2012. 4. 20-21 춘계심장학회_부산

Can Anti-hypertension Therapy Reverse Vascular Aging and Dementia?

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The Pulse : revived in Asia.
(www.pulseasia.org)
1st the Pulse of Asia, April 17-18th 2009, in Daegu, Korea
2nd April 2010 Tokyo, 3rd Nov. 2011 Beijing, 4th Sep 29-30. 2012 Sydney

Contents:

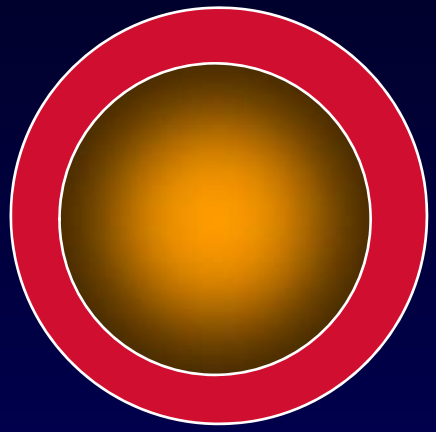
- Hypertension and vascular aging
- Vascular changes of brain in hypertension
- Hypertension and dementia
- Does Anti-hypertension therapy reverse those changes?
  - Effects of RAS blockade on vascular aging
  - Effect of BP reduction on brain damage and dementia

"Most cardiovascular disease risk factors result in progressive changes in blood vessels, including those of the brain..."

Arterial changes in Hypertension

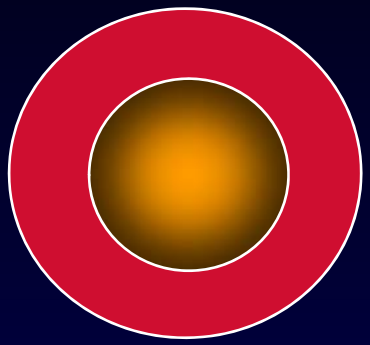
Normotension | **Hypertension**

Hemodynamic:
pressure, flow, cyclic stress



Extra/intracellular stimuli:
Ang II, ET-1, NO^-, O_2^- ...

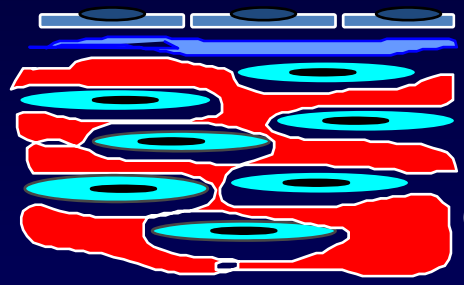
Structure



large → Hypertrophic

small → Eutrophic remodeling

Endothelium → Endothelial dysfunction

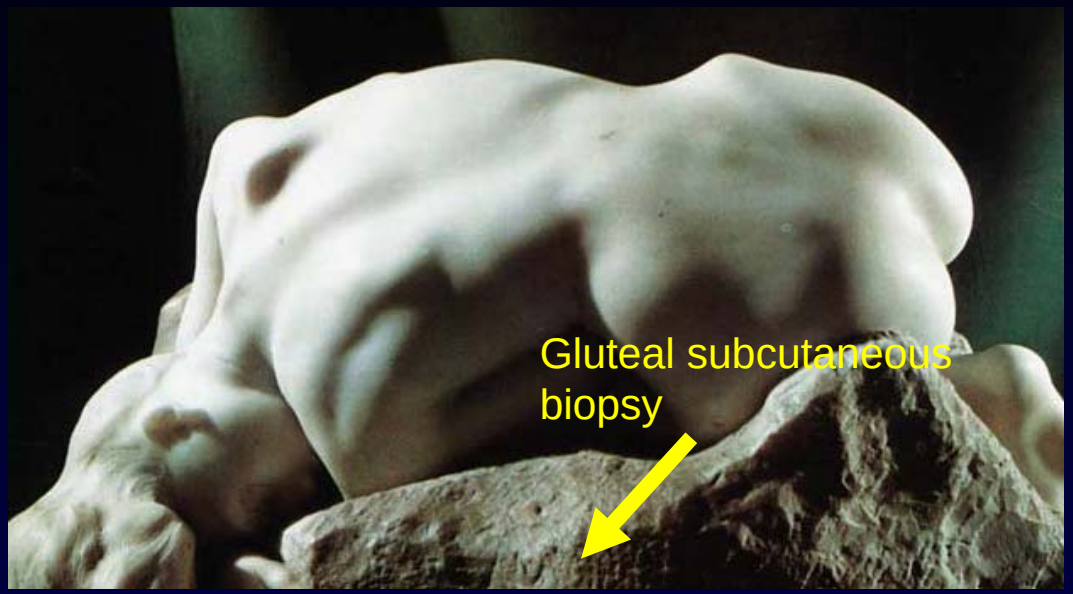


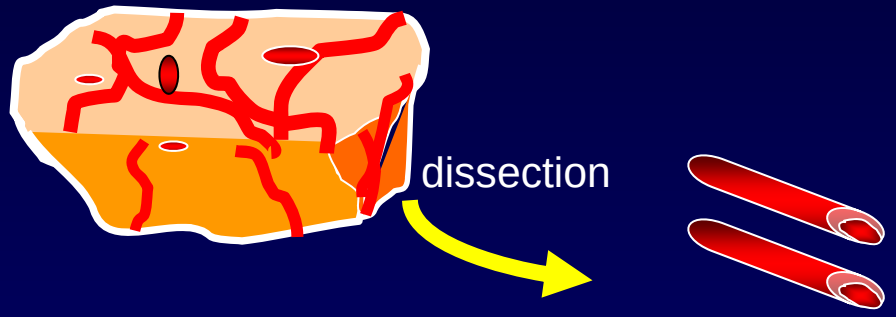
→ Altered vascular mechanics

ECM deposition

Park JB and Schiffrin EL. *Curr Hypertens Reports 2000*

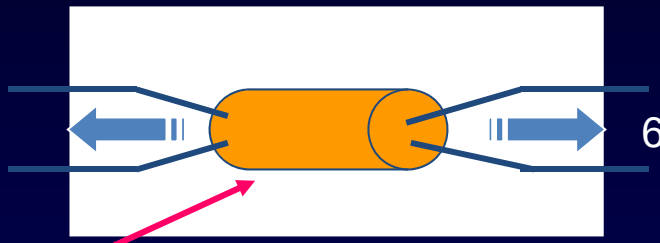
Resistance Artery Study in Human





Park JB 1999

Small artery studies (isobaric)



Structure; media to lumen ratio

Function; ach and nitroprusside

Mechanics

-intraluminal pressure = 3 - 140 mmhg

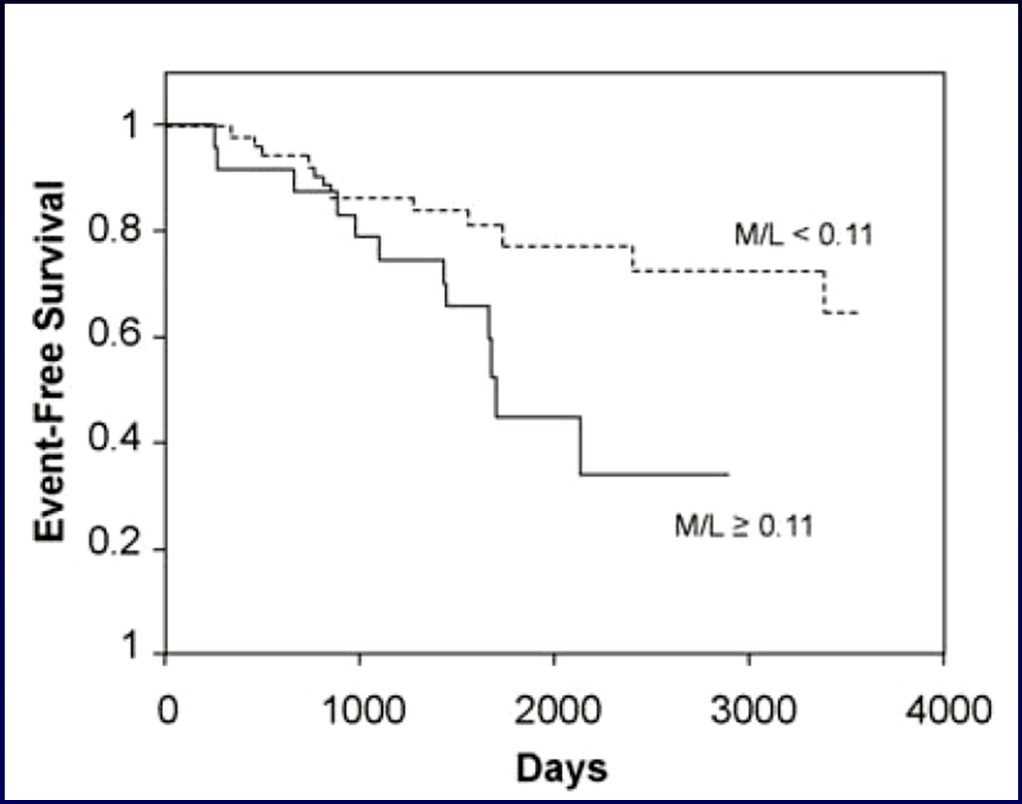
-lumen and media measurements

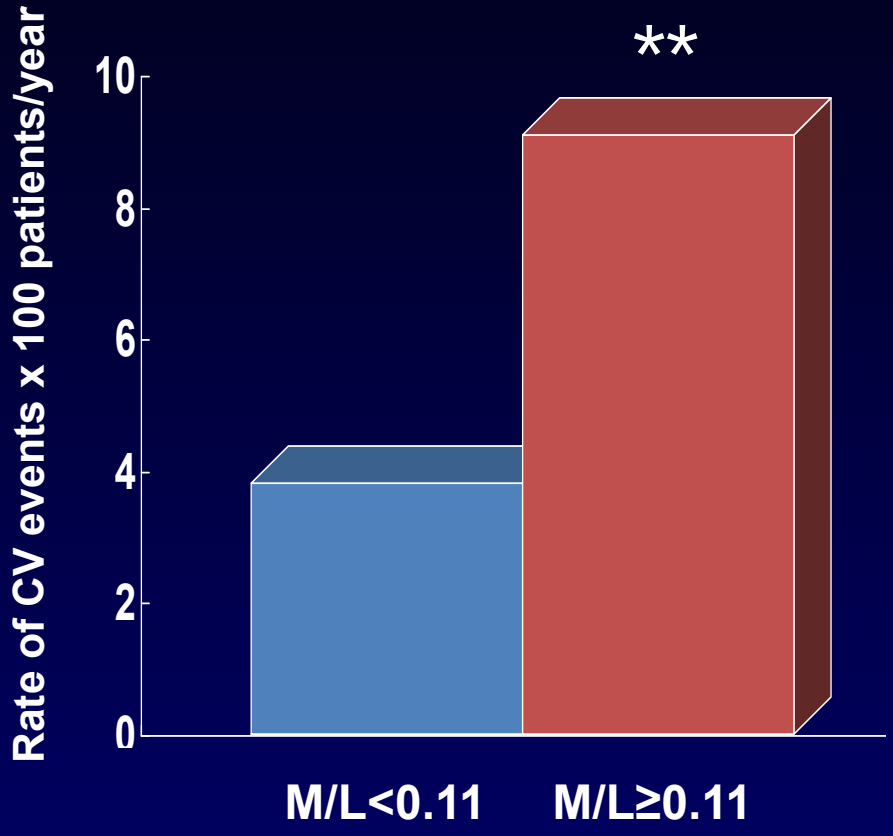
Small artery remodeling is the most prevalent (earliest?) form of target organ damage in mild essential hypertension.

	Hypertension	Prevalence (%)
Resistance Artery Vascular Remodeling - Media/Lumen ratio	↑	63 - 97
Endothelial Function - Ach response	↓	34 - 58
Vascular Stiffness - E_{inc} vs stress	↔	No change
LV Mass ECG/ECHO	↑	26 - 34

Park JB, Schiffrin EL. *J Hypertens* 2001;19:921

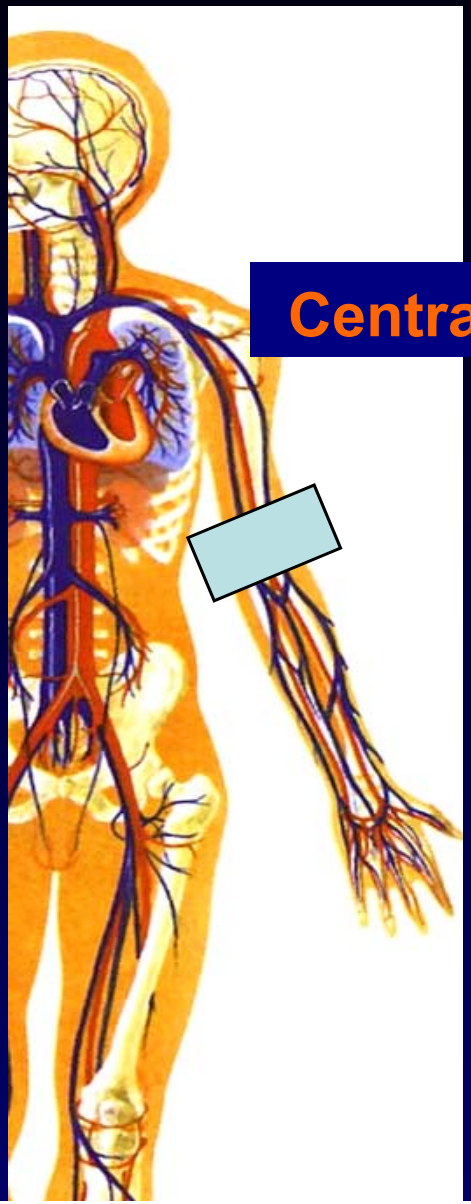
Event-free survival in patients with hypertension or diabetes and with a media–lumen (M/L) ratio of small arteries and Incidence of CV events





Rizzoni et al. Circulation 2003;108:2230

Large artery , Central Artery Changes



atherosclerosis

vascular endothelial damage
& mechanical fatigue

aortic stiffness
& arteriosclerosis

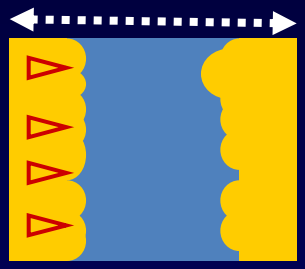
↑ central wave
reflection

↑ PP

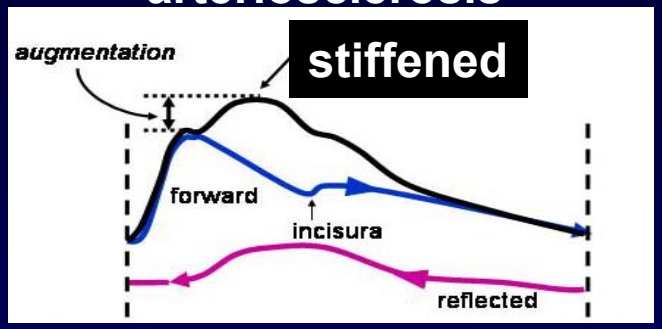
↑Central SBP

Central pressure

atherosclerosis



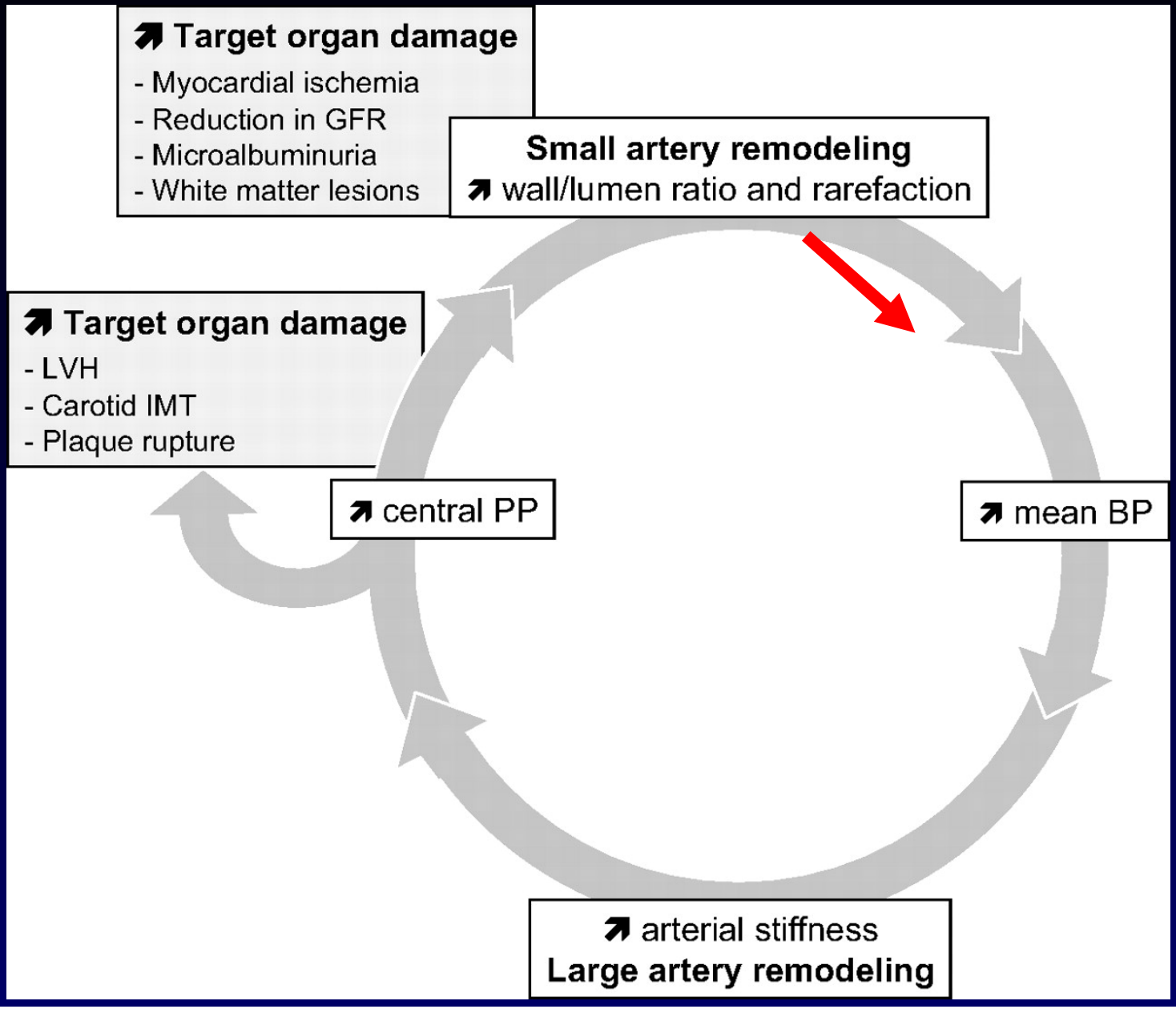
arteriosclerosis



↑ stroke
renal failure
IHD…

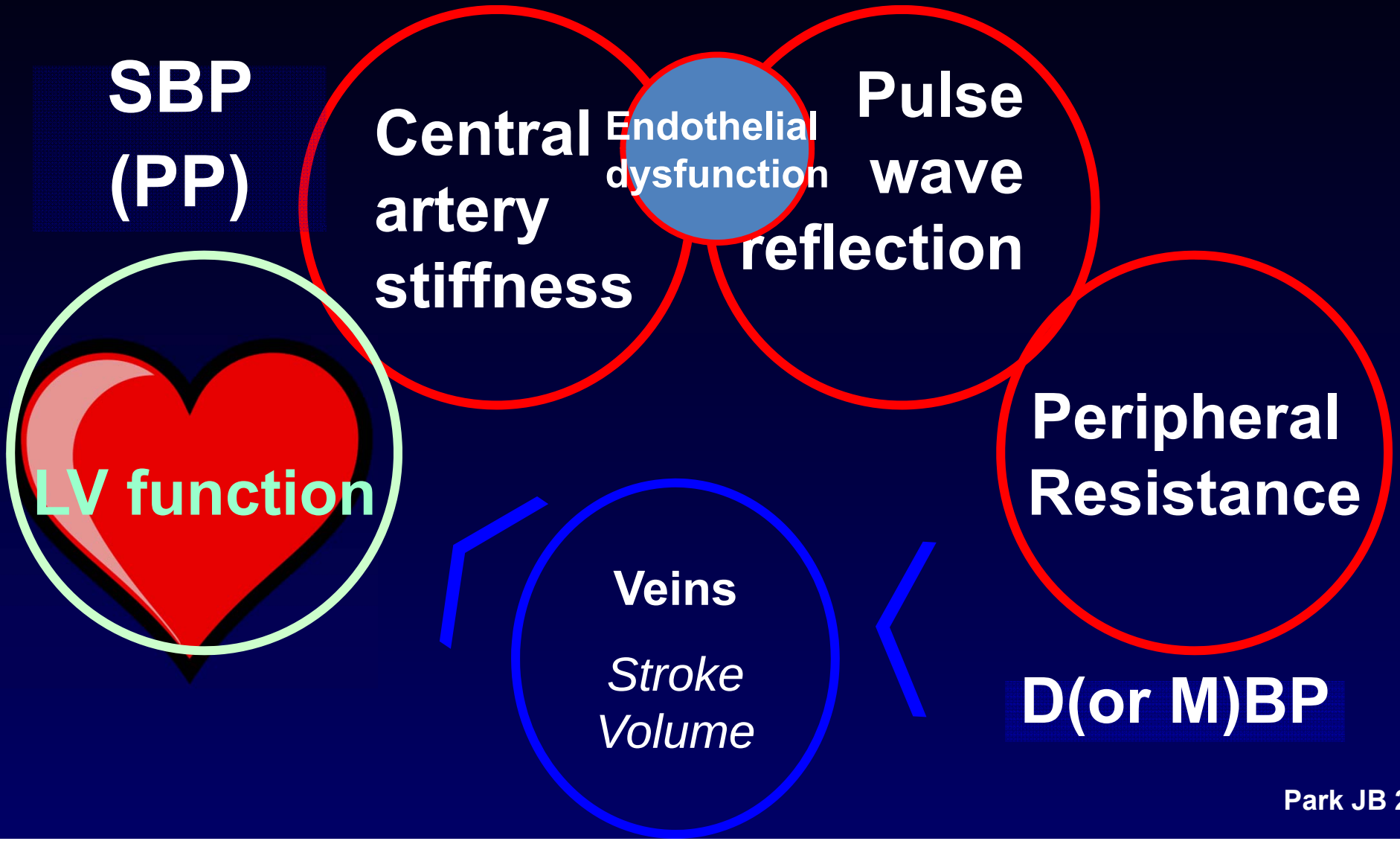
Park JB 2008

Large/small artery cross-talk



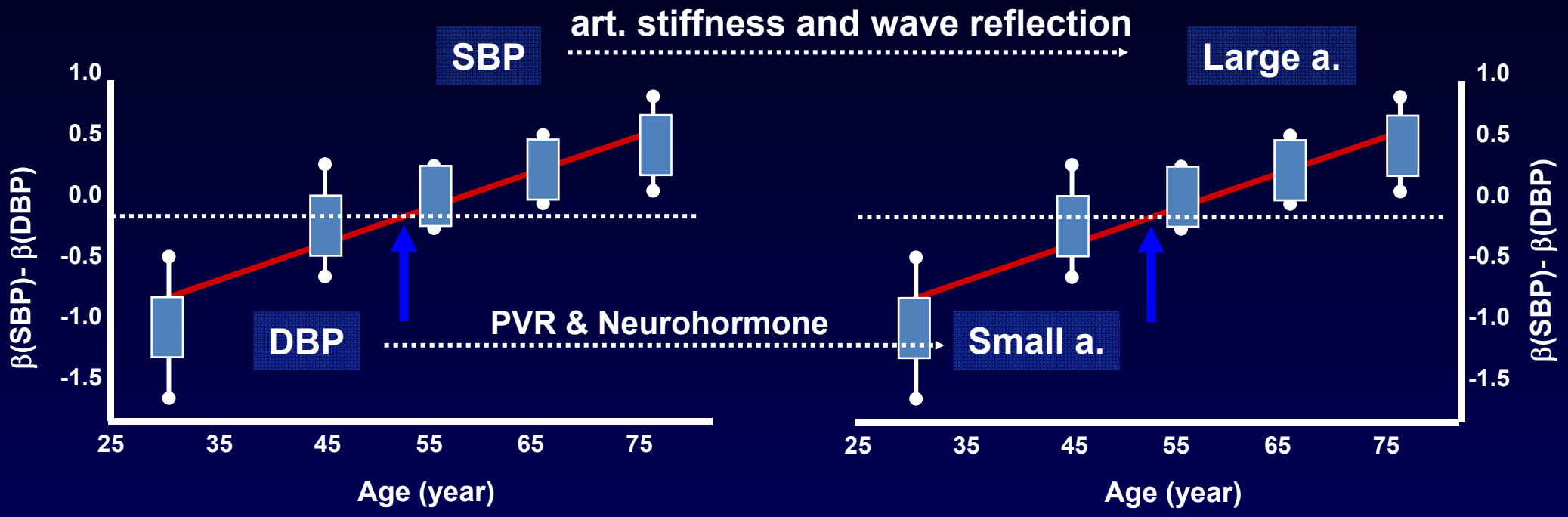
Laurent S et al.
Hypertension2009;54:388

Determinants of Arterial Pressure and its Reversal in Hypertension : Pulse and flow



Park JB 2009

Difference of CVD prediction between systolic and diastolic BP as a function of age

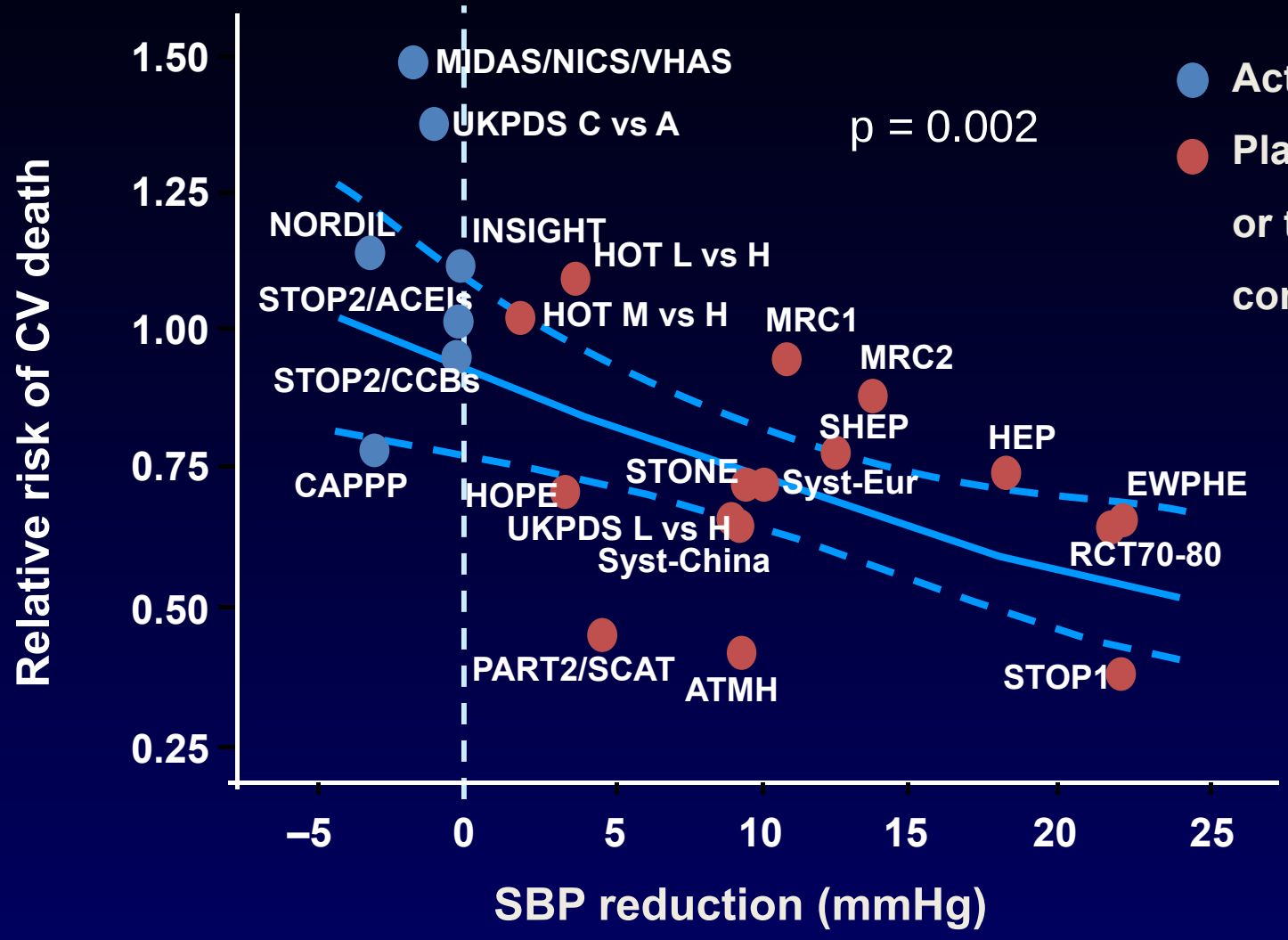


2003 JNC VII

Park JB 2006

Disparity of drug
on vascular changes
will results
in different outcome
in CVD and stroke?

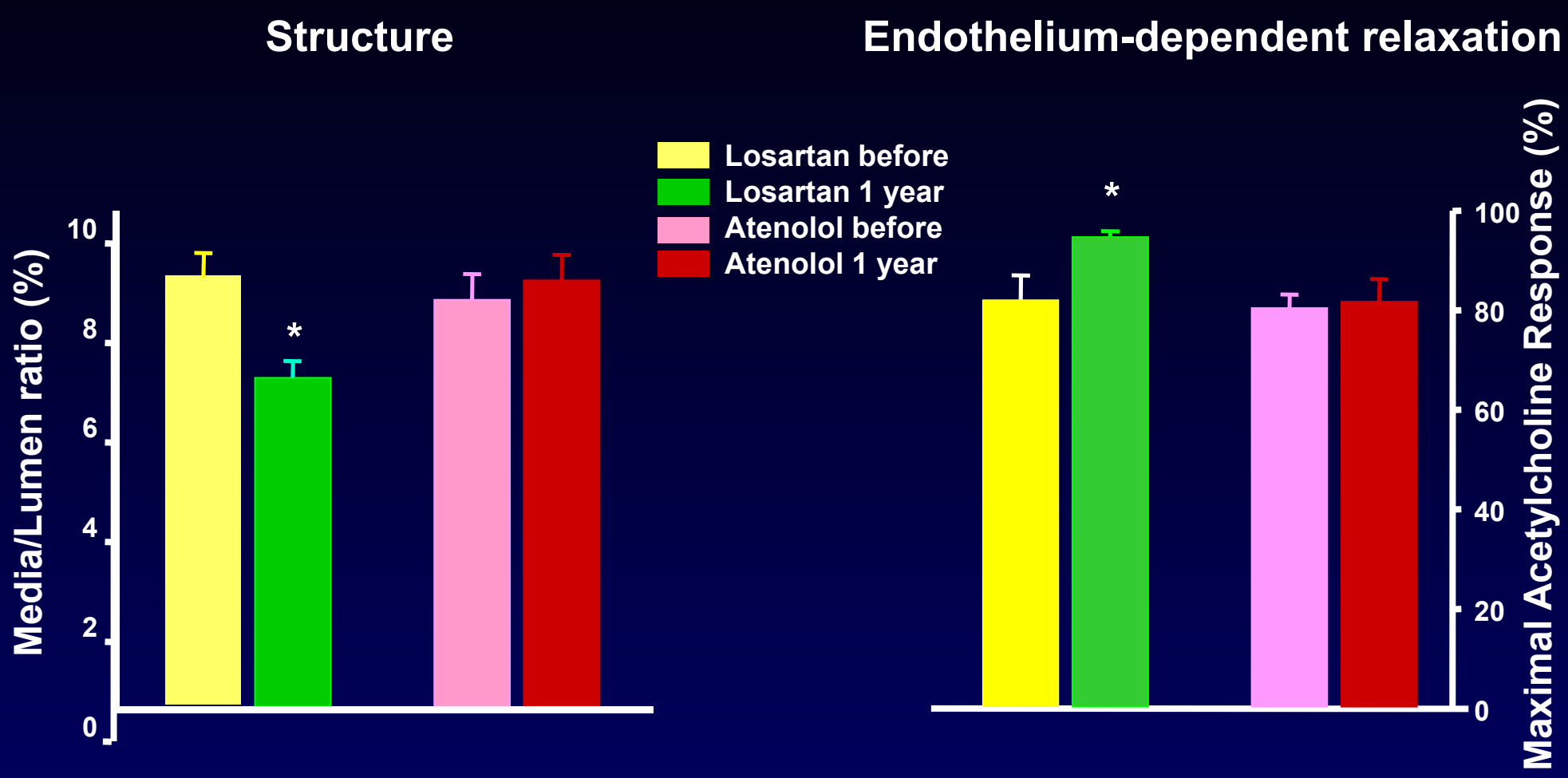
BP reduction reduces CV risk



Staessen et al. Hypertens Res. 2005;28:385-407.

Small artery

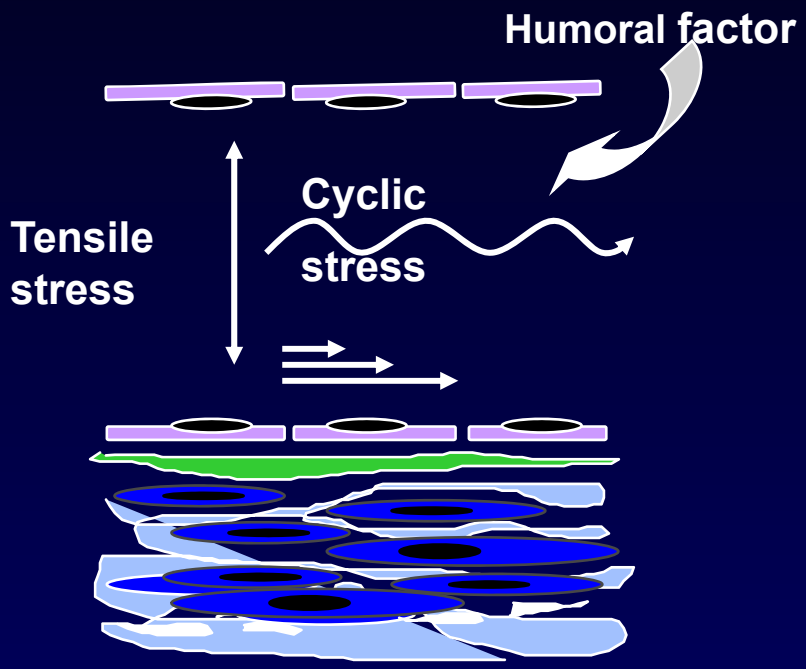
1-Year Treatment Effects of Losartan and Atenolol on Small Artery Structure and Function in Hypertension



Schiffrin and Park..Circulation 2000

Differential Effects of Antihypertensive Therapy on Small Artery in Hypertension : 1-Year F/U

Normotension	Hypertension	ACEi/ARB CCB	Atenolol



Hypertension	ACEi/ARB CCB		Atenolol
↑ Blood Pressure	↓	≈	↓
Vascular Remodeling ↑ media/lumen ratio	↓		↔
Endothelial Dysfunction ↓ Ach response	↑		↔
Vascular Stiffness ↔ stress/strain	↓		↔

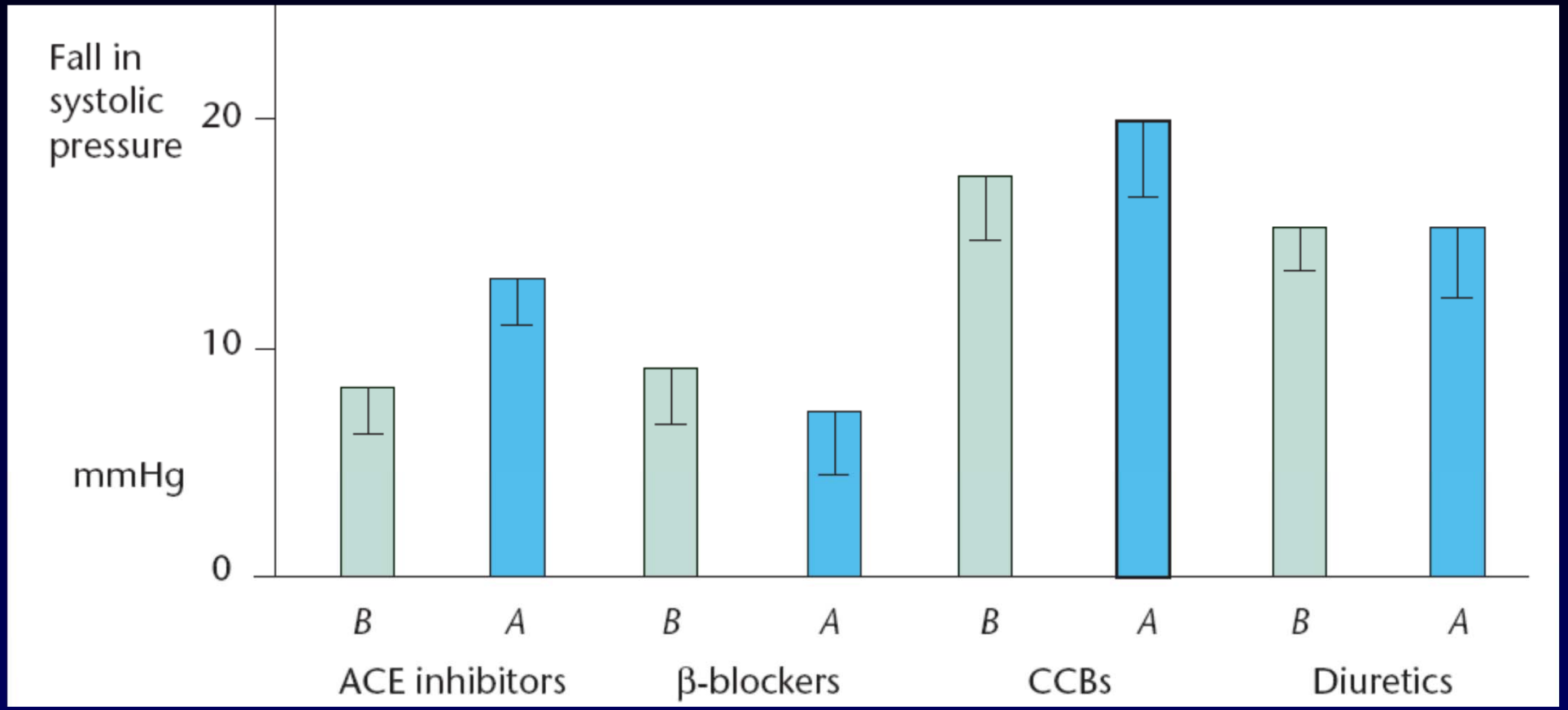
Park JB and Schiffrin EL et al. *Circulation, Hypertension, J Hypertens, Am J Hypertens, Curr Hypertens Reports, J Renin Angiotens System….*

Pharmacological treatment associated with a reduction in arterial stiffness

Antihypertensive treatment	ACE inhibitors/AT1 blockers Aldosterone blockers Calcium channel blockers Diuretics β-Blockers
Treatment of congestive heart failure	ACE inhibitors Nitrates
NO donors	Nitrates Sinitrodil
Phosphodiesterase type-5 inhibitors	Sildenafil
Hypolipidemic agents	Statins Ezetimibe
Anti-inflammatory drugs	TNFα antagonists
Antidiabetic agents	Thiazolidinediones
AGE breakers	Alagebrium (ALT-711)

Large artery

Effect of the 4 main classes of antihypertensive drug on aortic (A) and brachial (B) pressure.

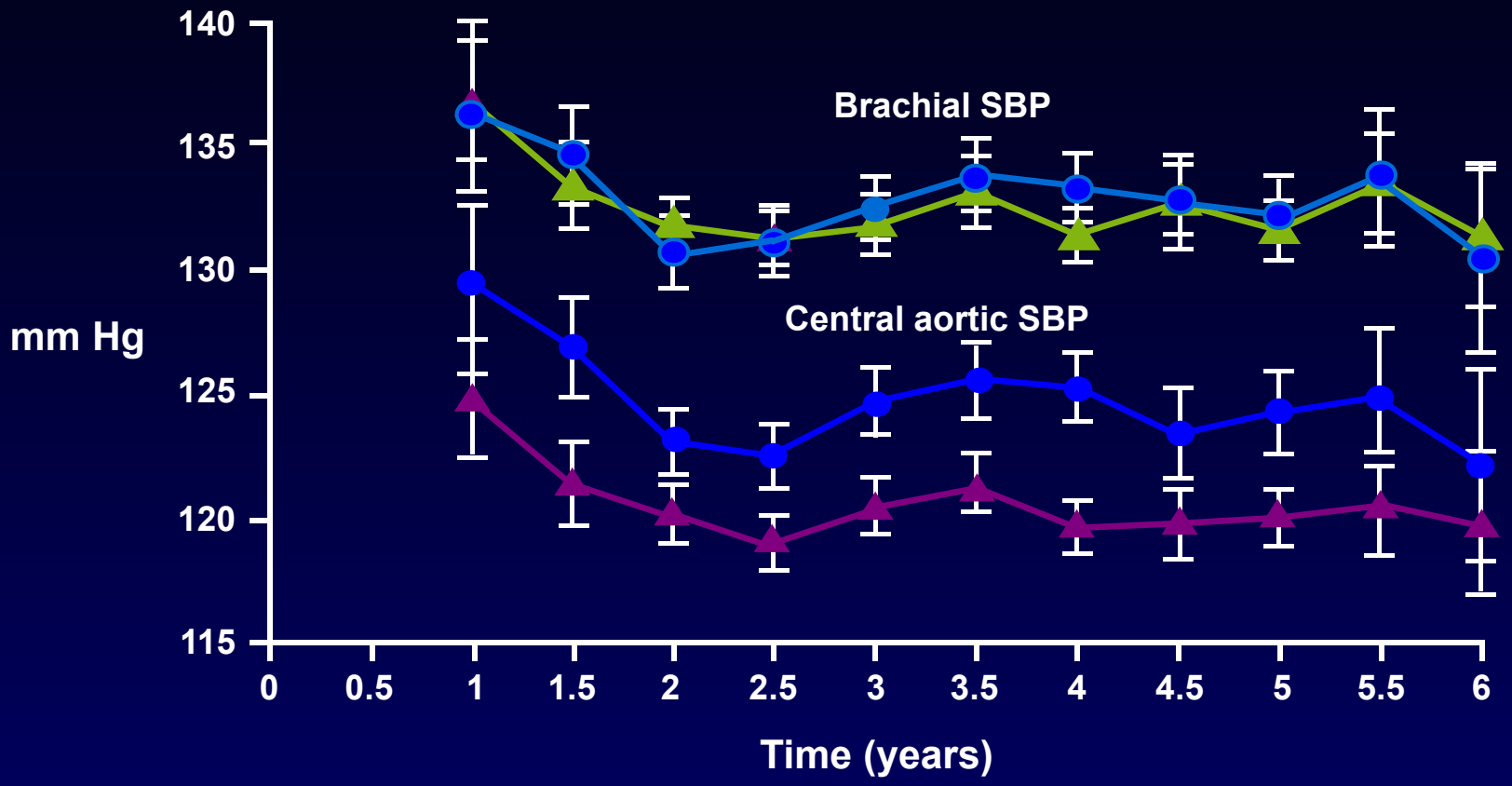


Morgan T, et al. Am J Hypertens 2004;17(2):118

Comparative effect of drugs on central hemodynamic indices

	Aortic pulse wave velocity	Augmentation index
ACE inhibitors	↓	↓↓
Angiotensin receptor blockers	↓	↓↓
β-Blockers	↓↓	↑
Calcium channel blockers	↓	↓↓
Thiazide diuretics	↔	↓
Nitrates	↔	↓↓↓
PD5 inhibitors	↓	↓

CAFE: Lower central aortic BP with newer vs older antihypertensive regimen despite similar brachial BP

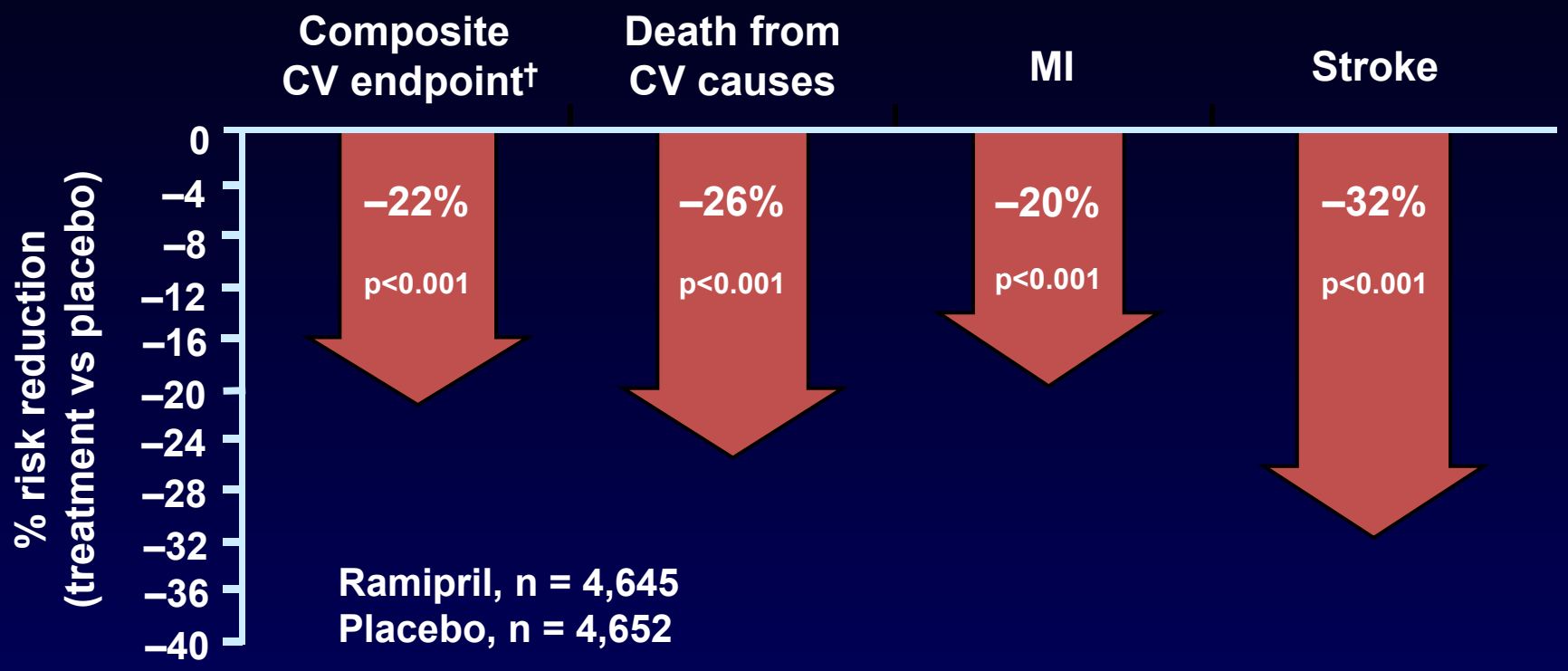


Amlodipine ± perindopril
Atenolol ± bendroflumethiazide

CAFE Investigators. *Circulation*. 2006;113:1213-25.

The ACEi ramipril reduces CV mortality and morbidity in CV high-risk patients

HOPE: CV high-risk patients; mean baseline SBP/DBP 139/79 mmHg

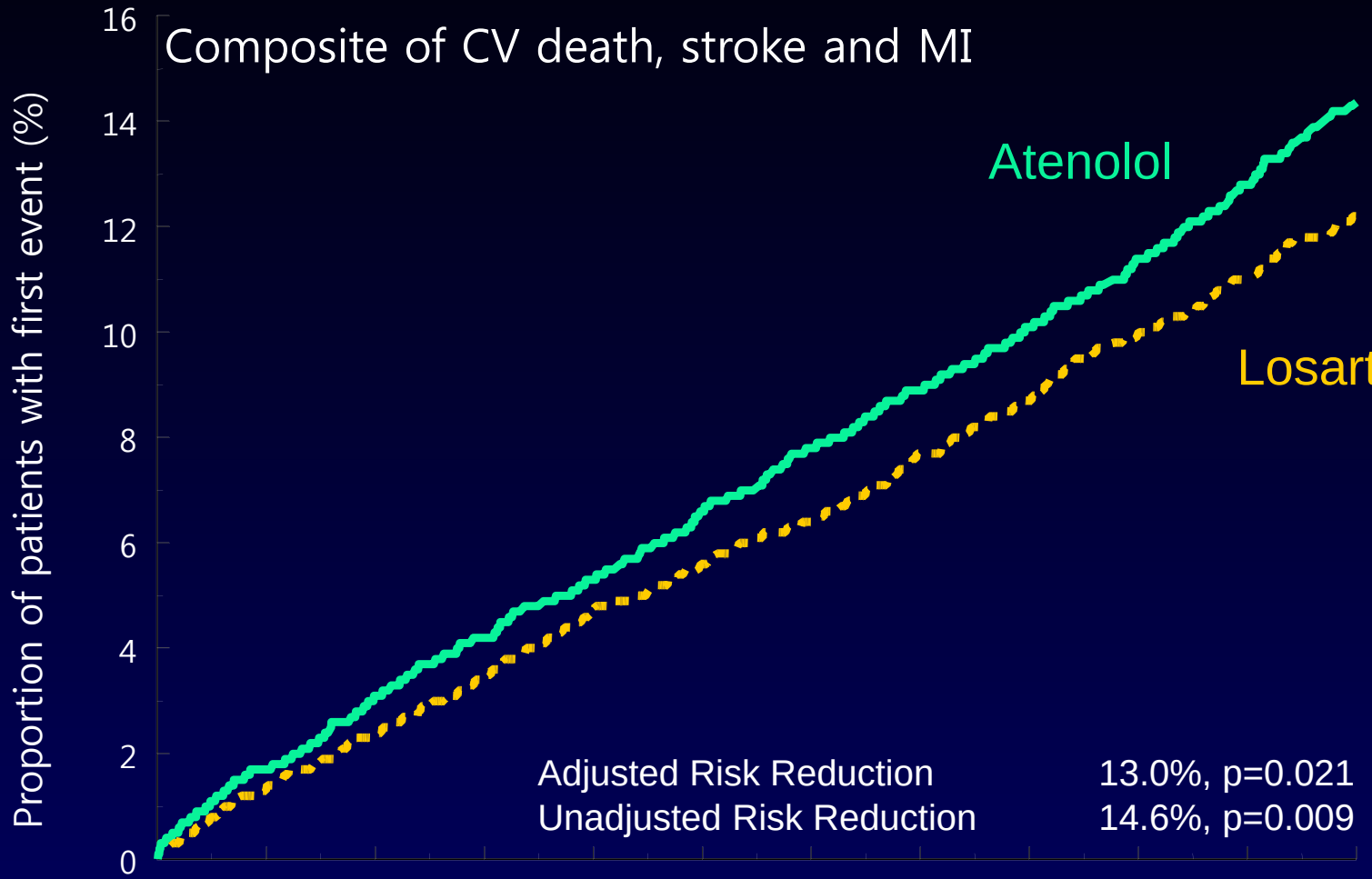


Ramipril, n = 4,645
Placebo, n = 4,652

† Composite CV endpoint = death from CV causes + MI + stroke
HOPE = Heart Outcomes Prevention Evaluation

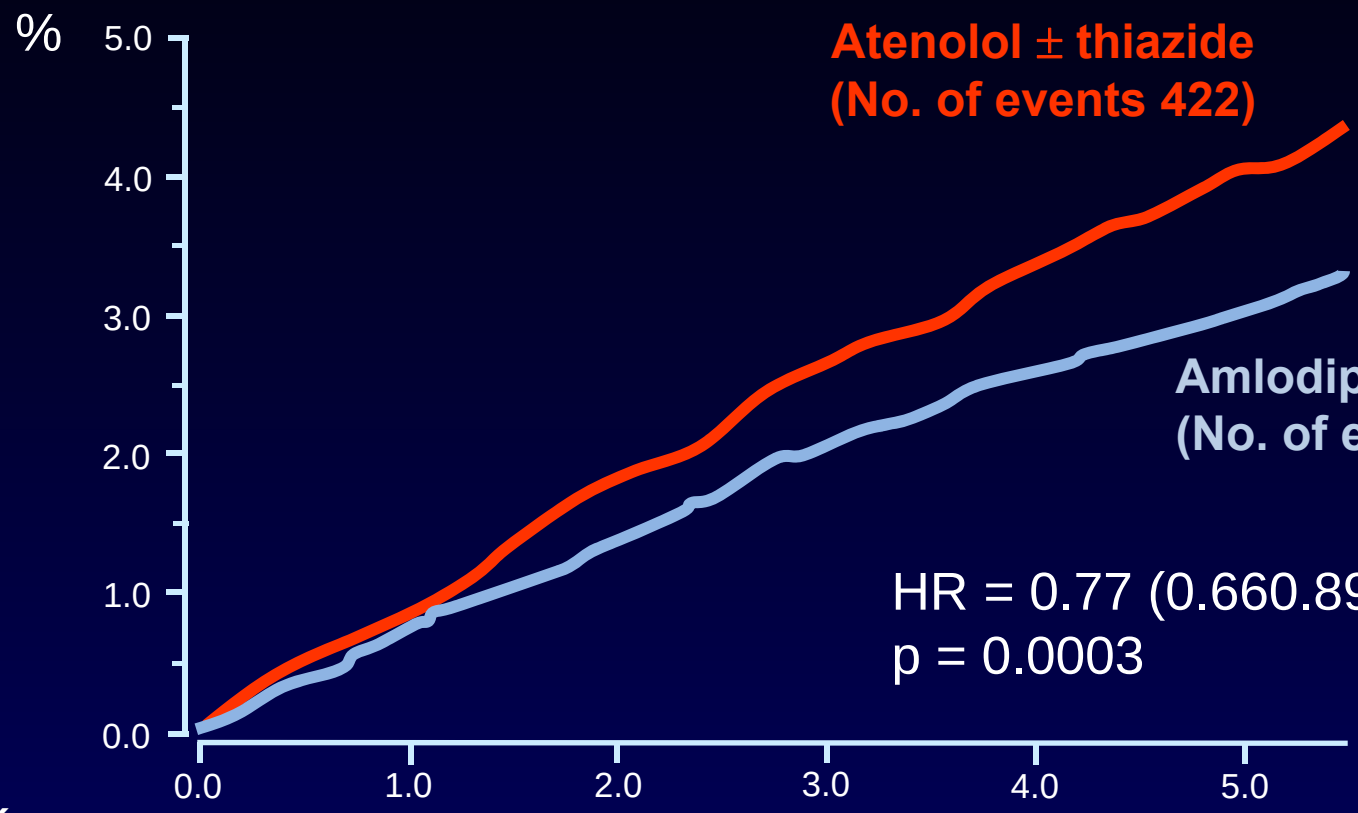
Yusuf et al. N Engl J Med 2000;342:145

LIFE Primary Composite Endpoint



Dahlöf B et al *Lancet* 2002;359:995-1003.

ASCOT: Fatal & Nonfatal Stroke

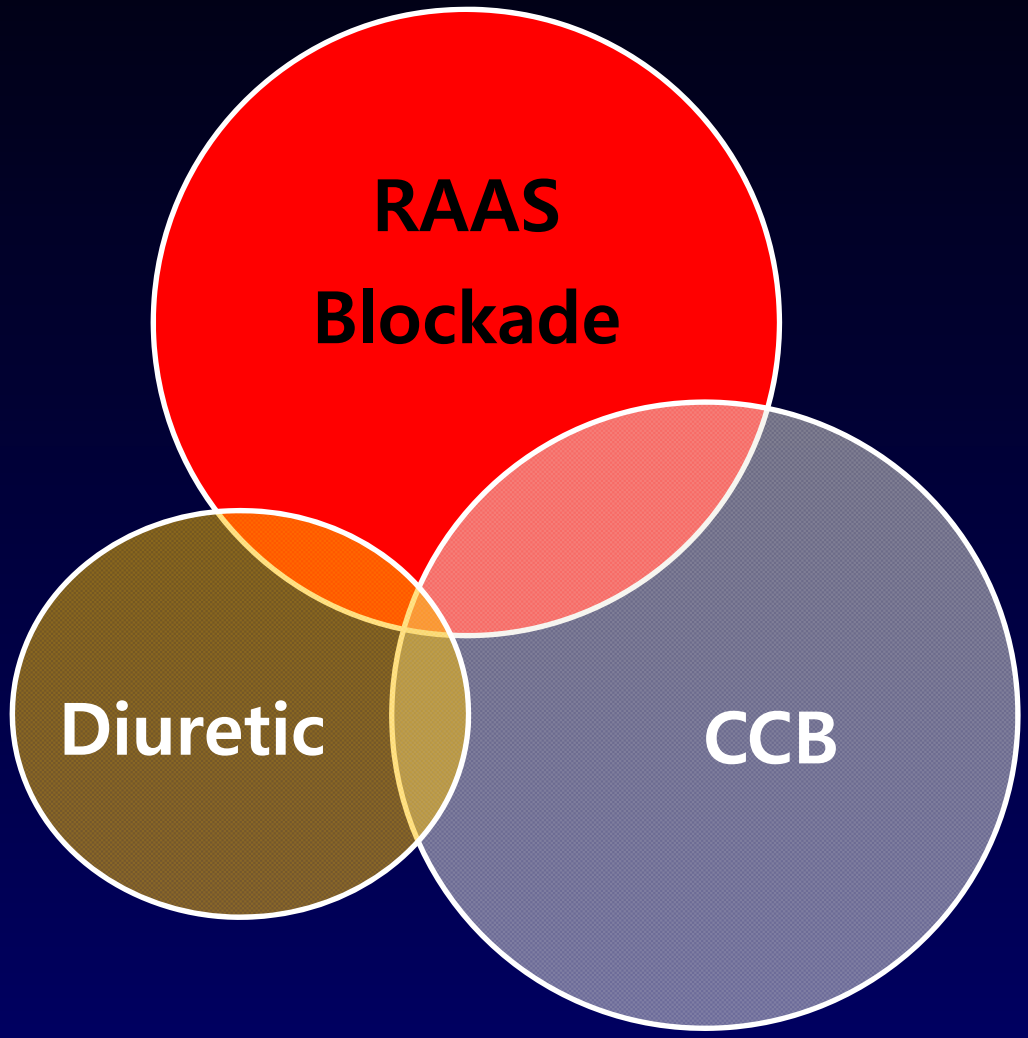


Number at risk

Amlodipine ± perindopril	9639	9483	9331	9156	8972	7863
Atenolol ± thiazide	9618	9461	9274	9059	8843	7720

Dahlöf et al. *Lancet* 2005;366:895-906

A, ~~B~~, C, and D drug in hypertension therapy



Vascular and Tissue Dysfunction in Hypertension

Vascular Dysfunction

Endothelial Dysfunction
Remodeling/Hypertrophy
Fibrosis
Atherosclerosis

Tissue Dysfunction

Cell loss
Fibrosis
Remodeling
Ischemia

Hypertension

Genetics,

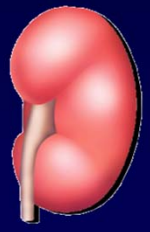
Risk factors (diabetes, hypercholesterolemia)

Environment (diet, smoking, stress)

Atherosclerosis*

Vasoconstriction
Vascular hypertrophy
Endothelial dysfunction

LVH
Fibrosis
Remodeling



GFR
Proteinuria
Aldosterone release
Glomerular sclerosis

Stroke

Hypertension

Heart failure
MI

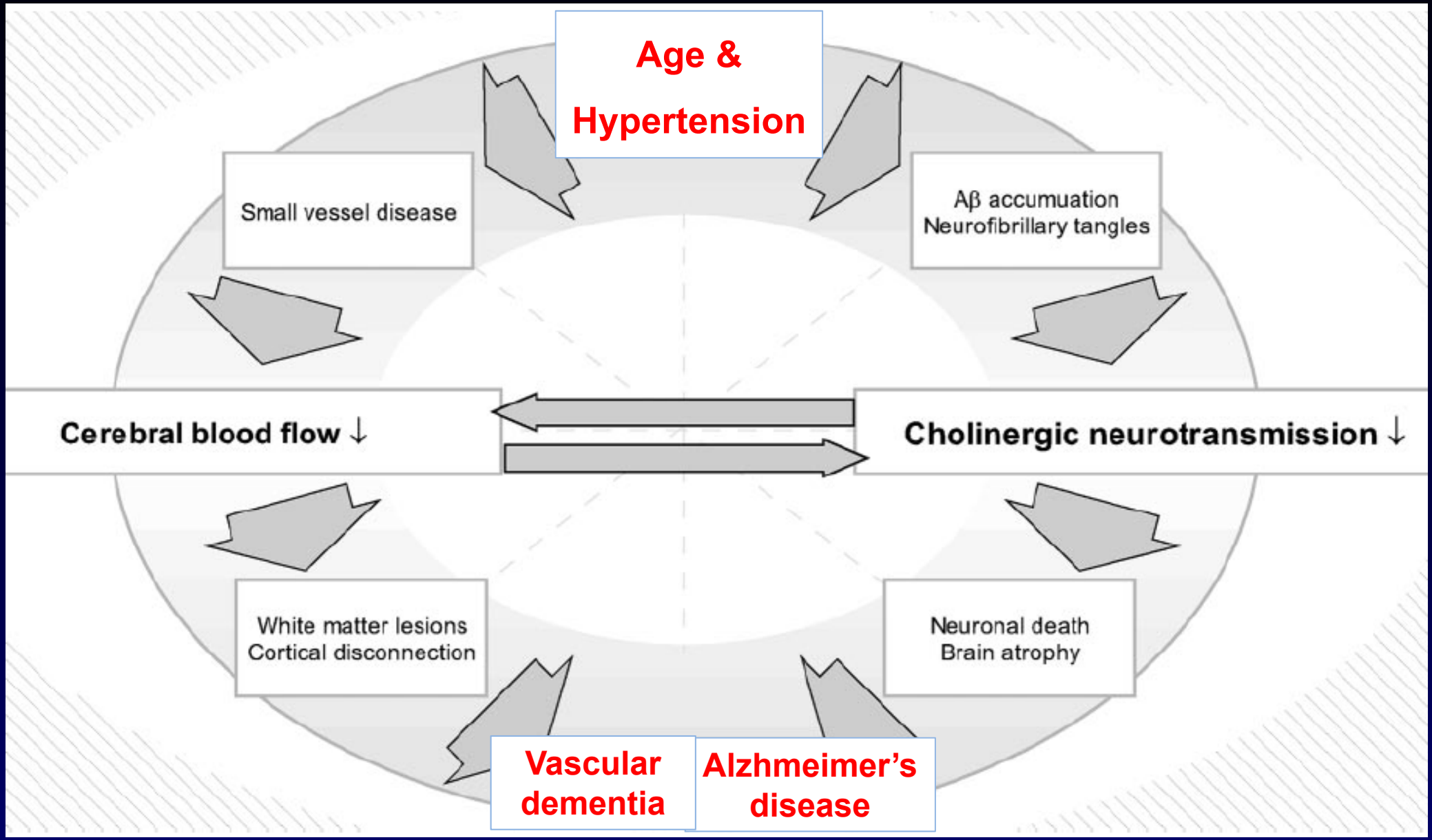
Renal failure

ACEi, ARB, CCB…

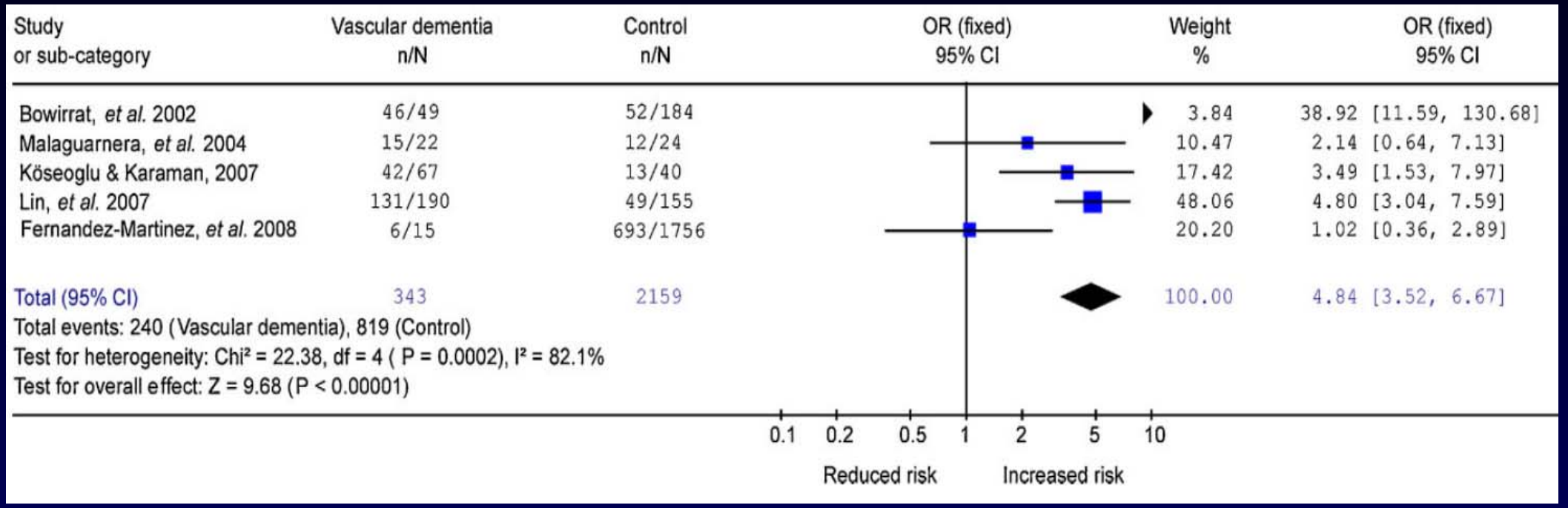
BP reduction reduces brain damage.

But how about on dementia ?

Hypertension aggravates dementia

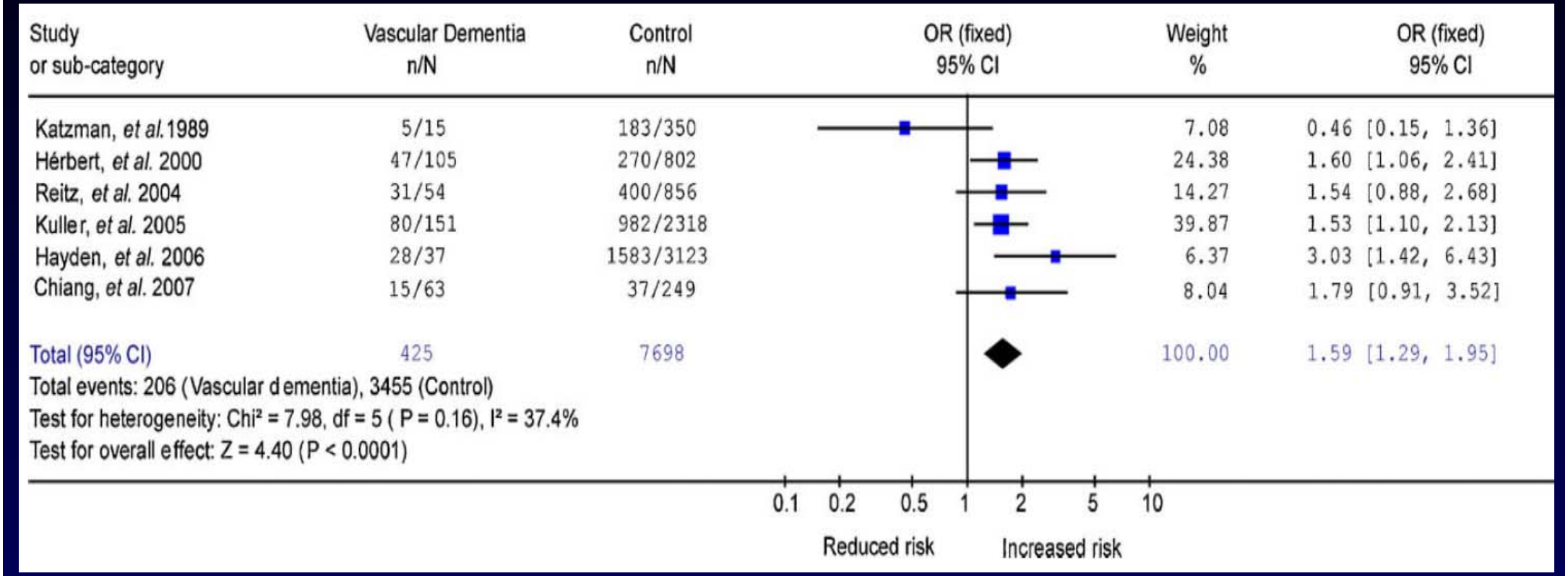


Association of hypertension with prevalence of vascular dementia.



Int J Geriatr Psychiatry 2011; 26: 661–669.

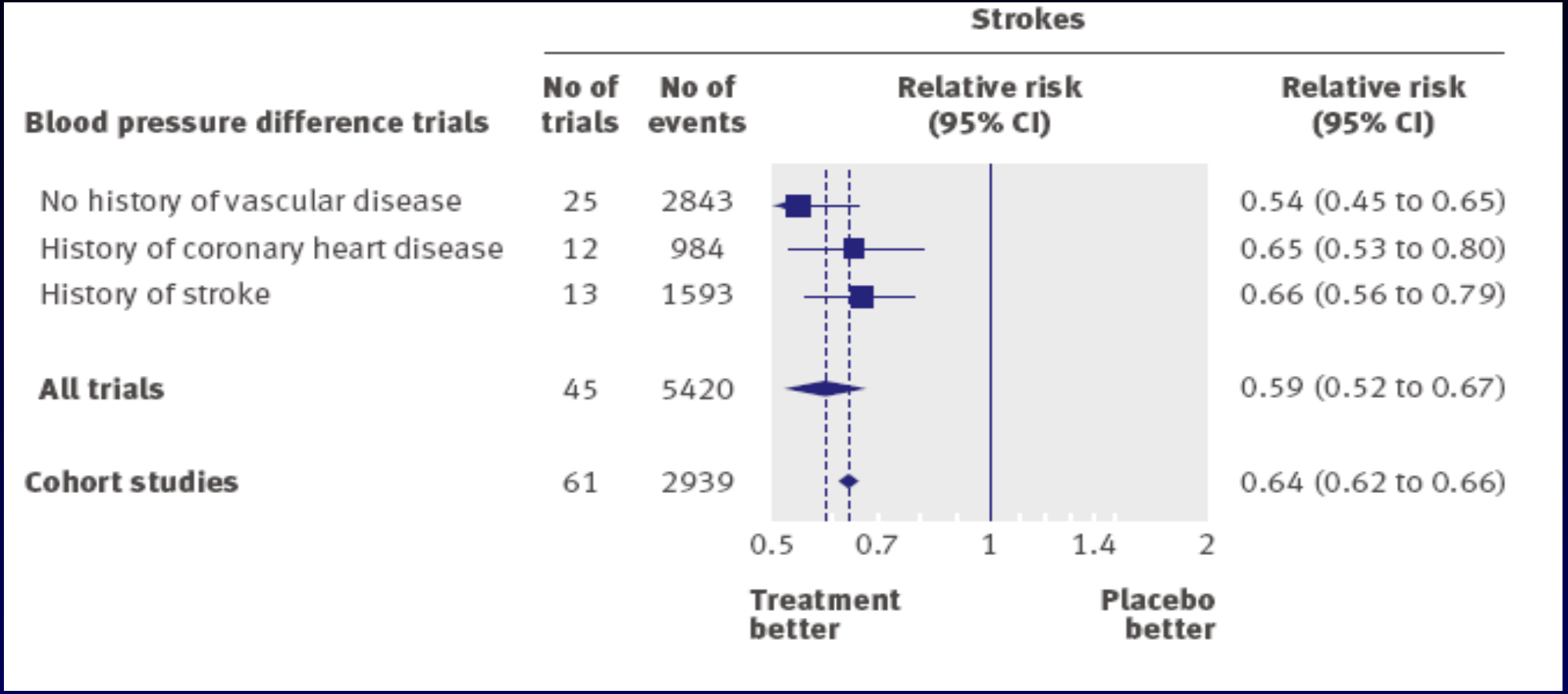
Association of hypertension with incidence of vascular dementia



Int J Geriatr Psychiatry 2011; 26: 661–669.

BP reduction and stroke

Law, BMJ 2009



Law, BMJ 2009

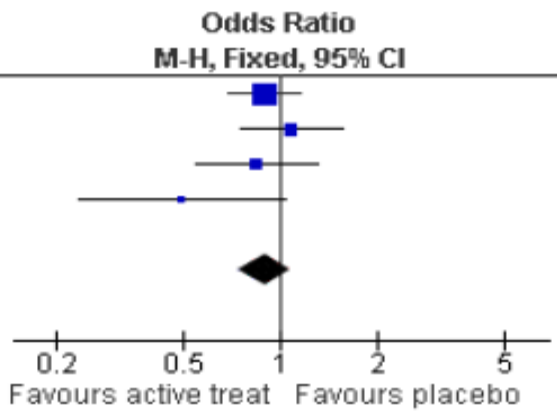
-> BP reduction reduces almost 40% of stroke incidence.

BP reduction and dementia

Incidence of Dementia

Study or Subgroup	Active treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
HYVET 2008	126	1687	137	1649	51.6%	0.89 [0.69, 1.15]
SCOPE 2003	62	2477	57	2460	22.4%	1.08 [0.75, 1.56]
SHEP 1991	37	2365	44	2371	17.4%	0.84 [0.54, 1.31]
Syst Eur 1997	11	1238	21	1180	8.6%	0.49 [0.24, 1.03]
Total (95% CI)		**7767**		**7660**	**100.0%**	**0.89 [0.74, 1.07]**
Total events	236		259			

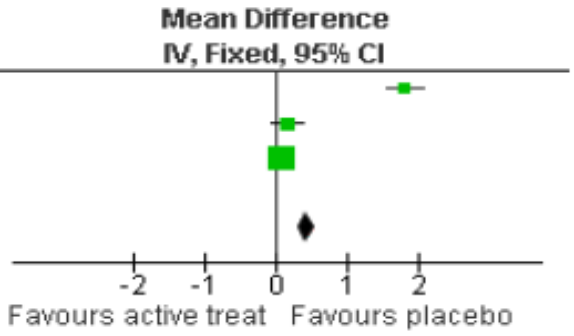
Heterogeneity: Chi² = 3.63, df = 3 (P = 0.30); I² = 17%
Test for overall effect: Z = 1.25 (P = 0.21)



Cognitive changes from baseline, outcome (MMSE)

Study or Subgroup	Active treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HYVET 2008	0.7	4	1687	-1.1	3.9	1649	18.9%	1.80 [1.53, 2.07]
SCOPE 2003	-0.49	4.07	2477	-0.64	4.07	2409	26.1%	0.15 [-0.08, 0.38]
Syst Eur 1997	0.08	1.76	1238	0.01	2.15	1180	55.1%	0.07 [-0.09, 0.23]
Total (95% CI)			**5402**			**5238**	**100.0%**	**0.42 [0.30, 0.53]**

Heterogeneity: Chi² = 126.25, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 7.03 (P < 0.00001)



➔ anti-HTN medication failed to show overall benefit over placebo in new dementia and worsening cognition

Mixed results on anti-hypertension drug on dementia & cognition

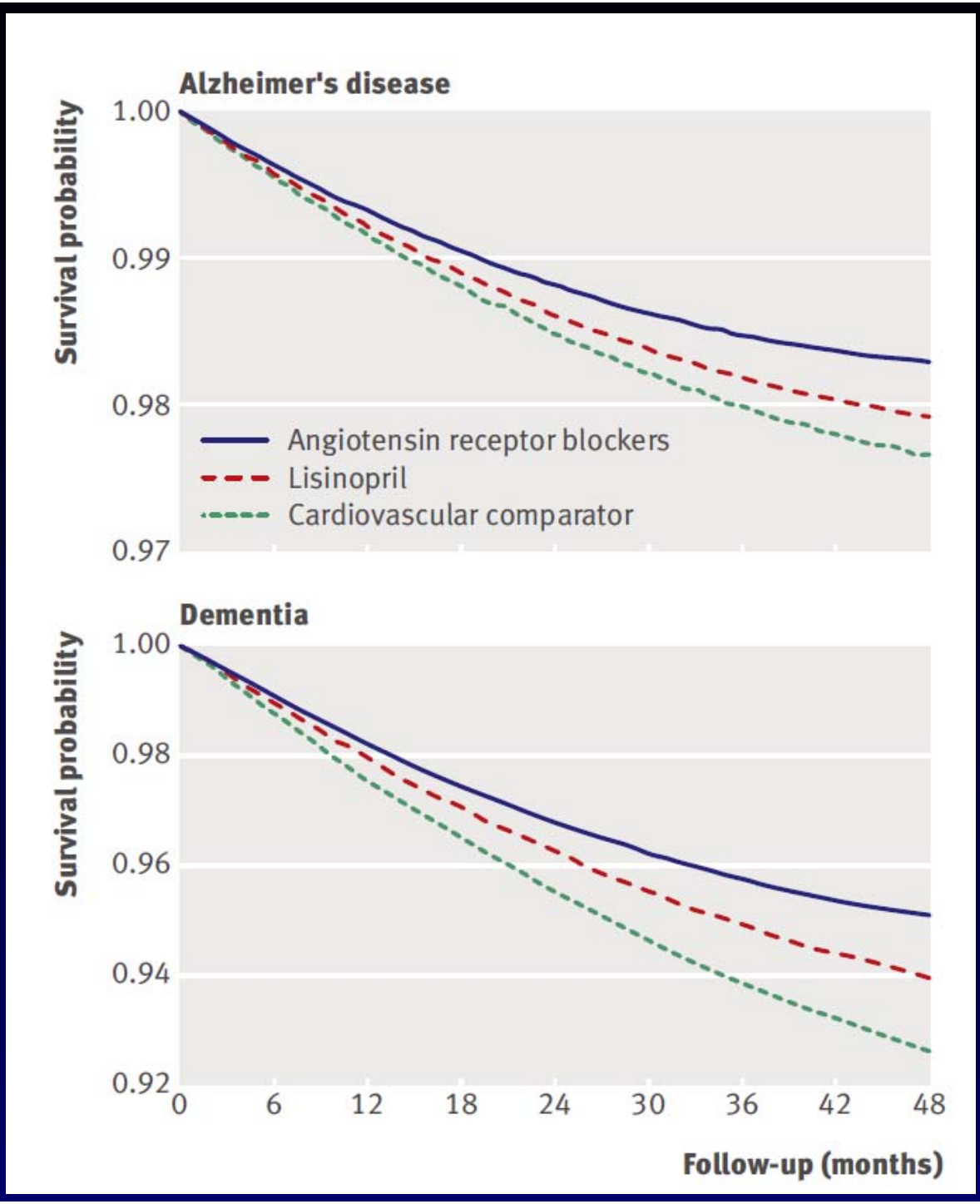
- Diuretics and ß-B were neutral in developing cognitive impairment in SHEP (1991, 1994) and MRC Older (1996, 1997) .
- Antihypertensive therapy might even reverse hypertension-related cognitive impairment (Starr et al., 1996).
- BP lowering in patients without prior cerebrovascular disease did not prevent cognitive impairment or dementia (2004).
- CCBs and ARBs have shown more positive outcomes, (Syst-Eur,1998 and SCOPE, 2003) along with preliminary data from OSCAR study (2007).
- Meta-analysis of 3 trials suggests a significant benefit with respect to cognition (2008).
- Use of antihypertensive drugs in a longitudinal study was associated with an 8% reduced risk per year for dementia and AD for people <75 years of age (2009).

Effects of RAS blockage on cognition and dementia in Hypertension?

Survival function for incident Alzheimer's disease and incident dementia in prospective study cohorts

Setting: Administrative database of the US Veteran Affairs, 2002-6.
Population: **819 491** predominantly male (98%) aged 65 or more with cardiovascular disease.

Nien-Chen Li et al.
BMJ 2010;340:b5465



Cox proportional hazard model for association between ARBs and incidence of Alzheimer's disease or dementia

	Incidence of Alzheimer's disease			Incidence of dementia		
Variables	Estimate (SE)	P value	Hazard rate (95% CI)	Estimate (SE)	P value	Hazard rate* (95% CI)
Angiotensin receptor blocker *v* lisinopril	−0.213 (0.089)	0.016	0.81 (0.68 to 0.96)	−0.207 (0.053)	<0.001	0.81 (0.73 to 0.90)
Angiotensin receptor blocker *v* cardiovascular comparator	−0.171 (0.085)	0.045	0.84 (0.71 to 1.00)	−0.269 (0.051)	<0.001	0.76 (0.69 to 0.84)
Lisinopril *v* cardiovascular comparator	0.043 (0.029)	0.145	1.04 (0.99 to 1.11)	−0.061 (0.017)	0.0004	0.94 (0.91 to 0.97)
Age	0.101 (0.001)	<0.001	1.11 (1.10 to 1.11)	0.087 (0.001)	<0.001	1.09 (1.09 to 1.09)
Cardiovascular disease	−0.011 (0.017)	0.505	0.99 (0.96 to 1.02)	0.062 (0.010)	<0.001	1.06 (1.04 to 1.09)
Diabetes	0.039 (0.020)	0.049	1.04 (1.00 to 1.08)	0.158 (0.011)	<0.001	1.17 (1.15 to 1.20)
Stroke	0.694 (0.018)	<0.001	2.00 (1.93 to 2.07)	0.940 (0.010)	<0.001	2.56 (2.51 to 2.61)

*Adjusted for age, stroke, cardiovascular disease, and diabetes.

BMJ 2010;340:b5465

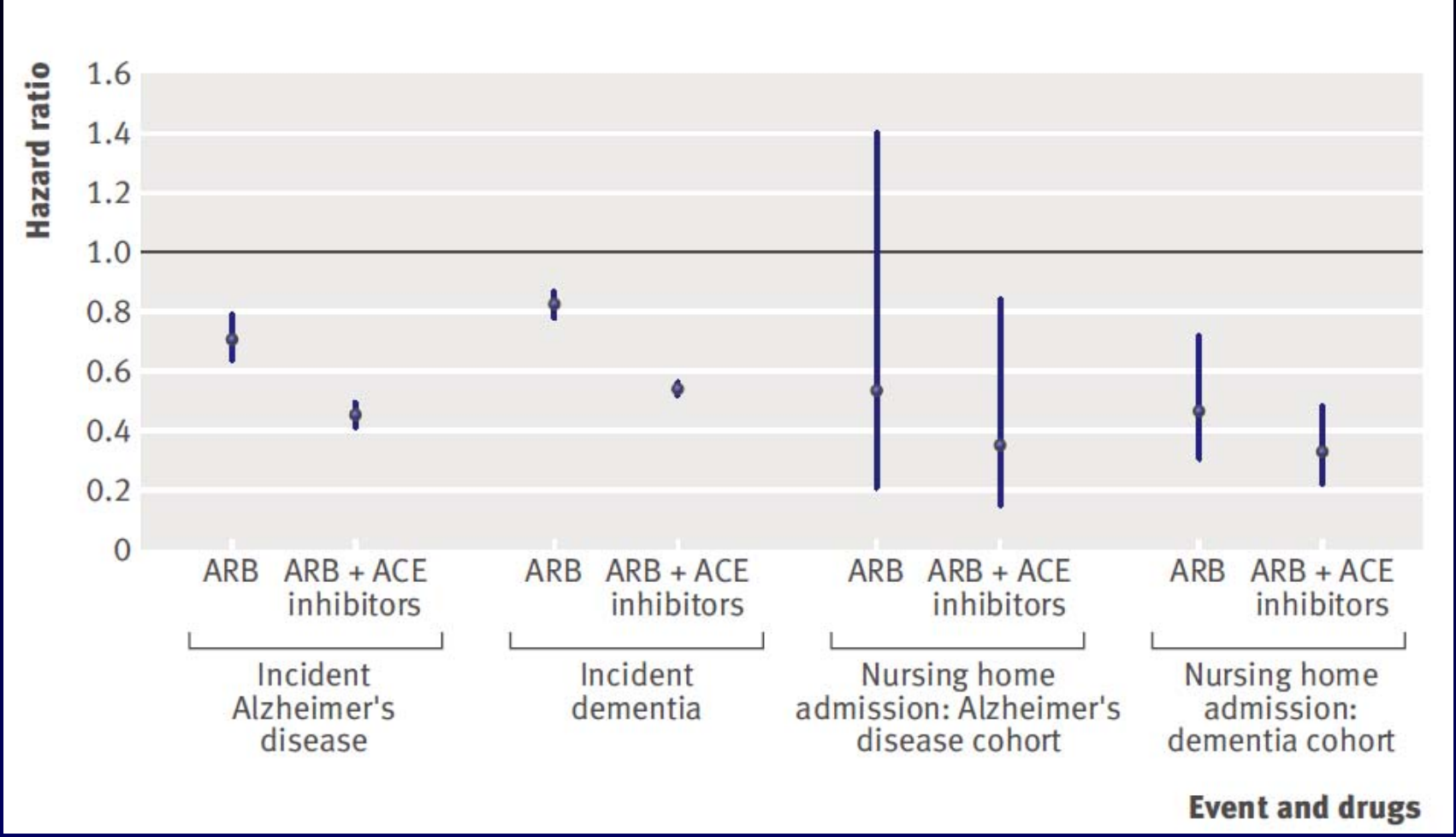
Effect of ARB dosage (high v low) on incidence of dementia

Angiotensin receptor blocker	Estimate (SE)	P value	Hazard rate* (95% CI)
Candesartan	−0.322 (0.076)	‹0.001	0.73 (0.62 to 0.84)
Irbesartan	−0.174 (0.044)	‹0.001	0.84 (0.77 to 0.92)
Losartan	−0.200 (0.066)	0.0025	0.82 (0.72 to 0.93)
Valsartan	−0.103 (0.198)	0.602	0.91 (0.61 to 1.33)

*Cox proportional hazard model adjusted for age, cardiovascular disease, diabetes, and stroke.

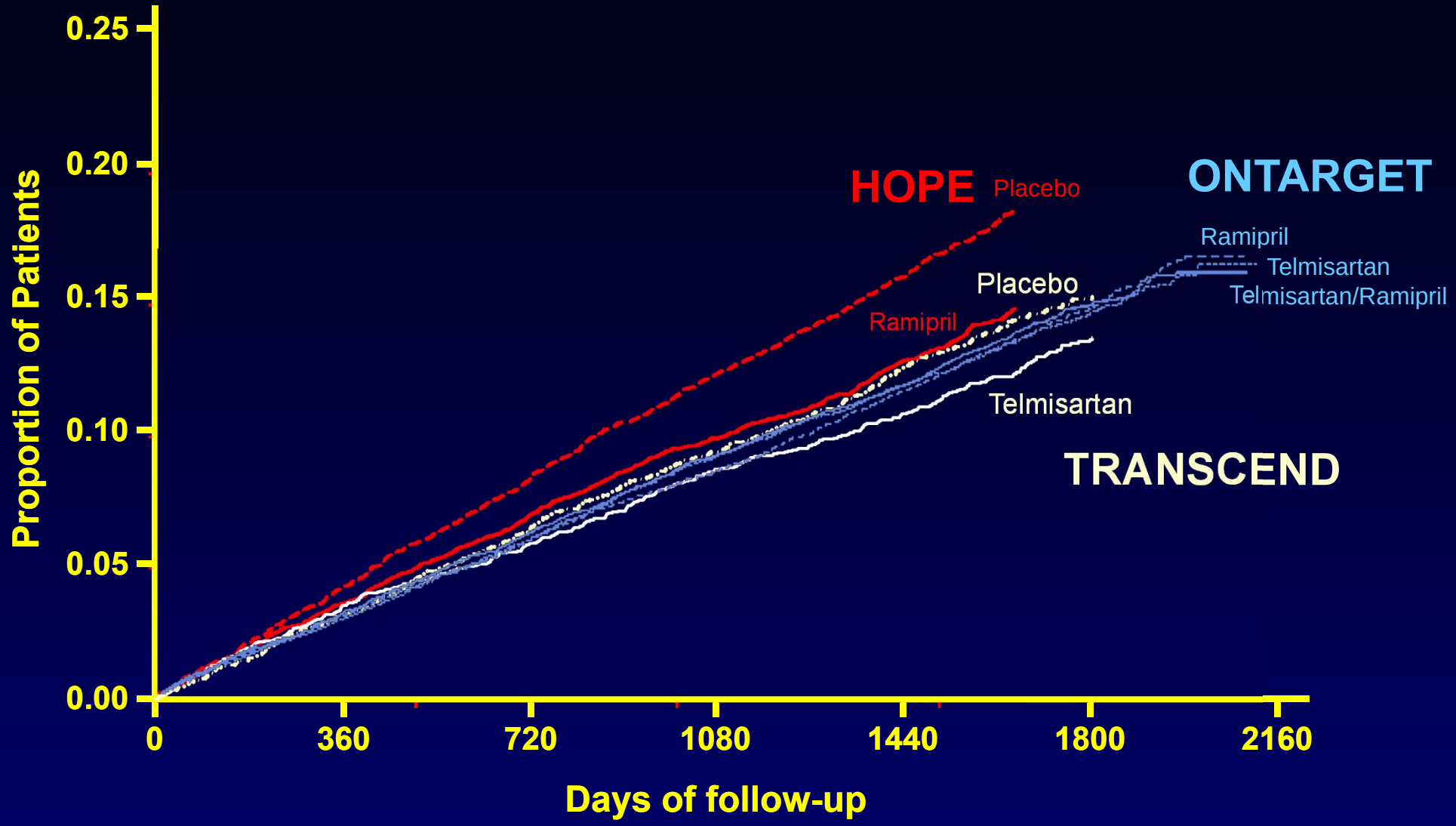
BMJ 2010;340:b5465

Additive effects of ARB and ACE inhibitors compared with single drug use. Hazard rates are adjusted for age, stroke, diabetes, and cardiovascular disease



BMJ 2010;340:b5465

Major Studies in RAS-Inhibition (HOPE Composite) Global Protection



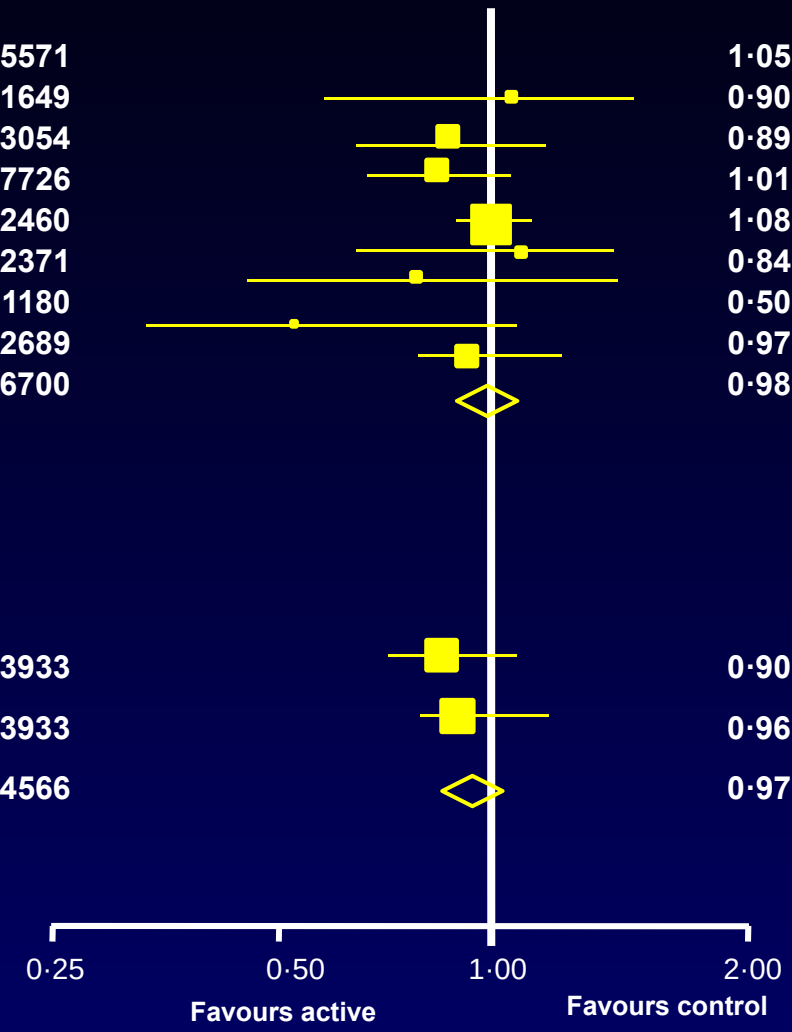
Cognitive outcomes in the TRANSCEND

	Telmisartan	Placebo	Telmisartan vs placebo	
			OR (95% CI)	p value
Number randomised	2954	2972	••	••
Number with MMSE	2642	2589	••	••
Primary outcomes				
▪ Cognitive impairment*	239/2694 (9%)	245/2689 (9%)	0·97 (0·81–1·17)	0·76
▪ Cognitive decline†	454/2642 (17%)	412/2589 (16%)	1·10 (0·95–1·27)	0·22
Secondary outcomes				
▪ Cognitive decline or impairment‡	520/2914 (18%)	487/2909 (17%)	1·08 (0·94–1·24)	0·27
▪ Cognitive impairment or stroke	318/2694 (12%)	330/2689 (12%)	0·96 (0·81–1·13)	0·60
▪ Cognitive impairment, MMSE score <18§	127/2917 (4%)	111/2932 (4%)	1·16 (0·89–1·50)	0·27

Lancet Neurol 2011; 10: 43–53

Effects of BP lowering on cognitive impairment

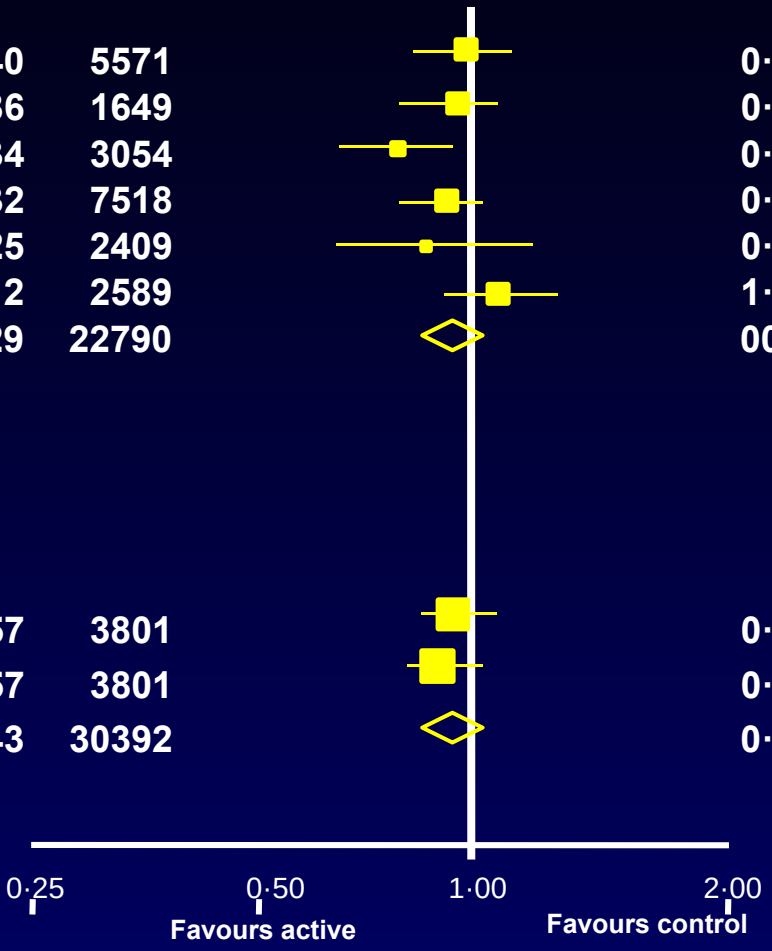
	Active		Control		Relative risk, random (95% CI)
	Event	n	Event	n	
Cognitive impairment					
Active vs placebo					
ADVANCE	39	5569	37	5571	1·05 (0·67–1·65)
HYVET-COG	126	1687	137	1649	0·90 (0·71–1·13)
PROGRESS	193	3051	217	3054	0·89 (0·74–1·07)
PRoFESS	1178	7739	1162	7726	1·01 (0·94–1·09)
SCOPE	62	2477	57	2460	1·08 (0·76–1·54)
SHEP	37	2365	44	2371	0·84 (0·55–1·30)
Syst-Eur	11	1238	21	1180	0·50 (0·24–1·03)
TRANSCEND	239	2694	245	2689	0·97 (0·82–1·15)
Subtotal	1885	26820	1920	16700	0·98 (0·92–1·04)
Test for homogeneity: χ^2=6·44; df=7 (p=0·49)					
Test for overall effect: Z=0·63 (p=0·53)					
Head to head					
ONTARGET (ARB vs ACEI)*	584	7897	326	3933	0·90 (0·79–1·03)
ONTARGET (ARB+ACEI vs ACEI)*	618	7807	326	3933	0·96 (0·84–1·09)
Total	3087	42424	2572	34566	0·97 (0·92–1·01)
Test for homogeneity: χ^2=7·73; df=9 (p=0·56)					
Test for overall effect: Z=1·39 (p=0·17)					



Lancet Neurol 2011; 10: 43–53

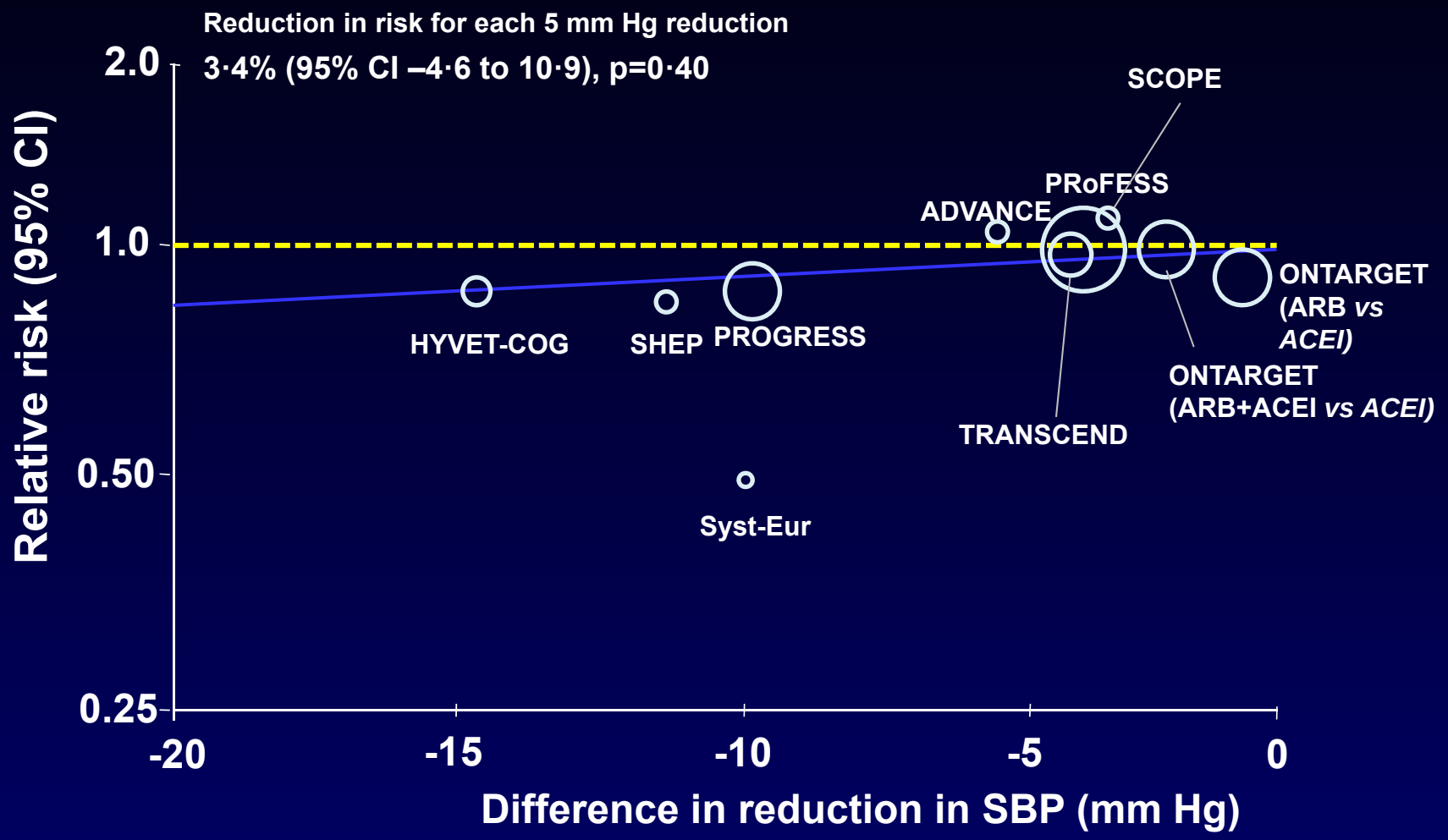
Effects of BP lowering on cognitive decline

	Active		Control		Relative risk, random (95% CI)
	Event	n	Event	n	
Cognitive decline					
Active vs placebo					
ADVANCE	633	5569	640	5571	0·99 (0·89–1·10)
HYVET-COG	485	1687	486	1649	0·98 (0·88–1·08)
PROGRESS	276	3051	334	3054	0·83 (0·71–0·96)
PRoFESS	795	7739	832	7518	0·95 (0·87–1·05)
SCOPE	113	2477	125	2409	0·90 (0·70–1·16)
TRANSCEND	454	2694	412	2589	1·08 (0·96–1·22)
Subtotal	2276	26820	2829	22790	00·97(0·91–1·03)
Test for homogeneity: χ^2=7·85; df=5 (p=0·17)					
Test for overall effect: Z=1·10 (p=0·27)					
Head to head					
ONTARGET (ARB vs ACEI)*	1279	7566	657	3801	0·98 (0·90–1·07)
ONTARGET (ARB+ACEI vs ACEI)*	1240	7461	657	3801	0·96 (0·88–1·05)
Total	5275	37923	4143	30392	0·97 (0·93–1·01)
Test for homogeneity: χ^2=7·73; df=9 (p=0·56)					
Test for overall effect: Z=1·39 (p=0·17)					



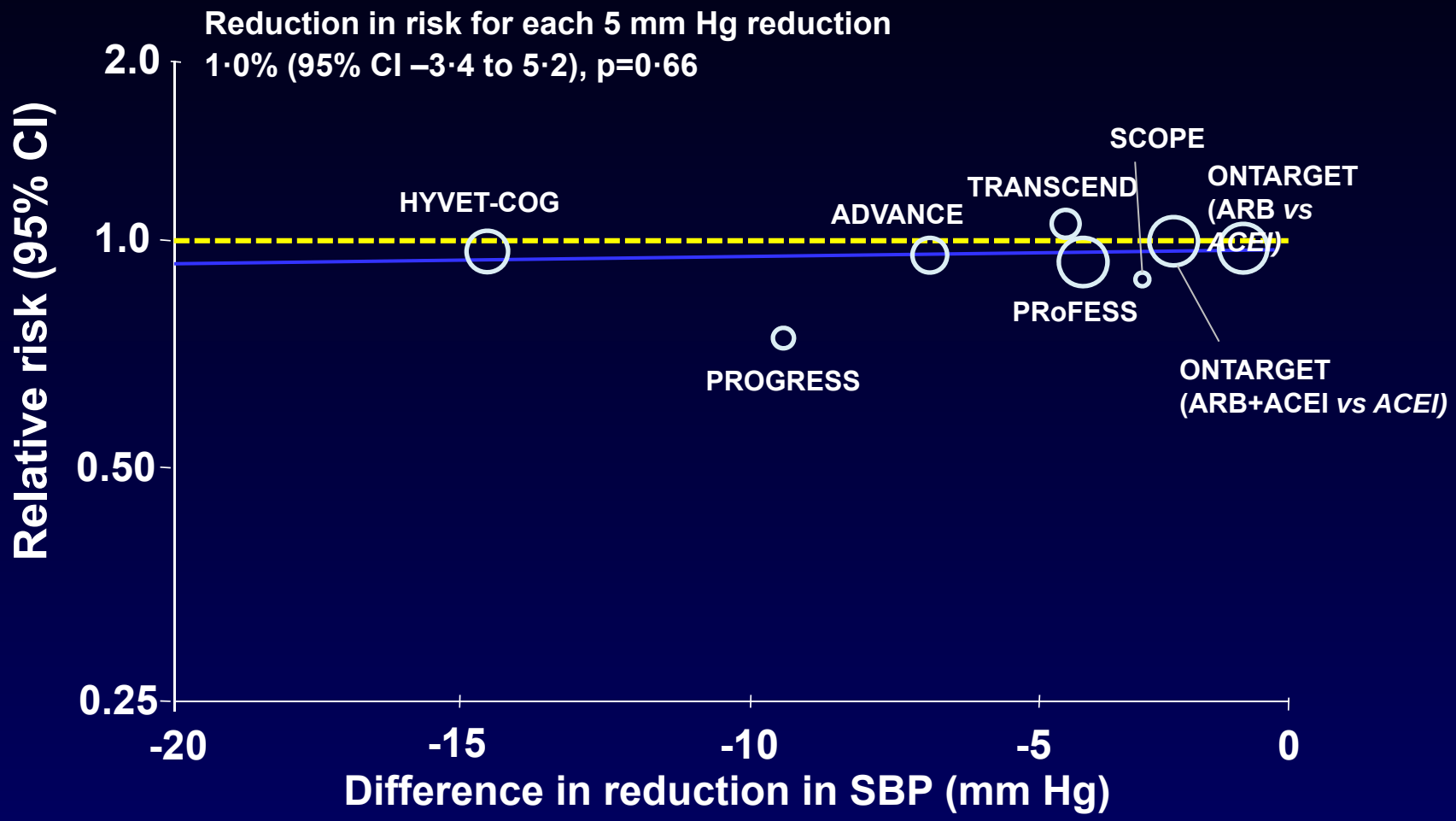
Lancet Neurol 2011; 10: 43–53

Association of reduction in SBP with risk reduction for cognitive impairment



Lancet Neurol 2011; 10: 43–53

Association of reduction in SBP with risk reduction for cognitive decline



Lancet Neurol 2011; 10: 43–53

Summary I: Brain and hypertension

- Hypertension is vascular damages in brain.
  - Atherosclerosis, in middle-sized arteries (ICA, MCA…)
  - Arteriolosclerosis, small arterioles (LS aa, perforating aa)
- Small-vessel disease in hypertension
  - Leukoaraiosis
  - Lacunar infarction
  - Cerebral microbleeds
- Cognitive decline in elderly
  - worsening under hypertension

Summary II: Brain and hypertension

- BP reduction is not a skeleton key for the reduction of cognitive impairment and dementia, even though hypertension treatment decrease stroke and CVD incidence.
  - No overall benefit of dementia incidence by hypertension treatment
  - Suggestive of worsening cognitive deficit by BP lowering?
- RAS blockade, esp. ARB may be better?

Perhaps?

Mechanisms of the potential superior effects of ARBs on cognition

- Restoring proper central endothelial function,
- Decreasing inflammation,
- Preventing neuronal degeneration through the selective non-inhibition of the type 2 angiotensin receptors in the brain.

Dr. Hajjar et al. *Arch Intern Med*. 2012;172:442-444

In conclusion,

some anti-hypertension therapies

reverse vascular aging,

but still not significantly dementia.

The 26th International Society of Hypertension Biennial Scientific Meeting 2016

September 24(Sat) – 29(Thu), 2016
COEX, Seoul, Korea

Please be safe from
- **Earthquake**
- **Tsunami**
- **Tornado**
- **Flood**
- **…**
- **Hypertension**
- **Dementia**

Thank you!