

BPH and Medical Treatment Options

BPH in Relation to LUTS (Lower Urinary Tract Symptoms)

BPH

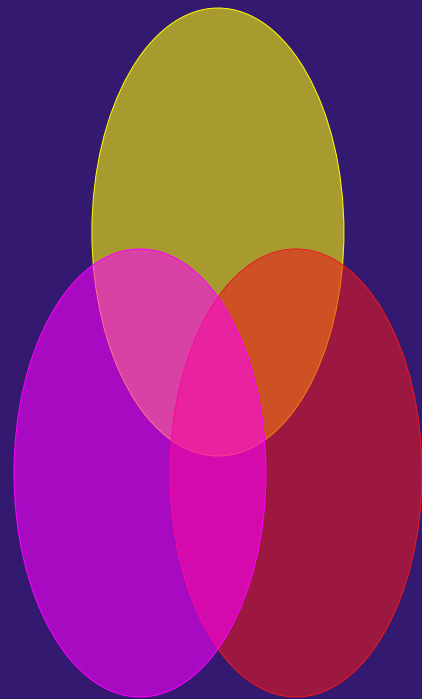
- Histologic evidence of stromoglandular hyperplasia

LUTS

- Presence of irritative and/or obstructive voiding symptoms

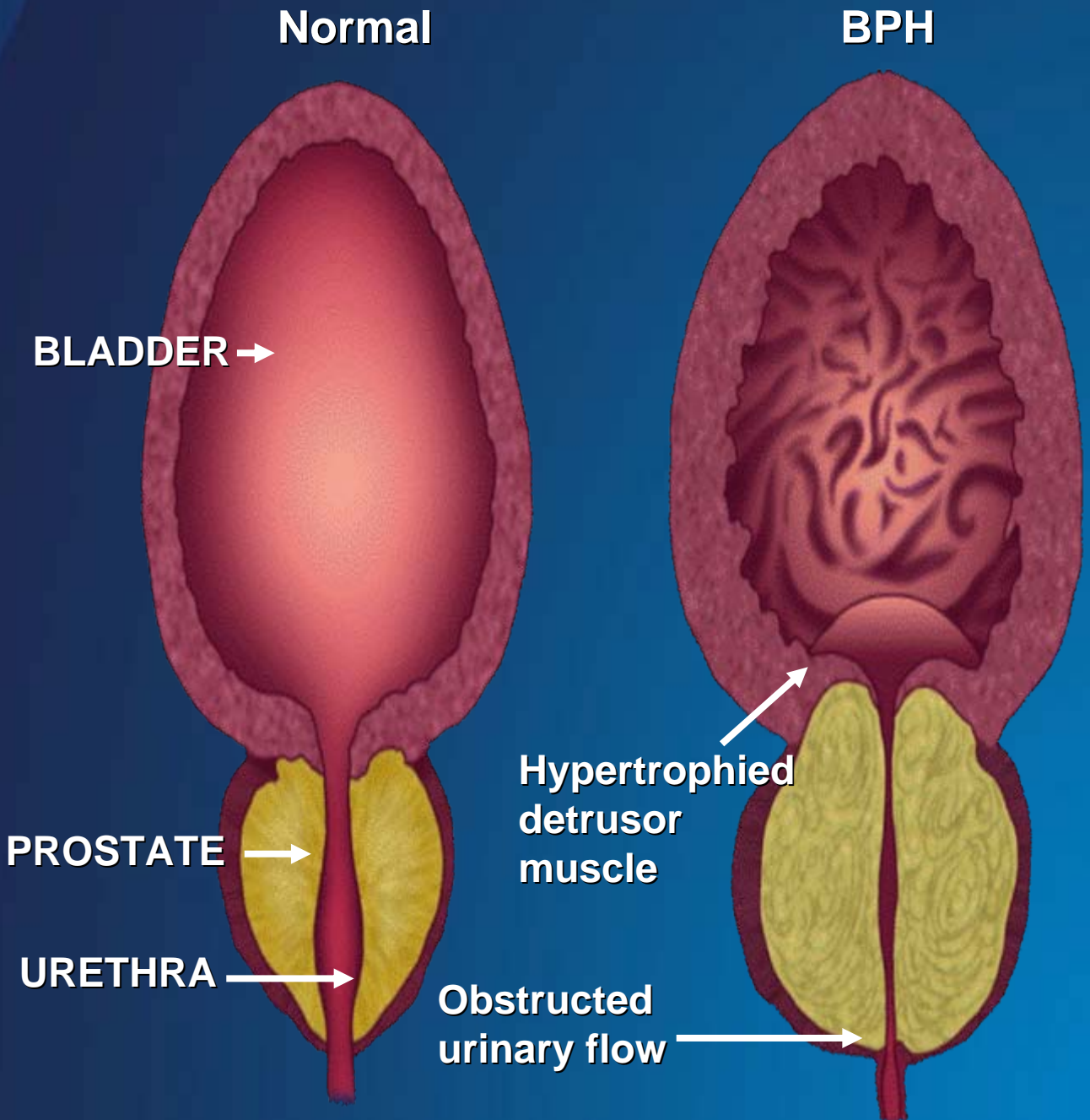
HALD Diagram

Symptoms LUTS



Obstruction Enlargement
Hyperplasia

Anatomy of BPH



Symptoms of BPH

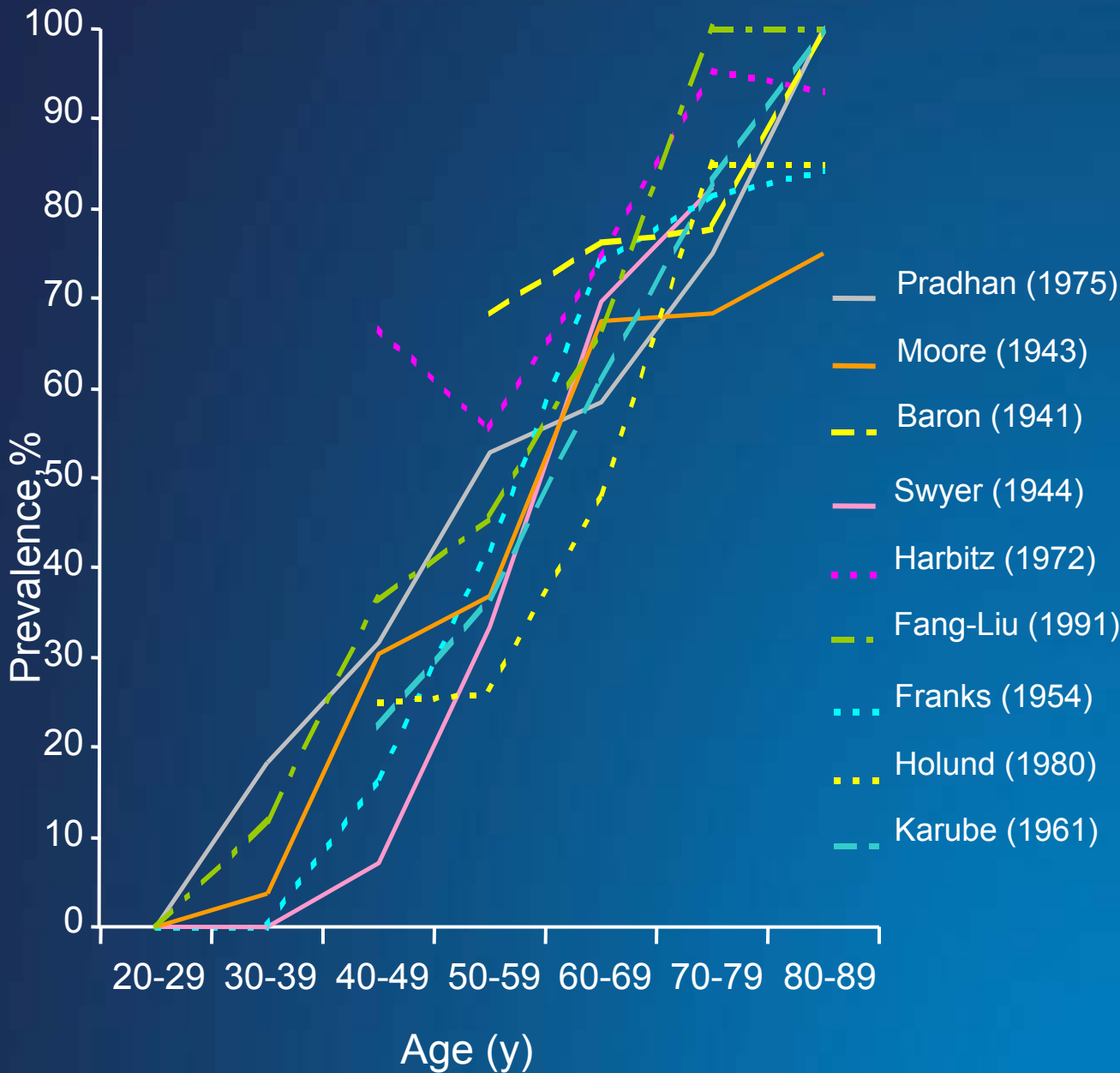
Obstructive Symptoms

- Hesitancy
- Weak stream
- Straining to pass urine
- Prolonged micturition
- Feeling of incomplete bladder emptying
- Urinary retention

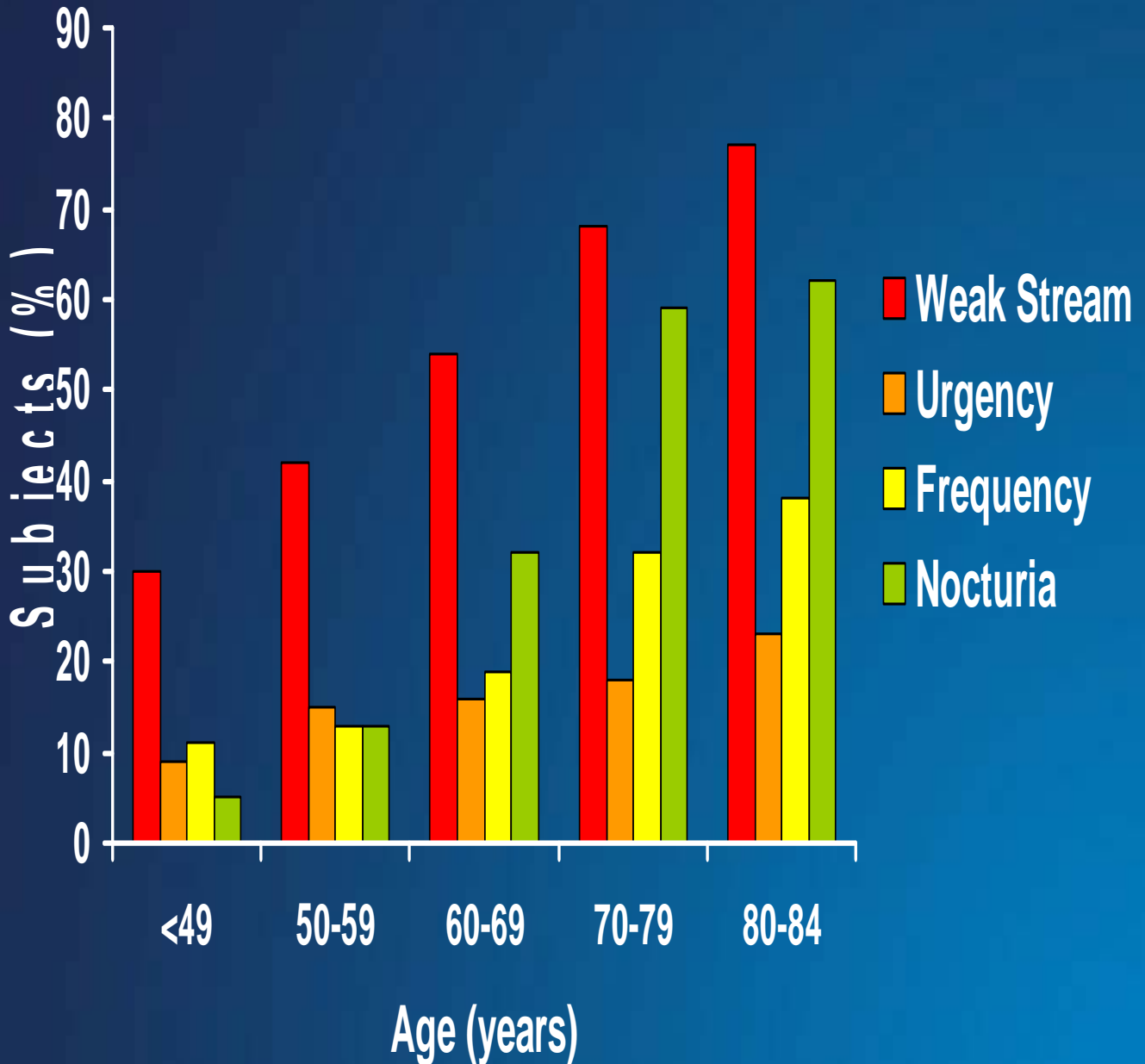
Irritative Symptoms

- Urgency
- Frequency
 - 71% of men > 50
- Nocturia
 - 87% of men > 50
- Urge incontinence

Prevalence of Histologic BPH Increases with Age



Prevalence of LUTS Increases With Age



N=168

Problems and Consequences of BPH

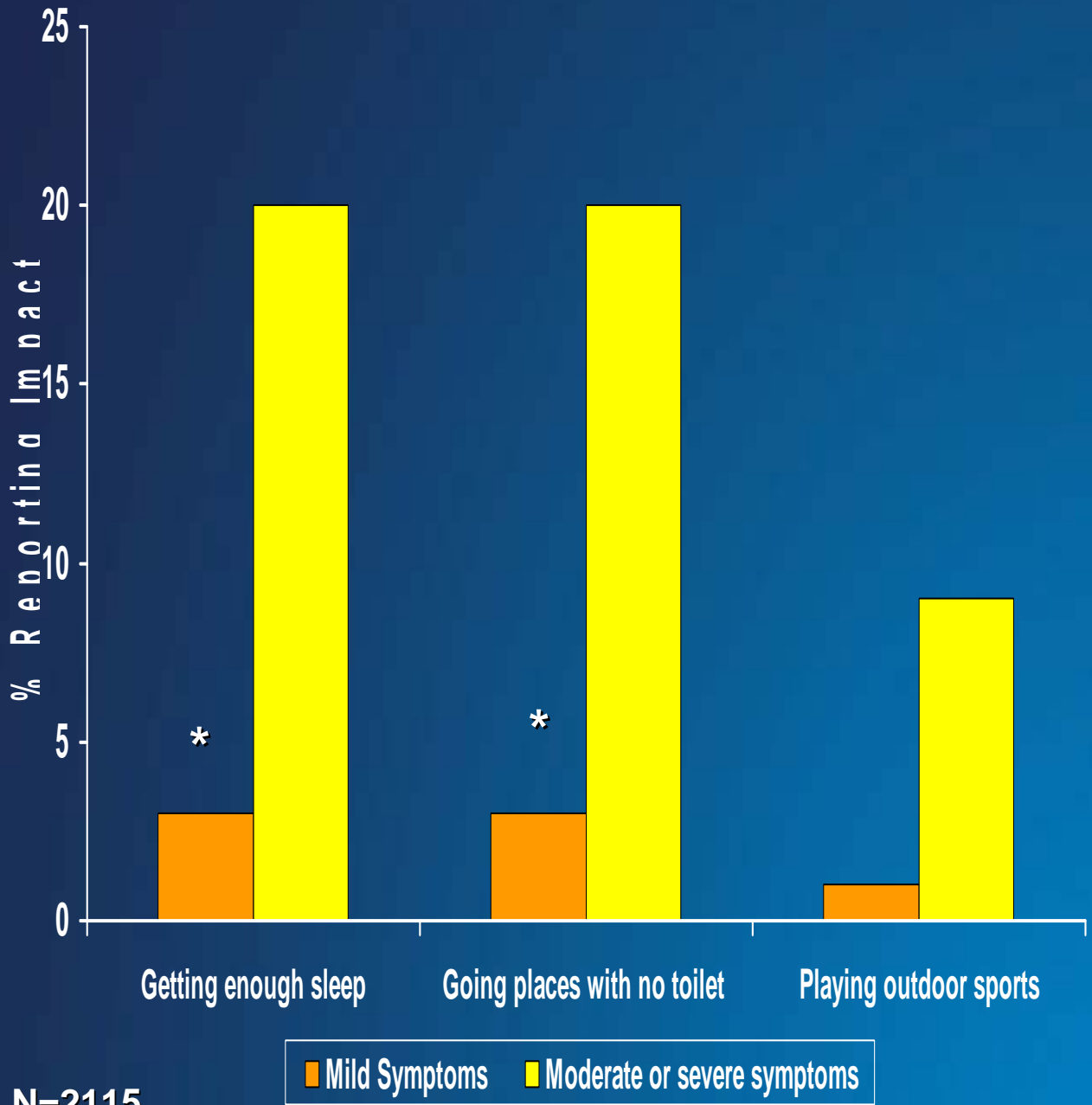
Established Problems and Consequences

Problem	Consequence
Histologic (Stromoglandular)	May not cause any problems by itself
LUTS	Bothersome symptoms; interference with QOL (quality of life); may affect sexual function
BPE (Benign Prostatic Enlargement)	AUR (Acute urinary retention); surgical intervention; secondary changes of bladder anatomy and function; other outcomes (eg, UTI (urinary tract infection); stones; renal failure)
BOO (Bladder Outlet Obstruction)	

AUA Practice Guidelines Committee. *J Urol* 2003; 170(2):530-547; Chatelain C, et al, eds.

Benign Prostatic Hyperplasia. 2001:519-534; Nordling J et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*.; Rosen R et al. *Eur Urol*. 2003; 44:637-649.

Impact on Daily QOL Increases with Symptom Severity



N=2115

*Reported as 2%-4%

Men with BPH/LUTS are at Increased Risk for Sexual Problems

- Sexual problems include¹
 - Erectile dysfunction (ED)
 - Ejaculatory dysfunction (EjD)
 - Desire disorder (ie, decreased libido)
 - Combination of the above
- Many treatments currently available for BPH/LUTS have sexual side effects^{2,3}

The MSAM-7 Study

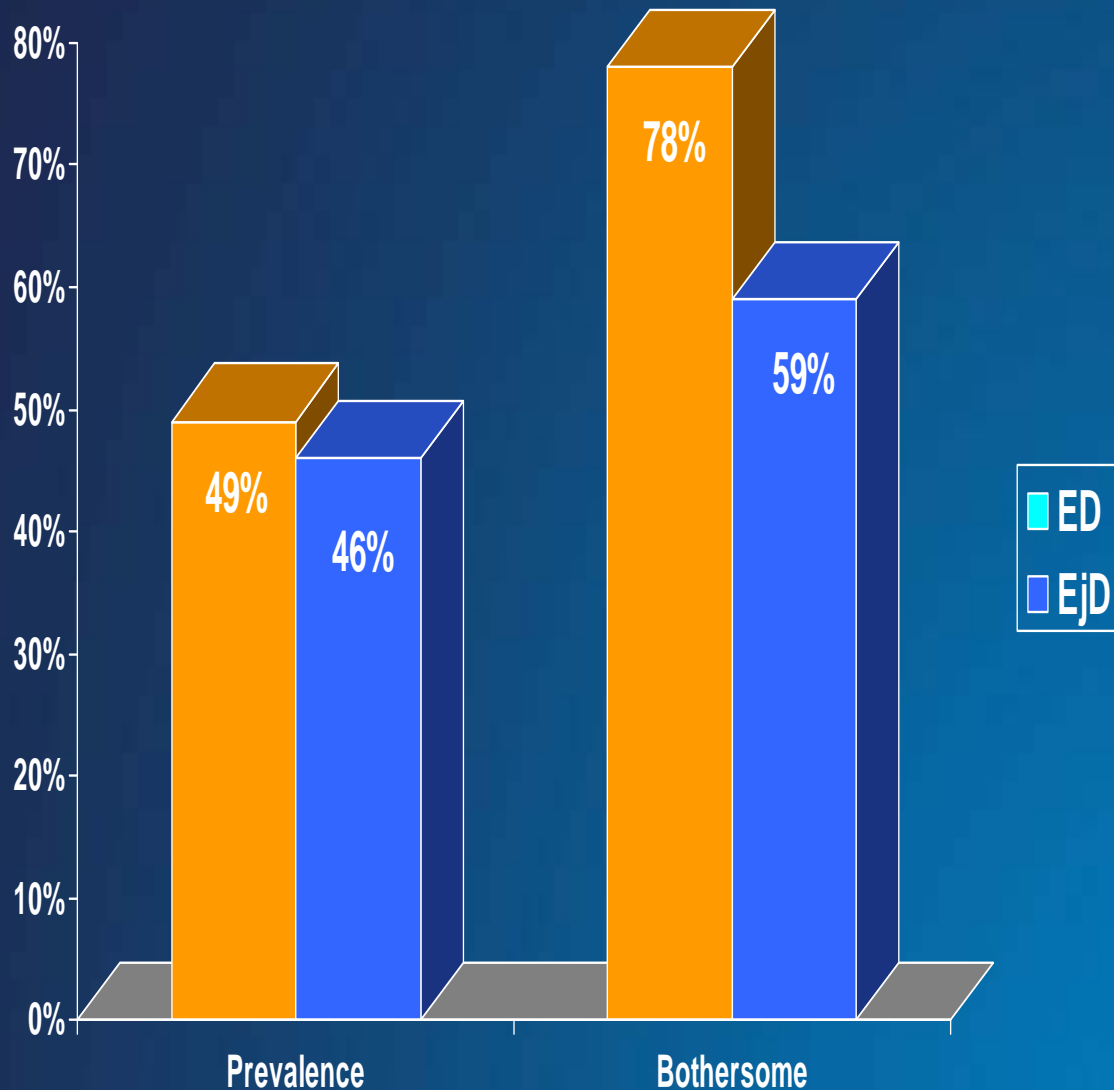
- **The first large-scale, multinational investigation of LUTS and sexual dysfunction in older men**
- **MSAM-7 surveyed 14,354 men (50-80) from 7 countries**

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

EjD: (Ejaculatory Dysfunction) Decreased Semen Volume or Anejaculation

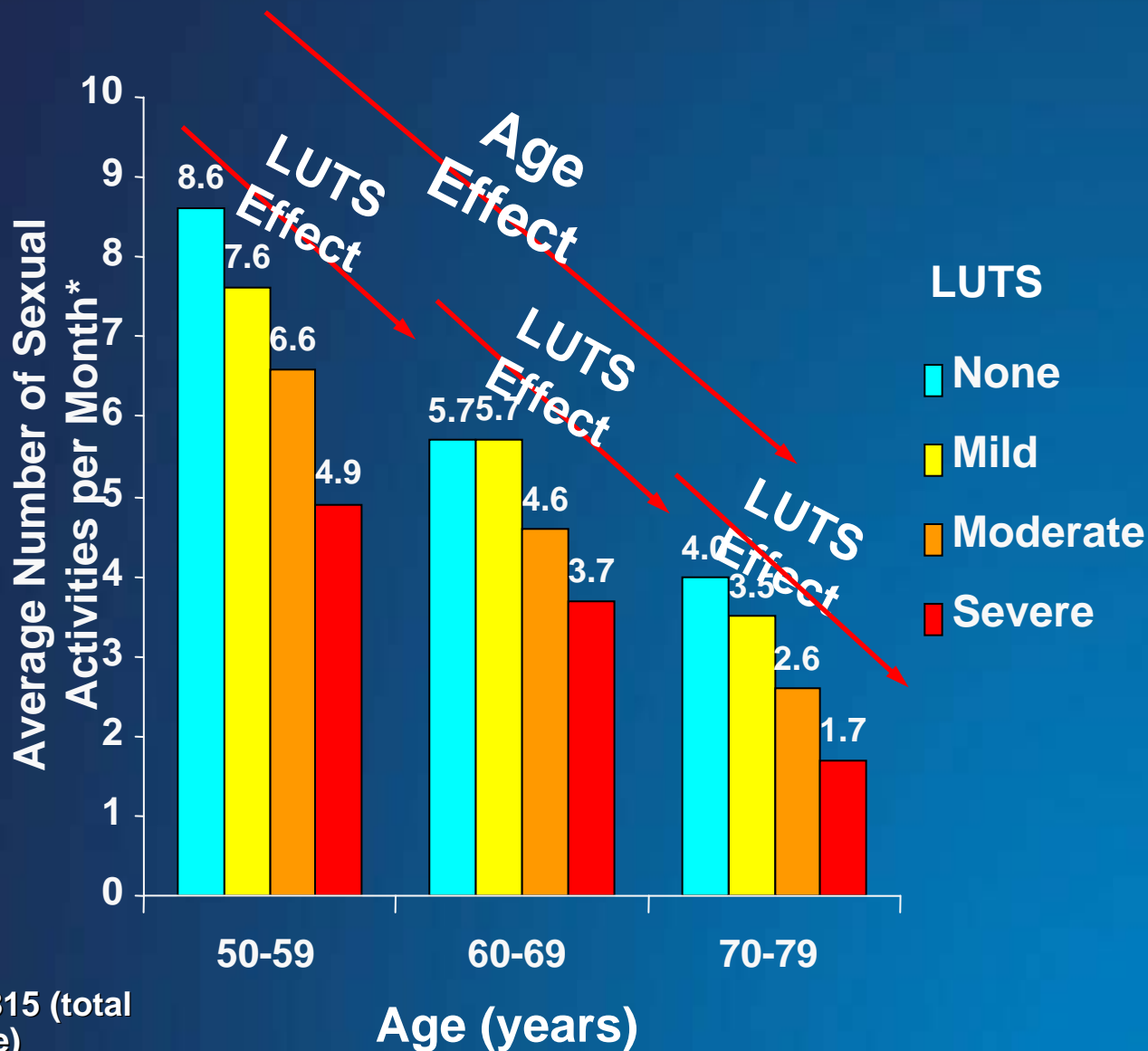
- **Decrease seminal vesicle/vas deferens contraction also decrease emissions:^{1,2}**
 - **No or reduced ejaculation (anejaculation)**
 - **Associated with reduced orgasmic pleasure?**
- **Excessive bladder neck relaxation¹**
 - **May cause retrograde ejaculation**
- **Effects likely mediated by spinal and central (CNS) pathways³**

EjD and ED Are Highly Prevalent and Bothersome in Men Aged 50-80



ED = Reduced or no erection / EjD = Reduced or no ejaculate

More Severe LUTS Impairs Sexual Function Independent of Age



N=12,815 (total sample)

*Among total sample.

Evaluation Techniques for BPH

American Urological Association Symptom Score (IPSS)

- **Quality of Life Assessment**
- **Bother Index**
- **Non-invasive Uroflowmetry**
 - **Peak Flow Rate (cc/second)**
- **Post Void Urinary Residual**
 - **Ultrasound bladder scan**

AUA Symptom Score/IPSS

- **Ranges from 0 to 35**
 - **7 or less – mild symptoms**
 - **8-19 – moderate symptoms**
 - **20-35 – severe symptoms**
- **Quality-of-Life Index**
 - **6 point rating scale**
 - **0 = delighted**
 - **6 = terrible**

Goals of Therapy for BPH

Successful treatment of BPH is measured by:

- Decreased symptoms (IPSS/AUA)
- Decreased bother (bother score) and interference with daily activities
- Decrease in prostate size or arrest of further growth
- Increase in peak flow rate
- Improvement in obstruction
- Prevention of long-term outcomes/complications

Understanding Efficacy vs Progression

- Therapeutic Effectiveness
 - Symptom / QOL **improvement**
 - Urodynamic improvement
- Reducing Disease Progression
 - Symptom **deterioration**
 - Urodynamic deterioration
 - Stopping prostate growth

Treatment Options

- **Pharmacologic therapy**
 - **Alpha-adrenergic blockers**
 - **5-Alpha-reductase inhibitors**
- **Watchful waiting**
- **Phytotherapy**
- **Minimally invasive surgery**
 - TUMT
 - TUNA
- **Laser/TURP/Open**
- **Less invasive surgery**
 - VLAP
 - ILC
 - TUVP
- **Major surgery**
 - TURP (gold standard)
 - TUIP
 - Open surgery (prostatectomy)

TUMT=Transurethral Microwave Thermotherapy

TUNA=Transurethral Needle Ablation

TURP=Transurethral Resection of Prostate

VLAP=Visual Laser Ablation of Prostate

ILC=Interstitial Laser Coagulation (also known as LITT)

TUVP=Transurethral Electroevaporation of Prostate

TUIP=Transurethral Incision of Prostate

WIT=Water-Induced Thermotherapy

Chatelain C et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001;519-534; DeBruyne FMJ et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001;397-421; AUA Practice Guidelines Committee. *J Urol*. 2003;170(2):530-547.

Watchful Waiting/Active Surveillance

- Patient is followed annually but receives no active intervention for symptoms¹
- Appropriate option for patients with mild symptoms, and for many with moderate to severe symptoms if they are not bothered¹
- May require yearly reassessment¹
- Symptoms, sexual dysfunction, urodynamic parameters, and prostate size may have variable progression^{1,2}

Pharmacologic Treatments for BPH

- **5-ARIs (5-Alpha-reductase inhibitors) Alpha-adrenergic blockers**

AUA Practice Guidelines Committee. *J Urol.* 2003;170:530-547; Therapies for the treatment of benign prostatic hyperplasia (BPH). Available at: <http://cpmcnet.columbia.edu/dept/urology/bphtherapy.html>; HYTRIN® (terazosin hydrochloride) prescribing Information, Abbott Laboratories; CARDURA® (doxazosin mesylate) Tablets Prescribing Information, Pfizer Inc.; FLOMAX® (tamsulosin hydrochloride) Prescribing Information, Boehringer Ingelheim Pharmaceuticals Inc.; Uroxatral® (alfuzosin HCl extended-release tablets) Prescribing Information, Sanofi-Synthelabo Inc.; PROSCAR® (finasteride) Tablets Prescribing Information, Merck & Co, Inc.; AVODART™ (dutasteride) Prescribing Information, GlaxoSmithKline.

5-ARIs for the Treatment of BPH

5ARIs (5-Alpha-Reductase Inhibitors): Pharmacologic Profile

Pharmacologic Effect	Finasteride ¹	Dutasteride ²
5-Alpha-reductase inhibition	Type II	Type I and II
Serum DHT	↓70%	↓ >90%
Serum T (median)	↑ 10%-20%	↑ 19%
Serum PSA	PSA ↓ 50% F/T ratio unchanged	Total PSA ↓ ~50%
Prostate volume	↓ 18%	↓ 27%
Serum half-life	8 hours	5 weeks
Dosage	5 mg once daily	0.5 mg once daily

1 PROSCAR (finasteride) prescribing information, 2003.

2 AVODART® (dutasteride) prescribing Information, 2003.

Clinical Efficacy and Adverse Effects of 5ARIs Are Comparable

	48-Month Controlled Trial in 3,040 Men ¹		24-Month Controlled Trial in 4,325 Men ²	
Efficacy Endpoints	Finaster.	Plac.	Dutaster.	Plac.
Volume changes	-18%	+14%	-26%	-2%
IPSS reduction	-3.3	-1.3	-4.5	-2.3
Q _{max} improvement (mL/s)	+1.9	+0.2	+2.2	+0.6
AUR risk reduction	57%		57%	
Surgery risk reduction	54%		48%	
Safety Endpoints				
Erectile dysfunction	8%	4%	7%	4%
Decreased libido	6%	3%	4%	2%
Ejaculatory disorder	4%	1%	2%	<1%
Gynecomastia and breast tenderness	1%	0.2%	2%	<1%

1 McConnell JD et al. N Engl J Med. 1998;338:557-563.

2 Roehrborn C et al. Urology. 2002;60:434-441.

Alpha-Blockers for the Treatment of BPH

AUA Guidelines

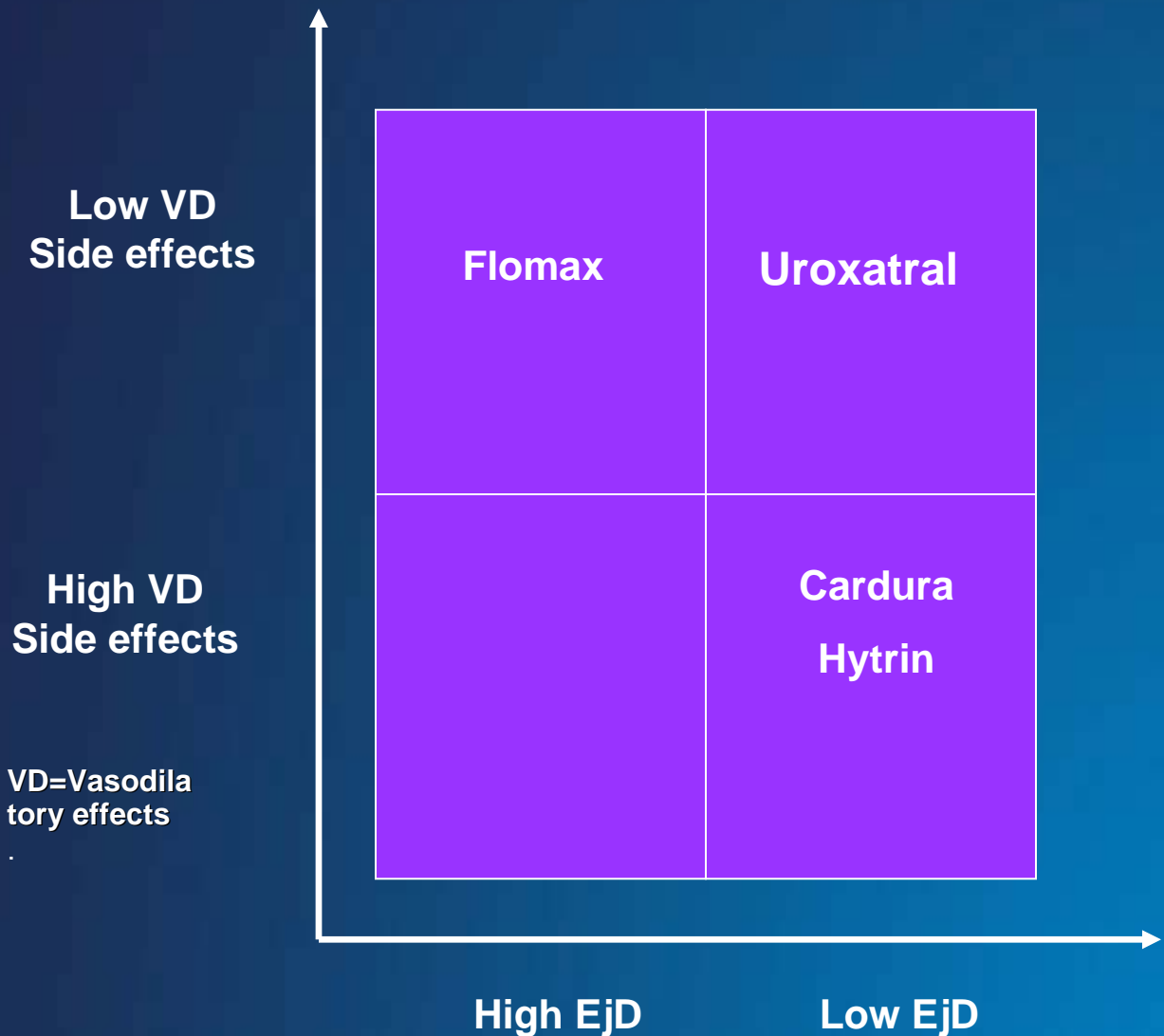
- “Alfuzosin, doxazosin, tamsulosin and terazosin are appropriate treatment options for patients with LUTS secondary to BPH. Although there are slight differences in the adverse-event profiles of these agents, the Panel believes that **all four agents have equal clinical effectiveness.**”
- “The adverse event profile appears slightly different between the four alpha-blocking agents, for example, **tamsulosin appears to have [...] a higher probability of ejaculatory dysfunction than the other alpha blockers.**”

Dosing of Alpha-Blockers for BPH

Agent	Dosing	Titration
Terazosin (HYTRIN®)	1, 2, 5, 10 mg	+
Doxazosin (CARDURA®)	1, 2, 4, 8, 16 mg	+
Tamsulosin (FLOMAX®)	0.4, 0.8 mg .5hr after meal	+/- (for improved efficacy)
Alfuzosin (Uroxatral®)	10 mg Immediately after meal	None

HYTRIN® (terazosin hydrochloride) Prescribing information, Abbott Laboratories; CARDURA® (doxazosin mesylate tablets) Prescribing Information, Pfizer Inc.; FLOMAX® (tamsulosin hydrochloride) Prescribing Information, Boehringer Ingelheim Pharmaceuticals, Inc.; UROXATRAL® (alfuzosin HCl extended-release tablets) Prescribing Information, Sanofi-Synthelabo Inc.

Side Effect Profiles Differentiate Alpha-Blockers



HYTRIN® (terazosin hydrochloride) Prescribing information, Abbott Laboratories;
 CARDURA® (doxazosin mesylate tablets) Prescribing Information, Pfizer Inc.; FLOMAX®
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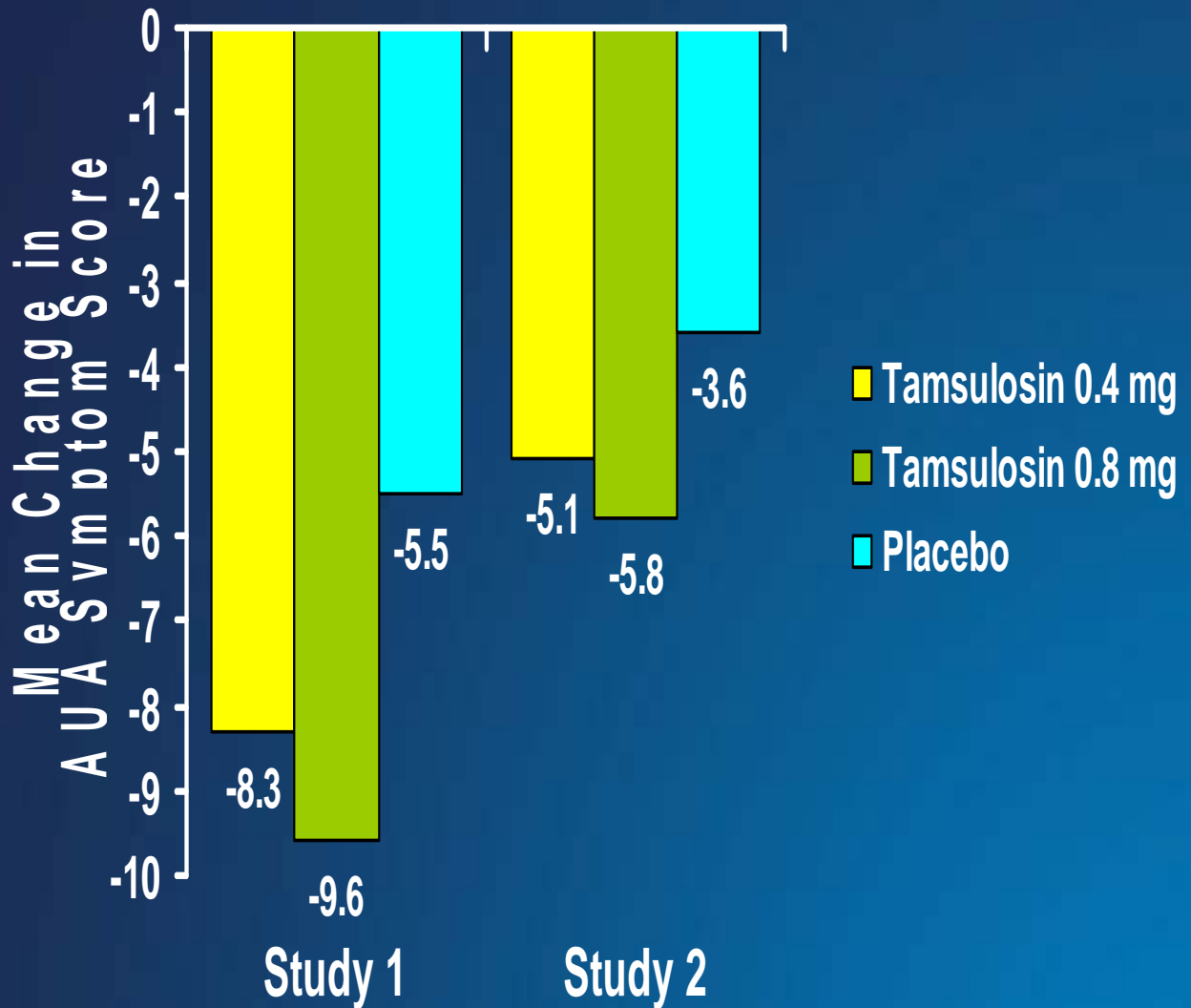
Terazosin: Adverse Events Occurring Significantly More Often Than With Placebo*

	BPH (N=996)	
	Terazosin (n=636)	Placebo (n=360)
Dizziness	9.1%	4.2%
Postural hypotension	3.9%	0.8%

*Events occurring more often with terazosin than with placebo ($P \leq .05$)

HYTRIN® (terazosin hydrochloride) Prescribing information, Abbott Laboratories

Tamsulosin vs Placebo: BPH Symptoms



No significant difference in improvement between 0.4-mg and 0.8-mg doses

N=1,486 (combined from both studies)

Statistically, all improvements with tamsulosin were significantly different from placebo ($P < .05$).

FLOMAX® (tamsulosin hydrochloride) Prescribing Information, Boehringer Ingelheim Pharmaceuticals, Inc

Tamsulosin Adverse Events: Abnormal Ejaculation and Rhinitis

	0.4 mg (n=502)	0.8 mg (n=492)	Placebo (n=493)
Abnormal ejaculation	8.4%	18.1%	0.2%
Rhinitis	13.1%	17.9%	8.3%
Dizziness	14.9%	17.1%	10.1%

Alfuzosin

A Selective Alpha-Adrenergic Blocker

**Fifteen years of worldwide experience
outside United States**

**More than 3.7 million patient-years of
therapy with
bid and tid dosing — now available in a
once-daily formulation**

**Approved by the FDA June 12, 2003 in a
10-mg formulation with the brand
Uroxatral[®] (alfuzosin HCl extended-
release tablets)**

**The 10-mg once-daily formulation
available in more than 49 countries
worldwide**

Absorption of Alfuzosin Less Affected by Food Than Tamsulosin

Figure-1¹

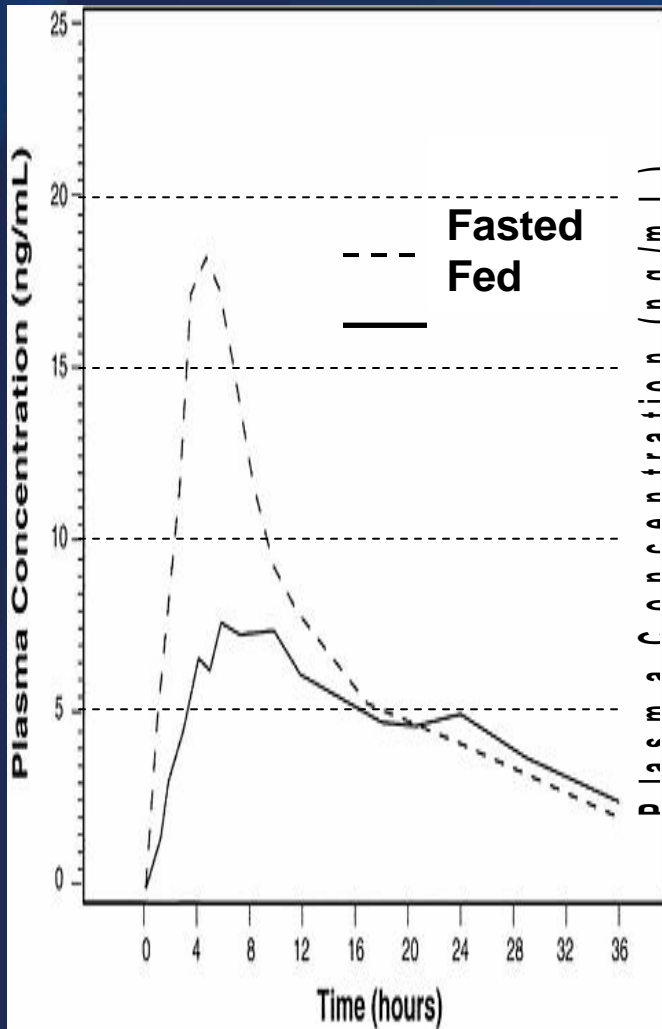
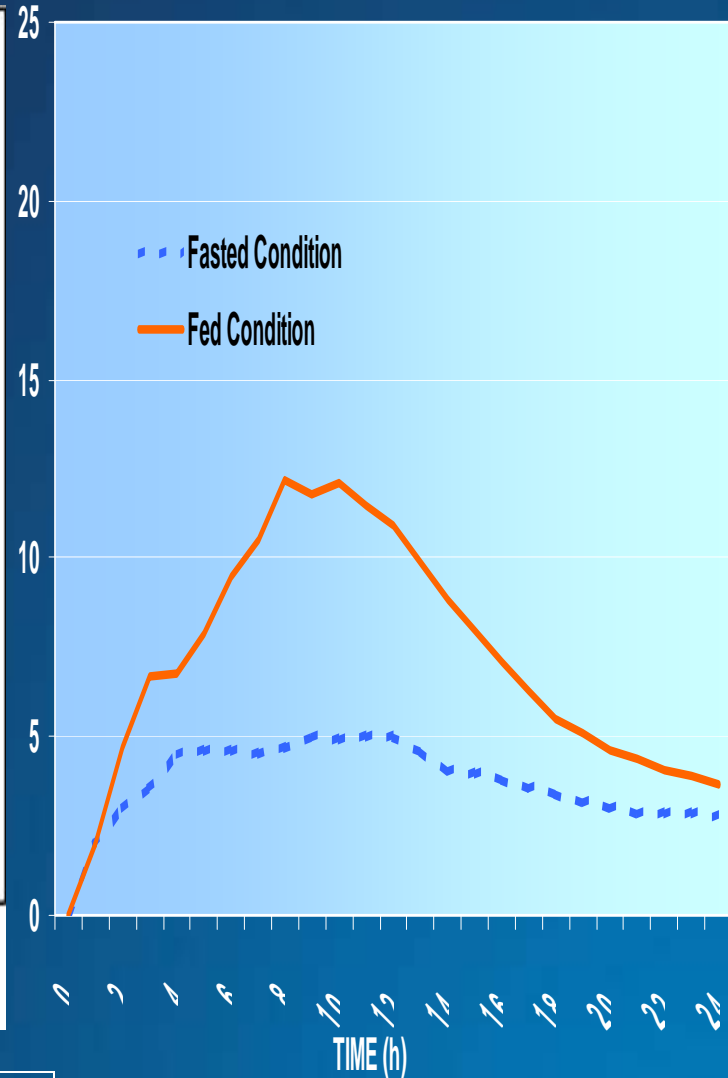


Figure-2²



In the fasting state, the absorption of tamsulosin is exaggerated, causing a spike in the time to peak concentration (occurring 1 to 2 hours earlier) and in the peak concentration (40%-70% increase).¹

In the fasting state, the extent of absorption of alfuzosin is decreased (50%), however the curve remains smooth without exaggerated peaks of drug.²

1. Flomax^R (tamsulosin hydrochloride) Prescribing Information,
 2. (alfuzosin HCl extended release tablets)

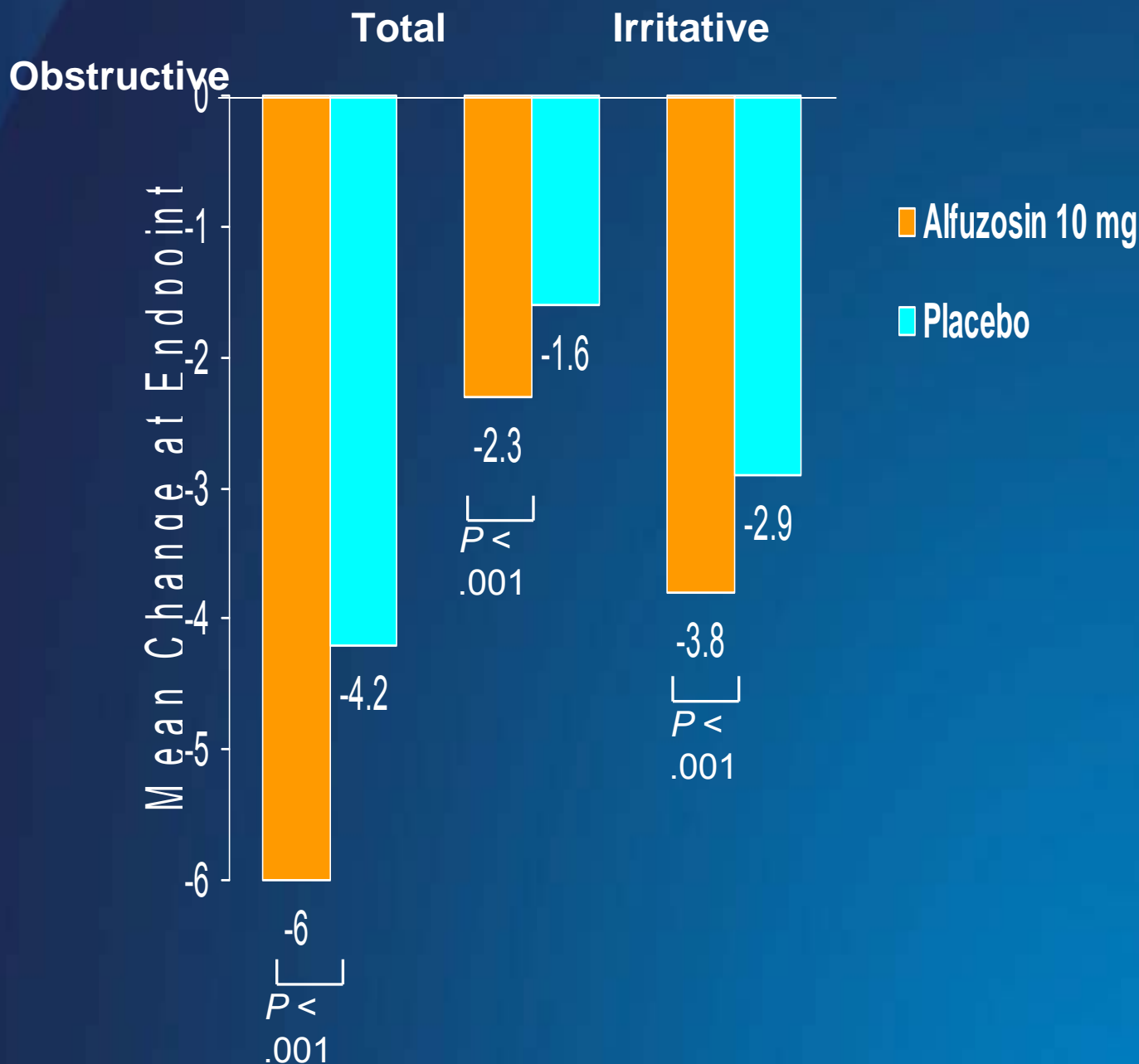
Uroxatral Works Fast: Improves Flow Rate At First Dose

**Peak flow rate improvement
over Baseline
8 hrs post-dose, Day 1 (ml/sec)**

	Uroxatral	Placebo	Mean Difference	p-value
Peak flow improvement ITT Population*	2.7	1.3	1.4	0.015
Peak flow improvement Evaluable Patients**	3.2	1.1	2.1	0.002

*ITT = all patients completing trial (n=45); **Evaluable = pts with complete data (n=34)

Uroxatral Improves Symptoms: Total IPSS Score and Subscores*



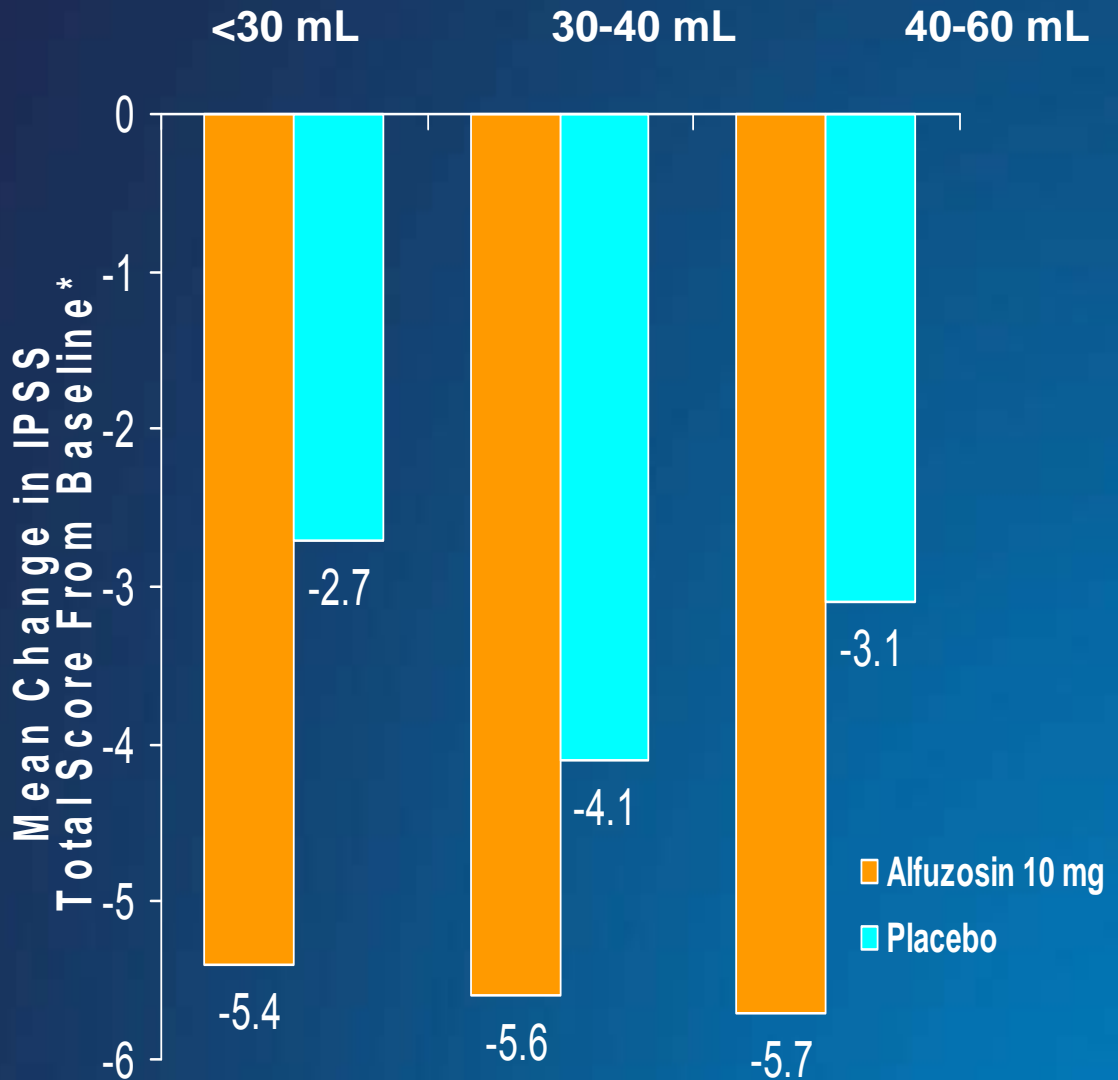
Irritative subscore (urgency, frequency, nocturia)

Obstructive subscore (weak stream, pushing & straining, stopping & starting)

*Pooled analysis.

Roehrborn C et al. *BJU Int.* 2003;92(3):257-261.

Uroxatral Improves Symptoms for **ALL PROSTATE VOLUMES**



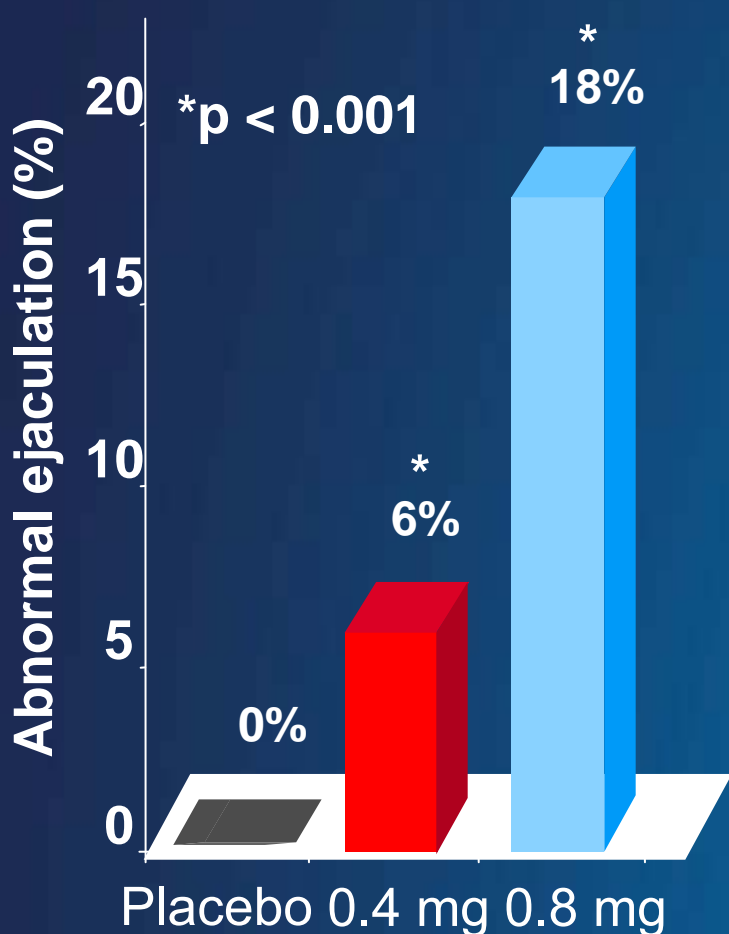
*Pooled analysis stratified by prostate volume.

Roehrborn C et al. *BJU Int.* 2003;92(3):257-261.

Alfuzosin NOT Associated with Increased Risk of EjD*

Results at 3 months in both trials

Tamsulosin¹



Alfuzosin²



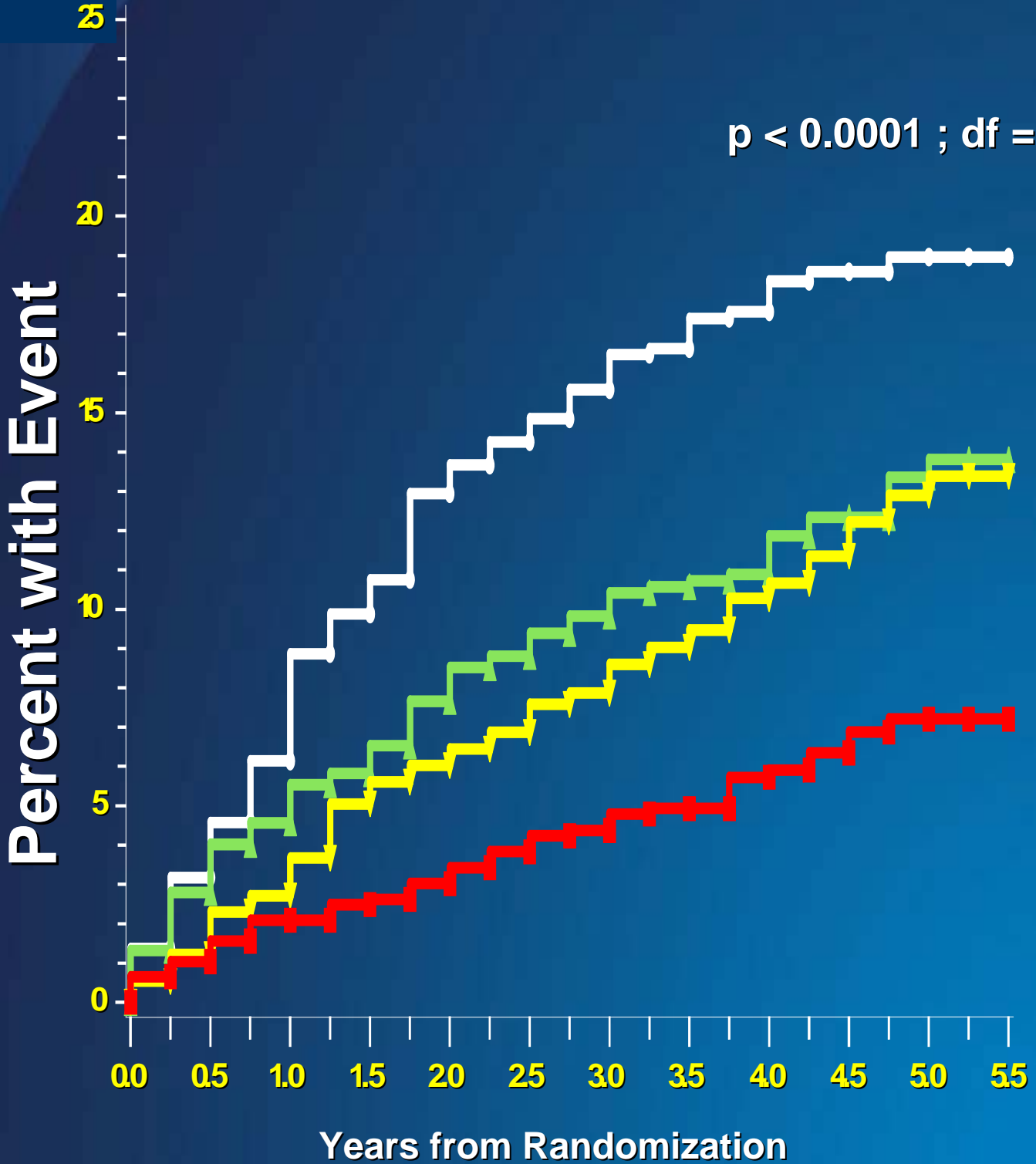
¹ Lepor et al., Urology 1998, 51, 892-900

² Roehrborn et al., Urology 2001, 58, 953-59

* Presented at AUA 2003, April 28, Plenary session "State of the Art Presentation - Medical Therapy for BPH" Steven Kaplan, MD

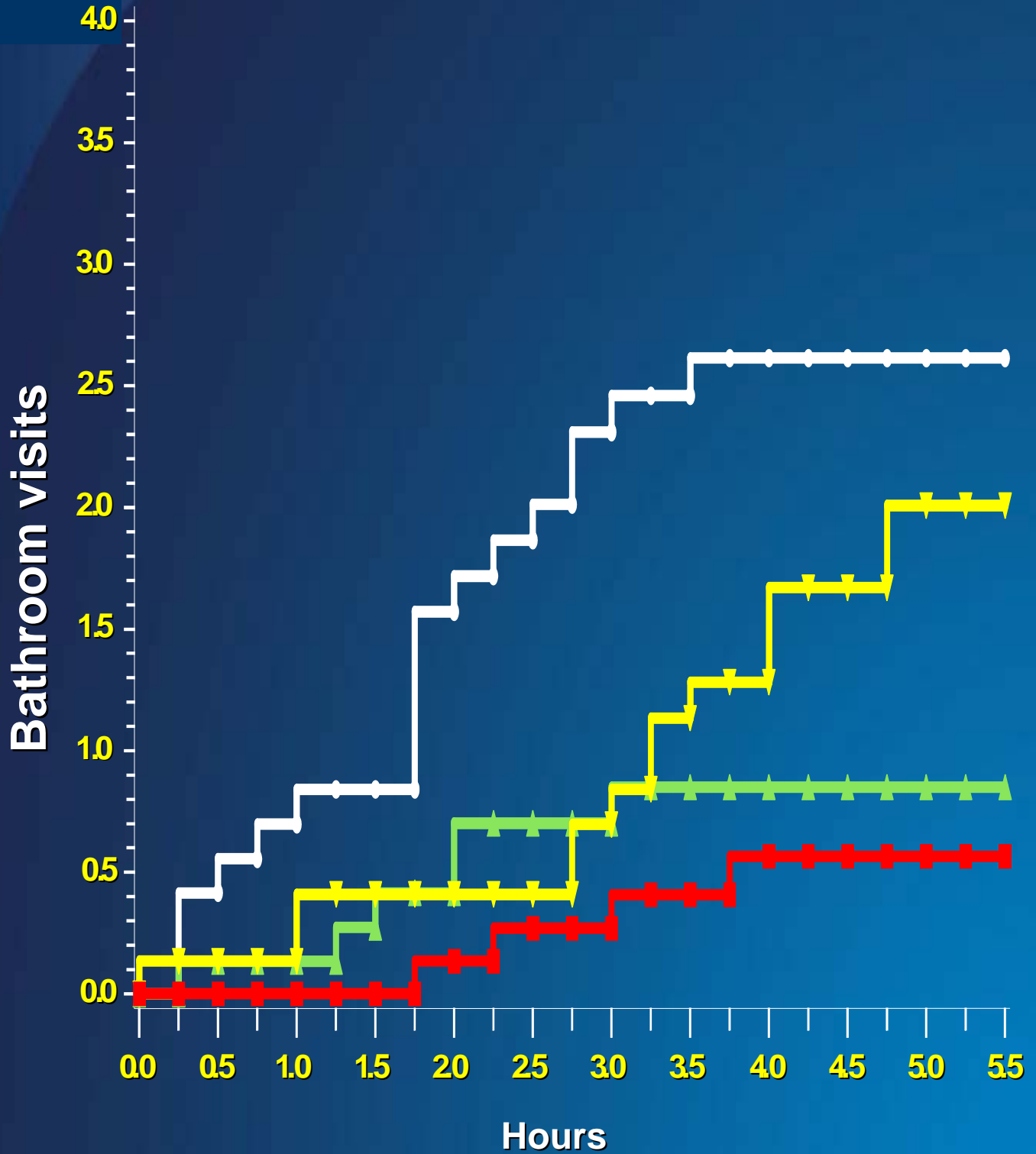
Combination Therapy in the Management of BPH

Cumulative Incidence of BPH Progression



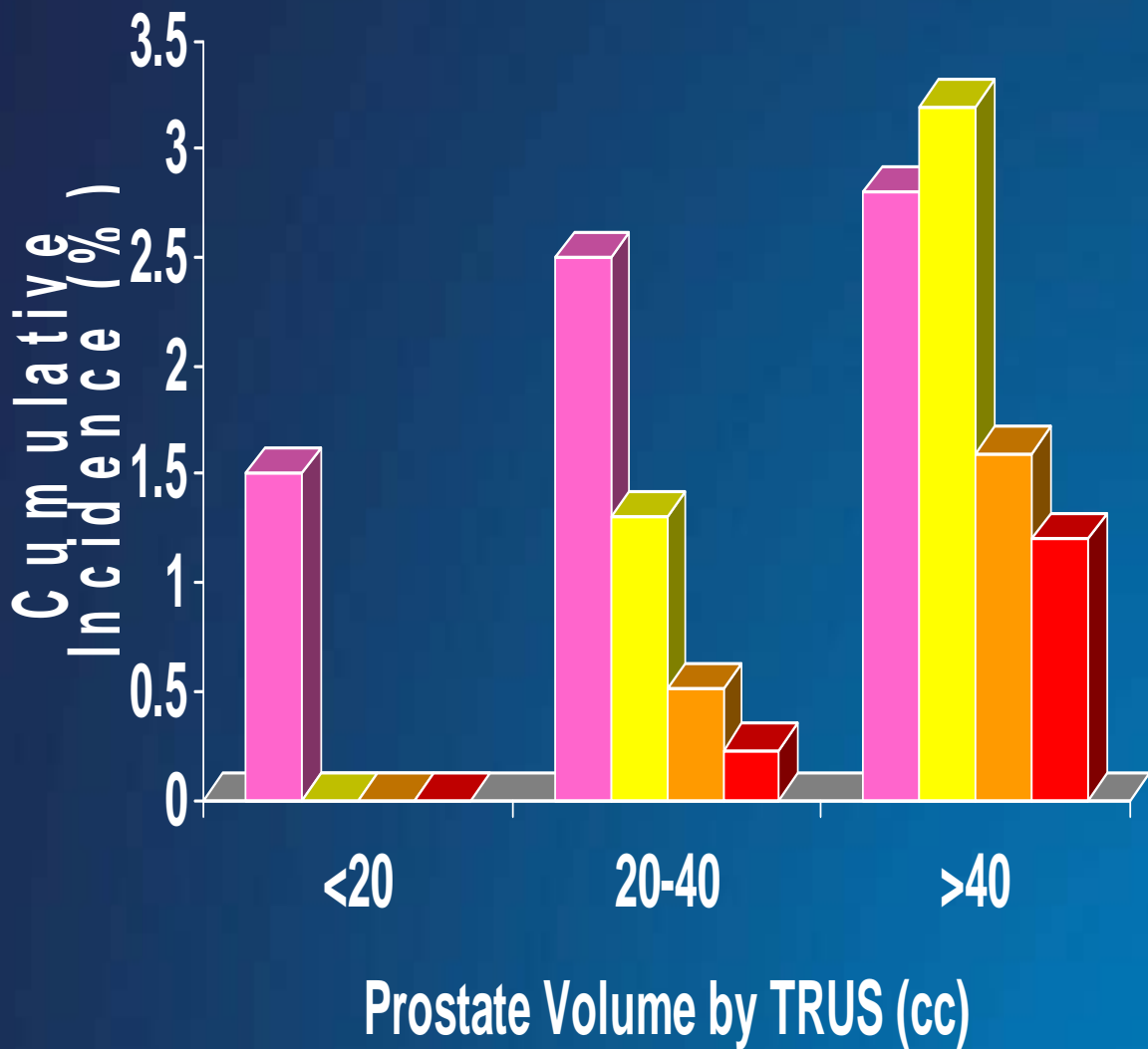
Plac. Doxazos. Finaster. Combination

Frequency of Urination



Plac. Doxazos. Finaster. Combination

Risk of AUR Depends on Prostate Volume



Placebo Dox Fin Comb

Combination Therapy

Conclusions

- **Combination is the most effective form of BPH medical therapy to:**
 - Reduce the risk of clinical progression
 - Improve the AUA symptom score
 - Improve maximum urinary flow rate
- **Monotherapy with doxazosin reduces the risk of BPH progression**
- **Finasteride and doxazosin significantly reduces the risk of AUR and invasive therapy**
- **Long-term mono and combo therapy is safe and effective**

Conclusions

- **BPH is a highly prevalent disease with significant morbidity related to:**
 - **Decreased quality of life**
 - **Decreased sexual function**
- **The ease of dosing for alfuzosin makes it the first line of treatment for BPH**
- **Alfuzosin is a selective alpha-blocker with efficacy comparable to other alpha blockers and a lower incidence of adverse events**