Πνεύμονες, Καρδιά & Σεξ

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Παθολόγος
Β' ΠΠ Κλινική ΑΠΘ

Δήλωση συμφερόντων

Δεν υπάρχει καμία σύγκρουση συμφερόντων σχετικά με αυτήν την παρουσίαση

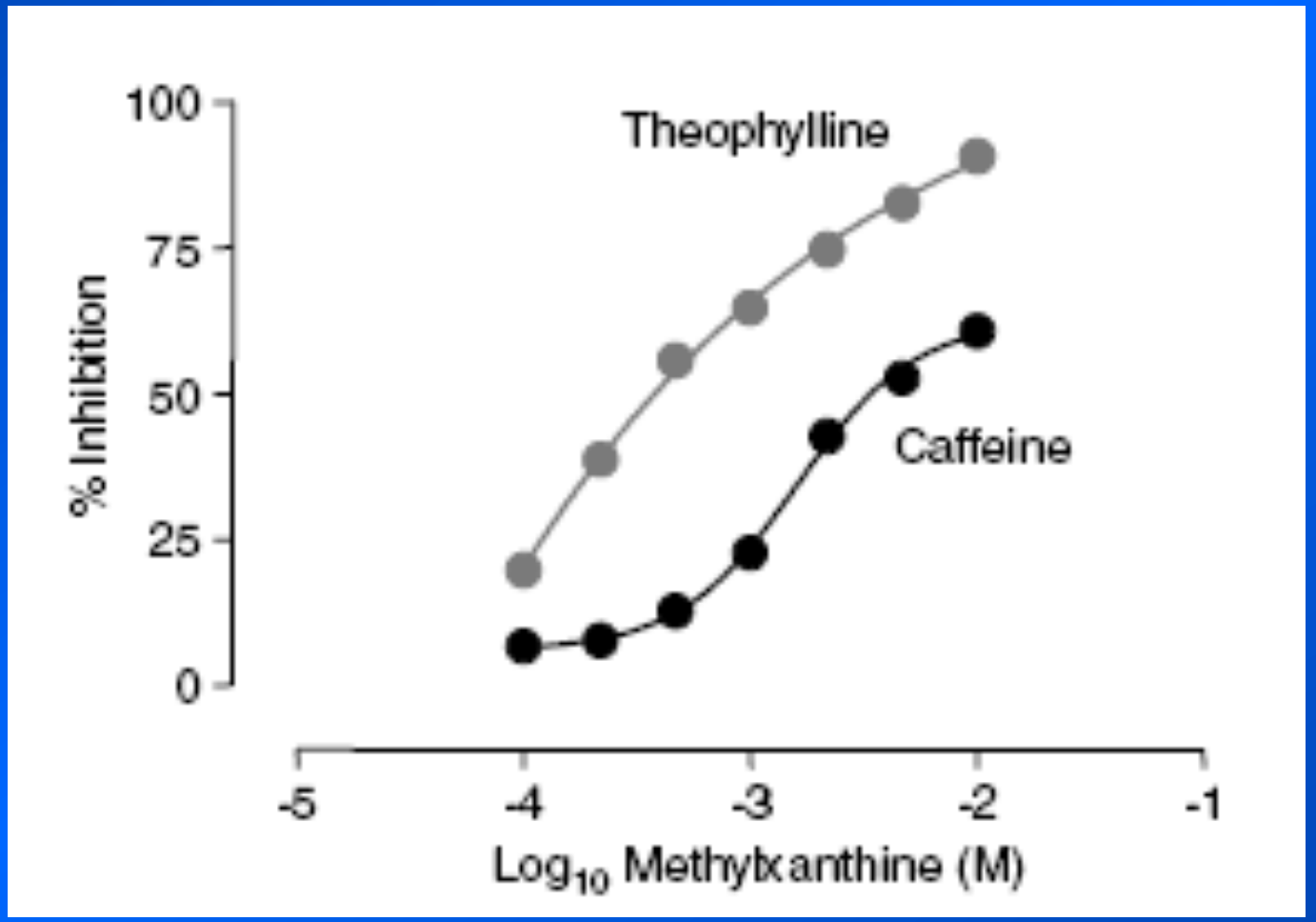
The beginning of the story

"When I drink a strong cup of coffee on an empty stomach, my breathing eases, I find substantial relief"

An asthmatic patient

Henry Hyde Salter, 1886

cAMP-PDE inhibition by methylxanthines



Butcher, J Biol Chem 1962

PDE superfamily

PDE isoenzyme	*No. of isoforms*	*Substrate*	*Km (μM) cAMP*	*Km (μM) GMP*	*Tissue expression*	*Specific inhibitors*
1	8	Ca^{2+}/calmodulin-stimulated	1–30	3	Heart, brain, lung, smooth muscle	KS-505a
2		cGMP-stimulated	50	50	Adrenal gland, heart, lung, liver, platelets	EHNA (MEP-1)
3	4	cGMP-inhibited, cAMP-selective	0.2	0.3	Heart, lung, liver, platelets, adipose tissue, inflammatory cells	Cilostamide Milrinone
4	20	cAMP-specific	4		Sertoli cells, kidney, brain, liver, lung, inflammatory cells	Rolipram, Roflumilast Cilomilast
5	3	cGMP-specific	150	1	Lung, platelets, vascular smooth muscle	Sildenafil, Zaprinast
6		cGMP-specific		60	Photoreceptor	Dipyridamole
7	3	cAMP-specific, high-affinity	0.2		Skeletal muscle, heart, kidney, brain, pancreas, T lymphocytes	BRL-50481
8		cAMP-selective,	0.06		Testes, eye, liver, skeletal muscle, heart, kidney, ovary, brain, T lymphocytes	none
9	4	cGMP-specific,		0.17	Kidney, liver, lung, brain	BAY 73-6691
10	2	cGMP-sensitive, cAMP-selective	0.05	3.0	Testes, brain	none
11	4	cGMP-sensitive, dual specificity	0.7	0.6	Skeletal muscle, prostate, kidney, liver, pituitary and salivary glands, testes	none

Br J Pharmacol 2006

PDE-5 inhibitors in asthma

Inhibition of exercise-induced asthma by an orally absorbed mast cell stabilizer (M&B 22948 – zaprinast).

Rudd, Br J Dis Chest 1983

But ..... Poor results

However: vasorelaxant properties

PDE-5 inhibition in angina

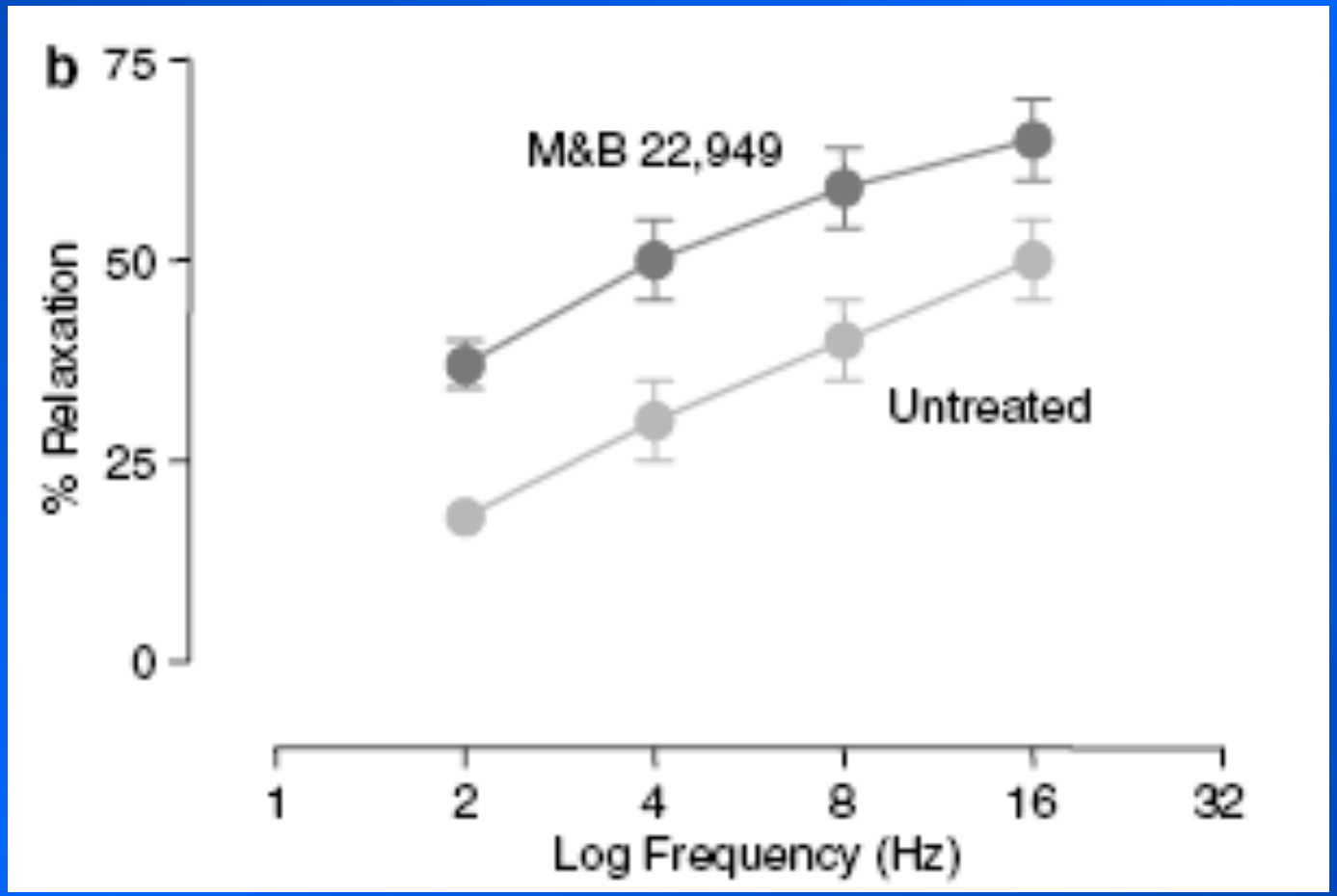
Phase I trials with sildenafil were disappointing

But

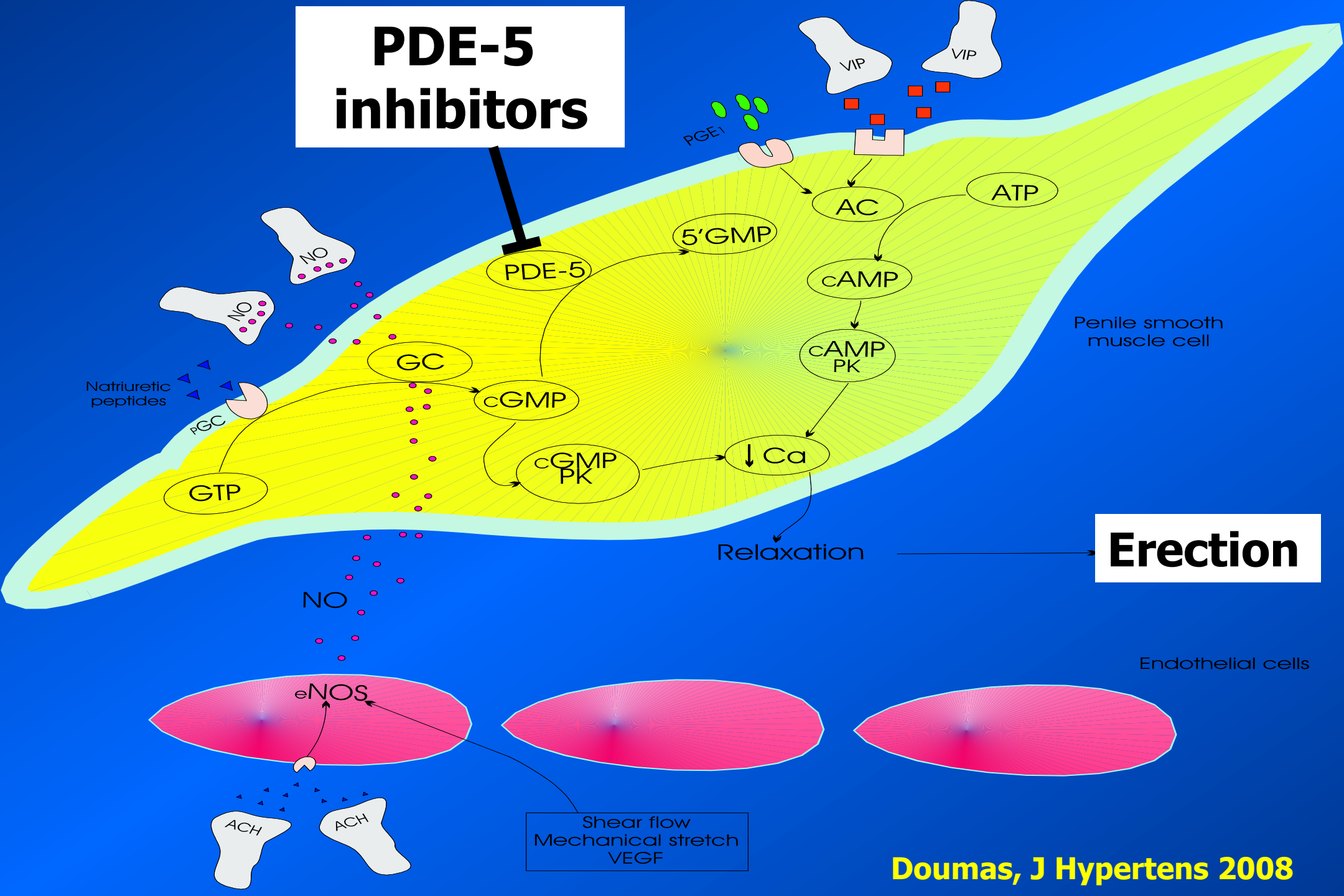
An unxepected side effect evolved

Penile erection

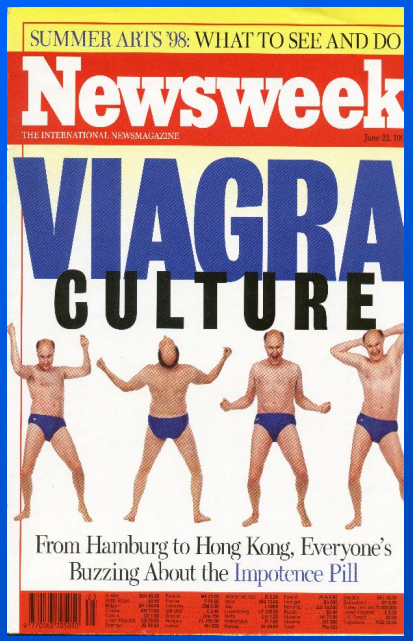
PDE-5 inhibition in penile tissue



Raijfer, NEJM 1992


PDE-5 inhibitors
VIP
VIP
PGE1
AC
ATP
5'GMP
PDE-5
cAMP
NO
NO
NO
GC
cAMP PK
Penile smooth muscle cell
Natriuretic peptides
pGC
cGMP
cGMP PK
↓ Ca
GTP
Relaxation
Erection
NO
Endothelial cells
eNOS
ACH
ACH
Shear flow
Mechanical stretch
VEGF
Doumas, J Hypertens 2008

The era of PDE-5 inhibitors
March 1998 FDA approval of sildenafil



“Man survives earthquakes,

experiences the horrors of illness ,

and all of the tortures of the soul.

But the most tormenting tragedy of all time is,

and will be, the tragedy of the bedroom.”

Tolstoy

Πνευμονικά νοσήματα
&
στυτική δυσλειτουργία

ED - asthma

- 17.032 άτομα, 3.466 με άσθμα
- 1,9 φορές μεγαλύτερος κίνδυνος για ΣΔ
- Συσχέτιση με τη βαρύτητα του άσθματος
  - 4,2 φορές σε >24 επισκέψεις/έτος
  - 3,5 φορές σε 12-24 επισκέψεις/έτος

Chou, J Sex Med 2011

ED - COPD

- 29.042 ασθενείς, ίσος αριθμός μαρτύρων
- 1,9 φορές μεγαλύτερος κίνδυνος για ΣΔ
- Συσχέτιση με τη βαρύτητα της νόσου
  - 11,5 φορές σε >5 εισαγωγές/έτος
  - 5,5 φορές σε >2 επισκέψεις/έτος στα ΤΕΠ

Shen, Medicine 2015

ED - OSAS

- 603 ασθενείς με ΣΥΑ, 17.182 με διαταραχές ύπνου, 35.570 ομάδα σύγκρισης
- 9,4 φορές μεγαλύτερος κίνδυνος για ΣΔ σε ΣΥΑ
- 3,7 φορές μεγαλύτερος κίνδυνος για ΣΔ σε διαταραχές ύπνου

Chen, Sleep Medicine 2016

Therapy for OSAS and ED

- 207 ασθενείς με ΣΥΑ
- ΣΔ: 61% σε ΣΥΑ, 72% σε σοβαρό ΣΥΑ
- 3 μήνες θεραπεία με CPAP
- Βελτίωση του IIEF score (18,2 σε 19,2)

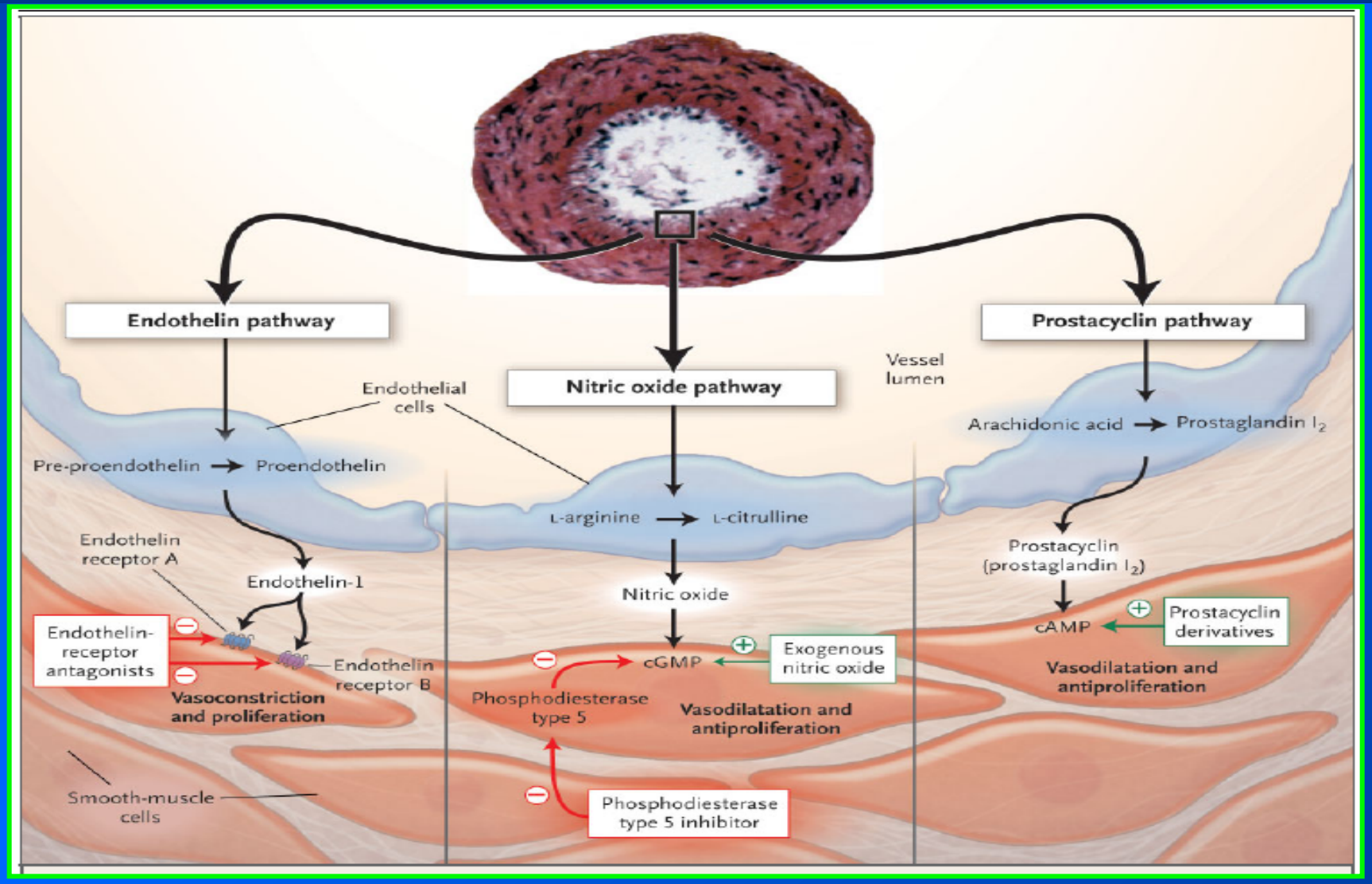
Zhang, Arch Sex Behav 2016

PDE-5 inhibitors for pulmonary disease

- Πειραματικές μελέτες: Βρογχοδιαστολή, ελαττωμένη παγίδευση αέρα
- Πιλοτικές μελέτες: Ενθαρρυντικές
- Μεγάλες μελέτες: Πτωχά αποτελέσματα σε ΧΑΠ, εμφύσημα, ιδιοπαθή πνευμονική ίνωση
- Διαταραχή αερισμού/αιμάτωσης
- TADA-PHiLD trial

PULMONARY HYPERTENSION

Therapeutic targets



Humbert, NEJM 2004

INITIAL THERAPY			
Recommendation-Evidence	WHO-FC II	WHO-FC III	WHO-FC IV
I-A	Ambrisentan, Bosentan, Sildenafil	Ambrisentan, Bosentan, Sitaxentan, Sildenafil, Epoprostenol i.v., Iloprost inhaled	Epoprostenol i.v.
I-B	Tadalafil†	Tadalafil†, Treprostinil s.c., inhaled†	
IIa-C	Sitaxentan	Iloprost i.v., Treprostinil i.v.	Ambrisentan, Bosentan, Sitaxentan, Sildenafil, Tadalafil†, Iloprost inhaled, and i.v., Treprostinil s.c., i.v., Inhaled† Initial Combination Therapy
IIb-B		Beraprost	

ESC guidelines 2009

PDE-5 inh vs ET-1 inh in PAH

	Bosentan Rubin L. *NEJM.* 2002	Sitaxsentan Barst R. *JACC.* 2006	Ambrisentan Galie N. *Circ.* 2008	Sildenafil Galie N. *NEJM.* 2005
Dose	125 mg	100 mg	10 mg	20 mg
Baseline 6MW Distance (m)	326	360	341	347
Final 6MW Distance (m)	361	385	385	390
Δ 6MW Distance (m)	28	25	44	43
	+ 8%	+ 7%	+ 13%	+ 12%

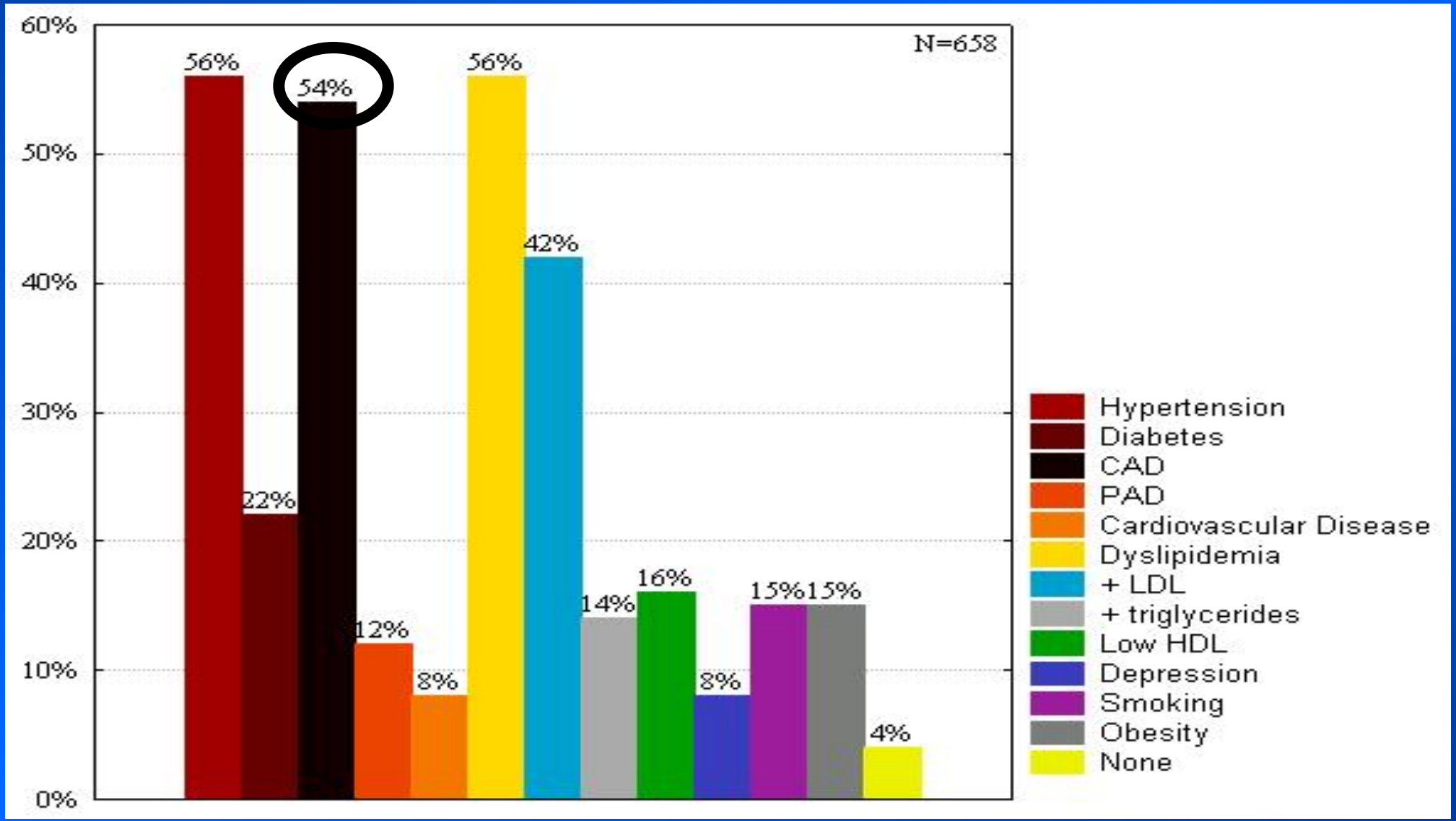
Doumas, Costa Navarino 2010

Comparison of Medical Treatments for PAH

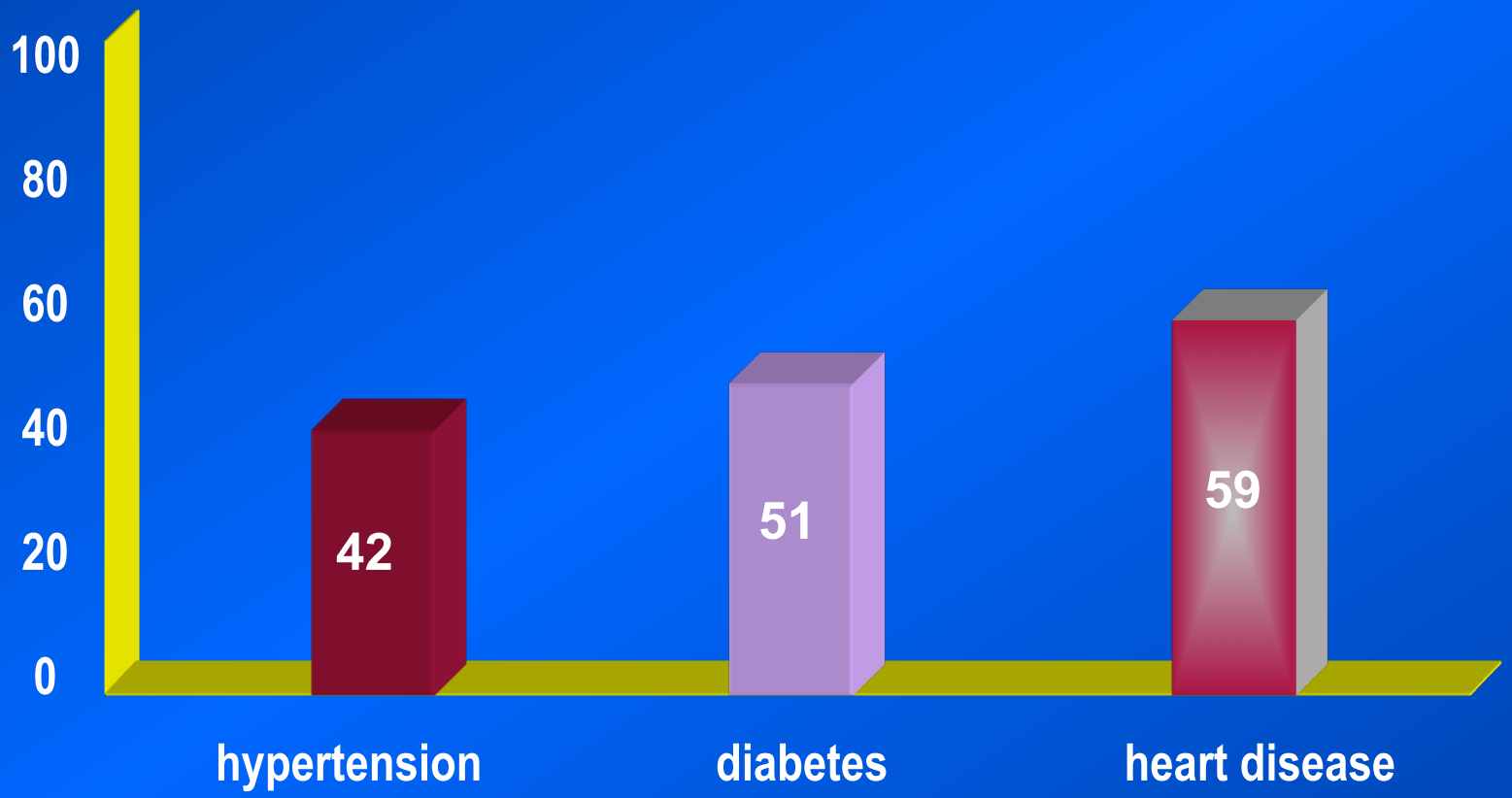
	Cost $ (annual)	Route	Frequency	Ease of Use	Side effects	Long-term Randomized data
Epoprostenol	~100,000	IV	Continuous	+	+++	No
Treprostinil	>175,000	SQ, IV, Inhaled	Continuous	++	+++	No
Iloprost	~175,000	Inhaled	6-9x per day	++	++	No
Sildenafil	~15,000	Oral	TID	+++	+	No
Tadalafil	~12,000	Oral	Daily	+++	+	No
Bosentan	~75,000	Oral	BID	++++	+	No
Ambrisentan	~75,000	Oral	Once a day	++++	+	No

Καρδιακά νοσήματα
&
στυτική δυσλειτουργία

Prevalence of Concomitant Conditions in ED Patients

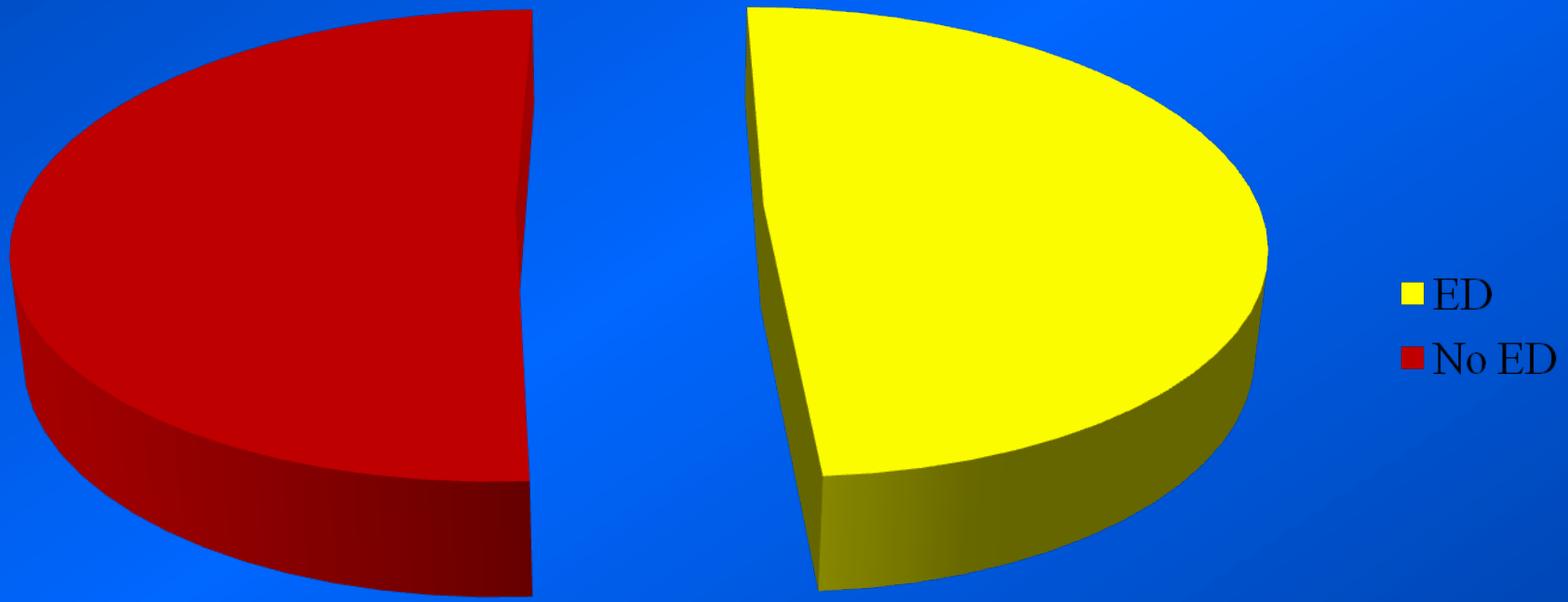


ED in cardiovascular disease



MMAS study

ED in ACS patients

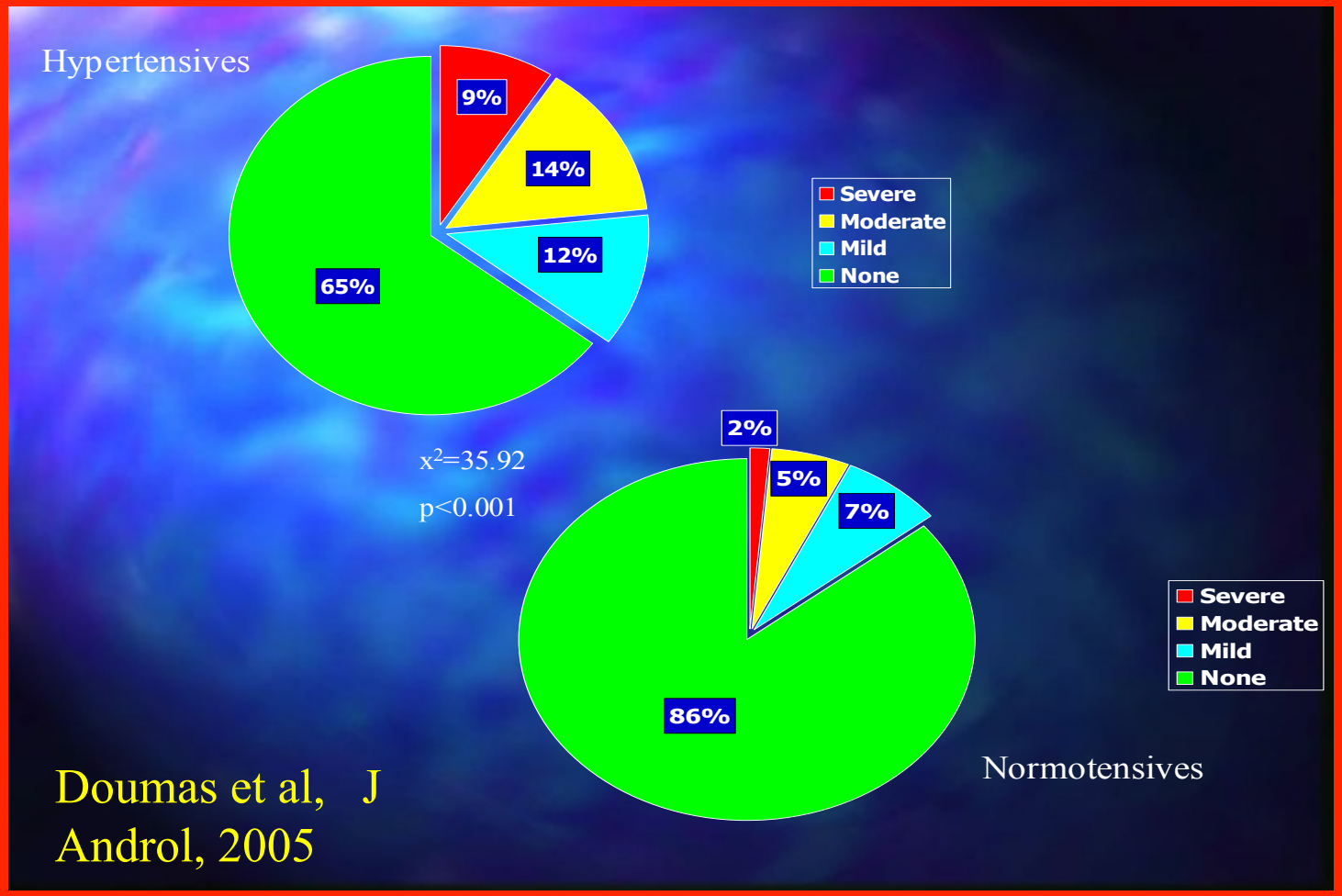


Montorsi, Eur Urol 2003

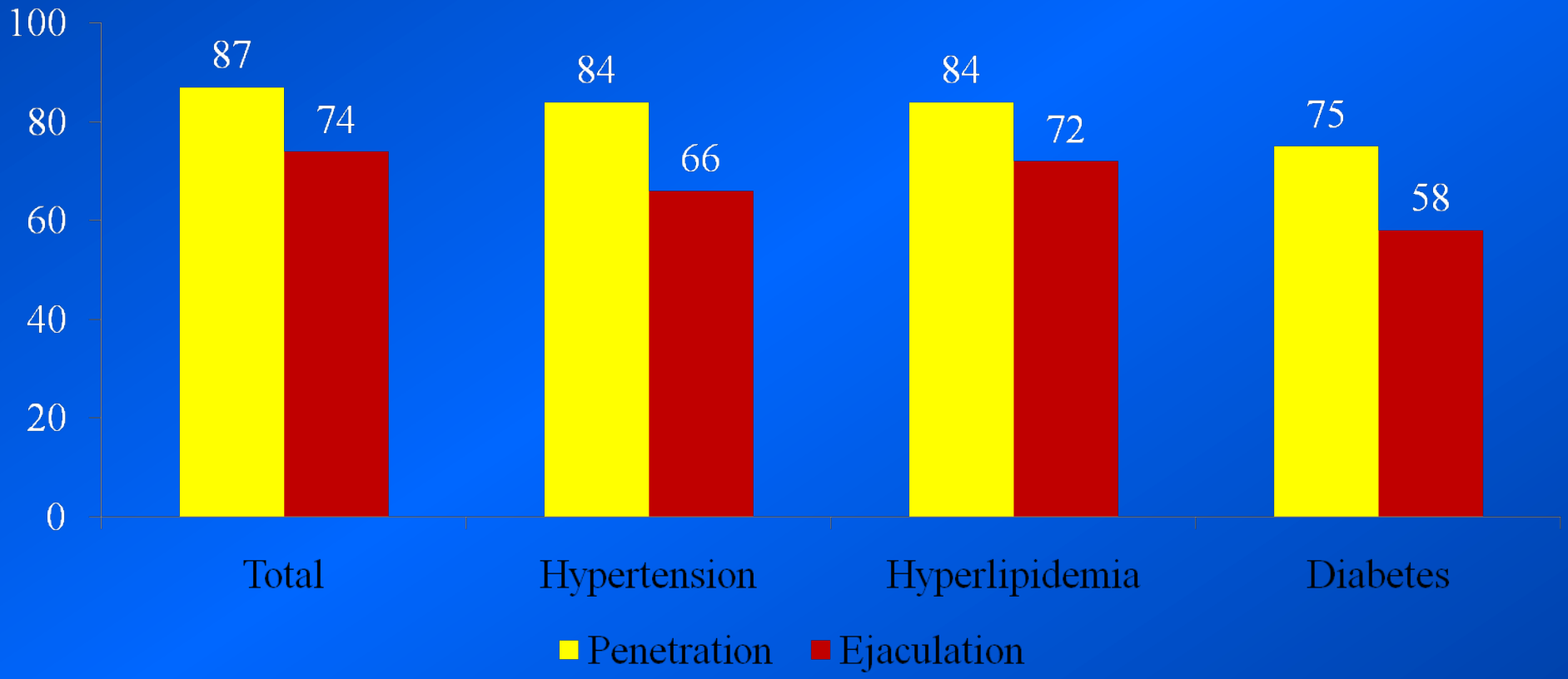
ARTERIAL HYPERTENSION

SAFETY
EFFICACY

Prevalence of erectile dysfunction



Efficacy



Valiquette, Int J Clin Pract 2006

Safety in hypertension

Concerns have been raised

regarding sildenafil use in patients taking

complicated, multidrug, antihypertensive regimens,

where sildenafil could be “potentially hazardous”.

ACC / AHA, JACC 1999

Safety in hypertension

Current available data strongly indicate that PDE-5 inhibitors may be effectively and safely co-administered with all classes of antihypertensive drugs, even in patients taking multiple antihypertensive agents.

Doumas, Hypertens Rev 2008

PDE-5 inhibitors and a-blockers

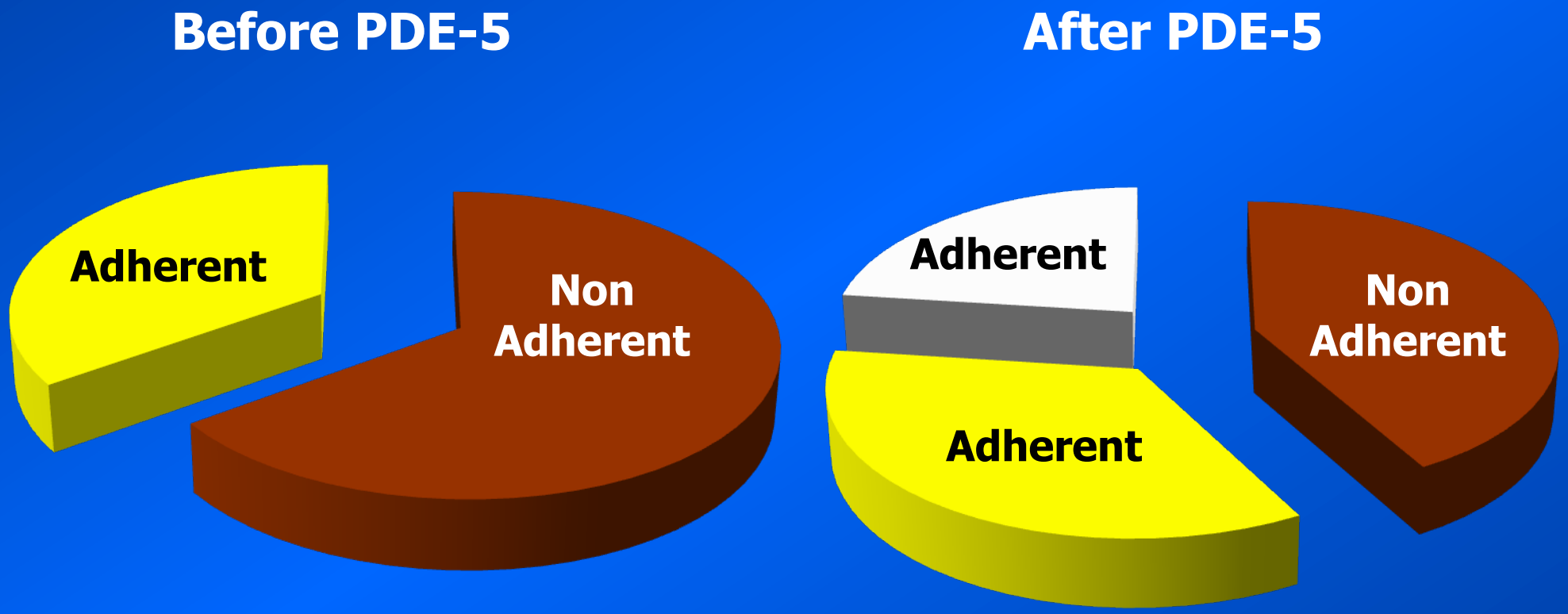
FDA label:
No contraindications, only precautions

alpha-blockers: start low dose PDE-5 inh

PDE-5 inh: start low dose a-blockers

Efficacy in hypertension

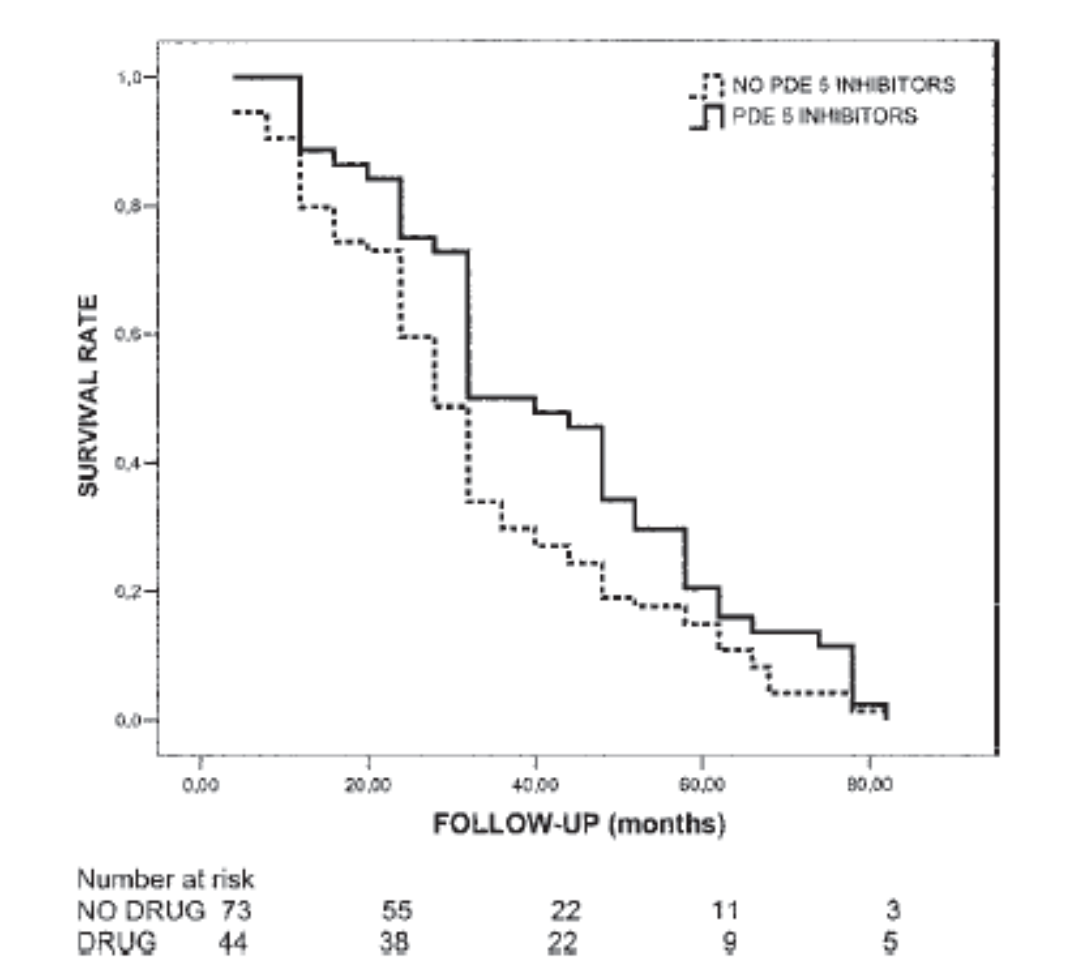
Increased compliance



McLauglin, Am J Ther 2005

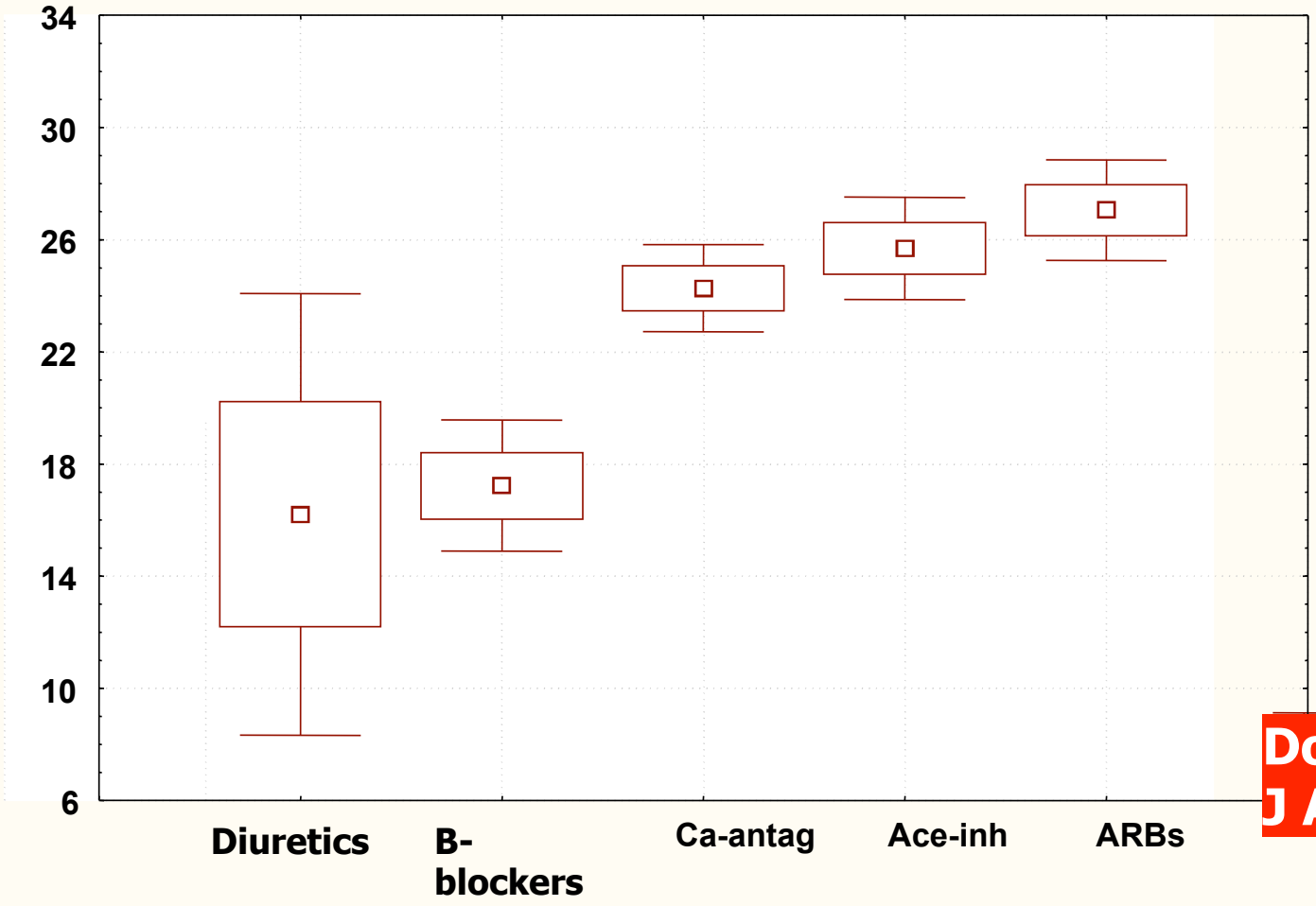
ED and death – Protection with PDE-5 inh

Type 2 diabetes mellitus



Gazzarusso et al. JACC 2008

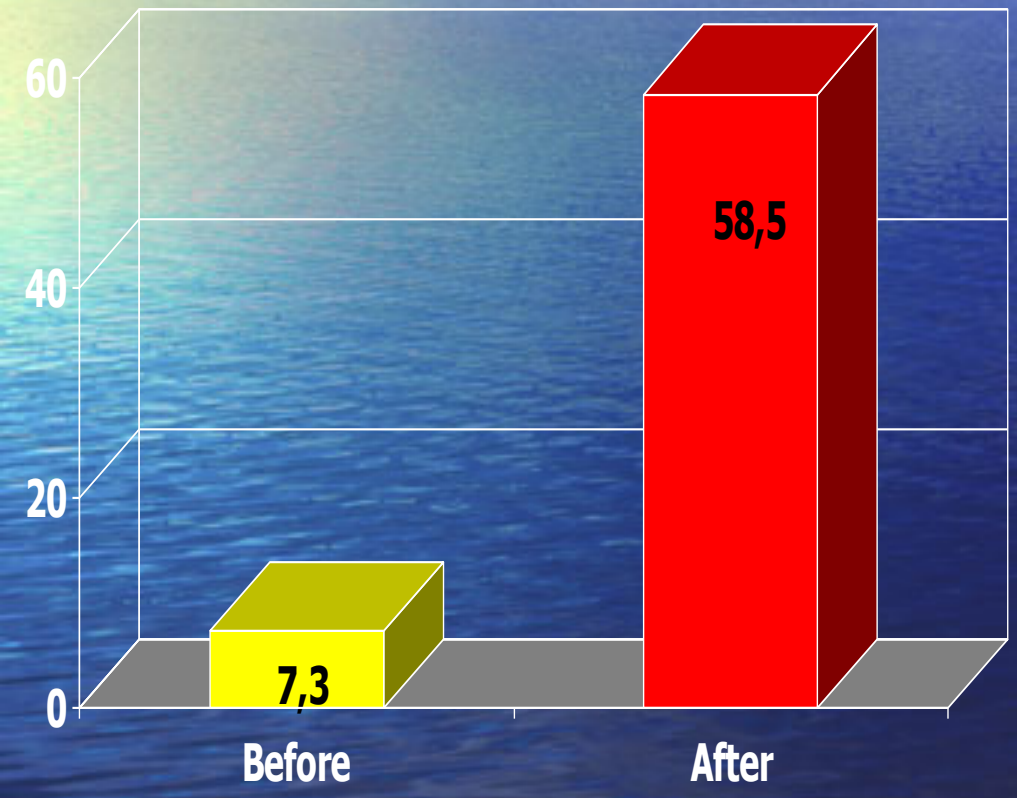
Data from everyday clinical practice



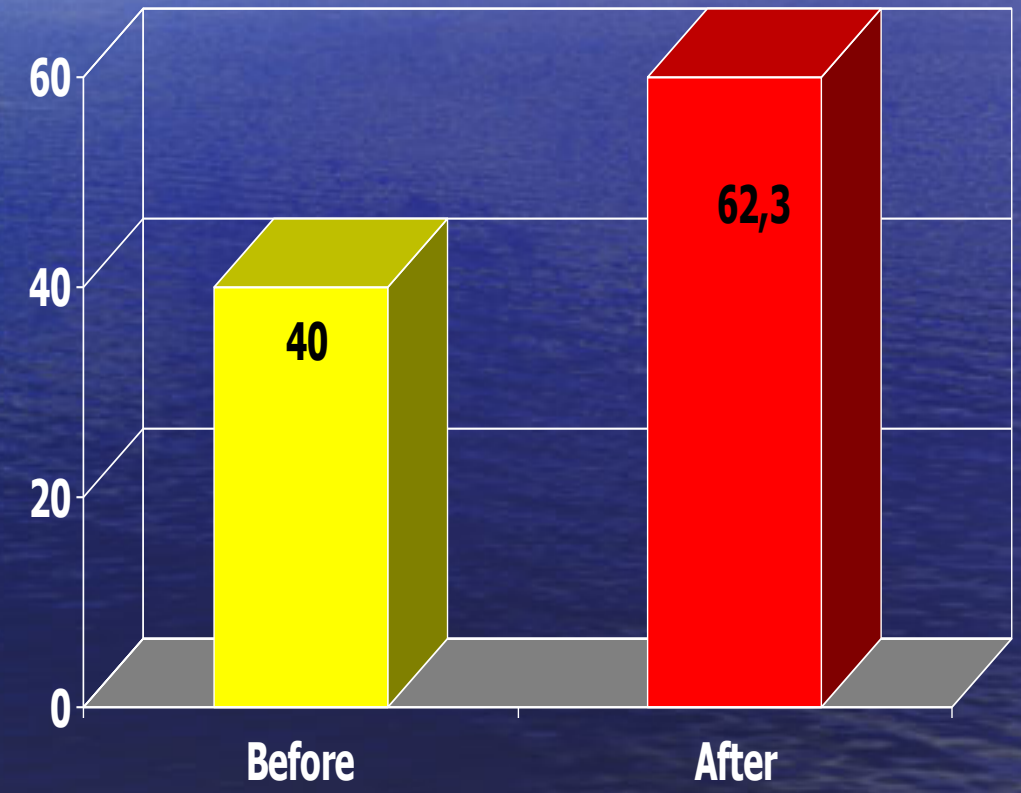
Doumas et al, J Androl, 2005

Change of previous therapy to losartan

Caro, Am J Med Sci 2001



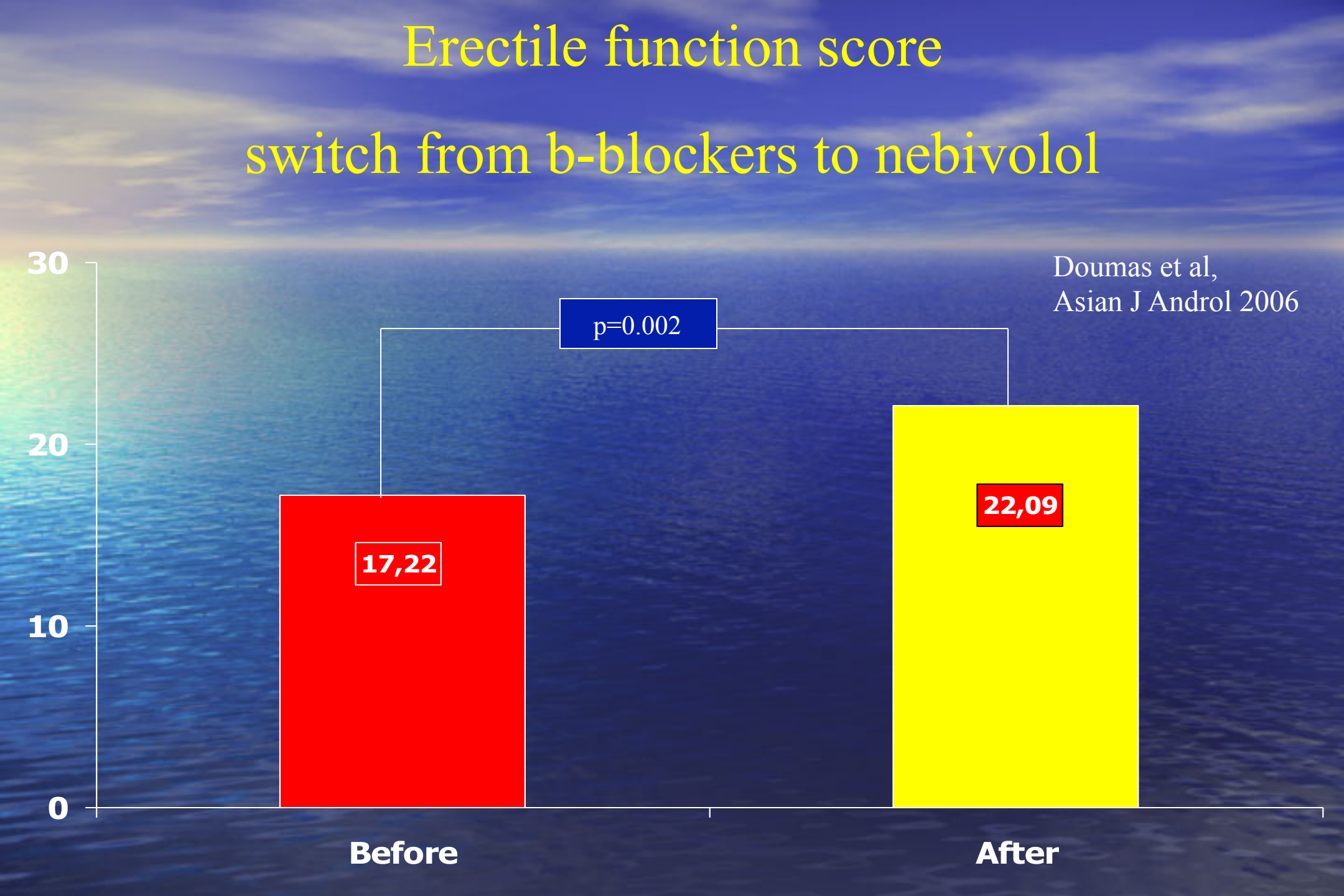
Sexual satisfaction



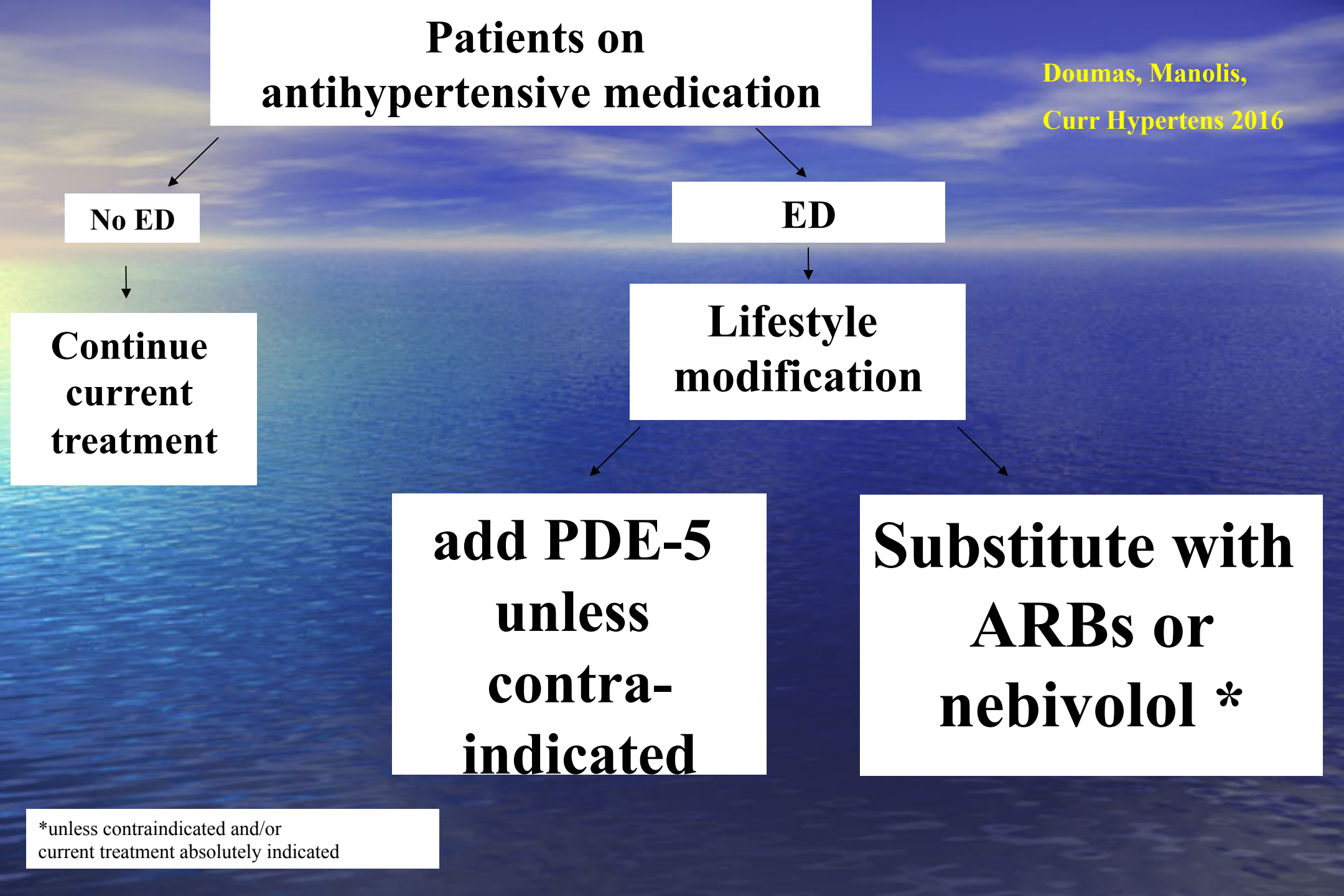
Sexual activity

Erectile function score

switch from b-blockers to nebivolol



Doumas et al,
Asian J Androl 2006


Patients on antihypertensive medication
Doumas, Manolis,
Curr Hypertens 2016
No ED
ED
Continue current treatment
Lifestyle modification
add PDE-5 unless contra-indicated
Substitute with ARBs or nebivolol *
*unless contraindicated and/or
current treatment absolutely indicated

Working Group
What *has* been done

European Society of Hypertension Scientific Newsletter:
Update on Hypertension Management

2011; 12: No. 32
revised version

SEXUAL DYSFUNCTION IN HYPERTENSION

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[4]Hypertension and Diabetes Dept., Gdansk Medical University, Poland

Introduction

Previously encountered as an unspoken reality, sexual dysfunction is now acknowledged as a clinical condition that impairs people's general health and well-being and has a major impact on the quality of life of both patients and their partners [1]. It is thus not surprising that sexual dysfunction represents a real therapeutic challenge to physicians of many specialties. Erectile dysfunction has been defined as the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse [2]. Female sexual dysfunction is described, in a more complex way, as a persistent or recurring decrease in sexual desire or in sexual arousal, the difficulty or the inability to achieve an orgasm, or the feeling of pain during sexual intercourse, which mirrors the multifold aspects of women sexuality [3].

Sexual dysfunction and cardiovascular disease: what is new?

USA in 1999) [13]. The disparity of available data reflects the differences in the study populations with regard to age, selection criteria, and cultural habits, in combination with the variant and often invalidated assessment methodologies; yet it highlights that sexual dysfunction is commonly encountered in the general population and may even represent a major burden in specific groups of patients.

Sexual dysfunction in hypertensive patients

Currently considered a disease of vascular origin [14], erectile dysfunction has been repeatedly found to be higher among hypertensive compared to normotensive subjects (i.e. 45.8% vs. 18.9% in Spain, 35.2% vs. 14.1% in Greece). Similarly, accumulating evidence shows that hypertensive women exhibit a higher prevalence of sexual dysfunction compared to normotensives (42.1% vs. 19.4% according to one study, odds ratio 3.2) [15]. Duration and severity of hypertension were positively correlated with the degree of sexual dysfunction [16]. Obstructive

Doumas, ASH NY 2012

Working Group
What *has* been done

Hypertension and sexual dysfunction: time to act

Margus Viigimaa[a], Michael Doumas[b], Charalampos Vlachopoulos[c], Panagiota Anyfanti[b], Jacek Wolf[d], Krzysztof Narkiewicz[d], Giuseppe Mancia[e], for the European Society of Hypertension Working Group on Sexual Dysfunction

Journal of Hypertension 2011, 29:403–407

Keywords: antihypertensive drugs, coronary artery disease, erectile dysfunction, hypertension, PDE-5 inhibitors, prevalence, sexual dysfunction

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ESH, European Society of Hypertension; PDE, phosphodiesterase

clinicians dealing with hypertensive patients (hypertension specialists, cardiologists, internists, nephrologists, diabetologists, and general practitioners) about the magnitude of the problem, the recognition of sexual dysfunction and its management in hypertensive patients. An equally important objective is to familiarize other medical specialties managing sexual dysfunction (urolo-

ESH guidelines 2013

Hypertension and erectile dysfunction

Erectile dysfunction is a prevalent condition in hypertensive patients and a predictor of future cardiovascular events. Screening and treatment of erectile dysfunction improves management of cardiovascular risk factors. After initiating therapy with phosphodiesterase (PDE) 5 inhibitors, patients are more likely to take antihypertensive medication and BP control is improved [272]. Older antihypertensive drugs (diuretics, β-blockers, centrally acting drugs) exert negative effects, whereas newer drugs have neutral or beneficial effects (calcium antagonists, ACE inhibitors, angiotensin receptor antagonists, nebivolol) [273].

J Hypertens, 2013

Working Group
on Sexual Dysfunction in Hypertension

"At 2016 >40% and at 2020 >80%

of hypertensive patients in Europe

will be asked about sexual dysfunction

and will be adequately managed"

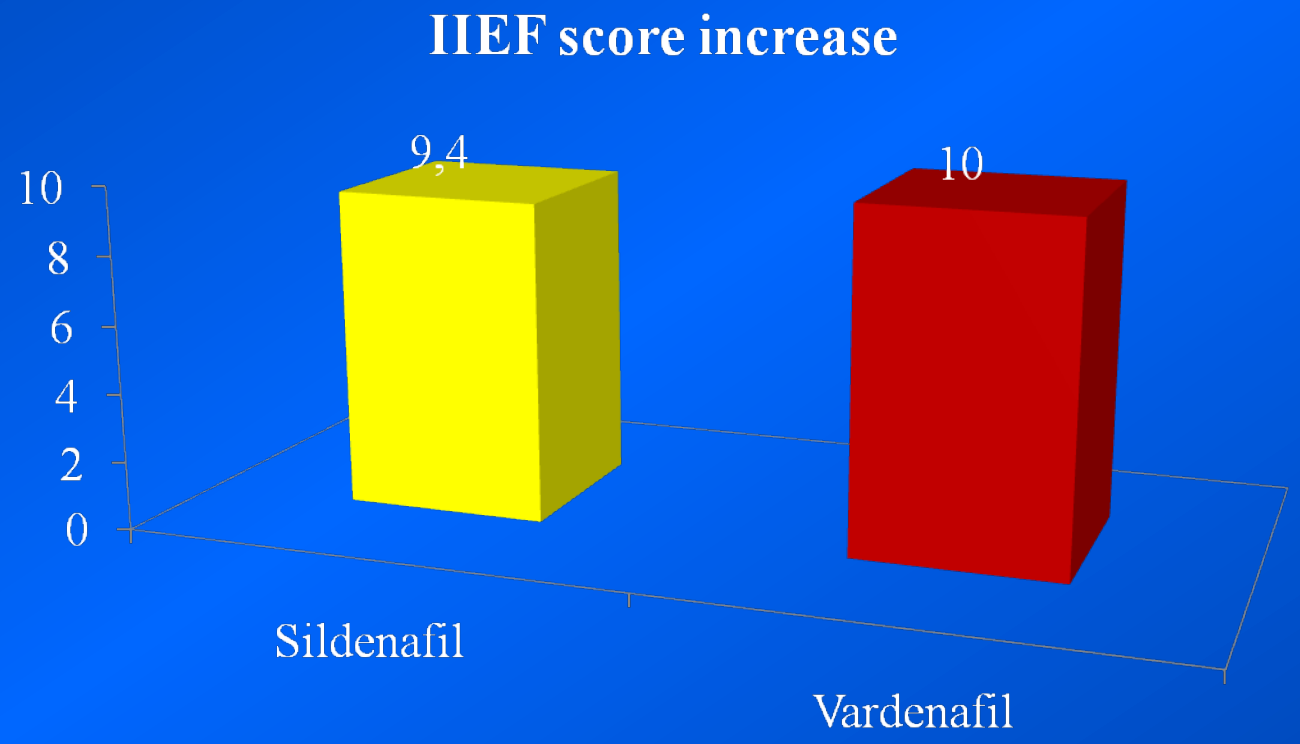
Doumas, ESH London 2012

PDE-5 inhibitors

&

CVD

PDE-5 inhibitors in CVD



Valiquette L, 2006

Nitrates after PDE-5 inh

- Safe 24h after sildenafil (6 lifetimes). In healthy subjects safe even after 4h.

Oliver, Int J Impot Res 2002

- Vardenafil: as sildenafil

Bayer-Glaxo 2003

- At least 48h after tadalafil under close medical supervision

Kloner, JACC 2003

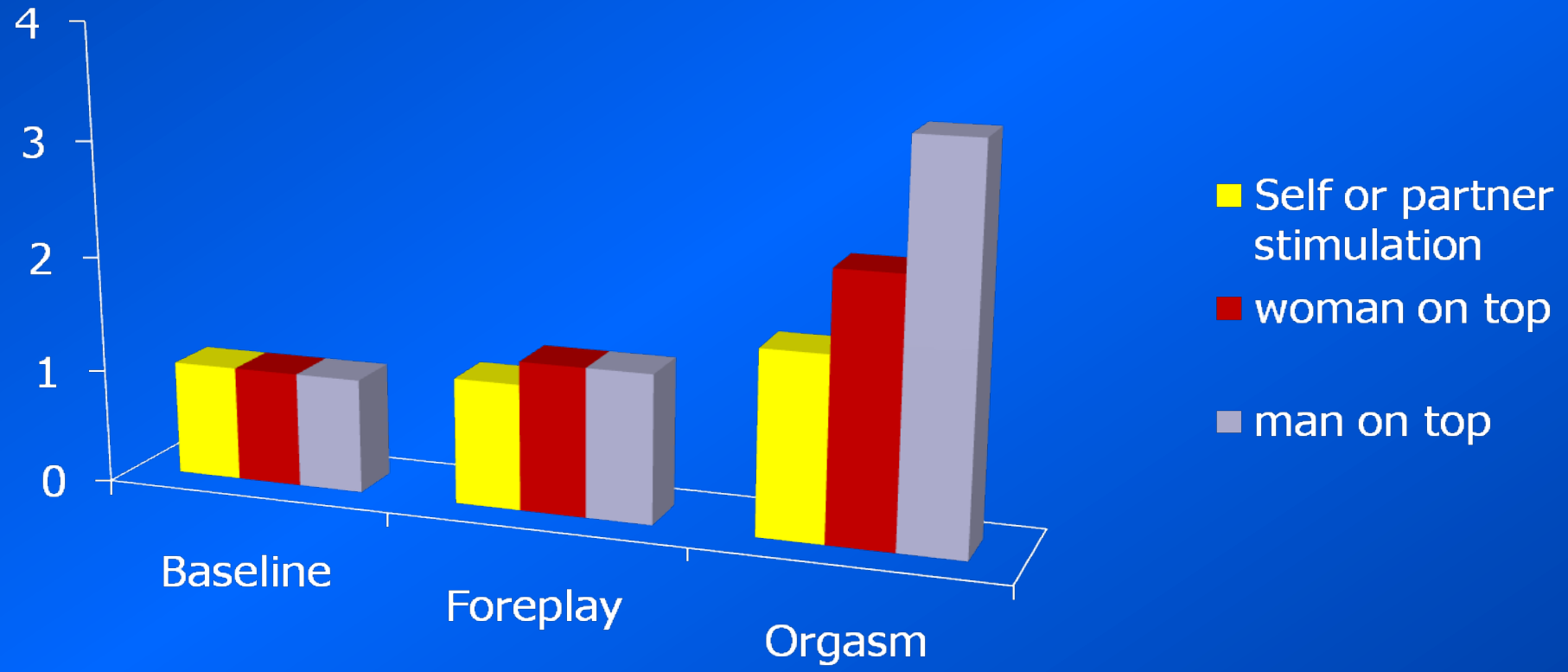
Σεξ

&

Καρδιά


BANX
'I've screened your heart
and it appears to be broken'

Metabolic needs during sexual intercourse

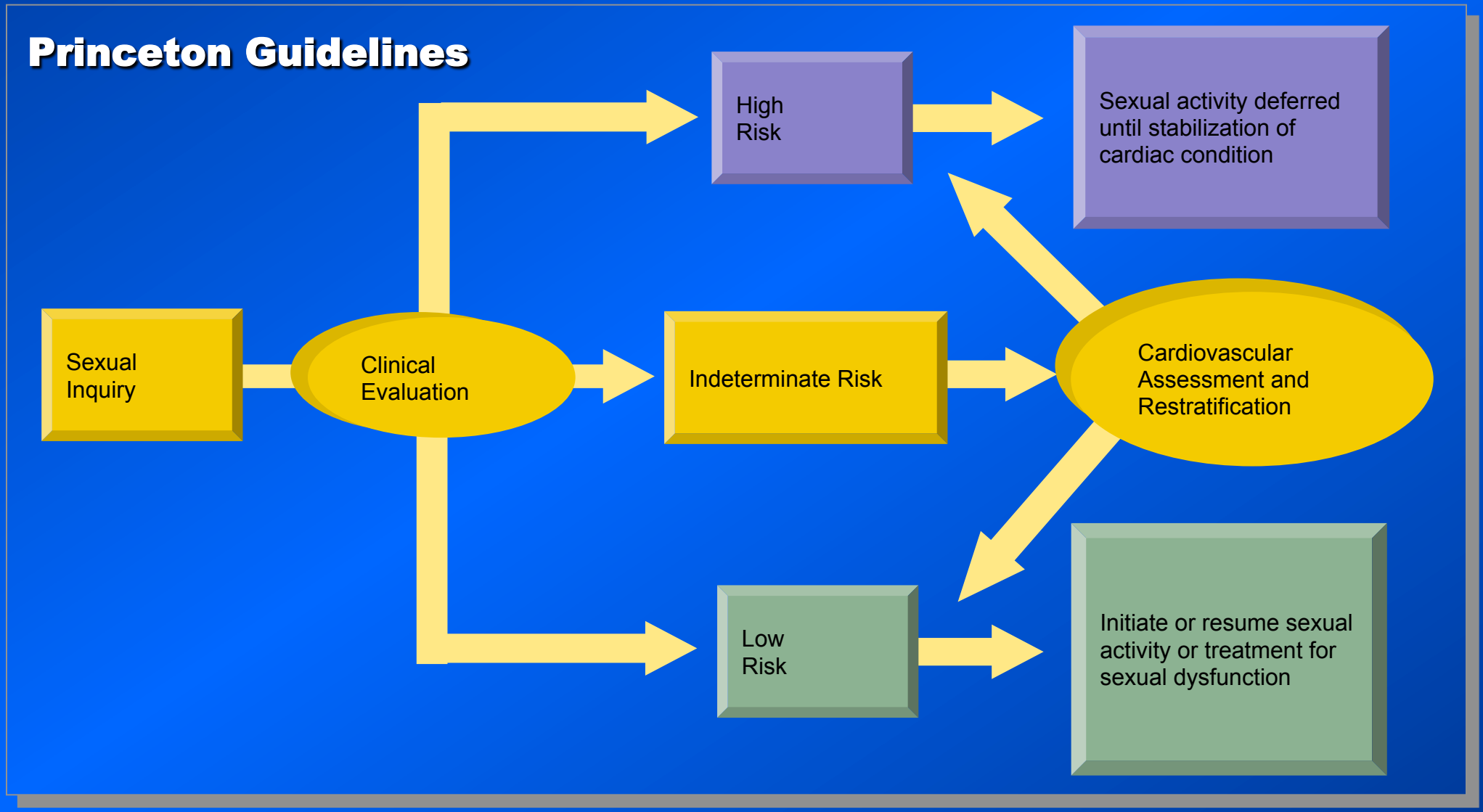


Bohlen, Arch Intern Med

METs during daily activities

• Female on top	2.5
• Male on top	3.3
• Extra-marital	5-6
• Walking	3.2
• Tennis	6.8
• Gardening	4.4
• Carpentry	5-7

Sexual Activity and Cardiac Risk Assessment



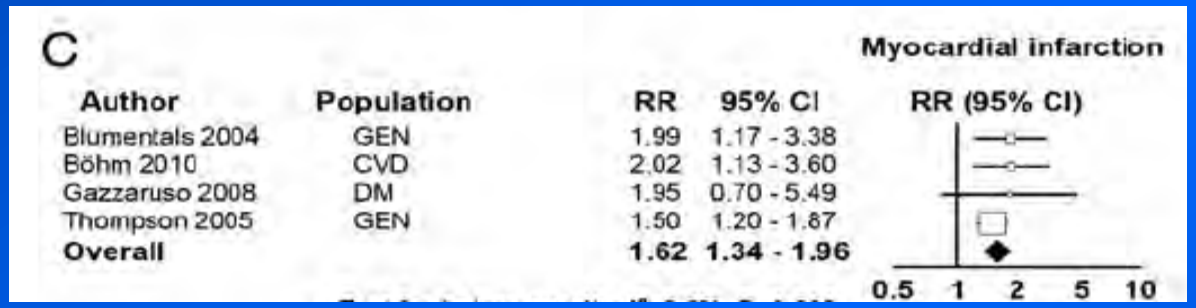
High risk patients
Second Princeton Consensus

- Unstable angina
- Recent AMI(<2 weeks)
- Heart failure (NYHA class III/IV)
- Malignant arrhythmias
- HOCAM
- Moderate to severe valvular disease
- Uncontrolled hypertension

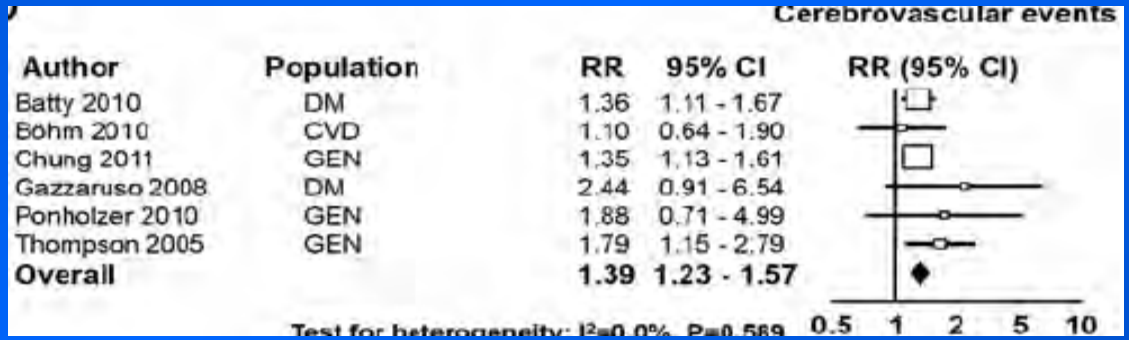
Kostis 2005

Η σεξουαλική δυσλειτουργία ως παράγοντας καρδιαγγειακού κινδύνου

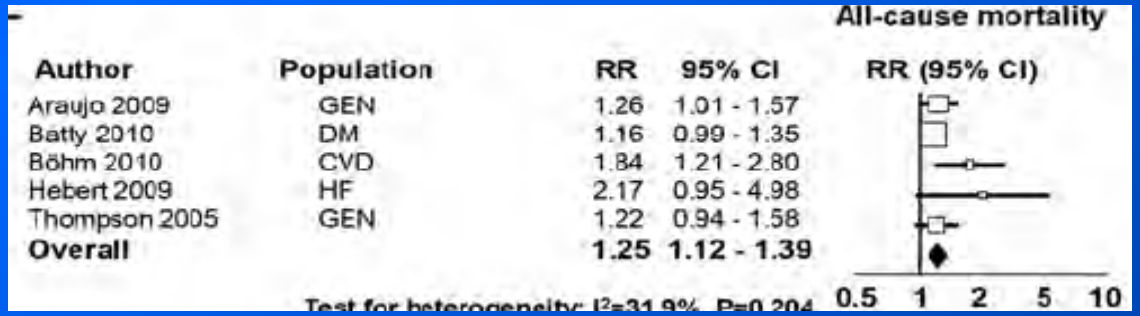
ED – CV events – mortality
Meta-analysis



62%



39%



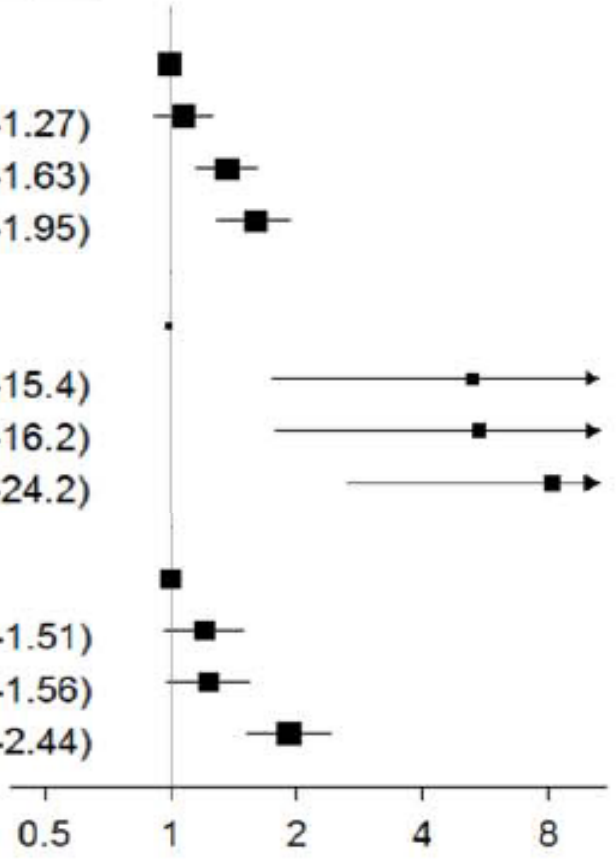
25%

Vlachopoulos, Circ Cardiov Qual Out 2013

ED as predictor of CV events and mortality
General population - 95,038 individuals

No Previous CVD

	Events/p-years	RR*	RR#(95% C.I)
Ischaemic Heart Disease			
No ED	358/72496	1.00	1.00
Mild ED	271/40625	1.11	1.08 (0.92-1.27)
Moderate ED	269/24329	1.51	1.37 (1.16-1.63)
Severe ED	227/13622	1.87	1.60 (1.31-1.95)
Heart Failure			
No ED	4/72999	1.00	1.00
Mild ED	19/40958	5.91	5.19 (1.75-15.4)
Moderate ED	23/24648	7.29	5.37 (1.78-16.2)
Severe ED	46/13861	12.5	8.00 (2.64-24.2)
All-cause mortality			
No ED	155/88681	1.00	1.00
Mild ED	165/49820	1.28	1.21 (0.97-1.51)
Moderate ED	177/29911	1.40	1.24 (0.98-1.56)
Severe ED	313/16775	2.27	1.93 (1.52-2.44)



Banks, PLOS Med 2013

ED and subsequent CHD type 2 diabetes mellitus

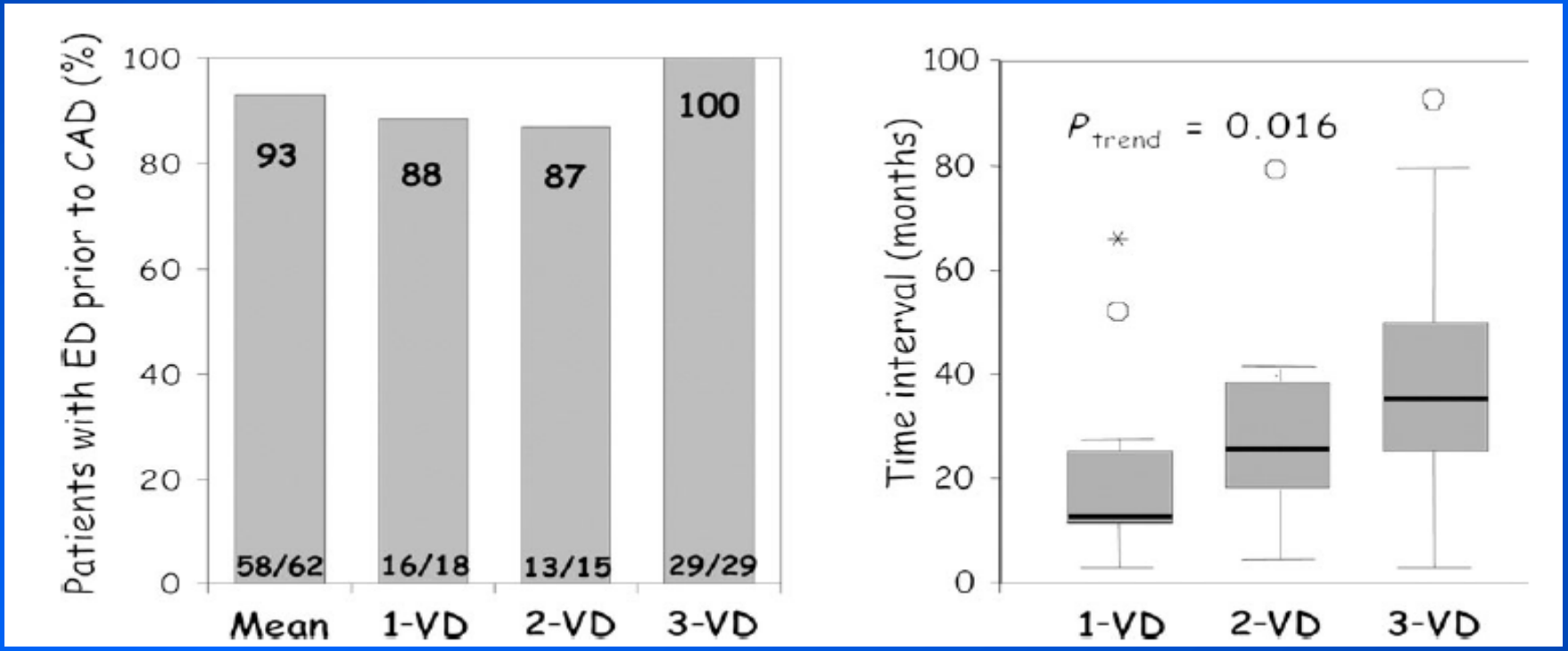
Table 3 Predictors of New Onset of CHD Events in 2,306 Chinese Men With Type 2 Diabetes With Multivariate Analysis

	Hazard Ratio	95% Confidence Intervals	p Value
Age	1.02	1.00–1.04	0.026
Duration of diabetes	1.03	1.00–1.06	0.025
Albuminuria			
Normoalbuminuria	1.00		
Microalbuminuria	1.28	0.81–2.03	0.30
Macroalbuminuria	2.16	1.37–3.41	0.001
Use of antihypertensive medications	1.58	1.06–2.35	0.025
Erectile dysfunction	1.58	1.08–2.30	0.018

Ma et al. JACC 2008

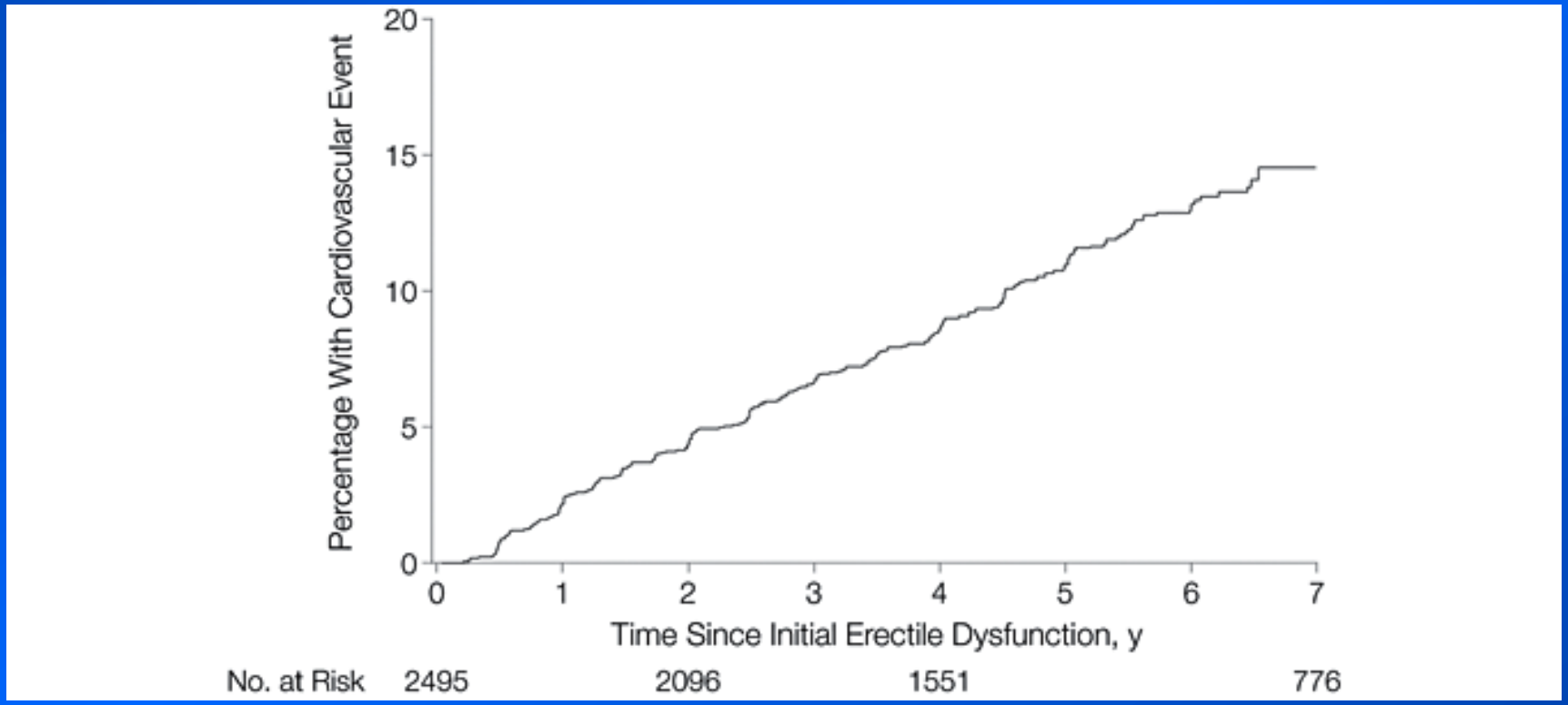
Χρονική αλληλουχία εμφάνισης σεξουαλικής δυσλειτουργίας και στεφανιαίας νόσου

ED precedes CAD
COBRA trial, 285 pts



Montorsi, Eur Heart J 2006

ED and subsequent CVD general population

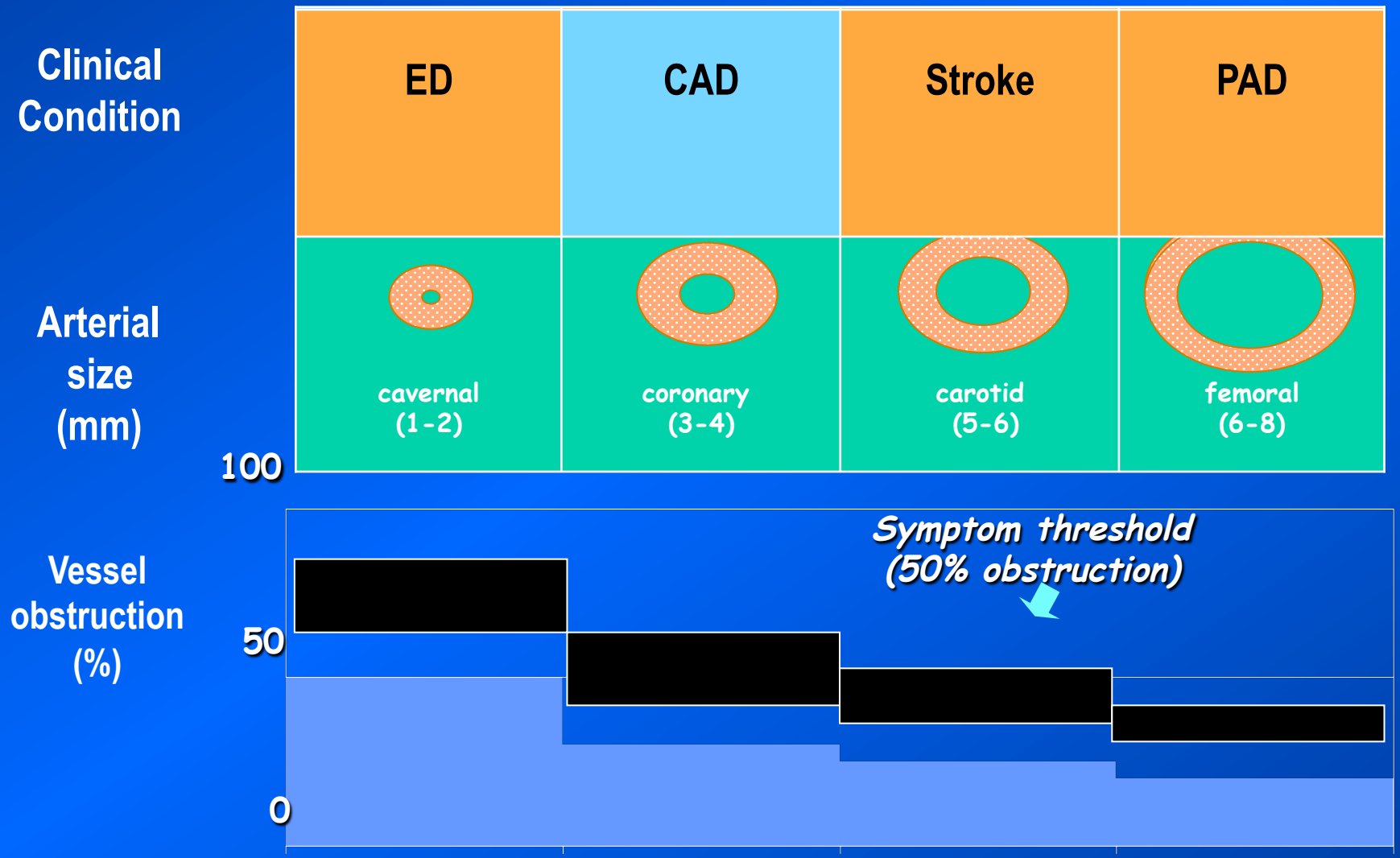


Thompson et al. JAMA 2005

Υπάρχει

παθοφυσιολογική ερμηνεία;;;

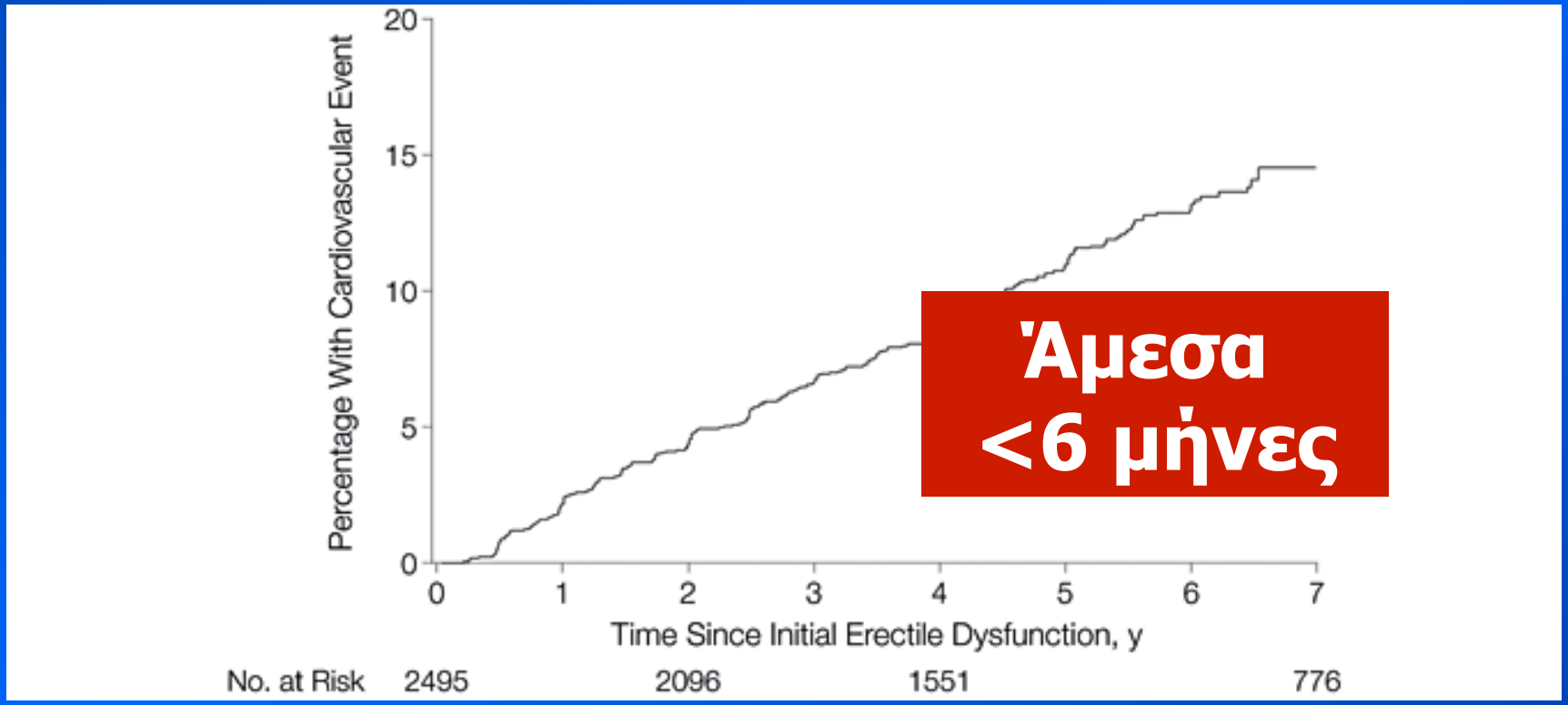
Artery size hypothesis



Πότε θα διερευνήσουμε

τους ασθενείς ;;;

ED and subsequent CVD general population



Thompson et al. JAMA 2005

Ποιους ασθενείς ;;;

Με ποιον τρόπο ;;;

Diagnostic – therapeutic algorithm

A. Patients without established CVD or diabetes

Low SCORE /FRS	Moderate SCORE/FRS	High or Very high SCORE/FRS
Exercise ability Lifestyle advice or intervention Treatment of RFs PDE5i	Exercise ability or stress test (in higher scores) Lifestyle intervention Consider drug intervention if RF uncontrolled PDE5i	Cardiologist referral Stress test Lifestyle intervention RF drug intervention PDE5i Tth‡
if biomarker abnormal and/or hypogonadism Exercise ability or stress test Lifestyle intervention RF drug intervention PDE5i Tth‡	*if biomarker abnormal and/or hypogonadism* Stress test Lifestyle intervention RF drug intervention PDE5i Tth‡	

Vlachopoulos, Eur Heart J 2013

Frequency of sexual activity and CV events

Multivariate Cox proportional hazards modeling estimates and 95% confidence intervals (CIs) for sexual function at baseline and incident cardiovascular disease

Model	Cardiovascular Disease			
	Measured by Self-Report, Medical Record, or NDI		Measured by Medical Record or NDI	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Frequency of sexual desire				
Framingham and covariate adjusted*				
Weekly or 2–3 times monthly vs ≥2–3 times weekly	1.05 (0.80–1.37)	0.72	0.88 (0.63–1.22)	0.43
Monthly or less vs ≥2–3 times weekly	1.20 (0.84–1.73)	0.32	1.29 (0.85–1.94)	0.23
Framingham, covariate, and erectile dysfunction adjusted†				
Weekly or 2–3 times monthly vs 2–3 times weekly	1.00 (0.76–	0.99	0.82 (0.59–1.15)	0.25
Monthly or less vs ≥2–3 times weekly		.84	1.08 (0.68–1.70)	0.75
Frequency of sexual activity				
Framingham and covariate adjusted*				
Weekly or 2–3 times monthly vs ≥2–3 times weekly		.44	1.01 (0.72–1.42)	0.95
Monthly or less vs ≥2–3 times weekly		.007	1.54 (1.07–2.22‡)	0.02
Framingham, covariate, and erectile dysfunction adjusted†				
Weekly or 2–3 times monthly vs ≥2–3 times weekly	1.10 (0.83–1.46)	0.52	0.99 (0.70–1.40)	0.97
Monthly or less vs ≥2–3 times weekly	1.45 (1.04–2.0‡)	0.03	1.43 (0.97–2.11)	0.07

+43% CV risk

Hall et al. Am J Cardiol 2010

Scientists prove:

THE MORE SEX MEN HAVE, THE LONGER THEY LIVE!


101
POSITIONS
102
EXCUSES