針對攝護腺肥大/下泌尿道症候群病患提供個人化的藥物治療

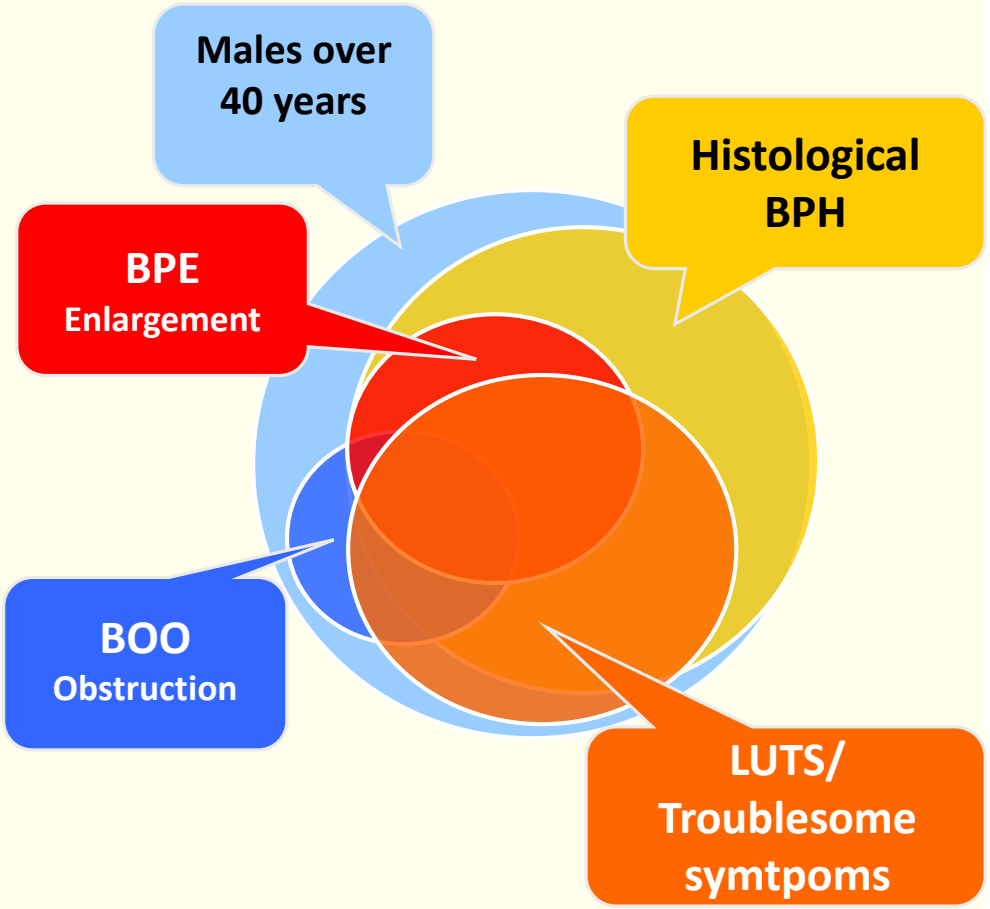
林威宇醫師　嘉義長庚醫院

Latest thinking on BPH, BPE, and BOO

Clinical, anatomical, and pathophysiological changes

- **What is BPH?**
  Histological findings: hyperplasia of the interstitial tissue of the prostate

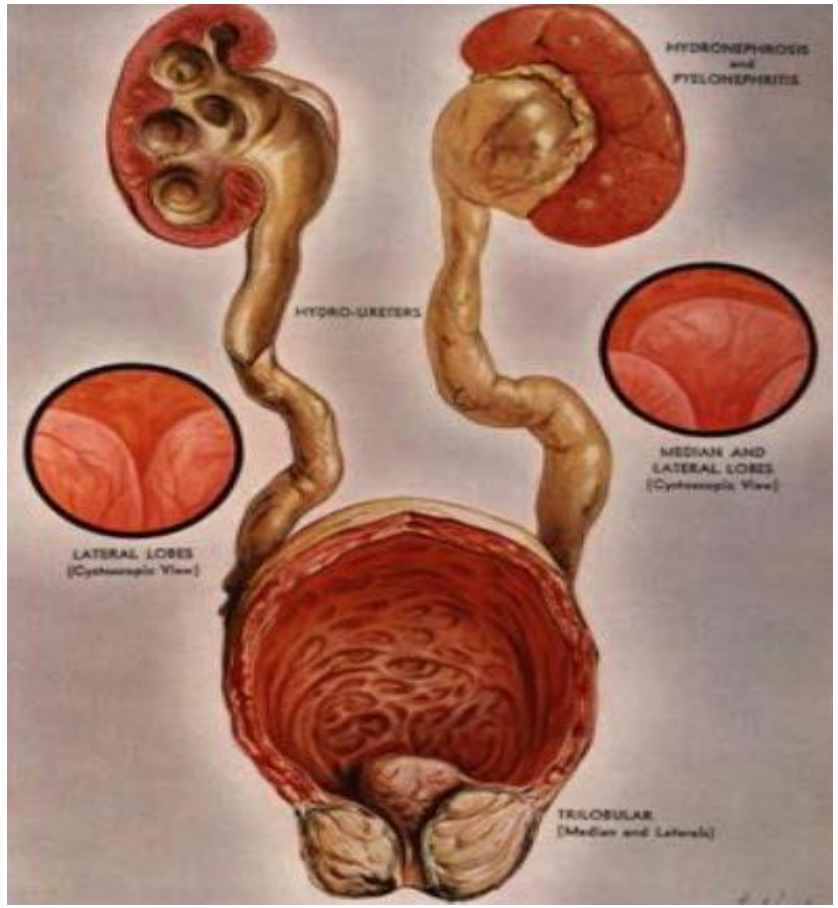
- **What is associated with BPH?**
  - **Clinical findings:** troublesome LUTS (voiding, storage and post-micturition symptoms)
  - **Anatomical finding:** benign prostatic enlargement (BPE)
  - **Pathophysiological finding:** urethral compression, which causes bladder outlet obstruction (BOO)



BPH: benign prostatic hyperplasia
BPE: benign prostatic enlargement
BOO: bladder outlet obstruction
LUTS: lower urinary tract symptoms

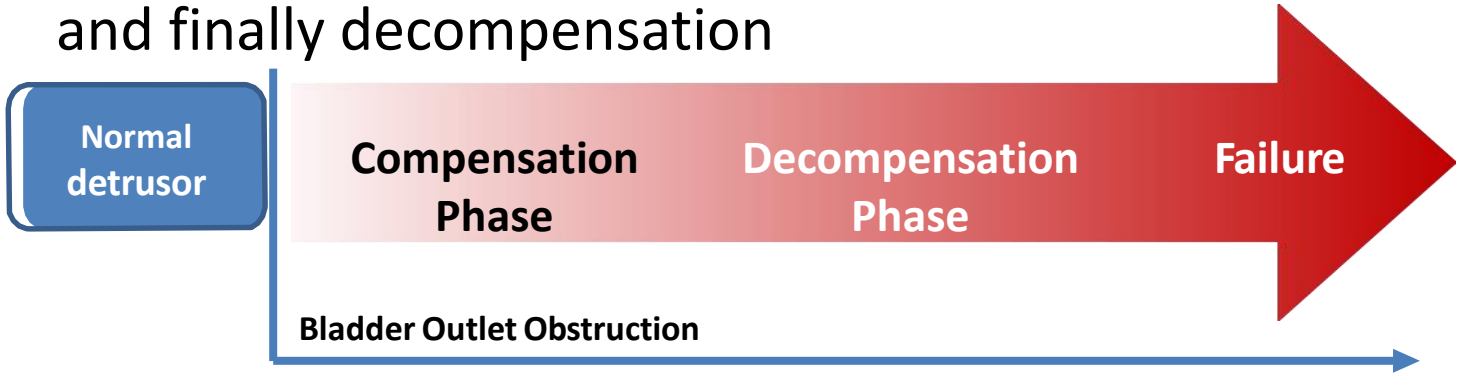
Abrams P et al. Male lower urinary tract dysfunction: evaluation and management. 2006

Natural history of Obstructive Uropathy



The bladder, like the heart, is a hollow muscular organ that receives fluid and forcefully expels it

Like the heart, it reacts to an increasing work load by going through the successive phases of compensation and finally decompensation



Emil A. Tanagho et al., Smith's General Urology, 17th Edition
Elmissiry MM., et al., Arab J Urol. 2014

Selecting Candidates for Medical Therapy

- Individuals with

  recurrent AUR

  recurrent UTIs,

  renal insufficiency,

  bladder calculi, and

  recurrent gross hematuria

  may develop life-threatening consequences from their BOO if it is not managed surgically.

- **patients with absolute indications for intervention should be discouraged from selecting medical therapy**

Differentiation. 2017

Case 1

- 80 y/o Male

  攝護腺肥大藥物 X 5年

- 主訴　**夜尿 2次**

Case 1

- 80 y/o Male
  攝護腺肥大藥物 X 5年

- 主訴 **夜尿 2次**

檢查:

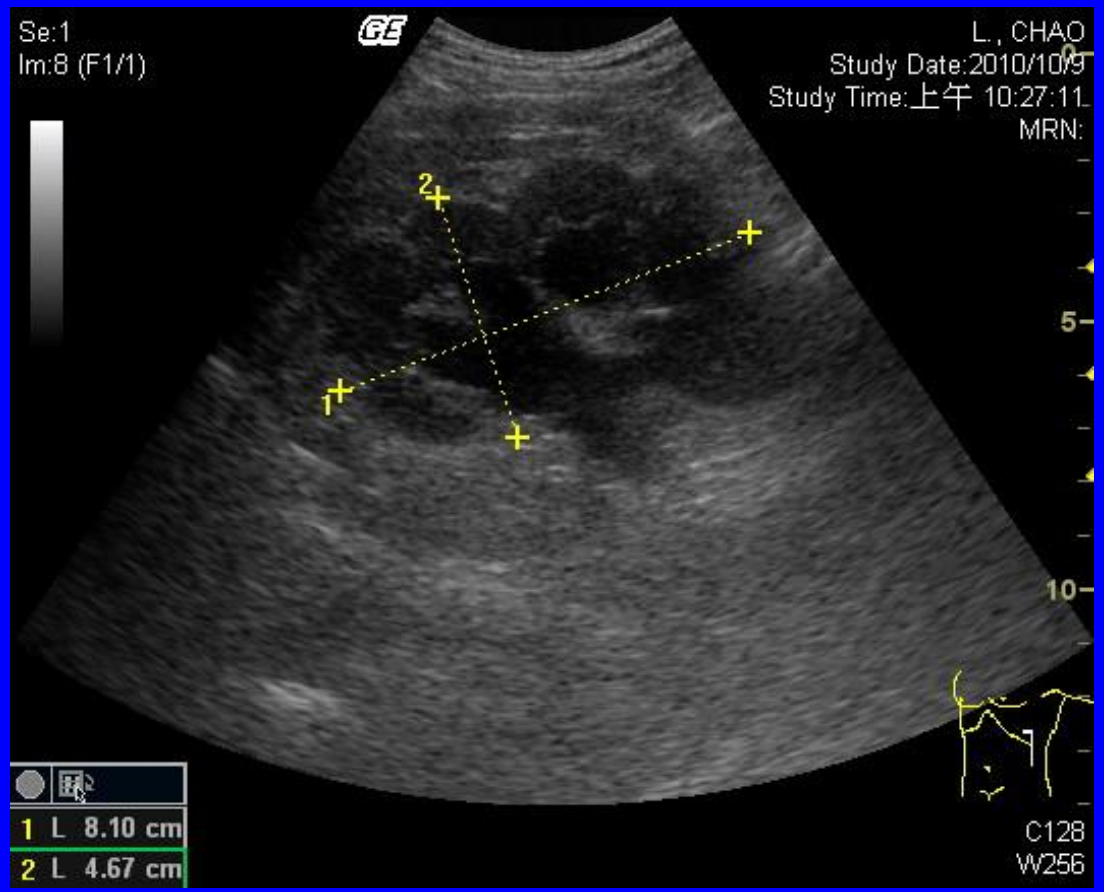
急性腎衰竭 (肌酸肝: 3.→9.25)

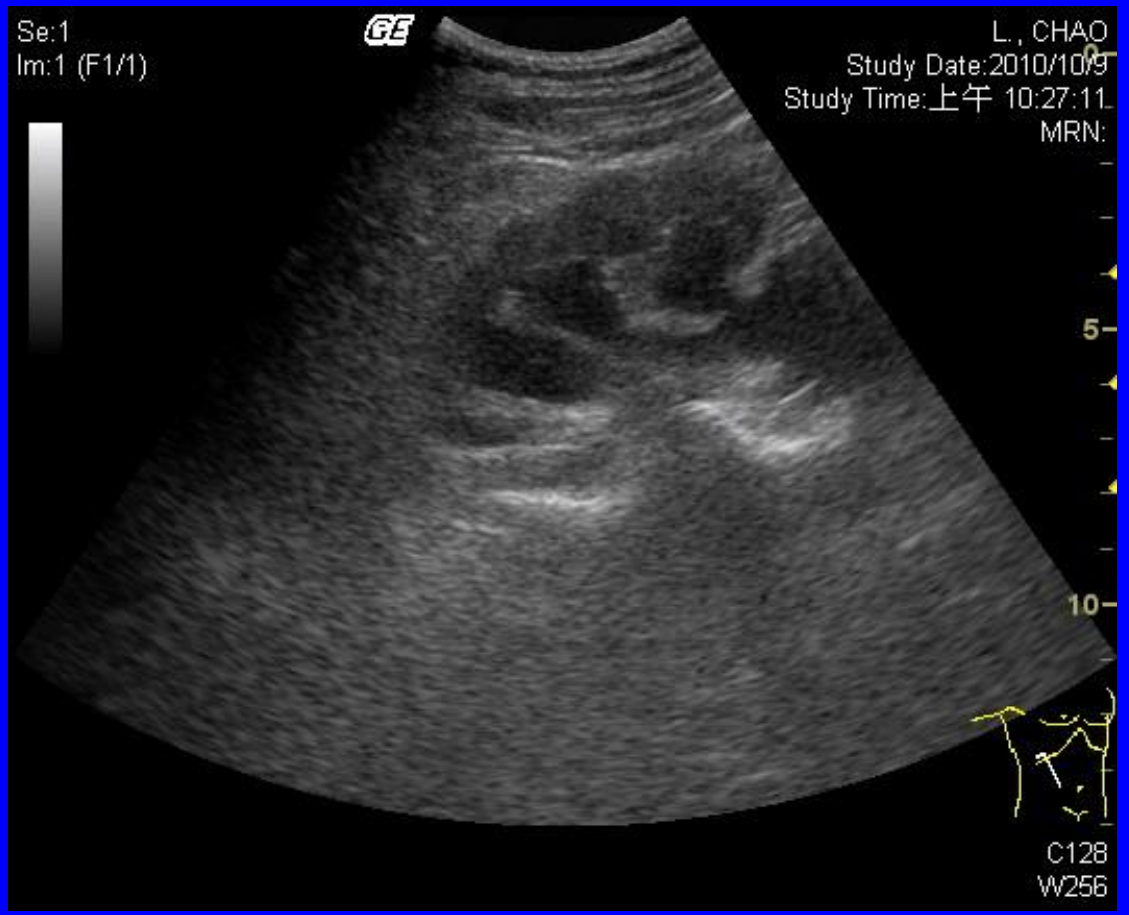
尿流速

最大流速 4,
排尿量 29 CC,
殘餘尿量 873 CC

腎臟超音波

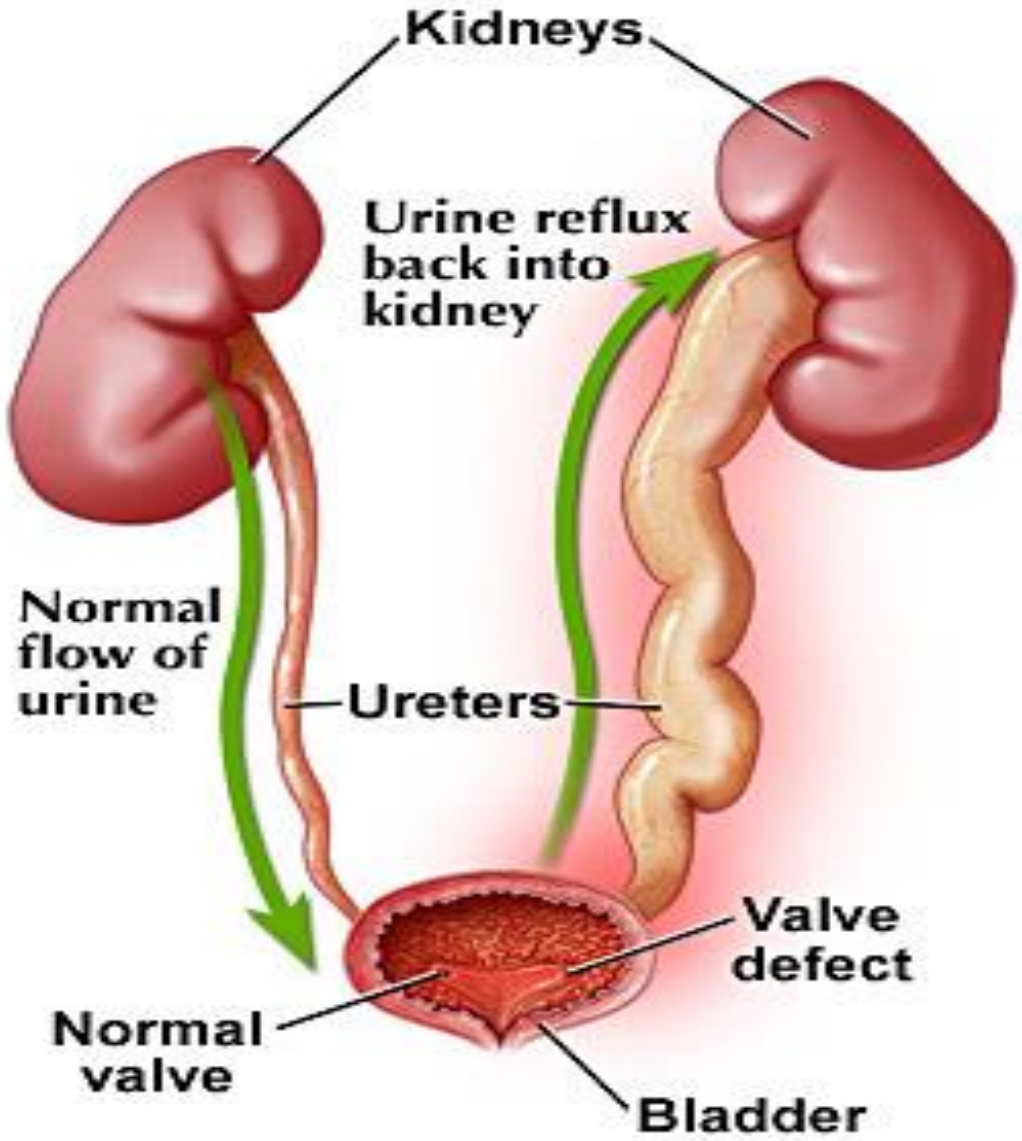
腎臟積水


Se:1
Im:8 (F1/1)
L., CHAO
Study Date:2010/10/9
Study Time:上午 10:27:11
MRN:
1 L 8.10 cm
2 L 4.67 cm
C128
W256


Se:1
Im:1 (F1/1)
L., CHAO
Study Date:2010/10/9
Study Time:上午 10:27:11
MRN:
C128
W256

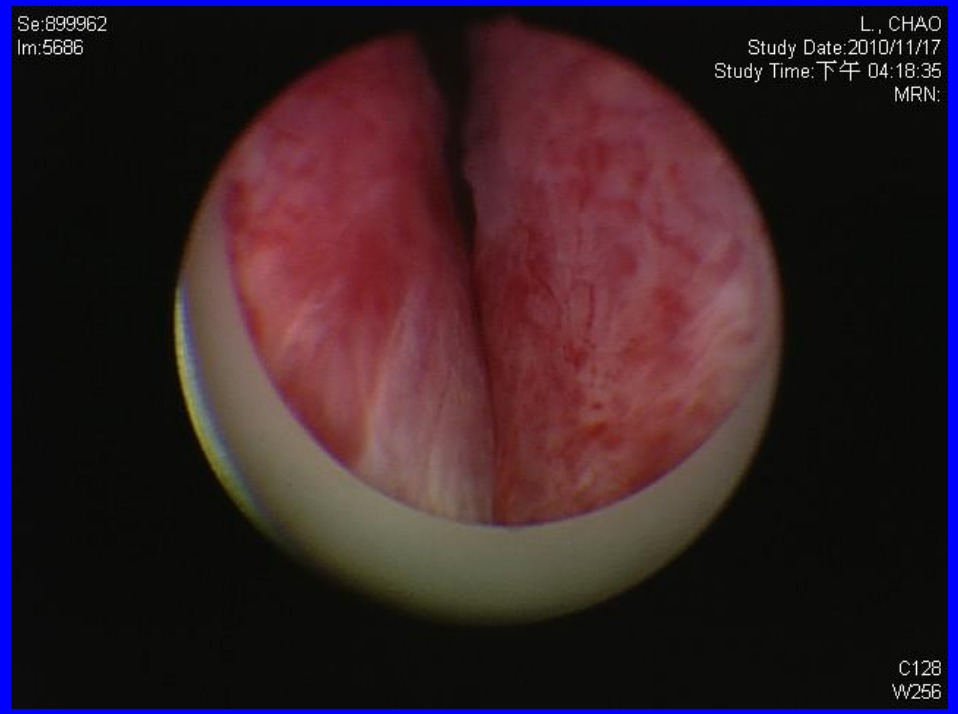
腎臟積水

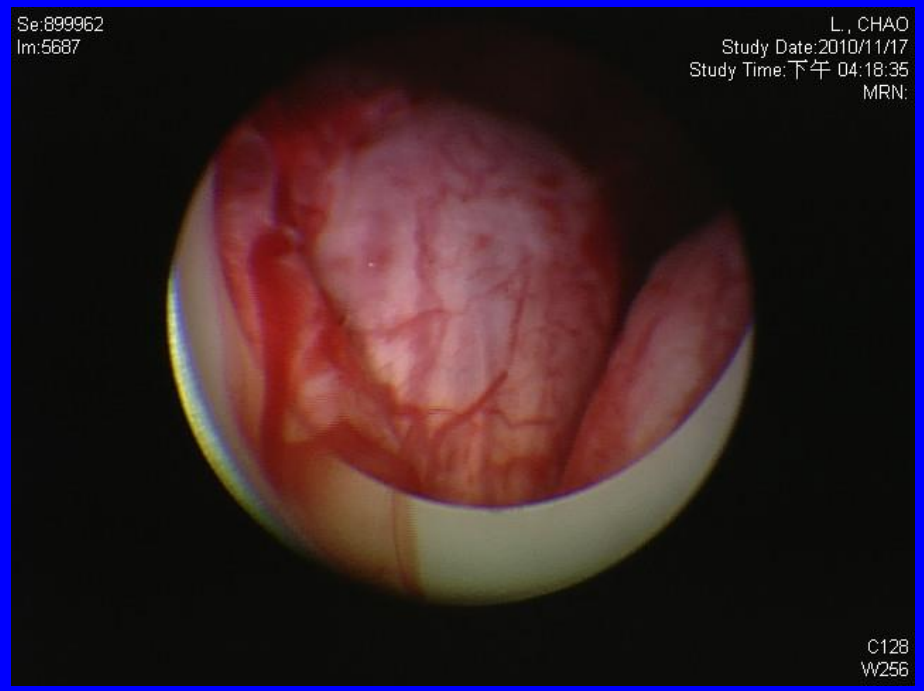
-).


Kidneys
Urine reflux back into kidney
Normal flow of urine
Ureters
Valve defect
Normal valve
Bladder

膀胱鏡

攝護腺肥大
尿道狹窄





攝護腺肥大之治療

- 藥物治療

  甲型交感神經拮抗劑 (放鬆尿管)

  5α還原酶抑制劑（縮小攝護腺）

  抗膽鹼藥物(抑制膀胱過動)

  B3腎上腺接受體促效劑(抑制膀胱過動)

  PDE5抑制劑(抑制膀胱過動)

手術時機

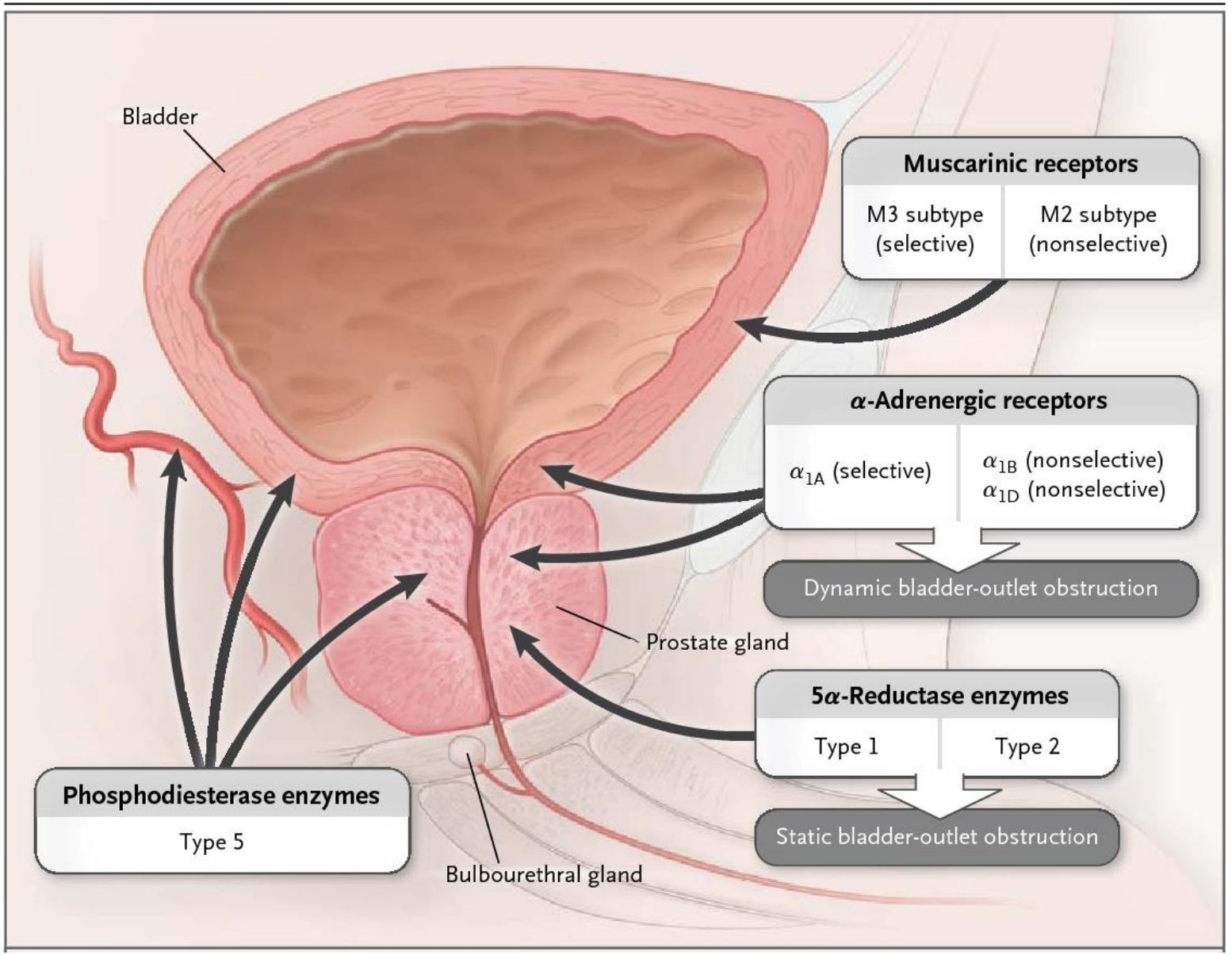
尿液滯留, 膀胱結石, 血尿 , 腎水腫, 感染

手術

攝護腺刮除手術

攝護腺雷射手術

Figure 1. Mechanisms of Action and Targets for Intervention in Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms. NEJM2012



Targeting phenotypic heterogeneity in benign prostatic hyperplasia

Differentiation. 2017

- There are currently no reliable biomarkers of specific phenotypes or progression.

- Accordingly, goals for the treatment of BPH/LUTS should be to

  1) identify specific BPH phenotype, for repurpose of targeted therapeutics

  2) identify biomarkers to prevent disease progression with early intervention

  3) identify the mechanisms of resistance to current therapies.

Targeting phenotypic heterogeneity in benign prostatic hyperplasia

Differentiation. 2017

- In the absence of tissue, blood or urinary biomarkers

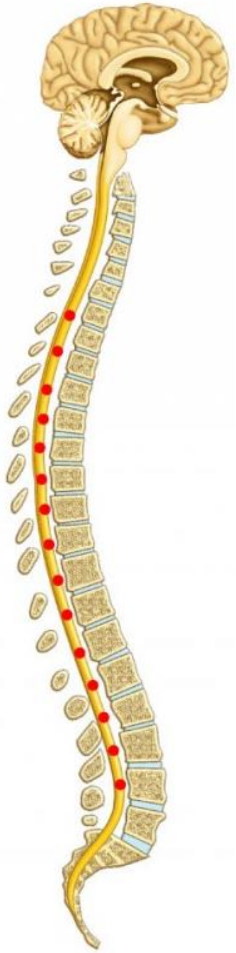
- Dynamic variables such as an

  increase in the AUA symptom score (AUASS) and

  PVR worsening

  are also good indicators of patients at risk of BPH progression

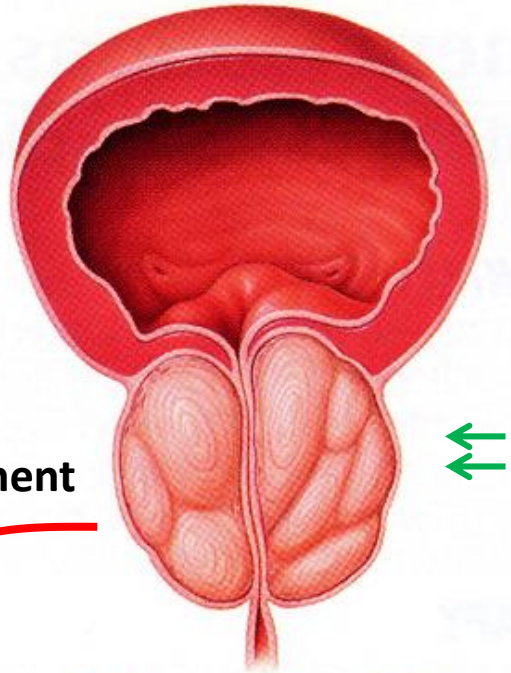
BPH/BPE/BOO/LUTS



Sympathetic system

Dynamic component

Static component



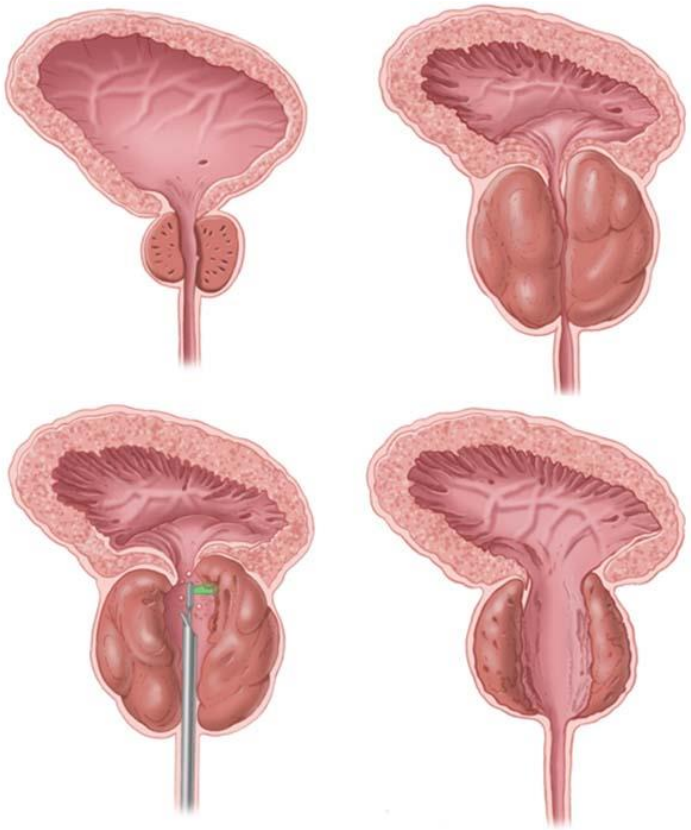
⇇ Surgery

Enlarged Prostate (BPE)

Bladder Outlet Obstruction (BOO)

Lower Urinary Tract Symptoms (LUTS)

The TURP/TUIP experience



Trials	Intervention	Patients (n)	Absolute decrease (%) in symptoms at 12 months		Q_{max} (mL/s) at 12 months	
			absolute	[%]	absolute	[%]
Dorflinger et al. (1992) (28)	TURP	31	-11.6 [a]	-88 [a]	+22.9 [a, b]	+294 [a, b]
	TUIP	29	-12.6 [a]	-85 [a]	+16.3 [a]	+223 [a]
Jahnson et al. (1998) (29)	TURP	43	-13 [a]	-82 [a]	+19.5 [a, b]	+229 [a, b]
	TUIP	42	-11.8 [a]	-77 [a]	+13.8 [a]	+148 [a]
Riehmann et al. (1995) (30)	TURP	61	-9.5 [a]	-67 [a]	no significant difference between groups	
	TUIP	56	-10 [a]	-63 [a]		
Saporta et al. (1996) (31)	TURP	20	-9.4 [a]	-63 [a]	+17.3 [a]	+266 [a]
	TUIP	20	-9.3 [a]	-64 [a]	+14.6 [a]	+197 [a]
		110			+20.1 [a]	+251 [a]
		110			+19.5 [a]	+246 [a]
		50	-12 *[a]	-70*	6.9 *[a]	+255 [a]
(2002) (12)	TUIP	50	-13 *[a]	-77*	7.6 *[a]	+222 [a]
Lourenco et al.	TURP	345	no significant difference between groups		no significant difference between groups	
		6				
		3	-11.2 to -13	-63 to -82	+17.3 to +22.9 [b]	+266 to +352 [b]
		2	-10 to -13.5	-63 to -83	+13.8 to +16.3	+189 to +223

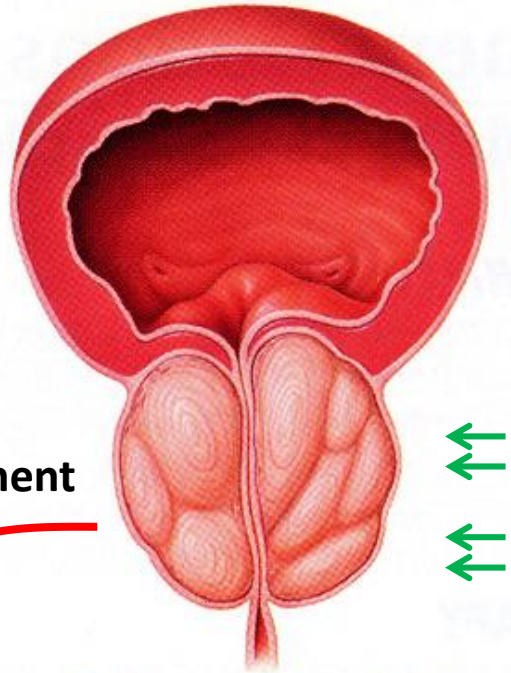
IPSS
↓10-13 points
(60-90%)

Qmax
↑14-23 ml/s
(150-300%)

What about drugs?

Sympathetic system

Static component



⇇ Surgery

⇇ 5ARI

Enlarged Prostate (BPE)

Bladder Outlet Obstruction (BOO)

Lower Urinary Tract Symptoms (LUTS)

Dynamic component

↑↑↑↑

α-blockers

Guidelines on the Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO)

S. Gravas (Chair), T. Bach, A. Bachmann, M. Drake, M. Gacci, C. Gratzke, S. Madersbacher, C. Mamoulakis, K.A.O. Tikkinen

eau European Association of Urology

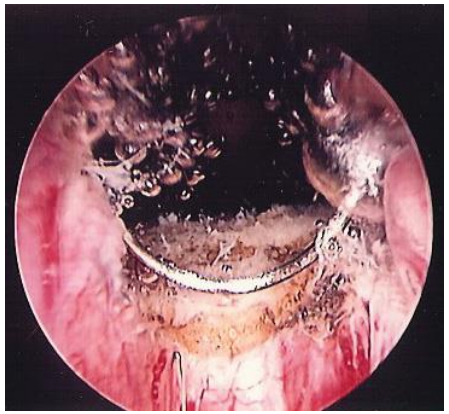
Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Change in symptoms (%)	Change in Q_{max} (mL/s)
Jardin et al. (1991) [14]	24	Placebo Alfuzosin 3 x 2.5 mg	267 251	-32 [a] -42 [a,b]	+1.3 [a] +1.4 [a]
Buzelin et al. (1997) [15]	12	Placebo Alfuzson 2 x 5 mg	196 194	-18 -31 [a,b]	+1.1 +2.4 [a,b]
van Kerrebroeck et al. (2000) [16]	12	Placebo Alfuzosin 3 x 2.5 mg Alfuzosin 1 x 10 mg	154 150 143	-27.7 -38.1 [a,b] -39.9 [a,b]	+1.4 +3.2 [a,b] +2.3 [a,b]
MacDonald and Wilt (2005) [17]	4-26	Placebo Alfuzosin: all formulations	1039 1928	-0.9 [b] (Boyarski) [†] -1.8 [b] (IPSS) [†]	+1.2 [b]
Kirby et al. (2001) [18]	13	Placebo Doxazosin 1 x 1-8 mg IR Doxazosin 1 x 4-8 mg GITS	155 640 651	-34 [a] -45 [a,b] -45 [a,b]	+1.1 [a] +2.6 [a,b] +2.8 [a,b]
McConnell et al. (2003) [8]	234	Placebo Doxazosin 1 x 4-8 mg	737 756	-29 -39 [b]	+1.4 +2.5 [a,b]
Chapple et al. (1996) [19]	12	Placebo Tamsulosin MR 1 x 0.4 mg	185 364	-25.5 -35.1 [a,b]	+0.6 +1.6 [a,b]
Lep		MR 1 x 0.4 MR 1 x 0.8	253 254 247	-28.1 -41.9 [a,b] -48.2 [a,b]	+0.5 +1.8 [a,b] +1.8 [a,b]
Cha (200		MR 1 x 0.4 OCAS 1 x 0.4 mg Tamsulosin OCAS 1 x 0.8 mg	350 700 354 707	-32 -43.2 [b] -41.7 [b] -42.4 [b]	- - - -
Wilt et al. (2002) [22]	4-26	Placebo	4122	-12 [b] (-1.1 Boyarski [†]) -11 [b] (-2.1 IPSS [†])	+1.1 [b]
Brawer et al. (1993) [23]			72 69	-11 -42 [a,b]	+1.2 +2.6 [a,b]
Roehrborn et al. (1996) [24]			973 976	-18.4 -37.8 [a,b]	+0.8 [a] +2.2 [a,b]
Wilt et al. (2000) [25]		Terazosin	5151	-37 [b] (-2.9 Boyarski [†]) -38 [b] (IPSS [†])	+1.7 [b]

IPSS
↓5-6 points
(30-40%)

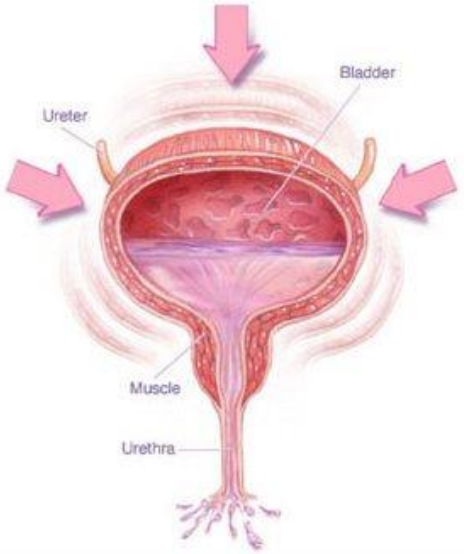
Qmax
↑1.4-3.2 ml/s
(20-25%)

Effect of Treatment on Q_{max}

TURP



Q_{max}
↑14-23 ml/s
(150-300%)



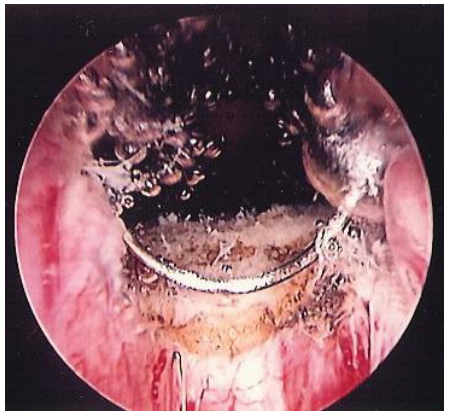
10 times >

Alpha-blocker

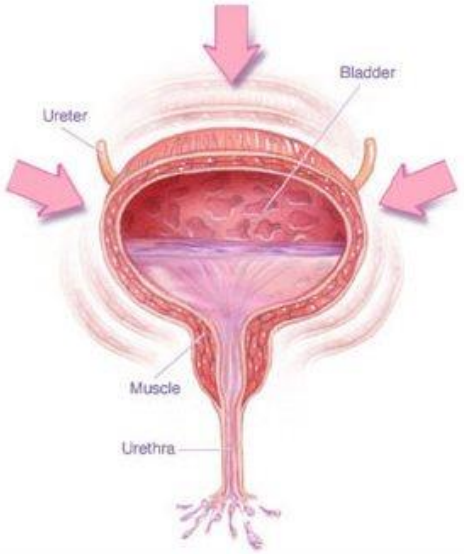
Qmax
↑1.4-3.2 ml/s
(20-25%)

Effect of Treatment on Symptoms

TURP



IPSS
↓10-13 points
(63-88%)

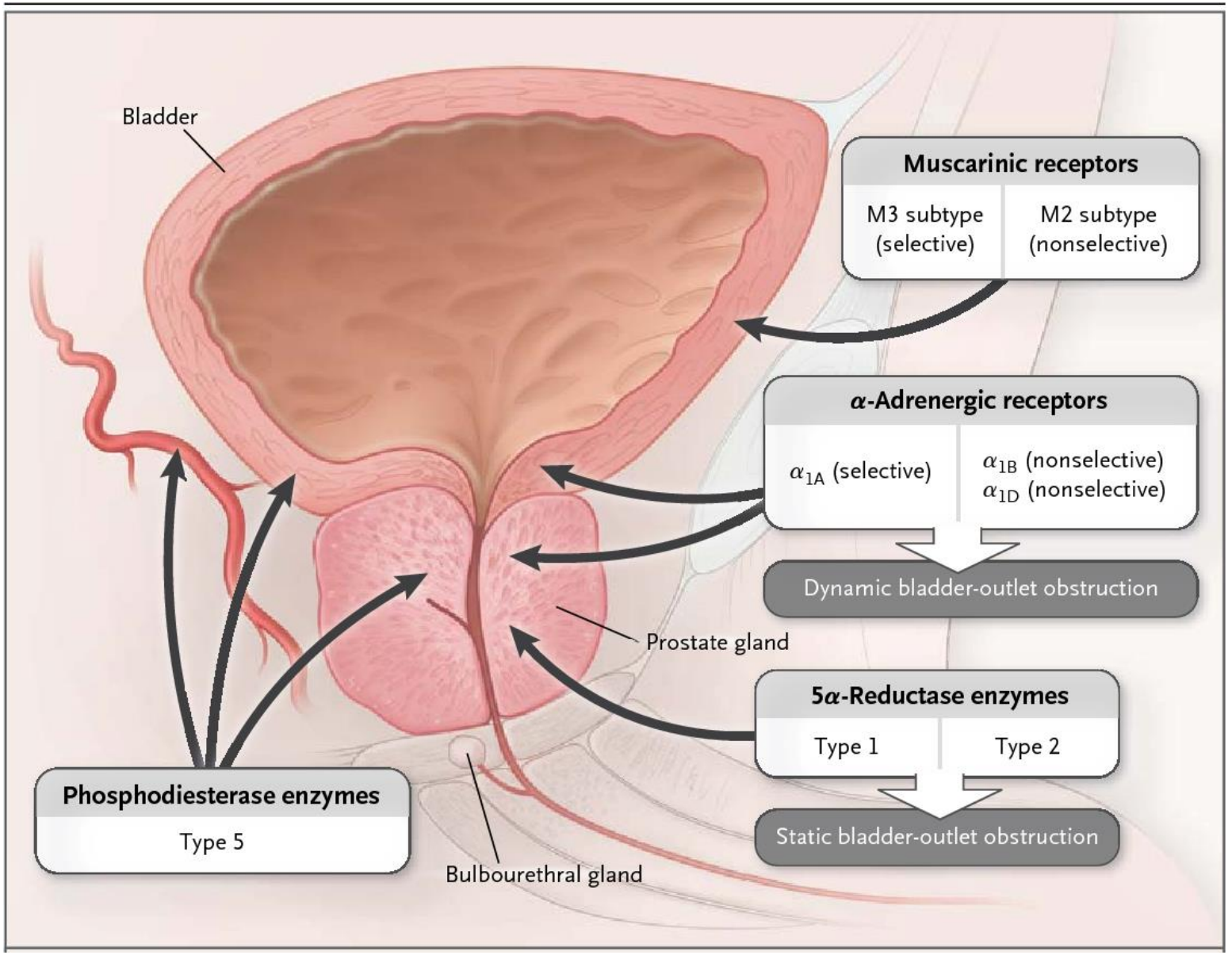


almost 2 times >

Alpha-blocker

IPSS
↓5-6 points
(30-50%)

Figure 1. Mechanisms of Action and Targets for Intervention in Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms. NEJM2012

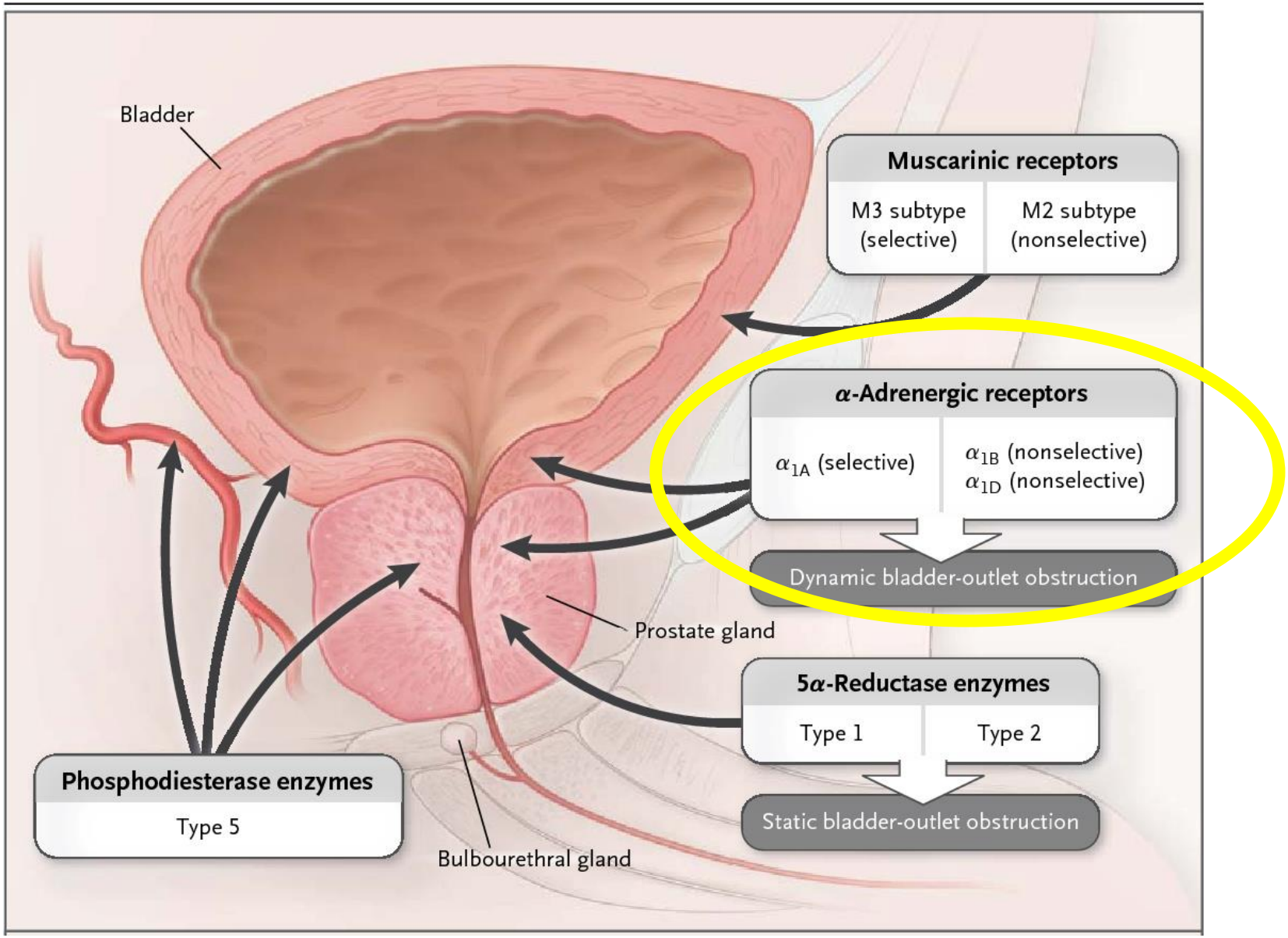


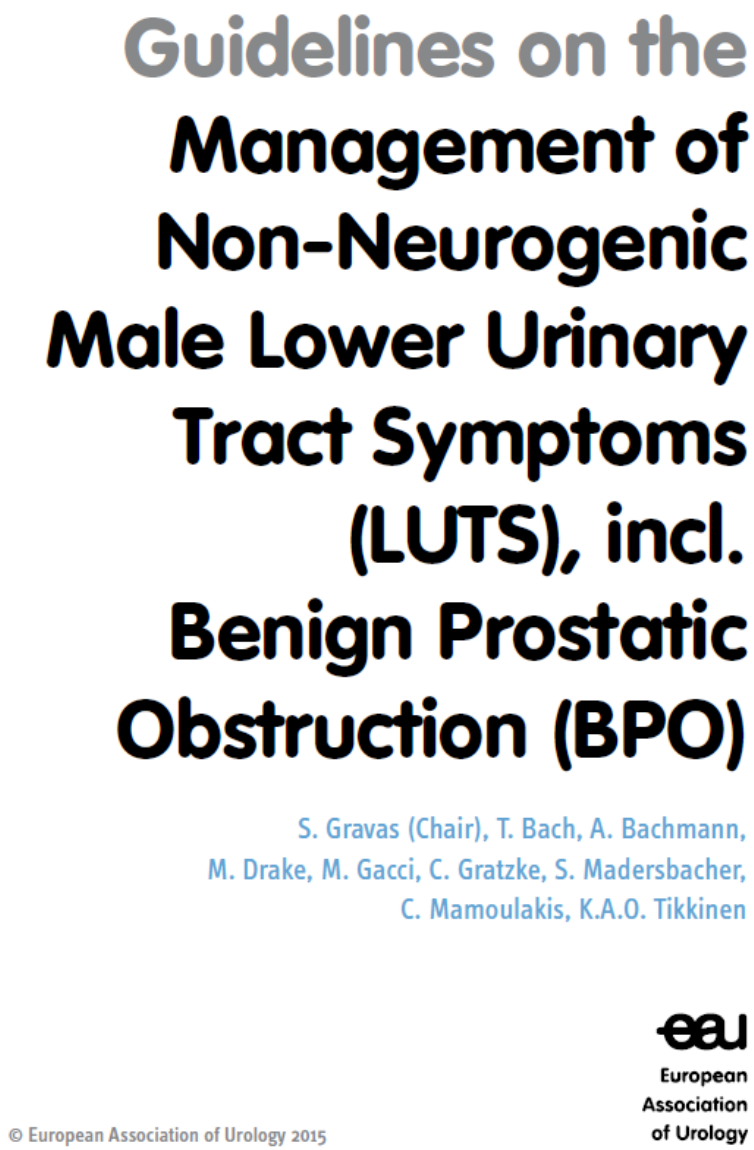
What is your **most frequent** choice

as a **first line** treatment

in men with BPH/LUTS?

Figure 1. Mechanisms of Action and Targets for Intervention in Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms. NEJM2012





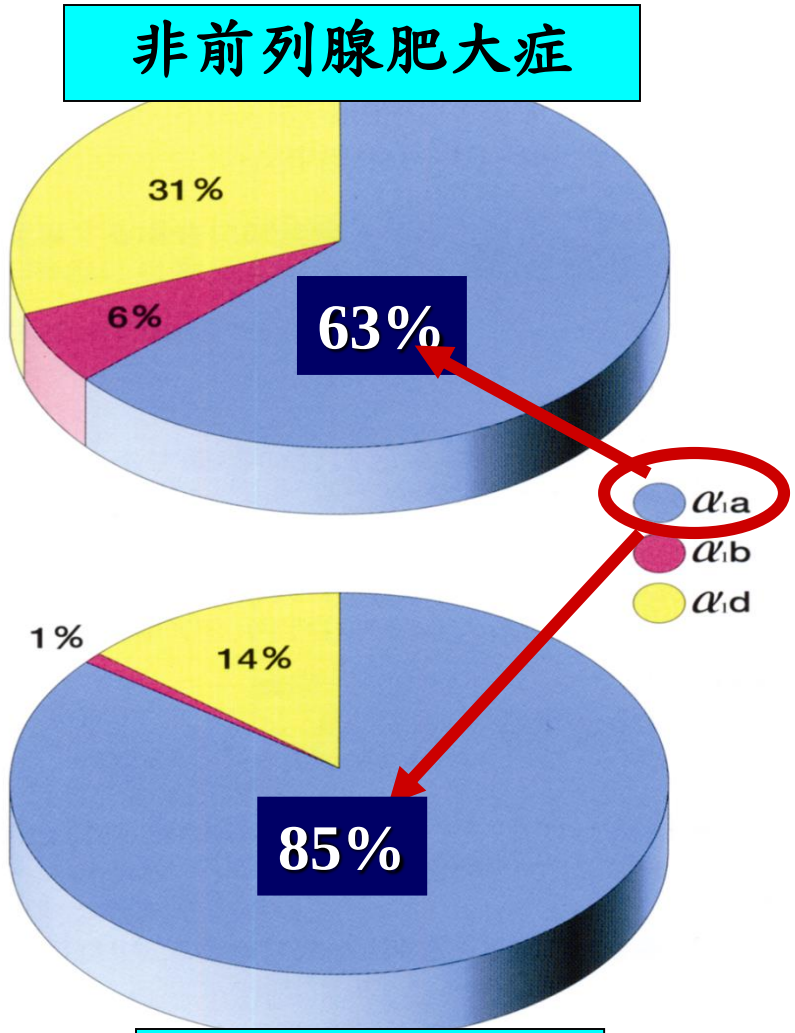
Practical Considerations:

α_1-blockers are often considered the first-line drug treatment of male LUTS

because of:

- rapid onset of action
- good efficacy
- low rate and severity of adverse events

α1-AR mRNA expression in the **human prostate**



Br.J.Pharmacol 1996, 119(5):797

α_1-blockers are different for:

1) Pharmacological selectivity for the α_{1A} subtype

Type of AB	$alpha_{1A}/alpha_{1B}$ Ratio	$alpha_{1A}/alpha_{1D}$ Ratio
Silodosin	162	55
Tamsulosin	9.55	2.51
Alfuzosin	0.309	0.617
Naftopidil	0.372	0.209
Terazosin	0.316	0.318

Subtypes of α_1-adrenoceptors in BPH: future prospects for personalized medicine

Nature Clinical Practice Urology 2009

- The expression of α1AR subtypes varies among symptomatic BPH patients, and expression-level differences may help predict which patients will respond to subtype selective α1AR antagonists

Targeting phenotypic heterogeneity in benign prostatic hyperplasia

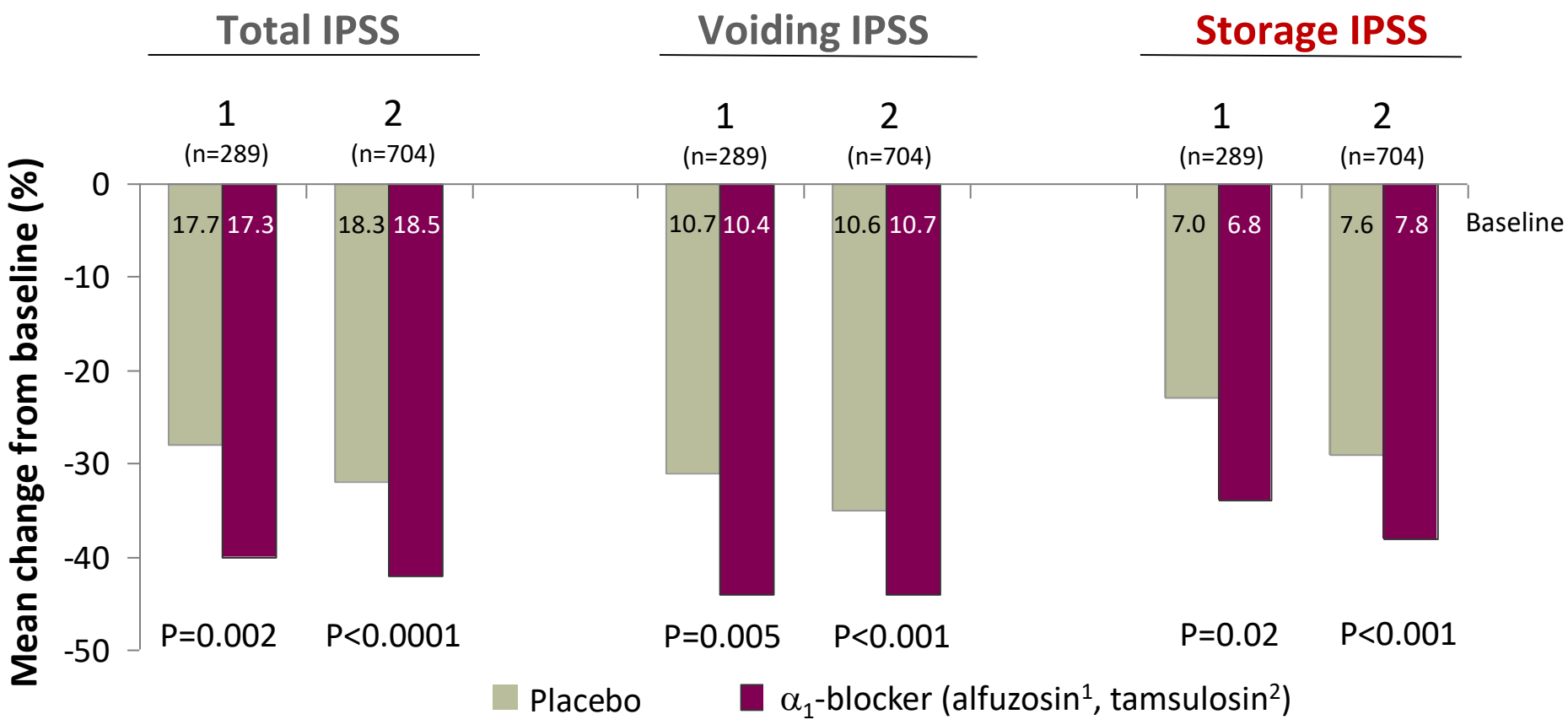
Differentiation. 2017

- The mechanism of action of α-blockers is to reduce smooth muscle tone, which increases peak urinary flow rate.

- It is notable that the clinical response to αblockers is proportional to the percent of prostate tissue occupied by smooth muscle, meaning that those patients with glandular hyperplasia are less likely to demonstrate a clinical response.

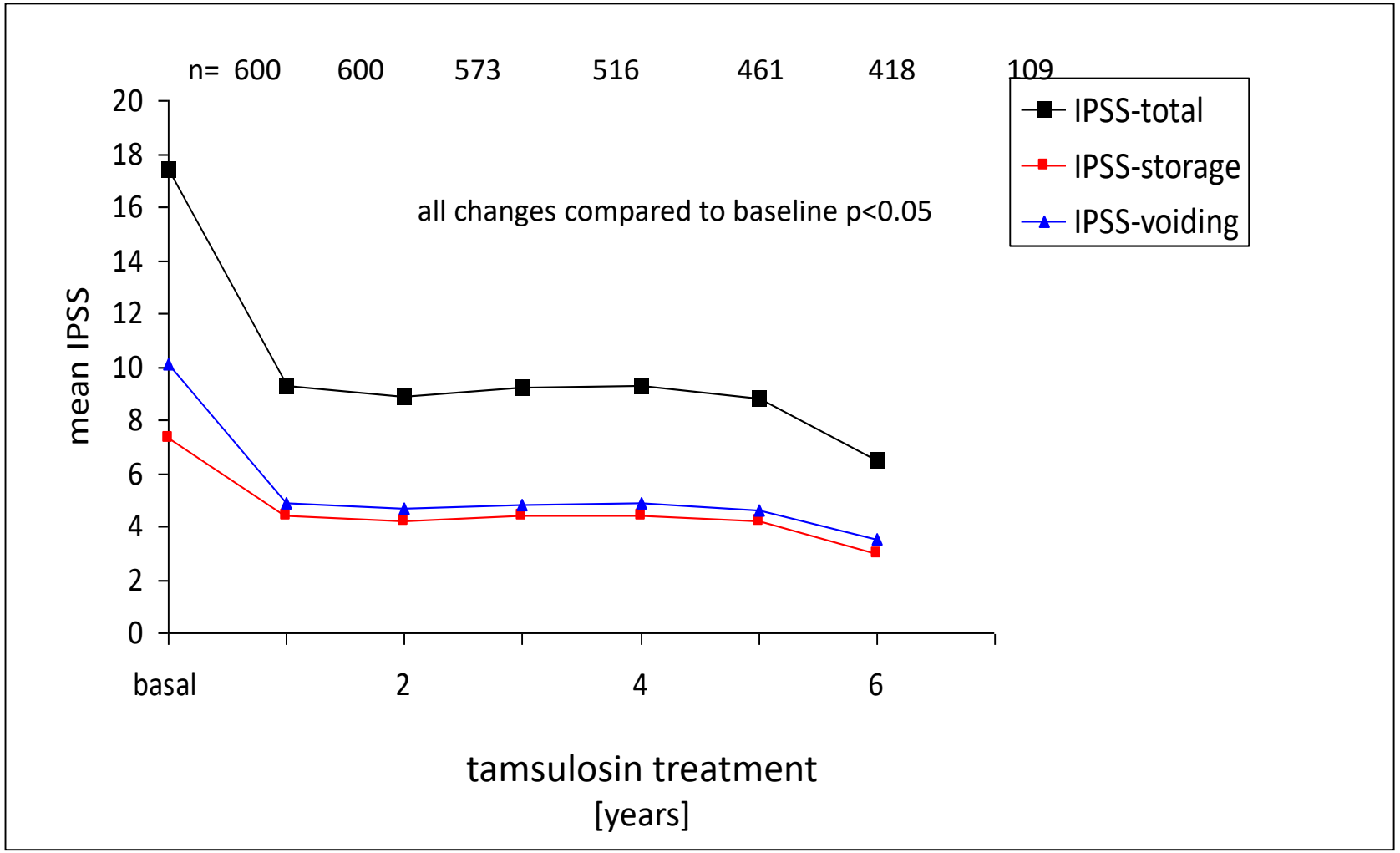
α_1-blockers relieve BOTH voiding and storage LUTS

12-w double-blind RCTs in men ≥45 or 50 yrs with baseline IPSS ≥13 and Q_{max} 4- 5 to 12 ml/s



[1] Adapted from van Kerrebroeck P et al. Eur Urol 2000; 37: 306 - 313
[2] Adapted from Chapple CR et al. Eur Urol Suppl 2005; 4: 33 - 44

α_1-blockers relieve BOTH voiding and storage LUTS- long-term data -



Narayan P et al. (2003) J Urol 170: 498-502

α1-Blockers Improve Benign Prostatic Obstruction in Men with Lower Urinary Tract Symptoms: A Systematic Review and Meta-analysis of Urodynamic Studies

Ferdinando Fusco [a,], Alessandro Palmieri [a], Vincenzo Ficarra [b,c], Gianluca Giannarini [c], Giacomo Novara [d], Nicola Longo [a], Paolo Verze [a], Massimiliano Creta [e], Vincenzo Mirone [a]*

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EUROPEAN UROLOGY XXX (2016) XXX–XXX

Table 1 – Characteristics of the studies included in the review

Study	Design	JS	Sample size (*n*) [a]	Control group (*n*)	Treatment protocol (drug and dosage)	Treatment (wk)	Obstruction at baseline, *n* (%)	Obstruction resolved, *n* (%) [b]
Gleason 1994 [24]	NRNCT	NA	17	NA	Terazosin 1 mg OAD, titrated up to 2, 5, and 10 mg OAD as tolerated	8	NR	NA
Witjes 1996 [13]	RCT	2	33	NA	Terazosin at bedtime and increased to maximum dose 10 mg OAD at 6 wk	26	22 (66.6)	NA
Witjes 1997 [12]	NRNCT	NA	60	NA	Terazosin increased to maximum of 10 mg OAD at 6 wk	112	30 (50)	NA
Tanaka 2002 [17]	NRNCT	NA	20	NA	Terazosin 1 mg OAD for the first 7 d and then 1 mg TAD	4	10 (50)	6 (60)
Gerber 1996 [15]	NRNCT	NA	44	NA	Doxazosin 1 mg OAD for 4 d, then 2 mg OAD for 4 d, then 4 mg OAD	12	30 (68.1)	9 (30)
Ozbey 1999 [20]	PC-RCT	2	21	18	Doxazosin 2 mg OAD, then 4 mg OAD	4	NR	NA
Abrams 1997 [9]	DB-PC-RCT	3	30	28	Tamsulosin 0.4 mg OAD	4	30 (100)	NA
Arnold 2001 [14]	NRNCT	NA	28	NA	Tamsulosin 0.4 mg OAD	12	30 (100)	21
Regadas 2013 [22]	DB-PC-RCT	3	20	20	Tamsulosin 0.4 mg OAD	4	12 (60)	NA
Yamanishi 2004 [10]	SB- RCT	2	24	12	Naftopidil 50–75 mg OAD	4–6	22 (61.1)	13 (59)
Martorana 1997 [19]	DB-PC-RCT	3	25	26	Alfuzosin 2.5 mg TID	4	NR	NA
Nishino 2006 [23]	CO-RCT	2	34	NA	Naftopidil 50 mg for 4 wk, followed by tamsulosin 0.2 mg for 4 wk (*n* = 17) Tamsulosin 0.2 mg for 4 wk, followed by naftopidil 50 mg for 4 wk (*n* = 17)	9	Naftopidil 28 (82.3) Tamsulosin 30 (88.2)	Naftopidil 21 (75) Tamsulosin 13 (43.3)
De Nunzio 2003 [21]	NRCT	NA	20	20	Alfuzosin SR 5 mg TAD	96	20 (100)	4, (20)
Sriplakich 2007 [25]	NRCT	NA	13	12	Alfuzosin SR 10 mg OAD	12	25 (100)	NA
Rossi 2001 [11]	NRCT	NA	163	NA	Alfuzosin 2.5 mg TID (*n* = 60) Terazosin 5 mg OAD (*n* = 66) Tamsulosin 0.4 mg. OAD (*n* = 37)	24	NR	NA
Matsukawa 2009 [18]	NRNCT	NA	57	NA	Silodosin 4 mg TAD	4	NR	NA
Yamanishi 2010 [16]	NRNCT	NA	27	NA	Silodosin 4 mg TAD	12	30 (83)	NA

SR = slow release; OAD = once a day; TAD = twice a day; TID = three times a day; NR = not reported; JS = Jadad score; NA = not applicable; NRNCT = not randomized, not controlled clinical trial; NRCT = not randomized controlled clinical trial; RCT = randomized controlled clinical trial; CO-RCT = crossover RCT; PC-RCT = randomized placebo-controlled clinical trial; DB-PC-RCT = double-blind RP-RCT; SB-RCT = single-blind RCT.

[a] Sample size based on data extracted for meta-analysis may differ from number reported in the original study.

[b] Percentage of patients who went from the obstructed to the equivocal or unobstructed class.

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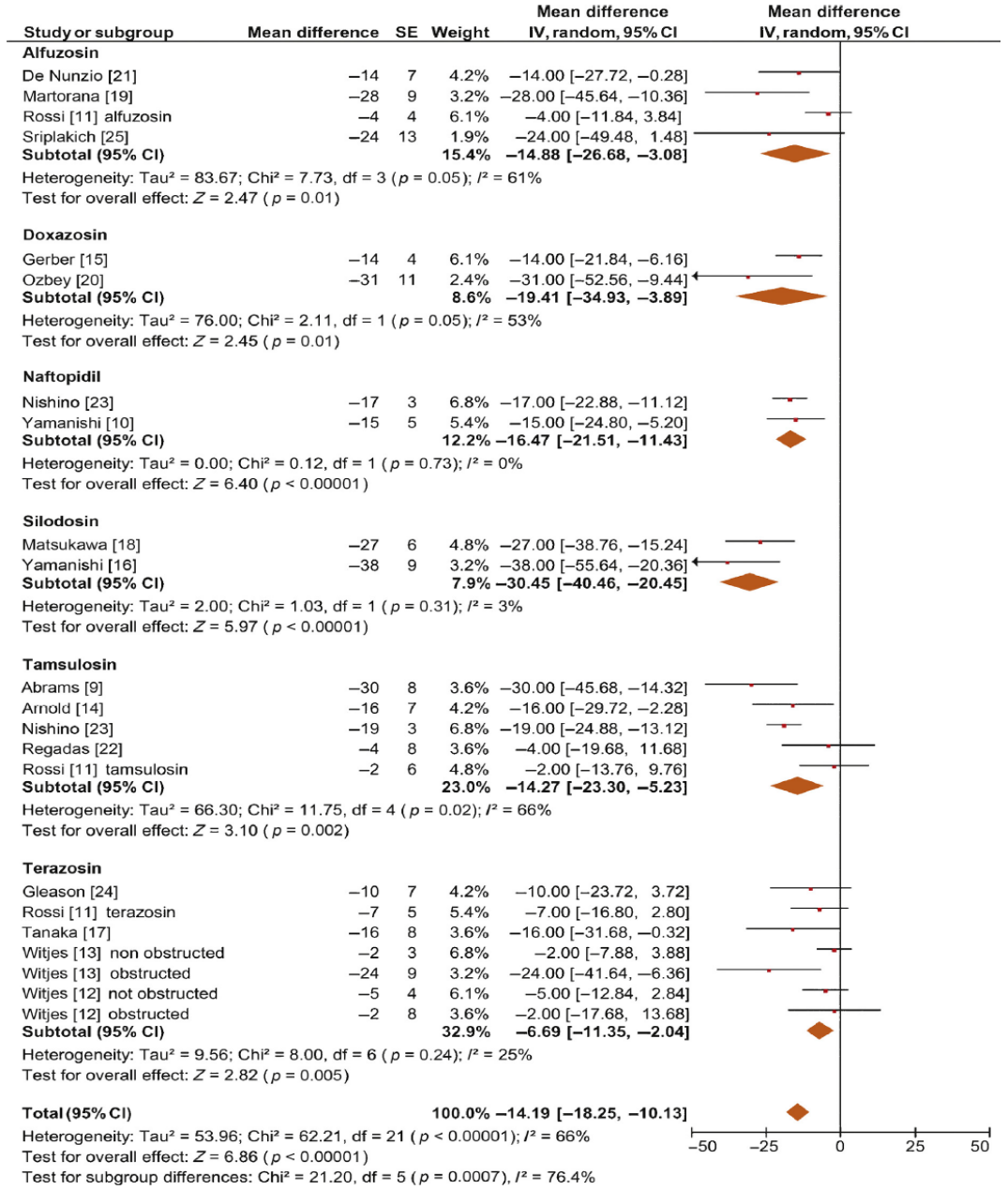
Fusco F, et al. a1-Blockers Improve Benign Prostatic Obstruction in Men with Lower Urinary Tract Symptoms: A Systematic Review and Meta-analysis of Urodynamic Studies. Eur Urol (2016), http://dx.doi.org/10.1016/ j.eururo.2015.12.034

All α_1-blockers have a <u>significant</u> urodynamic effect on BOO

Overall

≈ 14 points

BOOI decrease



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BPH & Metabolic syndrome

Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®
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See related article, pages 156–165

Old Drug, New Tricks

The Unexpected Effect of Doxazosin on High-Density Lipoprotein

Alan T. Remaley

Circ. Res. 2007;101;116-118

Controlled-release doxazosin in the treatment of benign prostatic hyperplasia

C Hernandez[1]*, R Duran[1], J Jara[1], I Castaño[1] & M Moralejo[1]
[1]*Hospital General Universitario Gregorio Marañón, Madrid, Spain*

3283 cases, Tx 2 months

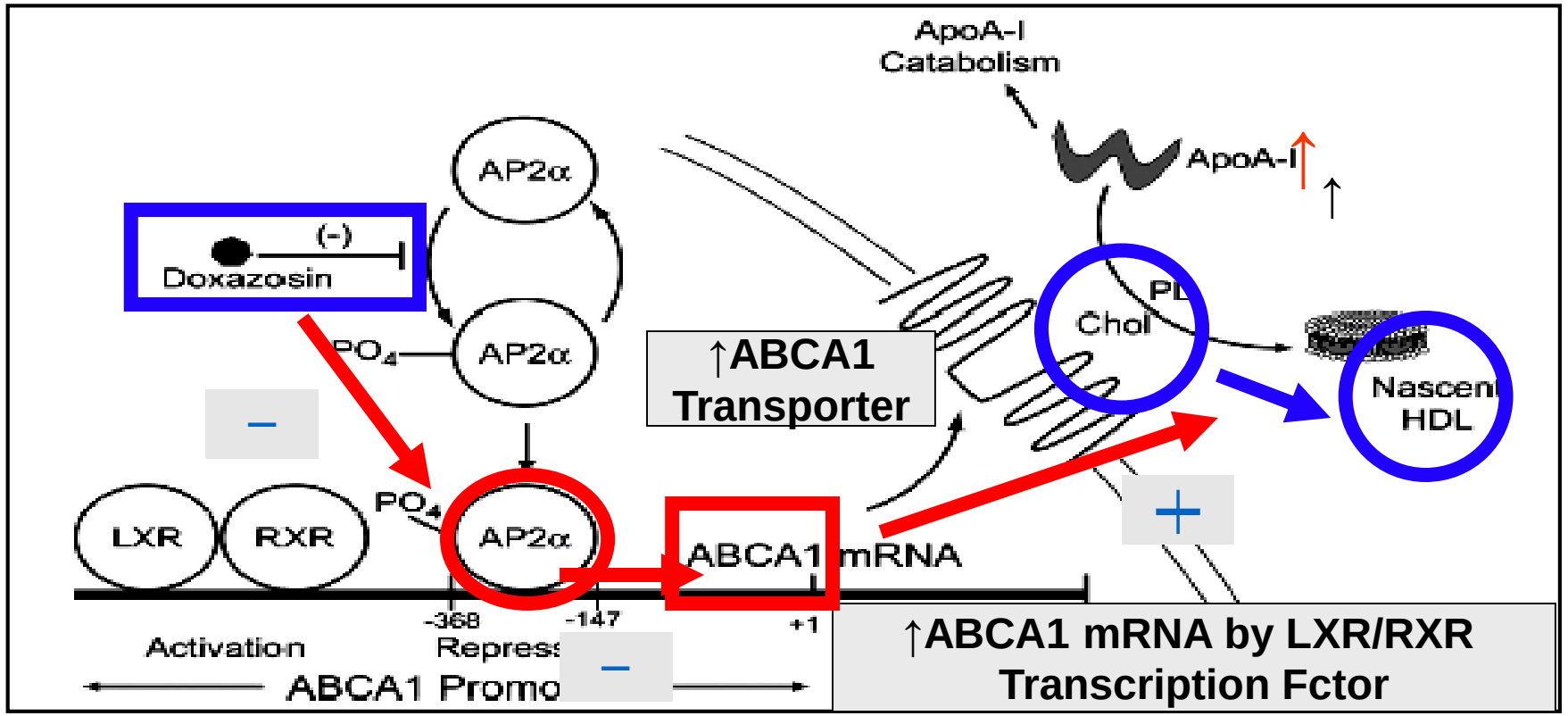
Prostate Cancer and Prostatic Diseases (2005) 8, 375–380

Table 2 Summary of laboratory parameters collected

Parameter	Patients (*n*)	Baseline (±s.d.)	Study end point (±s.d.)	Change from baseline (%)	*P*-value
Total cholesterol (mg/dl)	1048	222.46±38.19	217.18±33.85	−2.56	<0.0001
LDL cholesterol (mg/dl)	397	130.92±53.23	121.56±50.06	−5.52	<0.0001
Glucose (mg/dl)	1235	106.50±22.32	104.90±18.17	−0.99	0.0100
Uric acid (mg/dl)	1134	6.09±1.26	5.94±1.10	−1.57	0.0003
Triglycerides (mg/dl)	799	147.64±65.04	143.00±50.98	−1.02	0.1016
Urea (mg/dl)	1036	42.83±10.85	42.72±9.90	0.00	0.9127
BUN (mg/100 ml)	214	1.098±0.239	1.088±0.237	0.00	0.6663
PSA (ng/ml)	1664	2.164±1.099	2.135±1.104	0.00	0.4144
HDL cholesterol (mg/dl)	404	61.60±45.53	62.47±44.82	1.96	0.0040

Old Drug, New Tricks

the unexpected effect of doxazosin on HDL-C



Remelay AT. Circ Res 2007;101(July 20):116

台灣高血壓治療指引

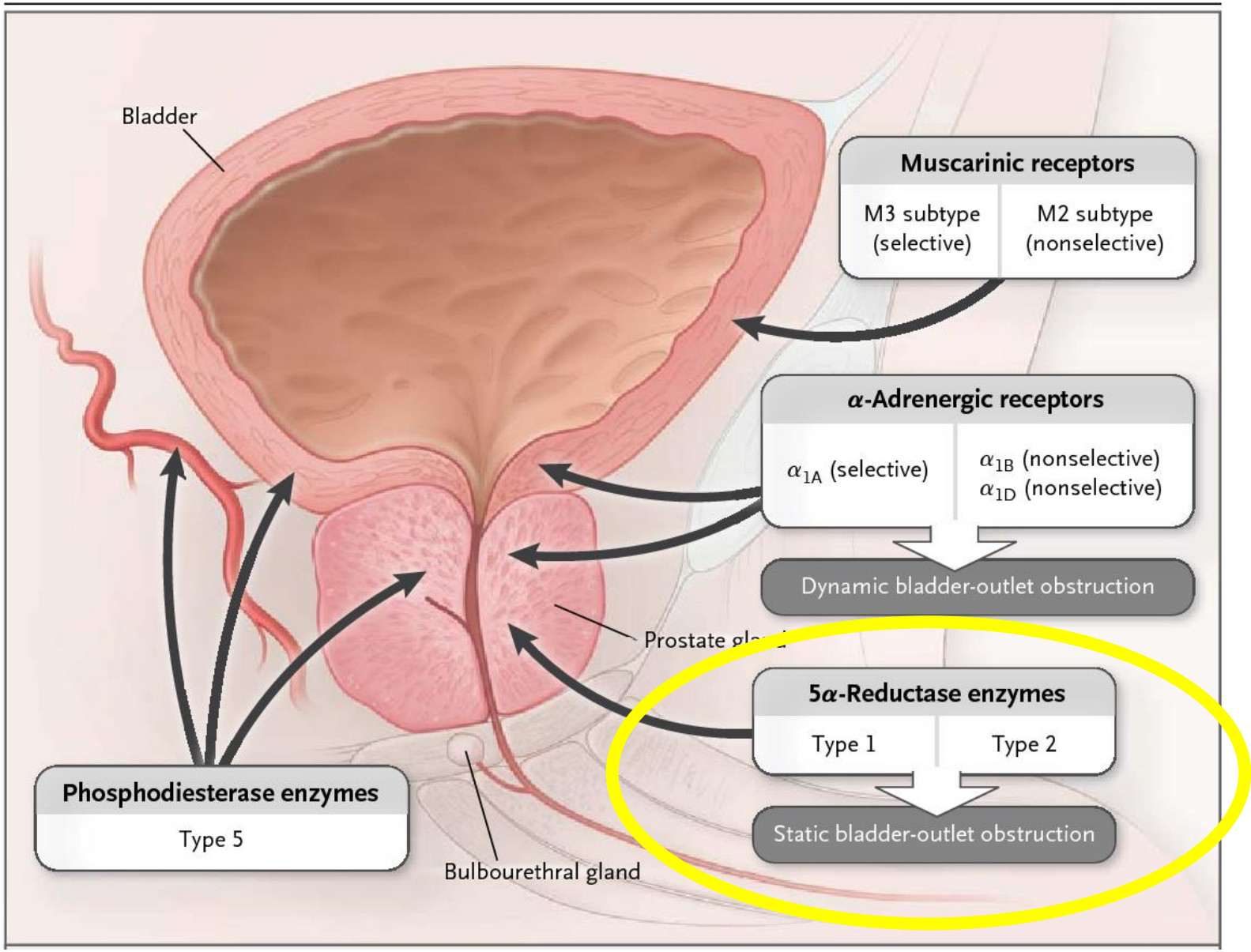
J Formos Med Assoc | 2010 • Vol 109 • No 10

Table 8. Recommended combinations

Clinical conditions	Single drug	2-drug combinations	3-drug combinations*
Target organ damage			
Left ventricular hypertrophy	ARB	ARB + D	ARB + CCB + D
Microalbuminuria	ACEI, ARB	ACEI + CCB, ARB + CCB, ACEI + D, ARB + D	ACEI + CCB + D, ARB + CCB + D
Asymptomatic atherosclerosis	CCB	ACEI + CCB, ARB + CCB	ACEI + CCB + D, ARB + CCB + D
Clinical events			
History of myocardial infarction	BB, ACEI, ARB	ACEI + BB, ARB + BB	ACEI + BB + D, ARB + BB + D
Coronary heart disease	BB, ACEI, ARB, CCB (long-acting)	BB + CCB, ACEI + CCB, ARB + CCB, ACEI + BB, ARB + BB	ACEI + CB + CCB, ARB + BB + CCB
Heart failure	BB, ACEI, ARB, D†	ACEI + BB, ARB + BB, ACEI + D†, ARB + D†, BB + D†	ACEI + BB + D†, ARB + BB + D†
Stroke	ACEI, ARB, D, CCB	ACEI + CCB, ARB + CCB, ACEI + D, ARB + D	ACEI + CCB + D, ARB + CCB + D
Chronic kidney disease	ACEI, ARB, loop diuretic	ACEI + loop diuretic, ARB + loop diuretic	ACEI + loop diuretic + CCB, ARB + loop diuretic + CCB
Peripheral artery disease	CCB	ACEI + CCB, ARB + CCB	ACEI + CCB + D, ARB + CCB + D
Diabetes mellitus	ACEI, ARB, DRI	ACEI + CCB, ARB + CCB, ACEI + D, ARB + D	ACEI + CCB + D, ARB + CCB + D
Associated conditions			
Isolated systolic hypertension	D, CCB, ARB	ARB + CCB, ARB + D, CCB + D	ARB + CCB + D
Metabolic syndrome	ACEI, ARB	ACEI + CCB, ARB + CCB	ACEI + CCB + α-Blocker, ARB + CCB + α-Blocker

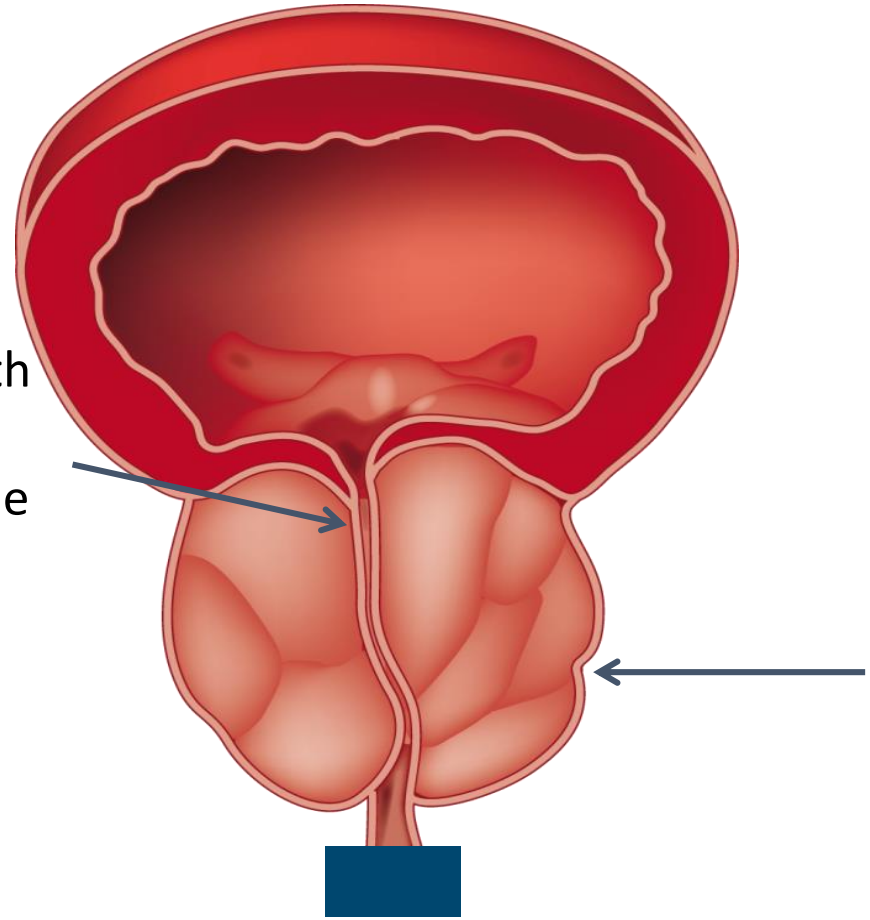
*Expert consensus; †thiazide diuretic, or loop diuretic, or aldosterone receptor blocker (preferred); ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = β-blocker; CCB = calcium channel blocker; D = thiazide diuretic.

Figure 1. Mechanisms of Action and Targets for Intervention in Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms. NEJM2012



BPH treatment: 5ARIs and α-blockers

α-blockers relax the smooth muscle receptors in the bladder neck and within the prostate



5ARIs
(5α reductase inhibitors)
inhibit the AR axis inhibiting the growth of the cells within the prostate

Barkin J. Patient Preference and Adherence 2011;5:483–490.

Targeting phenotypic heterogeneity in benign prostatic hyperplasia

Differentiation. 2017

- Men with prostate volume > 40cc are most likely to show a clinical response to 5ARI treatment.
- This is likely due to the fact that larger prostates are more likely to take on the form of glandular hyperplasia, tissues that are rich in androgen receptors to which 5ARIs are targeted.
- The mechanism of action of 5ARIs is to reduce local dihydrotestosterone (DHT) levels by inhibiting the conversion of testosterone to DHT, causing apoptosis of luminal epithelia.
- 5ARI treatment reduces prostate volume by an average of 19% across a patient population, which slows the progression of lower urinary tract symptom worsening.

α 1-blocker + 5 α -reductase inhibitor

- **MTOPS study, 4.5 years follow up**
  - **Significant** benefit for finasteride + doxazosin versus either monotherapy in reducing the risk of progression of BPH, AUR and surgery need
- **CombAT study, 4 years follow up**
  - Dutasteride + tamsulosin **significantly** reduced symptom deterioration and the relative risk of AUR or BPH op compared with tamusulosin monotherapy

N. Engl. J. Med.2003, 349:2387–98
Eur. Urol.2010, 57:123–31

Targeting phenotypic heterogeneity in benign prostatic hyperplasia

Differentiation. 2017

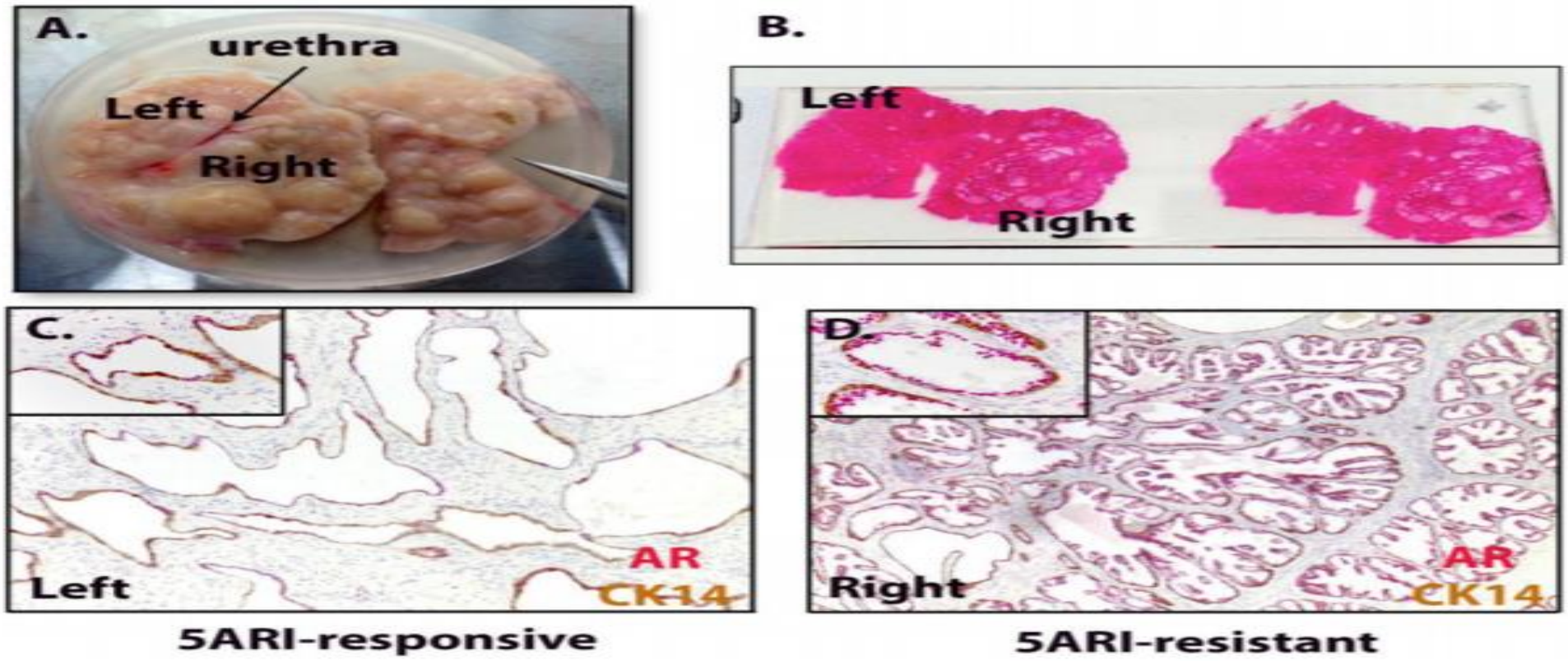


Figure 1. Regional 5ARI resistance in BPH
A, Coronal section of a 130g prostate from a BPH patient on 5mg/day finasteride for 5 years. **B**, H&E stained glass slide with serial sections showing morphological differences between atrophied left side and nodular right side. **C**, AR/CK14 dual IHC of atrophied left side shows loss of luminal epithelia. **D**, AR/CK14 IHC of right side shows strong AR staining of luminal epithelia in non-atrophied glands.

Targeting phenotypic heterogeneity in benign prostatic hyperplasia

Differentiation. 2017

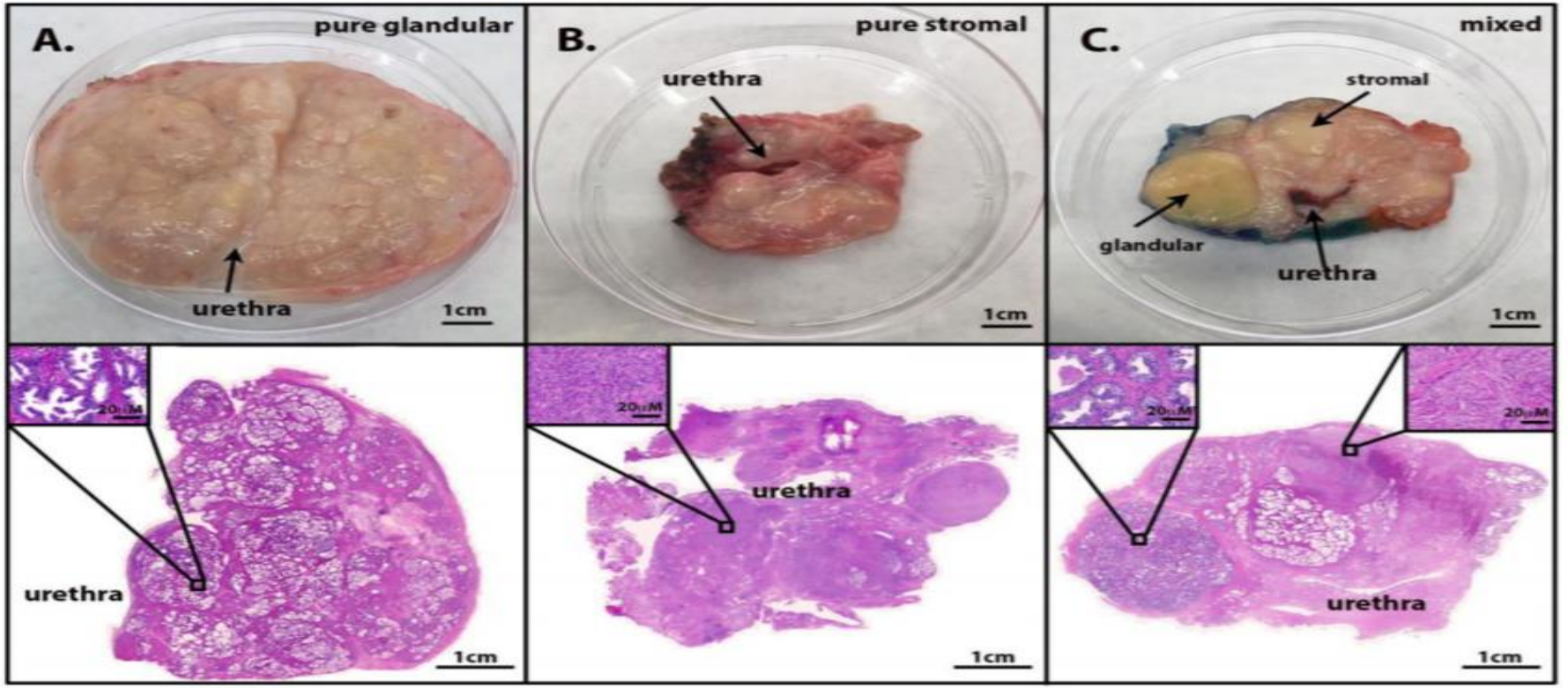


Figure 4. Examples of pure and mixed phenotypes in BPH

A, A coronal section of a purely glandular 250cc BPH specimen is shown in a 10cm dish. Only one hemisphere of the specimen fit onto a 2″×3″ glass slide subjected to high resolution scanning. **B,** A 100cc BPH specimen with a purely stromal composition. **C,** A 130cc specimen with both stromal and glandular hyperplasia.

Precision Medicine and Men's Health

American Journal of Men's Health 2017,

- epigenetic silencing of 5AR2 gene expression associated with increased body mass index and age is a risk marker for disease progression and medical therapy failure

(Bechis et al., 2015).

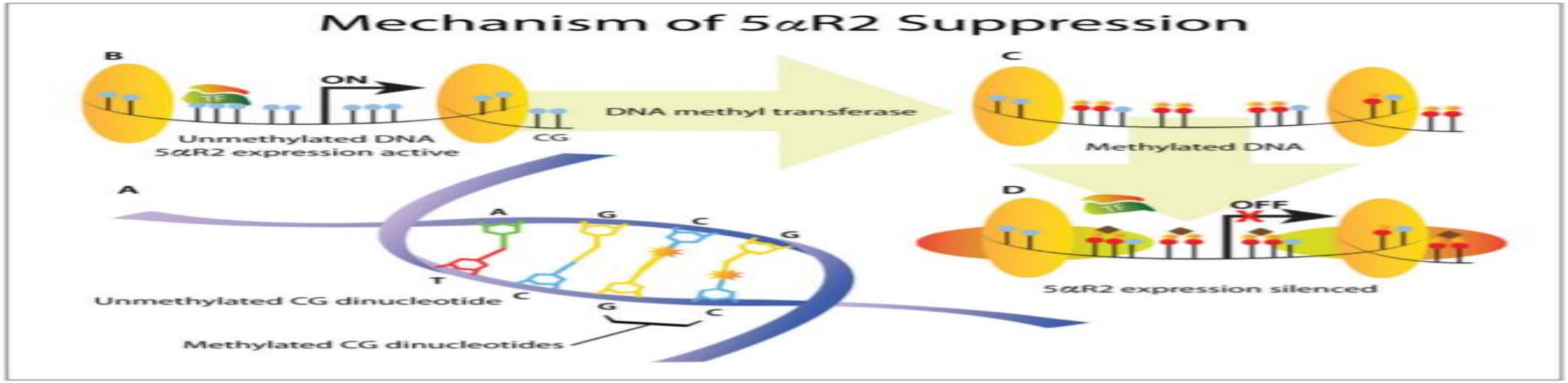
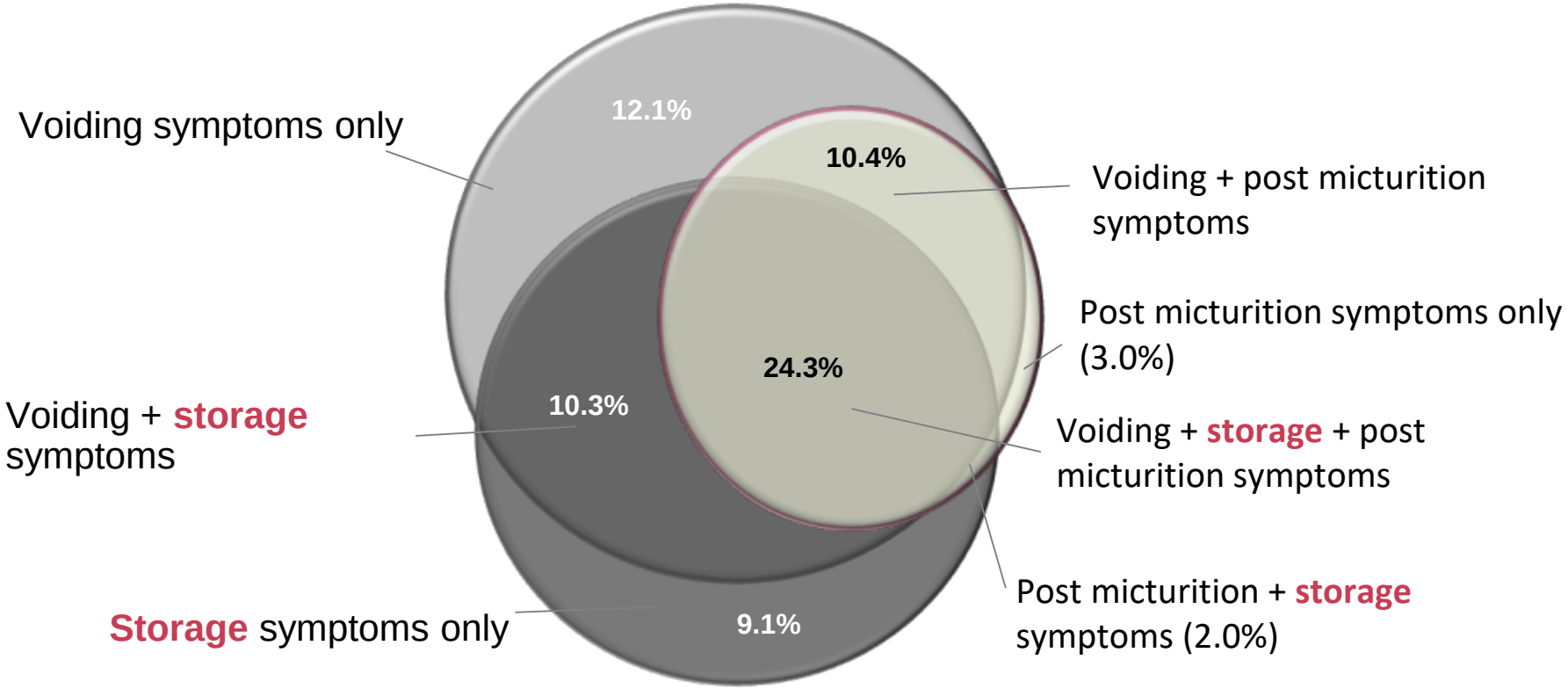


Figure 1.
Mechanism of 5AR2 suppression by DNA methylation. **(A)** DNA methylation adds a methyl group (star) at the carbon-5 position of cytosine residues in CG dinucleotides. **(B)** In unmethylated DNA (blue CG dinucleotides), chromatin is uncondensed and transcription factors (TF) can bind the gene promoter region, enabling gene expression. **(C–D)** DNA methylation (red CG dinucleotides with stars) attracts methylated DNA-binding proteins and histone deacetylase complexes (horizontal ovals and diamonds) to form condensed, inactive chromatin that prevents TF binding and silences gene expression (from ref[11]).

Most Men frequently have BOTH Voiding and Storage Symptoms

EpiLUTS 14,139 men ≥ 40 years old 71% reported LUTS

46% storage symptoms



Adapted from Sexton CC et al. BJU Int. 2009; 103, Suppl. 3: 12-23

The Role of Antimuscarinics in the Management of Men With Symptoms of Overactive Bladder Associated With Concomitant Bladder Outlet Obstruction: An Update

European Urology 2011

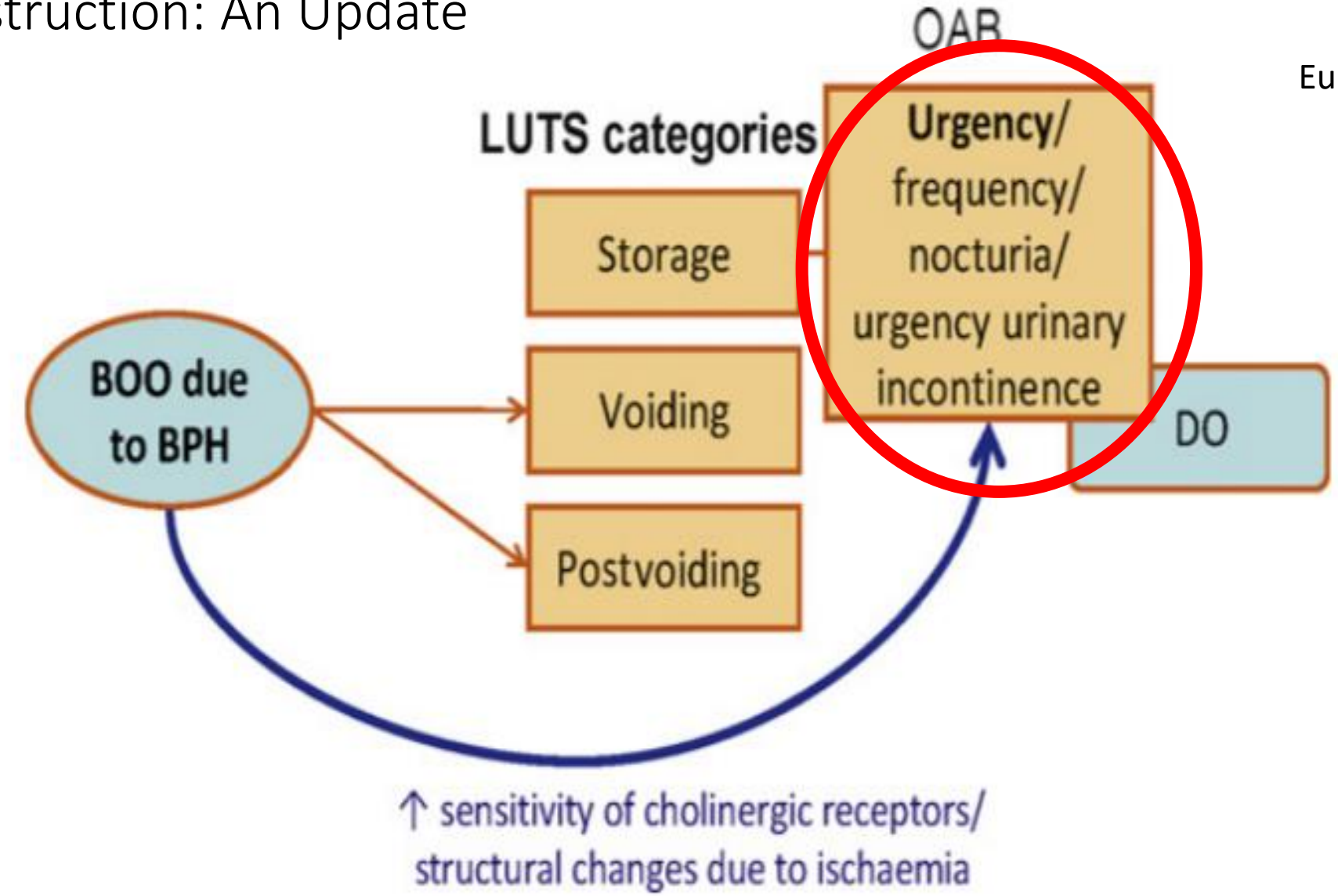
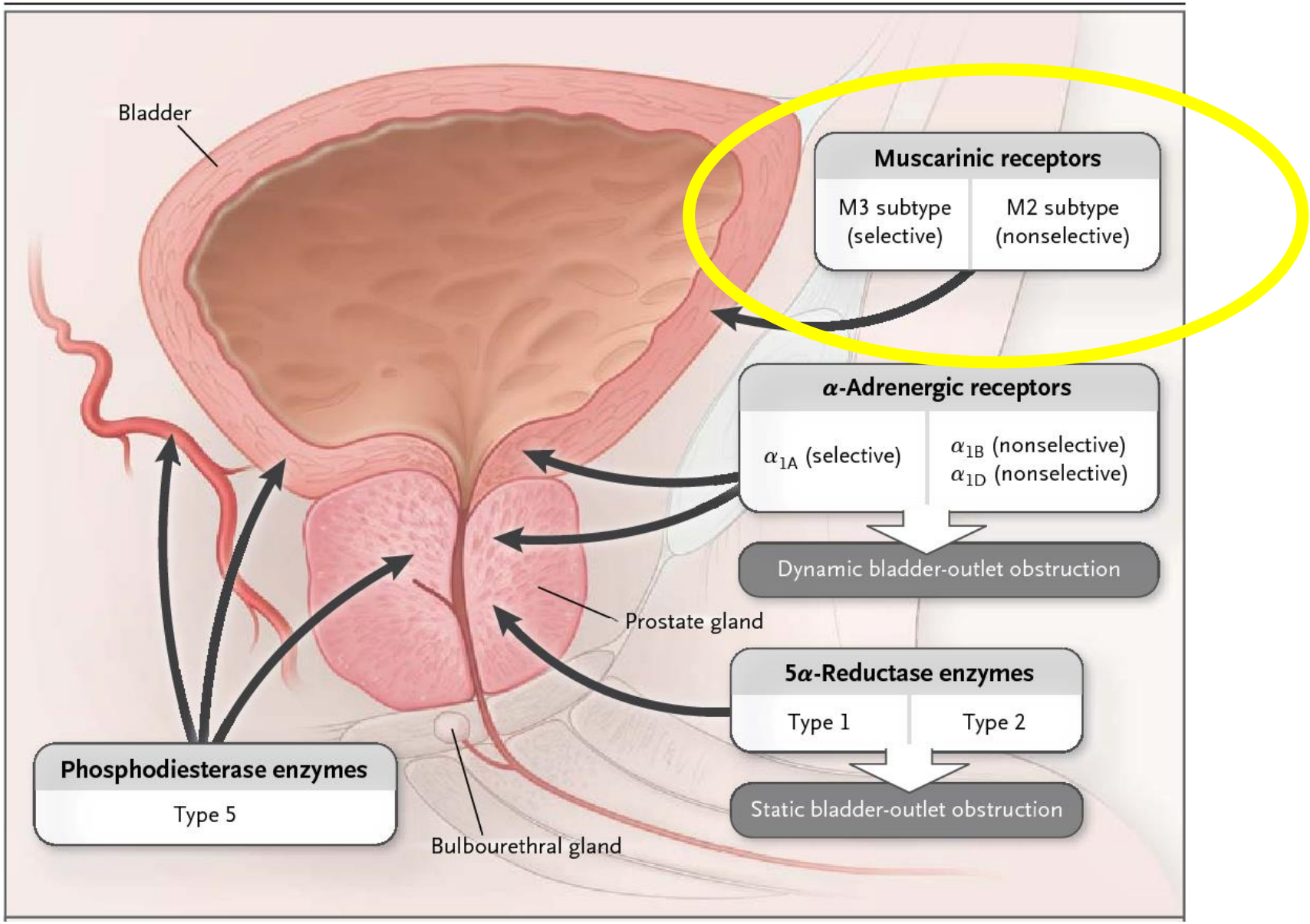
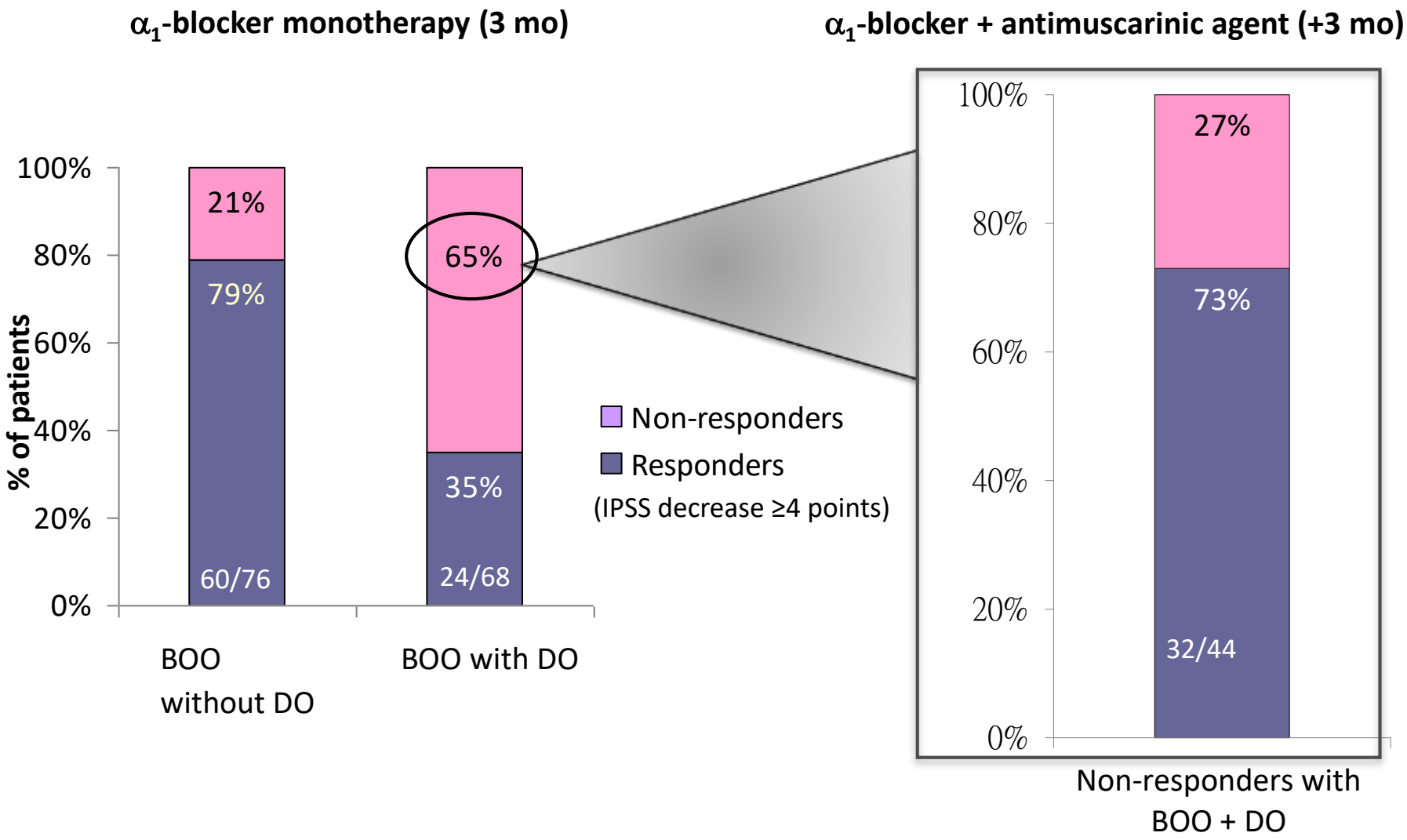


Figure 1. Mechanisms of Action and Targets for Intervention in Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms. NEJM2012



α-Blocker + Antimuscarinic



BOO = bladder outlet obstruction
IPSS = International Prostate Symptom Score

Lee JY et al. *BJU Int.* 2004; 94: 817 – 820.

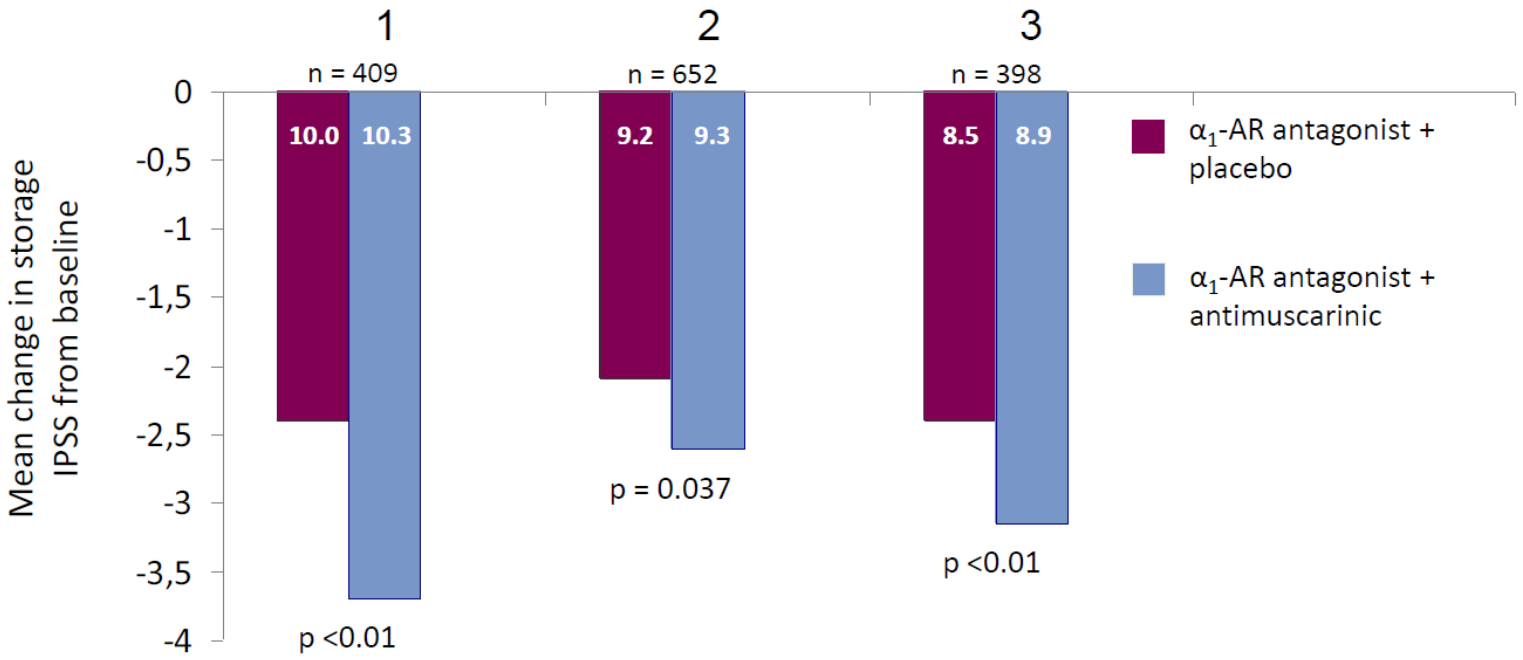
α 1-blocker + anti-muscarinics

- **TIMES study, 2006**
  - Some men bothered by LUTS and OAB might not respond to monotherapy with either α 1-blockers or antimuscarinics.
  - Tx with **tamsulosin plus tolterodine** resulted in statistically and clinically significant treatment benefits
- **VICTOR study, 2009**
  - Assessed safety and tolerability of **solifenacin** add-on therapy to a1-blocker treated men with residual urgency and frequency
  - Diary micturition, urgency episode, IPSS storage score and symptom bother were significantly improved
- **ASSIST study, 2011**
  - The add-on therapy of **solifenacin** in men for BPH with OAB symptoms treated by Tamsulosin
  - A statistically significant reduction of overactive bladder symptom score (OABSS)

JAMA 2006;296:2319-28
***J. Urol.* 2009; 182: 2825–30.**
***Urology* 2011; 78:126–33.**

Antimuscarinic Add-On to α-Blockers Improves Persistent Storage Symptoms

12-week, double-blind RCTs in men ≥40 or 45 yrs with OAB symptoms after ≥4 weeks on α_1-AR antagonist Q_{max} ≥4 or 5 ml/s; PVR ≤200 ml (type of active agents differs between studies)



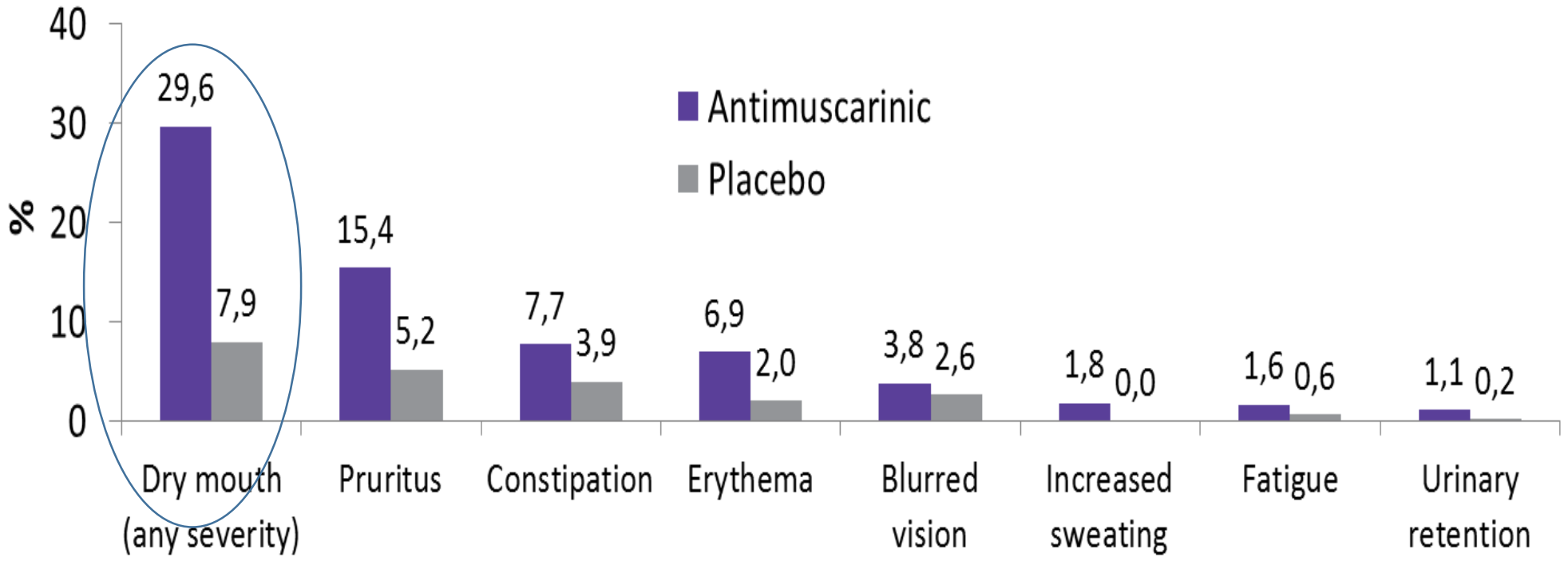
IPSS = International Prostate Symptom Score
RCT = randomized controlled trial
OAB = overactive bladder
PVR = post-void residual

[1] MacDiarmid SA et al. *Mayo Clin Proc.* 2008; 83: 1002 – 1010.
[2] Chapple C et al. *Eur Urol.* 2009; 56: 534 – 543.
[3] Kaplan SA et al. *J Urol.* 2009; 182: 2825 – 2830.

Dry mouth is the most common adverse event of AM agents

- Meta-analysis of 83 RCTs

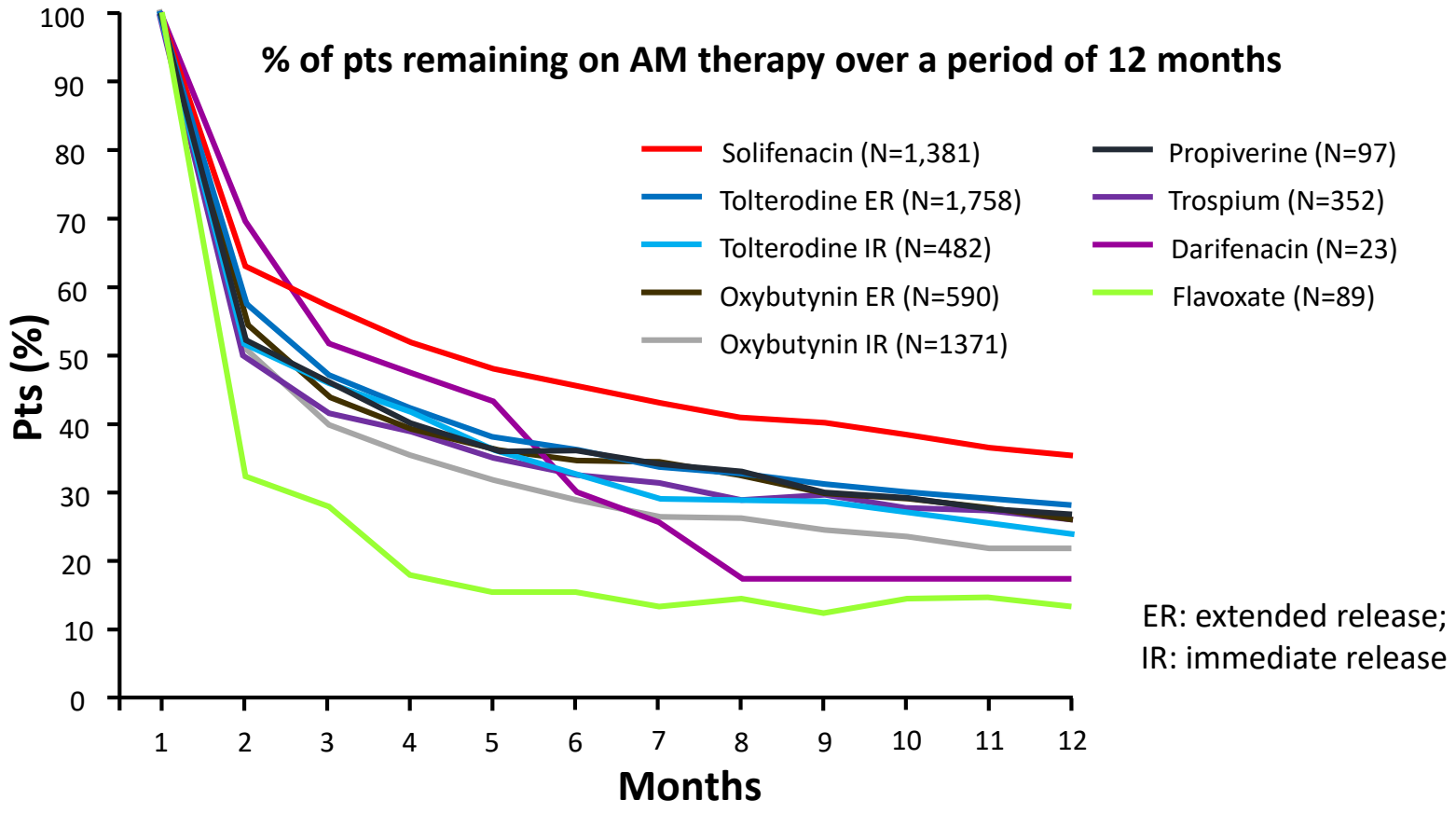
Adverse events reported at significantly higher levels with active treatments than with placebo



Adapted from Chapple CR et al. *Eur Urol.* 2008; 54: 543-62.

Persistence with AM agents is poor

12-month UK study on prescription data

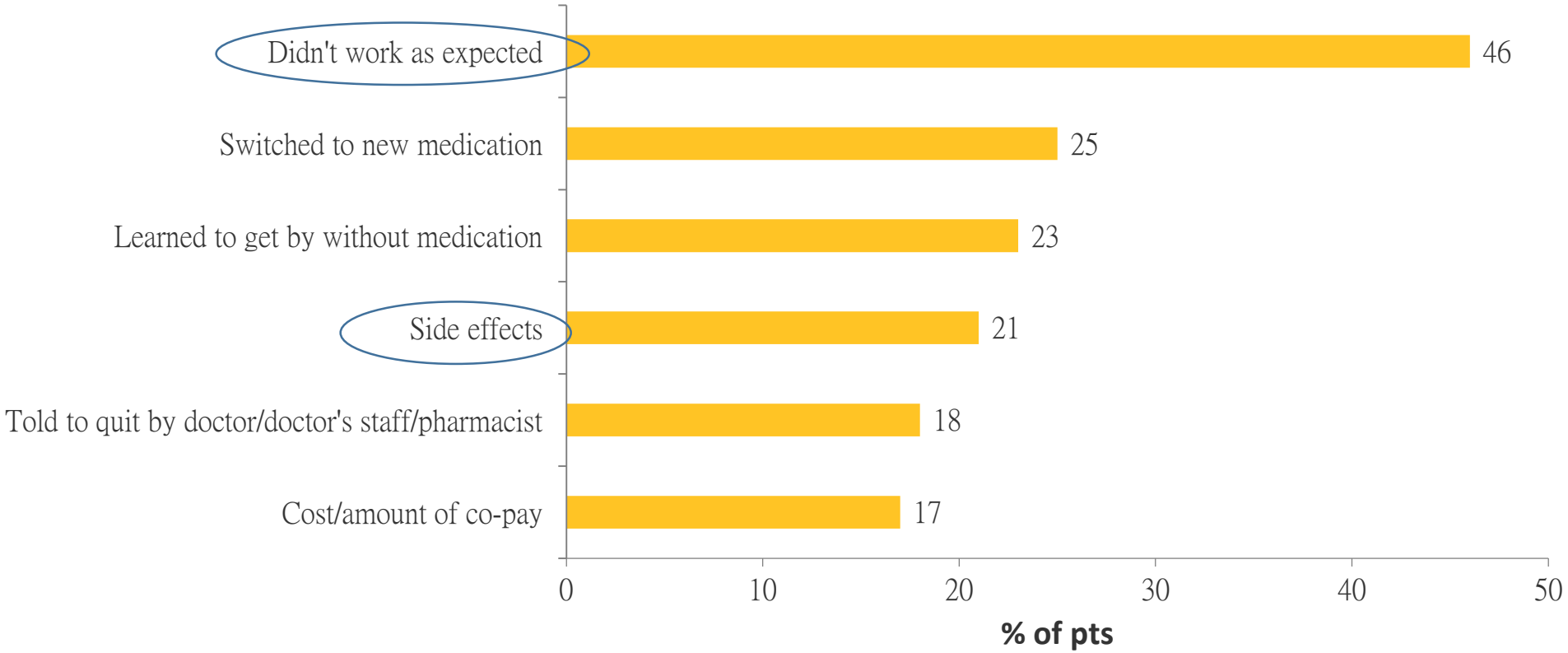


ER: extended release;
IR: immediate release

Wagg A et al. *BJU Int* 2012; 110: 1767 - 74.

Unmet treatment expectations and/or side effects are among the main reasons to discontinue AM therapy

- Survey in the USA: N=1,322 OAB pts. who discontinued AM therapy in the last year



Benner JS et al. *BJU Int.* 2010; 105: 1276-82.

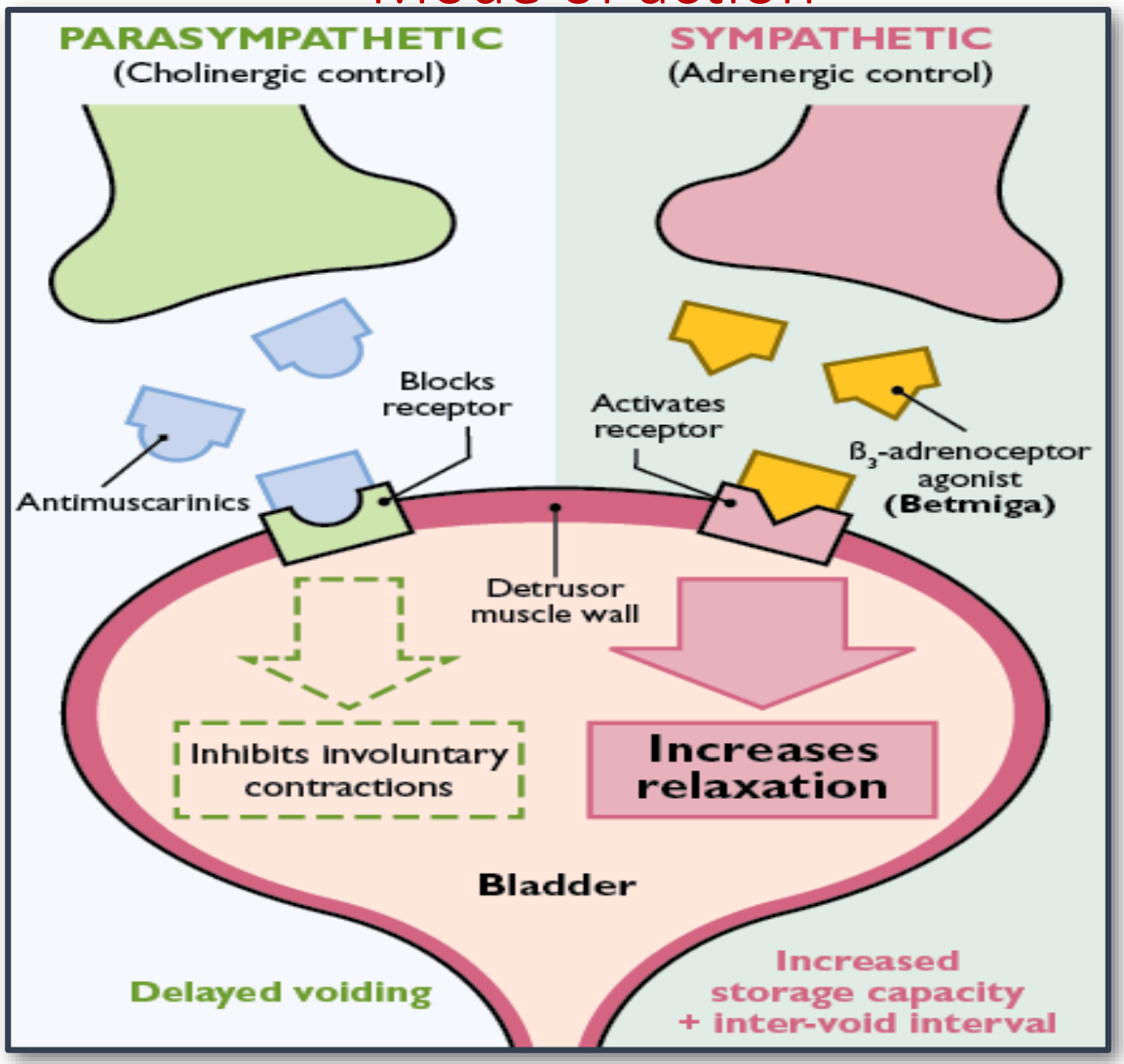
PVR and Urinary Retention
- antimuscarinic + α-blocker combination therapy -

TRIAL	DURATION [weeks]	TREATMENT	PATIENTS [n]	PVR [ml]	RETENTION n	RETENTION %
Saito et al. 1999	4	Tamsulosin 1 x 0.2 mg/d	59	- 5.5	0	0
		Tamsulosin 1 x 0.2 mg/d + Propiverine 1 x 20 mg/d	75	**+ 24**	2	**2.7**
Athanasopoulos et al. 2003	12	Tamsulosin 1 x 0.4 mg/d	25	- 8.2	0	0
		Tamsulosin 1 x 0.4 mg/d + Tolterodine 2 x 2 mg/d	25	**- 4.2**	0	**0**
Lee et al. 2004	12 + 8	Doxazosin 1 x 2-4 mg/d	84	-	0	0
		Doxazosin 1 x 2-4 mg/d + Tolterodine 2x2 mg/d	60	-	2	**3.3**
Lee et al. 2005	8	Doxazosin 1 x 4 mg/d	67	- 4.7	0	0
		Doxazosin 1 x 4 mg/d + Propiverine 1 x 20 mg/d	131	**+ 20.8 ***	0	**0**
Kaplan et al. 2006	12	Placebo	215	-3.6	3	1.4
		Tolterodine 1 x 4 mg/d + Tamsulosin 1 x 0.4 mg/d	217	**+6.4**	2	**0.9**
MacDiarmid et al. 2008	12	Tamsulosin 1 x 0.4 mg/d + Placebo	209	+ 7.8	1	0.5
		Tamsulosin 1 x 0.4 mg/d + Oxybutynin 1 x 10 mg/d	209	**+ 18.2 ***	6	**2.9**

Oelke M. UniMed Science. Hampel (Ed) 2009 pp. 84-97

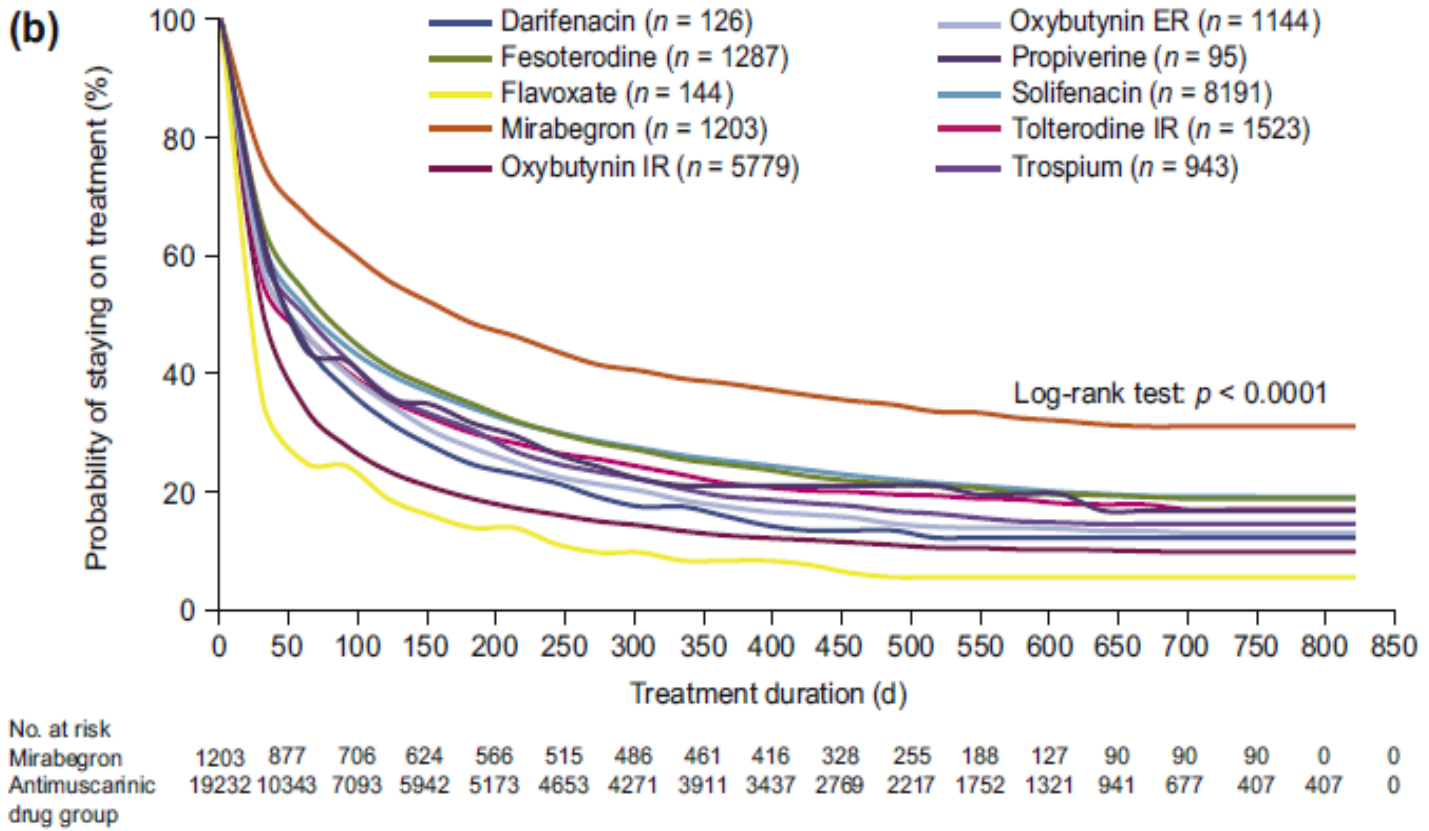
AM Agents and β_3-AR Agonists in OAB

- Mode of action -



Adapted from Chu FM and Dmochowski R. *Am J Med* 2006; 119 (3 Suppl 1): 3–8.

Persistence with Mirabegron is better than with Antimuscarinics



Chapple CR et al. *European Urology* 2017; 72: 389 - 99.

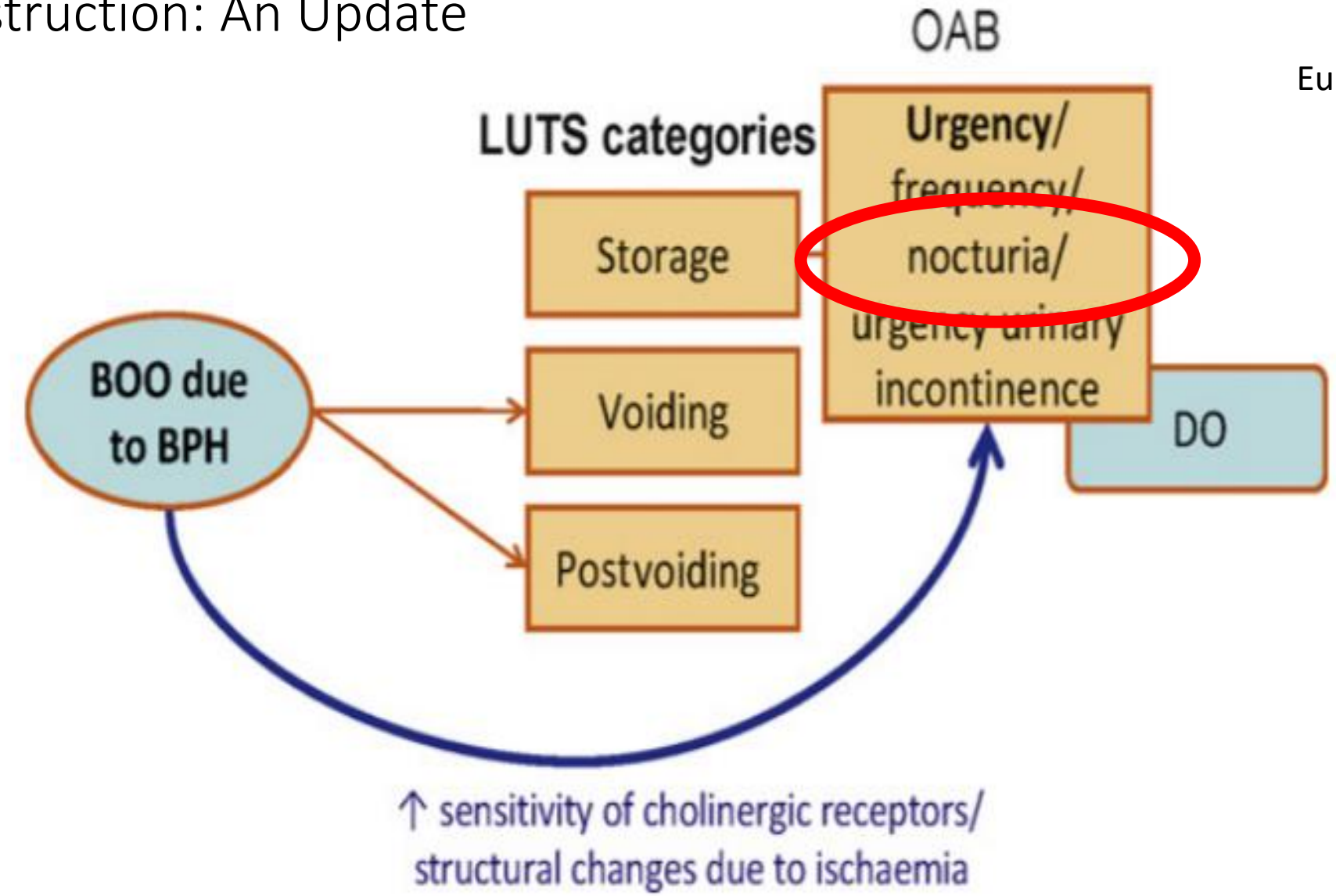
Potential Advantages of Mirabegron vs. Antimuscarinics

- Mirabegron therapy seems to be especially useful in patients with the following characteristics

  → High anticholinergic load
  → Cognitive dysfunction
  → Myasthenia gravis
  → Narrow angle glaucoma
  → Constipation
  → PVR or recurrent urinary retention

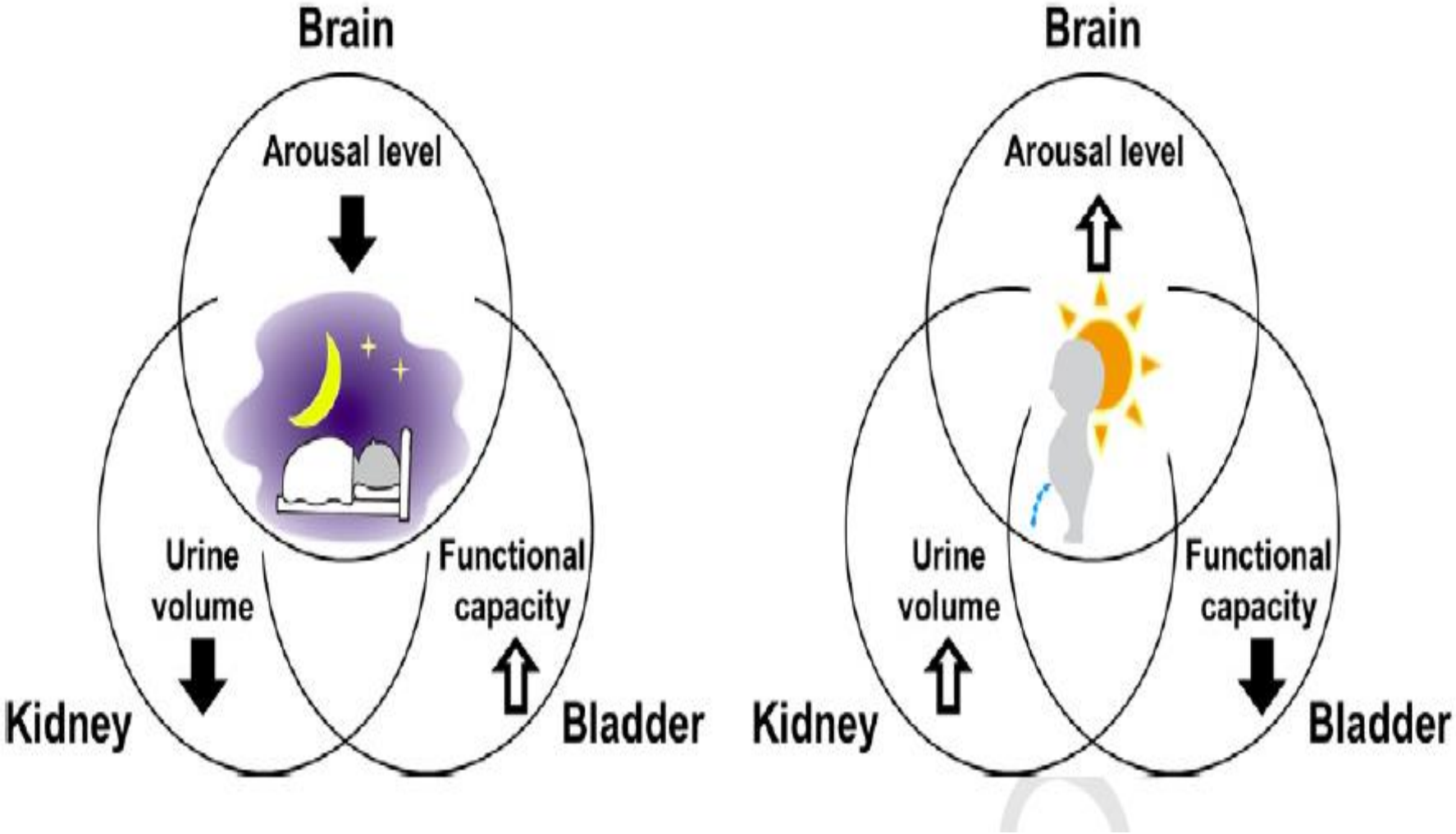
The Role of Antimuscarinics in the Management of Men With Symptoms of Overactive Bladder Associated With Concomitant Bladder Outlet Obstruction: An Update

European Urology 2011

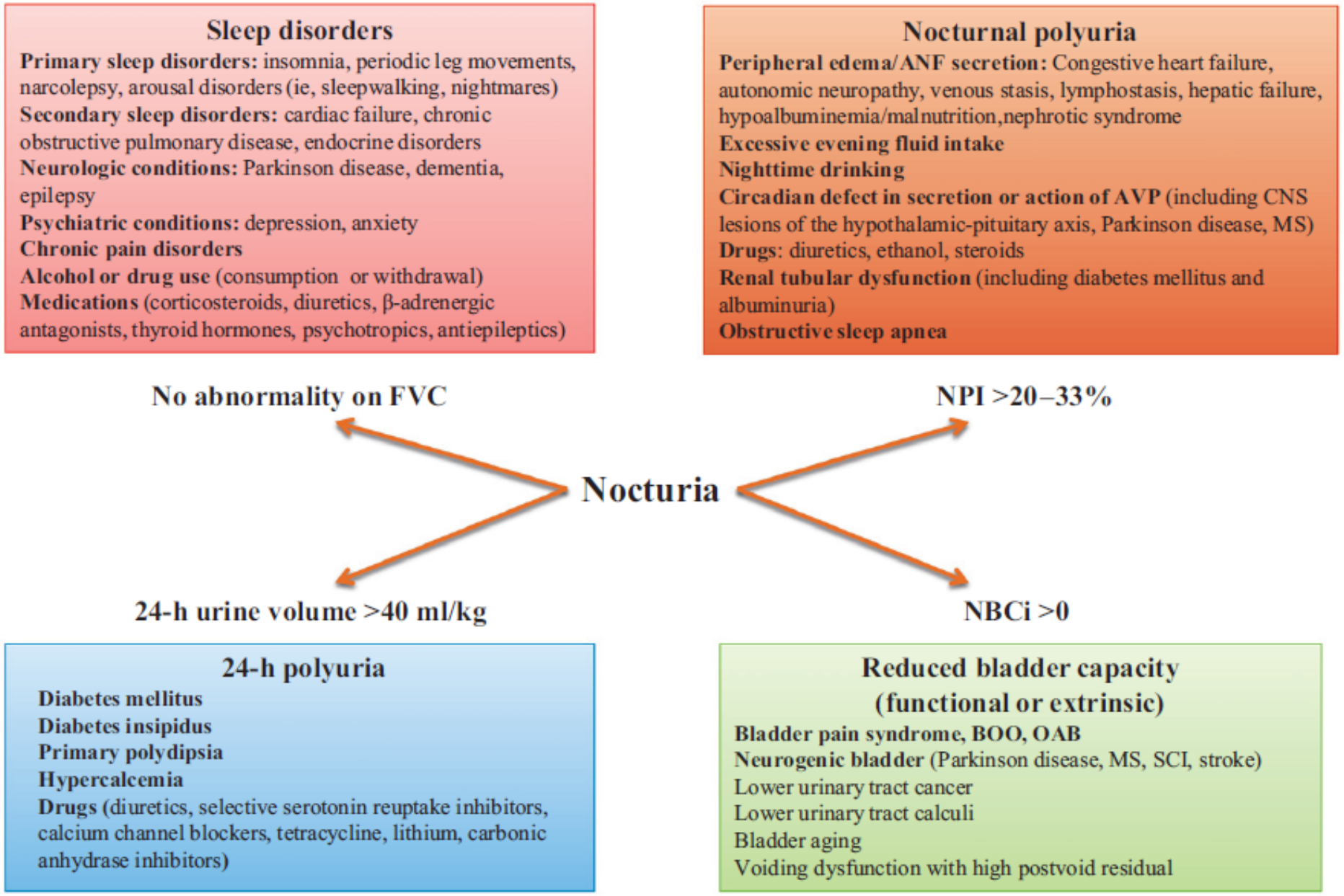


Chronobiology of Micturition: Putative Role of the Circadian Clock

J Uro 2013



Nocturia: Pathophysiology *EU 2012*

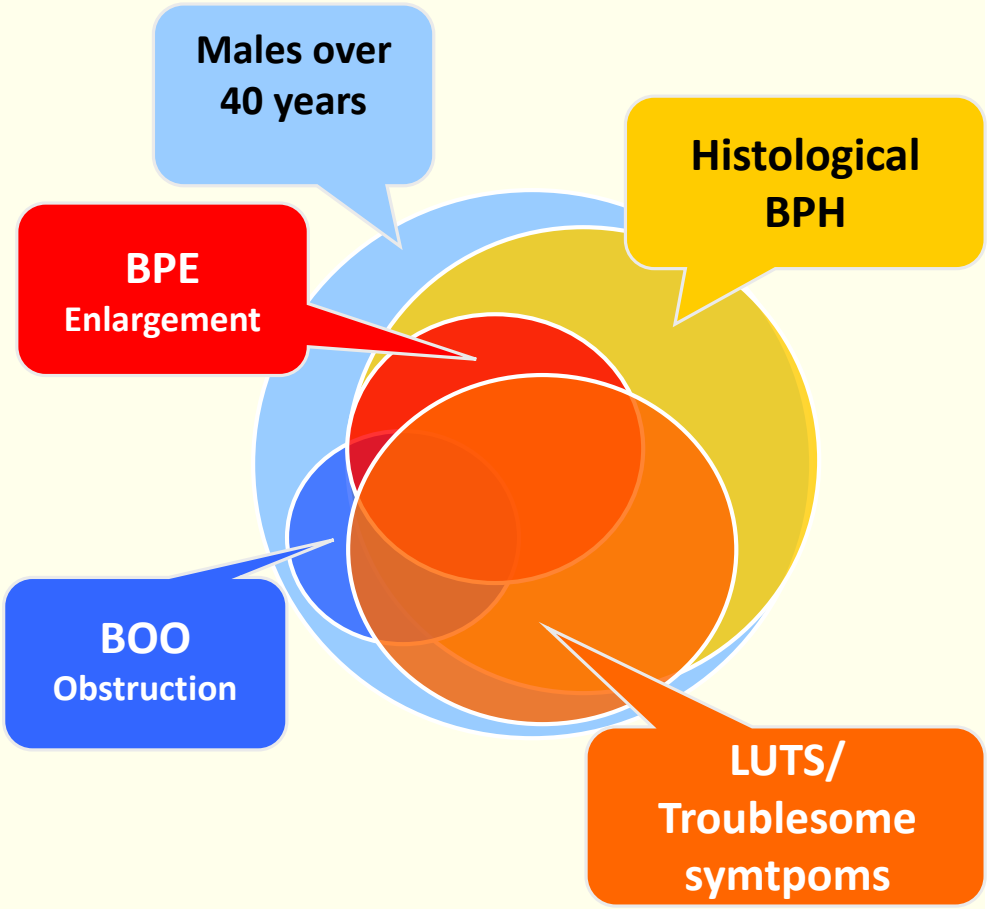


Latest thinking on BPH, BPE, and BOO

Clinical, anatomical, and pathophysiological changes

- **What is BPH?**
  Histological findings: hyperplasia of the interstitial tissue of the prostate

- **What is associated with BPH?**
  - **Clinical findings:** troublesome LUTS (voiding, storage and post-micturition symptoms)
  - **Anatomical finding:** benign prostatic enlargement (BPE)
  - **Pathophysiological finding:** urethral compression, which causes bladder outlet obstruction (BOO)

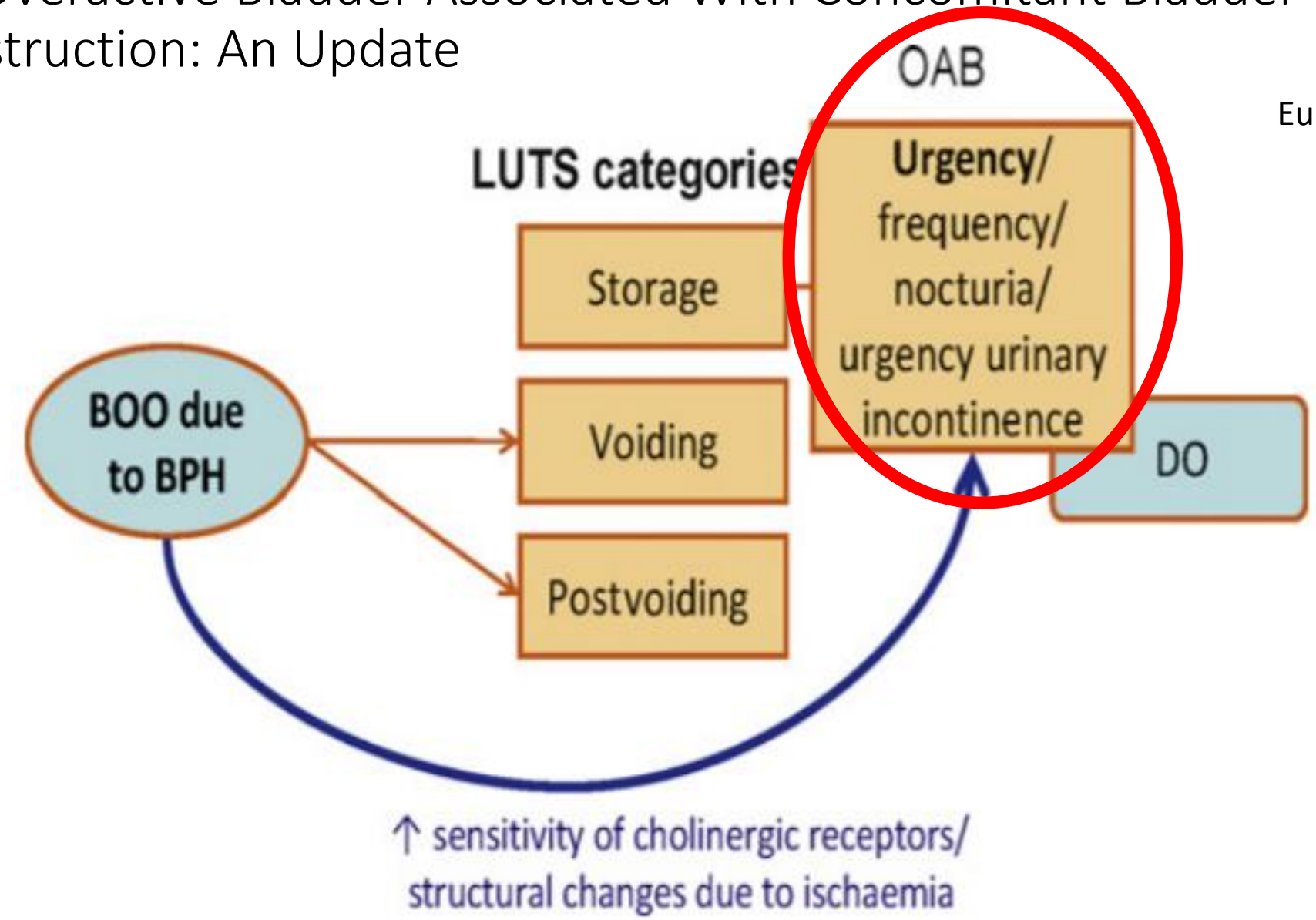


BPH: benign prostatic hyperplasia
BPE: benign prostatic enlargement
BOO: bladder outlet obstruction
LUTS: lower urinary tract symptoms

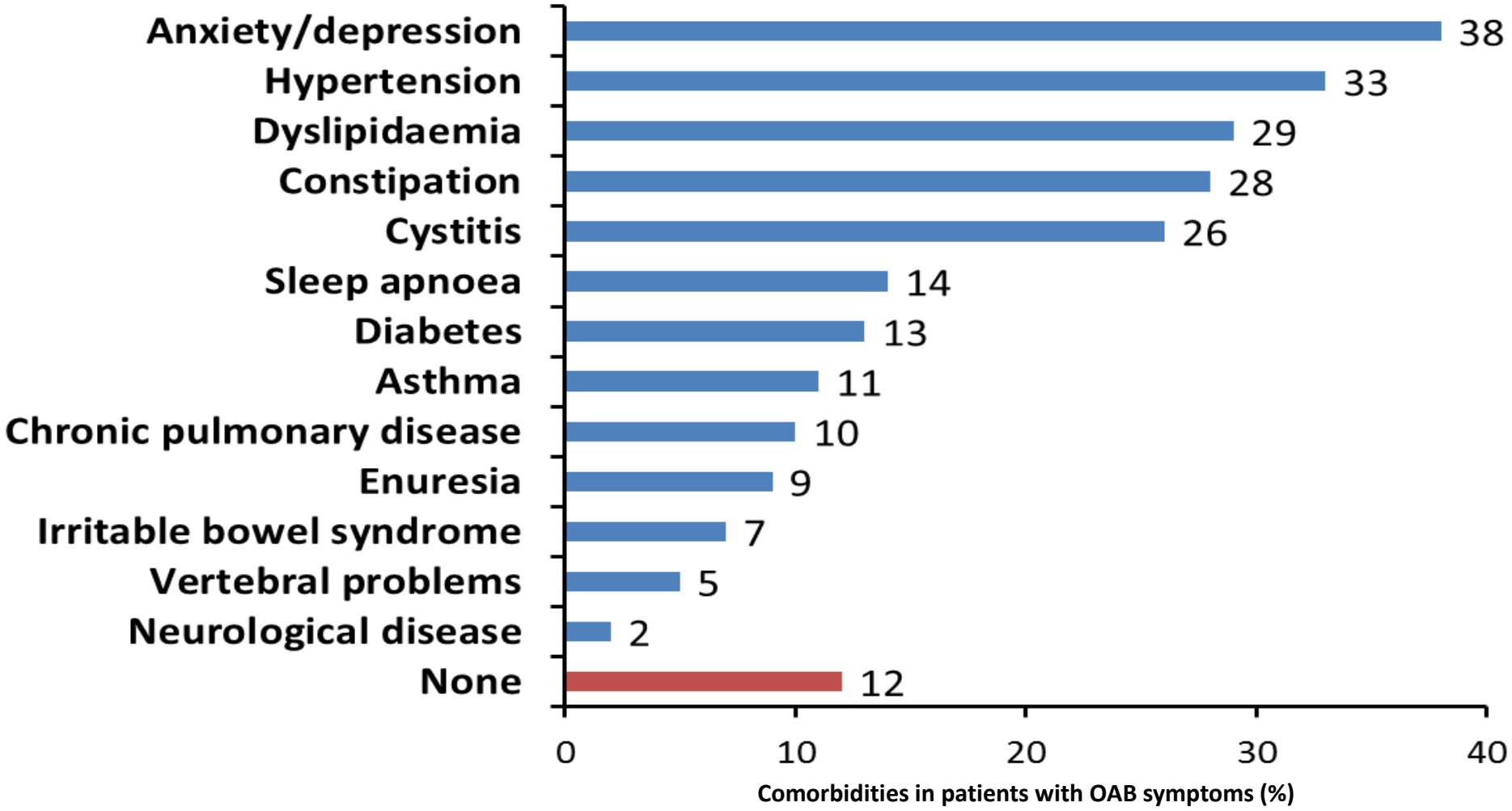
Abrams P et al. Male lower urinary tract dysfunction: evaluation and management. 2006

The Role of Antimuscarinics in the Management of Men With Symptoms of Overactive Bladder Associated With Concomitant Bladder Outlet Obstruction: An Update

European Urology 2011



Comorbidities are common in patients with OAB

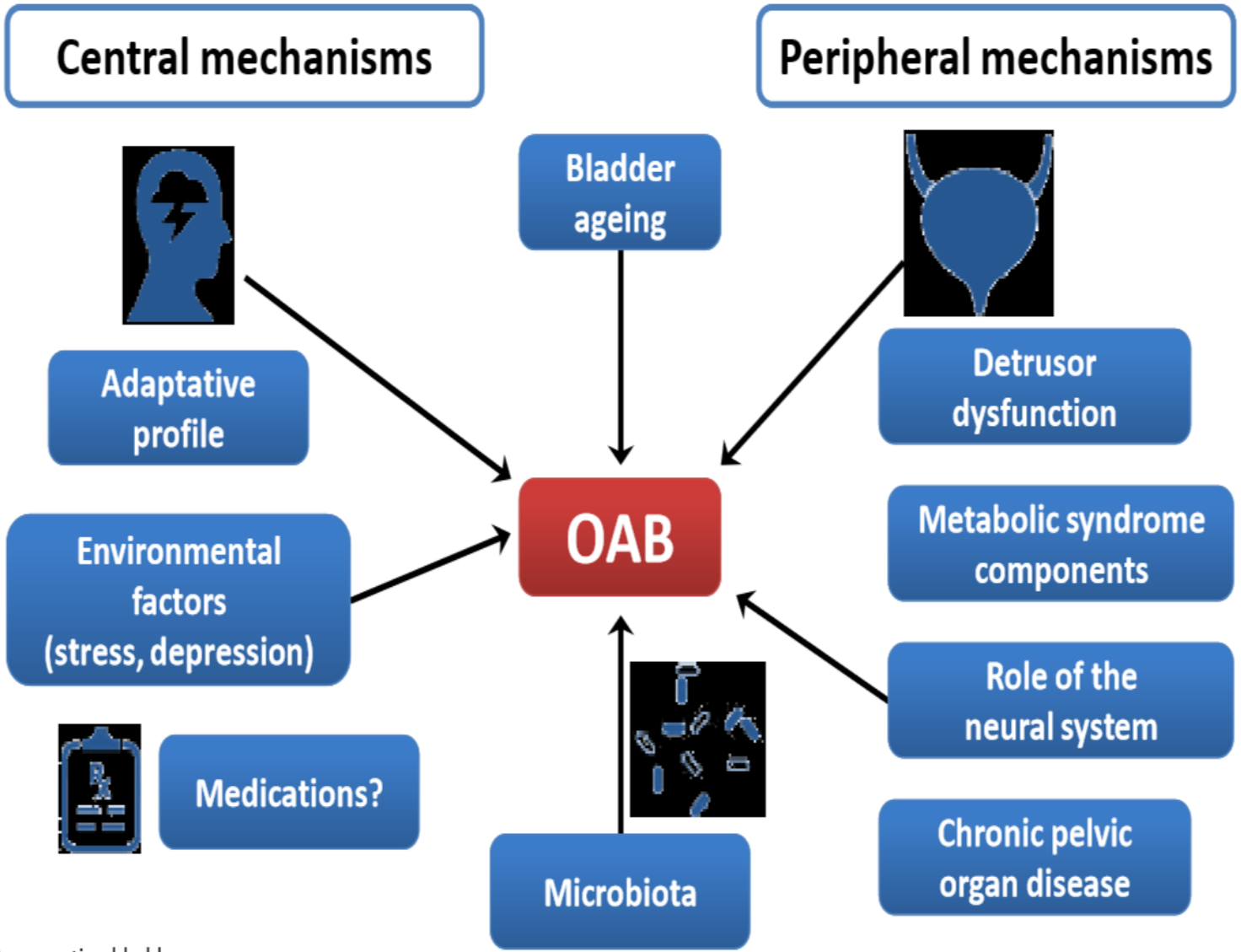


Only 12% of patients with OAB have no comorbidities

OAB, overactive bladder

Cornu JN. *Prog Urol* 2016

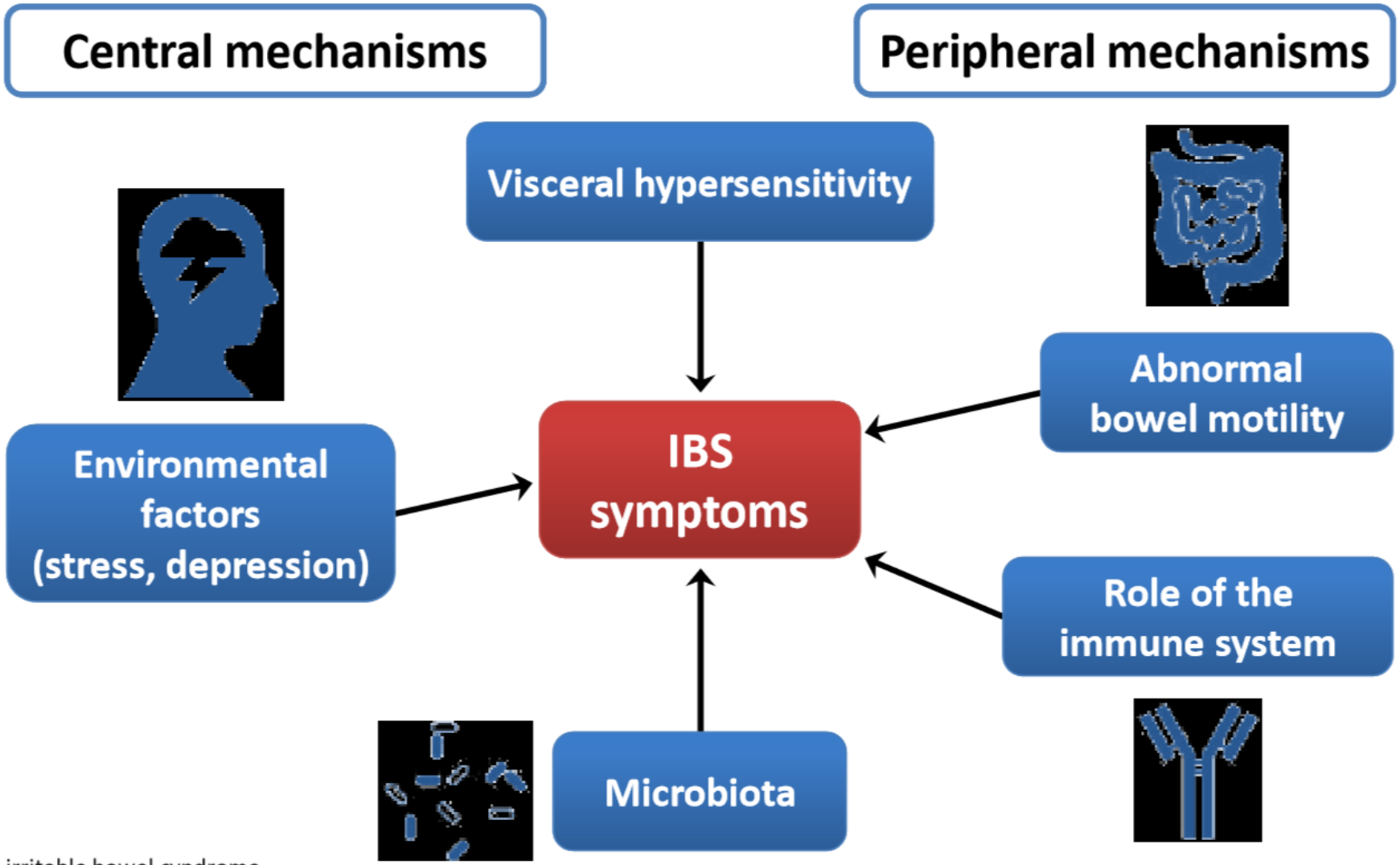
OAB is a multifactorial disease



OAB, overactive bladder

Cornu JN. Presentation at EAU 2017, London, UK.

Aetiology of IBS symptoms



IBS, irritable bowel syndrome

Cornu JN. Presentation at EAU 2017, London, UK.

Do you screen your OAB patients for IBS?

Maybe you should…

Potential impact of this knowledge:

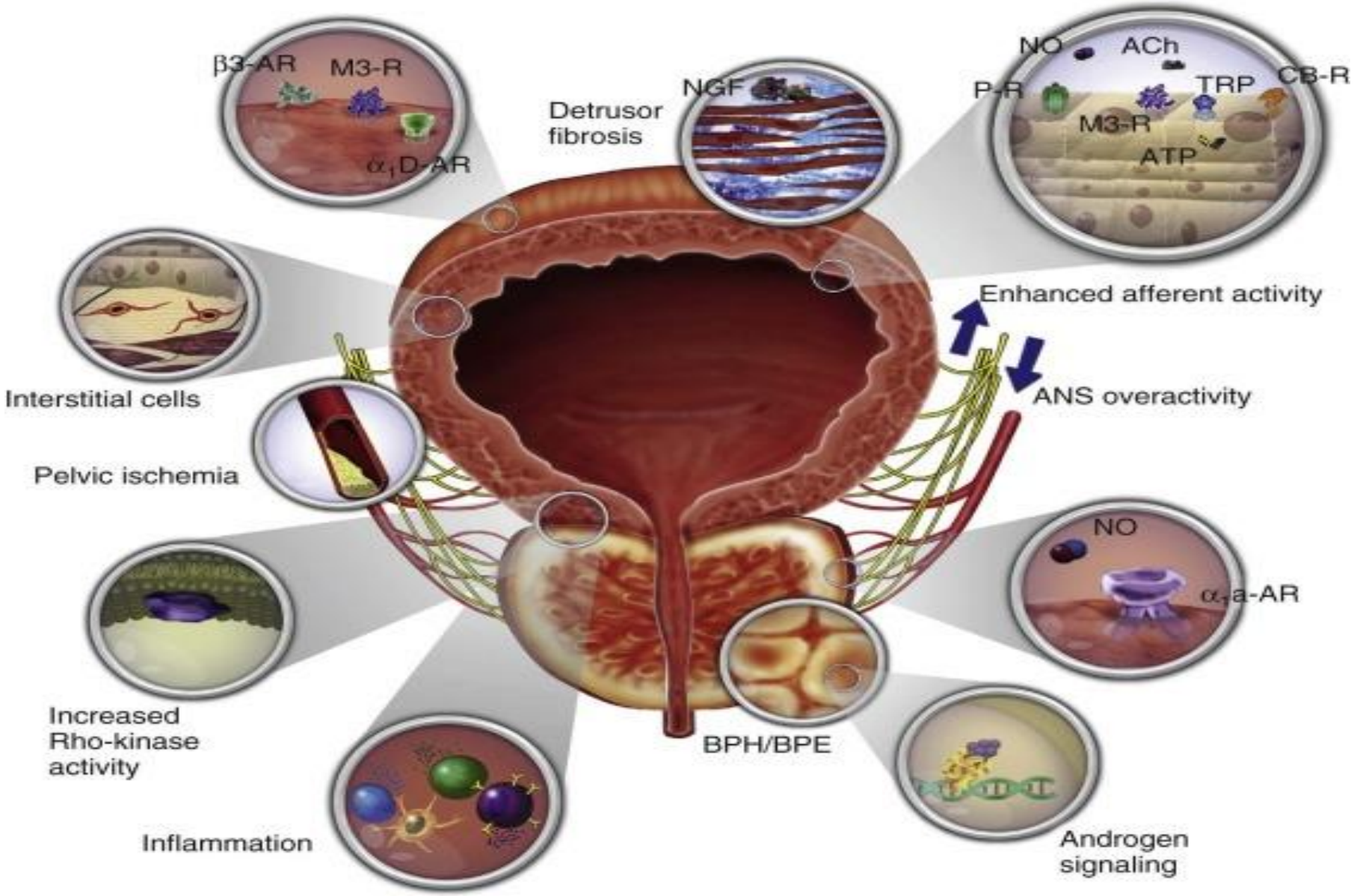
- Potential negative impact of antimuscarinics
- Treatment of IBS may positively impact OAB
- Potential benefit of neuromodulation
- Difficulty treating a chronic disease with sensitisation

IBS, irritable bowel syndrome; OAB, overactive bladder

Cornu JN. Presentation at EAU 2017, London, UK.

Pathophysiological mechanisms and targets for future nonsurgical therapy

EU2013



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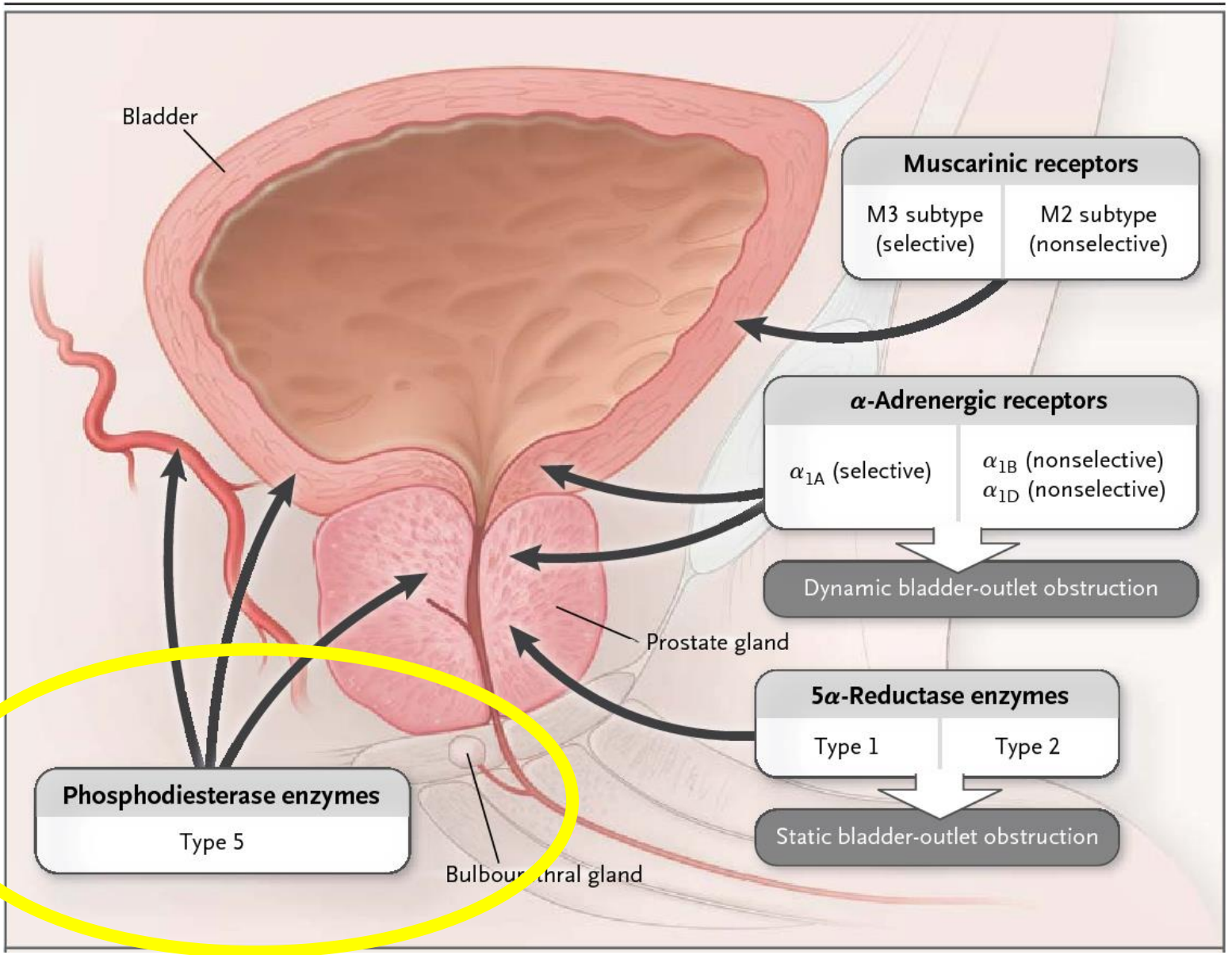


European Association of Urology

Platinum Priority – Collaborative Review – Benign Prostatic Enlargement

Editorial by Marcus J. Drake on pp. 134–135 of this issue

Latest Evidence on the Use of Phosphodiesterase Type 5 Inhibitors for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia

Mauro Gacci [a,], Karl-Erik Andersson [b], Christopher Chapple [c], Mario Maggi [d], Vincenzo Mirone [e], Matthias Oelke [f], Hartmut Porst [g], Claus Roehrborn [h], Christian Stief [i], François Giuliano [j]*

European Urology 2016, 70;124–133

REVIEW PAPER

FUNCTIONAL UROLOG

Current drug therapy of patients with BPH-LUTS with the special emphasis on PDE5 inhibitors

Konstantin Kolontarev[1], Alexander Govorov[1], George Kasyan[1], Diana Priymak[2], Dmitry Pushkar[1]

Cent European J Urol. 2016; 69: 398-40

Review Article

Testosterone replacement therapy and voiding dysfunction

Wesley Baas, Tobias S. Köhler

Division of Urology, Southern Illinois University School of Medicine, Springfield, IL, USA

Transl Androl Urol 2016;5(6):890-897

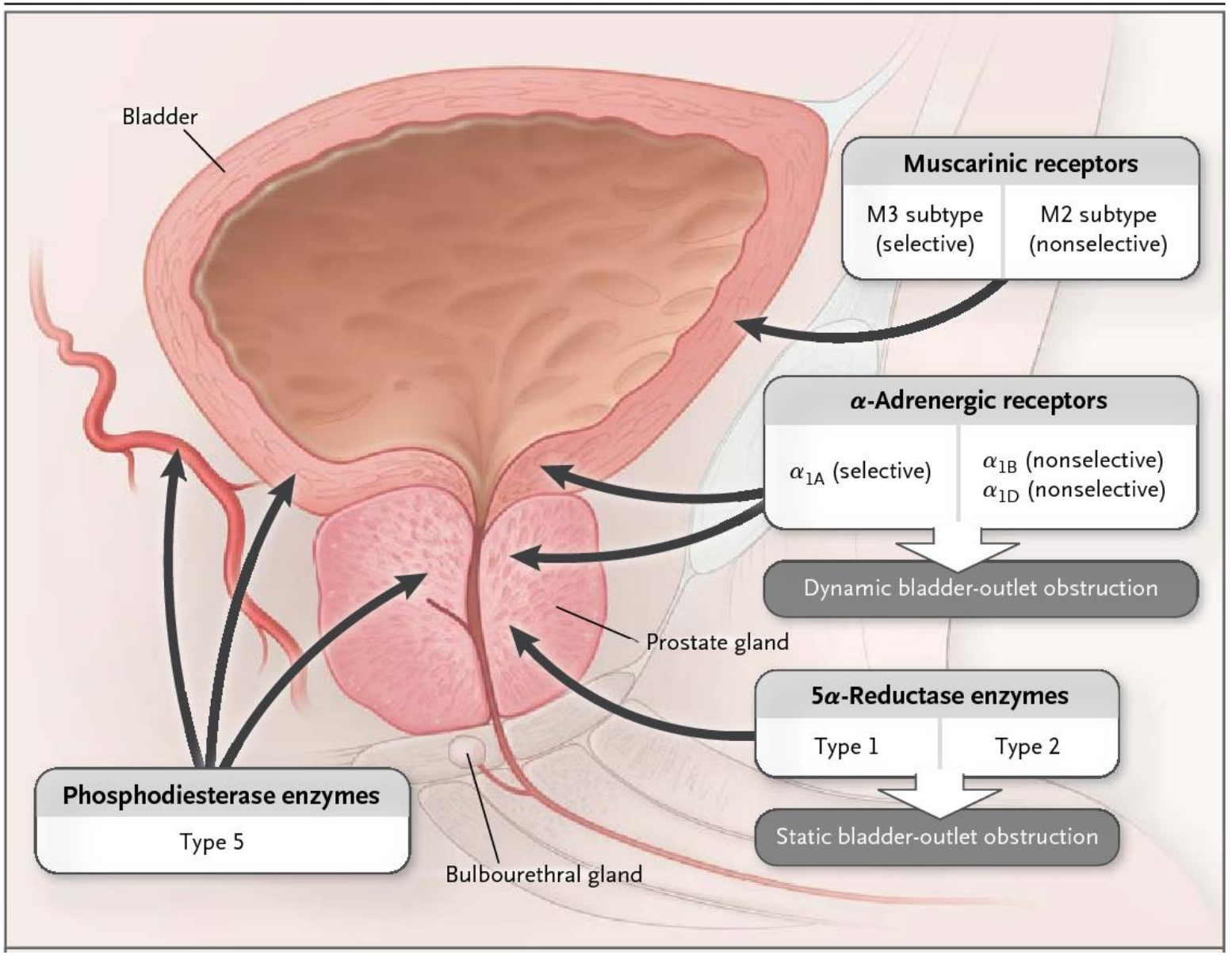
BENIGN PROSTATIC HYPERPLASIA (K MCVARY, SECTION EDITOR)

Testosterone Replacement Therapy and BPH/LUTS. What is the Evidence?

Wesley Baas[1] · Tobias S. Köhler[1]

Curr Urol Rep (2016) 17: 46

Figure 1. Mechanisms of Action and Targets for Intervention in Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms. NEJM2012



BENIGN PROSTATIC HYPERPLASIA (K MCVARY, SECTION EDITOR)

Can Long-term LUTS/BPH Pharmacological Treatment Alter the Outcomes of Surgical Intervention?

Fabrizio Presicce[1] · Cosimo De Nunzio[1] · Andrea Tubaro[1]

Curr Urol Rep (2017) 18: 72

- Patients who underwent immediate TURP showed significantly better outcomes than prolonged medical treatment
- Treatment failure rates (no improvements in symptoms) were 10% for early TURP vs 21% for prolonged medical treatment (p=0.0004)

REVIEW

The influence of the medical treatment of LUTS on benign prostatic hyperplasia surgery: do we operate too late?

Fabrizio PRESICCE [1] *, Cosimo DE NUNZIO [1], Mauro GACCI [2], Roman SOSNOWSKY [3], Riccardo LOMBARDO [1], Francesco PORPIGLIA [4], Andrea TUBARO [1]

Minerva Urologica e nefrologica 2017; 69(3):242-52

- Possible negative impact of prolonged medical therapy on a certain group of BPH patients at very high risk of progression.
- The symptomatic relief provided by medical treatment may mask the gradual increase of PVR and the concurrent asymptomatic detrusor functional deterioration

Case 2 攝護腺肥大

- 74 y/o male
- 夜尿 3
- 尿失禁 , 急迫性

Uroflow 2013/06/28
qmax14 , vol 182, PVR 33

攝護腺肥大

- 74 y/o male
- 夜尿 3
- 尿失禁 , 急迫性

Uroflow2013/06/28
qmax14 , vol 182, PVR 33

甲型交感神經拮抗劑 (放鬆尿管)
5α還原酶抑制劑（縮小攝護腺）
抗膽鹼藥物(抑制膀胱過動)
B3腎上腺接受體促效劑(抑制膀胱過動)
迷你寧 (減少夜尿)

幾年後--------

參加里民遊覽車上常忍不住

精神不如以前清楚敏捷

攝護腺肥大之治療

- 藥物治療

  甲型交感神經拮抗劑 (放鬆尿管)

  5α還原酶抑制劑（縮小攝護腺）

  抗膽鹼藥物(抑制膀胱過動)

  B3腎上腺接受體促效劑(抑制膀胱過動)

  PDE5抑制劑(抑制膀胱過動)

- 手術

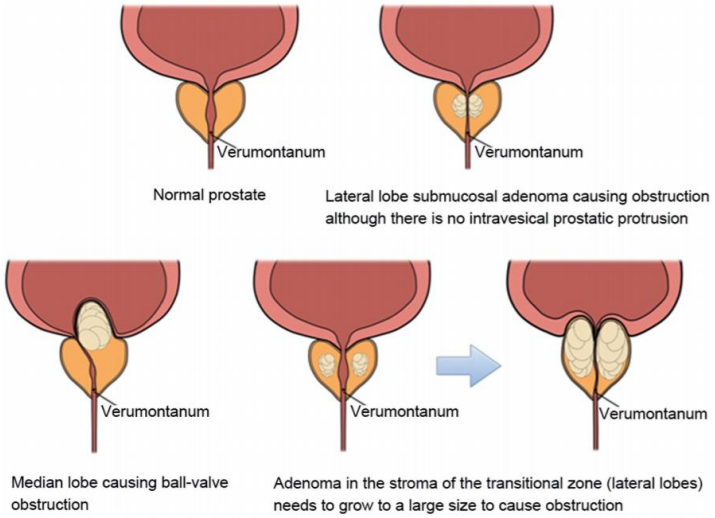
  攝護腺刮除手術

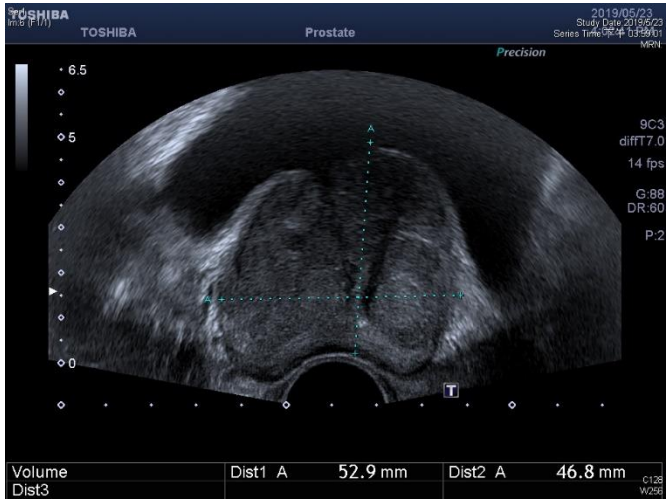
  攝護腺雷射手術

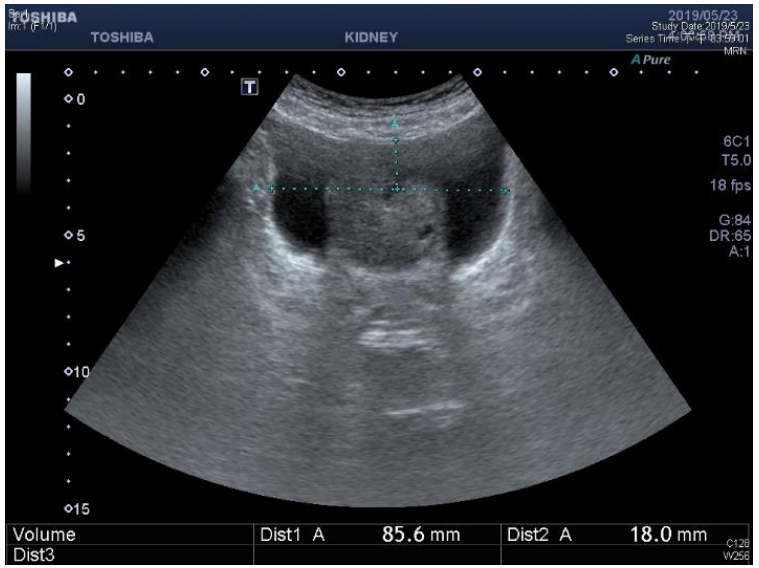
手術時機

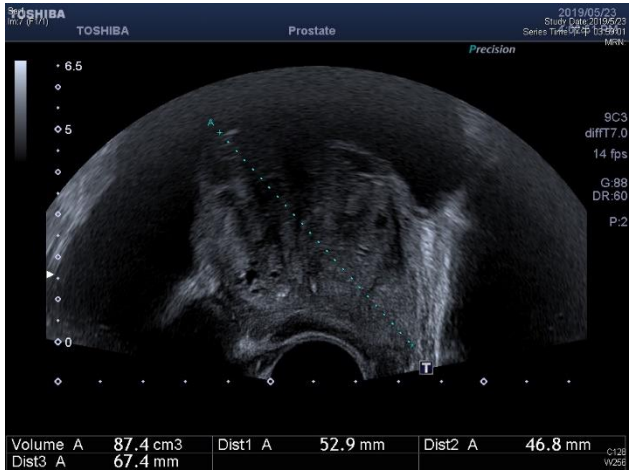
尿液滯留, 膀胱結石, 血尿 , 腎水腫, 感染

攝護腺肥大 ----深入膀胱


Verumontanum
Verumontanum
Normal prostate
Lateral lobe submucosal adenoma causing obstruction although there is no intravesical prostatic protrusion
Verumontanum
Verumontanum
Verumontanum
Median lobe causing ball-valve obstruction
Adenoma in the stroma of the transitional zone (lateral lobes) needs to grow to a large size to cause obstruction


TOSHIBA
Prostate
Precision
6.5
5
0
9C3
diffT7.0
14 fps
G:88
DR:60
P:2
Volume
Dist3
Dist1 A 52.9 mm
Dist2 A 46.8 mm


TOSHIBA
KIDNEY
A Pure
0
5
10
15
6C1
T5.0
18 fps
G:84
DR:65
A:1
Volume
Dist3
Dist1 A 85.6 mm
Dist2 A 18.0 mm


TOSHIBA
Prostate
Precision
6.5
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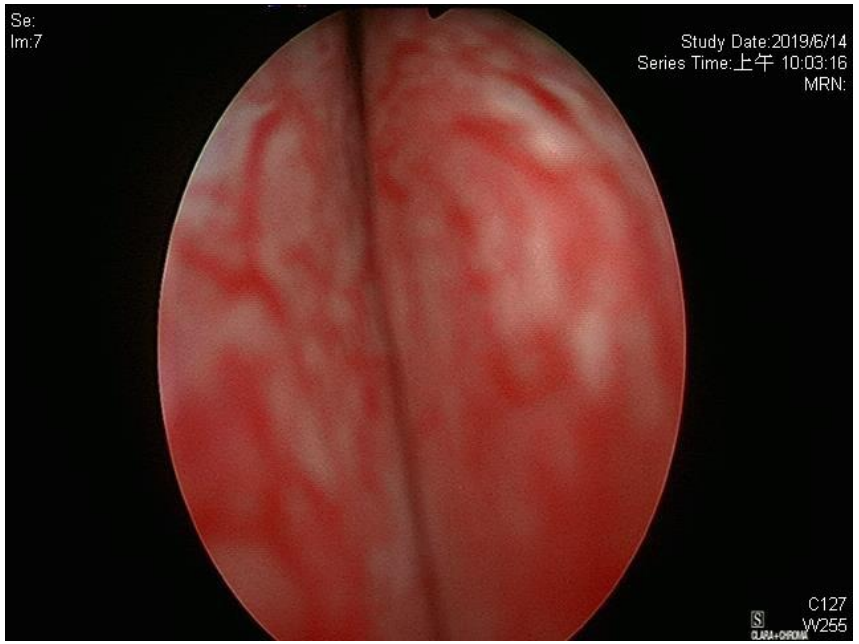
9C3
diffT7.0
14 fps
G:88
DR:60
P:2
Volume A 87.4 cm3
Dist3 A 67.4 mm
Dist1 A 52.9 mm
Dist2 A 46.8 mm

攝護腺肥大 ----伸入膀胱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Study Date:2019/6/14
Series Time:上午 10:03:16
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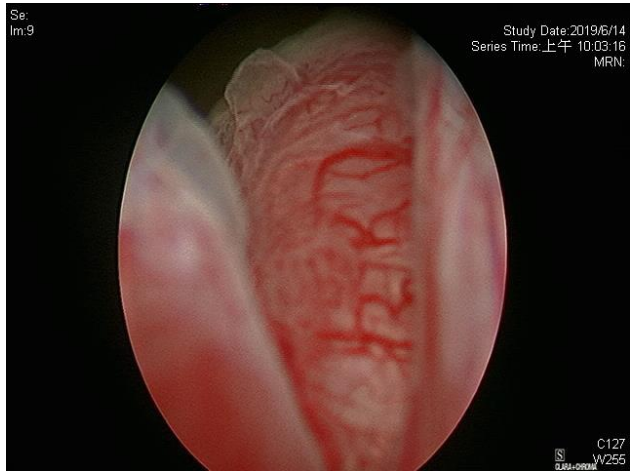
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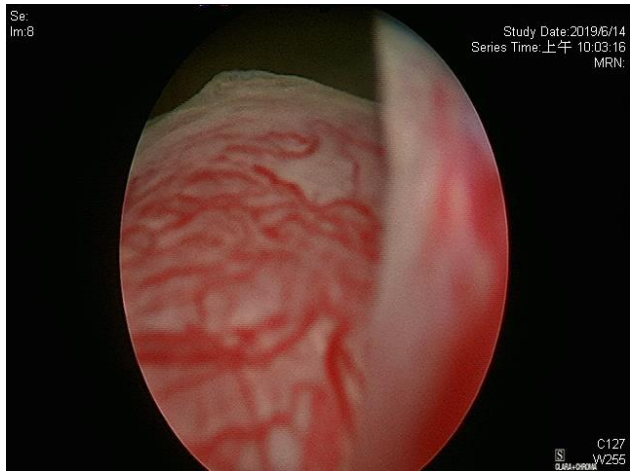
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Study Date:2019/6/14
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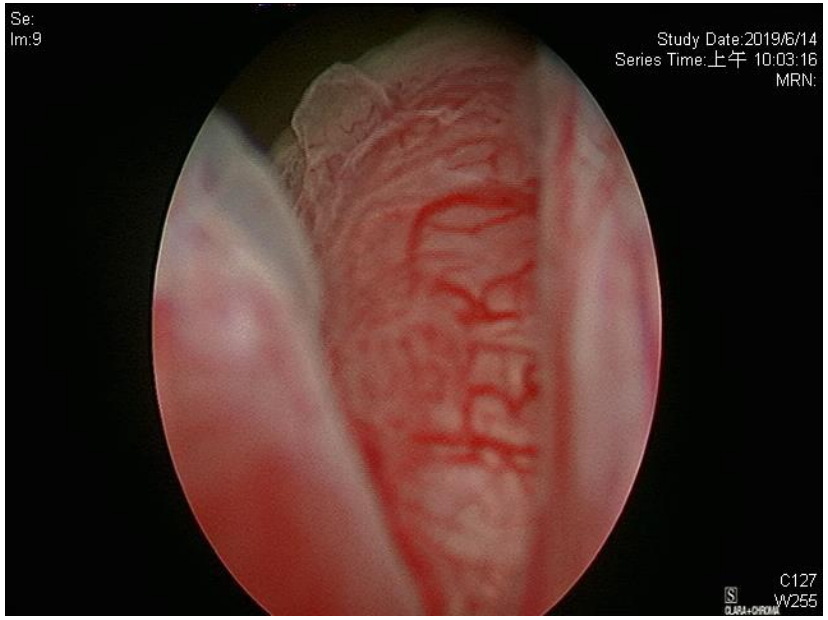
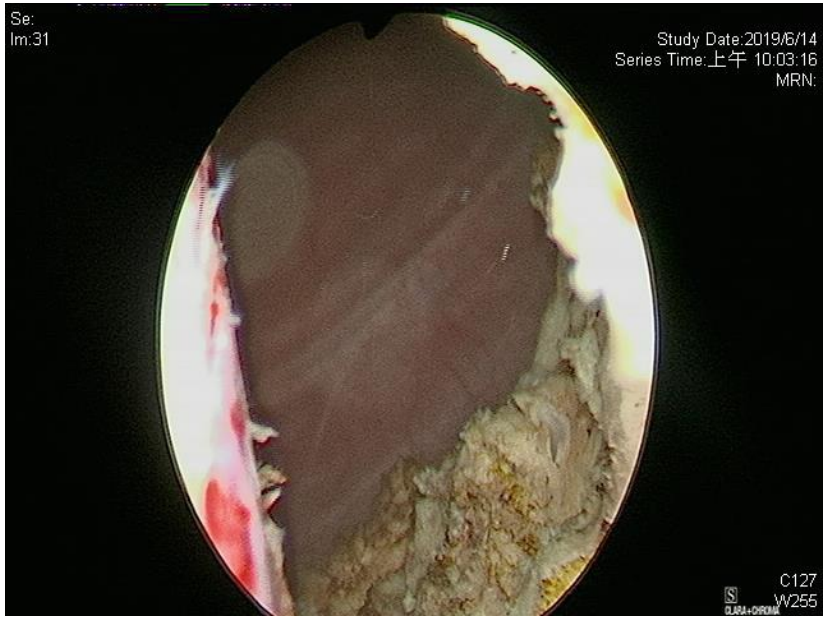
攝護腺肥大 ----- 雷射手術術後

手術前



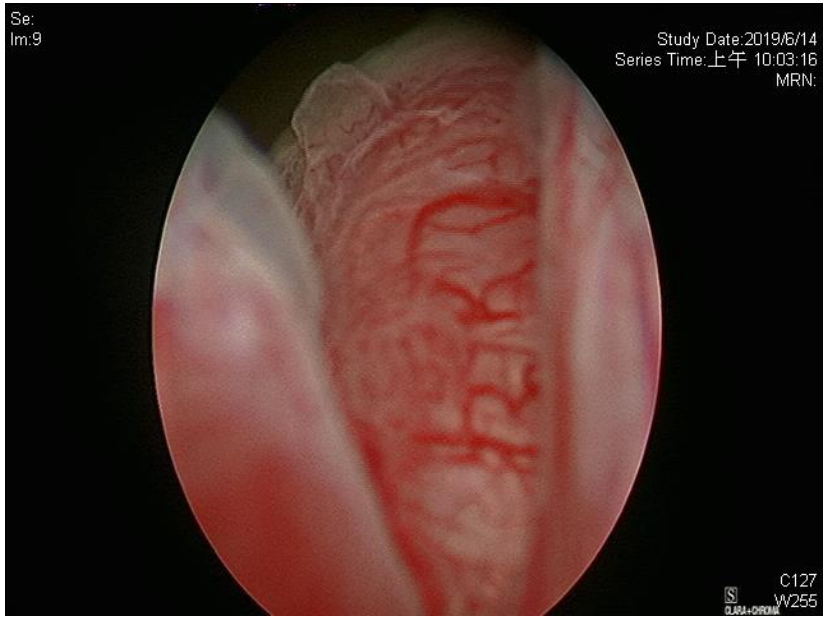
手術後



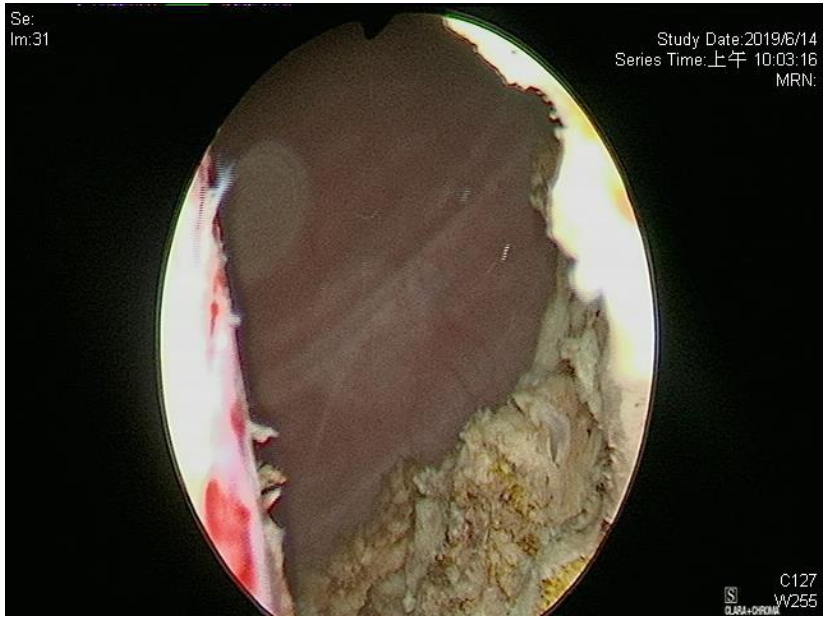
手術後隔天拔除尿管並出院

攝護腺肥大 ----- 雷射手術術後

手術前



手術後



~~甲型交感神經拮抗劑 (放鬆尿管)~~
~~5α還原酶抑制劑（縮小攝護腺）~~
~~抗膽鹼藥物(抑制膀胱過動)~~
~~B3腎上腺接受體促效劑(抑制膀胱過動)~~

針對攝護腺肥大/下泌尿道症候群病患提供個人化的藥物治療

Take Home Message

- Selecting Candidates for Medical Therapy

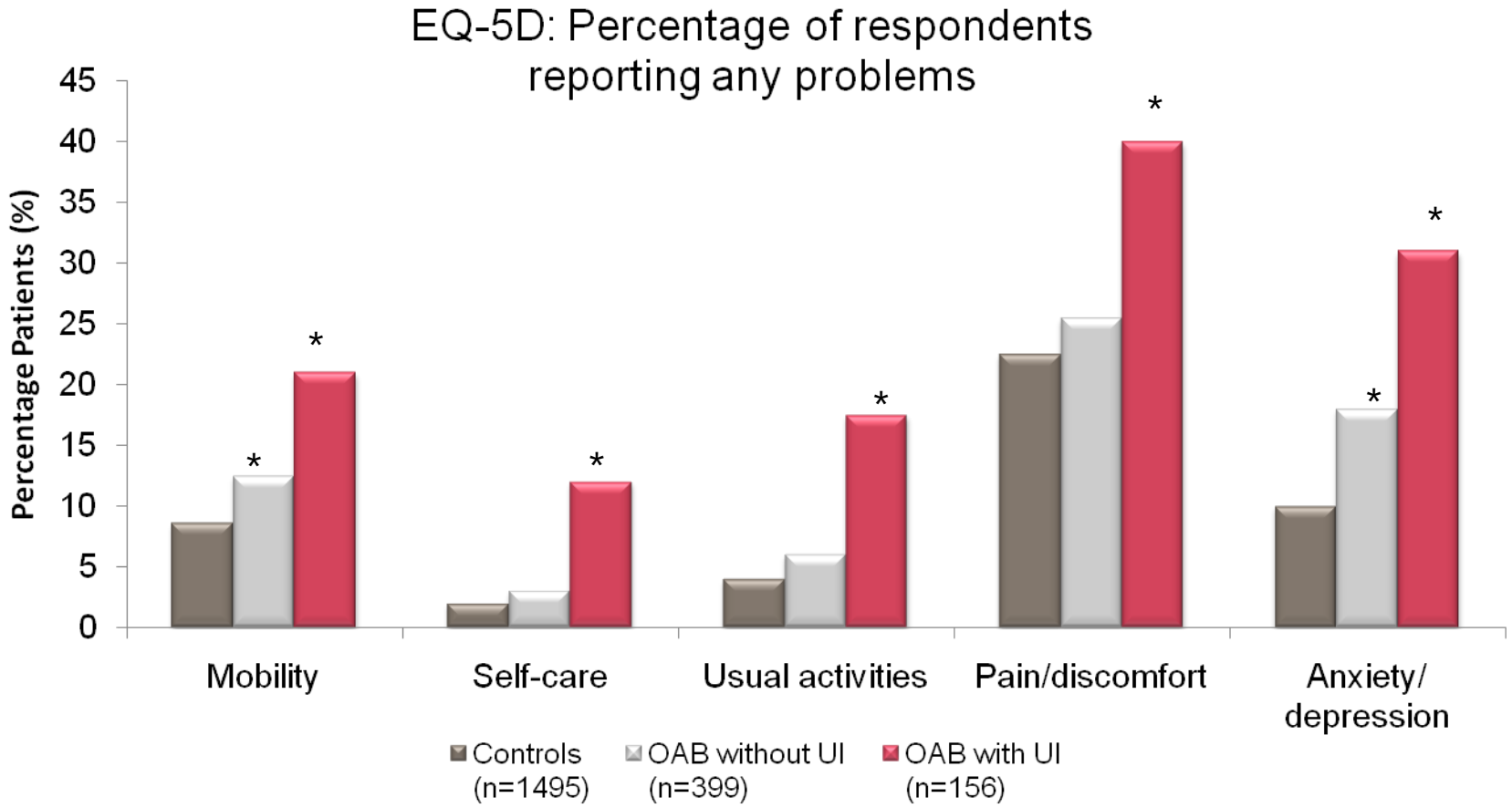
- No reliable biomarkers of specific phenotypes or progression

■A型腎上腺受體阻斷劑(**A blocker**)
■5alpha還原酶抑制(**5ARI**)
■抗膽鹼藥物
■β3腎上腺素接受體促效劑(**B3 agonist**)
■PDE5抑制劑(**PDE5I**)

- To develop research efforts for phenotype-specific therapies for LUTS, BPH, and prostatitis based on respective pathological criteria for enhancing efficacy, avoiding treatment failures, and improving cost effectiveness

- NIDDK Prostate Research Strategic Plan. 2008

Men with storage LUTS report a high degree of impairment in HRQOL



The EQ-5D is a 5-item generic QOL instrument to measure overall QOL

*$p \leq 0.05$ OAB vs. control

Adapted from Irwin DE, ICS 2006. Abstract 433

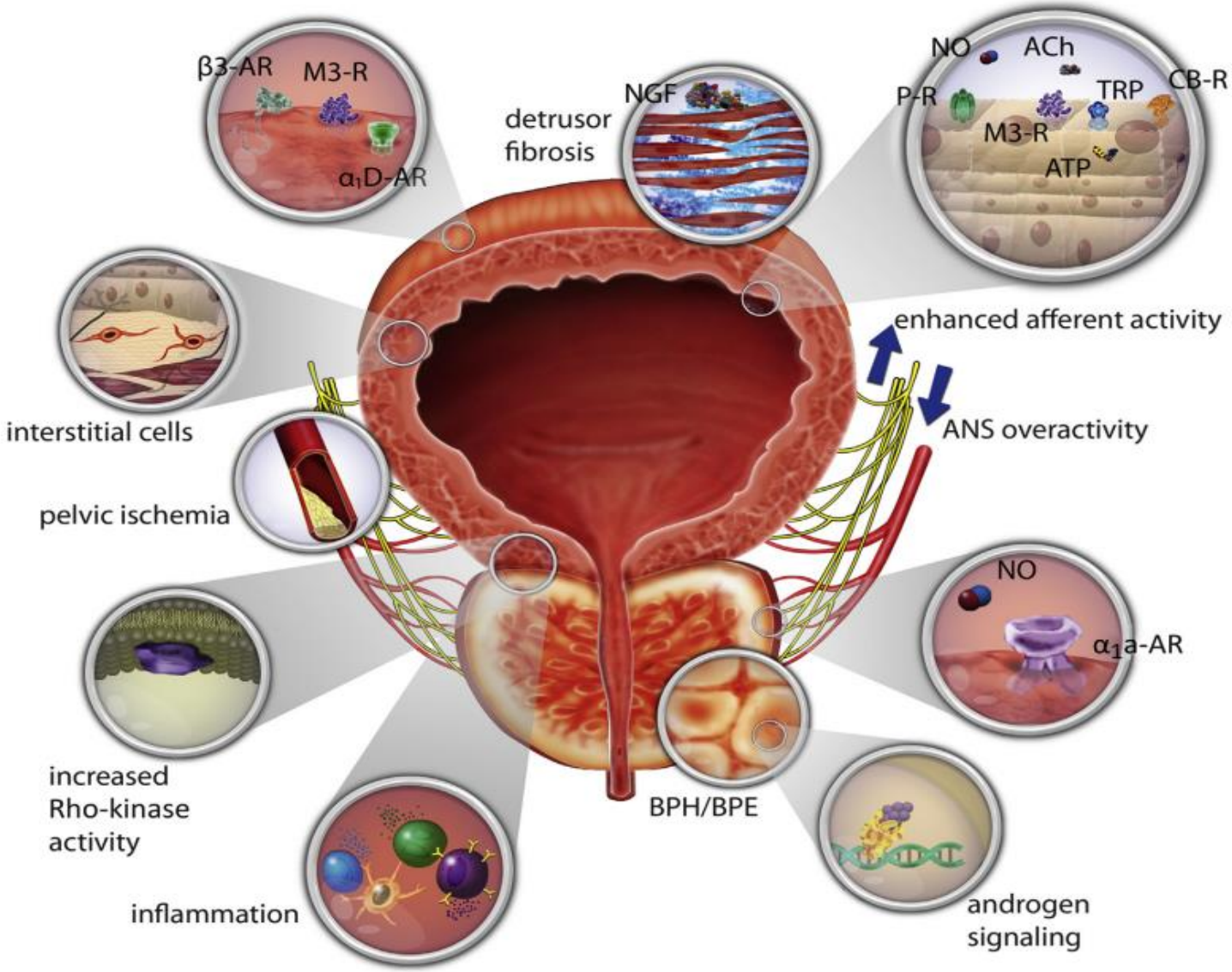
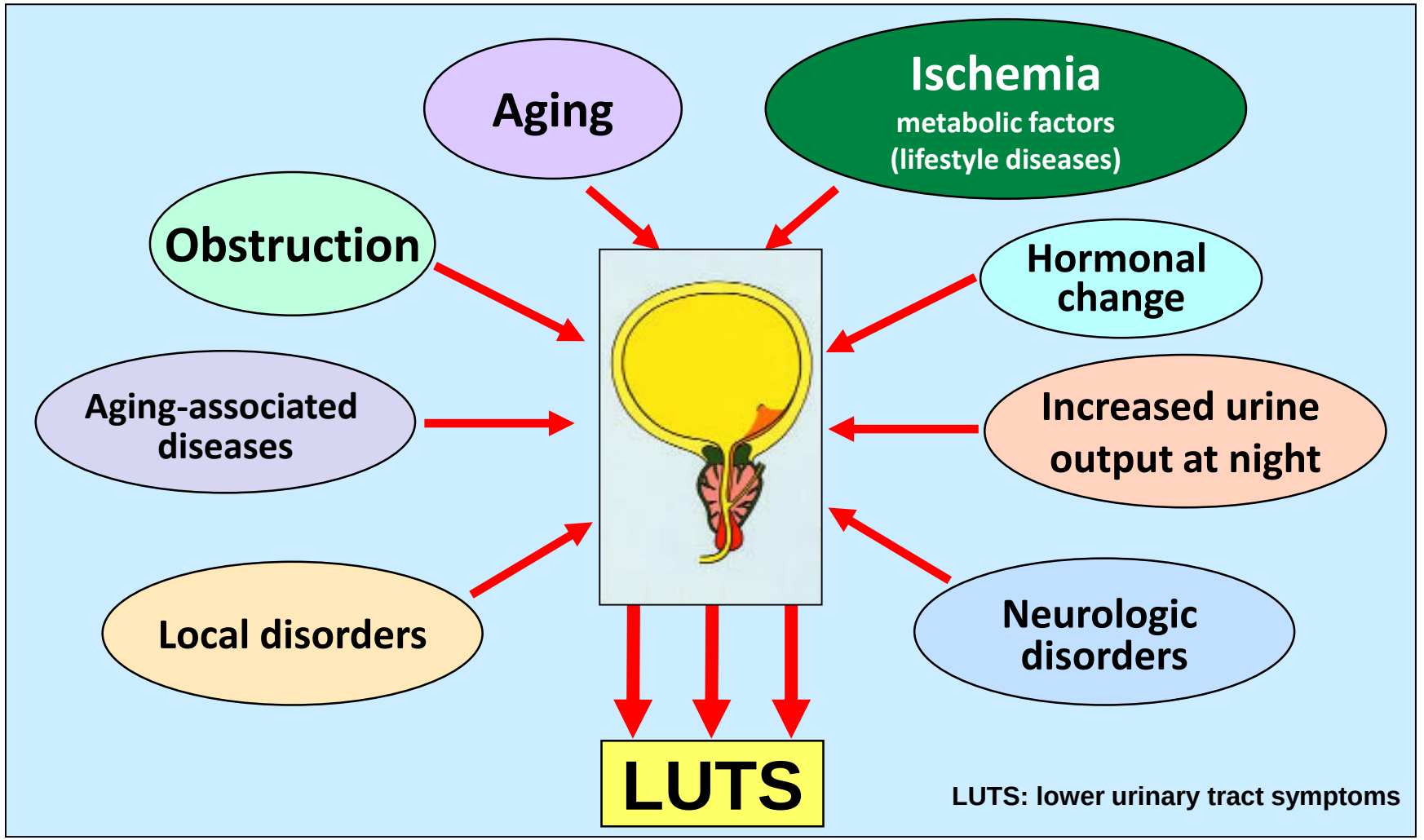


Fig. 1 – Pathophysiologic mechanisms and targets for pharmacotherapy for male lower urinary tract symptoms. Ach = acetylcholine; ANS = autonomic nervous system; ATP = adenosine triphosphate; CB-R = cannabinoid receptors; M3-R = M3 muscarinic receptor; NGF = nerve growth factor; NO = nitric oxide; P-R = purinergic receptors; TRP = transient receptor potential (channels); α_1a-AR = α_1A-adrenoreceptor; α_1D-AR = α_1D-adrenoreceptor; β3-AR = β3-adrenoreceptor.

European Urology 2013

Factors for development of LUTS

Andersson KE et al. Male lower urinary tract dysfunction: evaluation and management. 302, 2006



Bladder ischemia is receiving a lot of attention. Metabolic factors, such as hypertension, dyslipidemia and insulin resistance, cause atherosclerosis of blood vessels to LUT, resulting in ischemia. Ischemia causes oxidative stress, and leads in pathological changes in smooth muscle, mucosa and neurons in LUT. These changes may cause LUTS.

Many drugs used to treat comorbidities associated with OAB have an anticholinergic effect

Drugs with Possible Anticholinergic Effects

Generic Name	Brand Name
Alverine	Spasmonal™
Alprazolam	Xanax™
Atenolol	Tenormin™
Bupropion	Wellbutrin™, Zyban™
Captopril	Capoten™
Chlorthalidone	Diuril™, Hygroton™
Cimetidine	Tagamet™
Clorazepate	Tranxene™
Codeine	Contin™
Colchicine	Colcrys™
Diazepam	Valium™
Digoxin	Lanoxin™
Dipyridamole	Persantine™
Disopyramide	Norpace™
Fentanyl	Duragesic™, Actiq™
Furosemide	Lasix™
Fluvoxamine	Luvox™
Haloperidol	Haldol™
Hydralazine	Apresoline™
Hydrocortisone	Cortef™, Cortaid™
Isosorbide	Isordil™, Ismo™
Loperamide	Imodium™, others
Metoprolol	Lopressor™, Toprol™
Morphine	MS Contin™, Avinza™, Roxanol™
Nifedipine	Procardia™, Adalat™, Nifedical™
Prednisone	Deltasone™, Sterapred™
Quinidine	Quinaglute™
Ranitidine	Zantac™
Risperidone	Risperdal™
Theophylline	Theodur™, Uniphyl™
Trazodone	Desyrel™
Triamterene	Dyrenium™
Warfarin	Coumadin™

Drugs with Definite Anticholinergic Effects

Generic Name	Brand Name
Amantadine	Symmetrel™
Amitriptyline	Elavil™
Amoxapine	Asendin™
Atropine	Sal-Tropine™
Benztropine	Cogentin™
Brompheniramine	Dimetapp™, Lodrane™
Carbamazepine	Tegretol™
Cefuroxamine	Histex™, Cefobid™
Chlorpheniramine	Chlor-Trimeton™, Chlorphen™
Chlorpromazine	Thorazine™
Clemastine	Tavist™
Clomipramine	Anafranil™
Clozapine	Clozaril™
Cyclobenzaprine	Flexeril™
Darifenacin	Enablex™
Desipramine	Norpramin™
Dicyclomine	Bentyl™
Dimenhydrinate	Dramamine™, others
Diphenhydramine	Benadryl™, others
Doxepin	Sinequan™, Zonalon™
Flavoxate	Urispas™
Hydroxyzine	Atarax™, Vistaril™
Hyoscyamine	Anaspaz™, Cystospaz™, Levsin™
Imipramine	Tofranil™
Meclizine	Antivert™, Bonine™
Meperidine	Demerol™
Methocarbamol	Robaxin™
Nortriptyline	Pamelor™
Olanzapine	Zyprexa™
Orphenadrine	Norflex™
Oxcarbazepine	Trileptal™
Oxybutynin	Ditropan™
Paroxetine	Paxil™
Perphenazine	Trilafon™
Promethazine	Phenergan™
Propantheline	Pro-Banthine™
Quetiapine	Seroquel™
Scopolamine	Scopace™, Transderm Scop™
Thioridazine	Mellaril™
Tolterodine	Detrol™
Trifluoperazine	Stelazine™
Trihexyphenidyl	Artane™
Trimipramine	Surmontil™

Do you look carefully at all of the prescriptions of your OAB patients? ….. Maybe you should

OAB, overactive bladder

Boustani MA *et al. Aging Health* 2008;4:311–20; Campbell N *et al. Clin Interventions Aging* 2009;4:225–33.

Summary

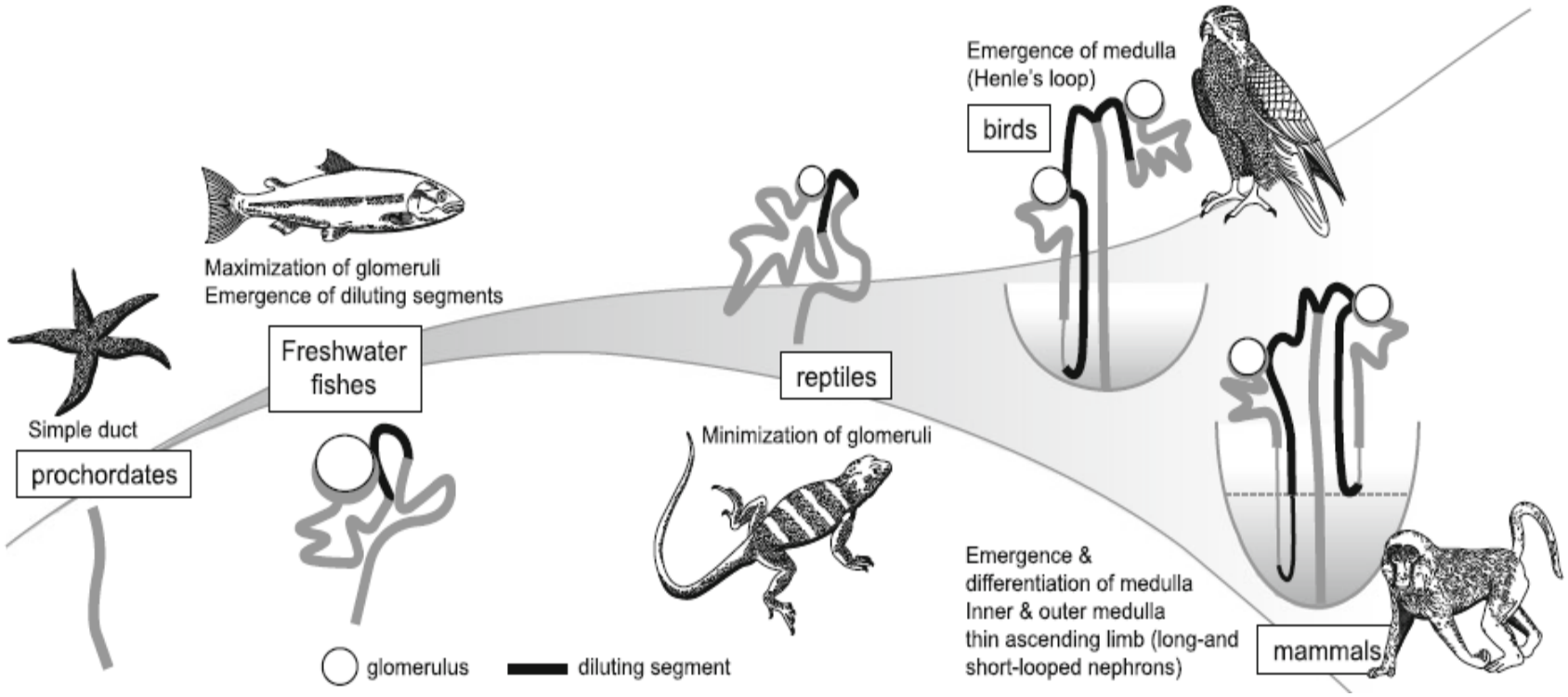
- Non-neurogenic OAB is associated with several conditions
- The concept of ‘idiopathic’ OAB may no longer be relevant
- In-depth extra-urological evaluation of OAB patients may lead to:
  - Personalised management
  - Treatment of associated conditions
  - Improved patient care

Disadvantages of FVC outcomes only

Burden	• FVC for several consecutive days • Adherence to instruction for proper use
Over/underestimation	• ±50% of women accurately report daytime urinary frequency using FVC • Over/underestimation of frequency of nocturia using FVC
Variation of content	• Great variety in content, format and duration of recall period • Only limited bladder diaries have been evaluated for criterion and construct validity, reliability and responsiveness

AVP (arginine vasopressin)

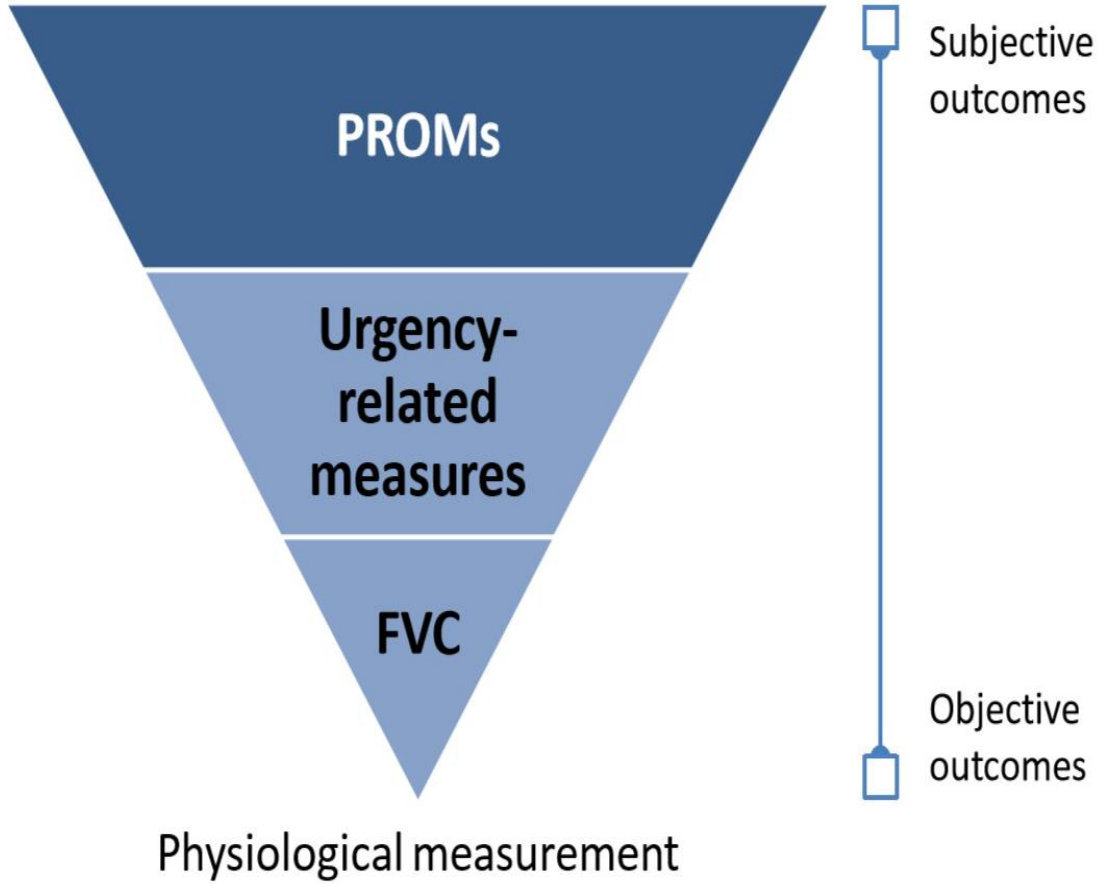
The evolutionary origin of the vasopressin/V2-type receptor/aquaporin axis and the urine-concentrating mechanism. *Juul KV. Endocrine. 2012 .*



Salt water vertebrates : simple nephron

Fresh water vertebrates :glomerular capillaries and tubules

Birds and Mammals : longer loops of Henle in both

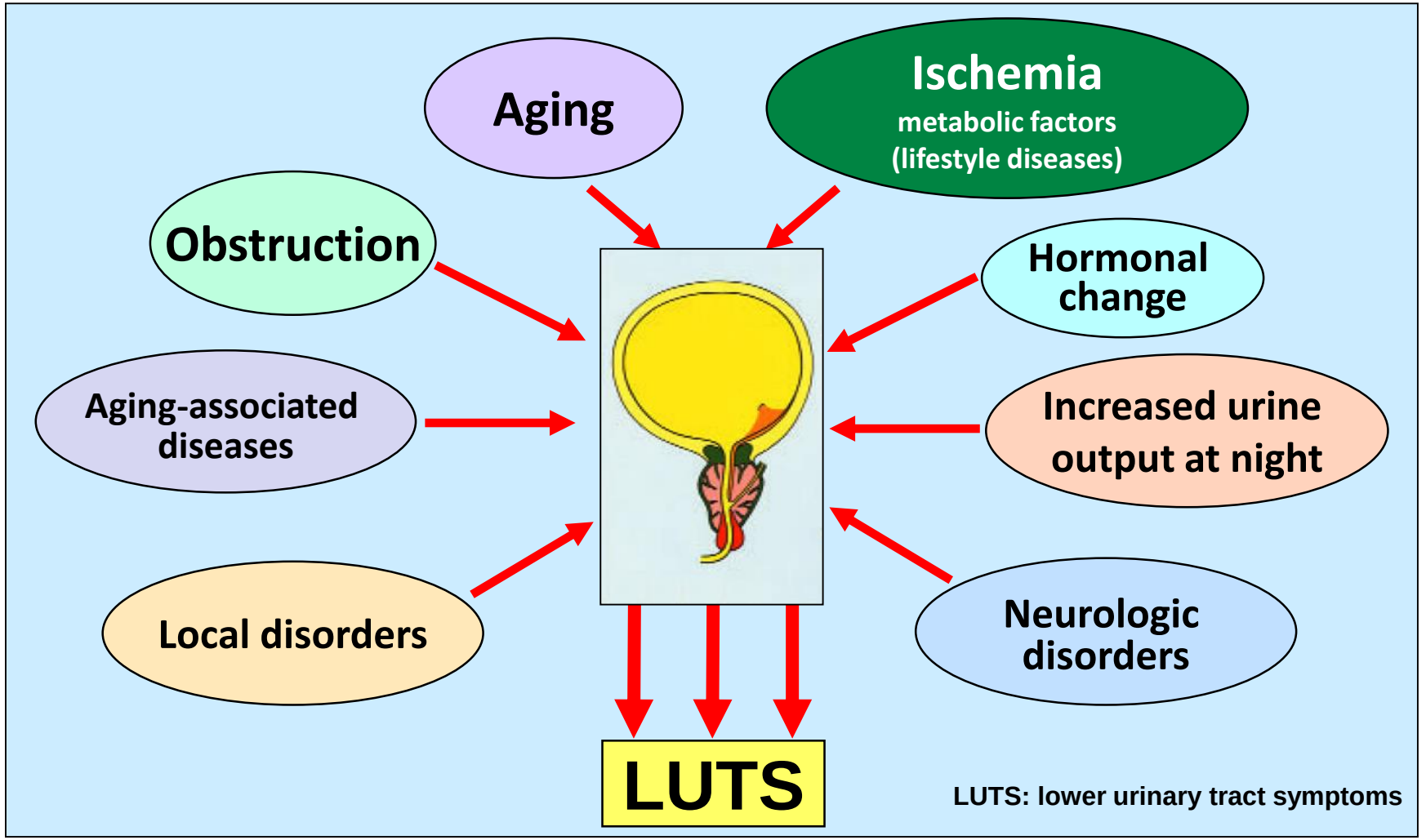


FVC, frequency volume chart; PROM, patient-reported outcome measure
Rademakers K. Presentation at EAU 2017, London, UK.

Patient reported outcomes (PROMs) in OAB: what are we measuring?

Factors for development of LUTS

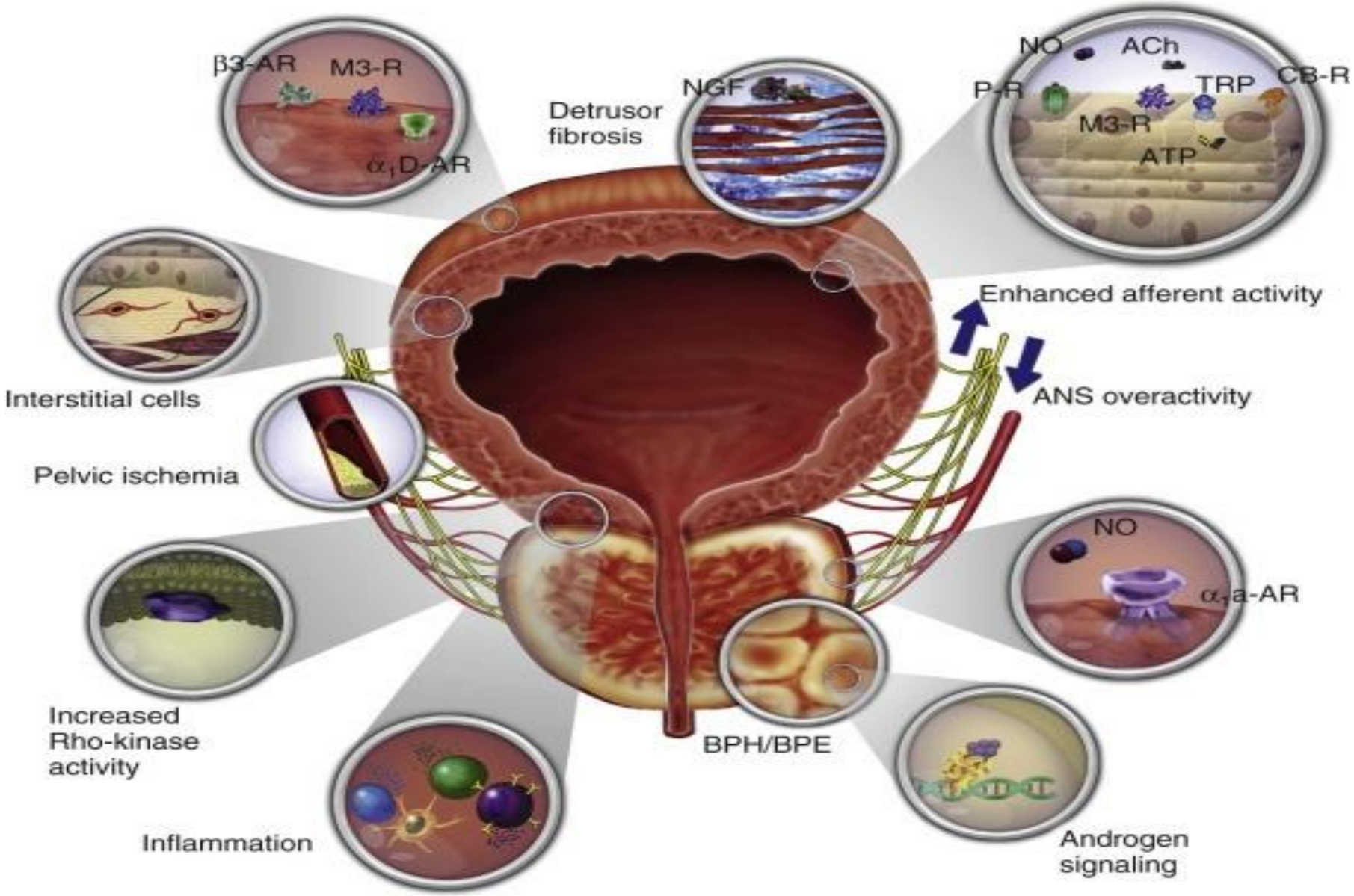
Andersson KE et al. Male lower urinary tract dysfunction: evaluation and management. 302, 2006



Bladder ischemia is receiving a lot of attention. Metabolic factors, such as hypertension, dyslipidemia and insulin resistance, cause atherosclerosis of blood vessels to LUT, resulting in ischemia. Ischemia causes oxidative stress, and leads in pathological changes in smooth muscle, mucosa and neurons in LUT. These changes may cause LUTS.

Pathophysiological mechanisms and targets for future nonsurgical therapy

EU2013



- Unfortunately, the few medical therapies approved for BPH/LUTS only decrease the risk of symptomatic progression by 30–40% across a large and diverse cohort (13).

- 5. α1-Blockers
- The α1-ARAs, including alfuzosin, doxazosin, tamsulosin, and terazosin, are considered (from the American Urological Association Guidelines in 2010) the most common therapy for BPH-related LUTS [72];
- all of these drugs are equally efficacious, even if they present adverse effects [72].
- The α1-ARAs' mechanism of action in BPH is the blockade of α1-adrenergic-receptors (α1-ARs), which are particularly present in the smooth muscle cells of the prostate and of the bladder neck [83].
- To date, three α1-AR subtypes, α1A, α1B and α1D, have been identified.
- The α1A subtype is usually implicated in the regulation of the tone of smooth muscle cells in the prostate and in the bladder neck, while the α1B subtype modulates blood pressure by contracting the smooth muscle cells in the blood vessels [83

- Furthermore, it was shown that α1-blocker doxazosin triggers prostate cell apoptosis in BPH patients [85].
- Doxazosin and terazosin block α1-adrenergic innervations and relax smooth muscle cells in the prostate; however, this action only partially accounts for the long-term clinical effects in the treatment of BPH [86,87].
- Experimental and clinical studies were performed to elucidate whether the activation of apoptosis in prostate cells by α1-adrenoceptor antagonists could represent a key molecular mechanism justifying their long-term efficacy in the management of BPH-associated LUTS and in the potential reduction of prostate cancer growth [88].

Precision Medicine and Men's Health

American Journal of Men's Health 2017,

- The expression of α1AR subtypes varies among symptomatic BPH patients, and expression-level differences may help predict which patients will respond to subtype selective α1AR antagonists (Kojima, et al2009).

- For example, epigenetic silencing of 5AR2 gene expression associated with increased body mass index and age is a risk marker for disease progression and medical therapy failure (Bechis et al., 2015).

- In up to 30% of men with BPH, silencing of the 5AR2 gene by DNA methylation is associated with resistance to medical therapy with finasteride (Niu et al., 2011).

- Use of these data in the evaluation of patients with new-onset BPH could be used to justify early surgical intervention in certain cases, obviating the need for years of office visits for failed medical therapies (Bechis et al., 2014).

Medical treatment for BPO patients

- A型腎上腺受體阻斷劑(**A blocker**)
- 5alpha還原酶抑制(**5ARI**)
- 抗膽鹼藥物
- β3腎上腺素接受體促效劑(**B3 agonist**)
- PDE5抑制劑(**PDE5I**)

Medical treatment for BPO patients

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- 5alpha還原酶抑制(**5ARI**)
- PDE5抑制劑(**PDE5I**)

LUTS in Men

Storage symptoms	Voiding symptoms	Post micturition symptoms
• Altered bladder sensations • Increased daytime frequency • Nocturia • Urgency • Urgency incontinence	• Hesitancy • Intermittency • Slow stream • Splitting/spraying • Straining • Terminal dribble	• Feeling of incomplete bladder emptying • Post micturition dribble

- Symptoms are unspecific, overlapping, multifactorial aetiology: bladder, prostate, urethra, central or peripherial nerve system …
- 45% of men with bladder outlet obstruction (BPO) also have concomitant OAB symptoms [2]

[1] Abrams P et al. Neurourol Urodyn. 2002; 21: 167-178
[2] Knutson T et al. Neurourol Urodyn. 2001; 20: 237-247