The Role of ADT

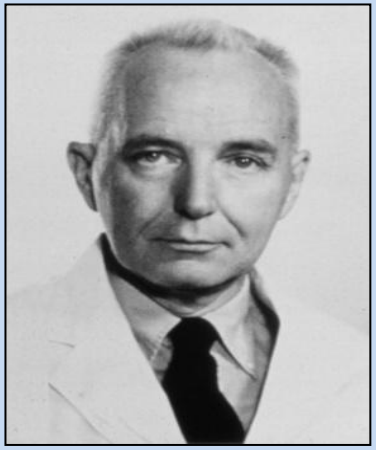
Heather Payne
Clinical Oncologist

Role of Testosterone in Prostate Cancer-

Over seventy years ago, Huggins demonstrated that castration reduced the prostate cancer markers, acid and alkaline phosphatase.

These results established androgen deprivation therapy (ADT) as the mainstay of management of advanced prostate cancer

And so our relationship with androgens and they androgen receptor began!



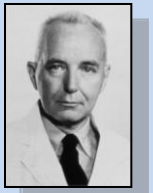
Charles Huggins
1901 – 1997
Winner of 1966
Nobel Prize

[1] Huggins and Hodges Cancer Res 1941;1:293-7

Early history of hormonal treatment – previous mainstay of first line therapy for advanced/metastatic Prostate Cancer

Surgical castration established by Huggins for the treatment of pts with prostate cancer

1941



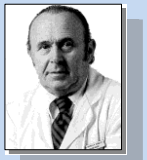
Charles Huggins

1970 **Medical castration investigated**

1977 **Oestrogen treatment** with DES demonstrated a comparable efficacy to castration but resulted in cardiovascular side-effects

GnRH agonists – Schally demonstrated tumour growth inhibition in pts treated with LHRH agonists

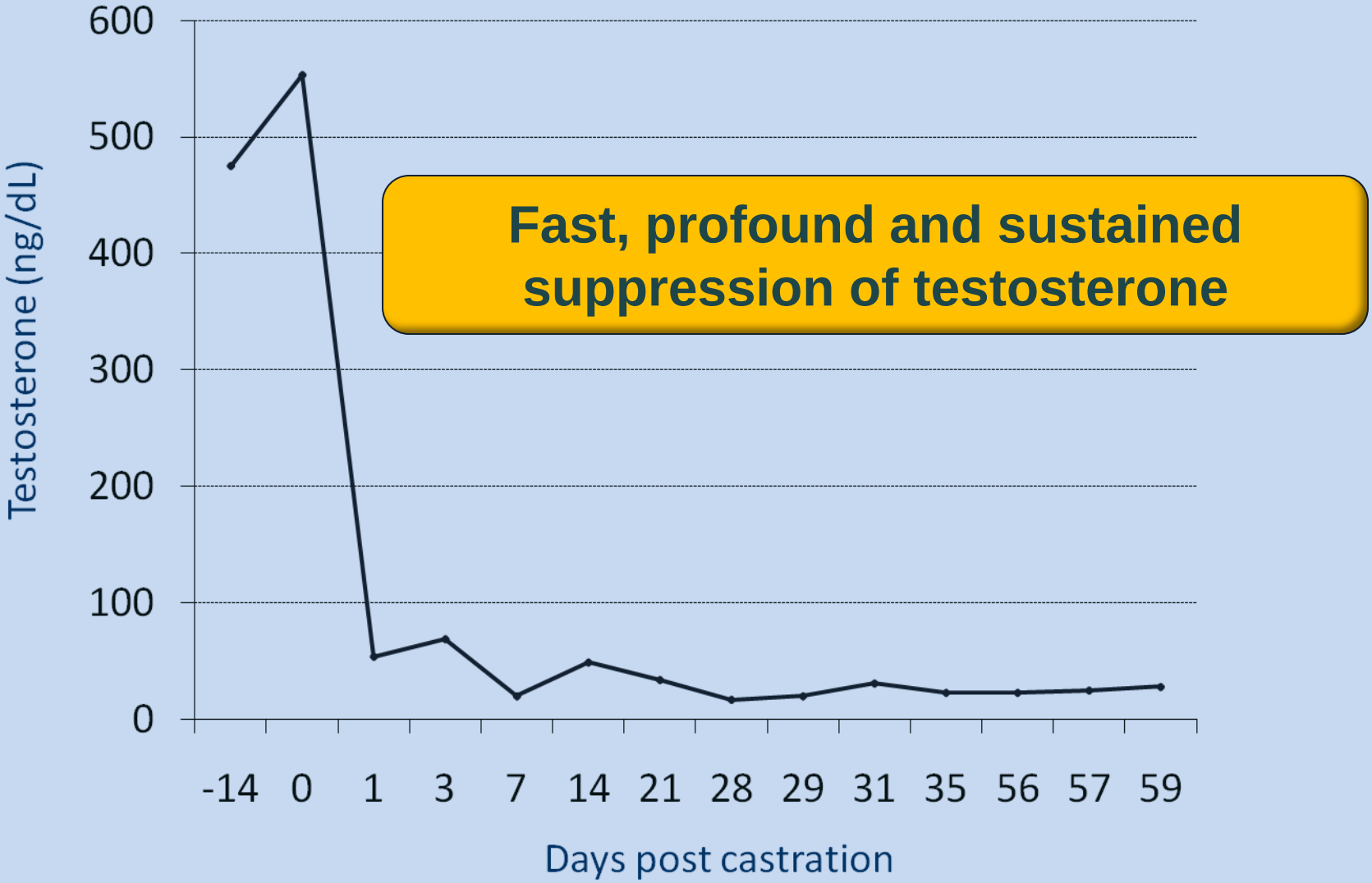
1982



Andrew Schally

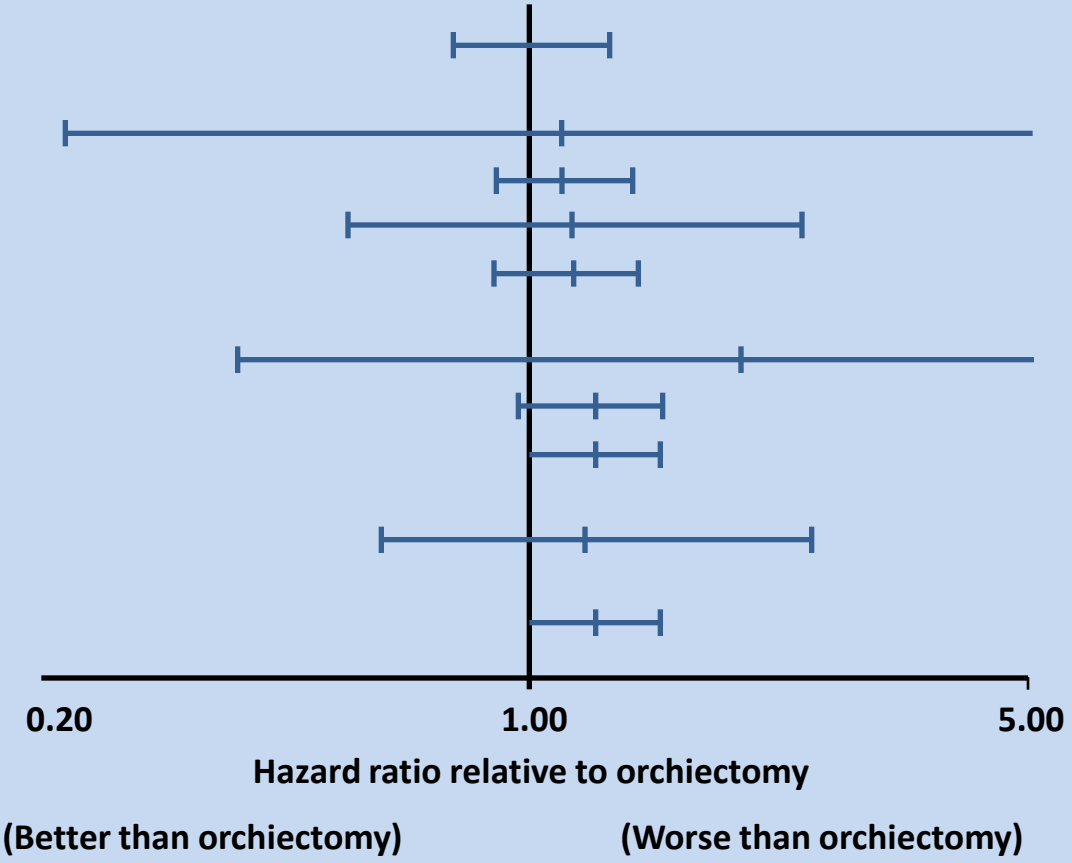
1985-9 **Leuprolide and goserelin** registered for treatment

What is Surgical Castration ?



Efficacy of Different Forms of ADT

Meta-analysis of survival at 2 years. Point estimates for hazard ratios (*center marks*) and 95% CIs (*error bars*) relative to orchiectomy for data on survival after 2 years of treatment



Seidenfeld *et al. Ann Intern Med* 2000;132:566–77

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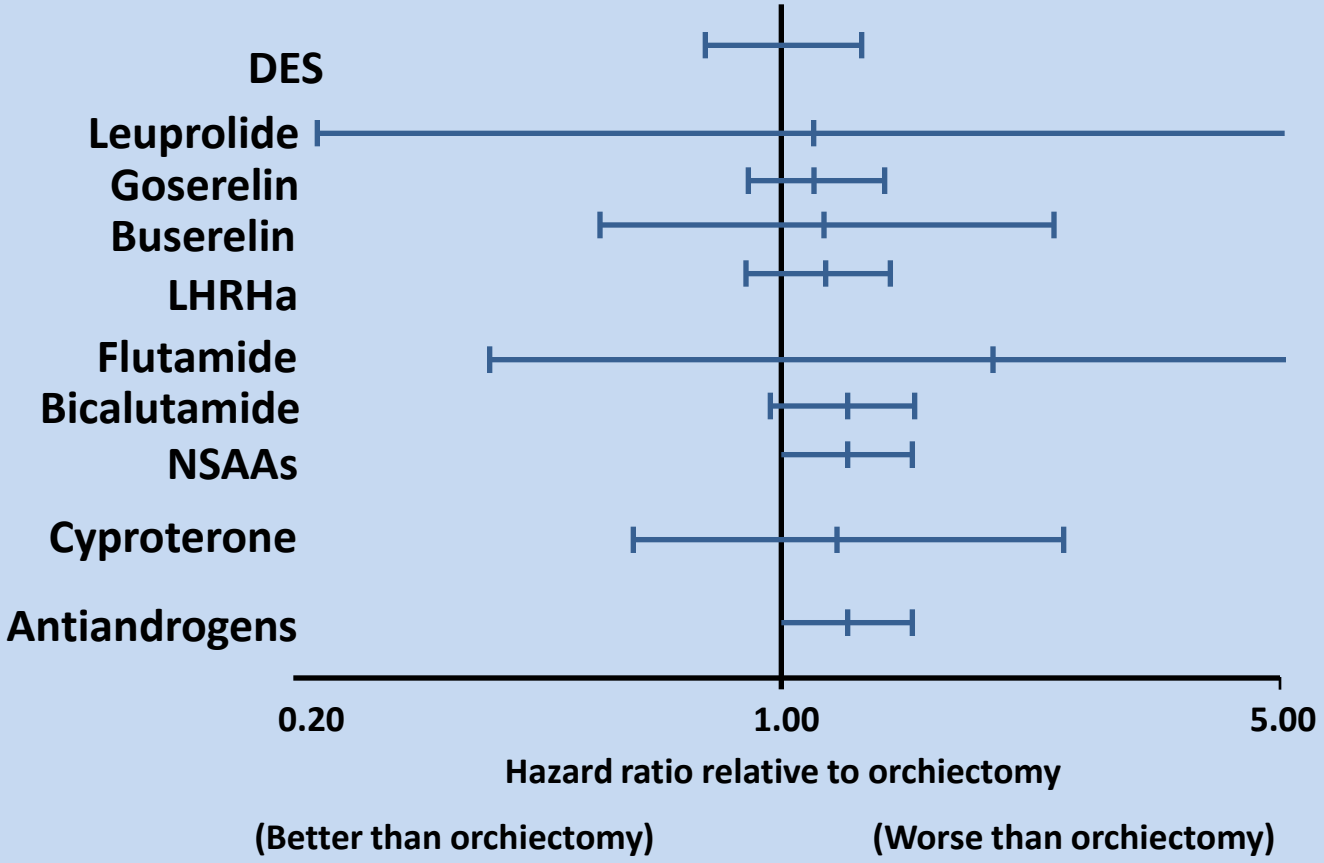
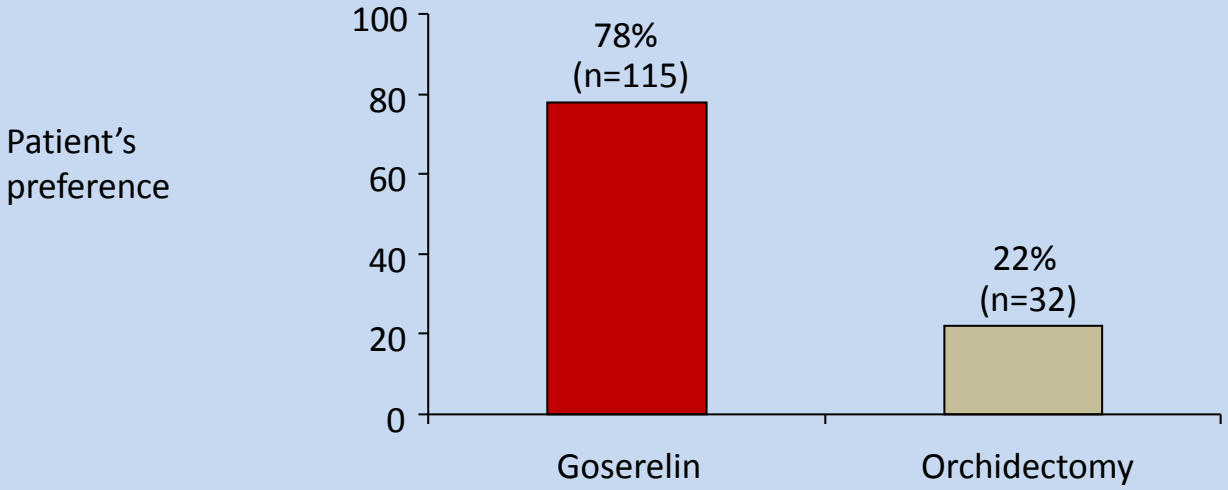


Seidenfeld *et al. Ann Intern Med* 2000;132:566–77

LHRH agonists are now widely used to suppress androgen production

- **Patients prefer injections of LHRH agonists (medical castration)**
  - 147 patients with previously untreated metastatic prostate cancer were asked to choose between a monthly injection of an LHRH agonist or surgical castration



Cassileth BR, et al. *Qual Life Res* 1992;1:323-330

Findings from the PCTCG meta-analysis (27 trials, n=8275)

5-year survival favoured CAB vs castration (25.4% vs 23.6%)

Outcome dependent on choice of anti-androgen

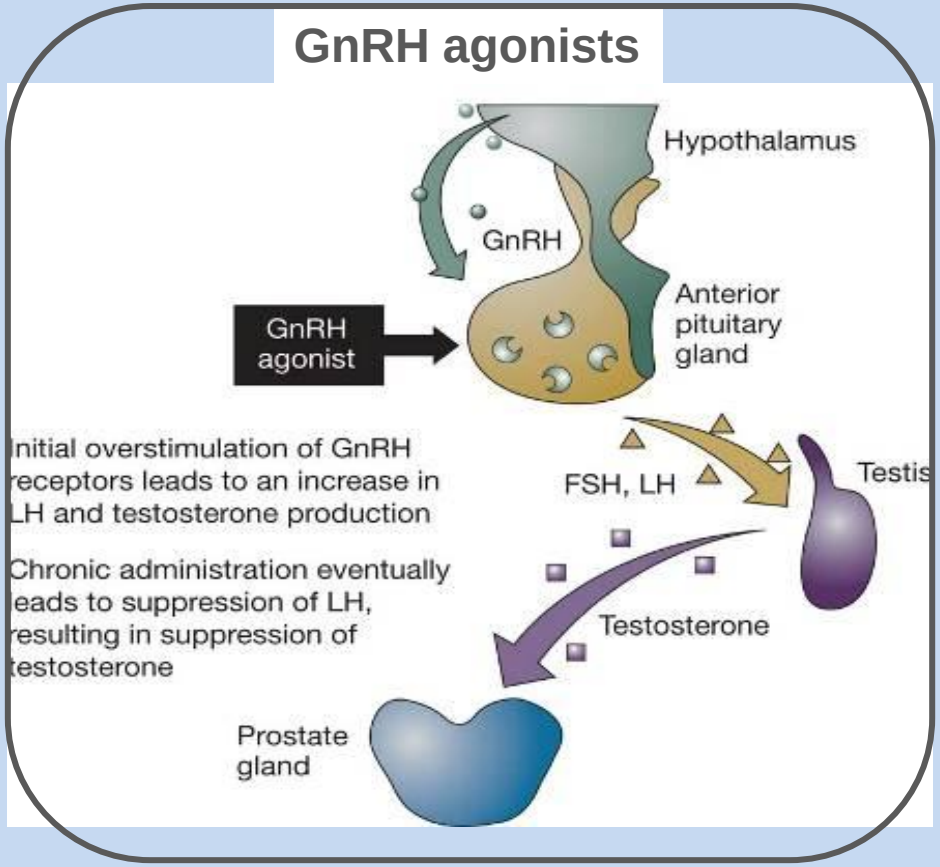
With non-steroidal anti-androgens (flutamide or nilutamide), there was a significant 8% reduction in the risk of death (p=0.005)

With steroidal anti-androgens (cyproterone acetate [CPA]), there was a significant 13% increase in the risk of death (p=0.04)

PCTCG, Prostate Cancer Trialists' Collaborative Group

PCTCG 2000

Mechanism of action of LHRH/GnRH agonists



- Acute pituitary effects
  - ➔ Surge in FSH, LH and testosterone
- Chronic pituitary effects
  - ➔ LH and testosterone suppression, but microsurges on repeat injection ('acute-on-chronic')

FSH, follicle-stimulating hormone; LH, luteinizing hormone

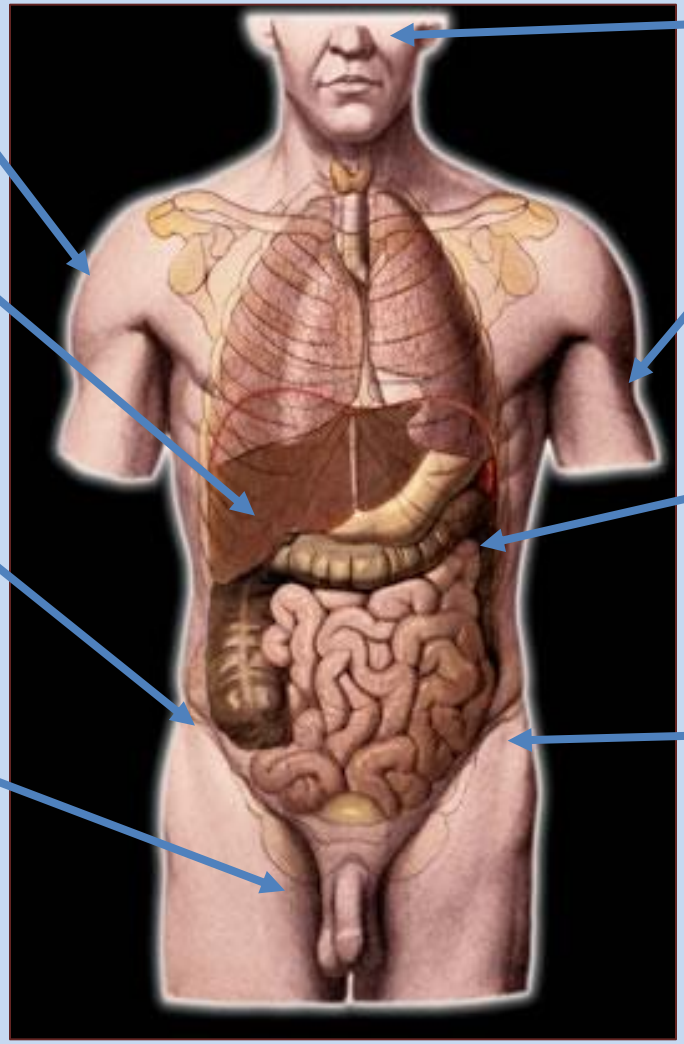
Testosterone is the major “male” hormone

Skin
Hair growth, balding, sebum production

Liver
Synthesis of serum proteins

Bone
Accelerated linear growth, closure of epiphyses

Male sexual organs
Penile growth, spermatogenesis, prostate growth and function



Brain
Libido, mood

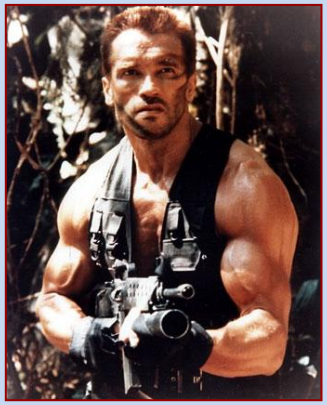
Muscle
Increase in strength and volume

Kidney
Stimulation of erythropoietin production

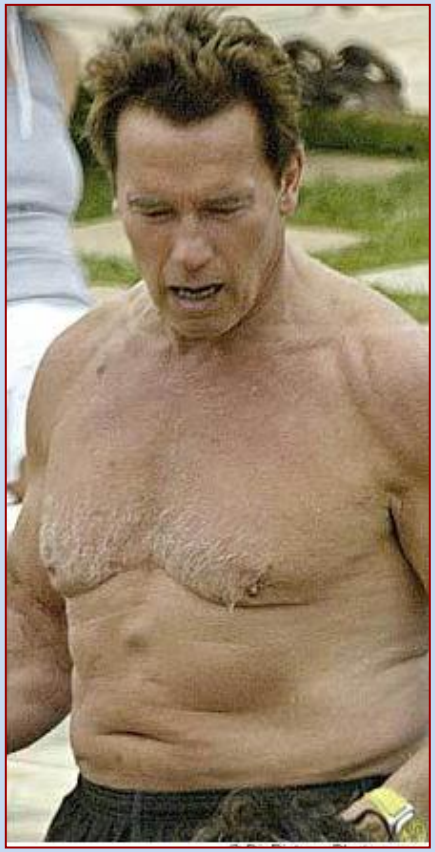
Bone marrow
Stimulation of stem cells

Short-term side effects of ADT

The castration syndrome



Castration



- Loss of libido and sexual interest, erectile dysfunction, impotence
- Fatigue
- Hot flushes
- Decline in intellectual capacity, emotional liability, depression
- Decrease in muscular strength
- Decline in physical activity and general vitality

The Androgen Deprivation Syndrome

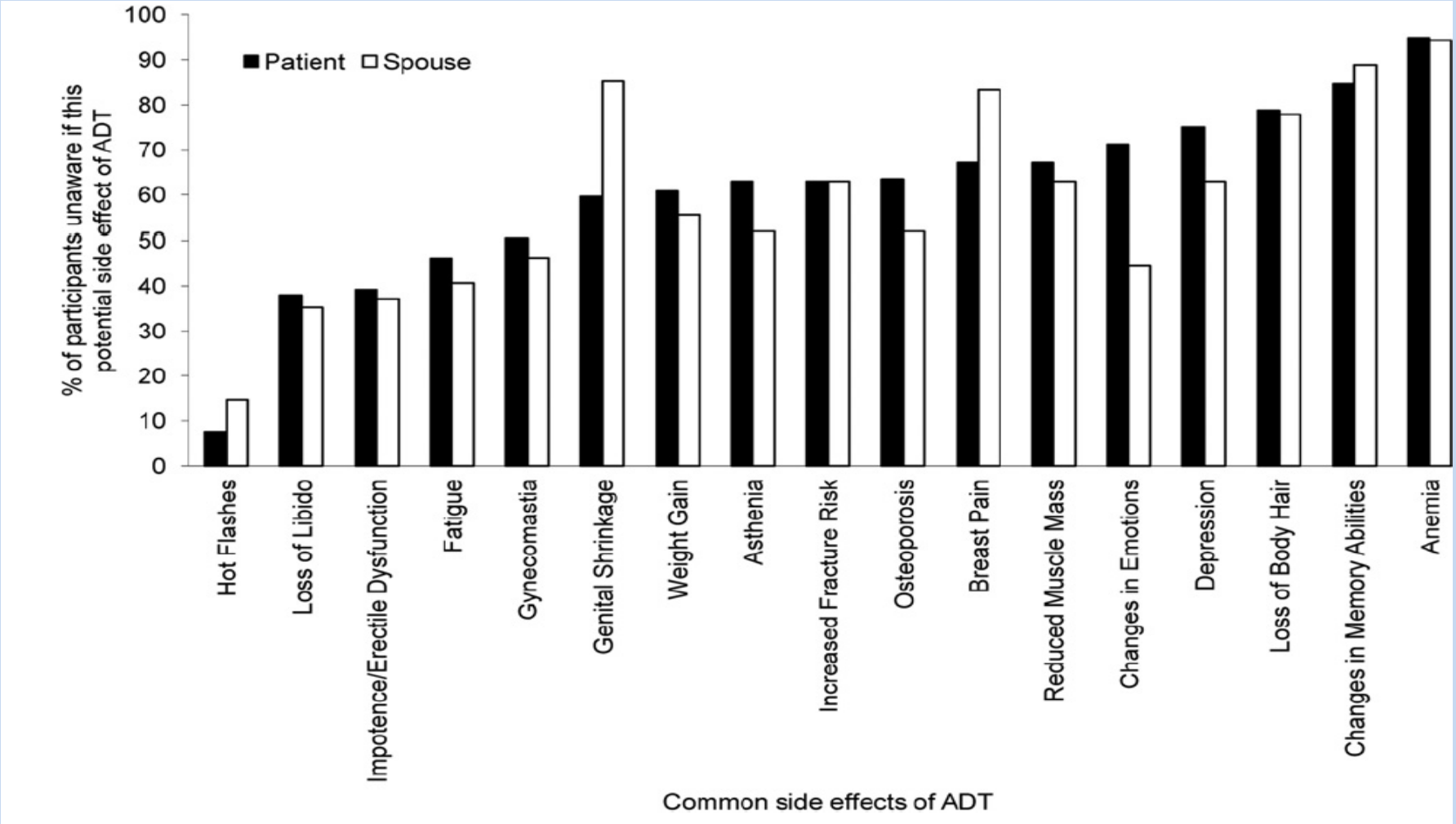
What patients expect

- Loss of libido
- Erectile dysfunction (impotence)
- Decreased energy
- Hot flushes
- Gynaecomastia and mastalgia

What they also get

- Metabolic syndrome
- Osteoporosis /fracture
- Loss of muscle mass
- Weight gain
- Anaemia
- Alteration in lipid profile
- Depression, personality change

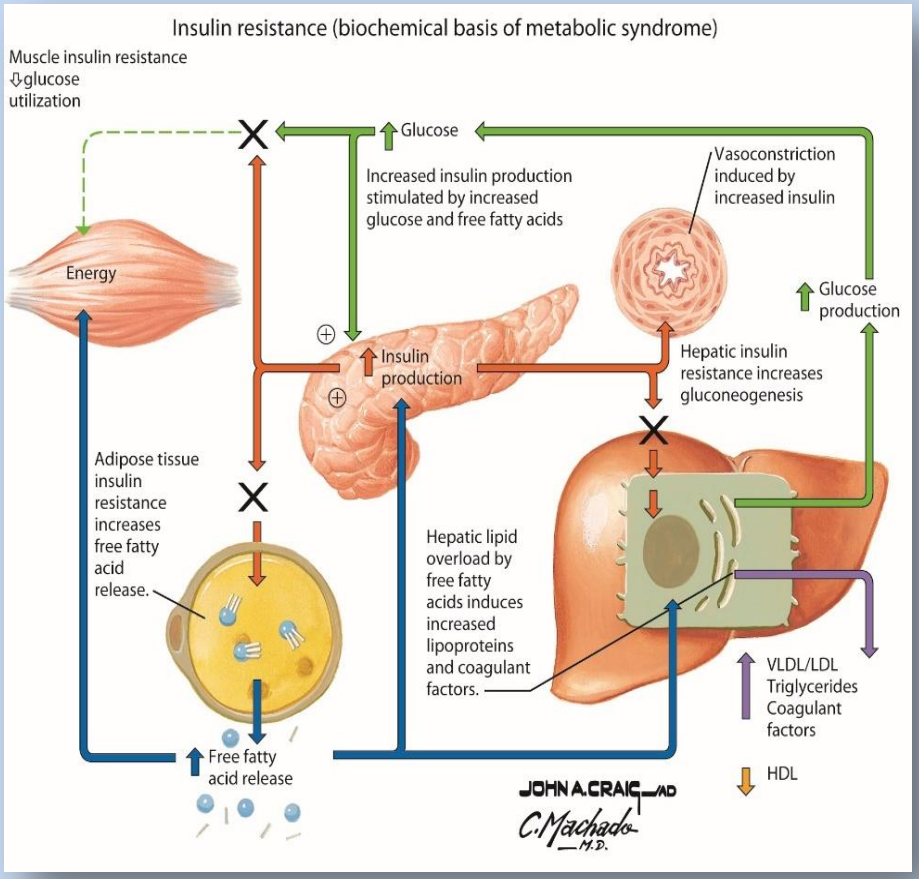
Patients often don’t know ADT’s Side-

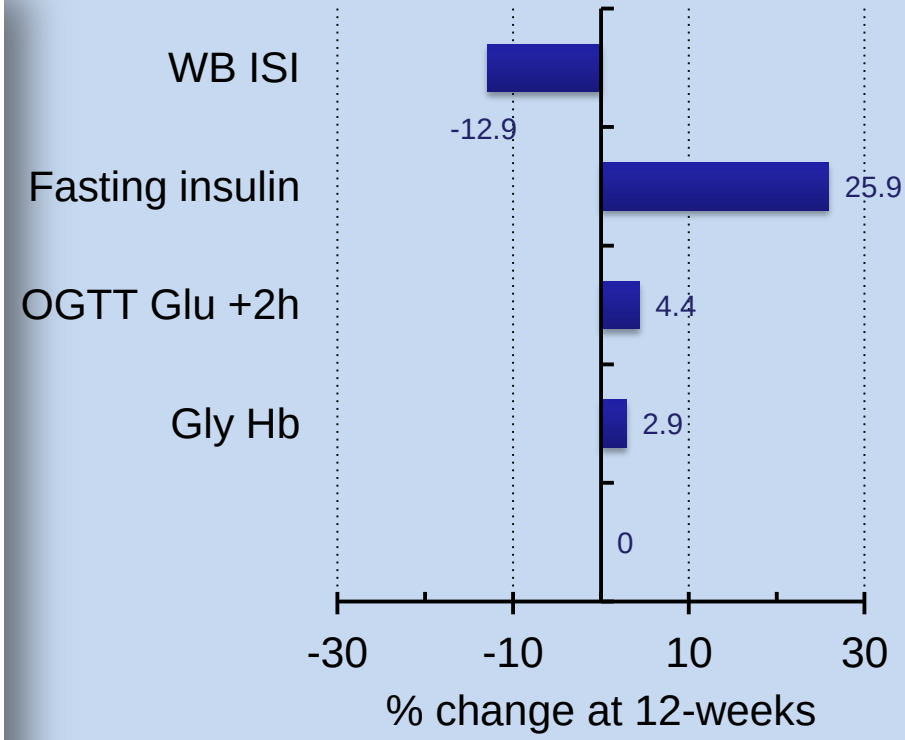


- Walker, Urol Oncol 2011

Long-term side effects of ADT

Peripheral insulin resistance





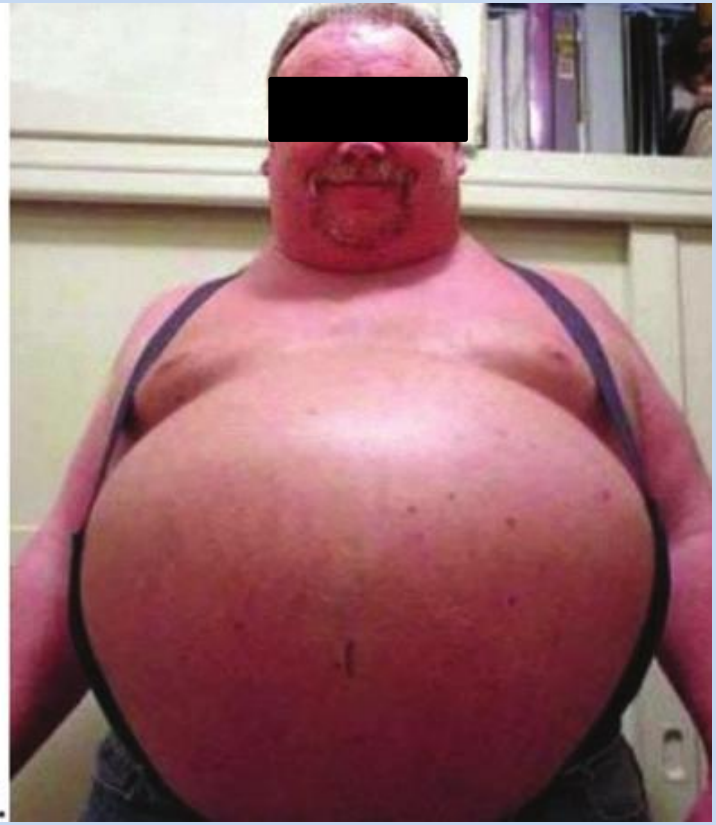
Prospective 12-week study, 25 men with locally advanced or recurrent prostate cancer, LHRH agonists
Smith MR et al. J Clin Endocrinol Metab 2006;91:1305–8

Metabolic Syndrome

Metabolic Syndrome vs. ADT Syndrome

ADT syndrome

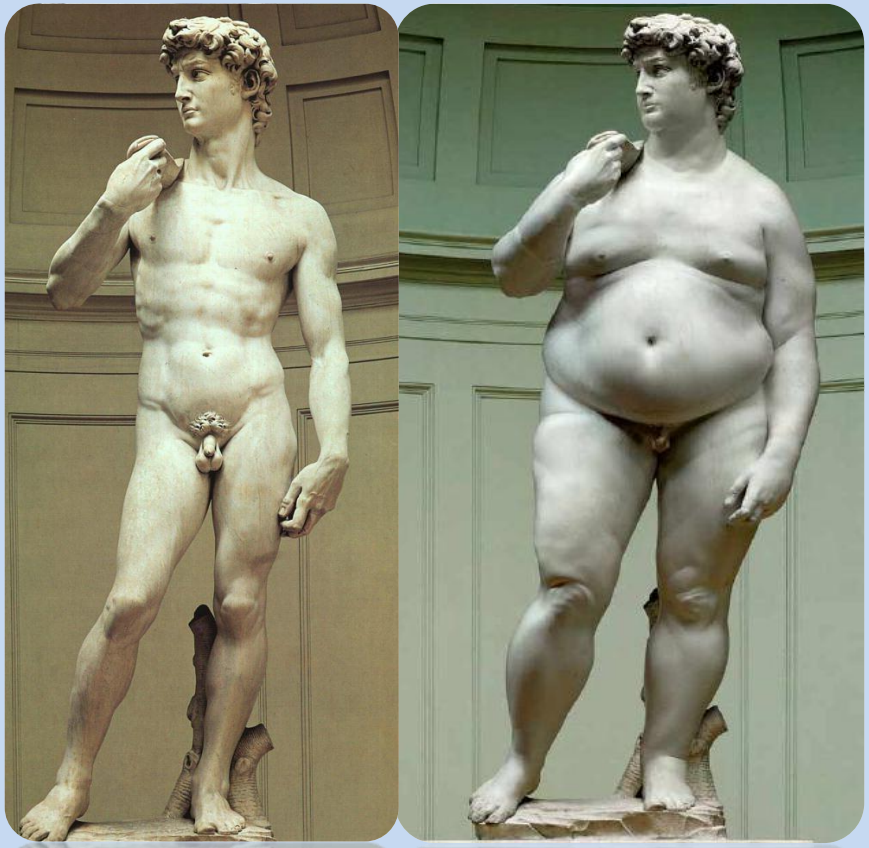
- Central obesity
- High blood pressure
- High triglycerides
- High HDL-cholesterol
- Insulin resistance

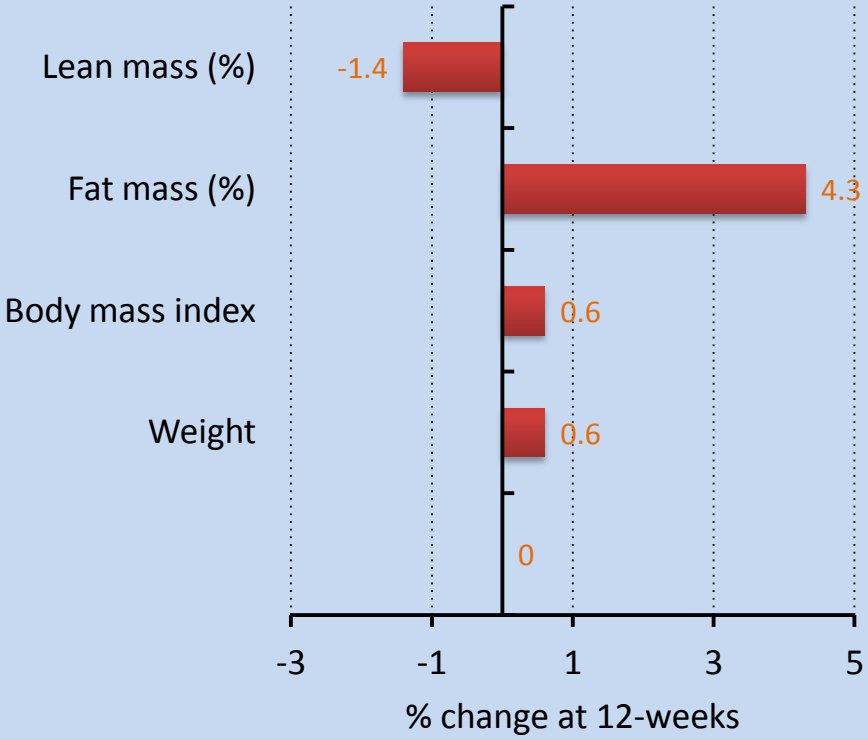


Ravindranath, Indian J Psychol Med 2012;34:247-54

Long-term side-effects of ADT

Sarcopenic obesity

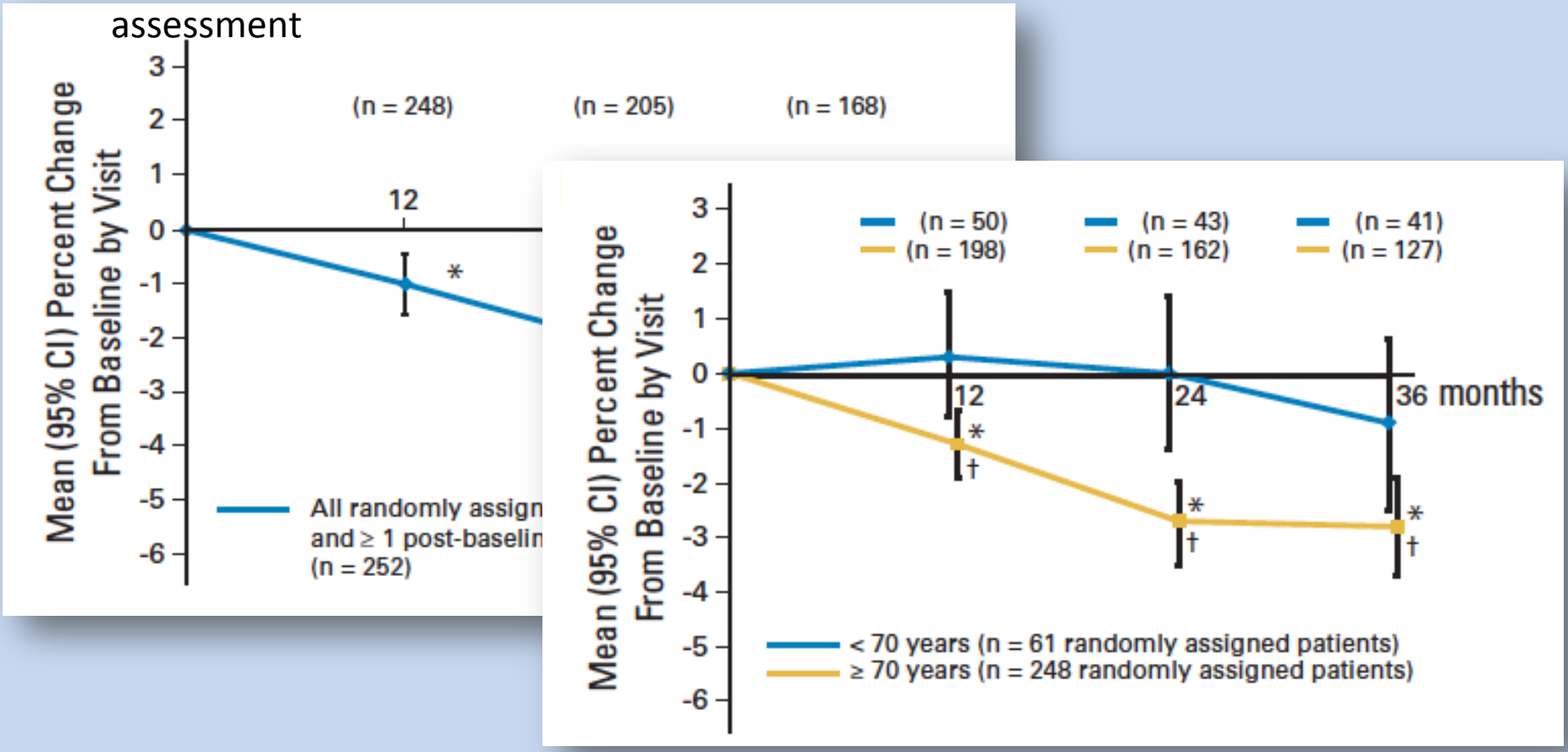




Prospective 12-week study, 25 men with locally advanced or recurrent prostate cancer, LHRH agonists
Smith MR et al. J Clin Endocrinol Metab 2006;91:1305–8

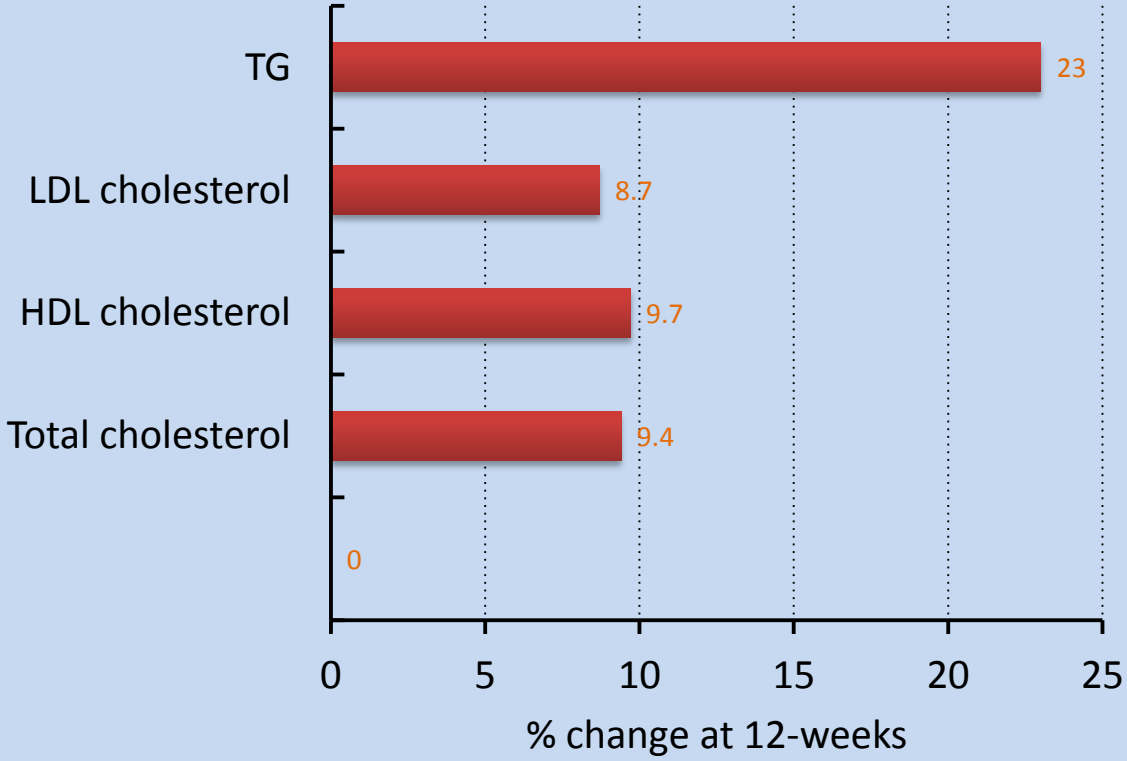
Sarcopenia (Sarcopenia is the degenerative loss of skeletal muscle mass, quality, and strength) during androgen-deprivation therapy for prostate cancer - *Smith MR et al. J Clin Oncol 2012 May 29*

- 252 patients from the denosumab osteoporotic fracture prevention trial (132 denosumab; 120 placebo), followed by whole lean body mass assessment



Dyslipidaemia and ADT

- Prospective 12-week study, 25 men with locally advanced or recurrent prostate cancer, LHRH agonists



Smith MR et al. J Clin Endocrinol Metab 2006;91:1305–8

Exercise reduces metabolic changes

Problem	Intervention	Study	Patients, *n*	Outcome
Metabolic syndrome	Resistance training	Segal et al. [40]	155	Increase in upper and lower body fitness; no effect on BMI or waist circumference
	Resistance vs aerobic exercise	Santa Mina et al. [41]	66	Aerobic-training group engaged in significantly more physical activity than the resistance-training group
	Cognitive-behavioral therapy for exercise	Carmack Taylor et al. [42]	134	No increase in exercise or QOL
	Metformin and exercise	Nobes et al. [39]	40	Decrease in abdominal girth, BMI, weight. and systolic BP

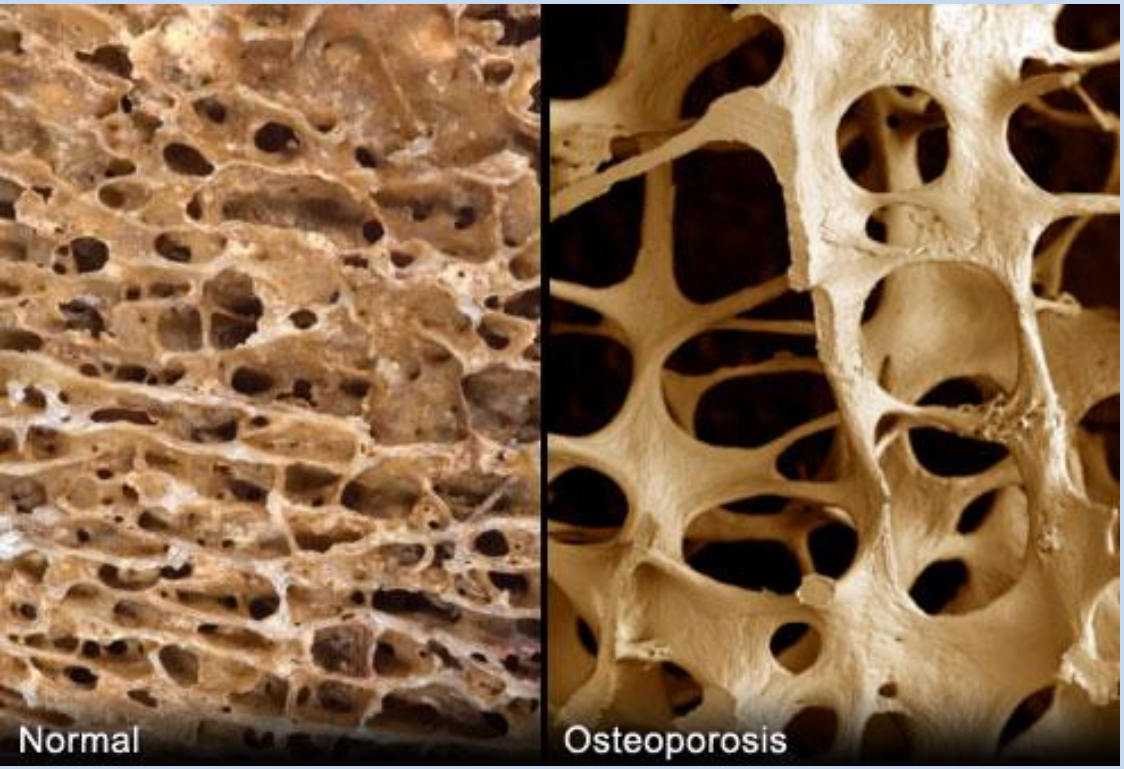
Metformin + Exercise Trial

- **RCT of 6 mos of metformin + exercise vs. observation in 40 men starting ADT**
- **Significant improvements in**
  - **abdominal girth (P= 0.05),**
  - **weight (P < 0.001), BMI (P < 0.001), systolic BP (P= 0.01)**
- **No difference in the biochemical markers of insulin resistance**

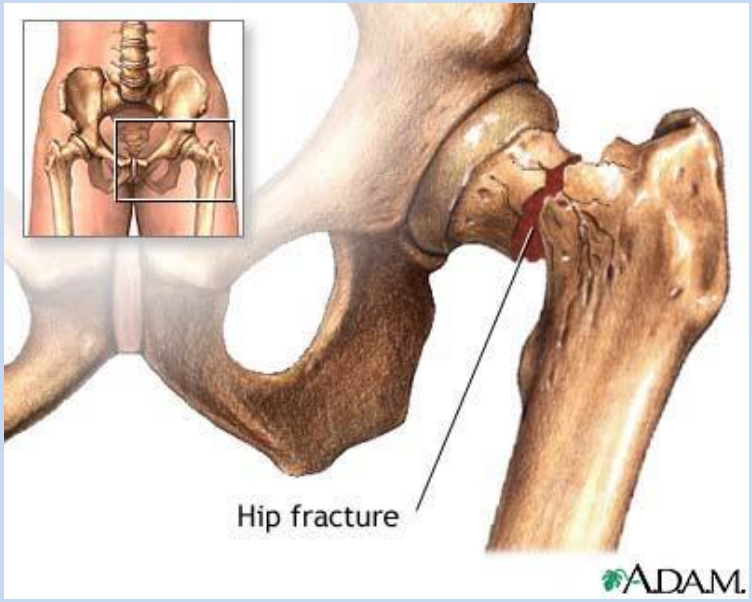
Nobes, BJUI 2012

Bone Health

Bone Health



www.webmd.com



http://www.healthcentral.com/osteoporosis/encyclopedia/hip-fracture-4004736/

Osteoporosis & fractures in prostate cancer

In newly presenting patients

- **40% osteopaenic; ≥ 14% osteoporotic at presentation[1,2]**

Fracture rate increased 3 to 12-fold in studies of castrate vs non-castrate age-matched men [3-5]

Risk of fracture resulting in hospitalization increases with no. of LHRHa doses [6]

1. Berrutti 2002 2. Hussain 2003 3. Daniell 1997
4. Melton 2003 5.Townsend 1997 6. Shahinian 2005

Fractures in prostate cancer, analysis of SEER database

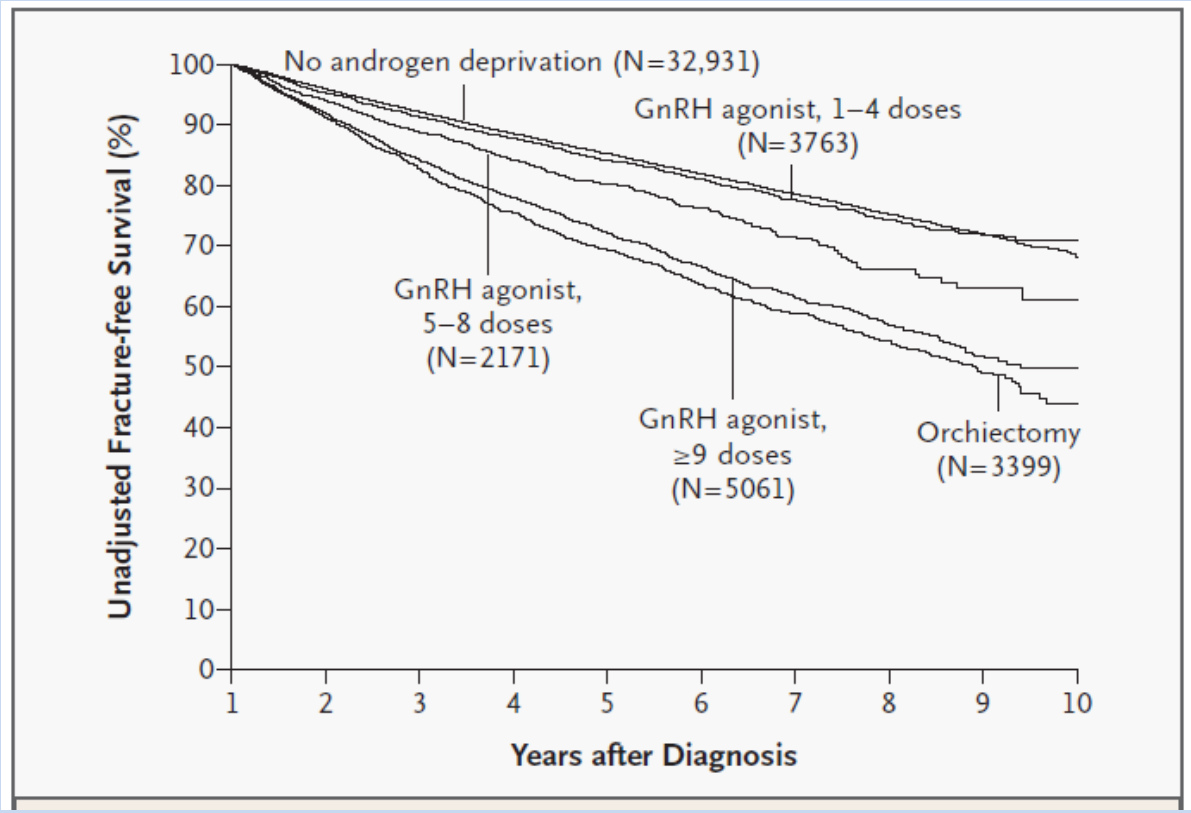
Records of 50,613 prostate patients analysed

- Fracture incidence over 5 years:-
  - # in 19.4% of patients given androgen deprivation
  - # in 12.6% of patients not androgen-deprived
- Fractures resulting in hospitalisation:- in 5.2% androgen-deprived, 2.4% of 'control' patients
- Relative risk of fractures increased with duration of LHRHa therapy

Shainian *et al* New Engl J Med 2005; 352: 154-164

Fracture Risk, Especially w/ >1yr ADT

- 5-10% decrease in bone density in 1yr
- Large increase in fractures among 5-yr survivors
- (19.4% w/ADT vs. 12.6% no ADT)



Shahinian, NEJM 2005

Treatments Demonstrating Improvement in Bone Mineral Density/Fracture Risk

Problem	Intervention	Study	Patients, *n*	Outcome
Bone health	Pamidronate	Smith et al. [15]	47	Prevents decrease in bone mineral density on ADT
	Risedronate	Choo et al. [16]	104	
	Zoledronic acid	Smith et al. [17]	106	Increase in bone mineral density while on ADT
	Alendronate	Greenspan et al. [18]	112	
		Klotz et al. [19]	191	
	Raloxifene	Smith et al., 22]	48	
	Denosumab	Smith et al. [21]	1468	Increase in bone mineral density while on ADT; decreased fracture risk
	Toremifene	Smith et al. [23]	1284	Increase in bone mineral density while on ADT; decreased fracture risk. Increased risk of DVT

Denosumab, Zoledronic Acid, Alendronate

Nguyen, Eur Urol, 2015

NCCN/NOF Recommendations

- Calcium (1200mg/d) and Vitamin D (800-1000 IU) for all men on ADT

- Additional treatment (Denosumab, Zoledronic Acid, Alendronate) if
  - DEXA scan shows osteoporosis (T-score less than -2.5)
  - **FRAX Algorithm indicates:**
    - **10-year risk of hip fracture >3%**
    - 10-year risk of major osteoporotic fracture >20%

Calculation Tool

https://www.shef.ac.uk/FRAX/

ADT counts as secondary osteoporosis

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID: About the risk

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 74 Date of Birth: Y: M: D:
2. Sex ◉ Male ○ Female
3. Weight (kg) 81.7
4. Height (cm) 175.3
5. Previous Fracture ◉ No ○ Yes
6. Parent Fractured Hip ◉ No ○ Yes
7. Current Smoking ◉ No ○ Yes
8. Glucocorticoids ◉ No ○ Yes
9. Rheumatoid arthritis ◉ No ○ Yes
10. Secondary osteoporosis ○ No ◉ Yes
11. Alcohol 3 or more units/day ◉ No ○ Yes
12. Femoral neck BMD (g/cm^2)

T-Score -2.0

Clear Calculate

BMI: 26.6
The ten year probability of fracture (%)
with BMD

Major osteoporotic	9.5
Hip Fracture	3.5

If you have a TBS value, click here: Adjust with TBS

Weight Conversion

Pounds → kg

180 Convert

Height Conversion

Inches → cm

69 Convert

04818364
Individuals with fracture risk assessed since 1st June 2011

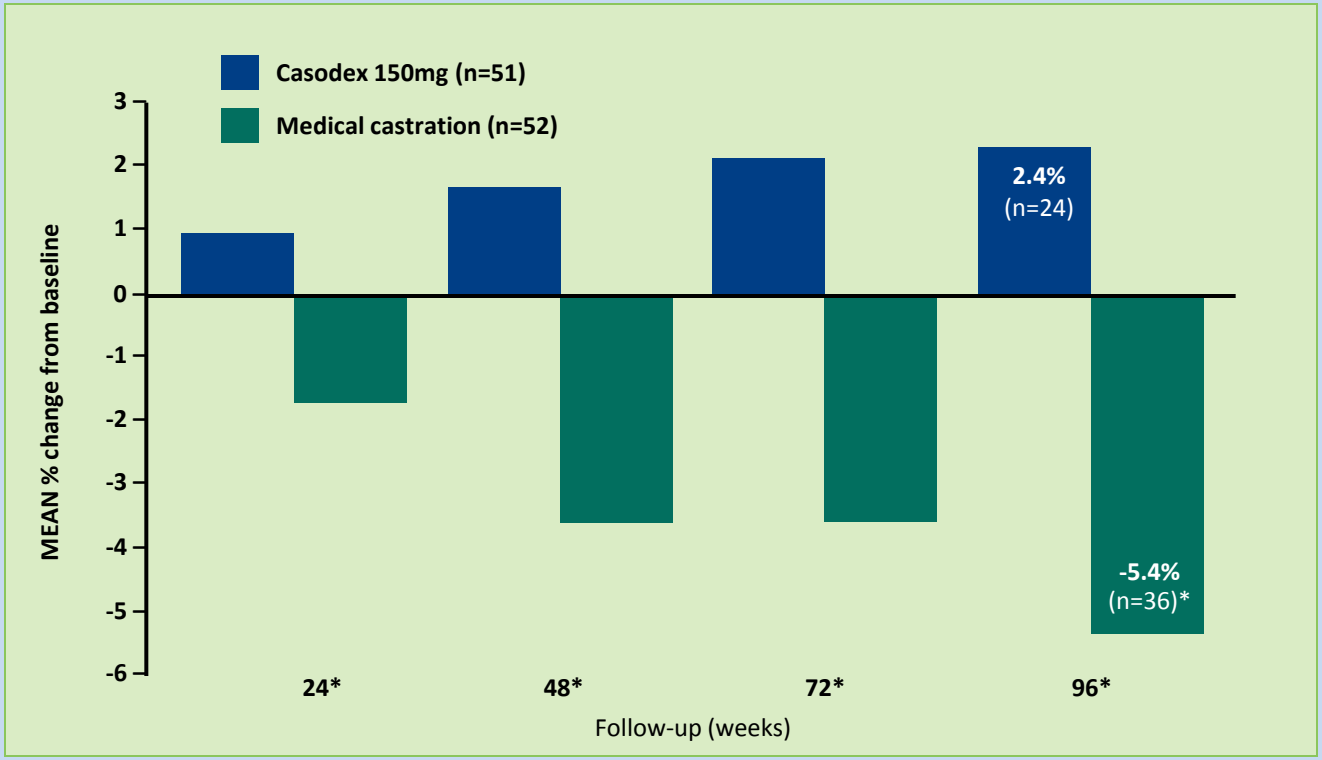
How many men on ADT have a FRAX Hip Fracture risk >3% ?

- Age<60: 0%
- Age 60-69: 4%
- Age 70-79: 77%
- Age>80: 98%

Saylor, J Urol 2011

Loss of Bone Density with Antiandrogens

Help maintain bone mineral density



Percentage change from baseline in lumbar spine bone mineral density over time[6]

Sieber PR, Keiller DL, Kahnoski RJ *et al* l Proc.ASCO 2002

***Significant between treatment group change from baseline**

(24 weeks p=0.0002; 48, 72,96 weeks: p<0.0001)

Cognition and Depression

VOLUME 33 · NUMBER 18 · JUNE 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Course and Predictors of Cognitive Function in Patients With Prostate Cancer Receiving Androgen-Deprivation Therapy: A Controlled Comparison

Brian D. Gonzalez, Heather S.L. Jim, Margaret Booth-Jones, Brent J. Small, Steven K. Sutton, Hui-Yi Lin, Jong Y. Park, Philippe E. Spiess, Mayer N. Fishman, and Paul B. Jacobsen

Listen to the podcast by Dr Slovin at www.jco.org/podcasts

- Evaluated 58 men at baseline, 6 months, and 12 months after starting ADT
- Cognitive performance compared against non-ADT controls

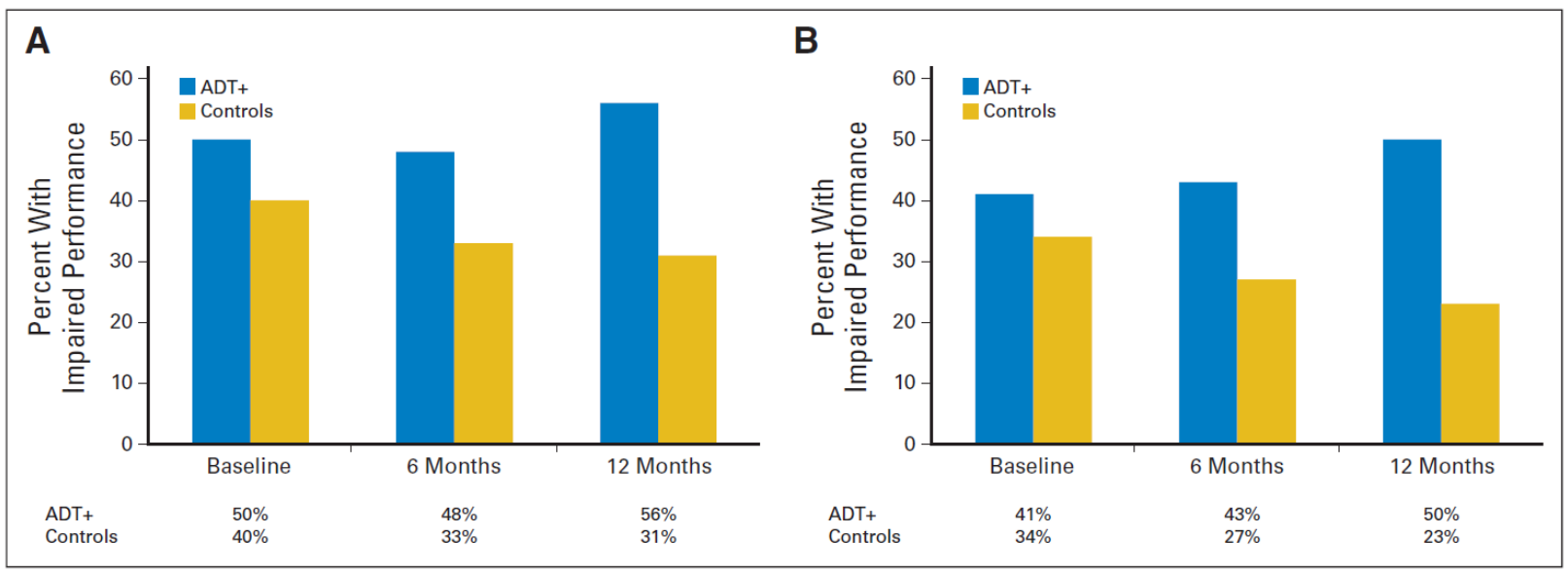


Fig 1. Observed rates of cognitive impairment in group of patients with prostate cancer receiving androgen-deprivation therapy (ADT+) and control group. Criteria for impaired cognitive performance: (A) scoring ≥ 1.5 standard deviations (SDs) below published norms on ≥ two tests or 2.0 SDs below published norms on ≥ one test (group differences in change over time $P = .05$); (B) scoring ≥ 2.0 SDs below published norms on ≥ one test (group differences in change over time $P = .01$).

ADT patients had more cognitive impairment at 6 and 12 months

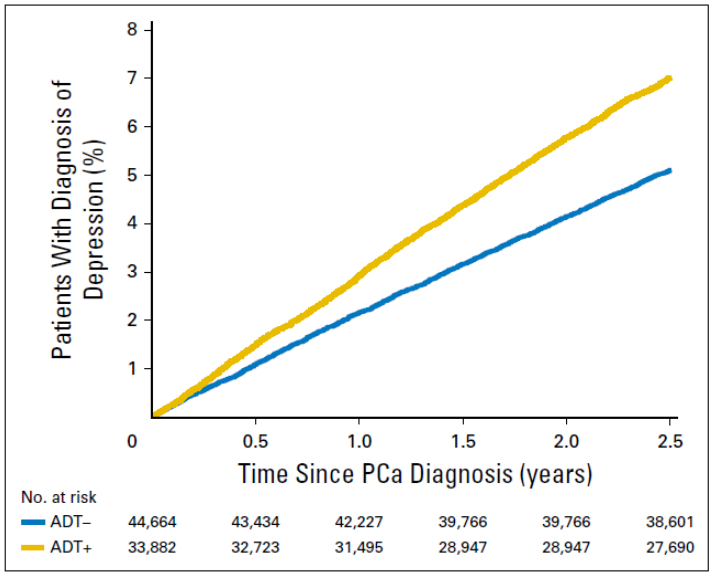
VOLUME 34 · NUMBER 16 · JUNE 1, 2016

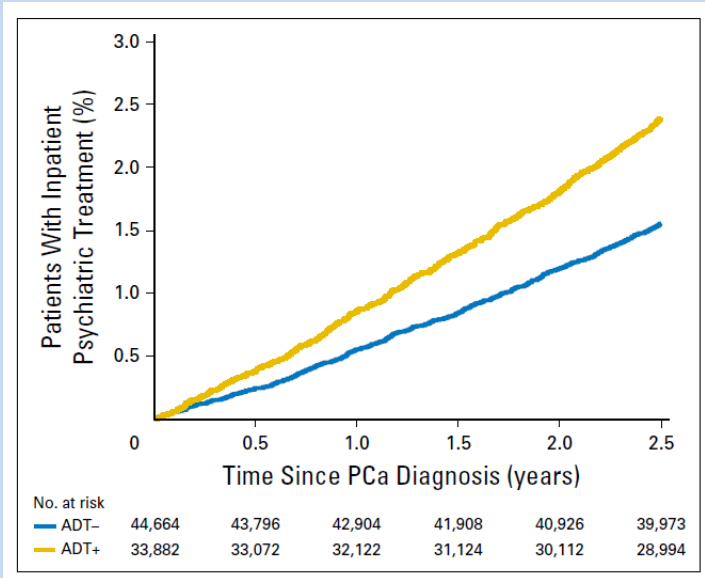
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Association of Androgen Deprivation Therapy With Depression in Localized Prostate Cancer

Kathryn T. Dinh, Gally Reznor, Vinayak Muralidhar, Brandon A. Mahal, Michelle D. Nezolosky, Toni K. Choueiri, Karen E. Hoffman, Jim C. Hu, Christopher J. Sweeney, Quoc-Dien Trinh, and Paul L. Nguyen





Depression risk increased with longer duration ADT

<6mos HR 1.12

6-12mo HR 1.26

>12mo HR 1.37

Cardiovascular Health

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;

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

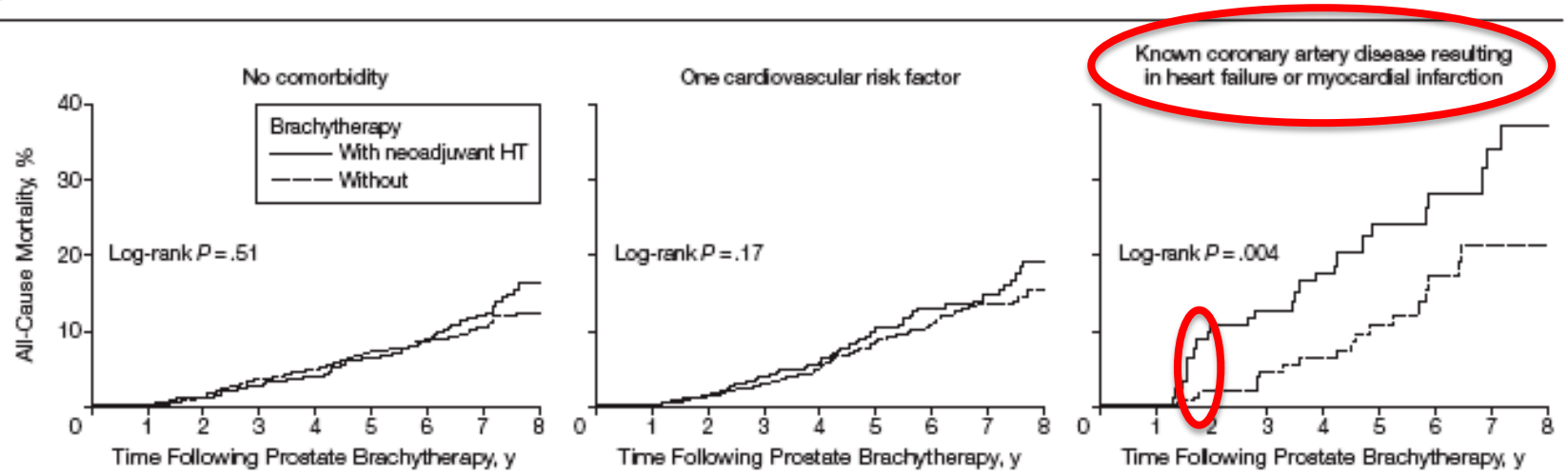
FDA
U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

[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

Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction

Nanda A et al. JAMA 2009;302(8):866–73

Figure. Risk of All-Cause Mortality in Men With Prostate Cancer Who Received Brachytherapy With or Without Neoadjuvant Hormonal Therapy (HT)



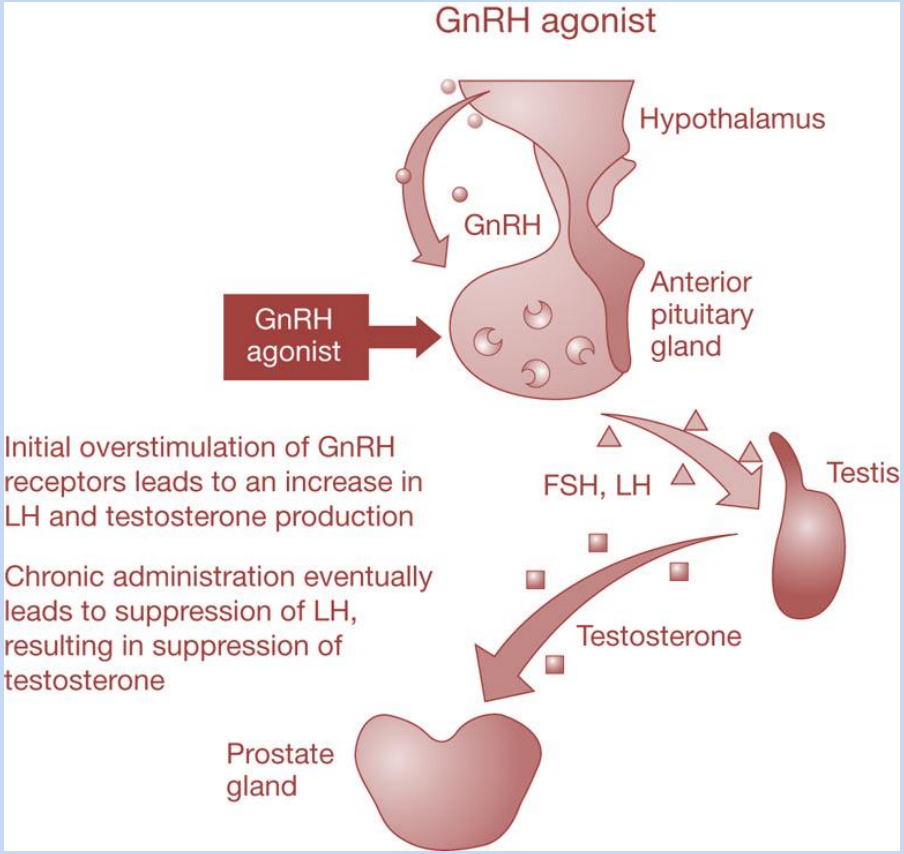
No. at risk

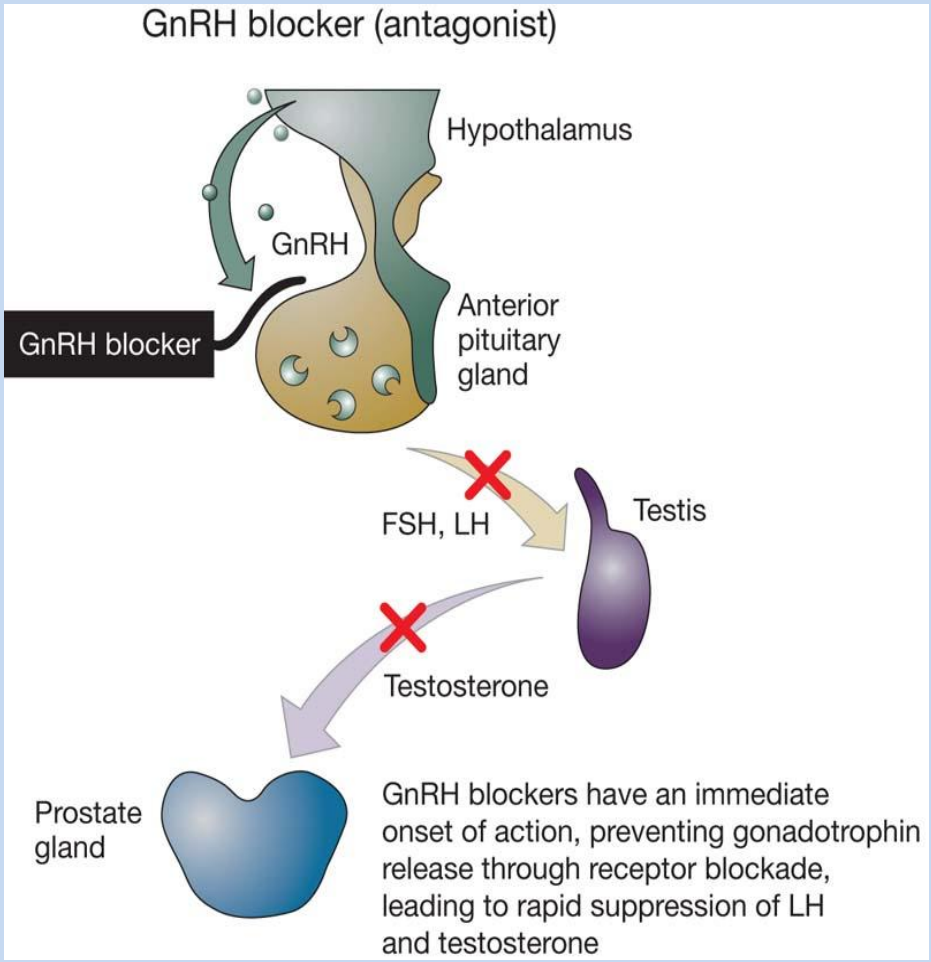
Brachytherapy															
With neoadjuvant HT	780	699	532	288	98	646	566	373	176	55	95	79	58	30	8
Without	1873	1582	1073	607	262	1522	1247	765	392	151	161	135	97	46	18

There were 2653 men with no comorbidity; 2168 with 1 cardiovascular risk factor including diabetes mellitus, hypercholesterolemia, or hypertension; and 256 with known coronary artery disease resulting in congestive heart failure or myocardial infarction. After applying the Bonferroni correction, *P* values <.017 are significant.

Nanda A et al. JAMA 2009;302(8):866–73

A new class of agents - GnRH receptor agonists and blockers





Brawer M. Rev Urol 2001; 3(Suppl 3): S1–S9

FSH, follicle-stimulating hormone; LH, luteinising hormone; GnRH, gonadotrophin-releasing hormone

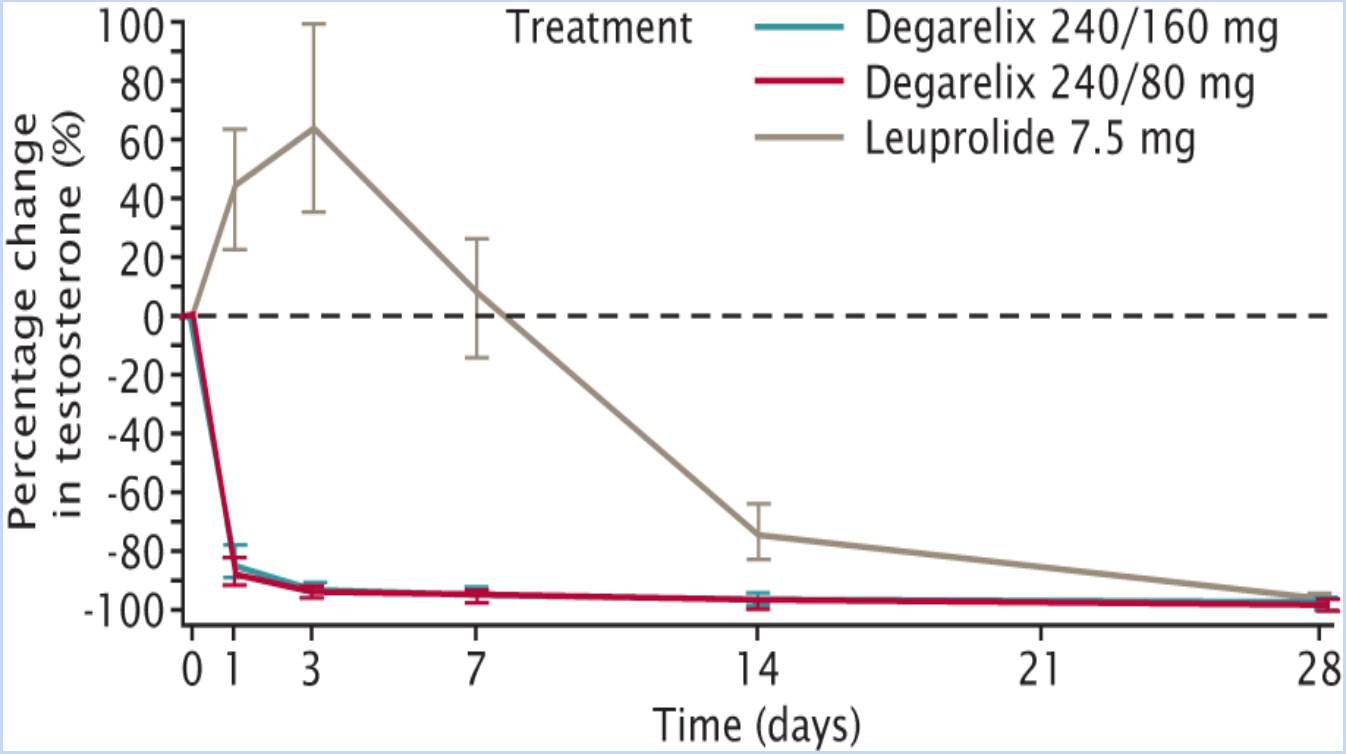
Degarelix – GnRH Antagonist

Phase III CS21 Study

	Degarelix 240➔160 mg	Degarelix 240➔80 mg	Leuprolide 7.5 mg
Number of patients (ITT)	202	207	201
Age (years)	72.1	71.6	72.5
Weight (kg)	78.7	79.8	79.4
BMI (kg/m^2)	26.6	26.7	26.9
PCA stage			
Localised	29%	33%	31%
Loc. Advanced	31%	31%	26%
Metastatic	20%	18%	23%
Not classifiable	20%	18%	19%
Gleason Score			
2-4	11%	10%	12%
5-6	33%	33%	32%
7	28%	30%	31%
8-10	28%	27%	26%

CS21

Median testosterone change from baseline from day 0 - 28



Leuprolide Testosterone day 3 +70%

Degarelix Testosterone day 3 - 96%

Ref: Data on file

Klotz *et al* BJU Int 2008 102 1531

CS21 Primary endpoint – results

Probability of testosterone ≤ 0.5 ng/mL from day 28 - 364

	Success criterion	Degarelix 240➔160 mg	Degarelix 240➔80 mg	Leuprolide 7.5 mg
Number of escapers		3/202	5/207	7/201
Response rate	FDA: CI ≥90 %	**98.3 %** (94.8-99.4 %)	**97.2 %** (93.5-98.8 %)	**96.4 %** (92.5-98.2 %)
Difference to leuprolide	EMEA: CI ≥-10 % points	**1.9 %** (-1.8 to 5.7%)	**0.9 %** (-3.2 to 5.0 %)	

Klotz *et al* BJU Int 2008 102 1531

CS21

Adverse Events

	Degarelix 240➔160 mg	Degarelix 240➔80 mg	Leuprolide 7.5 mg
Any AE	**83%**	**79%**	**78%**
Hot flush	26%	26%	21%
Injection site AEs	**44%**	**35%**	**<1%**
Weight increased	11%	9%	12%
ALT	8%	10%	5%
[ALT > 3 ULN (lab)]	7%	7%	6%
Back pain	6%	6%	8%
Arthralgia	3%	5%	9%
Hypertension	7%	6%	4%
Fatigue	6%	3%	6%
Urinary tract infection	1%	5%	9%
Nausea	5%	4%	4%

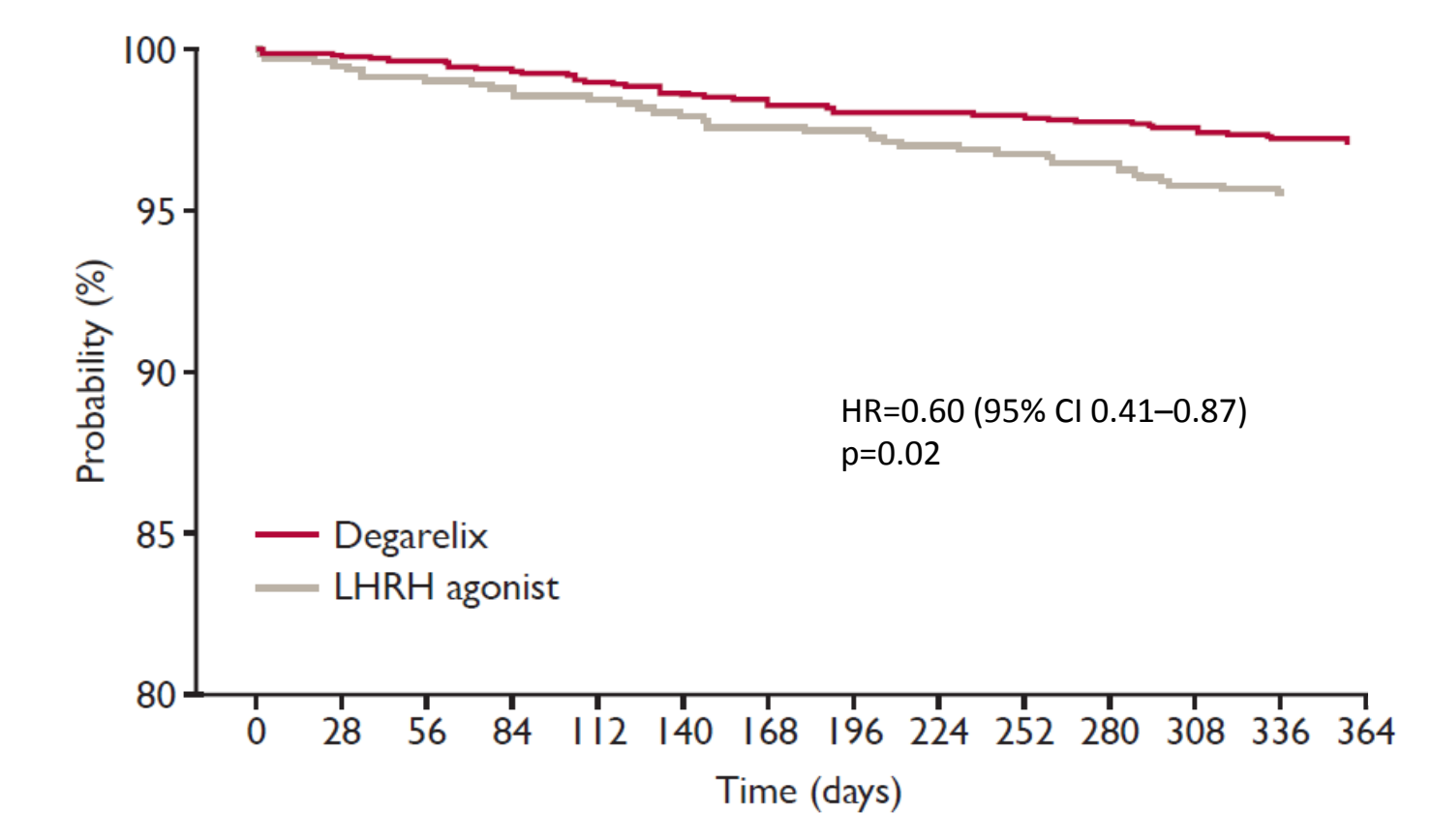
GnRH antagonist degarelix appears to have less impact on CV events

Comparison of the risk of cardiovascular events and death in patients treated with degarelix compared with LHRH agonists
Albersten et al. J Clin Oncol 2013;31 (suppl 6; abstract 42)

Materials, patients and methods

- Data were pooled from 6 prospective, randomized trials (n=2,328) comparing degarelix and LHRH agonists
- Event analysis was based on death from any cause or occurrence of a serious CV event
- A serious CV event was an event considered life-threatening or that required hospitalisation
- The treatment groups were balanced for common baseline and CV characteristics

Lower risk of CV event or death with degarelix (all patients)

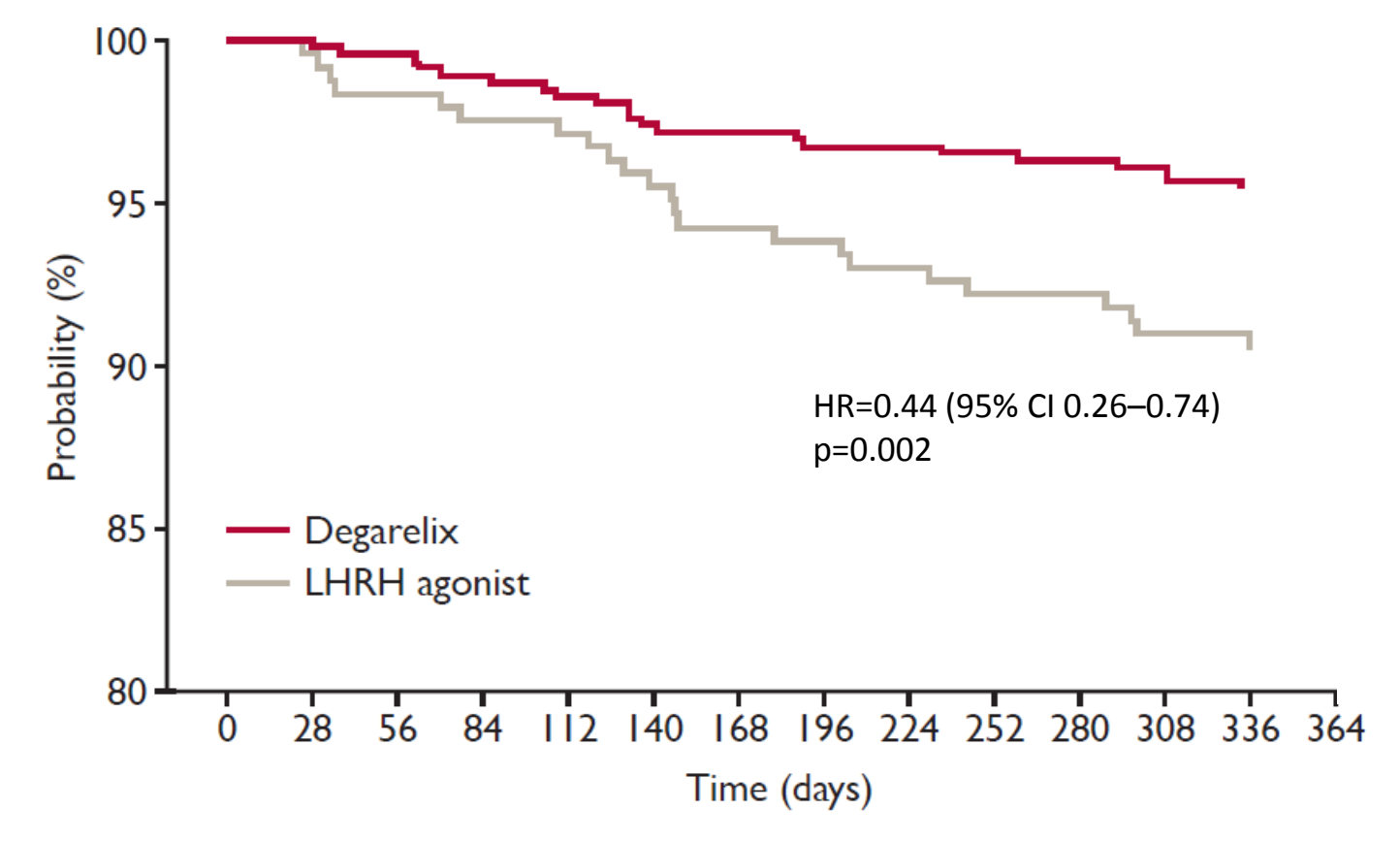


HR adjusted for common CV risk factors including age, statin use, hypertension and serum cholesterol by Cox regression

Albertsen PC et al. Euro Urol, submitted

Tombal B et al. EAU 2013, poster 677

Lower risk of CV event or death with degarelix in men with baseline CVD



HR adjusted for common CV risk factors including age, statin use, hypertension and serum cholesterol by Cox regression

Albertsen PC et al. Euro Urol; submitted

Tombal B et al. EAU 2013, poster 677

Conclusions

- Over one year of treatment, when patients with a history of CVD at baseline were treated with degarelix, they had:
  - A significantly lower probability of a serious CV event or death than those treated with a LHRH agonist.
  - A reduction in risk of experiencing a serious CV event of greater than 50% compared with those treated with a LHRH agonist.
- Men in need of ADT, especially those with a history of CVD, may have a significantly lower risk of CVD sequelae with the GnRH antagonist, degarelix, compared with a LHRH agonist.

Albertsen P et al. Poster 781. AUA 2013

Monitoring of ADT-treated patients

- Blood pressure
- Fat mass (abdominal perimeter or impedance technique)
- Cholesterol total and HDL
- Fasting glucose/HbA1C
- Triglycerides
- Bone Density
- Psychological Assessment

Ferrari F1

Ferrari F1