Managing cardiovascular and skeletal comorbidities

Amit Bahl
Consultant Oncologist
Bristol Cancer Institute, University Hospitals Bristol
Clinical Director, Spire Oncology Centre
UK

Disclosure

- Advisory boards and honoraria
  - Amgen, Astellas, Bayer, Ipsen, Janssen, MSD, Novartis, Sanofi Genzyme
- Research grants (To Instituion)
  - Sanofi Genzyme, Bayer, Janssen
- Meeting sponsorship
  - Astellas, Bayer, Ipsen, Janssen, MSD, Roche, Sanofi Genzyme

SIDE EFFECTS OF ADT

Side Effects

PROSTATE CANCER UK SEARCH Call Our Sp

Prostate information / Living with prostate cancer / How hormone therapy affects you

Why does hormone therapy cause side effects?

Hot flushes

Extreme tiredness (faitgue)

Changes to your sex life

Weight gain

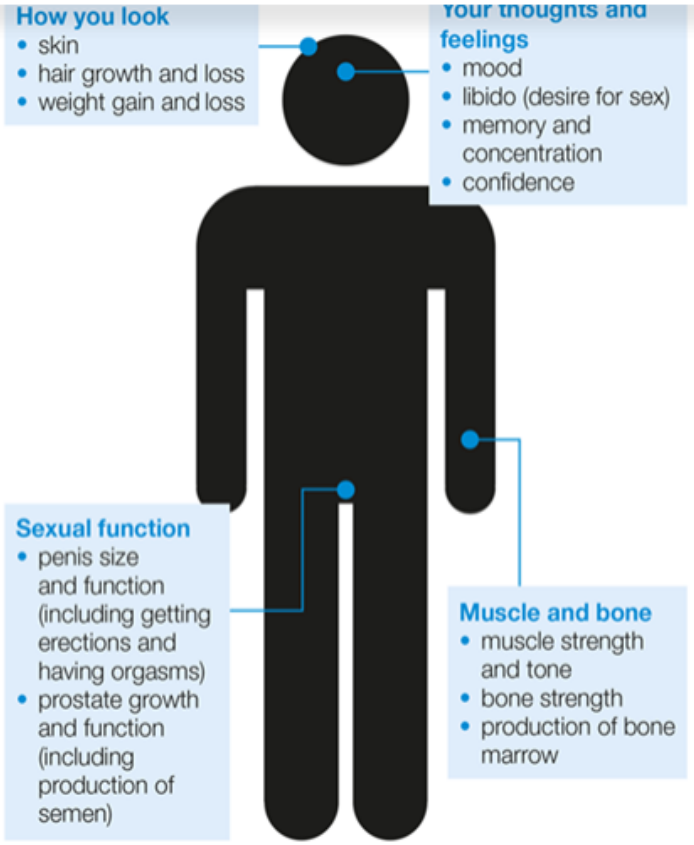
Strength and muscle loss

Changes to your memory and concentration

Breast swelling and tenderness

Bone thinning

Risk of other health problems



PCUK last accessed 17 September 2021

CARDIOVASCULAR DISEASE AND ADT

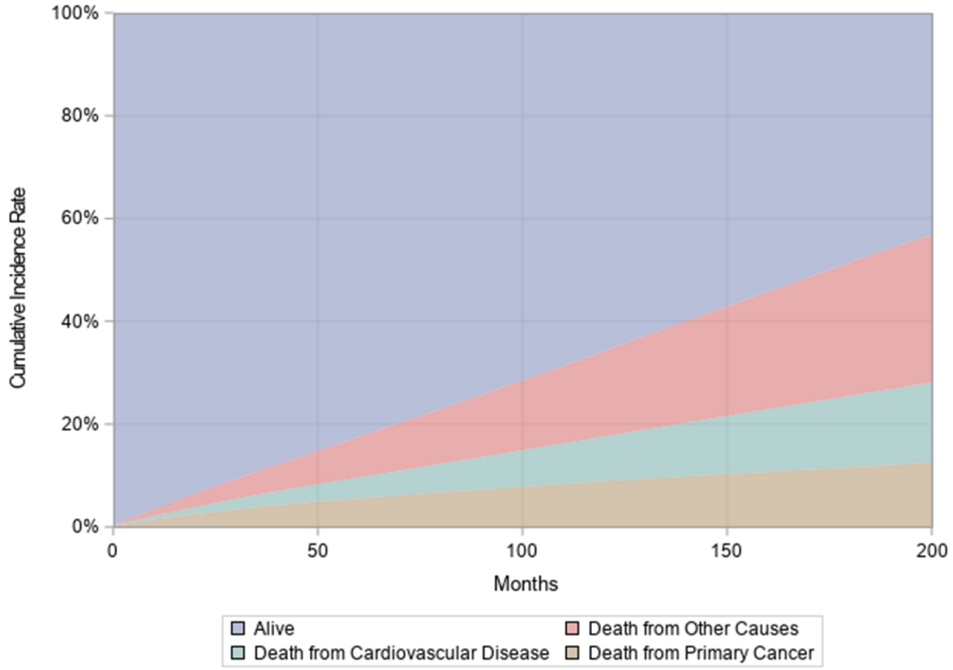
The Issue

- Men with Prostate Cancer have a reasonable cancer prognosis

- Short and long term consequences of therapy are important because they may affect men more than the cancer

Prostate cancer and cardiovascular disease

Competing risk analysis conducted for prostate cancer



Sturgeon KM et al. *Eur Heart J* 2019;40:3889–3897.

WHAT DOES THE EVIDENCE SHOW?

Observational Evidence

- Journal of Clinical Oncology, Keating et al. 2006
  - Observational study SEER database, n=73196
  - GnRH agonists associated with increased diabetes, myocardial infarction and sudden cardiac death
  - Orchiectomy (6% of population) associated with diabetes but not cardiovascular events
- World Journal of Urology, Davey et al. 2020
  - Observational study UK GP database, n=9081
  - GnRH antagonists lower risk cardiac events compared to GnRH agonist.
  - Those receiving Degarelix switched more often (33.7%) than those initiating agonist (6.7-18.6%)
  - However – n= 101/ 9081 on Degarelix

Meta-analysis of observational data

EUROPEAN UROLOGY 68 (2015) 386–396

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Prostate Cancer

Editorial by Paul L. Nguyen and Anthony V. D'Amico on pp. 397–398 of this issue

Quantifying Observational Evidence for Risk of Fatal and Nonfatal Cardiovascular Disease Following Androgen Deprivation Therapy for Prostate Cancer: A Meta-analysis

Cecilia Bosco[a,*], *Zsolt Bosnyak*[b], *Anders Malmberg*[b], *Jan Adolfsson*[c], *Nancy L. Keating*[d], *Mieke Van Hemelrijck*[a]

Meta-analysis of observational data

8 publications included – largely registry data >300,000 patients

	Increased risk of any non fatal CVD compared to men not treated with ADT
GNRH agonists	38%
Orchiectomy	44%
Anti-androgen	21%

GnRH agonists association with non fatal – 57%
GnRH agonists association with fatal MI/stroke – 51%

European Urology 2015

Meta-analysis of randomised clinical trials

Review

December 7, 2011

Association of Androgen Deprivation Therapy With Cardiovascular Death in Patients With Prostate Cancer

A Meta-analysis of Randomized Trials

Paul L. Nguyen, MD; Youjin Je, MS; Fabio A. B. Schutz, MD; et al

JAMA 2011

Meta-analysis of randomised clinical trials

- 8 randomised trials, >4000 men
- Men with unfavourable risk prostate cancer
- ADT was not associated with fatal CVD
- ADT was associated with lower PCSM
- ADT was associated with lower all cause mortality

JAMA 2011

Meta-analysis of randomised clinical trials Gonadotrophin Agonists v Antagonists

ELSEVIER

European Urology

Volume 65, Issue 3, March 2014, Pages 565-573

Platinum Priority – Prostate Cancer

Editorial by Derek J. Rosario, Liam Bourke and Nancy L. Keating on pp. 574–576 of this issue

Cardiovascular Morbidity Associated with Gonadotropin Releasing Hormone Agonists and an Antagonist

Peter C. Albertsen [a], Laurence Klotz [b], Bertrand Tombal [c], James Grady [a], Tine K. Olesen [d], Jan Nilsson [e]

European Urology 2014

Meta-analysis of randomised clinical trials Gonadotrophin Agonists v Antagonists

- 6 randomised (Ferring) trials, >2000 men
- Men were excluded if they had a abnormal QT / risk factors for heart failure
- Men were subcategorised to 3-7months of treatment versus 12 months of treatment
- Death from cardiac event or death from any cause

GnRH antagonists associated with a lower CVD event rate in men with pre-existing CVD comorbidities compared to GNRH agonists (absolute reduction 8.2%)

European Urology 2014

Oral Relugolix (LHRH antagonist) for Advanced Pca (HERO trial)

Event	Relugolix (N=622)		Leuprolide (N=308)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any adverse event — no. (%)	578 (92.9)	112 (18.0)	288 (93.5)	63 (20.5)
Serious adverse event — no. (%)	76 (12.2)	61 (9.8)	47 (15.3)	35 (11.4)
Fatal adverse event — no. (%)	7 (1.1)	—	9 (2.9)	—
MACE — no. (%)†	18 (2.9)	8 (1.3)	19 (6.2)	4 (1.3)
Without a history of MACE — no./total no. (%)	15/538 (2.8)	—	11/263 (4.2)	—
With a history of MACE — no./total no. (%)	3/84 (3.6)	—	8/45 (17.8)	—
Adverse events that occurred in >10% of patients in either group — no. (%)				
Hot flash	338 (54.3)	4 (0.6)	159 (51.6)	0
Fatigue	134 (21.5)	2 (0.3)	57 (18.5)	0
Constipation	76 (12.2)	0	30 (9.7)	0
Diarrhea	76 (12.2)	0	21 (6.8)	0
Arthralgia	75 (12.1)	2 (0.3)	28 (9.1)	0
Hypertension	49 (7.9)	10 (1.6)	36 (11.7)	2 (0.6)

Challenges in interpreting the literature

- Heterogenous populations
- Real life v trial enrolled patients
- Different primary end points in RCTs

My Opinion

- Firstly do no harm + counsel patients
- Ensure that ADT is used appropriately
- In men with increased cardiovascular risk at initiation of ADT: responsibility to consider the risks
- Clear evidence that ADT increases fat mass and decreases insulin sensitivity. Encourage men to adopt healthier lifestyle

Guidelines

- EAU 2021 acknowledges cardiac morbidity but makes no recommendations

- NICE – no real comment

- AUA and AHA and ACS – high risk patients merit close follow up (Hypertension, Hyperlipidaemia, Diabetes, Smoking)

Bone Health

Bone Health and ADT

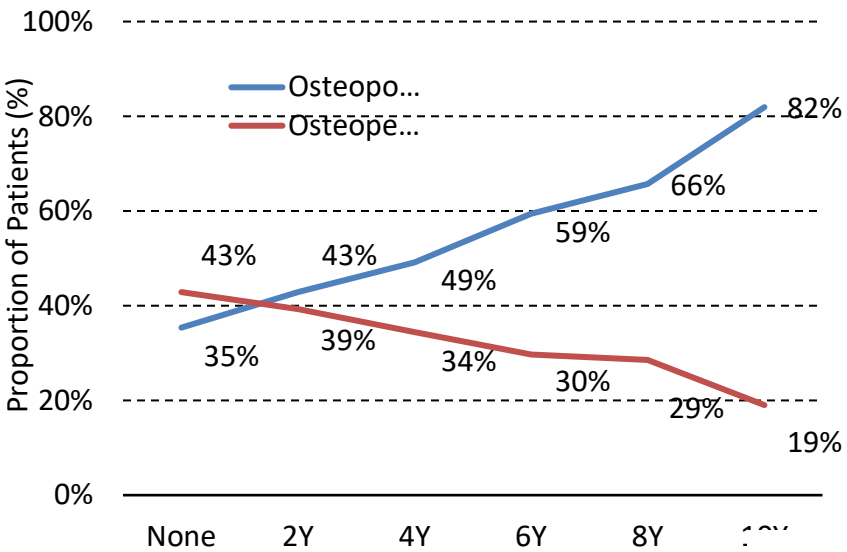
The prevalence of osteoporosis was high in hormone-naïve patients with prostate cancer (35.4%), and increased with duration of ADT:[10]

- 42.9% after 2 years of ADT
- 59.5% after 6 years of ADT
- 80.6% after 10 or more years of ADT

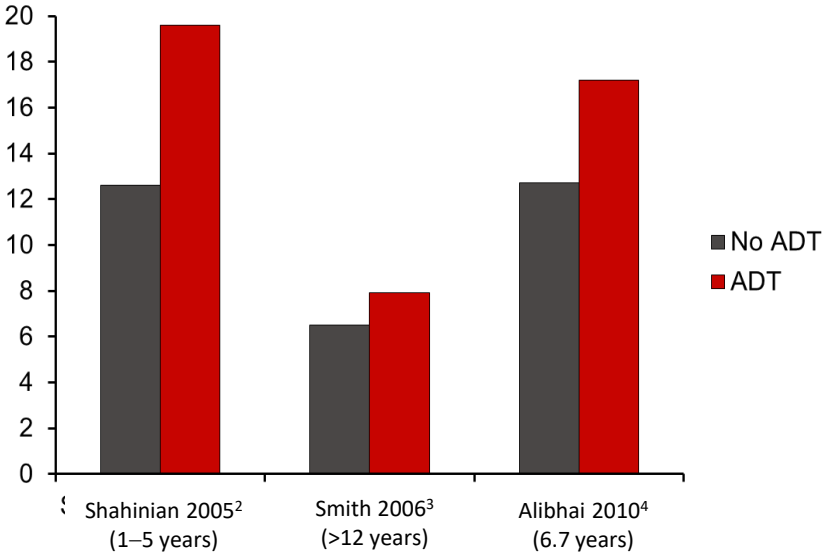
ADT increased the incidence of fractures in elderly men with both non-metastatic and metastatic prostate cancer[11]

PCa patients are at increased risk of osteoporosis and frailty fractures due to ADT

Rate of osteoporosis in men treated with ADT[1]



Fracture rate per person per year, %



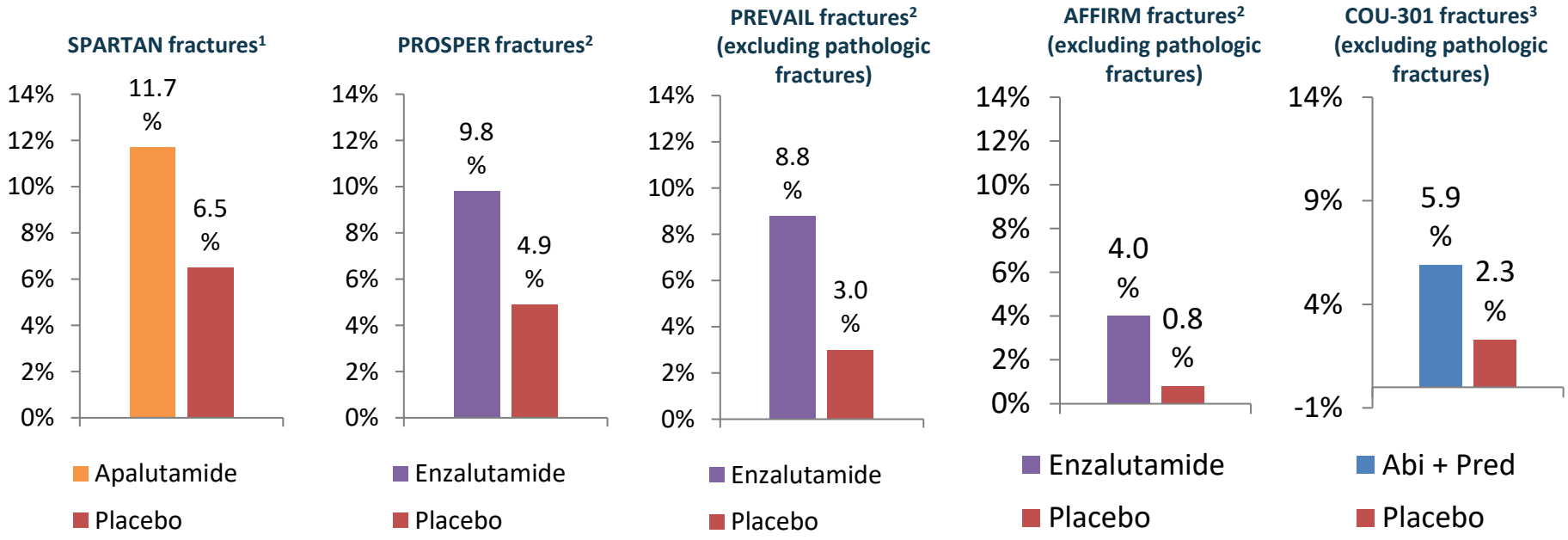
ADT, androgen deprivation therapy; CI, confidence interval;

1. Morote J et al. Urology 2007;69:500–504,
2. Shahinian, et al. N Engl J Med 2005;352:154–64;
3. Smith, et al. J Clin Oncol 2006;24:4448–56;
4. Alibhai, et al. J Urol 2010;184;918–24.

Bone Health and ARTA's

- The benefits of androgen receptor targeted agents include preventing or delaying skeletal-related events[12–16]
- But small increases in risk of non-pathological fractures have been shown[17,18]

Fractures are commonly reported in the investigational arm of phase III studies with new AR pathways inhibitors



1. Smith MR et al. N Engl J Med 2018; doi:10.1056/NEJMoa1715546 [Epub ahead of print].
2. Xtandi (enzalutamide) [prescribing information]. Astellas Pharma US, Inc., Northbrook, IL. July 2018.
3. Zytiga (abiraterone acetate) [prescribing information]. Janssen Biotech, Inc., Horsham, PA. February 2018.
4. Erleada (apalutamide) [prescribing information]. Janssen Products, LP, Horsham, PA. February 2018.

USPI, U.S. prescribing information.

Improving Bone Mineral Density

In patients with non-metastatic prostate cancer:

- Denosumab was associated with improvement in BMD and a reduction in osteoporotic fractures[21]
- Zoledronic acid increased BMD during ADT[22]
- Calcium/vitamin D supplementation is associated with increased BMD[23]

Consider assessing fracture risk in people with prostate cancer who are having ADT, in line with the NICE guideline on osteoporosis: assessing the risk of fragility fracture

Lifestyle Factors and Bone Health

Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline[24]

- "We suggest that men at risk of osteoporosis participate in weight-bearing activities for 30–40 min per session, three to four sessions per week"
- "We suggest that men at risk of osteoporosis who consume three or more units of alcohol per day reduce their alcohol intake"
- "We recommend that men at risk of osteoporosis who smoke cease smoking"

Regular sports activities can reduce the risk of fractures in older men[25]

What is Vigorous Activity?

- Physical activity score: MET (metabolic equivalent)-hours per week
- 1 MET-hour is the metabolic equivalent to sitting at rest for 1 hr
- Validated compendium of physical activities
- ≥6 METs is vigorous: running >5mph, cycling, shovelling, playing football, carrying a heavy load, playing tennis (singles, not doubles)

Brisk Walking Reduces Risk of Cancer Progression

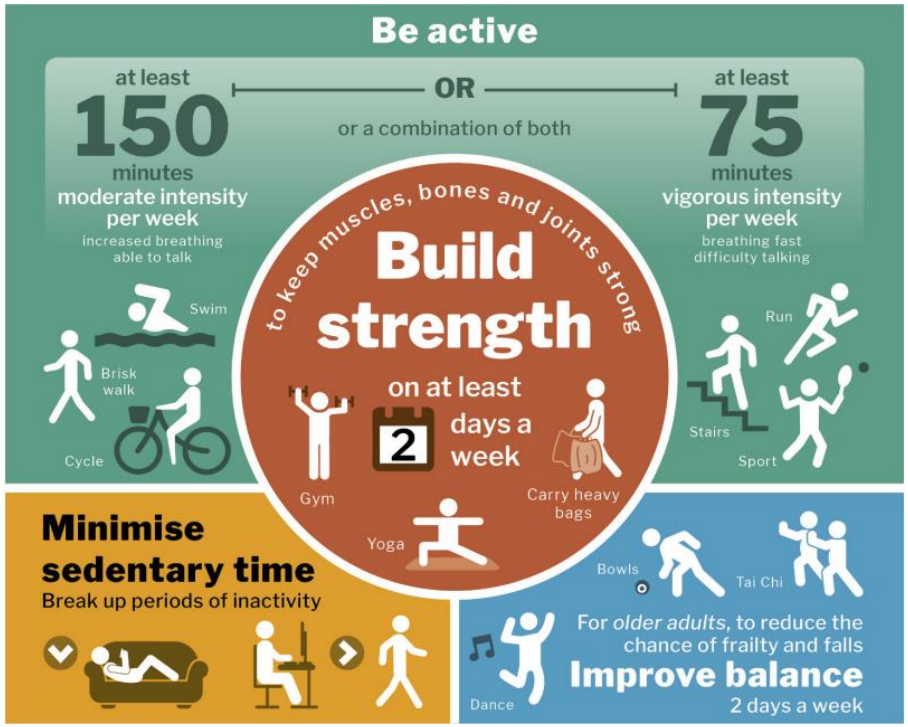
CaPSURE study: 1455 men with localized prostate cancer

- Walking briskly (≥3 mph) for ≥3hr/week reduced the risk of prostate cancer progression compared with walking <3 mph for <3hr/week

Vigorous Activity Reduces Mortality in Cancer Survivors

- Walking ≥90 mins at a normal to a very brisk pace reduced the risk of all-cause mortality compared with <90 mins at an easy pace
- Vigorous activity ≥3 hr/week reduced prostate cancer death compared with <1 hr/week vigorous activity

Key recommendations



GOV.UK. UK Chief Medical Officers' Physical Activity Guidelines. September 2019.