Combination Antihypertensive Therapy: When to use it Diabetes

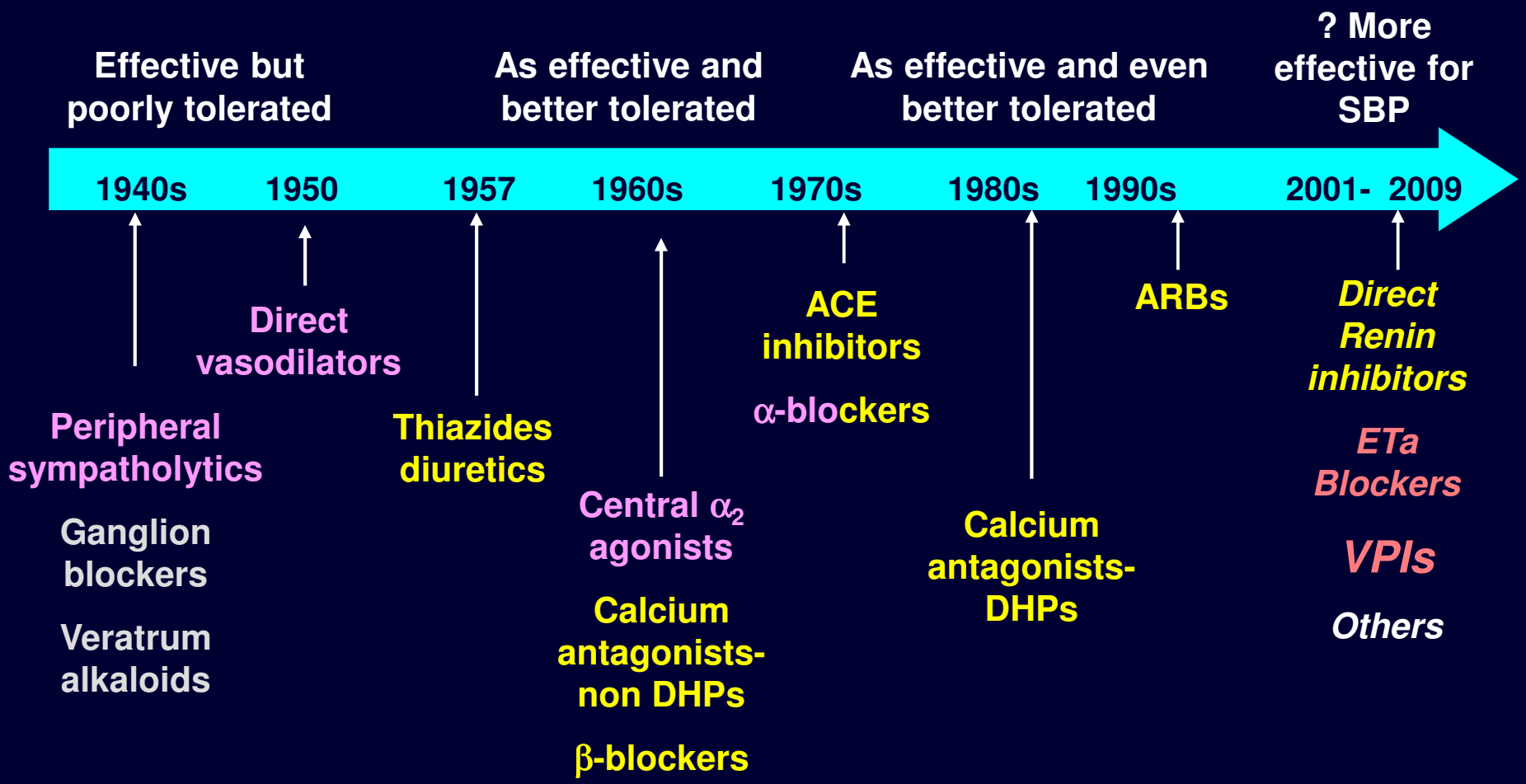
George L. Bakris, MD, F.A.S.N., F.A.S.H.

Professor of Medicine

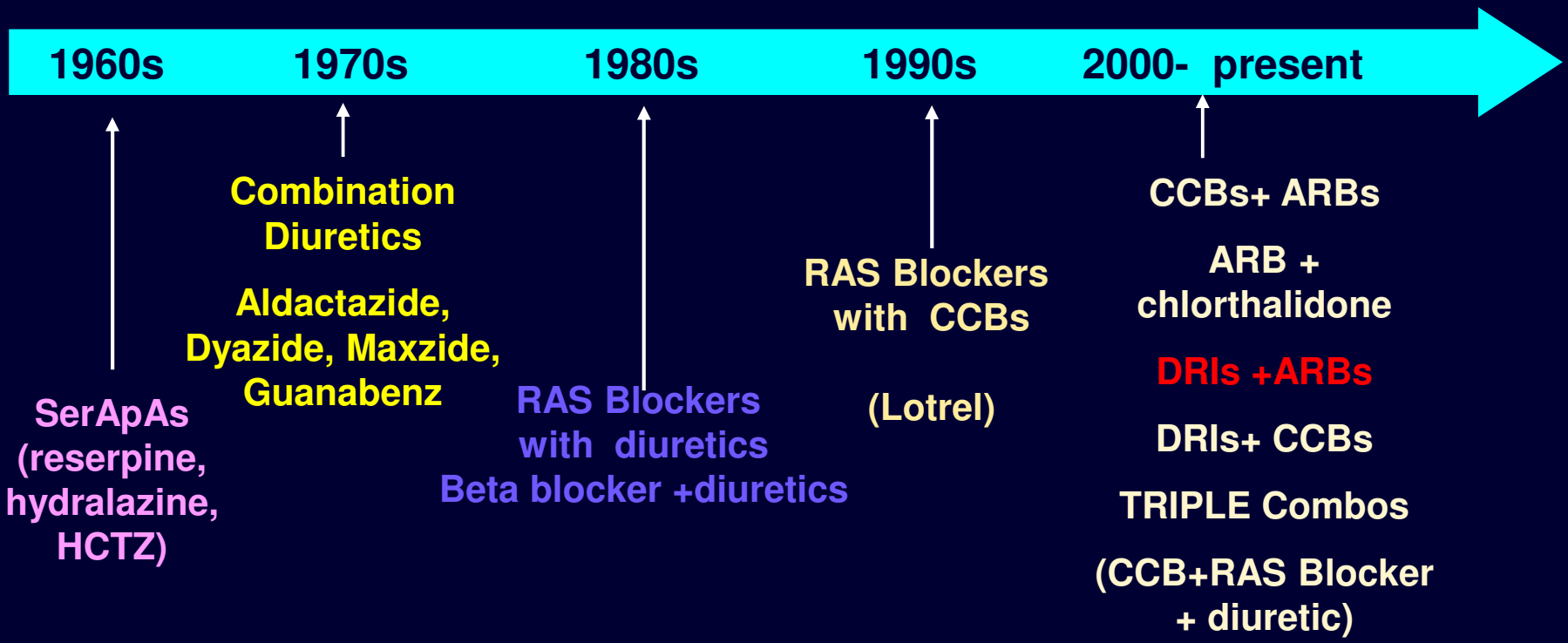
Director, ASH Comprehensive Hypertension Center

The University of Chicago Medicine

Development of Antihypertensive Therapies



Evolution of Fixed Dose Combination Antihypertensive Therapies



Rationale for Fixed-Dose 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, or <130/80 mm Hg for patients with diabetes or chronic renal disease)[4-6]

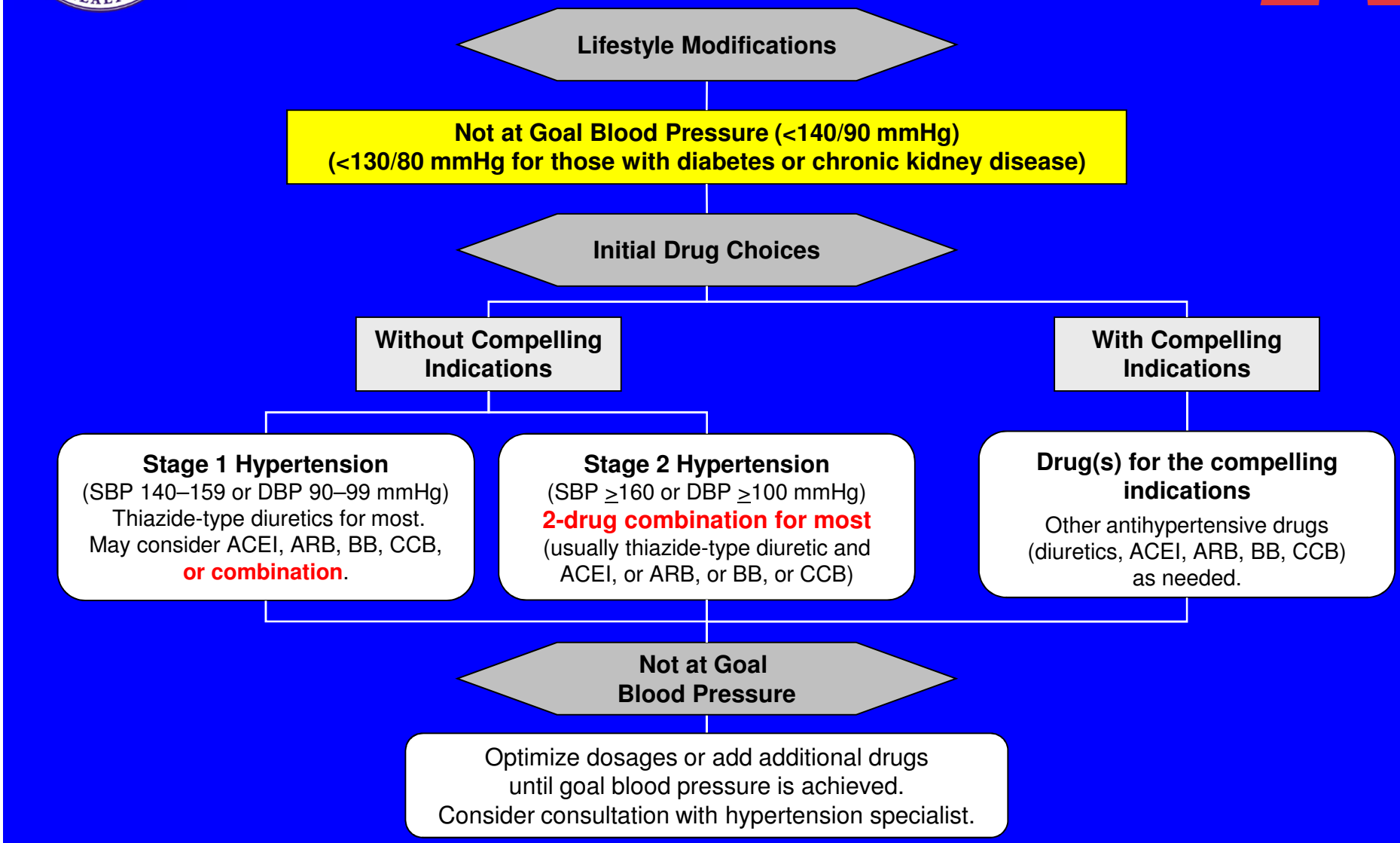
BP = blood pressure

1. Materson BJ et al. *J Hum Hypertens.* 1995;9(10):791-796.
2. Messerli FH. *J Hum Hypertens.* 1992;6 Suppl. 2:S19-S21.
3. Ram CV. *J Clin Hypertens (Greenwich).* 2004;6(10):569-577.
4. Chobanian AV, et al. *JAMA.* 2003;289(19):2560-2572.
5. Guidelines Committee. *J Hypertens.* 2003;21:1011-1053.
6. American Diabetes Association. *Diabetes Care.* 2002;25(Suppl.1):S71-S73.

Key Messages From JNC7

- Thiazide-type diuretics should be initial drug therapy for most, either alone or combined with other drug classes.
- Certain high-risk conditions are compelling indications for other drug classes.
- **Most patients will require two or more antihypertensive drugs to achieve goal BP. (most ≈ 76%)**
- **If BP is >20/10 mmHg above goal, initiate therapy with two agents, one usually should be a thiazide-type diuretic.**

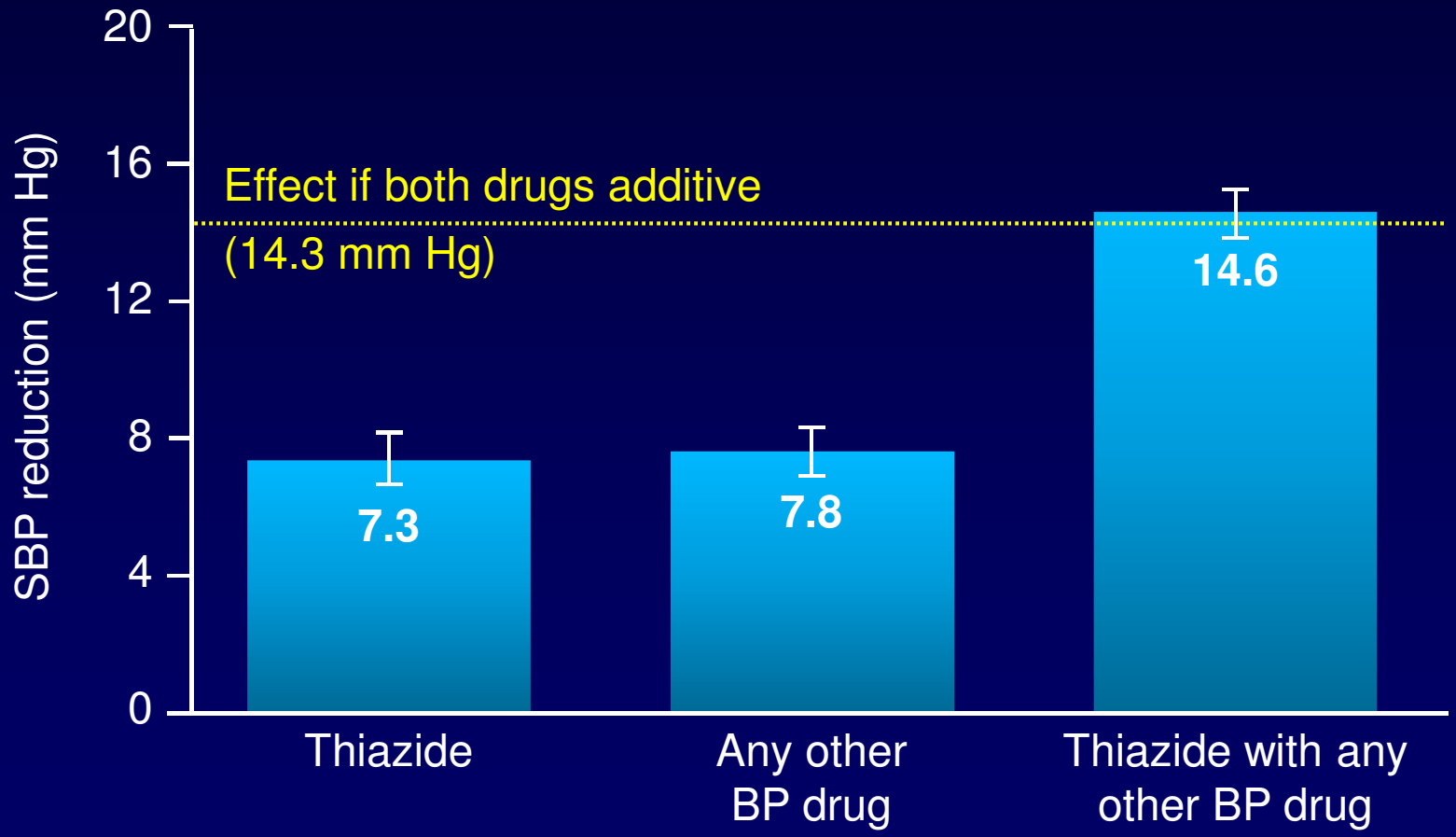
Algorithm for Treatment of Hypertension



2007 ESH-ESC Hypertension Guidelines: MONOTHERAPY VERSUS COMBINATION THERAPY

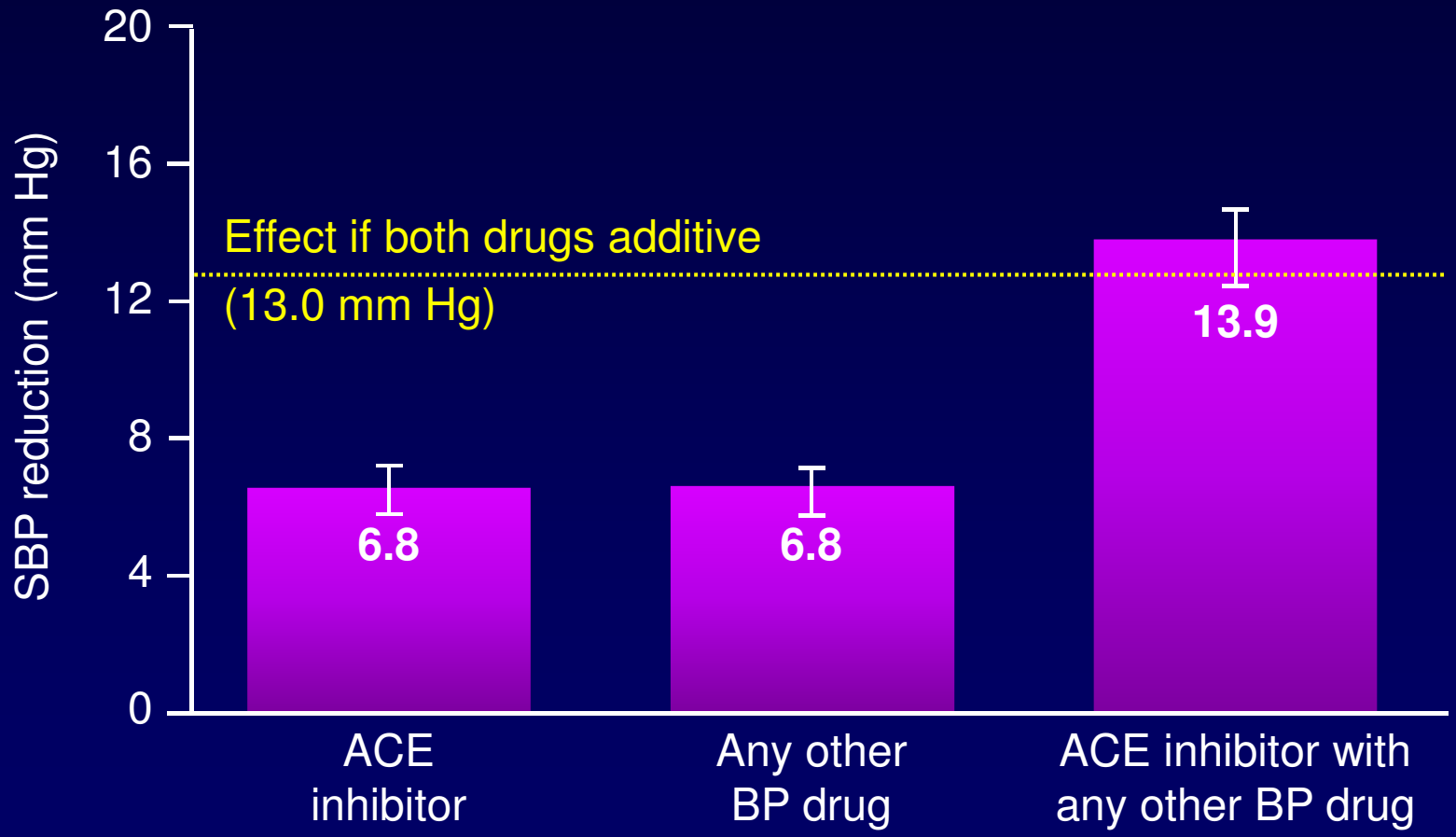
- Regardless of the drug employed, monotherapy allows to achieve BP target in only a limited number of hypertensive patients.
- Initial treatment can make use of monotherapy or combination of two drugs at low doses with a subsequent increase in drug doses or number, if needed.
- Fixed combinations of two drugs can simplify treatment schedule and favour improved adherence.

Mean Placebo-Subtracted SBP Reduction From a Meta-Analysis of 42 Randomized Trials of Combination vs Monotherapy



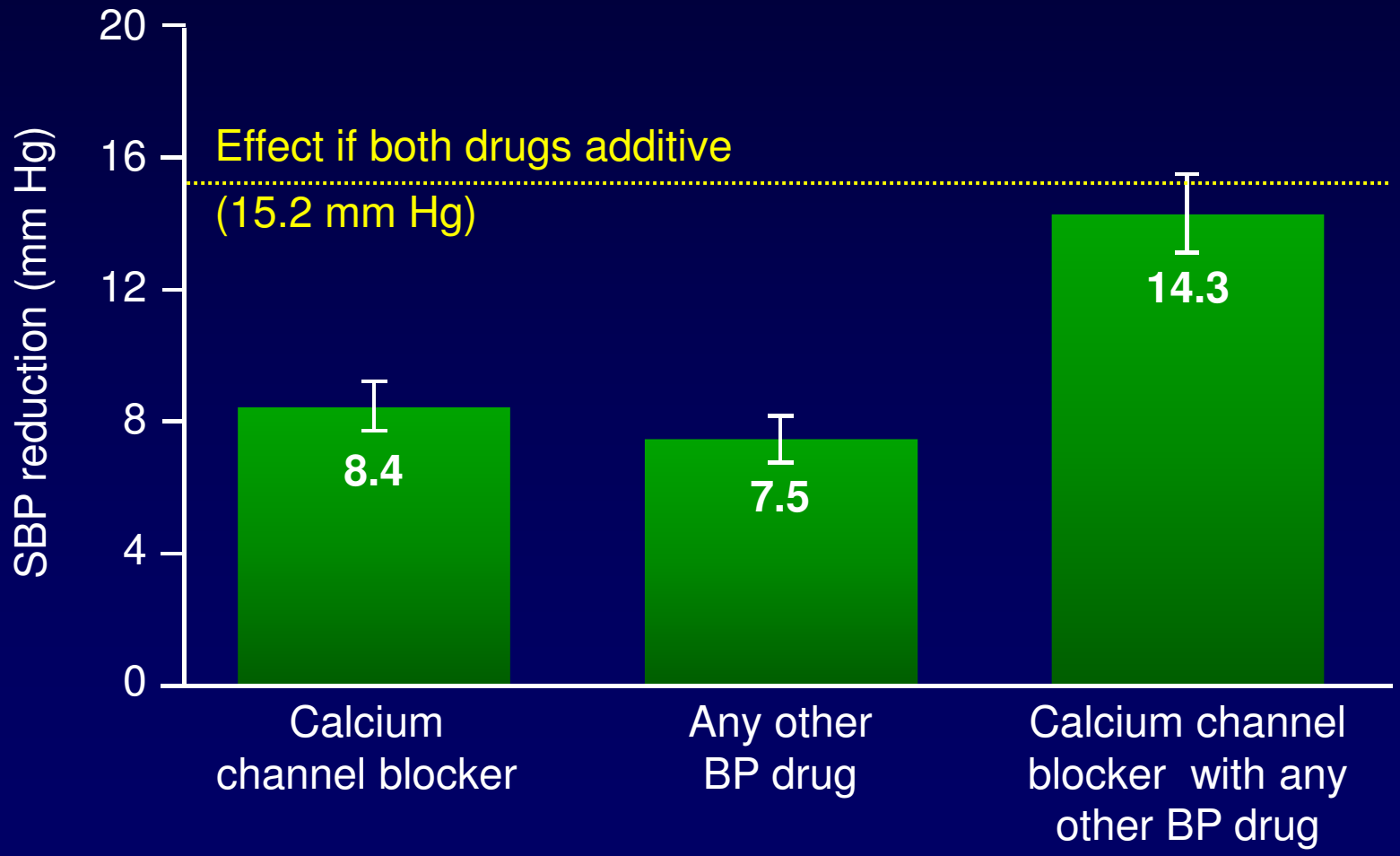
Wald DS et al. *Am J Med.* 2009;122:290-300.

Mean Placebo-Subtracted SBP Reduction From a Meta-Analysis of 42 Randomized Trials of Combination vs Monotherapy



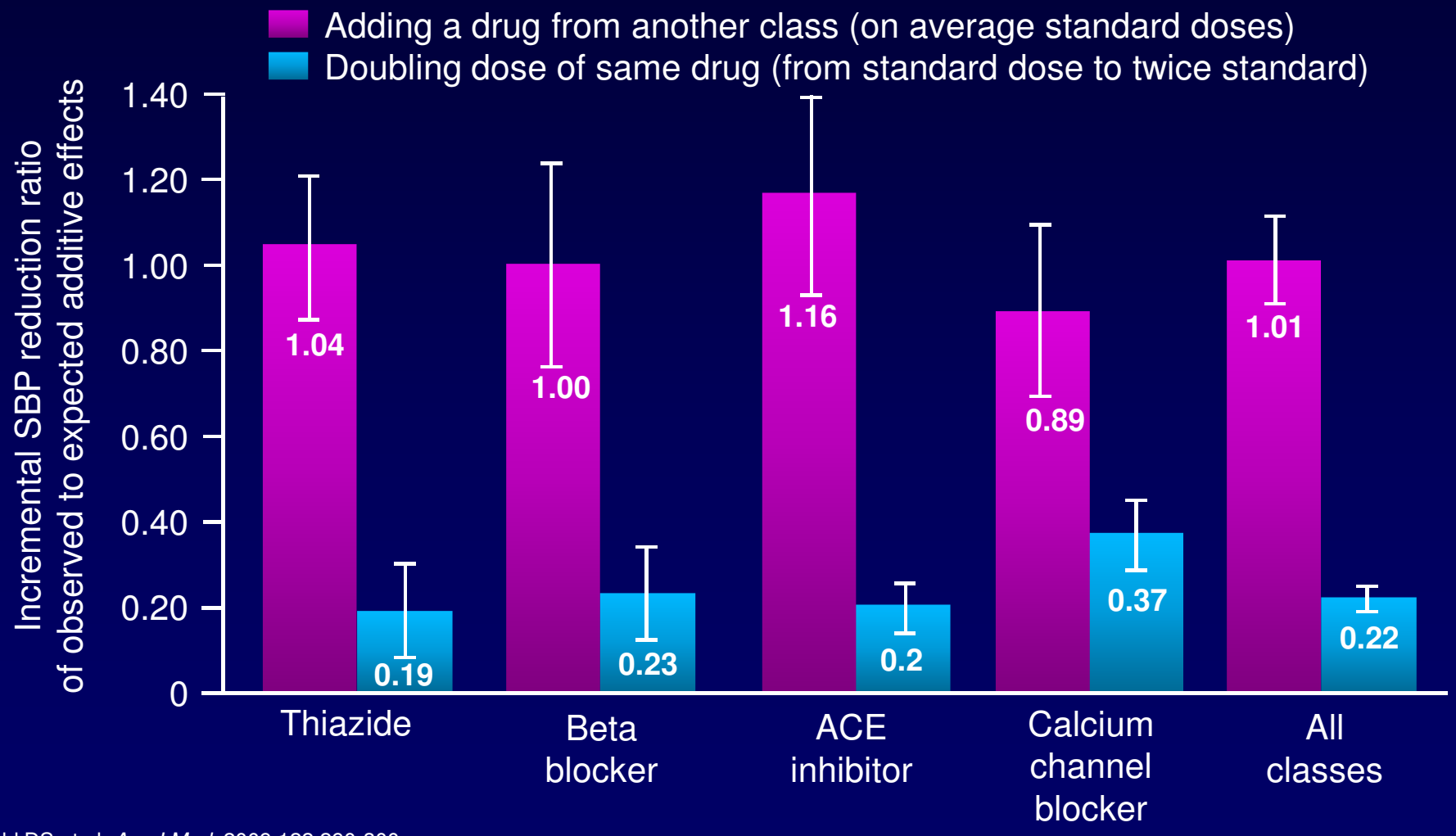
Wald DS et al. *Am J Med.* 2009;122:290-300.

Mean Placebo-Subtracted SBP Reduction From a Meta-Analysis of 42 Randomized Trials of Combination vs Monotherapy



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

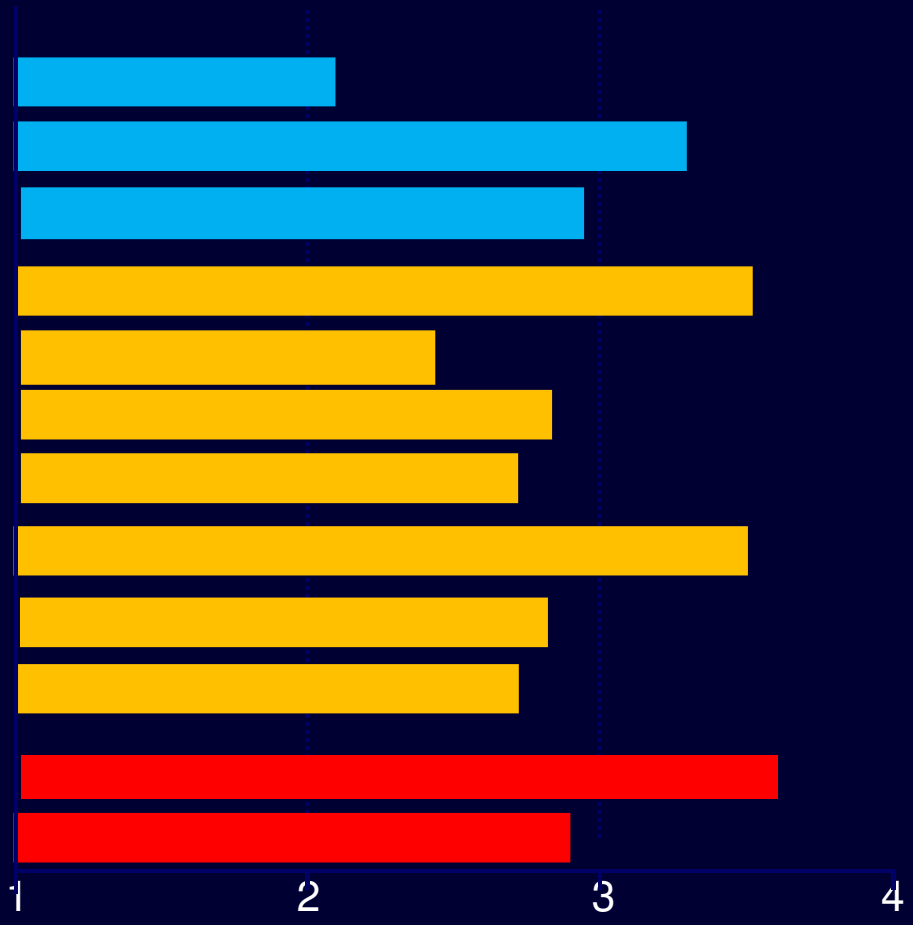
Ratio of Observed to Expected Incremental BP-Lowering Effects of Adding a Drug or Doubling the Dose According to Drug Class



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

Multiple Medications Are Required to Achieve BP Control in Clinical Trials

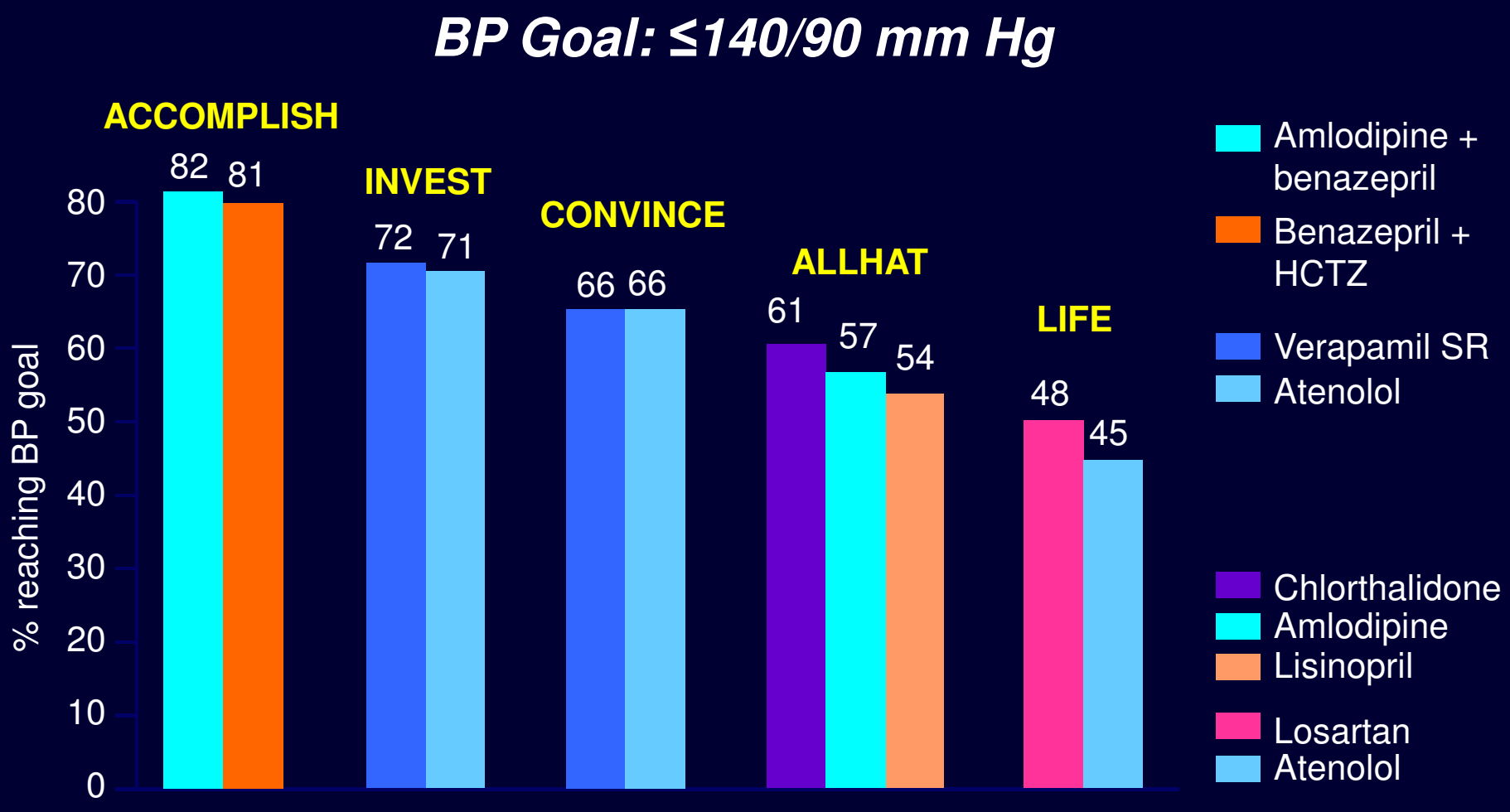
	Trial	SBP achieved (mm Hg)
Hypertension	ALLHAT	138
	HOT	138
	ACCOMPLISH	132
Diabetes	ACCORD (intensive)*	119
	ACCORD (standard)*	133
	INVEST	133
	IDNT	138
	RENAAL	141
	ABCD	132
	UKPDS	144
Kidney disease	MDRD	132
	AASK	128



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 Mar 14. [Epub ahead of print]

Percentage of Patients Who Reached JNC-7 BP Goals



Black HR et al for the CONVINCE Research Group. *JAMA*. 2003;289:2073-2082. Dahlöf B et al for the LIFE Study Group. *Lancet*. 2002;359:995-1003. Jamerson K et al for the ACCOMPLISH Trial Investigators. *Blood Pressure*. 2007:16:80-86. Pepine CJ et al for the INVEST Investigators. *JAMA*. 2003;290:2805-2816. The ALLHAT Officers and Coordinators for the ALLHAT Research Group. *JAMA*. 2002;288:2981-2897.

Combination Therapy Outcome Trials

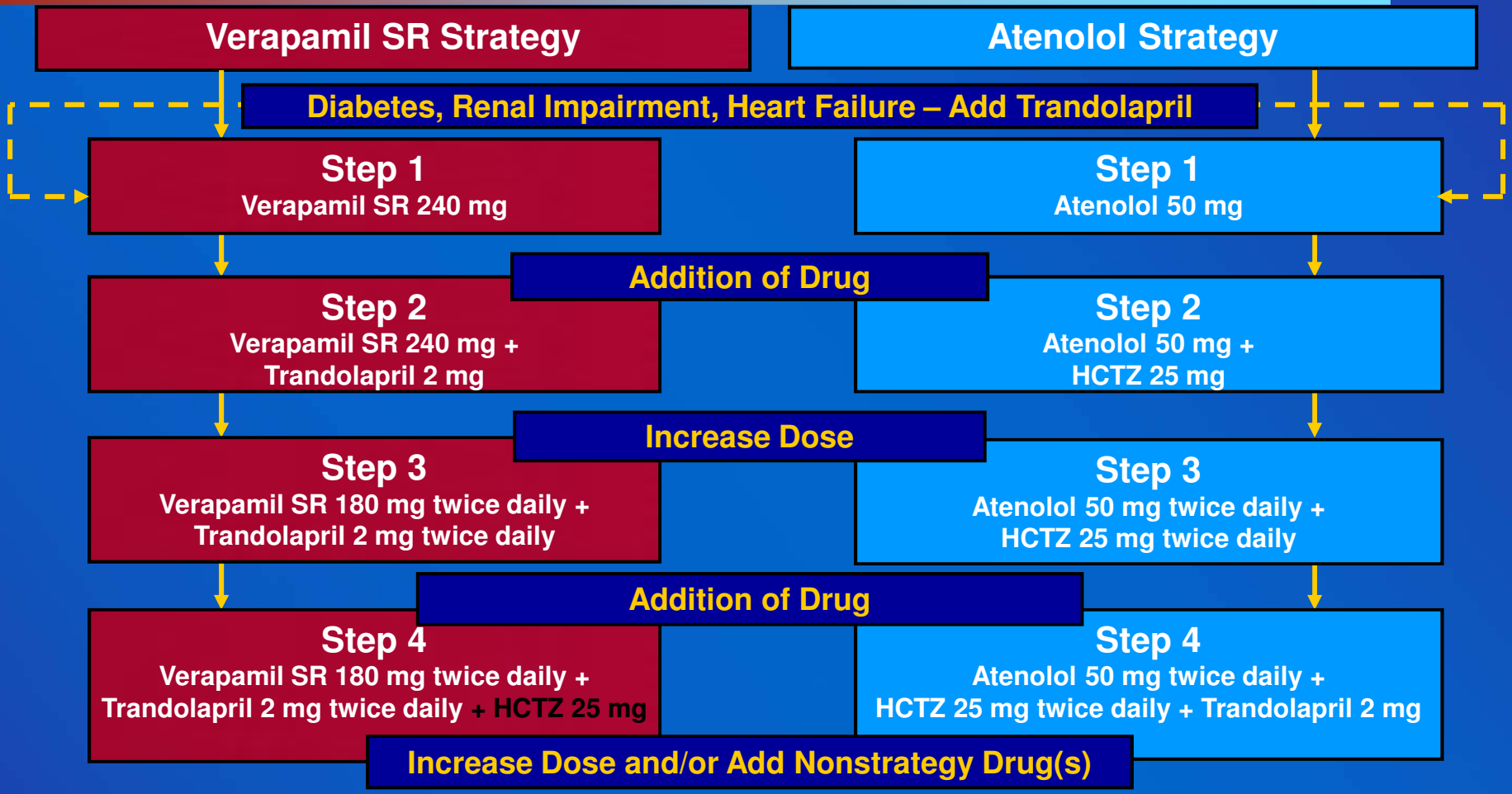
- INVEST
- ASCOT
- ACCOMPLISH (only fixed dose trial)

INVEST Trial Design[1]

- Prospective, Randomized, Open trial with Blinded Endpoint (PROBE) design[2]
- 22,576 patients with coronary artery disease (CAD) and hypertension in 14 countries
- Mean follow-up of 2.7 years (61,835 patient years)
- Hypothesis: risk of adverse outcomes is equivalent in hypertensive CAD patients treated with either a verapamil SR strategy or an atenolol strategy
- JNC VI blood pressure (BP) goals[3]
  - <140/90 mm Hg
  - <130/85 mm Hg for diabetes or renal impairment
- Primary Outcome- First occurrence of all-cause death, nonfatal myocardial infarction (MI), or nonfatal stroke

[1]Pepine, et al. *JAMA*. 2003;290:2805-16.
[2]Hansson, et al. *Blood Press.* 1992;1:113-9.
[3]JNC VI. Arch *Intern Med.* 1997;157:2413-46.

Treatment Strategies



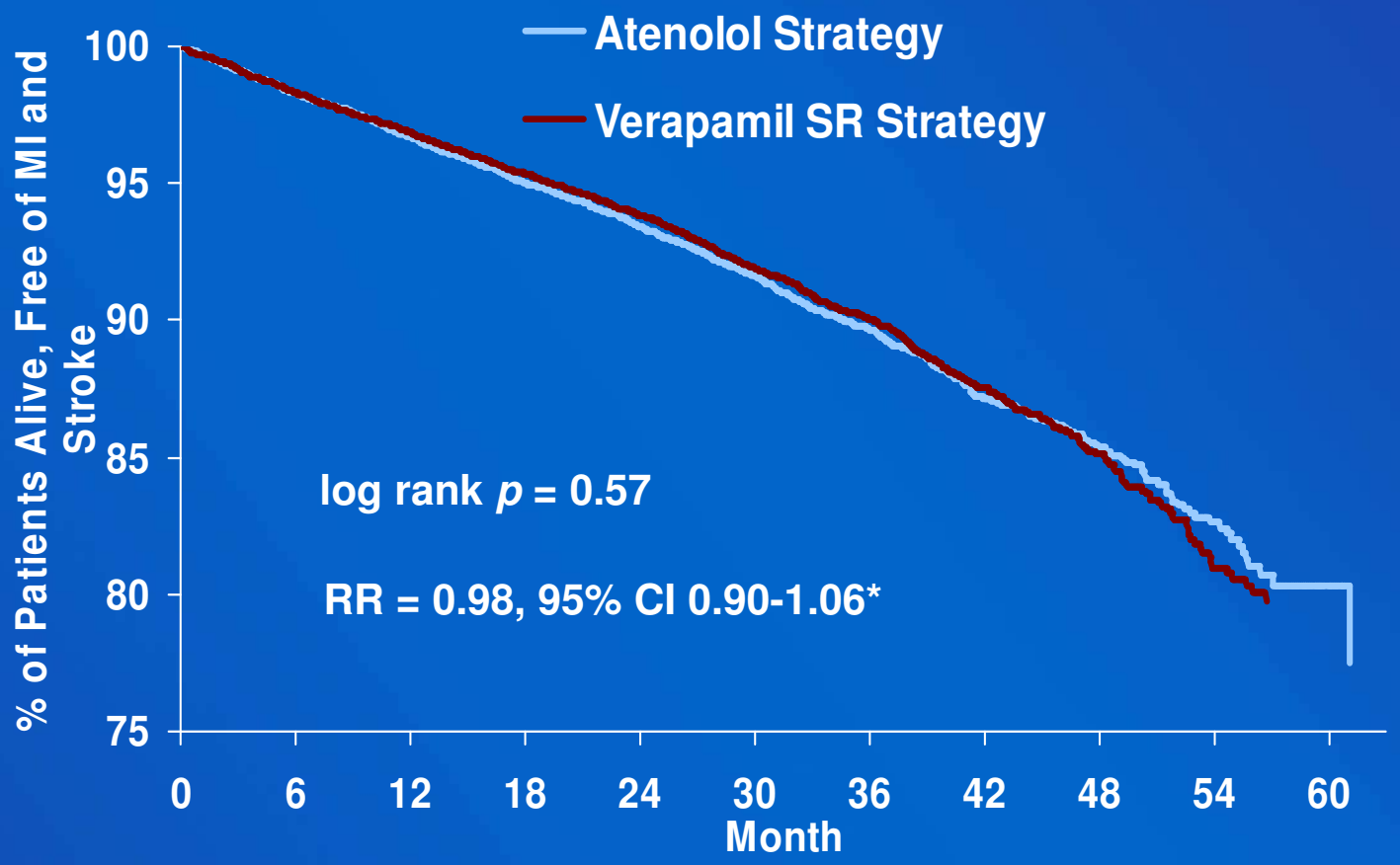
Strategy drugs could be titrated: verapamil SR 120-480 mg/d; trandolapril 0.5-8 mg/d; atenolol 25-200 mg/d; HCTZ 12.5-100 mg/d

INVEST INTERNATIONAL VERAPAMIL SR - TRANDOLAPRIL STUDY

HCTZ = hydrochlorothiazide.

Pepine, et al. *JAMA*. 2003;290:2805-16.

Time to Primary Outcome



*CI for equivalence 0.83-1.20

Total follow-up: 61,835 patient-yrs

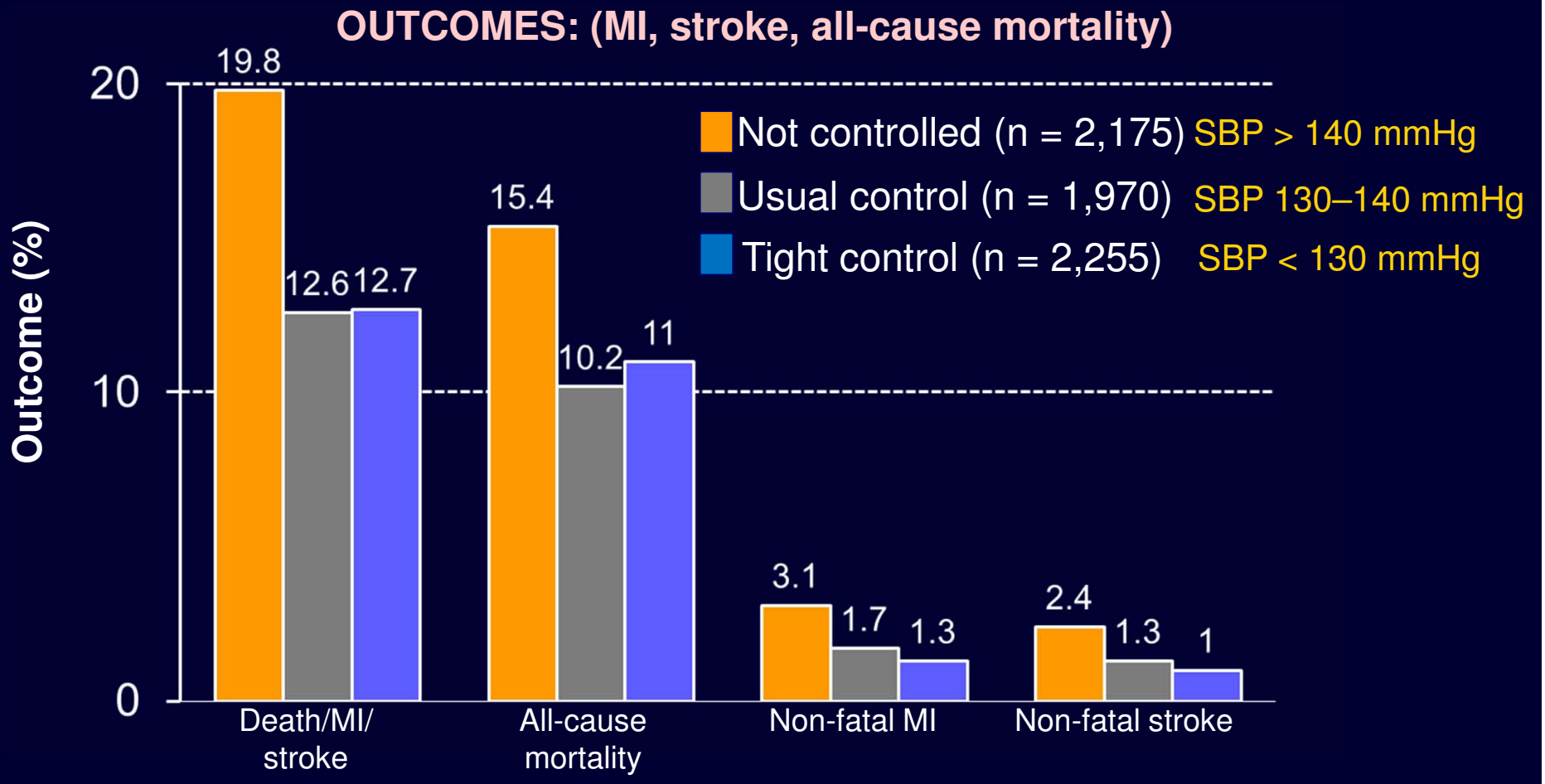
Mean follow-up: 2.7 yrs

Annual event rate: 3.6%

INVEST INTERNATIONAL VERAPAMIL SR - TRANDOLAPRIL STUDY

Pepine, et al. JAMA 2003; 290:2805-2816

CV outcomes from the Diabetes Subgroup of INVEST trial



DeHoff-Cooper R et.al. JAMA 2010;304:61-68.

ASCOT-BPLA: Study design

Design:	Prospective randomised open blinded endpoints (PROBE)
Population:	N = 19,257 with hypertension and ≥3 other CV risk factors
Treatment:	Amlodipine 5–10 mg ± perindopril 4–8 mg prn (n = 9639)
	Atenolol 50–100 mg ± bendroflumethiazide 1.25–2.5 mg/potassium prn (n = 9618)
Primary outcome:	Nonfatal MI (including silent MI) and fatal CHD
Secondary outcome:	All-cause mortality, stroke, nonfatal MI (excluding silent MI), all coronary events, CV events/procedures, CV mortality, fatal/nonfatal HF

ASCOT-BPLA: Treatment algorithm for BP targets

BP medication titrated to achieve target:

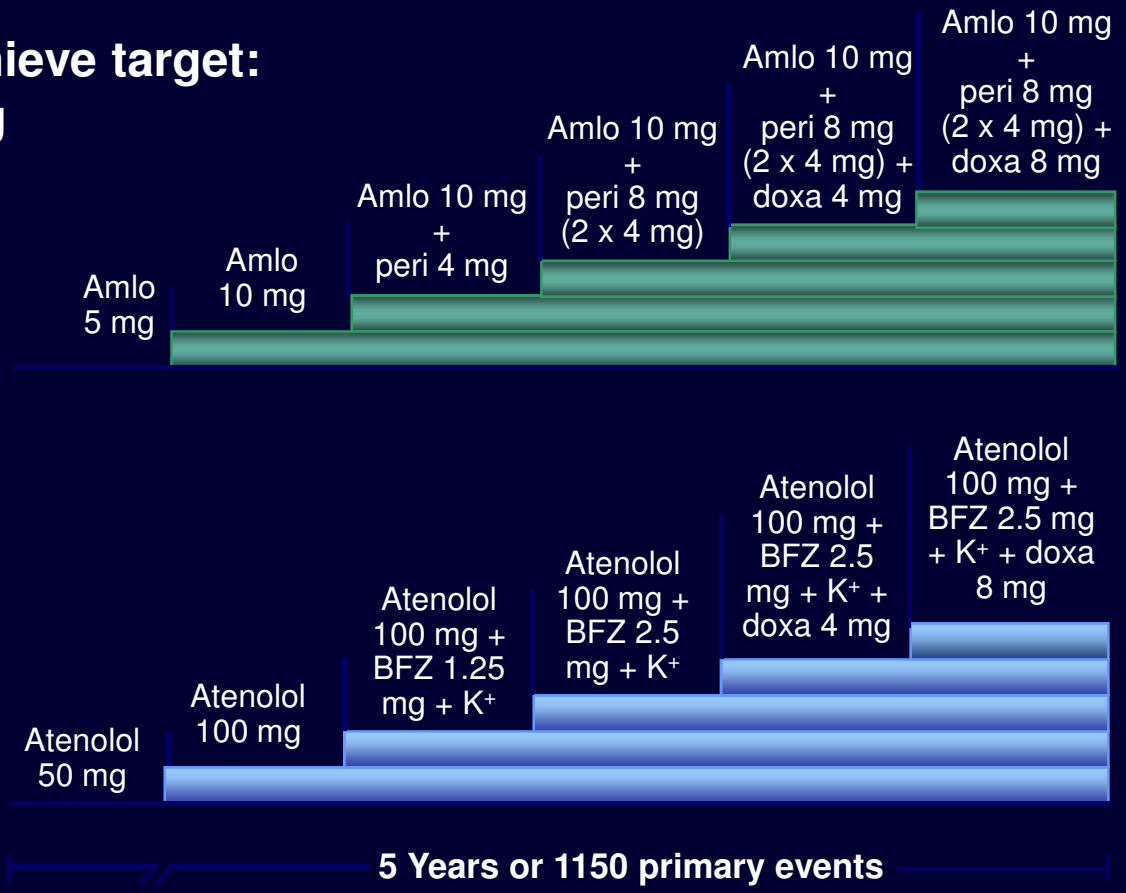
No diabetes: <140/90 mm Hg

Diabetes: <130/80 mm Hg

19,342 patients 40–79 y with
UNTREATED SBP ≥160 mmHg and/or DBP ≥100 mmHg
OR
TREATED SBP ≥140 mmHg and/or DBP ≥90 mmHg

RANDOMIZATION

In each arm, pts with total cholesterol ≤6.5 mmol/L randomized to atorvastatin (10 mg) or placebo daily (n = 10,297)



Amlo = amlodipine; Peri = perindopril; Doxa = doxazosin GITS (Gastrointestinal Transport System); BFZ = bendroflumethiazide

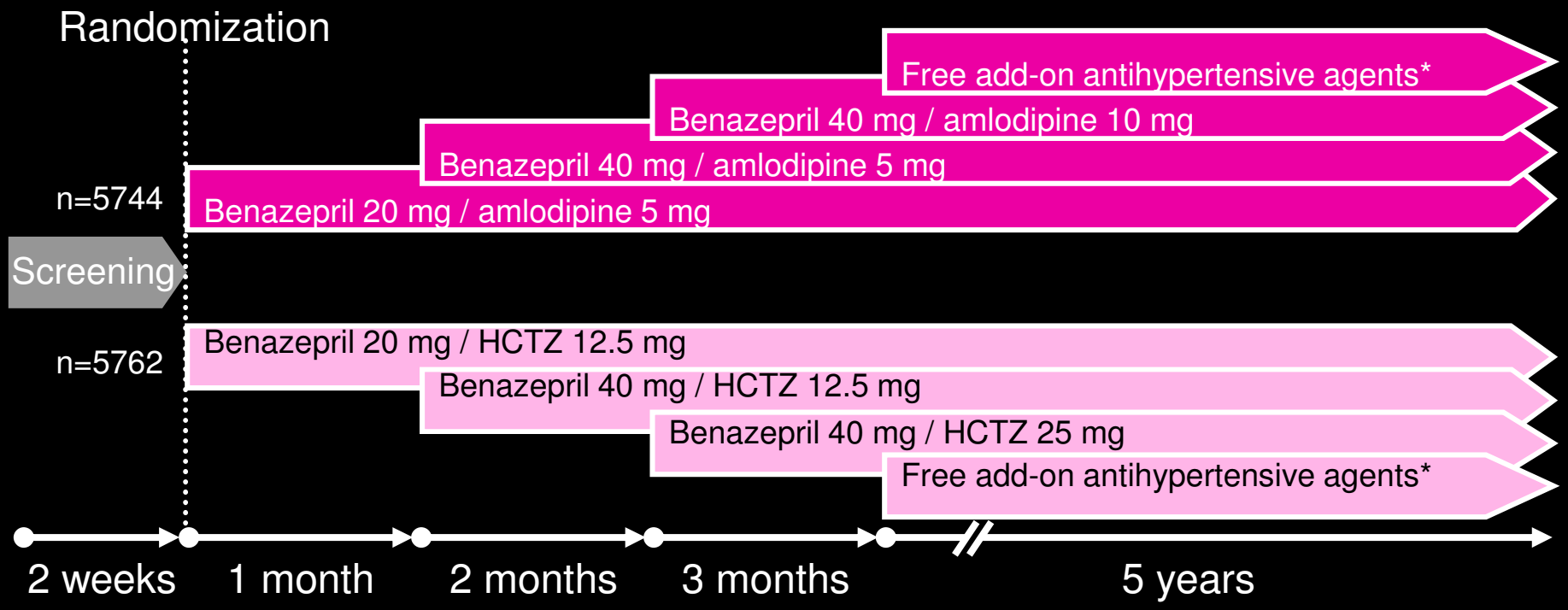
Sever PS et al. *J Hypertens.* 2001;19:1139-47.

ASCOT-BPLA: Overall results

- Study stopped prematurely after 5.5-year median follow-up because of higher death rate in assigned atenolol-based-regimen group
- Group receiving amlodipine-based regimen had nonsignificant 10% reduction in primary outcome (nonfatal MI plus fatal CHD) and significant reductions in nearly all secondary CV endpoints and new-onset diabetes

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

ACCOMPLISH study design



Up-titration performed for patients not achieving a BP of <140/90 mmHg (<130/80 mmHg for patients with diabetes or renal insufficiency)

*β-blockers, α-blockers, clonidine, loop diuretics

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

ACCOMPLISH

Patient baseline demographics

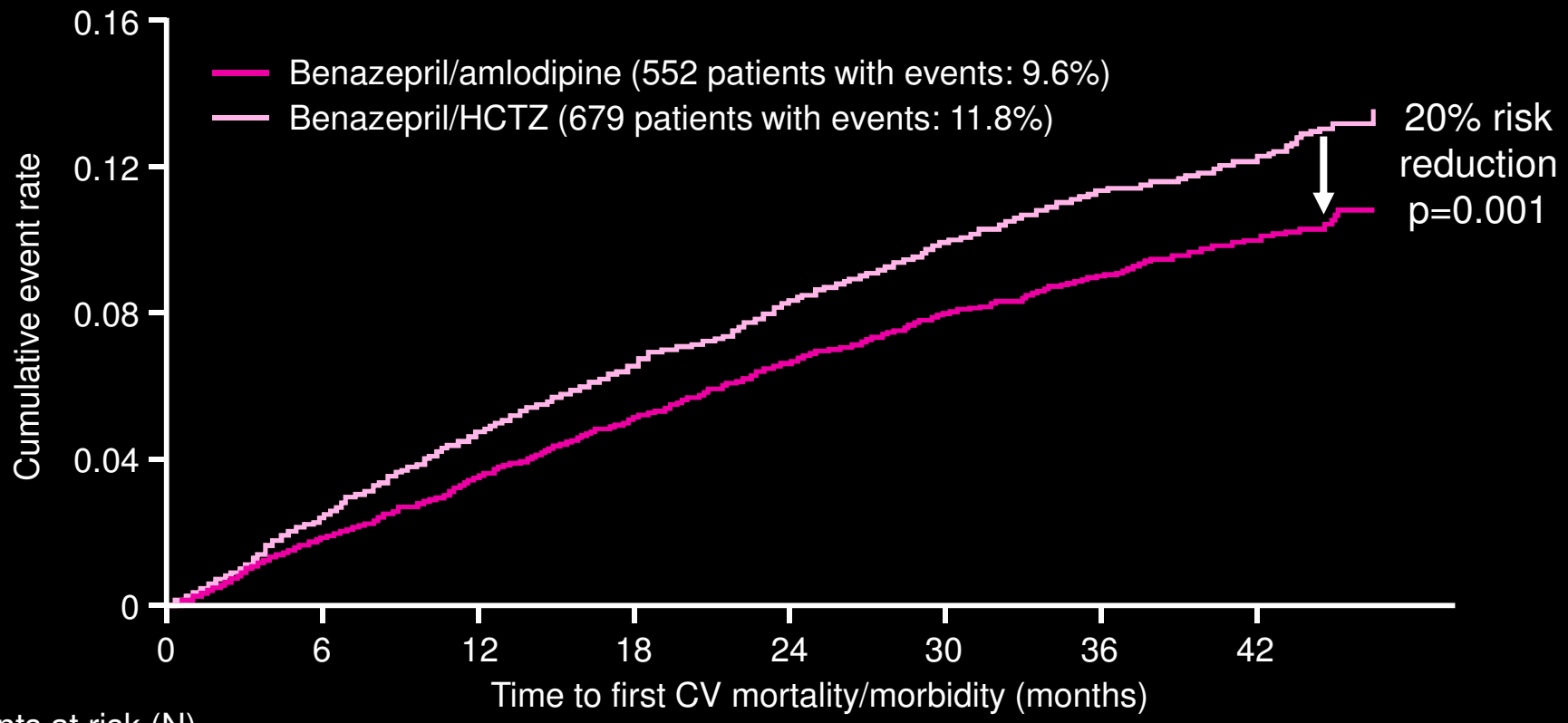
	Benazepril/amlodipine (n = 5744)	Benazepril/HCTZ (n = 5762)
Gender		
Male, n (%)	3448 (60.0)	3515 (61.0)
Female, n (%)	2296 (40.0)	2246 (39.0)
Race		
Caucasian, n (%)	4817 (83.9)	4795 (83.2)
Black, n (%)	697 (12.1)	719 (12.5)
Hispanic, n (%)	300 (5.2)	323 (5.6)
Other, n (%)	230 (4.0)	247 (4.3)
Age		
Mean, years	**68.4**	**68.3**
≥65, n (%)	**3813 (66.4)**	**3827 (66.4)**
≥70, n (%)	**2363 (41.1)**	**2340 (40.6)**
Region		
Nordic countries*, n (%)	1677 (29.3)	1676 (29.2)
United States, n (%)	4042 (70.7)	4059 (70.7)

*Denmark, Finland, Norway or Sweden

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

ACCOMPLISH Study
Baseline Patient Characteristics

Patient Characteristic	No Diabetes	All Diabetes	High Risk Diabetes**
Number of Patients	4559	6946	2842
Male	3,009 (66%)*	3,954 (57%)	1,830 (64%)*
Female	1,550 (34%)*	2,992 (43%)	1,012 (36%)*
Age	69.8 (7.0)*	67.5 (6.6)	66.9 (7.2)*
Age ≥ 65 yrs	3,344 (73)*	4,296 (62)	1,668 (59)*
Caucasian	4,075 (89%)*	5,537 (80%)	2,277 (80%)
Black	374 (8%)*	1042 (15%)	429 (15%)

* Significant differences from *"All Diabetes"* cohort

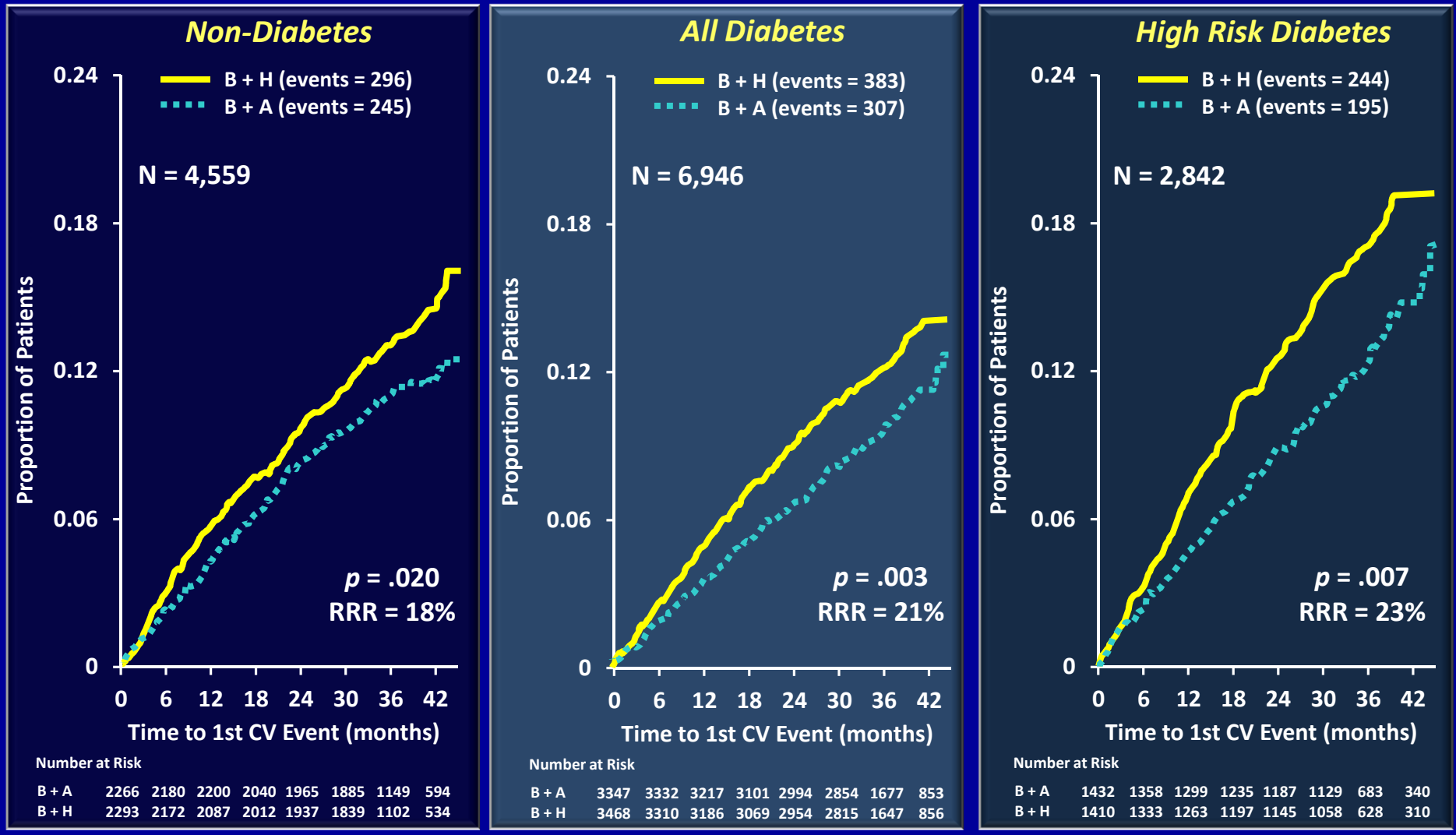
** Patients with diabetes and history of cardiac events, stroke, or renal disease

Values are absolute numbers (%) or mean (SD)

Adapted from: Weber MA, et al. *J Am Coll Cardiol*. 2010;56:77-85.

ACCOMPLISH Study

Primary Outcome in Treatment Groups*



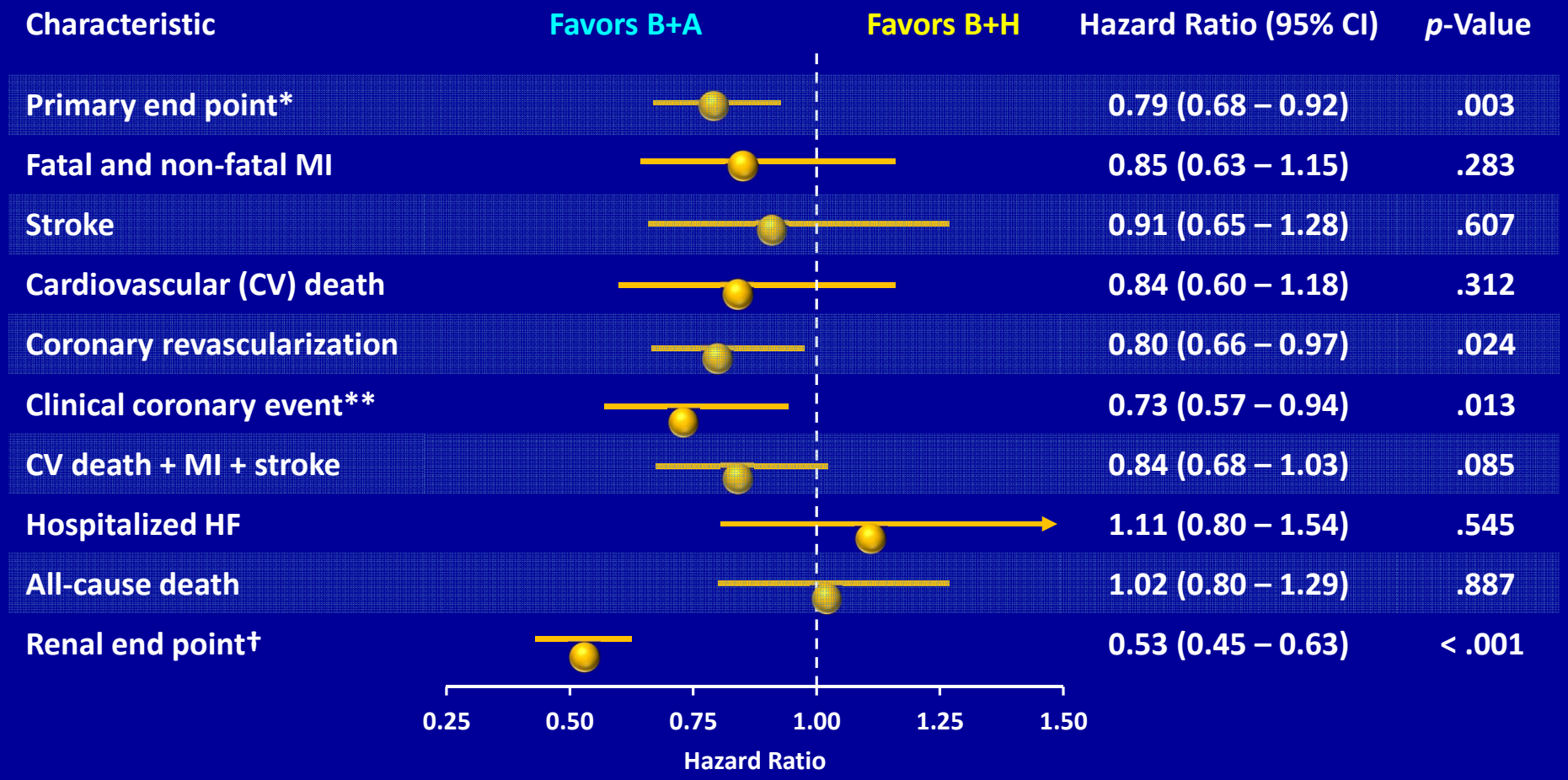
* Time to first event, defined as a composite of CV events or death from CV causes

B=benazepril; A=amlodipine; H=hydrochlorothiazide; RRR=relative risk reduction

Adapted from: Weber MA, et al. *J Am Coll Cardiol*. 2010;56:77-85.

ACCOMPLISH Study

End Points in All Patients With Diabetes



* Time to first event, defined as a composite of CV events or death from CV causes

** MI + Hospitalized unstable angina + Sudden cardiac death

† ≥ 50% increase in serum creatinine with final value above normal range

MI=myocardial infarction; HF=heart failure;
B=benazepril; A=amlodipine; H=hydrochlorothiazide

Adapted from:
Weber MA, et al.
J Am Coll Cardiol. 2010;56:77-85.

American Society of hypertension Evidenced 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

* SPC avaialble in US

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

Summary

- Initial combination therapy is indicated for anyone who has a BP >20/10 above 140/90 mmHg who is already on a low sodium diet
- Upcoming JNC 8 will address specific recommendations on initial combination therapy for CV risk reduction/mortality