In the world in 2001

- 1 heart attack every 4 sec
- 1 stroke every 5 sec

Haulay et al., Lancet 1999, 354, 1457

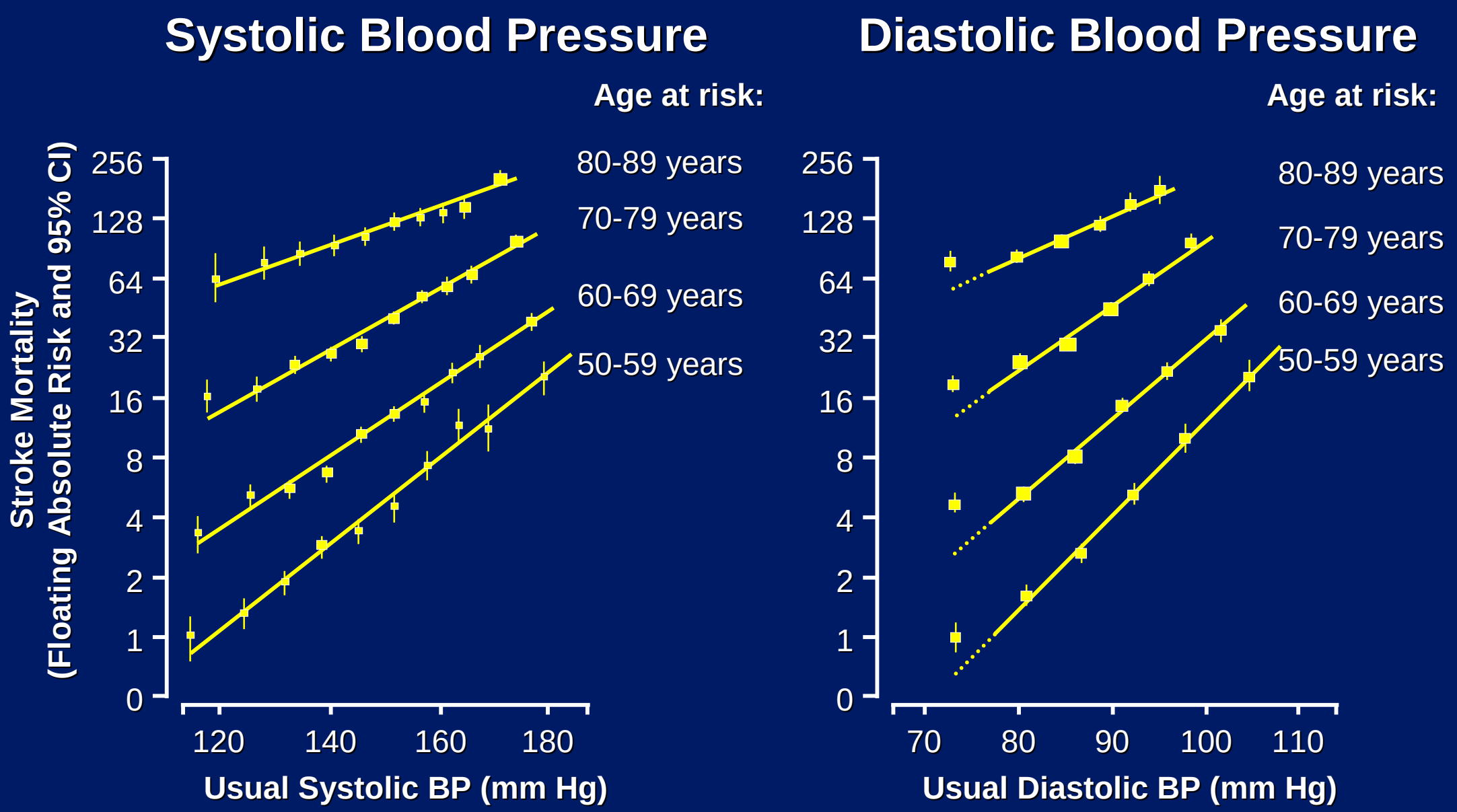
Factors that Increase the Risk of Stroke

Age
Family history of stroke
Male sex
Prior TIA / Stroke

Hypertension (HT) → Rate doubled for 7.5 mmHg DBP ↑
In more than 50% history of HT
Worldwide > 60% of strokes caused by HT

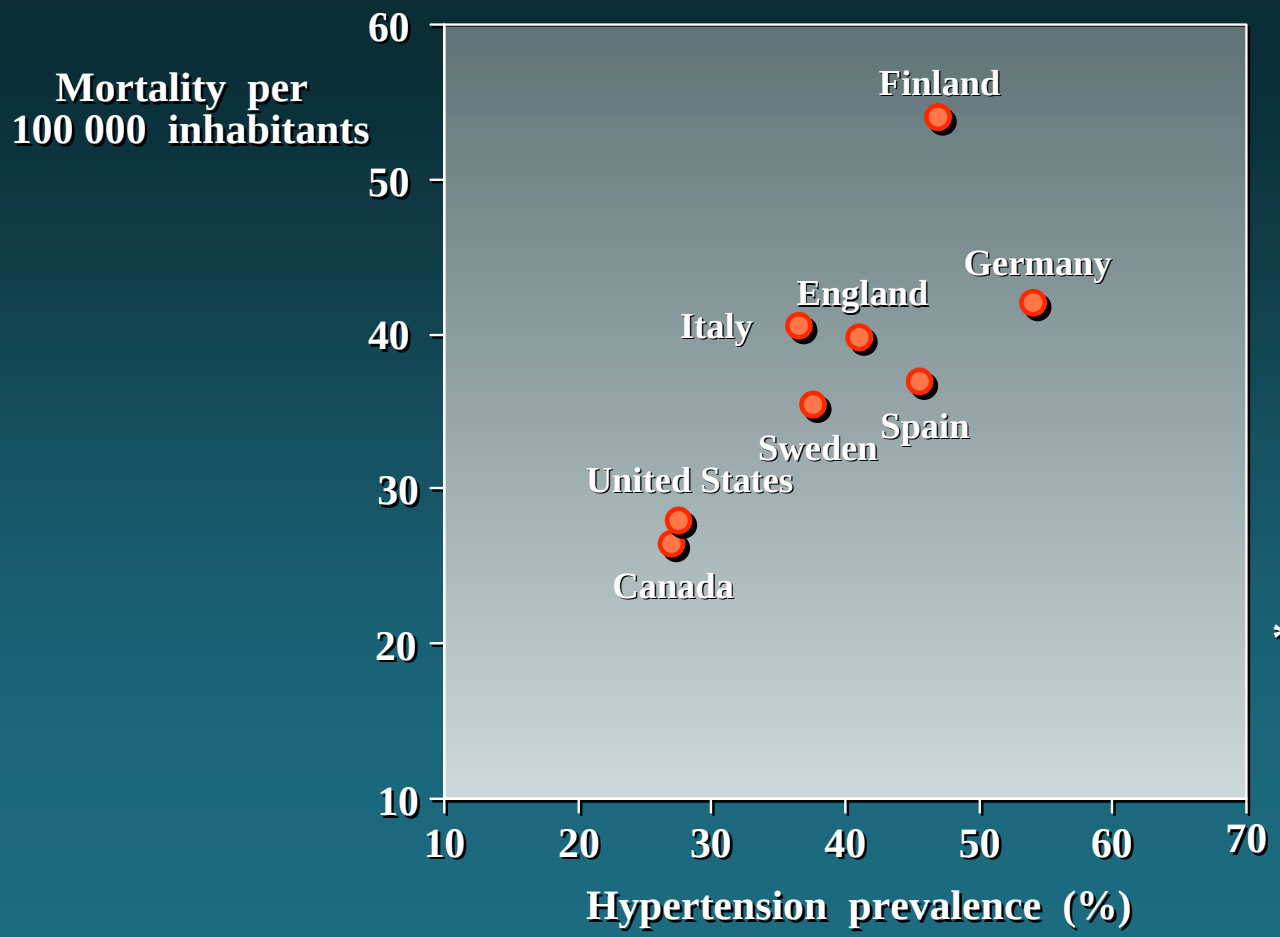
Diabetes
Dyslipidemia
Smoking
Atrial fibrillation
Sedentariety

Stroke Mortality and Usual BP by Age



Prospective Studies Collaboration. *Lancet*. 2002;360:1903-1913.

Hypertension Prevalences vs Stroke Mortality in 6 European and 2 North American Countries*



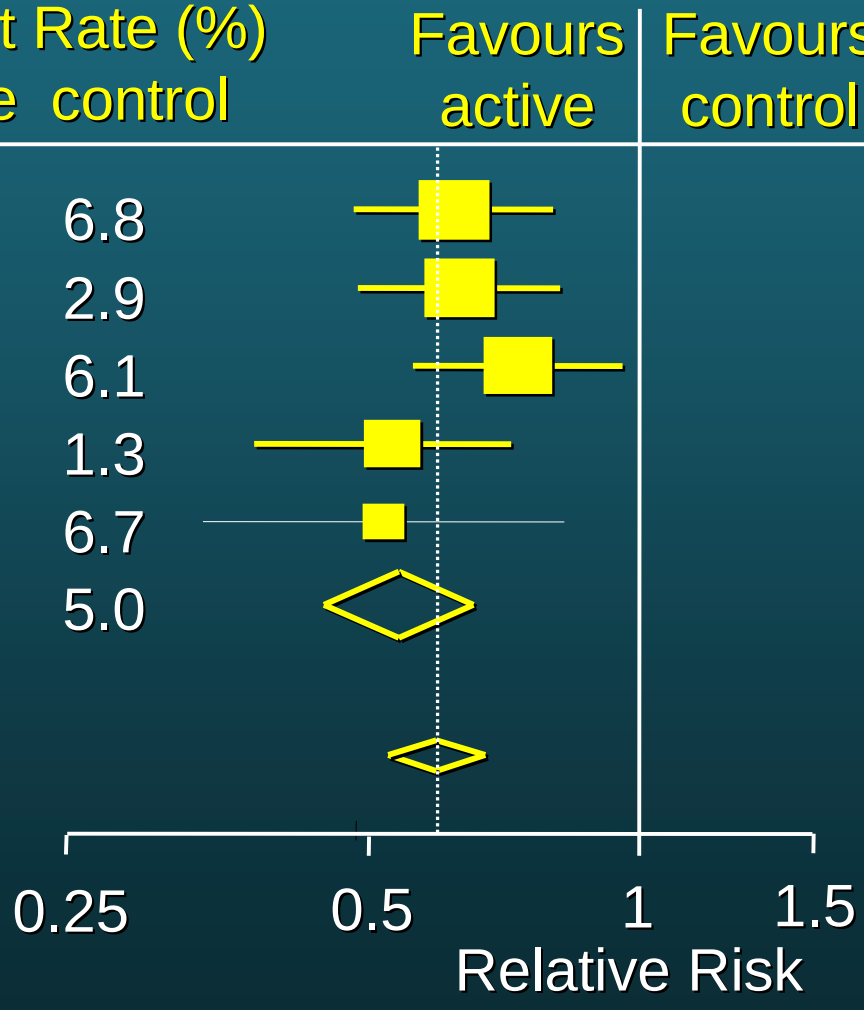
* Men and women combined (35-64 years), age adjusted

Wolf-Maier et al., JAMA 2003; 289: 2363

Can BP reductions reduce the cerebrovascular risk associated with BP elevations,i.e is the hypertension-related risk reversible ?

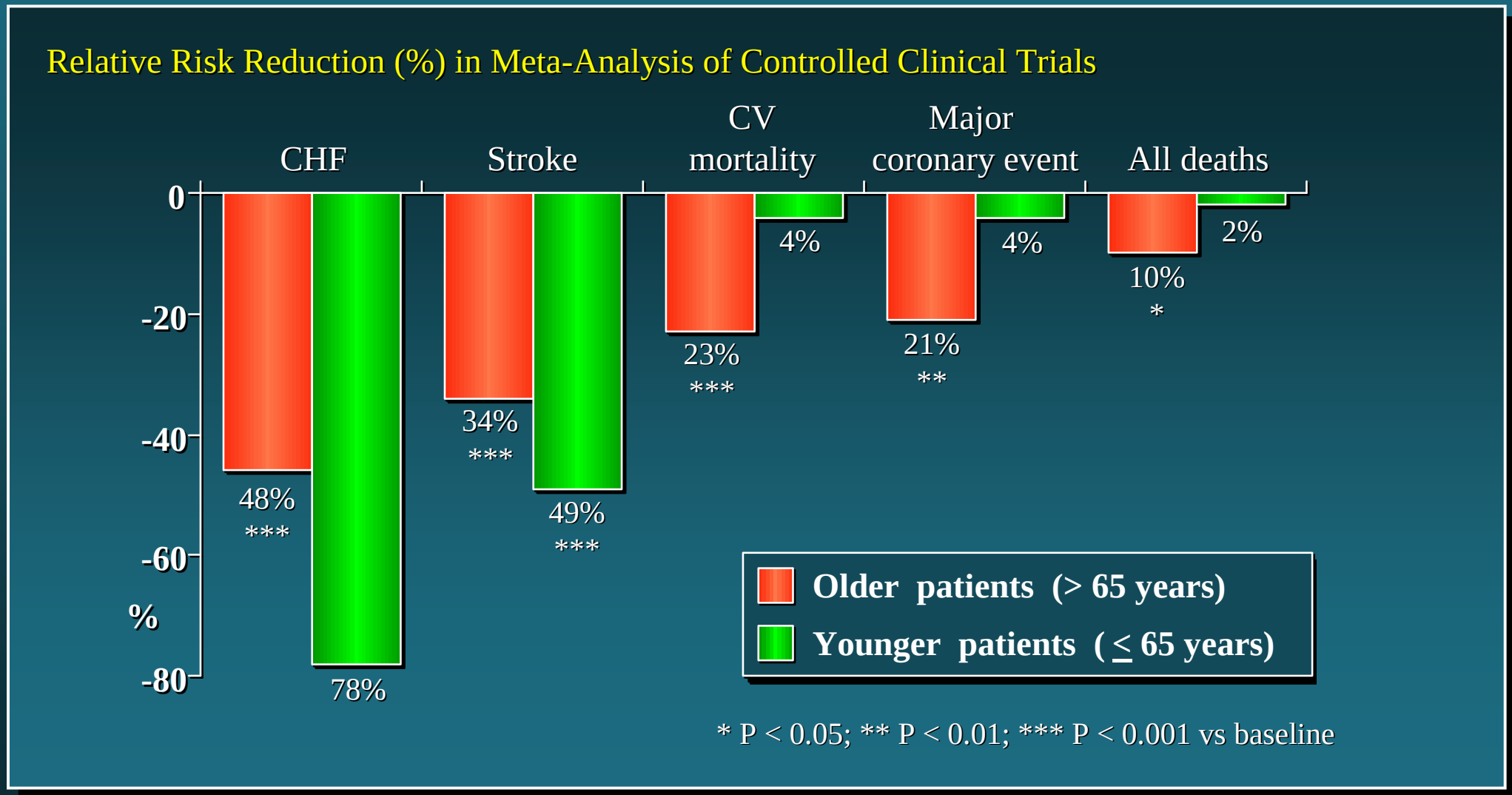
BP reduction and *primary* stroke:1995
10-12 mmHg systolic, 5-6 mmHg diastolic

Study	N	Event Rate (%) active	control	Relative risk (95% CI)
SHEP	4,736	4.4	6.8	35% (18-49%)
HDFP	10,940	1.9	2.9	35% (16-49%)
MRC older	4,396	4.6	6.1	25 % (3-41%)
MRC younger	17,354	0.7	1.3	44% (26-60%)
STOP-H	1,627	3.7	6.7	45% (16-65%)
12 smaller trials	8,600	3.0	5.0	40% (26-52%)
Overall	**47,653**			**37% (30-43%)**



Collins & MacMahon, Br Med Bull 1994;50:272-98

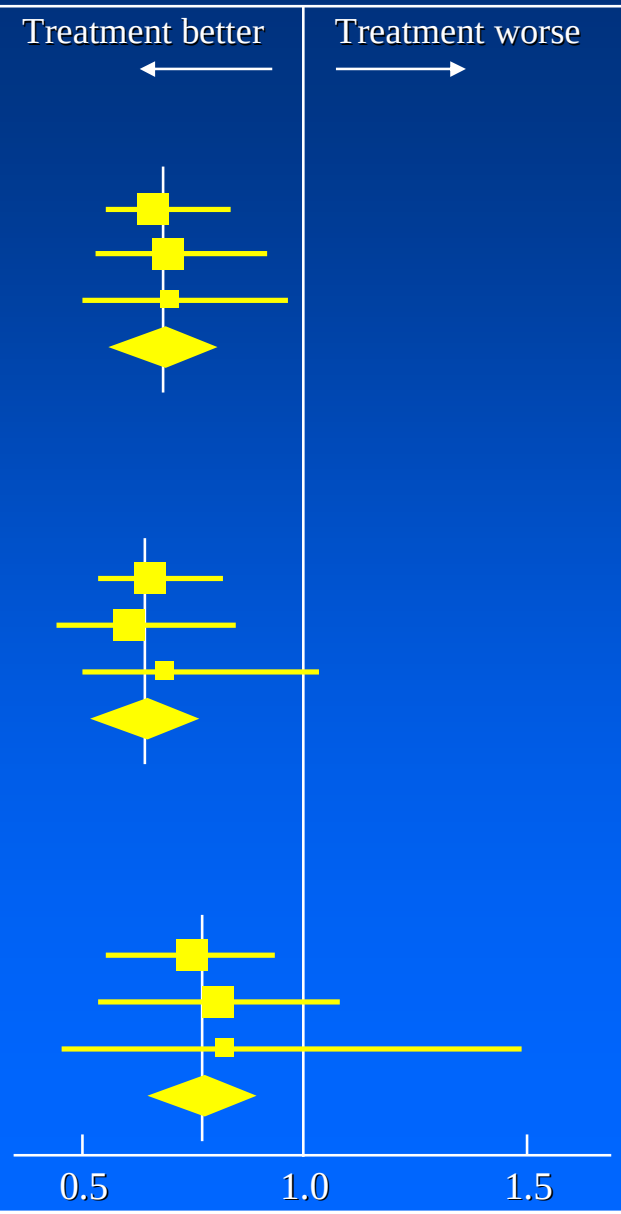
Treating Hypertension Reduces Cardiovascular Morbidity and Mortality



Gueyffier F et al., J Hum Hypertens 1996; 10: 1-8

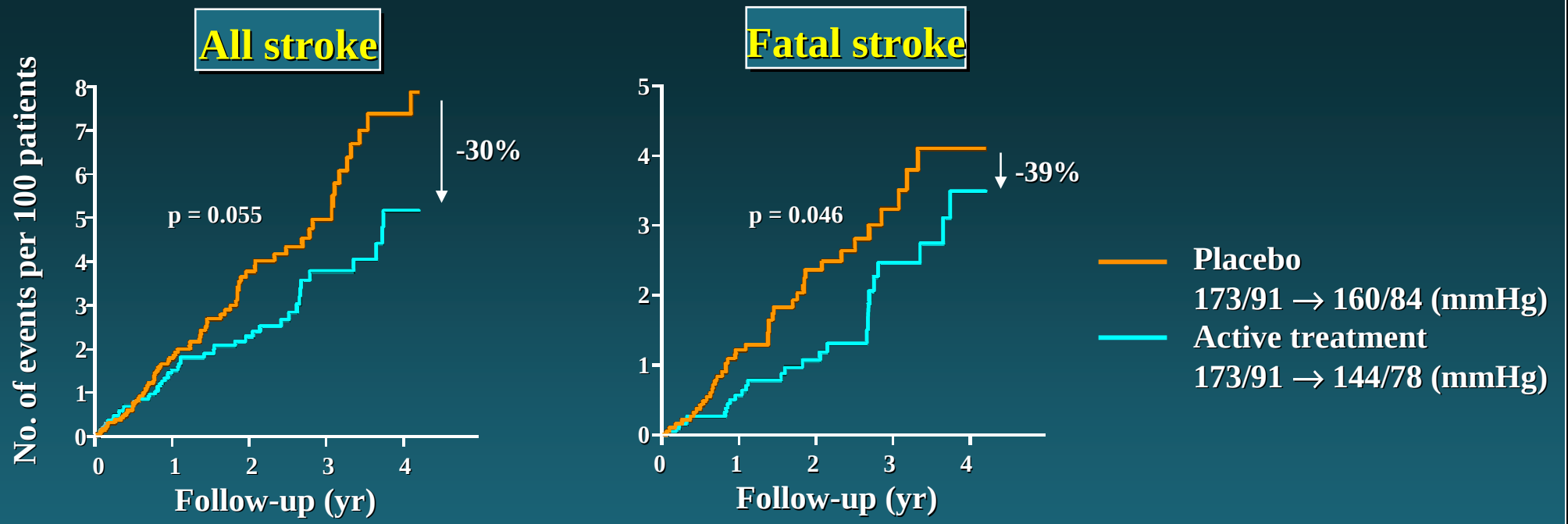
Benefit of antihypertensive drug treatment in older patients with ISH

Trial	Number of end-points Treat : Control	Reduction and SD
All cardiovascular endpoints		
SHEP	199 : 289	
SYST-EUR	137 : 186	
SYST-CHINA	74 : 94	
All	410 : 569	32% SD 5
Heterogeneity: P = 0.94		2P < 0.0001
Fatal and non-fatal stroke		
SHEP	103 : 159	
SYST-EUR	47 : 77	
SYST-CHINA	45 : 59	
All	195 : 295	37% SD 6
Heterogeneity: P = 0.83		2P < 0.0001
Fatal and non-fatal MI (including sudden death)		
SHEP	103 : 141	
SYST-EUR	58 : 72	
SYST-CHINA	20 : 23	
All	182 : 236	25% SD 8
Heterogeneity: P = 0.96		2P = 0.004



Staessen JA Eur Heart J 1999; (Suppl P): 3-8

Incidence of Stroke in HYVET



Goal SBP < 150 mmHg
Treatment: indapamide ± perindopril 2 or 4 mg
PP data: stroke -45%

17501 M

HYVET - Beckett, NEJM 2008; 358: 1

Is antihypertensive drug treatment beneficial also for secondary prevention of stroke?

Prognosis at 1 Year Distance from Ischemic Stroke

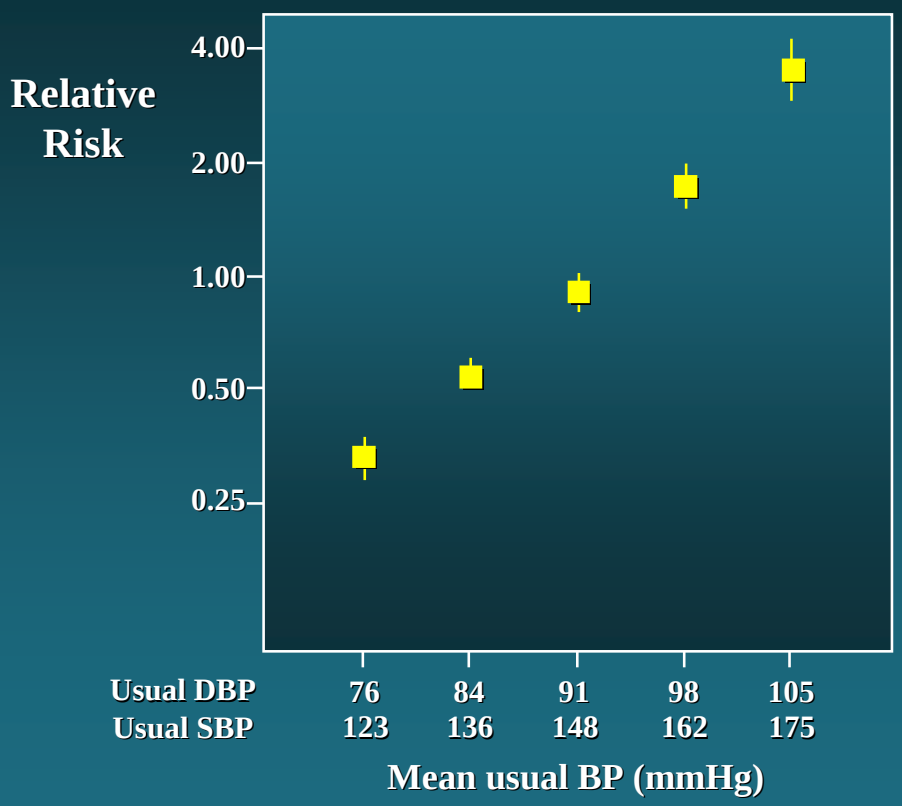
- Death 25%
- Disability 45%
- Recovery 30%

In stroke survivors depression is common

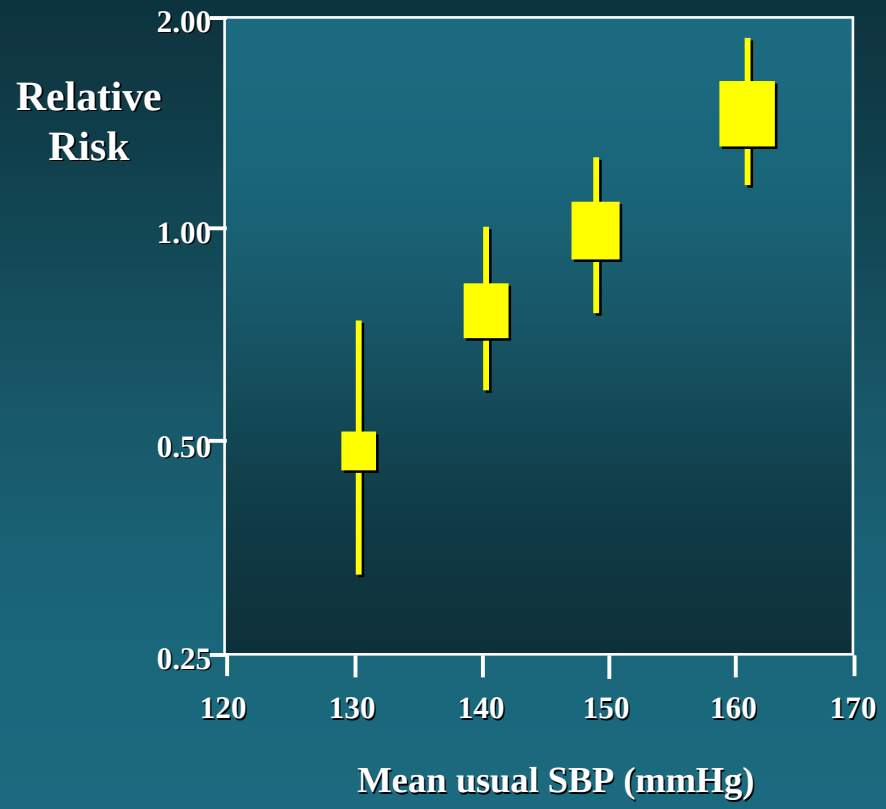
(27% mild / 24% severe / 51% total)

Relationship between BP and Stroke

BP and 1st stroke



BP and stroke recurrency

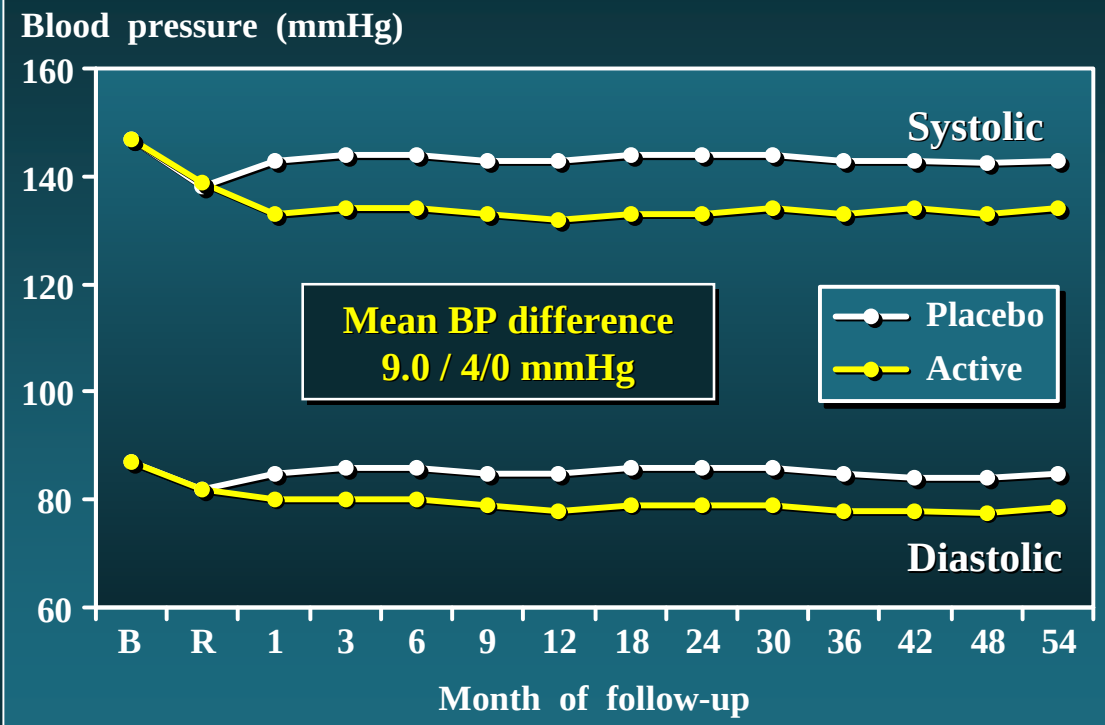


16995 M

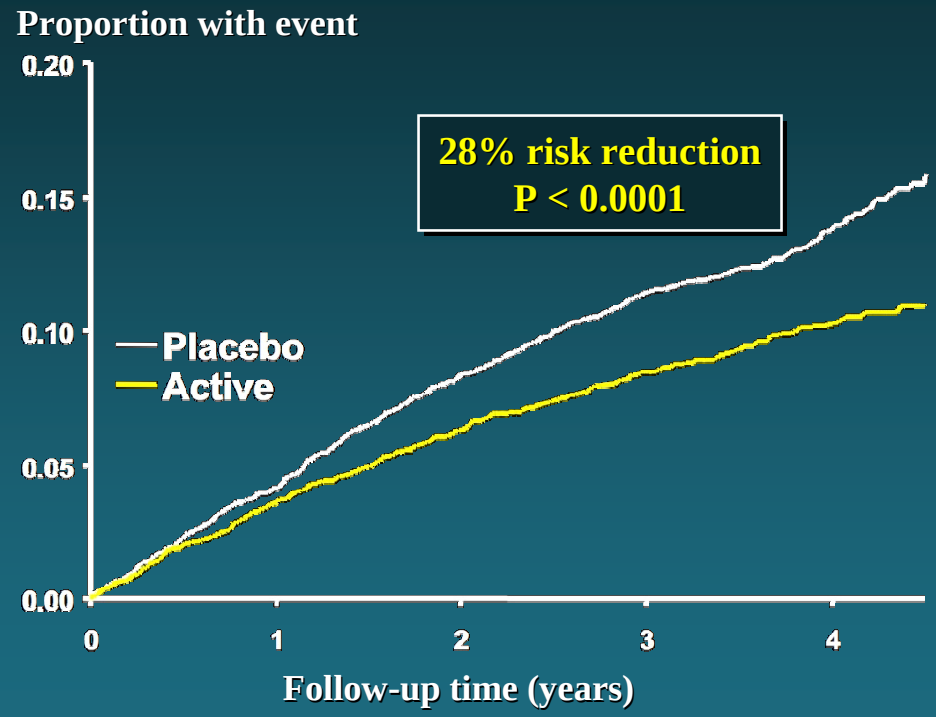
McMahon et al., Lancet 1990; 335: 765, Rodgers et al., BMJ 1996; 313: 147

BP during FU and Stroke Incidence in PROGRESS

BP during FU



Stroke incidence



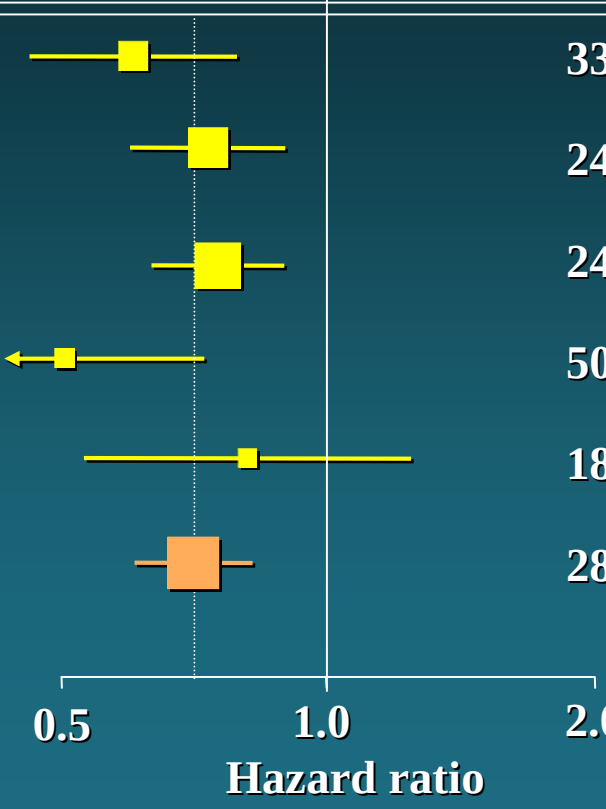
17492 M

PROGRESS Collaborative Group. Lancet 2001; 358: 1033-

Does the protective effect of BP reductions extend to all types of cerebrovascular lesions?

Stroke Severity and Subtype: Effects of Active Treatment PROGRESS

	Strokes active	Strokes placebo	Favours active	Favours placebo	Risk Reduction (95%CI)
Fatal/disabling	123	181			33% (15 to 46%)
Other stroke	201	262			24% (9 to 37%)
Cerebral infarction	246	319			24% (10 to 35%)
Cerebral haemorrhage	37	74			50% (26 to 67%)
Stroke type unknown	42	51			18% (-24 to 45%)
Total	307	420			28% (17 to 38%)

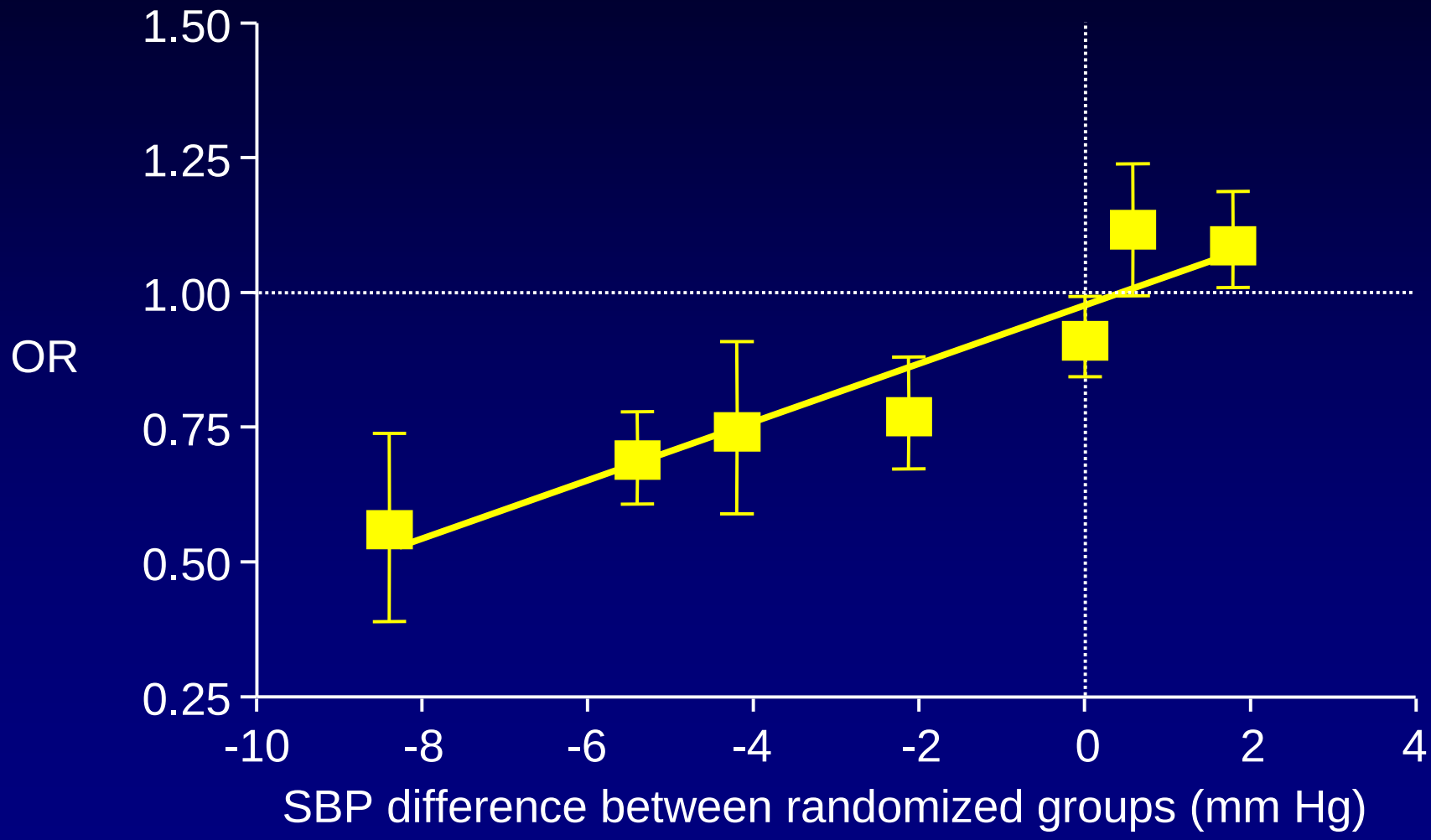


Chalmers J, Am J Cardiol 2003; 91: 3G-8G

Stroke and Chronic Antihypertensive Drug Treatment

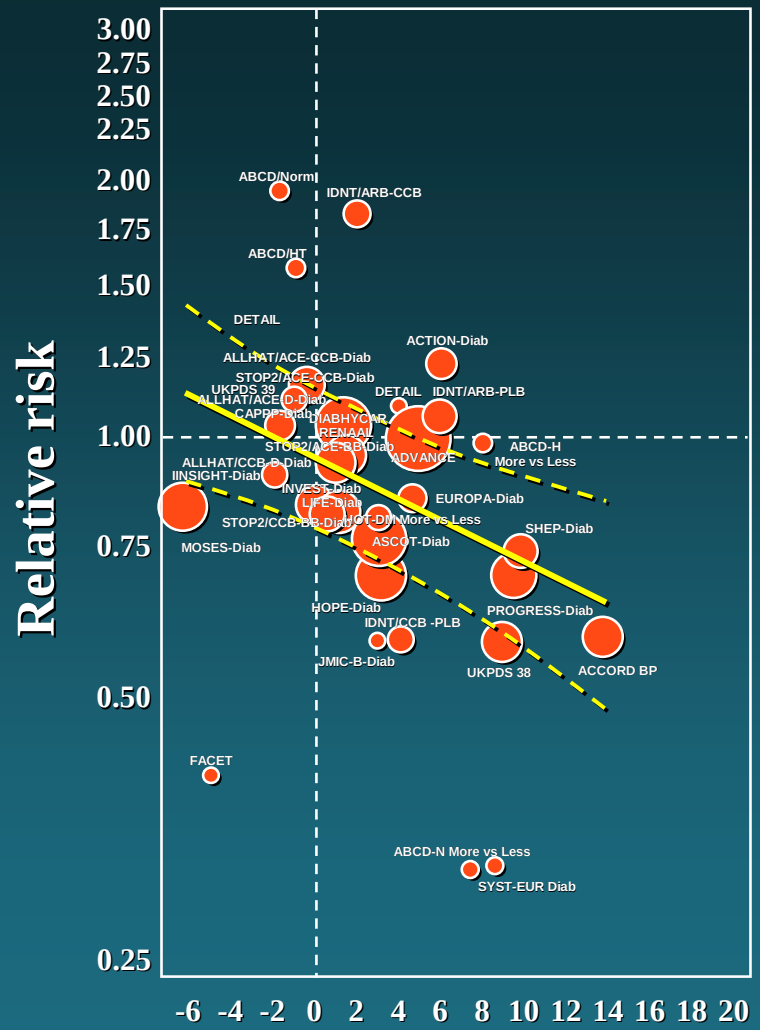
- Stroke reduction with treatment shown by RCTs in virtually all demografic/clinical conditions
- 35-40% less risk by 10-12 mmHg SBP fall
- Beneficial effects with all major drug classes
- cerebrovascular protection largely due to BP lowering "*per se*"

Blood Pressure Lowering Treatment Trialists' Collaboration: Stroke



CCB-PLA, ACEI-PLA, MORE-LESS, ARB-OTHER, CCB-OLD, ACEI-CCB, ACEI-OLD.
Turnbull F et al. *Lancet*. 2003;362:1527-1535.

Metaregression of Treatment-induced SBP Changes with Stroke in Diabetes

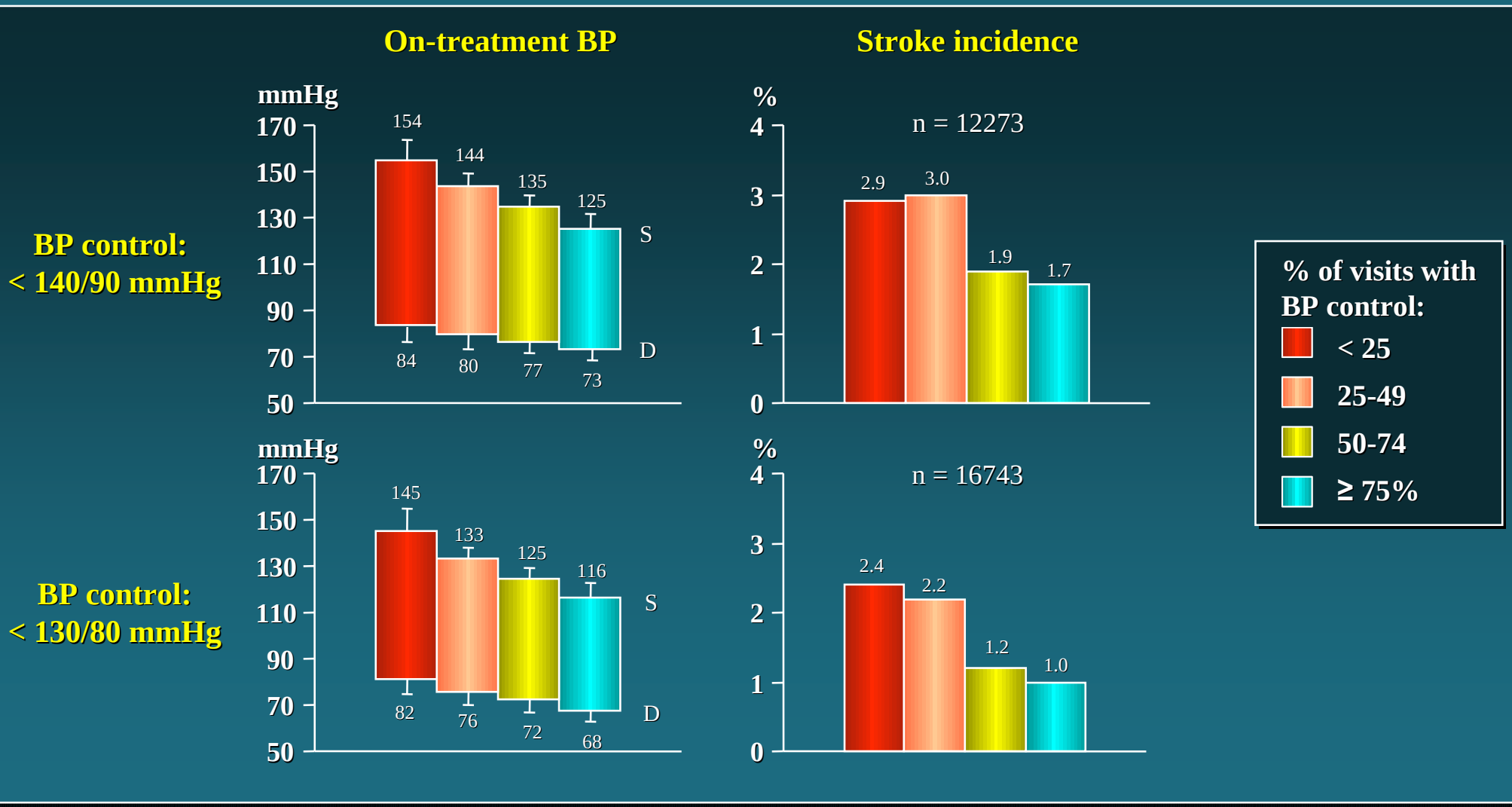


SBP difference between randomized groups (mmHg)

17493 M

Reboldi, Gentile, Angeli, Ambrosio, Mancia, Verdecchia, J Hypertens 2011; 29:

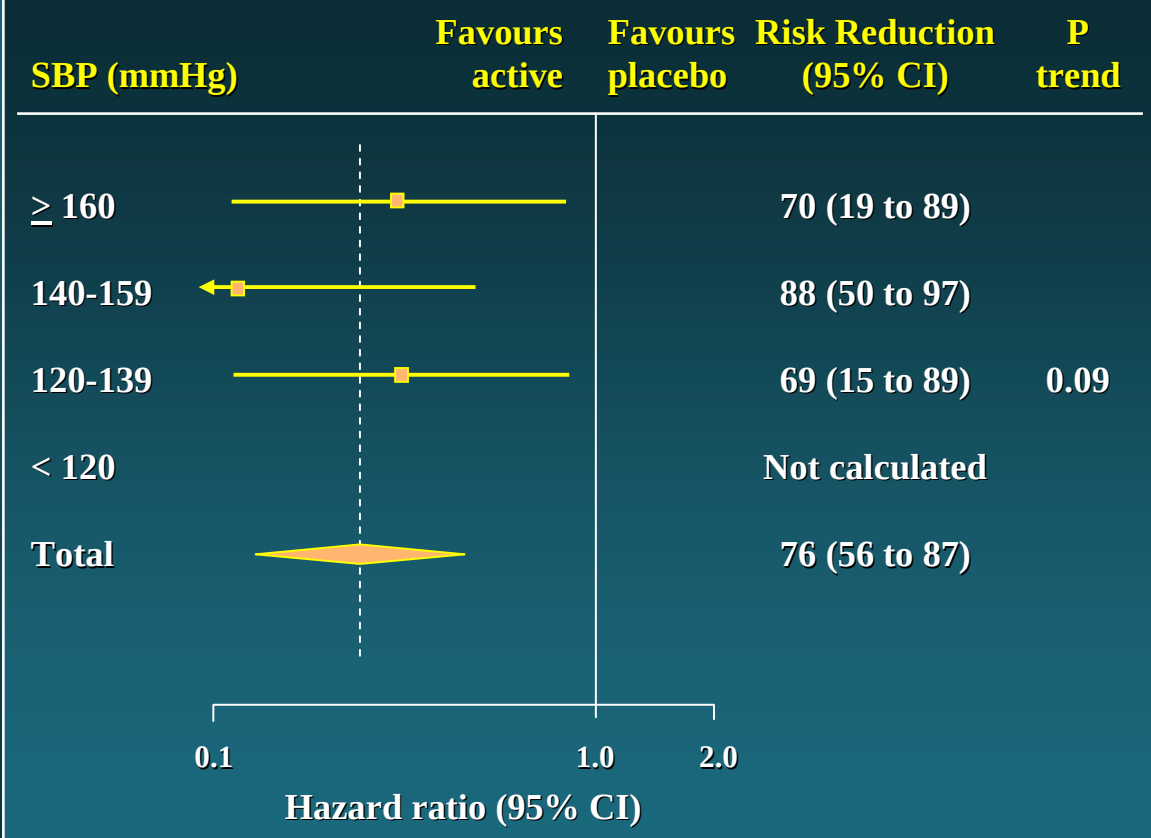
Relationship between Frequency of BP Control, Average On-treatment BP and Stroke Incidence in ONTARGET

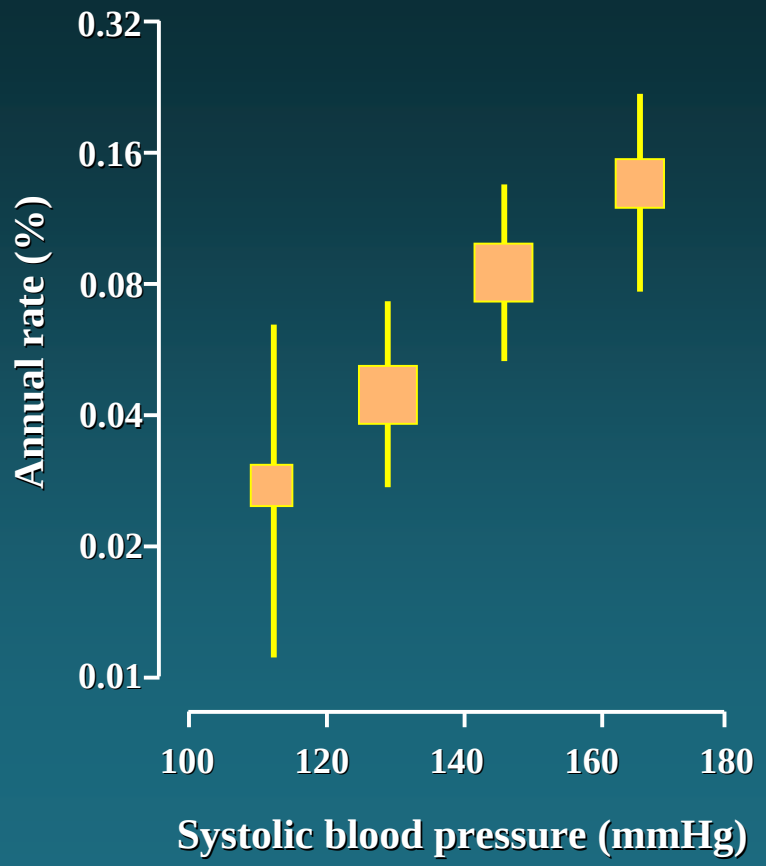


16223 M

Mancia et al., Circulation 2011; 124: 1727

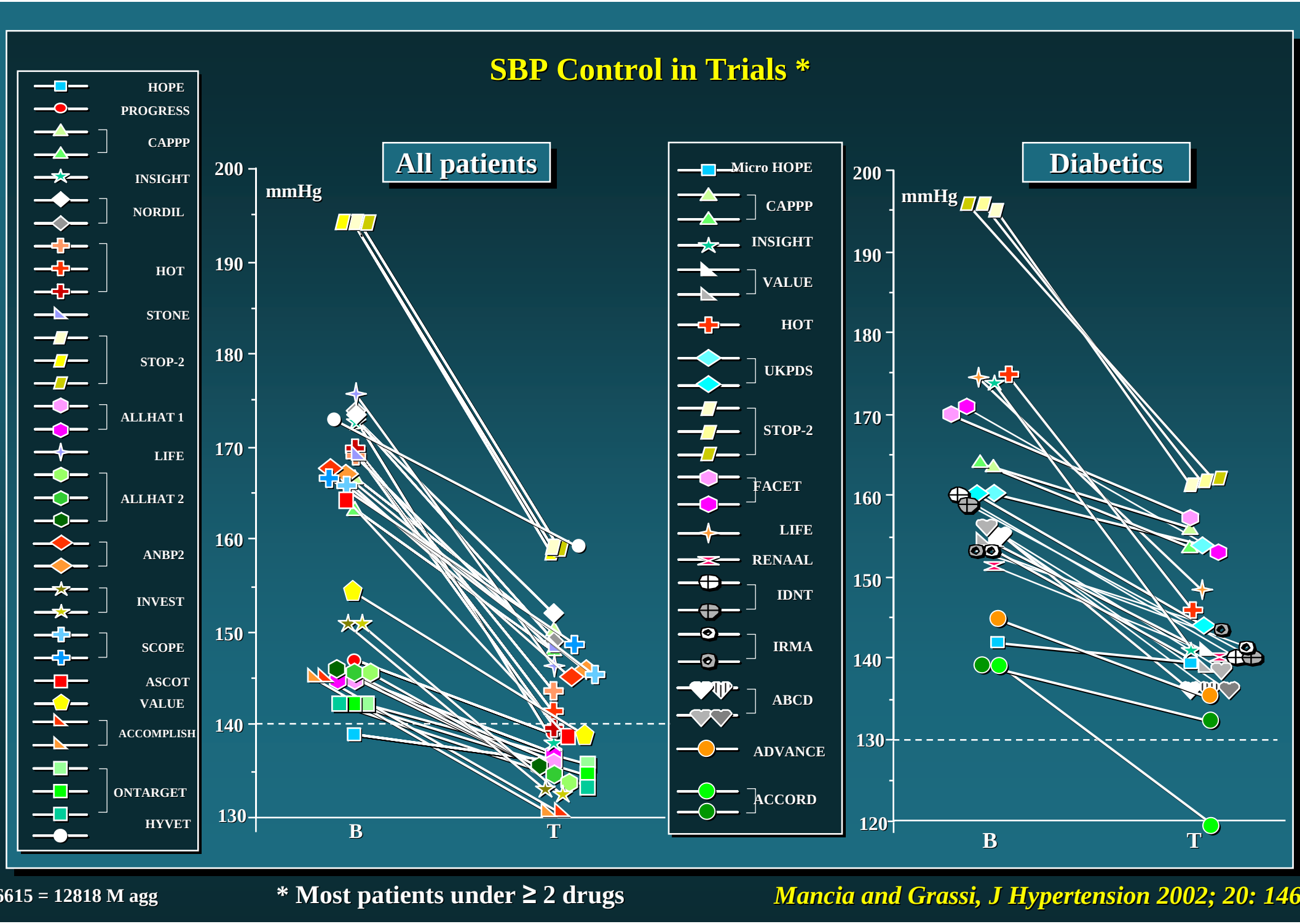
Reduction of Haemorrhagic Stroke by BP Reduction in PROGRESS





17820 M

Arima et al., J Hypertens 2006; 24: 1201

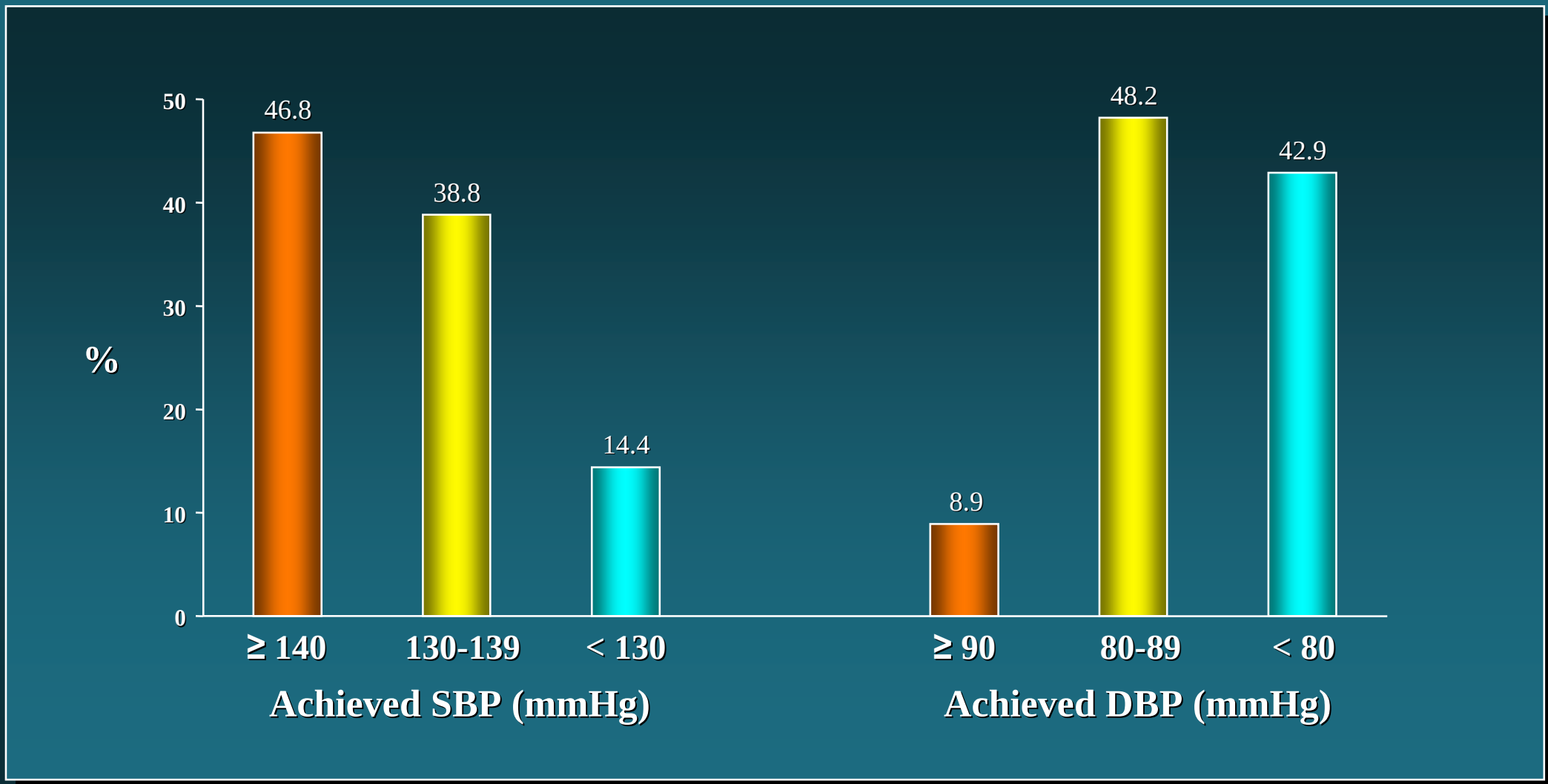


16615 = 12818 M agg

* Most patients under ≥ 2 drugs

Mancia and Grassi, J Hypertension 2002; 20: 1461

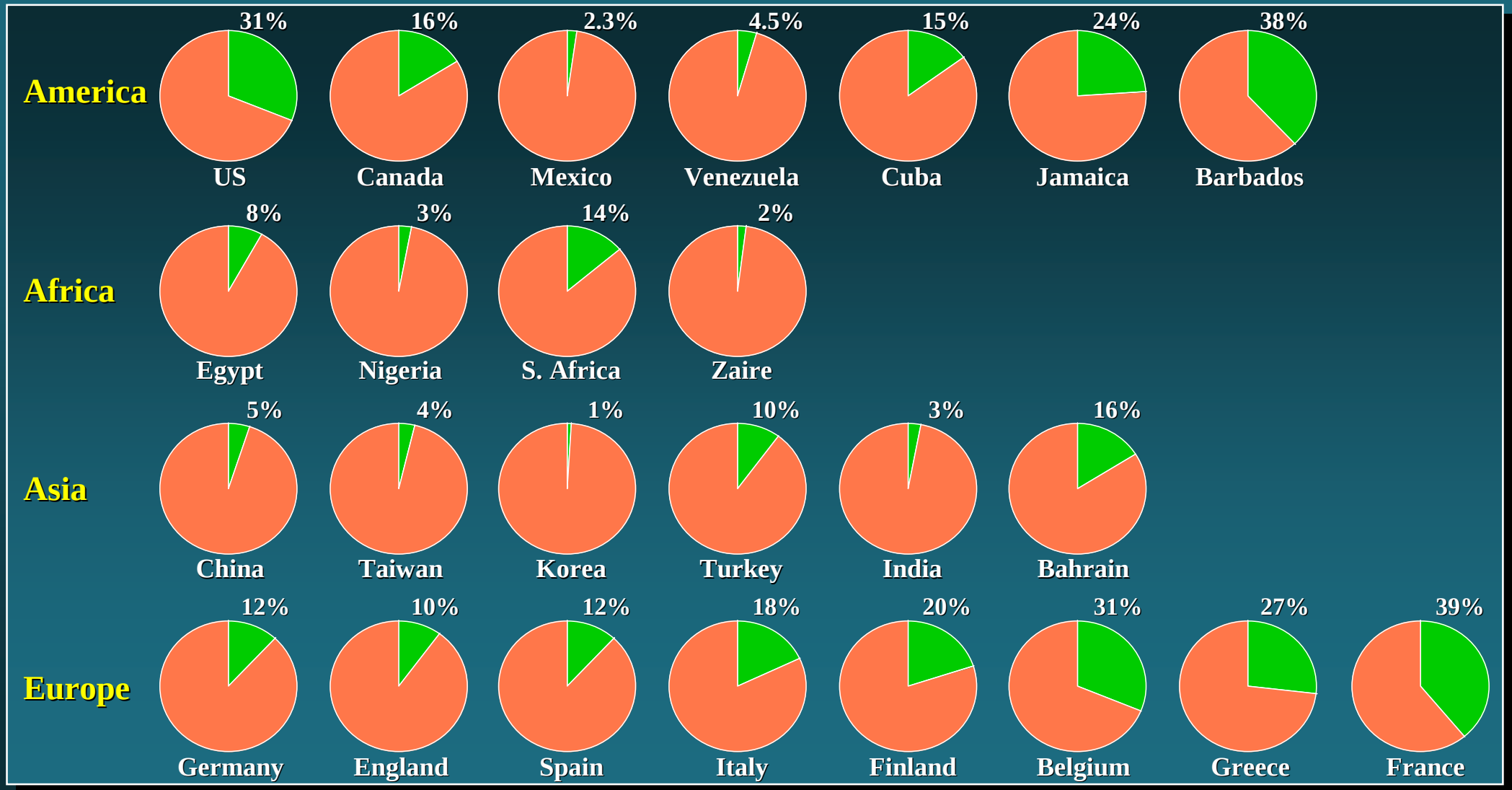
Mean Achieved BP in the High Risk Hypertensives of VALUE (n = 15245)



18741 M

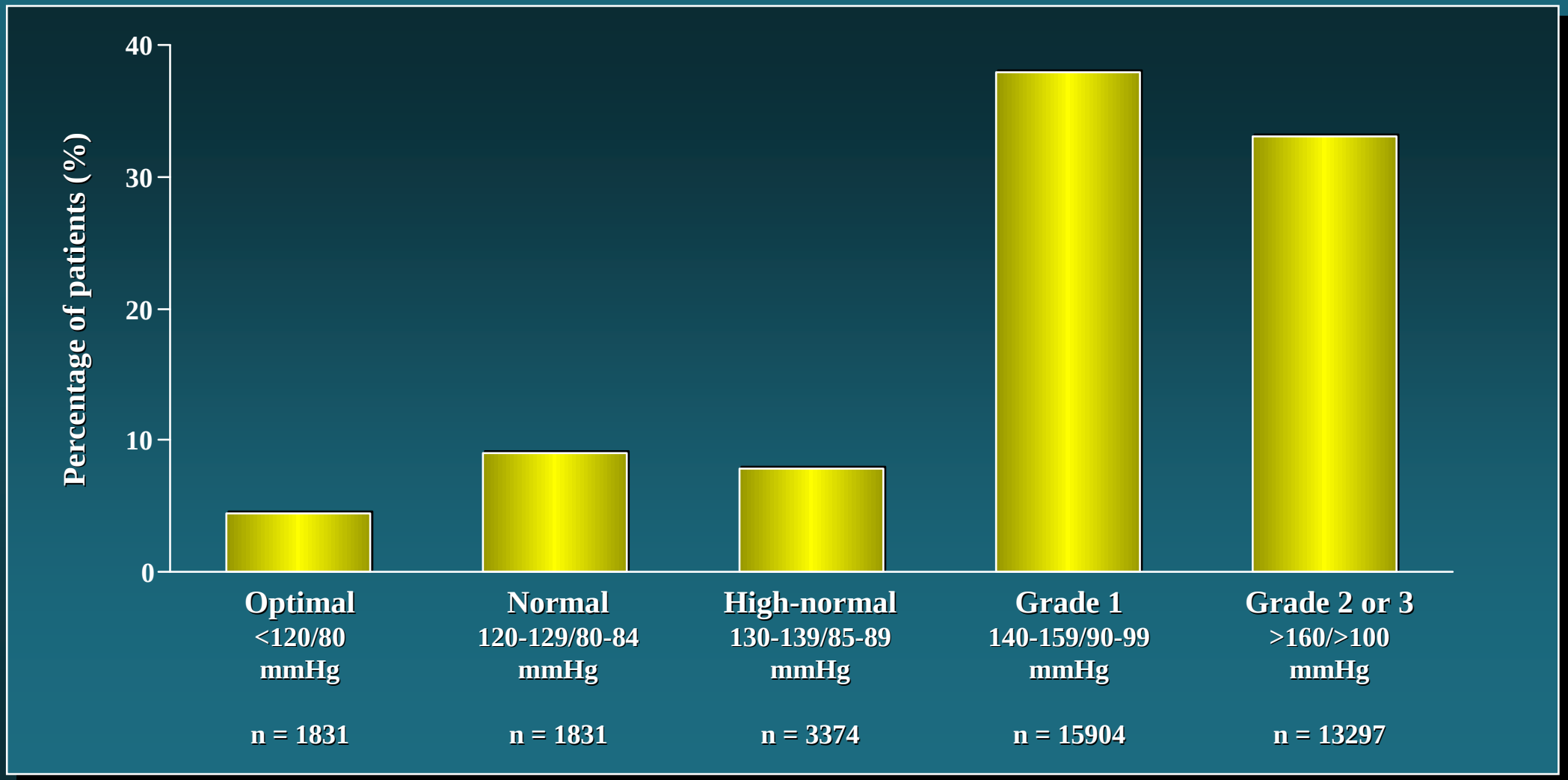
Mancia et al., in preparation

BP Control (< 140/90 mmHg) in Hypertensives from Different Countries



13481 M

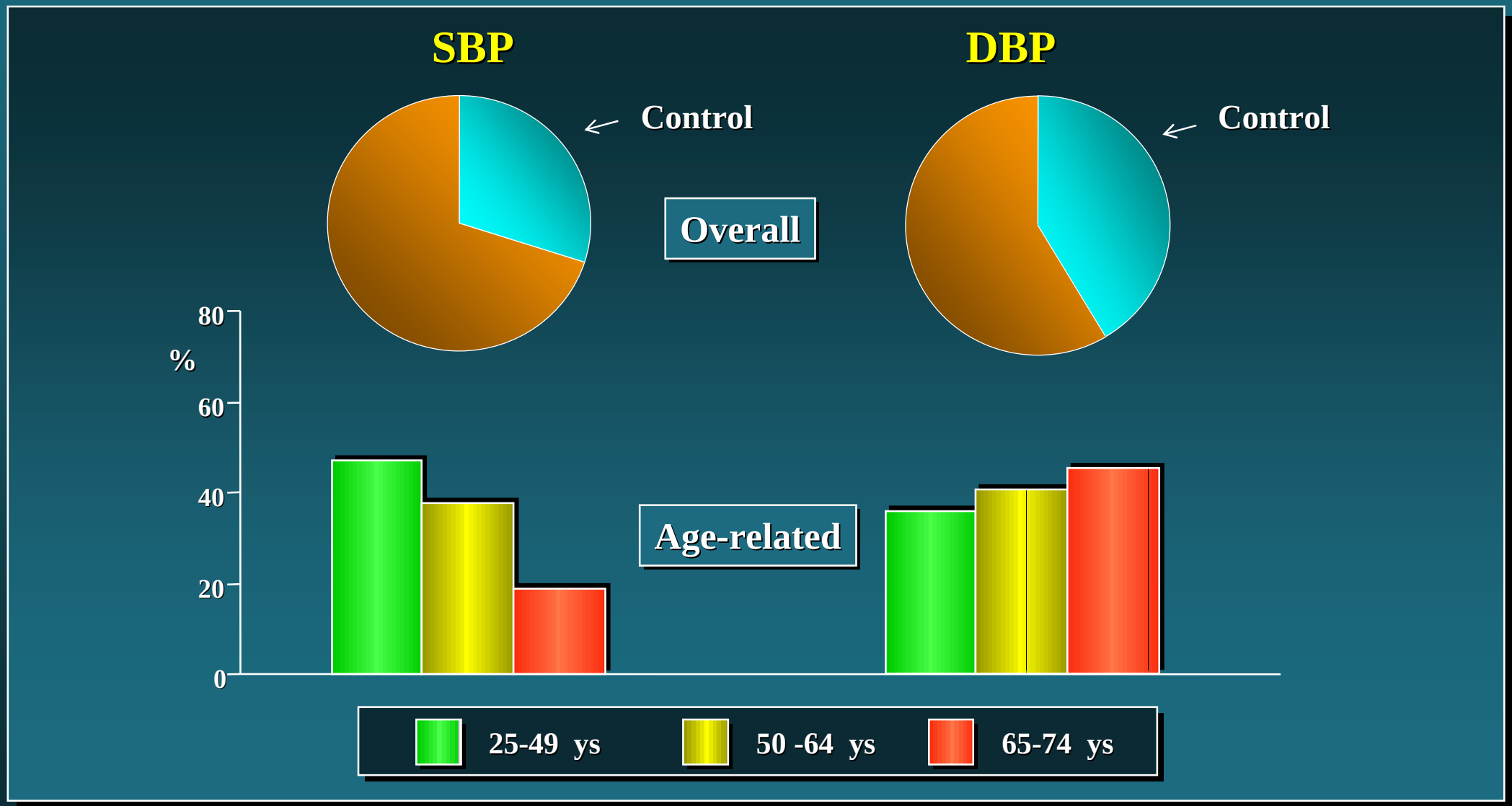
BP Stratification according to the ESH/ESC Guidelines



15884 M

Volpe M., Tocci G., Trimarco B., Agabiti Rosei, E., Borghi C., Ambrosioni E., Menotti A., Zanchetti A., Mancia G., J Hypertens 2007; 25: 1491

Office BP Control in PAMELA Population

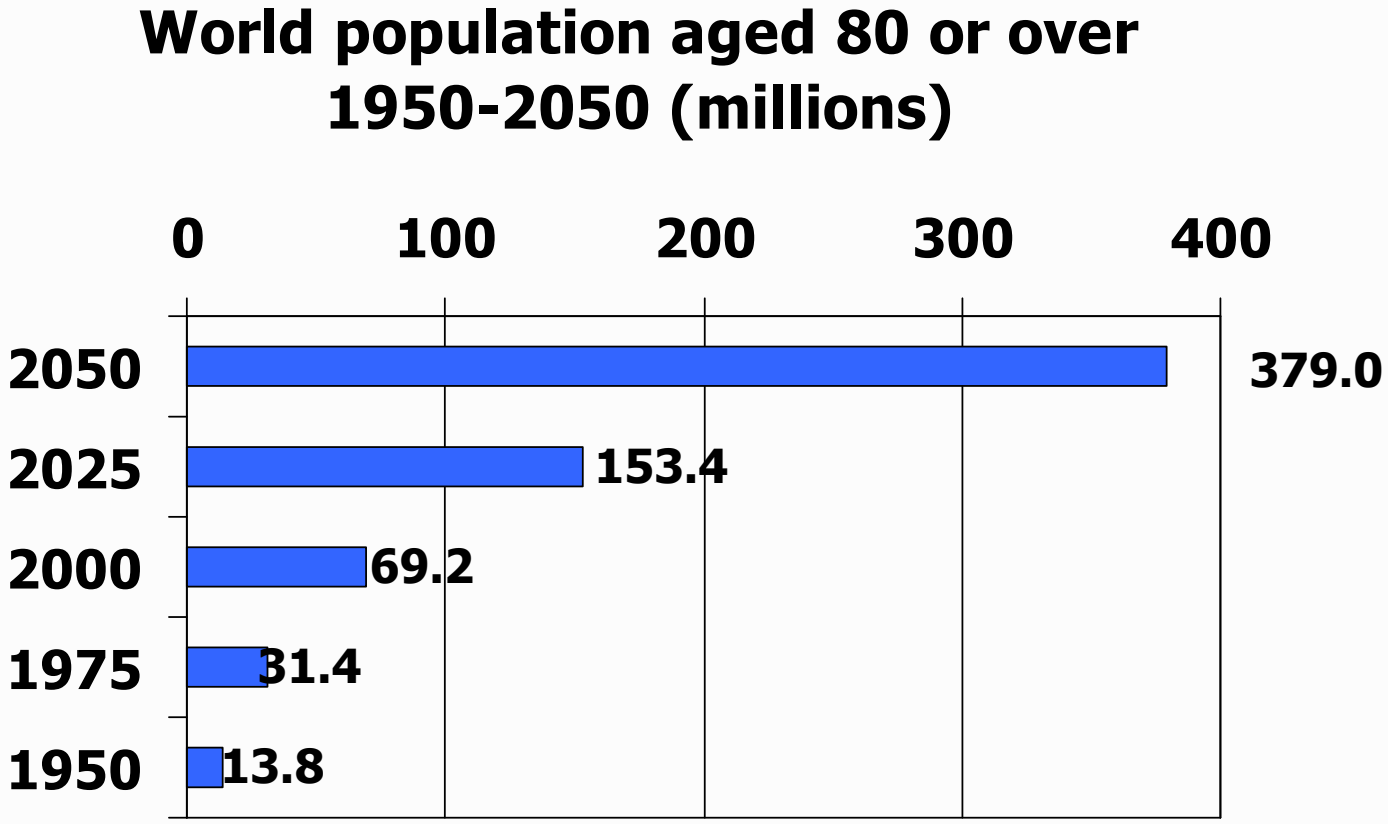


18779 = 16512 M mod

Mancia et al., Arch Intern Med 2002; 162: 582-586

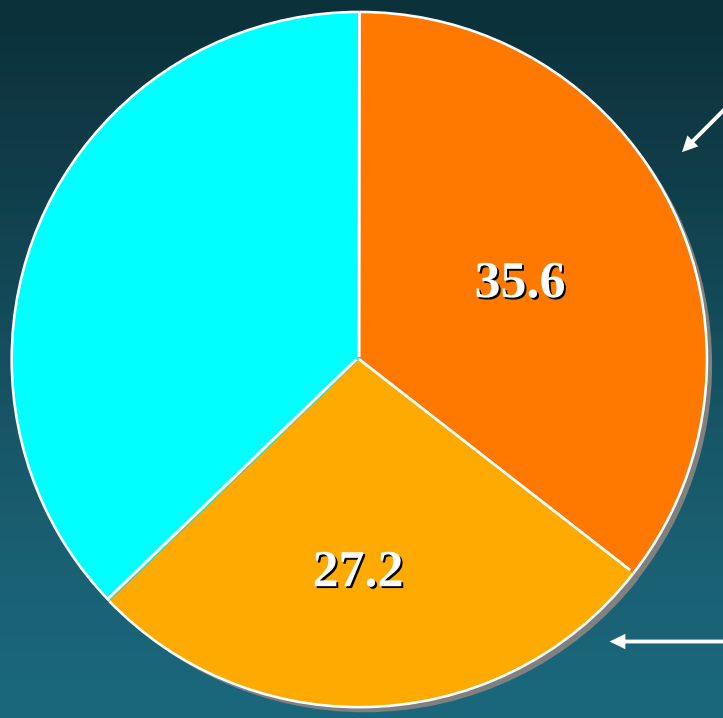
HYVET
HYPERTENSION IN THE VERY ELDERLY TRIAL

Global increase in population aged 80 and over



World Population Ageing 1950-2050, Population Div., DESA, United Nations

Discontinuation of Antihypertensive Treatment in Lombardy (793.000 subjects with initial antihypertensive drug prescription)



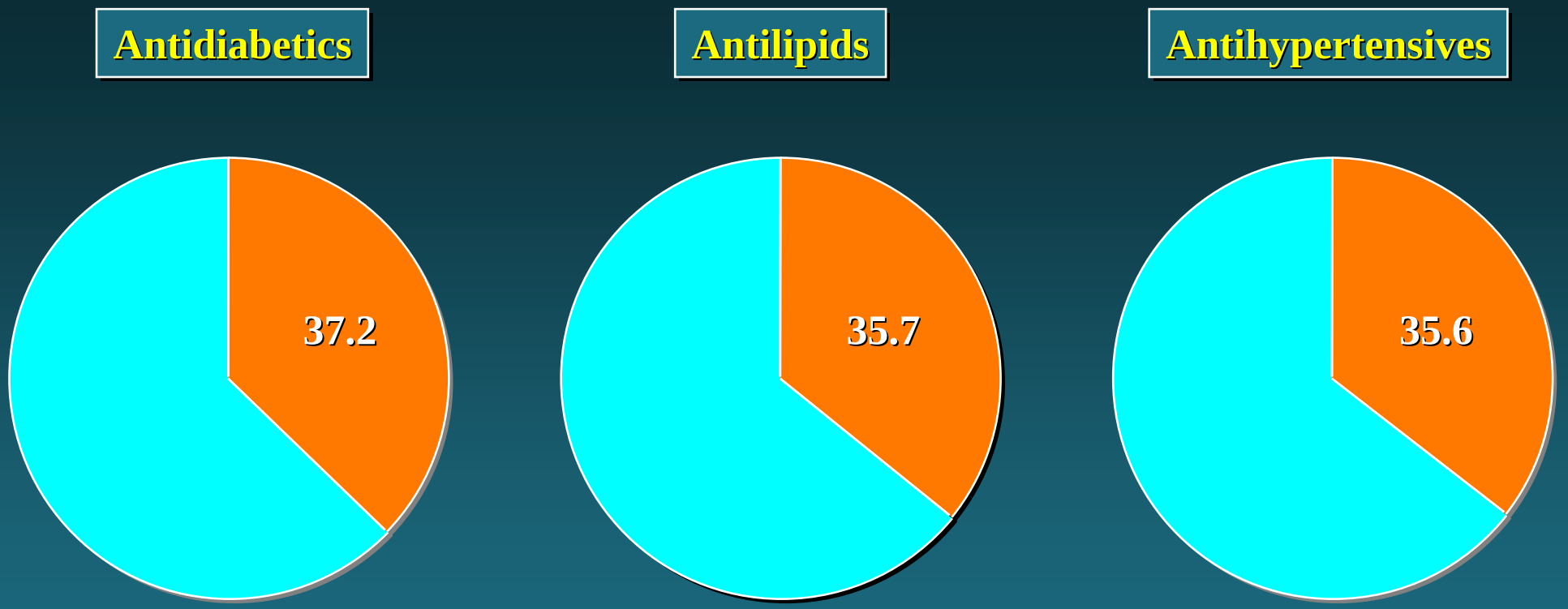
Discontinue after 1st prescription

Discontinuers 62.8%

Discontinue after 2 or more prescriptions

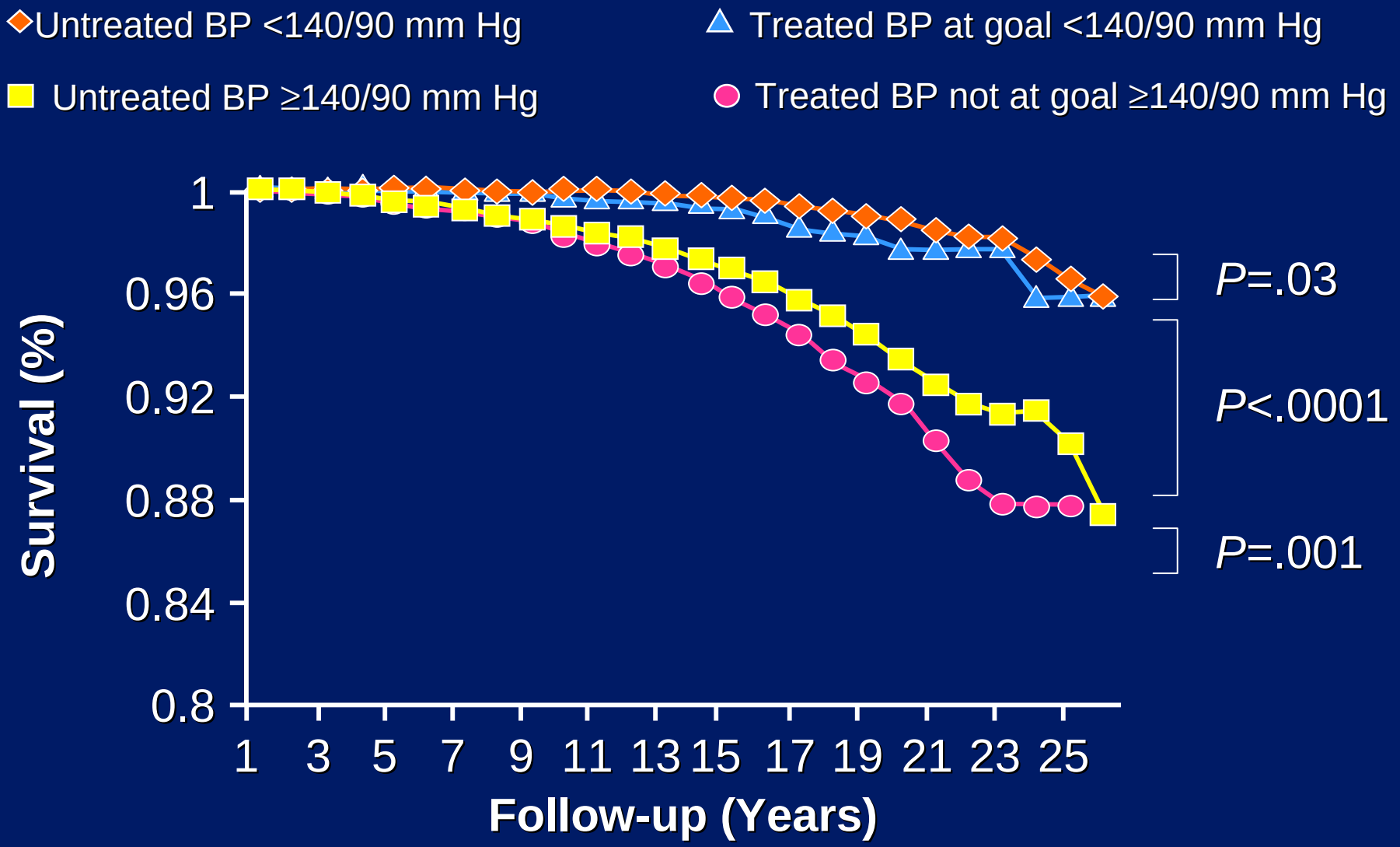
Corrao et al., Am J Hypertens 2012; 25: 549 - J Hypertens 2008; 26: 819

Proportion of Patients Discontinuing "CV Prevention" Drug Treatment after Initial Prescription in Lombardy



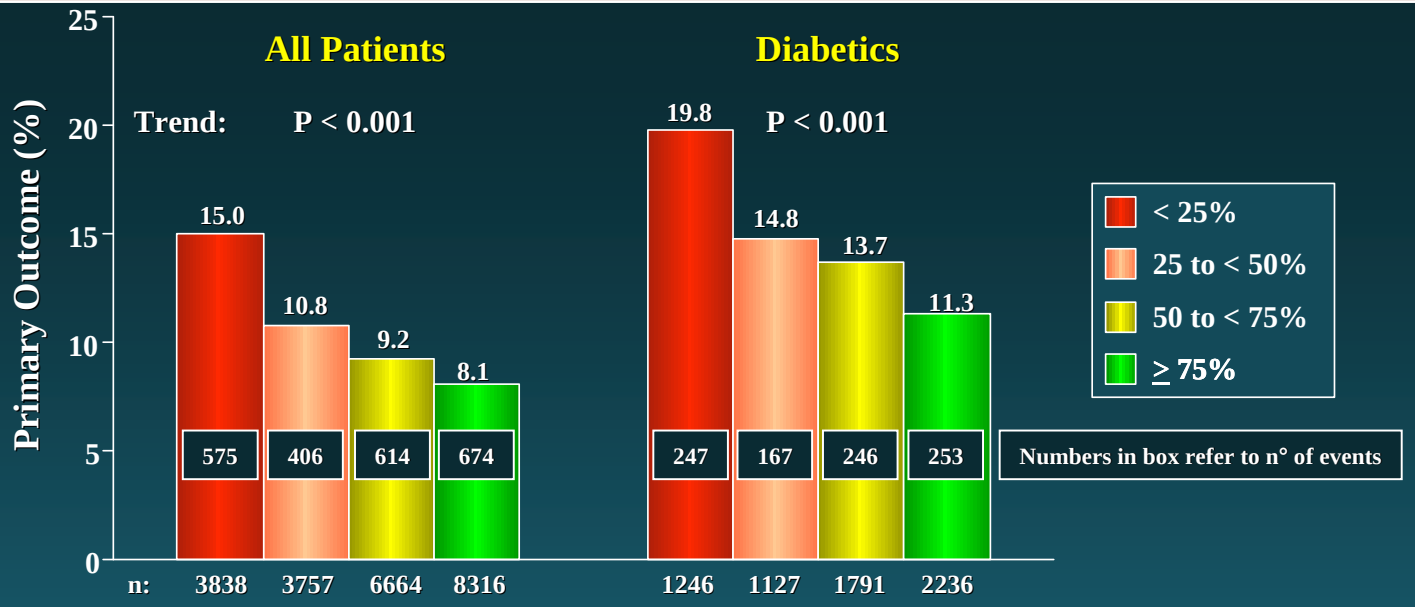
Corrao et al., Am J Hypertens 2012; 25: 549

CVD Survival in Treated Hypertensives at Goal and Not at Goal



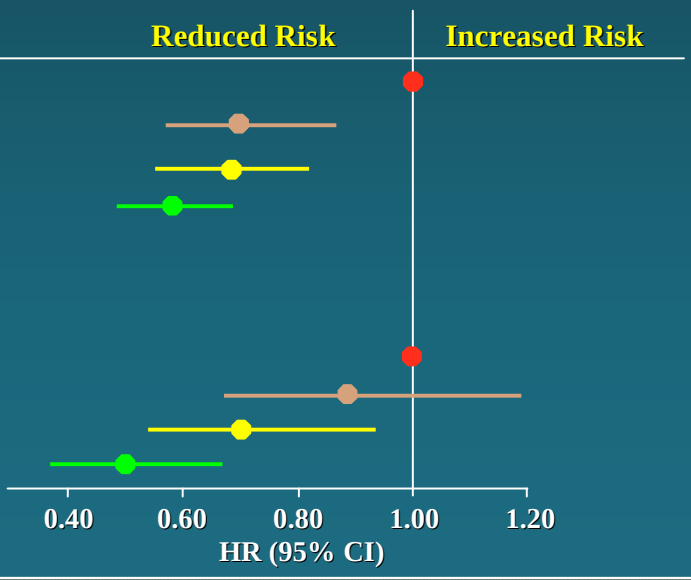
Benetos et al. *J Hypertens*. 2003;21:1635-1640.

Incidence and Adjusted* CV Risk according to Consistency of BP Control in INVEST



% of visits with BP < 140/90 mmHg	HR (95% CI), MI
< 25%	1.00
25 to < 50%	0.70 (0.57-0.86)
50 to < 75%	0.68 (0.56-0.81)
≥ 75%	0.58 (0.48-0.69)

% of visits with BP < 140/90 mmHg	HR (95% CI), Stroke
< 25%	1.00
25 to < 50%	0.89 (0.67-1.19)
50 to < 75%	0.70 (0.52-0.92)
≥ 75%	0.50 (0.37-0.68)

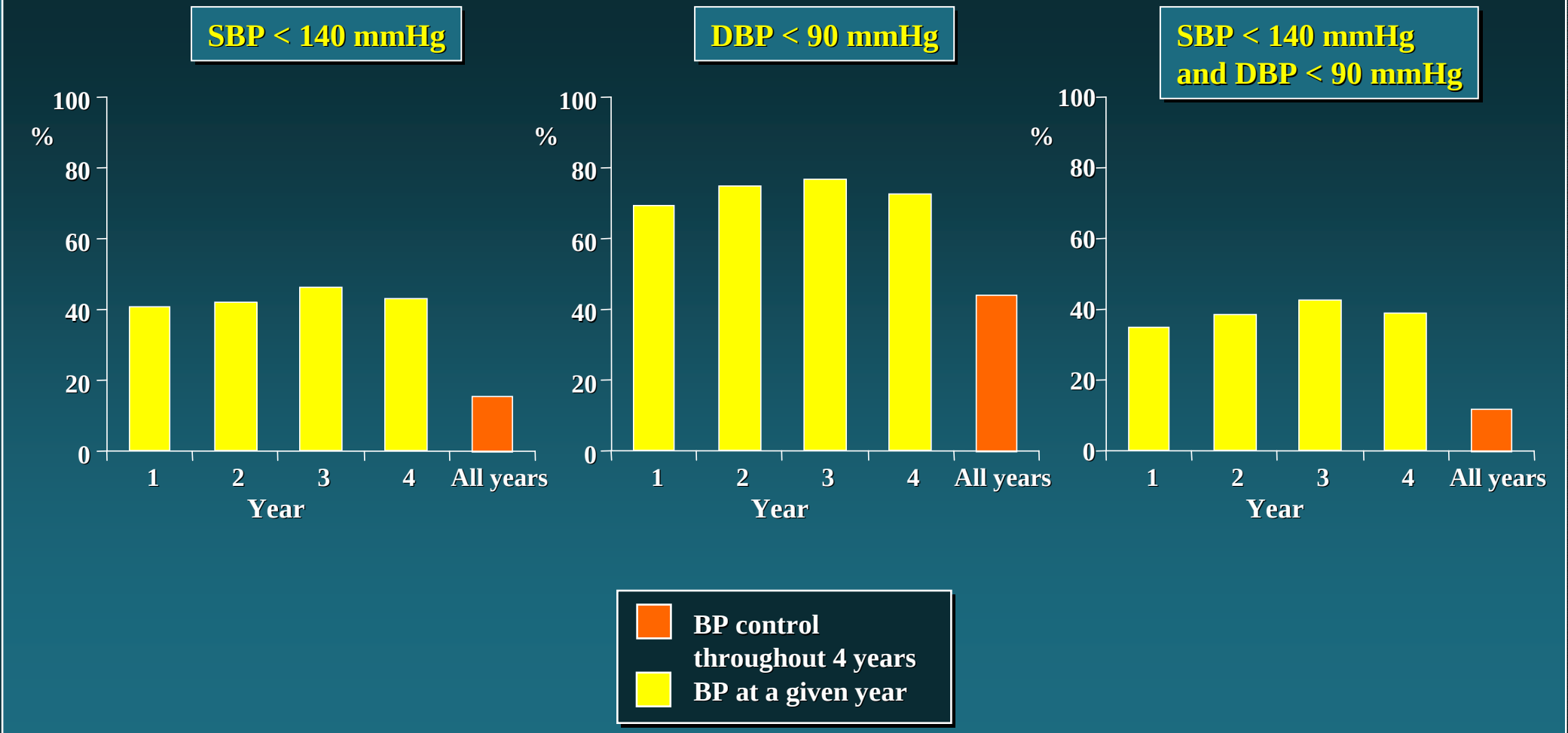


15962 M

* Adjustment includes in-treatment BP mean

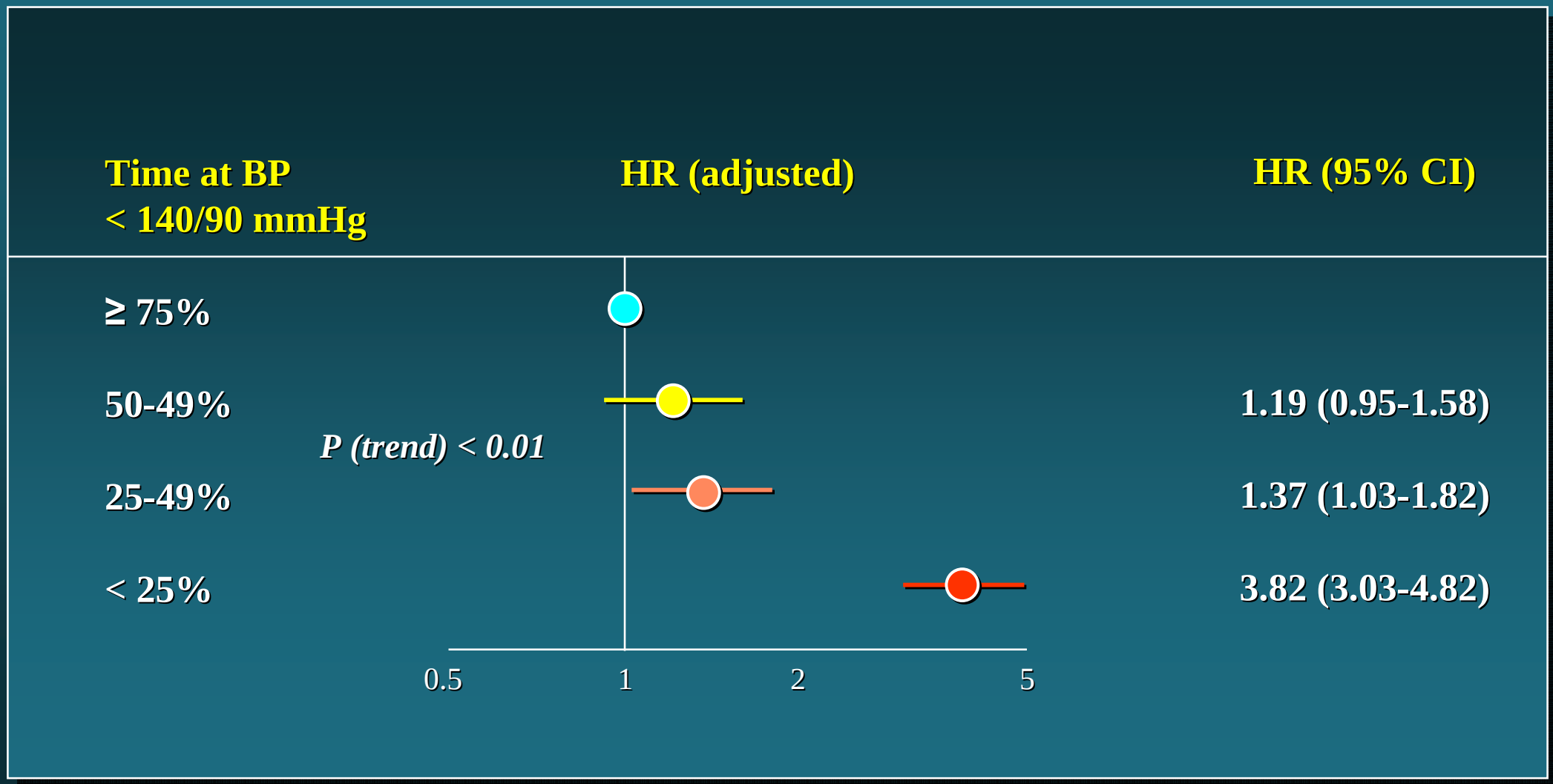
Mancia et al., Hypertension 2007; 50: 29

Rate of Clinic BP Normalization at Each Year and Throughout the 4 Years of Treatment in ELSA



Mancia et al., J Hypertens 2007; 25: 1087-1094

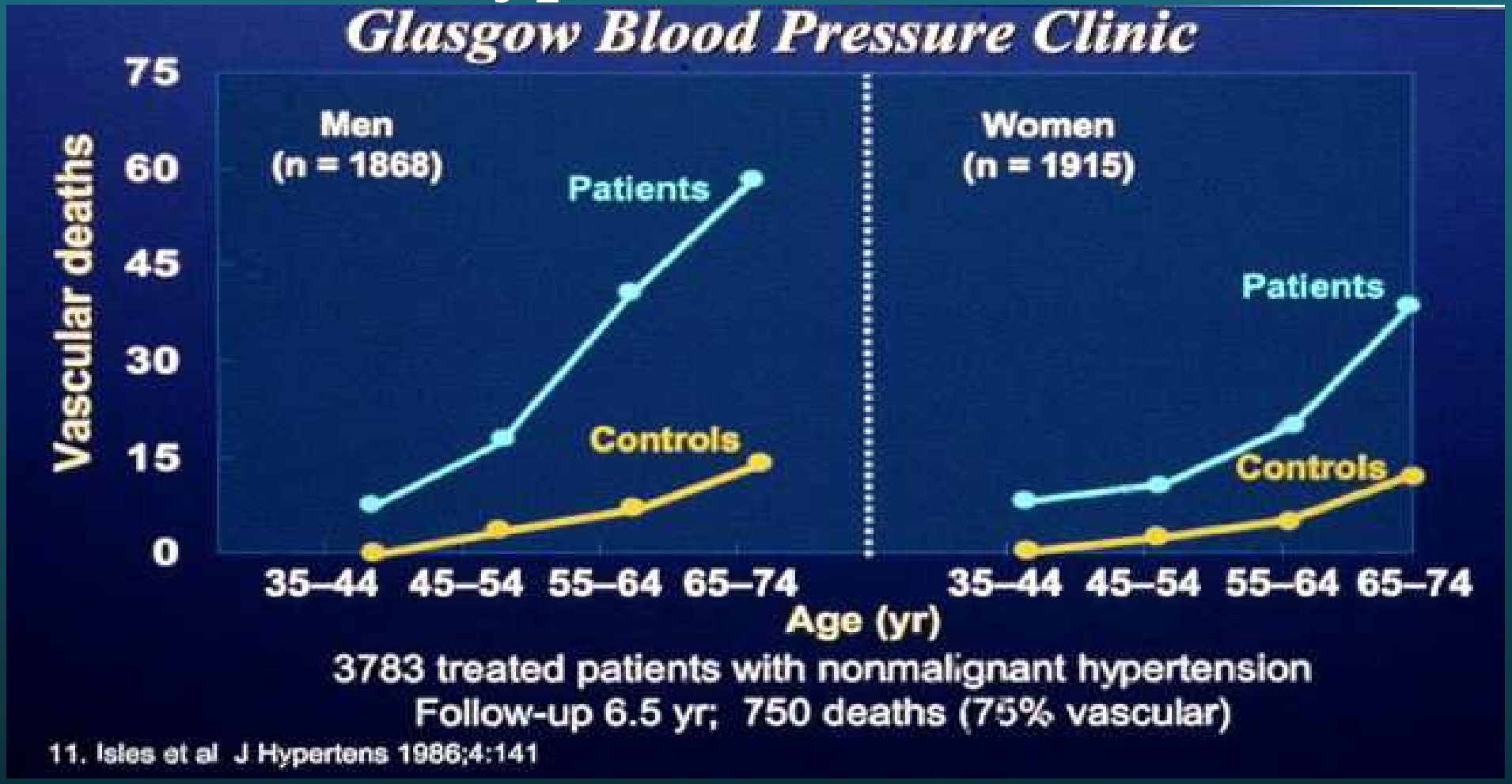
Adjusted Risk of Stroke according to Proportion of Time with BP < 140(ì/90 mmHg (VALUE)



18424 M

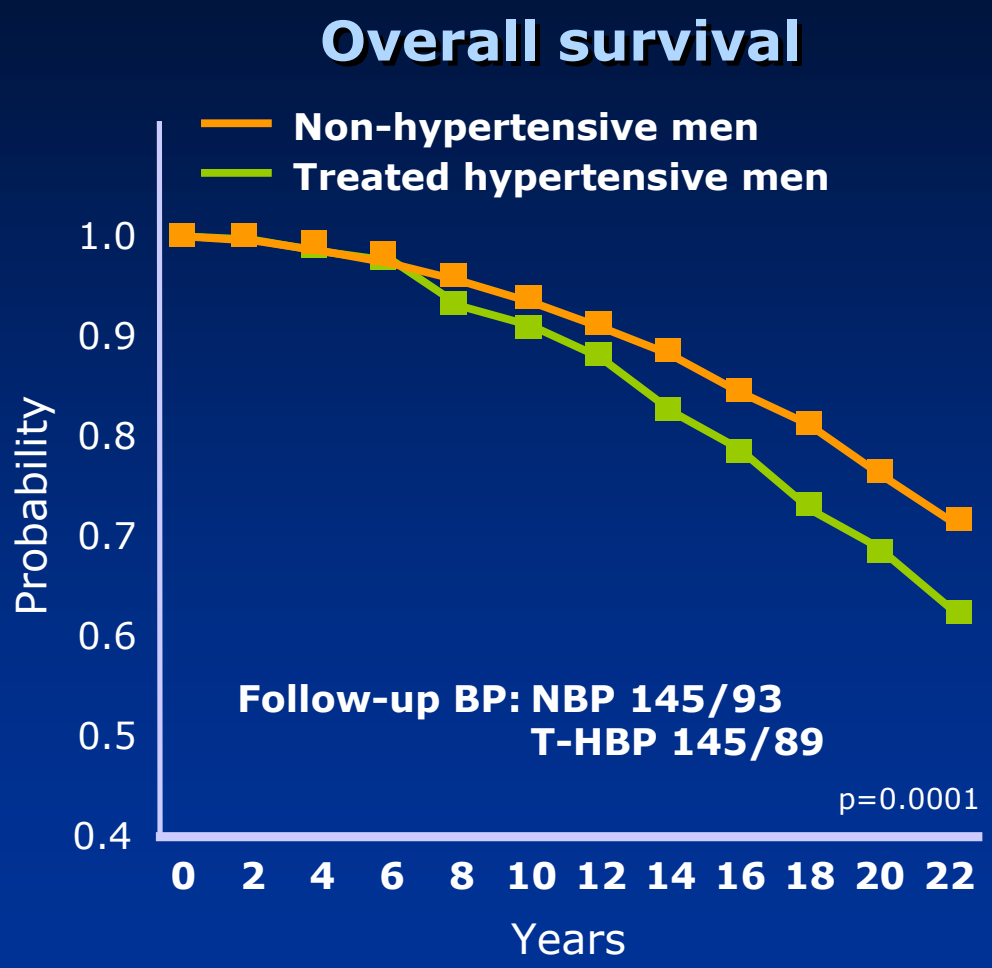
Mancia et al., submitted

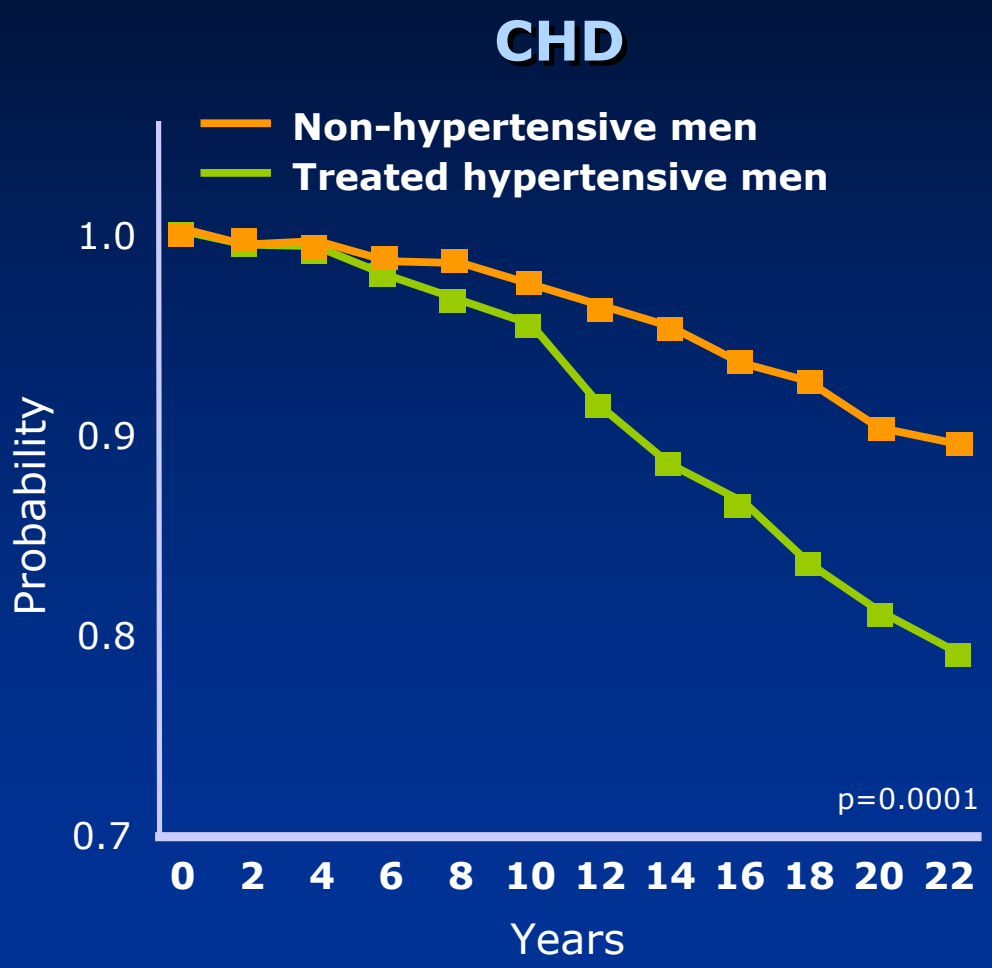
Persisting Cardiovascular Risk in Treated Hypertensive Patients



11. Isles et al J Hypertens 1986;4:141

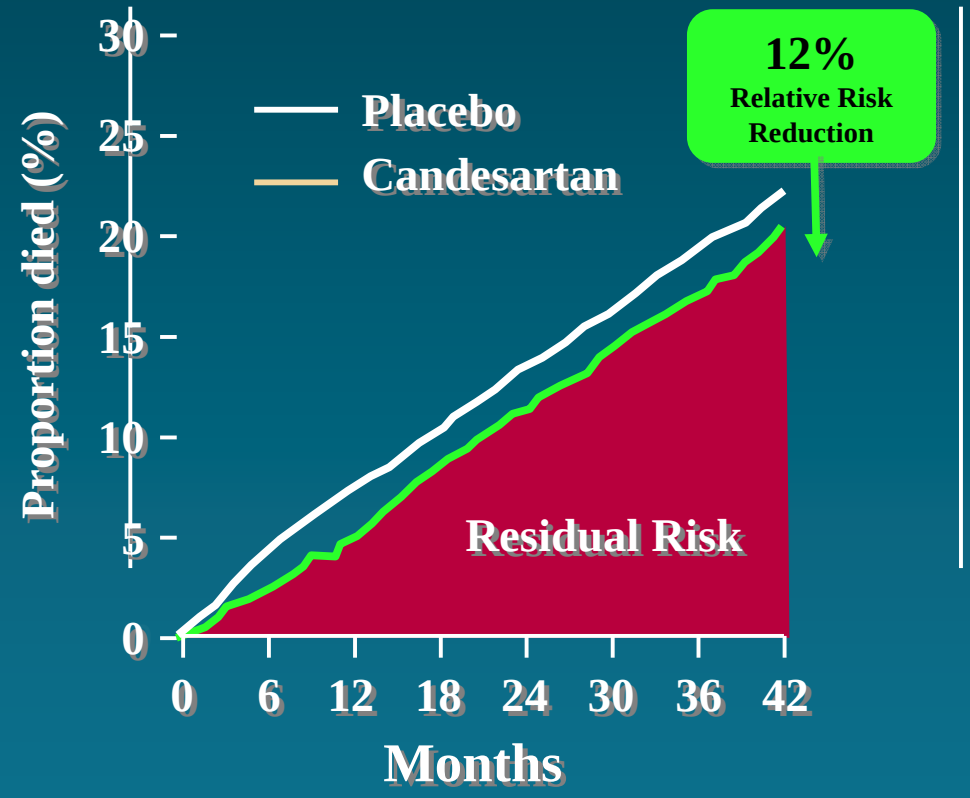
Cumulative probability of survival from all causes and from CHD in hypertensive men with normalized BP and in normotensive controls

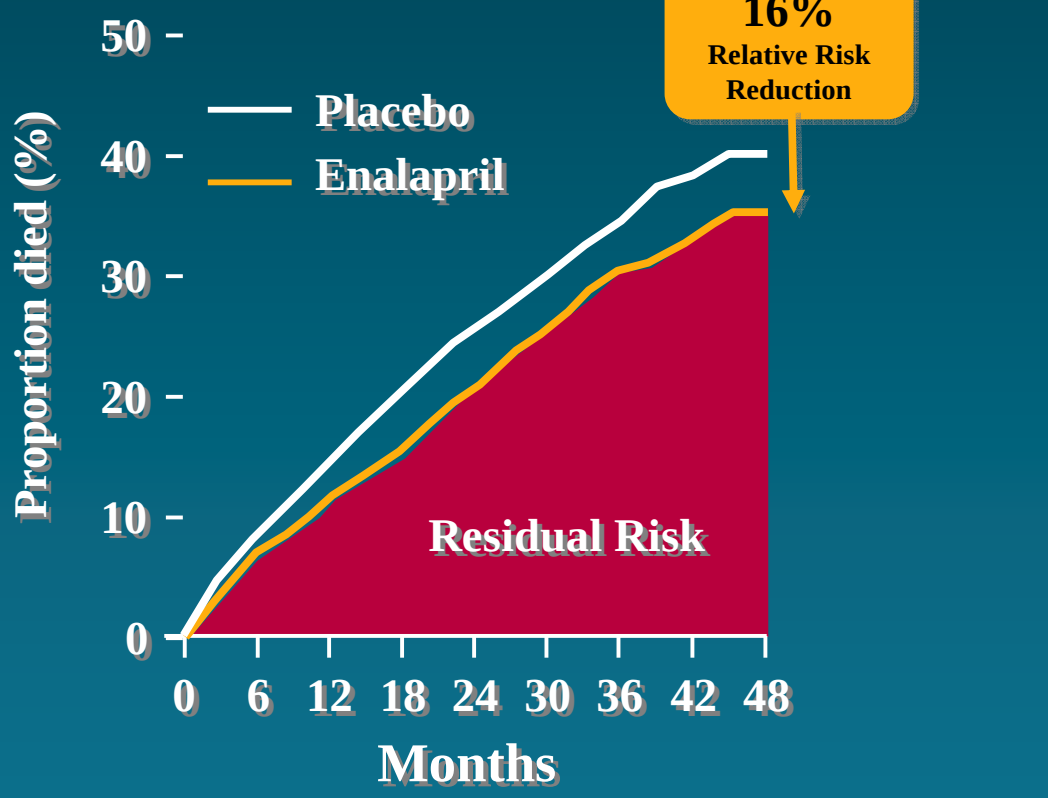




Andersson OK et al, 1998

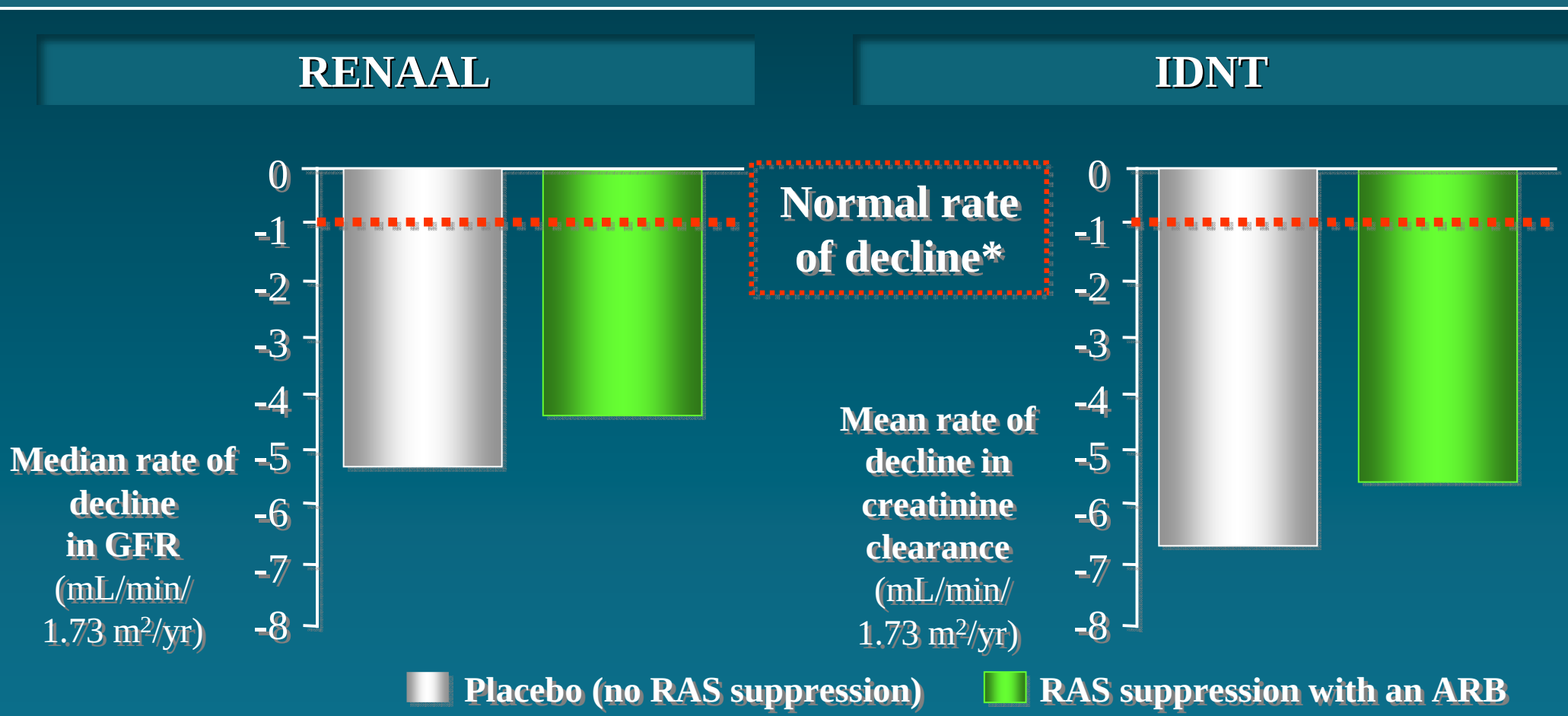
Residual morbidity and mortality in CHF remains high despite treatment with ACEIs/ARBs





SOLVD Investigators 1991; Pfeffer et al 2003

…but the Rate of Progression in ARB-Treated Patients is Still Elevated



**Mean decrease in GFR due to aging.*

IDNT, Irbesartan Diabetic Nephropathy Trial; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.

Brenner BM et al. N Engl J Med. 2001; 345: 861-869. Lewis EJ et al. N Engl J Med. 2001; 345: 851-860.
National Kidney Foundation. Am J Kidney Dis. 2002; 39 (suppl 1): S1-S266.

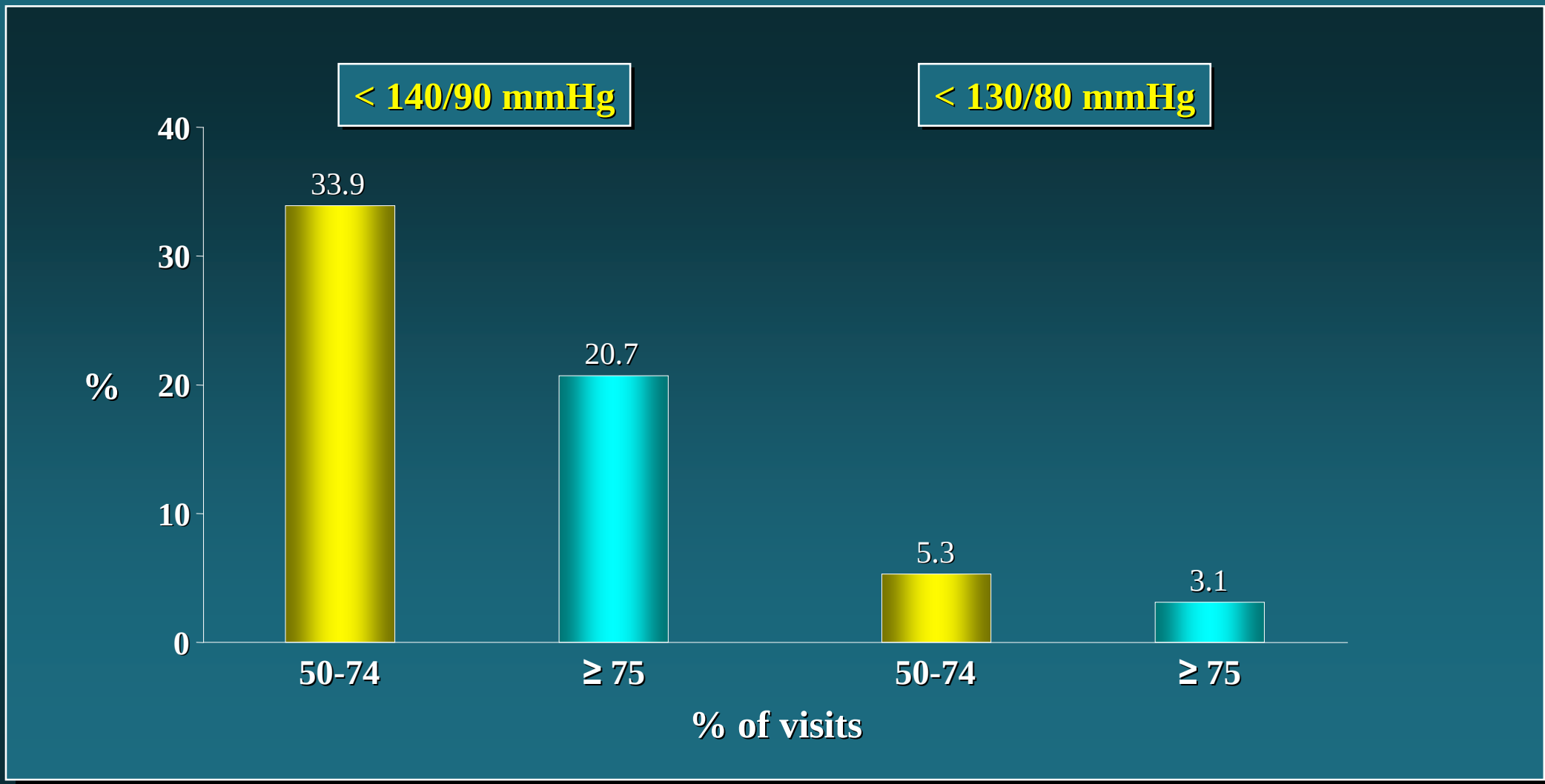
HYVET

HYPERTENSION IN THE VERY ELDERLY TRIAL

HYVET

HYPERTENSION IN THE VERY ELDERLY TRIAL

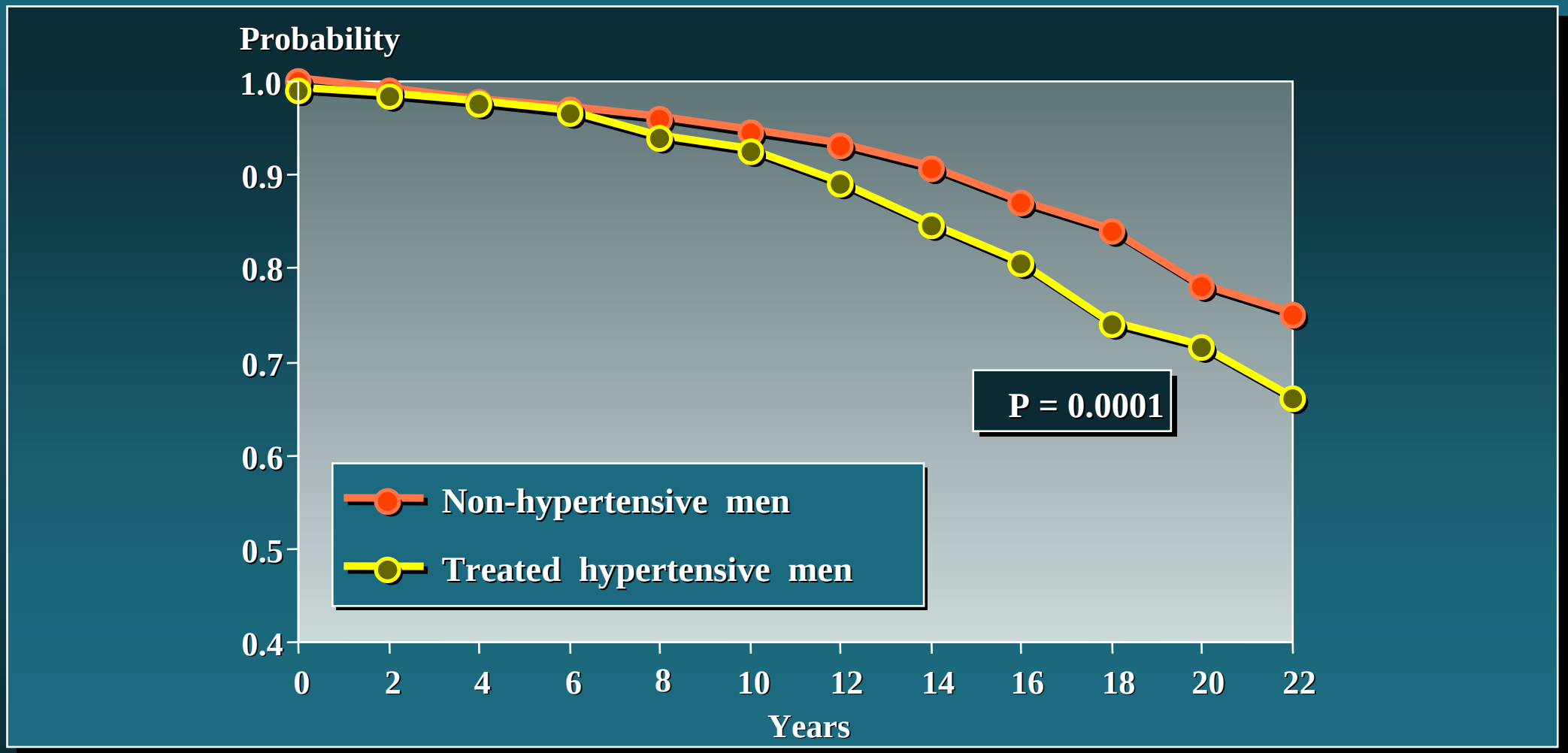
Proportion (%) of Visits with BP Controlled at Higher or Lower Target in the High Risk Hypertensives of VALUE (N=15245)



18740 M

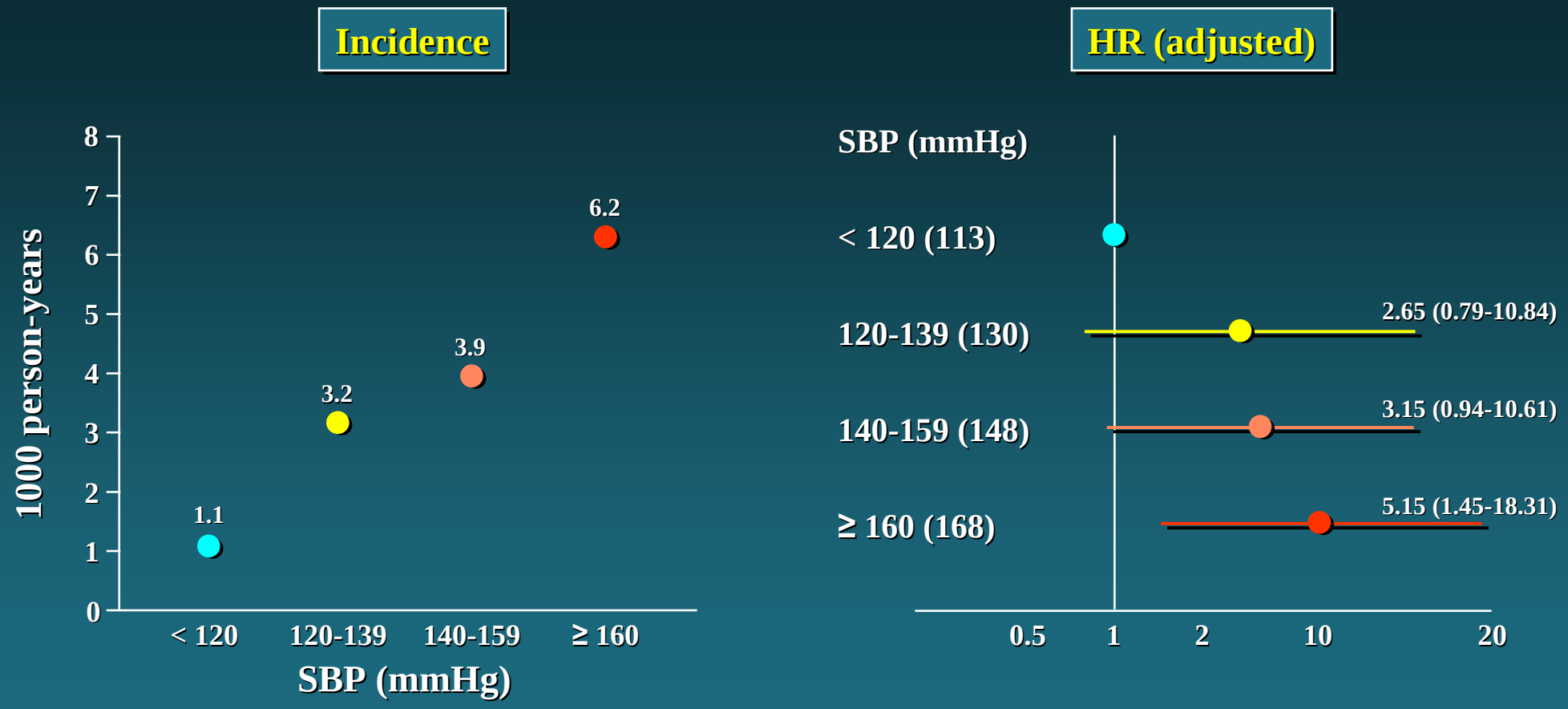
Mancia et al., in preparation

Cumulative probability of survival of 686 men treated for hypertension and 6810 non-hypertensive men in primary prevention study



Andersson et al, BMJ 1998; 317: 167

Intracranial Bleedings according to Achieved SBP in Patients under Antithrombotic Therapy (PROGRESS)



16781 M

Arima, Anderson, Omae, Woodward, MacMahon, Mancia, Bousser, Tzourio, Rodgers, Neal, Chalmers, PROGRESS Collaborative Group, Stroke 2012; 43: 1675-1677

Stroke and Chronic Antihypertensive Drug Treatment

- Stroke reduction with treatment shown by RCTs in virtually all demografic/clinical conditions
- 35-40% less risk by 10-12 mmHg SBP fall
- Beneficial effects with all major drug classes
- cerebrovascular protection largely due to BP lowering "*per se*"

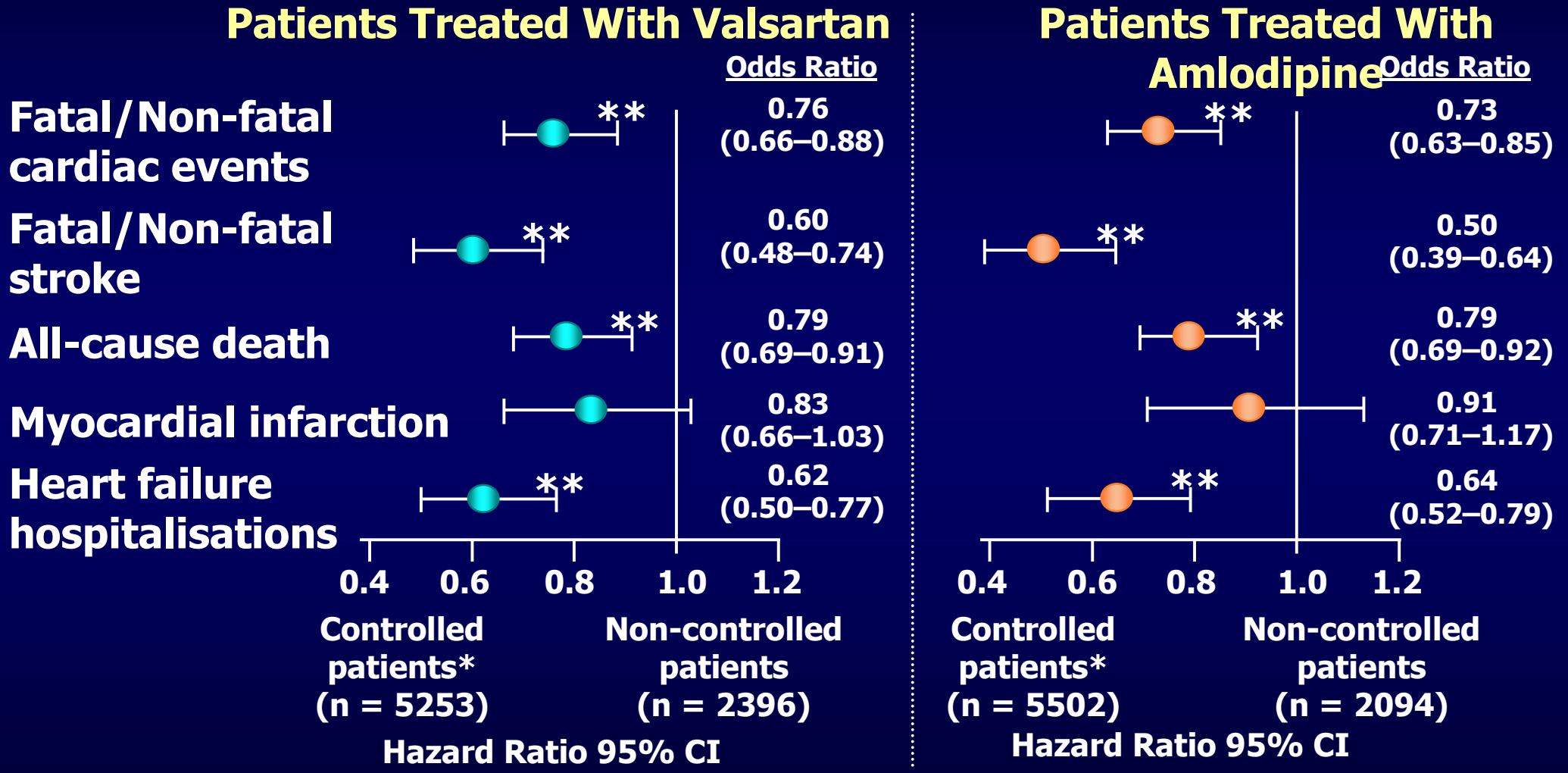
At whichOn-treatment BP Stroke Prevention is maximized?

< 140/90 mmHg?

< 130/80 mmHg?

The lower the better?

VALUE: Analysis of Results Based on BP Control at 6 Months

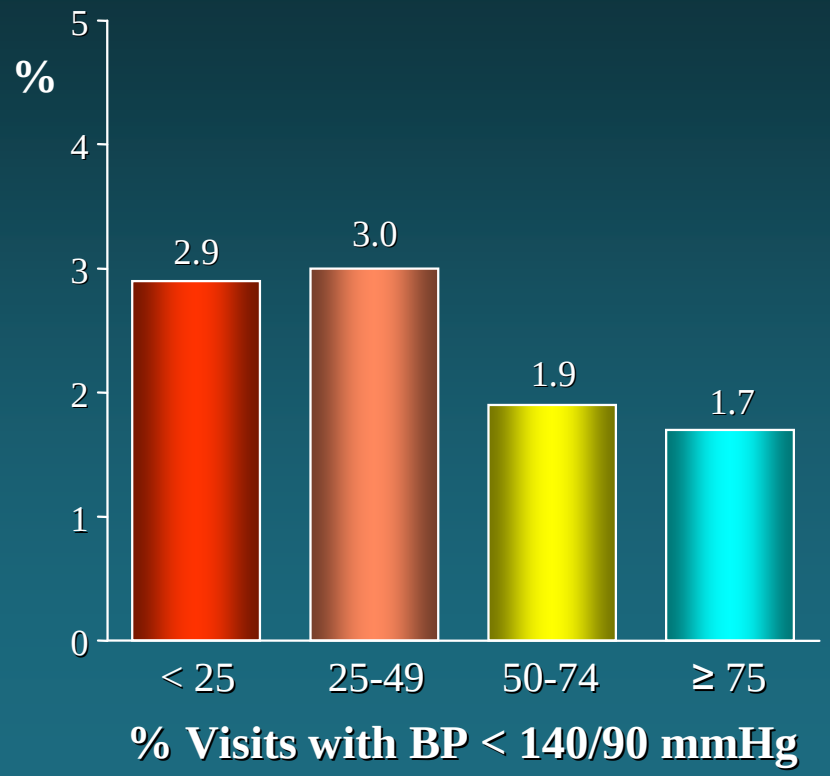


*SBP < 140 mmHg at 6 months.
**$P < 0.01$.
Weber MA et al. *Lancet.* 2004;363:2047–49.

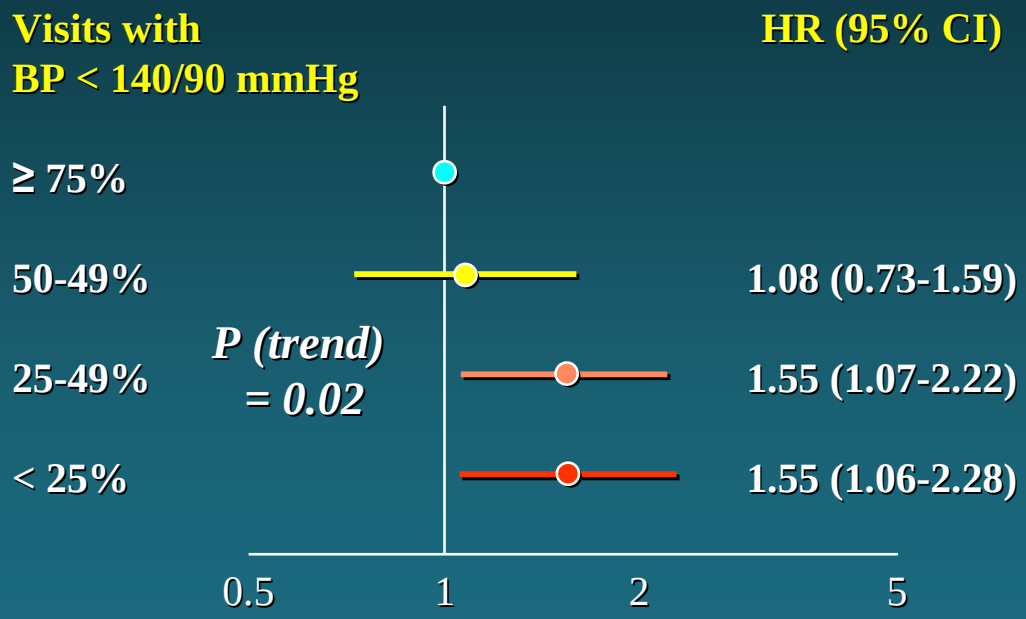
VALUE

Incidence and Risk of Stroke according to Achievement of BP < 140/90 mmHg (ONTARGET, n = 12273)

Stroke incidence



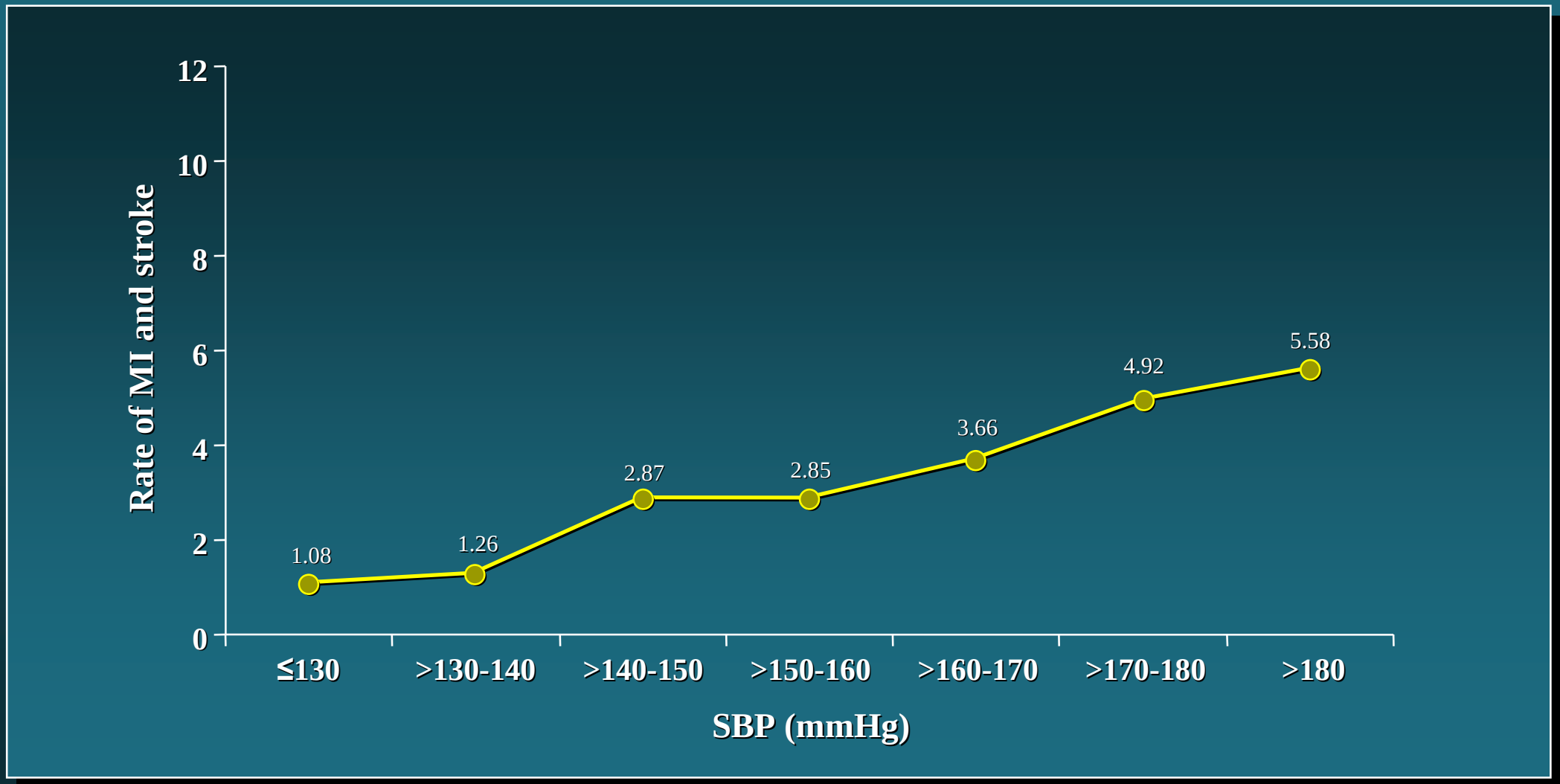
HR (adjusted)



18423 M

Mancia et al., Circulation 2011; 124: 1727

Rate of Stroke according to Achieved SBP in INVEST

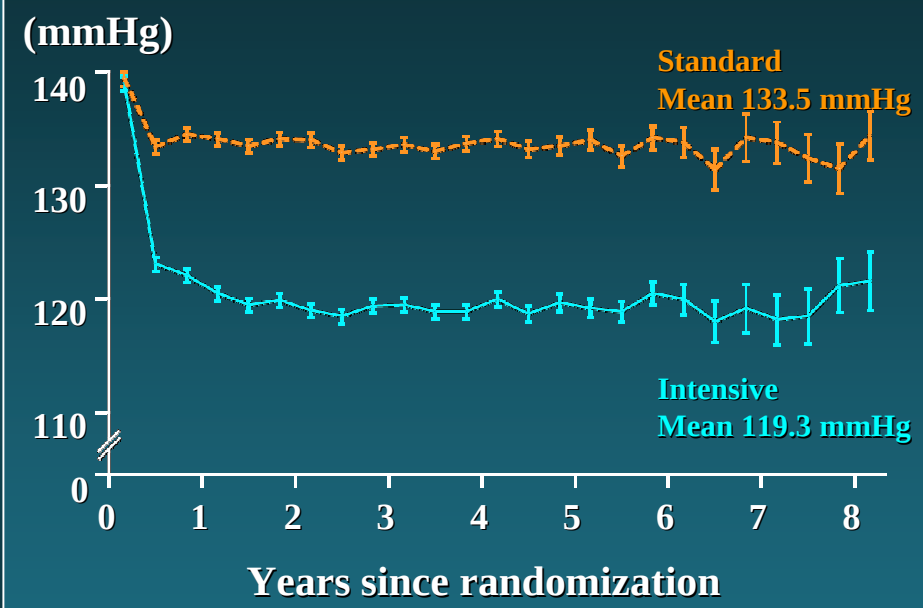


13621 M

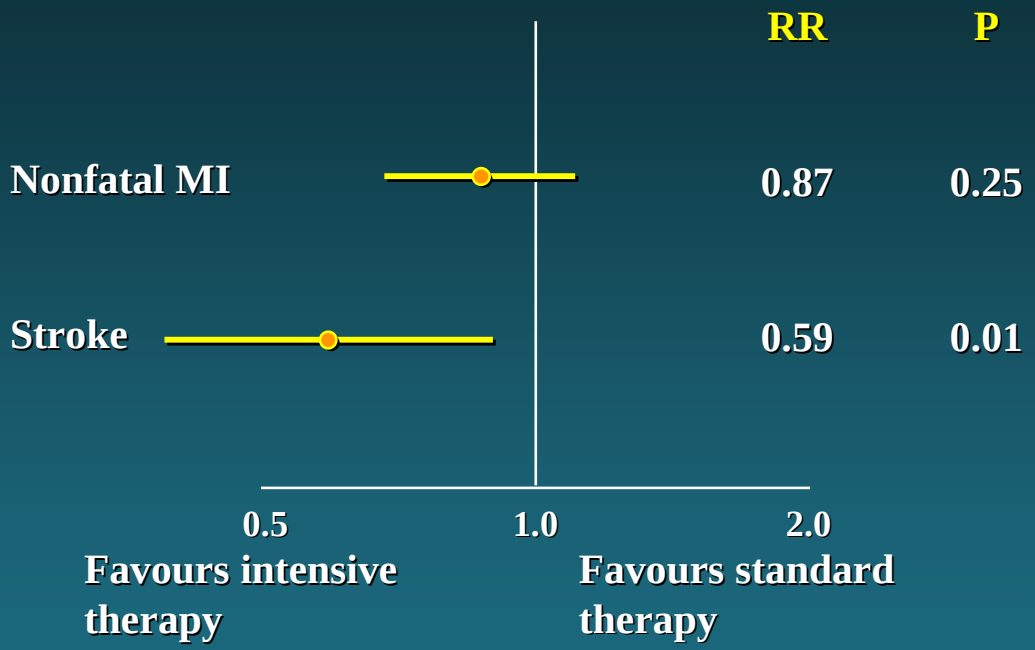
Messerli, Mancia et al., Ann Int Med 2006; 144: 884-893

Mean SBP and Risk of Stroke / MI in ACCORD

SBP



Relative risk

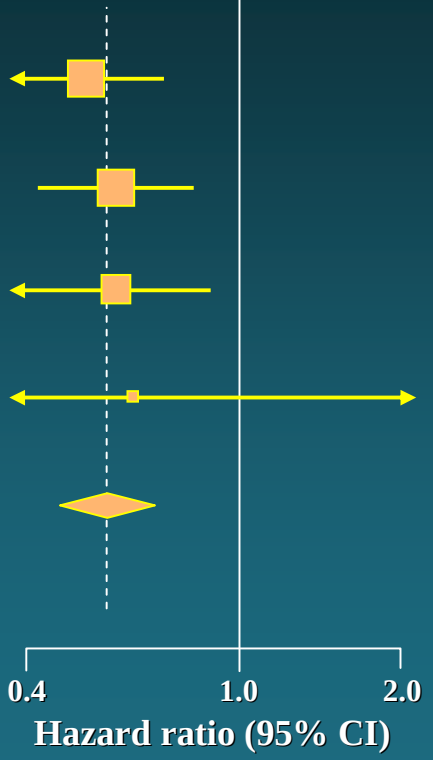


17502 M

The ACCORD Study Group, NEJM 2010, March

Effect of Randomized Treatment on Risk of Stroke among Patients on Perindopril / Indapamide Combination Treatment in PROGRESS (n = 3544 / 58%)

SBP (mmHg)	Events/patients Active	Placebo	SBP difference	Favours active	Favours placebo	Risk Reduction (95% CI)	P trend
≥ 160	57/524	106/543	14.2 mmHg			47 (27 to 62)	0.5
140-159	54/695	87/689	12.2 mmHg			41 (16 to 53)	
120-139	37/486	58/461	9.7 mmHg			41 (11 to 61)	
< 120	2/65	4/81	9.3 mmHg			36 (-249 to 88)	
Total	15091770	255/1774	12.3 mmHg			43 (30 to 54)	



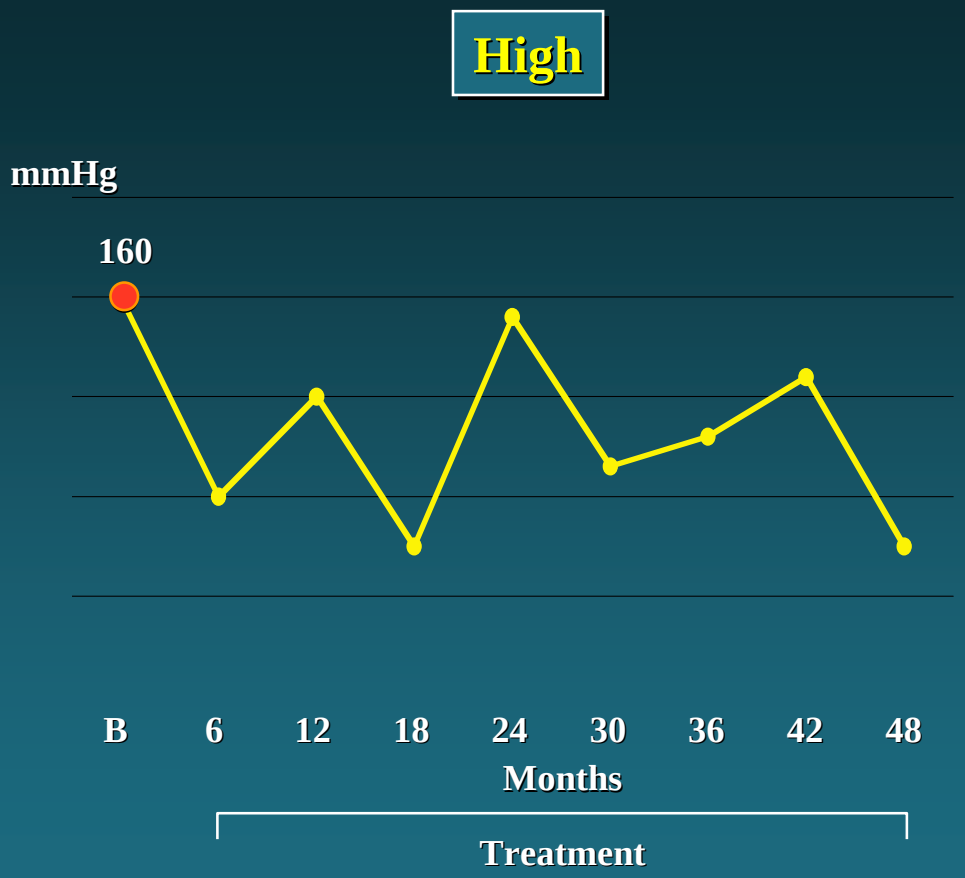
Mean BP reduction 14/5 mmHg

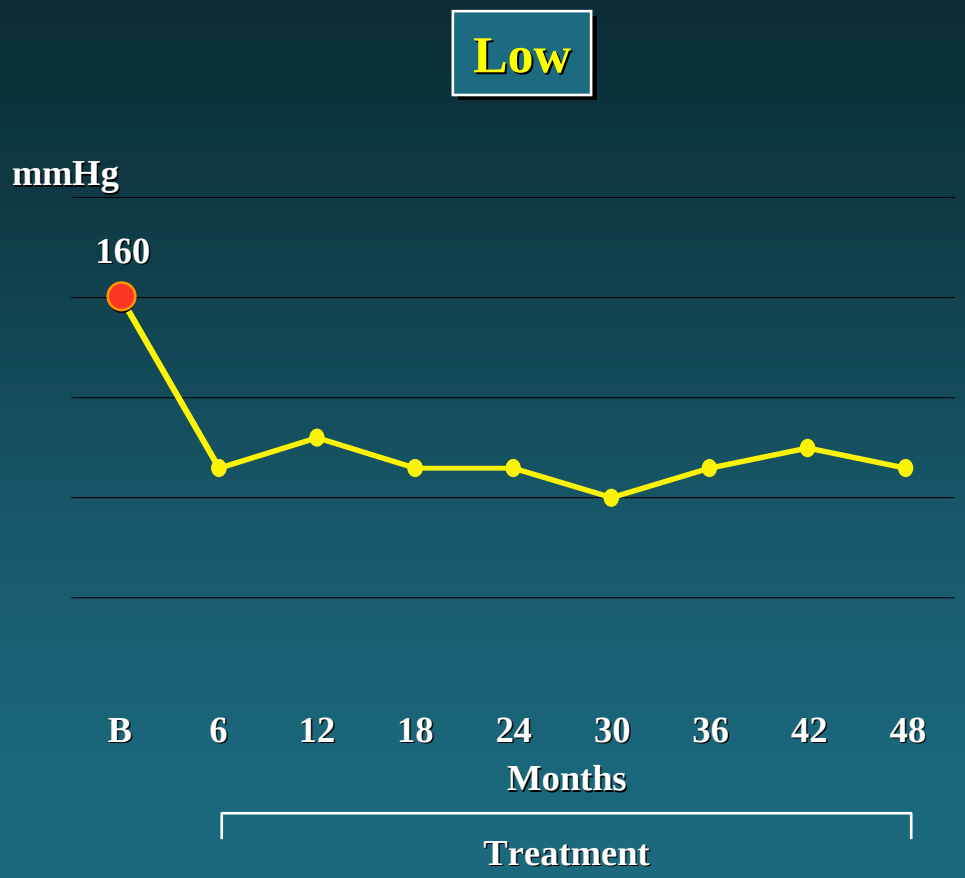
17499 M

Arima et al., J Hypertens 2006; 24: 1201

The lower the BP
the better may hold also
for secondary cerebrovascular
protection

Intra-individual SBP Variability during Treatment

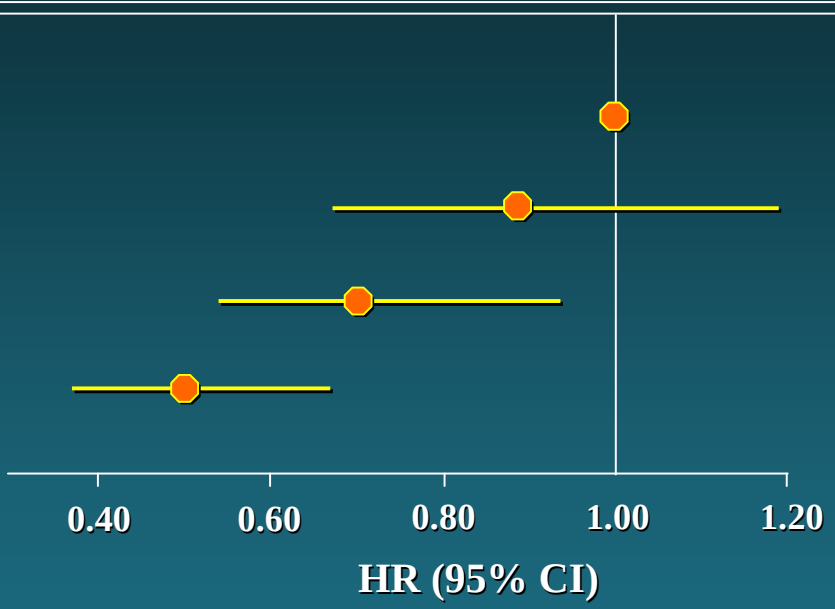




16425 M

Risk of Stroke by % of Visits with BP Control (< 140/90 mmHg) in INVEST (n = 22576)

Fatal and nonfatal stroke	HR (95% CI)
< 25%	1.00
25 to < 50%	0.89 (0.67-1.19)
50 to < 75%	0.70 (0.52-0.92)
≥ 75%	0.50 (0.37-0.68)



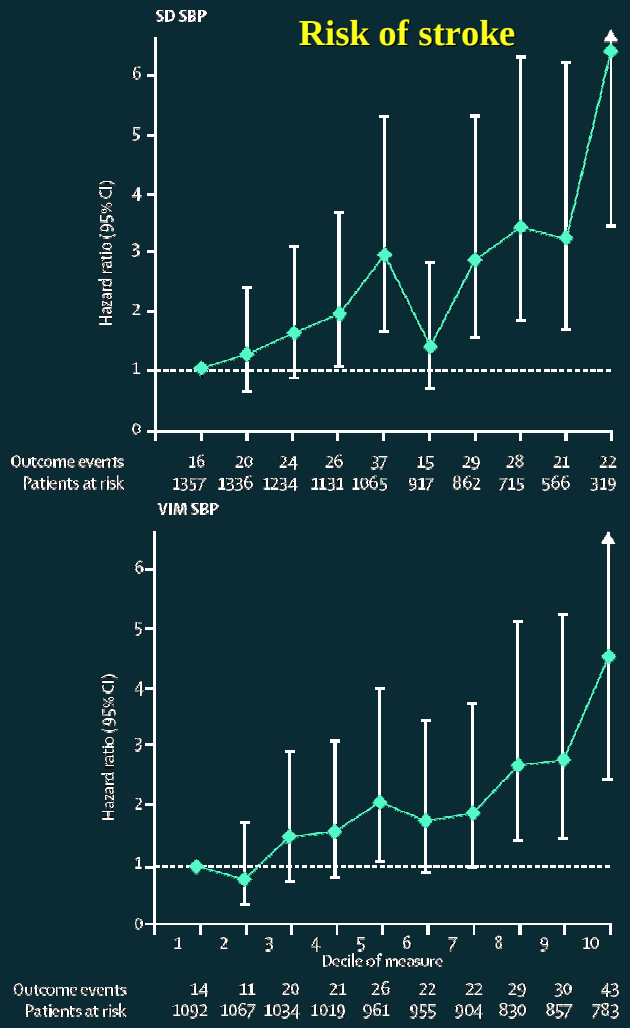
Adjusted Risk

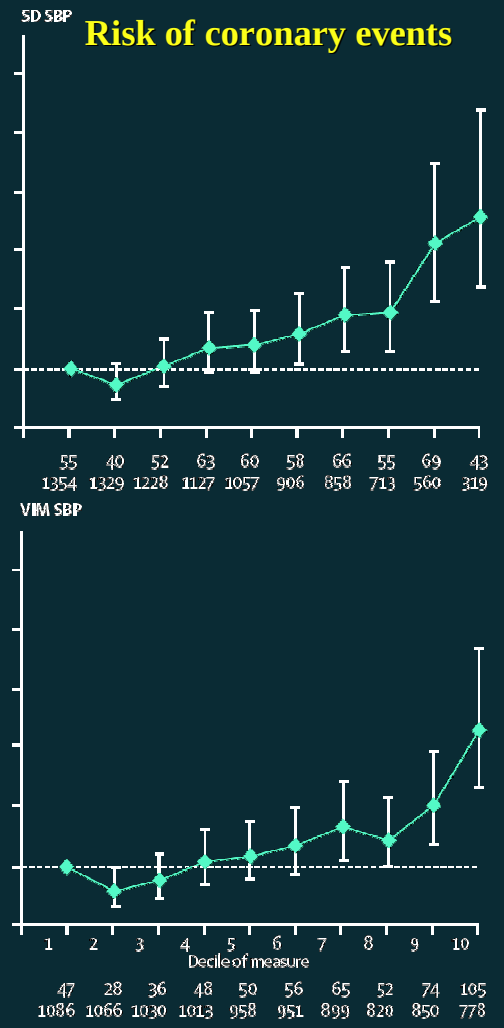
Stepwise model with 5 prespecified baseline covariates
(age, gender, race, prior MI, CHF) forced into model.Ad. Also for on-t BP
All other baseline covariates selected based on p-values ≤ 0.10.
Group with < 25% of visits with BP control used as reference.

13619 M

Mancia et al., Hypertension 2007; 50: 299

Risk of Stroke and Acute Coronary Events in ASCOT-BPLA Patients with Mean SBP during Follow-up Less than the Median Value for the Trial Population (<142·8 mmHg) by Deciles of SD and VIM SBP





15690 M

Rothwell PM et al., Lancet 2010; 375: 895-905

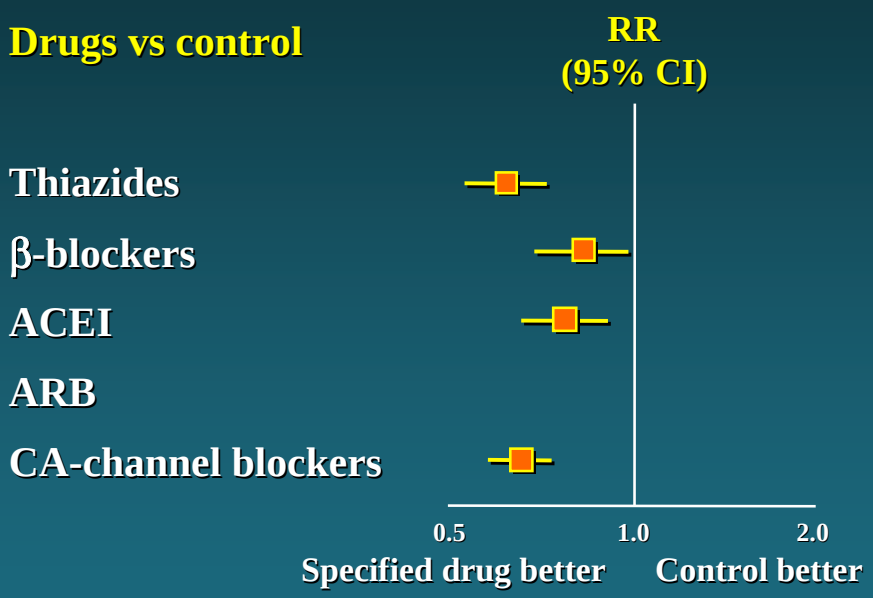
Achieving BP goal consistently is difficult

Effective BP drugs/Treatment strategies/Adherence to treatment are needed

Cerebrovascular protection by Antihypertensive Treatment

- DOES THE BP BP REDUCTION ENTIRELY EXPLAIN THE PROTECTIVE EFFECT ?
- ARE THERE BP-INDIPENDENT SPECIFIC PROTECTIVE PROPERTIES OF BP –LOWERING DRUGS ?
- BP-INDIPEDENT PROTECTIVE PROPERTIES ARE DESIRABLE BECAUSE EVEN WHEN BP IS CONTROLLED RESIDUAL RISK REMAINS HIGH

Relative Risk of Stroke - Comparing Drugs with Control and Other Drugs

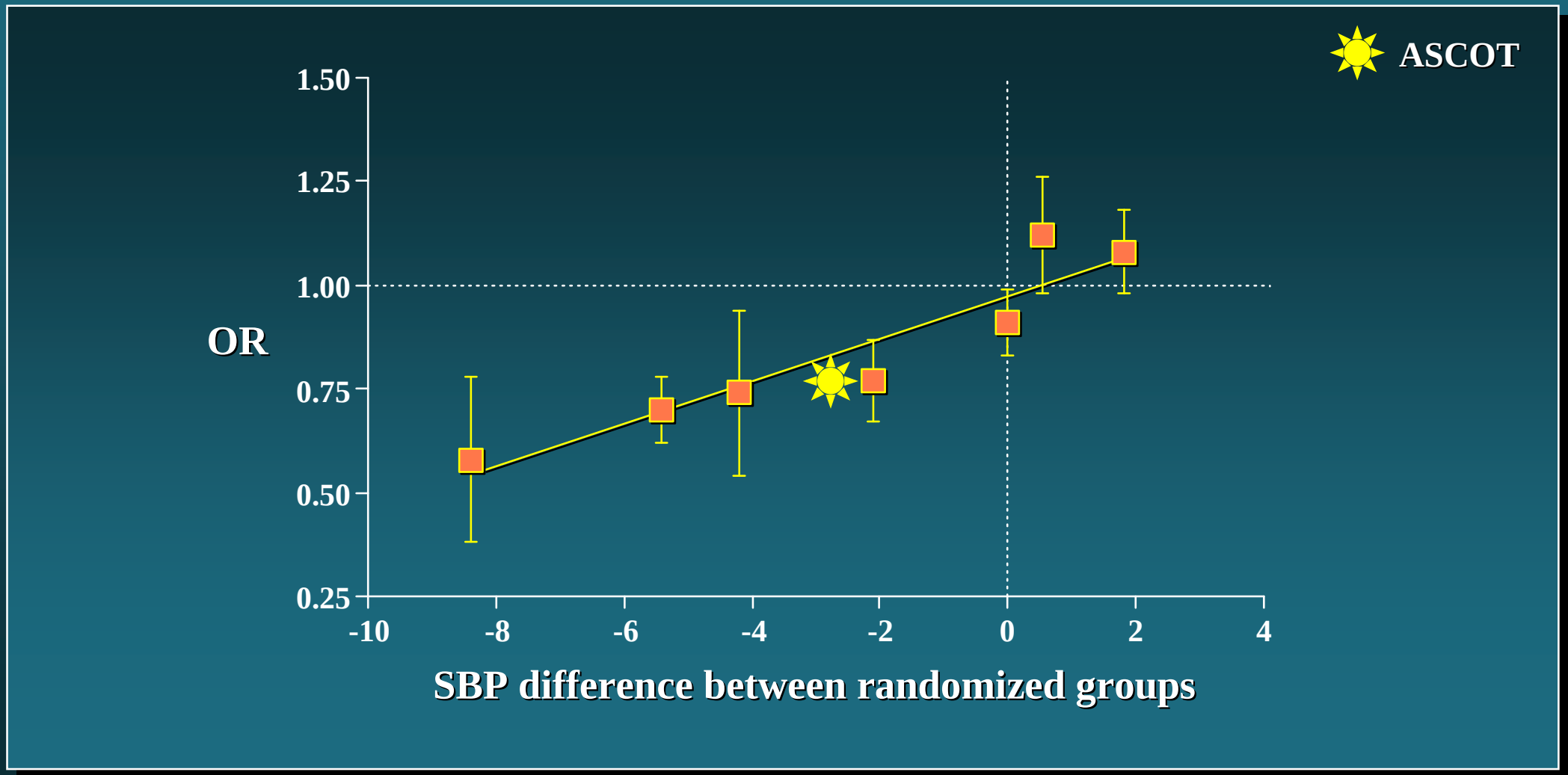


Drug vs any other	BP diff. (mmHg) SBP	DBP	RR (95% CI)	RR
Thiazides	-1.4	0.2		0.94
β-blockers	1.4	0.6		1.18
ACEI	0.9	0.4		1.06
ARB	-0.4	0.1		0.90
CCB	-0.4	-0.9		0.91

* CHD events in trials of β-blockers in CAD patients excluded
† Results not substantially altered by correction for BP Δ

Law et al., BMJ 2009; 338: b166

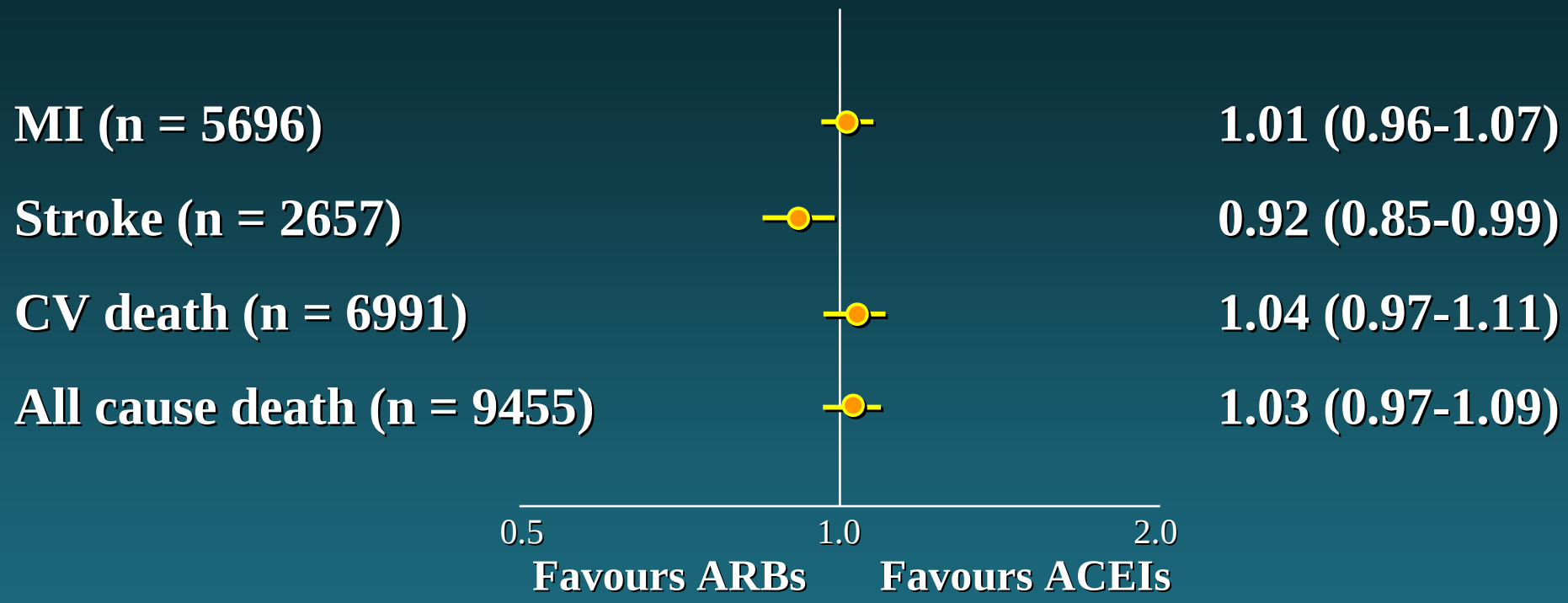
Relationship between the Reduction in SBP and the Risk of Stroke in the Meta-regression Analysis



12639 M

Mancia G & Zanchetti A, J Hypertens 2008; 26: 164-168

Comparisons between ARBs (n = 31632) and ACEIs (n = 31777)



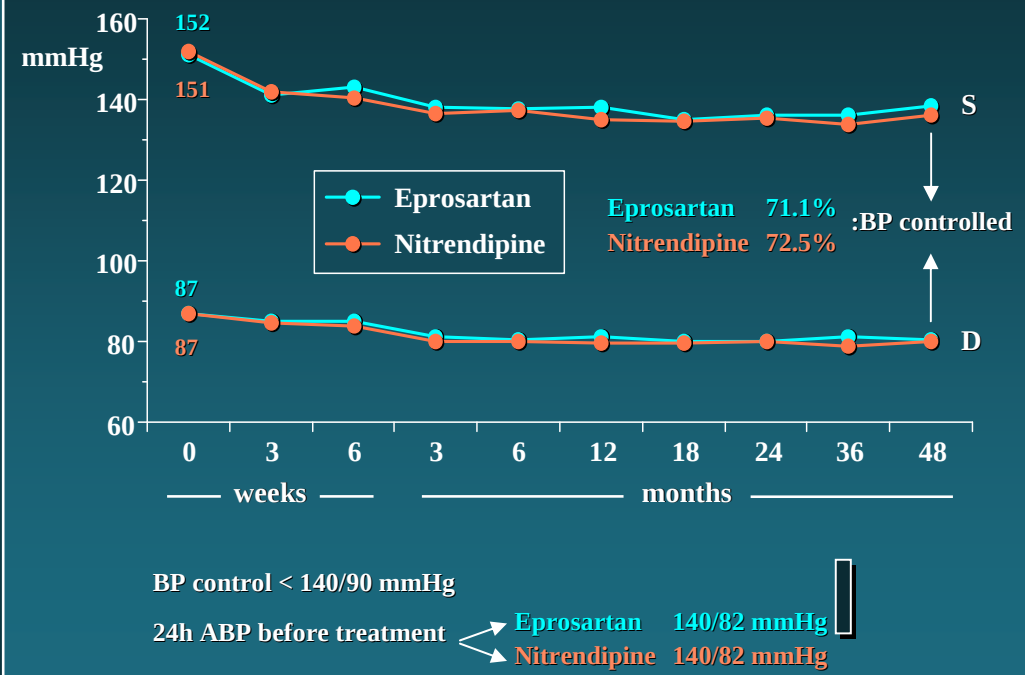
Trials ELITE / ELITE II / OPTIMAAL / DETAIL / VALIANT / ONTARGET

13600 M

Reboldi, Angeli, Cavallini, Gentile, Mancia, Verdecchia, J Hypert 2008; 26: 1282

MOSES - BP Values and Clinical Events

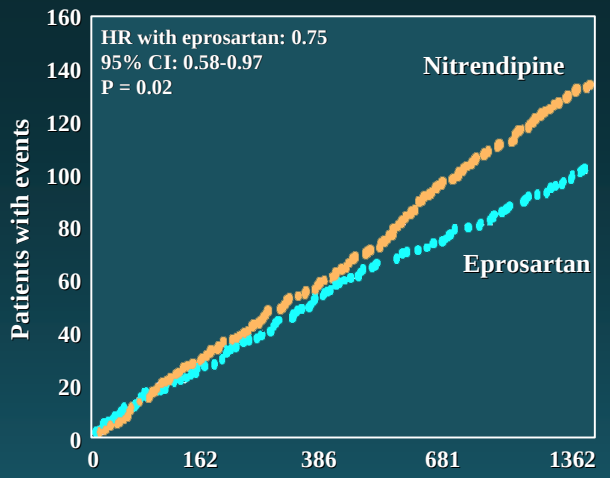
Blood pressure



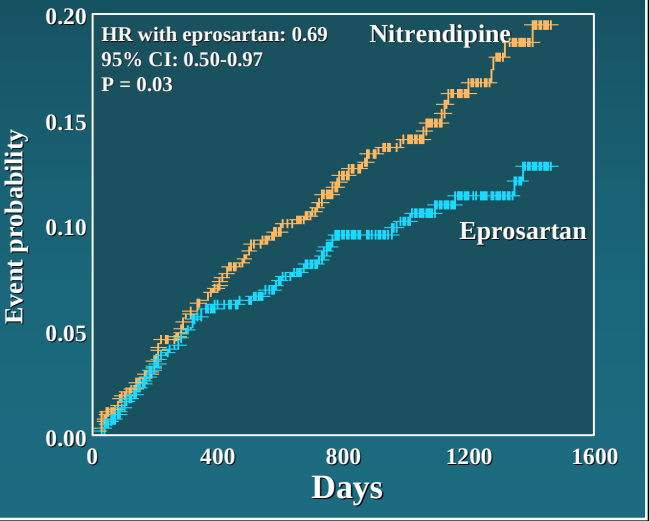
BP control < 140/90 mmHg

24h ABP before treatment → Eprosartan 140/82 mmHg; Nitrendipine 140/82 mmHg

Cerebrovascular events (1st + recurrent)



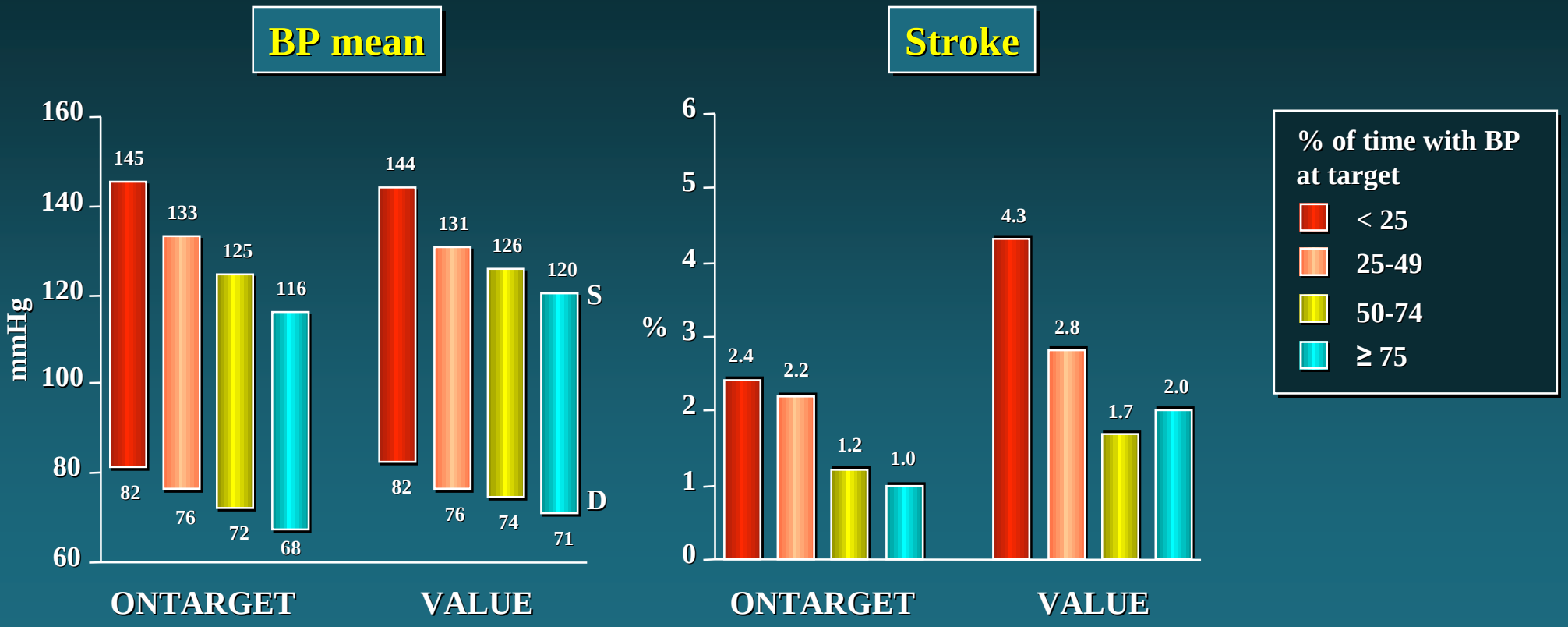
Cardiovascular events



12328 M

MOSES - Schrader, Stroke 2005; 36: 12

Stroke Incidence by % of Time with BP < 130/80 mmHg in ONTARGET and VALUE



17500 M

Mancia et al., Circulation 2011; 124: 1727, Mancia et al., unpub