Treating Hypertension in Patients with Diabetes and the Metabolic Syndrome

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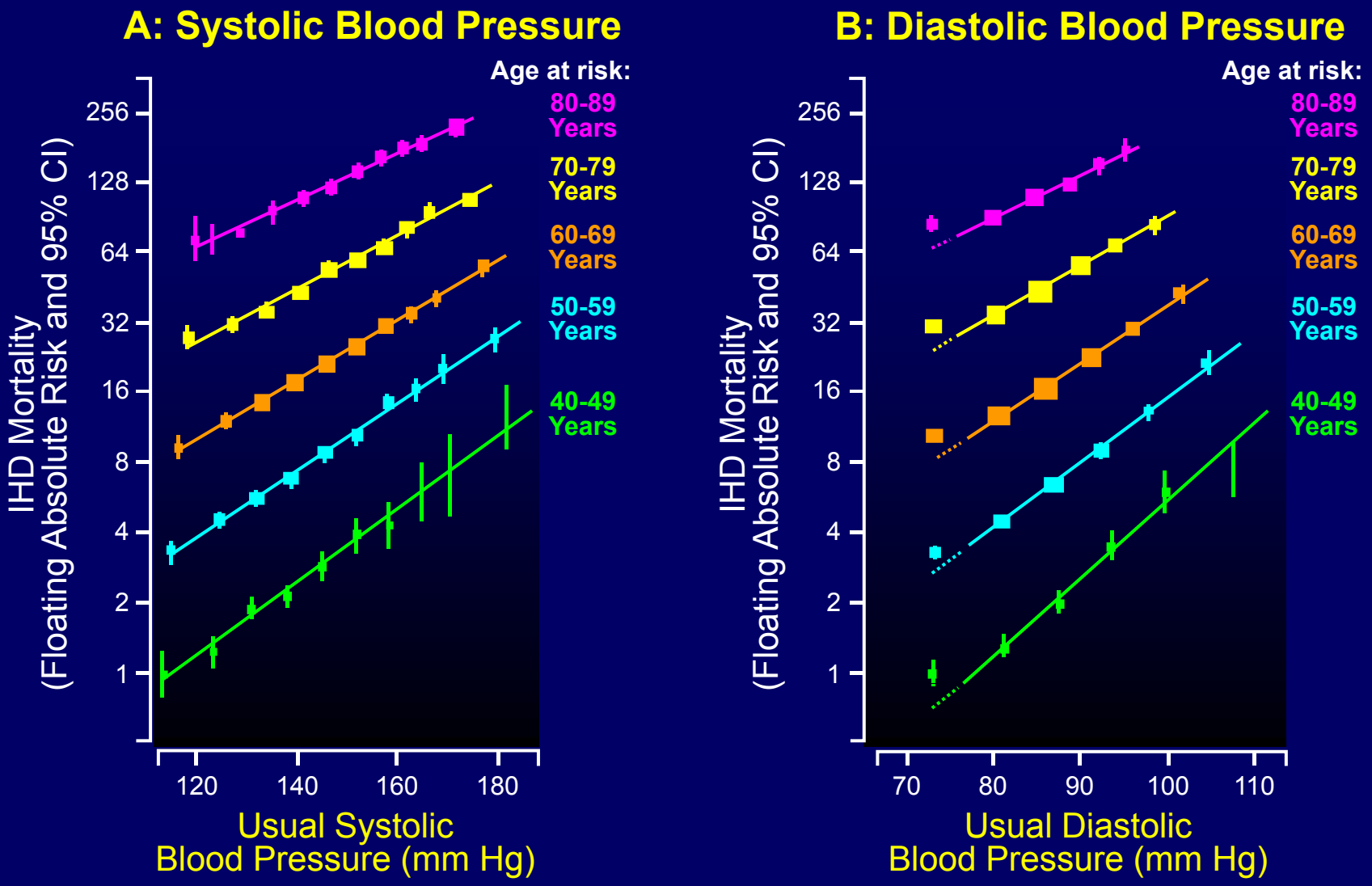
Main Conclusions: Treating Hypertension in Patients with Diabetes

- Treating BP to < 140/90 mmHg is clearly beneficial; lower BP values *might* possibly be justified
- ARB and thiazide combinations effectively achieve BP control in a majority of patient types
- Combining RAS blockers with amlodipine produces greatest CV & renal benefits (plus strong BP effects)
- ARBs (like ACE inhibitors) now established for renal & CV protection in high risk patients, particularly those with diabetes
- Studies of major intermediate vascular findings help explain these clinical benefits of RAS blockers

CHD Rates by SBP, DBP and Age

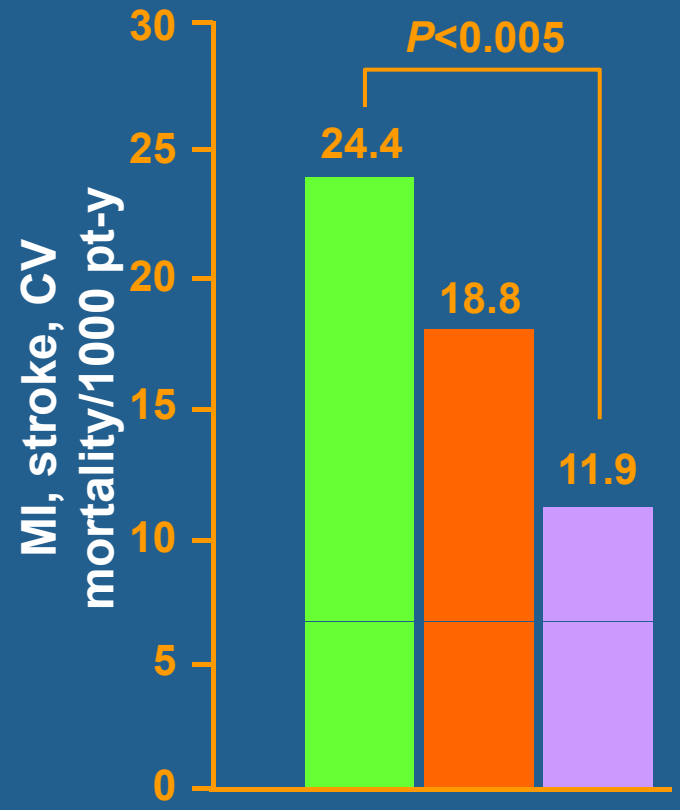


Adapted from Lewington et al. *Lancet*. 2002; 360:1903-1913.

V072004

BP Control Reduces CV Events: HOT Trial

Diabetes Subgroup



Goal of therapy: target diastolic BP

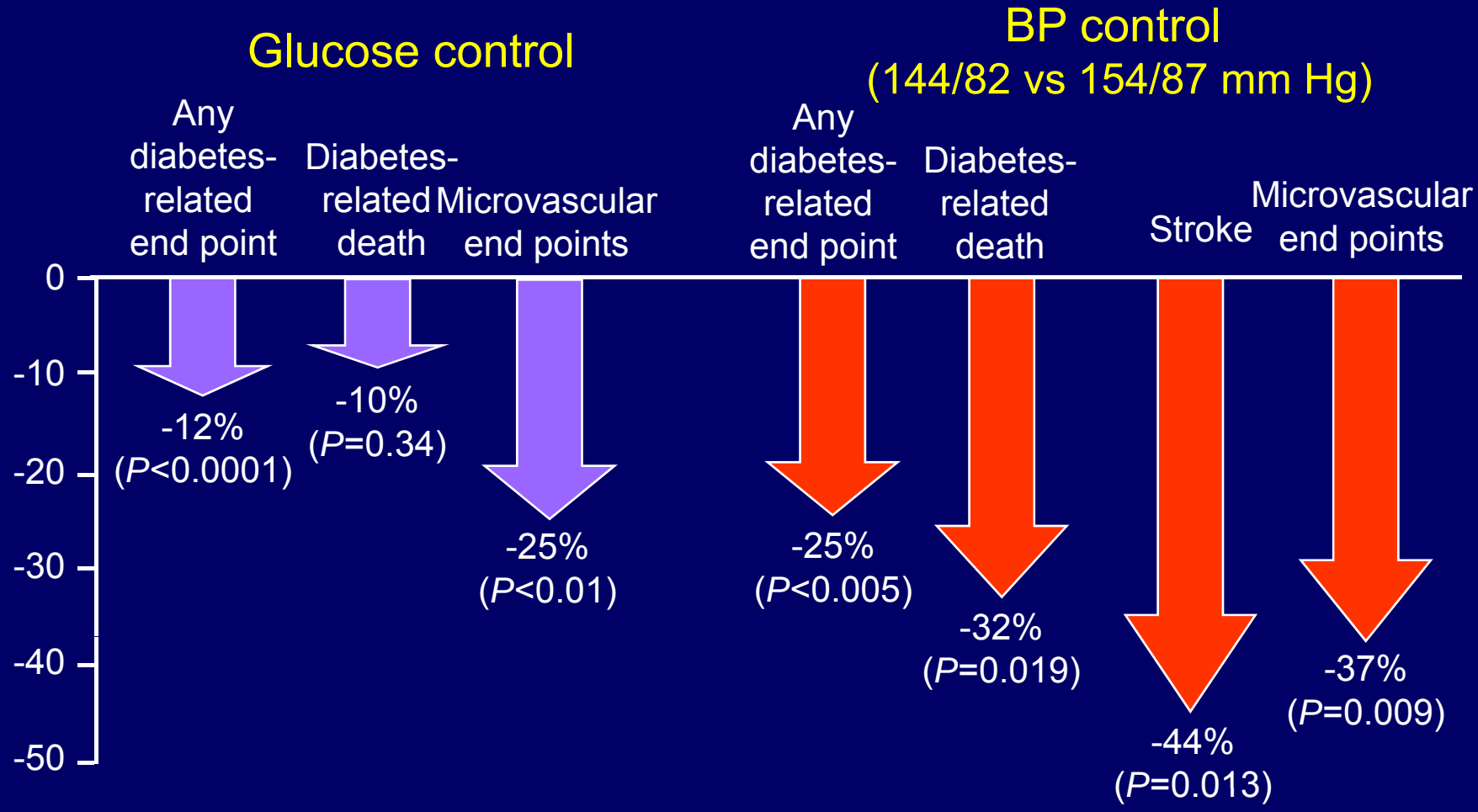
- ≤90 mm Hg (n=501)
- ≤85 mm Hg (n=501)
- ≤80 mm Hg (n=499)

Achieved

≤90 →	85.2 mm Hg
≤85 →	83.2 mm Hg
≤80 →	81.1 mm Hg

Hansson et al. *Lancet*. 1998;351:1755.

United Kingdom Prospective Diabetes Study (UKPDS): Results



UKPDS Group 38. *BMJ.* 1998;317:703–713.
UKPDS Group 33. *Lancet.* 1998;352:837–853.

Effects of Intensive Blood Pressure Control on Cardiovascular Events in Type 2 Diabetes Mellitus: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial

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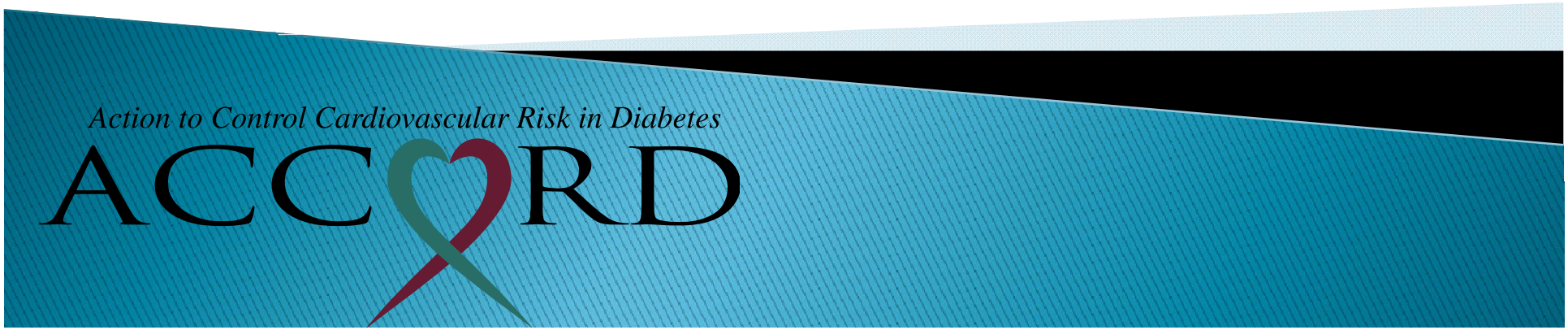
Veterans Affairs Medical Center, Memphis, TN

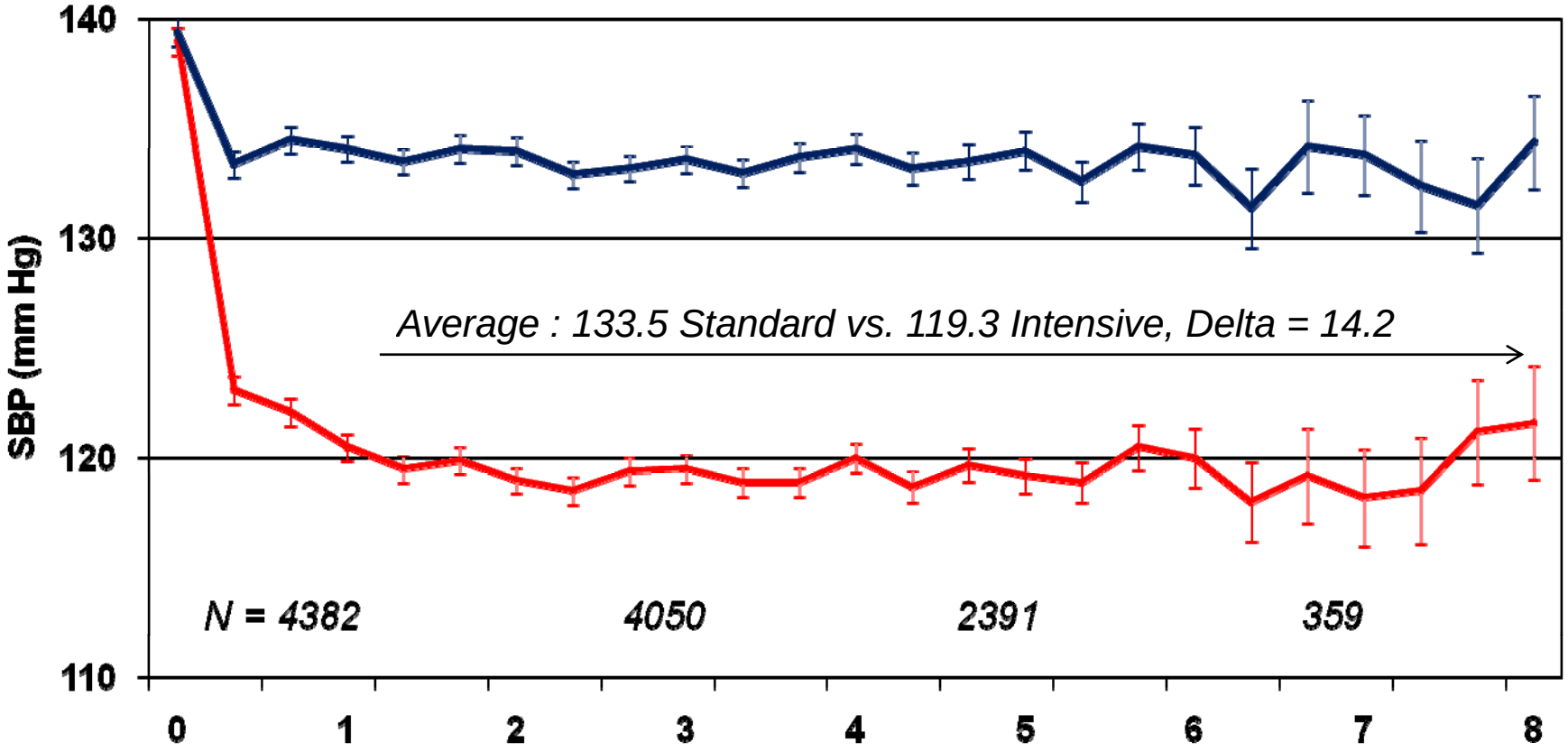
For The ACCORD Study Group



Systolic Pressures (mean ± 95% CI)

Mean # Meds

Intensive:	*3.2*	*3.4*	*3.5*	*3.4*
Standard:	*1.9*	*2.1*	*2.2*	*2.3*



Action to Control Cardiovascular Risk in Diabetes
ACCORD

Adverse Events

	Intensive N (%)	Standard N (%)	P
Serious AE	77 (3.3)	30 (1.3)	<0.0001
Hypotension	17 (0.7)	1 (0.04)	<0.0001
Syncope	12 (0.5)	5 (0.2)	0.10
Bradycardia or Arrhythmia	12 (0.5)	3 (0.1)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Renal Failure	5 (0.2)	1 (0.04)	0.12
eGFR ever <30 mL/min/1.73m^2	99 (4.2)	52 (2.2)	<0.001
Any Dialysis or ESRD	59 (1.2)	58 (1.2)	0.91
Dizziness on Standing†	217 (44)	188 (41)	0.39

† Symptom experienced over past 30 days from HRQL sample of N=943 participants assessed at 12 and 48 months post-randomization

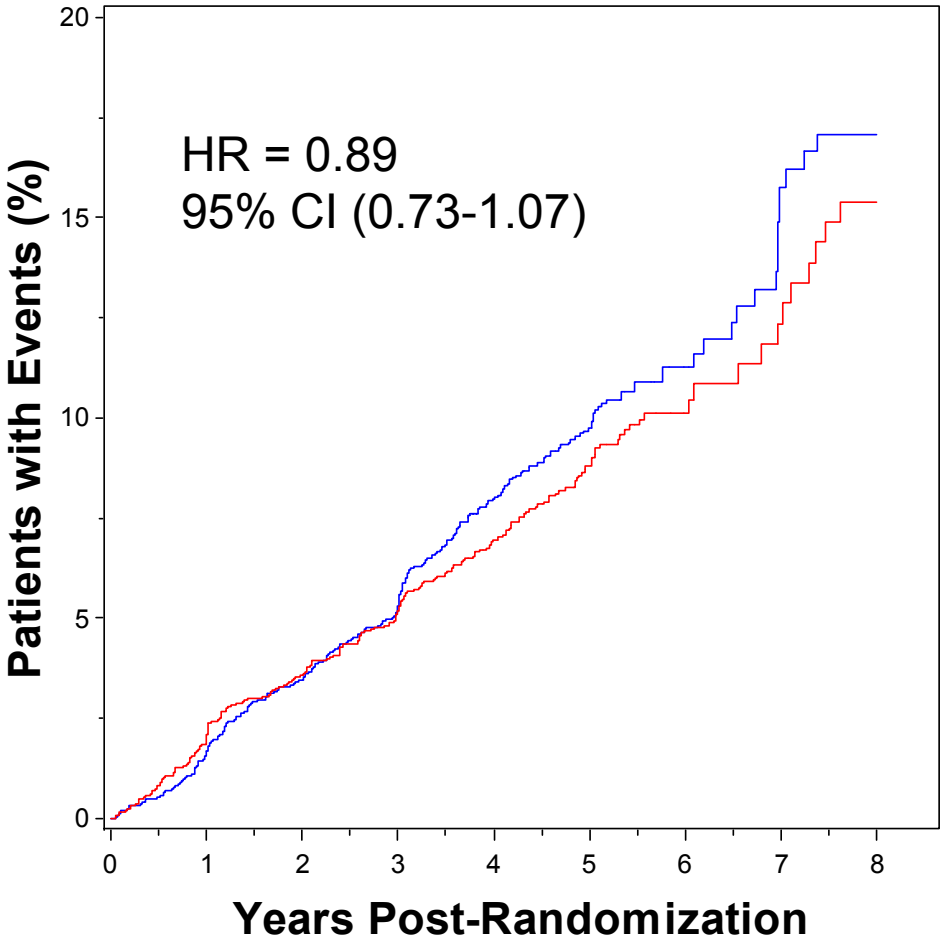
Primary & Secondary Outcomes

	Intensive Events (%/yr)	Standard Events (%/yr)	HR (95% CI)	P
Primary	208 (1.87)	237 (2.09)	0.89 (0.73-1.07)	0.20
Total Mortality	150 (1.28)	144 (1.19)	1.07 (0.85-1.35)	0.55
Cardiovascular Deaths	60 (0.52)	58 (0.49)	1.06 (0.74-1.52)	0.74
Nonfatal MI	126 (1.13)	146 (1.28)	0.87 (0.68-1.10)	0.25
Nonfatal Stroke	34 (0.30)	55 (0.47)	0.63 (0.41-0.97)	0.03
Total Stroke	36 (0.32)	62 (0.53)	0.59 (0.39-0.89)	0.01

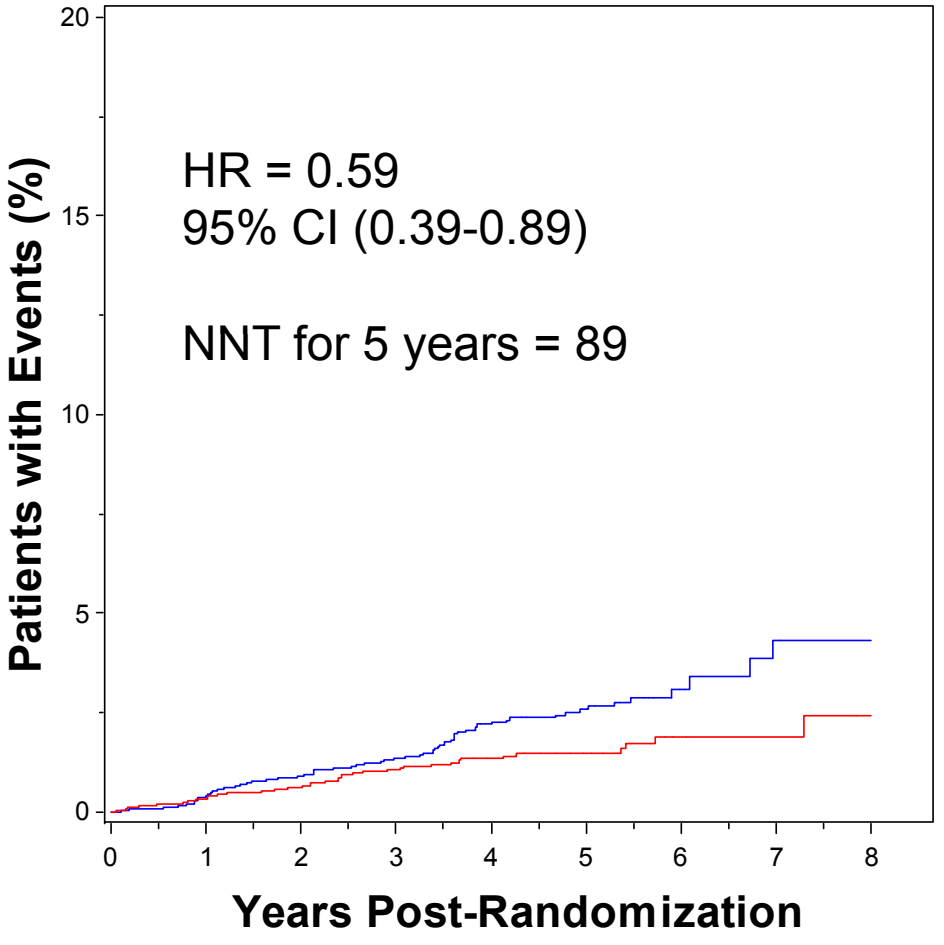
Also examined Fatal/Nonfatal HF (HR=0.94, p=0.67), a composite of fatal coronary events, nonfatal MI and unstable angina (HR=0.94, p=0.50) and a composite of the primary outcome, revascularization and unstable angina (HR=0.95, p=0.40)

Primary Outcome

Nonfatal MI, Nonfatal Stroke or CVD Death



Total Stroke



Intensive Standard

Action to Control Cardiovascular Risk in Diabetes
ACCORD

Rethinking Lower Blood Pressure Goals for Diabetic Patients with Coronary Artery Disease – Findings from the INternational VErapamil SR – Trandolapril STudy (INVEST)

Rhonda M. Cooper-DeHoff, Yan Gong, Eileen M. Handberg, Anthony A. Bavry, Scott J. Denardo, George L. Bakris and Carl J. Pepine

on behalf of the INVEST Investigators

University of Florida

Gainesville, FL

Hypothesis

Diabetic patients who achieved SBP <130 mm Hg would have reduced CV outcomes compared with diabetic patients who achieved SBP ≥130-<140 mm Hg

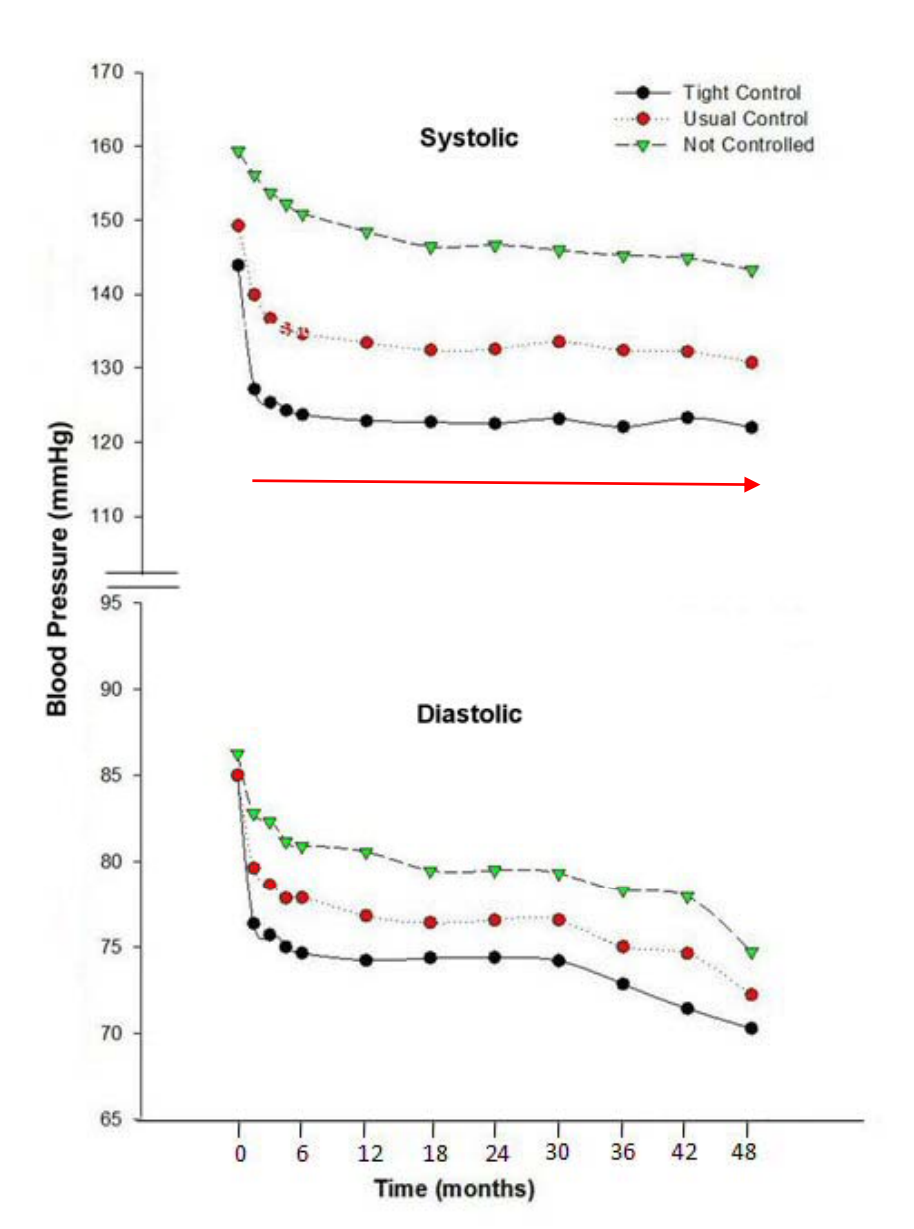
Methods

Patients with diabetes at baseline grouped according to mean on-treatment SBP

Tight Control	• <130 mm Hg
Usual Control	• ≥130-<140 mm Hg
Not Controlled	• ≥140 mm Hg

INVEST

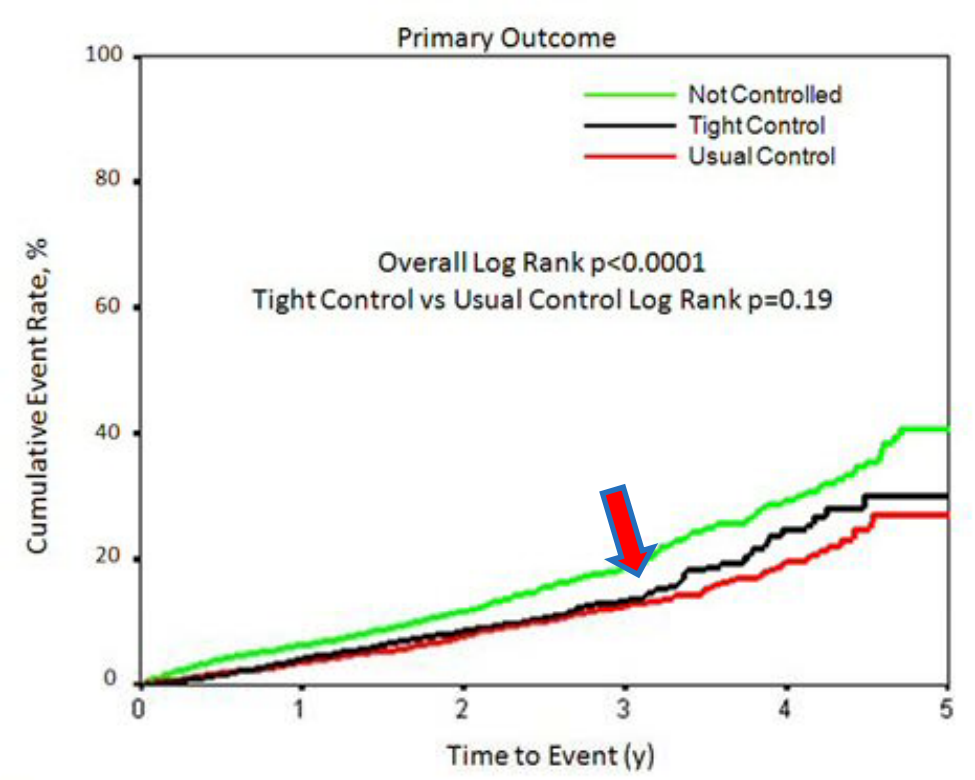
Results – BP Reduction

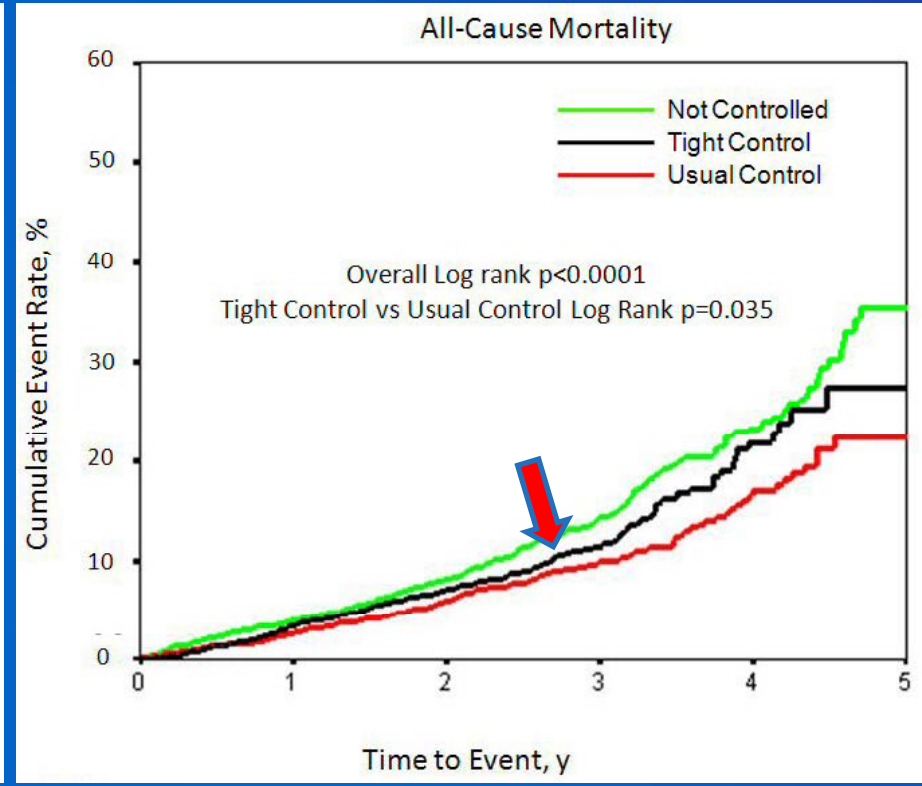


No difference comparing the two treatment strategies in terms of BP reduction achieved in any of the groups

INVEST

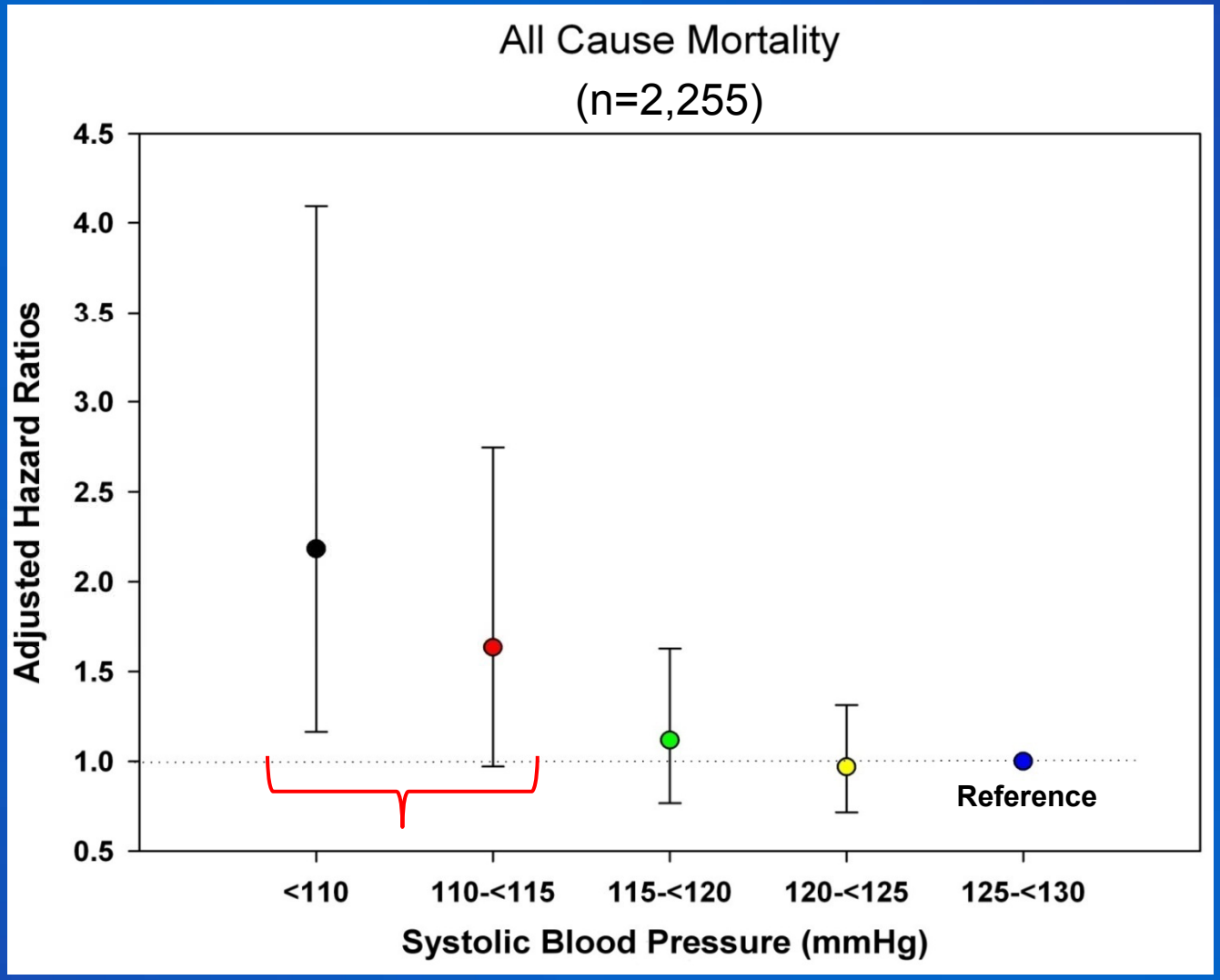
Results: Outcomes During INVEST





Nonfatal MI	• Tight Control vs Usual Control Log Rank p=0.49
Nonfatal Stroke	• Tight Control vs Usual Control Log Rank p=0.38

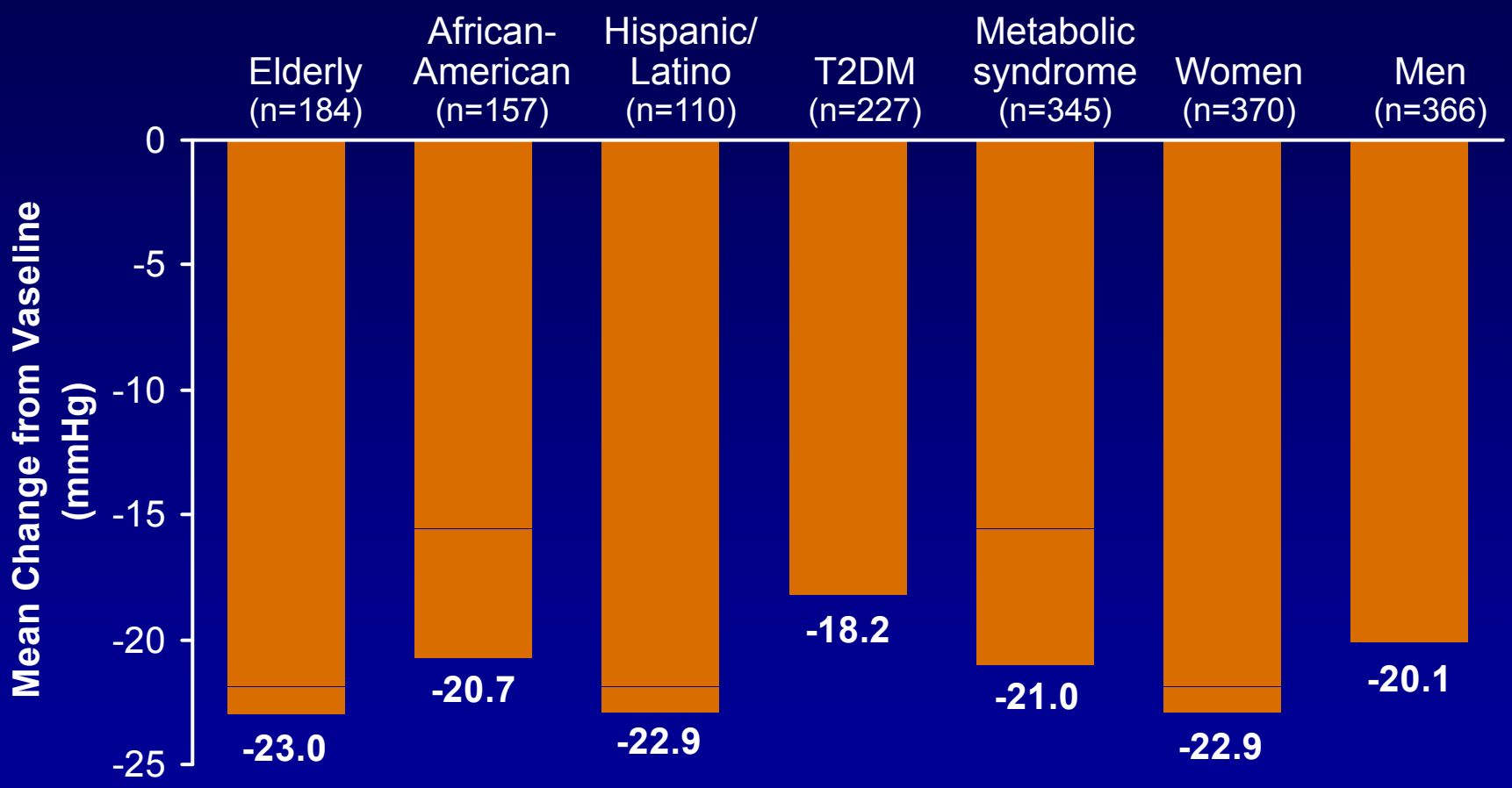
Results: Outcomes – Tight Control Group



Other significant variables in Cox regression model:

age, race, PAD, MI, CHF, US residency, renal impairment, LVH, TIA/stroke

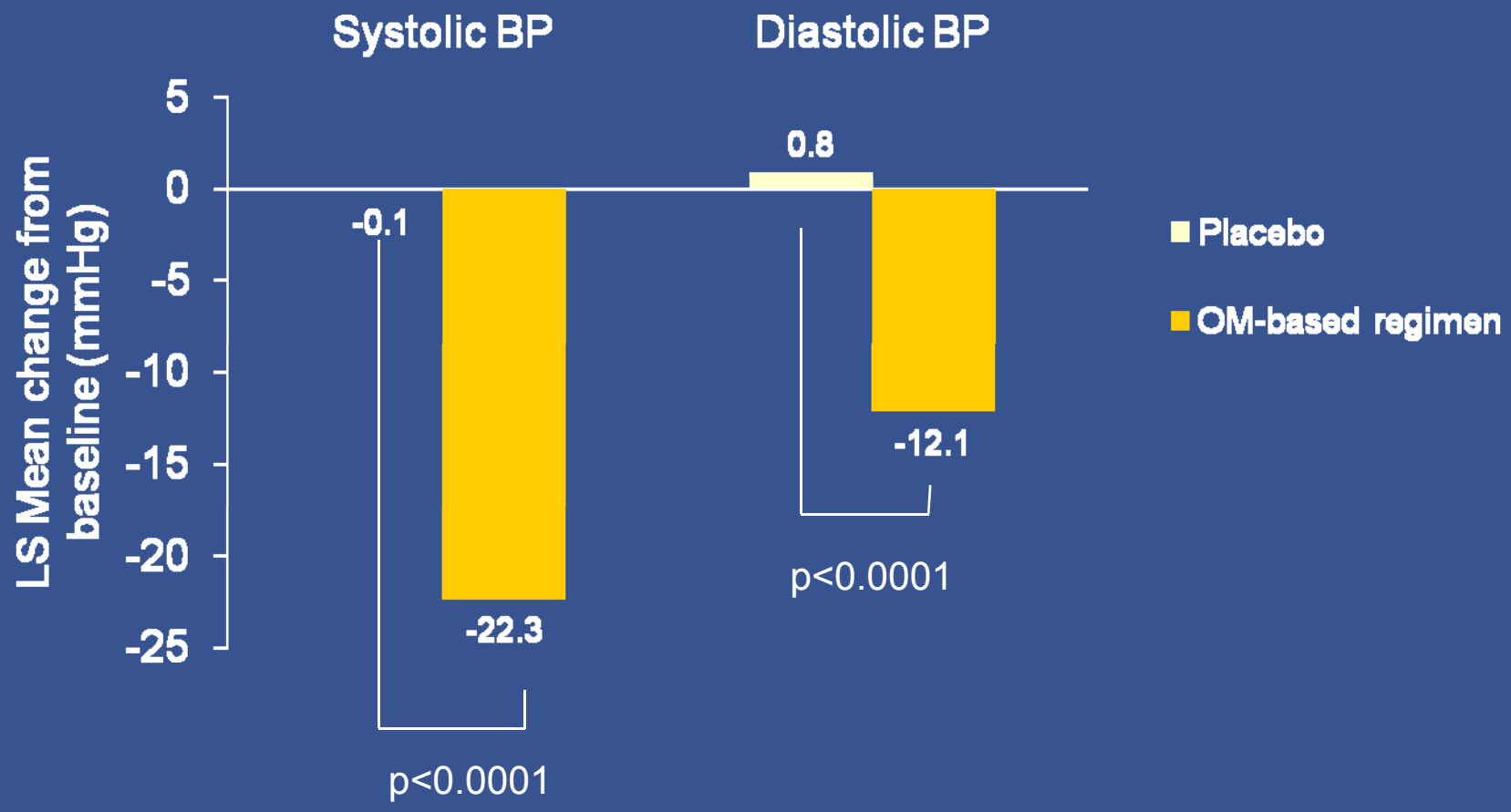
Effects of Combination Irbesartan/HCTZ Treatment on Systolic BP: Changes after 18 weeks by Subgroup



ITT population; T2DM, type 2 diabetes mellitus

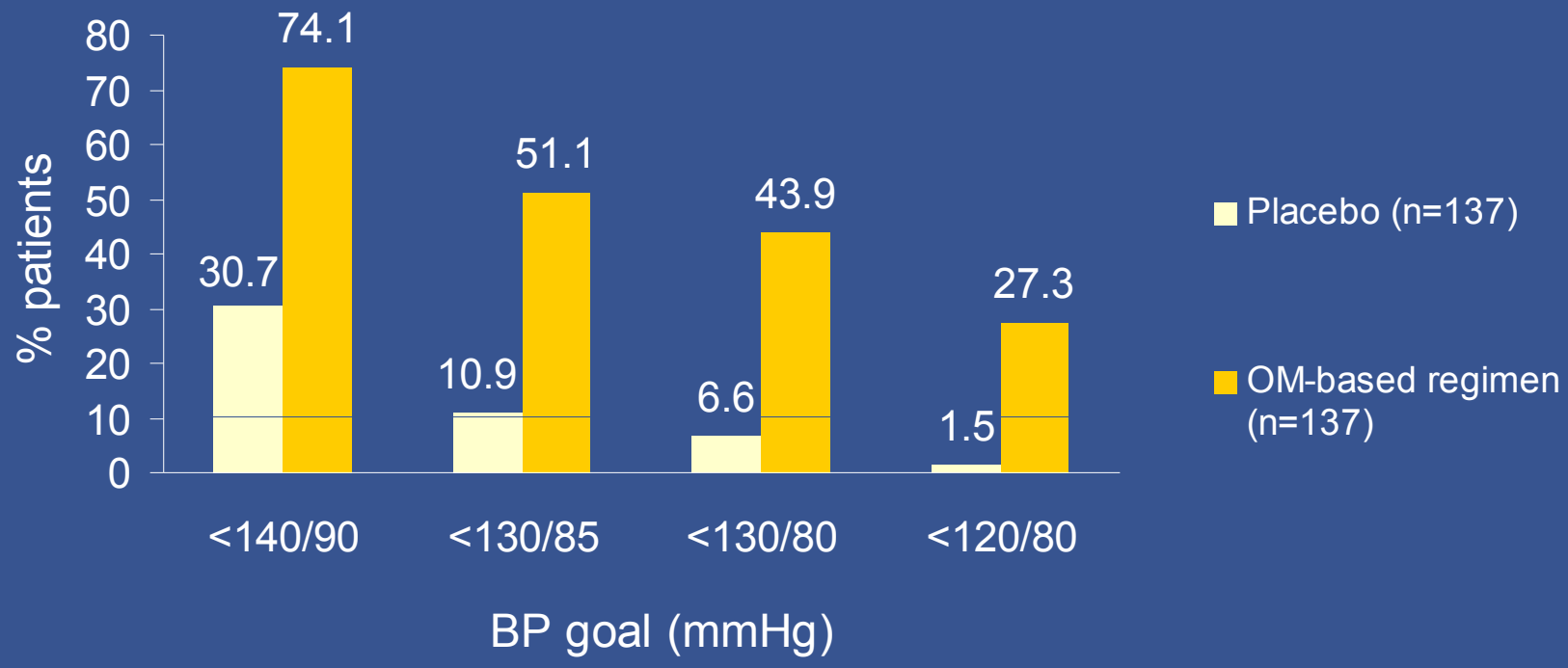
Neutel et al, J Clin Hypertens, 2007

Olmesartan (+/- Hydrochlorothiazide) in Patients with Stage 1 or 2 Hypertension
Change from Baseline BP at End of Study

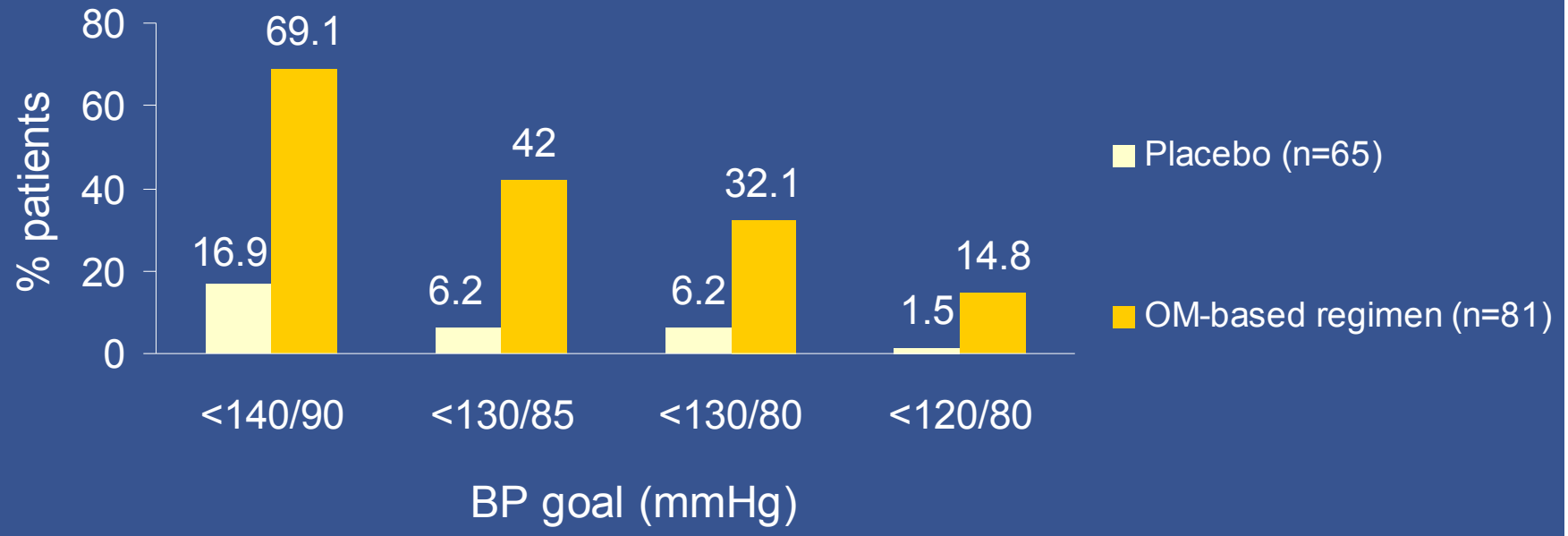


Baseline BP
Placebo: 155.2/93.7 mmHg
OM-based regimen: 156.7/94.0 mmHg

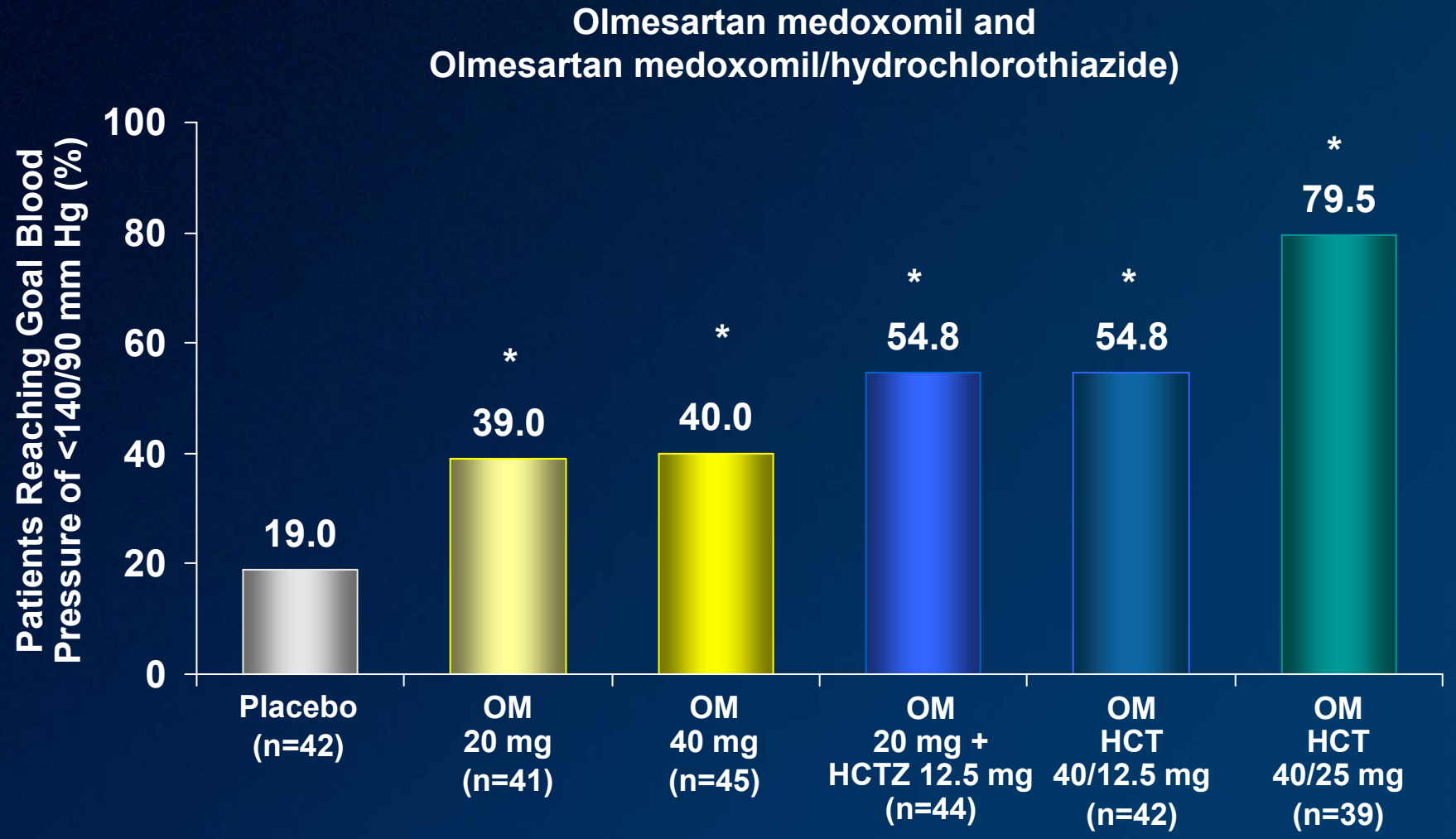
Secondary Endpoint: BP Goal Achievement at End of Study



Olmesartan/HCT --- Secondary Endpoint: BP Goal Achievement at End of Study – Patients with STAGE 2 Hypertension



Factorial Study: ARB, Diuretic or Combination BP Goal Attainment of <140/90 mm Hg



*P<.05 vs placebo.
Mean seated baseline BP=152-154/103-104 mm Hg.
Data on file, Daiichi Sankyo, Inc.; Kostis J, et al. *Am J Hypertens.* 2004;17:114A.

Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension

Kenneth Jamerson[1], George L. Bakris[2], Bjorn Dahlof[3], Bertram Pitt1, Eric J. Velazquez[4], Michael A. Weber[5]

for the ACCOMPLISH Investigators

1. University of Michigan Health System, Ann Arbor, MI; 2. University of Chicago-Pritzker School of Medicine, Chicago, IL; 3. Sahlgrenska University Hospital, Gothenburg, Sweden; 4. Duke University School of Medicine, Durham, NC; 5. SUNY Downstate Medical College, Brooklyn, NY

ACCOMPLISH: the first outcomes trial to compare initial therapy with two different combinations

Hypothesis

Benazepril/amlodipine combination will reduce CV morbidity and mortality by 15% compared with benazepril/HCTZ combination in patients with high-risk hypertension

CV = cardiovascular; HCTZ = hydrochlorothiazide

Jamerson K, et al. Am J Hypertens 2004;17:793–801

ACCOMPLISH

Primary and secondary endpoints

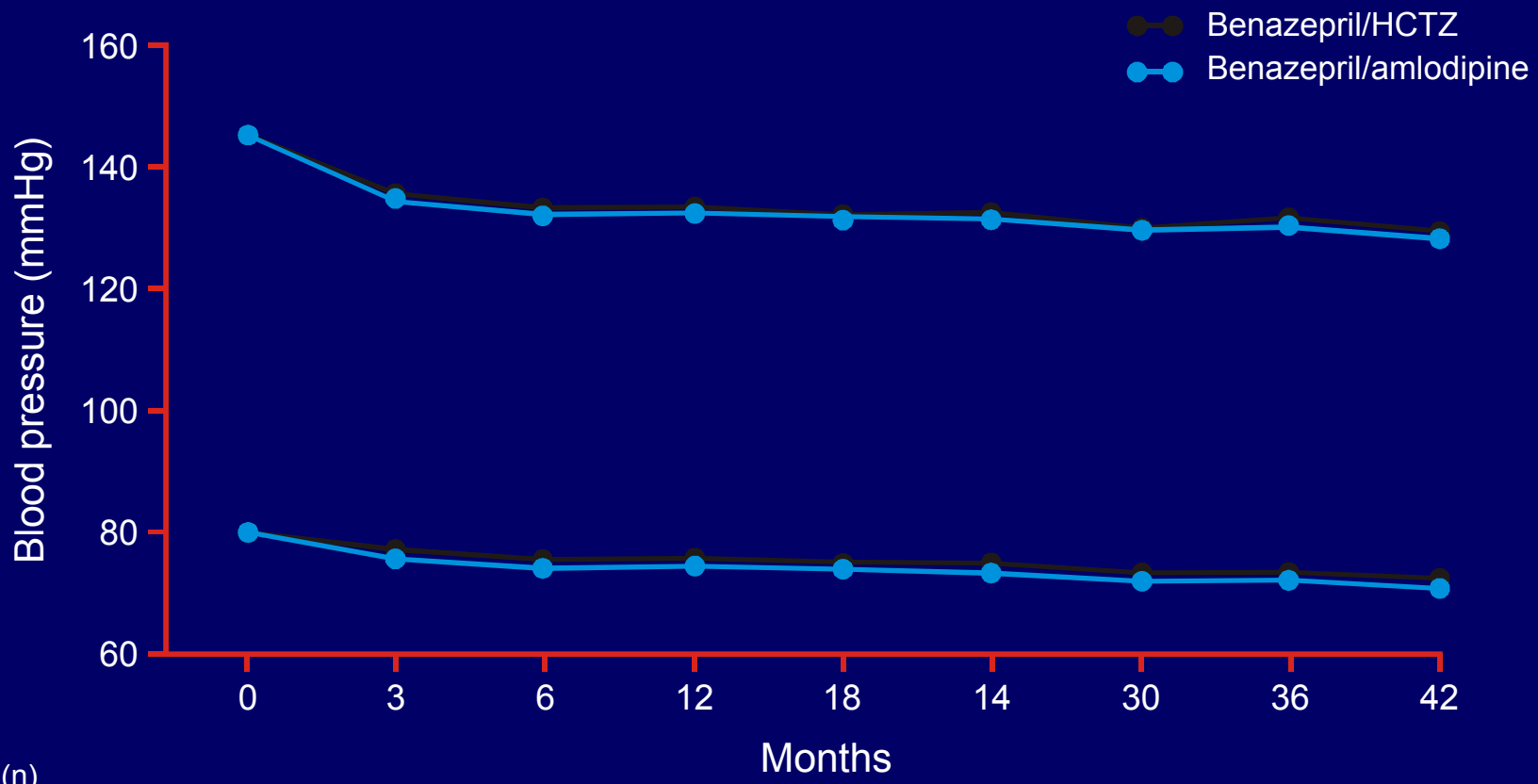
- Primary endpoint:
  - Composite of CV mortality and morbidity
    - (CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, coronary revascularization procedure [PCI or CABG], or resuscitated sudden death)
- Secondary endpoints:
  - Composite of CV morbidity
  - Composite of CV mortality, non-fatal stroke, or non-fatal MI

CV = cardiovascular; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft

Jamerson K, et al. Am J Hypertens 2004;17:793–801

ACCOMPLISH

SBP/DBP over time



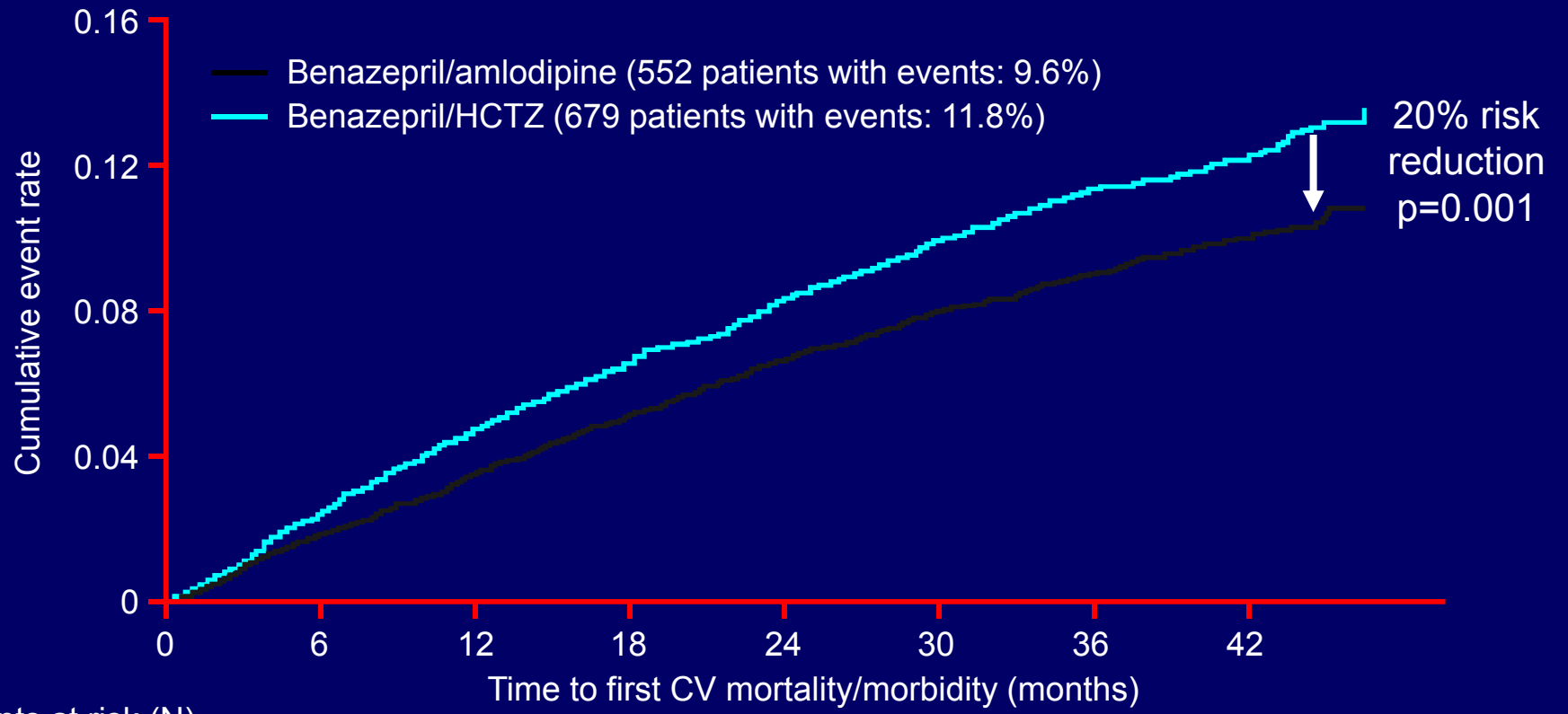
Patients (n)									
Benazepril/amlodipine	5740	5517	5404	5178	5010	4866	4298	2804	1074
Benazepril/HCTZ	5757	5537	5408	5222	5033	4825	4299	2529	1042

SBP = systolic blood pressure; DBP = diastolic blood pressure
HCTZ = hydrochlorothiazide

Jamerson K, et al. N Engl J Med 2008;359:2417–28

ACCOMPLISH

Kaplan-Meier curve for time to primary endpoint
(based on 1231 patients with primary events)

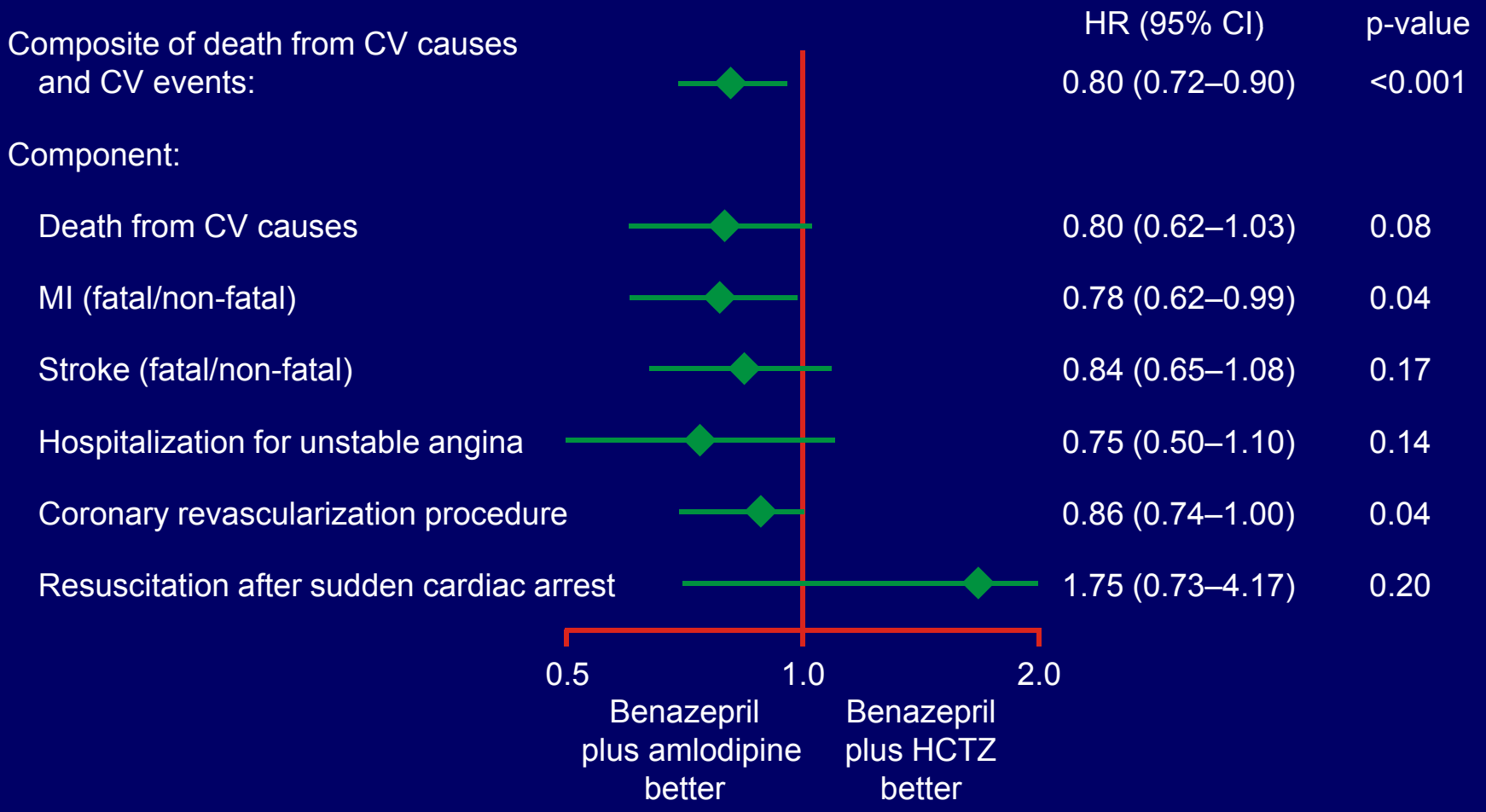


Patients at risk (N)							
Benazepril/amlodipine	5,512	5,317	5,141	4,959	4,739	2,826	1,447
Benazepril/HCTZ	5,483	5,274	5,082	4,892	4,655	2,749	1,390

*Hazard ratio (95% confidence interval): 0.80 (0.72, 0.90)
CV = cardiovascular; HCTZ = hydrochlorothiazide
Jamerson K, et al. N Engl J Med 2008;359:2417–28

ACCOMPLISH

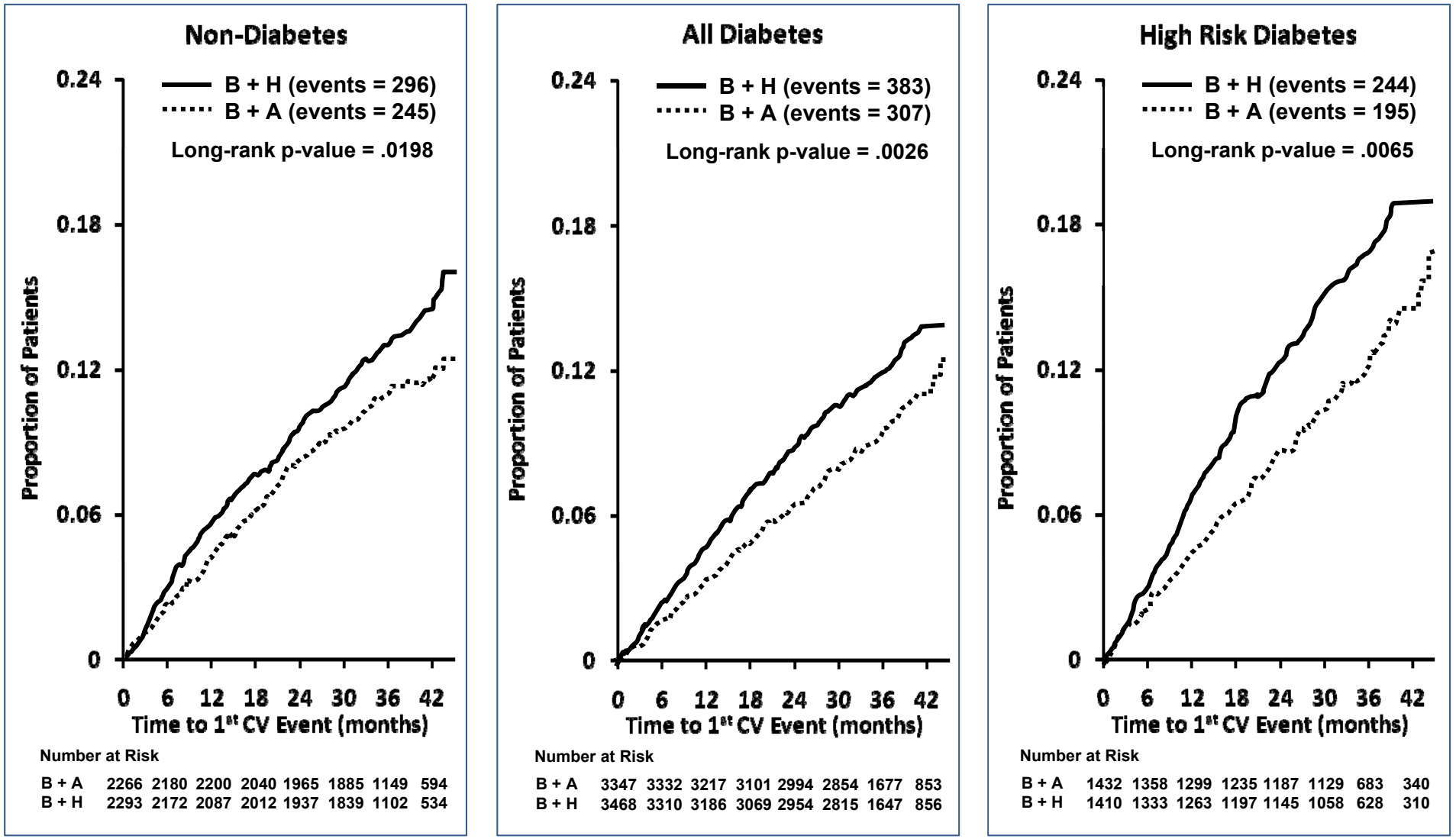
Primary endpoint and individual components



CV = cardiovascular; HR = hazard ratio; CI = confidence interval
MI = myocardial infarction; HCTZ = hydrochlorothiazide

Jamerson K, et al. N Engl J Med 2008;359:2417–28

ACCOMPLISH


Non-Diabetes
B + H (events = 296)
B + A (events = 245)
Long-rank p-value = .0198
Proportion of Patients
0.24
0.18
0.12
0.06
0
0 6 12 18 24 30 36 42
Time to 1st CV Event (months)
Number at Risk
B + A 2266 2180 2200 2040 1965 1885 1149 594
B + H 2293 2172 2087 2012 1937 1839 1102 534
All Diabetes
B + H (events = 383)
B + A (events = 307)
Long-rank p-value = .0026
Proportion of Patients
0.24
0.18
0.12
0.06
0
0 6 12 18 24 30 36 42
Time to 1st CV Event (months)
Number at Risk
B + A 3347 3332 3217 3101 2994 2854 1677 853
B + H 3468 3310 3186 3069 2954 2815 1647 856
High Risk Diabetes
B + H (events = 244)
B + A (events = 195)
Long-rank p-value = .0065
Proportion of Patients
0.24
0.18
0.12
0.06
0
0 6 12 18 24 30 36 42
Time to 1st CV Event (months)
Number at Risk
B + A 1432 1358 1299 1235 1187 1129 683 340
B + H 1410 1333 1263 1197 1145 1058 628 310

Characteristic	Benazepril + Amlodipine	Benazepril + HCTZ	Hazard Ratio (95% CI)	*p*-Value
Number of Patients	3,478	3,468	—	—
Primary endpoint	307 (8.8)	383 (11.0)	0.79 (0.68 – 0.92)	.003
Fatal and non-fatal MI	77 (2.2)	91 (2.6)	0.85 (0.63 – 1.15)	.283
Hospitalized UA	23 (0.7)	36 (1.0)	0.64 (0.38 – 1.08)	.092
Stroke	64 (1.8)	70 (2.0)	0.91 (0.65 – 1.28)	.607
CV death	62 (1.8)	74 (2.1)	0.84 (0.60 – 1.18)	.312
Revascularization	180 (5.2)	224 (6.5)	0.80 (0.66 – 0.97)	.024
Non-revasc. coronary event*	111 (3.2)	151 (4.4)	0.73 (0.57 – 0.94)	.013
CV death + MI + stroke	170 (4.9)	203 (5.9)	0.84 (0.68 – 1.03)	.085
Hospitalized HF	74 (2.1)	67 (1.9)	1.11 (0.80 – 1.54)	.545
All-cause death	141 (4.1)	139 (4.0)	1.02 (0.80 – 1.29)	.887
Renal endpoint**	231 (6.6)	422 (12.2)	0.53 (0.45 – 0.63)	<.001

Primary, Secondary and Individual Endpoints for the Diabetes Cohort

Values are absolute numbers (percentages).
Abbreviations: HCTZ=hydrochlorothiazide; MI=myocardial infarction; UA=unstable angina; CV=cardiovascular; HF=heart failure
* MI + UA + Sudden cardiac death
** $\geq$ 50% increase in serum creatinine with final value above normal range

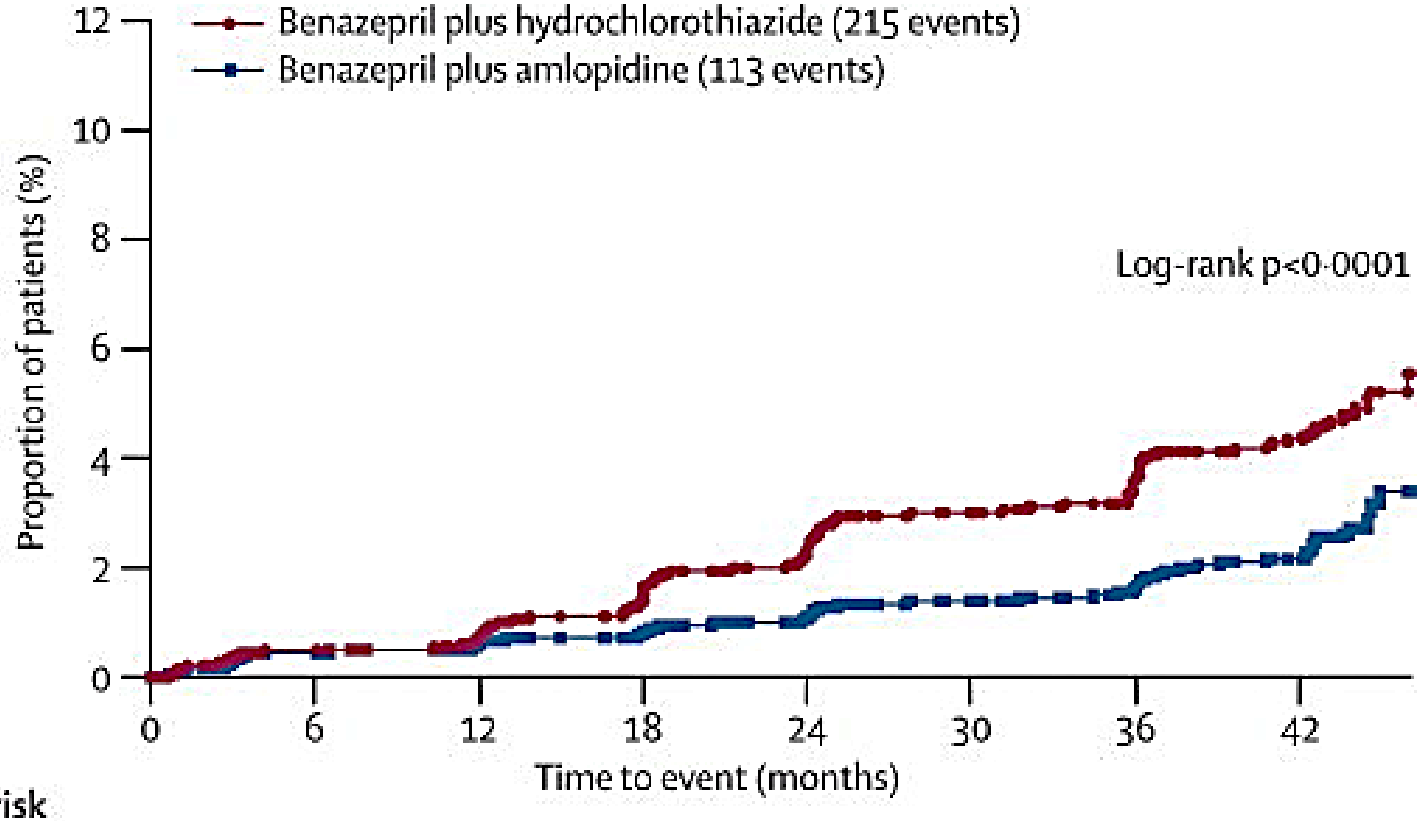
Weber et al, JACC (2010) in press

Characteristic	Benazepril + Amlodipine	Benazepril + HCTZ	Hazard Ratio (95% CI)	*p*-Value
Number of Patients	**2,266**	**2,293**	**—**	**—**
Primary endpoint	**245 (10.8)**	**296 (12.9)**	**0.82 (0.69 – 0.97)**	**.020**
Fatal and non-fatal MI	**48 (2.1)**	**68 (3.0)**	**0.70 (0.49 – 1.02)**	**.059**
Hospitalized UA	**21 (0.9)**	**23 (1.0)**	**0.91 (0.50 – 1.64)**	**.749**
Stroke	**48 (2.1)**	**63 (2.8)**	**0.76 (0.52 – 1.10)**	**.147**
CV death	**45 (2.0)**	**60 (2.6)**	**0.75 (0.51 – 1.10)**	**.137**
Revascularization	**154 (6.8)**	**162 (7.1)**	**0.95 (0.76 – 1.18)**	**.630**
Non-revasc. coronary event*	**83 (3.7)**	**106 (4.6)**	**0.78 (0.58 – 1.04)**	**.084**
CV death + MI + stroke	**118 (5.2)**	**161 (7.0)**	**0.73 (0.57 – 0.92)**	**.008**
Hospitalized HF	**26 (1.2)**	**29 (1.3)**	**0.89 (0.53 – 1.52)**	**.679**
All-cause death	**95 (4.2)**	**123 (5.4)**	**0.77 (0.59 – 1.00)**	**.052**
Renal endpoint**	**87 (3.8)**	**221 (9.6)**	**0.38 (0.30 – 0.49)**	**<.001**

Table 5. Primary, Secondary and Individual Endpoints for the Non-diabetes Cohort

Values are absolute numbers (percentages).
Abbreviations: HCTZ=hydrochlorothiazide; MI=myocardial infarction; UA=unstable angina; CV=cardiovascular; HF=heart failure
* MI + UA + Sudden cardiac death
** $\geq$ 50% increase in serum creatinine with final value above normal range

Kaplan-Meier curves for progression of chronic kidney disease for the intention-to-treat population

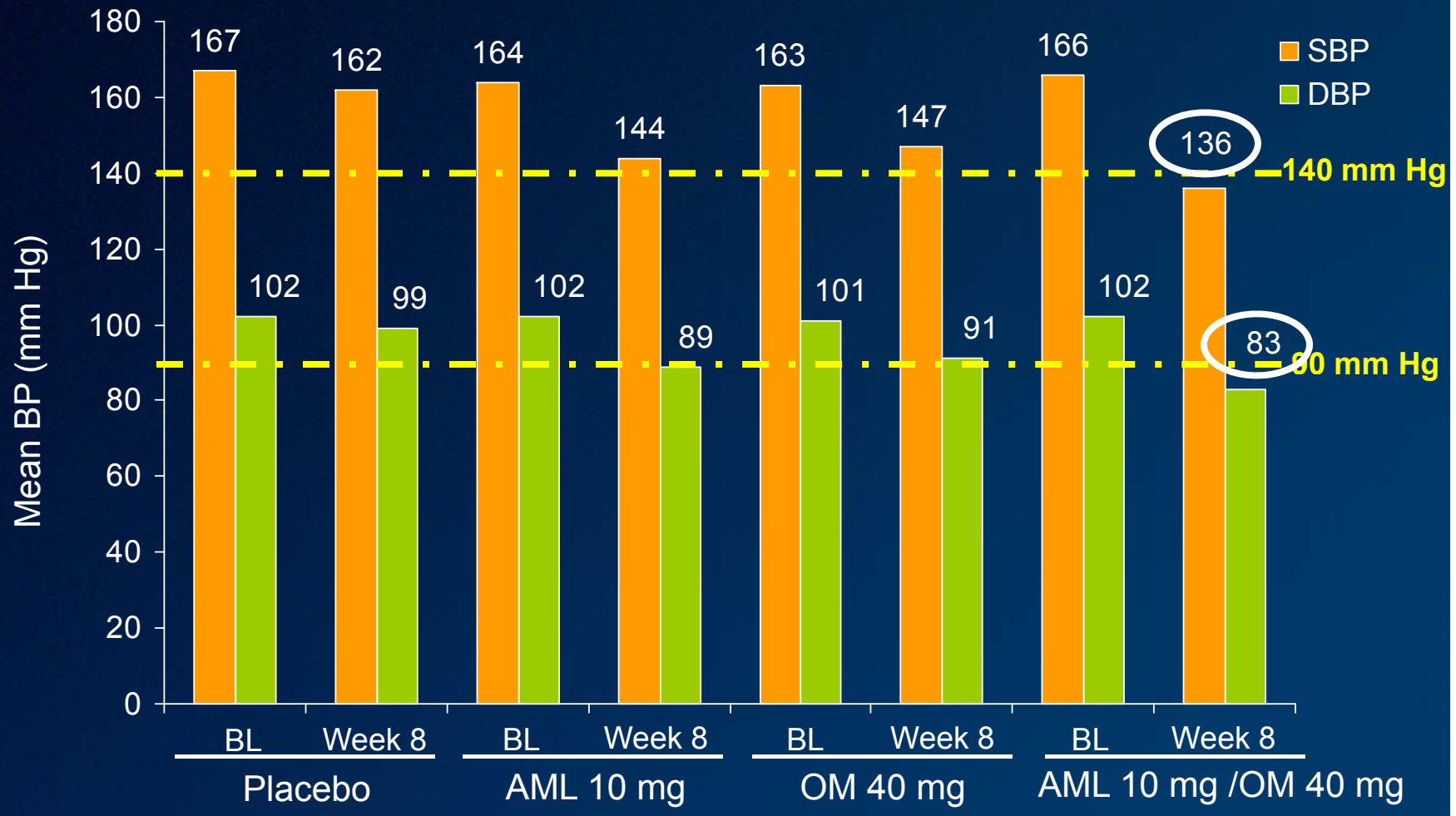


Number at risk								
Benazepril plus hydrochlorothiazide	5762	5576	5459	5307	5139	4936	2956	1506
Benazepril plus amlopidine	5744	5578	5452	5336	5203	5022	3016	1559

Bakris GL et.al. Lancet 2010, Feb 18th

Combination of Amlodipine and Olmesartan Medoxomil

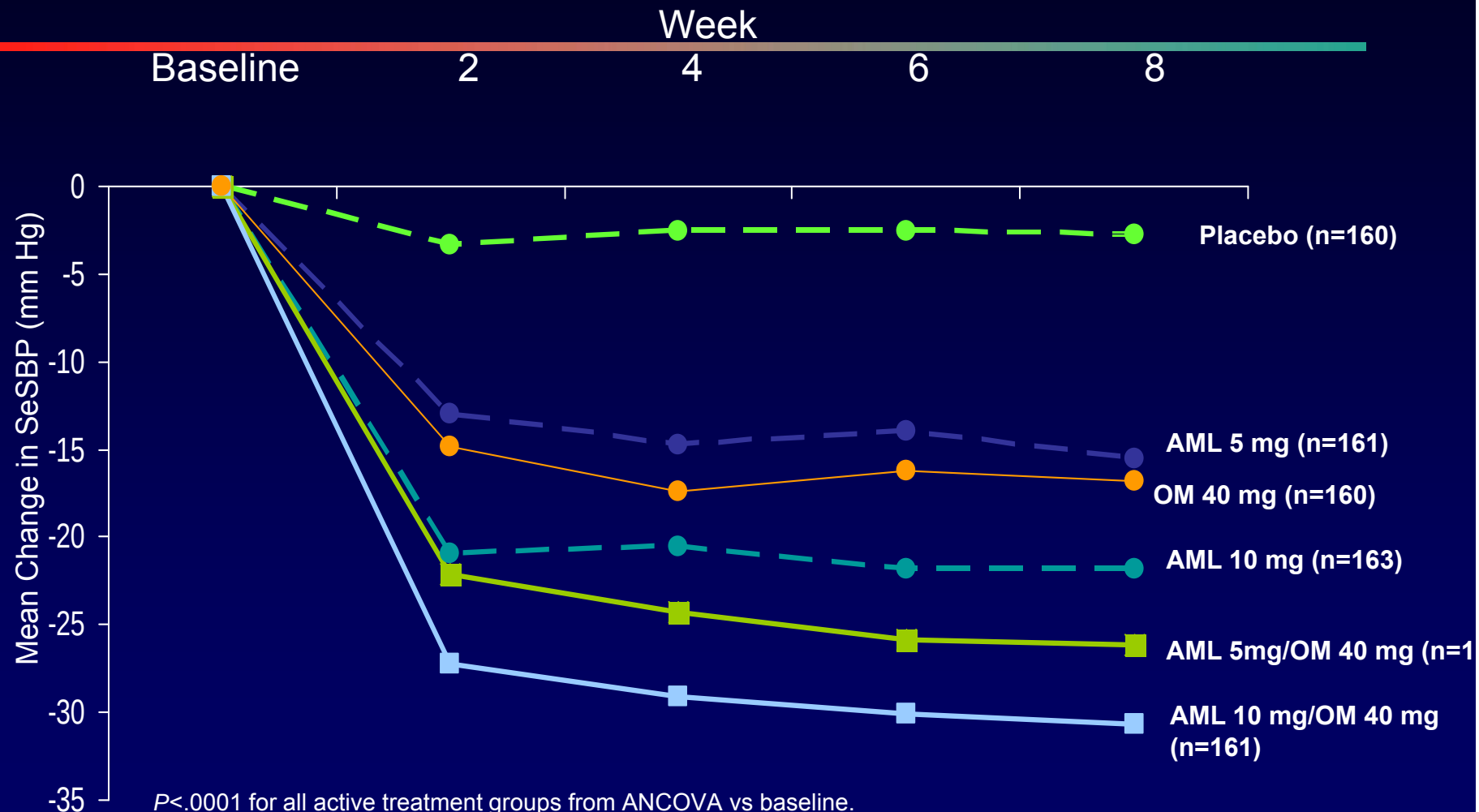
Baseline and On-Treatment Blood Pressures



AML=amlodipine; BL=baseline; OM=olmesartan medoxomil.

Chrysant SG et al. ASH 2007, Late Breaking Clinical Trial.

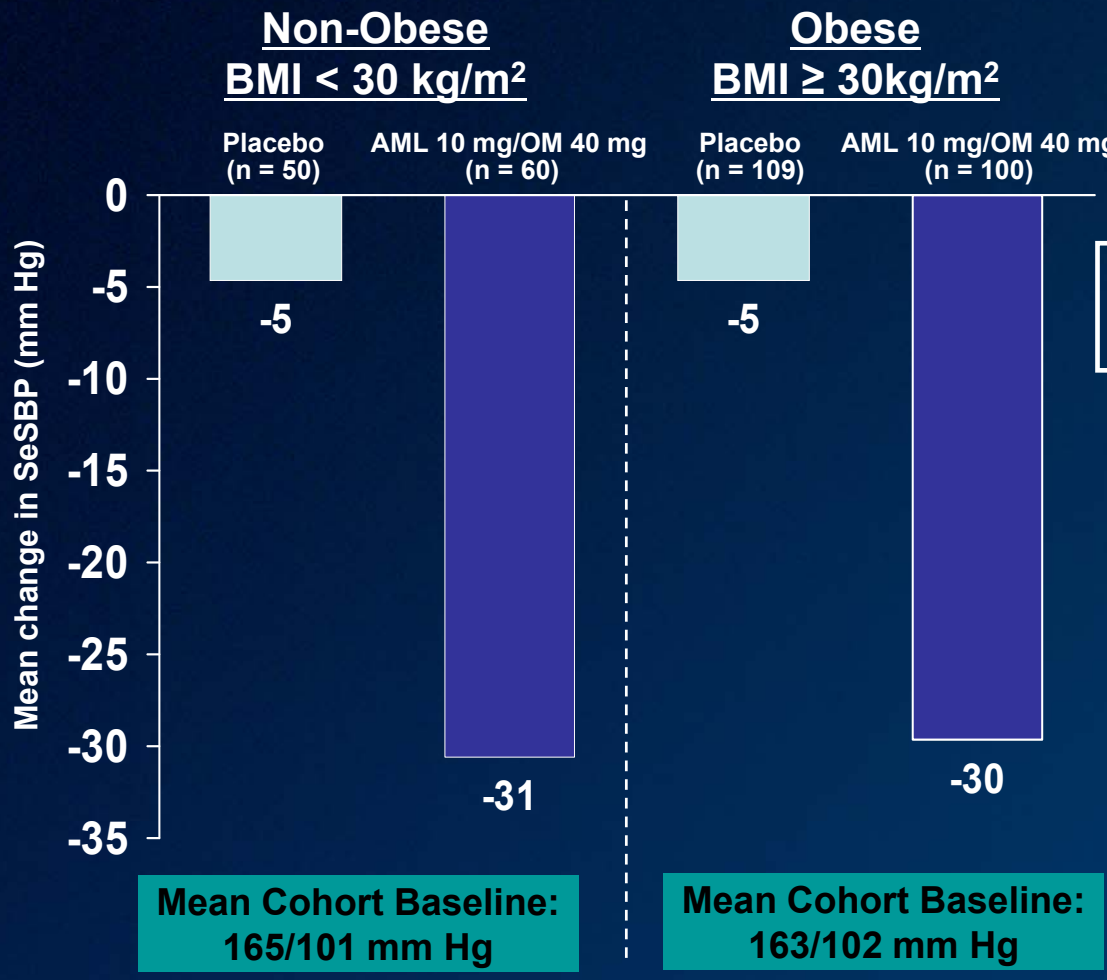
Mean Reduction in Systolic BP at weeks 2, 4, 6, and 8 Combinations of Amlodipine & Olmesartan Medoxomil)



P<.0001 for all active treatment groups from ANCOVA vs baseline.

Efficacy evaluations were based on the ITT population for the total population, without LOCF; Mean baseline SeSBP=164 mm Hg; Data on file, Daiichi Sankyo, Inc.

Mean Reduction in SeSBP: Obese Patients
Week 8 LOCF in Patients with BMI <30 and BMI ≥ 30

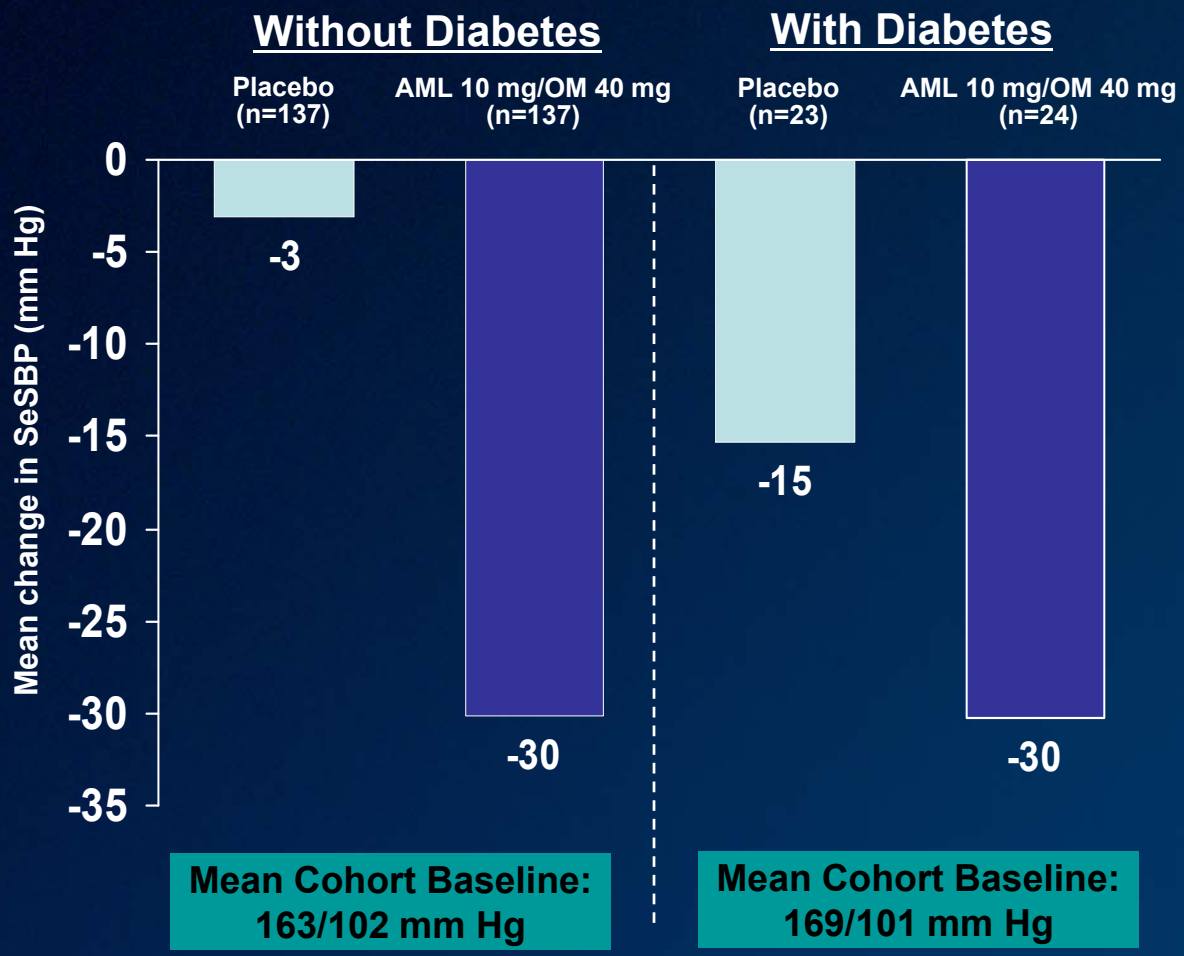


- 65% (1254) of the patients in the study were obese (BMI ≥30 kg/m^2)

Each active treatment group had a statistically significant mean reduction in SBP compared to baseline (*P*<.0001); Results presented are from a pre-specified subgroup analysis of patients with BMI <30 vs BMI ≥ 30 kg/m^2; data from 2 of 12 treatment arms; Efficacy evaluations were based on the ITT population for the total population and subgroup analysis; Data on file, Daiichi Sankyo, Inc.

Mean Reduction in SeSBP: Patients with Diabetes

Week 8 LOCF in Patients With and Without Diabetes

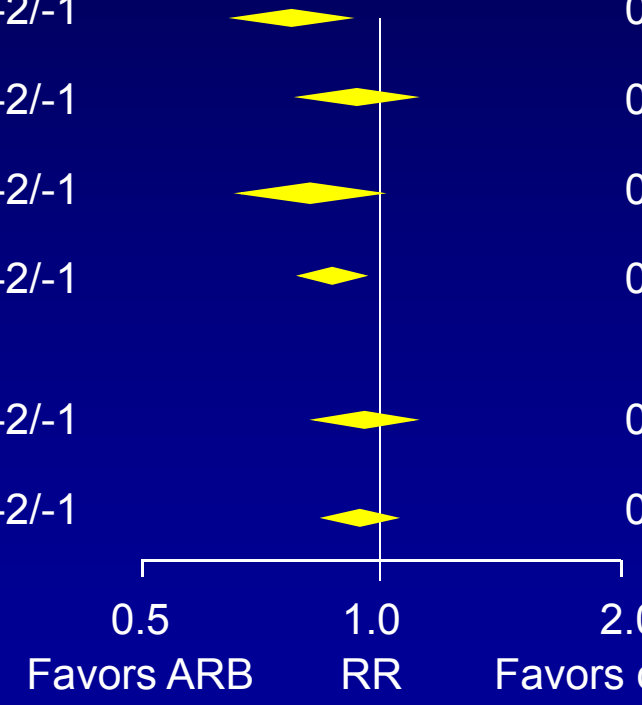


- 14% of the patients in the study had diabetes
- The antihypertensive effect of AZOR® was similar in patients with and without diabetes

Each active treatment group had a statistically significant mean reduction in SBP compared to baseline (*P* <.0001); Results presented are from a pre-specified subgroup analysis of patients with diabetes vs patients without diabetes; data from 2 of 12 treatment arms; Efficacy evaluations were based on the ITT population for the total population and subgroup analysis; Data on file, Daiichi Sankyo, Inc.

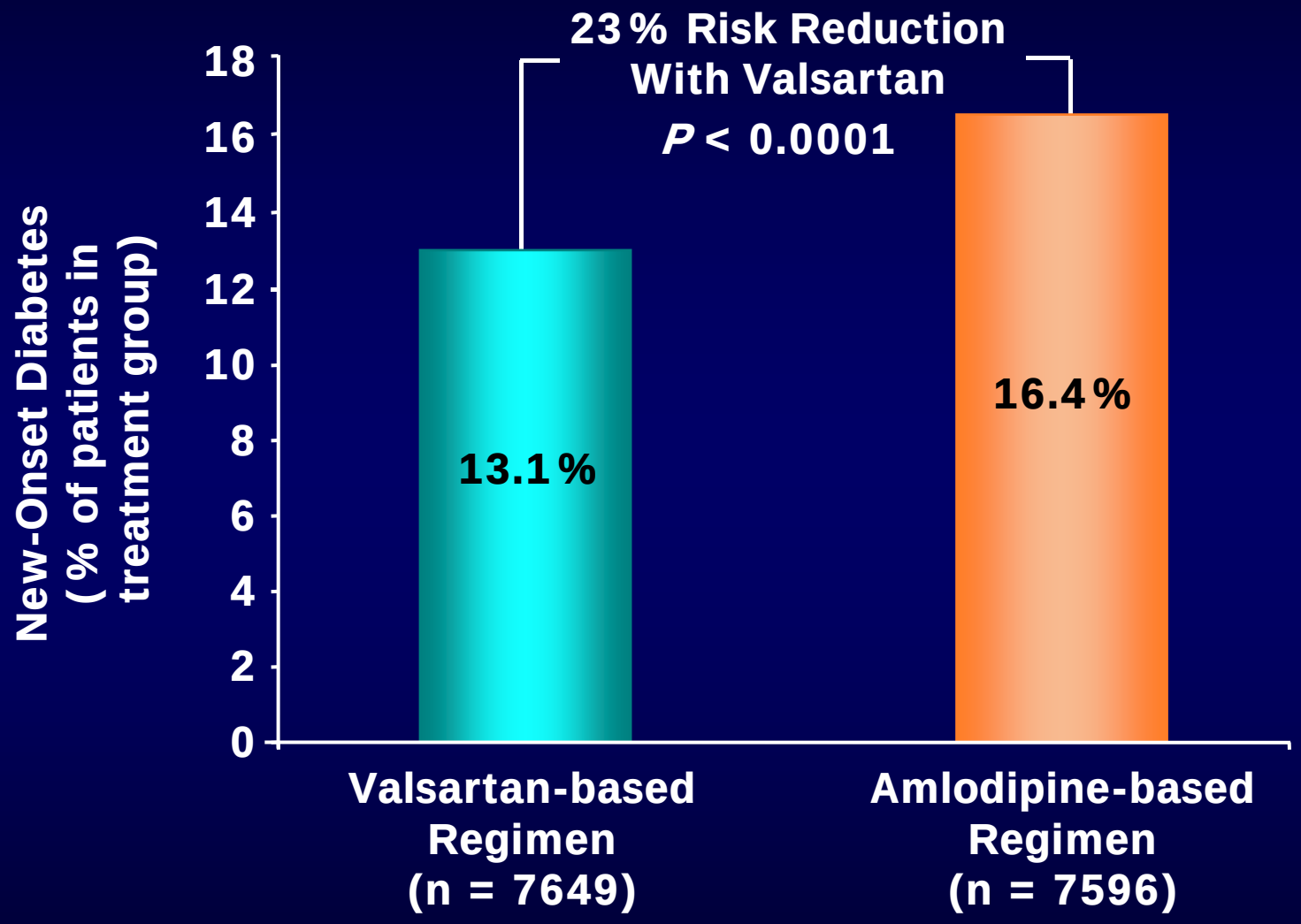
Comparison of ARB-Based and Control-Based Regimens

	Events/ participants		BP difference	RR
	ARB	Control		(95% CI)
Stroke*	396/8412	500/8379	-2/-1	0.79 (0.69-0.90)
CHD*	435/8412	450/8379	-2/-1	0.96 (0.85-1.09)
HF†	302/5935	359/5919	-2/-1	0.84 (0.72-0.97)
Major CV events*	1135/8412	1268/8379	-2/-1	0.90 (0.83-0.96)
CV death*	491/8412	511/8379	-2/-1	0.96 (0.85-1.08)
Total mortality*	887/8412	943/8379	-2/-1	0.94 (0.86-1.02)



*Includes SCOPE, IDNT, RENAAL, LIFE.
†Includes IDNT, RENAAL, LIFE.
Neal et al, for the Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet.* 2003;362:1527-1535.

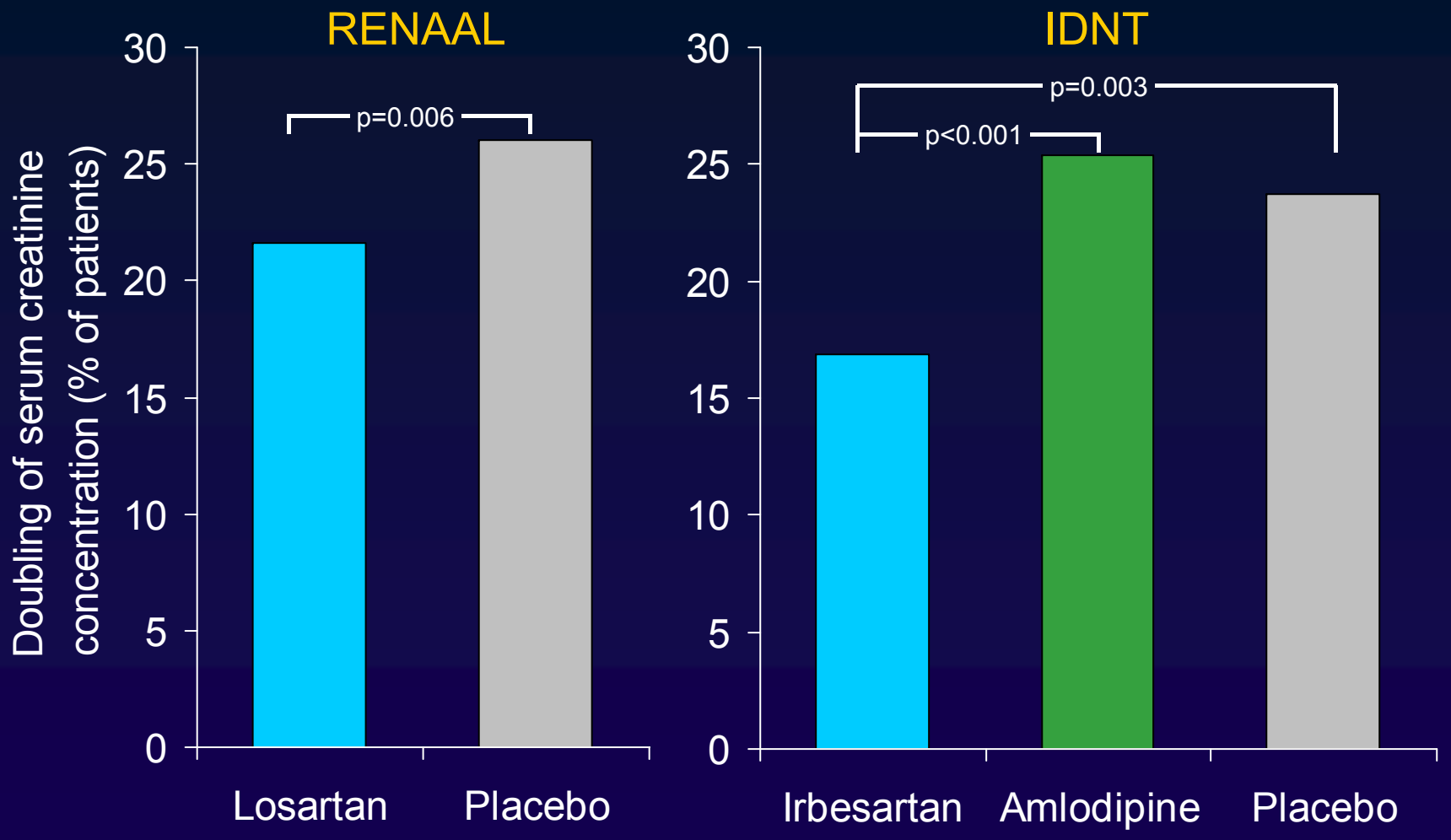
VALUE: Incidence of New-onset Diabetes



Julius S et al. *Lancet*. June 2004;363.

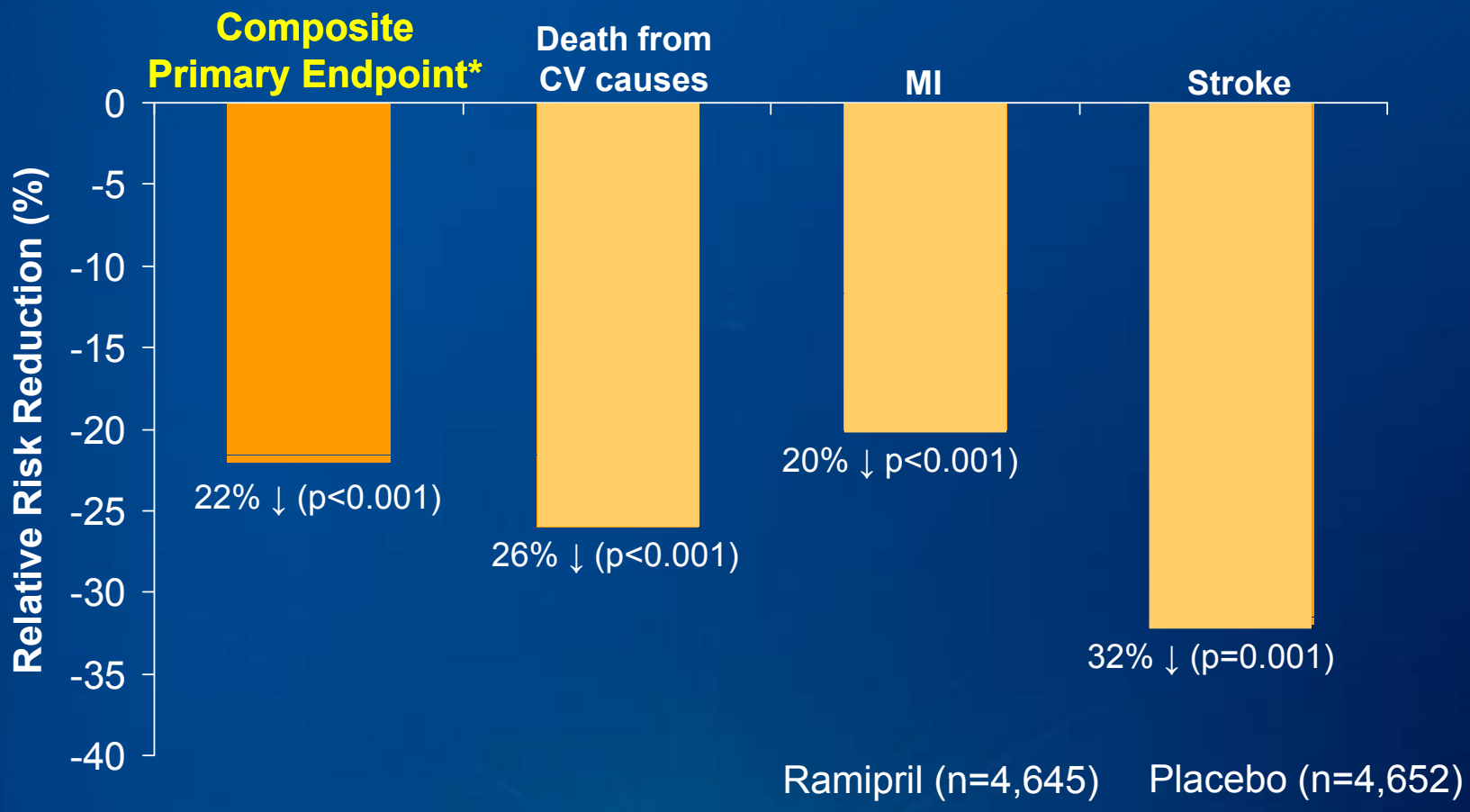
VALUE

Effects of ARBs on Progression to ESRD in diabetic nephropathy



Brenner et al. *N Engl J Med* 2001;345:861–869. Lewis et al. *N Engl J Med* 2001;345:851–860

HOPE: Relative Risk Reduction Ramipril vs Placebo



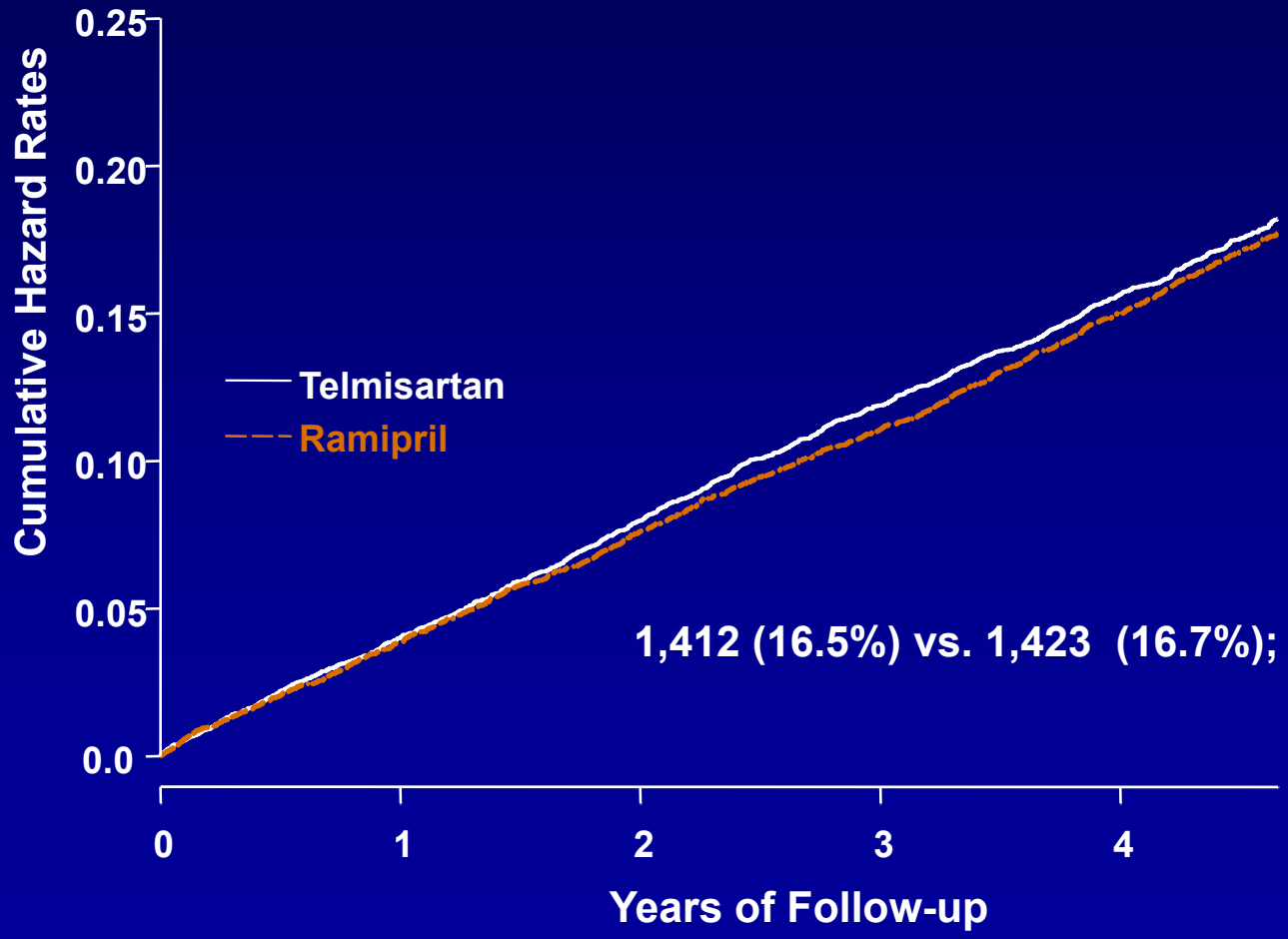
HOPE is a completed trial.

*Composite of MI, stroke, or death from CV causes.

Yusuf S, Sleight P, Pogue J, et al. *N Engl J Med*. 2000;342:145-153.

ONTARGET: Time to primary outcome (CV death, stroke, MI or HF)

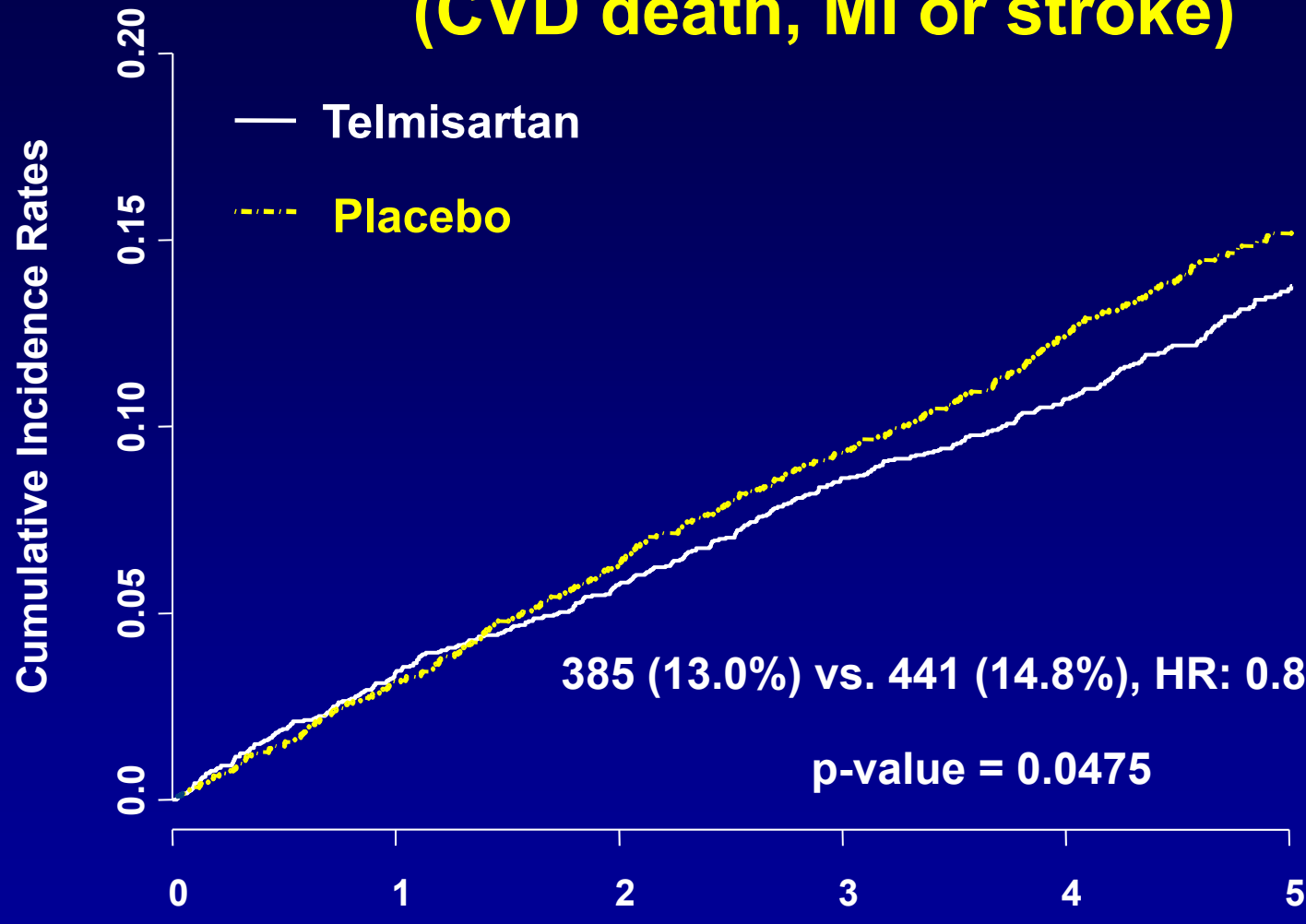
	# at Risk	Yr 1	Yr 2	Yr 3	Yr 4	Yr 4.5
T	8,542	8,177	7,778	7,420	7,051	4,575
R	8,576	8,214	7,832	7,472	7,093	4,562



1,412 (16.5%) vs. 1,423 (16.7%); RR 1.01 (0.94-1.09)

N Engl J Med 2008; 358: 1547-59

Time to HOPE outcome (CVD death, MI or stroke)



No. at Risk

T	2954	2839	2745	2634	2344	1127
Pl	2972	2866	2745	2626	2306	1103

MORE

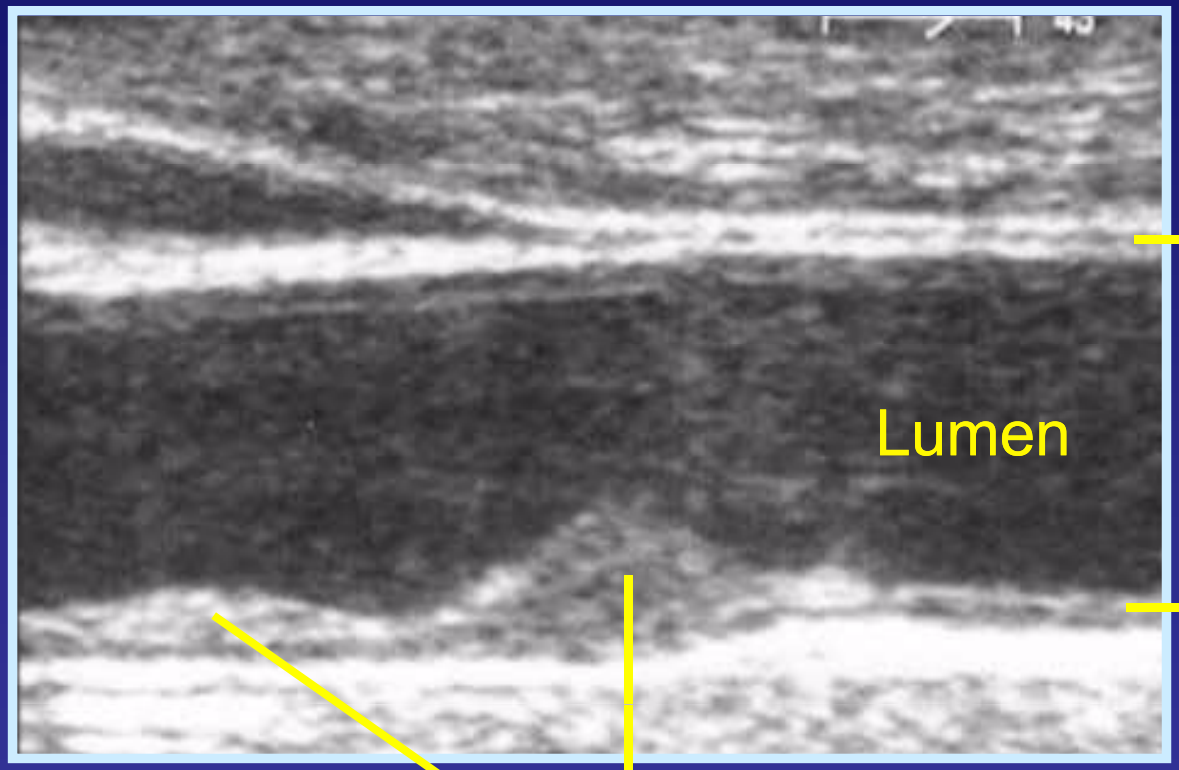
Study Aim

- To compare the effects of a 2 - year treatment based on either olmesartan or atenolol on intima-media thickness and volume of atherosclerotic plaques of common carotids as determined by 3 - dimensional (3D) ultrasound in hypertensive patients at increased cardiovascular risk

Presented at ESC 2006

Measurement of Intima-Media Thickness

B-scan pattern of a common carotid artery segment with focal intima-media thickening (Plaque)

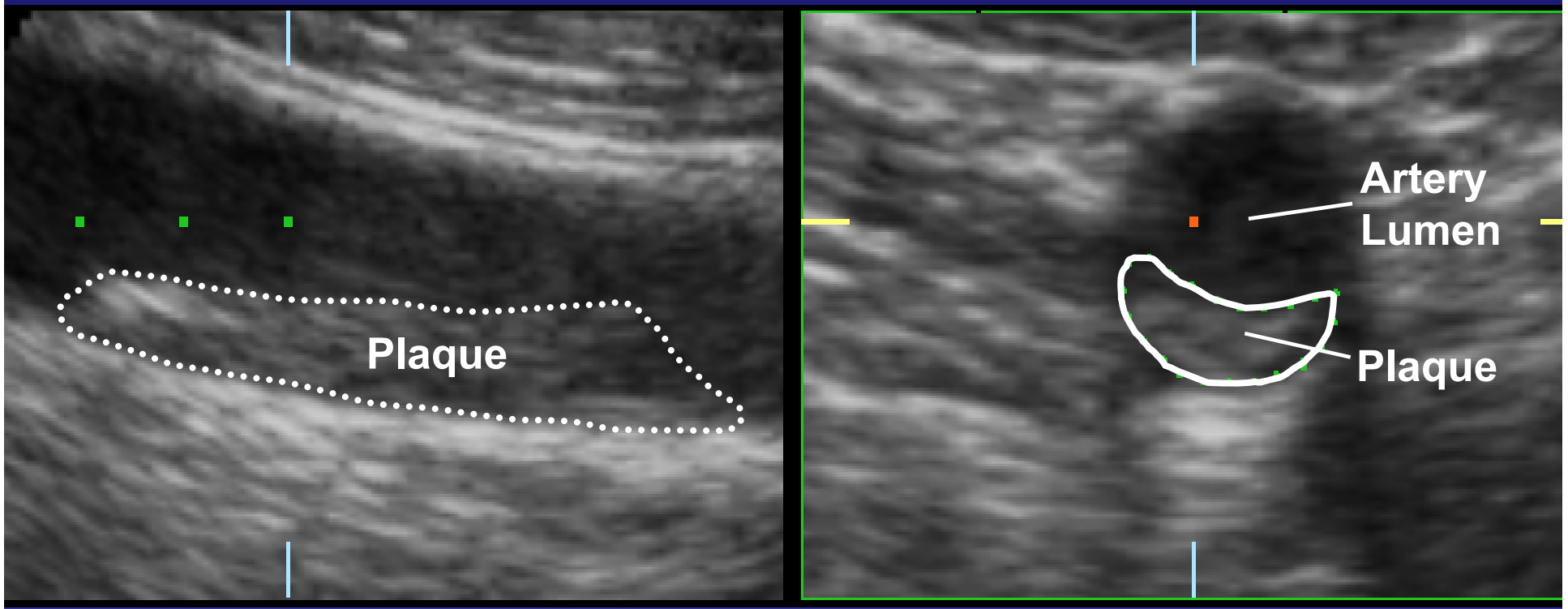


Measurement of plaque volume

- 3D ultrasonography -

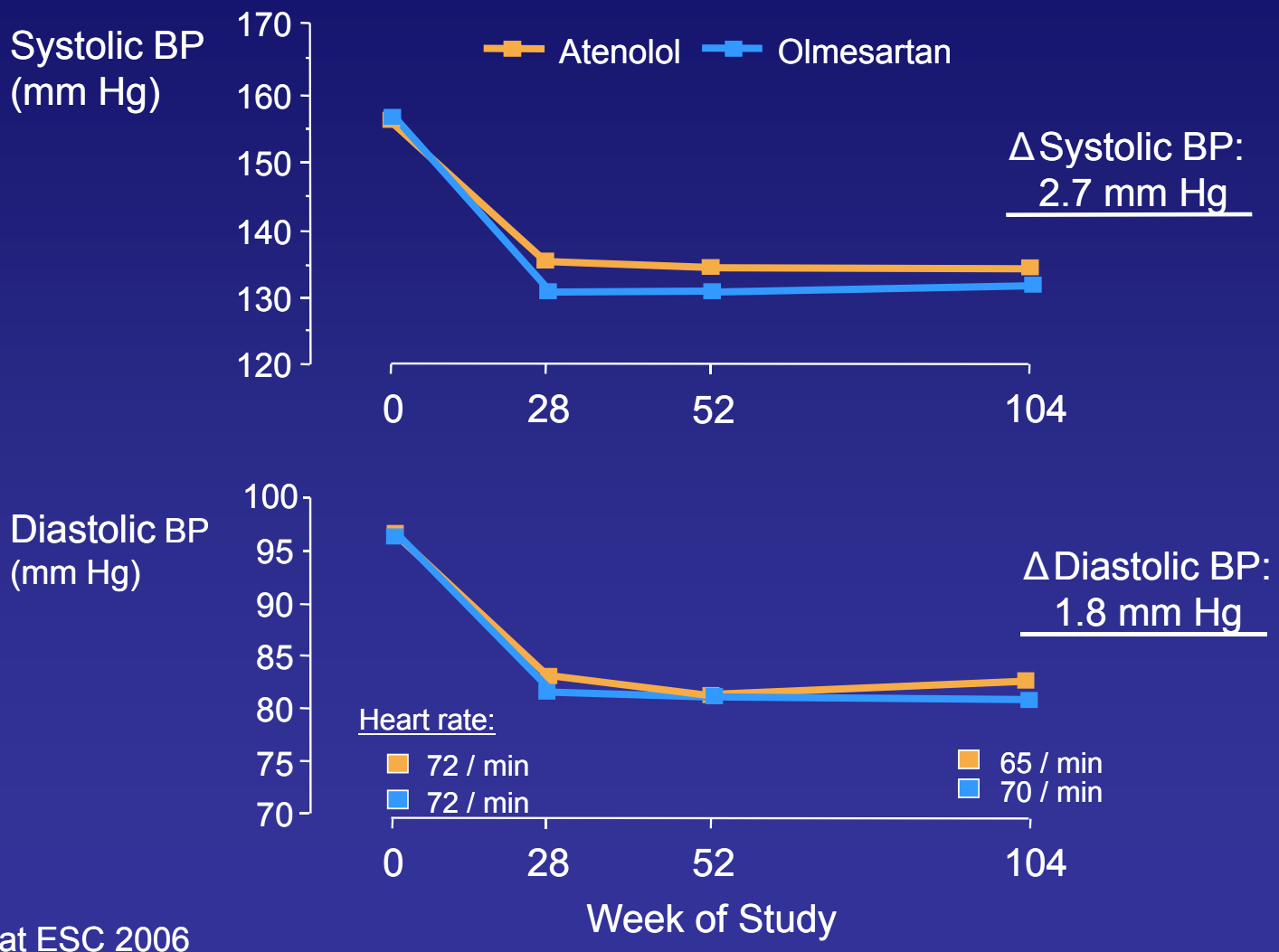
Longitudinal View
(section A)

Cross-sectional View
(section B)



MORE

Clinic Seated Systolic and Diastolic Blood Pressure



Presented at ESC 2006

MORE

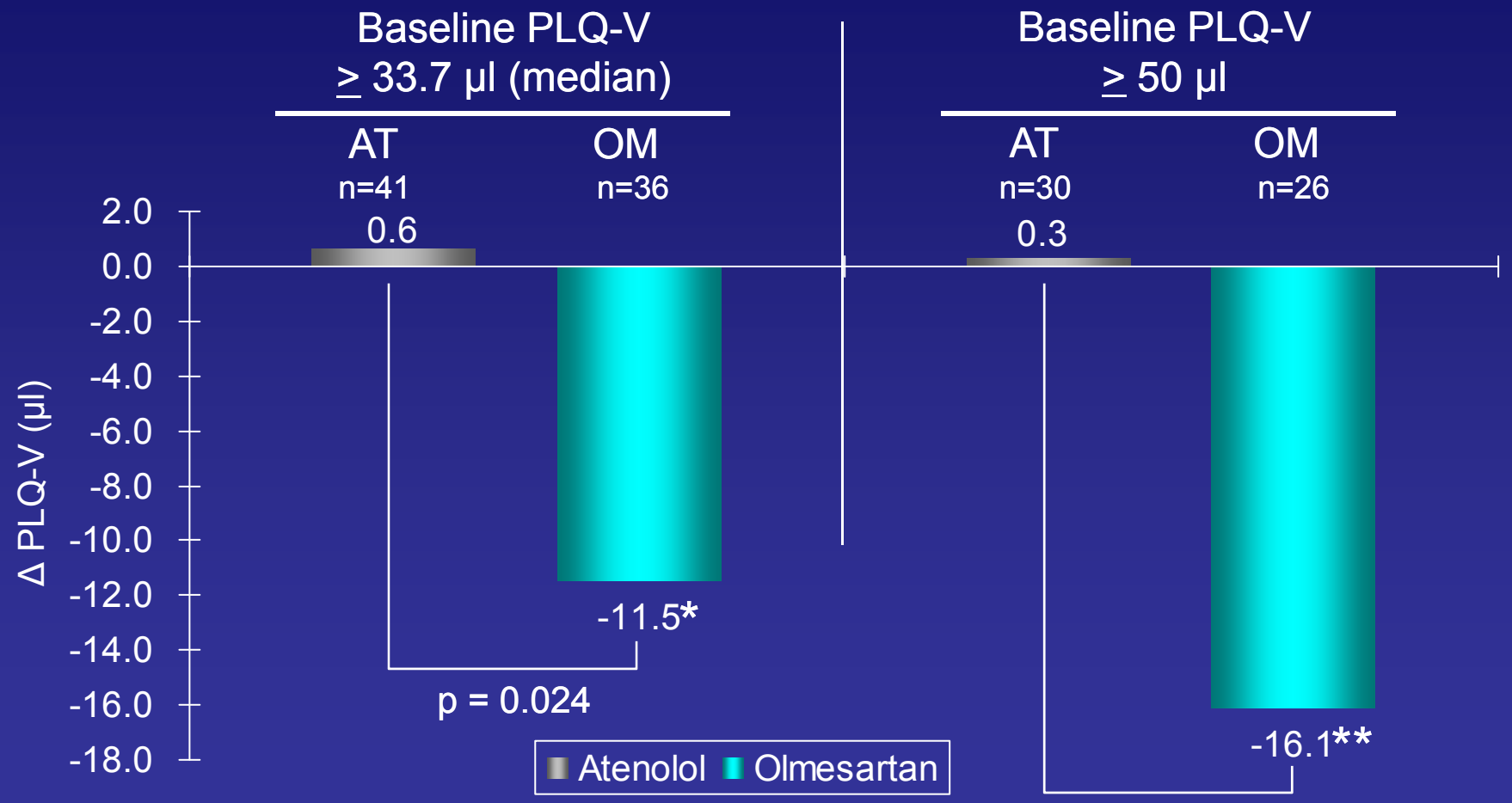
Mean (SD) baseline plaque volume (PLQ-V) and change in PLQ-V from baseline at 2-year follow-up for ITT-LOCF‡

Characteristic	Atenolol (n=76)	Olmesartan (n=78)
Baseline PLQ-V, µl	50.5 (40.6)	49.7 (46.6)
2 - year PLQ-V, µl	50.6 (40.9)	45.3 (38.2)
Change in PLQ-V, µl	0.1 (12.7)	-4.4 (20.3)

Presented at ESC 2006

MORE

Mean changes (Δ) in plaque volume (PLQ-V) from baseline at 2-year follow-up; grouped by different baseline PLQ-V



* p < 0.05; **p < 0.01
Presented at ESC 2006

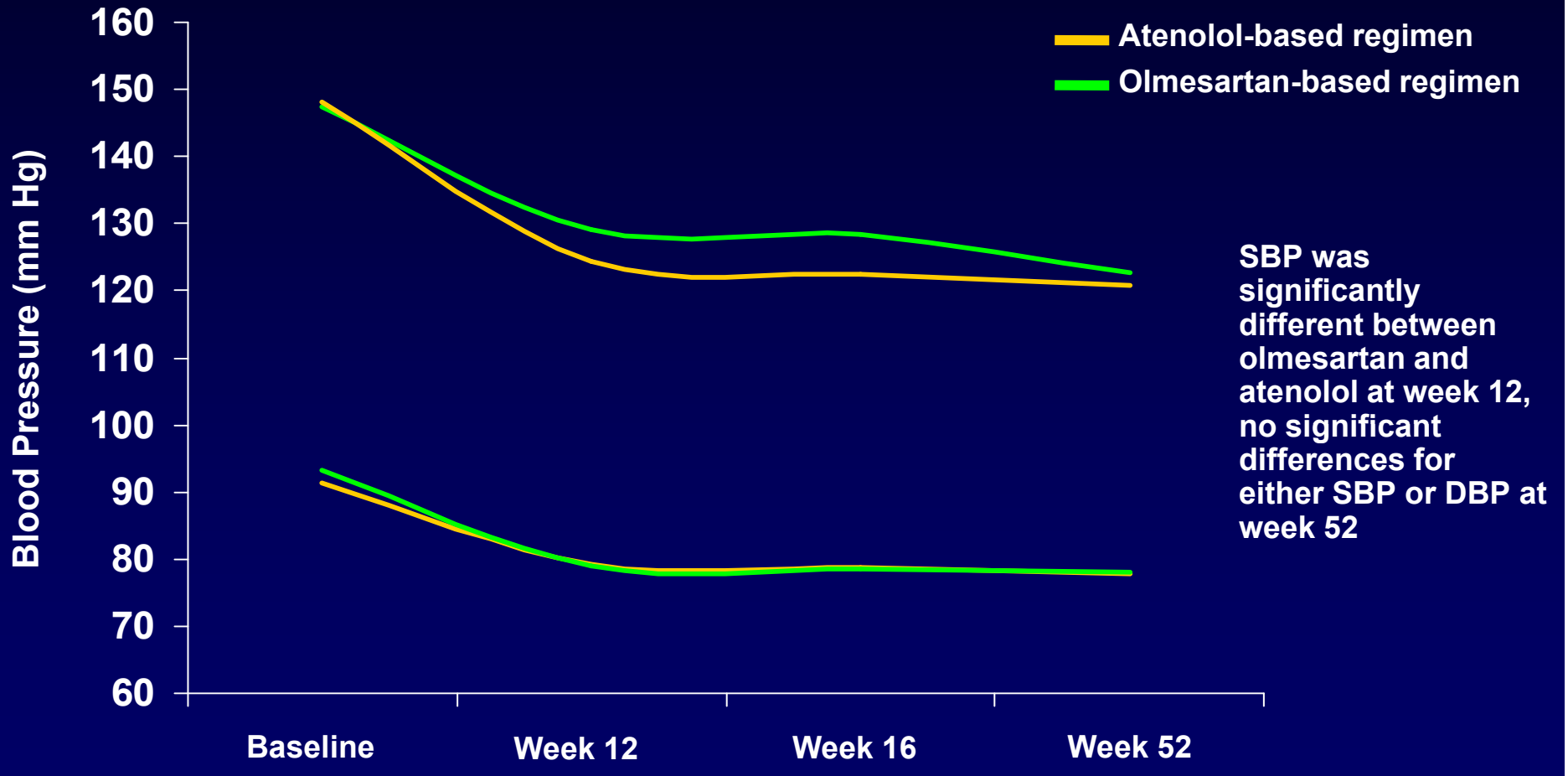
Reversal of vascular hypertrophy in hypertensive patients through blockade of angiotensin II receptors

RD Smith, H Yokoyama, DB Averill, EL Schiffrin, CM Ferrario

JASH 2008; 2(3): 165-172

FAQ 8

Blood Pressure Over Time – Total Cohort



Baseline BP: 147.3/91.4 (atenolol-treatment arm); 148.1/93.3 mm Hg (olmesartan-treatment arm)

Data on file, Daiichi Sankyo, Inc.

FAQ 12

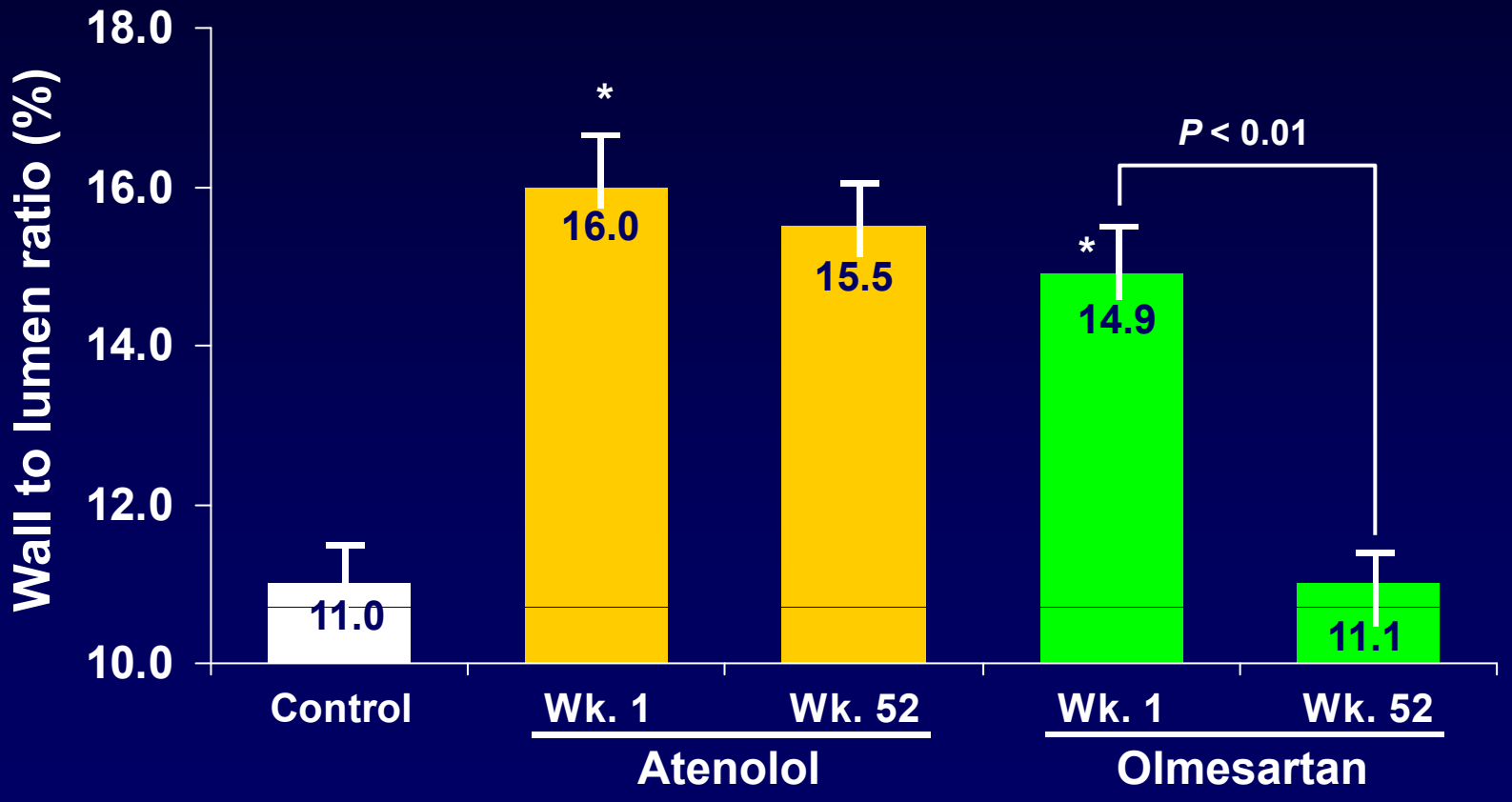
Morphological Characteristics of Resistance Arteries

Variable	Control	Olmesartan medoxomil		Atenolol	
		Before	1-year	Before	1-year
External diameter, *mm*	290 ± 19	339 ± 19	271 ± 14†	304 ± 19	287 ± 22
Lumen diameter, *mm*	238 ± 15	264 ± 17	223 ± 13	233 ± 16	221 ± 18
Wall Width, *mm*	26.1 ± 2.0	37.6 ± 2.1*	24.0 ± 1.2†	35.5 ± 1.8*	33.0 ± 2.3*‡
W/Lr, %	11.0 ± 0.6	14.9 ± 0.8*	11.1 ± 0.5†	16.0 ± 0.8*	15.5 ± 0.6*‡
MCSA, mm^2	22493 ± 3124	37728 ± 4087*	19527 ± 1999†	31551 ± 3808	29126 ± 4233

Values are mean ± SEM
NT: normotensive subjects
W/Lr: wall-to-lumen ratio
MCSA: media cross-sectional area
*P < 0.05 vs control
†P < 0.01 vs before treatment
‡P < 0.001 vs 1-year olmesartan treatment

Smith RD et al. JASH 2008; 2(3): 165-172.

Effects of Olmesartan and Atenolol on Vascular Hypertrophy

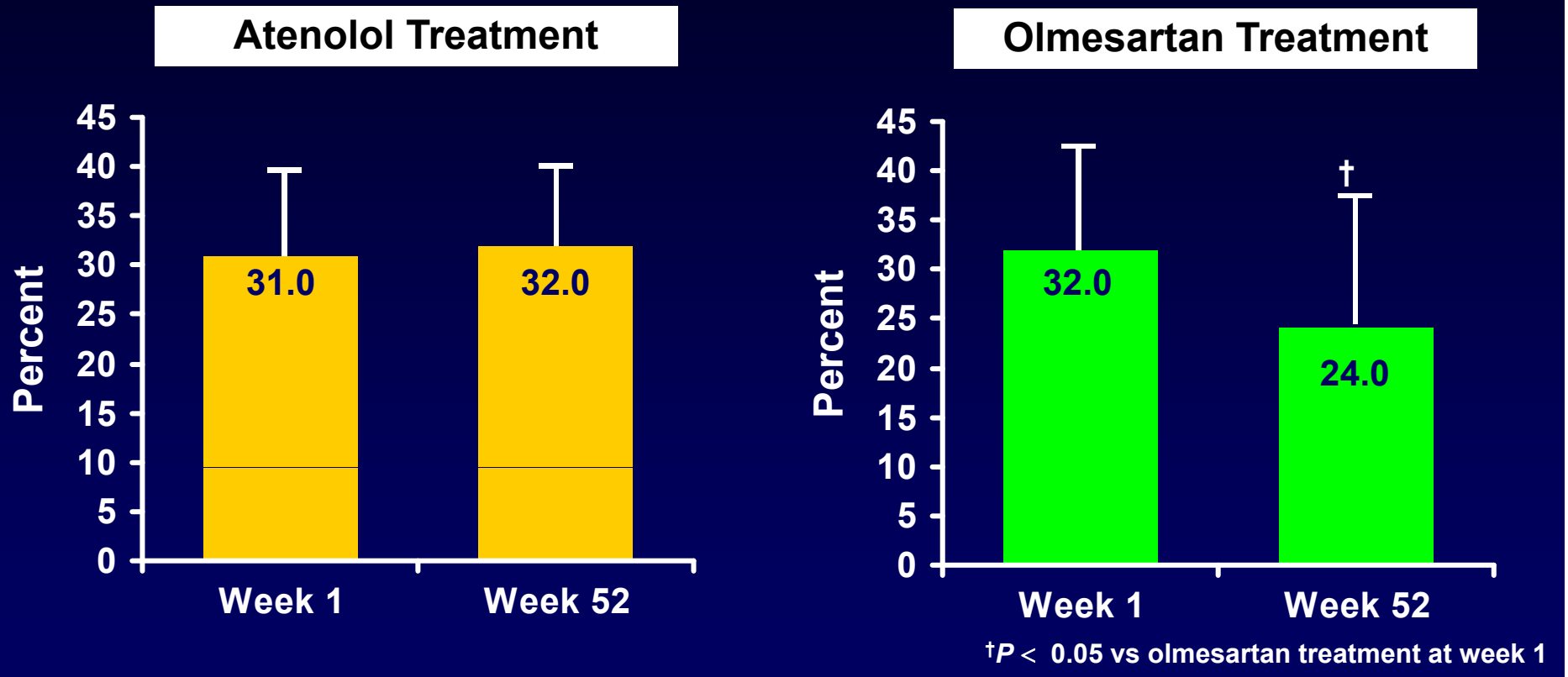


*P < 0.05 vs. control

Smith RD et al. JASH 2008; 2(3): 165-172.

FAQ 13

Effect of Treatments on Augmentation Index (AG/PP)



†$P <$ 0.05 vs olmesartan treatment at week 1

Values are Means ± SD

Smith RD et al. JASH 2008; 2(3): 165-172.

Main Conclusions: Treating Hypertension in Patients with Diabetes

- Treating BP to < 140/90 mmHg is clearly beneficial; lower BP values *might* possibly be justified
- ARB and thiazide combinations effectively achieve BP control in a majority of patient types
- Combining RAS blockers with amlodipine produces greatest CV & renal benefits (plus strong BP effects)
- ARBs (like ACE inhibitors) now established for renal & CV protection in high risk patients, particularly those with diabetes
- Studies of major intermediate vascular findings help explain these clinical benefits of RAS blockers