Personalized ADT

Thomas Keane MD

Conflicts

- Ferring
- Tolemar
- Bayer
- Astellas
- myriad

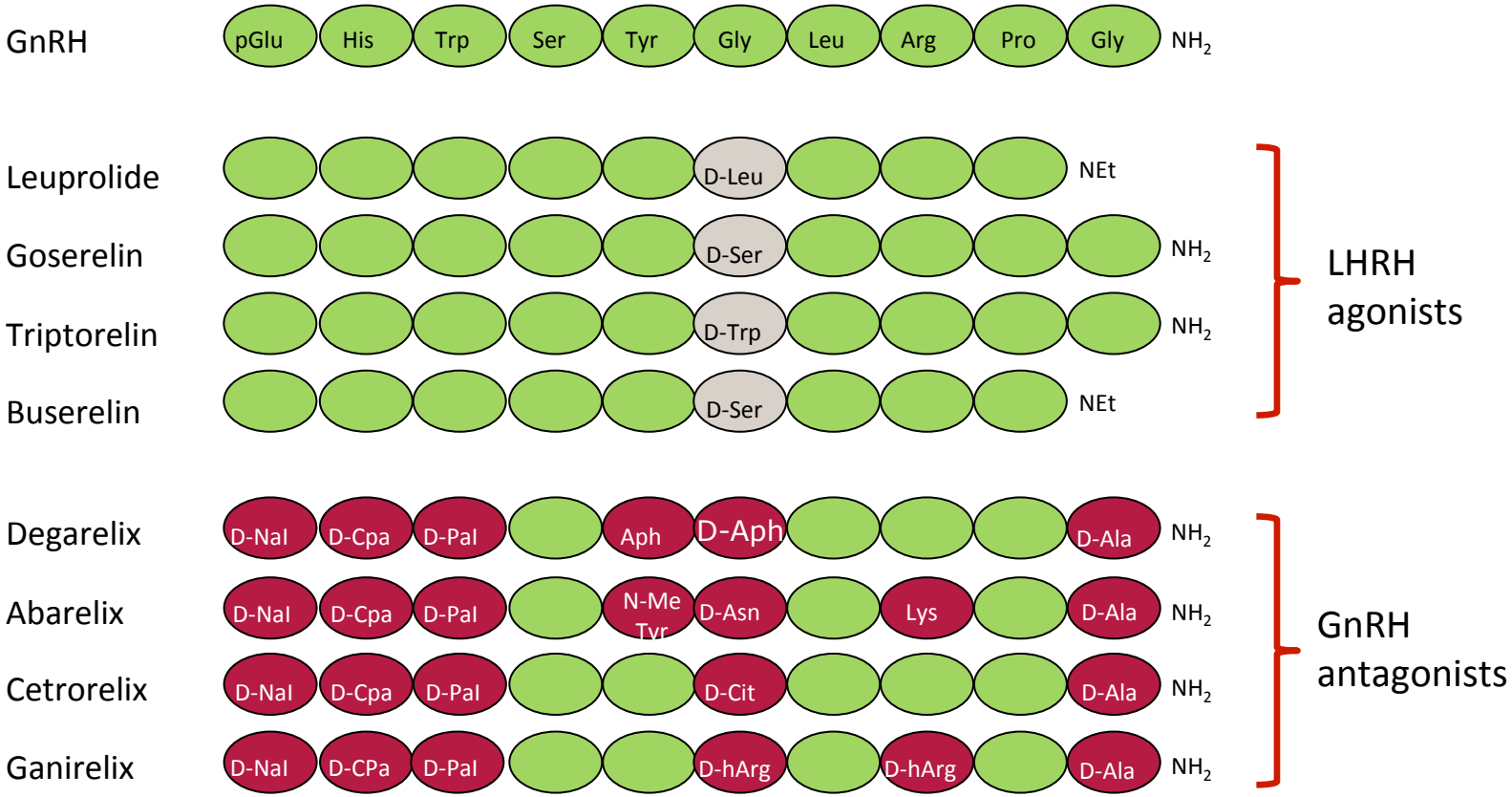
Personalized ADT for the Specific Patient

- **Cardiac**
- Obesity and testosterone
- Fsh
- High volume metastatic disease
- Docetaxol
- Significant LUTS

Cardiovascular risk profile and ADT

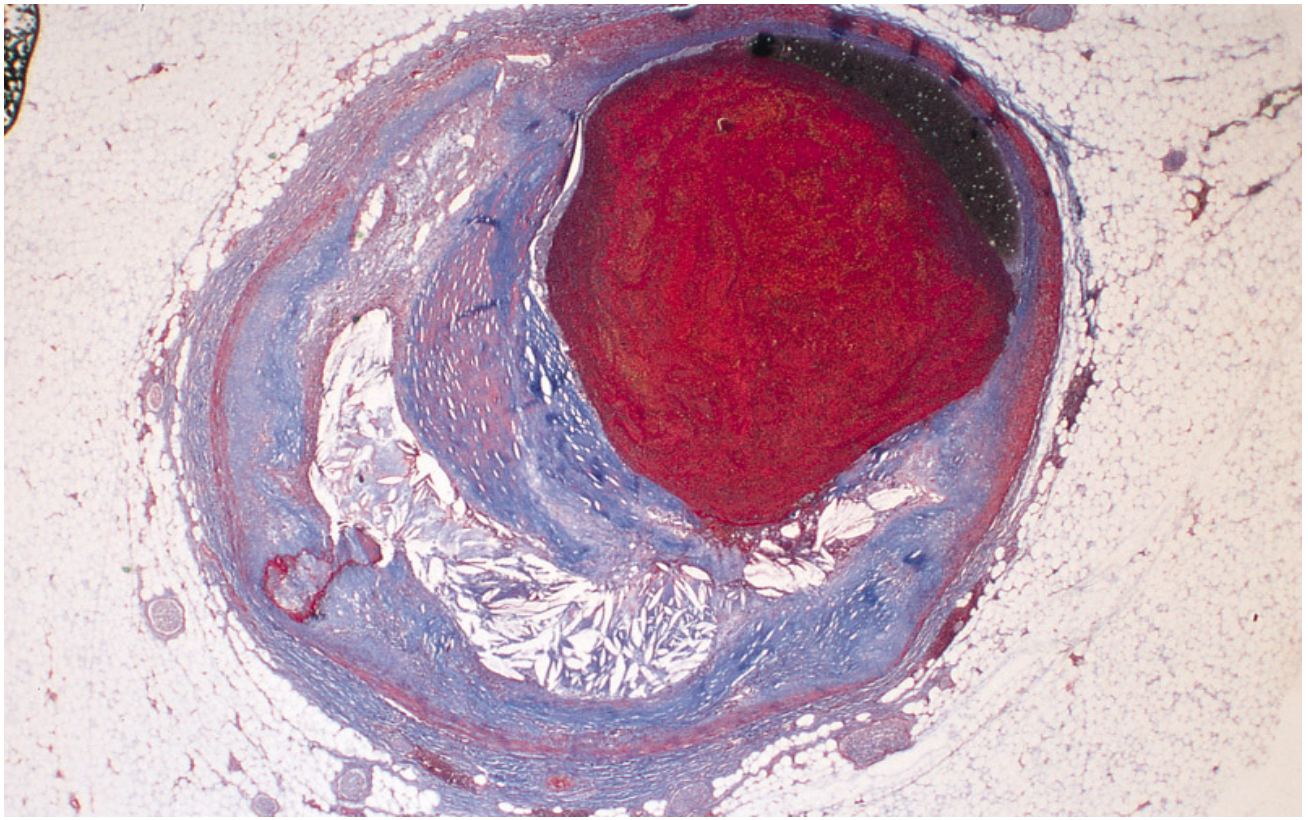
Is there a difference?

Degarelix belongs to a class of synthetic drug, GnRH antagonist (blocker)

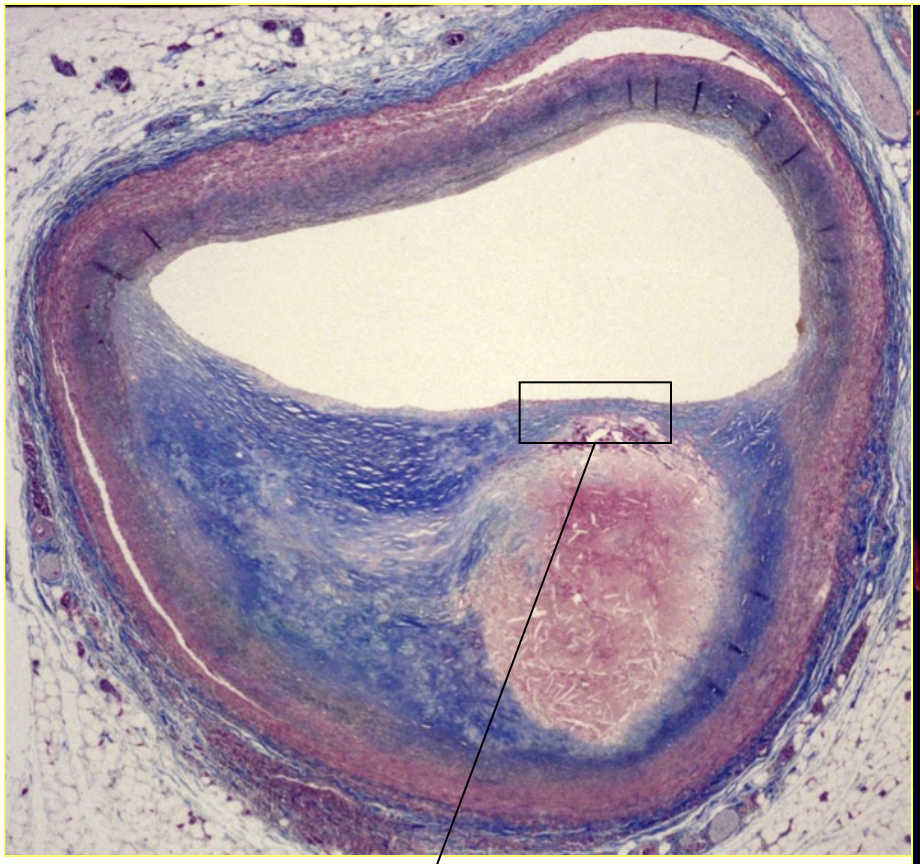


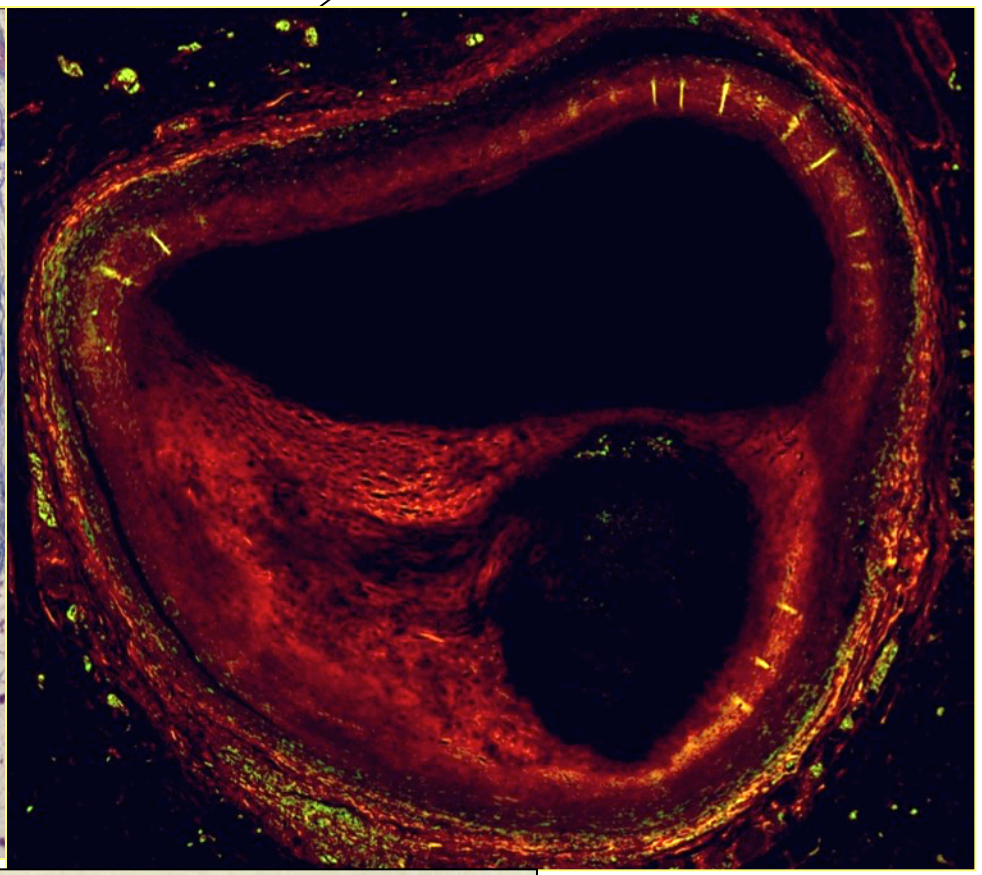
Millar RP, et al. Endocr Rev 2004;25:235–75

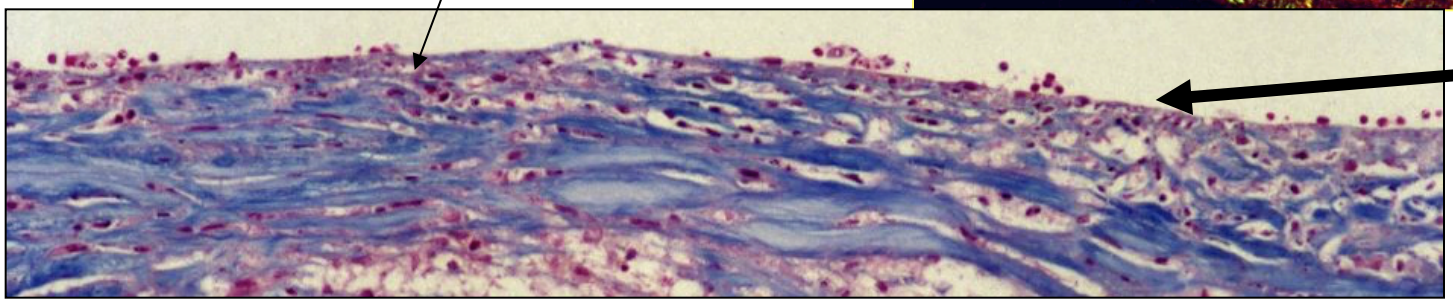
Most acute CVD events are caused by rupture of a vulnerable atherosclerotic plaque



The vulnerable plaque – thin cap with inflammation

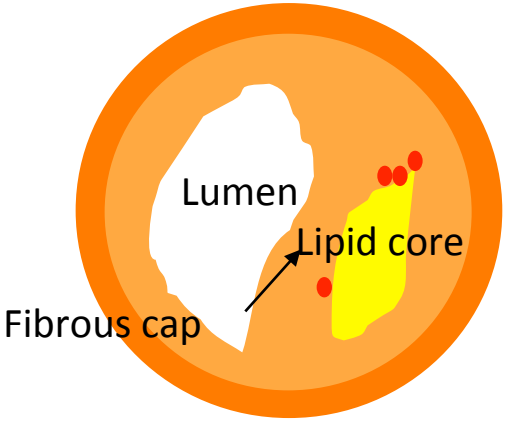




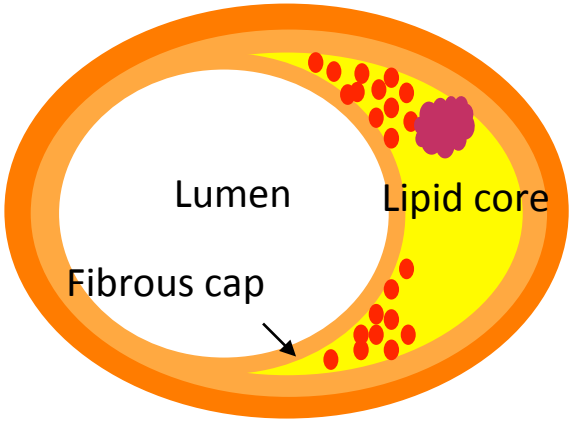


Plaque instability is at the heart of cardiovascular disease

Stable plaque



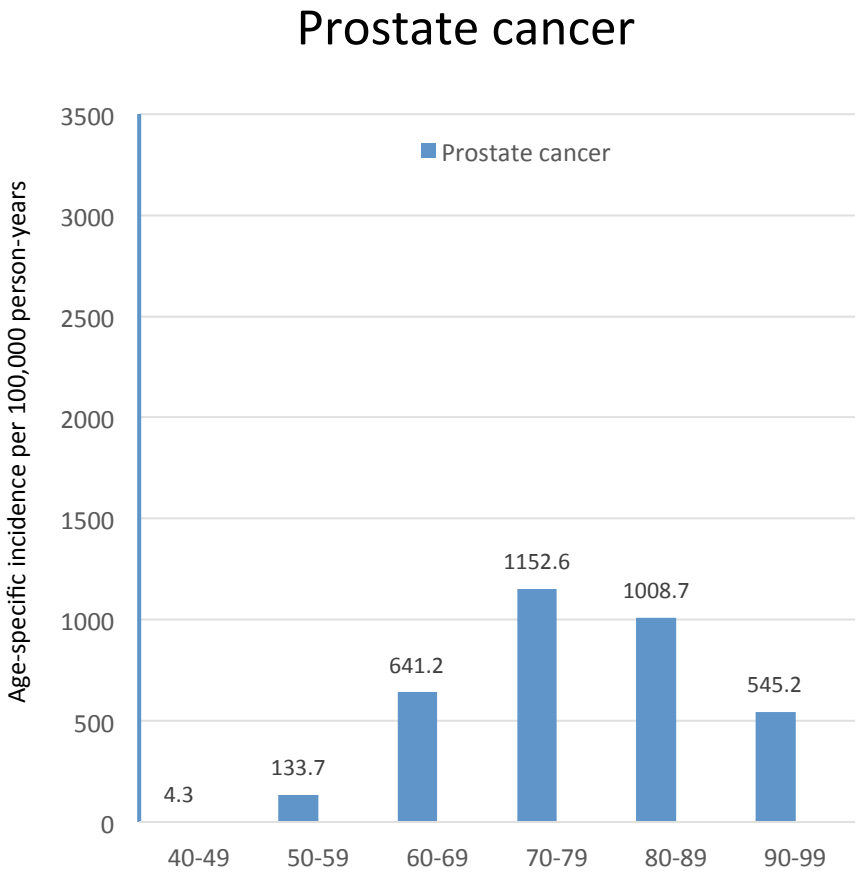
Vulnerable plaque

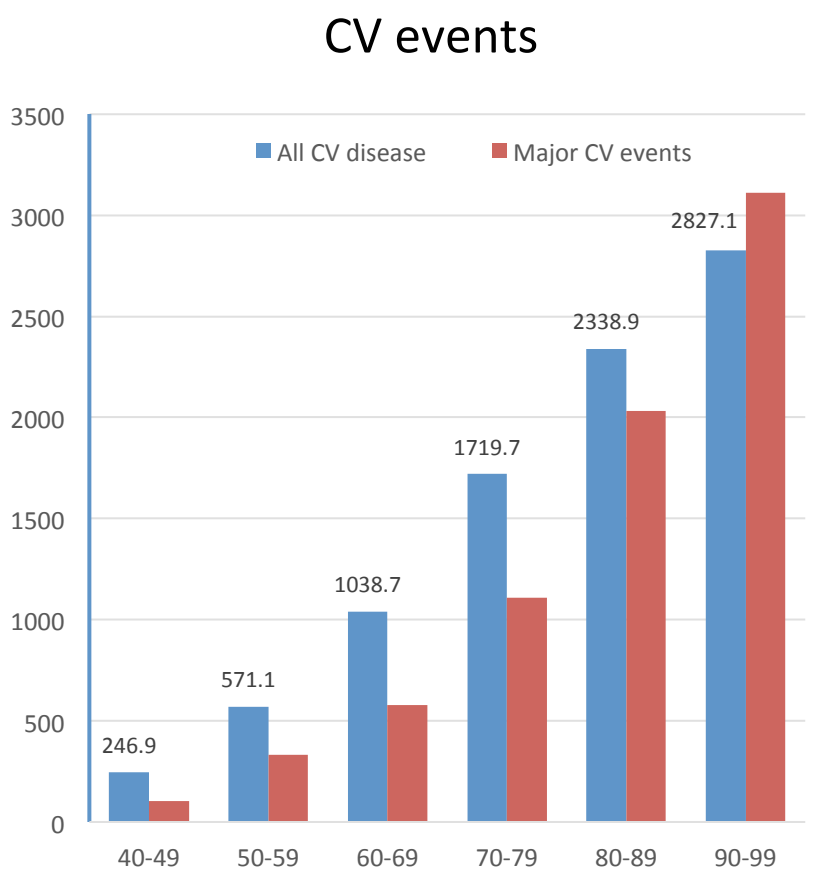


Thick	**Cap**	Thin
Rich in SMC and matrix	**Composition**	Rich in inflammatory cells: proteolytic activity
Poor	**Lipid**	Rich
Inflammatory	**Inflammatory state**	Highly inflammatory

Libby P. Circulation 1995;91:2844-2850

Incidence of both prostate cancer and CV events is highest in older men





CV, cardiovascular
Major CV events = myocardial infarction, stroke, or death due to CV disease
All CV disease = major CV events + self-reported angina or revascularisation procedures

Driver, et al. BMJ 2008;337:a2467

Men with prostate cancer and pre-existing CVD have an increased risk of death

Population	n (%)	Cumulative survival (%)		Adjusted HR (95% CI)
		1-year	5-years	
Overall	30,721 (100)	84.4	41.7	—
No IHD or stroke	25,114 (82)	85.4	43.5	1.0 (ref)
IHD	4,276 (14)	80.5	36.1	1.05 (1.00–1.10)
Stroke	1,331 (4)	77.6	26.5	1.20 (1.12–1.30)

*HR adjusted for age, stage, calendar period and comorbidity (excluding IHD and stroke)

Influence of prostate cancer therapy on mortality rates not assessed

CVD, cardiovascular disease
IHD, ischaemic heart disease

Jespersen CG, et al. BMC Cancer 2012;11:519

Oestrogen therapy increases risk of CV-related side effects

- 2,052 patients with stage I–IV prostate cancer treated using radical prostatectomy or orchiectomy with or without oestrogen
  - Survival significantly shorter in patients with stage I–III prostate cancer receiving oestrogens, but incidence of prostate cancer-related death reduced
  - Significant increase in deaths due to CV disease in patients treated with oestrogen

Cause of death	No oestrogen therapy (n=1,035)	Received oestrogen therapy (1,017)
Prostate cancer	149 (14.4%)	107 (10.5%)
CV	90 (8.7%)	149 (14.7%)
Pulmonary embolus	10 (1%)	11 (1.1%)
Other	85 (8%)	91 (9.0%)

Veterans Administration Co-operative Urological Research Group. Surg Gynecol Obstet 1967;124:1011-7

This association has been confirmed with other types of ADT

Treatment	Incident CHD	Myocardial infarction	Sudden cardiac death	Stroke
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
No ADT	Ref	Ref	Ref	Ref
GnRH agonist	1.19* (1.10–1.28)	1.28* (1.08–1.52)	1.35* (1.18–1.54)	1.21* (1.05–1.40)
Orchiectomy	1.40* (1.04–1.87)	2.11* (1.27–3.50)	1.29 (0.76–2.18)	1.49 (0.92–2.43)
CAB	1.27* (1.05–1.53)	1.03 (0.62–1.71)	1.22 (0.85–1.73)	0.93 (0.61–1.42)
Antiandrogen	1.10 (0.80–1.53)	1.05 (0.47–2.35)	1.06 (0.57–1.99)	0.86 (0.43–1.73)

*p<0.05

- Observational study of 37,443 men with prostate cancer
- 39% received some form of ADT during follow-up, primarily GnRH agonists (37.5%)
  - Few were treated with orchiectomy (0.8%) or oral antiandrogen monotherapy (3.3%) at any time or CAB (4.9%) for >6 weeks at the start of GnRH agonist therapy

ADT, androgen deprivation therapy
CAB, combined androgen blockade
CHD, coronary heart disease; ref, reference

Keating NL, et al. J Natl Can Inst 2010;102:39–46

The risk has been shown to be increased in older men and those with comorbidities

- Men aged ≥65 years receiving 6 months of ADT had shorter times to fatal myocardial infarction compared with RT alone (p=0.017)[1]
- Patients with moderate or severe comorbidities* had a greater risk of a fatal myocardial infarction when receiving RT + ADT compared with RT alone[2]

ADT, androgen deprivation therapy
RT, radiotherapy
*Based on Adult Comorbidity Evaluation 27 (ACE-27)

1. D'Amico AV, et al. J Clin Oncol 2007;25:2420–5
2. D'Amico AV, et al. JAMA 2008;299:289–95

… as well as those with pre-existing cardiac disease

- Significant increase in CV morbidity during oestrogen treatment in patients with a history of CVD ($p<0.001$)
  - 33% of these patients had a CV event during PEP treatment
- Oestrogen treatment was the greatest risk factor for CV events in a multivariate analysis ($p=0.029$)

CVD, cardiovascular disease
PEP, polyestradiol phosphate

Hedlund PO, et al. Scand J Urol Nephrol 2011;45:346–53

Based on the studies shown…

- The increase in risk of CV disease in men treated with ADT (orchiectomy, oestrogen or GnRH agonist) appears to be 20–25%
- In comparison, known major risk factors for CV disease increase lifetime risk as follows:
  - Smoking vs no smoking: 22%
  - Hypertension vs no hypertension: 20-93%
  - Low vs not low HDL cholesterol: 44%
  - High vs low total cholesterol: 73%
  - Diabetes vs no diabetes: 122%

Lloyd-Jones, et al. Circulation 2006;113:791-8

CVD is the second most common cause of death in men with prostate cancer

	Prostate cancer n (%)	CVD n (%)	Other n (%)
EORTC 30891[1]			
Immediate ADT	94 (37)	88 (34)	75 (29)
Delayed ADT	99 (35)	97 (34)	88 (31)
Total	193 (36)	185 (34)	163 (30)
SEUG 9401[2]			
Intermittent ADT	74 (44)	41 (24)	55 (32)
Continuous ADT	65 (39)	52 (31)	52 (31)
Total	139 (41)	93 (27)	107 (32)

1. Studer UE, et al. J Clin Oncol 2006;24:1868-76
2. Calais da Silva F, et al. Eur Urol 2009;55:1269–77

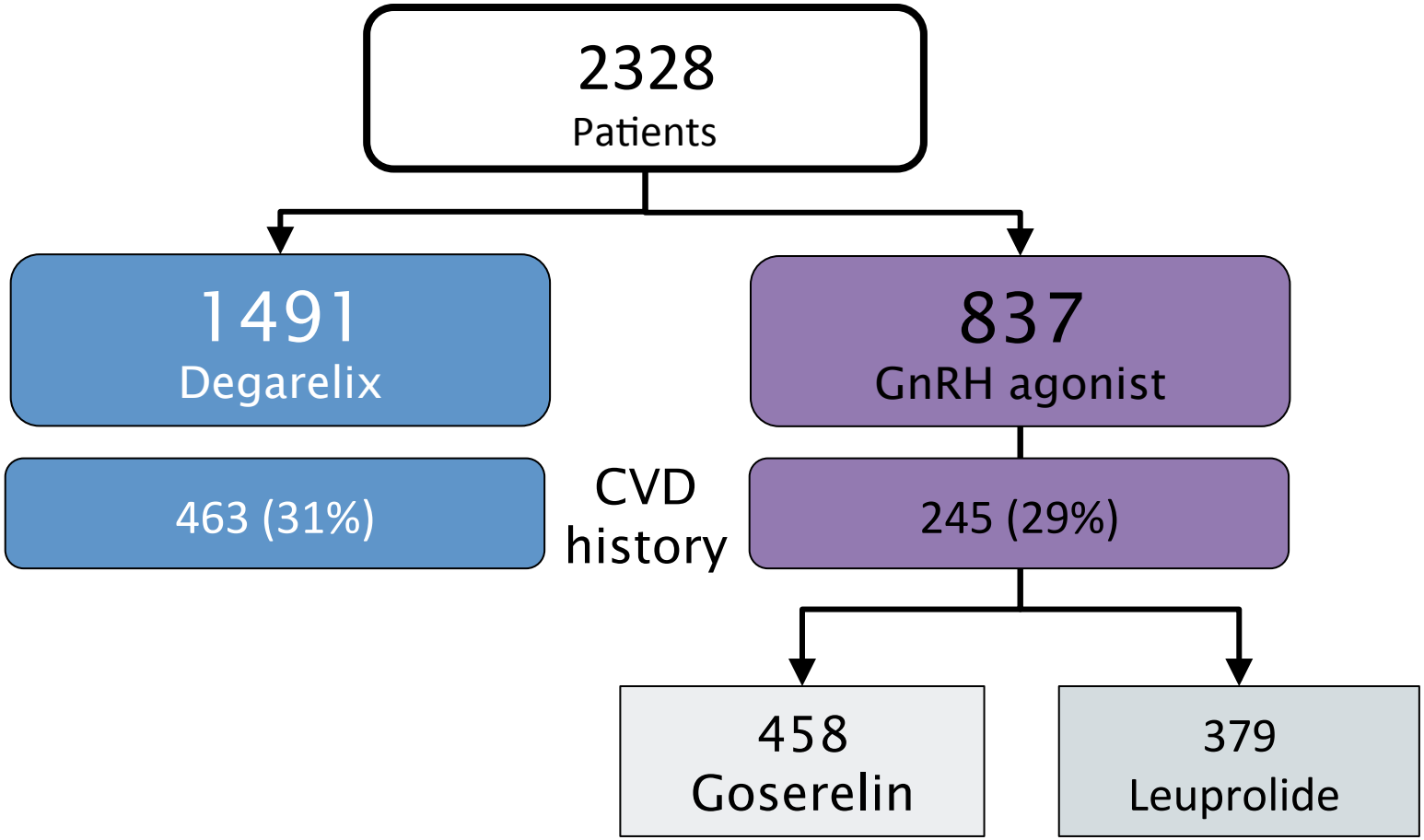
Pooled data from randomized phase III/IIIb trials of degarelix vs GnRH agonists

Study	Duration (months)	Comparator	Publication
CS21 Pivotal phase III, monthly dose	12	Leuprolide	Klotz et al. BJU Int 2008
CS35 3-month depot formulation	12	Goserelin	Shore et al. SIU 2012
CS37 Intermittent dosing	7-12	Leuprolide	Crawford et al. SUO 2013
CS28 LUTS relief	3	Goserelin*	Anderson et al. Urol Int 2012
CS30 Neoadjuvant to radical RT	3	Goserelin*	Mason et al. Clin Oncol 2013
CS31 TPV reduction	3	Goserelin*	Axcona et al. BJU Int 2012

*All patients on goserelin also received antiandrogen flare protection

LUTS, lower urinary tract symptoms
RT, radiotherapy
TPV, total prostate volume

Pooled analysis: Treatment groups



CVD, cardiovascular disease

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

Selected baseline demographics relating to CV risk

Variable	Degarelix n=1491	GnRH agonist n=837
Age (yrs)	71.7	71.6
Body mass index >30, n (%)	27.2 334 (22)	27.5 200 (24)
History of CVD, n (%)	463 (31)	245 (29)
History of smoking, n (%)	707 (47)	432 (52)
History of alcohol use, n (%)	889 (60)	475 (57)
History of hypertension, n (%)	1117 (75)	615 (74)
Serum cholesterol >6.2 mmol/L, n (%)	399 (27)	247 (30)
Statin medication use, n (%)	400 (27)	234 (28)
History of diabetes, n (%)	221 (15)	128 (15)

CVD, cardiovascular disease

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

Results: Overall incidence of CV events*

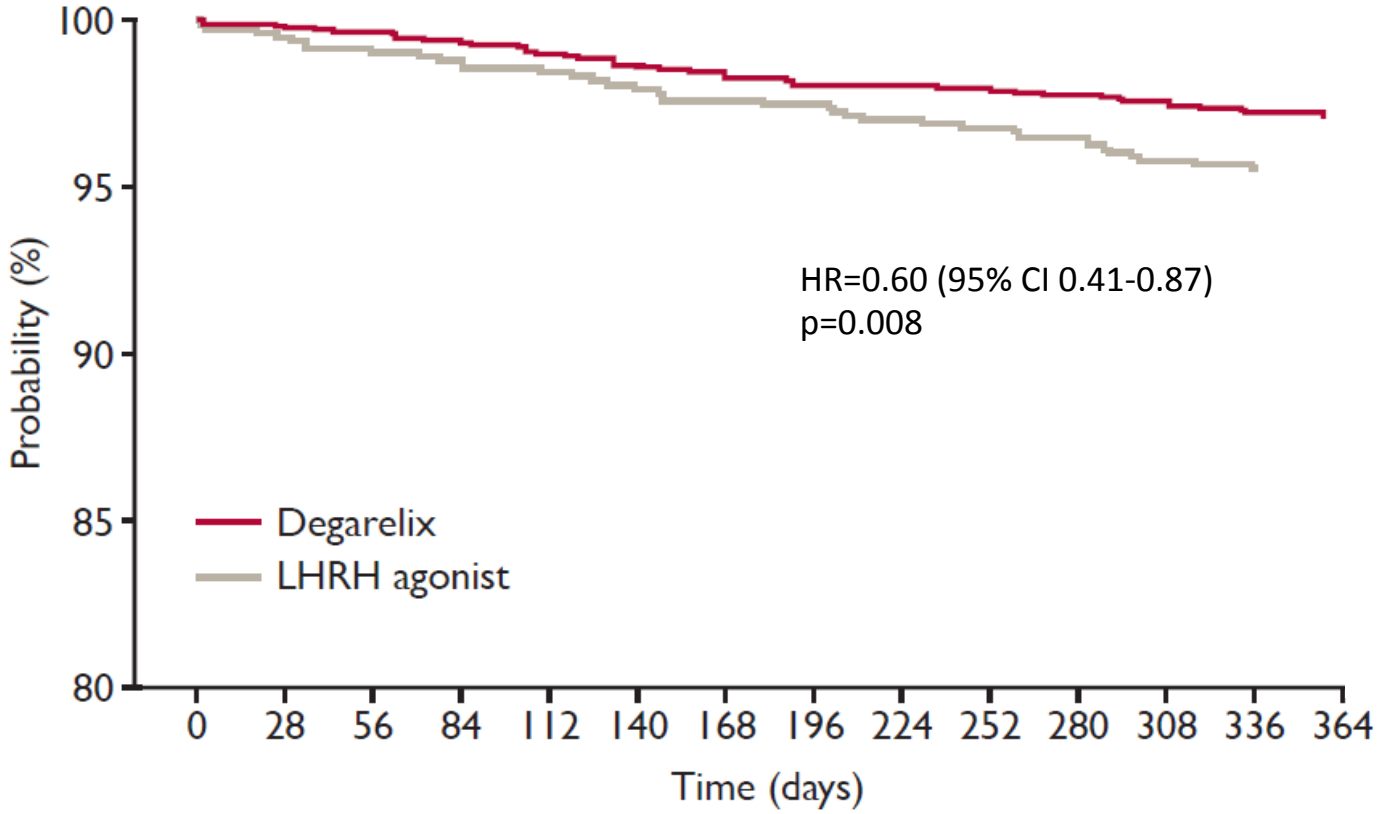
	Degarelix, n (%) n=1491	GnRH agonist, n (%) n=837
Any CV event	37 (2.5)	40 (4.7)
Serious CV event	25 (1.7)	24 (2.9)

- A serious CV event was an event considered life-threatening or that required hospitalization

*Data classified according to the MedDRA system

Albertsen PC, et al. Eur Urol 2014:65;565-73
Tombal B, et al. EAU 2013;Poster 677

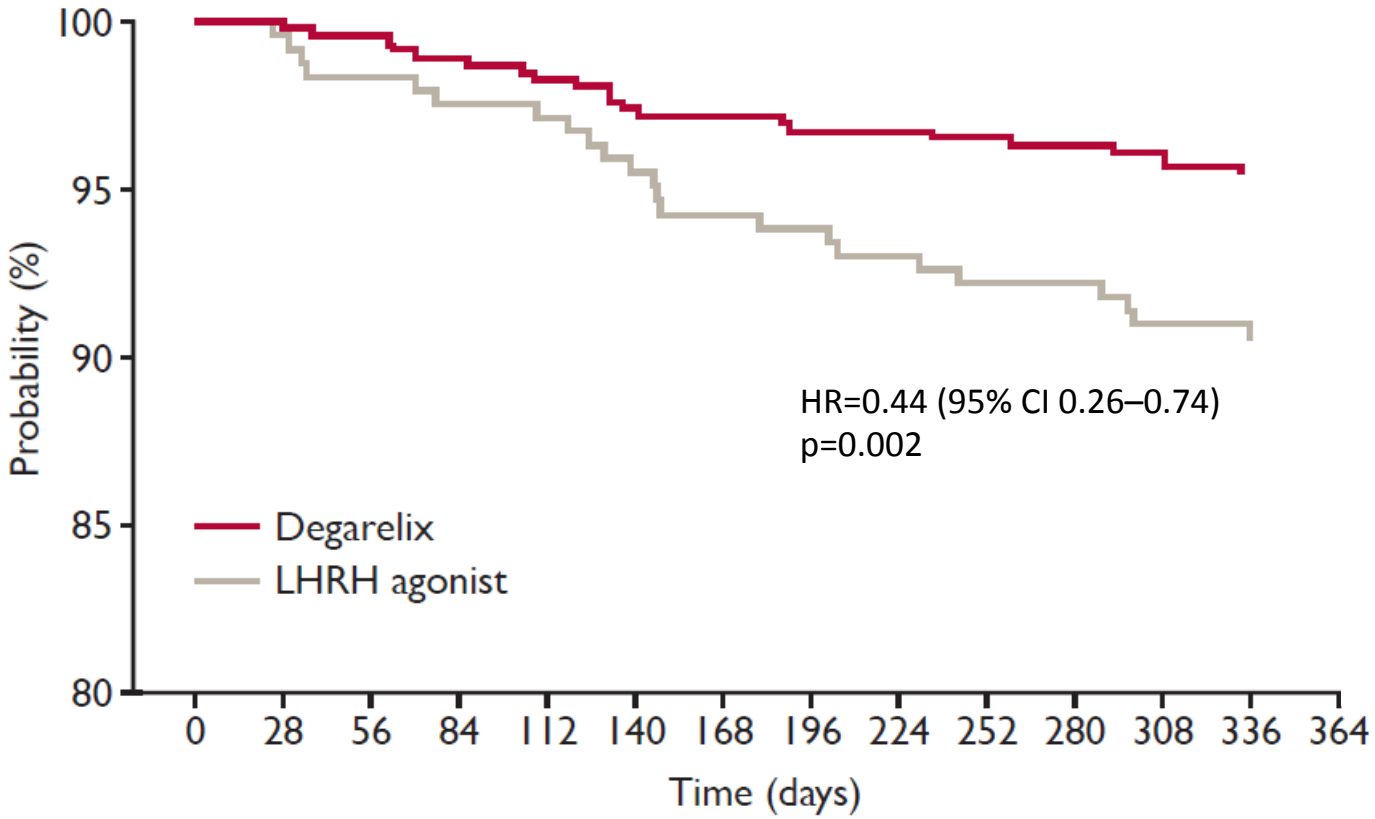
Lower risk of CV event or death with degarelix (all patients)



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

Albertsen PC, et al. Eur Urol 2014:65;565-73
Tombal B, et al. EAU 2013;Poster 677

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

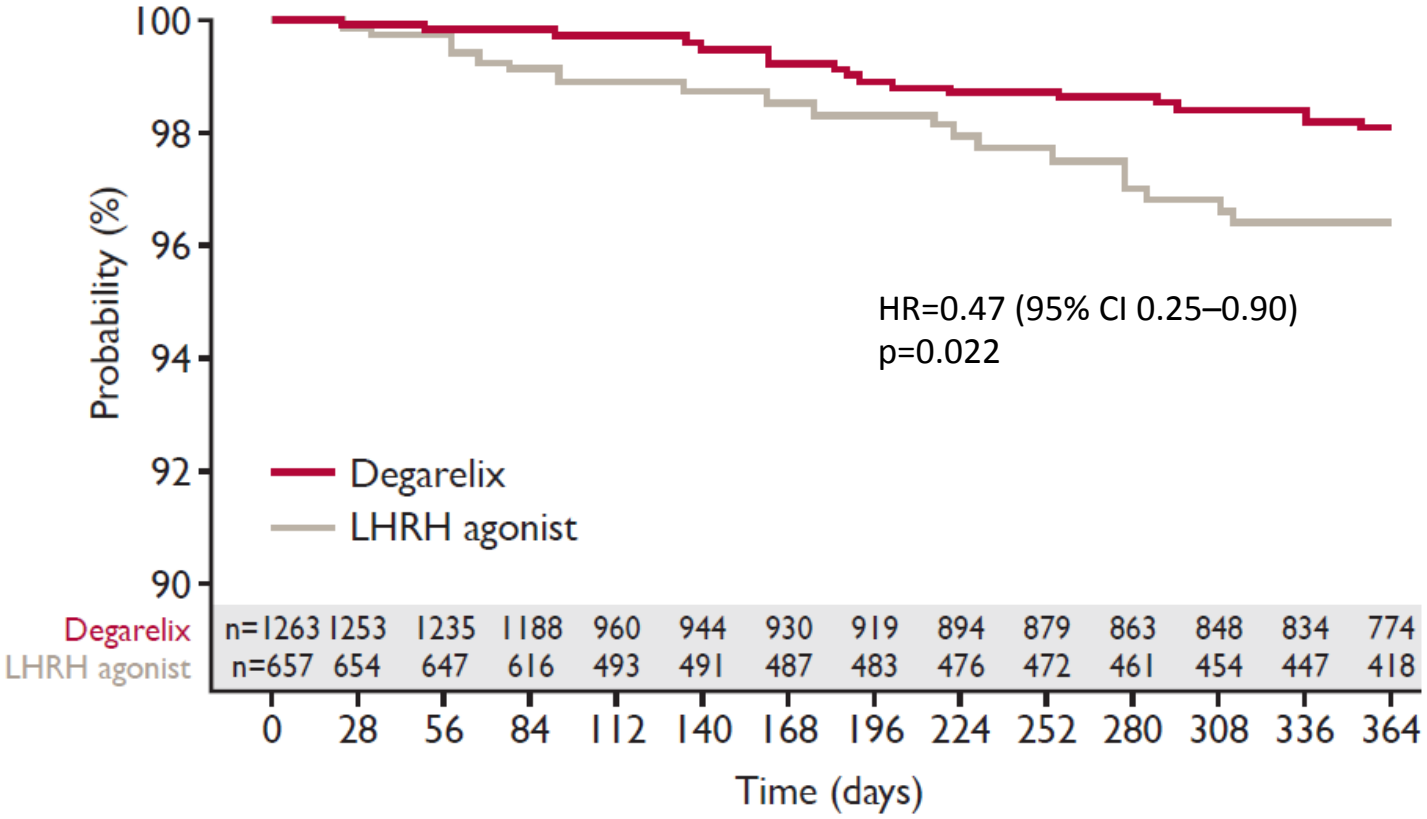


There is a >60% lower risk of serious CV event for men with CVD history receiving degarelix (HR=0.367, 95% CI 0.174-0.774, p=0.0086)

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

Albertsen PC, et al. Eur Urol 2014:65;565-73
Tombal B, et al. EAU 2013;Poster 677

Overall survival



Prostate cancer was not the cause of death in the majority of these patients.

CVD, cardiovascular disease

Miller K, et al. EAU 2013; Poster 678

Effect of degarelix remains when adjusted for common CVD variables

Covariate	HR estimate	95% CI	p-value
Degarelix treatment	0.44	0.26–0.74	**0.002**
Statin medication use	0.54	0.28–1.03	0.061
Alcohol consumption	0.43	0.24–0.77	0.005
Hypertension*	2.09	1.08–4.06	0.030
Cigarette smoking	1.26	0.72–2.19	0.417
Serum cholesterol >6.2 mmol/L	1.14	0.62–2.08	0.681
Treated type 2 diabetes	0.83	0.34–2.00	0.669
Treated hypertension	0.63	0.32–1.24	0.182
Age at baseline	1.03	0.99–1.07	0.152
Baseline testosterone	0.79	0.66–0.94	0.009
Baseline body mass index	0.97	0.91–1.04	0.357

*Diastolic >90 or systolic >140 mmHg
CVD, cardiovascular disease

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

Pooled analysis: Summary

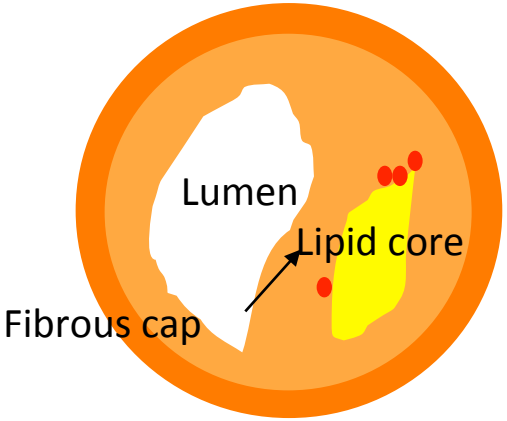
- When treated with degarelix compared with a GnRH agonist, patients with pre-existing CVD:
  - Had significantly fewer CV events during the first year of treatment
  - Had a relative risk reduction of >50% (absolute risk reduction 8.2%)

CVD, cardiovascular disease

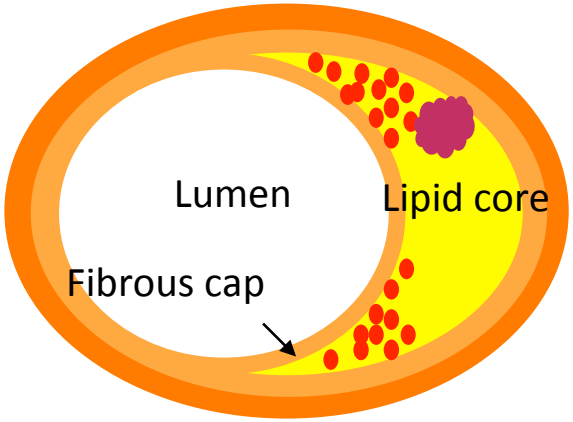
Albertsen PC, et al. Eur Urol 2014:65;565-73

Plaque instability is at the heart of cardiovascular disease

Stable plaque



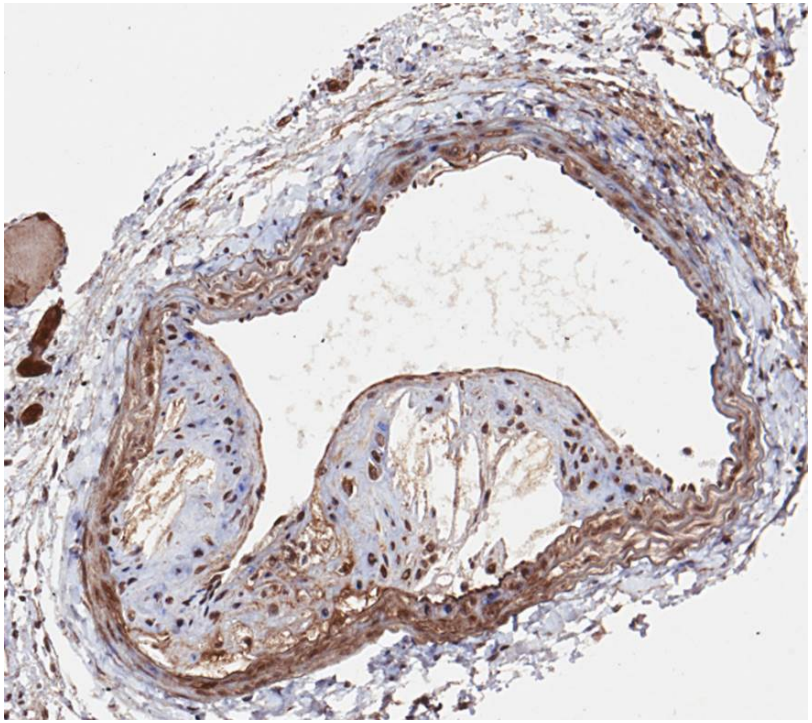
Vulnerable plaque

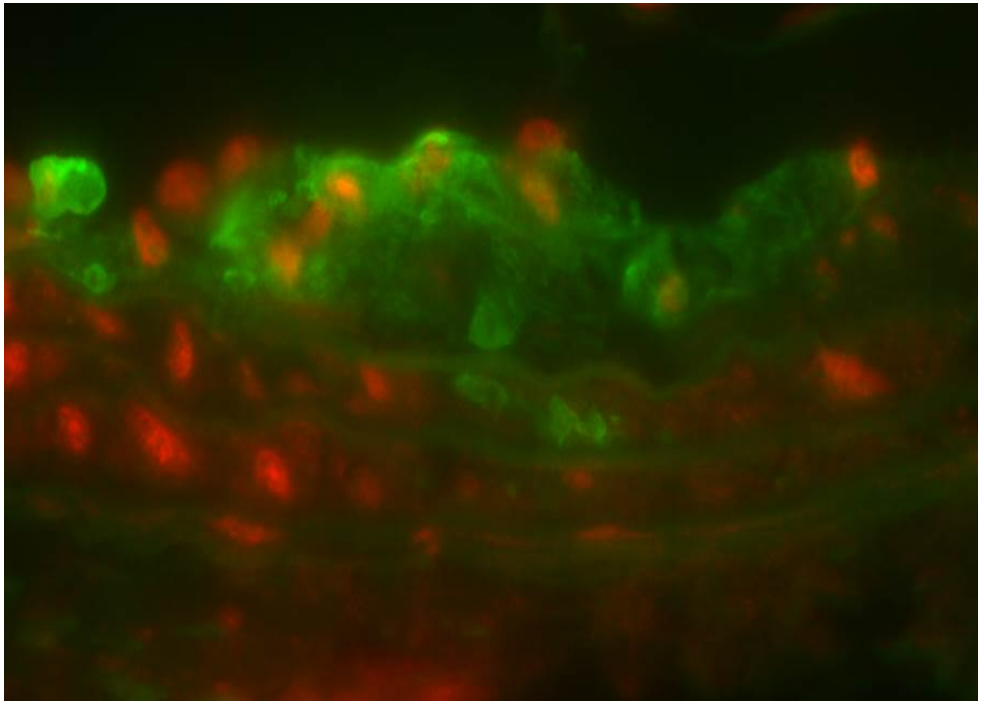


Thick	**Cap**	Thin
Rich in SMC and matrix	**Composition**	Rich in inflammatory cells: proteolytic activity
Poor	**Lipid**	Rich
inflammatory	**Inflammatory state**	More

Libby P. Circulation 1995;91:2844-2850

GnRH receptors are expressed by smooth muscle cells in atherosclerotic plaques

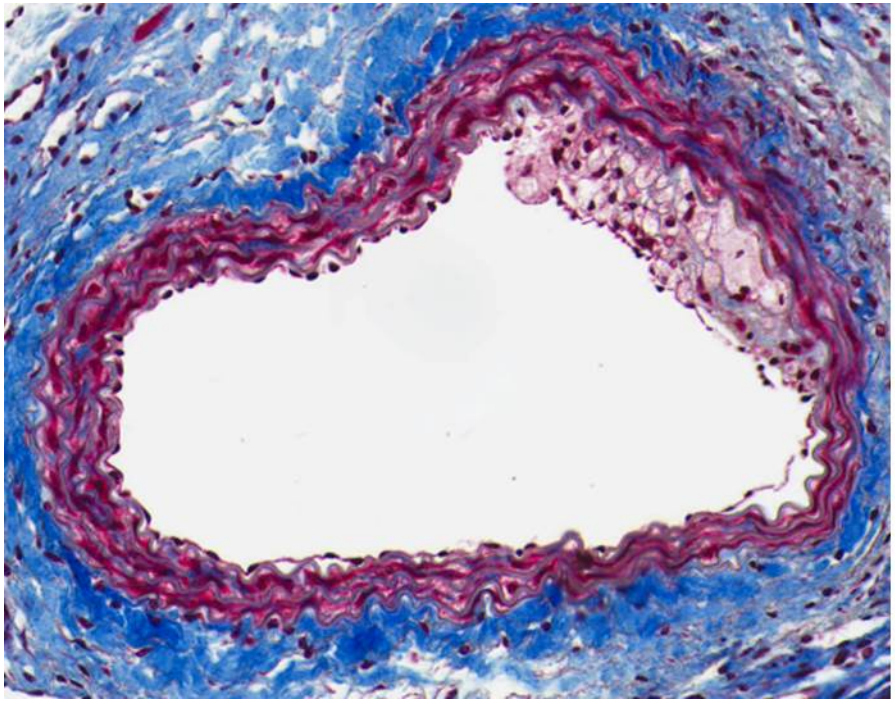




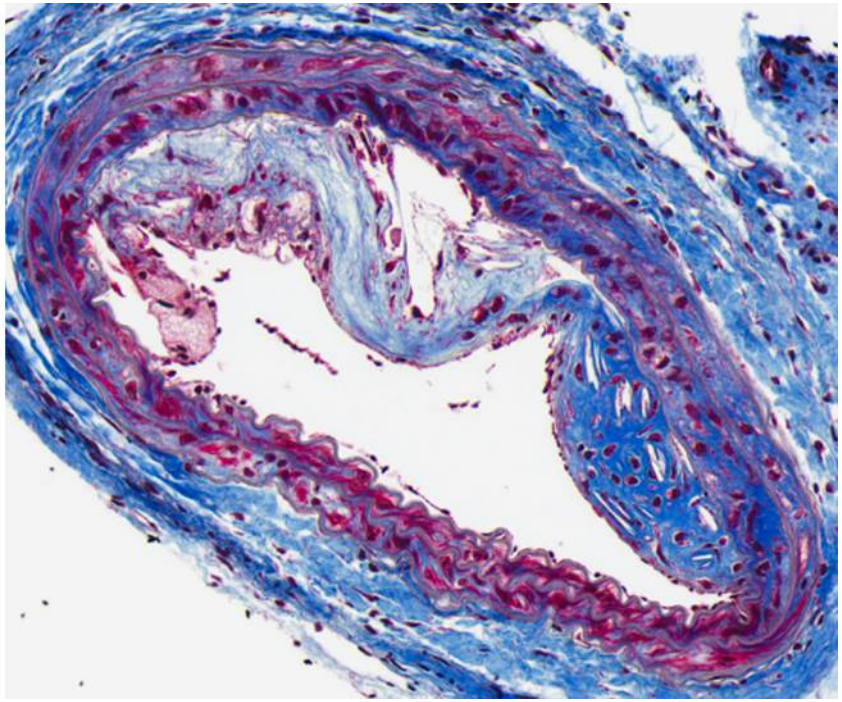
Hultgårdh, Nilsson et al, unpublished

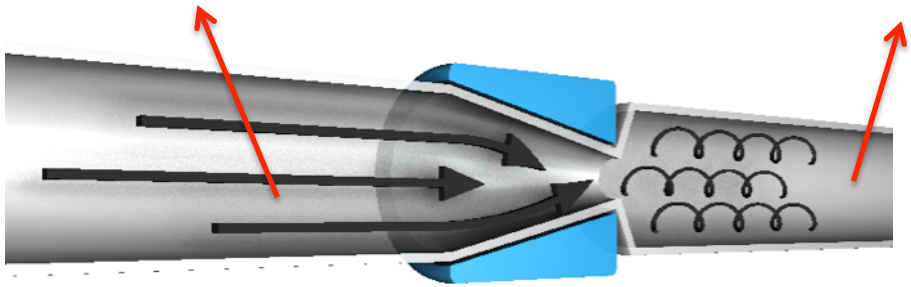
Atherosclerotic plaques induced by different types of shear stress

Unstable plaque (low shear)



Stable plaque (oscillatory shear)





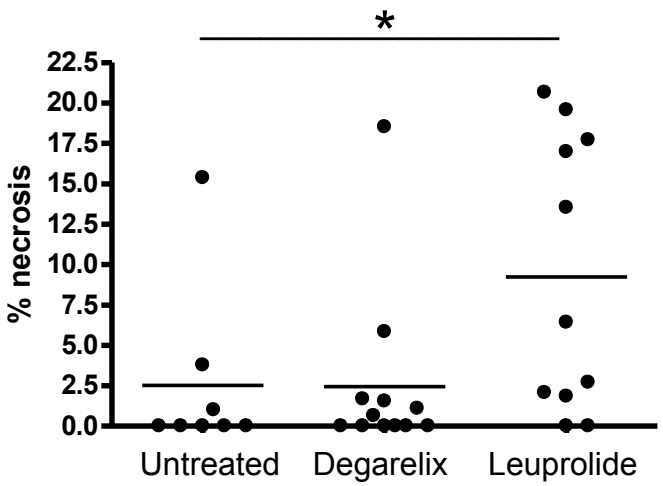
Leuprolide induces necrosis in stable oscillatory shear stress-induced plaques

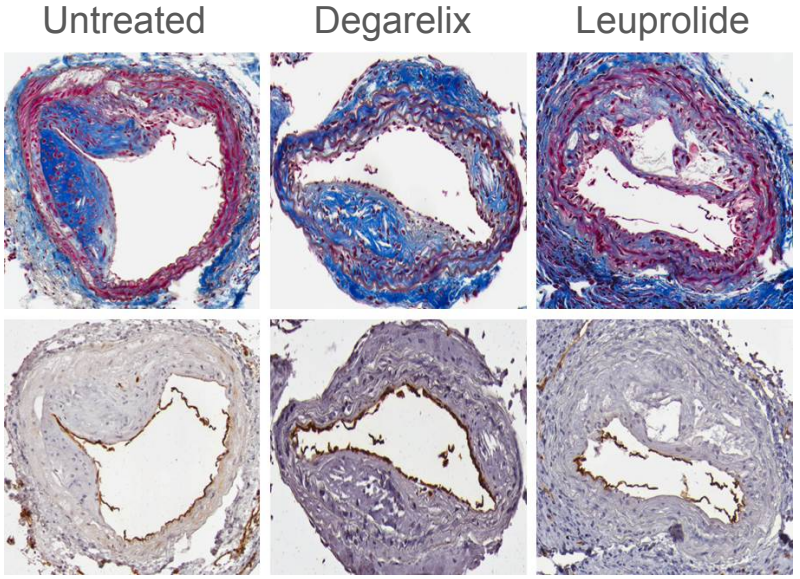
16 weeks
Cholesterol -rich diet

18 weeks
Shear stress-modifier

26 weeks
Degarelix
Leuprolide
Untreated

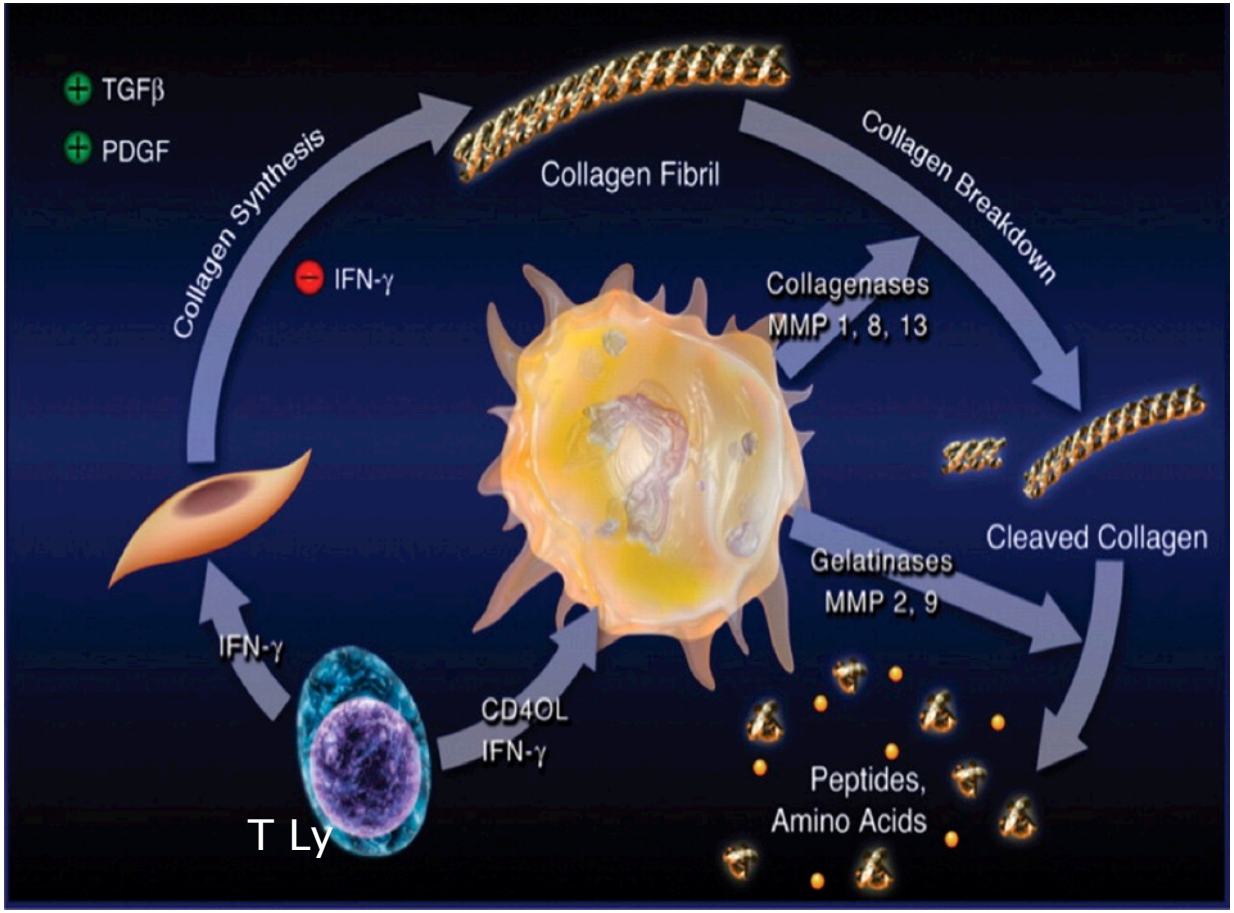
30 weeks
End point





Hultgårdh, Nilsson et al, unpublished

T lymphocytes are key drivers of collagen metabolism in atherosclerotic plaques



Disruption of the fibrotic cap

↓

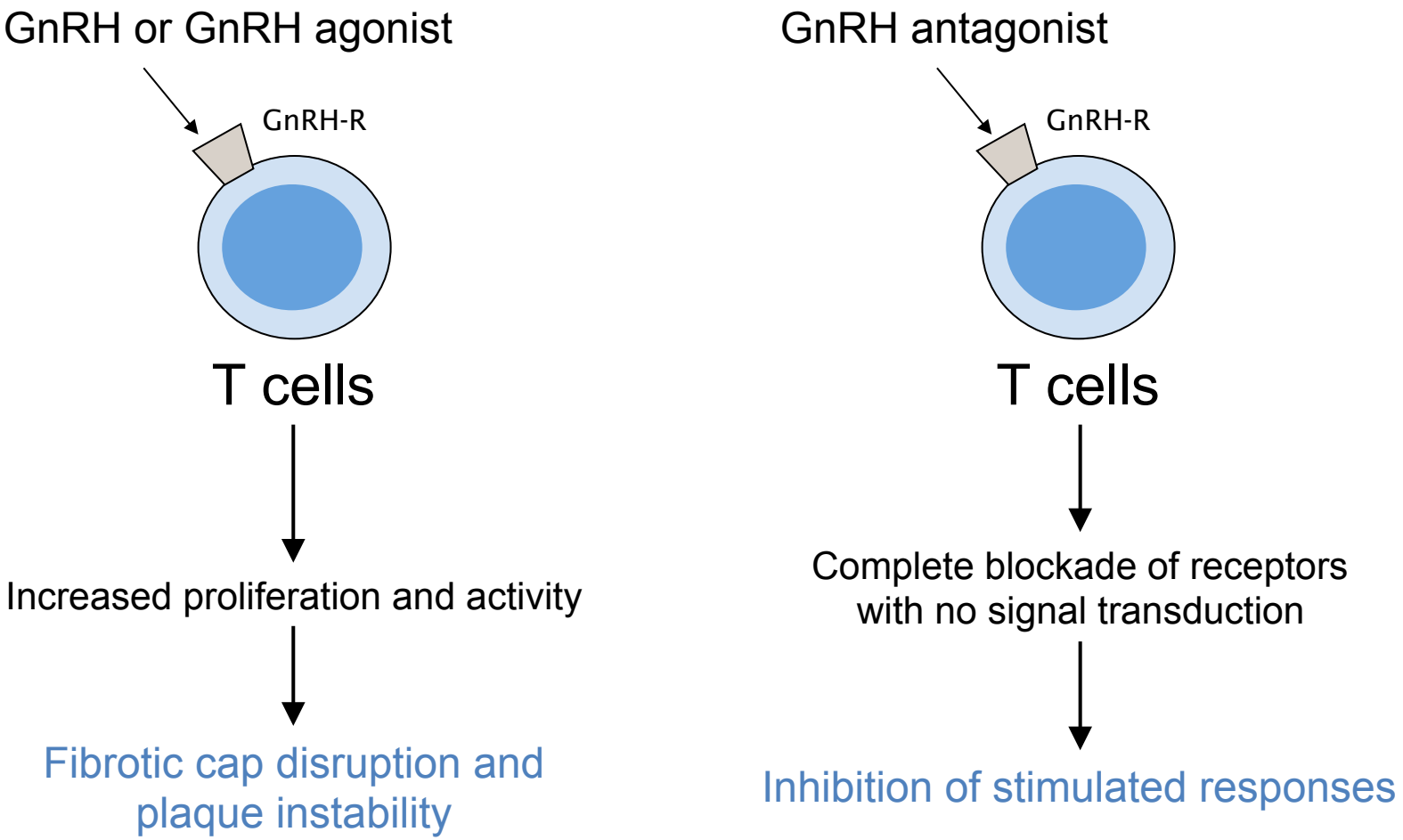
Plaque instability

↓

Increased risk of thrombo-embolic complications and cardiovascular disease

Libby P J. Lipid Res 2009;50:S352-S357

T cells express GnRH receptors: Agonists and antagonists have different effects



IFN, interferon

Chen HF, et al. J Clin Endocrinol Metab 1999;84:743-50
Tanriverdi F, et al. Clin Exp Immunol 2005;142:103-10
Grasso G, et al. Life Sci 1998;62:2005-14; Jacobson JD, et al. Endocrinol 1994;134:2516-23

Potential mechanisms for differences in CV risk with different forms of ADT

Differences in CV risk could be due to differences in the effect of different ADTs on:

1. Metabolic changes
2. GnRH receptor activation
3. FSH levels

Personalized ADT for the Specific Patient

- Cardiac
- **Obesity and testosterone**
- FSH
- High volume metastatic disease
- Docetaxol
- Significant LUTS

ADT has been associated with metabolic changes

- Metabolic syndrome is a disorder of energy utilisation and storage, diagnosed by co-occurrence of any 3 of:
  - Abdominal (central) obesity
  - Elevated blood pressure
  - Elevated fasting plasma glucose
  - High serum triglycerides
  - Low high-density (HDL) cholesterol levels
- Metabolic syndrome increases the risk of developing CVD
- ADT leads to:
  - Insulin resistance
  - Accumulation of subcutaneous fat and decreased lean body mass
  - Increased glucose levels
  - Abnormalities in lipid levels

Kelly DM, Jones TH. J Endocrinol 2013;217:R25-45

Metabolic syndrome and metabolic changes induced by ADT are different

Metabolic syndrome	Metabolic changes with ADT
Increased triglycerides	Increased triglycerides
Increased visceral fat	Increased subcutaneous fat
Reduced HDL	Increased HDL
Hypertension	Hypertension
Increased fasting glucose	Increased fasting glucose
Decreased adiponectin	Increased adiponectin
Increased C-reactive protein	Normal C-reactive protein

Saylor PJ, Smith MR. J Urol 2009;181:1998–2008

FSH and adipogenesis

- Stimulation of FSH receptors possibly alters endothelial cell function, lipid metabolism and fat accumulation
- Preclinical studies have shown:[1]
  - Mice treated with degarelix have lower FSH levels than those treated with LHRH agonist or orchiectomy
  - Degarelix-treated mice gain less weight and visceral fat than mice treated with LHRH agonists

1. Hopmans SN, et al. Urol Oncol 2014; In press

Personalized ADT for the Specific Patient

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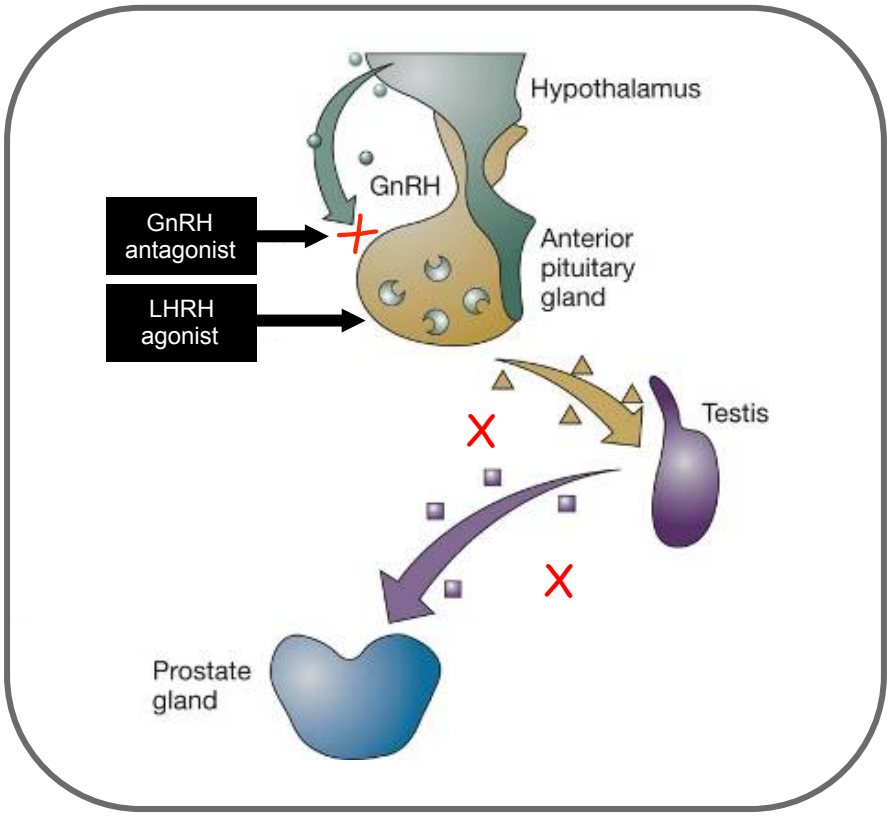
ADT: mechanism of action in relation to CV risk



Degarelix	LHRH agonists
Rapid suppression of FSH, LH and testosterone	Initial surge in FSH, LH and testosterone
No microsurges	Microsurges on repeat injection
Unlikely that testosterone suppression can explain differences in risk	
Inhibition of GnRH receptors	Stimulation of GnRH receptors
Potential for agonists to have a plaque destabilising effect due to induction of necrosis and T cell stimulation	
Prolonged suppression of FSH, LH and testosterone	FSH suppression not maintained long term
Increased potential for metabolic syndrome and atherogenesis with agonist therapy	

FSH, follicle-stimulating hormone
LH, luteinising hormone

FSH and LUTS

- **LHRH Antagonist Cetrorelix Reduces Prostate Size and Gene Expression of Proinflammatory Cytokines and Growth Factors in a Rat Model of BPH**. Ferenc G Rick et al. Andrew V schally, NormanL.Block. et al. The Prostate 71:736-747 (2011)

- **Relationship between serum sex hormones levels and degree of benign prostate hyperplasia in Chinese aging men.** Zeng QS, Xu CL, Liu ZY. et al. Asian Journal of Andrology (2012) 14, 773-777.

- **Degarelix versus Goserelin plus Bicalutamide Therapy for Lower Urinary Tract Symptom Relief, Prostate Volume Reduction and Quality of life Improvement in Men with ProstateCancer: A Systematic Reviewand Meta-Analysis.** Cui Y, Zong H, Yan H et al. Urol Int 2014; 93:152-159.

- **Disease Control Outcomes from Analysis of Pooled Individual Patient Data from Five Comparative Randomized Clinical Trials of Degarelix Versus Luteinising Hormone-releasing Hormone Agonists.** Klotz L, Miller K. Crawford E.D. et al. European Urology 66 (2014) 1101-1108

- **In Search of the Molecular Mechanisms Mediating the Inhibitory Effect of the GnRH Antagonist Degarelix on Human Prostate Cell Growth.** Sakai M, Martinez- Arguelles D, Patterson N. et al. PLOS ONE / DOI:10.1371/journal.pone.0120670 March 26, 2015.

LHRH Antagonist Cetrorelix Reduces Prostate Size and Gene Expression of Proinflammatory Cytokines and Growth Factors in a Rat Model of Benign Prostatic Hyperplasia

BACKGROUND. Recent findings suggest that BPH has an inflammatory component. Clinical trials have documented that therapy with LHRH antagonist Cetrorelix causes a marked and prolonged improvement in LUTS in men with symptomatic BPH. We investigated the mechanism of action and effect of Cetrorelix in a rat model of BPH.

METHODS. Adult male Wistar rats were used. BPH was induced in rats by subcutaneous injections of TE 2 mg/day for 4 weeks. Control animals received injections of corn oil. After induction of BPH, rats received depot Cetrorelix pamoate at the doses of 0.625, 1.25, and 12.5 mg/kg on days 1 and 22 and TE-control rats received vehicle injections. Whole prostates were weighed and processed for RNA and protein. Real-time RT-PCR assays for numerous inflammatory cytokines and growth factors were performed. Quantitative analyses of prostatic LHRH receptor, LHRH, androgen receptor (AR) and 5α-reductase 2 were done by real-time RT-PCR and immunoblotting; serum DHT, LH, PSA, and IGF-1 by immunoassays.

RESULTS. mRNA levels for inflammatory cytokines IFN-γ, IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, IL-15, and IL-17 and for growth factors EGF, FGF-2, FGF-7, FGF-8, FGF-14, TGF-β1, and VEGF-A were significantly reduced by Cetrorelix 0.625 mg/kg ($P < 0.05$). Prostate weights were also significantly lowered by any dose of Cetrorelix.

CONCLUSIONS. This study suggests that Cetrorelix reduces various inflammatory cytokines and growth factors in rat prostate and, at doses which do not induce castration levels of testosterone, can lower prostate weights. Our findings shed light on the mechanism of action of LHRH antagonists in BPH. *Prostate 71: 736–747, 2011.*

Degarelix versus Goserelin plus Bicalutamide Therapy for Lower Urinary Tract Symptom Relief, Prostate Volume Reduction and Quality of Life Improvement in Men with Prostate Cancer: A Systematic Review and Meta-Analysis

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- Literature review performed of all published RCTs that used degarelix vs. GnRH agonists + antiandrogens for treatment of Pca
- Degarelix vs. GnRH + Bicalutamide
  - Better IPSS reduction
  - Decreases in IPSS greater in patients with initial IPSS score >13
  - Prostate volume reduction similar for both groups
  - Quality of life related to urinary symptoms similar for both groups

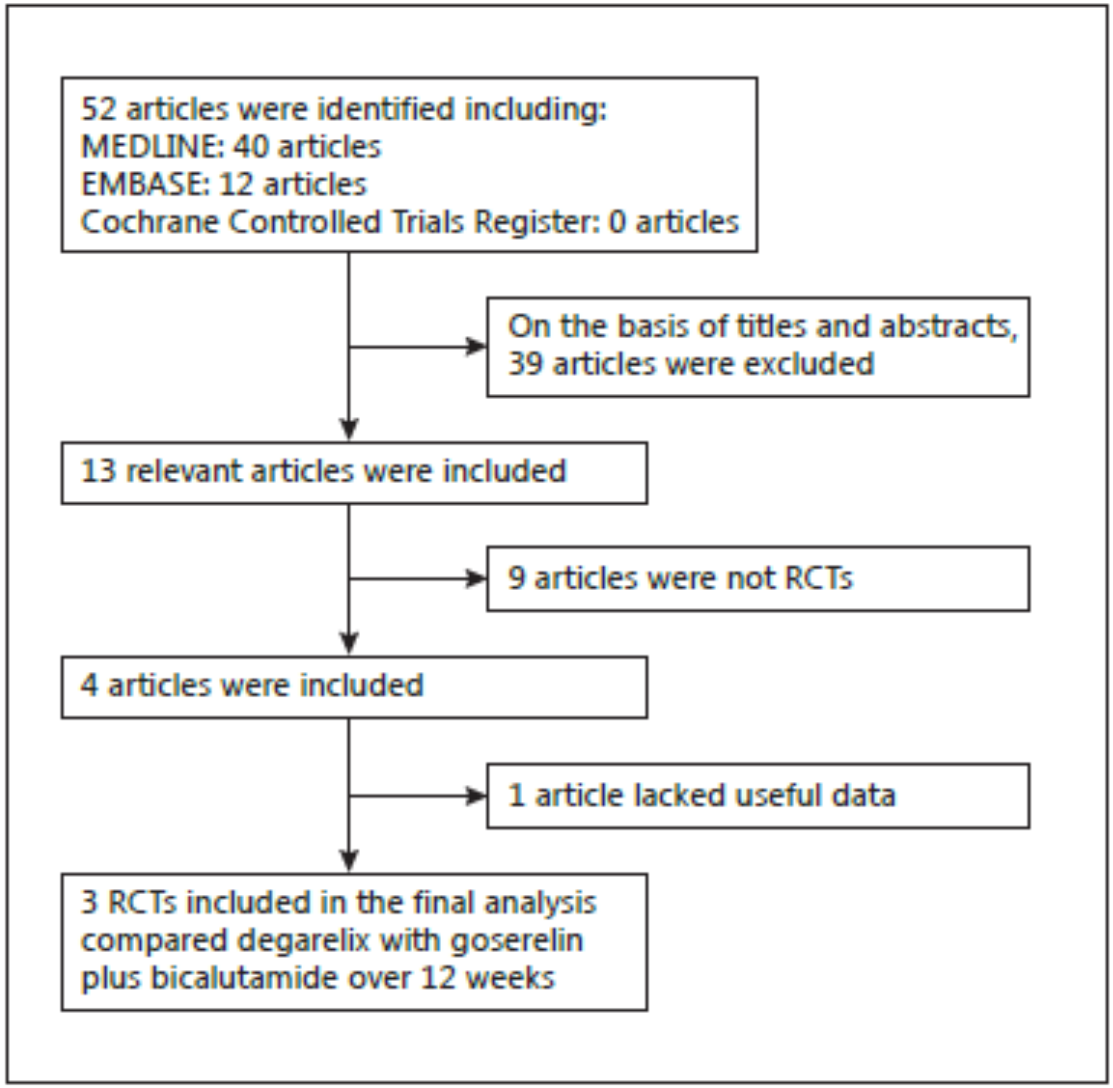
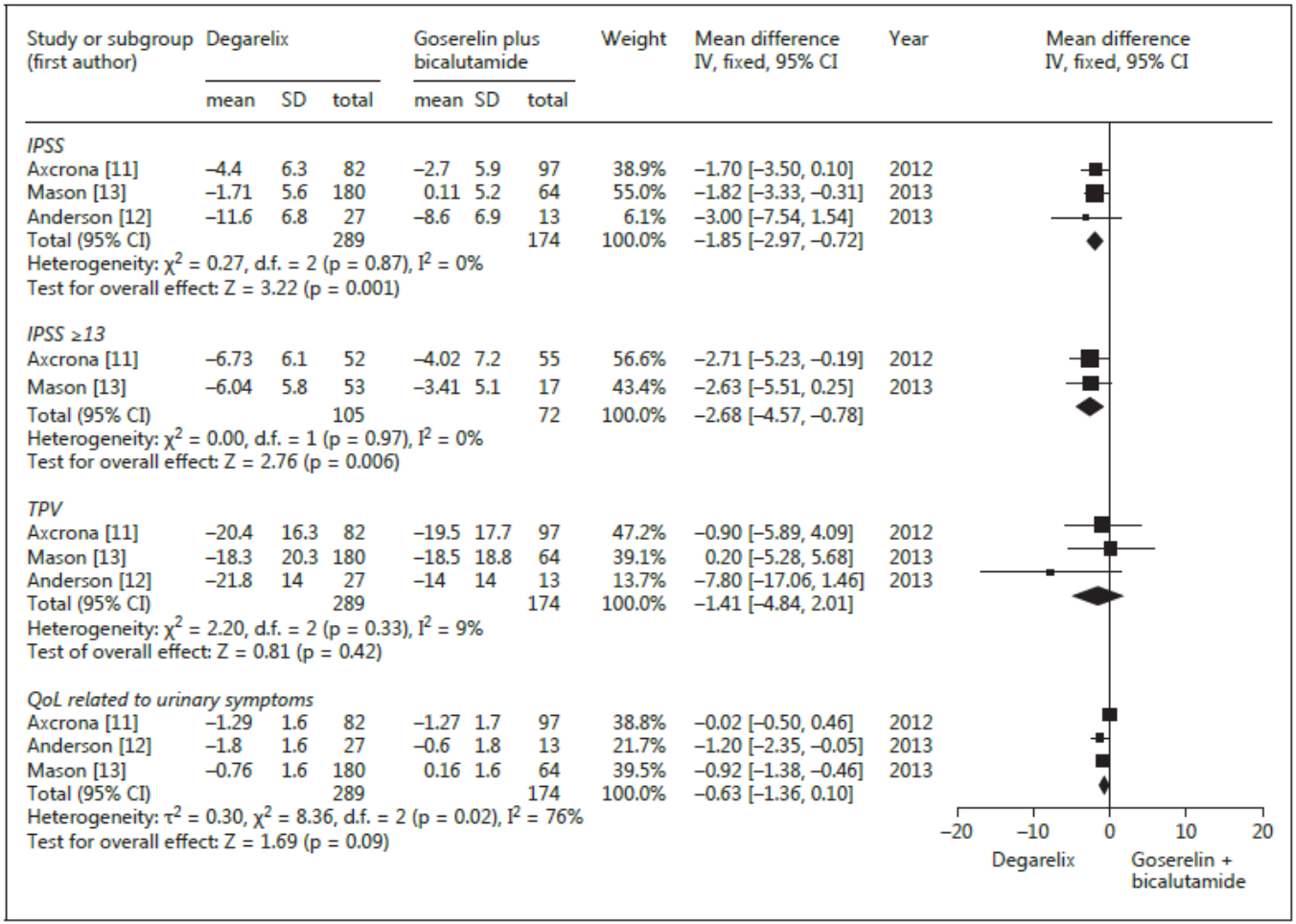
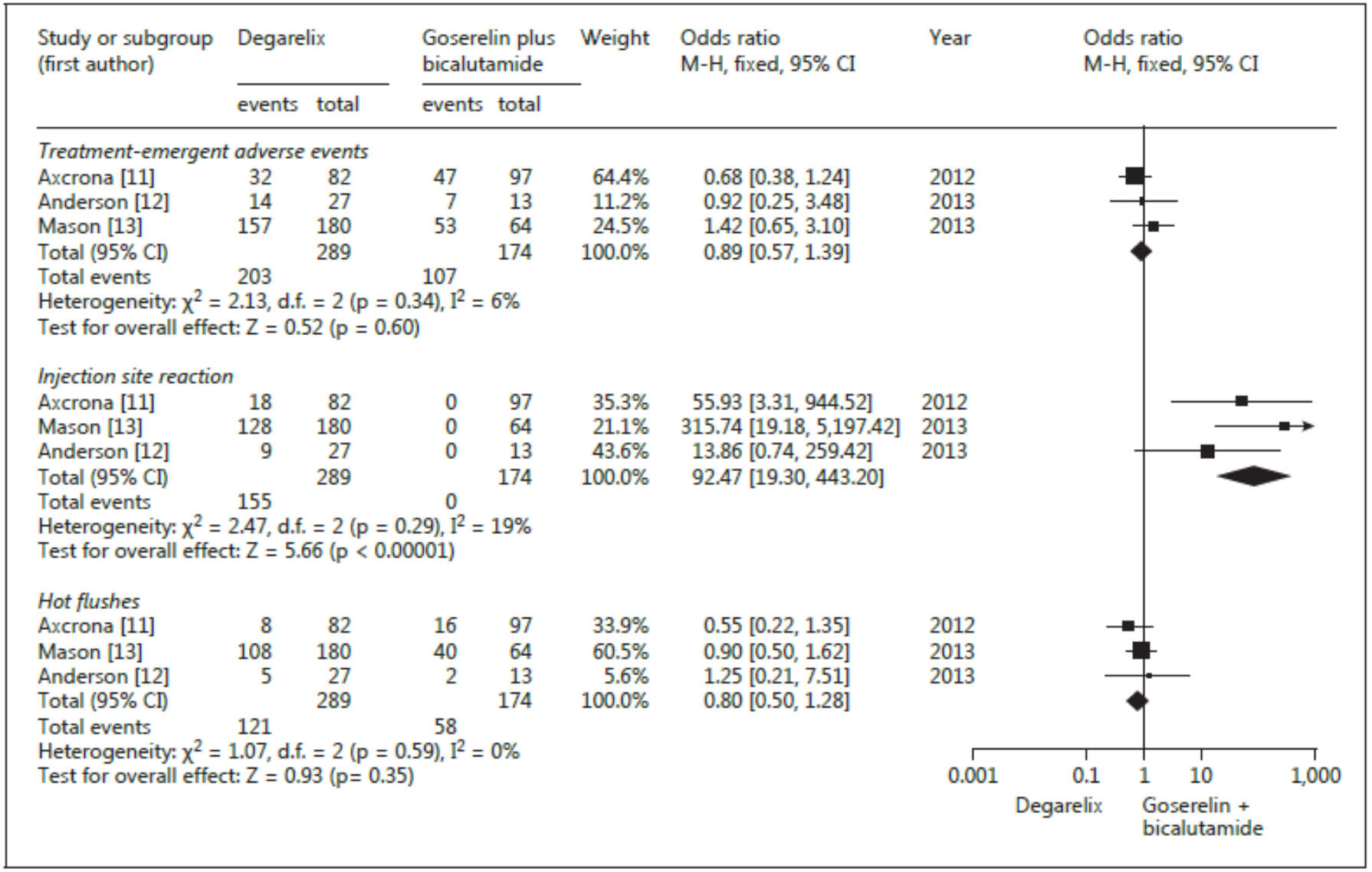


Fig. 1. Flow diagram of the study selection process.



Forest plots showing changes in IPSS, IPSS >= 13, TPC and QoL related to urinary symptoms in the treatment studies. SD = standard deviation; IV = inverse variance

- No heterogeneity among trials, pooled estimate of standardized mean difference is -1.85, 95% CI (-2.97 to -0.72) (p=0.001). Results suggest decreases in IPSS greater in degarelix.
- Patients with baseline IPSS >= 13 larger benefit in degarelix group



Forest plots showing changes in treatment-emergent adverse events, injection site reaction, and hot flushes in the treatment studies. M-H = Mantel-Haenszel

Table 1. Study and patient characteristics

Study (first author)	Therapy in experimental group	Therapy in control group	Country	Sample size		Inclusion population	Exclusion population	Duration of therapy	Form of experiment and dosing	Form of control and dosing
				experi-mental	con-trol					
Axcrona [11], 2012	degarelix	goserelin plus bicalutamide	Denmark	82	97	PCa (all stages), patients with PSA >2 ng/ml, TPV >30 ml, bone scan in the past 12 weeks	previous use of a urinary bladder catheter, treatment with a 5α-reductase inhibitor or botulinum toxin in the past 6 months, treatment with α-blocker in the past 4 weeks	12 weeks	I 240/80 mg	O 3.6 mg + 50 mg
Anderson [12], 2013	degarelix	goserelin plus bicalutamide	Switzerland	27	13	PCa (all stages), PSA >10 ng/ml, IPSS ≥12, Q_{max} ≤12 ml/s, prostate size >30 ml	treatment with a 5α-reductase inhibitor ≥6 months, treatment with α-blocker ≥8 weeks, prior transurethral resection of the prostate	12 weeks	I 240/80 mg	O 3.6 mg + 50 mg
Mason [13], 2013	degarelix	goserelin plus bicalutamide	UK	180	64	PCa TNM category T2b–T4, N0, M0, Gleason score ≥7, or PSA ≥10 ng/ml; TPV >30 ml	transurethral resection of the prostate; use of a urethral catheter; treatment with a 5α-reductase inhibitor or α-blocker in the past 12, 16 and 4 weeks, respectively	12 weeks	I 240/80 mg	O 3.6 mg + 50 mg

Q_{max} = Peak urinary flow; I = injection; O = oral.

Table 2. Baseline values of TPV, IPSS, QoL, PSA and testosterone

Study (first author)	TPV, ml		IPSS		QoL		PSA, ng/ml		Testosterone, ng/ml	
	D	G+B	D	G+B	D	G+B	D	G+B	D	G+B
Axcrona [11], 2012	54.8 (26)	49.9 (15.5)	14.3 (6.91)	13.4 (7.36)	2.85 (1.62)	2.73 (1.66)	277 (937)	148 (438)	4.25 (1.88)	4.43 (1.64)
Anderson [12], 2013	53.5 (14.0)	50.3 (14.0)	20.1 (6.8)	21.1 (6.9)	3.6 (1.6)	3.2 (1.8)	54.5 (8–1,914)	41.1 (14.6–348)	4.2 (1.1–6.7)	3.9 (2.7–7.4)
Mason [13], 2013	50.9 (20.3)	52.5 (18.8)	9.5 (6.71)	8.5 (6.30)	2.27 (1.63)	1.94 (1.56)	17.4 (30.1)	13.4 (12.9)	4.18 (1.72)	4.45 (1.49)

Values are presented as mean (standard deviation) or median with range (minimum–maximum).
D = Degarelix; G+B = goserelin plus bicalutamide.

Table 3. Quality assessment of individual studies

Study (first author)	Allocation sequence generation	Allocation concealment	Blinding	Loss to follow-up	Calculation of sample size	Statistical analysis	Intention-to-treat analysis	Level of quality
Axcrona [11], 2012	A	A	A	7	yes	analysis of covariance	yes	A
Anderson [12], 2013	A	A	A	0	yes	analysis of covariance	no	A
Mason [13], 2013	A	A	A	7	yes	analysis of covariance	yes	A

A = All quality criteria met (adequate) – low risk of bias; B = one or more of the quality criteria only partly met (unclear) – moderate risk of bias; C = one or more criteria not met (inadequate or not used) – high risk of bias.

No evidence of bias was found

Conclusion

- Meta-analysis indicates that compared to goserelin plus bicalutamide, degarelix has significantly more pronounced effects on LUTS

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

Randomized comparative phase 3 trials of degarelix and luteinizing hormone-releasing hormone agonists included in the pooled analysis (safety analysis set)

Authors/trial	Study arms (dose*, mg)	Patients, no.	Follow-up, mo	Main PCa inclusion criteria	Primary end point
Klotz et al. [1]/CS21	Degarelix (240/80) Degarelix (240/160) Leuprolide (7.5)	207 202 201	12	• TNM stage: any T, any N, any M, except for neoadjuvant hormonal therapy • Includes rising PSA after having undergone prostatectomy or radiotherapy with curative intent • PSA level at screening >2 ng/ml	• Probability of testosterone ≤0.5 ng/ml from days 28–364
Anderson et al. [4]/CS28	Degarelix (240/80) Goserelin (3.6)	27 13	3	• PSA level at screening >10 ng/ml • TNM staging at baseline: T3/4, any N, any M • IPSS ≥12	• Change from baseline in total IPSS at week 12 using the last observation carried forward approach
Mason et al. [5]/CS30	Degarelix (240/80) Goserelin (3.6)	181 64	3	• Planned for radical radiotherapy treatment and in whom neoadjuvant is indicated • TNM stage: T2 (b or c)/T3/T4, N0, M0; or Gleason score ≥7 or PSA level ≥10 ng/ml	• Mean percentage reduction in prostate volume at 12 wk as compared to baseline
Axcrona et al. [3]/CS31	Degarelix (240/80) Goserelin (3.6)	84 98	3	• TNM stage: any T, any N, any M • PSA level at screening >2 ng/ml • Prostate >30 ml	• Mean percentage reduction in prostate volume measured with TRUS at 12 wk compared to baseline
Shore et al. [6]/CS35	Degarelix (240/480) Goserelin (3.6/10.8)	565 283	12	• TNM stage: any T, any N, any M, except for neoadjuvant hormonal therapy • Includes rising PSA after having undergone prostatectomy or radiotherapy with curative intent • PSA level at screening >2 ng/ml	• Cumulative probability of testosterone at castrate level (≤0.5 ng/ml) from days 28–364 with degarelix • Difference in cumulative probability of testosterone at castrate level (≤0.5 ng/ml) from days 3–364 between degarelix and goserelin

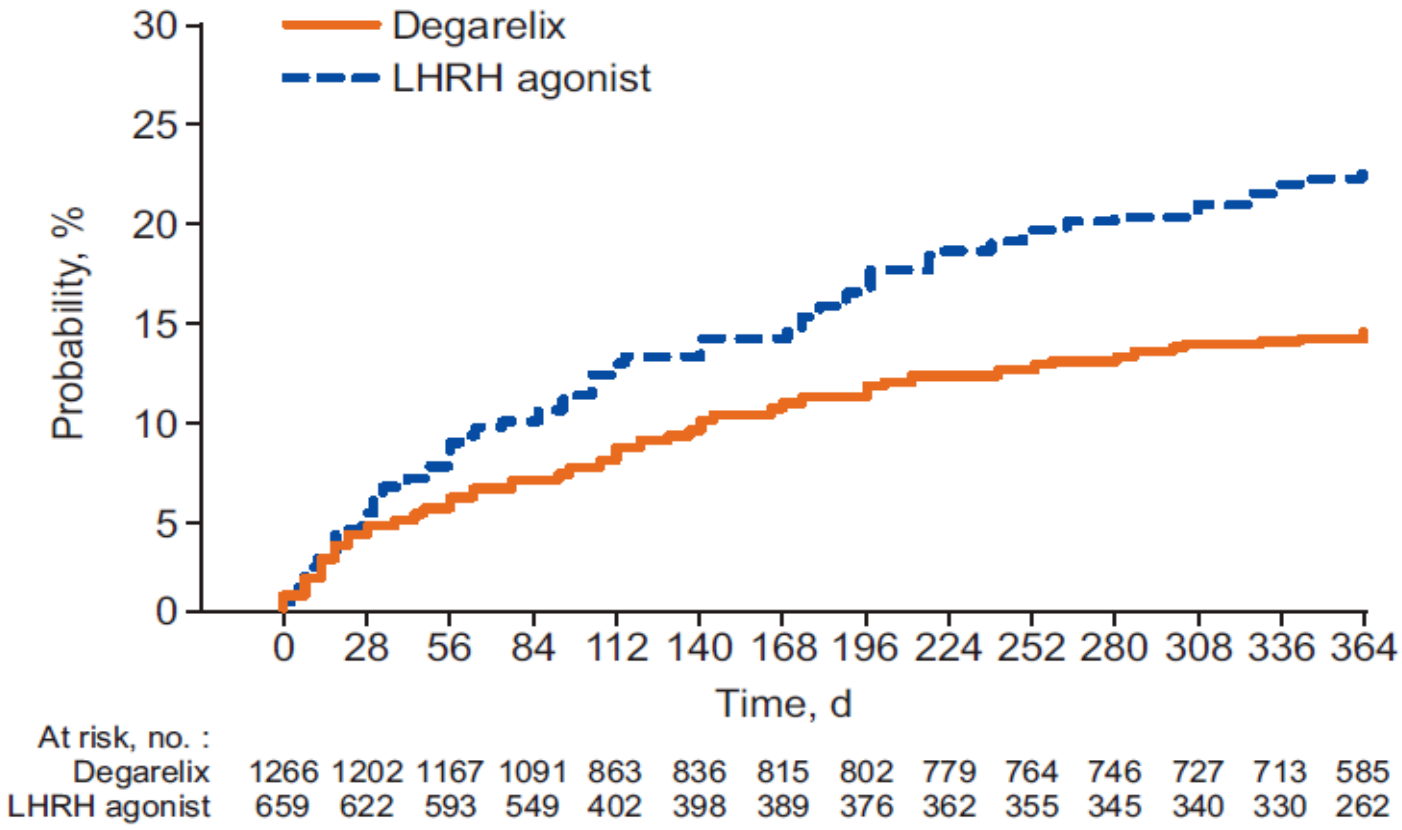
PCa = prostate cancer; PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score; TRUS = transrectal ultrasound.
* Values indicate initial dose and, if relevant, maintenance dose monthly or every 3 mo.

Treatment-emergent adverse events (>5% in either group)

Adverse event	Degarelix, no. (%)	LHRH agonist, no. (%)	*p* value*
Safety analysis set	1266 (100)	659 (100)	–
Any adverse event	942 (74)	445 (68)	0.002
Hot flush	386 (30)	171 (26)	0.039
Injection-site reactions			
Pain	380 (30)	6 (<1)	<0.001
Erythema	257 (20)	0 (0)	–
Swelling	76 (6)	0 (0)	–
Nodule	73 (6)	0 (0)	–
Fatigue	59 (5)	35 (5)	0.578
Back pain	50 (4)	41 (6)	0.031
Urinary tract infection	43 (3)	37 (6)	0.023
Arthralgia	45 (4)	34 (5)	0.115

LHRH = luteinising hormone-releasing hormone.
* Two-sided Fisher exact test.

Probability of experiencing renal or urinary tract-related adverse event



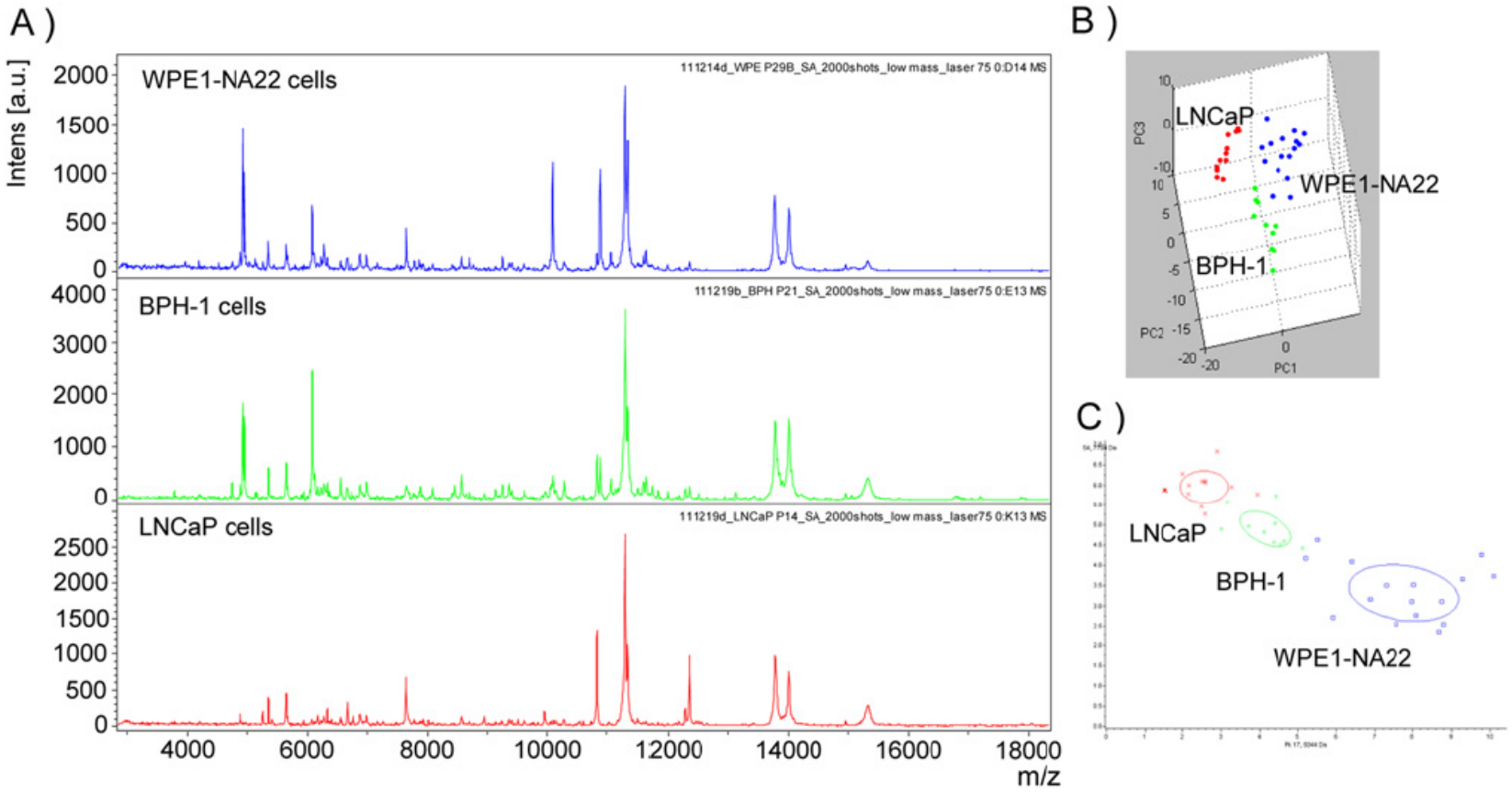
Conclusion

- Data indicate clinical benefits with degarelix including a significant improvement in PSA PFS and OS as well as reduced incidence of joint, musculoskeletal and urinary tract events compared with LHRH agonists.

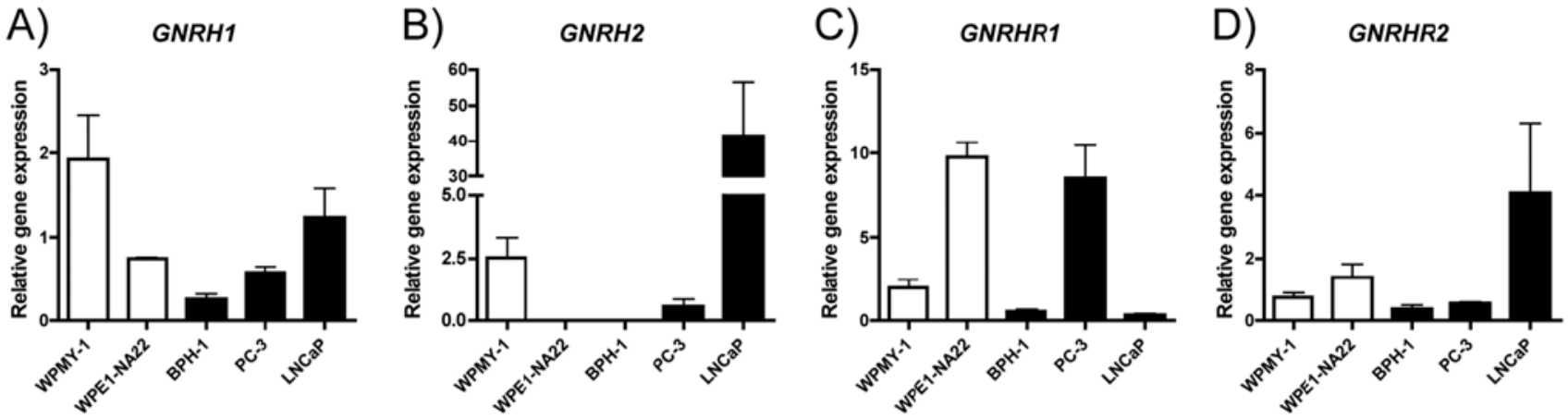
RESEARCH ARTICLE

In Search of the Molecular Mechanisms Mediating the Inhibitory Effect of the GnRH Antagonist Degarelix on Human Prostate Cell Growth

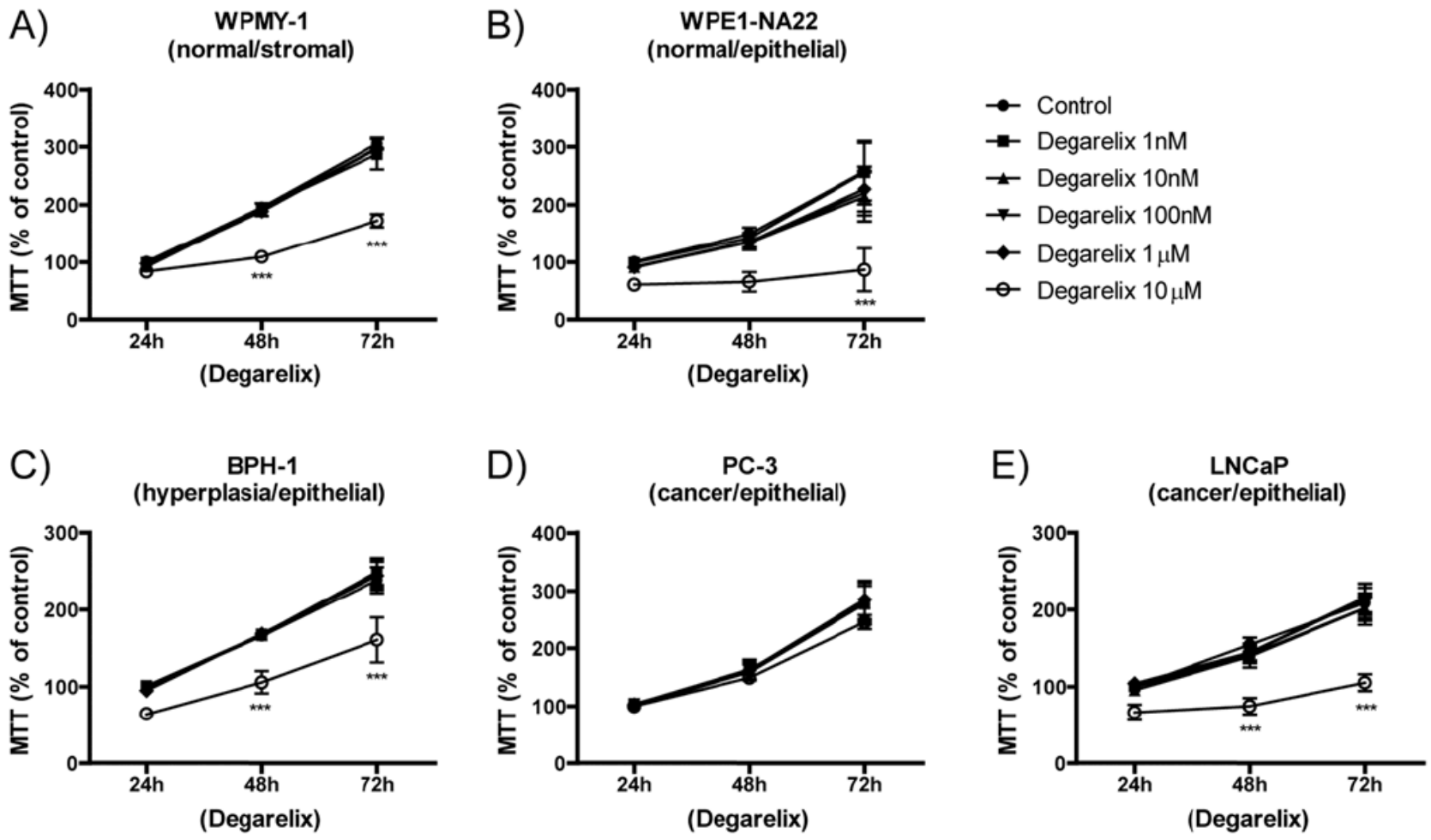
- Normal prostate myofibroblast WPMY-1 and epithelial WPE1-NA22 cells, BPH-1 cells, androgen independent and dependent (PC-3 and LNCAP) cells and VCaP cells from (CRPC) patient were used
- Discriminatory protein and lipid fingerprints of Normal, hyperplastic and Ca cells generated by matrix assisted laser desorption/ionization (MALDI) mass spec
- Investigated cell lines express GNRHR1 and GNRHR2 and their endogenous ligands
- Treatment with Degarelix reduced cell viability in all cell lines tested, except PC-3 cells, by increased apoptosis (increased caspase 3/7, 8 and 9 levels)
- Cell viability was not affected by treatment with GnRH agonists Leuprolide and Goserelin
- MALDI MS detected changes in m/z signals robust enough to create a complete discriminatory profile induced by Degarelix
- Transcriptomic analysis of BPH-1 cells provided a global map of genes affected by Degarelix, indicating the biological processes affected were related to cell growth, G-coupled receptors, the MAPK pathway, angiogenesis, and cell adhesion



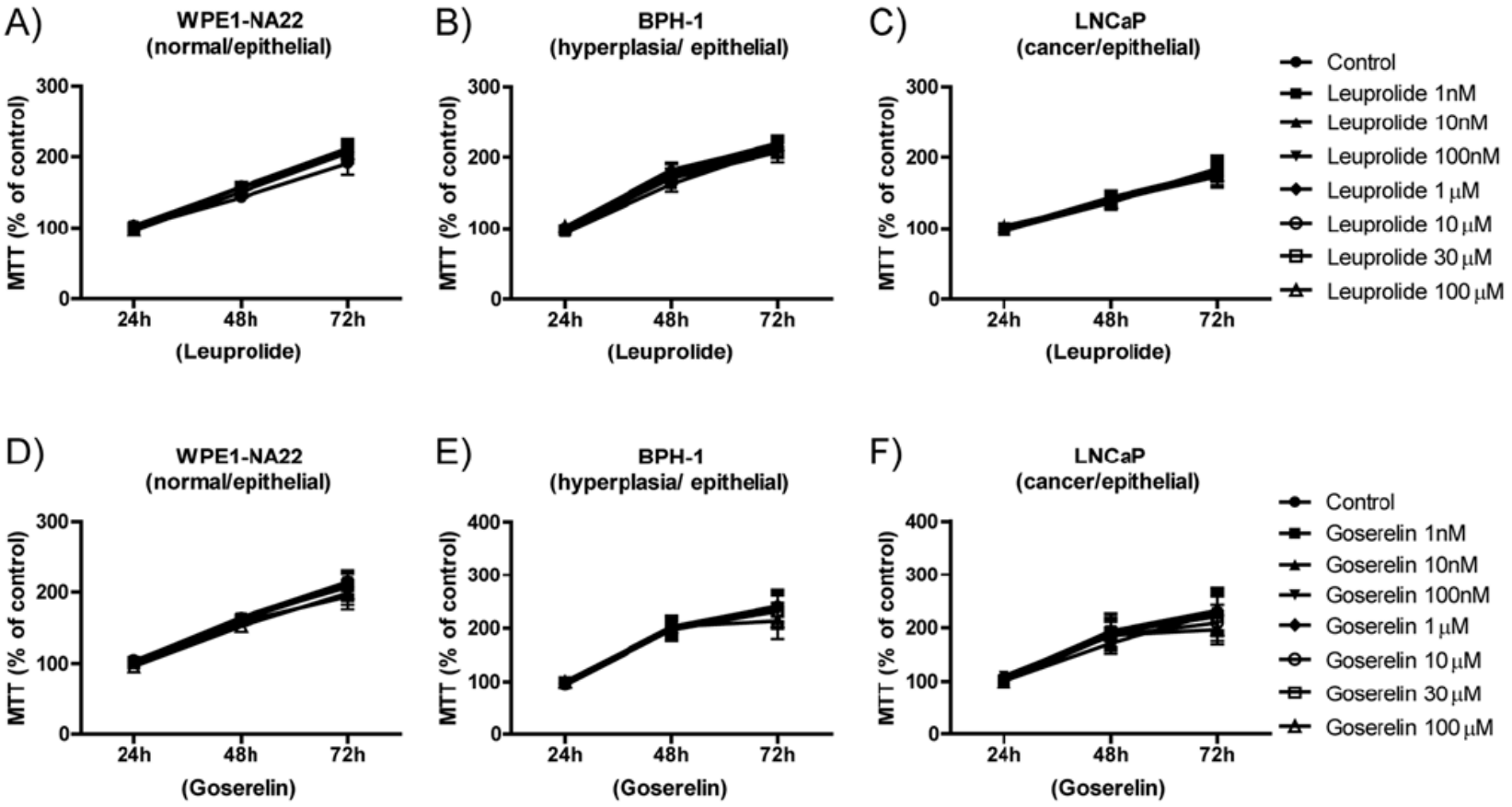
Protein spectra of human prostate cells. (A) MALDI MS protein mass spectra showing differential expression of protein signals between the 3 cell types. (B) principal component analysis (PCA) score plot, and (C) comparison of the two most discriminant peaks across samples. These analysis identify unique protein signatures for each cell line.



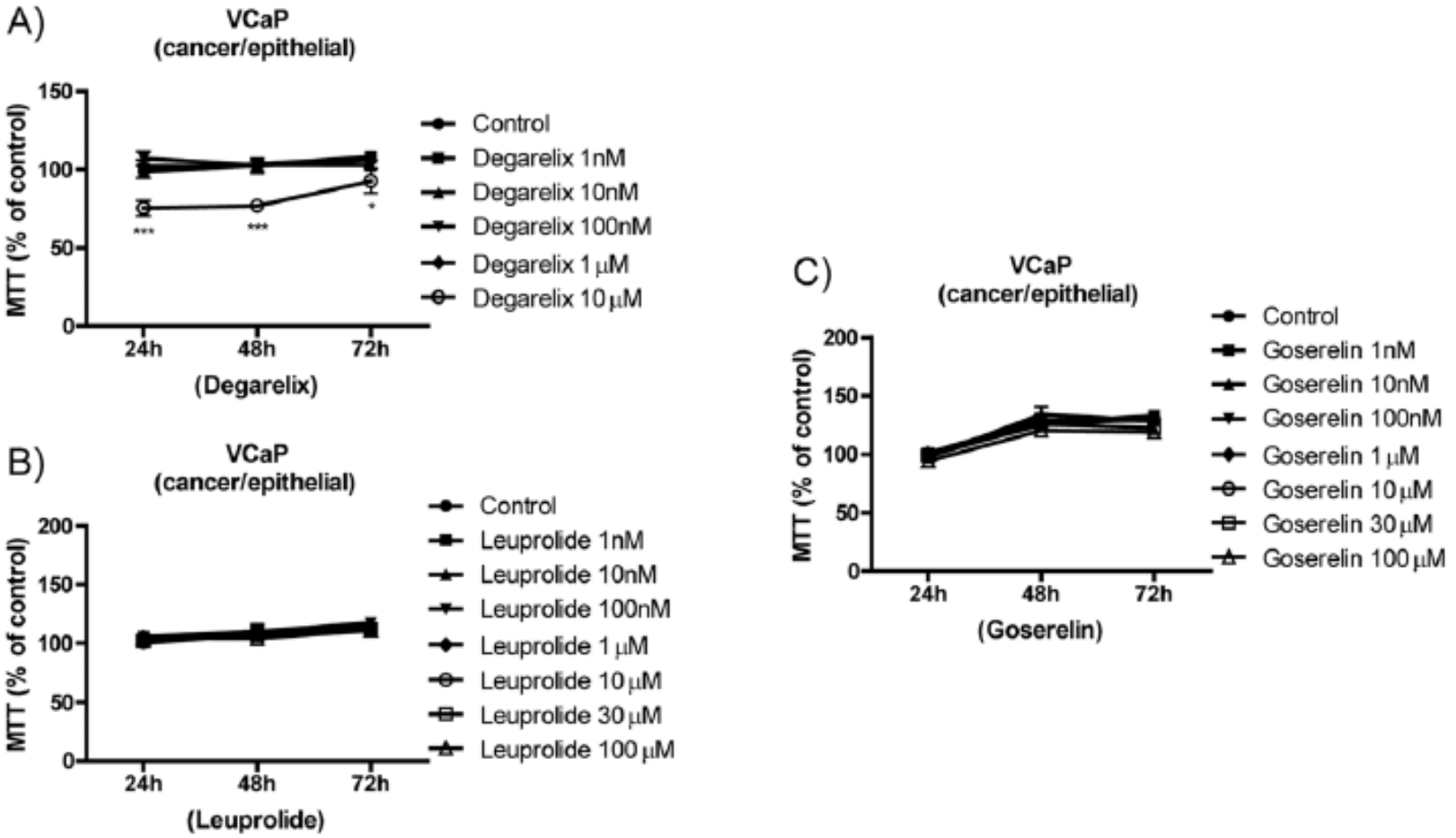
Gene expression of prostate human cell lines for GnRH and its receptor subtypes 1 and 2. (A) GNRH1, (B) GNRHR1, (C) GNRH2, and (D) GNRHR2. The white bars show normal cells and the black bars show hyperplasia or cancer cells. Results are presented as a ratio between the target gene relative to the reference gene normalized to the levels of the control.
Results shown are means +/- standard error from 3 independent experiments performed in triplicates. Results indicate significant differences between the various cell lines.



MTT assay showing the viability of prostate cell lines following treatment with the GnRH antagonist, degarelix. (A) WPMY-1, (B) WPE1-NA22, (C) BPH-1, (D) PC-3, and (E) LNCaP. Data are expressed as the percentage of the respective controls and the average +/- standard error. Each assay was done in triplicate in at least 3 independent experiments for each cell line. Two-way ANOVA indicated there was a significant difference overall for degarelix treatment ($p<0.001$), and the posttest indicated that there were differences against each control, as displayed in each graph (***$p<0.001$). For PC-3 cells only Time

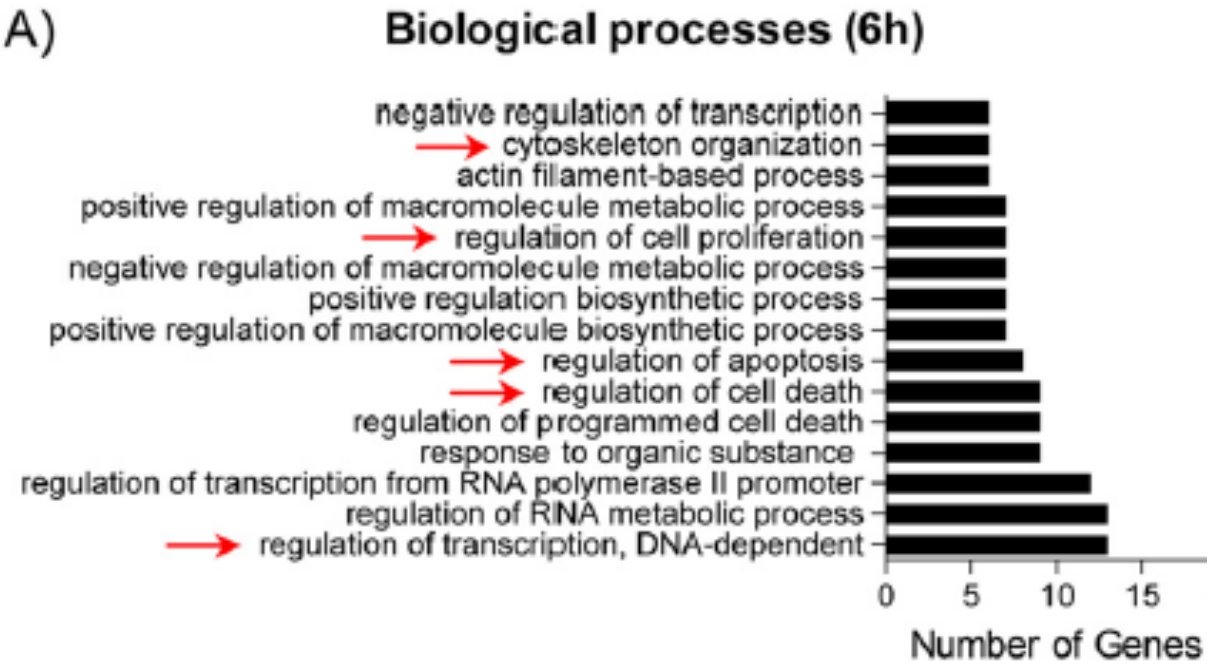


MTT assay showing the viability of WPE1-NA22, BPH-1, and LNCaP cell lines following treatment with GnRH agonists. (A-C) Leuprolide and (D-E) goserelin. Note that the different cell lines are displayed in each column. The data are expressed in terms of the percentage of the respective control and the average +/- standard error. Each assay was done in triplicate with at least n=3 independent experiments for each cell line. Two-way ANOVA displayed $p>0.05$; there was no difference overall for the treatments.

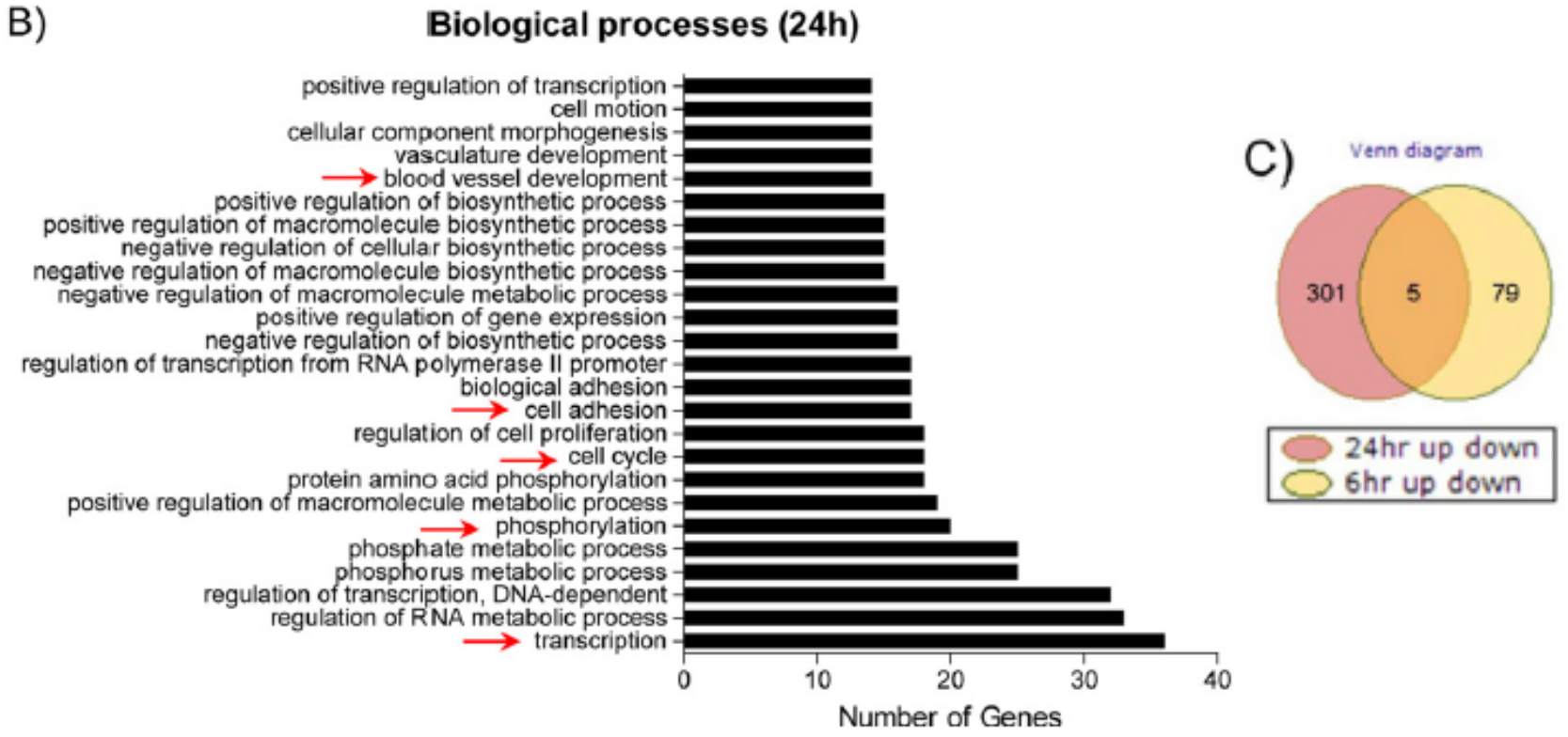


MTT assay showing the viability of the VCaP cell line after treatment with the GnRH antagonist or agonists. (A) Degarelix, (B) leuprolide, and (C) goserelin. The data are expressed in terms of the percentage of the respective control and the average +/- standard error. Each assay was done in triplicate with at least n=3 independent experiments for each cell line. Two-way ANOVA indicates that there was a significant difference overall for degarelix treatment ($p<0.001$), and the posttest indicated that there were differences against each control, as displayed in each graph (*$p<0.05$). ANOVA displayed $p>0.05$; for the leuprolide and goserelin groups, there was no difference overall for the treatments.

Gene Ontology Classification (Based on Biological Processes) of Degarelix-deregulated Genes on BPH-1 Cells



Gene Ontology Classification (Based on Biological Processes) of Degarelix-deregulated Genes on BPH-1 Cells



Gene ontology classification (based on biological processes) of degarelix-deregulated genes on BPH-1 cells. (A-B) The number of genes deregulated by degarelix in various biological processes after 6 and 24h, respectively. The arrows point to potential interesting processes in the BPH and degarelix context. (C) Venn diagram illustrating the number of genes deregulated by degarelix at 6 and 24h.

These data demonstrate…

1. Degarelix exerts a direct effect on prostate cell growth through apoptosis

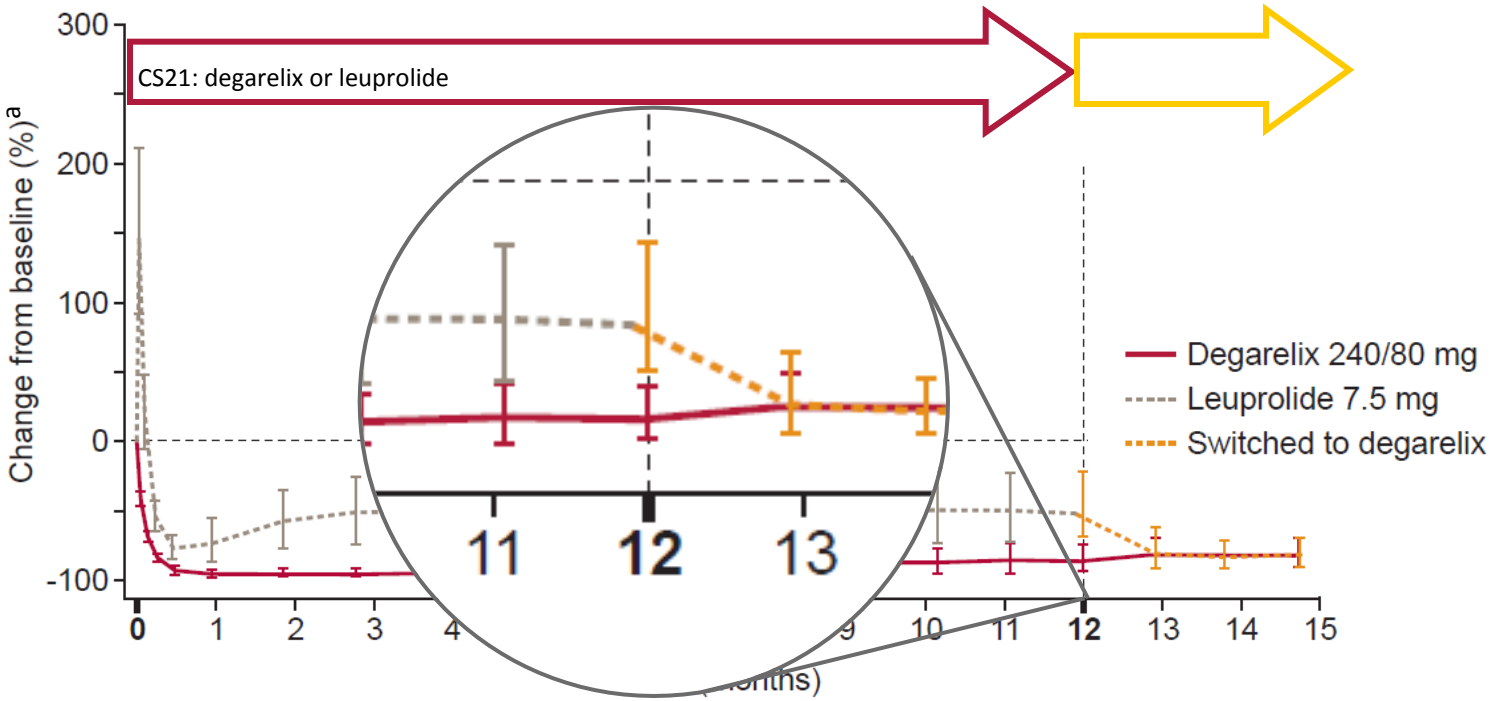
2. MALDI MS analysis provides a basis to fingerprint Degarelix-treated prostate cells

3. Clusters of genes affected by Degarelix suggest that in addition to use in prostate cancer, it may be efficacious in BPH

Conclusions

- Different types of human prostate cell lines (normal, hyperplasia and cancer are sensitive to the antiproliferative effect of Degarelix.
- Prostate cell growth was directly inhibited possibly involving a cell cycle – related mechanism and leading to apoptosis.
- Gene Array results indicate a few interesting early molecular changes induced by degarelix that could have an impact in the prostate context ,mainly controlling BPH growth.
- A maldi analysis provided the basis to discriminate between the specific proteins and lipids found following degarelix treatment.
- These findings suggest that GNRHR signaling within the prostate environment should be taken into consideration when designing therapies for the treatment of prostate diseases.

Further FSH suppression after crossover from leuprolide to degarelix

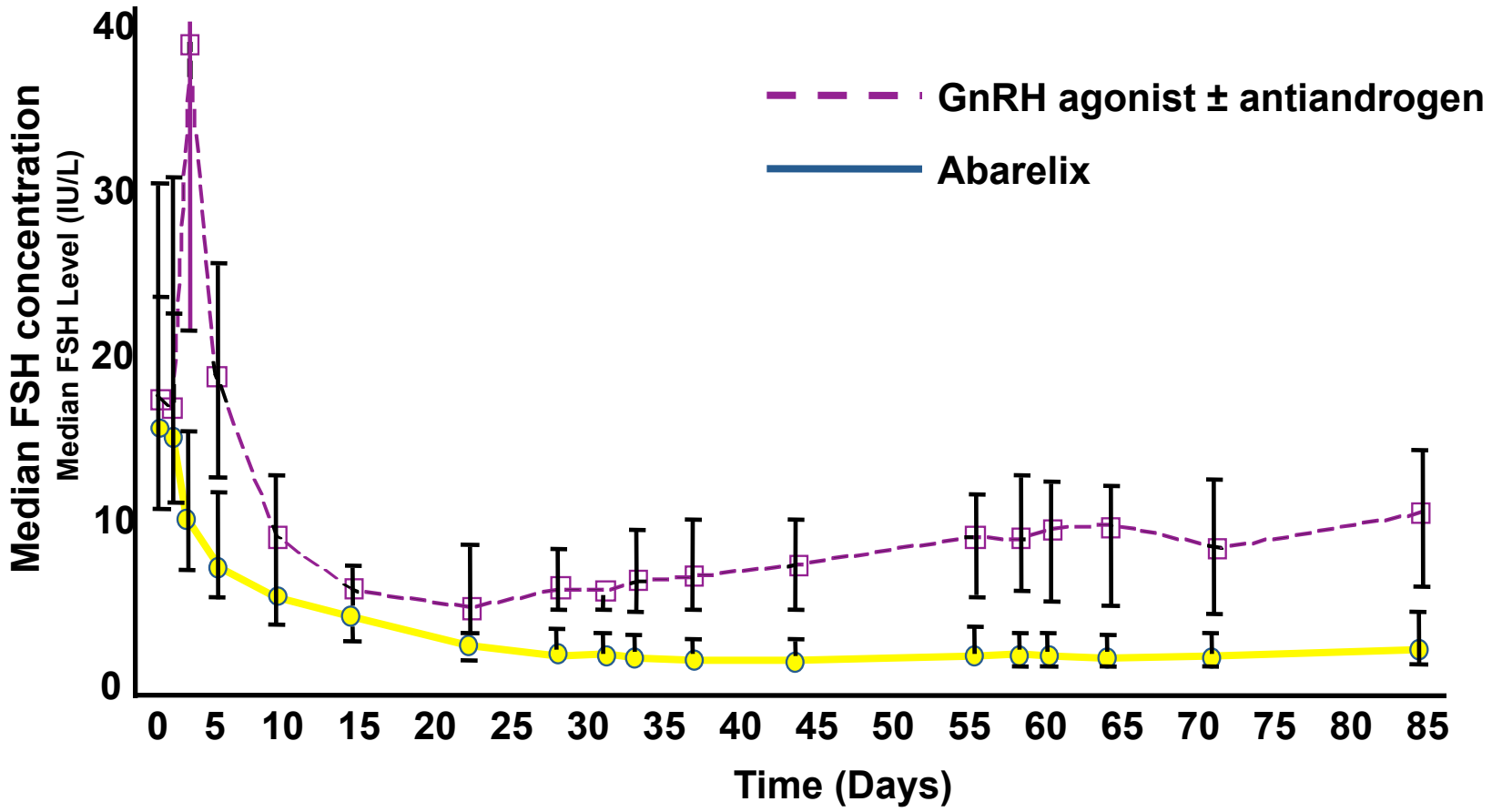


Time (days)	*0*	*28*	*56*	*84*	*112*	*140*	*168*	*196*	*224*	*252*	*280*	*308*	*336*	*364*	*392*	*420*	*448*
Number of patients																	
Degarelix	206	206	201	195	193	186	187	188	183	179	173	172	166	167	40	13	112
Leuprolide	199	196	195	191	190	190	185	188	183	181	178	179	172	171	124	120	113

[a]Median (quartiles) percentage change from baseline
FSH, follicle-stimulating hormone

Crawford ED, et al. J Urol 2011;186:889–97

Median Concentration of FSH after Abarelix and after GnRH-agonist with Antiandrogen

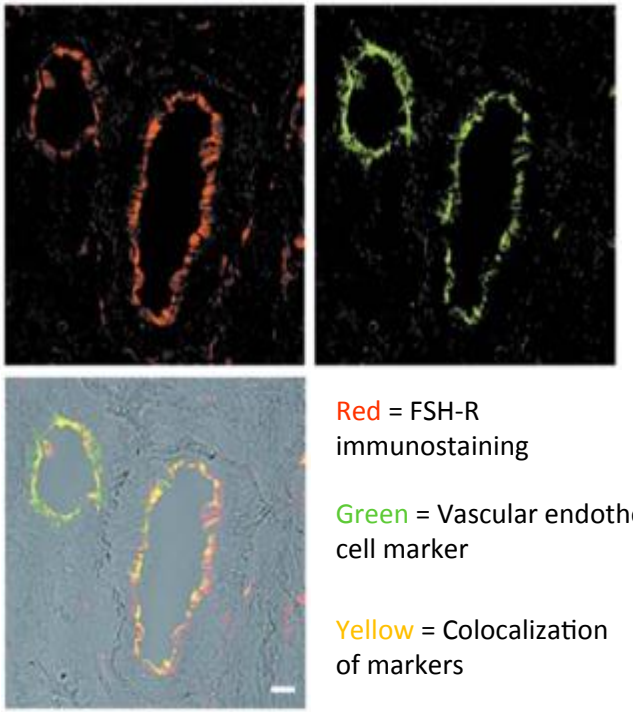


Garnick MB et al. *Mol Urol*. 2000;4:275-277.

FSH receptor is strongly expressed by human prostate tumor blood vessels

Analysis of samples from 773 patients with PCa; all samples expressed FSH receptor, whereas normal tissue had no receptor expression

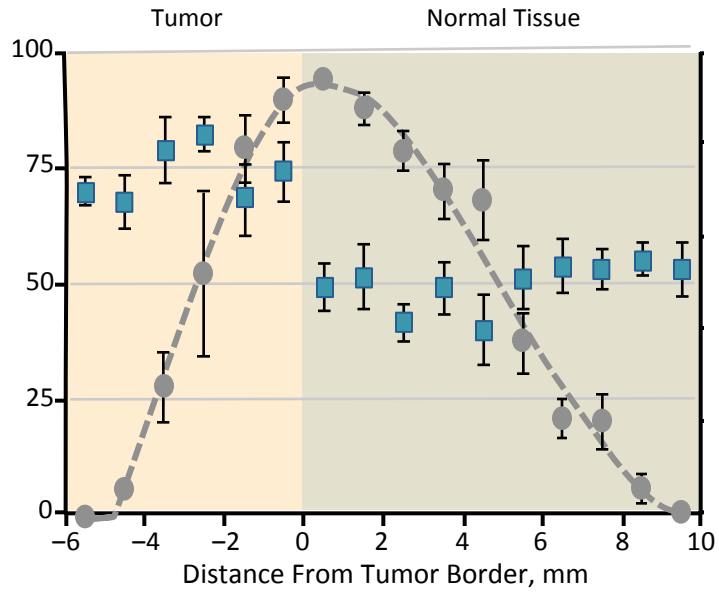
Human prostate tumor section labeled for FSH receptor and vascular endothelial cell marker



Red = FSH-R immunostaining

Green = Vascular endothelial cell marker

Yellow = Colocalization of markers



More FSH-R expressing vessels are present at or near the tumor border

FSH, follicle-stimulating hormone; PCa, prostate cancer

Radu A. *New Engl J Med*. 2010;363:1621–30

Personalized ADT for the Specific Patient

- Cardiac
- Obesity and testosterone
- FSH
- **High volume metastatic disease**
- Docetaxol
- Significant LUTS

High Volume Metastatic Disease

- Rapidity of Castration and PSA suppression
- Lack of flare and miniflare
- Better FSH suppression
- Better suppression of S-ALP
- Less SREs
- Longer duration of HSPCa state

Docetaxel PK varies with Castration State

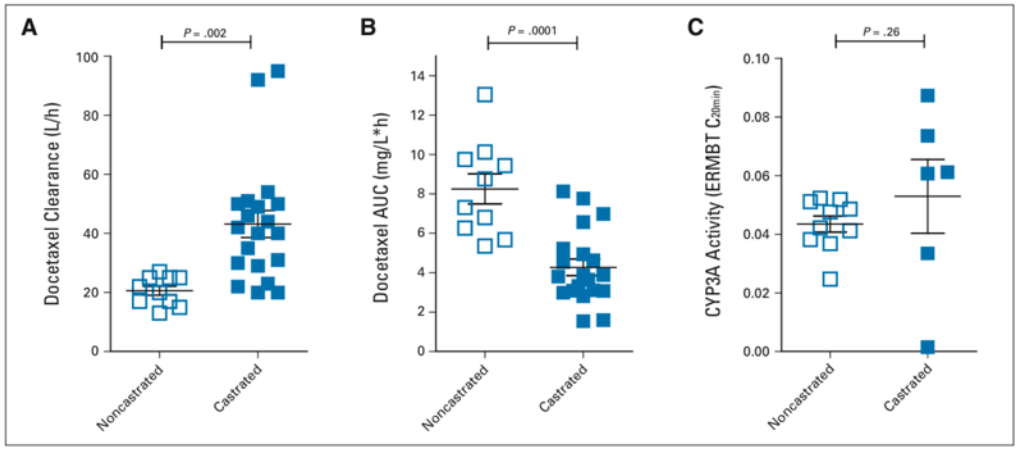


Fig 1. Effect of castration on (A) docetaxel clearance, (B) the area under the curve (AUC) of docetaxel normalized to 75 mg/m^2, and (C) hepatic CYP3A4 activity as determined by the erythromycin breath test (ERMBT) in noncastrated (open squares, n = 10) and castrated (closed squares, n = 20 for docetaxel studies and n = 6 for ERMBT) patients with prostate cancer. Each square represents an observation in a single patient, and horizontal lines and error bars represent mean and SE, respectively.

- 10 non-castrate and 20 castrate men with similar demographics
- Clearance of docetaxel in castrate men was 100% increased with 2 fold reduction in AUC
- Erythromycin breath test indicated hepatic CYP3A4 activity, for docetaxel metabolism, was not different
- Castrate rats have higher AUC of docetaxel in liver compared to intact animals

50% decrease in docetaxel clearance associated with >430% increase in odds of grade ¾ neutropenia*

Franke RM et al. J Clin Oncol 2010; 28:4562-67; *Bruno R et al. J Clin Oncol 1998; 16:187-96.

What are the Implications of these PK Differences?

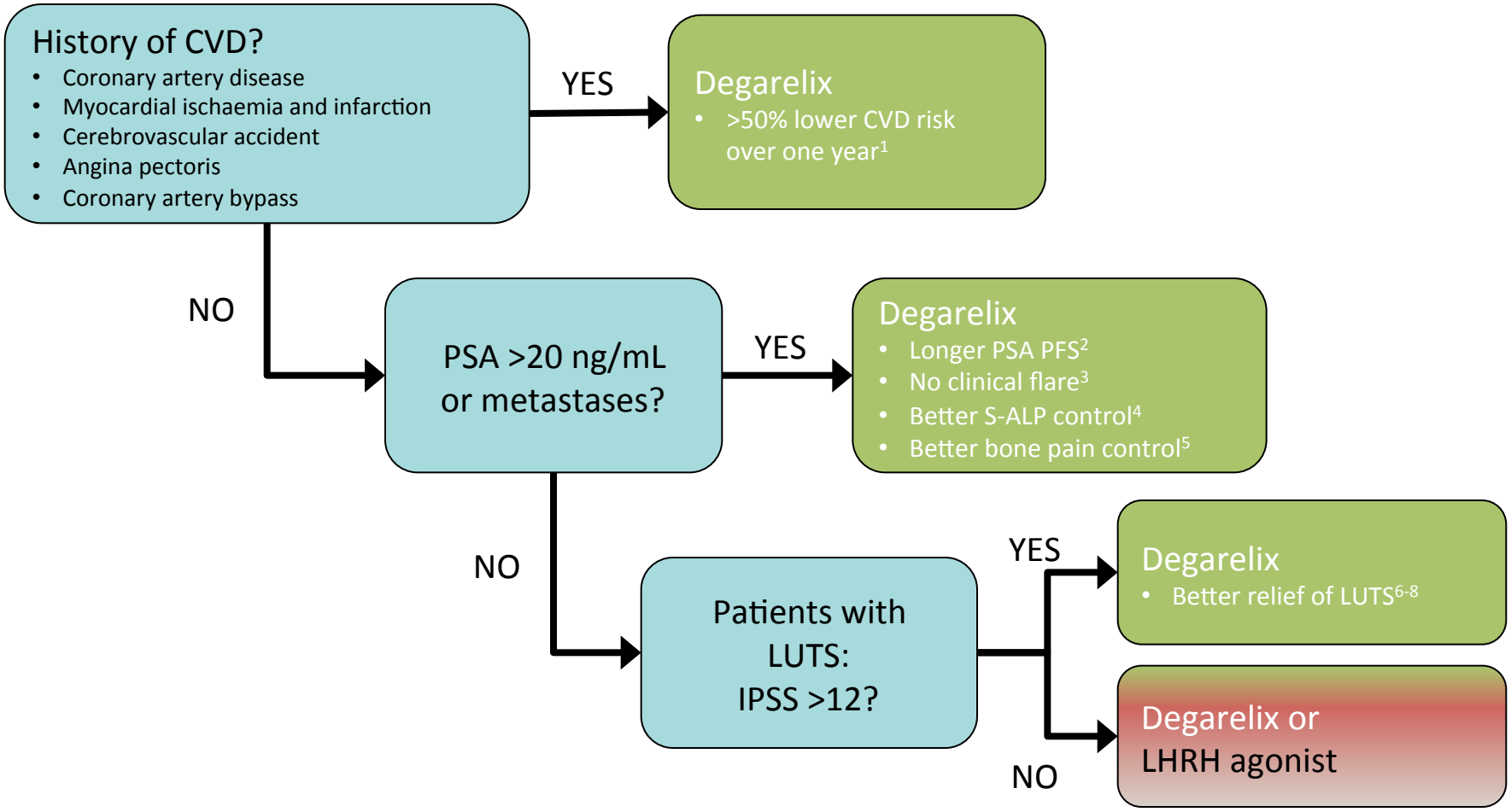
Between Different Trials

- May explain some of the greater hematologic toxicity but also survival benefit observed in castration-sensitive compared to castration-resistant trials
- Why was there greater hematologic toxicity in GETUG-AFU 15 compared to CHAARTED?
  - How many patients were non-castrate vs. castrate in each trial?
    - GETUG-AFU 15: 47% initiated ADT within 15 days of enrollment
    - CHAARTED: initiated ADT median 1.1 months to enrollment
  - How much GCSF was used in each trial?

For the Practicing Clinician

- Consider waiting until after 1-2 months of ADT or castrate testosterone levels have been reached before starting docetaxel?
- Use GCSF, at least for the first couple cycles, until castrate

Clinical considerations for the use of ADT: A hormonal therapy algorithm



1. Albertsen PC, et al. Eur Urol 2014;65:565–73; 2. Boccon-Gibod L, et al. Therap Adv Urol 2011;3:127–40; 3. Klotz L, et al. BJU Int 2008; 102:1531–8; 4. Schroder FH, et al. BJU Int 2010;106:182–7; 5. Shore N, et al. Presented at SUO 2012;Poster 84; 6. Anderson J, et al. Urol Int 2013;90:321–8; 7. Mason M, et al. Clin Oncol 2013;25:190–6; 8. Axcona K, et al. BJU Int 2012;110:1721–8