CUA Guideline on Androgen Deprivation Therapy: Adverse Events and Management Strategies

JUNE 2021

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EDITORIAL COMMITTEE

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)

INTRODUCTION

ADT IS IMPORTANT FOR CONTEMPORARY PC MANAGEMENT

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

Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print.

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

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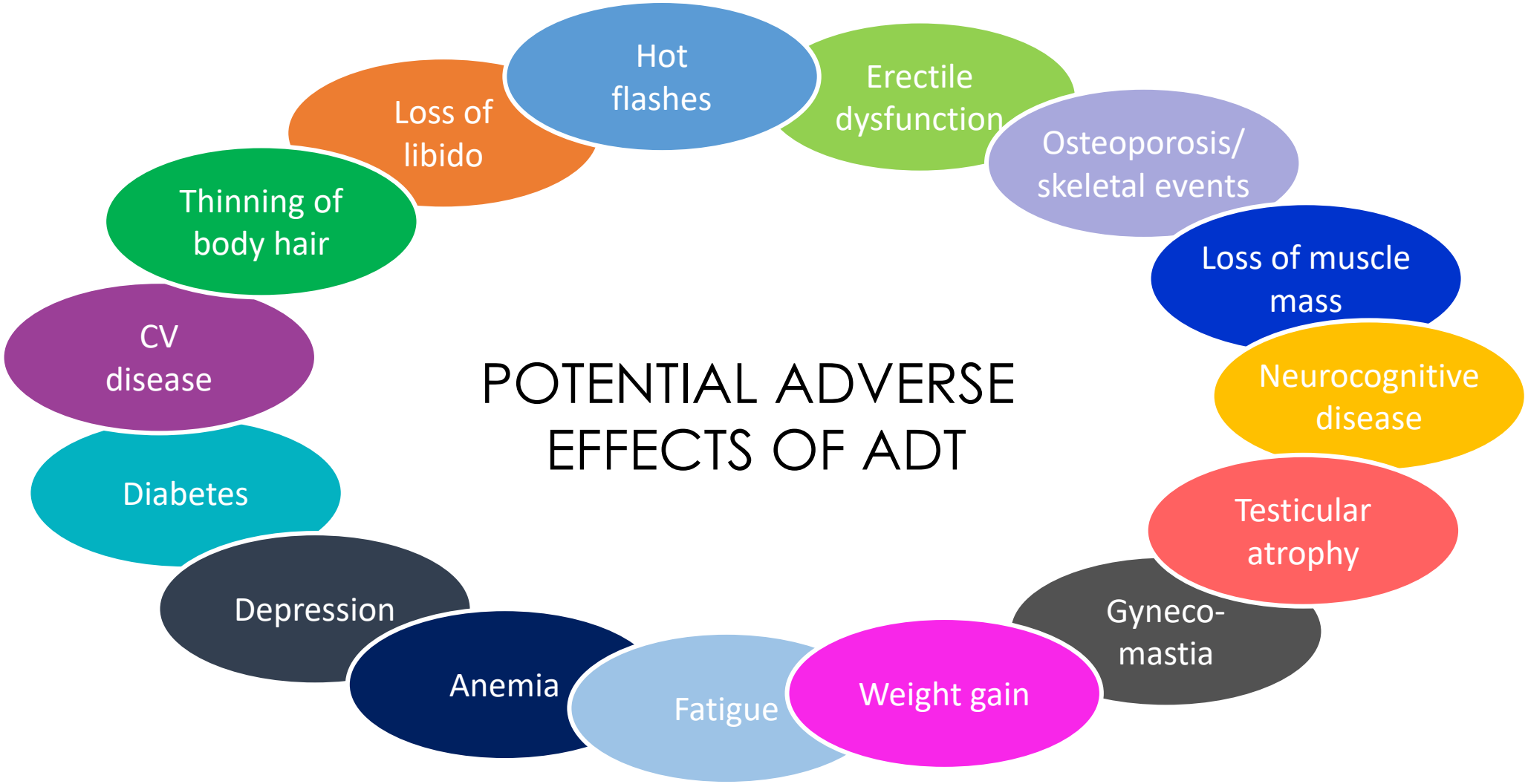
ADT ADVERSE EVENTS

- 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

Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print.


POTENTIAL ADVERSE EFFECTS OF ADT
Hot flashes
Erectile dysfunction
Osteoporosis/ skeletal events
Loss of muscle mass
Neurocognitive disease
Testicular atrophy
Gyneco-mastia
Weight gain
Fatigue
Anemia
Depression
Diabetes
CV disease
Thinning of body hair
Loss of libido

GOALS OF ADT THERAPY

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

Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print.

CUA GUIDELINE ON ADT: AEs AND MANAGEMENT STRATEGIES[1] QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

- Levels of evidence assigned using criteria from the Oxford Center for Evidence-based Medicine[2]
- Strength of recommendations – subjective consensus recommendations using best available evidence[2,3]
  - **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.

1. Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print.
2. CEBM, 2018. https://www.cebm.net
2. GRADE Working Group, 2018. http://www.gradeworkinggroup.org

DISCUSSION QUESTION

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 QUESTOIN

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

How might this change your approach to his management?

MI Myocardial infarction

CARDIOVASCULAR COMPLICATIONS

EVIDENCE SUMMARY – CARDIAC COMPLICATIONS OF ADT

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

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RECOMMENDATIONS – CARDIAC 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).

GnRH Gonadotropin-releasing hormone

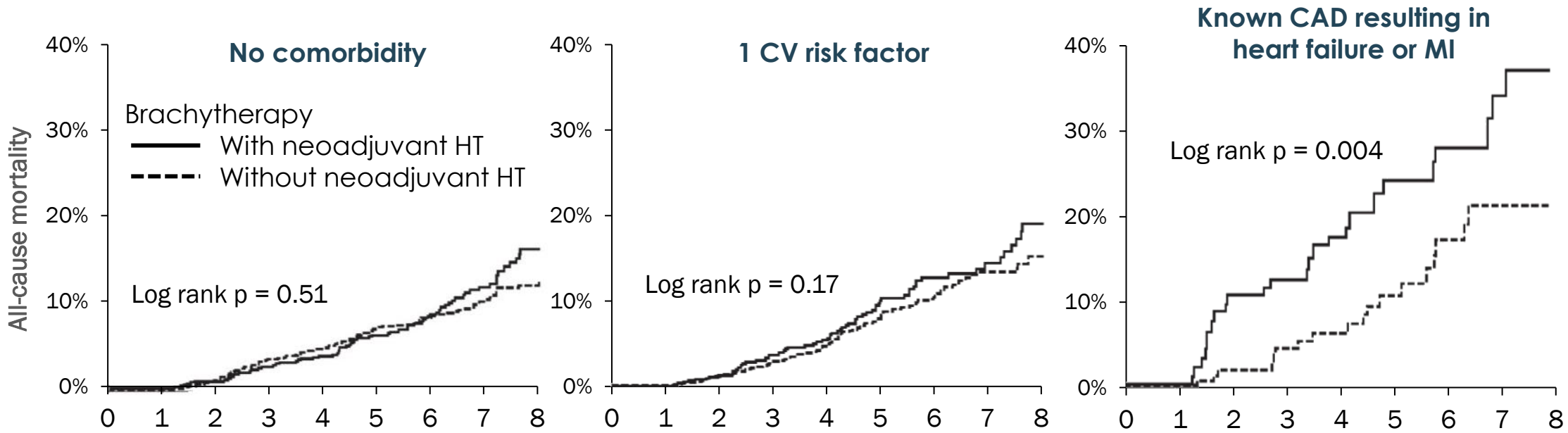
Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print.

LARGE OBSERVATIONAL COHORT STUDIES DESCRIBE A STRONG LINK BETWEEN ADT AND CVD

- Meta-analysis including 119,000 PC patients receiving ADT[1]
  - 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 studies[2]
  - 38% increase in nonfatal CVD for men treated with an LHRH agonist (RR 1.38; 95% CI 1.29–1.48)

1. Zhao J, et al. PLoS One 2014;9:e107516 **2.** Bosco C, et al. Eur Urol 2015;68:386-96

PRESENCE OF CARDIAC RISK FACTORS IMPACTS RISK OF CV MORTALITY WITH ADT



No. at risk															
Brachytherapy															
Neoadjuvant HT	780	699	532	288	98	646	566	373	176	55	95	79	58	30	8
No neoadjuvant HT	1,873	1,582	1,073	607	282	1,522	1,247	765	392	151	161	135	97	46	18

Presence of pre-existing MACE (CHF, ischemic heart disease, arrhythmia, stroke, prior MI) may increase risk of further events while on ADT

CAD Coronary artery disease **CHF** Congestive heart failure **HT** Hormone therapy

Nanda A, et al. JAMA 2009;302:866-73

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

Albertsen PC, et al. Eur Urol 2014;65:565-73

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***

*Relugolix is not approved for use in Canada

Shore ND, et al. N Engl J Med 2020;382:2187-96

HERO TRIAL: CV ADVERSE EVENTS

Men with prior history of MACE receiving leuprolide are 4.8 times more likely to experience MACE than those on relugolix.

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

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

Shore ND, et al. N Engl J Med 2020;382:2187-96

VENOUS THROMBOEMBOLISM AND CEREBROVASCULAR COMPLICATIONS

EVIDENCE SUMMARY – THROMBOEMBOLIC AND CEREBROVASCULAR EVENTS

- ***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***

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RECOMMENDATIONS – CEREBROVASCULAR EVENTS

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).

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ADT IS ASSOCIATED WITH INCREASED RISK FOR STROKE

- 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]

1. Keating NL, et al. J Natl Cancer Inst 2012;104:1518-23.
2. Bosco C, et al. Eur Urol 2015;68:386-96.

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

Klil-Drori, Yin H, Tagalakis, Aprikian, Azoulay. Eur Urol. 2016;70(1):56-61

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***

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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)

BMI Body mass index **BP** Blood pressure

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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***

1. Haseen F, et al. J Cancer Surviv 2010;4:128-39
2. Cheung AS, et al. Eur J Endocrinol 2018;179:21-9

SARCOPENIC OBESITY – CLINICAL IMPLICATIONS

- 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]

1. Storer DW, et al. Asian J Androl 2012;14:204-21
2. Cormie P, et al. Urol Oncol 2020;38:62-70
3. Bylow K, et al. Urology 2008;72:422-7

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***

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RECOMMENDATIONS – LIPID PROFILE CHANGES

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).

HDL High-density lipoprotein **LDL** Low-density lipoprotein

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LIPID PROFILE CHANGES

- Changes to the lipid profile in response to ADT include:
  - Increased triglyceride levels
  - Increased total cholesterol
  - Possible increase in LDL cholesterol

Smith MR, et al. Cancer 2008;112:2188-94
Yannucci J, et al. J Urol 2006;176:520-5
Bagatell CJ, et al. Ann Intern Med 1992;116(12 Pt 1):967-3
Eri LM, et al. J Urol 1995;154:100-4
Smith MR, et al. J Clin Oncol 2008;26:1824-9
Braga-Basaria M, et al. J Clin Oncol 2006;24:3979-83

RECOMMENDATION – DIABETES AND GLYCEMIC CONTROL

Patients should be screened for diabetes with fasting plasma glucose, oral glucose tolerance test, or HgbA1c level (Expert opinion).

HgbA1c Glycated hemoglobin

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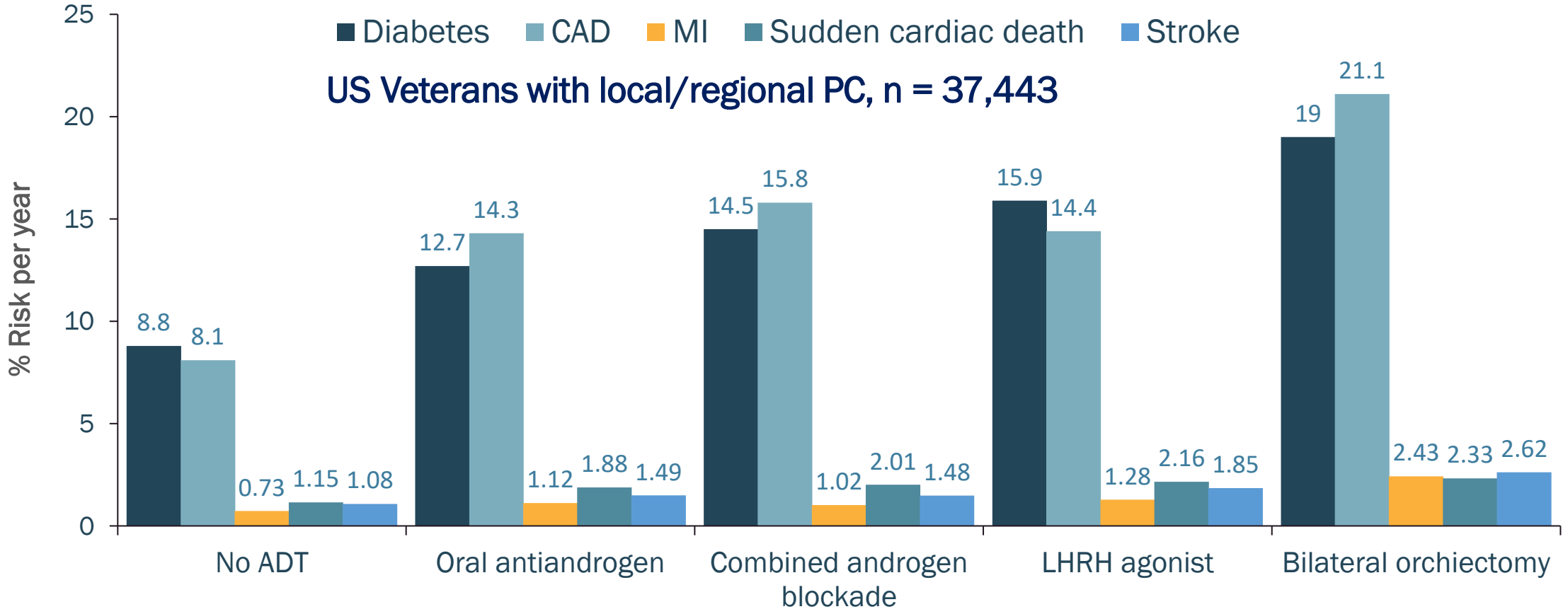
ADT IS ASSOCIATED WITH DEVELOPMENT OF DIABETES

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



Keating ML, et al. J Natl Cancer Inst 2010;102:39-46

RECOMMENDATION – METABOLIC SYNDROME

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.

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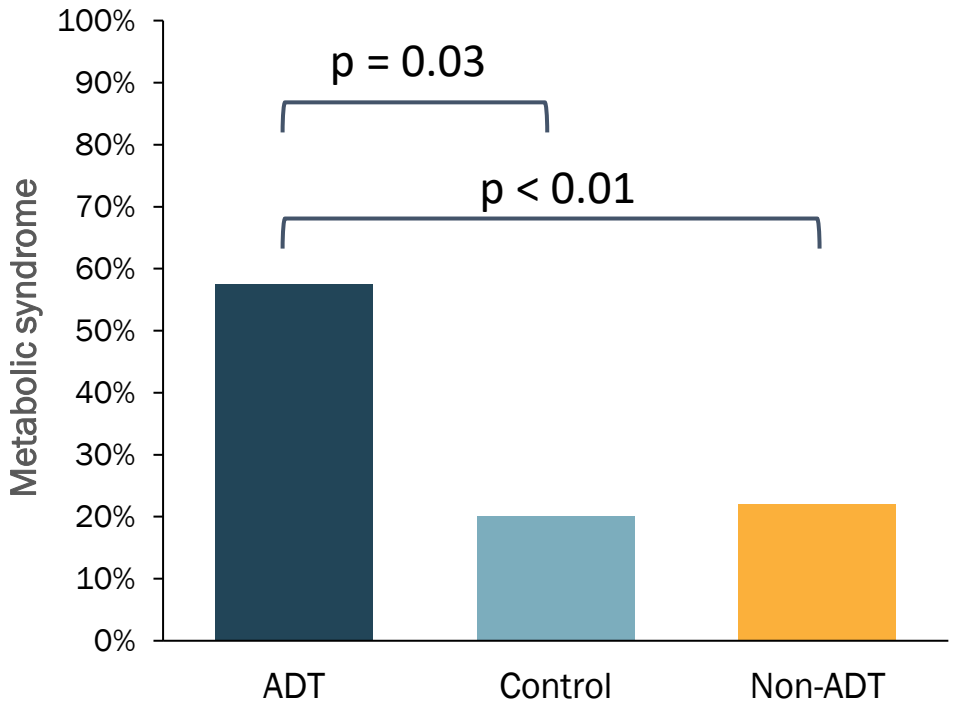
ADT IS ASSOCIATED WITH A HIGHER RISK OF METABOLIC SYNDROME

- 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



Braga-Basaria M, et al. J Clin Oncol 2006;24:3979-83

BENEFITS OF EXERCISE THERAPY IN MEN RECEIVING ADT

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

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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

Segal R, et al. Curr Oncol 2017;24:40-6
Cormie P, et al. Urol Oncol 2020;38:62-70

CARDIOMETABOLIC HEALTH – PUTTING IT ALL TOGETHER

- 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)

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BONE HEALTH

DISCUSSION QUESTION

What steps should be taken to ensure maintenance of bone health while a patient is undergoing ADT?

EVIDENCE SUMMARY – BONE HEALTH

- ***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***

Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print

RECOMMENDATION – BONE HEALTH

A comprehensive history and physical examination to include falls risk and height measurement should be performed prior to initiating ADT (Expert opinion).

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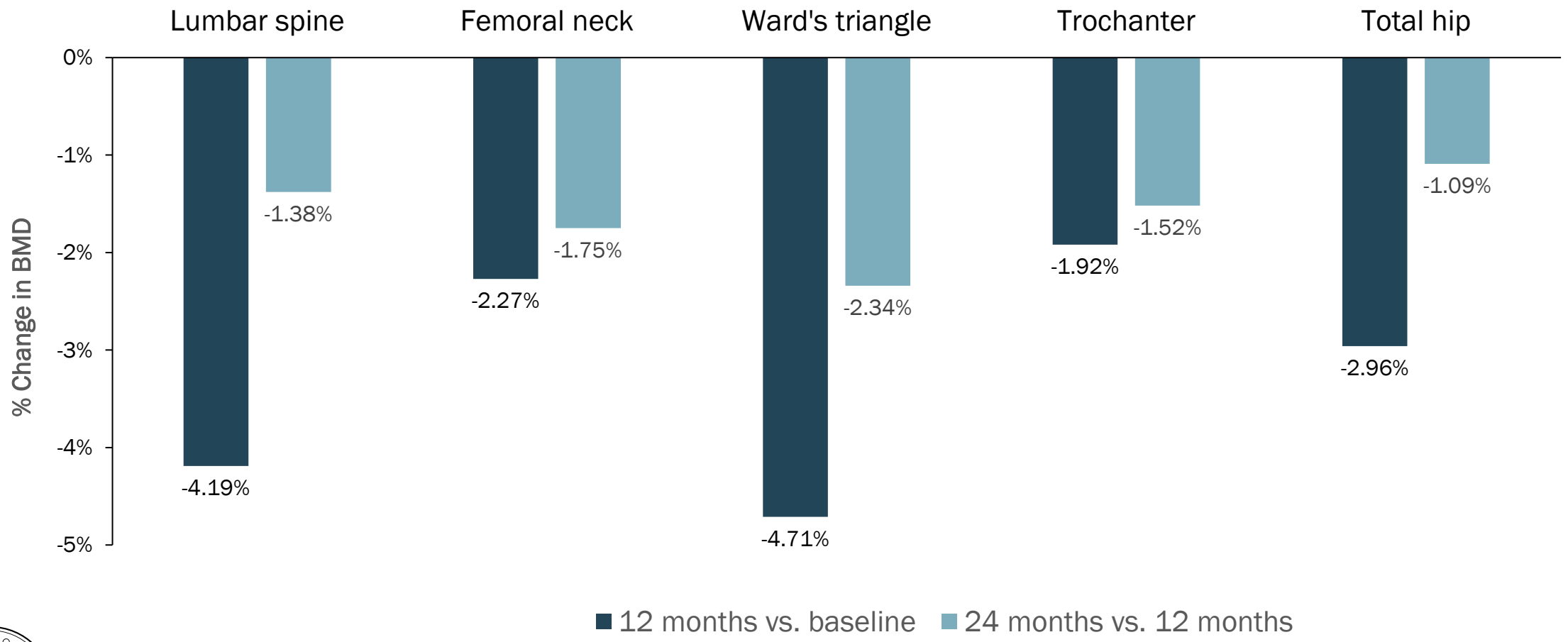
ADT USE RESULTS IN DECREASED BONE MINERAL DENSITY

- 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

Greenspan SL, et al. J Clin Endo Metab 2005:90;6410–7

MAXIMUM RATE OF BMD LOSS OCCURS DURING THE FIRST YEAR BUT CONTINUES TO DECLINE WITH PROLONGED USE OF ADT



Morote J, et al. J Urol 2006;175:1679-83.

RECOMMENDATION – BONE HEALTH

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).

DXA Dual-energy X-ray absorptiometry

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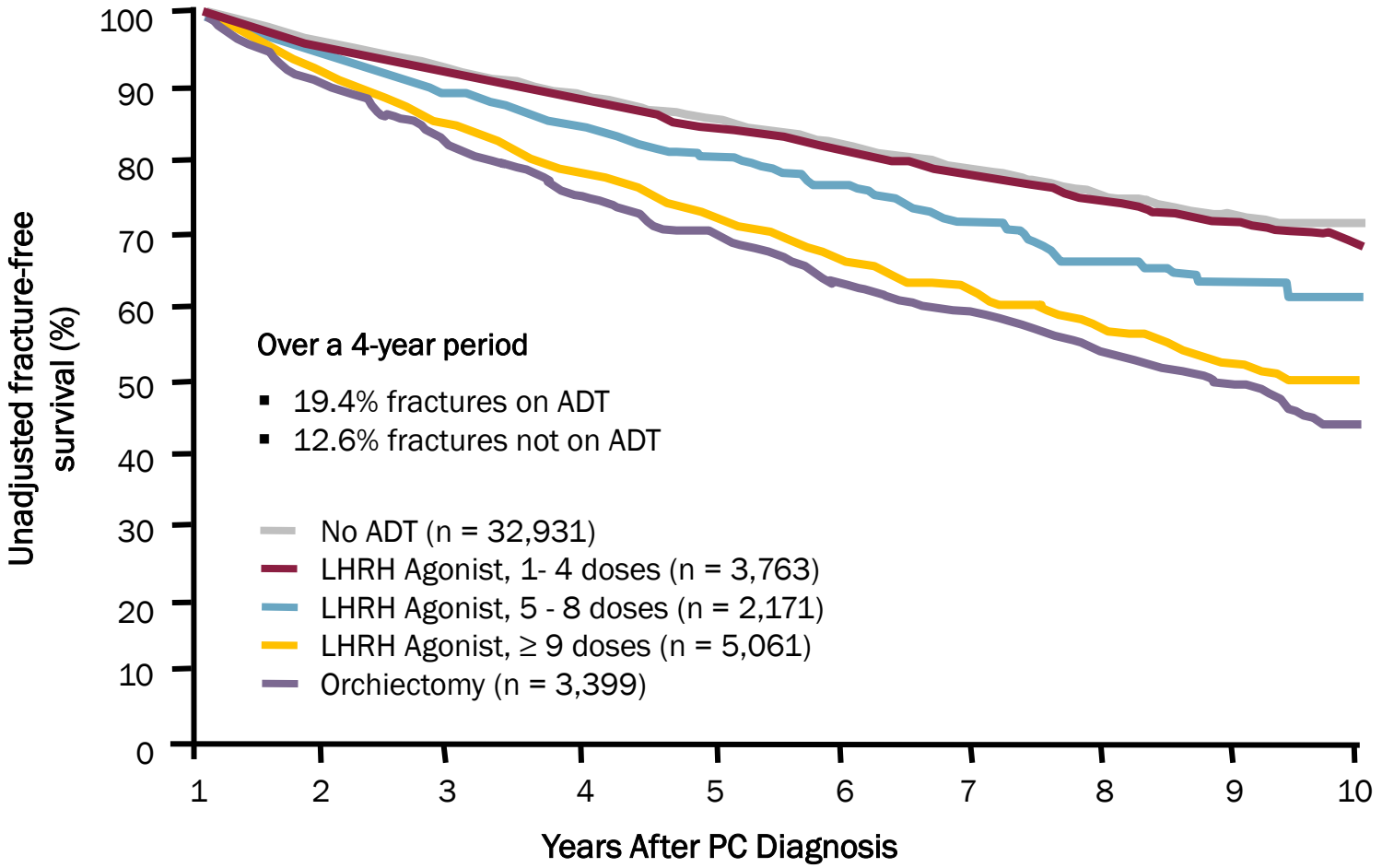
INCREASED RISK OF FRAGILITY FRACTURES WITH ADT

- 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

Shahinian VB, et al. N Engl J Med 2005;352:154-64

RECOMMENDATION – BONE HEALTH

A 10-year major osteoporotic fracture risk using a validated tool should be calculated (Expert opinion).

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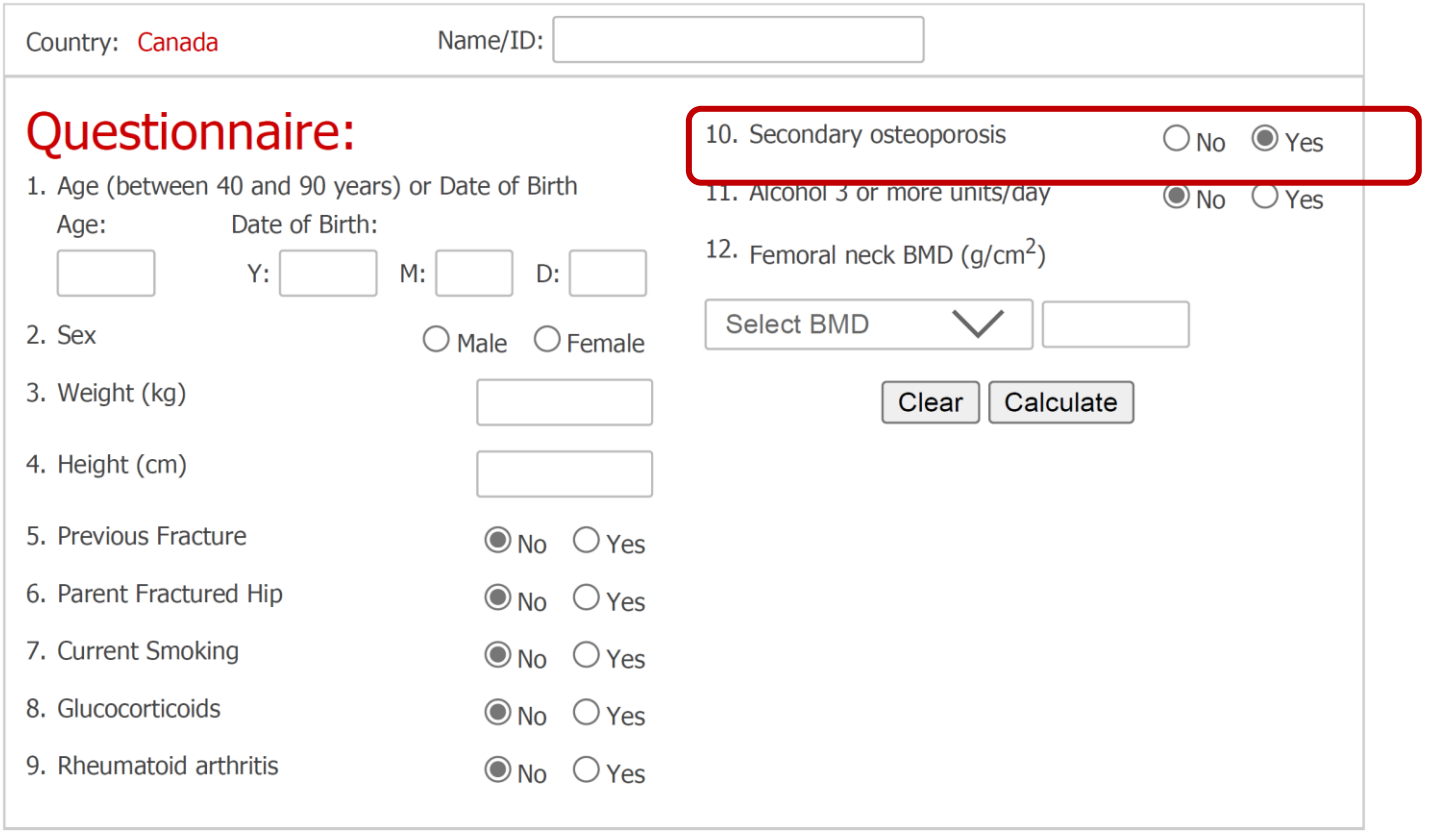
ASSESSMENT OF FRACTURE RISK – FRAX TOOL

- Calculates 10-year probability of fracture:
  - **LOW** < 10%
  - **MODERATE** 10-20%
  - **HIGH** > 20%
- Select "yes" for "secondary osteoporosis" for patients on ADT



www.sheffield.ac.uk/FRAX

RECOMMENDATION – BONE HEALTH

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).

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COMMON PHARMACOLOGICAL AGENTS USED FOR MANAGEMENT OF BONE AEs IN MEN ON ADT

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 IV annually
Denosumab (Prolia)	RANK ligand inhibitor	60 mg s.c. every 6 months

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RECOMMENDATION – BONE HEALTH

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).

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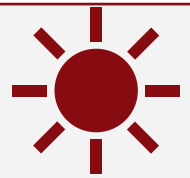
RECOMMENDATIONS – BONE HEALTH

- 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).

1. Papaioannou A, et al. CMAJ 2010;182:1864-73
2. Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print.

RECOMMENDATIONS – BONE HEALTH

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).

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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]

1. Lee CE, et al. Curr Oncol 2011;18:e163-72 **2.** Taaffe DR, et al. BJU Int 2019;123:261-9
3. Newton RU, et al. Med Sci Sports Exerc 2019;51:607-14

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.***

RECOMMENDATION – HOT FLASHES

Patients should be counselled on identification and avoidance of potential triggers
(Expert opinion).

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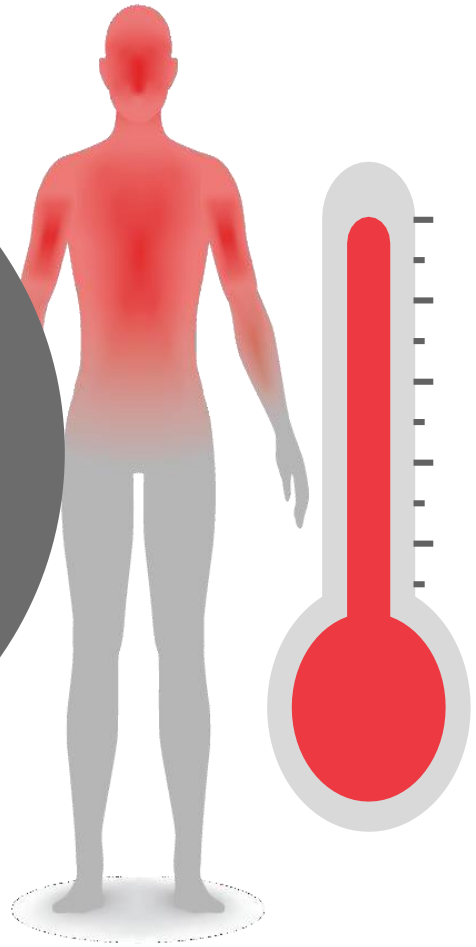
HOT FLASHES

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

1. Frisk J. Maturitas 2010;65:15-22 **2.** Dalal S, Zhukovsky DS. J Supportive Oncol 2006;4:315–20, 325
3. Richardson MK. Menopause 2013;20:980–2 **4.** Kaplan M, Mahon S. Clin J Oncol Nurs 2014;18 Suppl:59-67

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).

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COMMON PHARMACOLOGICAL AGENTS USED FOR THE TREATMENT OF HOT FLASHES

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 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

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RECOMMENDATION – HOT FLASHES

Acupuncture may have a beneficial effect and can be considered in patients unwilling or unable to use pharmacotherapy (LE: 3, weak recommendation).

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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

MEAN (SD)	WEEKS 0	4	10	p, ANOVA
Frequency of hot flashes				
Daytime, mean (SD)	7.2 (4.9)	3.8 (3.0)	2.2 (2.1)	< 0.05
Night-time, mean (SD)	6.3 (3.9)	3.0 (1.9)	1.9 (1.4)	< 0.05
Intensity*				
Daytime, mean (SD)	3.2 (0.8)	2.7 (1.5)	1.6 (1.4)	< 0.05
Night-time, mean (SD)	4.3 (0.9)	3.1 (1.6)	1.6 (1.3)	< 0.05

*On a scale of 1-6, where 6 = maximum intensity

Harding C, et al. BJU Int 2009;103:186-90

EFFECTS ON THE BREAST

EVIDENCE SUMMARY – GYNECOMASTIA AND MASTODYNIA

- ***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

Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print

RECOMMENDATIONS – EFFECTS ON THE BREAST

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).

RT Radiation therapy

Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print

COGNITIVE FUNCTION

EVIDENCE SUMMARY – 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.***

Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print

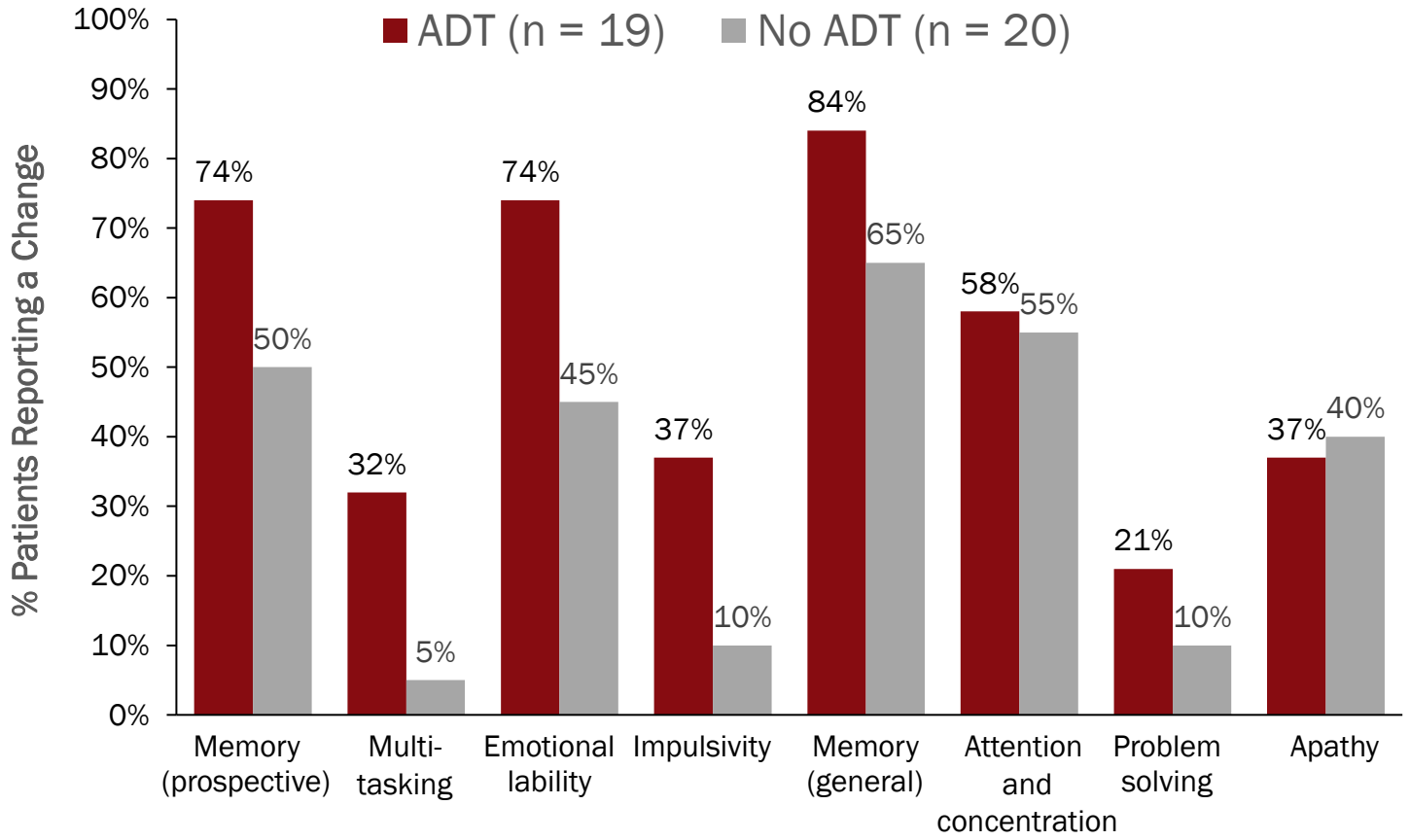
RECOMMENDATIONS – COGNITIVE FUNCTION

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

ADT MAY BE ASSOCIATED WITH CHANGES IN COGNITION AND DEPRESSION

Evidence related to causality remains weak, and further prospective data are needed.

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



Wu LM, et al. Soc Sc Med 2016;156:80-9

FATIGUE AND ANEMIA

DISCUSSION QUESTION

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?

EVIDENCE SUMMARY – FATIGUE AND ANEMIA

- ***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.***

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RECOMMENDATIONS – FATIGUE AND ANEMIA

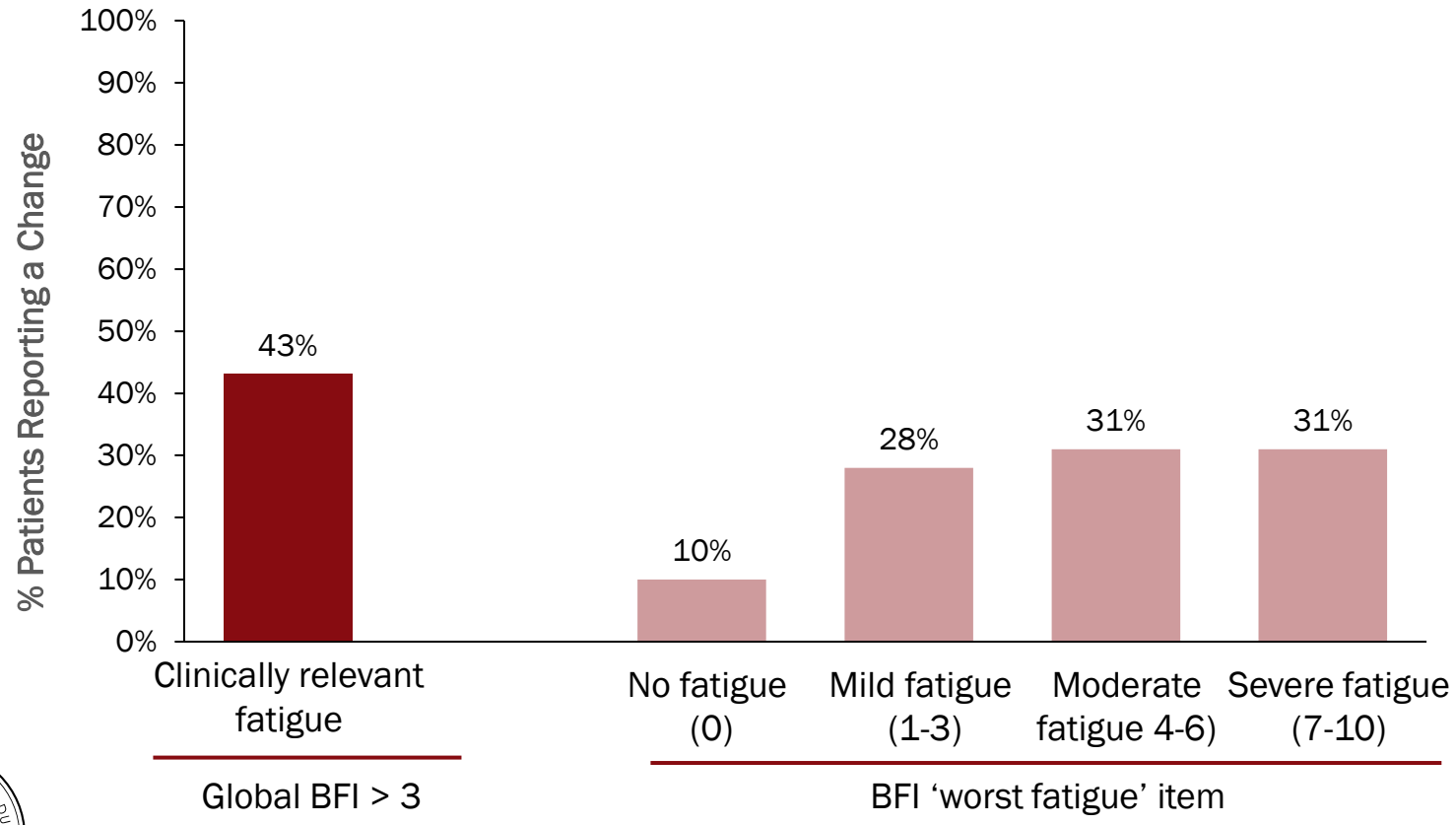
Men experiencing fatigue should be counselled to participate in exercise therapy (LE 2, strong recommendation).

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).

Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print

FATIGUE IS A NOTICEABLE SIDE EFFECT OF ADT

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



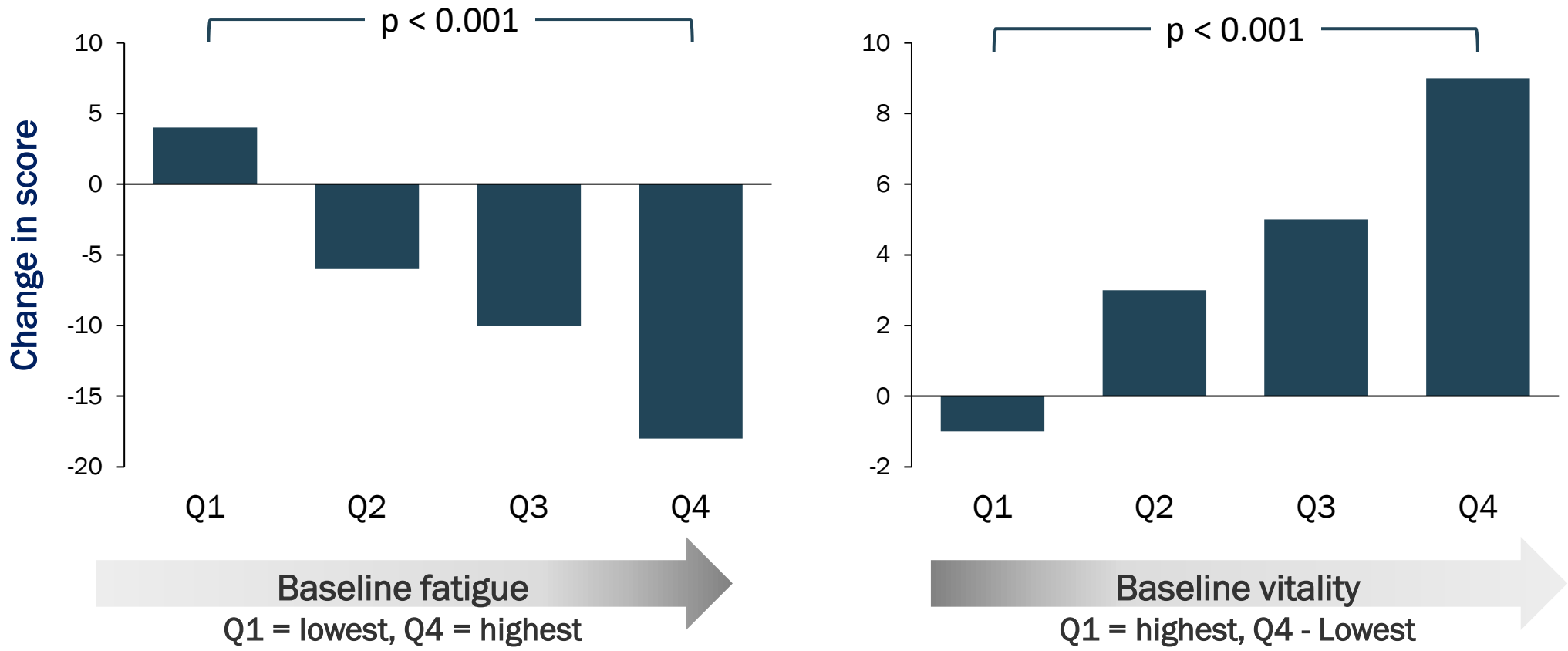
Clinically relevant fatigue may occur in more than 40% of men

BFI Brief fatigue inventory

Storey DJ, et al. Ann Oncol 2012;23:1542-9

EXERCISE HELPS REDUCE FATIGUE IN MEN RECEIVING ADT

Change in fatigue (EORTC QOL Questionnaire-Core 36) and vitality (Short Form-36) with 6–12 months of exercise according to baseline status*



EORTC QOL European Organization for Research and Treatment of Cancer Quality of Life

Taaffe DR, et al. Eur Urol 2017;72:293-9

ANEMIA

- 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

Grossmann M, Zajac JD. Asian J Androl 2012;14:187-92

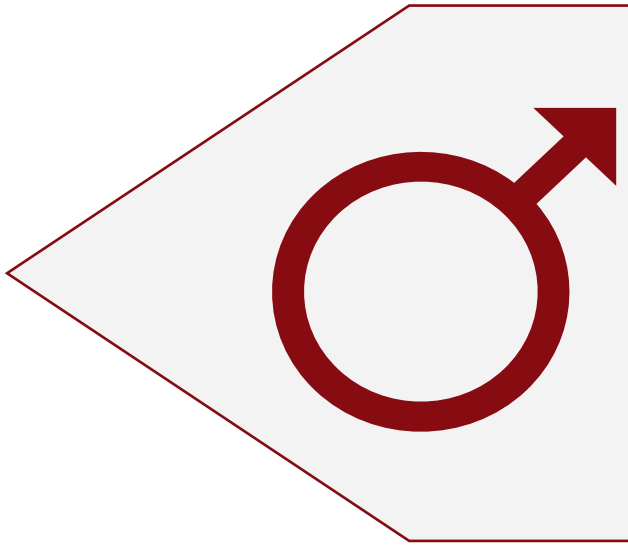
SEXUAL FUNCTION

EVIDENCE SUMMARY – SEXUAL FUNCTION

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

Higano CS. J Clin Oncol 2012;30:3720-5

RECOMMENDATION – SEXUAL FUNCTION



In men desiring improved sexual function, referral to a sex therapist for multimodal treatment should be considered (Expert opinion).

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ADT IMPACTS MULTIPLE DOMAINS OF SEXUAL FUNCTION

- Loss of libido[1]
- Decreased penile and testicular size[2,3]
- Decreased sensitivity to sexual stimulation[1]
- Erectile dysfunction[1]

Loss of libido may occur in up to 90% of men on ADT[1]

1. Higano CS. J Clin Oncol 2012;30:3720-5 **2.** Park KK, et al. J Sex Med 2011;8:3214-9
3. Nguyen PL, et al. Eur Urol 2015;67:825-36

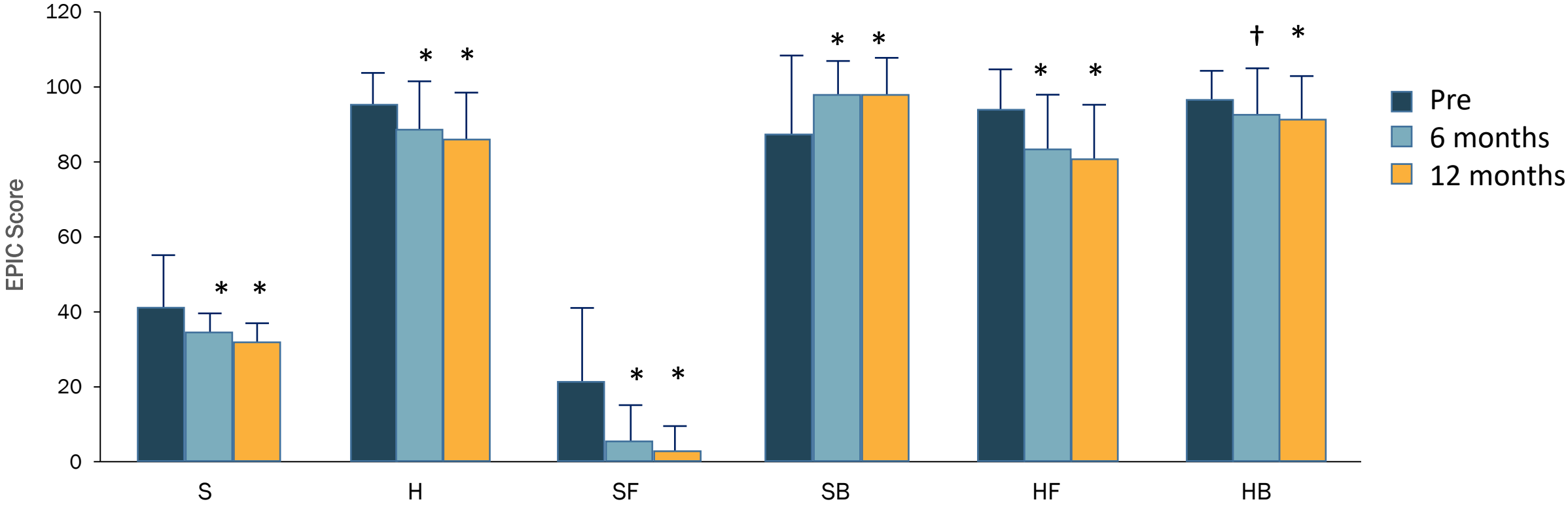
INTERVENTIONS TO HELP MEN MAINTAIN OR PRESERVE SEXUAL FUNCTION WHILE UNDERGOING ADT

- 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

Elliott S, et al. J Sex Med 2010;7:2996-3010

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



*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

Okamoto K, et al. Basic Clin Androl 2015;25:3

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?

EVIDENCE SUMMARY – HEALTH RELATED QUALITY OF LIFE

- ***Patients on ADT experience significant decrements in multiple health-related quality of life (HRQOL) domains.***

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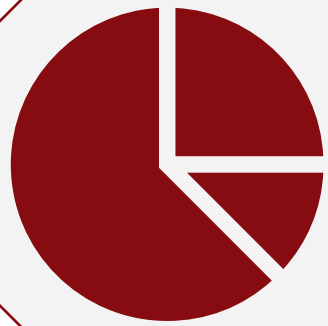
RECOMMENDATIONS – HRQOL

Exercise therapy should be encouraged in all men to improve HRQOL during treatment (LE 2, strong recommendation).

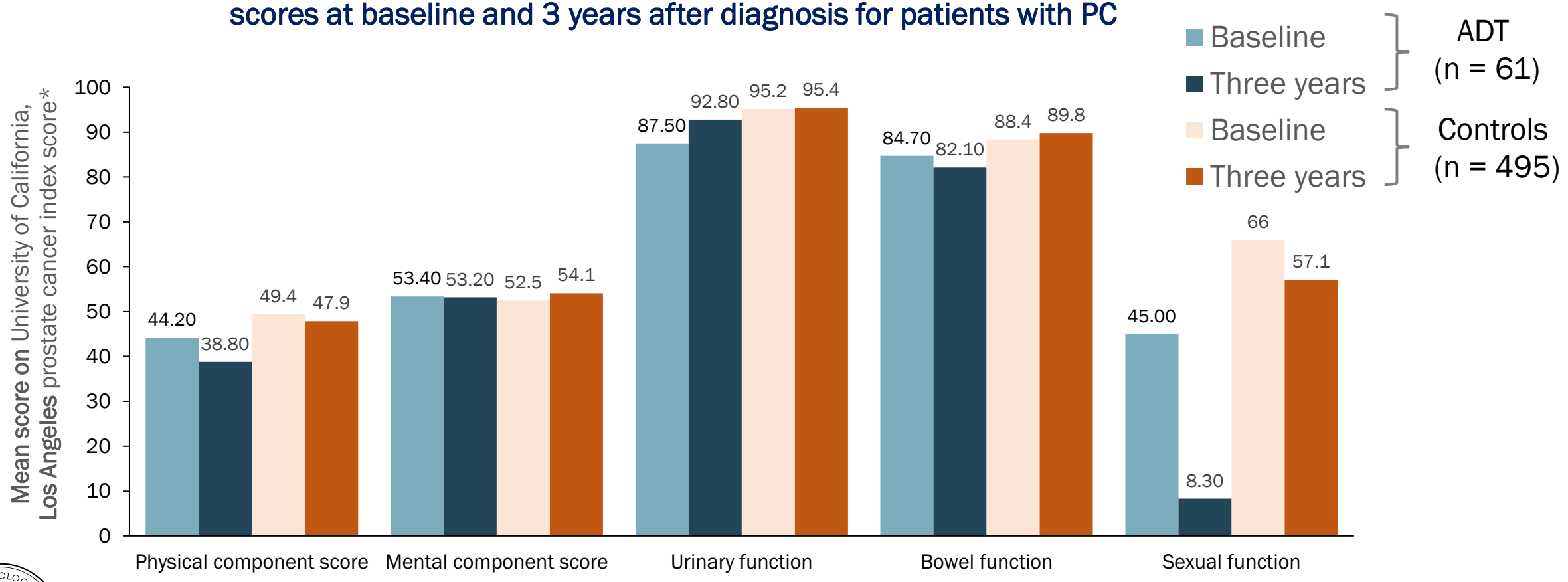


Intermittent ADT improves HRQOL and should be considered in appropriately selected patients (LE 1, strong recommendation).

Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print

ADT IMPACTS VARIOUS ASPECTS OF HRQOL

Mean unadjusted physical, mental, urinary, bowel, and sexual domain scores at baseline and 3 years after diagnosis for patients with PC



*Higher scores indicate better function

Smith DP, et al. BMJ 2009;339:b4817

EXERCISE POSITIVELY IMPACTS VARIOUS AEs ASSOCIATED WITH ADT

- Aerobic exercise
- Resistance exercise
- Impact exercise

OUTCOMES	EXERCISE MODALITY*	LEVEL OF EVIDENCE				
		MA	SR	RCT	OB	QUAL
Aerobic Fitness		✓	✓	✓	✓	✓
Muscular Strength		✓	✓	✓	✓	✓
Body Composition		✓	✓	✓	✓	✓
Fatigue/Energy		✓	✓	✓	✓	✓
Quality of Life		✓	✓	✓	✓	✓
Physical Function			✓	✓	✓	✓
Social Functioning			✓	✓		✓
Psychological Distress				✓	✓	✓
Bone Health				✓	✓	
Co-Morbid Disease Risk Factors				✓	✓	
Sexual Wellbeing				✓		✓
Bone Pain				✓		
Urinary Problems				✓		
Cognitive Decline				✓		

*Shown in order of importance for eliciting results

Cormie P, et al. Urol Oncol 2020;38:62-70

HRQOL – INTERMITTENT ADT

- 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

Kokorovic A, et al. CUAJ 2021 April 21; Epub ahead of print

SUMMARY AND CONCLUSIONS

MULTIDISCIPLINARY MANAGEMENT OF PATIENTS ON ADT

UROLOGIST

RADIATION ONCOLOGIST

MEDICAL ONCOLOGIST

PRIMARY CARE PHYSICIAN

CARDIOLOGIST, ENDOCRINOLOGIST, PSYCHOLOGIST, SEXOLOGIST, ETC

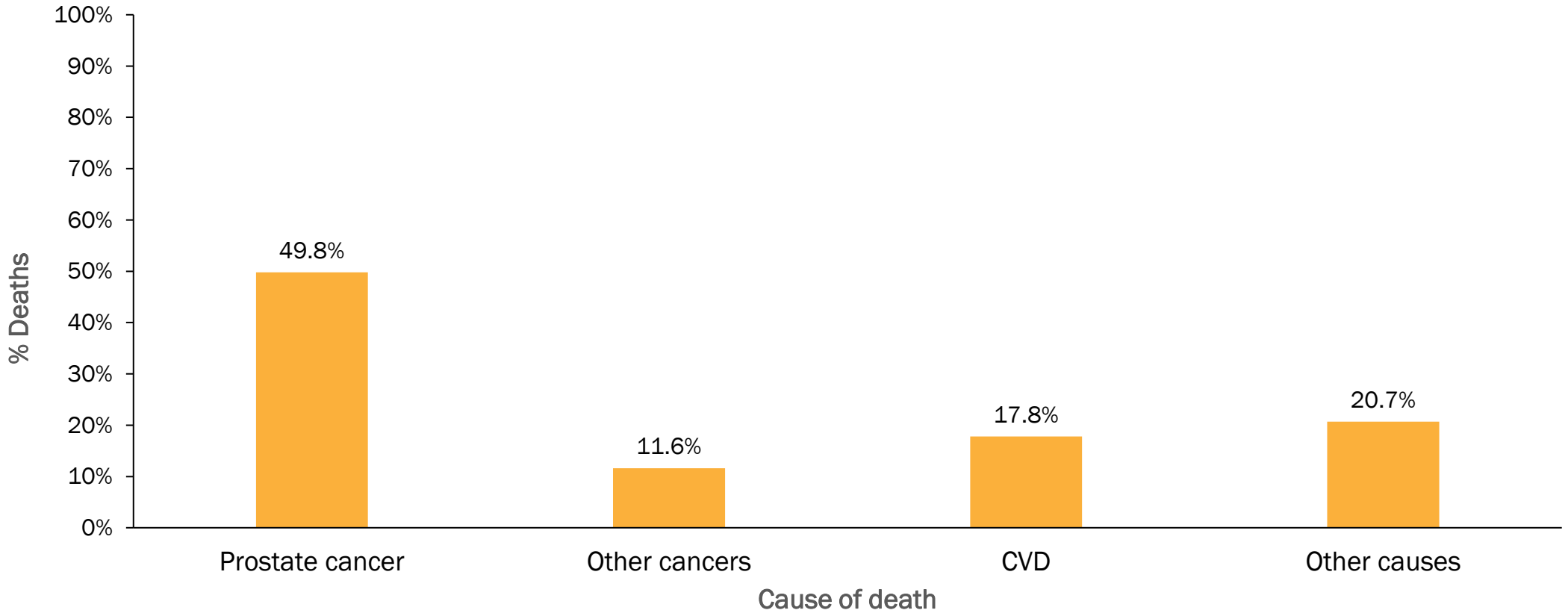
ADT initiation	Baseline investigations	Ongoing management	Monitoring and follow up
	• ***History:*** previous MACE, risk factors for cardiac disease, previous VTE or stroke, fall risk • ***Physical exam:*** weight, waist circumference, BMI, height, BP • ***Labs:*** Fasting plasma glucose, oral glucose tolerance test or HgbA1c, lipid profile, calcium, 25-hydroxyvitamin D • ***Other:*** BMD, 10-year major osteoporotic fracture risk	• General management of ADT-related complications	• 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

SUPPLEMENTARY SLIDES

CVD IS THE LEADING CAUSE OF DEATH IN MEN WITH PC NOT DYING OF THE DISEASE ITSELF

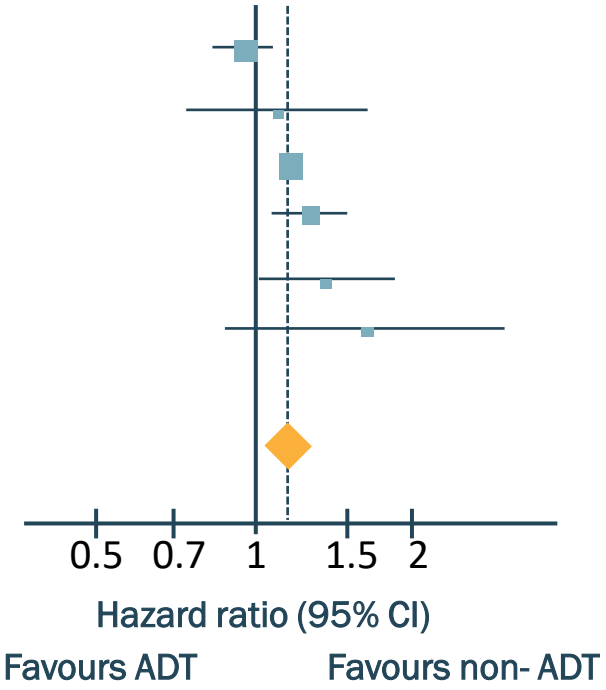


Chowdhury S, et al. BJU Int 2013;112:182-9

ASSOCIATION BETWEEN ADT AND CV MORTALITY

	ADT	Control	Hazard ratio IV, random (95% CI)
Alibhai et al 2009	399/19,079	436/19,079	0.96 (0.83-1.10)
Punnen et al 2011	89/1,087	106/5,676	1.11 (0.73-1.68)
Gandaglia et al 2014	10,592/59,994	11,720/82,535	1.18 (1.12-1.24)
Keating et al 2010	432/13,620	315/23,823	1.29 (1.08-1.55)
Hemelrijck et al 2010	2,434/24,432	1,063/19,526	1.38 (1.02-1.87)
Merino et al 2011	49/1,413	5/335	1.65 (0.87-313)
Total (95% CI)	**13,995/119,625**	**13,645/15,974**	**1.17 (1.04-1.32)**

Heterogeneity: p = 0.04; I^2 = 57%
Test for overall effect: p = 0.01



Zhao J, et al. PLoS One 2014;9:e107516

LINK BETWEEN LHRH AGONISTS AND INCREASE IN NONFATAL CVD

- 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)

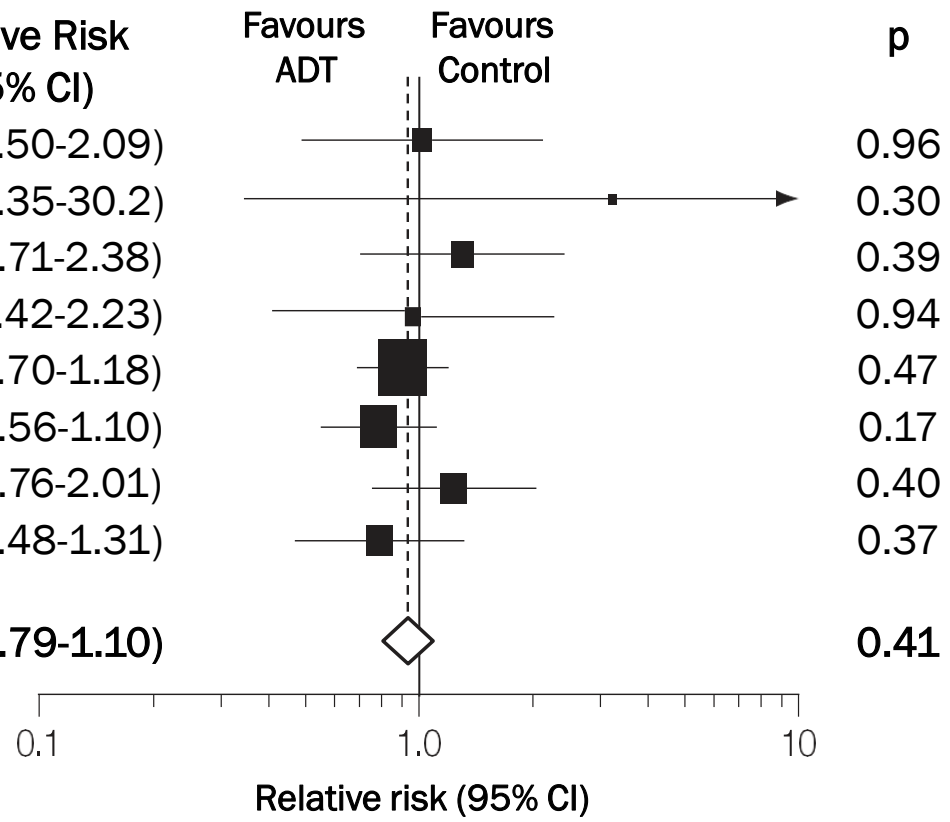
Bosco C, et al. Eur Urol 2015;68:386-96

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

CV MORTALITY

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

Test for heterogeneity: Q = 5.12, p = 0.64, I^2 = 0%



Nguyen PL, et al. JAMA 2011;306:2359-66

PRESENCE OF CARDIAC RISK FACTORS IMPACTS RISK OF CV MORTALITY WITH ADT

PATIENTS	5-YEAR CARDIAC-SPECIFIC MORTALITY, % (95% CI)
ALL PATIENTS, n = 5,077	
Neoadjuvant ADT	1.87 (1.21–2.77)
No neoadjuvant ADT	1.59 (1.13–2.17)
PATIENTS WITH NO CARDIAC COMORBIDITY, n = 2,653	
Neoadjuvant ADT	1.08 (0.48–2.14)
No neoadjuvant ADT	1.27 (0.76–2.00)
PATIENTS WITH DIABETES MELLITUS, HYPERTENSION, OR HYPERCHOLESTEROLEMIA, n = 2,168	
Neoadjuvant ADT	2.09 (1.05–3.76)
No neoadjuvant ADT	1.97 (1.20–3.05)
PATIENTS WITH CHF OR MI, n = 256	
Neoadjuvant ADT	7.01 (2.82–13.82)
No neoadjuvant ADT	2.01 (0.38–6.45)

Ziehr DR, et al. BJU Int 2015;116:358-65

ASSOCIATION BETWEEN CV RISK FACTORS AND USE OF ADT IN THE RADICAL-PC TRIAL

	ADT (VS. NO ADT)	
	UNIVARIABLE OR (95% CI)	MULTIVARIABLE OR (95% CI)
Hypertension	1.22 (1.03–1.43)	0.90 (0.75–1.09)
Diabetes	1.53 (1.23–1.89)	1.23 (0.96–1.56)
Total cholesterol > 4 mmol/L	0.77 (0.64–0.93)	1.07 (0.86–1.32)
Current/former smoker	1.28 (1.08–1.51)	1.12 (0.93–1.35)
Known CV disease	1.57 (1.29–1.90)	1.14 (0.91–1.41)
Framingham score ≥ 15	1.97 (1.64–2.36)	1.06 (0.86–1.29)

Although there is a positive association between a plan to use ADT and baseline CV risk factors, this association is explained by confounding factors.

Leong DP, et al. J Urol 2020;203:1109-16

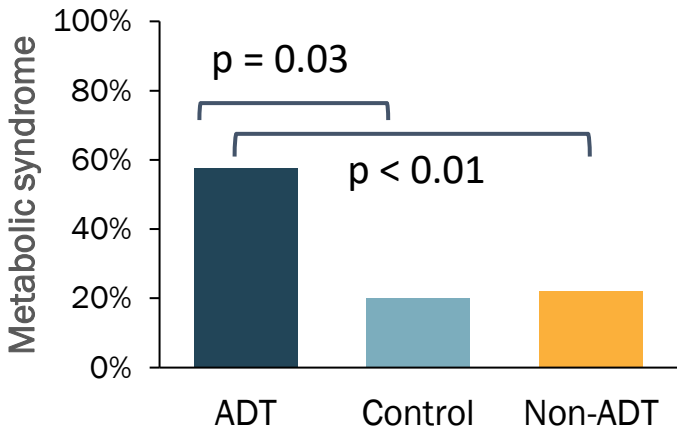
ADT IS ASSOCIATED WITH AN INCREASED RISK OF VTE

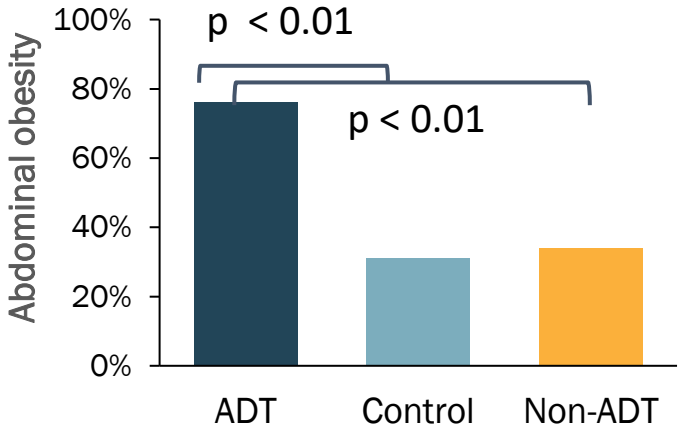
ADT EXPOSURE	EVENTS, N	PERSON-YEARS	INCIDENCE RATE (95% CI)*	CRUDE HR (95% CI)	ADJUSTED HR (95% CI)†
Nonuse	183	38,375	4.77 (4.10–5.51)	1.00 [ref]	1.00 [ref]
LHRH agonists only	195	24,607	7.92 (6.85–9.12)	1.86 (1.51–2.29)	1.52 (1.22–1.91)
LHRH agonists and oral antiandrogens	68	4,206	16.17 (12.55–20.50)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

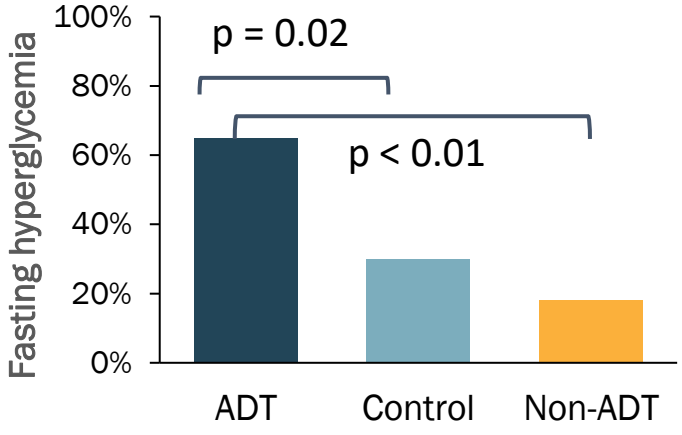
*Per 1,000 person-years
†Adjusted for age, year of PC diagnosis, excessive alcohol use, smoking status, obesity, chronic kidney disease, MI, ischemic stroke, transient ischemic attack, peripheral arterial disease, previous cancer, inflammatory bowel disease, aspirin, other nonsteroidal anti-inflammatory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

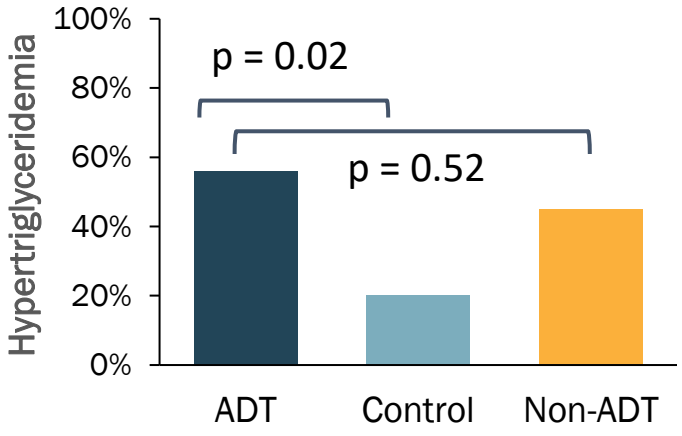
Klil-Drori, et al. Eur Urol 2016;70:56-61

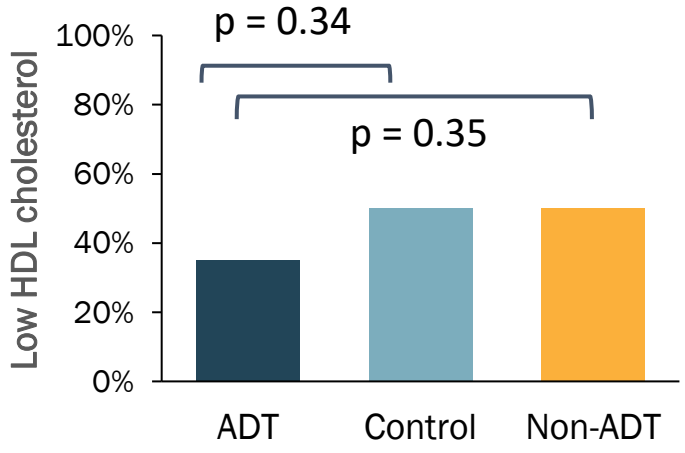
ADT IS ASSOCIATED WITH A HIGHER RISK OF METABOLIC SYNDROME

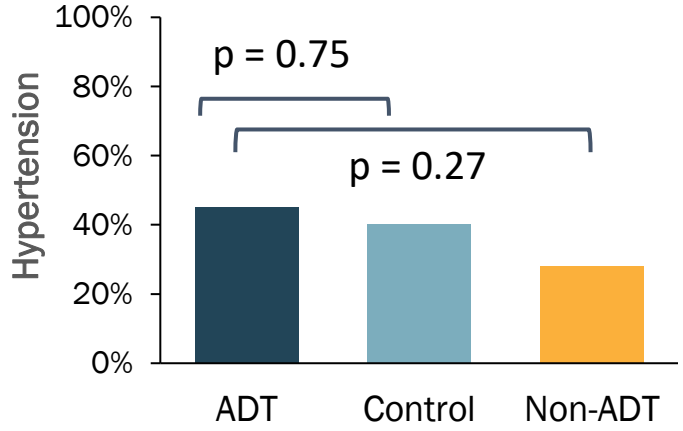








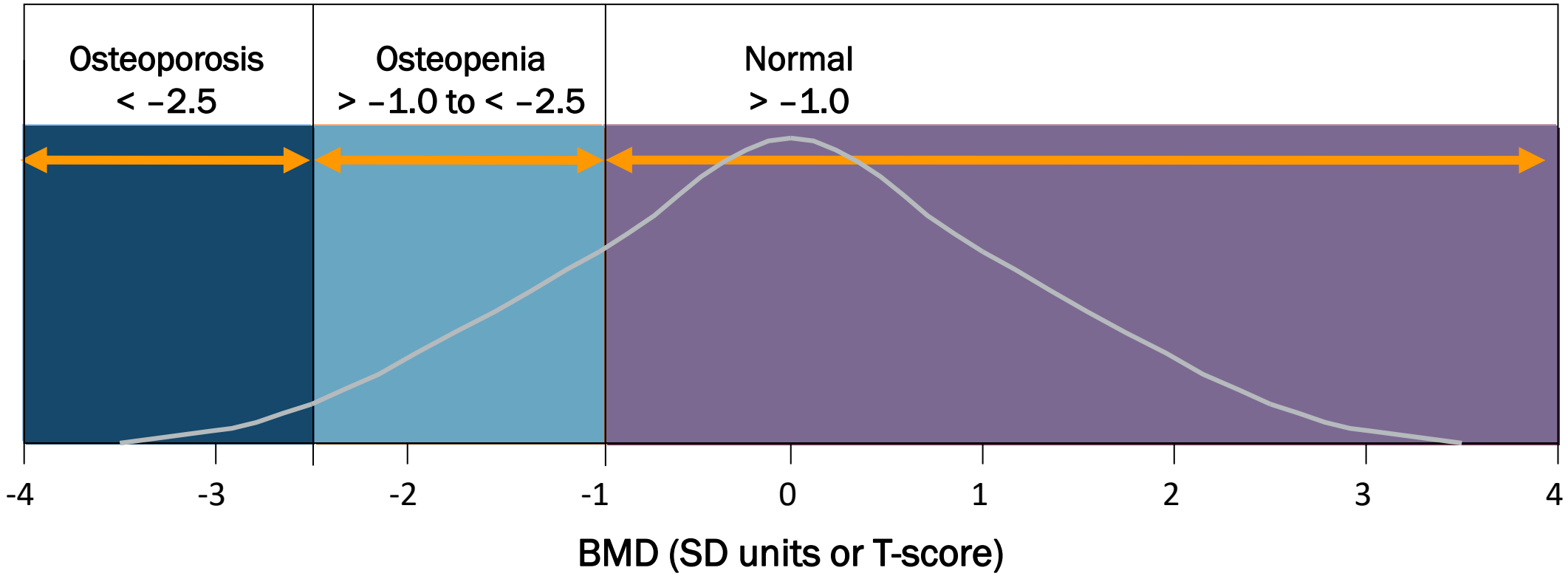




Braga-Basaria M, et al. J Clin Oncol 2006;24:3979-83

ASSESSMENT OF BONE HEALTH

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).



Papaioannou A, et al. CMAJ. 2010;182:1864-73

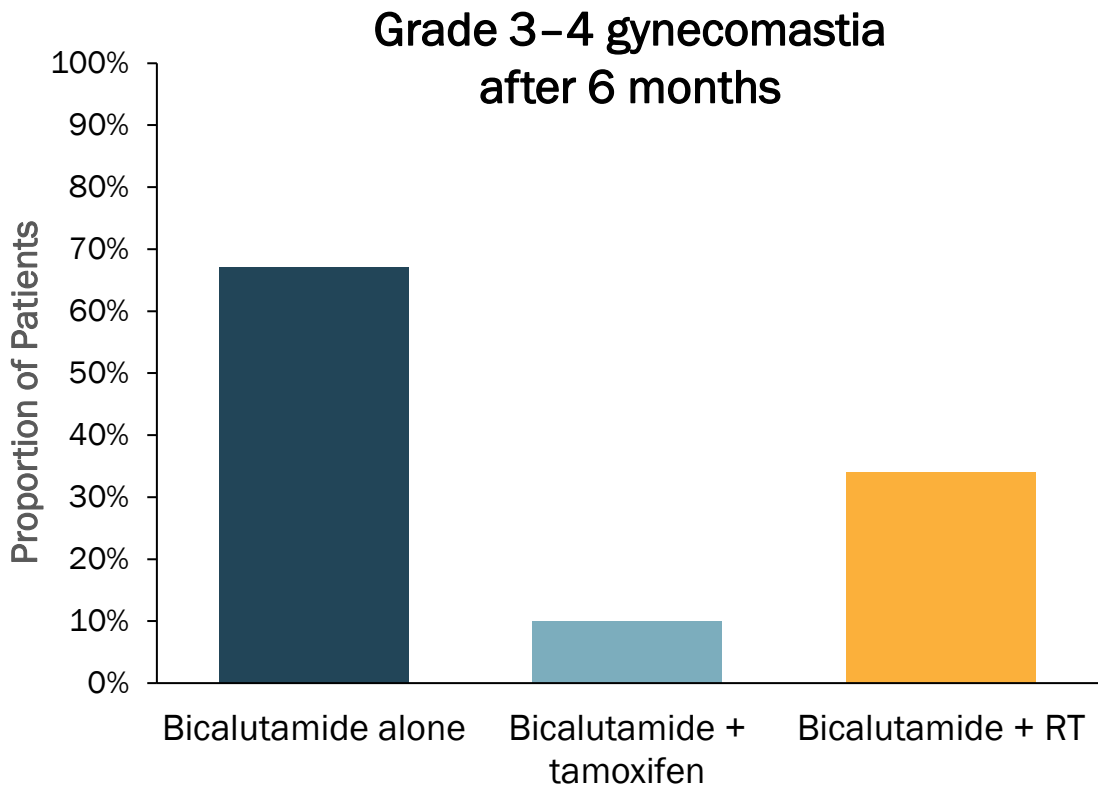
INTERMITTENT THERAPY MAY ALLEVIATE VASOMOTOR SYMPTOMS

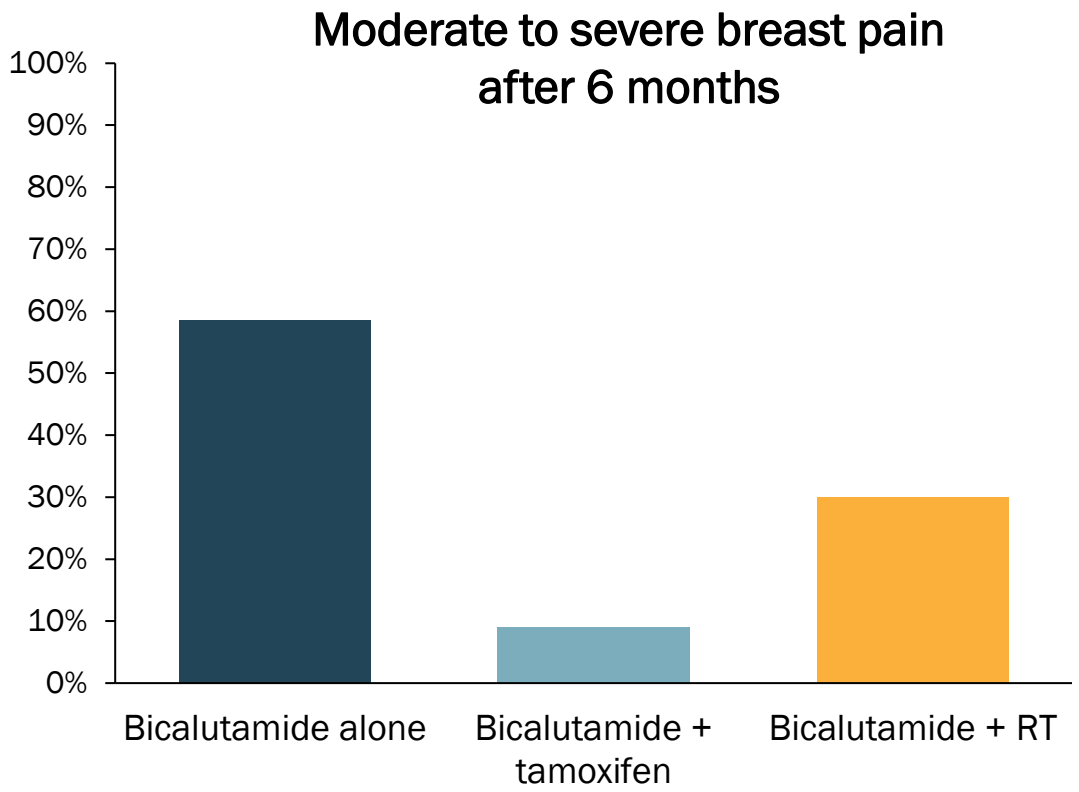
- RCT of CADT (n =696) vs. IADT (n = 690) after radiotherapy
- IADT was noninferior to CADT with respect to OS, with significantly better scores for:
  - Hot flashes ($p < 0.001$)
  - Desire for sexual activity ($p < 0.001$)
  - Urinary symptoms ($p = 0.006$)

CADT Continuous ADT
IADT Intermittent ADT

Crook JM, et al. N Engl J Med 2012;367:895-903.

GYNECOMASTIA AND MASTODYNIA





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

Perdonà S, et al. Lancet Oncol 2005;6:295-300