referred to as breast events, can be bothersome side effects of ADT and may occur concurrently or separately. Gynecomastia occurs as a result of peripheral conversion of testosterone to estradiol, which increases the ratio of estrogen to androgen activity. It is more pronounced with AA monotherapy, with incidence reported as high as 85% in men taking 150 mg of bicalutamide.[106] The incidence for patients on combined androgen blockade is lower, at 13–22%.[106] Several studies have demonstrated that both tamoxifen and RT are effective prophylactic treatments for breast events.[107-112] RCT data suggest that tamoxifen is more effective than a single 12-Gy fraction on the day of starting bicalutamide at preventing this complication.[107,108] Once breast events occur, treatments using tamoxifen or RT have been well-described.[107,113-115] Tamoxifen is more effective than a single 12-Gy fraction of RT at decreasing severity of breast events after they develop in men on bicalutamide therapy.[107]

3.5. Cognitive function

Summary of evidence

Use of ADT in men with PCa may be associated with changes in cognition, depression, and development of dementia; however, evidence related to causality remains weak and further prospective data are needed.

Recommendations

- **Men receiving ADT should be monitored for cognitive decline and depression throughout duration of treatment** *(Expert opinion)*.

The effect of ADT on cognition was measured by clinical studies, both subjectively (through self-reported symptoms) and objectively (using standardized cognitive tests). Changes in cognition have been associated with receiving ADT in 25–50% of patients.[116,117] Self-reported cognitive changes of ADT included difficulties with concentration, information processing, verbal fluency, visual information processing, visuospatial function, memory, and executive function, as well as neuro-fatigue and apathy. The severity of reported symptoms varied greatly from minor challenges like forgetting an item on a to-do list, to more serious effects that compromised daily functioning.[116,117] Studies that assessed cognition objectively have found men on ADT had impairments in verbal memory,[118] spatial abilities,[119] and attention.[120] However, other studies have found no appreciable effect of ADT on cognition,[116,121,122] or a decline for only a subset of participants.[123] Some studies have even reported an improvement in verbal memory[124] or a reduced risk of dementia.[125]

Furthermore, ADT may be associated with development of depressive symptoms.[126] Specifically, ADT has been associated with increased rates of major depression and worsening depressive symptoms without an increased risk of suicidality.[126] Several recent studies and a meta-analysis concluded that men receiving ADT are at increased risk for developing dementia and/or Alzheimer's disease compared to men with PCa not receiving ADT.[127] The differences in the studies' findings may reflect a variation in their methodology, including the regimen of ADT treatment (continuous or intermittent), methods (surgical or medical castration), the use of other concomitant treatments (e.g., radiation), and the nature of control groups (healthy control or men with PCa not on ADT).[128-130] Given the conflicting data, RCTs in this setting are warranted.

3.6. Fatigue and anemia

Summary of evidence

Fatigue is a noticeable side effect of ADT and the underlying cause is often multifactorial. Anemia occurs commonly in men receiving ADT but is mild in most cases and often does not warrant treatment.

Recommendations

- **Men experiencing fatigue should be counselled to participate in exercise therapy** *(LE 2, strong recommendation)*.
- **Men with severe anemia or those with a decline in hemoglobin that exceeds the expected response to ADT alone should be referred for further evaluation** *(Expert opinion)*.

Fatigue is a noticeable side effect of ADT.[131] The underlying mechanism likely relates to the detrimental physical effects of ADT combined with poor HRQOL in certain men. It may also be associated with depression.[132] Fatigue is best treated with exercise therapy, with multiple well-designed clinical trials reporting a beneficial outcome.[133] Recently, Taafee et al found that various exercise regimens are effective at reducing fatigue in men receiving ADT, and that men with the highest levels of fatigue were most likely to benefit from therapy.[134] Suggested exercise regimens are outlined in section 3.1.4.

Anemia is a common side effect of ADT and is usually normocytic and normochromic.[135] Most studies report a decrease in hemoglobin levels by 1–2 ng/dL from baseline,[135] which is unlikely to cause clinically relevant outcomes. However, symptomatic anemia may be more pronounced in men with metastatic PCa and pre-existing cancer-associated anemia.[135] The impact of anemia on fatigue in men receiving ADT remains unknown but is a likely contributor. Treatment is rarely indicated but may include blood transfusion and erythropoietin in severe cases. As most causes of anemia are multifactorial, patients should be investigated for common secondary underlying causes (i.e., iron deficiency, vitamin B12 or folate deficiency) if the anemia is severe or the hemoglobin decreases more than what is expected for ADT alone. In these cases, referral to a hematologist may be beneficial.

3.7. Sexual function

Summary of evidence

ADT impacts multiple domains of sexual function, including body image, loss of libido, and erectile function.

Recommendations

- **In men desiring improved sexual function, referral to a sex therapist for multimodal treatment should be considered** *(Expert opinion)*.
- **Intermittent ADT may improve libido and erectile function and should be considered in appropriately selected patients** *(LE 1, strong recommendation)*.

The effect of ADT on sexual dysfunction is profound. Multiple domains of sexual function are impacted, and include decreased penile and testicular size, loss of libido (in up to 90% of men), decreased sensitivity to sexual stimulation, and erectile dysfunction.[132] In one study, penile length decreased from an average of 10.76 cm to 8.05 cm after 15 months of ADT and plateaued thereafter.[136] Pathological studies have shown significant testicular atrophy in men receiving ADT.[106] These changes, combined with alterations in weight, muscle mass, and gynecomastia, may have a detrimental impact on self-perceived body image leading to poor sexual function and decreased partner intimacy.

Various interventions are available to help men improve sexual function while receiving ADT. Patients require appropriate pre-treatment counselling regarding side effects, particularly with respect to body image. Referrals to psychosocial support groups and/or sex therapists should be offered to interested patients. Erectile dysfunction may be treated with various interventions, including phosphodiesterase inhibitors; however, treatment efficacy may be poor without adequate mental and physical arousal.[137] Intermittent ADT has been shown to improve sexual function and should be considered in appropriate patients.

3.8. Health-related quality of life

Summary of evidence

Patients on ADT experience significant decrements in multiple HRQOL domains.

Recommendations

- **Exercise therapy should be encouraged in all men to improve HRQOL during treatment** *(LE 2, strong recommendation)*.
- **Intermittent ADT improves HRQOL and should be considered in appropriately selected patients** *(LE 1, strong recommendation)*.

3.8.1. Impact of ADT on HRQOL

The constellation of ADT-induced side effects involves multiple organ systems that have the potential to affect several functional and psychological domains. Not surprisingly, multiple HRQOL measures are impacted by hormonal therapy. Men with PCa are a vulnerable population that suffer from anxiety and distress, and the addition of further HRQOL stressors secondary to ADT warrants discussion.

Several reports regarding the impact of ADT on many HRQOL measures are available. In a population-based, prospective cohort study that included 1600 men with localized PCa and age-matched controls, patients on ADT were more

likely to experience a decline in general physical and mental health scores at three years of followup.[138] Likewise, Fowler et al found a profound decrement on multiple HRQOL indices in men receiving ADT following radical prostatectomy, including impact of cancer and treatment; worries about cancer and dying; and concerns regarding body image, mental health, general health, activity, and energy.[139] These results are compatible with RCT data, which have consistently demonstrated a significant deterioration in sexual function in men receiving various forms of ADT.[140,141] The aforementioned studies evaluated mostly historical cohorts, but contemporary data using validated questionnaires report similar findings. Specifically, studies have found lower vitality and hormonal HRQOL scores in patients receiving neoadjuvant ADT prior to RT.[142,143] The lower vitality and hormonal scores may indicate worse hot flashes, depression, lack of energy, and increased body weight. Overall, the data support a significant impact on various HRQOL measures in men with PCa receiving ADT.

3.8.2. Exercise therapy for improving HRQOL

The impact of ADT on HRQOL may in part be mitigated by exercise therapy. This intervention has been addressed by several RCTs, most of which have shown favorable results.[43,63] Systematic reviews on this topic have also reported an improvement in many HRQOL parameters in men receiving ADT undergoing exercise therapy.[144] Together, these data support exercise therapy as a reasonable strategy to offset detriments in HRQOL that occur with ADT. The duration and type of exercise for optimal benefit remains unknown, however, physicians may follow published guidelines regarding exercise therapy in patients with cancer,[70,71] reviewed elsewhere in this text.

3.8.3. Intermittent ADT

Another strategy to reduce the impact of ADT on HRQOL is use of intermittent therapy. The Canadian PR7 trial was a RCT that compared continuous vs. intermittent ADT in patients with biochemical recurrence after definitive RT and no evidence of metastases.[105] There was no difference in outcomes with respect to overall survival (8.8 vs. 9.1 years, HR 1.02, 95% CI 0.86–1.21) between the two treatment arms. A caveat to this finding is that an unplanned subgroup analysis demonstrated worse survival in men with Gleason >7 on intermittent therapy. Notably, more men in the intermittent group died of disease-specific causes, while men in the continuous arm experienced more non-cancer-related deaths. Improvements in multiple HRQOL domains were seen in the intermittent group, including physical function, fatigue, hot flashes, urinary problems, and erectile dysfunction. Desire for sexual activity was also improved in the intermittent group.

The role of intermittent ADT in men with metastatic disease is controversial. Hussein et al performed a phase 3 trial in men with newly diagnosed, metastatic, hormone-sensitive PCa randomized to continuous vs. intermittent ADT.[145] The co-primary endpoints were non-inferiority of intermittent ADT in terms of overall survival and assessment of HRQOL at three months following randomization. Men in the intermittent therapy arm appeared to have worse survival compared to continuous treatment, however, the results were deemed to be statistically inconclusive. At three months following randomization, there was a statistically significant improvement in erectile dysfunction and mental health for men receiving intermittent therapy. Physical functioning, libido, and vitality trended towards a benefit from intermittent ADT, however, the results did not reach statistical significance.

Overall, the decision to proceed with intermittent or continuous ADT must be individualized to patient preferences, expectations with respect to impact of therapy on HRQOL, and disease status. Appropriate counselling and shared decision-making are critical to assure an appropriate balance

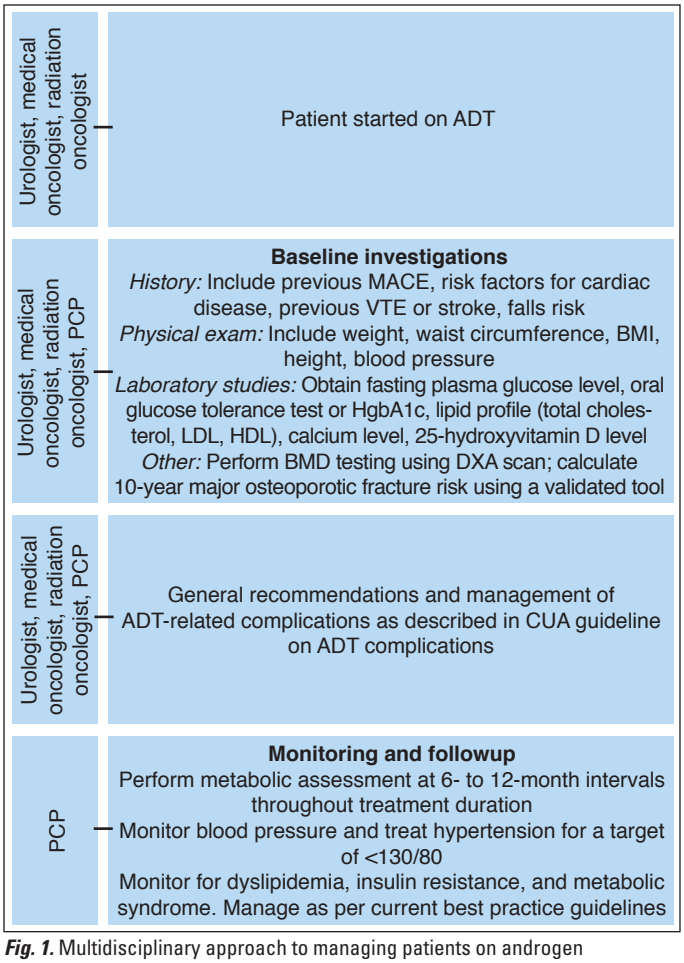

Fig. 1. Multidisciplinary approach to managing patients on androgen deprivation therapy (ADT). BMD: bone mineral density; BMI: body mass index; CUA: Canadian Urological Association; DXA: dual energy x-ray absorptiometry; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MACE: major adverse cardiac events; PCP: primary care physician; VTE: venous thromboembolism.

Table 5. Summary of adverse events associated with androgen deprivation therapy

Complication	Summary of events	Management
Cardiovascular disease	Increased risk of cardiac events Increased risk of stroke Increased risk of DVT/PE	1. Lifestyle changes to promote healthy diet and weight 2. Smoking cessation 3. Exercise therapy 4. Monitoring and medical optimization of blood glucose, blood pressure, lipid profiles
Change in body composition	Increased BMI Increased percentage body fat Decreased muscle mass	1. Lifestyle changes to promote healthy diet and weight 2. Exercise therapy 3. Monitoring and medical optimization of blood glucose, blood pressure, lipid profiles
Change in metabolic parameters	Insulin resistance/glucose intolerance Increased risk for incident diabetes Worse glycemic control Altered lipid profiles Increased risk for metabolic syndrome	1. Lifestyle changes to promote healthy diet and weight 2. Exercise therapy 3. Monitoring and medical optimization of blood glucose, blood pressure, lipid profiles
Bone health	Decreased BMD Increased risk for osteoporosis Increased risk for clinical fractures	1. Smoking and alcohol cessation 2. Adequate calcium intake (1200 mg daily) and vitamin D supplementation (800–1000 IU daily) 3. Exercise therapy 4. Pharmacological therapy with a bisphosphonate or denosumab for men with risk factors for bone fracture (i.e., previous history of low trauma fracture, diagnosis of osteoporosis, moderate or high 10-year fracture risk)
Hot flashes		1. Avoidance of triggers 2. Pharmacological therapy 3. Consider acupuncture 4. Consider intermittent ADT
Breast events	Gynecomastia Mastodynia	1. Treatment with tamoxifen or low-dose RT (tamoxifen preferred) 2. Surgical management for select patients
Cognitive function	Concentration Memory Dementia Depression	1. Evidence for causality is weak 2. Appropriate patient education and monitoring of symptoms
Fatigue and anemia		1. Exercise therapy for fatigue 2. Workup secondary causes of anemia and referral to hematology when indicated
Impaired sexual function	Decreased penile and testicular size Loss of libido Decreased sensitivity to sexual stimulation Erectile dysfunction	1. Appropriate pre-treatment counselling 2. Sex therapy 3. PDE-5 inhibitor and other ED therapies where appropriate 4. Consider intermittent ADT
Quality of life	Multiple domains	1. Exercise therapy 2. Consider intermittent ADT

ADT: androgen deprivation therapy; BMD: bone mineral density; BMI: body mass index; DVT: deep vein thrombosis; GnRH: gonadotropin releasing hormone; ED: erectile dysfunction; PE: pulmonary embolism; RT: radiation therapy.

between favorable HRQOL outcomes and acceptable oncological control. In general, men with non-metastatic PCa are likely to benefit from intermittent ADT without major concern for compromised oncological outcomes, while those with metastatic PCa should be considered for intermittent therapy with caution. The HERO trial assessing the efficacy and safety of the oral GnRH antagonist, relugolix, demonstrated substantially improved testosterone recovery in men receiving relugolix compared to leuprolide, which may have important implications for intermittent ADT and HRQOL.[31] This will need to be addressed in future clinical trial settings.

4. Conclusions and future directions

ADT improves survival in men with PCa; however, it is associated with multiple adverse events that span across multiple organ systems (Table 5). Patients require appropriate counselling regarding adverse effects, and therapy should be reserved only for patients that are likely to derive an oncological benefit. A partnership between the urologist and primary care providers using a multidisciplinary approach is imperative to mitigate complications that may occur in response to ADT (Fig. 1). This has become increas-

ingly important in an era of rapidly emerging and effective pharmacological therapies for advanced PCa, for which ADT remains a mainstay.

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Correspondence: Dr. Ricardo Rendon, Department of Urology, Dalhousie, University, Halifax, NS, Canada; rrendon@dal.ca