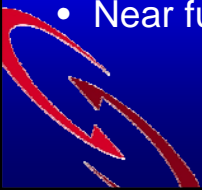


Benign Prostatic Hyperplasia

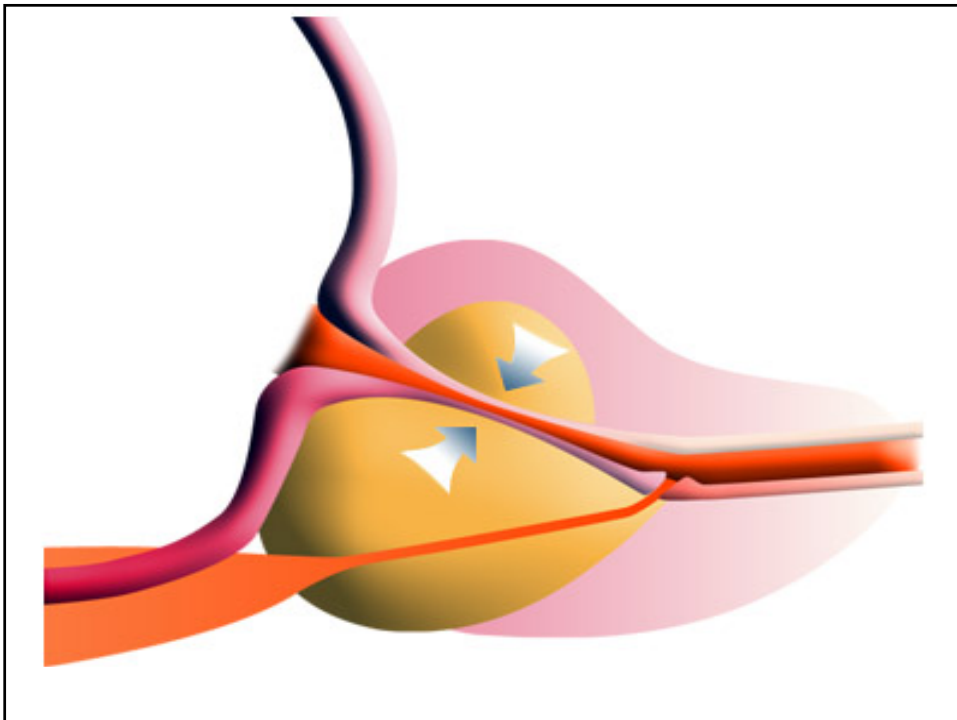
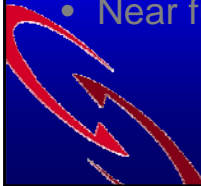
台大醫院
泌尿部
黃鶴翔醫師

Contents

- Benign prostatic hyperplasia
 - Dual 5α -reductase inhibitor - Avodart
 - 5α -reductase inhibitor monotherapy
 - Combination therapy
 - Safety
 - Near future.....
- 

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BPH - the Size of the Problem



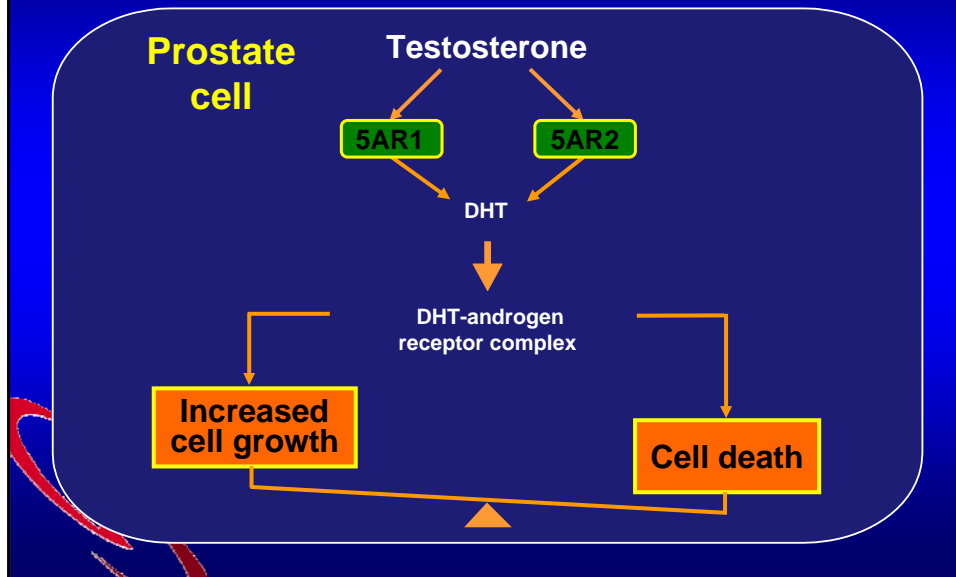
50% of men will have BPH symptoms at age 60
This rises to 90% by age 80
But only 25% of men aged 80 will be receiving BPH treatment

臨床症狀

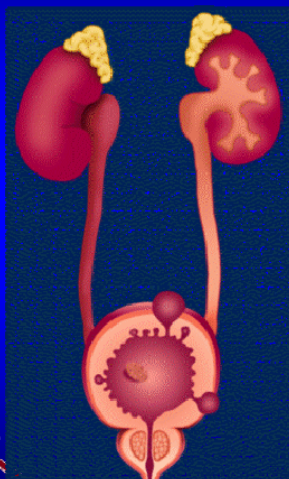
- 排尿期症狀
 - Weak urinary stream
(尿流慢)
 - Intermittency
(尿流中斷)
 - Straining to void
(解尿需用力)
 - Emptying incompletely
(解尿後有餘尿)
- 儲尿期症狀
 - Frequency
(頻尿)
 - Urgency
(尿急無法忍)
 - Nocturia
(夜晚需起床上廁所)

Wise & Fun

DHT Drive the Prostate Growth



病理變化



- 膀胱壁肥厚
- 反覆血尿
- 膀胱憩室
- 尿路感染
- 膀胱結石
- 輸尿管水腫
- 腎臟水腫

BPH: A Progressive Disease

- Over time, men with BPH may experience
 - Increase in prostate volume
 - Decrease in peak urinary flow rate (Q_{max})
 - Worsening of LUTS symptom
- Progression of BPH may lead to long-term complications
 - Acute urinary retention (AUR)
 - BPH-related surgery

Rhodes et al. *J Urol* 1999; 161: 1174–9; Emberton et al. *Urology* 2003; 61: 267–73

Treatments for BPH

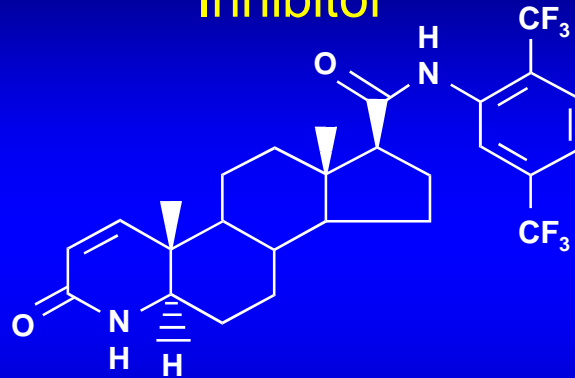
- Watchful waiting
- Medical therapy
 - α -adrenergic blockers
 - 5 α -reductase inhibitors
 - Combination therapy
 - Phytotherapy
- Office-based treatment
 - TUMT
 - TUNA
 - WIT
- Surgicenter/hospital-based treatment
 - TURP (gold standard)
 - TUIP
 - Open surgery (prostatectomy)
 - TUVP
 - ILC
 - VLAP
 - Prostatic stents

Chatelain C et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001:519-534. McConnell JD et al. Benign Prostatic Hyperplasia: Diagnosis and Treatment. Clinical Practice Guideline, Number 8. AHCPR Publication No. 94-0582. Columbia University website. Available at <http://cmprnet.columbia.edu/dept/urology/bphtherapy.html#trans/as> Accessed 8/23/01. Dreikorn K et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001:479-511.

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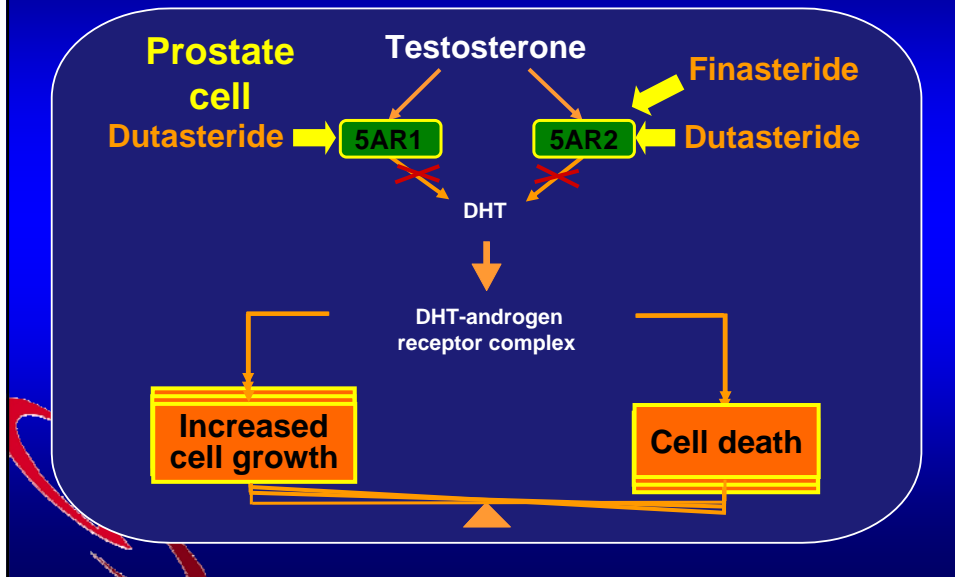
- Benign prostatic hyperplasia
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Avodart – Dual 5 α -Reductase Inhibitor

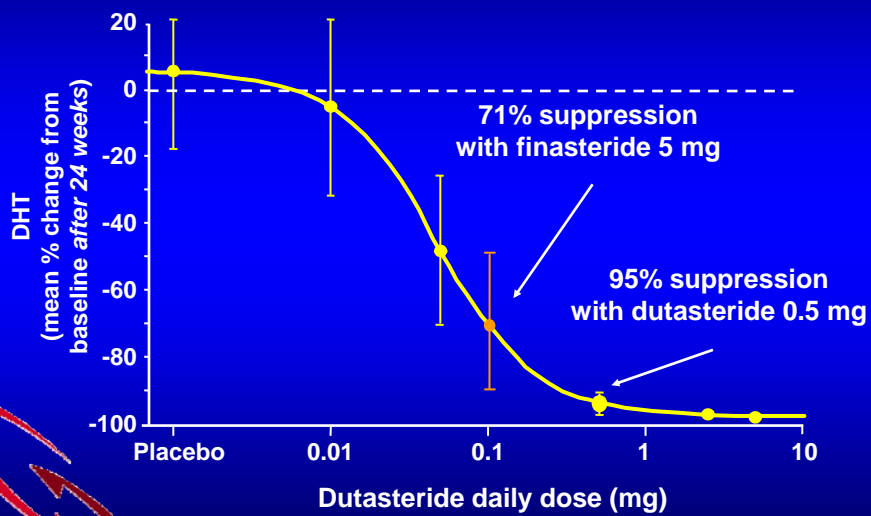


Δ^1 -4-azasteroid molecular formula: $C_{27}H_{30}F_6N_2O_2$
45-fold more potent inhibitor of type 1 5AR and 2.5-fold more potent inhibitor of type 2 5AR in vitro than finasteride.

Dual 5 α -Reductase Inhibitor



DHT Suppression



Bartsch G et al. *Eur Urol* 2000;37:367-380.

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Avodart Phase III Study Design

Randomisation to 2-year double-blind phase (n=4325)

Key inclusion criteria:

aged ≥ 50 years, diagnosis of BPH, PV ≥ 30 cc,
AUA-SI score ≥ 12 , Q_{max} ≤ 15 ml/s, PSA ≥ 1.5 ng/ml

Placebo
(n=2158)

Entered 2-year open-label
phase on dutasteride (n=1152)

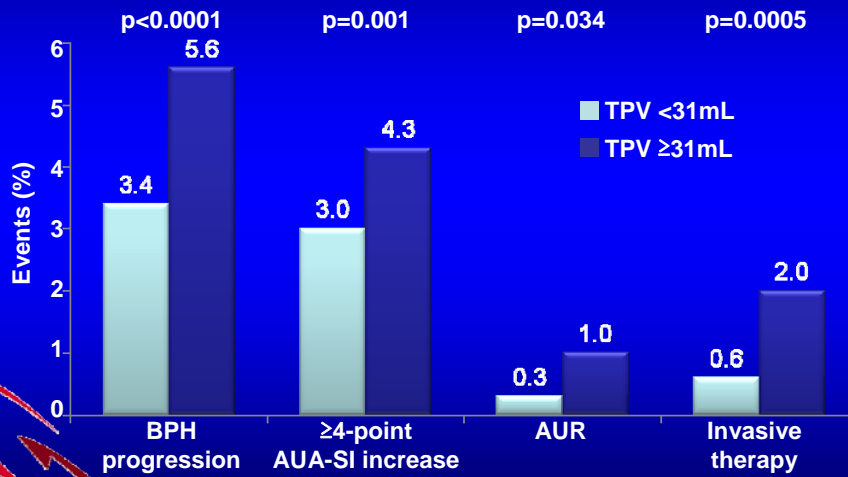
P/D

Dutasteride
(n=2167)

Entered 2-year open-label
phase on dutasteride (n=1188)

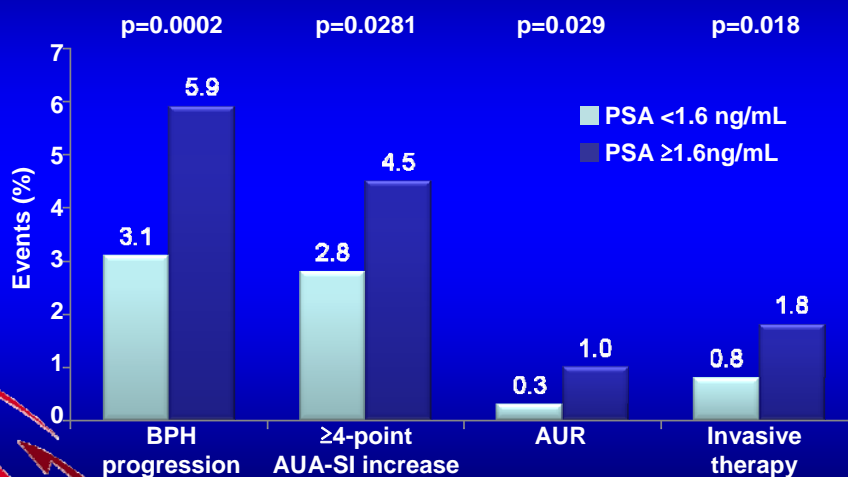
D/D

BPH progression events in MTOPS Risk by baseline TPV



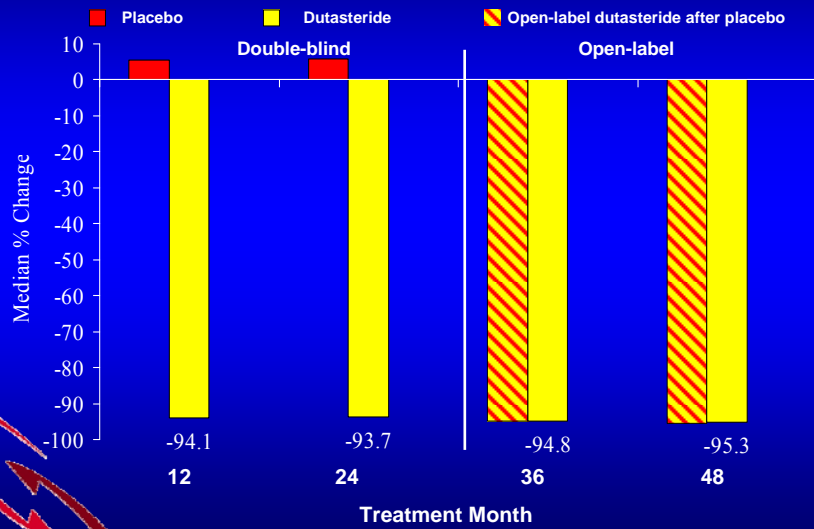
Crawford et al. J Urol 2006; 175: 1422-7

BPH progression events in MTOPS Risk by baseline PSA



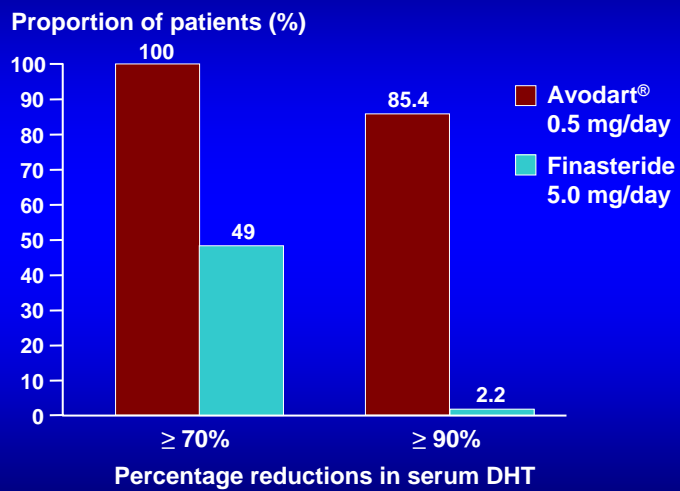
Crawford et al. J Urol 2006; 175: 1422-7

DHT Suppression



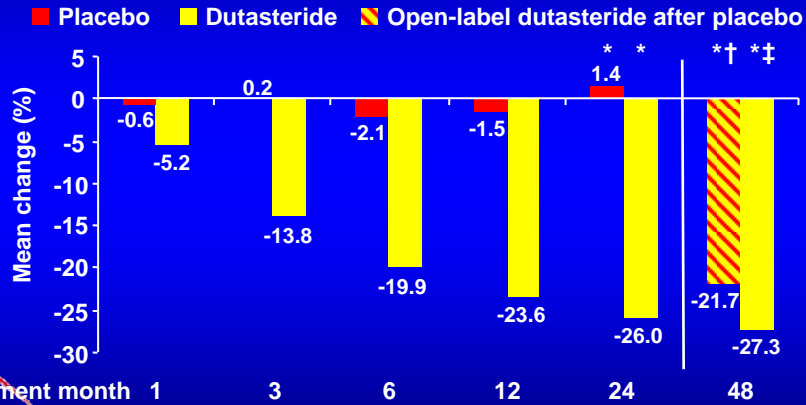
Claus G. Roehrborn, et al. *Urology* 2004; 63: 709-715

More Patients with $\geq 70\%$ DHT Suppression with Avodart® vs. Finasteride



Clark et al. *J Clin Endocrinol Metab* 2004;89 (5):2179-84

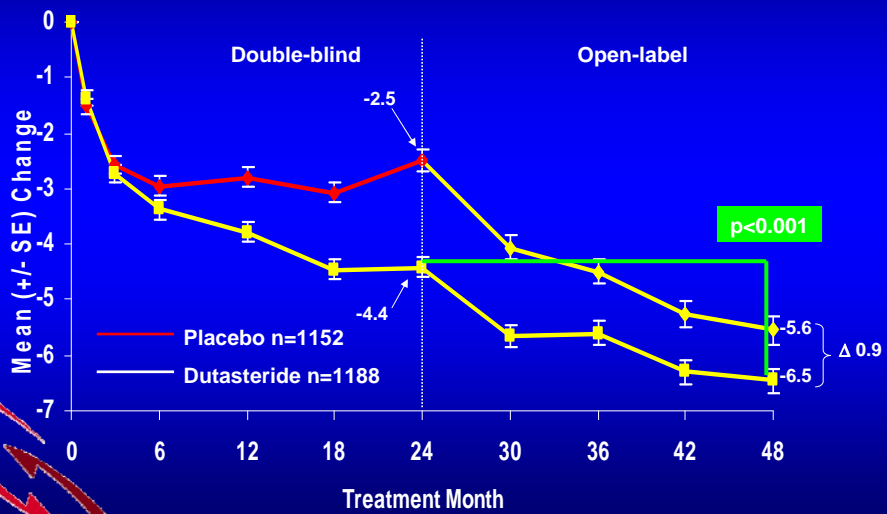
Reduction in Total Prostate Volume



*p<0.001 for differences between treatment groups
 †p<0.001 for change from Month 24 to Month 48
 ‡p=0.07 for change from Month 24 to Month 48

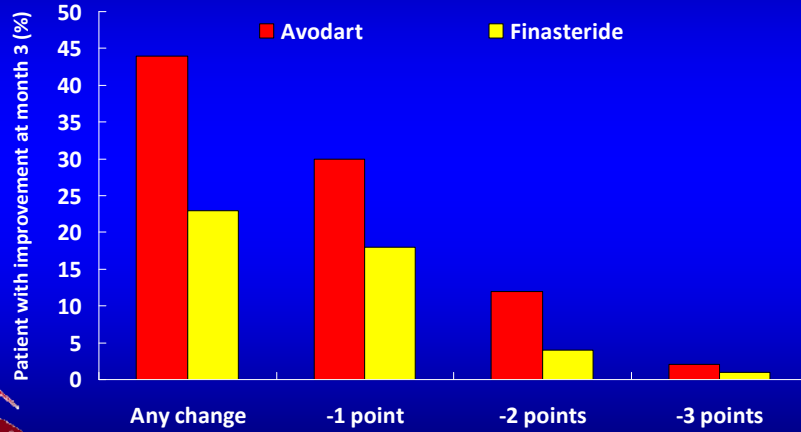
Frans et al, *European Urology* 2004; 46: 488-495

Mean Change in AUA-SI Scores



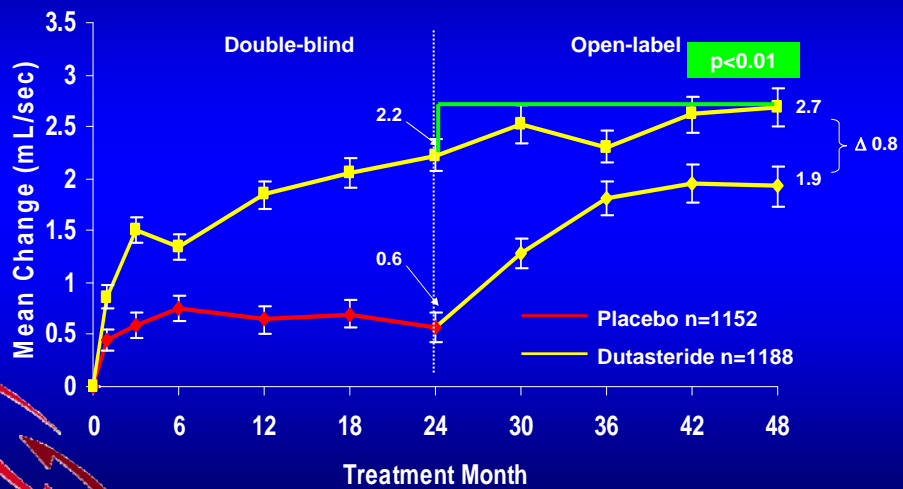
Frans et al, *European Urology* 2004; 46: 488-495

Faster Improvement Than Finasteride



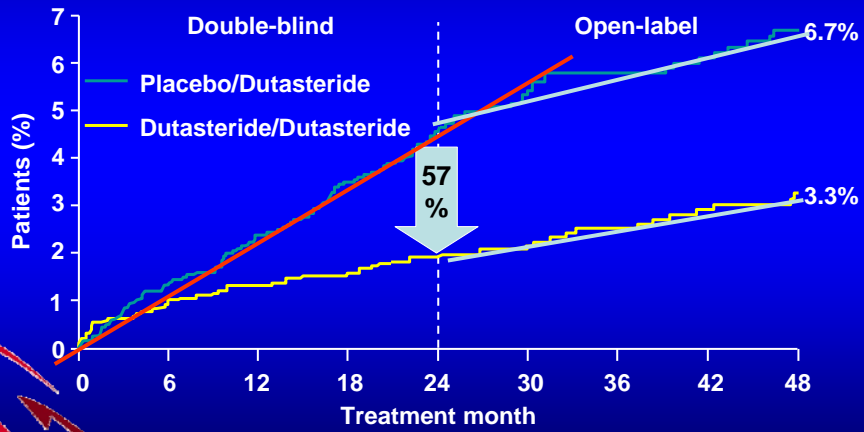
Rev Urol, 2004; 6(suppl 9): S31-S39

Mean Change in Qmax



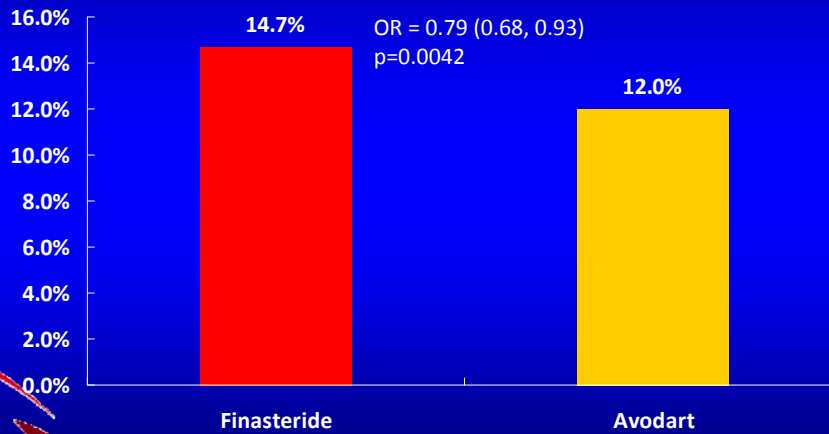
Frans et al, *European Urology* 2004; 46: 488-495

Acute Urinary Retention



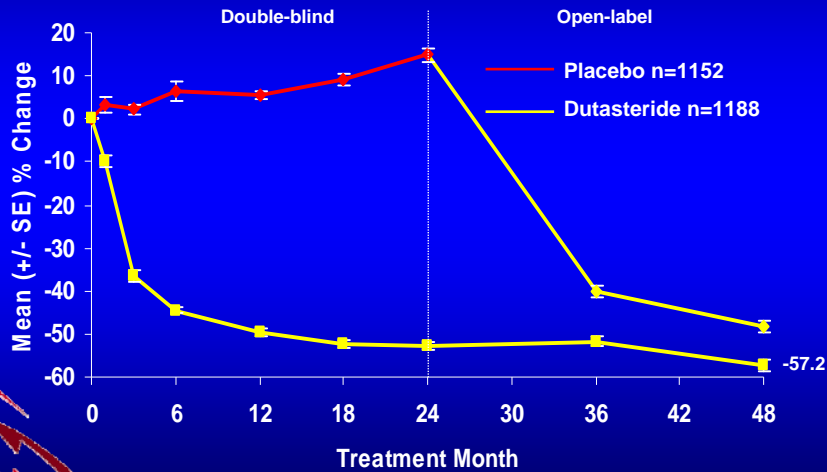
Roehrborn CG et al. *Urol* 2004; 63:709-15

Less AUR Than Finasteride



Am J Manag Care 2008; 14: S154-S159

Reduction of PSA with Avodart



Data on File GlaxoSmithKline

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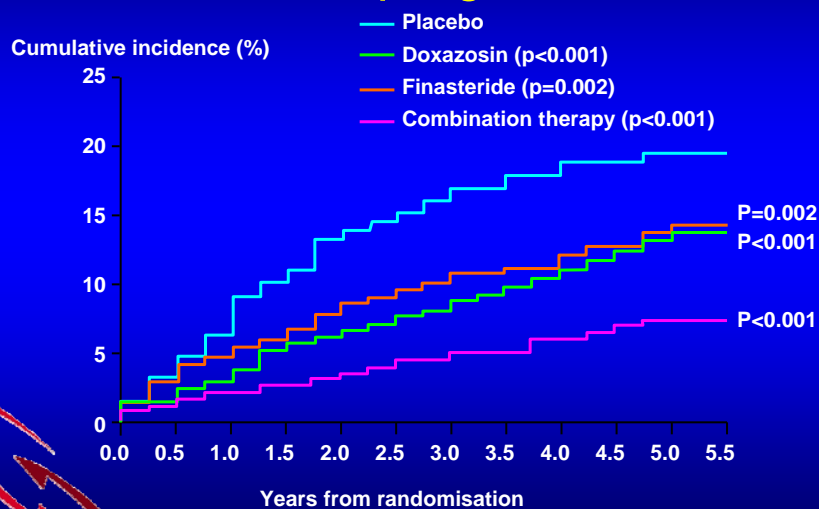
- Benign prostatic hyperplasia
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5ARIs及Alpha-Blockers藥物療效比較

	5ARIs	α -blockers
縮小攝護腺體積大小	✓	
改善症狀及尿流速	✓	✓
快速緩解症狀		✓
延緩症狀的持續惡化	✓	✓
降低急性尿滯留及BPH相關手術的機會	✓	

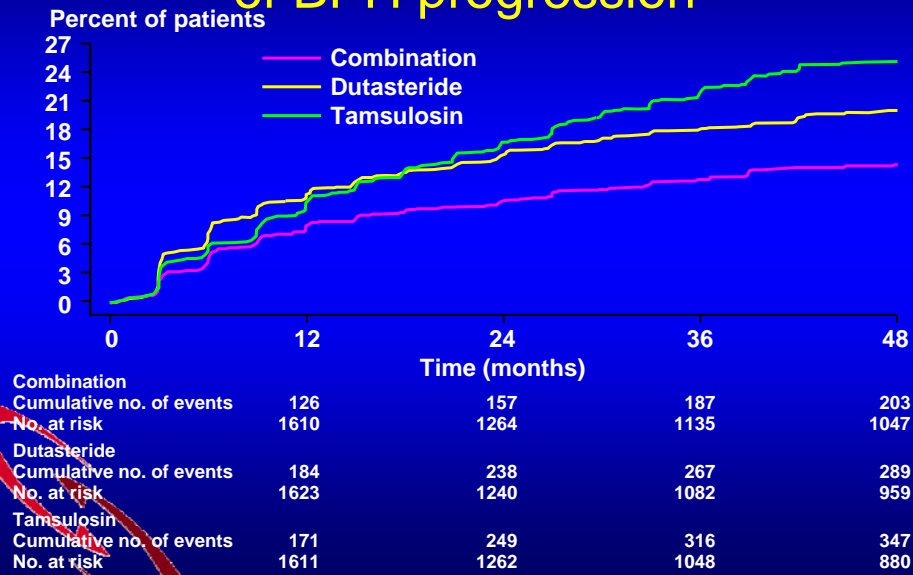
合併療法: 結合兩類藥物的優點

MTOPS: Cumulative incidence of BPH progression



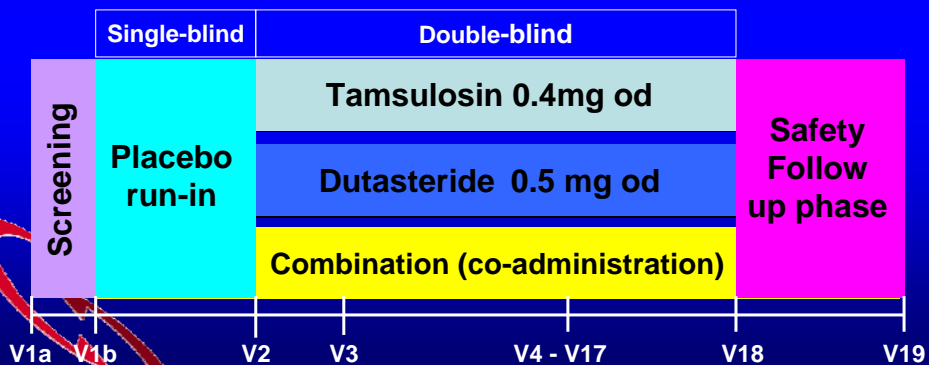
McConnell *et al.* NEJM 2003;349:2387-98

CombAT: Cumulative incidence of BPH progression



Combat Study Design

- Male age ≥ 50 years
- IPSS ≥ 12
- $1.5 \leq$ Serum PSA ≤ 10.0 ng/mL
- Minimum voided volume of ≥ 125 mL
- Diagnosis of BPH
- Prostate volume ≥ 30 cc
- $5 < Q_{max} < 15$ mL/sec



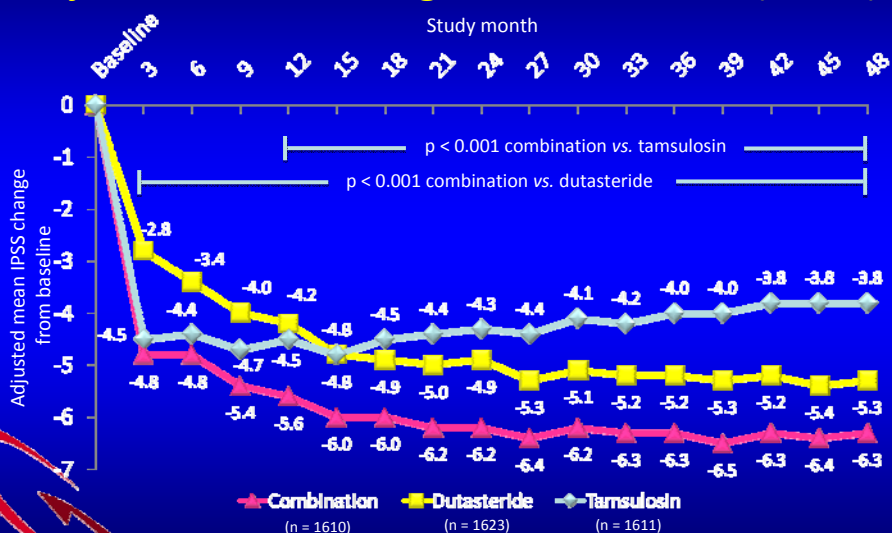
Baseline characteristics of CombAT relative to MTOPS

Mean ± S.D.	CombAT ¹ (n=4844)	MTOPS ² (n=3047)
Age (years)	66.1 ± 7.01	62.6 ± 7.3
Caucasian	4259 (88%)	2509 (82%)
Total IPSS	16.4 ± 6.16	16.9 ± 5.9
Total prostate volume (cc)	55.0 ± 23.58	36.3 ± 20.1
Serum PSA (ng/mL)	4.0 ± 2.08	2.4 ± 2.1
Qmax (mL/sec)	10.7 ± 3.62	10.5 ± 2.6
Post-void residual volume (mL)	67.7 ± 64.87	68.1 ± 82.9

¹Roehrborn *et al.* J Urol 2008;179:616–21;

²McConnell *et al.* NEJM 2003;349:2387–98

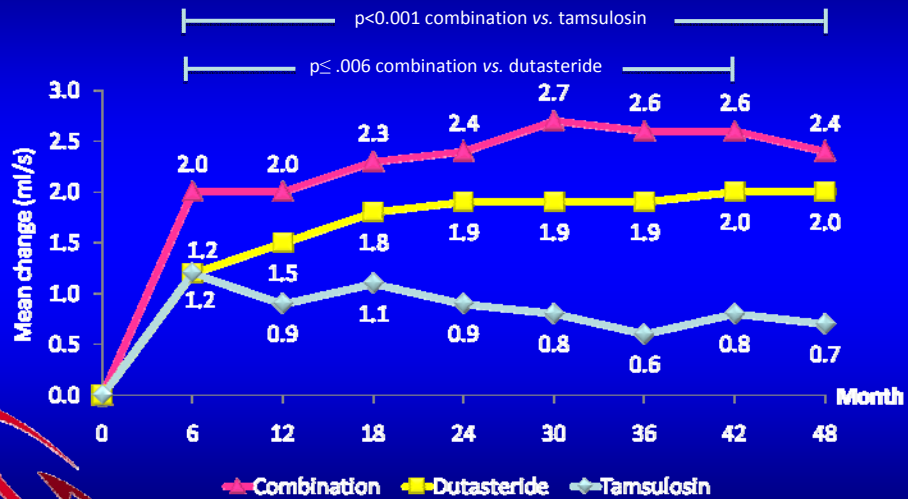
CombAT IPSS Adjusted mean change from baseline (LOCF)



Combination; dutasteride + tamsulosin

Roehrborn *et al.* In press with *Eur Urol*

CombAT Qmax Adjusted mean change from baseline (LOCF)



Roehrborn *et al.* In press with *Eur Urol*

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Incidence of Drug-Related Adverse Events Over Time

Adverse event	Placebo (n=2,158) (% of patients)				Dutasteride (n=2,167) (% of patients)			
	Study month							
	0-6	7-12	13-18	19-24	0-6	7-12	13-18	19-24
Erectile dysfunction	1.7	1.5	0.5	0.9	4.7	1.4	1.0	0.8
Decreased libido	1.4	0.6	0.2	0.1	3.0	0.7	0.3	0.3
Ejaculation disorders	0.5	0.3	0.1	0.0	1.4	0.5	0.5	0.1
Gynaecomastia	0.2	0.3	0.3	0.1	0.5	0.8	1.1	0.6

Gerald L. Andriole et al. *European Urology* 2003; 44: 82-88

Similar AE Profile with 5ARIs

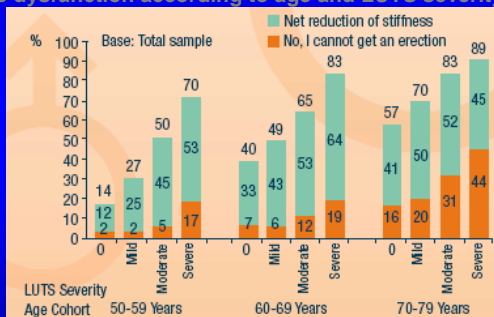
	Dutasteride 0.5mg n = 813	Finasteride 5mg n = 817
Any adverse event	17%	20%
Any sexual event	11%	14%
Impotence	7%	8%
Decreased libido	5%	6%
Ejaculatory disorder	1%	1%
Gynaecomastia	1%	1%

Rev Urol, 2004; 6(suppl 9): S31-S39

How prevalent is sexual dysfunction in men as they get older?

- Sexual dysfunction are strongly related to both **age** and the **severity of BPH symptoms**¹

Erectile dysfunction according to age and LUTS severity¹



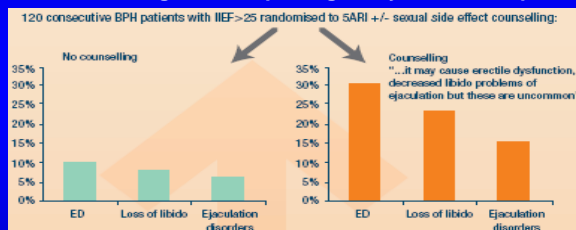
- Erection and ejaculation problems were strongly associated with **BPH symptom Severity** in each age category¹
- 50% of men of 50-59 years with moderate **LUTS** have erectile dysfunction
- Male patients who present with urinary symptoms should be carefully evaluated for the presence of sexual problems¹

¹ Rosen R et al. Eur Urol 2003;44:637-649.

The so called 'nocebo' effect may magnify the reported incidence of sexual side effects

- The incidence of **sexual side effects, erectile dysfunction, decreased libido and ejaculation disorders** was significantly increased in patients who had been counselled as to the possibility of them occurring (43.6% vs. 15.3% p=0.03)¹

Impact of counselling on AE reporting at 1-year follow-up¹



- A similar effect has been reported with β -blockers, where counselling increased the incidence of ED from 15.6% to 31.2%²
- The burden of this 'nocebo effect' has to be taken into account when managing 5AR1 sexual side-effects. The physician relationship with his/her patient is fundamental for a successful result in terms of a low incidence of sexual side-effects¹

1. Mondiani N et al. J Sex Med 2007;44:1708-1712.

2. Silvestri A et al. Eur Heart J 2003;24:1928-1932.

CombAT 4-Year drug-related adverse events occurring in $\geq 1\%$ of subjects in any treatment group

	Combination (n=1610)	Dutasteride (n=1623)	Tamsulosin (n=1611)
Erectile dysfunction	9%	7%	5%
Retrograde ejaculation	4%	<1%	1%
Altered (decreased) libido	4%	3%	2%
Ejaculation failure	3%	<1%	<1%
Semen volume decreased	2%	<1%	<1%
Loss of libido	2%	1%	1%
Dizziness	2%	<1%	2%
Gynecomastia	2%	2%	<1%
Nipple pain	1%	<1%	<1%
Breast tenderness	1%	1%	<1%

Pharmacokinetic Parameters

- Absorption
 - Tmax: 2-3 hr
 - Bioavailability: 60%
 - Absorption reduced by 10-15% when taken with food, not clinically significant
- Distribution
 - Large volume of distribution: 300-500 L
 - Highly protein bound (99%)
 - 6 months to steady state
- Metabolism
 - Extensively metabolised in the liver
- Excretion
 - Elimination half-life: ~ 5 weeks
 - Metabolites excreted in faeces, < 1% in urine

1 Avodart® UK SPC

2 Avodart® USA prescribing information

Dosage Adjustment in Special Populations

- Elderly
 - no dosage adjustment necessary
- Renal impairment
 - no dosage adjustment necessary
- Hepatic impairment
 - caution

1 Avodart® UK SPC

2 Avodart® USA prescribing information

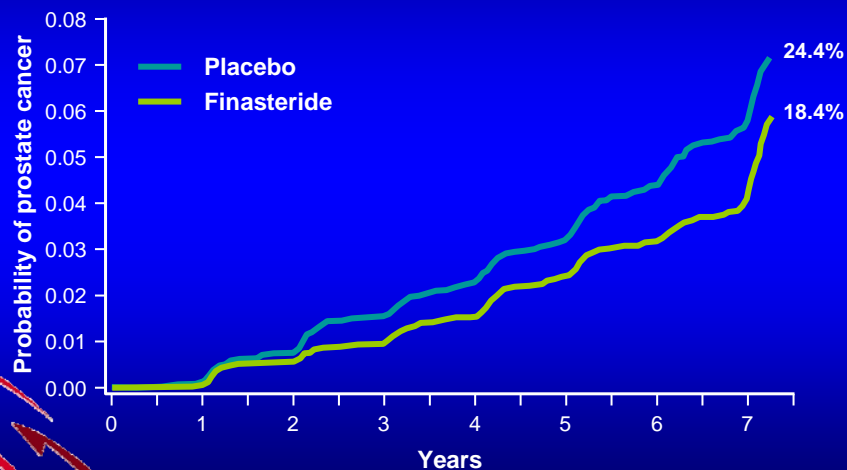
使用5ARI之健保相關規定

1. 限良性前列腺肥大且有阻塞症狀，經直腸超音波前列腺掃描(TRUS of prostate)測量前列腺大於20公克或最大尿流速(Qmax)小於15mL/sec之病人，前列腺特異抗原(PSA)高於正常值之病人，需經病理診斷無前列腺癌方可使用
2. 服藥後第一年，每半年需作直腸超音波前列腺掃描或尿流速儀(uroflow-metry)檢查，需證明前列腺有縮小或尿流速有增加，方得繼續使用

Contents

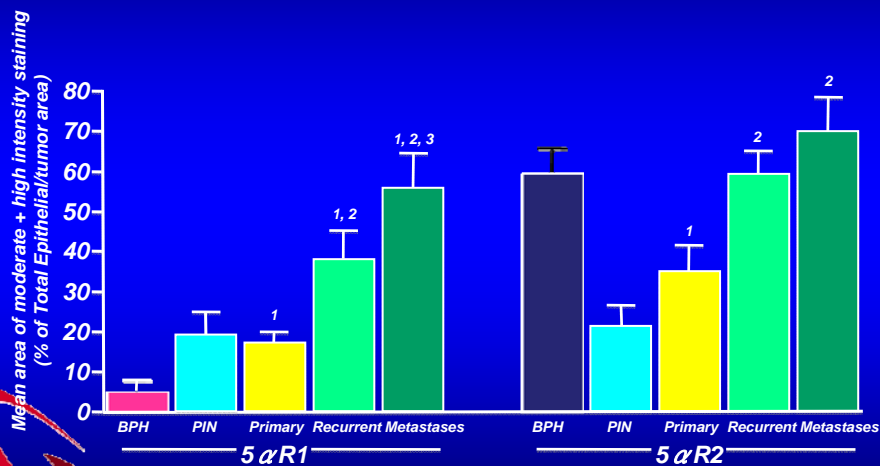
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Finasteride Reduced the Incidence of Prostate Cancer



Ian M. Thompson et al, *the New England Journal of Medicine* 2003; 349(3): 215-224

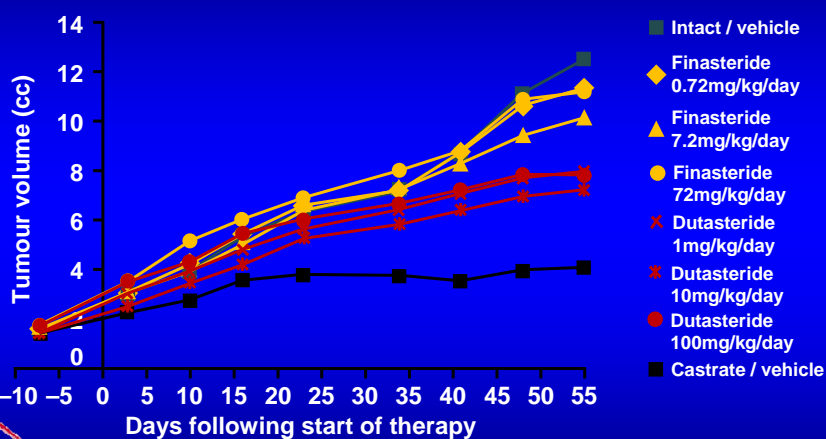
5AR-1 and 5AR-2 Levels Increase as PCa Progresses



¹Significantly different from BPH
²Significantly different from PIN, Primary
³Significantly different from Recurrent

Thomas et al. Prostate 2005;63:231.

Inhibition of PCa growth in a rat model with dutasteride



Dutasteride inhibits PCa growth to a greater extent than finasteride but not as much as castration

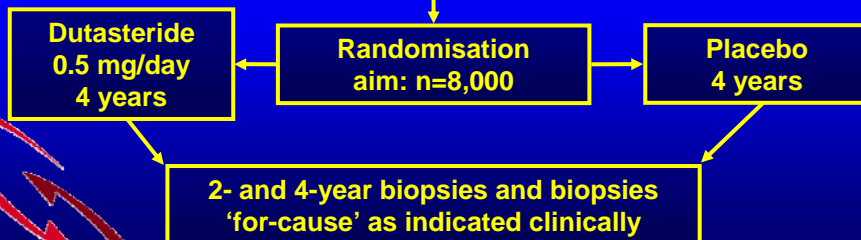
Xu Y, et al. 2006

REduction by DUtasteride of prostate Cancer Events (REDUCE) Study

Men aged 50–75 years with:

- One negative prostate biopsy within 6 months of study entry
- PSA ≥ 2.5 and ≤ 10 ng/mL
- IPSS < 25 and $Q_{max} \geq 5$ mL/sec
- Prostate volume ≤ 80 mL

1 month placebo run-in



Gerald Andriole et al, *The Journal of Urology* 2004; 172: 1314-1317

Differences Between PCPT and REDUCE

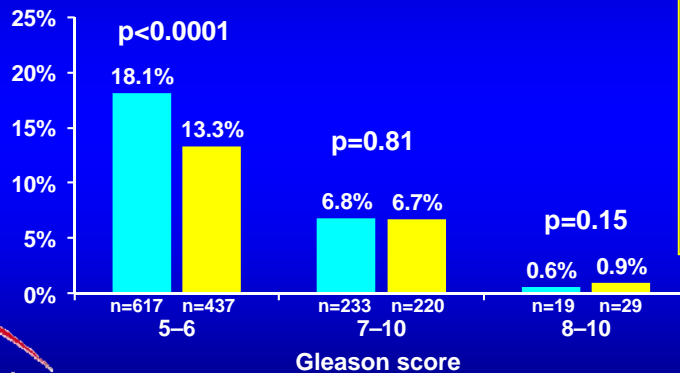
	PCPT	REDUCE
Duration (yrs)	7	4
Number	18882	8250
Location	USA	International
Age (yrs)	≥ 55	50-75
PSA @ Entry	≤ 3	2.5-10
5-AR Inhib.	Type 2	Types 1 and 2
Baseline Biopsy	No	Yes
# F/up Bx.	1 (FC or 7 yr)	2 protocol; FC
# Cores/Bx	6	10
PSA @ baseline	1.1	5.9
% Bx FC	39	12
%CaP @ FC	52	10

REDUCE: Primary endpoint

Dutasteride reduced
the risk of prostate
cancer over 4 years by
23%
 $p < 0.0001$
(857 placebo vs
659 dutasteride)

REDUCE: Gleason score distribution

Proportion of men



No
significant
increase in
high-grade
tumors
over 4
years

■ Placebo group (n=3406) ■ Dutasteride group (n=3298)

Maintenance of Prostate Health

Reduce progression

Progressive benign prostatic enlargement

Symptom relief

Reduce risk

Reduce progression

Slow progression

Prostate cancer

Normal

PIN

Histological
PCa

Localised
PCa

Advanced
PCa

Metastatic
PCa

Summary of Dutasteride vs Finasteride

	Dutasteride (0.5mg)	Finasteride (5mg)
5AR inhibition	Type 1 and 2	Type 2 only
% of DHT inhibition	93%	70%
Half-life	5 weeks	6 to 8 hours
Prostate size reduction	-25.7% (2 y) -27.3% (4 y)	-18% (4 y, PLESS) -16% (4.5 y, MTOPS)
Urinary Flow Improvement	2.2 mL/sec (2 y) 2.7 mL/sec (4 y)	1.7 mL/sec (4 y, PLESS) 2.2 mL/sec (4.5 y, MTOPS)
Improvement in symptoms	-4.4 (2 y) -6.5 (4 y)	-3.3 (4 y, PLESS) -5.0 (4.5 y, MTOPS)
% Reduction in AUR	57% (2 y)	57% (4 y, PLESS) 79% (4.5 y, MTOPS)
% Reduction in surgery	48% (2 y)	55% (4 y, PLESS) 69% (4.5 y, MTOPS)