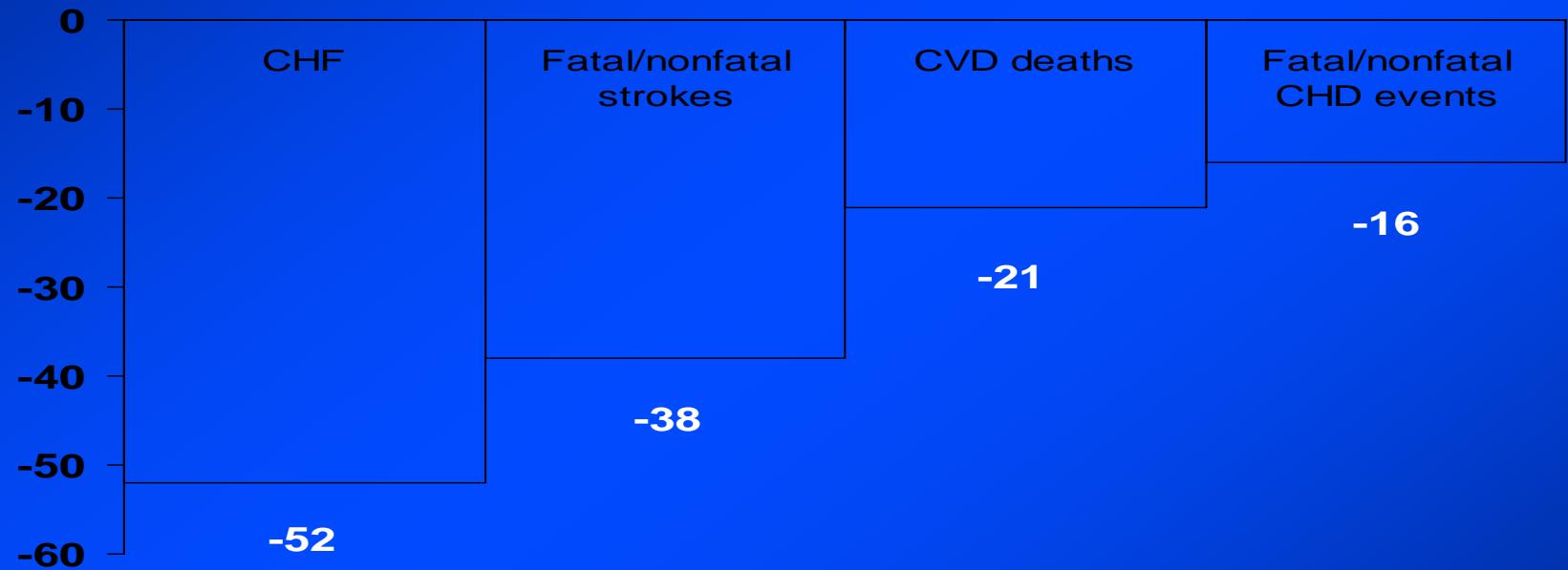


Δόκιμοι συνδυασμοί αντιυπερτασικών φαρμάκων

Μιχάλης Δούμας
Παθολόγος
Β'ΠΠ Κλινική ΑΠΘ

Οφέλη αντιπερτασικής θεραπείας



Ρύθμιση ΑΠ

248 μελέτες, 44 σχετικά ικανοποιητικές

Mean prevalence (standard deviation), expressed in %

Sex	Hypertension	Awareness	Treatment	Control ^a
All countries				
Men	37.8 (10.9)	46.2 (16.2)	29.2 (14.2)	31.9 (13.0)
Women	32.1 (10.6)	58.5 (16.2)	40.6 (16.2)	36.8 (14.0)
Developed				
Men	40.8 (9.8)	49.2 (15.9)	29.1 (14.6)	33.2 (13.6)
Women	33.0 (10.1)	61.7 (13.6)	40.6 (15.0)	38.4 (13.5)
Developing				
Men	32.2 (10.6)	40.6 (15.5)	29.2 (13.8)	29.6 (11.8)
Women	30.5 (11.5)	52.7 (19.1)	40.5 (18.7)	34.0 (14.8)

Ρύθμιση ΑΠ

248 μελέτες, 44 σχετικά ικανοποιητικές

Mean prevalence (standard deviation), expressed in %

Sex	Hypertension	Awareness	Treatment	Control ^a	Control ^b
All countries					
Men	37.8 (10.9)	46.2 (16.2)	29.2 (14.2)	31.9 (13.0)	10.5 (9.3)
Women	32.1 (10.6)	58.5 (16.2)	40.6 (16.2)	36.8 (14.0)	16.9 (12.0)
Developed					
Men	40.8 (9.8)	49.2 (15.9)	29.1 (14.6)	33.2 (13.6)	10.8 (9.7)
Women	33.0 (10.1)	61.7 (13.6)	40.6 (15.0)	38.4 (13.5)	17.3 (11.4)
Developing					
Men	32.2 (10.6)	40.6 (15.5)	29.2 (13.8)	29.6 (11.8)	9.8 (8.6)
Women	30.5 (11.5)	52.7 (19.1)	40.5 (18.7)	34.0 (14.8)	16.2 (13.2)

Ρύθμιση ΑΠ Copenhagen City Heart Study

Treatment of hypertension

- 1976-1978: 6.5%
- 2001-2004: 18.1%

Control of hypertension

- 1976-1978: 21% **1,4%**
- 2001-2004: 26% **4,7%**

Θάνατοι οφειλόμενοι σε υψηλή αρτηριακή πίεση

	Deaths			
	Stroke	Ischaemic heart disease	Hypertensive disease	Other cardiovascular disease
East Asia and Pacific	951	471	254	97
Europe and central Asia	709	1024	100	150
Latin America and the Caribbean	144	169	71	43
Middle East and north Africa	71	155	61	29
South Asia	449	711	62	75
Sub-Saharan Africa	179	148	50	52
Low-income and middle-income economies*	2502	2678	598	445
High-income economies	418	668	109	197
World†	2921	3346	706	642

7,6 εκατ.
ετησίως

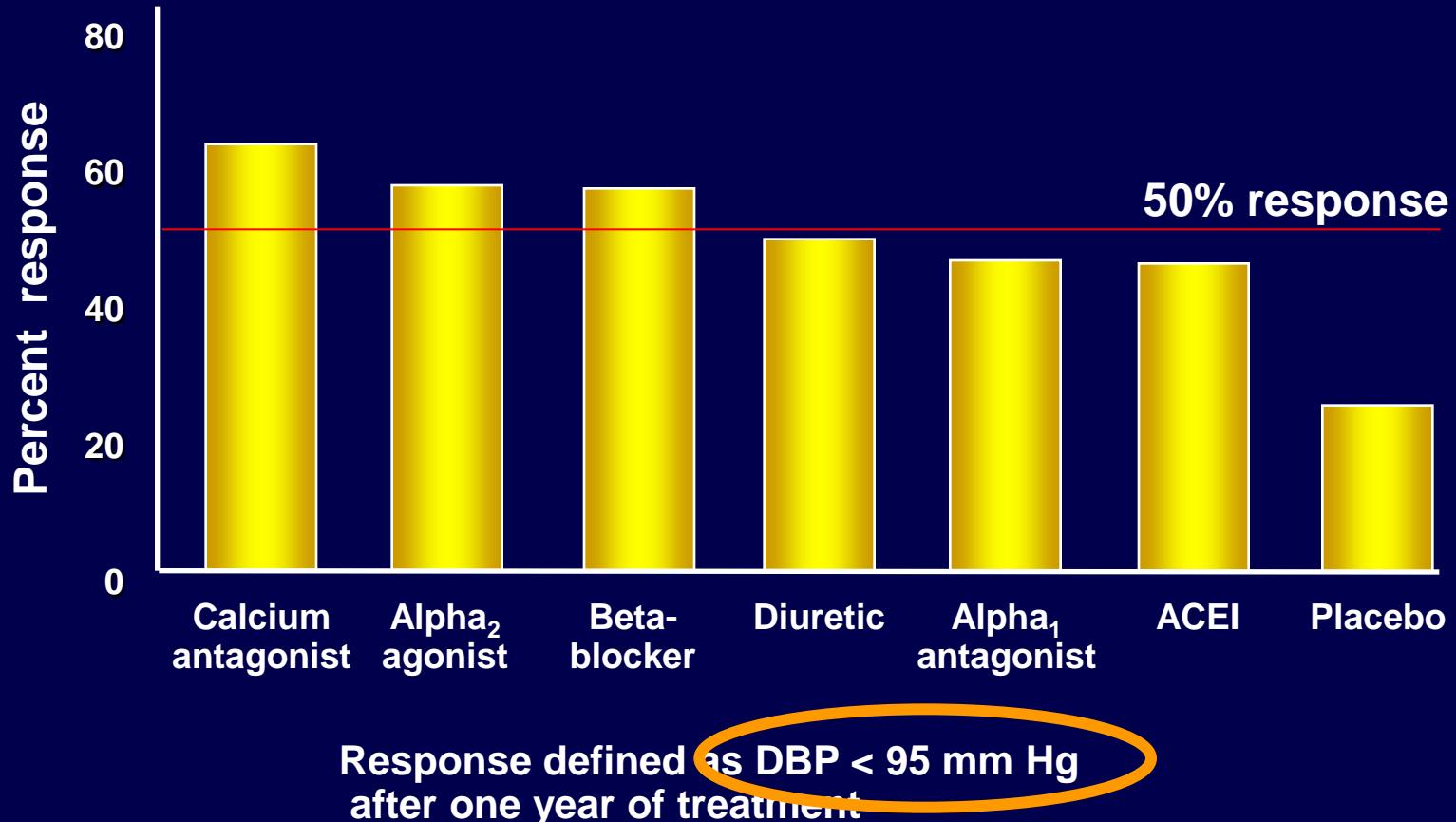
Τι μπορεί να ενθύνεται;

- Αδράνεια των ιατρών
- Εκτεταμένη χρήση μονοθεραπείας

“Clinical Inertia”

- **BP control:**
 - 40% had BP $\geq 160/90$ mm Hg
 - Only ~25% had BP $< 140/90$ mm Hg
- **Increases in therapy: only 6.7% of visits.**
- ***“Many physicians are not aggressive enough in their approach to hypertension.”***

Monotherapy in hypertension



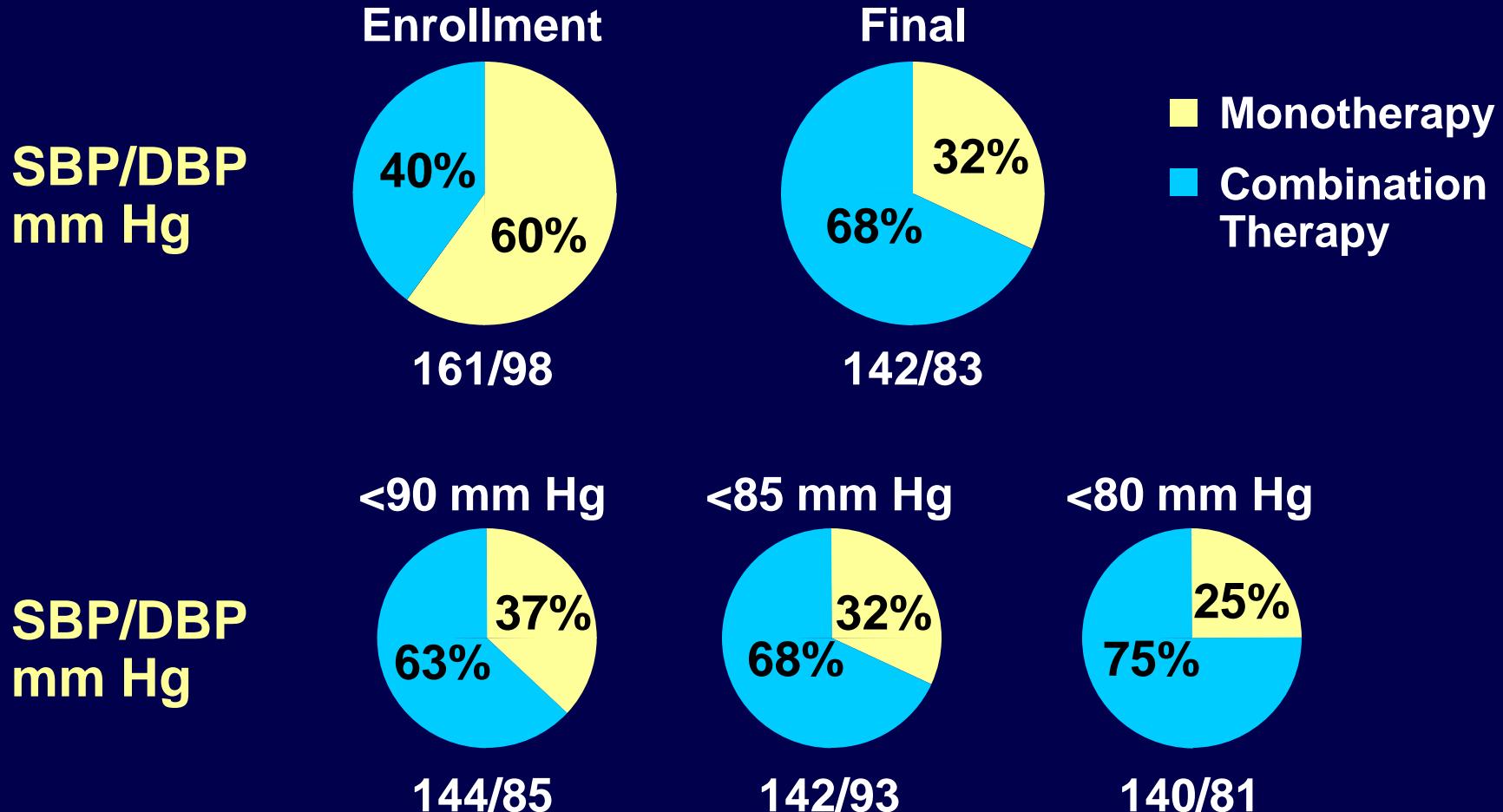
Materson et al. *Am J Hypertens.* 1993;8:189-192.

Monotherapy - doses

Table 2 Efficacy: average reductions* in blood pressure over 24 hours (treated minus placebo) according to category of drug and dose

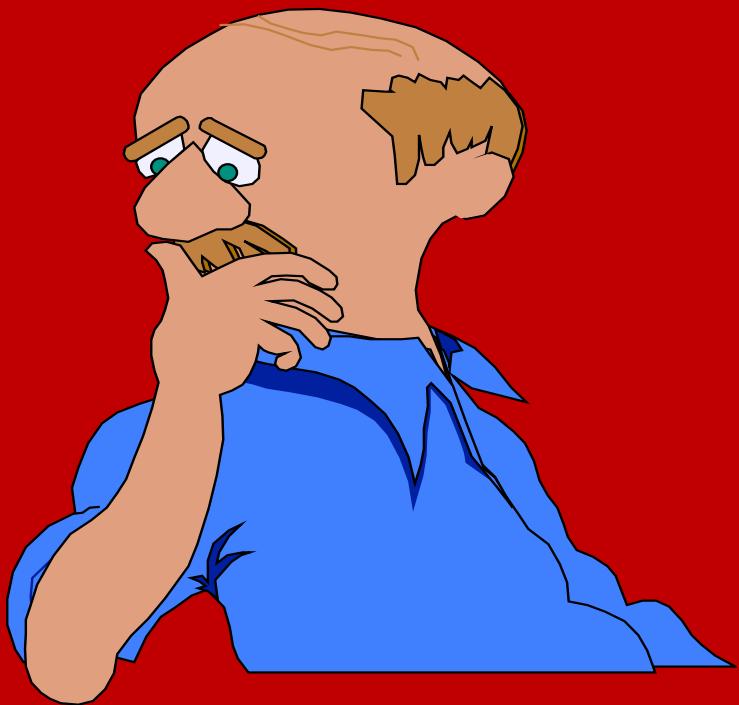
Category of drug	Fall in blood pressure (mm Hg) (95% CI)			Half standard v standard: proportional difference (%)
	Half standard dose	Standard dose	Twice standard dose	
Systolic blood pressure				
Category:				
Thiazides	 7,1mmHg	 9,1mmHg	 10,9mmHg	16
β blockers				20
ACE inhibitors				19
Angiotensin II receptor antagonists				24
Calcium channel blockers				33
All categories: average				22
Diastolic blood pressure				
Category:				
Thiazides	3.7 (3.2 to 4.2)	4.4 (4.0 to 4.8)	5.0 (4.4 to 5.7)	16
β blockers	5.6 (5.0 to 6.2)	6.7 (6.2 to 7.1)	7.8 (7.1 to 8.4)	16
ACE inhibitors	3.7 (3.2 to 4.2)	4.7 (4.4 to 5.0)	5.7 (5.4 to 6.0)	21
Angiotensin II receptor antagonists	4.5 (4.2 to 4.8)	5.7 (5.4 to 6.0)	6.5 (6.2 to 6.8)	21
Calcium channel blockers	3.9 (3.5 to 4.4)	5.9 (5.6 to 6.2)	7.9 (7.5 to 8.3)	34
All categories: average	4.4 (4.2 to 4.6)	5.5 (5.4 to 5.7)	6.5 (6.3 to 6.7)	20

Combination Therapy Needed to Achieve Target Blood Pressure



Adapted from Hansson L et al for the HOT Study Group. *Lancet.* 1998;351:1755-1762.

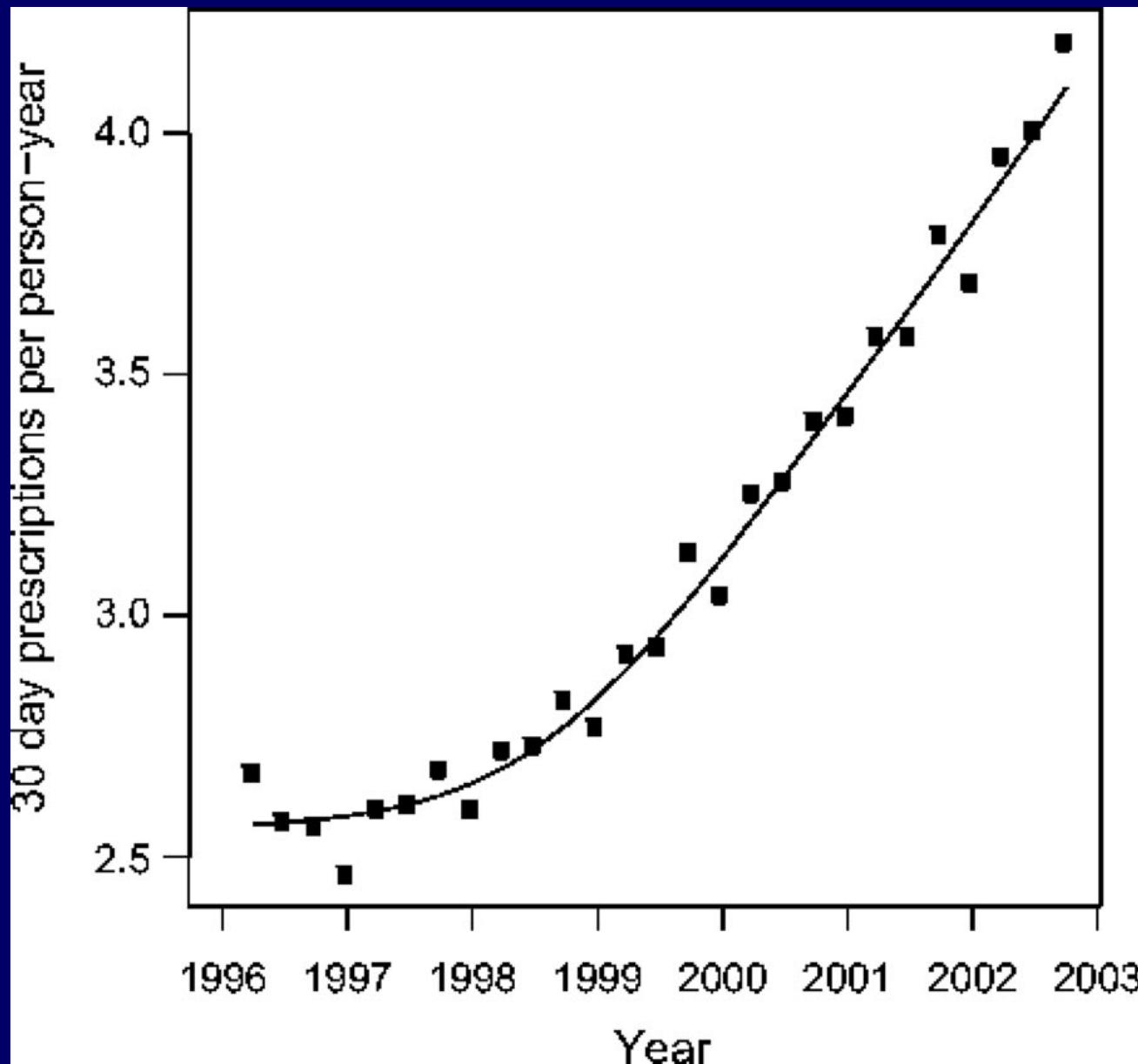
Ρύθμιση ΑΠ
Τι μπορούμε
να κάνουμε;



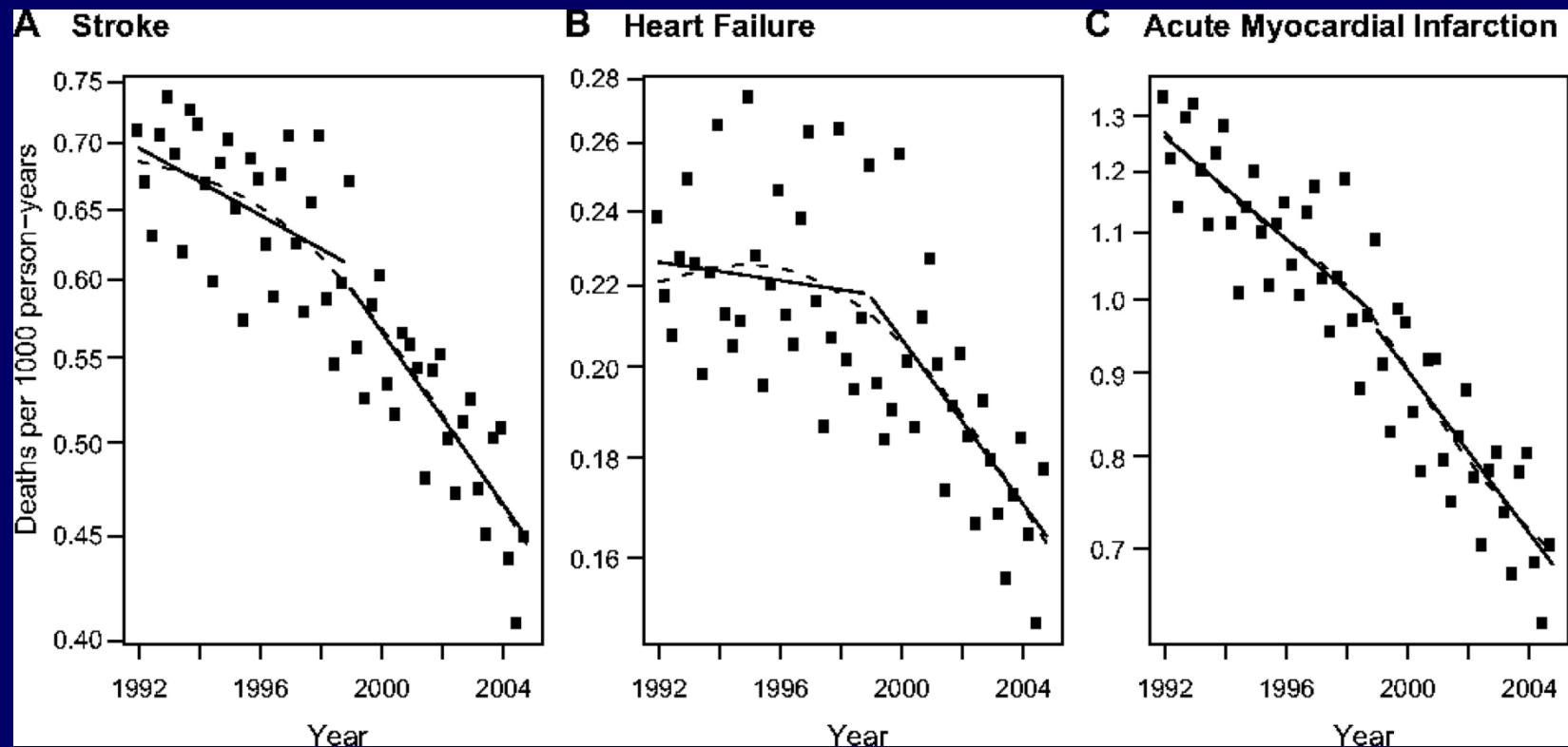
Μεγάλη Βρεττανία

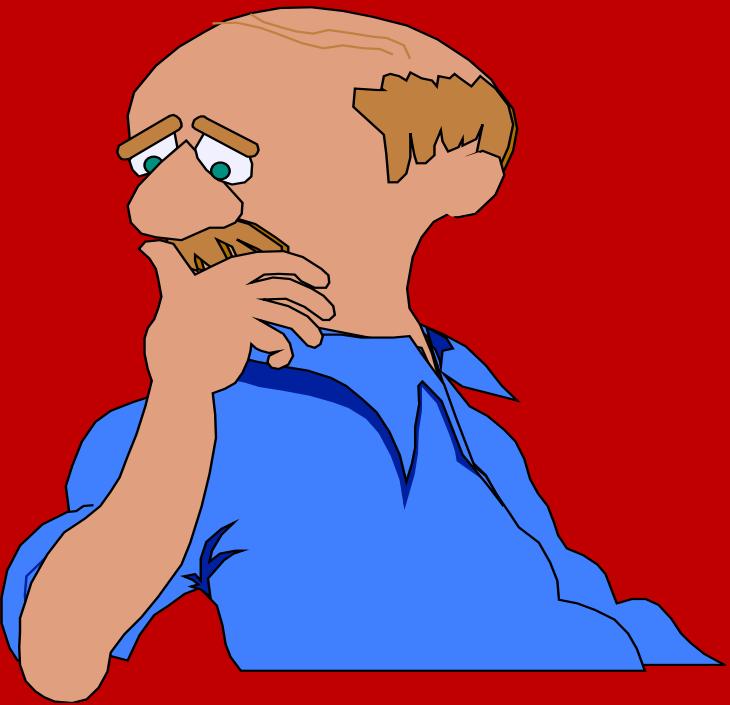
	1994	2003	2006
1 drug:	60%	44%	39%
2 drugs:	34%	38%	40%
≥3 drugs:	6%	18%	21%
Control rates:	6%	22%	28%

Kavdacs



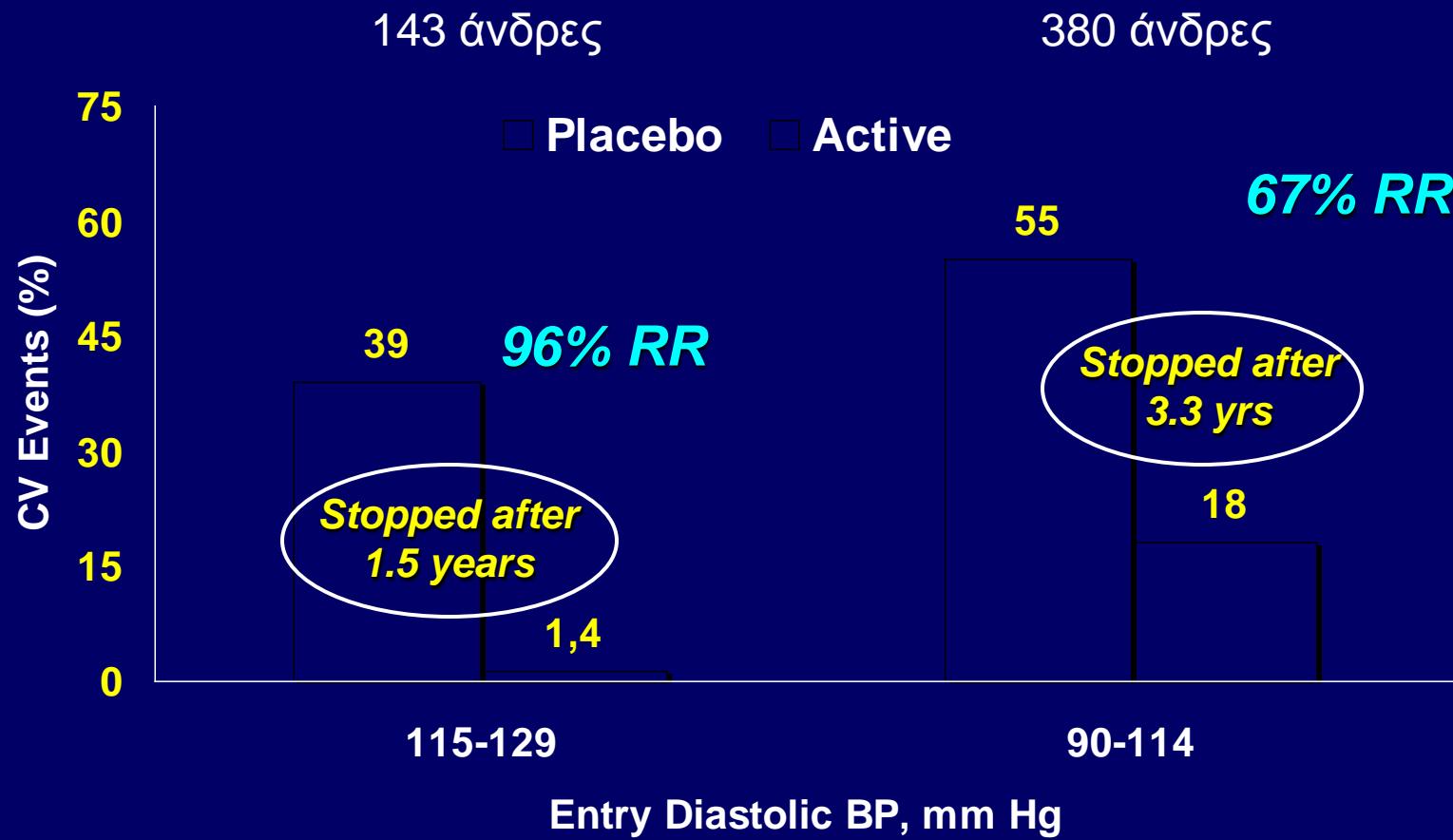
Kavadas





Συνδυασμένη θεραπεία

VA Cooperative Trials in Hypertension

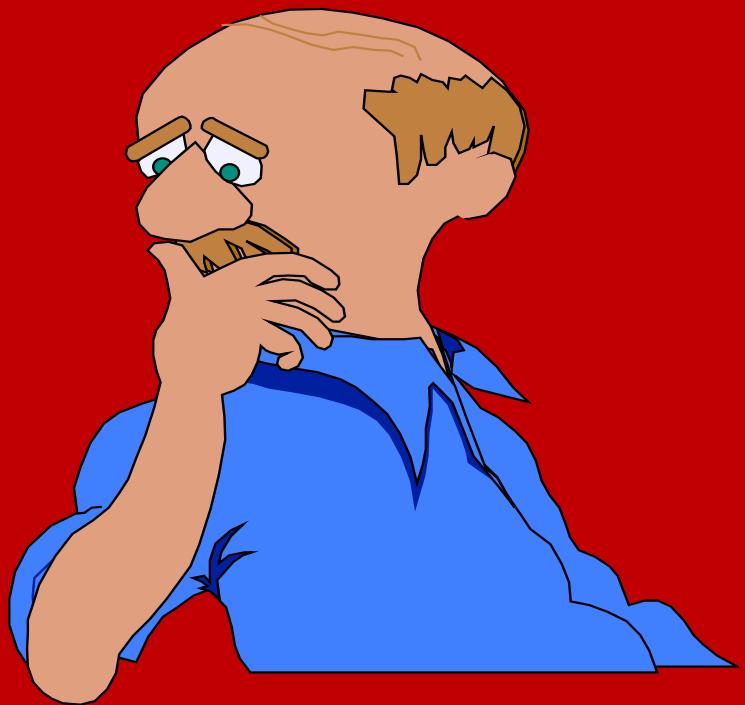


~~Blood pressure (BP) goal: DBP < 90 mm Hg~~

~~Therapy: HCTZ + reserpine + hydralazine~~

RR=risk reduction

JAMA 1967; 202(11):1028-1034
JAMA 1970; 213(7): 1143-1152



Πότε;;;
Ποιοι συνδυασμοί;;;
Ελεύθεροι ή
σταθεροί;;;

JNC VII & ESH/ESC 2003: Θεραπευτικές προσεγγίσεις

- Οι περισσότεροι ασθενείς με υπέρταση θα χρειαστούν 2 ή περισσότερα αντιυπερτασικά φάρμακα για τον έλεγχο της ΑΠ στις τιμές στόχο
- Σύμφωνα με την ΑΠ και την παρουσία ή απουσία άλλων ενδείξεων, η θεραπεία μπορεί να ξεκινήσει είτε με μονοθεραπεία ή με συνδυασμό 2 φαρμάκων
- Όταν η ΑΠ είναι $>20/10$ mm Hg πάνω από το στόχο, πρέπει κανείς να σκεφτεί τη χορήγηση συνδυασμού φαρμάκων, είτε σε ελεύθερο είτε σε σταθερό συνδυασμό.

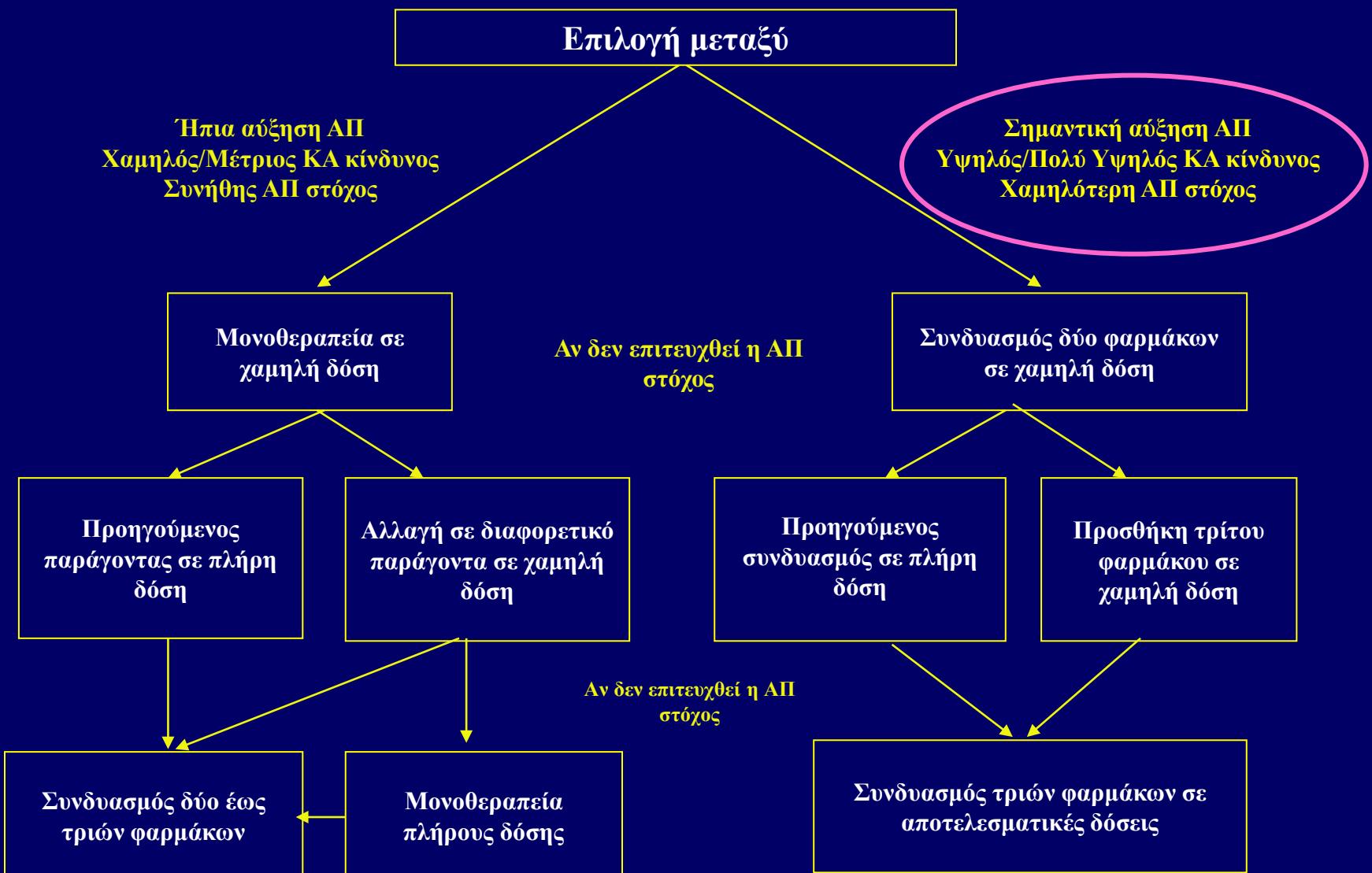
Combination Therapy in Hypertension

Alan H. Gradman, MD;¹ Jon N. Basile, MD;² Barry L. Carter, PharmD;³
George L. Bakris, MD;⁴ on behalf of the American Society of Hypertension
Writing Group

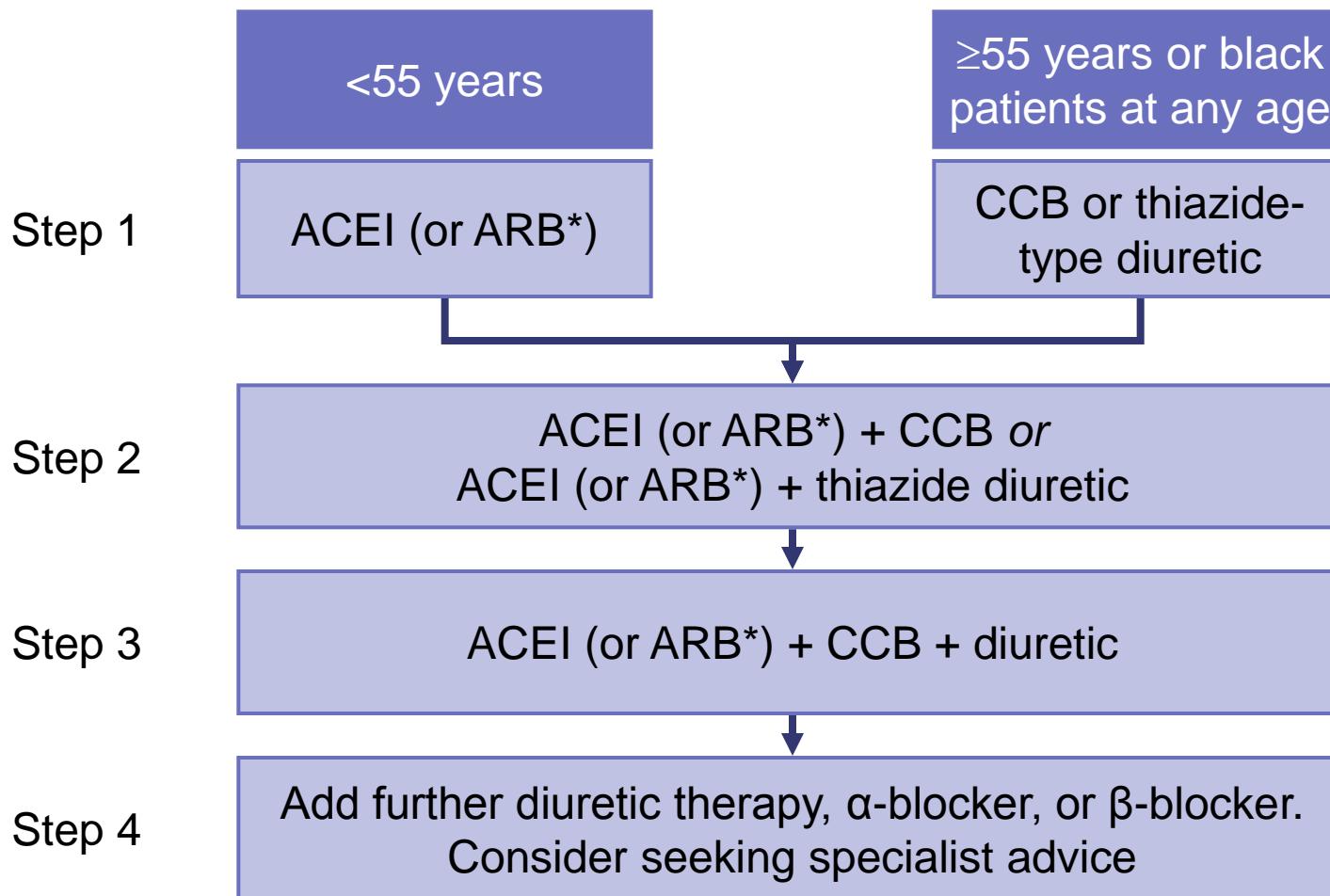
SUMMARY RECOMMENDATIONS

- Routinely use combination therapy to achieve BP targets
- Use only preferred or acceptable 2-drug combinations (Table)
- Routinely initiate combination therapy in patients who require $\geq 20/10$ -mm Hg BP reduction to achieve target BP
- Initiate combination therapy in stage 1 patients (at the physician's discretion), especially when the second agent will improve the side effect profile of initial therapy
- Use SPCs rather than separate individual agents in circumstances where convenience outweighs other considerations.

2007 ESC/ESH Guidelines: Θεραπευτική αγωγή

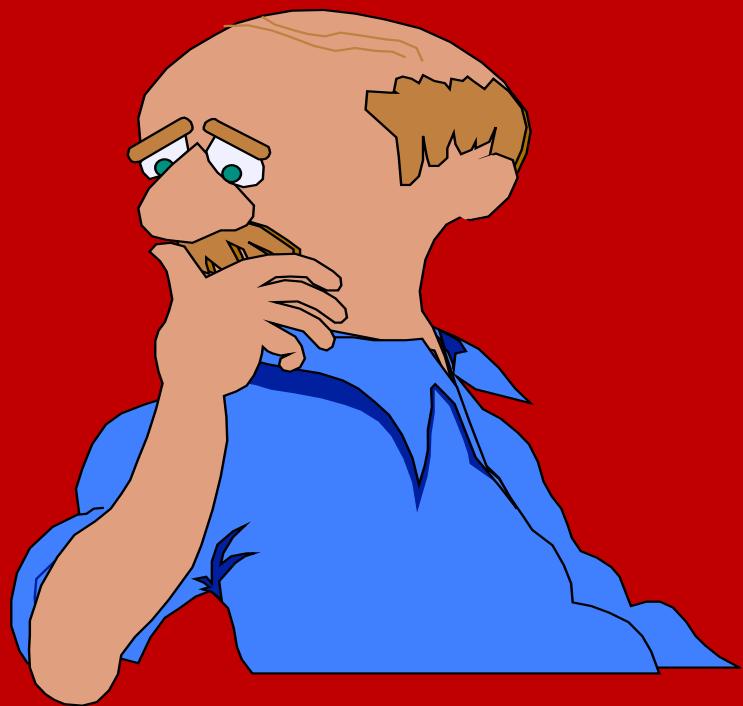


Updated UK NICE Guidelines for the Treatment of Newly Diagnosed Hypertension

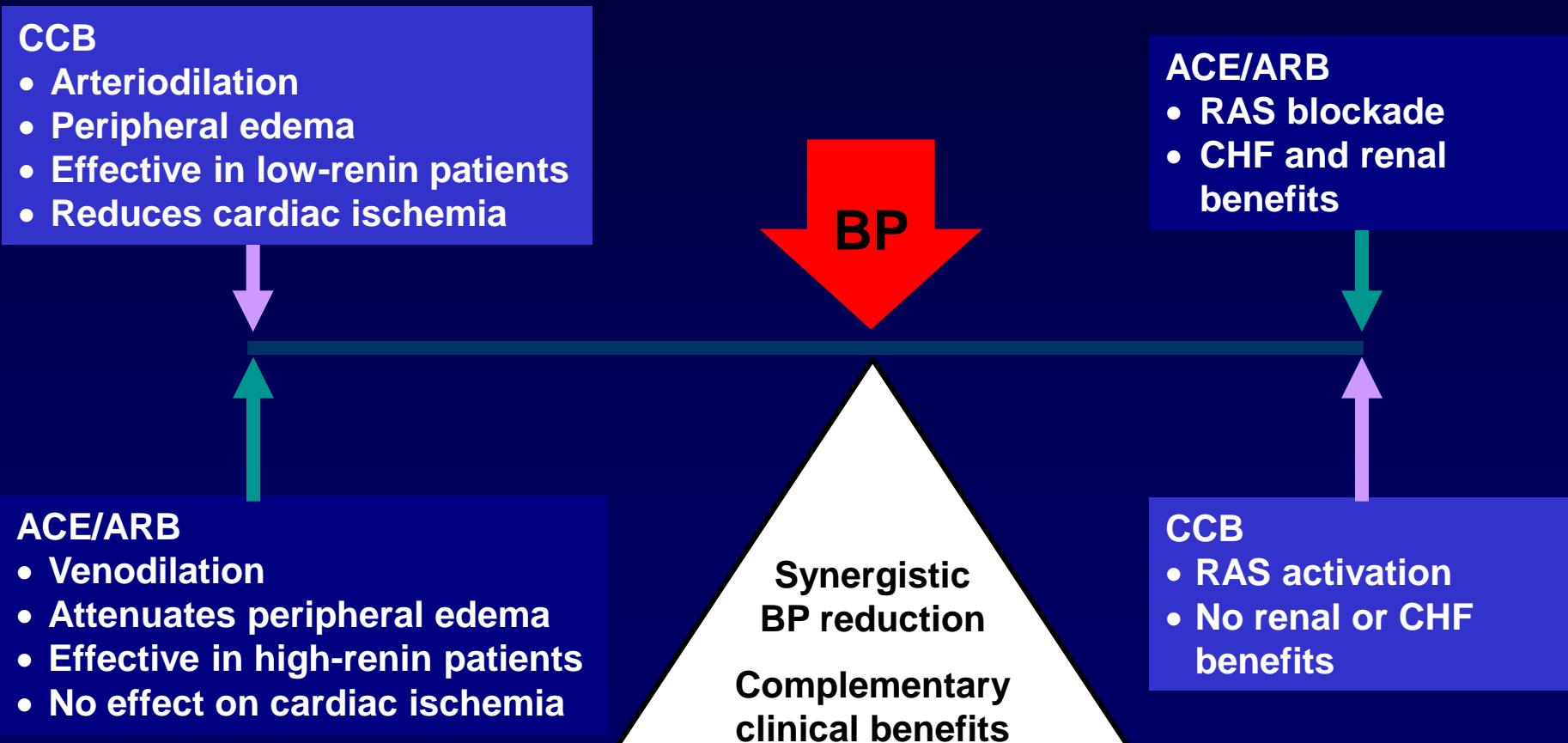


*If ACE inhibitor (ACEI) not tolerated

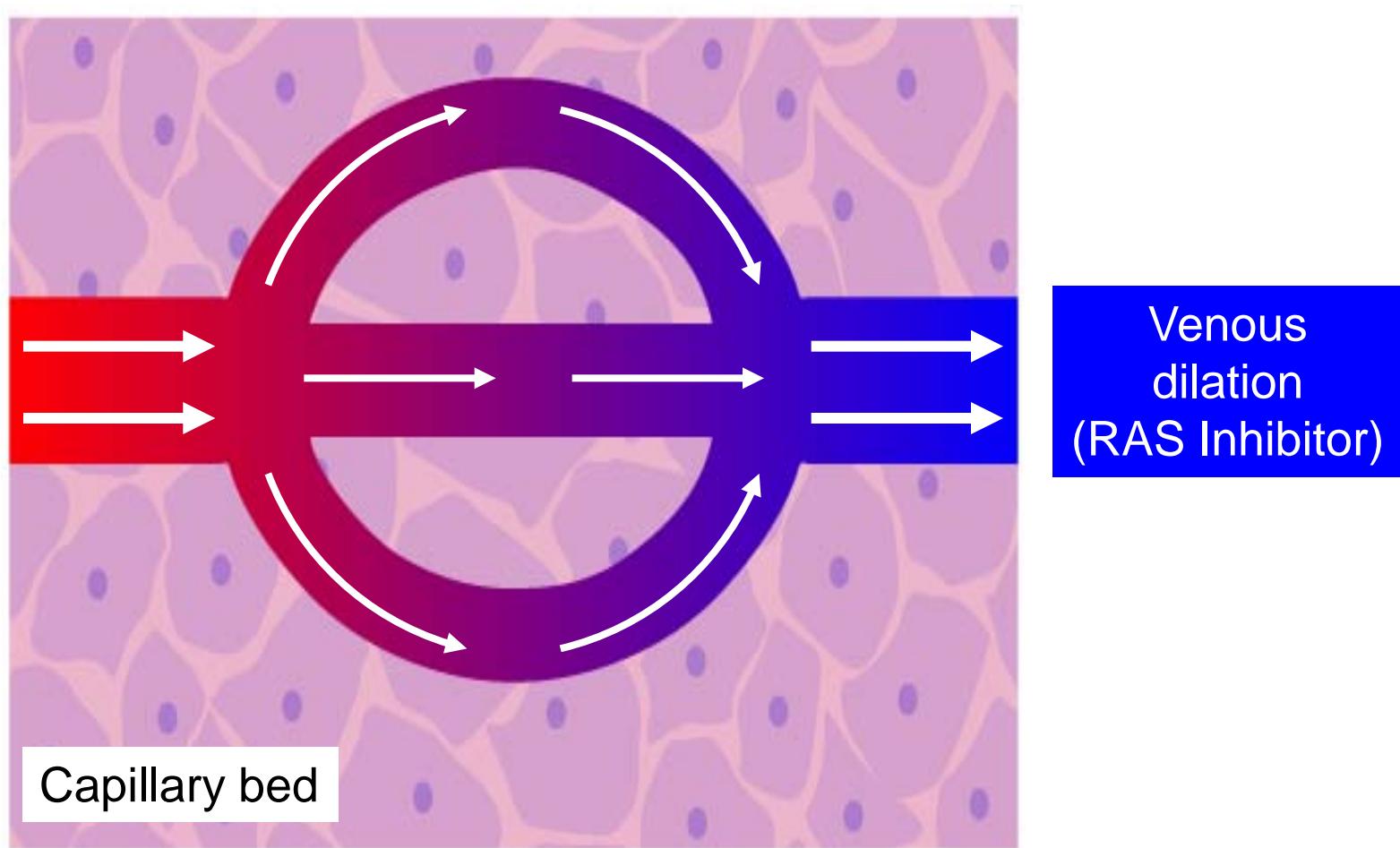
Ποιοι συνδυασμοί;;;



Λογική του συνδυασμού ανταγωνιστή Ca με αMEA ή ARB

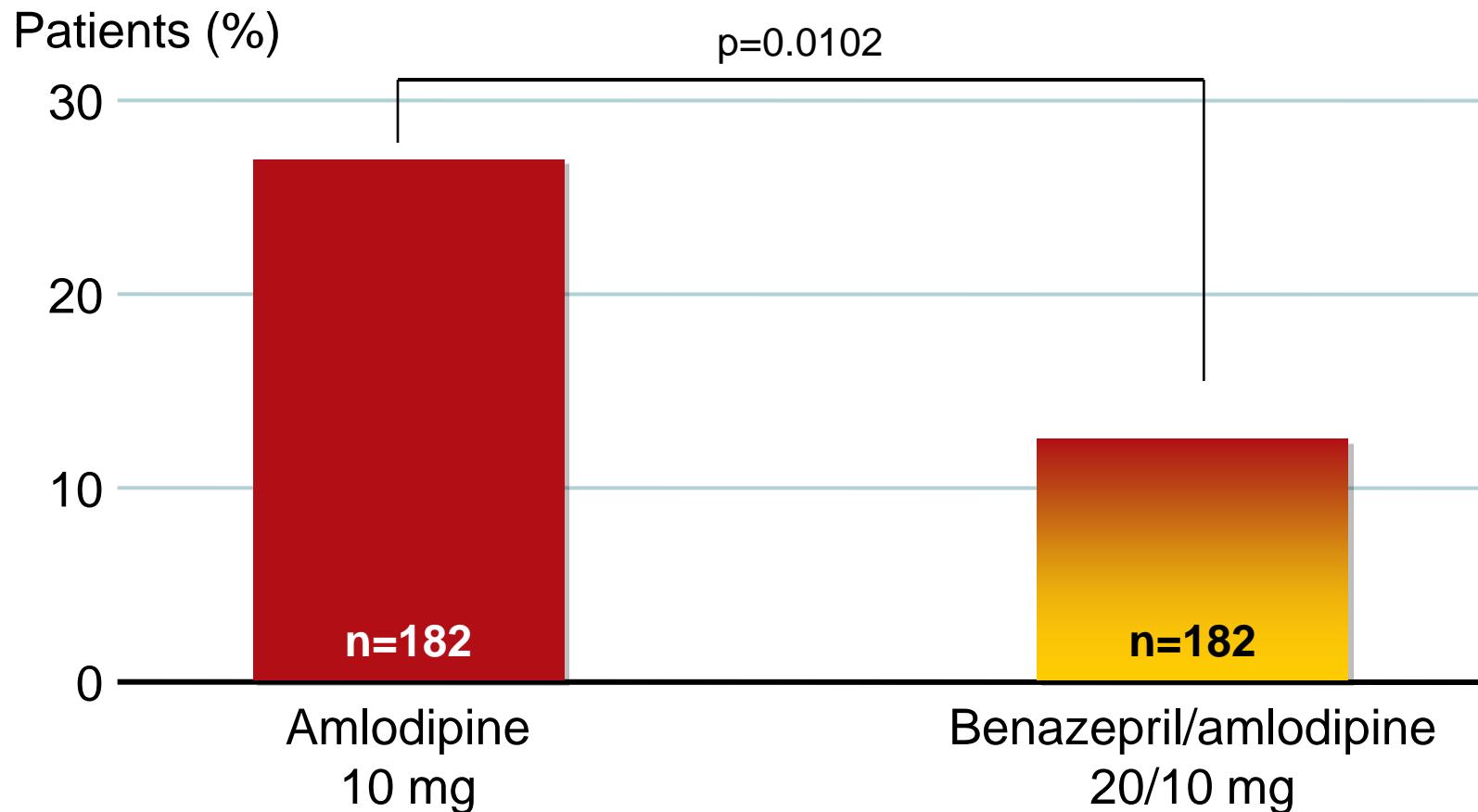


Complementary Effects of a CCB/RAS Inhibitor: Reduction of CCB-associated Edema



Opie. In: Opie LH, editor. Drugs for the Heart. 3rd ed. 1991:42–73
White et al. Clin Pharmacol Ther 1986;39:43–8; Gustaffson. J Cardiovasc Pharmacol 1987;10(Suppl. 1):S121–31; Messerli et al. Am J Cardiol 2000;86:1182–7

Attenuation of Peripheral Edema with Dual ACE Inhibitor/CCB Therapy Compared with CCB Monotherapy: Stage 2 Hypertension

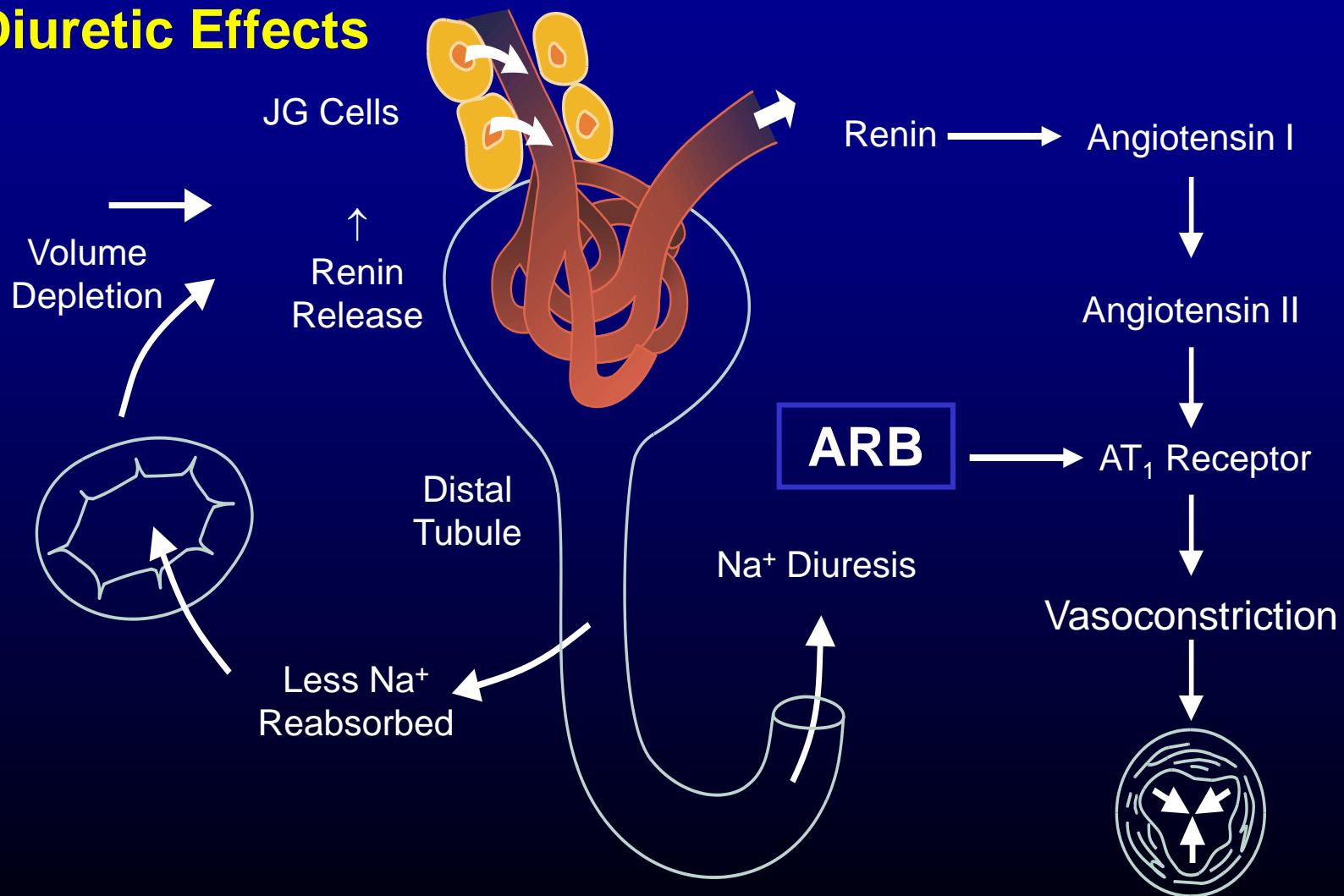


Adverse events reported at an incidence of $\geq 5\%$ in the safety population

Jamerson et al. Am J Hypertens 2004;17:495–501

Λογική του συνδυασμού αMEA ή ARB με διουρητικό

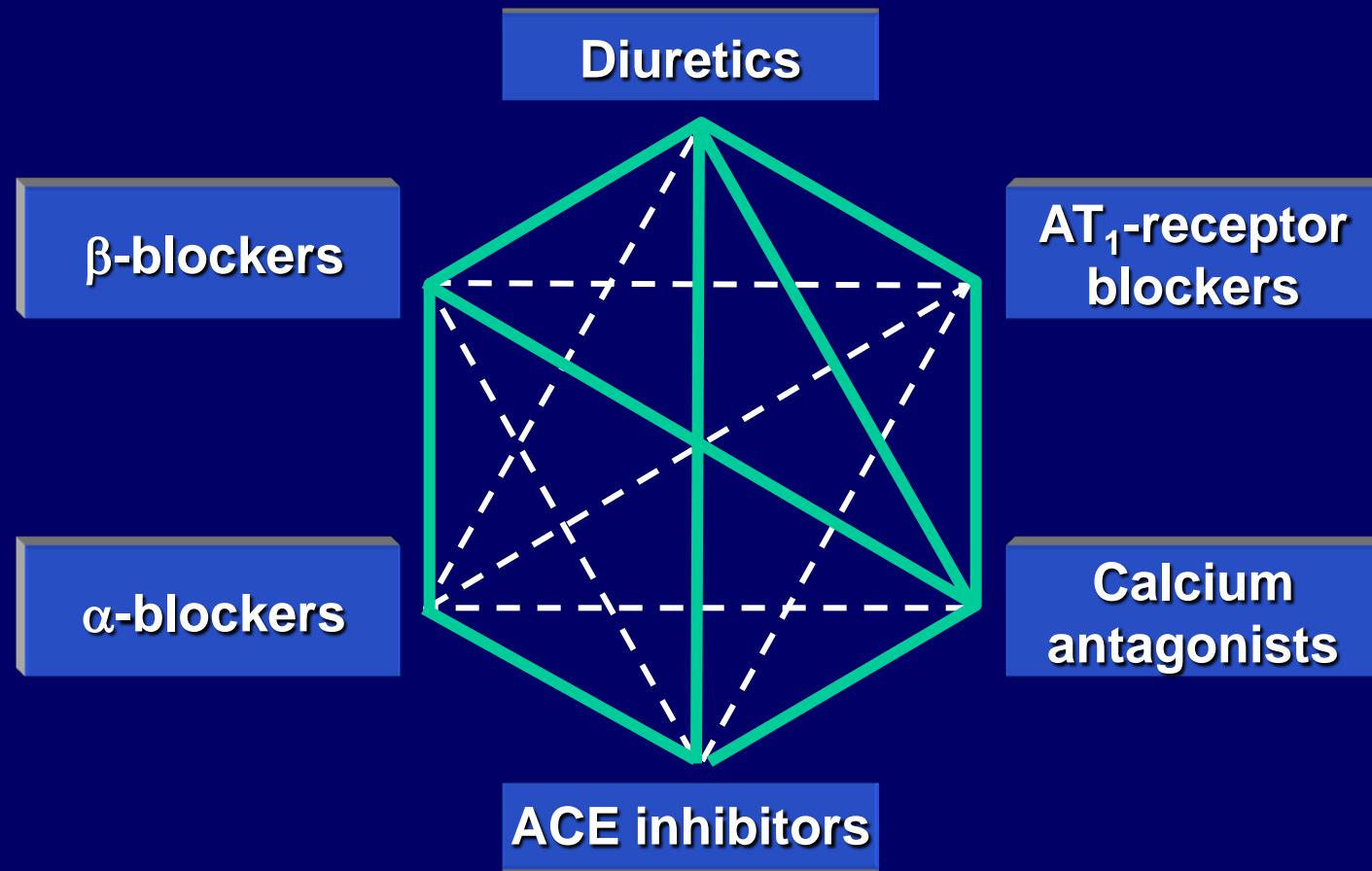
Diuretic Effects





ESH 2003: Possible Combinations of Different Classes of Antihypertensive Agents

The most rational combinations are represented as thick lines

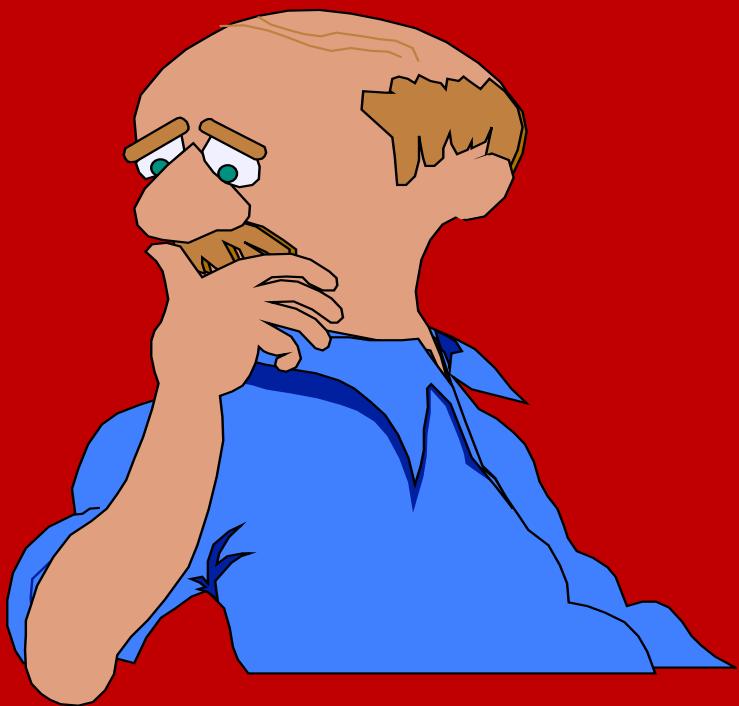


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Table. Drug Combinations in Hypertension:
Recommendations

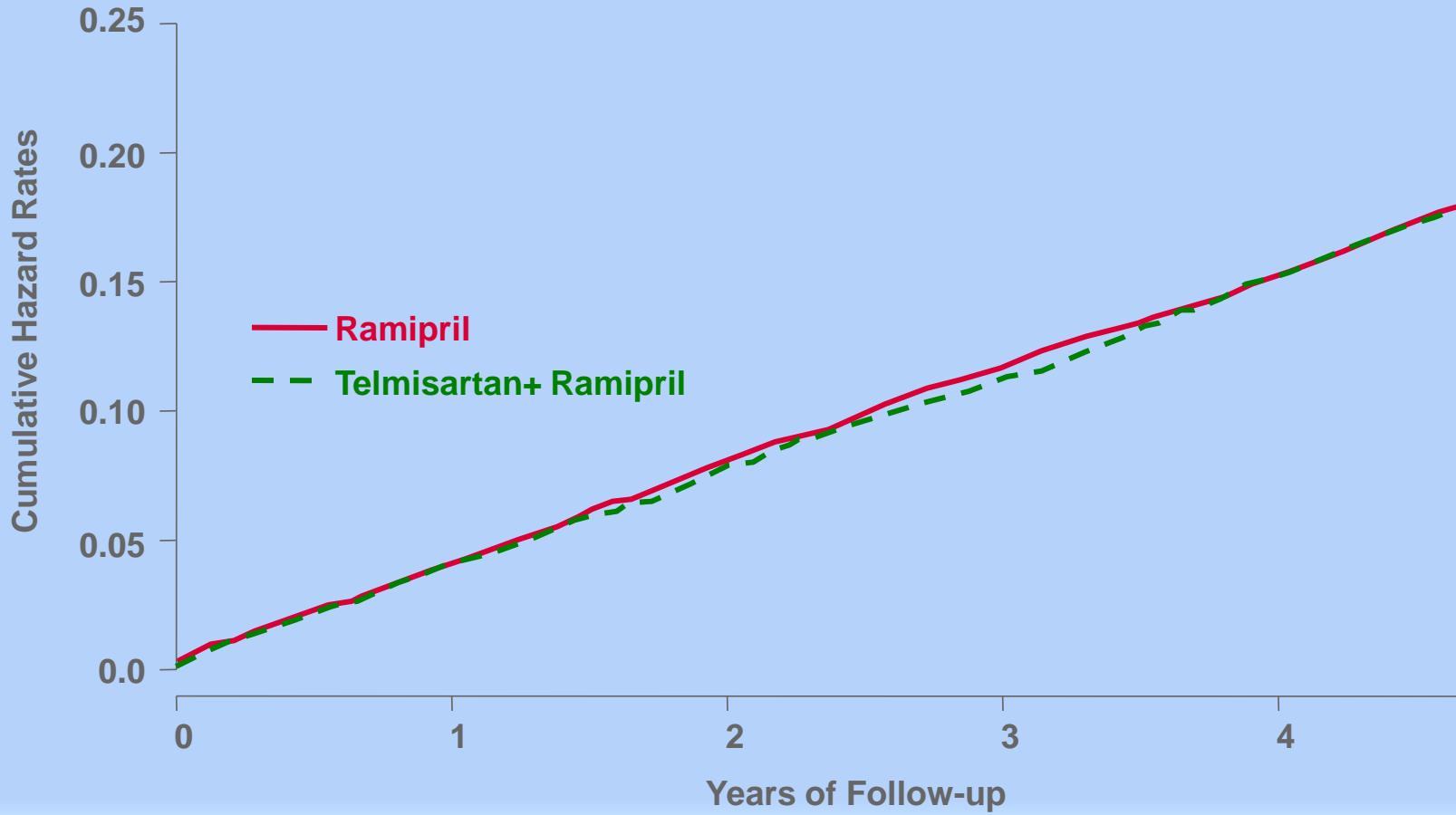
Preferred
ACE inhibitor/diuretic ^a
ARB/diuretic ^a
ACE inhibitor/CCB ^a
ARB/CCB ^a
Acceptable
β-Blocker/diuretic ^a
CCB (dihydropyridine)/β-blocker
CCB/diuretic
Renin inhibitor/diuretic ^a
Renin inhibitor/ARB ^a
Thiazide diuretics/K ⁺ -sparing diuretics ^a
Less effective
ACE inhibitor/ARB
ACE inhibitor/β-blocker
ARB/β-blocker
CCB (nondihydropyridine)/β-blocker
Centrally acting agent/β-blocker



Evidence Based Medicine

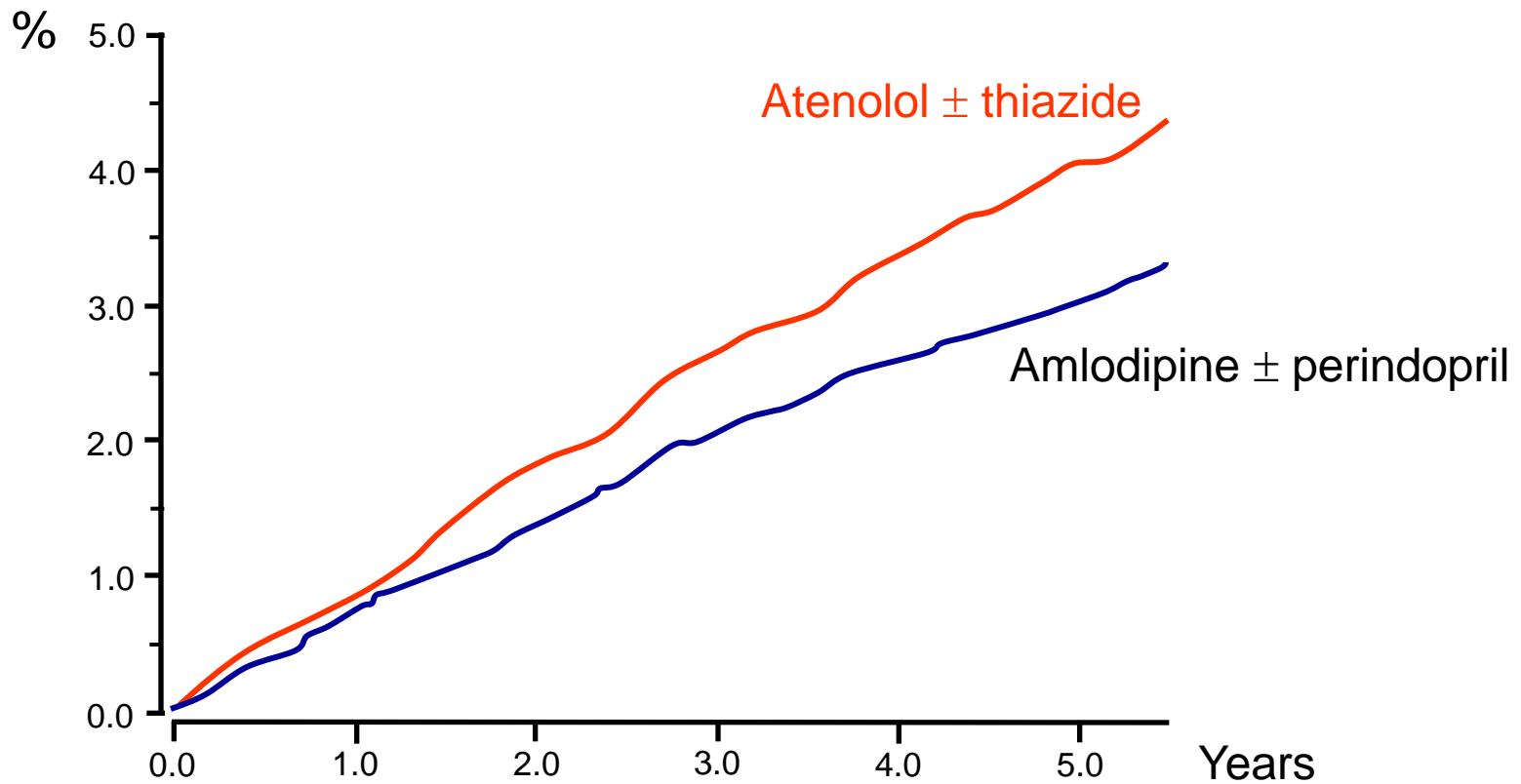
α -MEA+ARBs έναντι α -MEA

# at Risk	Yr 1	Yr 2	Yr 3	Yr 4
R 8576	8214	7832	7473	7095
T & R 8502	8134	7740	7377	7023

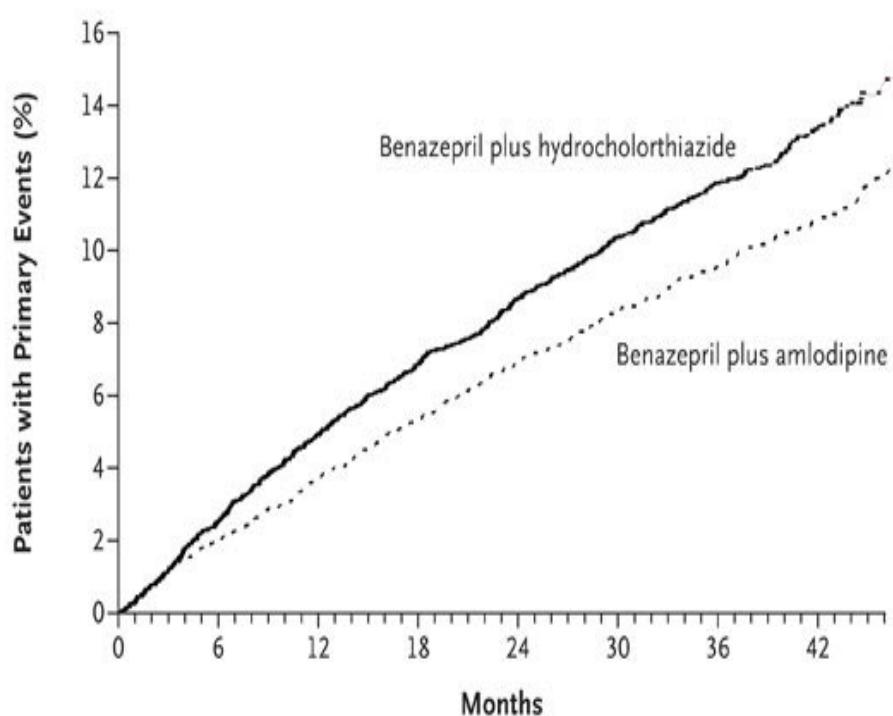


Adapted from The ONTARGET Investigators *N Engl J Med* 2008;358:1547-59.

CV events



ACCOMPLISH – Total population



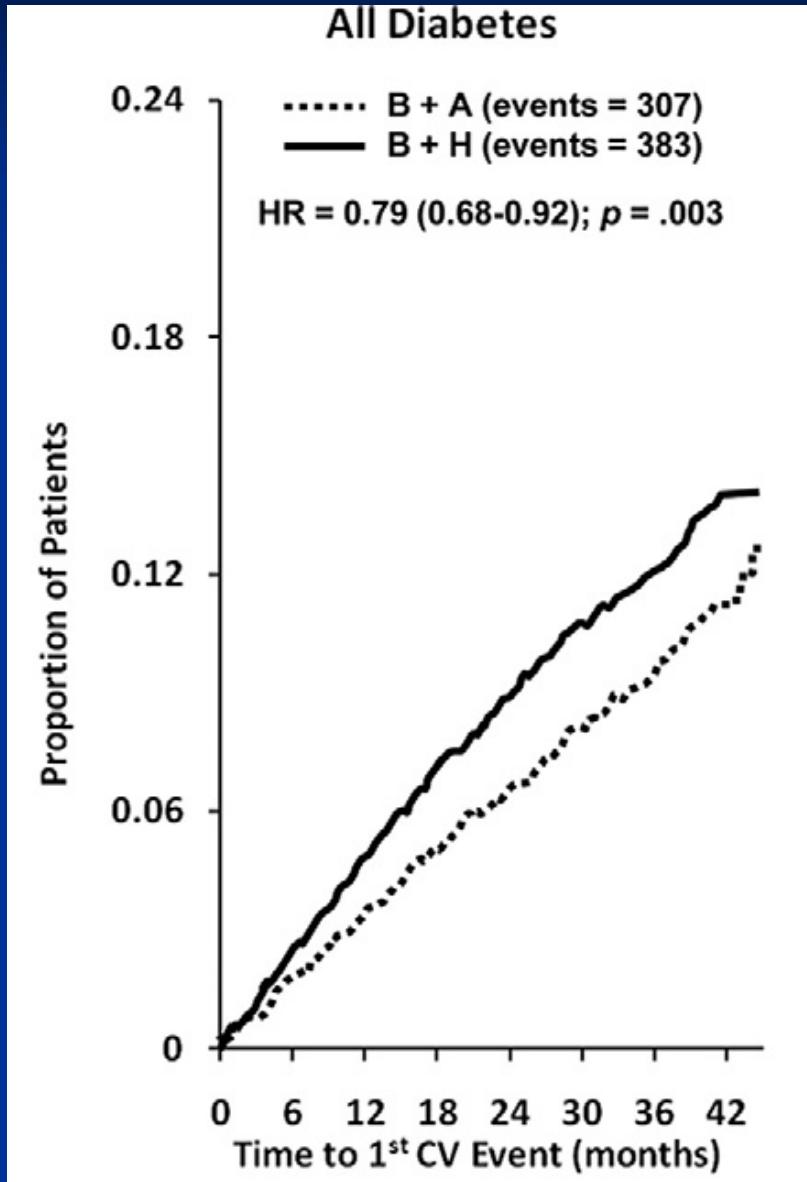
No. at Risk

Benazepril plus amlodipine	5512	5317	5141	4959	4739	2826	1447
Benazepril plus hydrochlorothiazide	5483	5274	5082	4892	4655	2749	1390

↓ 20%

ACCOMPLISH – Diabetics

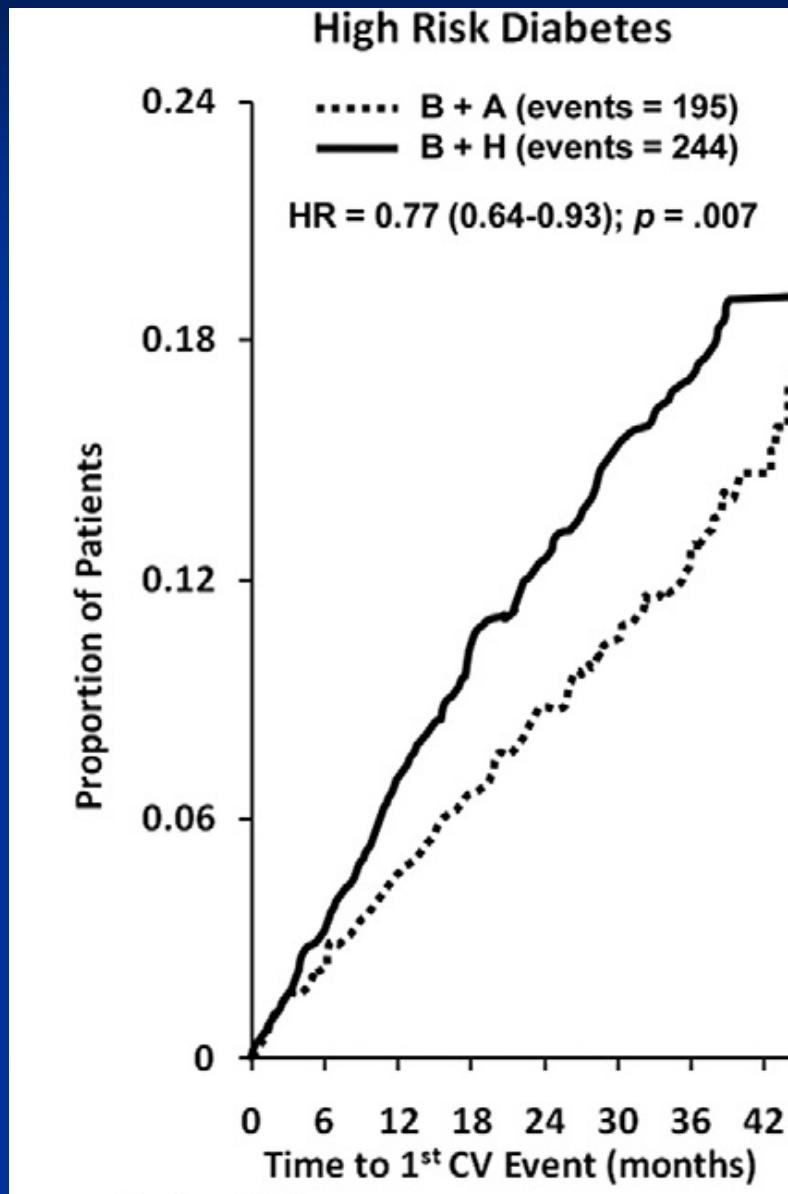
n=6,946



21% ↓

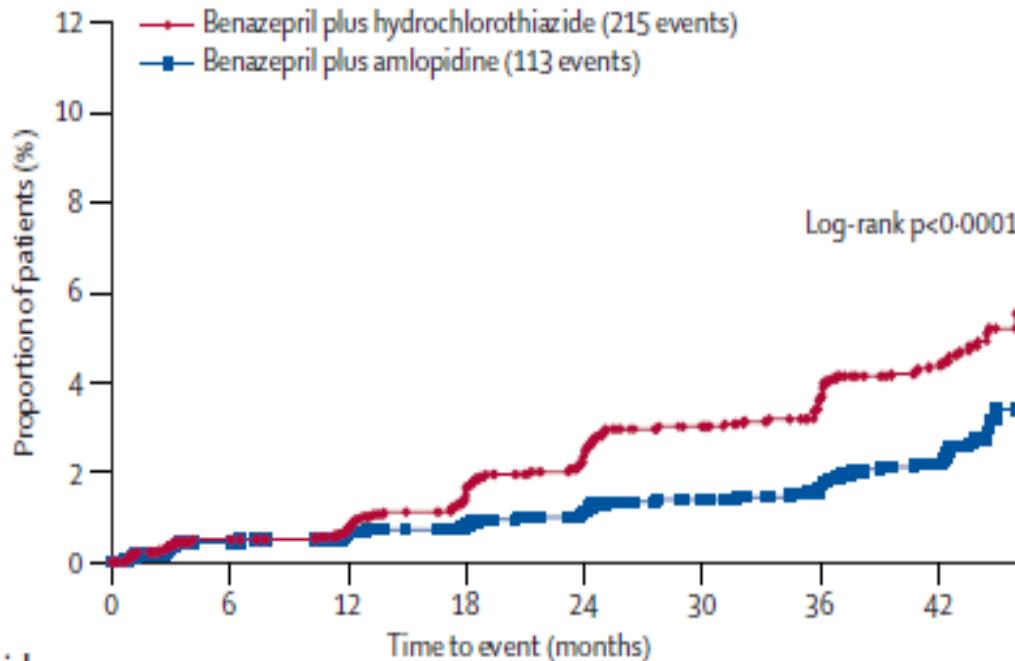
ACCOMPLISH – High risk Diabetics

n=2,842



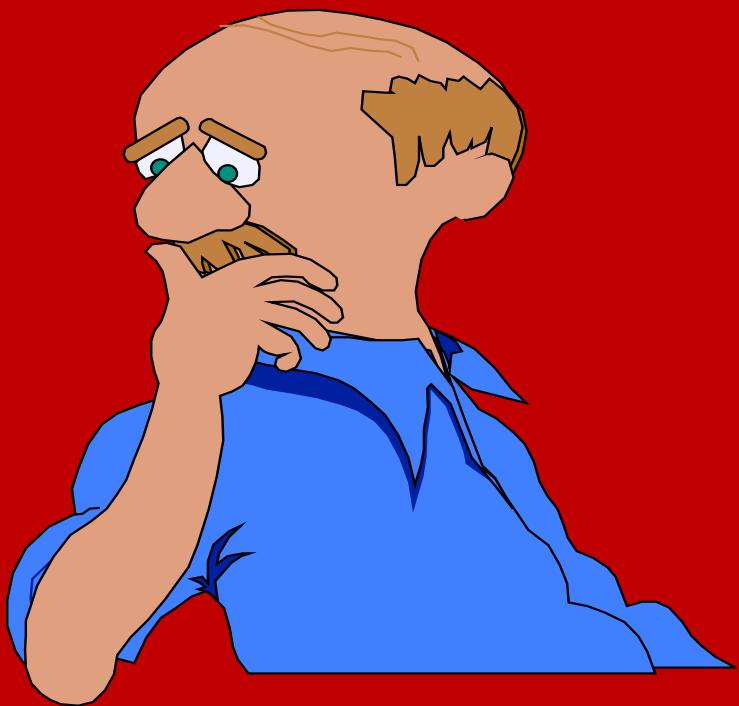
Weber, JACC 2010

ACCOMPLISH – Renal outcome



↓ 48%

Figure 1: Kaplan-Meier curves for progression of chronic kidney disease for the intention-to-treat population
Progression of chronic kidney disease was defined as doubling of serum creatinine concentration, estimated glomerular filtration rate less than 15 mL/min/1.73 m², or need for dialysis.



Σταθεροί
συνδυασμοί

Combination Antihypertensive Therapies

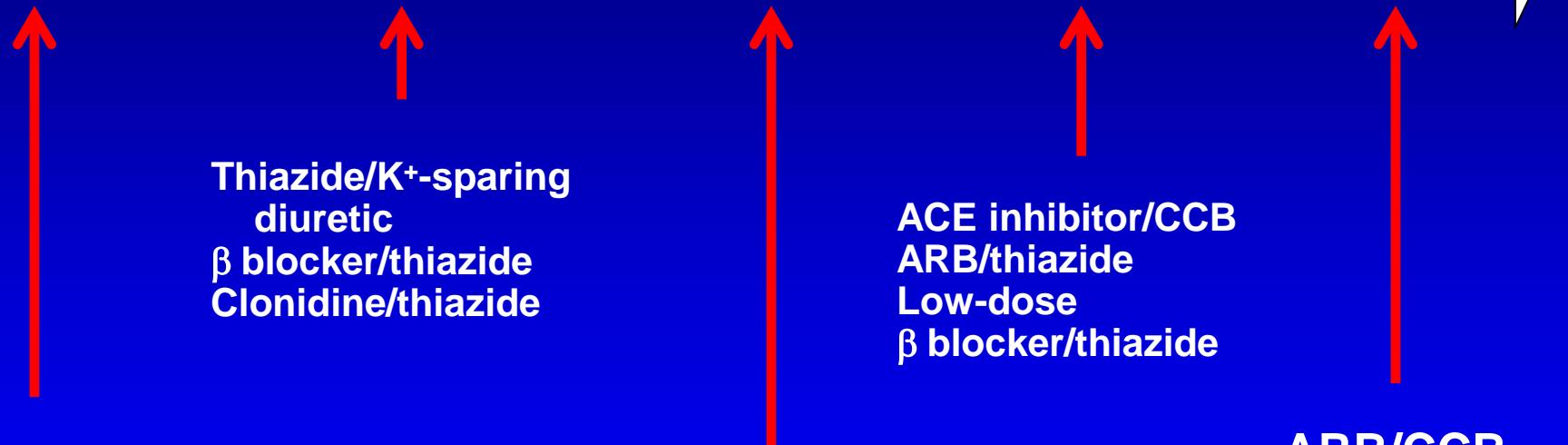
1960's

1970's

1980's

1990's
2000's

2000's
2010's



Ser-Ap-Es
(reserpine/hydralazine/
hydrochlorothiazide)
Methyldopa/thiazide

ACE inhibitor/thiazide

ARB/CCB

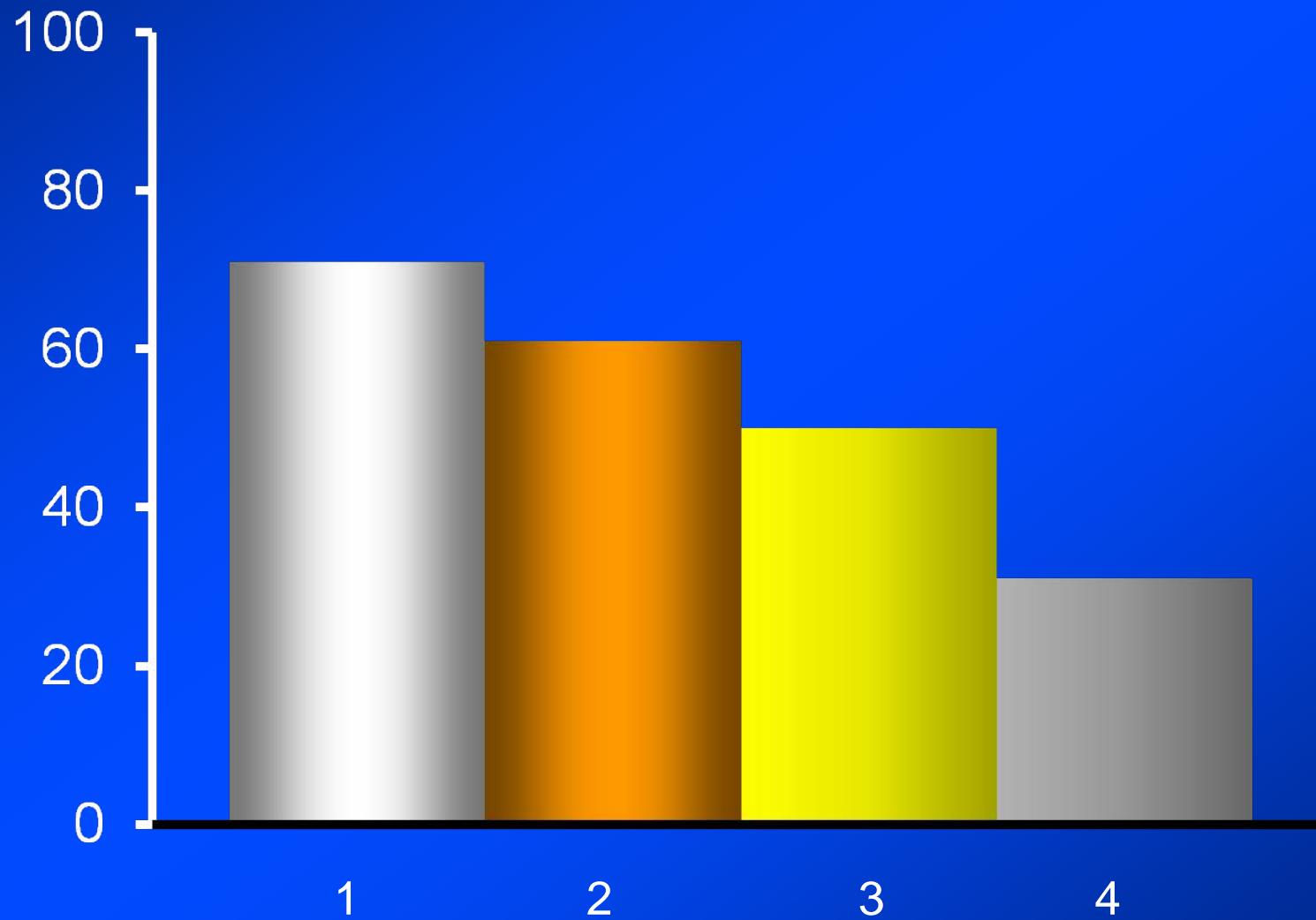
ARB/CCB/thiazide

Advantages of fixed versus liberal combinations of two antihypertensive drugs

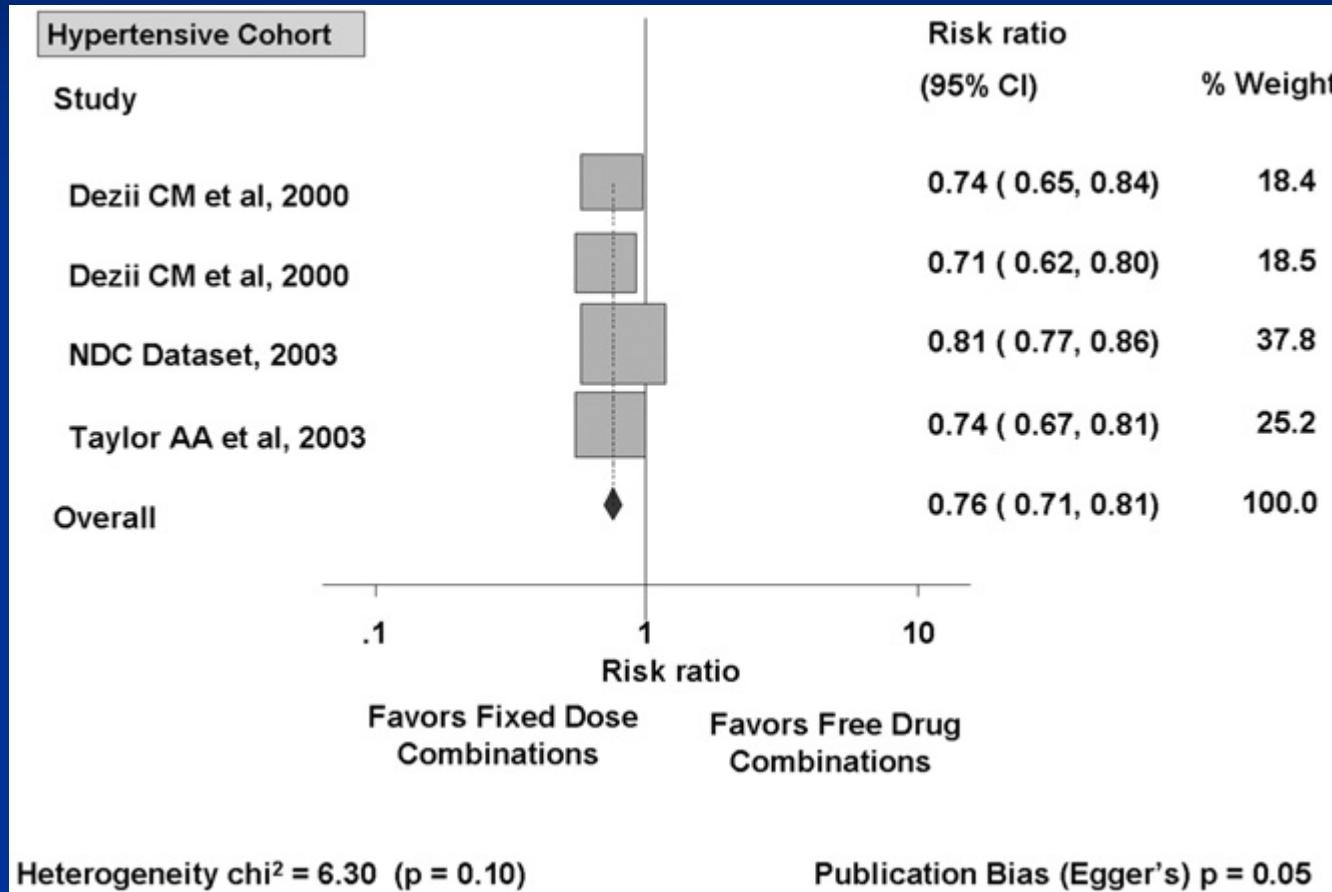
	Fixed	Liberal
Simplicity of treatment	+	-
Compliance	+	-
Efficacy	+	+
Tolerability	+ *	-
Price	+	-
Flexibility	-	+
Risk of administering contraindicated drug	+	-

* lower doses generally used in fixed-dose combinations

Συμμόρφωση ασθενών

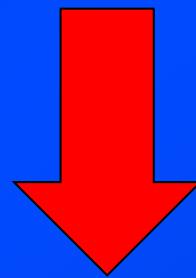


Effect of fixed combo on adherence



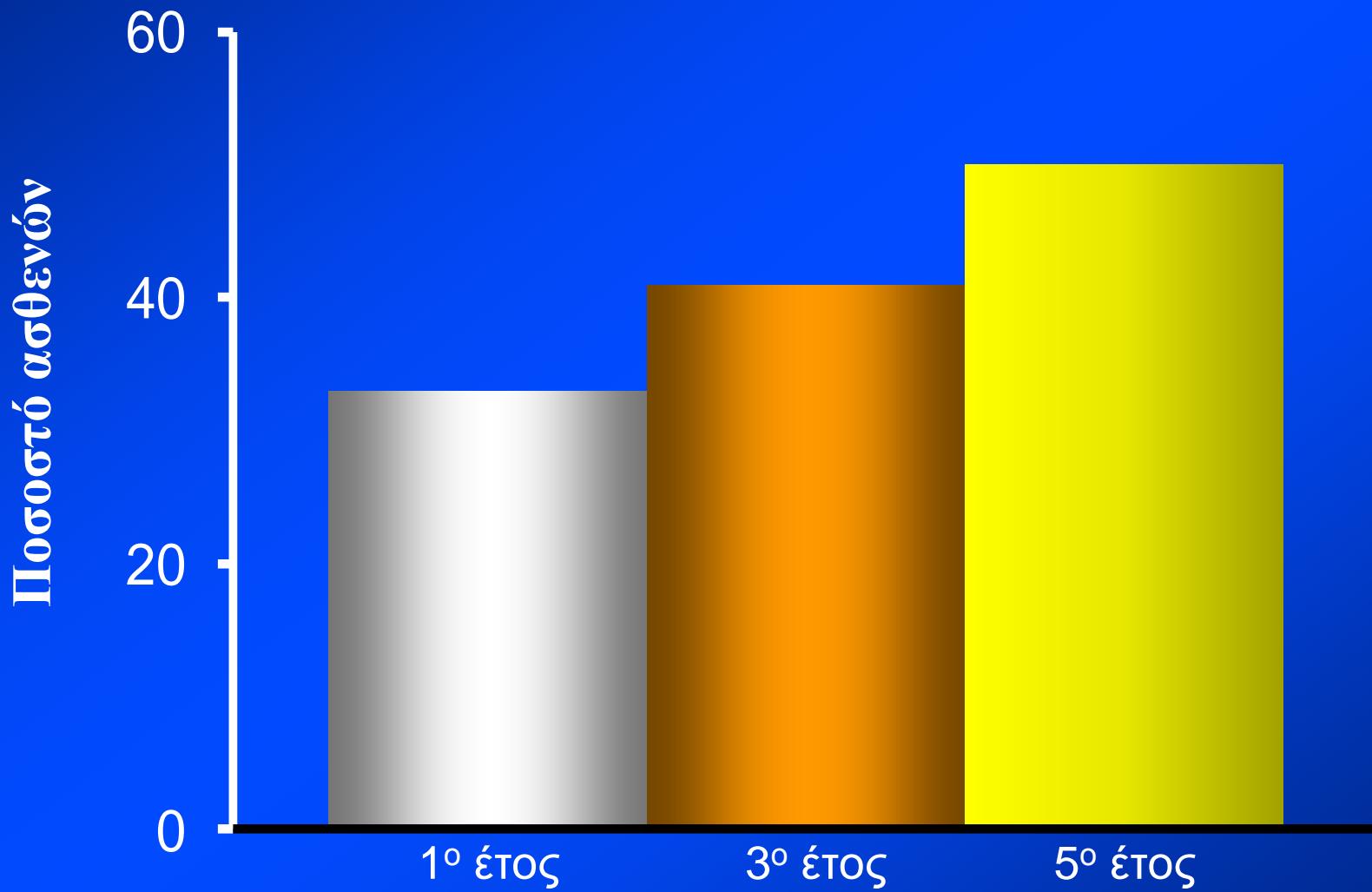
Ηθικό δίδαγμα

Απλοποίηση θεραπείας



Συμμόρφωση ασθενών

Treatment discontinuation



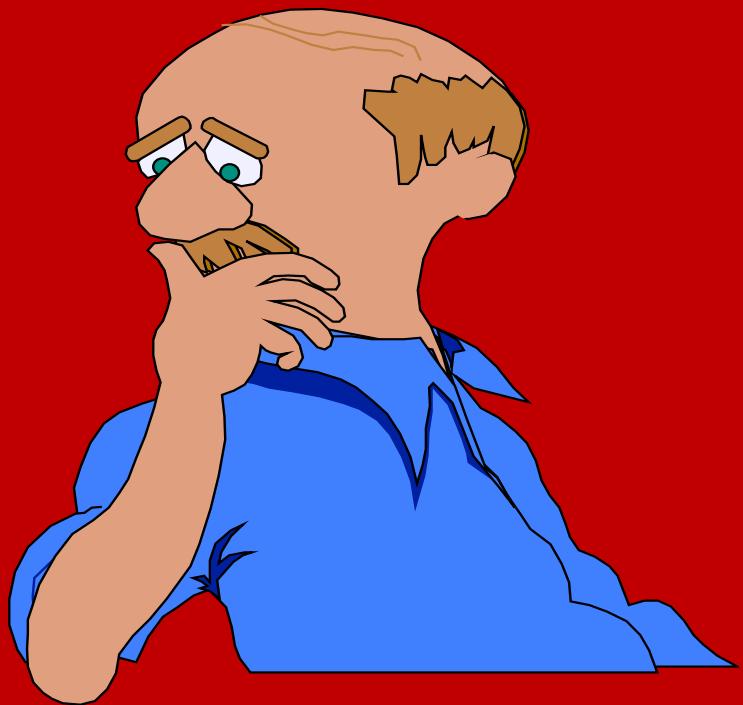
Combination Therapy in Hypertension

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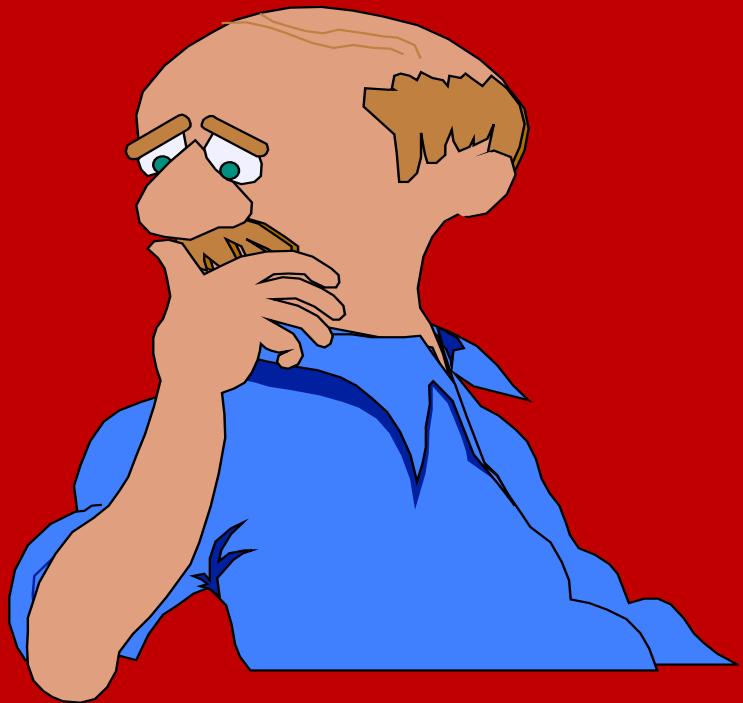
Τριπλός συνδυασμός



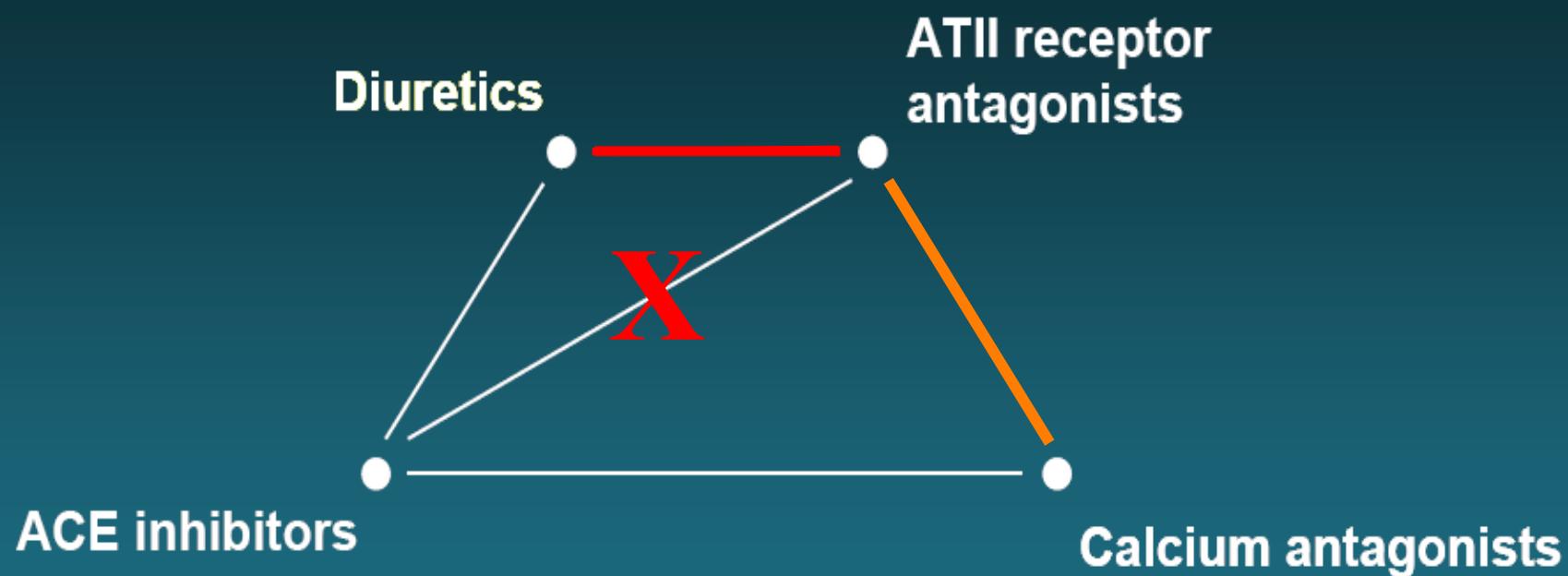
ESH guidelines re-appraisal

“When three drugs are required,
the most rational combination appears to be
a blocker of the renin-angiotensin system,
a calcium antagonist,
and a diuretic
at effective doses.”

Συμπέρασμα



Preferred combinations according to 2009 the ESH Update Guidelines



Συμπέρασμα

Περιορισμός στην κλινική αδράνεια

Εξατομίκευση

Combination Therapy in Hypertension

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ACE inhibitor/diuretic^a

ARB/diuretic^a

ACE inhibitor/CCB^a

ARB/CCB^a

Acceptable

β-Blocker/diuretic^a

CCB (dihydropyridine)/β-blocker

CCB/diuretic

Renin inhibitor/diuretic^a

Renin inhibitor/ARB^a

Thiazide diuretics/K+-sparing diuretics^a

Less effective

ACE inhibitor/ARB

ACE inhibitor/β-blocker

ARB/β-blocker

CCB (nondihydropyridine)/β-blocker

Centrally acting agent/β-blocker

Benjamin Franklin

“Keep your eyes
wide open before marriage,
half shut
afterwards.”

Παράφραση

“Κρατήστε τα μάτια, τα αυτιά
και προπάντων το μυαλό σας ανοιχτά,
όλα ή κάποια από
αυτά που ακούσατε σήμερα
μπορεί να μην ισχύουν αύριο”