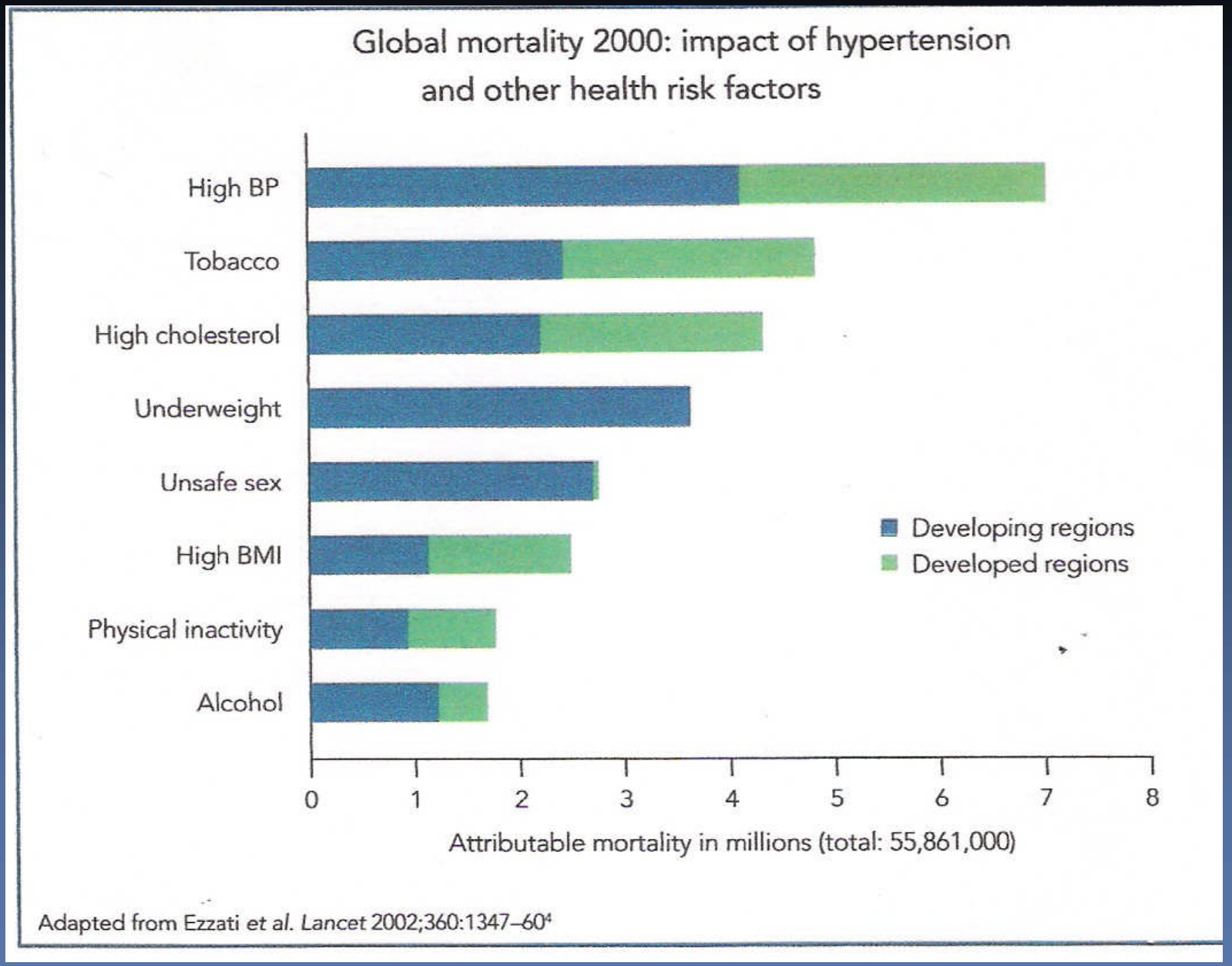
IPERTENSIONE ARTERIOSA:

TERAPIA DI ASSOCIAZIONE

Dott. O.CIARLA



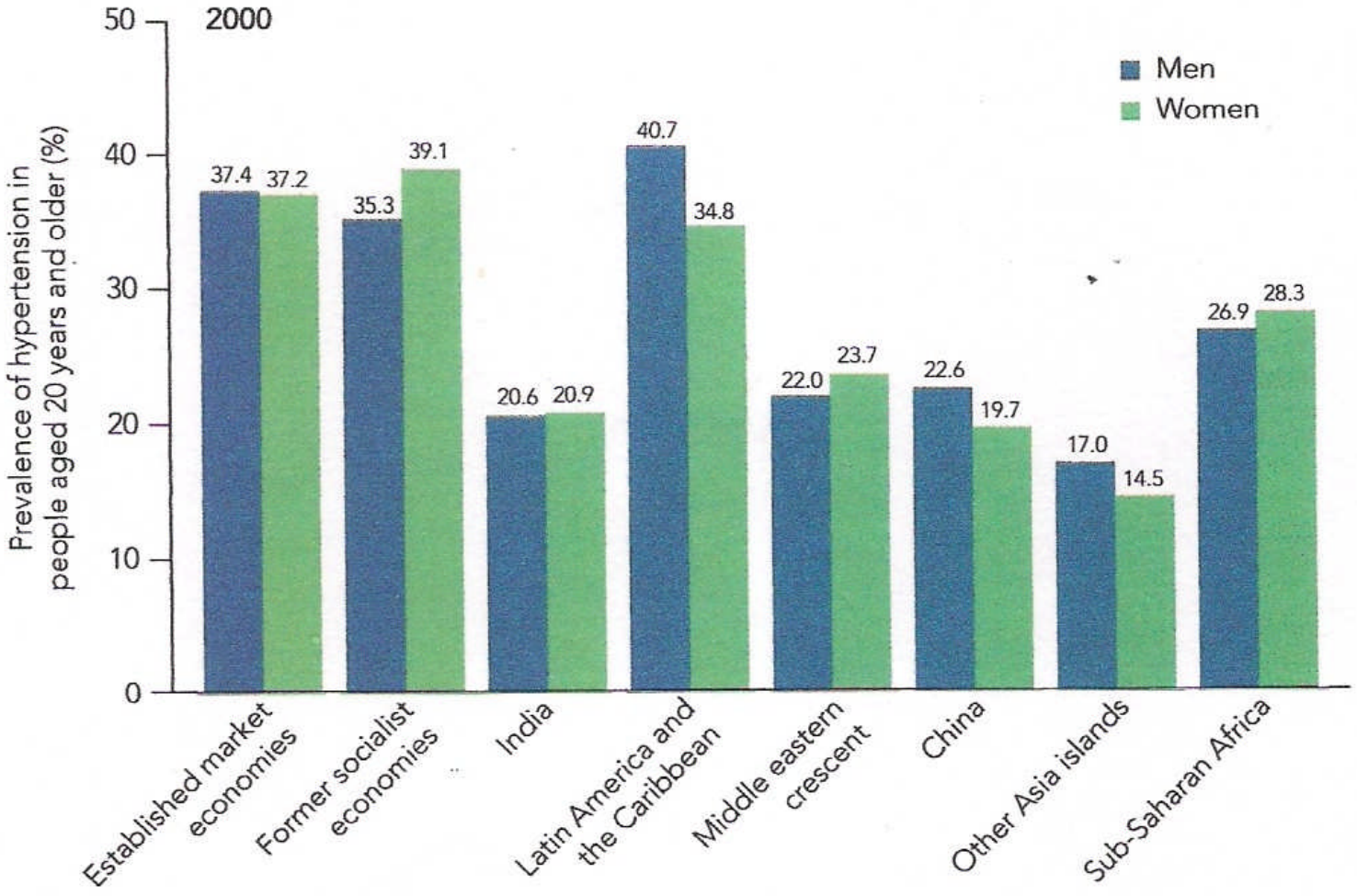
Adapted from Ezzati *et al. Lancet* 2002;360:1347–60[4]

Category	Systolic	Diastolic
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Grade 2 hypertension (moderate)	160–179	100–109
Grade 2 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90

Classification of BP Levels: American Guidelines[3]

BP classification	Systolic BP (mmHg)		Diastolic BP (mmHg)
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

Prevalence of hypertension is variably high around the world

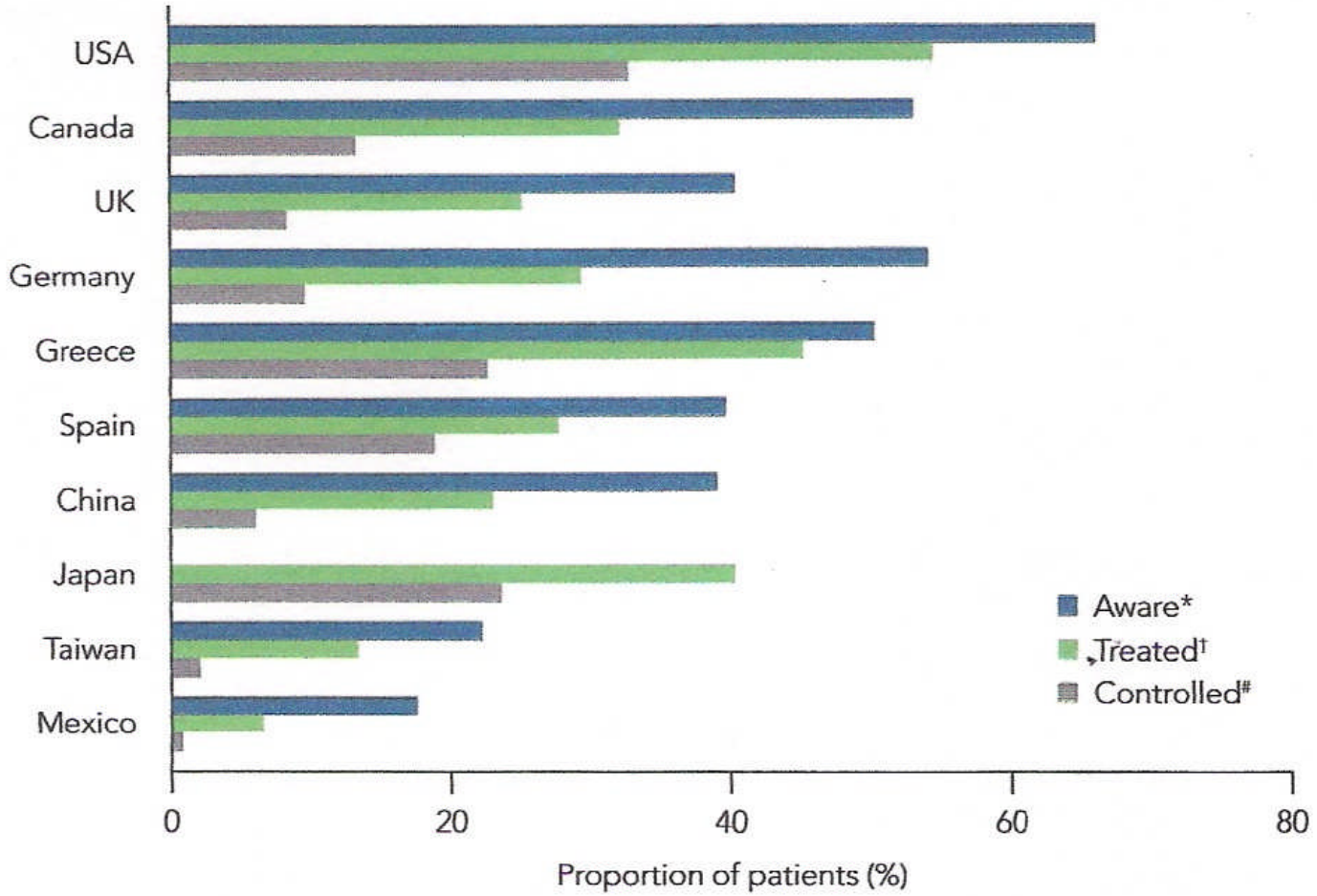


Kearney *et al. Lancet* 2005;365:217–23[5]

BP targets in various guidelines

	Patients		
Guidelines	**Uncomplicated hypertension**	**Diabetes**	**Chronic renal failure**
USA (JNC VII [2003])	<140/90 mmHg	<130/80 mmHg	<130/80 mmHg
Europe (ESH 2007)	<140/90 mmHg lower if tolerated	<130/80 mmHg	<130/80 mmHg
China (CSH 2005)	<140/90 mmHg (≤150 mmHg SBP for elderly)	<130/80 mmHg	<130/80 mmHg
Russia	<140/90 mmHg	<130/80 mmHg	<130/80 mmHg
Korea (KSH 2004)	<140/90 mmHg	<130/80 mmHg	<130/80 mmHg
WHO ISH	SBP <140 mmHg	<130/80 mmHg	<130/80 mmHg
BHS IV 2004	<140/85 mmHg	<130/80 mmHg	<130/80 mmHg

Awareness, treatment and control of hypertension around the world



*Prior diagnosis by health professional
†Use of BP medication
#On BP medication, with SBP/DBP<140/90 mmHg
Whelton. *J Clin Hypertens* 2004;6:636–42[1]

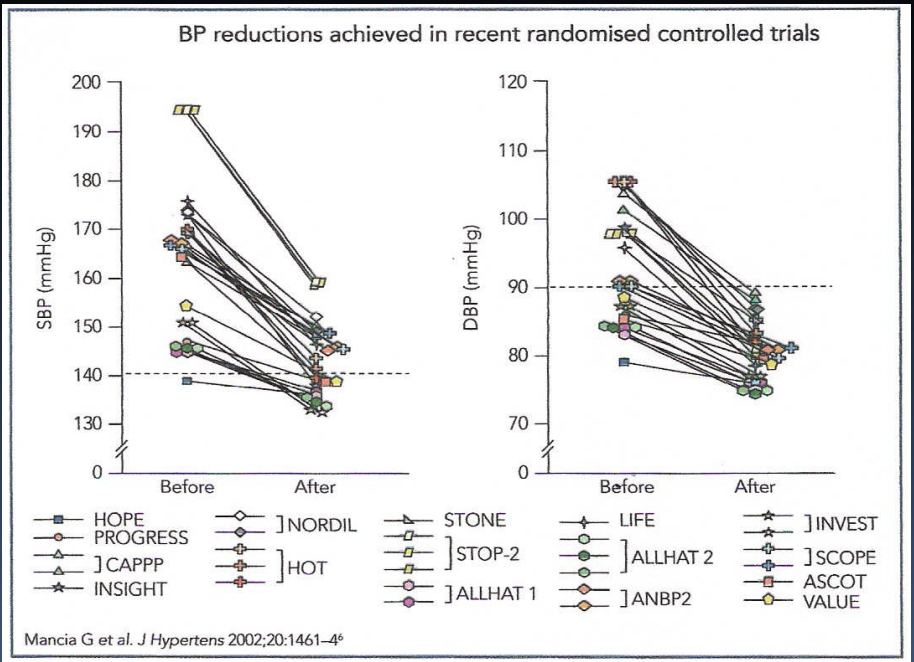
Awareness treatment and control† of hypertension*: Health Survey for England (HSE) (1994–2006)[2]

Year	Awareness (%)	Treated (%)	Controlled (%)
1994	40	26	6
1998	46	32	9
2003	62	48	22
2006	66	54	28

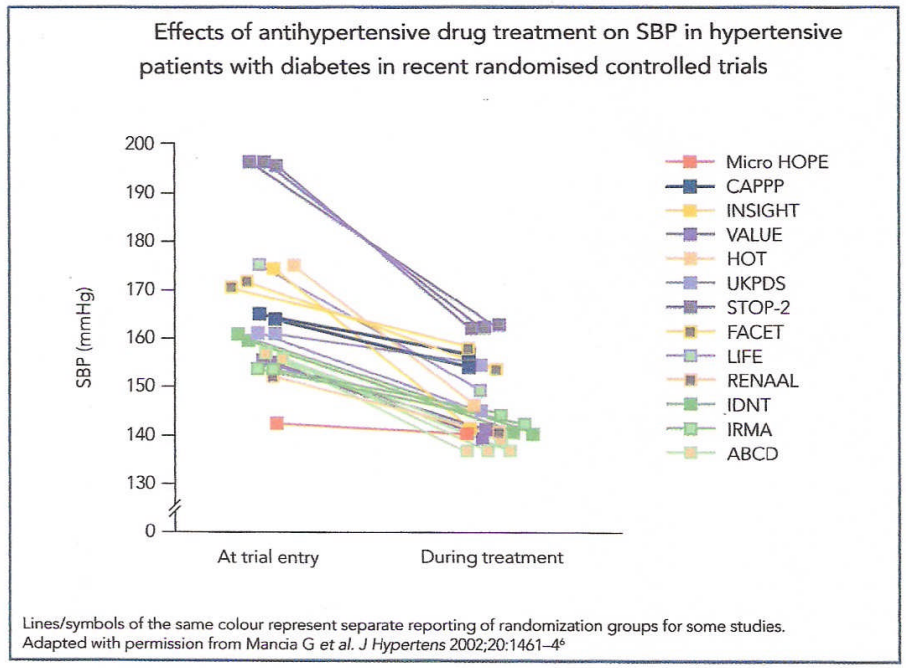
†On treatment for raised BP with SBP <140 mmHg and DBP <90 mmHg
*SBP ≥140 mmHg or DBP ≥90 mmHg or on treatment for hypertension

Number of drugs used by treated hypertensives: HSE (1994–2006)

	1994 (%)	1998 (%)	2003 (%)	2006 (%)
1 drug	60	60	44	39
2 drugs	34	33	38	40
≥3 drugs	6	7	18	21



Mancia G *et al. J Hypertens* 2002;20:1461–4[6]

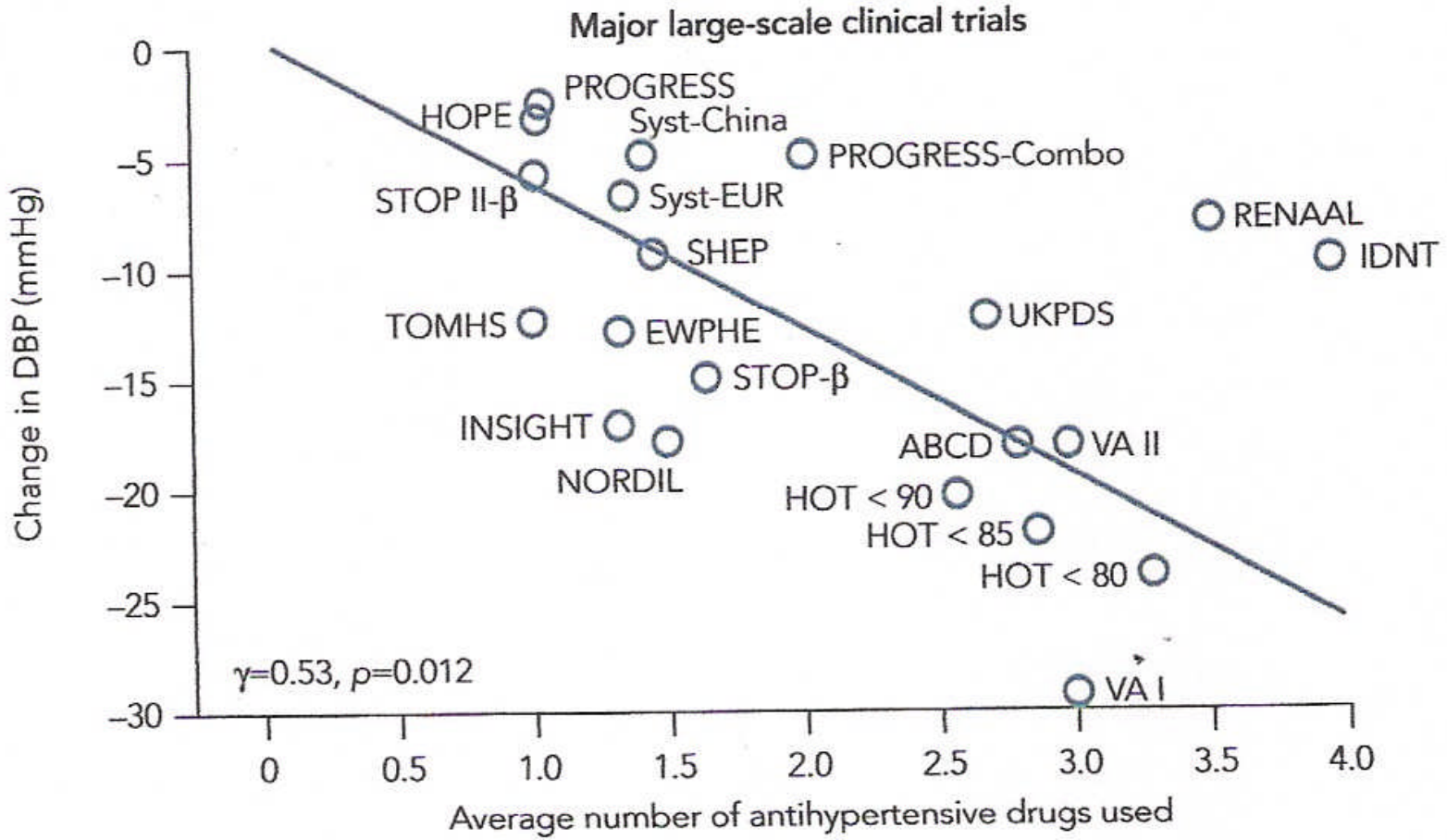


Lines/symbols of the same colour represent separate reporting of randomization groups for some studies.
Adapted with permission from Mancia G *et al. J Hypertens* 2002;20:1461–4[6]

Reasons for inadequate control of BP

- Ineffective drugs
- Resistant hypertension
- Guideline confusion
- Drug costs
- Drug side effects
- Poor compliance
- Physician inertia

Correlation between change in DBP and mean number of antihypertensive drugs used in randomised trials



Elliott WJ. *Curr Hypertens Rep* 2002;4:278–85[8]

Definition of resistant hypertension

Resistant Hypertension is defined as uncontrolled BP (i.e. ≥ 140/90 mmHg) despite treatment with three drug therapies (usually including a diuretic) at maximal recommended or tolerated doses.

Typical characteristics of patients with resistant hypertension

- Older age; especially >75 yrs
- High baseline BP and chronicity of uncontrolled hypertension
- Target organ damage: LVH and/or CKD
- Diabetes
- Obesity
- Atherosclerotic vascular disease
- Aortic stiffening
- Women
- Black
- Excessive dietary sodium

Secondary causes of hypertension that may present as resistant hypertension

Commoner causes:

- Primary hyperaldosteronism (Conn's adenoma)
- Atherosclerotic renovascular disease
- Sleep apnoea
- Chronic kidney disease

Uncommon causes:

- Phaeochromocytoma
- Aortic coarctation
- Cushing's disease
- Hyperparathyroidism

First-line therapy recommended in recent guidelines

JNC 7	ESH–ESC + ESH 2009	WHO–ISH	BHS/NICE 2006
Thiazide-type diuretics	Any of 5 (A^1,A^2,B^3,C^4,D^5)*	Low-dose diuretics	$A^{1,2}/C^4D^5$

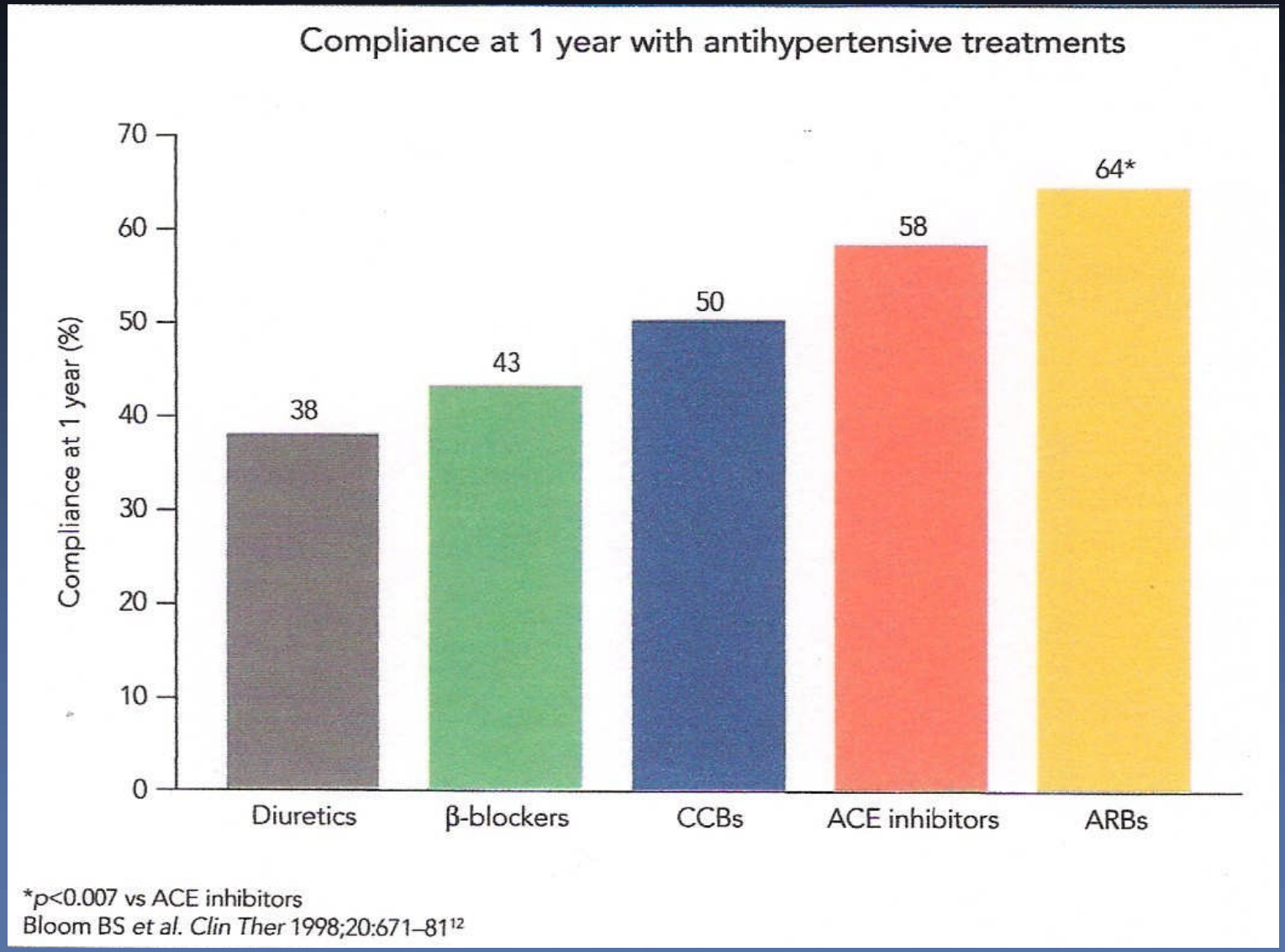
[1]ACE inhibitor, [2]ARB, [3]β-blocker, [4]CCB, [5]Diuretic

*ESC Guidelines 2207. Box 12. "Initial treatment can make use of monotherapy or combination of two drugs at low doses"

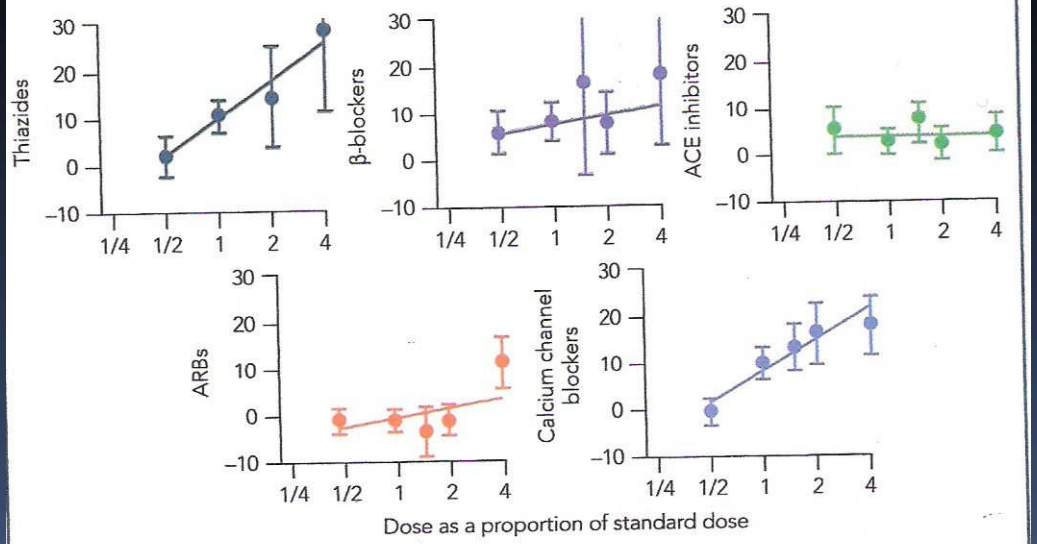
*Reappraisal of ESH Guidelines 2009. Box 6. "The combination of two antihypertensive drugs may offer advantages also for treatment initiation, particularly in patients at high cardiovascular risk in which early BP control may be desirable".

Anti-hypertensive agents used as monotherapy: England 2006[2]

Type of drug	Total, % (SE)
Diuretics	23 (1.8)
β-blockers	21 (1.8)
RAS blockers	34 (2.0)
Calcium antagonist	19 (1.7)
Other drugs affecting BP	3 (0.7


Compliance at 1 year with antihypertensive treatments
Compliance at 1 year (%)
70
60
50
40
30
20
10
0
38
43
50
58
64*
Diuretics
β-blockers
CCBs
ACE inhibitors
ARBs
*p<0.007 vs ACE inhibitors
Bloom BS et al. Clin Ther 1998;20:671–81[12]

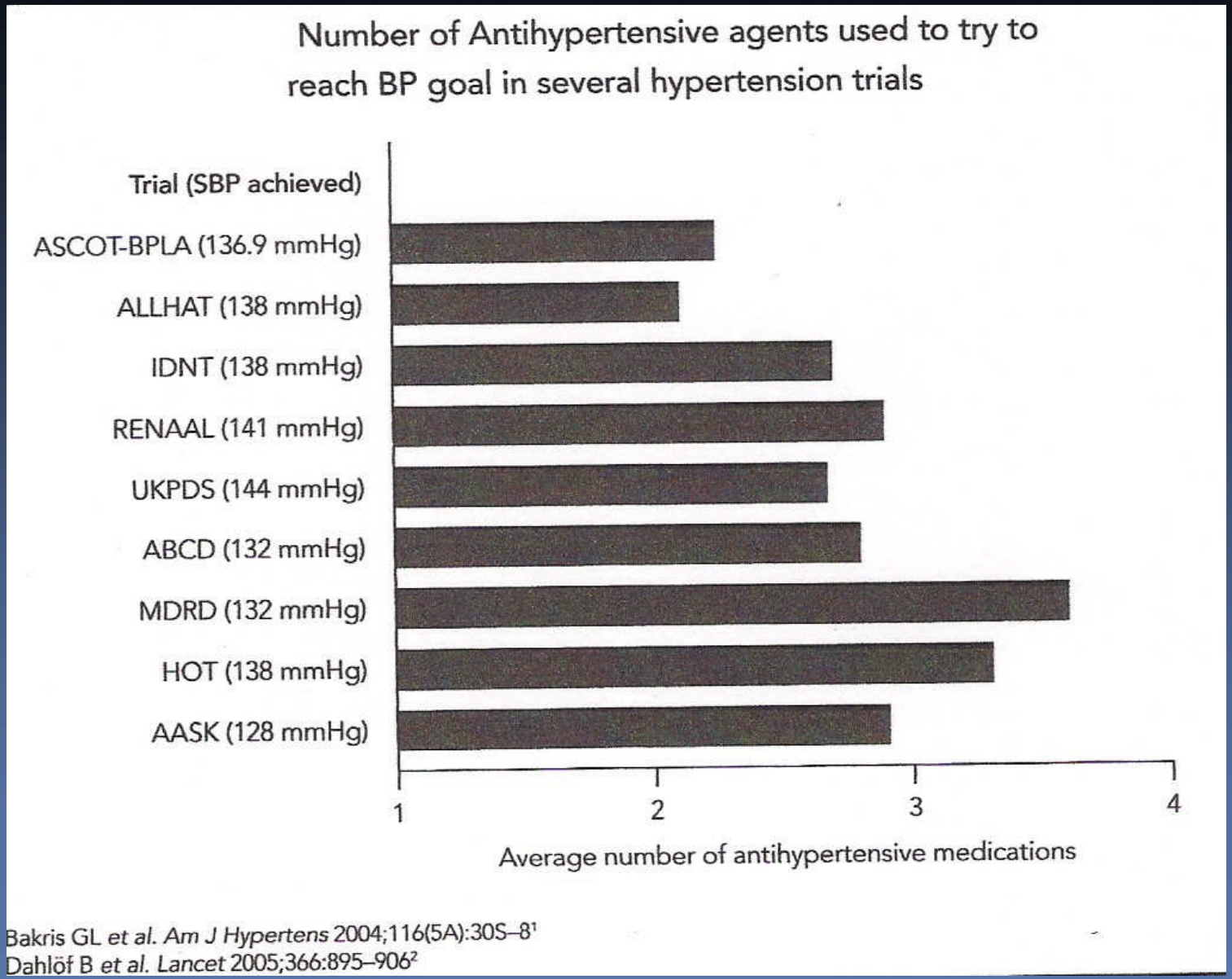
Proportions of people reporting one or more symptoms attributable to treatment according to category of drug and dose as a proportion of standard dose



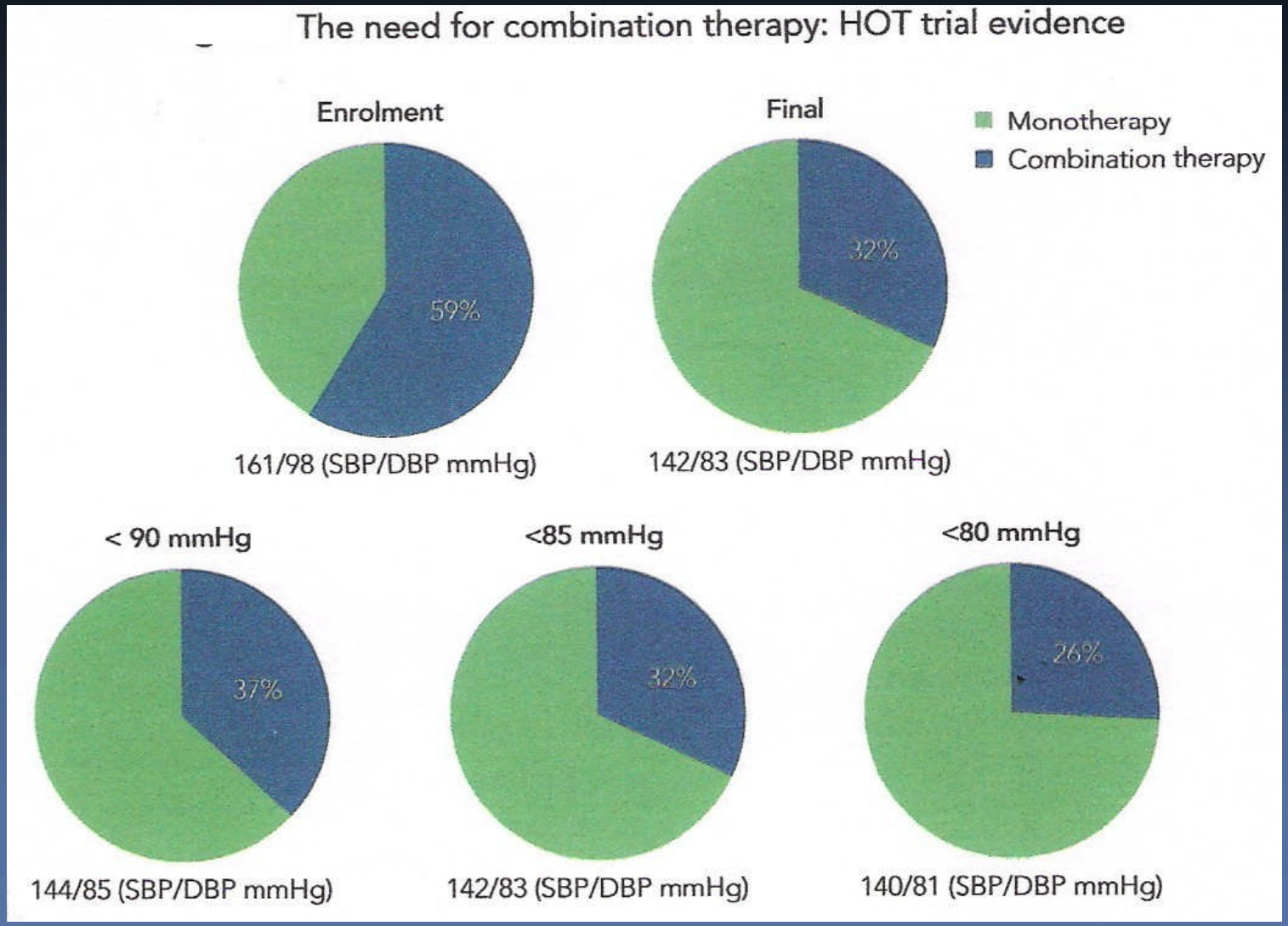
Law MR *et al. BMJ* 2003;326:1427[7]

Withdrawals from randomised treatment in hypertension trials – old and new

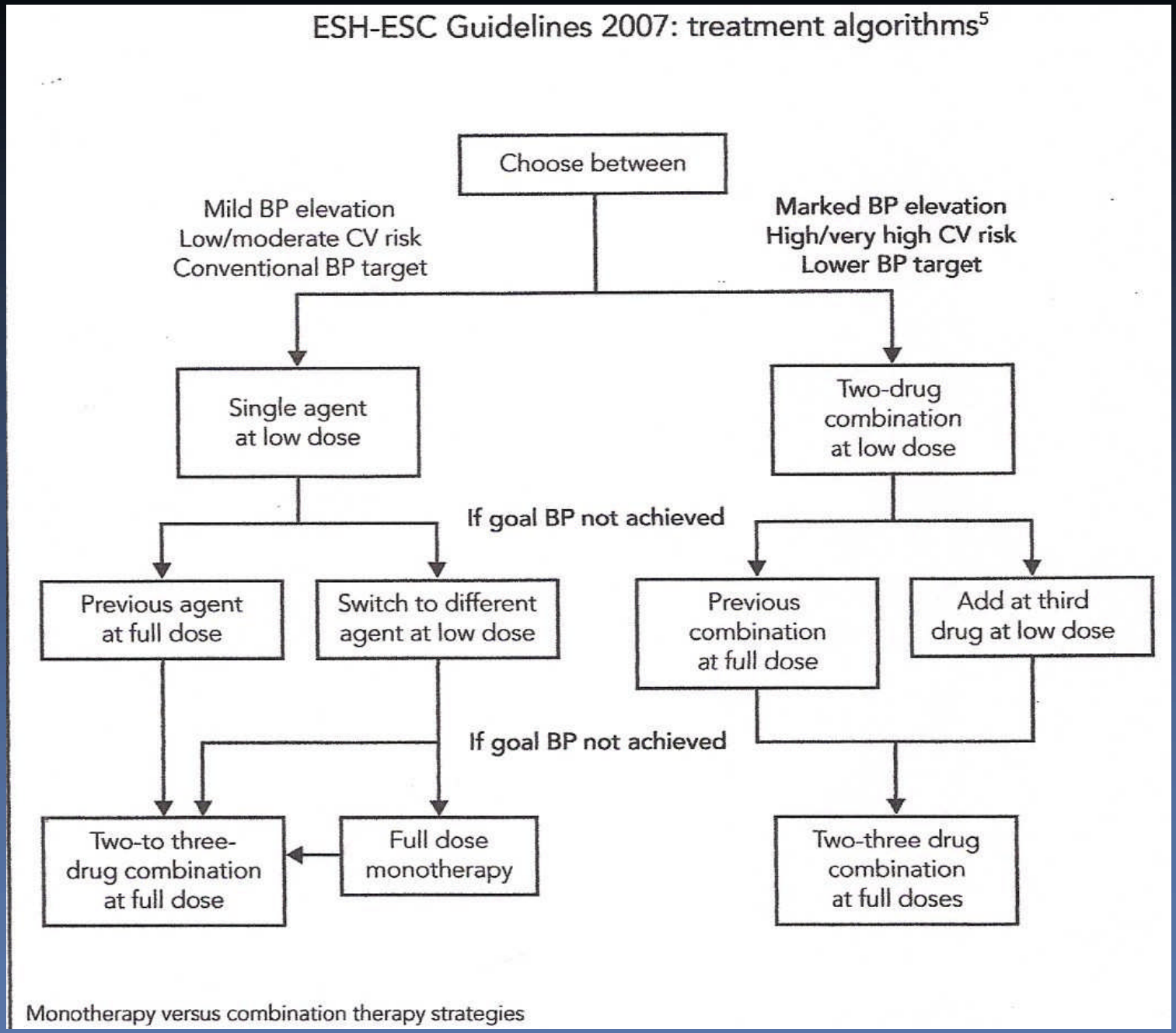
	%
IPPPSH	26
MRC	40
EWPHE	26
Australian	34
SHEP	37
STOP	20
MRC elderly	54
ONTARGET	27
ACCOMPLISH	30



Bakris GL *et al. Am J Hypertens* 2004;116(5A):30S–8[1]
Dahlöf B *et al. Lancet* 2005;366:895–906[2]

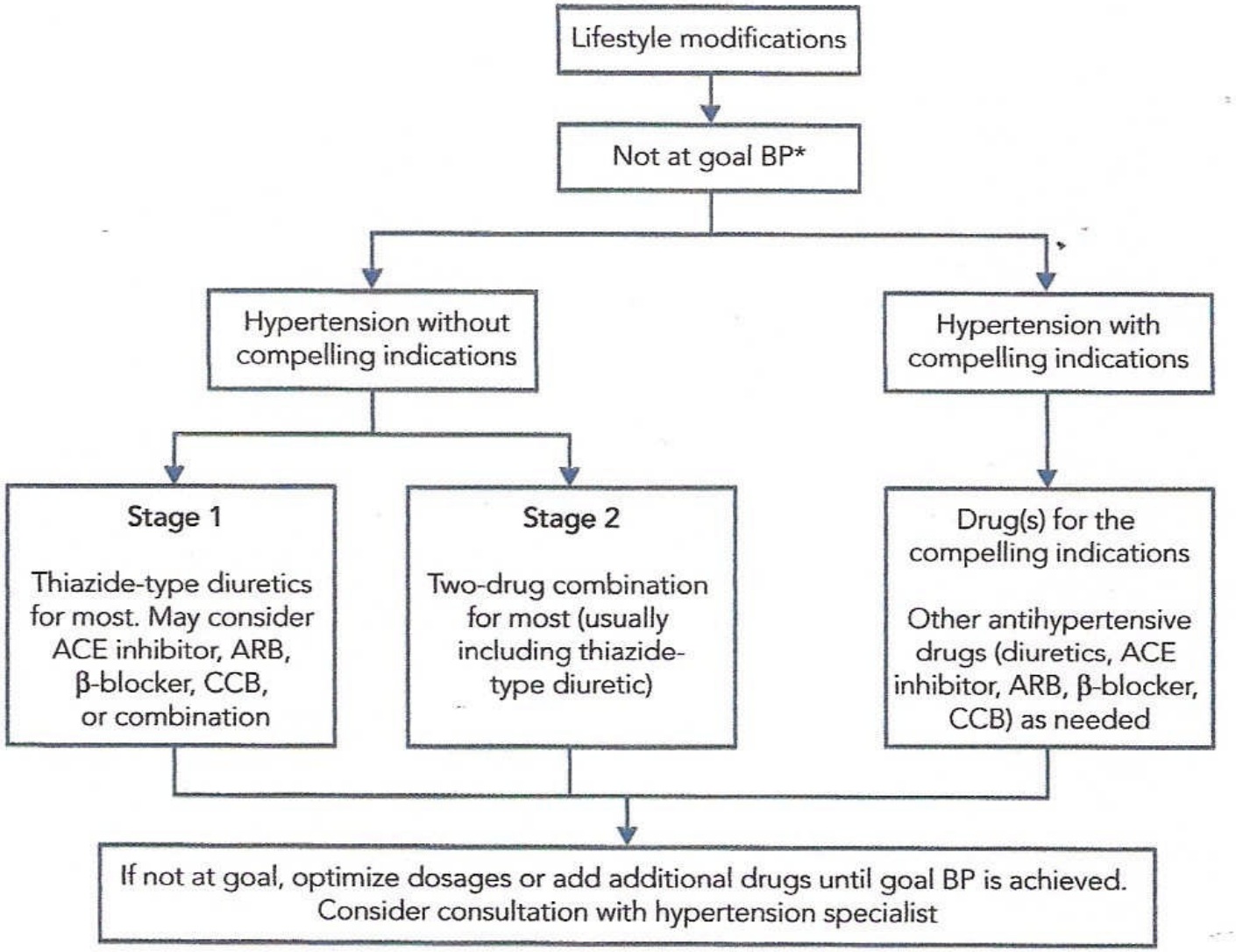

The need for combination therapy: HOT trial evidence
Enrolment
Final
Monotherapy
Combination therapy
59%
32%
161/98 (SBP/DBP mmHg)
142/83 (SBP/DBP mmHg)
< 90 mmHg
<85 mmHg
<80 mmHg
37%
32%
26%
144/85 (SBP/DBP mmHg)
142/83 (SBP/DBP mmHg)
140/81 (SBP/DBP mmHg)

ESH-ESC Guidelines 2007: treatment algorithms[5]



Monotherapy versus combination therapy strategies

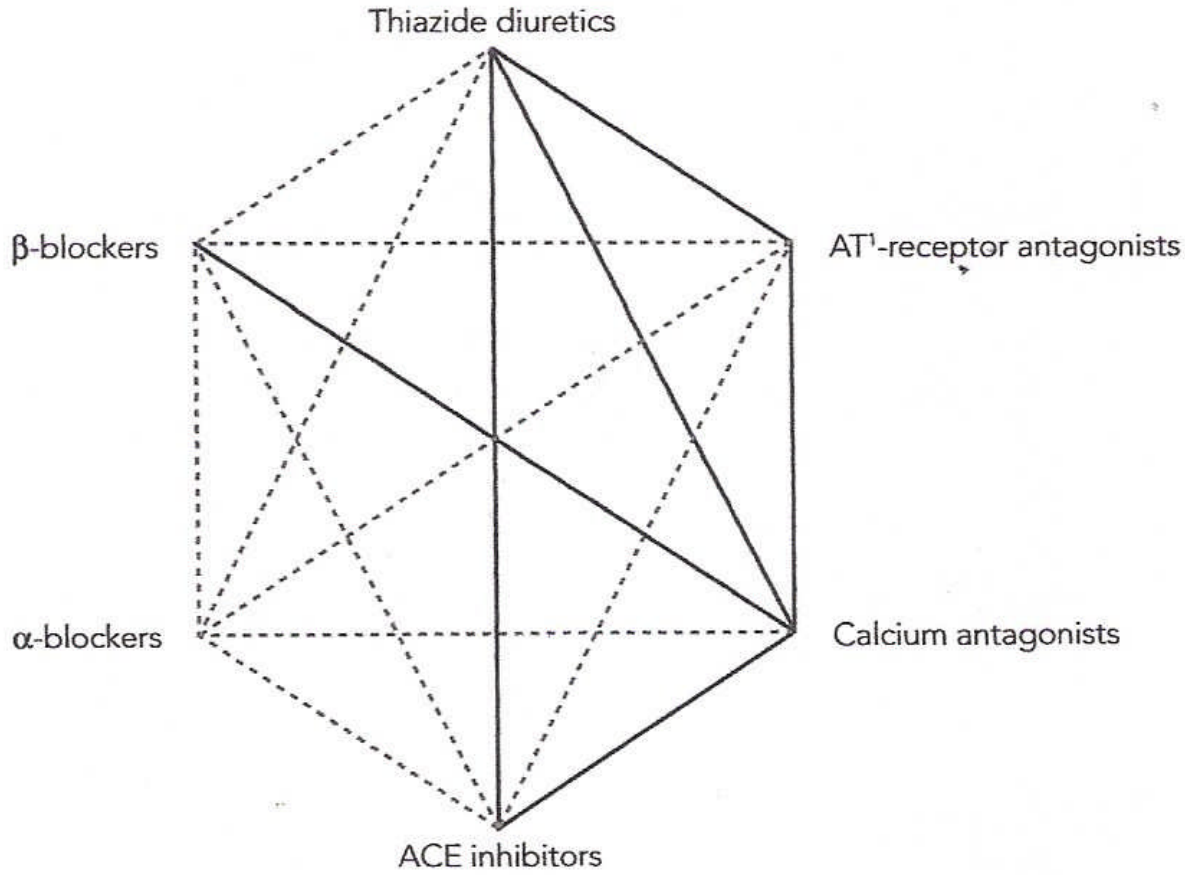
JNC 7: algorithm for treatment of hypertension



*BP goal <140/90 mmHg or <130/80 mmHg for those with diabetes or chronic kidney disease

Chobanian *et al. JAMA* 2003;289:2560–72[7]

Recommended combinations of anti-hypertensive drugs: ESH-ESC Guidelines 2007[6]

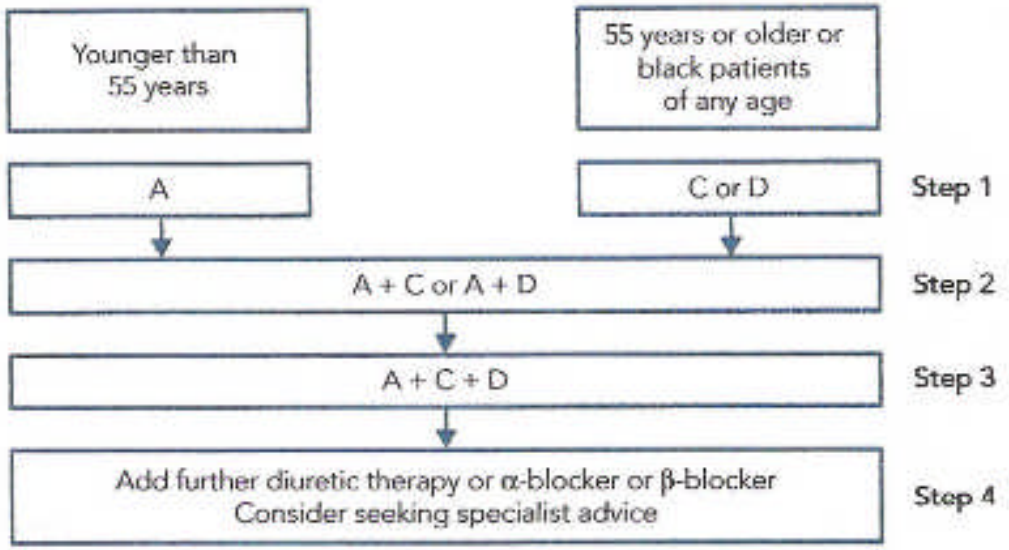


Mancia G *et al. J Hypertens* 2007;25:1105–87[6]

Priority antihypertensive drug combinations (European Guidance 2009)[17]

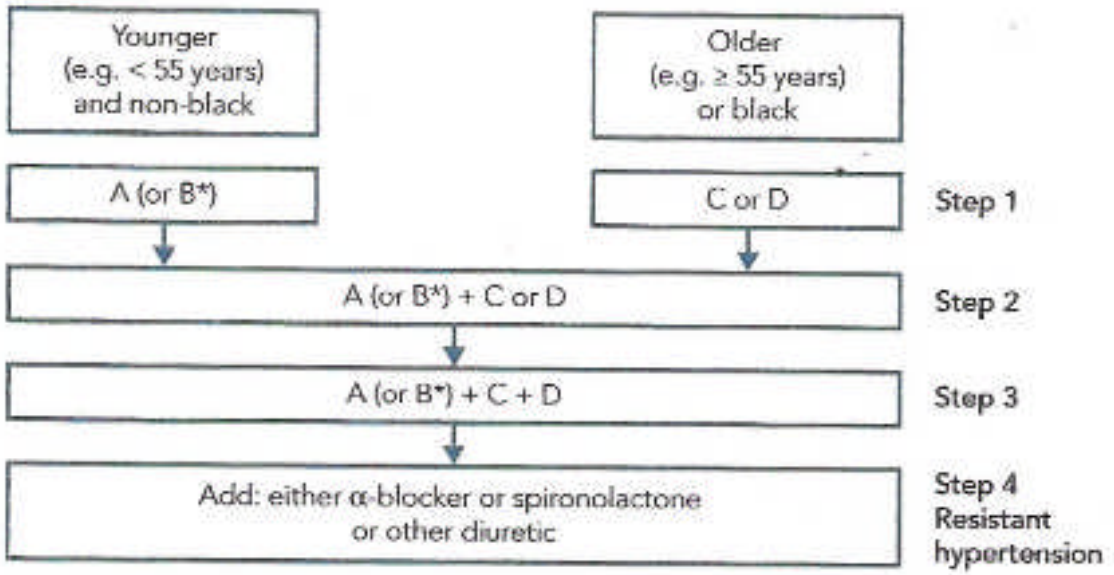
- Diuretic plus ACE inhibitor
- Diuretic plus ARB
- Diuretic plus CCB
- ACE inhibitor plus CCB
- ARB plus CCB

Choosing drugs for patients newly diagnosed with hypertension: NICE/BHS



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
NICE/BHS algorithm: June 2006[17]

The 2004 British Hypertension Society recommendations for combining blood pressure lowering drugs

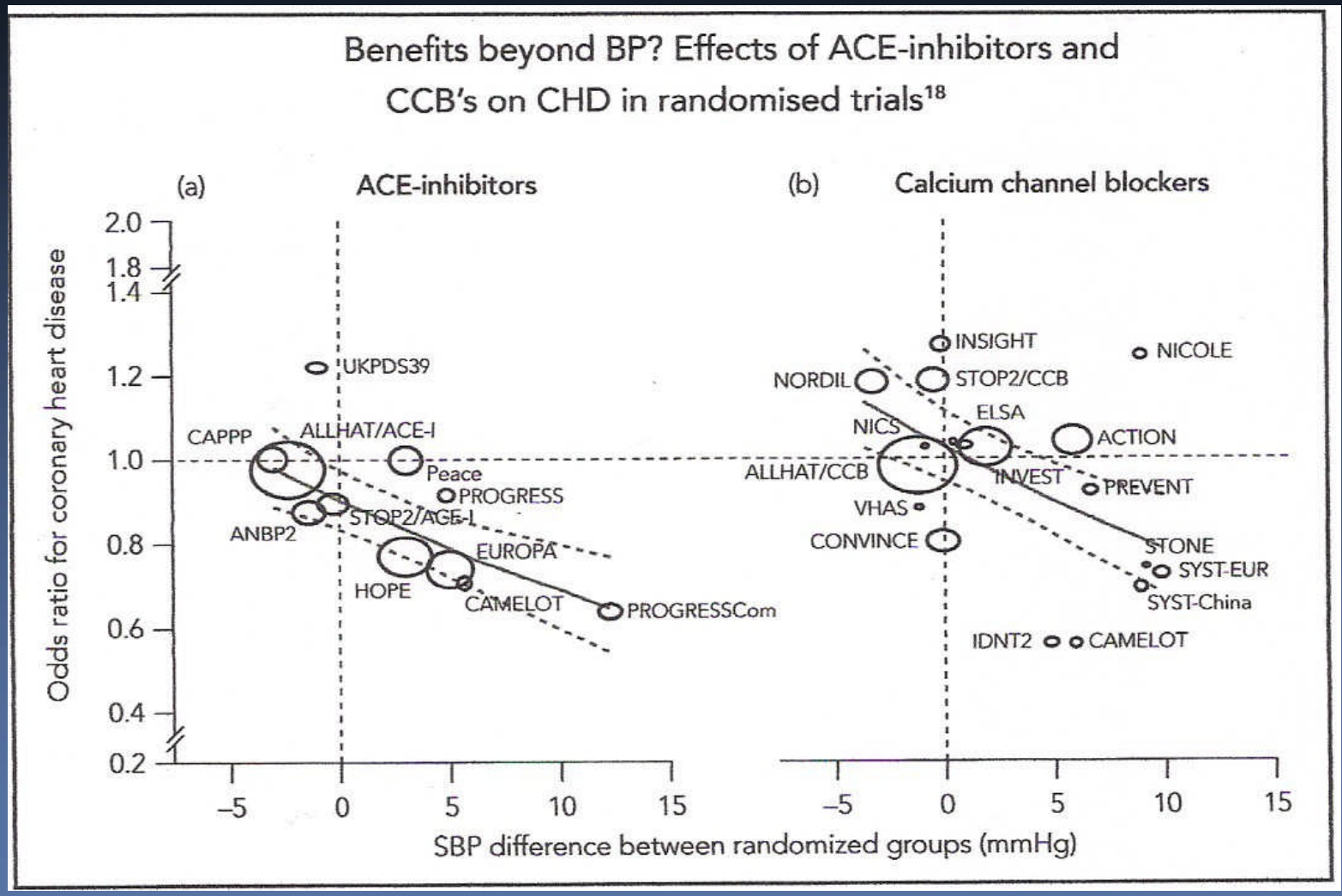


A, ACE inhibitor or angiotensin receptor blocker; B, β-blocker; C, calcium channel blocker; D, diuretic (thiazide)
*Combination therapy involving B and D may induce more new onset diabetes compared with other combination therapies

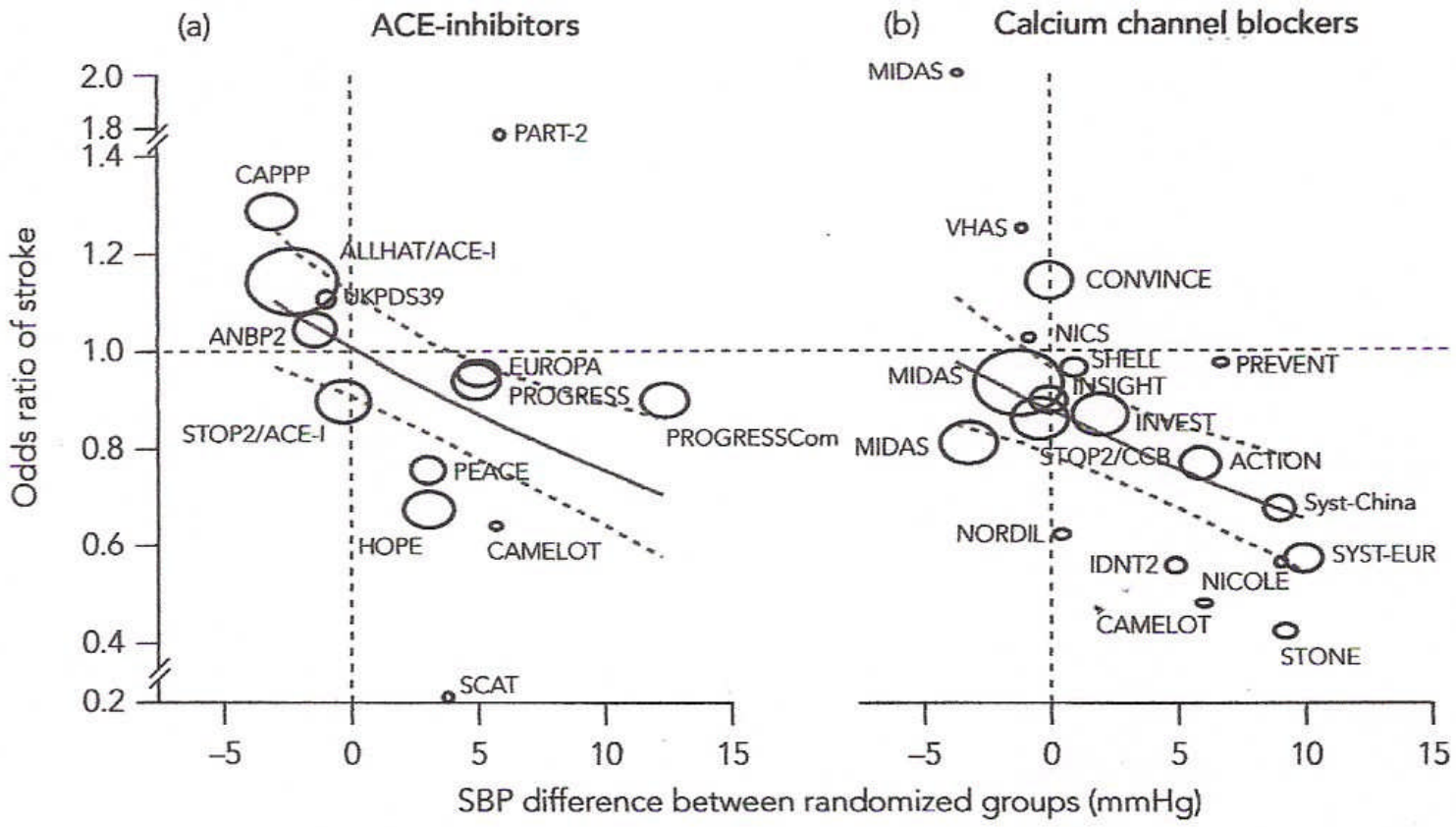
Summary of the Cochrane Review of β-blockers for hypertension: 2007

The available evidence does not support the use of β-blockers as first-line drugs in the treatment of hypertension. This conclusion is based on the relatively weak effect of β-blockers to reduce stroke and the absence of an effect on coronary heart disease when compared to placebo or no treatment. More importantly, it is based on the trend towards worse outcomes in comparison with calcium-channel blockers, renin-angiotensin system inhibitors, and thiazide diuretics.

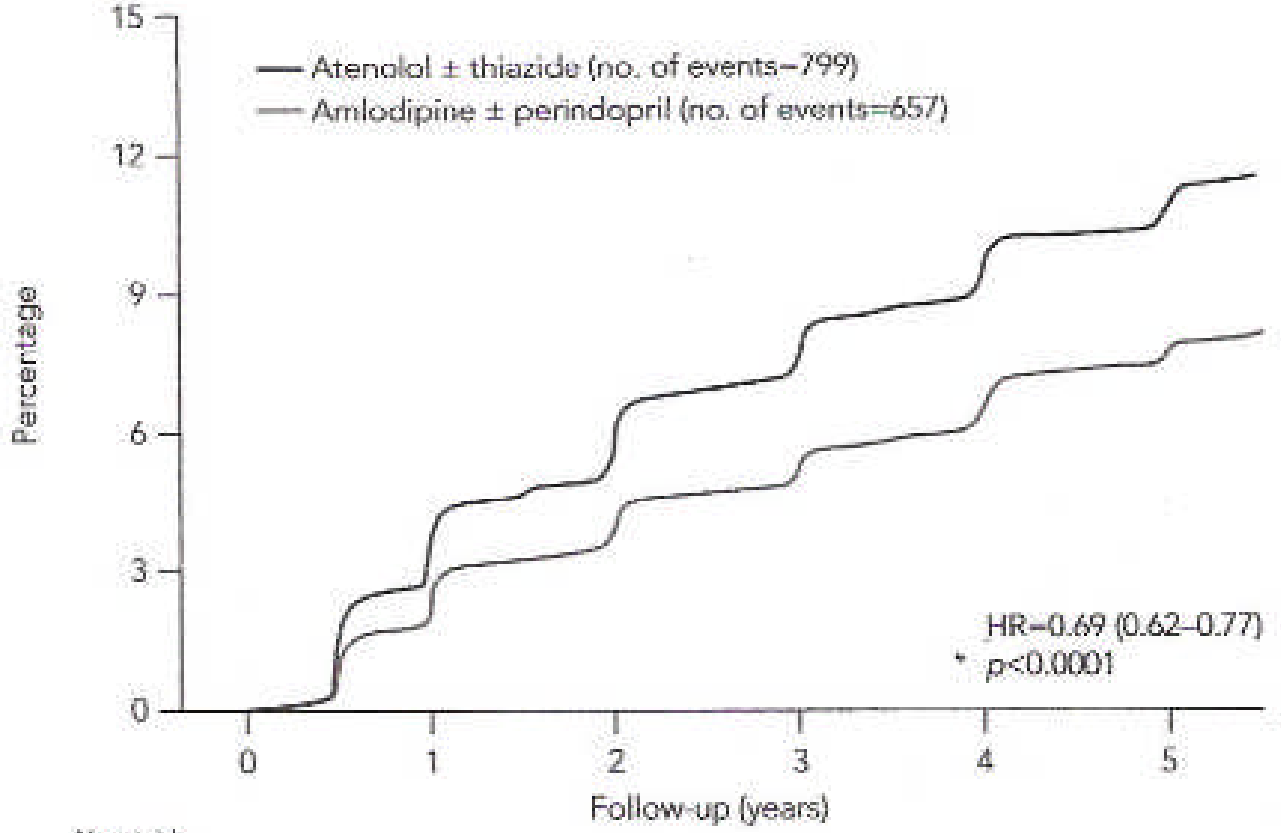
Wiysonge CS et al. *Cochrane Database Sys Rev* 2007;1:CD002003[9]


Benefits beyond BP? Effects of ACE-inhibitors and CCB's on CHD in randomised trials[18]
(a)
ACE-inhibitors
(b)
Calcium channel blockers
Odds ratio for coronary heart disease
2.0
1.8
1.4
1.2
1.0
0.8
0.6
0.4
0.2
UKPDS39
CAPPP
ALLHAT/ACE-I
Peace
PROGRESS
STOP2/ACE-I
ANBP2
EUROPA
HOPE
CAMELOT
PROGRESSCom
INSIGHT
NICOLE
NORDIL
STOP2/CCB
ELSA
NICS
ACTION
ALLHAT/CCB
INVEST
PREVENT
VHAS
CONVINCE
STONE
SYST-EUR
SYST-China
IDNT2
CAMELOT
–5
0
5
10
15
SBP difference between randomized groups (mmHg)

Benefits beyond BP? Effects of ACE-inhibitors and CCB's on stroke in randomised trials[18]

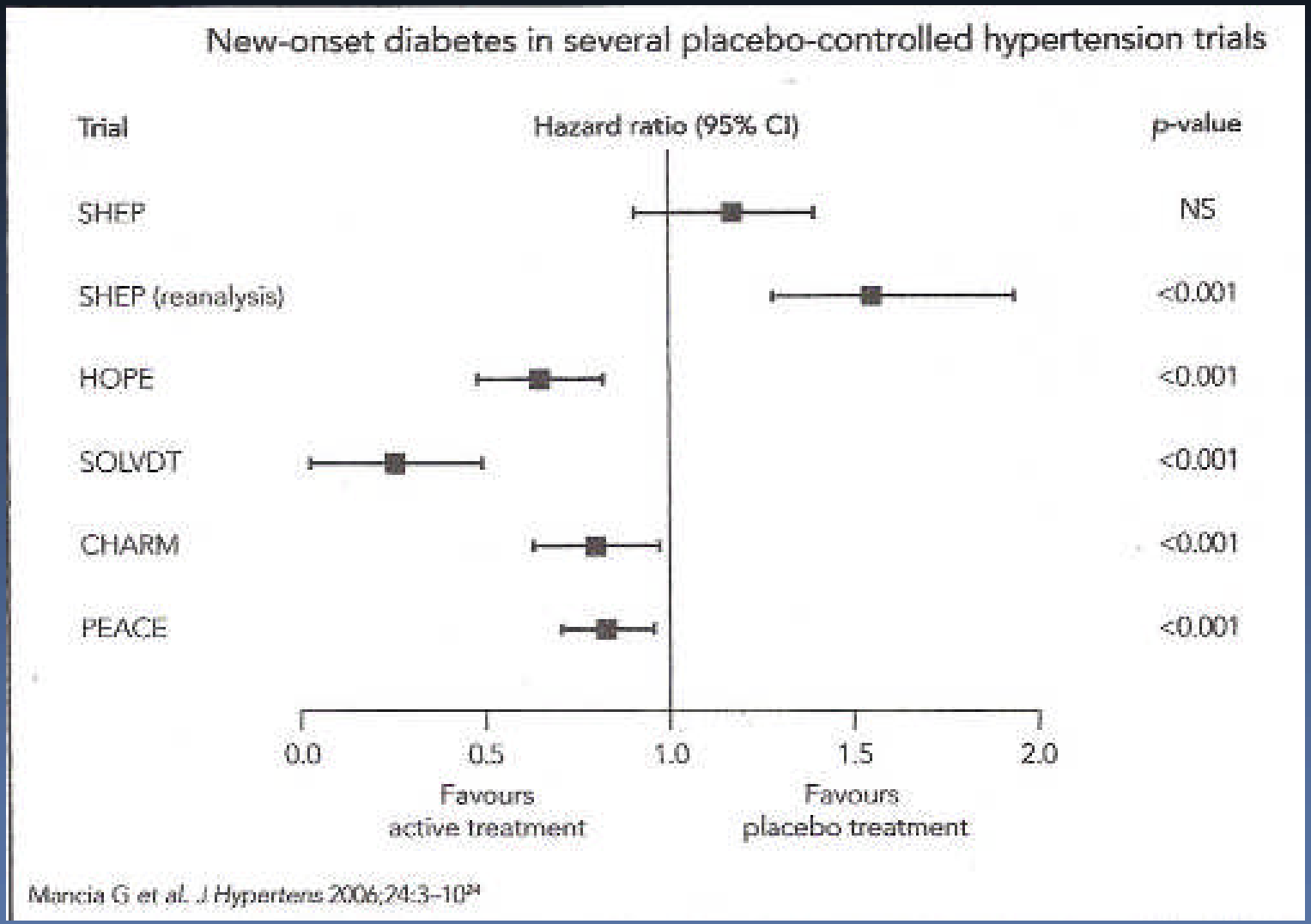


New-onset diabetes mellitus by randomised treatment in ASCOT-BPLA



No. at risk						
Amlodipine ± perindopril	7071	6853	6667	6508	6312	5513
Atenolol ± thiazide	7046	6743	6494	6262	6040	5226

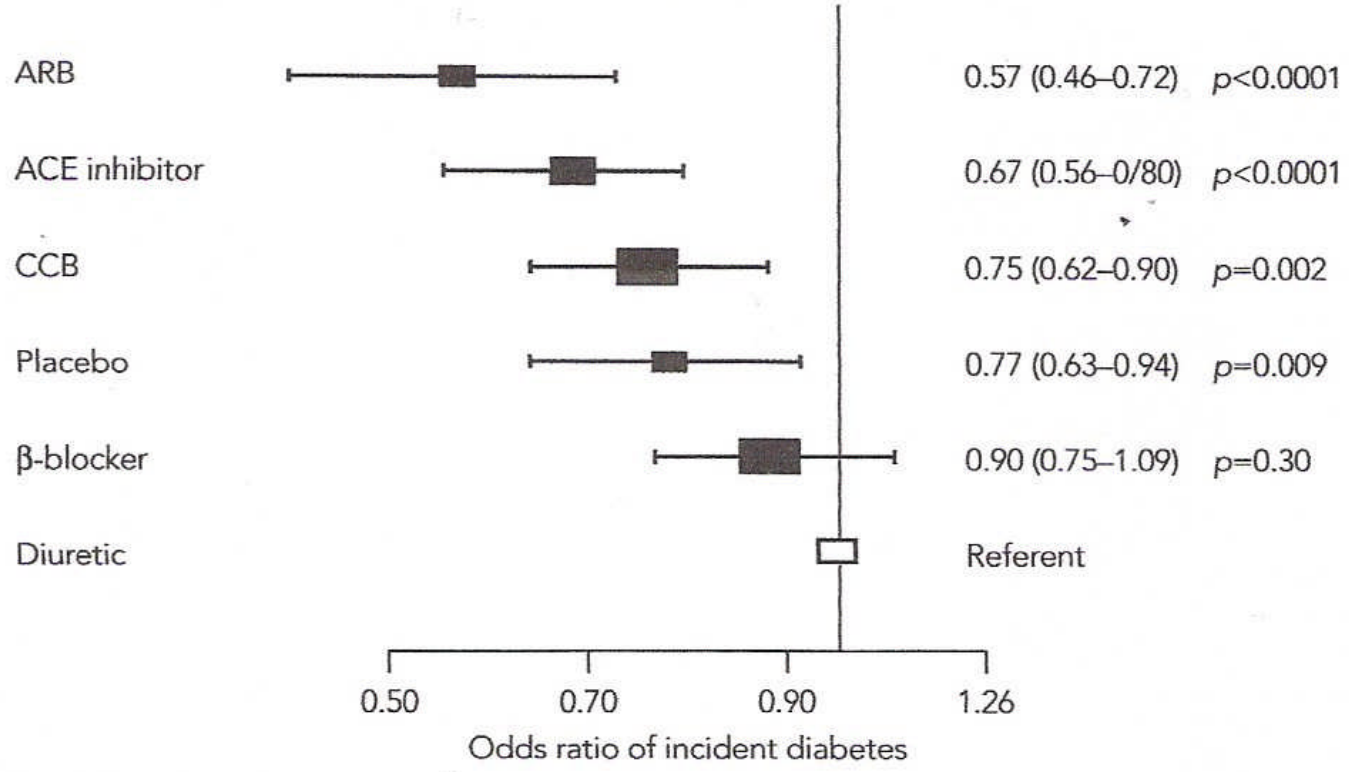
New-onset diabetes in several placebo-controlled hypertension trials



Mancia G et al. J Hypertens 2006;24:3–10[24]

Prevention of type 2 diabetes: impact of various antihypertensive agents

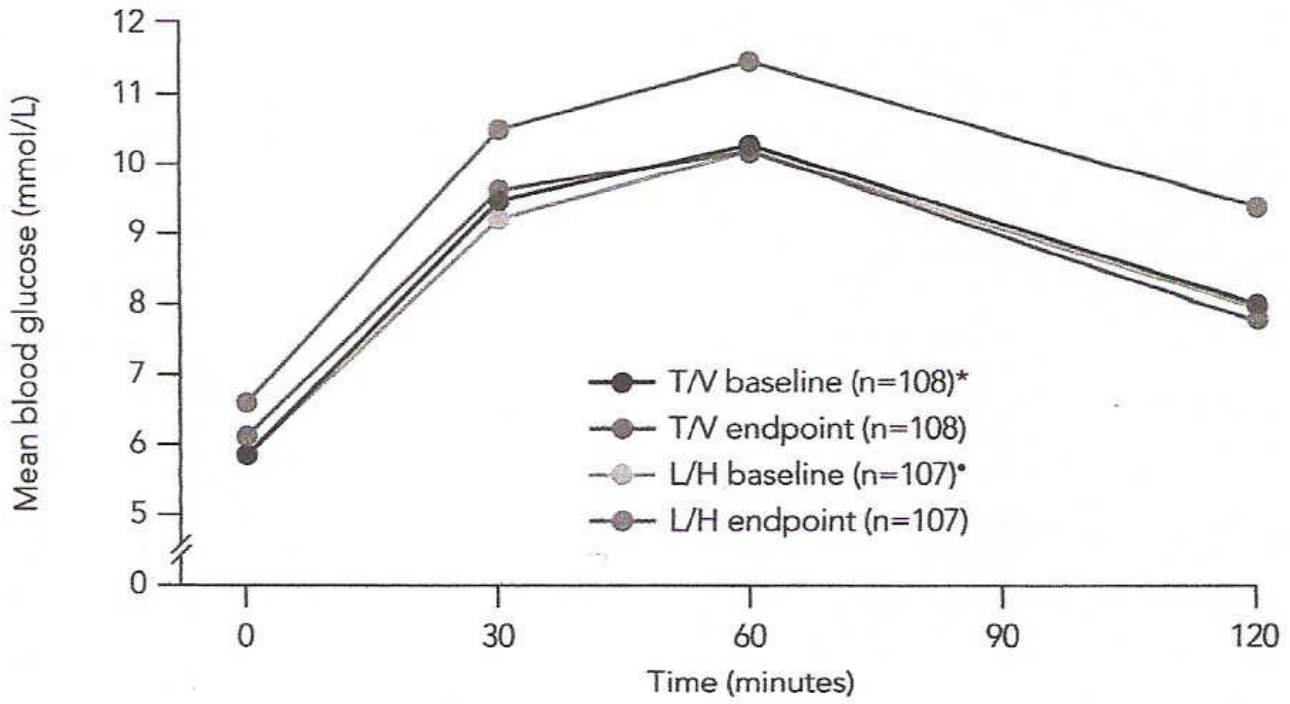
Results of network meta-analysis of 22 clinical trials



Incoherence=0.000017

Elliott W *et al. Lancet* 2007;369:201–7[25]

Adverse impact on glucose and new-onset diabetes of 'A+D'† drugs compared with 'A + C'◊ drugs



†ACE-inhibitor + diuretic; ◊ACE inhibitor + CCB; *Trandolapril/Verapamil; •Losartan/HCTZ

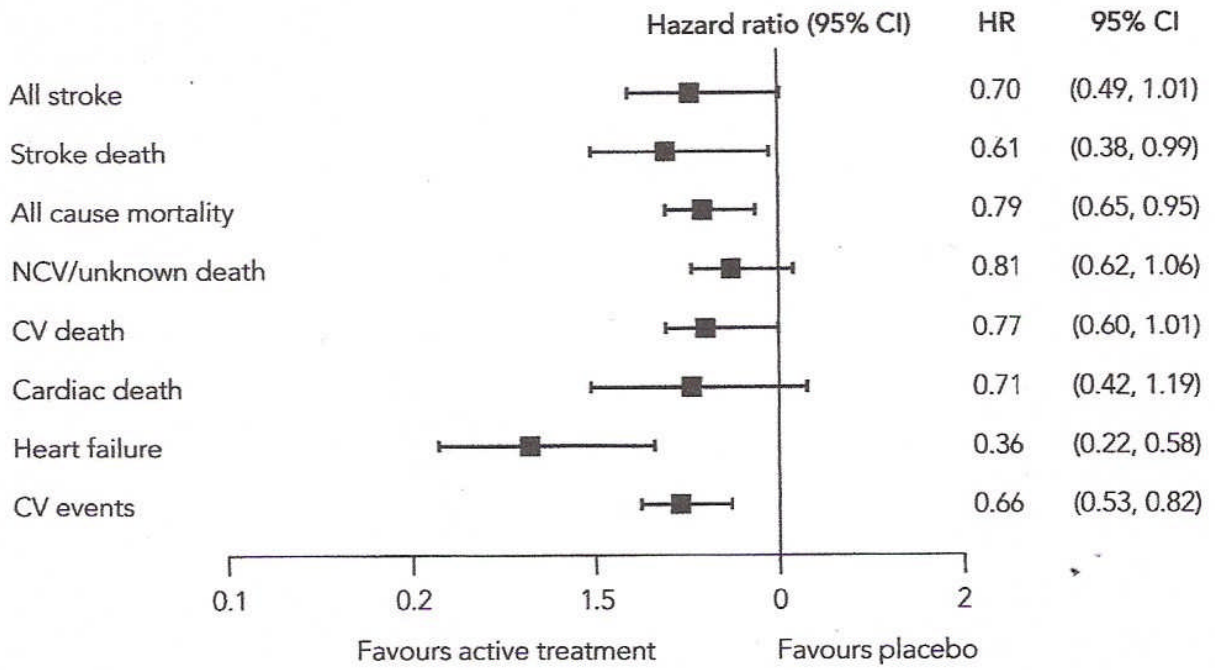
Bakris G *et al. Diabetes Care* 2006[26]

Life trial: effects on primary and other endpoints

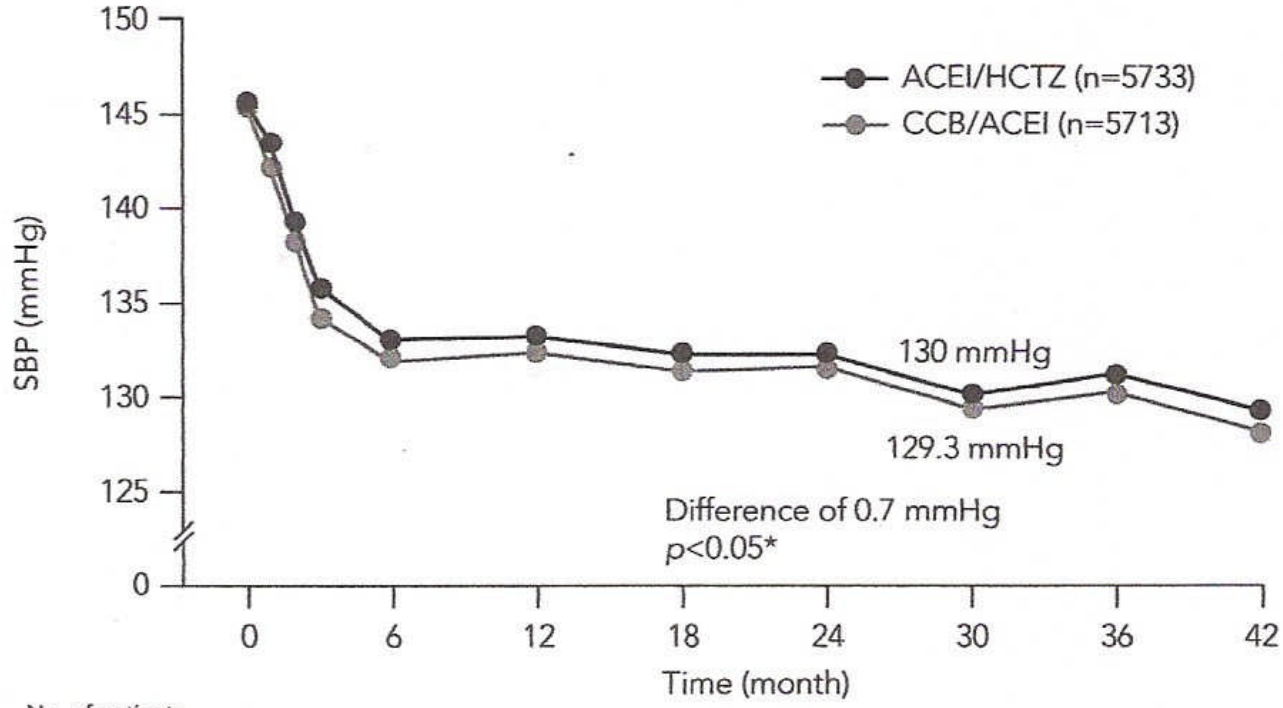
	Percentage Reduction in Event Rates
Major CV events	13%
All stroke	26%
All MI*	–5%*

*The minus sign indicates lower risk in the control (atenolol-based) group

HYVET: summary of major outcomes



ACCOMPLISH trial: systolic blood pressure changes over time



No. of patients

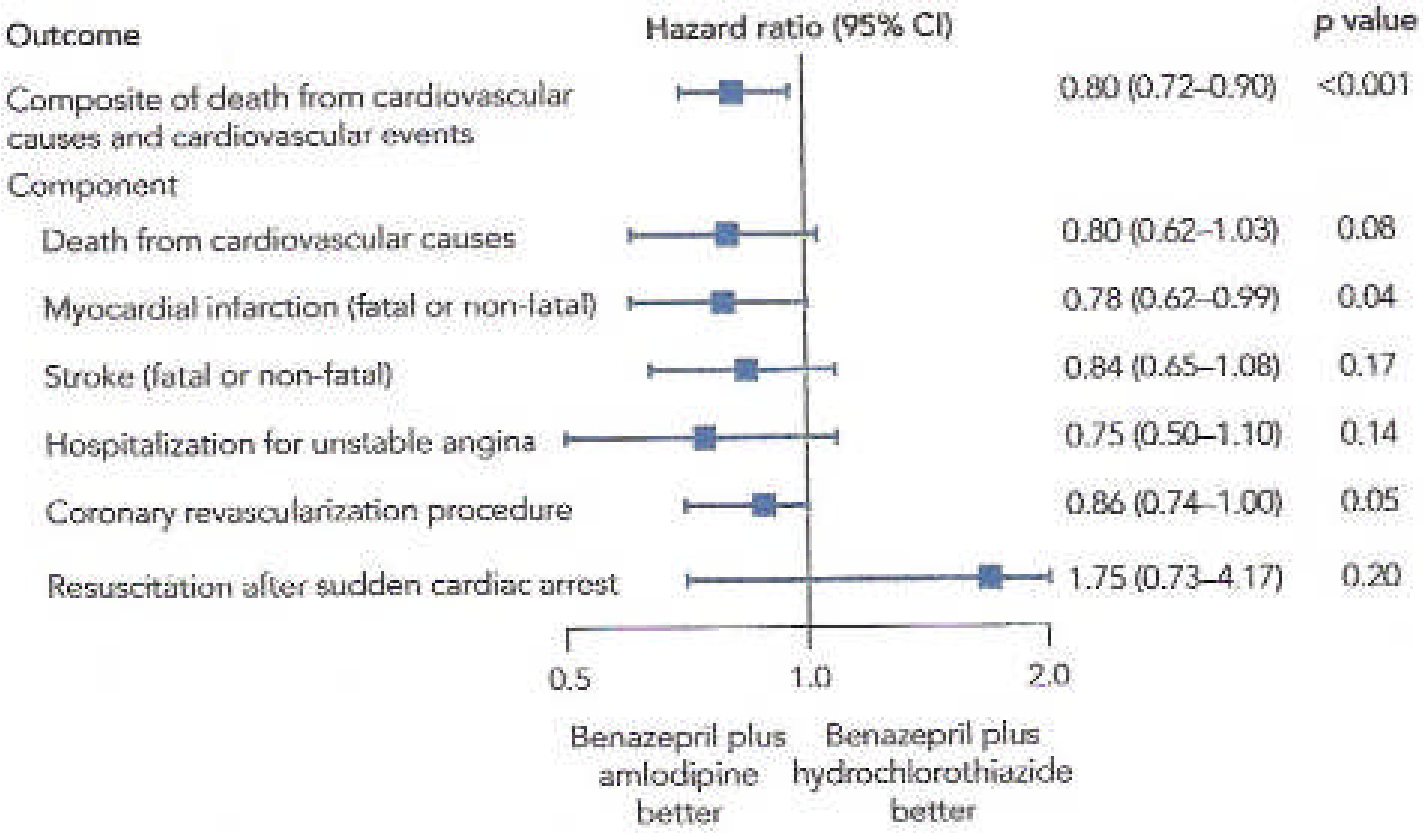
ACEI/HCTZ	5731	5387	5206	4999	4804	4285	2520	1045
CCB/ACEI	5709	5377	5154	4980	4831	4286	2594	1075

*Mean values are taken at 30 months F/U visit

ACCOMPLISH trial: adverse events

	Any		Drug-Related Serious	
Adverse Event	Benazepril-Amlodipine Group (N=5744)	Benazepril-Hydrochlorothiazid Group (N = 5762)	Benazepril-Amlodipine Group (N=5744)	Benazepril-Hydrochlorothiazide Group (N = 5762)
Dizziness	1189 (20.7)	1461 (25.4)	2 (<0.1)	5 (0.1)
Peripheral edema	1792 (31.2)	772 (13.4)	4 (0.1)	2 (<0.1)
Dry cough	1177 (20.5)	1220 (21.2)	3 (0.1)	3 (0.1)
Angioedema	53 (0.9)	34 (0.6)	2 (<0.1)	5 (0.1)
Hyperkalemia	34 (0.6)	33 (0.6)	6 (0.1)	6 (0.1)
Hypokalemia	3 (0.1)	17 (0.3)	1 (<0.1)	0
Hypotension	142 (2.5)	208 (3.6)	6 (0.1)	9 (0.2)

ACCOMPLISH trial: effects on primary and other endpoints



ACCOMPLISH trial: baseline characteristics

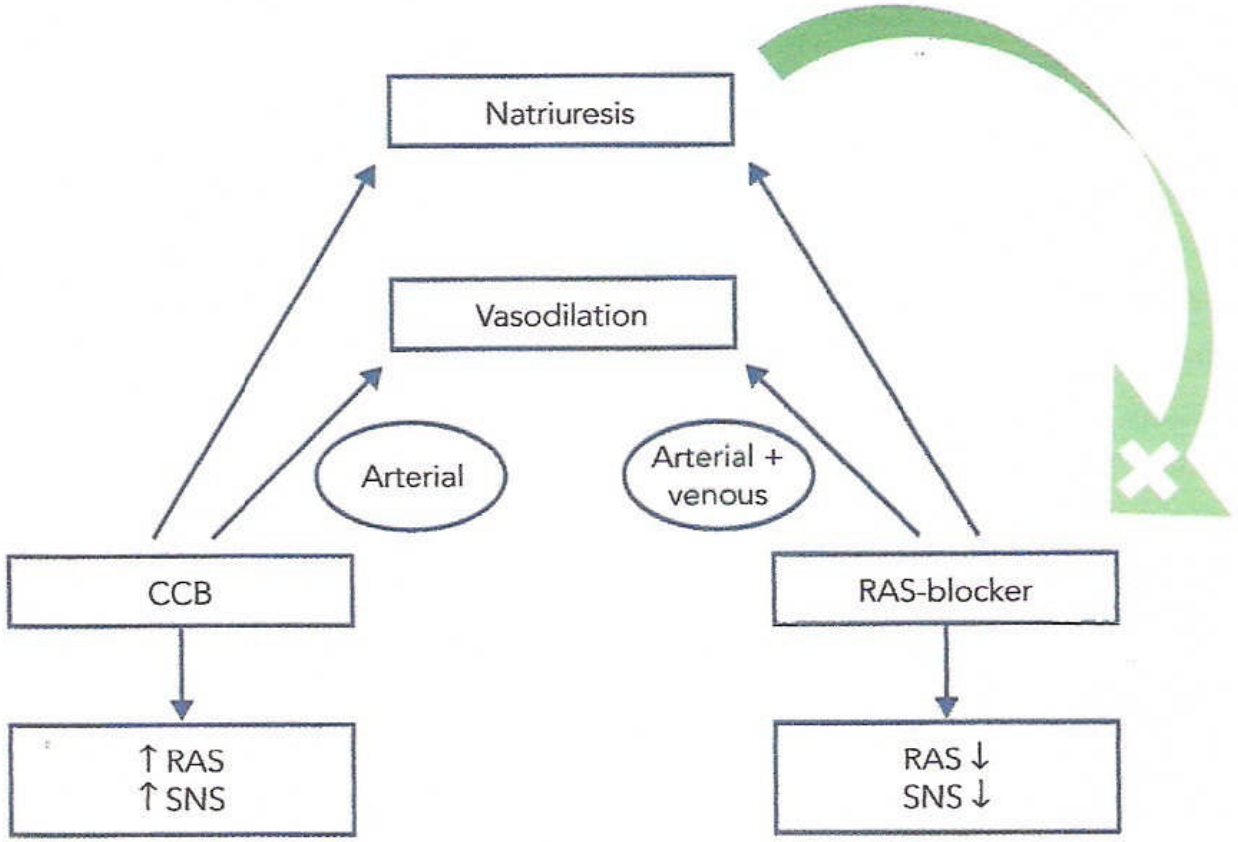
Characteristic	Benazepril-Amlodipine Group (N=5744)	Benazepril-Hydrochlorothiazide Group (N=5762)
Risk factors – no. (%)		
Previous myocardial infarction	1337 (23.3)	1372 (23.8)
Previous stroke	762 (13.3)	736 (12.8)
Previous hospitalization for unstable angina	653 (11.4)	671 (11.6)
Diabetes mellitus	3478 (60.6)	3468 (60.2)
Renal disease¶¶	352 (6.1)	353 (6.1)
Estimated glomerular filtration rate <60	1047 (18.2)	1030 (17.9)
Previous coronary revascularization	2044 (35.6)	2073 (36.0)
Coronary-artery bypass grafting	1248 (21.7)	1197 (20.8)
Percutaneous coronary intervention	1055 (18.4)	1123 (19.5)
Left ventricular hypertrophy**	763 (13.3)	758 (13.2)
Other		
Current smoking	641 (11.2)	658 (11.4)
Dyslipidemia	4221 (73.5)	4319 (75.0)
Atrial fibrillation	376 (6.5)	403 (7.0)

*Plus-minus values are means ± SD.
†Race or ethnic group was self-reported
‡The body-mass index is the weight in kilograms divided by the square of the height in metres.
§The estimated glomerular filtration rate was calculated with the use of the Modification of Diet in Renal Disease (MDRD) Study equation.
¶To convert the values for creatinine to micromoles per liter, multiply by 88.4; to convert the values for glucose to millimoles per liter, multiply by 0.05551; to convert the values for cholesterol to millimoles per liter multiply by 0.02586.
¶¶Renal disease was determined by the investigator on the basis of either a serum creatinine level of more than 1.5 mg per deciliter (133 ?mol per liter) in women or greater than 1.7 mg per deciliter (150 ?mol per liter) in men or the presence of macroalbuminuria, confirmed on two separate occasions at least 48 hours apart.
** Left ventricular hypertrophy was determined on the basis of electrocardiographic findings (central reading).

Summary

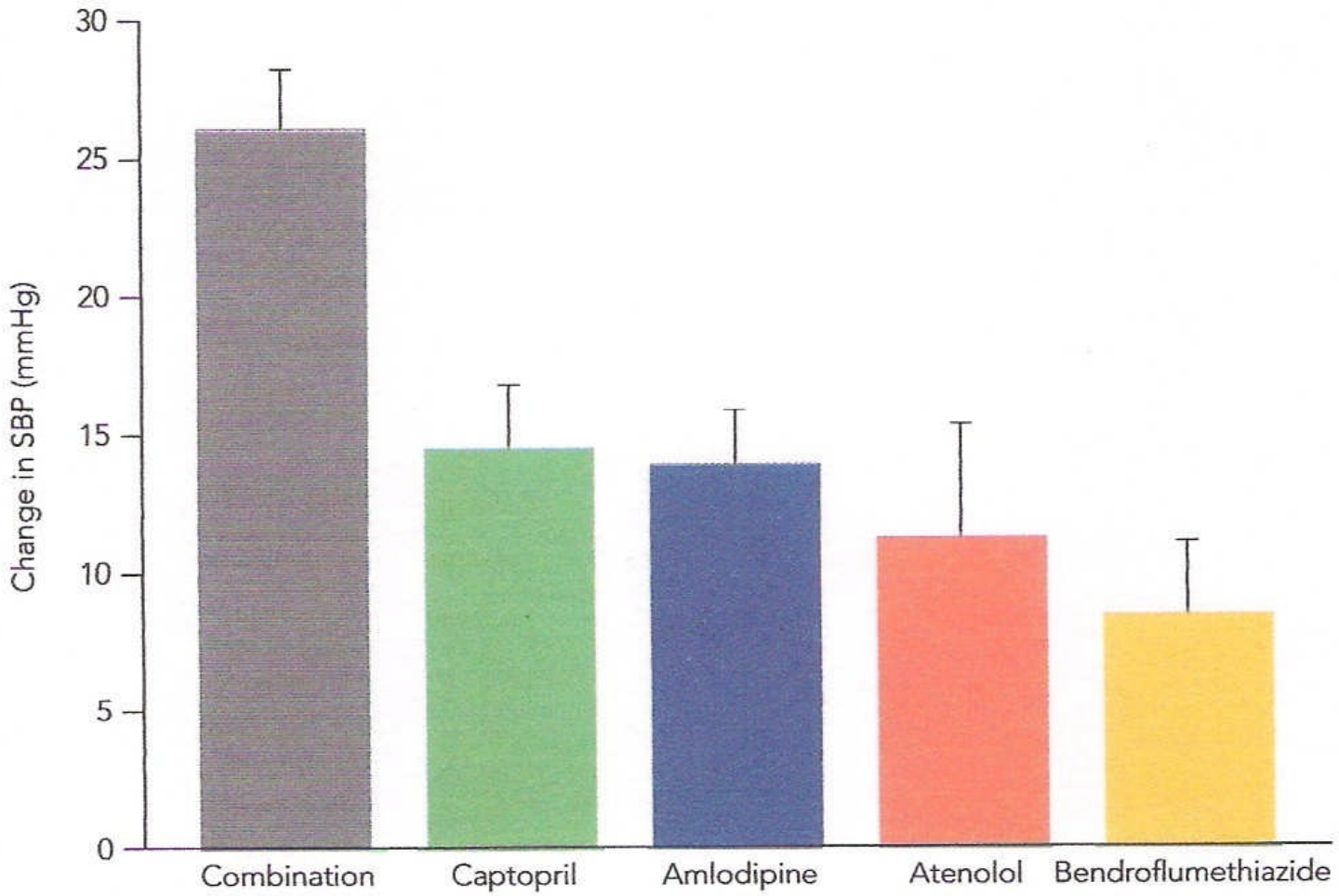
- Table 4.5 summarises the results of 16 RCT's of antihypertensive agents reported in the last decade with a major CV primary endpoint and in which over 50% of patients included in each trial were hypertensive.
- Latest European and American guidelines recommend the use of 2 agents as initial therapy for a large proportion of hypertensive patients.
- Guidelines worldwide are inconsistent with regard to which combinations of antihypertensive agents should be used.
- This inconsistency reflects the lack of inadequate and robust RCT data.
- ACE-inhibitors plus ARBs should probably not be combined in the management of hypertension (although possibly in the context of heart failure).
- RCT-based recommendations inevitably favour combinations of RAS blockers (ACE-inhibitors or ARBs) plus diuretics or RAS blockers plus calcium channel blockers with best evidence currently in favour of the latter combination.

Compensatory mechanisms of action of CCBs and RAS-blockers on vascular and renal function, SNS* and RAS – activity



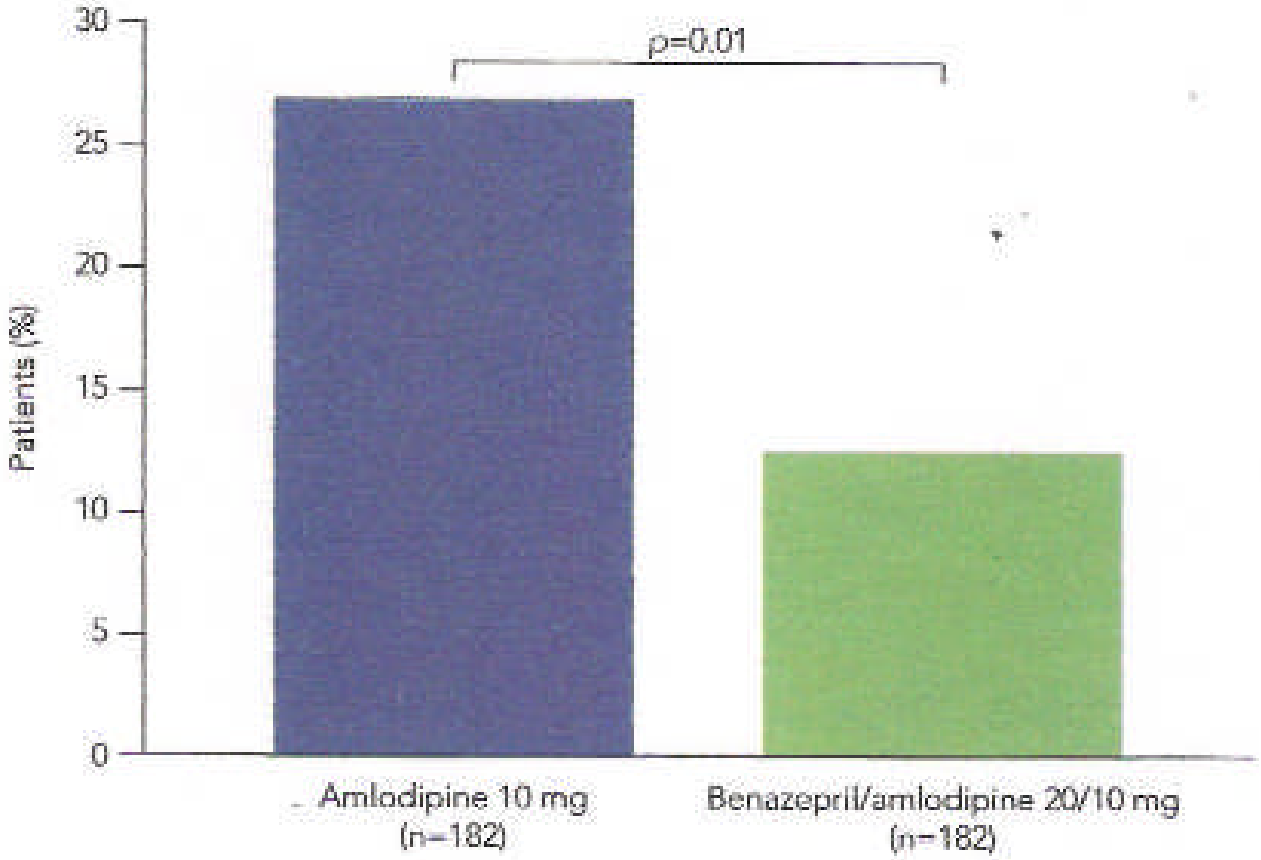
*Sympathetic nervous system
– Renin-angiotensin System

The impact on systolic BP of full-dose monotherapies compared with one tablet containing four drugs at quarter-doses



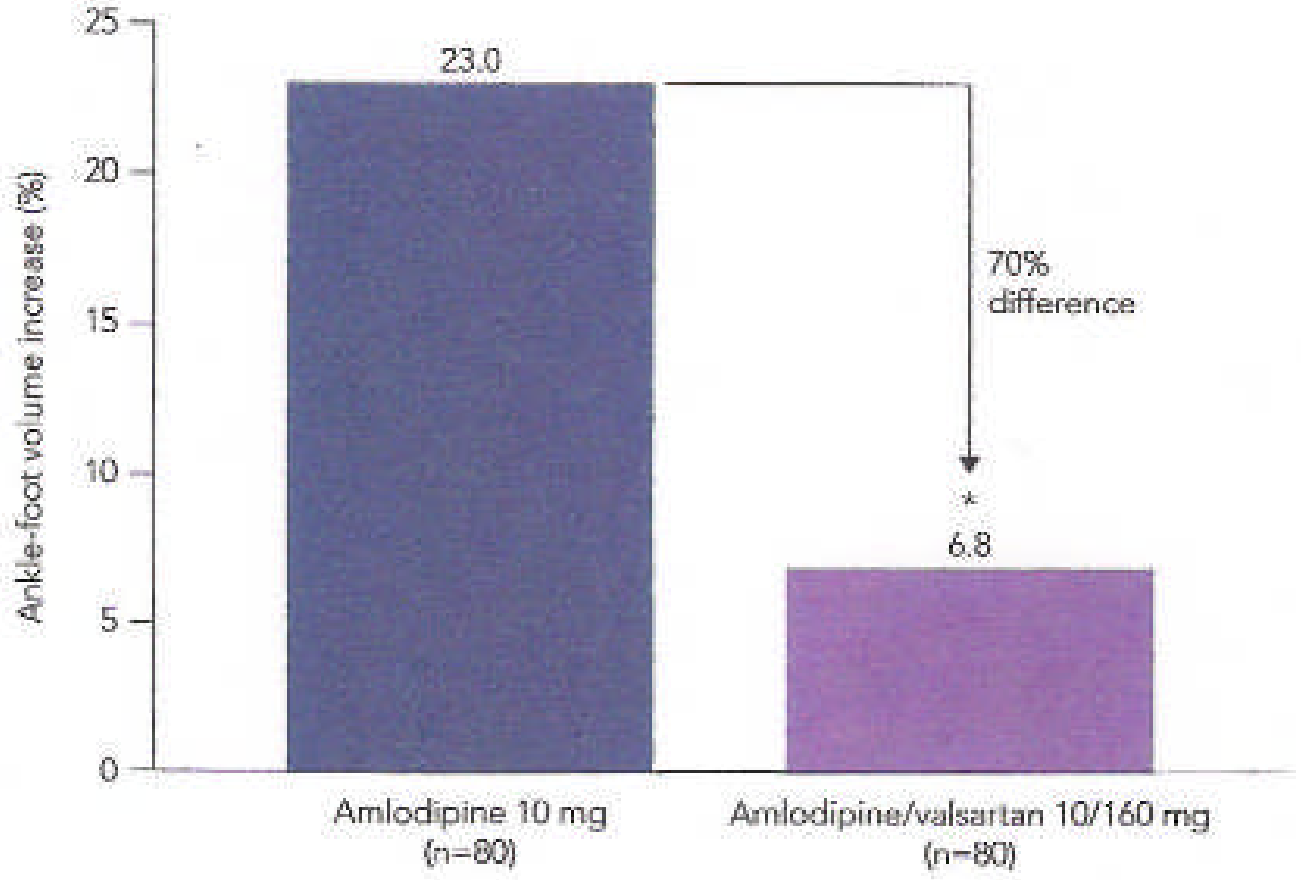
Mahmud. *Hypertension* 2007[5]

Attenuation of peripheral oedema with dual ACE inhibitor/CCB therapy compared with CCB monotherapy: stage 2 hypertension



Jamerson et al. Am J Hypertens 2004;17:495–501[3]

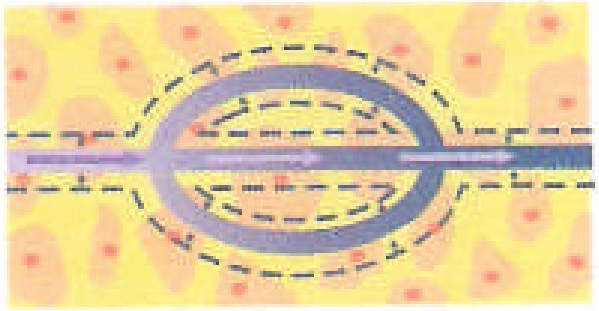
Attenuation of peripheral oedema with dual ARB/CCB therapy compared with CCB monotherapy



Fogari et al. *J Hum Hypertens* 2007;21:220–4[12]

Theoretical mechanism for reduction of CCB-associated oedema by CCB and RAS inhibitors

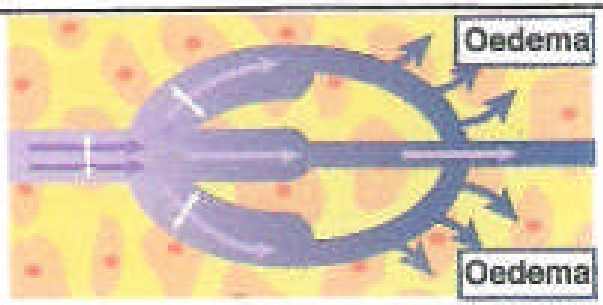
I.



Arterial hypertension

- Constricted blood vessels, high resistance

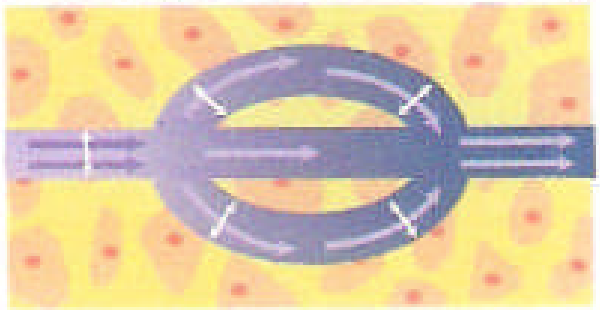
II.



CCBs

- BP reduction due to arterial vasodilation
- Tendency towards oedema due to absent venodilation
- BP reduction stimulates RAS and increases angiotensin II level

III.



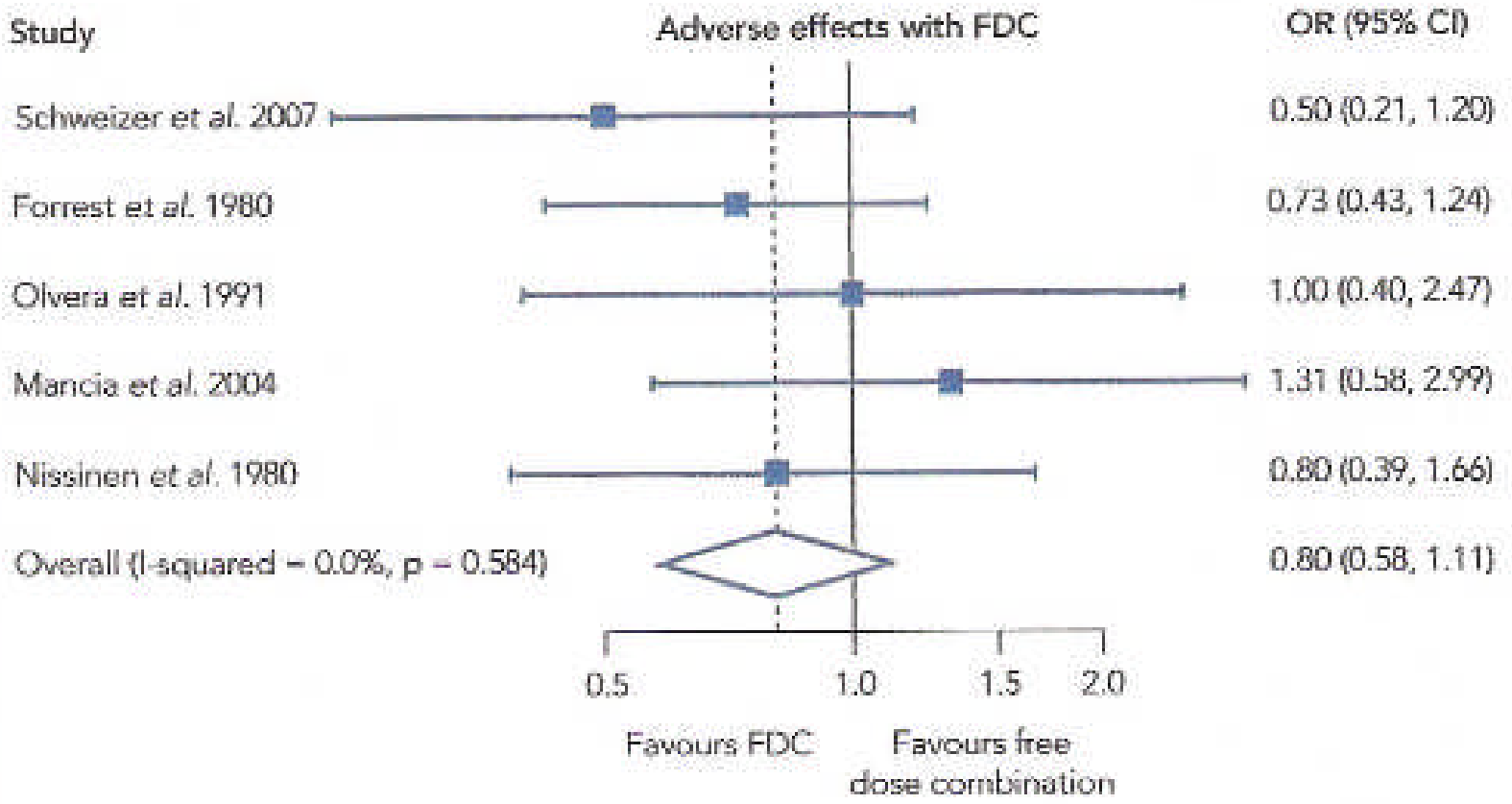
CCBs + RAS inhibitors*

- Blockade of RAS inhibits effects of angiotensin II, giving rise to additional BP reduction
- Additional venodilation by RAS inhibitors reduces oedema

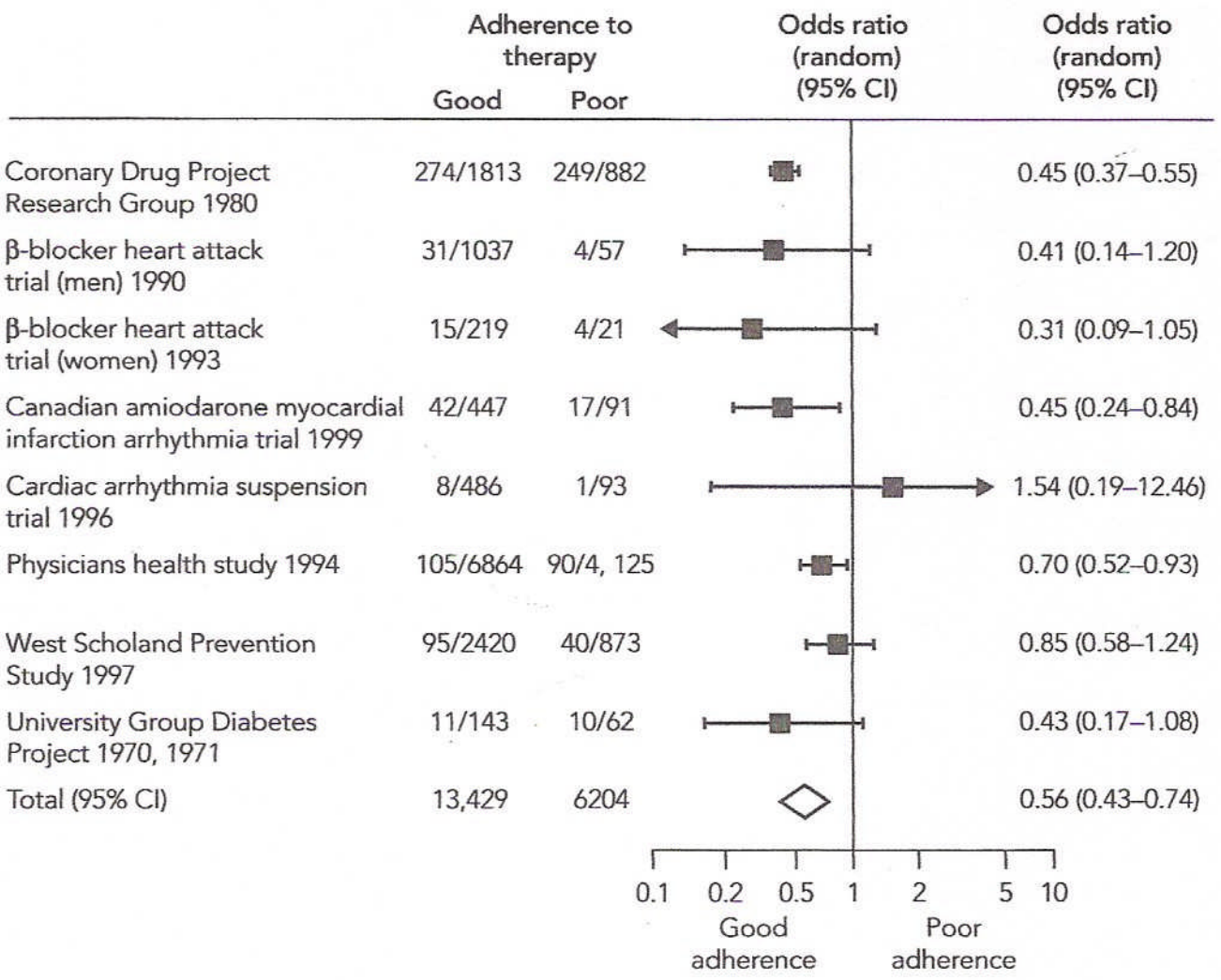
*Angiotensin receptor blockers or angiotensin-converting enzyme inhibitors

Messerli FH. *Am J Hypertens* 2001;14:978–91[1]

Systematic review of single-pill combinations of 2 antihypertensive agents vs. 2 agents supplied separately: effects on adverse events[12]

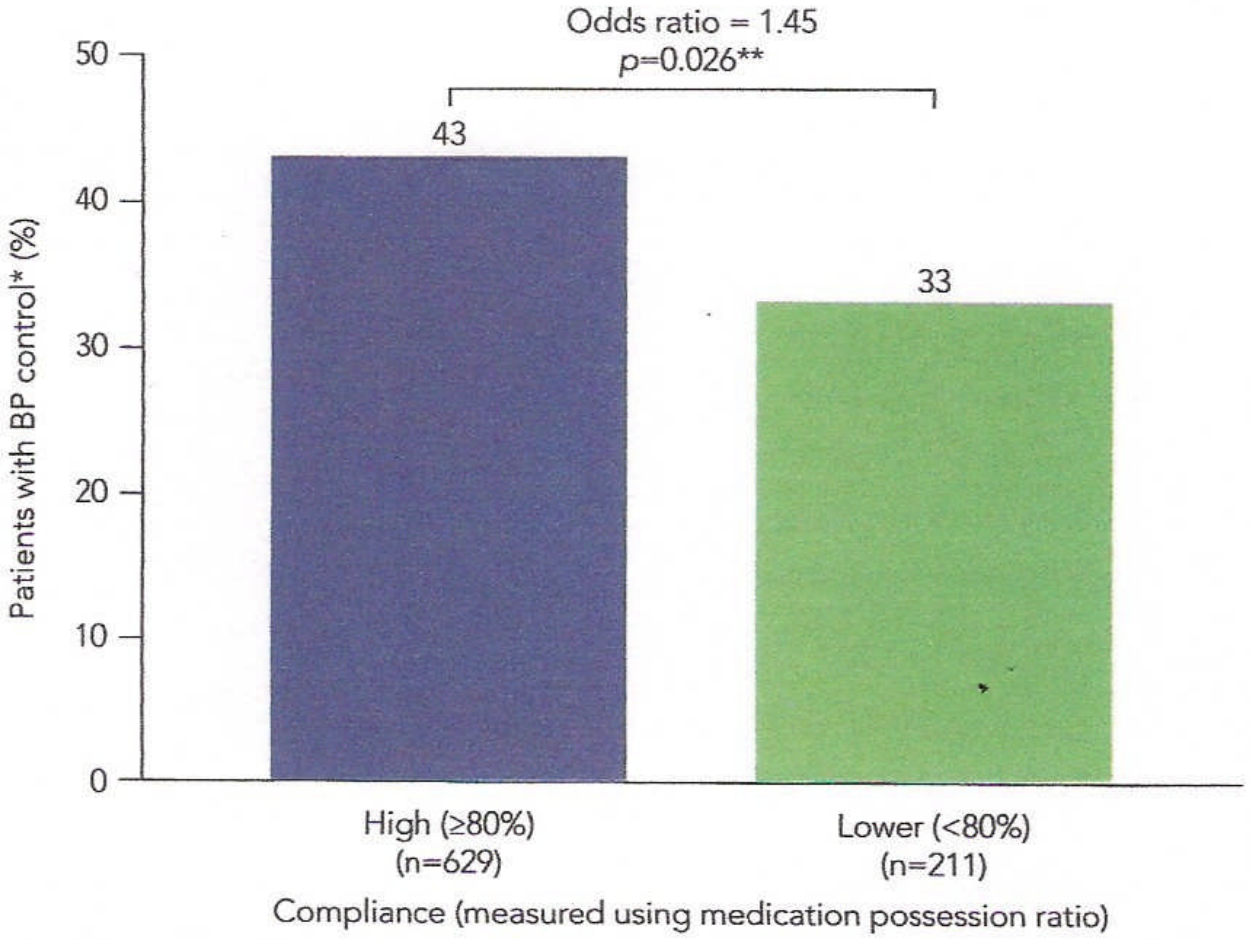


Association between adherence to placebo and mortality



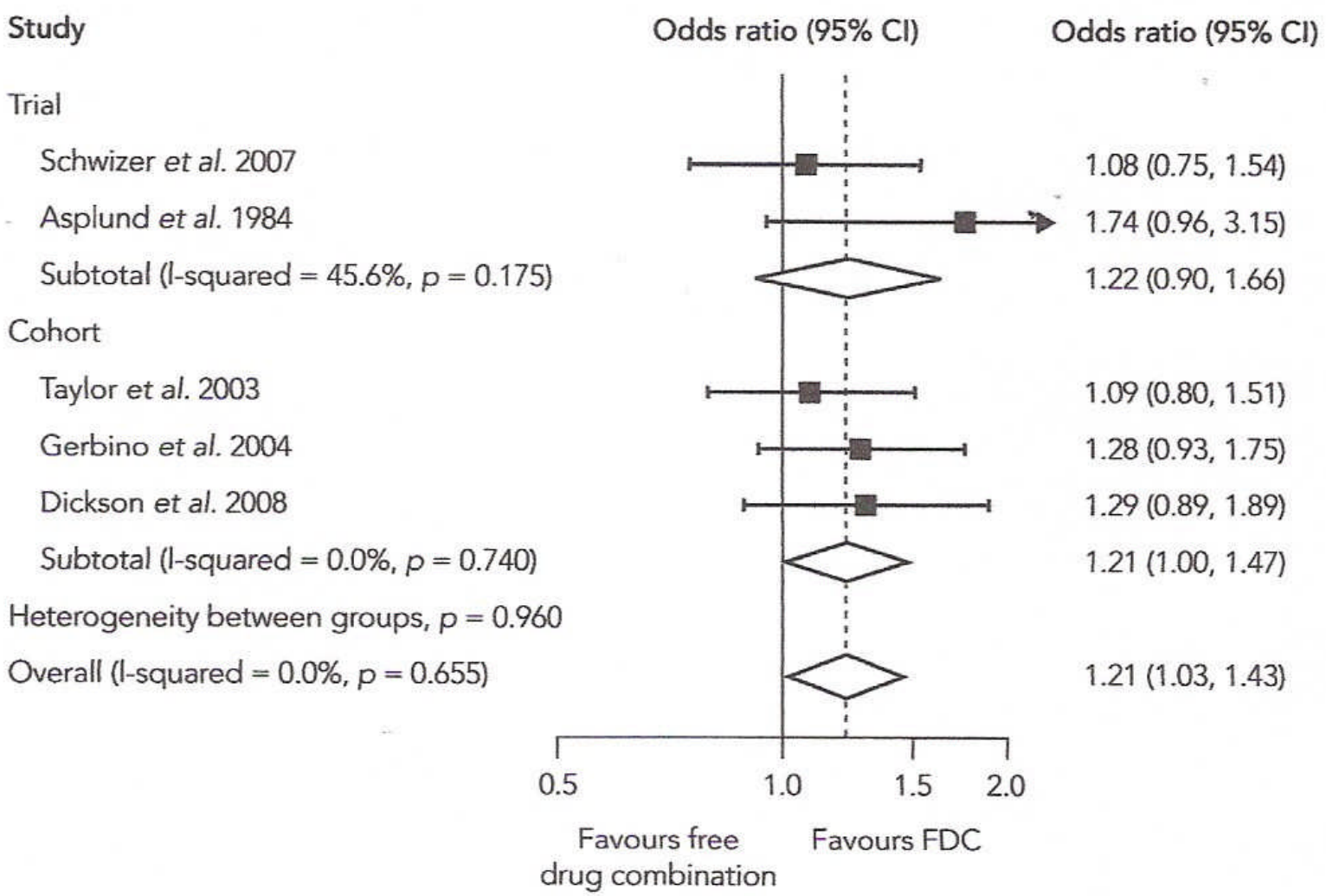
Simpson SH. *BMJ* 2006;333:15[13]

Association between drug compliance and achieving BP goal



*<140/90 mmHg or <130/85 mmHg for patients with diabetes
**controlling for age, gender and co-morbidities)
Bramley TJ *et al. J Manag Care Pharm* 2006;12:239–45[14]

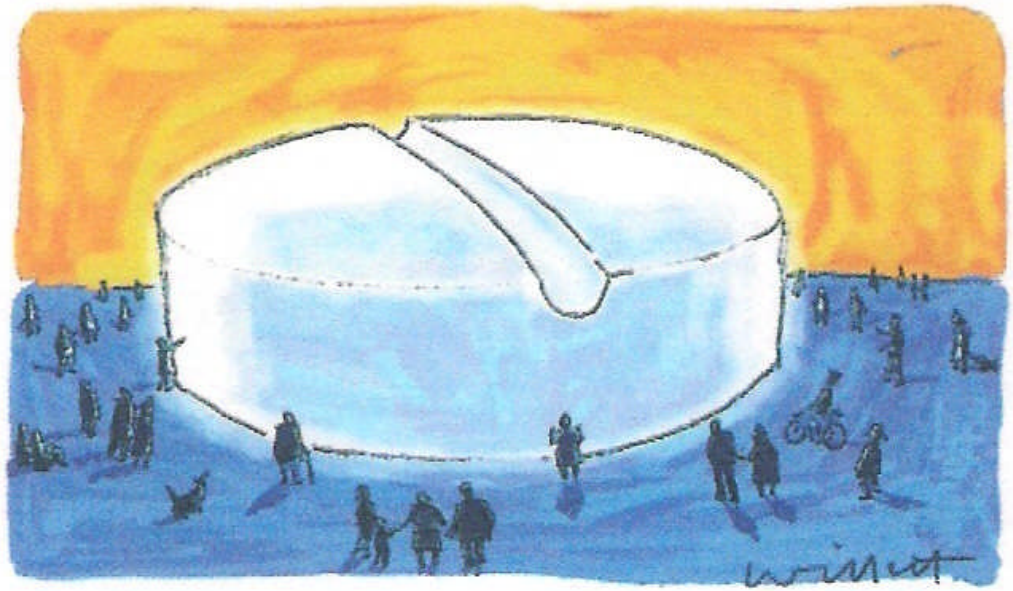
Systematic review of single-pill combinations of 2 antihypertensive agents vs. 2 agents supplied separately: effects on compliance ratios



Summary

- Formulations of 2 or more drugs supplied as single pills – traditionally called "Fixed Dose Combinations" (FDCs) are more accurately called "single pill combinations" or "flexible pill combinations" to reflect the reality of the available drug dosages.
- The use of FDCs in hypertension management, but not in many other areas of medicine, has traditionally been considered poor medicine. There is no apparent logic for this prejudice.
- Single pill combinations at low dose offer several potential advantages over single drugs at high dose – particularly fewer side effects – with at least as good BP-lowering effect.
- Single – pill combinations of 2 antihypertensive agents compared with supplying the 2 agents as separate pills offer the potential advantages of reduced direct and indirect costs, better compliance and thereby more-effective BP-lowering.

Polypill hits the headlines: "A pill to prevent 80% of heart attacks"



The most important *BMJ* for 50 years? Richard Smith, ed

BMJ 28 June 2003;vol 326'

Summary

- A 6 component polypill was recommended for the general population in 2003 with the aim of preventing 80% of heart attacks.
- The optimal components of a polypill for use in primary prevention of cardiovascular (CV) events in the general population are contentious with different concerns regarding 'costs' and 'benefits'.
- The use of a polypill for secondary prevention is a more likely development because it is currently standard medical practice to use several agents for patients with established CV disease or diabetes.
- The logistics – size, cost, pharmacodynamics and pharmacokinetics – are likely to have a major influence on which agents are included in any polypill.