Canadian Urological Association
The Voice of Urology in Canada

Association des Urologues du Canada
La voix de l'urologie au Canada

ADT Management

Ricardo A. Rendon, MD, MSc, FRCSC

Professor, Department of Urology
Dalhousie University

Chair, Genito-Urinary Cancer Site Team
Cancer Care Nova Scotia

VP Education, Canadian Urological Association

Disclosures

Relationships with financial sponsors:

- Advisory Board: Astellas, Amgen, AbbVie, AstraZeneca, Bayer, Ferring, Janssen, Sanofi, TerSera
- Speakers' Bureau: Amgen, Astellas, Bayer, Ferring, Janssen
- Grant/Honorarium: Astellas, Amgen, Bayer, Janssen
- Clinical Trial: Abbvie, Amgen, Astellas, AstraZeneca, Ferring, Janssen, Pfizer, Sanofi, Myovant

Learning Objectives

By the end of this presentation, participants will:

- discuss the adverse side effects of ADT for the treatment of prostate cancer

Androgen Deprivation Therapy: Adverse Events and How to Manage Them

Recommendations from the Canadian Urological Association (CUA)

CUA GUIDELINE

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

Andrea Kokorovic, MD[1]; Alan I. So, MD[2]; Hosam Serag, MD2; Christopher French, MD[3]; Robert J. Hamilton, MD[4]; Jason P. Izard, MD[5]; Jasmir G. Nayak, MD[6]; Fréderic Pouliot, MD[7]; Fred Saad, MD[1]; Bobby Shayegan, MD[8]; Armen Aprikian, MD[9]; Ricardo A. Rendon, MD[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

Androgen Deprivation Therapy

- Backbone therapy of the contemporary management of PCa
- Is associated with significant adverse events that span across multiple organ systems

The overall goal of the clinician is to optimize oncological outcomes while maintaining acceptable health related QoL

CV cancer survivorship issues begin at the time of diagnosis… not years after completion of treatment

Domains Affected by ADT


Cardiometabolic health


Bone health


Hot flashes


Breast events


Cognitive function


Fatigue and anemia


Sexual function


Health related quality of life

Cardiometabolic Health

Cardiometabolic Health

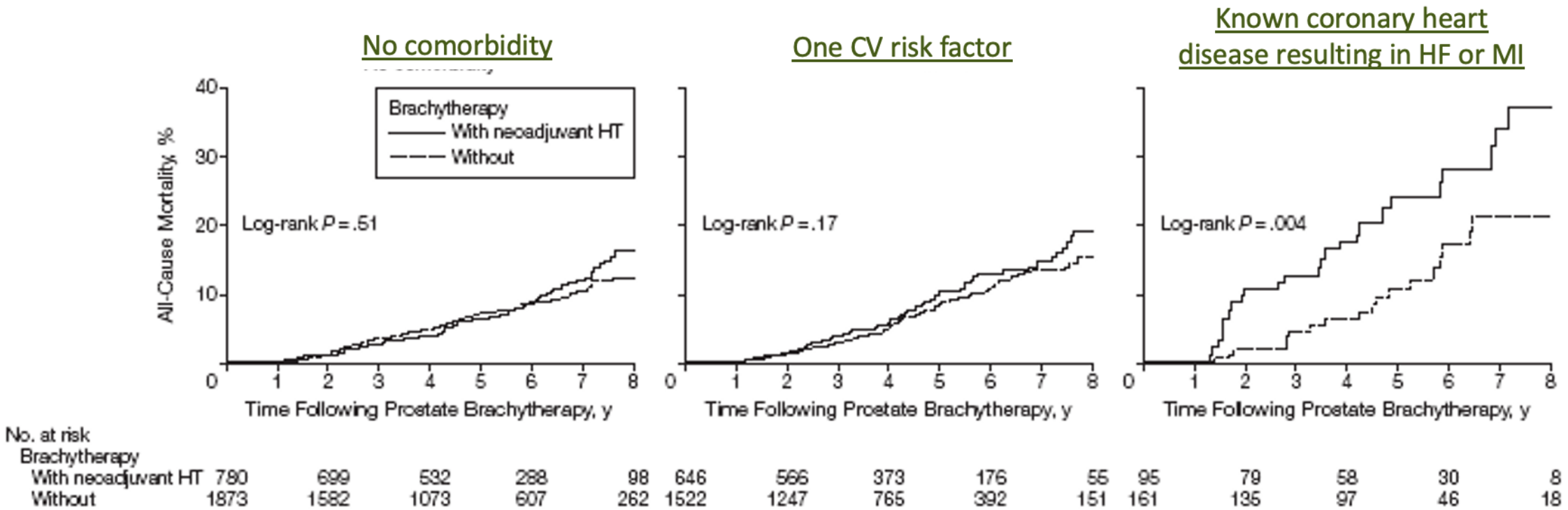
- The term cardiometabolic health collectively refers to the effects of ADT on CVD, body composition and metabolic parameters (lipid profiles, insulin resistance and glucose homeostasis)

- ADT impacts multiple domains of cardiometabolic health

- Medical optimization of risk factors is critical to mitigating ADT-related complications

Patients with pre-existing cardiovascular disease are at risk of new cardiovascular events.

Risk of **All-Cause Mortality** in 5077 localized/locally advanced PCa treated Brachytherapy ± Neoadjuvant HT (**median 4 months**)



HT: hormone therapy; CV: cardiovascular; HF: heart failure; MI: myocardial infarction.
Nanda et al. JAMA 2009; 302:866-73

- Proven impact on CV risk factor
- Proven impact on CV events
- Disputable effect of CV death

American Heart Association®
Learn and Live℠

Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology.
Levine et al. Circulation 2010;121;833-840;

FDA U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

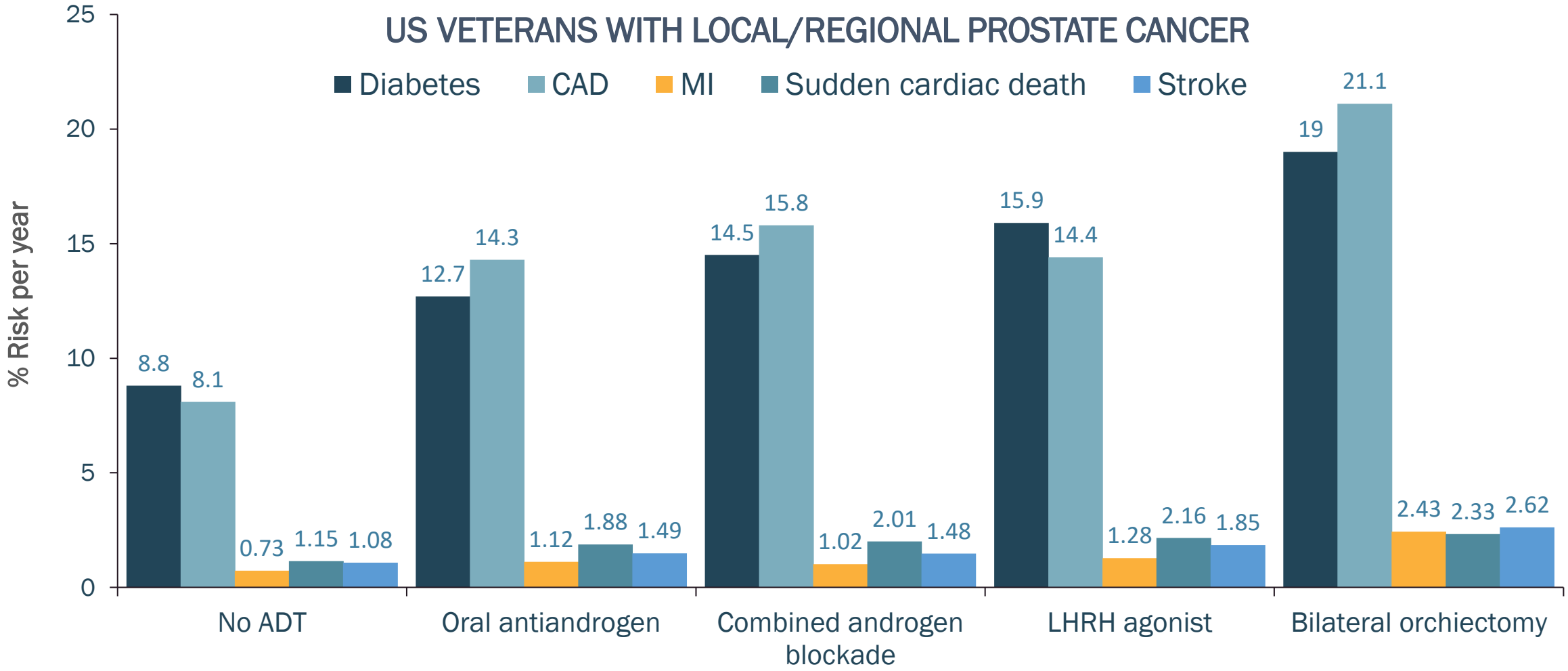
[10-20-2010] The U.S. Food and Drug Administration (FDA) has notified the manufacturers of the Gonadotropin-Releasing Hormone (GnRH) agonists of the need to add new safety information to the Warnings and Precautions section of the drug labels. This new information warns about increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer.

Recalls and safety alerts — Canada

GnRH Agonists: Heart-related Risk in Men Treated for Prostate Cancer

Starting date: September 8, 2011
Posting date: September 8, 2011

RISK OF DIABETES, CAD, MI, SUDDEN DEATH AND STROKE WITH ADT

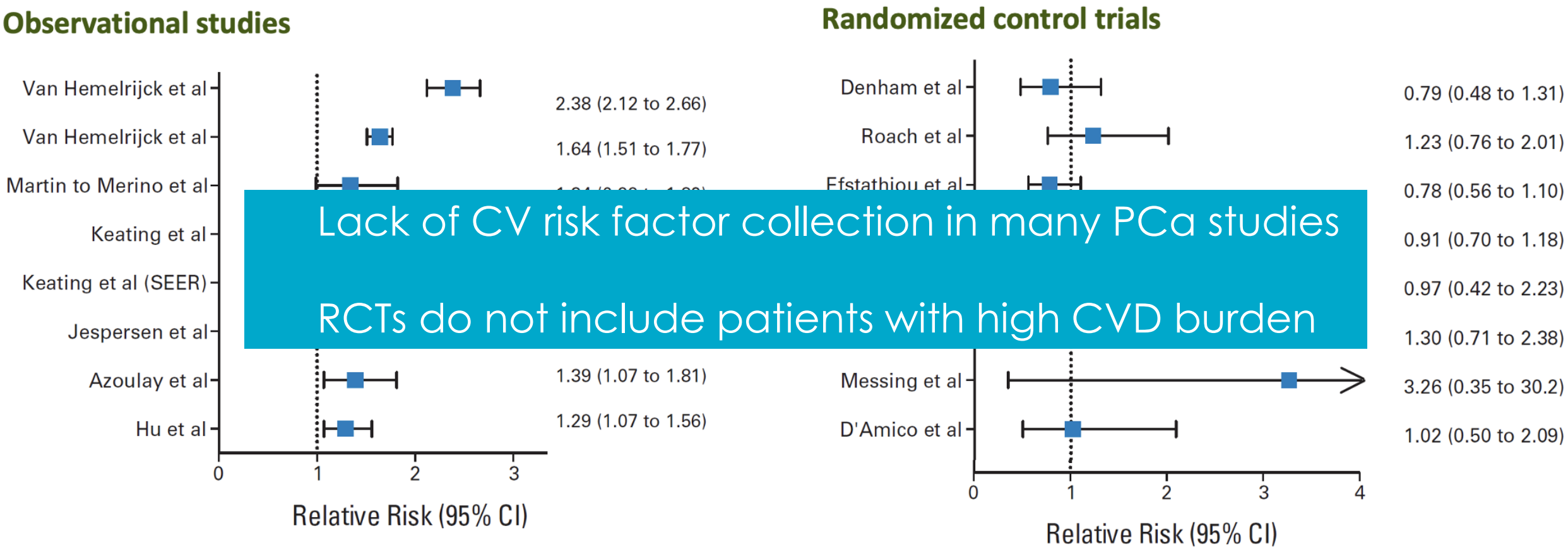


Combined androgen blockade, LHRH agonist treatment, and bilateral orchiectomy associated with increased risk for diabetes and CV events

CAD Coronary artery disease

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

Risk and timing of cardiovascular disease after ADT in men with PCa.



Lack of CV risk factor collection in many PCa studies

RCTs do not include patients with high CVD burden

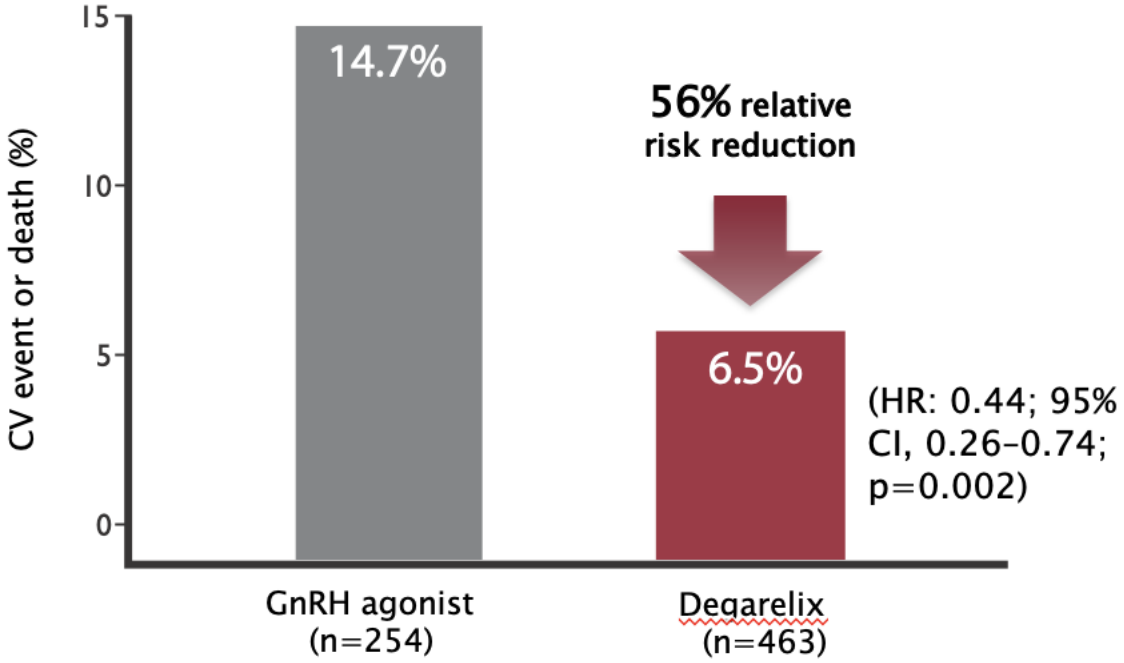
CI, confidence interval; CVD, cardiovascular disease; LHRH, luteinizing hormone-releasing hormone; RCT, randomized control trial; SEER, surveillance, epidemiology, and end results

O'Farrell S, et al. J Clin Oncol 2015;33:1243–51

GnRH Antagonists vs Agonists

Degarelix showed a 56% lower risk of a CV event or death during 1st year of treatment in men with pre-existing CVD compared to LHRH agonists.

Risk reduction of CV events or death after the first year of treatment in men with pre-existing CVD (n=708)



The absolute risk reduction after the first year was **8.2%**, which yielded a number needed to treat to avoid 1 CV event or death of 12

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; GnRH, gonadotropin-releasing hormone; HR, hazard ratio

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

Degarelix is associated with lower all-cause mortality rates and CV events as compared with GnRH agonists

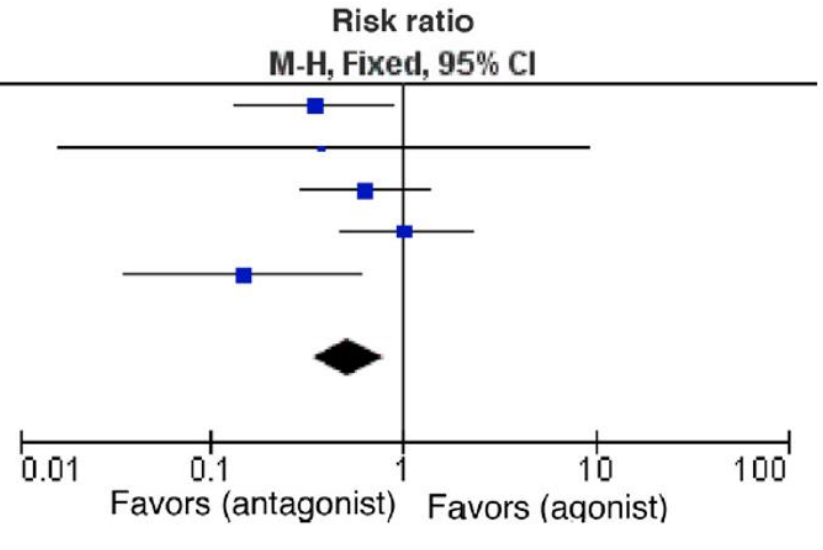
A total of 2,632 patients were included in the meta-analysis, 986 patients received an LHRH agonist (leuprorelin or goserelin) and 1,646 patients received degarelix®[1]

- Cardiovascular events were less frequent in the FIRMAGON® group vs the LHRH agonist group (RR: 0.52, 95% CI: 0.34– 0.80, p = 0.003)
- The probability of overall survival at 1 year was significantly higher for patients treated with FIRMAGON® vs LHRH agonists (RR: 0.48, 95% CI: 0.26–0.90, p = 0.02)

	Antagonist		Agonist			Risk ratio	
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
CS21	7	409	10	201	24.8%	0.34 (0.13, 0.89)	2009
CS31	0	81	1	92	2.6%	0.38 (0.02, 9.15)	2012
CS35	14	565	11	282	27.2%	0.64 (0.29, 1.38)	2015
CS37	13	225	10	178	20.7%	1.03 (0.46, 2.29)	2016
Margel 2019	2	41	13	39	24.7%	0.15 (0.04, 0.61)	2019
Total (95% CI)		**1321**		**792**	**100.0%**	**0.52 (0.34, 0.80)**	
Total events	36		45				

Heterogeneity: Chi² = 6.87, df = 4 (p = 0.14); I² = 42%

Test for overall effect: Z = 3.00 (p = 0.003)

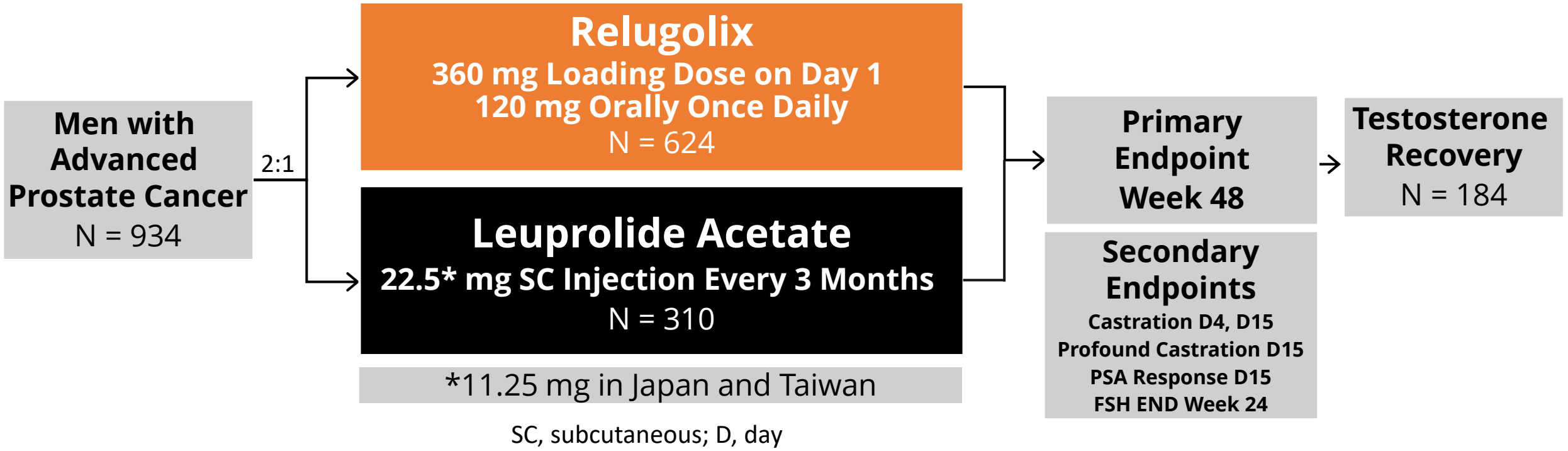


CI; confidence interval; CV: cardiovascular; LHRH, luteinising hormone-releasing hormone; OS, overall survival; RR, risk reduction.

Abufaraj VM et al. Eur Urol. 2021;79(1):44–53.

Phase 3 HERO Study Design

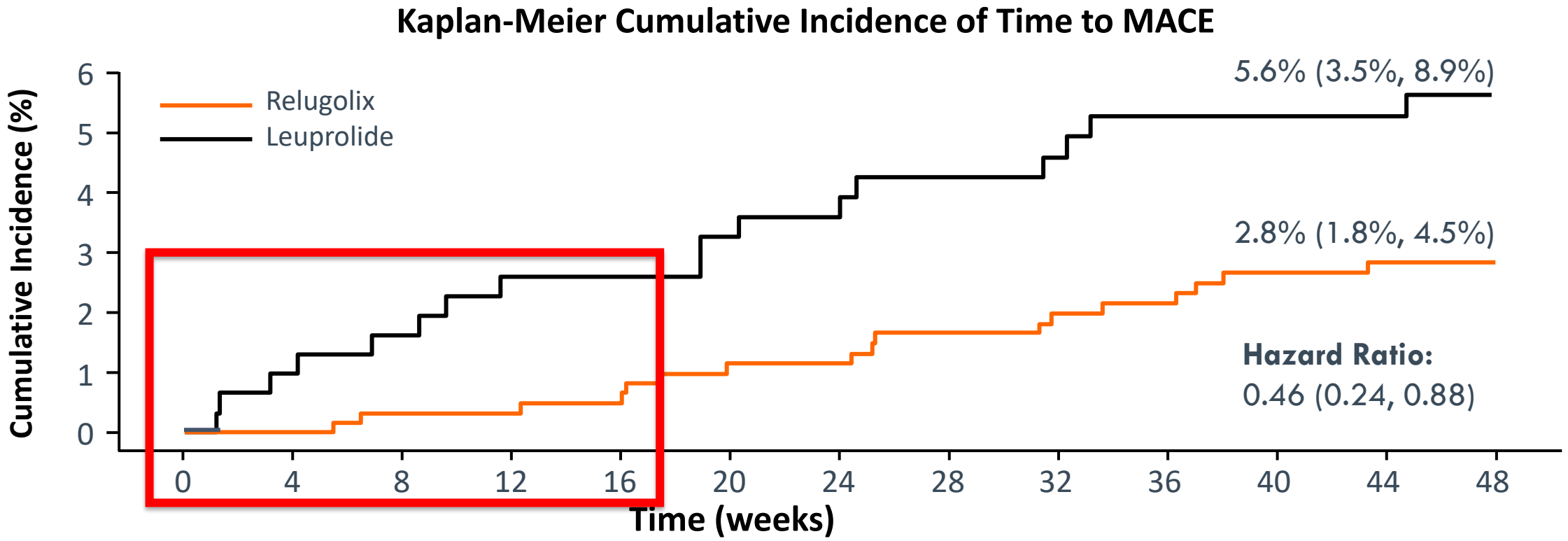
- A multinational phase 3 randomized, open-label, parallel group study to evaluate the safety and efficacy of relugolix in men with advanced prostate cancer
- **Primary Endpoint**: Sustained castration through 48 weeks (< 50 ng/dL)



SC, subcutaneous; D, day

Shore N, Saad F et al. N Engl J Med. 2020 Jun 4;382(23):2187-2196

54% Reduction in Risk of Major Adverse Cardiovascular Events (MACE)



No. of Patients at Risk

Relugolix	622	621	616	610	605	596	595	588	582	575	563	559	538
Leuprolide	308	305	303	298	298	293	292	288	281	279	278	269	259

MACE = non-fatal myocardial infarction + non-fatal stroke + all-cause mortality.

Shore N, Saad F et al. N Engl J Med. 2020 Jun 4;382(23):2187-2196

PRONOUNCE Trial

- The primary outcome (MACE):
  - 5.5% in the degarelix group
  - 4.1% in the leuprolide group (p = 0.53)
- Secondary outcomes:

Routine monitoring of adverse events and optimization of cardiac risk factors throughout ADT treatment may reduce cardiac morbidity

- The relative CV safety of these agents remains unknown

Cardiometabolic Health

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 / Cerebrovascular	• ADT may increase the risk of venous thromboembolism 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

Cardiometabolic Health – Summary of Evidence

Metabolic Parameters

- 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

Cardiometabolic Health – Recommendations

Role of the prescribing physician

- The patient's PCP should be informed that the patient has been initiated on ADT and that there may be adverse events associated with this therapy (EO)

History and physical examination

- Providers should obtain a comprehensive baseline PE prior to ADT initiation: BP, weight, waist circumference, and calculation of BMI (EO)

Laboratory investigations

- Providers should order baseline laboratory investigations: fasting plasma glucose and lipid profile (triglycerides, LDL cholesterol, HDL cholesterol, and total cholesterol) (EO)
- Pts should be screened for diabetes with fasting plasma glucose, oral glucose tolerance test or Hgb A1c level (EO)

IDENTIFICATION OF PATIENTS WITH PRE-EXISTING CV DISEASE

STAMP – Identification of patients with CV disease

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

In patients **without** pre-existing CV disease – calculate a Framingham or equivalent risk score and treat accordingly

Management

- Pts should have their BP monitored and HTN should be treated (EO)
- Dyslipidemia should be treated according to current best practice guidelines (EO)
- Continue metabolic assessments at 6–12-month intervals (EO)

Lifestyle Modifications

- Lifestyle modifications (smoking cessation, dietary modifications, exercise) should be strongly encouraged (EO)
- Pts should attend supervised exercise programs using resistance and aerobic training (Level of evidence [LE] 2, strong recommendation)

Other Recommendations

- In pts with a history of MI or stroke, referral to a cardiologist or cardio-onc may be considered for medical optimization prior to initiating ADT (EO)
- Use of a GnRH antagonist may be considered in men with a prior history of MI or stroke (LE 2, weak recommendation)

ENGAGING THE PCPs IN MANAGING CV RISK

Family physicians can play a key role in CV risk stratification:

- Routine medical history
- Physical exam
- Labs:
  - Lipid profile
  - HbA1c
  - Uric acid
  - Serum electrolytes
  - Creatinine
  - Complete blood count (CBC)
- Electrocardiogram (ECG)
- Calculate risk scores
- Working with patients to reduce their CV risk:
  - Encourage a healthier lifestyle
  - Address risk factor management (e.g., smoking cessation)

HbA1c Glycated hemoglobin

Kenk M, et al. Can Urol Assoc J 2020;14:E458-E464

Bone Health

Bone Health – Summary of Evidence

Use of ADT in men with PCa has detrimental effects on bone health

- decreased bone mineral density (BMD)
- osteoporosis
- increased risk for clinical fractures

Bone Health – Recommendations

History, Physical Examination and Laboratory Investigations

- Comprehensive history and physical examination should be performed prior to initiating ADT (Expert opinion)
  - fall risk
  - height measurement
- Obtain baseline calcium and 25-hydroxyvitamin D levels at the start of ADT (Expert opinion)

Bone Health – Recommendations

Lifestyle Recommendations

- Counsel patients regarding smoking and alcohol cessation (Expert opinion)
- Encourage patients to participate in exercise therapy (LE 2, strong recommendation)

Calcium and Vitamin D

- 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)

Bone Health – Fracture Risk Assessment

Assess all men initiating ADT for fracture risk

- Screen men initiating long-term ADT for osteoporosis with 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)
- Asses the osteoporotic fracture risk using a validated tool (Expert opinion)

Bone Health – Mitigate Fracture Risk

Men at risk for fracture should be treated and closely monitored

- Treat with a bisphosphonate or denosumab men with:
  - osteoporosis
  - history of fragility fractures in the hip or spine
  - history of multiple fragility fractures
  - moderate or high 10-year fracture risk

(LE 1, strong recommendation)

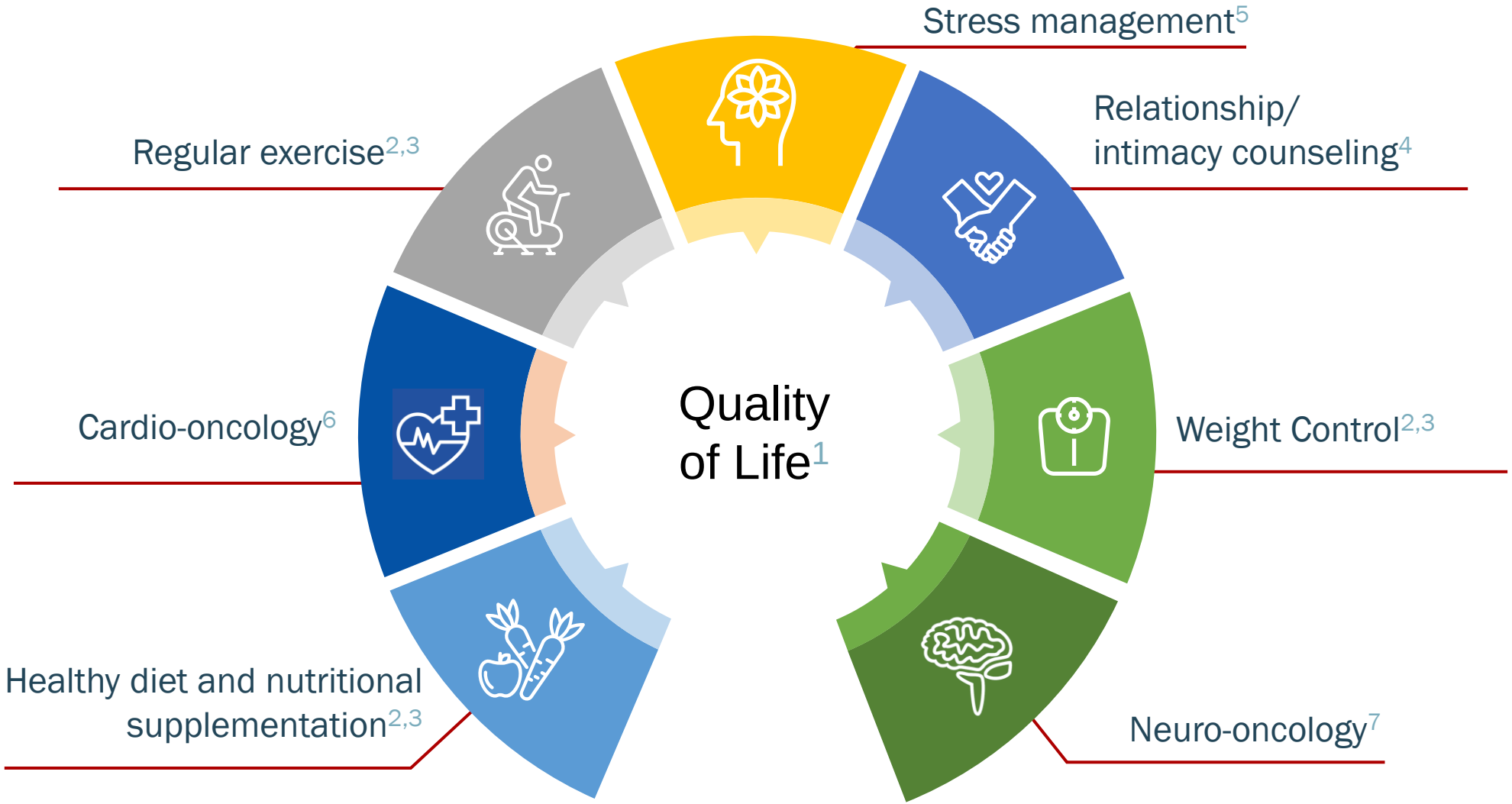
- DXA should be repeated every 2–3 years in men at low risk for fractures receiving ADT
- If osteopenia or a moderate or high risk for fractures, DXA should be repeated every 1–2 years until treatment cessation
- Patients started on pharmacological therapy should have f/u DXA to assess for treatment response

(Expert opinion)

ADT – Other Common Adverse Events

- Hot flashes
- Breast events
- Cognitive function
- Fatigue and anemia
- Sexual function
- HR QoL

MAINTAINING QUALITY OF LIFE WHILE ON ADT



1. Kokorovic A, et al. CUAJ 2021;15:7355 **2.** O'Neill RF, et al. J Cancer Surviv 2015;9:431-40 **3.** Ying M, et al. Jpn J Clin Oncol 2018;48:827-834
4. Duthie CJ, et al. Crit Rev Oncol Hematol 2020;153:103064 **5.**Penedo FJ, et al. J Clin Psychol Med Settings 2013;20:25-32
6. Latorzeff I, et al. Cancer Radiother 2016;20:405-10 **7.** Yiannopoulou KG, et al. Curr Urol 2020;14:169-177

Conclusions

Androgen Deprivation Therapy

- ADT improves survival in men with PC and is a mainstay of treatment
- ADT is associated with AEs that span multiple organ systems and should be reserved for those who are likely to derive an oncological benefit
- Even more relevant in the era of enhanced treatment for advanced PCa
- Patients require appropriate counselling regarding adverse events
- PCPs need to be involved in the management of these patients
- Multidisciplinary approach is needed to manage potential complications of ADT

CUA-developed Tools

UROpedia CANADA

www.cua.org/uropedia

ADT Adverse Events

Adverse event	Management (assess every 6-12 months while on therapy)	Date: MM/DD/YY
Cardiovascular disease Increased risk for cardiac events Increased risk for stroke Increased risk for DVT/PE PCP PCP + SPEC	Assess for symptoms of cardiovascular disease (eg. angina, SOB, decreased exercise tolerance, symptoms of HF, claudication) * Patients with a history of stroke or MI may be at increased risk for further major cardiovascular events as a result of ADT use and may benefit from referral to cardio-oncology Check and maintain good blood pressure control Counsel regarding importance of smoking avoidance/cessation	Symptoms ☐ Yes ☐ No Referral ☐ Yes ☐ No BP ☐ Smoker ☐ Yes ☐ No
Body composition Increased BMI Increased percentage body fat Decreased muscle mass PCP + SPEC	Maintain a healthy weight Recommend 150 minutes of aerobic and resistance exercise per week, preferably in a supervised setting	☐ Weight (kg) ☐ Waist circumference (cm) ☐ Height (cm) ☐ BMI (kg/m²) Meeting goal? ☐ Yes ☐ No
Metabolic changes Insulin resistance/glucose intolerance Increased risk for diabetes Worse glycemic control Altered lipid profile Increased risk for metabolic syndrome	Assess lipid profile and treat dyslipidemia as per best practice Assess glycemic control and treat hyperglycemia/diabetes as per best practice Assess for metabolic syndrome and treat as per best practice	LDL-C ☐ nonHDL-C ☐ On therapy? ☐ Yes ☐ No HgBA1c ☐ % Oral GTT ☐ Fasting BGL ☐ On therapy? ☐ Yes ☐ No

NOTICE OF POTENTIAL DRUG-DRUG INTERACTIONS

Patient Name: _____

Urology/Oncology Provider

Name: _____ Phone: (___) _____

Family Physician

Name: _____ Phone: (___) _____

Other Healthcare Professional

Name: _____ Phone: (___) _____

Prostate Cancer Diagnosis

- ☐ Metastatic hormone-sensitive prostate cancer
- ☐ Non-metastatic castration-resistant prostate cancer
- ☐ Metastatic castration-resistant prostate cancer

New Drug Prescribed

- ☐ **abiraterone acetate** (with prednisone)
- ☐ **apalutamide**
- ☐ **darolutamide**
- ☐ **enzalutamide**

For Patients and their Healthcare Professionals,

The patient above has been prescribed a drug therapy for prostate cancer, and there is a potential for drug-drug interactions with medication(s) the patient is currently taking, flagged below.

- **Note the flagged medications and possible impact on drug effects (see both sides of this page)**
- Contact the urology/oncology provider should there be concerns about drug therapy
- Patients should use one pharmacy only, and always carry a list of current medications
- Consider potential drug interactions with future treatment modifications, natural health products, and complementary or alternative medicines

The following tables include medications **more commonly** encountered in patients undergoing treatment for prostate cancer; these tables are **not comprehensive**.

☐ Abiraterone acetate

↑ Drug effects	↓ Drug effects	↑ Abiraterone effects	↓ Abiraterone effects
Monitor/Modify:	***Monitor/Modify:***		***Avoid combination:***
☐ Amitriptyline[1]	☐ Codeine[1]		☐ **Carbamazepine**[2]
☐ Aripiprazole[1]	☐ Tramadol[a,1]		☐ **Phenobarbital**[2]
☐ Brexpiprazole[1]			☐ **Phenytoin**[2]
☐ Carvedilol[1]			***Monitor/Modify:***
☐ Clomipramine[1]			☐ Primidone[1]
☐ Clozapine[1]			☐ Spironolactone[1]
☐ Desipramine[1]			
☐ Haloperidol[1]			
☐ Imipramine[1]			
☐ Metoprolol[1]			
☐ Nortriptyline[1]			
☐ Paroxetine[1]			
☐ Pioglitazone[1,2]			
☐ Propranolol[1]			
☐ Repaglinide[1,2]			
☐ Risperidone[1]			
☐ Tamsulosin[1]			

a. Abiraterone acetate may decrease serum concentrations of tramadol active metabolite(s) and increase tramadol serum concentrations; monitor for decreased opioid effects.

☐ Apalutamide

↑ Drug effects	↓ Drug effects		↑ Apalutamide effects	↓ Apalutamide effects
Monitor/Modify:	***Avoid combination:***	***Monitor/Modify cont.:***	***Monitor/Modify:***	
☐ Clopidogrel[1]	☐ **Apixaban**[1]	☐ Clarithromycin[a,1]	☐ Clarithromycin[a,1]	
	☐ **Dabigatran**[1]	☐ Clonazepam[1]	☐ Gemfibrozil[1,3]	
	☐ **Dronedarone**[1]	☐ Clozapine[1]	☐ Ketoconazole[b,3]	
	☐ **Esomeprazole**[1]	☐ Oxycodone[1]		
		☐ Perampanel[1]		
		☐ Phenytoin[1]		

Canadian Urological Association
The Voice of Urology in Canada

Association des Urologues du Canada
La voix de l'urologie au Canada

ADT Management

Ricardo A. Rendon, MD, MSc, FRCSC

Professor, Department of Urology
Dalhousie University

Chair, Genito-Urinary Cancer Site Team
Cancer Care Nova Scotia

VP Education, Canadian Urological Association