Evolving perspective of CCB focused on recent sub-analysis

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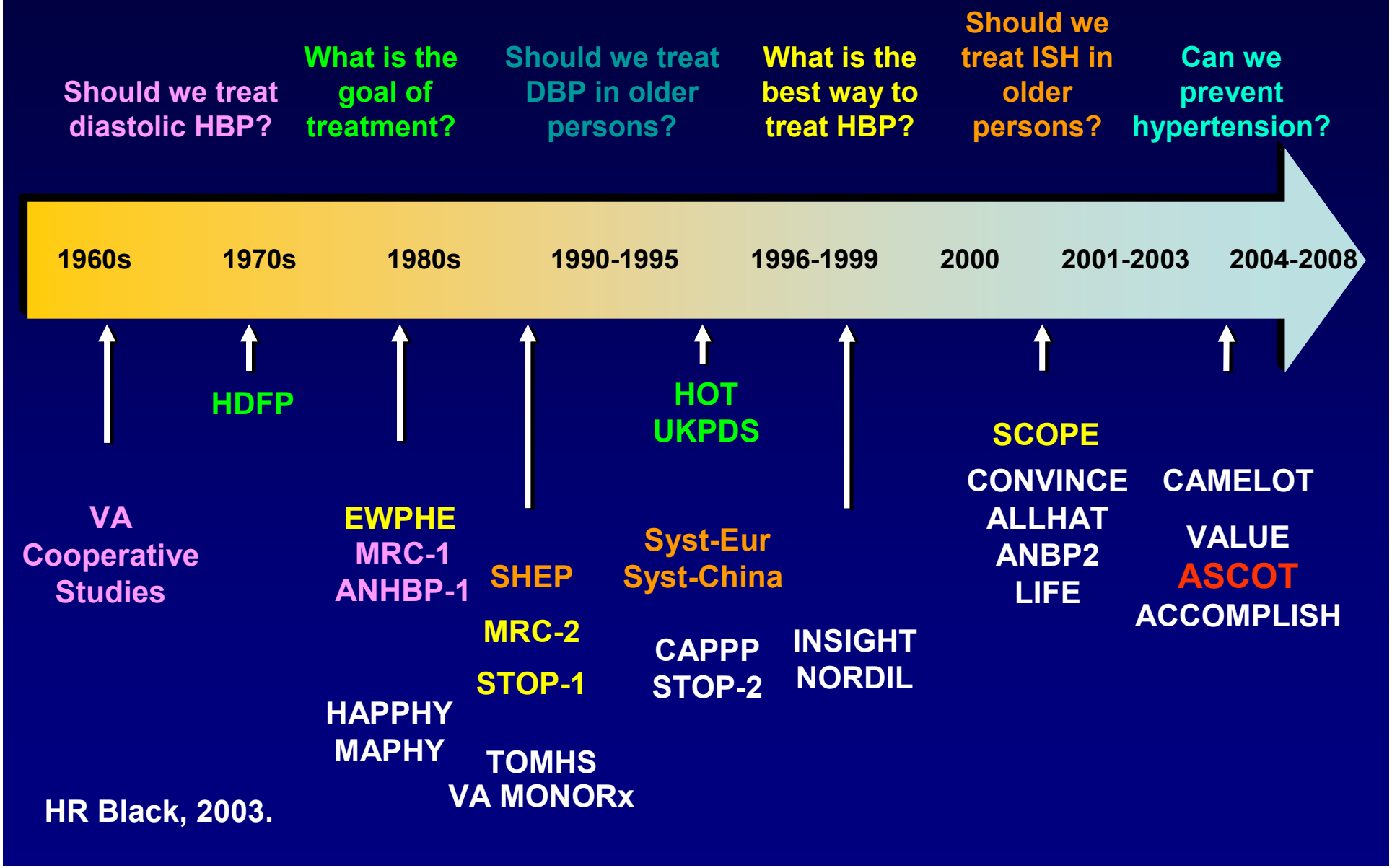
Clinical Trials in Hypertension



HR Black, 2003.

3 Trends in Clinical Trials of HT

- Which is better? Old vs. new drug
- Antihypertensive as antiatherosclerotic agent?
- Which is better? New vs. another new

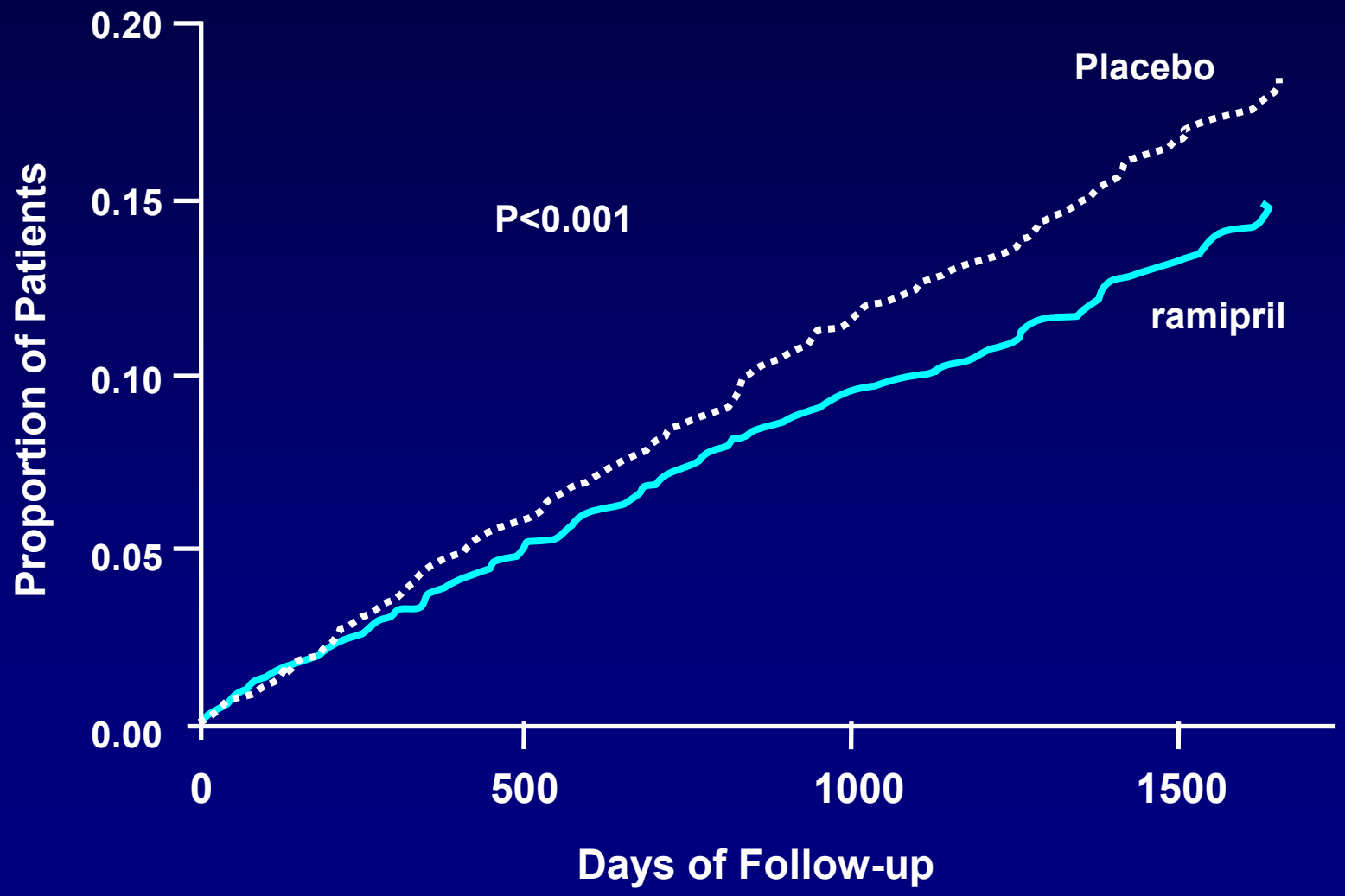
↓

Comparison of Surrogate end-points such as Af, DM, CRP

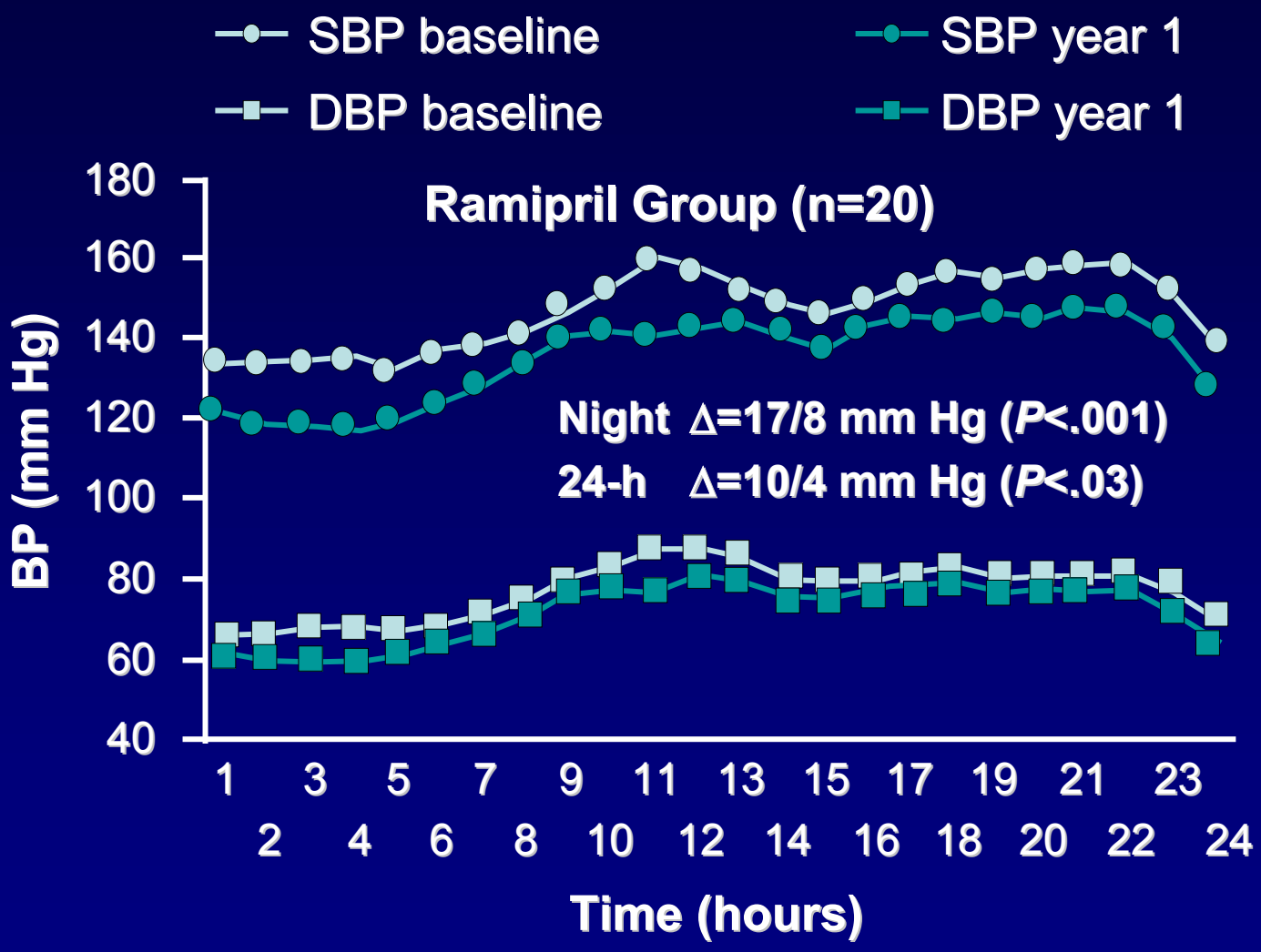
AntiHT is Antiatherosclerotic?

- BP lowering effect or not?
- HOPE
- EUROPA
- PEACE
- PREVENT/ELSA/CAMELOT
- PROGRESS?

HOPE Study


0.20
0.15
0.10
0.05
0.00
Proportion of Patients
Placebo
P<0.001
ramipril
0
500
1000
1500
Days of Follow-up

Hourly Means of Systolic and Diastolic Ambulatory BP in HOPE Substudy: Baseline and 1 Year



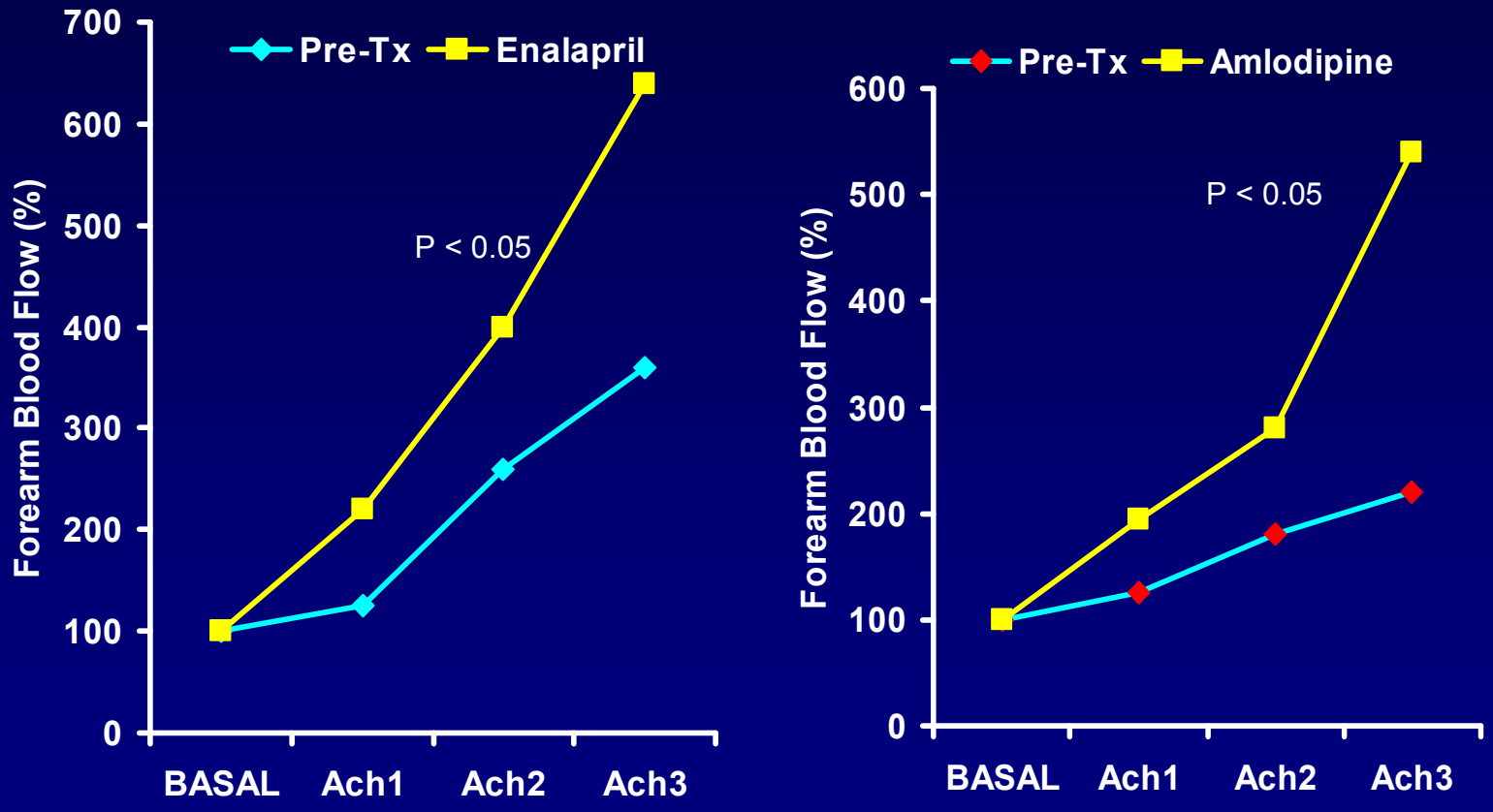
Svensson et al. *Hypertension.* 2001;38:e28-e32.

Most Direct Evidence of Antiatherosclerosis

- IVUS data
- Improvement of endothelial dysfunction
- Improvement of PWV(aortic compliance)

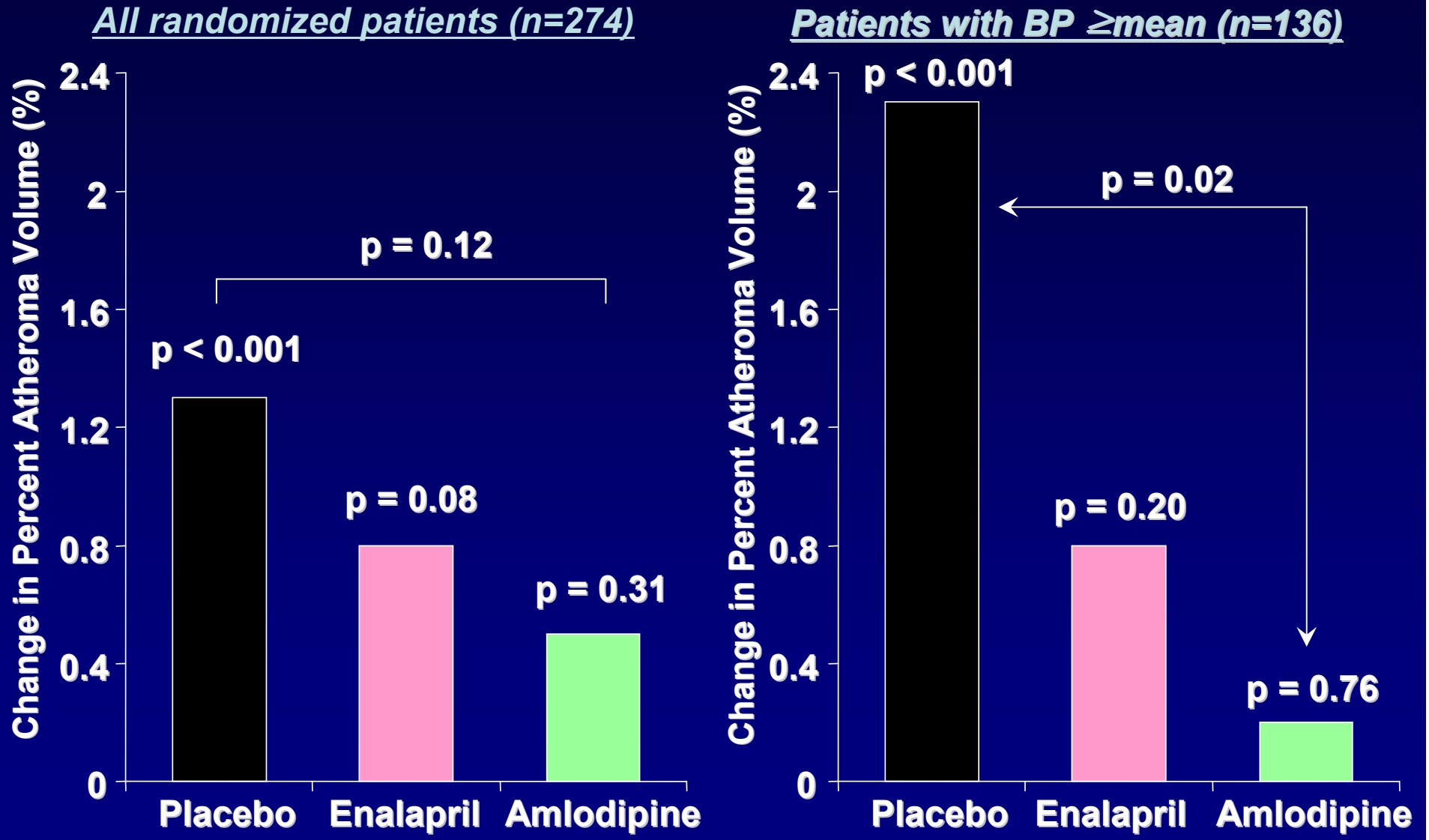
The Effects of ACEI and CCB on Endothelial Function

Patients with Essential Hypertension



On et al. *Hypertens Res* 2002;25:365-71

NORMALISE: IVUS PROGRESSION : PERCENT ATHEROMA VOLUME



Sub-analysis of CAMELOT

- 274 subjects with IVUS data
- Analysis done in Cleveland Clinic
- Volume of atheroma measured before and after trial
- Detailed method of IVUS analysis; refer to the original article

Basic Characteristic of Group's

Characteristic	Normal (n = 76)	Pre-Hypertensive (n = 157)	Hypertensive (n = 41)	p Value*
Age, yrs	53.0 ± 8.4	57.5 ± 9.4	61.9 ± 10.5	<0.001
Male	[illegible]	[illegible]	[illegible]	0.047
Body	[illegible]	[illegible]	[illegible]	0.15
Curre	[illegible]	[illegible]	[illegible]	0.90
History of hypertension	33 (43.4%)	110 (70.0%)	32 (78.0%)	<0.001
History of diabetes	10 (13.1%)	31 (19.7%)	6 (14.6%)	0.41
Lipid profile†				
Total cholesterol, mg/dl	183.2 ± 27.6	179.9 ± 34.7	173.7 ± 41.1	0.35
LDL cholesterol, mg/dl	100.0 ± 22.2	98.2 ± 27.8	94.6 ± 37.4	0.64
HDL cholesterol, mg/dl	41.1 ± 11.1	41.2 ± 11.7	44.4 ± 14.7	0.28
Triglycerides, mg/dl	194.1 ± 97.3	185.9 ± 118.1	170.5 ± 95.1	0.13
LDL/HDL cholesterol ratio	2.6 ± 0.8	2.6 ± 1.1	2.2 ± 0.8	0.07
Study medications				0.02
Amlodipine	26 (34.2%)	56 (35.6%)	9 (21.9%)	
Enalapril	33 (43.4%)	42 (26.7%)	13 (31.7%)	
Placebo	17 (22.3%)	59 (38.0%)	19 (46.3%)	
Concomitant medications				
Aspirin	75 (98.6%)	150 (95.5%)	38 (92.6%)	0.26
Beta-blocker	57 (75.0%)	134 (85.3%)	34 (82.9%)	0.15
Statin	66 (86.8%)	140 (89.1%)	34 (82.9%)	0.54

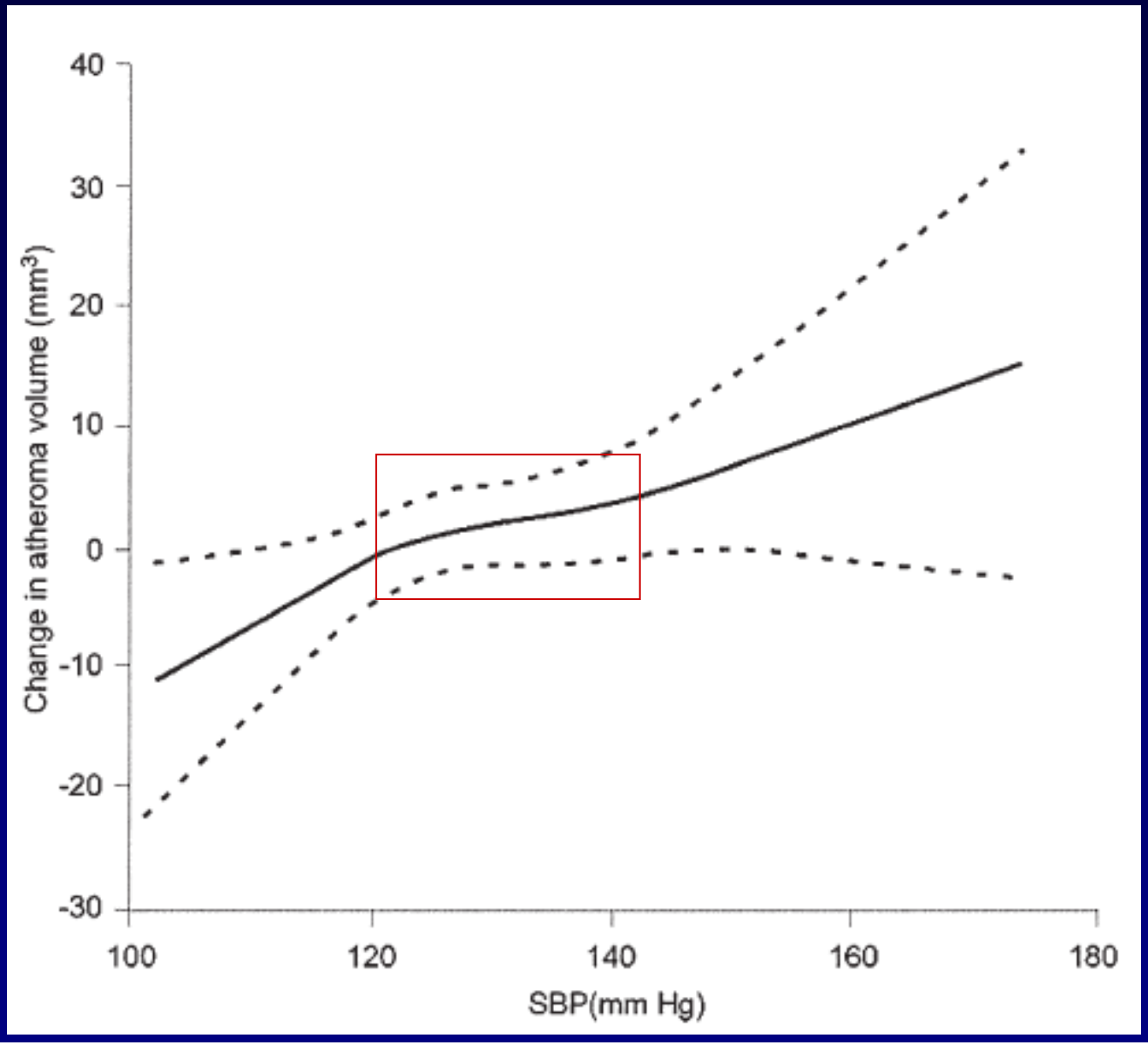
Higher age in normotensive group

Correlation with Atheroma Volume Change

	Correlation Coefficient	p Value
Age	0.04	0.53
Male gender	−0.004	0.95
Body mass index	0.02	0.69
Current smoking	0.02	0.81
History of hypertension	0.12	0.05
History of diabetes	−0.06	0.35
Lipid profile		
Total cholesterol	0.10	0.11
LDL cholesterol		
HDL cholesterol		
Triglycerides		
LDL/HDL cholesterol ratio	0.18	0.003
BP components		
SBP	0.14	0.02
DBP	0.09	0.15
Pulse pressure	0.11	0.06

LDL/HDL ratio, SBP; signficant correlation with atheroma change

Relation between SBP and Atheroma Change

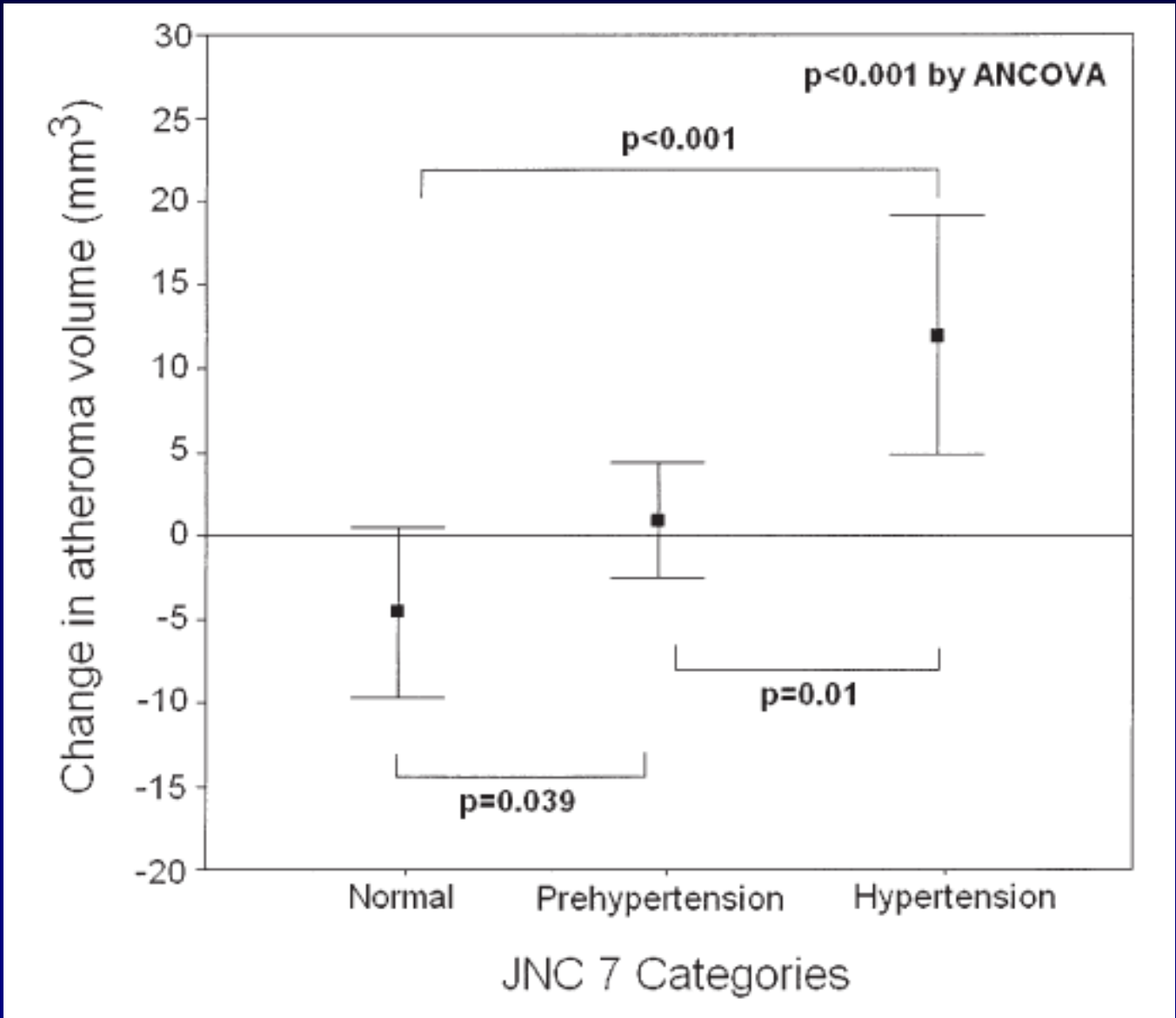


Multivariate Analysis to Atheroma Volume

	Correlation Coefficient	p Value
SBP	0.16	0.006
DBP	0.08	0.16
Pulse pressure	0.14	0.02

*Based on rank transformed data and adjusted for baseline atheroma volume, LDL/HDL cholesterol ratio, and triglycerides. For each blood pressure component, the average value observed throughout the study period was used. Since 2 patients had incomplete laboratory data, the results of 272 patients are shown.

Atheroma Change with BP Category



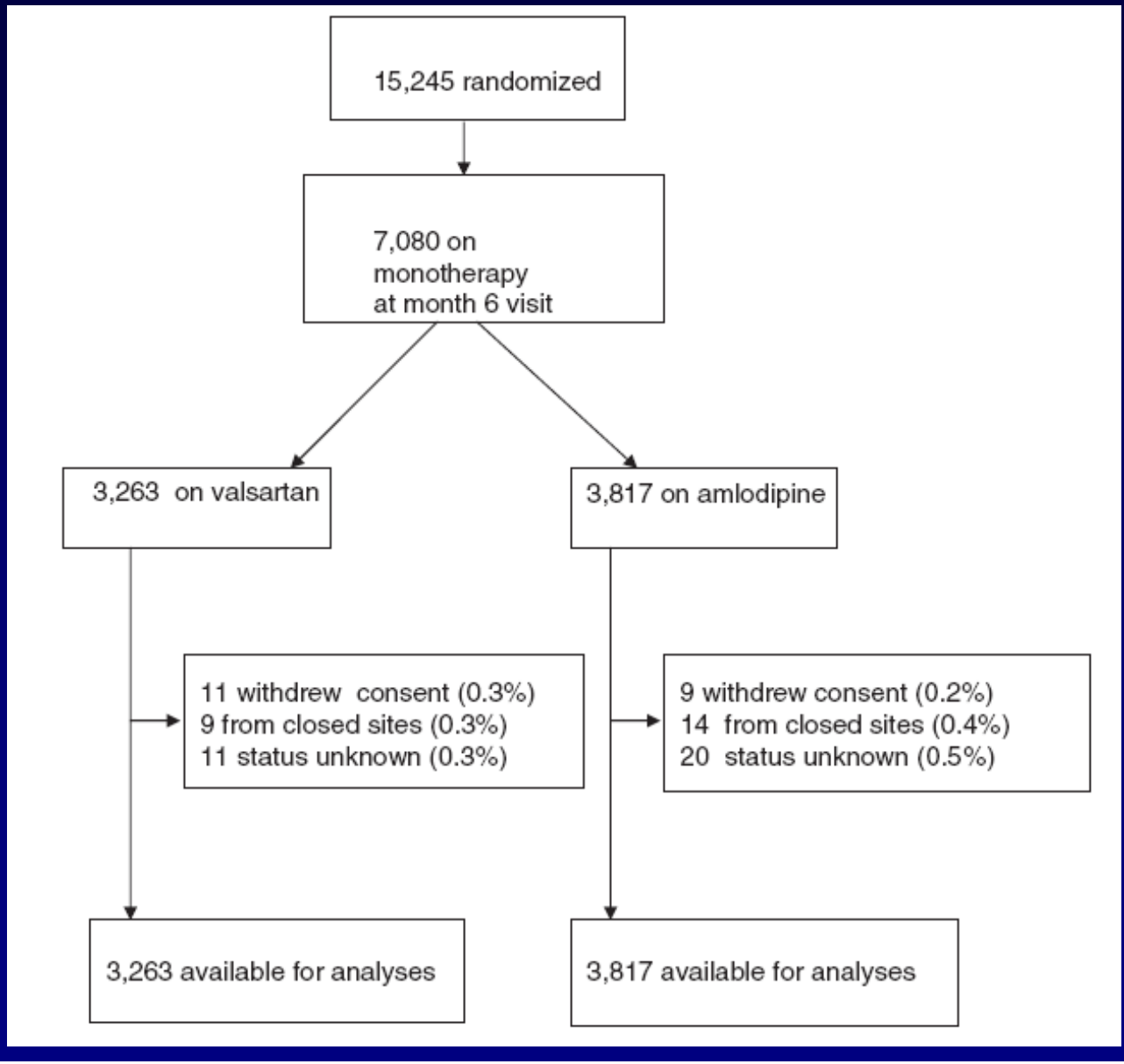
Atheroma Regression in HT

- What is more important? Lipid lowering vs. BP lowering?
- More aggressive reduction of blood pressure needed for atheroma reduction
- There must be limitation in BP reduction in real world
- Other risk reduction needed for atheroma regression

New vs. Another New?

- Excluding the effect on renoprotection
- MOSES in stroke prevention; ARB> CCB
- VALUE in high risk pt; CCB>ARB
- CAMELOT in high risk: CCB≥ACEI
- Substudy of ALLHAT

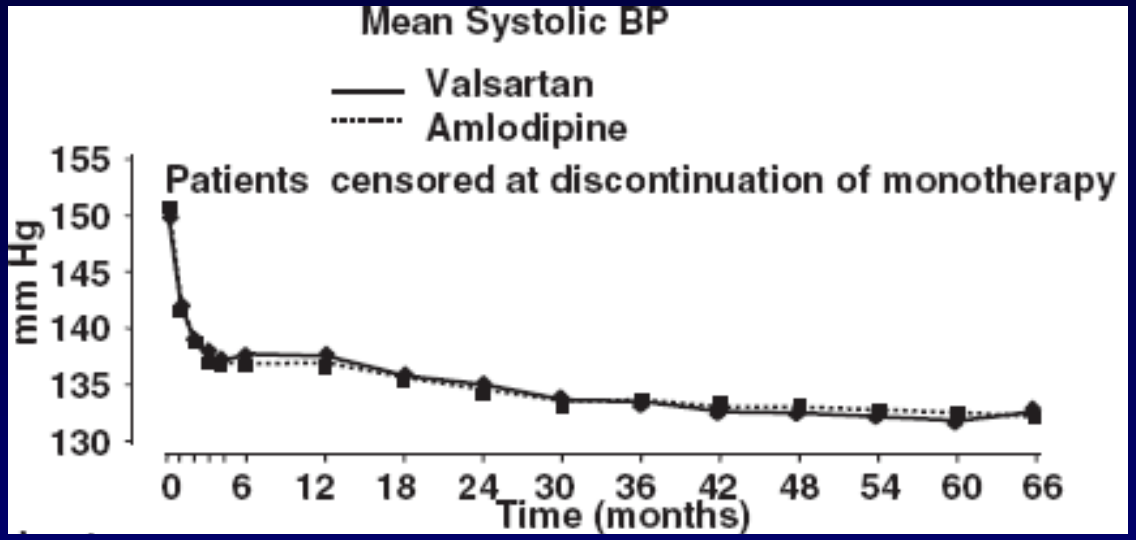
VALUE; Monotherapy

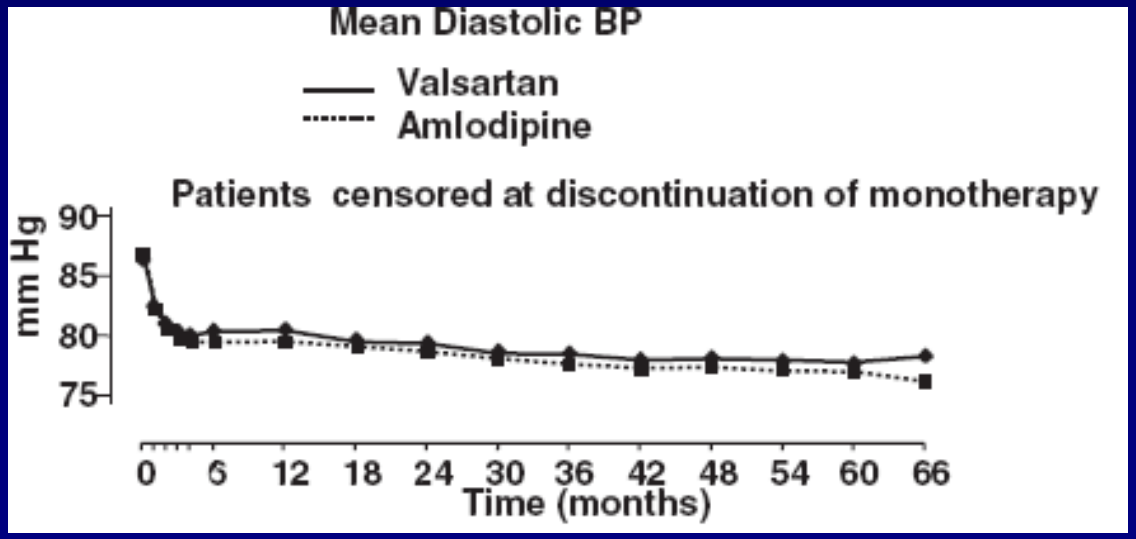


Characteristic of Monotherapy Group

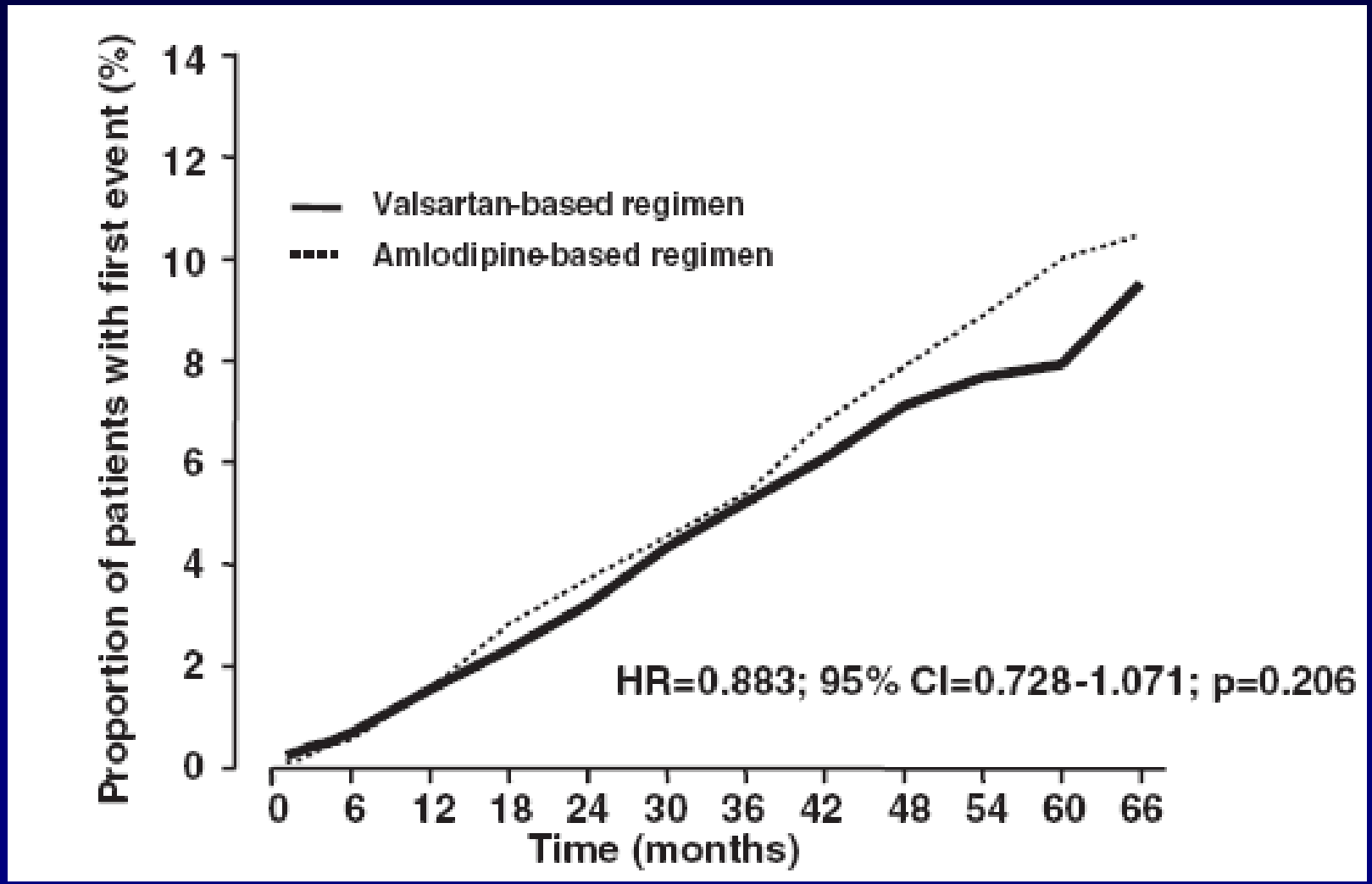
- Younger
- More male
- Less TOD
- Less RF
- More monotherapy or no therapy before trial

BP Change during Monotherapy

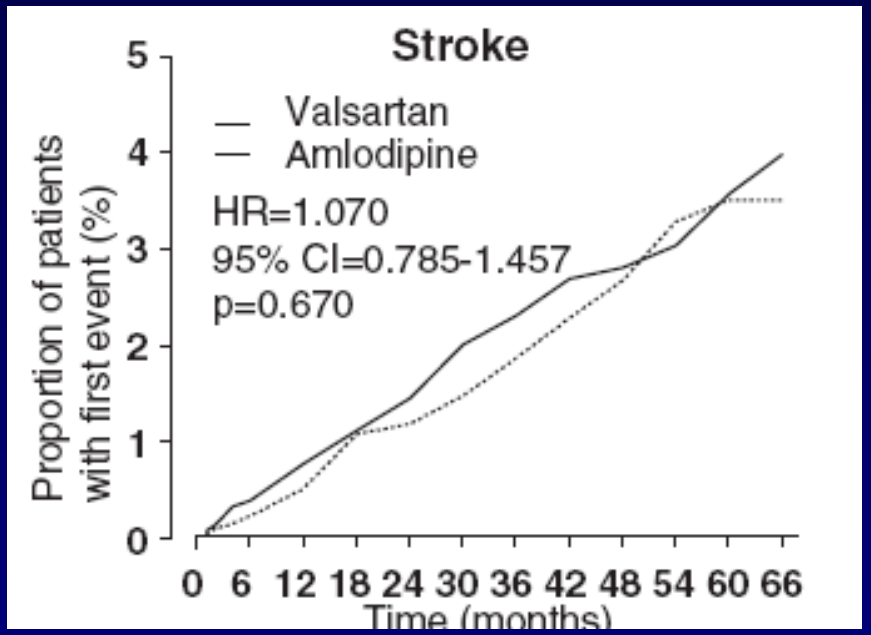


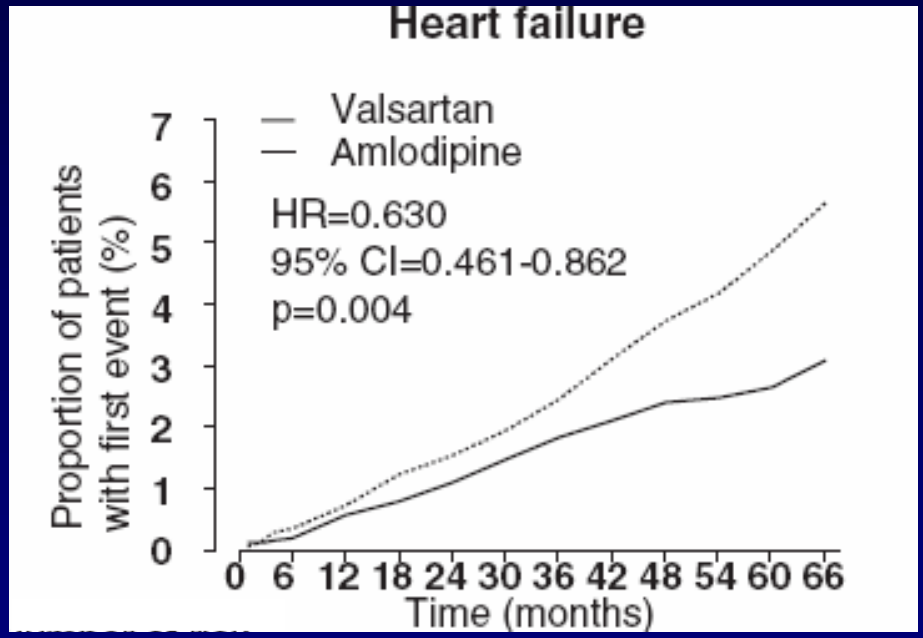


Primary Endpoint in Monotherapy

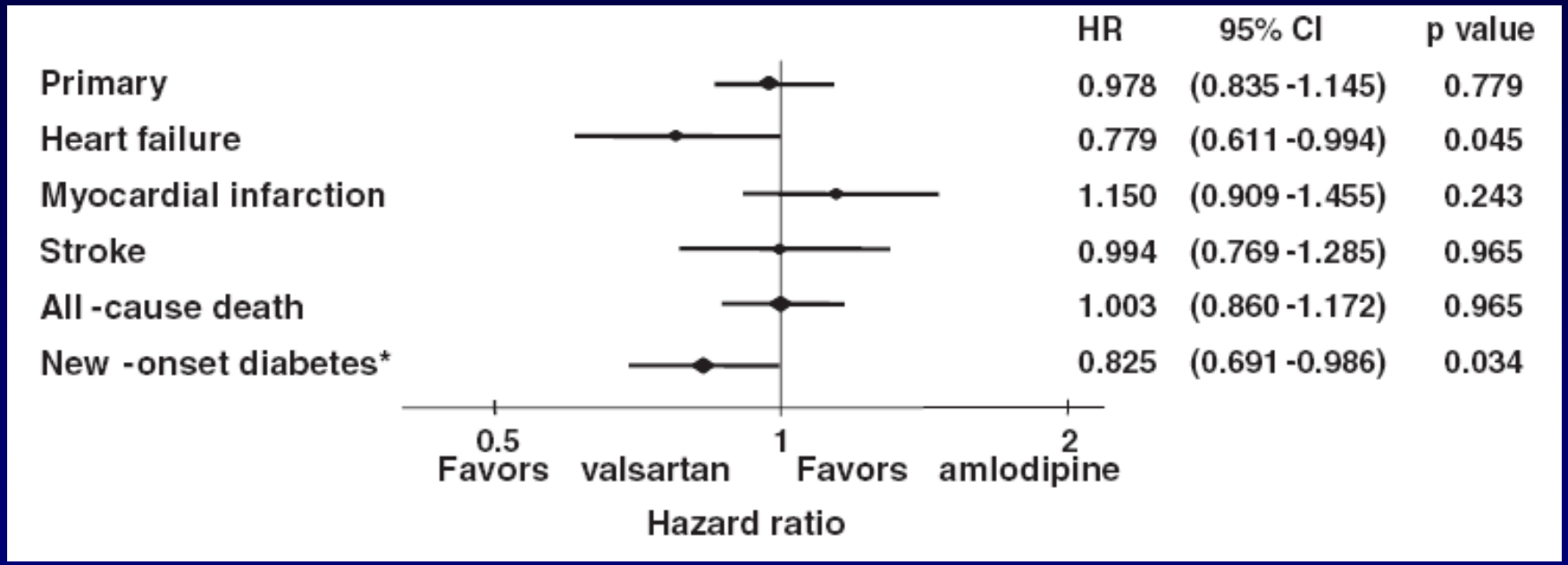


Stroke & HF in Monotherapy





Hazard Ratio between Two Groups



Lesson from VALUE Sub-study

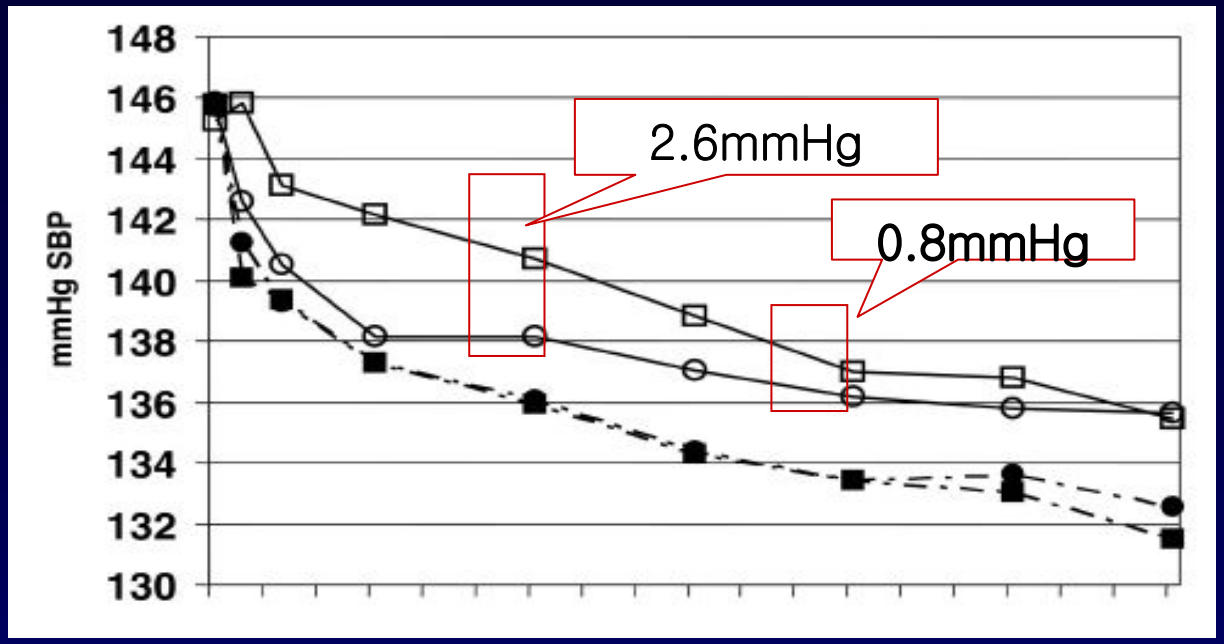
- Maybe nothing new
- Design of clinical trial should not be changed
- Bottom line; BP control is important >> selection of any class of drug

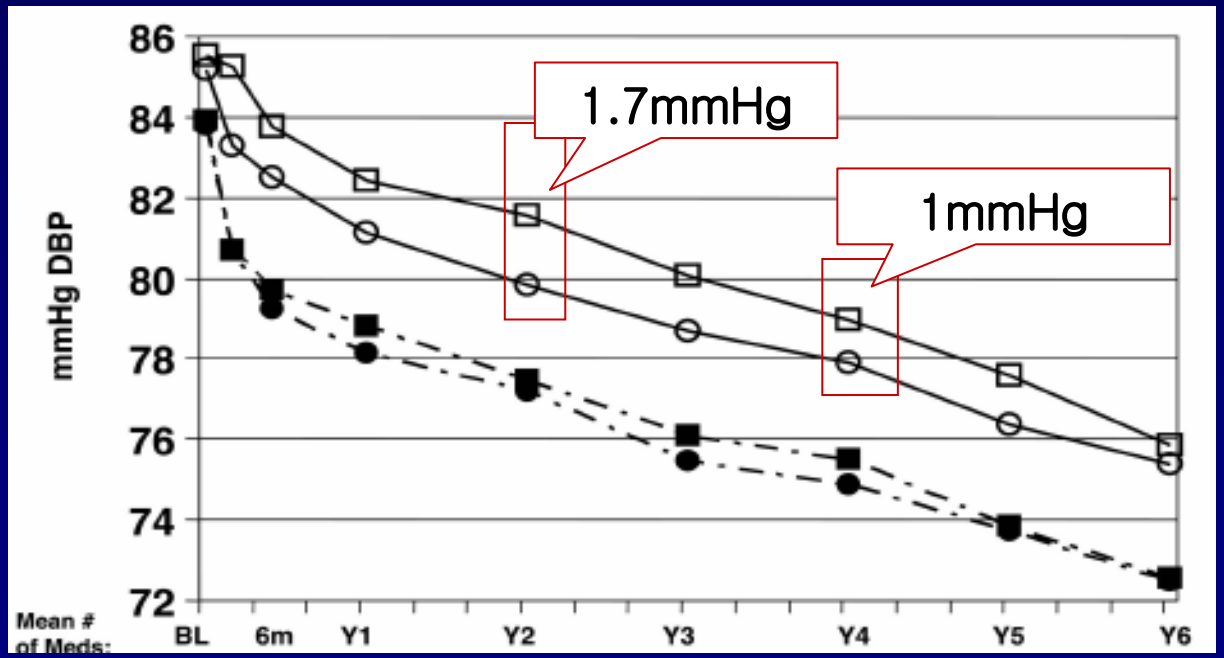
Sub-study of ALLHAT

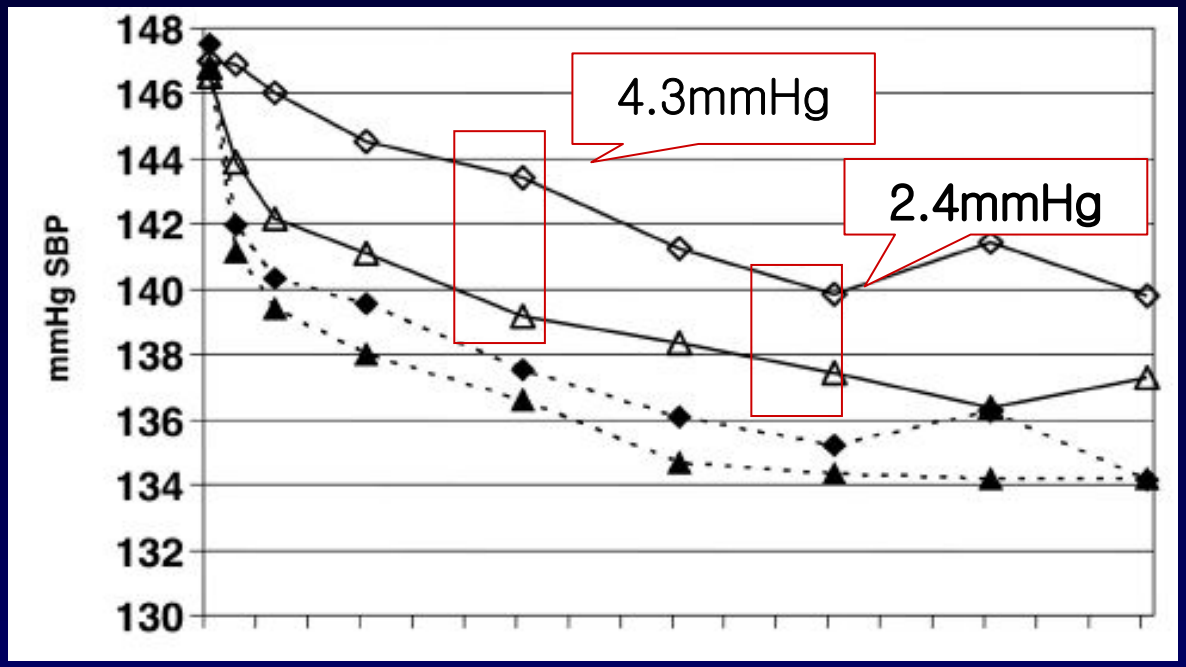
Clinical Events in High-Risk Hypertensive Patients Randomly Assigned to Calcium Channel Blocker Versus Angiotensin-Converting Enzyme Inhibitor in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

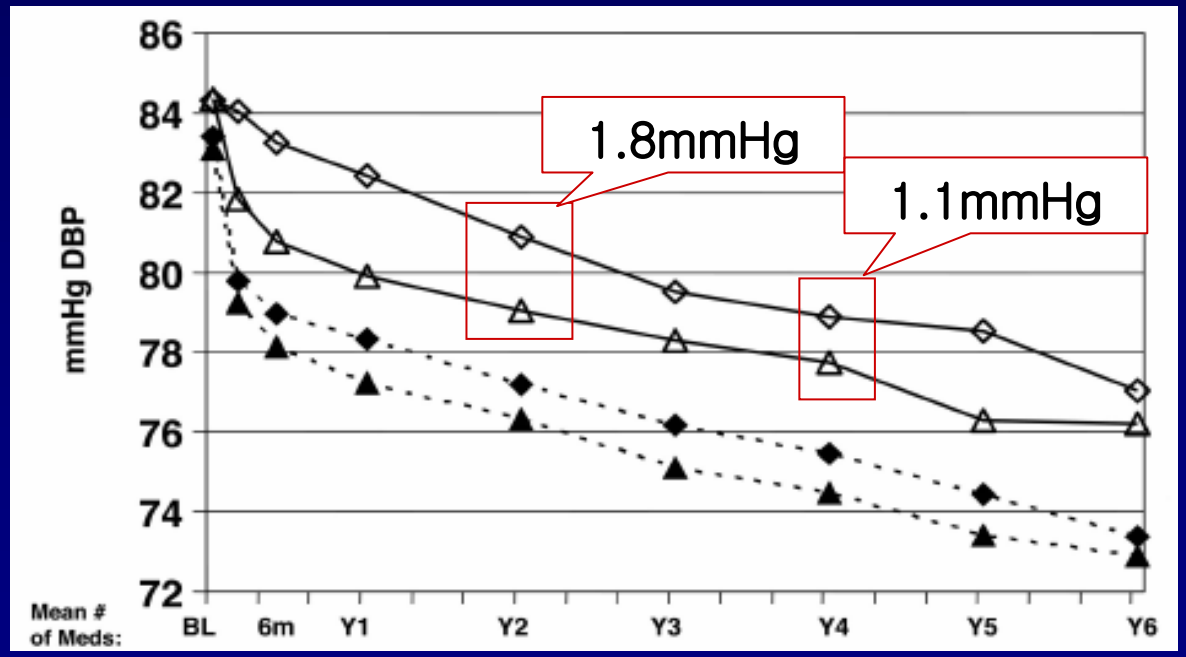
- Comparing the effect of amlodipine with that of lisinopril according to race and gender
- Highlighting the importance of consideration in race and gender in choosing the class of antihypertensive

Leenen et al (2006). Hypertension 48:374-384.


148
146
144
142
140
138
136
134
132
130
mmHg SBP
2.6mmHg
0.8mmHg


86
84
82
80
78
76
74
72
mmHg DBP
1.7mmHg
1mmHg
Mean # of Meds:
BL
6m
Y1
Y2
Y3
Y4
Y5
Y6
Amlodipine - Black Male
Lisinopril - Black Male
Amlodipine - Non-Black Male
Lisinopril - Non-Black Male


148
146
144
142
140
138
136
134
132
130
mmHg SBP
4.3mmHg
2.4mmHg


86
84
82
80
78
76
74
72
mmHg DBP
1.8mmHg
1.1mmHg
Mean # of Meds:
BL
6m
Y1
Y2
Y3
Y4
Y5
Y6


Amlodipine - Black Women
Lisinopril - Black Women
Amlodipine - Non-Black Women
Lisinopril - Non-Black Women

Change of Blood Glucose

Variable	Amlodipine	Lisinopril	*P* Value L vs A
Nondiabetics at baseline			
Impaired fasting glucose (6.1 to 6.9 mmol/L) if nondiabetic at baseline			
2 years, n (%)	166 (9.2)	136 (7.9)	0.12
4 years, n (%)	204 (13.0)	169 (9.4)	0.16
Diabetes (≥7.0 mmol/L) if nondiabetic at baseline			
2 years, n (%)	142 (7.8)	139 (7.9)	0.94
4 years, n (%)	163 (10.4)	139 (9.4)	0.30

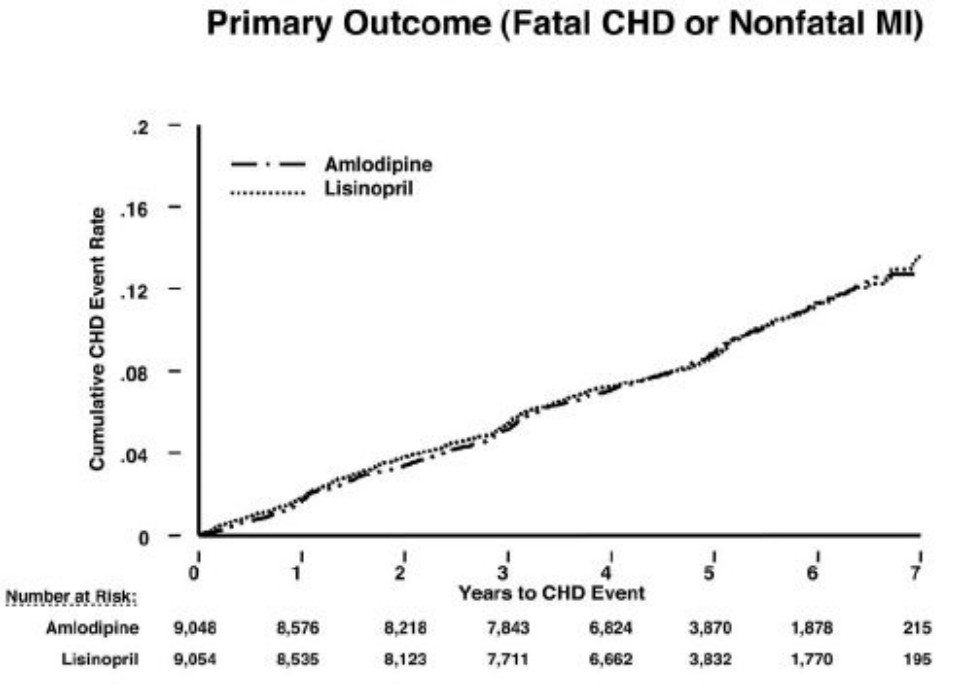
Change of Blood Glucose

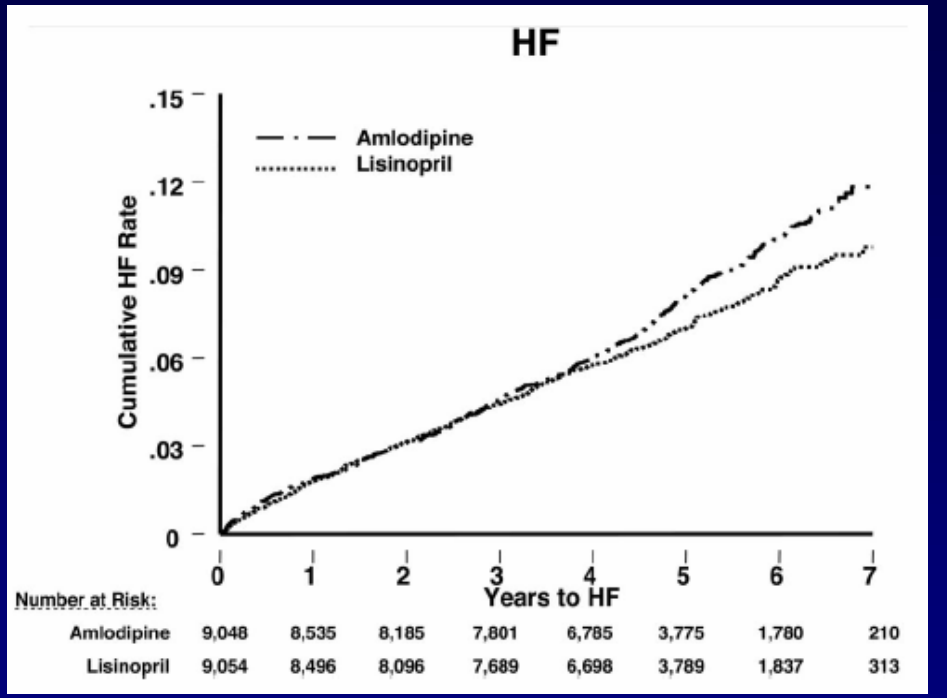
Variable	Amlodipine	Lisinopril	*P* Value L vs A
Impaired fasting glucose at baseline			
Fasting glucose, mmol/L			
Baseline, mean (SE)	6.5 (0.01)	6.5 (0.01)	
N	666	695	
2 years, mean (SE)	7.3 (0.14)	7.0 (0.12)	0.17
N	308	284	
4 years, mean (SE)	7.6 (0.16)	7.1 (0.14)	0.01
N	270	240	
Impaired fasting glucose (6.1 to 6.9 mmol/L) if impaired fasting glucose at baseline			
2 years, n (%)	69 (22.4)	75 (26.4)	0.49
4 years, n (%)	70 (25.9)	53 (22.1)	0.05
Diabetes (≥7.0 mmol/L) if impaired fasting glucose at baseline			
2 years, n (%)	134 (43.5)	111 (39.1)	0.53
4 years, n (%)	127 (47.0)	98 (40.8)	0.03

Change of GFR

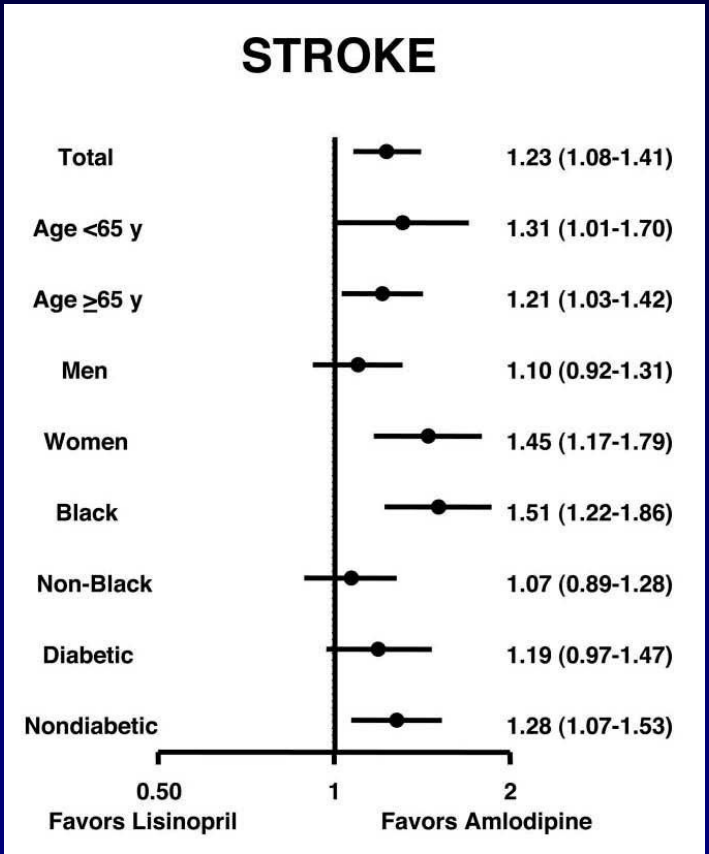
Variable	Amlodipine	Lisinopril	*P* Value L vs A
Estimated GFR, mL/min per 1.73 m² mean (SD)			
Baseline, mean (SD)	78.1 (19.7)	77.7 (19.9)	0.08
n	8640	8636	
2 years, mean (SD)	78.0 (20.5)	74.0 (20.0)	<0.001
n	5794	5516	
4 years, mean (SD)	75.1 (20.7)	70.7 (20.1)	<0.001
n	4924	4621	

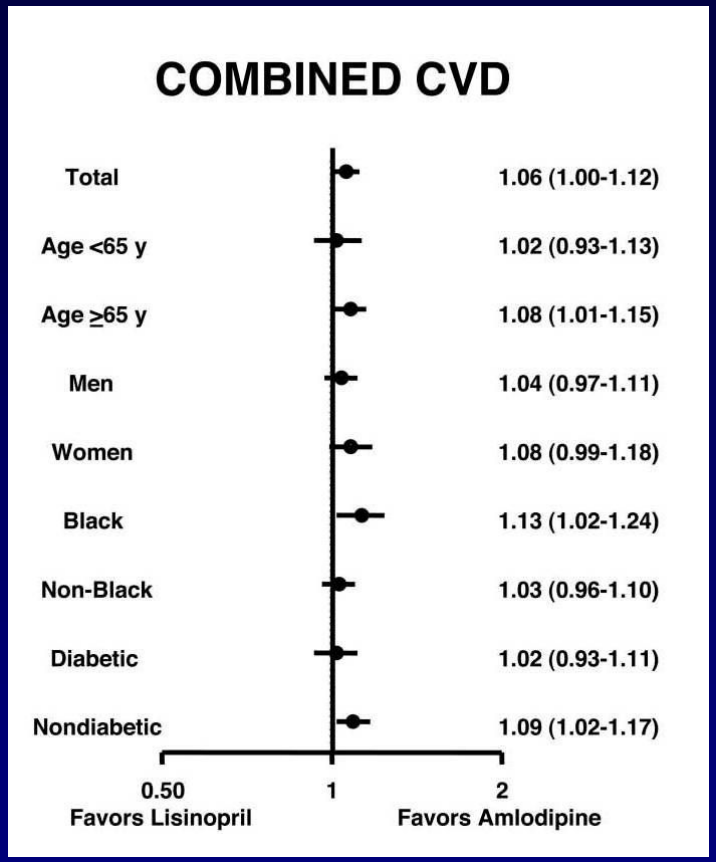
Primary Endpoint and HF





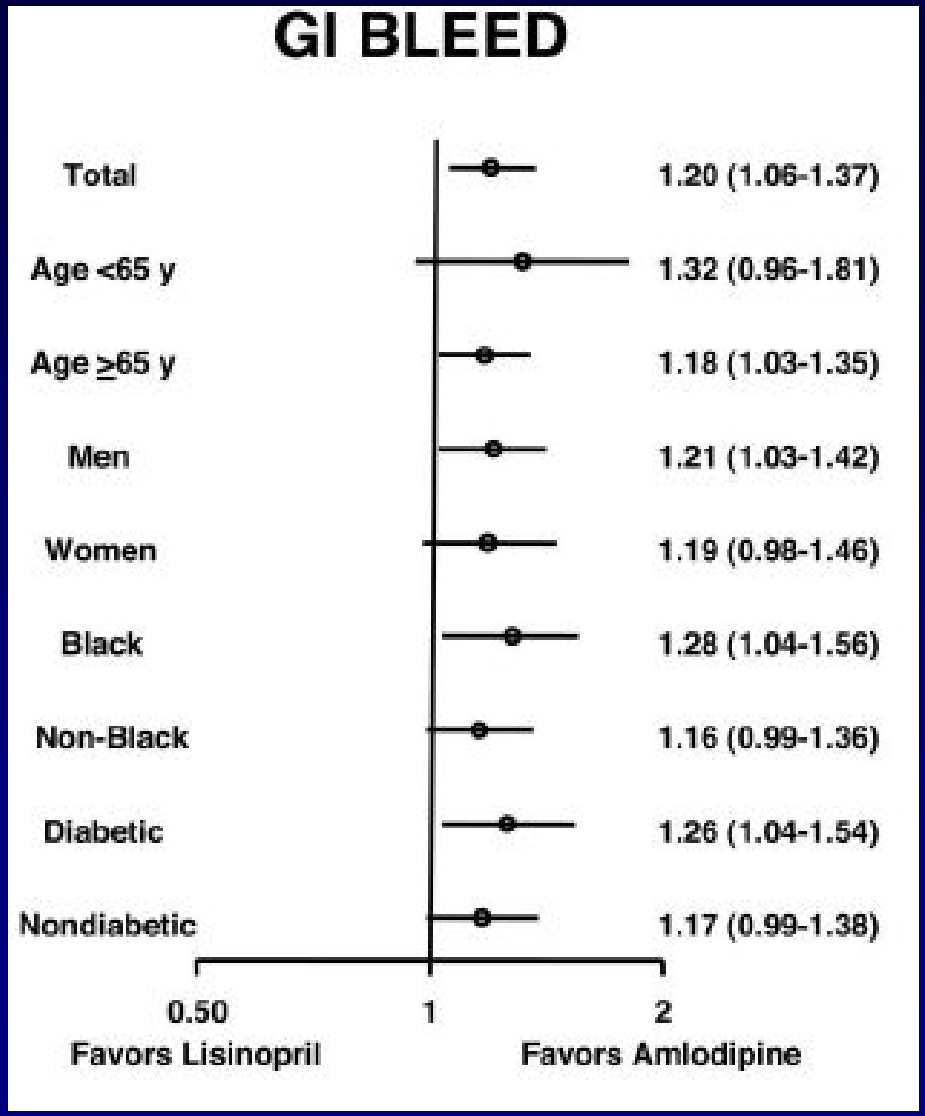
Stroke & Combined CVD



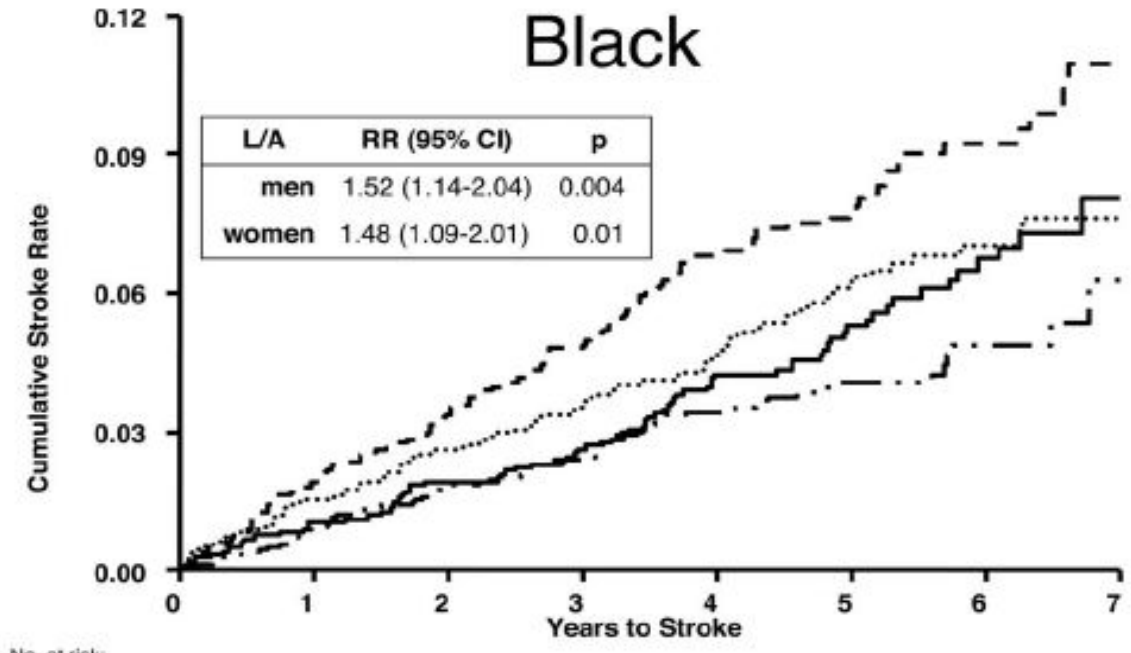


- Stroke rate was significantly greater with lisinopril (6.3%) than amlodipine (5.4%) [p=0.003]
- Combined CVD was also higher with lisinopril (33.3%) than amlodipine (32.0%) [p=0.047]

Fewer Events of GI Bleeding in CCB



Stroke in Blacks



Blacks

6-year event rate/100 persons (SE)

	Amlodipine	Lisinopril
Men	6.74 (0.8)	9.21 (0.9)
Women	4.86 (0.6)	7.04 (0.7)

Events Developed

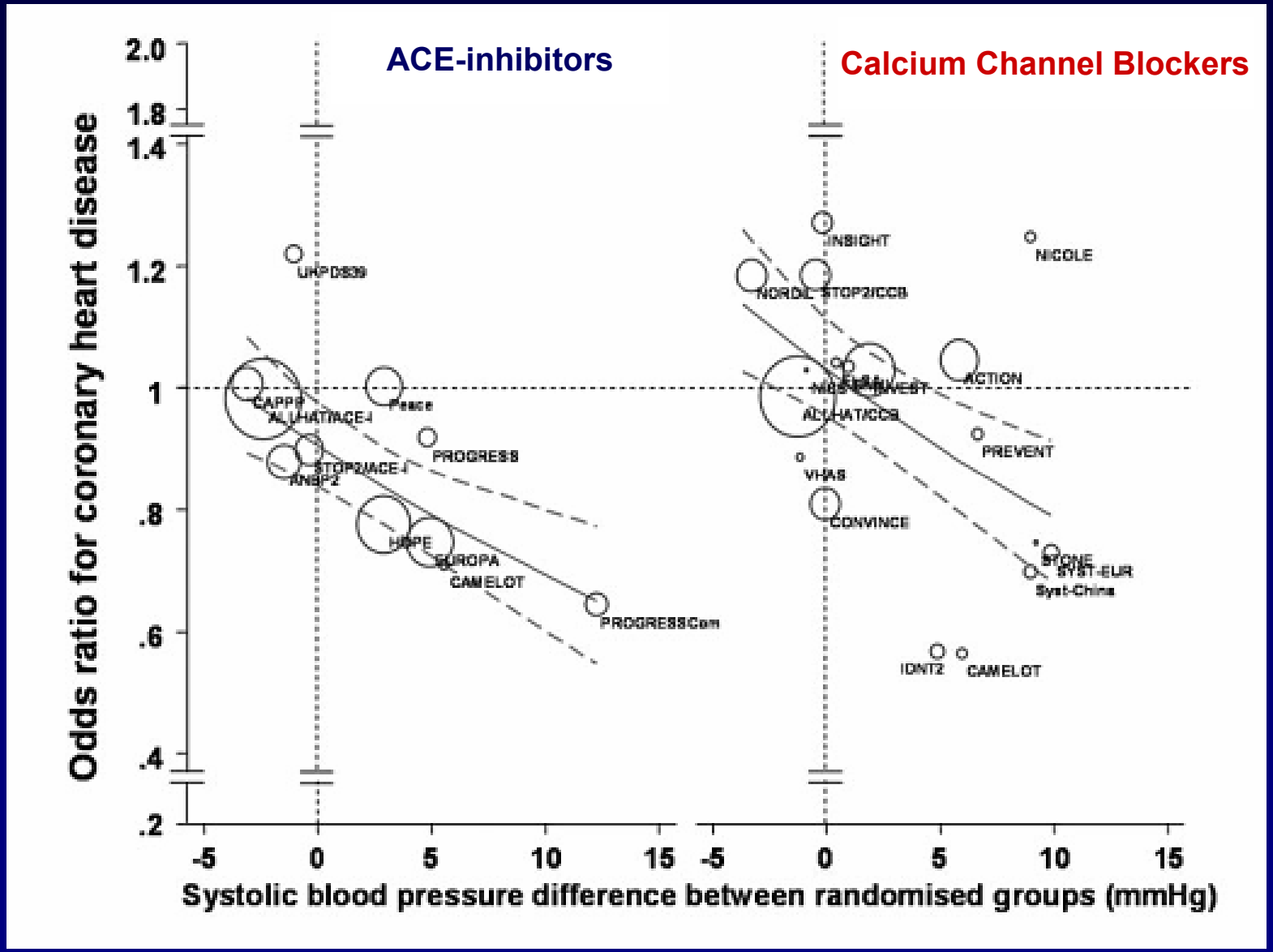
Variable	No CHD at Baseline		
	Amlodipine	Lisinopril	*P* Value Lisinopril vs Amlodipine
Time point, N of participants (%)			
Baseline	6777	6715	
Year 1	5678 (84)	5578 (83)	
Year 2	5155 (81)	4991 (74)	
Year 4	4199 (62)	3917 (58)	
% <140/90 at year 4	64.1	62.1	0.06
Events, N (6-year rate per 100 perso			
CHD	507 (9.6)	494 (9.4)	0.78
All-ca			
Comb			
Strok			
Combined CVD	1500 (26.8)	1555 (28.0)	0.16
HF	453 (8.7)	377 (7.4)	0.01
Angina	474 (8.5)	538 (9.8)	0.025
Coronary revascularization	410 (7.7)	394 (7.5)	0.65
PAD	153 (2.9)	207 (3.9)	0.003

More angina and PAD deveolped more in ACEI group

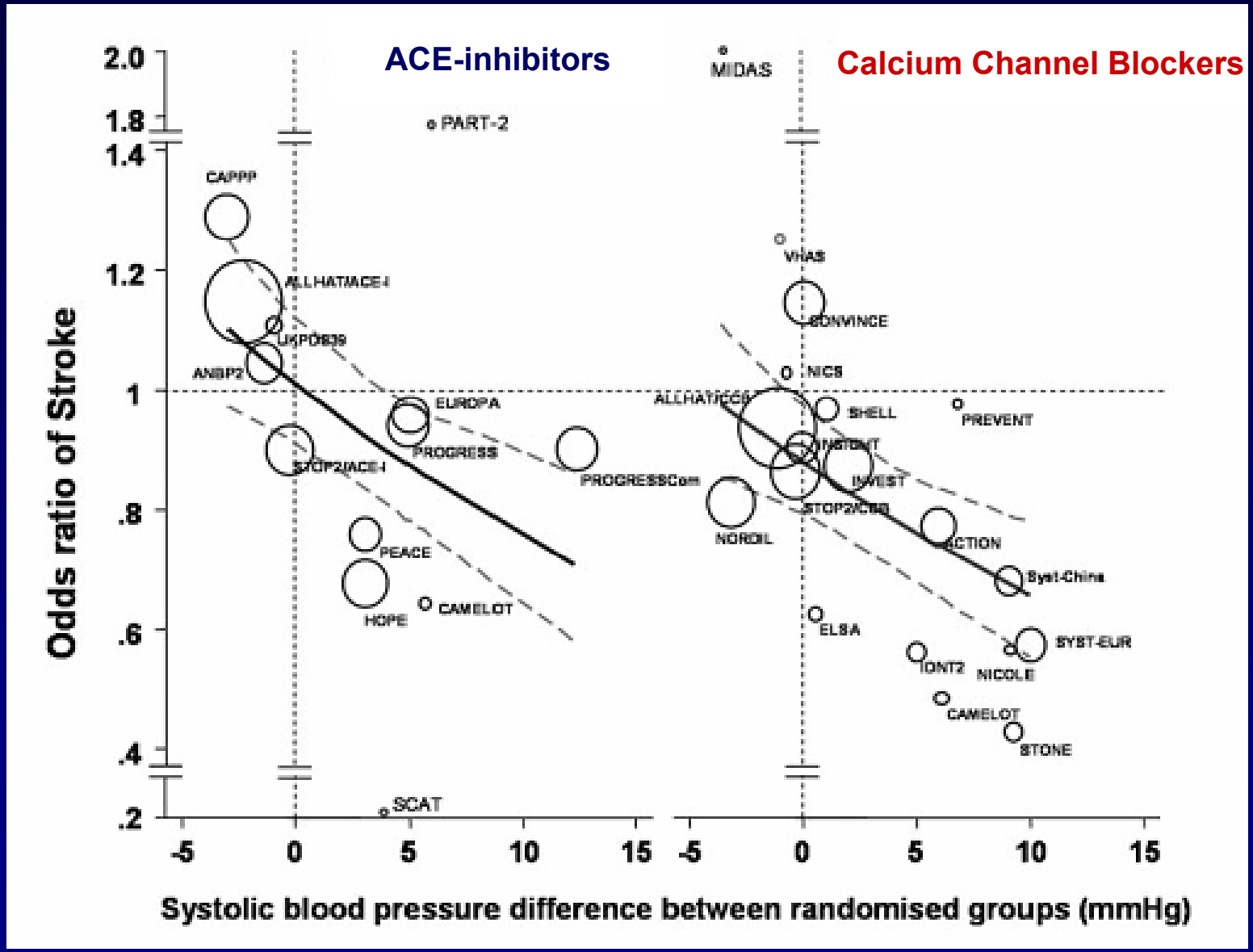
ALLHAT Sub-study Summary

- This ALLHAT sub-analysis of an ACE inhibitor versus a CCB found no apparent difference between treatments in fatal CHD or non-fatal MI
- Overall, amlodipine was superior over lisinopril in stroke, peripheral arterial disease, hospitalized angina, GI bleeding & angio-oedema, whereas lisinopril was better than amlodipine in heart failure

ACE inhibitor; Better for CHD



CCB; Better for Stroke?



Lessons Learned from ALLHAT Sub-study

- BP control >> drug selection
- GI bleeding/angioedema more in ACEI
- HF/IGT more in CCB
- Antiatherosclerotic effect better in CCB?
- Researchers, clinicians and others must be cautious in the interpretation and dissemination of the findings from observational studies of drugs, lest otherwise good therapies be lost. One should also consider that premature claims of dangers" of a particular drug (class) in the press may also jeopardize recruitment and retention of patients in ongoing clinical trials studying the drug (class), as was the case for ALLHAT.

Conclusion

- From the sub-analysis, it was certain than BP lowering is more important than choosing any class of drug
- Antiatherosclerotic effect may be related to the BP lowering.
- CCB is very potent, safe tool in lowering BP highlighted in recent sub-analysis