TURIN, 20TH—21ST NOVEMBER 2008

GREAT INNOVATIONS IN CARDIOLOGY

4TH JOINT MEETING WITH MAYO CLINIC

4TH TURIN CARDIOVASCULAR NURSING CONVENTION

SESSION III: **HOT SESSION**
NEW THERAPIES AND NEW TREATMENTS

F. Veglio (Torino)

Part I Combination therapy in the treatment of arterial hypertension

UNIVERSITA' degli STUDI di TORINO

FACOLTA' DI MEDICINA E CHIRURGIA
DIPARTIMENTO DI MEDICINA ED ONCOLOGIA SPERIMENTALE

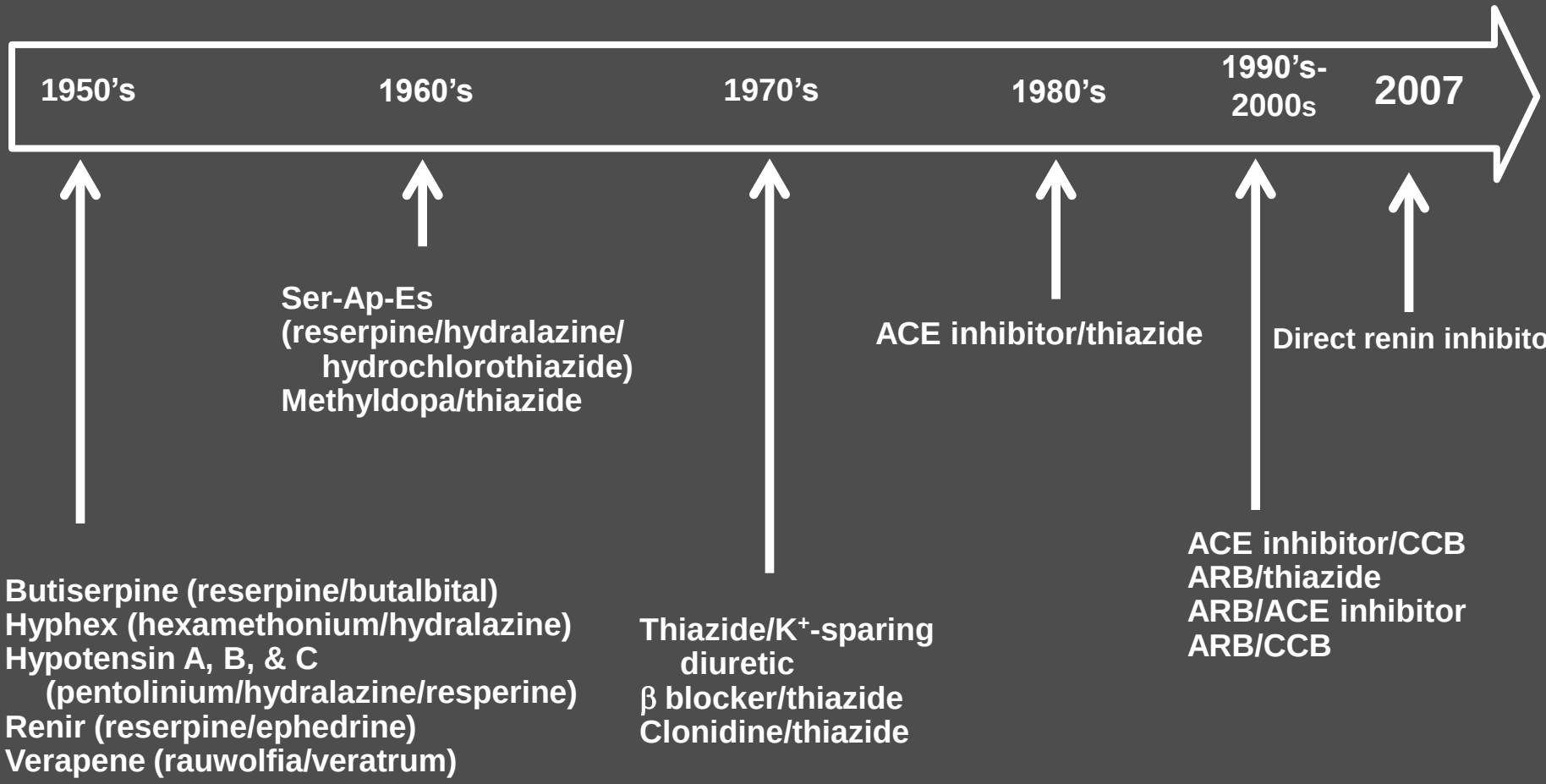
SCU MEDICINA INTERNA
CENTRO IPERTENSIONE ARTERIOSA
AOU S.GIOVANNI BATTISTA
TORINO

Combination therapy in the treatment of arterial hypertension

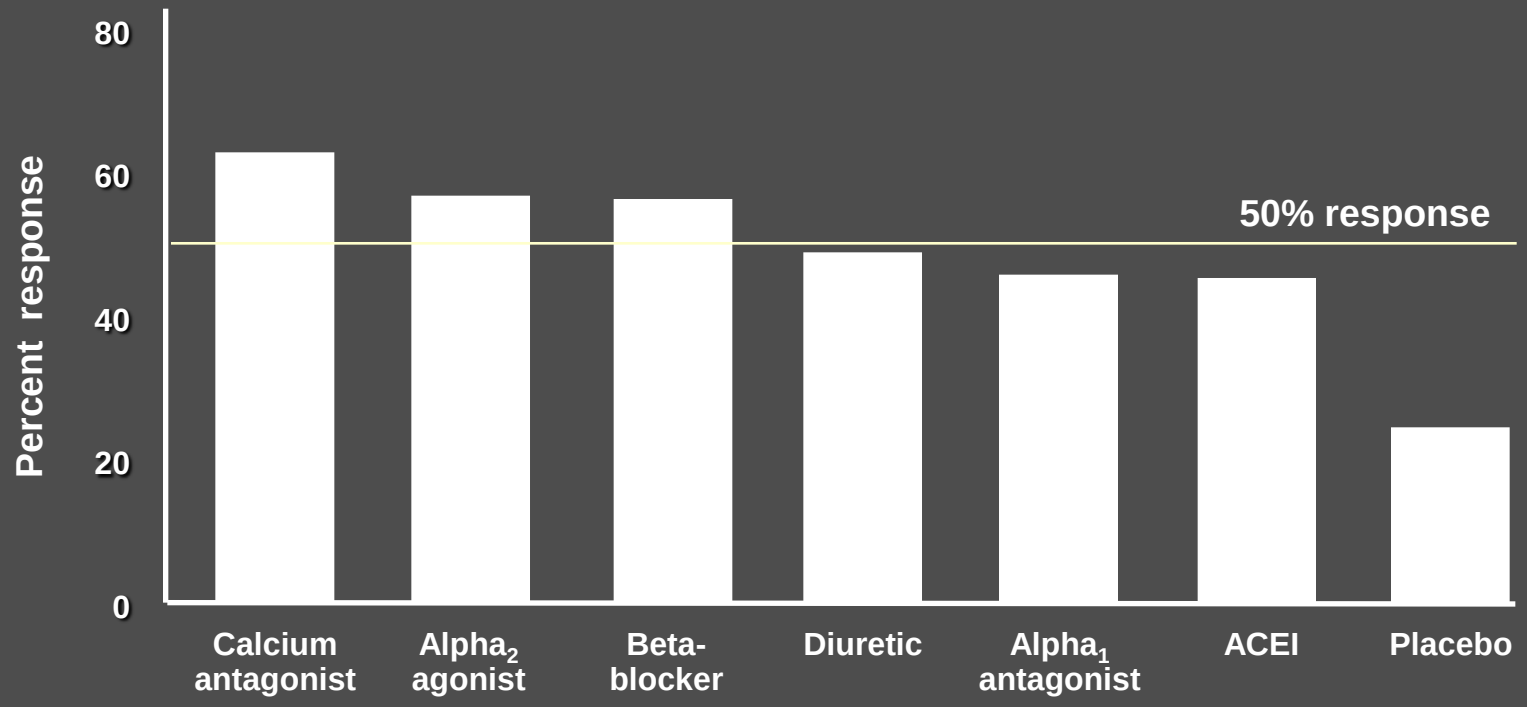
Franco Veglio

Torino, November 20th 2008

TIMELINE
COMBINATION THERAPY



MONOTHERAPY IS INADEQUATE IN 40%– 60% OF HYPERTENSIVE PATIENTS



Morgan, J Hypertens 2001

COMBINATION THERAPY IN TRIALS

Trial	Treatment groups (*n*)	Target BP (mmHg)	Treatment strategy		CV risk profile
			First line	Second line	
ALLHAT	15,255	SBP < 140, DBP < 90	D	BB	Hypertension + additional CV risk factors
	9048	SBP < 140, DBP < 90	CA	BB	
	9054	SBP < 140, DBP < 90	ACE-I	BB	
LIFE	4605	SBP ≤ 140, DBP ≤ 90	AT_1-B	D	Hypertension + left ventricular hypertrophy
	4588	SBP ≤ 140, DBP ≤ 90	BB	D	
VALUE	7649	SBP < 140, DBP < 90	AT_1-B	D	Hypertension + additional CV risk factors or disease
	7596	SBP < 140, DBP < 90	CA	D	
INVEST	11,267	SBP < 140, DBP < 90*	CA	ACE-I	Hypertension + coronary heart disease
	11,309	SBP < 140, DBP < 90*	BB	D	
ASCOT	9639	SBP < 140, DBP < 90†	CA	ACE-I	Hypertension + additional risk factors
	9618	SBP < 140, DBP < 90†	BB	D	

Struijker-Boudier, Int J Clin Pract, 2007

2007 ESH/ESC Guidelines

Main Requirements for Combination of Two or More Antihypertensive Drugs

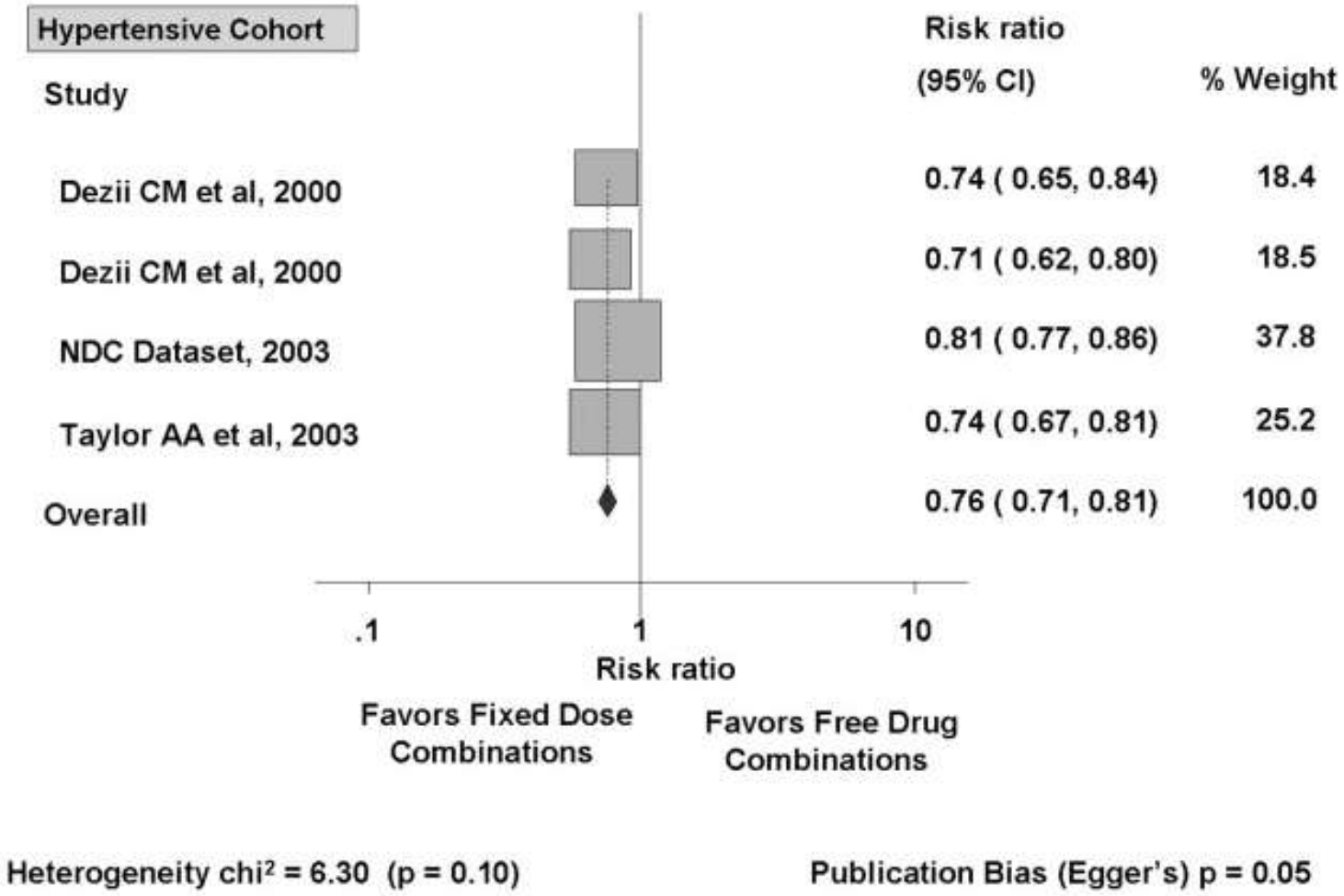
- BP ↓ by combination greater than that of combination components
- Different / complementary mechanisms of action
- Favourable tolerance profile, i.e. minimization of side effects of combination components

Advantages of fixed versus free-drug combination

	Fixed	Free-drug
Simple therapy	+	–
Compliance	+	–
Efficacy	+	+
Tolerability	+	–
Cost	+	–
Flexibility	–	+

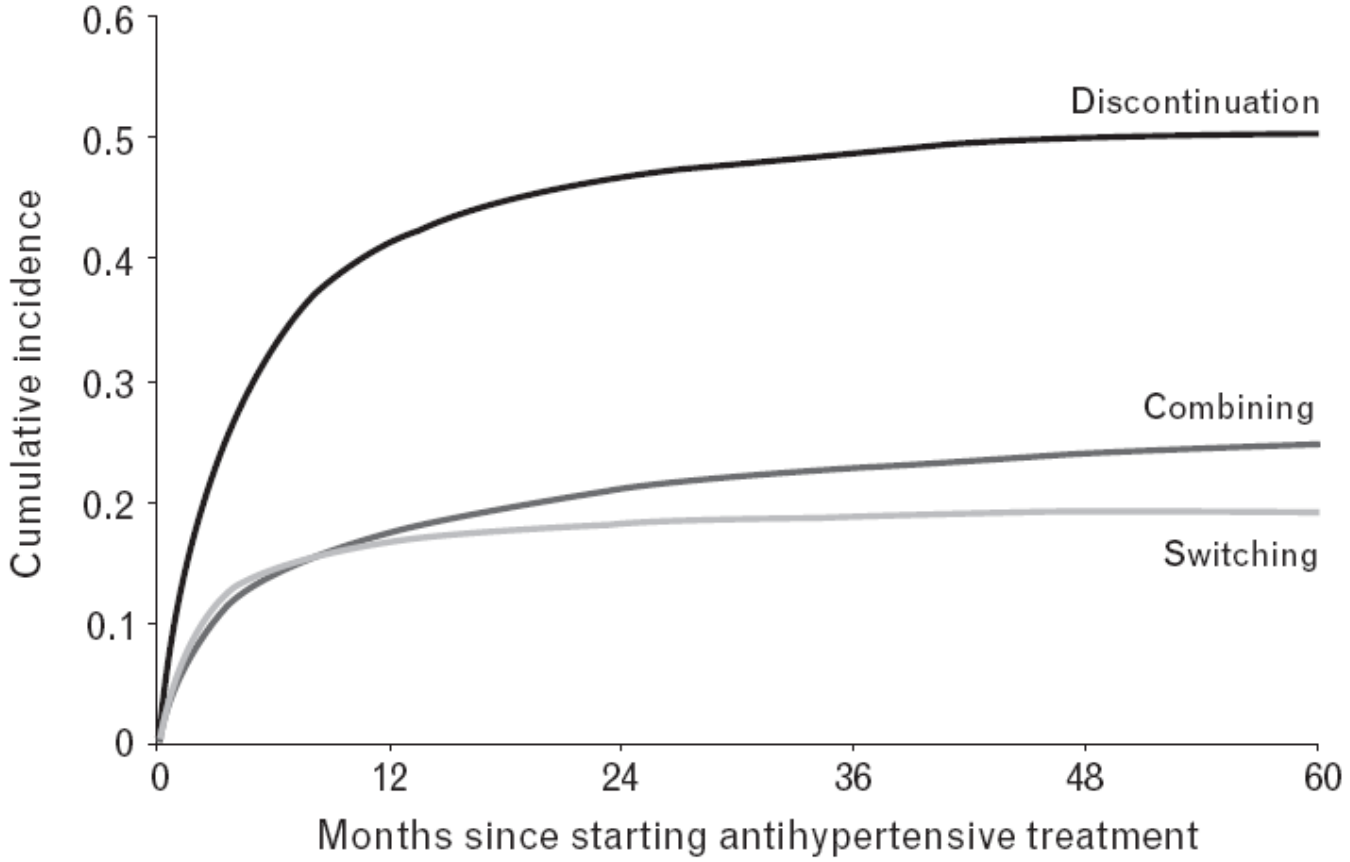
Neutel, Hypertension, 2005

Effect of fixed-dose combination vs free-drug combination the risk of medication non-compliance in cohort with hypertension.



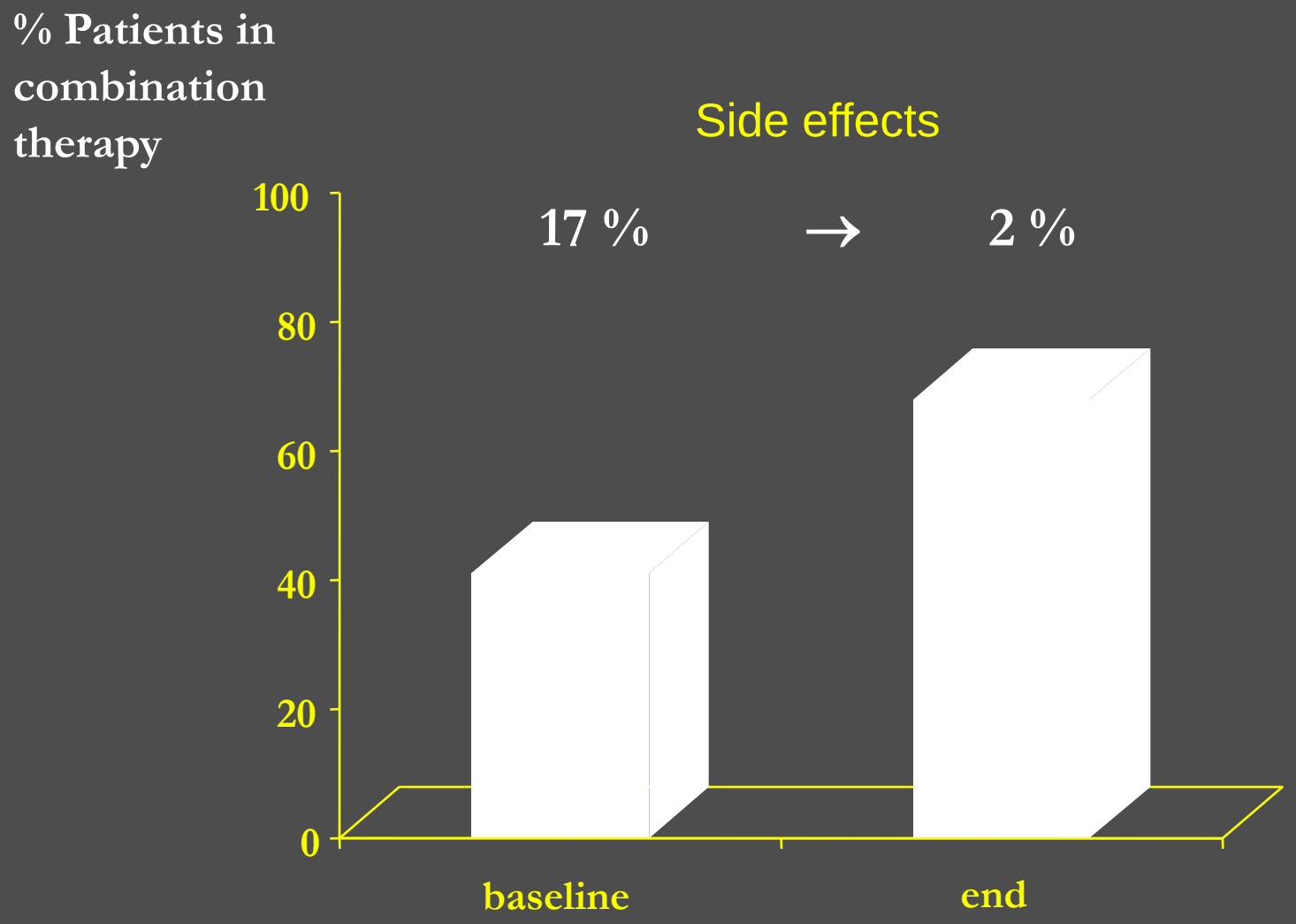
Bangalore, Am J Med 2007

Cumulative Incidence of Modification of Initial Monotherapy (Lombardia Data-base; n = 445356)



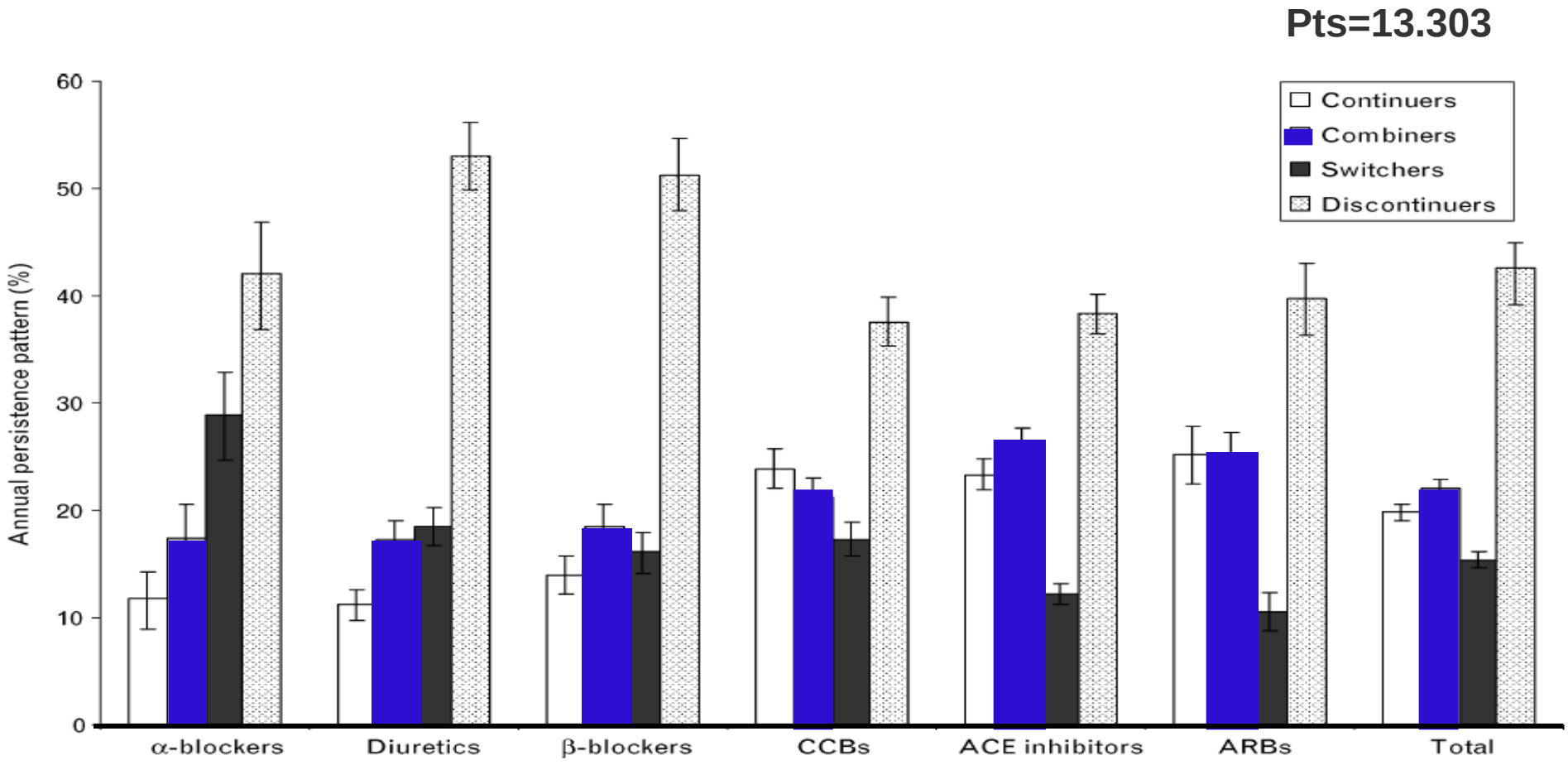
Corrao, J Hypert 2008

HOT study



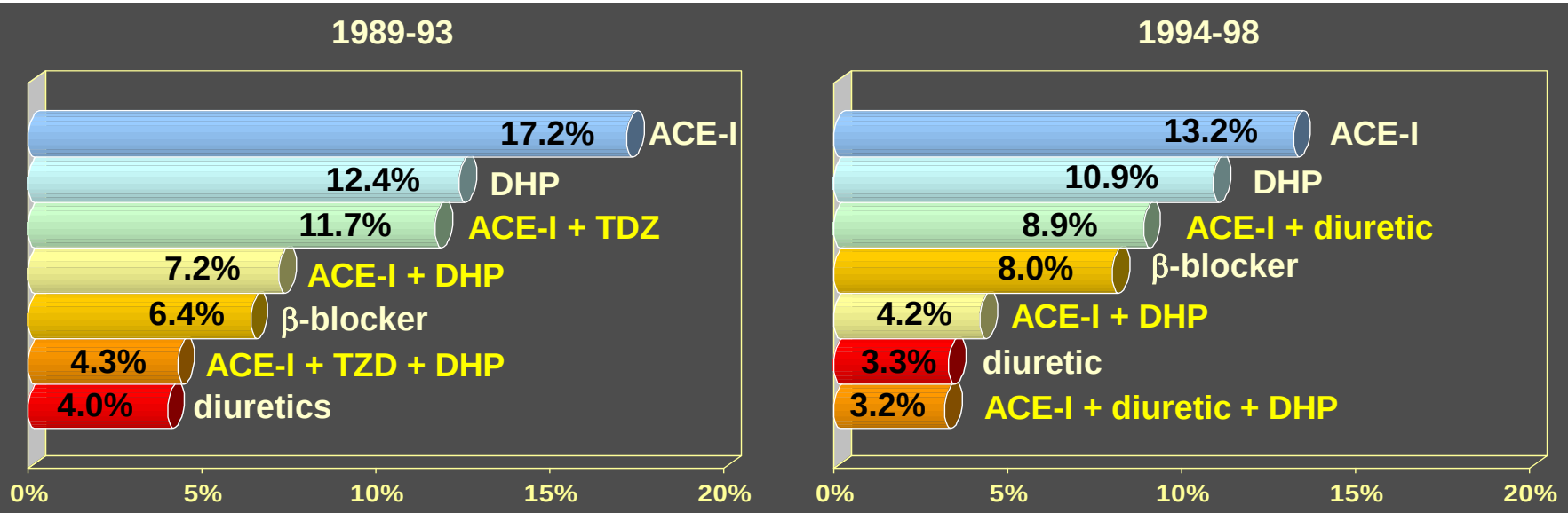
Hansson, Lancet 1998

TREND OF COMBINATION THERAPY IN ITALY

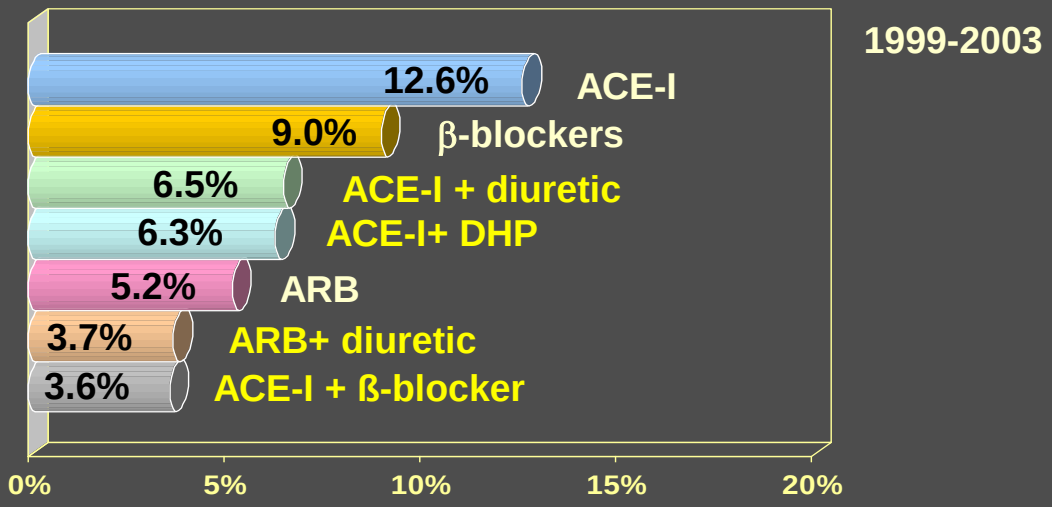


Mazzaglia, J Hypertension 2005

COMBINATION THERAPY



6261 patients (3343 females , 2918 males)



Veglio, J Human Hypert 2007

POOR OR TROUBLE COMBINATION THERAPY

β-blocker + α_2-stimulant	Not additive; has a potential for paradoxical BP rebound hypertension
β-blocker + ACE inhibitor (ARB?)	Not additive for hypertension
β-blocker + verapamil/diltiazem	May cause extreme bradycardia, advanced heart block, and systolic heart failure
α_2-stimulant + α_1-blocker	Not additive

Israili, Am J Ther, 2007

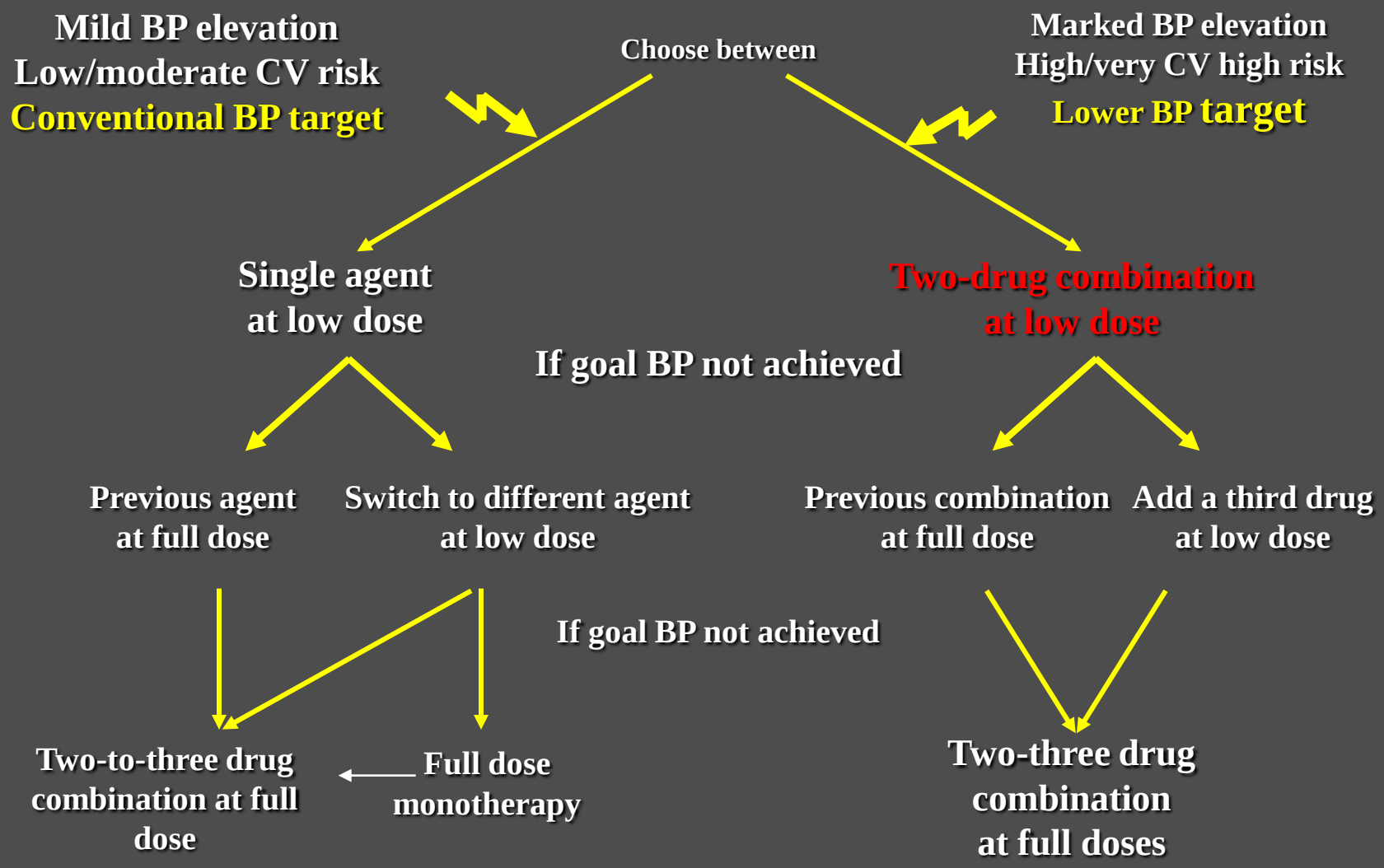
Recommendations for combination therapy in special populations

Condition	Combination therapy
Chronic kidney disease	
GFR >40 ml/min	Thiazide diuretic and ACE inhibitor/ARB
GFR 40 ml/min	
Proteinuria >1 g/day	Loop diuretic and ACE inhibitor/ARB
	ACE inhibitor and ARB
Diabetes mellitus	ACE inhibitor and CCB
	ACE inhibitor and diuretic
Heart disease	ACE inhibitor and CCB
	ACE inhibitor and diuretic
Cerebrovascular disease	ACE inhibitor and diuretic

Khanna, Current Opinion in Nephrology and Hypertension, 2008

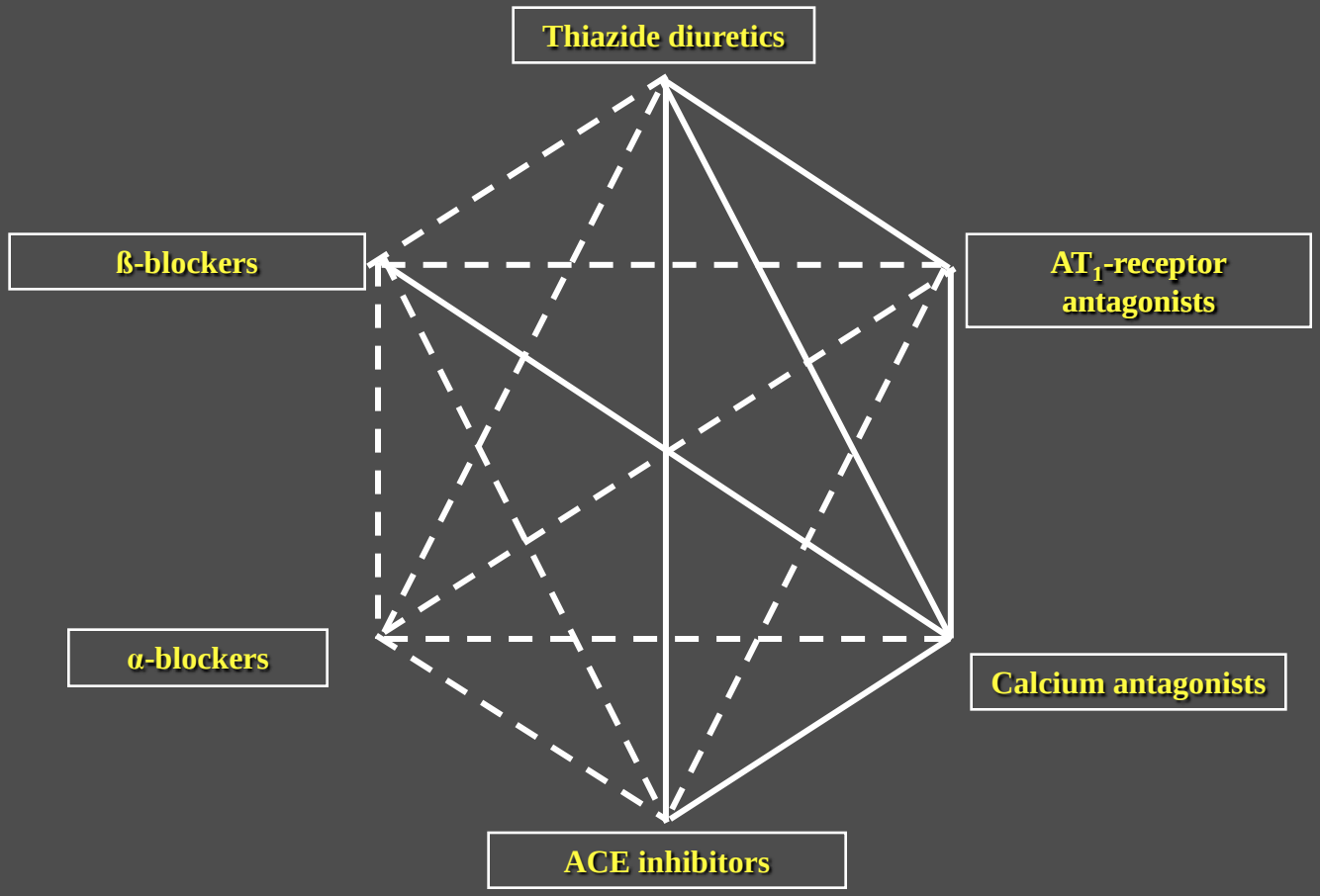
2007 ESH/ESC Guidelines

Monotherapy versus Combination Therapy Strategies



2007 ESH/ESC Guidelines

Combinations between Some Classes of Antihypertensive Drugs



The preferred combinations in the general hypertensive population are represented as thick lines. The frames indicate classes of agents proven to beneficial in controlled intervention trials.

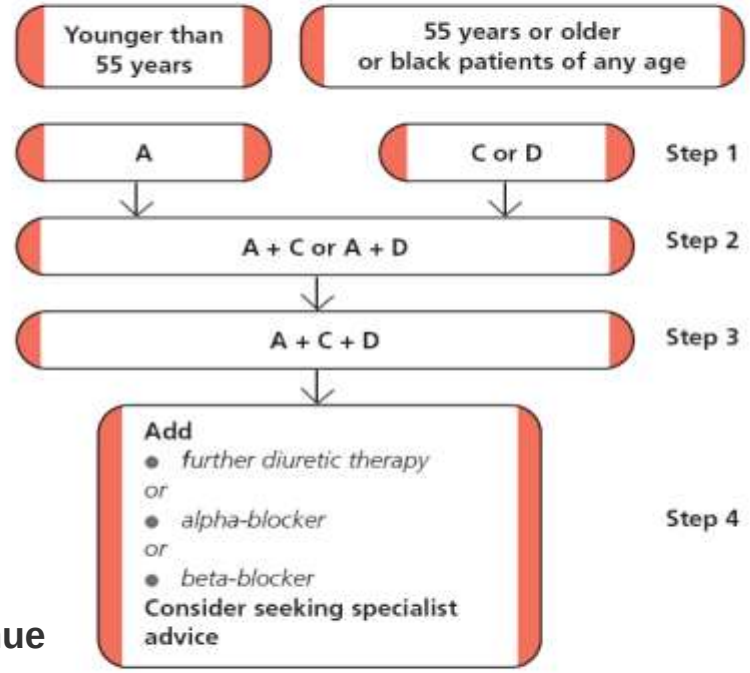
BHS
British Hypertension Society

GUIDELINES 2006

Choosing drugs for patients newly diagnosed with hypertension

Abbreviations:
A = ACE inhibitor
(consider angiotensin-II receptor antagonist if ACE intolerant)
C = calcium-channel blocker
D = thiazide-type diuretic

Black patients are those of African or Caribbean descent, and not mixed-race, Asian or Chinese patients



The BHS guideline working party and the BHS Executive recommends that UK practitioners continue to use the current NICE/BHS guidance.

BHS

NHS
National Institute for Health and Clinical Excellence

Effects of anti-Renin drugs on BP and PRA in untreated Hypertensive Patients

"V-type" / "R-type"

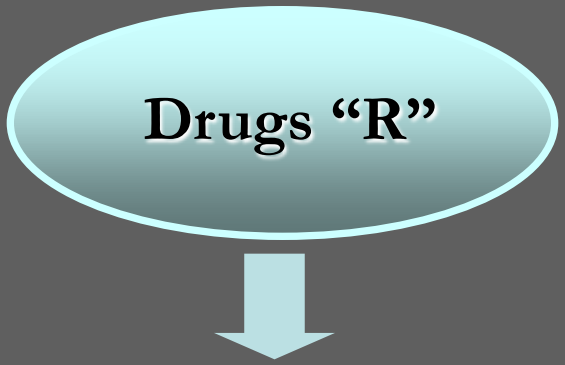
Anti-Na+-Volume

"V" Drugs:

Thiazides-Loop Diuretics

CCBs - α-Blockers

SARAs



Anti-renin angiotensin

"R" Drugs:

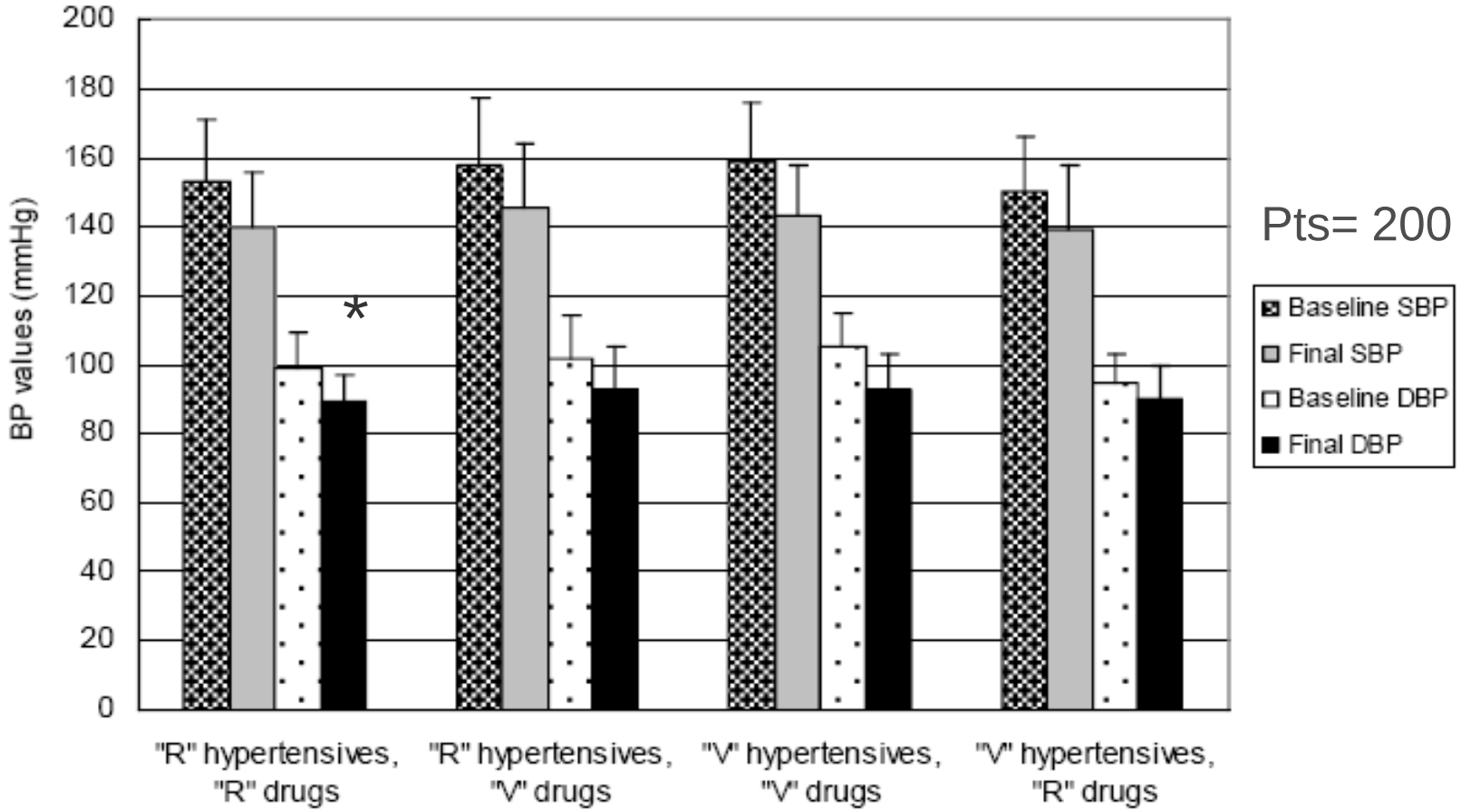
ACEI / AIIRA

β-Blockers

α_2-Central Blockers

Laragh , Am J Hyperten 2001

Efficacy of antihypertensive treatment based on plasma renin activity



* p<0.05

Veglio, Am J Hypertens, 2008 in press

2007 ESH/ESC Guidelines

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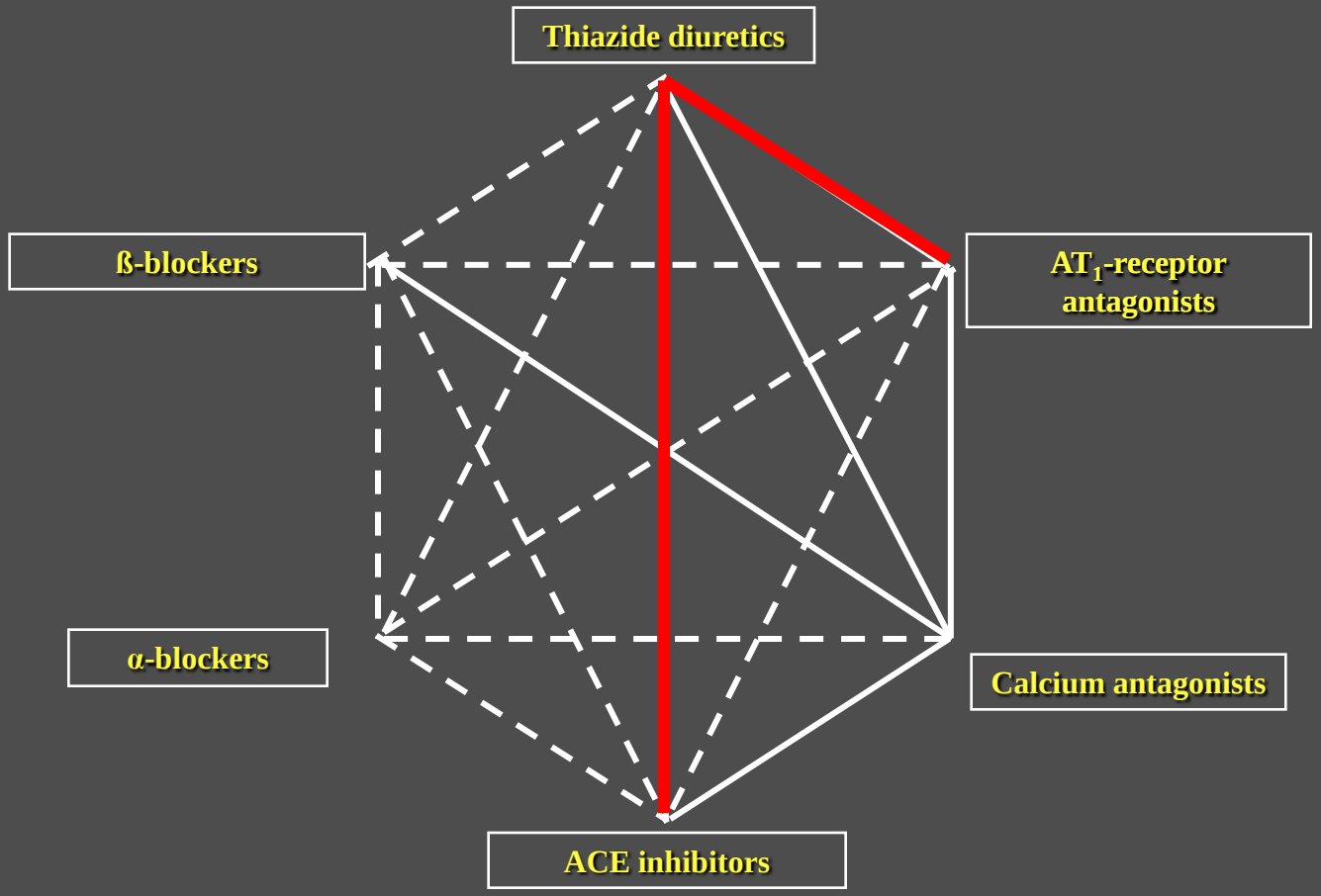
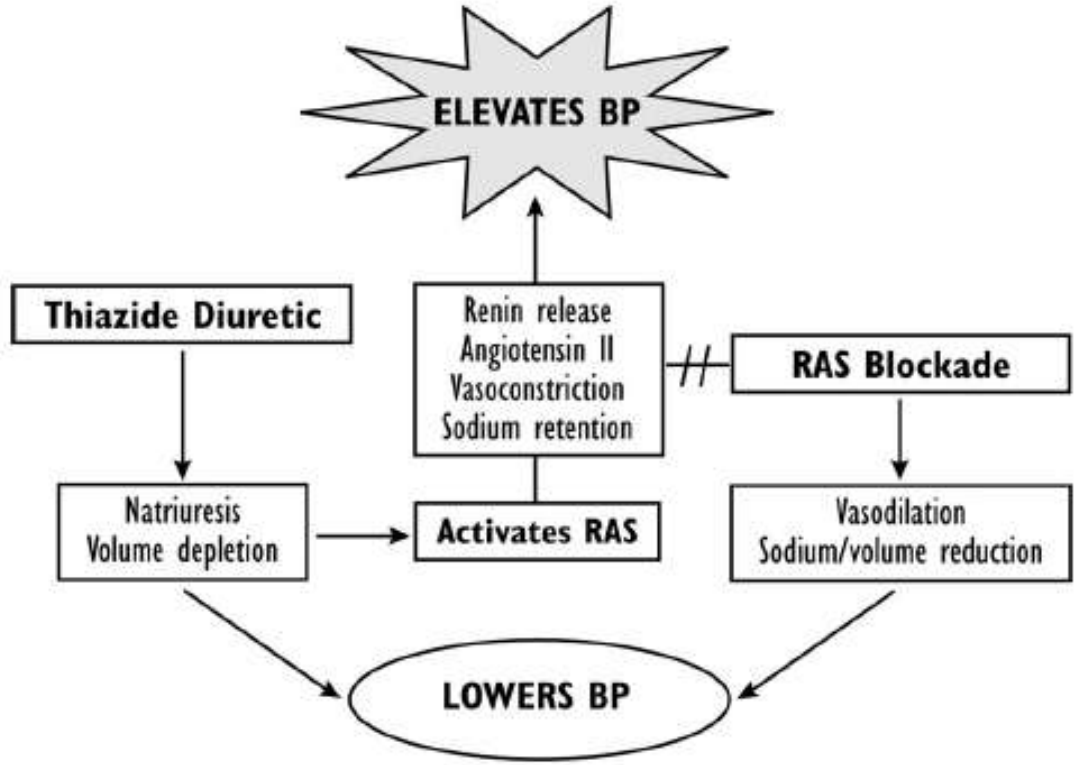


Rationale for combining thiazide diuretics and agents that block the renin-angiotensin system (RAS)



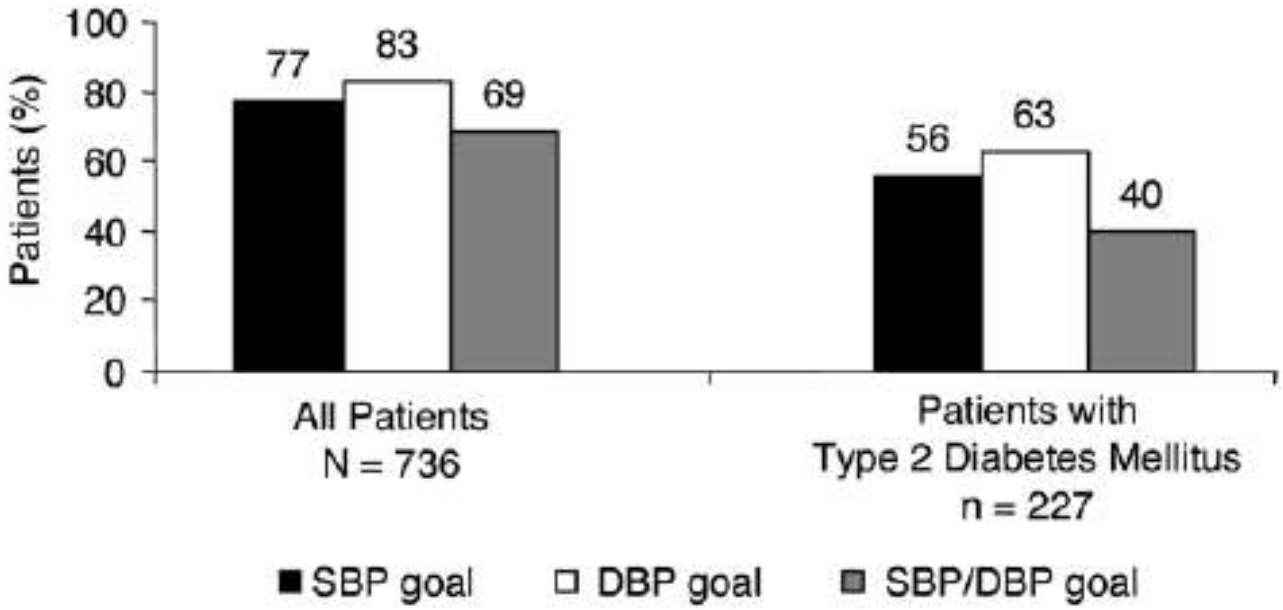
Nash, Southern Medical J, 2007

Improved persistence and adherence to diuretic fixed-dose combination therapy compared to diuretic monotherapy

Outcome measures	HCTZ	ARB/HCTZ	ACEI/HCTZ	BB/HCTZ
48,212 patients				
Persistence (%)	29.9	52.6	51.4	51.9
Adherence (%)	24.2	39.2	38.8	43.9
PDC[a] at end of follow-up (%)	32.5	53.7	50.9	51.3
MPR[b] ± SD	44.5 ± 34.5	60.5 ± 32.7	58.3 ± 34.2	62.1 ± 34.1
Days to therapy discontinuation ± SD	164.5 ± 141.8	240.1 ± 140.3	235.9 ± 140.8	238.2 ± 140.9

Patel, *BMC Family Practice* 2008

Irbesartan/HCTZ Blood Pressure Reductions in Diverse Patient Populations (INCLUSIVE)



Venkata, *The American Journal of Medicine , 2008*

2007 ESH/ESC Guidelines

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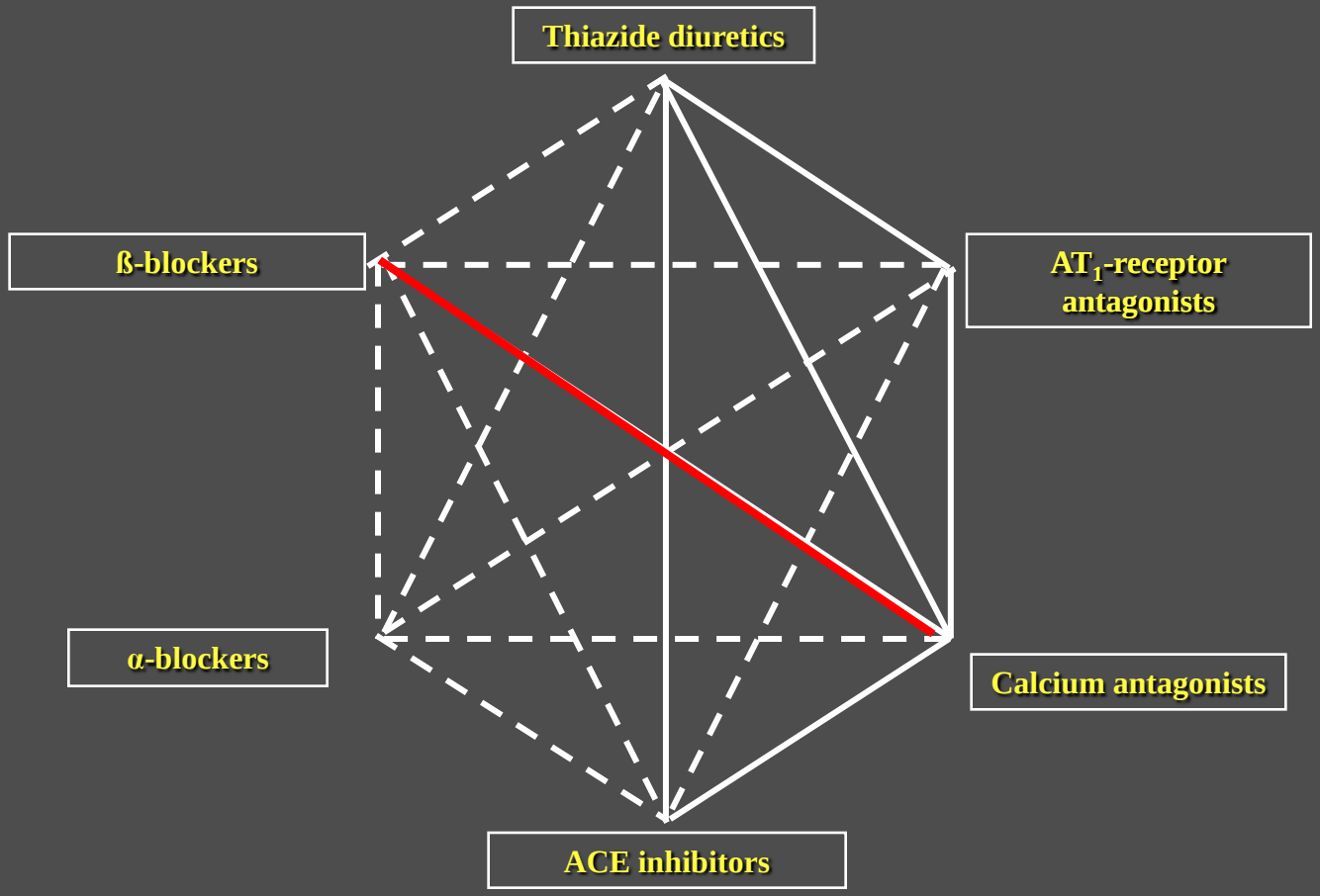
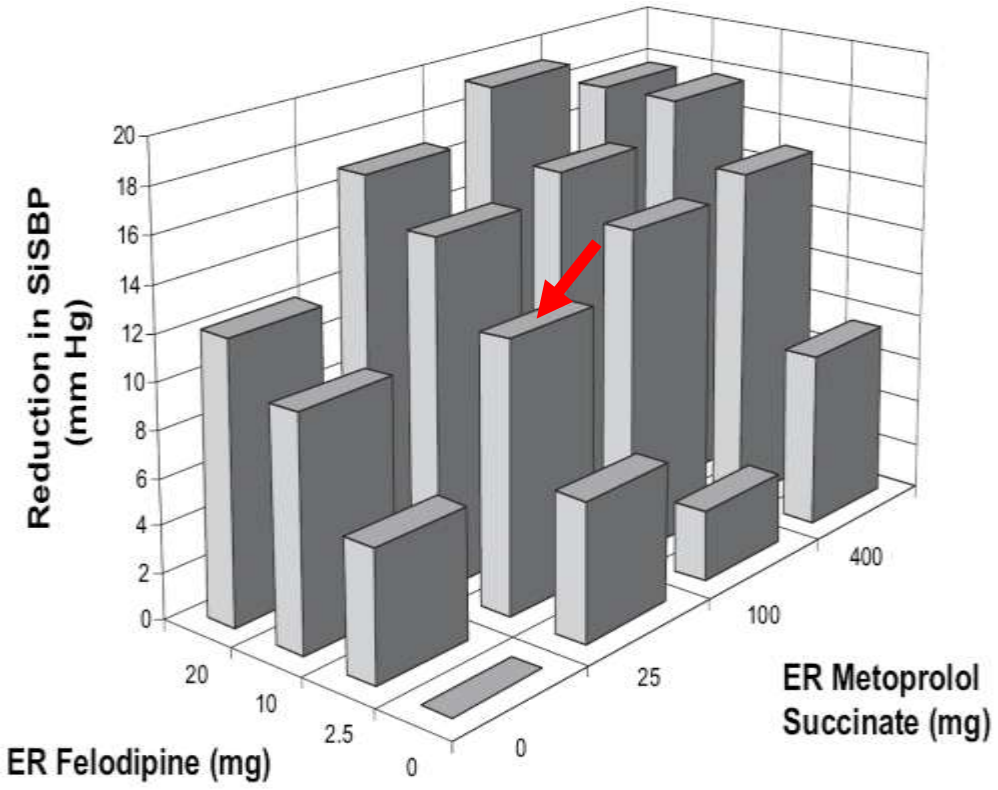
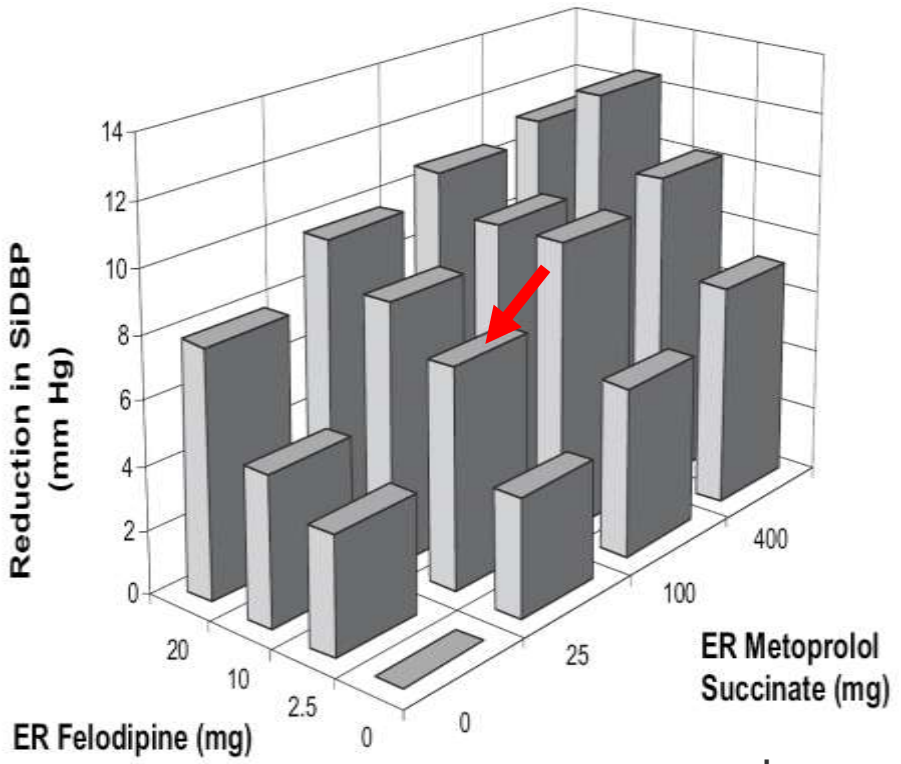


The preferred combinations in the general hypertensive population are represented as thick lines. The frames indicate classes of agents proven to beneficial in controlled intervention trials.

M-FACT STUDY





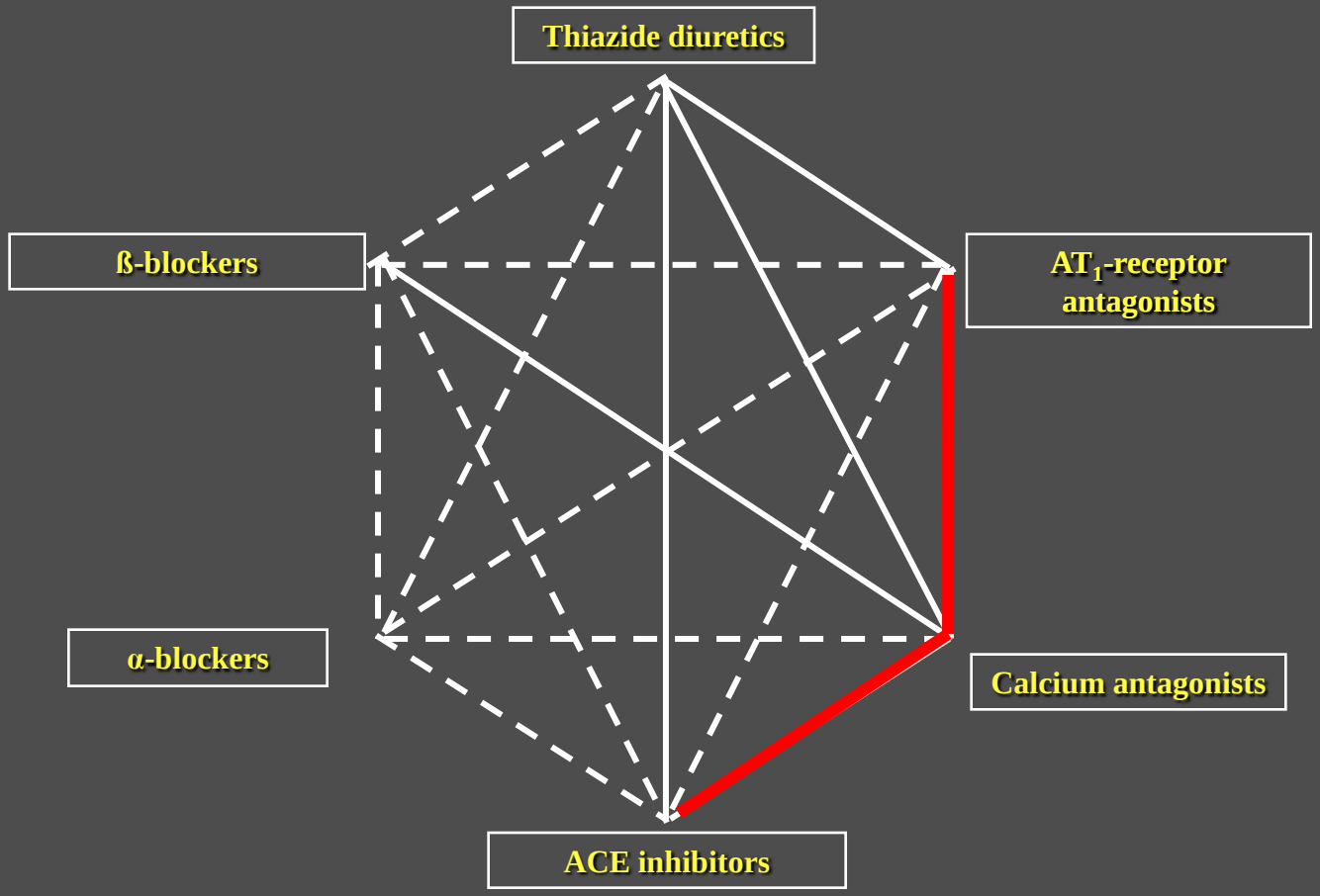
				p value
2.5/25 mg	VS	ER metoprolol 400 mg	0.0	(−2.2, 2.2)	.97
2.5/25 mg	VS	ER felodipine 20 mg	0.8	(−1.4, 3.0)	.49

Pts =1087

Frishman, Am J Hypert 2006

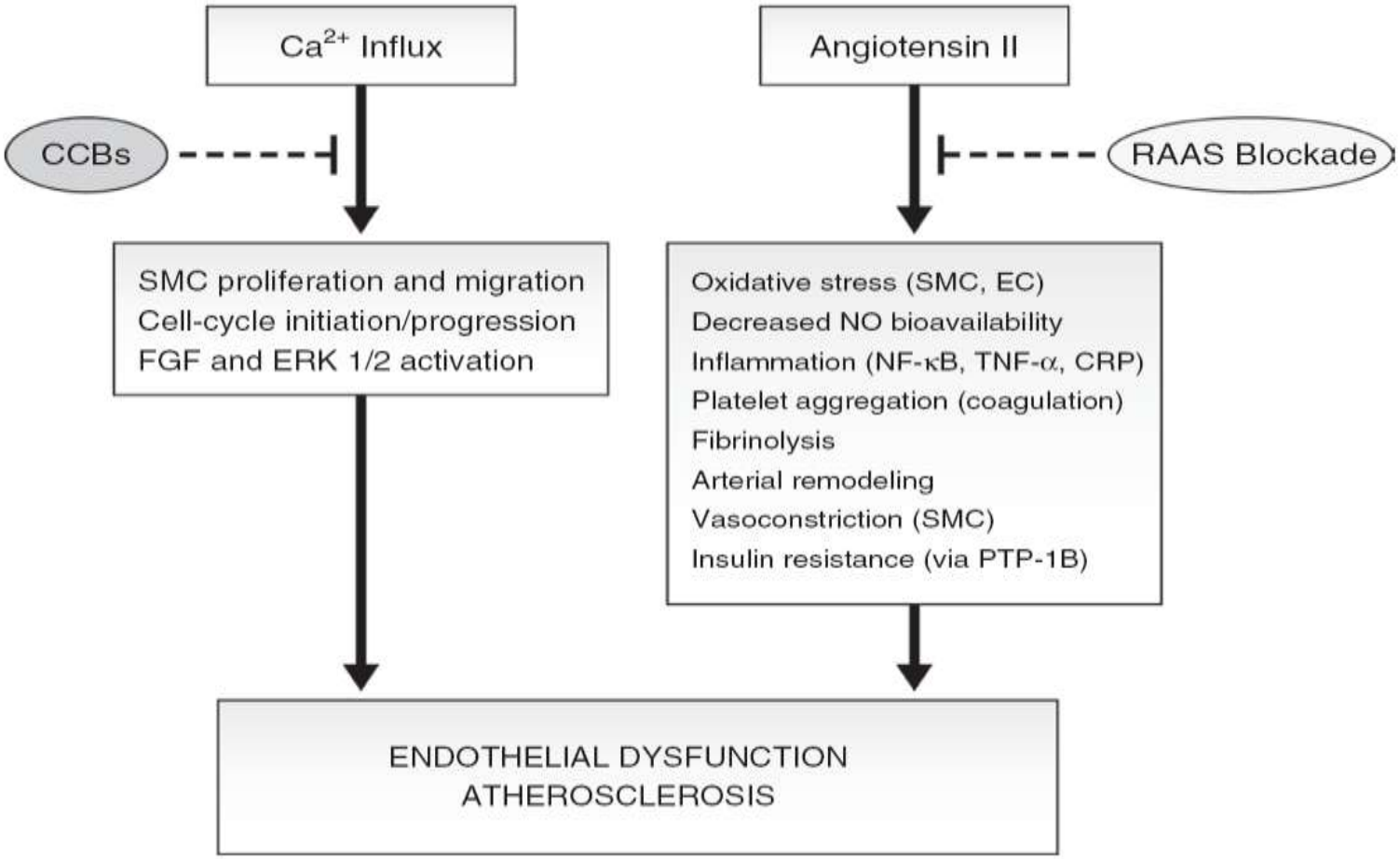
2007 ESH/ESC Guidelines

Combinations between Some Classes of Antihypertensive Drugs



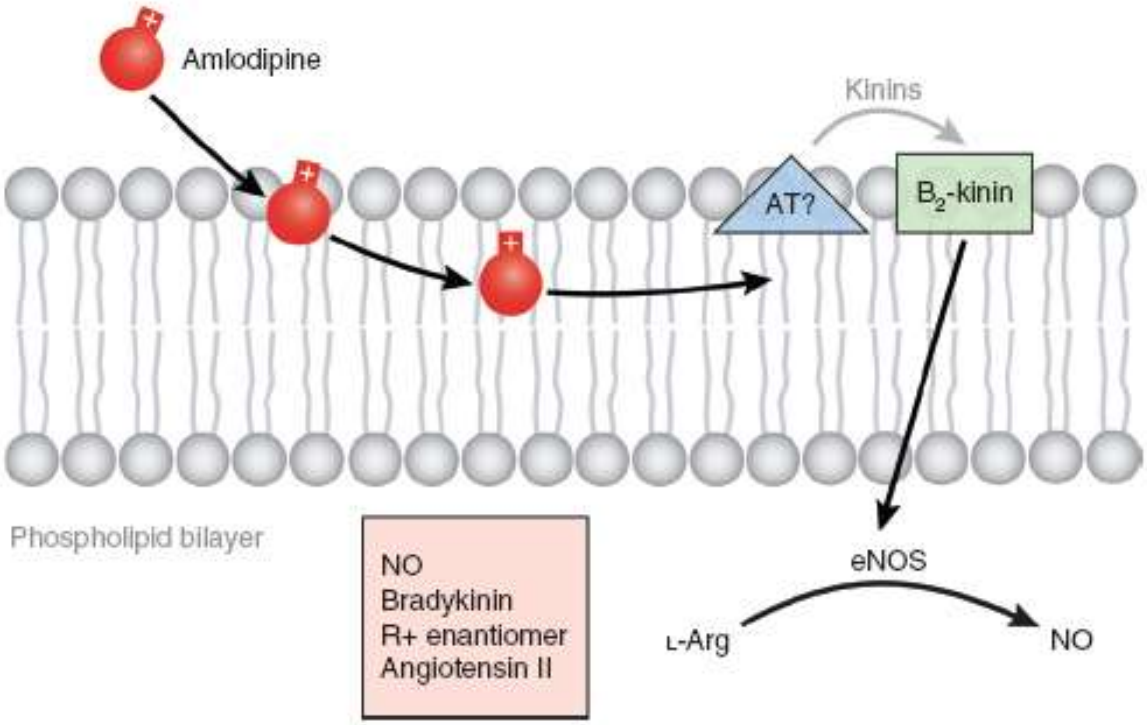
The preferred combinations in the general hypertensive population are represented as thick lines. The frames indicate classes of agents proven to beneficial in controlled intervention trials.

Rationale for the combined use of calcium channel blocker (CCB) and renin–angiotensin system (RAS) inhibitors



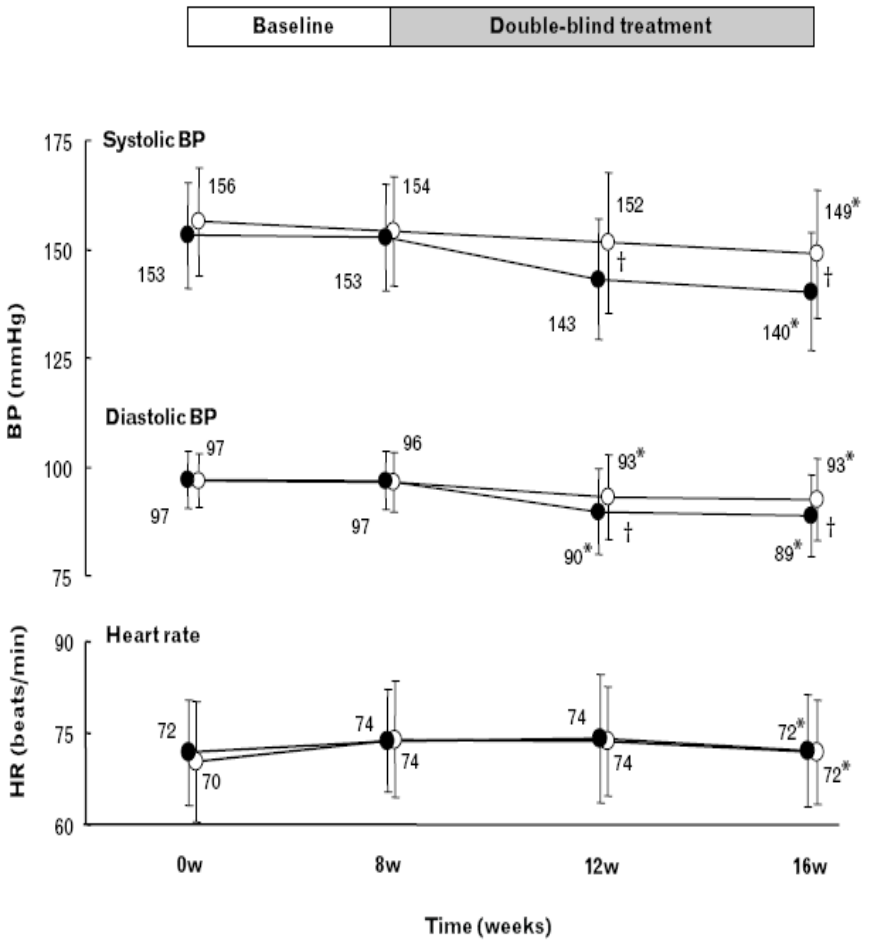
Mizuno, Am J Hyperten, 2008

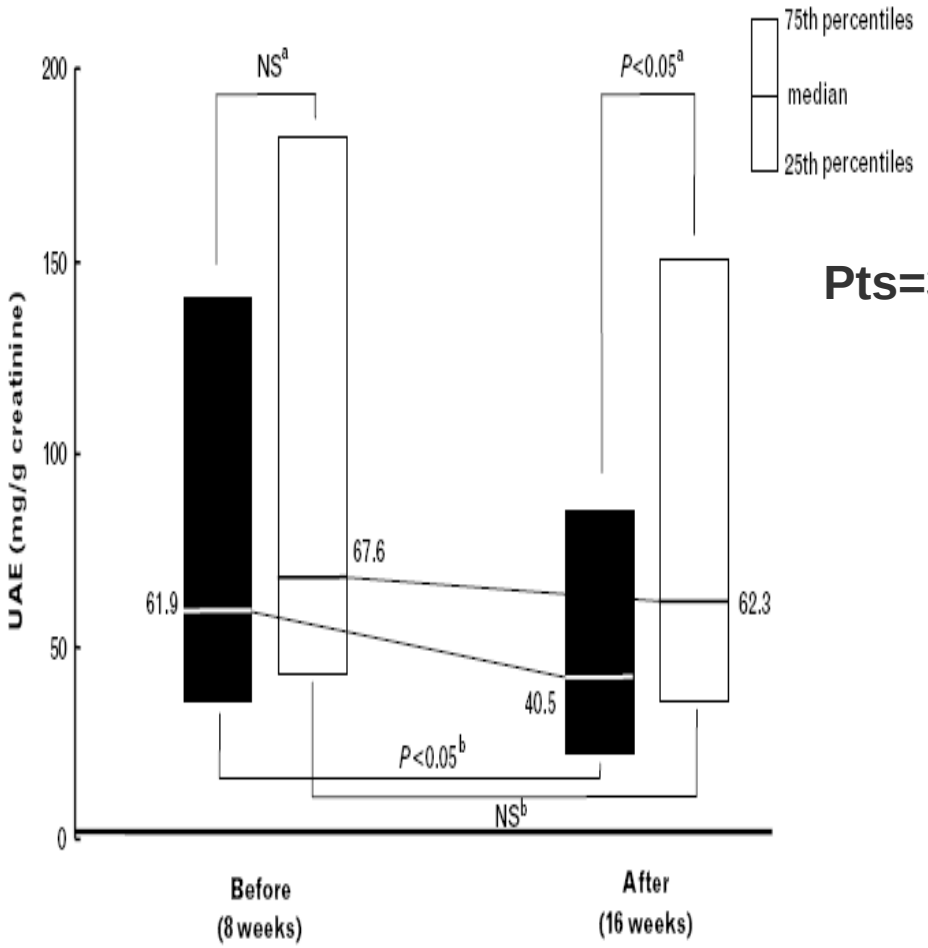
Biologic or pleiotropic actions independent of their interaction with the calcium channel



Mizuno, Am J Hyperten, 2008

NICE-Combi Study



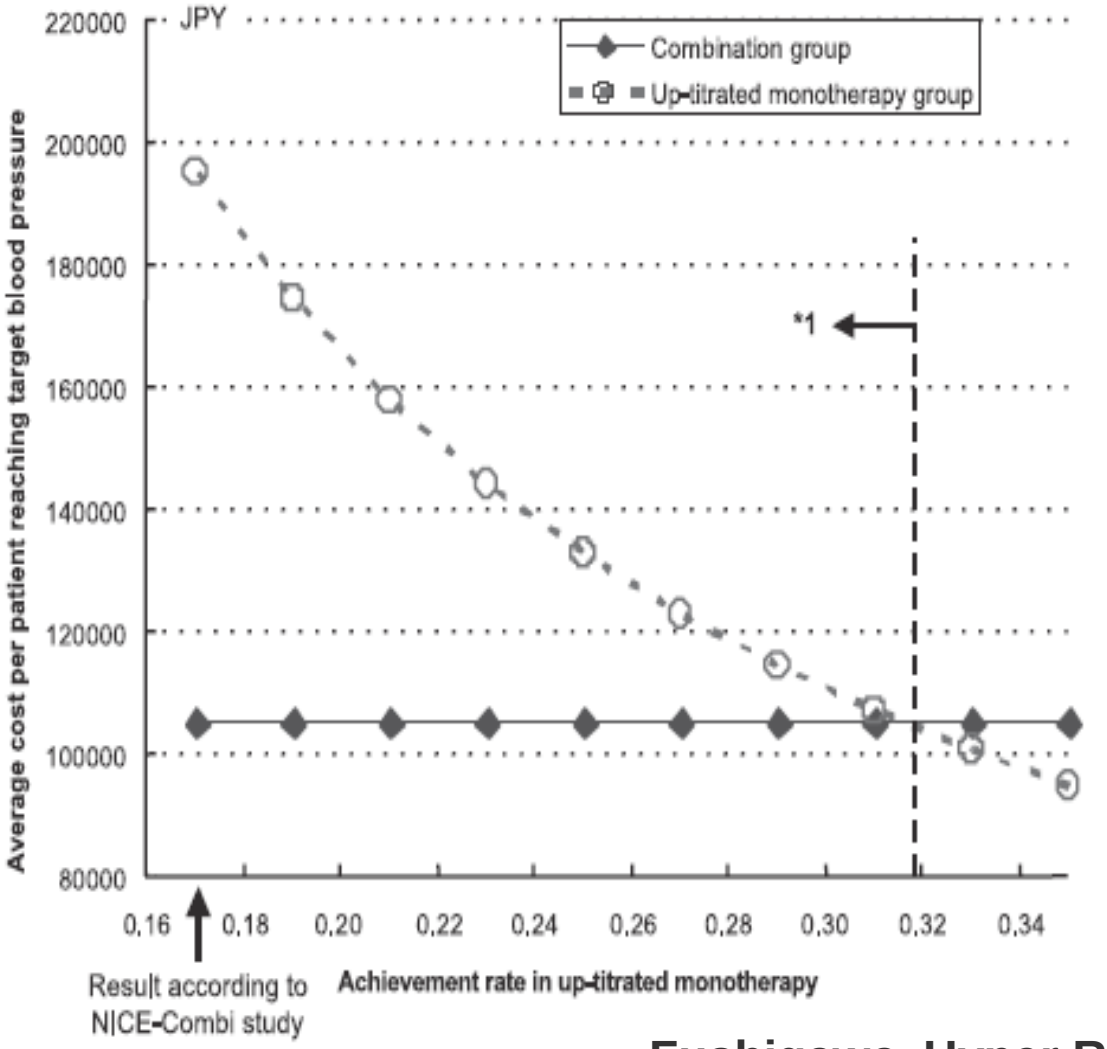


Pts=331

- **Nifedipine CR + Candesartan**
- Candesartan

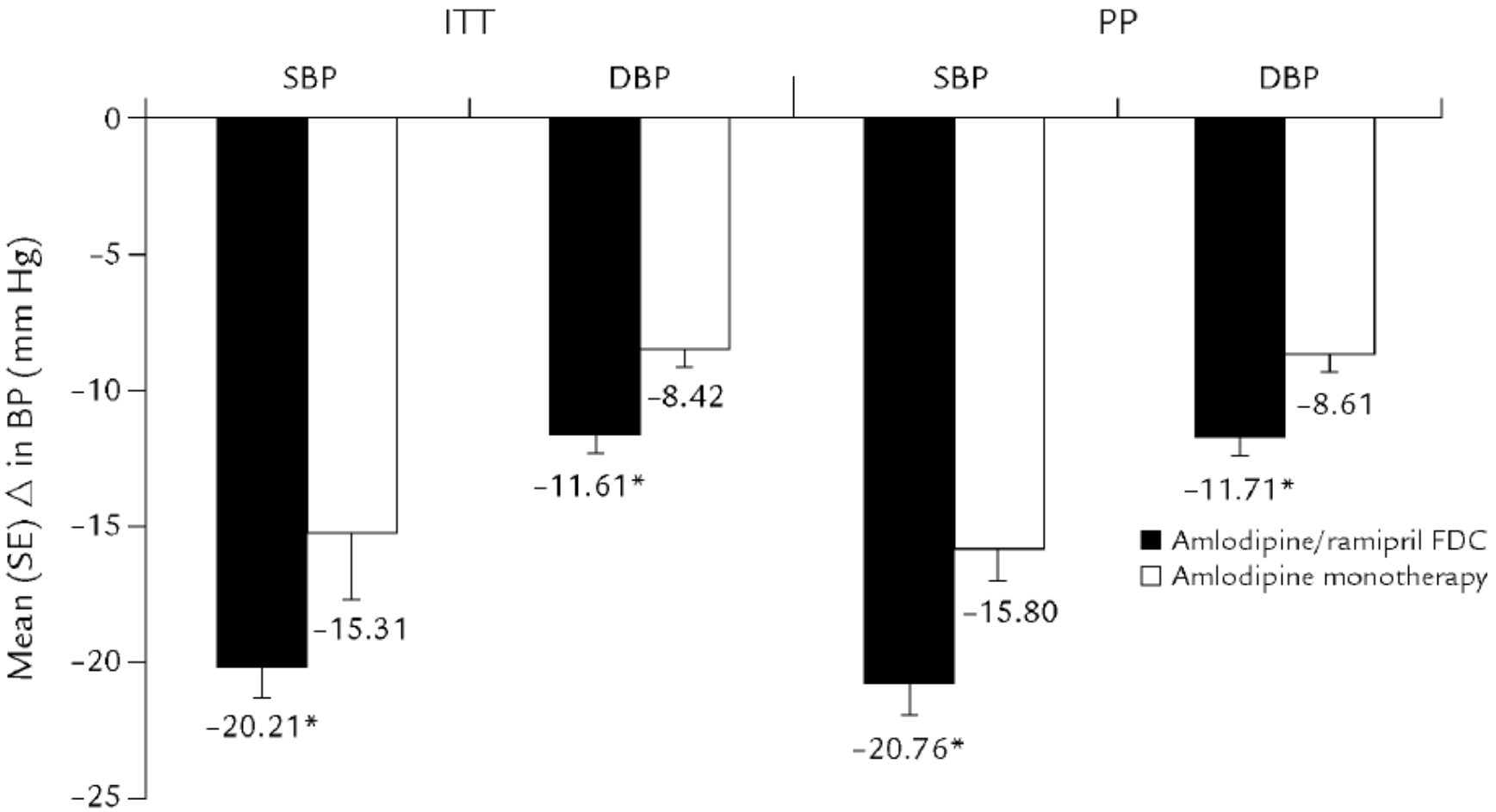
Hasebe, J Hypertension 2005

THERAPY COST COMBINATION
NICE-Comby STUDY



Fushigawa, Hyper Res 2005

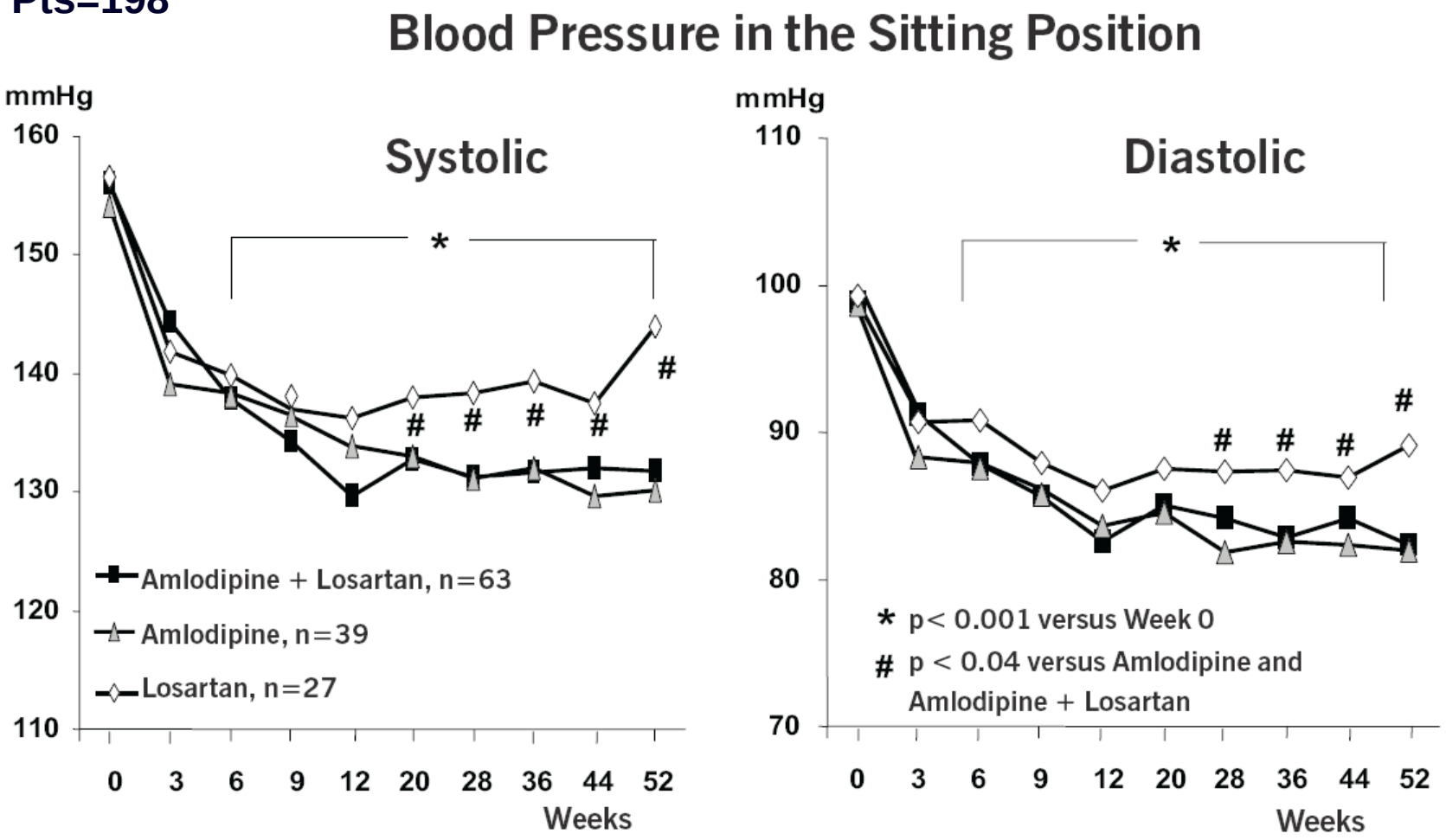
Combination Therapy of Amlodipine/Ramipril (ATAR) Study



Miranda, Clinical Therap, 2008

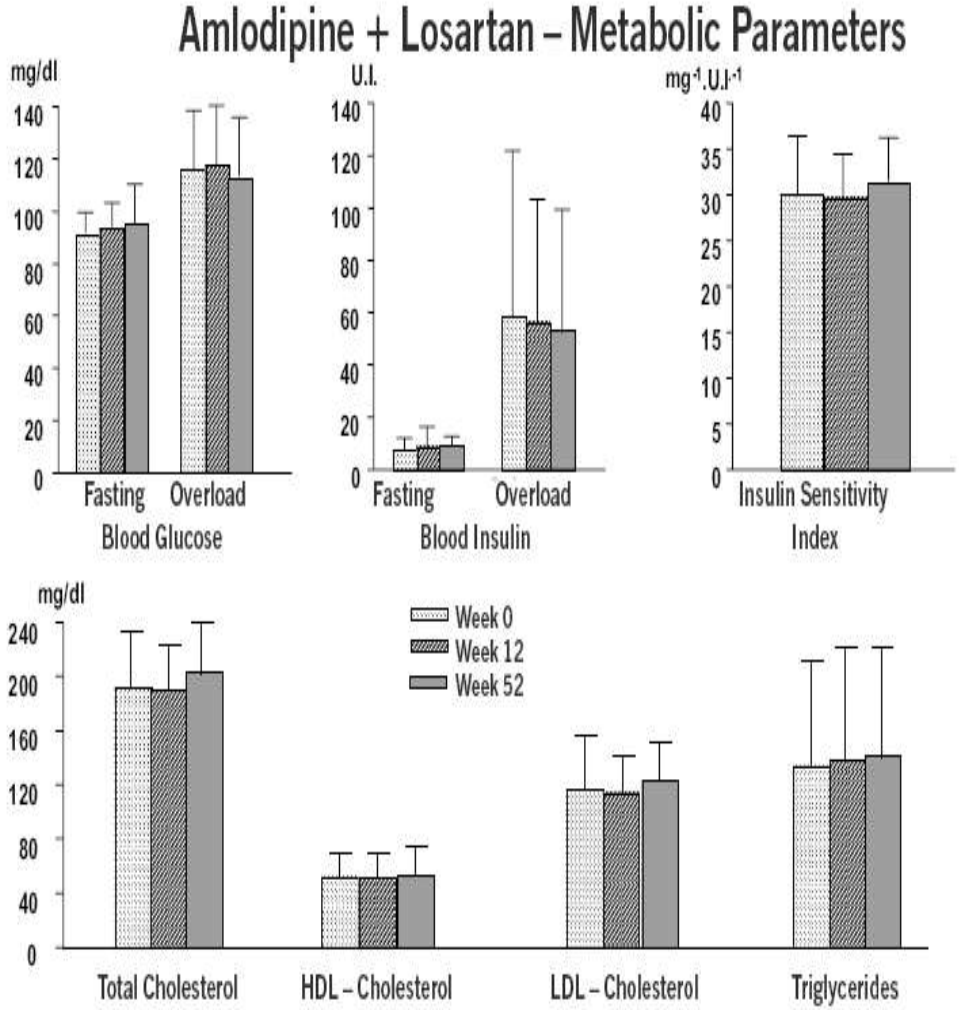
LOTHAR STUDY

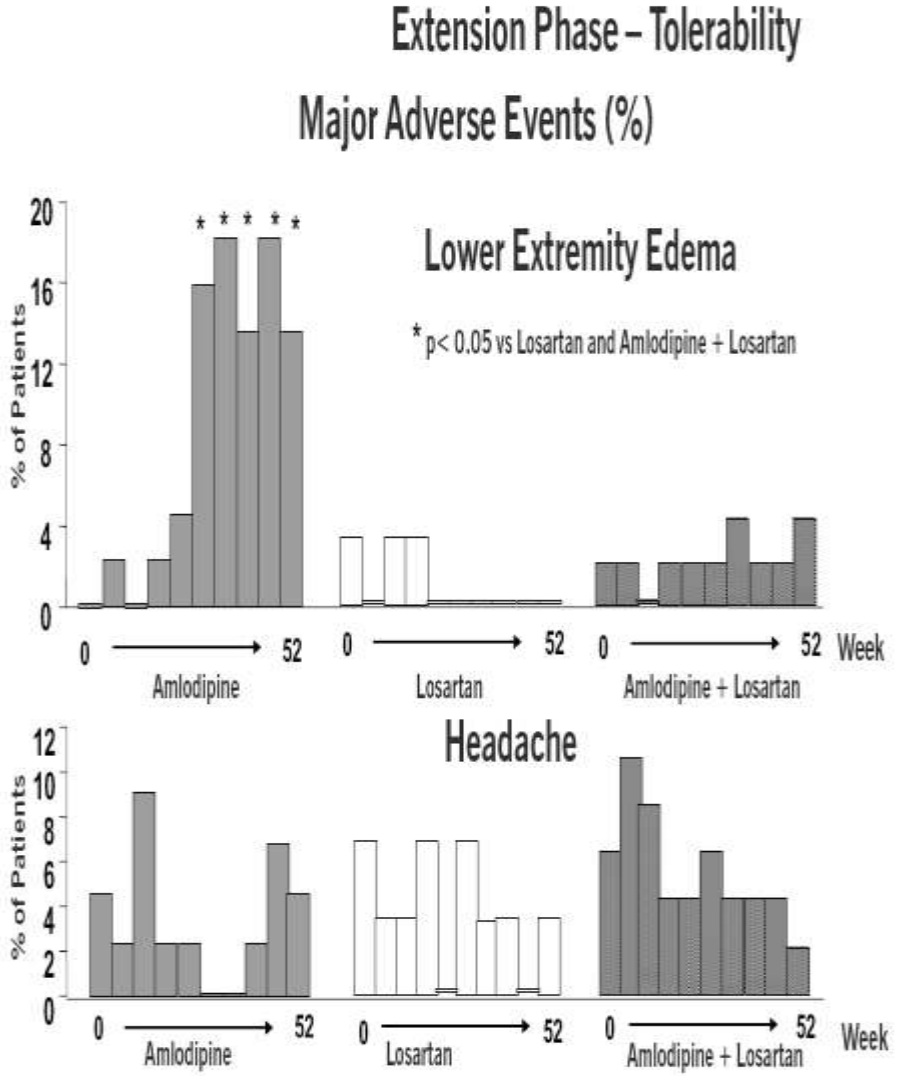
Pts=198



Kohlmann, Arch Br Cardiol, 2006

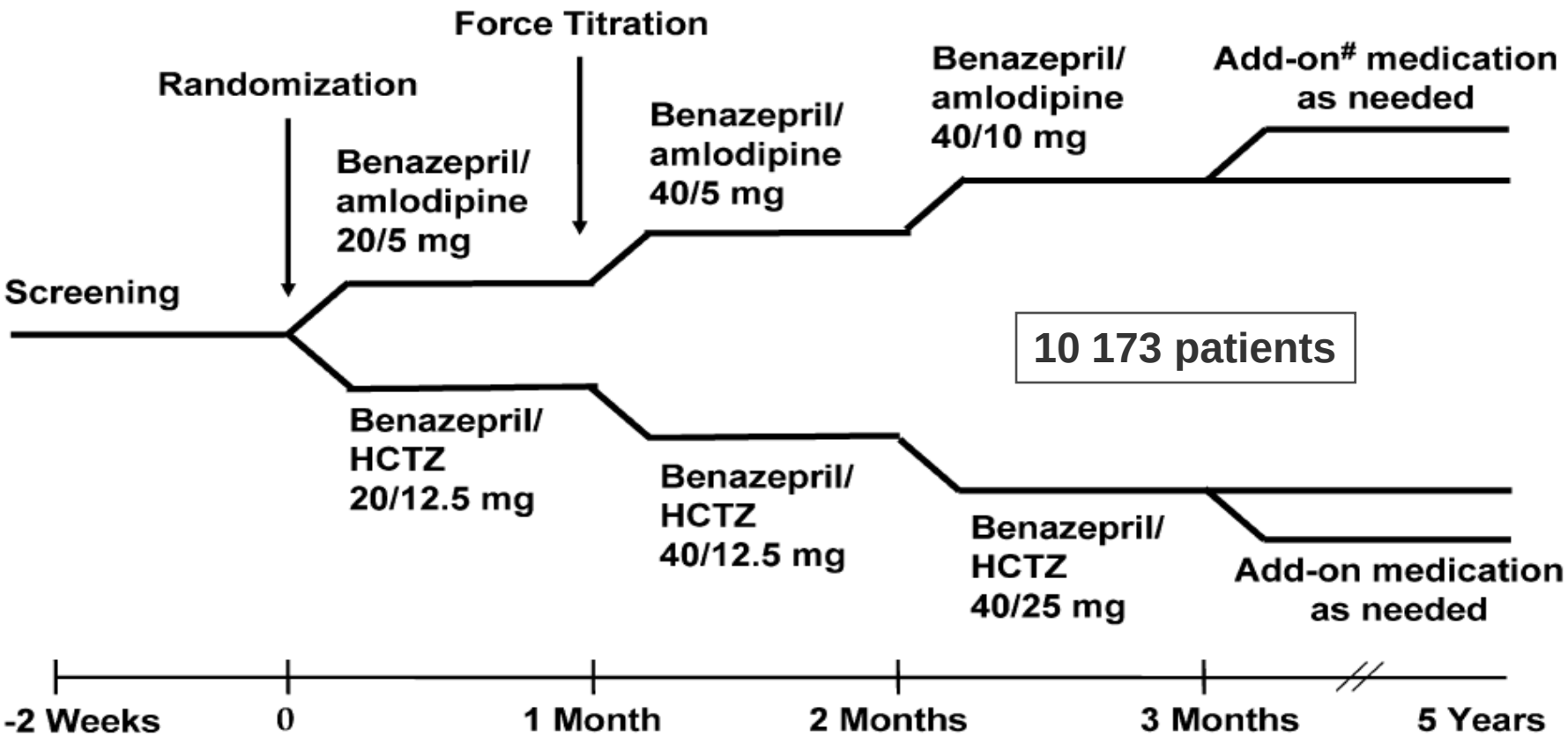
LOTHAR STUDY





The ACCOMPLISH Study

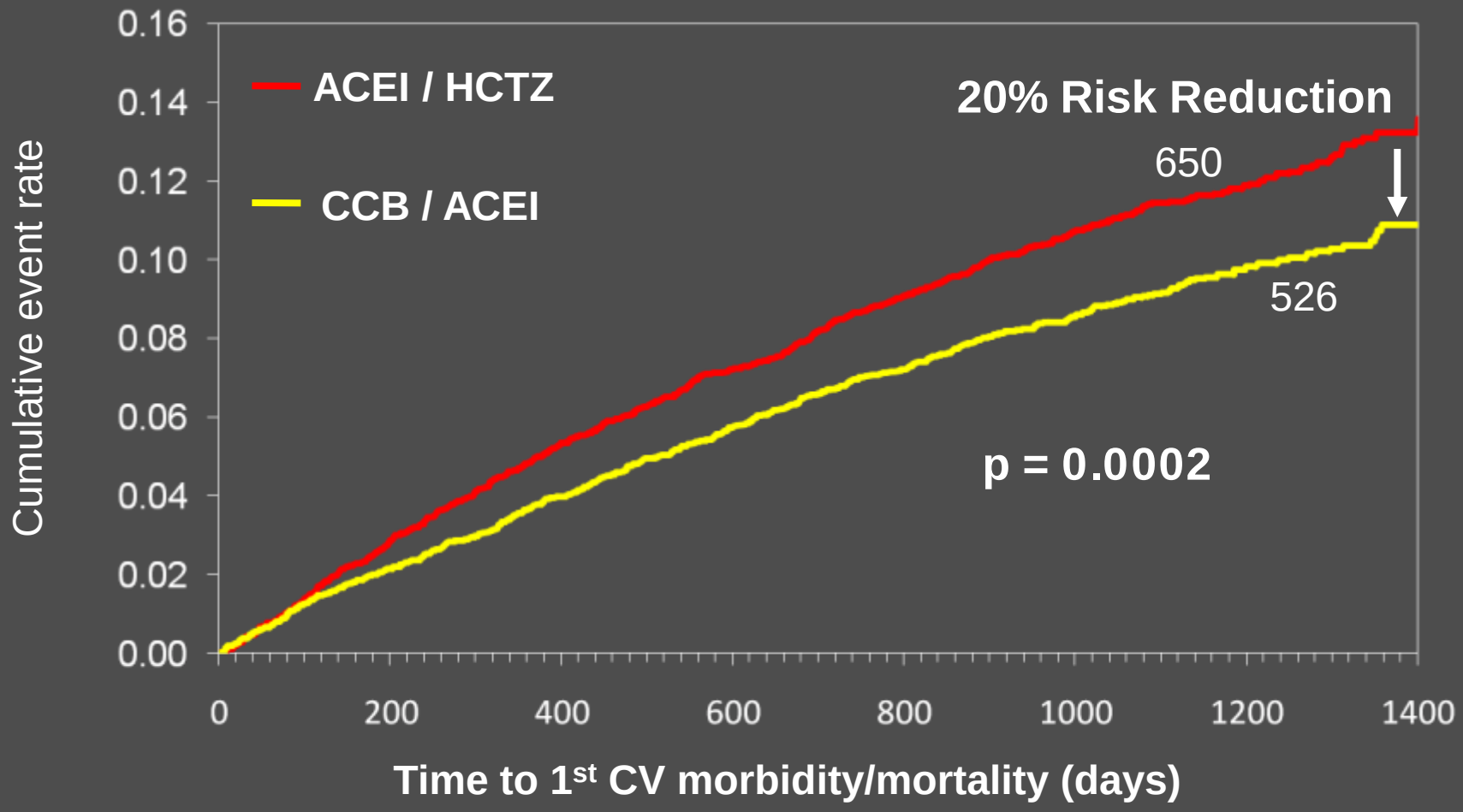
Scheme for uptitration of fixed combination treatment



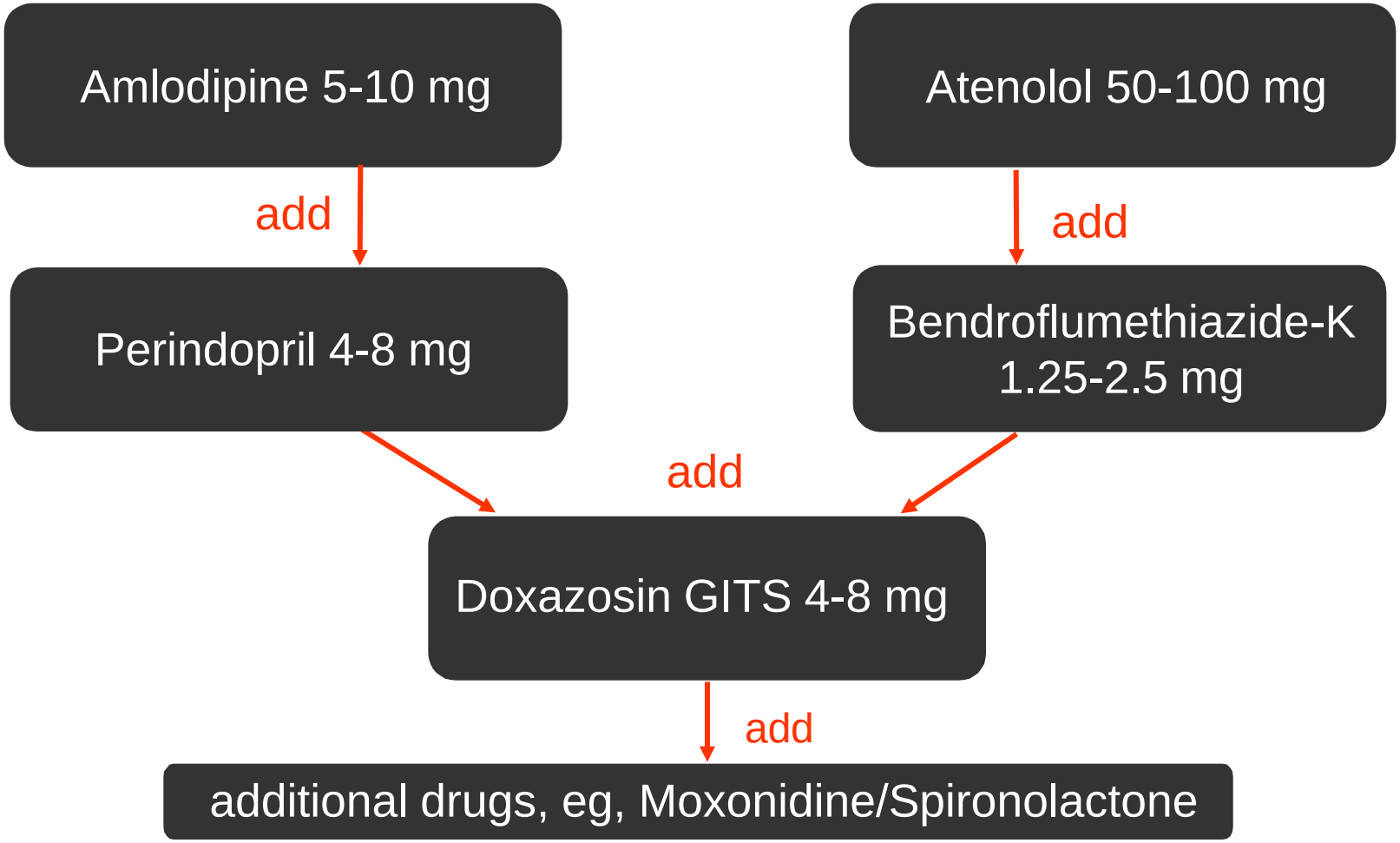
#: Add-on medications: beta-blockers, alpha-blockers, clonidine and loop diuretics.

Kjeldsen, Blood Press 2008

Primary Endpoint- ACCOMPLISH



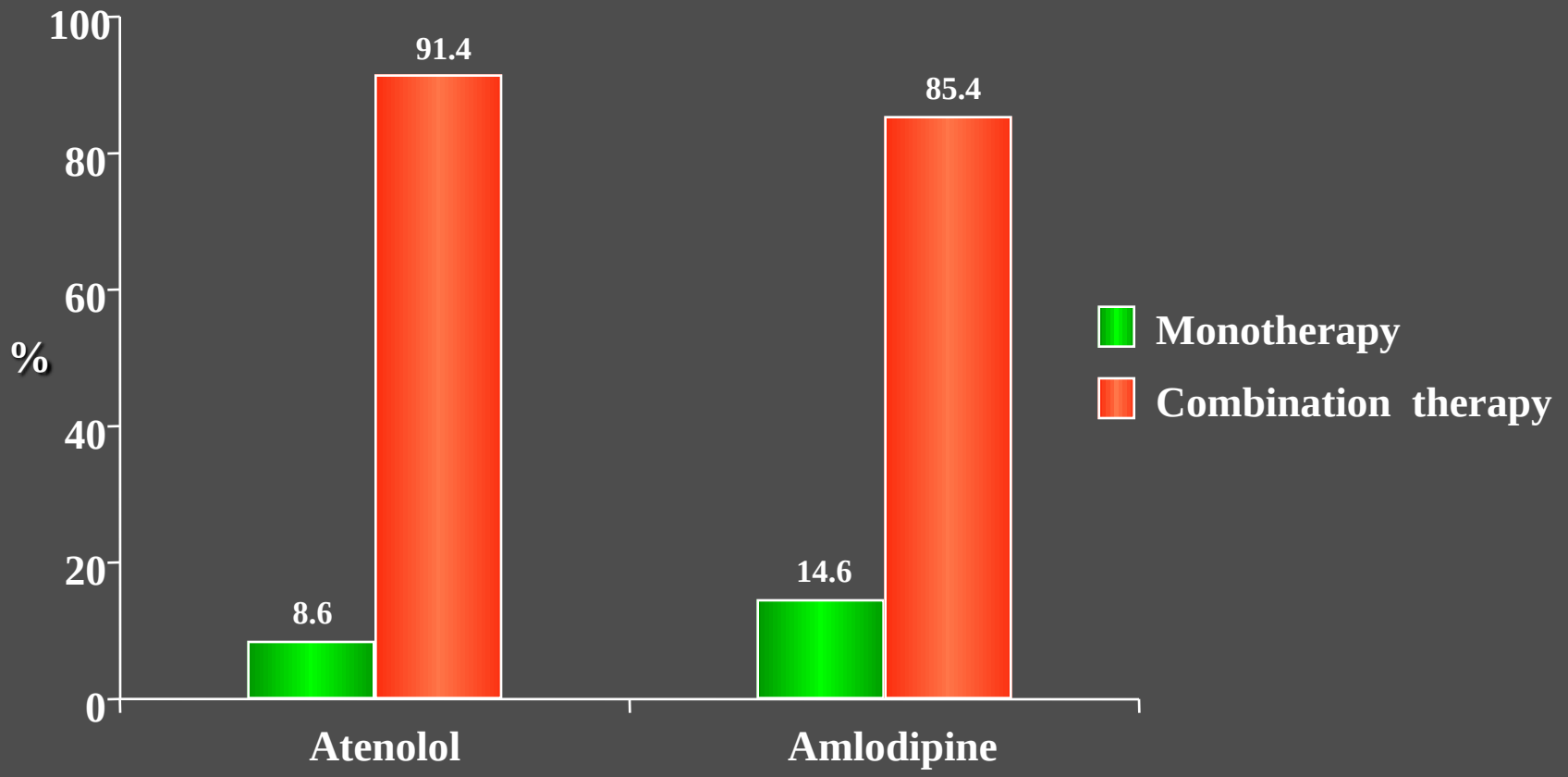
HR (95% CI): 0.80 (0.72, 0.90)



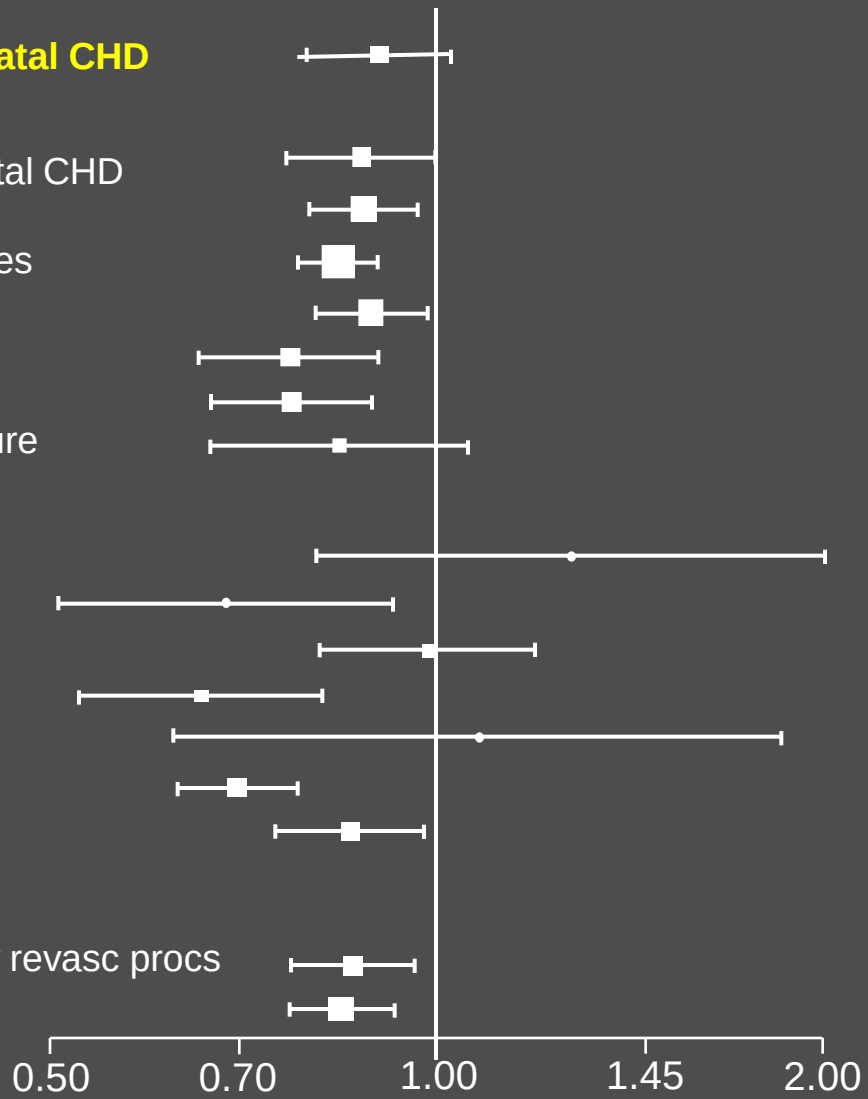
Lancet, 2005; 366,895-906

Anglo-Scandinavian ascot Cardiac Outcomes Trial

Rate of Mono / Combination Therapy in ASCOT



Summary of all end points

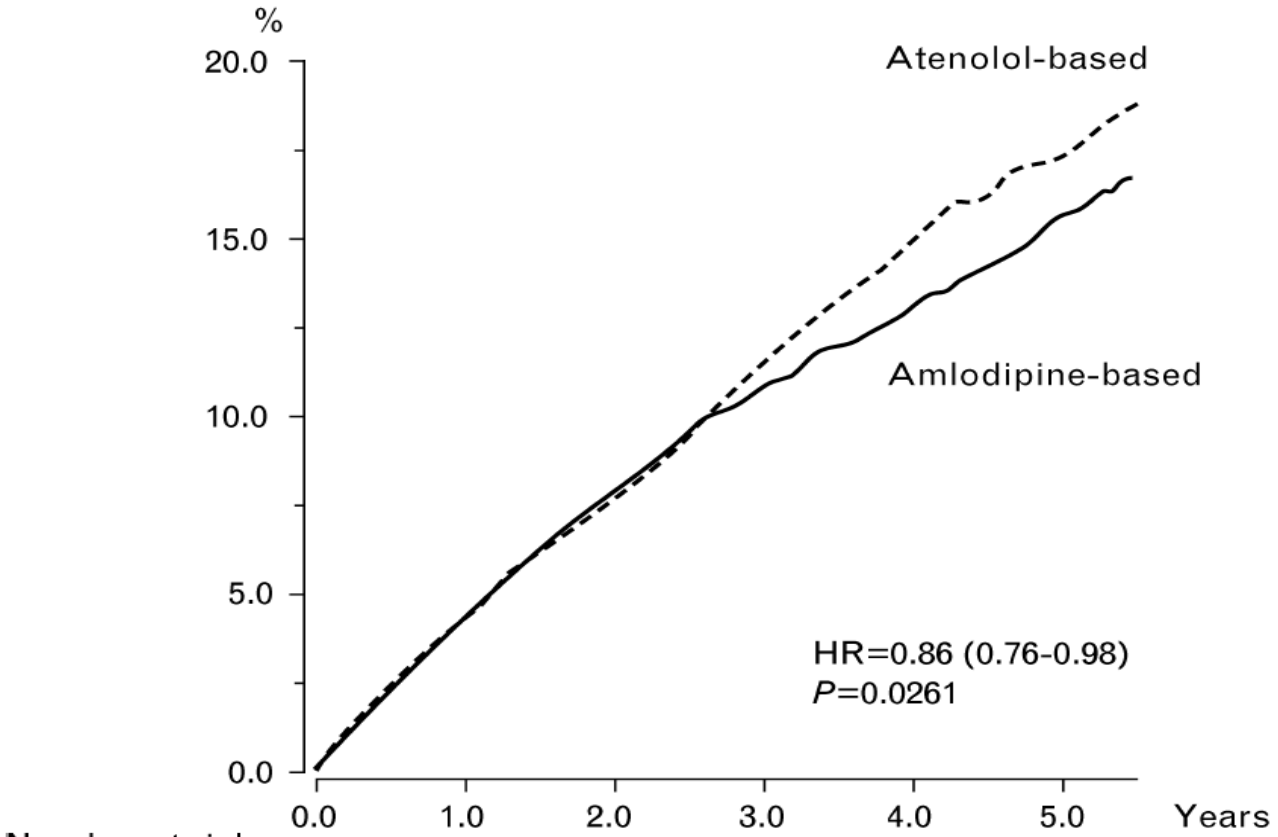


	Unadjusted Hazard ratio (95% CI)
Primary	
Non-fatal MI (incl silent) + fatal CHD	0.90 (0.79-1.02)
Secondary	
Non-fatal MI (exc. Silent) +fatal CHD	0.87 (0.76-1.00)
Total coronary end point	0.87 (0.79-0.96)
Total CV event and procedures	0.84 (0.78-0.90)
All-cause mortality	0.89 (0.81-0.99)
Cardiovascular mortality	0.76 (0.65-0.90)
Fatal and non-fatal stroke	0.77 (0.66-0.89)
Fatal and non-fatal heart failure	0.84 (0.66-1.05)
Tertiary	
Silent MI	1.27 (0.80-2.00)
Unstable angina	0.68 (0.51-0.92)
Chronic stable angina	0.98 (0.81-1.19)
Peripheral arterial disease	0.65 (0.52-0.81)
Life-threatening arrhythmias	1.07 (0.62-1.85)
New-onset diabetes mellitus	0.70 (0.63-.078)
New-onset renal impairment	0.85 (0.75-0.97)
Post hoc	
Primary end point + coronary revasc procs	0.86 (0.77-0.96)
CV death + MI + stroke	0.84 (0.76-0.92)

Effects in patients with type 2 diabetes

Anglo-Scandinavian ascot Cardiac Outcomes Trial

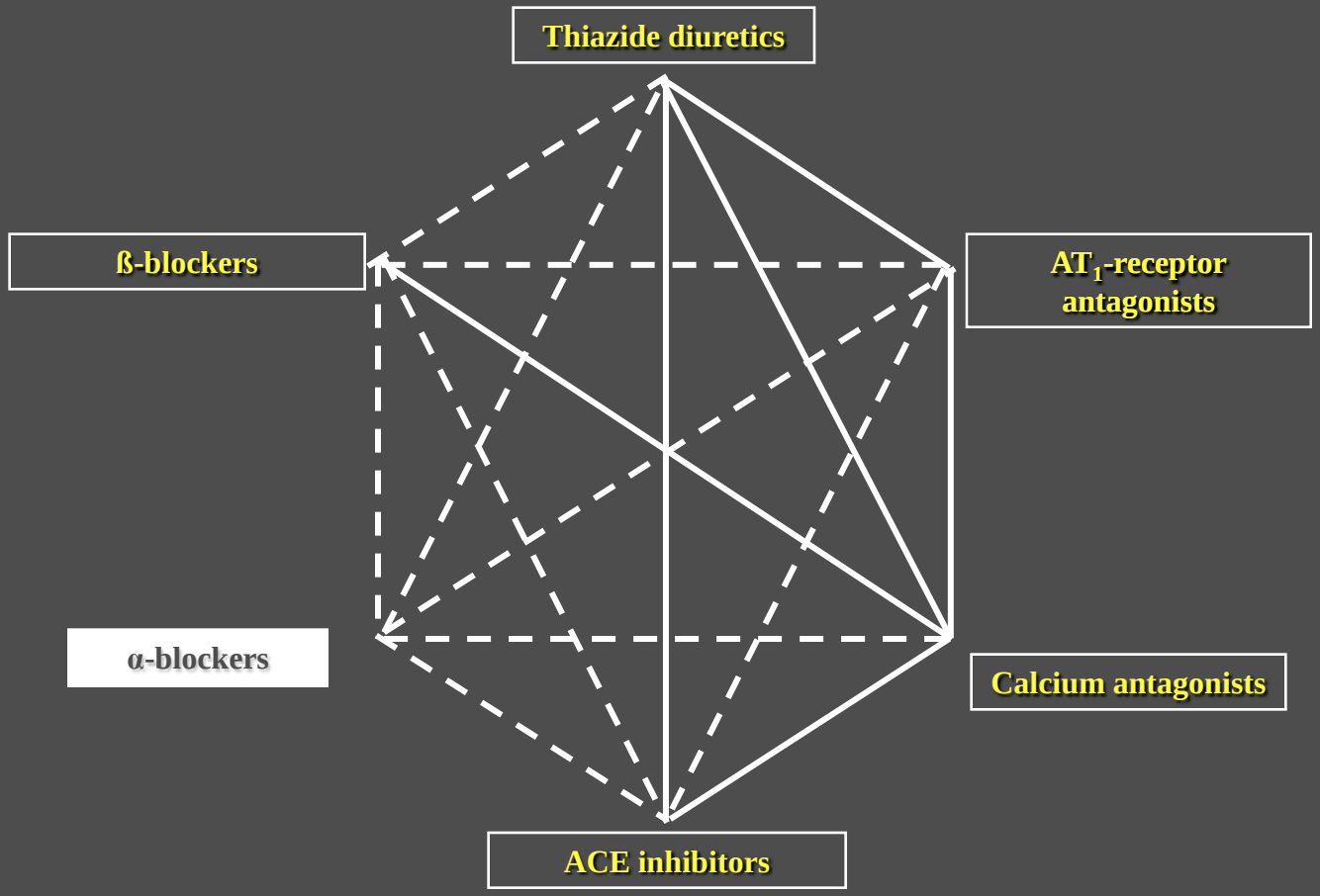
Cumulative incidence total card events and procedures



O¨ Stergren, J Hypertens, 2008

2007 ESH/ESC Guidelines

Combinations between Some Classes of Antihypertensive Drugs



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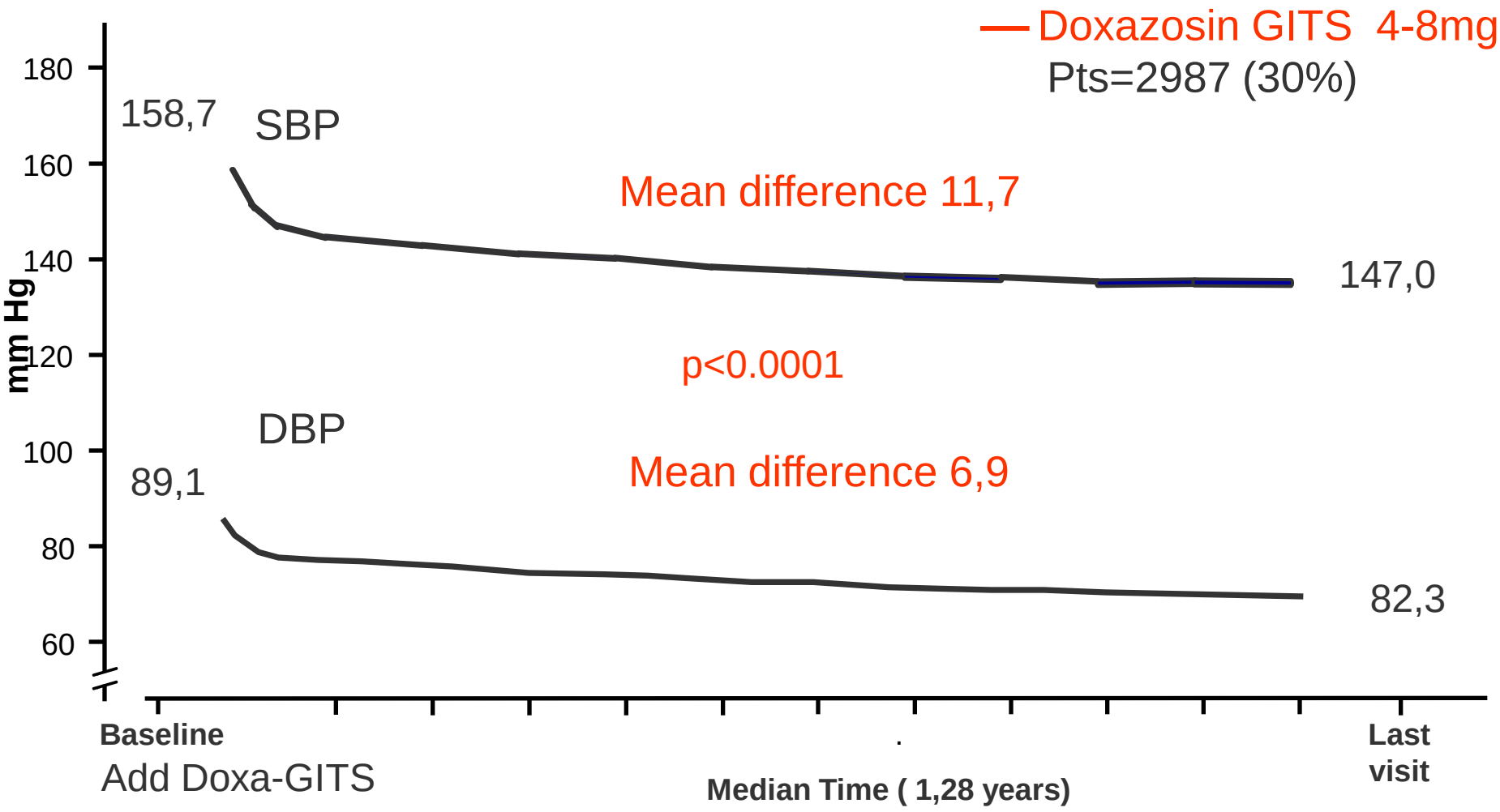
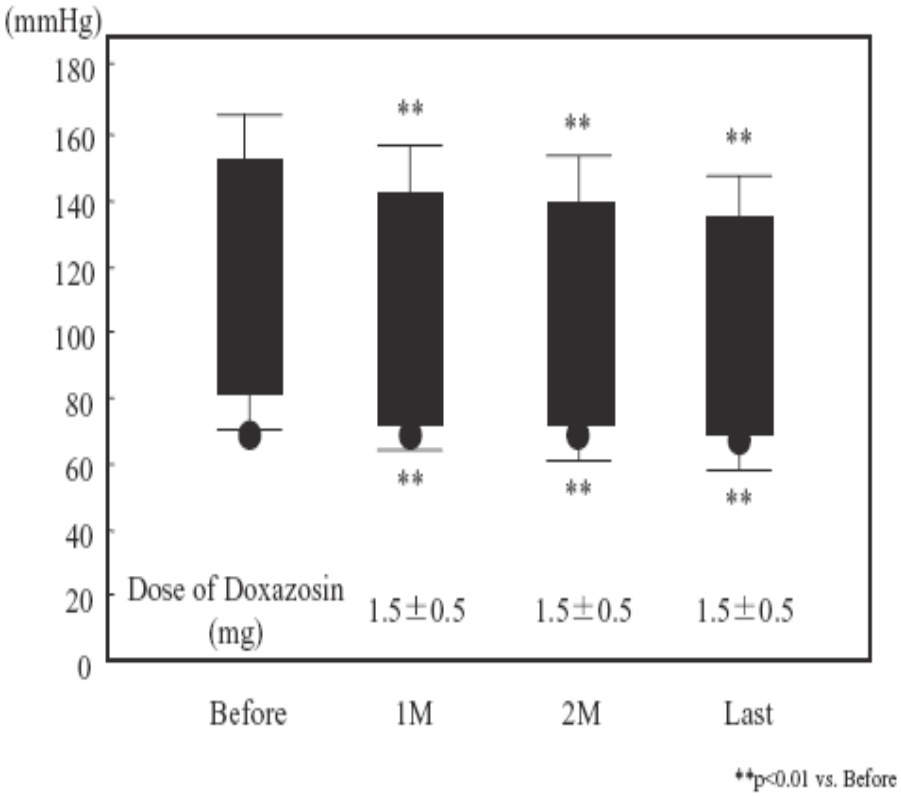
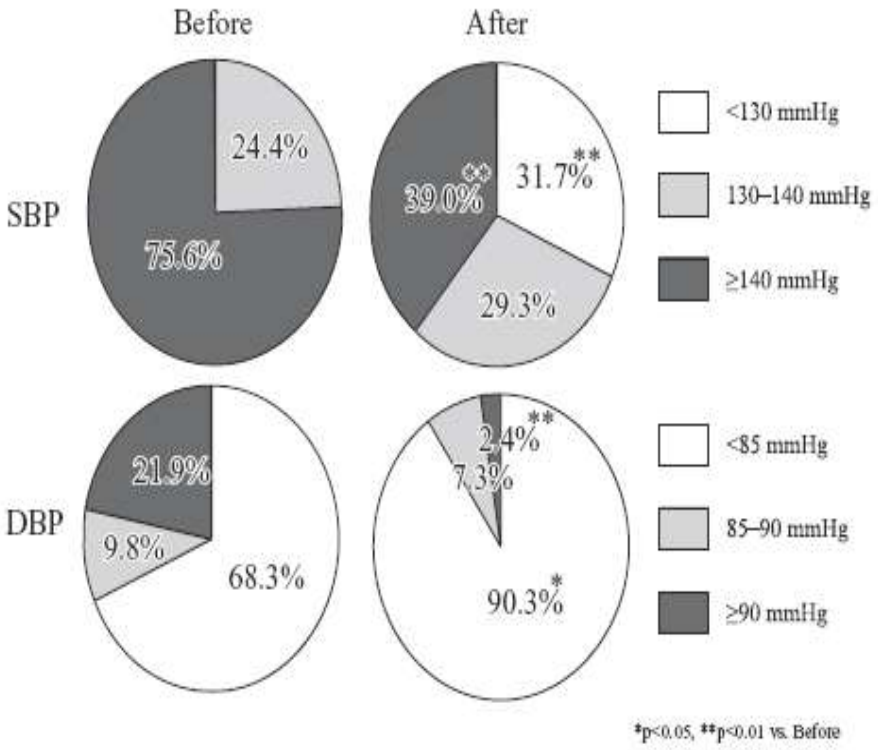
POST HOC ANALYSIS
ASCOT STUDY
DOXAZOSIN GITS EFFECTS ON BP



Unpublished data, B. Williams, 2006

Usefulness of the α1 - Blocker Doxazosin as a Third-Line Antihypertensive Drug

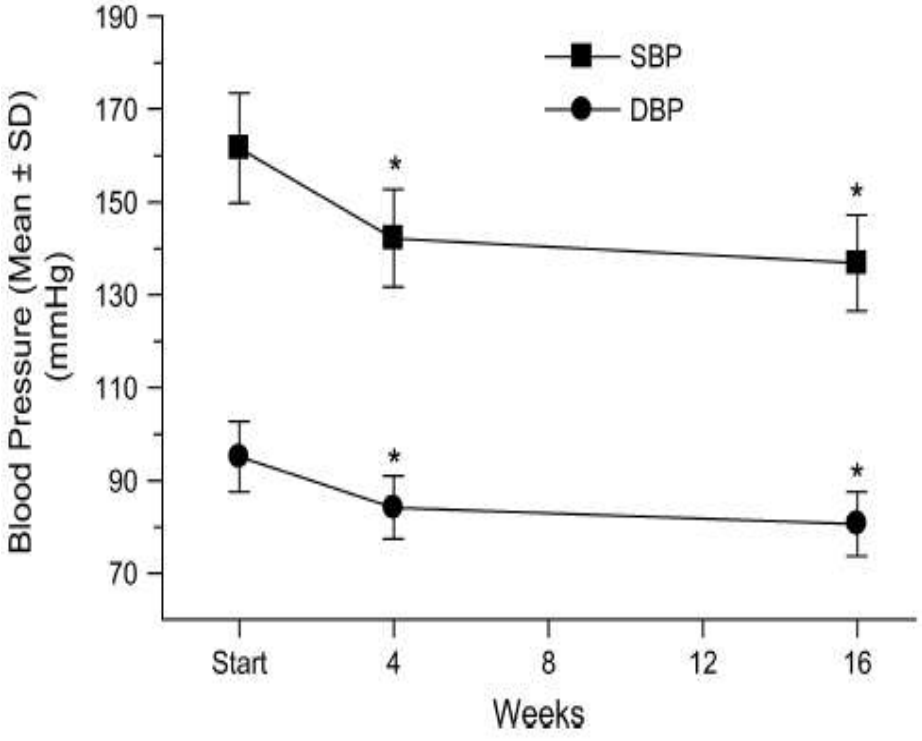




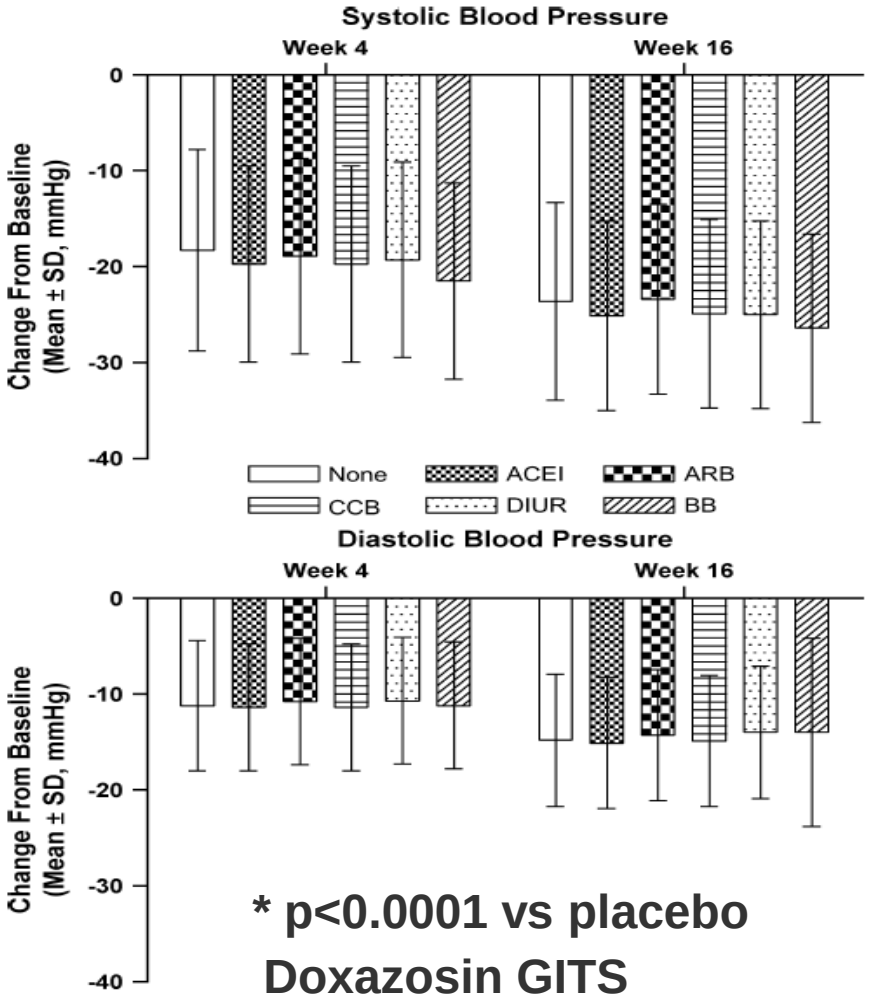
OHTA, *Hypertens Res* 2007

ASOCIA STUDY

Pts= 3200



*** p<0.0001 vs baseline**

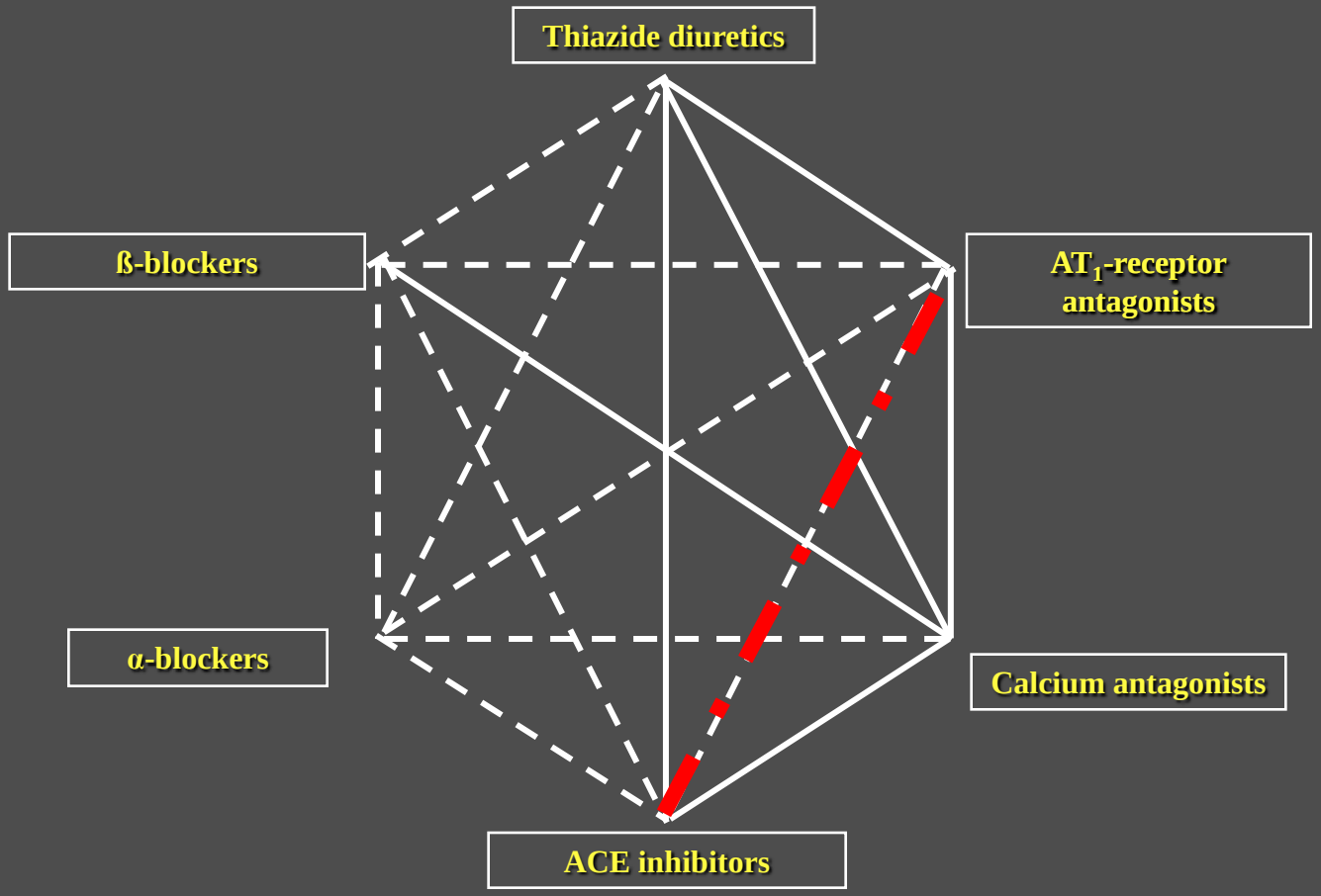


*** p<0.0001 vs placebo**
Doxazosin GITS

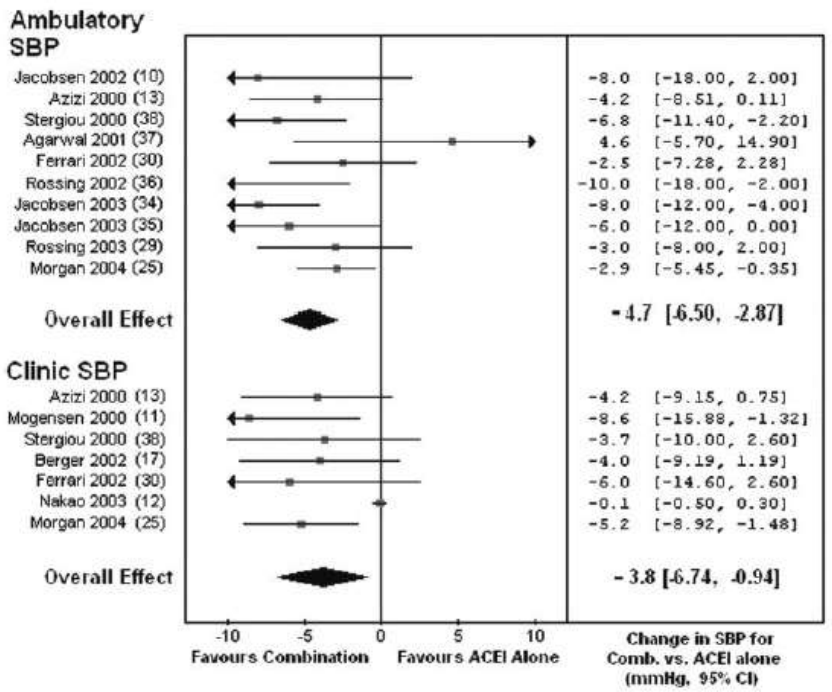
De Alvaro, J Cardiol Pharmacol 2006

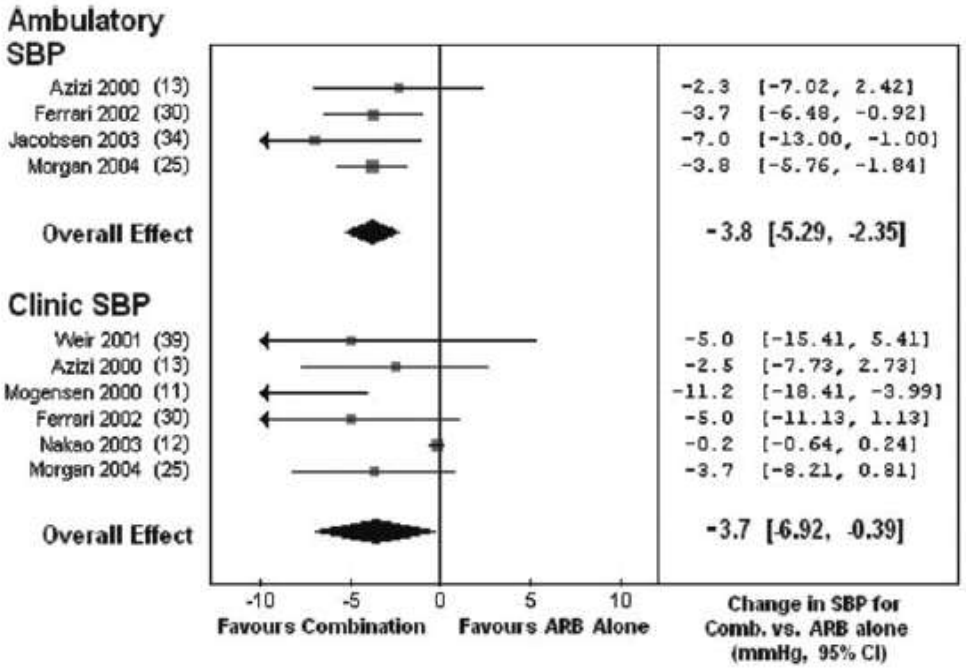
2007 ESH/ESC Guidelines

Combinations between Some Classes of Antihypertensive Drugs



Systematic Review of Combined ACEI & ARBS in Hypertension





ARBs+ACEIs vs ACEIs

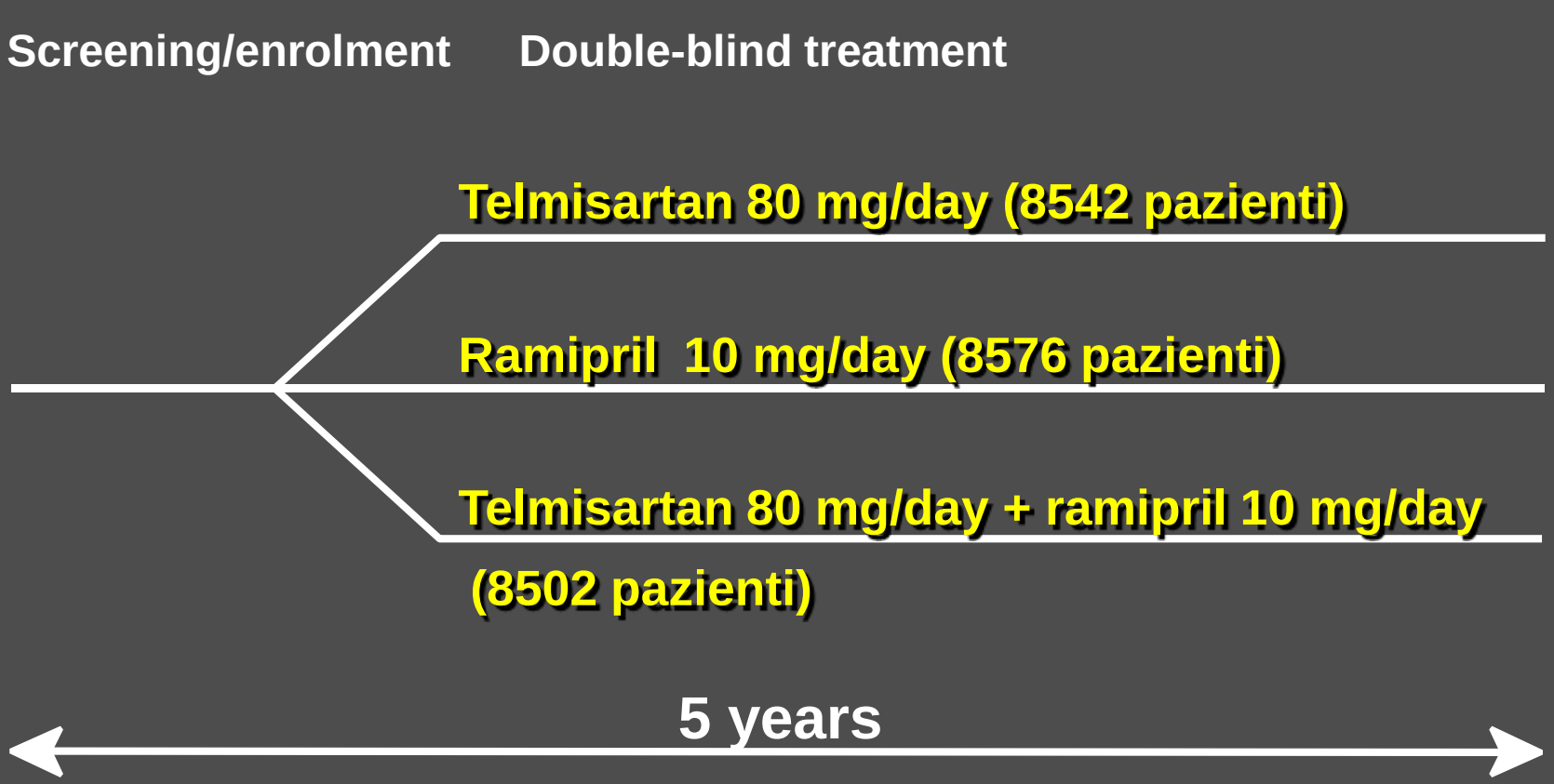
Δ BP: -4.7/-3.8 mmHg

ARBs+ACEIs vs ARBs

Δ BP: -3.8/-3.7 mmHg

Doulton , *Hypertension*. 2005;45:880-886

ONTARGET

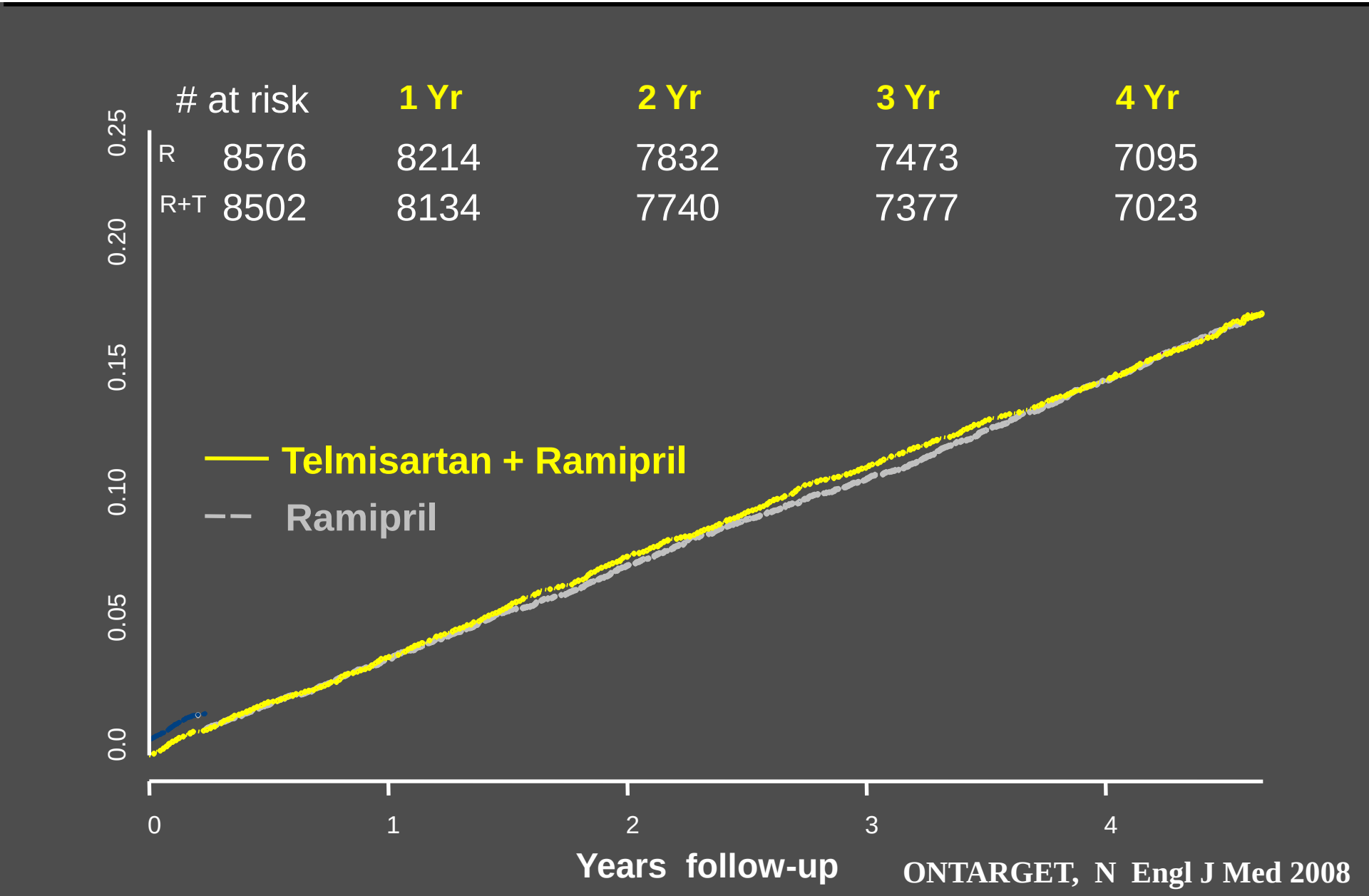


ONTARGET, N Engl J Med 2008

ONTARGET

	Ramipril	Telmisartan	Combination
Systolic BP	-6.0	-6.9	-8.4
Diastolic BP	-4.6	-5.2	-6.0

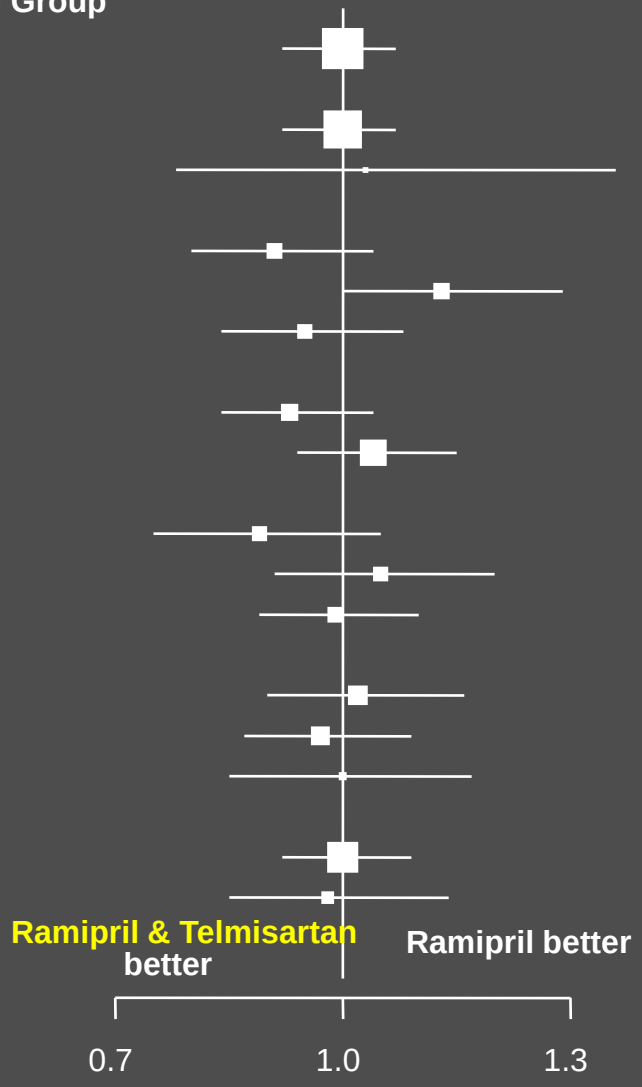
End-point primario



ONTARGET, N Engl J Med 2008

T+R vs R: PRIMARY COMPOSITE

	No. of Patients	Incidence of Primary Outcome in Ramipril Group
Primary Composite	17078	16.4
Hx of CVD	15589	16.7
No Hx of CVD	1484	13.1
SBP <= 134	5714	16.2
134 < SBP <= 150	6019	14.9
SBP > 150	5329	18.3
Diabetes	6364	20.6
No Diabetes	10709	14.0
HOPE Low Risk Score	5637	10.4
HOPE Medium Risk Score	5596	15.0
HOPE High Risk Score	5845	23.8
Age < 65	7362	13.0
65 <= Age < 75	7177	17.2
Age >= 75	2539	24.1
Male	12497	16.7
Female	4581	15.7



ONTARGET, N Engl J Med 2008

ONTARGET - renal outcomes

	Ramipril n (%)	Telmisartan n (%)	Ramipril+ telmisartan n (%)	Telmisartan vs ramipril HR (95% CI)	p	Ramipril+ telmisartan vs ramipril HR (95% CI)	p
All dialysis, doubling, death	1150 (13·4)	1147 (13·4)	1233 (14·5)	1·00 (0·92–1·09)	0·968	1·09 (1·01–1·18)	0·037
All dialysis and doubling	174 (2·03)	189 (2·21)	212 (2·49)	1·09 (0·89–1·34)	0·420	1·24 (1·01–1·51)	0·038
All dialysis	48 (0·56)	51 (0·60)	63 (0·74)	1·07 (0·72–1·58)	0·747	1·33 (0·92–1·94)	0·133
All death	1014 (11·8)	989 (11·6)	1065 (12·5)	0·98 (0·90–1·07)	0·641	1·07 (0·98–1·16)	0·144
Doubling	140 (1·63)	155 (1·81)	166 (1·95)	1·11 (0·88–1·39)	0·378	1·20 (0·96–1·50)	0·110
Acute dialysis	13 (0·15)	20 (0·23)	28 (0·33)	1·55 (0·77–3·11)	0·221	2·19 (1·13–4·22)	0·020
Chronic dialysis	33 (0·39)	31 (0·36)	34 (0·40)	0·94 (0·58–1·54)	0·817	1·05 (0·65–1·69)	0·854

Mann, *Lancet* 2008;

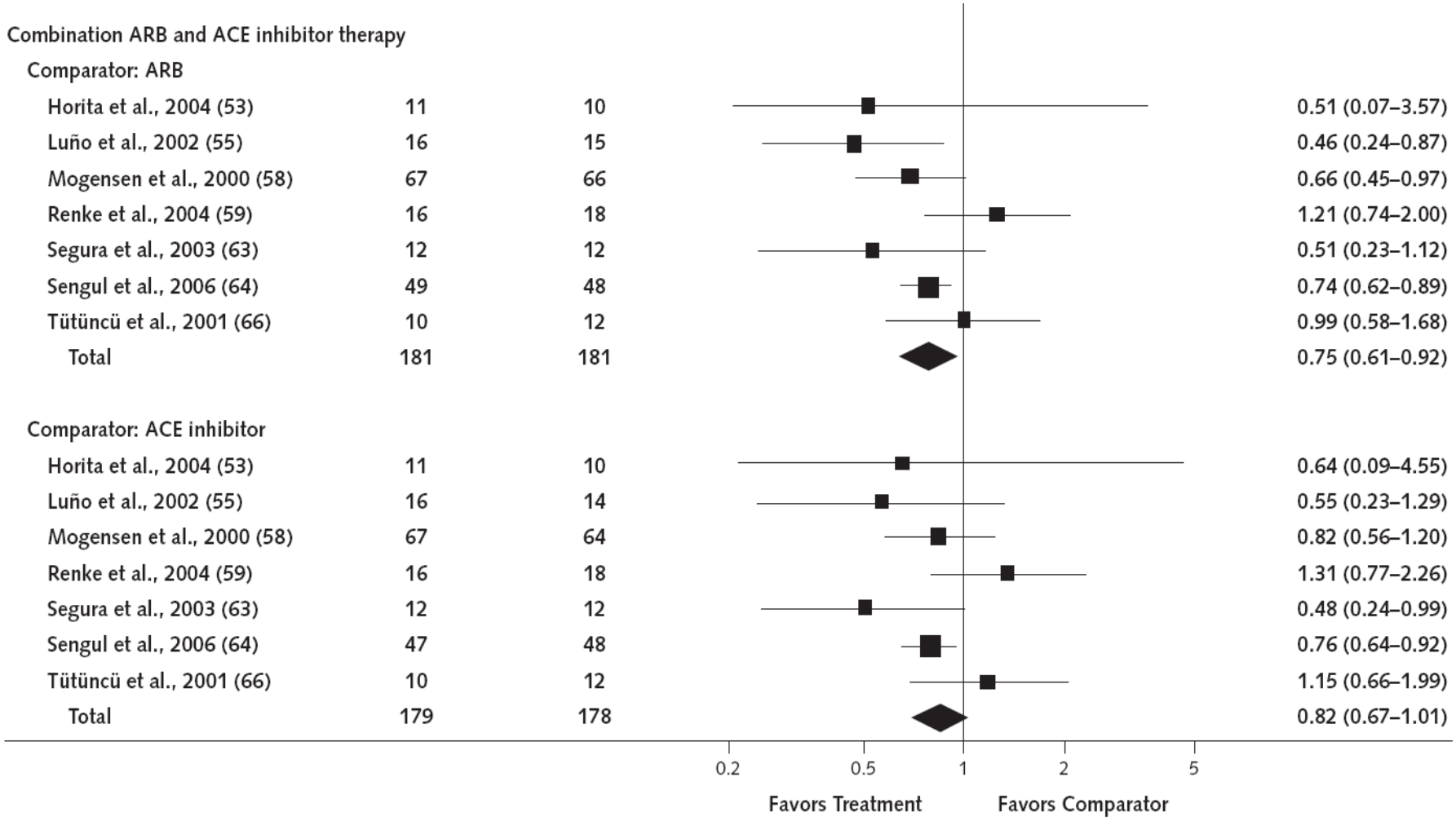
ONTARGET

Changes in log urine albumin to creatinine ratio

	Ramipril gMean (95% CI)	Telmisartan gMean (95% CI)	Ramipril+telmisartan gMean (95% CI)	Telmisartan vs ramipril p	Telmisartan+ramipril vs ramipril p
UACR, Baseline	0·81 (0·78–0·84)	0·83 (0·80–0·86)	0·81 (0·78–0·84)	0·246	0·923
2-year ratio to baseline	1·17 (1·13–1·20)	1·08 (1·05–1·12)	1·05 (1·02–1·08)	0·0013	<0·0001
Final ratio to baseline	1·32 (1·27–1·37)	1·25 (1·20–1·29)	1·22 (1·17–1·26)	0·033	0·0028
LO ratio to baseline	1·31 (1·26–1·35)	1·24 (1·20–1·28)	1·21 (1·17–1·25)	0·027	0·0009

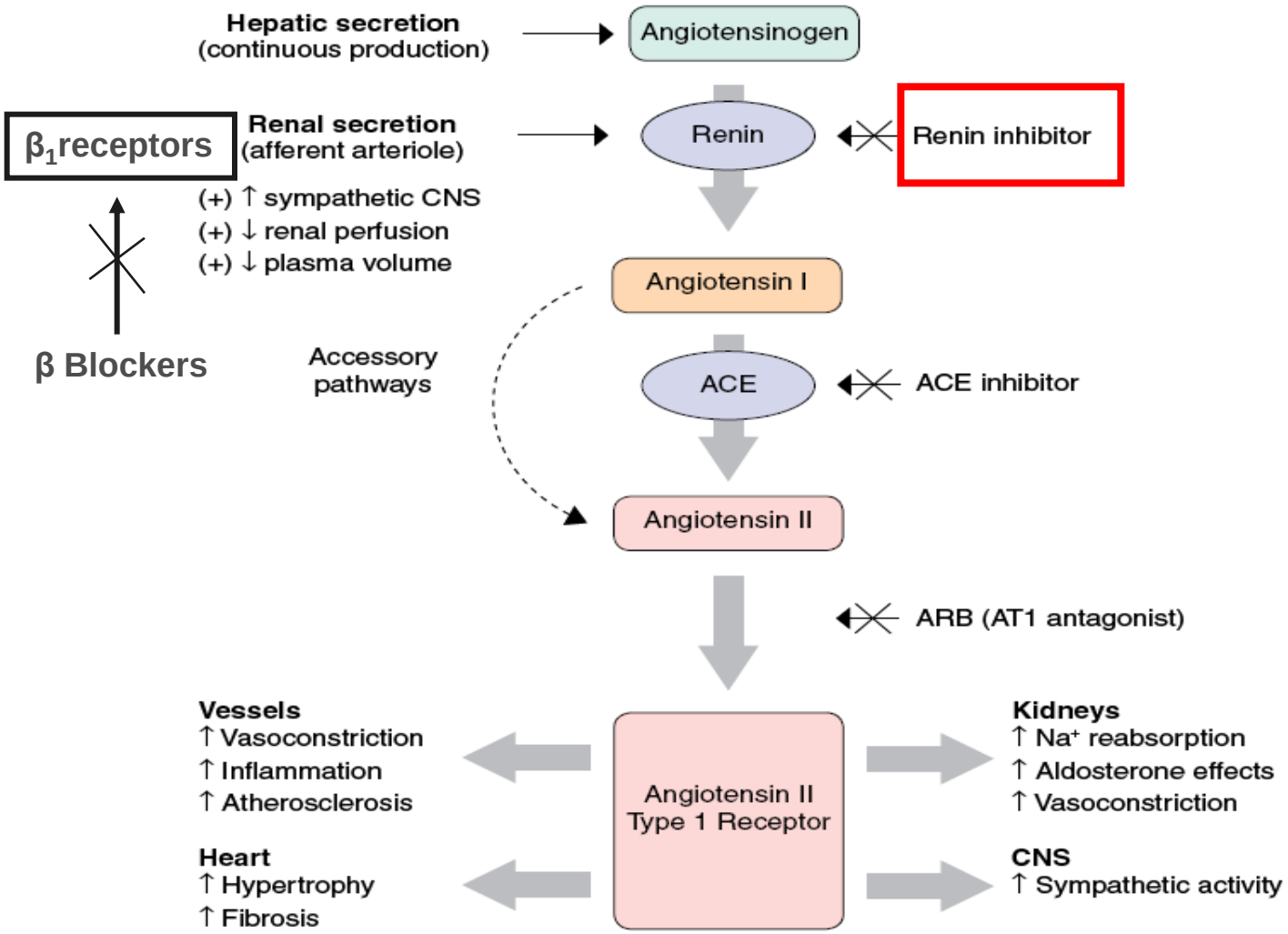
Mann, *Lancet* 2008

Combination Therapy with Inhibitors of the Renin–Angiotensin System on Proteinuria in Renal Disease



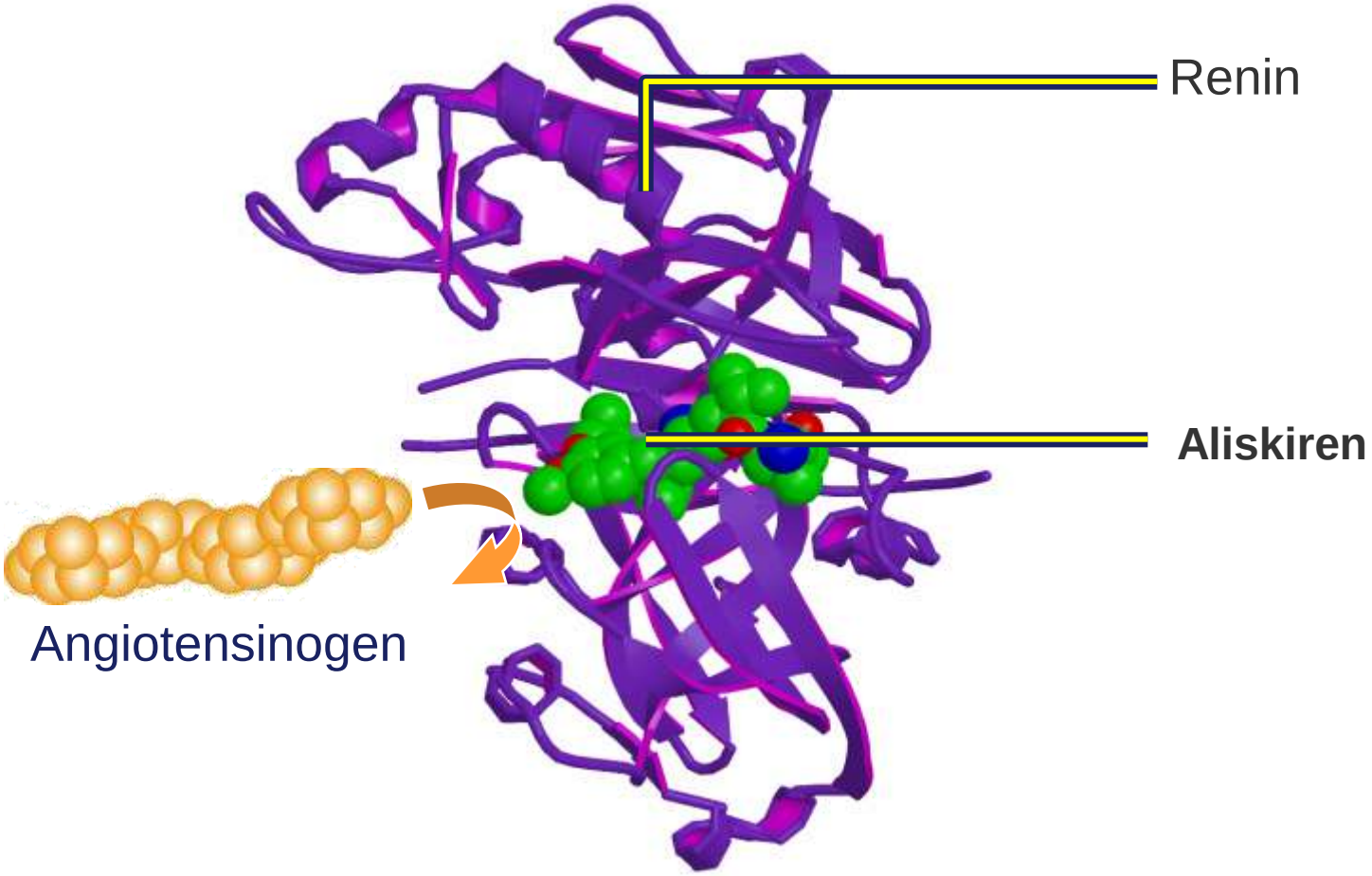
Kunz, *Ann Intern Med,* 2008

Effect of pharmacologic agents on the renin–angiotensin system



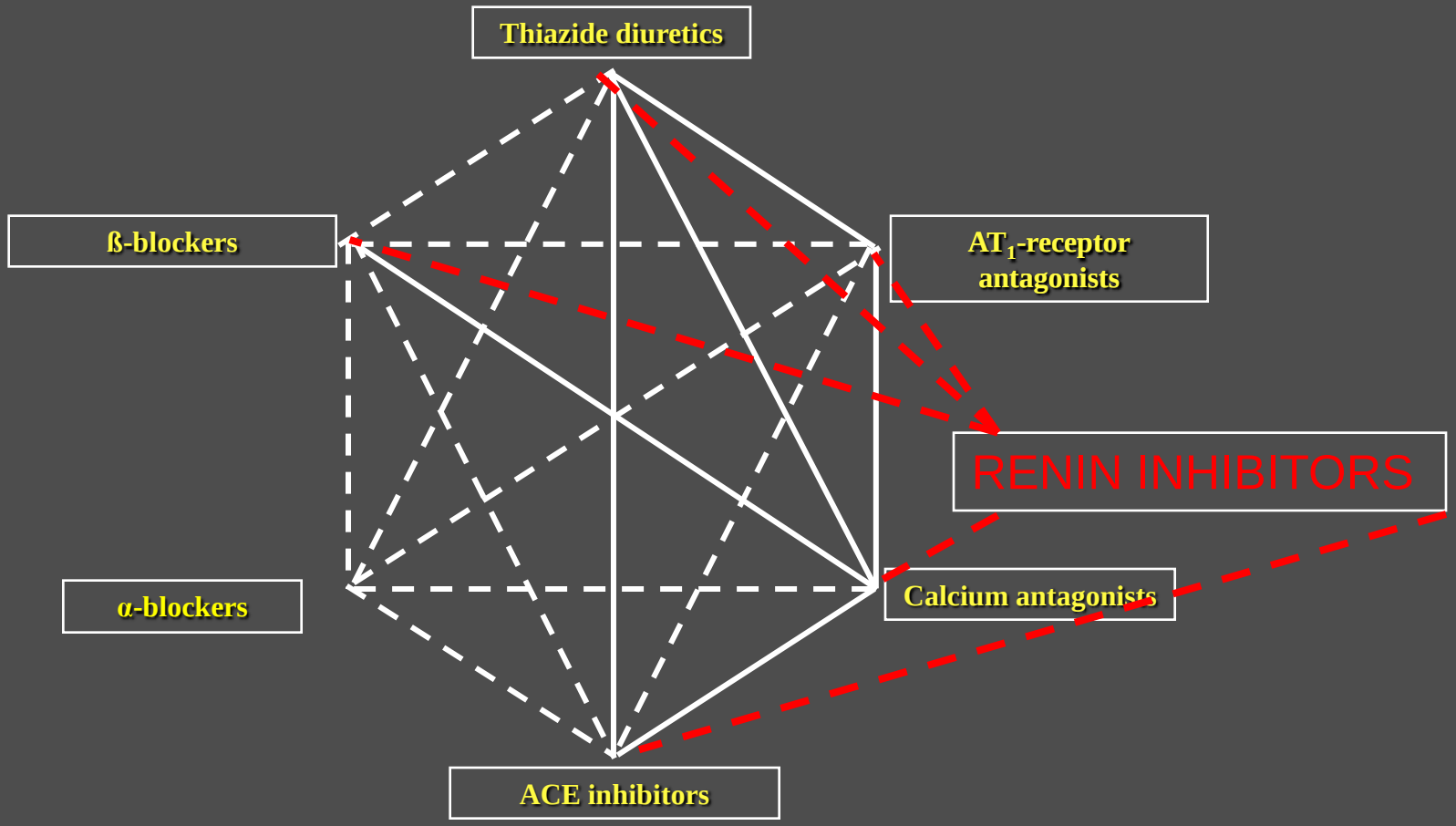
Van Tassell, *Ann Pharmacother,* 2007

Aliskiren binds to the active site of renin

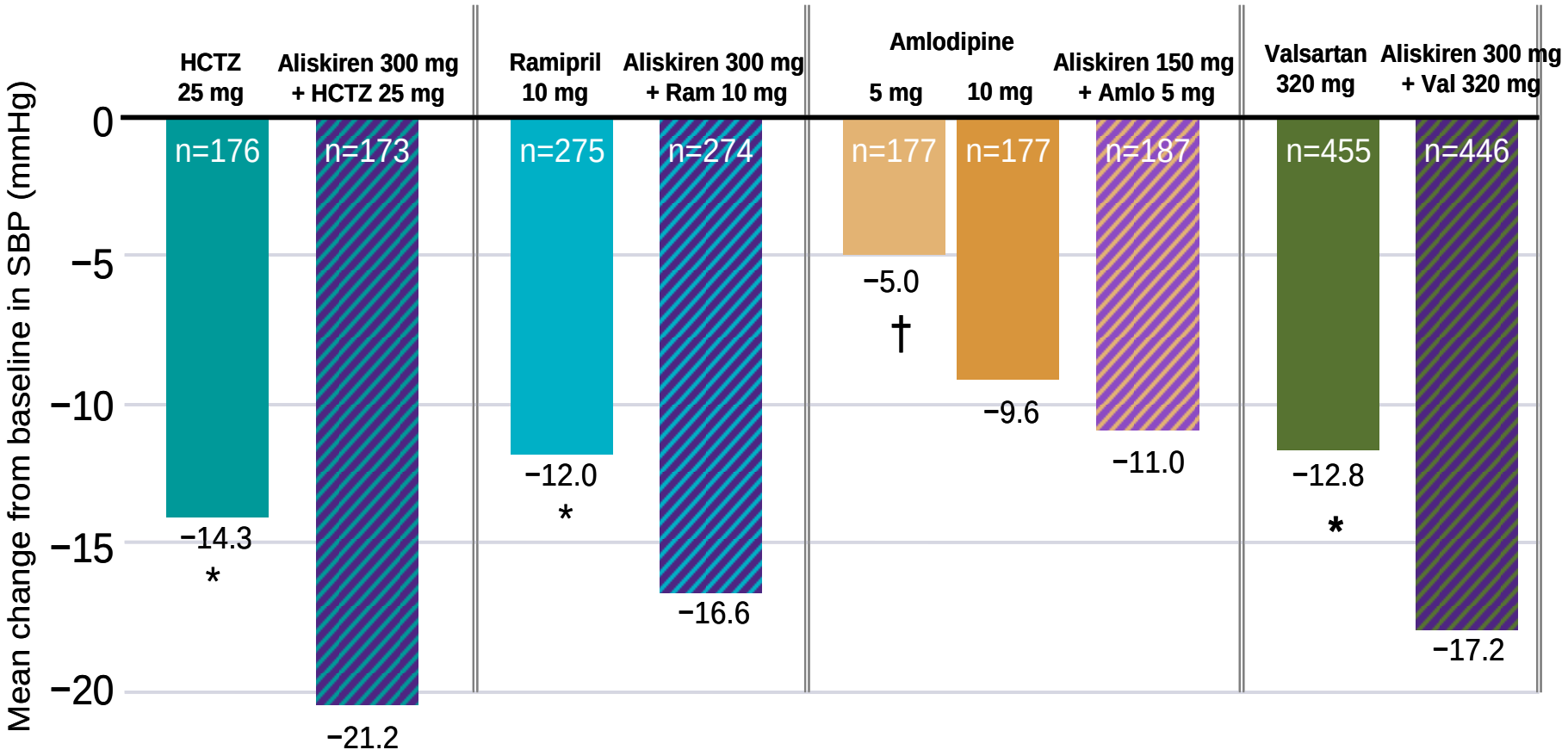


Azizi, J Hypertension, 2006

Combinations between Some Classes of Antihypertensive Drugs



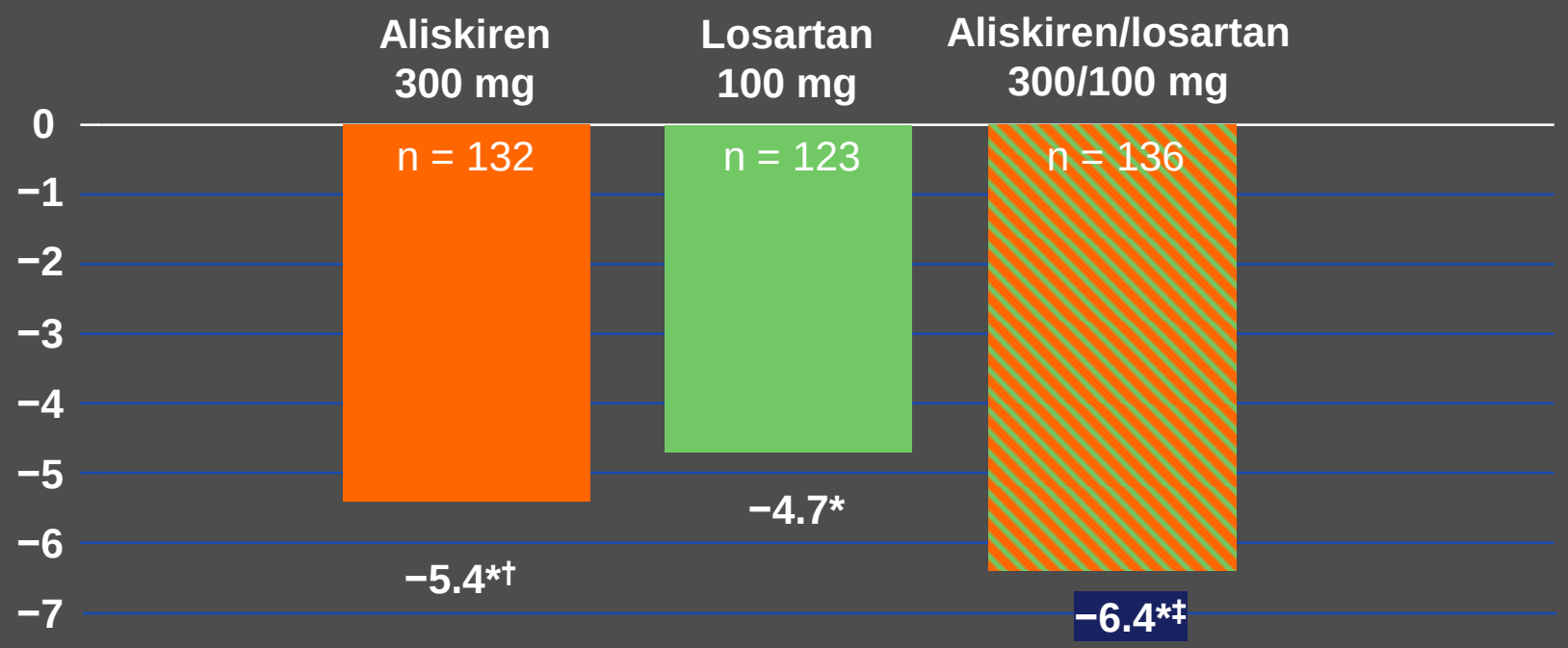
ALISKIREN COMBINATION THERAPY



Schmieder J Clin Hypertens, 2007; 9 Suppl A(5): A182 P-436
Uresin, J Hypertens, 2006; 24(Suppl 4): S82 P-269
Drummond, J Clin Hypertens, 2007; 9: 742-50.
Oparil, Lancet, 2007; 370: 221-229

ALLAY

Aliskiren/losartan combination therapy



Mean change from baseline in LVMI after 36 weeks' treatment (%)

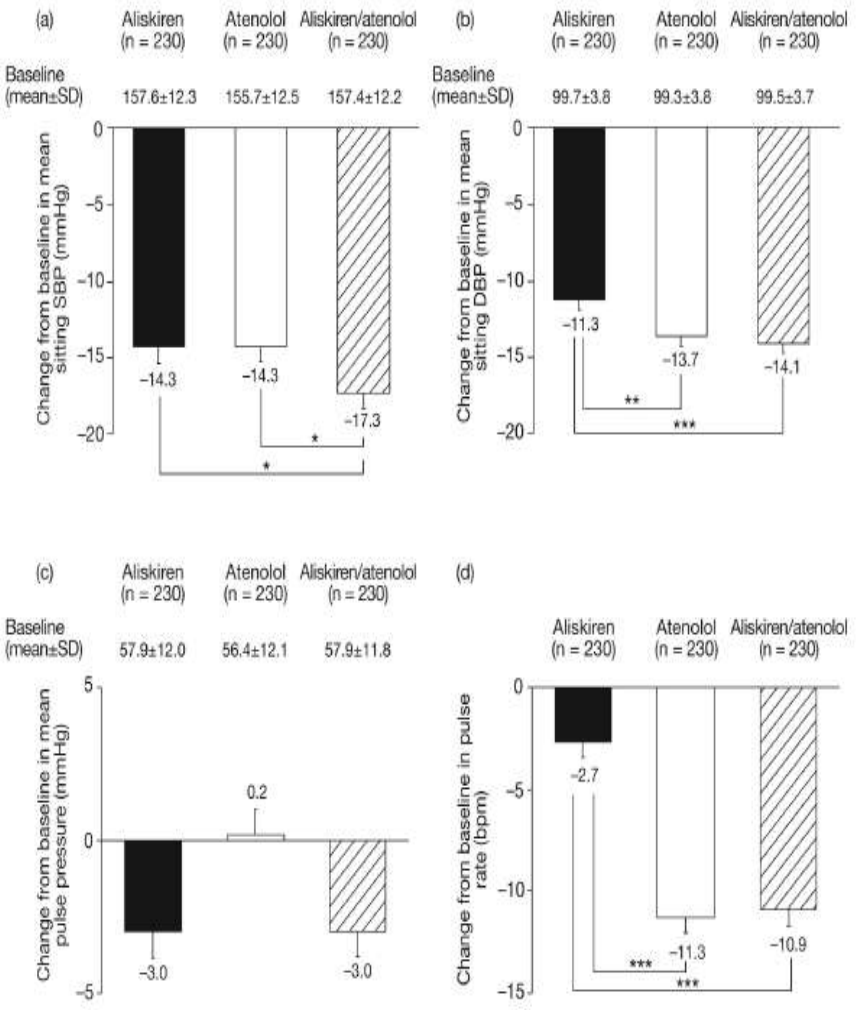
Baseline LVMI = 77.6, 79.4 and 78.4 g/m^2 in the aliskiren, losartan and aliskiren/losartan groups, respectively

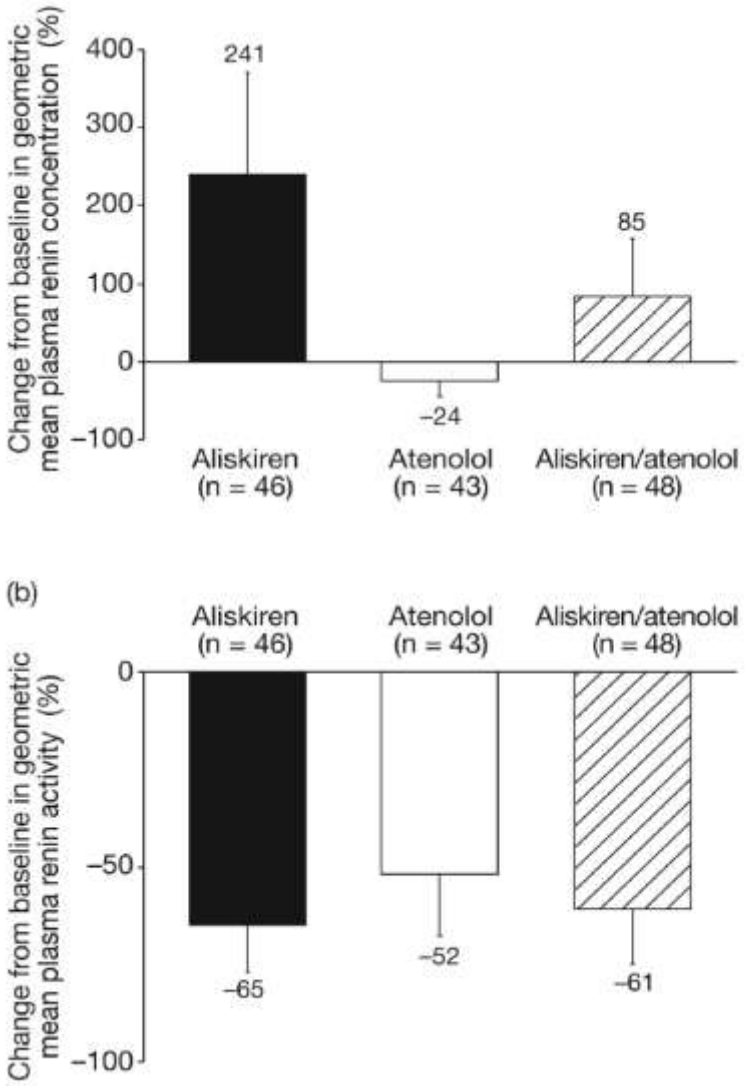
- Aliskiren monotherapy was non-inferior to losartan monotherapy in reducing LVMI
- Aliskiren/losartan combination therapy showed similar tolerability to monotherapy, with no significant differences between treatment groups in the incidence of adverse events or laboratory abnormalities

*p < 0.0001 vs baseline; †p < 0.0001 for non-inferiority vs losartan 100 mg; ‡p = 0.52 vs losartan 100 mg. Between-treatment analyses based on least-squares mean data

Solomon *et al.* 2008.

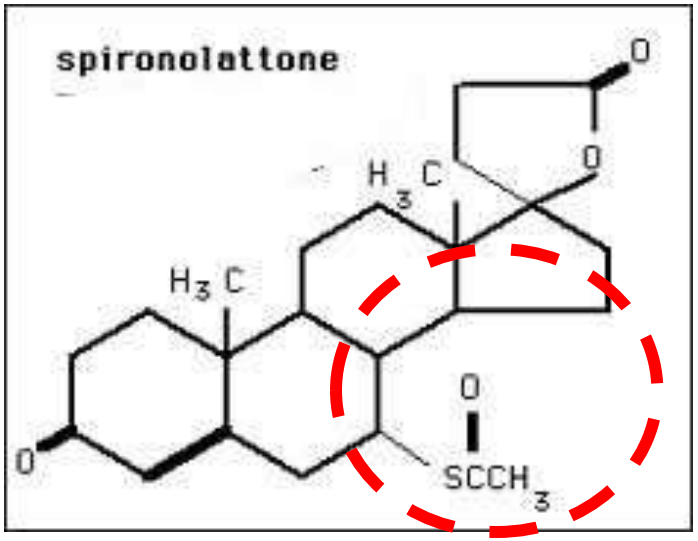
Effects of the direct renin inhibitor aliskiren and atenolol alone or in combination in patients with hypertension

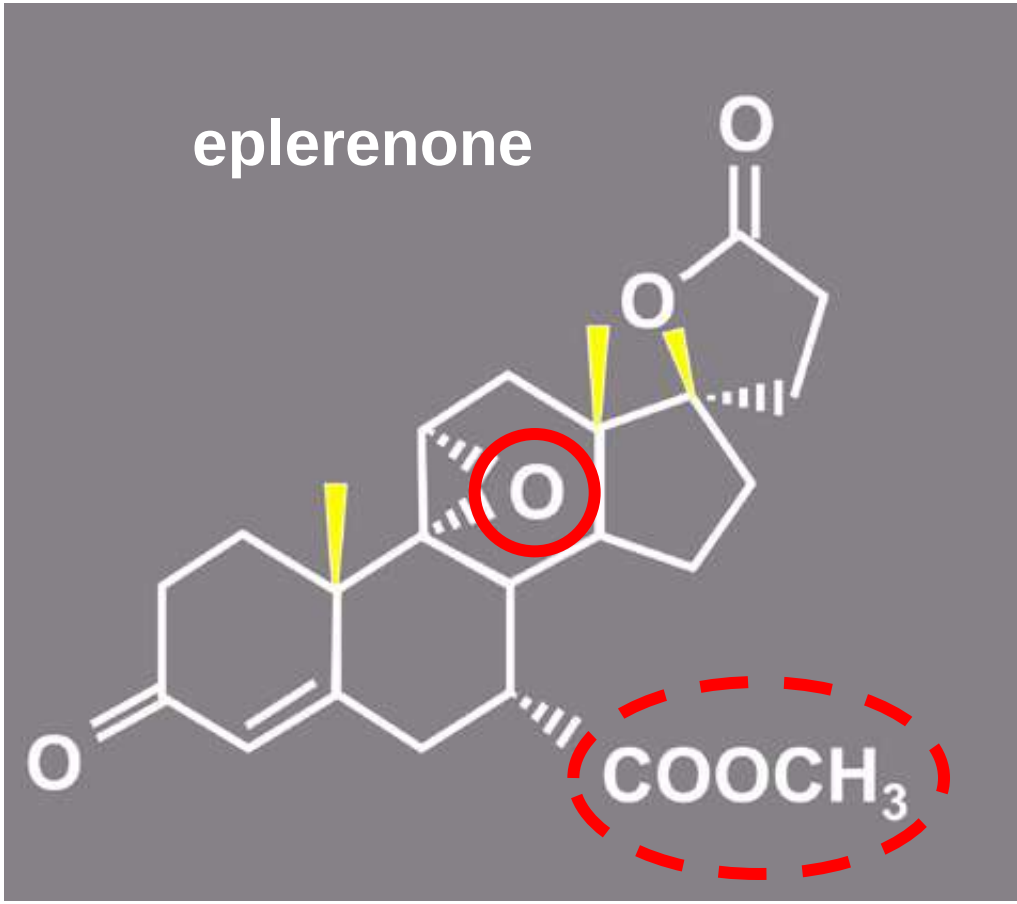




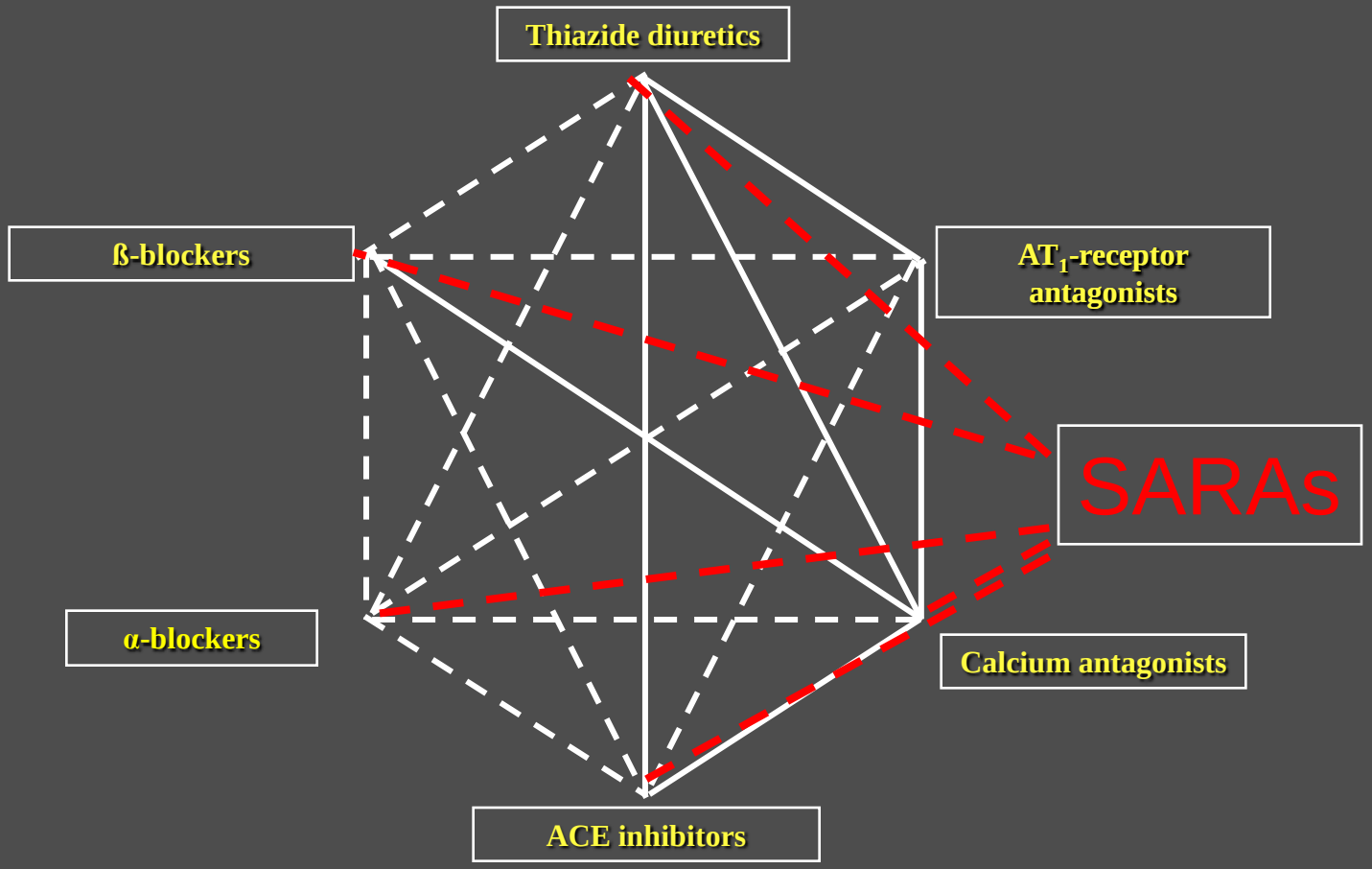
Dietz, J Renin Angiotensin Aldosterone Syst 2008

Molecular structure of SARAs (Facultative Diuretics)

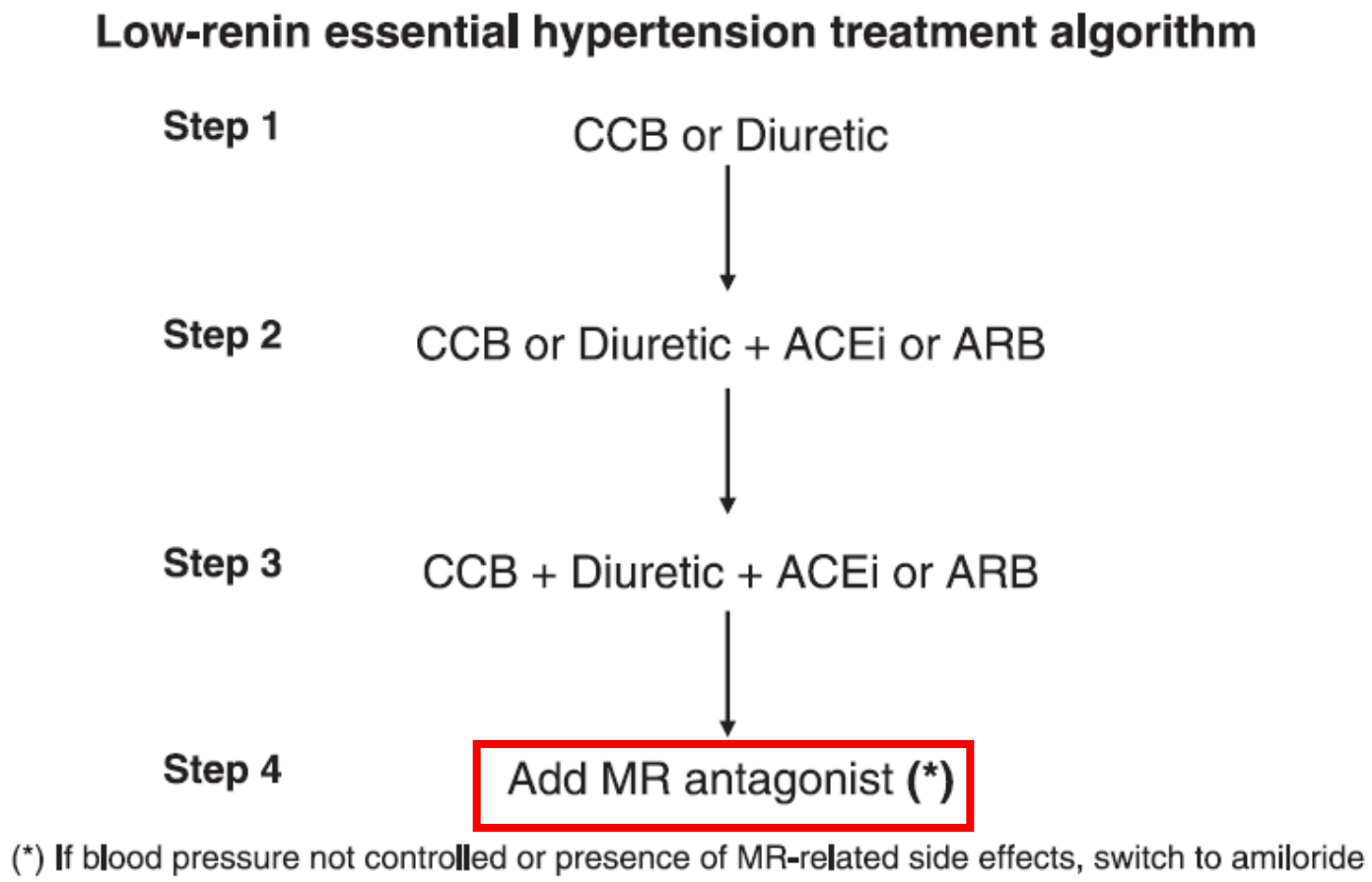




Combinations between Some Classes of Antihypertensive Drugs

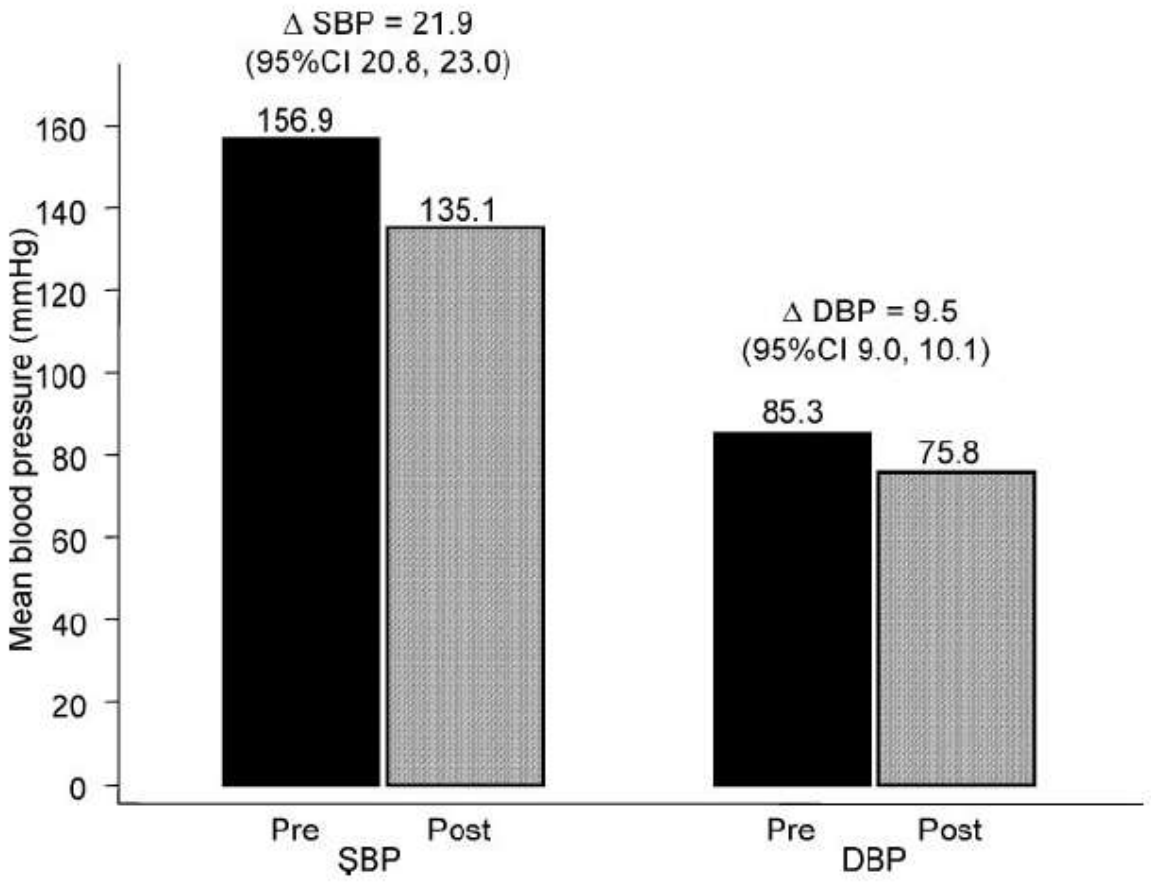


Treatment of low-renin essential hypertension



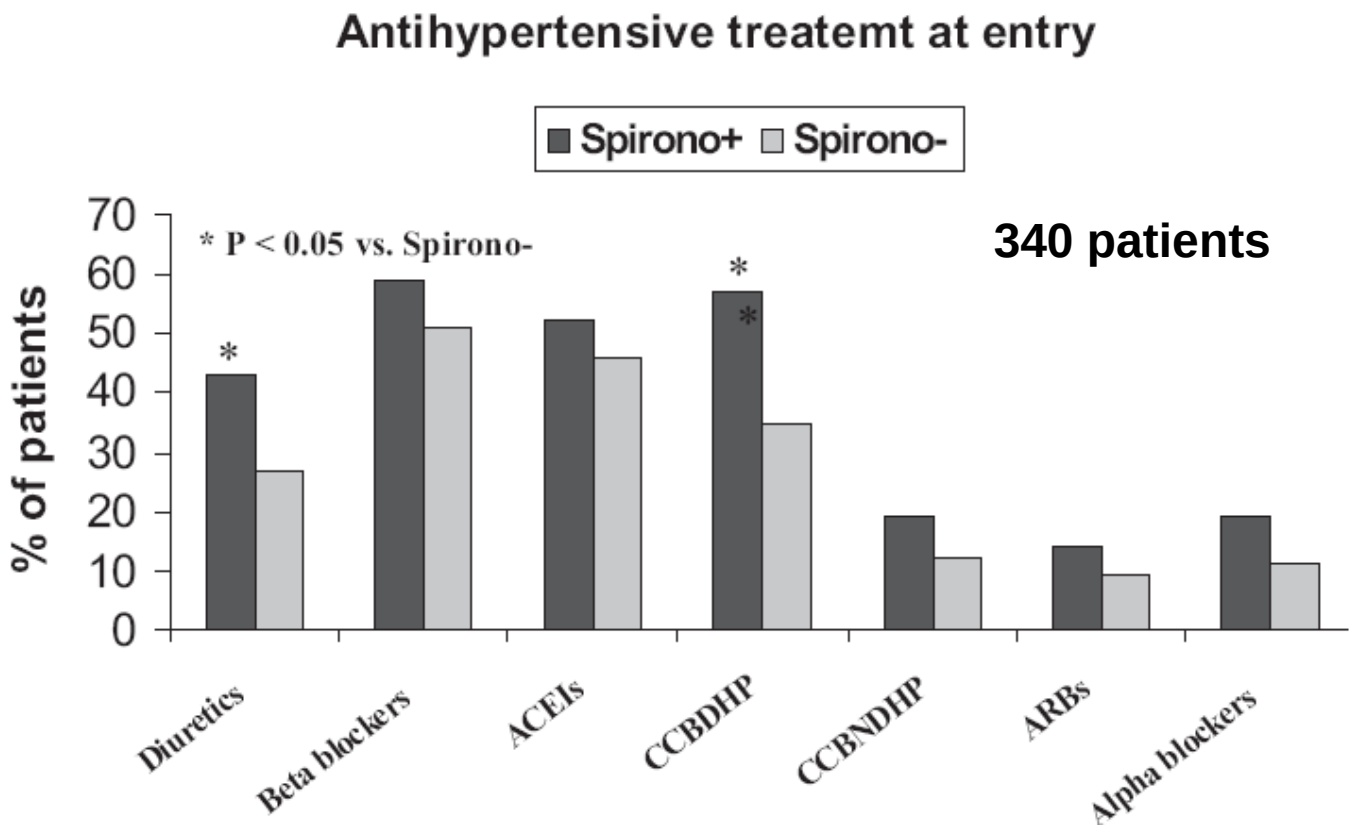
Mulatero & Veglio, Clinical Endocrinology 2007

POST HOC ANALYSIS ASCOT
SPIRONOLACTONE EFFECT ON BLOOD PRESSURE



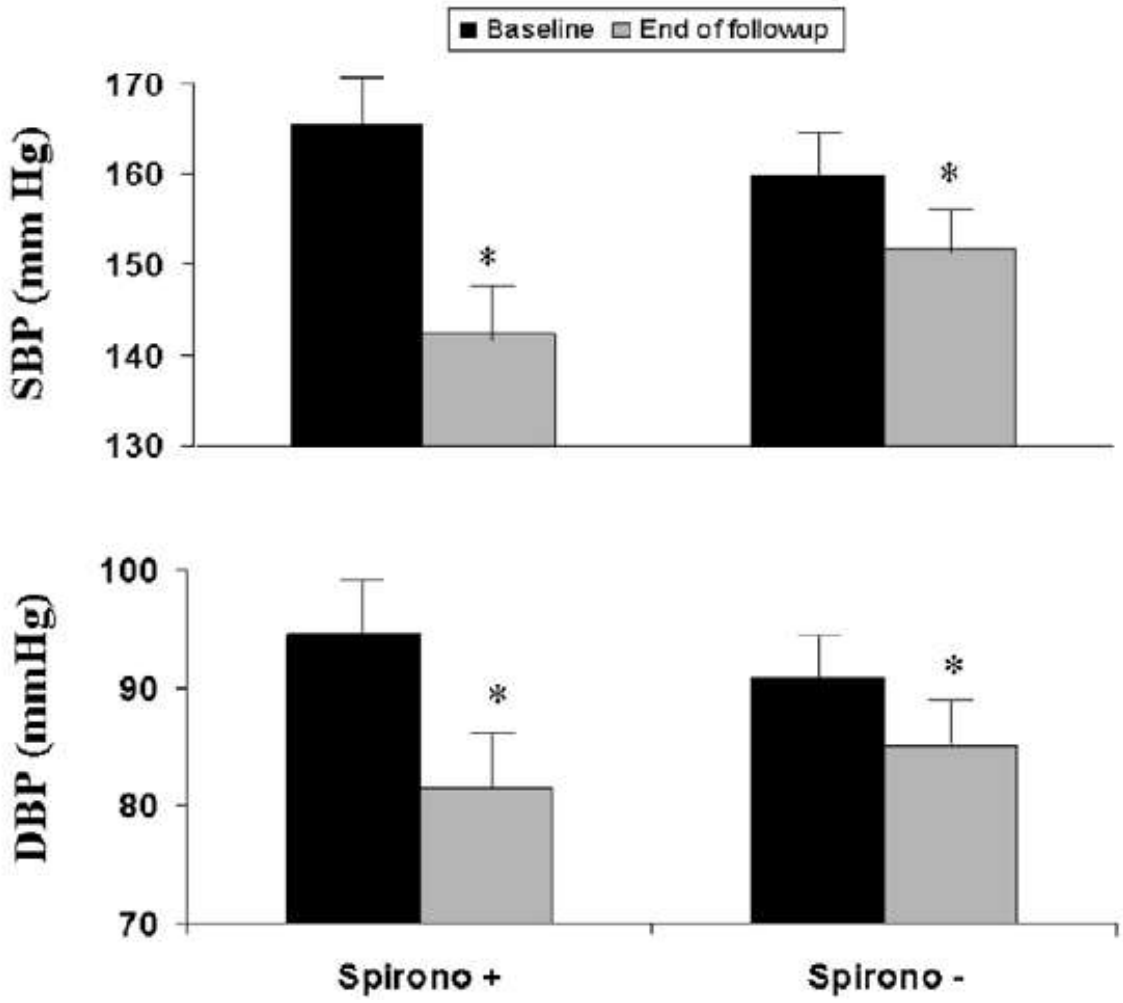
Chapman N, Hypertension 2007

Efficacy of Add-On Aldosterone Receptor Blocker in Uncontrolled Hypertension



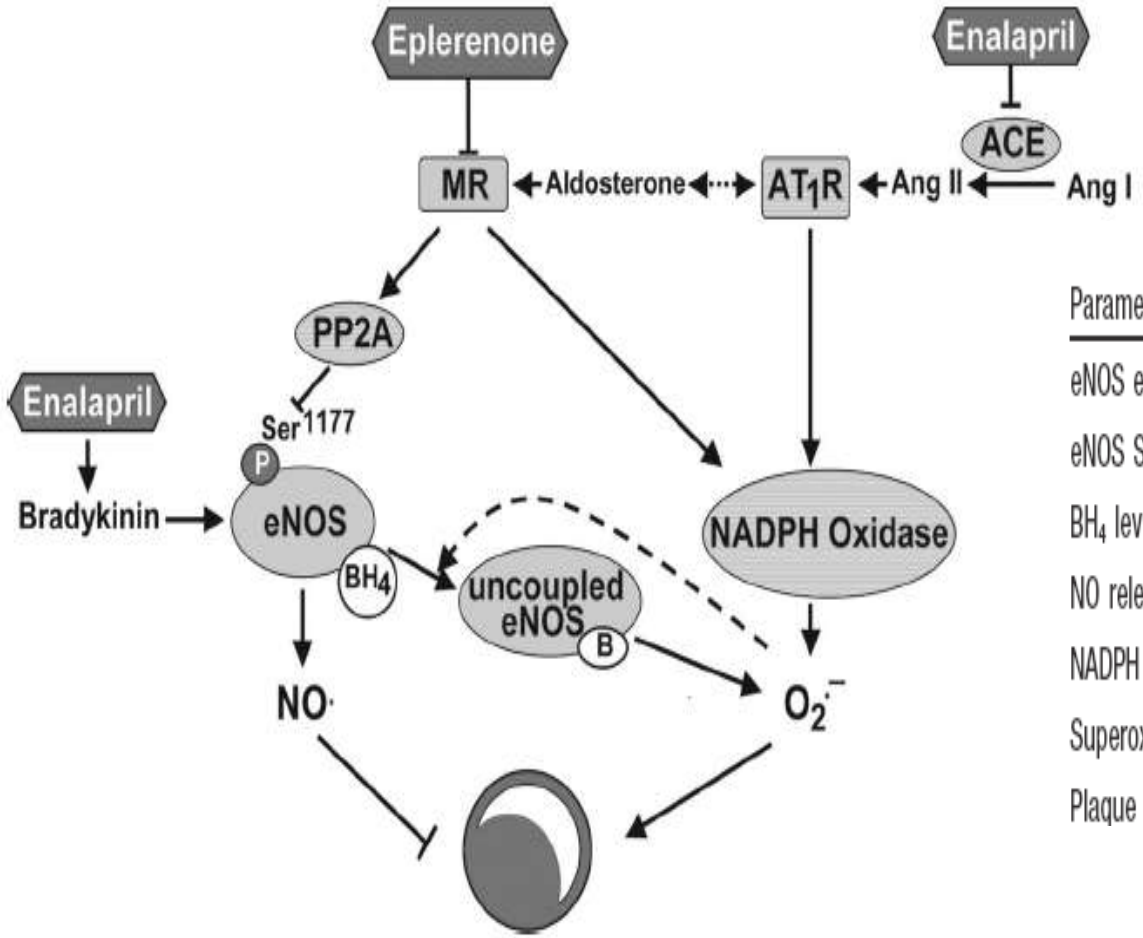
Sharabi, Am J Hypertens 2006

Efficacy of Add-On Aldosterone Receptor Blocker in Uncontrolled Hypertension



Sharabi, Am J Hypertens 2006

Combined Selective Mineralocorticoid Receptor Blockade and Angiotensin-Converting Enzyme Inhibition for Vascular Protection



Parameter	Eplerenone	Enalapril	Eplerenone Plus Enalapril
eNOS expression	(↑)	↑↑↑	↑↑↑
eNOS Ser 1177 phosphorylation	↑↑↑	(↑)	↑↑↑
BH_4 levels	↑	↑↑	↑↑↑
NO release	↑	↑↑	↑↑↑
NADPH oxidase activity	↓	↓↓	↓↓↓
Superoxide formation	↓	↓↓	↓↓↓
Plaque area	↓	↓↓	↓↓↓

Bauersachs, Hypertension 2008

Dihydropyridine Calcium Channel Blockers Have Mineralocorticoid Receptor Antagonist Activity

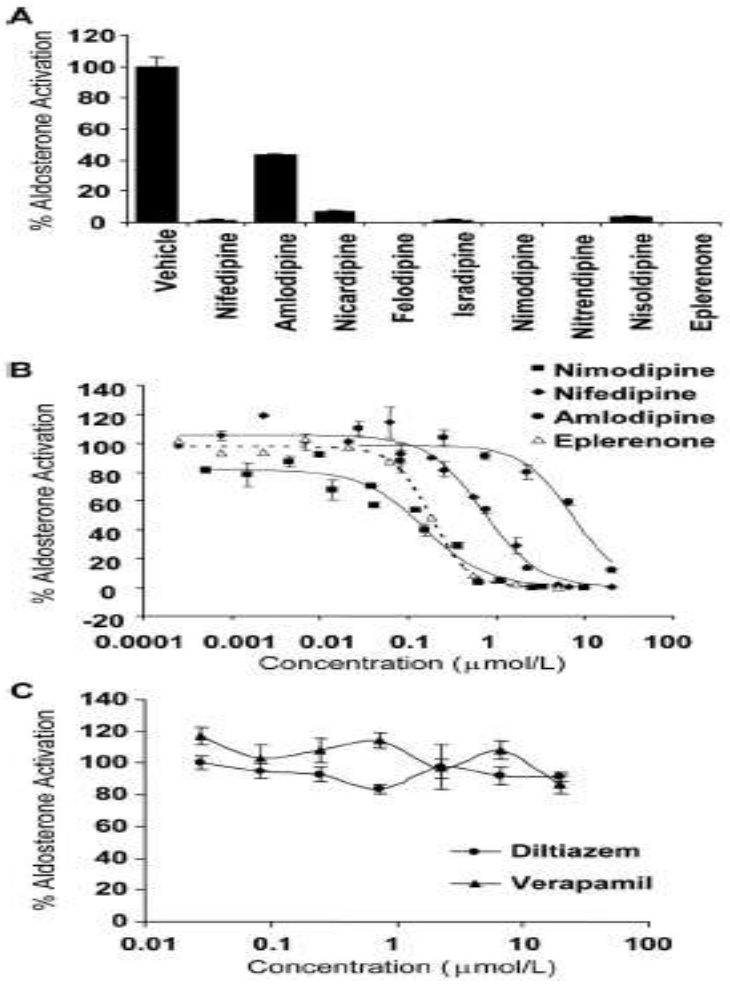


Table 1. Potencies of Dihydropyridine CCBs on MR

Compound	IC50 (μmol/L)±SE
Nifedipine	0.71±0.08
Amlodipine	7.40±1.73
Nicardipine	3.30±0.96
Felodipine	0.17±0.03
Isradipine	1.61±0.39
Nimodipine	0.16±0.03
Nitrendipine	0.45±0.08
Nisoldipine	3.00±0.65

Dietz, Hypertension 2008


Thanks