La terapia medica dell'IPB

IPB è una malattia che progredisce nel tempo

- Olmsted County study: IPSS + 0,34/anno
- PLESS : 7% AUR in 4 anni
- MTOPS: 18 % Progressione

Componente prostatica ➡ effetto massa

Componente vescicale ➡ deterioramento funzionale

Progressione dell' IPB

- Incidenza di ritenzione urinaria acuta
- Incidenza di chirurgia IPB-correlata

Fattori di rischio di progressione

Età:	**>62 anni ***
PSA:	**> 1,6 ng/mL ***
TRUS:	**> 31 mL ***
Qmax:	<10,6 mL/sec
AUASS:	>17
PVR:	>39 mL

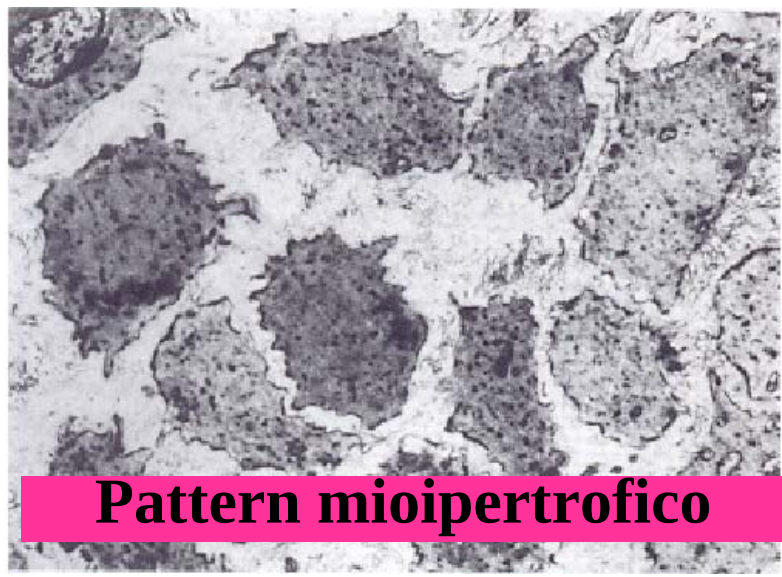
* p< 0,05

MTOPS

Alterazioni morfologiche del detrusore in pazienti ostruiti

Detrusore normale

BPH



Pattern mioipertrofico

"Ipertrofia cellulare"
"Spazi intercellulari più ampi"
"Incrementato deposito di collagene"

Elbadawi et al.J Urol 150: 1681, 1993

Terapia medica EBM

AUA/EAU guidelines

α1-litici

Alfu-tera-doxa-tamsulo

Inibitori 5α-reduttasi

Finasteride-Dutasteride

Terapia di combinazione

α1-litici + I5AR

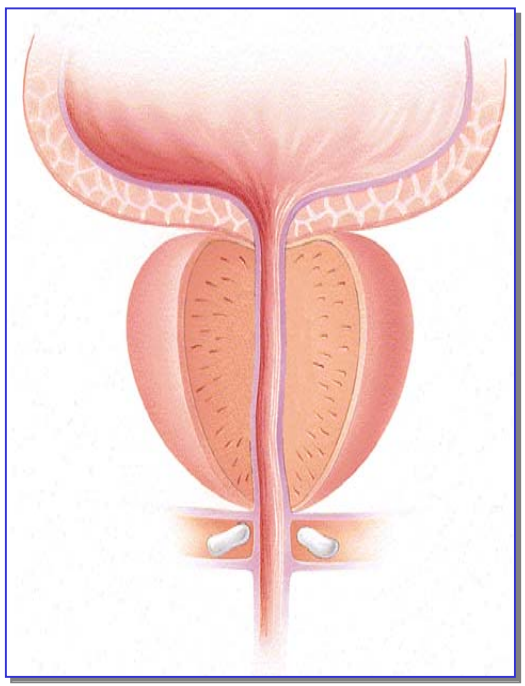
MTOPS

Medical Therapy

Two-Drug Therapy Activates Two Distinct and Complementary Mechanisms of Action

Alpha blockers

Improve symptoms and increase urinary flow rate by relaxing prostatic and bladder-neck smooth muscle through sympathetic activity blockade



5-Alpha reductase inhibitors

Improve symptoms, increase urinary flow rate, and prevent BPH outcomes by reducing prostate enlargement through hormonal mechanisms

Adapted from Roehrborn CG *Curr Opin Urol* 2001;11:17-25; National Cancer Institute. NIH Publication No. 99-4303, 1999.

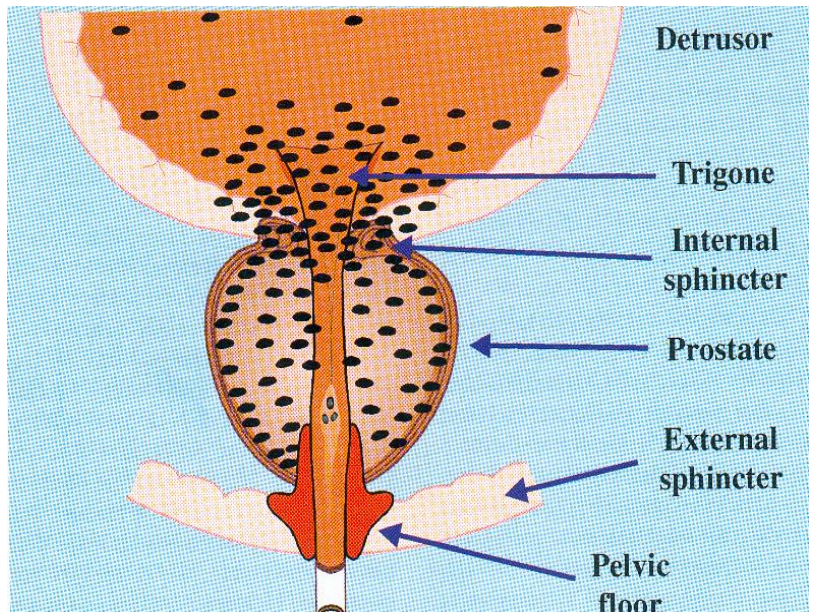
Alfa-litici

Alfa-litici

TRIALS

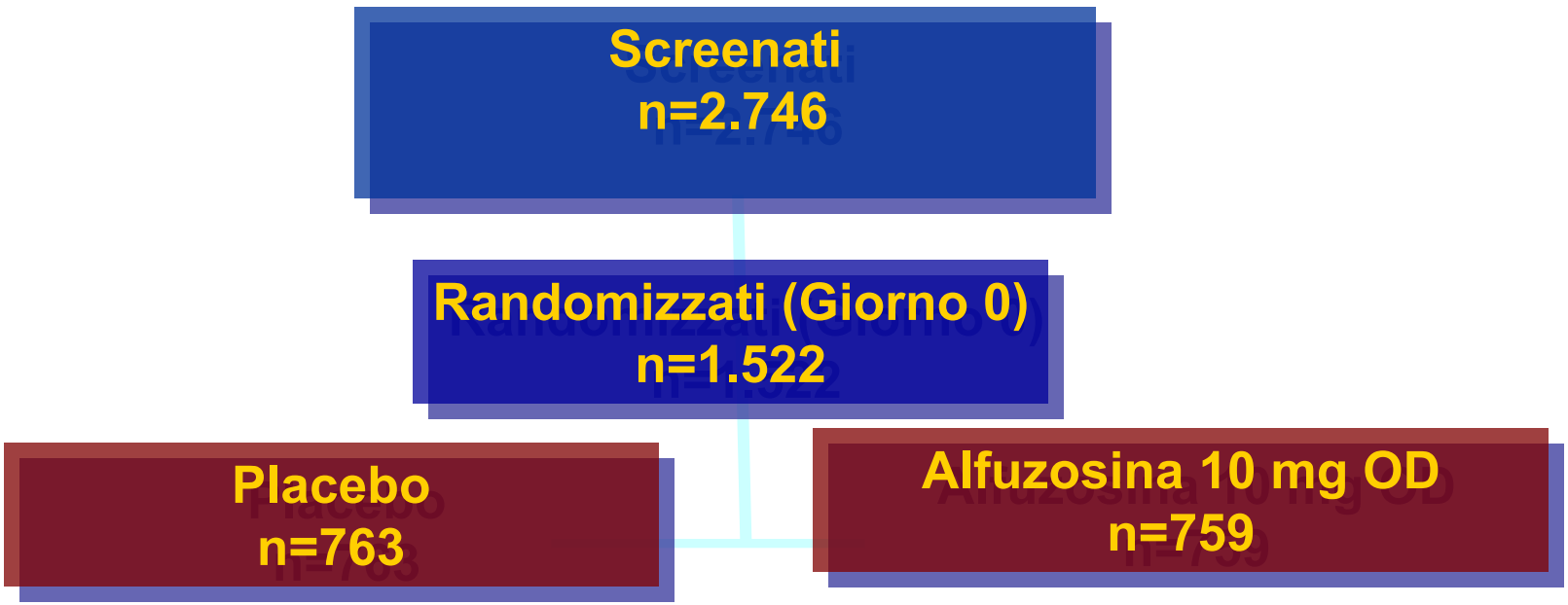
- Roehborn et al *Urology 1996*
  - *TERAZOSIN VS PLACEBO*
- McNeil et al. *BJU Int 1999*
  - *ALFUZOSIN VS PLACEBO*
- Chapple et al. *Curr Opin Urol 2001*
  - *ALFUZOSIN VS PLACEBO*
- Djavan et al. *Urology 2004*
- Roehborn et al *BJU Int 2006 ALTESS*
  - *ALFUZOSIN VS PLACEBO*

Distribuzione dei recettori α1 nelle basse vie urinarie



Studio ALTESS

Reclutamento e randomizzazione

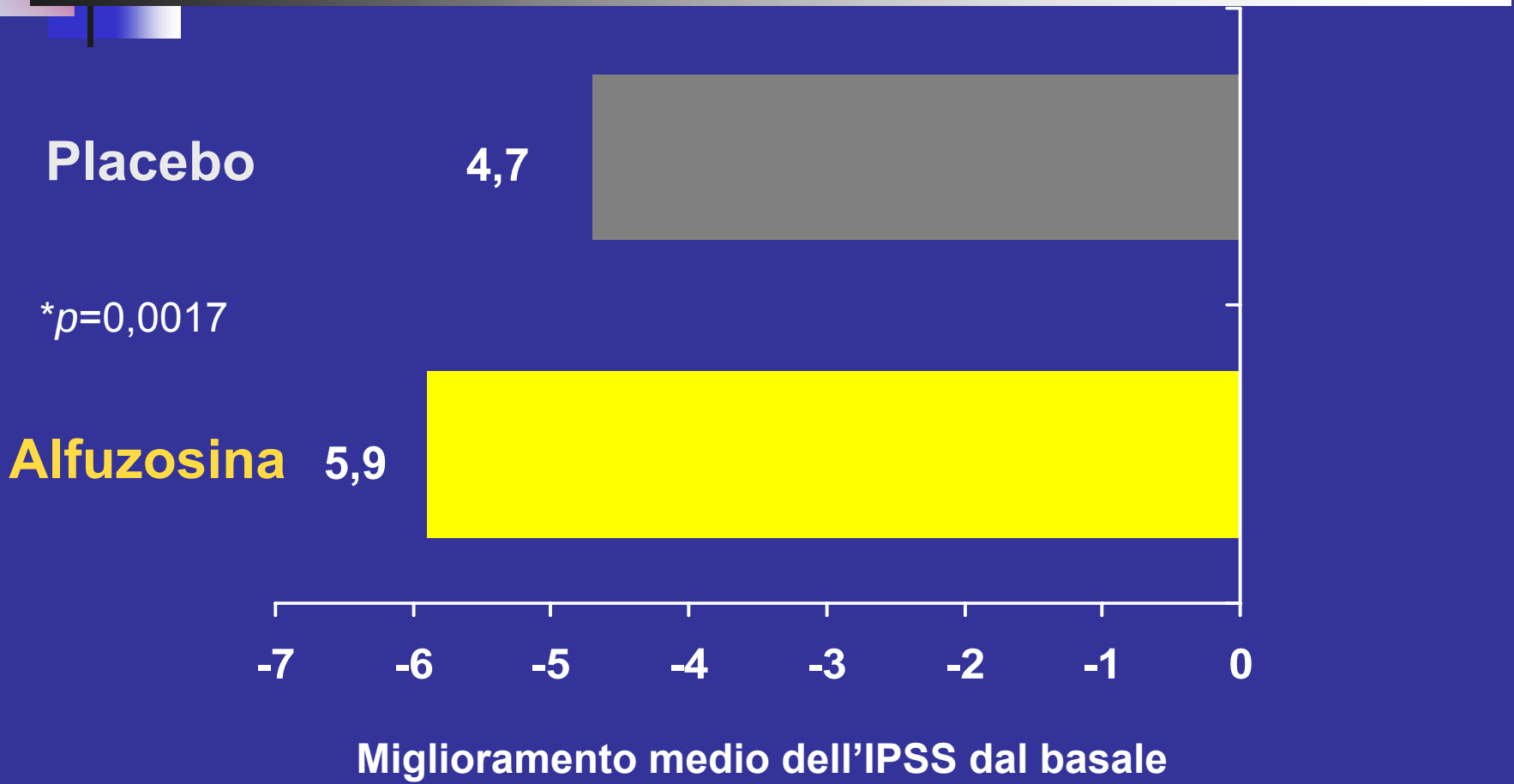


Follow up: 2 anni

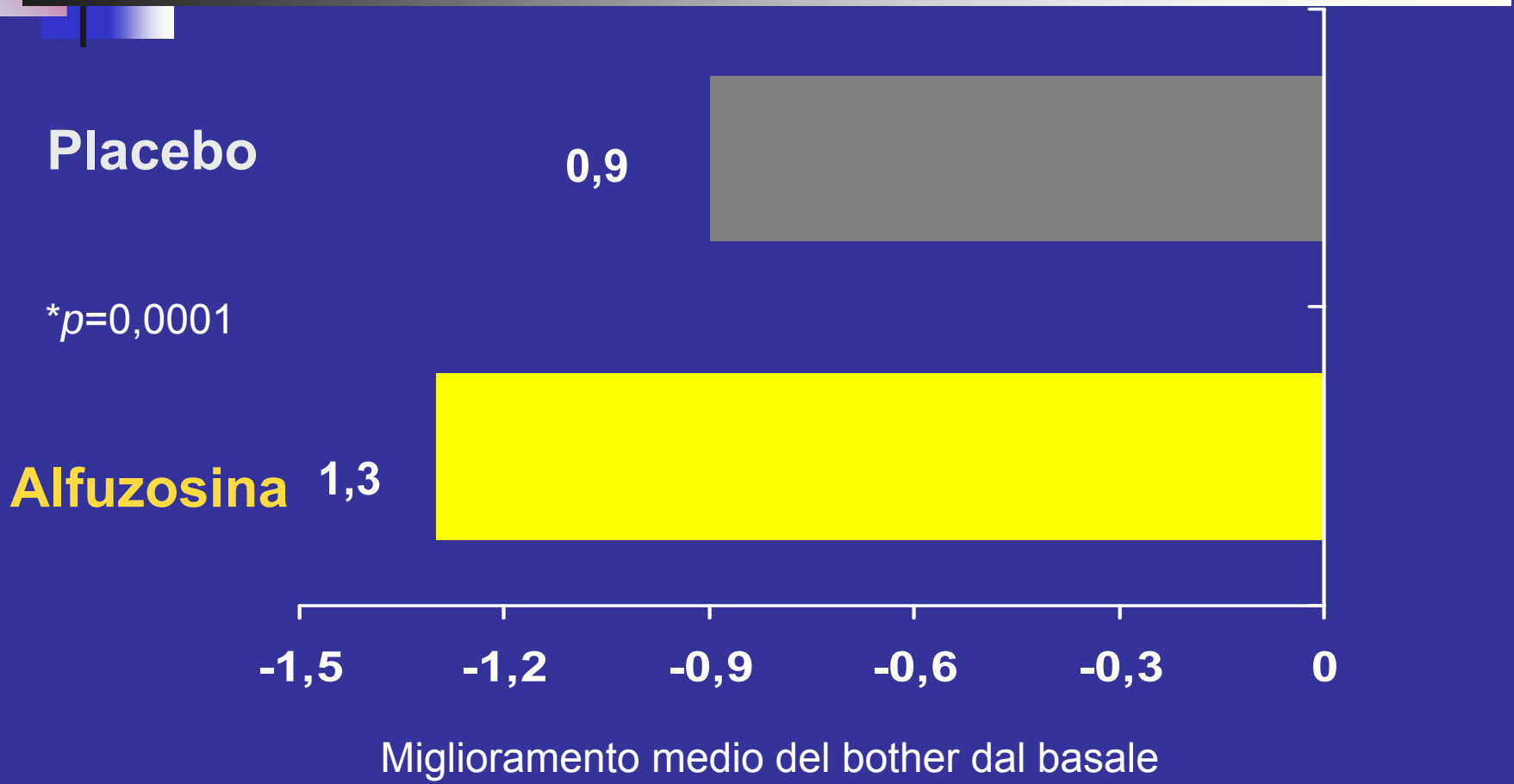
Roehrborn CG et al. BJU Int 2006;97:734-741

Studio ALTESS

Miglioramento dell'IPSS su 2 anni

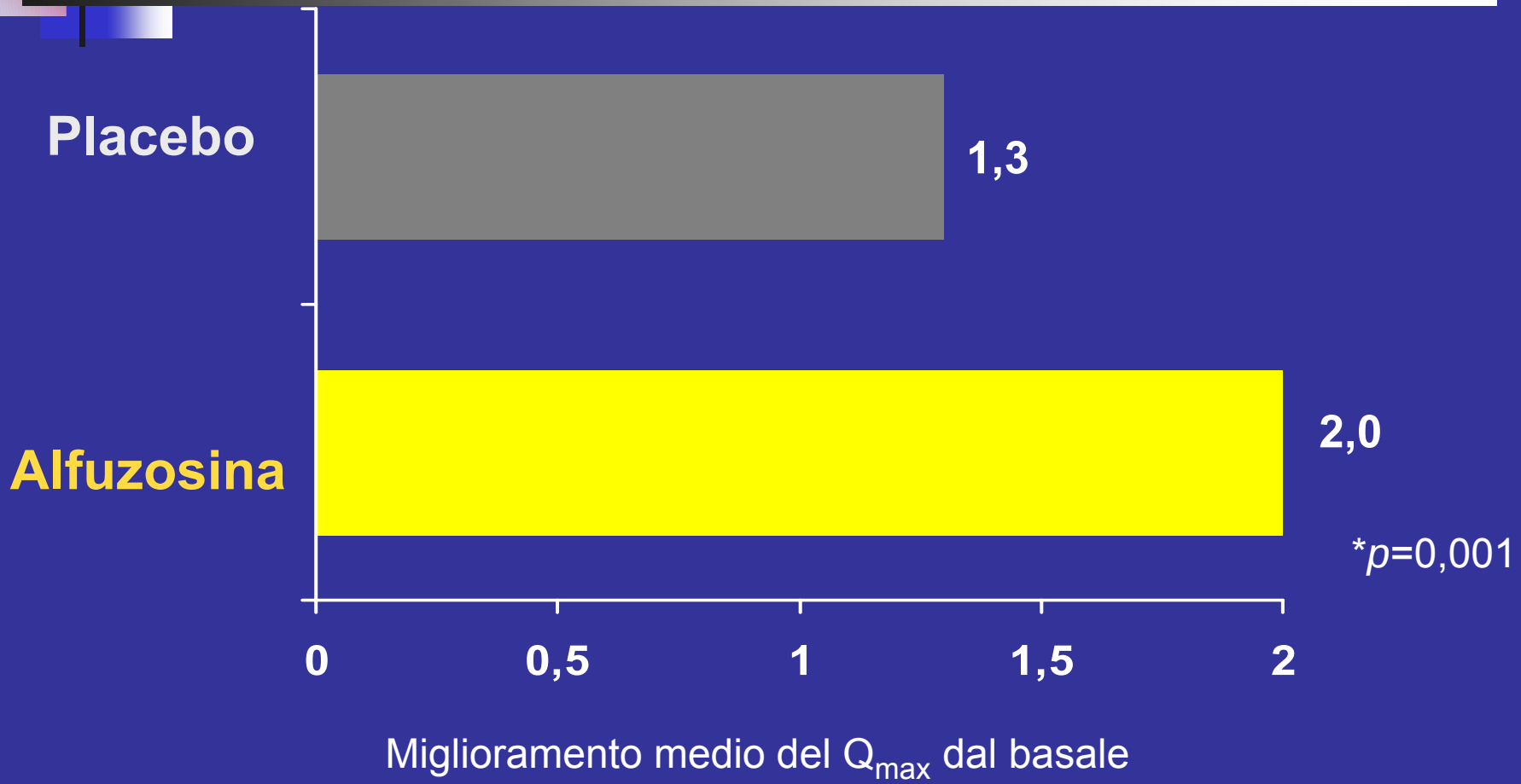


Studio ALTESS
Miglioramento della QoL su 2 anni



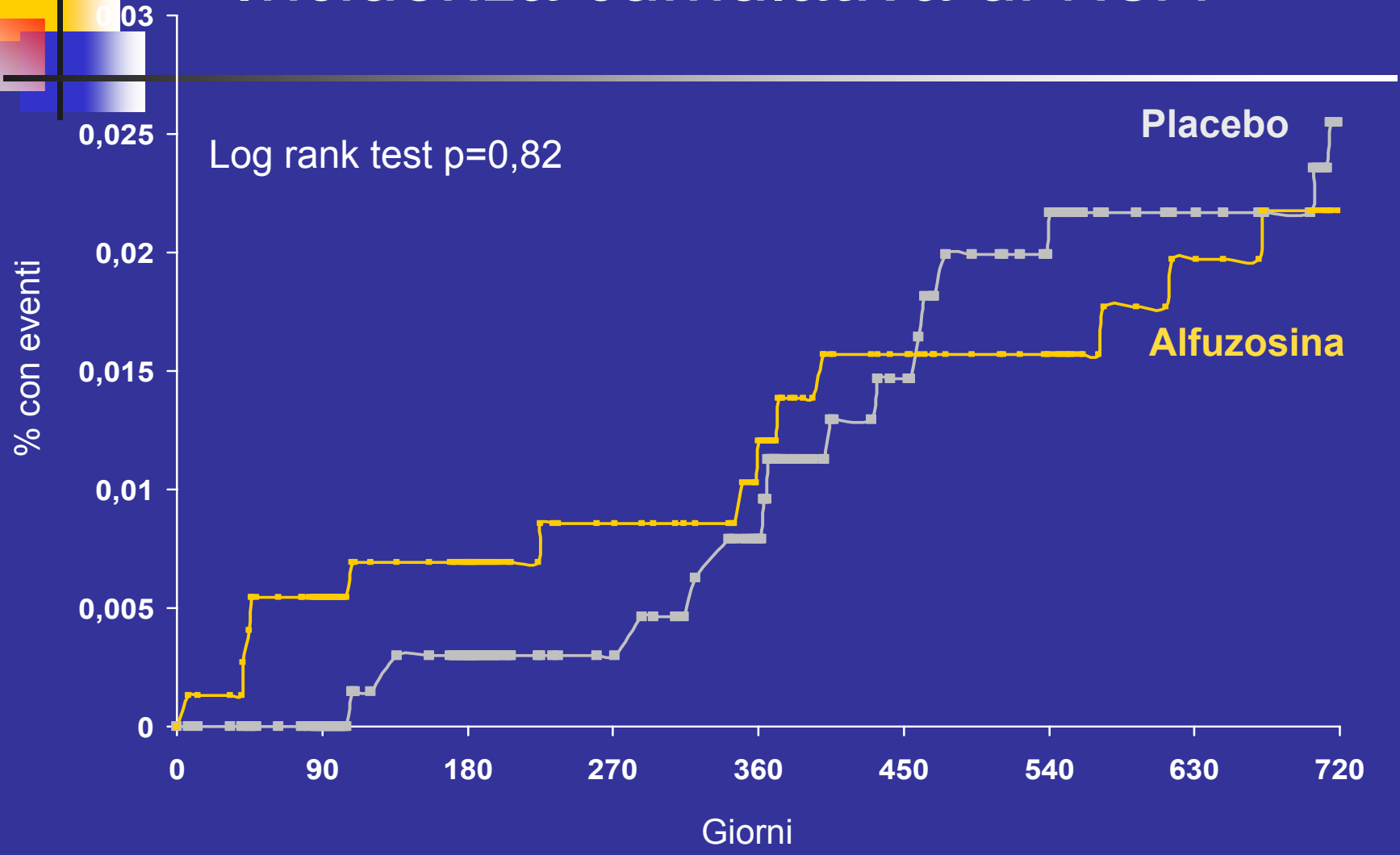
Studio ALTESS

Miglioramento del Q_{max} (Mese 12)



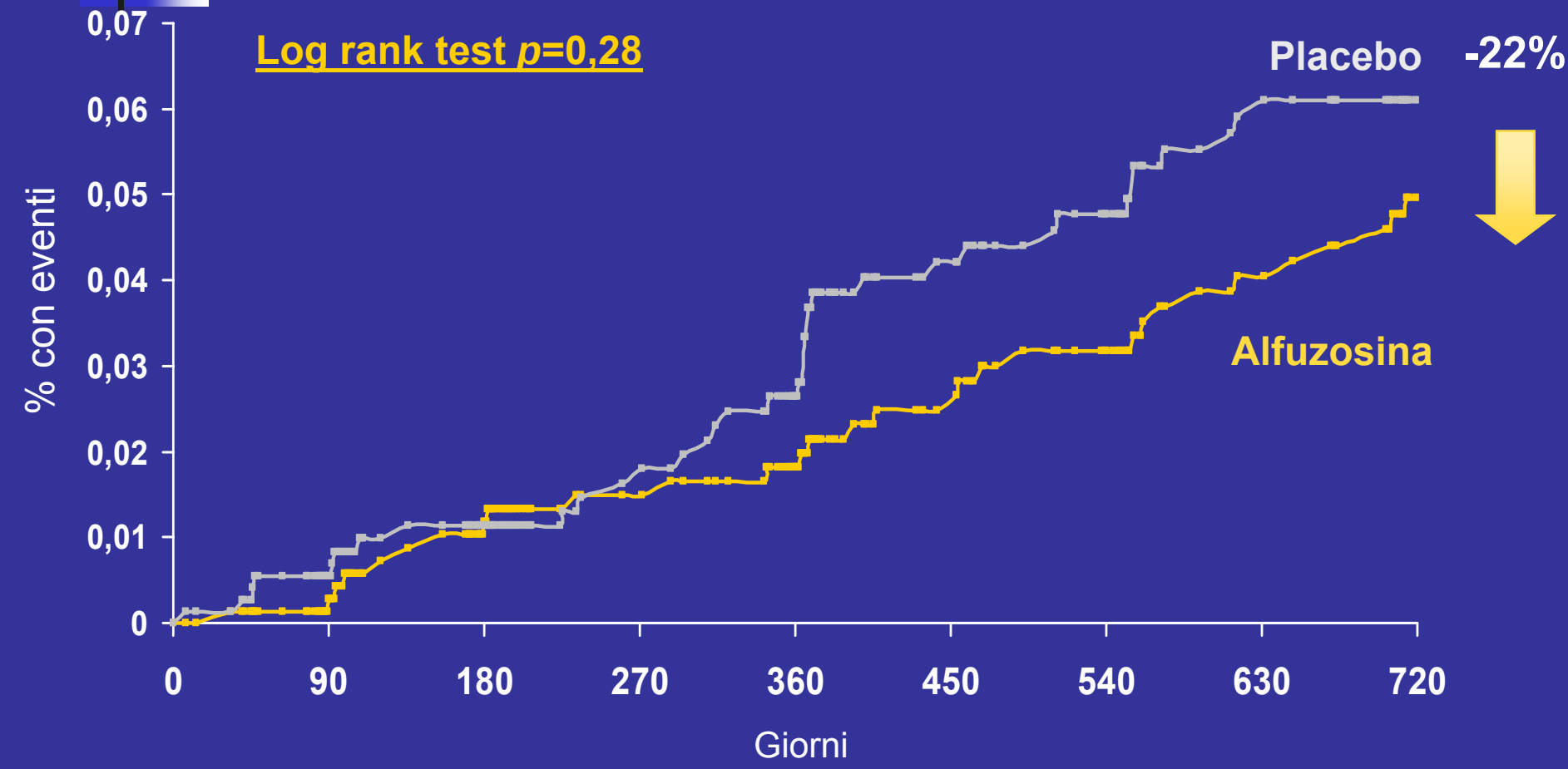
Studio ALTESS

Incidenza cumulativa di RUA



Studio ALTESS

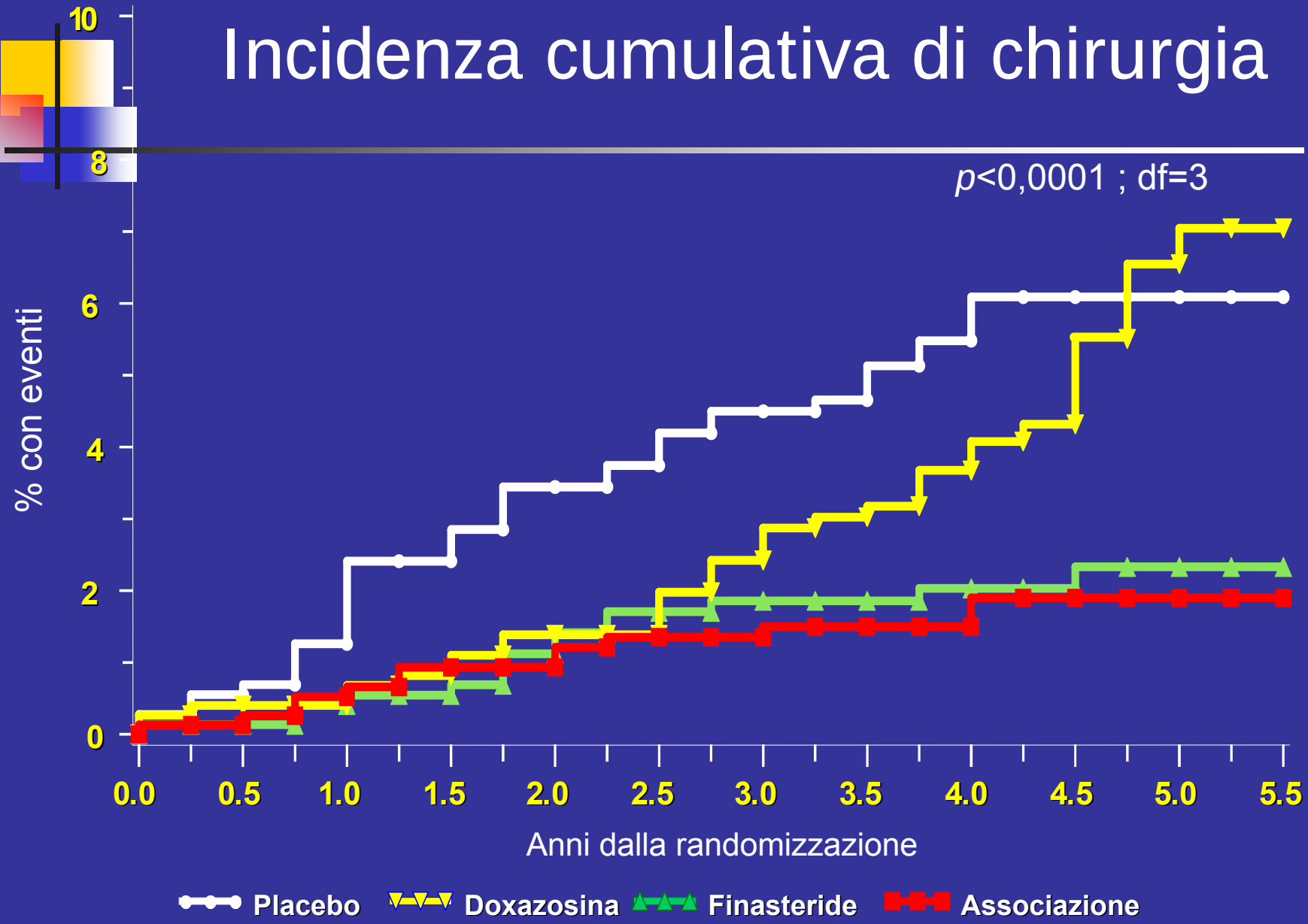
Incidenza cumulativa di chirurgia



Roehrborn CG et al. BJU Int 2006; 97:734-741

Studio MTOPS

Incidenza cumulativa di chirurgia



Quale alpha-litico ?

EAU Guidelines 2007

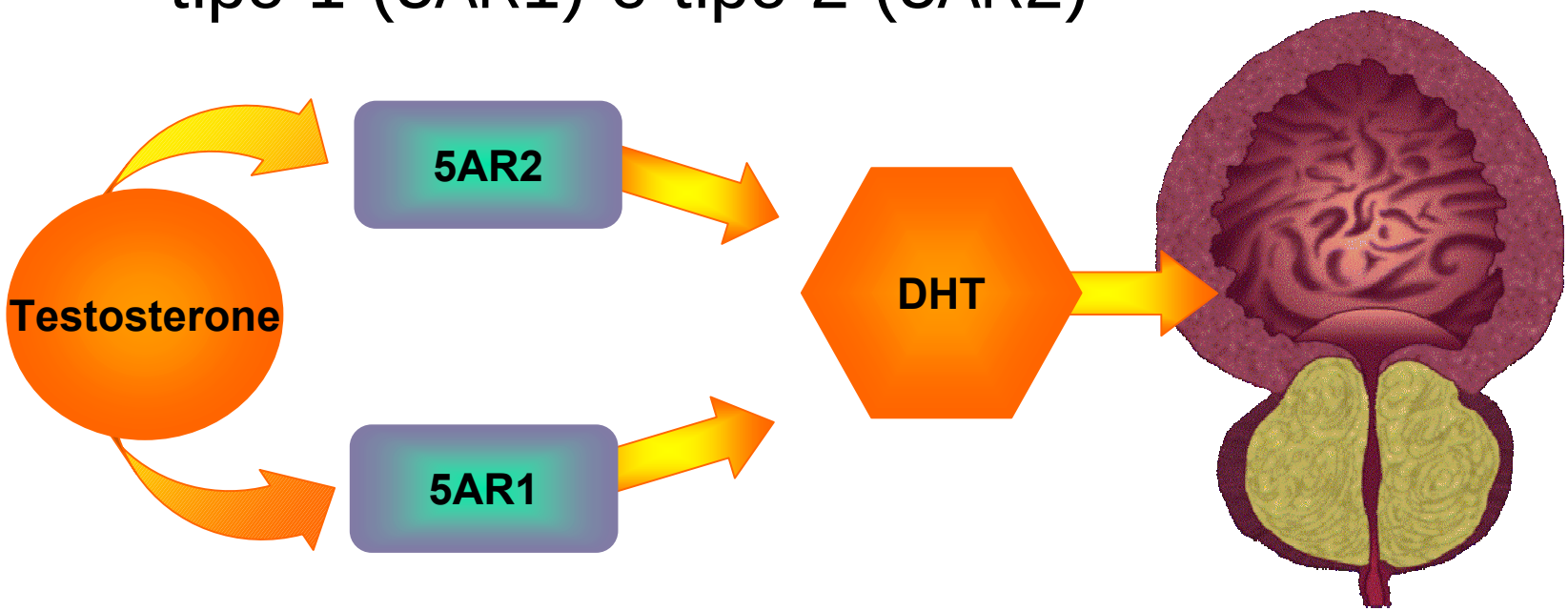
- *There is no difference between different alpha-blockers (tamsulosin, doxazosin, terazosin, alfuzosin) in terms of efficacy*

- *Altough the side-effect profiles for some drugs are reported to be more favourable, supportive data are weak*

Inibitori 5 alpha-reduttasi

Ruolo dei 5ARI

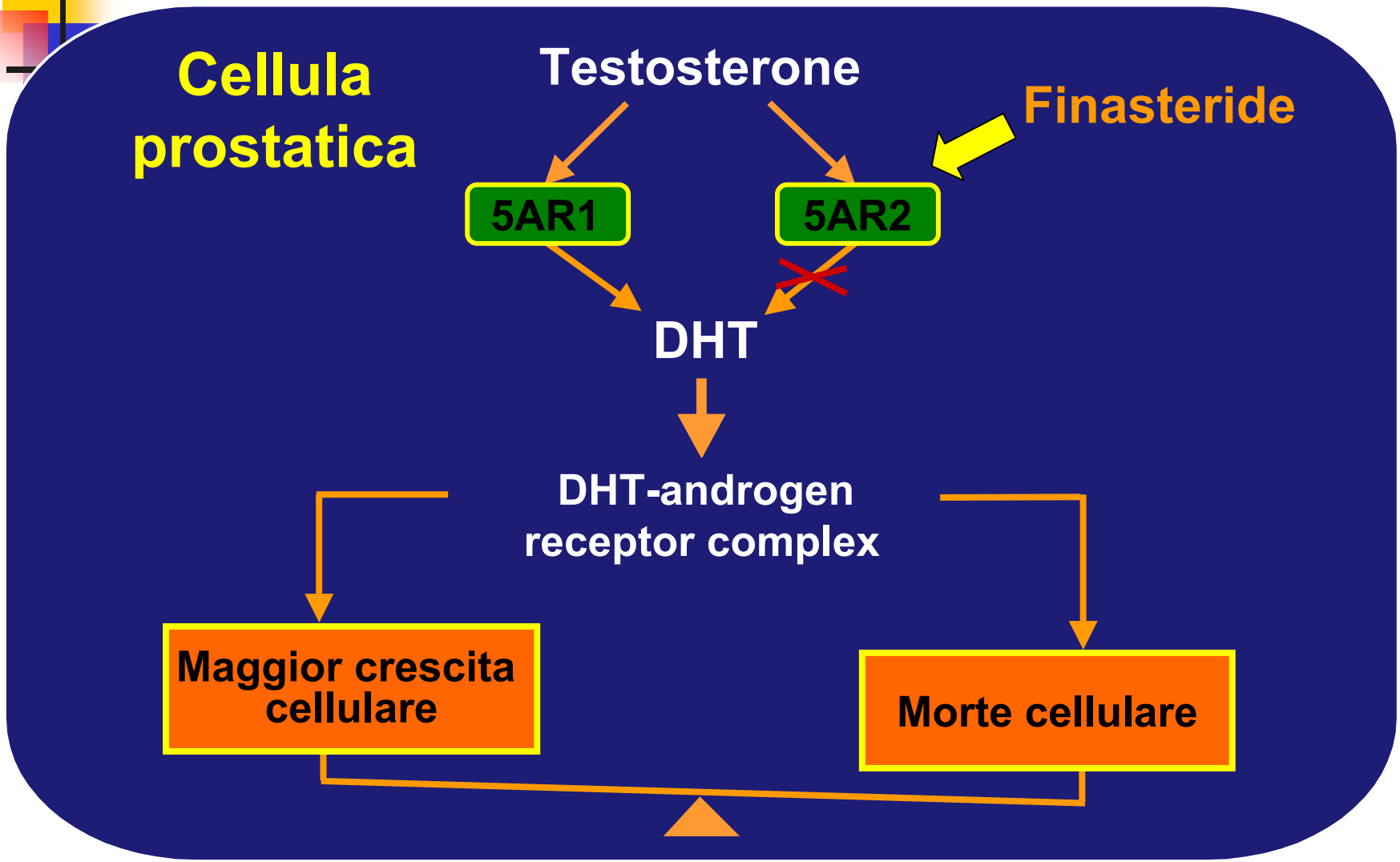
- La 5α-reduttasi (5AR) esiste in 2 isoenzimi: tipo 1 (5AR1) e tipo 2 (5AR2)



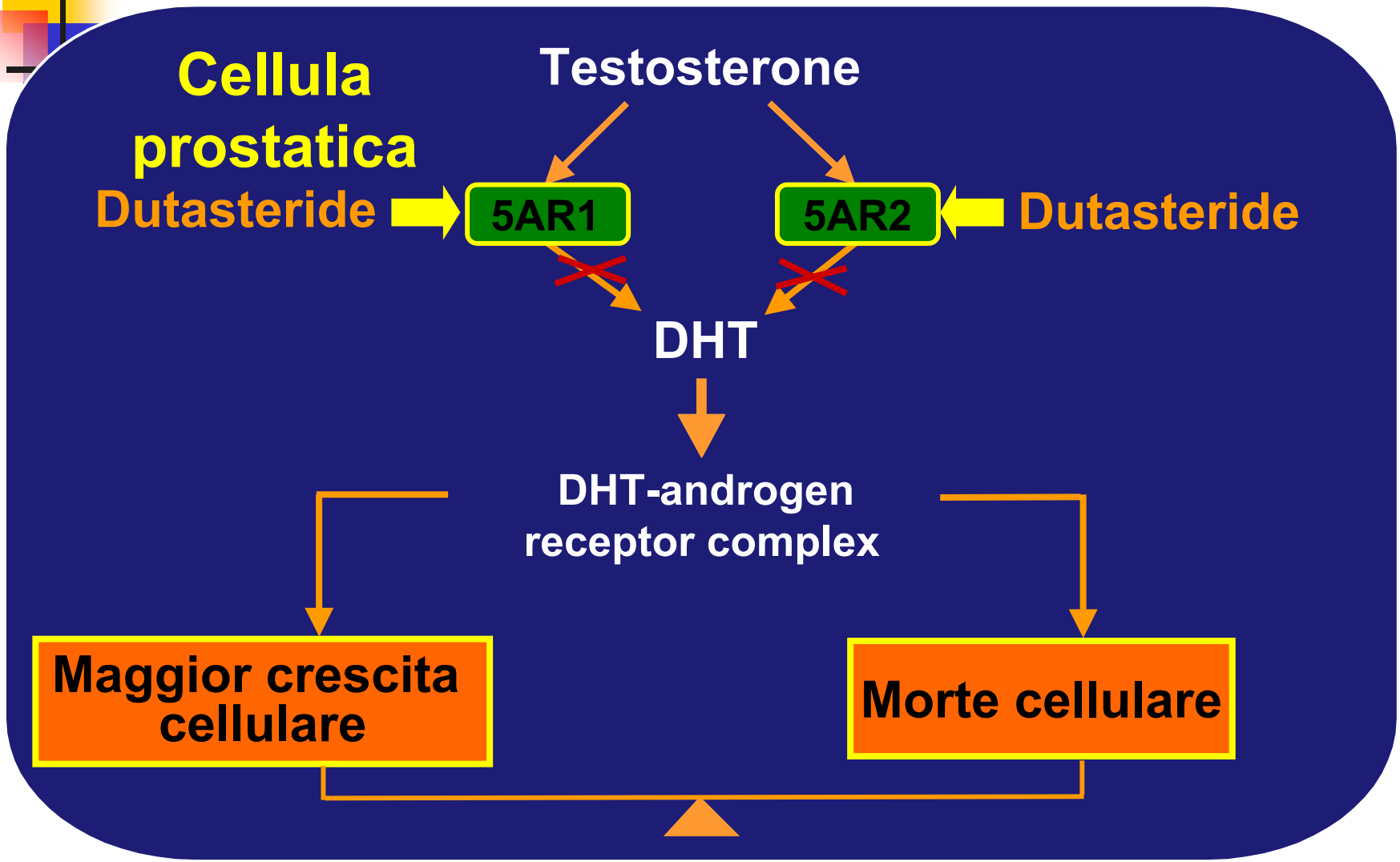
Ingrossamento della prostata

Russell et al. Annu Rev Biochem 1994;63:25–61

Meccanismo d'azione della finasteride



Meccanismo d’azione della dutasteride



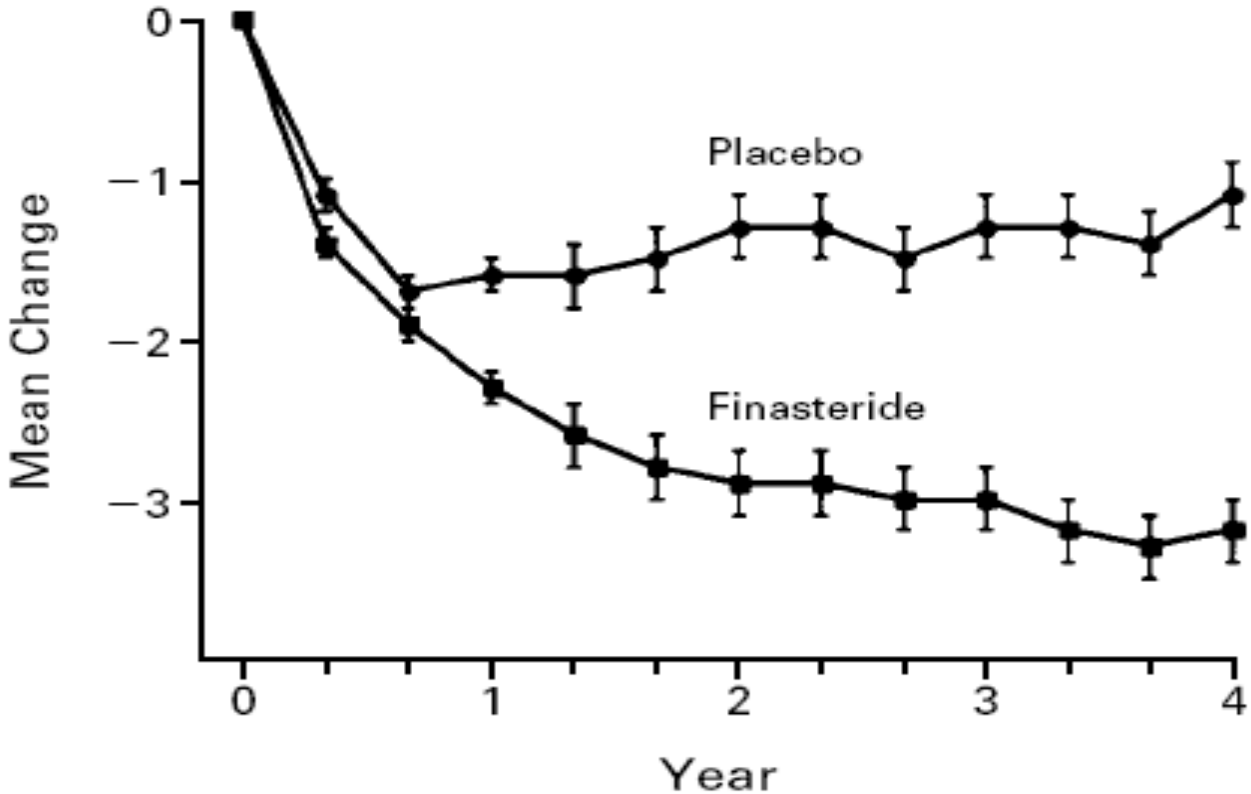
5ARI trials

- Andersen et al. *Urology 1995*
- Lepor et al. *N Engl J Med 1996*
- Nickel et al. *CMAJ 1996 PROSPECT*
- McConnell et al *N Engl J Med 1998 PLESS*
- Lowe et al. *Urology 2003*

"The effect of *FINASTERIDE* on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia"

PLESS study

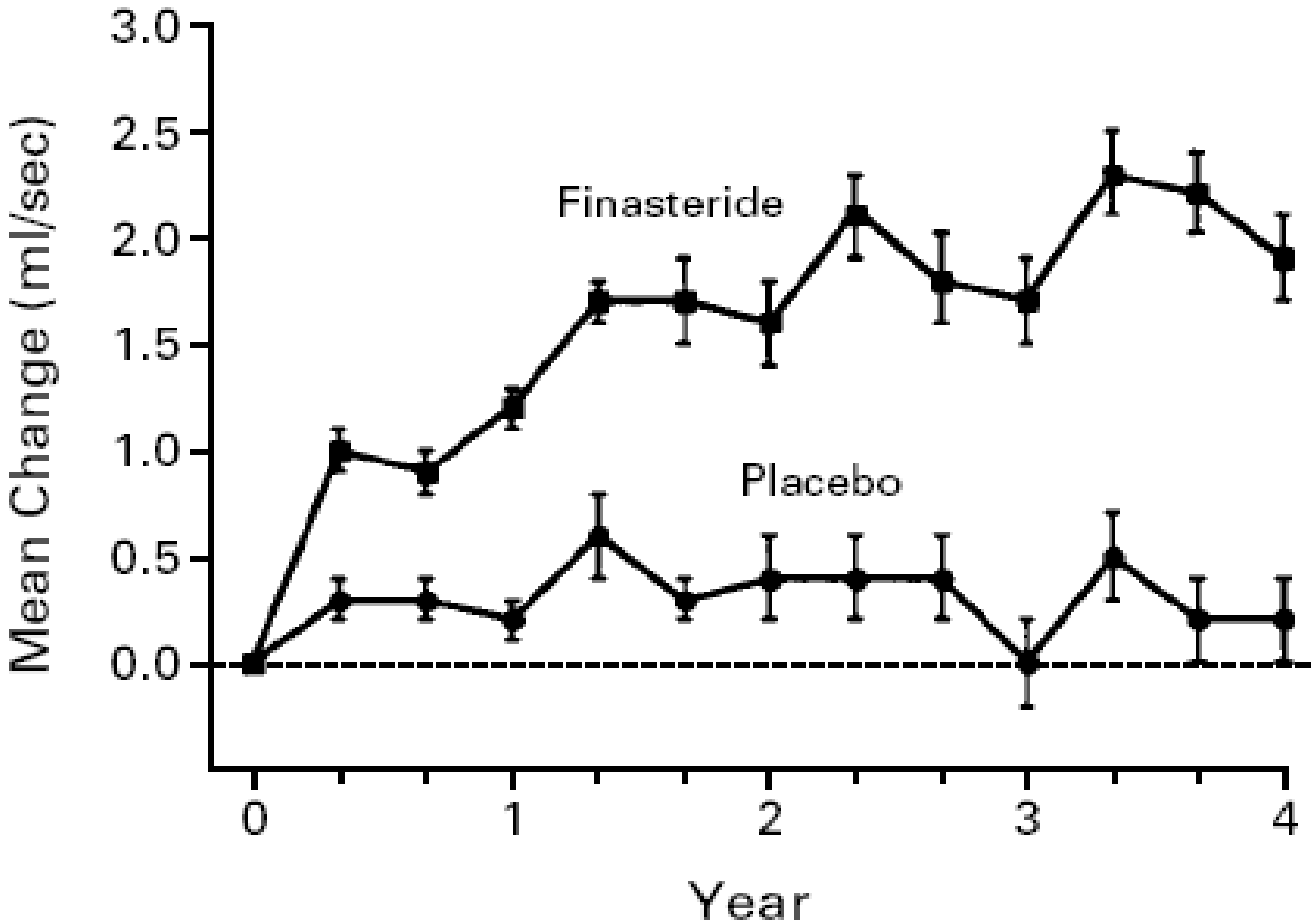
Symptom score



McConnell et al N Engl J Med 1998

PLESS study

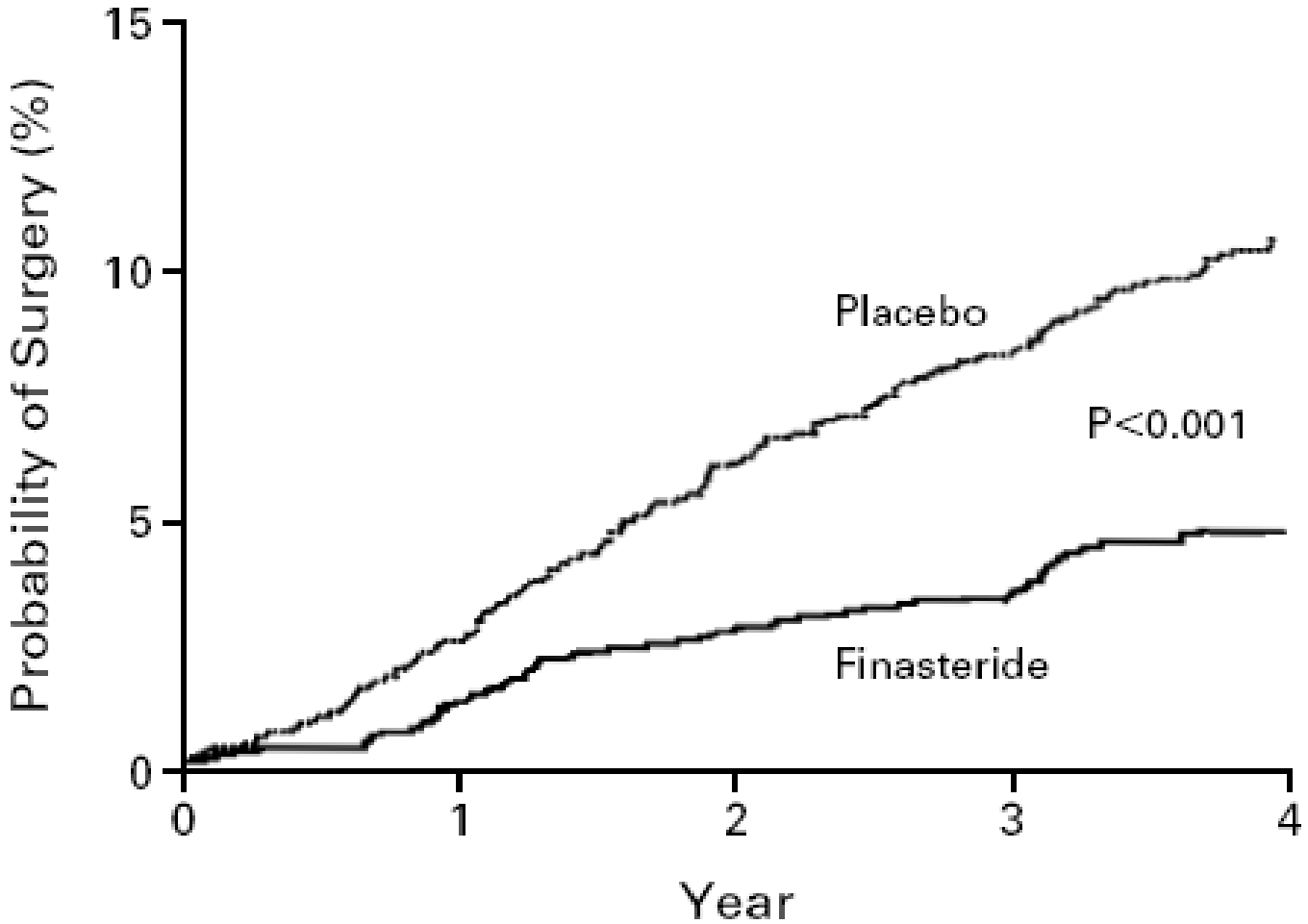
Maximal Urinary Flow Rate



N Engl J Med 1998

PLESS study

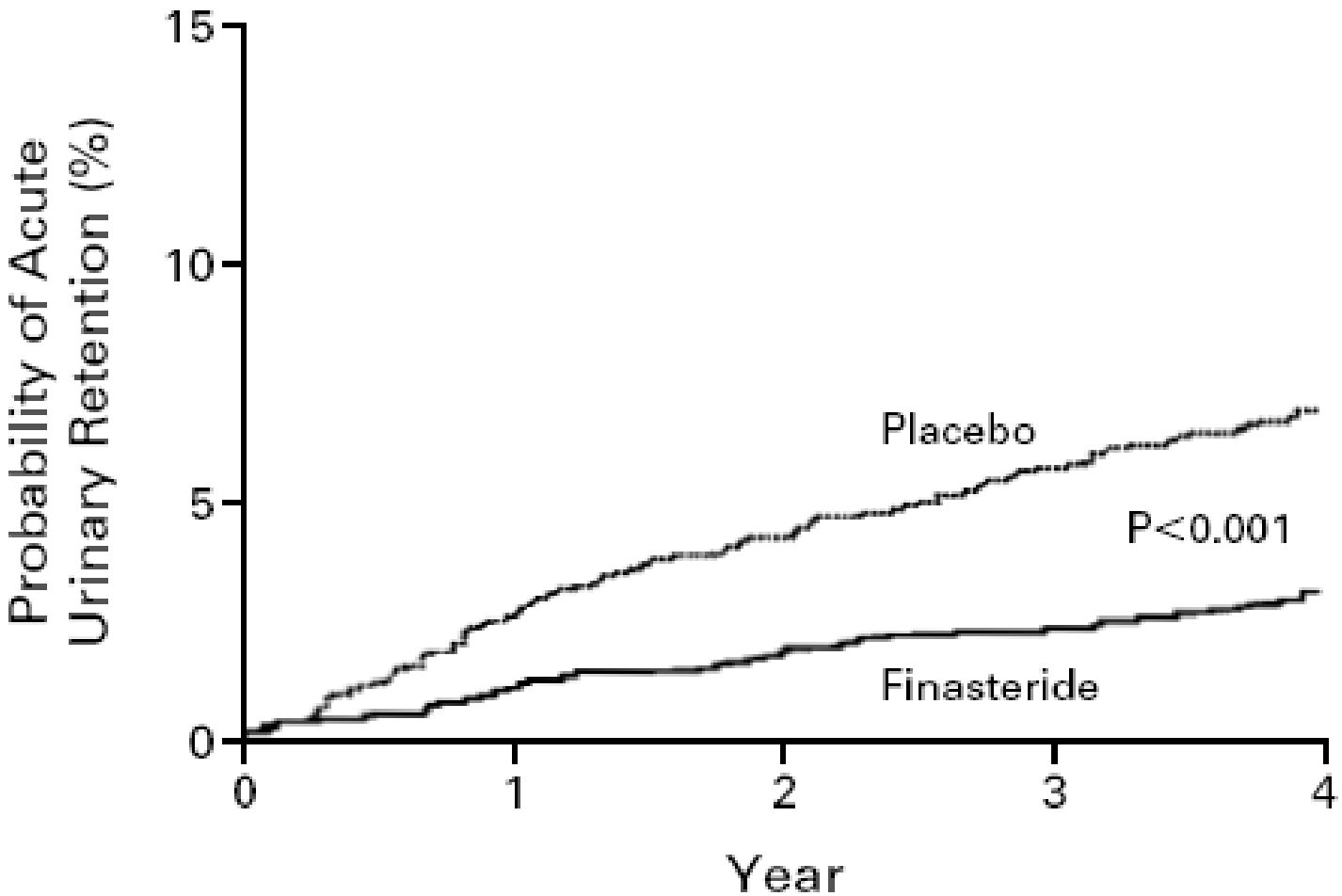
Probability of Surgery



N Engl J Med 1998

PLESS study

Probability of Acute Urinary Retention



N Engl J Med 1998

PCPT: Riduzione dell'incidenza del Carcinoma Prostatico (PCa) con i 5ARI

- Nel Prostate Cancer Prevention Trial (PCPT), 18.882 uomini sono stati randomizzati a ricevere il 5 ARI selettivo per il tipo-2, finasteride, 5 mg/giorno o il placebo per 7 anni.
- Nel gruppo con finasteride, l'incidenza di PCa è stata ridotta del 24.8% ($p<0.001$) in confronto al gruppo placebo.
- L'incidenza di tumori di grado elevato (Gleason grade 7–10), tuttavia, è più alta nel gruppo con finasteride rispetto al placebo (6.4% *vs.* 5.1%, $p=0.005$).

Thompson *et al*. *N Engl J Med* 2003;349(3):215–24

"*Efficacy and safety of long-term treatment with the dual 5 alpha-reductase inhibitor DUTASTERIDE in men with symptomatic benign prostatic hyperplasia*"

Debruyne et al Eur Urol 2004

3 large-scale, randomised, placebo-controlled Phase III studies

- Aria 3001
- Aria 3002
- Arib 3003

↓ BPH related surgery

↓ Urinary symptoms

↓ TPV

↓ Risk of AUR

↓ Flow rate

Maggiore soppressione dei livelli di DHT osservati con dutasteride in confronto con finasteride

Soppressione media (± SD) di DHT dopo 24 settimane di terapia

***Dutasteride* 0.5 mg/day**

-94.7%
± 3.3%

p<0.001

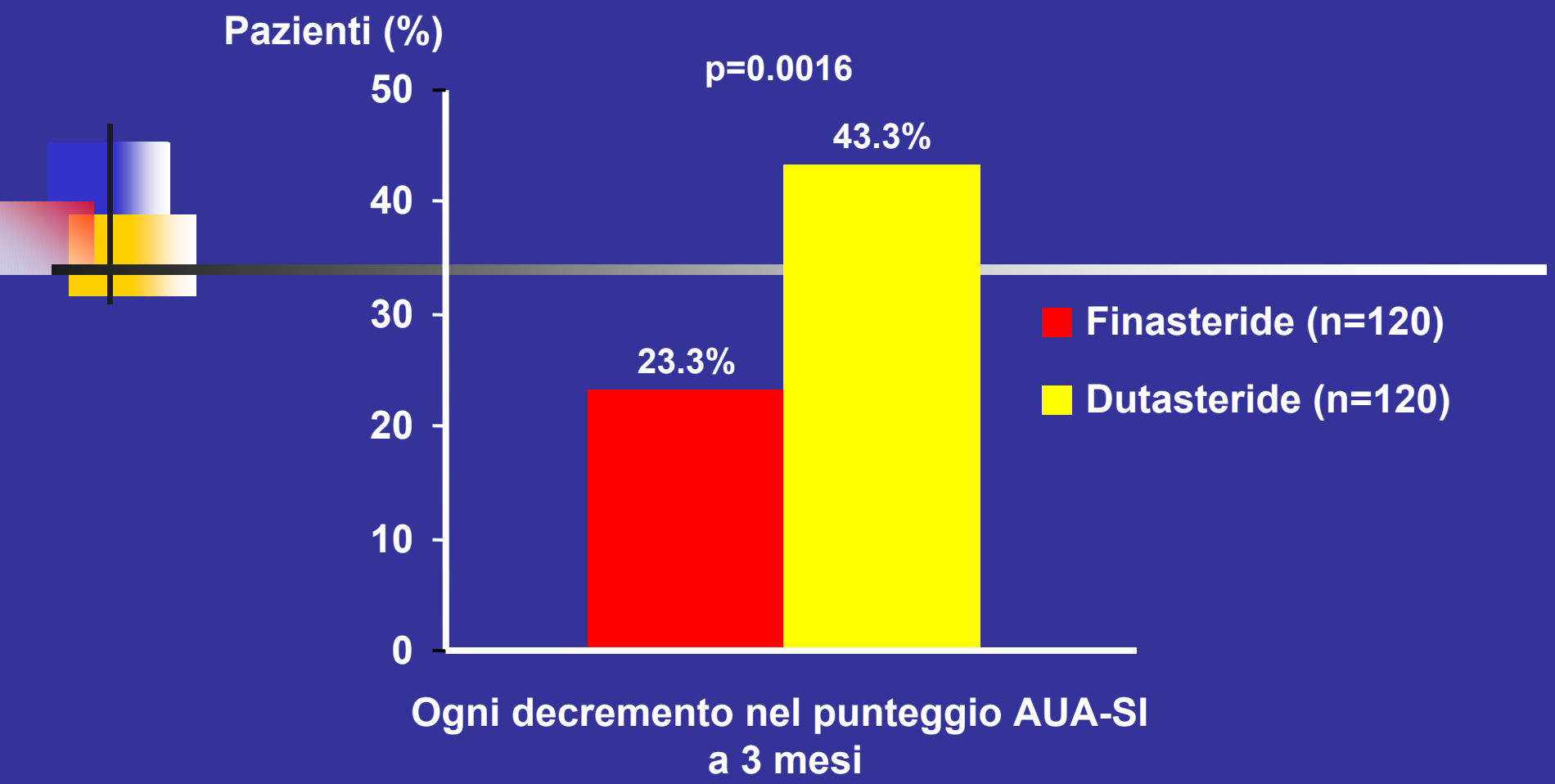
***Finasteride* 5.0 mg/day**

-70.8%
± 18.3%

Clark *et al.* J Clin Endocrinol Metab 2004; 89: 2179–84

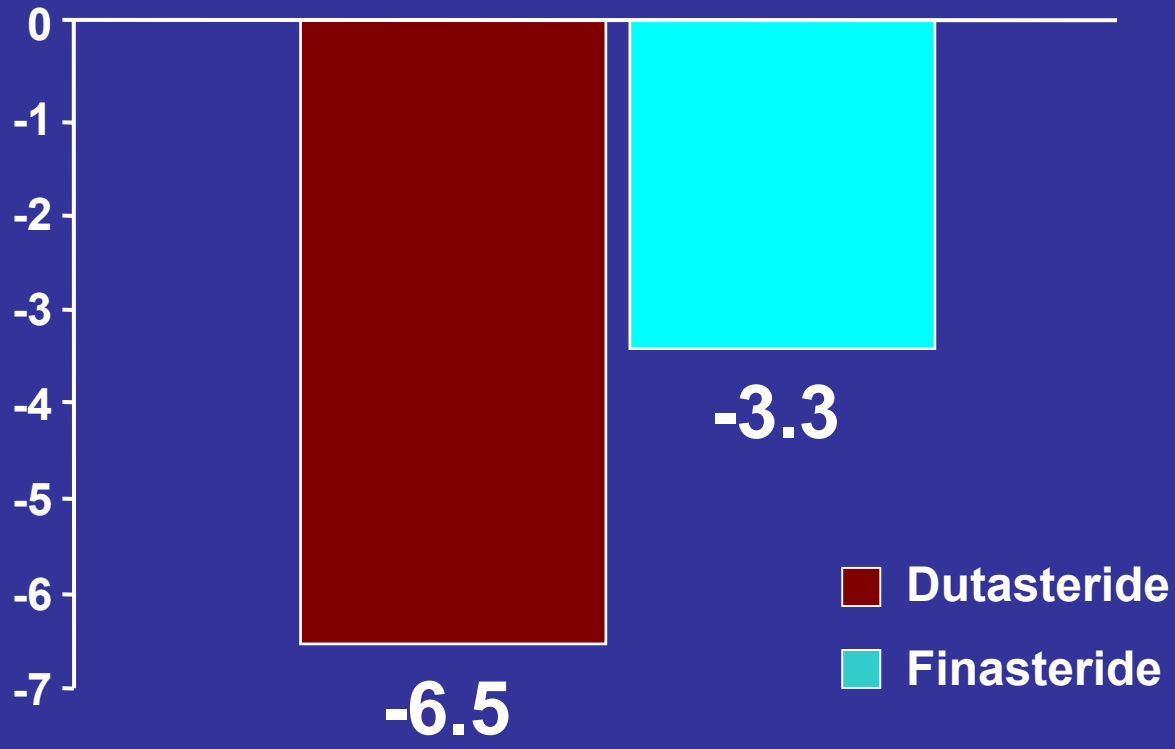
Dutasteride *versus* Finasteride

IPSS



Hagerty, Ginsberg and Harkaway. EAU 2004

Miglioramento dell' AUA-SI Score a 4 anni con Dutasteride *vs.* Finasteride



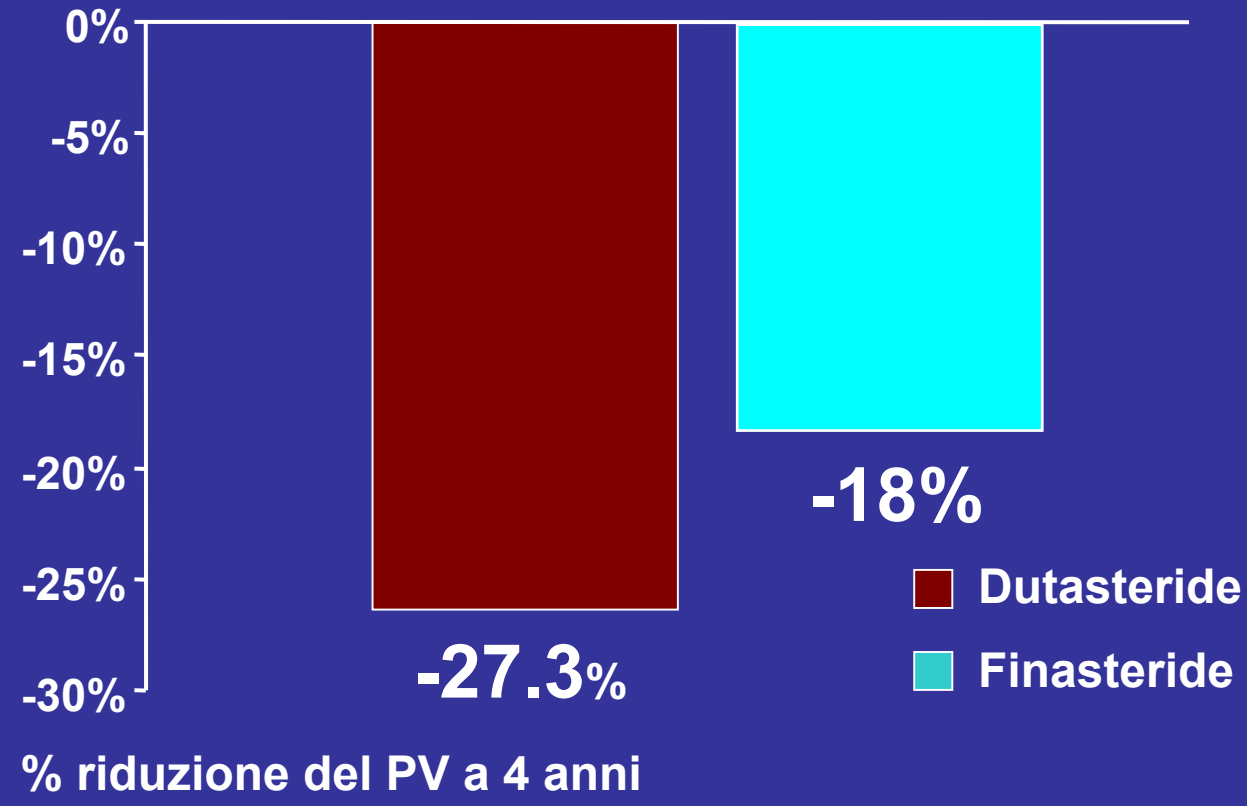
Variazione dell' AUA-SI score a 4 anni

Debruyne *et al*. *Eur Urol* 2004:46;488–95

McConnell *et al*. *N Engl J Med* 1998;338:557–63

Confronto indiretto di dutasteride dati a 4 anni *vs*. PLESS

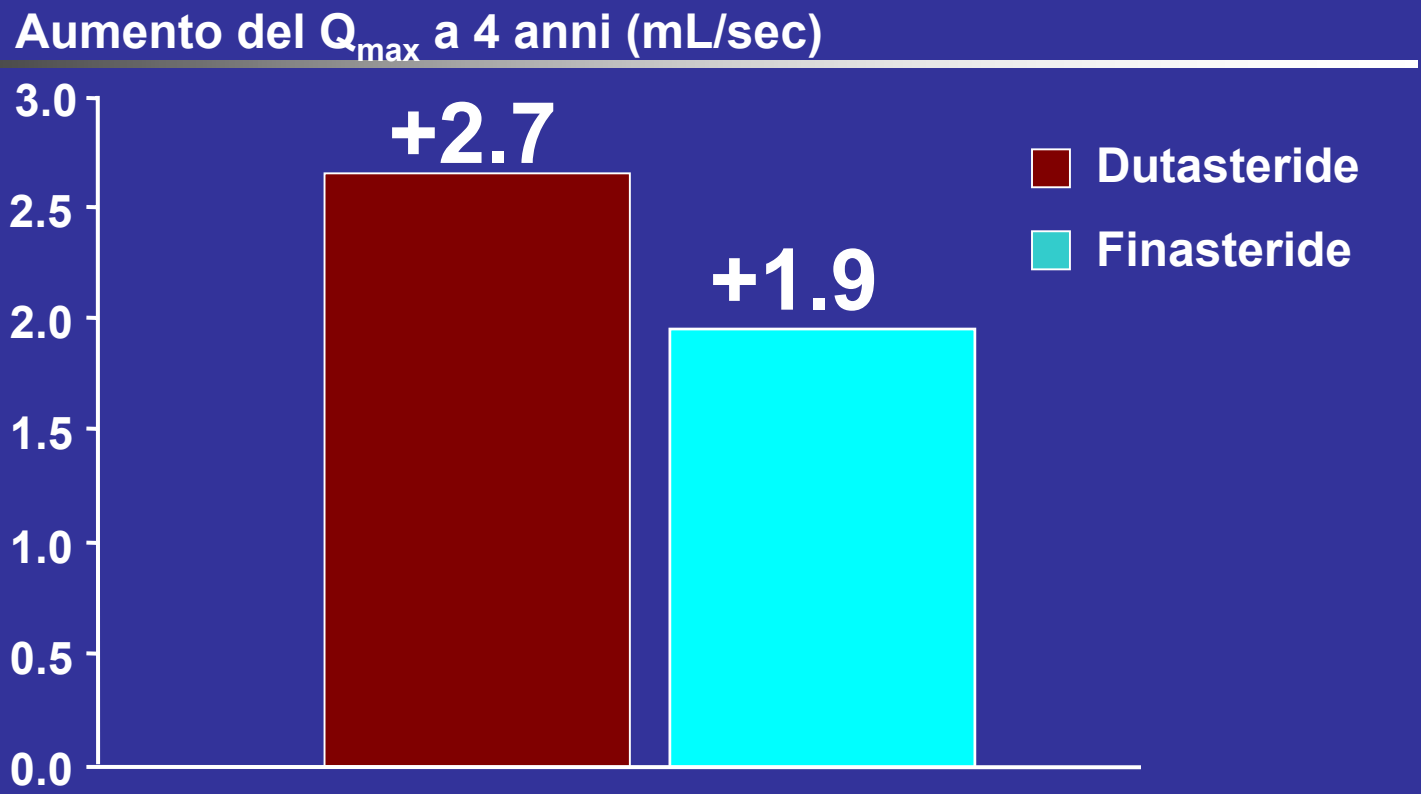
Riduzione del VOLUME PROSTATICO a 4 anni con Dutasteride *vs.* Finasteride



Debruyne *et al*. *Eur Urol* 2004:**46**;488–95
McConnell *et al*. *N Engl J Med* 1998;**338**:557–63

Confronto indiretto di dutasteride dati a 4 anni *vs*. PLESS

Miglioramento del Q_{max} a 4 anni con Dutasteride *vs.* Finasteride

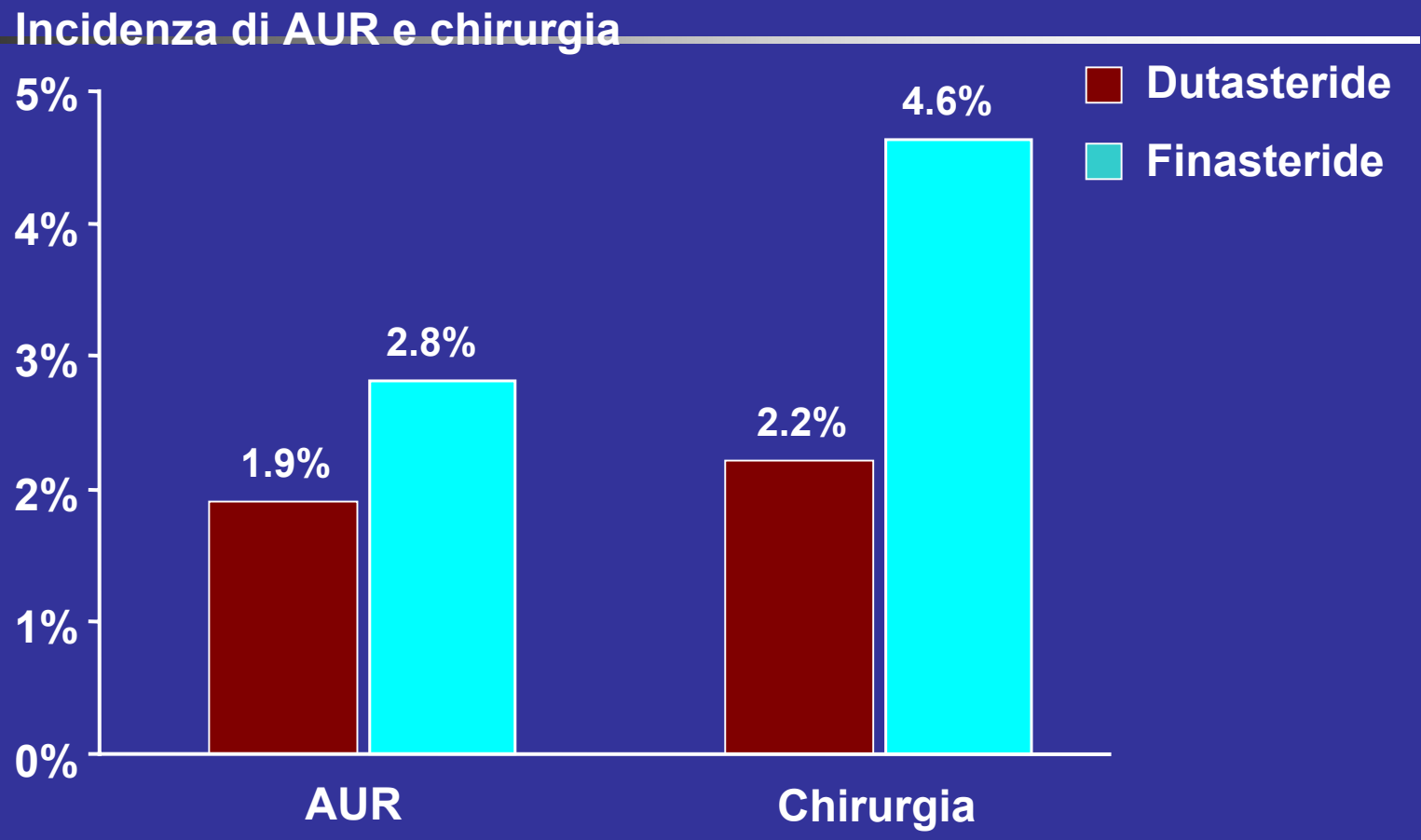


Debruyne *et al*. *Eur Urol* 2004:46;488–95

McConnell *et al*. *N Engl J Med* 1998;338:557–63

Confronto indiretto di dutasteride dati a 4 anni *vs*. PLESS

Rischio di AUR e di CHIRURGIA con Dutasteride *vs.* Finasteride



Roehrborn *et al*. *Urology* 2002:**60**;434–41

McConnell *et al*. *N Engl J Med* 1998;**338**:557–63

Confronto indiretto di dutasteride dati a 4 anni *vs*. PLESS

Terapia combinata

alfa-litici + 5ARI

Terapia combinata: il meglio di due mondi?

	5ARIs	α-bloccanti
Riduzione del VP	✓	
Mantenimento della riduzione del VP	✓	
Miglioramento dei sintomi e del flusso	✓	✓
Sollievo dai sintomi in 1-2 settimane		✓
Conservato miglioramento dei sintomi e del flusso	✓	✓
Prevenzione della progressione sintomatica	✓	✓
Riduzione a lungo termine del rischio di RUA e di intervento chirurgico	✓	✓

MTOPS (Medical Therapy Of Prostatic Symptoms)

- Double-blind, placebo-controlled, multicenter, randomized
  Average follow-up: 4.5 years

Randomized

N=3047

Entry Criteria

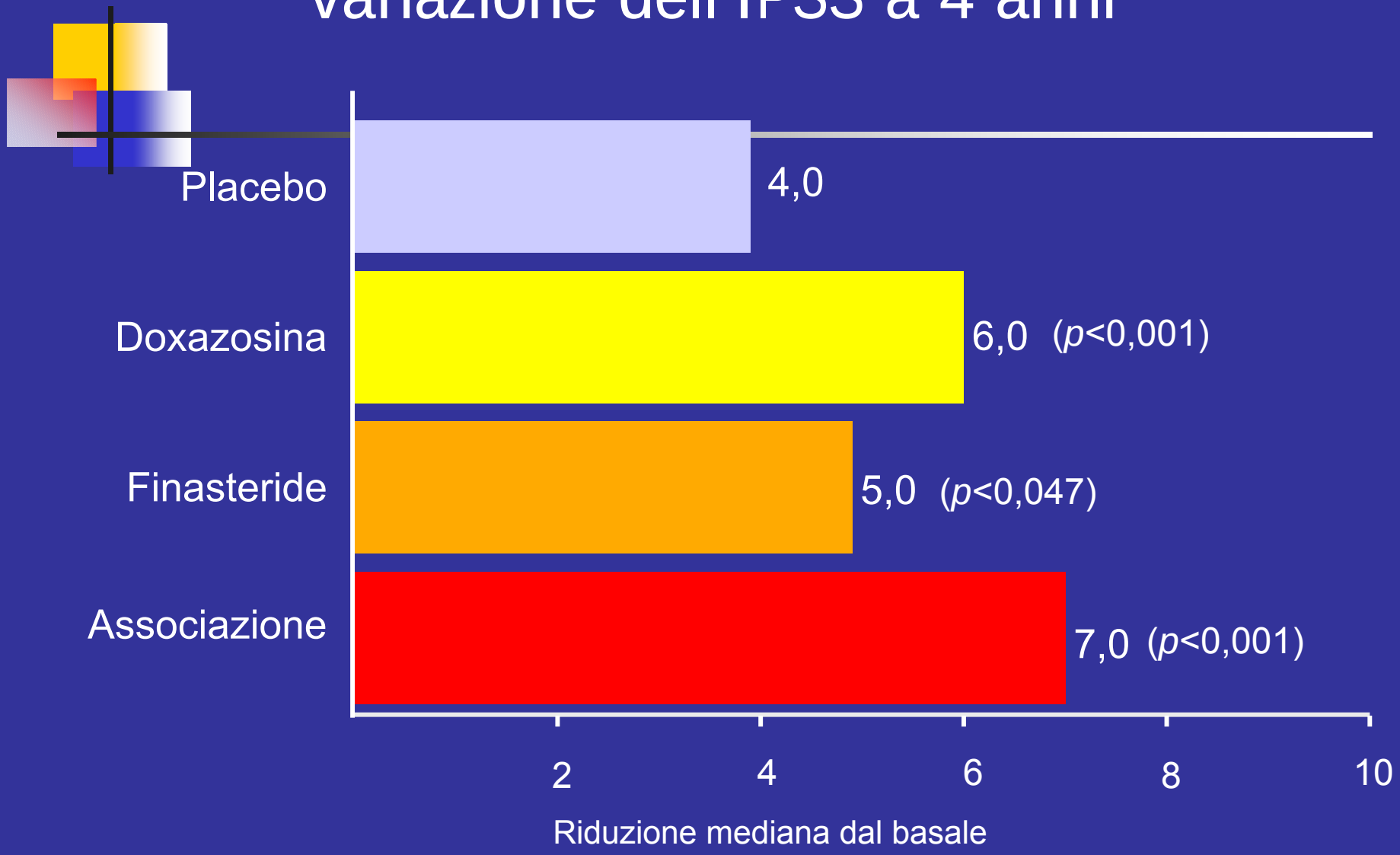
- Men ≥50 years of age
- AUA symptom score 8–30
- Q_{max} 4–15 ml/sec
- Voided volume ≥125 ml

Doxazosin (n=756)	**PROSCAR™** (n=768)	**PROSCAR** + doxazosin (n=786)	Placebo (n=737)

AUA=American Urological Association; Q_{max}=maximum urinary flow

Adapted from Bautista OM et al *Control Clin Trials* 2003;24:224-243.

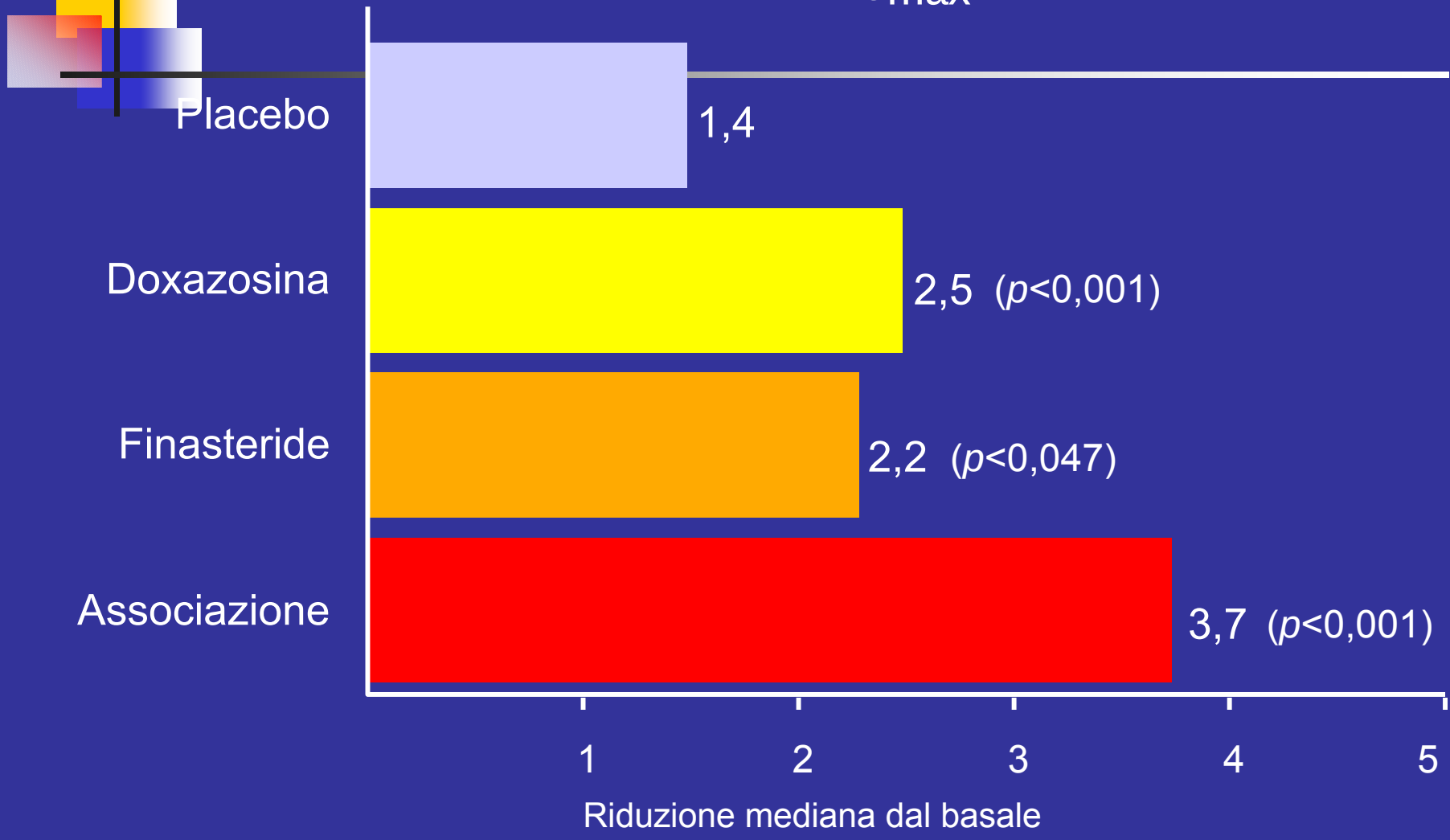
Studio MTOPS
variazione dell'IPSS a 4 anni



Valore mediano basale dell'AUA SI = 17,0

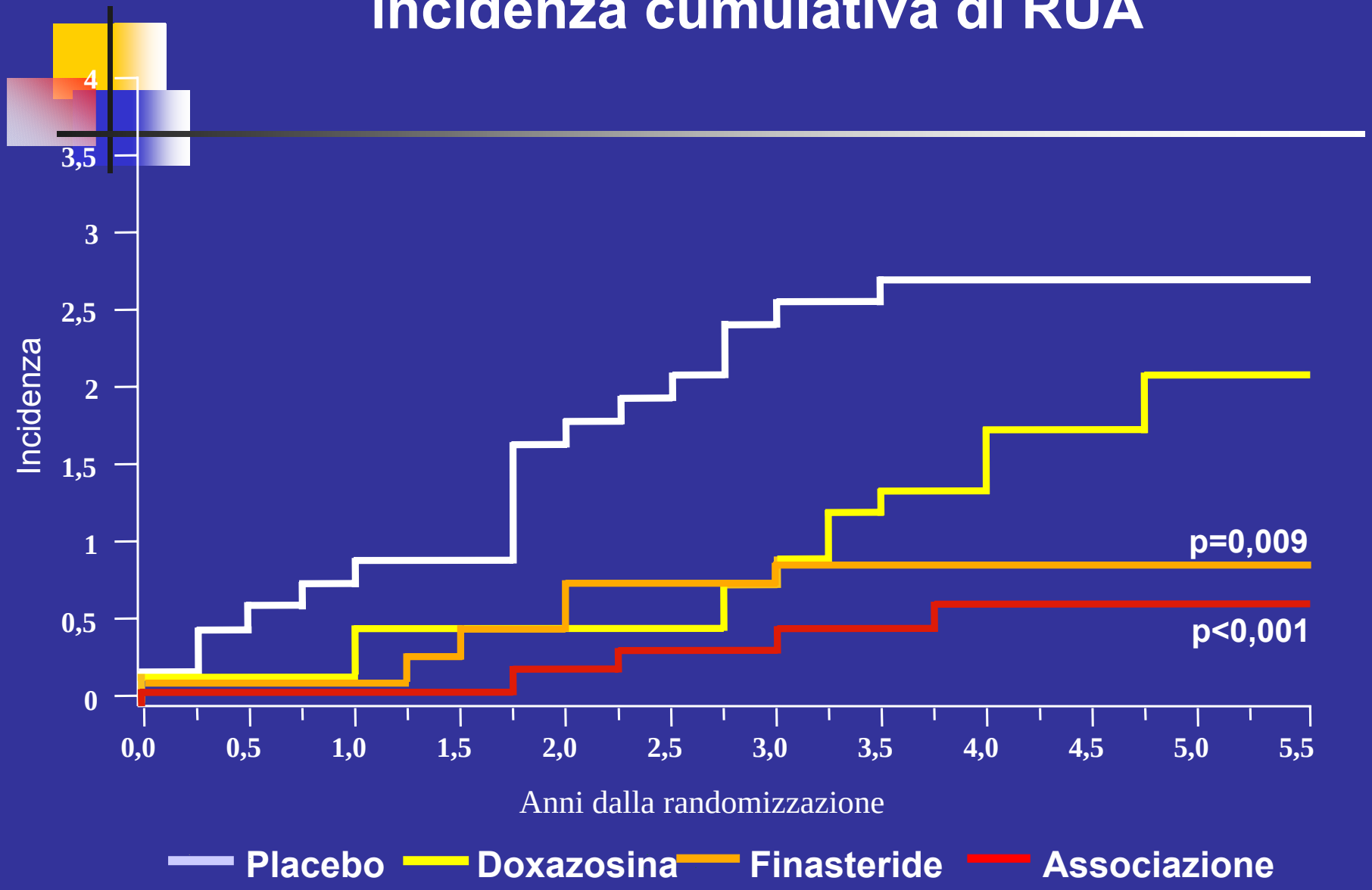
Studio MTOPS

Variazione del Q_{max} a 4 anni



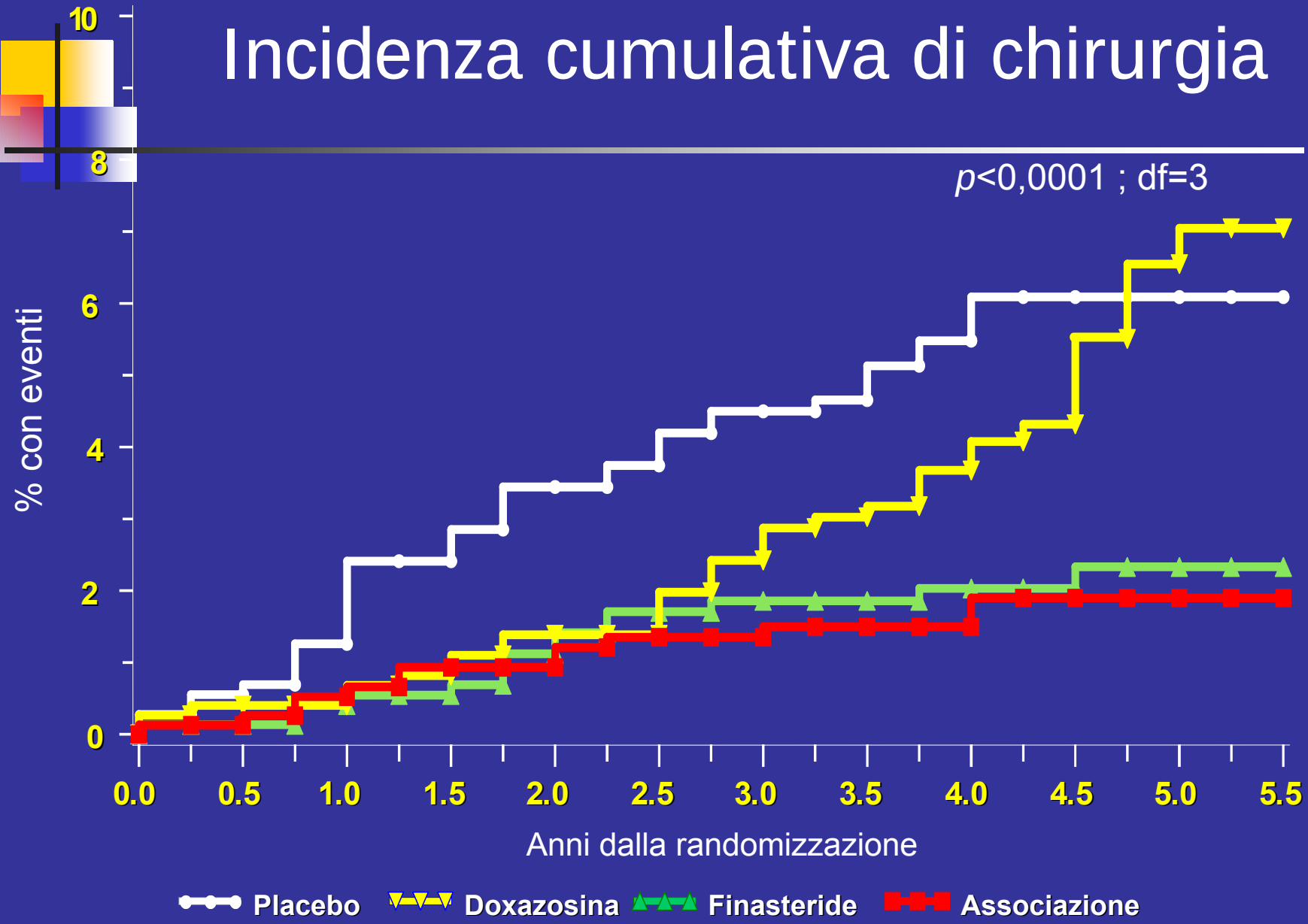
Valore mediano basale del Q_{max} = 10,6

Studio MTOPS
incidenza cumulativa di RUA



Studio MTOPS

Incidenza cumulativa di chirurgia



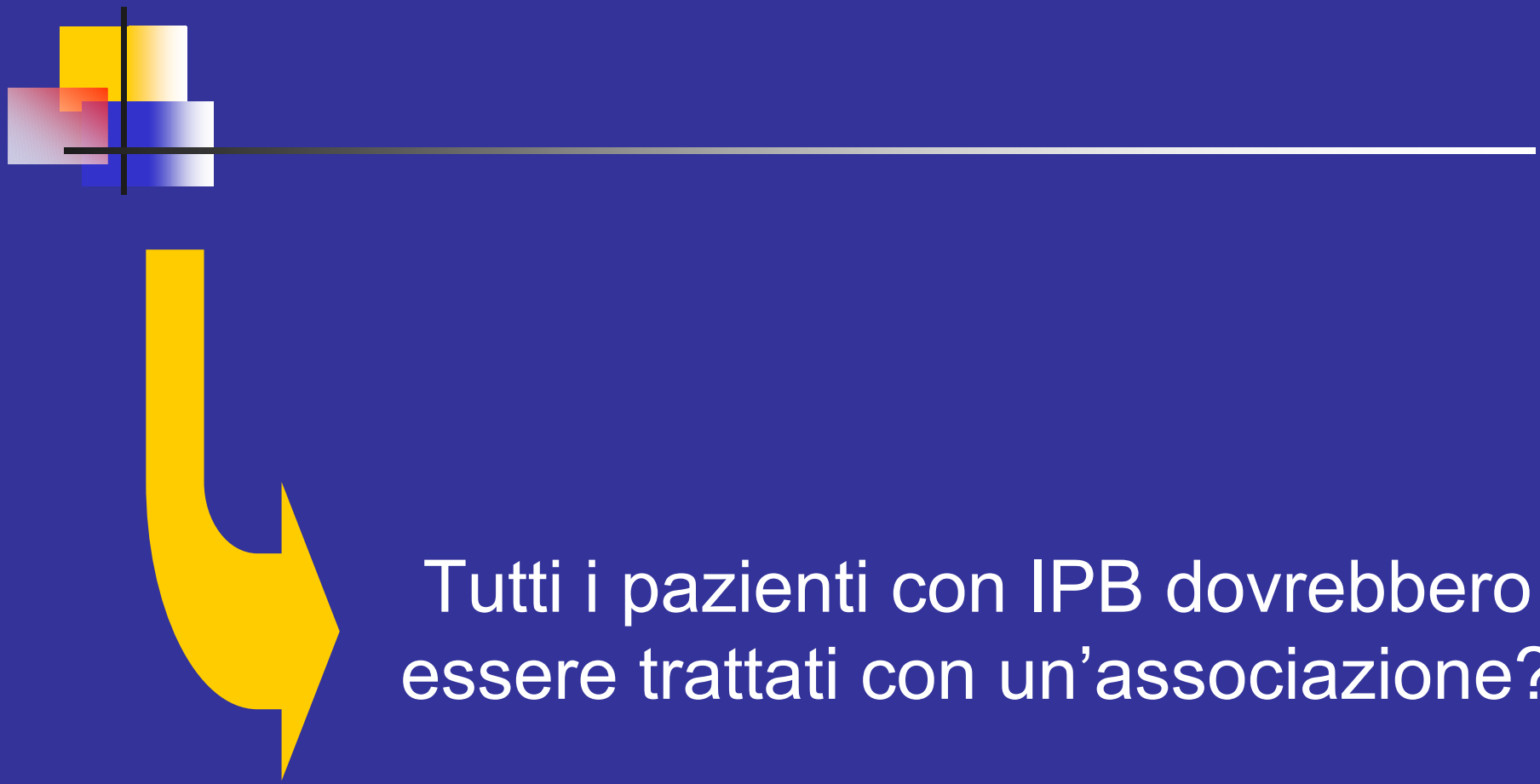
Conclusions

- Combination therapy is the most effective form of medical therapy for BPH
  - **66 % reduction** in risk of BPH progression (p<0.001*)
  - **64 % reduction** in worsening symptoms (p<0.001*)
  - **81 % reduction** in risk of AUR (p<0.001*)
  - **67 % reduction** in need for invasive BPH therapy (p<0.001*)

- Long-term monotherapy and combination therapy were well tolerated and effective

*vs. placebo at 4 years

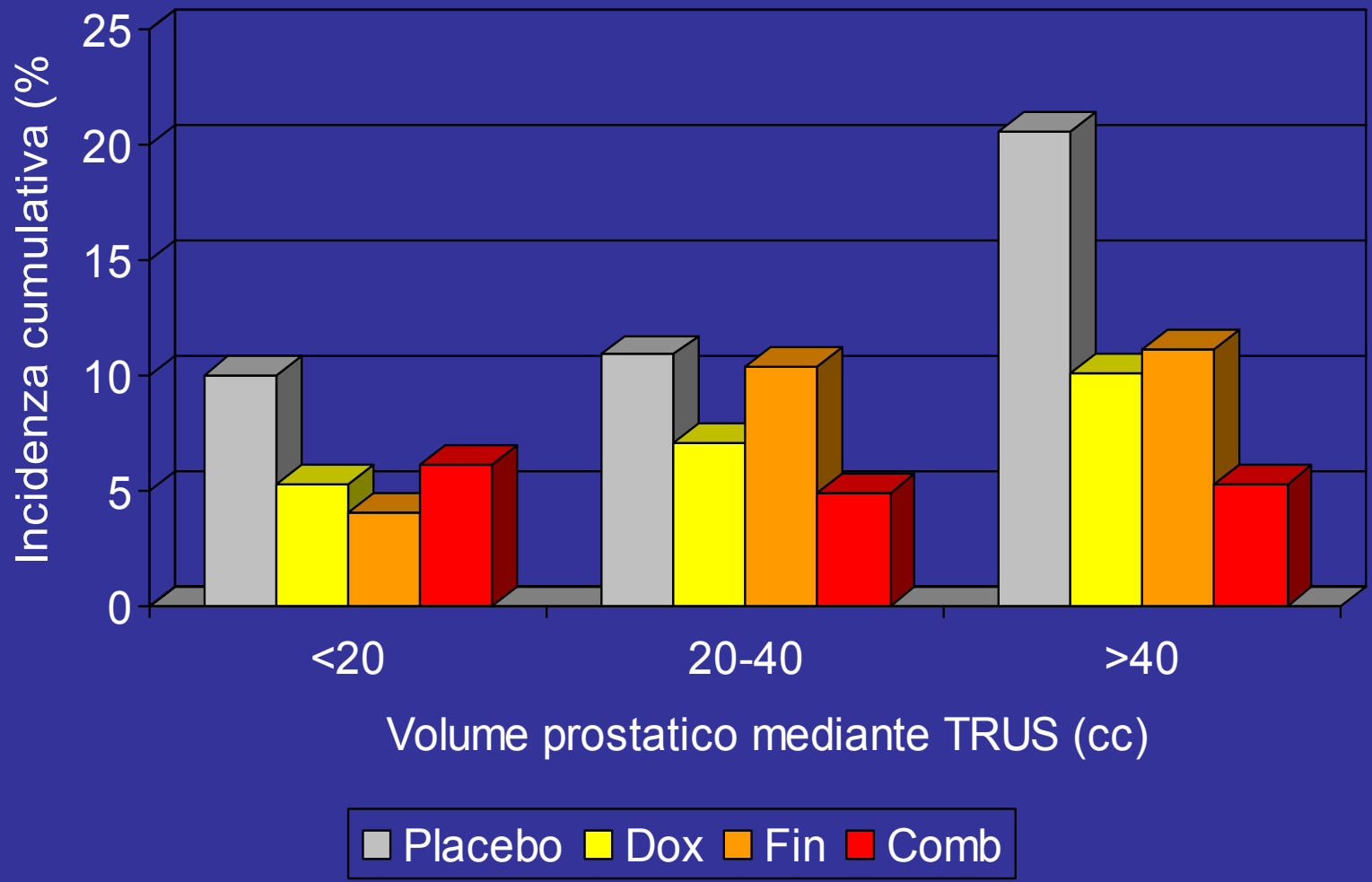
Adapted from McConnell JD et al *N Engl J Med* 2003;349(25):2385-2396.



Tutti i pazienti con IPB dovrebbero essere trattati con un’associazione?

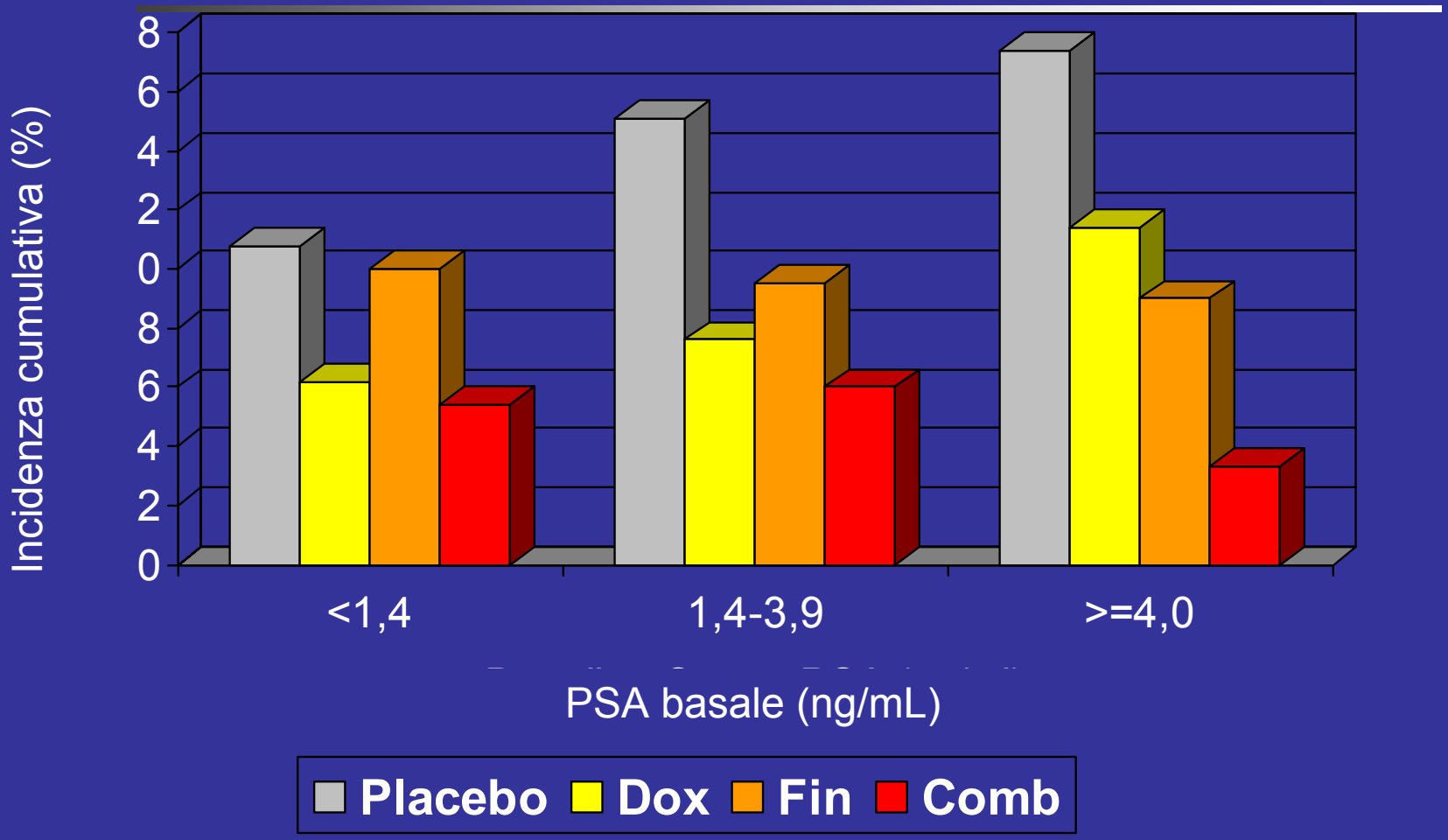
Aumento dell'AUA Symptom Score (≥4)

Rapporto con il volume prostatico



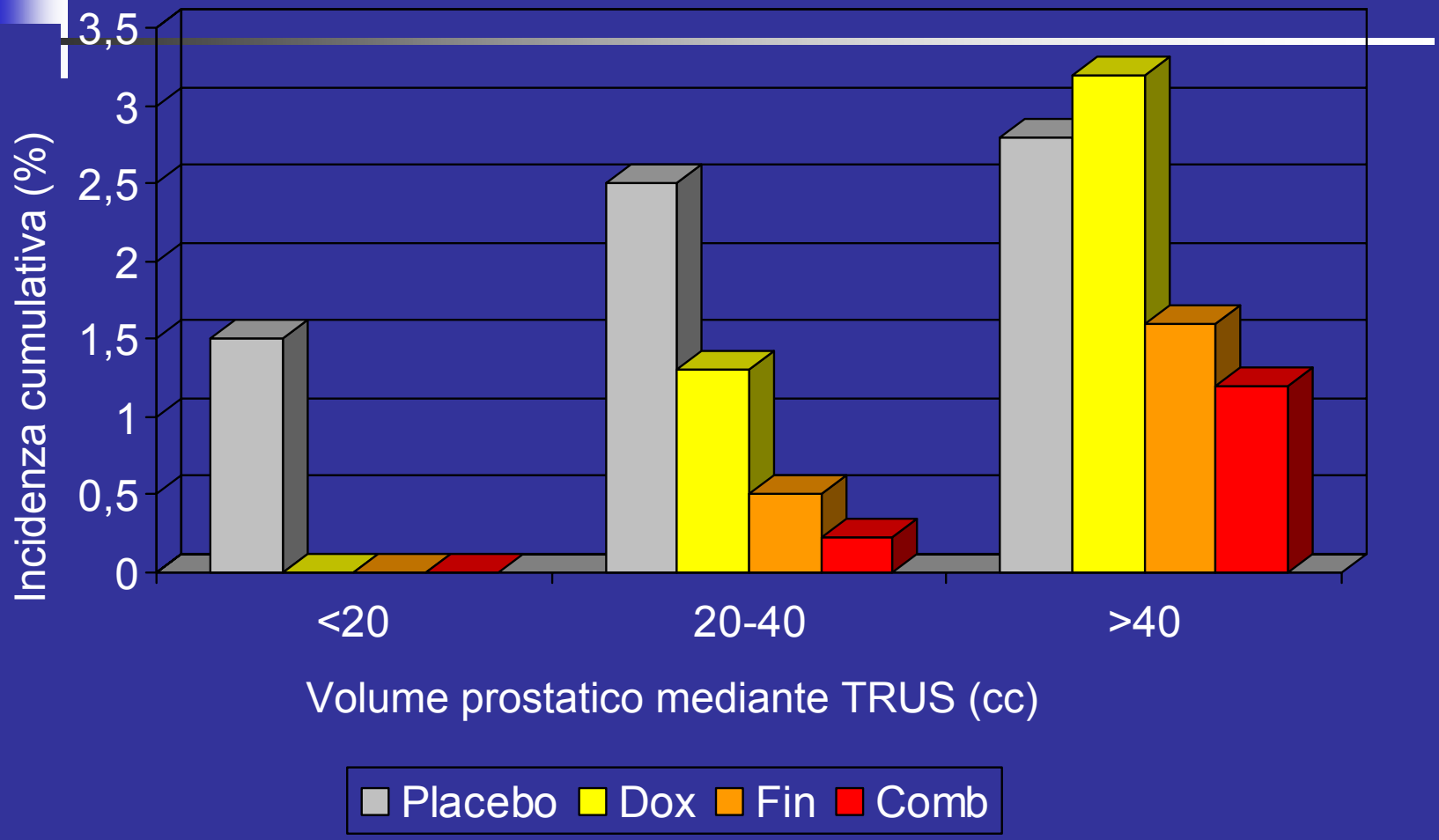
Aumento dell'AUA Symptom Score (≥4)

Rapporto con i valori di PSA



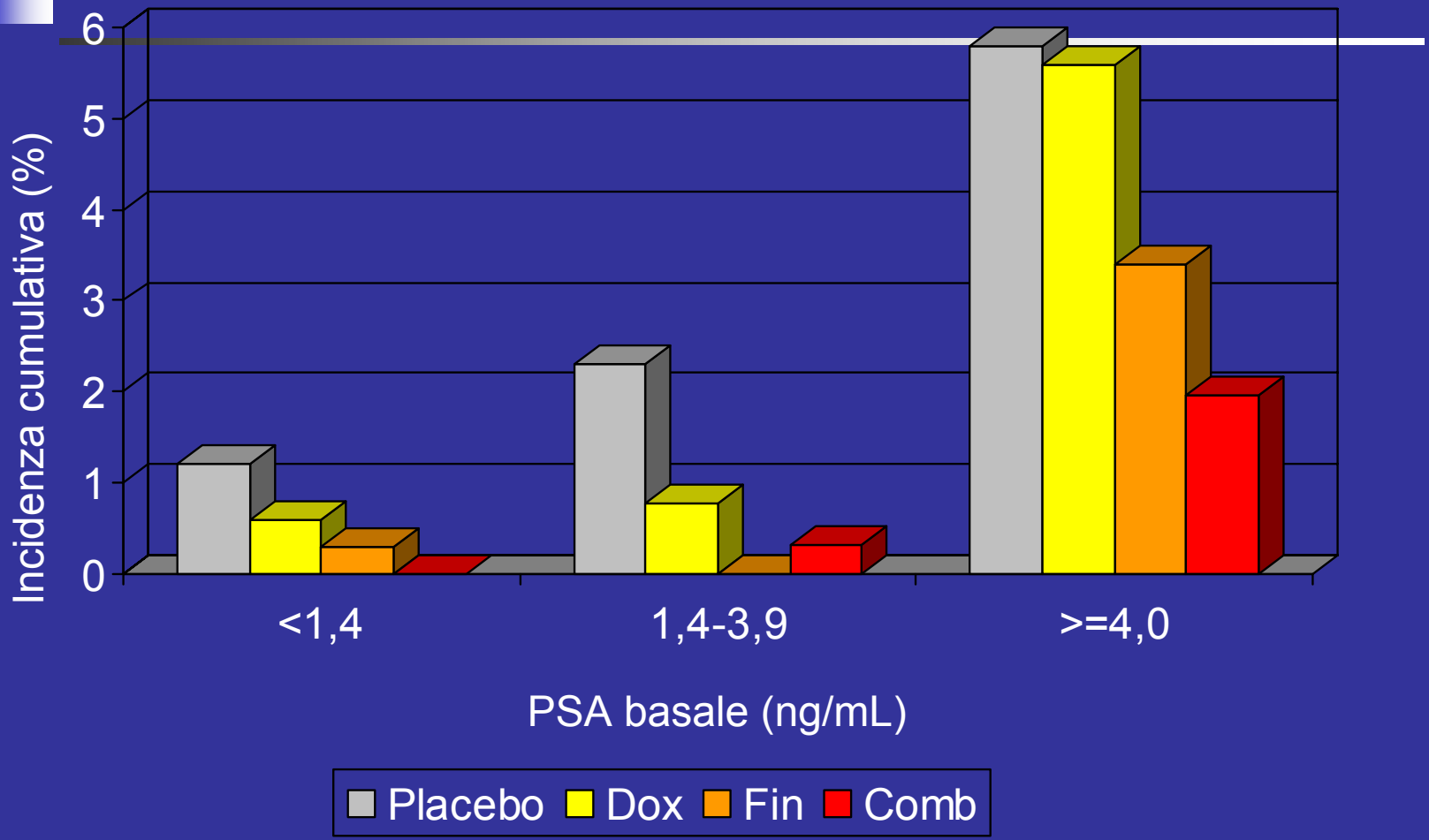
Ritenzione Urinaria Acuta

Rapporto con il volume prostatico



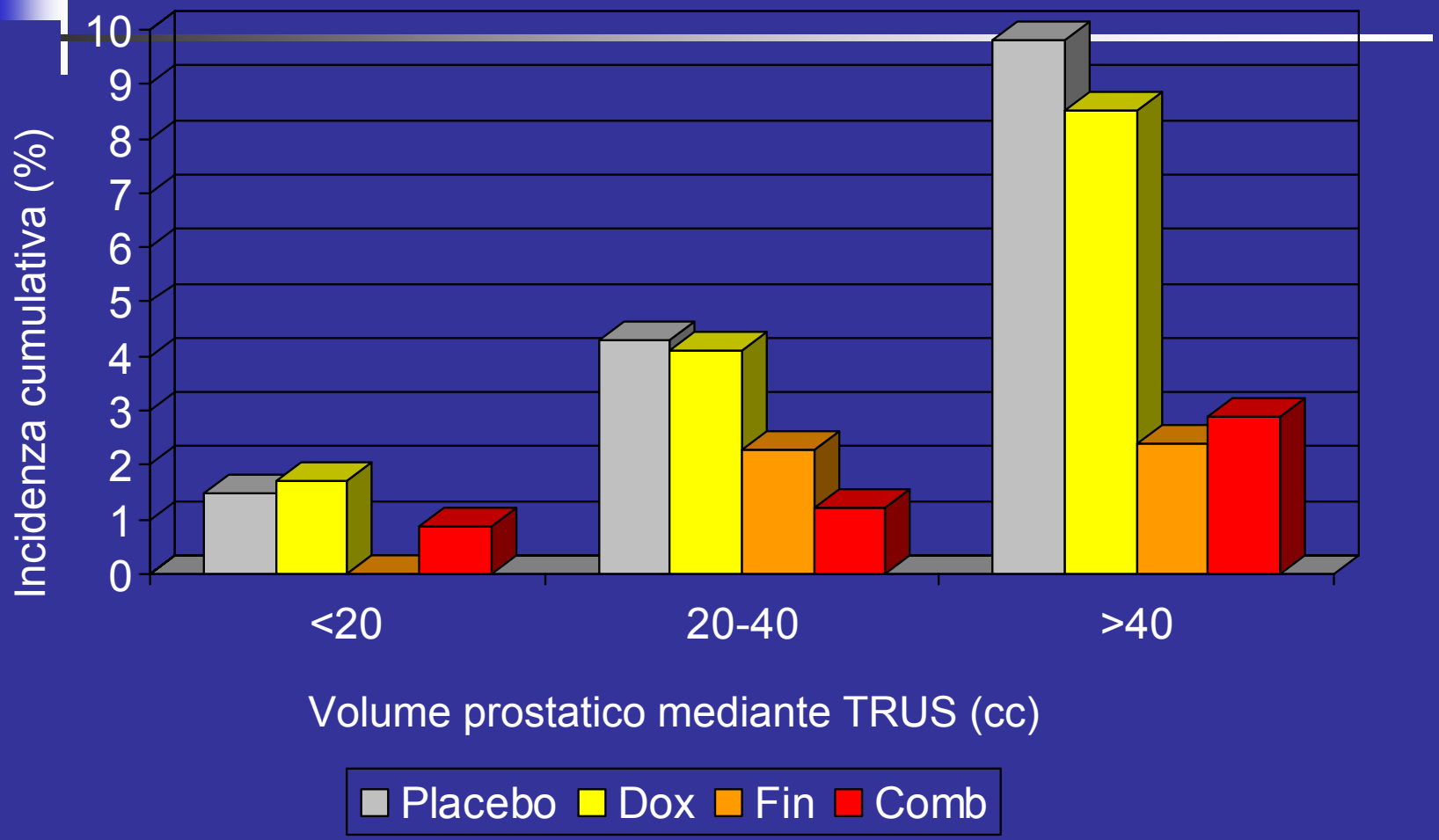
Ritenzione Urinaria Acuta

Rapporto con i livelli di PSA



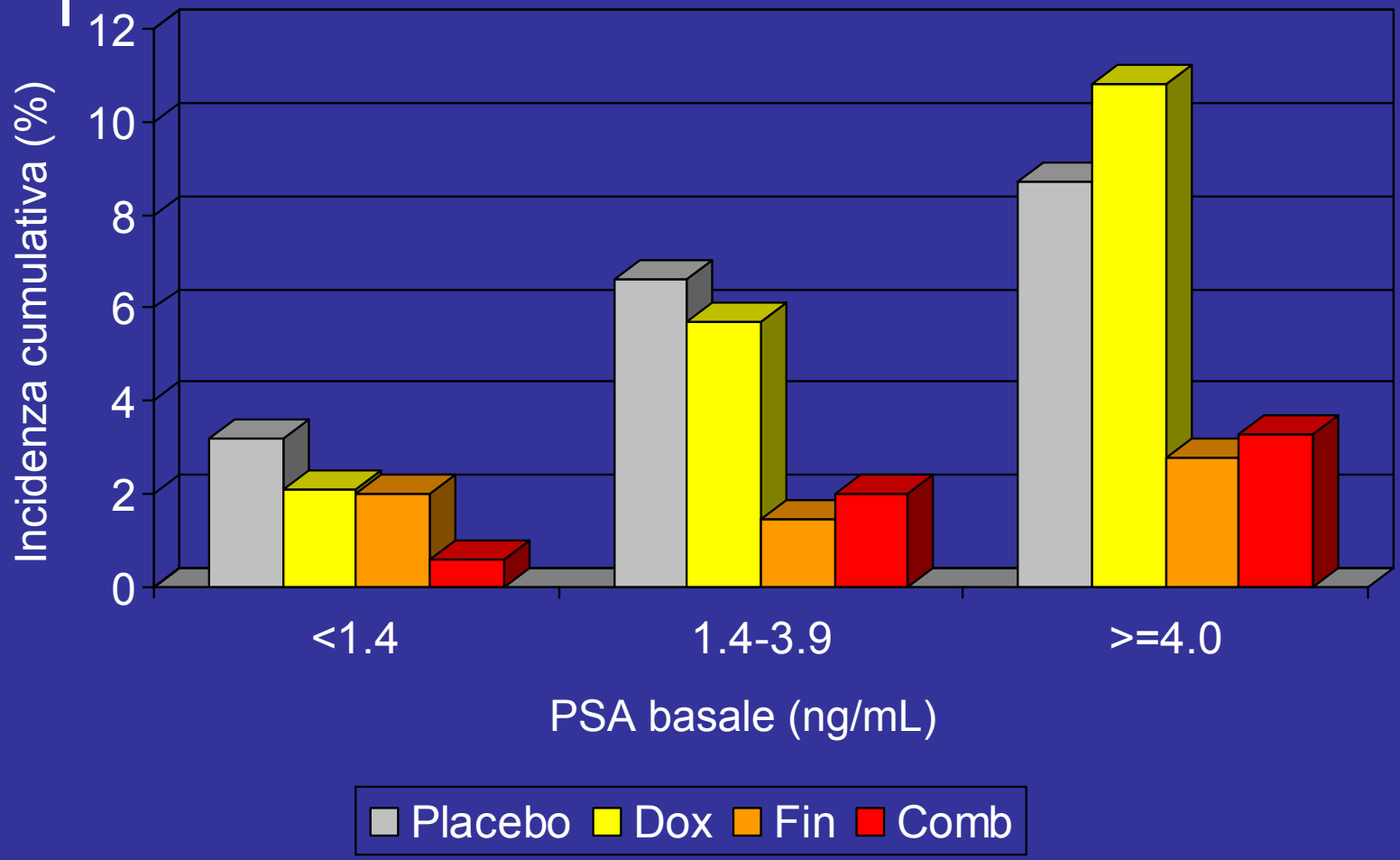
Terapia chirurgica dell'IPB

Rapporto con il volume prostatico

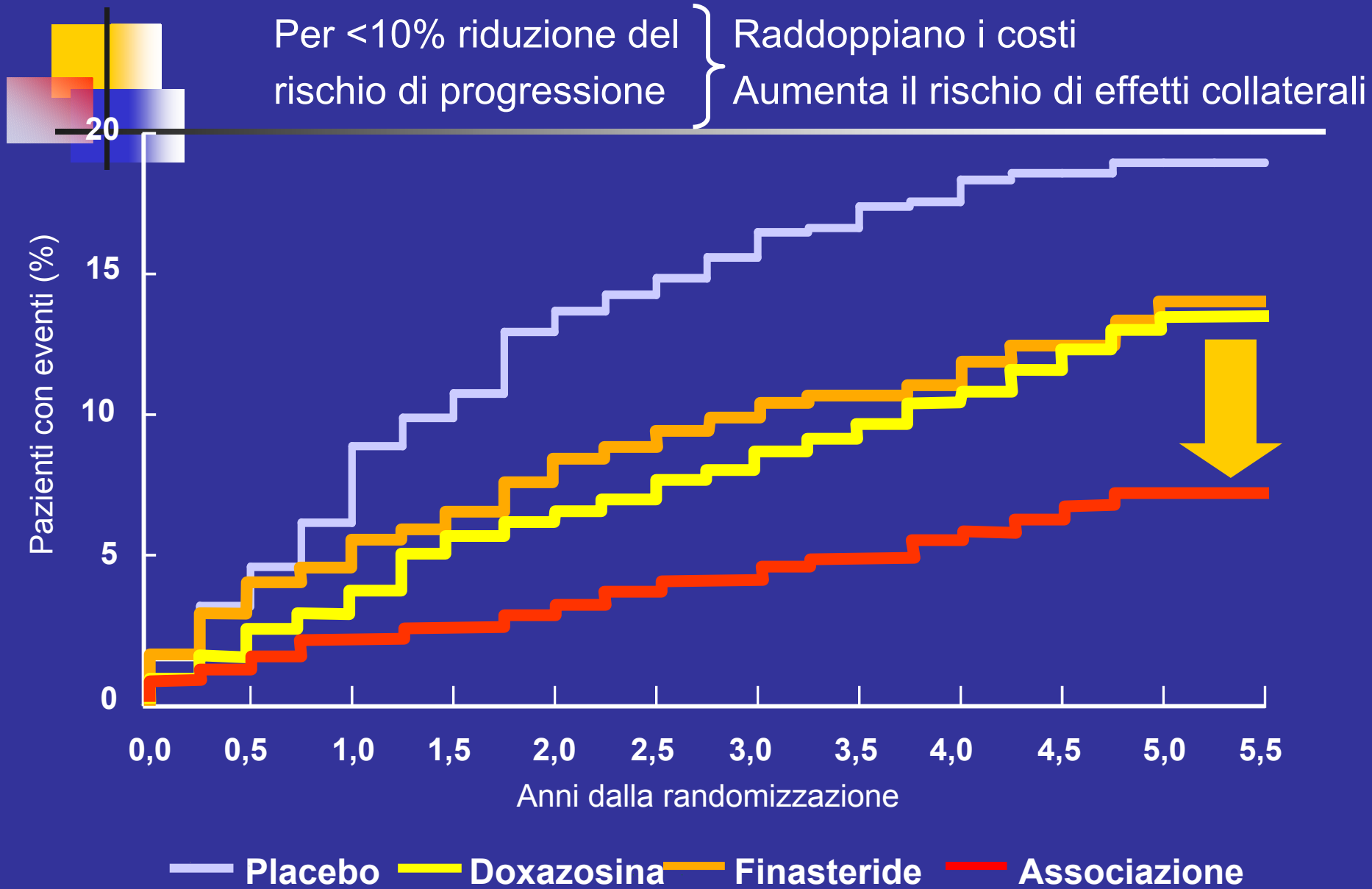


Terapia chirurgica dell'IPB

Rapporto con i livelli di PSA



Studio MTOPS: incidenza cumulativa di progressione



Studio MTOPS: effetti collaterali più frequenti

Incidenza su 100 pz/anno	Placebo	Doxazosina	Finasteride	Associazione
Disfunzione erettile	3,6	3,9	4,9*	*5,6**
Vertigini	2,5	4,8*	2,5	5,9*
Ipotensione ortostatica	2,5	4,4*	2,7	4,6*
Astenia	2,2	4,5*	1,7	4,6*
Riduzione libido	1,5	1,7	2,5*	2,8*
Disturbi eiaculazione	0,9	1,2	1,9*	3,4*
Edema periferico	0,7	1,0	0,8	*1,4**
Dispnea	0,6	1,0	0,6	*1,3**
Sonnolenza	0,4	0,9*	0,4	0,9*
Sincope	0,3	0,5	0,5	0,7*

*$p<0,05$ vs placebo

Impatto sulla pratica quotidiana?

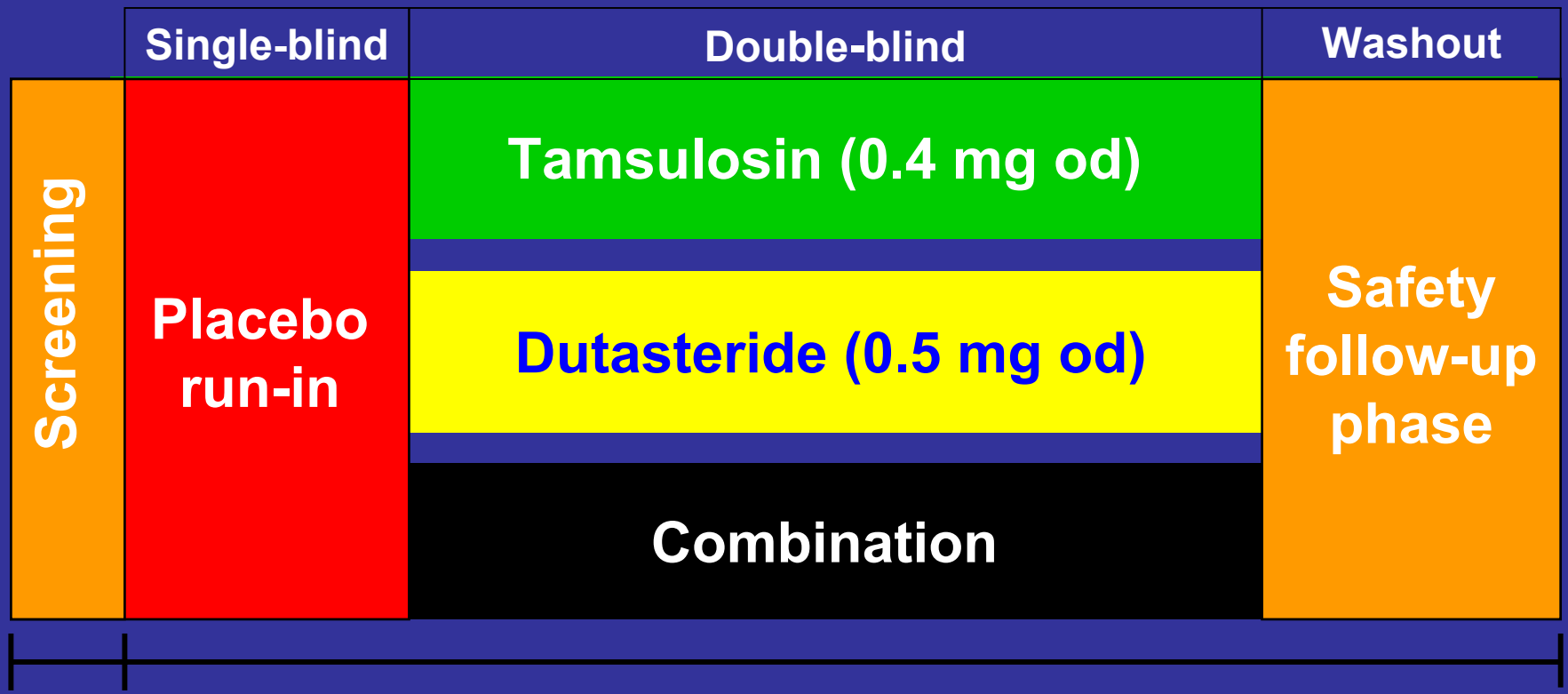
CUT-OFF di progressione

Età	>62
PSA	>1,6
TRUS	>31

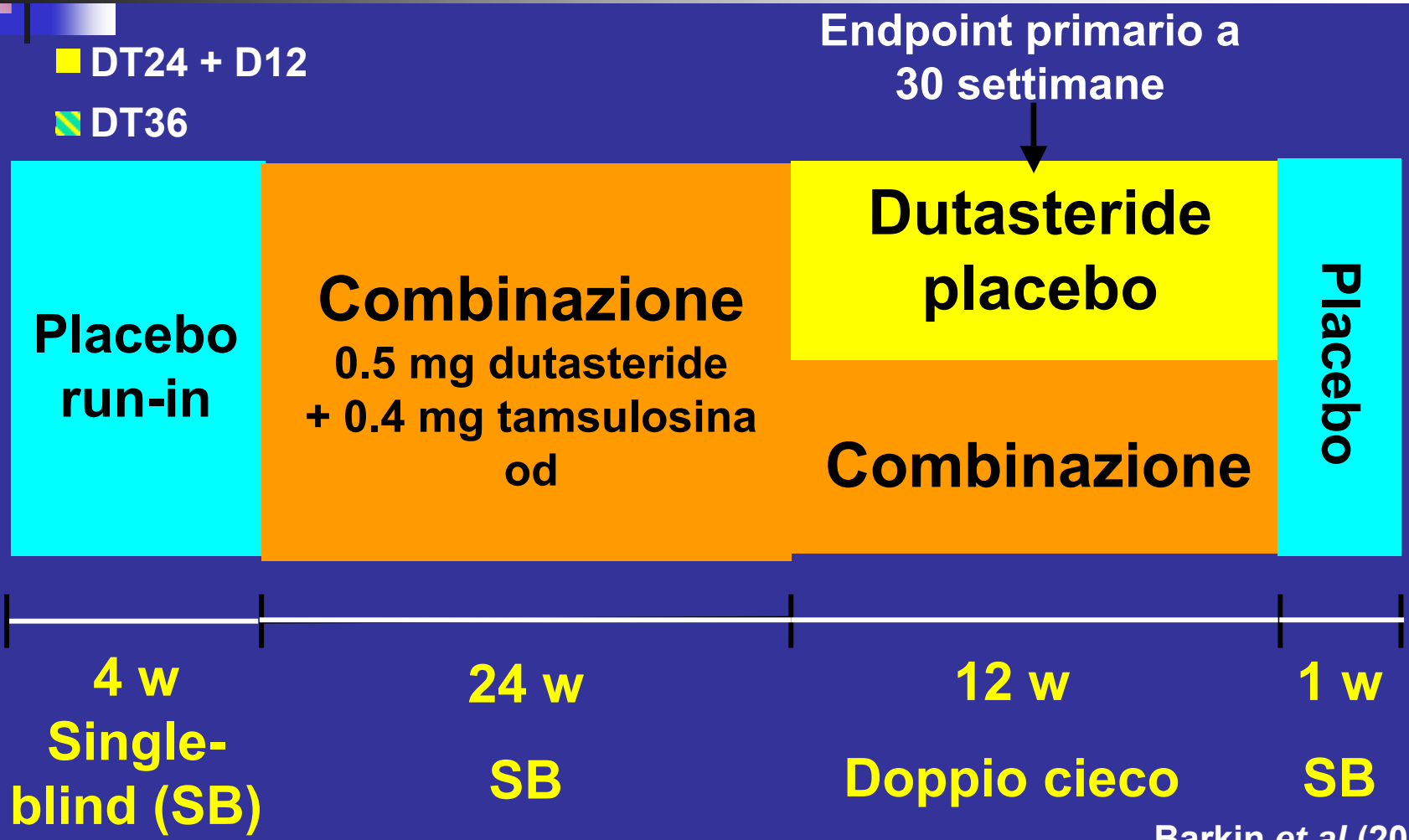
La maggior parte dei casi

Lo studio CombAT

ARTICLE IN PRESS



Symptom Management After Reducing Therapy: SMART–1

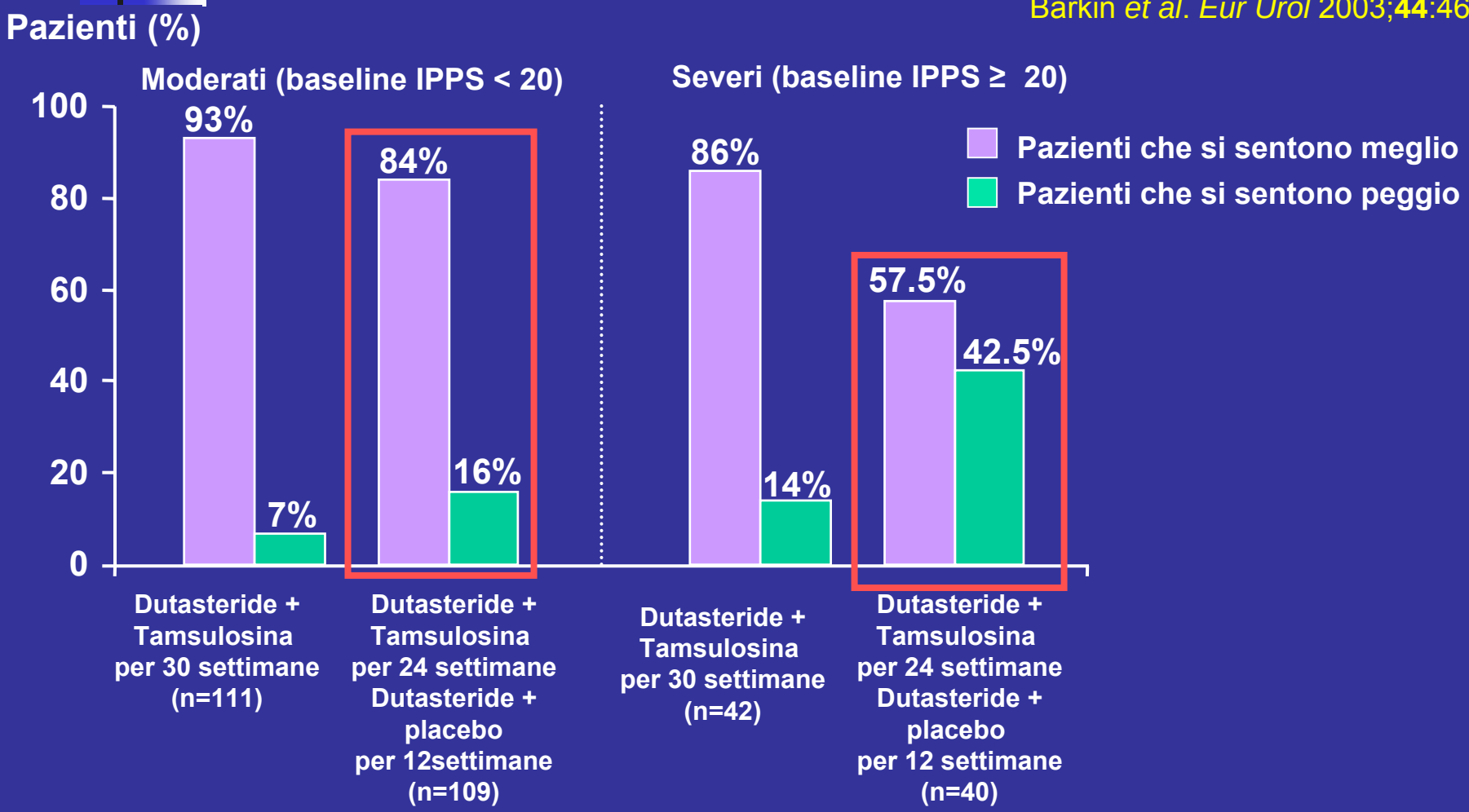


Barkin *et al* (2002)

SMART-1: Risultati chiave

Maggiori benefici nella continuazione della terapia di combinazione nei pazienti con sintomi più severi

Barkin *et al. Eur Urol* 2003;**44**:461–66



Plant extracts

- Further studies meeting the criteria proposed by WHO-BPH conference

  (12-month duration, randomised, placebo-controlled)

  are required before plant extracts can be recommended for the treatment of LUTS

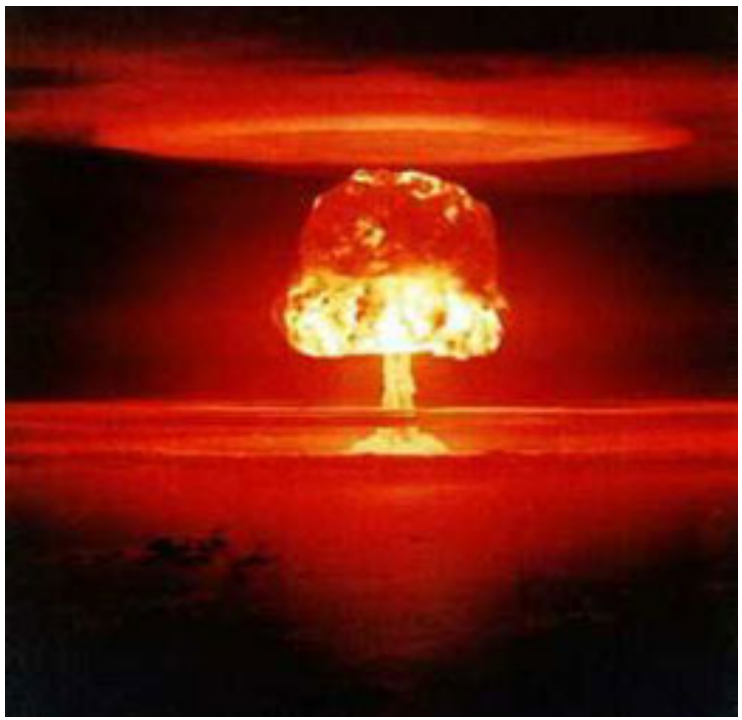
EAU Guielines 2007

Conclusioni

- Fitofarmaci ?
- Alfa-litici SEMPRE
- Terapia di combinazione

RISCHIO DI PROGRESSIONE	
Età	>62
PSA	>1,6
TRUS	>31

...Looking to the future...



New is not always better