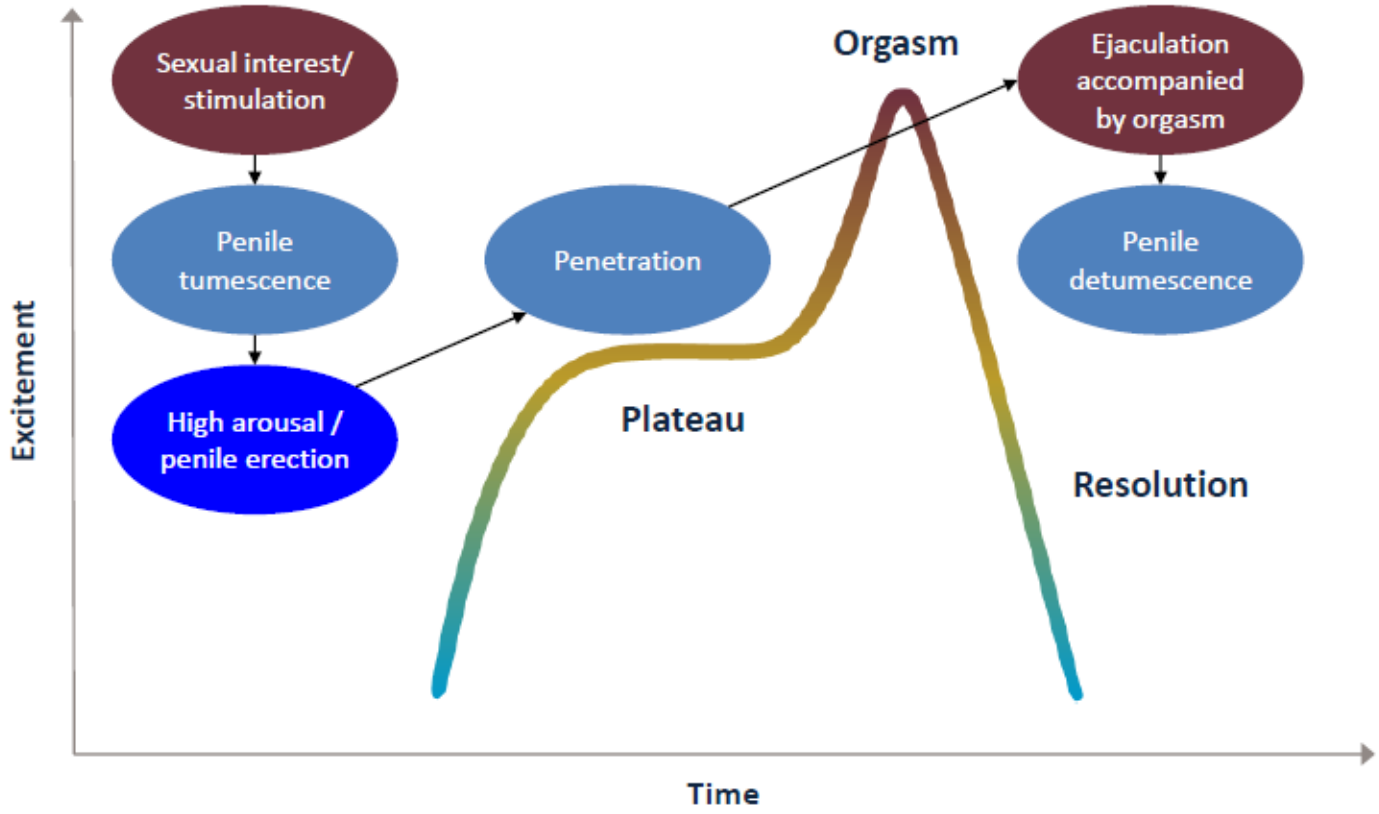
Ian Eardley
Department of Urology, Leeds Teaching Hospital Trust

2016 Update on the Management of Erectile Dysfunction

Outline

- Assessment of the man with ED
- Medical therapy for man with ED
- What to do when pills fail

Normal Male Sexual Response



Adapted from Donatucci CF :Etiology of ejaculation and pathophysiology of premature ejaculation. J Sex Med 2006, 3(suppl 4):303–308

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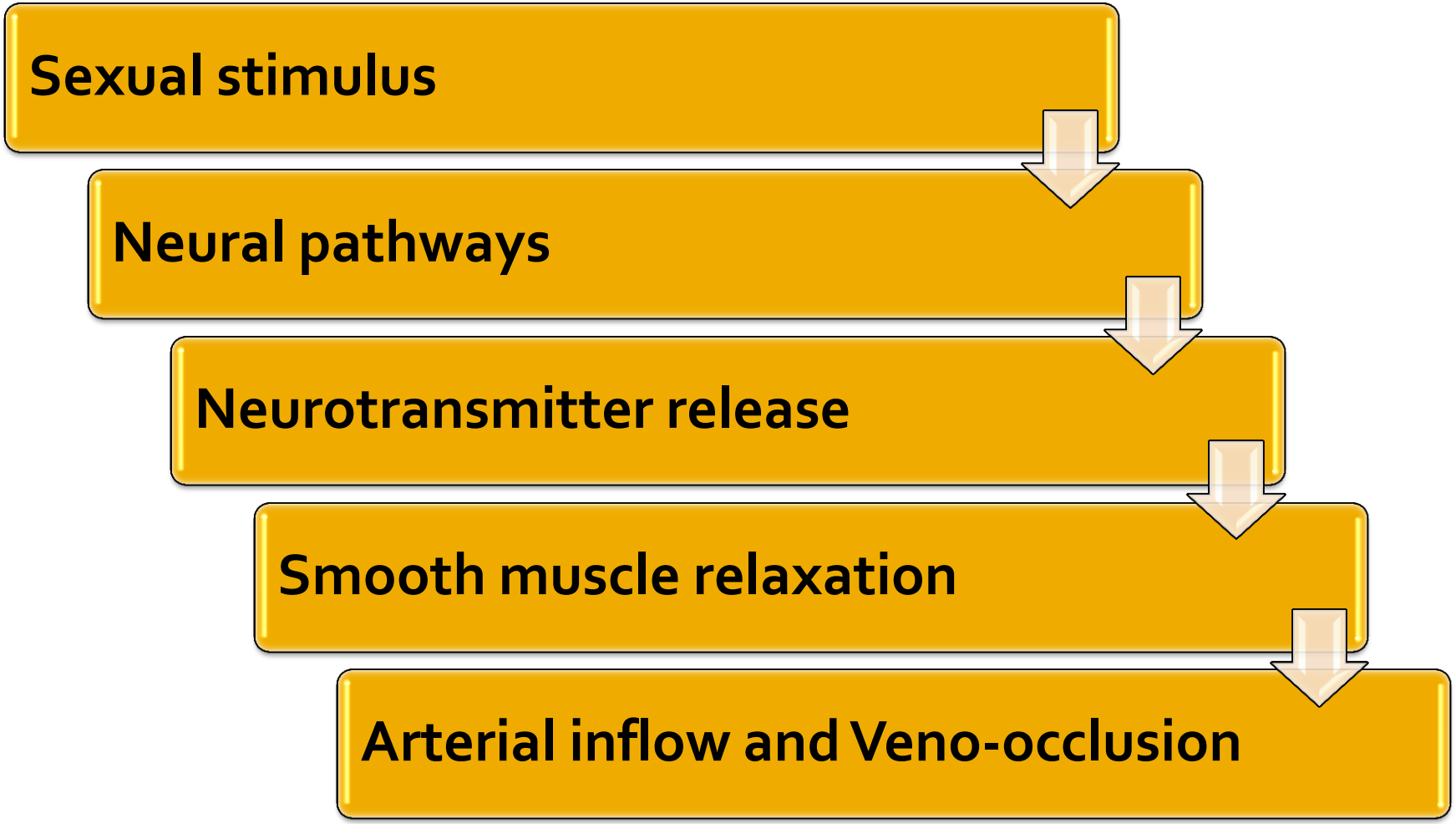
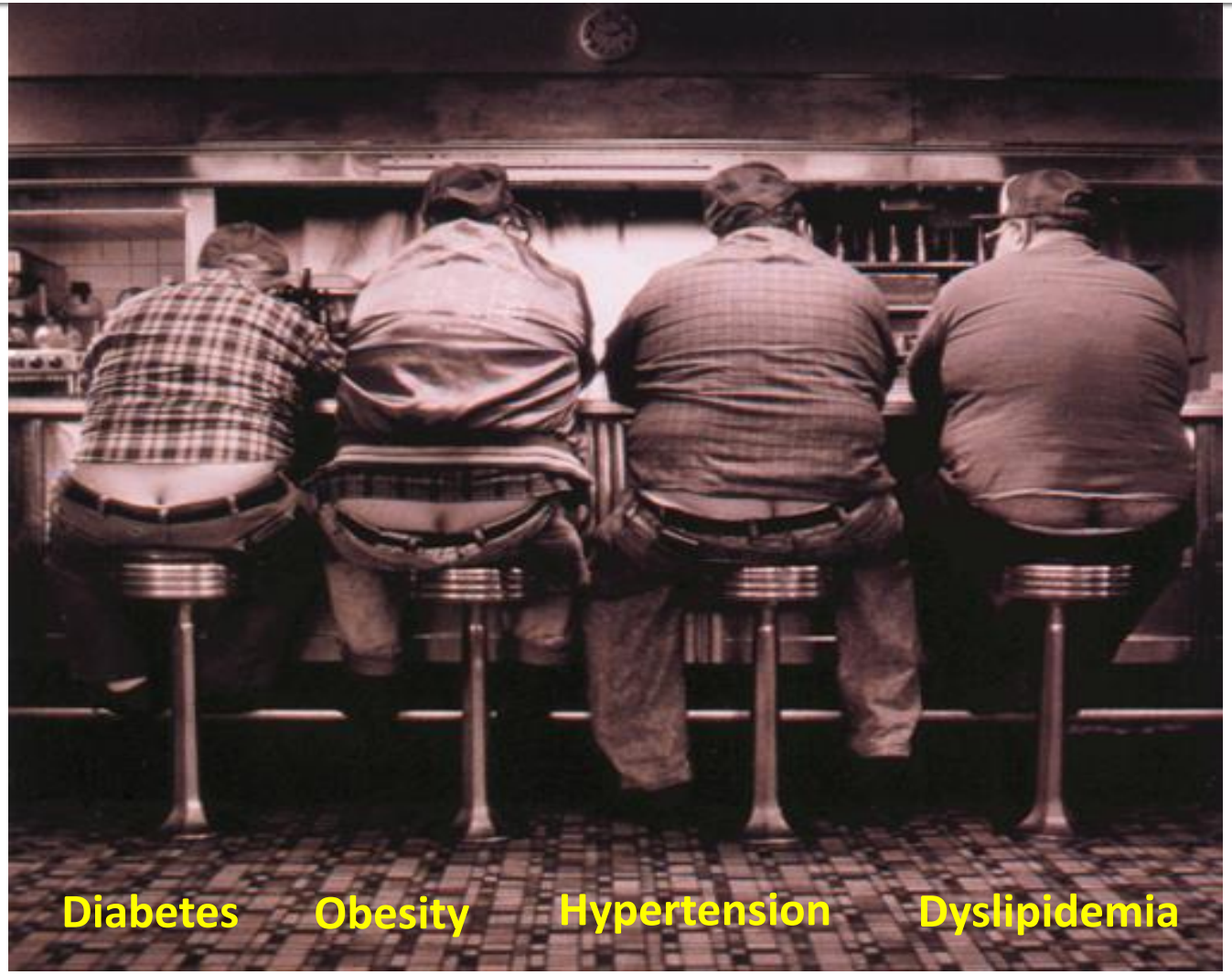
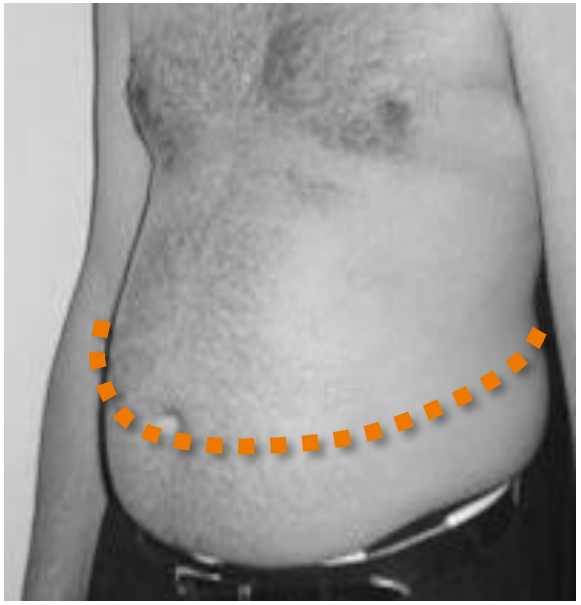


ED and CAD: The Deadly Quartet



BMI and Waist Circumference

189 cm, 93 kg = BMI 26



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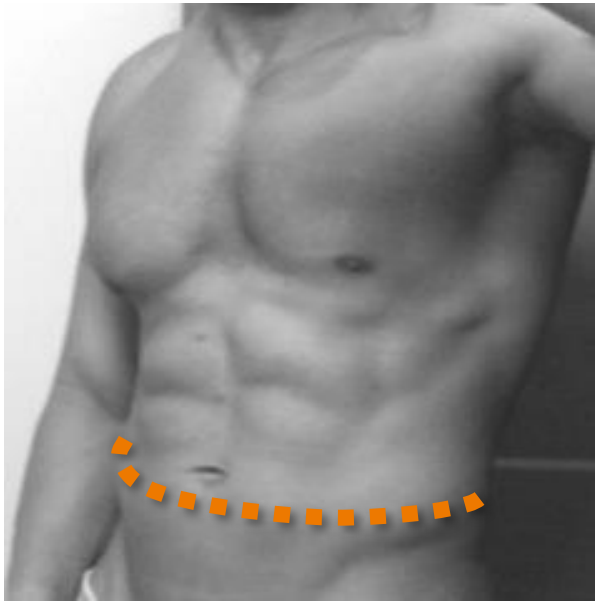
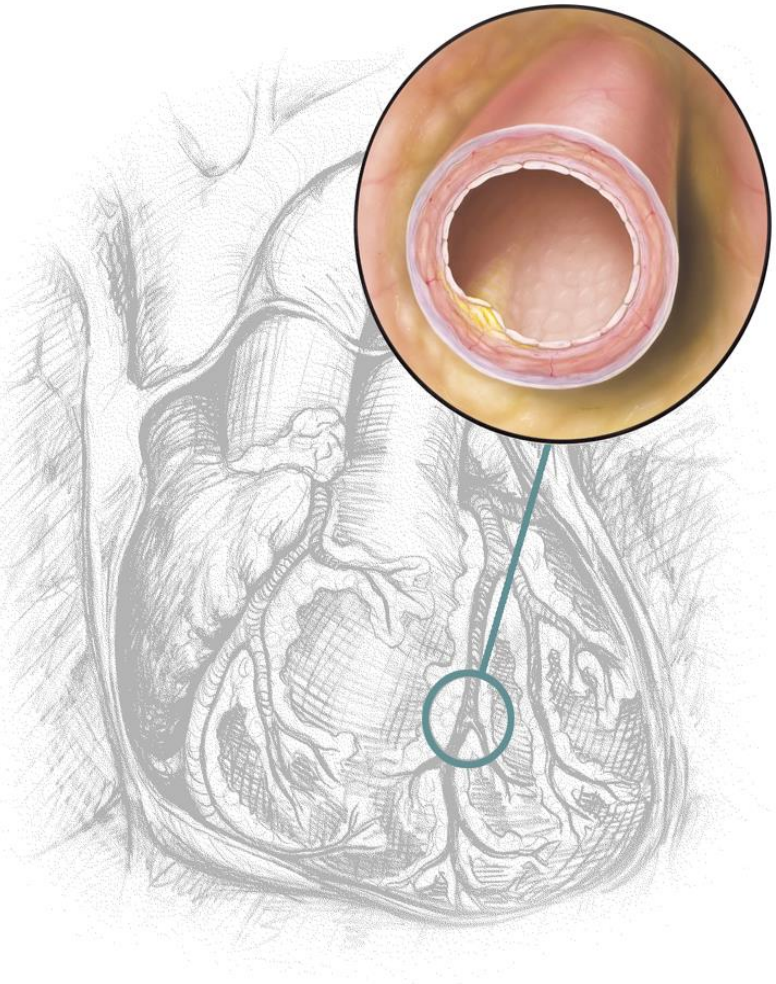
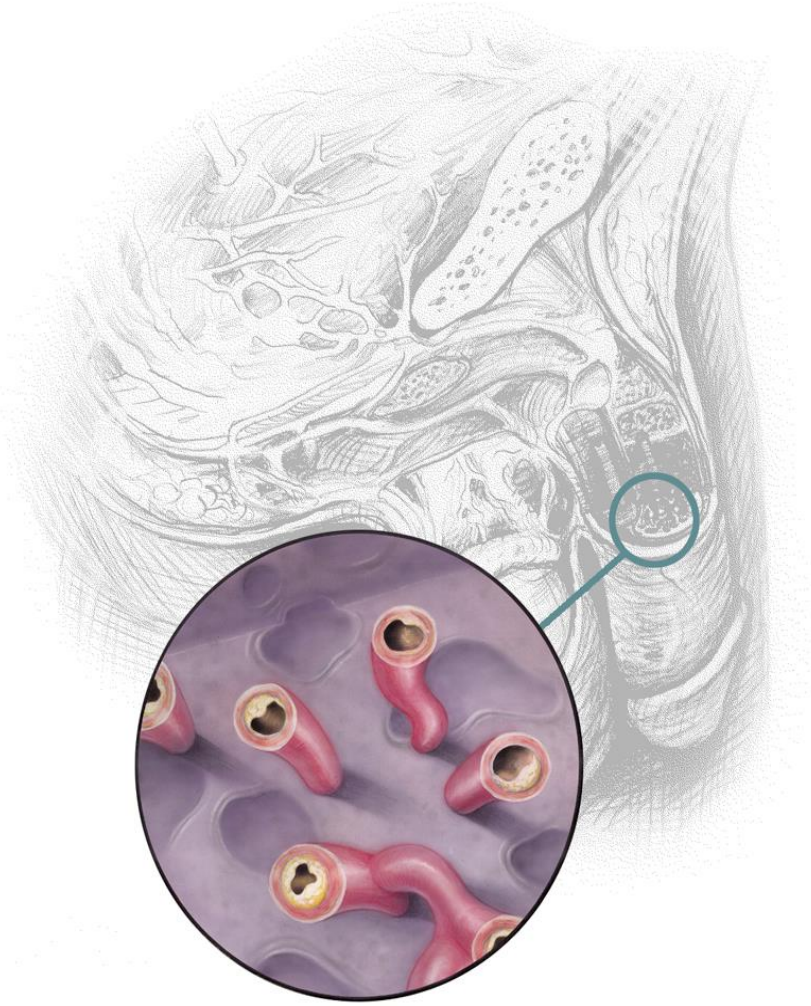


Waist circumference

Atherosclerosis in Coronary Vessels



Atherosclerosis in Penile Arteries



ED Predicts Coronary Events

- A significant proportion of men with erectile dysfunction (ED) exhibit early signs of coronary artery disease (CAD), and this group may develop more severe CAD than men without ED (Level 1, Grade A) [1]

- 1400 men 40-75, with no known CAD 10yr follow up [2]

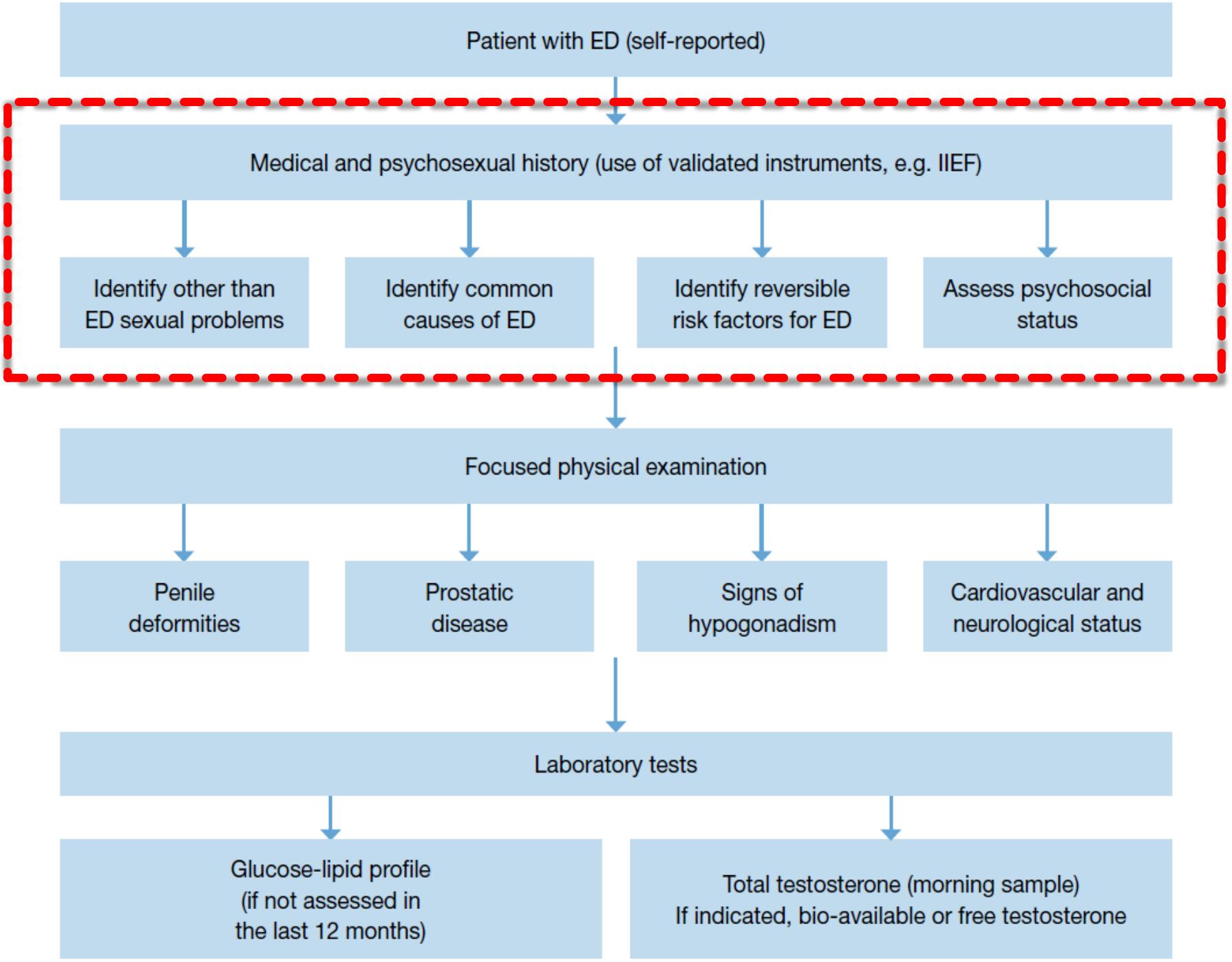
Age Group	CAD events per 1000 pt years with CI interval	
	ED at baseline	No baseline ED
40-49	48.52 (1.23-269.26)	0.94 (0.02-5.21)
50-59	27.15 (7.40-69.56)	5.09 (3.38-7.38)
60-69	23.97 (11.49-44.10)	10.72 (7.62-14.66)
70+	29.63 (19.37-43.75)	23.30 (17.18-30.89)

[1] Jackson et al, IJCP, 2010, 64; 848–857
[2] Inman et al Mayo Clin Pr 2009

Assessment of Man with ED

Case 1 - Michael

- A 54 yr old fit insurance salesman mentions sexual difficulties
- What would you like to know?


Patient with ED (self-reported)
Medical and psychosexual history (use of validated instruments, e.g. IIEF)
Identify other than ED sexual problems
Identify common causes of ED
Identify reversible risk factors for ED
Assess psychosocial status
Focused physical examination
Penile deformities
Prostatic disease
Signs of hypogonadism
Cardiovascular and neurological status
Laboratory tests
Glucose-lipid profile (if not assessed in the last 12 months)
Total testosterone (morning sample) If indicated, bio-available or free testosterone

Sexual History

- Clarify exactly what the patient's symptoms are
- **Some men confuse ED with disorders of ejaculation, orgasm or desire**
- The basic elements of the sexual history are as follows:
  - Nature of the problem
  - Psycho-social context of the problem
  - Chronology of the problem
  - Severity of the problem
  - Success with prior treatment
  - Definition of patient's needs and expectations

Psychogenic versus Organic ED

- Organic ED usually
  - Has gradual onset
  - Is constant
  - Affects non-coital erections
  - Occurs under all circumstances

- Psychogenic ED usually
  - Is sudden in onset
  - Situational with varying degrees of ED under different circumstances
  - Is associated with the presence of nocturnal or early morning erections

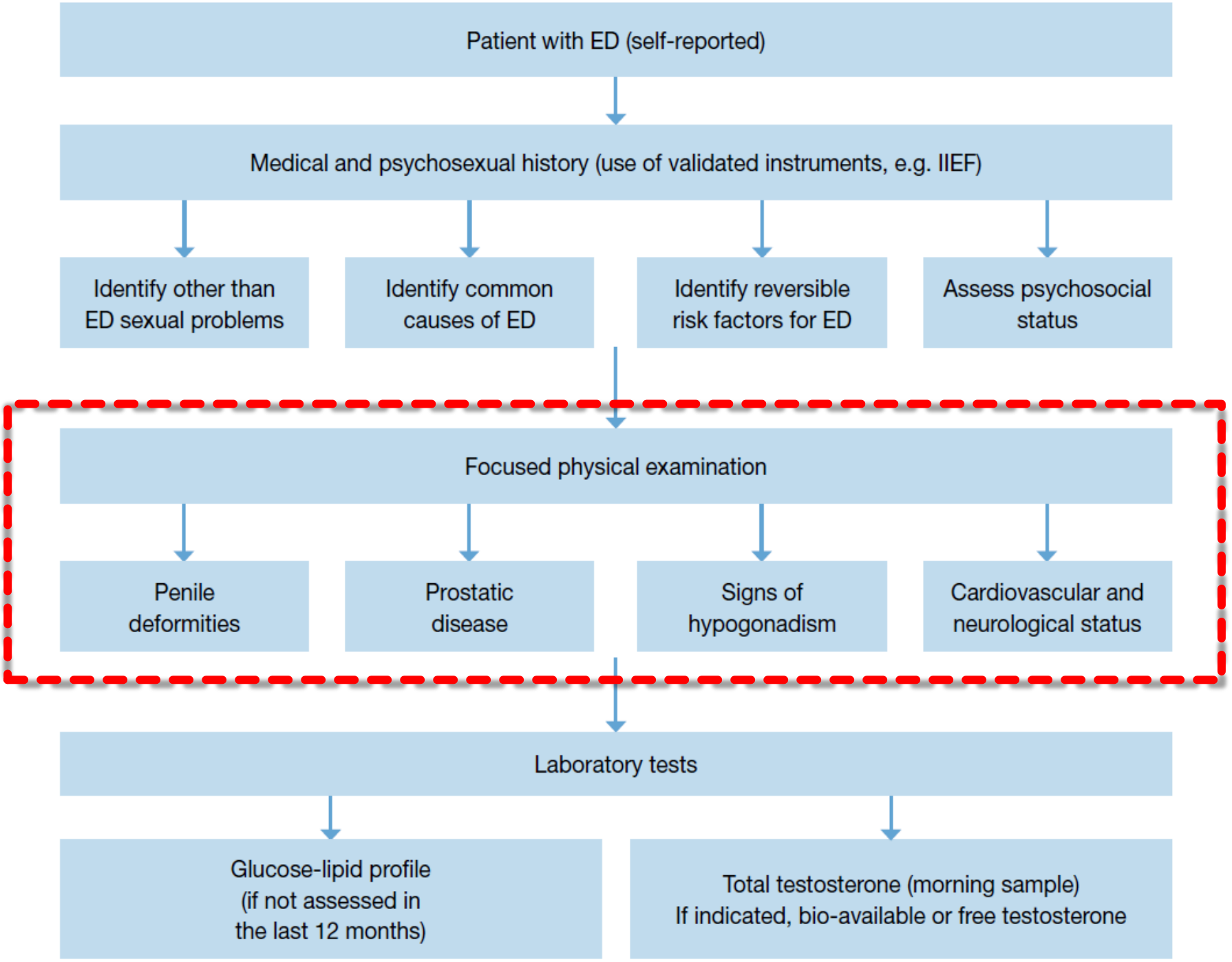
Medical History

- Ageing
- Hypertension
- Arteriosclerosis
- Diabetes mellitus
- Smoking
- Depression
- Dyslipidaemia
- Pelvic / Perineal / penile trauma or surgery
- Neurological illness
- Endocrine disease
- Prescription and recreational drugs

Drug type	Drug or class of drug	Effect
Antihypertensive drugs	Diuretics Beta blockers Centrally acting anti-hypertensive agents eg clonidine, methyl DOPA	ED ED ED
Centrally acting agents	Phenothiazines Butyrophenones Serotonin reuptake inhibitors Tricyclic antidepressants Phenytoin	ED, Reduced libido, Ejaculatory dysfunction ED ED, Ejaculatory dysfunction ED, Reduced libido ED, Reduced libido
Endocrine drugs	LHRH analogues Antiandrogens Oestrogens	ED, Reduced libido ED, Reduced libido ED, Reduced libido
Recreational drugs	Alcohol Marijuana Cocaine Opiates Amphetamines Anabolic steroids	ED, Reduced libido, Ejaculatory dysfunction ED ED ED, Reduced libido Reduced libido, Ejaculatory dysfunction ED, Reduced libido
Other drugs	Cimetidine Metoclopramide Digoxin	ED, Reduced libido ED, Reduced libido ED

Case 1 - Michael

- A 54 yr old fit insurance salesman mentions sexual difficulties
- He has had difficulty maintaining erection his erections for 12 months but worse last 3 months
- Night-time and early morning erections are absent
- He is happily married
- He is hypertensive and uses Ramipril 5mg
- What would you do?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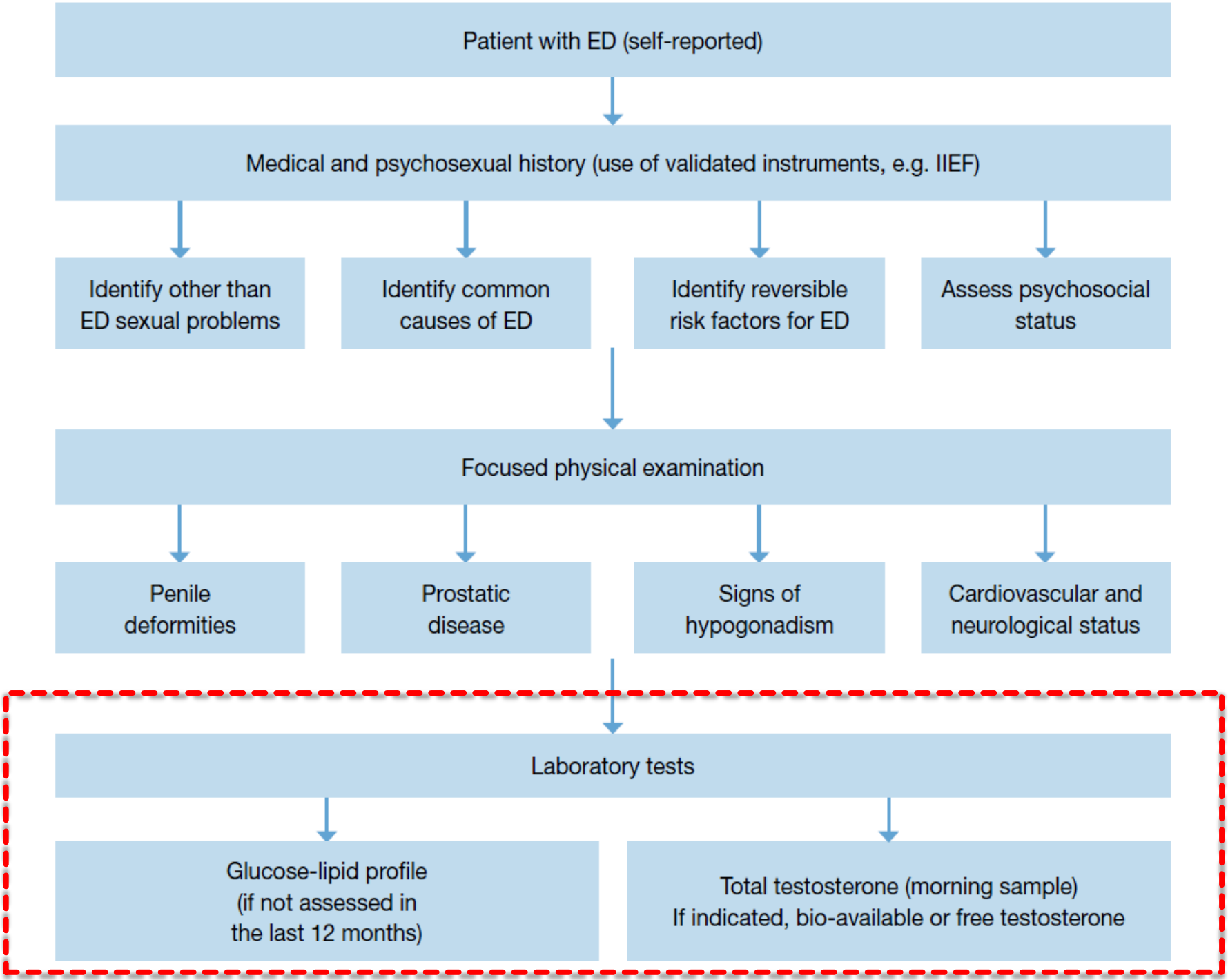
Case 1 - Michael

- A 54 yr old fit insurance salesman with 6 month's hypertension on Ramipril 5mg. Mentions difficulty maintaining erection for 12 months but worse last 3 months.
- Examination shows that he is overweight (BMI 30)
- BP 130/80
- What would you do?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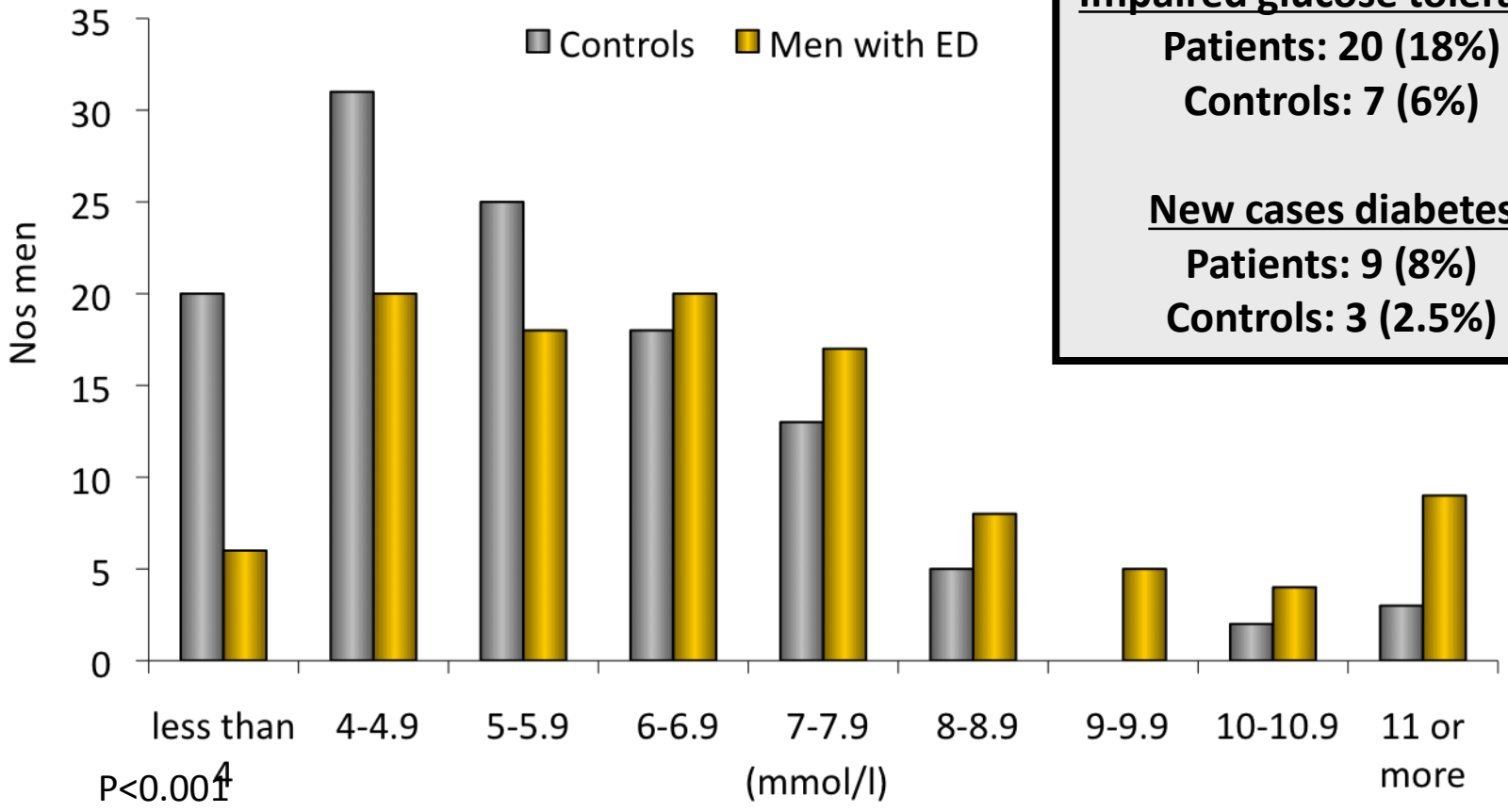
120 Minute Glucose

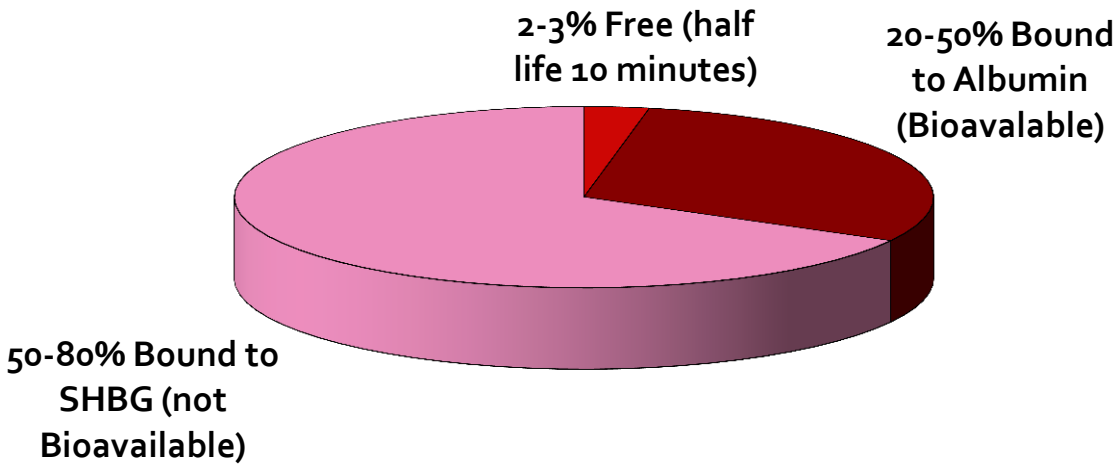


Impaired glucose tolerance
Patients: 20 (18%)
Controls: 7 (6%)

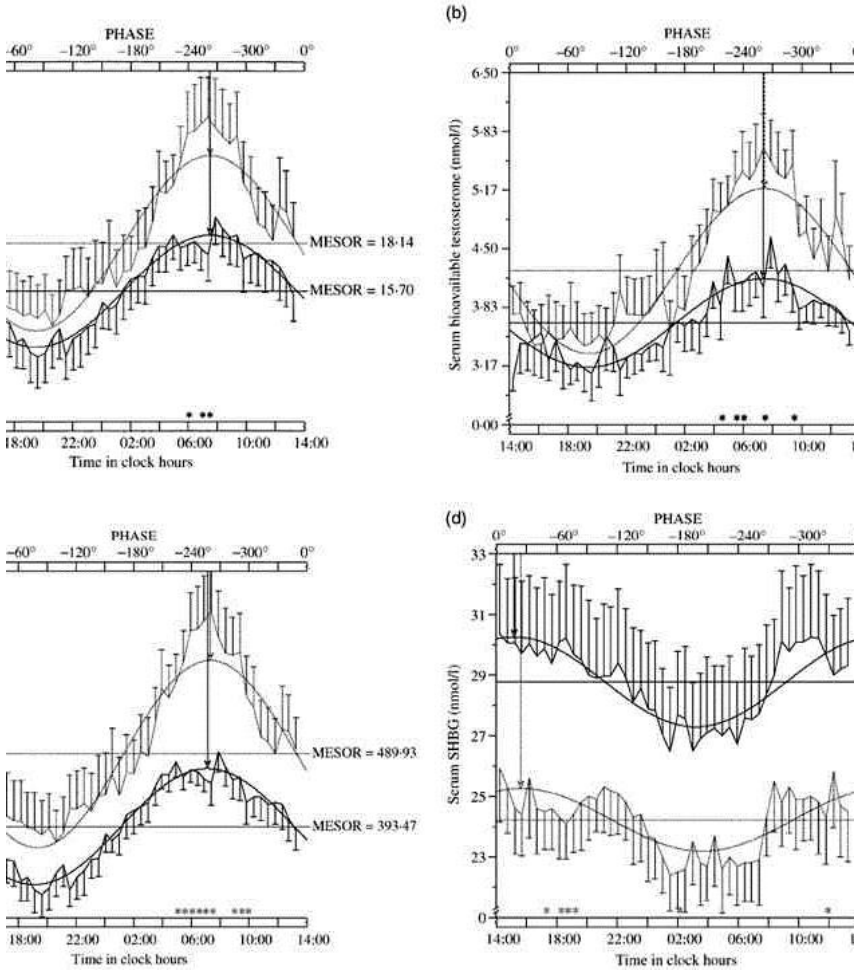
New cases diabetes
Patients: 9 (8%)
Controls: 3 (2.5%)

Baldo et al, EAU, 2008

Clinical Physiology of Testosterone



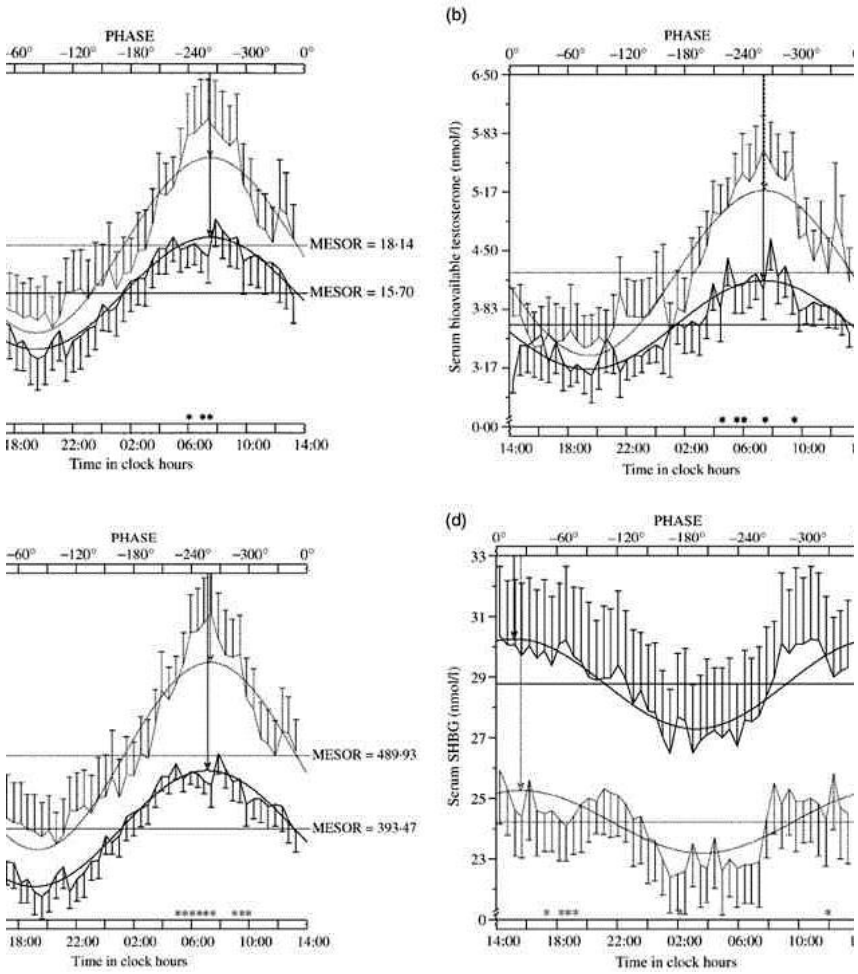
Total Testosterone



- There is no <u>generally accepted</u> lower limit of normal
- There is general agreement that
  - levels above 12nmol/l do not require substitution
  - levels below 8nmol/l will usually benefit from substitution

Wang et al, Eur Urol, 55: 121-130, 2009,

Free Testosterone



- If the level is between 8 and 12 nmol/l, then measured or calculated free testosterone may be helpful ***(Level 2b, Grade A)***
- Free testosterone levels less than 225 pmol/l can provide supportive evidence for testosterone replacement ***(Level 3, Grade C)***

Wang et al, Eur Urol, 55: 121-130, 2009,

Free & Bioavailable Testosterone calculator

www.issam.ch

These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole measurement of total serum testosterone. Testosterone and dihydrotestosterone (DHT) circulate in plasma unbound (free approximately 2 - 3%) ,bound to specific plasma proteins (sex hormone-binding globulin SHBG) and weakly bound to nonspecific proteins such as albumin. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Free testosterone measures the free fraction, bioavailable testosterone includes free plus weakly bound to albumin.

Albumin	4.3	g/dL
SHBG	50	nmol/L
Testosterone	13.1	nmol/L

Calculate

Explanation and examples

Free Testosterone	0.202 nmol/L = 1.54 %
Bioavailable Testosterone	4.74 nmol/L = 36.2 %

Disclaimer: Results from this calculator should NOT be solely relied upon in making (or refraining from making) any decision in any case/ circumstances without the prior consultation of experts or professional persons. No responsability whatsoever is assumed for its correctness or suitability for any given purpose.

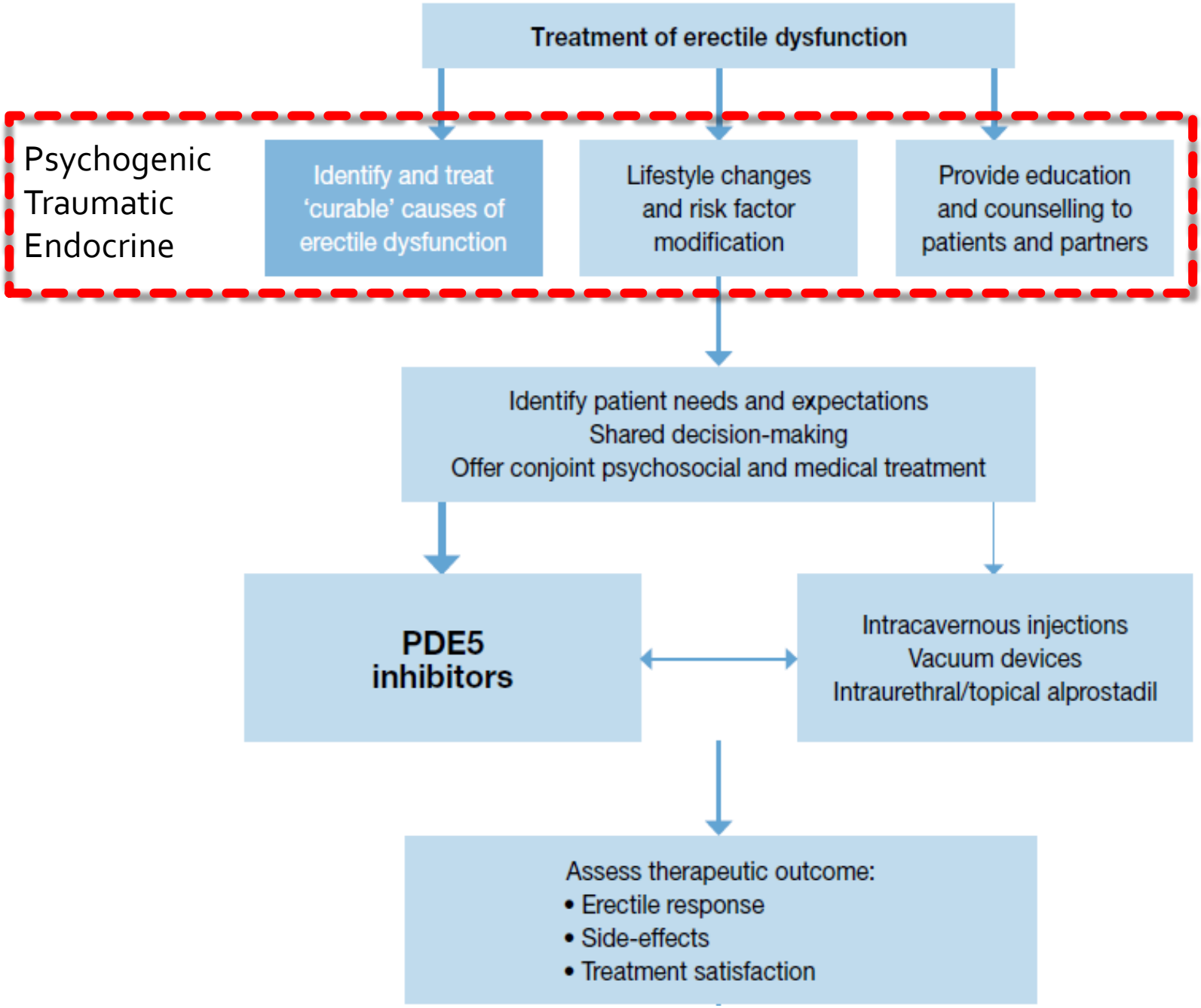
WARNING! The calculated free and bioavailable testosterone are reliable in most clinical situations, but should not be relied upon in situations with potential massive interference by steroids binding to SHBG; e.g. in women during pregnancy, in men during treatment inducing high levels of DHT (e.g. transdermal DHT, oral testosterone) or mesterolon

This calculator was developed at the Hormonology department, University Hospital of Ghent, Belgium. If you have suggestions to improve this calculator, or for further questions or help contact us Dr. Tom Fiers or Prof. Dr. J.M. Kaufman

Medical Management ED

Case 1 - Michael

- A 54 yr old fit insurance salesman (BMI 30) with 6 month's hypertension on Ramipril 5mg. Mentions difficulty maintaining erection for 12 months but worse last 3 months.
- Examination NAD. BP 130/80
- Bloods
  - FBG; 5.2
  - TC; 6.0, LDL; 3.7,
  - TT; 14.2nmol/l, PSA 0.7
- What would you do?


Treatment of erectile dysfunction
Psychogenic
Traumatic
Endocrine
Identify and treat 'curable' causes of erectile dysfunction
Lifestyle changes and risk factor modification
Provide education and counselling to patients and partners
Identify patient needs and expectations
Shared decision-making
Offer conjoint psychosocial and medical treatment
PDE5 inhibitors
Intracavernous injections
Vacuum devices
Intraurethral/topical alprostadil
Assess therapeutic outcome:
• Erectile response
• Side-effects
• Treatment satisfaction

Case 1 - Michael

- Ramipril changed to Losartan 150mg
- Commenced on simvastatin 40mg
- Exercise and life style advice
- Erections returned to normal within 4 weeks with complete spontaneity in relationship.
- Learning points ; Early detection of ED can be treated with risk and lifestyle management without the need for ED specific medication

Risk Factors

	Effect	Cause	Treatment
Hypertension	The risk of ED is twice that of a normotensive man of the same age	Endothelial dysfunction Atherosclerosis	Antihypertensives
Diabetes	The risk of ED is twice that of a non diabetic man of the same age	Endothelial dysfunction Atherosclerosis Neuropathy hypogonadism	Diabetic treatment Weight loss
Dyslipidaemia	For men under 55 yrs there is no effect For men over 55 the risk of ED is almost doubled	Endothelial dysfunction Atherosclerosis	Statins

Risk Factor Modification

Antihypertensive drugs	Effect on erectile function
Central acting	- - -
Diuretics	- -
Beta-blockers	-
Calcium antagonists	±
ACE-inhibitors	±
Alpha-blockers	+
Angiotensin receptor blockers	+ +

- Hypertension
  - Most antihypertensive agents increase risk of ED (by around 20%)
    - Certainly beta blockers and thiazides
  - Angiotensin II inhibitors (ARBs) probably improve erectile function [2-4]
    - Mechanism probably improved penile SM relaxation due to Ang II

[1] Saltzman et al, J Urol. 172:255-8, 2004
[2] Caro et al, JAMA, 2000, 283: 2013-2014
[3] Dusing et al, Blood press suppl, 2003, 2: 29-34
[4] Baumhakel et al, IJIR, 2008, 20: 493-500
[5] Romeo et al, J Urol, 2005
[6] Do et al, Drug Safety. 32(7):591-7, 2009
[7] Hermann et al, JSM. 3:303-8, 2006

From: **The Effect of Lifestyle Modification and Cardiovascular Risk Factor Reduction on Erectile Dysfunction: A Systematic Review and Meta-analysis**

Arch Intern Med. 2011;171(20):1797-1803. doi:10.1001/archinternmed.2011.440

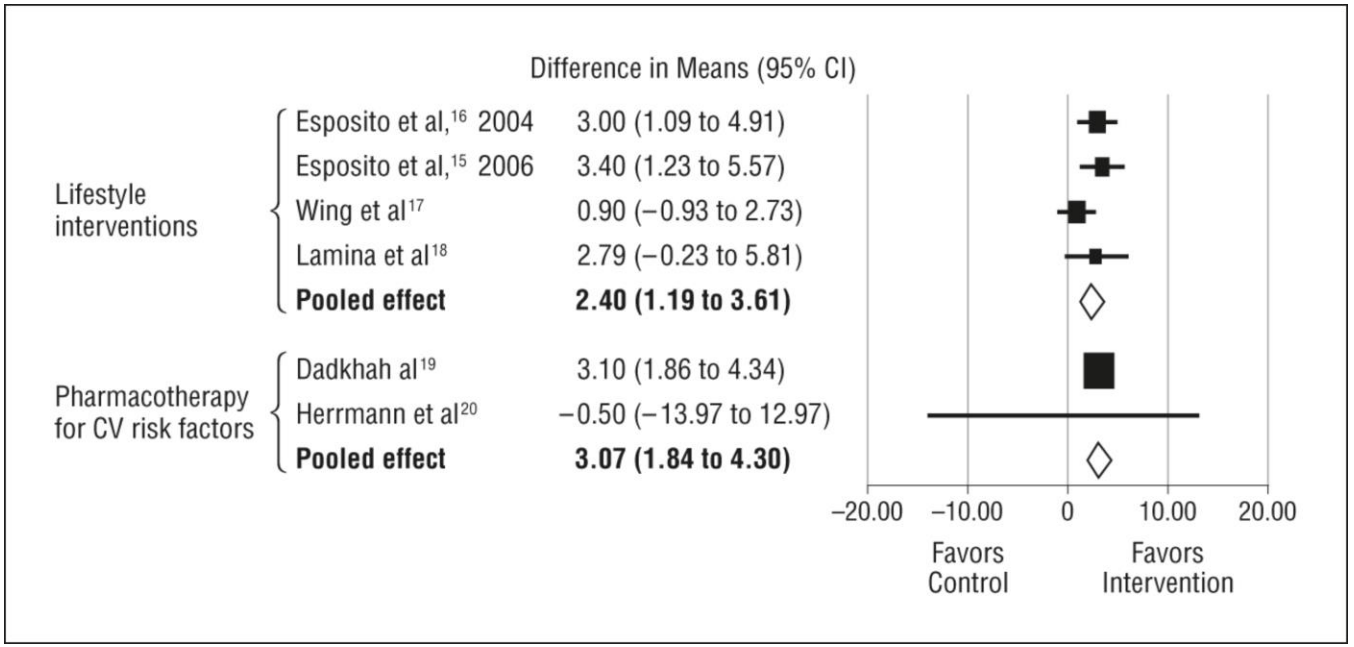
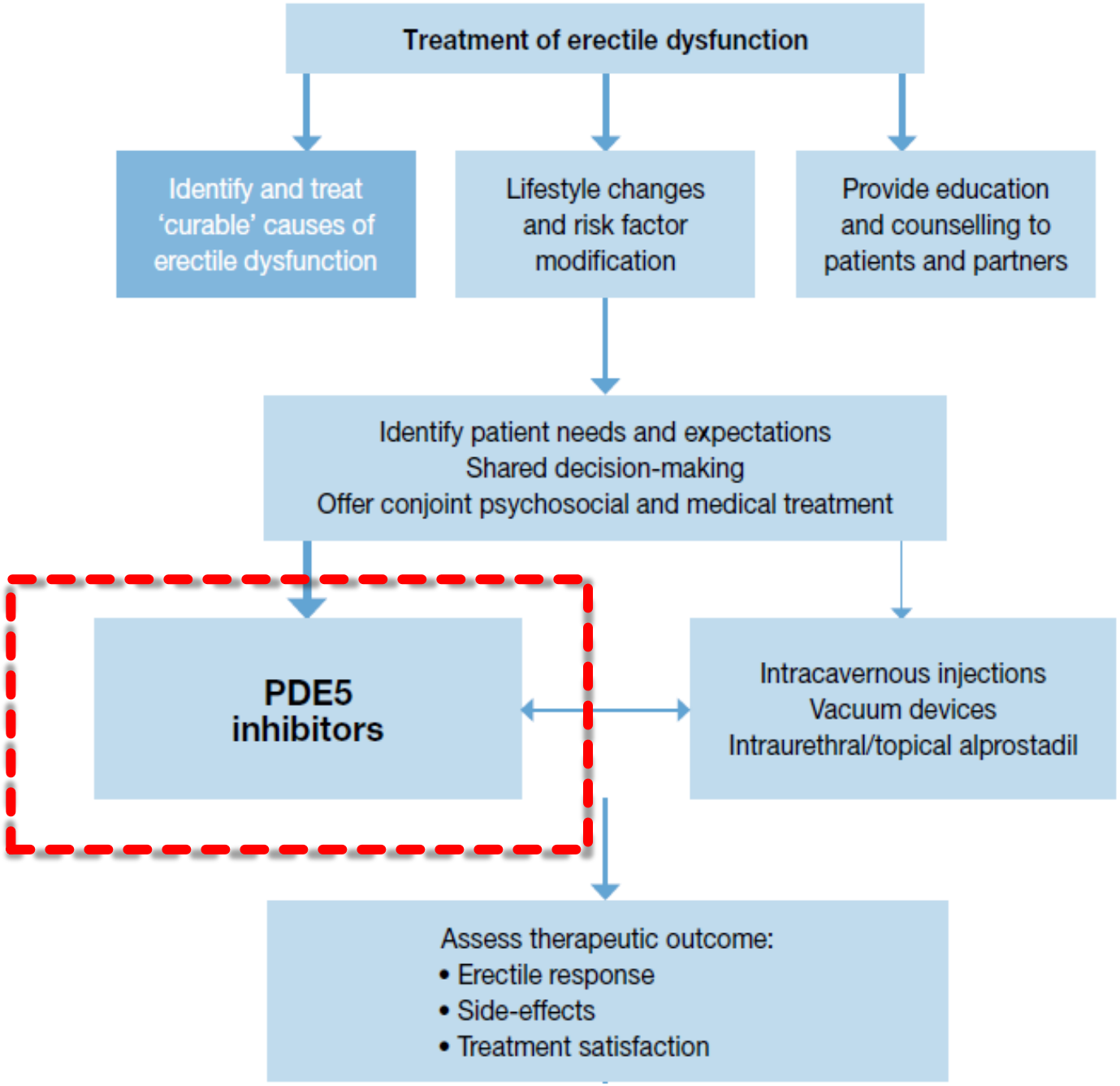


Figure Legend:

Figure 3. Forest plot shows the standardized difference in means of International Index of Erectile Dysfunction (IIEF-5) score after lifestyle intervention only and pharmacotherapy for cardiovascular (CV) risk factors.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• Side-effects
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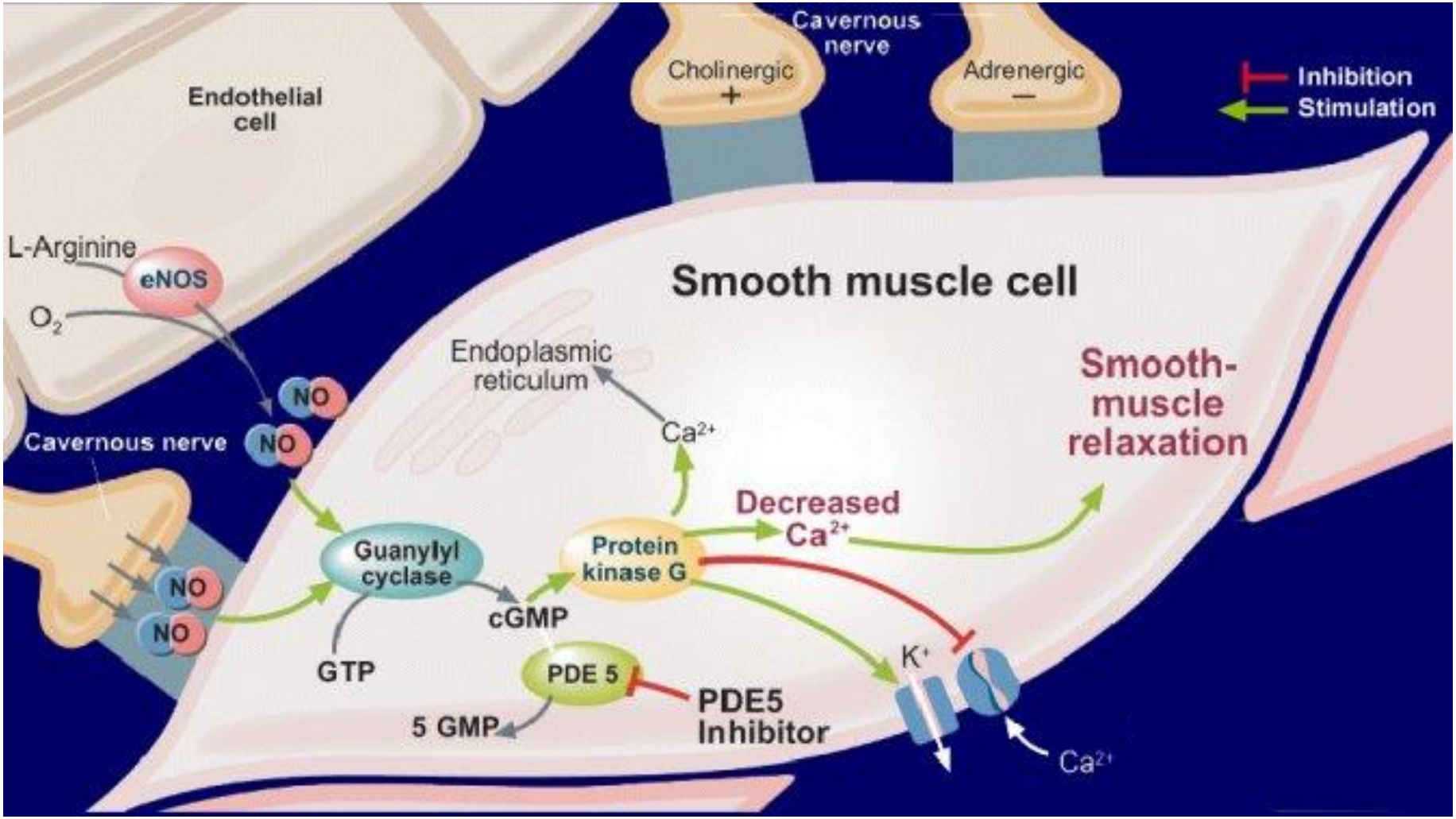
Physiology and PDE5 Inhibitors



PDE5i: Efficacy

	Efficacy Successful Intercourse (SEP3)	
	Broad population	Diabetes
Sildenafil	69%	59%
Tadalafil	68%	48%
Vardenafil	68%	54%
Avanafil	57%	40%

Goldstein et al, NEJM, 1998

Hatzichristou et al, Eur Urol, 2003

Carson et al, BJUI, 2004

Boulton et al, Diabet, 2001

Saenz de Tejada et al, Diabet Care, 2004

Goldstein et al, Diabet, 2003

Goldstein et al, JSM, 2012

Goldstein et al, Mayo Clin Proc, 2012

Pharmacology of the PDE5i's Pharmacokinetics

	Sildenafil	Vardenafil	Tadalafil	Avanafil
T max (hrs)	1.16	0.66	2.0	0.6
T ½ (hrs)	3.82	3.94	17.5	1.5-5

PDE5i: Tolerability

- Headache 10-15%
- Flushing 5-10%
- Indigestion 5-15%
- Nasal congestion 3-10%
- Blue vision 0-5% (Sildenafil)
- Back pain 5-10% (Tadalafil)

Practical Issues

- Generic issues
  - Sexual stimulation
  - Delay between taking drug and intercourse
  - Side effects
  - Nitrates and alpha blockers
- Drug specific issues
  - Cost
  - Other indications (LUTS)
  - Timing of dosing
  - Duration of action
  - Food interactions
  - Drug interactions

Salvaging the PDE5 Non-Responder

- 20-60% patients fail to respond to PDE5i
- Salvage techniques include:
  - Dose titration – use the top dose
  - Correct timing – initially be conservative
  - Food issues – initially use on empty stomach
  - Risk factor management
  - Testosterone
  - Continuous dosing
  - Alternative therapies

Testosterone and the Treatment of ED

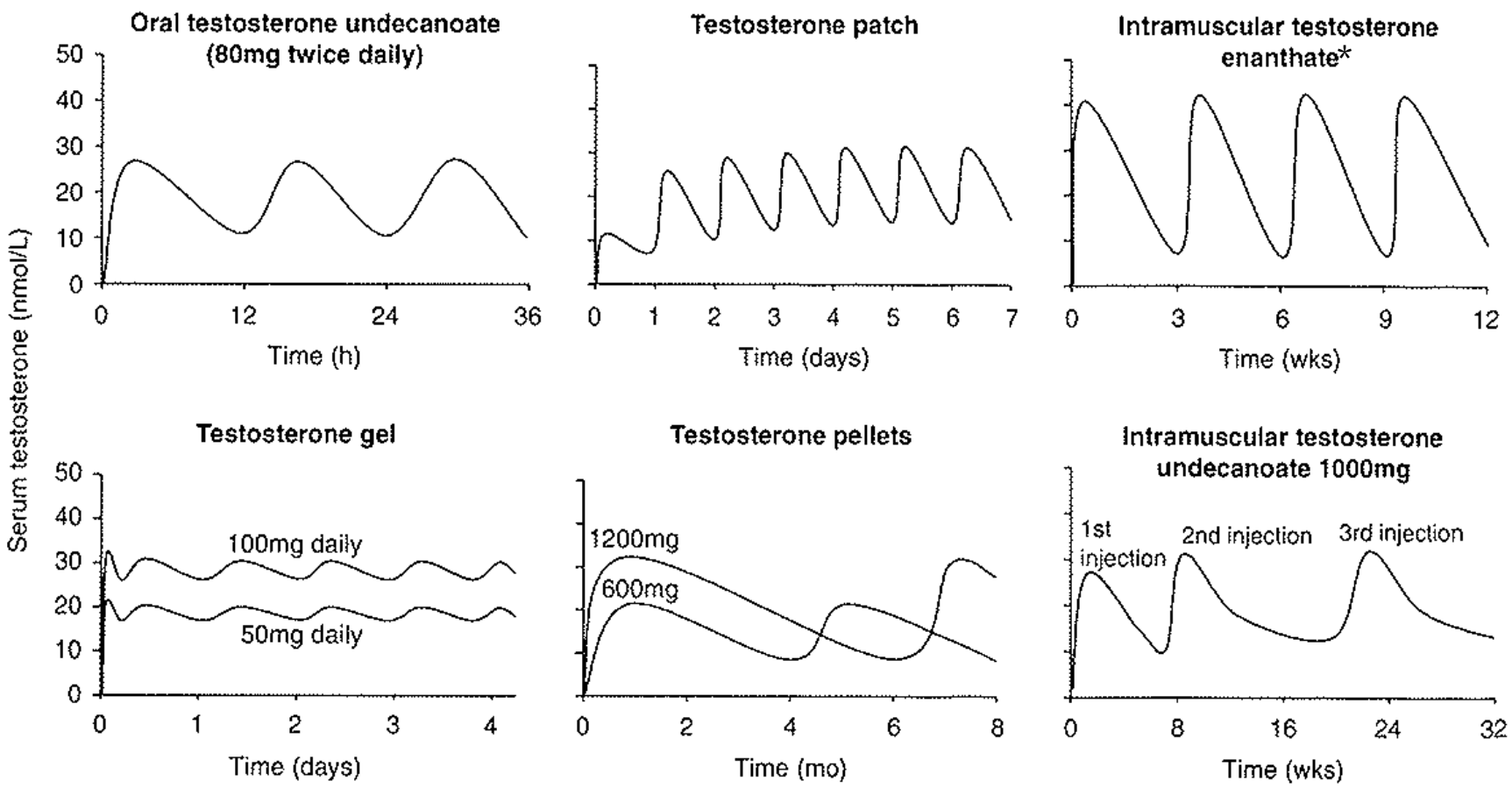
Testosterone: Indications

- Primary and Secondary hypogonadism
- [Late onset hypogonadism]

Testosterone Therapy Contraindications

- Controversial
- (Established prostate cancer)
- Breast cancer
- Erythrocytosis (PCV > 50%)
- Sleep apnoea
- (Severe LUTS)

Pharmacokinetics of Testosterone



*Testosterone enanthate is not available in the UK. It is a 250mg 3-weekly injection, which is the most widely-used testosterone therapy in Europe

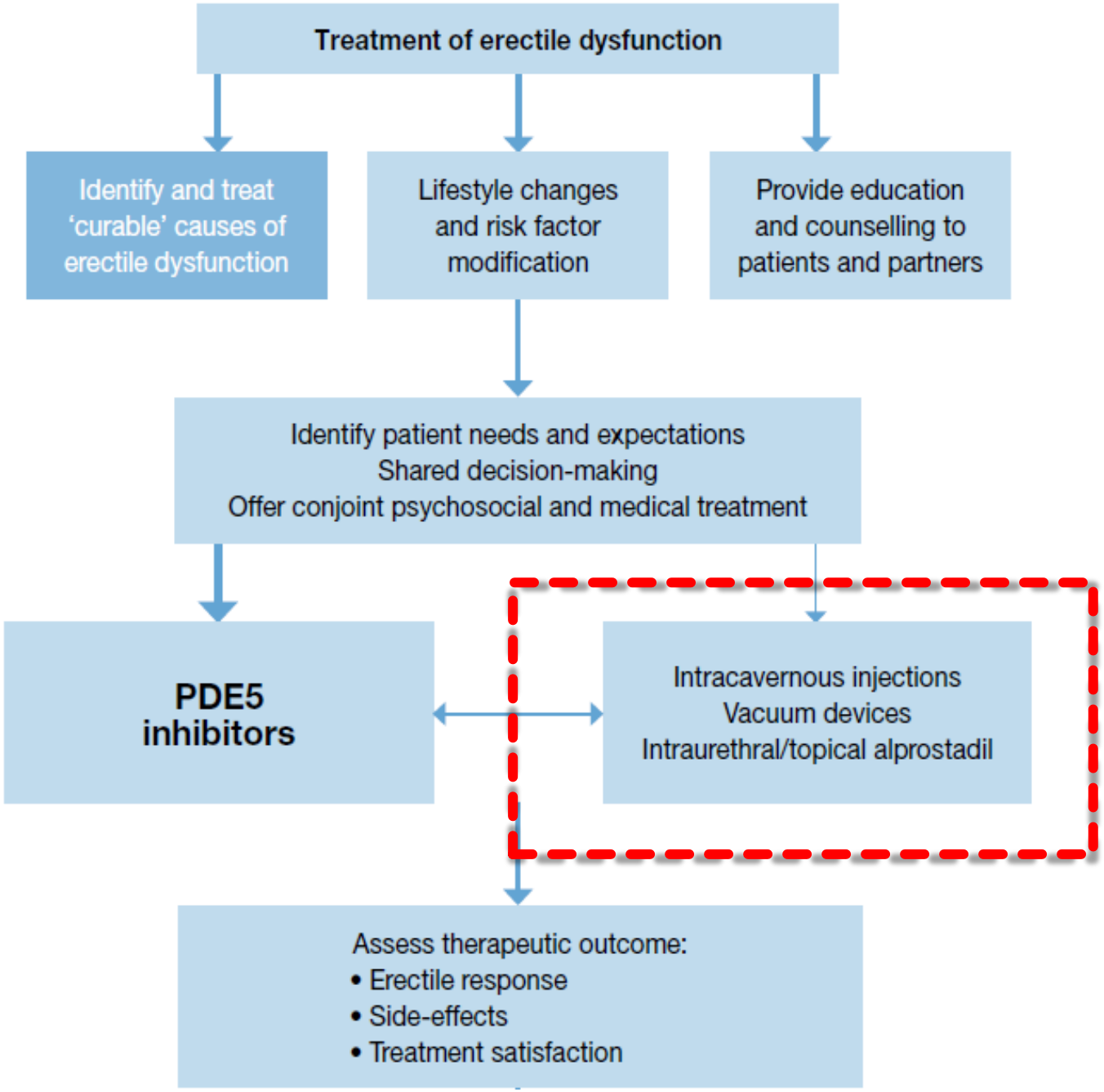
1. Gooren LJG et al. *Drugs* 2004.64(17):1861-1891.

Monitoring

- Symptoms
- DRE
- Testosterone levels
  - After 1 month with gels (at least 4 hours after application)
  - After 6-9 months with injections
- Safety parameters
  - PSA
  - Lipids
  - FBC

Testosterone: Side Effects

- Erythrocytosis
- Acne / Oily skin
- Reduced sperm production and reduced fertility
- Deterioration of pre-existing sleep apnoea
- [Prostate problems]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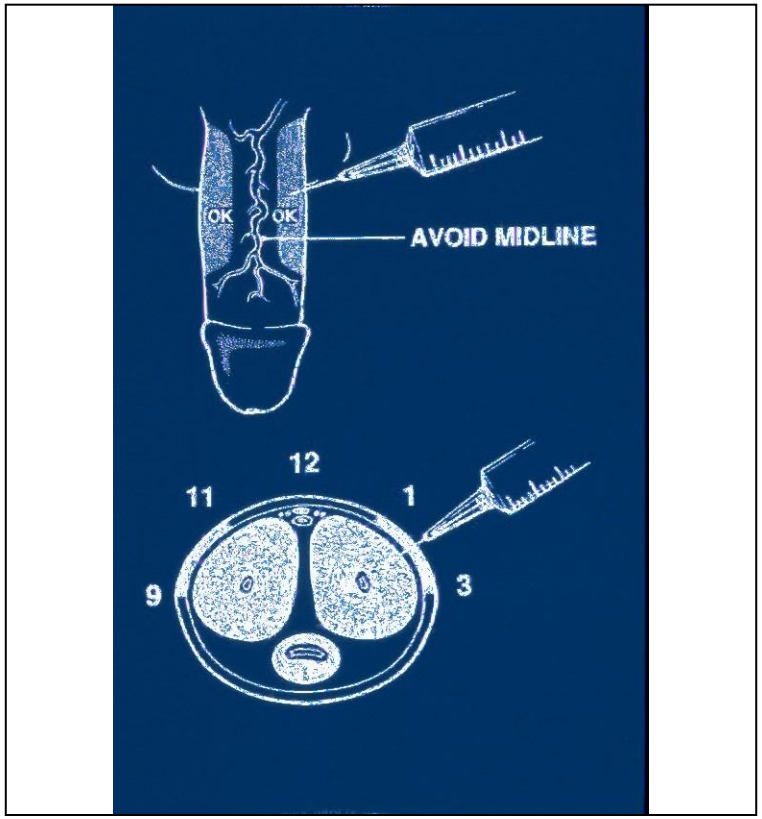
Intracavernosal Alprostadil

Pros

- Effective
- Rigidity
- Reliability

Cons

- Lack of spontaneity
- Invasive
- Complications
- Risk of priapism
- High drop out rate
- Expensive



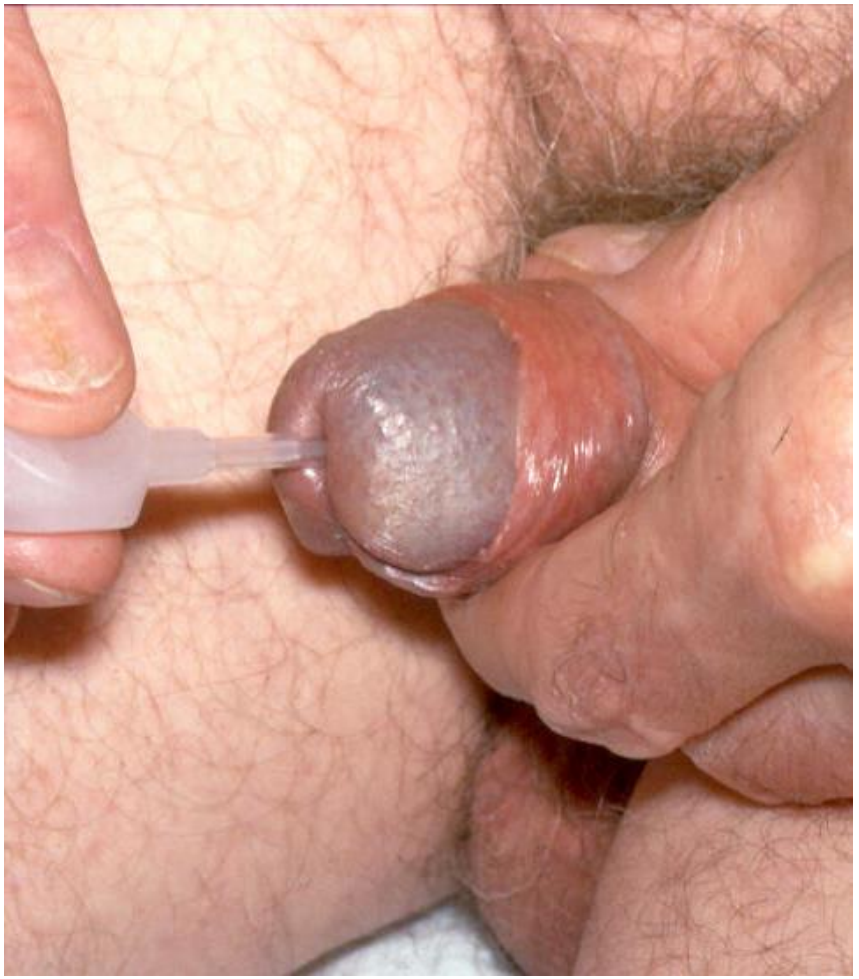
Topical and Urethral Alprostadil

Pros

- Relatively non invasive
- Low complication rates
- Rapidly acting

Cons

- Poor efficacy
- Side effects
  - Flushing, pain, transmission to partner



Vacuum Erection Devices

Pros

- Potentially effective for all
- Non invasive
- Low complication rates
- No restriction of frequency

Cons

- Needs manual dexterity
- Quality of erection
- Side effects
  - Pivoting, Discolouration, Temperature, Bruising, Blocks ejaculation
- Cost

Penile Implants

Pros

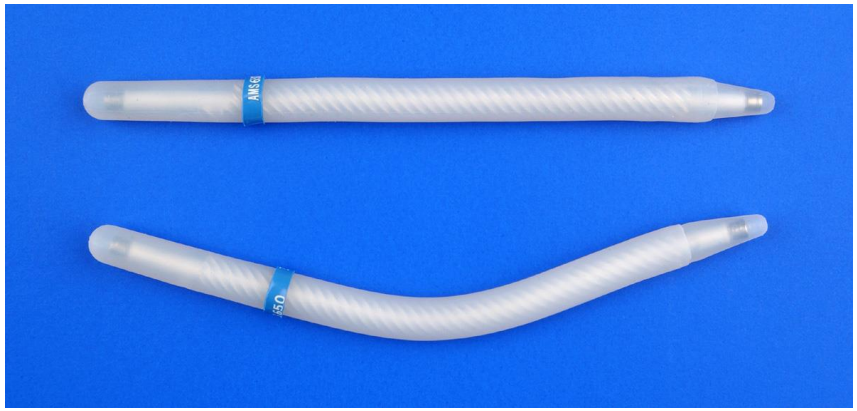
- Efficacy
- Rigidity
- Satisfaction

Cons

- End stage treatment
- Complications
- Cost

Issues

- Expectations
- Needs manual dexterity
- Quality of erection



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- Efficacy
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Conclusion

- ED is a symptom
- Assessment should involve a wider consideration of men's health
- Treatment is effective and escalating
- Consider partner's needs