Blood Pressure Control and Vascular Protection

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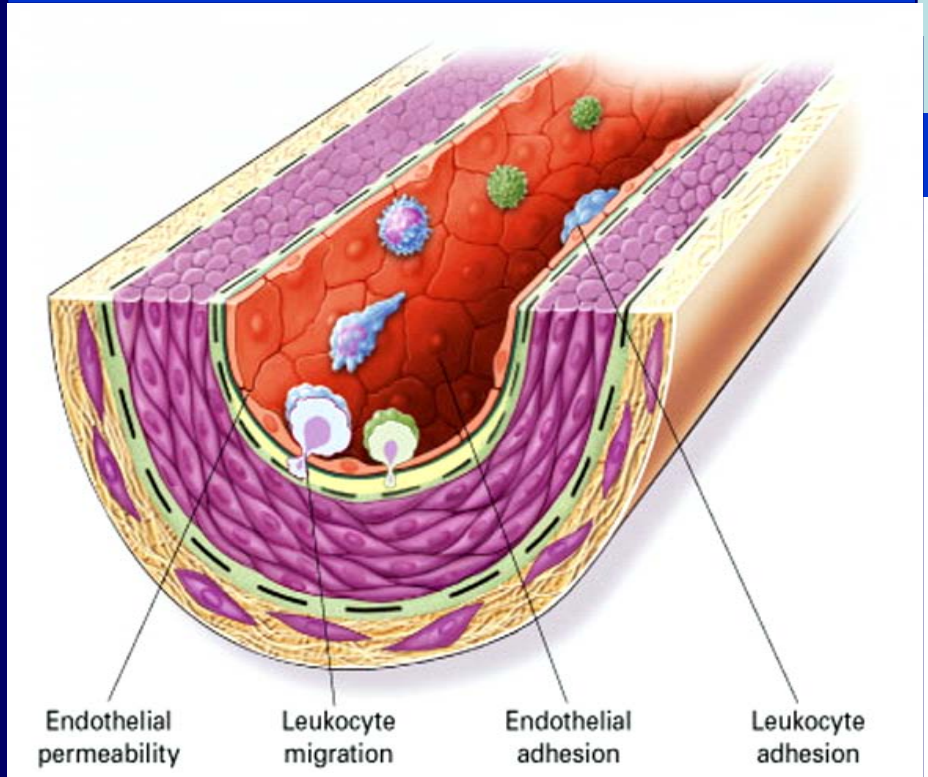
CV Risk Factors and Vascular Disease

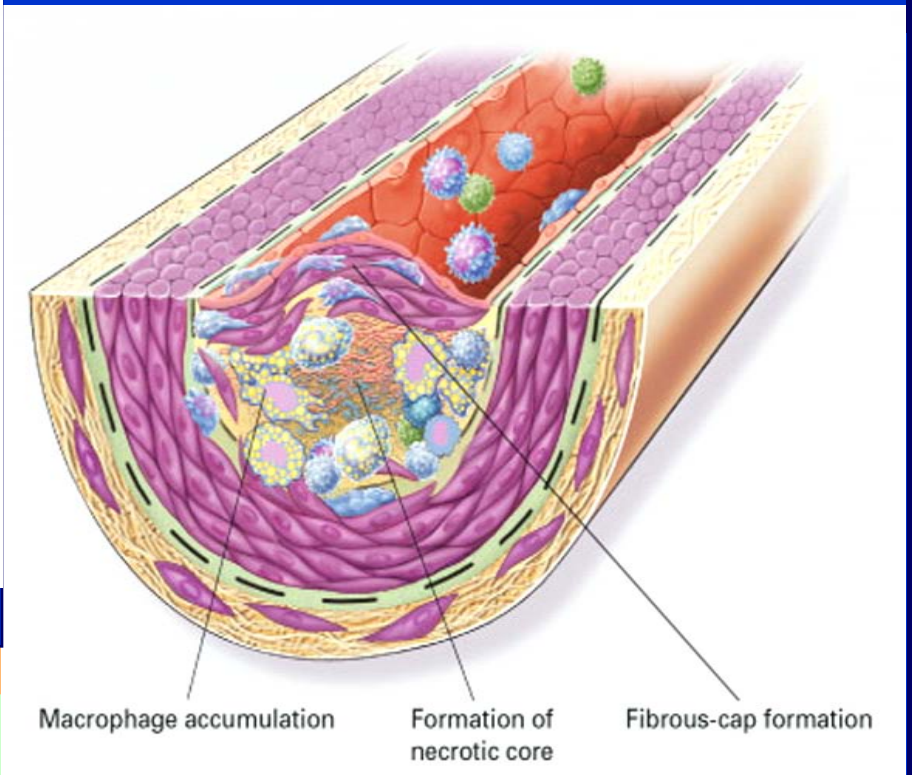
Endothelial Dysfunction



Ross. *N Engl J Med*. 1999;340:115-126.

Dysli

Oxidative Stress & Inflammation



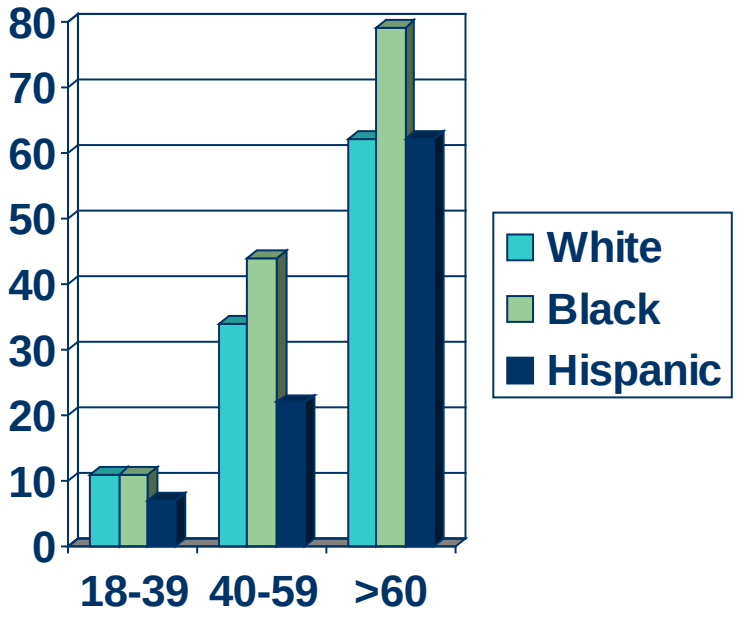
Ross. *N Engl J Med*. 1999;340:115-126.

Diab

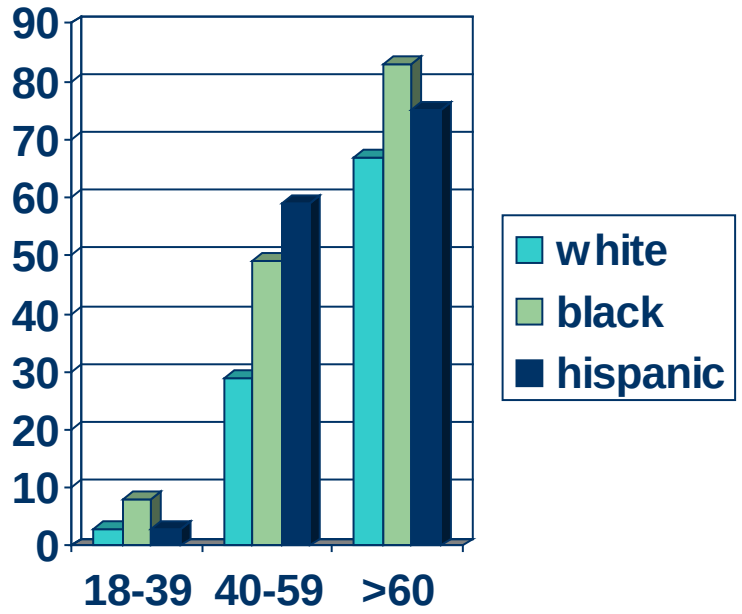
The Blood Pressure Epidemic

- Hypertension is a Vascular disease
- Over 73 million Americans
- More than 1 billion world wide
- Among those >55 years of age there is a risk of >90% for developing hypertension in their lifetime
- The estimated cost of treating hypertension in the US is>$70 billion/year

Prevalence of Hypertension



Men



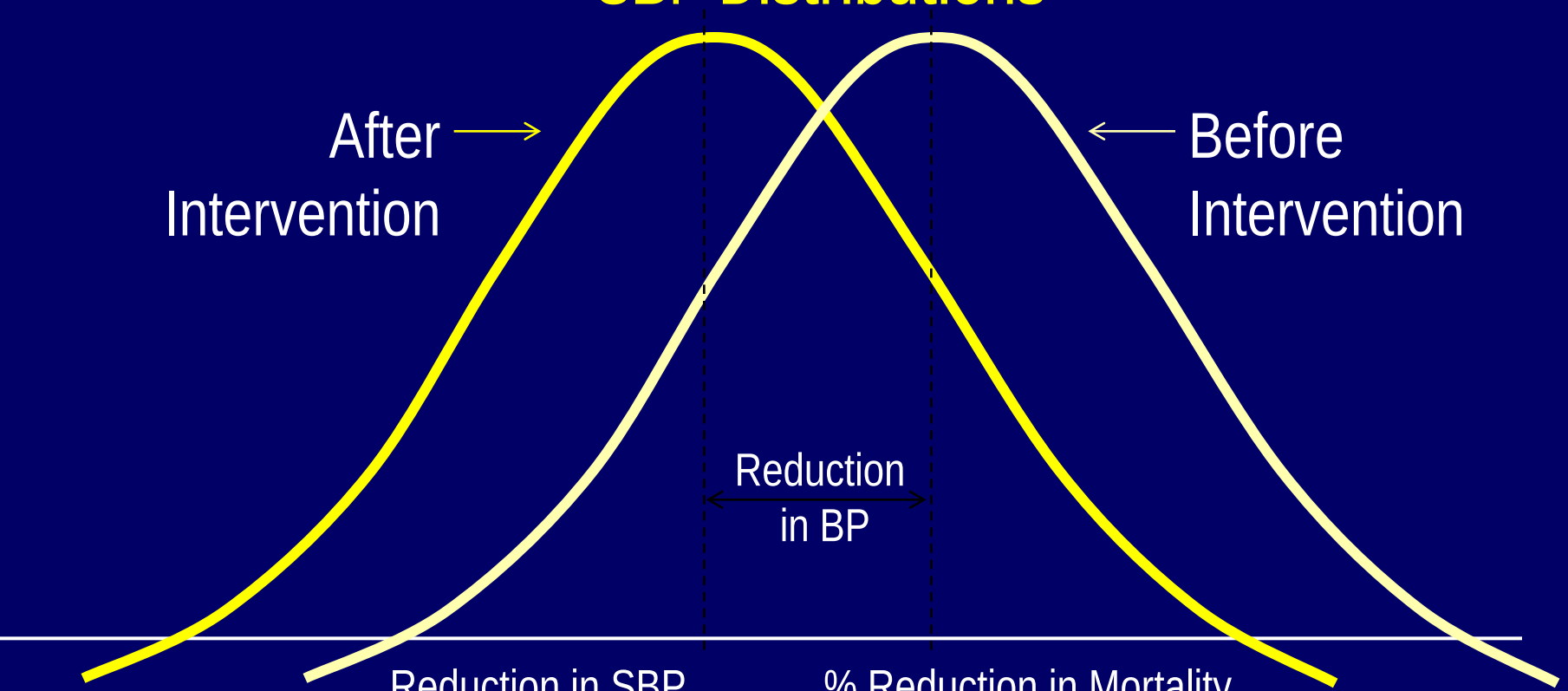
Women

Blood Pressure Control and CV Outcomes

- In clinical trials small reductions in diastolic BP (5-6 mmHg) resulted in:
  - 42% reduction in stroke
  - 52% reduction in HF
  - 21% reduction in cardiac death
  - 16% reduction in non-fatal MI

Population-Based Strategy

SBP Distributions



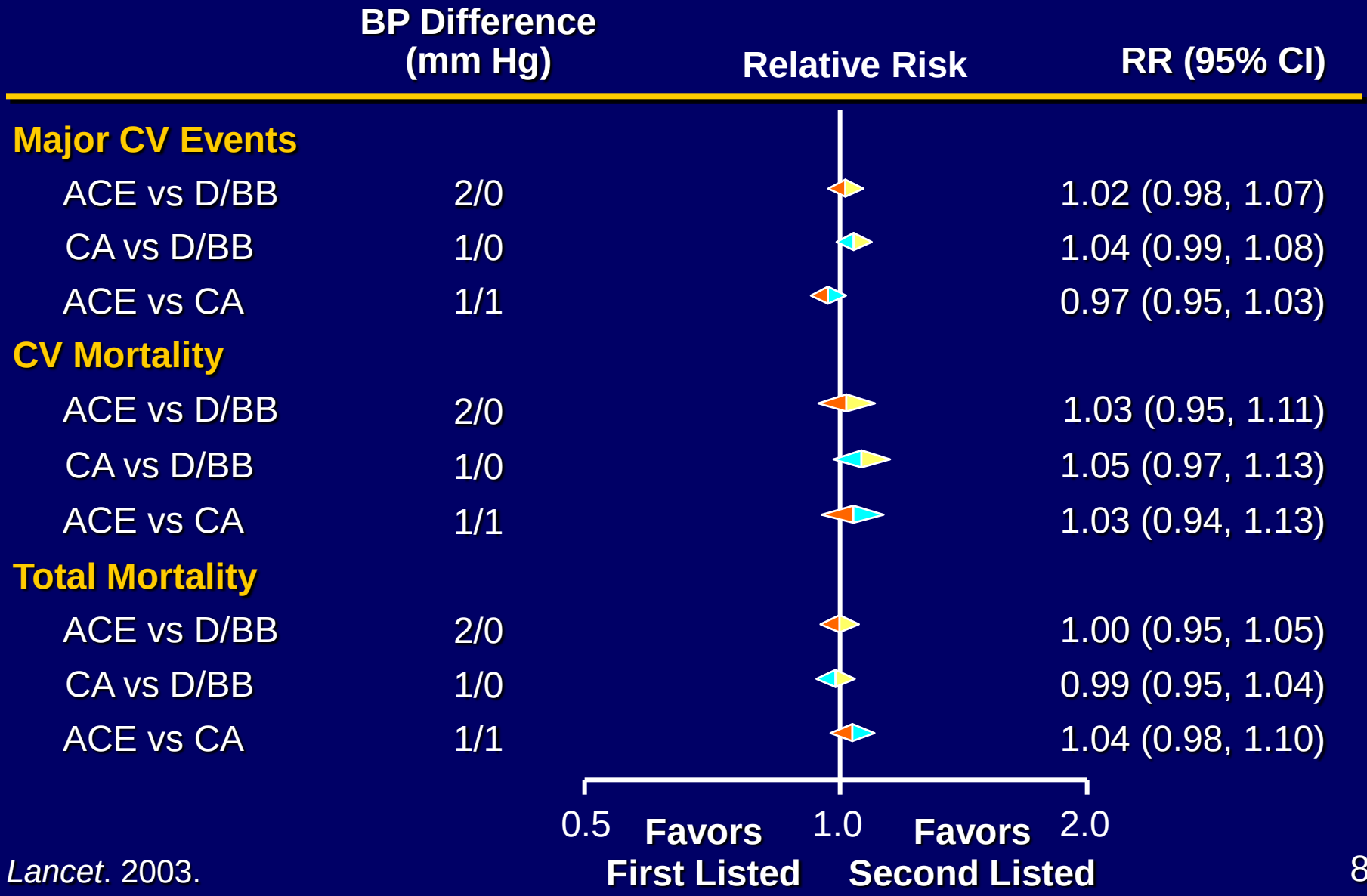
Reduction in SBP mmHg	% Reduction in Mortality		
	Stroke	CHD	Total
2	–6	–4	–3
3	–8	–5	–4
5	–14	–9	–7

Treatment of Hypertension to Prevent Vascular Events

- Is it Just Blood Pressure Reduction?
- Does the type of Drug make a difference?
- Are there other factors that influence outcomes?

BP-Lowering Treatment Trialists

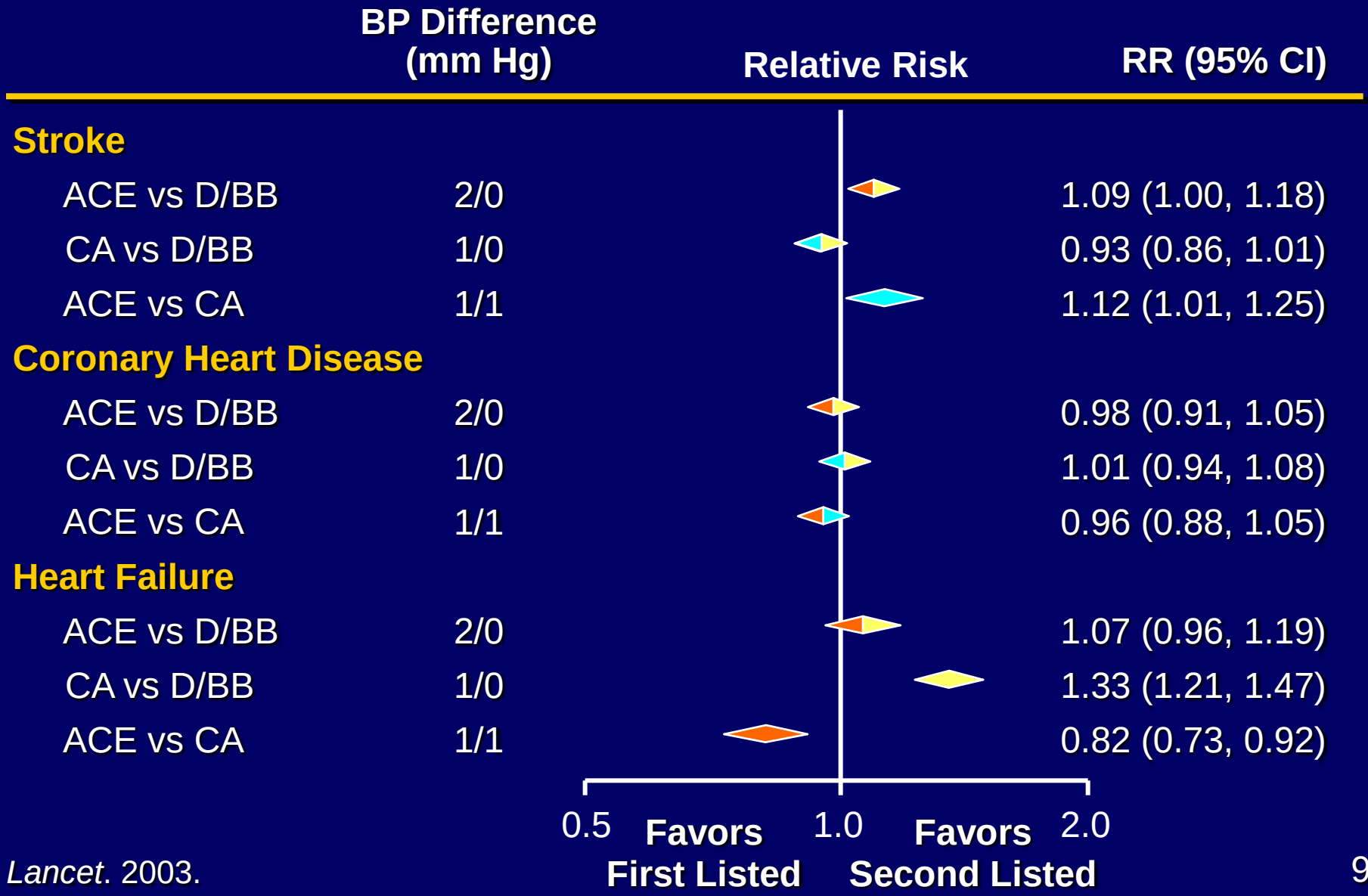
N-162,000



Lancet. 2003.

BP-Lowering Treatment Trialists

Comparisons of different active treatments



Lancet. 2003.

It Is Not Beyond the Blood Pressure; It Is the Blood Pressure (stupid, Ray Gifford)

William J. Elliott, MD, PhD; M. Charlotte Jonsson; Henry R. Black, MD

Blood Pressure Differences and Major CV Outcomes in Large Actively Controlled Clinical Trials of Antihypertensive Agents

	Concordance Between			Discordance Between	
Trial	ΔSBP,* mm/Hg	Patients With Major CV Events,† n (OR, *P*)	Trial	ΔSBP,* mm Hg	Patients With Major CV Events,† n (Odds Ratio, *P*)
ALLHAT (D vs α)	2.4	2829 vs 1947 (0.83, <0.001)	ANBP-2 (D vs ACE-I)	1.4	394 vs 429 (0.88, 0.07)
ALLHAT (D vs ACE-I)	2.3	3941 vs 2514 (0.91, <0.001)	INSIGHT (D vs CCB)	0.1	397 vs 383 (0.96, 0.57)
ALLHAT (D vs CCB)	1.1	3941 vs 2432 (0.96, 0.12)	MOSES (CCB vs ARB)	1.5	171 vs 149 (0.82, 0.12)
ASCOT (β vs CCB)	−2.7	1602 vs 1362 (1.20, <0.0001)	SHELL (D vs CCB)	1.1	66 vs 65 (0.98, ≈0.92)
INVEST (β vs CCB)	−0.3	1119 vs 1150 (0.97, 0.56)			
VALUE (CCB vs ARB)	2.2	1021 vs 1074 (est, 1.05, ≈0.28)			
STOP-2 (D/β vs CCB)	−0.3	637 vs 636 (0.99, 0.90)			
STOP-2 (D/β vs ACE-I)	−0.3	637 vs 586 (0.90, 0.10)			
LIFE (β vs ARB)	−1.4	588 vs 508 (0.85, 0.0009)			
NORDIL (D/β vs CCB)	3.1	453 vs 466 (1.04, 0.53)			
CAPPP (β vs ACE-I)	3.0	438 vs 401 (1.10, 0.18)			
CONVINCE (D/β vs CCB)	−0.1	365 vs 364 (0.99, 0.88)			

D indicates diuretic; α, α-blocker; est, estimated; and β, β-blocker. "Large" indicates that there were >50 major CV events in each randomized arm.
*Change in systolic blood pressure for first mentioned agent minus that of second mentioned agent.
†As defined by each trial.

Is it the Pressure or the Drug?

CONTROVERSIES IN CARDIOVASCULAR MEDICINE

Management of hypertension: is it the pressure or the drug?

Blood Pressure Reduction Is Not the Only Determinant of Outcome

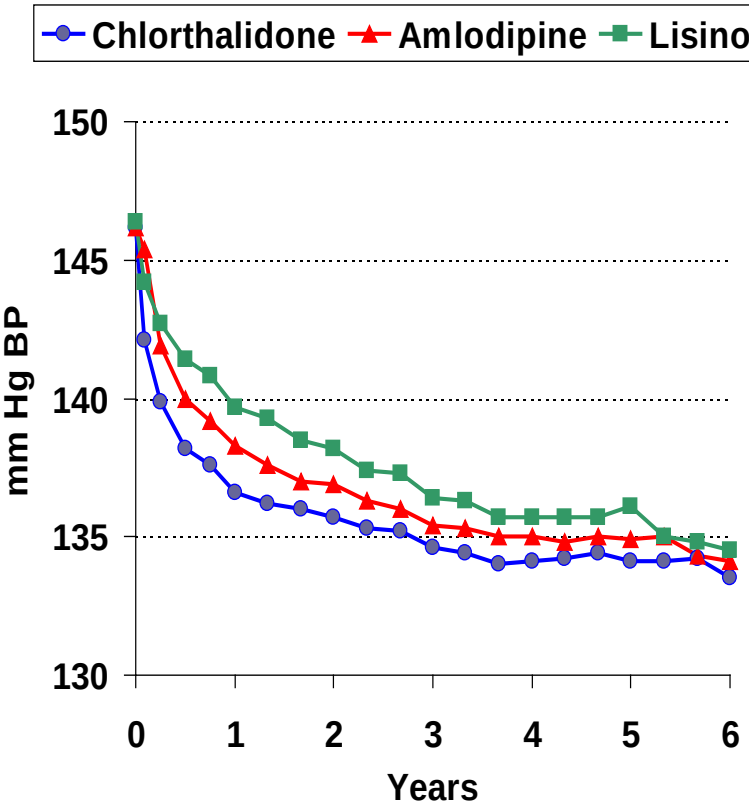
Peter S. Sever, FRCP; Neil R. Poulter, FRCP

Circulation 2006;113:2754-74

In the Litterature

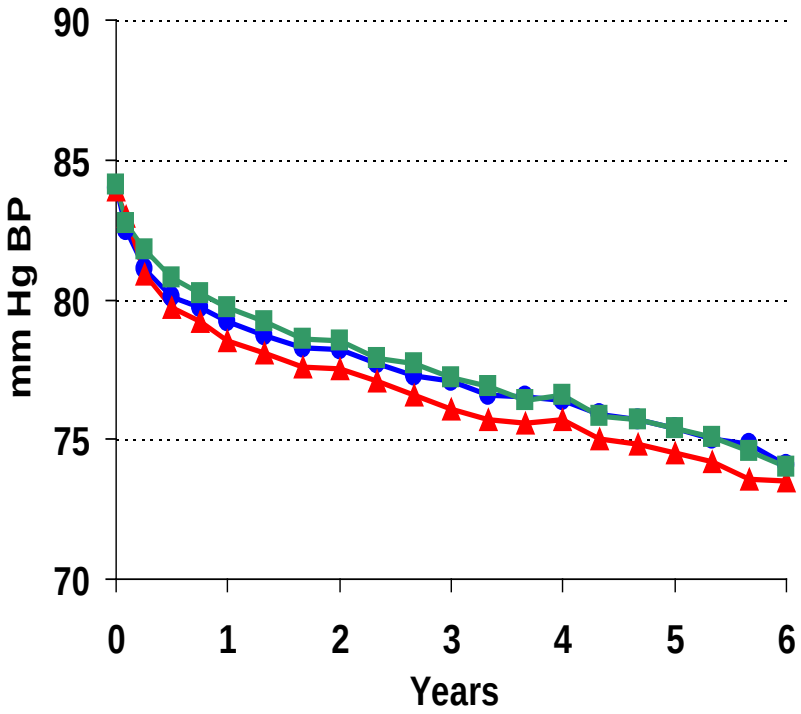
- Conflicting studies
- Conflicting results

ALLHAT BP Results by Treatment Group



Compared to chlorthalidone:

SBP significantly higher in the amlodipine group (~1 mm Hg) and the lisinopril group (~2 mm Hg).

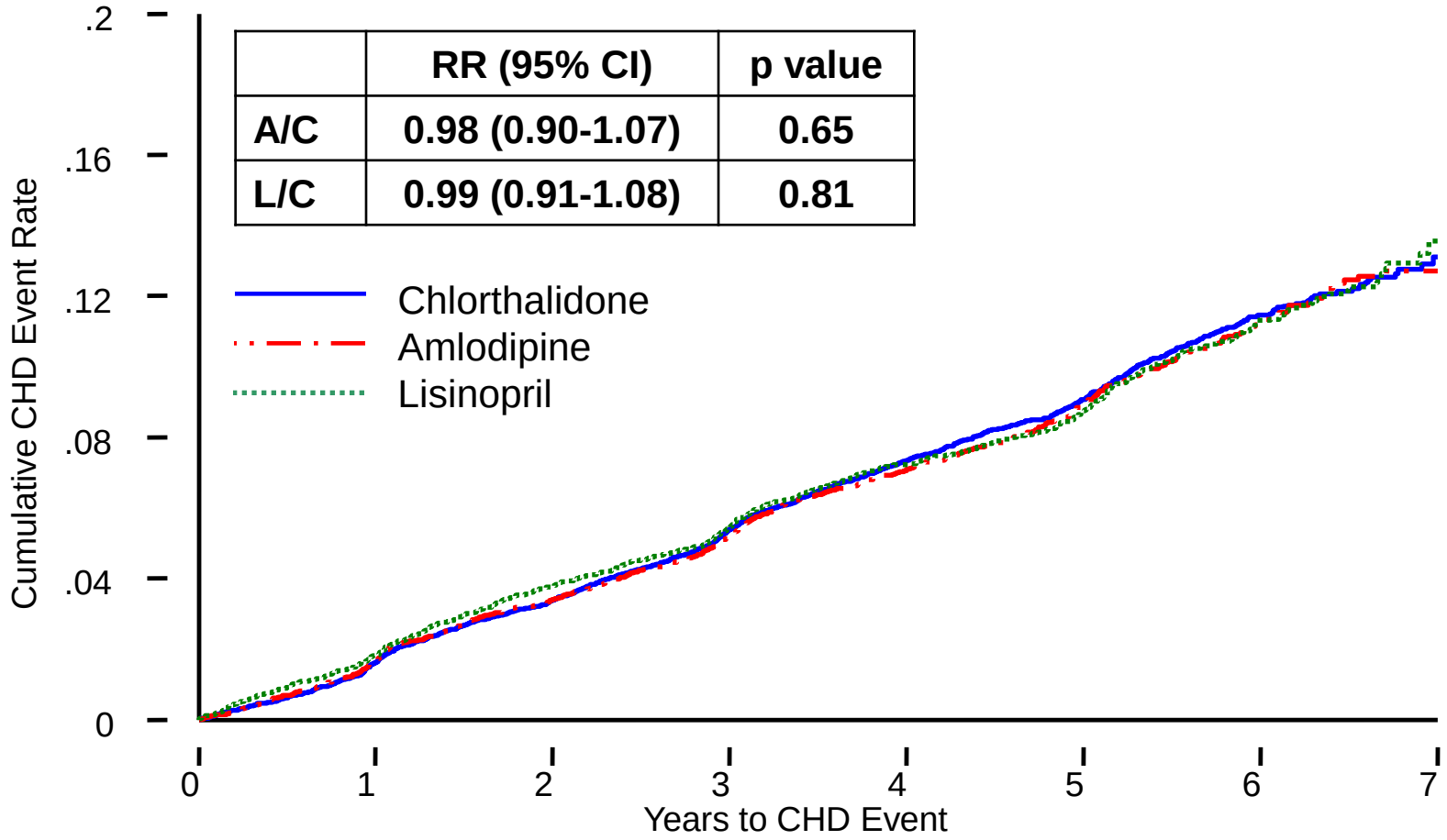


Compared to chlorthalidone:

DBP significantly lower in the amlodipine group (~1 mm Hg).

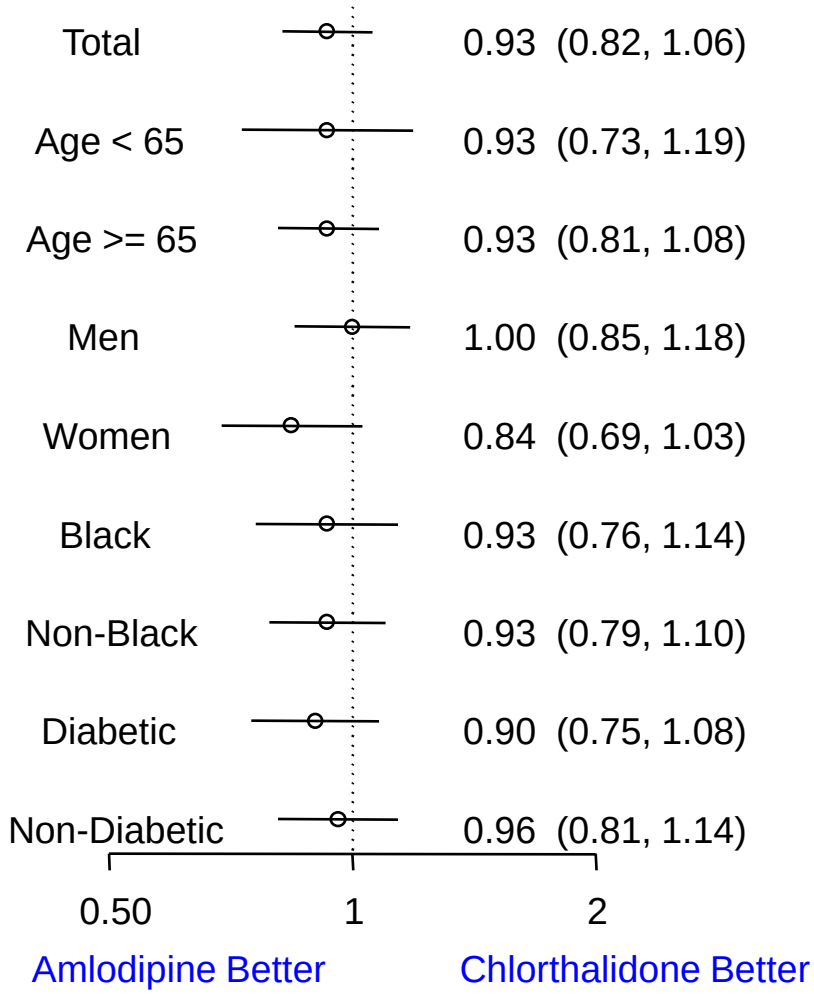
Cumulative Event Rates for the Primary Outcome (Fatal CHD or Nonfatal MI) by ALLHAT Treatment Group

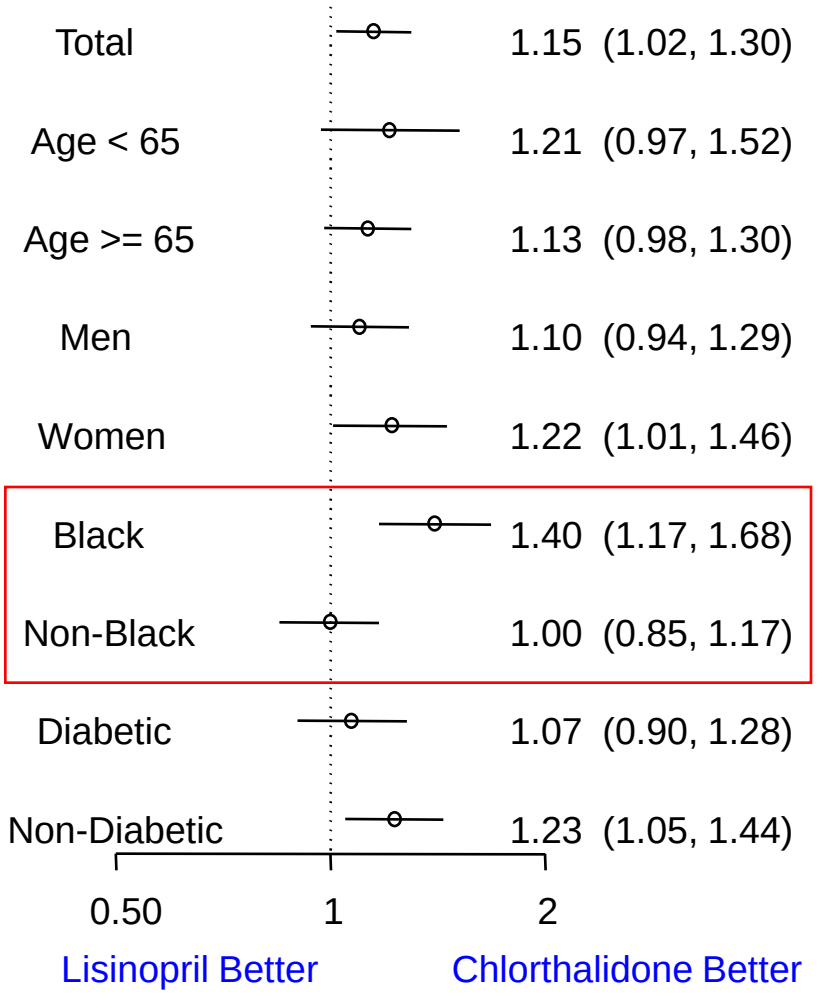
	RR (95% CI)	p value
A/C	0.98 (0.90-1.07)	0.65
L/C	0.99 (0.91-1.08)	0.81



Number at Risk:								
Chlorthalidone	15,255	14,477	13,820	13,102	11,362	6,340	2,956	209
Amlodipine	9,048	8,576	8,218	7,843	6,824	3,870	1,878	215
Lisinopril	9,054	8,535	8,123	7,711	6,662	3,832	1,770	195

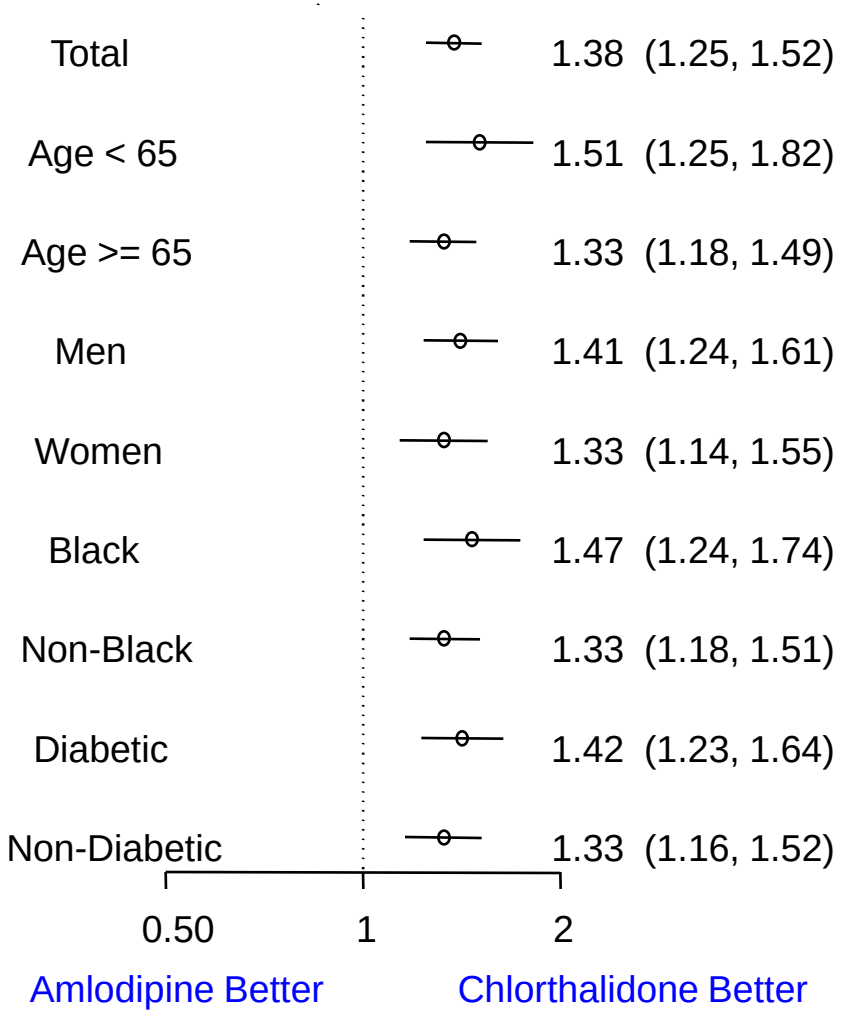
Stroke – Subgroup Comparisons – RR (95% CI)

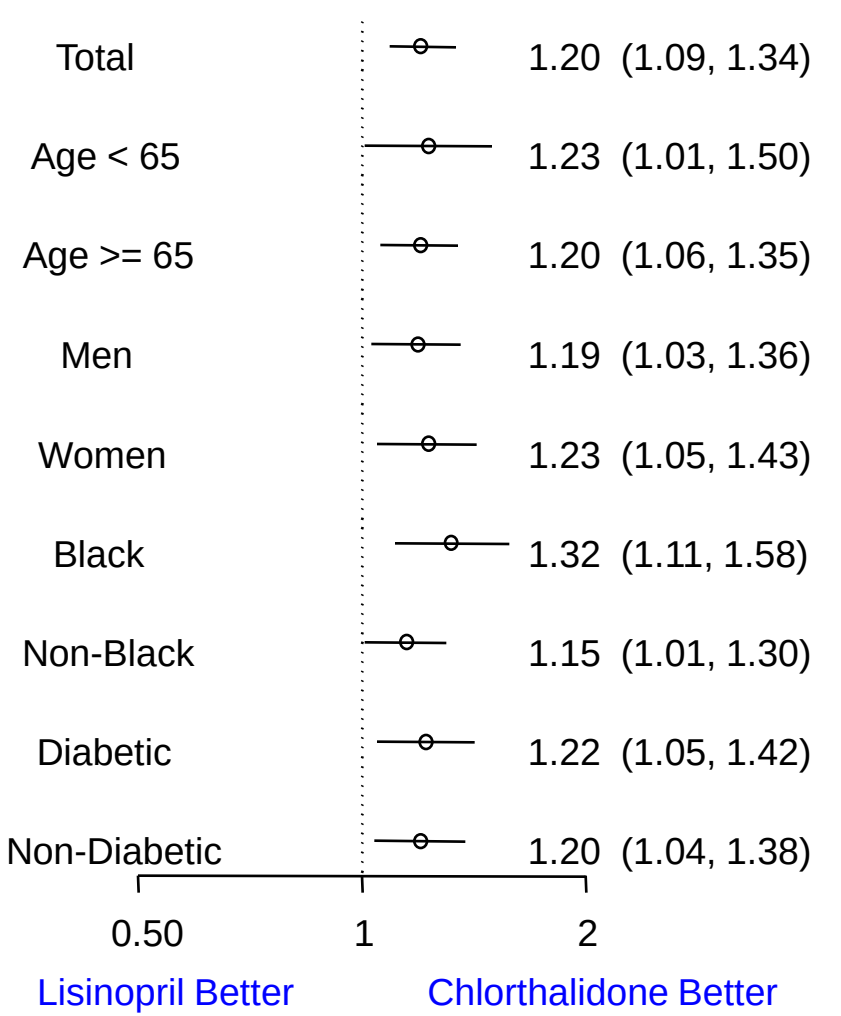




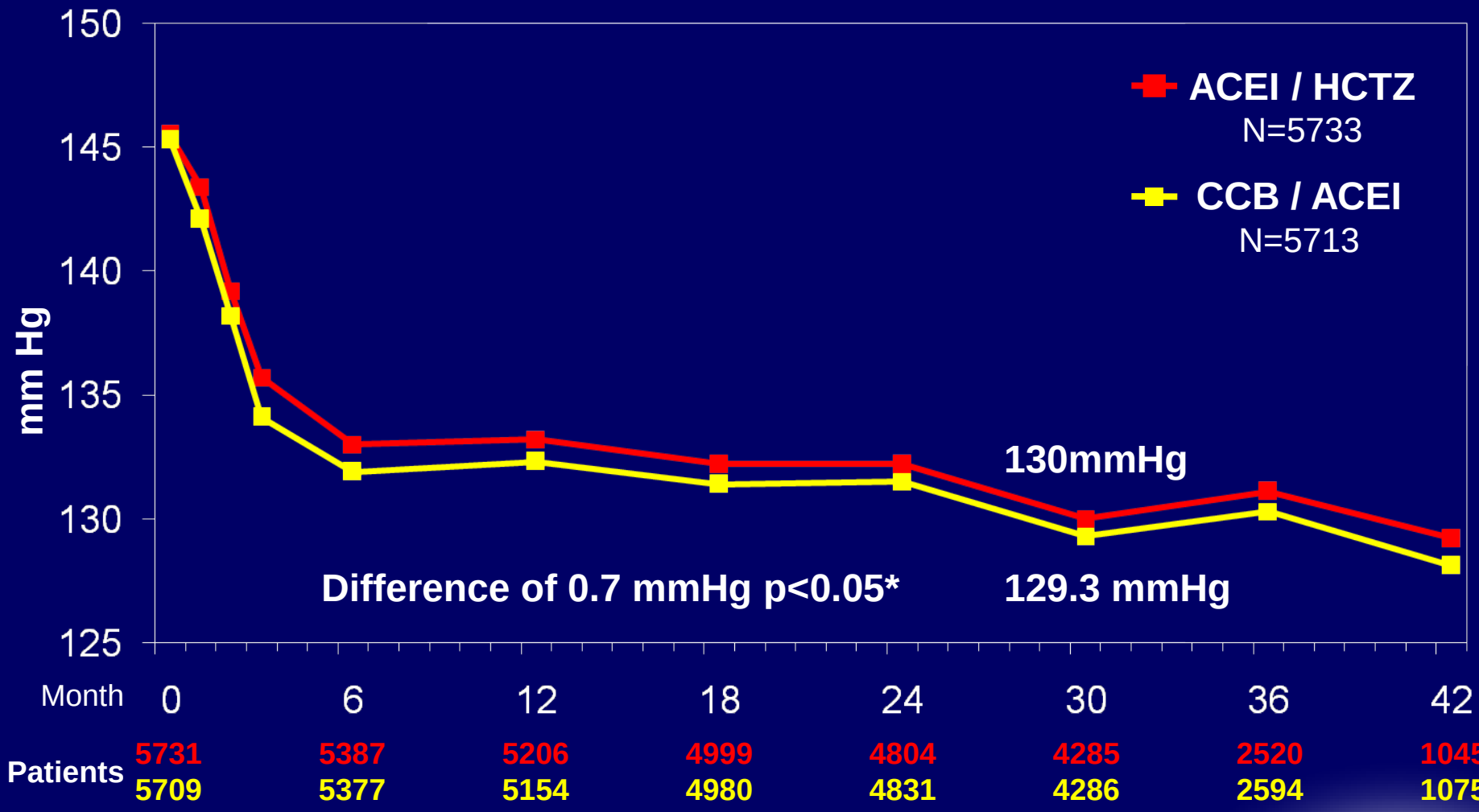
P = .01 for interaction

Heart Failure – Subgroup Comparisons – RR (95% CI)





ACCOMPLISH:
Systolic Blood Pressure Over Time

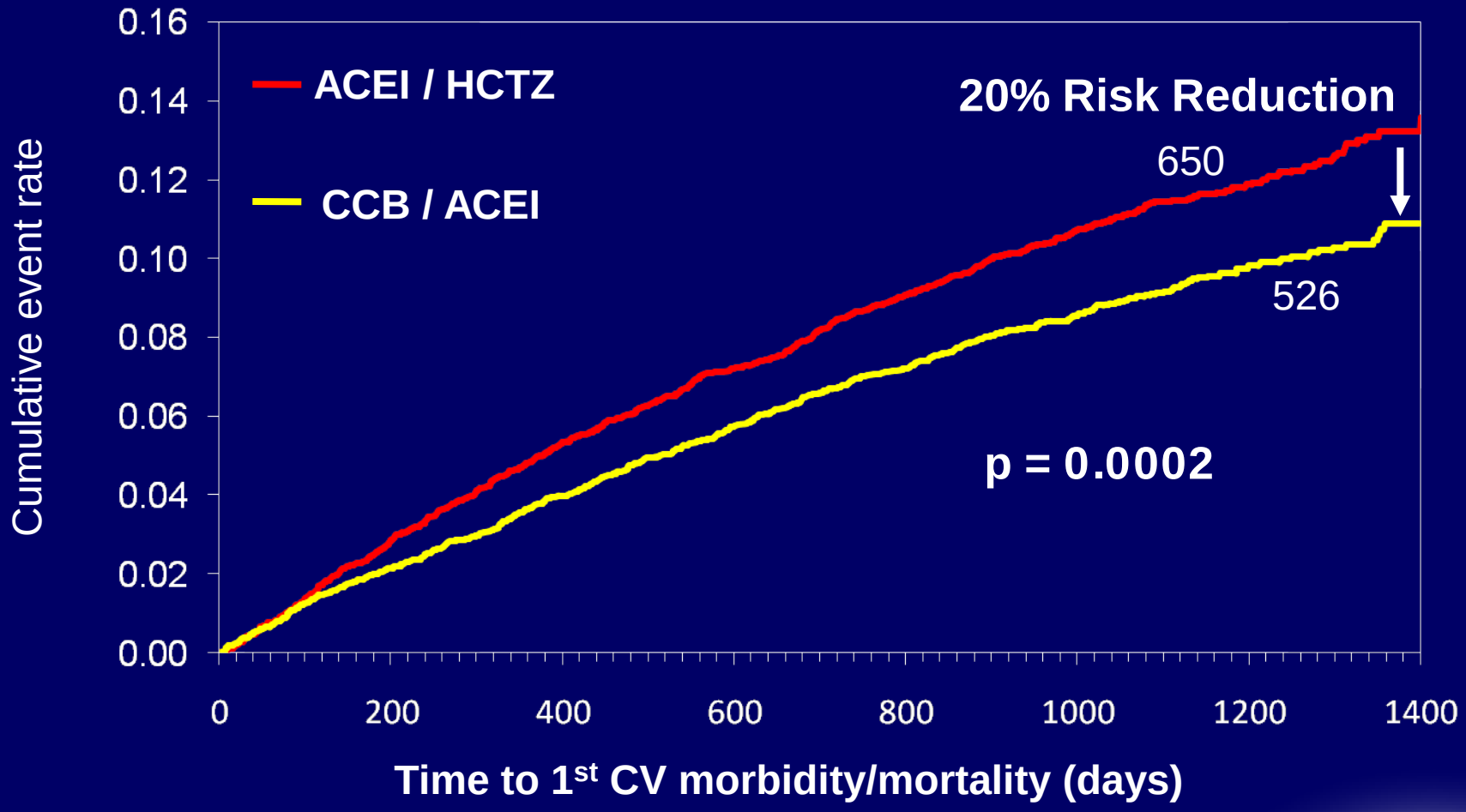


*Mean values are taken at 30 months F/U visit

DBP: 71.1 DBP: 72.8

ACCOMPLISH

ACCOMPLISH:
Kaplan Meier for Primary Endpoint



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

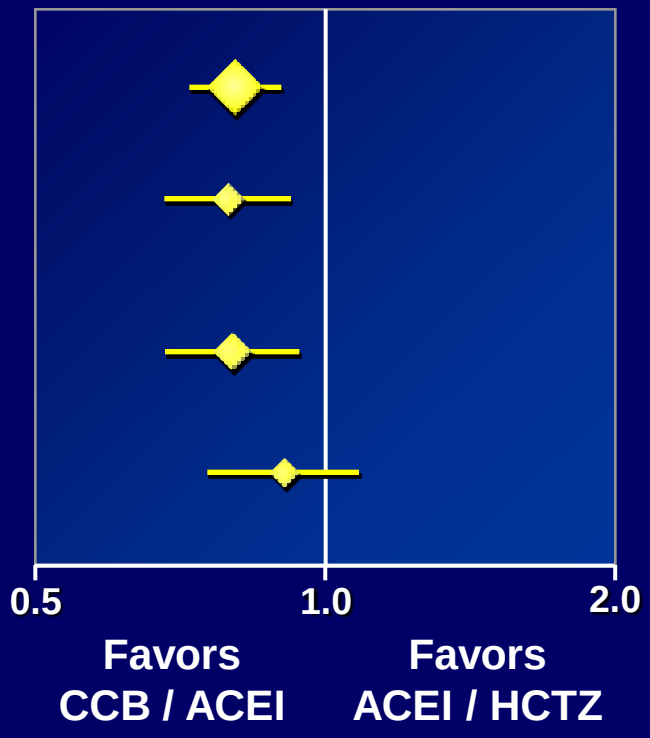
INTERIM RESULTS Mar 08

ACCOMPLISH

Primary and Other Endpoints

Incidence of adjudicated primary endpoints, based upon cut-off analysis date 3/24/2008

(Intent-to-treat population)



	Risk Ratio (95%)
Composite CV mortality/morbidity	0.80 (0.72–0.90)
Primary w/o revascularization	0.79 (0.68–0.92)
Hard CV endpoint (CV death, non-fatal MI, non-fatal stroke)	0.80 (0.68–0.94)
All cause mortality	0.90 (0.75–1.08)

INTERIM RESULTS Mar 08

ACCOMPLISH

What can we do to Better Taylor our Therapies? To better improve vascular protection

- Personalized Medicine
  - Pharmacogenomics
  - Pharmacogetics
- Pleotropic Effects of Medicine
  - Focus on RAAS Blockers
  - On ARBs

Personalized Medicine

- Pharmacogenetics / pharmacogenomics examine the impact of genetic variation on the response to medications.
- This approach is aimed at tailoring drug therapy being most appropriate for an individual patient
- Potential benefits of increasing the efficacy and safety of medications.
- Provide Therapies that optimize Vascular protection
- Gene-centered research may also speed the development of novel therapeutics.

HTN: The Problem

- Treatment of hypertension is by trial and error of drugs from the five first-line drug classes
  - diuretics, β-blockers, ACEI, ARB, CCB
- Current approach not working well
  - Estimated that only 34% of HTN with controlled BP
- High rate of polypharmacy, due in part to the use of drug that are ineffective at BP lowering
- Equal BP reduction with different drugs may not mean equal event reduction
- Potential for pharmacogenomics: Through use of genetic and non-genetic information prior to therapy, identify more optimal therapy for the patient

Personalized Medicine for the Treatment of Hypertension

- "Individualized" approach now encourages selection of treatment based on:
  - Age,
  - Race
  - Co morbidities
  - Cost
  - Potential side effects

  Does not much mechanism of action with underlying pathophysiology
- Laragh " Vasoconstriction-Volume Analysis" Based on Plasma Renin Activity
  - Low 27%
  - Nomral 57%
  - High 16%
- Personalized Medicine more ambitious
- Pharmacogenetics/Pharmacogenomics to determine:
  - BP response and
  - vascular protection

Personalized Medicine

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®
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Relevance of Genetics and Genomics for Prevention and Treatment of Cardiovascular Disease

A Scientific Statement From the American Heart Association Council on Epidemiology and Prevention, the Stroke Council, and the Functional Genomics and Translational Biology Interdisciplinary Working Group

Donna K. Arnett, PhD, FAHA, Chair; Alison E. Baird, MD, PhD; Ruth A. Barkley, PhD; Craig T. Basson, MD, FAHA; Eric Boerwinkle, PhD; Santhi K. Ganesh, MD; David M. Herrington, MD, FAHA; Yuling Hong, MD, PhD, FAHA; Cashell Jaquish, PhD; Deborah A. McDermott, MS; Christopher J. O'Donnell, MD, FAHA

Circulation **June 5, 2007**

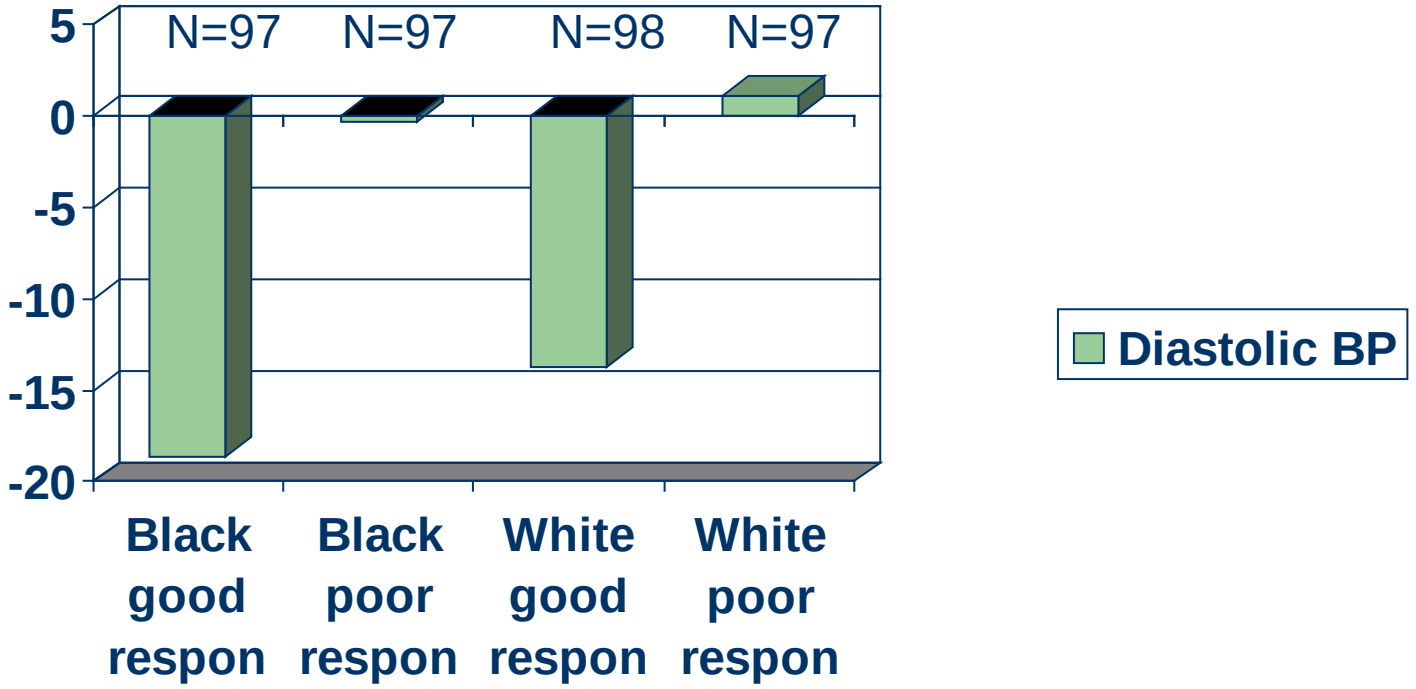
Candidate Genes Implicated in Hypertension

TABLE 3. Select Candidate Genes Implicated in High Blood Pressure and Essential Hypertension

Gene Symbol (Former Gene Symbol)	Gene	Selected References
HSD11B2	11-β-Hydroxysteroid dehydrogenase type II	177
ADD1	Adducin 1	178
ADRA1B	α-1b Adrenergic receptor	179, 180
ADRA2A	α-2a Adrenergic receptor	181
CYP11B2	Cytochrome P450, subfamily XIB, polypeptide 2	182, 183
ACE	Angiotensin I–converting enzyme	184, 185
AGTR1	Angiotensin receptor 1	186
NPPA (ANP)	Natriuretic peptide precursor A	187
AGT	Angiotensin I	188
ADRB2	β-2 Adrenergic receptor	189, 190
BDKRB2	Bradykinin receptor B2	191, 192
C3	Complement component 3	193
EDNRA	Endothelin receptor, type A	194
NOS3 (ENOS)	Nitric oxide synthase 3	195
EDN1	Endothelin 1	196
EDN2	Endothelin 2	197
SCNN1B	Sodium channel, non–voltage-gated 1, β-subunit	134
GNB3	Guanine nucleotide-binding protein, β-3	198
GCCR (NR3C1, GCR)	Glucocorticoid receptor	199
GH1	Growth hormone 1	200
INSR	Insulin receptor	201
IGF1	Insulin-like growth factor I	202
LPL	Lipoprotein lipase	203
PLA2G1B (PLA2)	Phospholipase A2, group IB	204
PTGIS	Prostaglandin I2 synthase	205
PTGER2	Prostaglandin E receptor 2, EP2 subtype	206
REN	Renin	207
SAH	Hypertension-associated SA, rat, homolog of	208
SLC4A5	Solute carrier family 4 (sodium bicarbonate cotransporter), member 5	176
SLC12A3 (TSC)	Solute carrier family 12 (sodium/chloride transporter), member 3	209
SLC12A1 (NKCC2)	Solute carrier family 12 (sodium/potassium/chloride transporter), member 1	210
SLC9A3 (NHE3)	Solute carrier family 9, isoform a3	211
TNFRSF1B	Tumor necrosis factor receptor subfamily, member 1B	212
DRD1	Dopamine receptor D1	213

Portions adapted from tables presented in Oparil and Weber[144] (copyright 2000, with permission from Elsevier) and Kaplan et al[129] (copyright 2002, with permission from Lippincott Williams and Wilkins).

Single Nucleotide Polymorphism (SNP) for Blood Pressure Control



Hypertension 2008;52:359-65

Genomic Association Analysis Suggests Chromosome 12 Locus Influencing Antihypertensive Response to Thiazide Diuretic

- Haplotype trend regression identified a region of chromosome 12q15 in which haplotypes constructed from three successive SNPs:
  - rs 317689
  - rs 315135
  - rs 7997610

  Were significantly associated with diastolic BP response.

Hypertension 2008;52:359-65

The GenHAT study-Genetic ALLHAT

Pharmacogenetic Association of the *NPPA* T2238C Genetic Variant With Cardiovascular Disease Outcomes in Patients With Hypertension

Amy I. Lynch, PhD
Eric Boerwinkle, PhD
Barry R. Davis, MD, PhD
Charles E. Ford, PhD
John H. Eckfeldt, MD, PhD
Catherine Leiendecker-Foster, MS
Donna K. Arnett, PhD

Context The *NPPA* gene codes for the precursor of atrial natriuretic polypeptide, suggesting that *NPPA* may modulate the efficacy of some antihypertensive drugs.

Objective To test whether participants with minor *NPPA* alleles in the T2238C or G664A variants had different rates of cardiovascular disease or blood pressure (BP) changes than common allele homozygotes when treated with a diuretic vs other antihypertensive medications.

Design, Setting, and Patients Post hoc analysis of 38 462 participants with hypertension from ALLHAT, a multicenter randomized clinical trial conducted in the United States and Canada. Genotyping was performed from February 2004 to January 2005.

Intervention Participants were randomly assigned to receive a diuretic (chlorthalidone; n = 13 860), a calcium antagonist (amlodipine; n = 8174), an angiotensin-converting enzyme inhibitor (lisinopril; n = 8233), or an α-blocker (doxazosin; n = 8195).

Main Outcome Measure The primary outcome measure was coronary heart disease (CHD), defined as fatal CHD or nonfatal myocardial infarction (mean follow-up, 4.9 years). Secondary outcomes were stroke, all-cause mortality, combined cardiovascular disease outcomes, and 6-month systolic and diastolic BP changes. Genotype × treatment interactions were tested where genotypes were modeled additively and dominantly.

Results Depending on genotype, the event rates per 1000 person-years were 15.3 to 19.7 for CHO, 9.6 to 15.4 for stroke, and 27.4 to 30.7 for all-cause mortality. For the *NPPA* T2238C variant, lower event rates were found for the C allele carriers than for the TT homozygous individuals when comparing chlorthalidone and amlodipine (CHD: CC = 0.86; TC = 0.90; TT = 1.09; *P* = .03 [dominant model]; stroke: CC = 1.18; TC = 0.82; TT = 1.26; *P* = .01 [additive and dominant models]; all-cause mortality: CC = 0.87; TC = 0.98; TT = 1.12; *P* = .05 [dominant model]). Combined end points yielded similar results. Consistent with these clinical findings, 6-month changes in systolic BP for those with the CC genotype showed larger reductions with chlorthalidone (−6.5 mm Hg) than with amlodipine (−3.8 mm Hg), lisinopril (−2.4 mm Hg), or doxazosin (−3.8 mm Hg). Among those with the TT genotype, systolic BP differences between drugs were less (range, −5.4 to −7.5 mm Hg; *P* value, <.001 to .003 for interaction); diastolic BP showed similar results. We found no pharmacogenetic associations with the *NPPA* G664A variant.

Conclusions The *NPPA* T2238C variant was associated with modification of antihypertensive medication effects on cardiovascular disease and BP. Minor C allele carriers experienced more favorable cardiovascular disease outcomes when randomized to receive a diuretic, whereas TT allele carriers had more favorable outcomes when randomized to receive a calcium channel blocker.

JAMA. 2008;299(3):296-307
www.jama.com

APPROXIMATELY 71 MILLION individuals in the United States have 1 or more types of cardiovascular disease (CVD), at least 65 million of whom have hypertension.[1] Although control of hypertension has been improving in recent years, among those treated, only about two-thirds have their hypertension controlled.[2] Seeking ways to reduce CVD morbidity and mortality by tailoring treatment to a patient's particular genotype is a laudable goal. To date, studies of gene polymorphisms in hypertension candidate genes, such as angiotensin-converting enzyme (*ACE*) and the angiotensin II receptor, have been shown to predict response to treatments such as ACE inhibition and angiotensin II blockade.[3] However, the use of information on genetic variability to predict response to antihypertensive therapy and, thus, guide therapeutic choices, has yet to be realized in the clinical setting.

The *NPPA* (atrial natriuretic precur-

JAMA 2008;299:296-307

Baseline Characteristics

	Chlorthalidone 15,255	Amlodipine 9,048	Lisinopril 9,054
Mean SBP/DBP	146 / 84	146 / 84	146 / 84
Treated (90%)	145 / 83	145 / 83	145 / 84
Untreated (10%)	156 / 89	157 / 90	156 / 89
Mean age, y	67	67	67
Black, %	35	36	36
Women, %	47	47	46
Current smoking %	22	22	22
History of CHD, %	26	24	25
Type 2 diabetes, %	36	37	36

Pharmacogenetic Association of the *NPPA* T2238C Genetic Variant With Cardiovascular Disease Outcomes in Patients With Hypertension

Objective To test whether participants with minor *NPPA* alleles in the T2238C or G664A variants had different rates of cardiovascular disease or blood pressure (BP) changes than common allele homozygotes when treated with a diuretic vs other antihypertensive medications.

Design, Setting, and Patients Post hoc analysis of 38 462 participants with hypertension from ALLHAT, a multicenter randomized clinical trial conducted in the United States and Canada. Genotyping was performed from February 2004 to January 2005.

JAMA 2008;299:296-307

Blood Pressure Reduction in Patients with CC Genotype

- Chlorothalidone -6.5 mmHg
- Amlodipine -3.8 mmHg
- Lisinopril -2.4 mmHg
- Doxazosin -3.8 mmHg

IS THE BENEFIT DUE TO BP REDUCTION?

JAMA 2008;299:296-307

The GenHAT study

Table 2. Main Effects of *NPPA* Gene Variants on CVD Outcomes

Outcome	*NPPA* T2238C TT (n = 23 177)	TC (n = 12 540)	CC (n = 2711)	*P* Value: Additive Genetic Model[a]	*P* Value: Dominant Genetic Model[b]	(
CHD (primary end point)						
Event frequency	1986	1077	199			
Event rate per 1000 person-years	19.7	19.6	16.3			
Unadjusted HR (95% CI)	1.0	1.00 (0.93-1.07)	0.82 (0.71-0.95)	.03	.32	
Adjusted HR (95% CI)[c]	1.0	1.05 (0.97-1.14)	0.92 (0.78-1.08)	.19	.44	
Stroke						
Event frequency	984	573	147			
Event rate per 1000 person-years	9.6	10.3	12.0			
Unadjusted HR (95% CI)	1.0	1.08 (0.97-1.19)	1.25 (1.05-1.48)	.03	.04	
Adjusted HR (95% CI)[c]	1.0	0.99	1.08	.64	.96	

The GenHAT study

End-stage renal disease				
Event frequency	260	156	55	
Event rate per 1000 person-years	2.5	2.8	4.4	
Unadjusted HR (95% CI)	1.0	1.10 (0.90-1.34)	1.74 (1.30-2.33)	<.001
Adjusted HR (95% CI)[c]	1.0	0.89 (0.71-1.12)	1.21 (0.87-1.69)	.19
Combined CHD				
Event frequency	3751	1924	379	
Event rate per 1000 person-years	39.0	36.7	32.3	
Unadjusted HR (95% CI)	1.0	0.94 (0.89-0.99)	0.83 (0.75-0.92)	<.001
Adjusted HR (95% CI)[c]	1.0	1.04	1.02	.39

JAMA 2008;299:296-307

The GenHAT study

Heart failure				
Event frequency	1627	829	179	
Event rate per 1000 person-years	16.1	15.1	14.7	
Unadjusted HR (95% CI)	1.0	0.94 (0.86-1.02)	0.91 (0.78-1.06)	.19
Adjusted HR (95% CI)[c]	1.0	0.92 (0.84-1.01)	0.90 (0.75-1.07)	.15
All-cause mortality				
Event frequency	3010	1768	404	
Event rate per 1000 person-years	27.4	29.7	30.7	
Unadjusted HR (95% CI)	1.0	1.08 (1.02-1.14)	1.10 (1.00-1.23)	.02
Adjusted HR (95% CI)[c]	1.0	1.04	1.02	.44

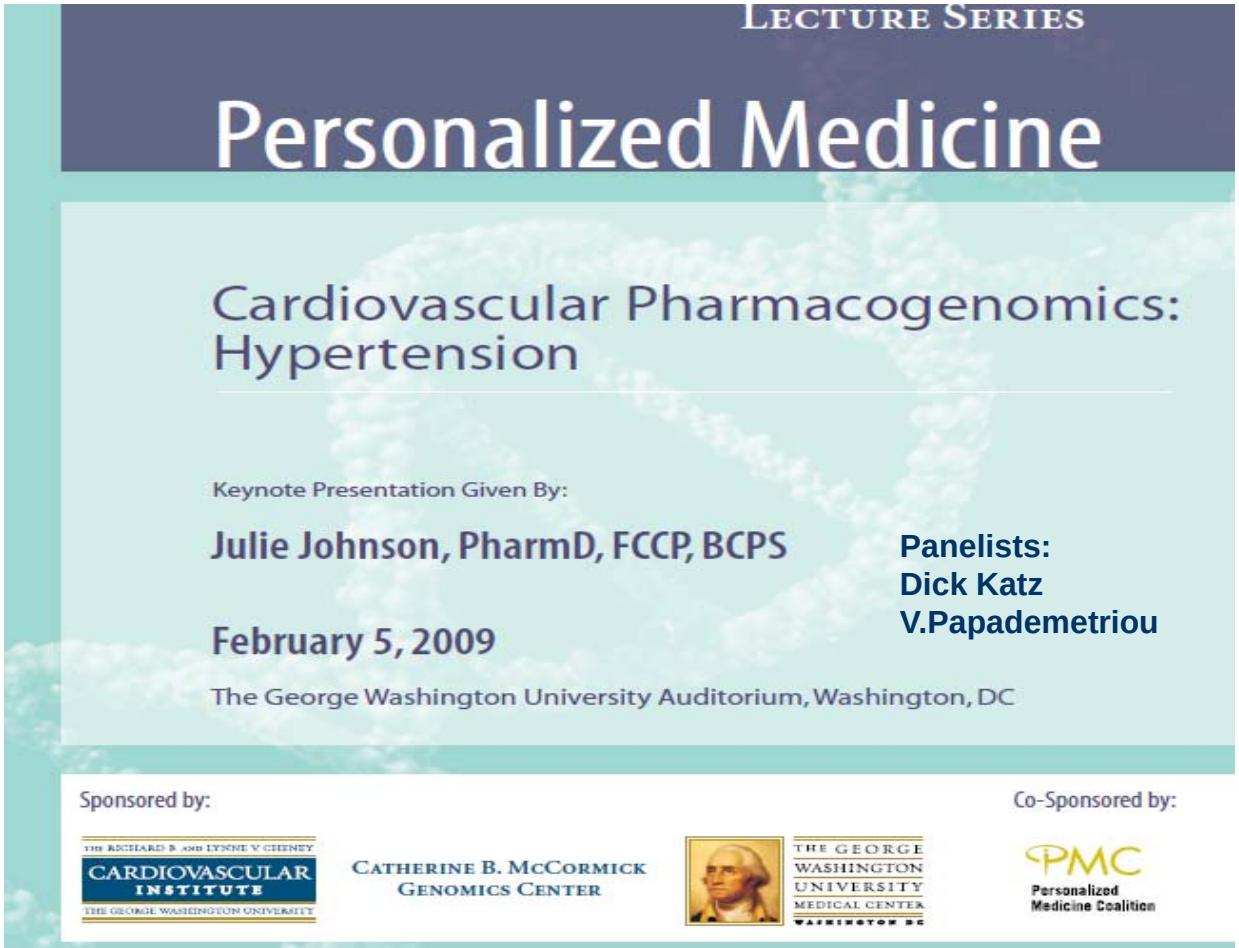
JAMA 2008;299:296-307

The GenHAT study

- The T2238C variant was associated with modification of drug effects on BP and CV events
- C allele carriers did better on Chlorothalidone
- TT allele carriers did better on amlodipine
- Not clear if differences in outcomes were related to differences in BP response or different susceptibility to vascular event

JAMA 2008;299:296-307

Personalized Medicine
Pharmacogenomics of Hypertension



Hypertension Pharmacogenetics: From BP response to outcomes

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Center for Pharmacogenomics
University of Florida
Gainesville, FL

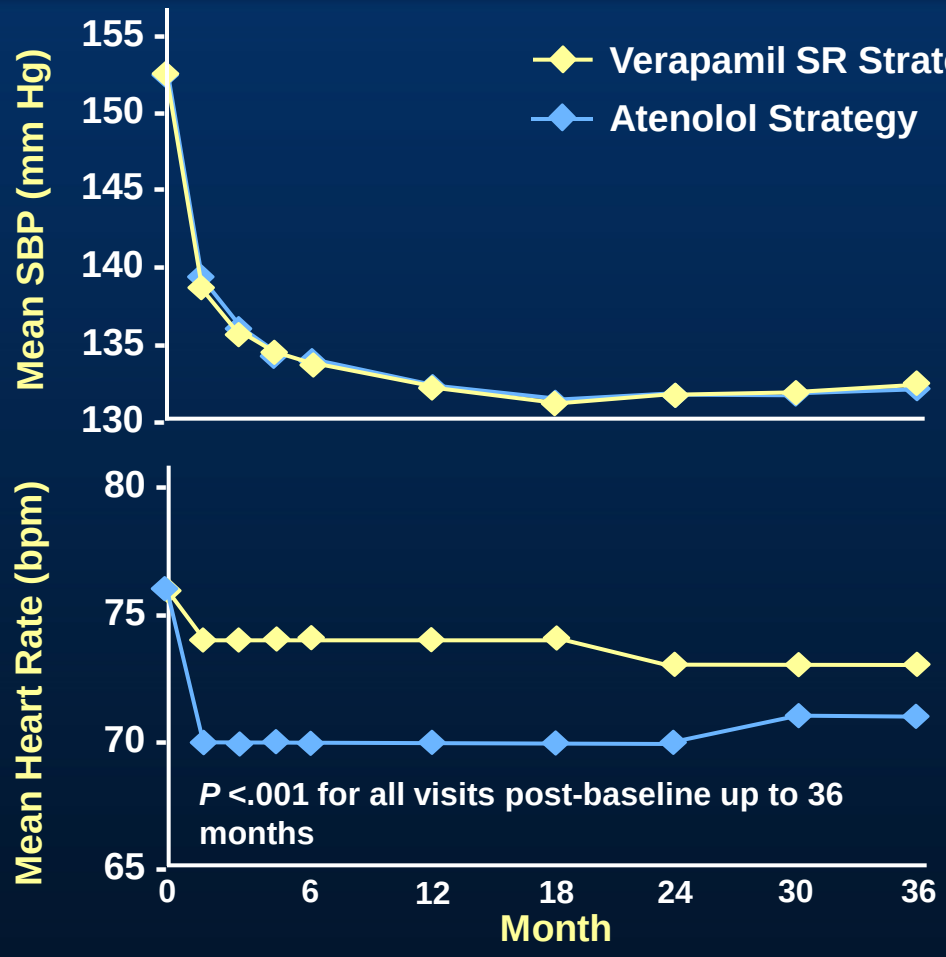
INVEST

(**IN**ternational **VE**rpamil Trandolapril **ST**udy)

- 22,599 patient international trial of primary care patients with CAD and hypertension
  - Genetic samples collected from 5,979 patients
- Patients randomized to:
  - Calcium channel blocker strategy
    - Trandolapril → HCTZ added for BP control
  - Beta-blocker strategy
    - HCTZ →trandolapril added for BP control
- Primary endpoint: death, nonfatal stroke, nonfatal MI
  - No differences in primary outcome between treatment strategies, with equal BP attained

Pepine, et al JAMA 2003;290:2805

INVEST: Reduced CV Risk With SBP Maintained Below Goal, Less Effect on Heart Rate

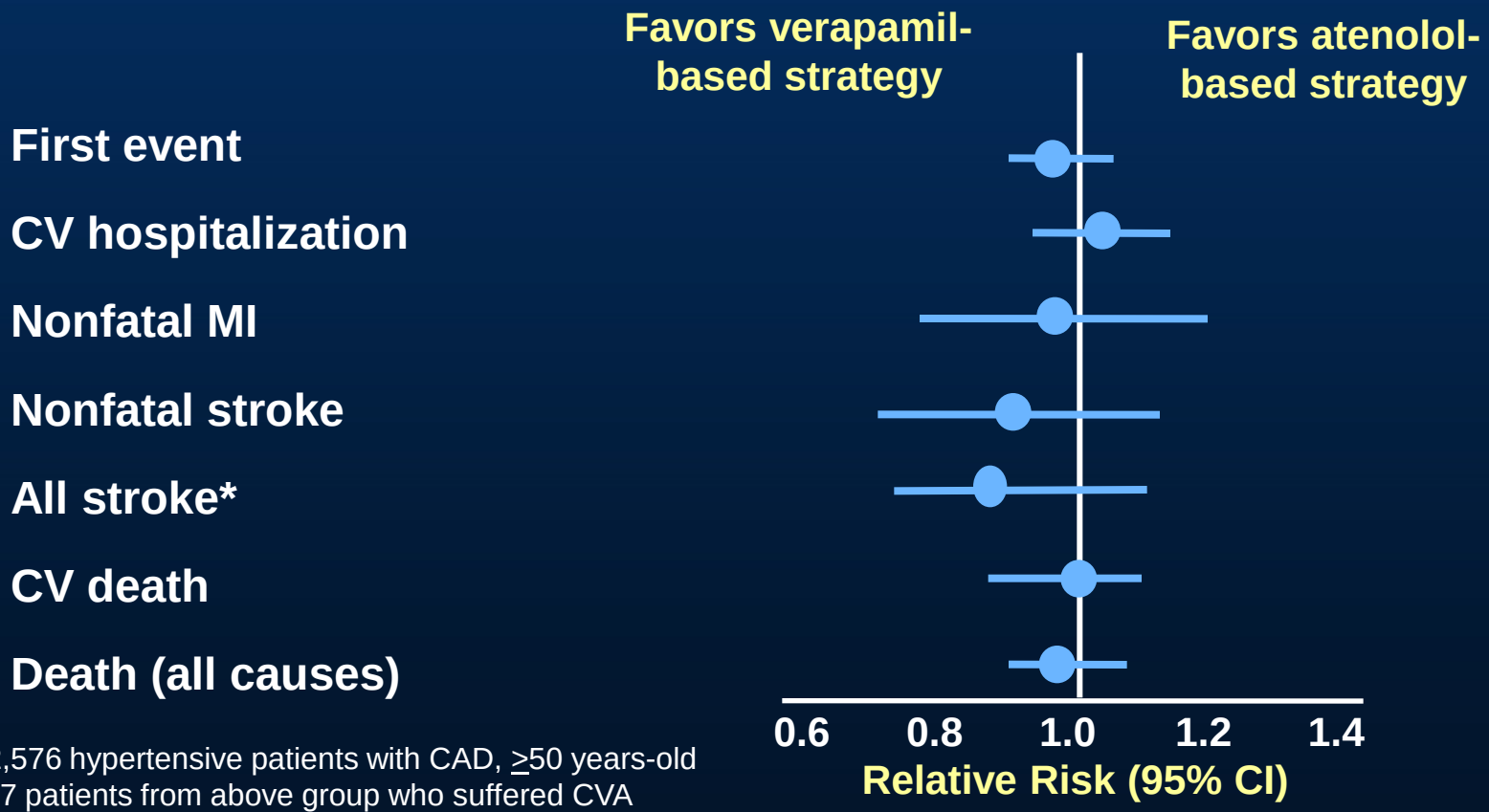


No. of Patients							
Verapamil SR Strategy	5335	4000	4081	3732	3788	2685	1400
Atenolol Strategy	5282	3959	4127	3701	3803	2743	1427

Cooper-DeHoff RM et al. Blood Pressure Control, Angina Episodes, and Cardiovascular Outcomes in Patients With Ischemia: The INternational Verapamil/Trandolapril STudy. Poster Presented at the Annual Scientific Session of the American College of Cardiology; March 2004; New Orleans, LA.

Trandolapril + Verapamil SR Reduces CV Risk in CAD Patients

CCB-based strategy equivalent to β-blocker-based strategy in patients with CAD



N = 22,576 hypertensive patients with CAD, ≥50 years-old
*N = 377 patients from above group who suffered CVA

Pepine CJ et al. *JAMA*. 2003;290:2805-2816.
Pepine C et al. Poster presented at ACC Annual Scientific Session 2005; March 6-9, 2005; Orlando, FL.

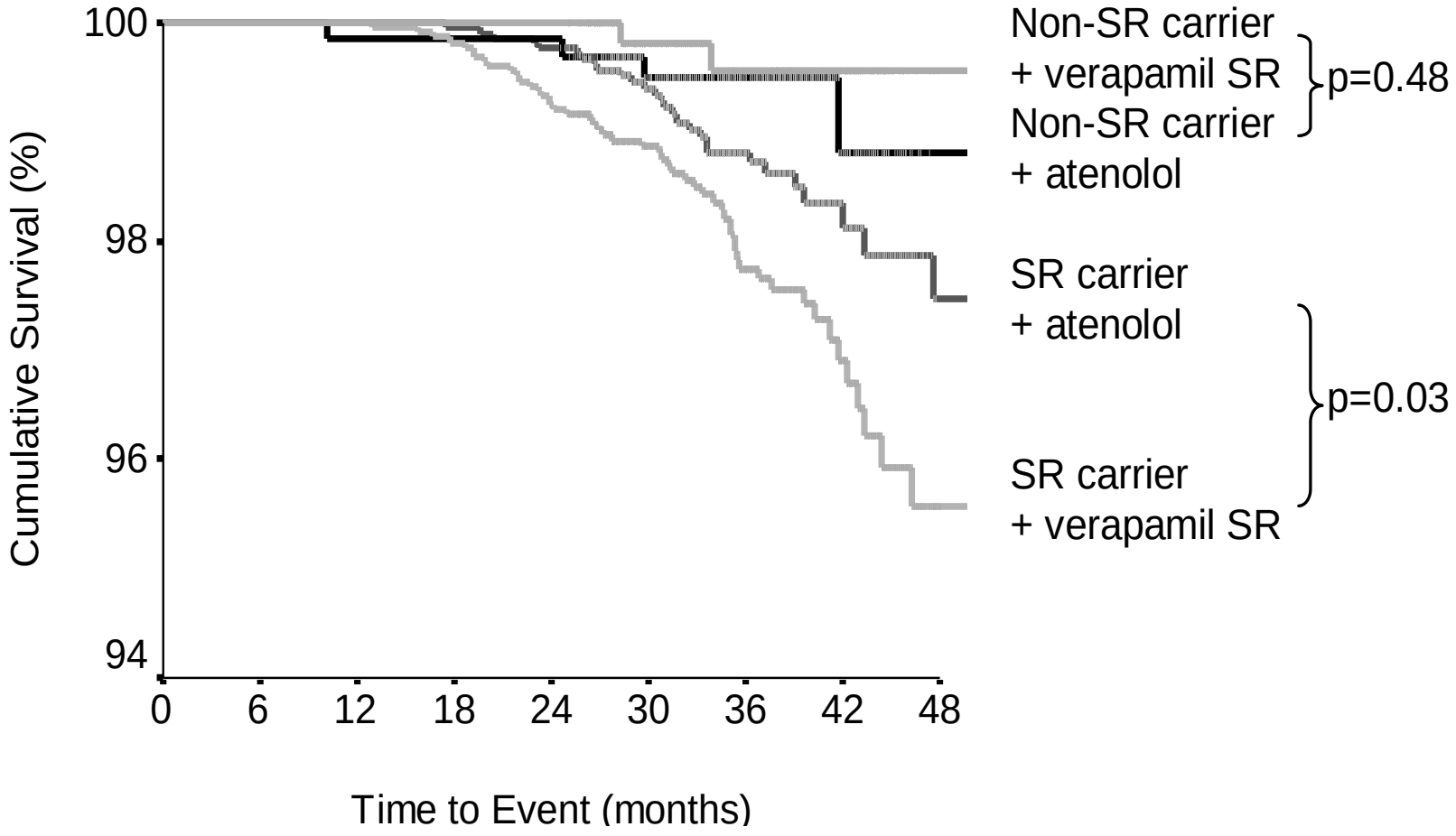
ADRB1 and INVEST-GENES Primary and Secondary Outcome Events

Incidence of outcome per 1000 patient years			
	SR carrier	**SR noncarrier**	**Adj HR(95%CI) SR vs non SR**
Primary Outcome	17.0	10.7	1.48 (1.05-2.08)
Secondary Outcomes			
Death	7.0	1.8	3.67 (1.69-7.97)
Nonfatal Stroke	5.2	5.0	0.99 (0.59-1.66)
Nonfatal MI	5.2	3.7	1.27 (0.71-2.29)

Clin Pharmacol Ther PMID: 18615004

ADRB1 pharmacogenetics and all cause mortality

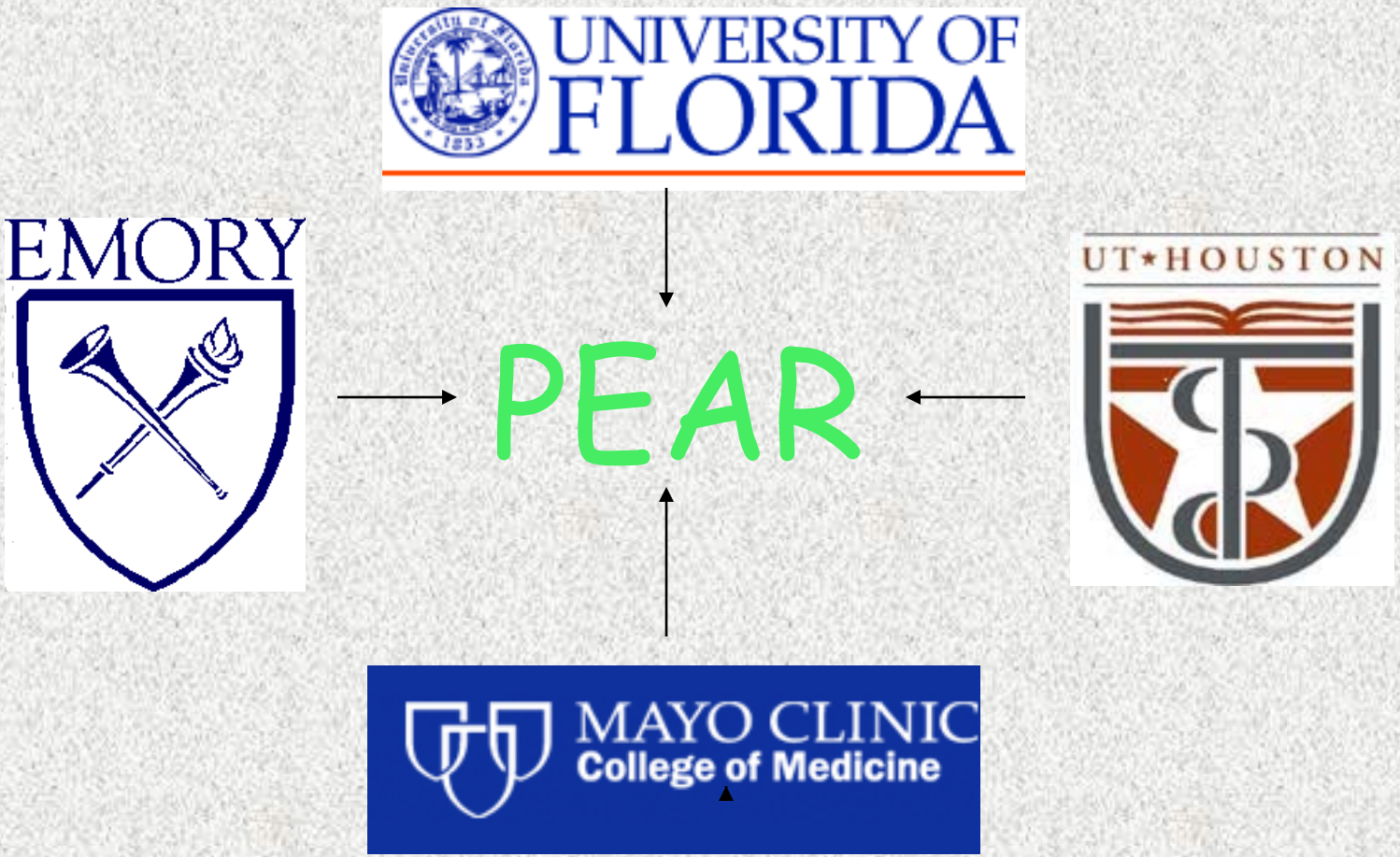
BP:



Clin Pharmacol Ther PMID: 18615004

PharmacoGenetics Research Network

Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR)



PEAR

- 800 subject study of response to thiazide diuretic (HCTZ) or β-blocker (atenolol) monotherapy and the combination
- Genetic associations with BP lowering (home and ambulatory BP) and adverse metabolic responses
- 70 candidate genes
- Genome-wide association

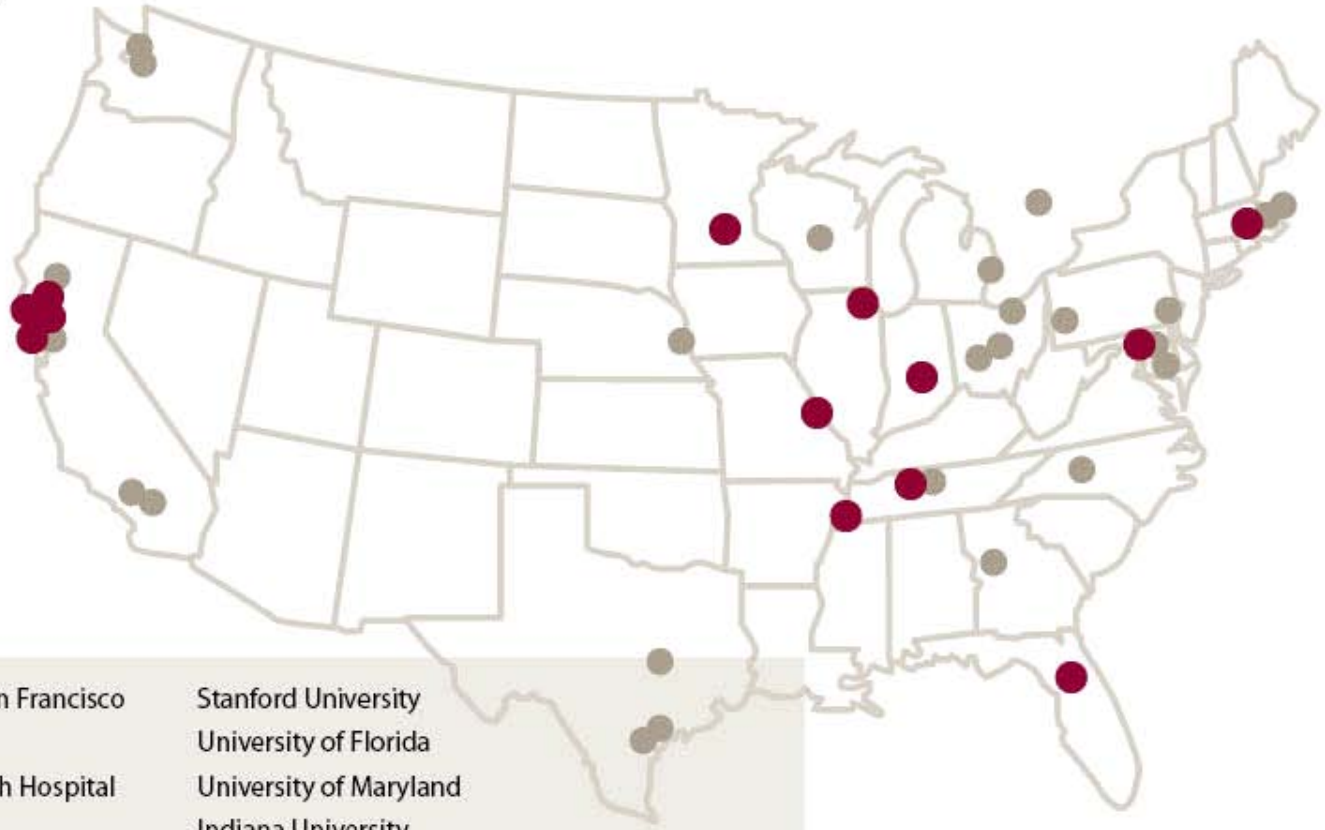
Pharmacogenetics Research Network

National Institutes of Health
U.S. Department of Health & Human Services

Research Sites

NIH Funding Institutes

NIGMS
NHLBI
NIDA
NCI
NIEHS
NIMH
NHGRI
NLM
ORWH



University of California, San Francisco
University of Chicago
St. Jude Children's Research Hospital
Mayo Clinic
Vanderbilt University
Washington University
SRI International
Stanford University
University of Florida
University of Maryland
Indiana University
Brigham and Women's Hospital
Children's Hospital of Oakland Research Institute

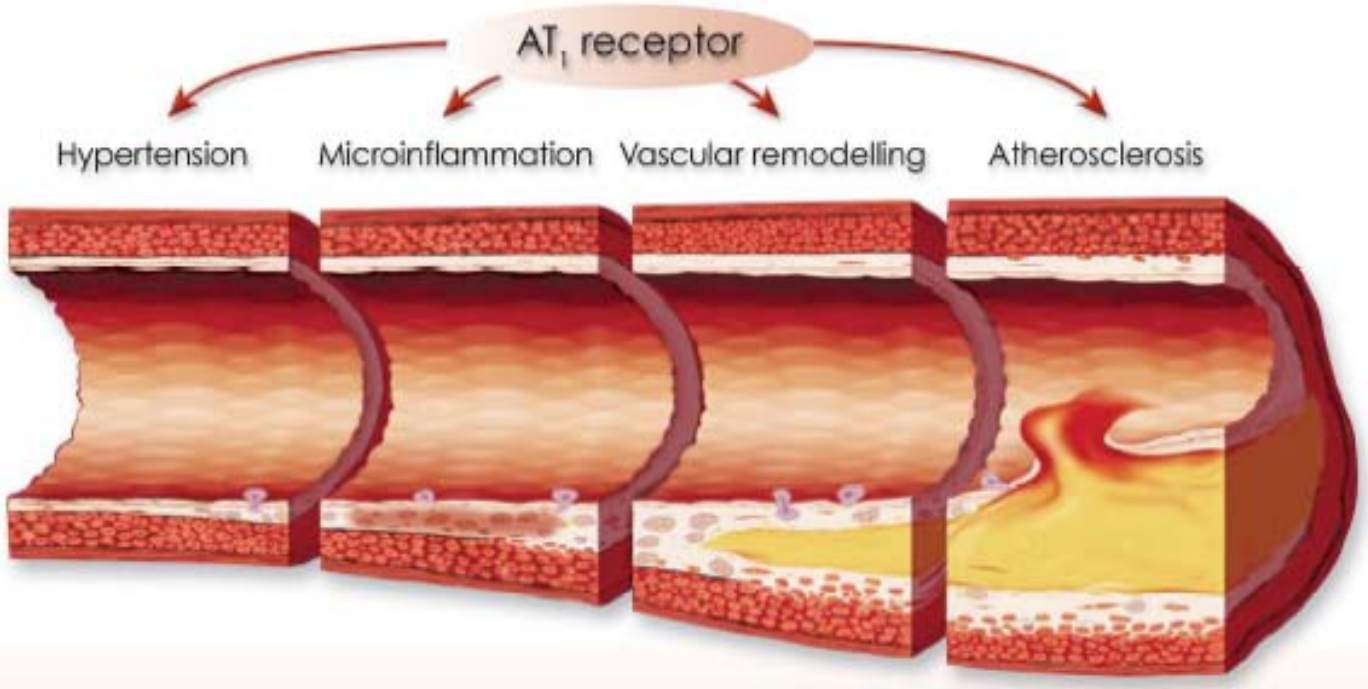
Primary Investigator Site
Co-Investigator Site

Vascular Protection with Angiotensin Receptor Blockers

DIRECT

- Vascular effects not related to blood pressure
- Effects of Angiotensin II on vascular biology
- Effects of ARBs on Prevention of Vascular disease

From hypertension to atherosclerosis

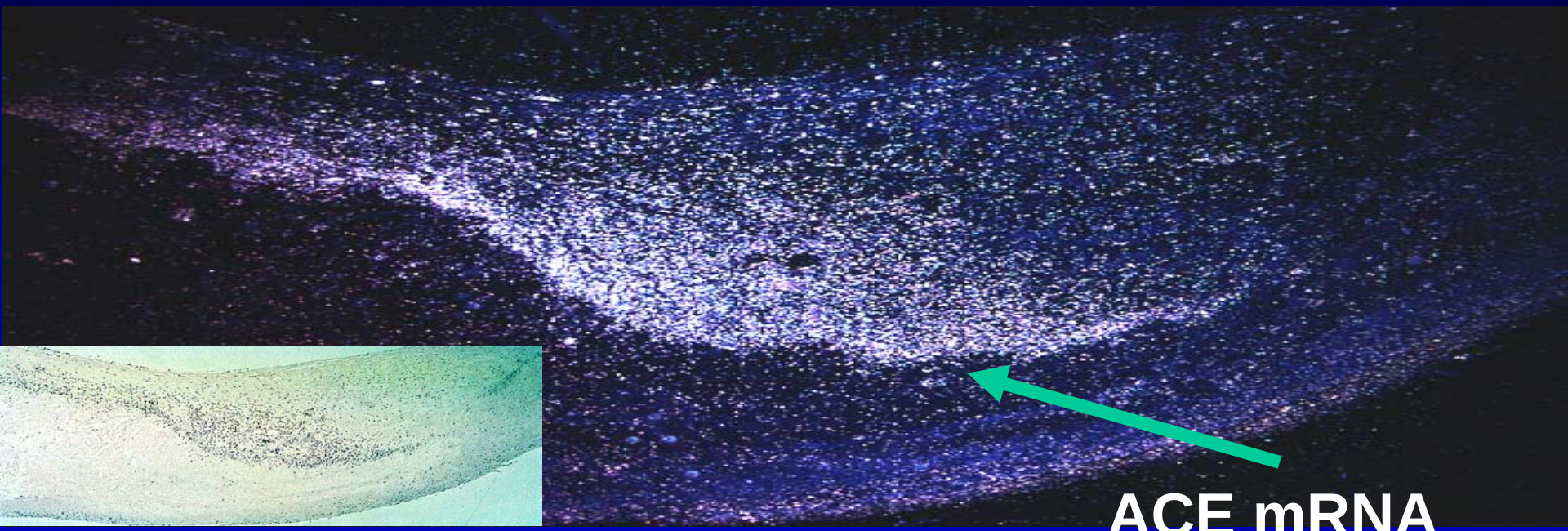


a continuum in which AT_1 receptors are involved at every stage: [1,2]

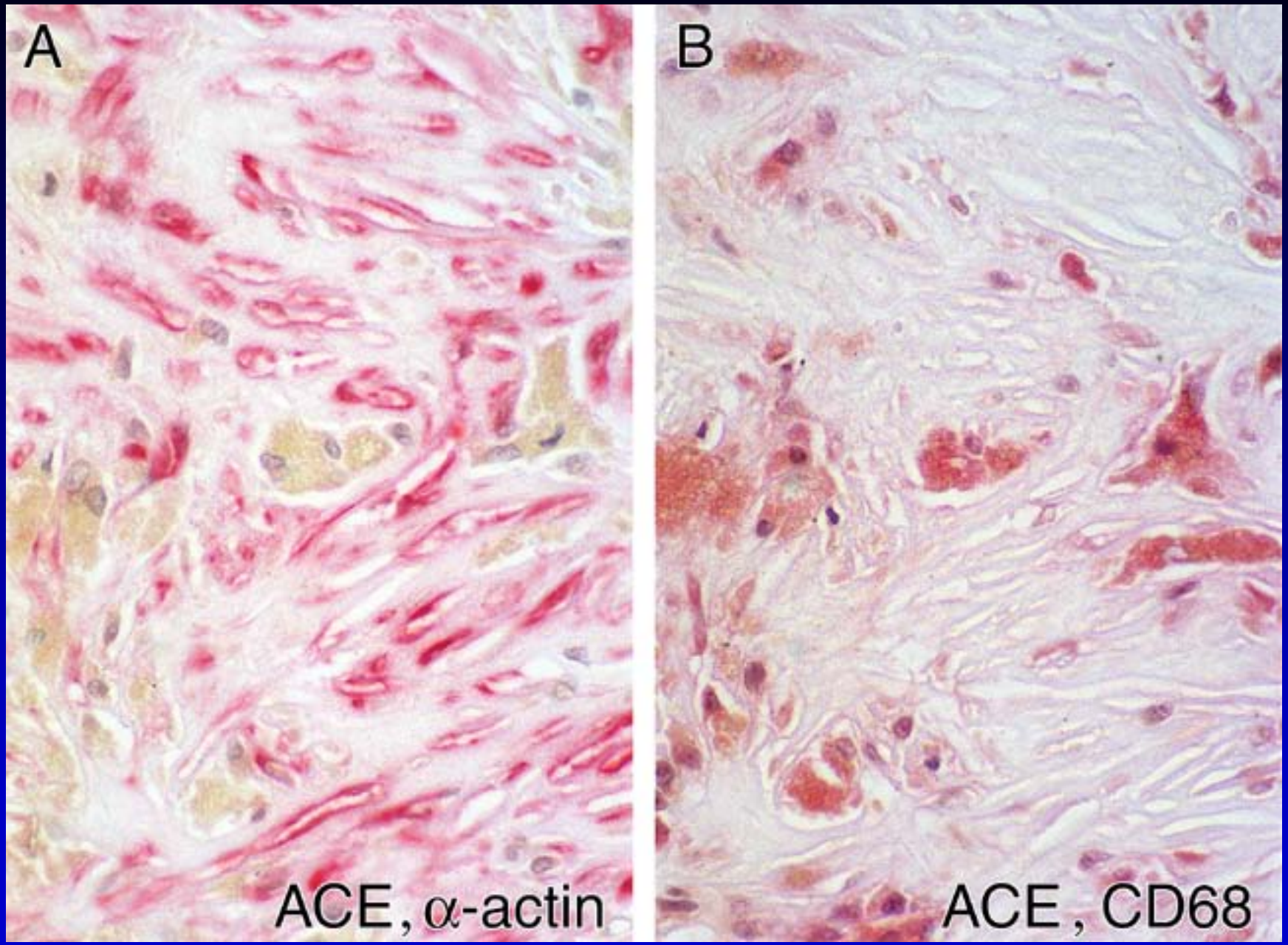
- **increase hypertension**
- ***contribute to inflammatory responses***
- ***promote vascular remodelling***
- ***promote atherogenesis***

it is time to ask for MORE from the antihypertensive drug you choose

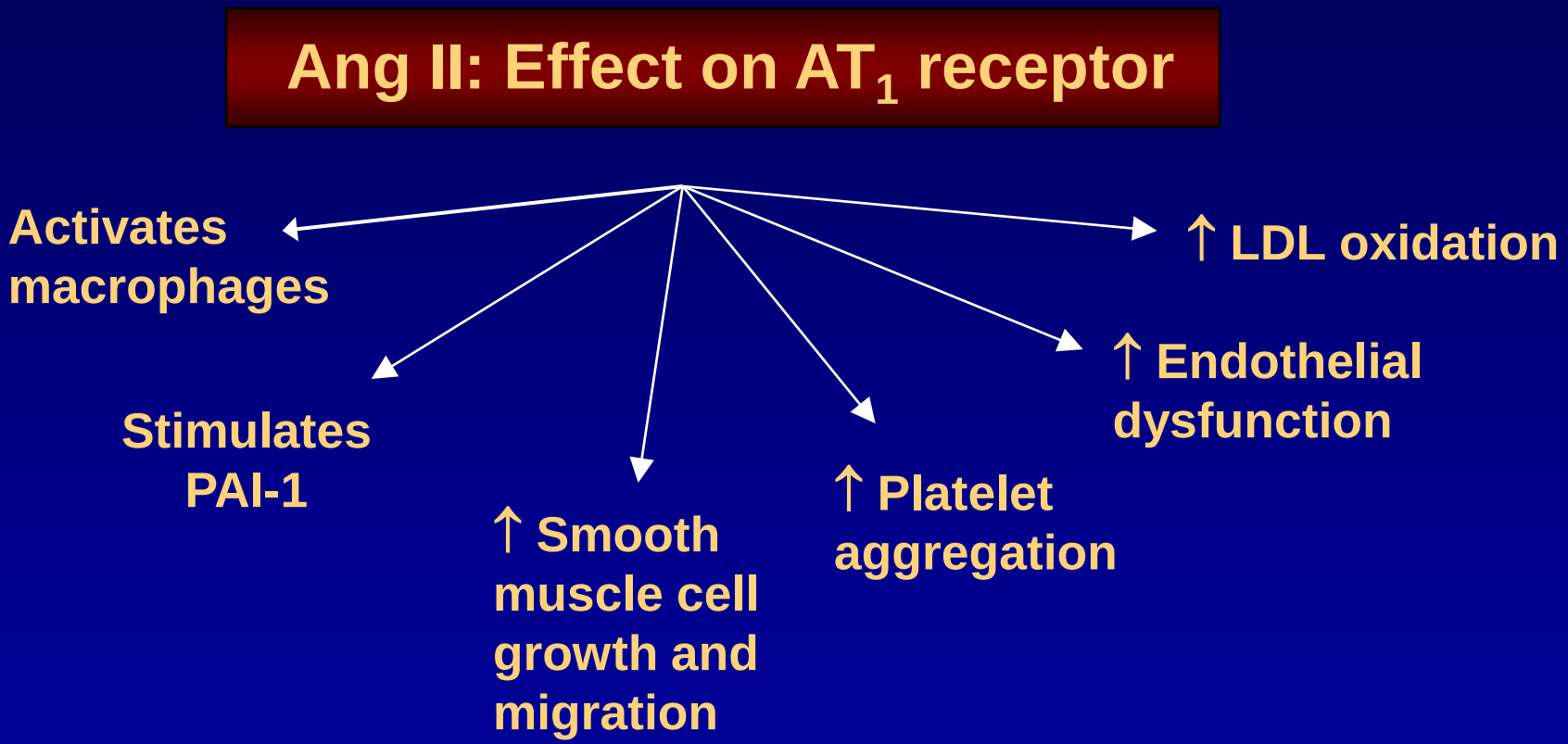
lumen



ACE mRNA


A
ACE, α-actin
B
ACE, CD68

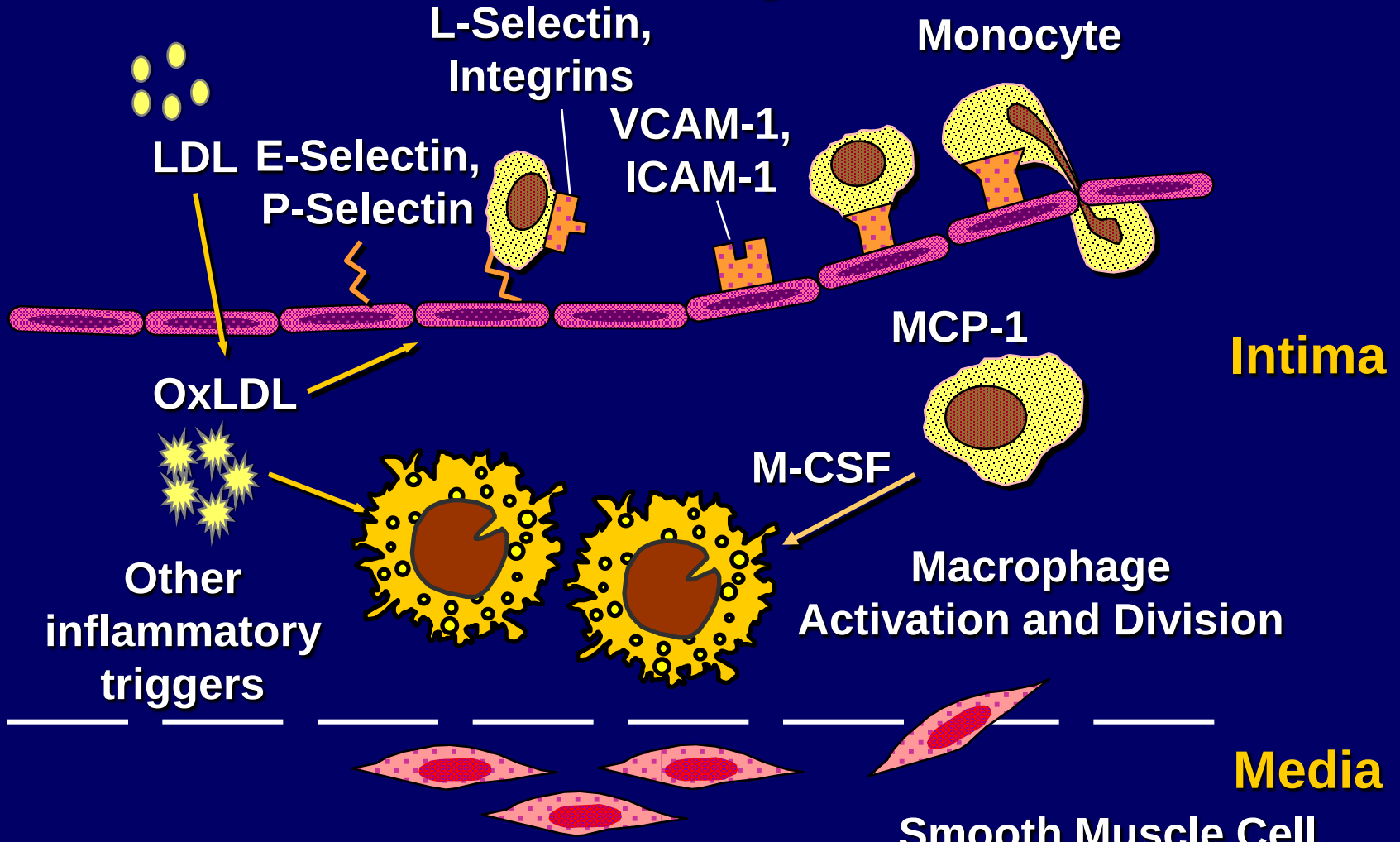
Angiotensin II and atherosclerosis



impact

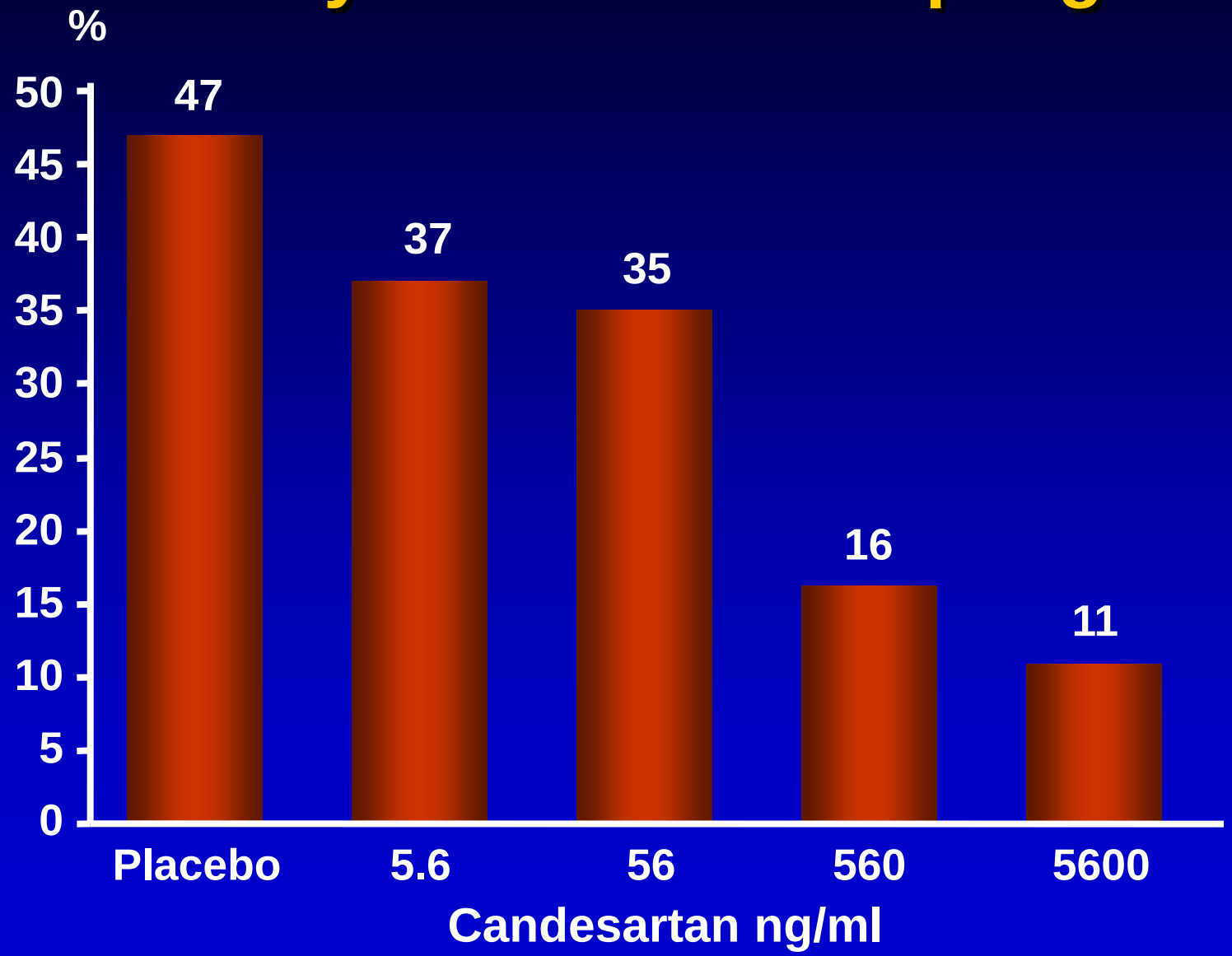
Adapted from: Weir M. Dzau VJ. *Am J Hypertens.* 1999;12:205S-213S and Dzau VJ, Gibbons GH. *Hypertension*. 1994;23:1132-1140

Hypothesis: Atherosclerosis Is an Inflammatory Disease



Libby et al. *Circulation.* 2002;105:1135-1143.

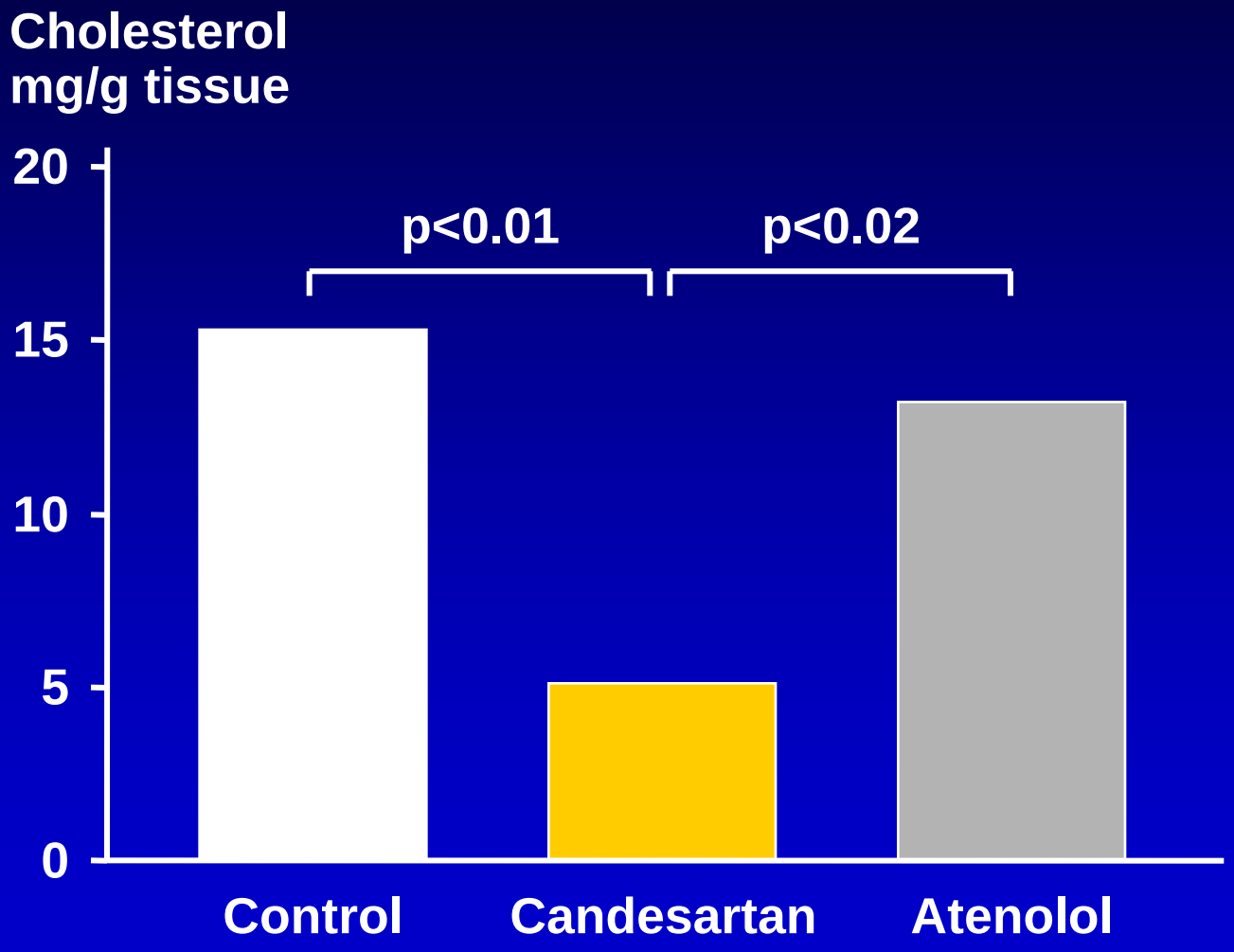
Effect of ARB on Uptake of Oxidized LDL- C by cultured macrophages



Papademetriou et al :RAAS 2001

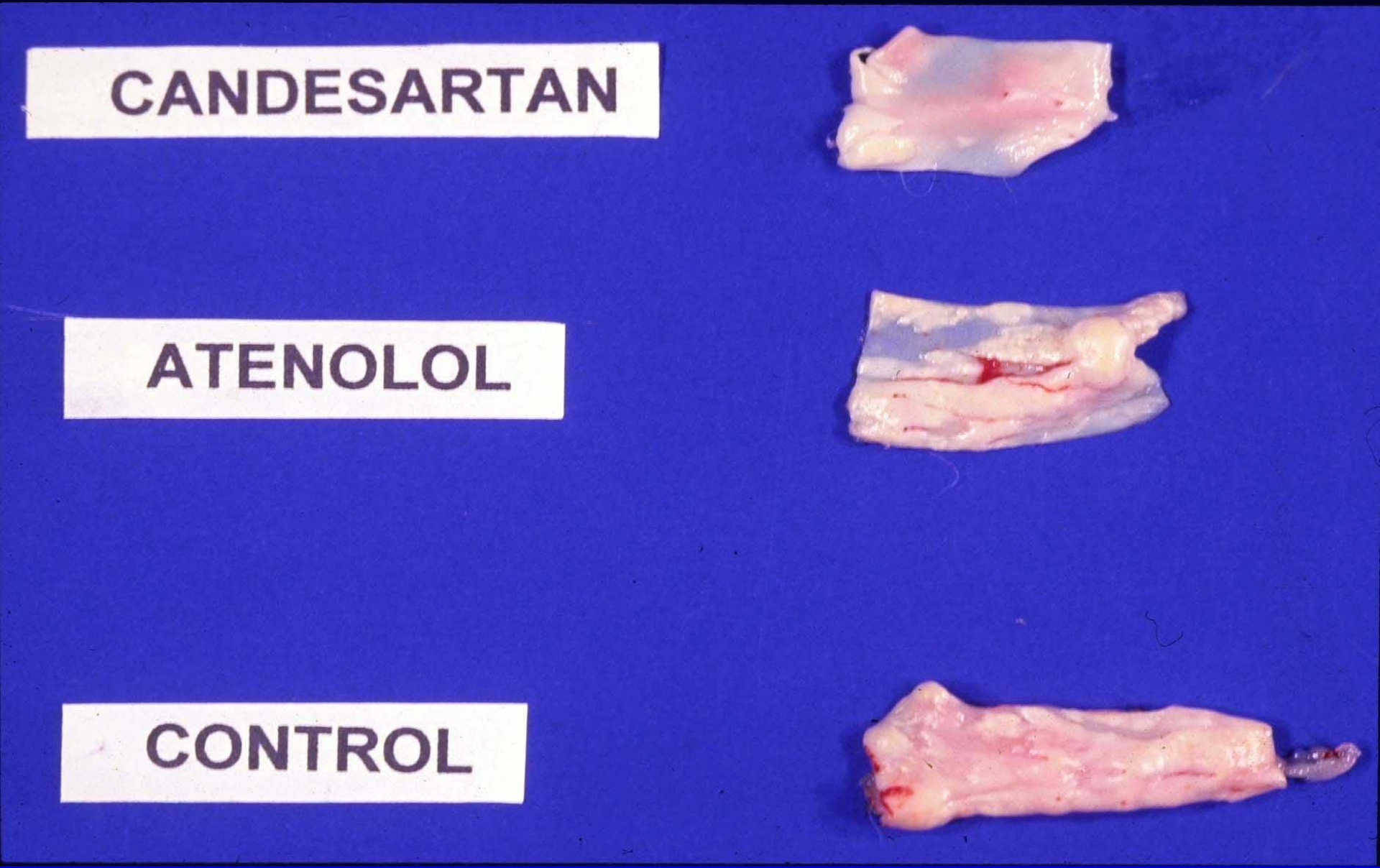
Candesartan in Experimental Atherosclerosis

Thoracic aorta/WHHL rabbits



Papademetriou et al, JRAAS 2001

Extent of Atherosclerosis in Watanabe Rabbits



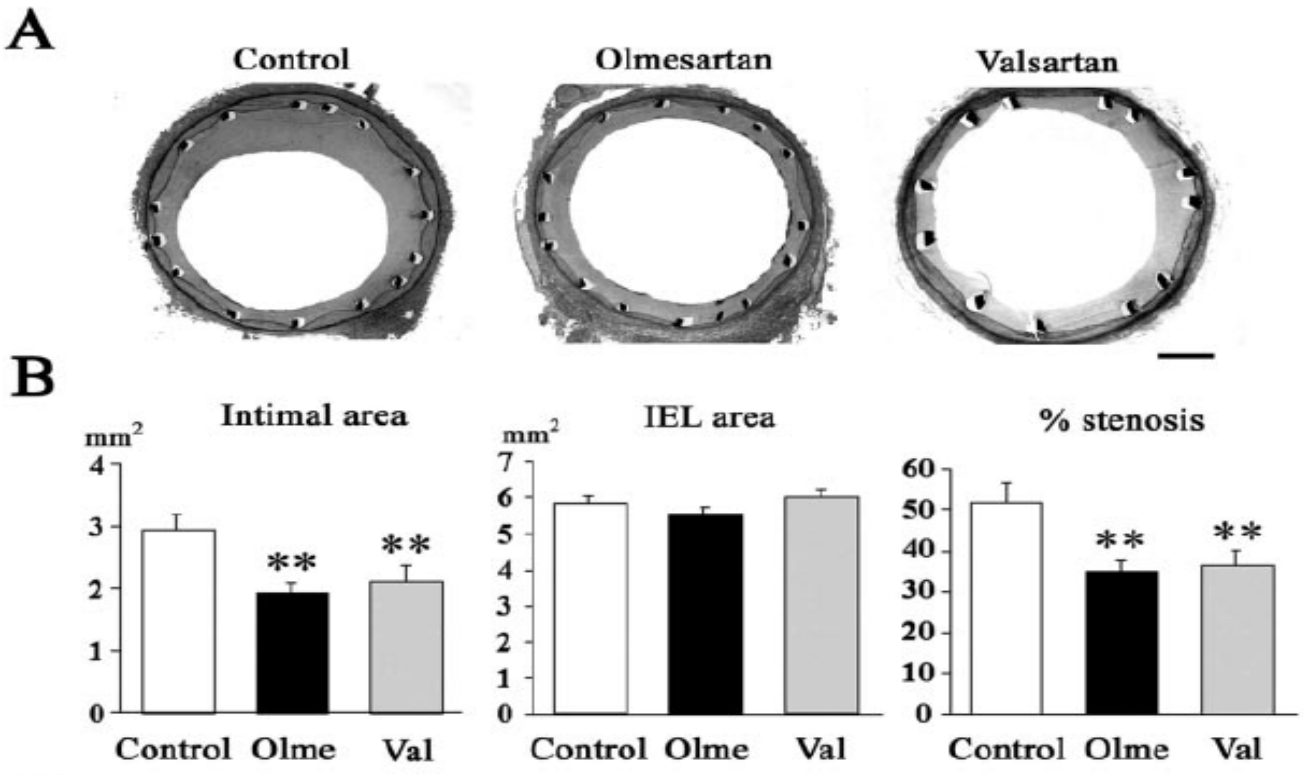
Papademetriou et al :RAAS 2001

Angiotensin II Type 1 Receptor Blockade Attenuates In-Stent Restenosis by Inhibiting Inflammation and Progenitor Cells

- Investigate the mechanism of in-STENT restenosis
- Cynomolgus monkeys and rabbits were fed high cholesterol diets and allocated to control or ARB groups
- 5 days later, multilink stents implanted in the ileac artery
- Results evaluated at 28 days of treatment

Hypertension 2006;48;664-70

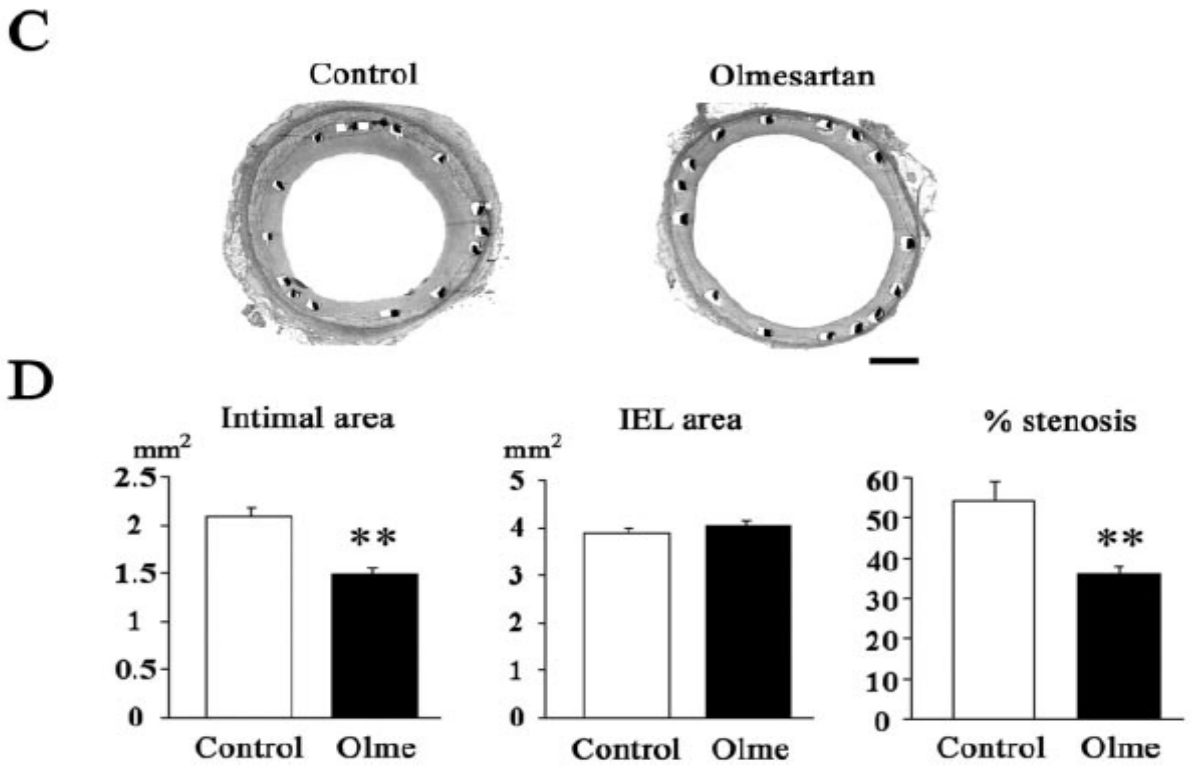
Effect of ARB on Neointima Formation in Cynomolgus Monkeys: 28 days after implantation



IEL=internal elastic lamina

Hypertension 2006;48;664-70

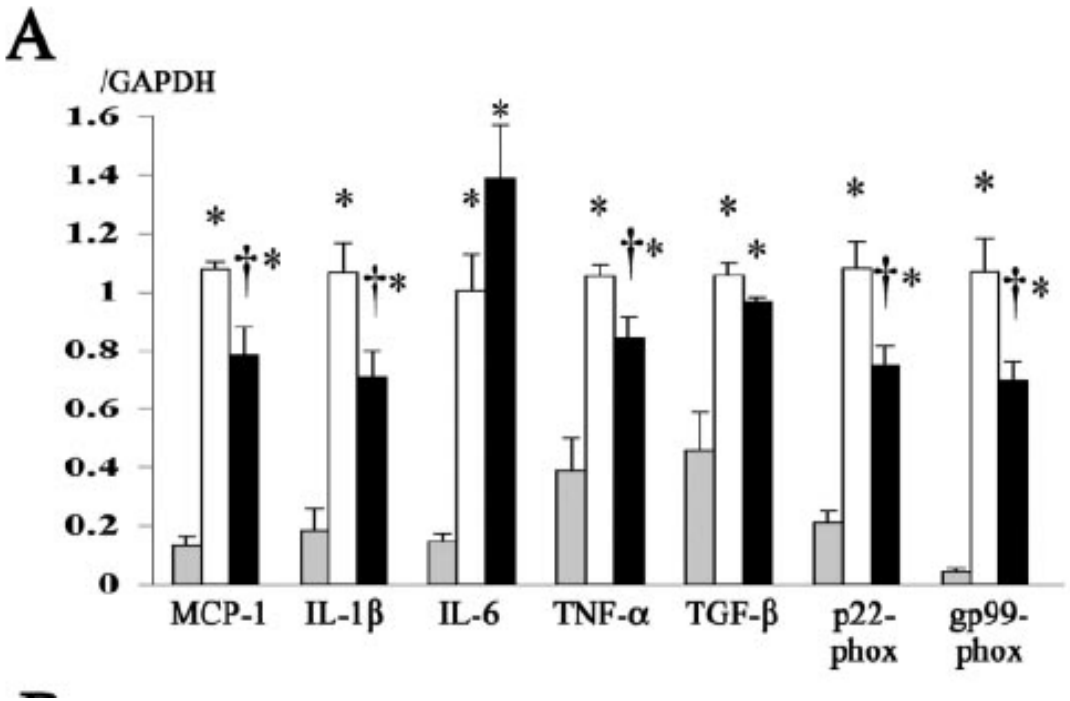
Effect of ARB on Neointima Formation in Rabbits : 28 days after implantation



IEL=internal elastic lamina

Hypertension 2006;48;664-70

Effects of Olmesartan on Gene Expression of Proinflamatory Factors



Hypertension 2006;48;664-70

Conclusions of the authors

- Olmesartan attenuates neo-intimal proliferation in rabbits and monkeys, undergone vascular injury.
- The beneficial effects were associated with reduced oxidative stress , MCP-1 and other inflammatory factors
- The beneficial effects were independent of blood pressure or lipid changes

Pravastatin Enhances Beneficial Effects of Olmesartan on Vascular Injury of Salt-Sensitive Hypertensive Rats, via Pleiotropic Effects

Arteriosclerosis, Thrombosis, and Vascular Biology
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Pravastatin Enhances Beneficial Effects of Olmesartan on Vascular Injury of Salt-Sensitive Hypertensive Rats, via Pleiotropic Effects

Eiichiro Yamamoto, Takuro Yamashita, Tomoko Tanaka, Keiichiro Kataoka, Yoshiko Tokutomi, Zhong-Fang Lai, Yi-Fei Dong, Shinji Matsuba, Hisao Ogawa and Shokei Kim-Mitsuyama

Arterioscler. Thromb. Vasc. Biol. 2007;27;556-563; originally published online Dec 14, 2006;
DOI: 10.1161/01.ATV.0000254855.24394.f9
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1079-5642. Online ISSN: 1524-4636

Study design

- To examine the impact of Olmesartan, pravastatin or the combination of the two on vascular injury is DS rats and to examine the relative role of reactive oxygen species and eNOS in their pleotropic effects.
- Rats were fed high salt diet and randomized to one of the experimental groups.
- Blood pressure and plasma lipids were periodically measured.
- None of the treatments had any significant effects on BP or plasma cholesterol.

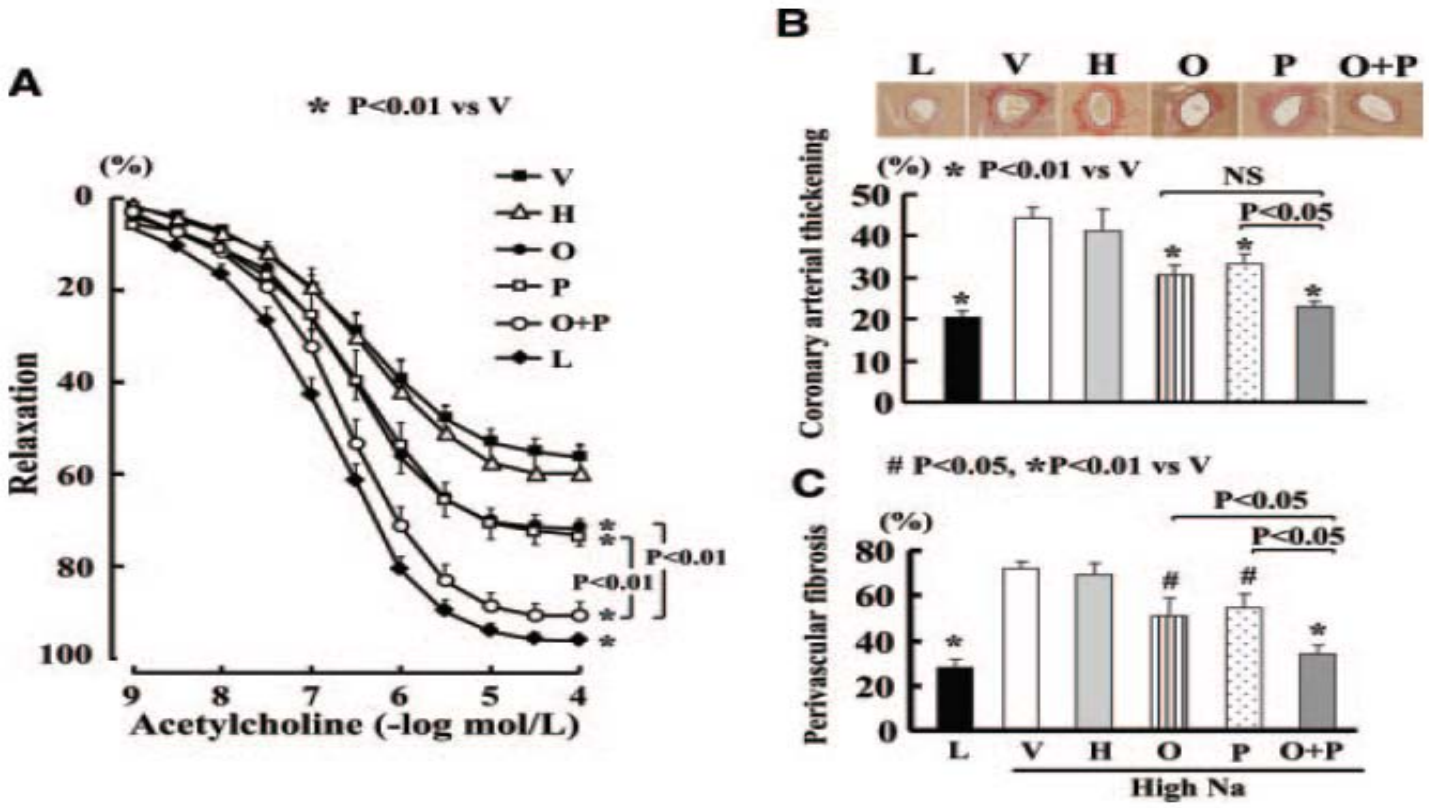
Arteriosc,Thromb Vasc Biol, 2007;556-563

Study design: Group Randomization

- L= low salt -Control
- V=Vehicle
- H=Hydralazin
- O=Olmesartan
- P=Pravastatin
- O+P combination

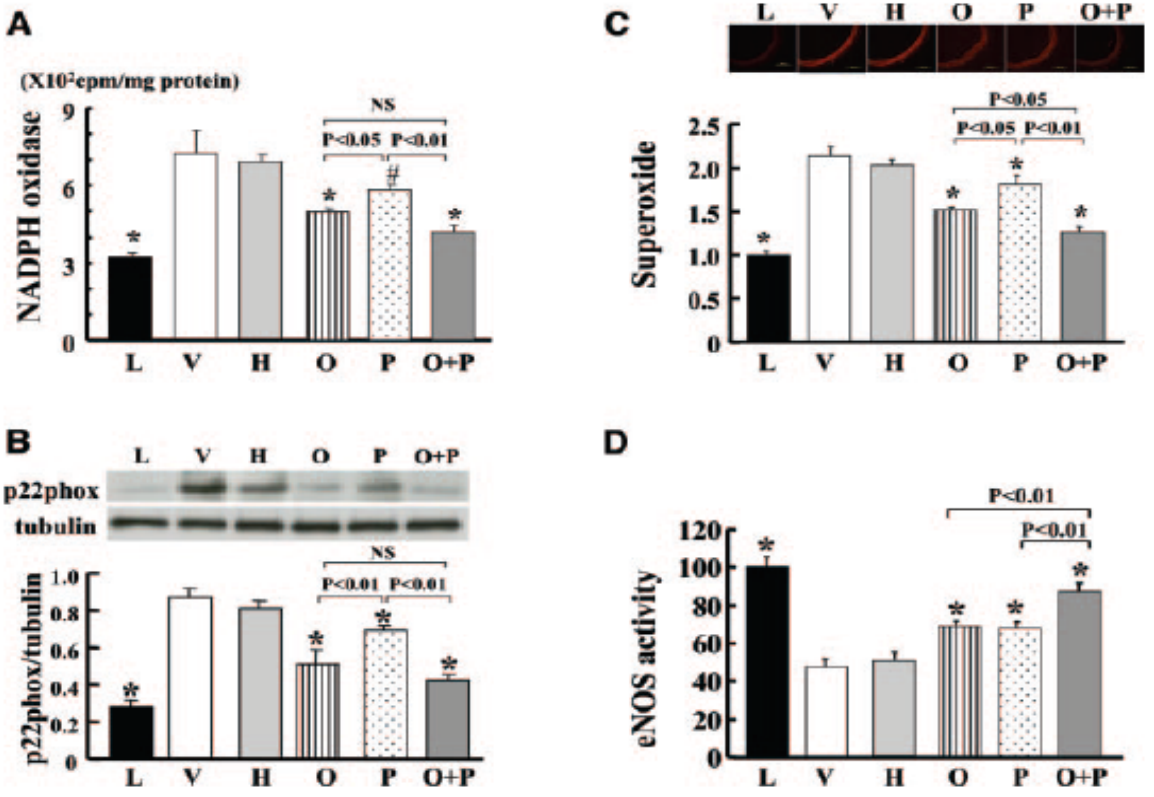
Arteriosc,Thromb Vasc Biol, 2007;556-563

Effect of Treatment on a) acetylcholine induced vascular Relaxation, b) arterial thickening and c) Perivascular fibrosis



Arteriosc,Thromb Vasc Biol, 2007;556-563

Effect of Treatment on NADPH oxidase, Superoxide, p22phox/tubuline and eNOS activity



Arteriosc.Thromb Vasc Biol. 2007:556-563

Conclusions of the authors

- Olmesartan and Pravastatin exert beneficial vascular effects in salt sensitive hypertension
- Vascular protection seems to be mediated via different pleiotropic effects
- Pravastatin enhances vascular protective effects of Olmesartan
- The combination of an ARB with a statin may have therapeutic value in salt sensitive hypertension

VASCULAR PROTECTION with Olmesartan

- Three recently published studies in Humans:
  - EUTOPIA Study *:**A strong inflammatory effect***

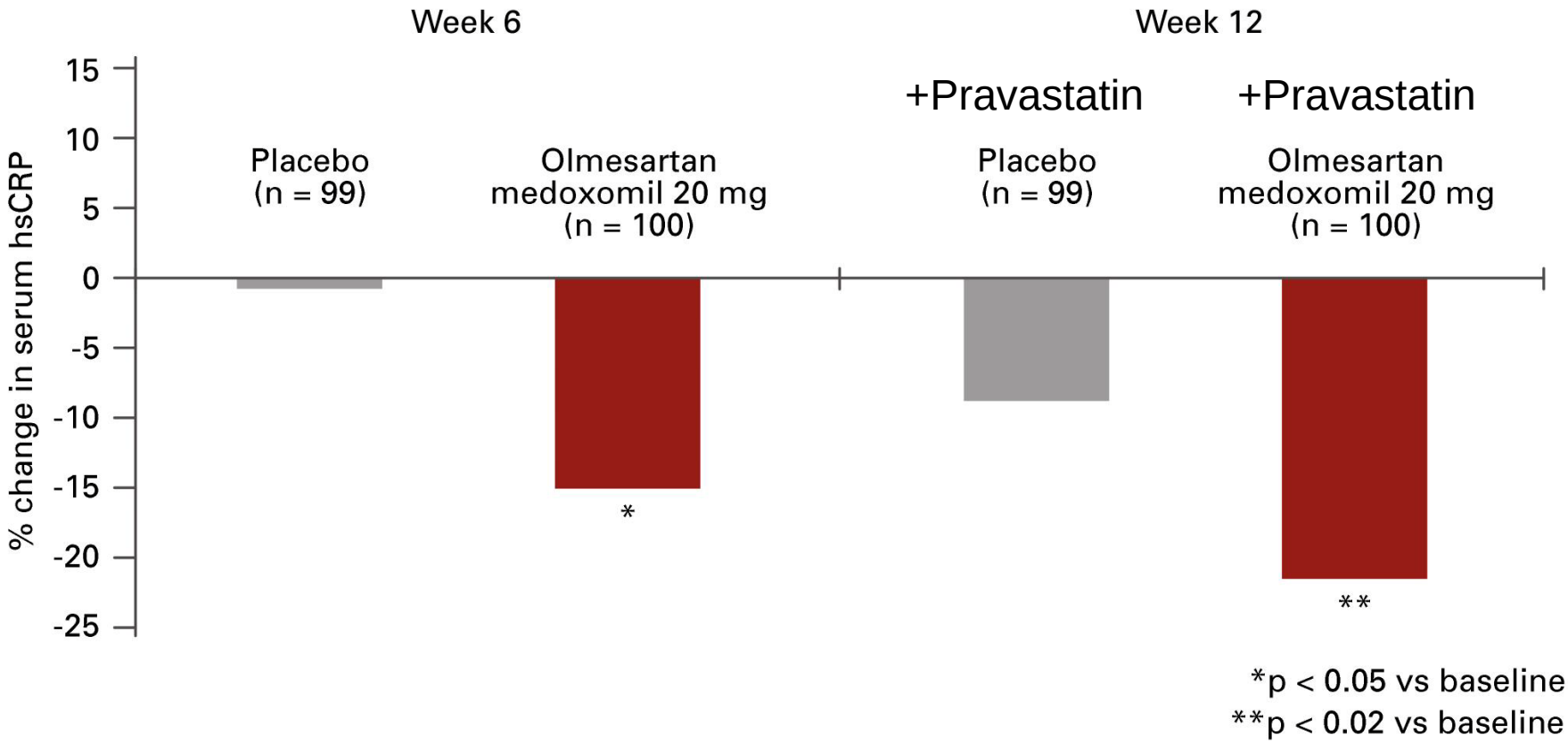
  -VIOS Study - **A complete reversal of vascular remodelling**
  - MORE Study :**A decrease of atherosclerotic plaque volume**,

The European Trial on Olmesartan and Pravastatin in Inflammation and Atherosclerosis: EUTOPIA

- Multicenter, Double blind, prospective study
- 199 patients initially randomized to Olmesartan or placebo for 6 weeks, then pravastatin added to both arms for another 6 weeks
- End point: Markers of inflamation
  - **hsCRP**
  - **hsTNFa**
  - **IL-6**

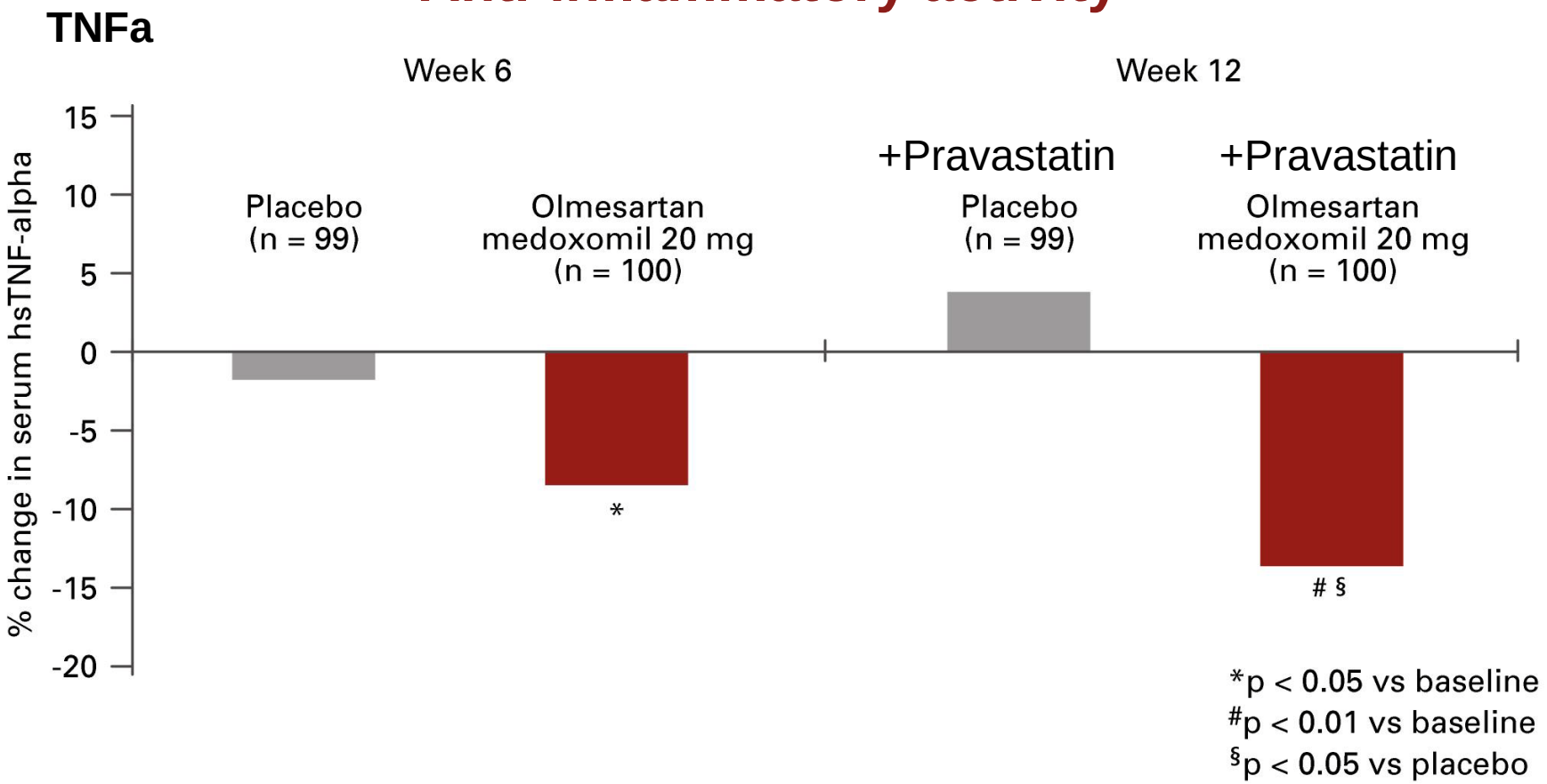
Anti-inflammatory activity

hsCRP



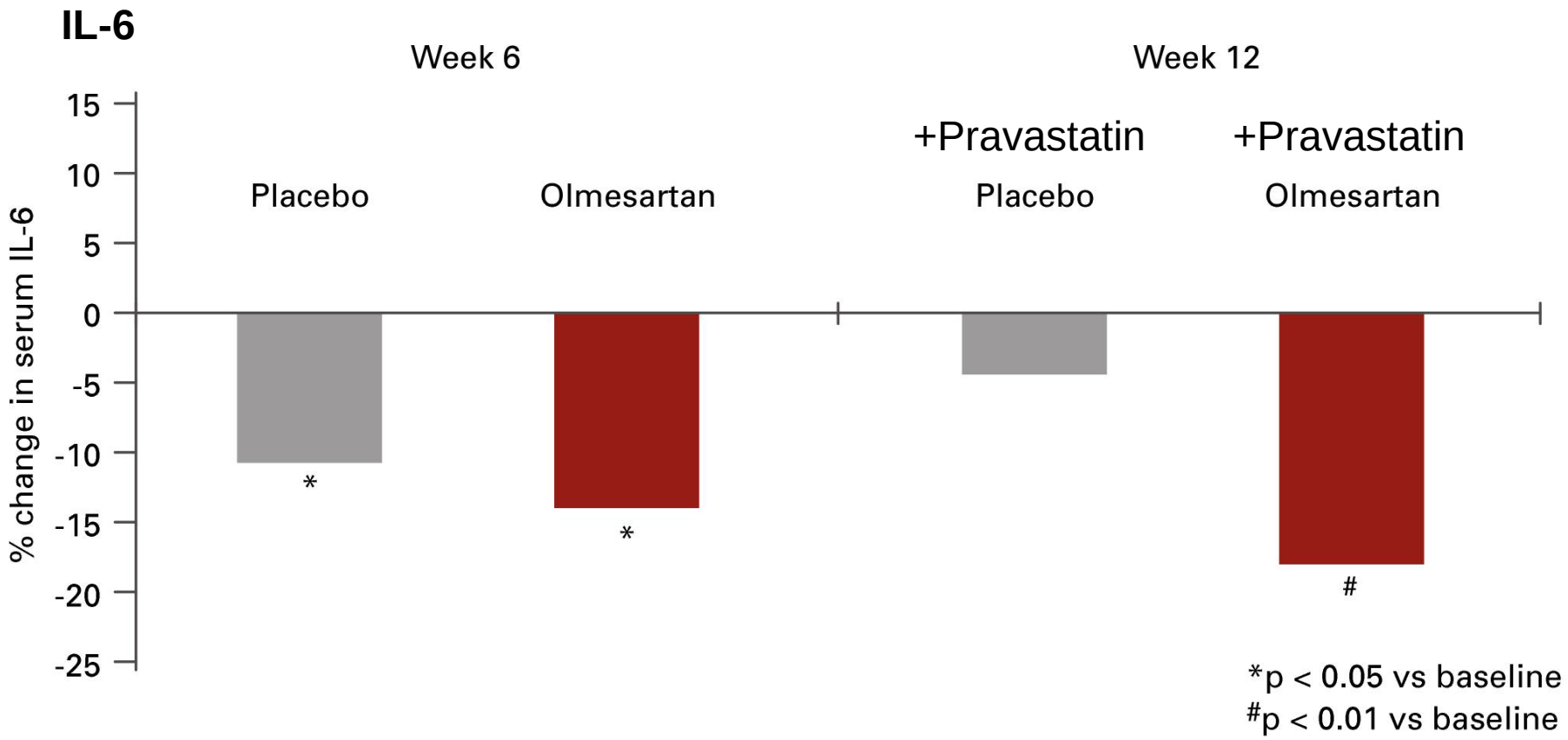
Fliser D. et al., Circulation; 2004

Anti-inflammatory activity



Fliser D. et al., Circulation; 2004

Anti-inflammatory activity



Fliser D. et al., Circulation; 2004

Conclusions of the authors: EUTOPIA

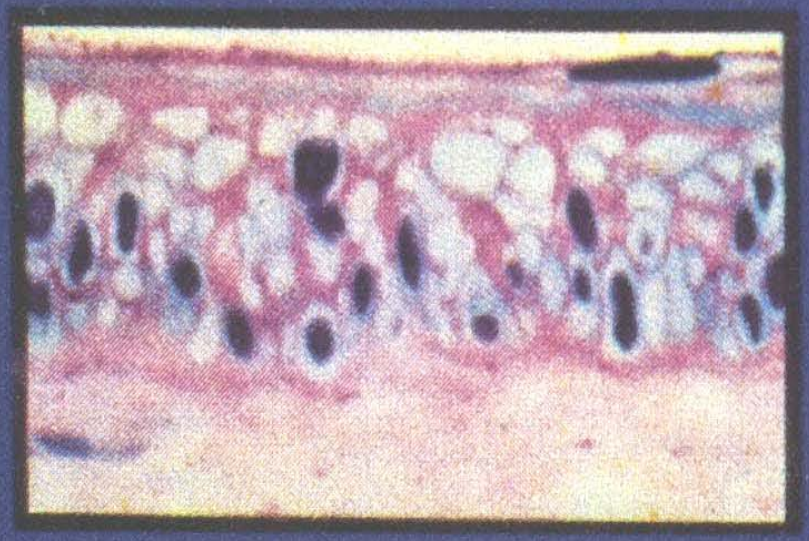
- Olmesartan medoxomil significantly reduces the biochemical markers of vascular inflammation in patients with essential hypertension.
- These anti-inflammatory properties of Olmesartan medoxomil may have additional beneficial cardiovascular effects (Pleotropic effects)

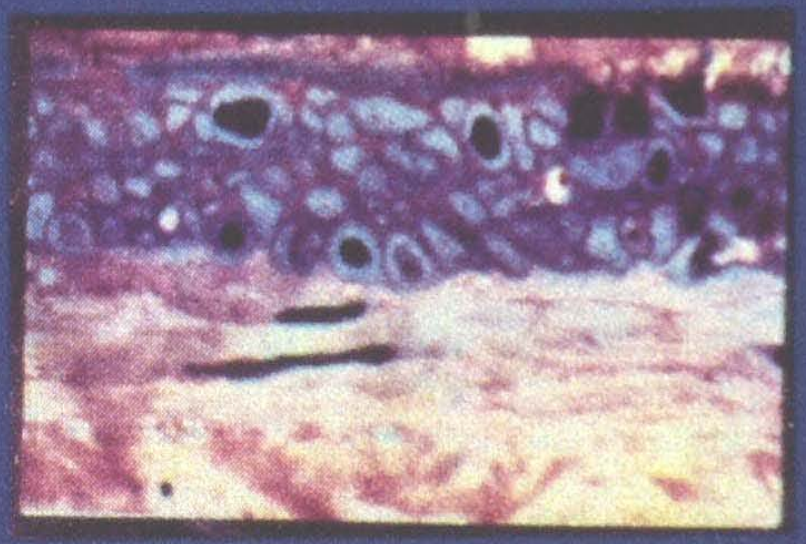
Fliser D. et al., Circulation; 2004

Effect of Olmesartan as compared to Atenolol on Vascular Remodeling: The VIOS study

- Aim: To compare olmesartan to atenolol on vascular remodeling when BP was controlled close to normal
- Multicenter, double blind, randomized study
- 100 patients with stage I hypertension
- Gluteal biopsies at baseline and aftrer 1 year of treatment to assess lumen to wall thickness in small arteries
- Primary end point; degree of vascular remodeling and inflammatory markers

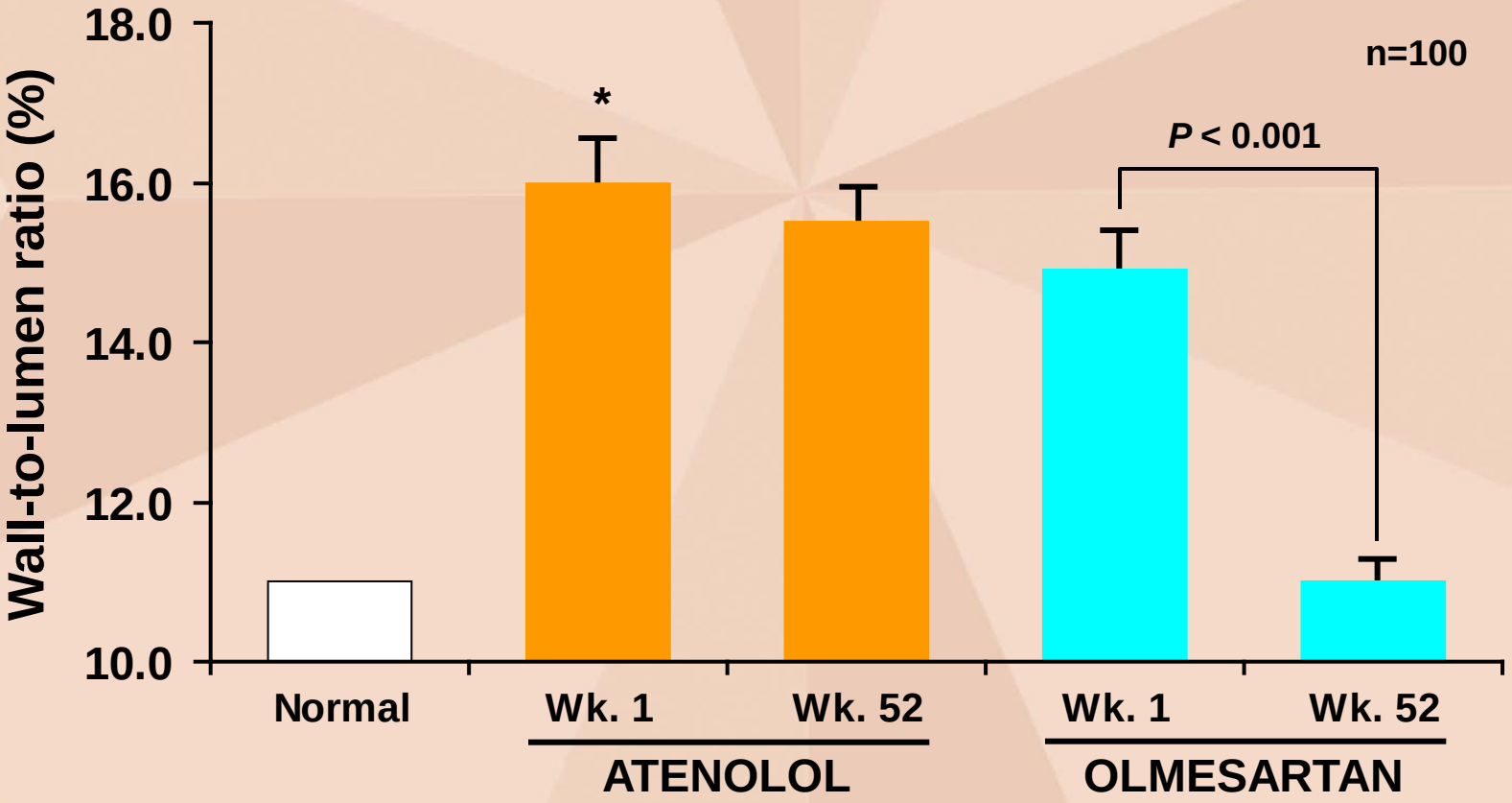
Smith, Yokoyama and Ferrario. Am J Hypertens 2005





VASCULAR PROTECTION – VIOS Study

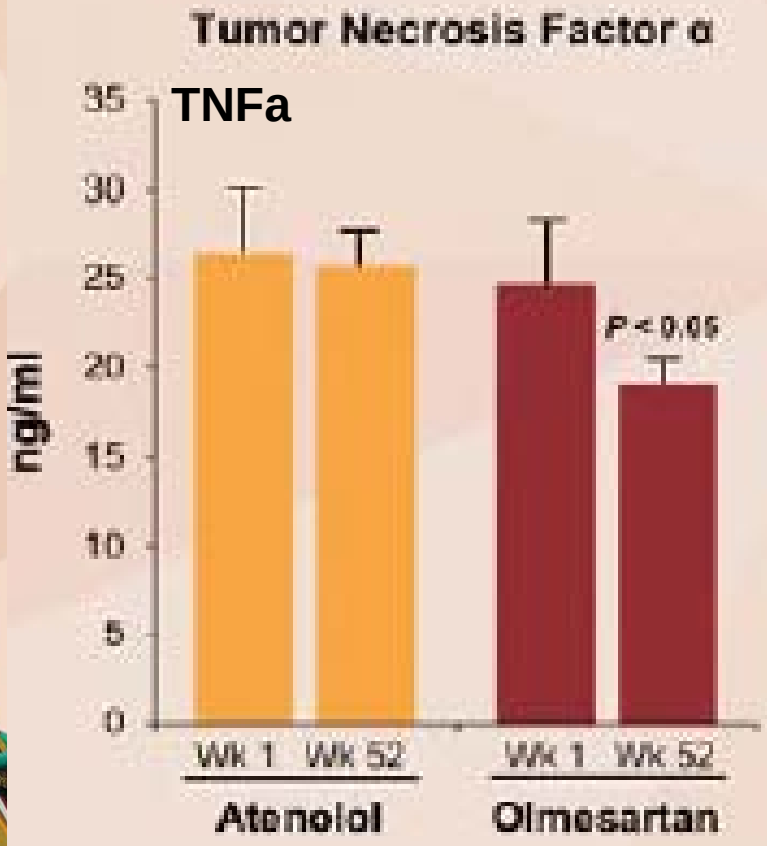
Olmesartan but not Atenolol Reverses Vascular Hypertrophy

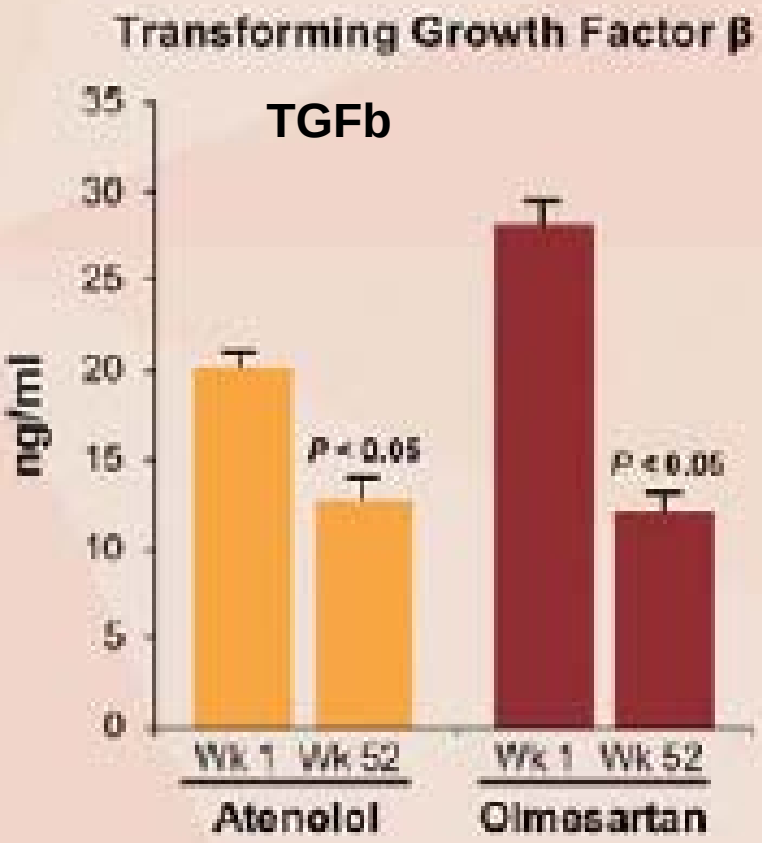


Smith, Yokoyama and Ferrario. Am J Hypertens 2005

VIOS study

Effect of treatments on inflammatory cytokines





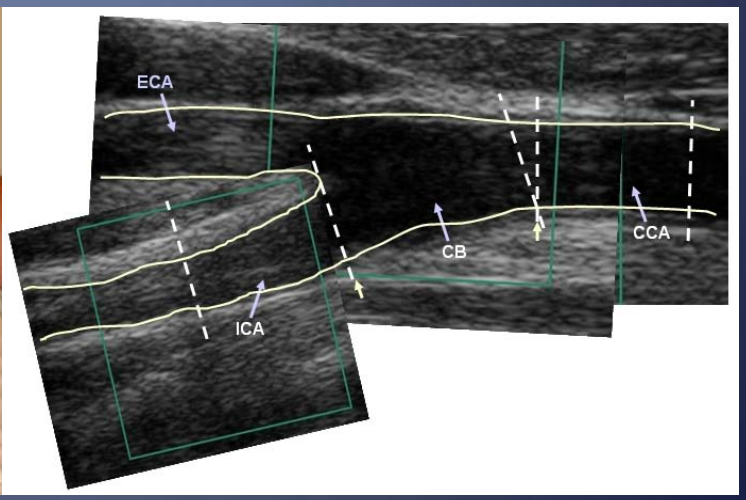
Vascular Protection with Olmesartan as compared to Atenolol: The MORE study

- Multicenter, double blind study to assess atherosclerosis regression by Ultrasound
- 165 patients with stage I-II hypertension, randomized to olmesartan 20-40 mg or atenolol 50-100 mg
- Ultrasound performed at baseline and at week 28,52 and 104.
- End point: Change from baseline in BP, CC-IMT and atheroma volume

ENHANCE cIMT Methodology

Carotid Intima-Media thickness (cIMT) measurements

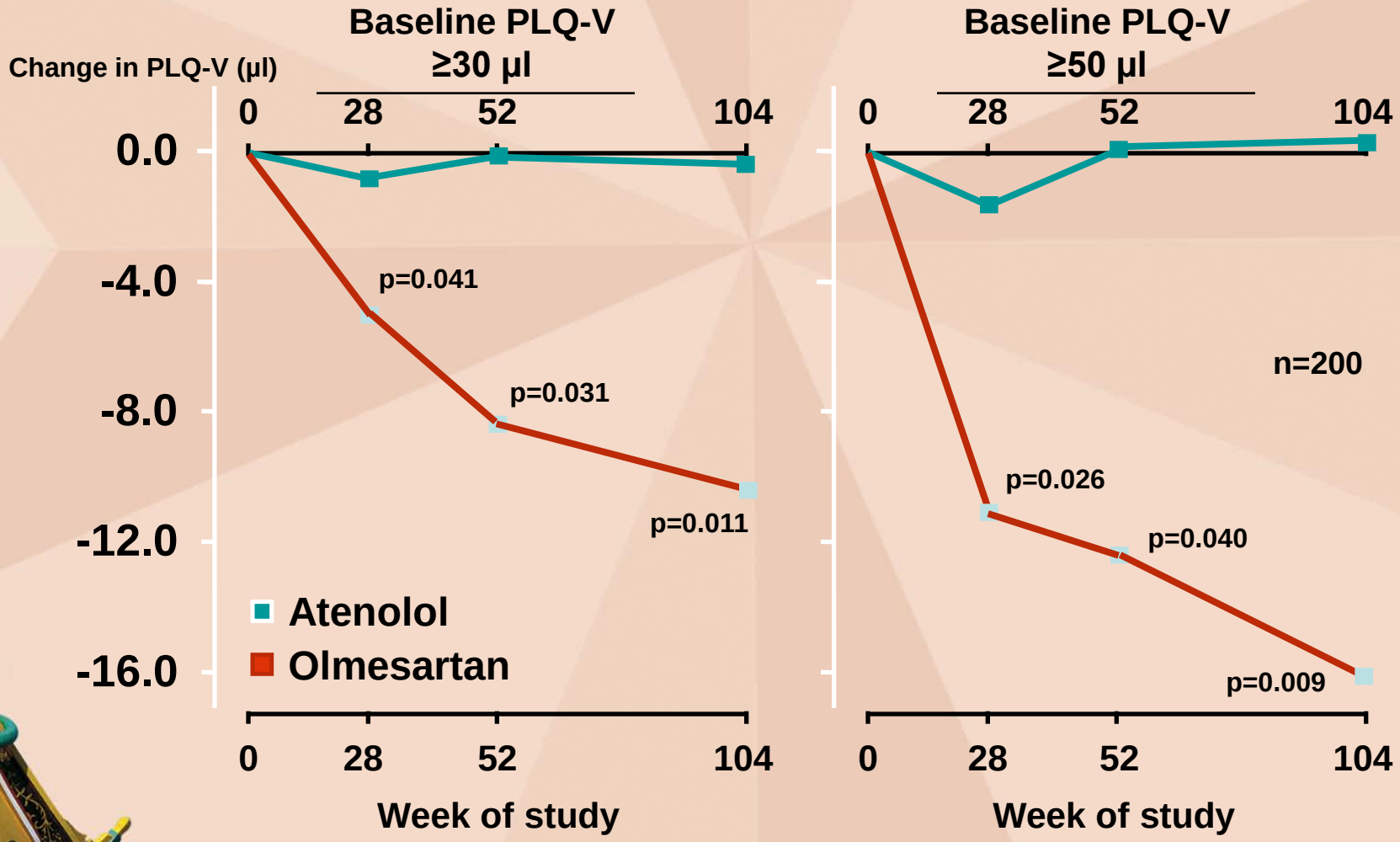
- Measurements were made at a predefined angle of insonation
- Only the far-walls of all segments were imaged
- Images were stored in DICOM for offline image analyses



de Groot E, et al. Circulation. (2004) 109[Suppl III]:III-33-III-38.

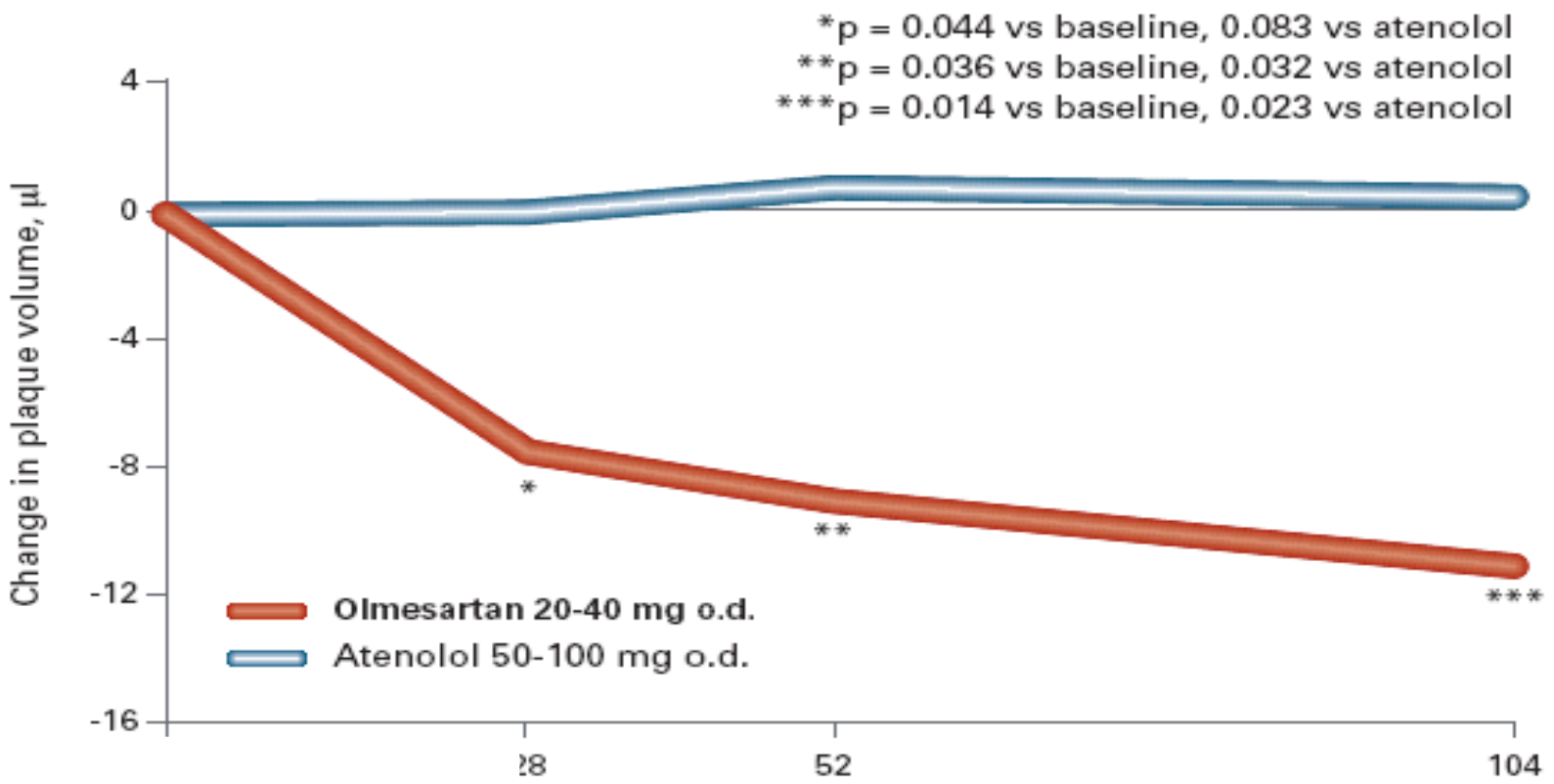
VASCULAR PROTECTION – MORE Study

Mean changes in Plaque Volume from baseline at 28-, 52- and 104-week follow-up



Regression of Atheroma with Olmesartan, but not Atenolol: The MORE study

Significantly more effective than atenolol in patients with large atherosclerotic plaques [8]



No difference in BP or CC-IMT change between Atenolol and Olmesartan

We can Conclude

- These findings are very encouraging
- Still “surrogate or intermediate endpoint”
- Do the translate into clinical benefit?
- Should we include into personalized medicine some of these surrogate end points?
- Can we develop better models that can be more predictive of better hard outcomes?

Antihypertensive Prescriptions in Canada from 1996 to 2003

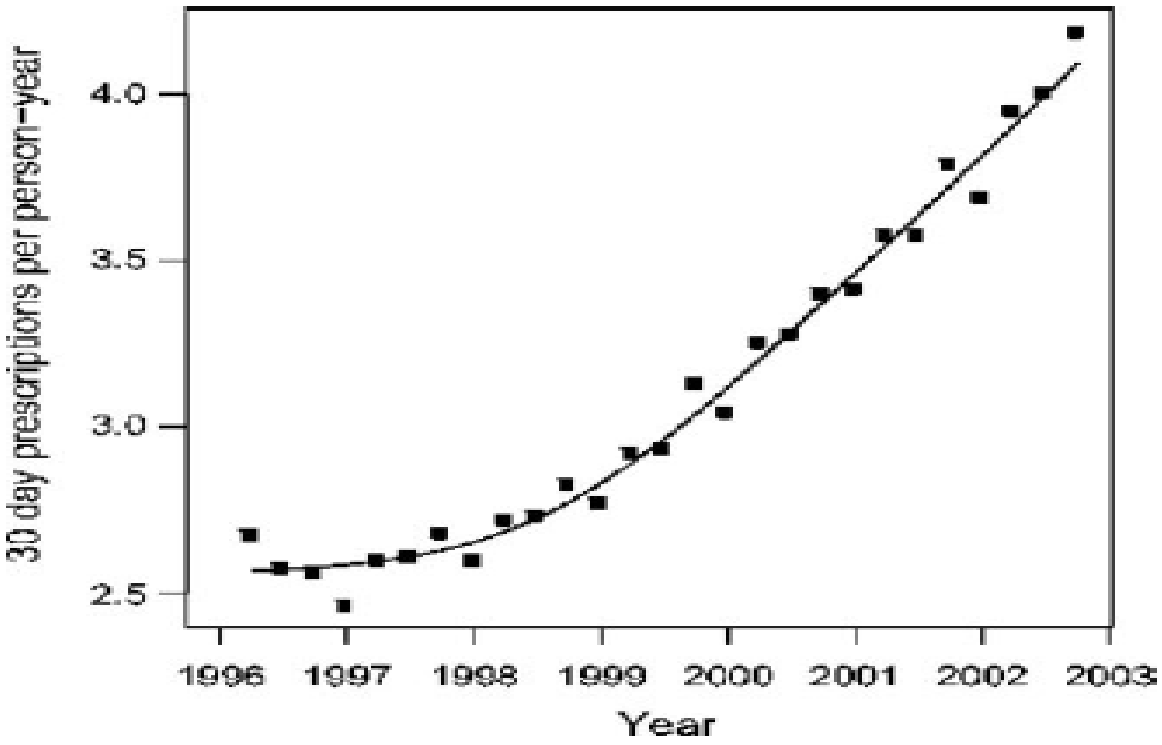


Figure 1. Total antihypertensive prescription sales (IMS Health-Canada) in Canada from 1996 to 2003. The prescription rates for 30-day prescriptions per person-year. The line is a nonparametrically modeled average, and the squares represent quarterly population-adjusted rates.

Mortality Rates from Stroke, HF and Acute MI in Canada from 1992 to 2003

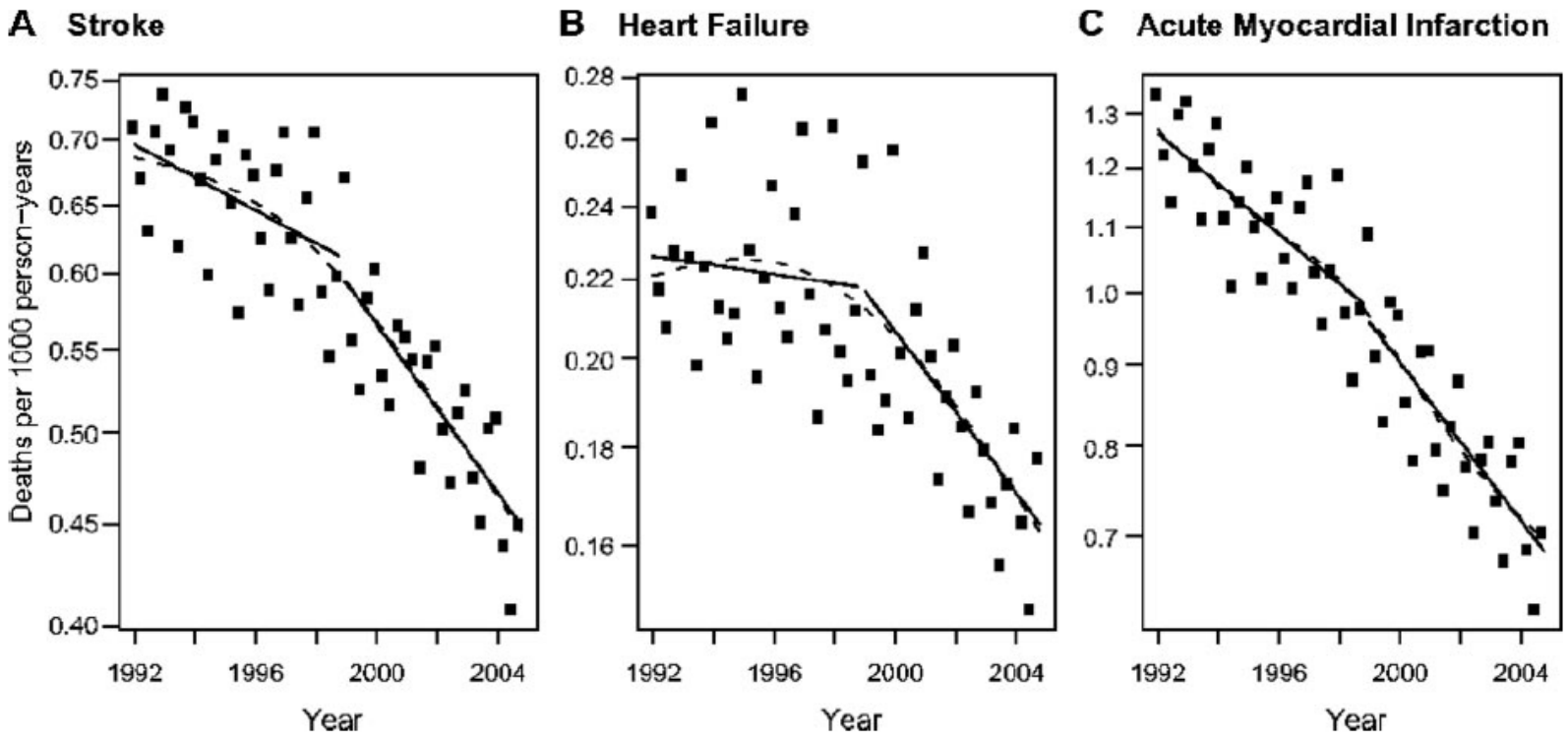
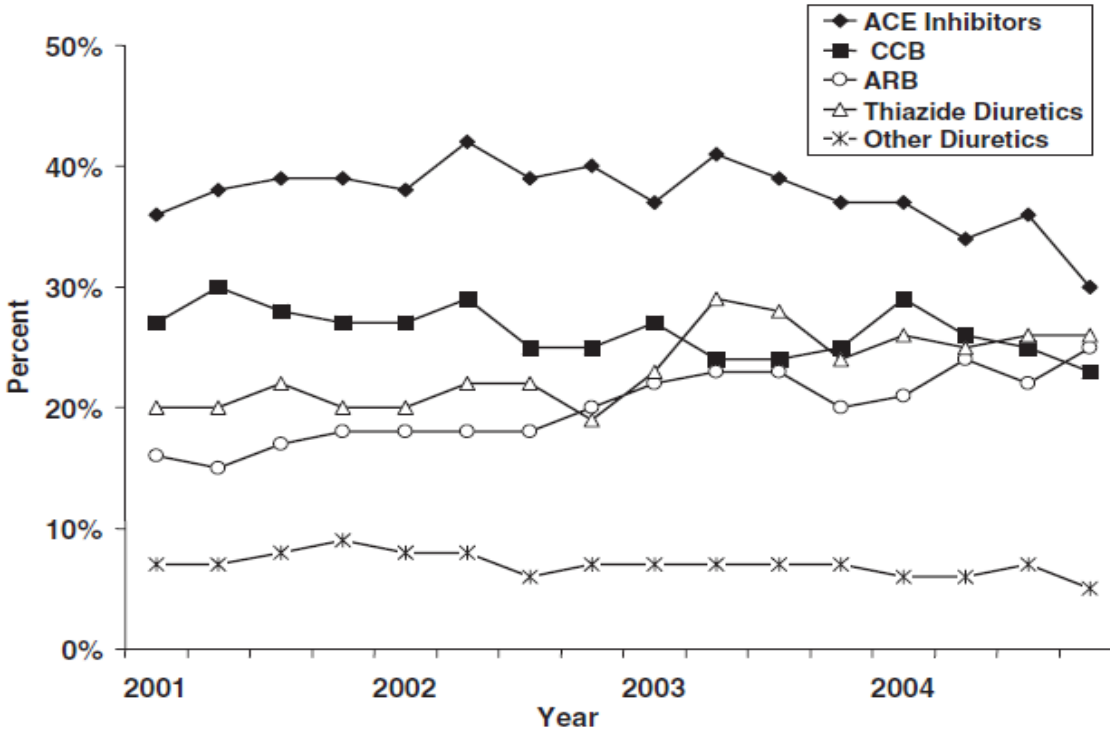


Figure 2. Mortality rates from stroke (A), HF (B), and AMI (C) in Canada from 1992 to 2003. The squares are quarterly rates adjusted for age and gender per 1000 population. The dark line is linear modeling for 1992–1998 and 1999–2003, and the dotted line is a nonparametrically modeled line.

(*Hypertension*. 2009;53:128-134.)

Short term changes in antihypertensive Prescribing by Office-Based Physicians in the United States



ACEI

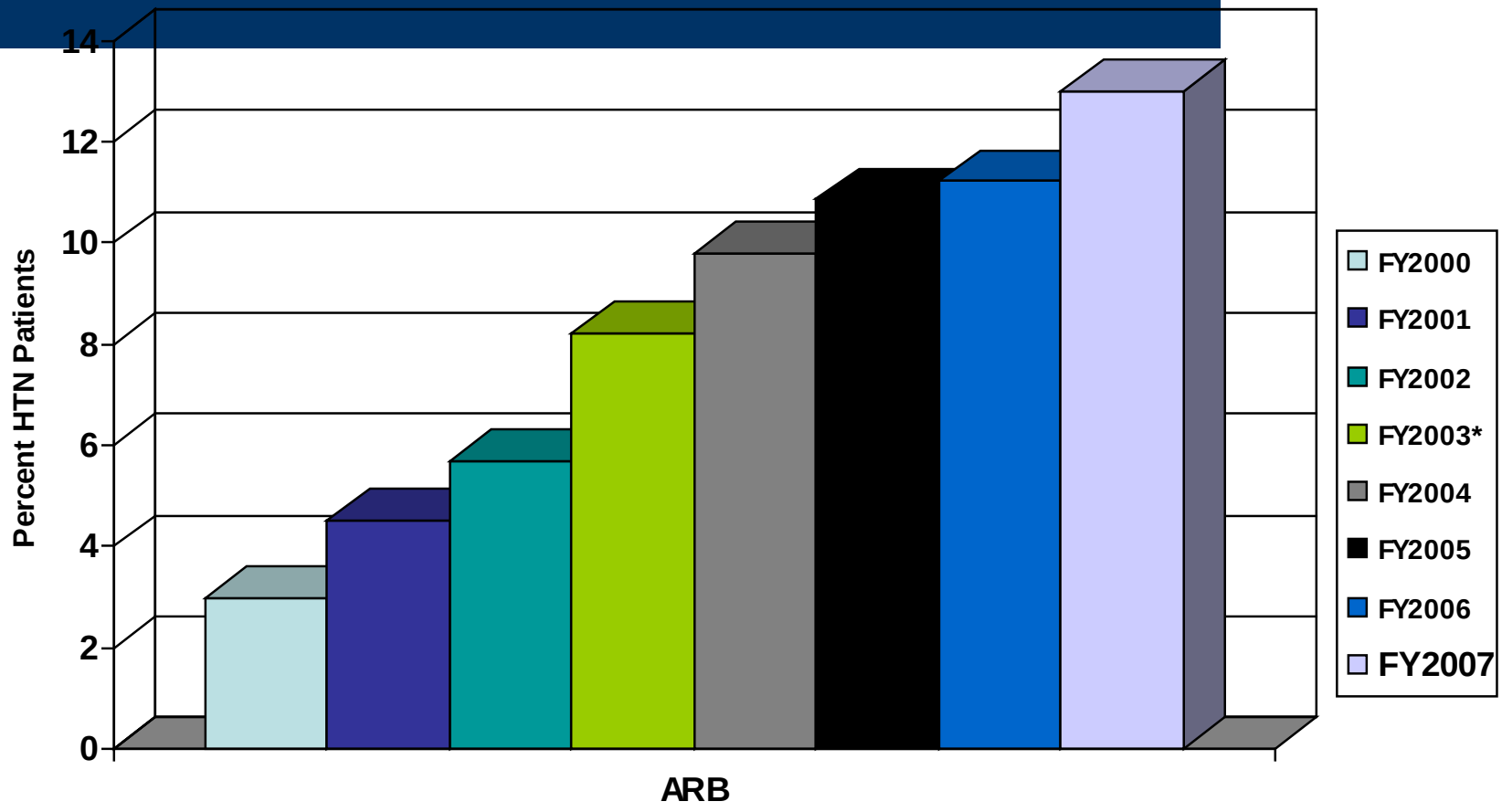
Diuretics, ARBs

CCBs

Other diuretics

Stafford et al;Hypertension,2006;48:213-8

Prescribing Trends of ARBs at the Department of Veterans Affairs 2000-2006 N=1,619,824 (total N=7,000,000)



J Clin Hypertens (Greenwich). 2008 Oct;10(10):770-8

Advantages of ARBs

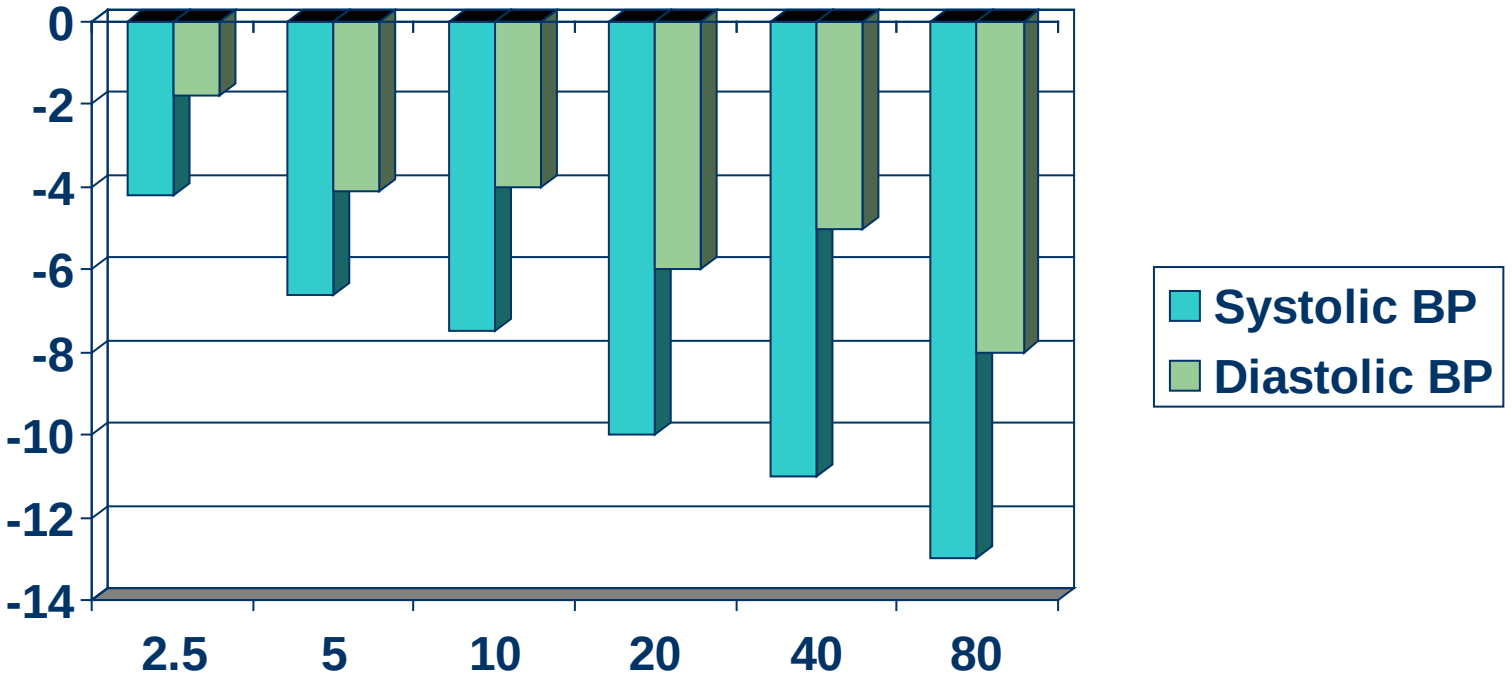
- Effective for BP reduction
- Safe
- Well tolerated
- May have added vascular protective effects
- **Olmesartan has optimal profile**

Dose –Response Characteristics of Olmesartan Metoxomil

- Analysis of 7 US and European randomized, placebo controlled trials
- 3055 patients with hypertension treated with Olmesartan 2.5 to 80 mg daily or placebo
- Duration of treatment : 8 weeks

Smith DHG, AJCardDis 2007

Dose Response of BP Reduction with Olmesartan: A Meta -analysis N=3055



Smith DHG, AJCardDis 2007

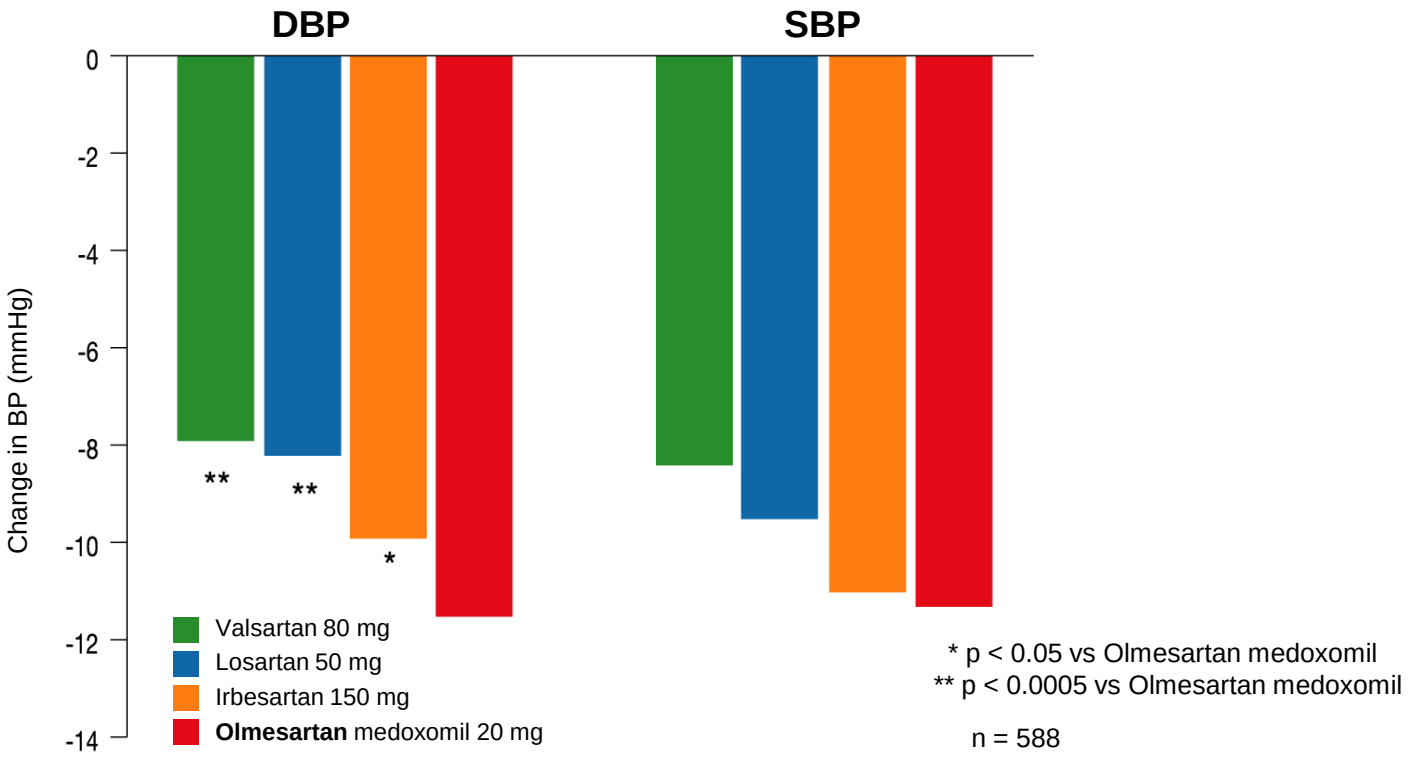
Olmesartan compared to other drugs

- Better blood pressure reduction still important

Olmesartan

Olmesartan medoxomil vs valsartan, losartan and irbesartan

CUFF BP reduction



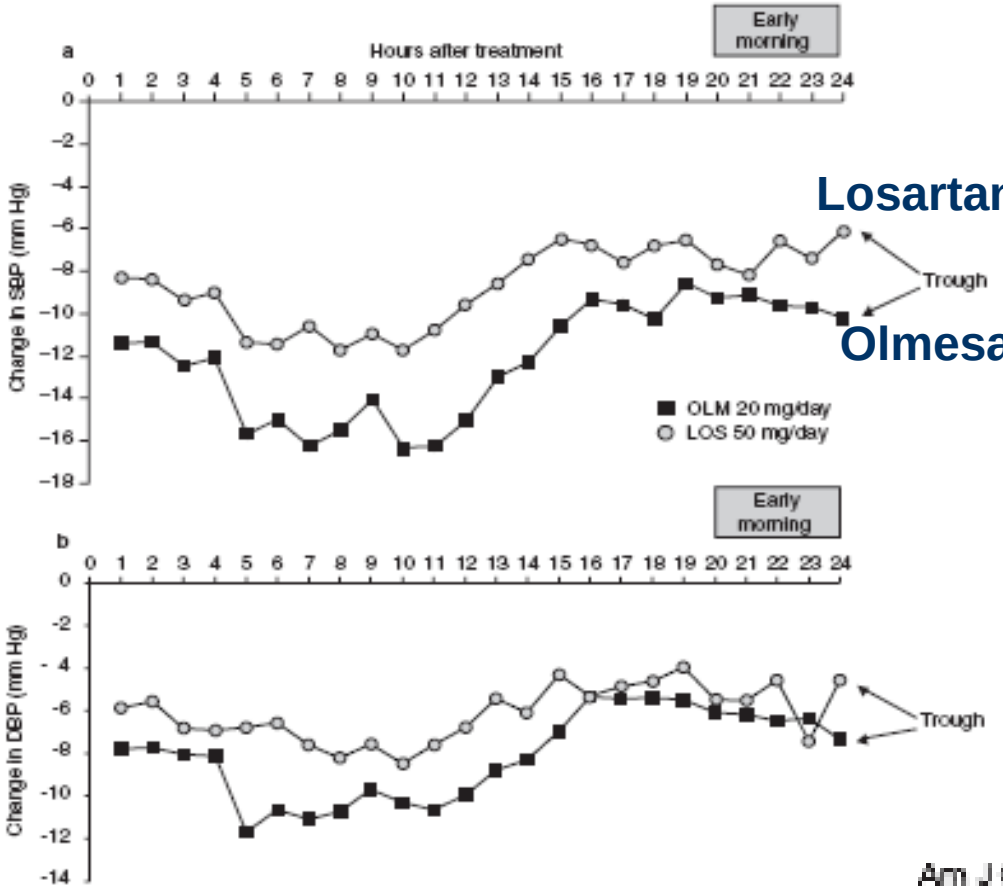
Oparil S.: J Human Hypertens, 16 (S 2): S 17 - S 23, 2002
Oparil S. et al.: J Clin Hypertens, 3 (5): 283-291, 2001

Menarini International

24 Hr ABPM to assess Antihypertensive Efficacy

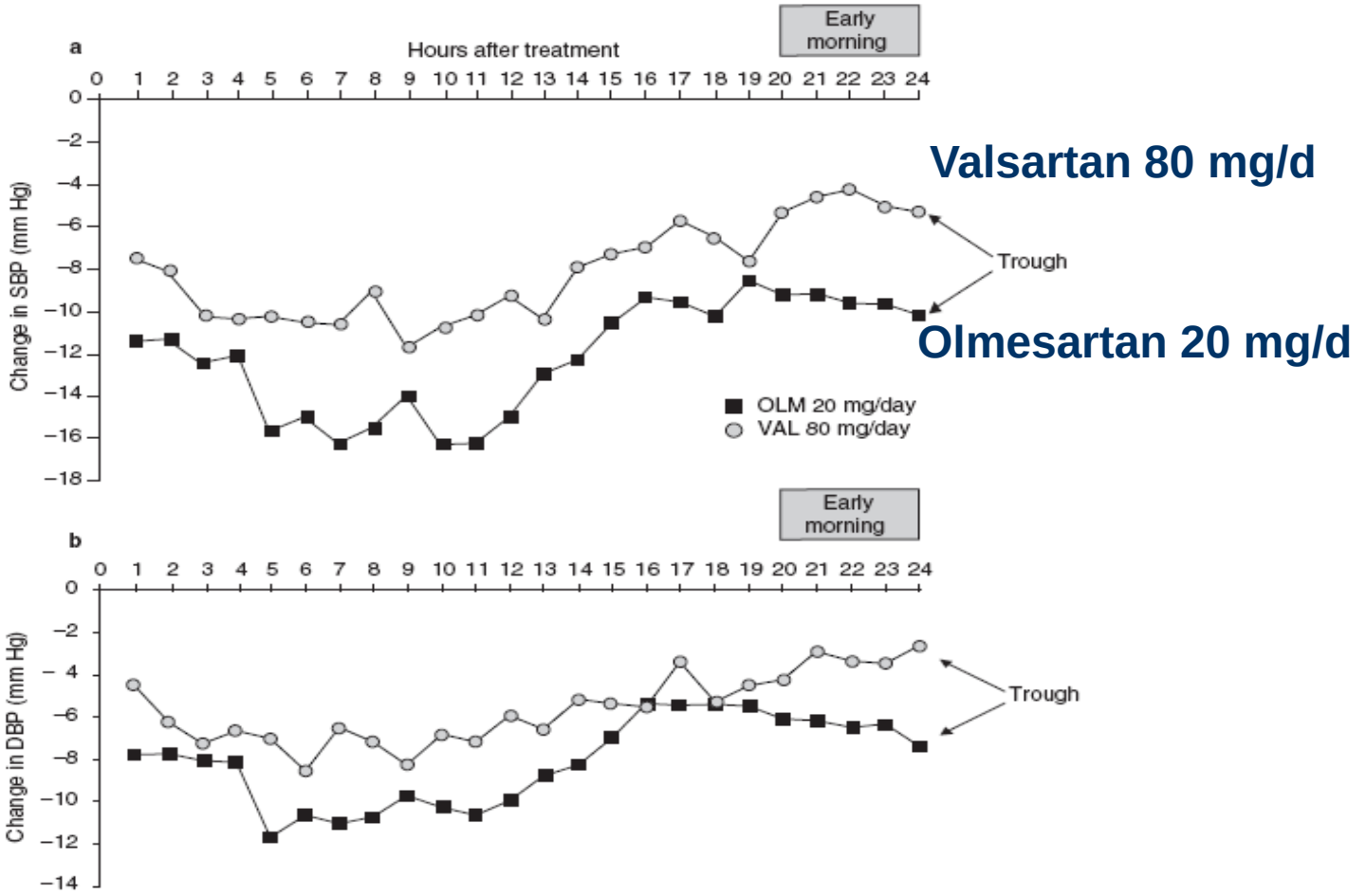
- 440 patients with mild to moderate HTN
- Randomized to:
  - Olmesartan 20mg N=136
  - Losartan 50 mg N=134
  - Valsartan 80 mg N=130
  - Irbesartan 150 mg N=134
- Followed for 12 weeks
- ABPM performed at baseline and end of study.

24 Hr ABPM to assess Antihypertensive Efficacy



Am J Cardiovasc Drugs 2005; 5 (1)

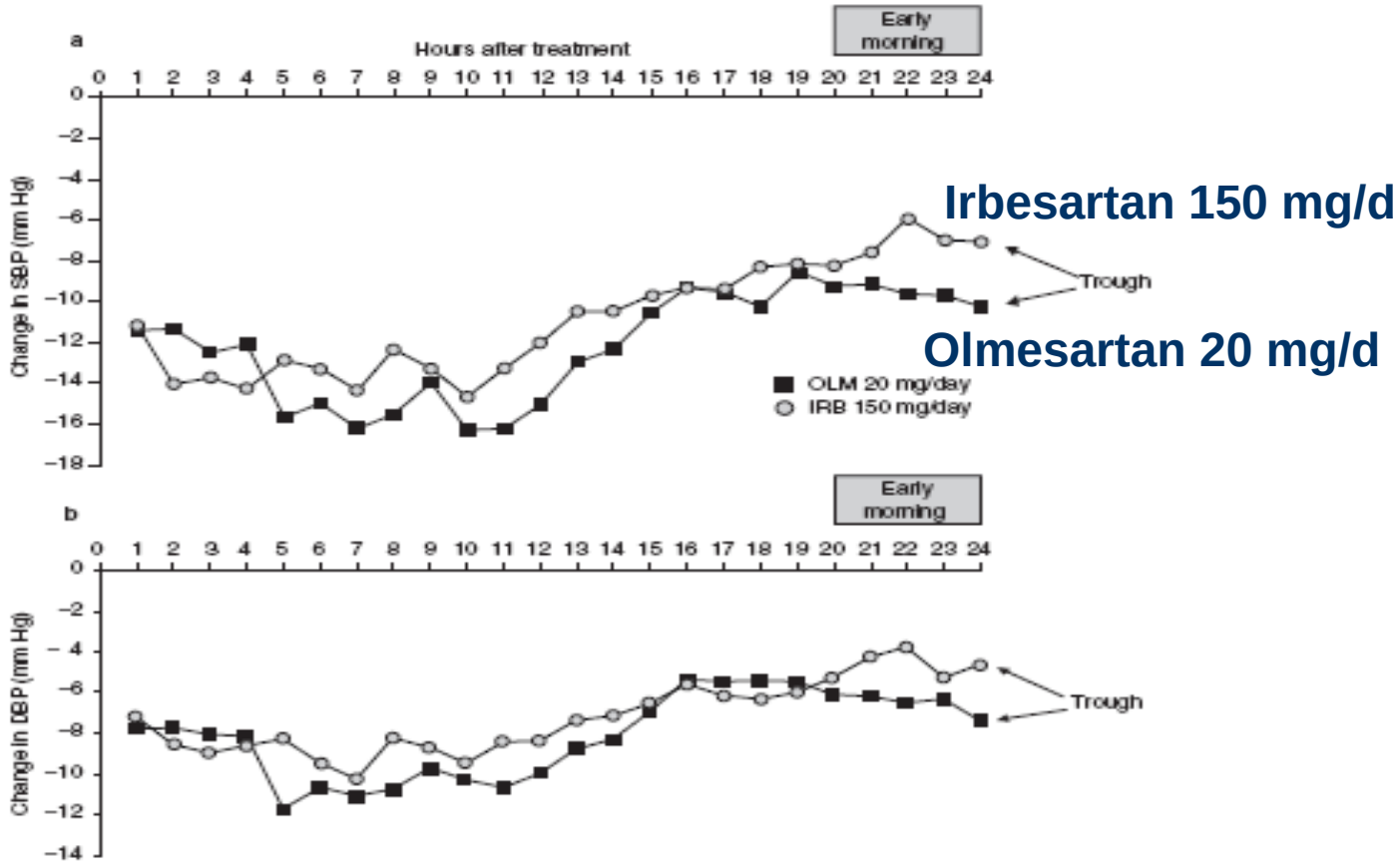
24 Hr ABPM to assess Antihypertensive Efficacy



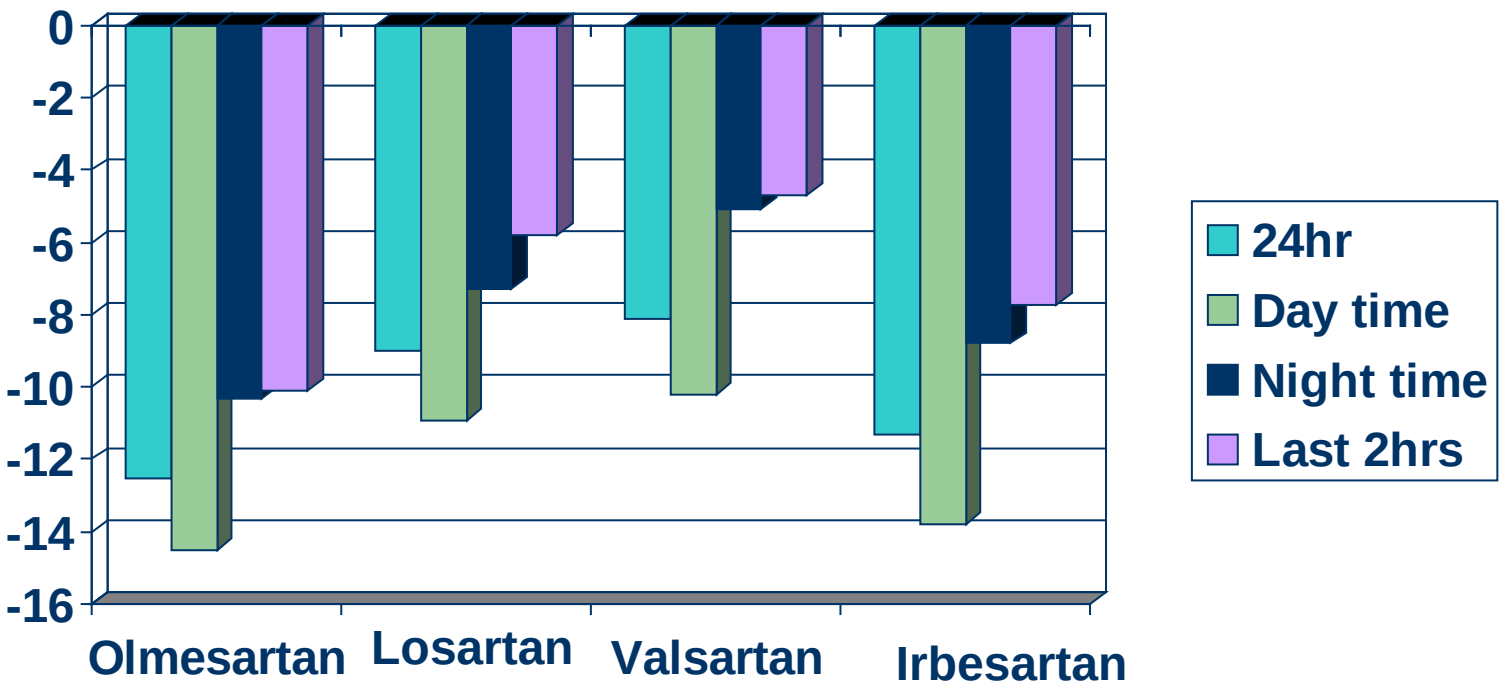
Valsartan 80 mg/d

Olmesartan 20 mg/d

24 Hr ABPM to assess Antihypertensive Efficacy



Change in Systolic BP as Assessed by ABPM



Efficacy and Safety of Olmesartan Medoxomil and Hydrochlorothiazide Compared with Benazepril and Amlodipine Besylate

Background: Most patients with stage 2 hypertension require two or more antihypertensive agents in order to achieve the BP goals recommended in current treatment guidelines. Accordingly, combinations of two drugs with different mechanisms of antihypertensive action are widely used.

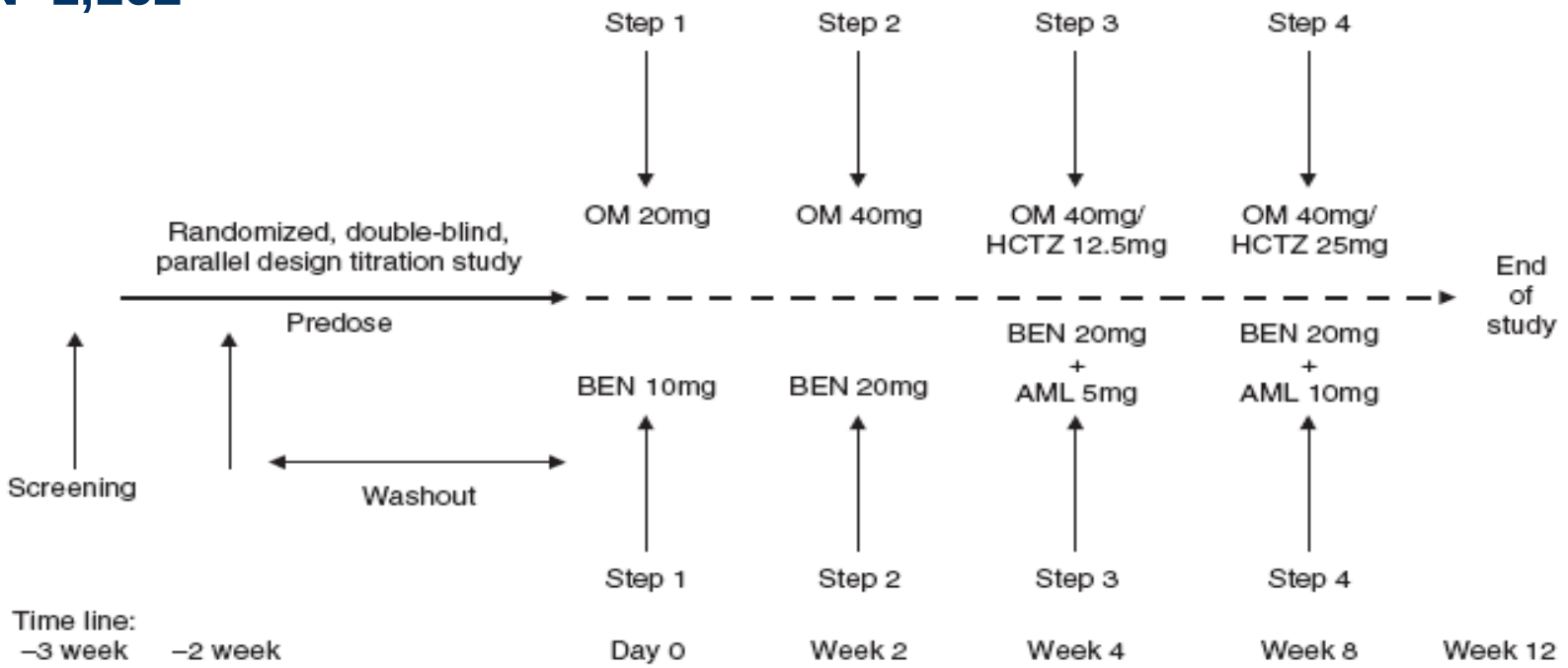
Objective: The aim of this randomized, double-blind, multicenter 12-week study was to compare the efficacy, safety, and tolerability of a combination of olmesartan medoxomil/hydrochlorothiazide (HCTZ) with that of benazepril plus amlodipine besylate in patients with stage 2 hypertension.

Methods: Patients were eligible for randomization following a 3- to 4-week placebo run-in period if they had either (i) mean seated DBP ≥90mm Hg but <115mm Hg and mean seated SBP ≥160mm Hg but <200mm Hg, or (ii) mean seated DBP ≥100mm Hg but <115mm Hg. The difference in mean seated SBP measured on two separate visits during the run-in period was required to be ≤15mm Hg. In addition, a mean 8-hour daytime ambulatory DBP ≥95mm Hg and <115mm Hg or SBP >145mm Hg and ≤190mm Hg were required. Eligible patients were randomized 1 : 1 to treatment with olmesartan medoxomil (20 mg/day for 2 weeks; then 40 mg/day for 2 weeks; then olmesartan medoxomil/HCTZ 40/12.5 mg/day for 4 weeks; then olmesartan medoxomil/HCTZ 40/25 mg/day for 4 weeks) or benazepril (10 mg/day for 2 weeks; then 20 mg/day for 2 weeks; then benazepril 20 mg/day plus amlodipine besylate 5 mg/day for 4 weeks; then benazepril 20 mg/day plus amlodipine besylate 10 mg/day for 4 weeks). The primary endpoint was change from baseline in mean SBP at the end of week 12 (end of study). Secondary endpoints included DBP after completion of monotherapy and combination therapy at the end of weeks 4 and 12, SBP at the end of week 4, and percentage of patients attaining BP goals of <140/90mm Hg, <130/85mm Hg, and <130/80mm Hg at the end of weeks 4 and 12.

Results: One-hundred and ninety patients were randomized and received at least one dose of study medication. The primary efficacy endpoint of change in mean seated SBP at week 12 was significantly greater with olmesartan medoxomil/HCTZ than with benazepril plus amlodipine besylate (least square [LS] mean change: −32.5 vs −26.5mm Hg, p = 0.024; LS mean treatment difference −6.0mm Hg; 95% CI −11.1, −0.8mm Hg). The LS mean change for reduction in DBP approached statistical significance with olmesartan medoxomil/HCTZ compared with the benazepril-based regimen (p = 0.056) at week 12 (end of study). BP reductions showed statistically significant differences between treatment groups favoring olmesartan medoxomil/HCTZ in both SBP and DBP at week 8. The percentage of patients achieving goal rates at the end of the study for olmesartan medoxomil/HCTZ and benazepril plus amlodipine besylate, respectively, were 66.3% versus 44.7% (p = 0.006)

Efficacy of Olmesartan+ HCTZ compared to Benazepril + Amlodipine

N=1,162



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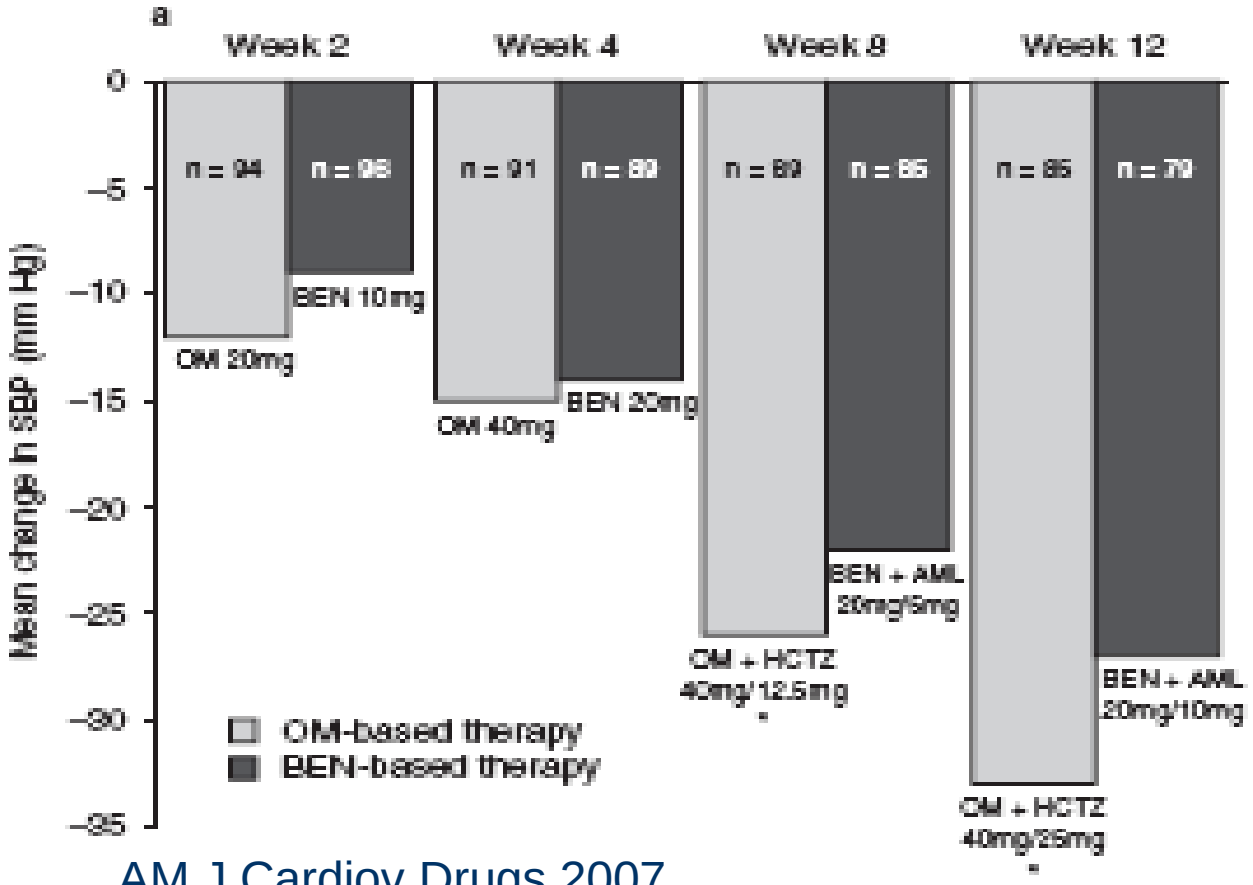
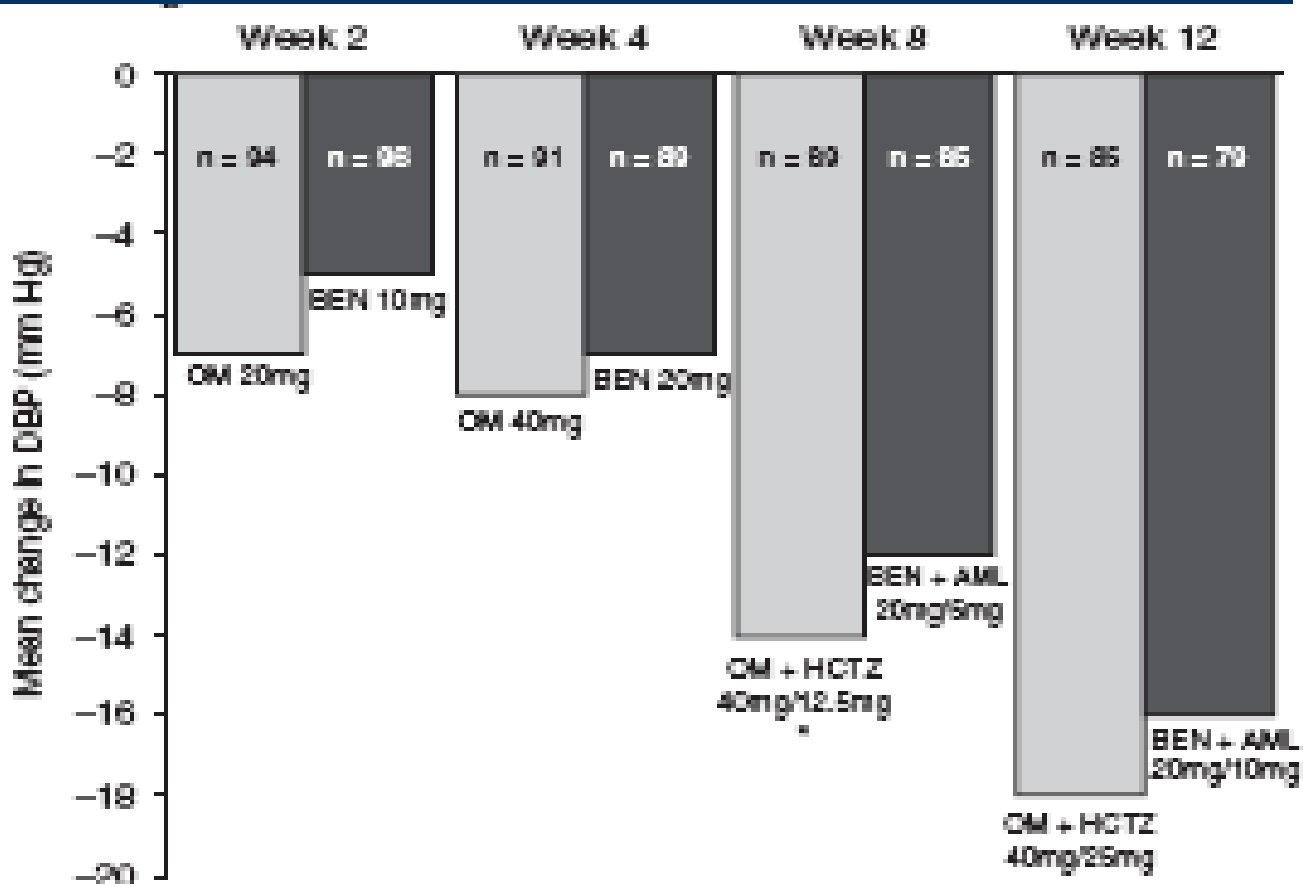
Systolic BP Reduction with Olmesartan+ HCTZ or Benazepril + Amlodipine



AM J Cardiov Drugs 2007

Diastolic BP Reduction with Olmesartan+ HCTZ or to Benazepril + Amlodipine



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Treatment of Hypertension to Prevent Vascular Events: So Where do we Stand?

- Phenotype of patients is still very important for drug selection
- Genomics seem very promising
- Taking into consideration drug specific effects, pleatropic effects and certain genotypes may lead to better BP control and better outcomes
- Blood pressure control still remains the primary goal

Final Conclusions: What now?

- Intensify efforts for better BP control in the population
- Tailoring therapy, personalize it as much as you can
- Take into consideration the phenotype, genotype and clinical profile of the patient
- Better days are yet ahead of us!!!