Optimizing Antihypertensive Therapies in High-Risk and Difficult-to-Treat Patients with Hypertension

Supported by an educational grant from Forest Laboratories, Inc.

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- During the panel discussion, please use the Question Cards located on each table.
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Opening Remarks

George L. Bakris, MD, FAHA, FASN
Professor of Medicine
Director, ASH Comprehensive Hypertension Center
University of Chicago Medicine
Pritzker School of Medicine
Chicago, Illinois

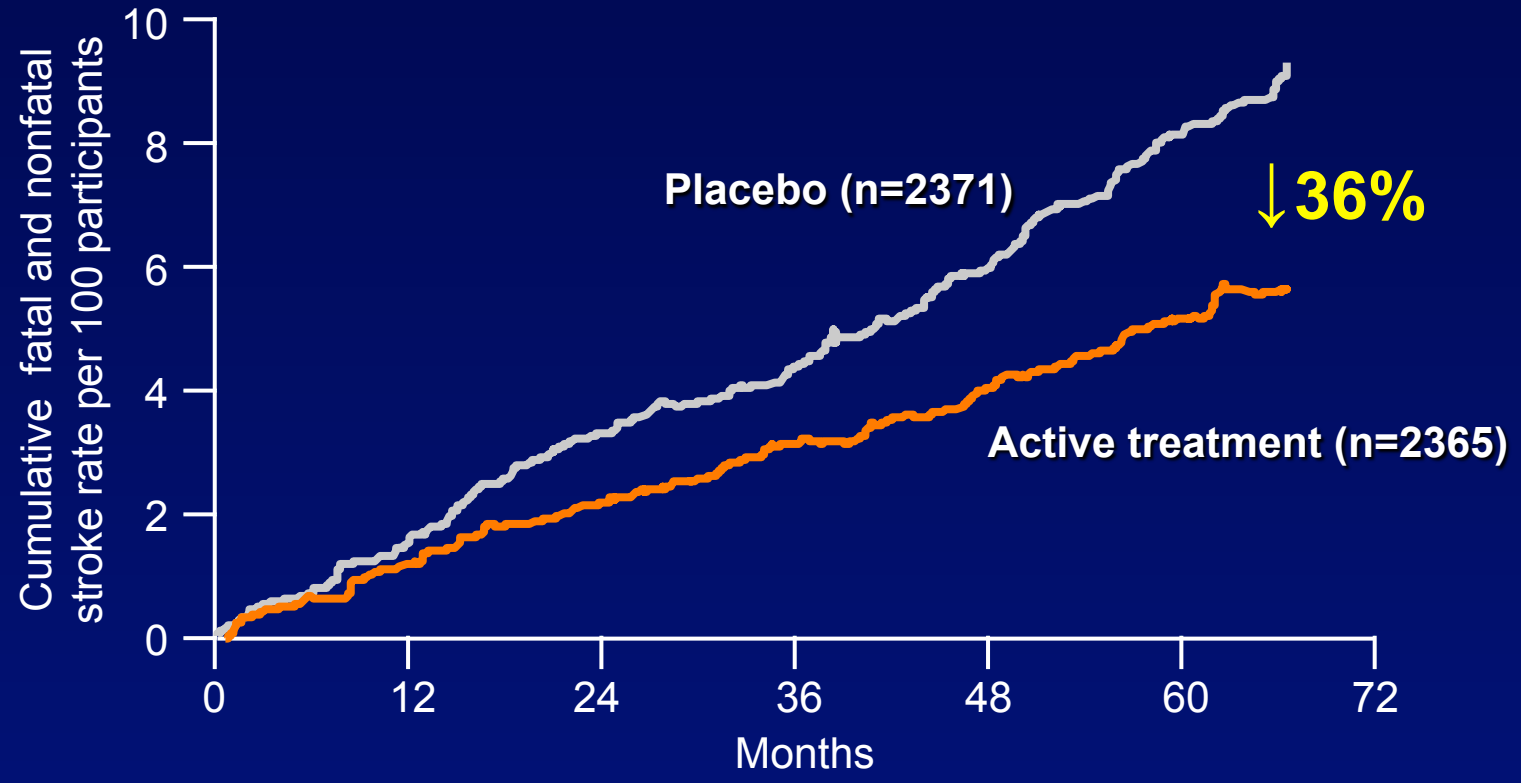
Hypertension Guidelines Update: Current Controversies and Clinical Implications

Michael A. Weber, MD, FACP, FACC, FAHA
Professor of Medicine
State University of New York,
Downstate College of Medicine
Brooklyn, New York

Systolic Hypertension in the Elderly Program (SHEP)

Multicenter, randomized, double-blind, placebo-controlled, patients ≥60 years, systolic BPs ≥160 mm Hg & diastolic BPs <90 mm Hg, using 12.5-25 mg chlorthalidone + other drugs if needed

(Starting SBP: 170 mm Hg; achieved SBP: Placebo 155 mm Hg, active treatment 143 mm Hg)

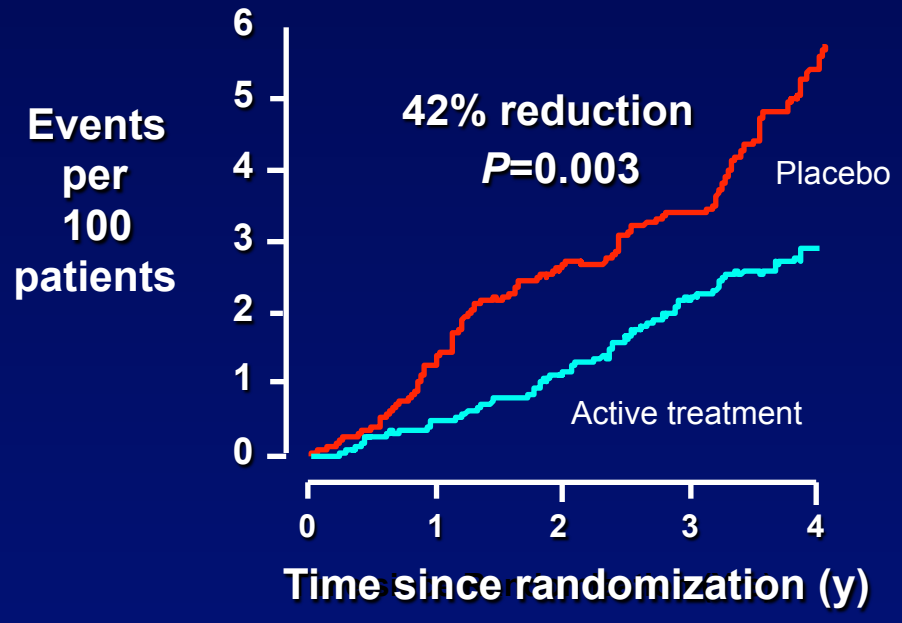


SHEP Cooperative Research Group. JAMA. 1991;265:3255-64.

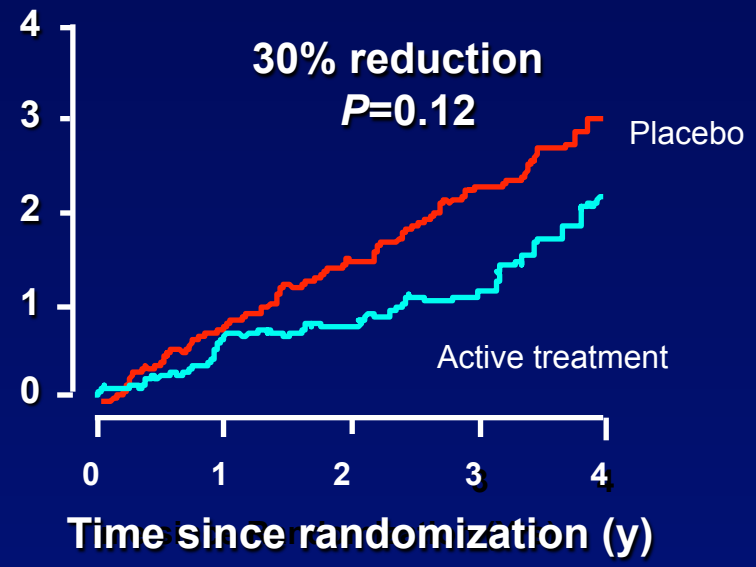
Systolic Hypertension in Europe Trial *(Syst-Eur)*

Randomized, double-blind placebo trial of patients aged ≥60 years with isolated systolic hypertension, placebo vs nitrendipine 10-40 mg ± enalapril 5-20 mg ± HCTZ.
Goal: Lower SBP by 20 mm Hg to <150 mm Hg: In reality, placebo = 161 mmHg; active = 151 mmHg

Fatal and Nonfatal Strokes



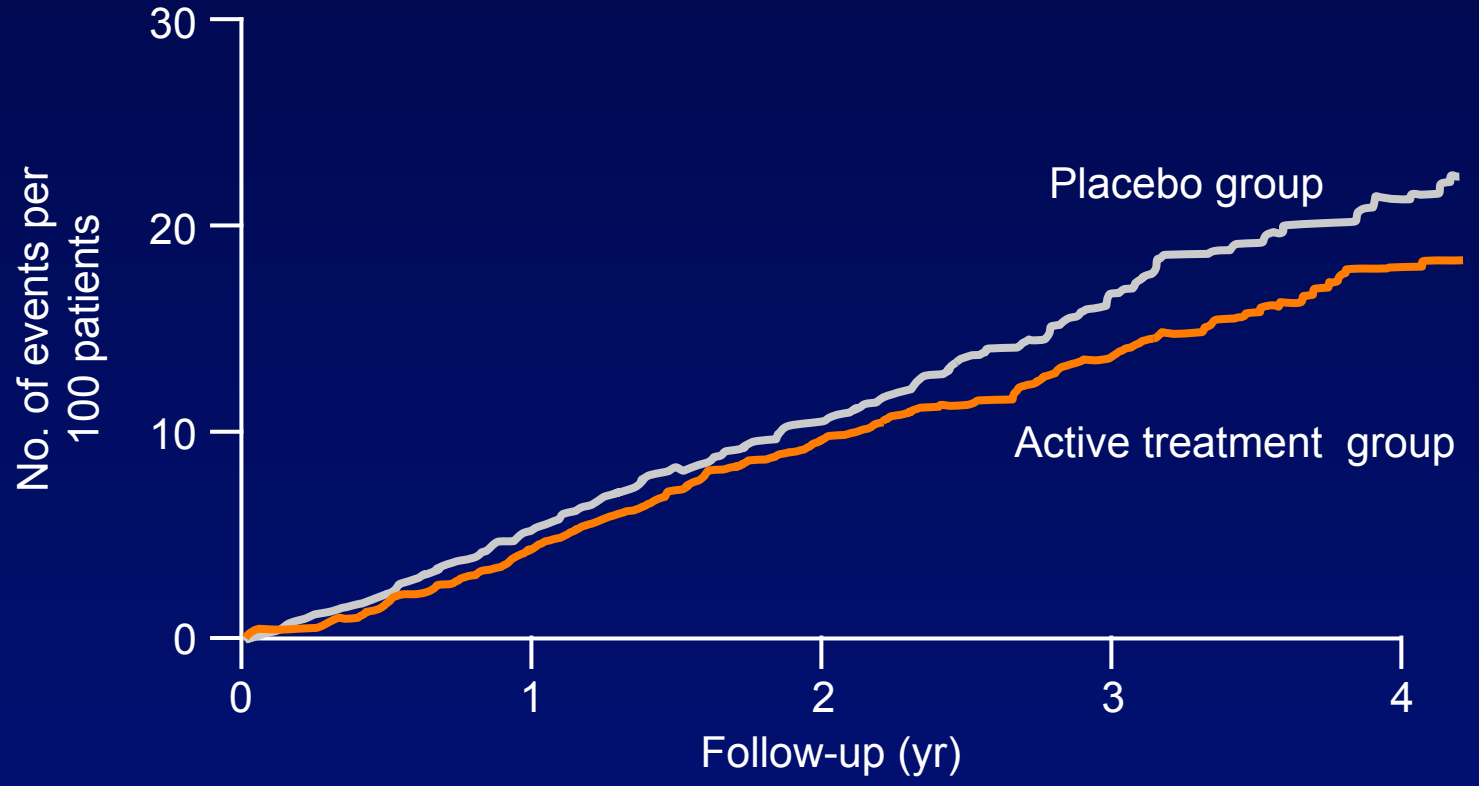
Fatal and Nonfatal Myocardial Infarction



Staessen et al. Lancet. 1997;350:757-64.

HYVET: 21% Reduced Mortality With Active Treatment

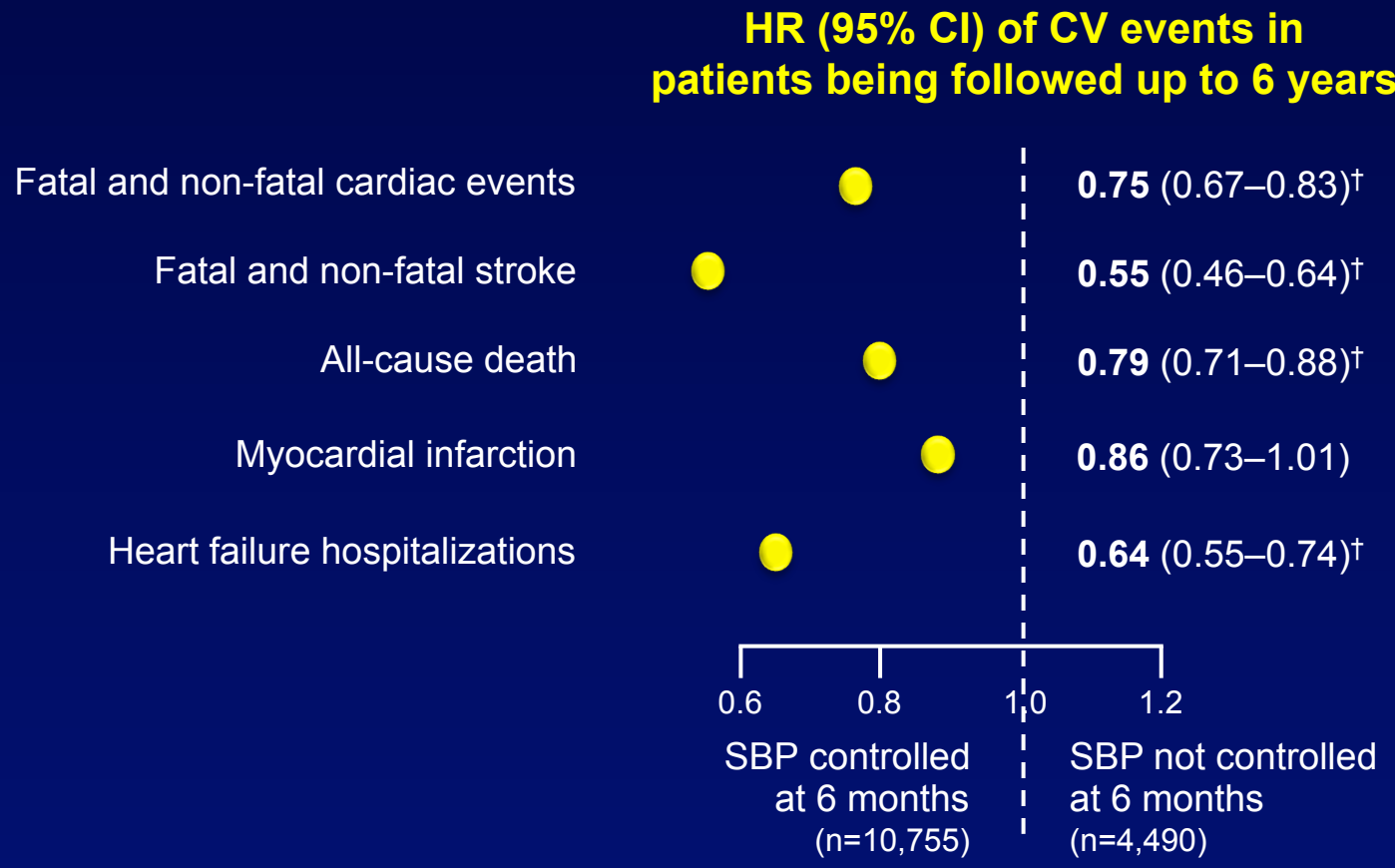
(SBP: 143 mm Hg) versus placebo (SBP: 158 mm Hg) in patients aged 80 or older



No. at risk					
Placebo group	1912	1492	814	379	202
Active-treatment group	1933	1565	877	420	231

Beckett et al. N Engl J Med. 2008;358:1887–1998.

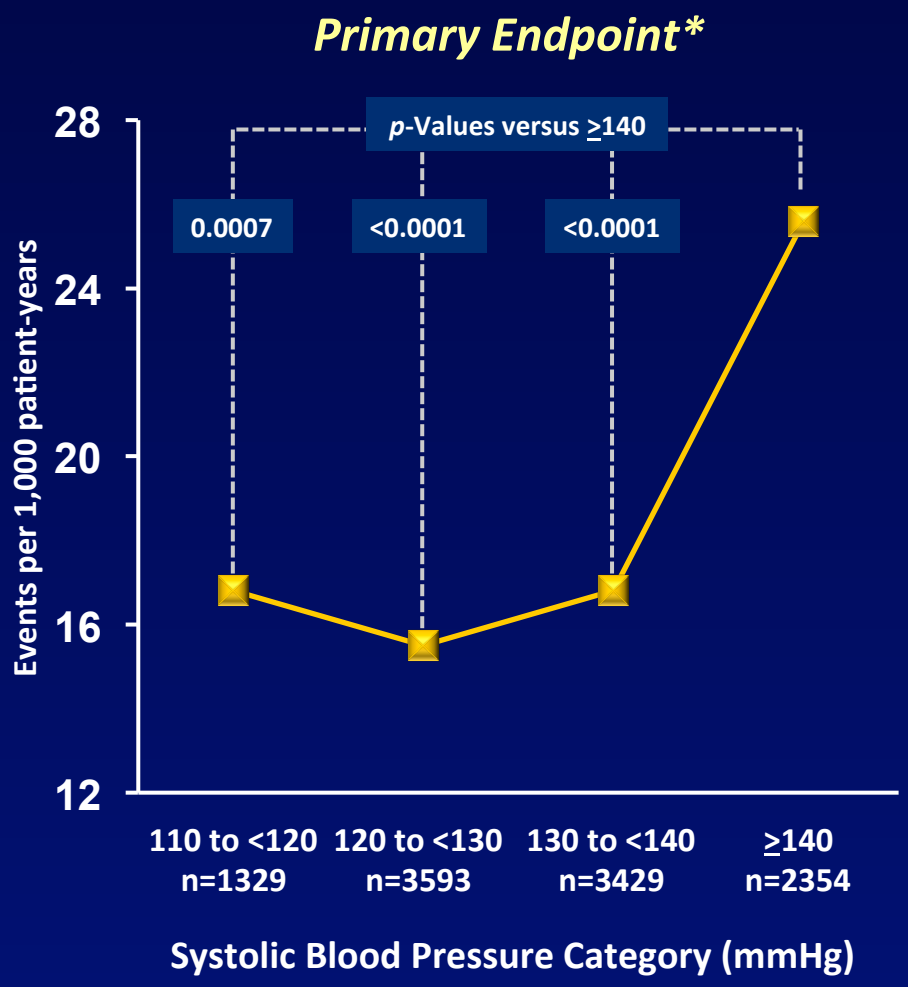
Effective BP Control (SBP <140 mmHg) Reduces Cardiovascular Risk (VALUE Trial)

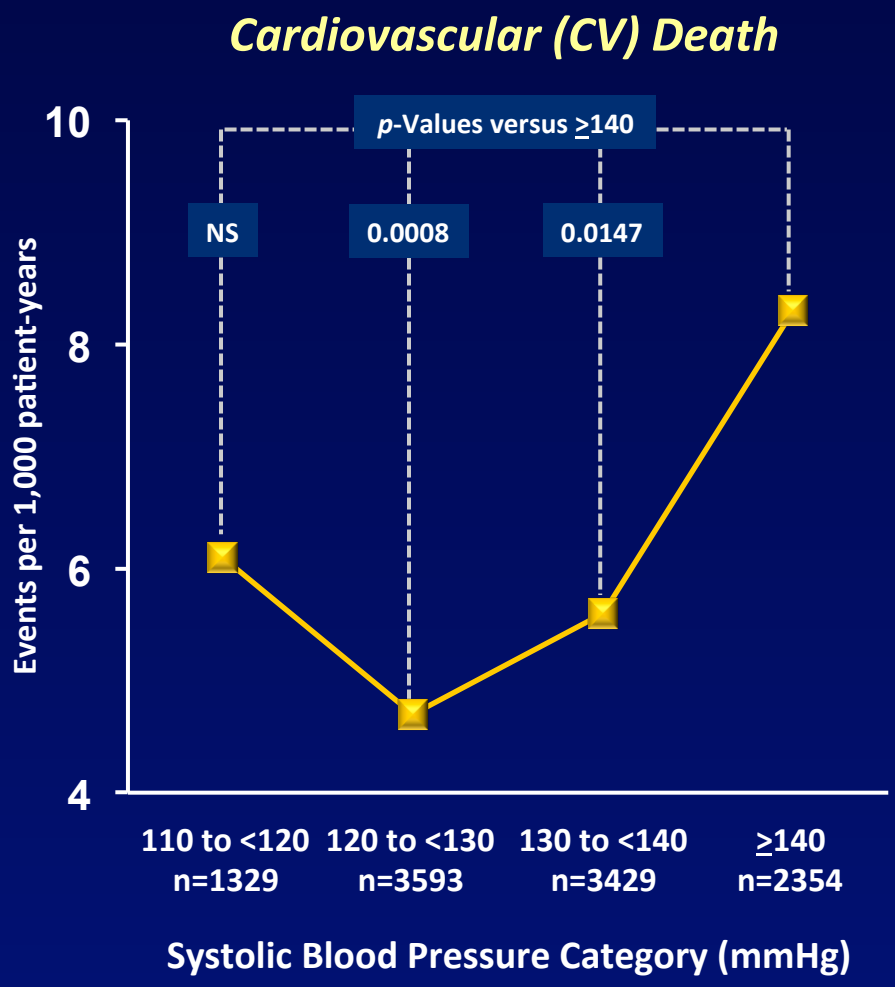


*Pooled analysis of patients enrolled in the VALUE trial; blood pressure control defined as SBP <140 mmHg
†Statistically significant difference ($p<0.05$) vs SBP not controlled at 6 months
BP=blood pressure; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; SBP=systolic blood pressure; VALUE=Valsartan Antihypertensive Long-term Use Evaluation

Weber et al. Lancet 2004;363:2049-51.

Major Outcomes by Achieved Systolic Blood Pressure Category in the ACCOMPLISH Trial





***CV Death or Non-fatal MI or Non-fatal Stroke**

Weber et al. Am J Med. 2013; 126:501-8.

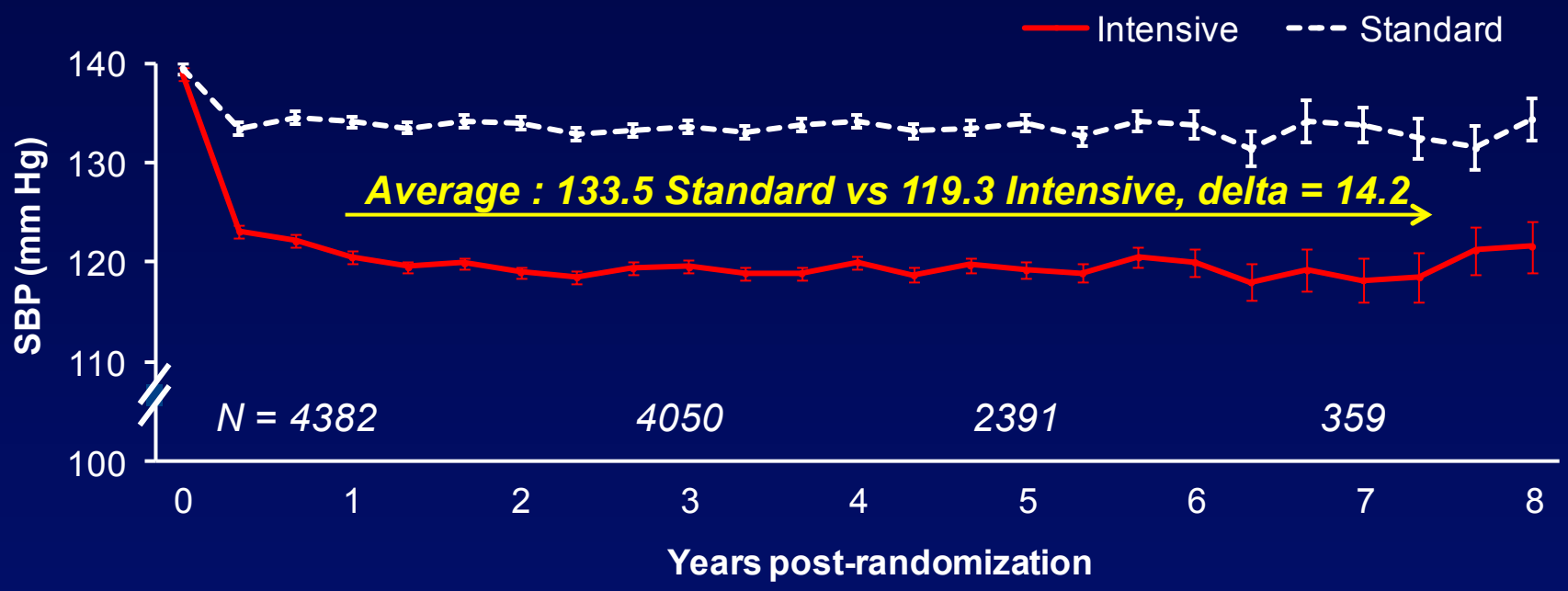
Post Hoc Analysis of INVEST Trial
Achieved treatments: SBP <140 vs. <150 mmHg

	<140 mmHg	140- <150 mmHg	RR (95%CI)	P value
CV Death	12.2	15.9	0.74(0.63, 0.86)	<0.0001
Total MI	12.1	14.6	0.77(0.59, 1.01)	0.0603
Total Stroke	4.5	9.2	0.45(0.31, 0.66)	<0.0001
Heart Failure	7.2	6.2	1.07(0.72,1.60)	0.7401
Total Death	29.6	34.9	0.79(0.66,0.93)	0.0056

Values are events/1000 patient years

Derived from Bangalore S et al. JACC 2014;64:784-793

ACCORD: Mean Systolic Pressures in Treatment Groups Over Time

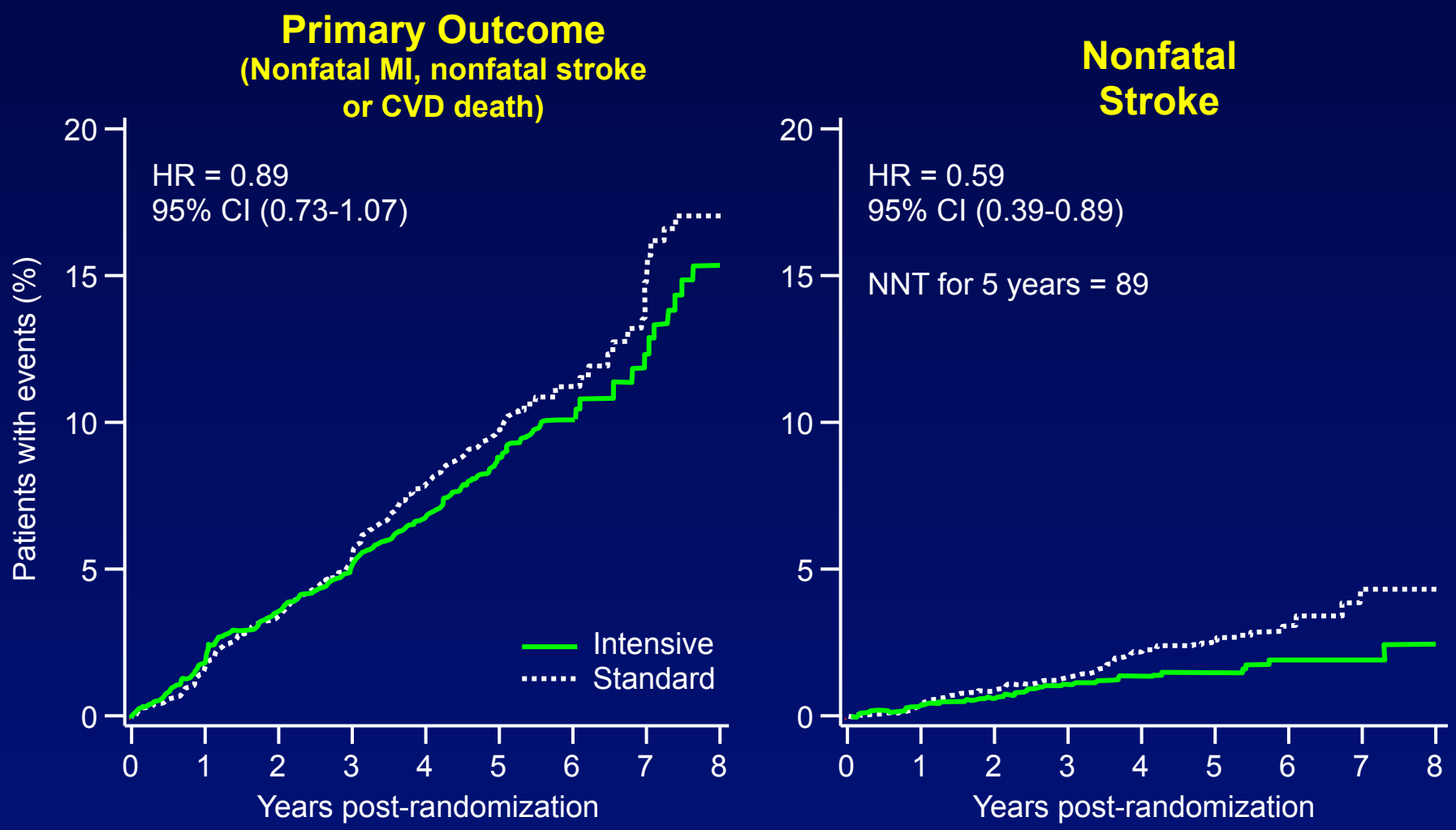


Mean number of medications								
Intensive:	**3.2**	**3.4**	**3.4**	**3.5**	**3.5**	**3.5**	**3.4**	**3.4**
Standard:	**1.9**	**2.1**	**2.1**	**2.2**	**2.2**	**2.3**	**2.3**	**2.3**
Number of patients								
Intensive:	**2,174**	**2,071**	**1,973**	**1,792**	**1,150**	**445**	**156**	**156**
Standard:	**2,208**	**2,136**	**2,077**	**1,860**	**1,241**	**504**	**203**	**201**

Data shown are mean ± 95% CI.

ACCORD study group. N Engl J Med. 2010;362:1575–85.

ACCORD: Primary Outcome and Total Stroke



ACCORD study group. N Engl J Med. 2010;362:1575–85.

Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH; Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

James et al. JAMA. 2013 Dec 18. doi: 10.1001/jama.2013.284427.

Authors of JNC 8 Panel: Recommendation 1

In the general population aged 60 years or older, initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP) of 150 mm Hg or higher or diastolic blood pressure (DBP) of 90 mm Hg or higher and treat to a goal SBP lower than 150 mm Hg and goal DBP lower than 90 mm Hg.

Strong Recommendation – Grade A

Note: This was one of only two of the nine recommendations of the panelists that claimed to be "Strong" and "Grade A"

Original Research | 14 January 2014

Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in Patients Aged 60 Years or Older: The Minority View FREE ONLINE FIRST

Jackson T. Wright Jr., MD, PhD; Lawrence J. Fine, MD, DrPH; Daniel T. Lackland, PhD; Gbenga Ogedegbe, MD, MPH, MS; and Cheryl R. Dennison Himmelfarb, PhD, RN, ANP

Wright et al. Ann Intern Med. January 2014. doi: 10.7326/M13-2981.

How These Concerns Played Out…

- The 150/90 mm Hg threshold recommended by the panelists has been claimed to reduce the use of drugs and other resources
- But, if the generally used 140/90 mm Hg threshold is more correct, then these savings in money would be at the expense of increased major cardiovascular events—particularly strokes—in the large high-risk group of hypertensive people aged 60 to 80

Wide agreement that 140 vs.150 mm Hg exposes an evidence gap that must be addressed

Therapy

- Most evidence now supports 3 drug types: the RAS blockers (ACE inhibitors or ARBs); calcium channel blockers; and thiazide diuretics. Evidence for beta blockers weaker, except in HF, post-MI, angina, AF
- Among the major classes, ethnicity, age and concomitant conditions will influence the selection of drugs
- Combination treatment is required in >50% of patients: most patients finish up with 2- or 3- drug combinations, most often utilizing a RAS blocker, a calcium channel blocker, and a thiazide

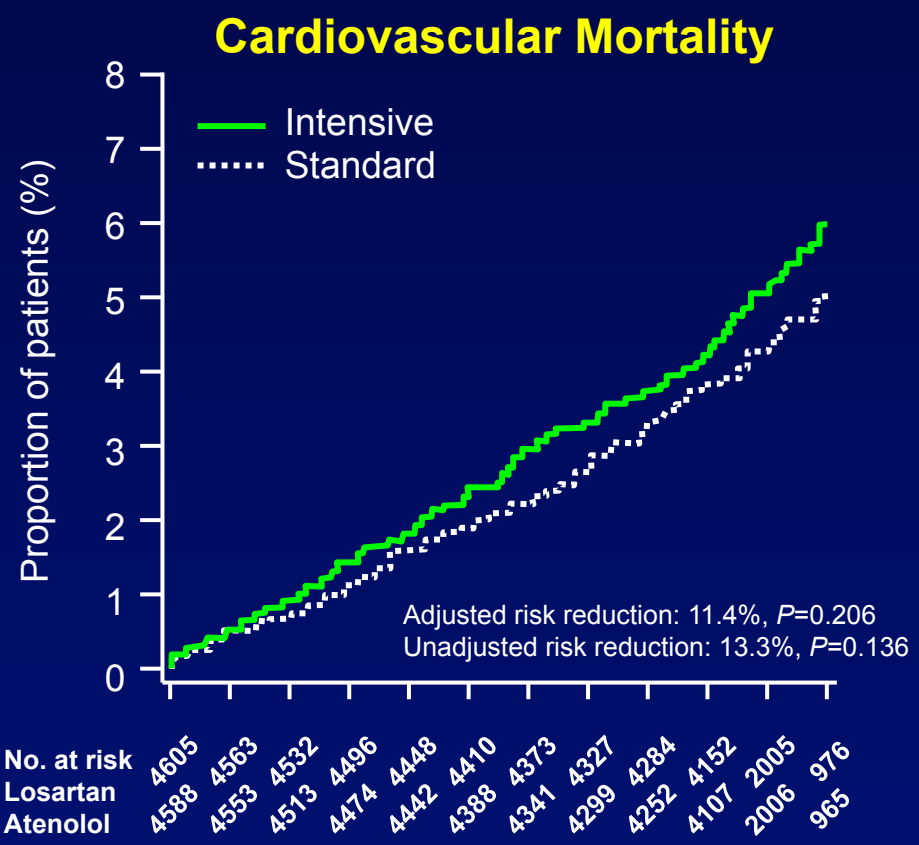
Chlorthalidone (CLD) Had Positive Effects on Cardiovascular Outcomes in Landmark Studies

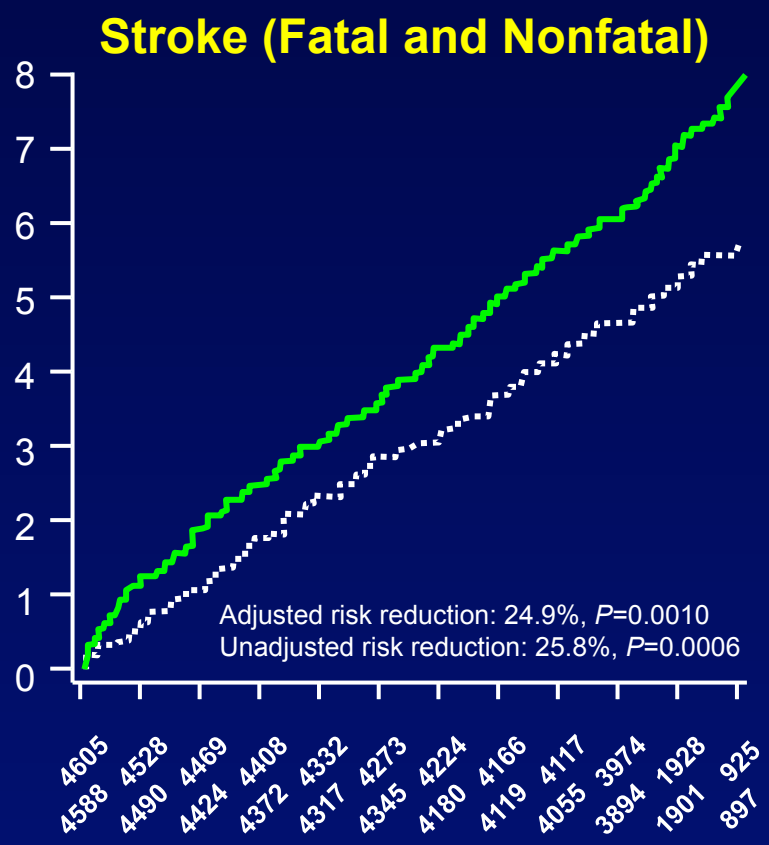
Clinical study	Population studied and duration of study	Comparators	Significant findings
HDFP[1]	• 10,940 adults with HTN • Over 5 years	• CLD • Usual care	• CLD reduced mortality by 17% vs usual care
MRFIT[2,3]	• 12,866 high risk males with HTN • Over 10.5 years	• CLD • HCTZ • Usual care	• CLD reduced mortality rate vs HCTZ • CLD lowered risk for CV events by 21% vs HCTZ
SHEP[4]	• 4,736 adults >60 years of age with ISH • Over 5 years	• CLD • Placebo	• CLD lowered risk for CVD by 32% vs placebo
ALLHAT[5]	• 33,357 high risk adults with HTN • Over 4.9 years	• CLD • Amlodipine • Lisinopril	• CLD was superior to amlodipine and lisinopril in prevention of CVD • Recommend thiazide-type diuretics for first-line treatment of HTN

ALLHAT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CLD=chlorthalidone; CVD=cardiovascular disease; CV=cardiovascular; HCTZ=hydrochlorothiazide; HDFP=Hypertension Detection and Follow-up Program; HTN=hypertension; ISH=isolated systolic hypertension; MRFIT=Multiple Risk Factor Intervention Trial; SHEP=Systolic Hypertension in the Elderly Program

1. Hypertension Detection and Follow-up Program Cooperative Group. JAMA. 1979;242:2562-71.
2. Multiple Risk Factor Intervention Trial Research Group. Circulation. 1990;82:1616-28.
3. Dorsch et al. Hypertension. 2011;51:689-94.
4. SHEP Cooperative Research Group. JAMA. 1991;265:3255-64.
5. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002;288:2981-97.

LIFE Trial: Losartan vs Atenolol as Initial Therapy





Dahlöf et al. Lancet 2002; 359: 995–1003.

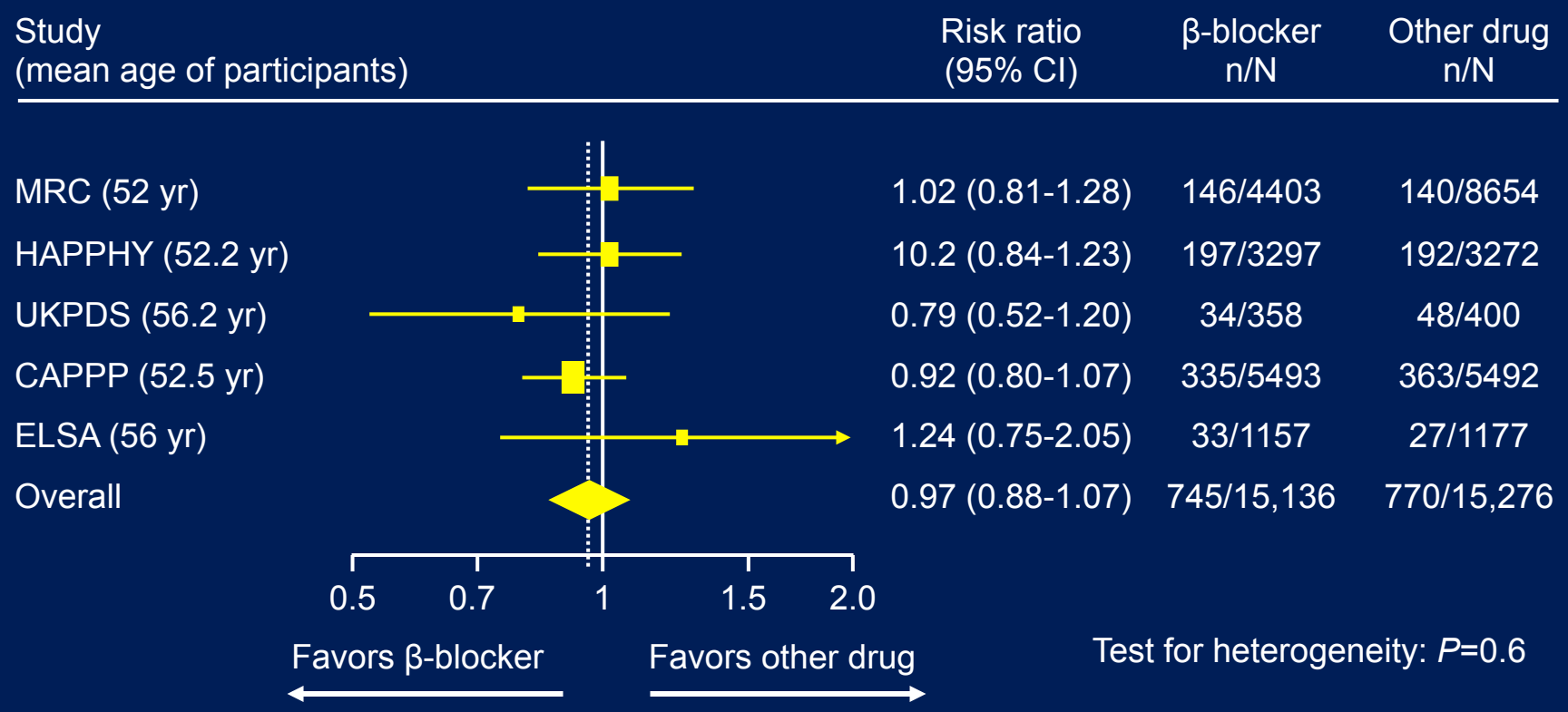
Choice of Antihypertensive Drugs

- Main benefits of treatment depend on BP lowering per se
- Confirmation that initiation / maintenance of treatment can make use of
  - Diuretics
  - Beta-blockers
  - Calcium antagonists
  - ACE-inhibitors
  - Angiotensin receptor blockers

Mancia et al. J Hypertension 2013; 31: 1281-1357.

β-blocker Meta-analysis: Age-dependent Effects on Endpoints

Patients <60 Years of Age



Risk ratios for the composite outcome (death, stroke, MI) in patients receiving β-blockers or other antihypertensive drugs.

Khan, McAlister. CMAJ. 2006;174:1737-42.

Clinical Practice Guidelines for the Management of Hypertension in the Community
A Statement by the American Society of Hypertension and the International Society of Hypertension

Michael A. Weber, MD;[1] Ernesto L. Schiffrin, MD;[2] William B. White, MD;[3] Samuel Mann, MD;[4] Lars H. Lindholm, MD;[5] John G. Kenerson, MD;[6] John M. Flack, MD;[7] Barry L. Carter, Pharm D;[8] Barry J. Materson, MD;[9] C. Venkata S. Ram, MD;[10] Debbie L. Cohen, MD;[11] Jean-Claude Cadet, MD;[12] Roger R. Jean-Charles, MD;[13] Sandra Taler, MD;[14] David Kountz, MD;[15] Raymond R. Townsend, MD;[16] John Chalmers, MD;[17] Agustin J. Ramirez, MD;[18] George L. Bakris, MD;[19] Jiguang Wang, MD;[20] Aletta E. Schutte, MD;[21] John D. Bisognano, MD;[22] Rhian M. Touyz, MD;[23] Dominic Sica, MD;[24] Stephen B. Harrap, MD[25]

Weber et al. J Clin Hypertens. 2014;16:14-26.

Headlines from New Guidelines (ASH/ISH, AHA/ACC, NICE, ESH/ESC, "JNC" 8 Panelists): BP Thresholds

- Diagnose hypertension at 140/90 mm Hg or above, and treat it to <140/90 mm Hg
- For patients between 60 and 80 years, use 140/90 mm Hg *if tolerated (JNC states 150/90, but 140/90 is "reasonable")*
- For patients aged 80 or more, use 150/90 mm Hg
- For patients with diabetes use 140/90 mm Hg at all ages (not 130/80 mm Hg as in the past)
- For patients with chronic kidney disease use 140/90 mm Hg at all ages (not 130/80 mm Hg as in the past)
- ***SUMMARY: 140/90 mm Hg is the threshold for almost all patients aged below 80***

Beta Blockers: Where Do They Stand in Hypertension?

- Based on LIFE trial, beta blockers no longer first step drugs in JNC 2013 article (Note: In African American patients, beta blockers actually superior to ARB)
- Based on ASCOT trial, beta blockers no longer first step drugs in NICE
- In both LIFE and ASCOT, atenolol was used. Might results have been different with other – vasodilating - beta blockers?
- European Guidelines (ESH/ESC 2013) and Canadian 2014 still maintain beta blockers among first-line drugs
- All guidelines (including ASH/ISH) agree that beta blockers mandated in hypertensive patients with systolic heart failure, post-MI, angina, atrial fibrillation

Pharmacology of Beta Blockers and the Role of Nitric Oxide in Vasodilation

Keith C. Ferdinand, MD
Professor of Clinical Medicine
Tulane University School of Medicine
New Orleans, Louisiana

Topics Covered

- Role of nitric oxide in the vasculature
- Selective versus nonselective beta blockers
- Vasodilating versus nonvasodilating beta blockers
- Side effects of vasodilating beta blockers versus older beta blockers
- The impact of vasodilating beta blockers on endothelial function and global cardiometabolic risk factors

Topics Covered

- **Role of nitric oxide in the vasculature**
- Selective versus non-selective beta blockers
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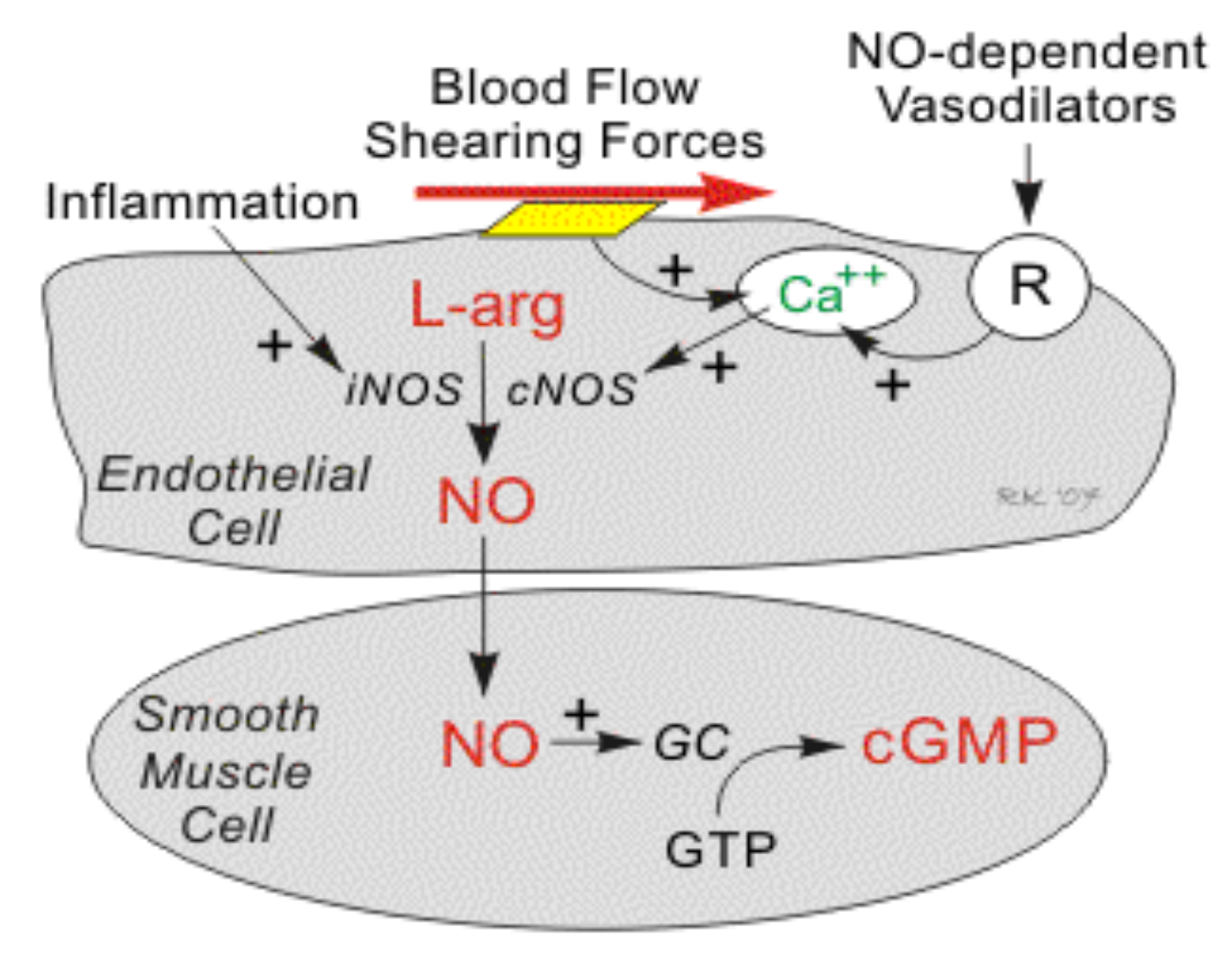
Nitric oxide (NO) Biosynthesis Nitric Oxide Synthase (NOS)



cvphysiology.com/Blood Flow/BF011.htm

Vascular Effects of NO

- Direct vasodilation (flow dependent and receptor mediated)
- Indirect vasodilation by inhibiting vasoconstrictor influences (e.g., inhibits Ang II and sympathetic vasoconstriction)

Vascular Effects of NO

- Anti-thrombotic - inhibits platelet adhesion to vascular endothelium
- Anti-inflammatory - inhibits leukocyte adhesion to vascular endothelium; scavenges superoxide anion
- Anti-proliferative - inhibits smooth muscle hyperplasia

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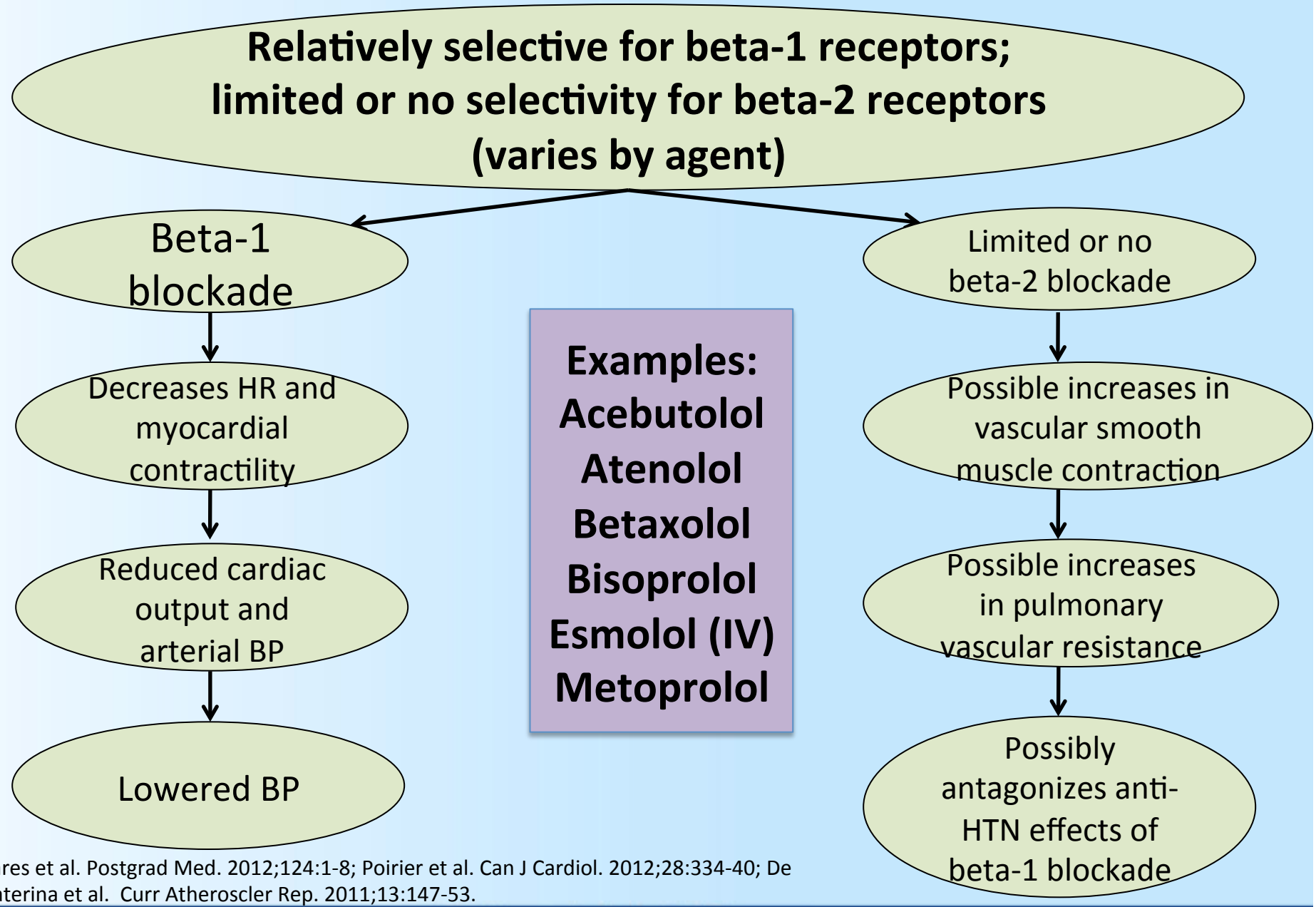
Ƀ-blockers

- Highly heterogeneous with respect to various pharmacologic effects:
  - Intrinsic sympathomimetic activity (ISA)
    - **Ƀ-1 selectivity**
    - a1-adrenergic–blocking effect
    - tissue solubility
  - routes of systemic elimination, potencies/ duration of action, and specific effects may be important in the selection of a drug for clinical use



Fares et al. Postgrad Med. 2012;124:1-8; Poirier et al. Can J Cardiol. 2012;28:334-40; De Caterina et al. Curr Atheroscler Rep. 2011;13:147-53.

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Vasodilating Beta Blockers

- **Labetalol**
  - Non-selective for beta-1 and -2 receptors
  - Alpha-1 receptor-blocking activity
  - Minimal intrinsic sympathomimetic activity
- **Carvedilol**
  - Nonselective for beta-1 and -2 receptors
  - Alpha-1 receptor-blocking activity
  - No intrinsic sympathomimetic activity
- **Nebivolol**
  - Highly selective for beta-1 receptors
  - Improves endothelial function
  - Induces release of nitric oxide
  - May be beneficial in patient populations with heightened endothelial dysfunction

Fares et al. Postgrad Med. 2012;124:1-8; Ram. Am J Cardiol 2010;106:1819–25; Mason et al. J Cardiovasc Pharmacol. 2009;54:123-28; Mason. Circulation. 2005;112:3795-3801.

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β-Blocker Tolerability

- Common tolerability issues with **nonvasodilating** agents[1]
  - Lethargy, drowsiness, depression, decreased exercise tolerance, vascular effects, sexual dysfunction
  - May lead to poor patient adherence
  - New onset diabetes[2]
- Vasodilating agents have little/no effect on sexual function[3,4]
- Lesser incidence of cold extremities vs atenolol[5]
- Do not worsen glucose tolerance[3]

1. Weber et al. J Hypertens 2014;32:3-15. 2. Fares et al. Postgrad Med. 2012;124:1-8. 3. Mancia et al. Eur Heart J. 2013;34:2159-2219. 4. Boydak et al. Clin Drug Investig. 2005;25:409-16. 5. Jonsson et al. Cardiology. 2005;103:148-55.

Topics Covered

- Role of nitric oxide in the vasculature
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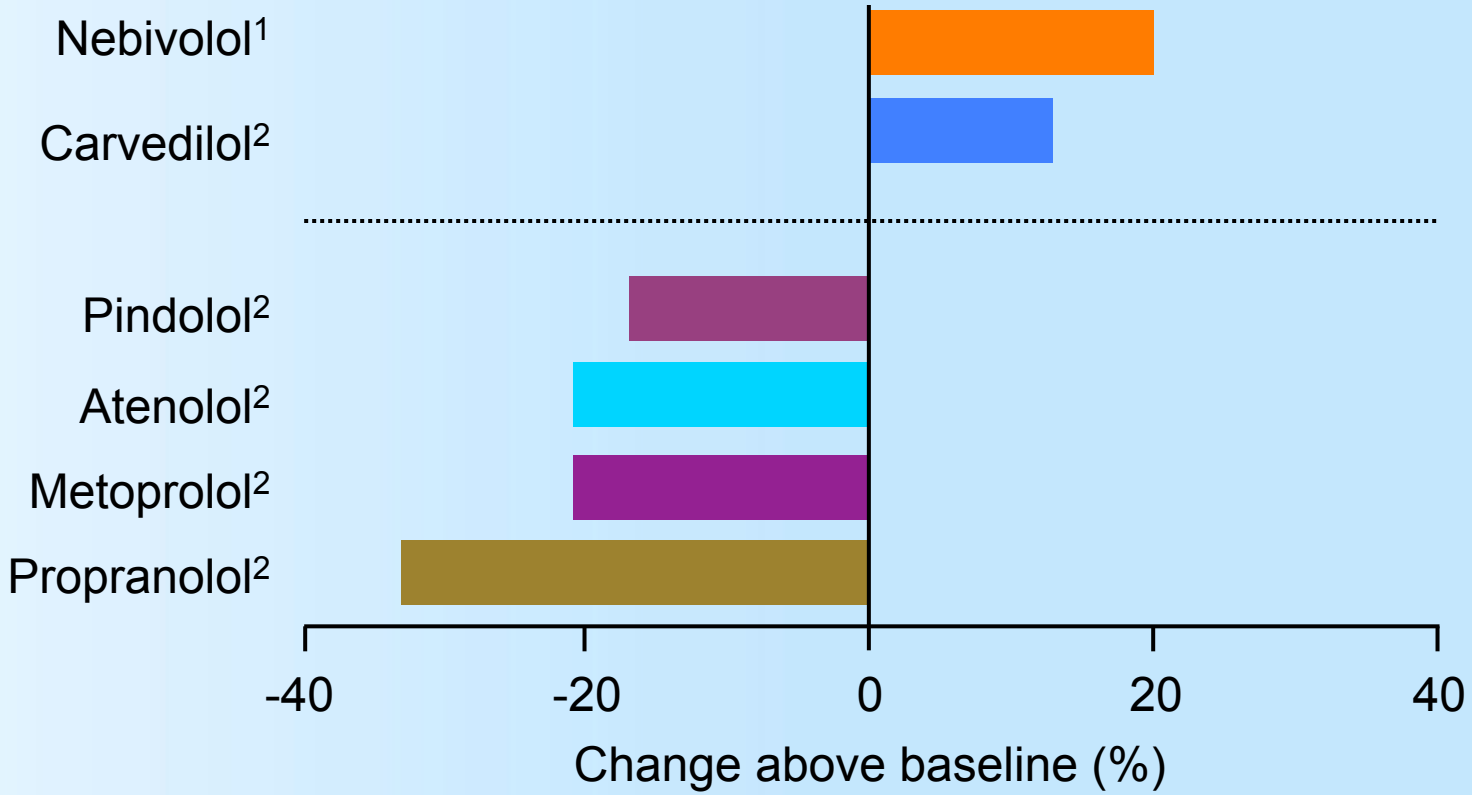
Effects of β-Blockers on Insulin Sensitivity in HTN

Difference between **vasodilating and nonvasodilating** β-blockers approximately 30% (similar to insulin-sensitizers)



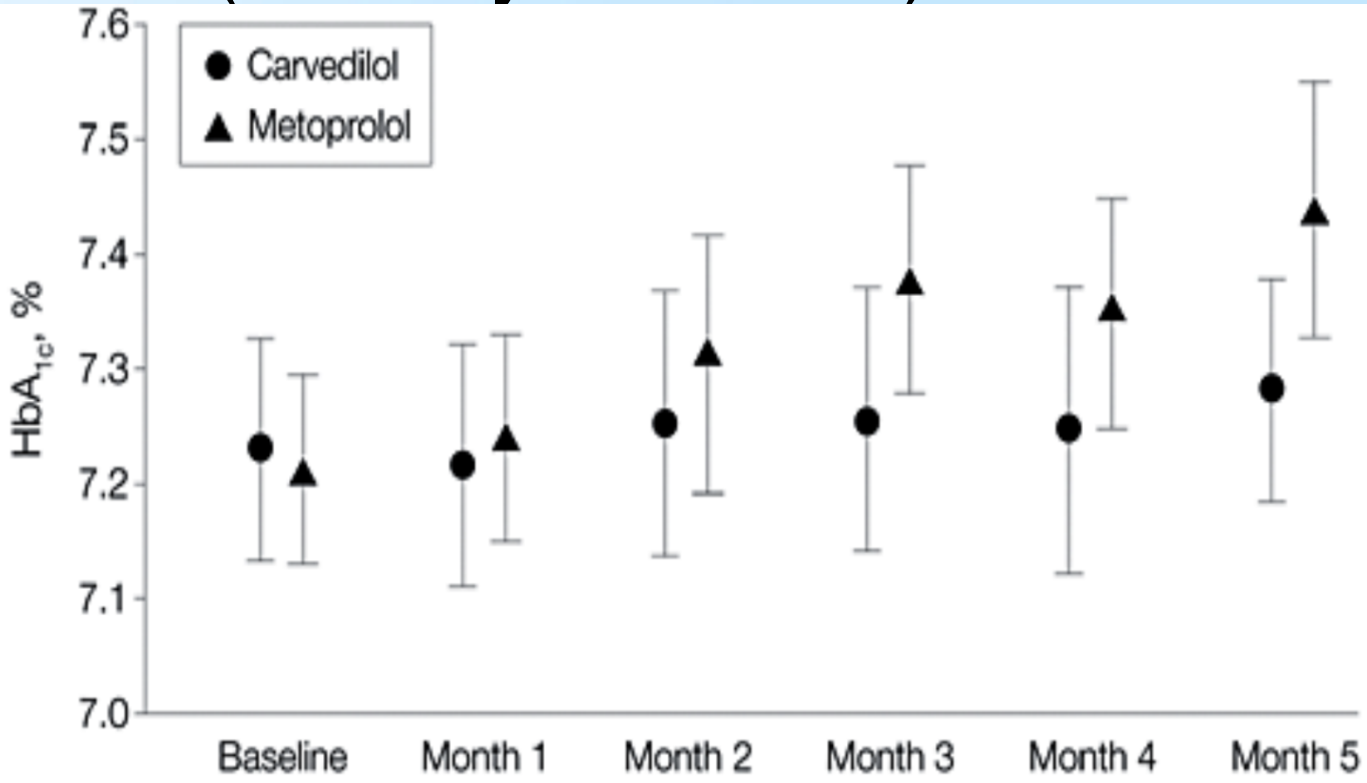
Celik et al. J Hypertens. 2006;24:591-96; Jacob et al. Am J Hypertens 1998;11:1258-65.

GEMINI

- 205 US sites; N=1235
- Aged 36 to 85 yrs with HTN (>130/80 mm Hg) and
- Type 2 DM (HbA_{1c} 6.5%-8.5%)
- Carvedilol (n = 498) mean dose of 18 mg BID or
- Metoprolol tartrate (n = 737) mean dose of 128 mg BID

Bakris et al. JAMA. 2004;292:2227–36.

GEMINI: HbA1c Change Baseline to Month 5 (Primary Outcome)

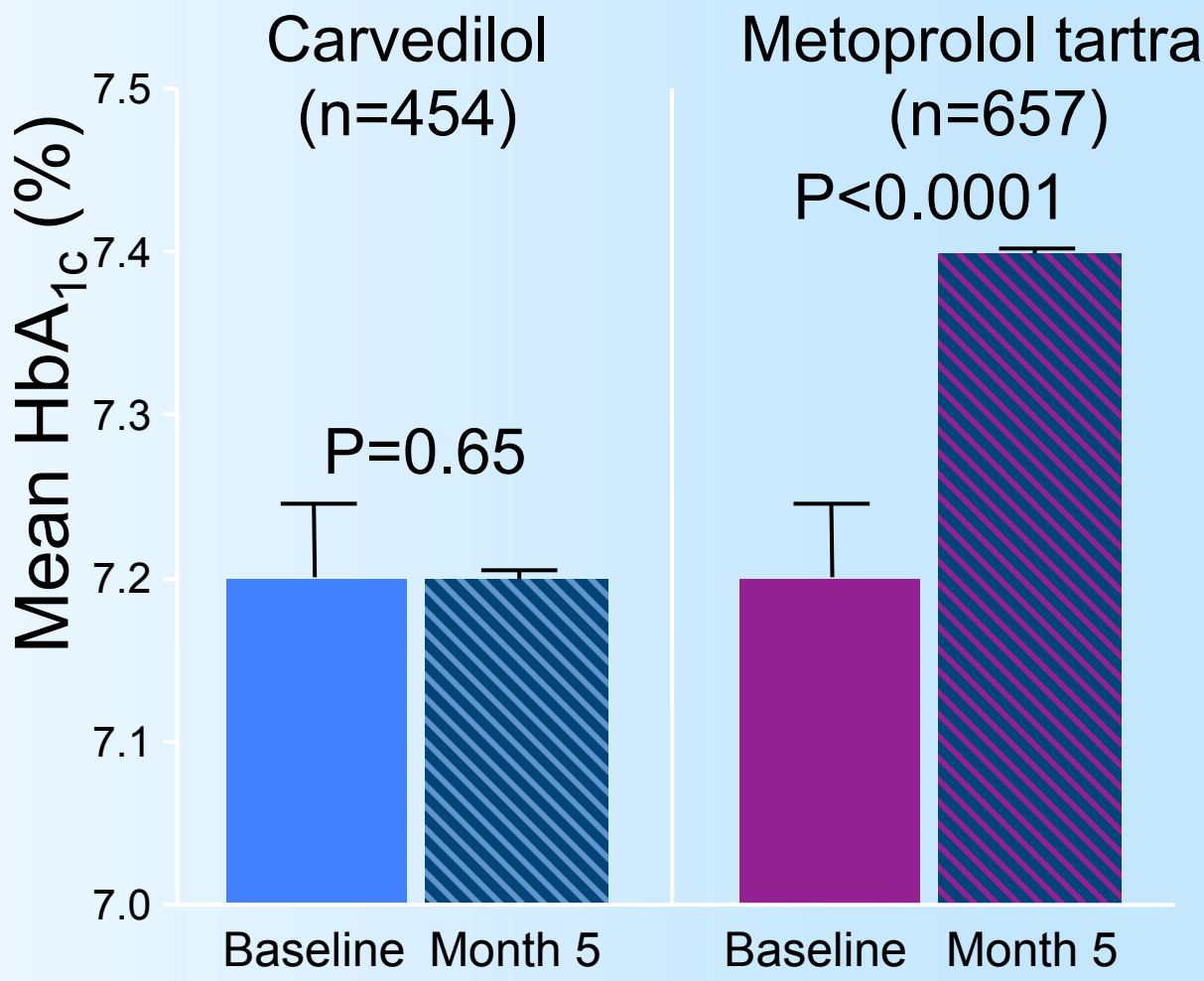


No. of Participants						
Carvedilol	454	390	449	452	453	454
Metoprolol	654	550	643	655	655	657

Significant (mean [SD], 0.13% [0.05%]; 95% CI,–0.22% to –0.04%; P = .004)

Bakris GL, et al. JAMA. 2004;292:2227–36.

GEMINI: Hemoglobin A_{1c}



Treatment Diff. Carvedilol vs Metoprolol tartrate -0.13% (-0.22, -0.04) P=0.004

1111 patients (90%) evaluable for efficacy, both valid baseline and at least 1 on-therapy HbA_{1c} assessment.

Bakris et al. JAMA. 2004;292:2227-36..

GEMINI

- Carvedilol improved insulin sensitivity and glycemic control, less wt. gain and reduced progression to microalbuminuria with equivalent BP lowering
- Appears pharmacologic differences among β-blockers can affect clinical utility in hypertensive patients with DM

Bakris et al. JAMA. 2004;292:2227-36.

Best Beta Blocker for Specific Patients

- β-blockers recommended as 2nd or 3rd line
- Because major adverse BBs effects may be mediated by peripheral vasoconstriction and increasing insulin resistance….
- New third-generation β-blockers (such as nebivolol) or blocking both α and β receptors (e.g., carvedilol) may prove to be particularly beneficial
- These agents cause vasodilatation and an increase in insulin sensitivity.

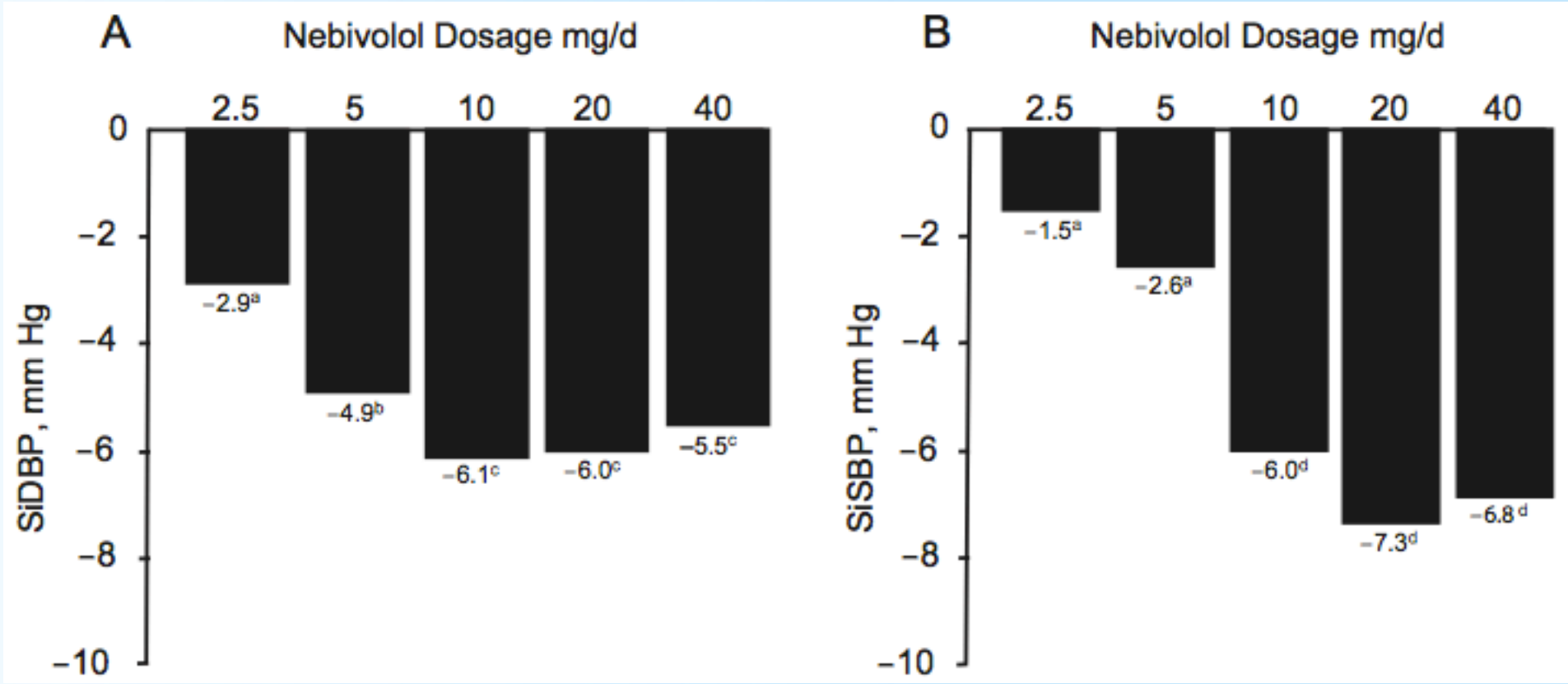
AACE Hypertension Task Force. Endocr Pract. 2006;12:193-222.

Vasodilating β-blockers: Black Patients

- HTN in black patients associated with more pronounced endothelial dysfunction
  - Low bioavailability of NO from endothelium
  - Results in smooth-muscle-cell proliferation, migration; adhesion of leukocytes to endothelium; platelet aggregation
  - Contributes to pathogenesis of vascular diseases
- Nebivolol improves endothelial function, induces release of NO

Mason. Circulation. 2005;112:3795-3801.

Nebivolol versus Placebo in African Americans



Placebo-subtracted least squares mean reductions from baseline to study end in trough SiDBP (A) and trough sitting SiSBP) (B). [a]p=not significant vs placebo. [b]p=.004 vs placebo. [c]p≤.001 vs placebo. [d]p≤.045 vs placebo.

Saunders et al. J Clin Hypertens. 2007;9:866-75.

Take-Home Messages

Beta Blockers Are Not All the Same

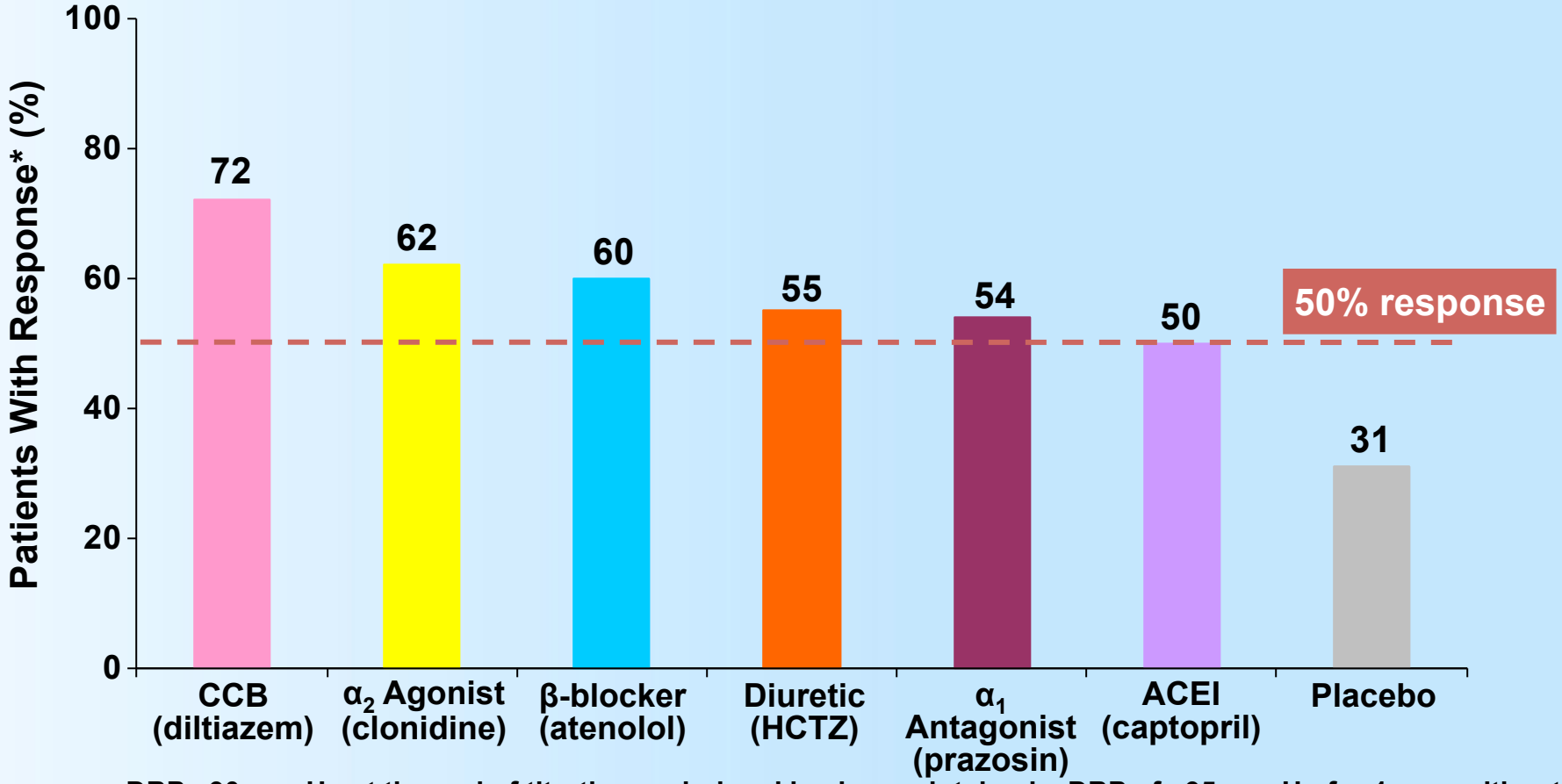
- But there are important differences among agents in:
  - Mechanisms of action (MOAs) and pathophysiologic effects
  - Effects in different hypertensive populations
  - Safety and tolerability profiles

Thank You!

Combination Antihypertensive Therapy: Today's Options, Tomorrow's Possibilities

George L. Bakris, MD, FAHA, FASN
Professor of Medicine
Director, ASH Comprehensive Hypertension Center
University of Chicago Medicine
Pritzker School of Medicine
Chicago, Illinois

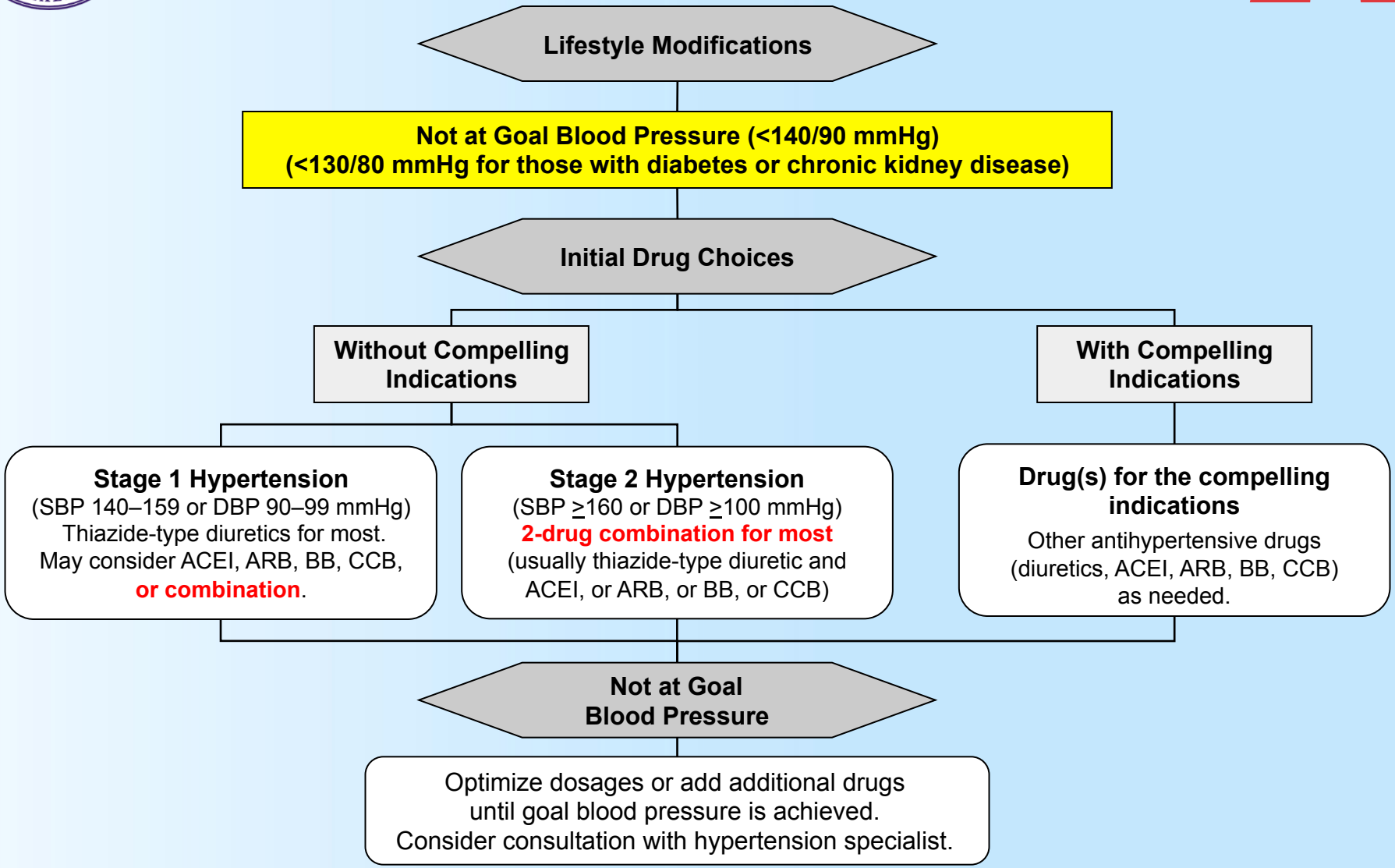
Monotherapy for Hypertension Is Inadequate in ~40% to 50% of Patients



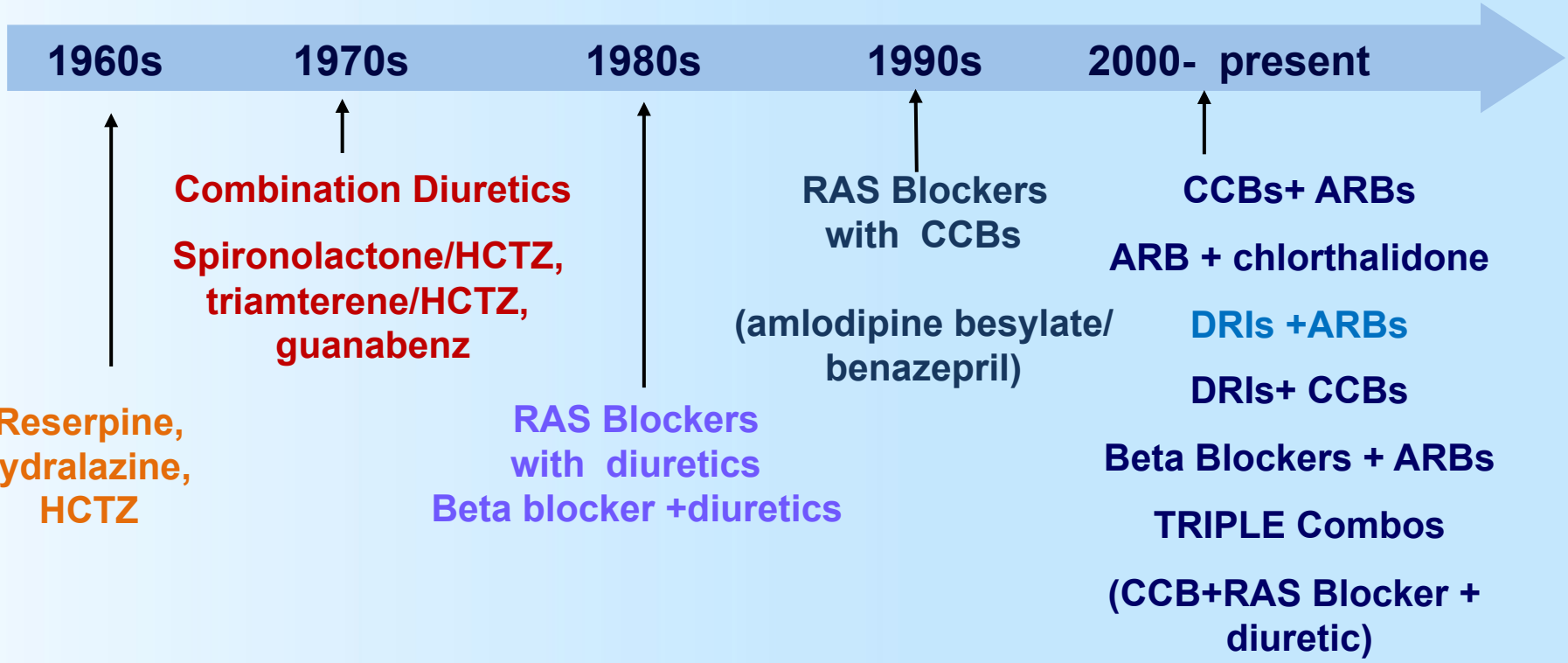
***Response = DBP <90 mm Hg at the end of titration period and having maintained a DBP of <95 mm Hg for 1 year without drug tolerance.**
Mean baseline BP = 152/99 mm Hg.

Adapted from Materson BJ et al. Am J Hypertens. 1995;6:189-92.

Algorithm for Treatment of Hypertension



Evolution of Single Pill Combination Antihypertensive Therapies



CCB=calcium channel blocker; ARB=angiotensin II receptor blocker; DRI=direct renin inhibitor; RAS=renin-angiotensin system

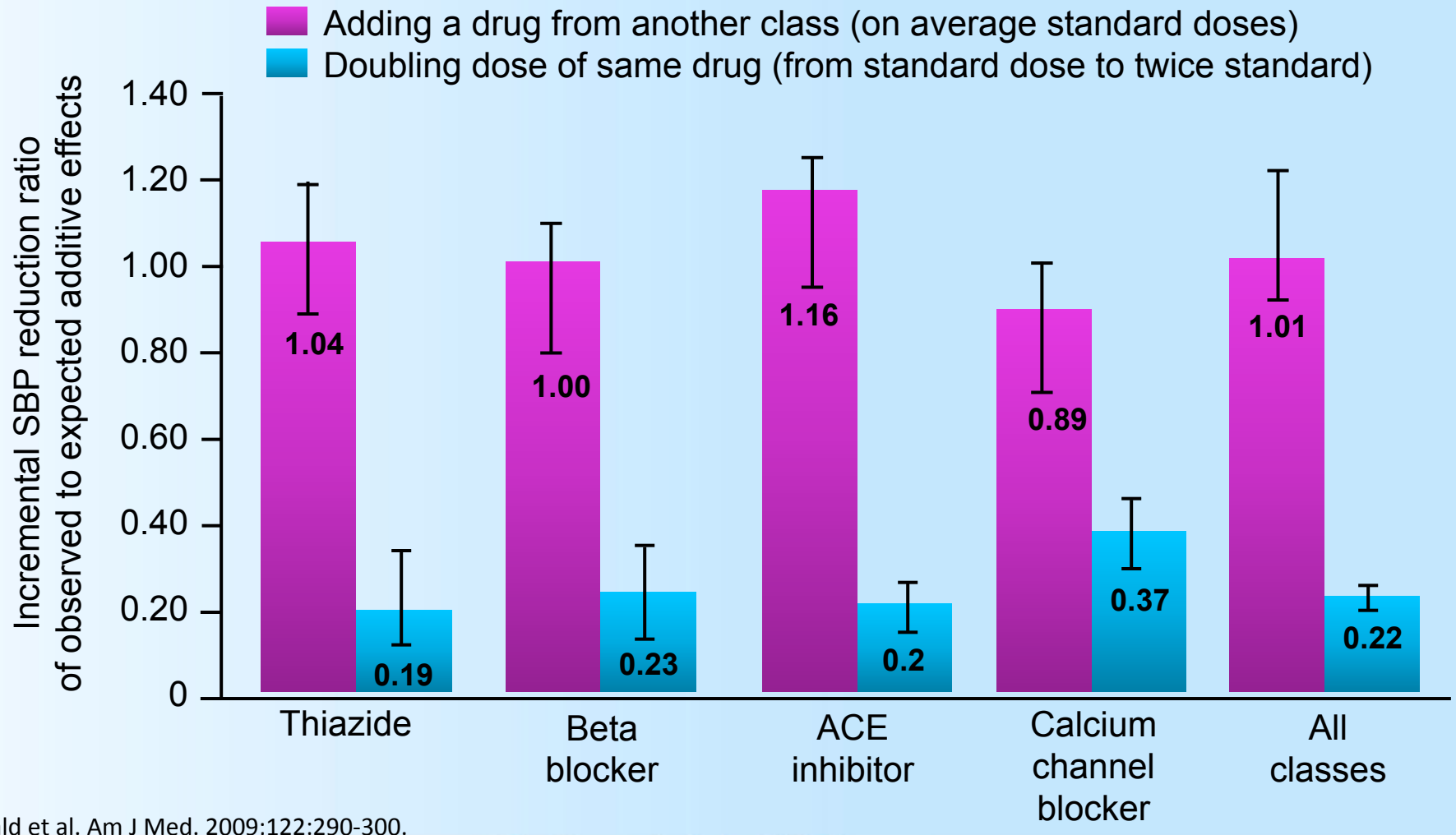
Rationale for Single-Pill Combination Therapy: Background

- Traditional antihypertensive therapy yields goal BP in <60% of treated hypertensive patients[1-3]
- Switching from one monotherapy to another is effective in only about 50% of patients[1]
- Most patients will require at least two drugs to attain goal BP (<140/90 mm Hg)[4-6]

BP = blood pressure

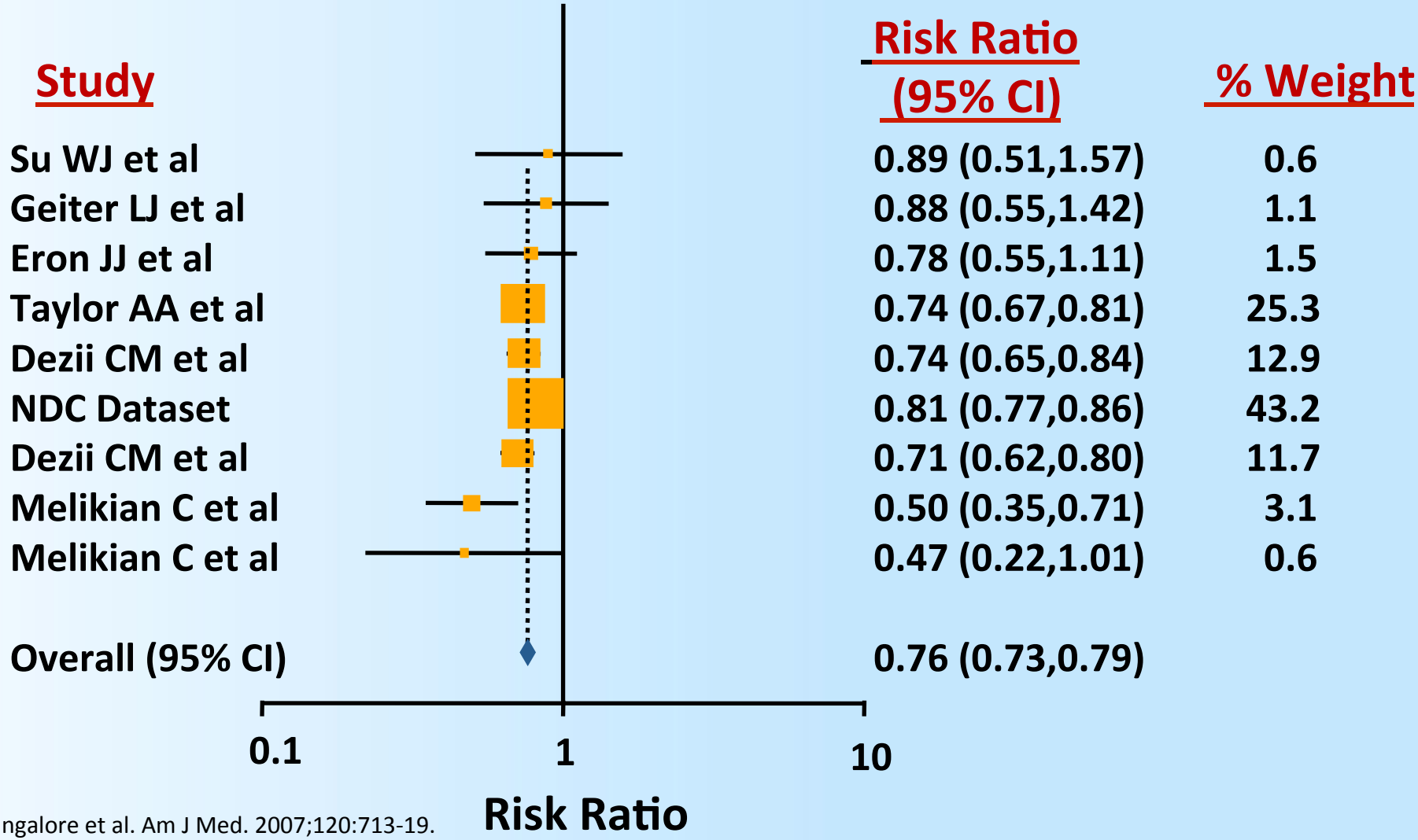
1. Materson et al. J Hum Hypertens. 1995;9(10):791-796.
2. Messerli. J Hum Hypertens. 1992;6 Suppl. 2:S19-S21.
3. Ram. J Clin Hypertens (Greenwich). 2004;6(10):569-577.
4. Chobanian et al. JAMA. 2003;289(19):2560-2572.
5. Weber et al. J Clin Hypertens. 2014;16:14-26.
6. American Diabetes Association. Diabetes Care. 2002;25(Suppl.1):S71-S73.

Ratio of Observed to Expected Incremental BP-Lowering Effects of Adding a Drug or Doubling the Dose According to Drug Class



Wald et al. Am J Med. 2009;122:290-300.

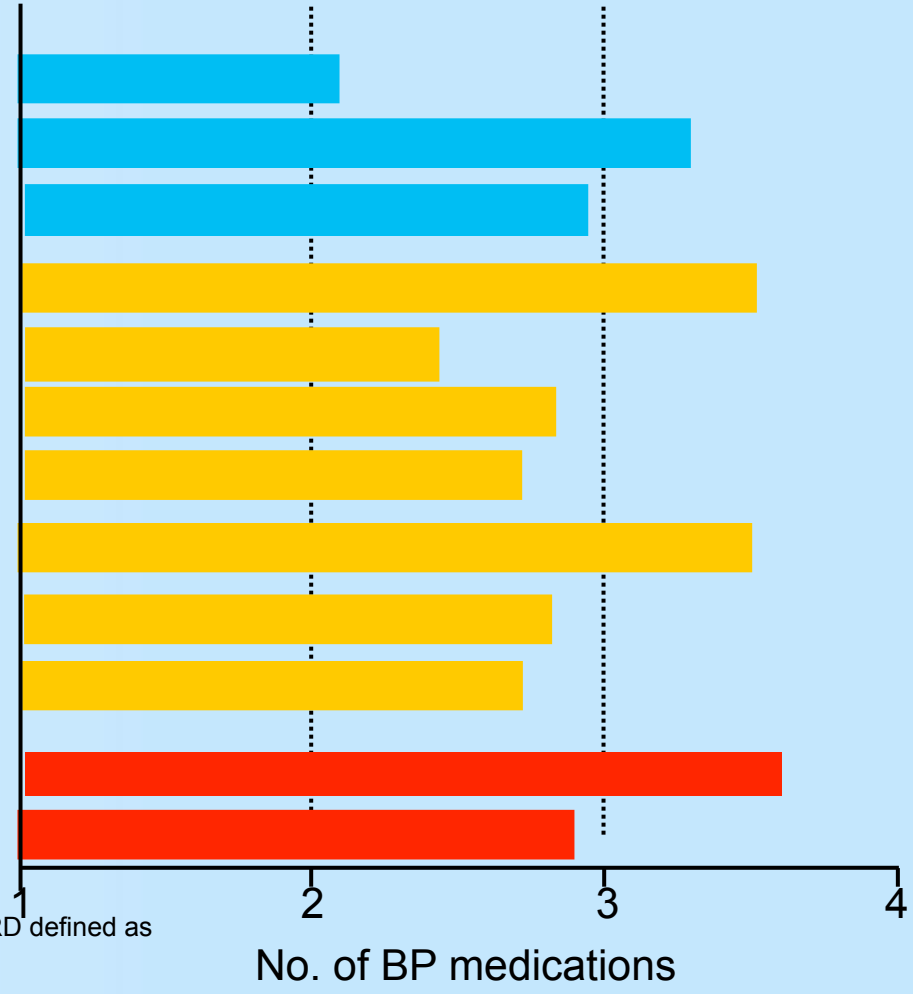
Adherence With Single Pill Combinations Compared With Free-Drug Combinations



Bangalore et al. Am J Med. 2007;120:713-19.

Multiple Medications Are Required to Achieve BP Control in Clinical Trials

	Trial	SBP achieved (mm Hg)
Hypertension	ALLHAT	138
	HOT	138
	ACCOMPLISH	132
Diabetes	ACCORD (intensive)*	119
	ACCORD (standard)*	133
	INVEST	133
	IDNT	138
	RENAAL	141
	ABCD	132
	UKPDS	144
Kidney disease	MDRD	132
	AASK	128

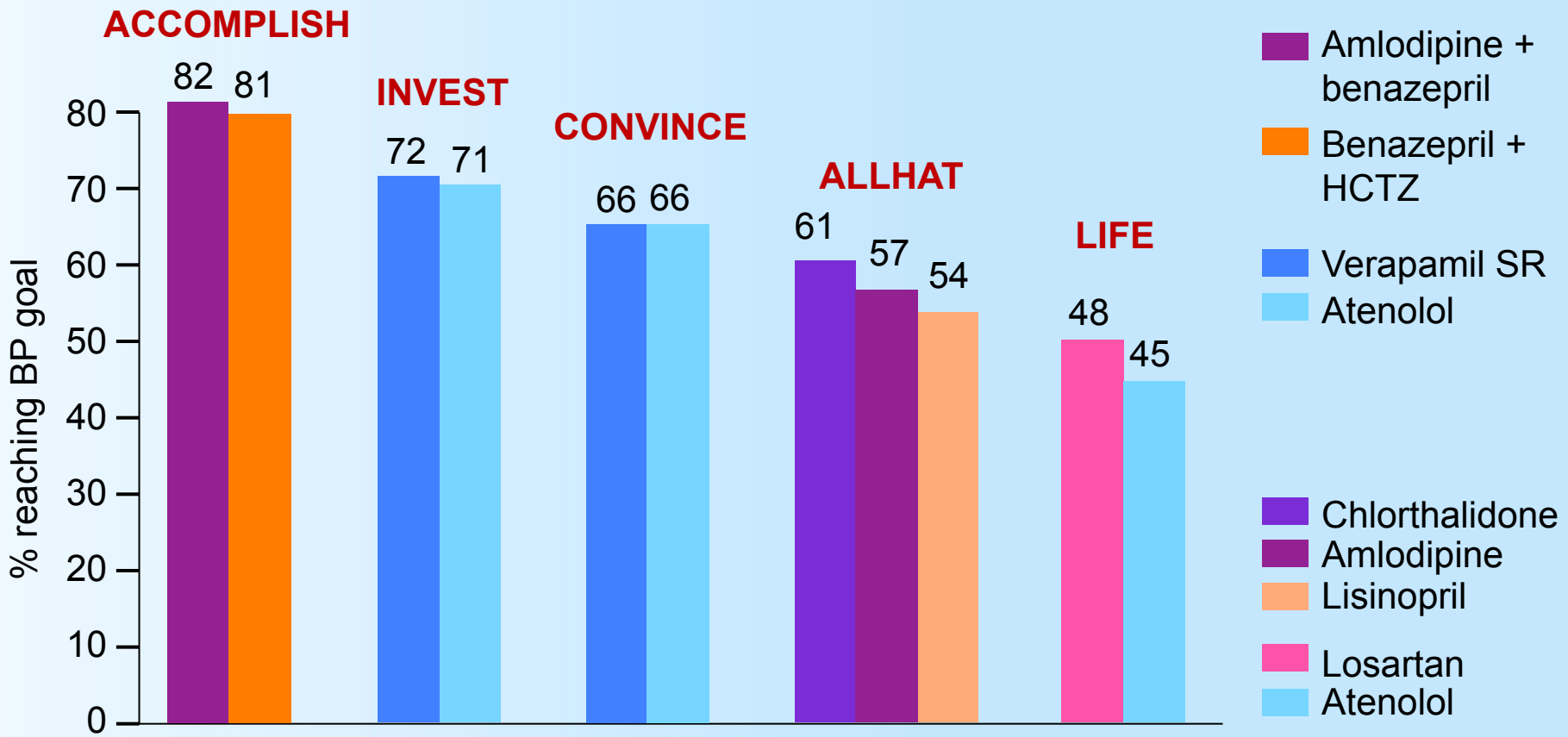


SBP=systolic blood pressure. *Target blood pressure control groups in ACCORD defined as <120 mm Hg (intensive) and <140 mm Hg (standard).

Copley JB, Rosario R. *Dis Mon*. 2005;51:548-614.
The ACCORD Study Group. *N Engl J Med*. 2010;362:1575-85.

Percentage of Patients Who Reached JNC-7 BP Goals

BP Goal: ≤140/90 mm Hg

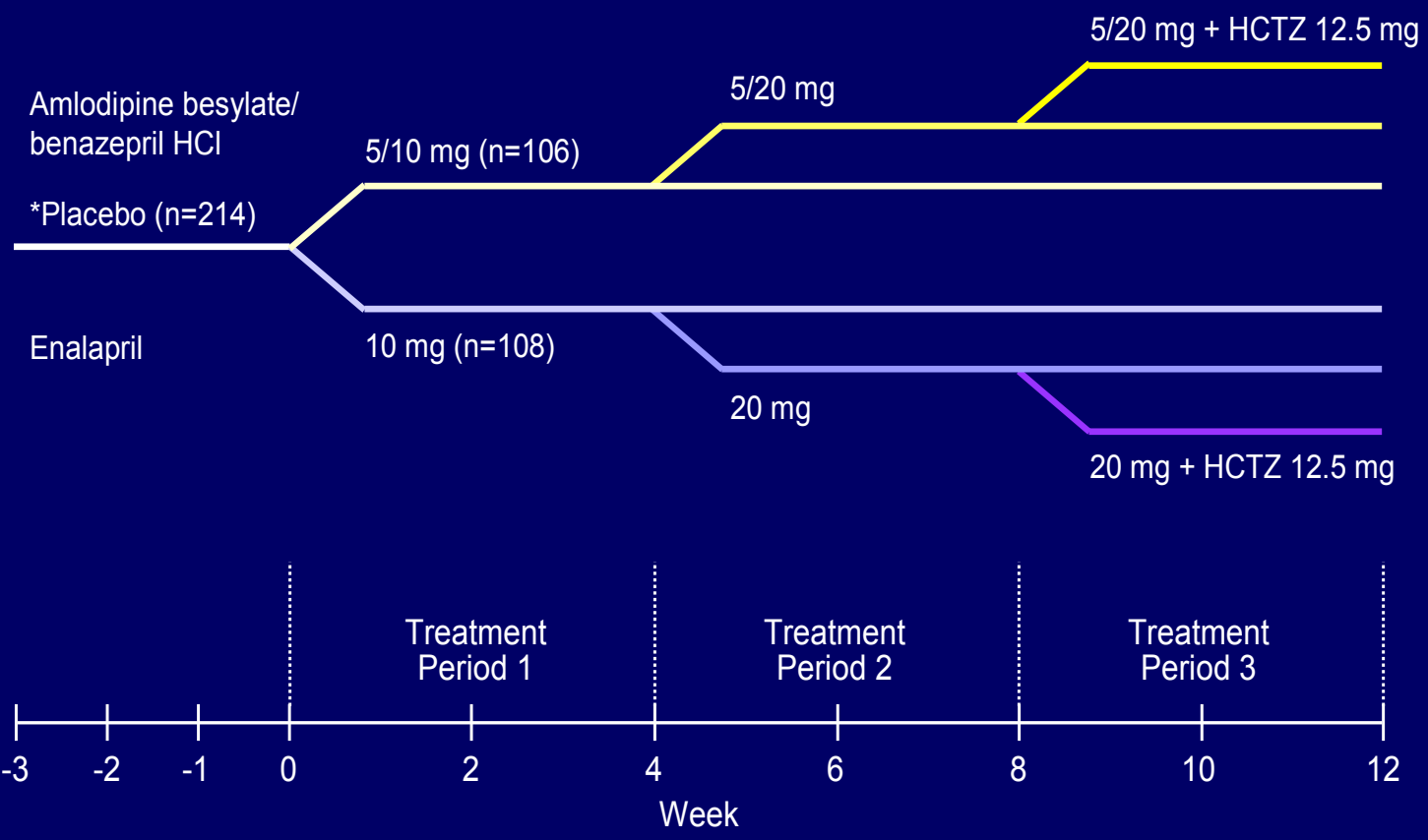


Black et al. JAMA. 2003;289:2073-2082. Dahlöf et al. Lancet. 2002;359:995-1003. Jamerson et al. Blood Pressure. 2007:16:80-86. Pepine et al. JAMA. 2003;290:2805-2816. The ALLHAT Officers and Coordinators. JAMA. 2002;288:2981-2897.

Trials With Initial Single Pill Combinations That Evaluated Time to BP Control

- **SHIELD** (Study of Hypertension and the Efficacy of Lotrel in Diabetes and Hypertension)
- **STITCH** (Simplified Treatment Intervention to Control Hypertension)
- **ACCELERATE** (Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for HTN control)

SHIELD: Study Design

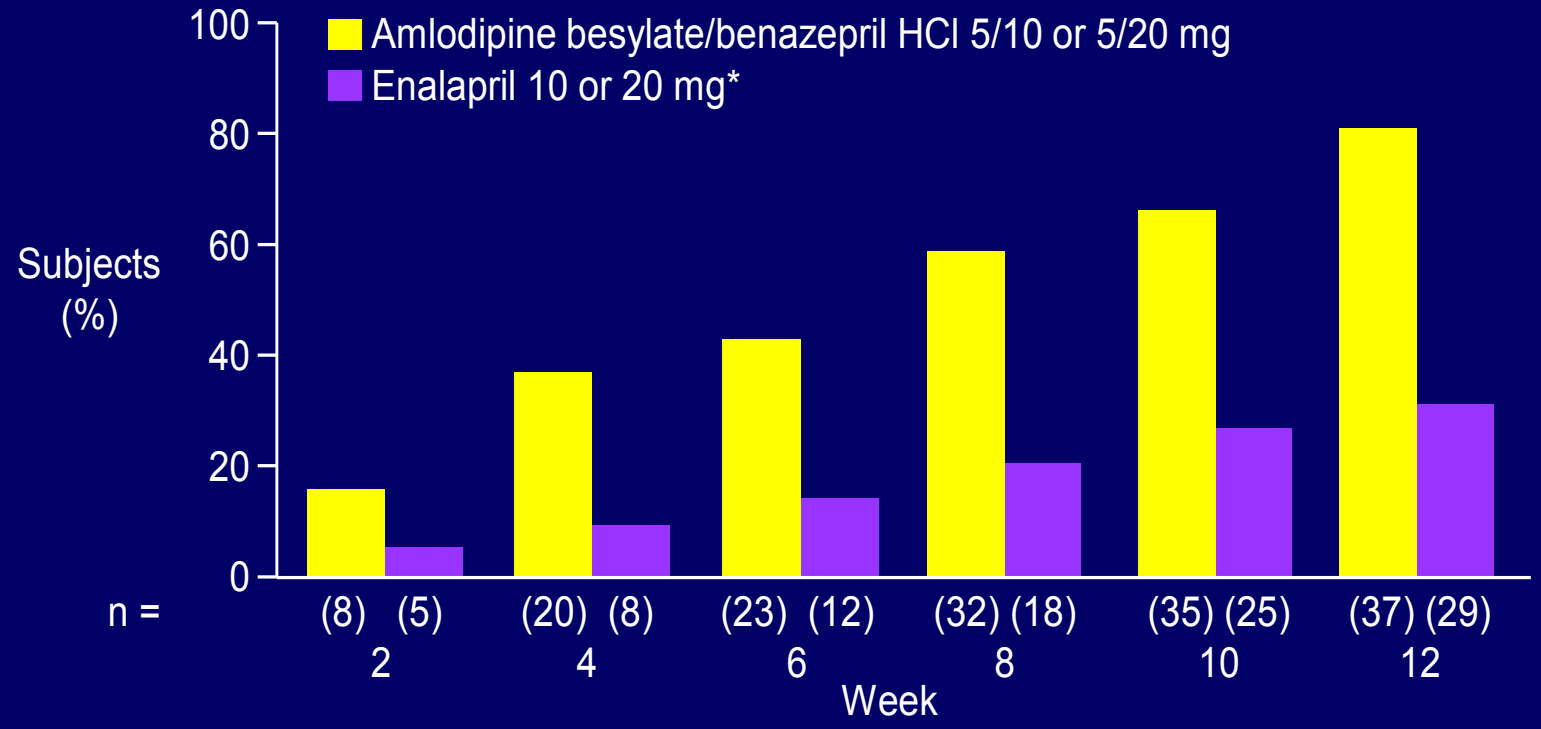


Data on file, Novartis Pharmaceuticals Corporation.

*Wash out from prior Medication

SHIELD: Cumulative Percentage of Subjects With First-Treatment Success (BP <130/80 mm Hg)

ITT Population



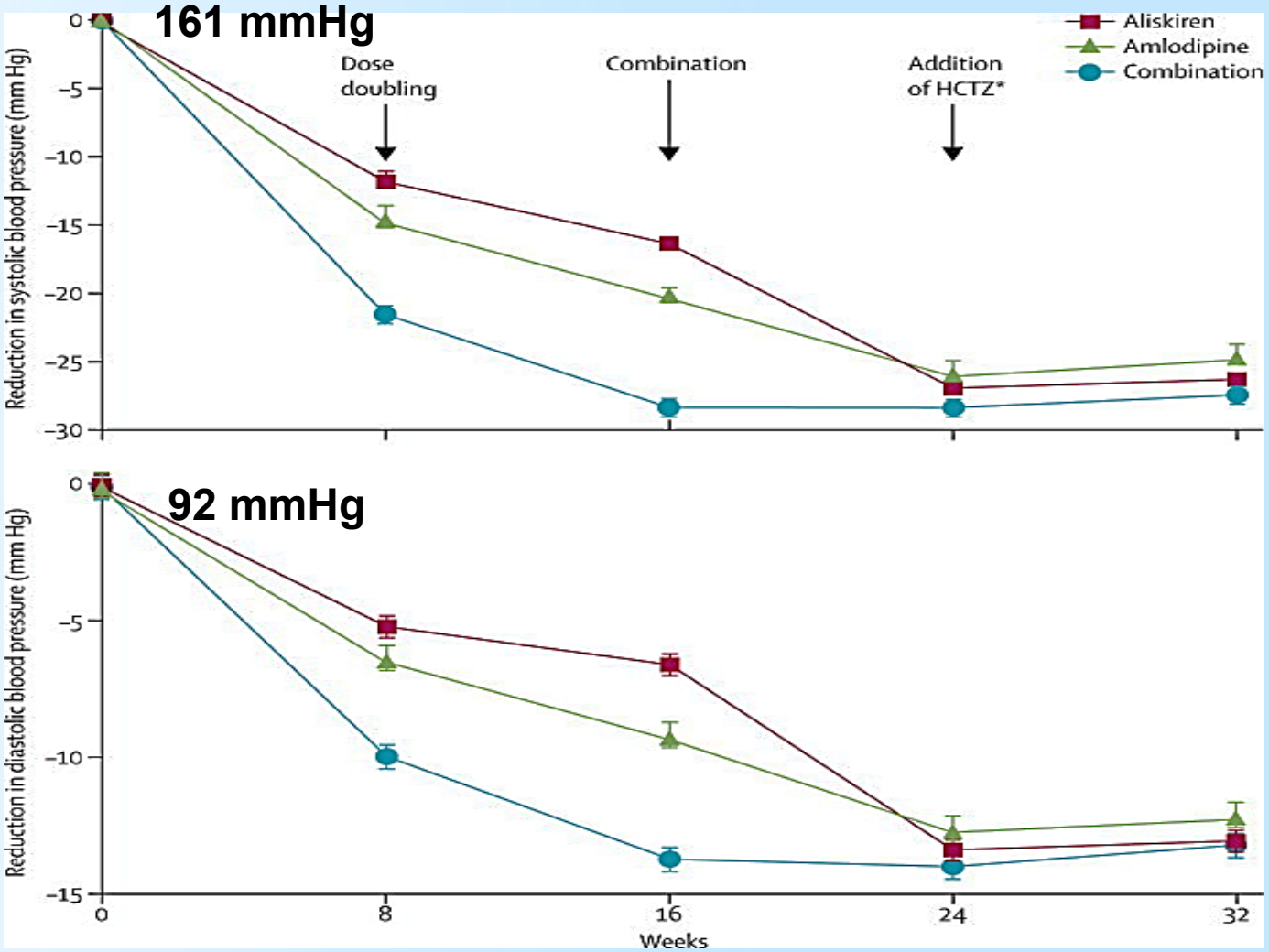
n=cumulative number of subjects with first-treatment success.
*Hydrochlorothiazide (HCTZ) 12.5 mg was added at Week 8 if target BP was not reached.
Amlodipine besylate/benazepril HCl subjects given HCTZ were excluded from data analysis.
Bakris G et al. J Clin Hypertens 2003;5:202-209

Demographic and Baseline Characteristics of ACCELERATE

	Aliskiren plus amlodipine group (N=620)*	Aliskiren group (N=318)*	Amlodipine group (N=316)*
Age (years)	58·1 (10·8)	58·4 (10·8)	58·1 (10·9)
Number of women	305 (49%)	154 (48%)	160 (50%)
Ethnic origin			
White	477 (77%)	251 (79%)	245 (78%)
Black	32 (5%)	17 (5%)	16 (5%)
Asian	13 (2%)	4 (1%)	6 (2%)
Native American	19 (3%)	9 (3%)	8 (3%)
Other	79 (13%)	37 (12%)	41 (13%)
Body-mass index (kg/m²)	29·8 (5·6)	29·5 (5·2)	29·8 (5·7)
Number of smokers	89 (14%)	48 (15%)	37 (12%)
Number of treatment-naive patients	270 (44%)	133 (42%)	118 (37%)
Number with diabetes	77 (12%)	42 (13%)	37 (12%)
Systolic blood pressure (mm Hg)	161·8 (8·4)	161·2 (8·5)	161·1 (8·2)
Diastolic blood pressure (mm Hg)	92·5 (9·0)	92·0 (10·6)	93·0 (9·1)

Brown et.al. Lancet 2011;377:312-320; Lazich, Bakris. Lancet 2011;377;278-279

Reductions in Blood Pressure at 2, 4, 6 and 8 Months

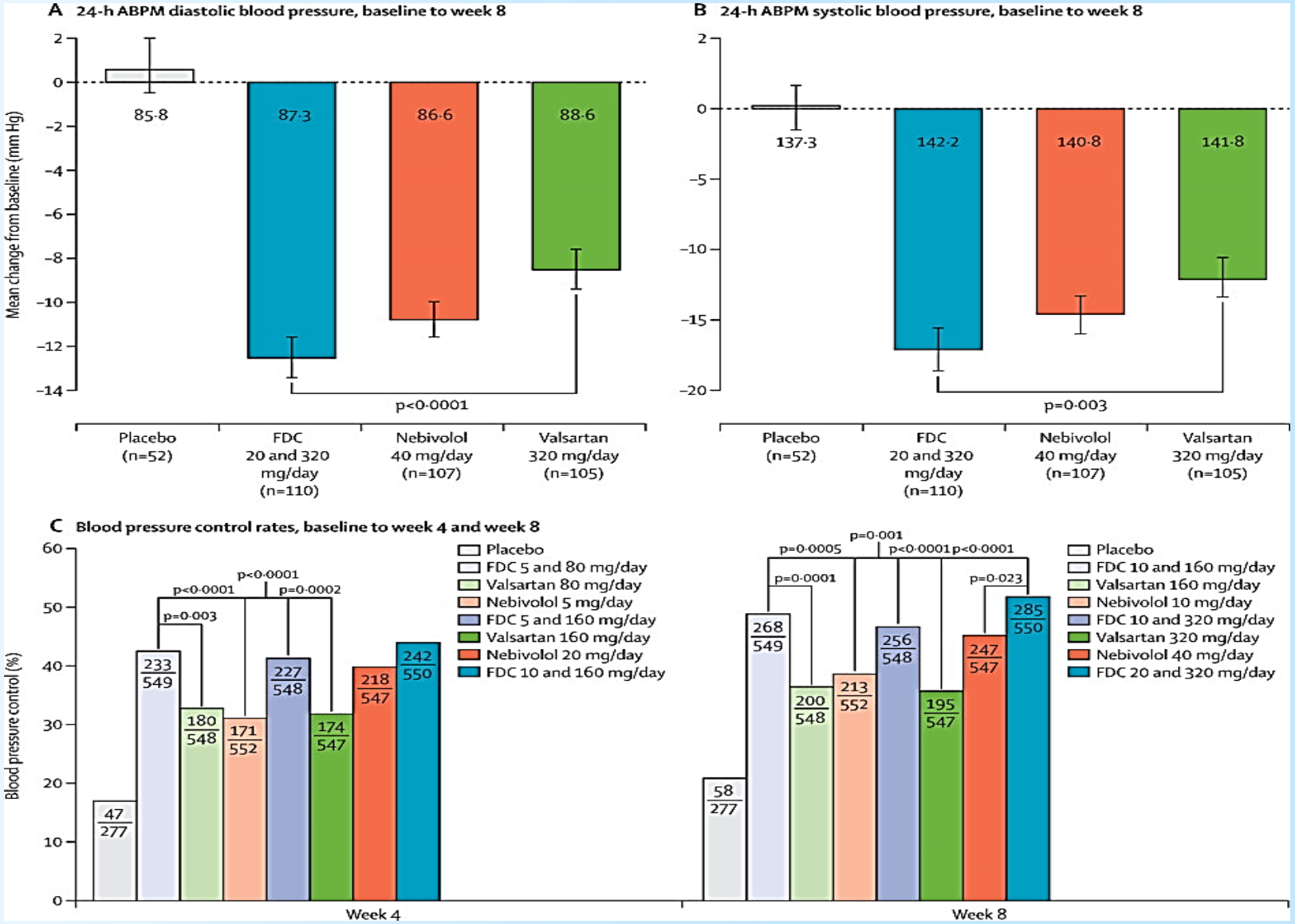


All patients had a doubling of their doses at 8 weeks. At 16 weeks, patients on monotherapy advanced to combination treatment.

Brown et.al. Lancet 2011;377:312-320; Lazich, Bakris. Lancet 2011;377;278-279

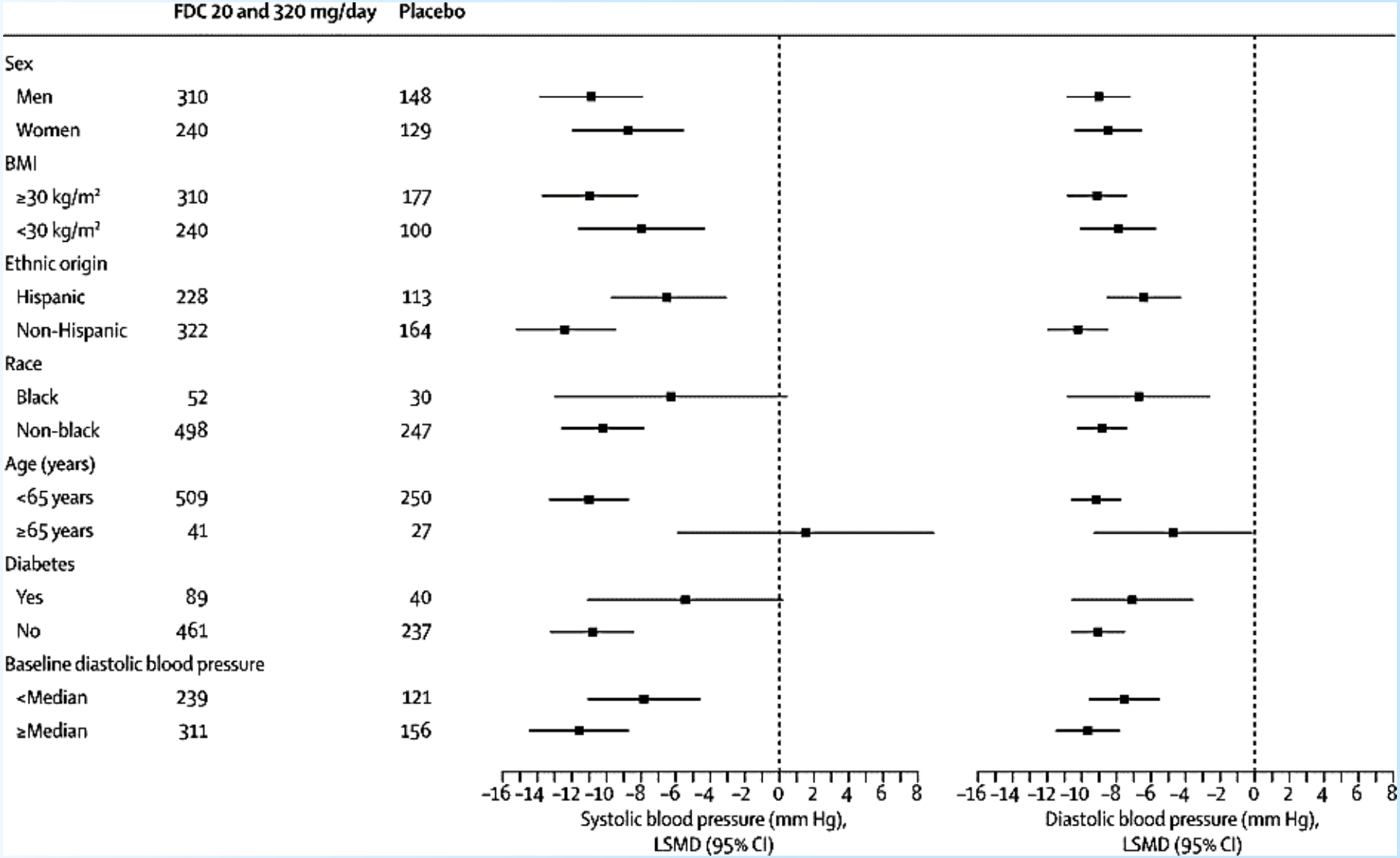
	Placebo (n=277)	Nebivolol and valsartan fixed-dose combination, final dose			Nebivolol, final dose		Valsartan, final dose	
		10 and 160 mg/day (n=555)	10 and 320 mg/day (n=555)	20 and 320 mg/day (n=554)	10 mg/day (n=555)	40 mg/day (n=554)	160 mg/day (n=555)	320 mg/day (n=554)
Age (years)	51·1 (10·4)	50·9 (10·1)	51·6 (9·8)	50·8 (9·7)	51·7 (10·2)	51·5 (10·8)	51·7 (9·9)	51·1 (10·7)
Sex								
Men	148 (53%)	300 (54%)	315 (57%)	313 (56%)	307 (55%)	297 (54%)	333 (60%)	295 (53%)
Women	129 (47%)	255 (46%)	240 (43%)	241 (44%)	248 (45%)	257 (46%)	222 (40%)	259 (47%)
Race								
White	231 (83%)	464 (84%)	475 (86%)	474 (86%)	452 (81%)	471 (85%)	481 (87%)	475 (86%)
Black	30 (11%)	56 (10%)	56 (10%)	52 (9%)	69 (12%)	54 (10%)	43 (8%)	51 (9%)
Other	16 (6%)	35 (6%)	24 (4%)	28 (5%)	34 (6%)	29 (5%)	31 (6%)	28 (5%)
Ethnic origin								
Hispanic	113 (41%)	252 (45%)	239 (43%)	231 (42%)	206 (37%)	220 (40%)	207 (37%)	216 (39%)
Non-Hispanic	164 (59%)	303 (55%)	316 (57%)	323 (58%)	349 (63%)	334 (60%)	348 (63%)	338 (61%)
Weight (kg)	93·6 (20·6)	91·1 (20·4)	92·2 (20·0)	92·2 (20·8)	92·4 (21·2)	91·3 (21·2)	92·3 (20·8)	92·1 (20·8)
Body-mass index (kg/m^2)	32·6 (6·0)	31·9 (6·3)	32·0 (6·0)	32·0 (6·5)	32·1 (6·3)	32·0 (6·3)	31·8 (6·0)	32·0 (6·0)
Type 2 diabetes	40 (14%)	81 (15%)	88 (16%)	89 (16%)	82 (15%)	86 (16%)	84 (15%)	88 (16%)
Previously diagnosed with hypertension	264 (95%)	532 (96%)	524 (94%)	522 (94%)	533 (96%)	532 (96%)	526 (95%)	535 (97%)
Antihypertensive treatment before enrolment*	212/264 (80%)	429/532 (81%)	420/524 (80%)	402/522 (77%)	408/533 (77%)	432/532 (81%)	420/526 (80%)	427/535 (80%)
Trough seated SBP (mm Hg)†	155·4 (11·2)	154·6 (11·8)	155·4 (11·1)	154·6 (11·5)	155·1 (11·8)	155·1 (11·6)	155·8 (12·1)	155·1 (11·7)
Trough seated DBP (mm Hg)†	99·8 (3·5)	99·6 (3·5)	99·6 (3·5)	99·9 (3·7)	99·9 (3·5)	99·8 (3·6)	99·8 (3·8)	99·7 (3·6)
Trough seated pulse ratio (beats per min)†	78·0 (10·7)	77·8 (11·0)	77·3 (10·7)	78·2 (10·8)	77·0 (10·7)	77·6 (10·8)	77·5 (10·7)	77·1 (11·4)
Participation in the ABPM substudy	52 (19%)	108 (19%)	109 (20%)	110 (20%)	106 (19%)	109 (20%)	104 (19%)	107 (19%)

Giles et.al. The Lancet 2014;383:1888-1898



Giles et.al. The Lancet 2014;383:1888-1898

Antihypertensive Effects of Fixed-dose Combination 20 and 320 mg/day (placebo-subtracted values) by Subgroup



Giles et.al. The Lancet 2014;383:1888-1898

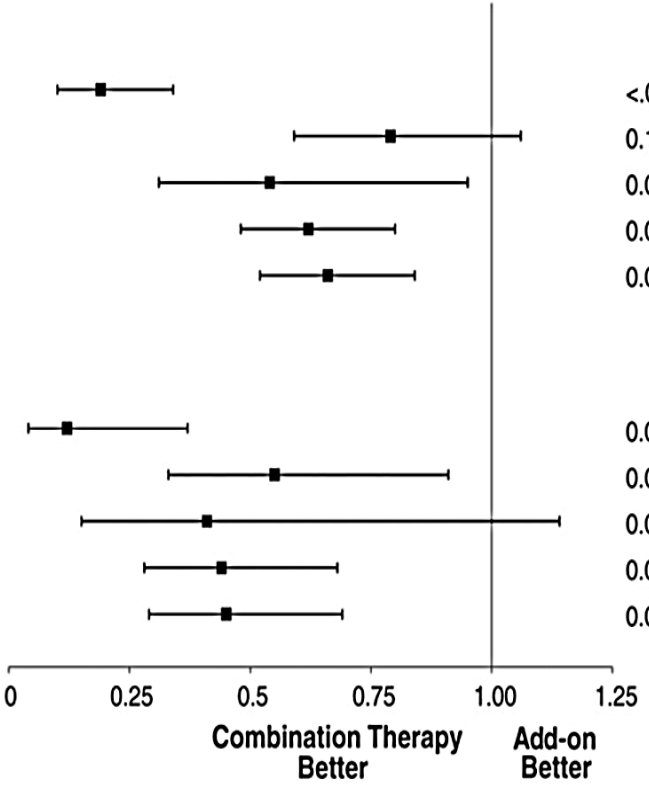
Baseline Characteristics of the Matched Cohorts

Characteristics	Combination Therapy (n=1762)	Add-On (n=1762)	P Value*
Treatment patterns			
Follow-up, d, mean±SD	982±526	1100±450	<0.0001
Time to switch, d, mean±SD [median]		521±388 [412]	
Demographics†			
Age, mean±SD	60.7±13.8	60.4±13.5	0.5587
Women, n (%)	975 (55.3)	1019 (57.8)	0.1239
White, n (%)	1720 (97.6)	1707 (96.9)	0.1823
Comorbidities‡			
Anemia, n (%)	90 (5.1)	91 (5.2)	0.9394
Chronic kidney disease, n (%)	161 (9.1)	177 (10.0)	0.3540
Diabetes mellitus, n (%)	564 (32.0)	544 (30.9)	0.4103
Gastroesophageal reflux disease, n (%)	224 (12.7)	220 (12.5)	0.8403
Hyperlipidemia (high cholesterol), n (%)	766 (43.5)	788 (44.7)	0.4326
Blood pressure, mm Hg‡			
Systolic value, mean±SD	150.5±14.7	150.3±14.3	0.5591
Diastolic value, mean±SD	84.3±10.5	84.5±10.5	0.6592
n (%)‡			
Smoking			
Yes	145 (8.2)	159 (9.0)	0.4011
Obese: ≥30	613 (34.8)	613 (34.8)	1.0000
Overweight: 25-29	236 (13.4)	238 (13.5)	0.9213
eGFR, mL/min			
Yes: ≥110	372 (21.1)	357 (20.3)	0.5265
Elevated LDL or low HDL			
Yes	216 (12.3)	231 (13.1)	0.4398

Gradman et.al. Hypertension 2013;61:309

Incidence Rates and Incidence Rate Ratios of Cardiovascular (CV) Events

	Incidence Rate* (Combination Therapy vs. Add-on)	IRR (95% CI)†	*P*-Value†
All Patients			
(1762 Patients in Each Cohort)			
Acute Myocardial Infarction	0.45 vs. 0.99	0.19 (0.10 - 0.34)	<.0001
Stroke/TIA	2.57 vs. 2.84	0.79 (0.59 - 1.06)	0.1172
Hospitalization for Heart Failure	0.55 vs. 0.78	0.54 (0.31 - 0.95)	0.0311
Overall	3.34 vs. 4.10	0.62 (0.48 - 0.80)	0.0002
Overall (With Death)	3.58 vs. 4.28	0.66 (0.52 - 0.84)	0.0008
Excluding Patients with Diabetes or CKD			
(803 Patients in Each Cohort)			
Acute Myocardial Infarction	0.24 vs. 0.68	0.12 (0.04 - 0.37)	0.0002
Stroke/TIA	1.89 vs. 2.58	0.55 (0.33 - 0.91)	0.0200
Hospitalization for Heart Failure	0.34 vs. 0.63	0.41 (0.15 - 1.14)	0.0875
Overall	2.39 vs. 3.55	0.44 (0.28 - 0.68)	0.0002
Overall (With Death)	2.49 vs. 3.68	0.45 (0.29 - 0.69)	0.0002



IRR=incidence rate ratio; CI=confidence interval; TIA=transient ischemic attack; CKD=chronic kidney disease.

* Number of patients with an event per 100 person-year.

† Statistical differences between exposure groups, as well as CIs, were calculated using conditional Poisson regressions adjusting for matched pairs.

Gradman et al. Hypertension. 2013;61:309-318

American Society of Hypertension Evidence-Based Fixed Dose Antihypertensive Combinations

Preferred
• ACE inhibitor/diuretic*
• ARB/diuretic*
• ACE inhibitor/CCB*
• ARB/CCB*
Acceptable
• Beta blocker/diuretic*
• CCB (dihydropyridine)/β-blocker
• CCB/diuretic
• Renin inhibitor/diuretic*
• Renin inhibitor/ARB*
• Thiazide diuretics/K+ sparing diuretics*
Less Effective
• ACE inhibitor/ARB
• ACE inhibitor/β-blocker
• ARB/β-blocker
• CCB (nondihydropyridine)/β-blocker
• Centrally acting agent/β-blocker

Gradman et.al. J Am Soc Hypertens 2010;4:42-50

* Single-pill combination available in US

Summary/Conclusions

- Single pill combinations clearly show that BP goal can be achieved earlier than with monotherapy
- Single pill combinations are consistently associated with a better patient medication adherence
- Combinations of a RAS blocker with either a thiazide-like diuretic or calcium antagonist are preferred as an initial therapy because of CV outcome data from trials

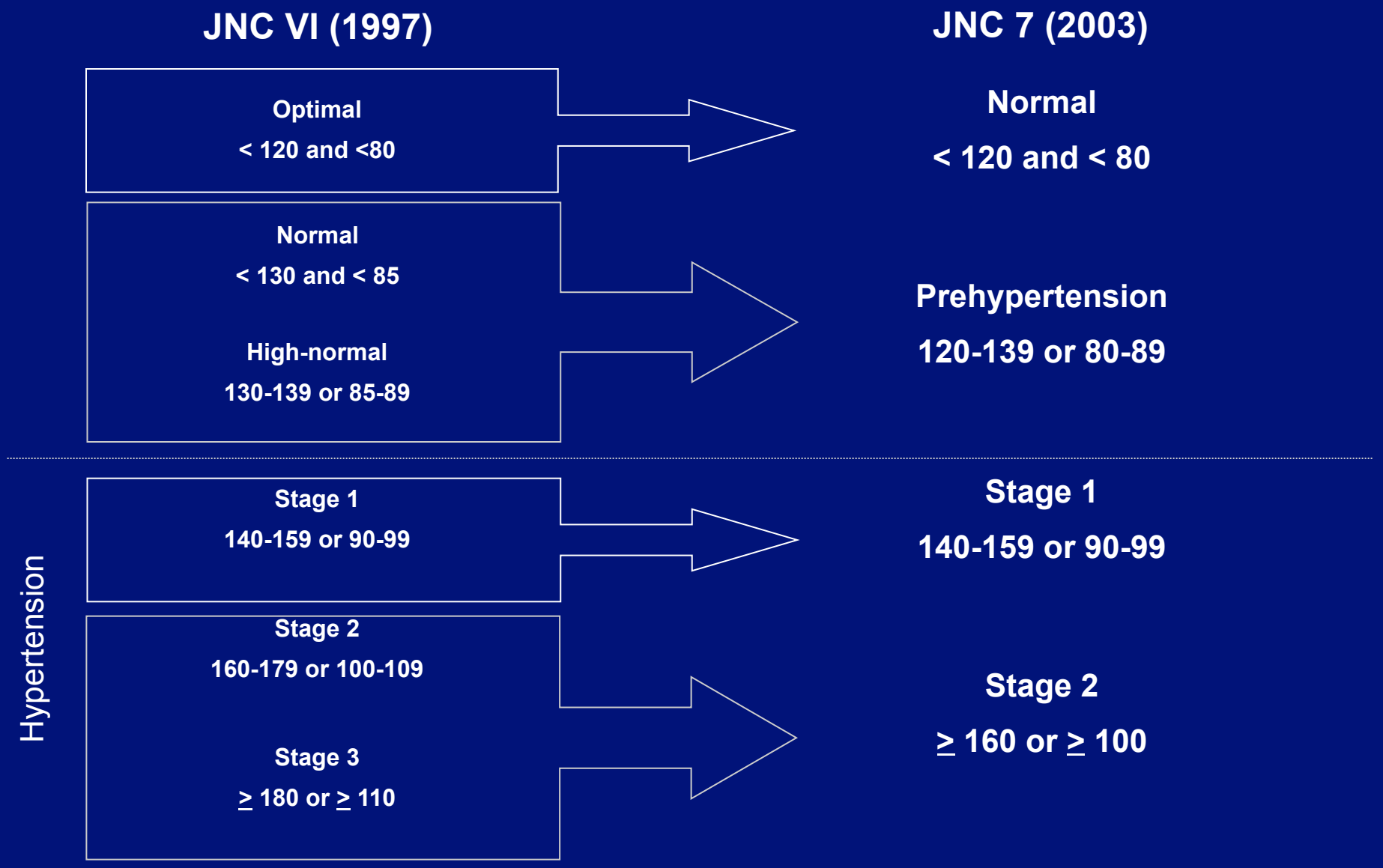
Complex Cases in Hypertension: Optimizing Antihypertensive Therapy in Difficult-to-Treat Patients

Thomas D. Giles, MD
Clinical Professor of Medicine
Heart and Vascular Institute
Tulane University School of Medicine
New Orleans, Louisiana

Some Current Issues

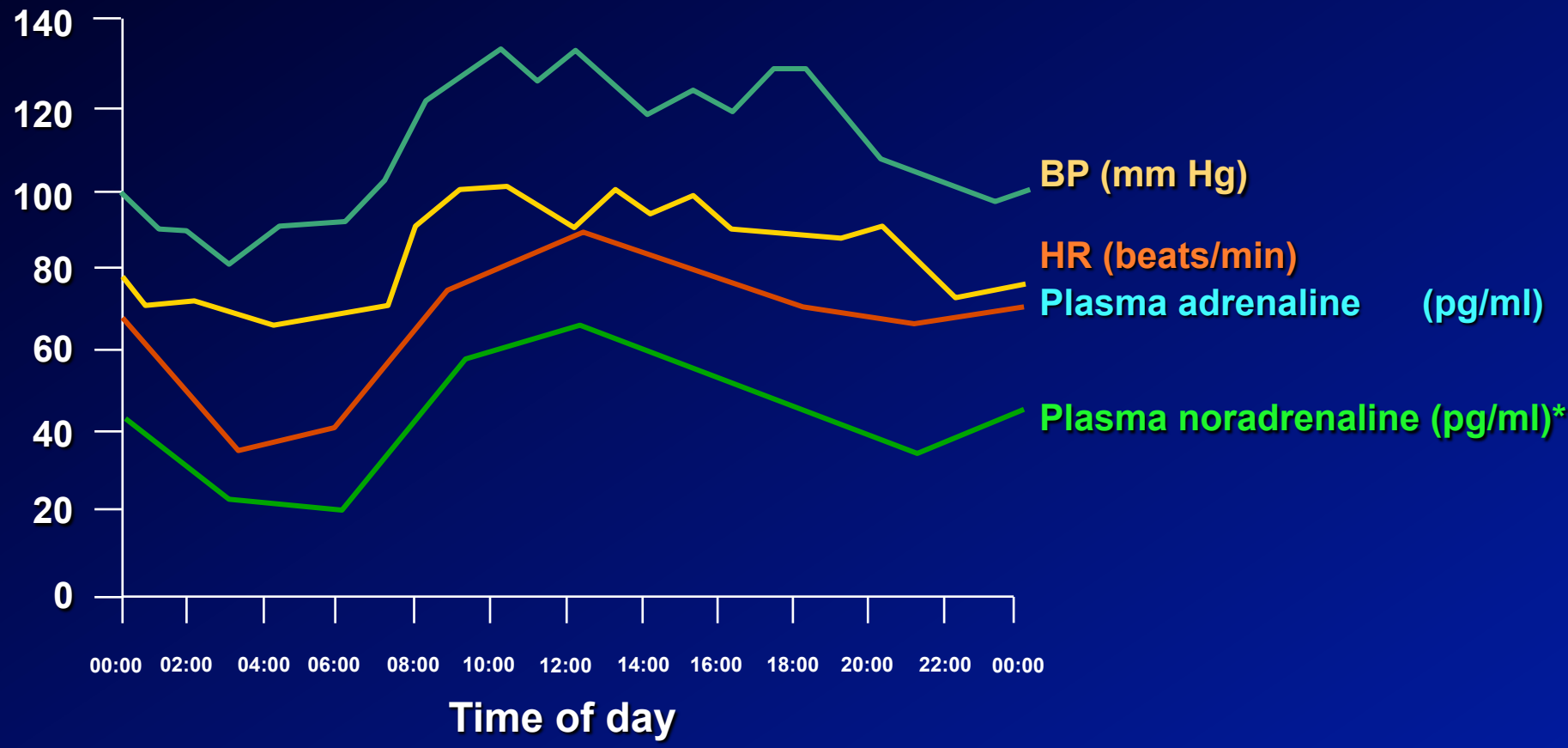
- Pre-hypertension
- Ambulatory blood pressure monitoring
- Resistant hypertension inventory

JNC 7 Re-Classification of SBP/DBP



JNC VI. Arch Intern Med. 1997;157:2413-2446. JNC 7. JAMA. 2003; 289:2560-2572.

Circadian Variation in Haemodynamics and Catecholamine Levels



* Noradrenaline levels have been reduced by 3.5 times for uniformity of scaling

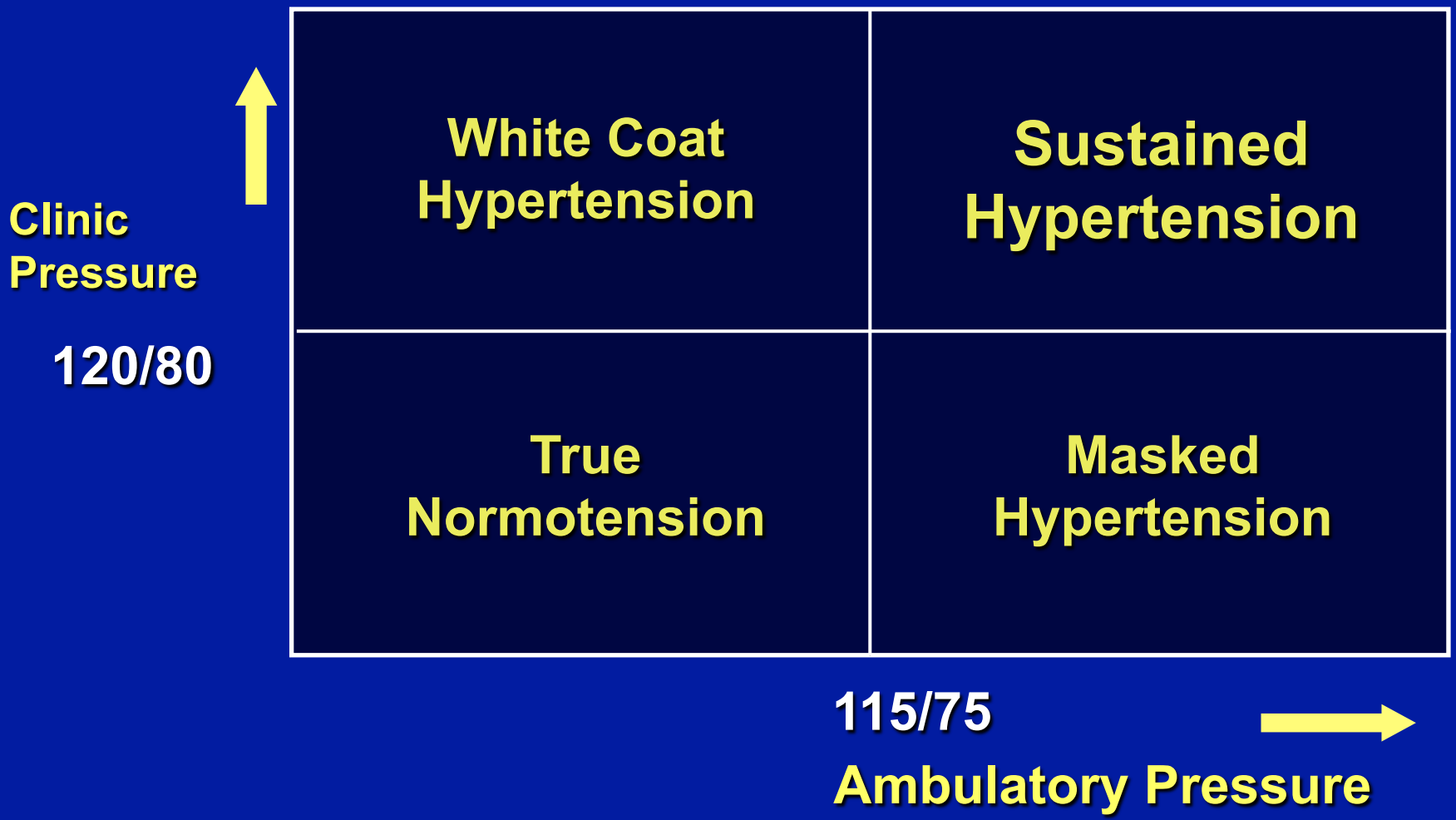
Mulcahy. Blood Pressure Monitoring 1996;1(Suppl 1):S13–6.

Blood Pressure Thresholds (mmHg) for Definition of Hypertension with Different Types of Measurement

	SBP	DBP
Office or Clinic	140	90
24-hour	125-130	80
Day	130-135	85
Night	120	70
Home	130-135	85

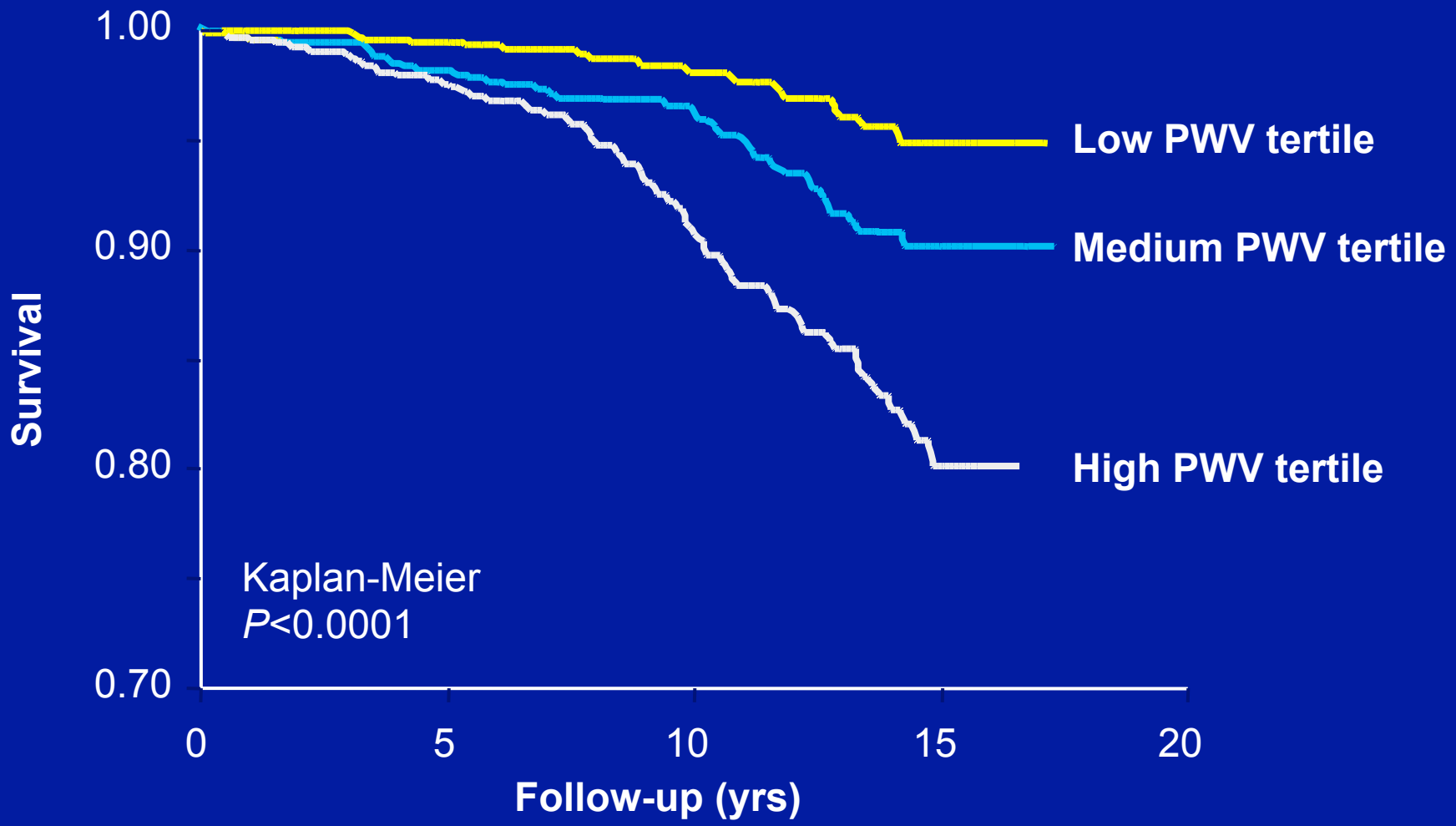
Mancia et al. J Hypertension. 2007;25:1105-87.

Clinic BP versus ABP ?



ABP=ambulatory blood pressure

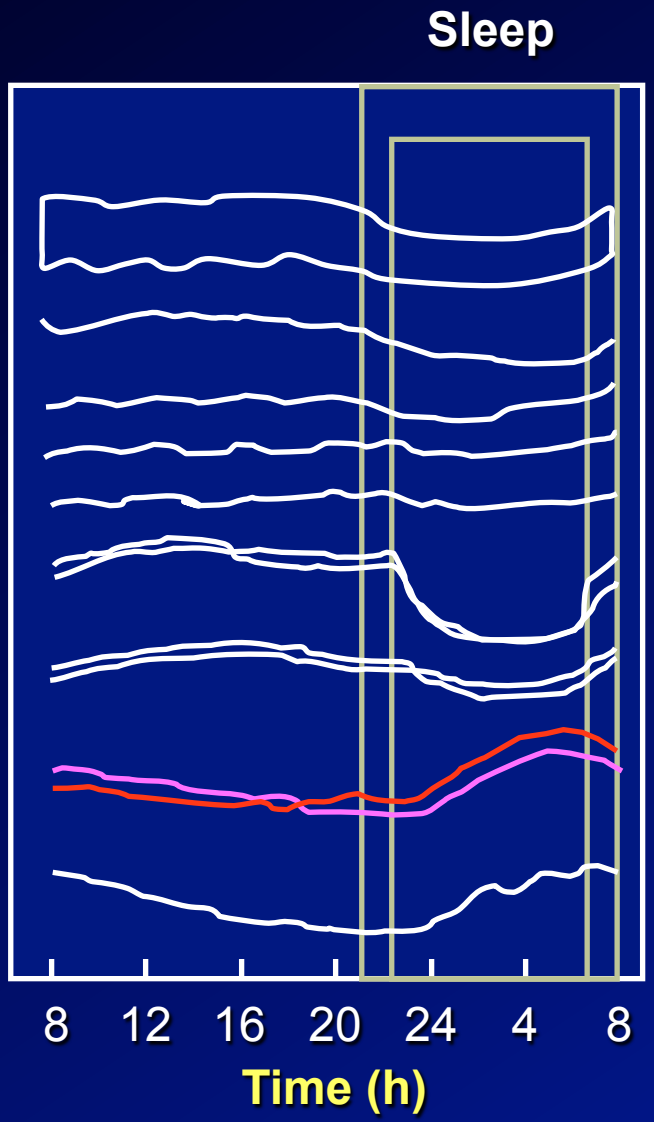
PWV and All-Cause Mortality



PWV=pulse wave velocity

Laurent et al. Hypertension. 2001.

Circadian Variation of Haemodynamics, Electrolytes and Neurohormones



BP -15%

HR -10%

TPR -10%

CO -5%

GFR -5%

Hemodynamic

Na, Cl | -67%

K, HCO_3 | -50%

Electrolyte excretion

PRA, PA | +200%

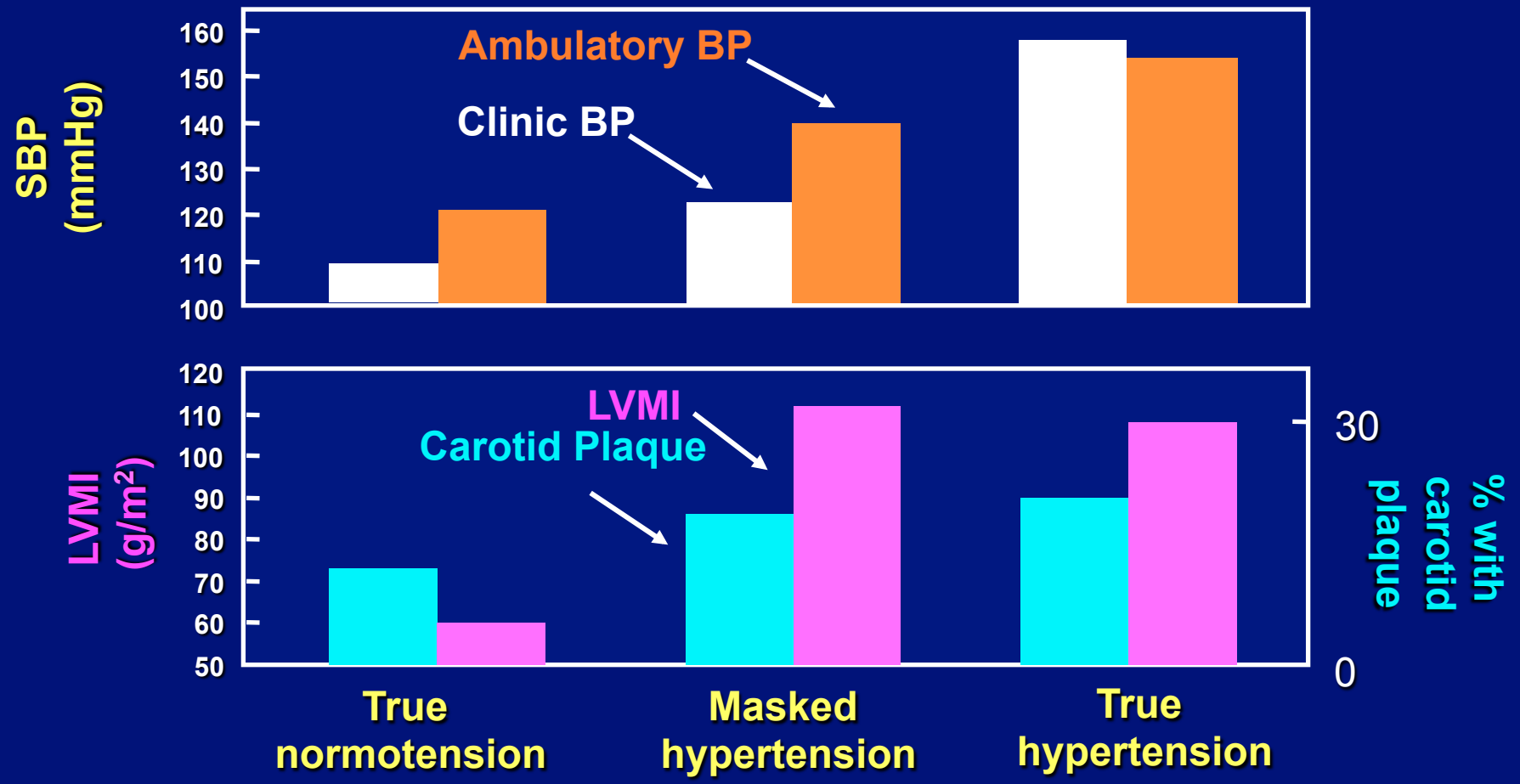
Cortisol +100%

Hormonal

PRA=plasma renin activity

PA=plasma aldosterone

Masked Hypertension (White-coat Normotension) Is Associated with Higher LV Mass and More Carotid Plaque



Liu et al. Ann Intern Med 1999;131:564–72.

Conclusions

- 24-hour blood pressure measurement gives the best prediction of cardiovascular risk
- Patients with white-coat hypertension are at relatively low risk
- 24-hour blood pressure measurement gives the best correlation with the effects of drug treatment on target organ damage

Take-Home Messages

- 10% to 20% of patients diagnosed as having hypertension do not have it!
- 20% to 30% of patients diagnosed as having "resistant" hypertension have a persistent "white coat effect"
- Many patients who do not improve with antihypertensive therapy have "masked hypertension"

Resistant Hypertension Inventory

- Improper BP measurement
- Poor compliance to medications
- Identifiable (secondary) causes
  - Medication-related
  - Renal
  - Renovascular
  - Endocrine
  - Sleep apnea
  - Other
  - Lifestyle

Taler. Curr Hypertens Rep. 2005;7:323-29.

Medications that Can Interfere with Blood Pressure Control

- Non-Narcotic Analgesics
- Non-steroidal anti-inflammatory agents including aspirin
- Selective COX-2 inhibitors
- Sympathomimetic agents (decongestants, diet pills, cocaine)
- Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil)
- Alcohol
- Oral contraceptives
- Cyclosporine
- Erythropoietin
- Natural licorice
- Herbal compounds (ephedra or ma huang)

Secondary Causes of Resistant Hypertension

Common

- Obstructive sleep apnea
- Renal parenchymal disease
- Primary aldosteronism
- Renal artery stenosis

Uncommon

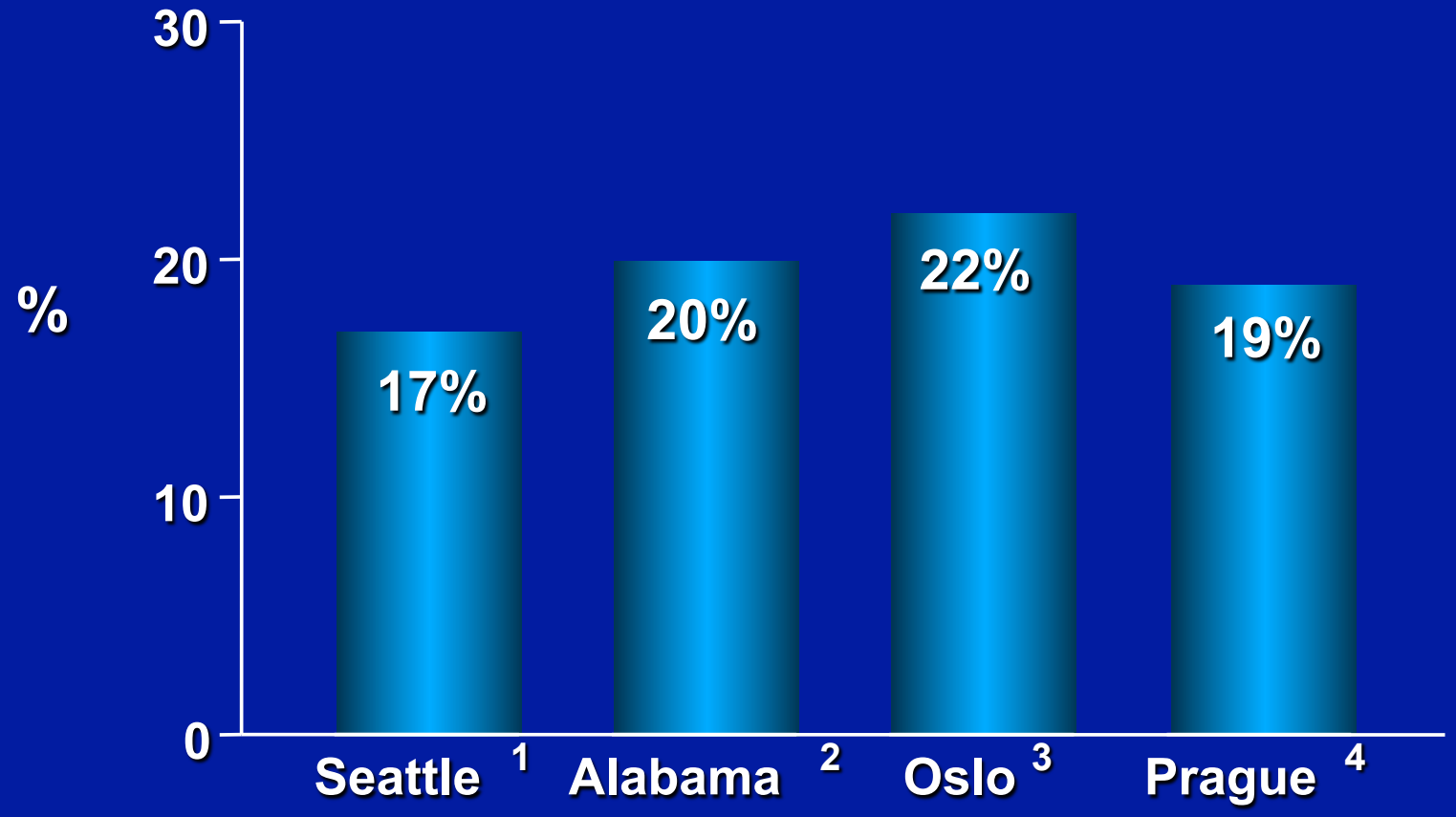
- Pheochromocytoma
- Cushing's disease
- Hyperparathyroidism
- Aortic coarctation
- Intracranial tumor

Obstructive Sleep Apnea (OSA) and RH

- Hypertension is often refractory to treatment until OSA is corrected
- All patients with RH should undergo inquiry about sleep apnea and/or be referred for a sleep study
- OSA contributes to sympathetic hyperactivity seen in obese patients
- OSA correlates with ↑aldosterone…

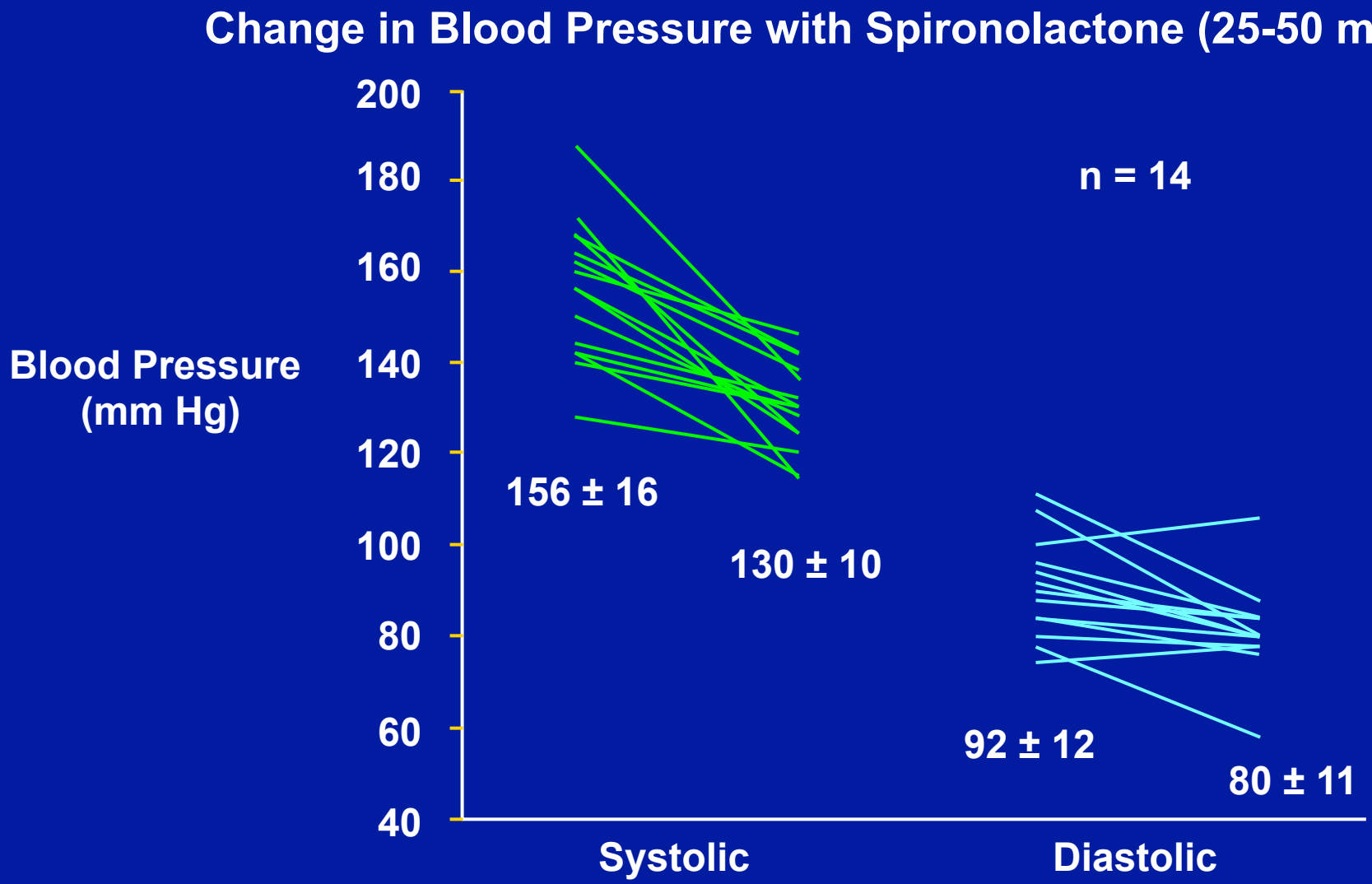
Calhoun et al. Chest. 2004; 125:112–17.
Vidt. Minerva Med. 2003;94:201-14.

Prevalence of Primary Aldosteronism in Patients with Resistant Hypertension



Am J Kid Dis. 2002.
Calhoun et al. Hypertension. 2002;40:892-96;
Eide et al. J Hypertension. 2004;22:2217-26.
Strauch et al. J Human Hypertens. 2003;17:349-52.

Efficacy of Add-On Aldosterone Blockade in Black and White Subjects with Resistant Hypertension



Calhoun et al. Hypertension. 2002;40:892-96.

Difficult-to-Treat Hypertension

- Ambulatory blood pressure monitoring
- Resistant hypertension
- Pathogenesis of hypertension