Agonists and antagonists: A Review of what is known and Recent data on disease-related outcomes from a pooled analysis

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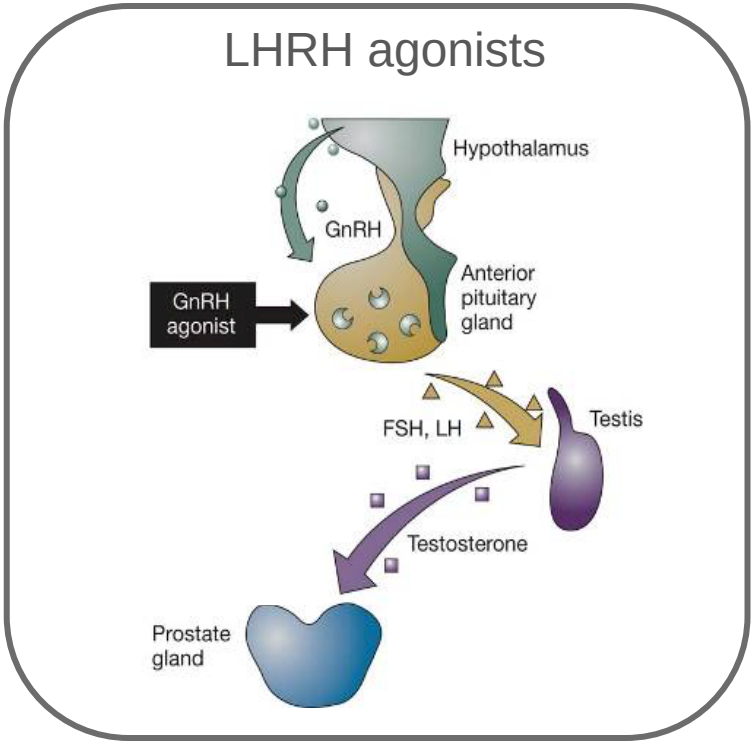
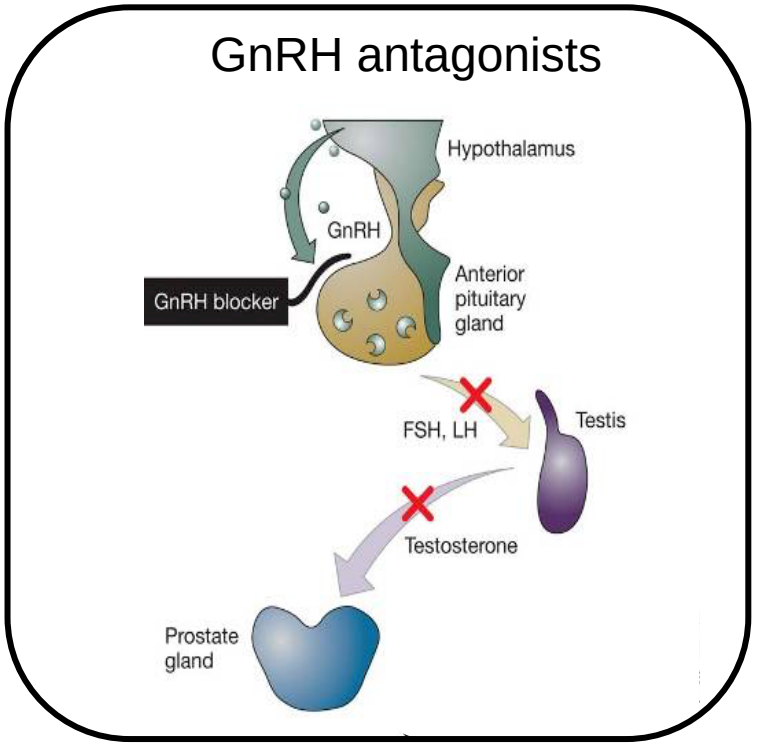
Contents

- Mechanism of action
  - How do GnRH antagonists and agonists differ?
- Pivotal phase III trial CS21 and extension CS21A
- Disease-control and cardiovascular outcomes from a pooled database of phase III clinical trials
- Conclusions

Mechanism of action of GnRH antagonists differs significantly from that of agonists





- Surge in FSH, LH and testosterone before suppression
- Microsurges in LH and testosterone on repeat injection
- FSH suppression, but not maintained long term

- Immediate suppression of FSH, LH and testosterone
- No microsurges
- Prolonged suppression of FSH, LH and testosterone

FSH, follicle-stimulating hormone; LH, luteinizing hormone

Combined Androgen Blockade

- Does not abrogate the initial testosterone surge intrinsic to LHRH agonists
- Marketed antiandrogens do not completely inhibit the cytoplasmic androgen receptor, thus allowing endogenous androgens to stimulate non-inhibited androgen receptors
- Mutations of the androgen receptor induced by antiandrogens are common and may result in the development of hormonal refractory state. Antiandrogens thus act as agonists of the androgen receptor.
- The initial standard treatment for managing CRPC in patients on CAB is to "withdraw" the antiandrogen
  - This maneuver results in a 25-30% response rate
- Antiandrogens have a spectrum of adverse events independent of testosterone suppression
- CAB does not cause complete suppression of FSH
- FSH may be involved in the development of prostate cancer and the transition to a hormonally refractory state

GNRH Antagonists

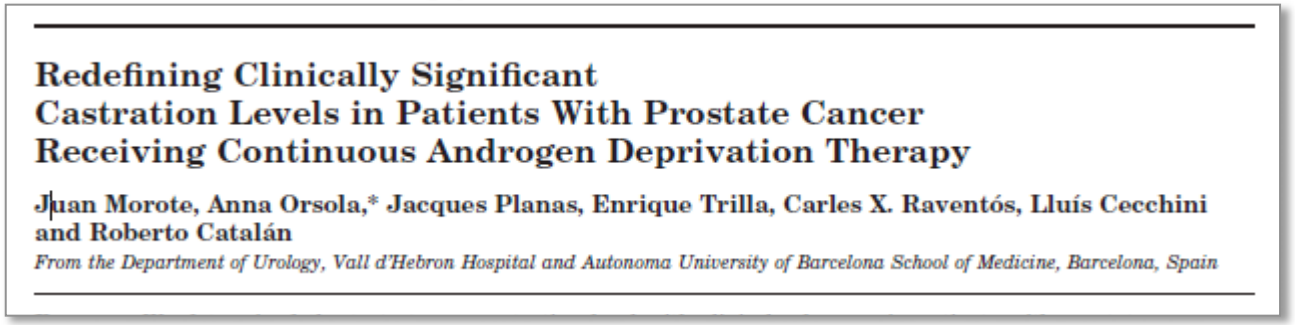
- Completely avoids the testosterone surge and causes more rapid medical castration
- Does not affect the androgen receptor
- Devoid of antiandrogen adverse events
- More profound suppression of FSH, acutely and chronically

Questions

- What is an appropriate castrate testosterone testosterone
- Do differences exist between the efficacy and benefits of GnRH agonists and antagonists
  - Time to castration onset and PSA suppression
  - PSA PFS (time to castration resistance), particularly in those at greater risk of progression
  - Overall survival
- Are there significant differences in the safety profile of GnRH agonists and antagonists
  - Control of skeletal metastases
  - Cardiovascular events

Clinical impact of low testosterone levels: two peer-reviewed articles

- Morote – Urology 2007



Redefining Clinically Significant Castration Levels in Patients With Prostate Cancer Receiving Continuous Androgen Deprivation Therapy

Juan Morote, Anna Orsola,* Jacques Planas, Enrique Trilla, Carles X. Raventós, Lluís Cecchini and Roberto Catalán

From the Department of Urology, Vall d'Hebron Hospital and Autonoma University of Barcelona School of Medicine, Barcelona, Spain

- Perachino – BJUI 2009

BJUI

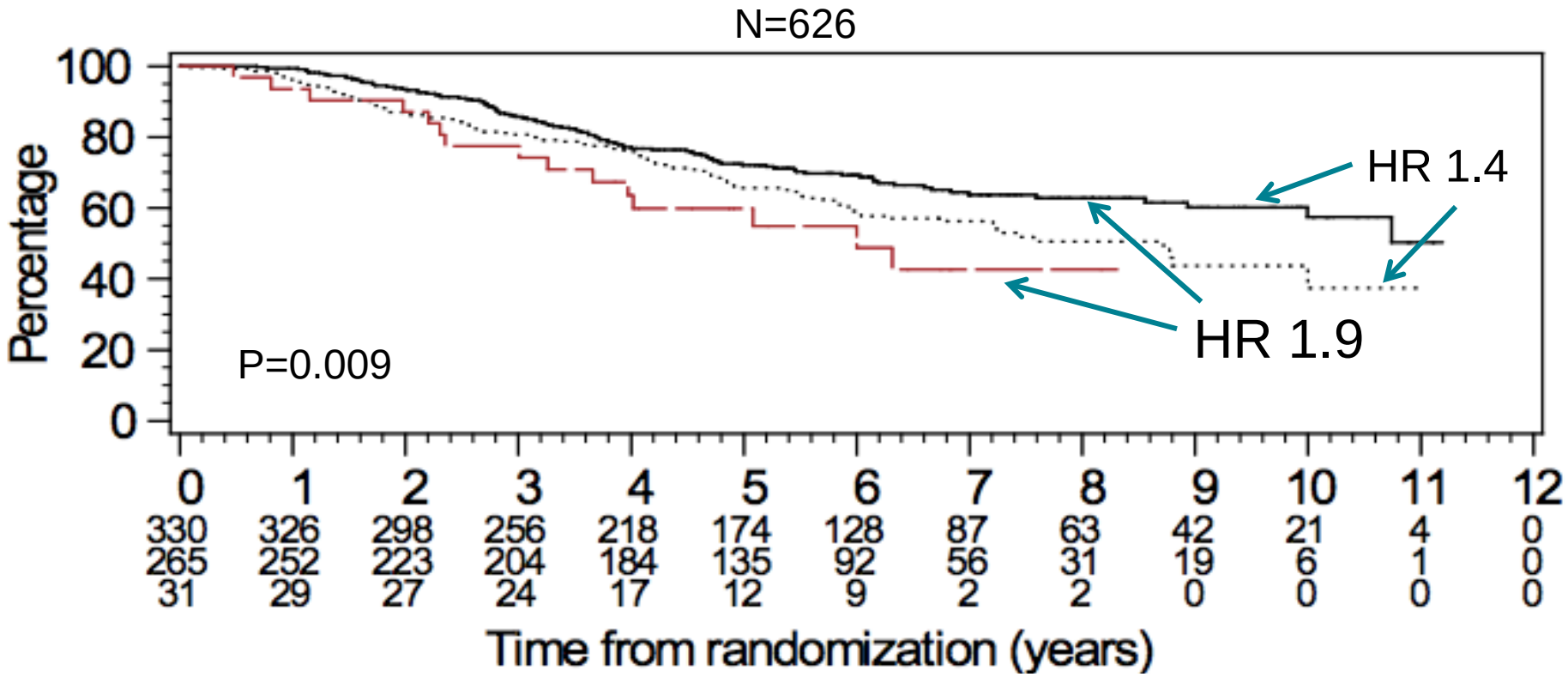
Testosterone levels in patients with metastatic prostate cancer treated with luteinizing hormone–releasing hormone therapy: prognostic significance?

Massimo Perachino, Valerio Cavalli and Fabio Bravi*

*Department of Urology, Santo Spirito Hospital, Casale Monferrato, Alessandria, and *Department of Biometry, Ibis Informatica s.r.l., Milan, Italy*

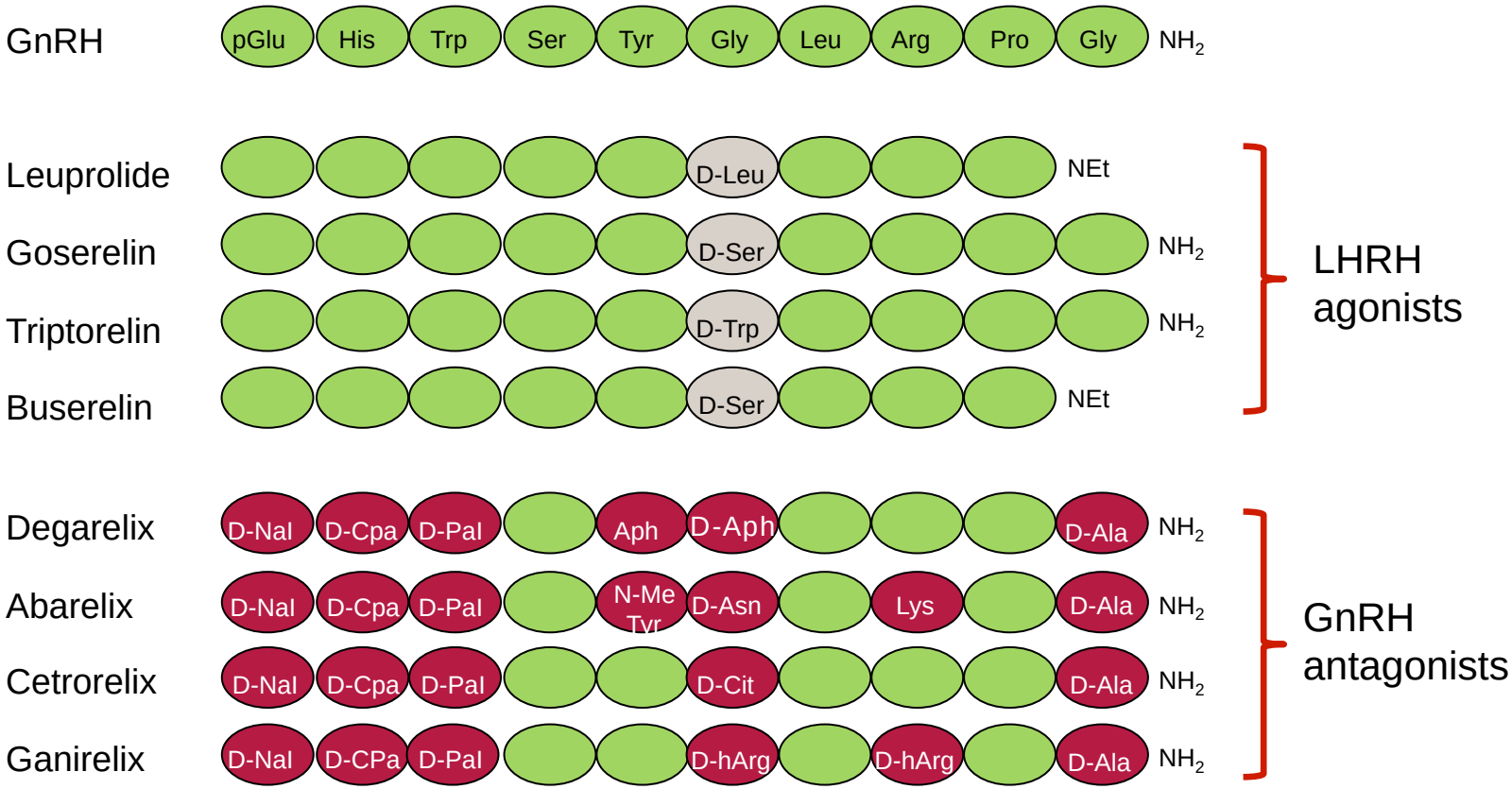
Accepted for publication 5 June 2009

Time to hormonal resistance by median T in year 1 in continuous arm: Secondary analysis of NCIC CTG PR7



Median T based on ≥3 Ts in the first year, for each patient, segregated as to <20 (0.7), 20-50 (0.7-1.7), and >50 ng/mL (>1.7 nM)

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



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

Prostate Cancer Patient Populations Studied with ADT.

- Stage D1/D2 (asymptomatic)
- Rising PSA
- Neoadjuvant/adjuvant/salvage Hormonal Therapy,
- Intermittent Hormonal Therapy
  - Randomized, controlled (vs L, L+C, Z+C) Pivotal Studies
- Symptomatic, advanced patients
  - Spinal Cord Compression, Urinary Tract Obstruction, Hydronephrosis, Skeletal Pain requiring Narcotic Analgesics
- Others
  - Prostate Gland Volume Reduction, Androgen Independent Disease

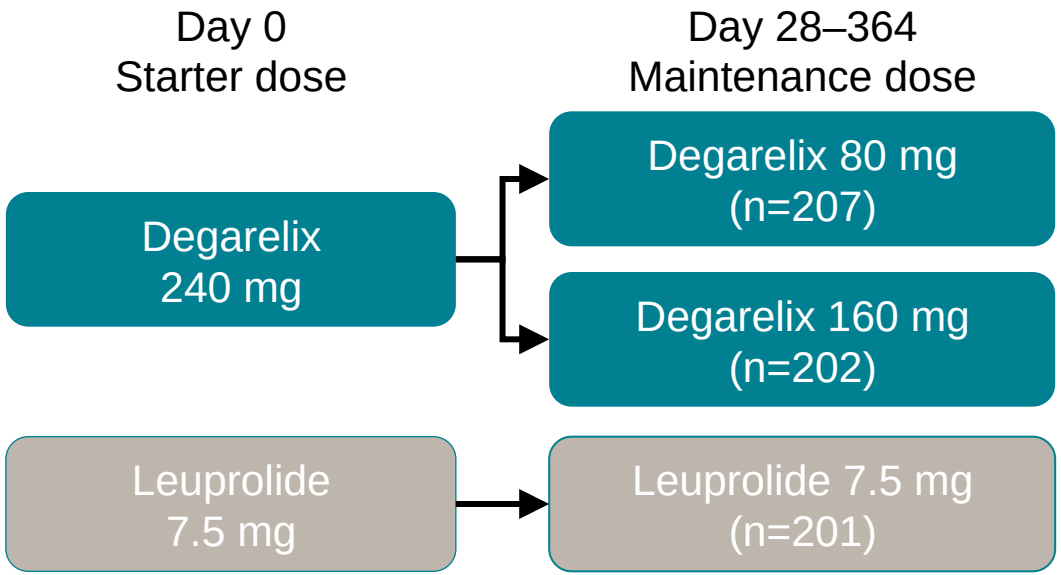
Why GNRH antagonists for Hormonally Responsive Prostate Ca?

- Developed to avoid known complications of LHRH agonist induced testosterone surge and disease worsening
- Provide a superior therapy to Maximum Androgen Blockade (CAB, TAB, MAB) with one drug and avoid AE's of antiandrogens -
- Avoid necessity for surgical castration

Why GNRH antagonists for Androgen Independent Prostate Ca?

- Assess the potential importance of FSH differential effects compared to LHRH agonists

CS21: A randomised phase III trial comparing degarelix with leuprolide



- Previous or current hormonal treatment not allowed, except as neoadjuvant or adjuvant to curative intent (≤6 months treatment, discontinued for >6 months)
- Antiandrogen flare protection in agonist arm at investigator discretion
- Primary endpoint: Testosterone ≤50 ng/dL at any monthly measurement

Klotz L, et al. BJU Int 2008;102:1531–8

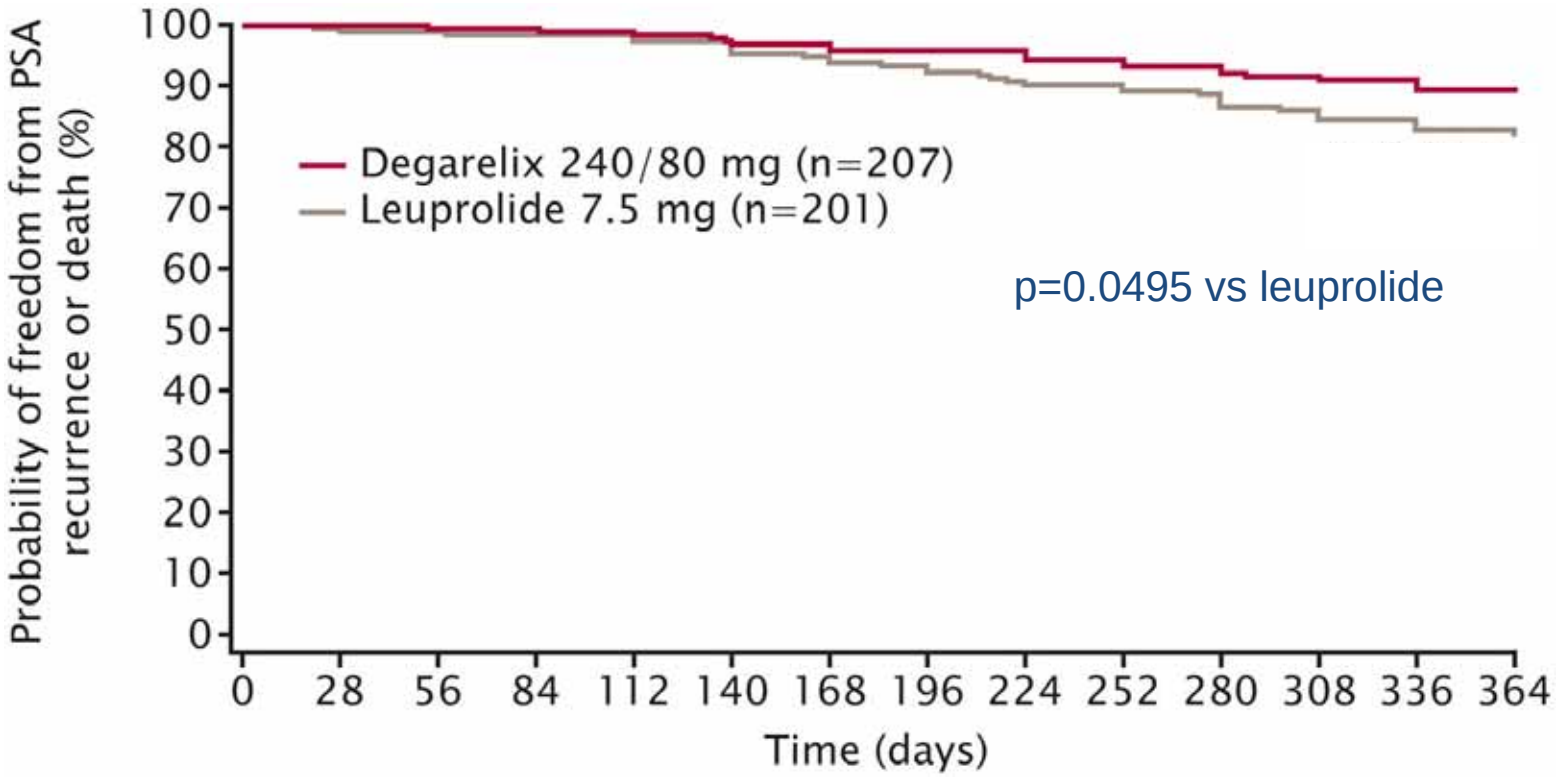
Study endpoints

- Primary endpoint
  - Cumulative probability of testosterone ≤50 ng/dL at all monthly measurements from day 28 through day 364 – Non inferior
- Secondary endpoints
  - Proportion of patients with testosterone surge -Significantly different
  - Proportion of patients with testosterone ≤50 ng/dL at day 3 (testosterone microsurges) - Significantly different
  - Percentage change in PSA from baseline to day 28 and time to PSA failure – Significantly different
  - Frequency and severity of adverse events – no difference except ISR
  - Frequency of PSA progression – Significantly different

PSA, prostate-specific antigen

Klotz L, et al. BJU Int 2008;102:1531–8

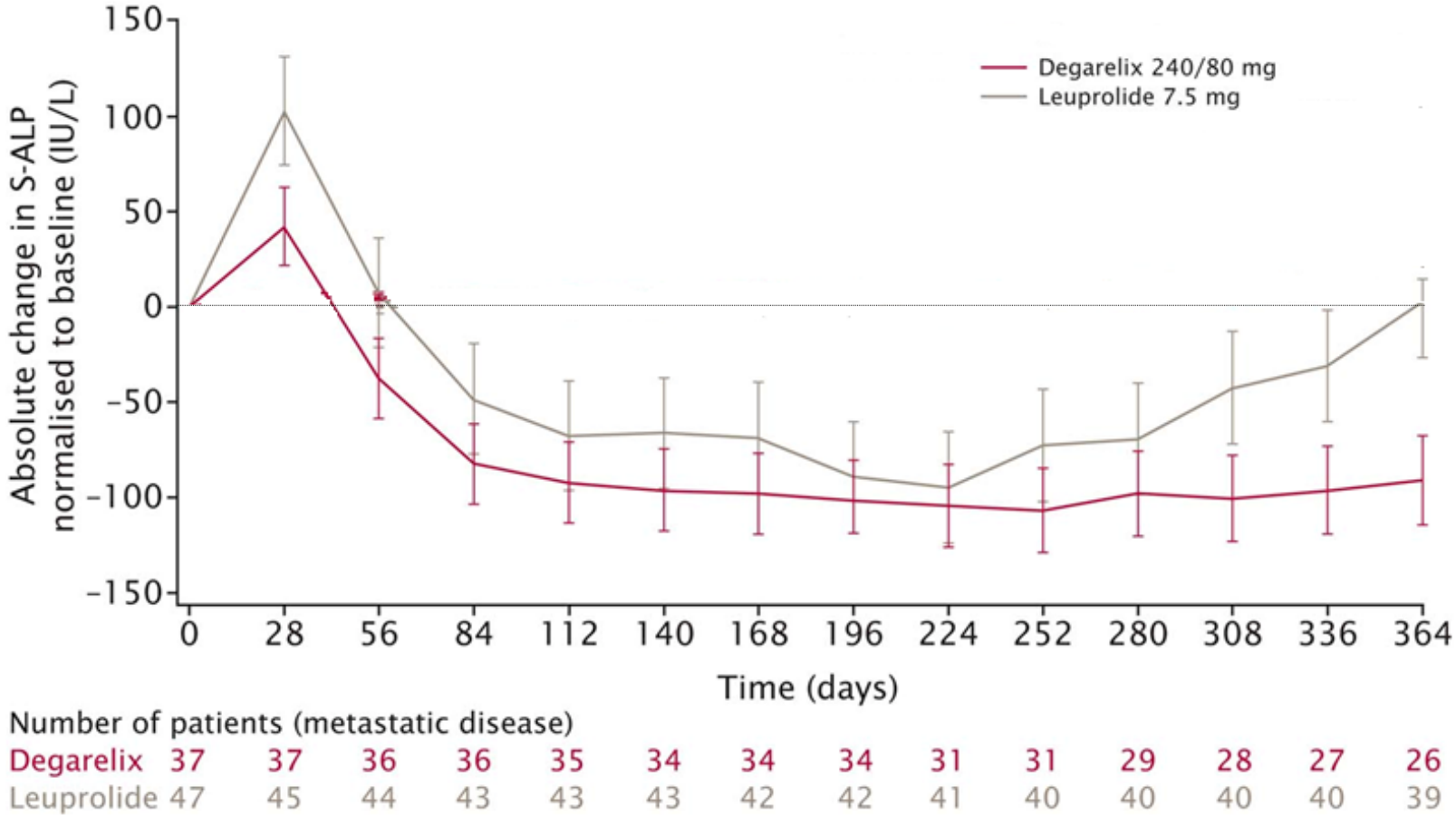
Degarelix significantly reduces the risk of PSA progression (castration resistance) or death



- Also, significantly more men with baseline PSA >20 ng/mL have PSA progression when treated with leuprolide vs degarelix (p=0.0436)

Tombal B, et al. Eur Urol 2010;57:836–42

S-ALP: Metastatic disease*



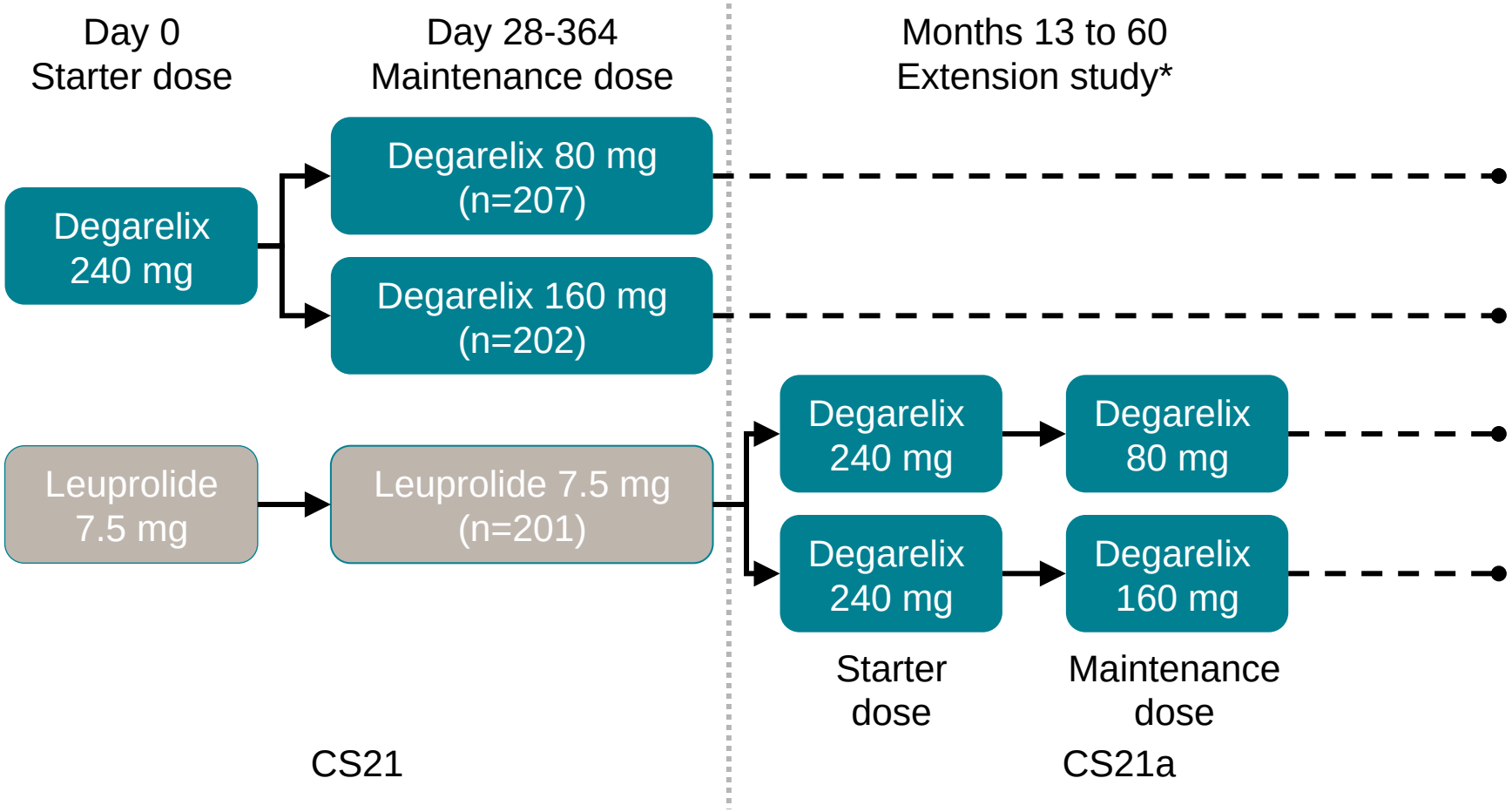
Number of patients (metastatic disease)

Degarelix	37	37	36	36	35	34	34	34	31	31	29	28	27	26
Leuprolide	47	45	44	43	43	43	42	42	41	40	40	40	40	39

* Retrospective analysis from non-inferiority design pivotal trial

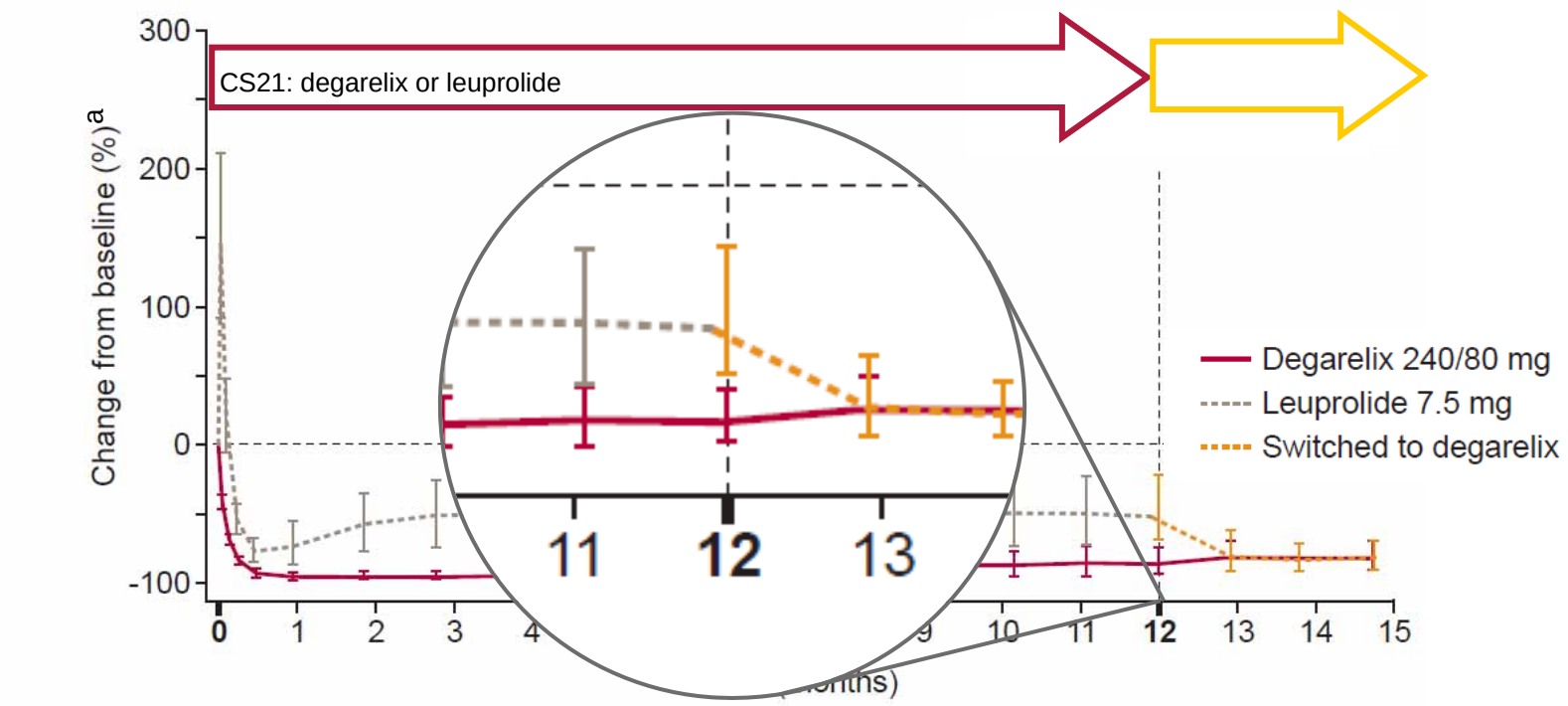
Schröder FH, et al. Eur Urol Suppl. 2009;8:130 [abstract].

CS21A extension study: Up to 5 years of degarelix treatment



*Cross-over at 12 months was preplanned and not due to failure of leuprolide treatment

Further FSH suppression after crossover from leuprolide to degarelix

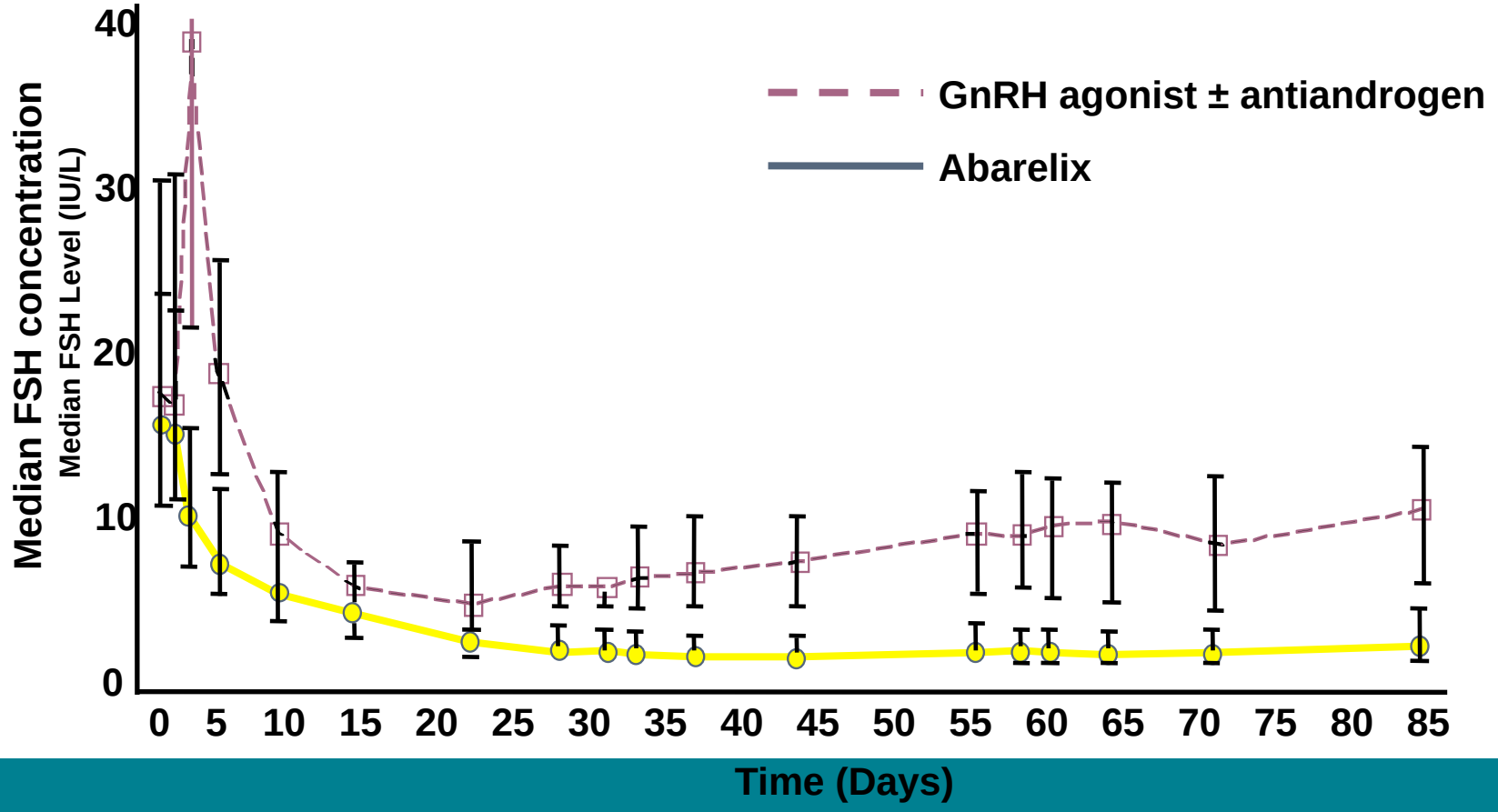


Time (days)	*0*	*28*	*56*	*84*	*112*	*140*	*168*	*196*	*224*	*252*	*280*	*308*	*336*	*364*	*392*	*420*	*448*
Number of patients																	
Degarelix	206	206	201	195	193	186	187	188	183	179	173	172	166	167	40	13	112
Leuprolide	199	196	195	191	190	190	185	188	183	181	178	179	172	171	124	120	113

[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

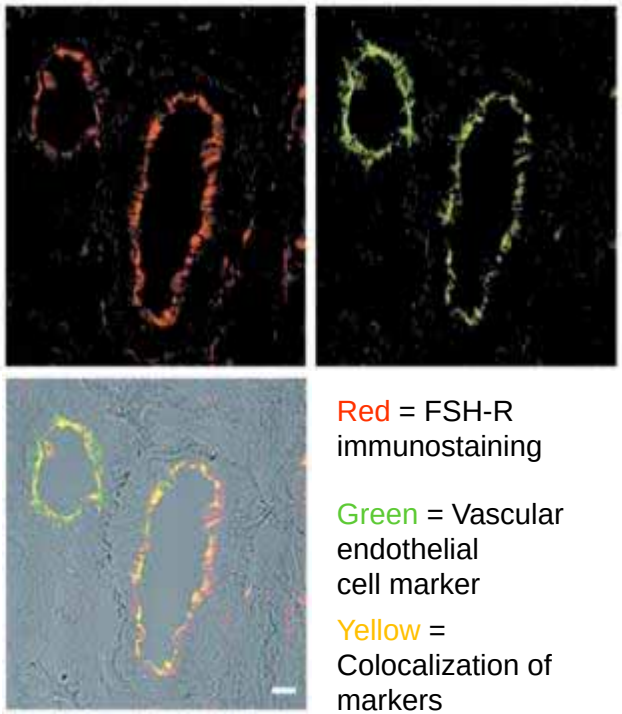


Garnick MB et al. *Mol Urol*. 2000;4:275-277.

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

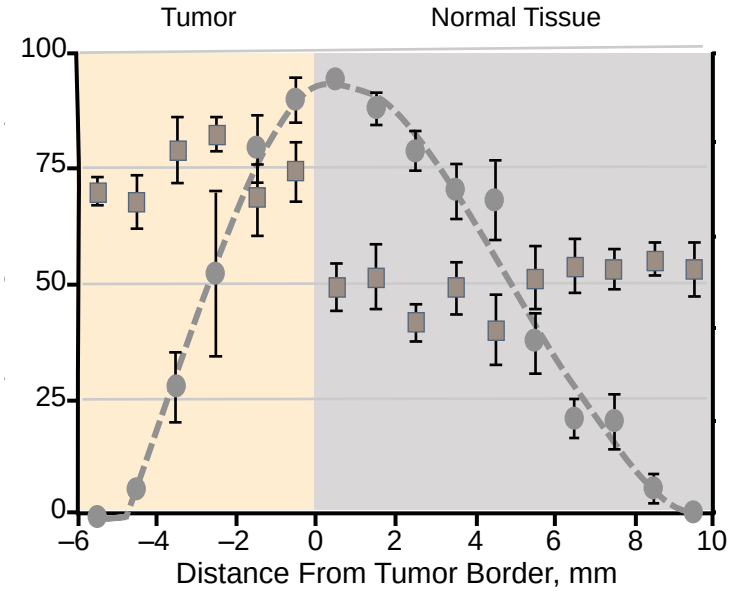
Human prostate tumor section labeled for FSH receptor and vascular endothelial cell marker



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

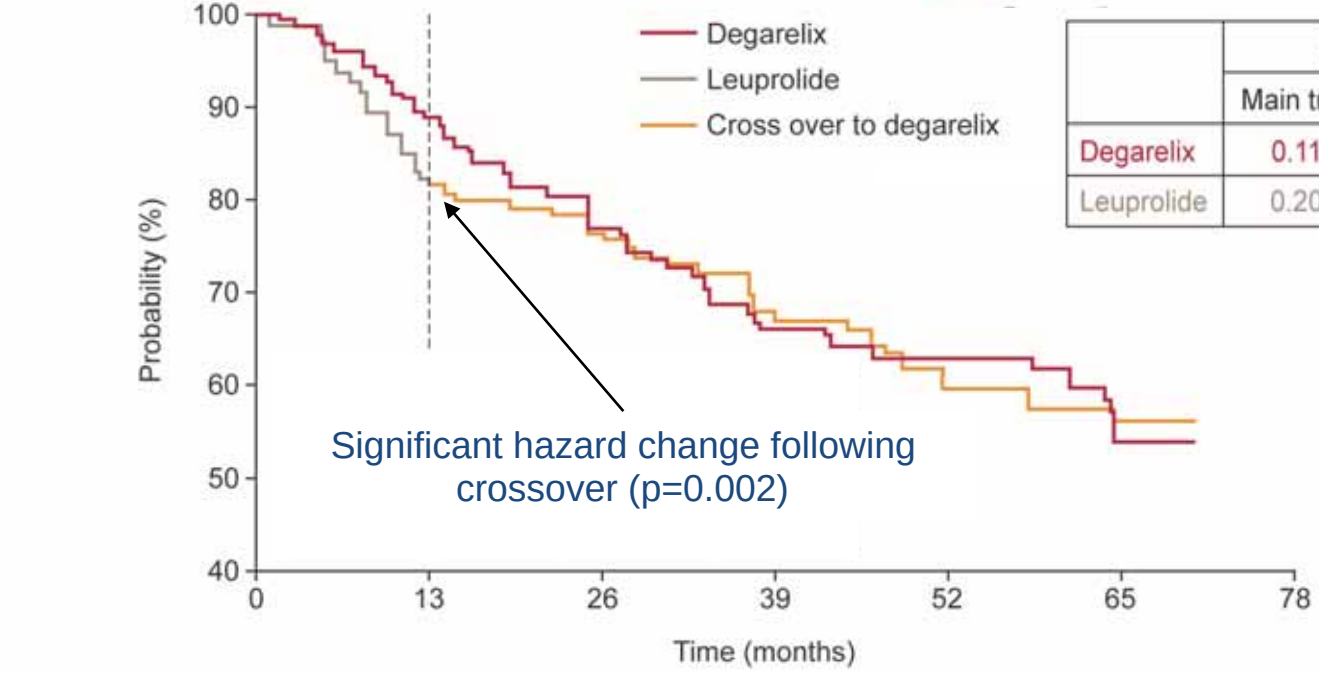
FSH, follicle-stimulating hormone; PCa, prostate cancer

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

PSA PFS is improved after crossover from leuprolide to degarelix

CS21: degarelix or leuprolide

CS21A: all patients received degarelix



	PSA PFS hazard rate		
	Main trial	Extension	p-value
Degarelix	0.11	0.12	p=0.863
Leuprolide	0.20	0.09	p=0.002

Number of patients at risk							
Degarelix	207	152	89	70	60	35	1
Leuprolide	201	144	85	69	55	29	1

Crossover was preplanned; patients were not switched to degarelix because of agonist failure
PFS, progression-free survival

Crawford ED, et al. J Urol 2011;186:889–97
Crawford ED, et al. Urology 2014;83:1122–8

CS21/21A: Overall summary

- Compared with LHRH agonist therapy, degarelix offers:
  - Faster castration onset and PSA suppression, with no risk of clinical flare[1]
  - Longer PSA PFS, especially in those at greatest risk of progression (PSA>20 ng/mL)[2]
- For up to 5 years of degarelix treatment:
  - PSA PFS is improved after crossover from leuprolide to degarelix[3,4]
  - Therapy was well tolerated[3,4]

1. Klotz L, et al. BJU Int 2008;102:1531–8; 2. Tombal B, et al. Eur Urol 2010;57:836–42
3. Crawford D, et al. J Urol 2011;186:889–97; 4. Crawford ED, et al. Urology 2014;83:1122–8

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- Disease-control and cardiovascular outcomes from a pooled database of phase III clinical trials
  - How does the control of disease outcomes with degarelix and LHRH agonists compare?
- Conclusions

Data from six randomized phase III/IIIb trials of degarelix vs LHRH agonists were pooled

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. SUO 2012
CS37[a] Intermittent dosing	7-12	Leuprolide	Crawford et al. SUO 2013
CS28 LUTS relief	3	Goserelin[b]	Anderson et al. Urol Int 2012
CS30 Neoadjuvant to radical RT	3	Goserelin[b]	Mason et al. Clin Oncol 2013
CS31 TPV reduction	3	Goserelin[b]	Axcona et al. BJU Int 2012

- Efficacy data was collected from the degarelix clinical trials database
- Safety data was patient reported and categorised by MedDRA criteria

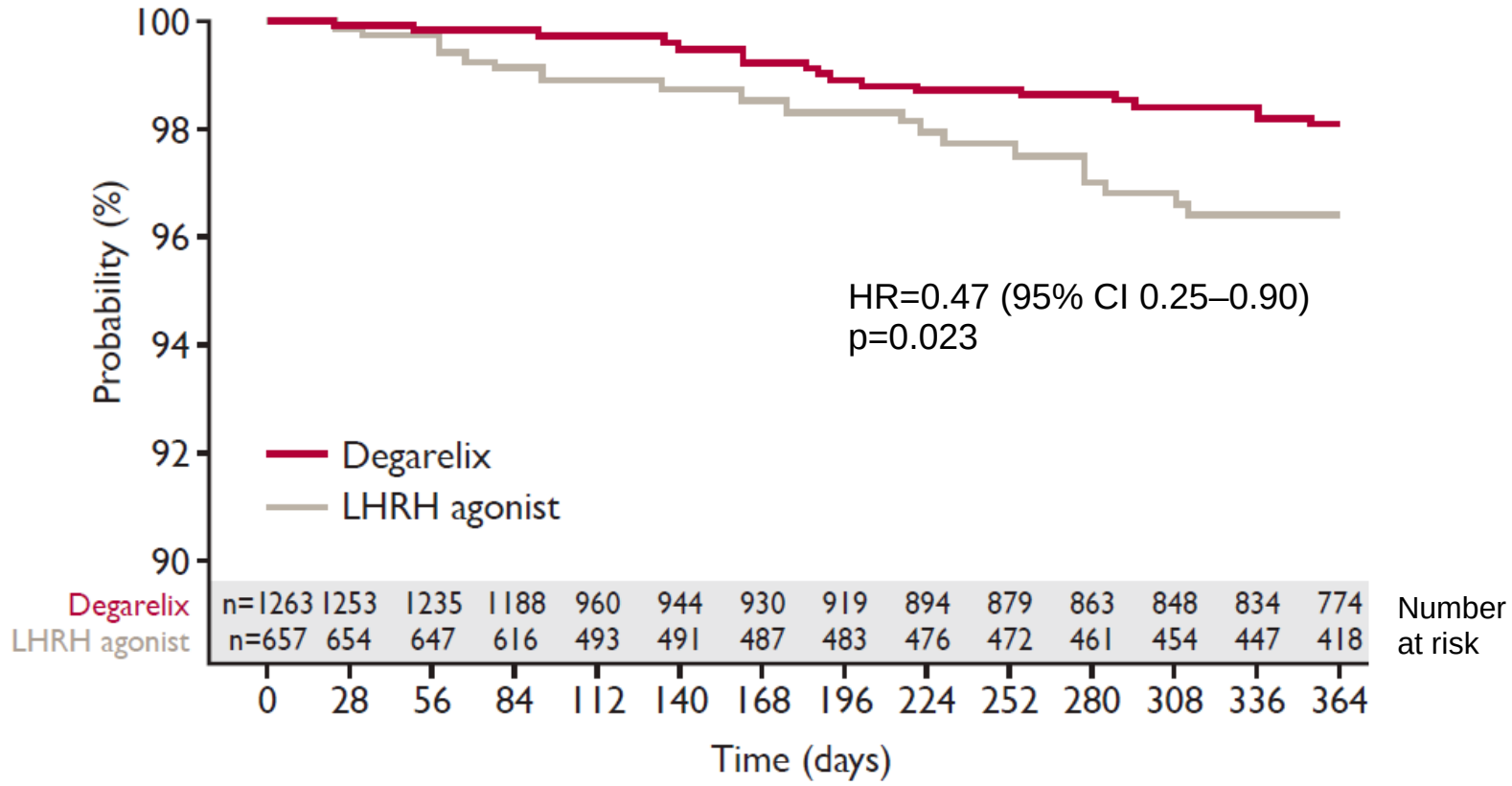
[a]Excluded from efficacy-related outcomes analysis as recruited population comprised patients with early disease with biochemical failure after primary definitive therapy; [b]All patients on goserelin also received antiandrogen flare protection.
LUTS, lower urinary tract symptoms; TPV, total prostate volume; RT, radiotherapy

Baseline patient characteristics were comparable across treatment groups

Variable	Degarelix n=1263	LHRH agonist n=657
Age, years (SD)	71.7 (8.0)	71.8 (7.9)
Median testosterone, ng/mL (25-75 percentile)	4.2 (3.1–5.4)	4.3 (3.3–5.4)
Median PSA, ng/mL (25-75 percentile)	17.3 (8.6–53.7)	16.7 (7.7–51.1)
Disease stage, n (%)		
Localized	432 (34)	226 (34)
Locally advanced	375 (30)	170 (26)
Metastatic	282 (22)	153 (23)
Not classifiable	174 (14)	108 (16)
Gleason score, n (%)		
2-4	91 (7)	41 (6)
5-6	381 (30)	179 (27)
7-10	784 (62)	436 (66)
PSA category, n (%)		
0 – 10	391 (31)	224 (34)
10 – 20	283 (23)	140 (21)
20 – 50	250 (20)	124 (19)
50+	328 (26)	165 (25)

Data on file

Superior overall survival with degarelix vs LHRH agonists (all patients)[1]

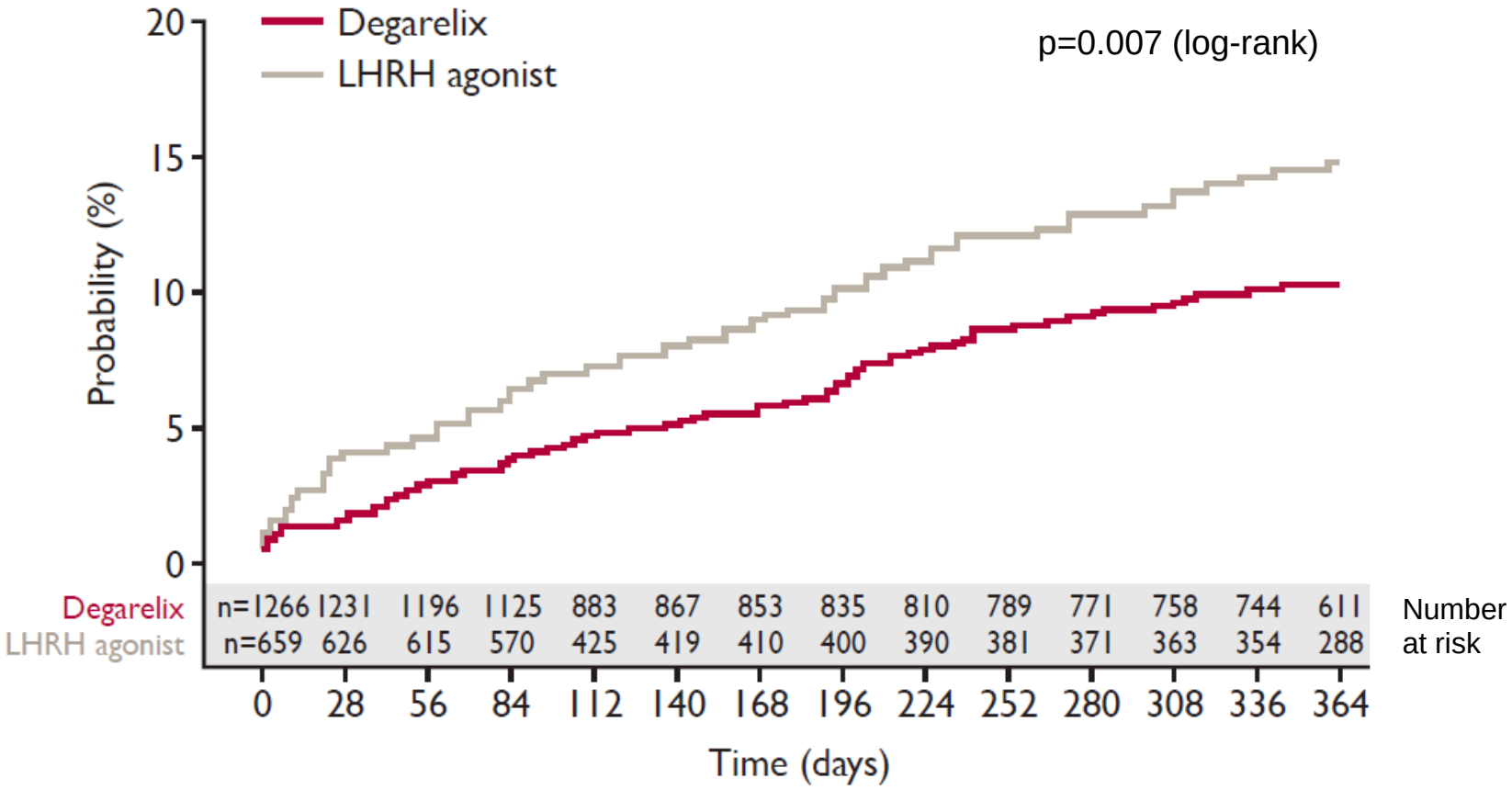


- Very few patients died of prostate cancer over the year of the study
- Most men with prostate cancer die of other causes such as CVD[2,3]

CVD, cardiovascular disease

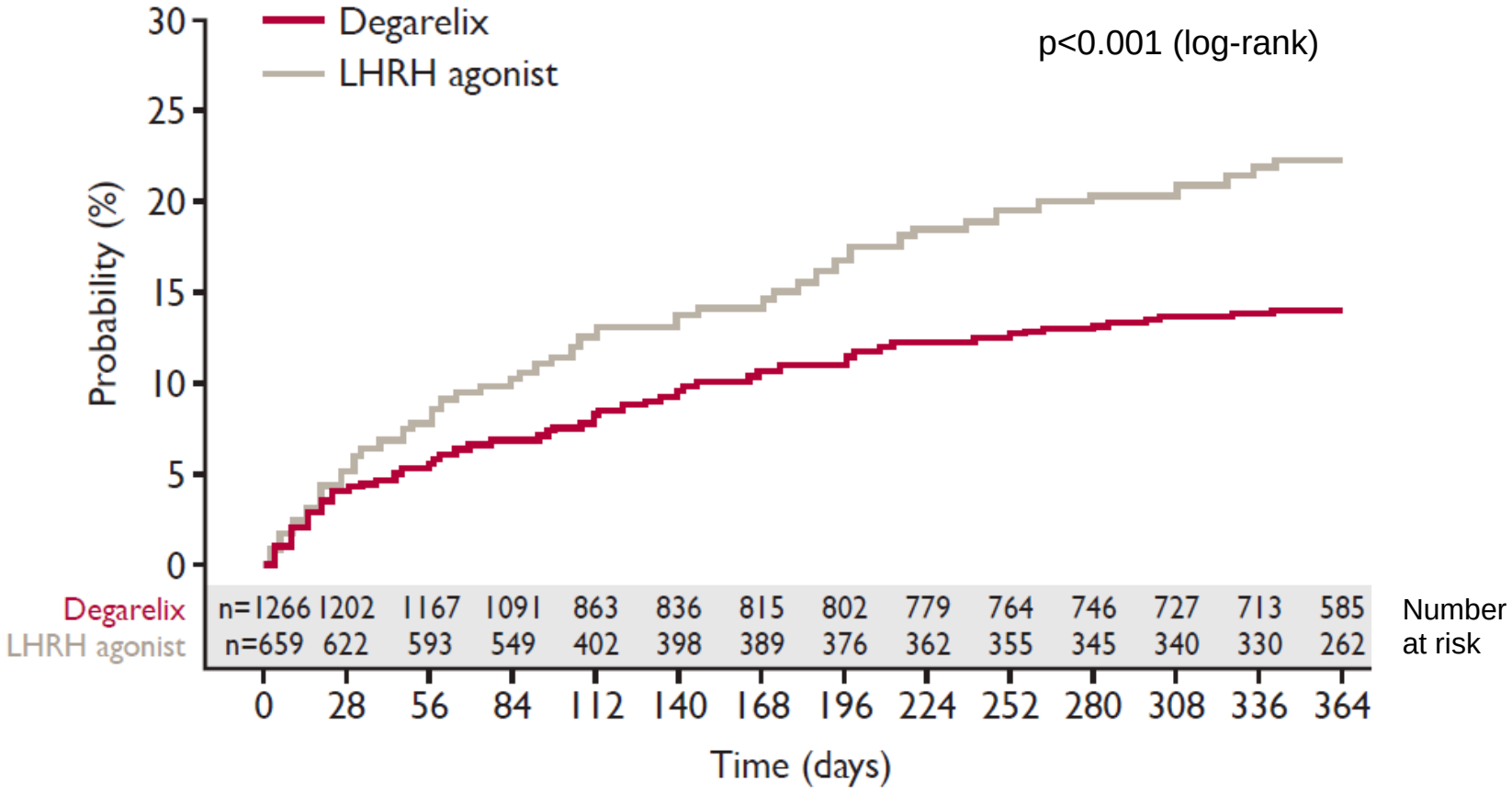
1. Klotz L, et al. Eur Urol 66 (2014) 1101-1108.
2. Epstein MM, et al. J Natl Cancer Inst 2012;104:1335–42
3. Ketchandji M, et al. J Am Geriatr Soc 2009;57:24–30

Lower probability of musculoskeletal events with degarelix vs LHRH agonists (all patients)



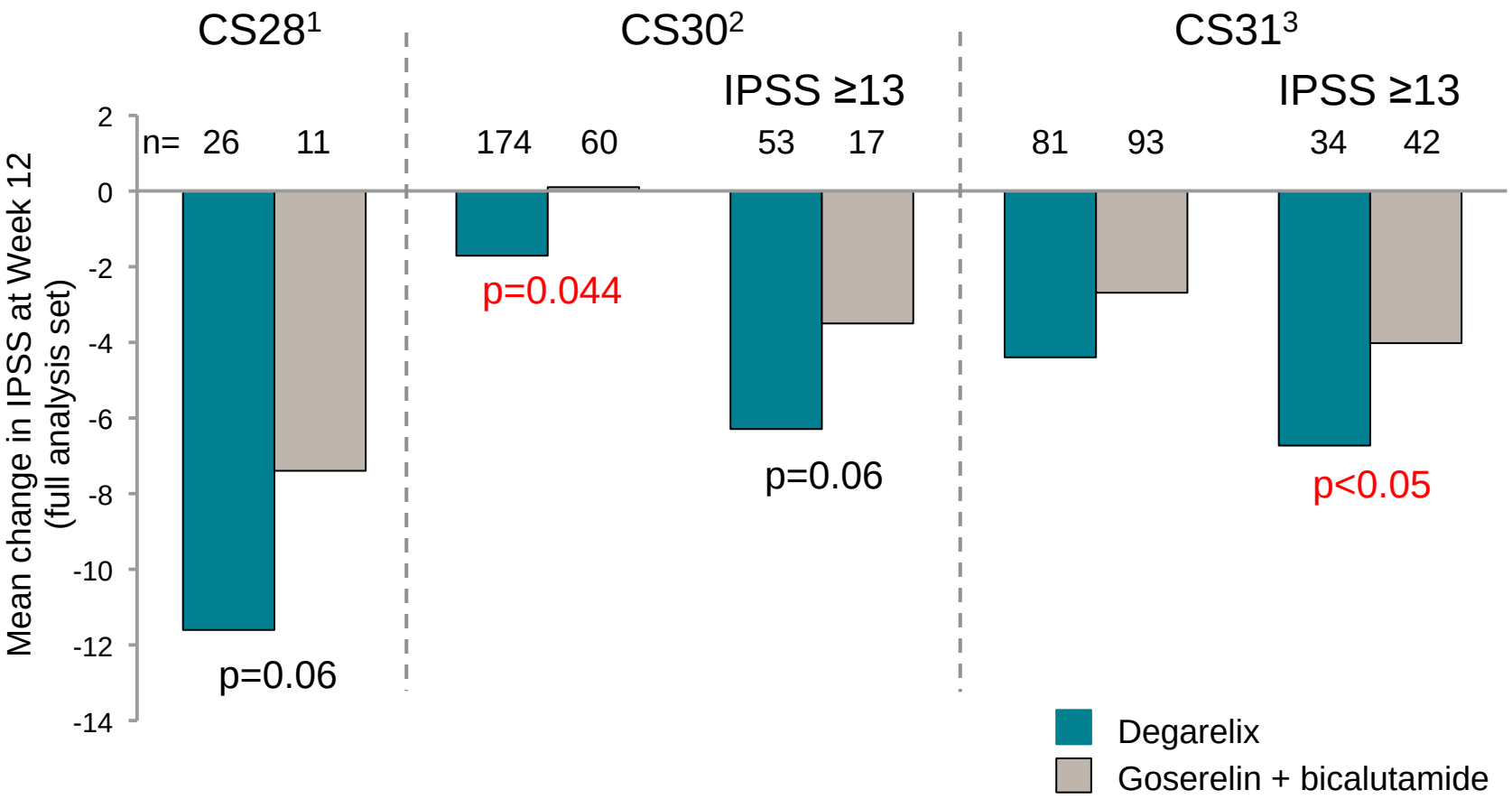
Klotz L, et al. Eur Urol (66) 2014 1101-1108;

Lower probability of a urinary tract event with degarelix vs LHRH agonists (all patients)



Klotz L, et al. Eur Urol (66) 2014 1101-1108

LUTS control:
Degarelix vs. goserelin + bicalutamide



Data are not directly comparable between studies

1. Anderson et al. Urol Int 2013;90:321–8
2. Mason M, et al. Clin Oncol 2013;25:190–6
3. Axcrona K, et al. BJU Int 2012;110:1721–8

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ADT and risk of CVD

- ADT is associated with an increased risk of CV events
  - LHRH agonists linked to increased CV morbidity compared to orchiectomy[1]
  - Men with history of CVD most at risk[2,3]
- Degarelix has a distinct mechanism of action to LHRH agonists
  - Risk of CV events may also be different
- The risk of CV events in men receiving LHRH agonists or degarelix was assessed in a pooled analysis of 6 randomized phase III trials

ADT, androgen deprivation therapy
CVD, cardiovascular disease

1. Taylor LG, et al. Cancer 2009;115:2388–99
2. Nanda AN, et al. JAMA 2009;302:866–73
3. Hedlund PO, et al. Scand J Urol Nephrol 2011;45:346–53

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

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
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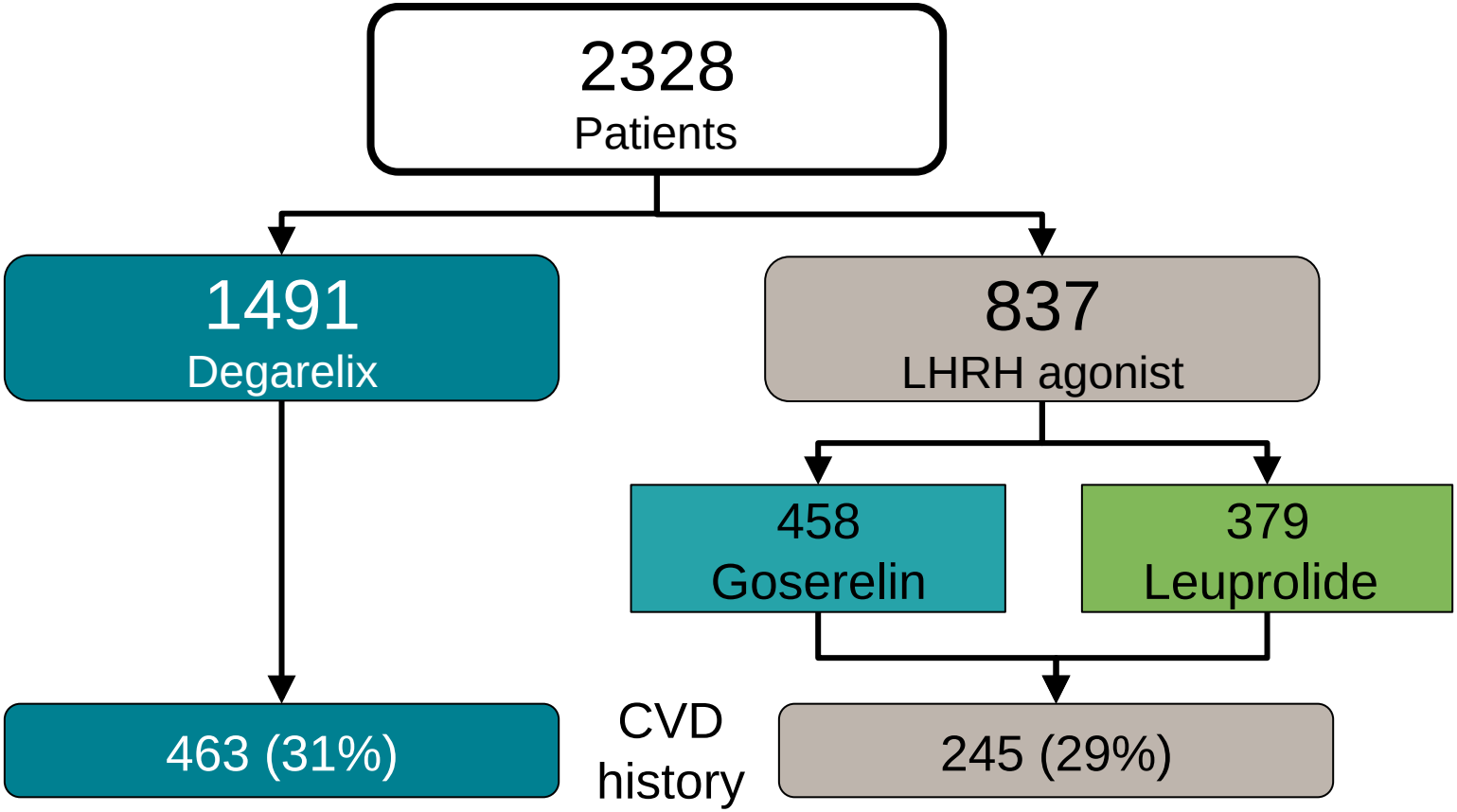
*All patients on goserelin also received antiandrogen flare protection

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

Pooled database: Treatment groups and CVD history



CVD history was defined as an event of myocardial ischaemia, coronary artery disease, myocardial infarction, cerebrovascular accident, angina pectoris or coronary artery bypass at baseline

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

Baseline demographics relating to CV risk were balanced

Variable	Degarelix n=1491	LHRH agonist n=837
Age, years (range)	71.7 (46–94)	71.6 (51–98)
Body mass index >30, n (%)	27.2 334 (22.4)	27.5 200 (23.9)
History of CVD, n (%)	463 (31.1)	245 (29.3)
History of smoking, n (%)	707 (47.4)	432 (51.6)
History of alcohol use, n (%)	889 (59.6)	475 (56.8)
History of hypertension, n (%)	1117 (74.9)	615 (73.5)
Serum cholesterol >6.2 mmol/L, n (%)	399 (26.8)	247 (29.5)
Statin medication use, n (%)	400 (26.8)	234 (28.0)
History of diabetes, n (%)	221 (14.8)	128 (15.3)

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

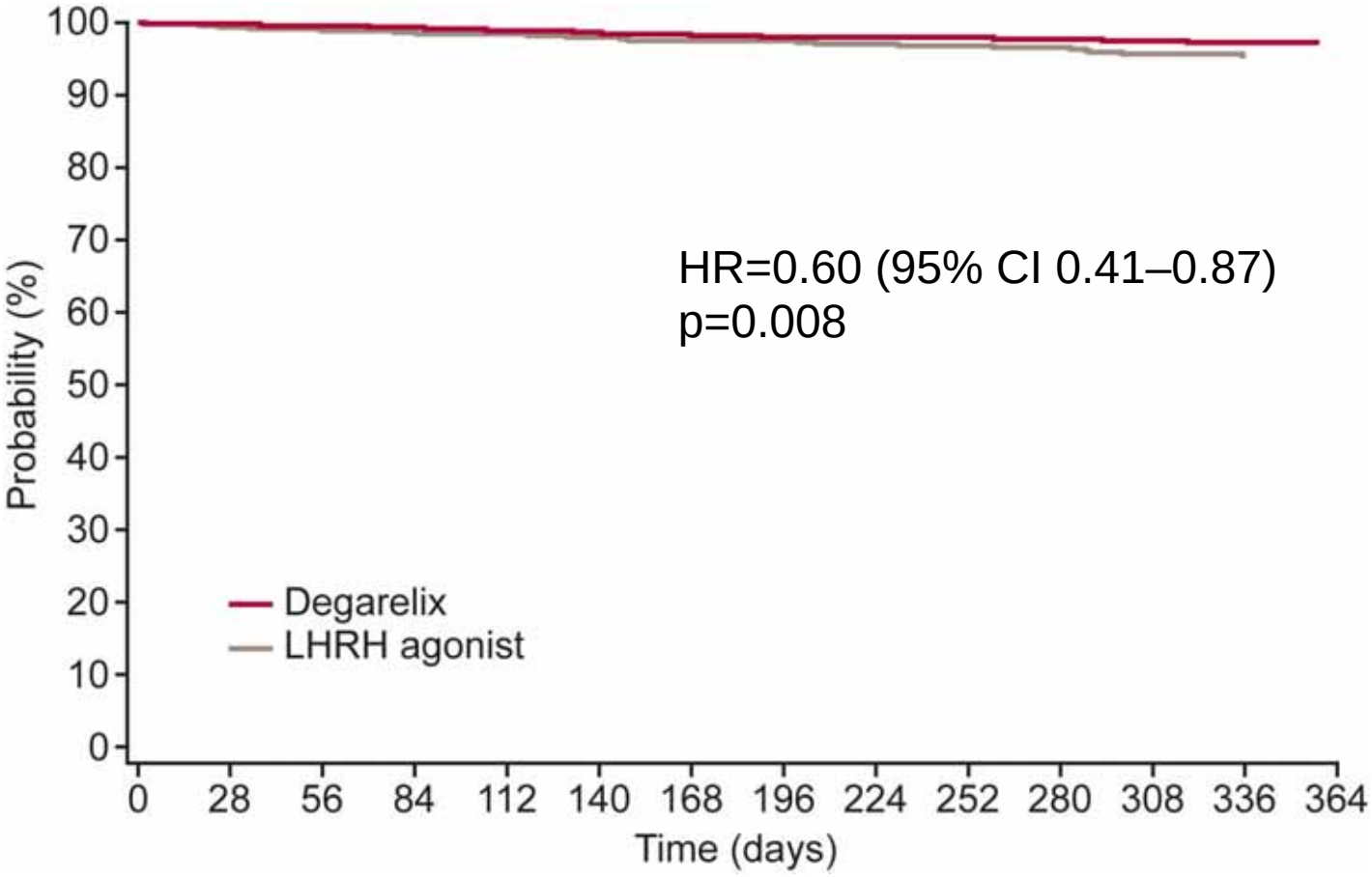
Higher incidence of CV events with LHRH agonists than degarelix (all patients)*

	Degarelix, n (%) n=1491	LHRH agonist, n (%) n=837
Any CV event	42 (2.8)	37 (4.4)
Death	20 (1.3)	22 (2.6)

*Data classified according to the MedDRA system

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

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



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

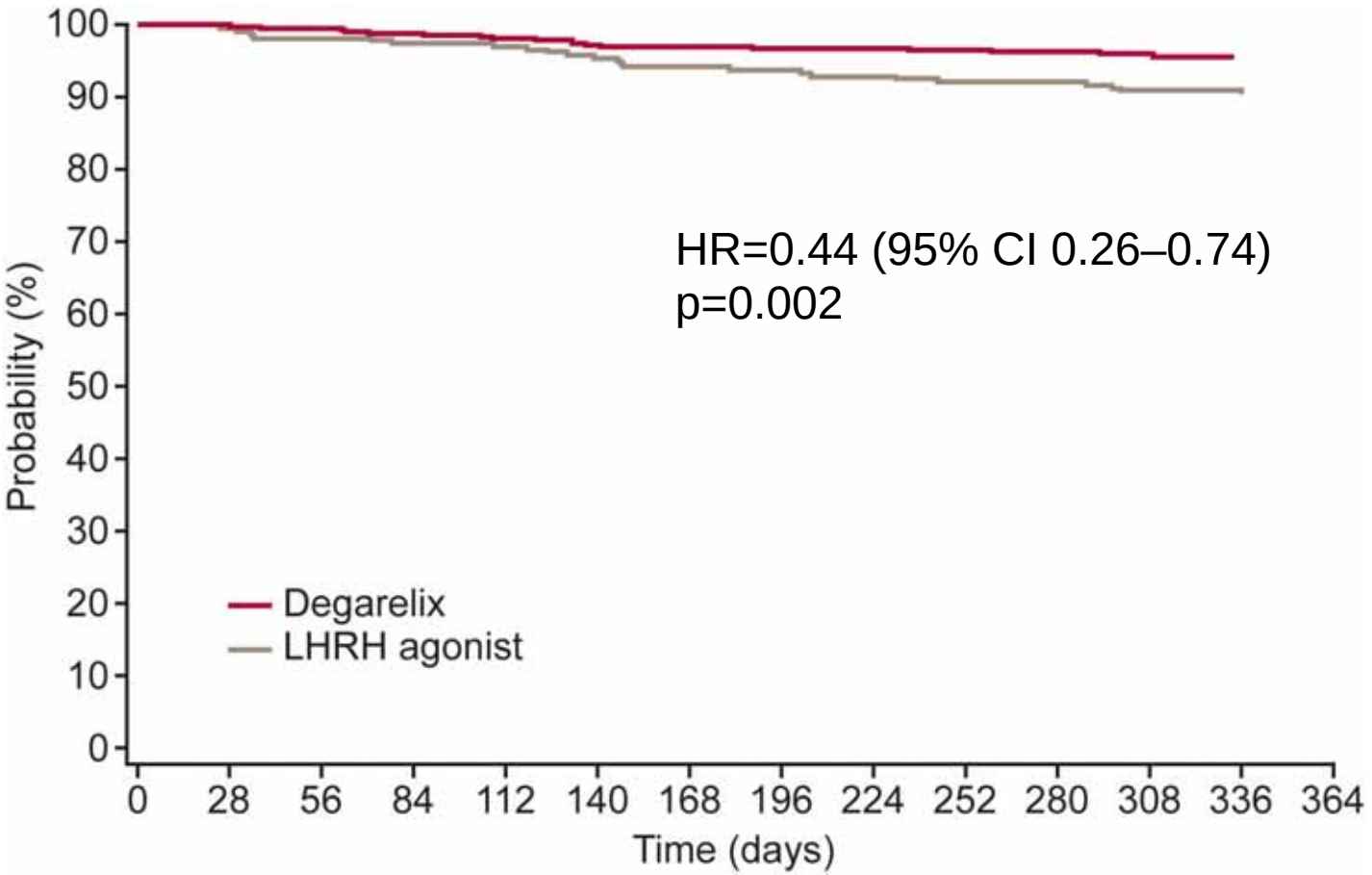
Higher incidence of CV events with LHRH agonists than degarelix (patients with CV history)*

	Degarelix, n (%) n=463	LHRH agonist, n (%) n=245
Any CV event	21 (4.5)	23 (9.4)
Death	9 (1.9)	13 (5.3)

*Data classified according to the MedDRA system

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

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



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

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

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

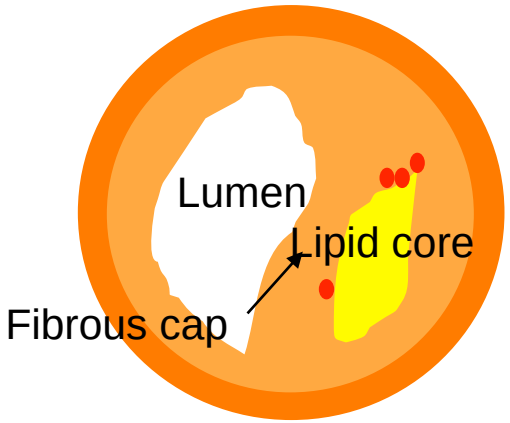
Metabolic syndrome and metabolic changes induced by ADT are different

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

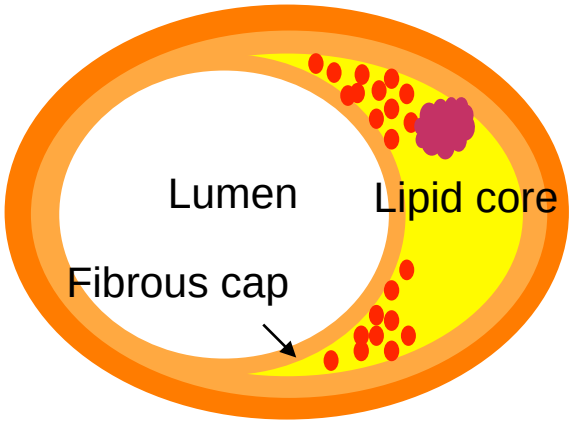
Saylor PJ, Smith MR. J Urol 2009;181:1998–2008

Plaque instability is at the heart of cardiovascular disease

Stable plaque



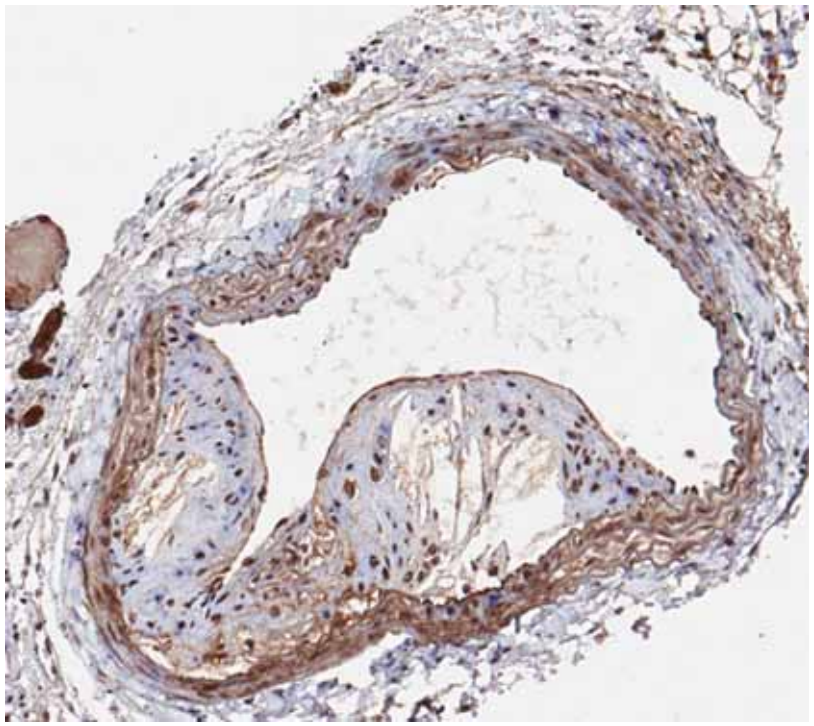
Vulnerable plaque

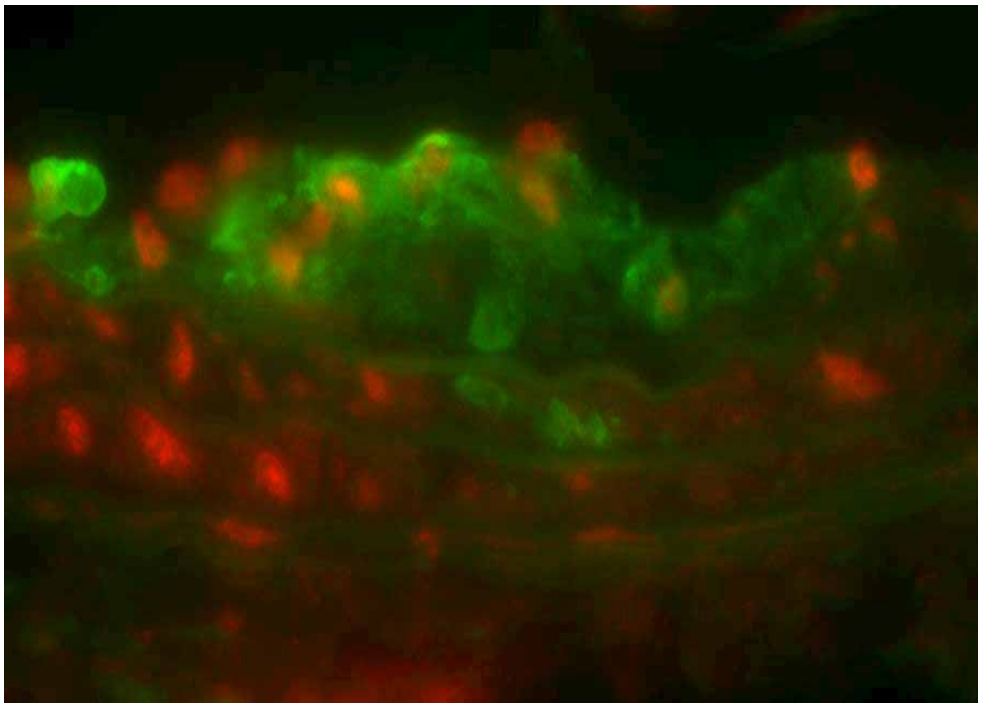


Thick	**Cap**	Thin
Rich in SMC and matrix	**Composition**	Rich in inflammatory cells: proteolytic activity
Poor	**Lipid**	Rich
inflammatory	**Inflammatory state**	More

Libby P. Circulation 1995;91:2844-2850

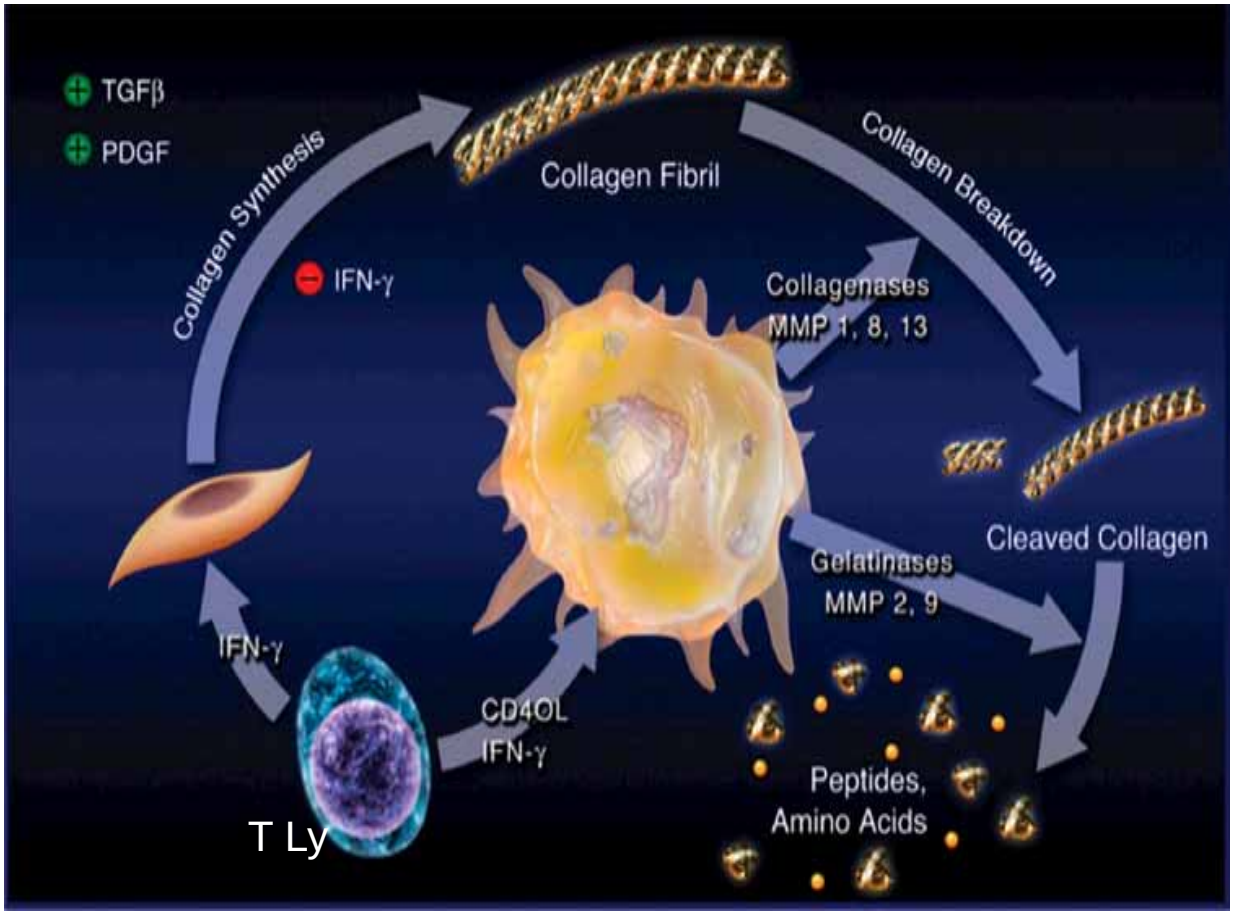
GnRH receptors are expressed by smooth muscle cells in atherosclerotic plaques





Hultgårdh, Nilsson et al, unpublished

T lymphocytes are key drivers of collagen metabolism in atherosclerotic plaques



Disruption of the fibrotic cap

↓

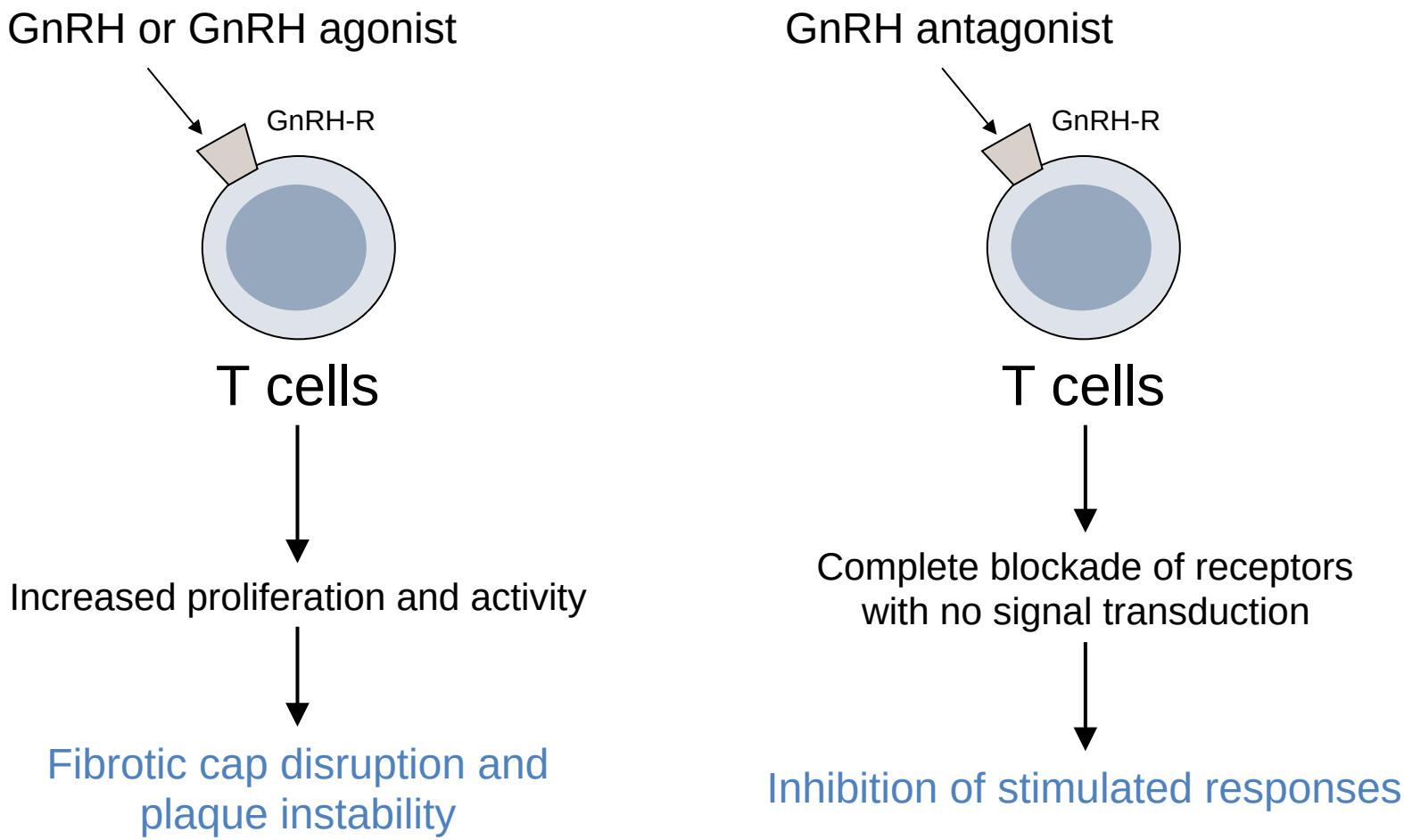
Plaque instability

↓

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

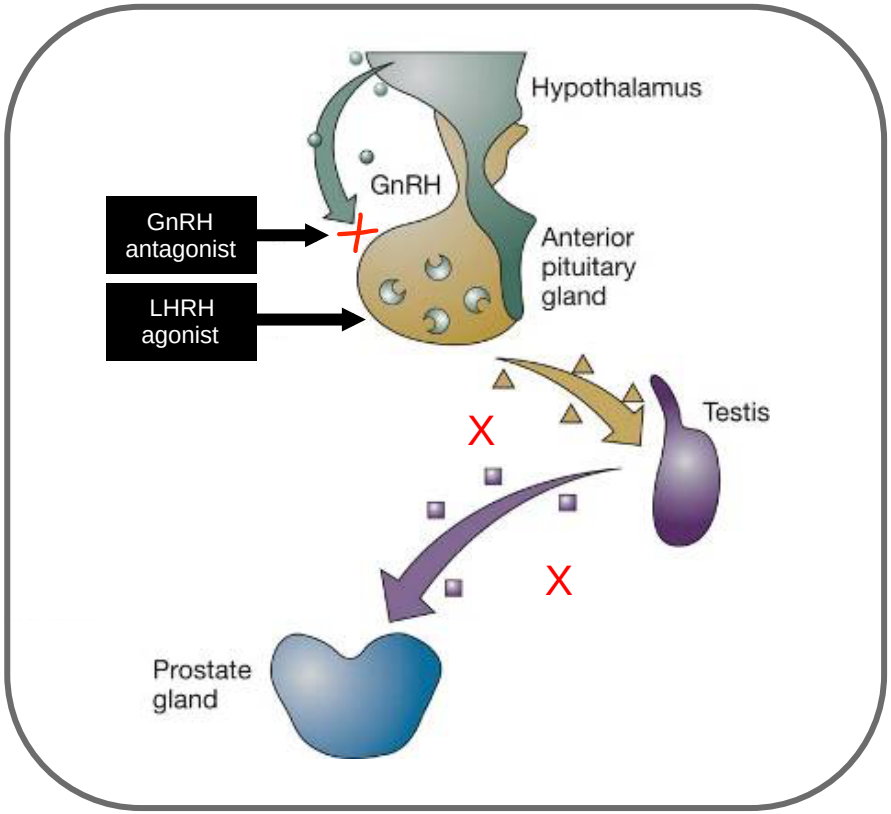
Chen HF, et al. J Clin Endocrinol Metab 1999;84:743-50
Tanriverdi F, et al. Clin Exp Immunol 2005;142:103-10
Grasso G, et al. Life Sci 1998;62:2005-14; Jacobson JD, et al. Endocrinol 1994;134:2516-23

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

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

What does this mean for our patient?

- From your perspective as urologists:
  - Consider which therapy will treat his prostate cancer effectively
  - Consider which therapy will control disease symptoms effectively
  - Consider minimising side effects
- In the absence of CV risk, probably little to choose between LHRH agonists and degarelix
- In the presence of CV risk (obesity, diabetes, prior MI), degarelix may be preferred

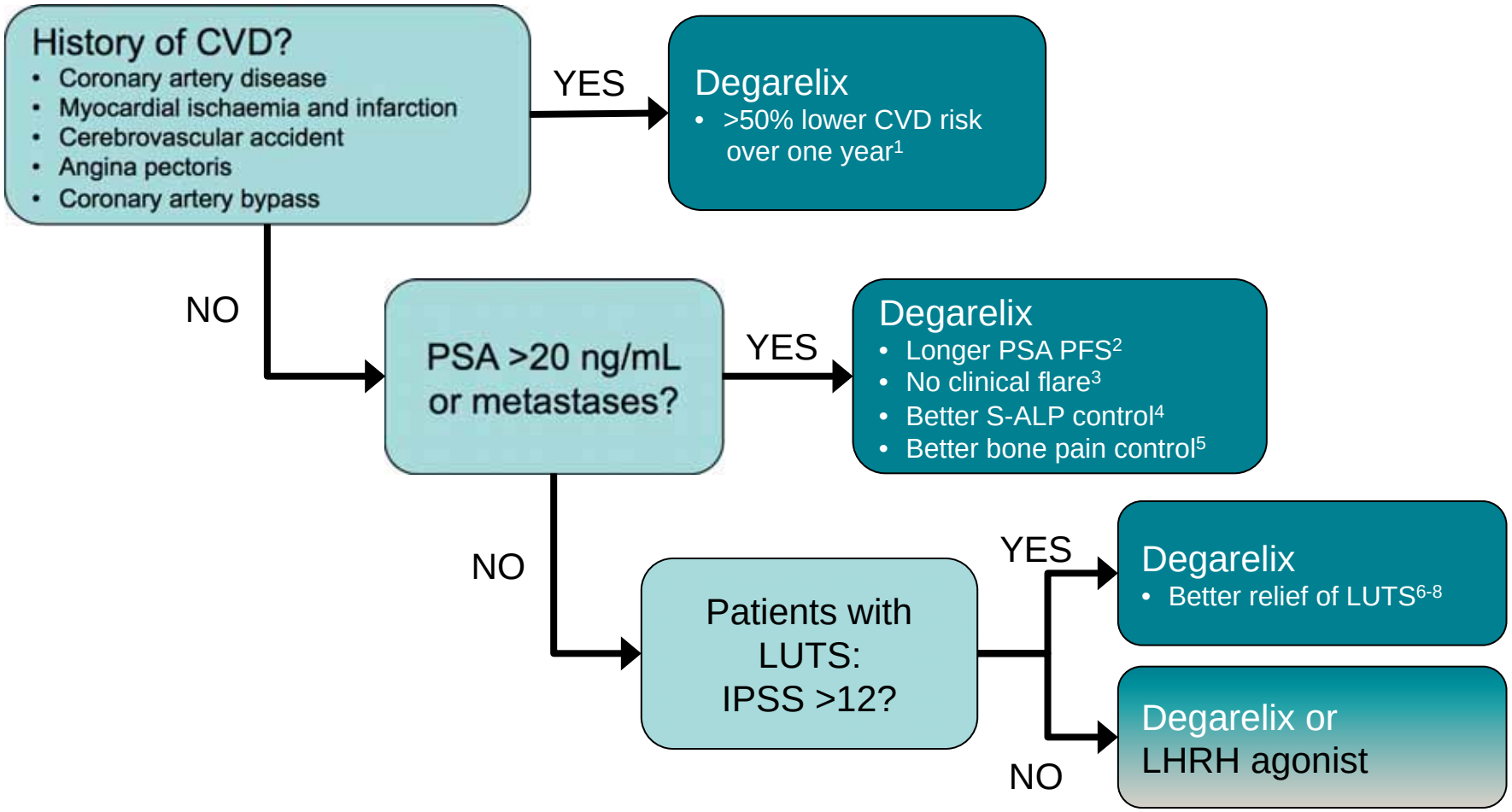
Summary

- ADT is associated with an increased risk of CV events, particularly in those with a history of CVD
- The GnRH antagonist, degarelix, may be associated with a lower incidence of CV events than LHRH agonists
- The difference in risk appears likely to be due to the differing mechanisms of actions of the types of ADT
- Risk of CVD should be carefully assessed prior to using ADT and risk minimised where possible

ADT and CVD: Conclusions

- When treated with degarelix rather than a LHRH agonist, patients with pre-existing CVD:
  - Had significantly fewer CV events during the first year of treatment
  - Had a relative risk reduction of >50%

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

Abiraterone Clinical Summary

Mechanism of action

- Irreversible inhibitor of CYP17A
- Inhibits testosterone production in testis, adrenal glands and prostate
- Abi, 1000mg oral plus prednisone 5mg bid, non-fed state

Pre-docetaxel phase III trial (COU-302) asymptomatic or mildly symptomatic mCRPC[3] co-primary endpoints-OS & rPFS

- Median rPFS not reached vs 8.28 months, respectively; HR=0.425; 95% CI 0.347–0.522; P<0.0001
- Median OS was longer for ZYTIGA® plus prednisone compared with placebo plus prednisone
  - 35.3 months vs 30.1 months, respectively; HR=0.792; 95% CI 0.655–0.956; P=0.0151 (pre-specified value for statistical significance not reached)

Post-docetaxel phase III trial (COU-301) in mCRPC[1] with primary endpoint OS

- Abiraterone plus prednisone improved OS in patients with (COU-301) mCRPC post- docetaxel[1,2]
- 3.9 month OS benefit(4.6 final...HR=0.74; 95% CI: 0.638, 0.859)[2]
- AEs of special interest - fluid retention hypokalemia, hypertension, and liver-function test abnormalities – abiraterone vs placebo (55% vs 43%, P<0.001)[1]

CI, confidence interval
HR, hazard ratio
OS, overall survival

1. de Bono et al. N Engl J Med 2011;364:1995-2005
2. Zytga™ (abiraterone acetate) SPC 2011; 3. www.clinicaltrials.gov (accessed February 2012); 4. Mostaghel et al. Clin Can Res 2011;17:5913-25

Enzalutamide Clinical Summary

Mechanism of action:

- Designed to have high affinity and selectivity for the androgen receptor
- An androgen receptor inhibitor that targets multiple steps in the androgen receptor signaling pathway in the tumor cell
- Enzalutamide, 160mg oral qd, no steroid or food requirement

Post-docetaxel phase III trial (AFFIRM) in mCRPC[1] with primary endpoint OS

- Enzalutamide improved OS in patients with mCRPC post- docetaxel[1,2]
  - 4.8 months OS benefit (HR = 0.631 (0.529, 0.752) P < 0.0001 37% Reduction in Risk of Death)[2]
- AE's of special interest: 0.9% seizure incidence, grade 1-4 neutropenia (15% vs. 6%), Grade 1 or 2 hallucinations (1.6%)
- Pre-CTX(PREVAIL) completed: improved OS in Pts with mCRPC .
- Benefit seen in pts with visceral disease and bony metastatic disease.

Tran C, et al. *Science*. 2009;324:787-790
Scher HI, Fizazi K, Saad F, et al. *N Engl J Med.* 2012;367:1187-1197.

Key Study Design Differences

Category	PREVAIL	COU-AA-302
Control Group	Placebo	Prednisone
Eligibility Criteria	Visceral disease allowed	Visceral disease excluded
	Blood pressure <170/105 mmHg	Blood pressure <160/95 mmHg
	Excluded patients with NYHA class 3 or 4 CHF	Excluded patients with NYHA class 2, 3, or 4 CHF
	Allowed patients with atrial fibrillation and other arrhythmias requiring therapy	Excluded patients with atrial fibrillation and any arrhythmia that requires therapy
Study Conduct	Patients were allowed to continue study drug up until initiation of cytotoxic chemotherapy or an investigational agent	Patients needed to discontinue study drug if need for opiates to treat cancer pain, SRE, ECOG PS of 3 or higher
	Provenge, systemic radiopharmaceuticals, allowed during treatment	Provenge, systemic radiopharmaceuticals excluded during treatment

Selected Demographic and Disease Characteristics

	PREVAIL		302	
Demographic/Baseline Characteristics	**Enza (N=872)**	**Placebo (N=845)**	**Abi + prednisone (N=546)**	**Placebo + Prednisone (N=542)**
Median age in yrs (range)	72 (43 – 93)	71 (42 – 93)	71 (44 – 95)	70 (44 – 90)
Median baseline PSA	54.1	44.2	42.0	37.7
Median baseline LDH (IU/L)	185	185	187	184
Presence of bone metastases at entry (%)	85.0%	81.7%	83%	80%
Presence of soft tissue disease at entry (%)	59.3%	59.6%	49.1%	50.0%
Presence of visceral disease at entry (%)	11.2%	12.5%	0%	0%

Abiraterone data taken from Ryan et al NEJM 2013

Exposure to Study Drug

	PREVAIL		Abiraterone 302	
	Enzalutamide (N=871)	**Placebo (N=844)**	**Abi+pred (N=542)**	**Placebo+pred (N=540)**
Treatment Duration (Months)				
Median	16.6	4.6	13.8	8.3

Subsequent Therapy

	PREVAIL		Abiraterone 302	
Parameter (n%)	**Enza (N=872)**	**Placebo (N=845)**	**Abi + pred (N=546)**	**Placebo + Pred (N=542)**
Median Follow-Up Time (months)	22.3 months		22.3 months	
Use of Subsequent Therapy:				
Docetaxel	32.8%	56.7%	38%	53%
Cabazitaxel	5.8%	13.0%	8%	10%
Abiraterone	20.5%	45.6%	5%	10%
Enzalutamide	1.0%	4.4%	--	--

Abiraterone data taken from ASCO 2012 (presentation)/NEJM 2013/EPAR 2013

Efficacy Data

	PREVAIL	Abiraterone 302
Overall Survival	HR = 0.706 P < 0.0001	HR = 0.792 P = 0.0151 (Not significant)
rPFS	HR = 0.186 P < 0.0001	HR = 0.530 P < 0.0001
Time to Cytotoxic Chemotherapy	HR = 0.350 P < 0.0001	HR = 0.580 P < 0.0001
Time to PSA Progression	HR=0.169 P < 0.0001	HR=0.488 P < 0.0001
Degradation FACT-P	HR=0.625 P < 0.0001	HR=0.778 P = 0.0028
Best Overall Soft Tissue Response	Measurable disease: 45% vs. 45% Responders: 59% vs. 5%, p<0.0001 CR: 20% vs. 1% PR: 39% vs. 4%	Measurable disease: 40% vs. 40% Responders: 36% vs. 16%, p<0.0001 CR: 11% vs. 4% PR: 25% vs. 12%

Question-In pre-docetaxel setting

- PREVAIL/Cougar 302 are positive
  - Give enzalutamide first?
    - No steroids, No food effect
    - Fluid retention(NYHA),IDDM
  - Give abiraterone first?
    - More experience with drug
    - Seizure (neuro)history
    - Does baseline T level matter?
    - Sequencing more favorable?
  - Give as combination?

Cross Resistance Between Abiraterone and Enzalutamide

Sequencing-Non-mCRPC

- No therapy has been shown to improve survival in this setting
- Observation is reasonable for those with slow PSAV
- Consider secondary hormonal therapies
- Phase III trials (ARSI)-Enzalutamide & ARN-509

Practice-Changing Results for Metastatic Prostate Cancer

Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (**CHAARTED**)

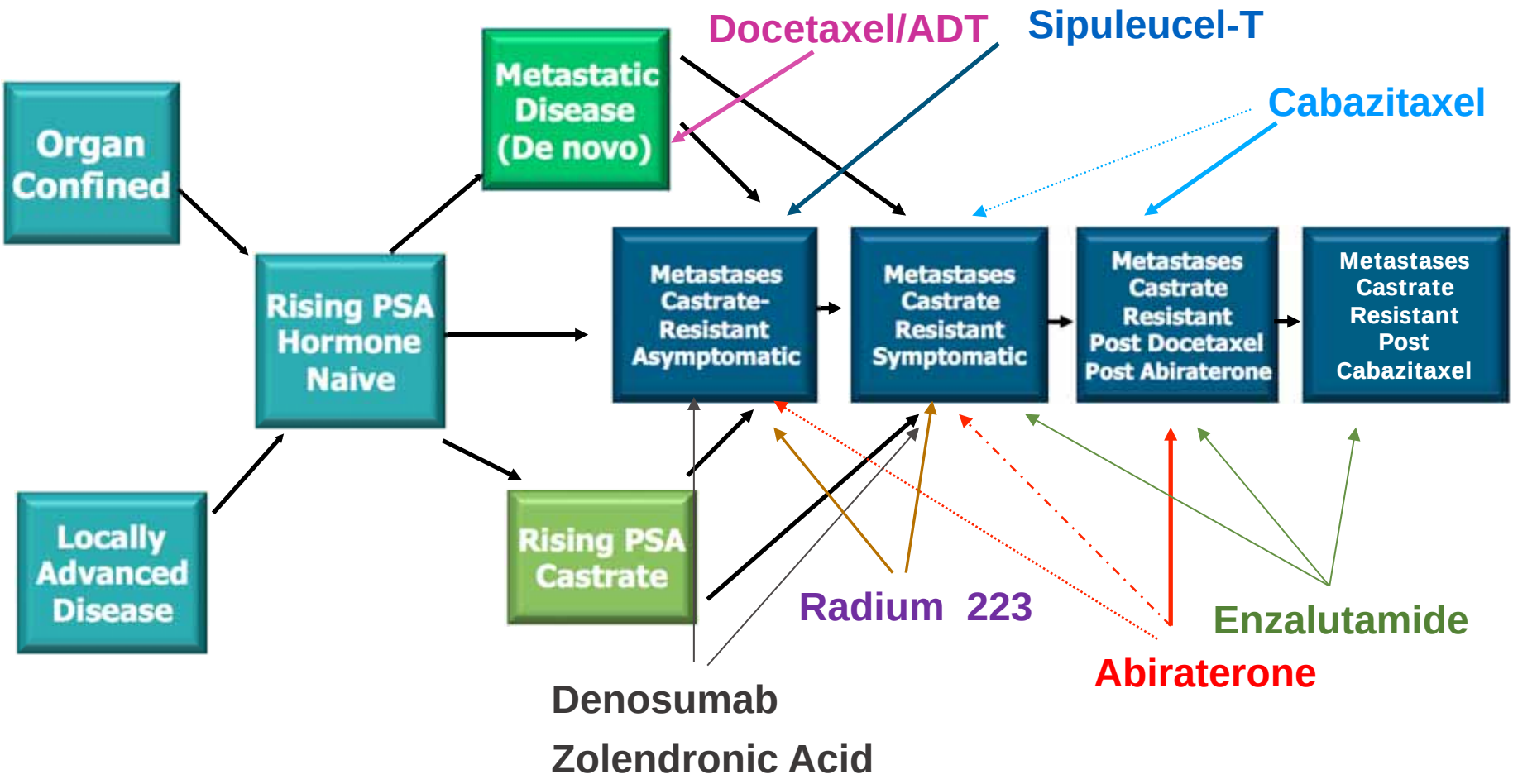
"Upfront" chemotherapy (docetaxel) plus ADT vs ADT alone in men with

metastatic prostate cancer

Dr. Christopher Sweeney

Sweeney et al. *J Clin Oncol.* 32:5s, 2014 (suppl; abstr LBA2)

Clinical States In Prostate Cancer

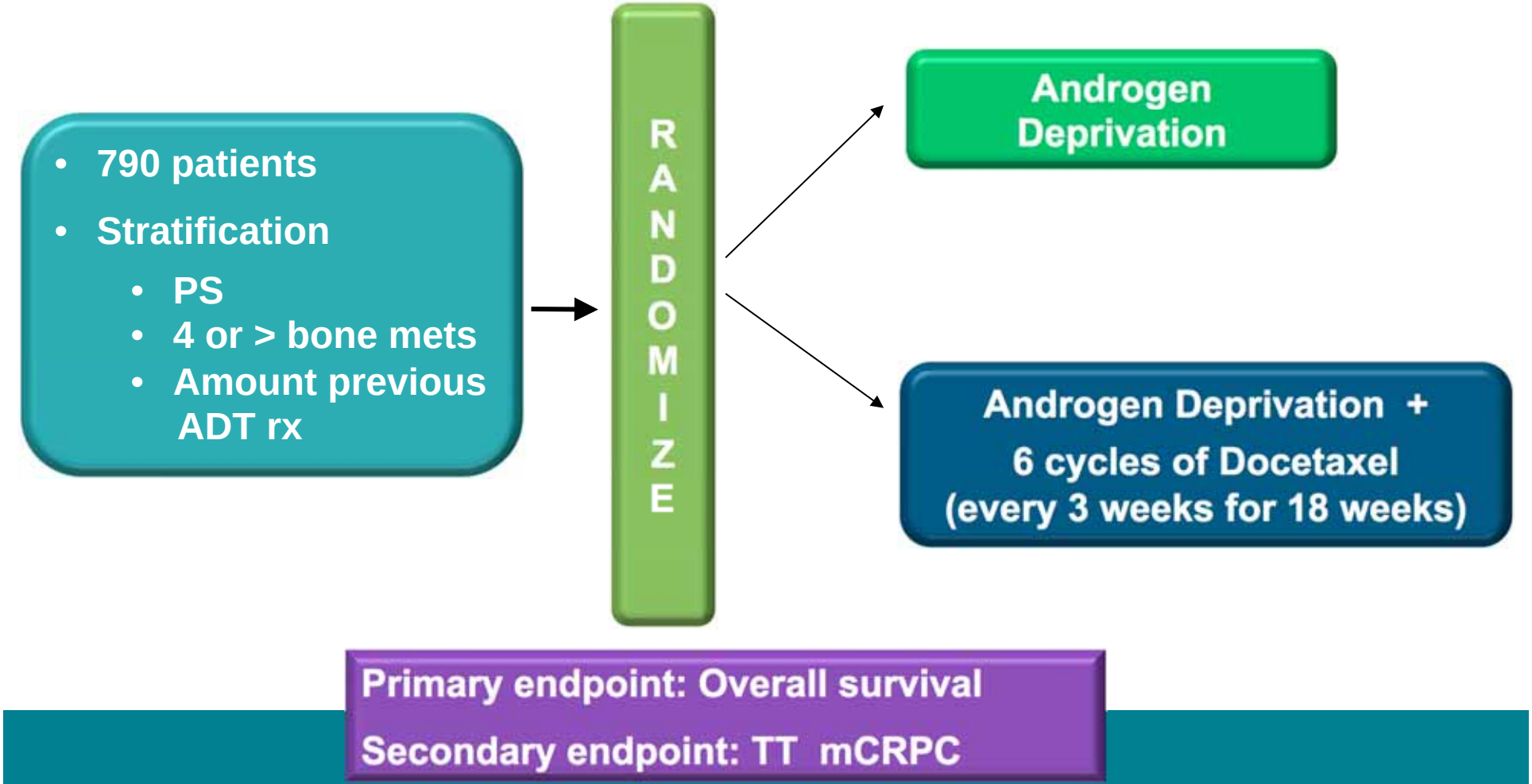


Modified from Scher H, et al. Urology 2000

Key Questions

- Are there therapies that are better given early?
- Are certain therapies designed to work better later in CRPC? Or not?
- Is the efficacy of prior therapies diminished by subsequent treatment?
- Is the efficacy of the administration of later agents diminished by their precedents?
- Can therapeutic resistance be modulated by specific concurrent targeted therapy?
- Are there patient characteristics or biomarkers that help match patients and specific therapies?
- Since Docetaxel is being given earlier (non CRPC) should these be also.

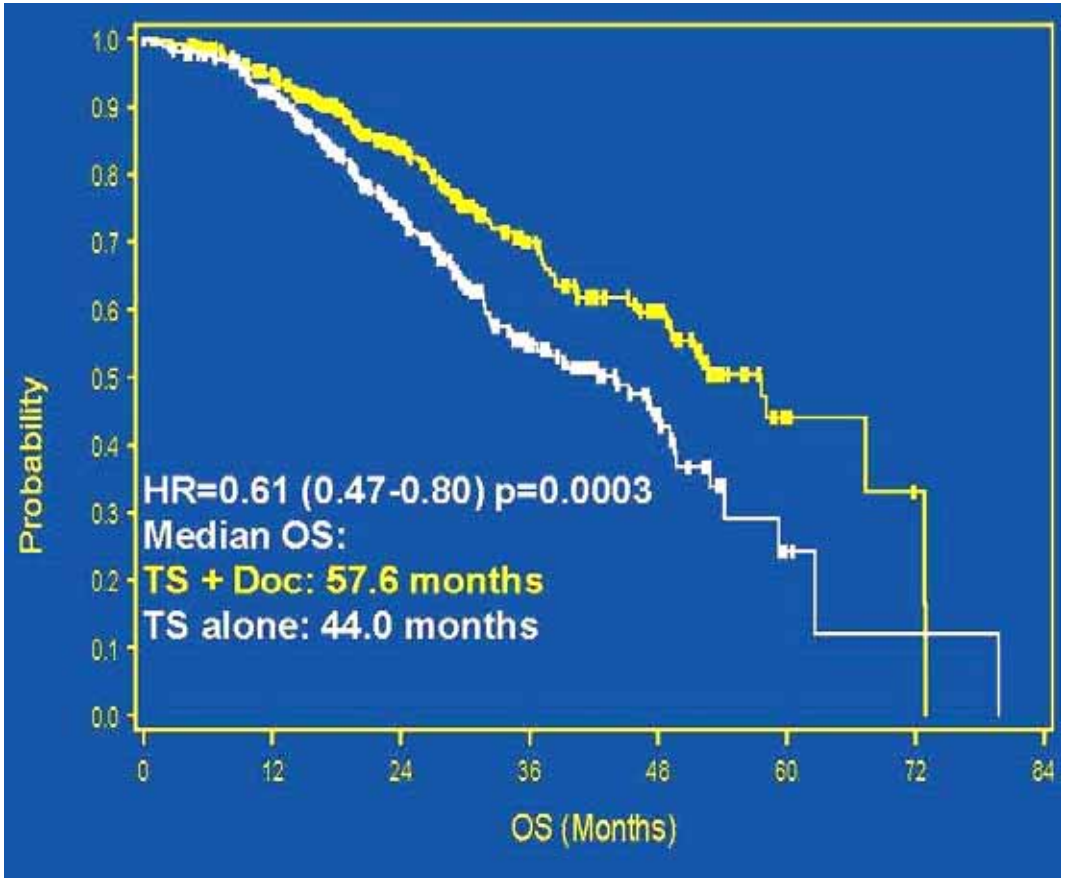
CHAARTED (E3805): ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer



ClinicalTrials.gov Identifier: NCT00309985

CHAARTED
Overall Survival (OS)

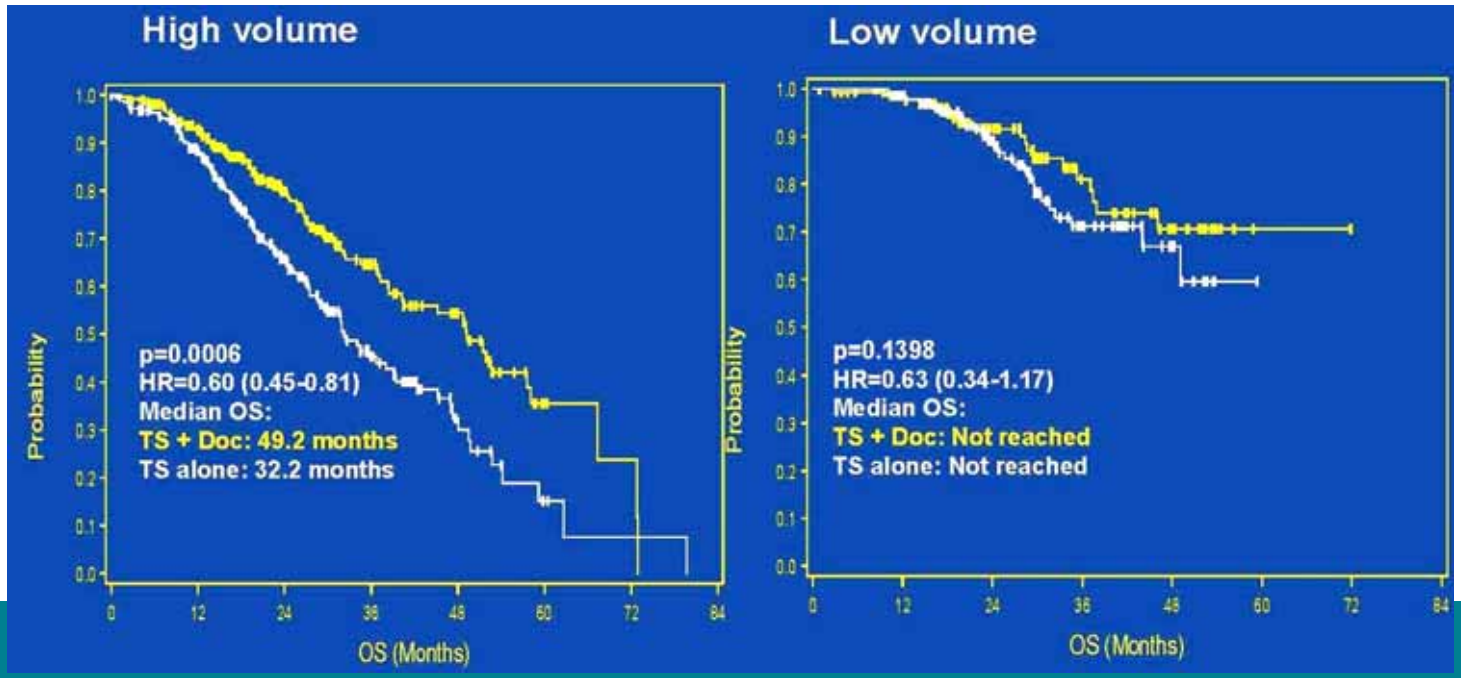
- Median OS was **improved by 13 months** in patients treated with **ADT plus docetaxel**
  - 57.6 months for men on ADT plus docetaxel
  - 44.0 months for men on ADT alone
- Median time to CRPC and time to clinical progression was greater for ADT + docetaxel



Sweeney et al. *J Clin Oncol.* 32:5s, 2014 (suppl; abstr LBA2)

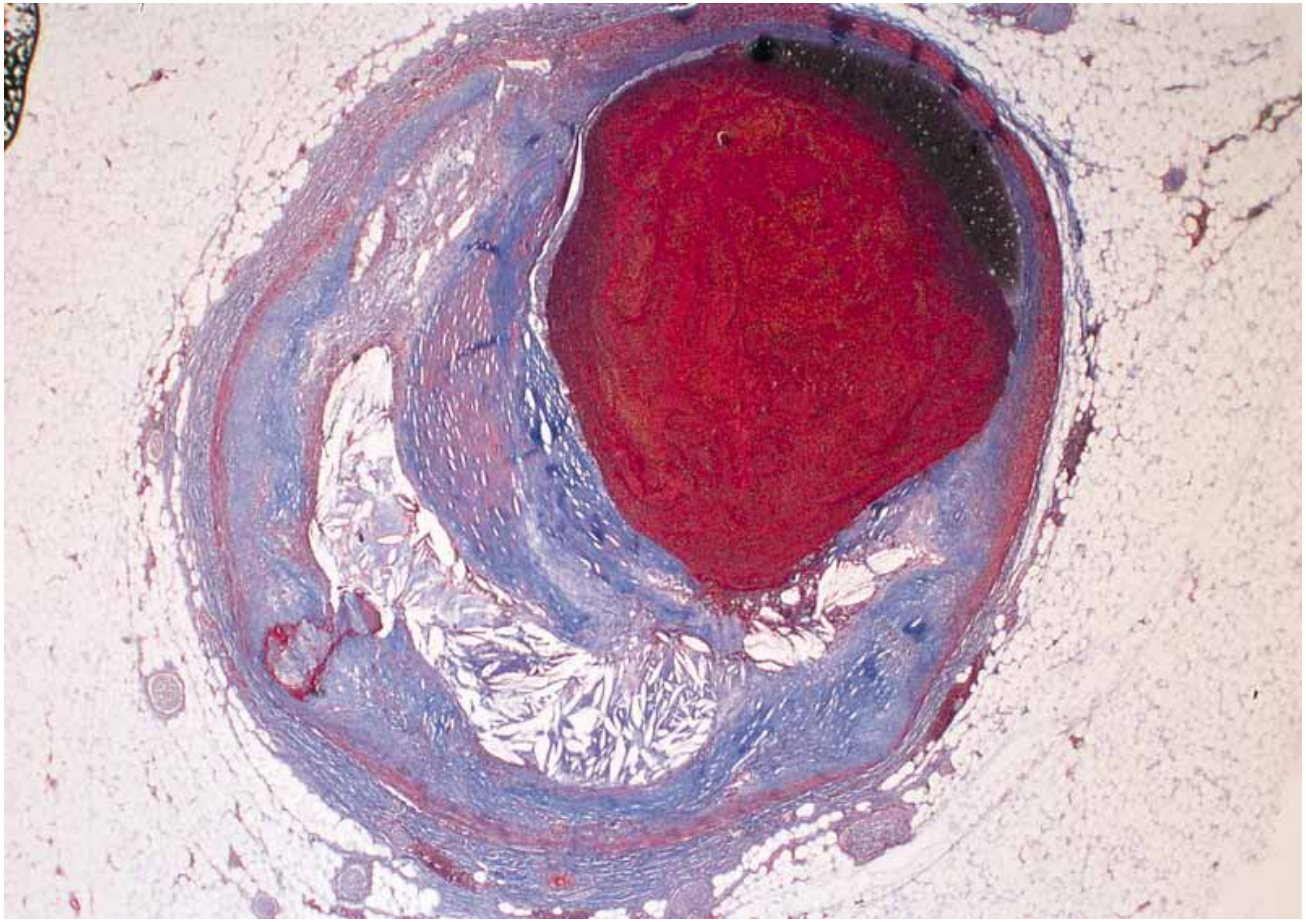
CHAARTED
OS by Extent of Disease

- The median OS was **improved by 17 months in men with high-volume disease**
  - 49.2 months for men on ADT + docetaxel
  - 32.2 months for men on ADT alone
- The median OS for low-volume disease has not yet been reached.

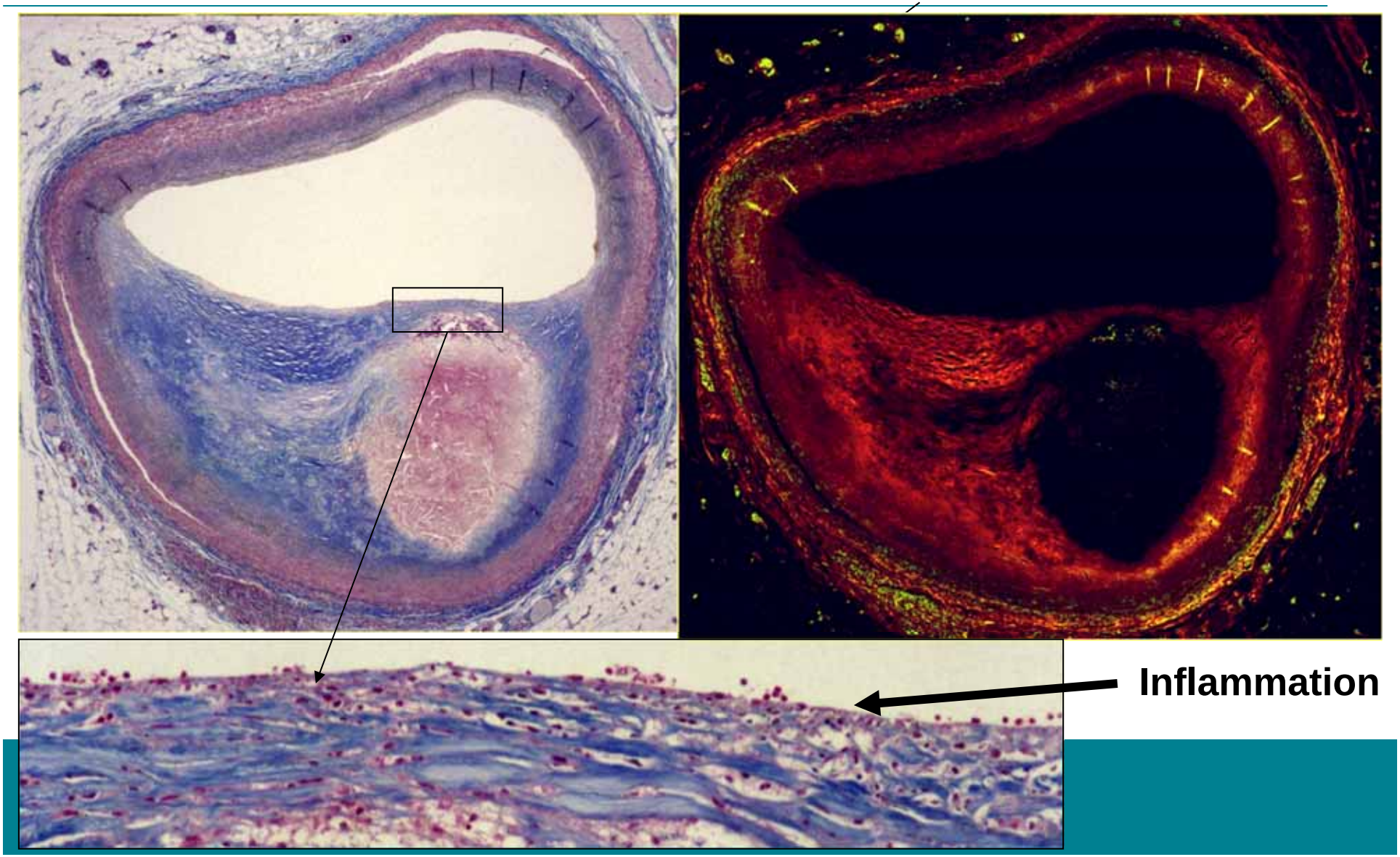


Sweeney et al. *J Clin Oncol.* 32:5s, 2014 (suppl; abstr LBA2)

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

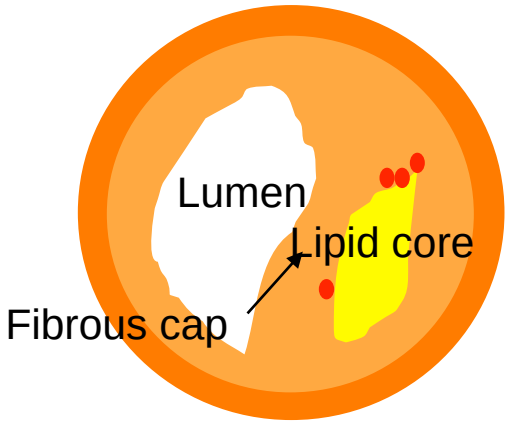


The vulnerable plaque – thin cap with inflammation

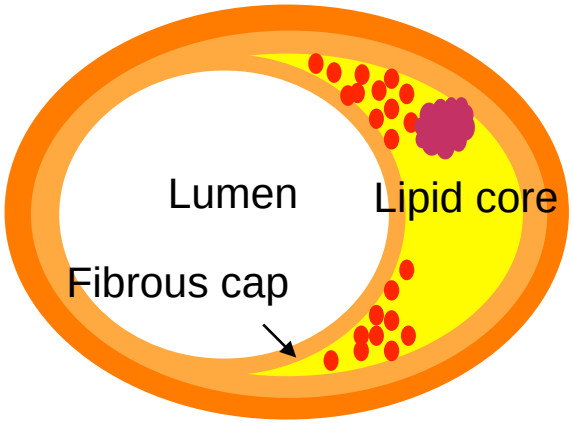


Plaque instability is at the heart of cardiovascular disease

Stable plaque



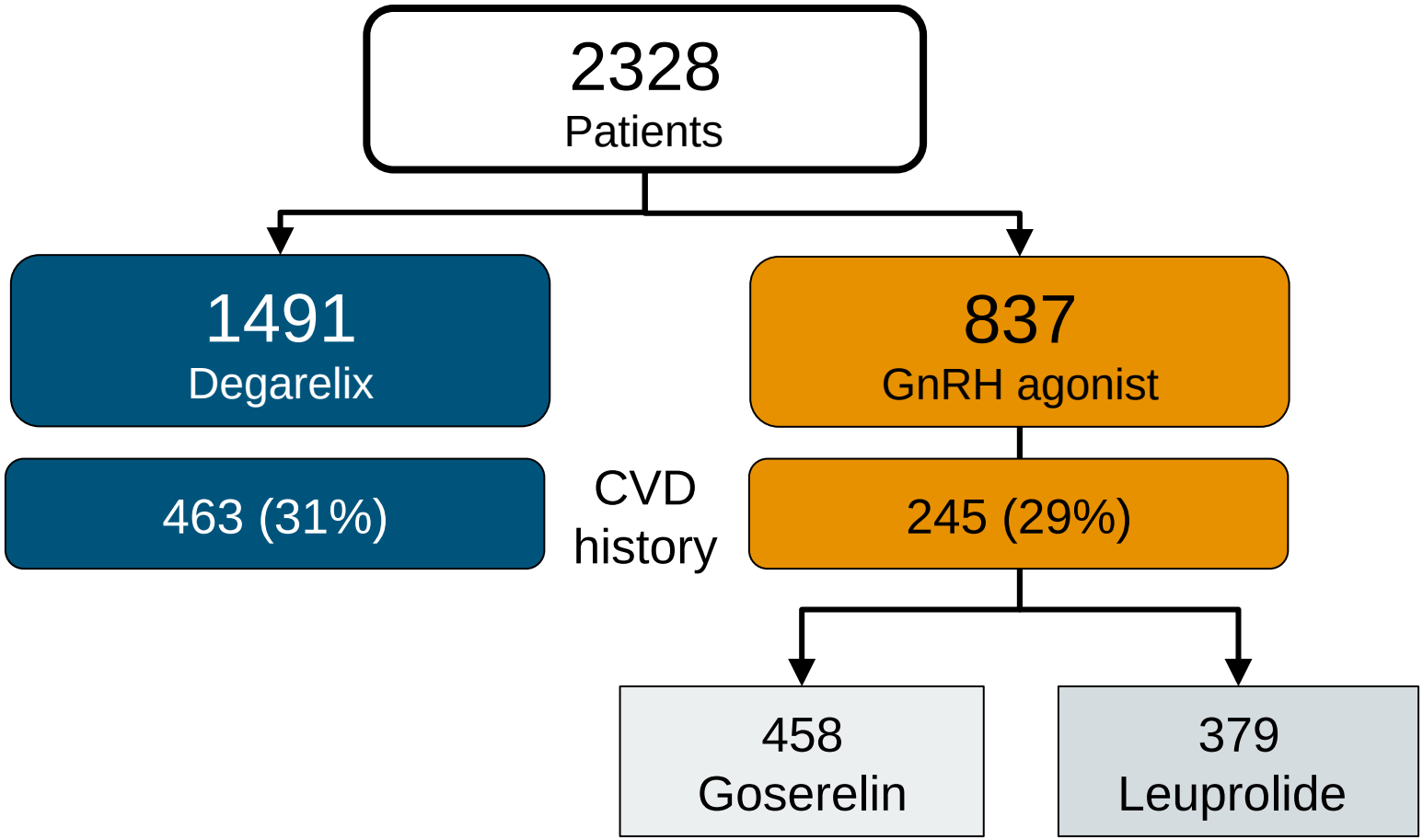
Vulnerable plaque



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

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

Tom Keane is planning to show this table and the next three KM curves but keep to reinforce data and make the point that most of the OS difference is likely due to CV events

Results: Overall incidence of CV events*

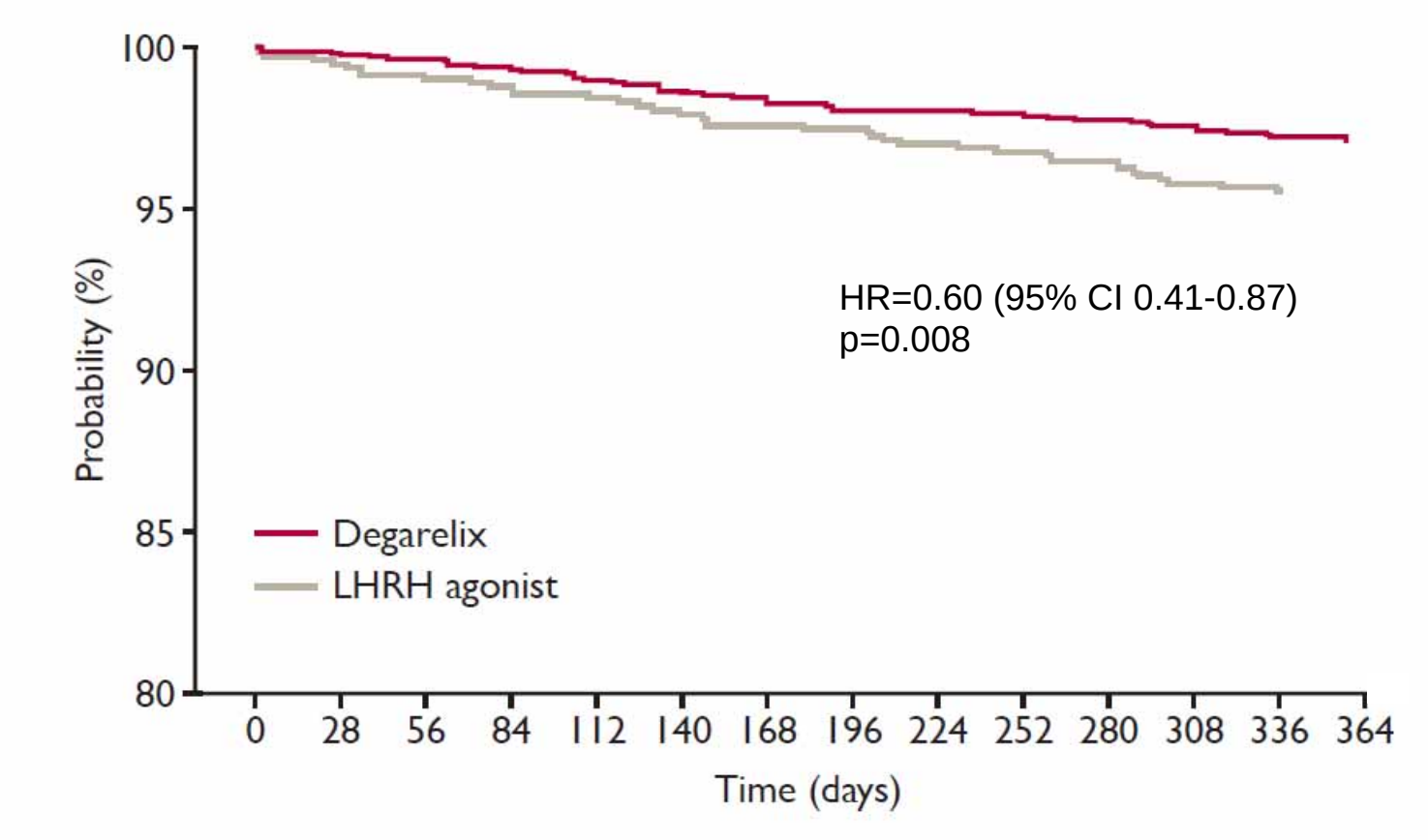
	Degarelix, n (%) n=1491	GnRH agonist, n (%) n=837
Any CV event	37 (2.5)	40 (4.7)
Serious CV event	25 (1.7)	24 (2.9)

- 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

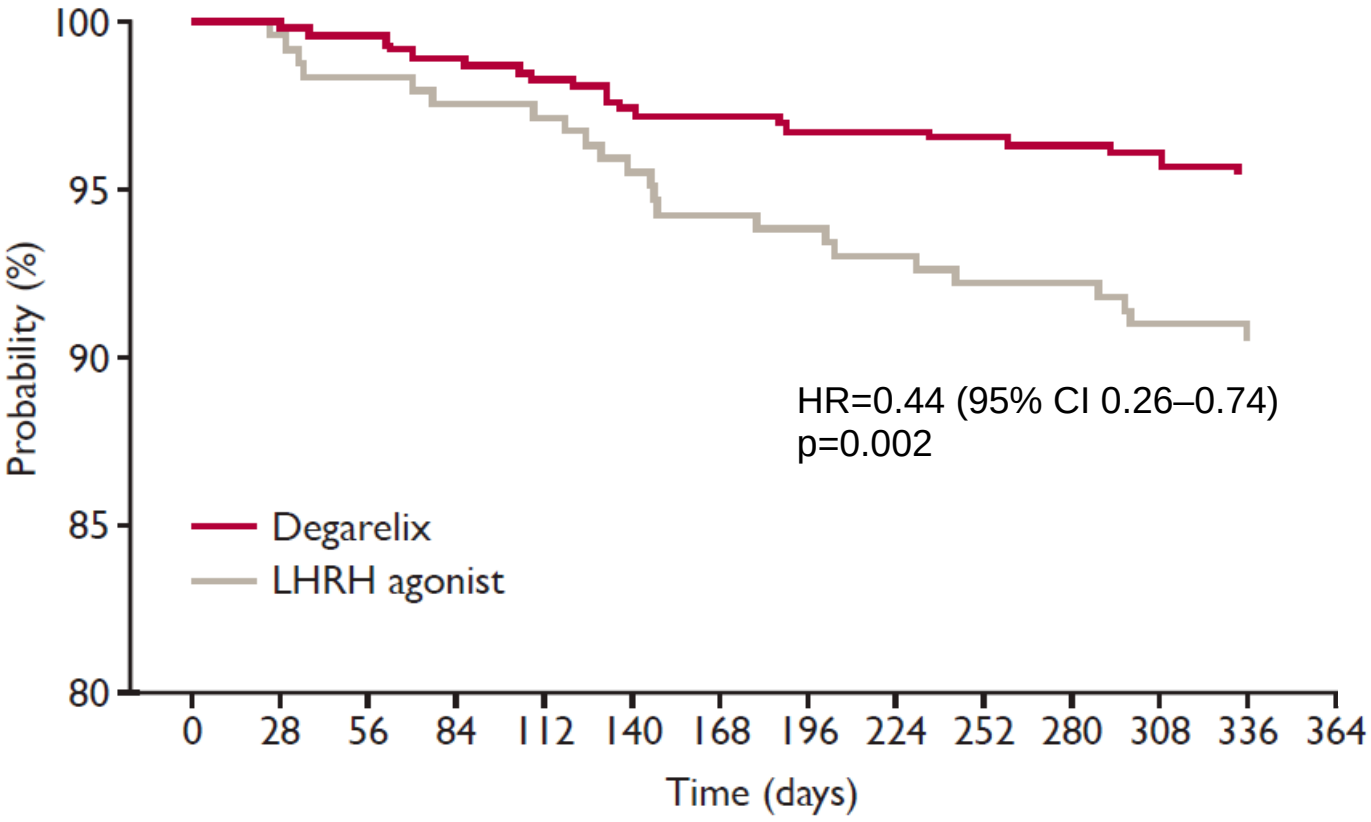
Lower risk of CV event or death with degarelix (all patients)



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



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
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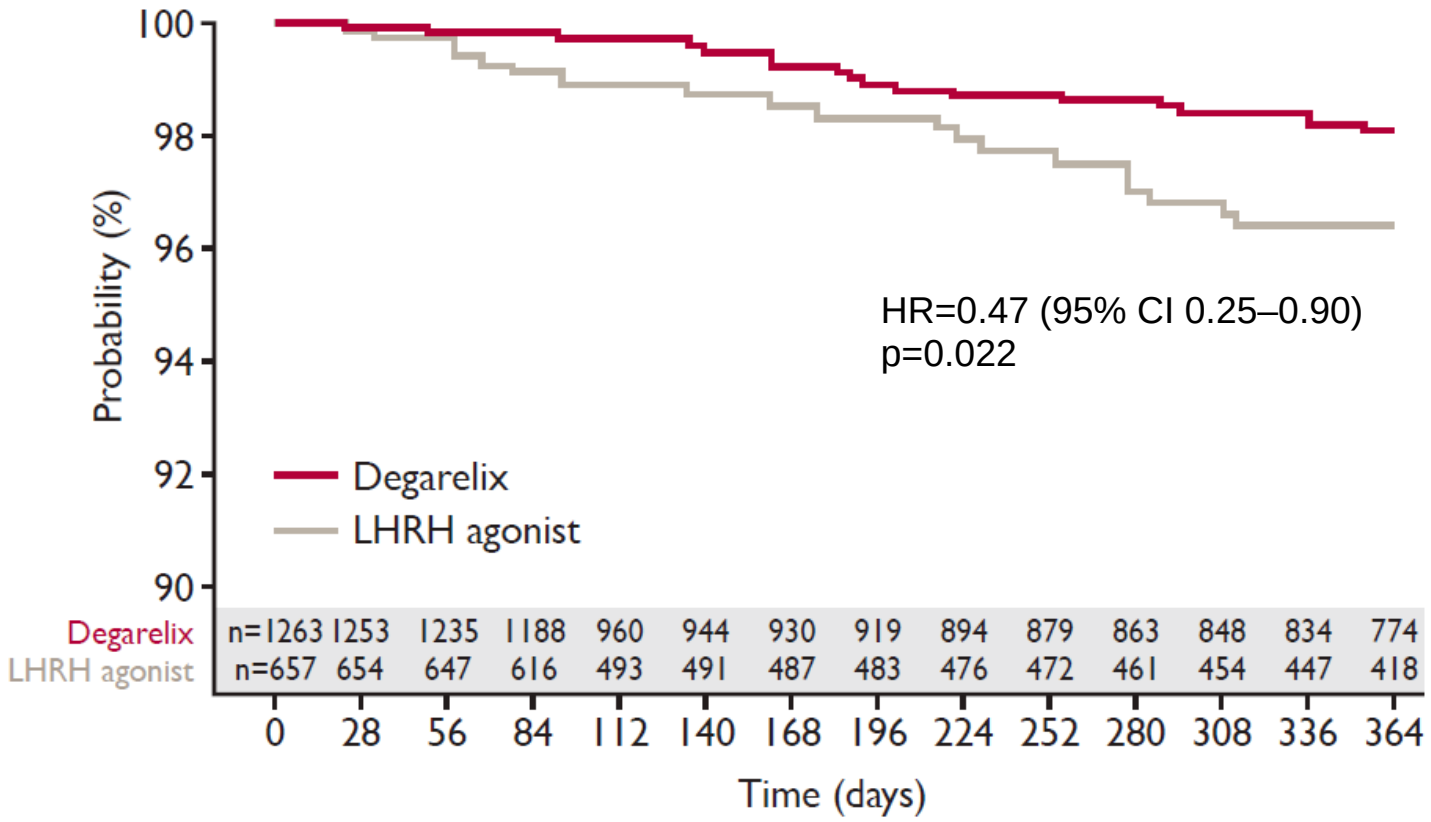
Overall survival



CVD, cardiovascular disease

Klotz et al. Eur Urol 66(2014) 1101-1108