



ΕΛΛΗΝΙΚΟ  
ΔΙΑΔΡΑΣΤΙΚΟ  
ΣΧΟΛΕΙΟ  
ΟΥΡΟΛΟΓΙΑΣ

# ΜΕΤΑΒΟΛΙΚΟ ΣΥΝΔΡΟΜΟ ΚΑΙ ΣΤΥΣΗ

Mission Impossible?



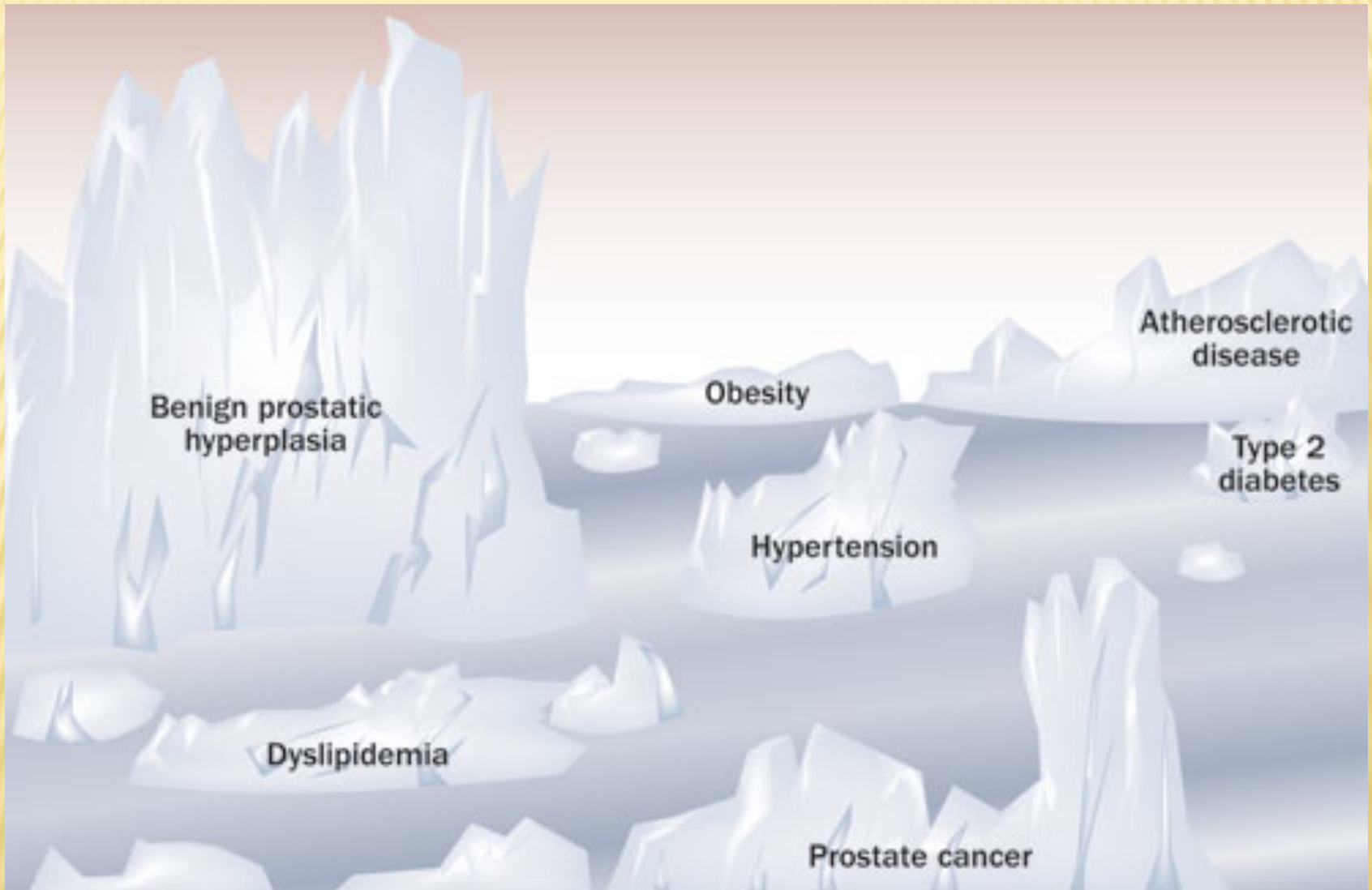
Δημήτρης Χατζηχρήστου

Δ. Χατζηχρήστου  
Δήλωση συμφερόντων

Ερευνητής / μέλος advisory board:

- Bayer
- GSK
- Lilly
- Medispec
- Menarini

Metabolic syndrome: type 2 diabetes, obesity, hypertension, and others—are only the tip of the iceberg.



Hammarsten J & Peeker R: *Nature Reviews Urology* 8, 483-494, 2011.

# Παράγοντες κινδύνου για στυτική δυσλειτουργία

Υπέρταση	2x
Καρδιοπάθειες	2x
Κατάθλιψη	3.5x
Διαβήτης	4x
Ανεργία	2x
Υπερχολ/ναιμία	4x

Circulation 1997; 95:1132-37 & 1996; 94:3123-29

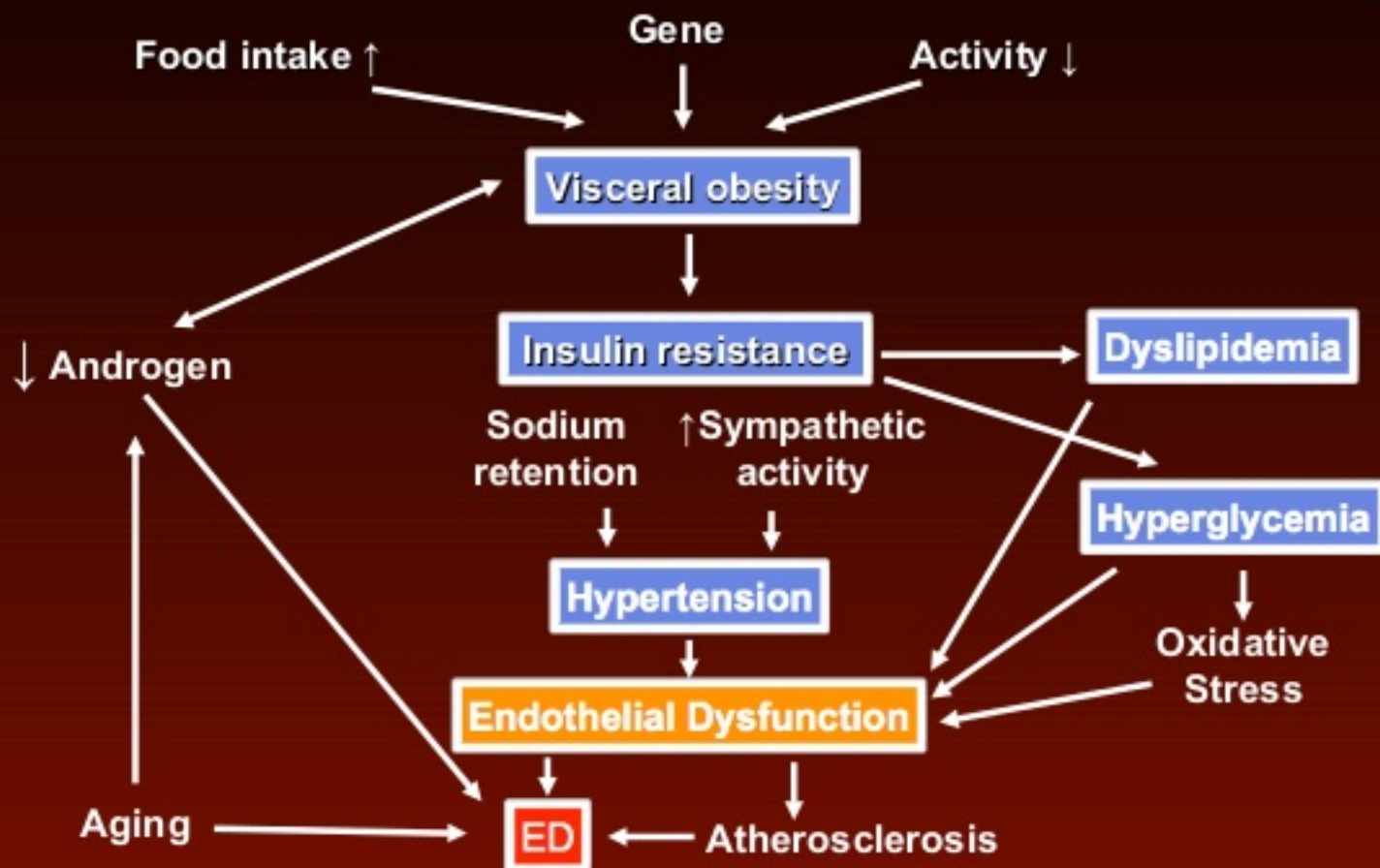
Stroke 1998; 29:1329-32 & 1998:1341-46

JAMA 1996; 275: 1405-09

J Am Med Assoc 1999; 281: 537-544.

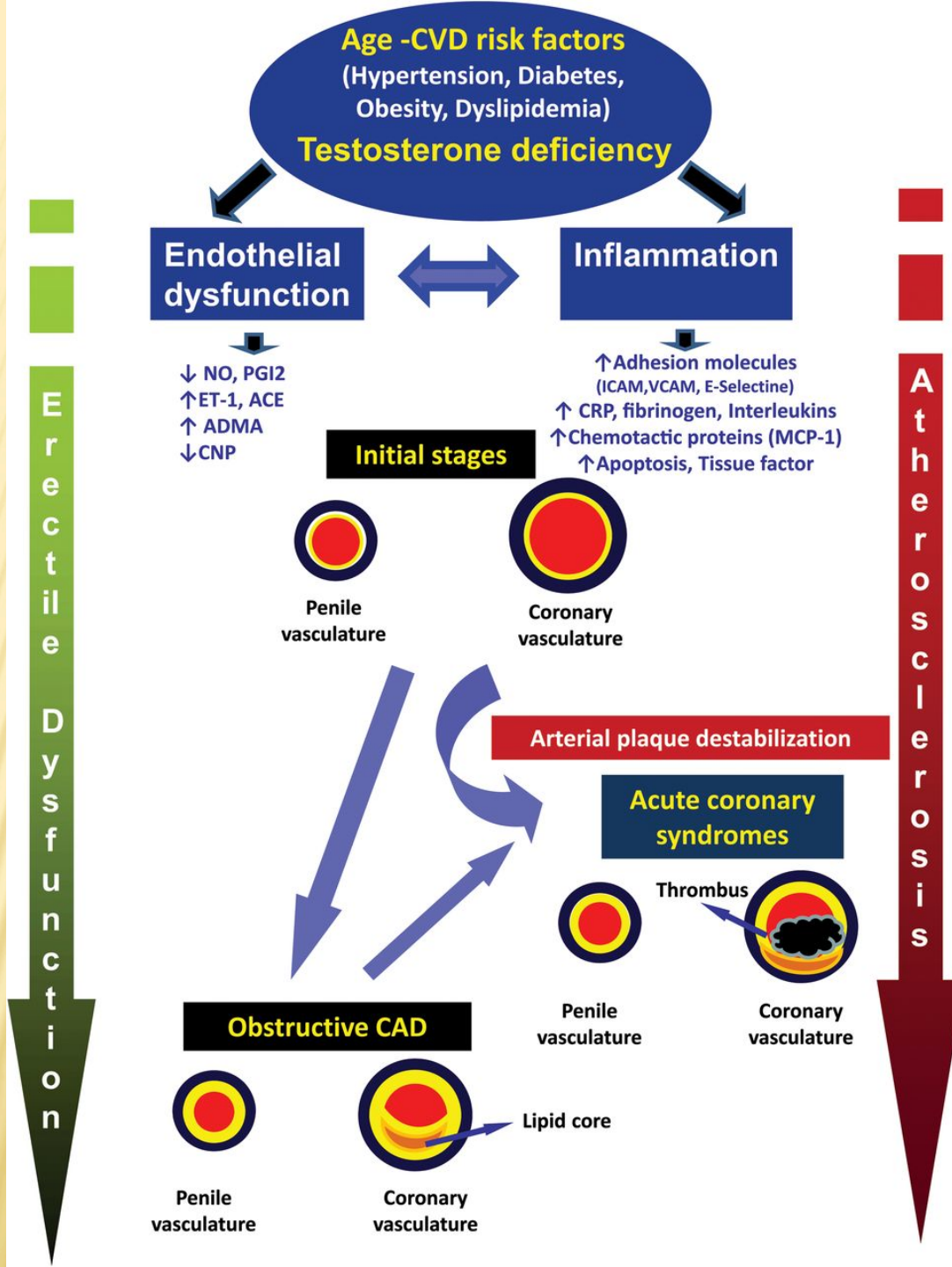
J Impot Res 2001; 12; 305-11.

# The Pathogenesis of ED in Metabolic Syndrome



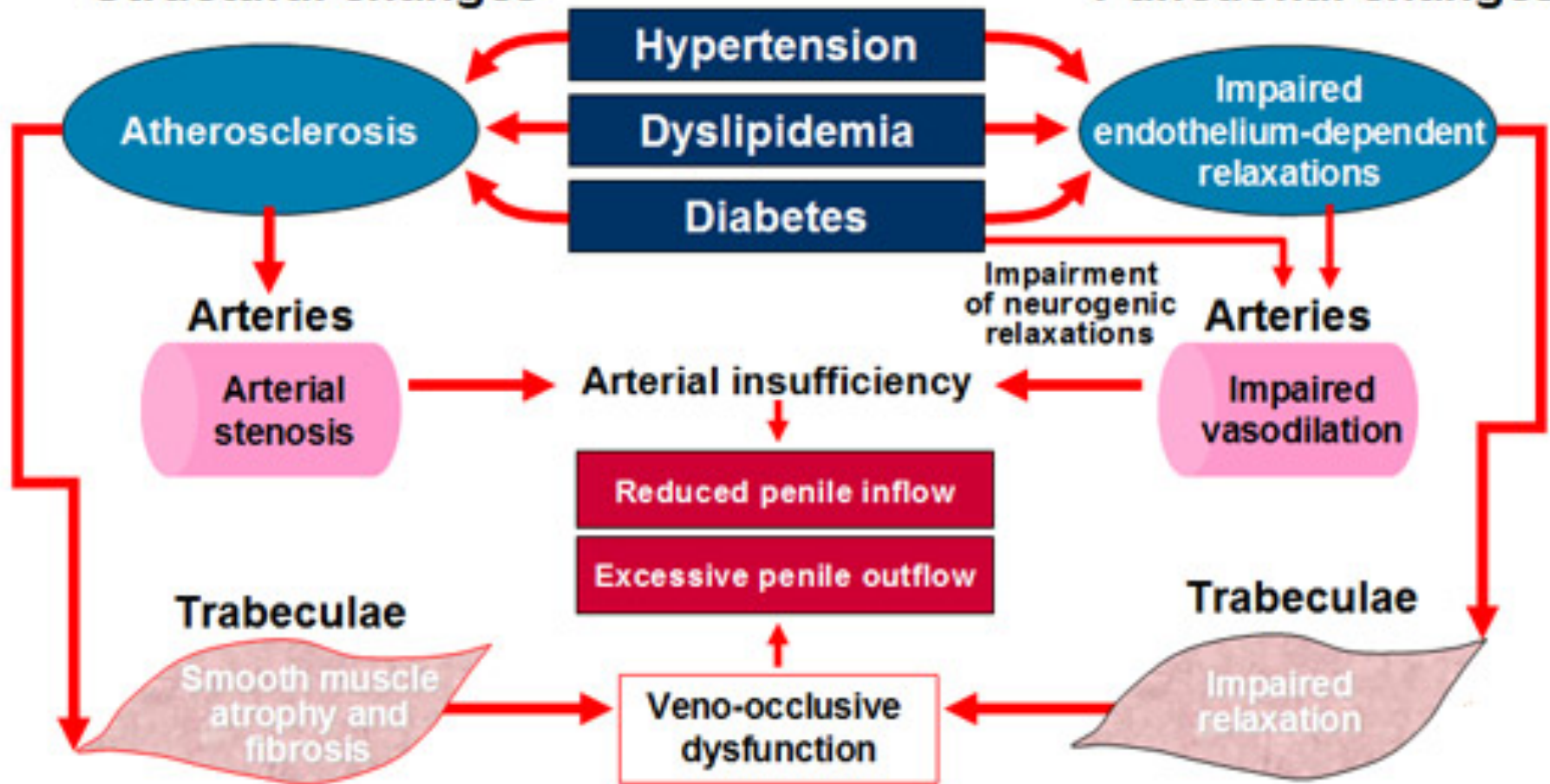
## Causes and main interventions in endothelial dysfunction

<b>Factors associated with endothelial dysfunction</b>	<b>Interventions to correct endothelial dysfunction</b>
Aging	L-arginine
Male sex	Estrogens
Cigarette smoking	Smoking cessation
History of CHD	Antioxidants
Low HDL- and high LDL-COL	Statins
Hypertension	ACE-i
Hyperhomocysteinemia	Homocysteine lowering (folates)
Diabetes/obesity	Exercise
Erectile dysfunction	PDE5-i



## Structural changes

## Functional changes





# Men with Metabolic Syndrome Have Impaired Endothelial Function

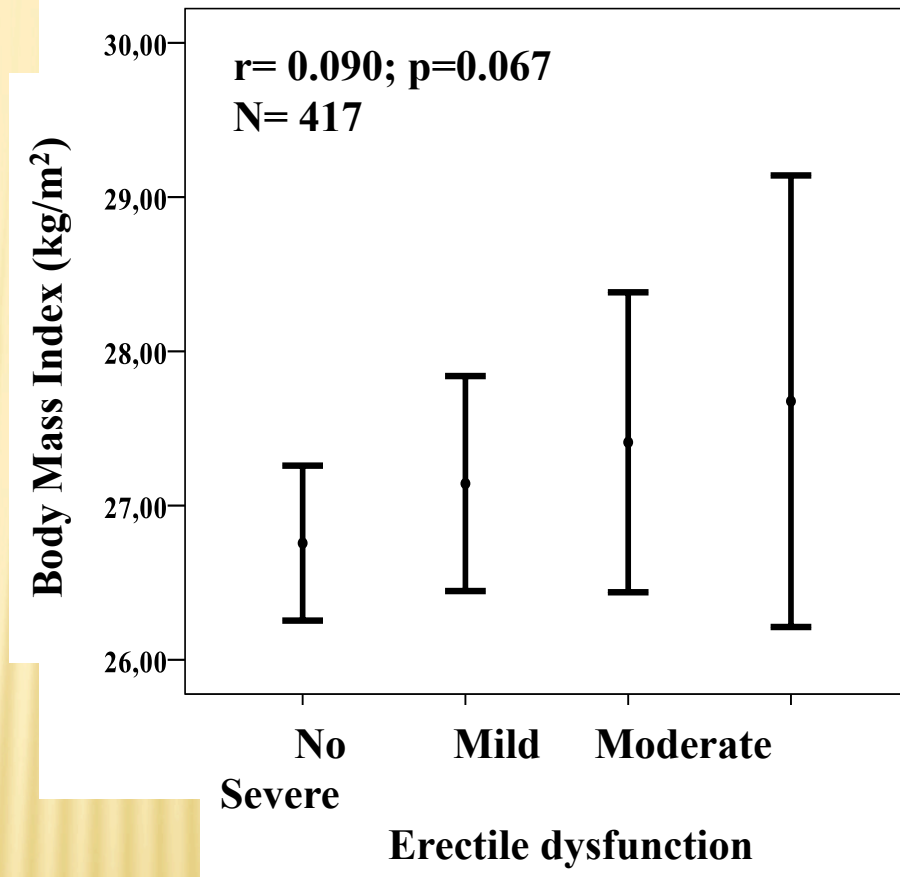
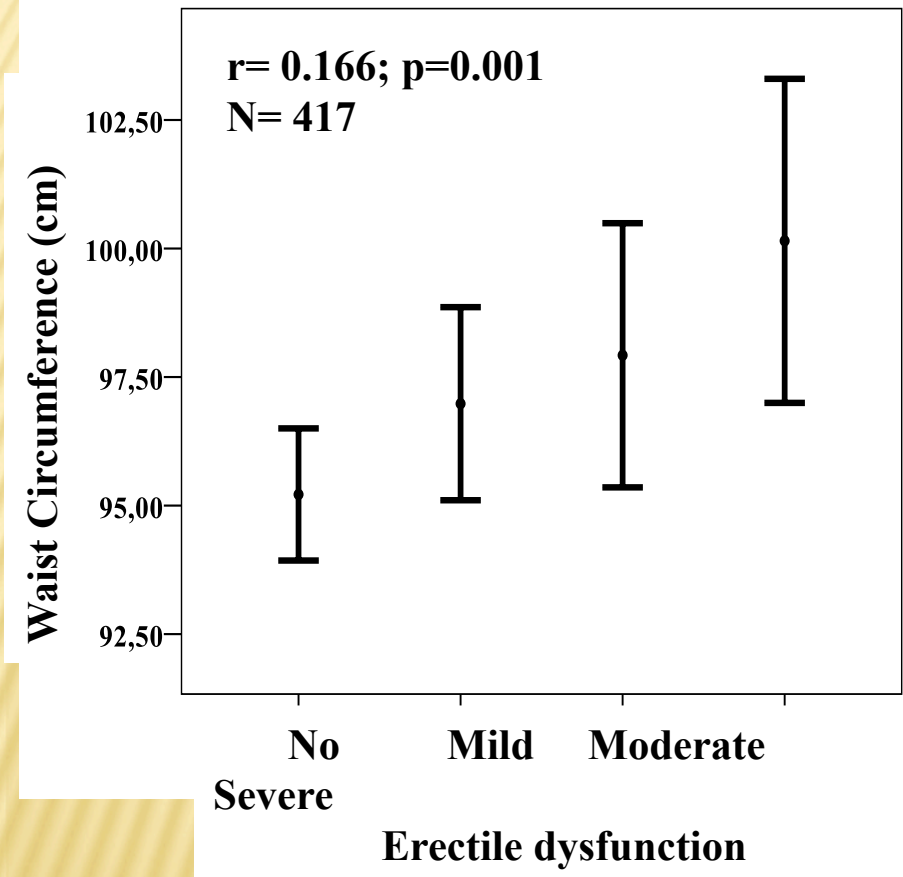
## Endothelium-dependent vasodilation

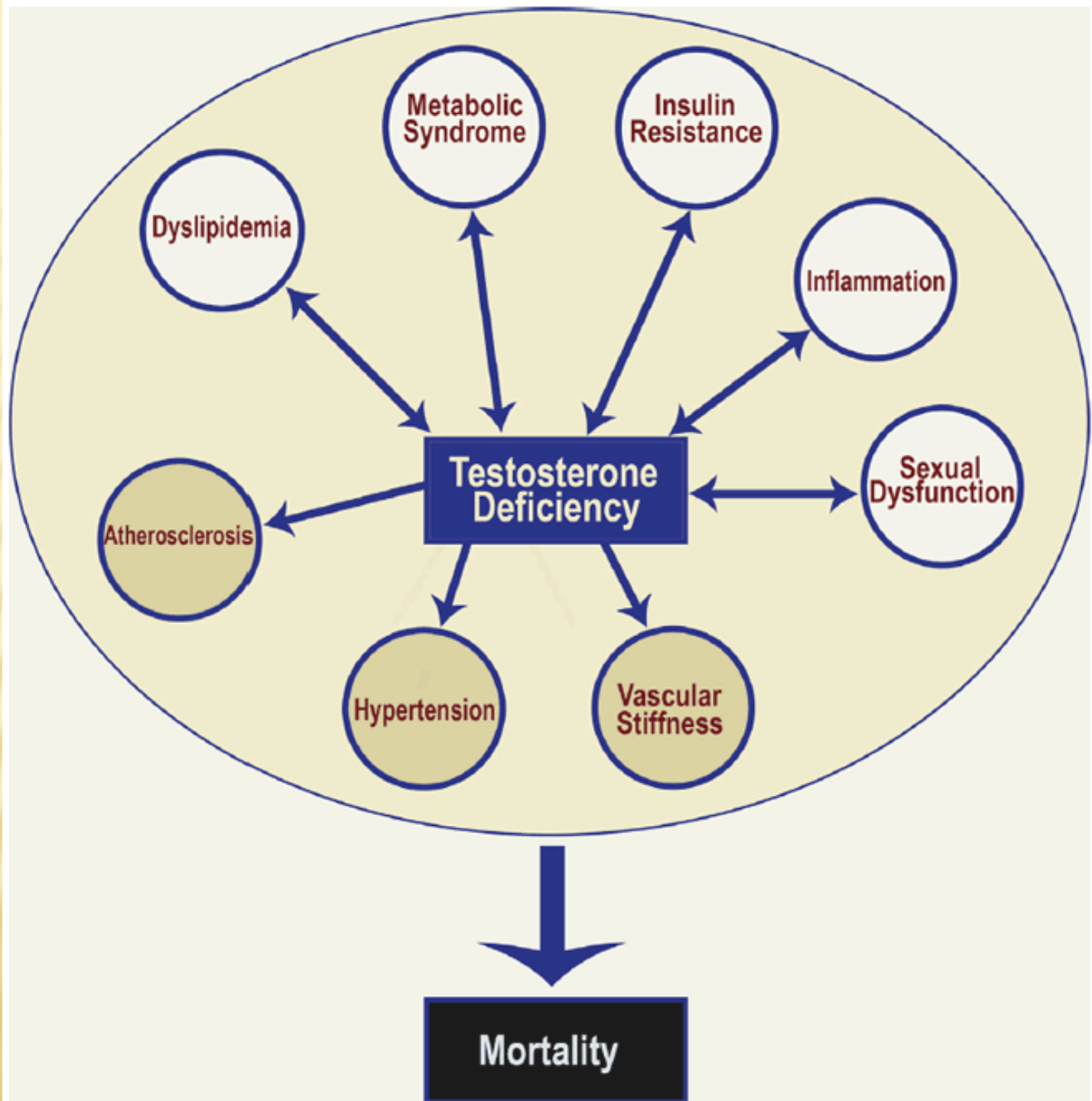
Change of forearm blood flow in response to infusion of 50g/min of acetylcholine



Lind L, Endothelium-dependent vasodilation, insulin resistance and the metabolic syndrome in an elderly cohort: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. *Atherosclerosis*. 2008 Feb;196(2):795-802

# Relationship between ED and obesity





## Declining androgen levels associated with components of the Metabolic Syndrome

Obesity

Inverse correlation between plasma T levels and BMI, WC, WHR and amount of visceral fat

Dyslipidemia

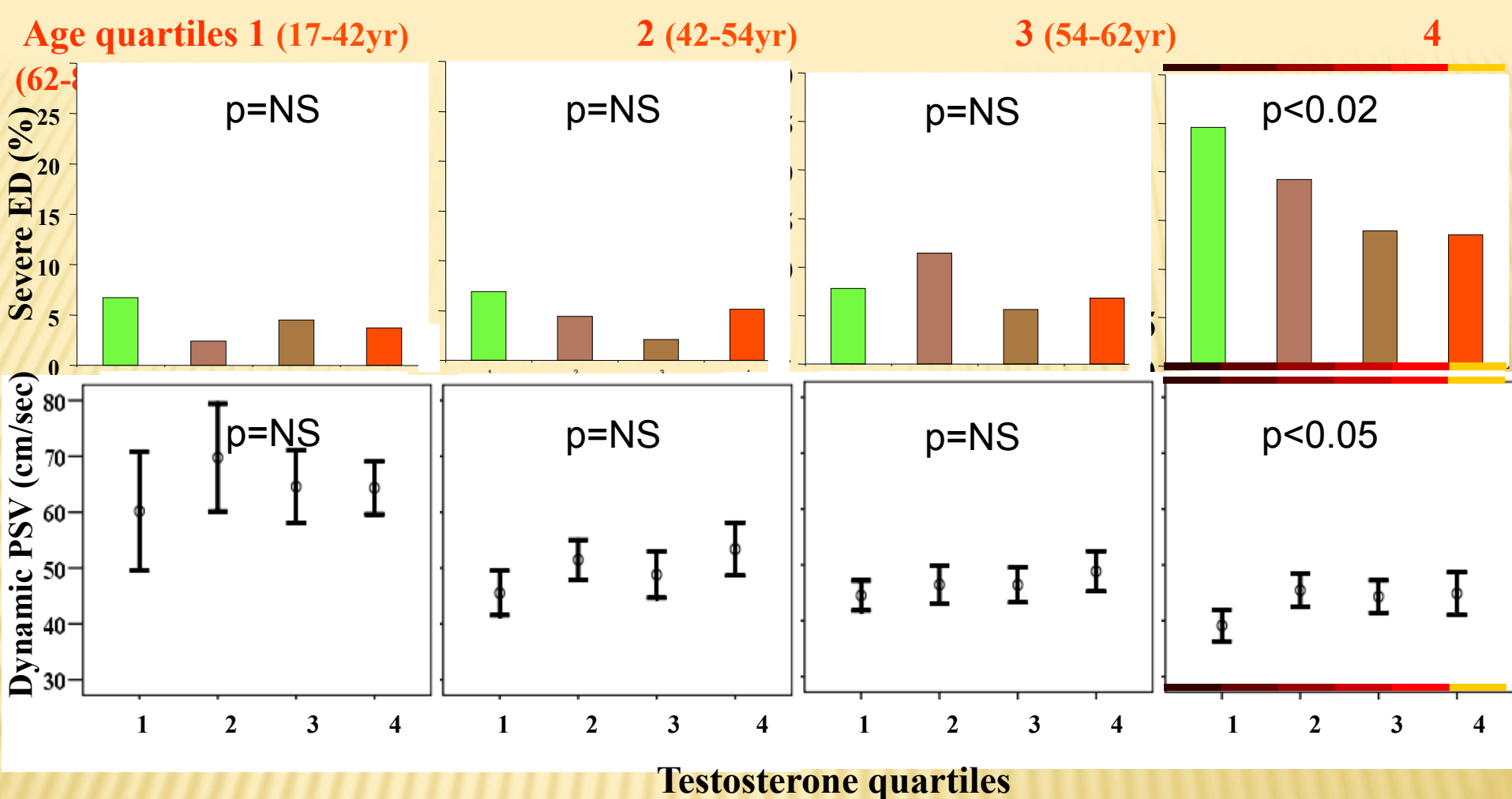
Positive correlation between plasma T levels and HDL-C; inverse correlation with triglycerides, total cholesterol and LDL-C

Hypertension

Inverse correlation between T levels and SBP/DBP; ↑ hypogonadal men with history of hypertension in HIM study

Impaired glucose tolerance

Low T is associated with insulin resistance; diabetic men have low T levels



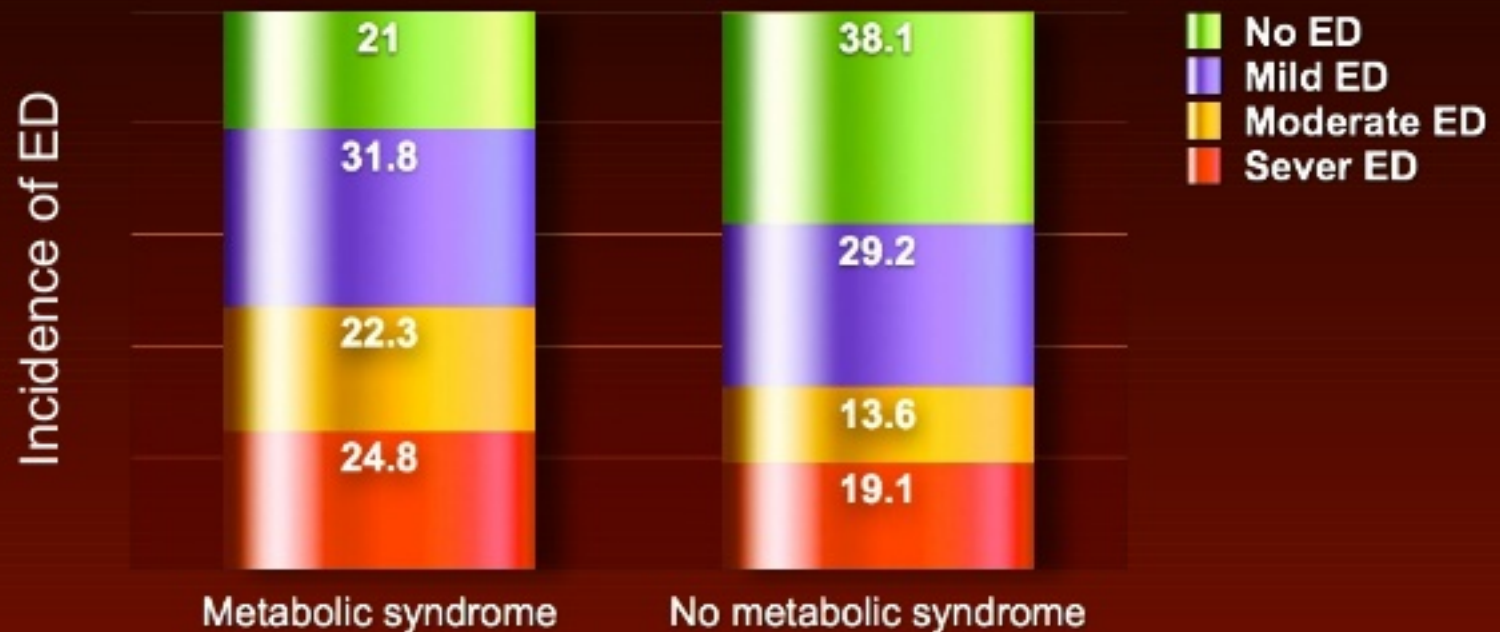
**Adjusted for:**

- age
- smoking habit
- diabetes mellitus
- waist circumference

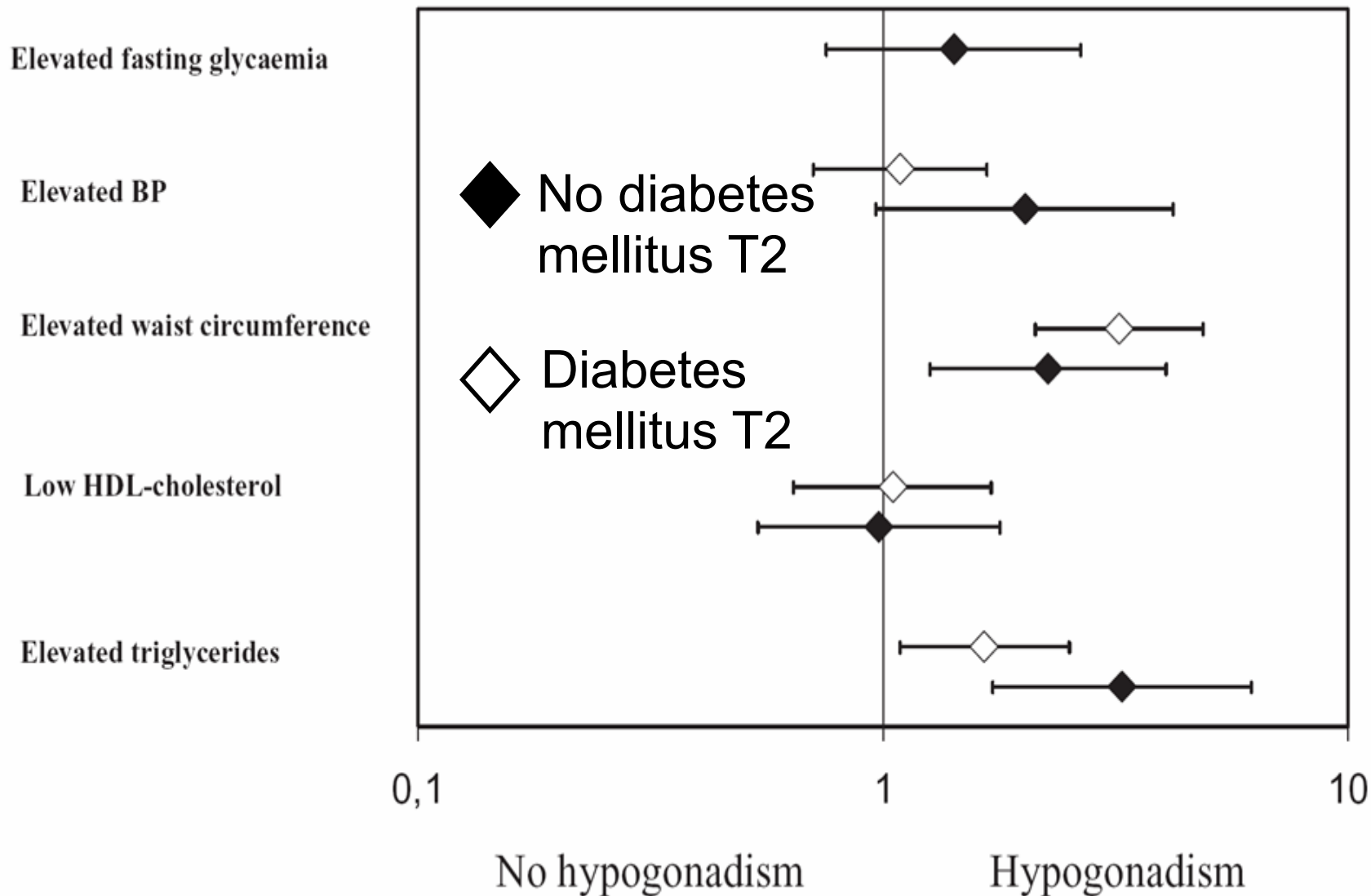
**Testosterone, prevalence of ED and penile blood flow according to age quartiles**

# The relationship between Metabolic Syndrome and severity of ED

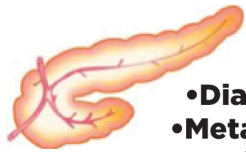
393 urological patients, 39.9% met MetS criteria



# Metabolic characteristics of 1.134 men with sexual dysfunction



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



- Diabetes
- Metabolic syndrome

7

- Hypertension
- Coronary Artery Disease
- Heart failure



1

2

- Peripheral arterial disease



3

- Raynaud's phenomenon



4

- Preeclampsia



5

- Pulmonary arterial hypertension
- High-altitude pulmonary edema



6

- Erectile dysfunction





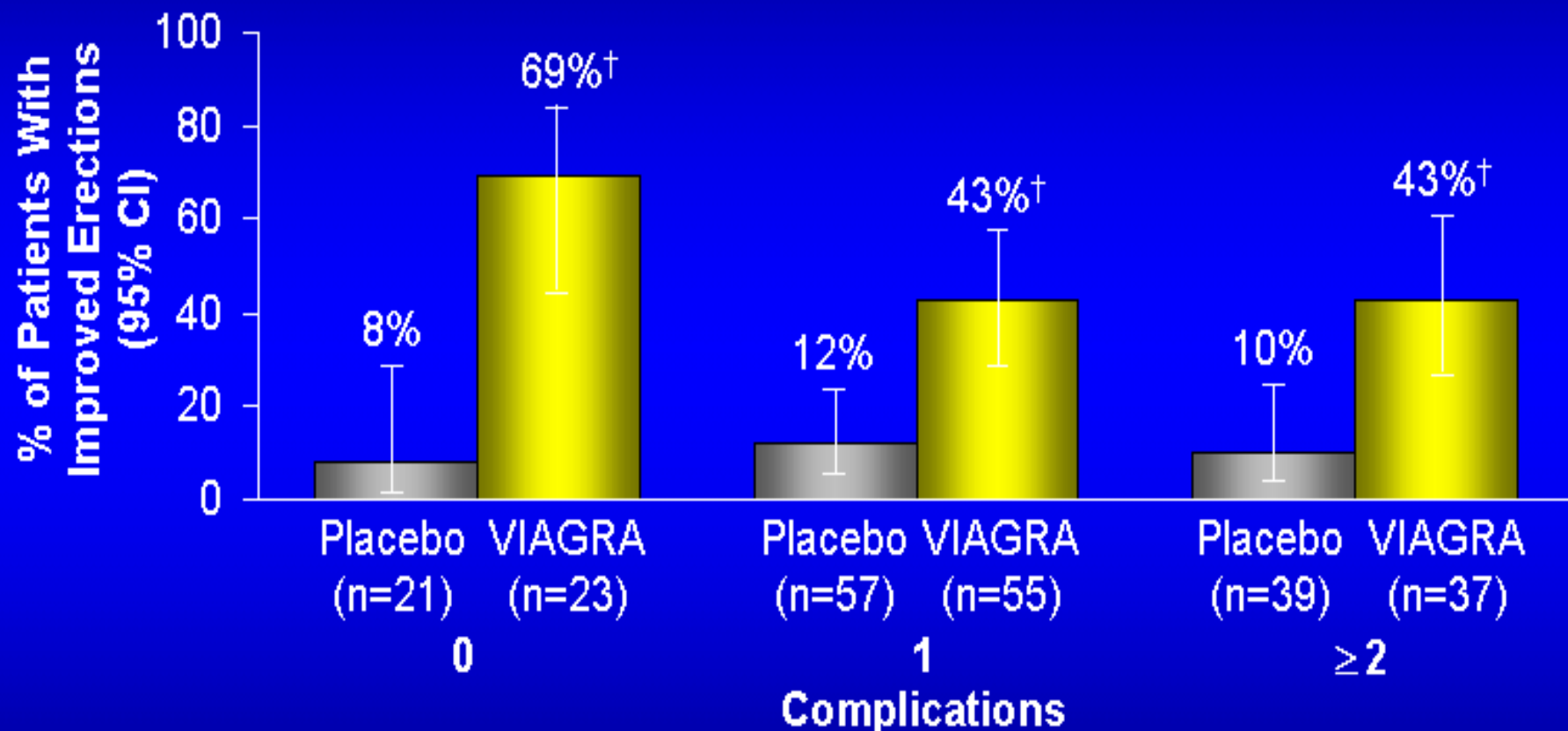
**Table 1. Sexual and Extrasexual Effect of Chronic Tadalafil Administration in Clinical Trials**

System	Effect	Adverse Events	Reference
Penile	Improvement in penile vascular circulation and resumption of morning erections	None	Proietti M. J Rheumatol 2007; 34(8): 1712-7
Vascular endothelium	Decrease pro-atherogenic markers Increased NO availability Rehabilitation	None	Rosano GM. Eur Urol 2005; 47(2): 214-20
Heart	Cardio-protection Myocardial remodelling Favorable safety profile	Delayed nitrate administration for MI	Kukreja & Salloum. Int J Impot Res 2007; 19(2): 226-7
Eye	Improvement of microcirculation	Change in color vision (<0.1%) NAION	Padma-Nathan H. Am J Cardiol 2003; 92: 9M-25M
Ear-Nose-Throat	Not known	Hearing loss	MedWatch FDA, 2007
Endocrine	Increase T and T:E ratio	None	Greco EA. J Sex Med 2006; 3(4): 716-22
Pulmonary	Reduction of pulmonary pressure	None	Mukhopadhyay S Circulation 2006; 24(114): 1807-10
Prostate	Improvement of LUTS in BPH	None	McVary KT. J Urol 2007; 177: 1401-7
Metabolic	Improvement of insulin release	Not known	Aversa A. Int J Impot Res 2007; 19(2): 200-7
Liver	None	Interaction with medications metabolized by the cytochrome P450	Ring BJ. Clin Pharmacol Ther 2005; 77(1): 63-75
Skeletal muscle	No improvement in exercise capacity	Myalgia and back pain	Di Luigi L. Int J Sports Med 2007; 5: [Epub]
Bone marrow	Increases of EPC	Autonomous cell Proliferation?	Foresta C. Int J Impot Res 2006; 18(5): 484-8

Legends: NAION= Non-arteritic Anterior Ischaemic Optic Neuropathy; MI=myocardial infarction; EPC=endothelial progenitor cells; LUTS=lower urinary tract symptoms; BPH=benign prostatic hyperplasia; T=testosterone; E=estradiol.



# VIAGRA® (sildenafil citrate): Erections Improved\* in Patients With and Without Diabetic Complications

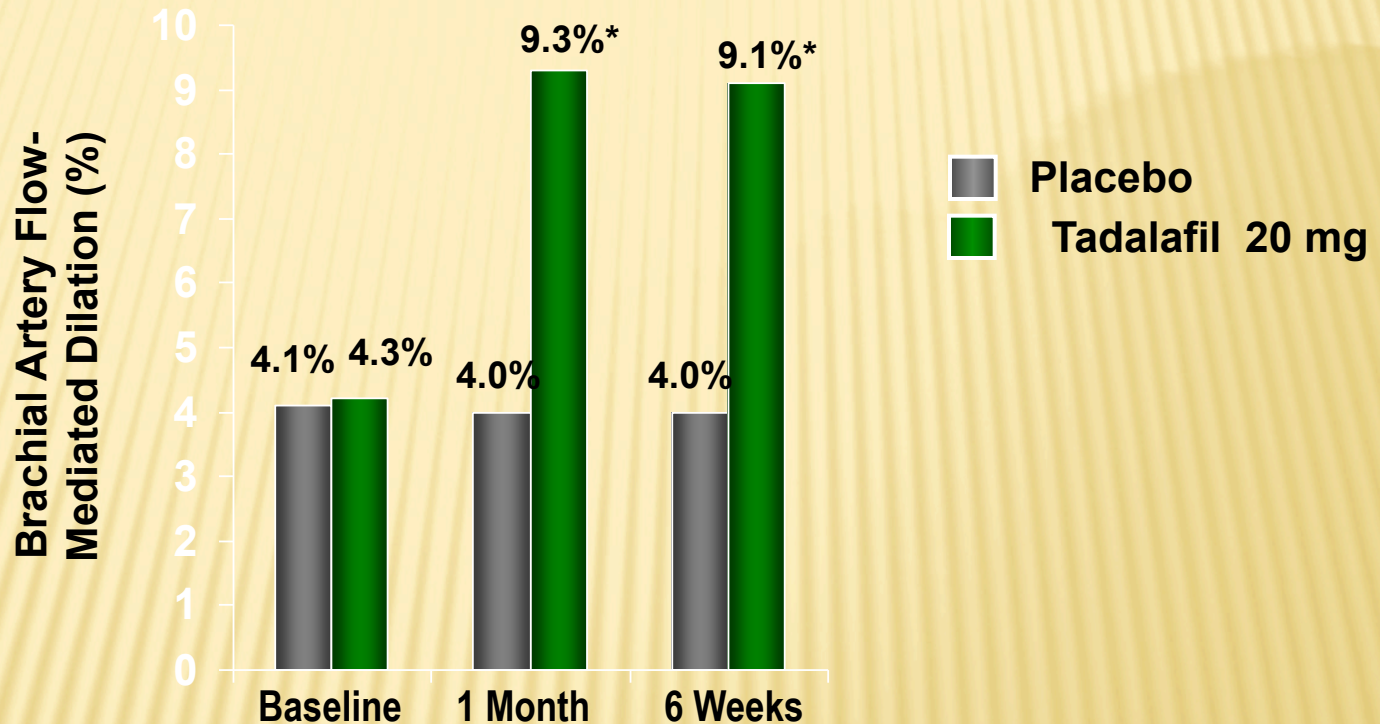


\* Global Efficacy Assessment Question.

†  $P=0.001$  VIAGRA versus placebo.

Data on file, Pfizer Inc., New York, NY. Based on a randomized, double-blind, placebo-controlled, clinical trial.

# EFFECT OF TADALAFIL ON ENDOTHELIAL DYSFUNCTION: FLOW-MEDIATED DILATION



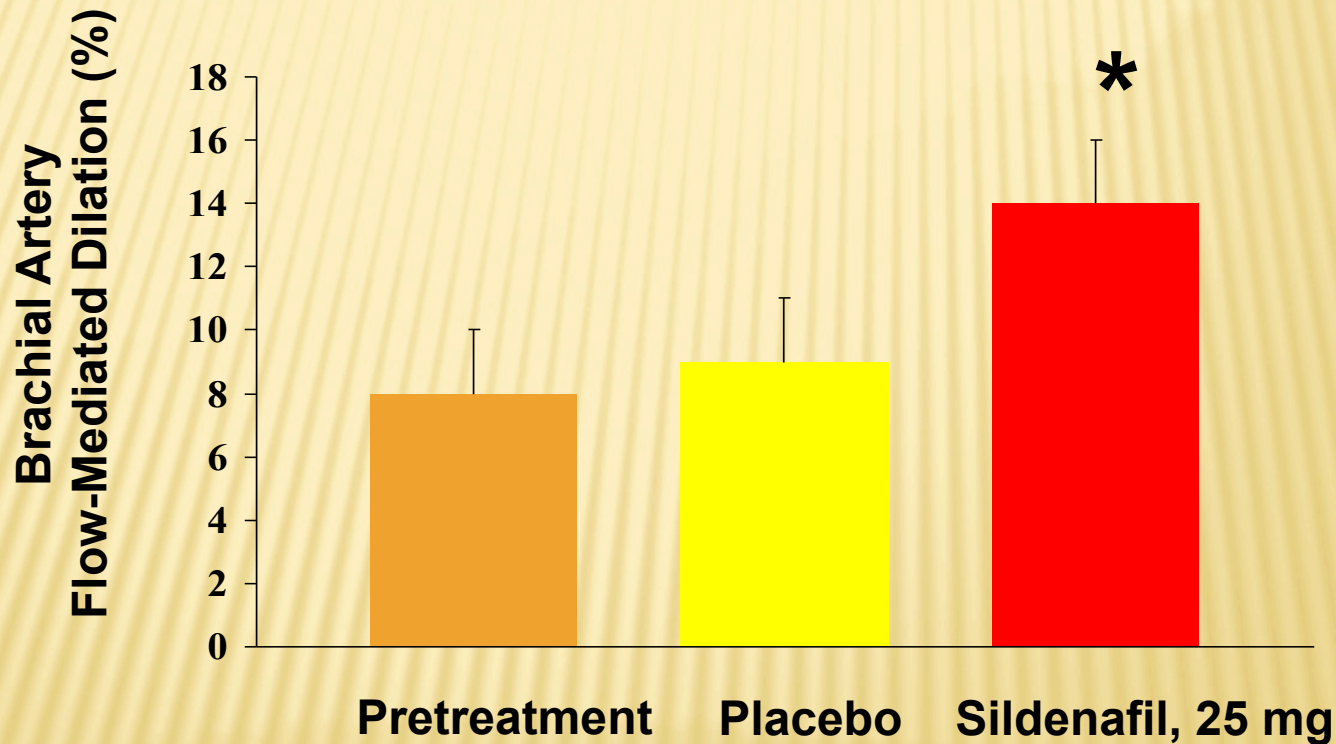
- ✦ 32 patients randomized to receive tadalafil 20 mg or matching placebo every other day

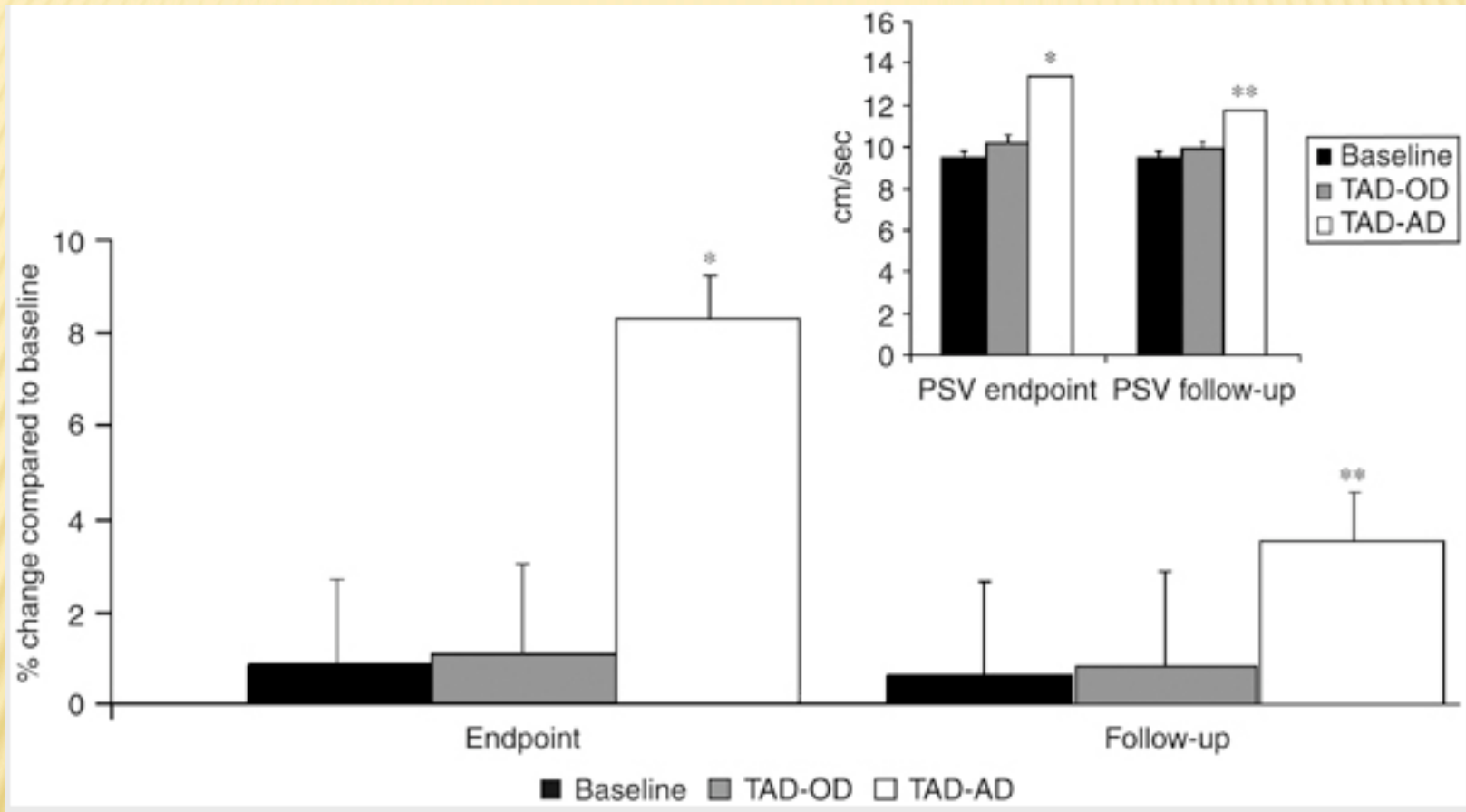
\* $P=0.01$  versus baseline.

Rosano GM et al. *J Am Coll Cardiol.* 2004;43(suppl A). A1141-194.

# INHIBITION OF PDE-5 AUGMENTS ENDOTHELIAL FUNCTION IN TYPE 2 DIABETICS

24 hours following the administration of sildenafil 25 mg/day/placebo x 14 days





Percent change compared with baseline in endothelial function of cavernous arteries (FMD) in patients treated with TAD-AD and TAD-OD after 4 weeks of therapy and after 2 weeks of discontinuation of therapy. Inset indicates variations in cavernous arteries inflow as recorded by color-duplex ultrasound in the flaccid state. The *P*-values refer to comparison between end point vs baseline. \*  $P < 0.0001$ ; \*\*  $P < 0.005$ .

N= 120 patients (aged  $58.0 \pm 6.0$  years)

3 groups:

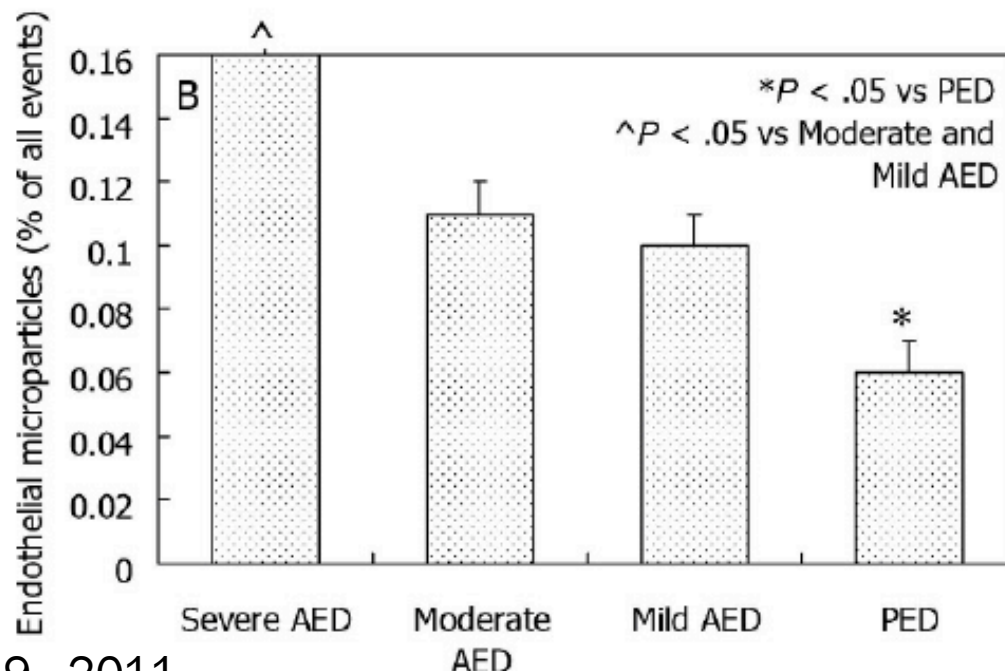
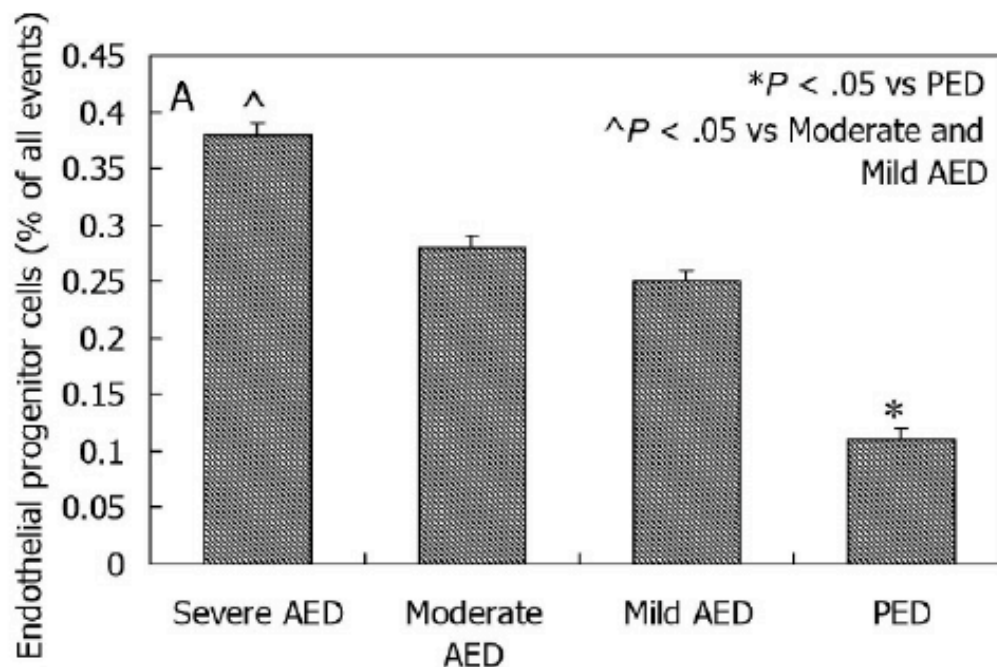
Group A: 37 patients with PSV <25 cm/s (severe arterial insufficiency);

Group B: 40 patients with PSV between 25 and 29 cm/s (moderate arterial insufficiency);

Group C: 43 patients with PSV between 30 and 34 cm/s (mild arterial insufficiency).

Control: 20pts (aged  $60.0 \pm 3.0$  years) with psychogenic erectile dysfunction (PED)

- Group A showed serum concentrations of EPCs and EMPs significantly higher compared with other groups with AED.

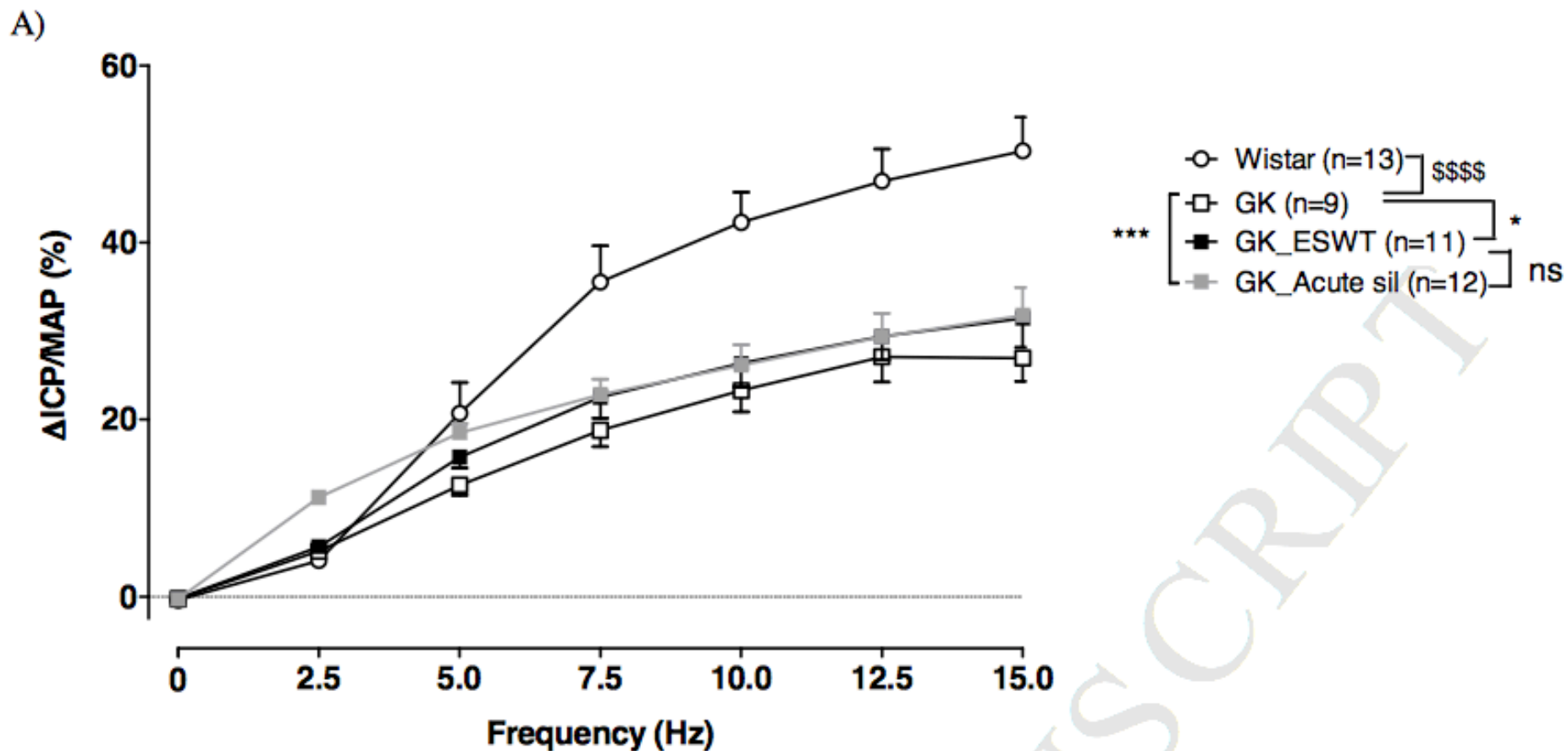


<b>Author, year</b>	<b>Active compound</b>	<b>NNT</b>
Price <i>et al.</i> , 1998 <sup>[25]</sup>	Sildenafil 25 mg	2.5
Price <i>et al.</i> , 1998 <sup>[25]</sup>	Sildenafil 50 mg	2.4
Rendell <i>et al.</i> , 1999 <sup>[26]</sup>	Sildenafil 25-100 mg	2.2
Boulton <i>et al.</i> , 2001 <sup>[27]</sup>	Sildenafil 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

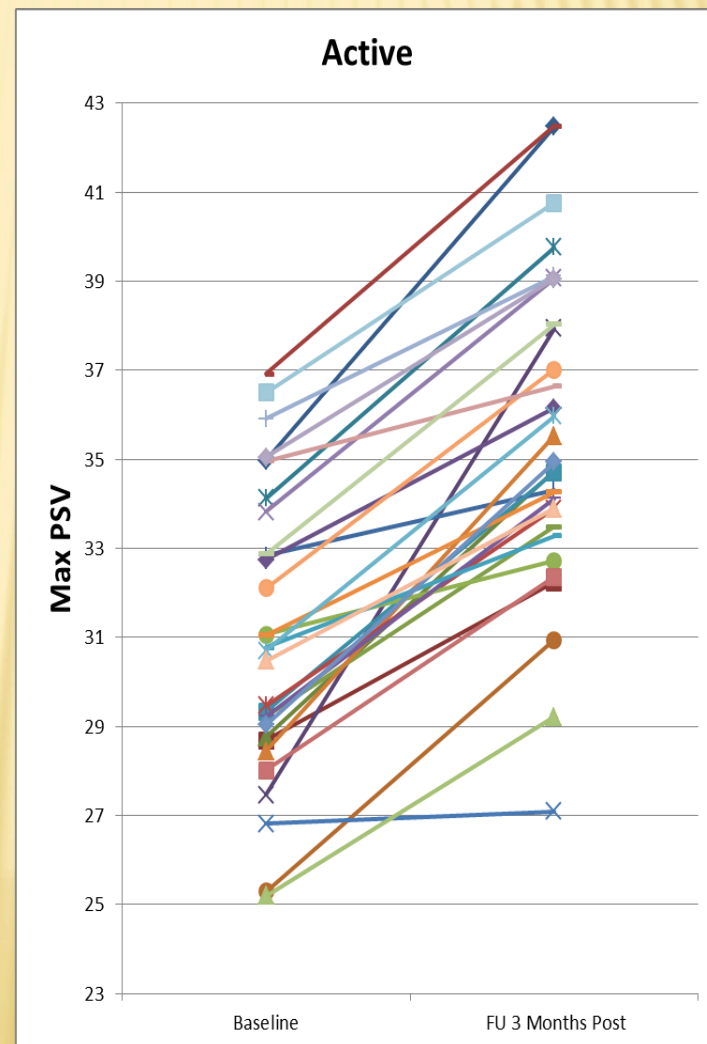
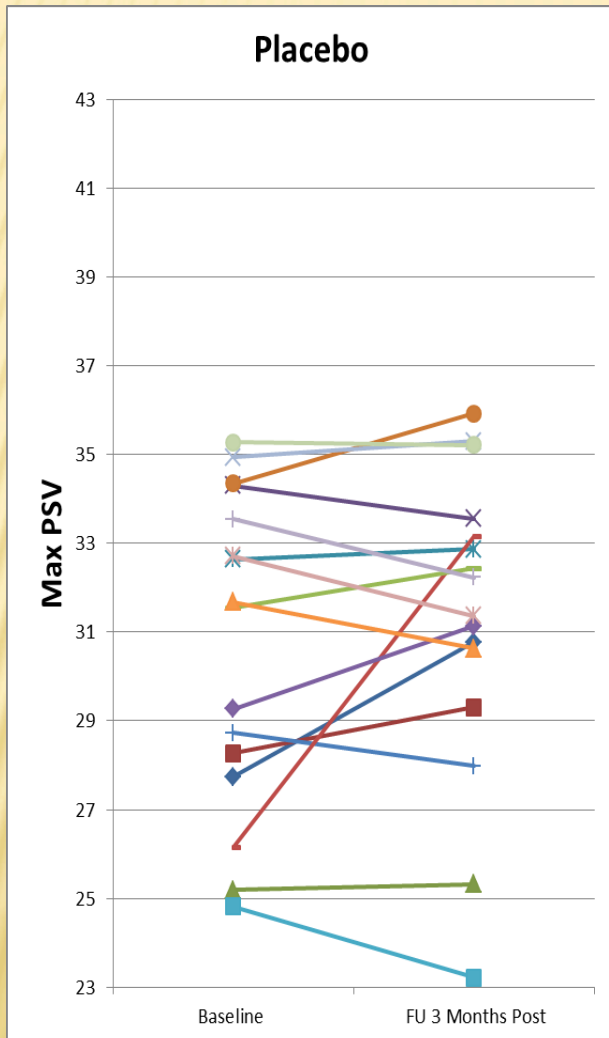
NNT: Number needed to treat



# Low Intensity Extracorporeal Shockwave Therapy (Li-ESWT) Improves Erectile Function in a model of Type II Diabetes Independently of NO/cGMP Pathway.



# Individual Plots Describing Maximal Peak Systolic Volume



# ADDITION OF T TO NON-RESPONDERS TO TADALAFIL 10MG OAD IS ONLY BENEFICIAL WHEN $T \leq 3\text{NG/ML}$

223 men (45-80y),  $TT \leq 4 \text{ ng/ml}$  and/or  $BT T \leq 1 \text{ ng/mL}$ , non-responders to the highest available dosage of sildenafil, tadalafil, or vardenafil

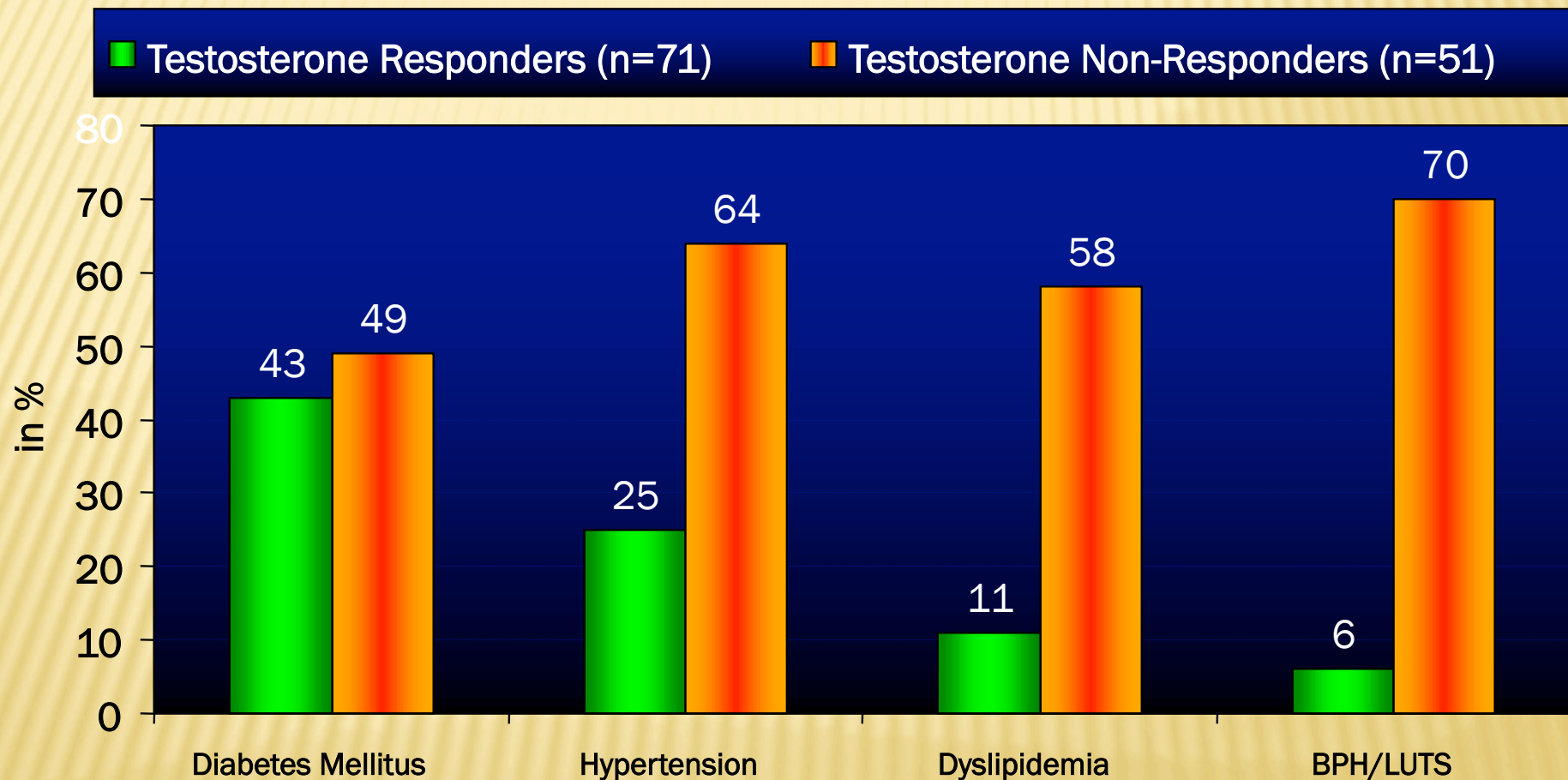
Results of Tadalafil 10mg OAD:

- 17% responders (score 4 or 4 to IIEF Q3 and Q4)
- 14.6% normal erectile function (EFD  $\geq 26$ )

1/9 will go back to normal sex life!

Total testosterone (ng/mL)	No patients testosterone/ placebo	Increase in EFD score			Increase in SEP 3 rate (%)		
		Testosterone gel	Placebo gel	<i>P</i>	Testosterone gel	Placebo gel	<i>P</i>
$\leq 4$	126 59/67	5.23 (7.06)	3.96 (6.73)	NS	36.6 (32.6)	29.7 (40.4)	NS
$\leq 3.46$	98 48/50	5.78 (6.93)	4.09 (6.68)	NS	38.3 (34.9)	28.1 (37.6)	NS
$\leq 3$	73 41/32	6.18 (6.17)	2.33 (7.02)	0.027	33.1 (33.3)	13.4 (30.2)	0.038
$\leq 2.31$	40 23/17	5.65 (5.84)	1.13 (6.54)	0.035	32.2 (34.0)	9.4 (25.1)	0.065

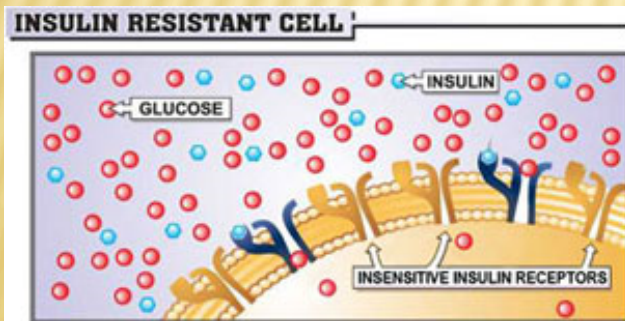
# Proportion of co-morbidities in 122 hypogonadal men with ED (71 Responders and 51 Non-Responders to monotherapy with Nebido®)



*There are patients with multiple co-morbidities*

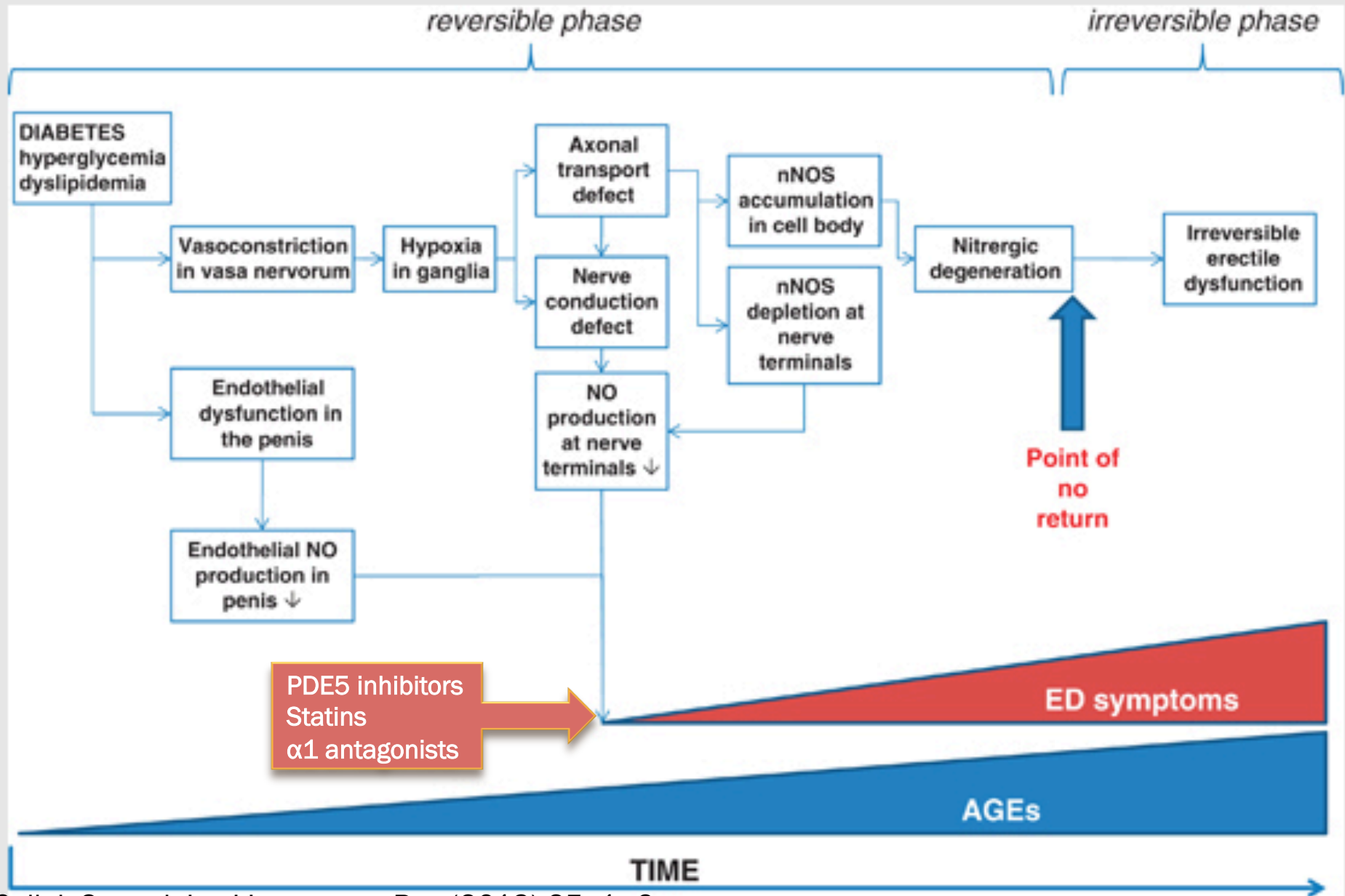
# Η σχέση: ED-METS-IR

SHIM	Metabolic syndrome	Insulin resistance (%)
Mild	14.5	14.8
Moderate	35.5	32.8
Severe	50.0	44.2



Bansal et al., J. Sex. Med. 2005; 2: 96-103

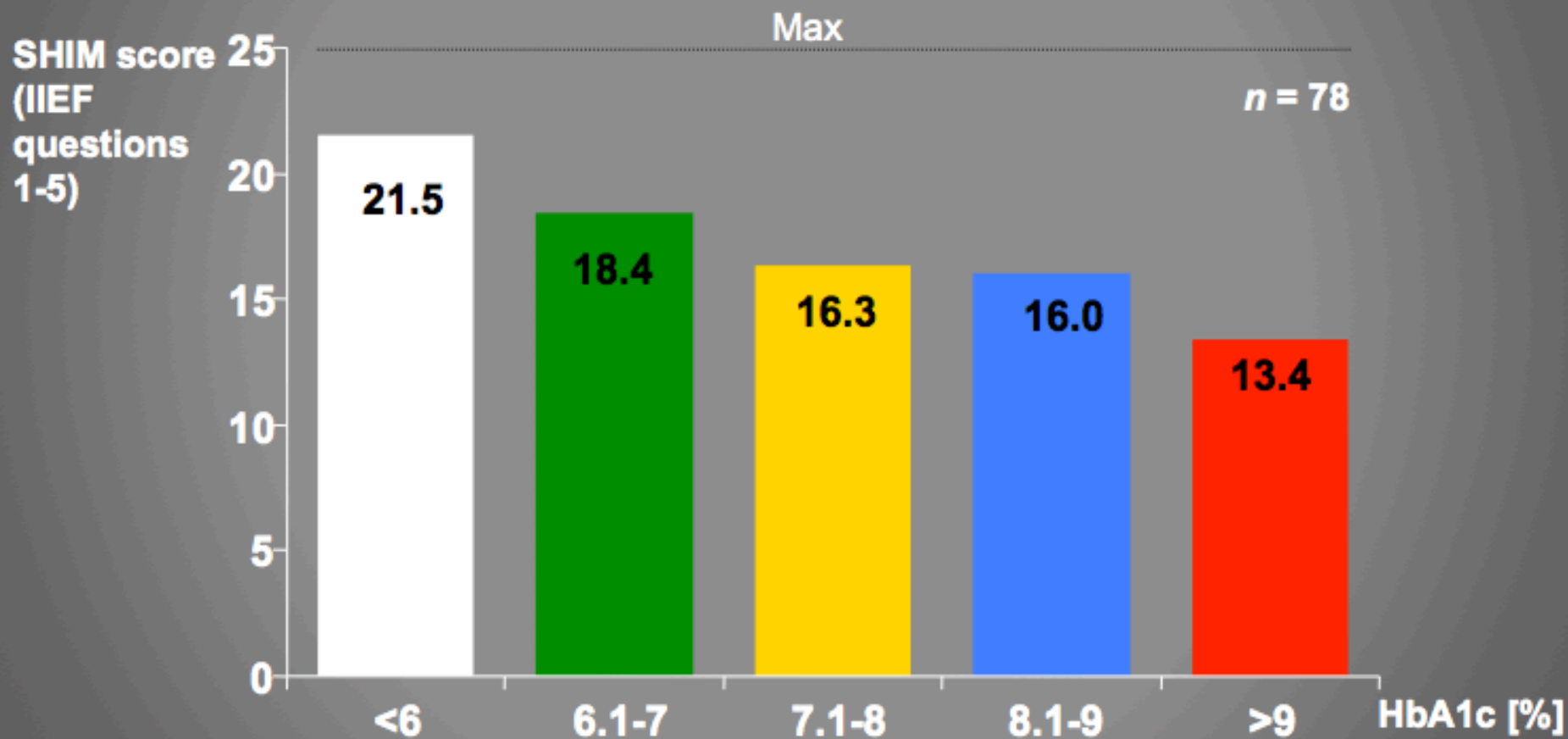
# DIABETES MELLITUS AND ED



# Μπορούμε να τον βοηθήσουμε;



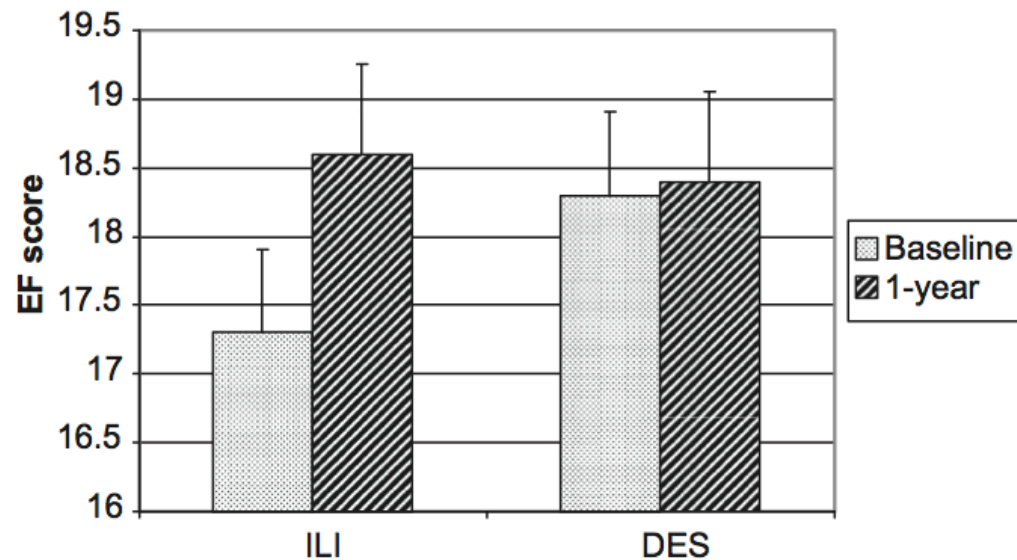
# Diabetes: Glycaemic control correlates with ED





Η εκπαίδευση δεν αρκεί...

Η παρέμβαση οδηγεί σε βελτίωση της στύσης



**Figure 2** Scores on the erectile function (EF) subscale of the International Index of Erectile Function at baseline and year 1 for men in the intensive lifestyle intervention (ILI) or in the control group given diabetes support and education (DSE).



ΕΥΧΑΡΙΣΤΩ