



*La terapia medica dell'IPB*

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# 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

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

## Fattori di rischio di progressione

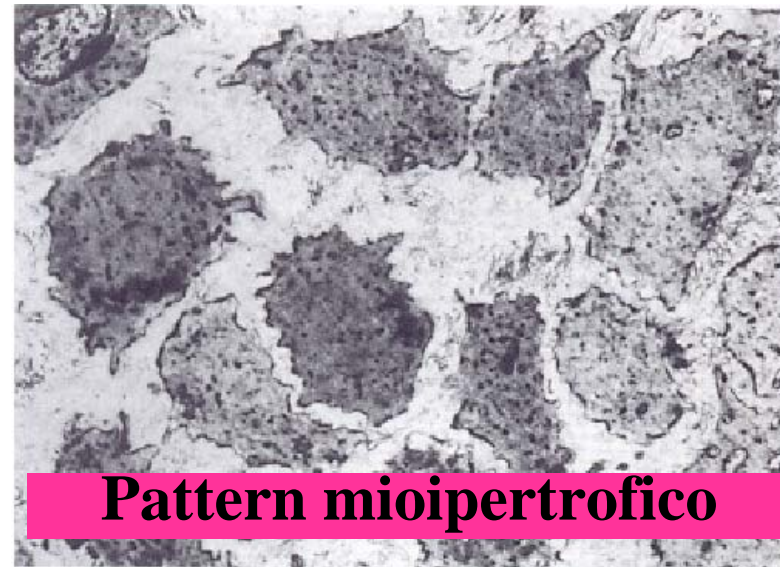
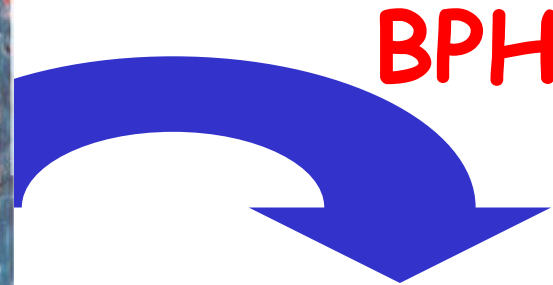
<b>Età:</b>	<b>&gt; 62 anni *</b>
<b>PSA:</b>	<b>&gt; 1,6 ng/mL *</b>
<b>TRUS:</b>	<b>&gt; 31 mL *</b>
Qmax:	<10,6 mL/sec
AUASS:	>17
PVR:	>39 mL

\*  $p < 0,05$

# Alterazioni morfologiche del detrusore in pazienti ostruiti



**Detrusore normale**



**Pattern mioipertrofico**

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

# Terapia medica EBM

## AUA/EAU guidelines

### **$\alpha$ 1-litici**

Alfu-tera-doxa-tamsulo

### **Inibitori 5 $\alpha$ -reduttasi**

Finasteride-Dutasteride

### **Terapia di combinazione**

**$\alpha$ 1-litici + I5AR**

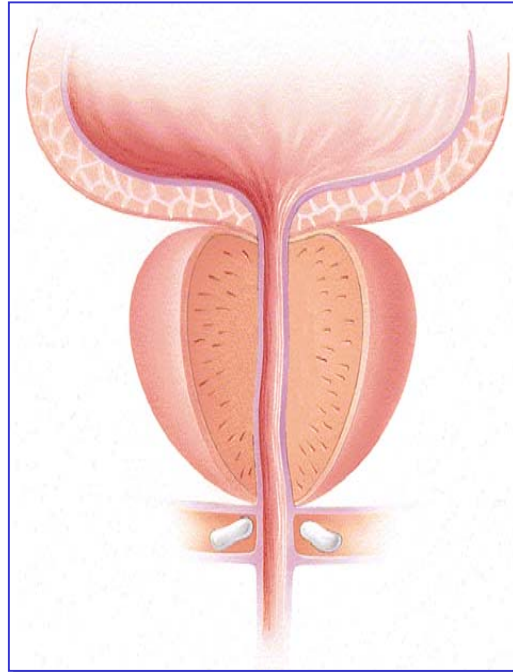
**MTOPS**

# 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**

# Alfa-litici

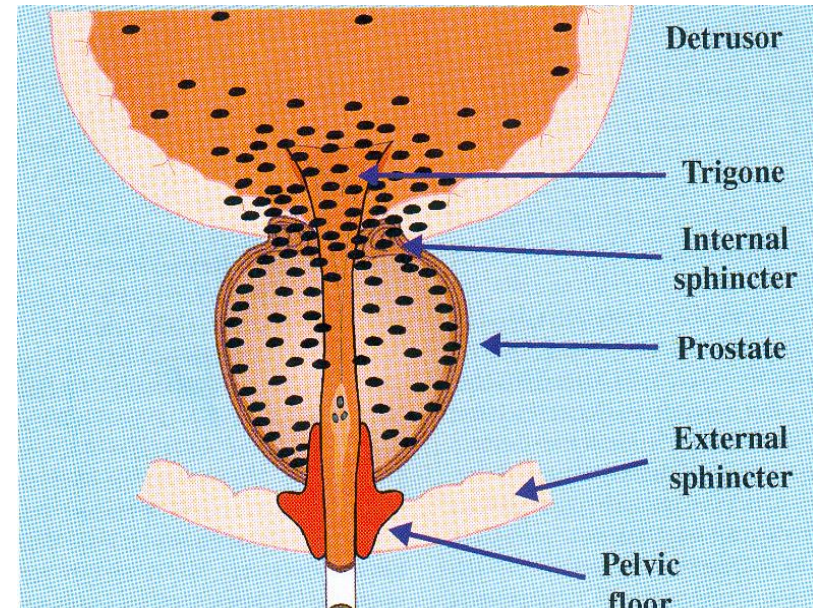


# Alfa-litici

## TRIALS

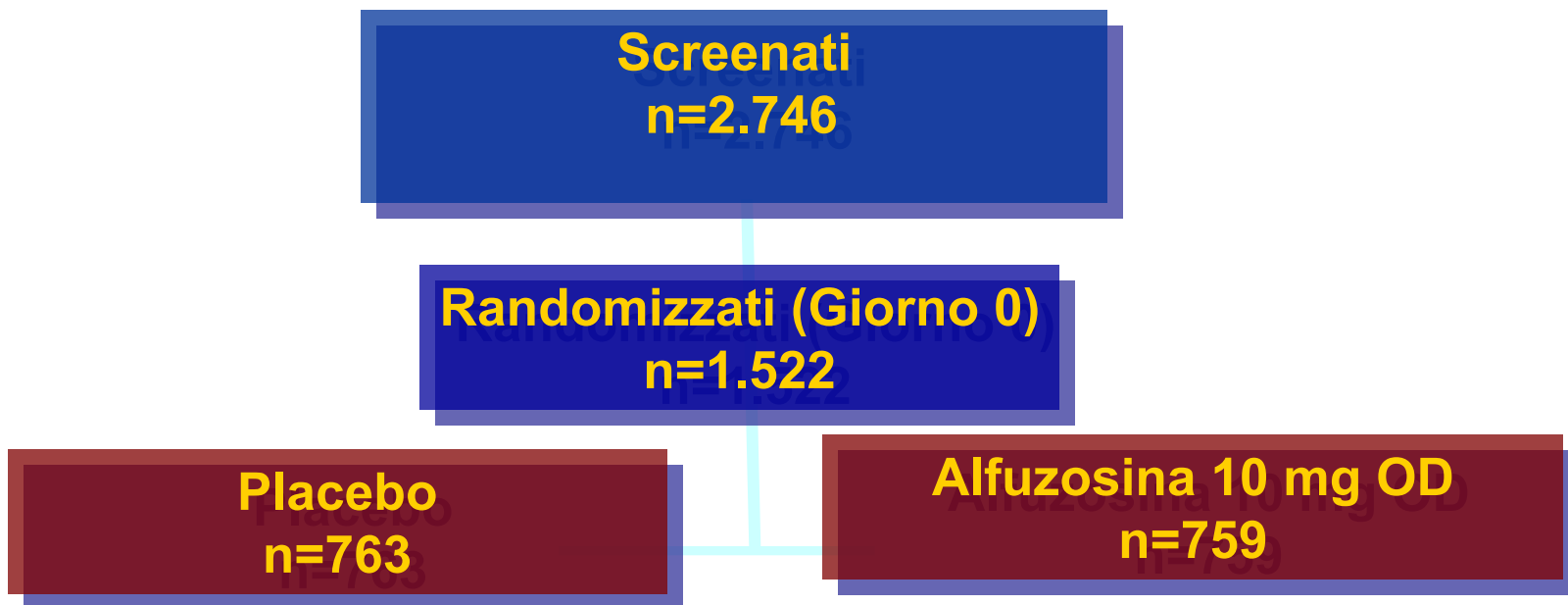
- Roehborn et al. *Urology* 1996  
- *TERAZOSIN VS PLACEBO*
- McNeil et al. *BJU Int* 1999  
- *ALFUZOSIN VS PLACEBO*
- Chapple et al. *Curr Opin Urol* 2001  
- *ALFUZOSIN VS PLACEBO*
- Djavan et al. *Urology* 2004
- Roehborn et al. *BJU Int* 2006 ALTESS  
- *ALFUZOSIN VS PLACEBO*

## Distribuzione dei recettori $\alpha_1$ nelle basse vie urinarie



# *Studio ALTESS*

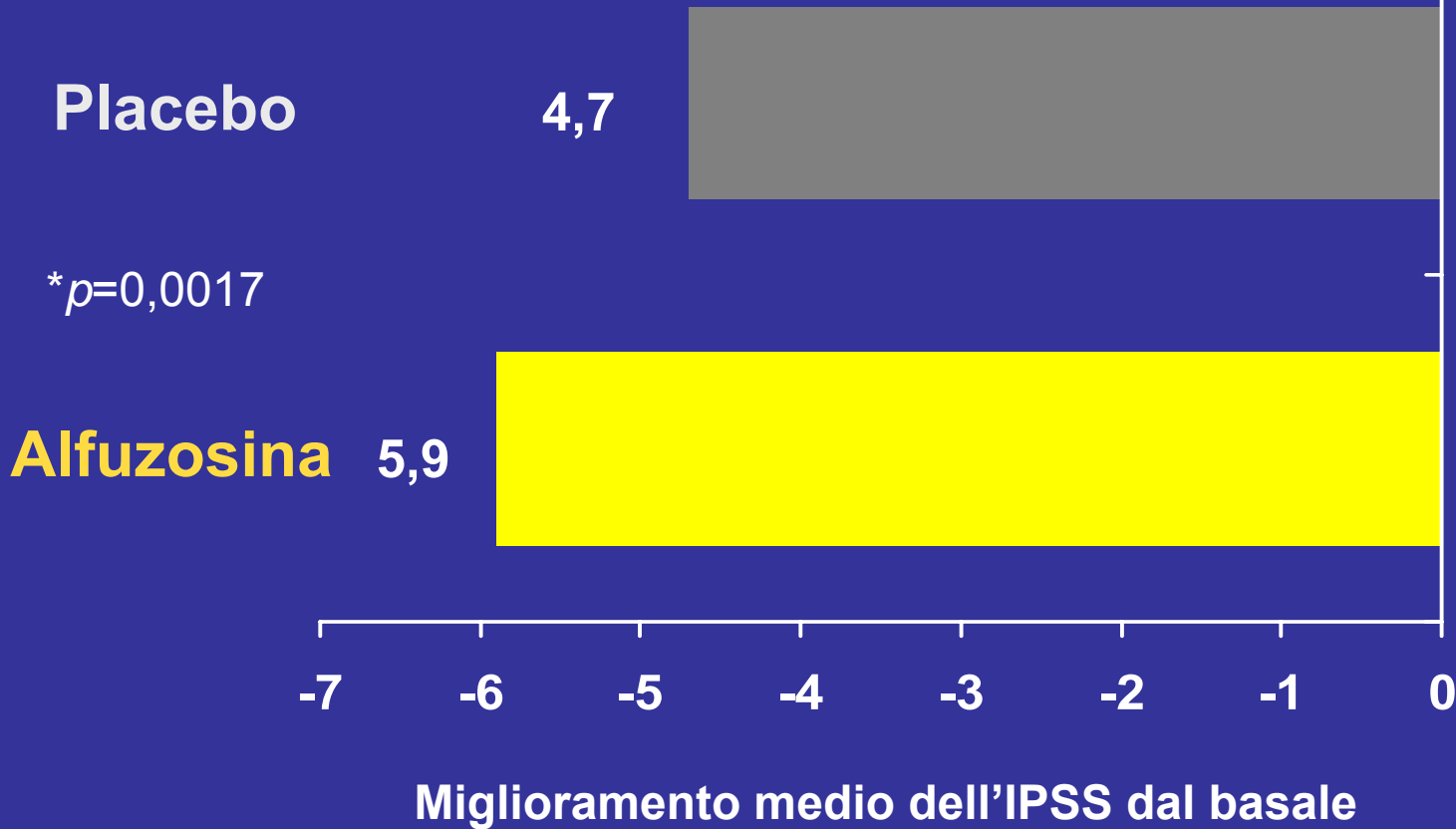
## Reclutamento e randomizzazione



Follow up: 2 anni

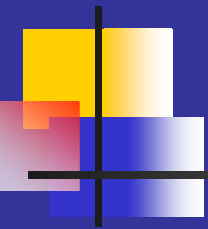
# Studio ALTESS

## Miglioramento dell'IPSS su 2 anni



# Studio ALTESS

Miglioramento della QoL su 2 anni



**Placebo**

0,9

\* $p=0,0001$

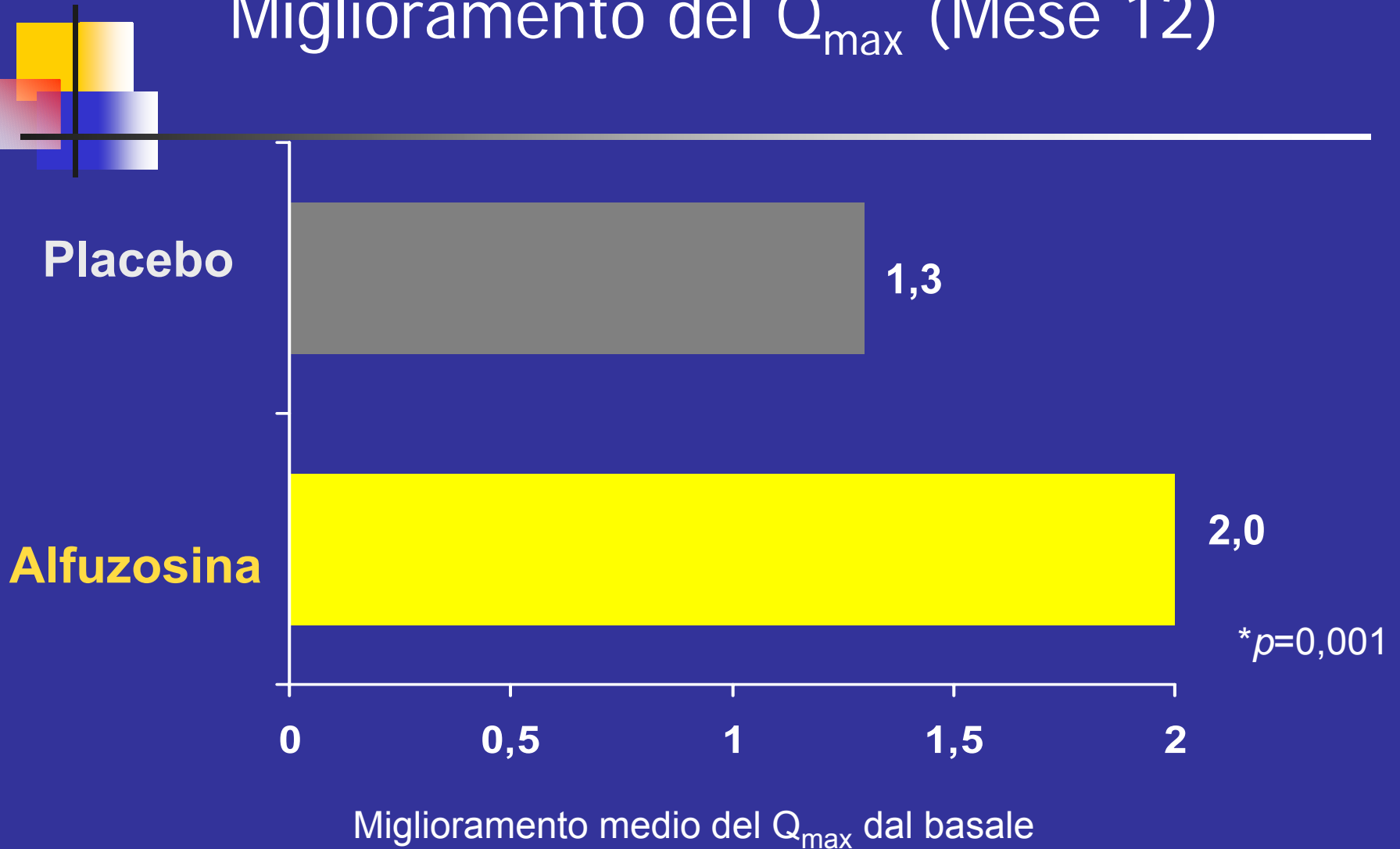
**Alfuzosina** 1,3



Miglioramento medio del bother dal basale

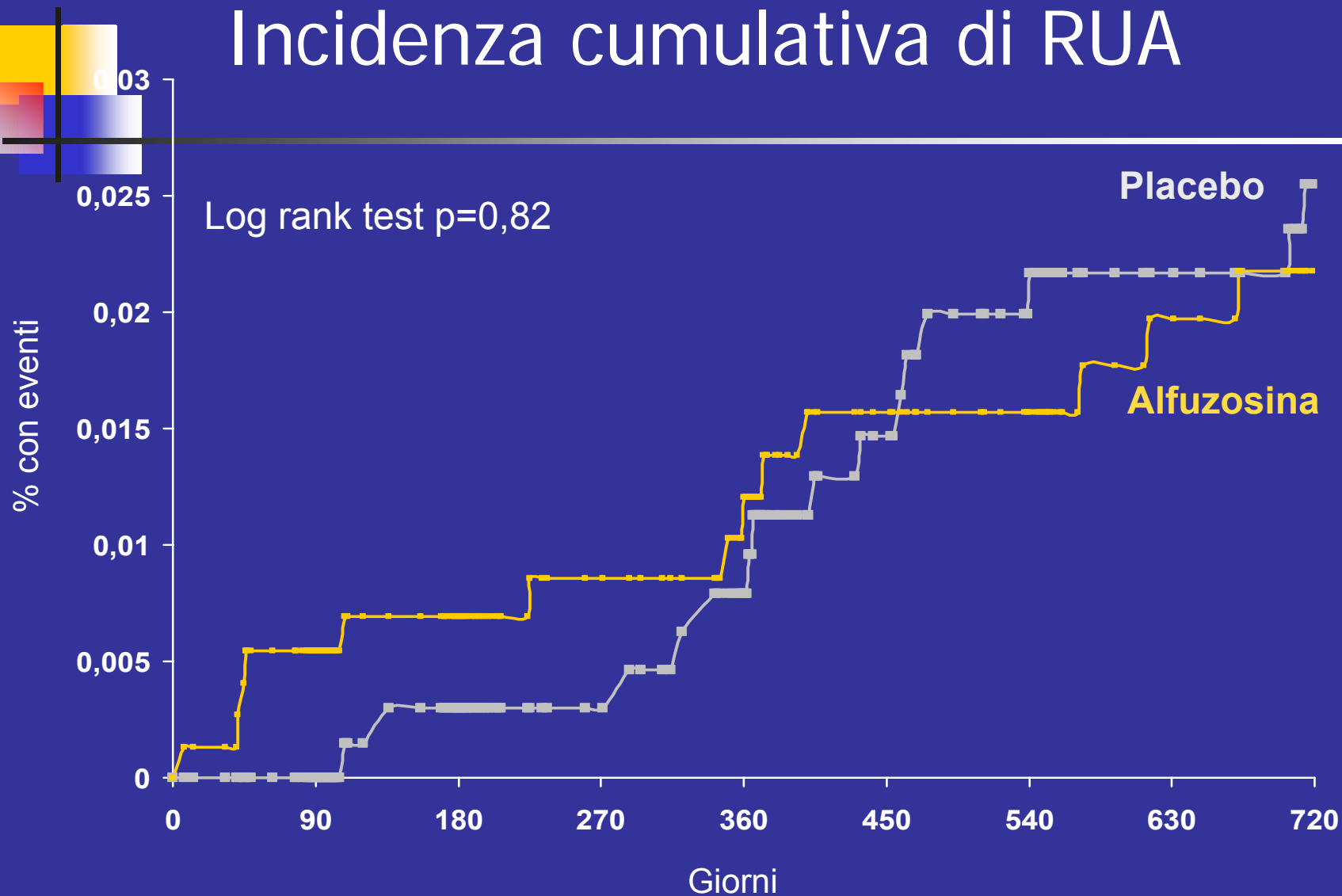
# Studio ALTESS

Miglioramento del  $Q_{\max}$  (Mese 12)



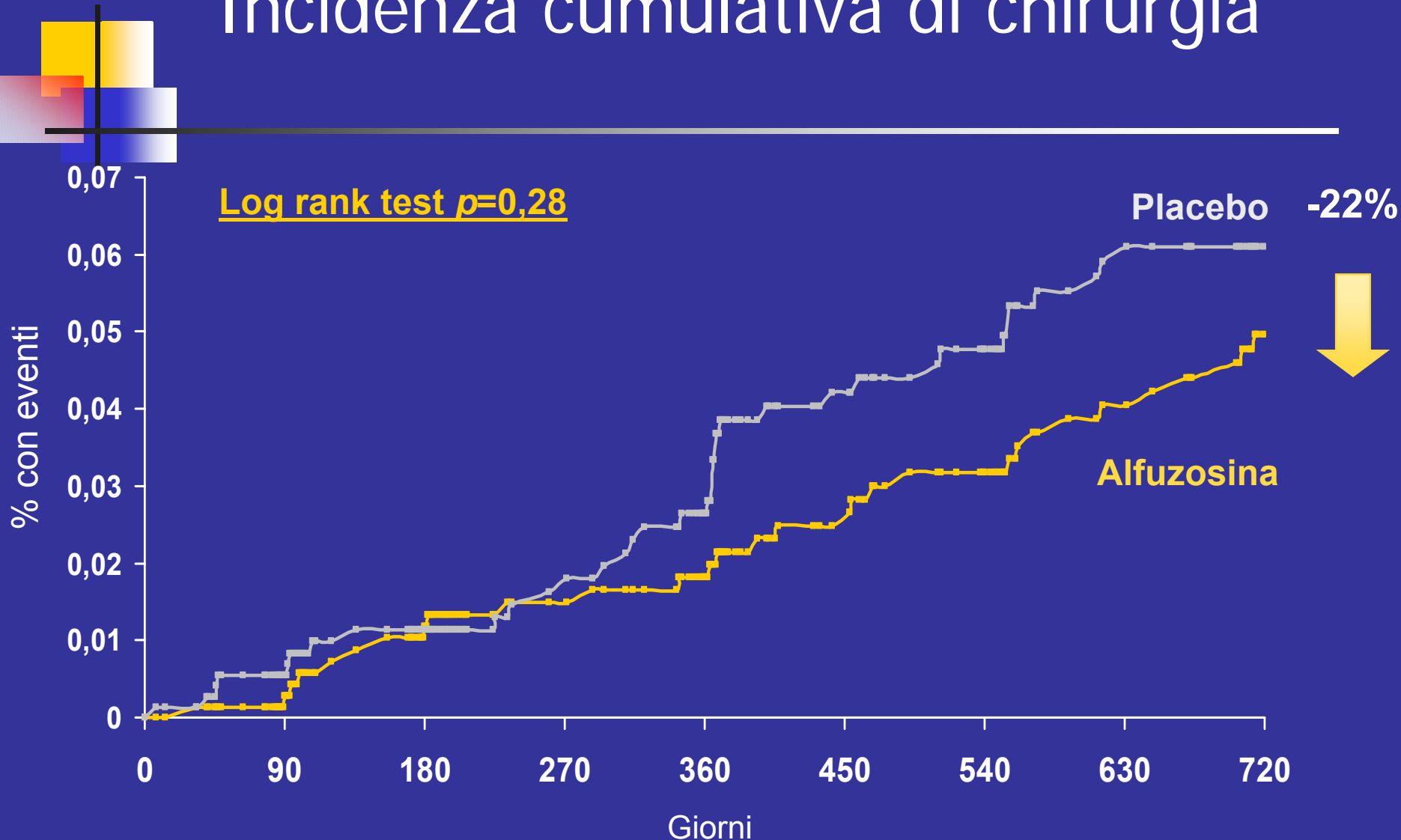
# Studio ALTESS

## Incidenza cumulativa di RUA



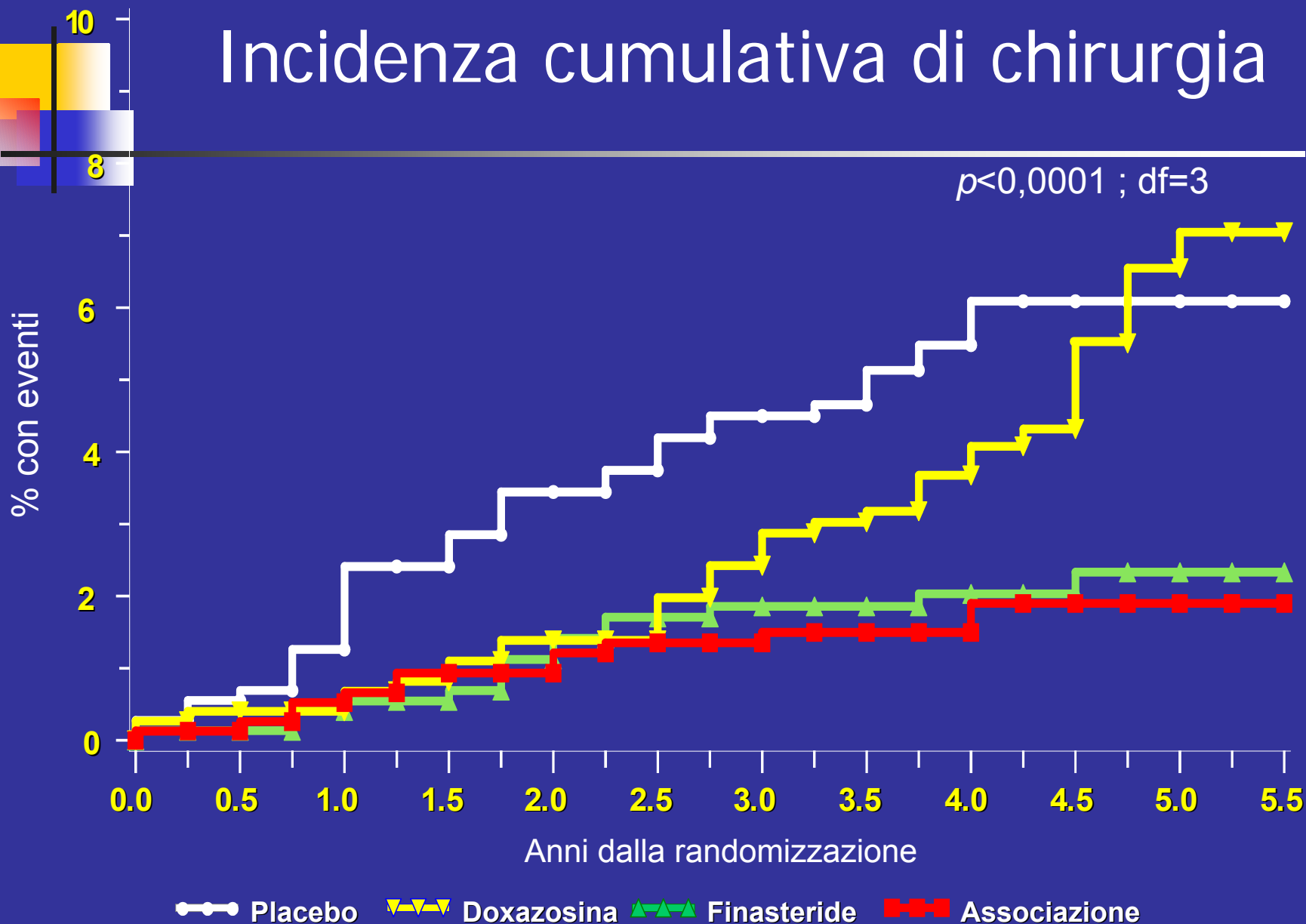
# Studio ALTESS

## Incidenza cumulativa di chirurgia



# Studio MTOPS

## Incidenza cumulativa di chirurgia



# Quale alpha-litico ?

EAU Guidelines 2007

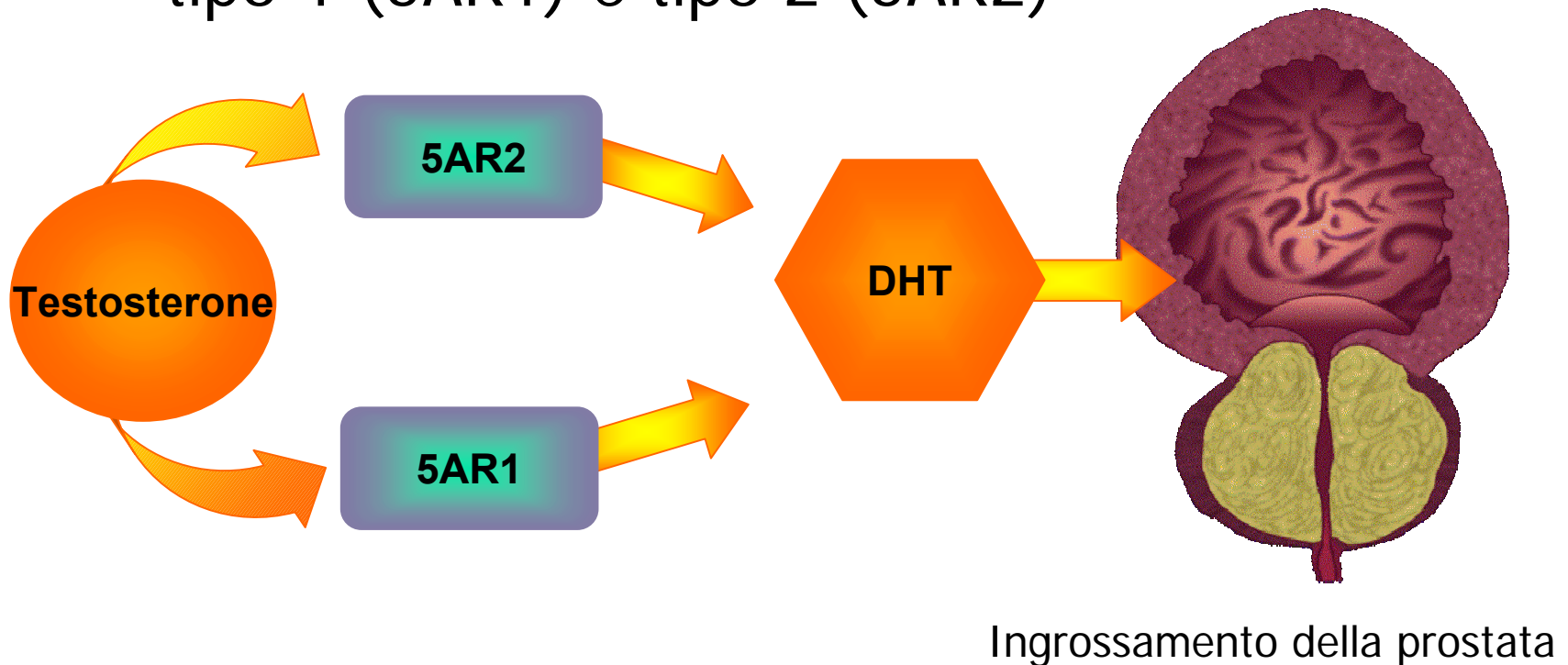
- There is no difference between different alpha-blockers (tamsulosin, doxazosin, terazosin, alfuzosin) in terms of efficacy
- Although the side-effect profiles for some drugs are reported to be more favourable, supportive data are weak

# Inibitori 5 alpha-reduttasi



# Ruolo dei 5ARI

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



# Meccanismo d'azione della finasteride

**Cellula  
prostatica**

**Testosterone**

**Finasteride**

**5AR1**

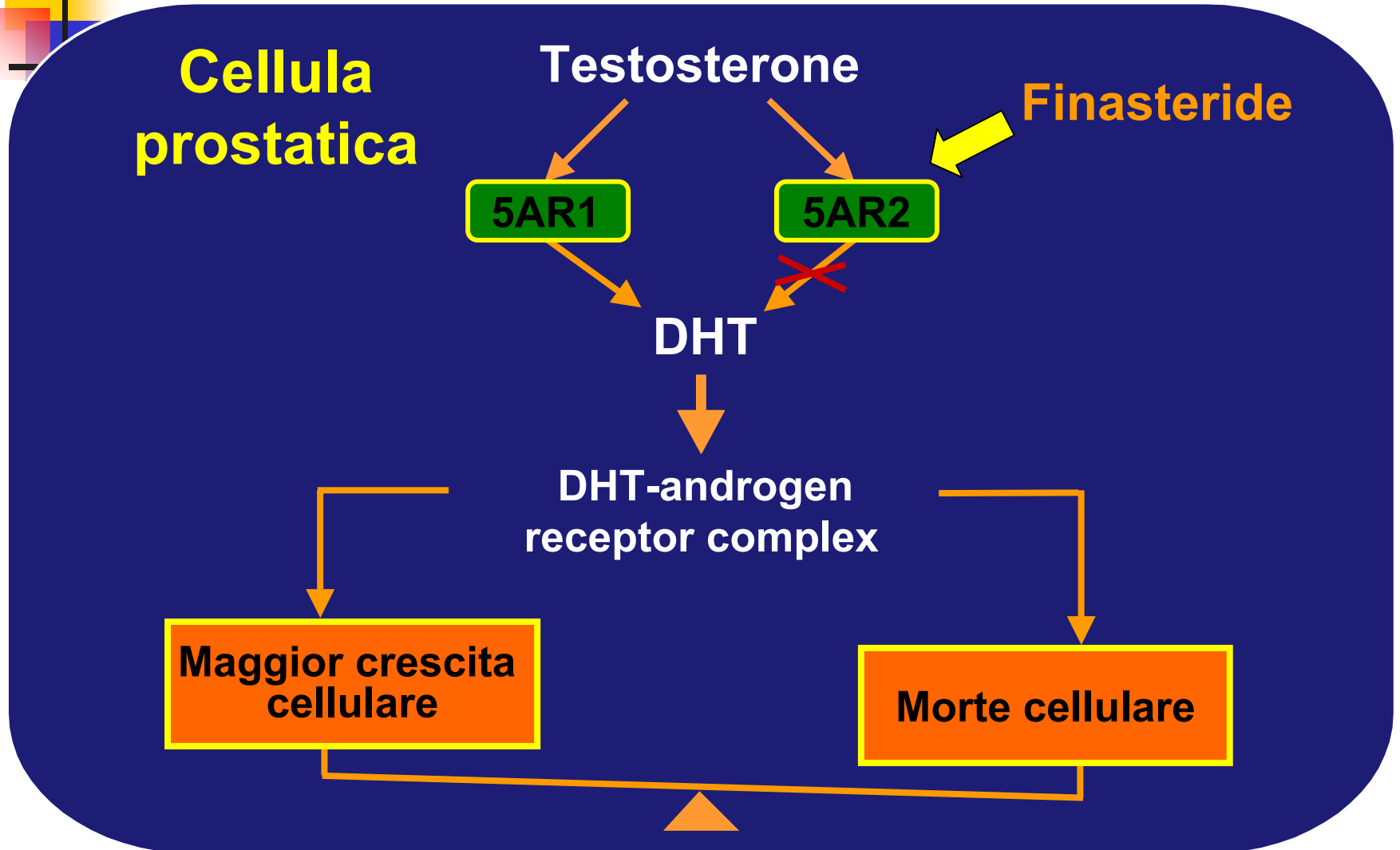
**5AR2**

**DHT**

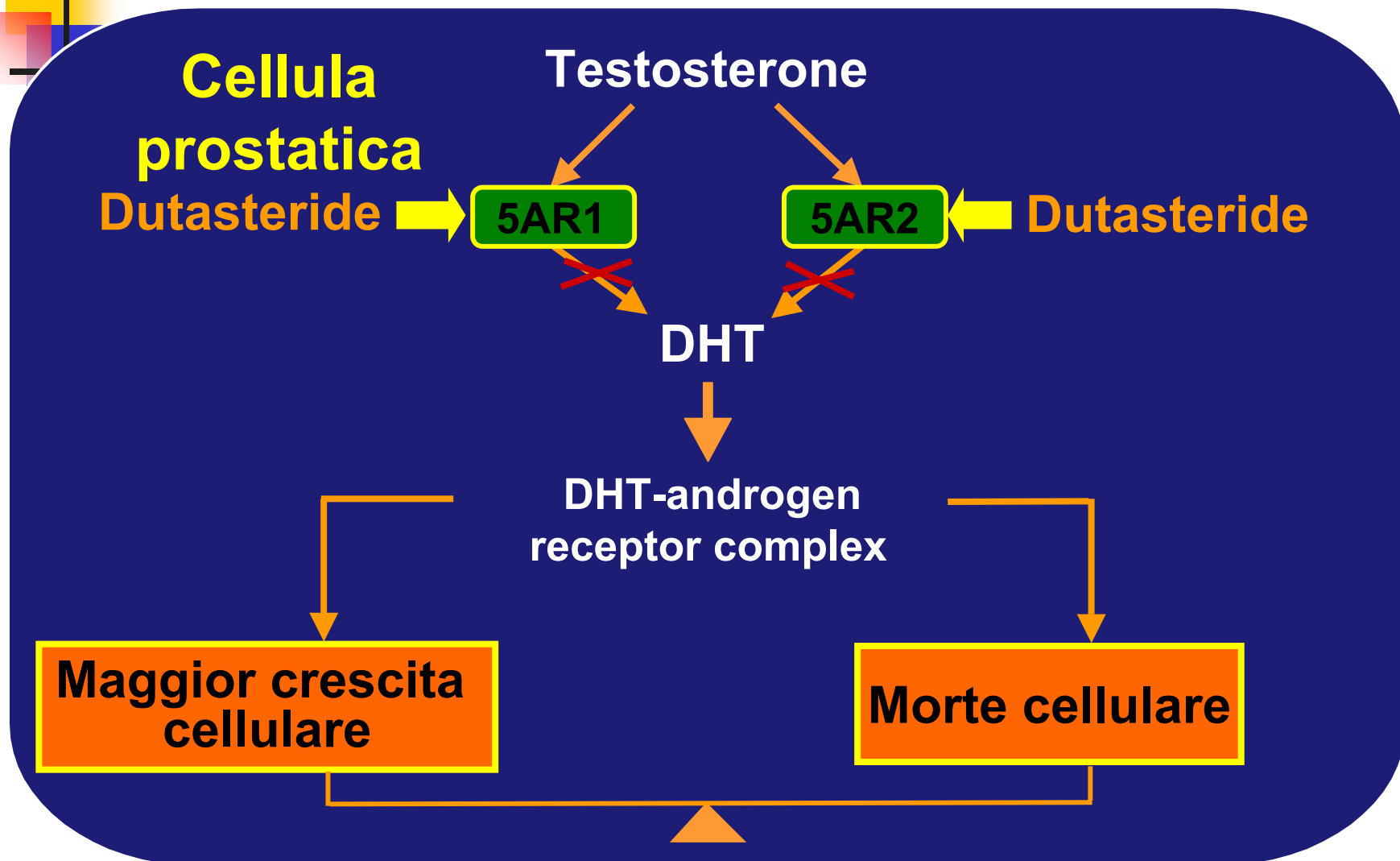
**DHT-androgen  
receptor  
complex**

**Maggior crescita  
cellulare**

**Morte cellulare**



# Meccanismo d'azione della dutasteride





# 5ARI trials

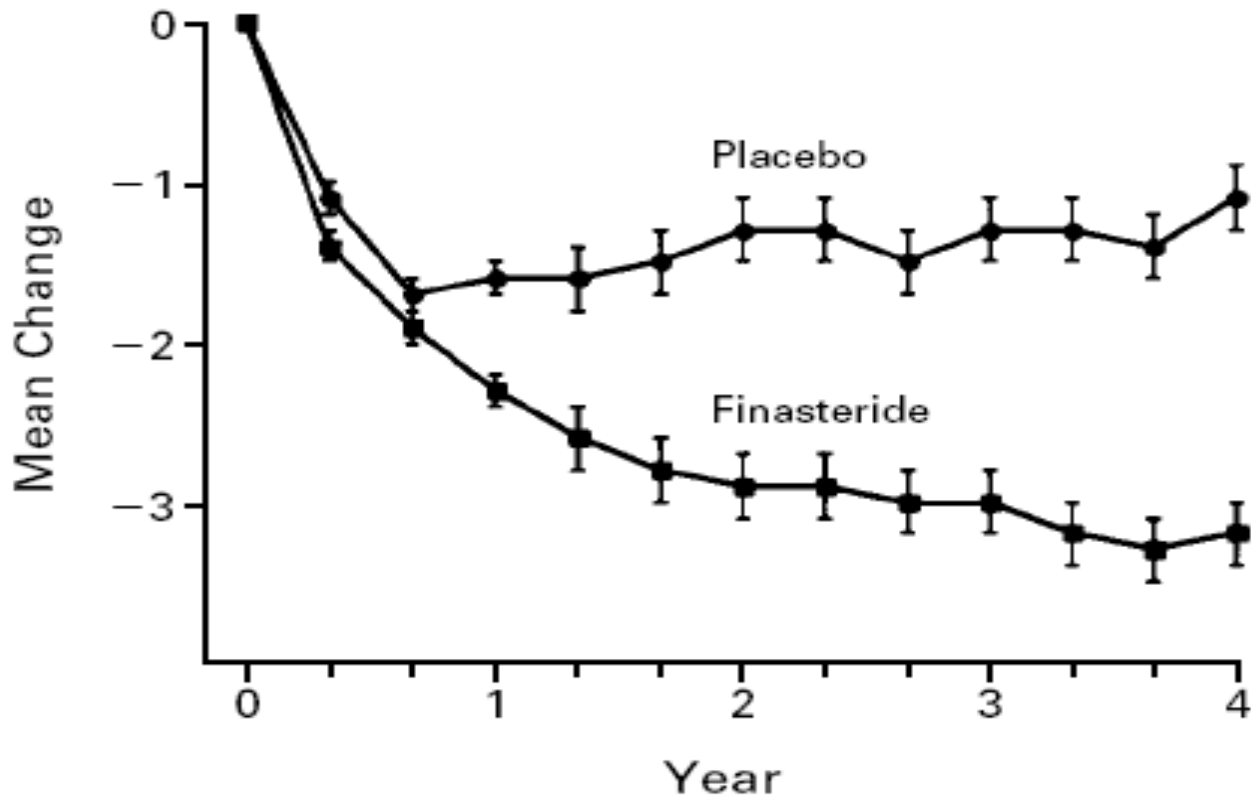
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- Andersen et al. *Urology 1995*
- Lepor et al. *N Engl J Med 1996*
- Nickel et al. *CMAJ 1996 PROSPECT*
- **McConnell et al** *N Engl J Med 1998 PLESS*
- Lowe et al. *Urology 2003*

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

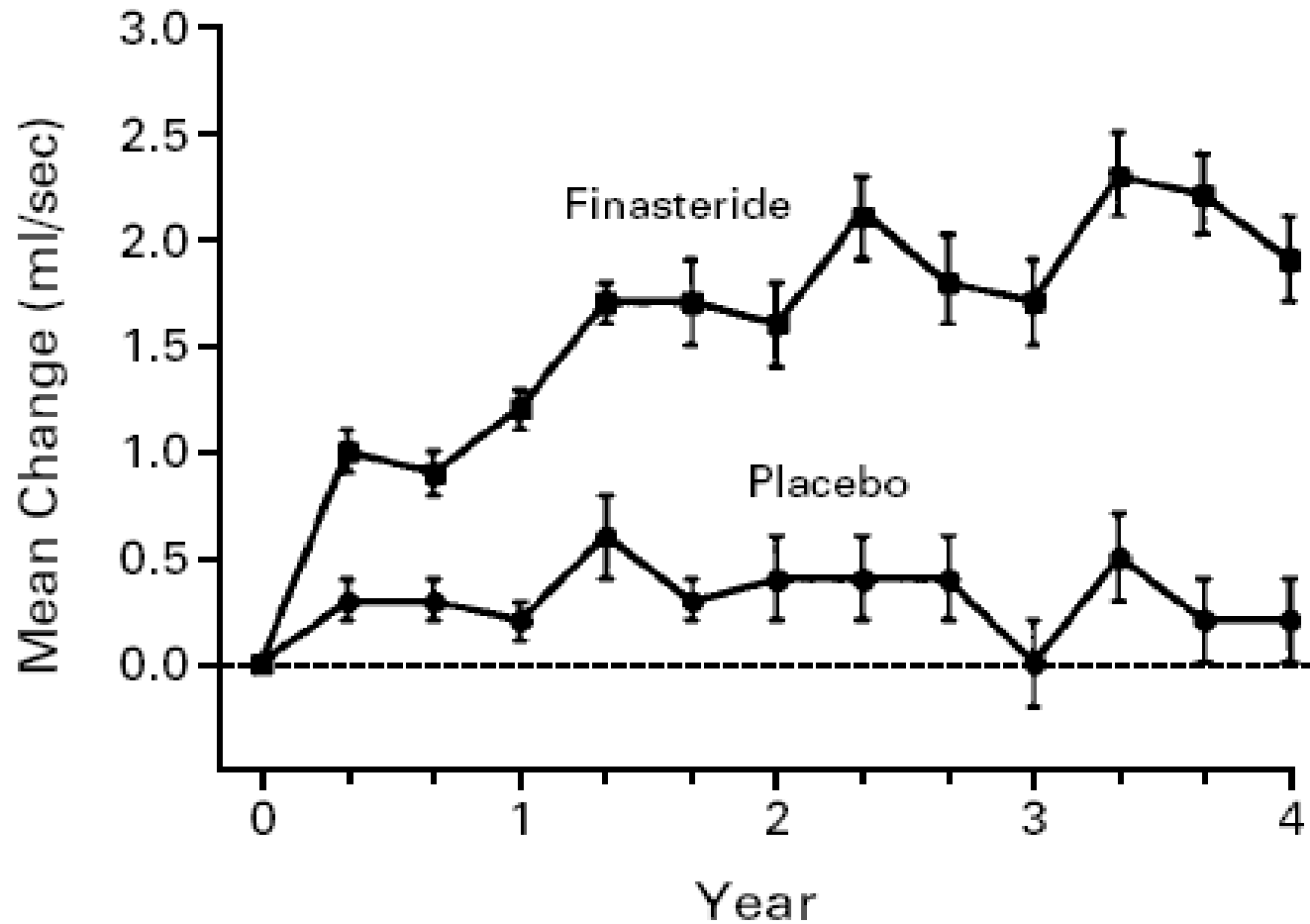
*PLESS study*

*Symptom score*



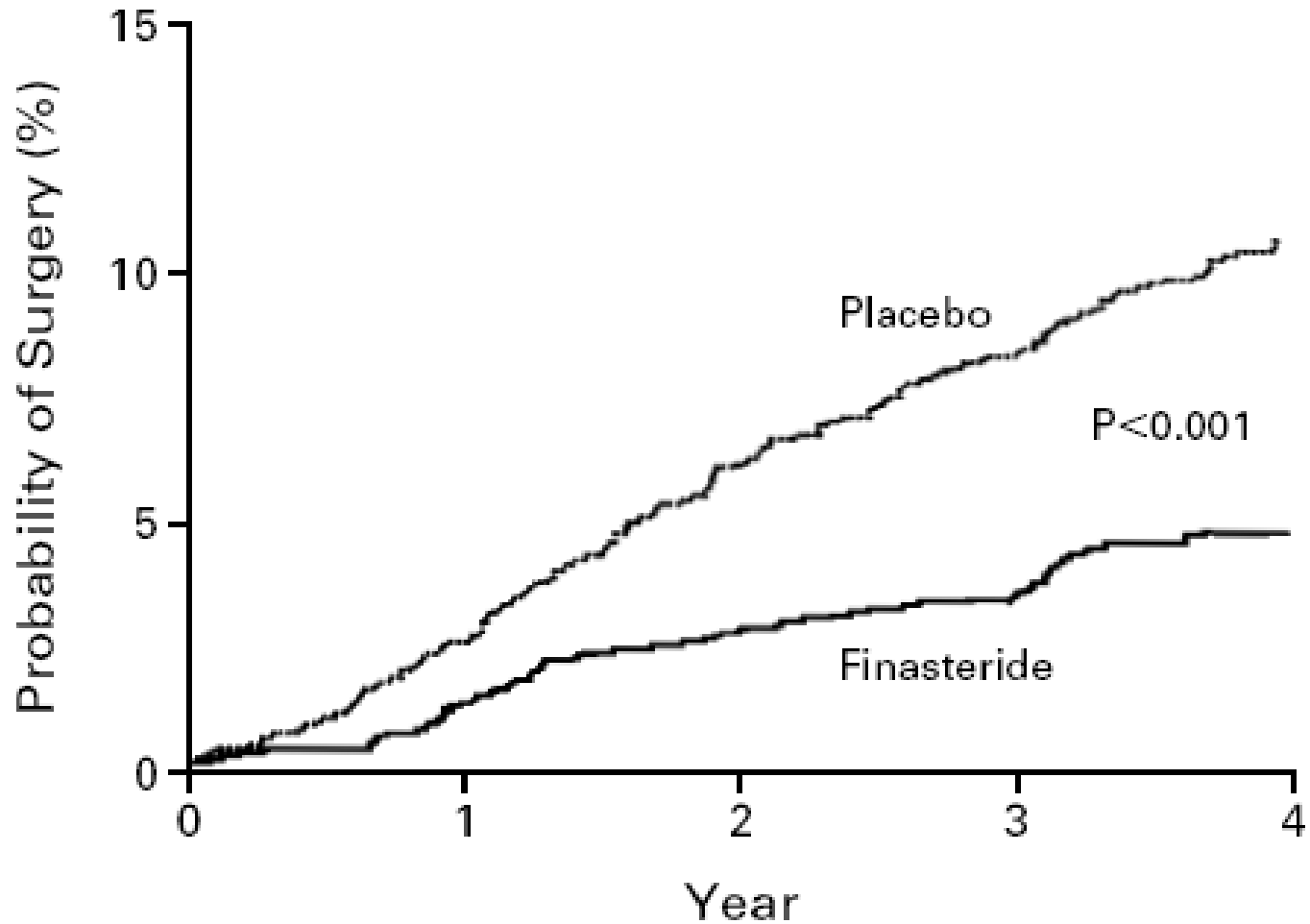
## PLESS study

### Maximal Urinary Flow Rate



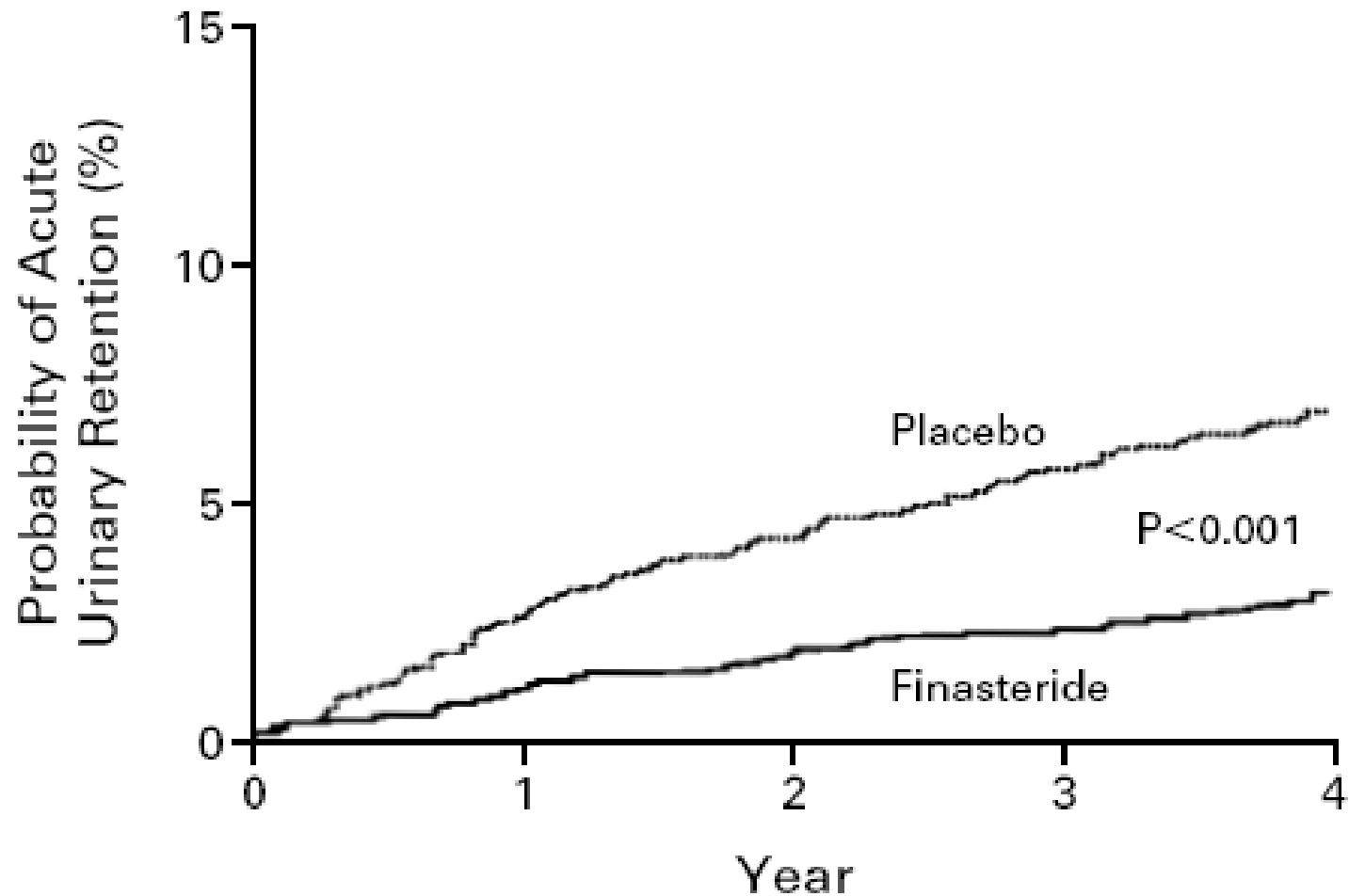
PLESS study

Probability of Surgery



## PLESS study

### Probability of Acute Urinary Retention





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

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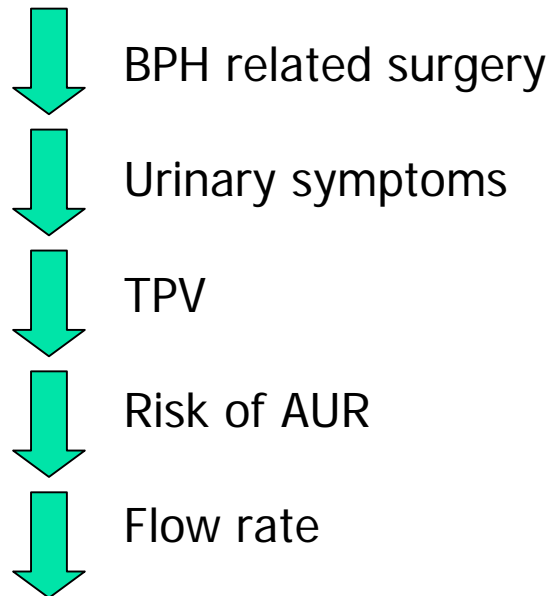
- Nel Prostate Cancer Prevention Trial (PCPT), 18.882 uomini sono stati randomizzati a ricevere il 5 ARI selettivo per il tipo-2, finasteride, 5 mg/giorno o il placebo per 7 anni.
- Nel gruppo con finasteride, l'incidenza di PCa è stata ridotta del 24.8% ( $p < 0.001$ ) in confronto al gruppo placebo.
- 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%,  $p = 0.005$ ).

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

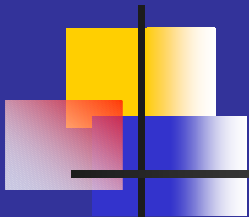
Debruyne et al Eur Urol 2004

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

- Aria 3001
- Aria 3002
- Arib 3003

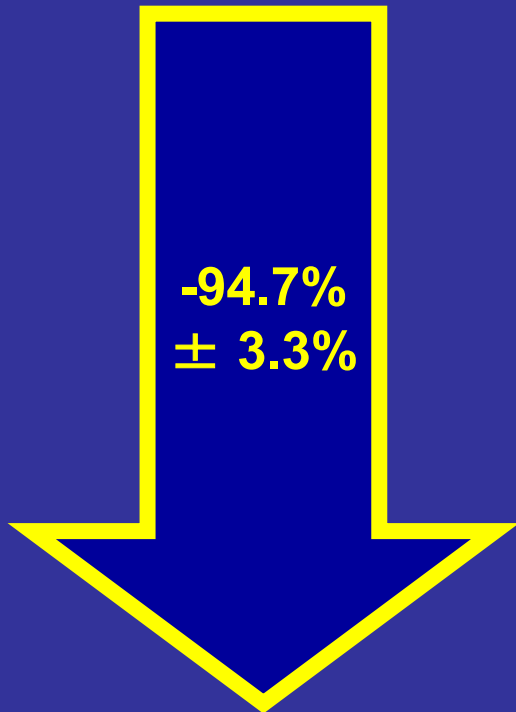


# Maggiore soppressione dei livelli di DHT osservati con dutasteride in confronto con finasteride



Soppressione media ( $\pm$  SD) di DHT dopo 24 settimane di terapia

Dutasteride 0.5 mg/day



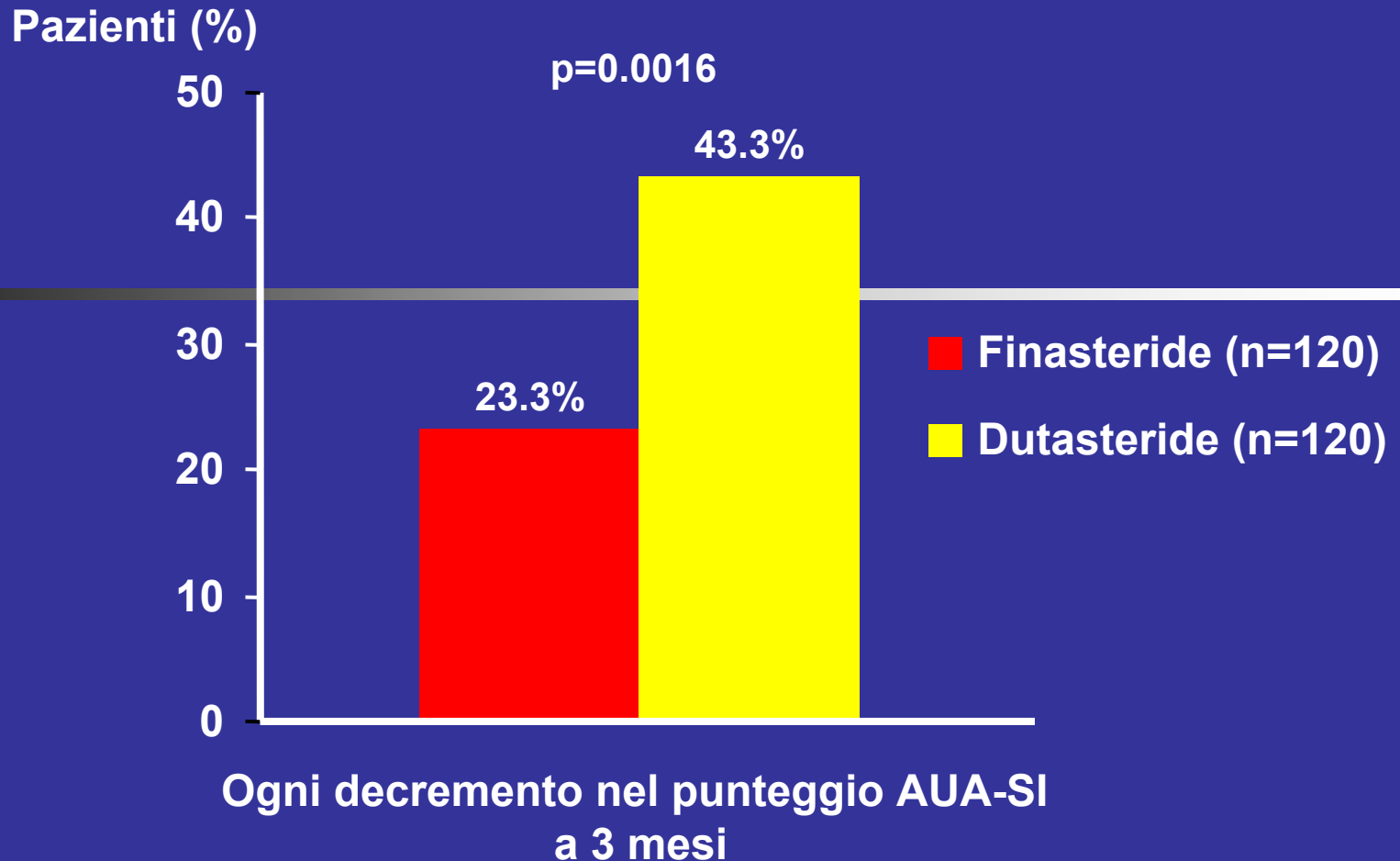
$p < 0.001$

Finasteride 5.0 mg/day

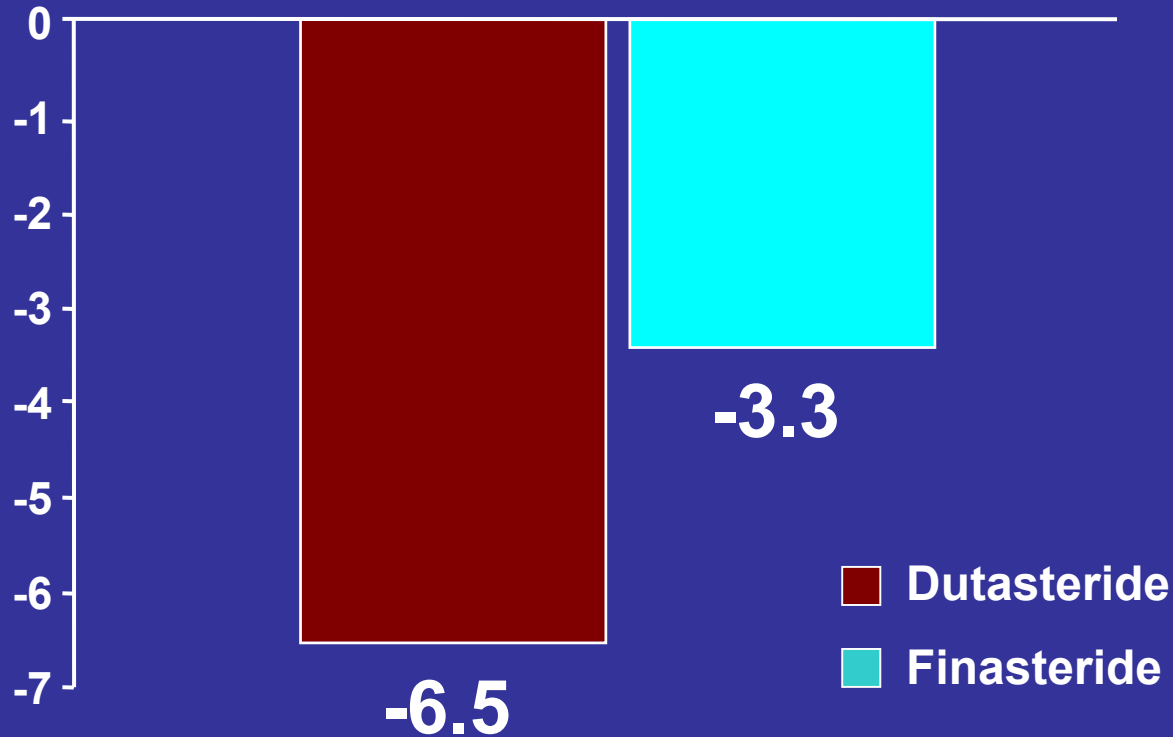


# Dutasteride *versus* Finasteride

## IPSS

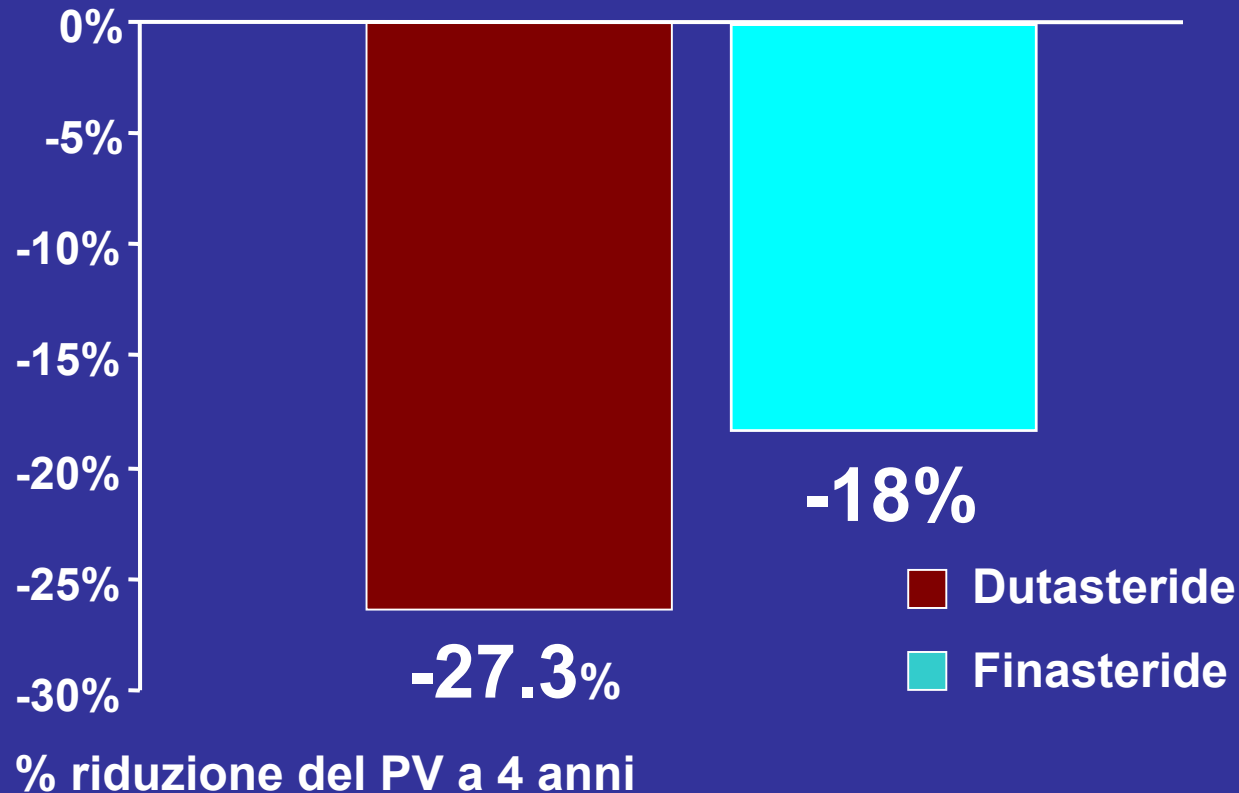


# Miglioramento dell' AUA-SI Score a 4 anni con Dutasteride vs. Finasteride



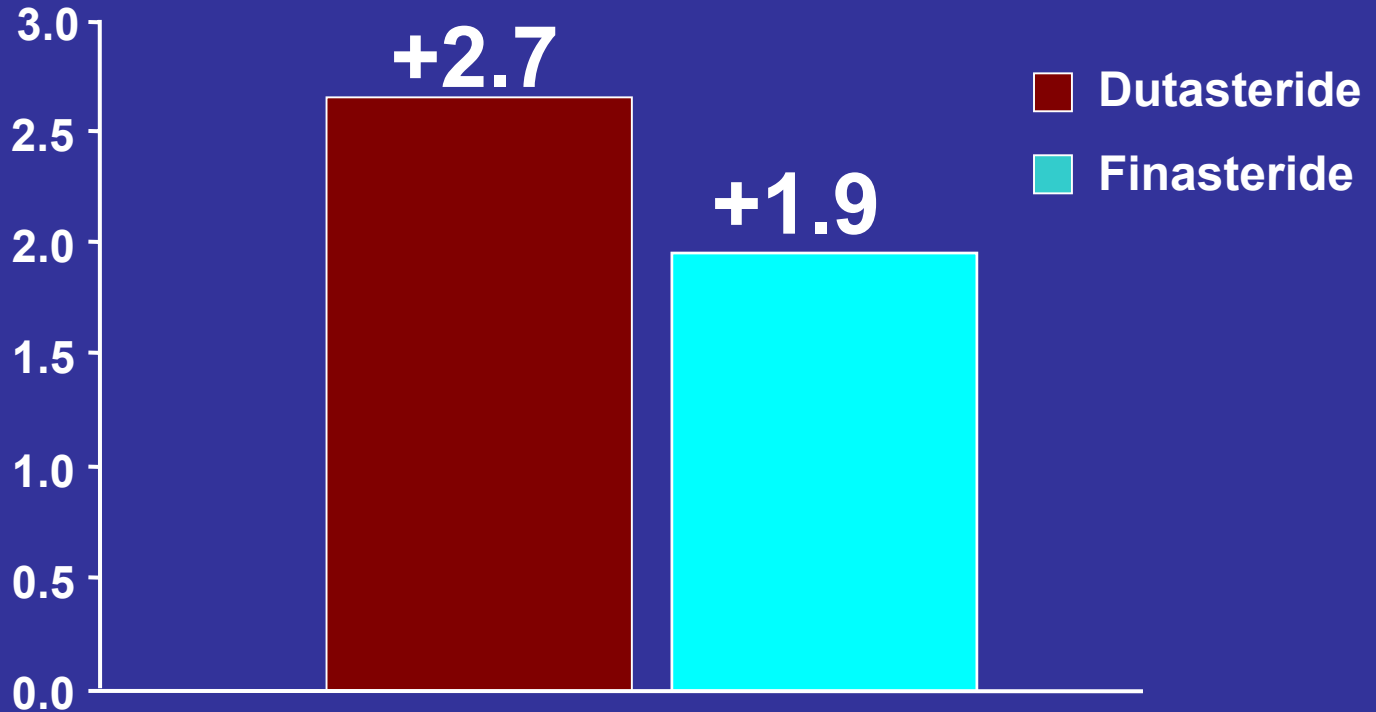
Variazione dell' AUA-SI score a 4 anni

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



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

Aumento del  $Q_{max}$  a 4 anni (mL/sec)



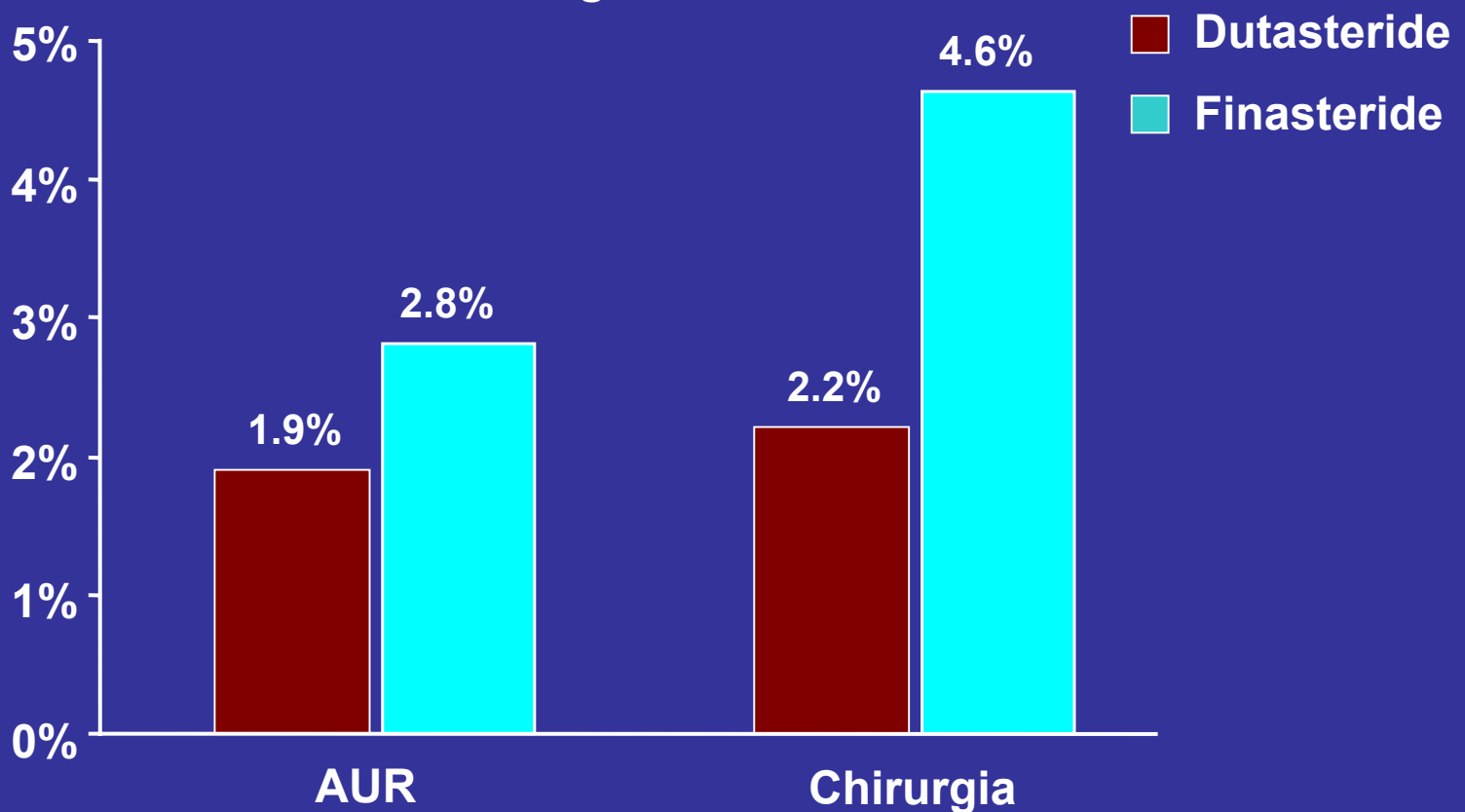
Debruyne *et al. Eur Urol* 2004;46:488–95

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

Incidenza di AUR e chirurgia



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

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

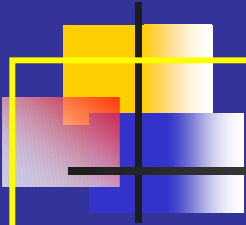
Confronto indiretto di dutasteride dati a 4 anni vs. PLESS

# Terapia combinata

*alfa-litici + 5ARI*



# Terapia combinata: il meglio di due mondi?



5ARIs

$\alpha$ -bloccanti

Riduzione del VP



Mantenimento della riduzione del VP



Miglioramento dei sintomi e del flusso



**Sollievo dai sintomi in 1-2 settimane**



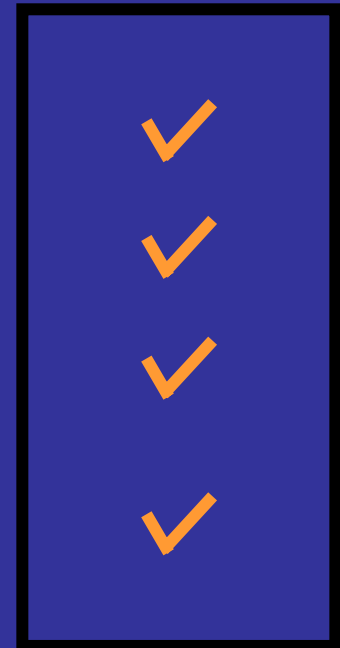
Conservato miglioramento dei sintomi  
e del flusso



Prevenzione della progressione sintomatica

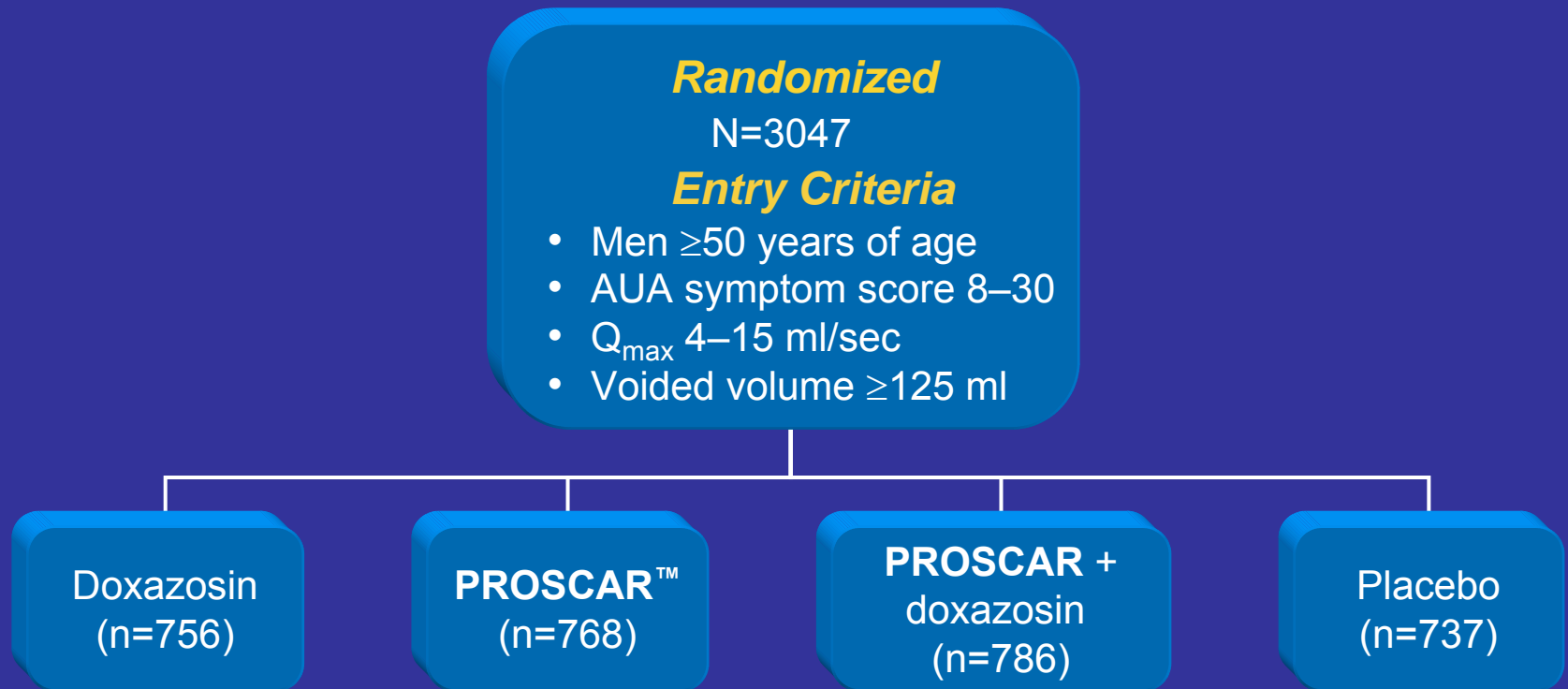


Riduzione a lungo termine del rischio di RUA  
e di intervento chirurgico



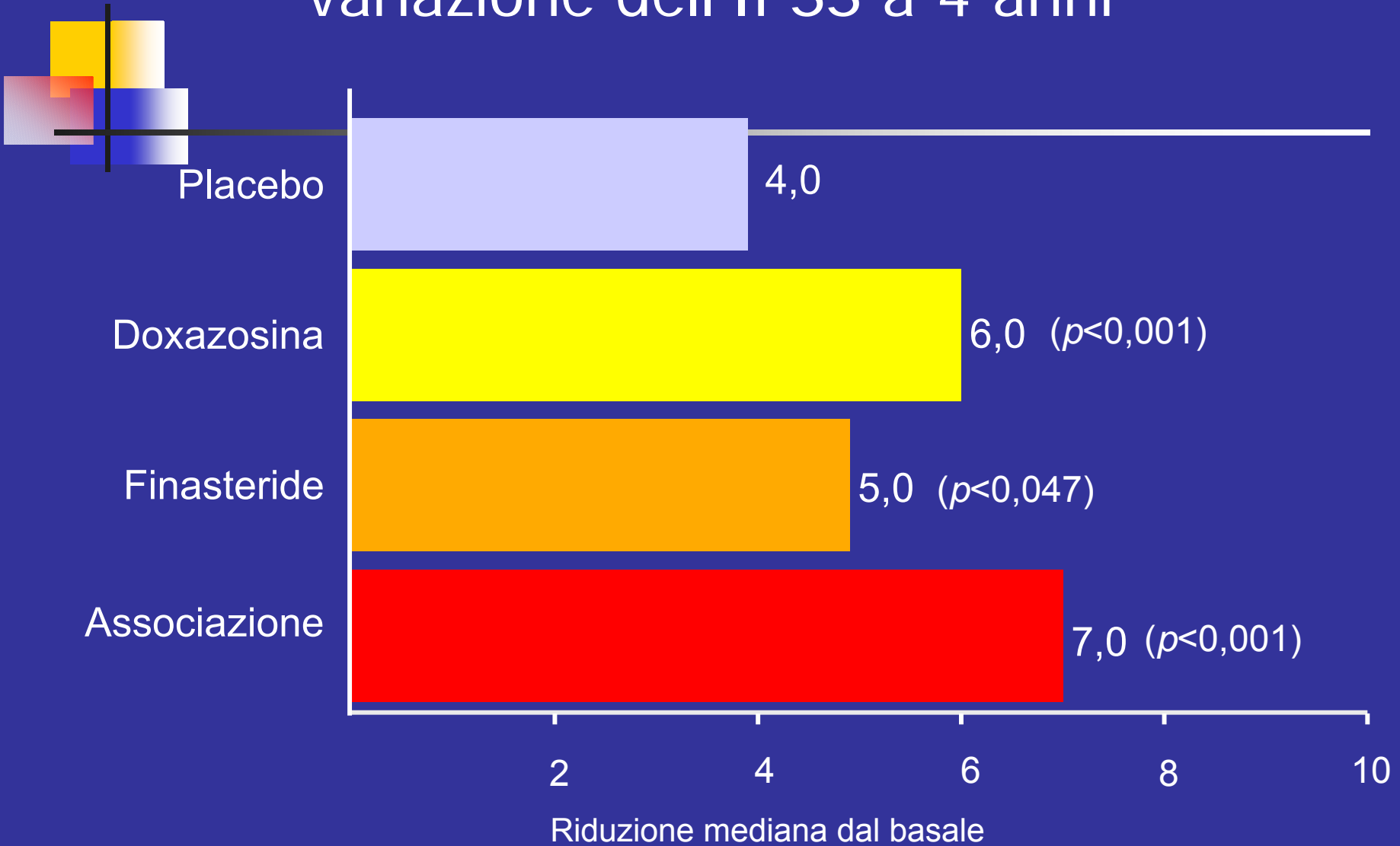
# MTOPS (Medical Therapy Of Prostatic Symptoms)

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



# Studio MTOPS

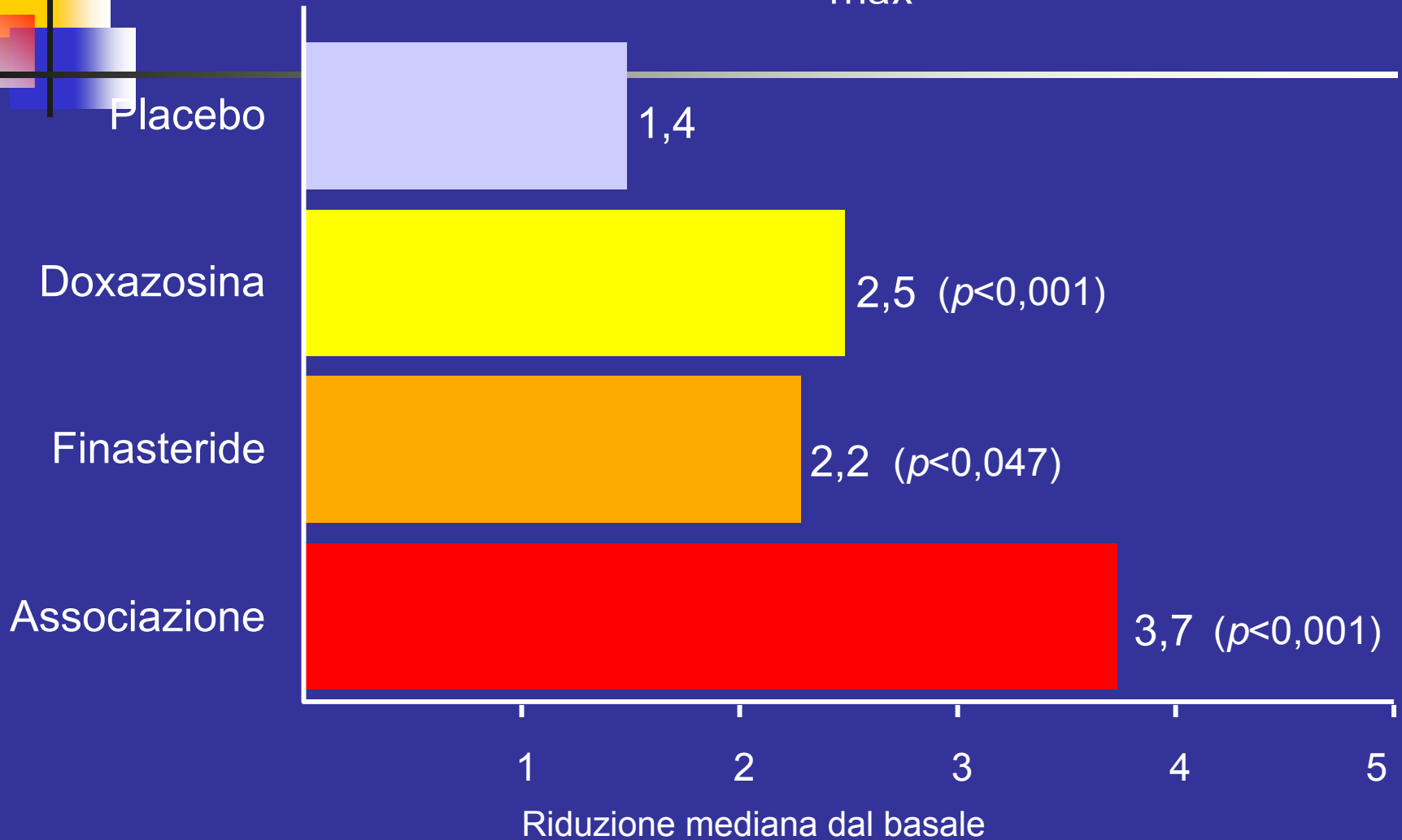
variazione dell'IPSS a 4 anni



Valore mediano basale dell'AUA SI = 17,0

# Studio MTOPS

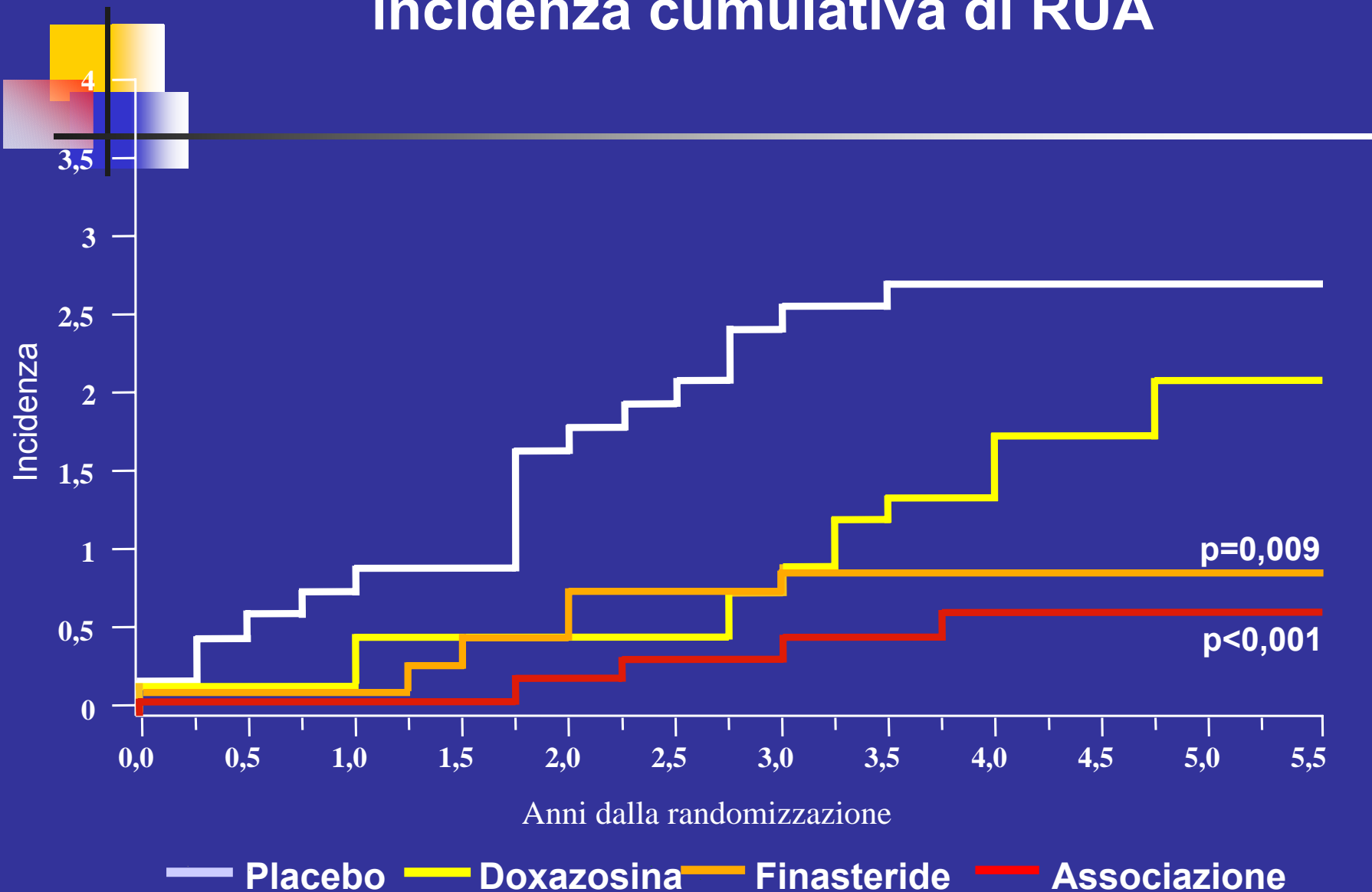
## Variazione del $Q_{max}$ a 4 anni



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

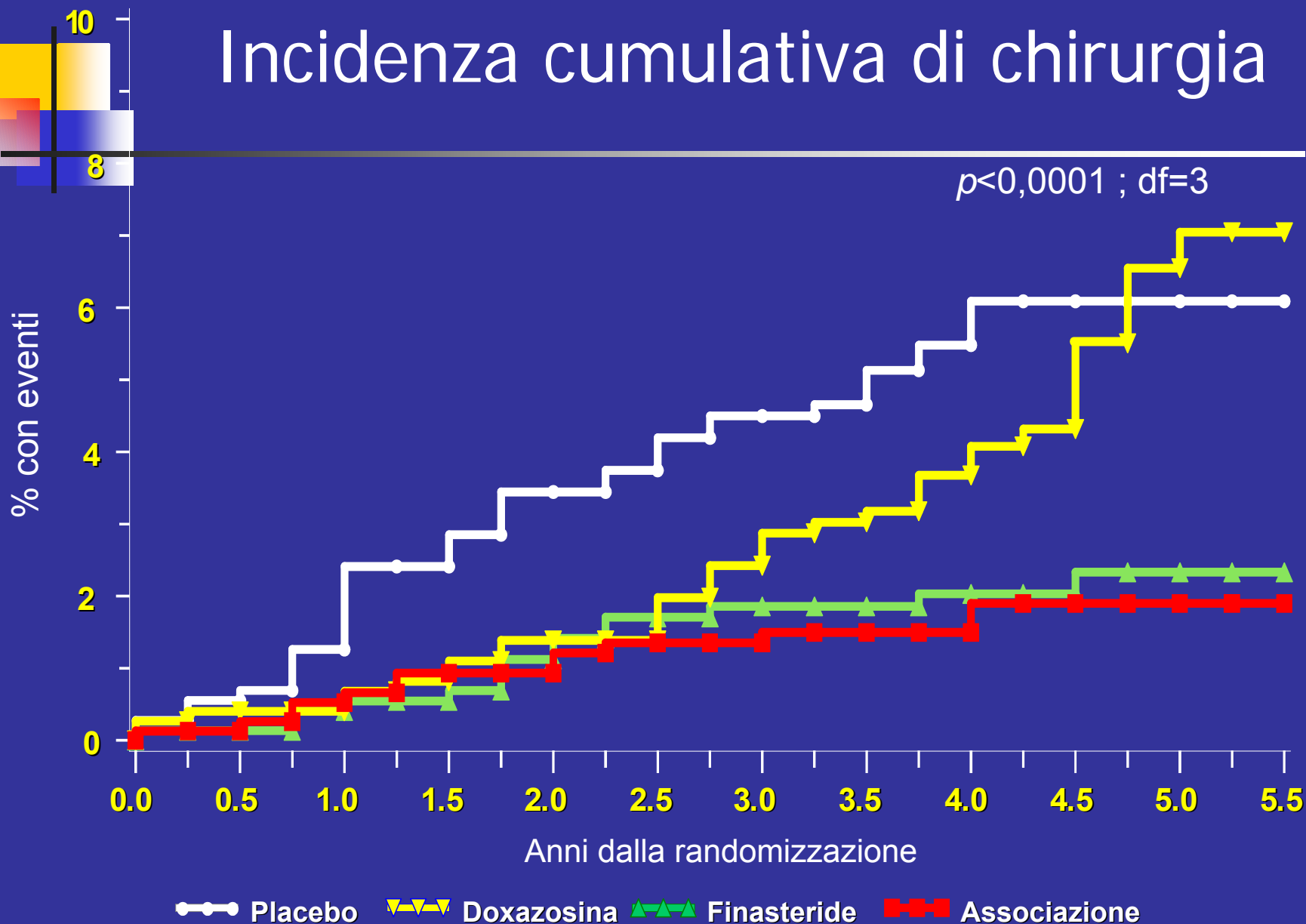
# Studio MTOPS

## incidenza cumulativa di RUA



# Studio MTOPS

## Incidenza cumulativa di chirurgia



# Conclusions

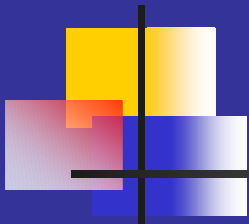
■ Combination therapy is the most effective form of medical therapy for BPH

- **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

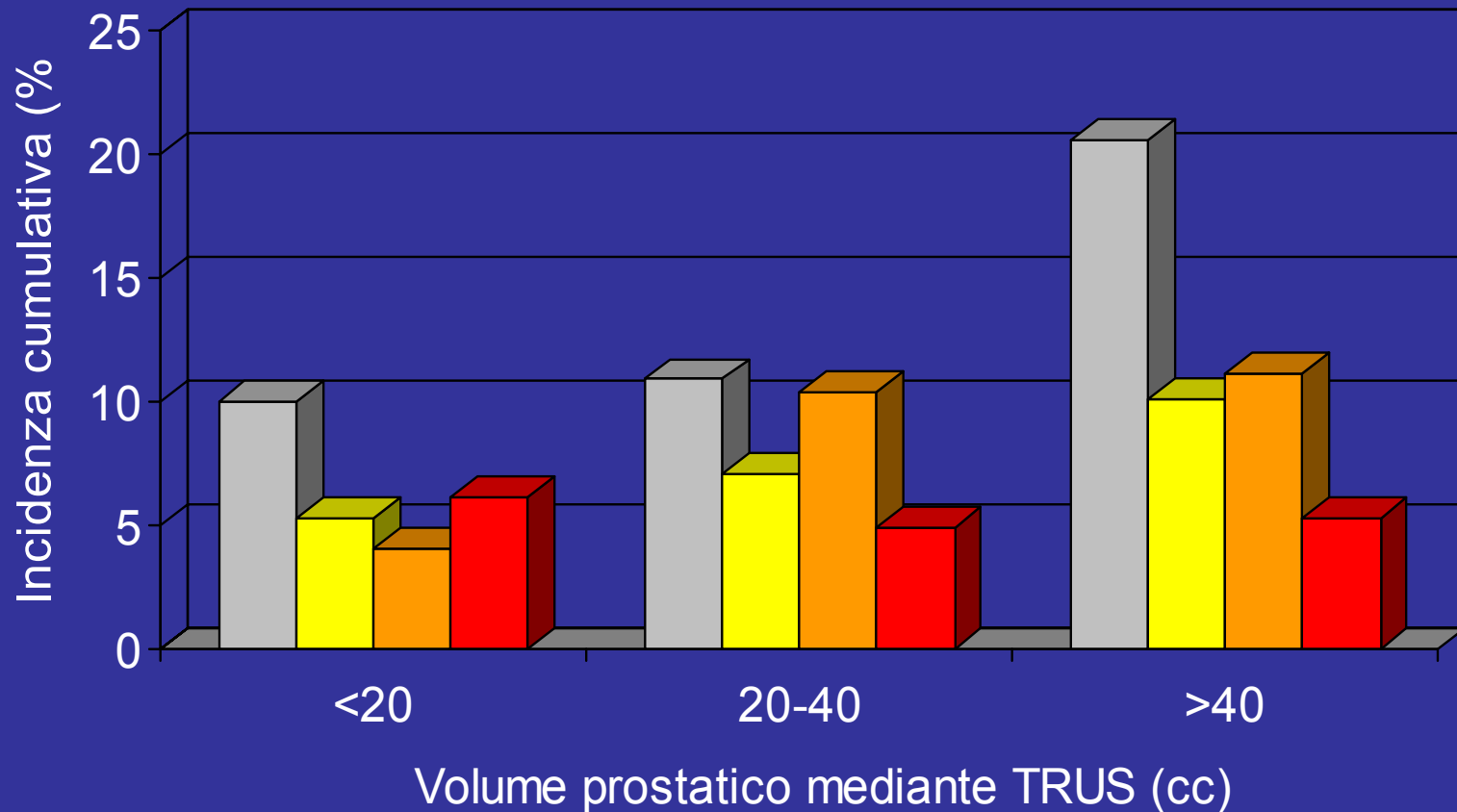
Adapted from McConnell JD et al *N Engl J Med* 2003;349(25):2385-2396.



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

# Aumento dell'AUA Symptom Score ( $\geq 4$ )

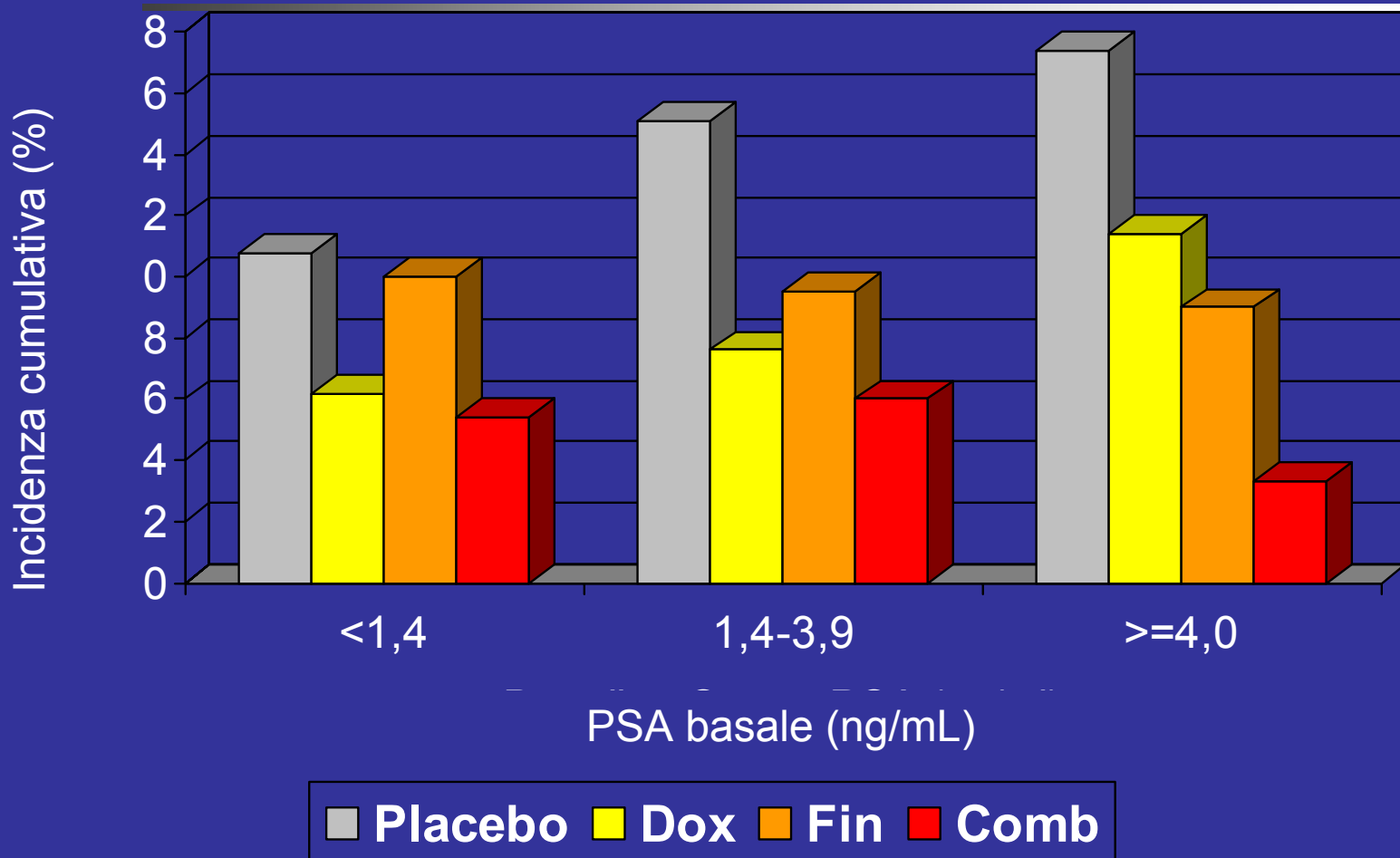
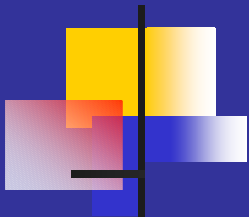
## Rapporto con il volume prostatico



Placebo Dox Fin Comb

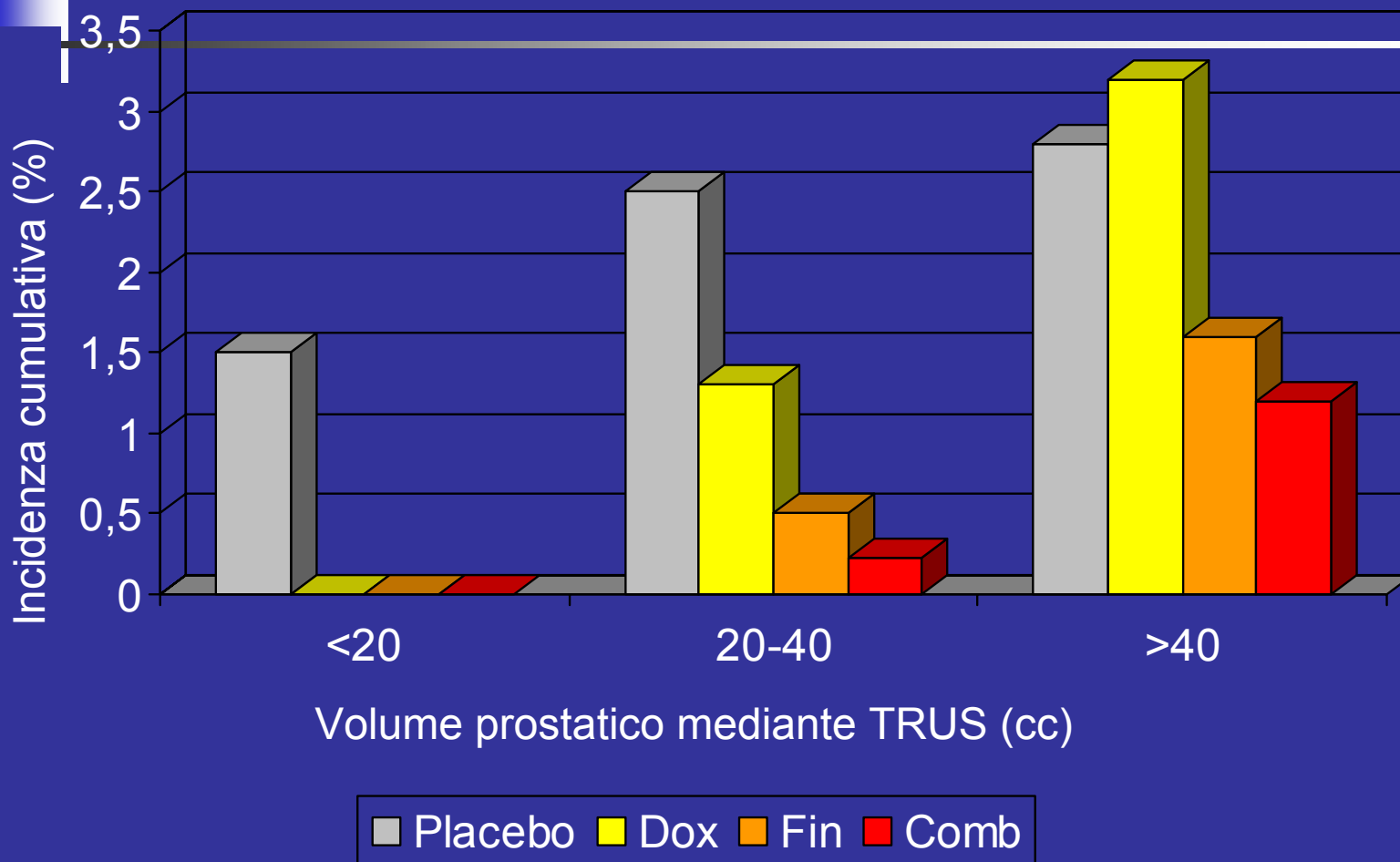
# Aumento dell'AUA Symptom Score ( $\geq 4$ )

## Rapporto con i valori di PSA



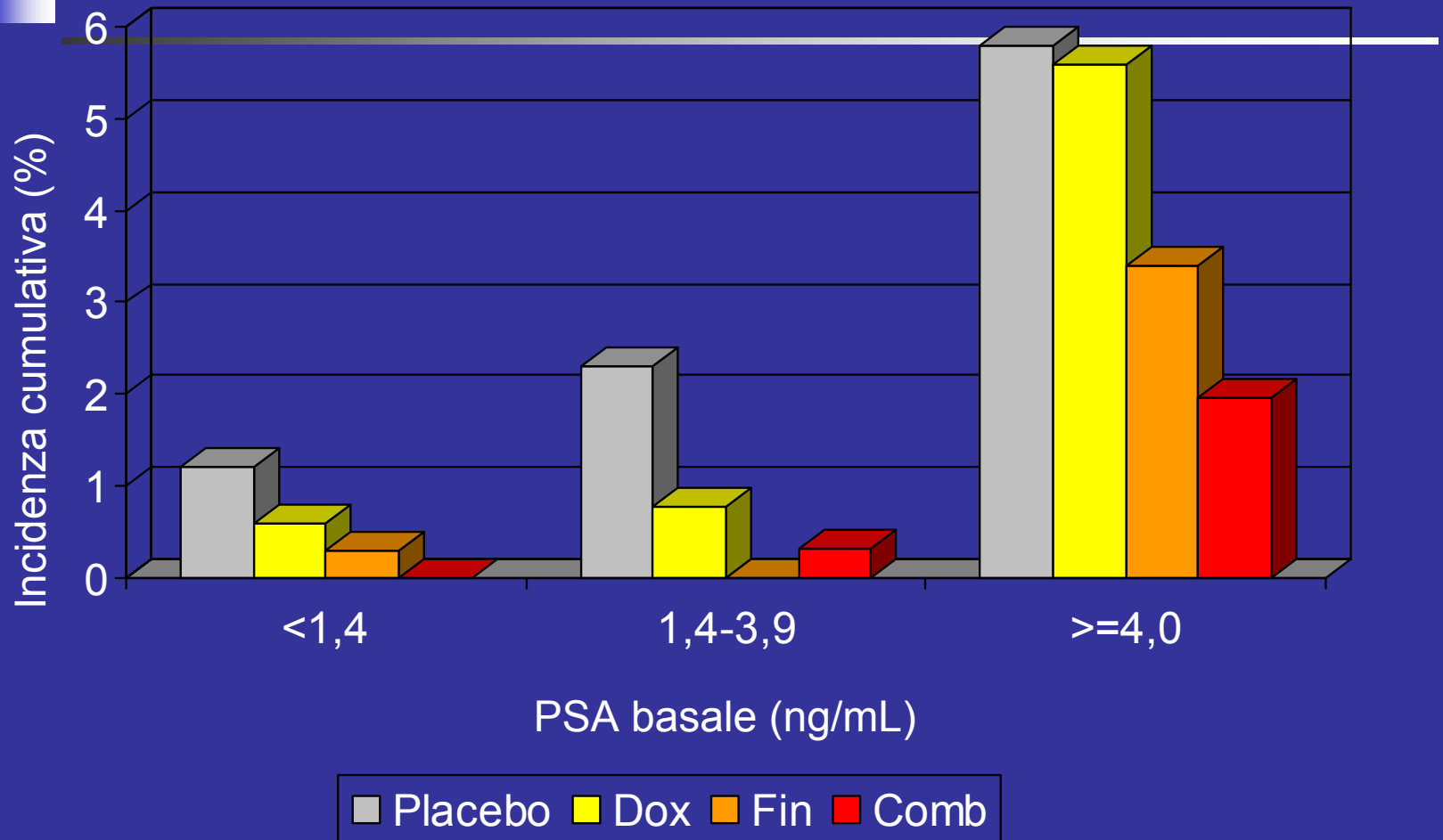
# Ritenzione Urinaria Acuta

## Rapporto con il volume prostatico



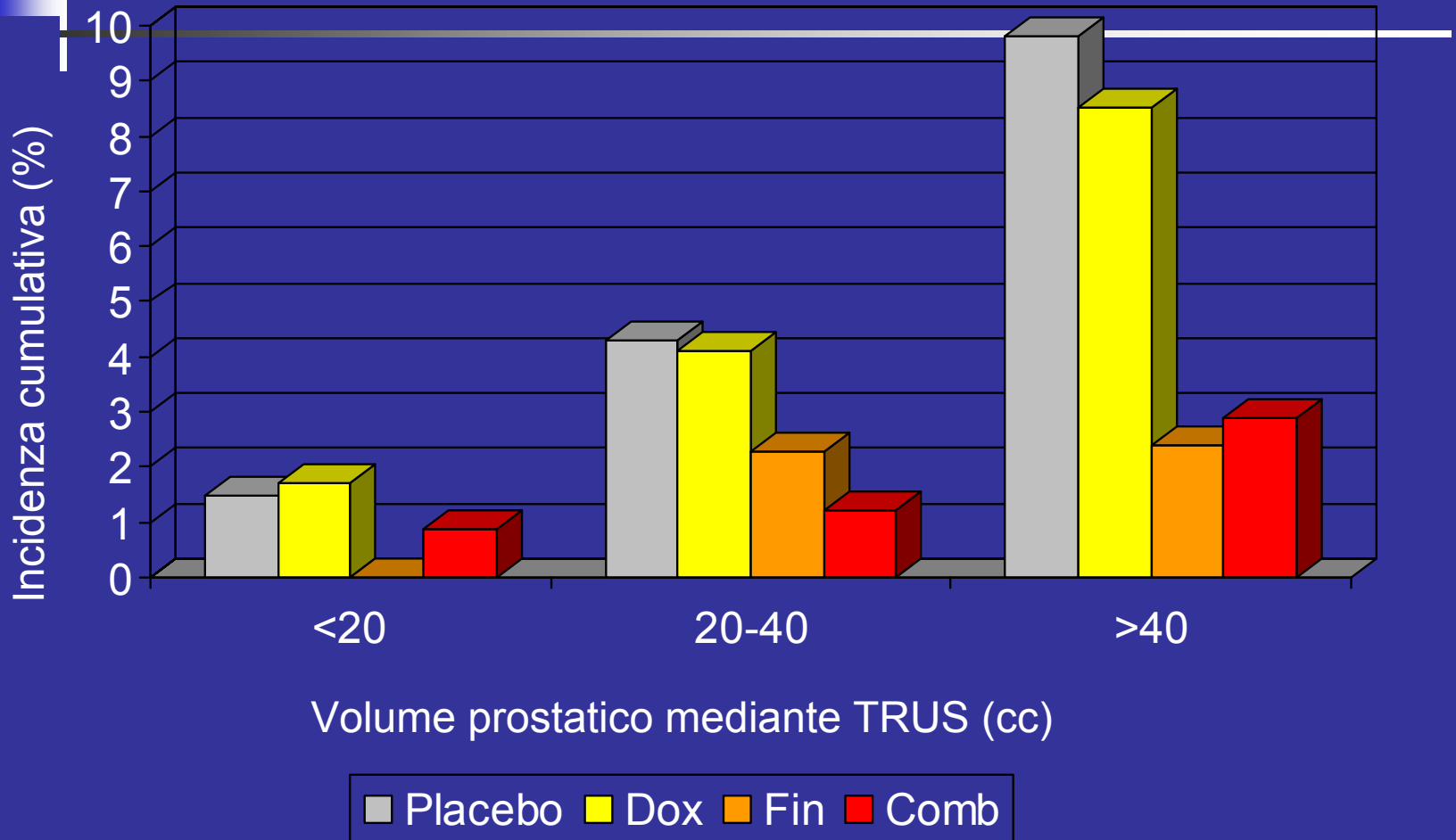
# Ritenzione Urinaria Acuta

## Rapporto con i livelli di PSA



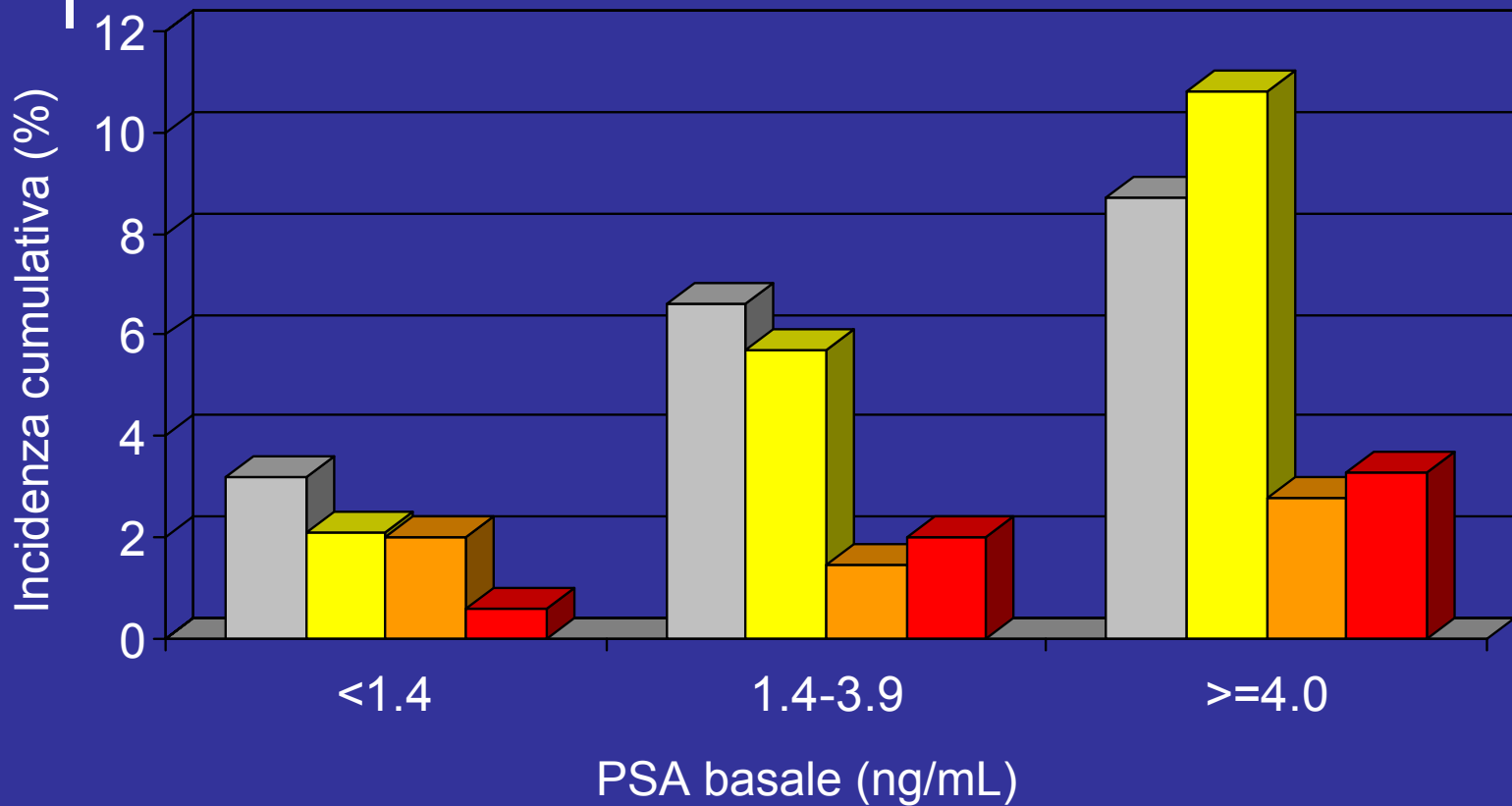
# Terapia chirurgica dell'IPB

## Rapporto con il volume prostatico



# Terapia chirurgica dell'IPB

## Rapporto con i livelli di PSA



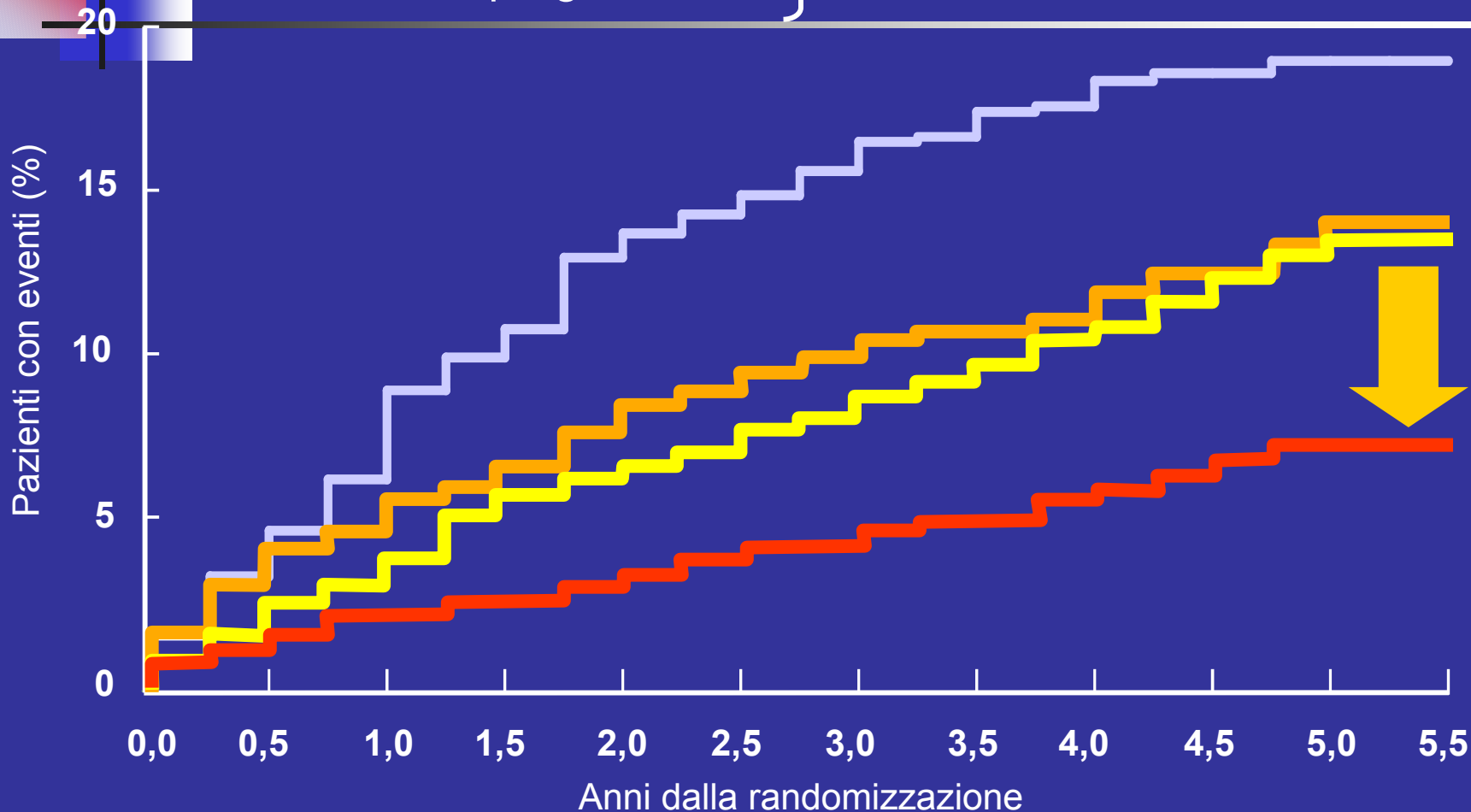
Placebo Dox Fin Comb

# Studio MTOPS: incidenza cumulativa di progressione

Per <10% riduzione del rischio di progressione

Raddoppiano i costi

Aumenta il rischio di effetti collaterali



— Placebo — Doxazosina — Finasteride — Associazione

# Studio MTOPS: effetti collaterali più frequenti

Incidenza su 100 pz/anno	Placebo	Doxazosina	Finasteride	Associazione
Disfunzione erettile	3,6	3,9	4,9*	<u>5,6*</u>
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	<u>1,4*</u>
Dispnea	0,6	1,0	0,6	<u>1,3*</u>
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?



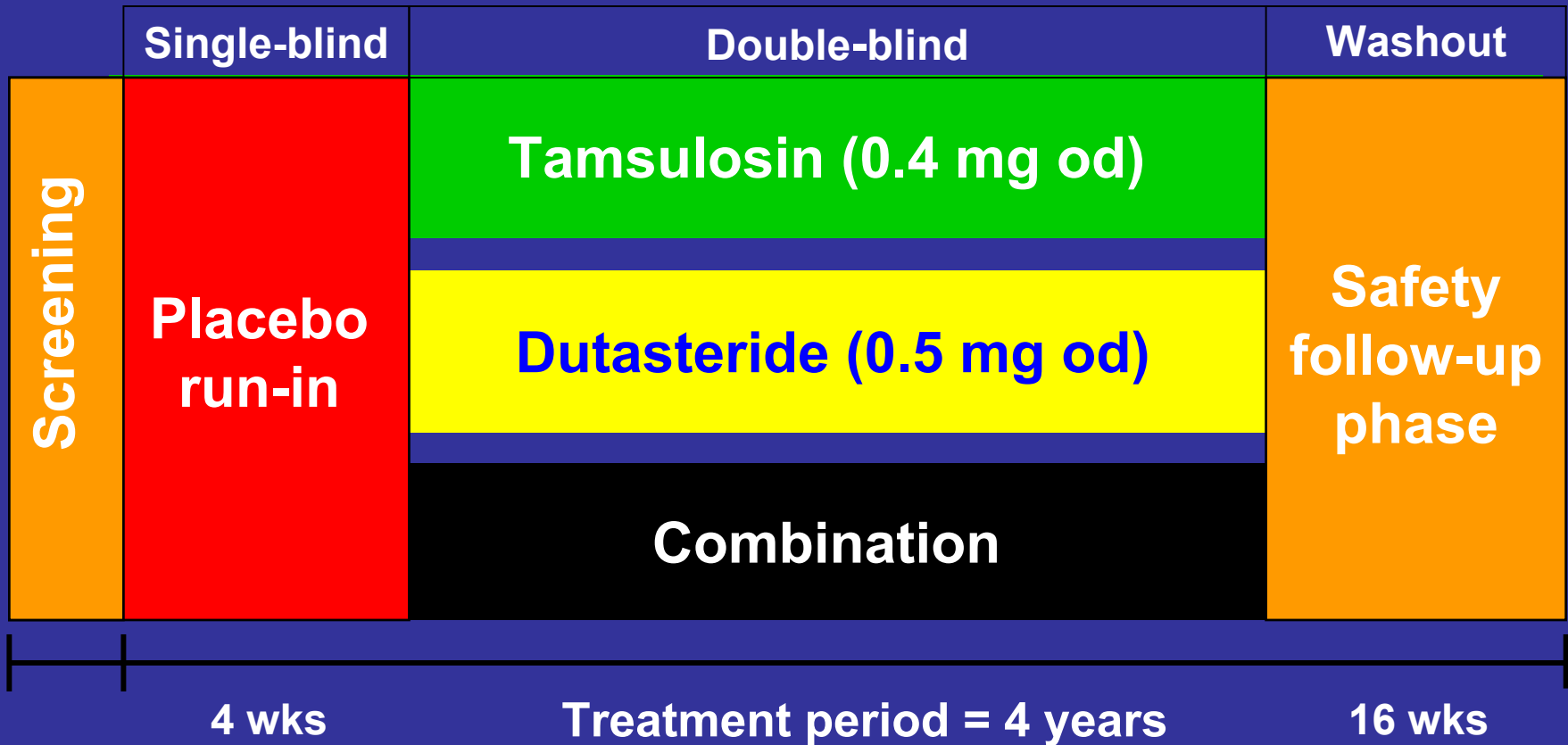
CUT-OFF di progressione

Età	>62
PSA	>1,6
TRUS	>31

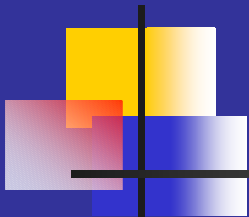
*La maggior  
parte dei casi*

# Lo studio CombAT

ARTICLE IN PRESS



# Symptom Management After Reducing Therapy: SMART-1



- DT24 + D12
- DT36

Endpoint primario a 30 settimane



4 w  
Single-blind (SB)

24 w  
SB

12 w  
Doppio cieco

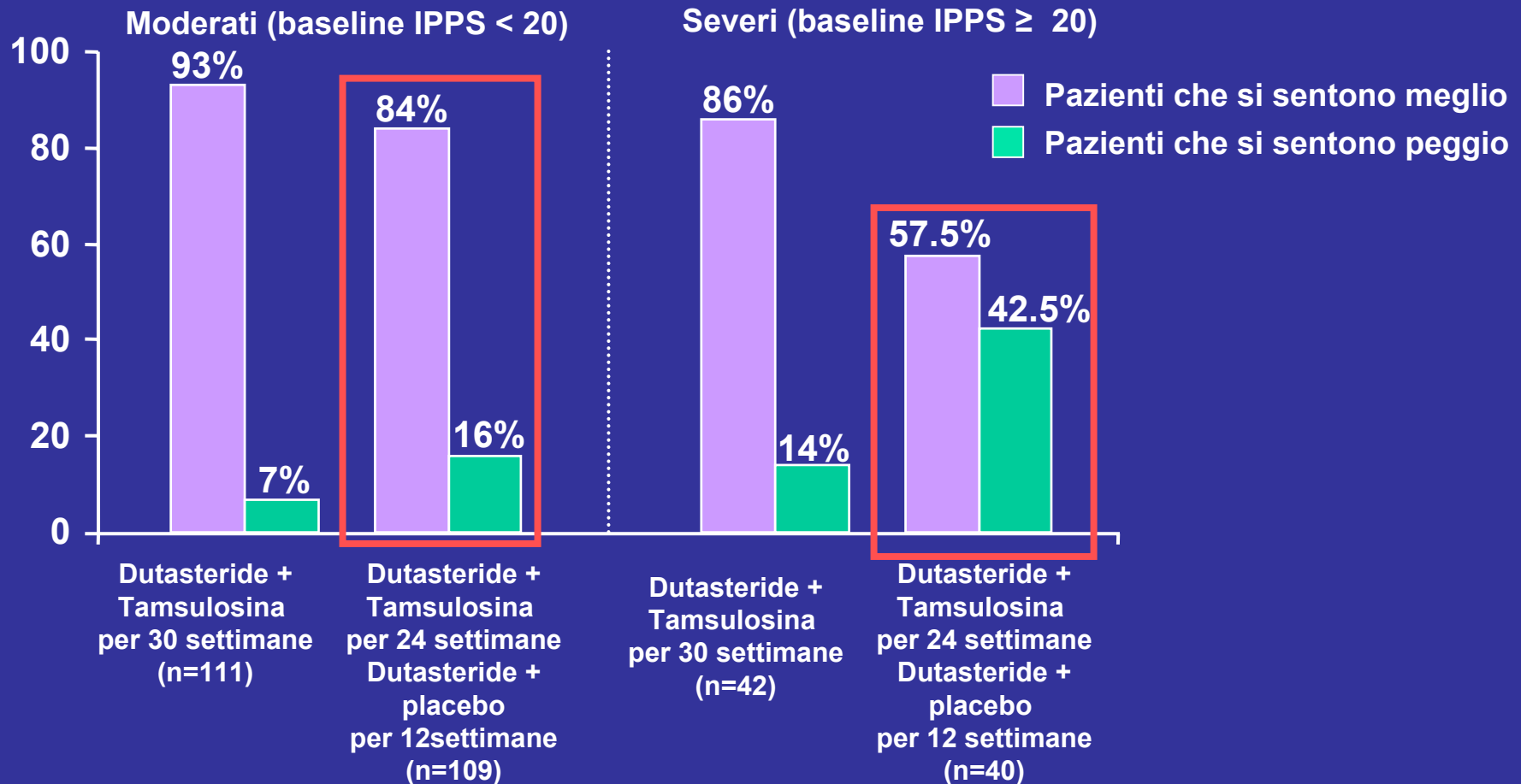
1 w  
SB

# 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

Pazienti (%)





# Plant extracts

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- 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



# Conclusioni

■ Fitofarmaci

?

■ Alfa-litici

SEMPRE

■ Terapia di combinazione

RISCHIO DI PROGRESSIONE

Età >62

PSA >1,6

TRUS >31



...Looking to the future...

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*New is not always better*