Οι ανεπιθύμητες ενέργειες από το καρδιαγγειακό σύστημα

Michael Doumas
Aristotle University of Thessaloniki
George Washington University, Washington, DC

Δήλωση συμφερόντων

Δεν υπάρχει σύγκρουση συμφερόντων σχετικά με το περιεχόμενο της παρουσίασης αυτής

Wisdom for Thought

"Doctors pour drugs of which they know little for disorders of which they know less into patients of which they know nothing."

Voltaire

Overactive bladder

Anti-muscarinic

Mirabegron

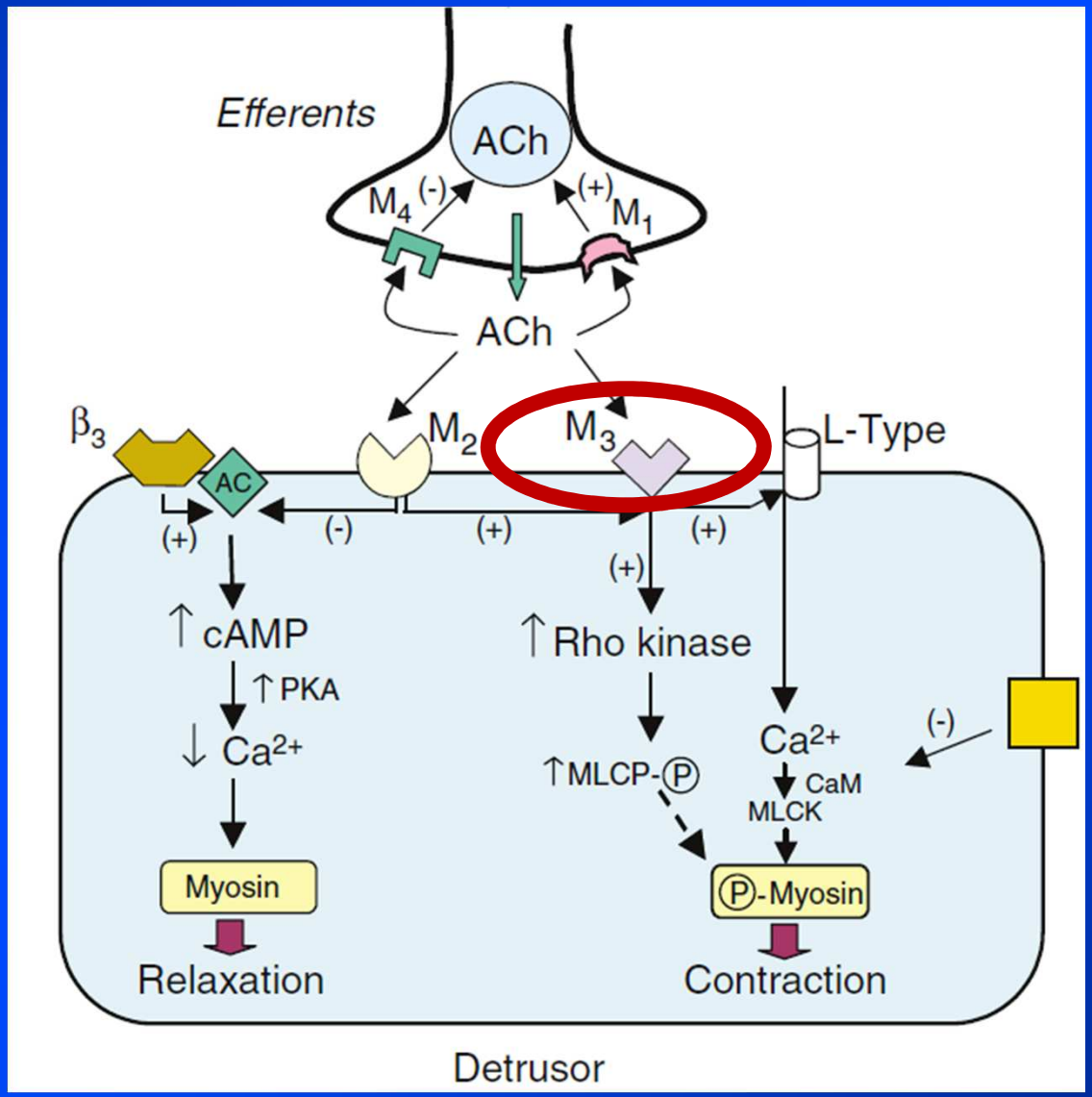
Desmopressine

Αντιχολινεργικά

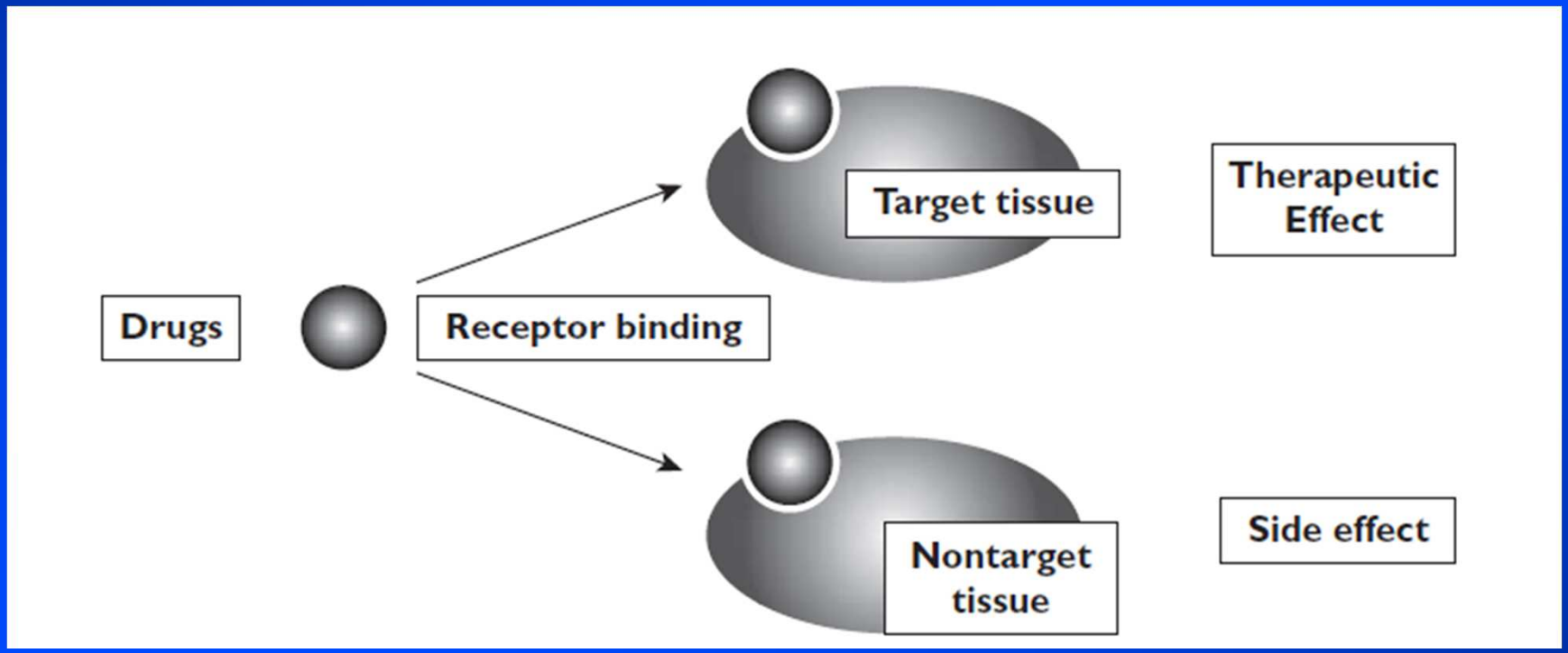
Χολινεργικοί υποδοχείς

- Ουροδόχος κύστη
- Σιελογόνοι αδένες
- Γαστρεντερικό σύστημα
- Εγκέφαλος
- Οφθαλμοί
- Καρδιά

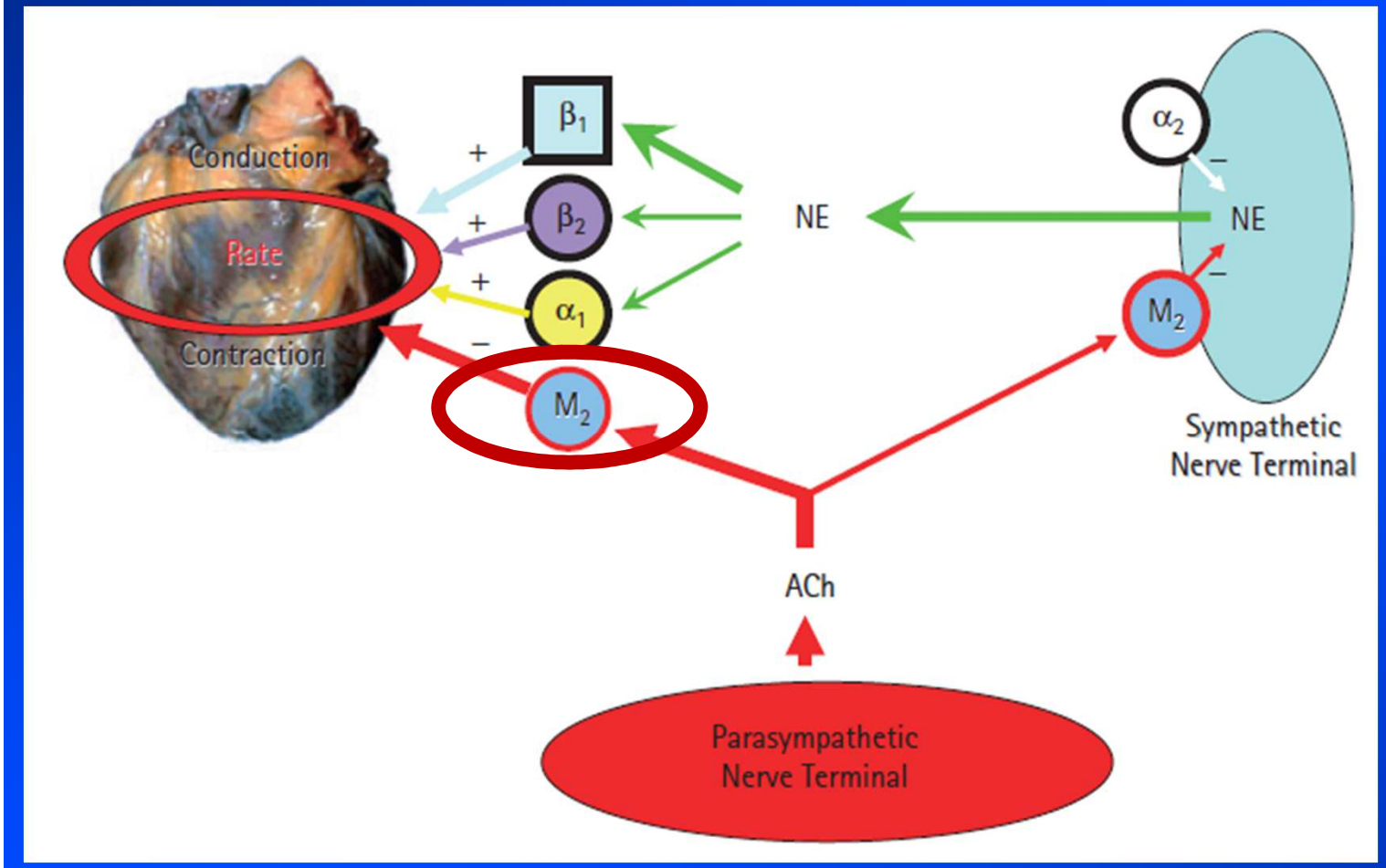
Μηχανισμός δράσης

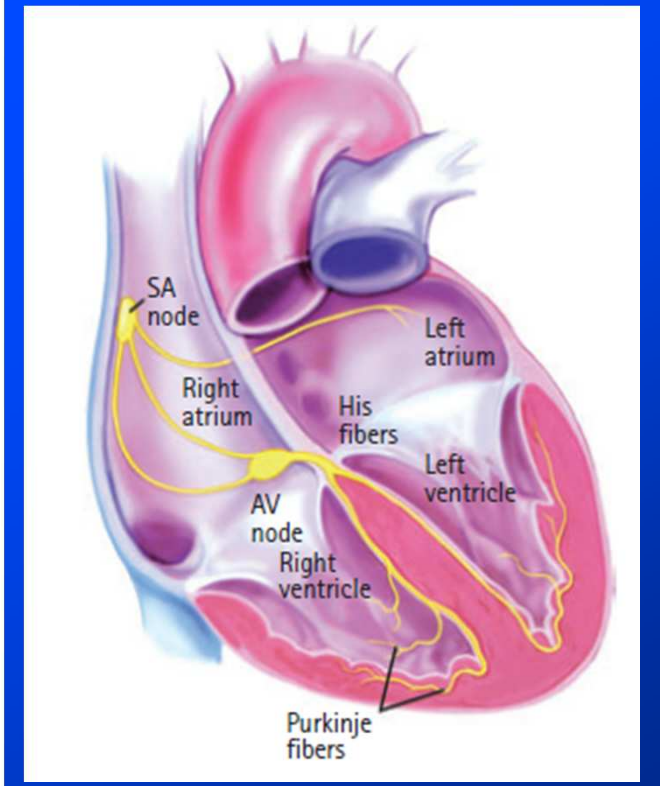


Μηχανισμός δράσης – ανεπιθυμήτων ενεργειών



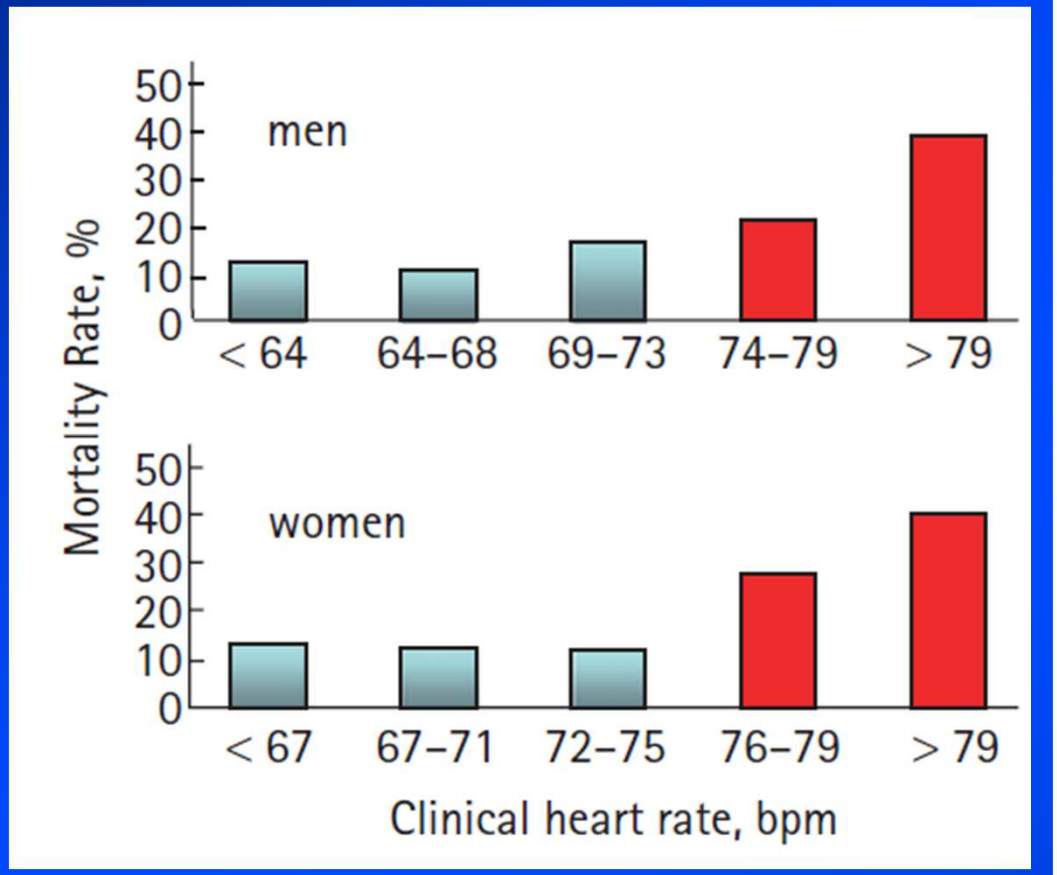
Έλεγχος καρδιακού ρυθμού

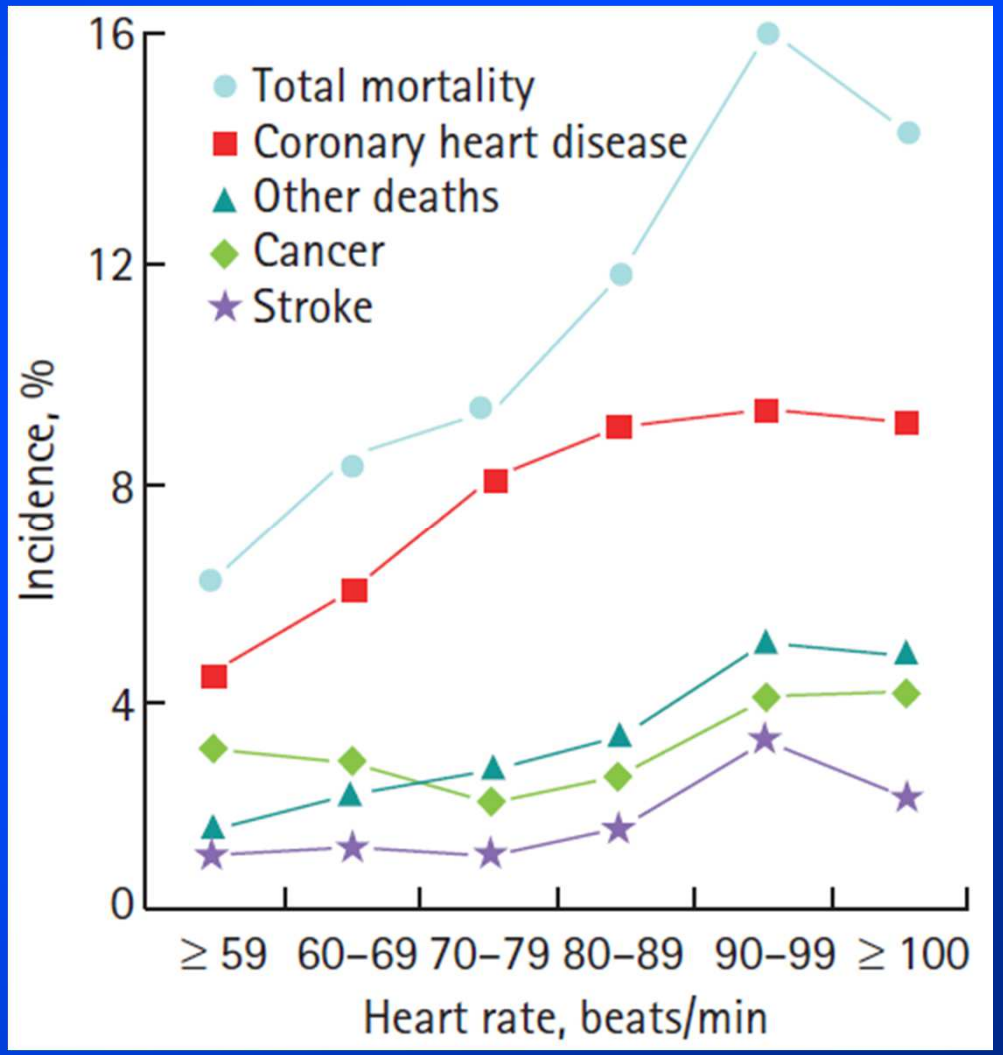




Andersson, BJU International 2007

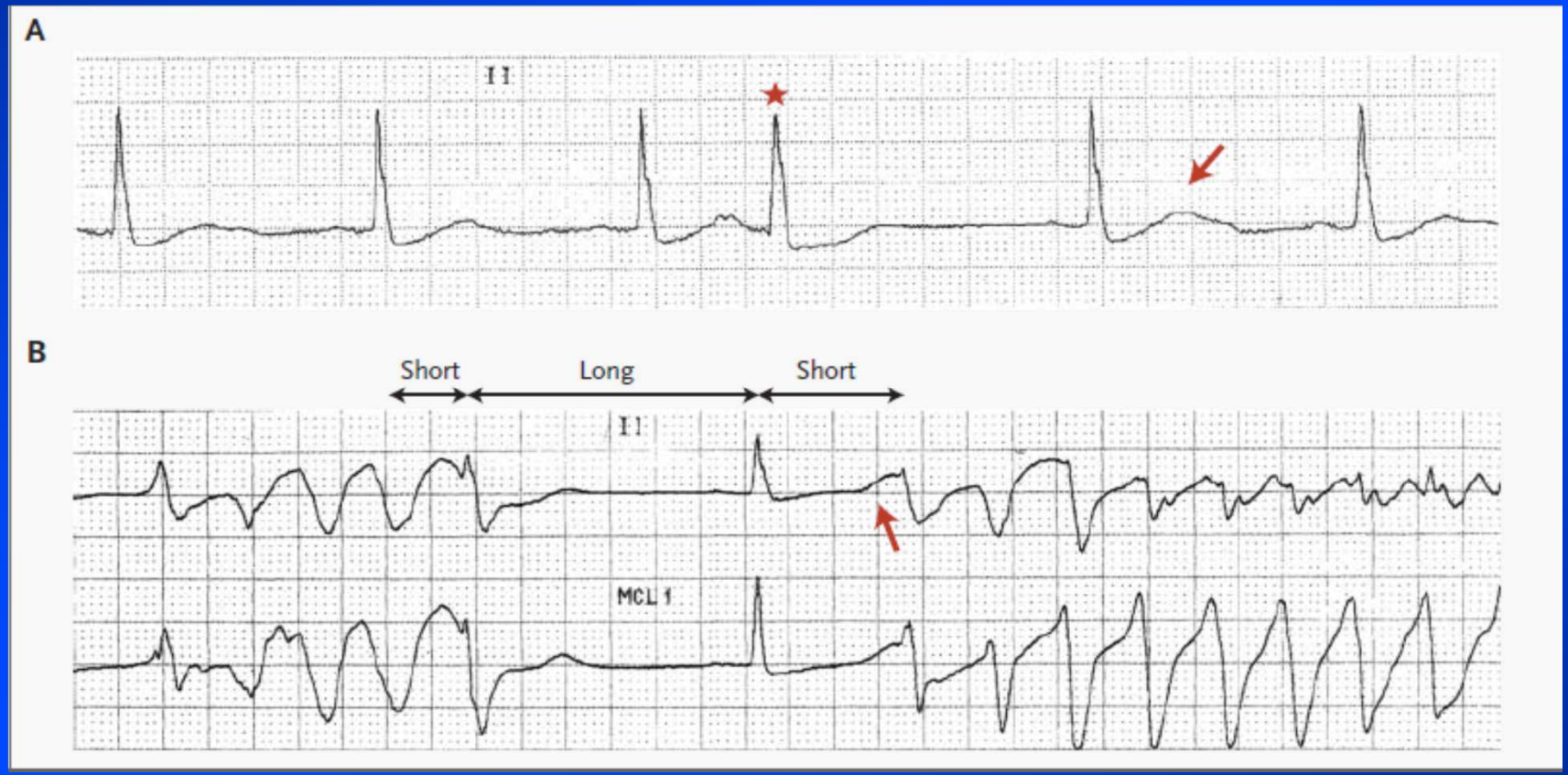
HR-CV risk





Palatini, Arch Intern Med 2002; Wilhemlsen, Eur Heart J 1988

QT prolongation
Torsades de pointes



Doumas, Agria 2014

Αντιχολινεργικά και υποδοχείς

Molecule	M_1	M_2	M_3	M_4	M_5
Oxybutynin	1.0	6.7	0.67	2.0	11.0
Tolterodine	3.0	3.8	3.4	5.0	3.4
Darifenacin	7.3	46.0	0.79	46.0	9.6
Solifenacin	25	125	10	NR	NR
Trospium	0.75	0.65	0.50	1.0	2.3

(a) *Affinity (pK_i) of antimuscarinic compounds for the human recombinant receptor subtypes M_1–M_5*

	M_1	M_2	M_3	M_4	M_5
Darifenacin	8.2 (0.04)	7.4 (0.10)	9.1 (0.10)	7.3 (0.10)	8.0 (0.10)
Tolterodine	8.8 (0.01)	8.0 (0.10)	8.5 (0.10)	7.7 (0.10)	7.7 (0.03)
Oxybutynin	8.7 (0.04)	7.8 (0.10)	8.9 (0.10)	8.0 (0.04)	7.4 (0.03)
Propiverine	6.6 (0.10)	5.4 (0.10)	6.4 (0.10)	6.0 (0.10)	6.5 (0.10)
Trospium	9.1 (0.10)	9.2 (0.10)	9.3 (0.10)	9.0 (0.10)	8.6 (0.10)

(b) *Comparison of the M_3 selectivity of each compound*

	M_3 *versus* M_1	M_3 *versus* M_2	M_3 *versus* M_4	M_3 *versus* M_5
Darifenacin	9.3***	59.2***	59.2***	12.2***
Tolterodine	0.6*[a]	3.6***	7.3***	6.3***
Oxybutynin	1.5*[a]	12.3***	6.9***	27.0***
Propiverine	0.6*[a]	9.6***	2.8***	0.8
Trospium	1.5	1.3	2.0*	4.6***

Hedge, Br J Pharmacol 2006, Abrams, Br J Pharmacol 2006

Αντιχολινεργικά και καρδιαγγειακό

Ουσία	Εκλεκτικότητα	Καρδιακή συχνότητα	QT	Μελέτες
Darifenacin	>>> M3	-	-	Oslansky, 2008 Oslansky, 2008
Fesoterodine	M3 = M2	+3.00 σφ/min (4mg) +11.60 σφ/min (28mg) +3-5 σφ/min (8mg)	-	Chapple, 2007
Oxybutynin	>>> M3	-	?	Abrams, 2006 Chapple, 2005
Propiverine	M3 = M2	↑↑	-	Dorschner, 2000 Abrams, 2006
Solifenacin	>>> M3	-	↑ QT 30mg>10mg Torsade de pointes	Michel, 2008 Asajima, 2008
Tolterodine	M3 = M2	+1.84 (4mg) +2.00 (4mg) +6.30 (8mg)	± ?	Malhotra, 2007 Oslansky, 2008
Trospium	M3 = M2	+9.1 (20mg) +18.0 (100mg)	-	Guay, 2005 Zinner, 2004 Rudy, 2006
Terodiline			+++ Torsade de pointes	Stewart, 1992 Thomas, 1995

Doumas, Agria 2014

Γενικό σχόλιο

- Δεν υπάρχουν μακροχρόνιες τυχαιοποιημένες μελέτες
- Δεν υπάρχουν αρκετές μελέτες άμεσης σύγκρισης
- Δεν υπάρχουν μεγάλες μελέτες σε ηλικιωμένους
- Δεν υπάρχουν μελέτες σε ασθενείς με καρδιαγγειακά νοσήματα

Comorbidities

Condition	OAB patients, % ($N = 41\,440$)	Non-OAB patients, % ($N = 77\,272$)	P
CV co-morbidities			
Any CV co-morbidity	57.60	44.62	<0.001
Congenital heart disease	0.30	0.27	0.010
Ischaemic heart disease	10.80	8.92	<0.001
Other forms of heart disease	6.30	5.22	<0.001
Conduction disorders	8.50	7.28	<0.001
Heart failure	3.60	2.71	<0.001
CV symptoms	5.60	4.56	<0.001
Hypertension	44.20	32.00	<0.001
Hypotension	1.20	0.62	<0.001
Pulmonary heart disease	1.00	0.69	<0.001
Cerebrovascular disease	7.50	4.39	<0.001
Disease of blood vessels	5.50	4.04	<0.001
Diabetes	15.50	10.96	<0.001
Renal diseases	3.30	2.33	<0.001

Asche, BJUI 2011

Φάρμακα που προκαλούν παράταση QT

Drugs commonly involved

Disopyramide

Dofetilide

Ibutilide

Procainamide

Quinidine

Sotalol

Bepridil

Other drugs†

Amiodarone

Arsenic trioxide

Cisapride

Calcium-channel blockers: lidoflazine (not marketed in the United States)

Antiinfective agents: clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin

Antiemetic agents: domperidone, droperidol

Antipsychotic agents: chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide

Methadone

Roden, NEJM 2004

Παράγοντες κινδύνου για παράταση QT

- Female sex[10]
- Hypokalemia[11,12]
- Bradycardia[11,12]
- Recent conversion from atrial fibrillation, especially with a QT-prolonging drug[13,14]
- Congestive heart failure[15]
- Digitalis therapy[16]
- High drug concentrations (with the exception of quinidine)
- Rapid rate of intravenous infusion with a QT-prolonging drug[17]
- Base-line QT prolongation[16]
- Subclinical long-QT syndrome[18,19]
- Ion-channel polymorphisms[20-22]
- Severe hypomagnesemia

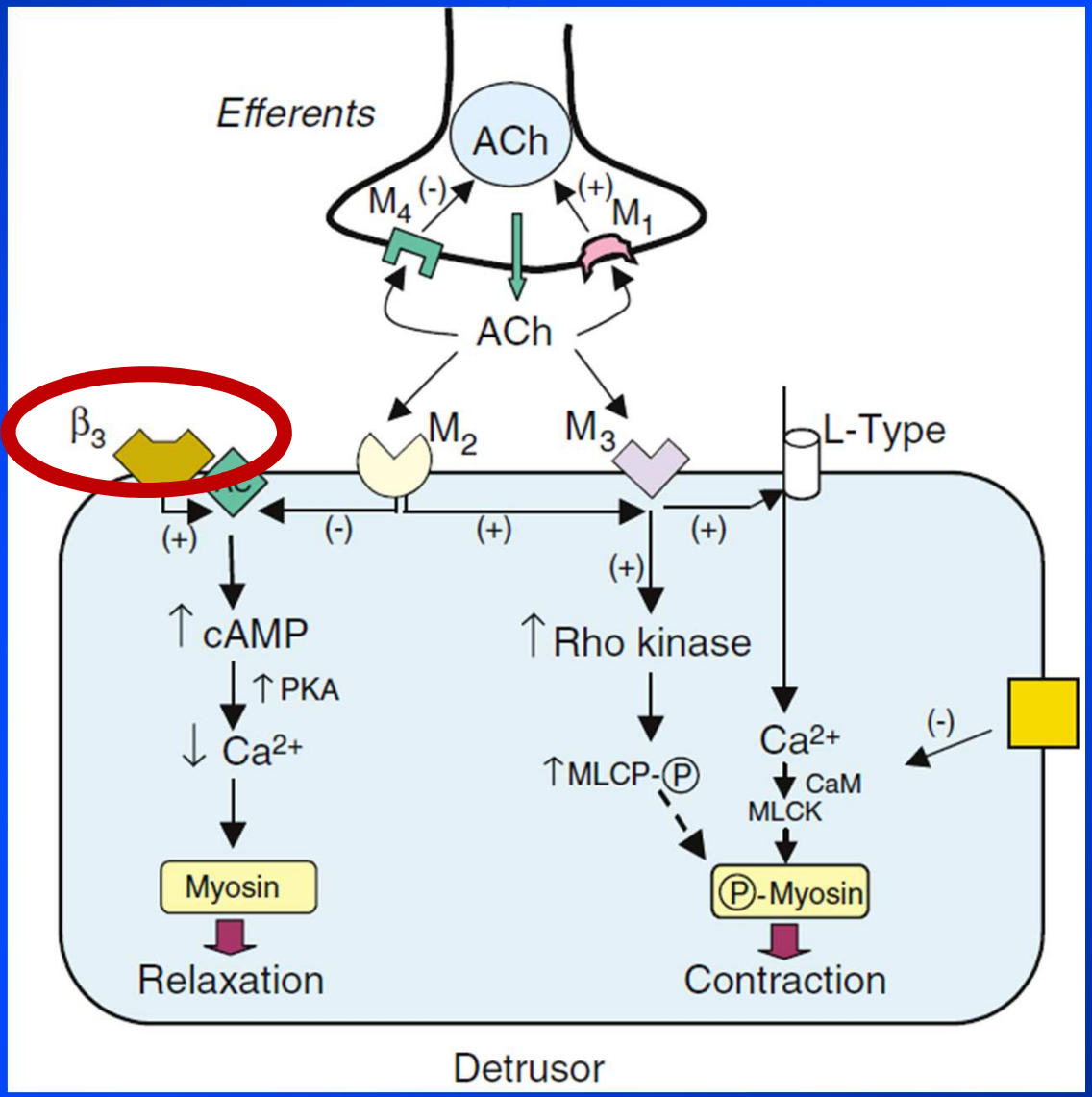
Roden, NEJM 2004

Τι να κάνουμε

- Προσοχή σε ασθενείς που έχουν καρδιολογικά προβλήματα – ταχυκαρδία
- Προσοχή σε ασθενείς που έχουν σύνδρομο μακρού QT ή λαμβάνουν φάρμακα που επιμηκύνουν το QT διάστημα
- Προσοχή στη συγχορήγηση με κινολόνες, μακρολίδες, διουρητικά, αντιαρρυθμικά

Μιραμπεγρόνη

Μηχανισμός δράσης



Prescribing information

Mirabegron can increase blood pressure.

Periodic blood pressure determinations are recommended, especially in hypertensive patients.

Mirabegron is not recommended for use in patients with severe uncontrolled hypertension (>180/110 mmHg)

Γιατί;;;

Αύξηση της ΑΠ κατά 3.5/1.5 mmHg στα 50mg στις μελέτες φάσης Ι.

Δοσο-εξαρτώμενη - 200mg: 9.7 mmHg.

'Αγνωστες δράσεις;

Απώλεια εκλεκτικότητας σε υψηλές δόσεις;

Safety – 12 weeks
Pooled analysis of 3 phase III trials

Number of patients (%)	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total (n = 2736)	Tolterodine ER 4 mg (n = 495)
Any TEAE	658 (47.7)	210 (48.6)	647 (47.1)	402 (43.3)	1259 (46.0)	231 (46.7)
Drug-related TEAE	232 (16.8)	87 (20.1)	256 (18.6)	172 (18.5)	515 (18.8)	131 (26.5)
TEAE leading to discontinuation	46 (3.3)	17 (3.9)	53 (3.9)	34 (3.7)	104 (3.8)	22 (4.4)
Drug-related TEAE leading to discontinuation	27 (2.0)	11 (2.5)	35 (2.5)	25 (2.7)	71 (2.6)	20 (4.0)
SAE	29 (2.1)	7 (1.6)	29 (2.1)	26 (2.8)	62 (2.3)	11 (2.2)
Drug-related SAE	6 (0.4)	3 (0.7)	7 (0.5)	3 (0.3)	13 (0.5)	6 (1.2)
Common TEAEs by preferred term (reported by ≥ 3% in total mirabegron group)						
Hypertension	105 (7.6)	49 (11.3)	103 (7.5)	48 (5.2)	200 (7.3)	40 (8.1)
Nasopharyngitis	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	14 (2.8)
Urinary tract infection	25 (1.8)	18 (4.2)	40 (2.9)	25 (2.7)	83 (3.0)	10 (2.0)
Antimuscarinic AEs of interest by preferred term (reported by ≥ 2% in any group)						
Headache	43 (3.1)	10 (2.3)	47 (3.4)	23 (2.5)	80 (2.9)	18 (3.6)
Dry mouth	29 (2.1)	8 (1.9)	23 (1.7)	23 (2.5)	54 (2.0)	50 (10.1)
Constipation	20 (1.4)	7 (1.6)	22 (1.6)	15 (1.6)	44 (1.6)	10 (2.0)
Drug-related* TEAEs by preferred term (reported by ≥ 2% in any group)						
Hypertension	63 (4.6)	30 (6.9)	65 (4.7)	32 (3.4)	127 (4.6)	30 (6.1)
Headache	18 (1.3)	4 (0.9)	28 (2.0)	12 (1.3)	44 (1.6)	11 (2.2)
Dry mouth	22 (1.6)	7 (1.6)	13 (0.9)	20 (2.2)	40 (1.5)	47 (9.5)

Nitti, Int J Clin Practice 2013

Safety
Pooled analysis of 3 phase III trials

	Placebo (n = 1380)		Mirabegron 25 mg (n = 432)		Mirabegron 50 mg (n = 1375)		Mirabegron 100 mg (n = 929)	
	AM	PM	AM	PM	AM	PM	AM	PM
Blood pressure (mmHg)								
SBP								
N	1329	1326	410	410	1327	1327	891	890
Baseline, mean (SE)	125.9 (0.47)	125.0 (0.41)	129.2 (0.81)	129.0 (0.71)	126.4 (0.47)	125.6 (0.43)	125.0 (0.55)	123.7 (0.49)
Final Visit, mean (SE)	126.2 (0.45)	125.7 (0.41)	128.8 (0.75)	128.3 (0.67)	127.2 (0.46)	126.6 (0.41)	125.6 (0.51)	125.2 (0.46)
Adjusted change from baseline, mean (SE), (95% CI)†	0.2 (0.25), (−0.3, 0.7)	0.6 (0.25), (0.1, 1.1)	−0.3 (0.52),	−0.5 (0.53),	0.8 (0.25), (0.3, 1.3)	1.1 (0.25), (0.6, 1.6)	0.6 (0.32),	1.4 (0.33),
Difference vs. placebo, mean (SE), (95% CI)‡	–	–	−0.5 (0.57),	−1.0 (0.58), (−2.2, 0.1)	0.6 (0.35), (−0.1, 1.3)	0.5 (0.36), (−0.2, 1.2)	0.4 (0.41),	0.9 (0.42),
DBP								
N	1329	1326	410	410	1327	1327	890	890
Baseline, mean (SE)	77.1 (0.26)	75.3 (0.23)	78.2 (0.48)	76.1 (0.46)	77.2 (0.25)	75.4 (0.24)	77.4 (0.30)	75.3 (0.28)
Final Visit, mean (SE)	77.2 (0.25)	75.7 (0.24)	77.6 (0.43)	75.7 (0.42)	77.6 (0.24)	76.2 (0.24)	77.7 (0.28)	76.3 (0.28)
Adjusted change from baseline, mean (SE), (95% CI)†	0.0 (0.16), (−0.3, 0.3)	0.4 (0.16), (0.1, 0.7)	−0.1 (0.33), (−0.8, 0.5)	0.1 (0.34), (−0.6, 0.7)	0.4 (0.16), (0.1, 0.7)	0.7 (0.16), (0.4, 1.1)	0.2 (0.21), (−0.2, 0.6)	0.9 (0.21), (0.5, 1.3)
Difference vs. placebo, mean (SE), (95% CI)‡	–	–	−0.1 (0.37), (−0.9, 0.6)	−0.3 (0.37), (−1.0, 0.4)	0.4 (0.22), (−0.1, 0.8)	0.4 (0.23), (−0.1, 0.8)	0.2 (0.26), (−0.3, 0.7)	0.5 (0.27), (−0.0, 1.0)

Nitti, Int J Clin Practice 2013

Safety – Heart rate

Αύξηση του καρδιακού ρυθμού στις μελέτες φάσης Ι, δοσο-εξαρτώμενη 6.7-17 b/min

Σε μία μελέτη φάσης ΙΙ (Dragon)
100mg: 2.15 – 200mg: 4.66 b/min

Chapple, Int Urogynecol J 2013

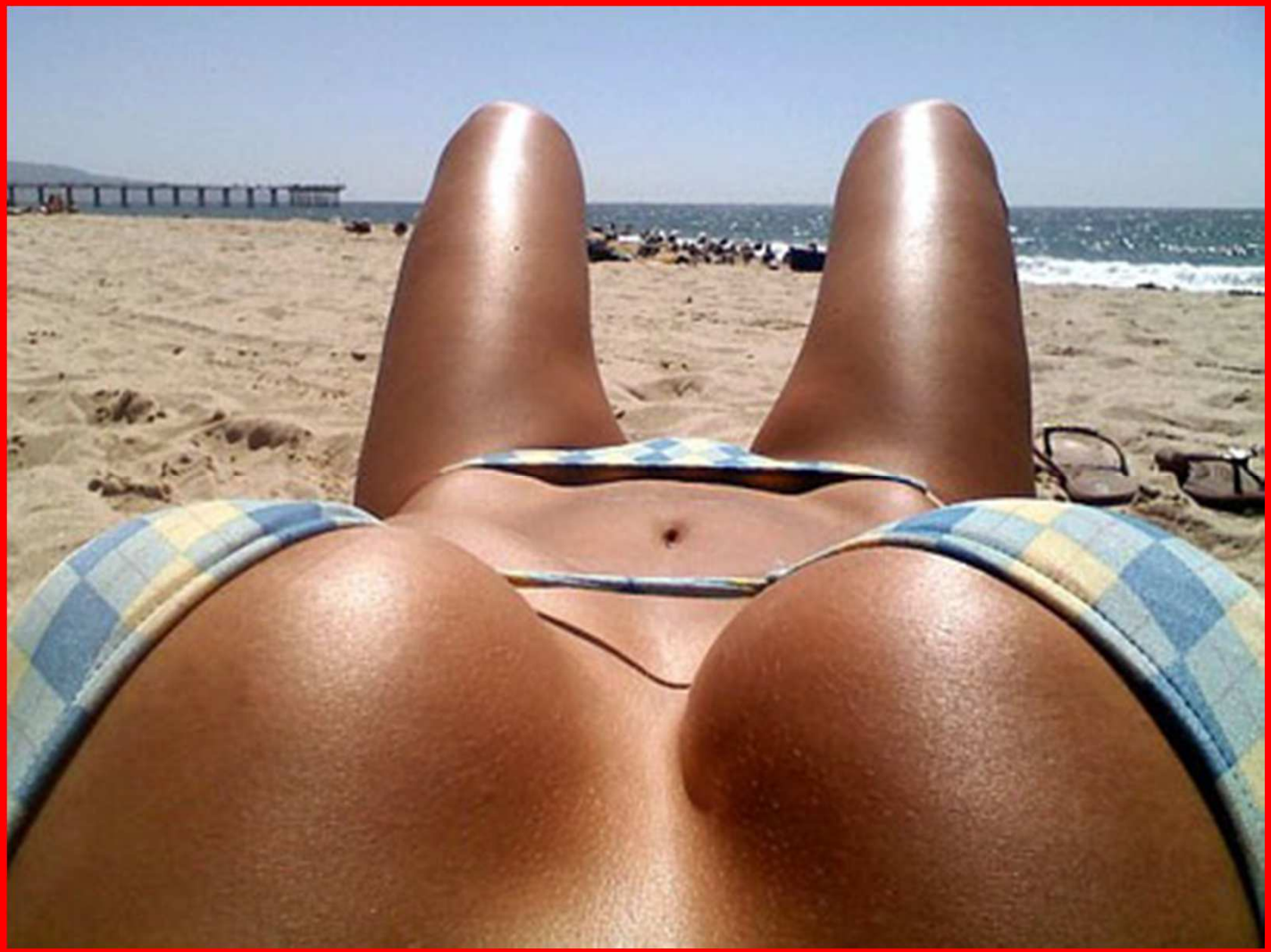
Pulse rate (bpm)								
N	1329	1326	410	410	1327	1327	891	890
Baseline, mean (SE)	70.5 (0.28)	75.3 (0.29)	71.0 (0.50)	75.5 (0.51)	70.4 (0.28)	74.9 (0.28)	70.4 (0.34)	74.4 (0.34)
Final Visit, mean (SE)	70.9 (0.29)	74.7 (0.29)	71.7 (0.52)	75.3 (0.53)	71.8 (0.29)	75.5 (0.28)	72.9 (0.34)	76.5 (0.34)
Adjusted change from baseline, mean (SE), (95% CI)†	0.4 (0.17), (0.1, 0.8)	−0.4 (0.18), (−0.8, −0.1)	1.3 (0.36), (0.6, 2.0)	0.2 (0.37),	1.4 (0.17),	0.6 (0.18),	2.3 (0.22),	1.9 (0.23), (1.4, 2.3)
Difference vs. placebo, mean (SE), (95% CI)‡	–	–	0.9 (0.40),	0.6 (0.41), (−0.2, 1.4)	1.0 (0.24), (0.5, 1.5)	1.0 (0.25), (0.5, 1.5)	1.9 (0.28), (1.3, 2.5)	2.3 (0.29),
Incidence of tachycardia (%)*								
Tachycardia events, N (%)	43 (3.1)		21 (4.9)		52 (3.8)		43 (4.6)	

Nitti, Int J Clin Practice 2013

Safety – 1 year

Preferred term	Mirabegron		Tolterodine SR 4 mg
Adverse event, *n* (%)	50 mg (*n* = 812)	100 mg (*n* = 820)	(*n* = 820)
Any AE	485 (59.7)	505 (61.5)	508 (62.6)
Hypertension	75 (9.2)	80 (9.8)	78 (9.6)
Urinary tract infection	46 (5.7)	45 (5.5)	52 (6.4)
Nasopharyngitis	32 (3.9)	35 (4.3)	25 (3.1)
Headache	33 (4.1)	26 (3.2)	20 (2.5)
Back pain	23 (2.8)	29 (3.5)	13 (1.6)
Constipation	23 (2.8)	25 (3.0)	22 (2.7)
Influenza	21 (2.6)	25 (3.0)	28 (3.4)
Dry mouth	23 (2.8)	19 (2.3)	70 (8.6)
Sinusitis	22 (2.7)	18 (2.2)	12 (1.5)
Diarrhoea	15 (1.8)	24 (2.9)	16 (2.0)
Arthralgia	17 (2.1)	19 (2.3)	16 (2.0)
Dizziness	22 (2.7)	13 (1.6)	21 (2.6)
Cystitis	17 (2.1)	11 (1.3)	19 (2.3)
Tachycardia	8 (1.0)	19 (2.3)	25 (3.1)

Sacco, Ther Adv Urol 2012



Σχόλιο

- Δεν υπάρχουν αξιόπιστα στοιχεία
- Placebo effect δεν παρατηρείται - Symplicity III
- Στοιχεία σε υπερτασικούς – νορμοτασικούς
- Σε σοβαρή υπέρταση; - Μηχανισμός;
- Σε συνυπάρχοντα καρδιακά νοσήματα

- 24ωρη μέτρηση της ΑΠ ή ΗΒΡ

Drug – induced hypertension

Table 2: Drugs inducing or exacerbating hypertension.

(i) Nonsteroidal anti-inflammatory drugs
(ii) Oral contraceptives
(iii) Sympathomimetics
(iv) Illicit drugs
(v) Glucocorticoids
(vi) Mineralocorticoids
(vii) Cyclosporine, tacrolimus
(iix) Erythropoietin
(ix) Herbal supplements
(x) VEGF inhibitors

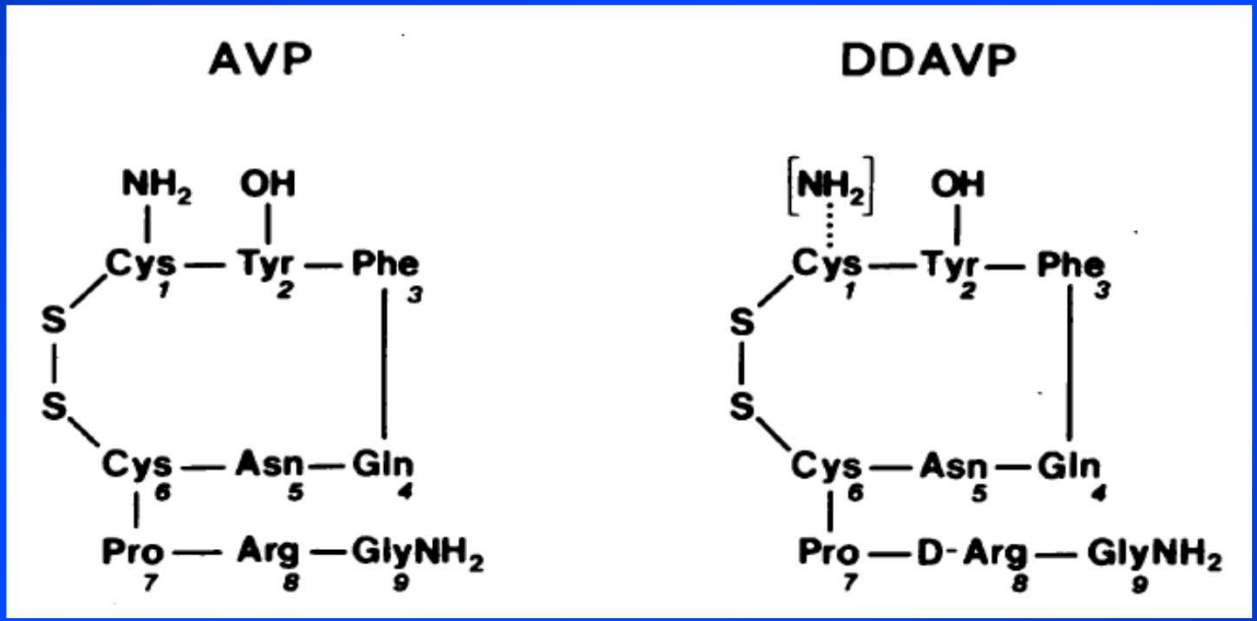
Doumas, Int J Hypertens 2011

Τι να κάνουμε

- Αποφυγή σε ασθενείς με σοβαρή υπέρταση
- Προσοχή σε ασθενείς που έχουν υπέρταση
- Περιορισμός του νατρίου
- Προσοχή στη συγχορήγηση άλλων φαρμάκων που αυξάνουν την αρτηριακή πίεση και ιδιαίτερα ΜΣΑΦ

Δεσμοπρεσσίνη

Δεσμοπρεσσίνη



Hyponatremia Induced by Vasopressin or Desmopressin in Female and Male Rats[1,2]

Joseph G. Verbalis[3]

Hyponatraemia following desmopressin

EDITOR,—M Hamed and colleagues report on a case of hyponatraemic convulsion associated with desmopressin and imipramine treatment.[1] We are aware of six previous reports of hyponatraemic convulsion associated with the use of desmopressin.[2-7] Five of the six patients had ingested an excessive amount of fluid in the evening or days preceding the seizure. Four of the patients complained of vomiting before the seizure, three of headache, and one of nausea. All six patients recovered completely. One of the patients reported

BMJ VOLUME 307 3 JULY 1993

Dangers of intranasal desmopressin for nocturnal enuresis

Sir,

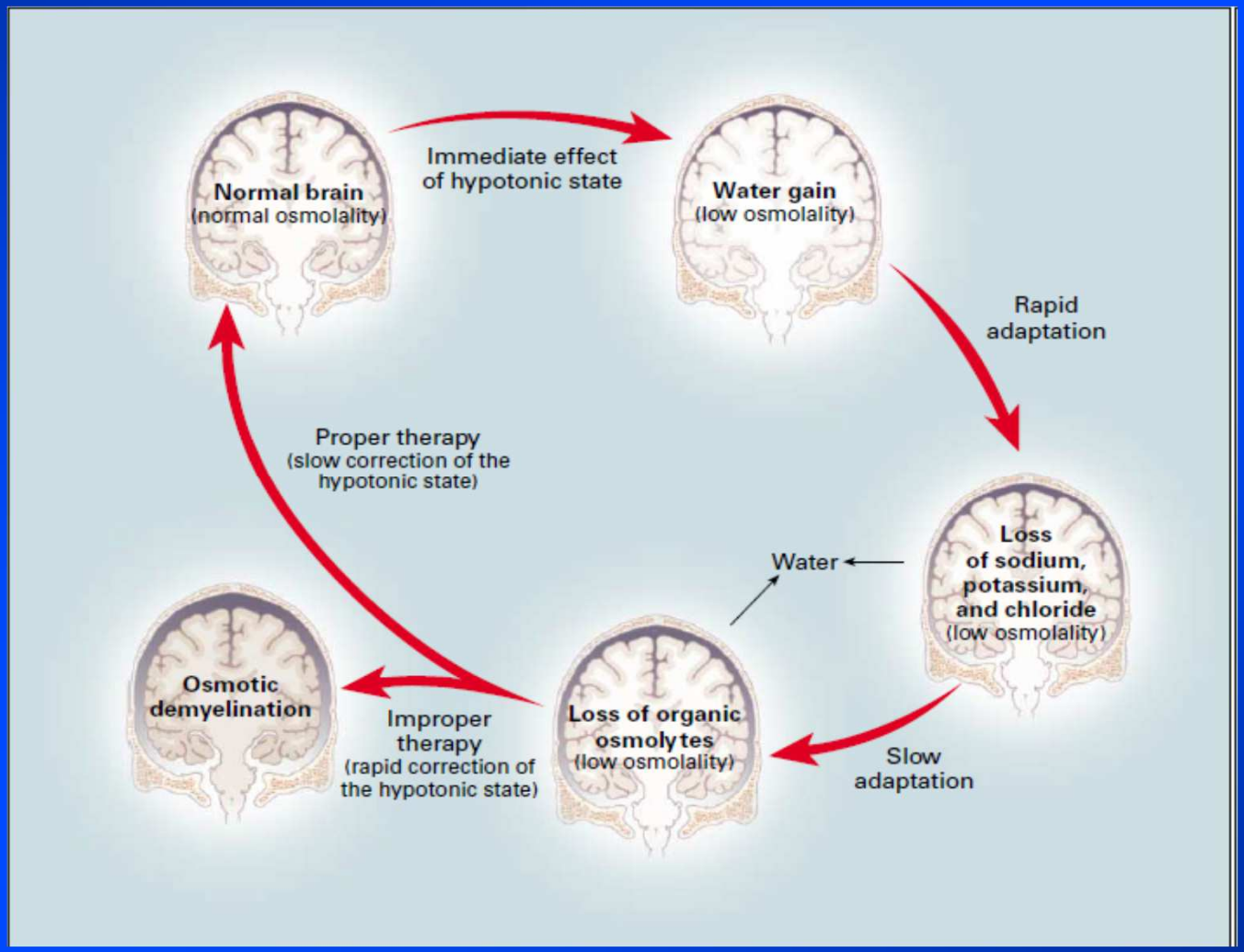
The recent advocacy of desmopressin as an apparently successful treatment for nocturnal enuresis[1] should be noted with caution because of the potential side effects. A recent case has been noted in which a child with cystic fibrosis had a severe adverse response to desmopressin.[2]

Hyponatraemic seizures resulting from inadequate post-operative fluid intake following a single dose of desmopressin

Zoltán Molnár[1], Viktor Farkas[1], László Nemes[2], György S. Reusz[1] and Attila J. Szabó[1]

[1]First Department of Pediatrics, Semmelweis University, Budapest and [2]National Haemophilia Center, National Medical Center, Budapest, Hungary

Κίνδυνοι υπονατριαιμίας, ταχείας διόρθωσης



Madias, NEJM 2000

Αίτια υπονατριαιμίας

IMPAIRED CAPACITY OF RENAL WATER EXCRETION

Decreased volume of extracellular fluid

- Renal sodium loss
  - Diuretic agents
  - Osmotic diuresis (glucose, urea, mannitol)
  - Adrenal insufficiency
  - Salt-wasting nephropathy
  - Bicarbonaturia (renal tubular acidosis, disequilibrium stage of vomiting)
  - Ketonuria
- Extrarenal sodium loss
  - Diarrhea
  - Vomiting
  - Blood loss
  - Excessive sweating (e.g., in marathon runners)
  - Fluid sequestration in "third space"
    - Bowel obstruction
    - Peritonitis
    - Pancreatitis
    - Muscle trauma
    - Burns

Increased volume of extracellular fluid

- Congestive heart failure
- Cirrhosis
- Nephrotic syndrome
- Renal failure (acute or chronic)
- Pregnancy

Essentially normal volume of extracellular fluid

- Thiazide diuretics*
- Hypothyroidism
- Adrenal insufficiency
- Syndrome of inappropriate secretion of antidiuretic hormone
  - Cancer
    - Pulmonary tumors
    - Mediastinal tumors
    - Extrathoracic tumors
  - Central nervous system disorders
    - Acute psychosis
    - Mass lesions
    - Inflammatory and demyelinating diseases
    - Stroke
    - Hemorrhage
    - Trauma
  - Drugs
    - Desmopressin
    - Oxytocin
    - Prostaglandin-synthesis inhibitors
    - Nicotine
    - Phenothiazines
    - Tricyclics
    - Serotonin-reuptake inhibitors
    - Opiate derivatives
    - Chlorpropamide
    - Clofibrate
    - Carbamazepine
    - Cyclophosphamide
    - Vincristine
  - Pulmonary conditions
    - Infections
    - Acute respiratory failure
    - Positive-pressure ventilation
  - Miscellaneous
    - Postoperative state
    - Pain
    - Severe nausea
    - Infection with the human immunodeficiency virus
- Decreased intake of solutes
  - Beer potomania
  - Tea-and-toast diet

EXCESSIVE WATER INTAKE

- Primary polydipsia†
- Dilute infant formula
- Sodium-free irrigant solutions (used in hysteroscopy, laparoscopy, or transurethral resection of the prostate)‡
- Accidental intake of large amounts of water (e.g., during swimming lessons)
- Multiple tap-water enemas

Drugs
- Desmopressin
- Oxytocin
- Prostaglandin-synthesis inhibitors
- Nicotine
- Phenothiazines
- Tricyclics
- Serotonin-reuptake inhibitors
- Opiate derivatives
- Chlorpropamide
- Clofibrate
- Carbamazepine
- Cyclophosphamide
- Vincristine

Madias, NEJM 2000

Συχνότητα

	Dose titration	
	Desmopressin	
	No. (%)	*E*
Patients exposed	224 (100)	
Total adverse events	158 (71)	398
Serious adverse events	5 (2)	10
Deaths*	2 (1)	3
Adverse events related to study medication	109 (49)	231
Most frequently reported (>3%) adverse events related to study medication		
Headache	50 (22)	63
Nausea	17 (8)	18
Hyponatremia	14 (6)	15
Abdominal pain	9 (4)	10
Dry mouth	9 (4)	9
Micturition frequency	8 (4)	9
Dizziness	7 (3)	7
Fatigue	7 (3)	8
Peripheral edema	7 (3)	9

Lose, Am J Obstet Gynecol 2003

Συχνότητα

Study	Study population	Length of follow up	Desmopressin formulation	Incidence of hyponatremia (%)
Asplund et al. [1998]	Men and women aged over 60	3 weeks	Oral	2/23 (8.7)
Asplund et al. [1999]	Men and women aged over 60	2 weeks	Oral	1/17 (5.9)
Cannon et al. [1999]	Men aged over 50	2–4 weeks	Nasal	1/20 (5.0)
Chancellor et al. [1999]	Men with benign prostatic hyperplasia	3 months	Nasal	0/12 (0.0)
Mattiasson et al. [2002]	Men aged over 18 (mean in treatment group 64.5)	3 weeks	Oral	49/224 (21.9)
Kuo [2002]	Men and women aged over 65	2 weeks	Oral	1/30 (3.3)
Rembratt et al. [2003]	Men and women aged over 65	3 days	Oral	4/72 (5.6)

7,6%

Weatherall, Neurourol Urod 2004

Βαρύτητα, παράγοντες κινδύνου
Ενδορινικά, <14d

Table 1 Clinical and laboratory data in subjects with severe signs of hyponatremia secondary to desmopressin treatment for enuresis.

	All cases	Severely altered mental status	Convulsions	Significance
N	54	8	46	
Desmopressin, nasal/oral	47/7	5/3	42/4	Not significant
Gender, male/female	34/20	2/6	32/14	$P < 0.05$
Age, years	9.0 [6.5–11]	9.0 [7.8–19]	9.0 [6.0–11]	Not significant
Age ≤6.0 years, *N*	11	1	10	Not significant
Blood sodium level, mmol/L	119 [116–122]	124 [120–125]	118 [115–121]	$P < 0.01$
Contributing factors:				
Excess fluid intake, *N*	25	4	21	
Intercurrent illness, *N*	6	1	5	
Total, *N*	31	5	26	Not significant

Lucchini, J Paediatr Urol 2013

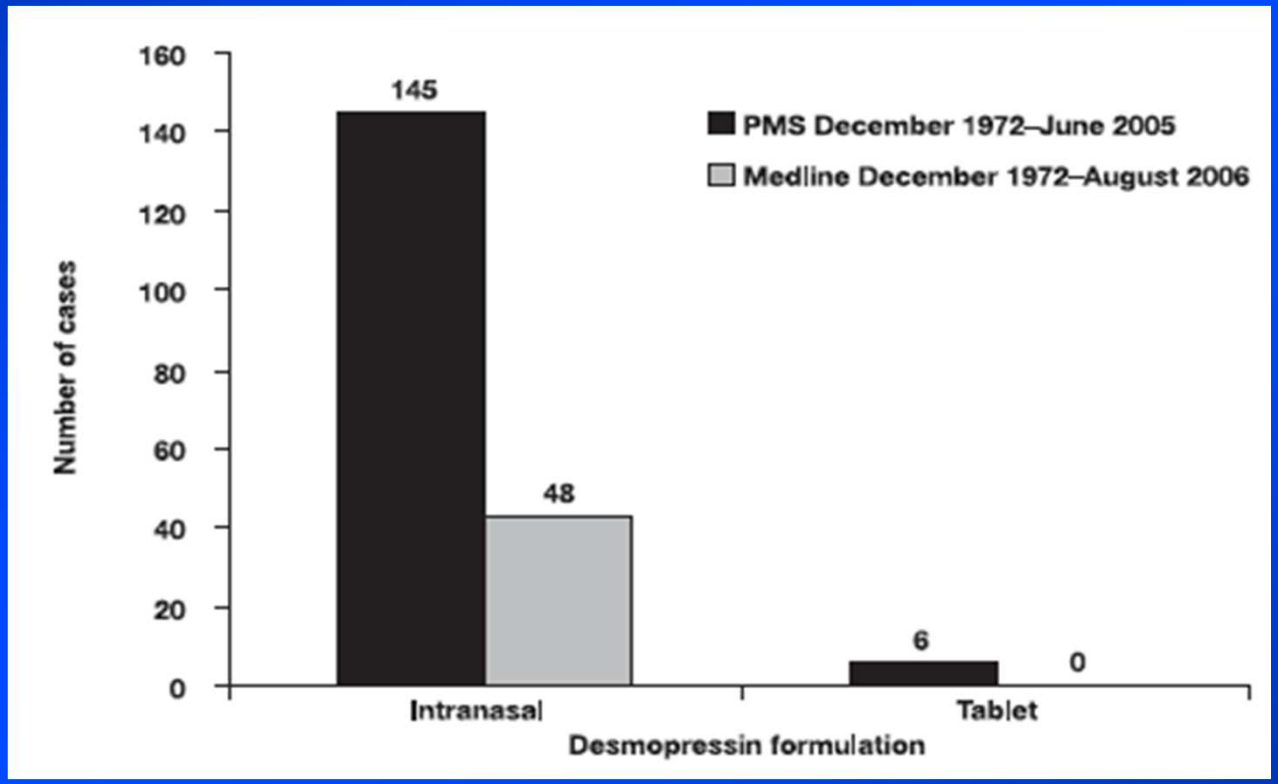
Συχνότητα, βαρύτητα, παράγοντες κινδύνου

	All		Male study		Female study		Mixed study	
	n	%	n	%	n	%	n	%
Exposed patients	632	100	224	100	224	100	184	100
Non-hyponatremic	537	85	181	81	198	88	158	86
Hyponatremic	95	15	43	19	26	12	26	14
Borderline (134–130 mmol/L)	64	10	34	15	13	6	17	9
Significant (<130 mmol/L)	31	3	8	4	5	2	5	3
(<125 mmol/L)	*13*	*2*	*1*	*<1*	*8*	*4*	*4*	*2*
Symptomatic hyponatremia	27	4	11	5	13	6	3	2
Adverse event	29	5	9	4	14	6	6	3
Serious adverse event	*2*	*<1*	*0*	*0*	*2*	*<1*	*0*	*0*

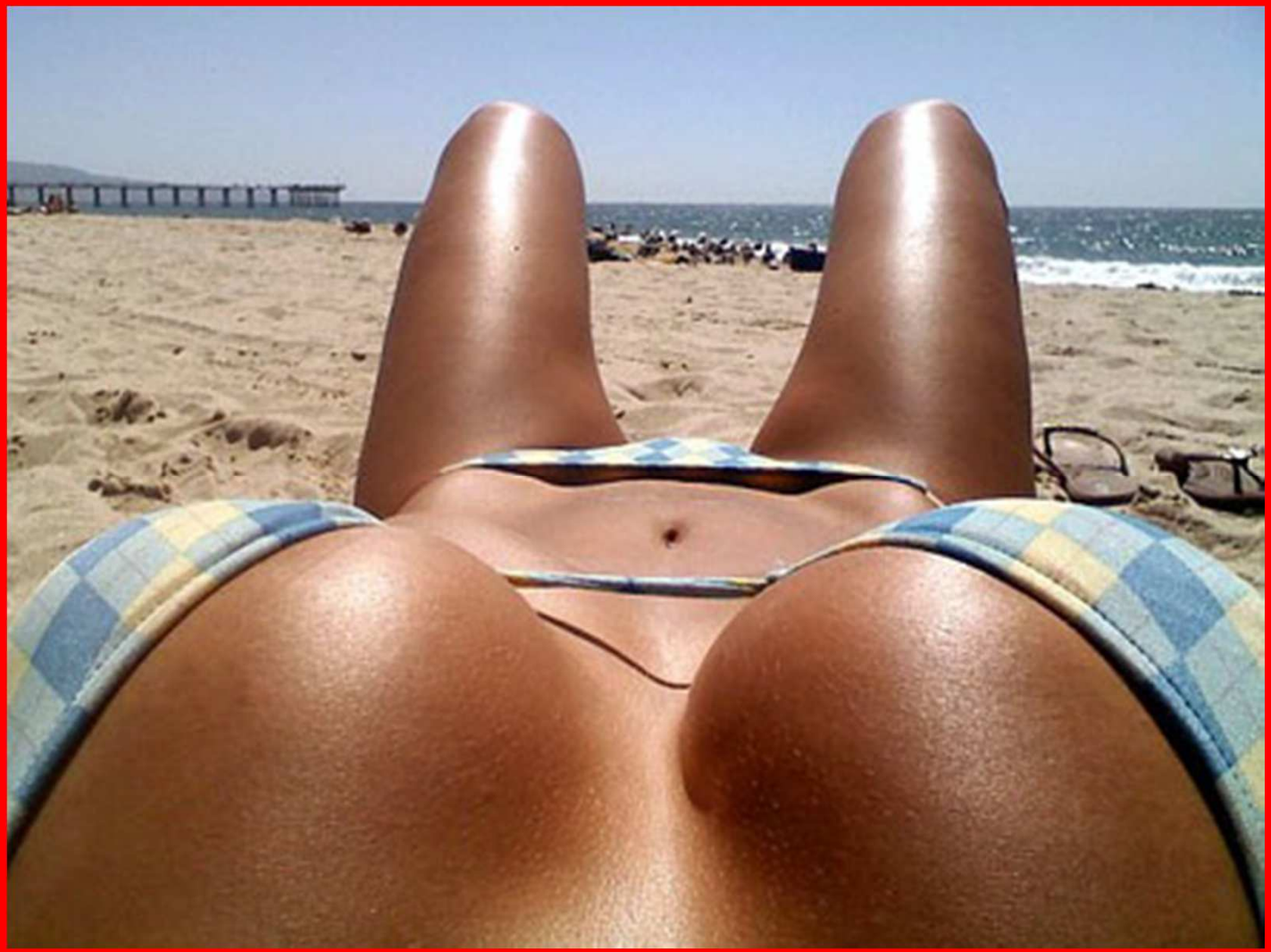
	Odds ratio	95% Wald confidence limits		*P*-value
Age (years)	1.16	1.09	1.25	<0.0001
Baseline (24 h) urine volume/bodyweight (ml/kg)	1.09	1.04	1.16	0.0016
Baseline serum sodium (mmol/L)	0.76	0.64	0.91	0.0025
Weight gain at time of minimum s-sodium (%)	1.31	1.07	1.61	0.0106

Rembratt, Neurourol Urod 2006

Oral vs intranasal



Robson, J Urol 2007



Τι να κάνουμε

- Αποφυγή λήψης υγρών
- Προσοχή στην υπερδοσολογία
- Επαγρύπνηση για συμπτωματολογία
  - Κεφαλαλγία, ναυτία, έμετος
- Έλεγχος νατρίου
- Διακοπή φαρμάκου
- Προσοχή στη συγχορήγηση με διουρητικά

BPH – sexual dysfunction

a-blockers

PDE-5 inhibitors

PDE-5 inhibitors

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

Efficacy and safety in hypertensives

- **Efficacy: 70% compared to 20% with placebo**
  - **Irrespective of the number of antihypertensive agents**
- **Discontinuation due to AE: 2% with both sildenafil and placebo**

Pickering…Mancia, Am J Hypertens 2004

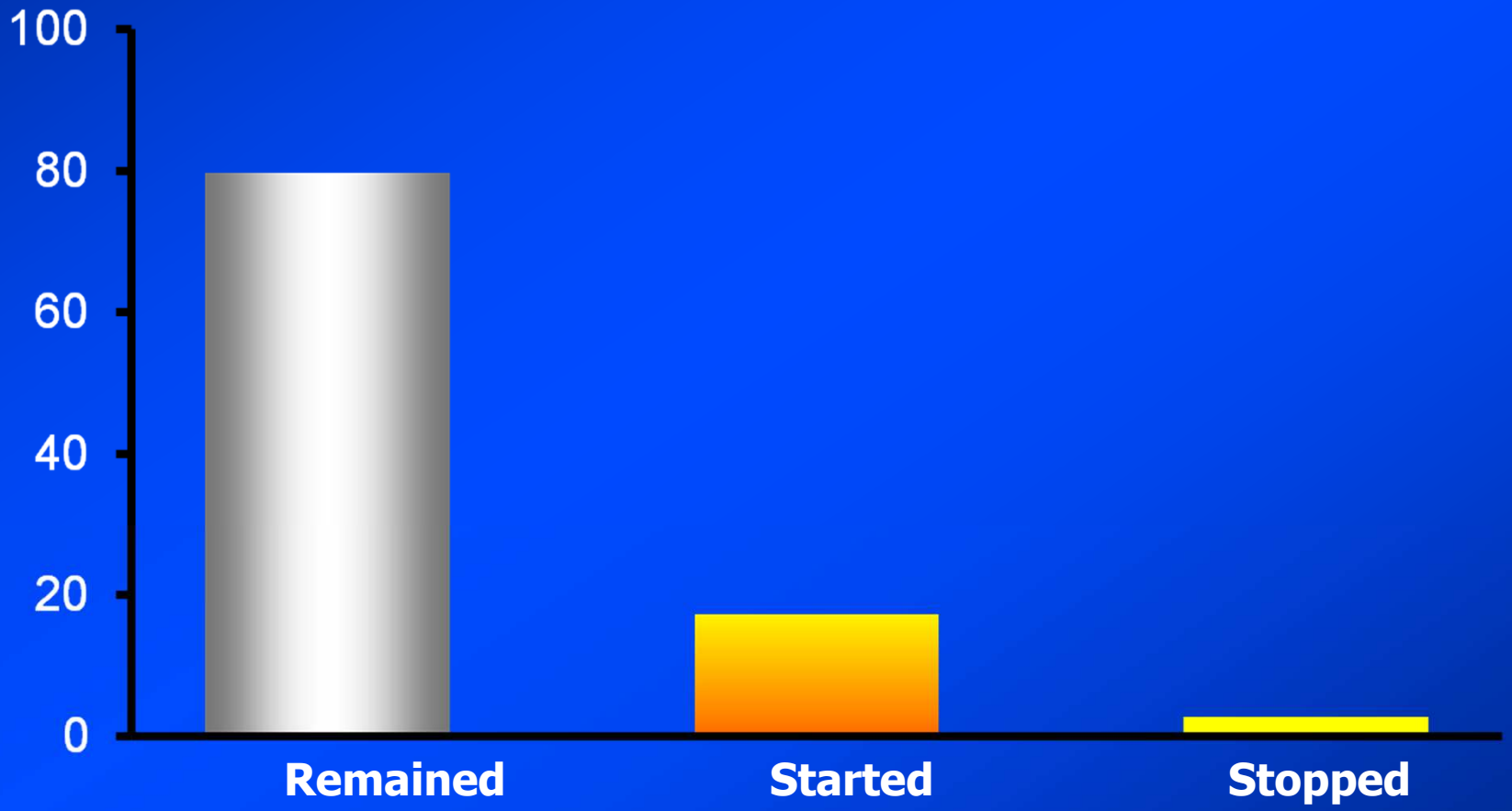
Safety in hypertension

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

Doumas, Hypertens Rev 2008

Efficacy in hypertension

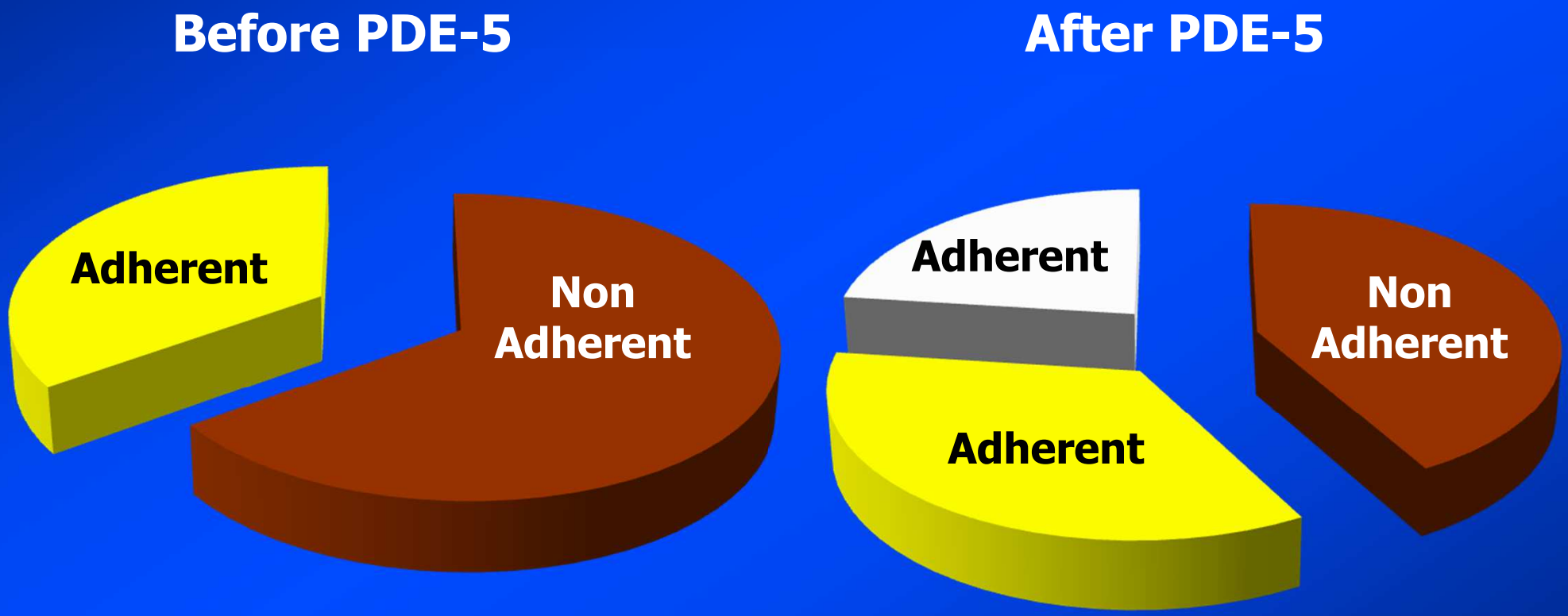
Increased compliance



Scranton, Am J Cardiol 2007

Efficacy in hypertension

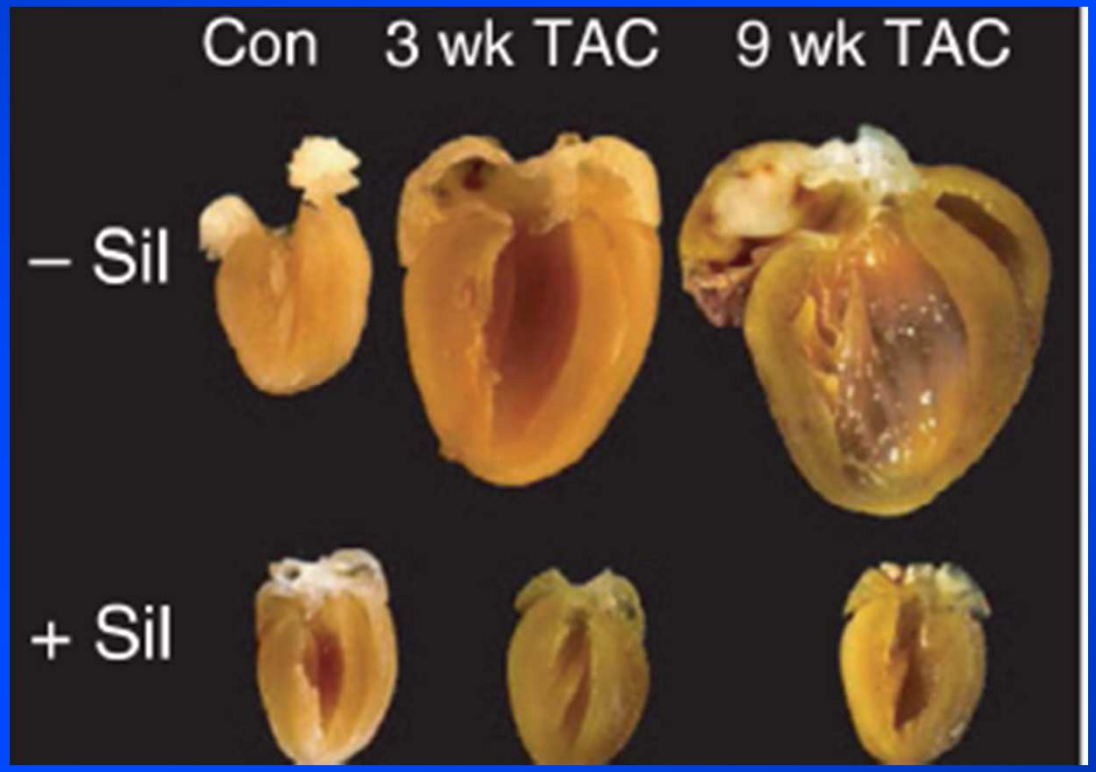
Increased compliance



McLauglin, Am J Ther 2005

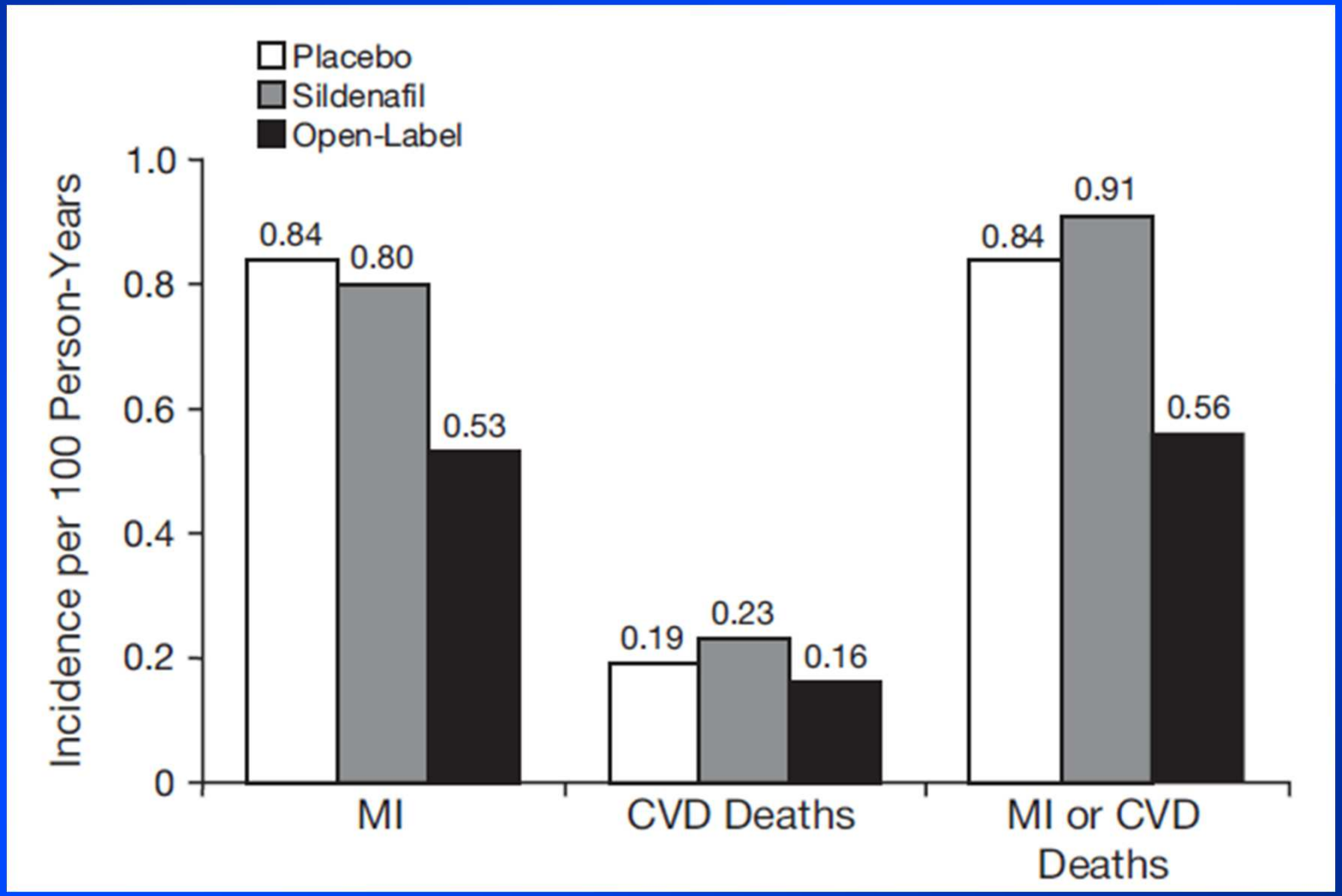
Efficacy in hypertension

LV hypertrophy



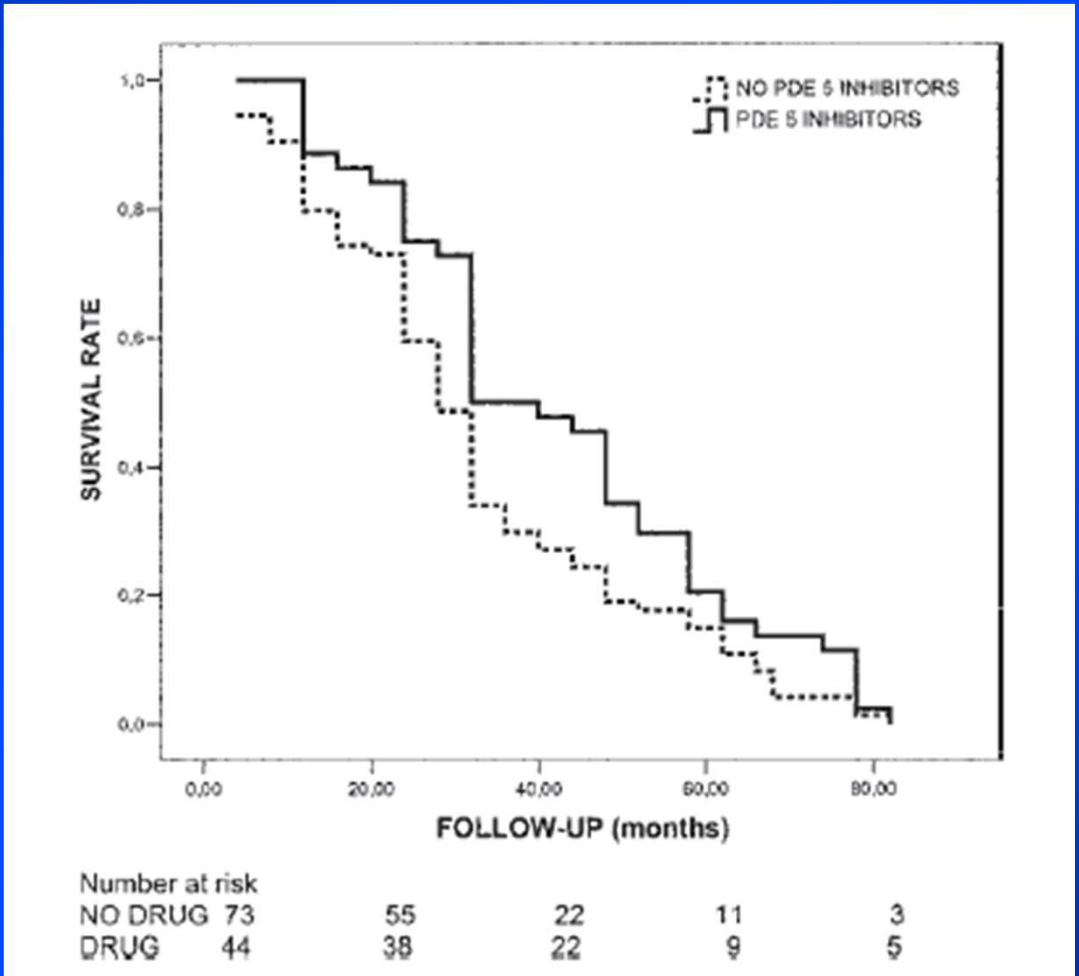
Takimoto, Nature Medicine

PDE-5 inh και καρδιαγγειακά συμβάματα



Mittleman, Int J Clin Pract 2003

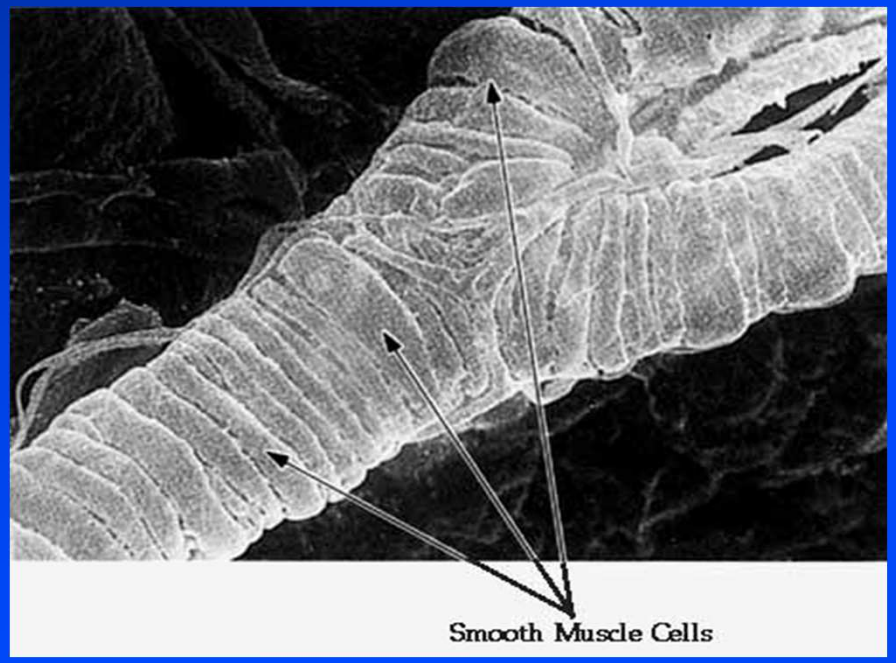
ED and death – Protection with PDE-5 inh type 2 diabetes mellitus

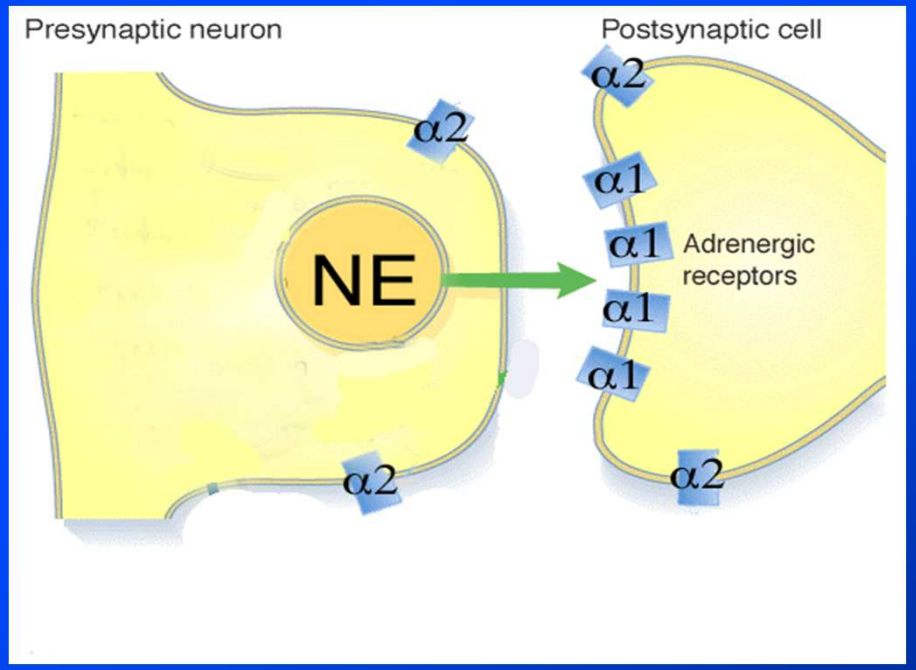


Gazzarusso et al. JACC 2008

α-αποκλειστές

Alpha blockers





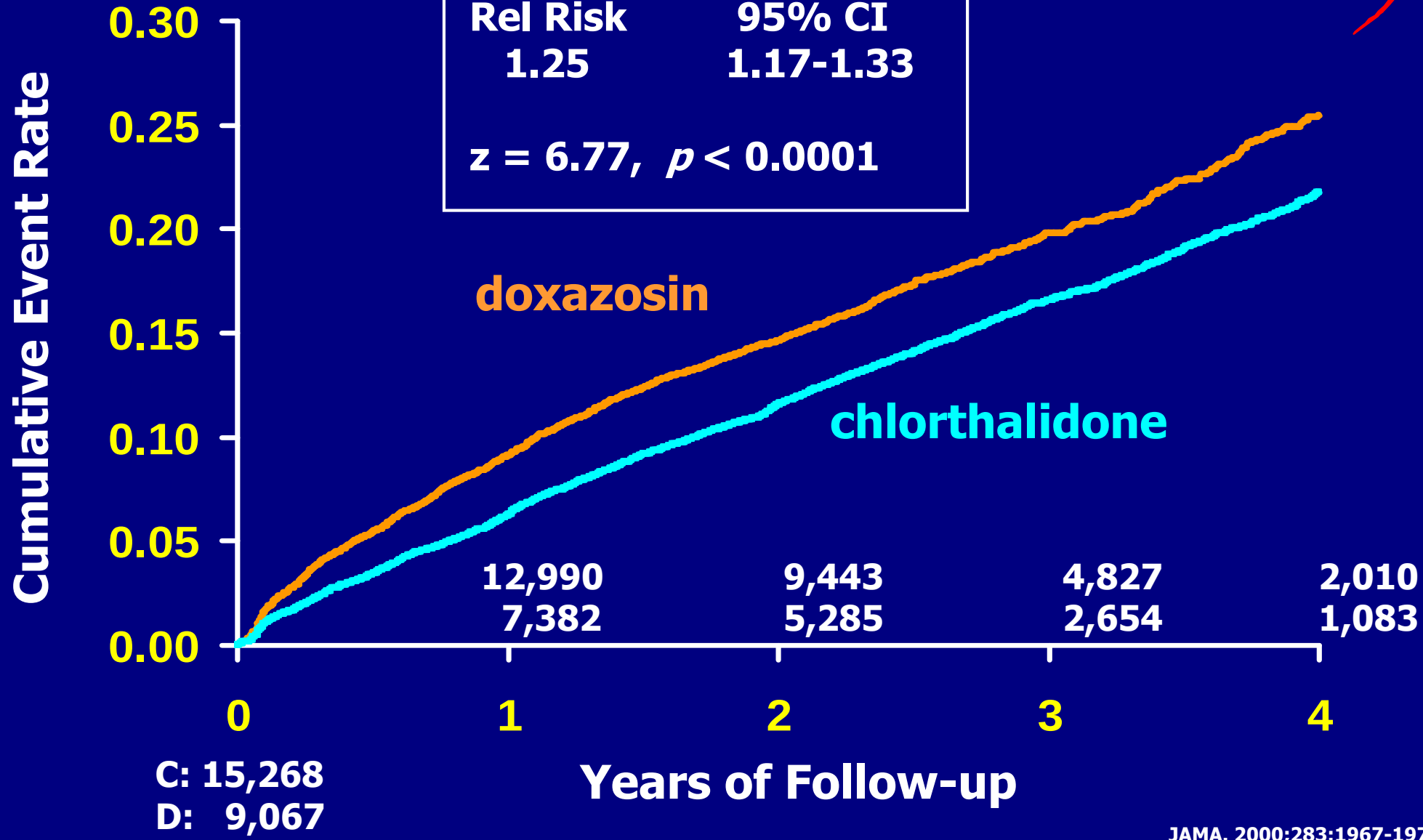
Doumas, Loutraki 2011

Cardiovascular Disease

ALLHAT

Rel Risk	95% CI
1.25	1.17-1.33

$z = 6.77$, $p < 0.0001$



C: 15,268
D: 9,067

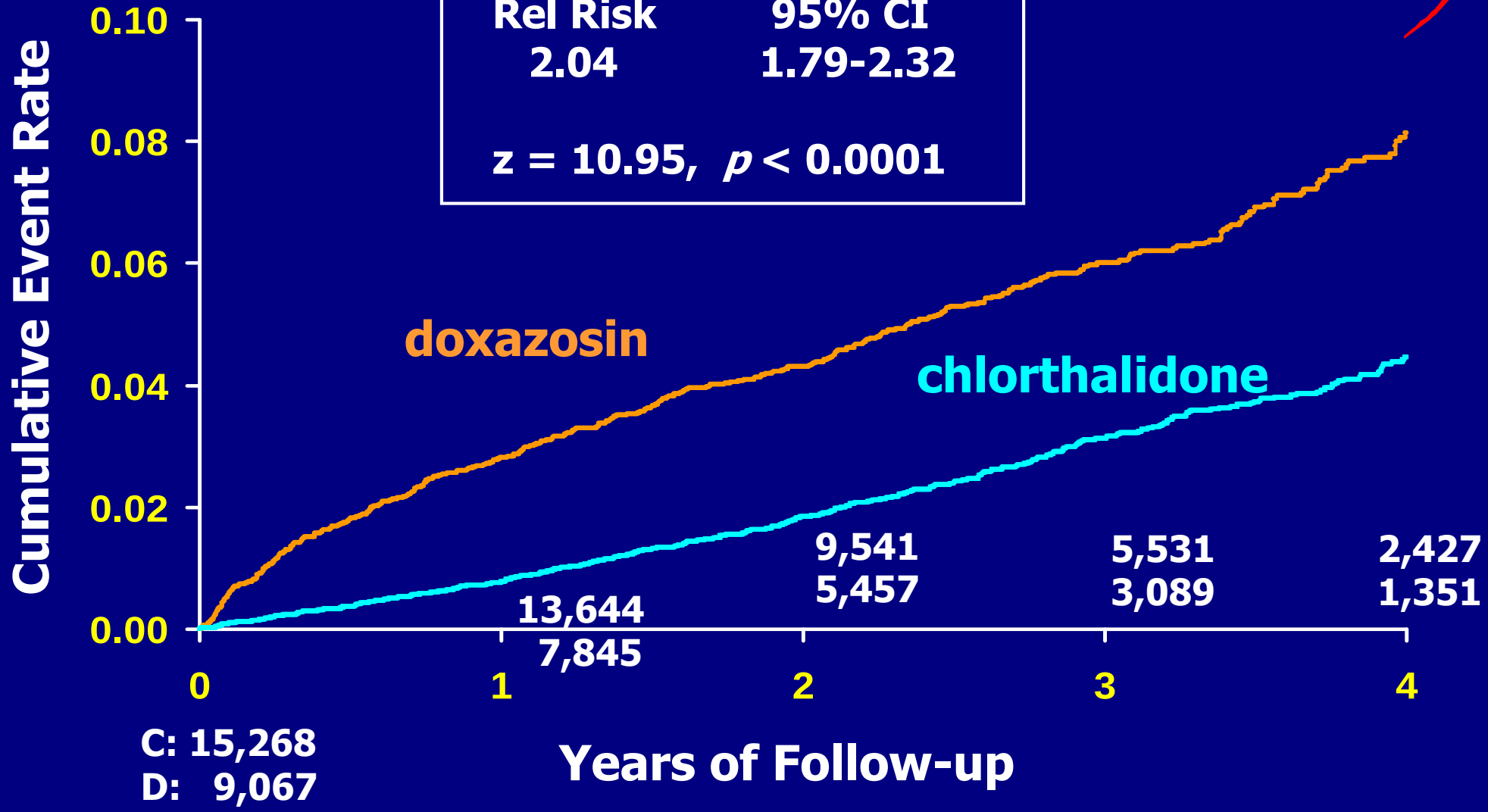
JAMA. 2000;283:1967-1975

Heart Failure

ALLHAT

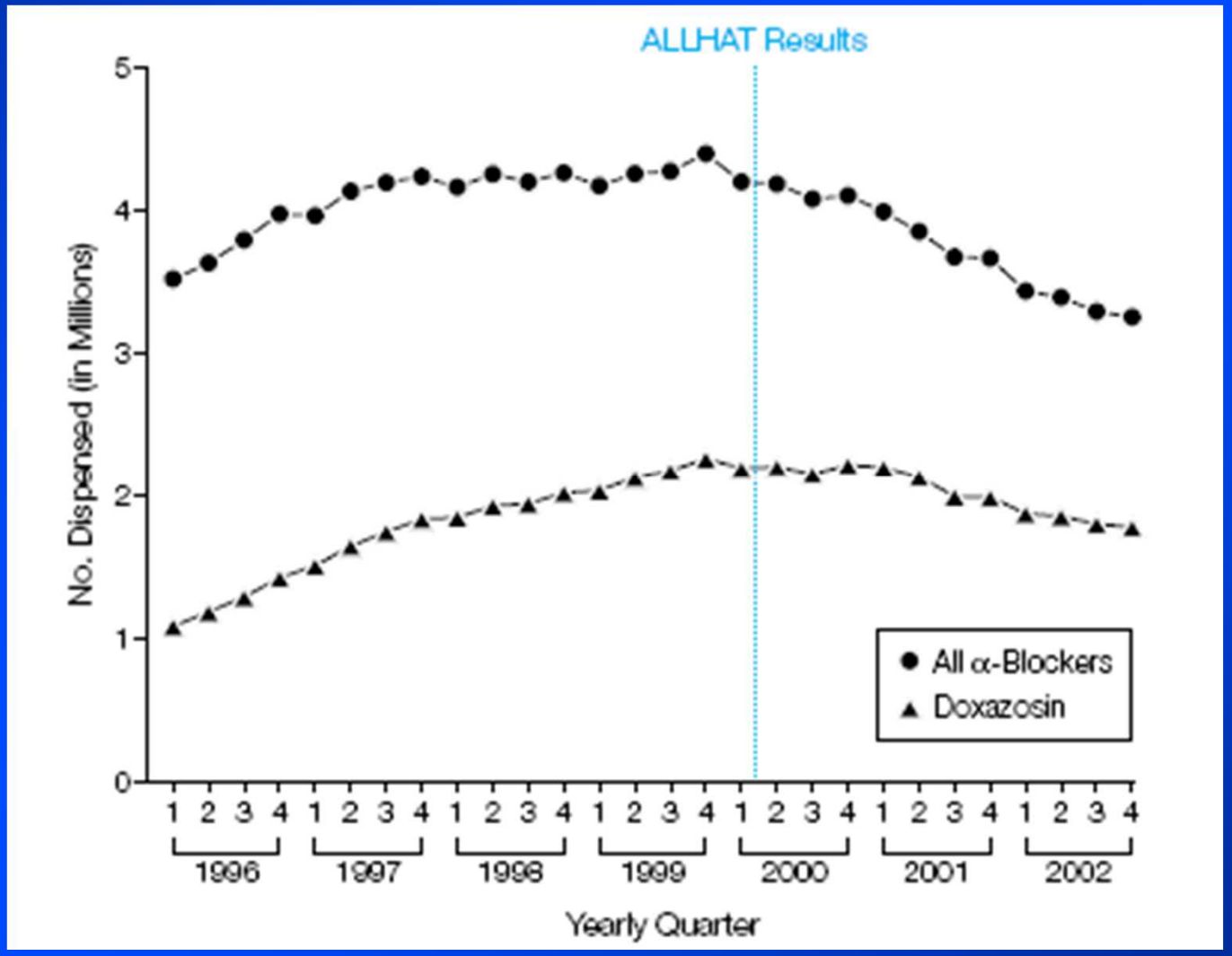
Rel Risk	95% CI
2.04	1.79-2.32

$z = 10.95,\ p < 0.0001$



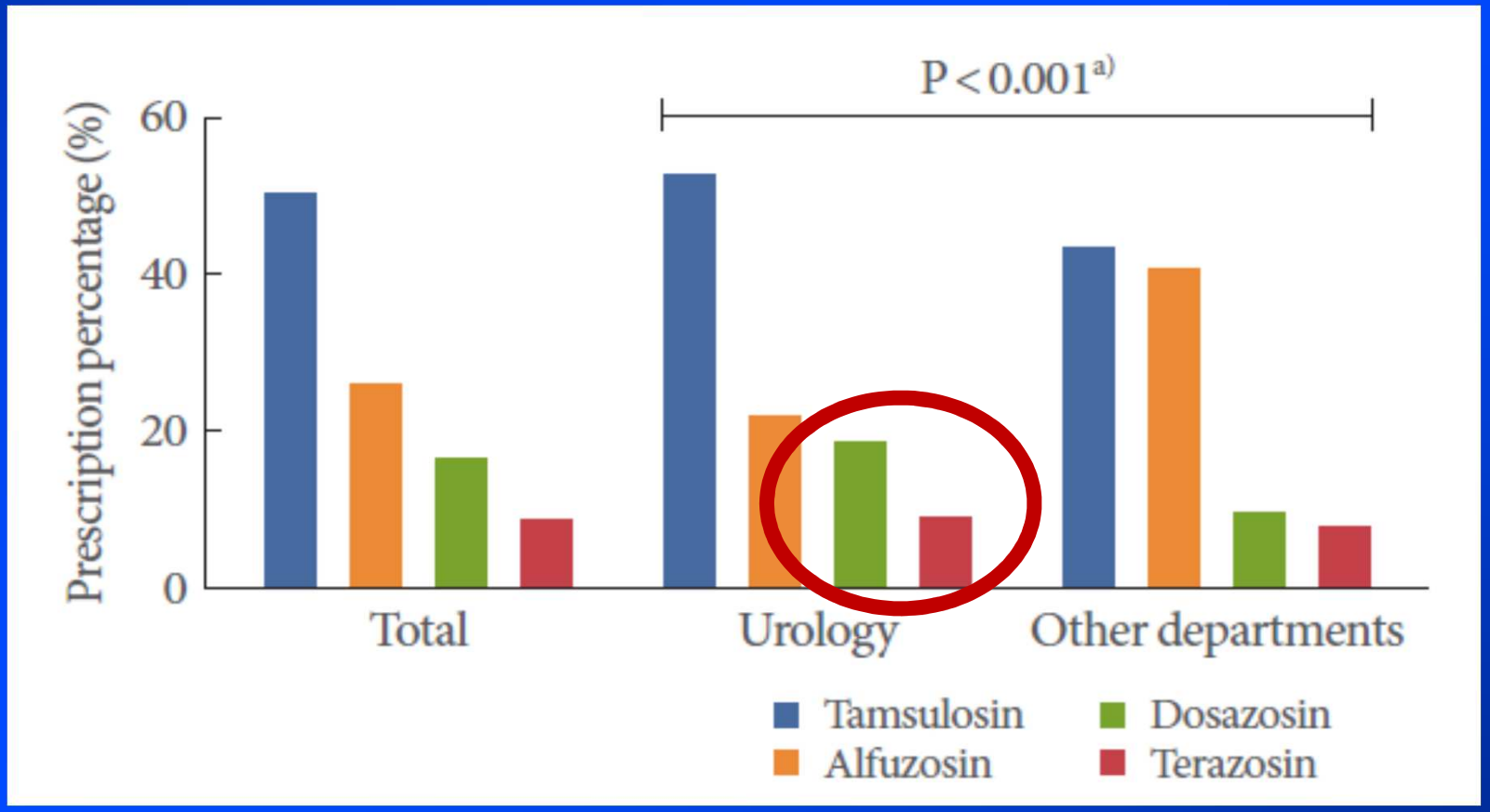
JAMA. 2000;283:1967-1975

a-blockers prescription patterns



Stafford, JAMA 2004

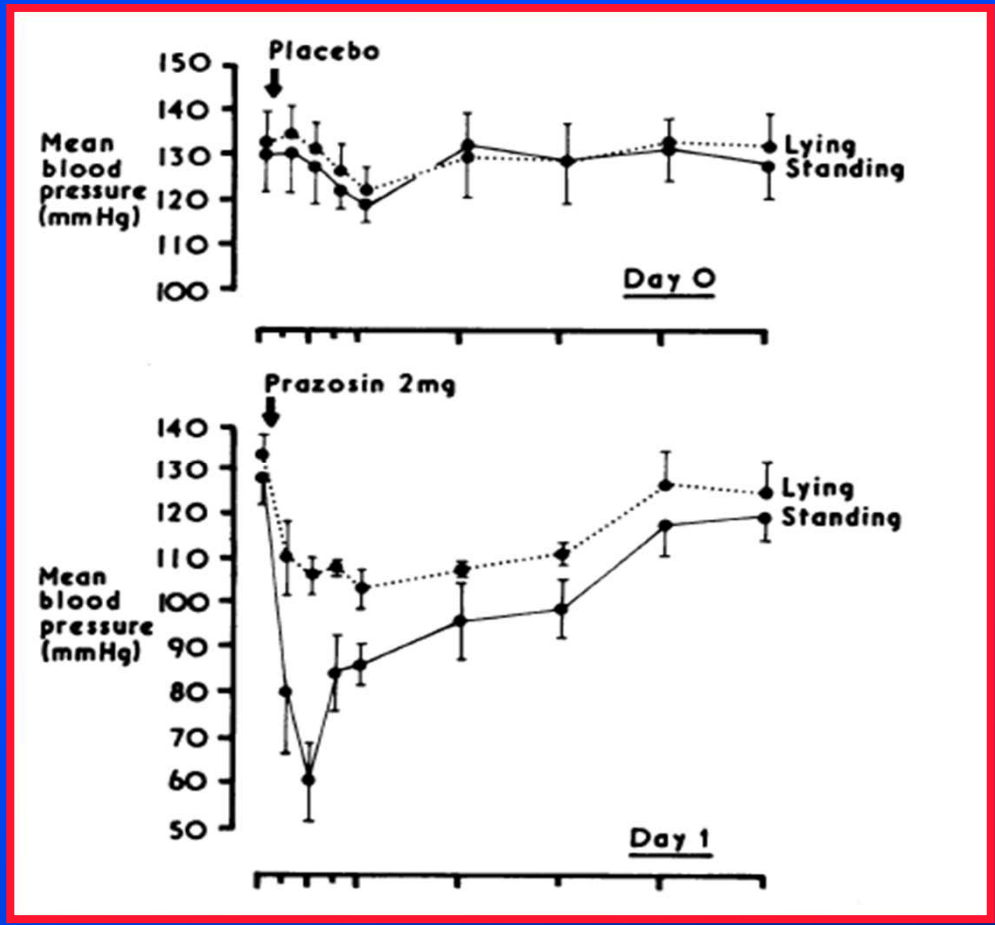
Αναγραφή α-αποκλειστών



Kang, Int Neurourol J 2011

Adverse effects

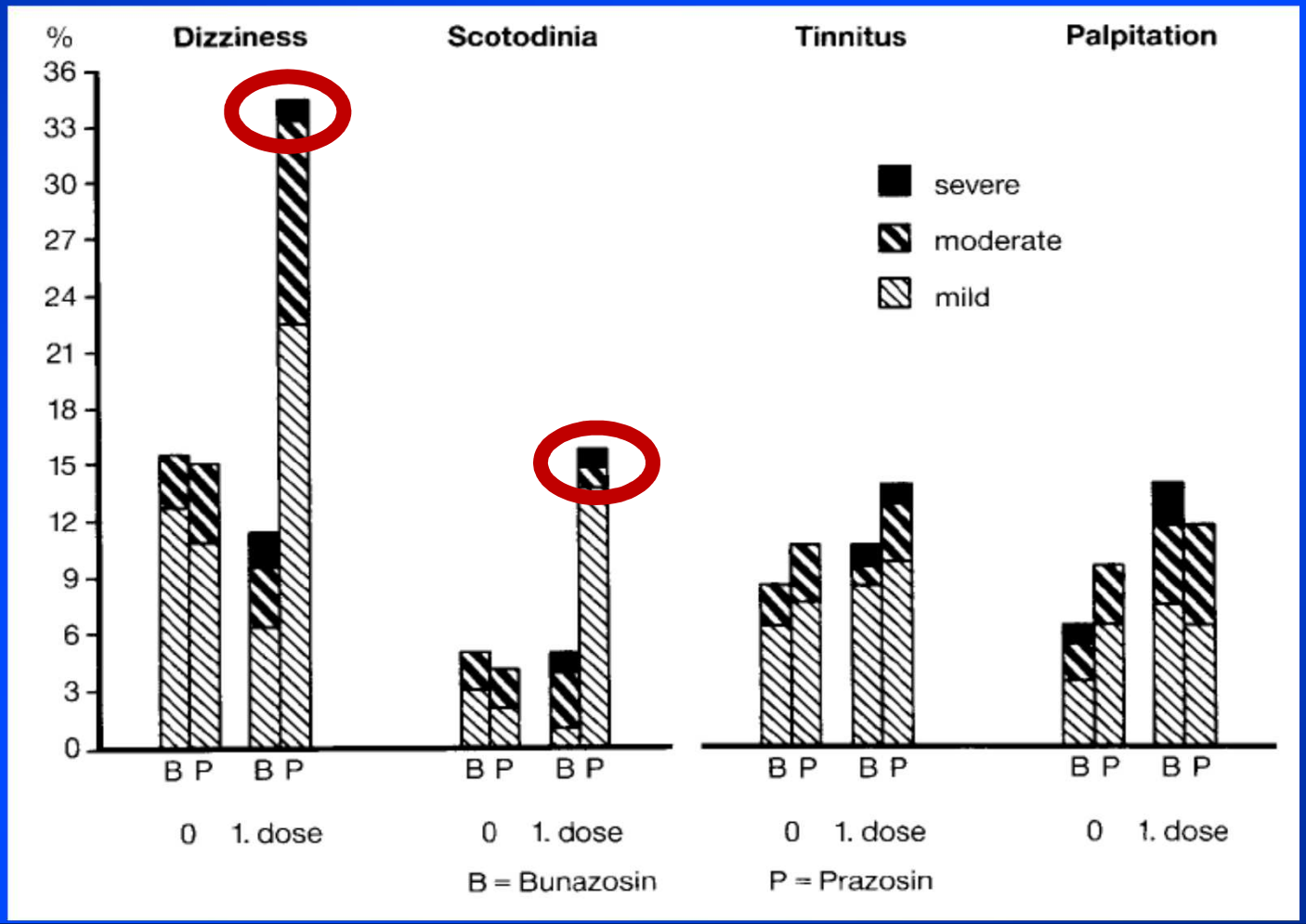
- First dose effect
- Orthostatic hypotension



Graham, BMJ 1976

Doumas, Loutraki 2011

Συμπτώματα ορθοστατικής υπότασης



Rieckert, Am J Hypertens 1996

Συγχορήγηση PDE-5 με δοξαζοσίνη
Μέγιστη πτώση – Κλινική σημασία

Criteria	Tadalafil + Doxazosin	Placebo + Doxazosin	Mean Difference	95% CI for Mean Difference
Standing:				
Max decrease SBP (mm Hg)	27.8	17.9	9.8*	4.1, 15.5
Max decrease DBP (mm Hg)	14.4	9.1	5.3*	0.6, 10.0
Max increase heart rate (bpm)	16.1	12.3		0.5, 7.2
Supine:				
Max decrease SBP (mm Hg)	19.6	15.9	3.6	−1.5, 8.8
Max decrease DBP (mm Hg)	11.5	8.7	2.8*	0.2, 5.4
Max increase heart rate (bpm)	11.9	8.1	3.8*	0.3, 7.2

	No. (%)	
	Tadalafil 20 Mg + Doxazosin 8 Mg	Placebo + Doxazosin 8 Mg
Total pts		18
Standing SBP less than 85 mm Hg	5 (28)	1 (6)
Standing DBP less than 45 mm Hg	1 (6)	0 (0)
Supine SBP less than 85 mm Hg	0 (0)	1 (6)
Supine DBP less than 45 mm Hg	0 (0)	0 (0)
Change in standing SBP greater than 30 mm Hg	5 (28)	2 (11)
Change in standing DBP greater than 20 mm Hg	2 (11)	1 (6)
Change in supine SBP greater than 30 mm Hg	1 (6)	1 (6)
Change in supine DBP greater than 20 mm Hg	2 (11)	0 (0)

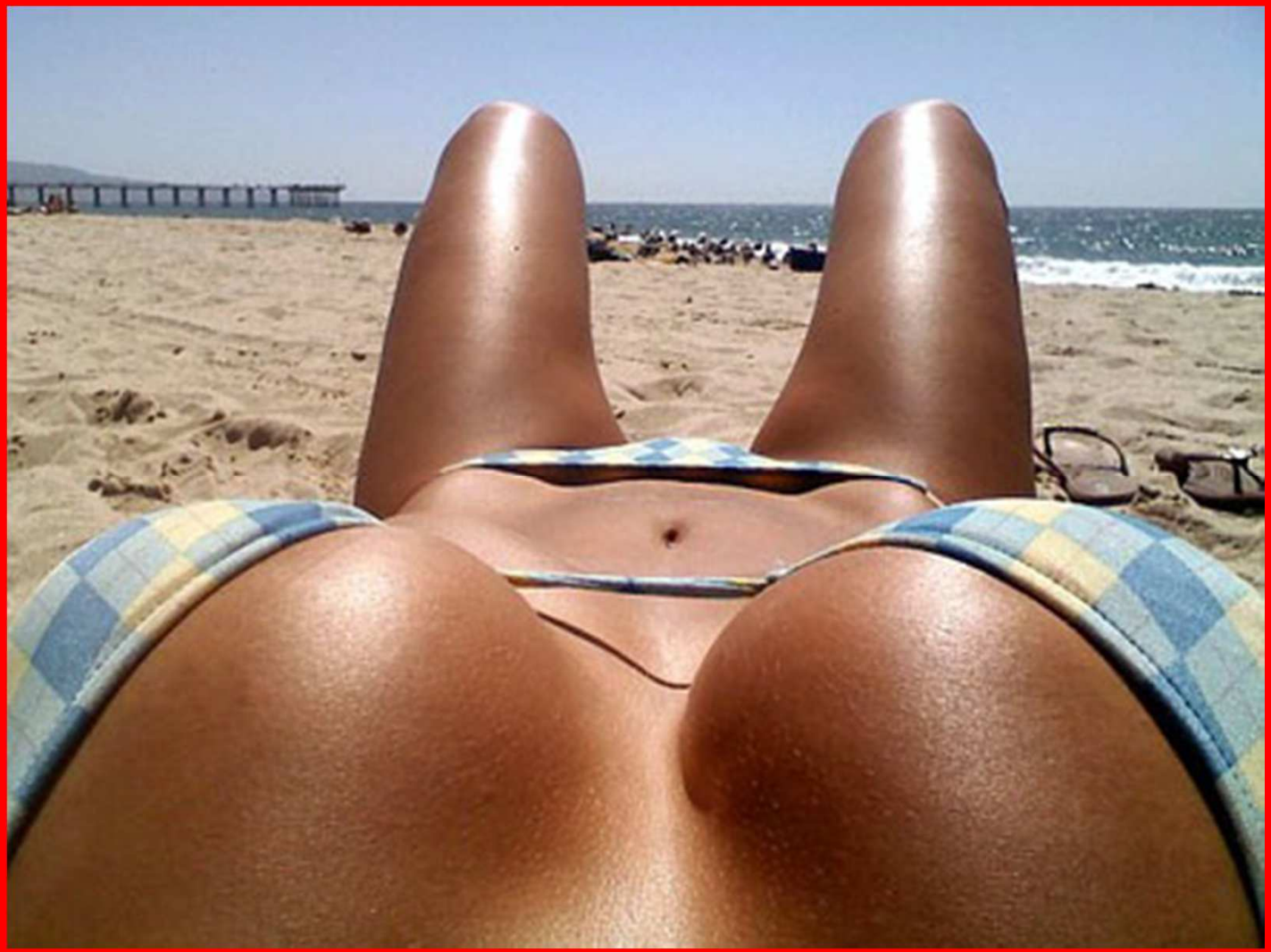
Kloner, J Urology 2004

Συγχορήγηση PDE-5 με ταμσουλοζίνη
Μέγιστη πτώση – Κλινική σημασία

Criteria	Tadalafil 10 Mg + Tamsulosin	Tadalafil 20 Mg + Tamsulosin	Placebo + Tamsulosin	Mean Difference (tadalafil 10 mg minus placebo)	95% CI for Mean Difference	Mean Difference (tadalafil 20 mg minus placebo)	95% CI for Mean Difference
Standing:							
Max decrease SBP (mm Hg)	19.4	20.1	17.7	1.7	−4.7, 8.1	2.3	−4.1, 8.7
Max decrease DBP (mm Hg)	13.1	10.3	8.1	5.0*	1.4, 8.6	2.2	−1.4, 5.8
Max increase heart rate (bpm)	14.9	15.2	13.3	1.6	−1.4, 4.6	1.8	−1.2, 4.8
Supine:							
Max decrease SBP (mm Hg)	17.6	17.6	14.4	3.2	−2.3, 8.6	3.2	−2.3, 8.7
Max decrease DBP (mm Hg)	11.6	11.3	8.3	3.2	−0.6, 7.0	3.0	−0.8, 6.8
Max increase heart rate (bpm)	12.4	12.9	9.2	3.2	−1.0, 7.4	3.8	−0.4, 8.0

	No. (%)		
	Tadalafil 10 Mg + Tamsulosin	Tadalafil 20 Mg + Tamsulosin	Placebo + Tamsulosin
Total pts	18	18	18
Change in standing SBP greater than 30 mm Hg	2 (11)	2 (11)	1 (6)
Change in standing DBP greater than 20 mm Hg	3 (17)	0 (0)	1 (6)
Change in supine SBP greater than 30 mm Hg	1 (6)	1 (6)	2 (11)
Change in supine DBP greater than 20 mm Hg	1 (6)	2 (11)	0 (0)

Kloner, J Urology 2004



Τι να κάνουμε

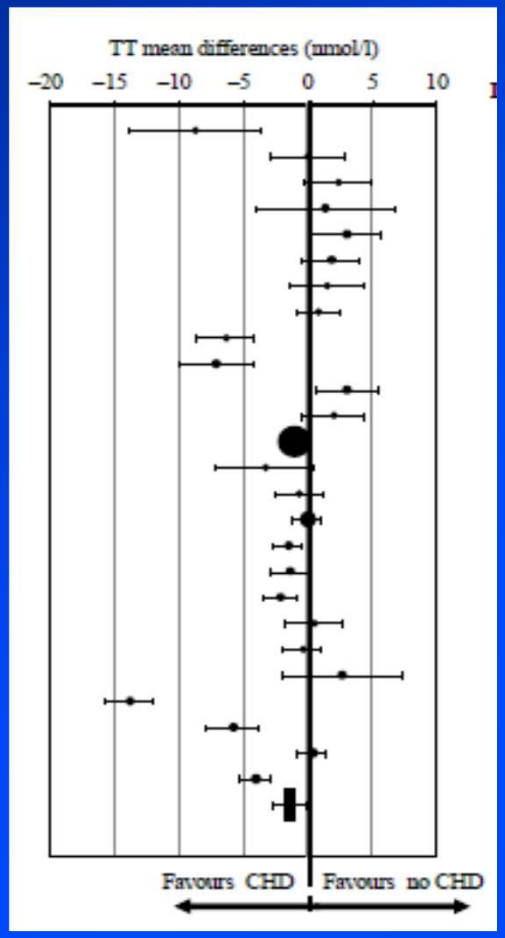
- Χαμηλή δόση α-αποκλειστών όταν λαμβάνονται συστηματικά PDE-5 inh
- Χαμηλή δόση PDE-5 inh όταν λαμβάνονται συστηματικά α-αποκλειστές
- Προτίμηση στους εκλεκτικούς α-αποκλειστές
- Προσοχή να μην συμπίπτουν οι μέγιστες συγκεντρώσεις φαρμάκων (>4h διαφορά λήψης)

Doumas, Agria 2014

Τεστοστερόνη

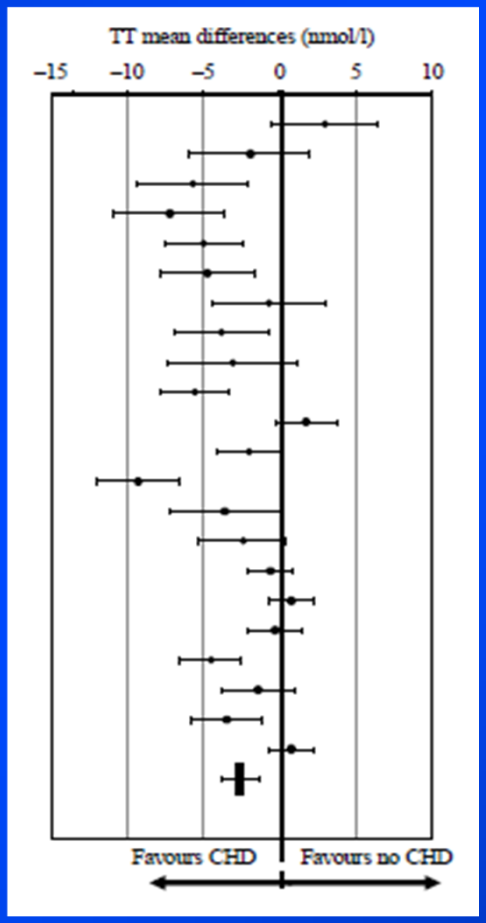
Τεστοστερόνη και καρδιαγγειακή νόσος

ΣΝ χωρίς αγγειογραφία



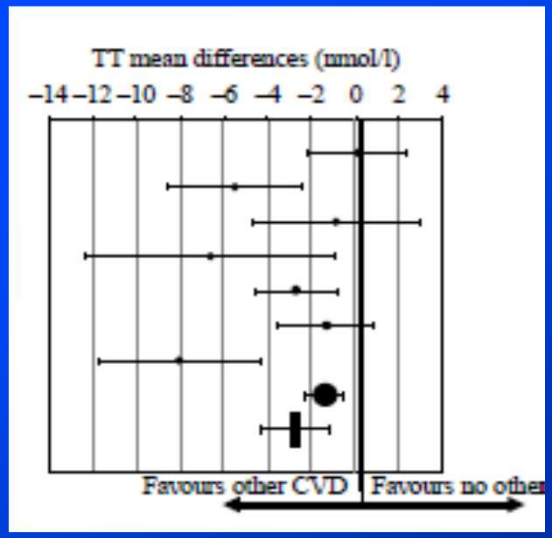
-1.44; CI: -2.72, -0.16

ΣΝ με αγγειγραφία



-2.57; CI: -3.82, -1.31

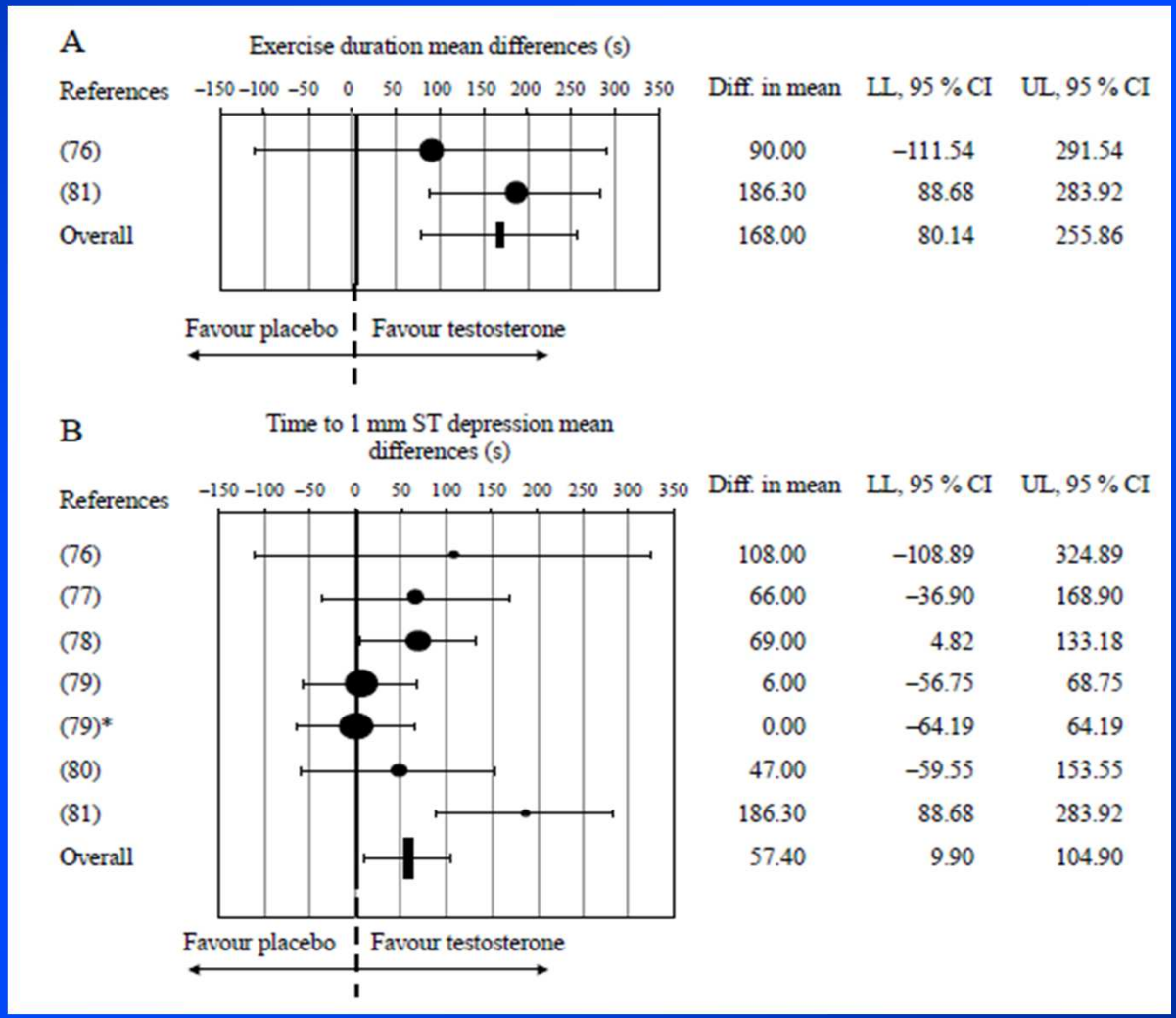
Άλλα ΚΑ νοσήματα



-2.71; CI: -4.26, -1.15

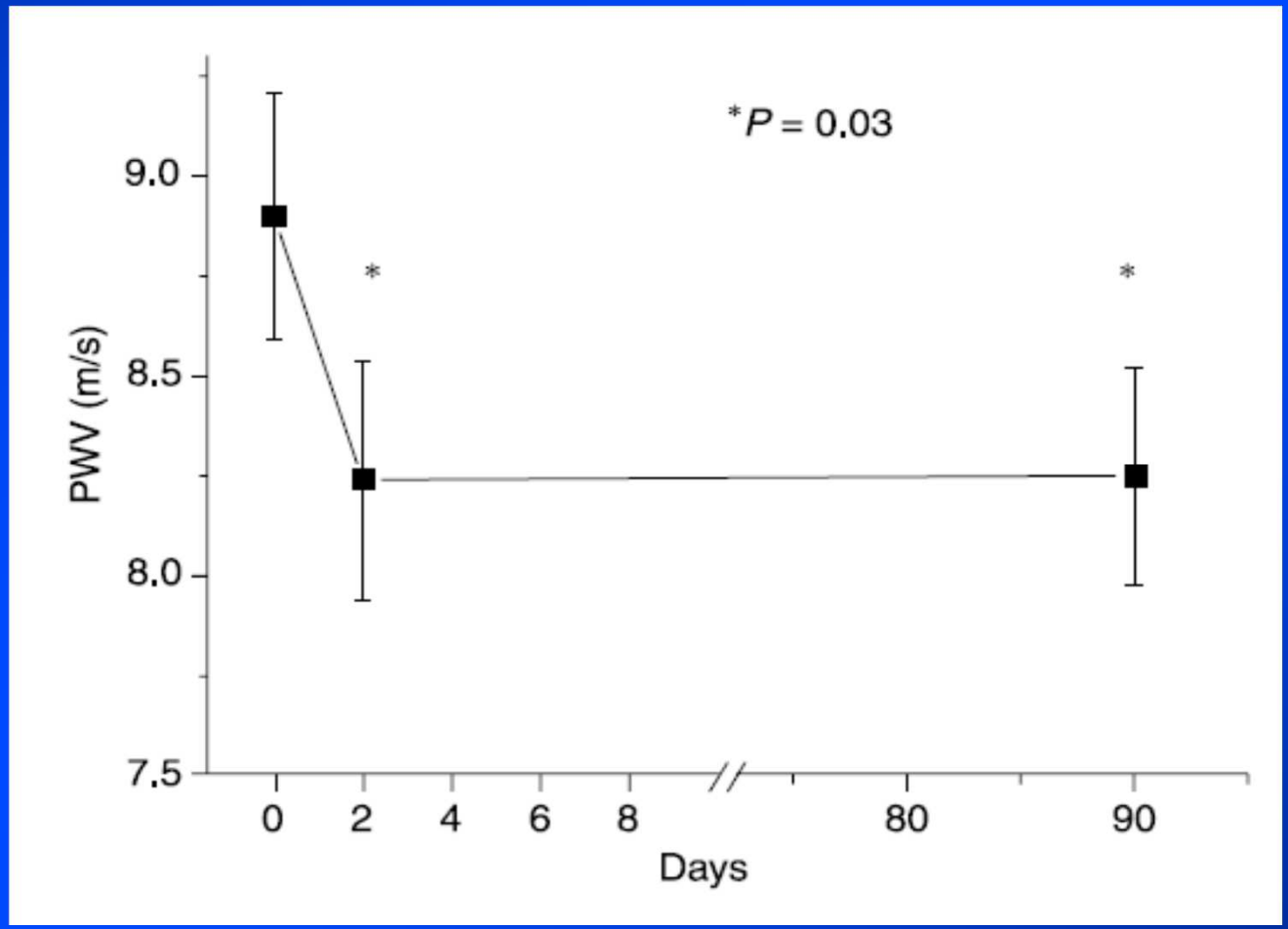
Corona, Eur J Endocrinol 2011

Ικανότητα προς άσκηση
Ισχαιμία



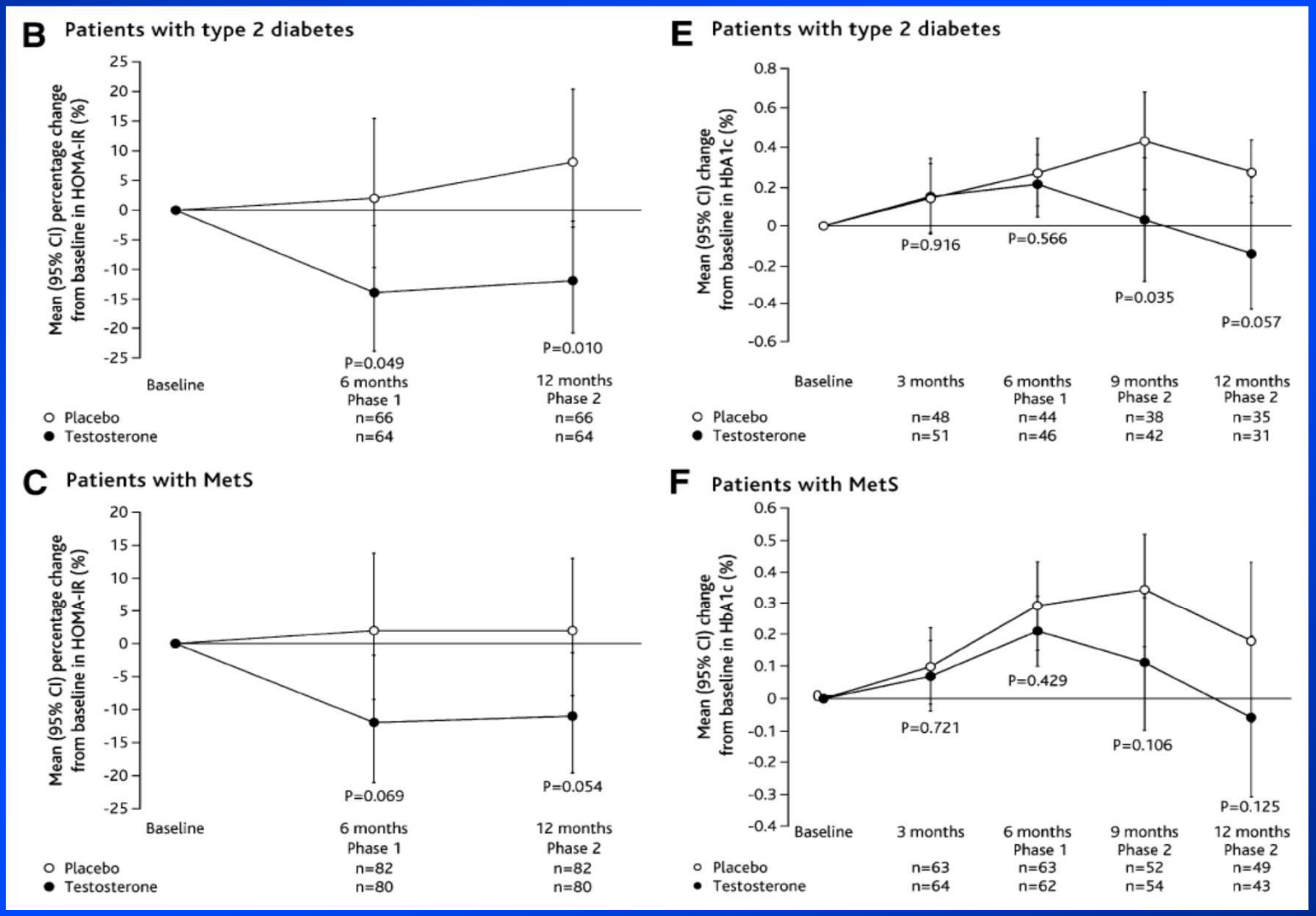
Corona, Eur J Endocrinol 2011

Αορτική σκληρία



Yaron, Eur J Endocrinol 2009

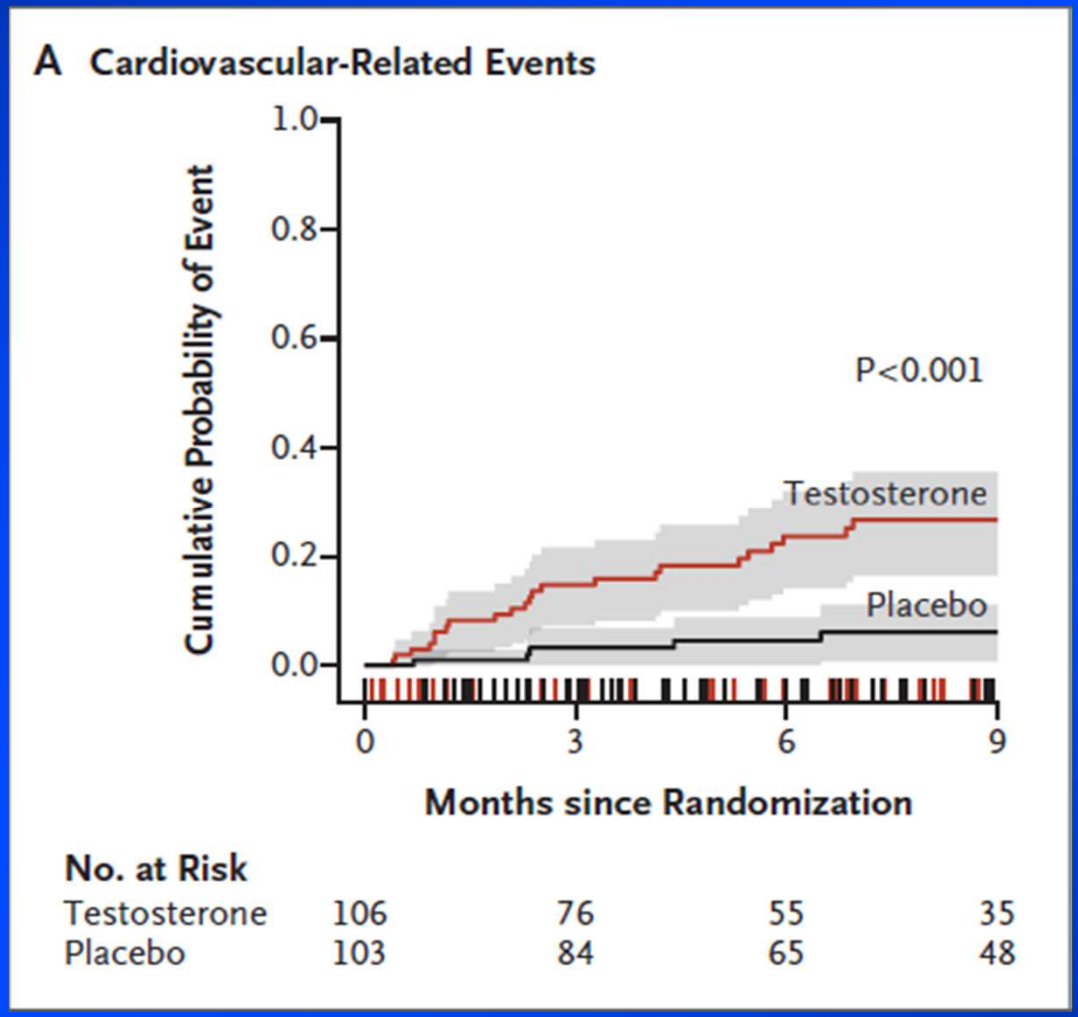
Αντίσταση στην ινσουλίνη – γλυκαιμικός έλεγχος



Jones, Diabetes Care 2011

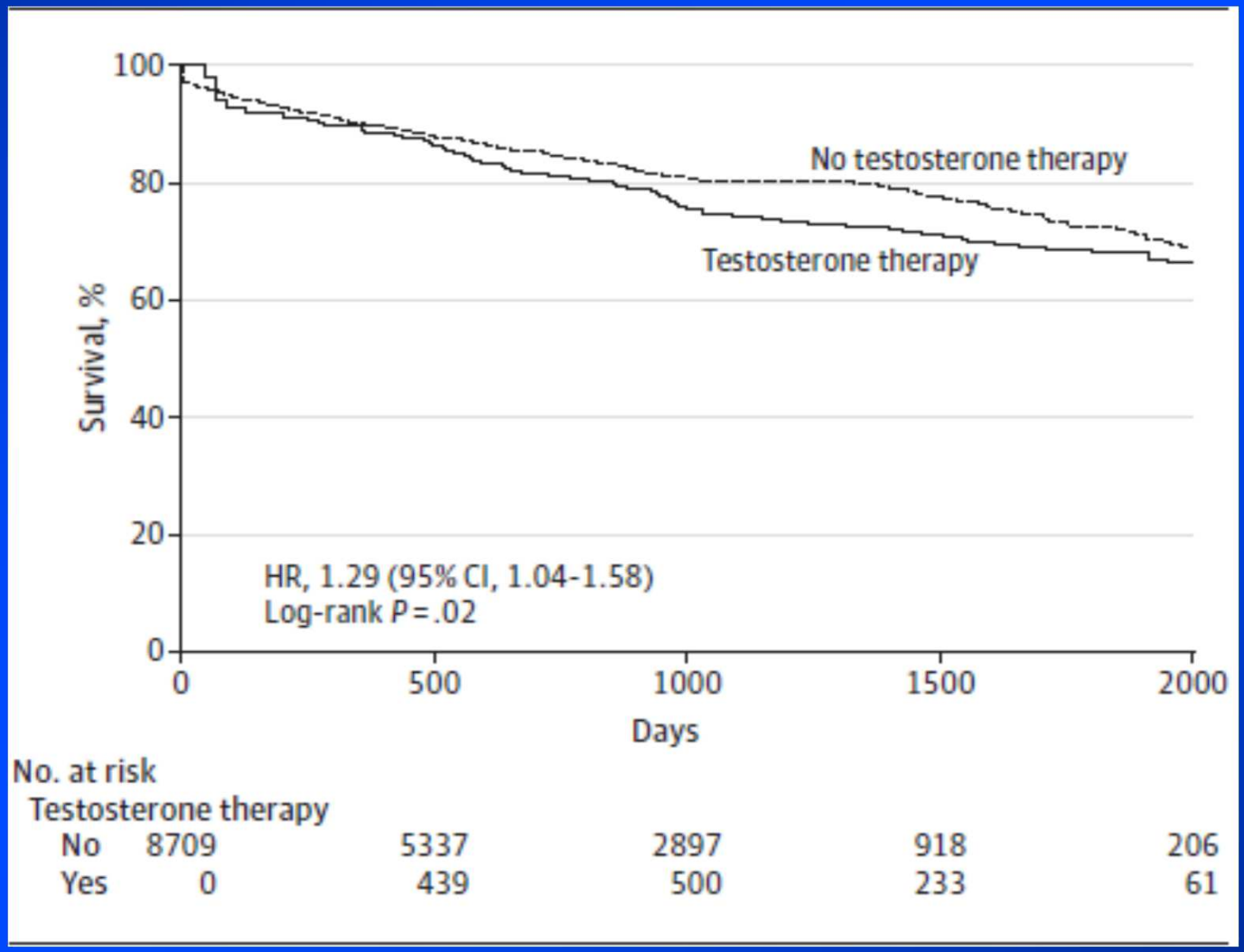
Αλλά...

Θεραπεία υποκατάστασης και καρδιαγγειακά



Basaria, NEJM 2010

Θεραπεία υποκατάστασης και επιβίωση



Vigen, JAMA 2013

Θεραπεία υποκατάστασης και ΟΕΜ

	Heart Disease History		No Heart Disease History	
	TT Prescription	PDE5I	TT Prescription	PDE5I
Age <65 Years				
Patients (N)	4,006	10,681†	44,533	130,831†
Pre-prescription				
Cases	21	65	135	491
Rate per 1,000 PY (95%CI)	5.26 (3.43, 8.06)	5.26 (3.43, 8.06)	3.04 (2.57, 3.60)	3.04 (2.57, 3.60)
Post-prescription				
Cases	15	20	30	99
Rate per 1,000 PY (95%CI)	15.22 (9.18, 25.25)	7.34 (6.89, 7.82)	2.73 (1.91, 3.91)	3.01 (2.95, 3.08)
Rate Ratio (post/pre) (95%CI)	[illegible]	1.4 (0.91, 2.14)	[illegible]	0.99 (0.84, 1.17)
RRR‡ (95%CI)	2.07 (1.05, 4.11)		0.91 (0.60, 1.37)	
Age ≥65 Years				
Patients (N)	2,047	5,492†	5,057	20,275†
Pre-prescription				
Cases	15	35	22	104
Rate per 1,000 PY (95%CI)	7.36 (4.44, 12.22)	7.36 (4.44, 12.22)	4.41 (2.90, 6.7)	4.41 (2.90, 6.7)
Post-prescription				
Cases	8	13	12	20
Rate per 1,000 PY (95%CI)	15.91 (7.96, 31.81)	8.35 (7.36, 9.48)	9.74 (5.53, 17.14)	4.04 (3.69, 4.42)
Rate Ratio (post/pre) (95%CI)	[illegible]	1.13 (0.68, 1.88)	[illegible]	0.92 (0.60, 1.39)
RRR‡ (95%CI)	1.90 (0.66, 5.50)		2.41 (1.12, 5.17)	

Finkle, PLos One 2014

The Opinion Pages | Editorial

Overselling Testosterone, Dangerously

By THE EDITORIAL BOARD FEB. 4, 2014

The study, published last week in the online journal PLOS One, provides the most compelling evidence yet that many American men have embarked on a perilous course of overtreatment. Testosterone is clearly indicated to treat abnormally low levels of the hormone because of genetic or pathological causes, a condition known as hypogonadism. But a huge upsurge in prescriptions in recent years suggests that testosterone is now being prescribed to men who are simply reluctant to accept the fact that they are getting older. In many cases, doctors are prescribing testosterone without even ascertaining whether a patient's testosterone levels are actually low or whether he has a medical condition that justifies it. The reason seems clear. Drug companies have shamelessly pushed the notion, to doctors and to the public, that their testosterone-boosting product can overcome a supposed disease called "low T."[1]

NY Times


CBS
NEWS

Θεραπεία υποκατάστασης και καρδιαγγειακά

Μικρός αριθμός ασθενών

Basaria, NEJM 2010

Θεραπεία υποκατάστασης και επιβίωση

Αμφισβητούμενη στατιστική ανάλυση

Vigen, JAMA 2013

Θεραπεία υποκατάστασης και ΟΕΜ

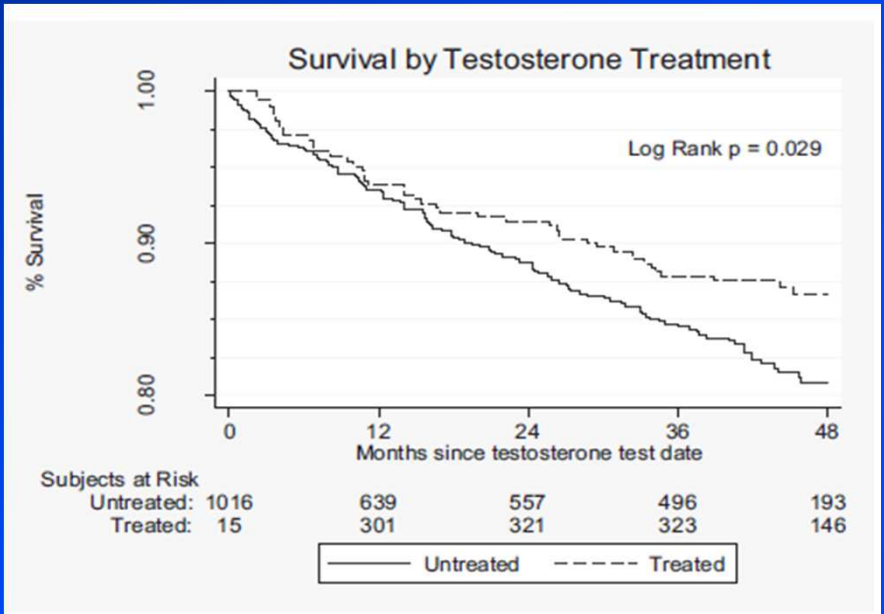
	Age ≥65 Years
Patients (N)	7,054
Pre-prescription	
Cases	37
Rate per 1,000 PY (95%CI)	5.27 (3.81, 7.27)
Post-prescription	
Cases	20
Rate per 1,000 PY (95%CI)	11.52 (7.43, 17.86)
Rate Ratio (post/pre) (95%CI)	2.19 (1.27, 3.77)

Αδόκιμη σύγκριση

Απόλυτος κίνδυνος;

Finkle, PLos One 2014

Θεραπεία υποκατάστασης και θνητότητα



Subgroups[a]	Hazard ratio (95% CI) and *P* value
Age	
41–59 yr (n = 454)	0.43 (0.20–0.92); 0.03
60+ years (n = 577)	0.68 (0.45–1.03); 0.07
Prevalent diabetes	
Yes (n = 393)	0.44 (0.23–0.84); 0.013
No (n = 638)	0.72 (0.46–1.13); 0.155
Prevalent cardiac disease	
Yes (n = 226)	0.82 (0.42–1.61); 0.56
No (n = 805)	0.55 (0.36–0.84); 0.006

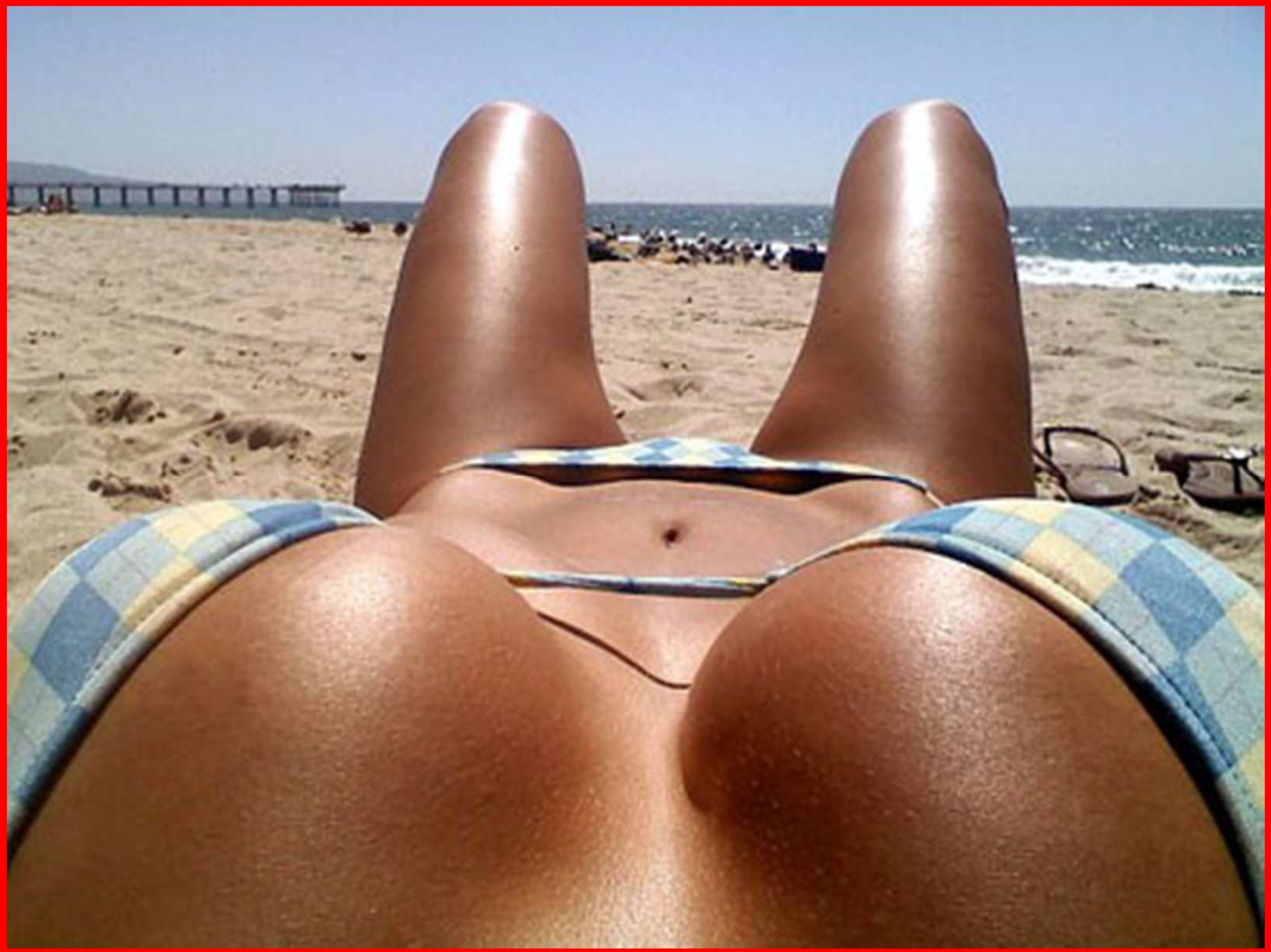
Testosterone exposure	Person-years	Deaths	Mortality per 100 person-years	Fully adjusted HR (95% CI)[a]
Untreated (n = 633)	2290	131	5.73	1.00 (reference)
Treated (n = 398)	1190	41	3.44	0.61 (0.42–0.88); *P* = 0.008
Total (n = 1031)	3480	172	4.95	

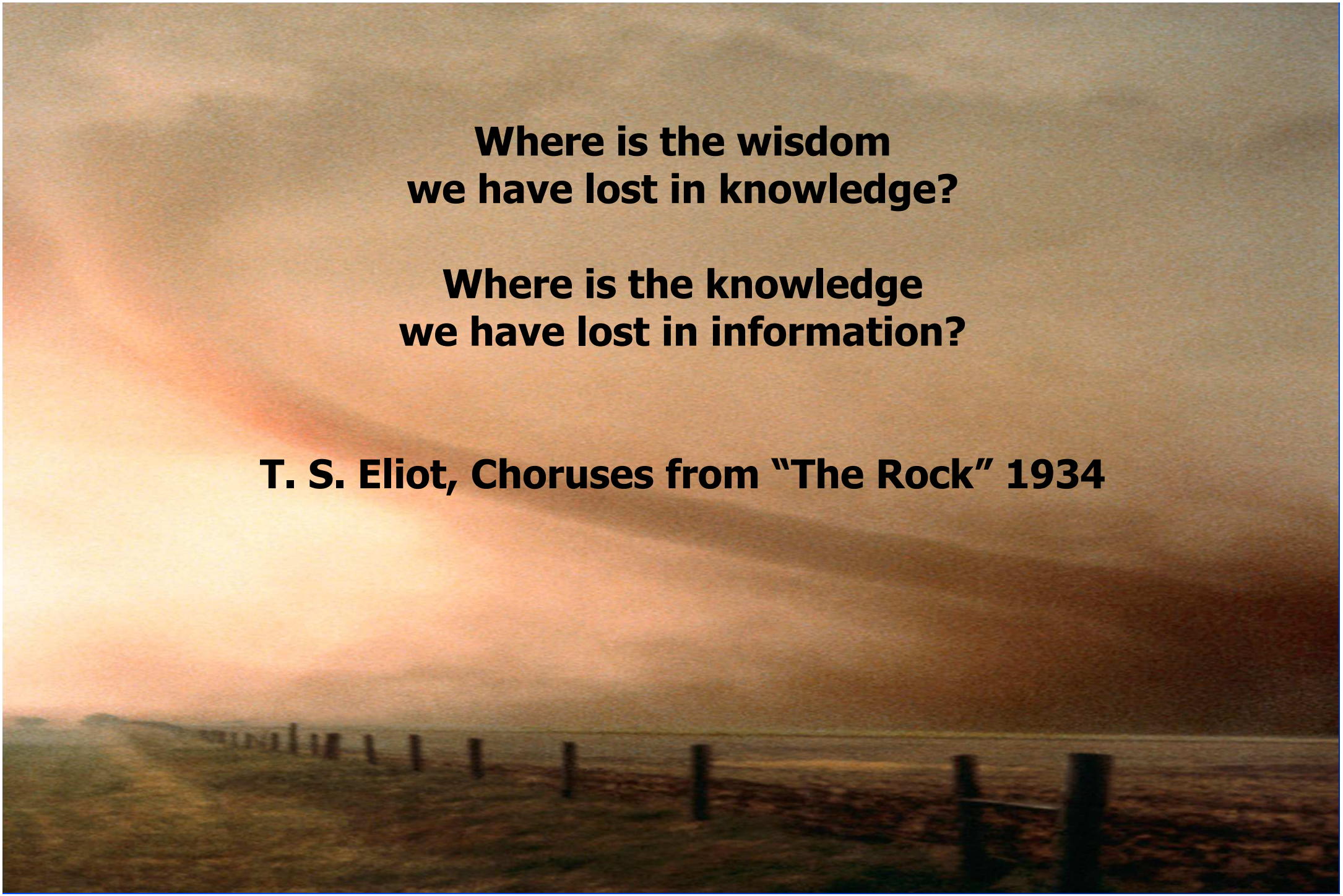
Shores, J Clin Endocrinol Metab 2012

Θεραπεία υποκατάστασης και θνητότητα

- 581 άνδρες με ΣΔ τύπου 2
- 5.8 έτη παρακολούθησης
- Θνητότητα:
- 17.2% vs 9% χαμηλή vs φυσιολογική τεστο
- 8.4% vs 19.2% θεραπεία υποκατάστασης vs όχι
- HR: 2.3 (95% CI: 1.3-3.9)

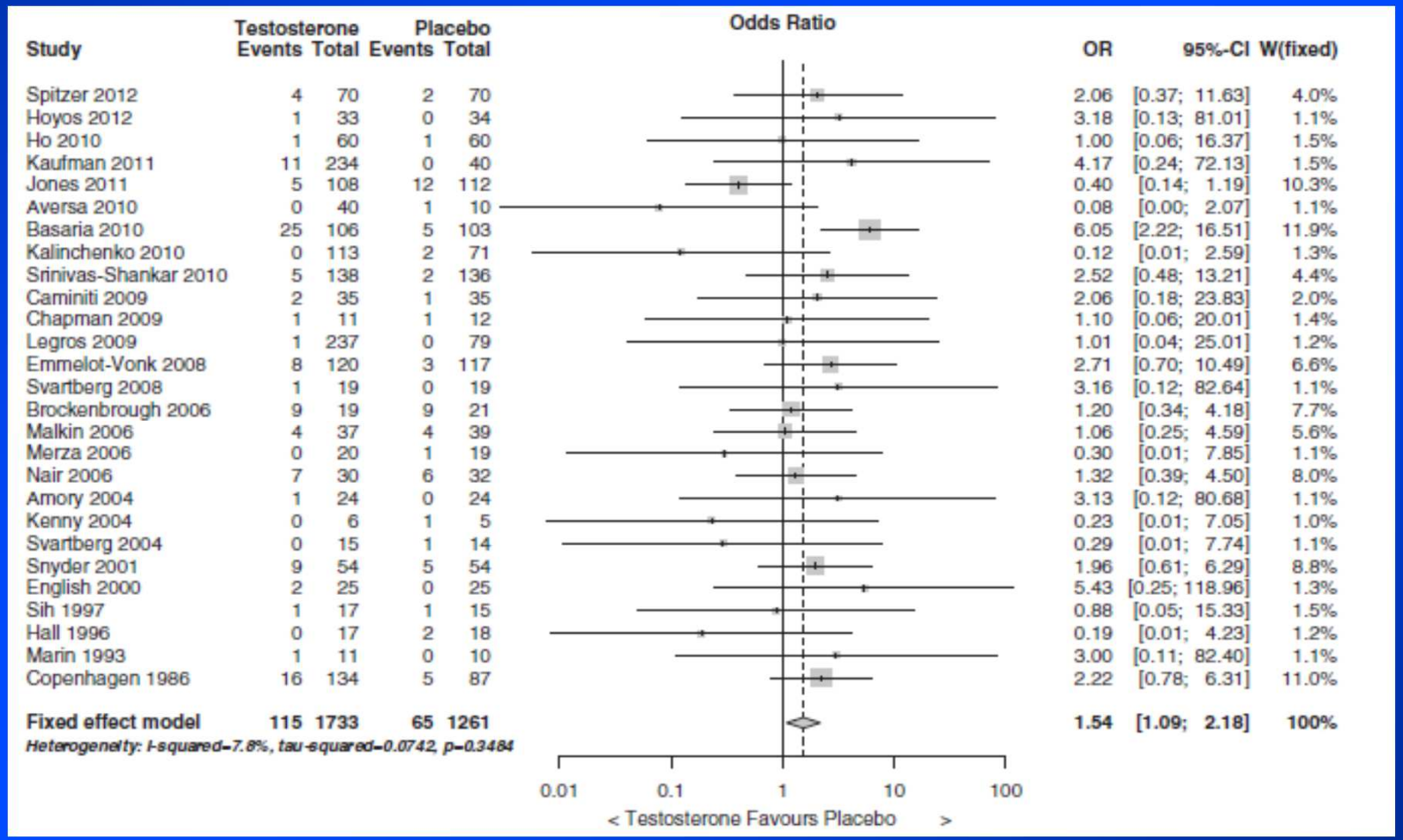
Muraleedharan, Eur J Endocrinol 2013



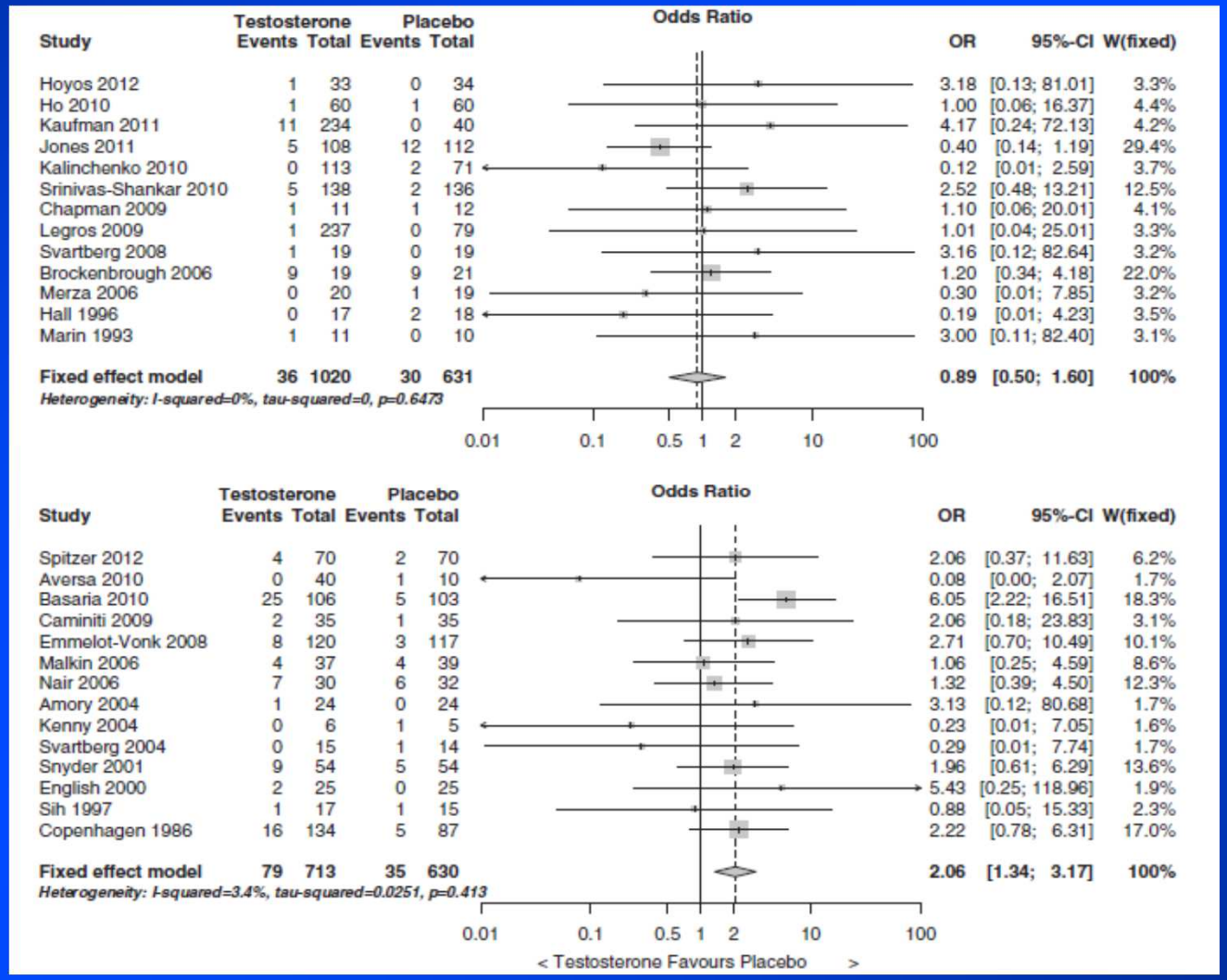

Where is the wisdom
we have lost in knowledge?
Where is the knowledge
we have lost in information?
T. S. Eliot, Choruses from “The Rock” 1934

Καρδιαγγειακό σύστημα

Θεραπεία υποκατάστασης και καρδιαγγειακά



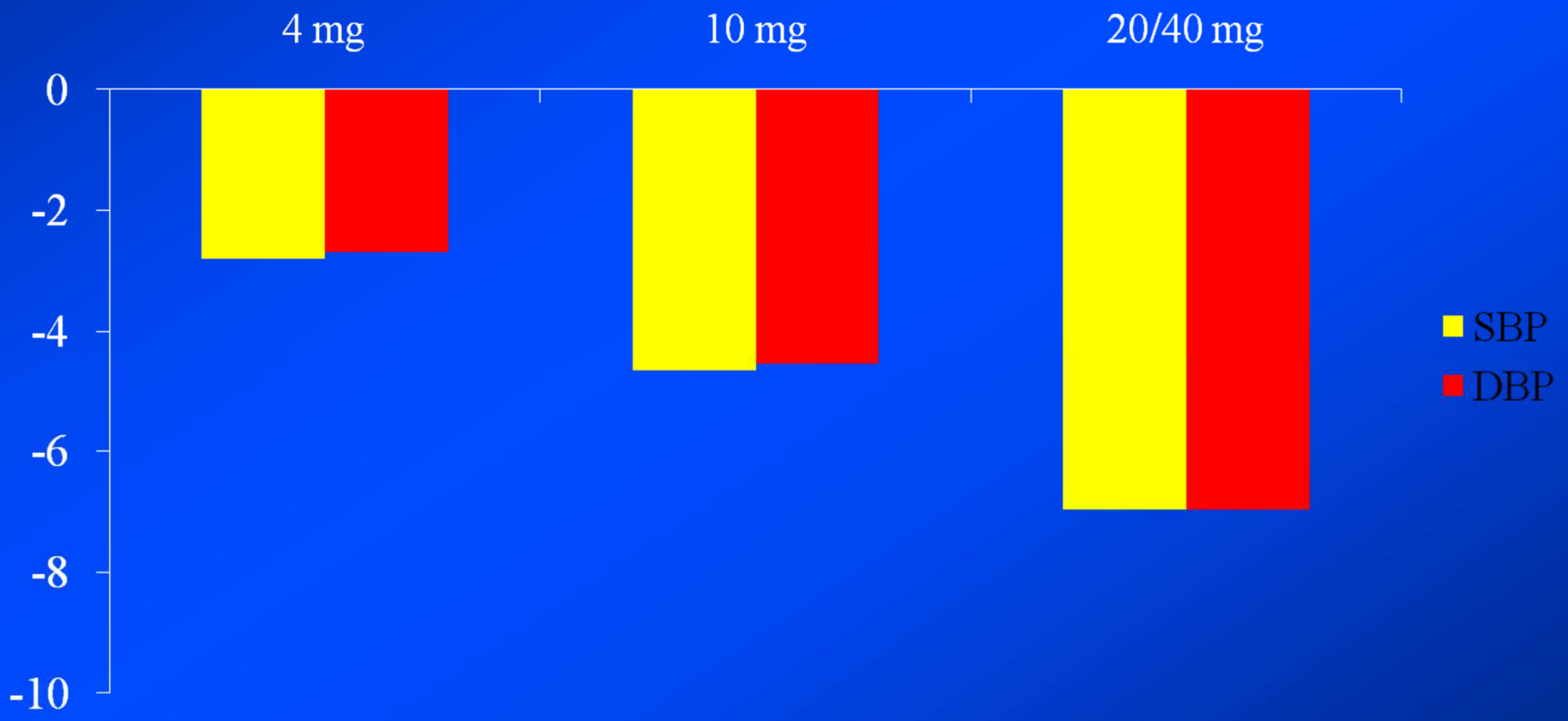
Θεραπεία υποκατάστασης και καρδιαγγειακά ανάλογα με τη χρηματοδότηση της μελέτης



Xu, BMC Medicine 2013

Efficacy in hypertension

Blood pressure reduction – PF00489791



Wolk, Hypertension 2009

Efficacy in hypertension

Resistant hypertension

Clinical potential of combined organic nitrate and phosphodiesterase type 5 inhibitor in treatment-resistant hypertension.

BP reduction: 26/18 mmHg

Without significant AE

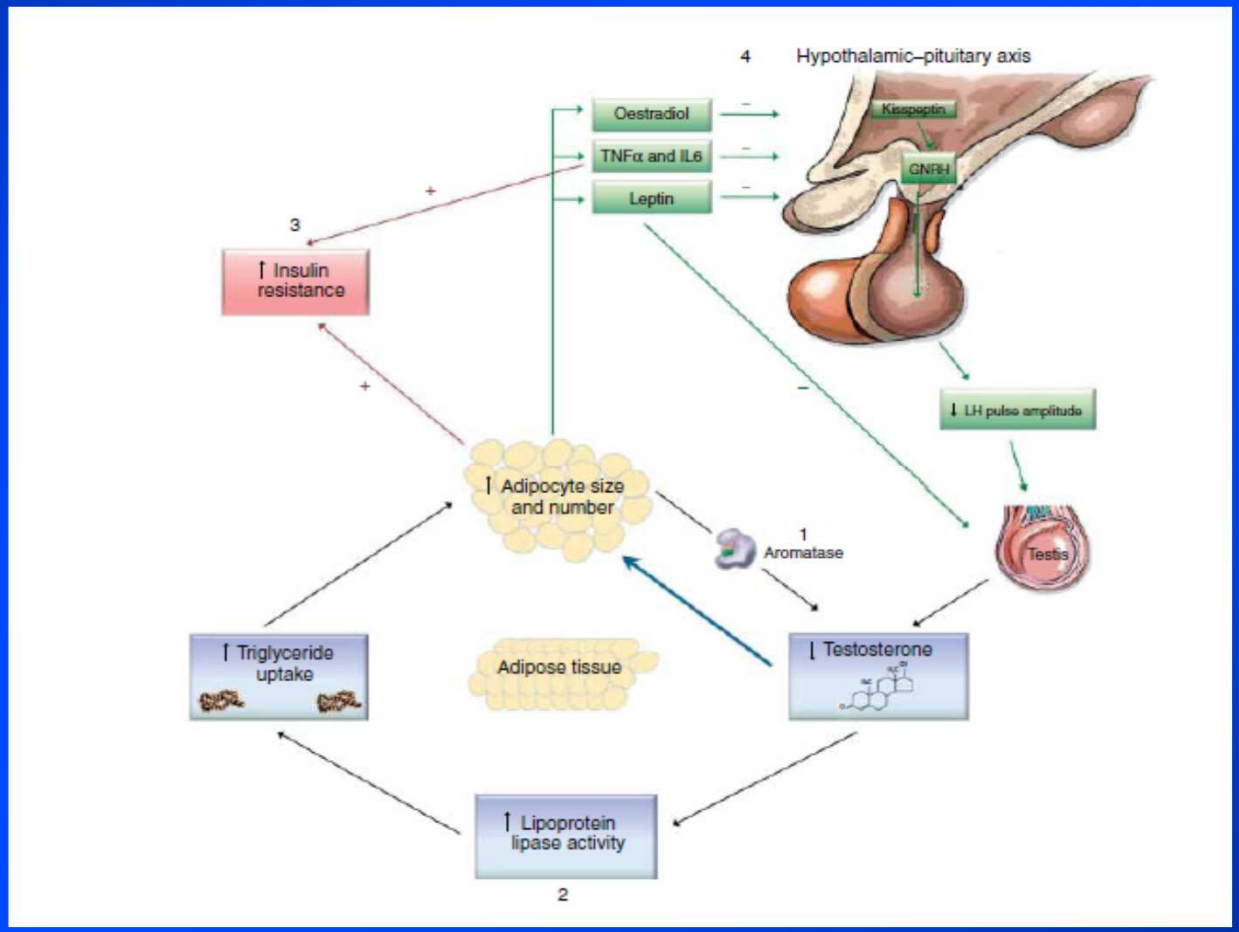
But … be careful

Oliver, Hypertension 2010

Χολινεργικοί υποδοχείς

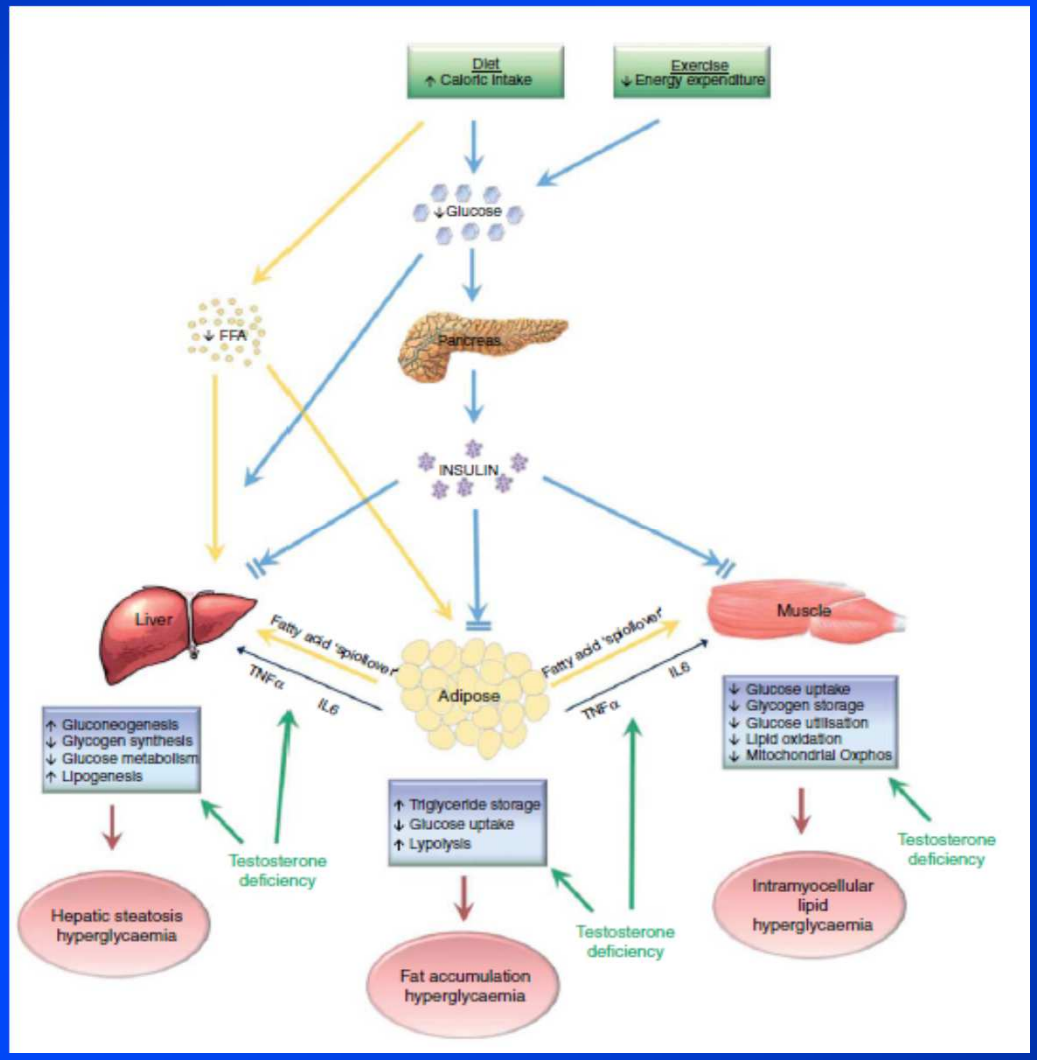
- Ουροδόχος κύστη
- Σιελογόνοι αδένες
- Γαστρεντερικό σύστημα
- Εγκέφαλος
- Οφθαλμοί
- Καρδιά

Τεστοστερόνη



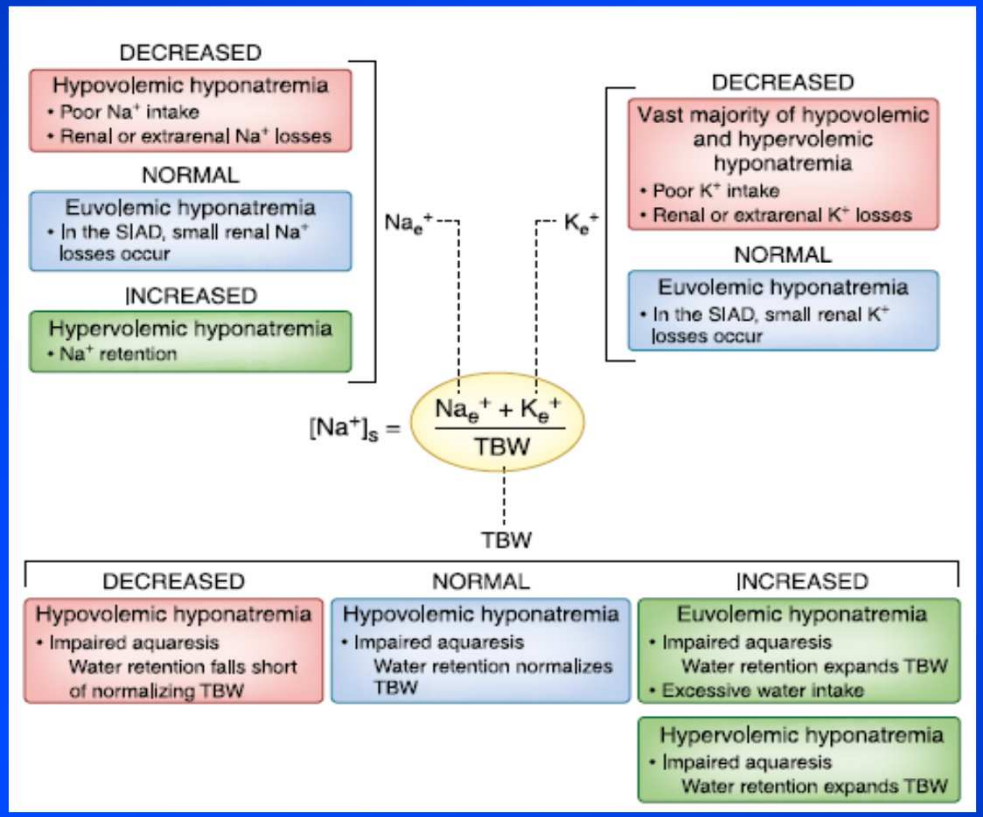
Kelly, J Endocrinol 2013

Τεστοστερόνη



Kelly, J Endocrinol 2013

HR-CV risk

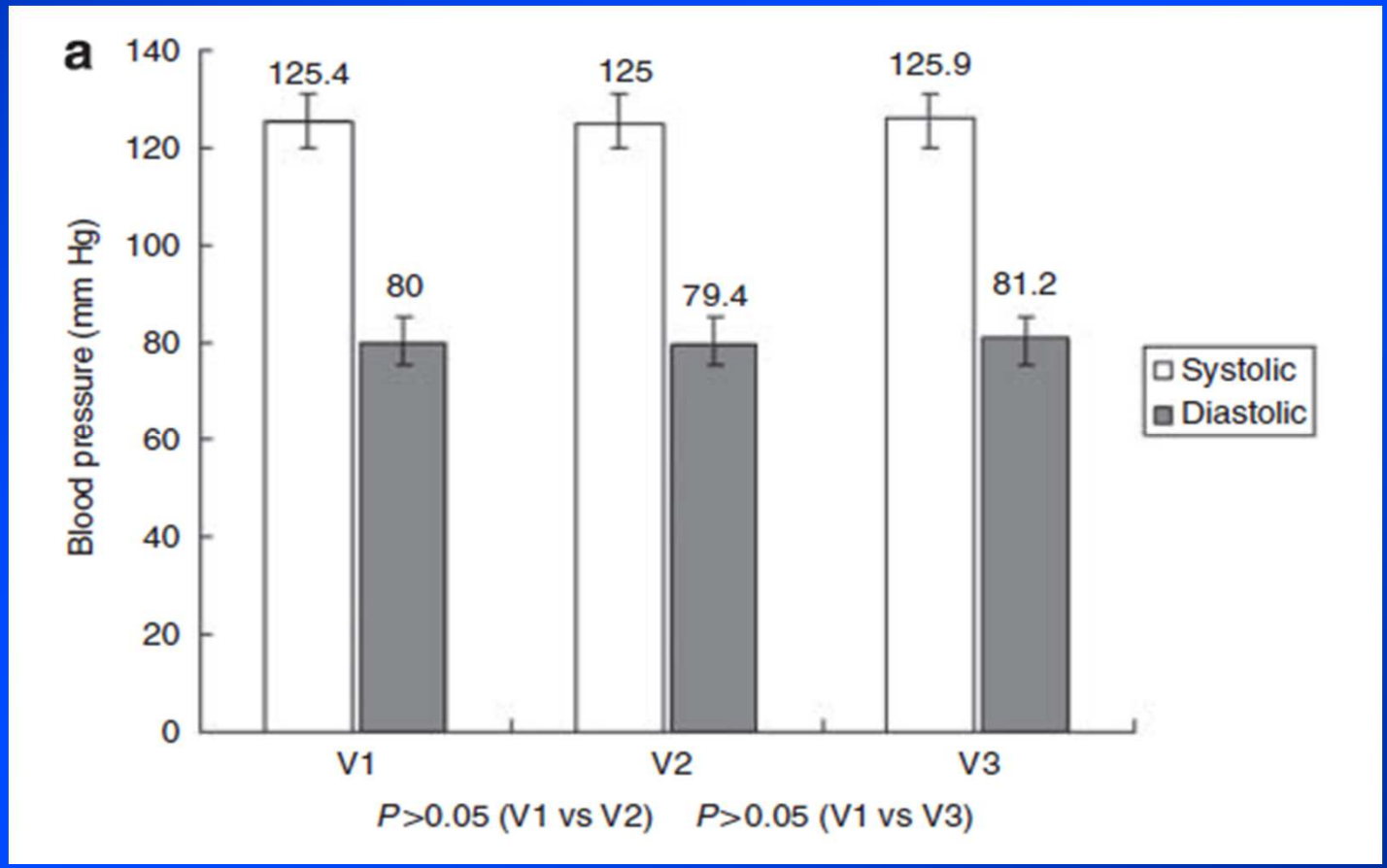

DECREASED
Hypovolemic hyponatremia
• Poor Na+ intake
• Renal or extrarenal Na+ losses
NORMAL
Euvolemic hyponatremia
• In the SIAD, small renal Na+ losses occur
INCREASED
Hypervolemic hyponatremia
• Na+ retention
Nae+
Ke+
DECREASED
Vast majority of hypovolemic and hypervolemic hyponatremia
• Poor K+ intake
• Renal or extrarenal K+ losses
NORMAL
Euvolemic hyponatremia
• In the SIAD, small renal K+ losses occur
[Na+]s = Nae+ + Ke+ / TBW
TBW
DECREASED
Hypovolemic hyponatremia
• Impaired aquaresis
Water retention falls short of normalizing TBW
NORMAL
Hypovolemic hyponatremia
• Impaired aquaresis
Water retention normalizes TBW
INCREASED
Euvolemic hyponatremia
• Impaired aquaresis
Water retention expands TBW
• Excessive water intake
Hypervolemic hyponatremia
• Impaired aquaresis
Water retention expands TBW

HR-CV risk

Infusate			Fluid Loss		
	$[Na^+ + K^+]$ (mEq/L)	Effect on $[Na^+]_s$ per 1 L (mEq/L)		$[Na^+ + K^+]$ (mEq/L)	Effect on $[Na^+]_s$ per 1 L (mEq/L)
3% NaCl	513	↑ 13.0	Aquaresis (*e.g.*, primary polydipsia)	20	↑ 3.1
0.9% NaCl	154	↑ 1.4	Natriuresis (*e.g.*, furosemide)	55	↑ 1.9
0.9% NaCl + 30 mEq KCl per L	184	↑ 2.4	Viral/bacterial diarrhea	90	↑ 0.7
Ringer's lactate	135	↑ 0.8	Osmotic diarrhea	40	↑ 2.4
0.45% NaCl	77	↓ 1.1	Gastric fluid	70	↑ 1.4
5% dextrose	0	↓ 3.5			

a

Συγχορήγηση με ουδεναφίλη



Chung, Int J Imp Res 2009

Συγχορήγηση με ταδαλαφίλη

	V1	V2	V3	P	
				V1 vs V2	V1 vs V3
Systolic BP, mm Hg[a]	124.18 ± 10.42	124.06 ± 10.36	121.78 ± 9.23	.261	.241
Diastolic BP, mm Hg[a]	76.27 ± 8.02	75.57 ± 8.34	75.06 ± 7.56	.729	.395
Systolic BP, mm Hg[b]	126.61 ± 11.15	126.27 ± 10.91	125.39 ± 7.30	.647	.534
Diastolic BP, mm Hg[b]	78.10 ± 8.54	77.73 ± 8.85	77.35 ± 7.93	.822	.634
Heart rate, beats/min	73.31 ± 6.64	72.69 ± 8.64	72.86 ± 8.44	.760	.678

Doumas, Agria 2014

Υπόταση στις μελέτες

Treatment-related Adverse Events	Placebo N = 678, n (%)	Alfuzosin OD 10 mg N = 473, n (%)	Alfuzosin OD 15 mg N = 335, n (%)
Patients with ≥1 adverse event	219 (32.3)	197 (41.6)	137 (40.9)
Upper respiratory tract infection (URI, rhinitis, sinusitis, laryngitis, and pharyngitis combined)	23 (3.4)	29 (6.1)	19 (5.7)
Dizziness (dizziness and malaise combined)	19 (2.8)	27 (5.7)	30 (9.0)
Headache	12 (1.8)	14 (3.0)	8 (2.4)
Fatigue (fatigue and asthenia combined)	12 (1.8)	13 (2.7)	14 (4.2)
Impotence	4 (0.6)	7 (1.5)	4 (1.2)
Ejaculatory failure/disorder	0	3 (0.6)	1 (0.3)
Hypotension/postural hypotension	0	2 (0.4)	2 (0.6)
Syncope	0	1 (0.2)	2 (0.6)

Roehrbron, Urology 2001

Ταμσουλοζίνη και αντιυπερτασικά

	Baseline	Change	
	Day 4 (placebo)	Day 11 (0.4 mg/day)	Day 19 (0.8 mg/day)†
Nifedipine			
SBP (mm Hg)			
Tamsulosin	129.5/152.3‡	−9.0/−2.0	−11.4/−1.1
Placebo	122.0/149.0	−1.5/−3.5	−7.0/−3.5
DBP (mm Hg)			
Tamsulosin	83.7/99.7	−4.5/−2.0	−3.1/−2.0
Placebo	77.0/95.0	−0.5/1.0	−5.0/0.5
Enalapril			
SBP (mm Hg)			
Tamsulosin	115.7/146.3‡	0.0/+2.7	+1.3/+3.3
Placebo	111.5/140.0	+8.0/+9.0	+3.0/−0.5
DBP (mm Hg)			
Tamsulosin	74.7/99.0	−0.3/−5.0	+2.0/−4.7
Placebo	73.0/93.5	−0.5/−0.5	−4.0/0.0
Atenolol			
SBP (mm Hg)			
Tamsulosin	117.0/150.5‡	−2.7/−8.5	−8.0/−5.7
Placebo	124.5/161.0	−3.0/−6.0	−11.5/−4.7
DBP (mm Hg)			
Tamsulosin	77.5/96.7	−4.0/−4.7	−4.7/−5.5
Placebo	77.5/96.0	−2.0/−2.0	−6.0/−1.5

Lowe, Clin Ther 1997

Έλεγχος παρασυμπαθητικού τόνου

- Καρδιακή συχνότητα στην ηρεμία
- Καρδιακή συχνότητα κατά την επαναφορά
- Μεταβλητότητα καρδιακής συχνότητας
- Ευαισθησία τασεο-αντανακλαστικού

Χολινεργικοί υποδοχείς στην καρδιά

- M1, M2, M3, M5
- Ρύθμιση καρδιακής συχνότητας: M2 υποδοχείς
- M1, M3, M5 χωρίς λειτουργική σημασία
  - Φαρμακολογικές μελέτες
  - 'Σβήσιμο' γονιδίων σε πειραματόζωα

Comorbidities

Characteristics	OAB patients	Non-OAB patients	*P*
Total number of patients	41 440	77 272	
Women, %	83.6%	83.2%	0.040
Age, years (mean ± SD [median])	62.47 ± 13.46 (65)	61.46 ± 13.58 (64)	0.002
Age ≥ 65 years, %	53.57	49.74	<0.001
Clinical characteristics			
Baseline HR, beats/min (mean ± SD [median])	75.67 ± 11.15 (76)	75.11 ± 11.50 (74)	<0.001
Patients' HR, %			
61–70 beats/min	22.92	24.27	<0.001
71–80 beats/min	43.54	42.16	0.001
81–90 beats/min	16.31	15.11	<0.001
91–100 beats/min	6.25	5.87	0.028
Higher HR (≥80 beats/min)	31.36	19.62	<0.001
Baseline SBP (mean ± SD [median])	130.65 ± 18.25 (130)	129.57 ± 18.07 (130)	0.004
Baseline DBP (mean ± SD [median])	75.74 ± 10.34 (76)	75.33 ± 10.25 (76)	<0.001
BMI (mean ± SD [median]), kg/m^2	30.15 ± 7.31 (28.86)	29.07 ± 6.73 (27.93)	<0.001
Framingham risk score	9.93	9.62	<0.001

Asche, BJU International 2011

Διαφορές φύλου

Sex differences in vasopressin V_2 receptor expression and vasopressin-induced antidiuresis

Jun Liu,[2] Nikhil Sharma,[1] Wei Zheng,[2] Hong Ji,[2] Helen Tam,[1] Xie Wu,[2] Michaele B. Manigrasso,[1] Kathryn Sandberg,[2] and Joseph G. Verbalis[1]

[1]Division of Endocrinology and Metabolism and [2]Division of Nephrology and Hypertension, Department of Medicine, Georgetown University Medical Center, Washington, District of Columbia

Submitted 6 April 2010; accepted in final form 27 November 2010

Gender difference in antidiuretic response to desmopressin

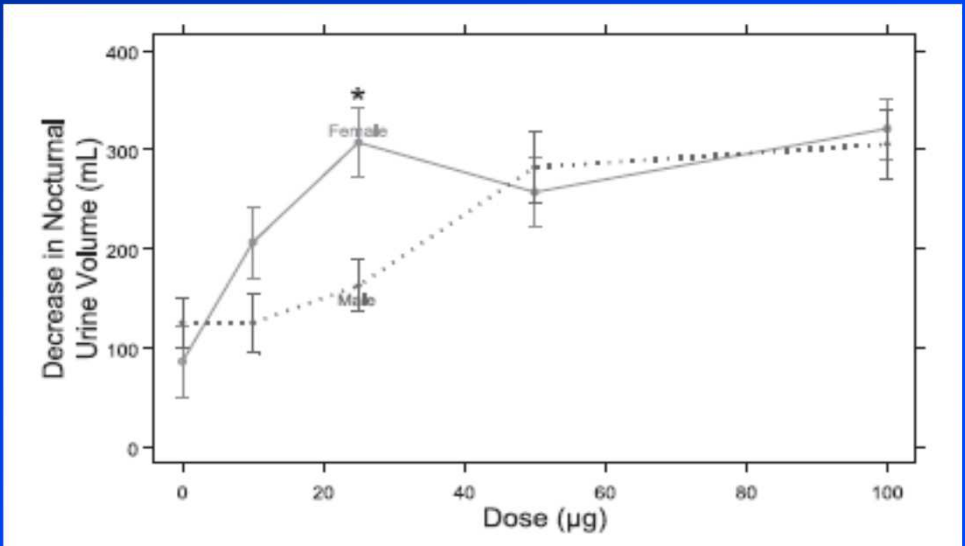
Kristian Vinter Juul, Bjarke Mirner Klein, Rikard Sandström, Lars Erichsen, and Jens Peter Nørgaard

Ferring Pharmaceuticals, Copenhagen S, Denmark

Submitted 27 December 2010; accepted in final form 25 February 2011

Doumas, Agria 2014

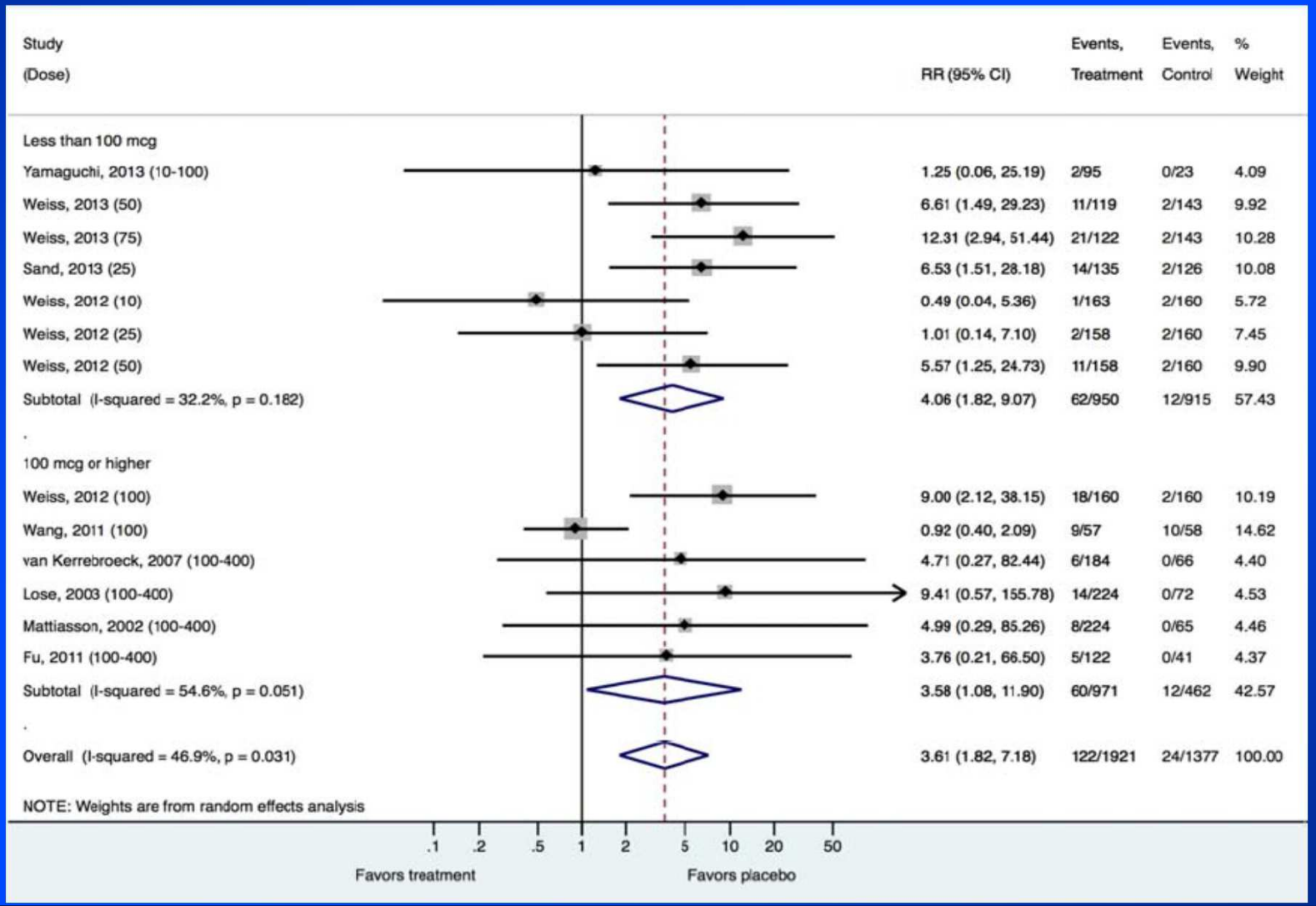
Διαφορές φύλου



Dose, µg	% of Maximum Effect (Men)	% of Maximum Effect (Women)	Change in Sodium, mmol/l: Women >50 yr old	Change in Sodium, mmol/l: Men >50 yr old
0	0 (-)	0 (-)	−0.48 (0.32)	0.31 (0.20)
10	19 (8)	38 (20)	−0.21 (0.35)	−0.57 (0.25)
25	37 (11)	61 (20)	−1.1 (0.31)	−0.51 (0.21)
50	54 (12)	76 (17)	−2.2 (0.40)	−0.89 (0.32)
100	70 (10)	86 (13)	−3.3 (0.50)	−1.7 (0.34)

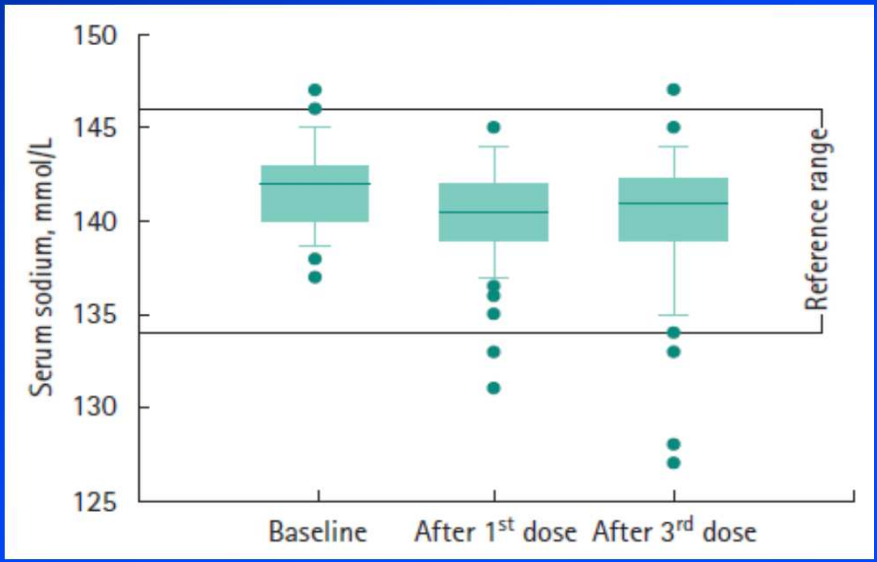
Vinter Juul, Am J Physiol Renal Physiol 2011

Συχνότητα
Μετα-ανάλυση



Ebell, J Urol 2014

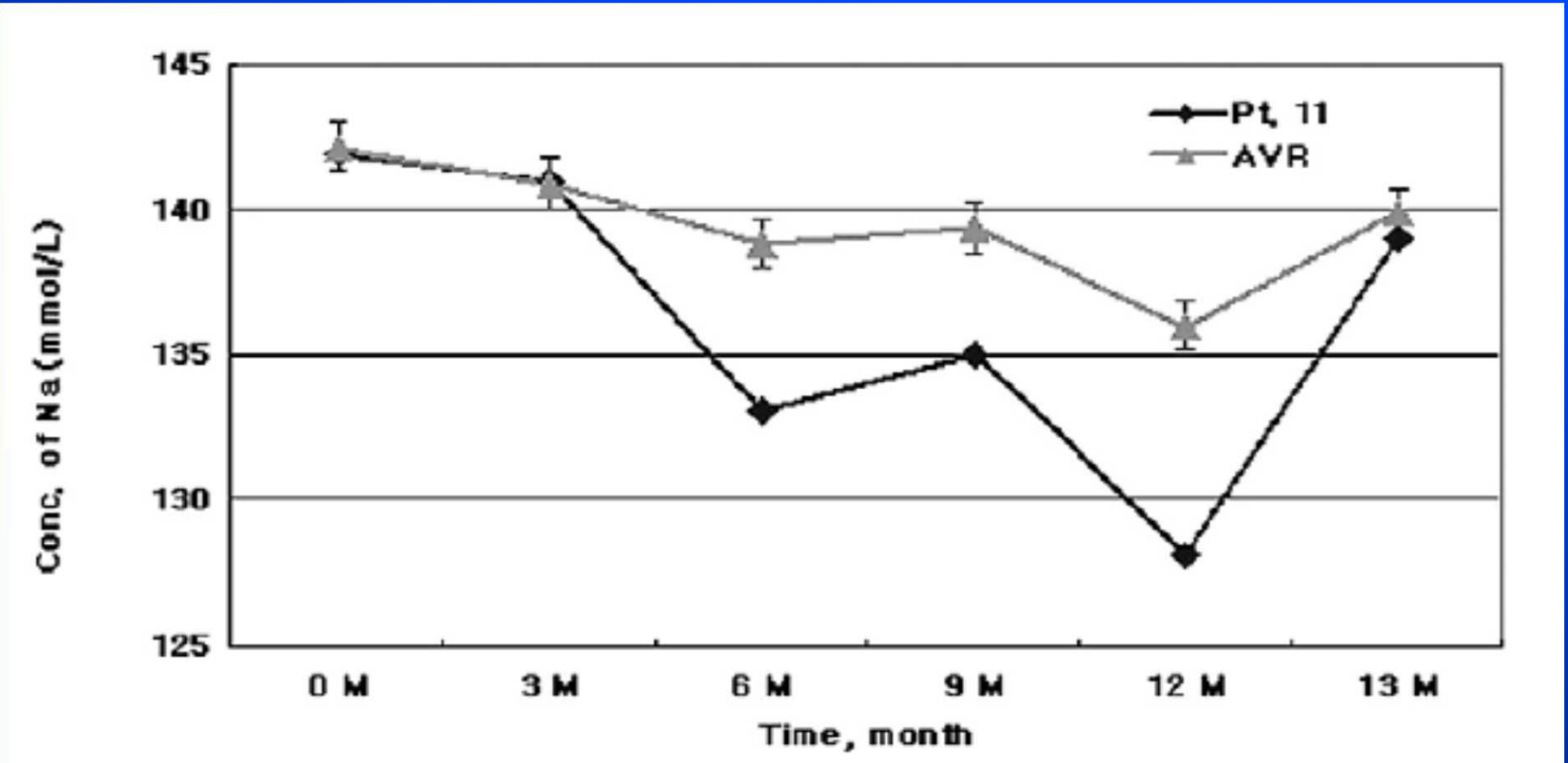
Oral – short term



Sex/age, years	Serum sodium (mmol/L) Baseline	After 1st dose	After 3rd dose
Sensitive to change in serum sodium			
F/82	146	141	135
F/79	142	137	135
M/89	144	139	134
M/77	143	139	136
M/79	140	136	128
M/79	137	133	127
Serum sodium below normal range			
M/79	140	139	133
M/73	138	131	135

Rembratt, BJU Intern 2003

Oral – long-term



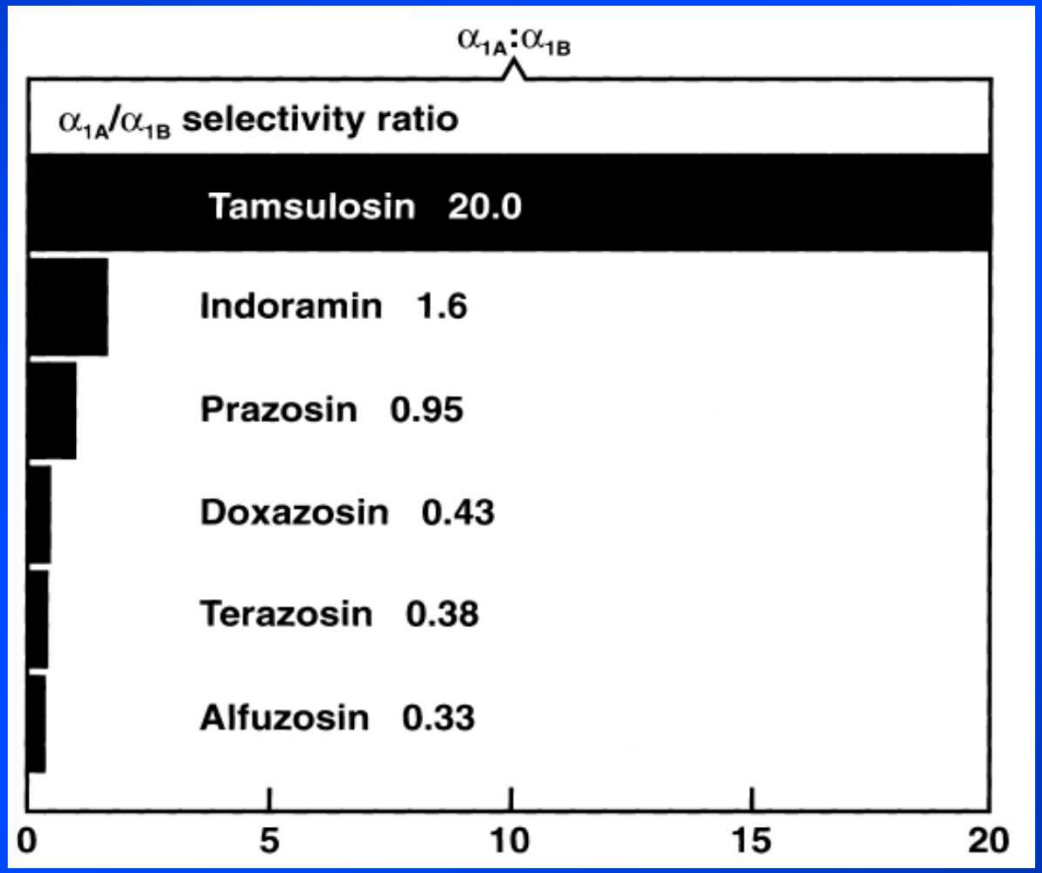
Bae, J Urol 2007

Έμφραγμα μυοκαρδίου και PDE-5 inh

	All Ages	Age <65 Years	Age ≥65 Years
Patients (N)	167,279†	141,512†	25,767†
Pre-prescription			
Cases	695	556	139
Rate per 1,000 PY (95%CI)	3.48 (3.02, 4.01)	3.22 (2.75, 3.77)	5.27 (3.81, 7.27)
Post-prescription			
Cases	152	119	33
Rate per 1,000 PY (95%CI)	3.75 (3.19, 4.40)	3.42 (2.76, 4.24)	6.06 (4.26, 8.63)
Rate Ratio (post/pre) (95%CI)	1.08 (0.93, 1.24)	1.06 (0.91, 1.24)	1.15 (0.83, 1.59)

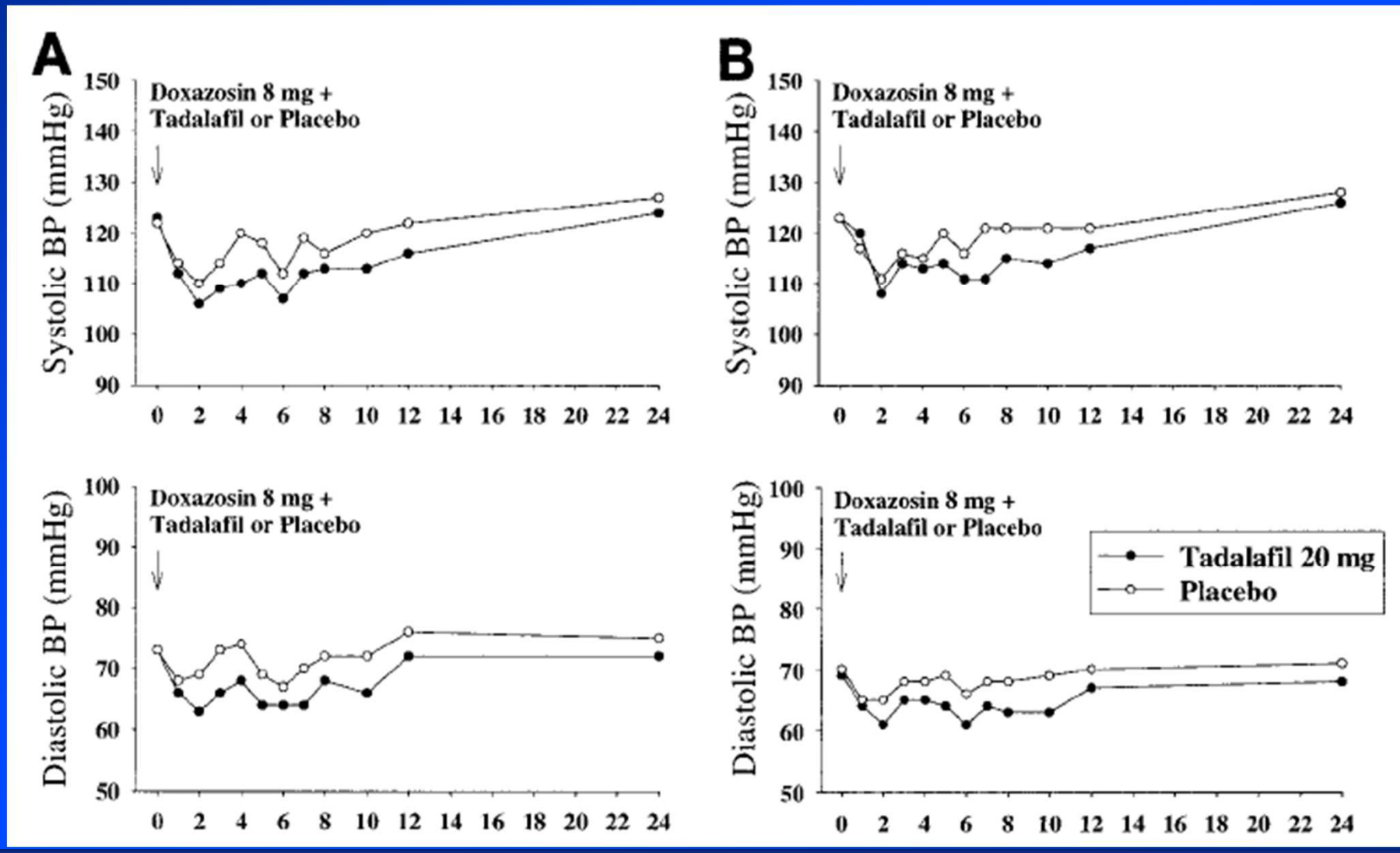
Finkle, PLos One 2014

Εκλεκτικότητα α-αποκλειστών



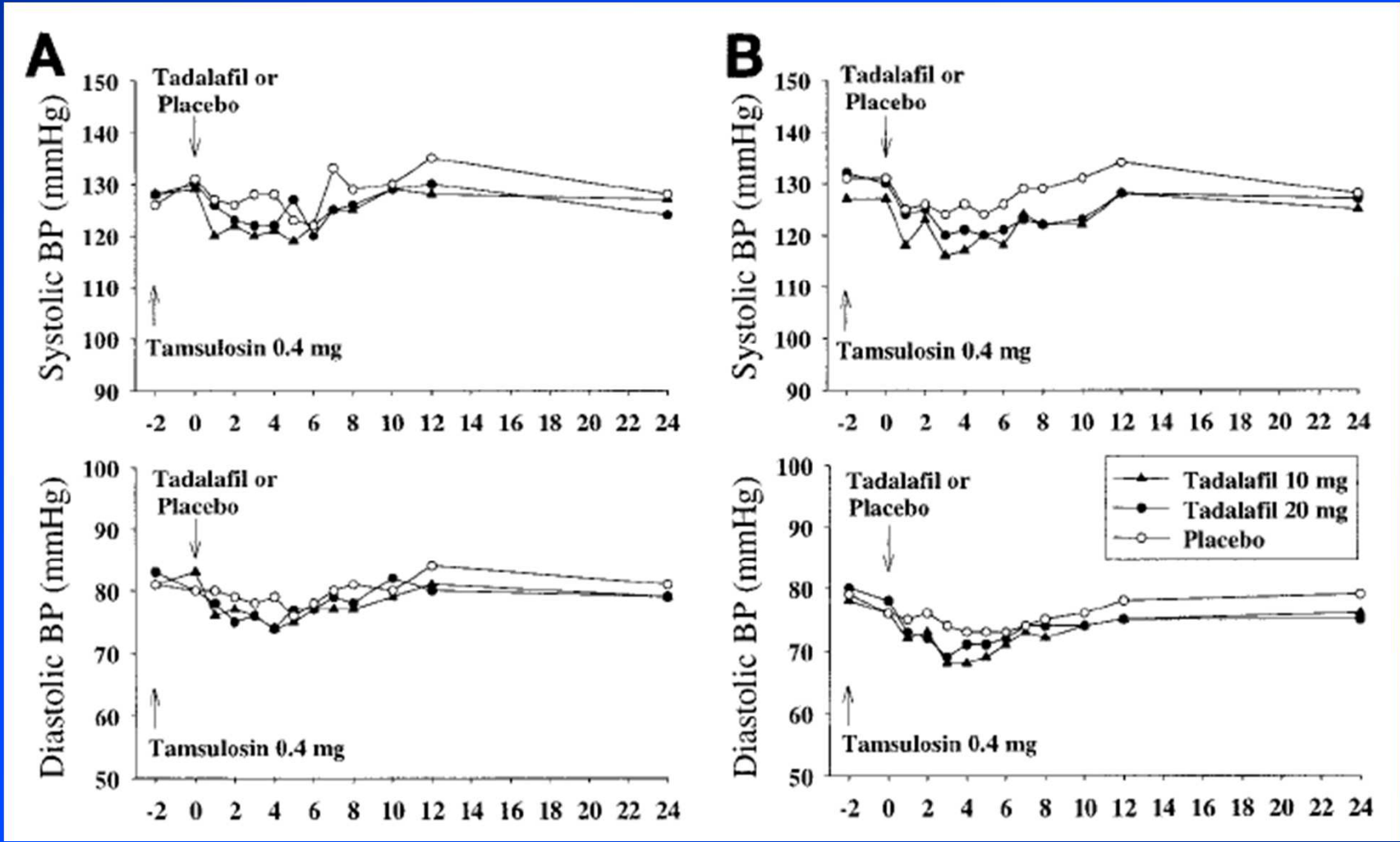
Doumas, Agria 2014

Συγχορήγηση PDE-5 με δοξαζοσίνη ΑΠ όρθια-ύπτια θέση



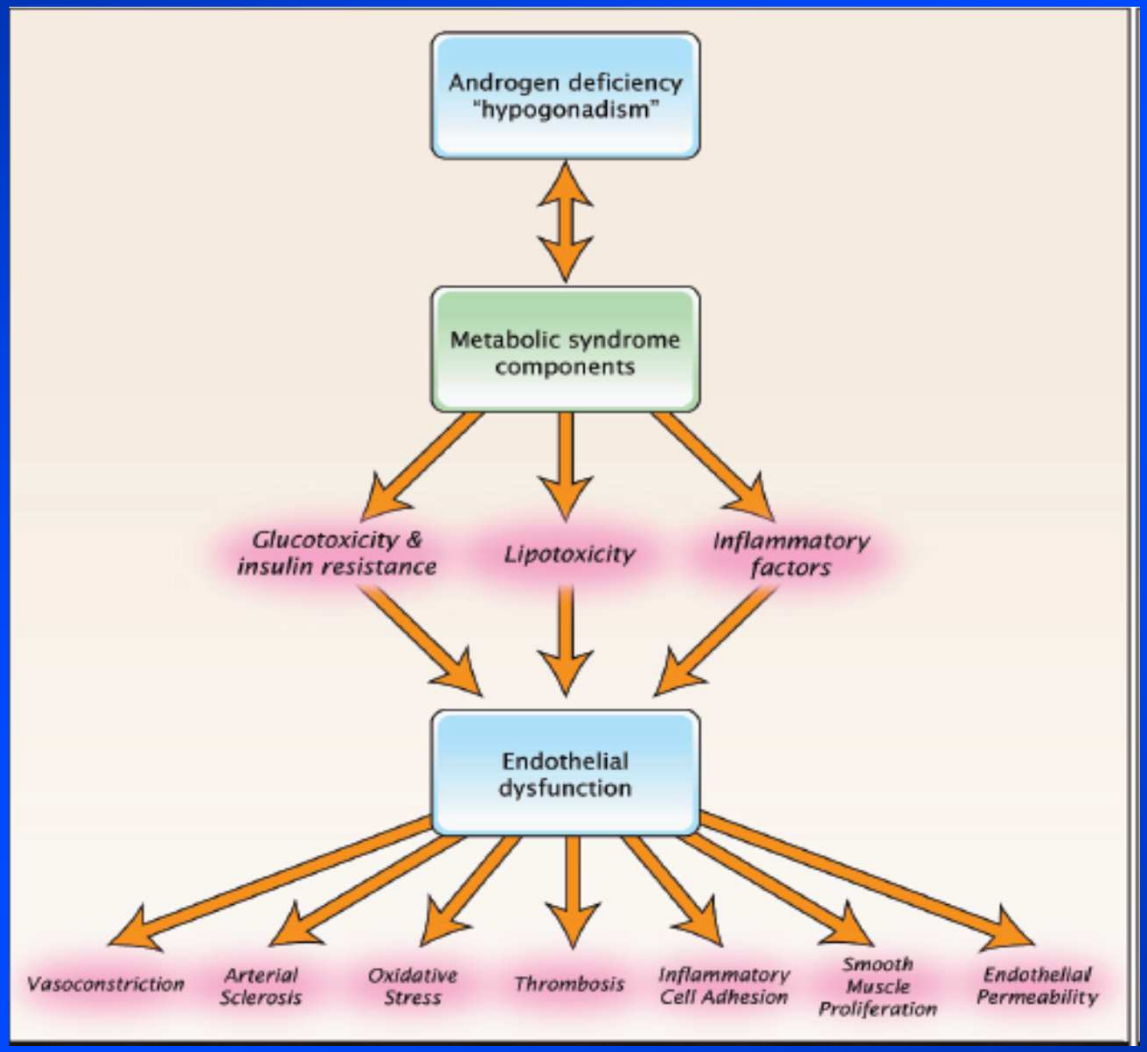
Kloner, J Urology 2004

Συγχορήγηση PDE-5 με ταμσουλοζίνη ΑΠ όρθια-ύπτια θέση



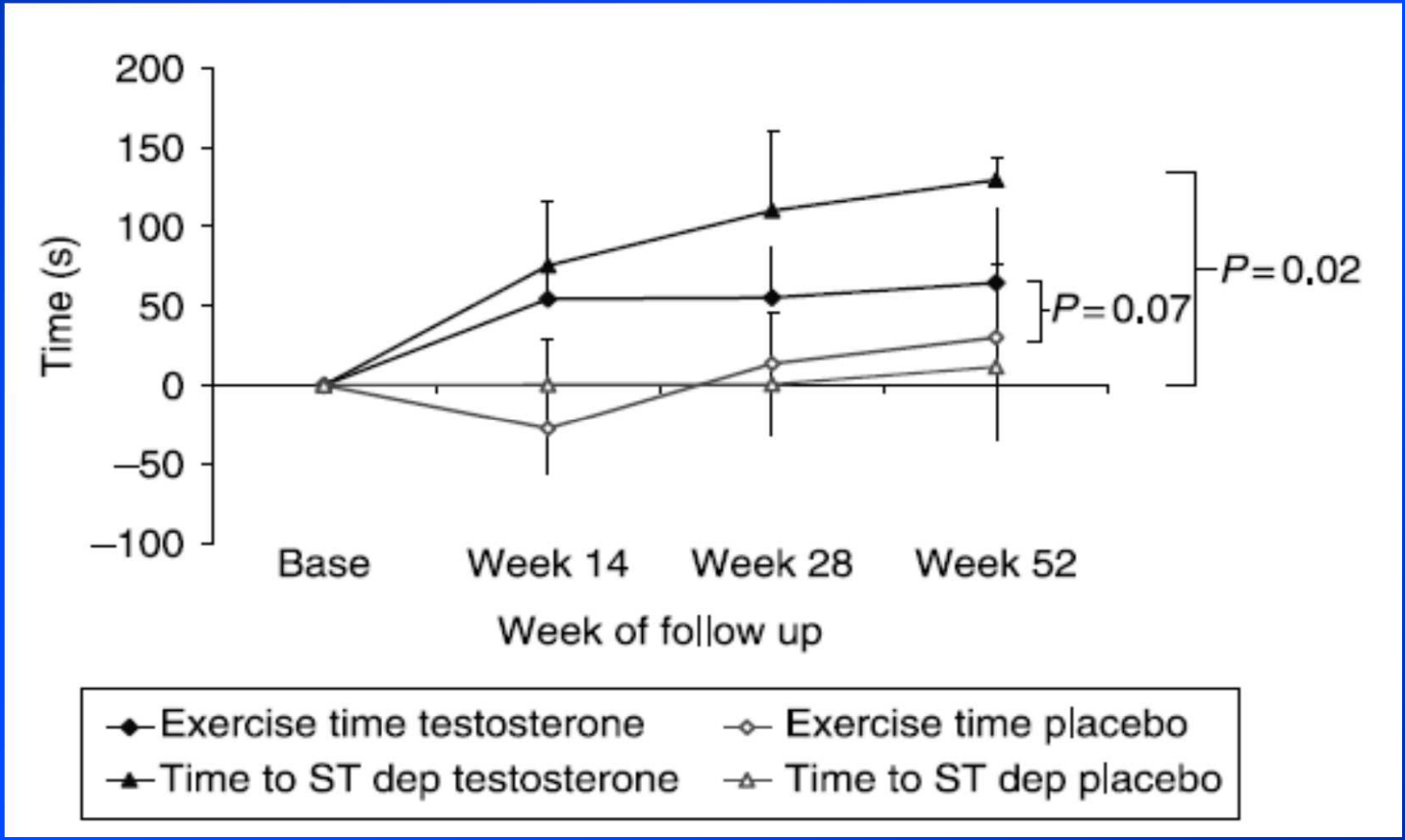
Kloner, J Urology 2004

Τεστοστερόνη και καρδιαγγειακός κίνδυνος
Μηχανισμός



Traish, J Androl 2009

Ικανότητα προς άσκηση
Ισχαιμία



Mathur, Eur J Endocrinol 2009

Θεραπεία υποκατάστασης και ΟΕΜ

	All Ages	Age <65 Years	Age ≥65 Years
Patients (N)	55,593	48,539	7,054
Pre-prescription			
Cases	193	156	37
Rate per 1,000 PY (95%CI)	3.48 (3.02, 4.01)	3.22 (2.75, 3.77)	5.27 (3.81, 7.27)
Post-prescription			
Cases	65	45	20
Rate per 1,000 PY (95%CI)	4.75 (3.72, 6.05)	3.76 (2.81, 5.04)	11.52 (7.43, 17.86)
Rate Ratio (post/pre) (95%CI)	1.36 (1.03, 1.81)	1.17 (0.84, 1.63)	2.19 (1.27, 3.77)

Finkle, PLos One 2014