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ALL FACULTY HAVE ADHERED TO THE:

• CMA Code of Ethics and Professionalism (2018)
• CMA Guidelines for Physician Interactions with Industry (2007)
• Innovative Medicines Canada (2020)
LEARNING OBJECTIVES

By participating in this educational session, health care providers can expect to:

• Summarize the major adverse events (AEs) associated with conventional androgen deprivation therapy (ADT)
• Review the evidence-based strategies to mitigate the AEs associated with ADT in men with prostate cancer (PC)
ADT remains the backbone of treatment for PC across various stages of the disease

- Localized PC treated with radiation therapy
- Advanced or metastatic PC with or without additional therapy
AVAILABLE HORMONAL THERAPIES FOR PC TREATMENT

- Surgical castration
- Medical castration
  - Gonadal androgen ablation
    - LHRH agonists: leuprolide, goserelin, and triptorelin
    - LHRH antagonists: degarelix, relugolix
- Androgen receptor antagonists (AA)
  - First generation: bicalutamide
  - Second generation: enzalutamide, apalutamide and darolutamide
- Androgen synthesis inhibitors (CYP17 adrenal inhibitors): abiraterone acetate, ketoconazole

LHRH: luteinizing hormone-releasing hormone

Kokorovic A. et al. CUAJ 2021 April 21; Epub ahead of print.
• Men with advanced PC have prolonged survival due to significant medical advancements
• ADT is associated with multiple AEs across various organ systems

Management of AEs is becoming increasingly important
POTENTIAL ADVERSE EFFECTS OF ADT

- Erectile dysfunction
- Loss of libido
- Osteoporosis/skeletal events
- Loss of muscle mass
- Neurocognitive disease
- Thinning of body hair
- CV disease
- Diabetes
- Depression
- Testicular atrophy
- Anemia
- Gynecomastia
- Fatigue
- Weight gain
In partnership with a multidisciplinary team, the overall goal of the urologist is to optimize oncological outcomes while maintaining acceptable health related quality of life.
QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

• Levels of evidence assigned using criteria from the Oxford Center for Evidence-based Medicine

• Strength of recommendations – subjective consensus recommendations using best available evidence

  • Strong — supported by high-quality and consistent evidence or where there is unanimous expert consensus
  • Weak — supported by low quality evidence and where there is a large amount of uncertainty.
  • Expert opinion — not supported by explicit evidence but with sufficient biological plausibility to warrant a recommendation.

Before your patient with PC begins his ADT, which side effects do you counsel him to look out for?
CARDIOMETABOLIC HEALTH

- Cardiovascular complications
  - Venous thromboembolism (VTE) and stroke
- Body composition
- Metabolic changes
- Management of cardiometabolic changes
  - Screening and treatment
  - Exercise therapy
DISCUSSION QUESTION

What if your patient has experienced an MI in the past 5 years?

How might this change your approach to his management?
CARDIOVASCULAR COMPLICATIONS
ADT may increase the risk of cardiac complications, especially in patients with preexisting CV disease or a history of major adverse cardiac events (MACE)

MACE is a cumulative term for adverse CV events and is defined as MI, coronary revascularization, stroke, and hospitalization because of heart failure.
In patients with a history of MI or stroke, referral to a cardiologist or cardio-oncologist may be considered for assessment and medical optimization prior to initiating ADT (Expert opinion).

Use of a GnRH antagonist may be considered in men with a prior history of MI or stroke (LE 2, weak recommendation).
LARGE OBSERVATIONAL COHORT STUDIES DESCRIBE A STRONG LINK BETWEEN ADT AND CVD

- Meta-analysis including 119,000 PC patients receiving ADT¹
  - Use of ADT associated with a significant risk of CV mortality
    (HR 1.17; 95% CI 1.04–1.32)

- Meta-analysis of 8 observational studies²
  - 38% increase in nonfatal CVD for men treated with an LHRH agonist
    (RR 1.38; 95% CI 1.29–1.48)

Presence of pre-existing MACE (CHF, ischemic heart disease, arrhythmia, stroke, prior MI) may increase risk of further events while on ADT.
IS THERE A DIFFERENT RISK PROFILE FOR AGONISTS VERSUS ANTAGONISTS?

• Pooled analysis of 6 RCTs found that men with pre-existing CVD treated with a GnRH antagonist (compared to agonist) were 56% less likely to have a CV event within 1 year of beginning ADT

• Studies have several limitations and results remain controversial

RCT Randomized, controlled trial
HERO TRIAL

- Phase III RCT assessing efficacy and safety of the oral GnRH antagonist *relugolix* compared with leuprolide in men with advanced PC

- Primary outcome measure – sustained castrate levels of testosterone
  - Relugolix was noninferior and superior to leuprolide in achieving castrate testosterone levels through 48 weeks

- Development of MACEs were studied as part of pre-specified safety analysis
  - **MACE was defined as nonfatal MI, nonfatal stroke, and death from any cause**
Men with prior history of MACE receiving leuprolide are 4.8 times more likely to experience MACE than those on relugolix.

<table>
<thead>
<tr>
<th>EVENT</th>
<th>RELUGOLIX* (N = 622)</th>
<th>LEUPROLIDE (N = 308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE, any grade – n (%)</td>
<td>18 (2.9%)</td>
<td>19 (6.2%)</td>
</tr>
<tr>
<td></td>
<td>HR 0.46 (95% CI 0.24 – 0.88)</td>
<td></td>
</tr>
<tr>
<td>Without a history of MACE – n/total n (%)</td>
<td>15/538 (2.8%)</td>
<td>11/263 (4.2%)</td>
</tr>
<tr>
<td></td>
<td>OR 1.5 (95% CI 0.7, 3.4)</td>
<td></td>
</tr>
<tr>
<td>With a history of MACE – n/total n (%)</td>
<td>3/84 (3.6%)</td>
<td>8/45 (17.8%)</td>
</tr>
<tr>
<td></td>
<td>OR 4.8 (95% CI 1.5, 23,3)</td>
<td></td>
</tr>
</tbody>
</table>

*Relugolix is not approved for use in Canada
MACE Major adverse cardiovascular events (nonfatal myocardial infarction + non-fatal stroke + all-cause mortality)

VENOUS THROMBOEMBOLISM AND CEREBROVASCULAR COMPLICATIONS
• ADT may increase the risk of venous thromboembolism (VTE)
• Many studies assessing CV risk included stroke as an endpoint – they suggest an increased risk for stroke complications
In patients with a history of MI or stroke, referral to a cardiologist or cardio-oncologist may be considered for assessment and medical optimization prior to initiating ADT (Expert opinion).

Use of a GnRH antagonist may be considered in men with a prior history of MI or stroke (LE 2, weak recommendation).
Observational study of > 37,000 men with local or regional PC\(^1\)
- LHRH agonist associated with increased risk of stroke vs. no treatment (HR 1.22; 95% CI 1.10 to 1.36).
- Longer durations of ADT associated with an increased number of events

Meta-analysis of 8 observational studies
- 51% increase in relative risk of stroke for men treated with an LHRH agonist vs. those without (RR 1.51; 95% CI 1.24–1.84).\(^2\)

ADT IS ASSOCIATED WITH AN INCREASED RISK OF VTE

- Large population-based cohort study including 22,000 patients
- Current ADT use associated with 84% increased risk of VTE, with risk elevated for most ADT types

Currently, there is insufficient evidence to recommend routine use of VTE prophylaxis in men receiving ADT

BODY COMPOSITION AND METABOLIC CHANGES
EVIDENCE SUMMARY – 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
**RECOMMENDATIONS – BODY COMPOSITION**

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 BP, weight, waist circumference, and calculation of BMI (Expert opinion).

Patients should be encouraged to attend supervised exercise programs using a combination of resistance and aerobic training (LE 2, strong recommendation).
EFFECT OF ADT ON BODY COMPOSITION

• ADT causes increased weight gain, increased BMI and an increase in percentage body fat (by 7.7%) \(^1\)
  • Worse with longer duration of therapy and may persist for 2 years after treatment cessation \(^1,2\)

• ADT also causes a loss of muscle mass with decrease in percentage lean mass by 2.8\% \(^1\)

• The loss of lean body mass and accumulation of fat mass is collectively termed **sarcopenic obesity**

• Sarcopenic obesity:\(^1\)
  • Decreases grip strength
  • Decreases absolute muscular strength
  • Decreases gait speed

• ADT also results in detrimental changes to multiple other physical parameters:\(^2,3\)
  • Aerobic fitness
  • Overall physical function

• *Together, these changes increase falls and fracture risk*\(^3\)

---

EVIDENCE SUMMARY – METABOLIC COMPLICATIONS

- 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.
Providers should order baseline laboratory investigations including fasting plasma glucose and lipid profile (triglycerides, LDL cholesterol, HDL cholesterol and total cholesterol) (Expert opinion).

Dyslipidemia should be treated according to current best practice guidelines (Expert opinion).

Continue assessments at 6- to 12-month intervals for a minimum of 24 months from treatment initiation (Expert opinion).
LIPID PROFILE CHANGES

- Changes to the lipid profile in response to ADT include:
  - Increased triglyceride levels
  - Increased total cholesterol
  - Possible increase in LDL cholesterol
Patients should be screened for diabetes with fasting plasma glucose, oral glucose tolerance test, or HgbA1c level (Expert opinion).
ADT IS ASSOCIATED WITH DEVELOPMENT OF DIABETES

**LHRH agonist use is associated with increased risk of incident diabetes (adjusted HR, 1.28, 95% CI = 1.19 to 1.38)**

- Diabetes
- CAD
- MI
- Sudden cardiac death
- Stroke

US Veterans with local/regional PC, n = 37,443

Patients should have their BP monitored and hypertension should be treated (Expert opinion).

*All previous recommendations for lipid profile and body composition should be followed.*
ADT IS ASSOCIATED WITH A HIGHER RISK OF METABOLIC SYNDROME

• Metabolic syndrome may be present in up to 50% of men receiving ADT
• Patients with metabolic syndrome are at increased risk for developing type 2 diabetes and CVD
• Early identification and prevention are essential

## Multiple benefits of exercise therapy for cardiometabolic health

### Physical domains
- Prevention of muscle loss and resultant decline in lean body mass
- Decreased BMI
- 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
RECOMMENDATIONS – EXERCISE THERAPY

• Assess patients for appropriateness to engage in rigorous physical activity prior to and during therapy
• 150 mins moderate-intensity aerobic exercise spread over 3-5 days
• Resistance training 2 to 3 times per week
• Supervised exercise therapy is superior to self-implemented exercise regimens
• Physicians who are prescribing ADT are encouraged to become familiarized with regional resources that are available to patients

• ADT affects multiple cardiometabolic health domains
• Medical optimization of risk factors is critical to mitigating ADT-related AEs

The patient’s primary care provider should be informed that the patient has been initiated on ADT, and that there may be AEs associated with this therapy (Expert opinion)
BONE HEALTH
What steps should be taken to ensure maintenance of bone health while a patient is undergoing ADT?
• Use of ADT in men with PC has detrimental effects on bone health, including decreased bone mineral density (BMD), osteoporosis, and increased risk for clinical fractures.
A comprehensive history and physical examination to include falls risk and height measurement should be performed prior to initiating ADT (Expert opinion).
• ADT decreases BMD, resulting in osteoporosis and increased risk for clinical fractures
• 12 months of therapy decreases BMD at the femoral neck and lumbar spine by 2.5% and 4.0%, respectively
Maximum rate of BMD loss occurs during the first year but continues to decline with prolonged use of ADT.
Providers should screen men initiating long-term ADT for osteoporosis using BMD testing with DXA (as per the 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada) (Expert opinion).
INCREASED RISK OF FRAGILITY FRACTURES WITH ADT

- Fracture incidence in men receiving ADT 19% vs. 13% in non-ADT group
- The number needed to harm (cause one fracture) = 28 for men receiving an LHRH agonist


*Surveillance, Epidemiology, and End Results (SEER)-Medicare Database
A 10-year major osteoporotic fracture risk using a validated tool should be calculated (Expert opinion).
ASSESSMENT OF FRACTURE RISK – FRAX TOOL

• Calculates 10-year probability of fracture:
  • **LOW** < 10%
  • **MEDIUM** 10-20%
  • **HIGH** > 20%

• Select “yes” for “secondary osteoporosis” for patients on ADT

![Questionnaire](www.sheffield.ac.uk/FRAX)
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).
<table>
<thead>
<tr>
<th>NAME OF AGENT</th>
<th>MECHANISM OF ACTION</th>
<th>DOSES (SELECT ONE OPTION)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax)</td>
<td>Bisphosphonate</td>
<td>10 mg orally daily 70 mg orally weekly</td>
</tr>
<tr>
<td>Risedronate (Actonel)</td>
<td>Bisphosphonate</td>
<td>5 mg orally daily 35 mg orally weekly 150 mg orally monthly</td>
</tr>
<tr>
<td>Zoledronic acid (Aclasta)</td>
<td>Bisphosphonate</td>
<td>5 mg IV annually</td>
</tr>
<tr>
<td>Denosumab (Prolia)</td>
<td>RANK ligand inhibitor</td>
<td>60 mg s.c. every 6 months</td>
</tr>
</tbody>
</table>
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 follow-up DXA to assess for treatment response until recovery of testosterone (Expert opinion).
RECOMMENDATIONS – BONE HEALTH

• All men receiving ADT should be encouraged to maintain basic bone health standards, as outlined by the Osteoporosis Canada guidelines.¹

  Providers should obtain baseline calcium and 25-hydroxyvitamin D levels at the start of ADT (Expert opinion).

  Men should maintain adequate calcium intake (1,200 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).

² Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print.
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).
BONE HEALTH AND LIFESTYLE CHANGES

• Lifestyle modifications:
  • Smoking and alcohol use are associated with bone loss and fractures\(^1\)
  • Exercise therapy improves multiple physical domains in men with PC receiving ADT, including preservation of muscle mass and strength, which may decrease risk of fractures\(^2\)
  • Exercise also appears to preserve BMD in men receiving ADT\(^3\)

HOT FLASHES
DISCUSSION QUESTION

Your patient with PC undergoing ADT finds that he has difficulty participating in many of the activities that he used to enjoy, because he has frequent hot flashes throughout the day. What advice would you give him to help reduce his hot flashes?
EVIDENCE SUMMARY – HOT FLASHES

• Hot flashes are a common and bothersome side effect of ADT.
Patients should be counselled on identification and avoidance of potential triggers (Expert opinion).
Up to 80% of men on ADT have vasomotor symptoms\(^1\) (up to 27% report hot flushes as the most bothersome AE)

- Avoid caffeine
- Wear light clothes
- Exercise
- Avoid heat
- Avoid spicy foods
- Drink cold beverages

References:
1. Frisk J. Maturitas 2010;65:15-22
3. Richardson MK. Menopause 2013;20:980–2
RECOMMENDATION – HOT FLASHES

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).
<table>
<thead>
<tr>
<th>NAME OF AGENT</th>
<th>DOSE</th>
<th>MECHANISM OF ACTION</th>
<th>HEALTH CANADA APPROVED FOR HOT FLASHES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>20 mg orally daily</td>
<td>Synthetic derivative of progesterone</td>
<td>No</td>
</tr>
<tr>
<td>acetate (Provera)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Megestrol acetate (Megace)</td>
<td>20 mg orally twice daily</td>
<td>Synthetic derivative of progesterone</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyproterone acetate (Androcur)</td>
<td>50 mg orally daily</td>
<td>Antiandrogen</td>
<td>No (approved for palliative treatment of patients with advanced prostate adenocarcinoma)</td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>900 mg orally daily</td>
<td>Antiepileptic agent</td>
<td>No</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>75 mg orally daily</td>
<td>Selective serotonin reuptake inhibitor</td>
<td>No</td>
</tr>
</tbody>
</table>
Acupuncture may have a beneficial effect and can be considered in patients unwilling or unable to use pharmacotherapy (LE: 3, weak recommendation).
ACUPUNCTURE AS A NOVEL TREATMENT FOR VASOMOTOR SYMPTOMS ASSOCIATED WITH ADT

• 60 men with PC treated with an LHRH agonist
• Weekly acupuncture of the ear for 10 weeks

<table>
<thead>
<tr>
<th>MEAN (SD)</th>
<th>WEEKS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Frequency of hot flashes</td>
<td></td>
</tr>
<tr>
<td>Daytime, mean (SD)</td>
<td>7.2 (4.9)</td>
</tr>
<tr>
<td>Night-time, mean (SD)</td>
<td>6.3 (3.9)</td>
</tr>
<tr>
<td>Intensity*</td>
<td></td>
</tr>
<tr>
<td>Daytime, mean (SD)</td>
<td>3.2 (0.8)</td>
</tr>
<tr>
<td>Night-time, mean (SD)</td>
<td>4.3 (0.9)</td>
</tr>
</tbody>
</table>

*On a scale of 1-6, where 6 = maximum intensity
EFFECTS ON THE BREAST
• ADT-related breast events include gynecomastia and mastodynia.

• Gynecomastia occurs most commonly with anti-androgen (AA) monotherapy* and is a rare complication of LHRH monotherapy or combined androgen blockade.

*AA monotherapy is an alternative to ADT but is not ADT.
Prophylaxis for the prevention of gynecomastia in men receiving ADT is not currently recommended (Expert opinion).

Tamoxifen or RT may be used for prevention and treatment of breast events in men receiving bicalutamide monotherapy; tamoxifen is more effective than RT (LE 1; strong recommendation).
COGNITIVE FUNCTION
• Use of ADT in men with PC 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 – COGNITIVE FUNCTION

Men receiving ADT should be monitored for cognitive decline throughout duration of treatment (Expert opinion).
Evidence related to
causality remains weak,
and further prospective
data are needed.

ADT MAY BE ASSOCIATED WITH CHANGES IN COGNITION AND DEPRESSION

Select cognitive and neurobehavioral symptoms reported by patients with nonmetastatic PC treated with ADT or observation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>ADT (n = 19)</th>
<th>No ADT (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory (prospective)</td>
<td>74%</td>
<td>50%</td>
</tr>
<tr>
<td>Multi-tasking</td>
<td>50%</td>
<td>32%</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>74%</td>
<td>45%</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>45%</td>
<td>37%</td>
</tr>
<tr>
<td>Memory (general)</td>
<td>84%</td>
<td>65%</td>
</tr>
<tr>
<td>Attention and concentration</td>
<td>58%</td>
<td>55%</td>
</tr>
<tr>
<td>Problem solving</td>
<td>21%</td>
<td>10%</td>
</tr>
<tr>
<td>Apathy</td>
<td>37%</td>
<td>40%</td>
</tr>
</tbody>
</table>

FATIGUE AND ANEMIA
Since starting his ADT, your patient finds that he tires easily and has to take frequent naps throughout the day. What advice might you give to help him reduce the fatigue he is experiencing?
• 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.
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 (1-2 ng/dl) should be referred for further evaluation (Expert opinion).
FATIGUE IS A NOTICEABLE SIDE EFFECT OF ADT

Self-report measures of fatigue in 160 men with PC on long-term ADT

Clinically relevant fatigue may occur in more than 40% of men
Change in fatigue (EORTC QOL Questionnaire-Core 36) and vitality (Short Form-36) with 6–12 months of exercise according to baseline status*

Baseline fatigue
Q1 = lowest, Q4 = highest

Baseline vitality
Q1 = highest, Q4 - Lowest

p < 0.001
• Impact of anemia on fatigue in men receiving ADT remains unknown

• Treatment is rarely indicated, but may include blood transfusion and erythropoietin if severe

• Most causes of anemia are multifactorial and can include:
  • Iron deficiency
  • Vitamin B12 deficiency
  • Folate deficiency

• If anemia is severe, refer to a hematologist
SEXUAL FUNCTION
• ADT impacts multiple domains of sexual function, including body image, loss of libido, and erectile function.
In men desiring improved sexual function, referral to a sex therapist for multimodal treatment should be considered (Expert opinion).
ADT IMPACTS MULTIPLE DOMAINS OF SEXUAL FUNCTION

- Loss of libido
- Decreased penile and testicular size
- Decreased sensitivity to sexual stimulation
- Erectile dysfunction

Loss of libido may occur in up to 90% of men on ADT

INTERVENTIONS TO HELP MEN MAINTAIN OR PRESERVE SEXUAL FUNCTION WHILE UNDERGOING ADT

• Pre-treatment counselling regarding side effects
• Psychosocial support groups and/or sex therapists for interested patients
• Erectile dysfunction may be treated with phosphodiesterase inhibitors
  • Efficacy may be poor without adequate mental and physical arousal
• Intermittent ADT may be considered in appropriate patients

EFFECTS OF LHRH AGONIST TREATMENT ON SEXUAL AND HORMONAL FUNCTIONS IN MEN WITH PC

Mean sexual and hormone domain scores before and after treatment with an LHRH agonist in men with PC

EPIC Score

Mean sexual and hormone domain scores before and after treatment with an LHRH agonist in men with PC

* $p < 0.01$ † $p < 0.05$

EPIC Expanded Prostate Cancer Index Composite
Summary score: S Sexual summary score including sexual function and sexual bother scores. H hormone summary score including hormone function and hormone bother scores.
Subscale scores: SF Sexual function SB Sexual bother HF Hormonal function HB Hormone bother

HEALTH-RELATED QUALITY OF LIFE (HRQOL)
DISCUSSION QUESTION

What are the key things that a patient should be told to help maximize his quality of life while undergoing ADT?
• Patients on ADT experience significant decrements in multiple health-related quality of life (HRQOL) domains.
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).
Mean unadjusted physical, mental, urinary, bowel, and sexual domain scores at baseline and 3 years after diagnosis for patients with PC

- Baseline
- Three years

ADT (n = 61)

Controls (n = 495)

*Higher scores indicate better function

EXERCISE POSITIVELY IMPACTS VARIOUS AEs ASSOCIATED WITH ADT

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>EXERCISE MODALITY*</th>
<th>LEVEL OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MA</td>
</tr>
<tr>
<td>Aerobic Fitness</td>
<td>✓</td>
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<tr>
<td>Muscular Strength</td>
<td>✓</td>
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<td>Co-Morbid Disease Risk Factors</td>
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<td>Sexual Wellbeing</td>
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<td>✓</td>
</tr>
<tr>
<td>Cognitive Decline</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

*Shown in order of importance for eliciting results

Aerobic exercise
Resistance exercise
Impact exercise

Intermittent ADT improves multiple HRQOL domains in men with PC and should be considered in appropriately selected patients:
- Libido
- Erectile function
- Hot flashes
- Mental health
SUMMARY AND CONCLUSIONS
MULTIDISCIPLINARY MANAGEMENT OF PATIENTS ON ADT

UROLOGIST
RADIATION ONCOLOGIST
MEDICAL ONCOLOGIST

PRIMARY CARE PHYSICIAN
CARDIOLOGIST, ENDOCRINOLOGIST, PSYCHOLOGIST, SEXOLOGIST, ETC

<table>
<thead>
<tr>
<th>ADT initiation</th>
<th>Baseline investigations</th>
<th>Ongoing management</th>
<th>Monitoring and follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History:</strong> previous MACE, risk factors for cardiac disease, previous VTE or stroke, fall risk</td>
<td><strong>History:</strong> previous MACE, risk factors for cardiac disease, previous VTE or stroke, fall risk</td>
<td><strong>History:</strong> previous MACE, risk factors for cardiac disease, previous VTE or stroke, fall risk</td>
<td><strong>History:</strong> previous MACE, risk factors for cardiac disease, previous VTE or stroke, fall risk</td>
</tr>
<tr>
<td><strong>Physical exam:</strong> weight, waist circumference, BMI, height, BP</td>
<td><strong>Physical exam:</strong> weight, waist circumference, BMI, height, BP</td>
<td><strong>Physical exam:</strong> weight, waist circumference, BMI, height, BP</td>
<td><strong>Physical exam:</strong> weight, waist circumference, BMI, height, BP</td>
</tr>
<tr>
<td><strong>Labs:</strong> Fasting plasma glucose, oral glucose tolerance test or HgbA1c, lipid profile, calcium, 25-hydroxyvitamin D</td>
<td><strong>Labs:</strong> Fasting plasma glucose, oral glucose tolerance test or HgbA1c, lipid profile, calcium, 25-hydroxyvitamin D</td>
<td><strong>Labs:</strong> Fasting plasma glucose, oral glucose tolerance test or HgbA1c, lipid profile, calcium, 25-hydroxyvitamin D</td>
<td><strong>Labs:</strong> Fasting plasma glucose, oral glucose tolerance test or HgbA1c, lipid profile, calcium, 25-hydroxyvitamin D</td>
</tr>
<tr>
<td><strong>Other:</strong> BMD, 10-year major osteoporotic fracture risk</td>
<td><strong>Other:</strong> BMD, 10-year major osteoporotic fracture risk</td>
<td><strong>Other:</strong> BMD, 10-year major osteoporotic fracture risk</td>
<td><strong>Other:</strong> BMD, 10-year major osteoporotic fracture risk</td>
</tr>
</tbody>
</table>

**Monitoring and follow up**

- Metabolic assessments at 6-12 mo intervals
- Monitor BP, treat hypertension for target of < 130/80 mmHg
- Monitor for dyslipidemia, insulin resistance, metabolic syndrome – manage as per current best practice guidelines
SUMMARY

• ADT improves survival in men with PC and is a mainstay of treatment.

• ADT is associated with AEs that span multiple organ systems
  • Should be reserved for those who are likely to derive an oncological benefit

• Patients require appropriate counselling regarding AEs

• Multidisciplinary approach is needed to manage potential complications of ADT
CVD IS THE LEADING CAUSE OF DEATH IN MEN WITH PC NOT DYING OF THE DISEASE ITSELF

Chowdhury S, et al. BJU Int 2013;112:182-9
ASSOCIATION BETWEEN ADT AND CV MORTALITY

<table>
<thead>
<tr>
<th>Study</th>
<th>ADT</th>
<th>Control</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alibhai et al 2009</td>
<td>399/19,079</td>
<td>436/19,079</td>
<td>0.96 (0.83-1.10)</td>
</tr>
<tr>
<td>Punnen et al 2011</td>
<td>89/1,087</td>
<td>106/5,676</td>
<td>1.11 (0.73-1.68)</td>
</tr>
<tr>
<td>Gandaglia et al 2014</td>
<td>10,592/59,994</td>
<td>11,720/82,535</td>
<td>1.18 (1.12-1.24)</td>
</tr>
<tr>
<td>Keating et al 2010</td>
<td>432/13,620</td>
<td>315/23,823</td>
<td>1.29 (1.08-1.55)</td>
</tr>
<tr>
<td>Hemelrijck et al 2010</td>
<td>2,434/24,432</td>
<td>1,063/19,526</td>
<td>1.38 (1.02-1.87)</td>
</tr>
<tr>
<td>Merino et al 2011</td>
<td>49/1,413</td>
<td>5/335</td>
<td>1.65 (0.87-3.13)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>13,995/119,625</td>
<td>13,645/15,974</td>
<td>1.17 (1.04-1.32)</td>
</tr>
</tbody>
</table>

Heterogeneity: $p = 0.04$; $I^2 = 57$
Test for overall effect: $p = 0.01$
• Meta-analysis of 8 observational studies examining association between ADT and CVD outcomes

• Risk of CVD with LHRH agonists vs. no ADT:
  • Any type of nonfatal CVD: RR 1.38 (95% CI 1.29–1.48)
  • Nonfatal ischemic heart disease: RR 1.39 (95% CI 1.26–1.54)
  • Nonfatal or fatal MI: RR 1.57 (95% CI 1.26–1.94)
  • Nonfatal or fatal stroke: RR 1.51 (95% CI 1.24–1.84)

• Risk of non-fatal CVD with other types of ADT:
  • Orchiectomy vs. no ADT: RR 1.44 (95% CI 1.28–1.62)
  • Antiandrogens vs. no ADT: RR 1.21 (95% CI 1.07–1.367)
### CV MORTALITY

<table>
<thead>
<tr>
<th>Study</th>
<th>ADT</th>
<th>Control</th>
<th>Relative Risk (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>D'Amico et al 2008 – DFCI 95-096</td>
<td>13/102</td>
<td>13/104</td>
<td>1.02 (0.50-2.09)</td>
<td>0.96</td>
</tr>
<tr>
<td>Messing et al 2006 – ECOG/EST 3886</td>
<td>3/47</td>
<td>1/51</td>
<td>3.26 (0.35-30.2)</td>
<td>0.30</td>
</tr>
<tr>
<td>Bolla et al 2010 – EORTC 22863</td>
<td>22/207</td>
<td>17/208</td>
<td>1.30 (0.71-2.38)</td>
<td>0.39</td>
</tr>
<tr>
<td>Schroder et al 2009 – EORTC 30846</td>
<td>10/119</td>
<td>10/115</td>
<td>0.97 (0.42-2.23)</td>
<td>0.94</td>
</tr>
<tr>
<td>Studer et al 2006 – EORTC 30891</td>
<td>88/492</td>
<td>97/493</td>
<td>0.91 (0.70-1.18)</td>
<td>0.47</td>
</tr>
<tr>
<td>Efstathiou et al 2009 – RTOG 85-31</td>
<td>52/447</td>
<td>65/468</td>
<td>0.78 (0.56-1.10)</td>
<td>0.17</td>
</tr>
<tr>
<td>Roach et al 2008 – RTOG 86-10</td>
<td>31/224</td>
<td>26/232</td>
<td>1.23 (0.76-2.01)</td>
<td>0.40</td>
</tr>
<tr>
<td>Denham et al 2011 – TROG 96.01</td>
<td>36/532</td>
<td>23/270</td>
<td>0.79 (0.48-1.31)</td>
<td>0.37</td>
</tr>
<tr>
<td>Overall</td>
<td>255/2,200</td>
<td>252/1,941</td>
<td>0.93 (0.79-1.10)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Q = 5.12, p = 0.64, I² = 0%

META-ANALYSIS OF UNFAVOURABLE-RISK PC SHOWED NO INCREASED RISK OF CV MORTALITY WITH ADT

Nguyen PL, et al. JAMA 2011;306:2359-66
# Presence of Cardiac Risk Factors Impacts Risk of CV Mortality with ADT

<table>
<thead>
<tr>
<th>Patients</th>
<th>5-Year Cardiac-Specific Mortality, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients, n = 5,077</strong></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant ADT</td>
<td>1.87 (1.21–2.77)</td>
</tr>
<tr>
<td>No neoadjuvant ADT</td>
<td>1.59 (1.13–2.17)</td>
</tr>
<tr>
<td><strong>Patients with No Cardiac Comorbidity, n = 2,653</strong></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant ADT</td>
<td>1.08 (0.48–2.14)</td>
</tr>
<tr>
<td>No neoadjuvant ADT</td>
<td>1.27 (0.76–2.00)</td>
</tr>
<tr>
<td><strong>Patients with Diabetes Mellitus, Hypertension, or Hypercholesterolemia, n = 2,168</strong></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant ADT</td>
<td>2.09 (1.05–3.76)</td>
</tr>
<tr>
<td>No neoadjuvant ADT</td>
<td>1.97 (1.20–3.05)</td>
</tr>
<tr>
<td><strong>Patients with CHF or MI, n = 256</strong></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant ADT</td>
<td>7.01 (2.82–13.82)</td>
</tr>
<tr>
<td>No neoadjuvant ADT</td>
<td>2.01 (0.38–6.45)</td>
</tr>
</tbody>
</table>
Although there is a positive association between a plan to use ADT and baseline CV risk factors, this association is explained by confounding factors.
ADT IS ASSOCIATED WITH AN INCREASED RISK OF VTE

<table>
<thead>
<tr>
<th>ADT EXPOSURE</th>
<th>EVENTS, N</th>
<th>PERSON-YEARS</th>
<th>INCIDENCE RATE (95% CI)*</th>
<th>CRUDE HR (95% CI)</th>
<th>ADJUSTED HR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonuse</td>
<td>183</td>
<td>38,375</td>
<td>4.77 (4.10–5.51)</td>
<td>1.00 [ref]</td>
<td>1.00 [ref]</td>
</tr>
<tr>
<td>LHRH agonists only</td>
<td>195</td>
<td>24,607</td>
<td>7.92 (6.85–9.12)</td>
<td>1.86 (1.51–2.29)</td>
<td>1.52 (1.22–1.91)</td>
</tr>
<tr>
<td>LHRH agonists and oral antiandrogens</td>
<td>68</td>
<td>4,206</td>
<td>16.17 (12.55–20.50)</td>
<td>3.47 (2.62–4.59)</td>
<td>2.69 (2.00–3.62)</td>
</tr>
<tr>
<td>Oral antiandrogens only</td>
<td>32</td>
<td>3,974</td>
<td>8.05 (5.51–11.37)</td>
<td>1.66 (1.51–2.29)</td>
<td>1.43 (0.98–2.10)</td>
</tr>
<tr>
<td>Other combinations</td>
<td>40</td>
<td>919</td>
<td>43.53 (31.10–59.27)</td>
<td>11.33 (7.98–16.08)</td>
<td>8.38 (5.79–12.12)</td>
</tr>
<tr>
<td>Bilateral orchiectomy</td>
<td>5</td>
<td>581</td>
<td>8.61 (2.79–20.08)</td>
<td>2.07 (0.85–5.04)</td>
<td>1.56 (0.63–3.81)</td>
</tr>
<tr>
<td>Estrogens only</td>
<td>7</td>
<td>166</td>
<td>42.17 (16.95–86.88)</td>
<td>10.72 (5.02–22.90)</td>
<td>7.41 (3.43–16.01)</td>
</tr>
</tbody>
</table>

*Per 1,000 person-years
†Adjusted for age, year of PC diagnosis, excessive alcohol use, smoking status, obesity, chronic kidney disease, MI, ischemic stroke, transient ischemic attack, peripheral arterial disease, previous cancer, inflammatory bowel disease, aspirin, other nonsteroidal anti-inflammatory drugs, clopidogrel, warfarin, statins, prostate-specific antigen level, and type of metastasis

ADT IS ASSOCIATED WITH A HIGHER RISK OF METABOLIC SYNDROME

- **Metabolic syndrome**: p = 0.03
- **Abdominal obesity**: p < 0.01
- **Fasting hyperglycemia**: p < 0.01
- **Hypertriglyceridemia**: p = 0.02
- **Low HDL cholesterol**: p = 0.34
- **Hypertension**: p = 0.75
Providers should screen men initiating long-term ADT for osteoporosis using BMD testing with DXA (as per the 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada) (Expert opinion).

![Graph showing BMD (SD units or T-score) categories]

- **Osteoporosis**: < -2.5
- **Osteopenia**: > -1.0 to < -2.5
- **Normal**: > -1.0
• RCT of CADT (n = 696) vs. IADT (n = 690) after radiotherapy

• IADT was noninferior to CADT with respect to OS, with significantly better scores for:
  • Hot flashes (p < 0.001)
  • Desire for sexual activity (p < 0.001)
  • Urinary symptoms (p = 0.006)
GYNECOMASTIA AND MASTODYNIA

Grade 3–4 gynecomastia after 6 months

- Bicalutamide alone: 70%
- Bicalutamide + tamoxifen: 10%
- Bicalutamide + RT: 20%

Moderate to severe breast pain after 6 months

- Bicalutamide alone: 50%
- Bicalutamide + tamoxifen: 10%
- Bicalutamide + RT: 30%

RT Radiotherapy (one 12-Gy fraction on the day of starting bicalutamide)