Case studies LUTS

Professor Mike Kirby FRCP

Editor Trends in Urology & Men's Health

Disclosures

- Michael Kirby has received funding for research, advice, conference attendance and lecturing from the pharmaceutical industry including:
  - Astellas Pharma
  - Pfizer
  - Takeda
  - Astra Zeneca
  - GSK
  - MSD
  - Sanofi
  - Menarini Group
- He is an advisor to the NHS prostate cancer advisory group and the prostate cancer risk management programme

Max Z., 66 y/o, Fireman

Main complaints:	Urgency, frequency & nocturia X 2 ?Weak Stream
Bother:	Worse over last 3 years
LUTS medication:	Herbal treatment

What to do?

Max Z., 66 y/o, Fireman

Prostate Volume	40 G approx
PSA	2.1 ng/ml
DRE	soft enlarged gland, no hard nodules
IPSS	20, driven by urgency, frequency & nocturia
Comorbidities	CAD, Hypertension
Meds	Aspirin, Beta-Blocker, statin

Max Z., 66 y/o, Fireman

Recommendations: ?????

Max Z., 66 y/o, Fireman

Prostate Volume	40 mls
PSA	2.1 ng/ml
DRE	not suspicious for PC
Qmax	11.5 ml/sec
PVR	80 ml
IPSS	20, driven by urgency, frequency & nocturia
Comorbidities	CAD, Hypertension
Meds	Aspirin, Beta-Blocker, statin

8 weeks later:

Prostate Volume	40 mls
PSA	1.9 ng/ml
Qmax	14 ml/sec
PVR	80 ml
IPSS	12
Frequency Volume Chart	Less than 30% at night 2,010 mls

What are lower urinary tract symptoms (LUTS)?

- LUTS can be categorised into storage, voiding and post micturition symptoms:[1,2]

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

- Storage symptoms are associated with bladder dysfunction , e.g. overactive bladder (OAB) symptoms or urodynamic detrusor overactivity (DO)3
- Storage symptoms may be secondary to bladder outlet obstruction, though relationship is uncertain
- Voiding symptoms are typically attributed to prostatic factors, e.g. prostate enlargement or benign prostatic hyperplasia (BPH)3

1. Abrams P et al. Urology 2003; 61:37-49.
2. Oelke M et al. EAU Guidelines on the Management of Male LUTS. Feb 2013.
3. Andersson KE. Urology 2003; 62:3-10.

Male LUTS have multifactorial aetiology

Prostate

Benign prostatic hyperplasia

↓

Benign prostatic enlargement

↓

Benign prostatic obstruction

LUTS

Bladder

Overactive bladder symptoms

Cardiac disease
Metabolic syndrome

Endocrine system
Low testosterone

Detrusor overactivity

Neurological disease

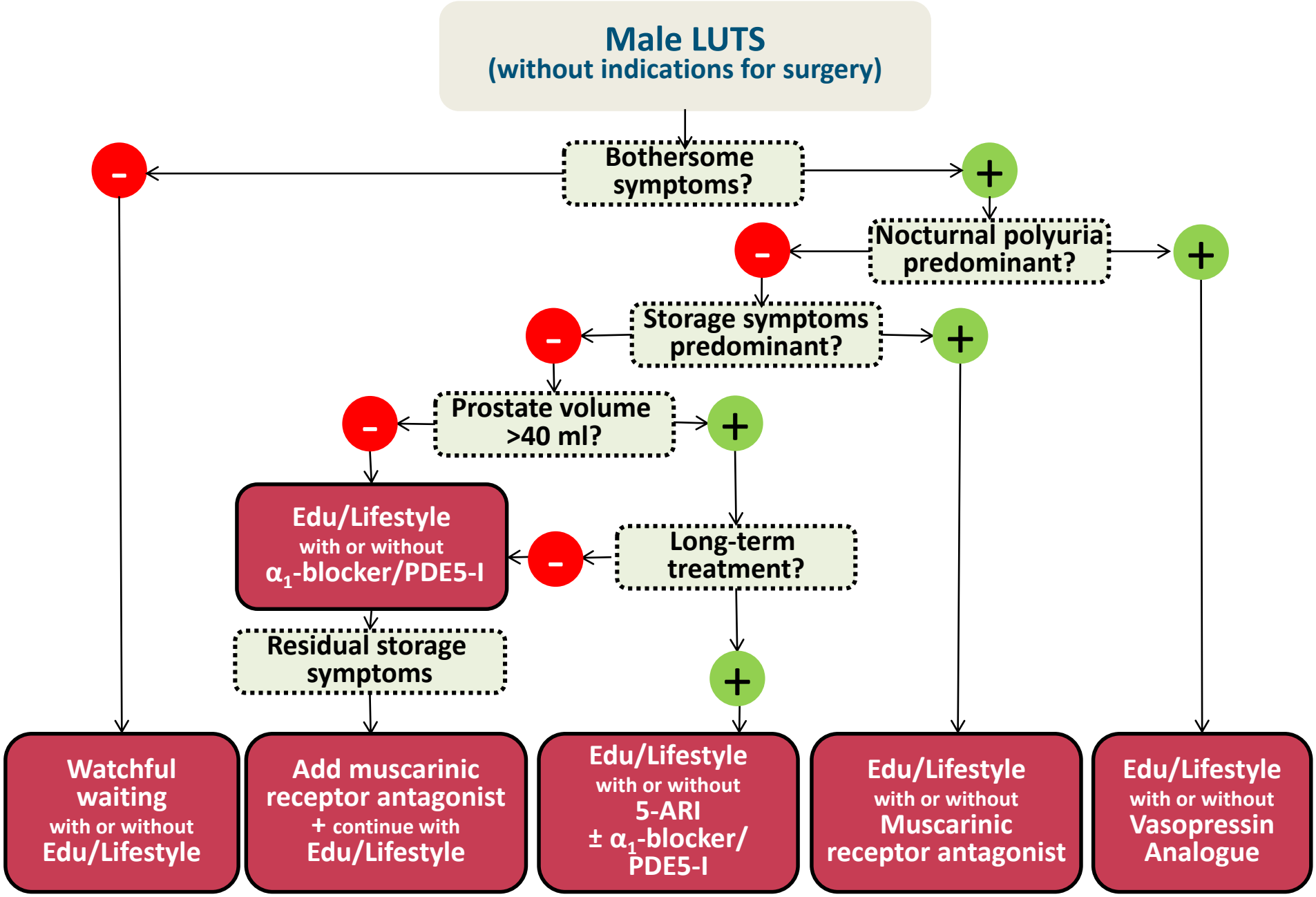
- Neurogenic detrusor overactivity
  - Parkinson's disease
  - Cerebral ischaemia

Others

- Urinary tract infection
- Stone disease
- Urethral stricture
- Inflammation
- Medication

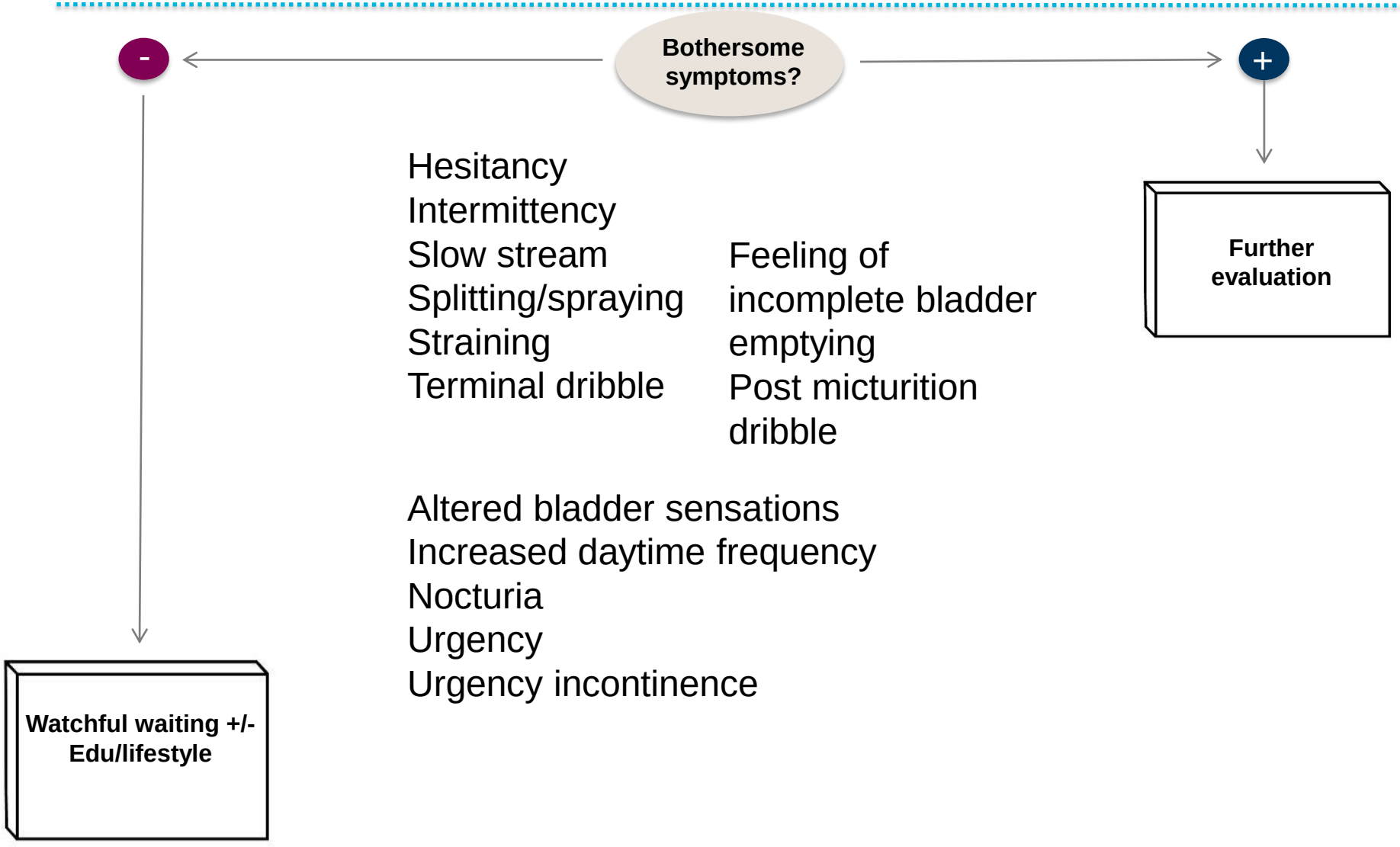
LUTS = lower urinary tract symptoms

Adapted from Speakman MJ. *Eur Urol Suppl* 2008;7:680–689 and Chapple CR et al. *Eur Urol* 2006;49:651–659.



Adapted from Oelke M et al. Eur Urol 2013;64:118-40

Current management of men with bothersome LUTS



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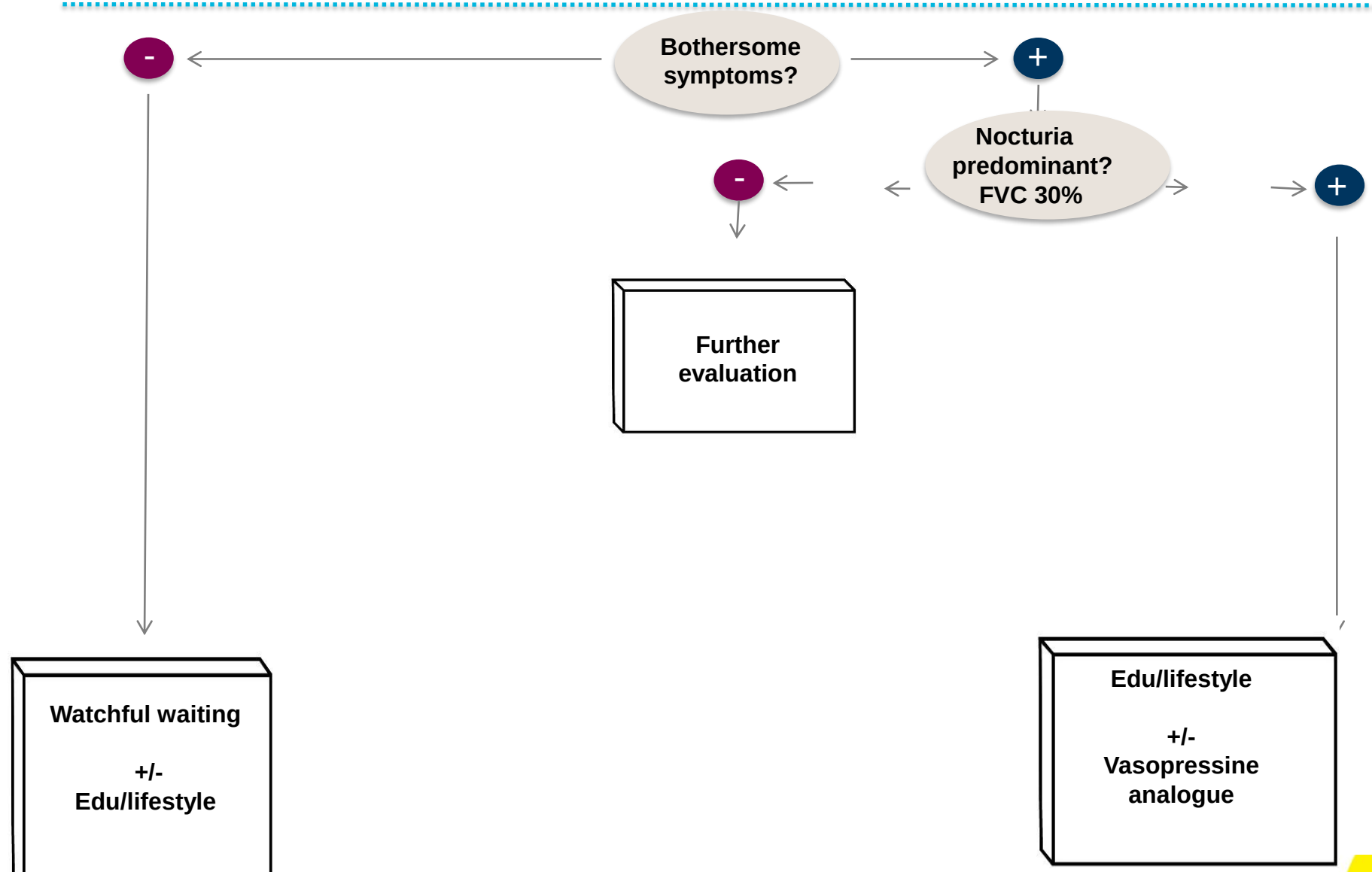

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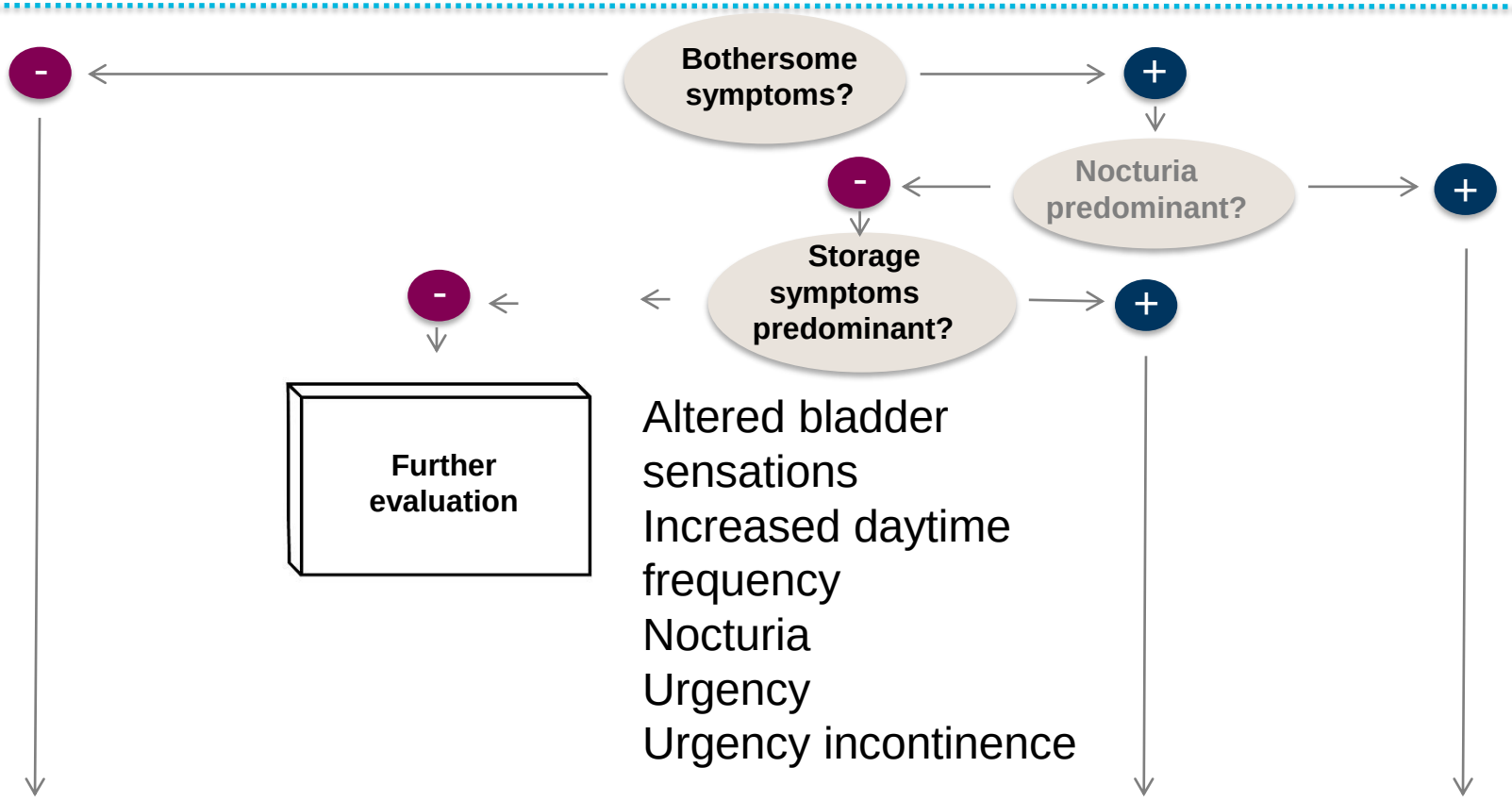

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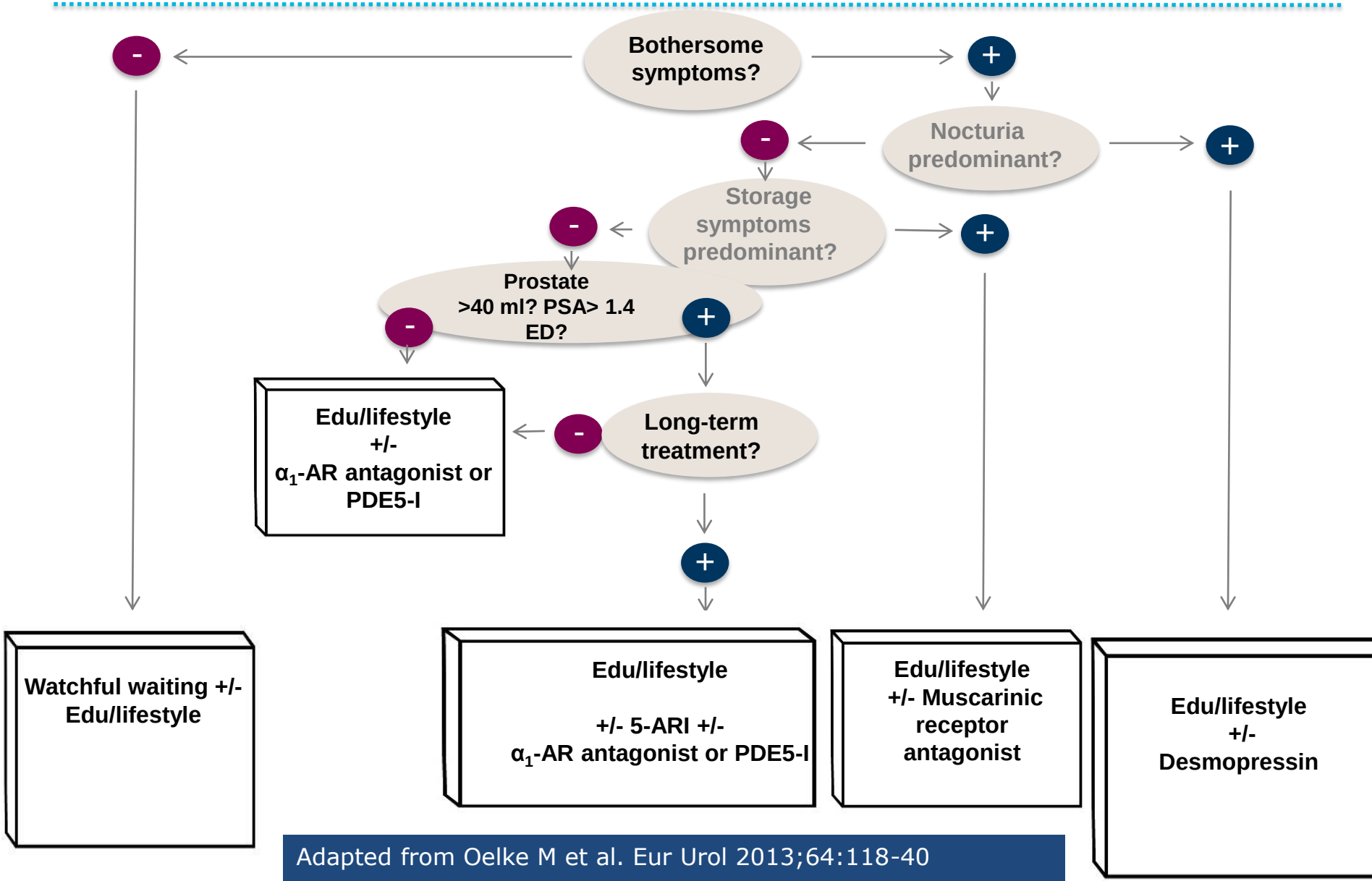
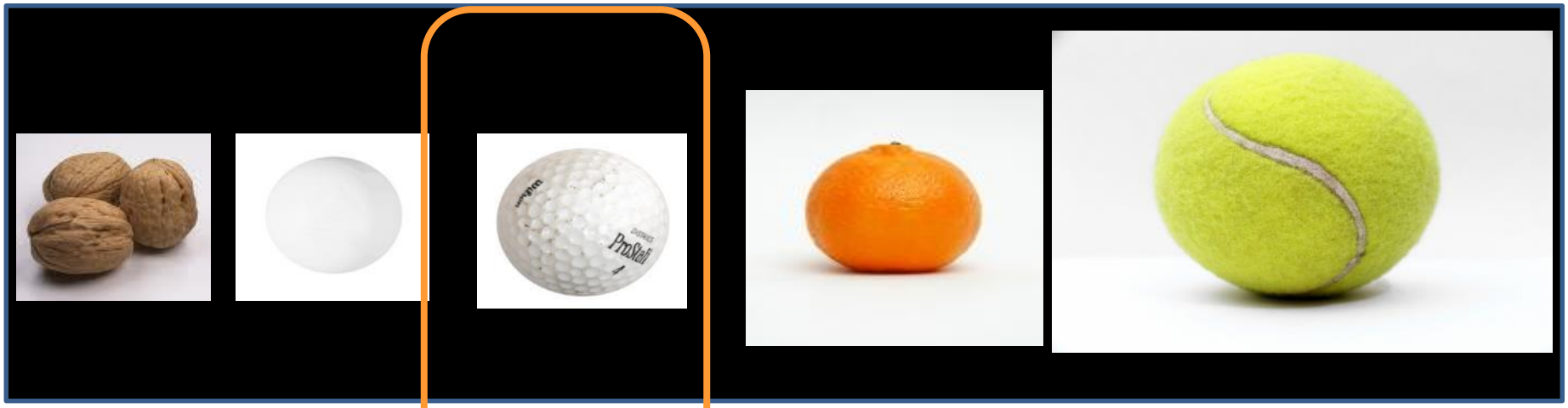


Adapted from Oelke M et al. Eur Urol 2013;64:118-40

Some common comparisons to help assess prostate size

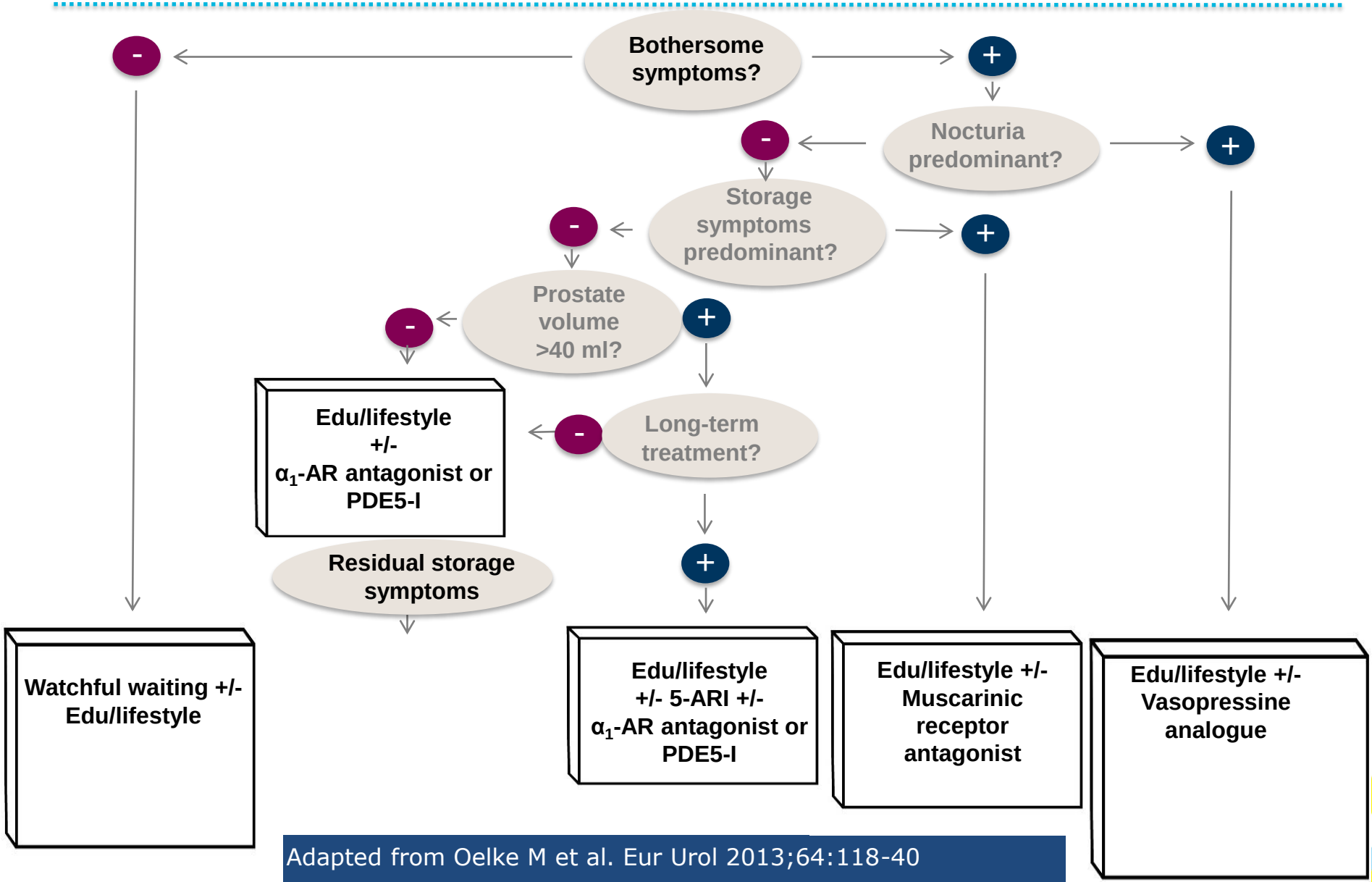


Walnut	Ping Pong Ball	Golf Ball	Clementine	Tennis Ball
3.2cm diameter	4cm diameter	4.3cm diameter	5cm diameter	6.3 diameter
Approx 20cc	Approx 33cc	Approx 40cc	Approx 65cc	Approx 130 cc

- A 30 cc prostate is approximately the size of a ping pong ball

Current management of men with bothersome LUTS

Adapted from Oelke M et al. Eur Urol 2013;64:118-40



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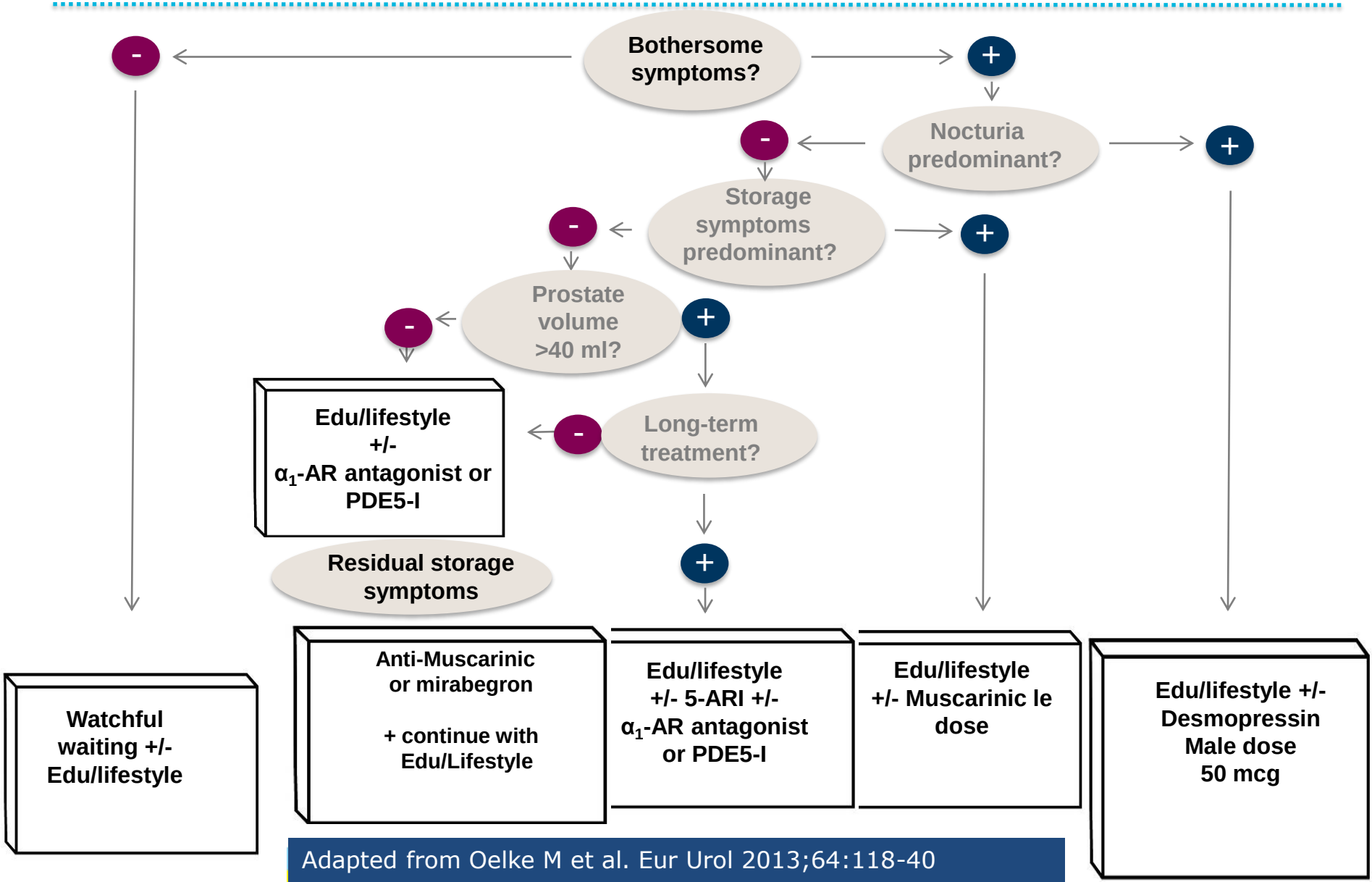
Current management of men with bothersome LUTS



Adapted from Oelke M et al. Eur Urol 2013;64:118-40

α-blocker monotherapy

Recommendations	LE	GR
α_1-blockers should be offered to men with moderate-to-severe lower urinary tract symptoms	1a	A

- α_1-blockers are considered as the first-line drug treatment of moderate-to-severe LUTS
- All α_1-blockers are equally effective
- Because of their rapid onset of action, α_1-blockers can be considered for intermittent use in patients with symptoms of fluctuating intensity

5-ARIs should be considered in men with bothersome LUTS and an enlarged prostate

	5-ARI
Total IPSS	↓~15-30%
Q_{max}	↑~1.5-2.0 ml/s
Onset of action	Very slow (6-12 mo)
Prostate volume	↓~18-28%
Duration of efficacy	Long-term (years)
Long-term risk of AUR or BPH-related surgery	+

AUR: acute urinary retention; BPH: benign prostatic hyperplasia;
IPSS: International Prostate Symptom Score; Q_{max}: maximum urinary flow rate

Oelke M et al. EAU Guideline on Male LUTS. Update February 2012

EAU recommendations

European Association of Urology

5-ARI monotherapy

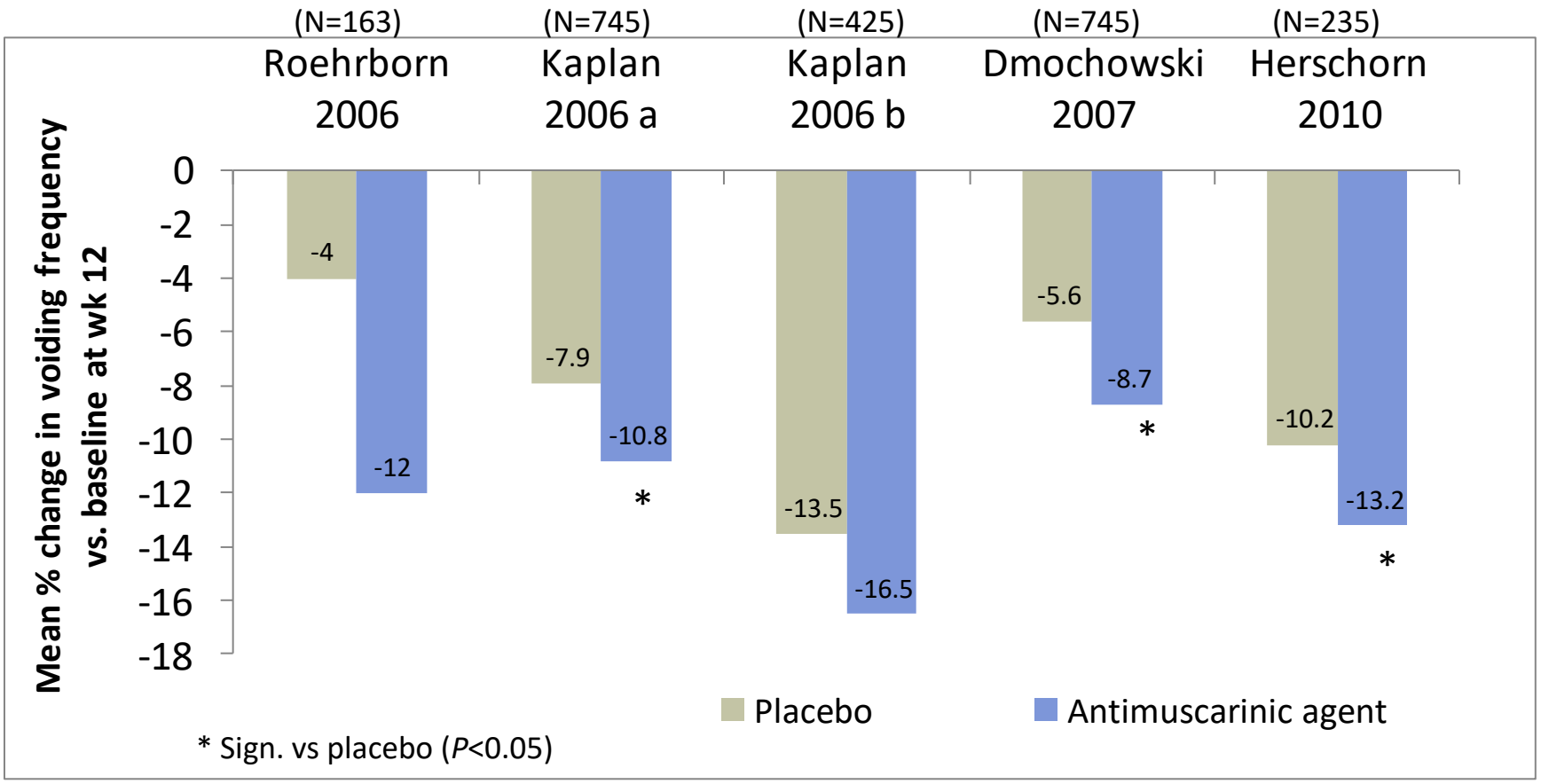
Recommendations	LE	GR
5-ARIs should be offered to men with moderate-to-severe LUTS and enlarged prostates (>40 ml) or elevated PSA-concentrations (>1.4 - 1.6 µg/l). 5-ARIs can prevent disease progression with regard to acute urinary retention and need-for-surgery	1b	A

5ARI combination therapy

Recommendations	LE	GR
Combination treatment with α_1–blocker together with 5-ARI should be offered to men with moderate-to-severe LUTS, enlarged prostates (>40 ml) and reduced Q_{max} (men likely to develop disease progression). Combination treatment is not recommended for short-term treatment (<1 year)	1b	A

Antimuscarinic monotherapy for men with predominant storage symptoms

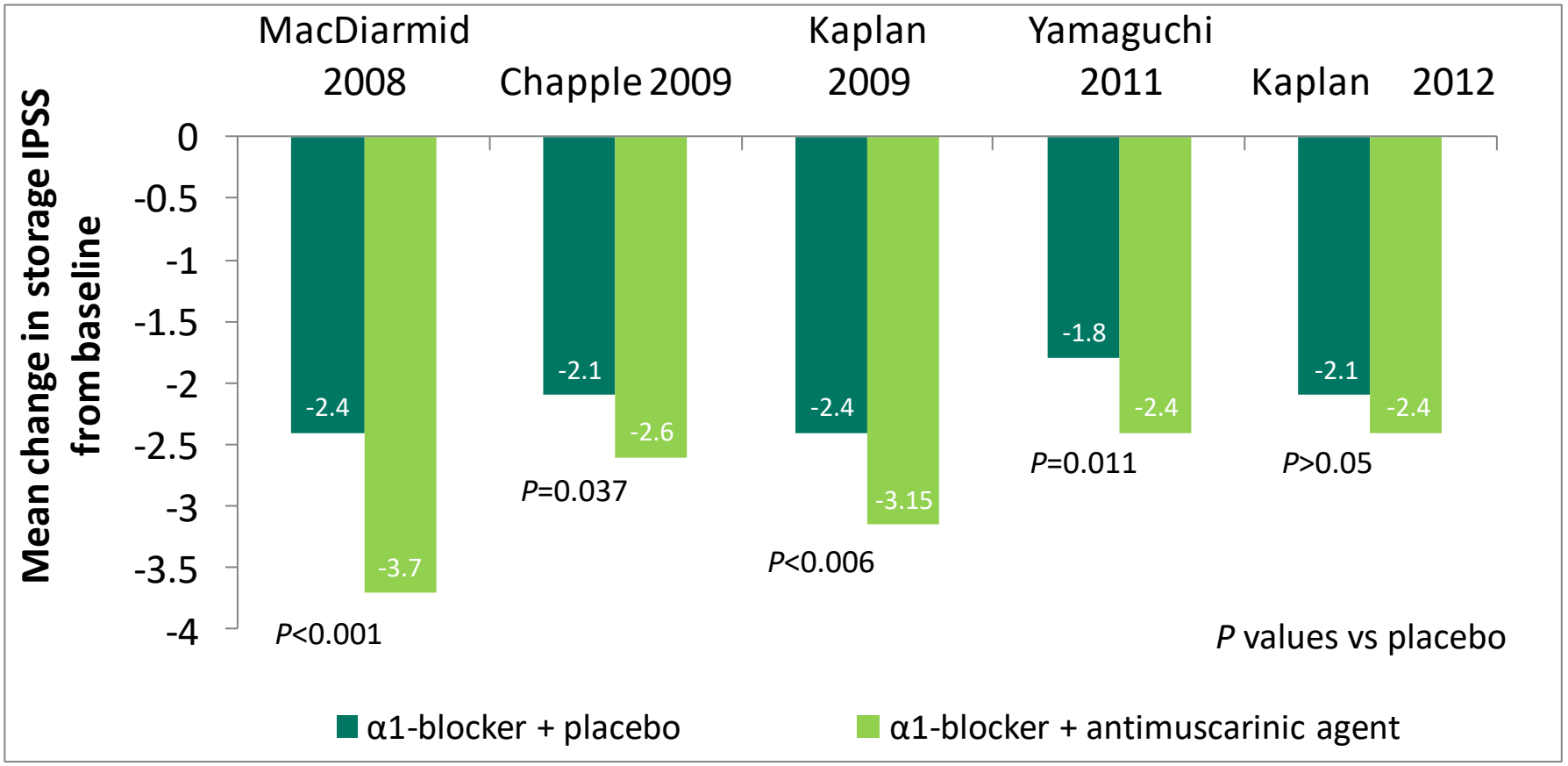
12-wk placebo-controlled studies in men with predominant storage LUTS



Oelke M et al. EAU Guideline on Male LUTS. Update February 2012

Addition of an antimuscarinic to an α_1—blocker improves persistant storage symptoms

12-wk double-blind, placebo-controlled add-on studies in pts with OAB symptoms after 4 weeks of α_1-AR antagonist treatment



MacDiarmid SA et al. Mayo Clin Proc 2008;83:1002-10; Chapple CR et al. Eur Urol 2009;56:534-43; Kaplan SA et al. J Urol 2009;182:2825-30; Yamaguchi O et al. Urology 2011;78:126-33; Kaplan SA et al. BJU Int 2012;109:1831-40

EAU recommendations

European Association of Urology

Antimuscarinic monotherapy

Recommendations	LE	GR
Muscarinic receptor antagonists might be considered in men with moderate-to-severe LUTS who have predominantly bladder storage symptoms	1b	B
Caution is advised in men with bladder outlet obstruction	4	C

Antimuscarinic + α_1-blocker combination therapy

Recommendations	LE	GR
Combination treatment with a muscarinic receptor antagonist and an α_1-blocker and might be considered in patients with moderate-to-severe LUTS if symptom relief has been insufficient with monotherapy with either drug	1b	B
Combination treatment should be used cautiously in men suspected of having bladder outlet obstruction	2b	B

Oelke M et al. EAU Guideline on Male LUTS. Update February 2012

What is the PVR above which you would avoid using an antimuscarinic agent (alone or in combination)?

1. 50 ml
2. 100 ml
3. 200 ml
4. 300 ml
5. 50% of bladder volume
6. Any volume is potentially significant
7. Doesn’t matter

PDE5-inhibitors: an option for men with ED?

- Meta-analysis:

7 RCTs (N=3,214): PDE-5 inhibitor vs placebo	Group difference	*P* value
IIEF	+5.5	<0.0001
IPSS	-2.8	<0.0001
Q_{max}	-0 ml/s	NS
5 RCTs (N=216): α_1-AR antagonist + PDE-5 inhibitor vs α_1-AR antagonist monotherapy	**Group difference**	***P* value**
IIEF	+3.6	<0.0001
IPSS	-1.8	0.05
Q_{max}	+1.5 ml/s	<0.0001

IIEF: International Index of Erectile Function score; higher score = better function; NS: not significant

Gacci M et al. Eur Urol 2012;61:994-1003

PDE5-inhibitors: tolerability

- Typical adverse events: headache, flushing, dizziness, dyspepsia, nasal congestion, myalgia, hypotension, syncope, tinnitus, conjunctivitis and altered vision (blurred, discoloraton)
- Contraindicated in men with K+ channel opener or nicorandil due to the risk of hypotension and consecutive myocardial ischaemia
- Should not be used with the α–blockers doxazosin or terazosin

EAU Guideline on Male LUTS.

Tadalafil

- ✓ RCT 12 week
- ✓ Men ≥45, IPSS ≥13 and Qmax ≥4-≤15 mL/s
- ✓ Tadalafil 5 mg vs. Tamsulosin 0.4 mg vs. Placebo.

Table 4 – Uroflowmetry and postvoid residual volume

	Placebo (n = 172)	Tadalafil 5 mg (n = 171)	Tamsulosin 0.4 mg (n = 168)
Q_{max}, ml/s:	n = 147	n = 156	n = 144
Baseline	10.5 ± 4.1	9.9 ± 3.6	9.4 ± 3.3
Mean change	1.2 ± 4.8	2.4 ± 5.5	2.2 ± 4.1
Median change	0.3	1.6	1.6
p value vs placebo	–	0.009	0.014

Tadalfil 5 mg and Tamsulosin 0,4 mg improve IPSS *and* Q_{max}

Oelke et al, Eur Urol 2012

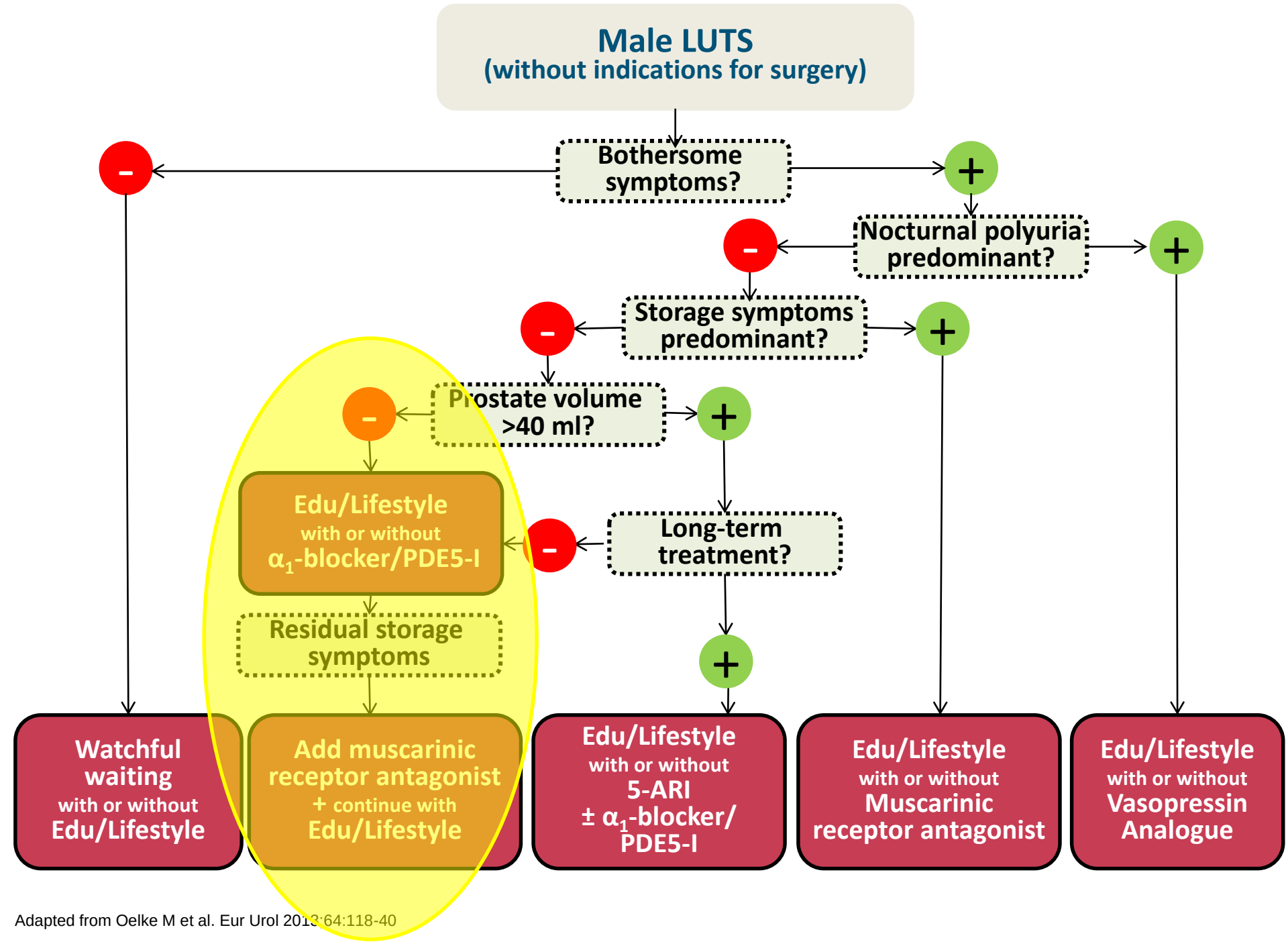
EAU recommendations:

PDE-5 inhibitor

European Association of Urology

Recommendations	LE	GR
PDE-5 inhibitors reduce moderate to severe male LUTS in men with or without erectile dysfunction	1b	A

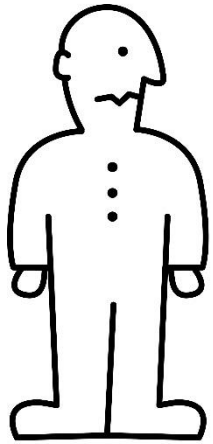
Oelke M et al. Eur Urol 2013;64:118-40



Adapted from Oelke M et al. Eur Urol 2013;64:118-40

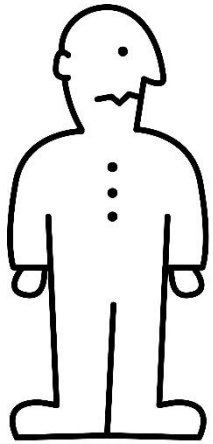
Mr. TM:

- A 56 year-old married father of 4, managerial position, very inactive
- Symptoms of reduced urinary flow, frequency + some urgency, and the need to get out of bed 4-5 times/night
- IPSS score: 26, IPSS QoL score: 5
- PSA: 1.2 ng/ml
- Erectile function poor
- Previous history of umbilical hernia
- Suffered some stress over the previous 2 years due to family problems
- Non-smoker and light drinker, consuming a glass of wine or 3-4 bottles of beer per week



Mr. TM: on examination

- Blood pressure (BP): 156/88 mmHg
  Pulse: 71 bpm
  Weight: 95 kg
  Waist: 106 cm
  BMI: 31 kg/m^2
- The prostate felt firm and slightly enlarged
  ? 30G
- Urine NAD



Activity, weight and LUTS

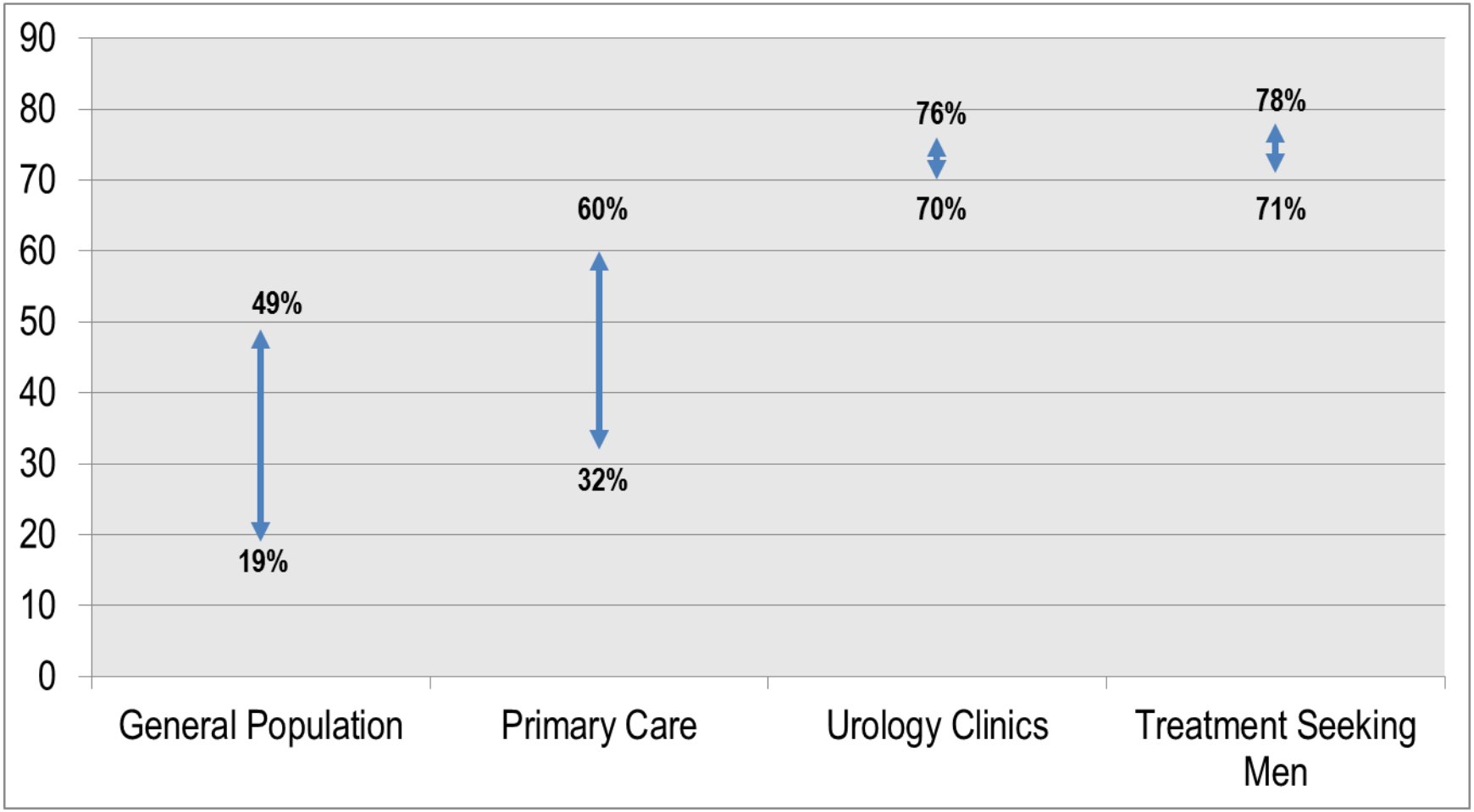
- Prospective cohort study: Osteoporotic Fractures in Men Study (MrOS); N=1,695 men ≥65 yrs; mean follow-up 4.6 yrs

	Odds ratio for developing LUTS	*P*-value
BMI • 25-29.9 vs. < 25 • > 30 vs. < 25	 1.29 1.41	 0.05 0.03
High physical activity vs. low physical activity	0.71	0.03
Daily walking vs. no daily walking	0.80	0.03

- **Overweight and obese men have higher risk of developing LUTS**
- **Physical activity reduces risk of developing LUTS**

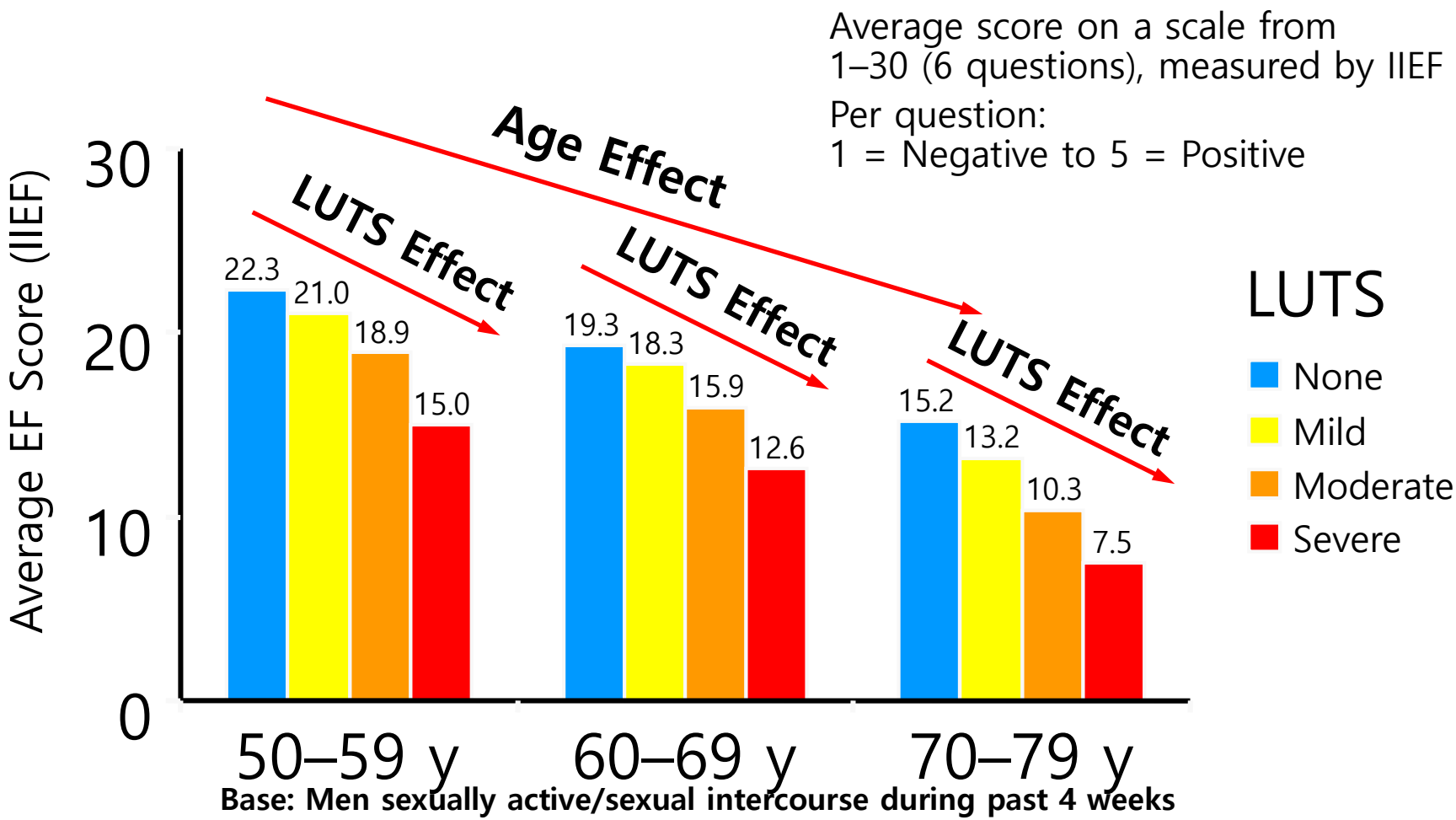
Parsons JK et al. Eur Urol 2011;60:1173–80

LUTS & ED, how often do they co-exist??
A systematic review



Seftel AD et al Int J Clin Practice 2012: doi:10.1111/ijcp.12044

MSAM-7: Erectile Function Declines With Increasing Severity of LUTS Independent of Age



IIEF, International Index of Erectile Function;
MSAM-7, Multinational Survey of the Aging Male

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

IJCP THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Slides to accompany

Erectile dysfunction and lower urinary tract symptoms: A consensus on the importance of co-diagnosis

M. Kirby[1], C. Chapple[2], G. Jackson[3], I. Eardley[4], D. Edwards[5], G. Hackett[6], D. Ralph[7], J. Rees[8], M. Speakman[9], J. Spinks[10], K. Wylie[11]

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3. Department of Cardiology, Guys and St Thomas Hospitals London, London, UK.
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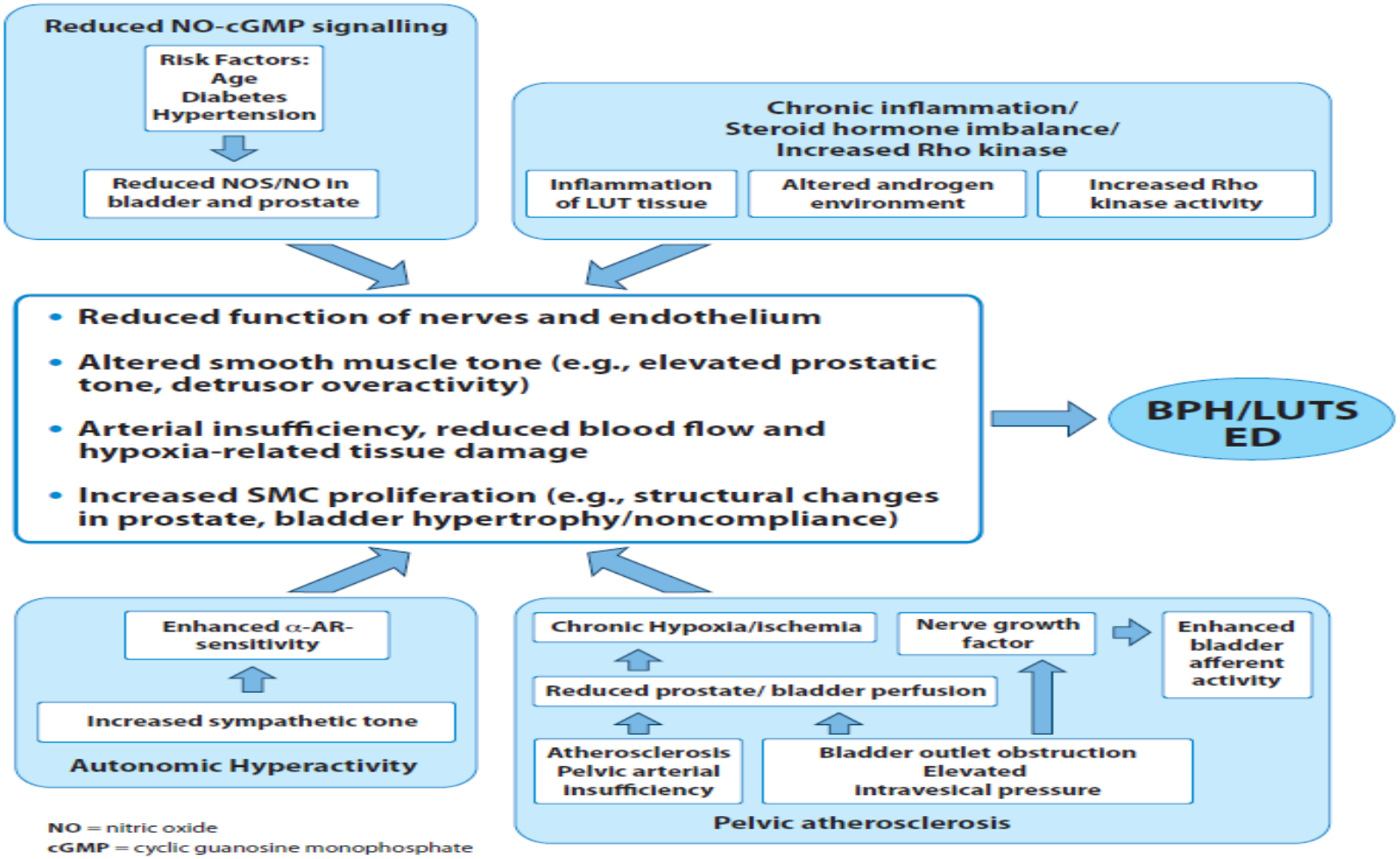
9. Department of Urology, Taunton and Somerset NHS Foundation Trust, Taunton, Somerset, TA1 5DA, UK.
10. Court View Surgery, 2a Darnley Road, Strood, Kent, ME2 2HA, UK.
11. Department of Urology, Royal Hallamshire Hospital, Sheffield, S10 2JF, UK.

<<IJCP DOI to be included>>

Potential pathophysiological pathways leading to LUTS in men: Preclinical evidence



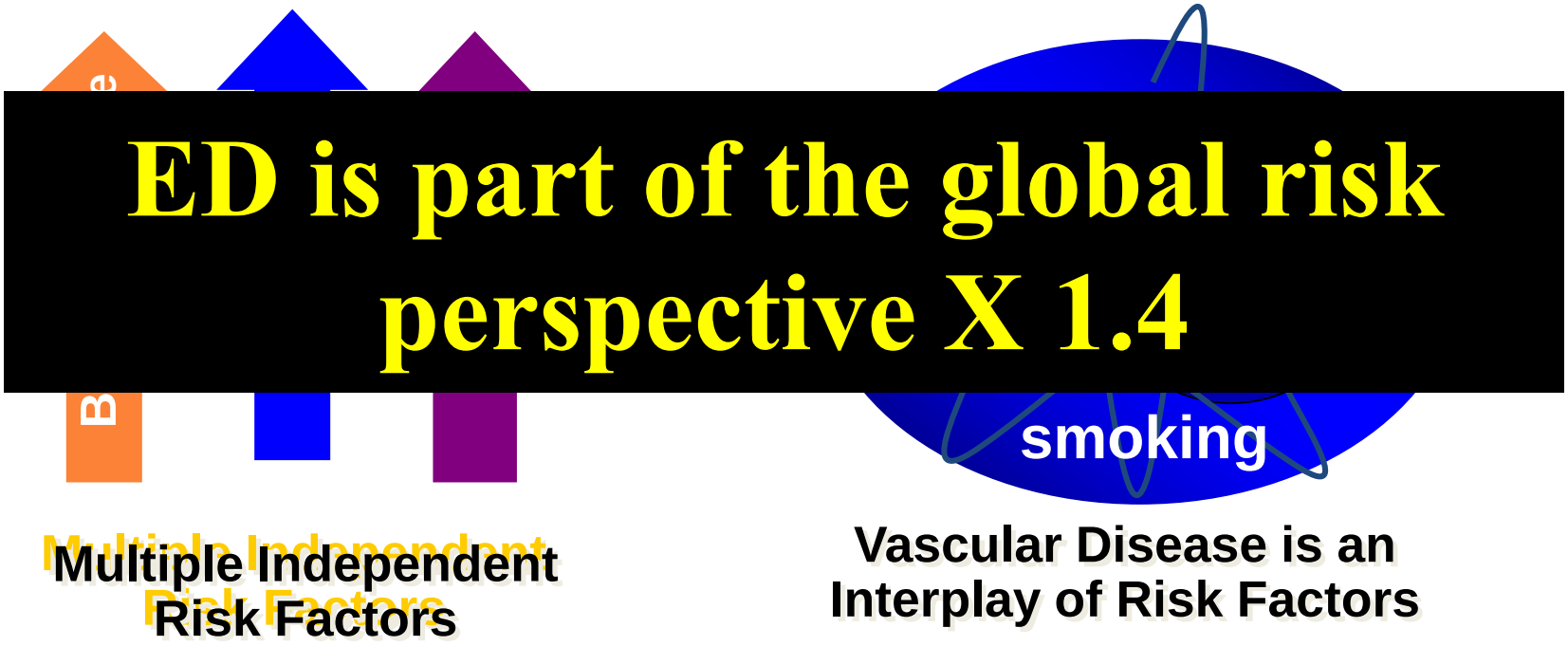
NO = nitric oxide
cGMP = cyclic guanosine monophosphate
NOS = nitric oxide synthase
Rho kinases = (ROCKs) are serine/threonine kinases that are important in fundamental processes of cell migration, cell proliferation and cell survival.
SMC = smooth muscle cell
AR = adrenergic receptor

Adapted from Gacci 2011 and Andersson 2011

Evolution in the Understanding of CVD

Traditional CVD Perspective

Global CV Risk Perspective



ED is part of the global risk perspective X 1.4

Multiple Independent Risk Factors

Multiple Independent Risk Factors

Vascular Disease is an Interplay of Risk Factors

The temporal relationship between ED and CVD & why don't men talk about it ?

- 207 CVD men attending cardiac rehab
- 165 age matched controls
- ED in 66% with CVD – discussed in 53%
- ED in 37% controls – discussed in 43%
- ED on average 5 years before CVD

In half the men there were missed opportunities to assess CVD risk and treat to goal

"Men with ED should be specifically targeted for CVD preventative strategies in terms of lifestyle changes and pharmacological treatments"

Hodges Kirby et al Int J Clin. Pract 2007;61:2019-25

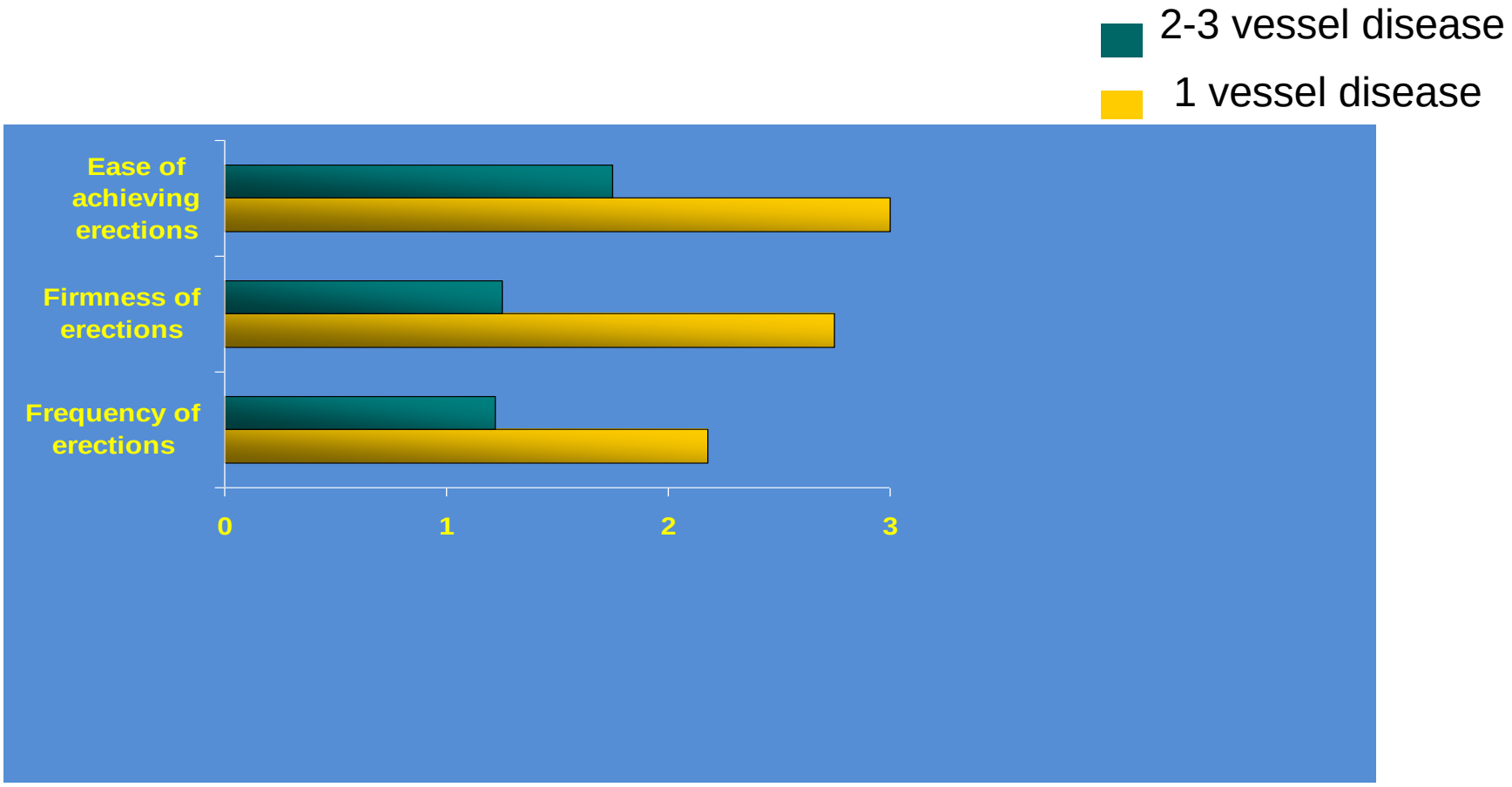
ED Predicts coronary events

1400 men 40-75, with no known CAD 10yr follow up

Inman et al Mayo Clin Pr 2009;84:108-113

Age Group	ED at baseline	No baseline ED
40-49	**48.52 (1.23-269.26)**	**0.94 (0.02-5.21)**
50-59	27.15 (7.40-69.56)	5.09 (3.38-7.38)
60-69	23.97 (11.49-44.10)	10.72 (7.62-14.66)
70+	29.63 (19.37-43.75)	23.30 (17.18-30.89)
	CAD events per 1000 pt years with CI interval	Inman et al Mayo Clin Pr 2009

DEGREE of ED & EXTENT of CAD



(Adapted from Greenstein et al, Int J Impot Res 1997;9:123-6)

If you can’t get an erection, your heart is headed in the wrong direction

BUT

SO IS THE BLADDER!

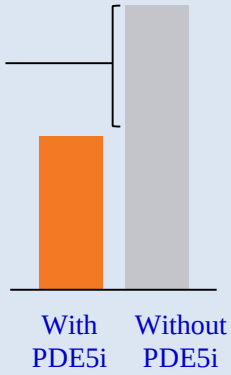
SO PDE5is for both??

Mark Pritzker 2002

What are some recent data on PDE5 inhibitors?

2016: PDE5 inhibitor use in patients with T2DM is associated with a reduction in all-cause mortality (**N=5956**)[1]

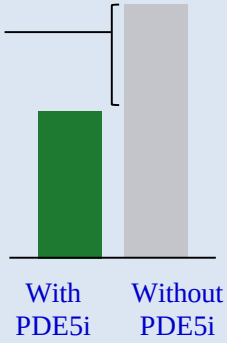
31%
less risk of all-cause mortality over 7.5 years



Controlled for: age; eGFR; smoking status; prior cerebrovascular accident; hypertension; prior MI; systolic blood pressure; use of statins, metformin, aspirin, and beta-blockers

2017: ED treatment with PDE5 inhibitor after a first MI had a reduced risk of mortality (**N=43,145**)[2]

38%
less risk of all-cause mortality over mean 3.3 years



Less risk of heart failure, MACE, non-CVD death, and CVD death

MACE = major adverse cardiac events.

1. Anderson SG, et al. *Heart*. 2016;102(21):1750-1756. 2. Andersson DP, et al. *Heart*. 2017;103(16):1264-1270.

The Interpersonal Dilemma

Question to the audience

Do you perform a metabolic screen on men with LUTS?

1. Yes
2. No

Metabolic, Cardiovascular and Endocrine Factors Contribute to Male Pelvic Health…..

- Increasing evidence pointing towards relationship between LUTS and presence of metabolic syndrome
  - Recent epidemiological findings
  - Pathophysiological links have been proposed
- Bear this in mind when developing treatment strategies
  - **Consideration of MSx and CVD and relevant links to LUTS and ED**

Kasturi S et al Curr Urol Rep 2006; 7:288-292

Kaplan SA EU Urol 2007; 52: 316-1317

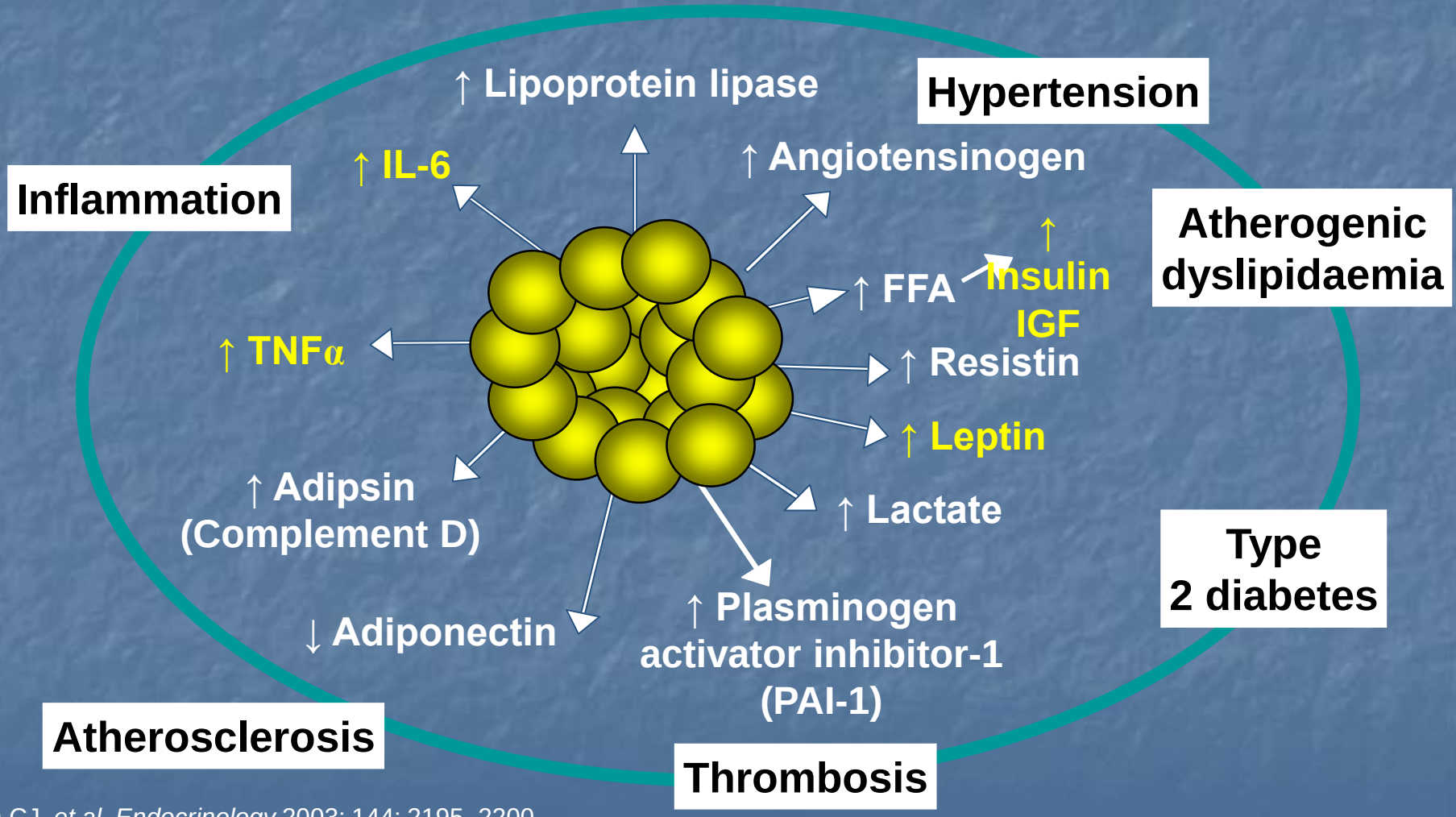
Metabolic syndrome: International Diabetes Federation definition

Focus on waist circumference (WC)

- Abdominal obesity:
  Europids: ♂ WC >94 cm, ♀ WC >80 cm
- Plus any 2 of (or treatment for) the following:
  - Elevated triglycerides: ≥1.7 mmol/l
  - Reduced HDL-cholesterol: <1.03 mmol/l (♂)
    <1.29 mmol/l (♀)
  - Raised BP: ≥130/85 mmHg
  - Raised fasting plasma glucose: ≥5.6 mmol/l

IDF Guidelines, 2006. International Diabetes Federation www.idf.org;
http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf

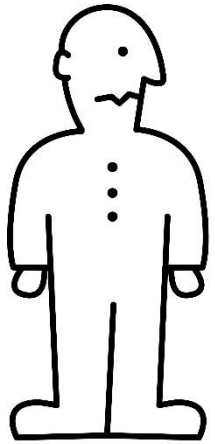
Visceral fat is an active endocrine organ, promotes insulin resistance and increased CV risk



Lyon CJ, *et al. Endocrinology* 2003; 144: 2195–2200.
Trayhurn P, *et al. Br J Nutr* 2004; 92: 347–355.
Eckel RH, *et al*. *Lancet* 2005; 365: 1415–1428.

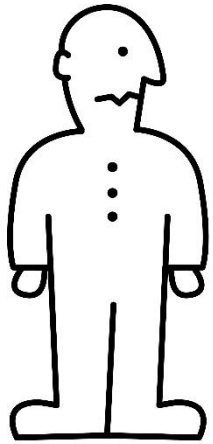
Mr. TM: metabolic screen

- Total cholesterol 6.5 mmol/l
  LDL: 4.3 mmol/l
  HDL: 1 mmol/l
  triglycerides: 2.7 mmol/l
  haemoglobin A1c (HbA1c): 44 mmol/mol (6.2%)
- BP: 156/86 mmHg
- 10-yr CVD risk calculated at 16%
- Referred for lifestyle advice as first measure
- Urine cultures were negative
- Need to check testosterone



Mr. TM: further follow-up

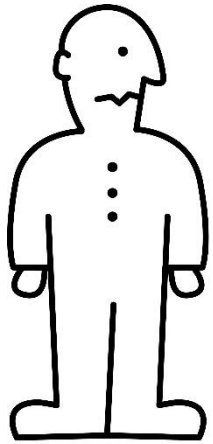
- Diastolic BP increased 10 mmHg
  Total cholesterol increased to 7.3 mmol/l
  LDL cholesterol increased to 5.5 mmol/l
- Mr. TM was therefore
  - re-advised on diet and exercise
  - prescribed atorvastatin 40 mg, ACE inhibitor and aspirin 75 mg
  - Statin therapy:
  - Target:
  - Total cholesterol < 4 mmol/l
  - Non HDL cholesterol < 2.5



Questions to the audience

Mr. TM reminder

- A 56 year-old married father of 4, managerial position, very inactive
- Symptoms of reduced urinary flow, frequency + some urgency, and the need to get out of bed 4-5 times/night
- IPSS score: 26, IPSS QoL score: 5
- PSA: 1.2 ng/ml
- Erectile function poor
- Previous history of umbilical hernia
- Suffered some stress over the previous 2 years due to family problems
- Non-smoker and light drinker, consuming a glass of wine or 3-4 bottles of beer per week

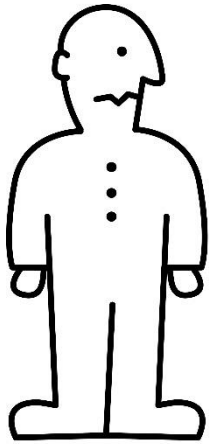


Which treatment would you recommend for this patient's LUTS?

1. Watch and wait
2. α_1-AR antagonist
3. 5α-reductase inhibitor
4. Antimuscarinic agent
5. PDE5-inhibitor
6. Mirabegron
7. Don't forget FVC!

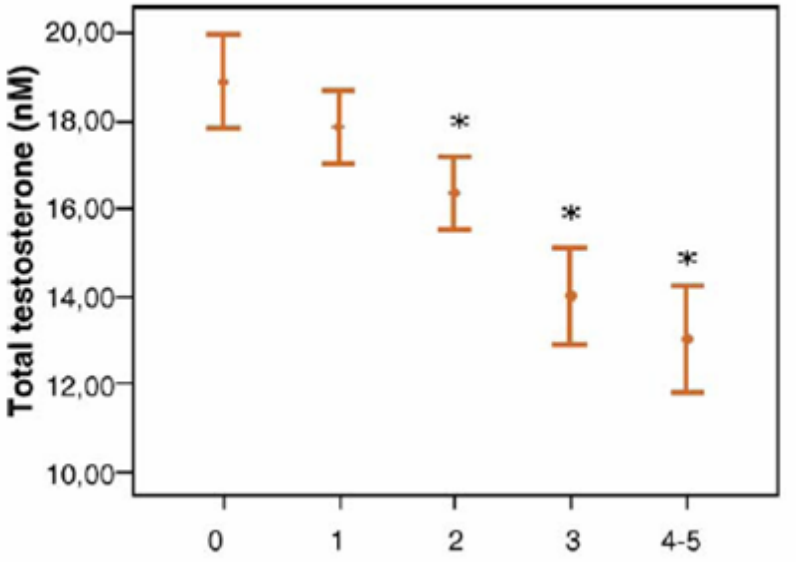
Mr. TM

- Started on α_1-AR antagonist tamsulosin 0.4 mg for his LUTS
- + on demand sildenafil
- Was asked to follow a twice-daily exercise programme + Mediterranean diet to help him lose some weight
- Testosterone was below lower limit of normal
- (10nmol/l)
- Booked for a follow-up consultation few weeks

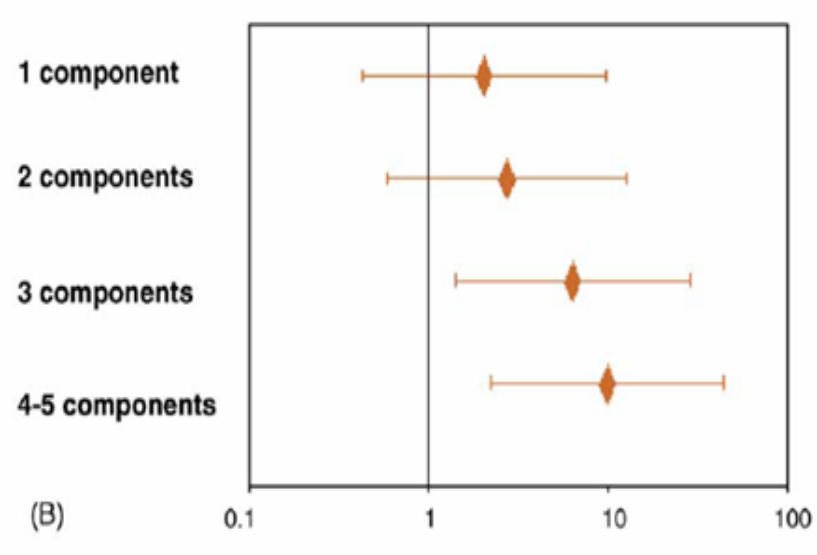


Components of the Metabolic Syndrome and Testosterone Levels

In a cohort of 803 male outpatients



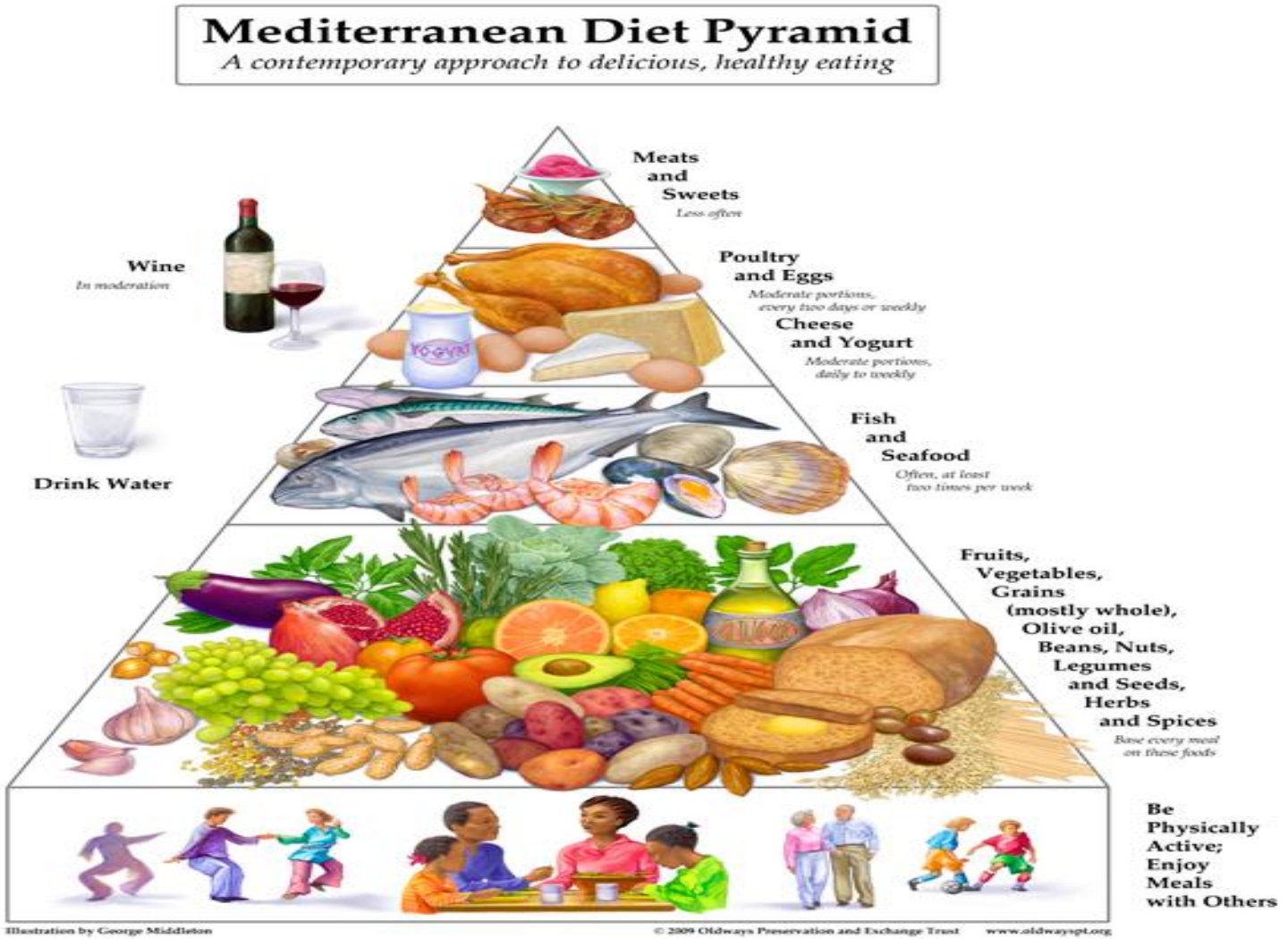
Number of components of metabolic syndrome



Relative risk of hypogonadism (TT<8.0nmol/L)

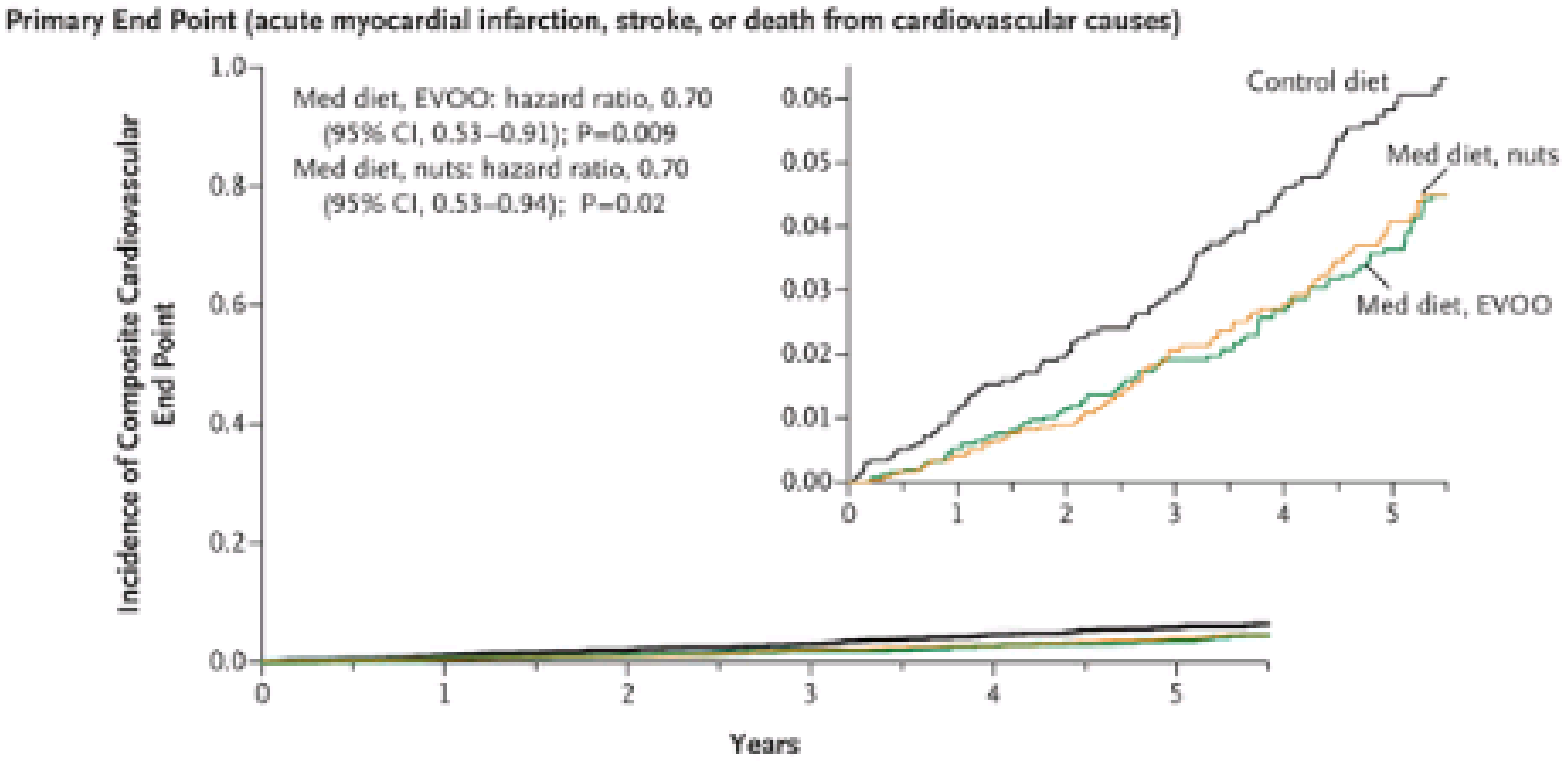
Corona G et al. *Eur Urol* 2006; 50: 595–604.

Mediterranean diet



http://oldwayspt.org/resources/heritage-pyramids/Mediterranean-pyramid/overview; March 2014

In patients with a high CV risk, a Mediterranean diet reduces the incidence of major cardiovascular events

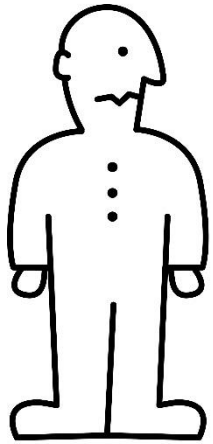


No. at Risk						
Control diet	2450	2268	2020	1383	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

Estruch R et al. N Engl J Med 2013;368:1279-90

Mr. TM: further follow-up

- Continues on atorvastatin 40 mg, ezetimibe 10 mg, ramipril 5 mg, aspirin 75 mg, tamsulosin 0.4 mg
- 1 month later: 4 kg weight loss and symptom improvement
- 3 months later:
- Still unhappy about sexual function



Question to the audience

Mr. TM: what's next?

1. No change
2. 5α-reductase inhibitor
3. Antimuscarinic agent
4. Combined antimuscarinic agent and α_1-AR antagonist
5. Mirabegron
6. DailyPDE5-inhibitor
7. Check testosterone again
8. TURP