



# ΚΑΙ ΣΤΥΣΗ



Καθημερινά  
στο  
**2310 992547**  
ραντεβού



Δημήτρης Χατζηχρήστου  
Καθηγητής Ουρολογίας ΑΠΘ



# Φυσιολογία – Παθοφυσιολογία στύσης



# Το ΚΝΣ ελέγχει τη στύση

Εγκεφαλικά κέντρα



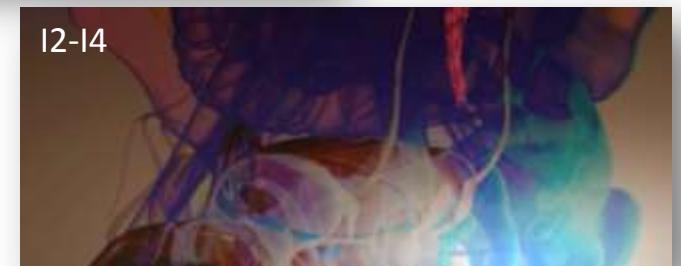
Νωτιαίος μυελός



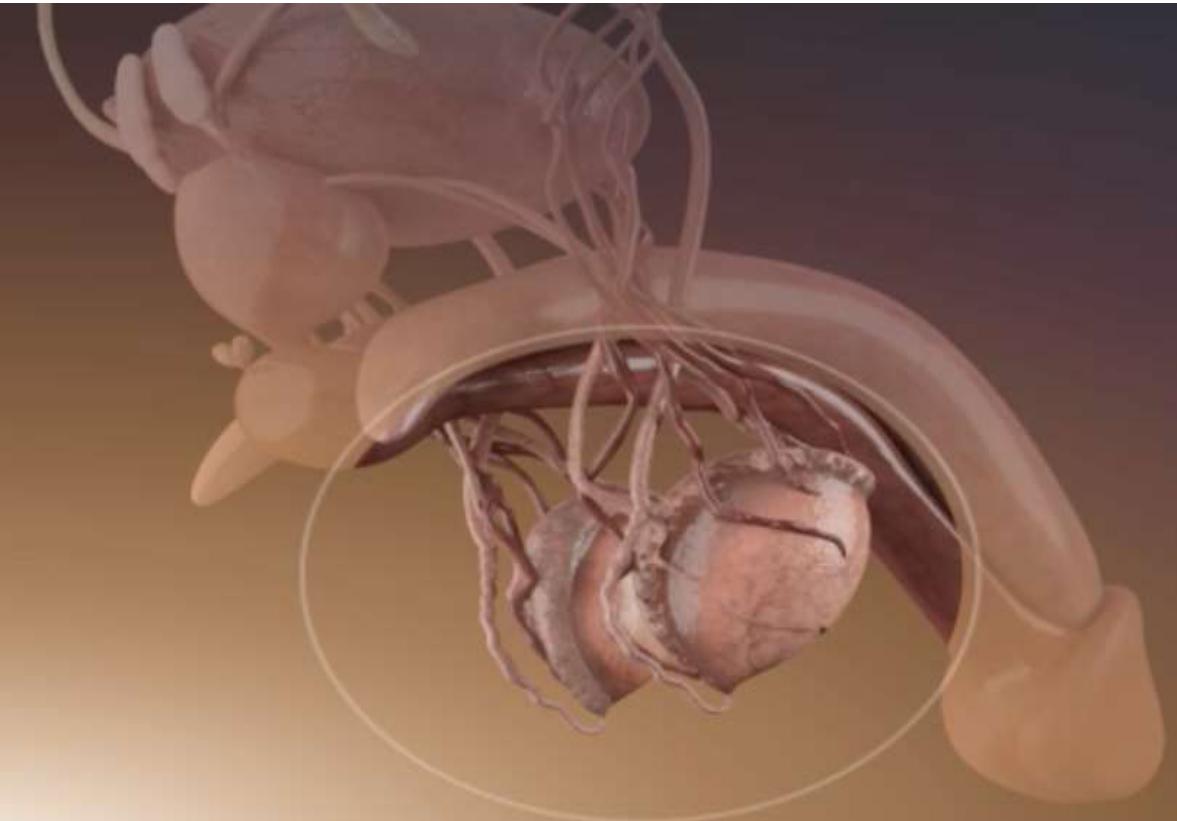
θ11-ο2



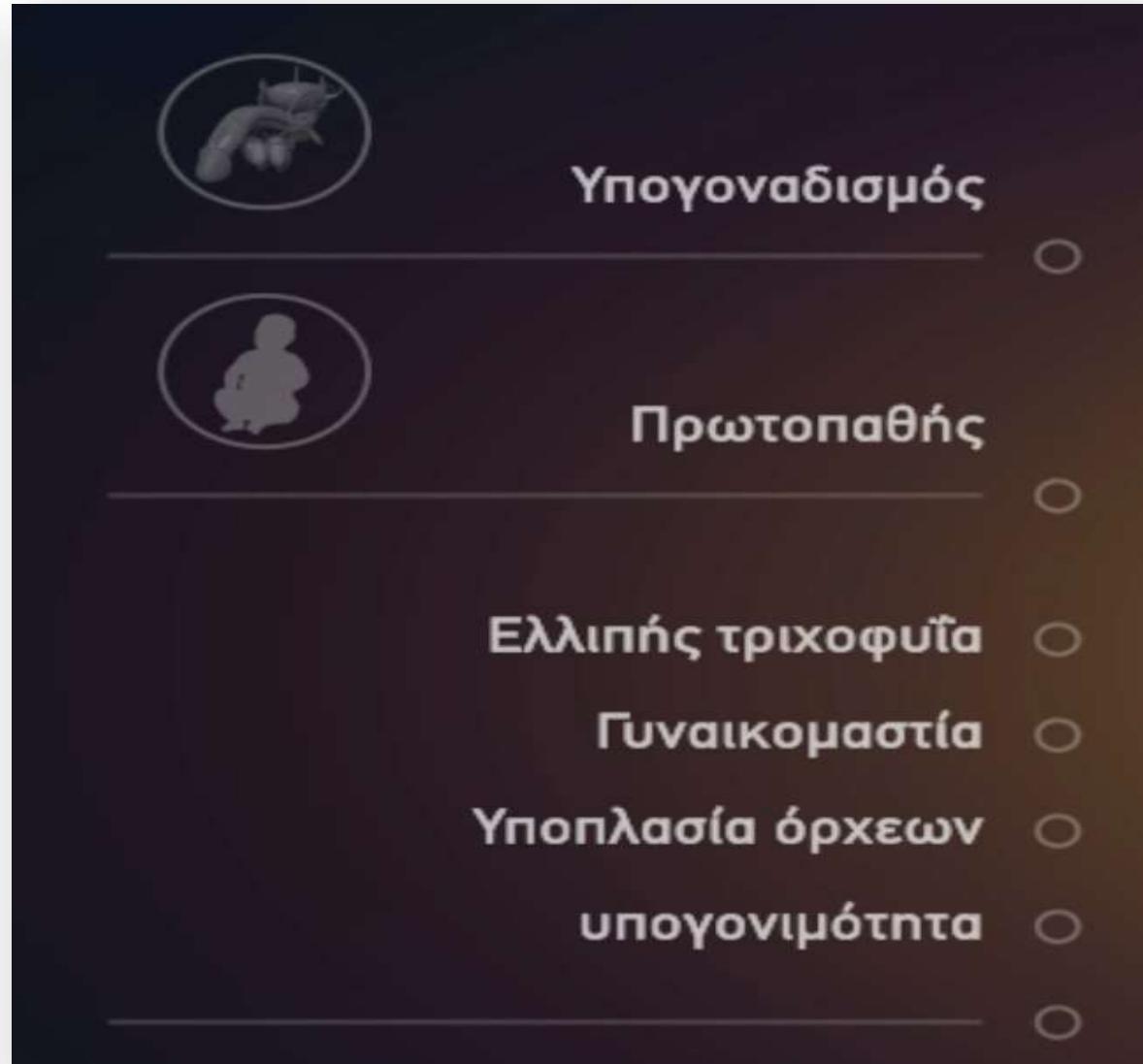
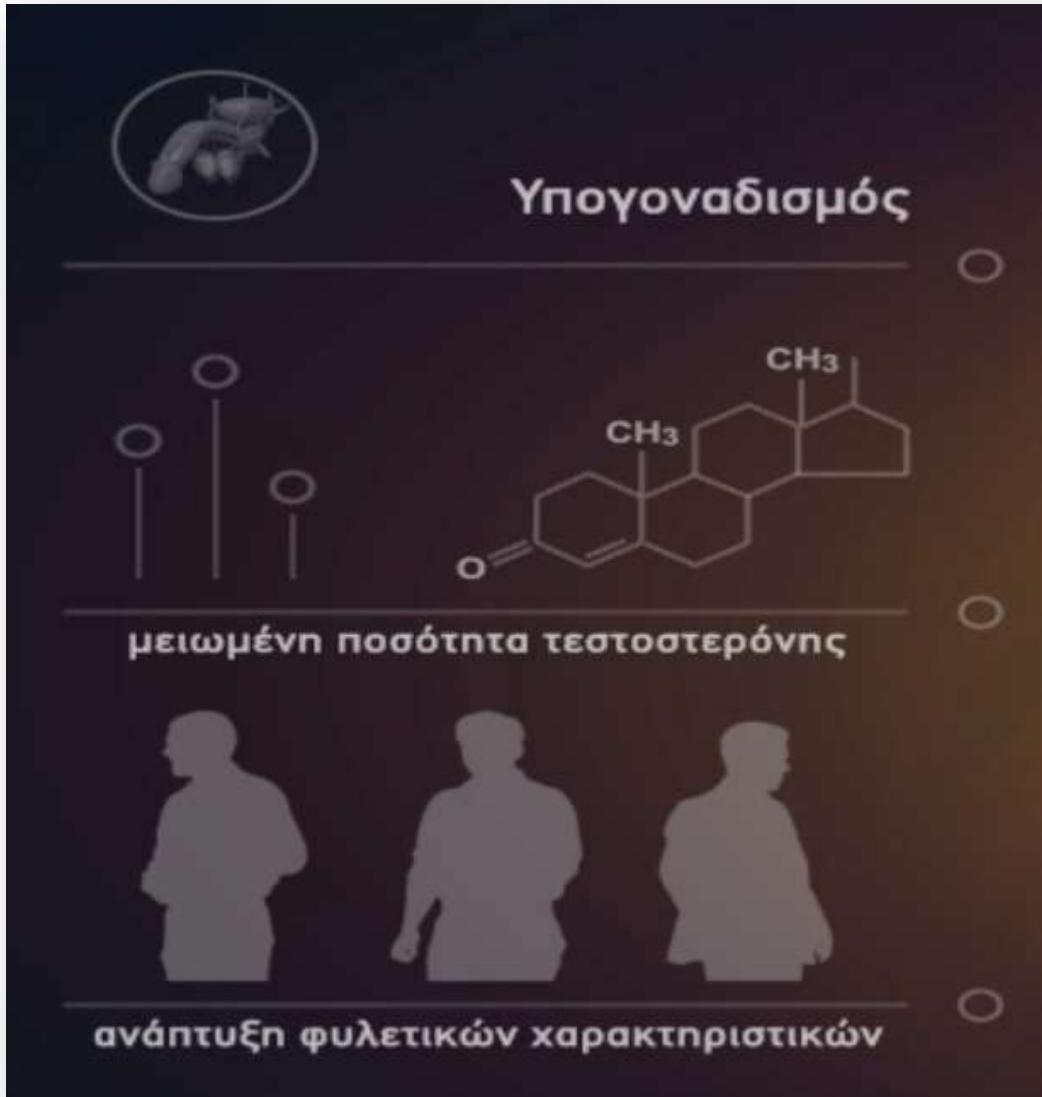
Ι2-Ι4



# Ο κεντρικός έλεγχος

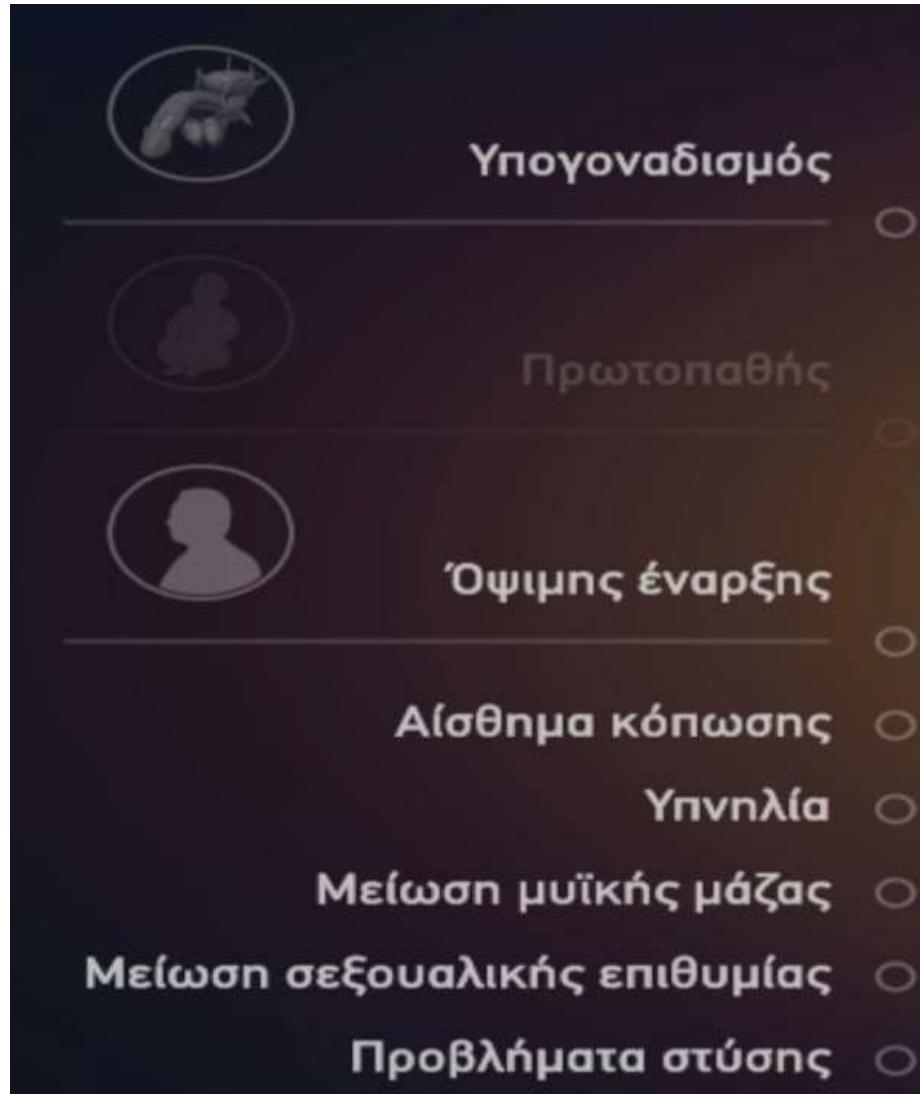


# Υπογοναδισμός

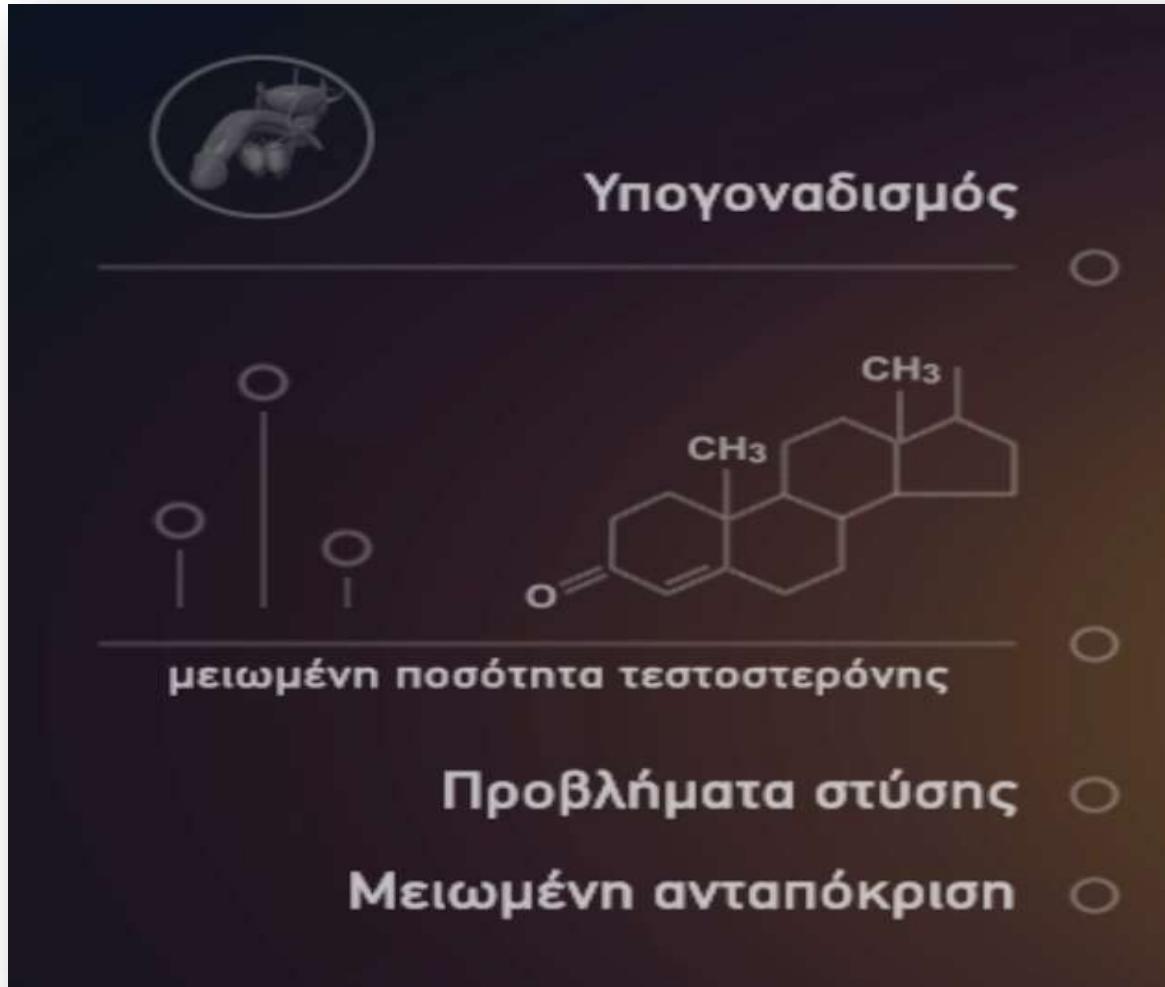




# Όψιμης έναρξης υπογοναδισμός



# Πότε χορηγούμε τεστοστερόνη;



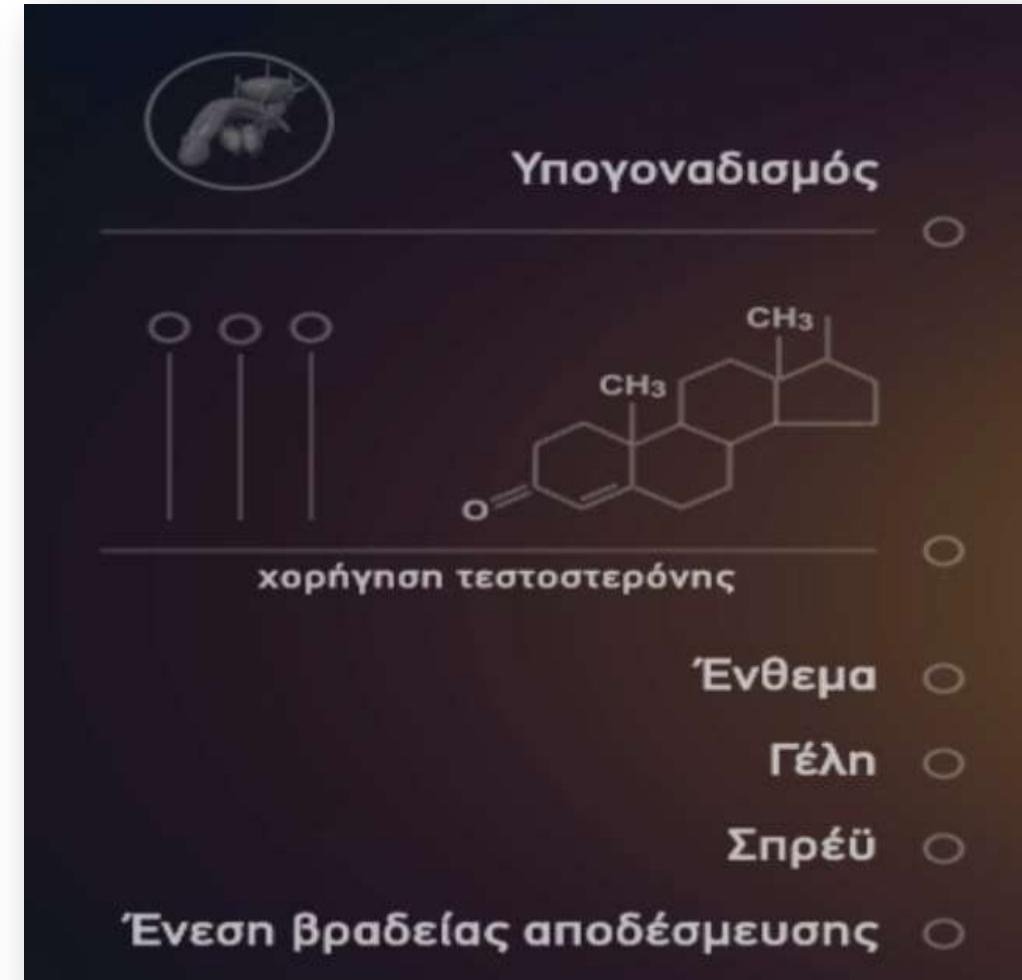
Υπογοναδισμός

μειωμένη ποσότητα τεστοστερόνης

Προβλήματα στύσης

Μειωμένη ανταπόκριση

Chemical structure of Testosterone (C<sub>21</sub>H<sub>30</sub>O<sub>2</sub>):

CC1(C)CCC2=C1C=CC3=C2C=CC(=O)C3

Υπογοναδισμός

χορήγηση τεστοστερόνης

Ένθεμα

Γέλη

Σπρέϋ

Ένεση βραδείας αποδέσμευσης

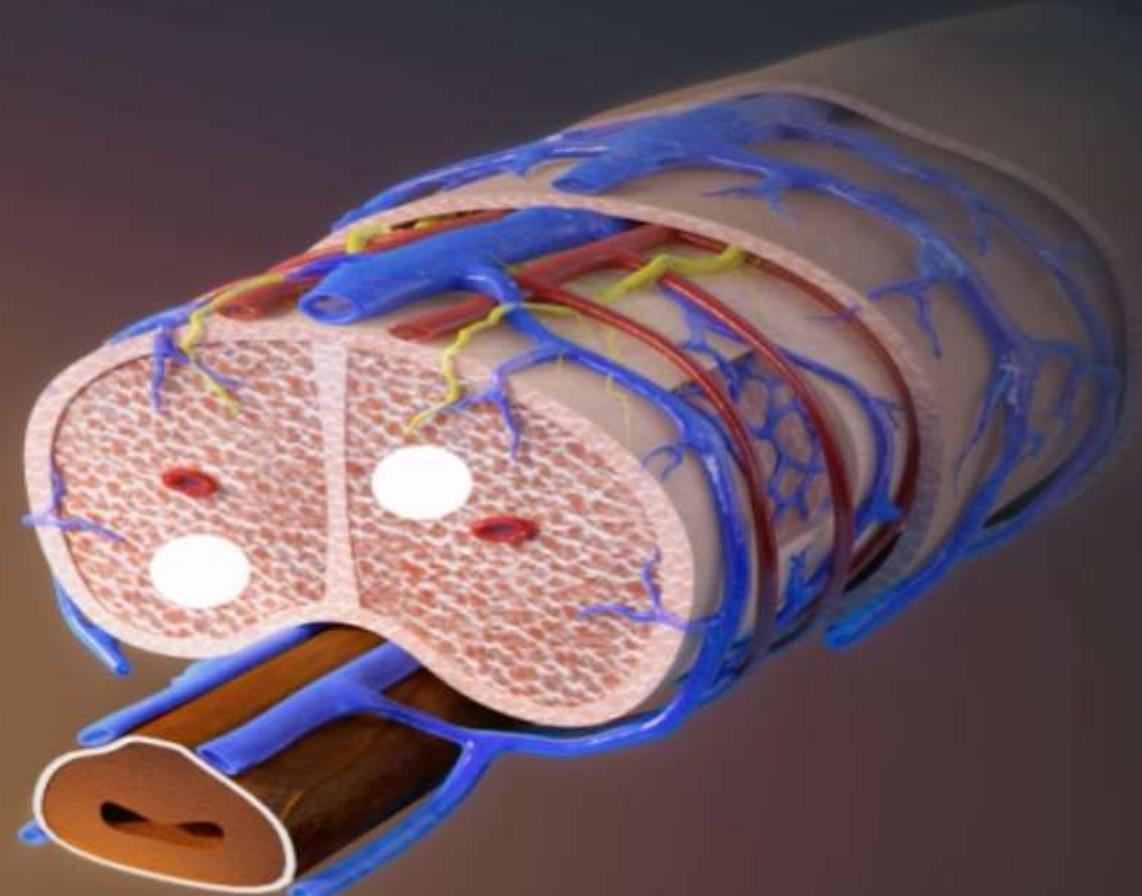
Chemical structure of Testosterone (C<sub>21</sub>H<sub>30</sub>O<sub>2</sub>):

CC1(C)CCC2=C1C=CC3=C2C=CC(=O)C3

# Ανατομική θεώρηση

[www.imop.gr](http://www.imop.gr)

Σπραγγώδη σώματα

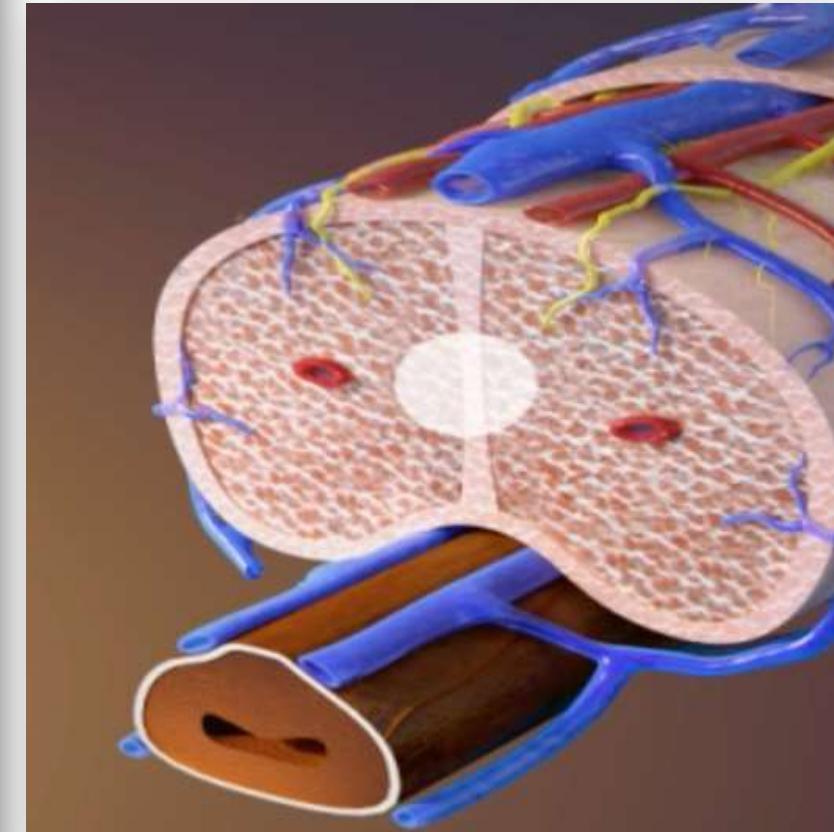
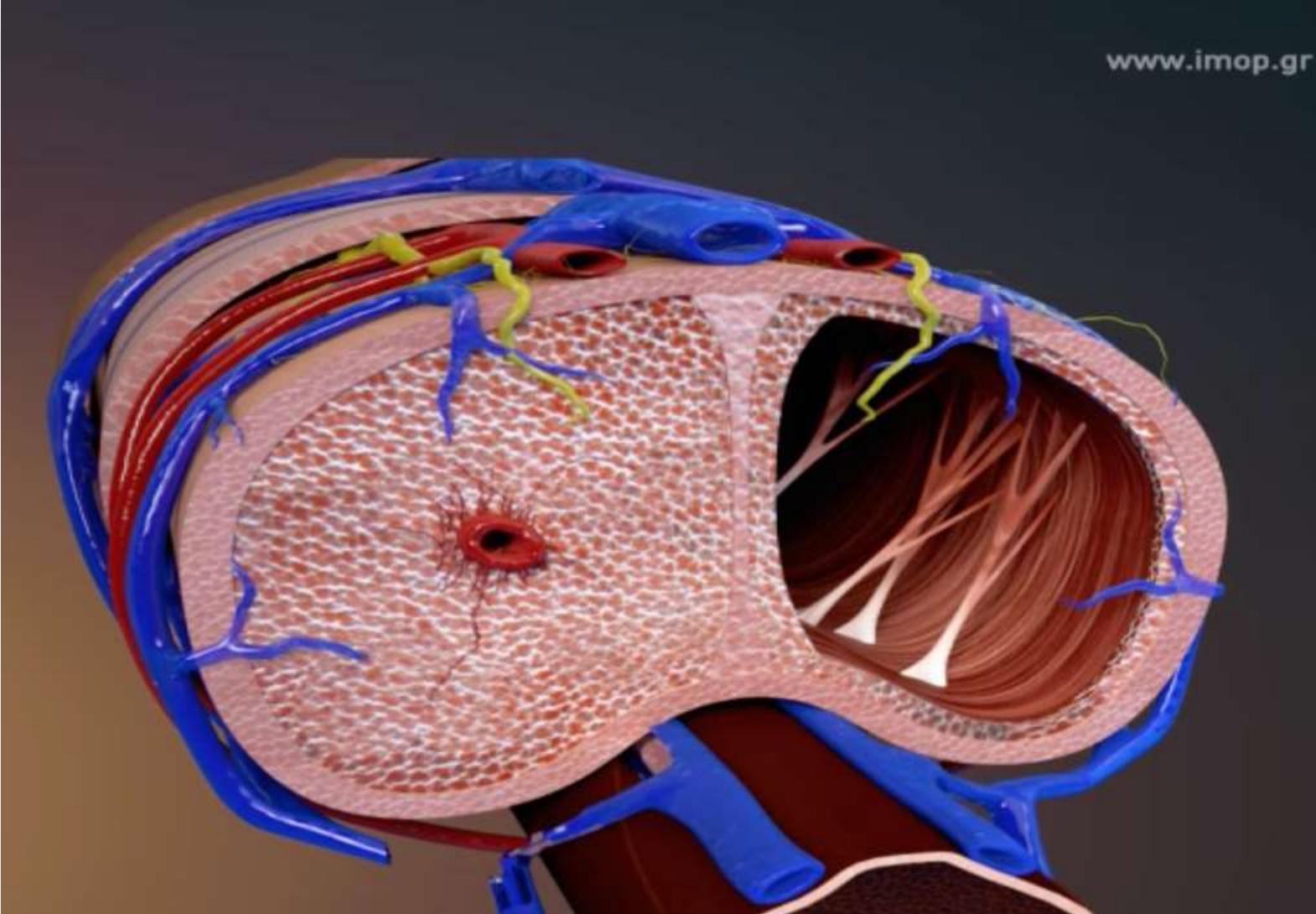




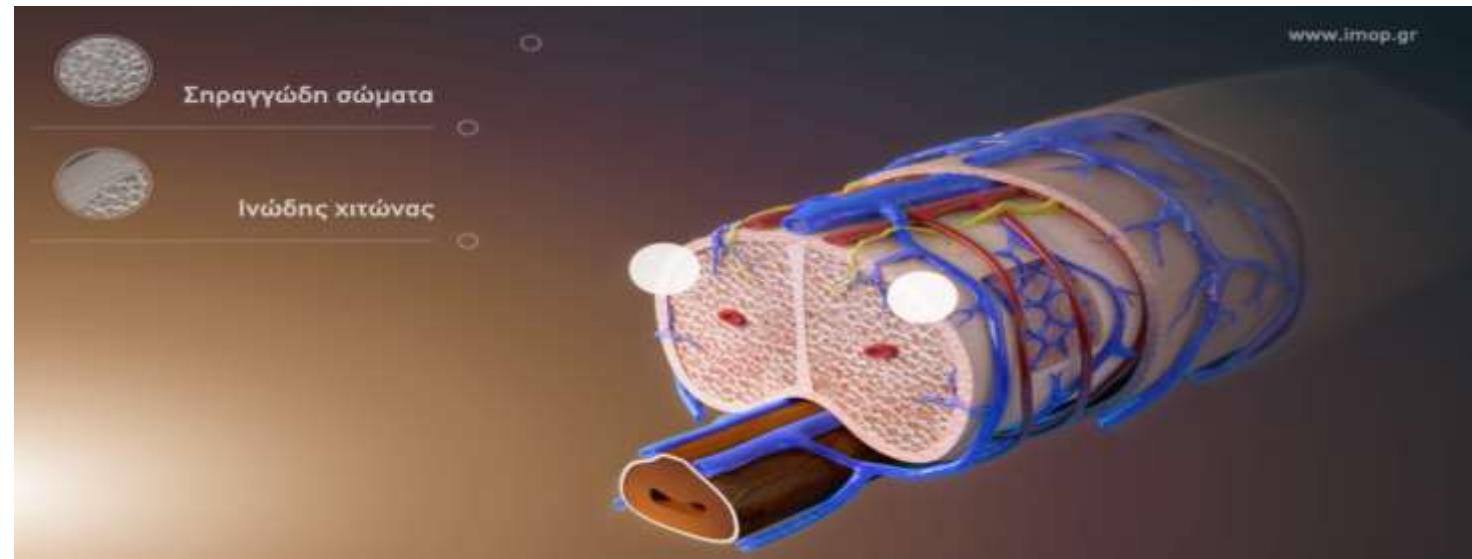
# Σηραγγώδεις και ελικοειδείς αρτηρίες – αιματικοί κόλποι



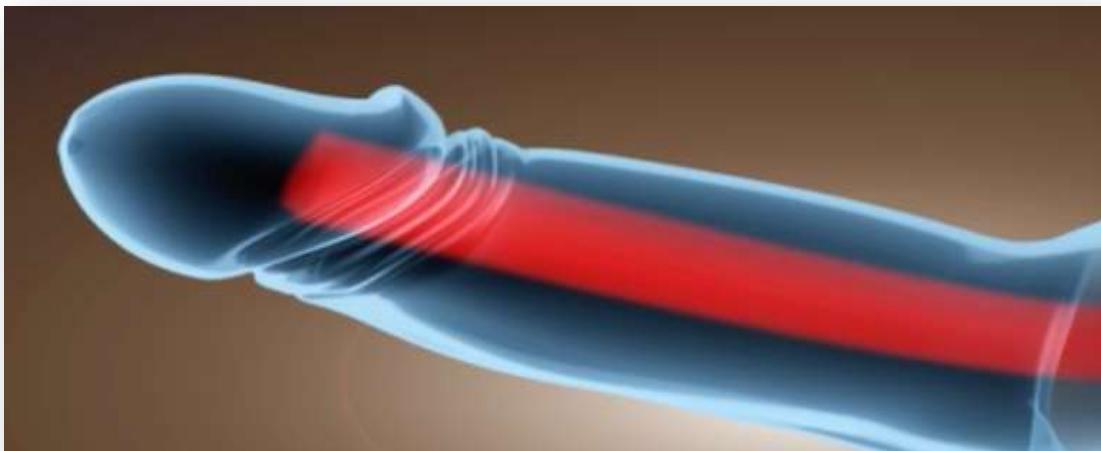
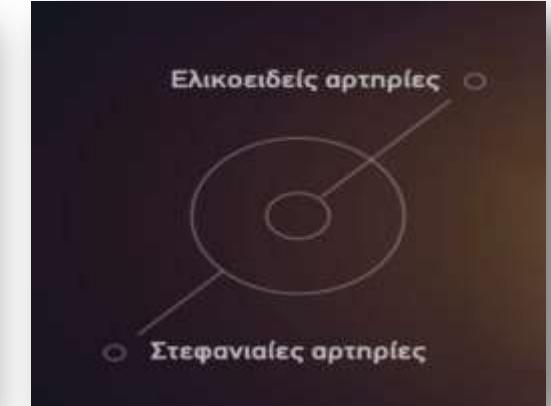
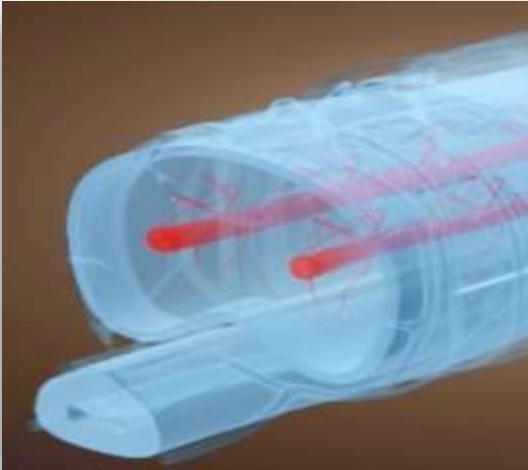
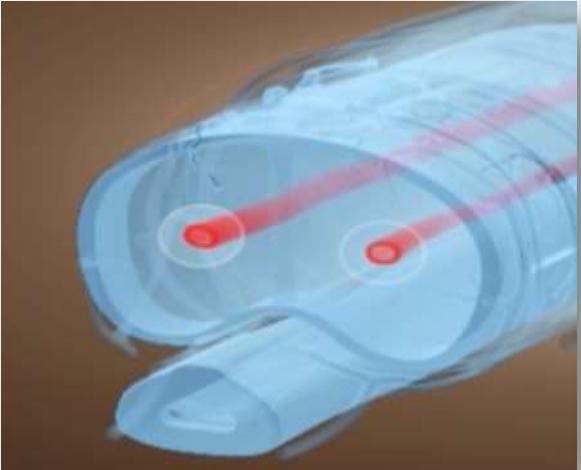
# Διάφραγμα και δοκίδες σηραγγωδών σωμάτων



# Ινώδης χιτώνας



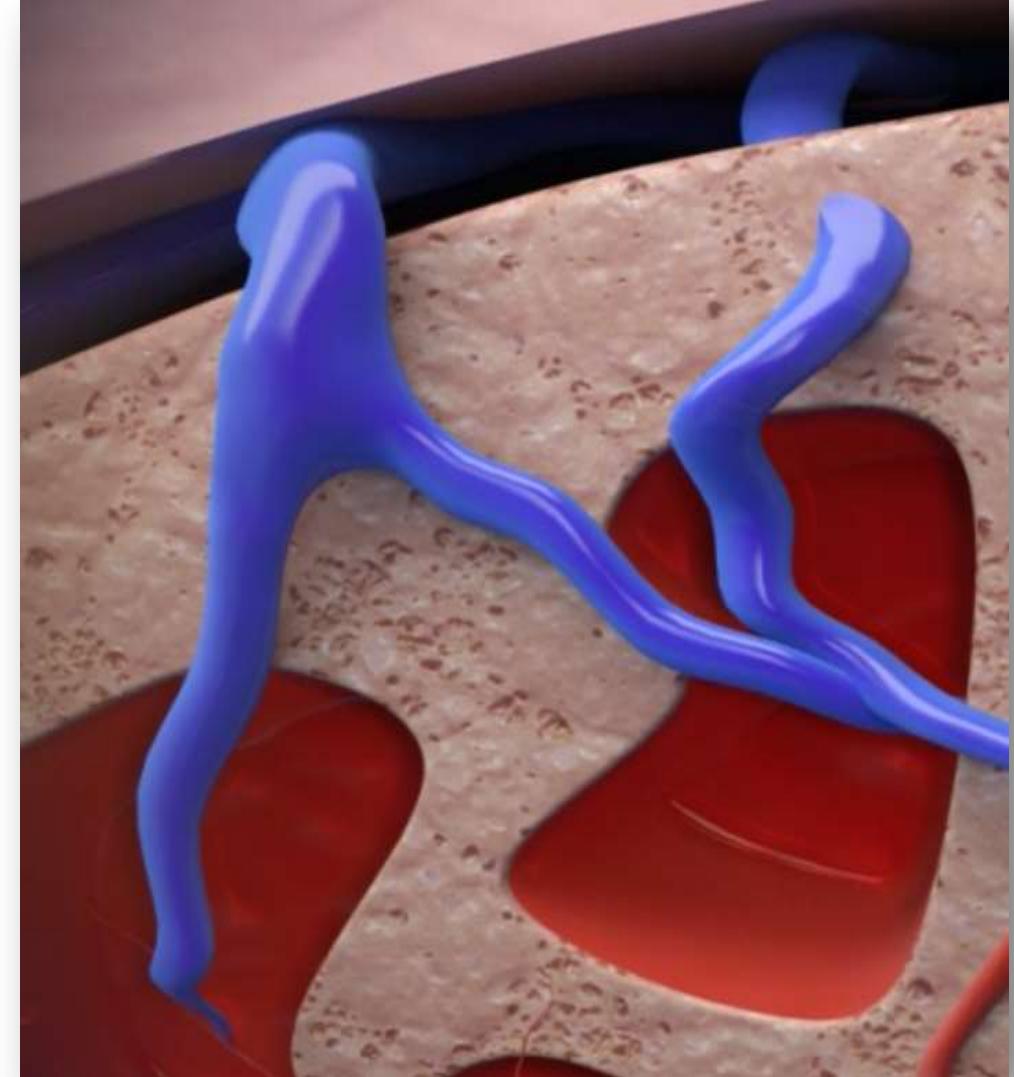
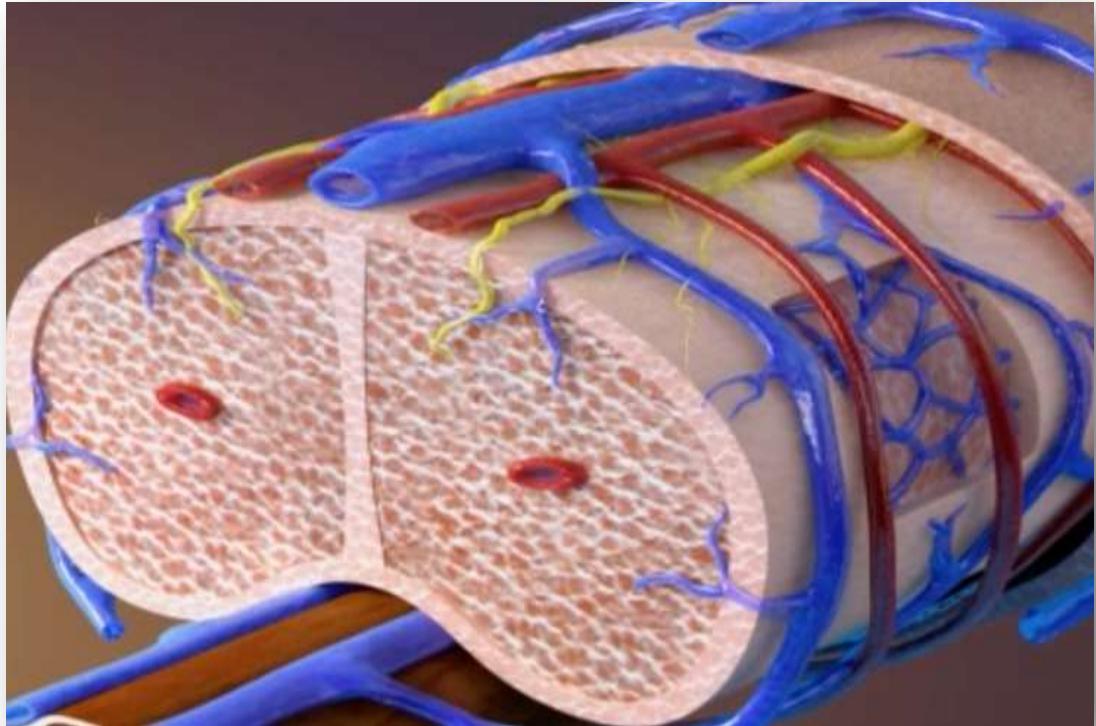
# Αρτηριακή ανεπάρκεια



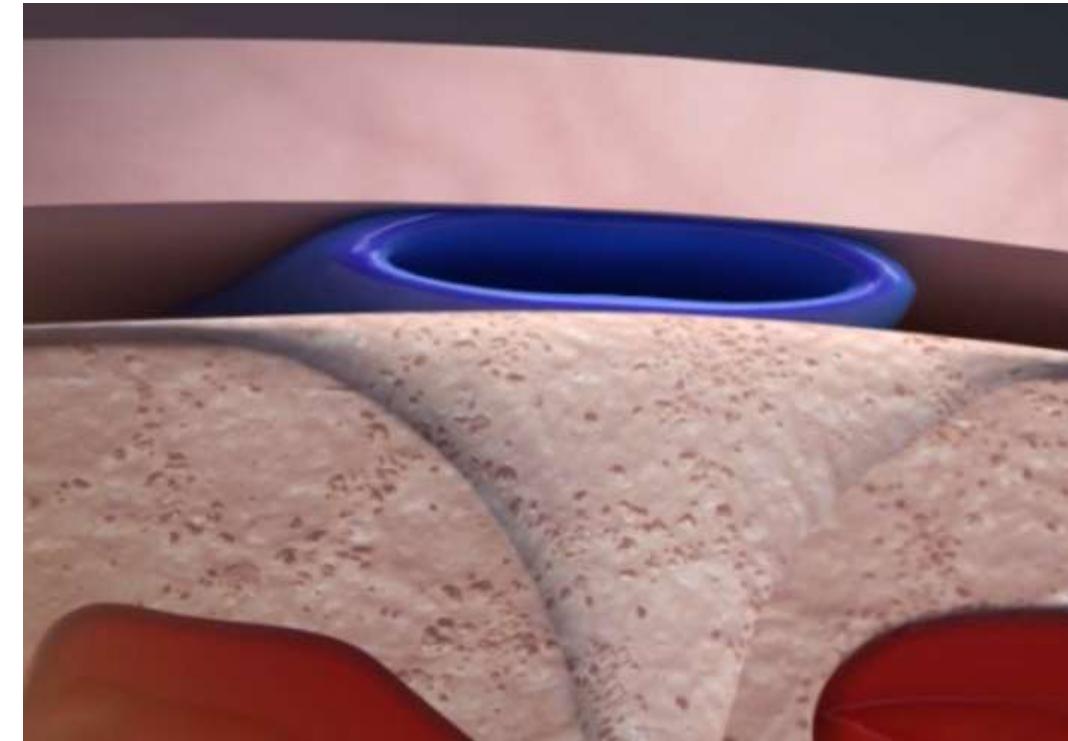
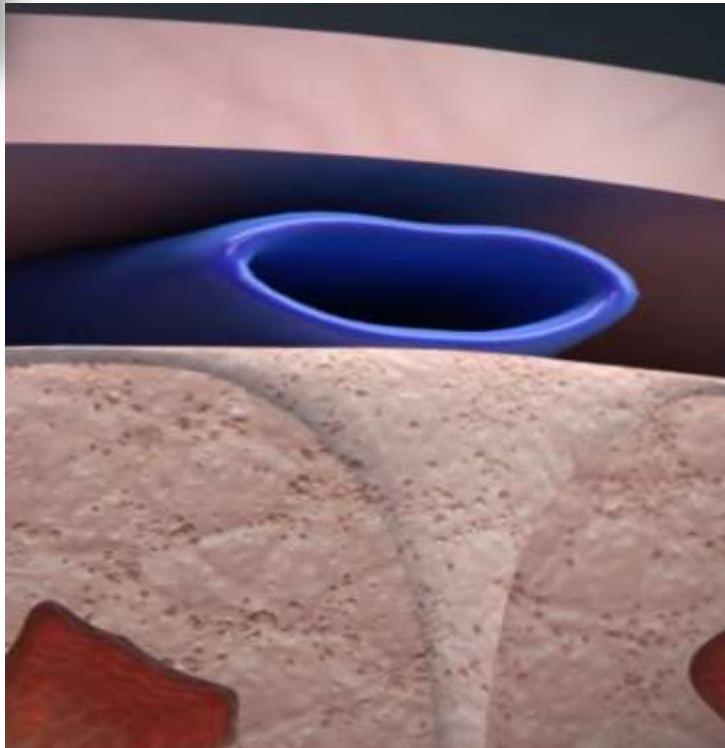
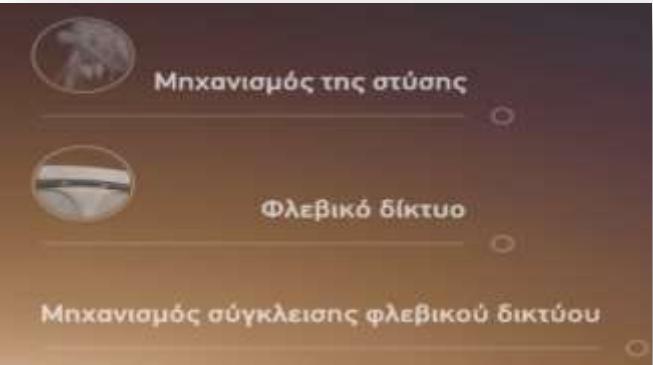
- Αρτηριακή ανεπάρκεια
- Σακχαρώδης διαβήτης
- Υπέρταση
- Καρδιαγγειακή νόσος
- Υπερχοληστεριναιμία



# Το φλεβικό δίκτυο του πέους

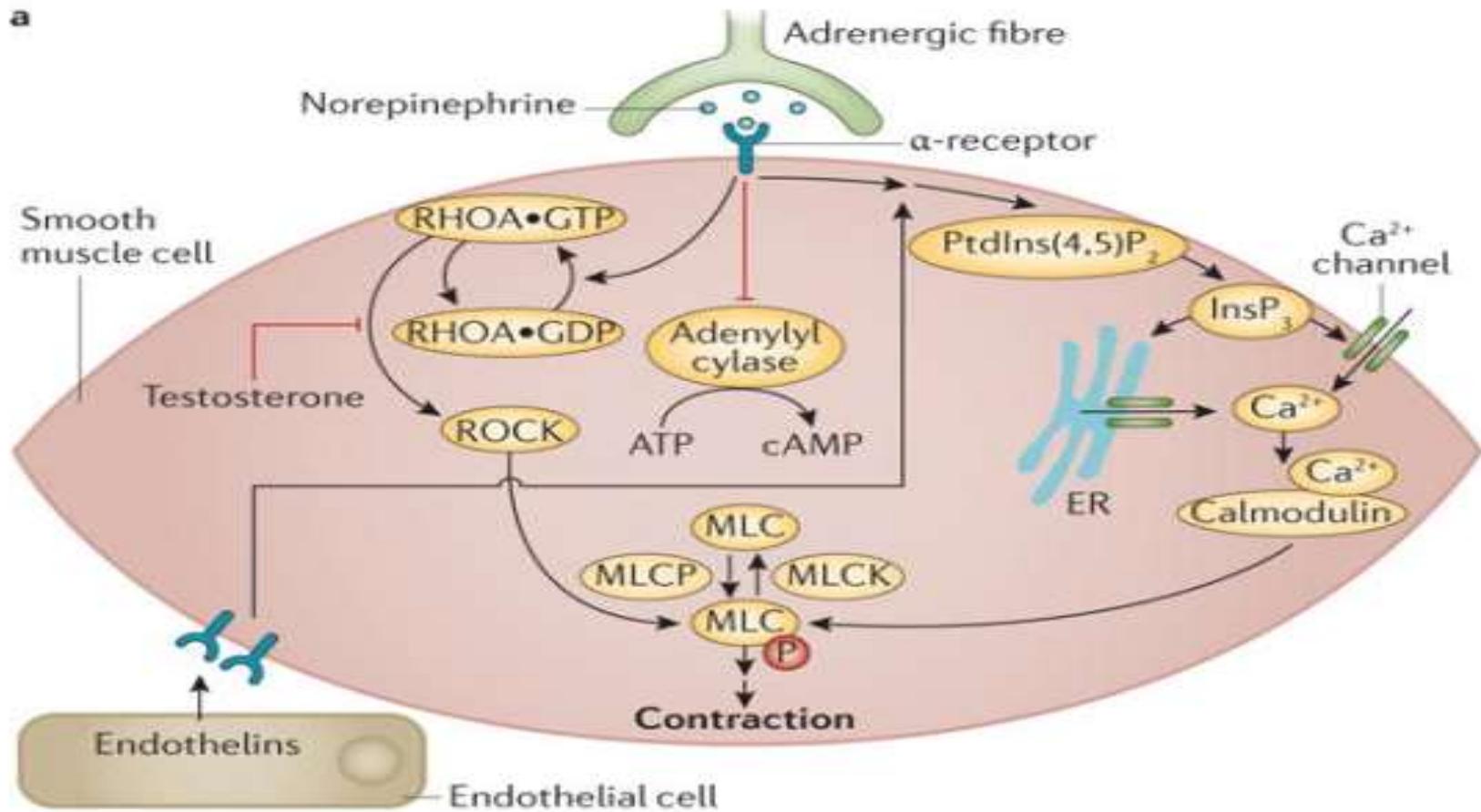


# Μηχανισμός φλεβικής σύγκλεισης

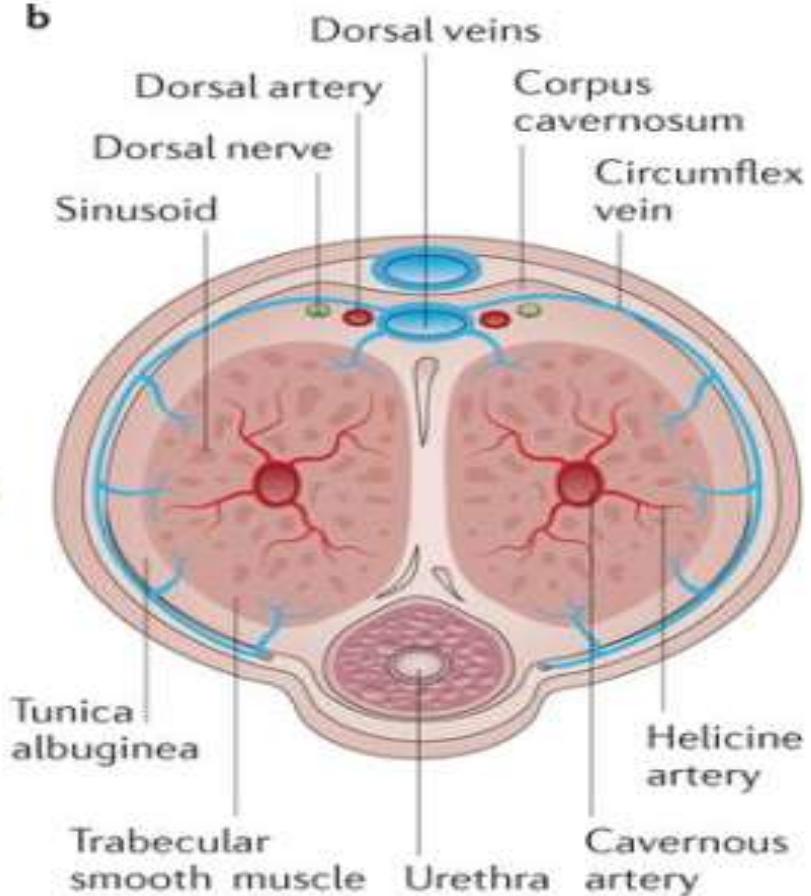


# Flaccid state

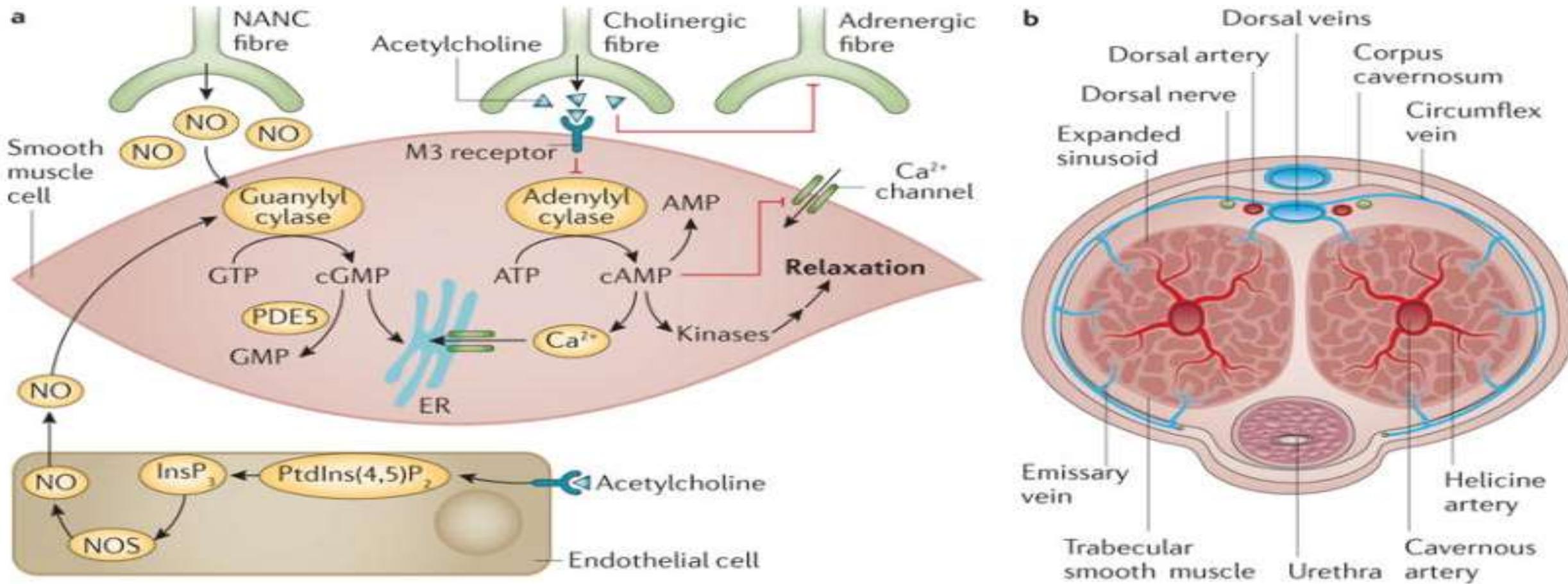
a



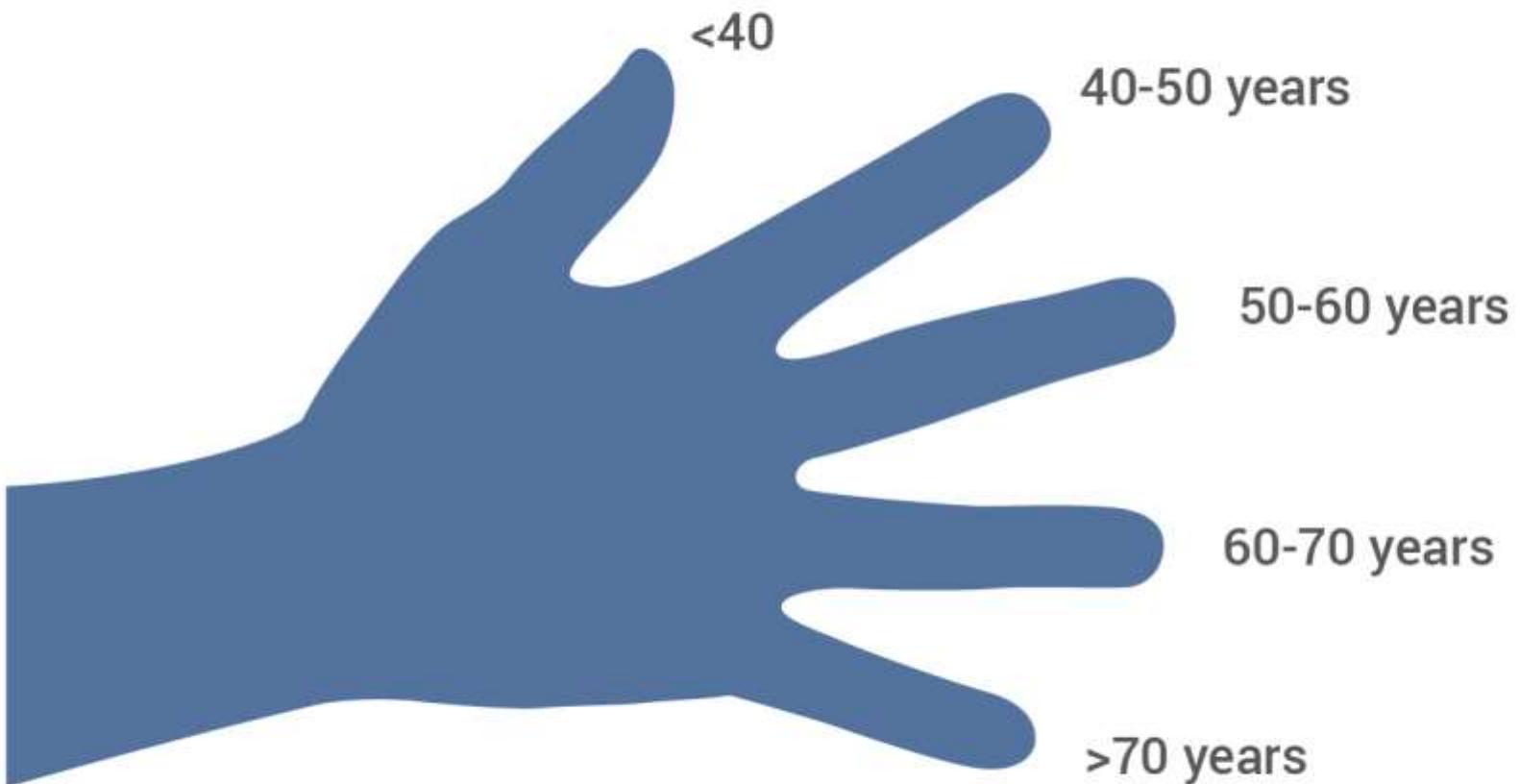
b



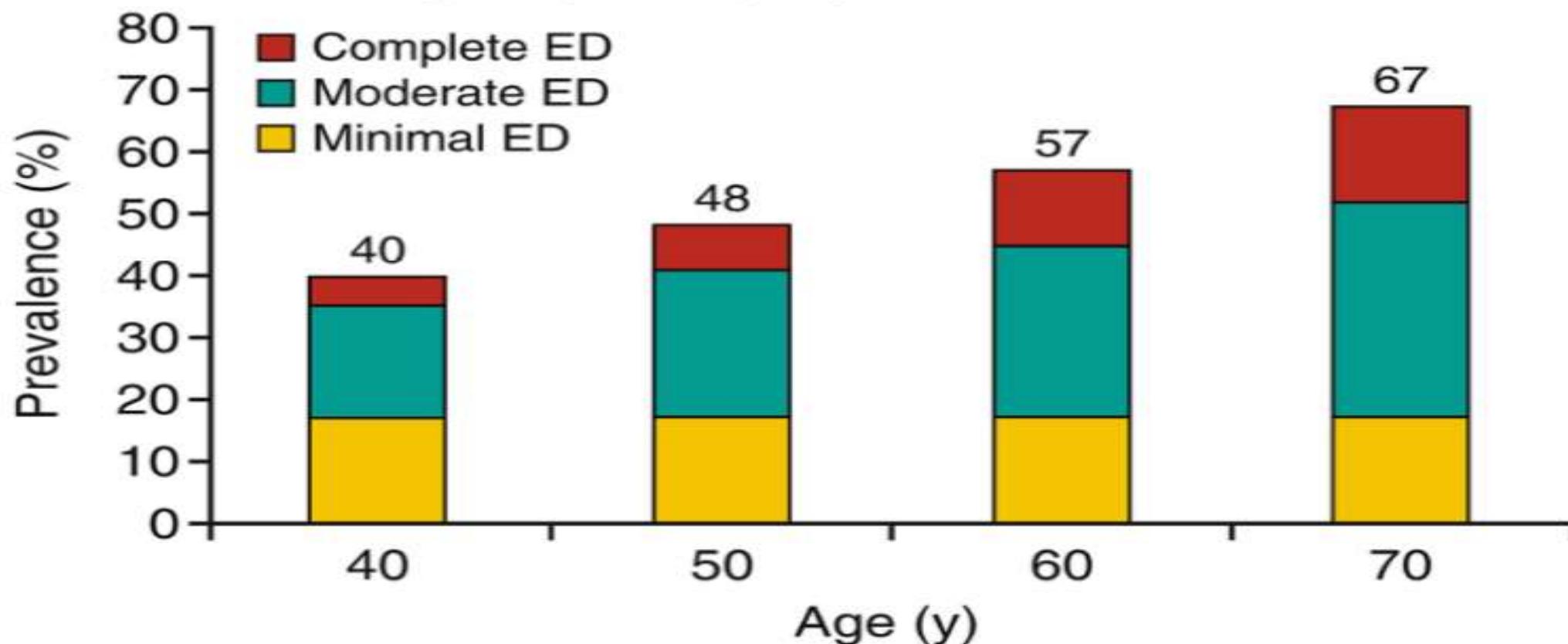
# Erect state

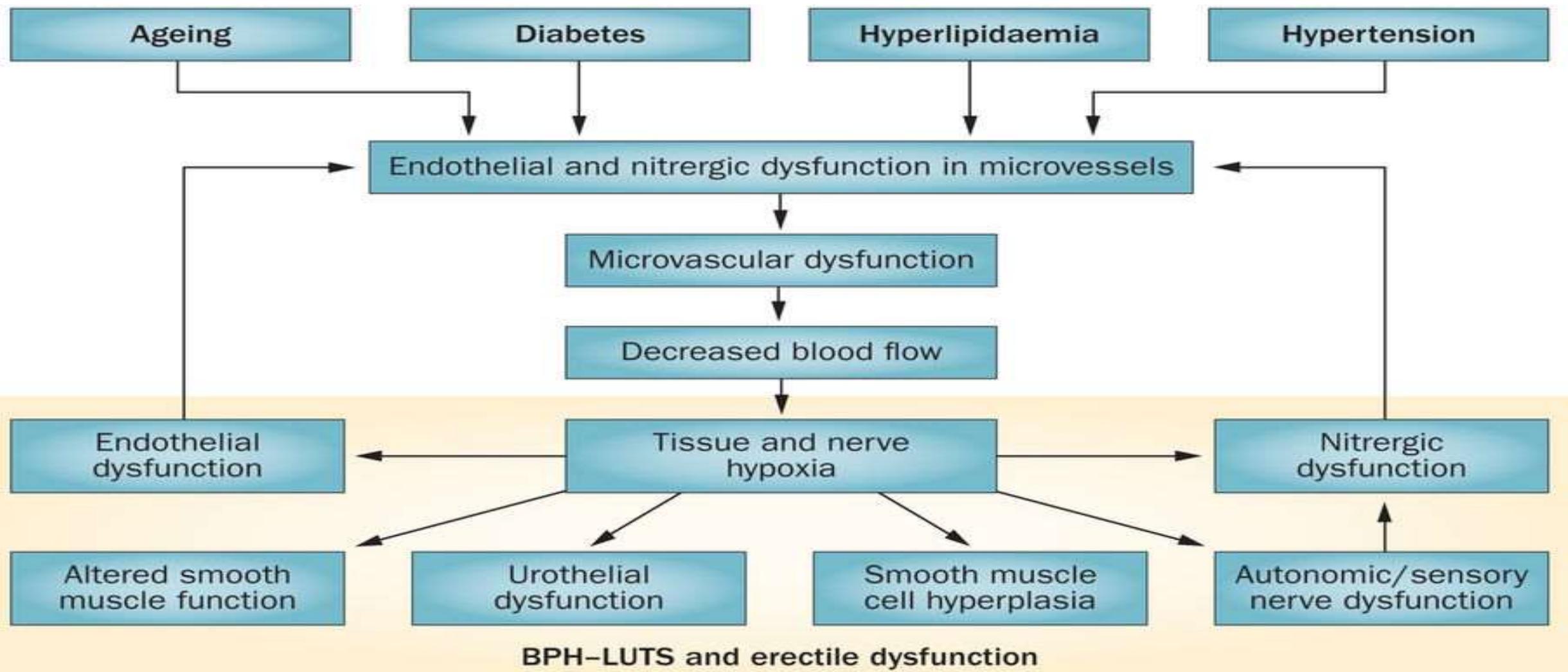


## Erectile function by age

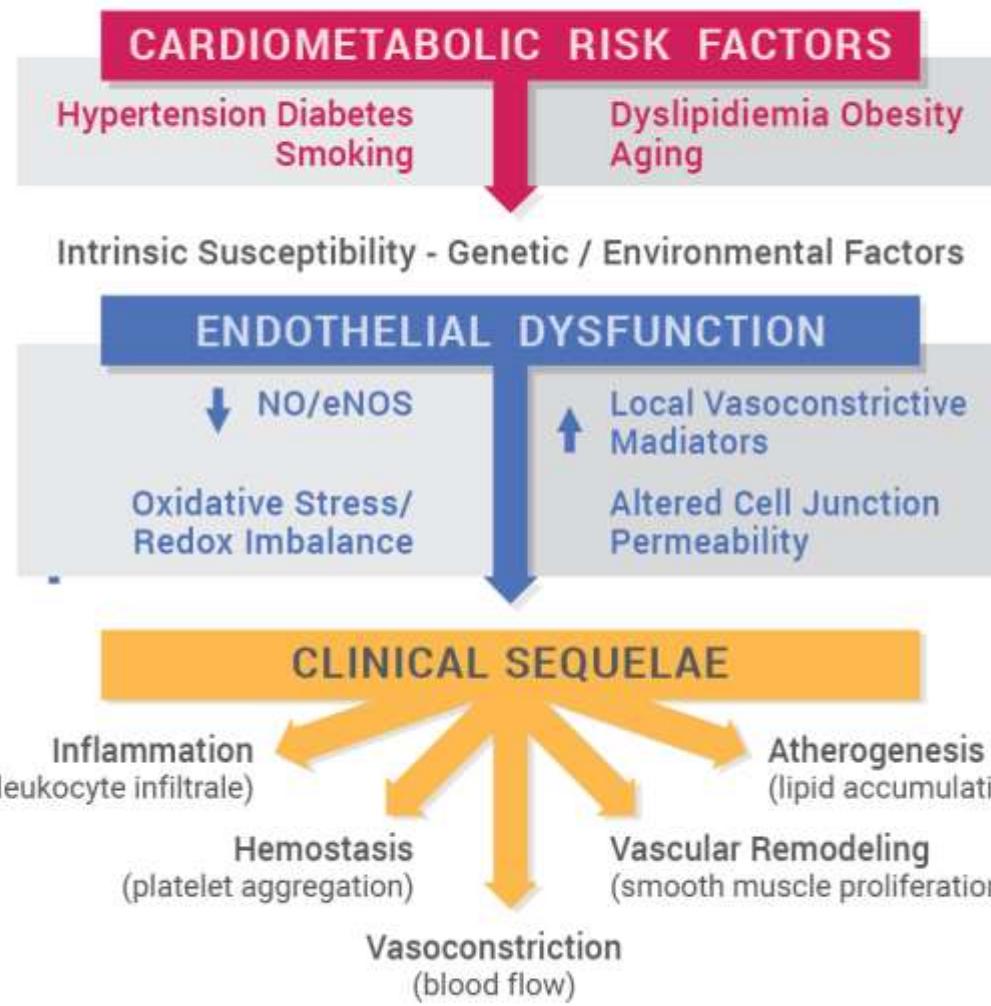


## MMAS: Age-adjusted progression of ED





# Cardiometabolic Risk Factors of ED



# Association of Erectile Dysfunction With Undiagnosed Hypertension, Hypercholesterolemia, and Diabetes Among Men Aged ≥20 Years in NHANES

Characteristic	Undiagnosed Hypertension (n=2,224)		Undiagnosed Hypercholesterolemia (n=2,287)		Undiagnosed Diabetes (n=1,417)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Erectile dysfunction	2.35 (1.78–3.11)	1.27 (0.87–1.85)	0.73 (0.47–1.15)	0.67 (0.42–1.07)	4.58 (2.54–8.24)	2.20 (1.10–4.37) <sup>a</sup>
Age-group, y						
20–39 (ref)	1.00	1.00	1.00	1.00	1.00	1.00
40–59	2.47 (1.69–3.61)	2.38 (1.55–3.66) <sup>a</sup>	1.88 (1.25–2.84)	1.84 (1.24–2.75) <sup>a</sup>	8.24 (2.49–27.19)	5.56 (1.78–17.35) <sup>a</sup>
≥60	7.29 (4.90–10.84)	7.41 (4.43–12.37) <sup>a</sup>	1.12 (0.76–1.65)	1.45 (0.87–2.43)	14.83 (5.19–42.34)	8.70 (2.91–26.03) <sup>a</sup>
Ethnicity						
Non-Hispanic white (ref)	1.00	1.00	1.00	1.00	1.00	1.00
Non-Hispanic black	1.47 (1.07–2.02)	1.99 (1.34–2.97) <sup>a</sup>	0.76 (0.47–1.23)	0.87 (0.54–1.40)	0.78 (0.39–1.56)	1.25 (0.57–2.71)
Mexican American	0.64 (0.41–0.98)	0.90 (0.60–1.35)	0.92 (0.64–1.31)	0.97 (0.65–1.46)	0.25 (0.11–0.58)	0.53 (0.21–1.33)
Other	0.66 (0.34–1.30)	0.92 (0.46–1.85)	1.13 (0.64–1.99)	1.37 (0.77–2.44)	1.21 (0.46–3.15)	2.39 (0.87–6.55)
Physically active	0.99 (0.77–1.28)	0.84 (0.62–1.13)	0.82 (0.59–1.14)	0.84 (0.60–1.18)	0.70 (0.33–1.47)	0.73 (0.35–1.55)
Alcohol use						
Never (ref)	1.00	1.00	1.00	1.00	1.00	1.00
Former						1.42 (0.47–4.30)
Current						0.67 (0.29–1.55)
Current smoker						1.00 (0.41–2.41)
History of hypertension						1.83 (0.92–3.65)
History of high cholesterol						1.55 (0.81–2.99)
History of diabetes						n/a <sup>b</sup>
History of cardiovascular disease						0.46 (0.18–1.17)
Family history of hypertension						0.96 (0.54–1.72)
Family history of angina/heart attack	0.59 (0.38–0.92)	0.68 (0.41–1.13)	1.12 (0.71–1.78)	1.18 (0.74–1.90)	1.36 (0.65–2.86)	1.26 (0.50–3.14)
Family history of diabetes	0.93 (0.74–1.18)	1.02 (0.78–1.32)	1.33 (0.95–1.87)	1.30 (0.92–1.84)	2.24 (1.40–3.59)	2.35 (1.50–3.68) <sup>a</sup>
Weight status						
Normal weight/underweight (ref)	1.00	1.00	1.00	1.00	1.00	1.00
Overweight	2.10 (1.45–3.04)	1.75 (1.15–2.67) <sup>a</sup>	2.23 (1.51–3.30)	2.17 (1.46–3.23) <sup>a</sup>	2.83 (0.74–10.81)	2.28 (0.74–6.99)
Obese	3.11 (2.18–4.46)	2.37 (1.64–3.43) <sup>a</sup>	2.79 (1.70–4.58)	2.74 (1.68–4.47) <sup>a</sup>	5.98 (1.69–21.10)	3.60 (1.30–9.93) <sup>a</sup>

For the average man aged 40 to 59 years, the predicted probability of having undiagnosed diabetes increased from 1 in 50 in the absence of erectile dysfunction to 1 in 10 in the presence of erectile dysfunction.

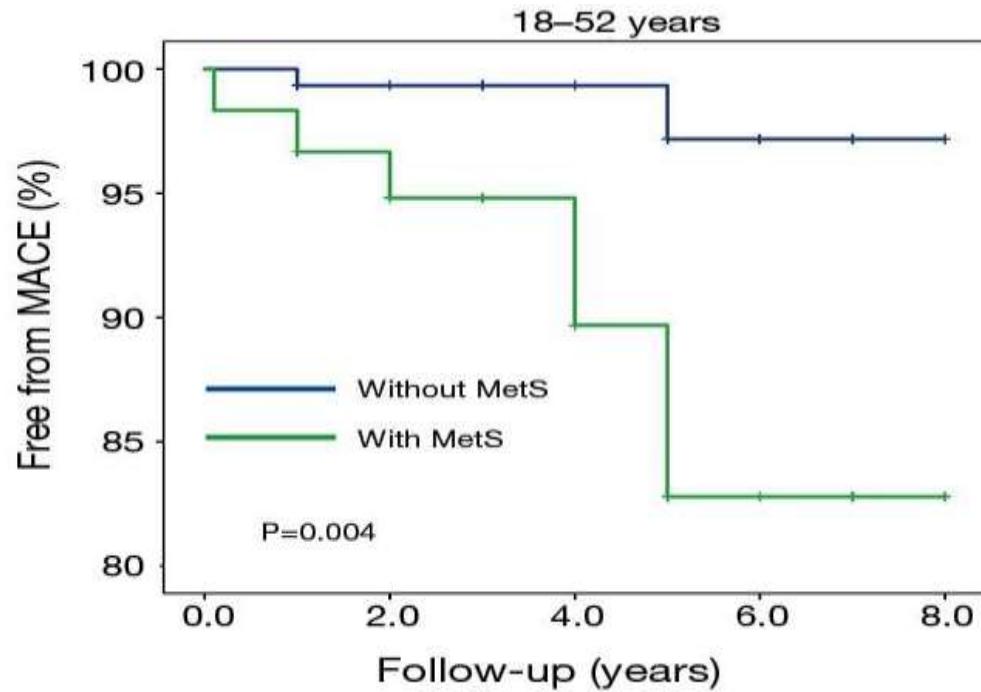
n/a = not applicable; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; ref = reference group.

<sup>a</sup>Statistically significant ( $P < .05$ ).

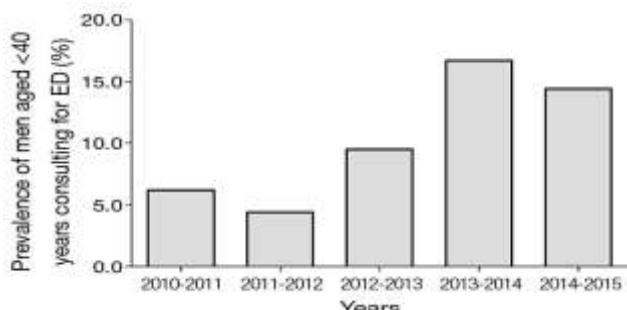
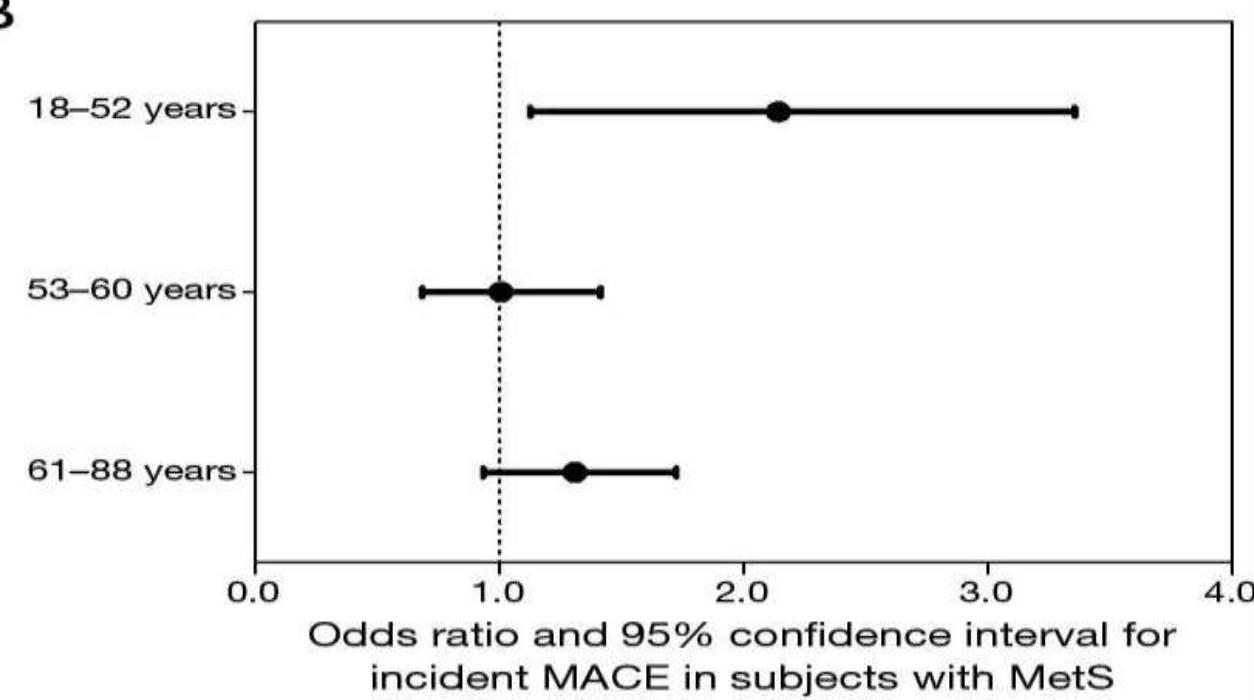
<sup>b</sup>Men with previous history excluded.

# Association between metabolic syndrome (MetS) at baseline and incidence of major adverse cardiovascular events (MACE) during a follow-up of 4.3 years

A



B



- 
- ED is an independent marker of increased risk for CVD.
  - The relevant CV risk is higher in men **40-49 years** with ED (Vlachopoulos et al. 2013) and those with **diabetes** (Miner et al. 2012)

# Risk Factors for CAD and ED

## CAD

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- Age
- Dyslipidemia
- Hypertension
- Diabetes
- Smoking
- Sedentary lifestyle
- Obesity
- Depression
- Male, post-menopausal female

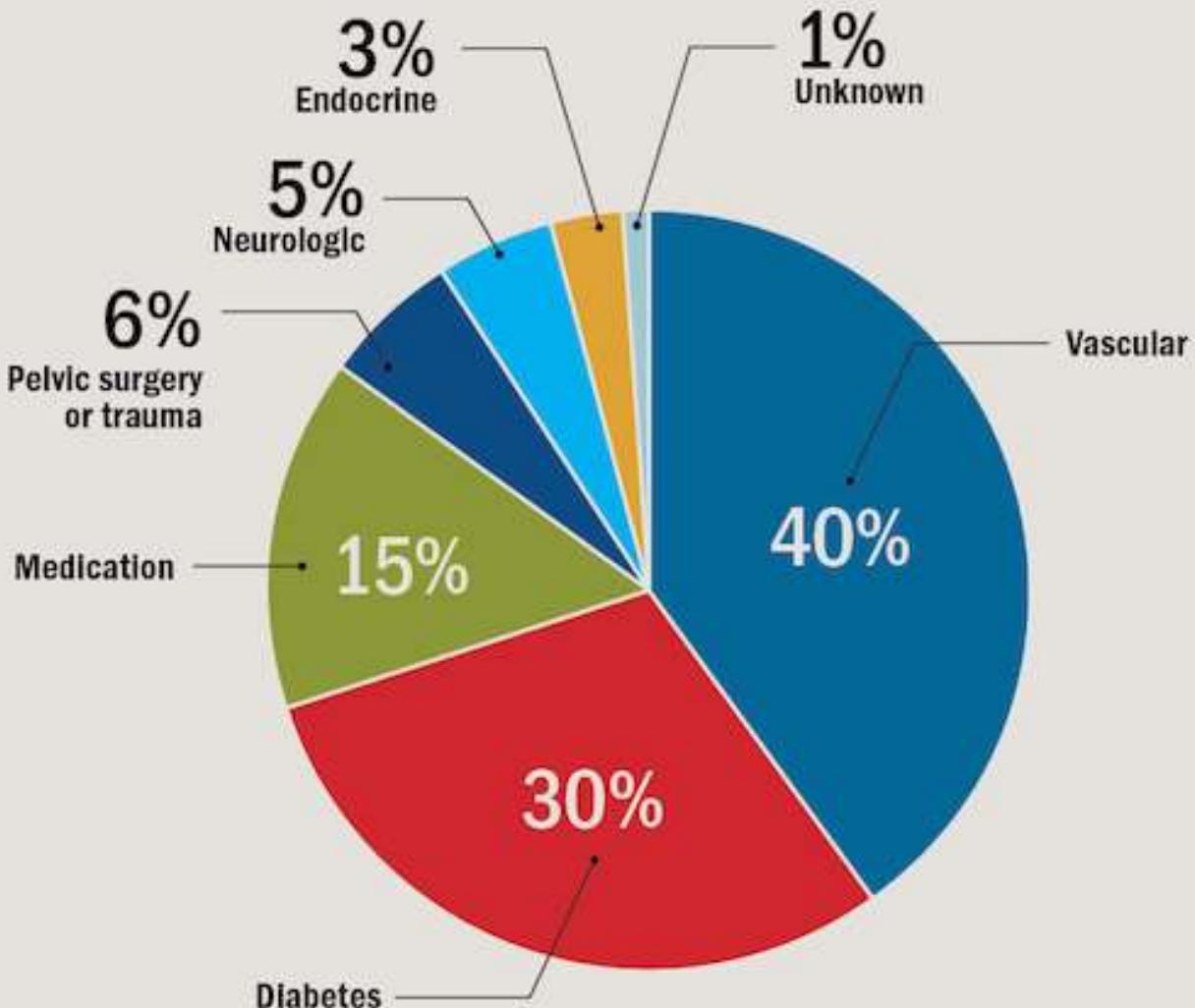
## ED

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- Age
- Dyslipidemia
- Hypertension
- Diabetes
- Smoking
- Sedentary lifestyle
- Obesity
- Depression
- CAD, peripheral vascular disease

# Στύση και διαβήτης: οι αριθμοί

JUT Figure 1 ( Organic causes of erectile dysfunction

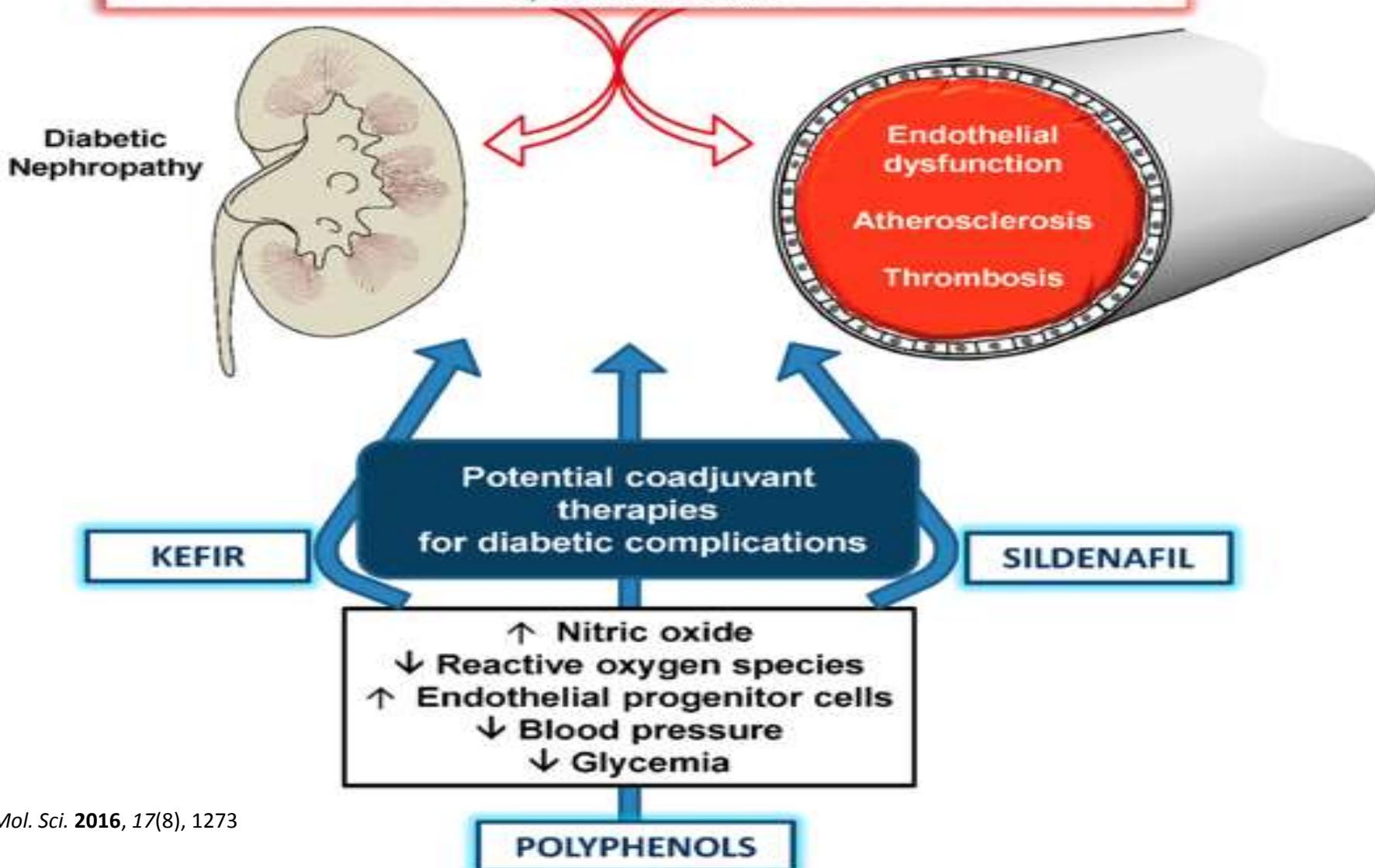


Source: Adapted from Shabsigh R, MD, Lue TF, MD. "A Clinician's Guide to ED Management." New York: Haymarket Media Inc., 2006

# Diabetes Mellitus

Hyperglycemia | Insulin Resistance | Excess Free Fatty Acids | Inflammation

- 1) Receptor for Advanced Glycation End Products (RAGE) Activation
- 2) Protein Kinase C Activation
- 3) Oxidative Stress



Το πρώτο σύμπτωμα του διαβήτη!



Οι διαβητικοί παρουσιάζουν συχνότερα  
στυτική δυσλειτουργία!

ΣΧ

Σε πόσα χρόνια από την έναρξη του διαβήτη  
εμφανίζεται το πρόβλημα στη στύση;

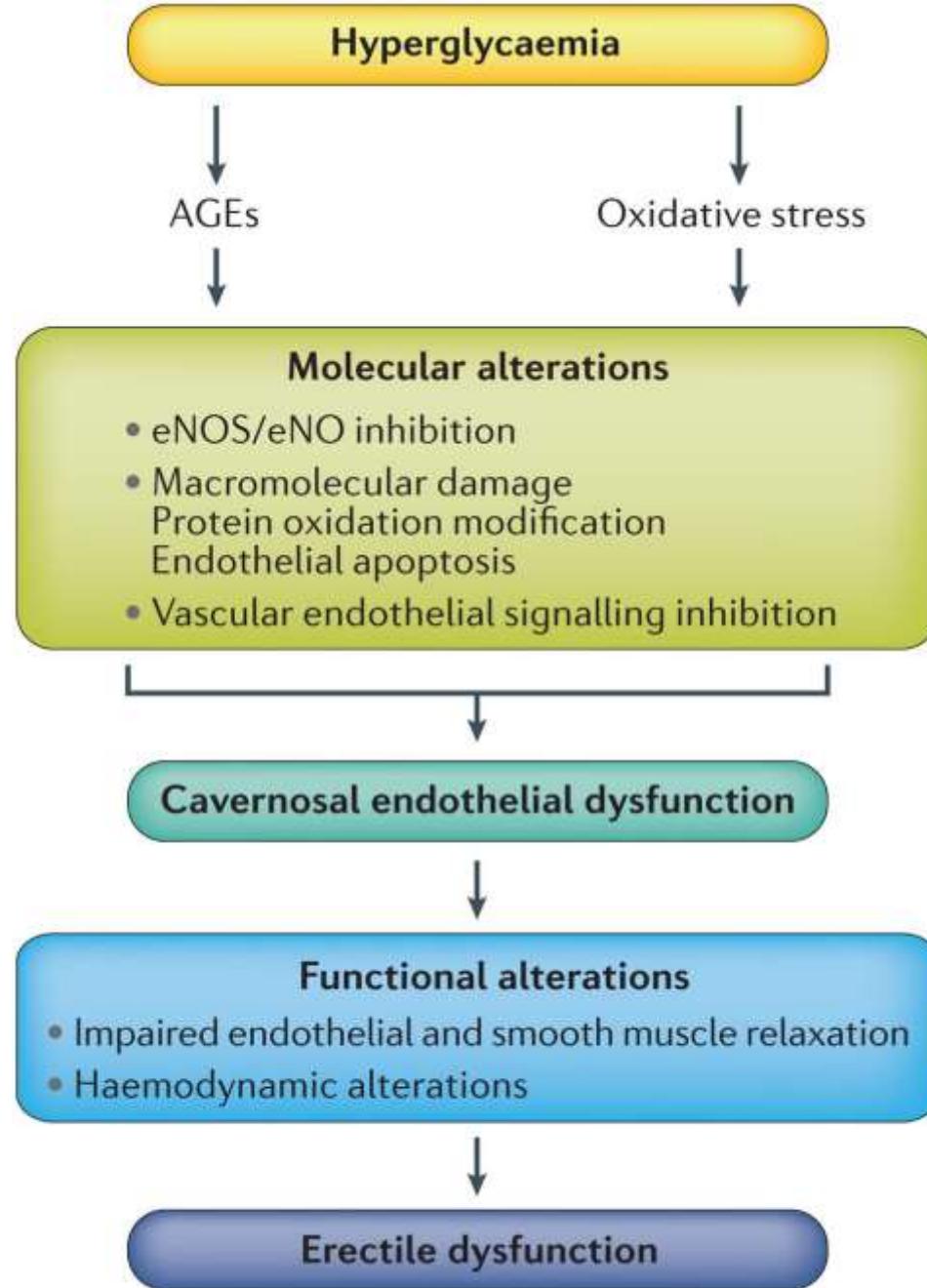


50%

Πόσο συχνή είναι η στυτική δυσλειτουργία στους διαβητικούς;



70  
YEARS



# Mean HbA1c levels by erectile dysfunction status at EDIC year 10 adjusted odds of erectile dysfunction per 10% higher HbA1c levels

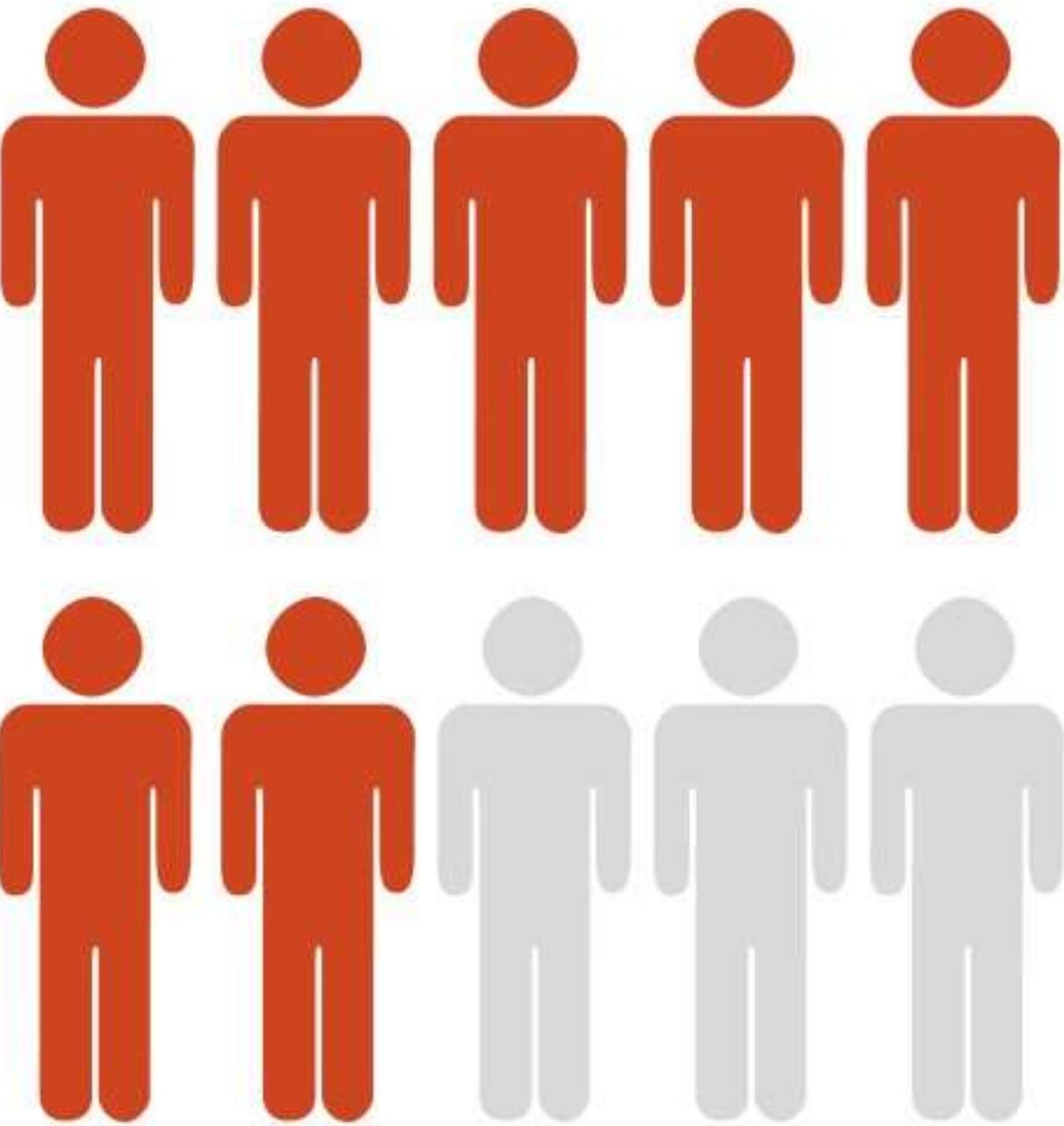
	No Erectile Dysfunction		Erectile Dysfunction		% Increase in Odds per 10% Higher HbA1c(95% CI)*	Adjusted P value*
	N	Mean±SD	N	Mean±SD		
<b>A. DCCT HbA1c (1983–1993)</b>						
<b>Primary Prevention Cohort</b>	230	8.06±1.34	61	8.68±1.67	21.5% (1.2, 46.0%)	0.04
<b>Secondary Intervention Cohort</b>	209	7.89±1.25	71	8.63±1.30	55.0% (27.4, 88.5%)	<0.0001
<b>B. DCCT/EDIC HbA1c (1983–2003)</b>						
<b>Primary Prevention Cohort</b>	230	7.94±0.99	60	8.73±1.32	74.4% (34.4, 126%)	<0.0001
<b>Secondary Intervention Cohort</b>	209	7.90±1.00	69	8.56±1.04	97% (51.2, 256%)	<0.0001

# Vascular: Glycaemic Control Correlates with ED Romeo et al J Urol 2002

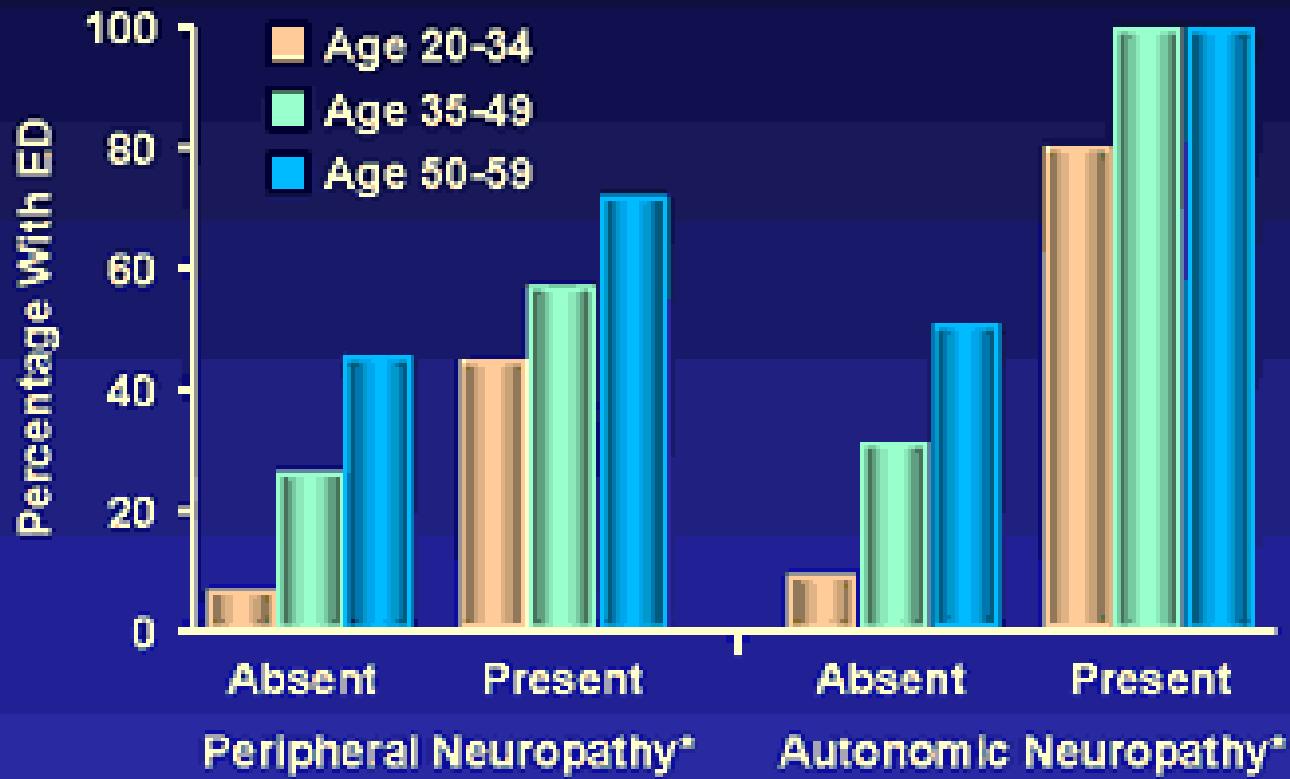


**↑70%**

Up to 70% of people with diabetes have nerve damage which impacts the neurological response and limits the signal to increase arterial blood flow.<sup>10</sup>



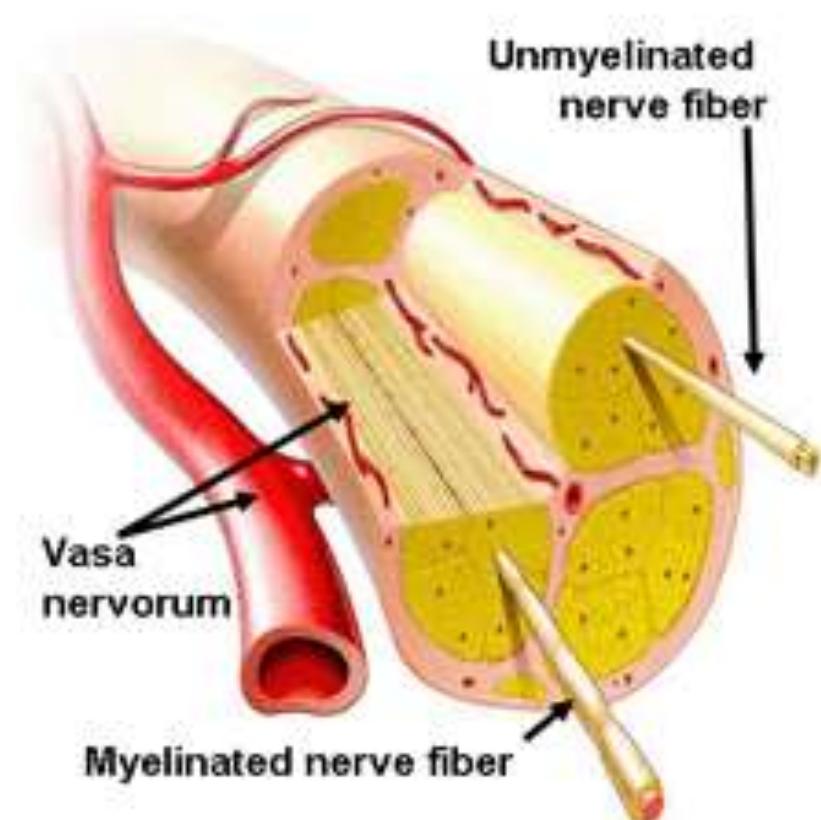
# ED in Men With Diabetes



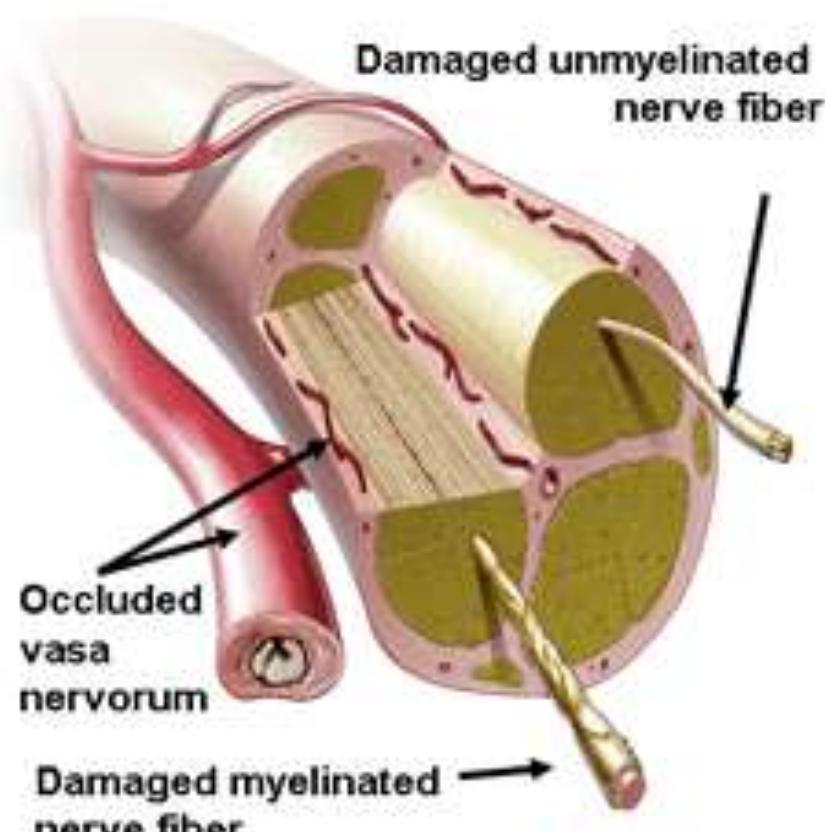
\*Significant association with ED. McCulloch DK et al. *Diabetologia*. 1980;18:279-283.

# Diabetic Peripheral Neuropathy

Healthy Nerves and Blood Vessels



Nerves and Blood Vessels Damaged by DPN



## Small-fibre neuropathy in men with type 1 diabetes and erectile dysfunction: a cross-sectional study

Neuropathy assessments for control participants vs participants with type 1 diabetes mellitus and no erectile dysfunction vs type 1 diabetes and erectile dysfunction

Variable	Control participants ( <i>n</i> = 34)	Type 1 diabetes, no ED ( <i>n</i> = 29)	Type 1 diabetes, ED ( <i>n</i> = 41)	<i>p</i> value
NSP (/38) <sup>a</sup>	0.2 ± 0.1***	1.8 ± 1.2	5.3 ± 0.9	0.03
Neuropathy Disability Score (/10) <sup>a</sup>	0.7 ± 0.2***	2.8 ± 0.7	4.1 ± 0.6	0.1
VPT (V) <sup>a</sup>	6.2 ± 0.9***	10.7 ± 2.4	18.3 ± 1.9	0.02
Sural nerve amplitude (μV) <sup>a</sup>	17.9 ± 1.5***	11.7 ± 1.5	5.0 ± 1.1	0.002
Sural nerve conduction velocity (m/s) <sup>a</sup>	49.0 ± 0.6***	42.6 ± 1.9	37.9 ± 1.4	0.07
Peroneal nerve amplitude (mV) <sup>a</sup>	6.2 ± 0.3***	4.7 ± 0.5	2.1 ± 0.4	<0.001
Peroneal nerve conduction velocity (m/s) <sup>a</sup>	48.8 ± 0.7***	41.9 ± 2.0	34.8 ± 1.5	0.01
CT (°C) <sup>a</sup>	28.2 ± 0.4***	27.3 ± 1.8	19.7 ± 1.4	0.003
WT (°C) <sup>a</sup>	37.6 ± 0.7***	39.0 ± 0.9	42.9 ± 0.8	0.005
IENFD (n/mm) <sup>a</sup>	10.5 ± 0.7***	5.9 ± 0.7	2.8 ± 0.7	0.008
Automated CNFD (n/mm <sup>2</sup> ) <sup>a</sup>	30.1 ± 1.2***	23.9 ± 2.0	12.6 ± 1.5	<0.001
Automated CNBD (n/mm <sup>2</sup> ) <sup>a</sup>	37.1 ± 2.7***	31.6 ± 3.3	12.7 ± 2.5	<0.001
Automated CNFL (mm/mm <sup>2</sup> ) <sup>a</sup>	17.1 ± 0.6***	14.5 ± 1.0	8.3 ± 0.7	<0.001
DB-HRV (beats/min) <sup>a</sup>	31.0 ± 2.2***	30.0 ± 3.7	21.5 ± 3.1	0.001

Data are means ± SEM

<sup>a</sup>Adjusted for age using ANCOVA

\*\*\**P* < 0.001, control participants vs men with type 1 diabetes mellitus

Azmi S et al: Diabetologia. 2017; 60(6): 1094–1101.

*p* value is for comparison between participants with and without erectile dysfunction

ED = erectile dysfunction

# Corneal confocal microscopy (CCM)\*



CCM images of the corneal sub-basal nerves of: (a) a control participant; (b) a participant with type 1 diabetes mellitus and no erectile dysfunction; and (c) a participant with type 1 diabetes mellitus and erectile dysfunction. Scale bar, 50 µm

Azmi S et al: Diabetologia. 2017; 60(6): 1094–1101.

\*CCM is a rapid, non-invasive ophthalmic examination technique that objectively evaluates small-fibre neuropathy in patients with diabetes and is comparable with skin biopsy in the diagnosis of diabetic neuropathy



# Treatment & Care

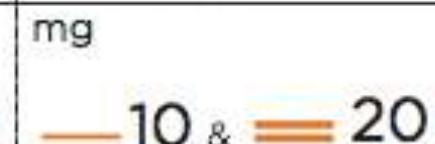
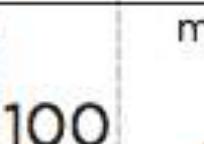
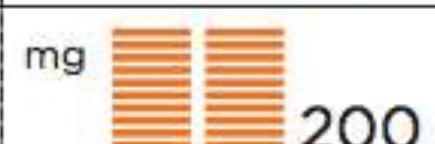
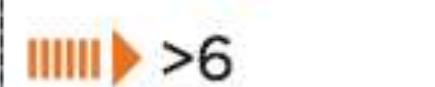
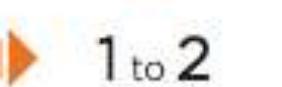
## Suggested recommendations on lifestyle changes to be observed in order to prevent/treat erectile dysfunction

Table 1: Suggested recommendations on lifestyle changes to be observed in order to prevent/treat erectile dysfunction

Risk factor	Strategy	Recommendation	Level of evidence
Sedentary lifestyle	Physical activity	30 min at least per day or 150 min week <sup>-1</sup> of moderate intensity aerobic activity	A*
Overweight/obesity	Weight loss	5%-10% of weight reduction	A*
Unhealthy diet	Improvement of diet quality	Increase in consumption of fruit and vegetables, whole grains and legumes; limit red meat and processed food; reduction of saturated fat to <10% calories, increase in intake of monounsaturated and polyunsaturated fatty acids; abolition of added sugars-beverages	A*
Alcohol abuse	Avoid excessive alcohol consumption	1-2 drinks maximum per day	B
Cigarette smoking	Educate on current cessation options	Smoking cessation	B*

A: evidence from intervention studies; B: evidence from prospective cohort studies or case-control studies. \*Few studies with small number

# FEATURES OF ED DRUGS

	AVANAFIL	VARDENAFIL	SILDENAFIL	TADALAFIL	ALPROSTADIL
<b>MODE OF ADMINISTRATION</b>	Oral tablets 	oral tablets or disintegrating oral tablets	Oral tablets 	Oral tablets 	Penile injection 
<b>DOSAGE</b>	mg  100 &  200	mg  10 &  20	mg  25  50 &  100	mg  5  10 &  20	μg  20 
usual MAXIMUM daily dose (in mg)	mg  200	mg  20	mg  100	mg  20	μg  40 
usual time needed from drug intake to <b>drug action</b> (in hours)	hours  About 0,5	hours  About 1	hours  About 1	hours  1-2	hours  0,2
usual duration of action since drug intake (in hours)	 >6	 6 to 12	 6 to 12	 up to 36	 1 to 2
Is sexual arousal necessary?	YES	YES	YES	YES	NO

SOURCES: Hatzichristou D. Erectile Dysfunction. In V. Mirone: Uroandrology, Springer, 2014

# Pleiotropic **beneficial** effects of phosphodiesterase type-5 inhibitors

Schwartz BG et al: Am J Med 2013;126(3):192-9 Chrysant SG,  
Chrysant GS.: J Clin Hypertens 2012;14(9):644-9  
source: [www.imop.gr](http://www.imop.gr)

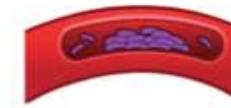
1

- Hypertension
- Coronary Artery Disease
- Heart failure



2

- Peripheral arterial disease



3

- Raynaud's phenomenon



4

- Preeclampsia



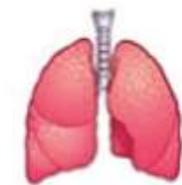
7

- Diabetes
- Metabolic syndrome



- Erectile dysfunction

6

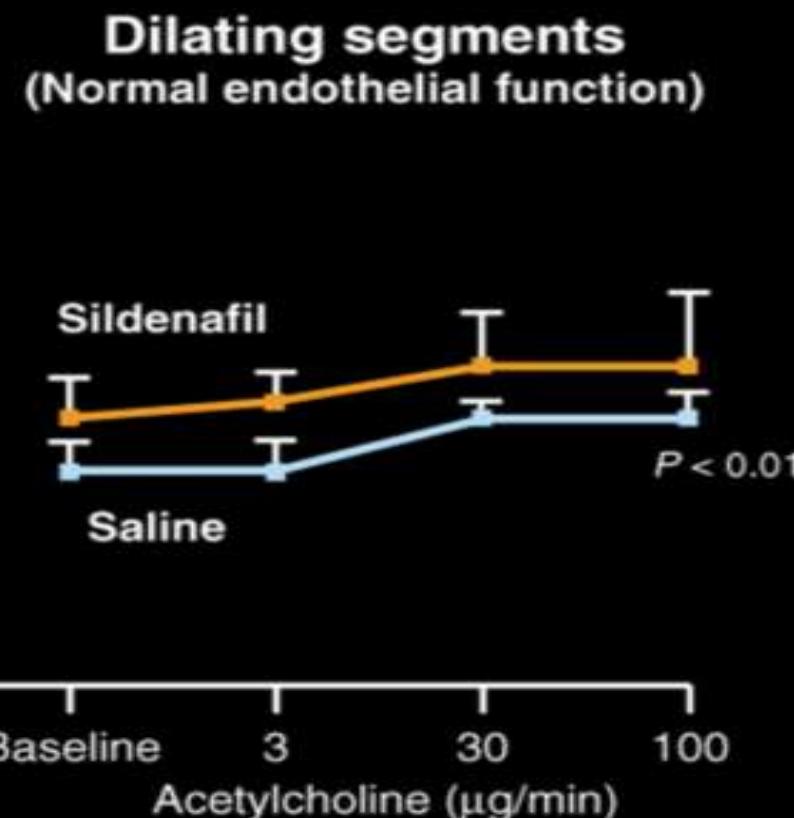
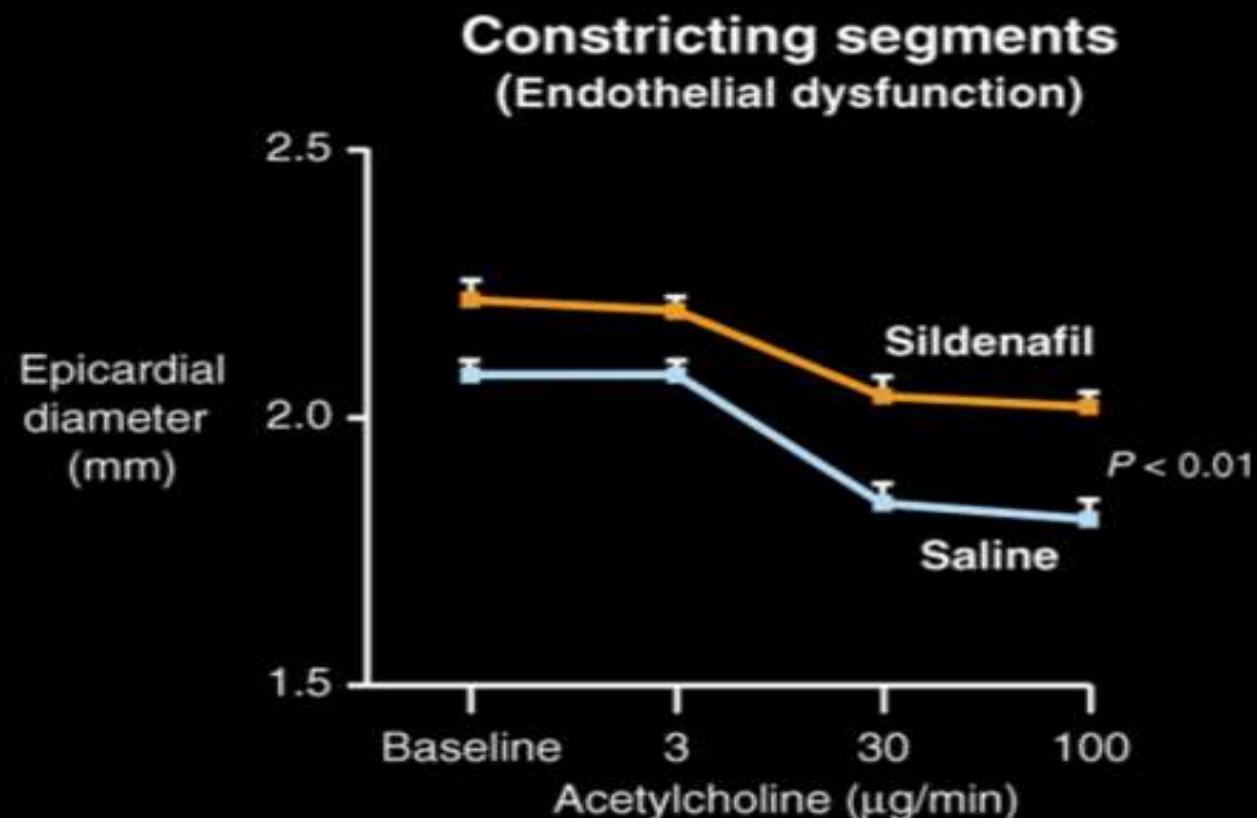


- Pulmonary arterial hypertension
- High-altitude pulmonary edema

5

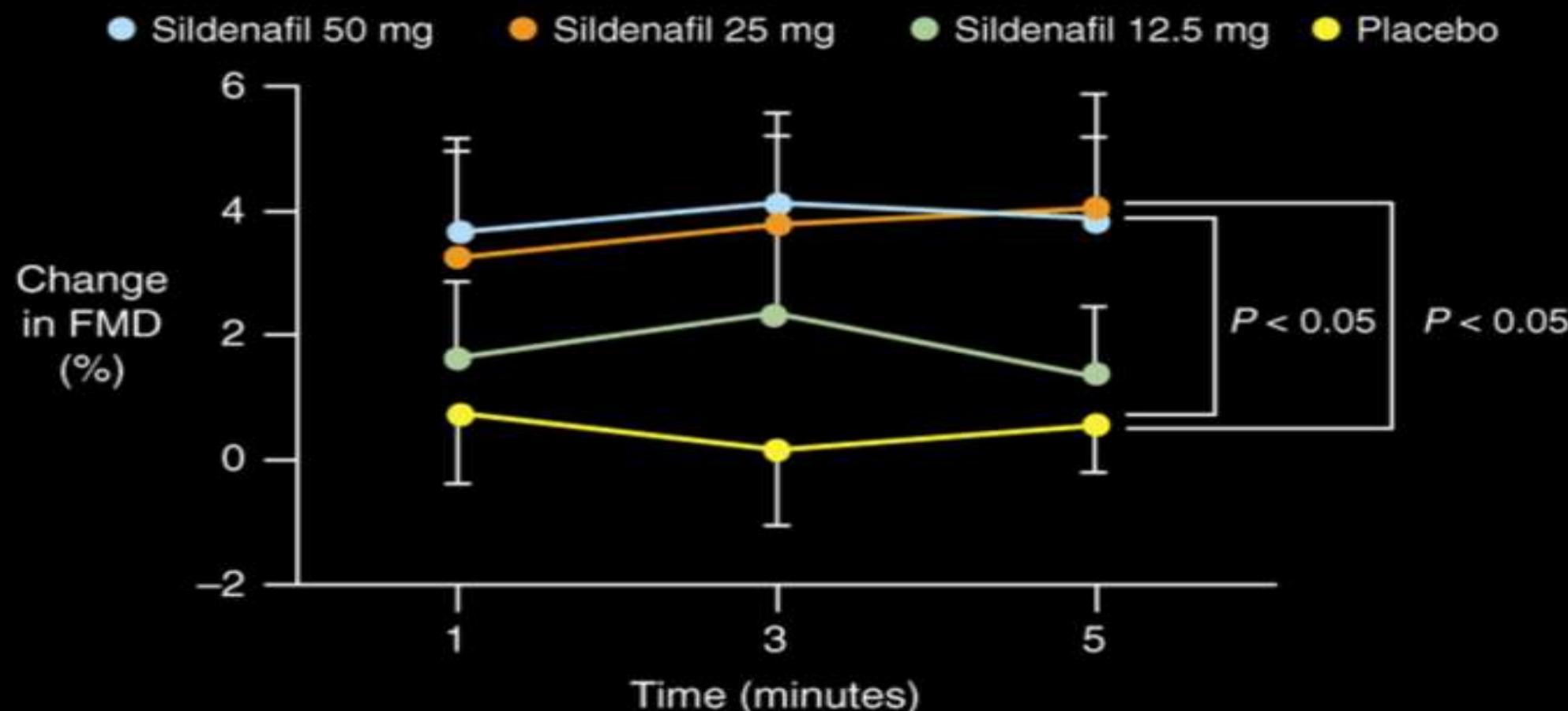
# PDE5 inhibition improves coronary artery endothelial function

24 patients undergoing cardiac catheterization for chest pain and/or abnormal noninvasive cardiac investigations (CAD, n = 15; angiographically normal arteries, n = 9)

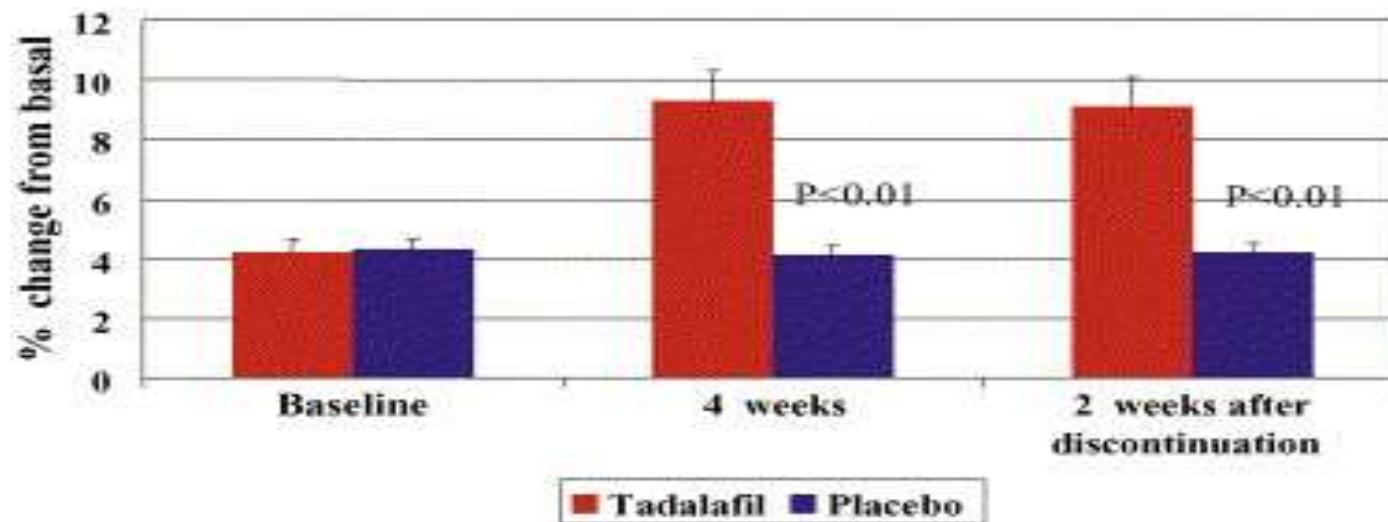


# PDE5 inhibition: Dose-dependent effect on endothelial function in patients with heart failure

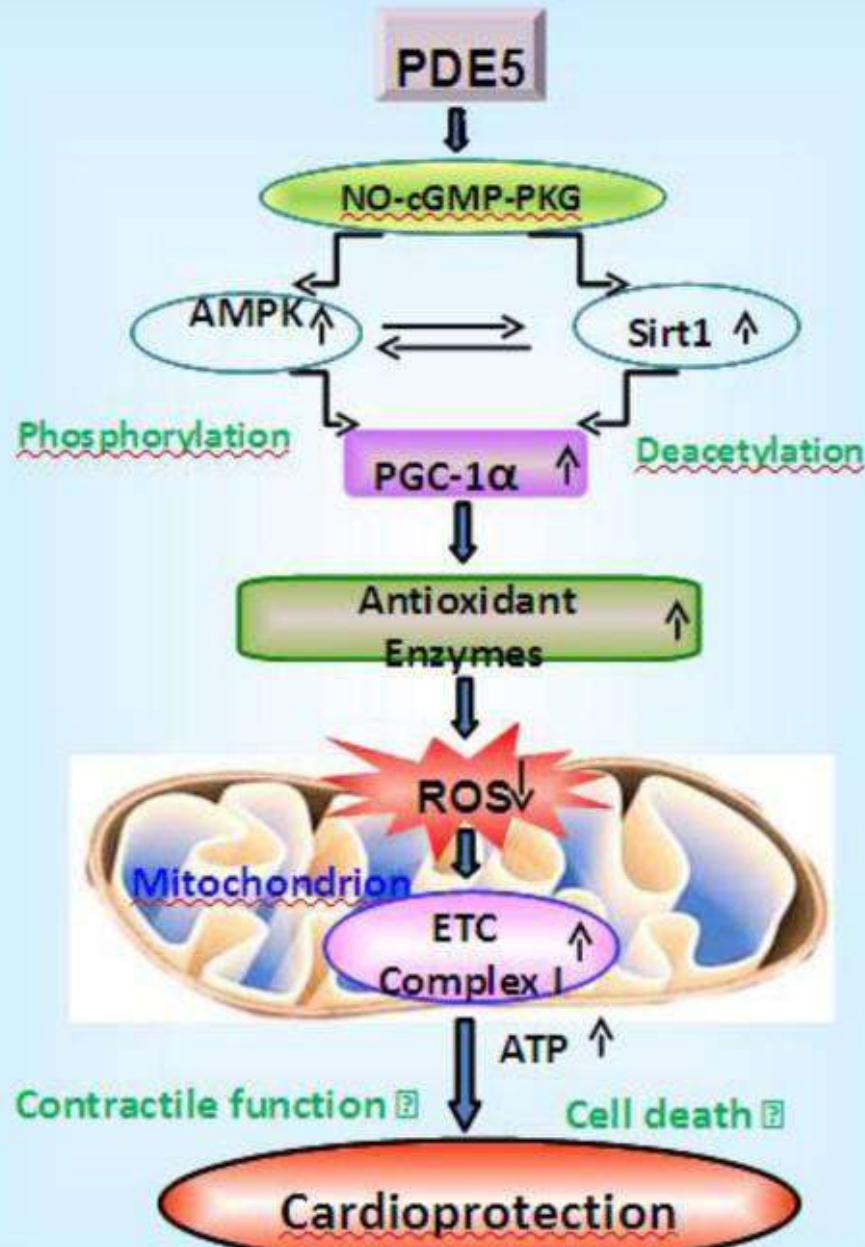
Change in flow-mediated dilatation (FMD) from pretreatment



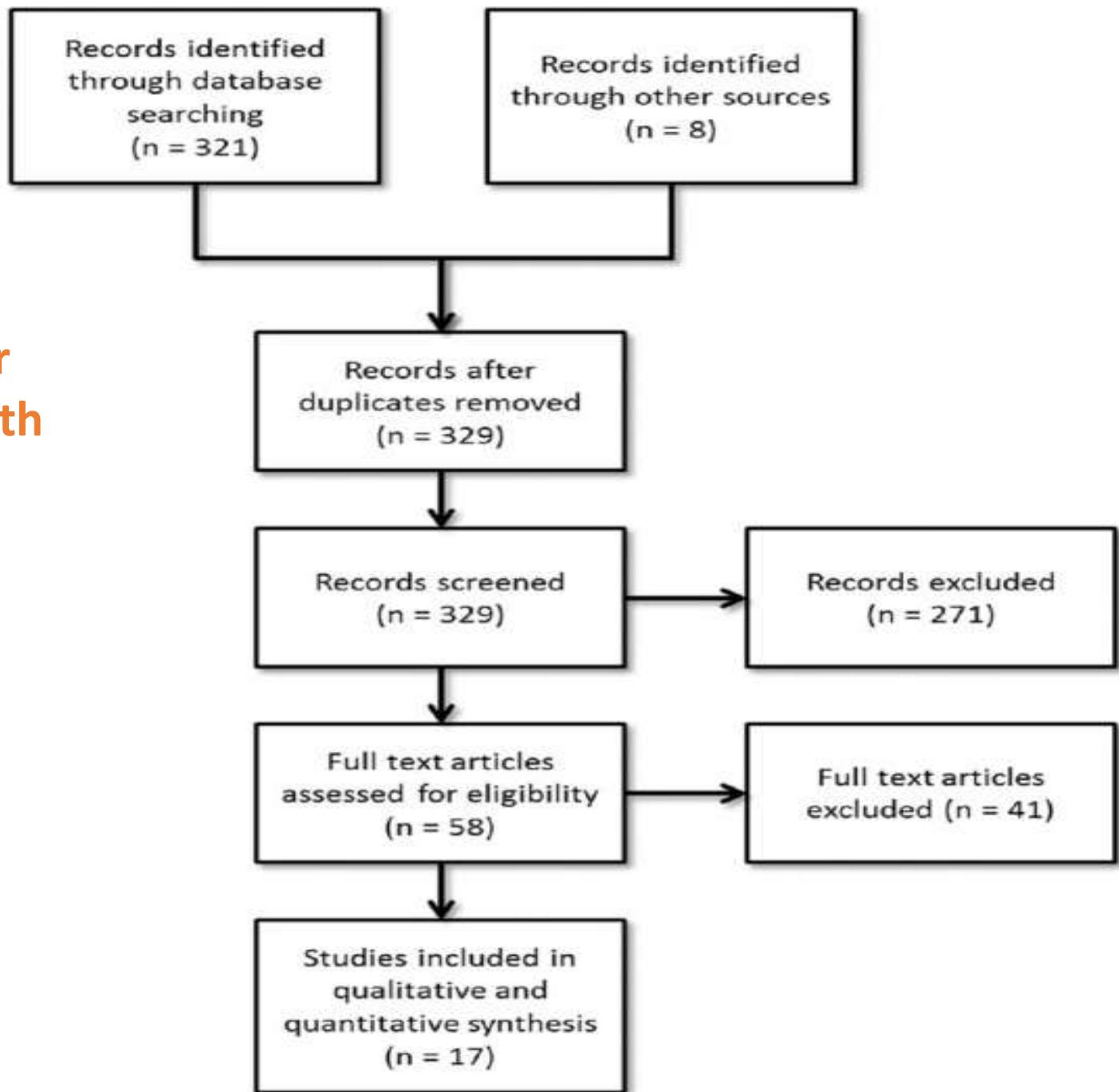
# Chronic Treatment with Tadalafil Improves Endothelial Function in Men with Increased Cardiovascular Risk



Percent change compared to baseline in endothelial function (FMD) in patients treated with tadalafil and placebo after 4 weeks of therapy with Tadalafil 20 mg on alternate days and after 2 weeks of discontinuation of therapy



# Phosphodiesterase-5 inhibitors for erectile dysfunction in patients with diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials



## NNT for placebo controlled studies

### Phosphodiesterase-5 inhibitors for erectile dysfunction in patients with diabetes mellitus: Number needed to treat (NNT)

Author, year	Active compound	NNT
Price <i>et al.</i> , 1998 <sup>[25]</sup>	Sildenafil 25 mg	2.5
Price <i>et al.</i> , 1998 <sup>[25]</sup>	Sildenafil 50 mg	2.4
Rendell <i>et al.</i> , 1999 <sup>[26]</sup>	Sildenafil 25-100 mg	2.2
Boulton <i>et al.</i> , 2001 <sup>[27]</sup>	Sildenafil 25-100 mg	1.8
Tejada <i>et al.</i> , 2002 <sup>[28]</sup>	Tadalafil 10 mg	3.2
Tejada <i>et al.</i> , 2002 <sup>[28]</sup>	Tadalafil 20 mg	2.6
Goldstein <i>et al.</i> , 2003 <sup>[29]</sup>	Vardenafil 10 mg	4.0
Goldstein <i>et al.</i> , 2003 <sup>[29]</sup>	Vardenafil 20 mg	3.6
Stuckey <i>et al.</i> , 2003 <sup>[30]</sup>	Sildenafil 25-100 mg	3.3
Fonseca <i>et al.</i> , 2004 <sup>[31]</sup>	Tadalafil 10 mg	3.2
Fonseca <i>et al.</i> , 2004 <sup>[31]</sup>	Tadalafil 20 mg	2.2
Safarinejad, 2004 <sup>[32]</sup>	Sildenafil 100 mg	2.7
Ishii <i>et al.</i> , 2006 <sup>[34]</sup>	Vardenafil 10 mg	4.5
Ishii <i>et al.</i> , 2006 <sup>[34]</sup>	Vardenafil 20 mg	3.6
Ziegler <i>et al.</i> , 2006 <sup>[35]</sup>	Vardenafil 5-20 mg	5.0
Hatzichristou <i>et al.</i> , 2008 <sup>[36]</sup>	Tadalafil 2.5 mg	3.1
Hatzichristou <i>et al.</i> , 2008 <sup>[36]</sup>	Tadalafil 5 mg	2.8
Park <i>et al.</i> , 2010 <sup>[37]</sup>	Mirodenafil 100 mg	1.7
Moon <i>et al.</i> , 2011 <sup>[39]</sup>	Udenafil 100 mg placebo	2.9
Moon <i>et al.</i> , 2011 <sup>[39]</sup>	Udenafil 200 mg placebo	1.9
Chen <i>et al.</i> , 2012 <sup>[40]</sup>	Tadalafil 5 mg	1.8
Goldstein <i>et al.</i> , 2012 <sup>[41]</sup>	Avanafil 100 mg	7.2
Goldstein <i>et al.</i> , 2012 <sup>[41]</sup>	Avanafil 200 mg	5.1

NNT: Number needed to treat

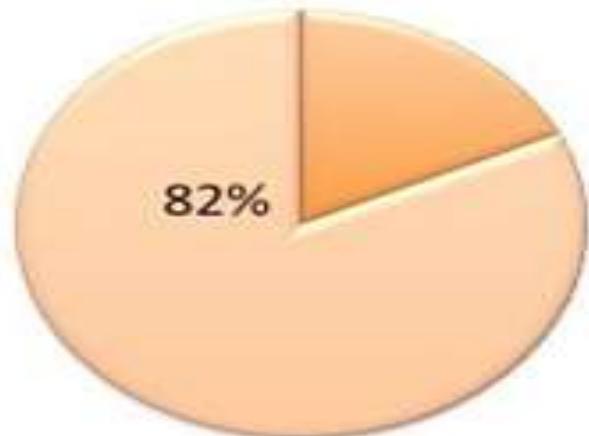
## PDE5 inhibitors in diabetic patients with ED: systematic review and meta-analysis

- In pooled analysis, the Number needed to Treat (NNT) for any PDE5 inhibitor: 3.0
  - Sildenafil: 2.4
  - Tadalafil: 2.6
  - Vardenafil: 4.1
- 
- The most common side effects were headache, flushing, and nasal congestion.

# EFFICACY OF CURRENT USED PDE5i DRUGS

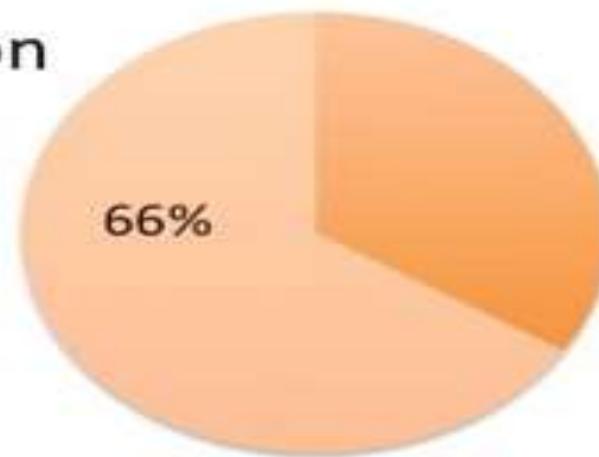
Based on Patient questionnaires

Global assessment Question

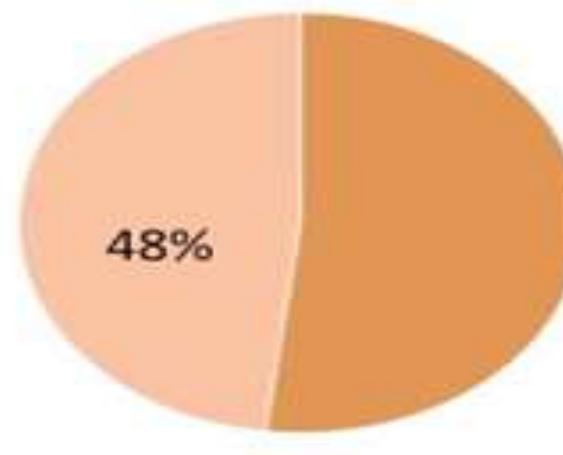
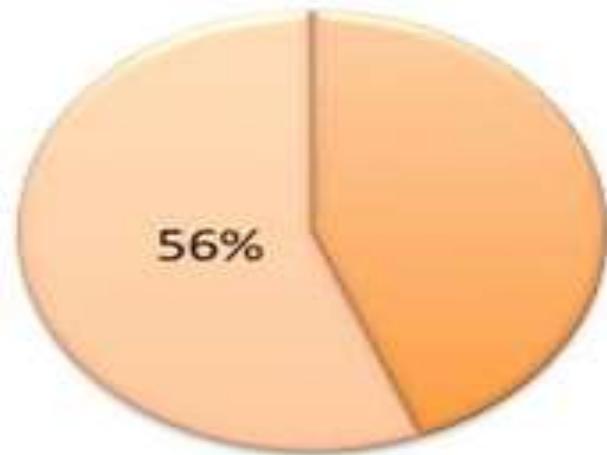


Sexual Encounter Profile (SEP)  
SEP 2/3

Mixed population



Diabetes



# PDE5i in patients with diabetes mellitus

In a review of randomized clinical trials of PDE5i in diabetic patients, the weighted mean difference for the IIEF-EF and the percentage of successful attempts in the PDE-5 inhibitors and in the control arm was 26.7 and 6.6 respectively (Vardi and Nini 2007).

Diabetes-induced ED is multifactorial:

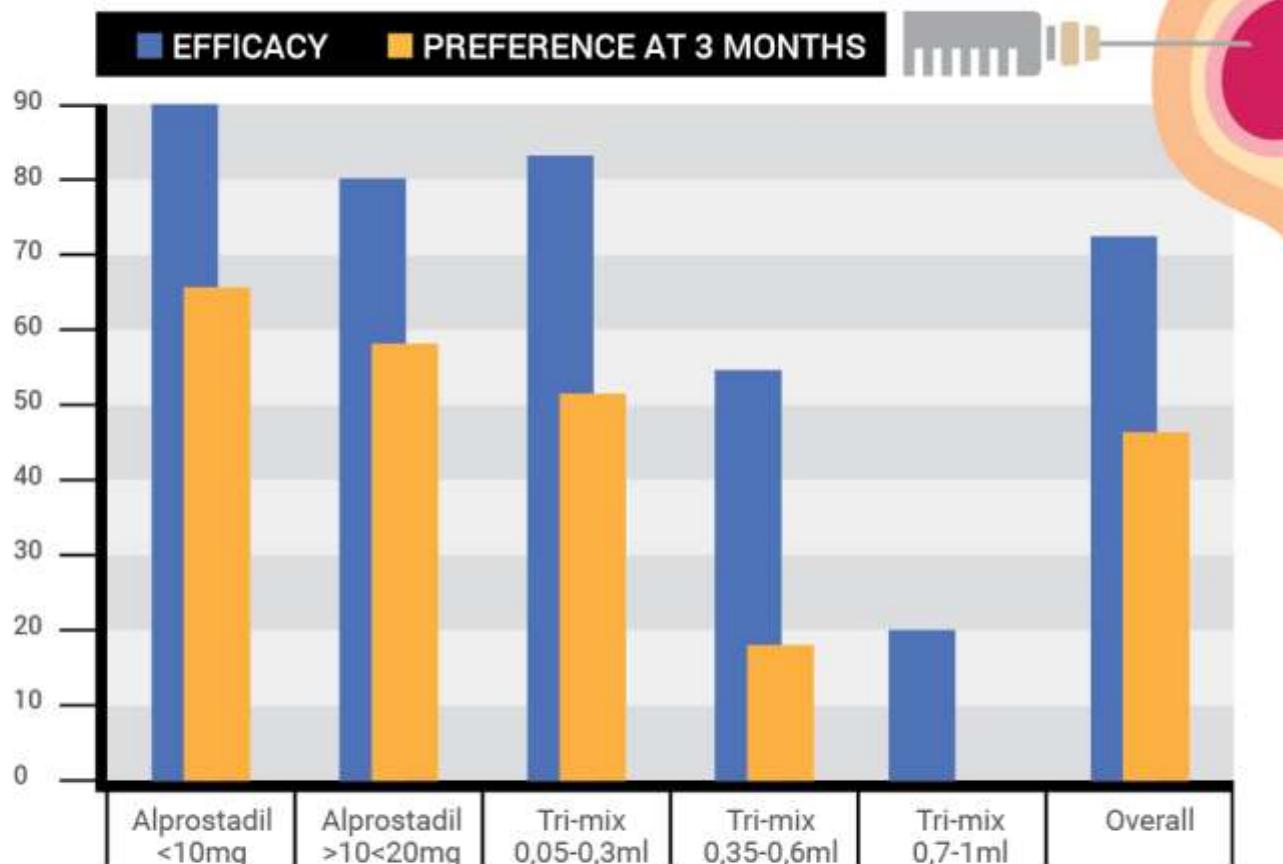
- elevated advanced glycation endproducts,
- high levels of oxygen free radicals,
- impaired nitric oxide synthesis,
- increased endothelinB receptor binding sites
- up-regulated RhoA/Rho-kinase pathway,
- neuropathic damage
- impaired cyclic guanosine monophosphate (cGMP)- dependent protein kinase-1

The only existing strategy to improve response rates include initially **management of the underlying hyperglycemia and comorbidities, as well as to start early treatment with PDE5i** (also to prevent or halt the progression of disease).

Efficacy only in pts with good, long term blood glucose control

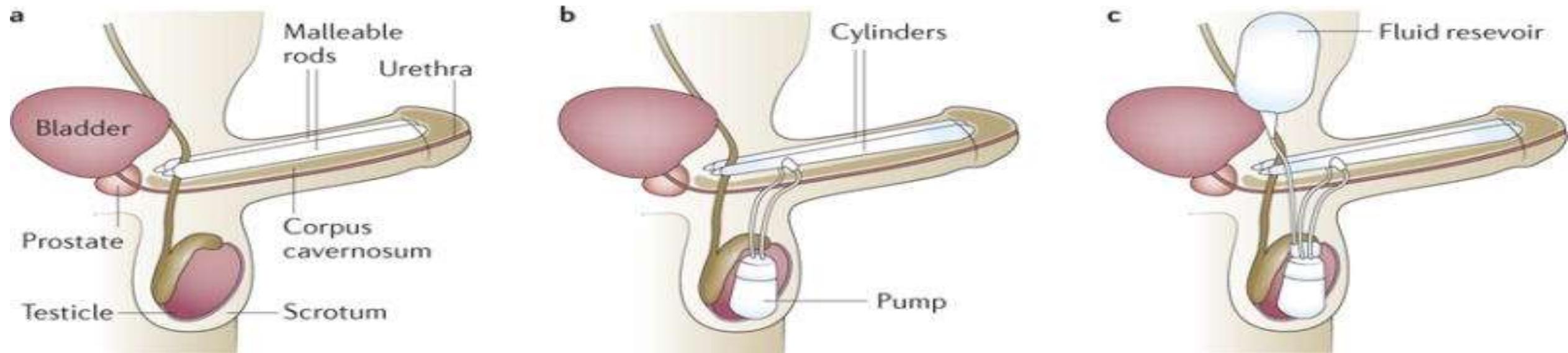
1 out of 2 pts will respond to treatment

Treat any comorbidity



Differences in efficacy of sildenafil and preference by group in overall study sample of 155 patients. Tri-mix, combined papaverine, phentolamine and prostaglandin E1.

# Types of penile prostheses



Screen all men with DM for ED

Screen for hypogonadism  
(Testosterone level)

Modify risk factors<sup>1</sup>

PDE-5 inhibitors<sup>2</sup>

Consider Testosterone replacement<sup>3</sup>

Urology Referral

PDE-5 inhibitor

**Early Death**

**Endothelial  
Dysfunction-  
risk factors**

**Early  
Detection-  
health check**

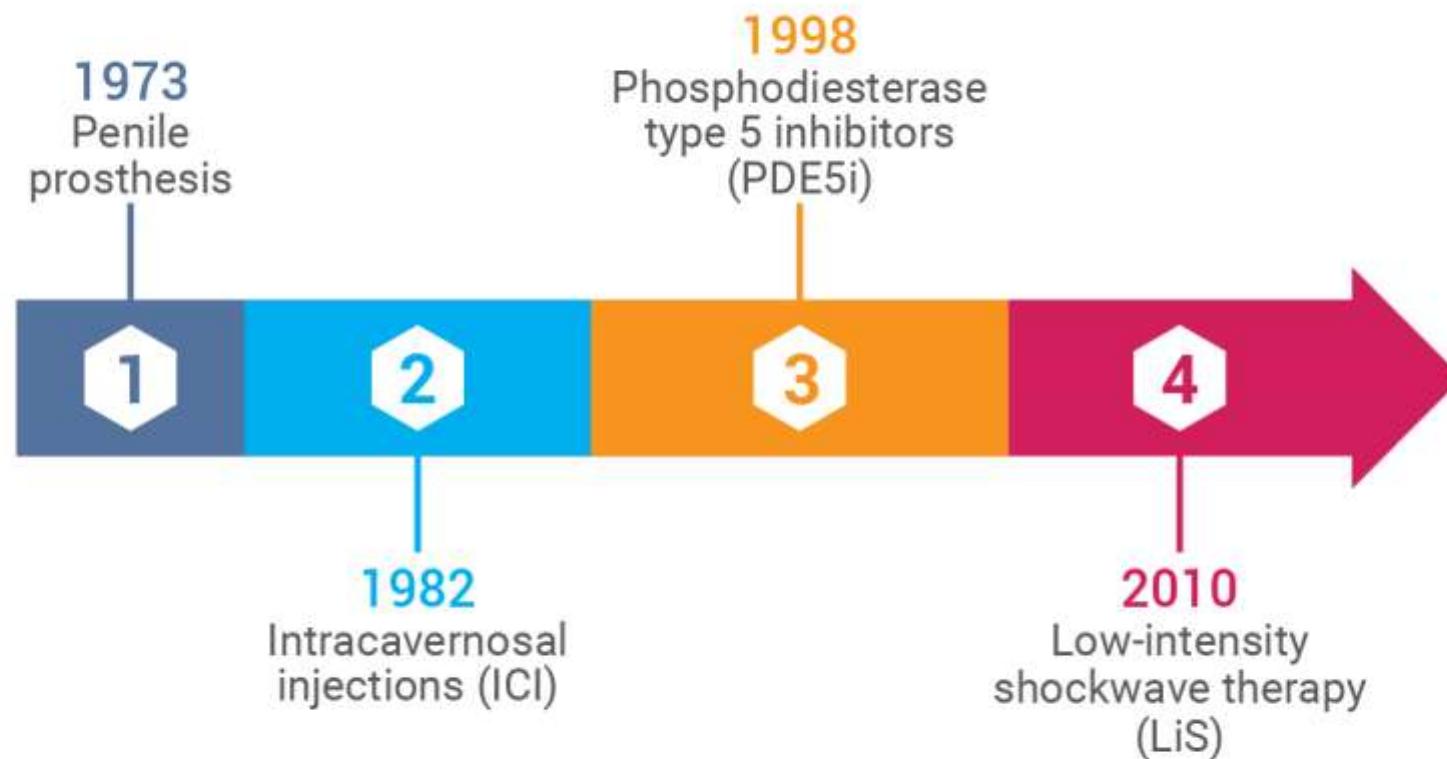
**E.D.**

**Education -  
lifestyle**

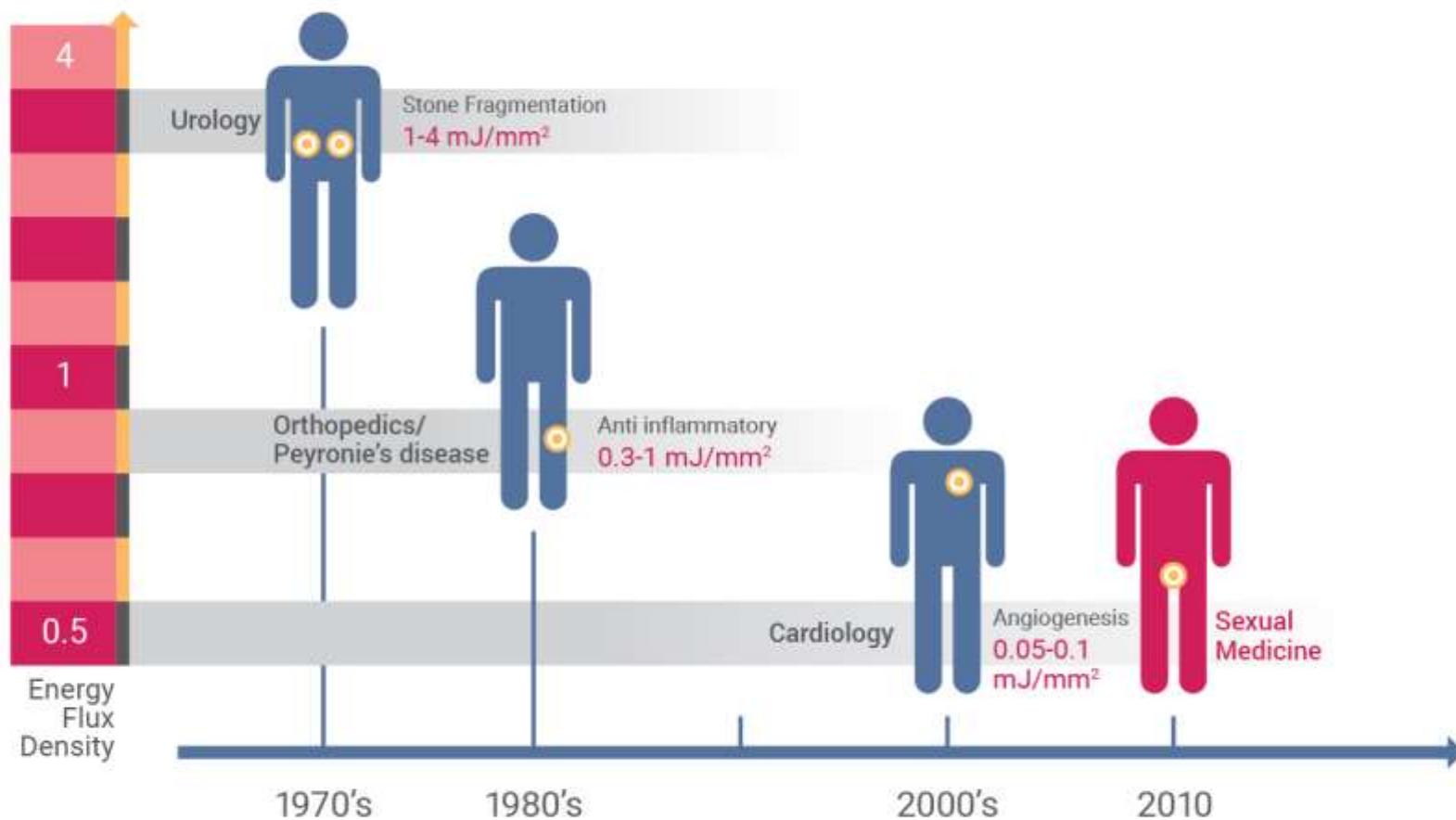
**Erectile  
Dysfunction**



# Milestones in erectile dysfunction therapy



# Shockwave therapies history



# The effect of low-intensity shockwave therapy on cavernosal arterial supply



# ED: the effect of low-intensity shockwaves (LiS)

Occlusion of the arterioles



LiS therapy

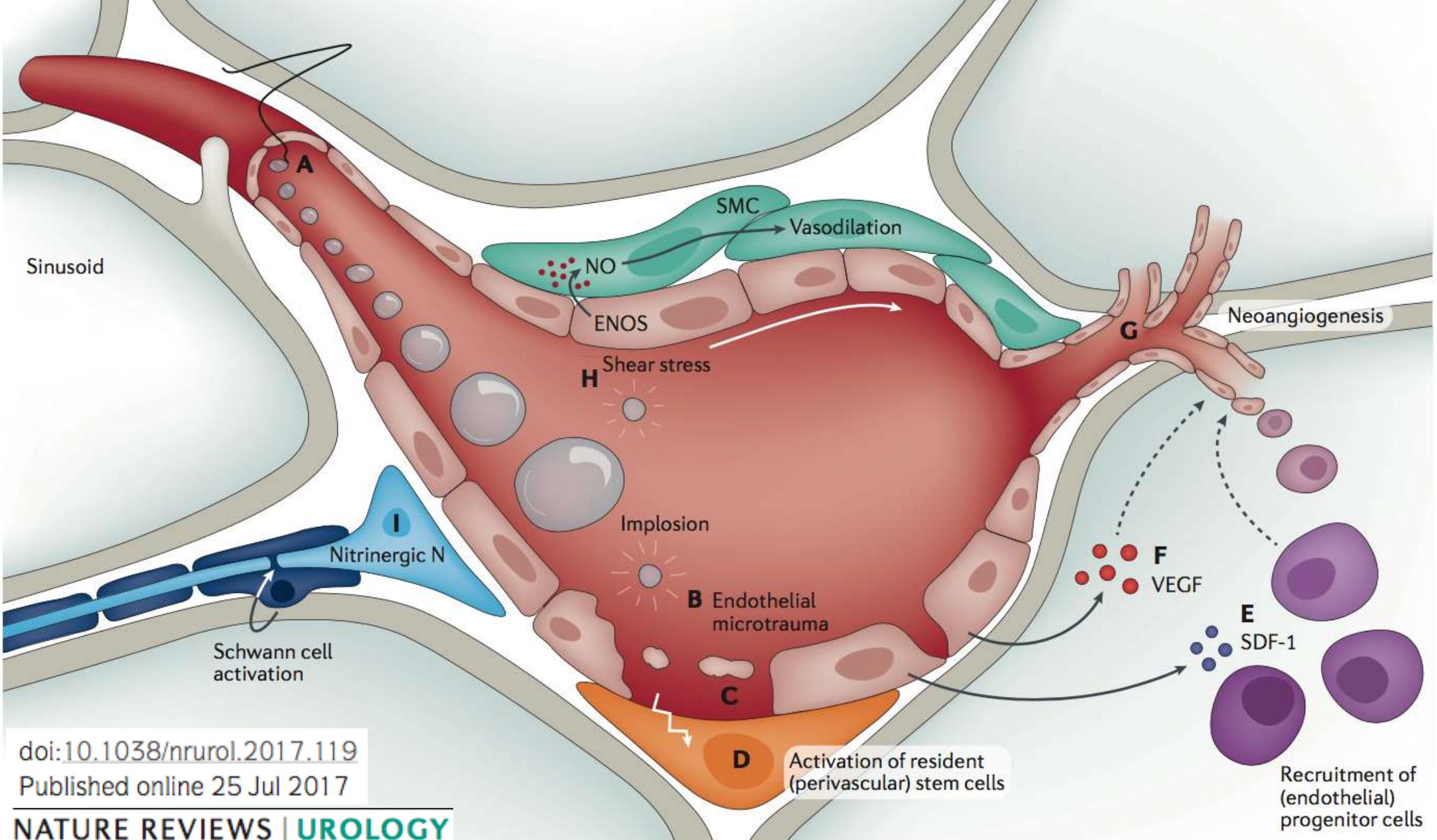


New arterioles (angiogenesis)

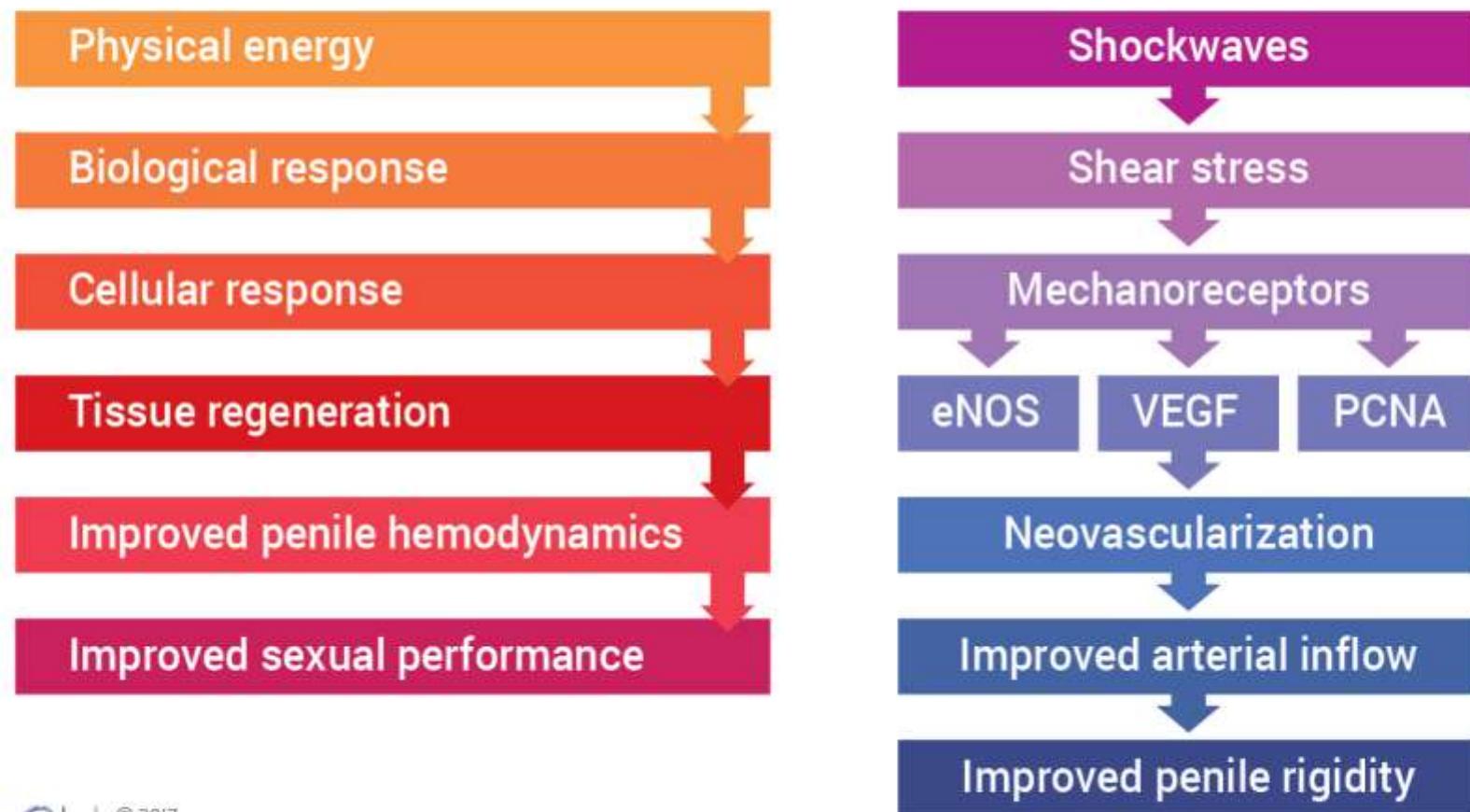


# ED therapies: the differences

	Reverse pathology	Symptom Relief	Side effects Complications	Invasiveness
Intracavernosal Injections		✓	✓	✓
Phosphodiesterase Type 5 inhibitors		✓	✓	
Penile prosthesis		✓	✓	✓
Low-intensity shockwave therapy	✓	✓		



Low-intensity shockwaves: physical energy initiates a cascade of biologic responses, leading to reversal of vasculogenic ED



# Low-intensity Shockwaves for Erectile Dysfunction

Clinical evidence  
Evidence-based protocol

Dimitris Hatzichristou, MD, PhD, FEJCSM

# Low-intensity shockwaves (LiS) for ED 7 years clinical experience

## 2010: The novel treatment is invented!

Vardi, Y., Appel, B., Jacob, G., Massarwi, O. and Gruenwald, I. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. *Eur Urol* 58: 243-248, 2010.

## 2012: LiS is better than placebo!

Vardi, Y., Appel, B., Kilchevsky, A. and Gruenwald, I. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. *J Urol* 187: 1769-1775, 2012.

## 2016: LiS is able to shift PDE5i non-responders to responders!

Kitrey ND, Gruenwald I, Appel B, Shechter A, Massarwa O, Vardi Y. Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: a double-blind, sham controlled study. *J Urol* 195(5):1550-5, 2016.

## 2017: LiS improves penile hemodynamics!

Kalyvianakis D, Hatzichristou D. Low intensity shock wave therapy improves hemodynamic parameters in patients with vasculogenic erectile dysfunction: a triplex ultrasonography-based sham-controlled trial. *J Sex Med* 14:891-897, 2017.

## Low-intensity shockwave therapy for erectile dysfunction: is the evidence strong enough?

Mikkel Fode<sup>1</sup>, Georgios Hatzichristodoulou<sup>2</sup>, Ege Can Serefoglu<sup>3</sup>, Paolo Verze<sup>4</sup> and Maarten Albersen<sup>5</sup> on behalf of the Young Academic Urologists Men's Health Group

### NATURE REVIEWS | UROLOGY

doi:10.1038/nrurol.2017.119

Published online 25 Jul 2017

Table 2 | Systematic reviews and meta-analyses of Li-ESWT for ED

Study	Design	IIEF improvement	EHS improvement	Limitations
Fojecki et al. <sup>53</sup> (2016)	<ul style="list-style-type: none"> <li>• Systematic review (PROSPERO: CRD42015015665)</li> <li>• Vardi et al.<sup>39</sup></li> <li>• Olsen et al.<sup>40</sup></li> <li>• Srini et al.<sup>45</sup></li> <li>• Yee et al.<sup>41</sup></li> <li>• n = 337</li> <li>• Vasculogenic ED</li> </ul>	"Effects of ESWT on IIEF in ED patients are inconsistent..."	"...data on EHS does imply that the treatment potentially may recover natural erection in PDE5I responders."	<ul style="list-style-type: none"> <li>• No meta-analysis</li> <li>• No assessment of biases</li> </ul>
Lu et al. <sup>52</sup> (2016)	<ul style="list-style-type: none"> <li>• Systematic review and meta-analyses of RCTs only</li> <li>• Vardi et al.<sup>39</sup></li> <li>• Olsen et al.<sup>40</sup></li> <li>• Srini et al.<sup>45</sup></li> <li>• Yee et al.<sup>41</sup></li> <li>• Chitale et al.<sup>71</sup> Poulakis et al.<sup>64</sup></li> <li>• Zimmermann et al.<sup>87</sup></li> <li>• n = 501 (from meta-analysis only)</li> <li>• All ED aetiologies</li> </ul>	2.00 (95% CI 0.99–3.00); P < 0.0001 compared with placebo	0.16 (95% CI, 0.04–0.29)	<ul style="list-style-type: none"> <li>• Inclusion of studies at high risk of bias and with ED as a secondary end point (Peyronie's disease, pelvic pain)</li> <li>• Inclusion of nonrandomized trial in meta-analysis (Poulakis et al.<sup>64</sup>)</li> <li>• Inclusion of trials on Peyronie's disease with ESWT directed at plaque only, not corpora</li> <li>• Incorrect citation of IIEF data</li> </ul>
Angulo et al. <sup>54</sup> (2016)	<ul style="list-style-type: none"> <li>• Systematic review and meta-analyses</li> <li>• Vardi et al.<sup>39</sup></li> <li>• Olsen et al.<sup>40</sup></li> <li>• Srini et al.<sup>45</sup></li> <li>• Yee et al.<sup>41</sup></li> <li>• n = 337</li> <li>• Vasculogenic ED</li> </ul>	2.54 (95% CI 2.12–2.95); P < 0.0001 compared with placebo	NA	No assessment of biases
Clavijo et al. <sup>55</sup> (2017)	<ul style="list-style-type: none"> <li>• Systematic review and meta-analyses</li> <li>• Vardi et al.<sup>38</sup></li> <li>• Srini et al.<sup>44</sup></li> <li>• Yee et al.<sup>40</sup></li> <li>• Hatzichristou &amp; Kalyvianakis (abstract)<sup>80</sup></li> <li>• Fojecki et al. (abstract)<sup>82</sup></li> <li>• Feldman et al. (abstract)<sup>81</sup></li> <li>• Kitrey et al.<sup>8</sup></li> <li>• n = 602</li> <li>• Vasculogenic ED</li> </ul>	4.17 (95% CI -0.5–8.3); P < 0.0001 compared with placebo	NA	<ul style="list-style-type: none"> <li>• Inclusion of studies at high risk of bias or with inadequate assessment of bias</li> <li>• Use of unpublished data (quality assessment virtually impossible in abstract versus published full text) and unclear whether overlap exists between the "Israel" groups in Feldman et al.<sup>81</sup> and previous trials</li> </ul>

# Low-intensity shockwave therapy for erectile dysfunction

## Development of an evidence-based protocol



### RESEARCH TEAM

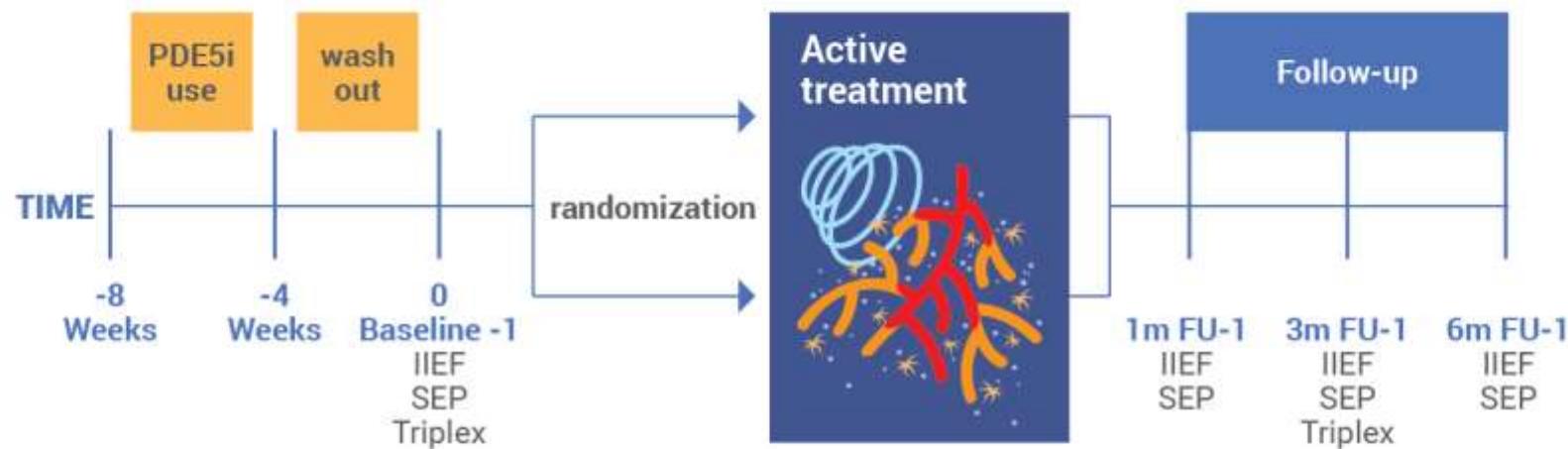
- Dimitris Kalyvianakis, MD, PhD candidate
- Voula Kapoteli, MSc, Research Coordinator
- Vangelis Memmos, MD, MSc
- Yannis Mykoniatis, MD, MSC
- Dimitris Memmos, MD
- Dimitris Hatzichristou, MD, PhD





# Low-intensity shockwaves for erectile dysfunction

## Identical study design in all studies



**STUDY DESIGN:**  
randomized, parallel arms, open label  
**INCLUSION CRITERIA**  
History indicating vasculogenic ED  
ED duration: >6 months  
IIEF-EF domain: <26 without PDE5i  
Previous ED treatment: only PDE5i users  
Peak Systolic Velocity: <35cm/sec  
Stable heterosexual relationship  
Informed consent: written

**REGISTRY:** ClinicalTrials.gov  
**EXCLUSION CRITERIA:** Peyronie's disease, neurogenic/psychiatric disease, untreated but diagnosed medical condition, cancer, hemophilia.

## How to perform the treatment low-intensity shockwave therapy for erectile dysfunction?

1

Move slowly the probe along the length of both corpora cavernosa back and forth (1500 shocks each side)



2

Put the probe on the peno-scrotal junction in parallel to the pubic bone (500 shocks each side)



5

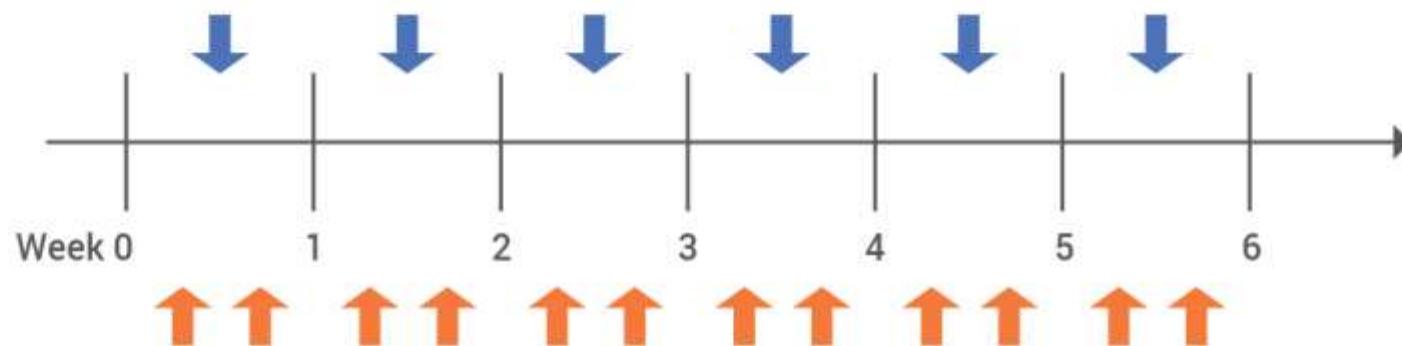
Put the probe on the crura (500 shocks each side)



## Study design: 6 vs 12 sessions –1 vs 2 sessions/week

### Group A :

1x / week, total 6 sessions



### Group B :

2x / week, total 12 sessions

Each session: 5000 shockwaves, 0.05 mJ/mm<sup>2</sup>, 8Hz

## Minimal Clinically Important Differences (MCID)\* at 6 months follow up: 6 vs 12 sessions

% MCID	Mild-Mod ED	Moderate ED	Severe ED	Total
Group A (6 sessions)	83% (10/12)	43% (3/7)	0% (0/2)	62% (13/21)
Group B (12 sessions)	89% (8/9)	67% (6/9)	33% (1/3)	71% (15/21)

\*MCID definitions:

- mild ED:  $\geq 2$  points increase
- moderate:  $\geq 5$  points increase
- severe:  $\geq 7$  points increase

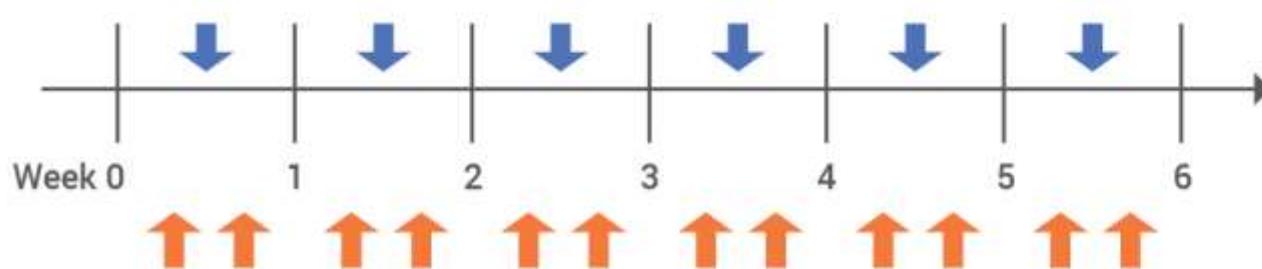
Rosen RC et al:  
Eur Urol 2011; 60: 1010

## Repeat study design

### Group A :

1x / week,  
total 6 sessions

### Study Phase 1: 6 versus 12 sessions



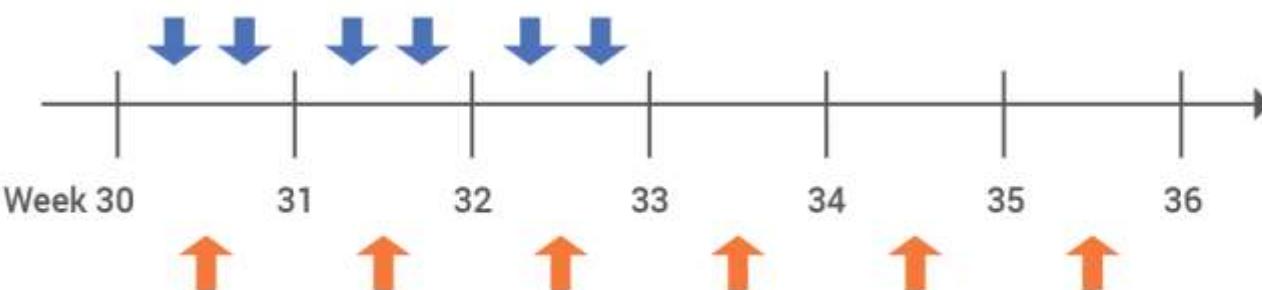
### Group B :

2x / week,  
total 12 sessions

### Group A :

2x / week,  
total 6 sessions

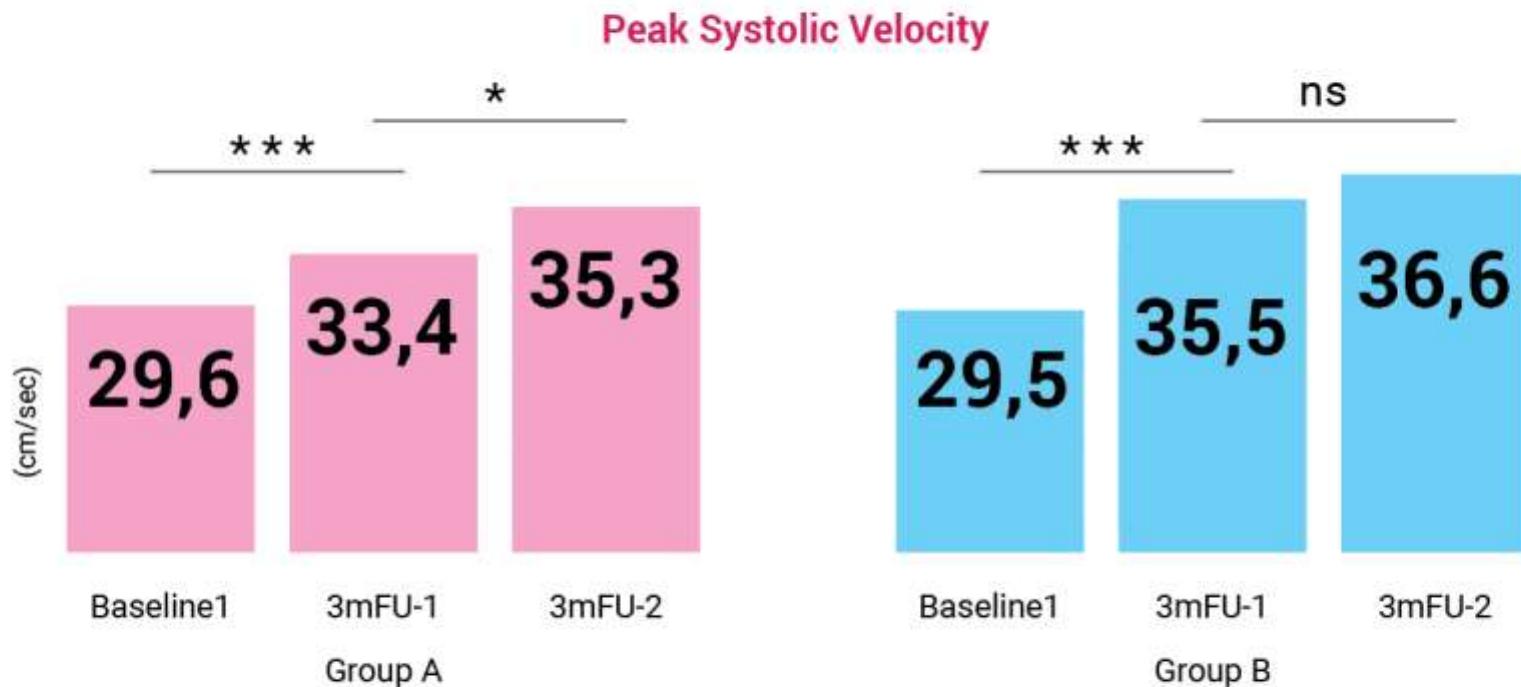
### Study Phase 2: repeat ESWT after 6 months



### Group B :

1x / week,  
total 6 sessions

## Triplex ultrasonography: changes in penile hemodynamic parameters at 3 months follow up: Repeat study



**Peak systolic velocity** improvement:  
Group A (6+6 sessions): **+1.9** cm/sec  
Group B (12+6 sessions): **+0.1** cm/sec

ns = not significant  
\* p < 0.05  
\*\*\* p < 0.005

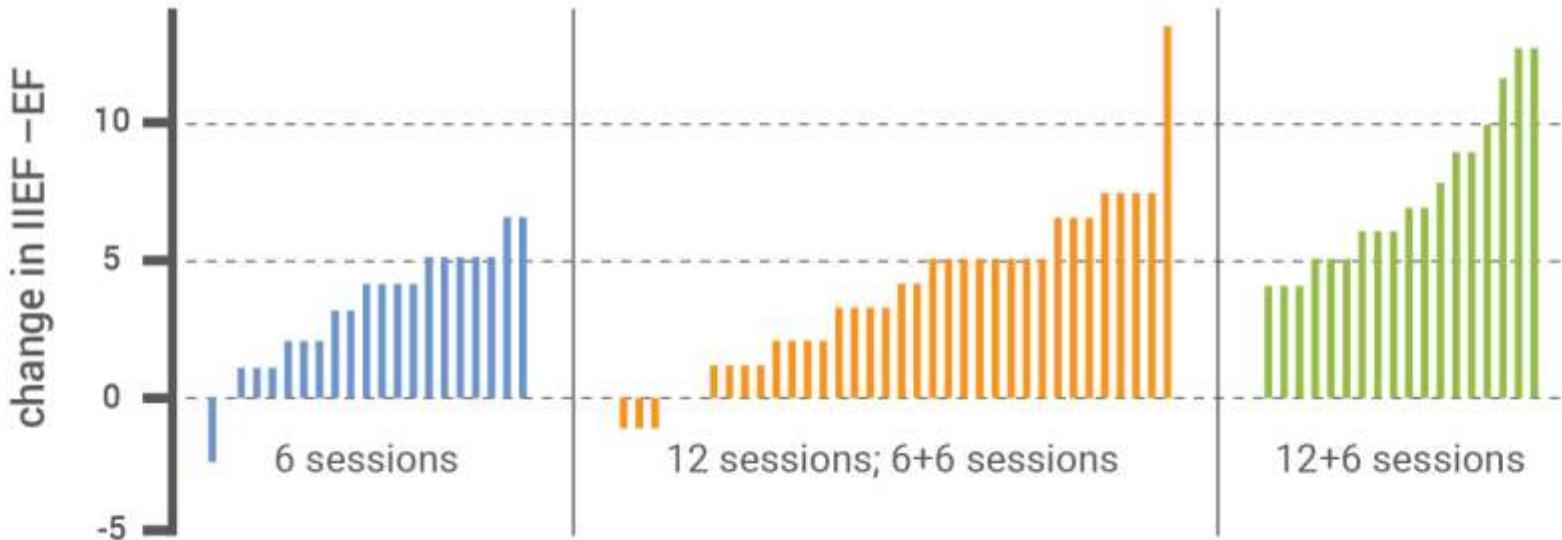
## Minimal Clinically Important Differences (MCID) at 6 months follow up by number of sessions\*

Session number	Patients	Percentage (%)
6	13/21	61.9
12*	29/39	74.4
18*	15/18	83.3

\*Mix of patients receiving sessions at different time intervals (combined results of 2 randomized trials)

## Changes in IIEF-EF domain score by subject: repeat study

- After 18 sessions, all patients achieved at least 4 point increase in IIEF-EF score\*
- **83.3% of the patients achieved Minimal Clinically Important Difference (MCID)**



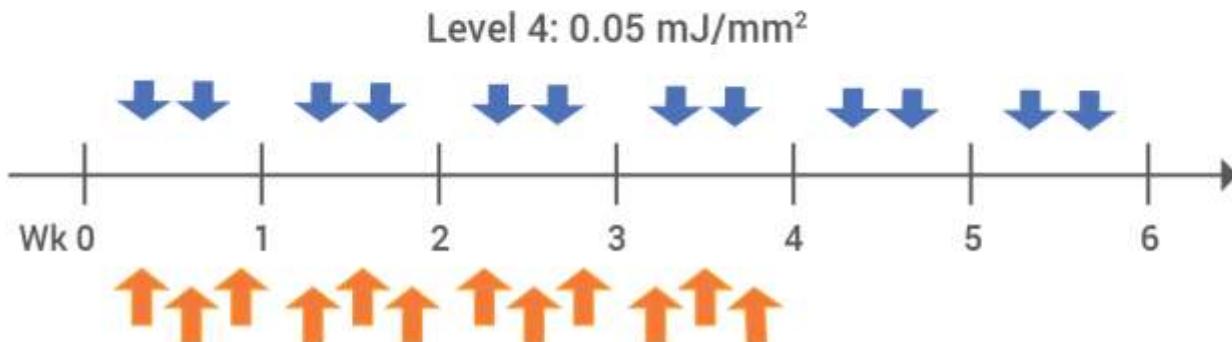
\*A 4-point increase in IIEF-EF domain score is associated with the following odds ratios of success for each IIEF-EF question:

- 6.1 for getting an erection
- 29.2 for having a firm erection
- 10.0 for able to penetrate
- 12.8 for maintaining erection
- 4.0 for maintaining erection to completion
- 3.7 for erection confidence

Cappelleri JC et al:  
JSM 2016; 13:690

# The EFD study: study design

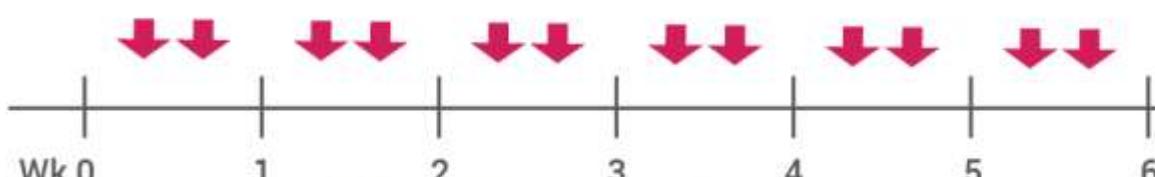
**Group A :**  
2x / week, L4  
total 12 sessions



**Group B :**  
3x / week, L4  
total 12 sessions

**Group C :**  
2x / week, L7  
total 12 sessions

Level 7: 0.10 mJ/mm<sup>2</sup>



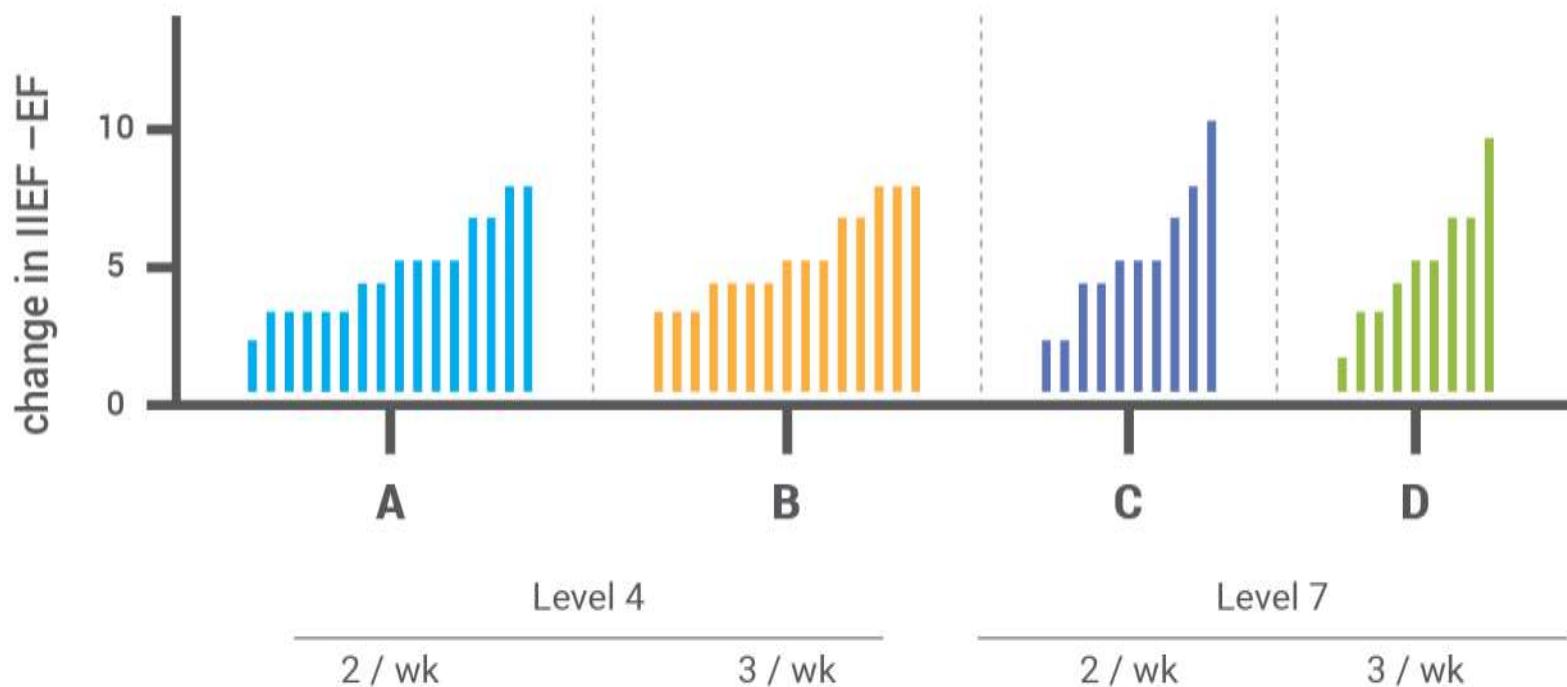
**Group D :**  
3x / week, L7  
total 12 sessions



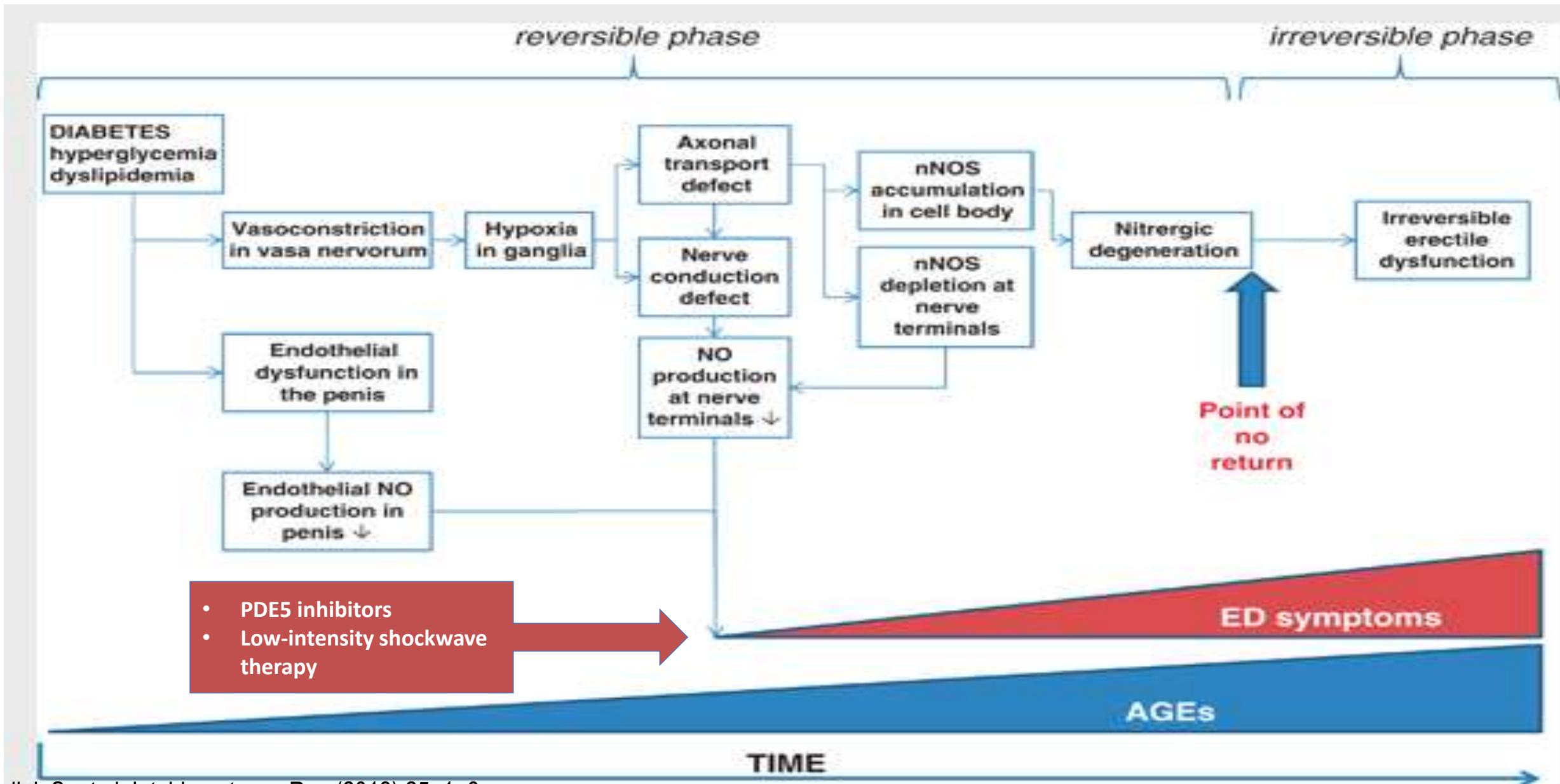
L4: 5000 SW, 0.05 mJ/mm<sup>2</sup>, 8Hz;  
L7: 5000 SW, 0.10 mJ/mm<sup>2</sup>, 5Hz

**Energy flux density (EFD).** The energy delivered by the shockwave-generating source at the focussed point is called *energy flux density* and is normally recorded in energy per surface area units (mJ/mm<sup>2</sup>).

## Change in IIEF-EF score at 3 months follow up



# Diabetes mellitus and ED: point of no return





1. Ρωτήστε τους άντρες ασθενείς σας εάν έχουν πρόβλημα στύσης ή χρησιμοποιούν φάρμακα για τη στύση
2. Ενημερώστε τους για τα κρουστικά κύματα!
3. Εντελώς δωρεάν μπορούν να συμμετέχουν στην μελέτη των διαβητικών ασθενών με στυτική δυσλειτουργία

Καθημερινά  
στο  
**2310 992547**  
ραντεβού για κρουστικά