Minimizing morbidity and maximizing outcome with ADT

Southwest Prostate Cancer Symposium 2018

Developments in last decade:

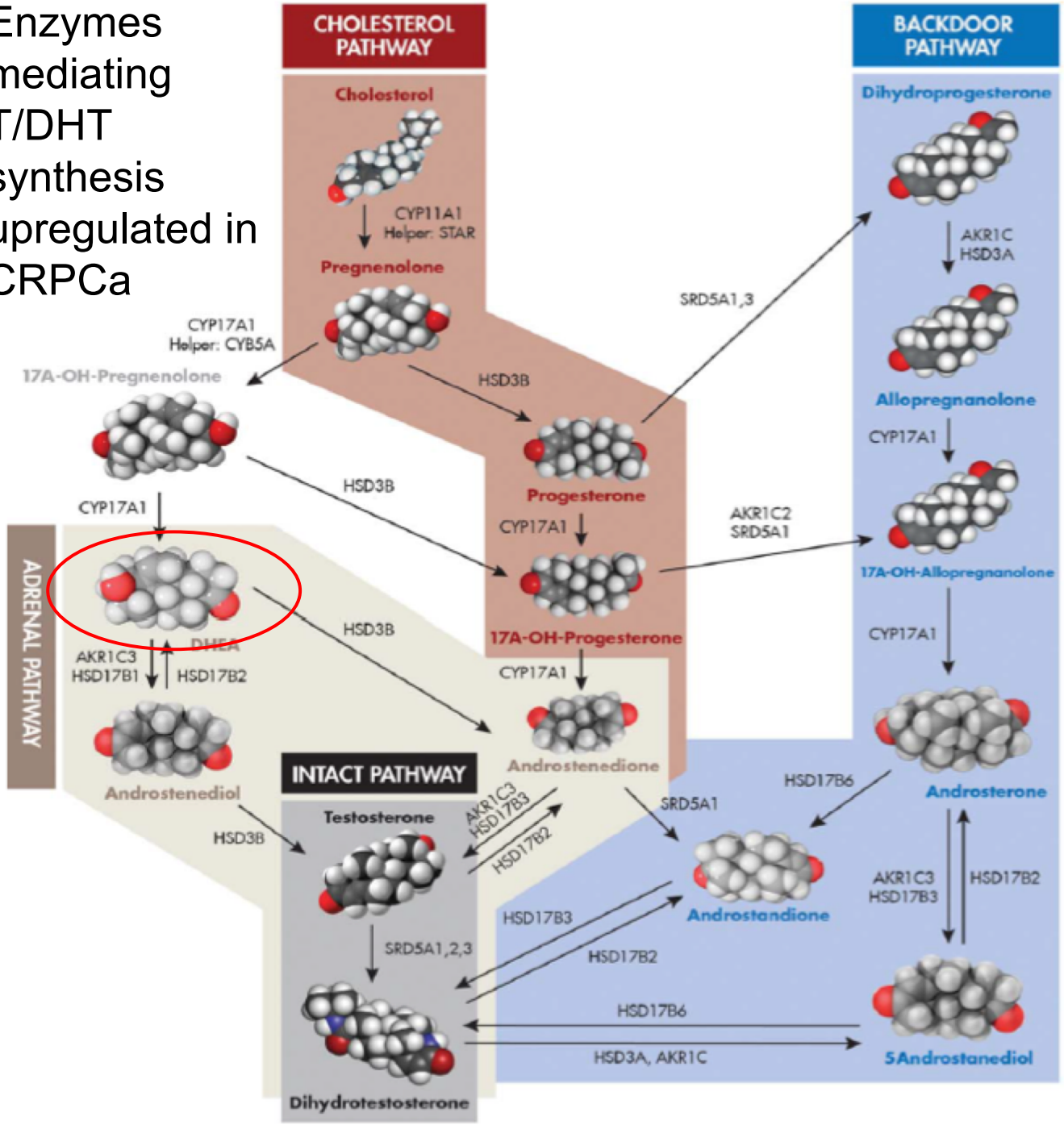
- Understanding of mechanisms of castration resistance (autocrine androgen synthesis, AR mutations, splice variants, other AR pathway alterations)
- Dynamic treatment induced biological evolution
- Systemic/Metabolic/CV effects of ADT
- Intermittent therapy: data from large RCTs
- Importance of testosterone levels on ADT
- LHRH antagonists
- Survival benefit in HSPC and CRPC with new AR pathway targeted agents

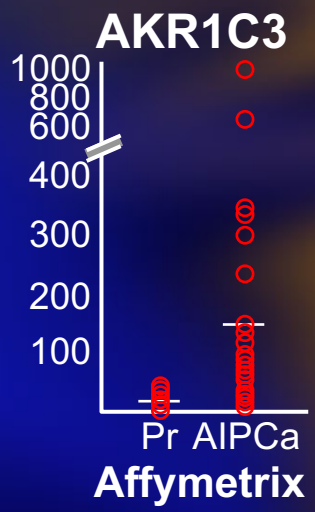
First: Some recent observations about ADT

ADT: minimising adverse events

Therapy	Treatment/prophylaxis
Loss of libido	**Intermittent ADT** (↓ most adverse effects)
Erectile dysfunction	PDE5s, intracavernosal injection, vacuum device
Hot flashes	DES, Cyproterone, Venlafaxine Clonidine, **Evening Primrose Oil**
Gynaecomastia and breast pain	Prophylactic XRT, mammectomy, liposuction; tamoxifene, aromatase inhibitors
Increase in body fat	Diet (fish and vegetables)
Muscle wasting	**Resistance Training**
Diabetes	Diet and weight control, **monitor Hb1Ac**
Cardiovascular disease	Smoking cessation, monitor blood pressure, serum lipids**, statins, LHRH antagonists**
Cognitive decline	Memory exercises
Decrease in bone mineral density	Exercise/lifestyle, calcium+ vitamin D, **bisphosphonates (aledronate), Denosomab q 6/12**

Enzymes mediating T/DHT synthesis upregulated in CRPCa

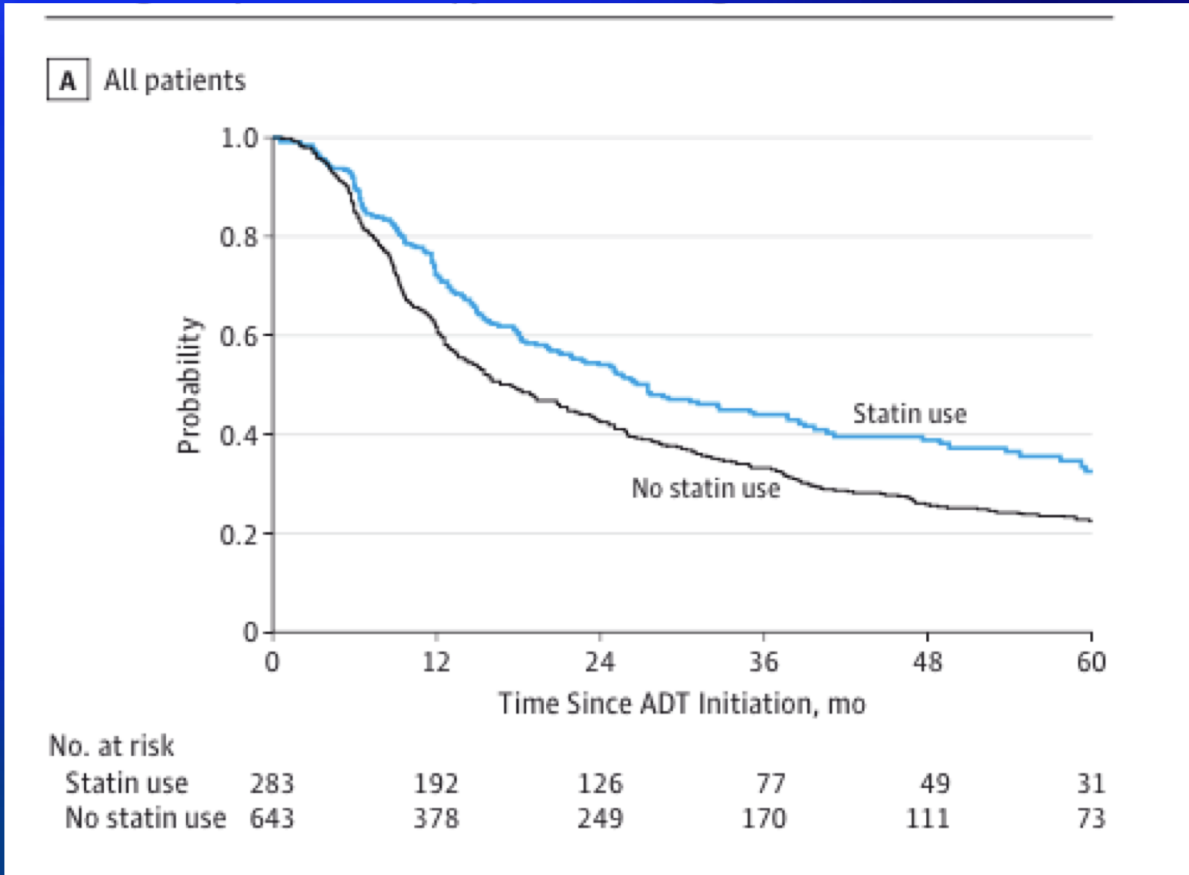




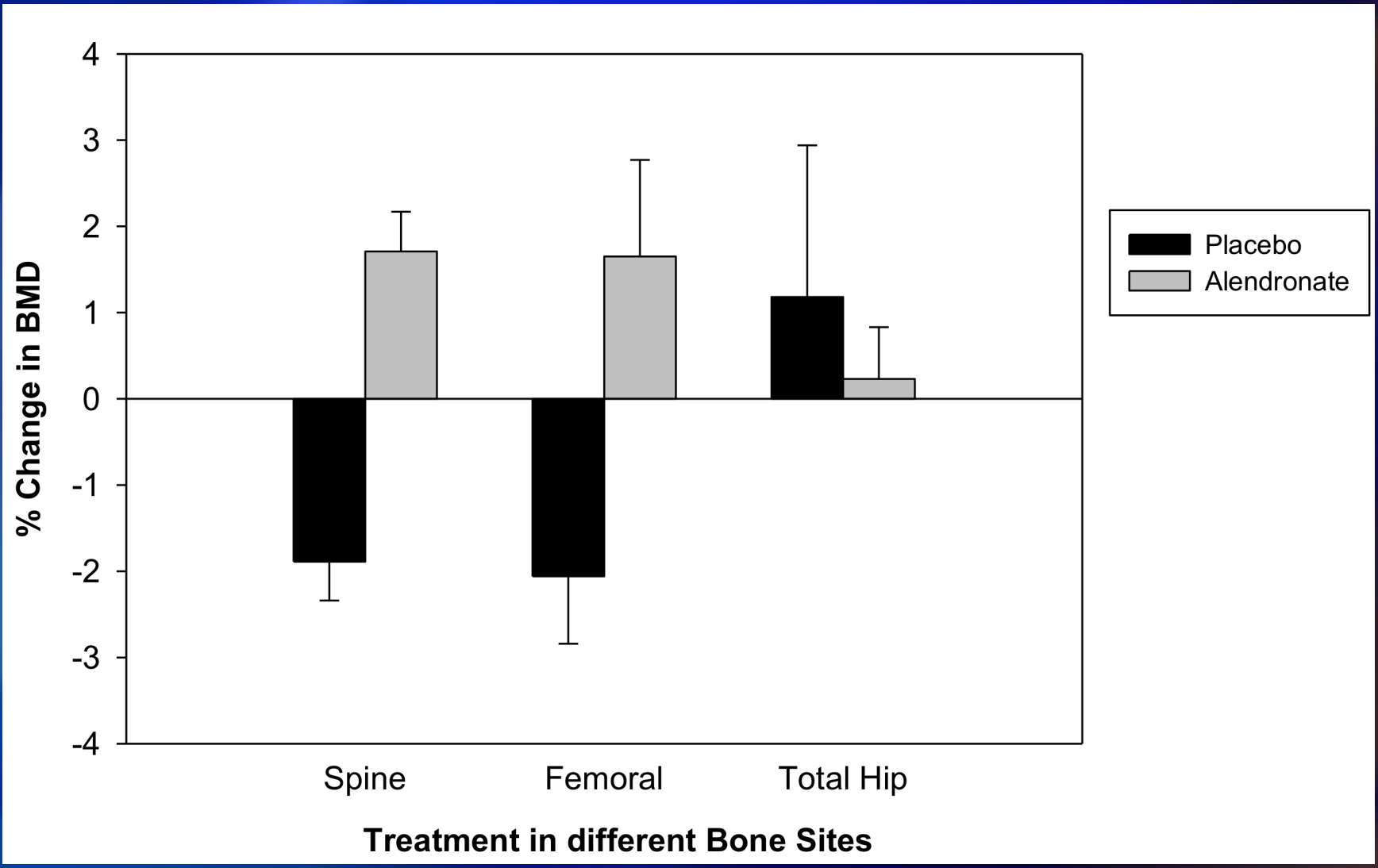
Time to progression in men on ADT: Statins

Harshman L et al *JAMA Oncol*. 2015;1(4):495-504.

- DHEA sulfate: Testosterone precursor of adrenal origin
- Dependent on transporter SLCO2B1 to enter cells
- Statins also SLCO2B1 dependent, competes with DHEAS uptake, reduces intracellular T

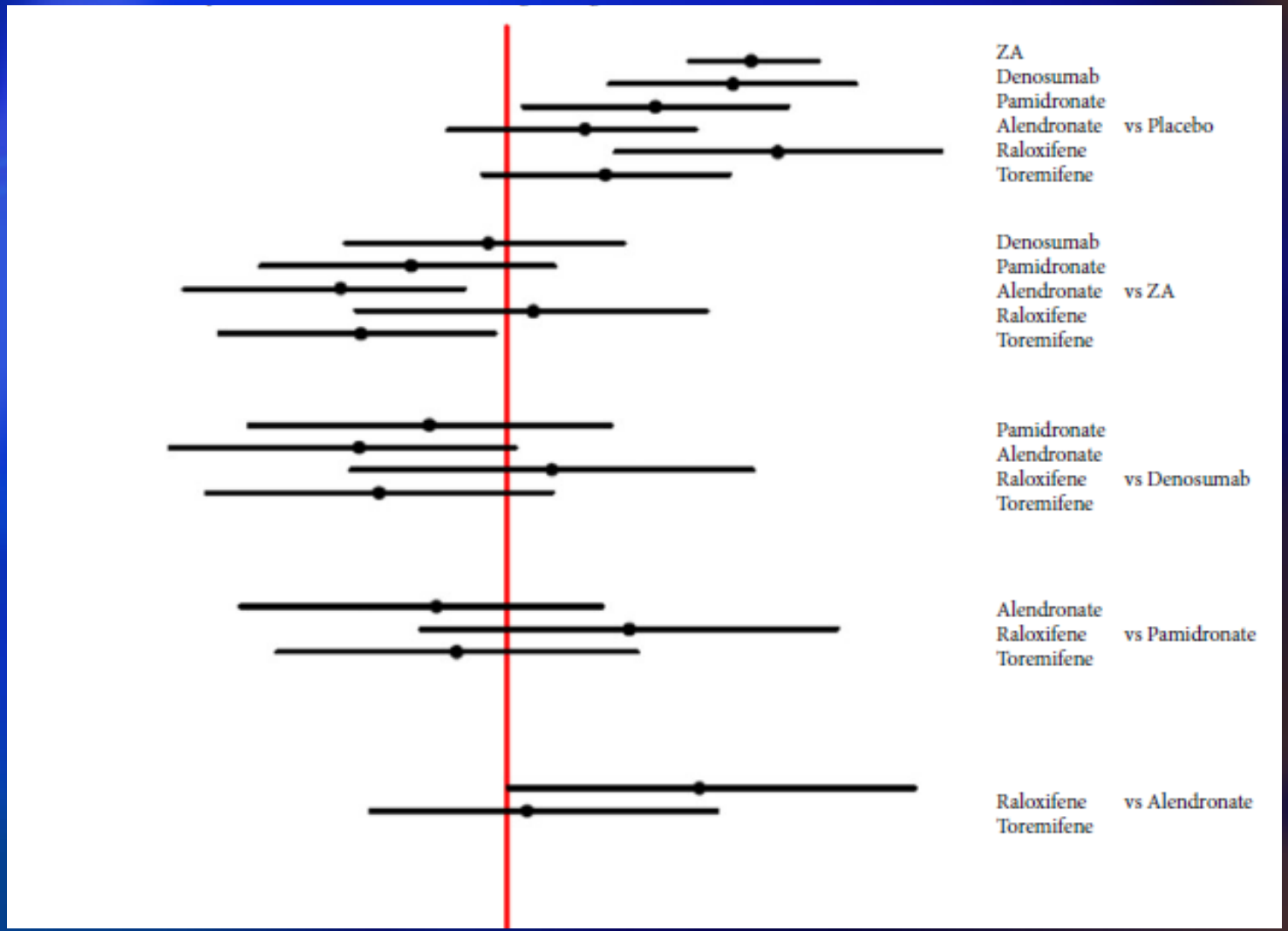


BMD after 1 year of Lupron + Aledronate 70 mg/week vs placebo Klotz L et al, J Urol 2013 N=100



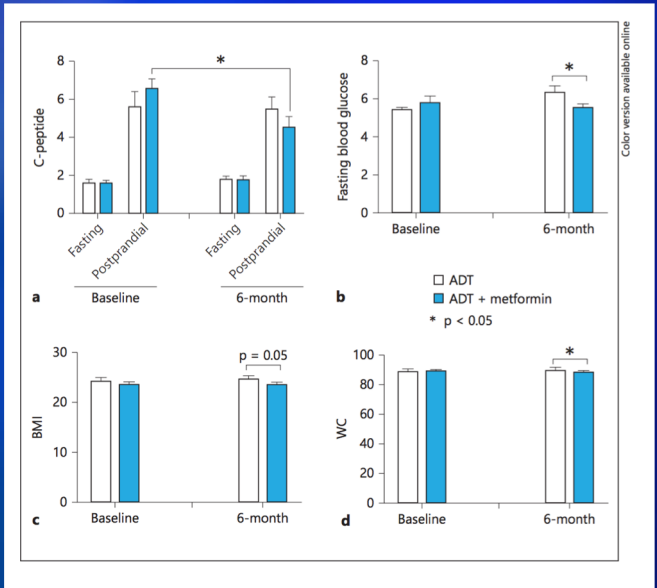
Efficacy of osteoporotic medications in men on ADT to reduce risk of fragility fractures Poon Y et al, BJU Int 2018; 121: 17–28

Total hip: Mean % change in BMD



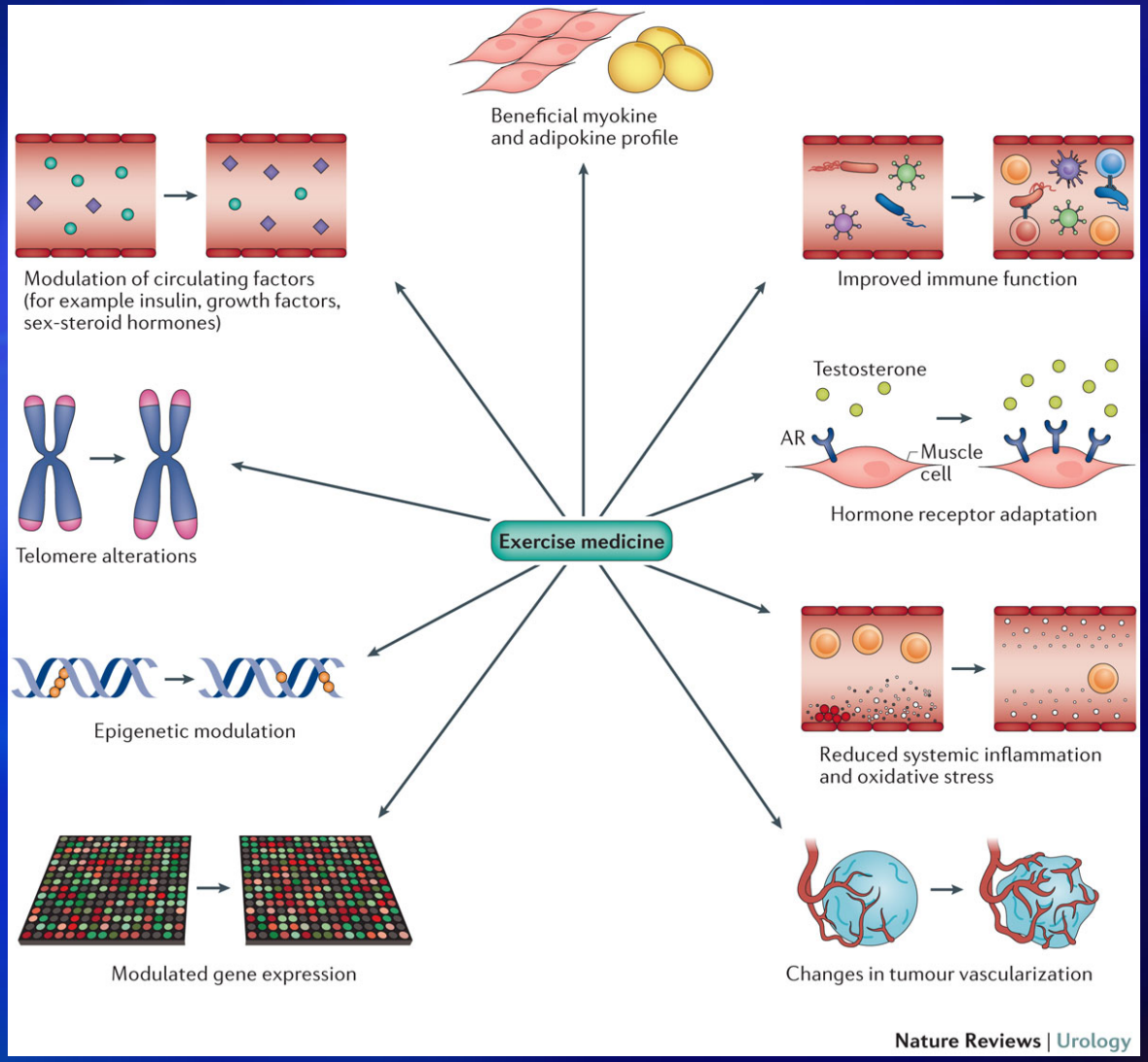
Metformin with ADT.

- Zhu W, Urol Int. 2017;98(1):79-84
- 62 men randomized between ADT and ADT + Metformin 500 mg tid x 6/12
- ADT group had higher fasting glucose and waist circumference (WC)



- Nobes J BJU Int. 2012 May;109(10):1495-502
- 60 patients randomized to ADT +/- metformin 850-1700 mg/day + low Glycemic diet + exercise x 6 months
- • Significant improvements in abdominal girth, weight , BMI, and BP in Metformin group

Potential mechanisms by which exercise delays the progression of prostate cancer



Galvão, D. A. *et al.* (2016) Enhancing active surveillance of prostate cancer: the potential of exercise medicine *Nat. Rev. Urol.*

Intermittent therapy (IADT) and on-treatment testosterone levels

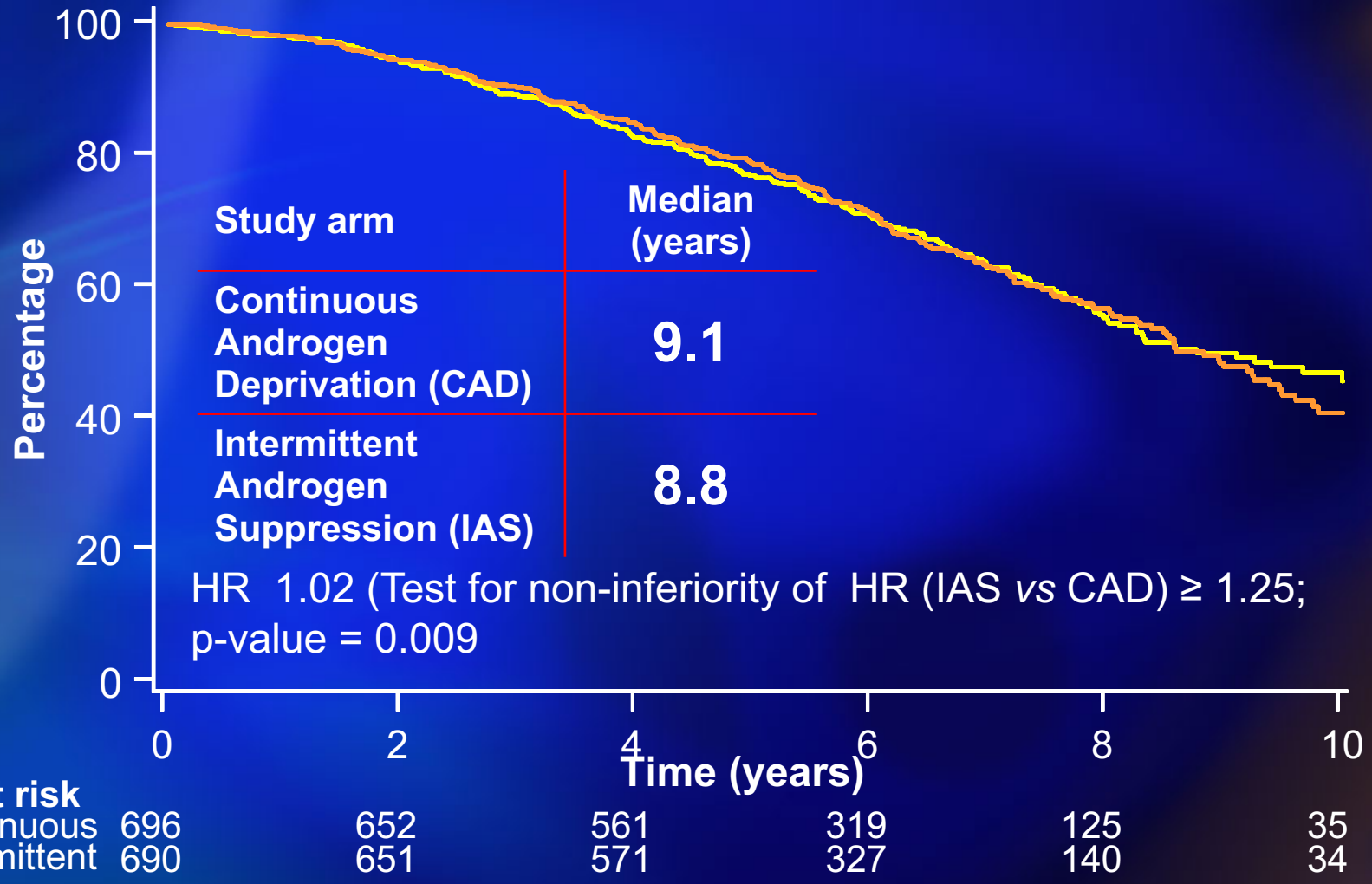
- IADT widely accepted for nmHSPC (PSA failure)
- Controversial for mHSPC
  - Role limited to those with complete PSA response (< 0.2 ng)

Phase 3 Trials of IAS with > 100 patients

Trial	Mo IAD	Stage	N	Results
PR7 (Canada)	8	PSA failure	1486	IAS Non-inferior
SWOG 9346	7	M1	1500	Inconclusive
ICELAND	6	PSA failure	701	IAS Non inferior
SEUG (Portugal)	3	T3,4 or M1	914	No difference in OS
AP17/95 (Germany)	6	T3,4 or M1	335	No diff in TTP or OS
EC507 (Europe)	6	Post RP rising PSA	167	No diff TTP
Erasmus	6	M1	366	QOL better
FinnProstate VII	6	T3,4, M1	564	Pending
TULP (Netherlands)	6	T3,4, M1	193	Longer TTP in CAS (NS)
Yamanaka	6	T3,4, adjuvant	188	Short f/u, no diff

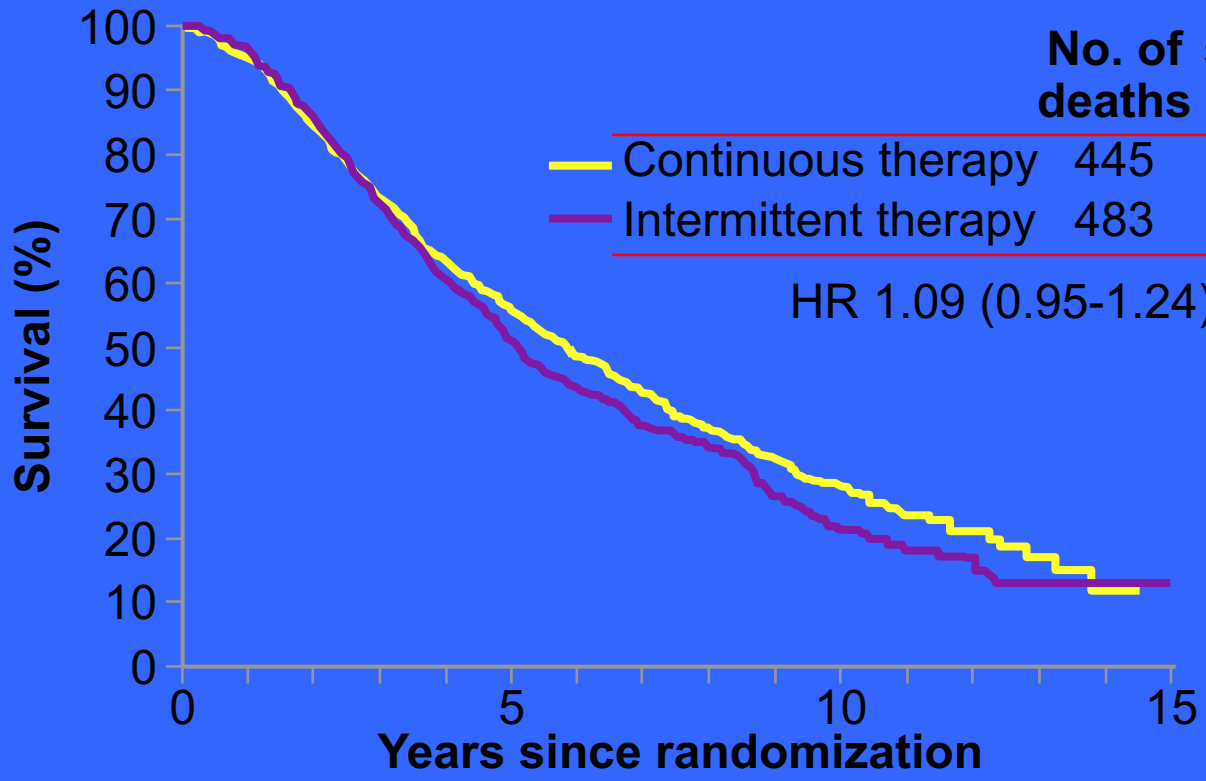
PR7: Overall survival (ITT)

- **1486 men with PSA recurrence: cycles of 8 mo IADT induction vs continuous life long ADT**



SWOG 9346 survival: M Hussain, NEJM 2013

Conclusion: 'Results inconclusive'



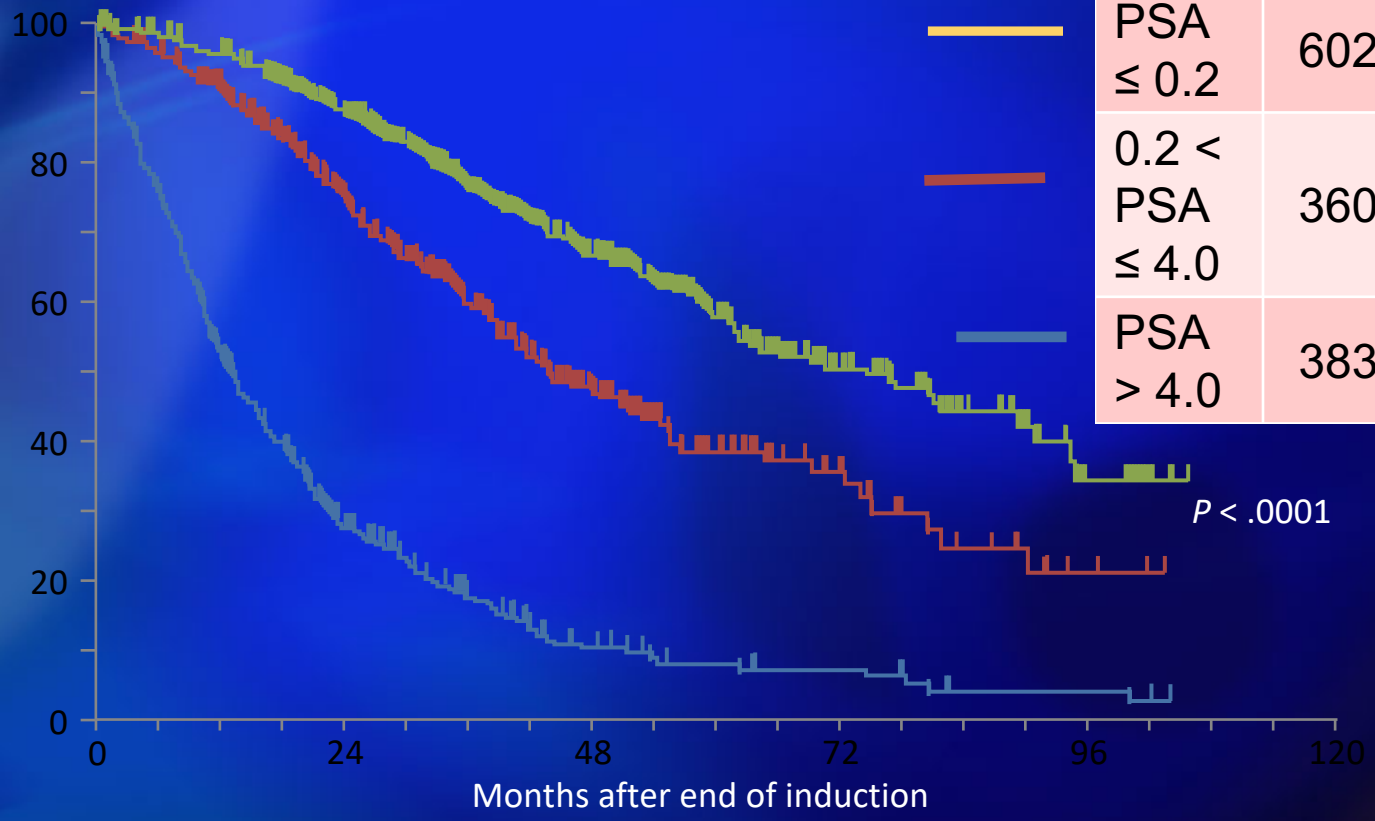
	No. of deaths	Median survival (years)
Continuous therapy	445	5.8
Intermittent therapy	483	5.1

HR 1.09 (0.95-1.24)

No. at risk

Continuous therapy	765	325	64
Intermittent therapy	770	291	52

PSA Response is Predictive of Outcome:
PSA at end of 7-month induction period and OS

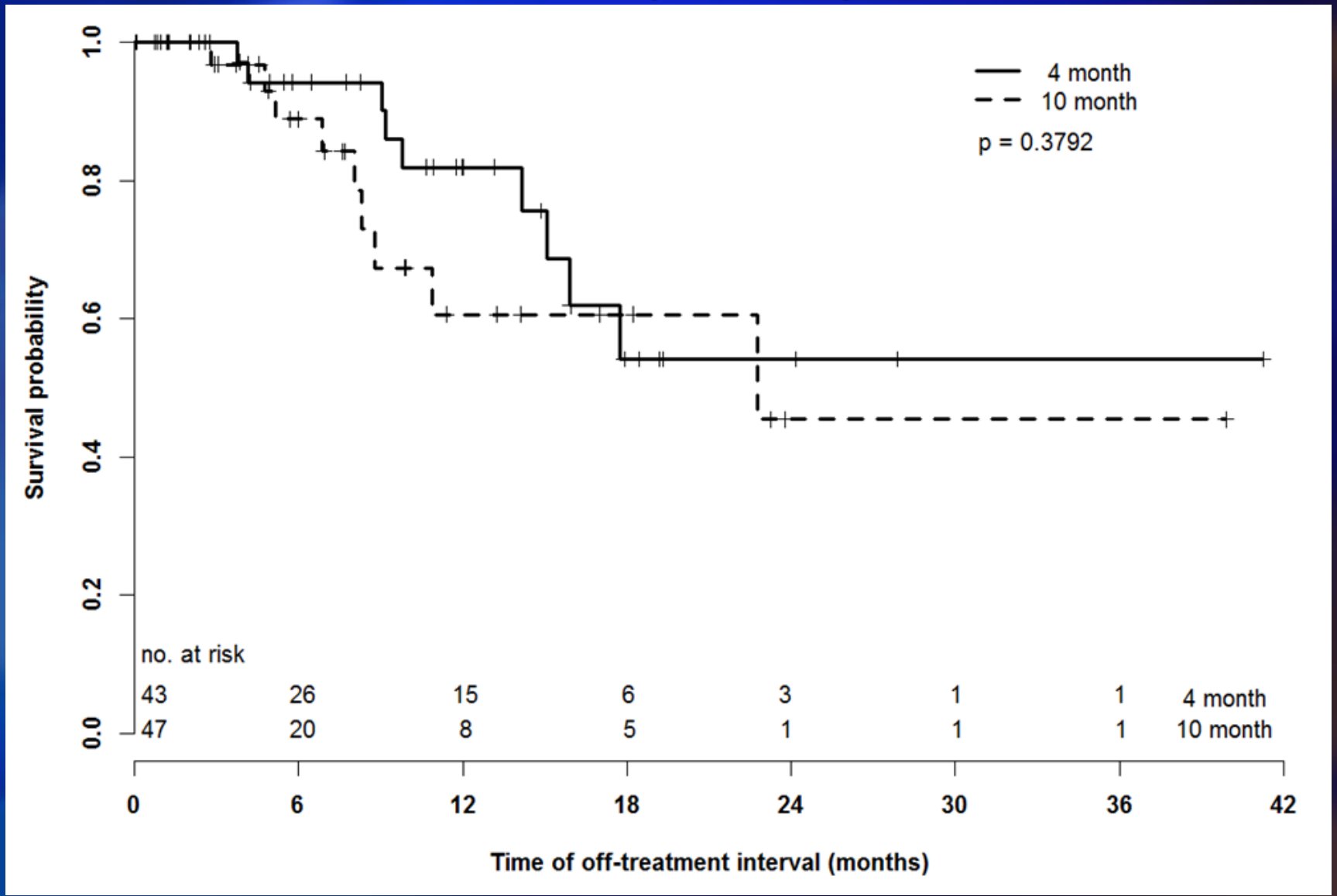


	At Risk	Deaths	Median in Months
PSA ≤ 0.2	602	199	75
0.2 < PSA ≤ 4.0	360	166	44
PSA > 4.0	383	322	13

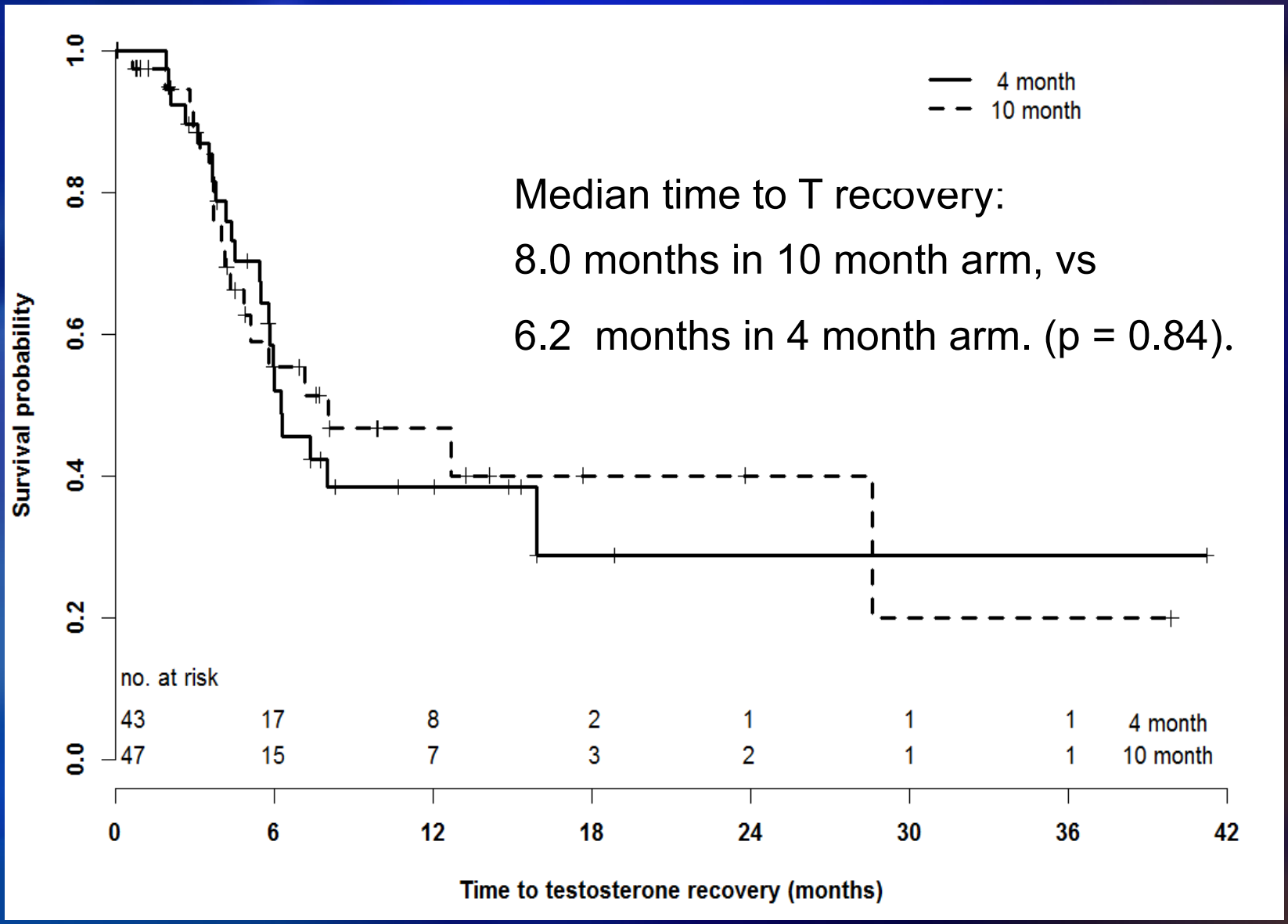
Hussain M, *et al. J Clin Oncol*. 2006;24:3984-3990.

4 vs 10 month study (FIT): Klotz L, AUA 2017

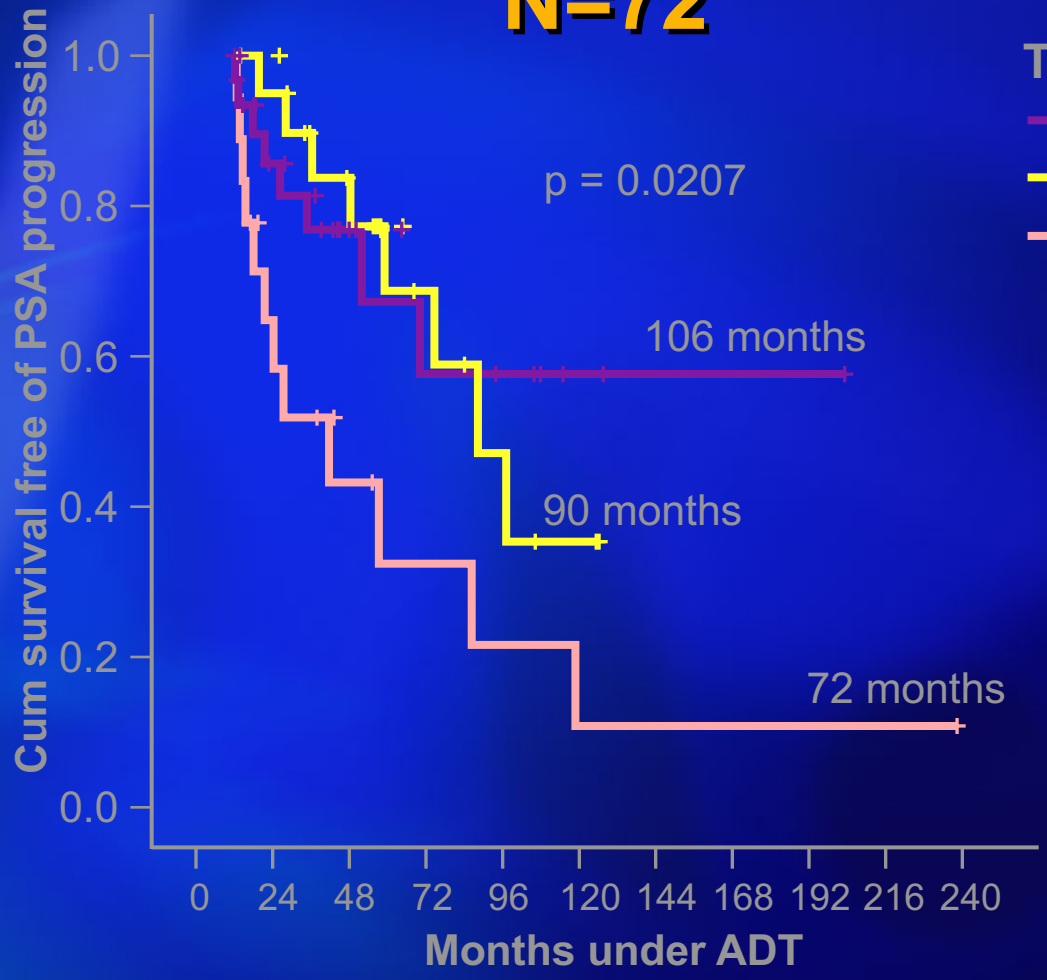
Median off treatment interval: ~24 months both arms (p=0.38)



Time to T recovery > 8 nM: No difference



Time to CRPC according to serum testosterone on ADT. Morote et al. *J Urol*. 2007;178:1290–1295



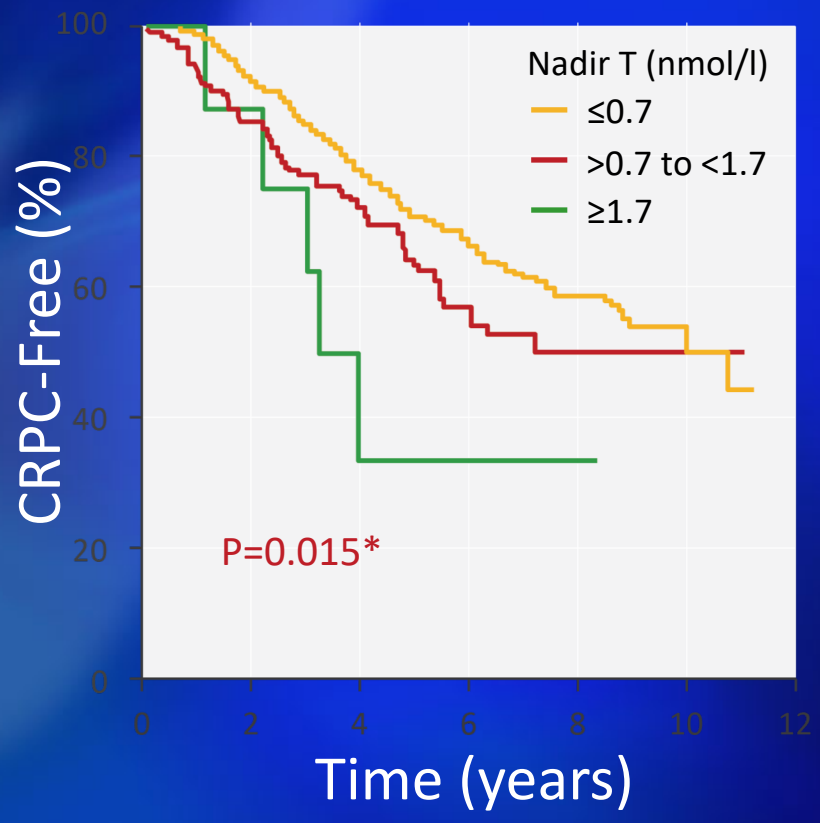
20 ng/dL = 0.7 nmol/L
50 ng/dL = 1.7 nmol/L

Prospective Analysis of PR7 Trial ADT Outcomes by T Level

- Prospective secondary analysis of the randomized, open label PR7 trial
- N=626
  - patients with biochemical progression after radical therapy
  - treated with continuous ADT*
- Hypothesis was that lower nadir testosterone in the first year would correlate with longer time to CRPC and longer CSS

Klotz L, et al. J Clin Oncol 2015;33:1151-6

PR7 Time to CRPC Relative to Nadir T Level



Nadir T (nmol/l)	Median (years)	HR [95% CI]
≤0.7	10.0	1
>0.7 to <1.7	7.21	1.62 [1.20-2.18]
≥1.7	3.62	1.90 [0.98-4.70]

Nadir testosterone level ≤0.7 nmol/l was associated with a lower risk of developing CRPC compared with higher levels (P=0.02)

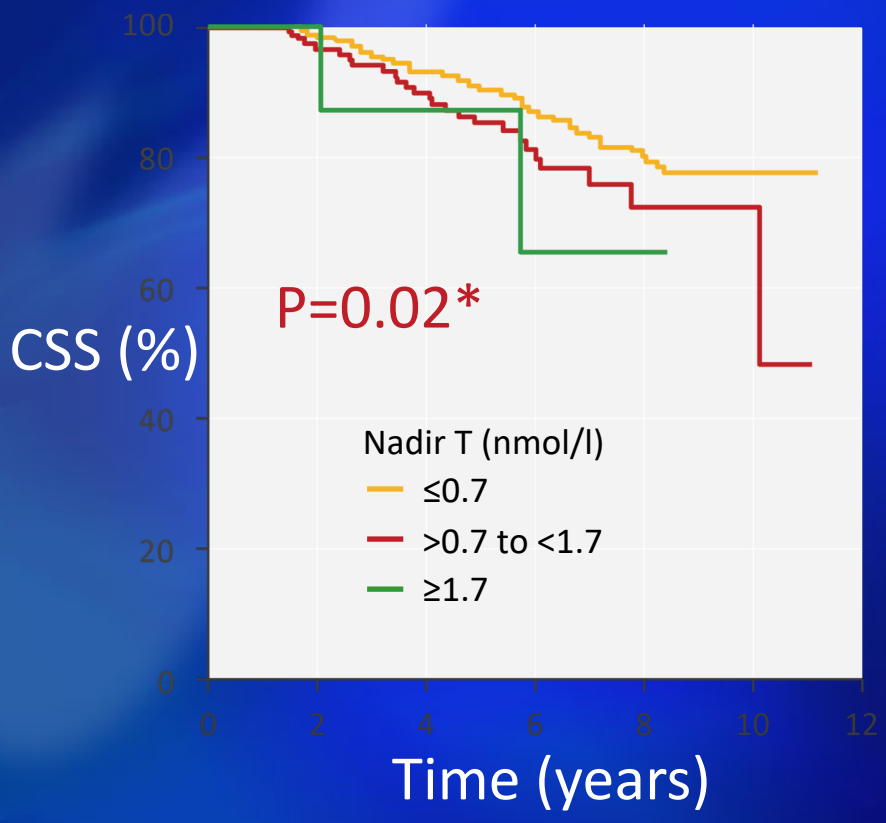
*Adjusted for multiple test based on the Hochberg method

CRPC = castration-resistant prostate cancer

T = testosterone

Klotz L, et al. J Clin Oncol 2015;33:1151-6

PR7 Cause-Specific Survival Relative to Nadir T Level



Nadir T (nmol/l)	Median (years)	HR [95% CI]
≤0.7	Not reached	1
>0.7 to <1.7	10.07	2.08 [1.28-3.38]
≥1.7	Not reached	2.93 [0.70-12.30]

*Adjusted for multiple test based on the Hochberg method

CSS = cause-specific survival

T = testosterone

Klotz L, et al. J Clin Oncol 2015;33:1151-6

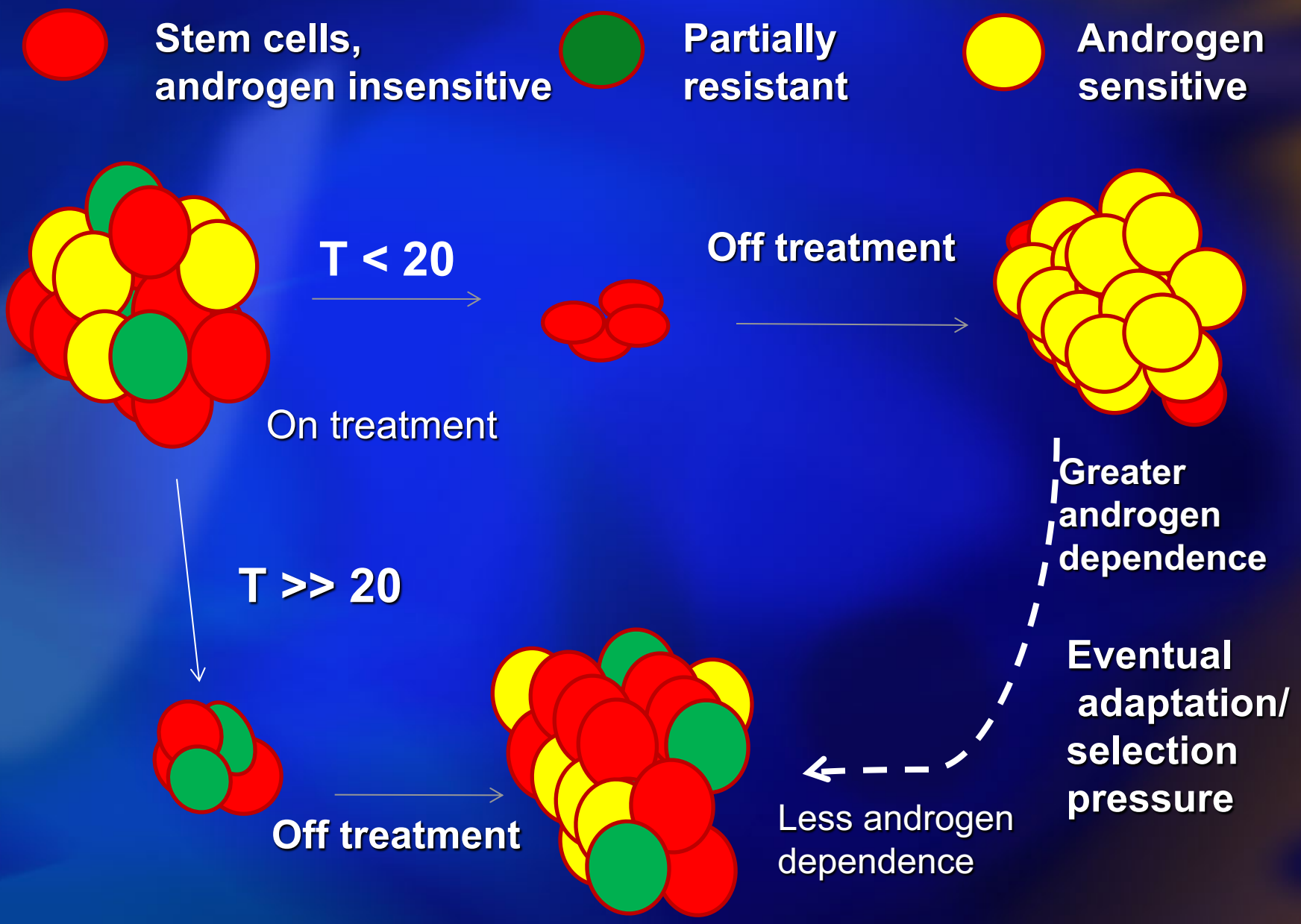
Retrospective Data on T and outcome

ADT * Study	N/Setting Assay Timing	T Level	Assoc. between Low T and Outcome		
			PFS	OS/CSS	PSA level
Pickles 2012[1] Database Review	2196/L, LA Variable	Breakthrough >1.1 or >1.7 nmol/l vs no breakthrough			✓ P=0.008 and P=0.003
Kamada 2015[2] Multi-Center	225/L, LA & Met Multiple	Nadir: <0.7 vs ≥0.7 nmol/l	X P=0.1163	✓ P<0.0014	
Perachino 2010[3] Single-Center	129/Met Every 3 mo.	1.4 (6 mo. mean)		✓ P<0.05	
Shiota 2016[4] Single-Center	96/LA & Met Random, median 2x	Mean: 0.1 vs 0.1-2.6 nmol/l	X P=0.70	✓ P=0.014	
Morote 2007[5] Single-Center	73/L, LA Every 6 mo., ≥3x	Breakthrough: <0.7 vs 0.7-1.7 vs >1.7 nmol/l	✓ P=NR		
Yasuda 2015[6]	69/Met Every 3-6 mo., mean 5.5x	Median: <0.7 vs ≥0.7 nmol/l		X OS: P=0.17 CSS: P=0.29	X P=0.66**

Prospective Data on T Levels on ADT and PCa Outcomes

ADT * Study	N/Setting	T Level	Assoc. between Low T and Outcome		
			Time to CRPC	PFS	OS
Klotz 2015[1] RCT, Multi-center	626/Recur-rent	Nadir: ≤0.7 nmol/l vs >0.7 to <1.7 vs ≥1.7 nmol/l	✓ P=0.015		✓ CSS: P=0.02
Wang 2016[2] Single-center	206/Met	≤0.9 nmol/l vs >0.9 nmol/l	✓ P=0.0004		
		<0.7 nmol/l vs ≥0.7 nmol/l;		X TTP: P=0.12	✓ P=0.020
Bertaglia 2013[3] Single-center	153/Met	≤1.0 nmol/l vs >1.0 nmol/l;		X TTP: P=0.30	✓ P=0.034
		<1.7 nmol/l vs ≥1.7 nmol/l		X TTP: P=0.51	X P=0.32
Kawakami 2013[4] Single-center	69/ Met	≤0.7 nmol/l vs >0.7 nmol/l	✓ P=0.003**		
Dason 2013[5] Cohort Study	32/L, LA, Met	<1.1 nmol/l vs 1.1-1.7 nmol/l	✓ P=0.05		

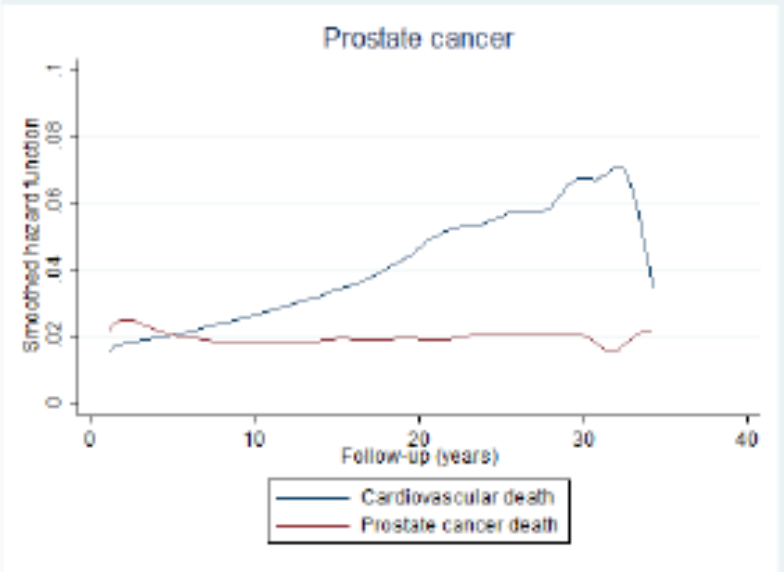
3 cell type model can explain conundrum



CV disease: LHRH Agonist vs Antagonist

Point #1: I hope we agree that

PC patients are at high risk of CVD



Hazard of CV and PC death as a function of time from PC diagnosis in men from the SEER registry.

Leong D et al not published

Point #1:

PC patients are at high risk of CVD

- Risk of MI, stroke, or CV death in PC patients >2% per year[1, 2]
- Risk of MI, stroke, or CV death in PC patients on ADT >4% per year[1, 2]
- CVD risk considered high if global risk estimate for hard CVD events of ≥2% per year[3]

1. Keating, *et al. JNCI* 2010; 102: 39
2. O'Farrell, *et al. JCO* 2015; 102: 39
3. Greenland *et al.* 2010 American Heart Association Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults. *Circulation* 2010; 122: e584

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European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by XXX on pp. x–y 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]

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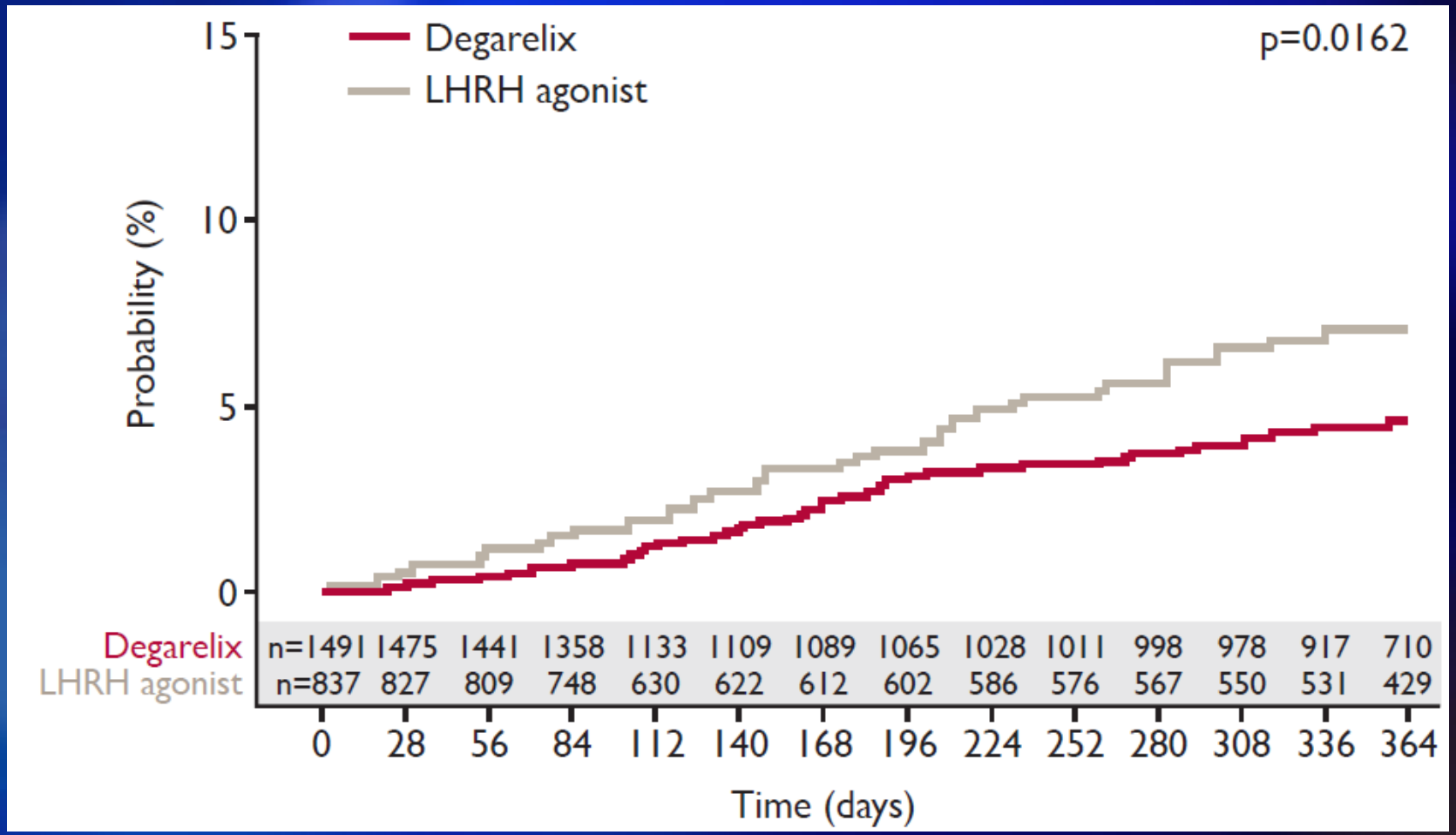
Prostate Cancer

Disease Control Outcomes from Analysis of Pooled Individual Patient Data from Five Comparative Randomised Clinical Trials of Degarelix Versus Luteinising Hormone-releasing Hormone Agonists

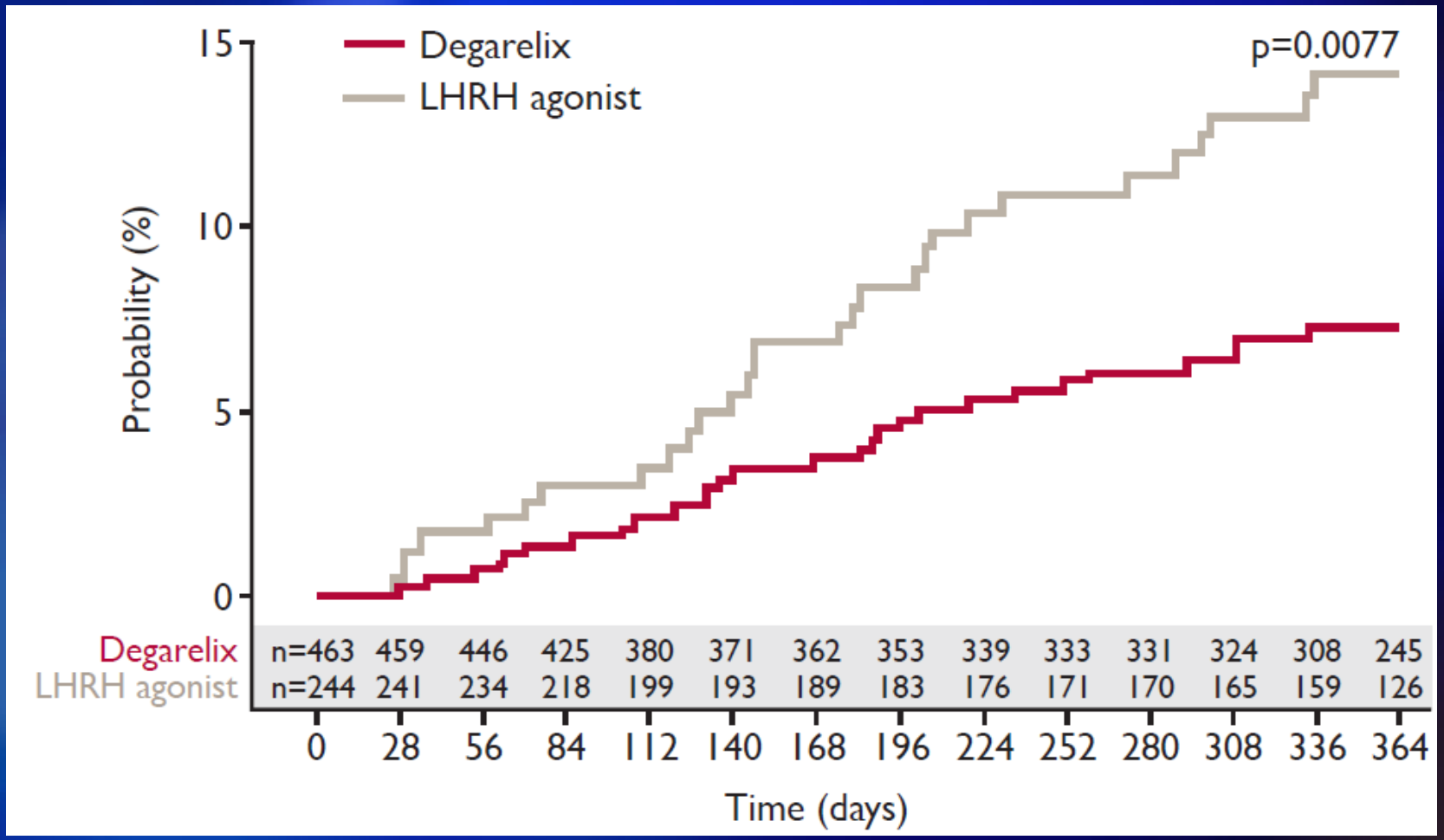
Laurence Klotz[a,*], *Kurt Miller*[b], *E. David Crawford*[c], *Neal Shore*[d], *Bertrand Tombal*[e], *Cathrina Karup*[f], *Anders Malmberg*[f], *Bo-Eric Persson*[g]

[a] *Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada;* [b] *Charité Universitätsmedizin Berlin, Berlin, Germany;* [c] *University of Colorado, Denver, CO, USA;* [d] *Carolina Urologic Research Center, Myrtle Beach, SC, USA;* [e] *Cliniques Universitaires Saint Luc/Université Catholique de Louvain, Brussels, Belgium;* [f] *Ferring Pharmaceuticals, Copenhagen, Denmark;* [g] *Ferring Pharmaceuticals, Saint-Prex, Switzerland*

Risk of CV event or death (all patients)



Risk of CV event or death in men with baseline CVD



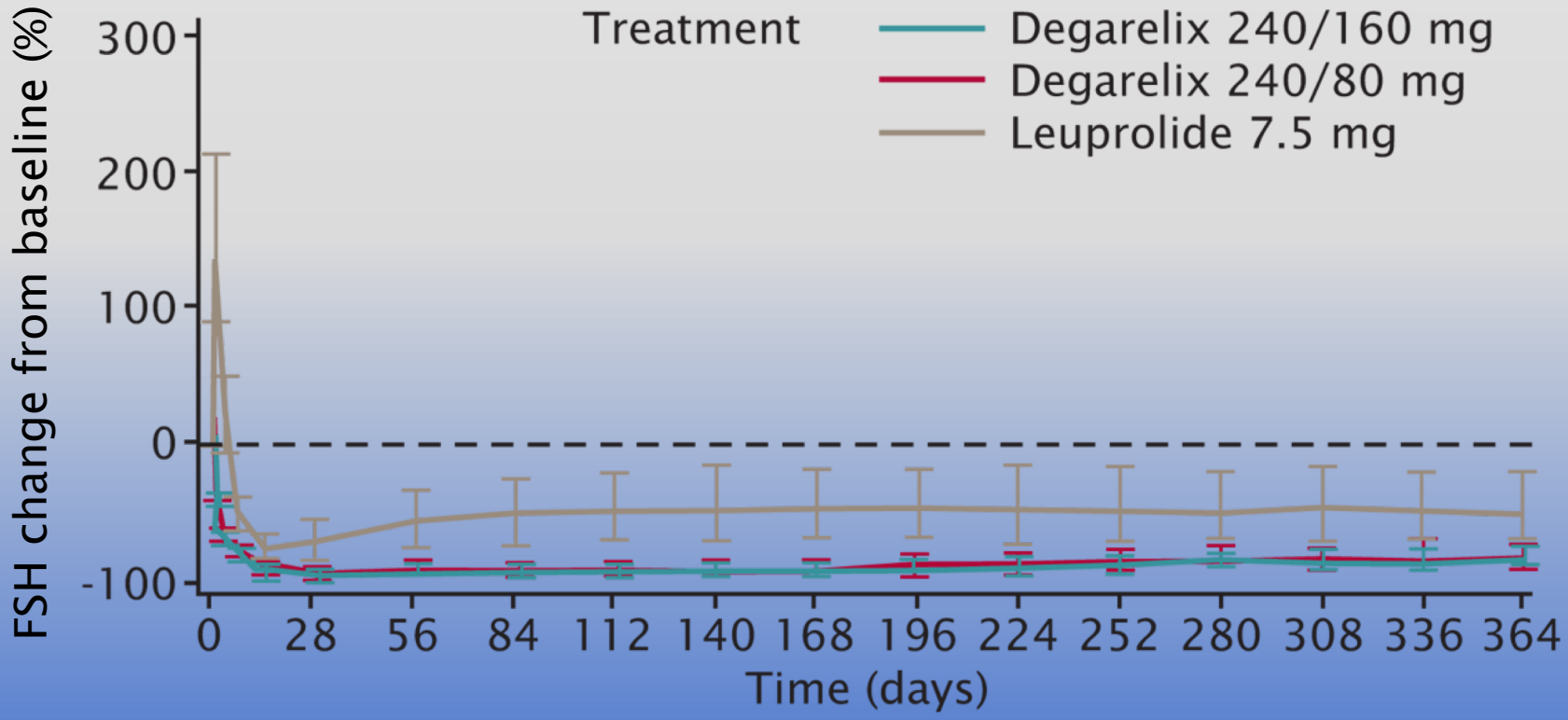
Relative risk reduction of 50%
Absolute risk reduction 7%

Biologically plausibility:

- Conventional wisdom: CV events related to metabolic syndrome and other effects of androgen deprivation
- But several other explanations:
  - FSH receptor activity in prostate cancer, endothelium, adipocytes, bone mineral density
  - LHRH receptors in endothelial plaque macrophages and T cells

Degarelix -FSH

FIRMAGON rapidly decreased FSH and maintained lower levels than leuprolide during the 1-year study



Klotz L, et al. *BJU Int*. 2008;102:1531-1538.

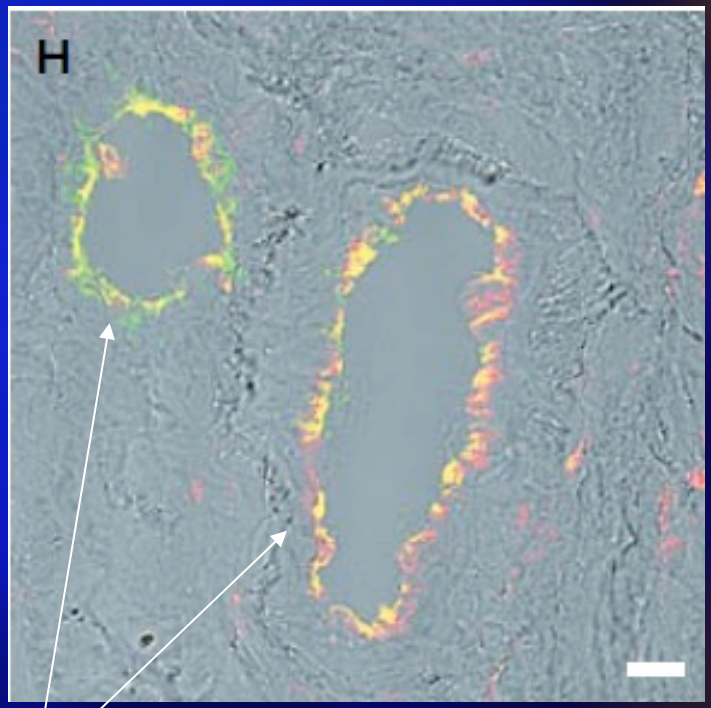
FSH receptors identified on prostate tumour blood vessels

Radu A et al. N Engl J Med 2010;363:1621-30

Tumour blood vessels become resistant to therapy

FSH receptor signalling may be associated with tumour cell proliferation

Lowering FSH levels decreases proliferation of PCa cells

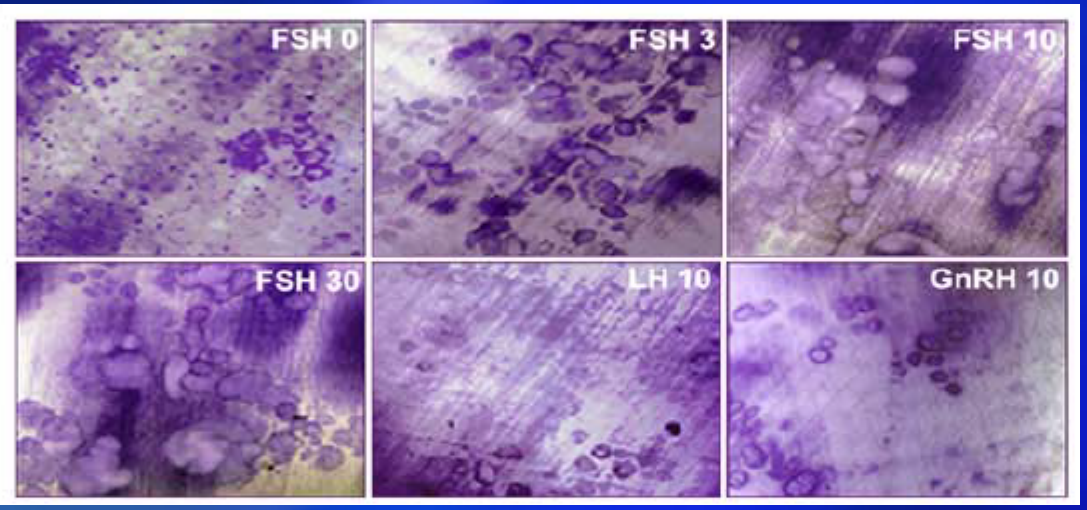


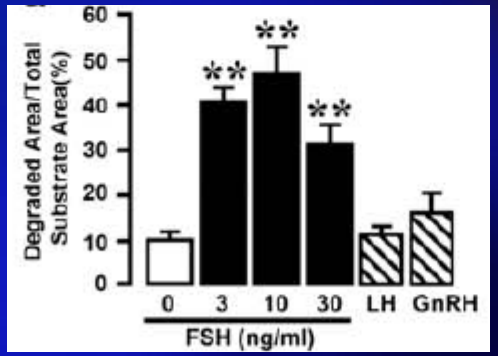
Cells expressing FSH receptors

Cell

FSH Directly Regulates Bone Mass

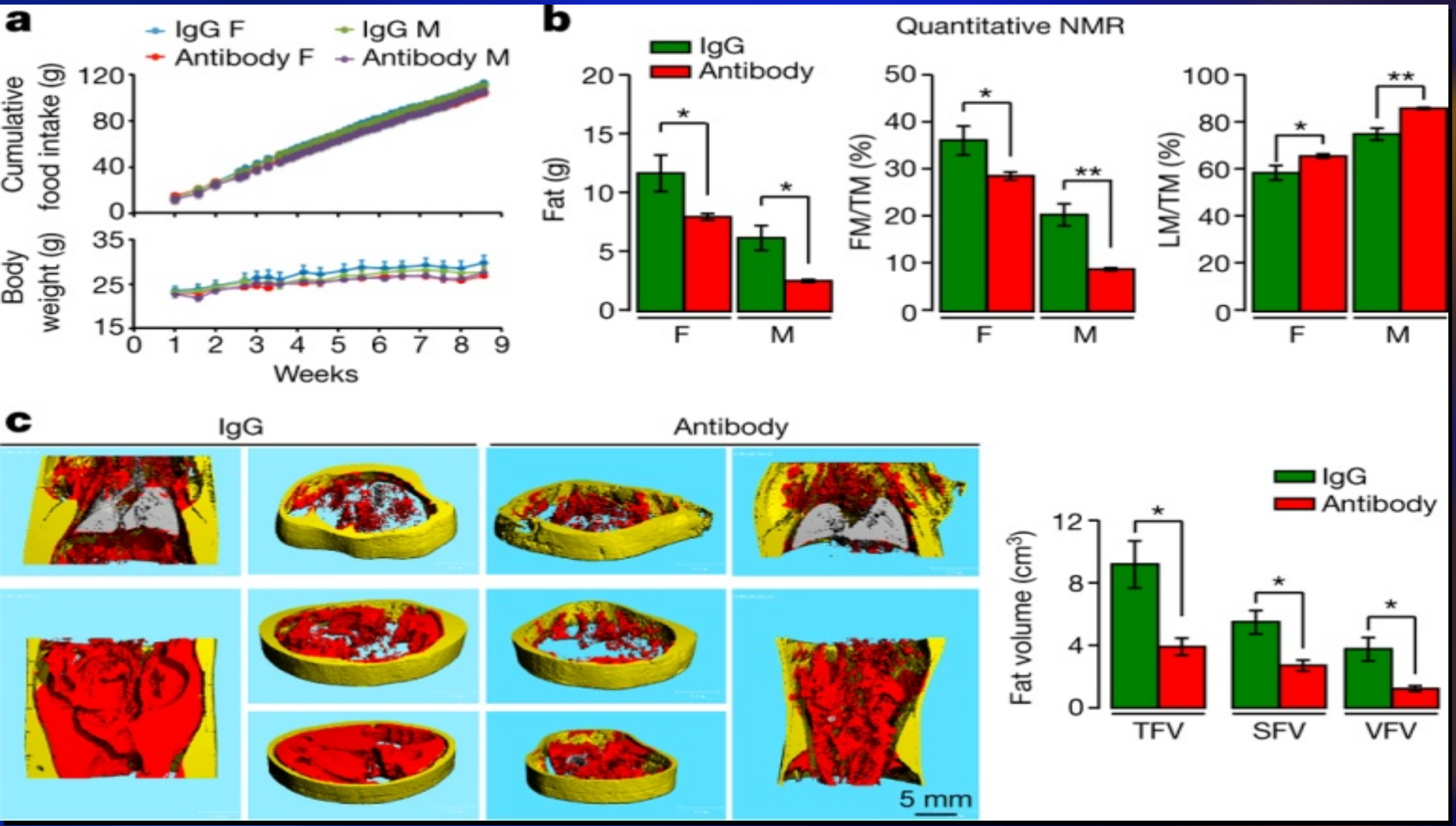
Li Sun,[1] Yuanzhen Peng,[1] Allison C. Sharrow,[2,3] Jameel Iqbal,[1] Zhiyuan Zhang,[1] Dionysios J. Papachristou,[2,3] Samir Zaidi,[1] Ling-Ling Zhu,[1] Beatrice B. Yaroslavskiy,[2,3] Hang Zhou,[1] Alberta Zallone,[4] M. Ram Sairam,[5]





- FSH directly increases osteoclastogenesis and resorption
- Gi2a-coupled FSH receptors activate osteoclast NF-kB, and Akt resulting in enhanced osteoclast formation and function.
- High circulating FSH causes hypogonadal bone loss.

FSH antibody reduces obesity in mice on a high-fat diet. P Liu *et al. Nature* 1–6 (2017)



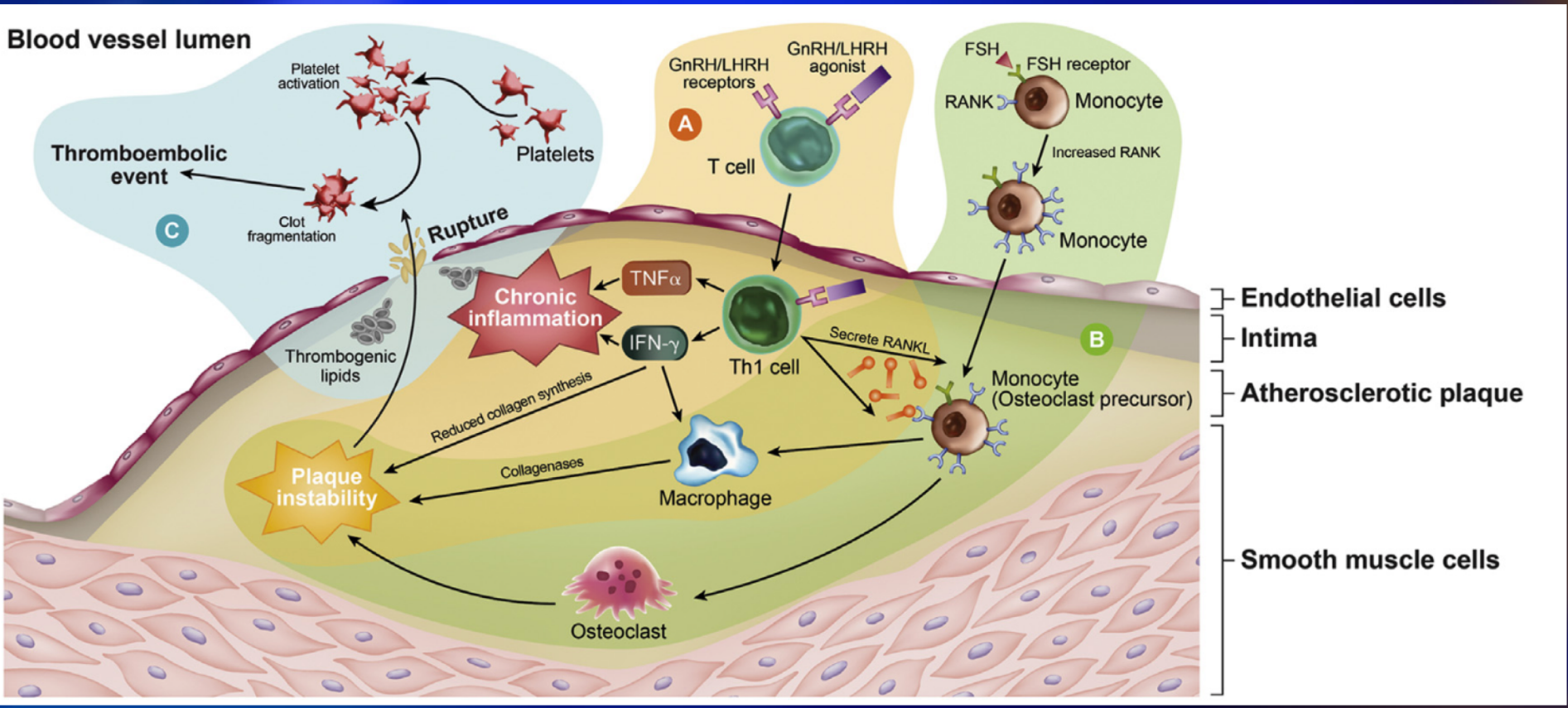
Lean mass/total mass (LM/TM) and Fat mass/Total mass (FM/TM)

nature

T cell activation by GnRH agonists may explain the increase in CV events

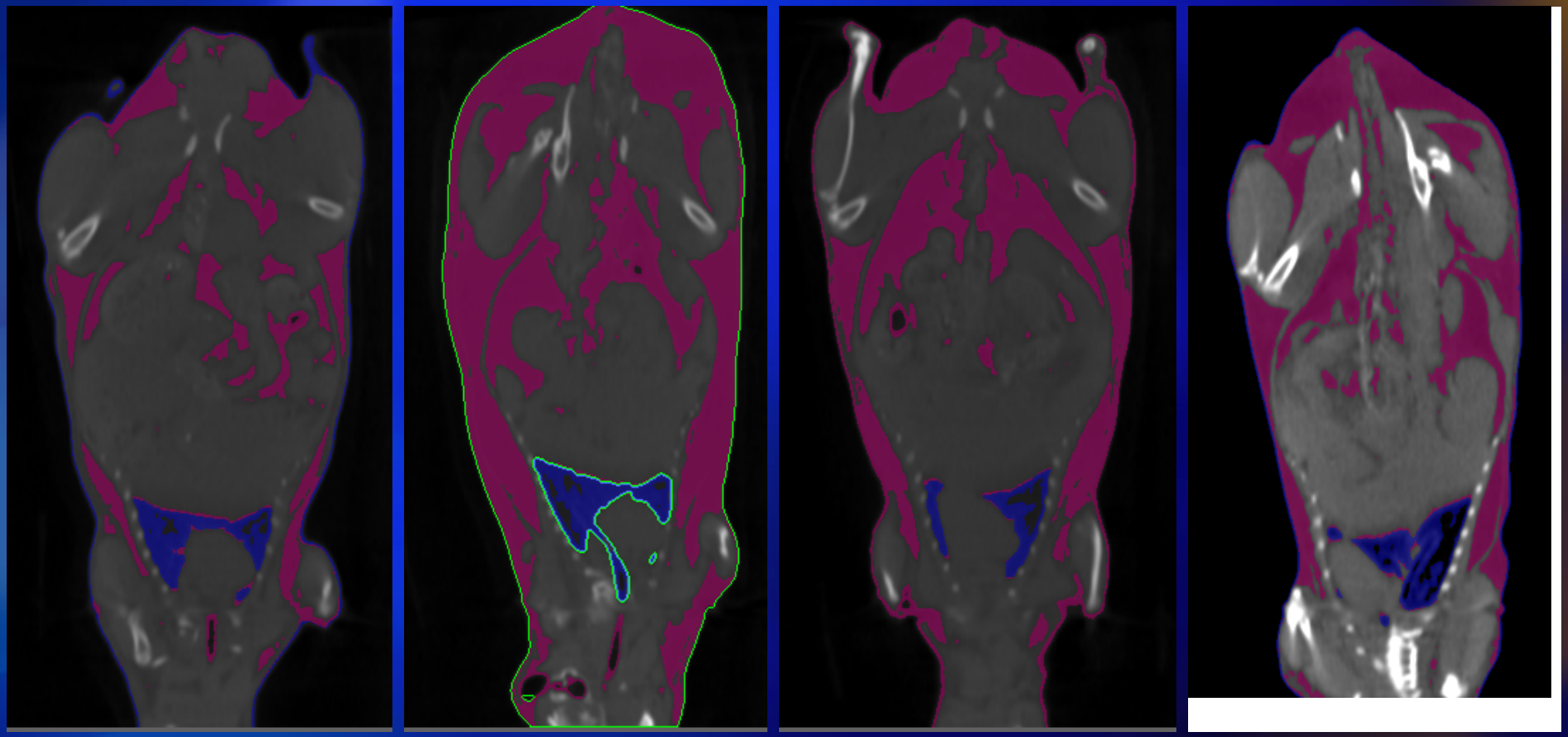
- Most acute CV events caused by rupture of atherosclerotic plaque
- Plaque degradation by infiltrating macrophages releasing matrix-degrading proteases
- Proinflammatory T-helper 1 (Th1) lymphocytes are macrophage activators; dominant in arterial plaques
- These express GnRH receptors
- GnRH activation stimulates T-cell expansion and Th1 differentiation
- GnRH agonists could promote plaque destabilization

Interactions between ADT, immune system, FSH, and atherosclerotic plaques



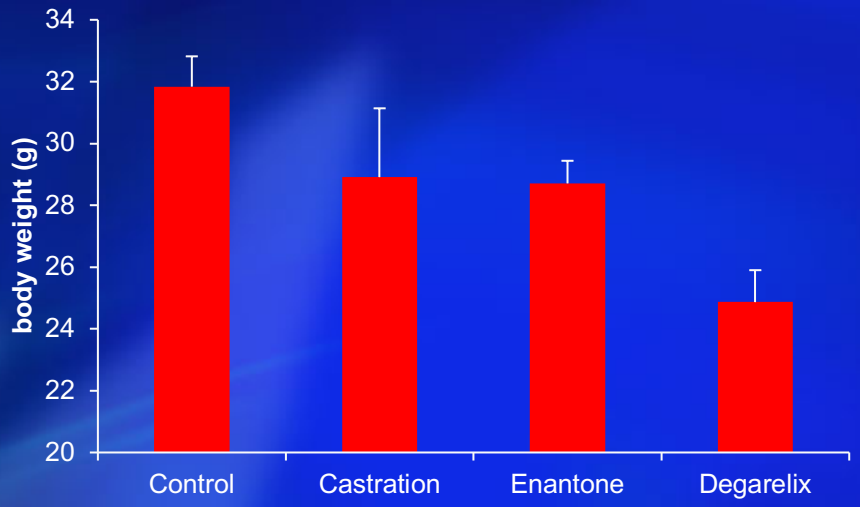
Differential adiposity between differernt types of ADT. Hopmans S, Klotz L, Pinthus J. Urol Oncol 32(8):1126-34, 2014

control | castration | LHRH agonist | degarelix

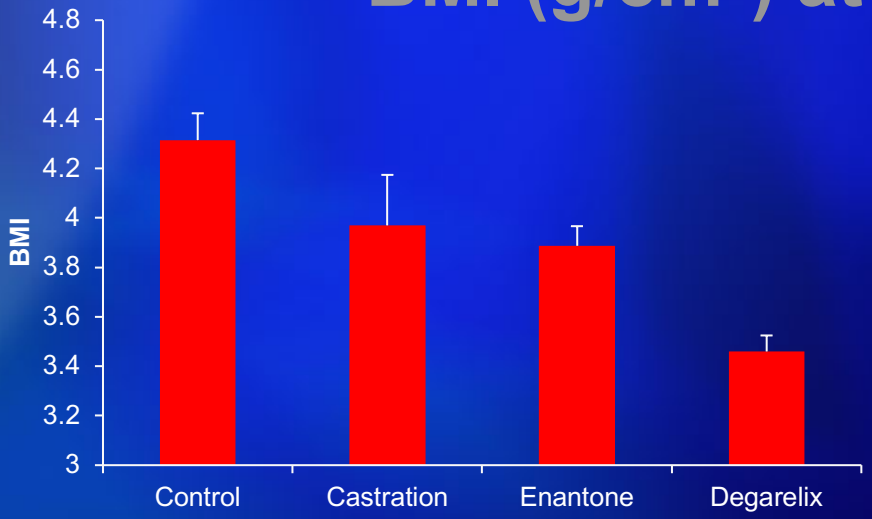


Pink: adipose tissue
Blue: Lung tissue

Total body weight (g) at 4 months

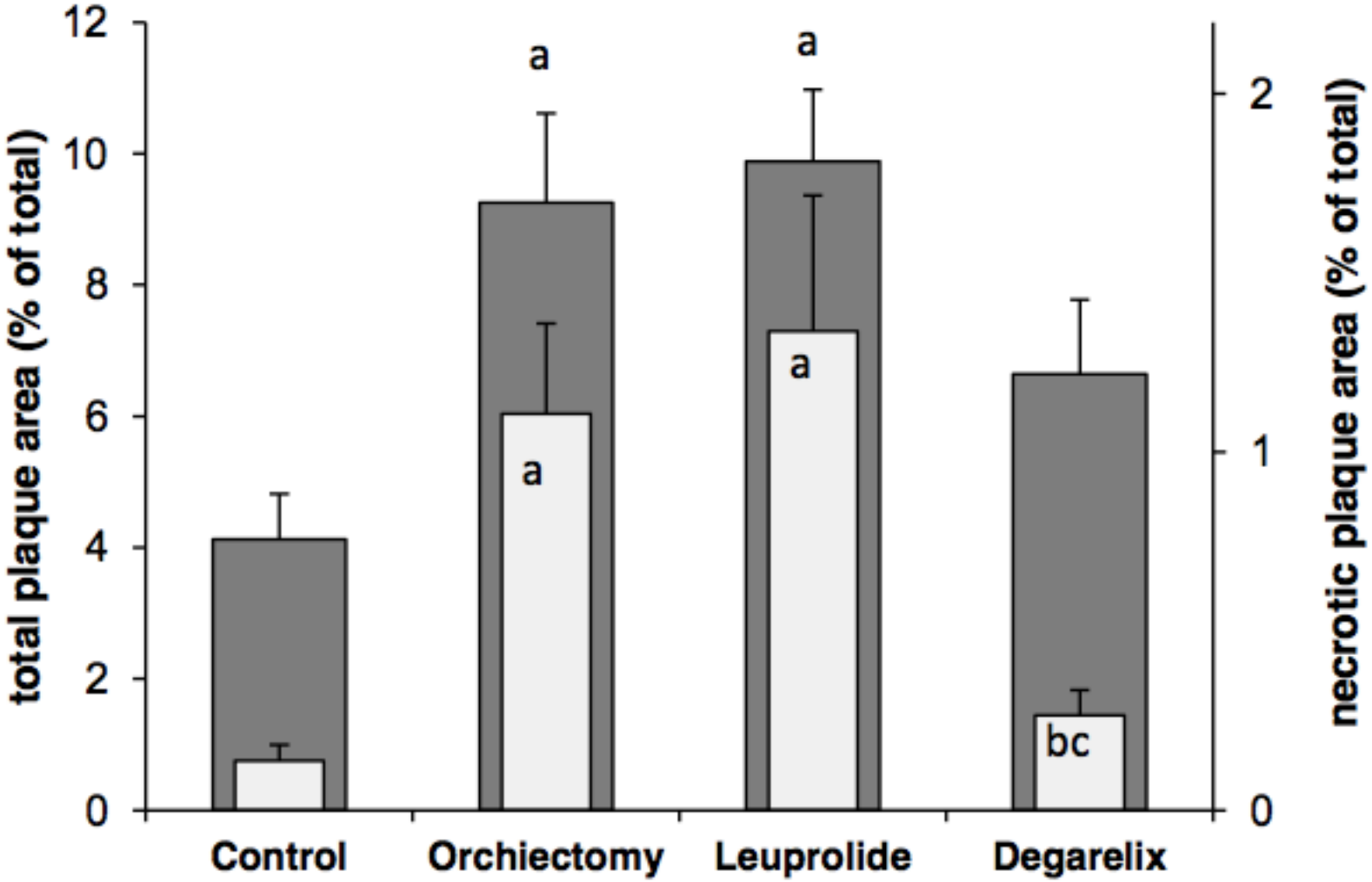


BMI (g/cm^2) at 4 months

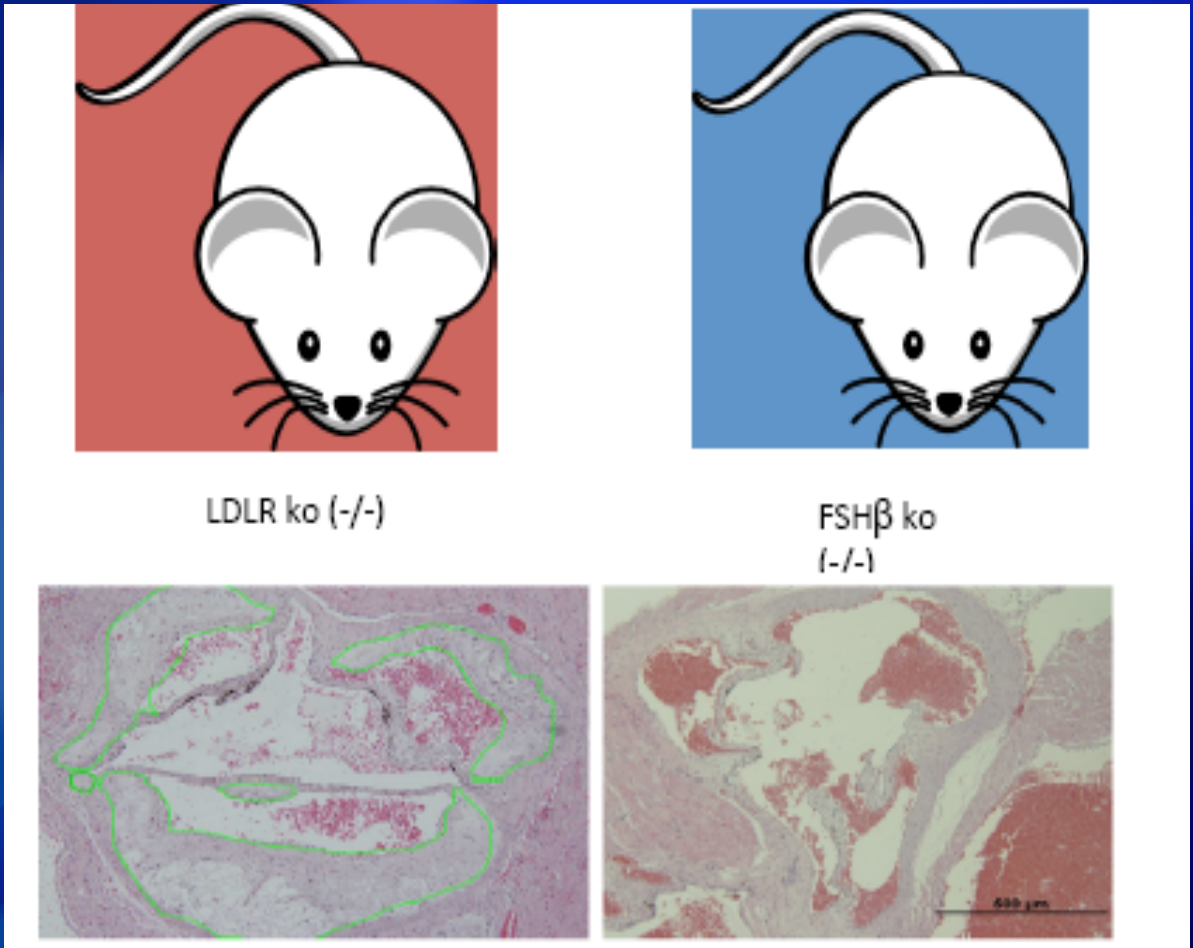


Hopmans S, Klotz L, Pinthus J. Urol Oncol 32(8):1126-34, 2014

Total plaque area and necrotic plaque area. Hopmans S et al, Urol Oncol 32(8): 1126-34, 2014



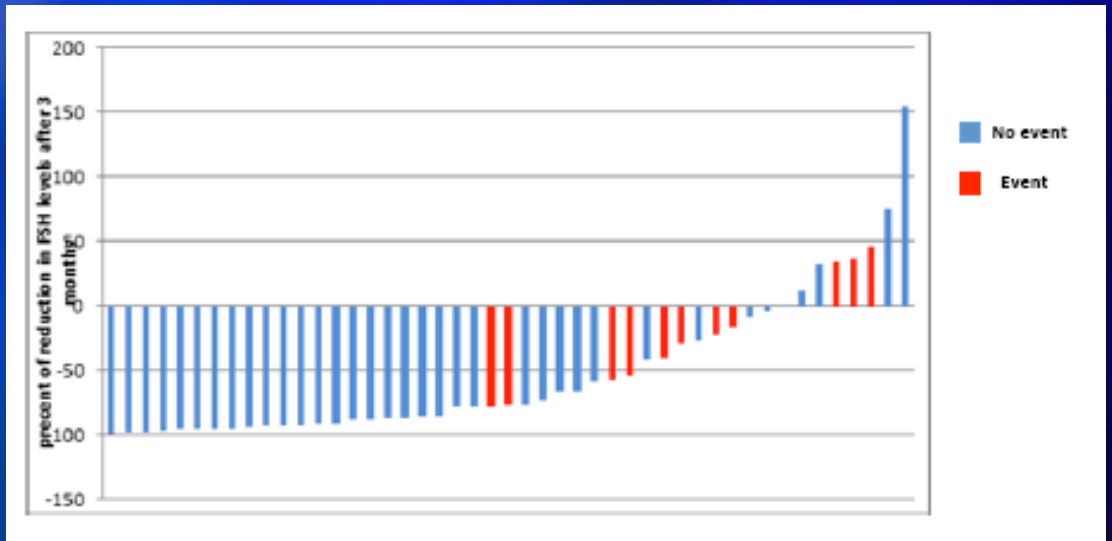
Aortic sections from LDLR$^{-/-}$ and FSHβ$^{-/-}$ mice on a high fat diet post orchiectomy. Atherosclerosis (green line) and necrosis only in LDLR$^{-/-}$ mice. Pinthus J et al, AUA 2017



Agonist vs antagonist: randomized trial

Margel D, AUA 2017 Abst. 3358

- 59 men with pre-existing CV disease randomized between 2 drugs
- 9 CV eventys in agonist arm vs 1 in antagonist arm (p=.004)
- 47% of group with < 60^ reduc tion in FSH had an event vs 7% of those with > 60% decrease
- If < 40% decrease in FSH, HR 2 x greater for CV event



Practical considerations for ADT use 2018

- Counsel patients re diet, exercise, smoking cessation
- Low dose statin (ie, atorvastatin 10 mg/day)
- Oral bisphosphonate (aledronate 70 mg/wk)
- IADT for non-metastatic HSPC
- Trial of IADT in selected metastatic patients with PSA < 0.2 after 4-6 months
- 4-6 months of induction therapy (if PSA < 0.2)
- Monitor T during ADT, change drug if T > 20 ng/0.7 nM
- Consider Degarelix if pre-existing CV disease
- Emerging role for AR targeted agents in HSPCa