Importance of Combination Therapy in Controlling Blood Pressure

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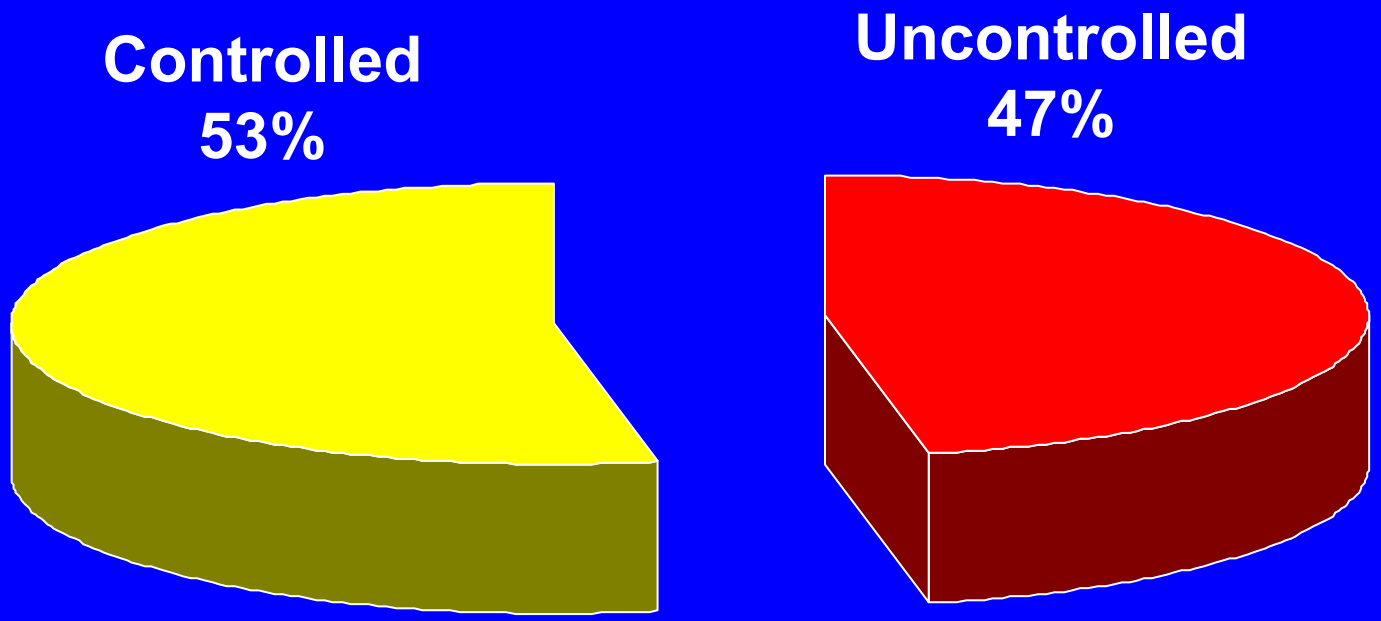
Hypertensives on Treatment

5 out of 10 Treated Hypertensive Patients are not at Goal BP

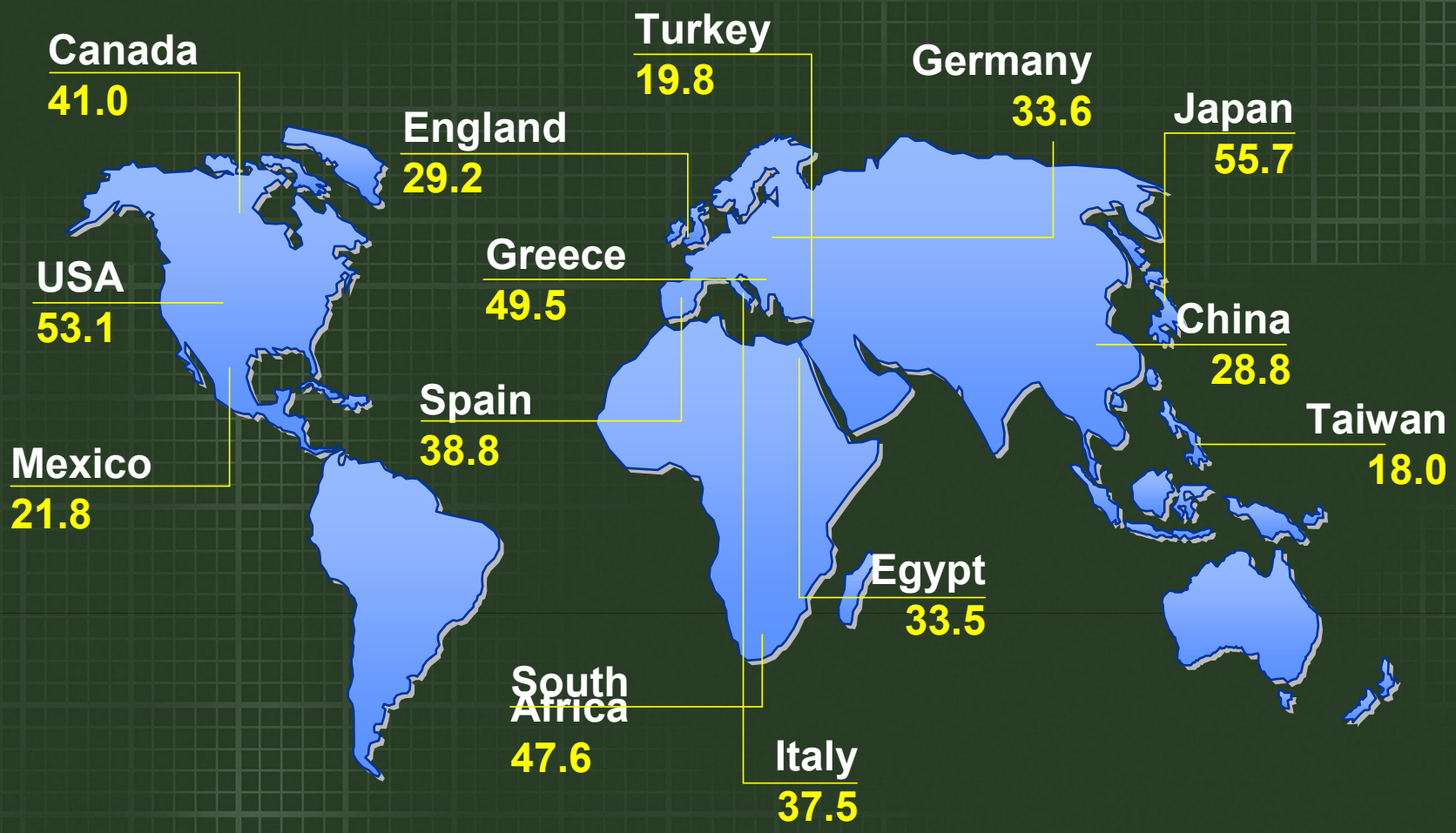


69% of hypertensive Americans are aware of their disease

58% of hypertensive Americans are receiving treatment for their disease

Hajjar I, Kotchen TA. *JAMA*. 2003;290:199-206.
Burt et al. *Hypertention*. 1995;25:305-313; Hyman et al. *N Engl J Med*. 2001;345:479-486; .

Worldwide Blood Pressure Control in Treated Hypertensive Patients



Updated from Kearney et al. J Hypertens 2004; 22: 11-19

Most Patients with Diabetes are NOT at BP Goal

- **JNC 7[1] / ADA / NFK blood pressure goal for diabetics:**

  <130/80 mmHg

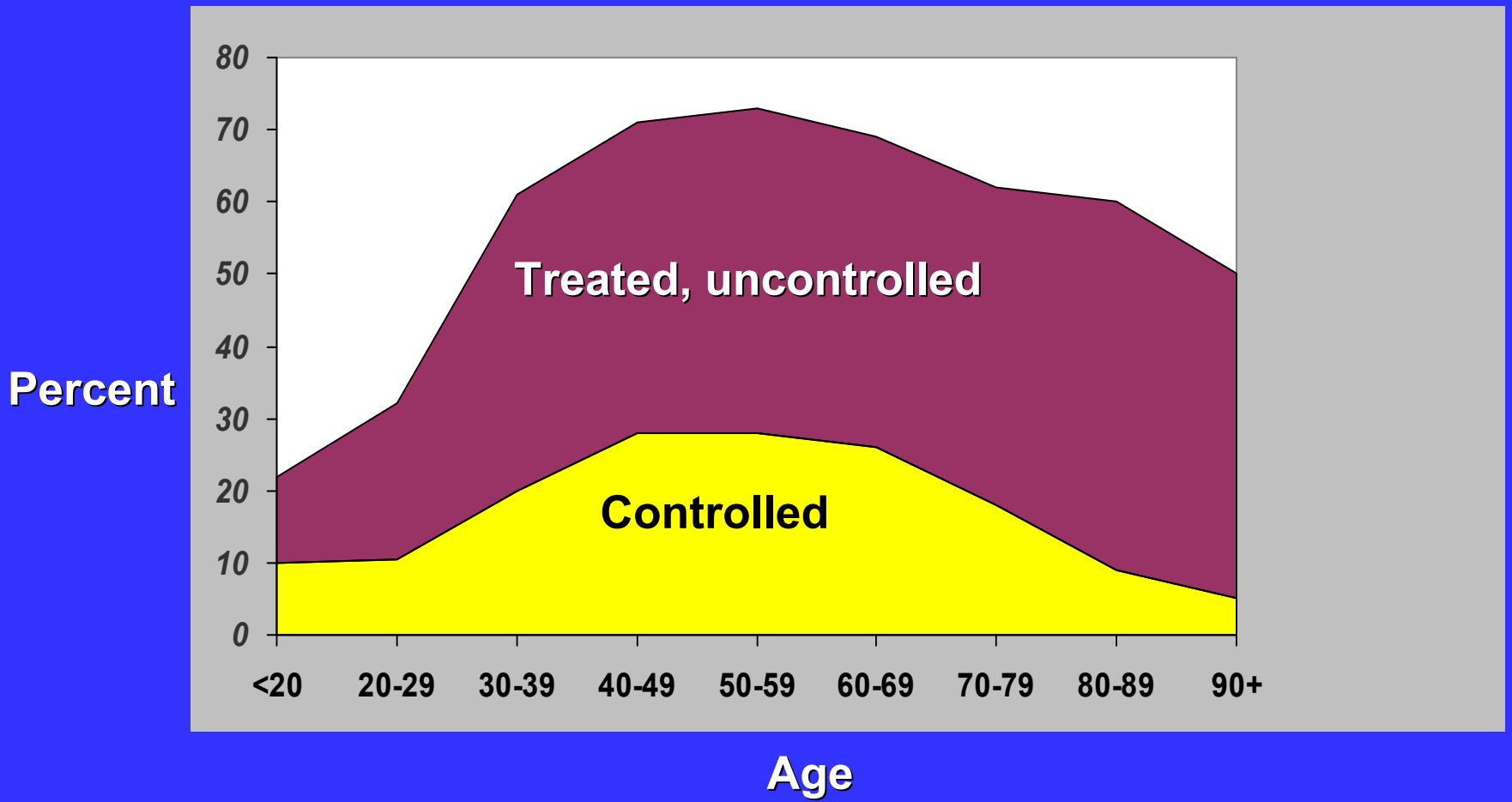
- **Only 10-20% patients with diabetes are at BP goal[2-5]**

JNC, Joint National Committee; ADA, American Diabetes Association; NFK, National Kidney Foundation

[1]*JAMA*. 2003;289:2560-2572. [2] *Med Care*. 2006;44:39-46. [3]*Endocr Pract.* 2005;11:172-9.

[4]*Diabetes Care*. 2005;28:337-342. [5]*Diabetes Care*. 2005;28:514-520.

Even With Current Treatments, Hypertension Remains a Major Public Health Issue

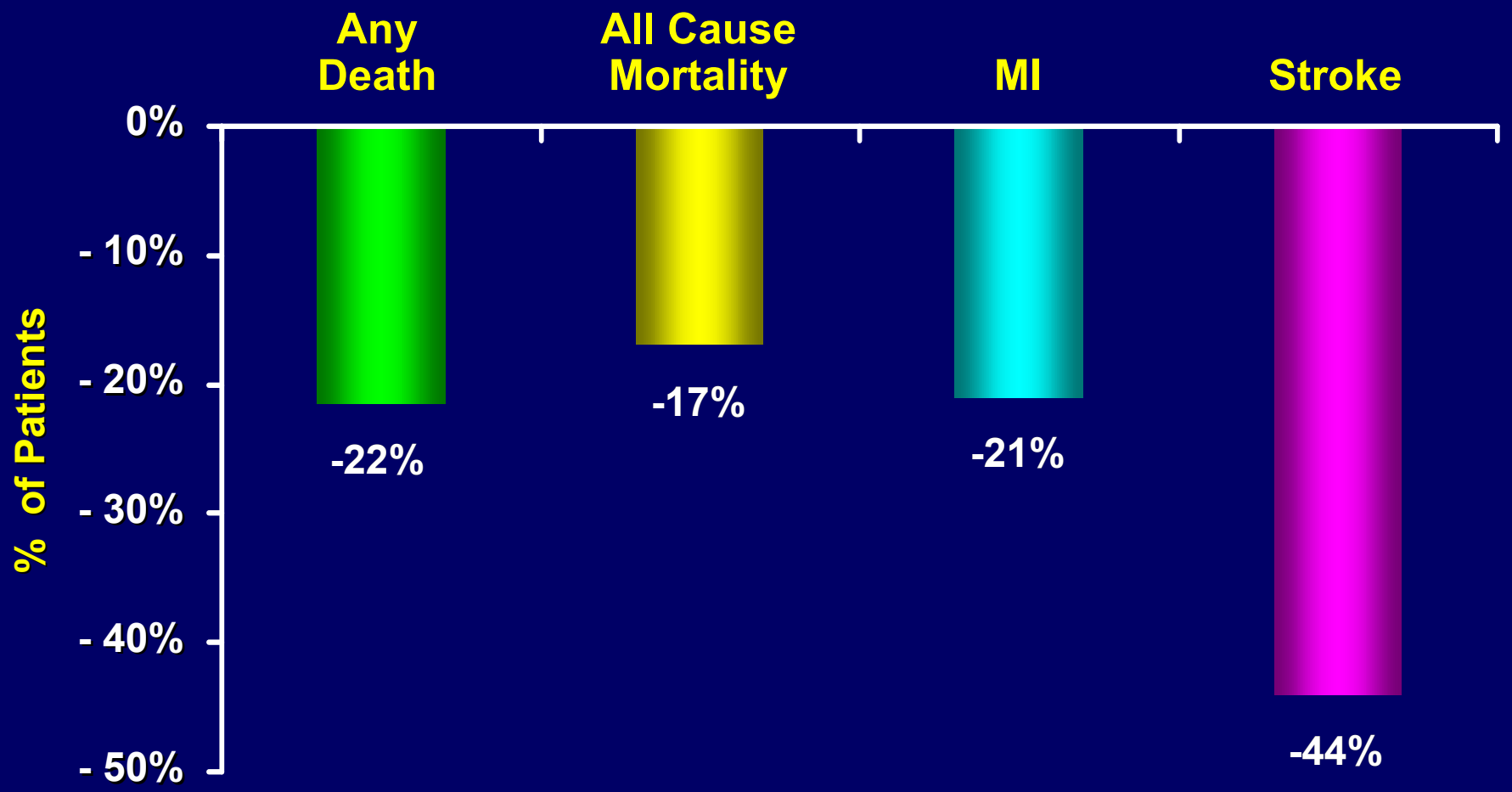


Kannel, W., *J. Hyper.* 1999. 17:S188

UKPDS Mean Blood Pressures

	Baseline (mm Hg)	Mean BP Over 9yrs (mm Hg)
Less tight control	160/94	154/87
Tight control	161/94	144/82
Difference	1/0	10/5
P	n.s	p<0.0001

Difference in Number of Events
Tight vs. Less tight BP control (10/5mm Hg)

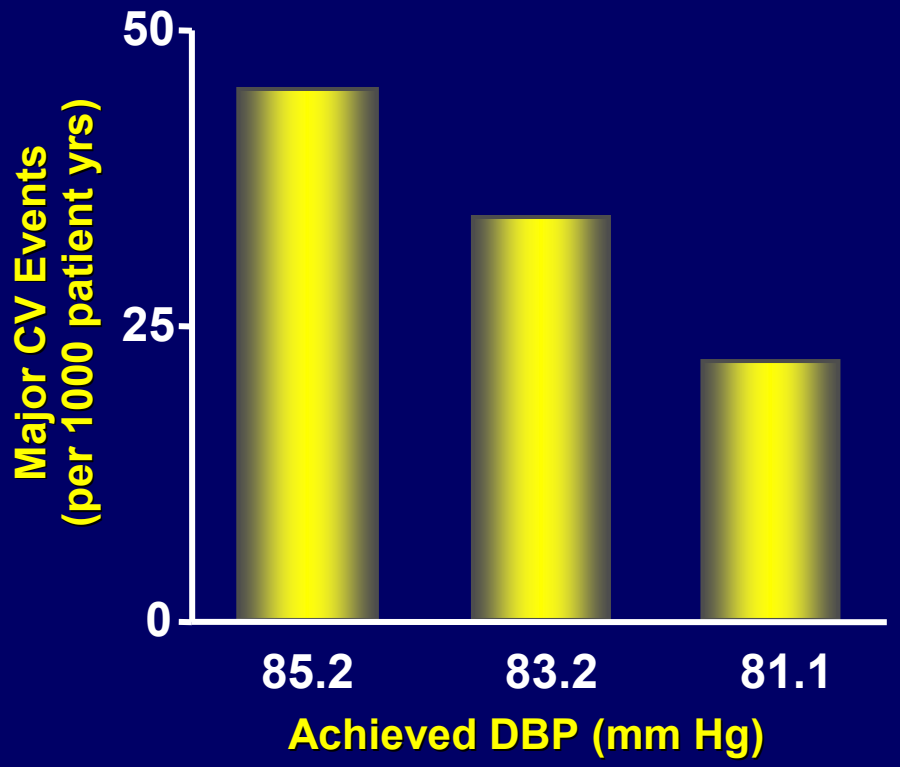


Hansson L et al. *Lancet.* 1998;351;1755-1762.

Benefits of BP Reduction in the Hypertension Optimal Treatment (HOT) Trial: Diabetic Cohort

Target DBP (mm Hg)	Achieved SBP (mm Hg)	Achieved DBP (mm Hg)
≤ 90	143.7	85.2
≤ 85	141.4	83.2
≤ 80	139.7	81.1

Achieved = mean of all BPs from 6 months of follow-up to end of study



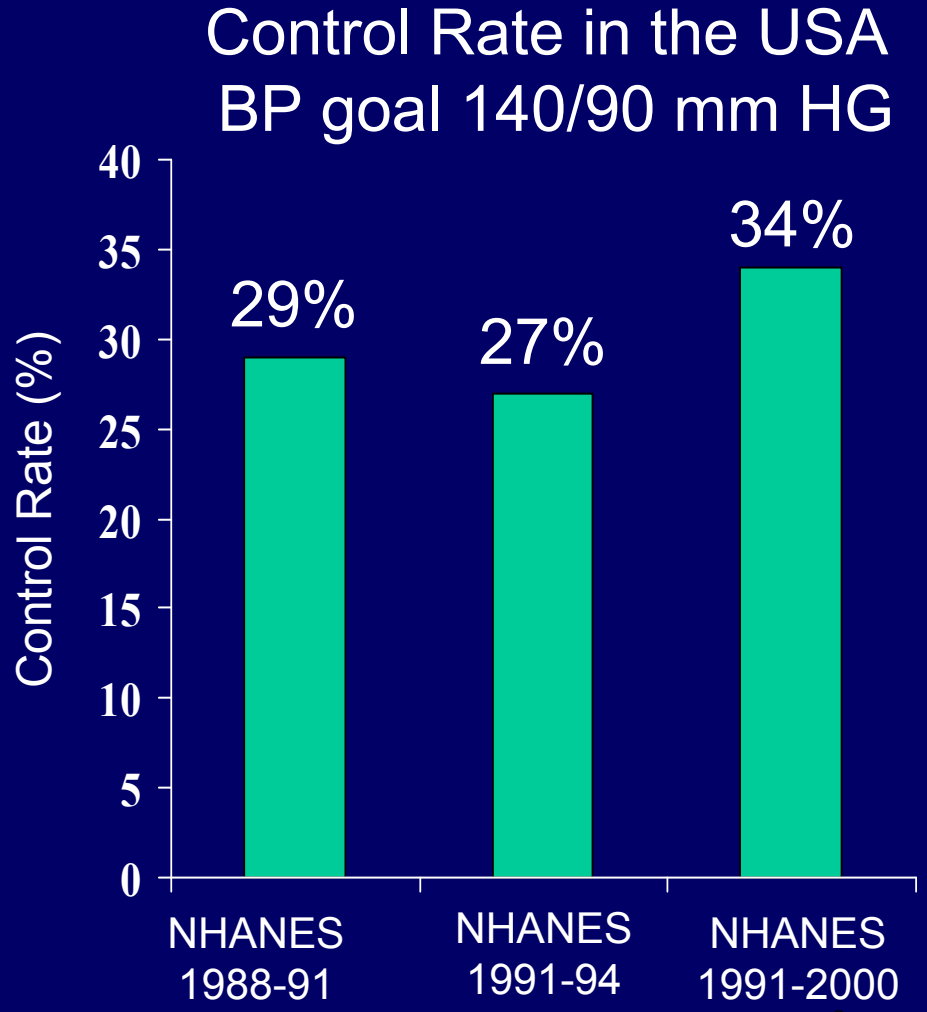
P = 0.05 for trend

Adapted from Hansson L, et al. Lancet. 1998;351:1755-62.

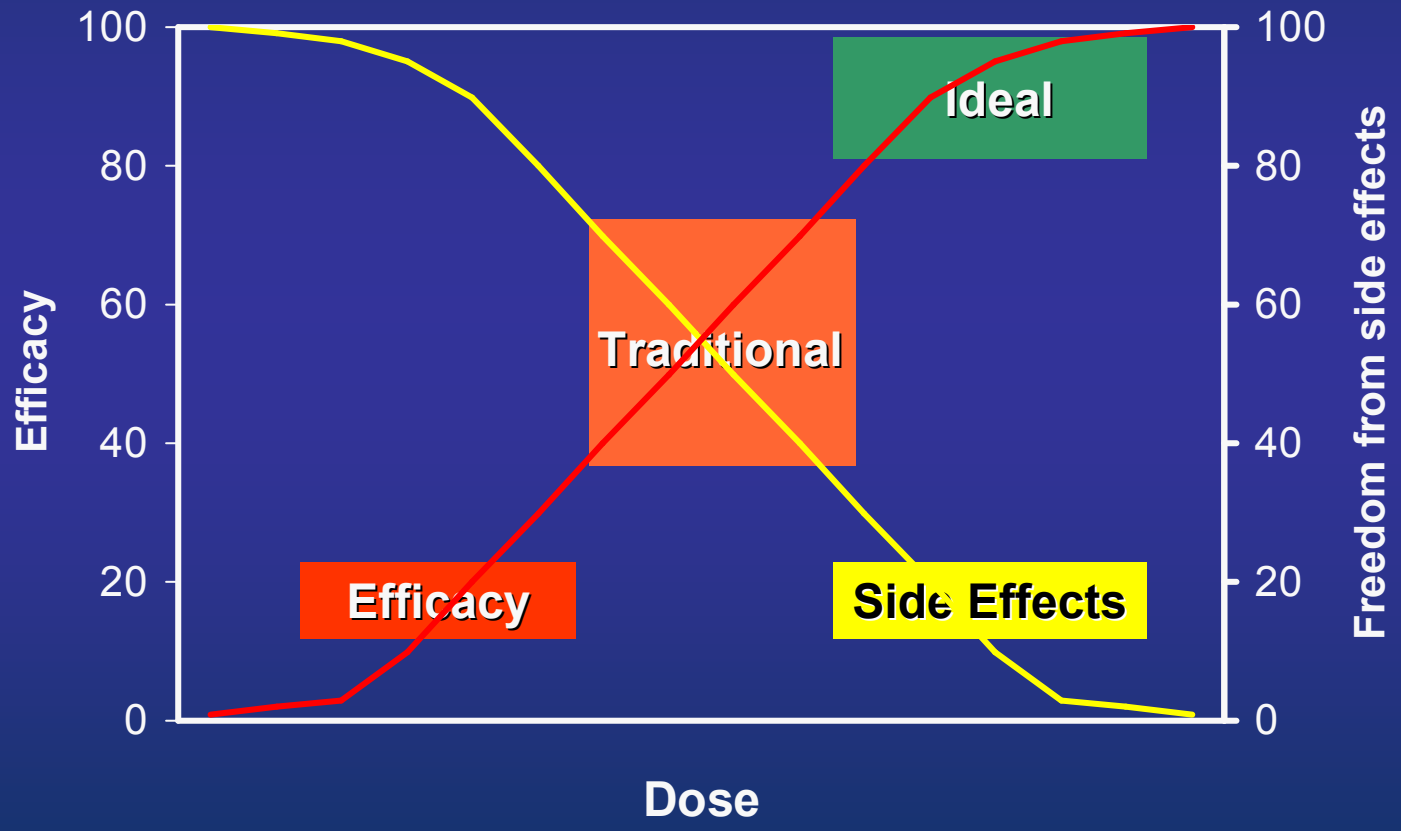
Failure of the Stepped Care Approach

Why Has the Stepped Care Approach to the Management of Hypertension Failed?

4 JNC Reports Between 1988 and 2000

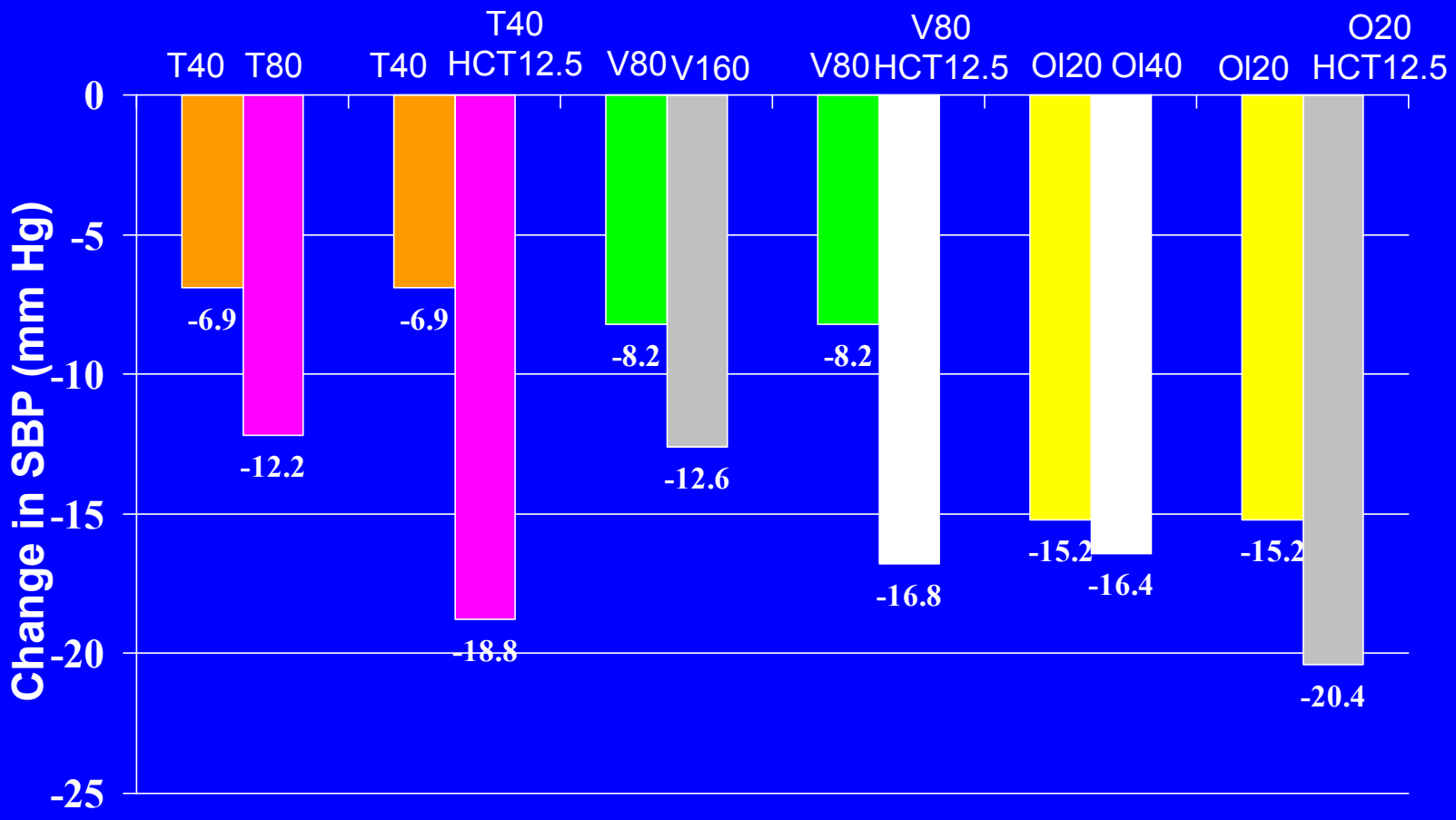


The New Therapeutic Window in Hypertension

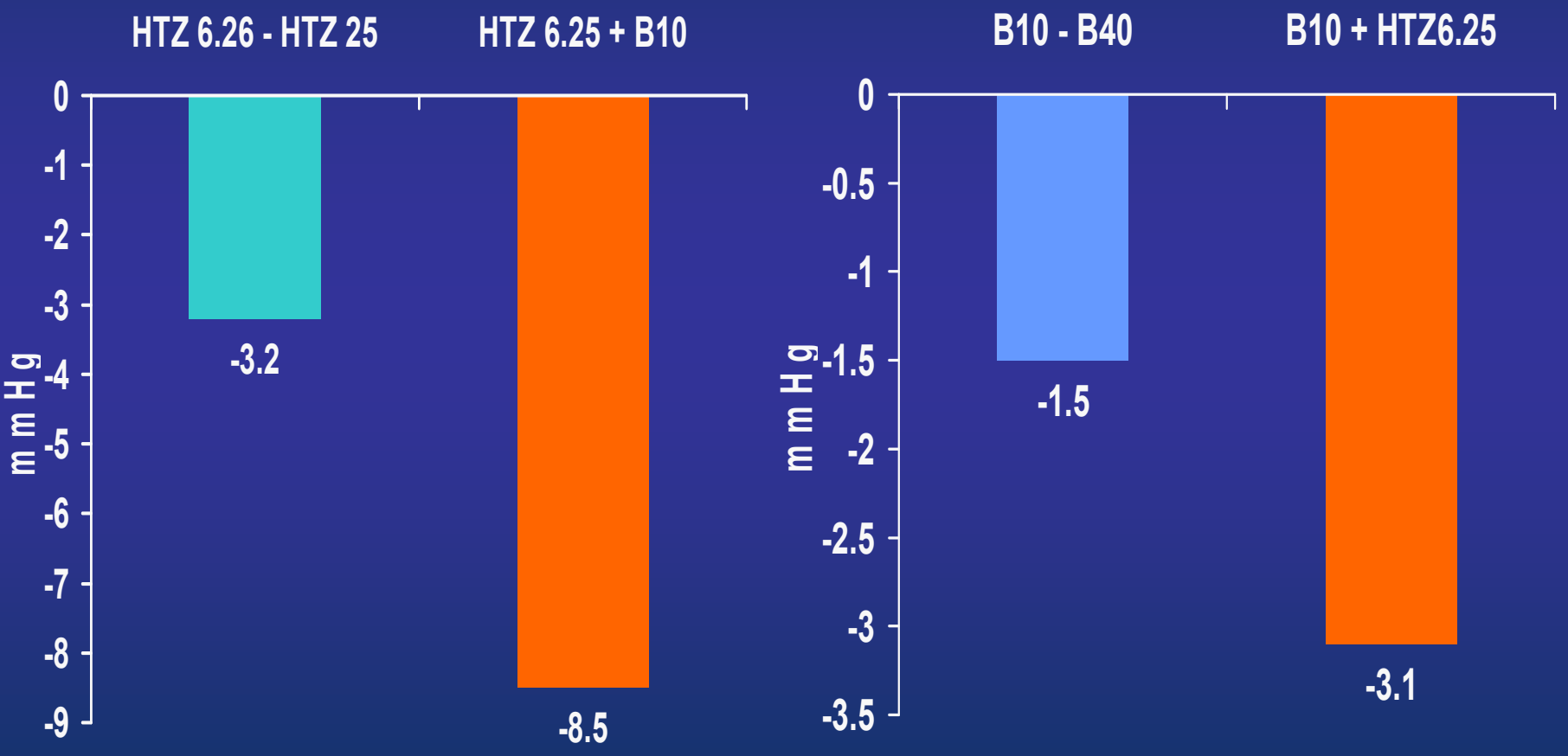


Man Int Veld AJ, Journal of Hypertens 1997;15 (suppl 7): S27-S33

Efficacy: Up-titration vs Combination

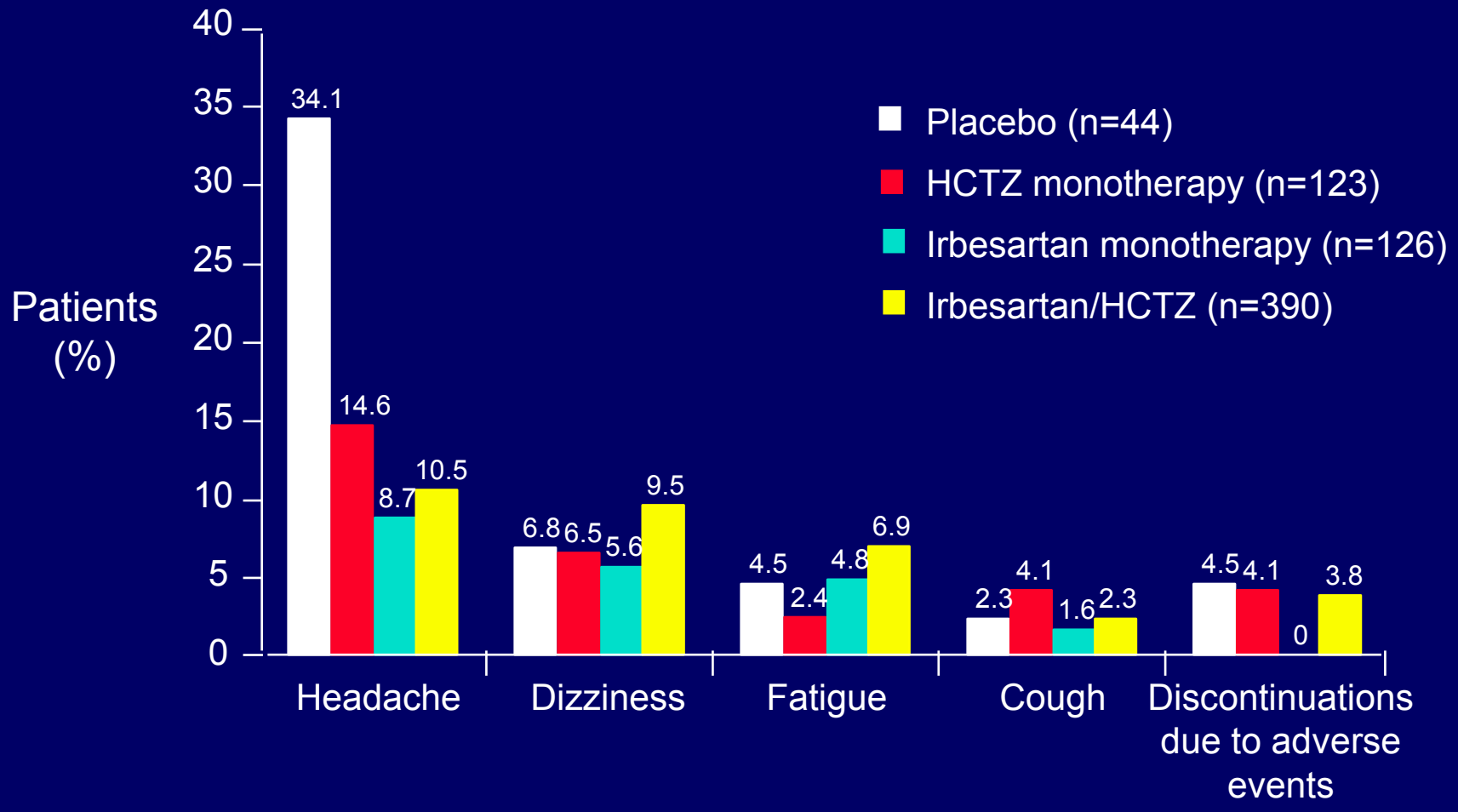


Titration vs. Combination



Frishman WH et al,Arch Intern Med 1994;154, 1461-1468

Tolerability of Irbesartan Combination Therapy and Components



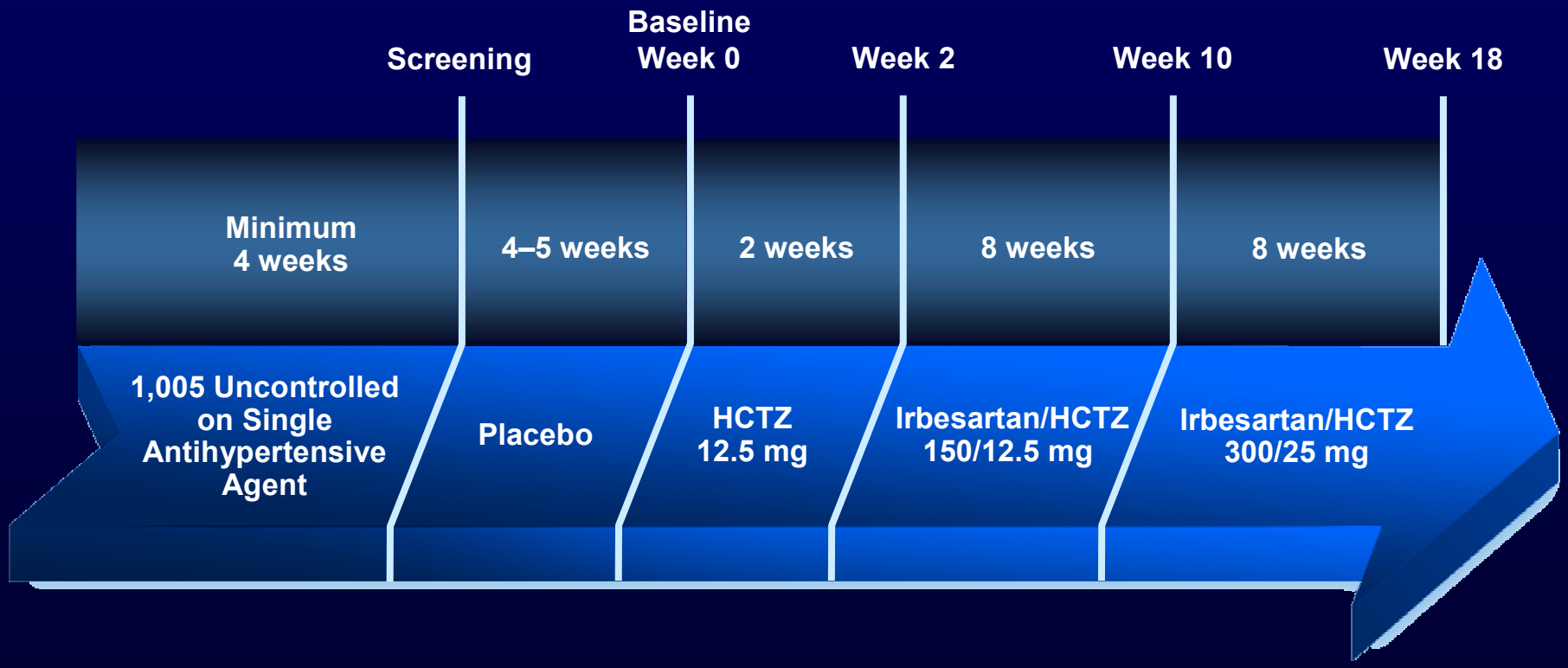
INCLUSIVE Study

Unique Study Features

- All patients uncontrolled for hypertension on monotherapy
- Focused on systolic BP
- Performed in a real world clinical setting
- Included all difficult to control sub-groups of hypertensive patients (AA, II D/M, Elderly, Hispanics, Metabolic syndrome)

INCLUSIVE Study Design

Design: Multicenter (119 sites across the US), prospective, open-label, single-arm study with titration to BP response



n=736, ITT population

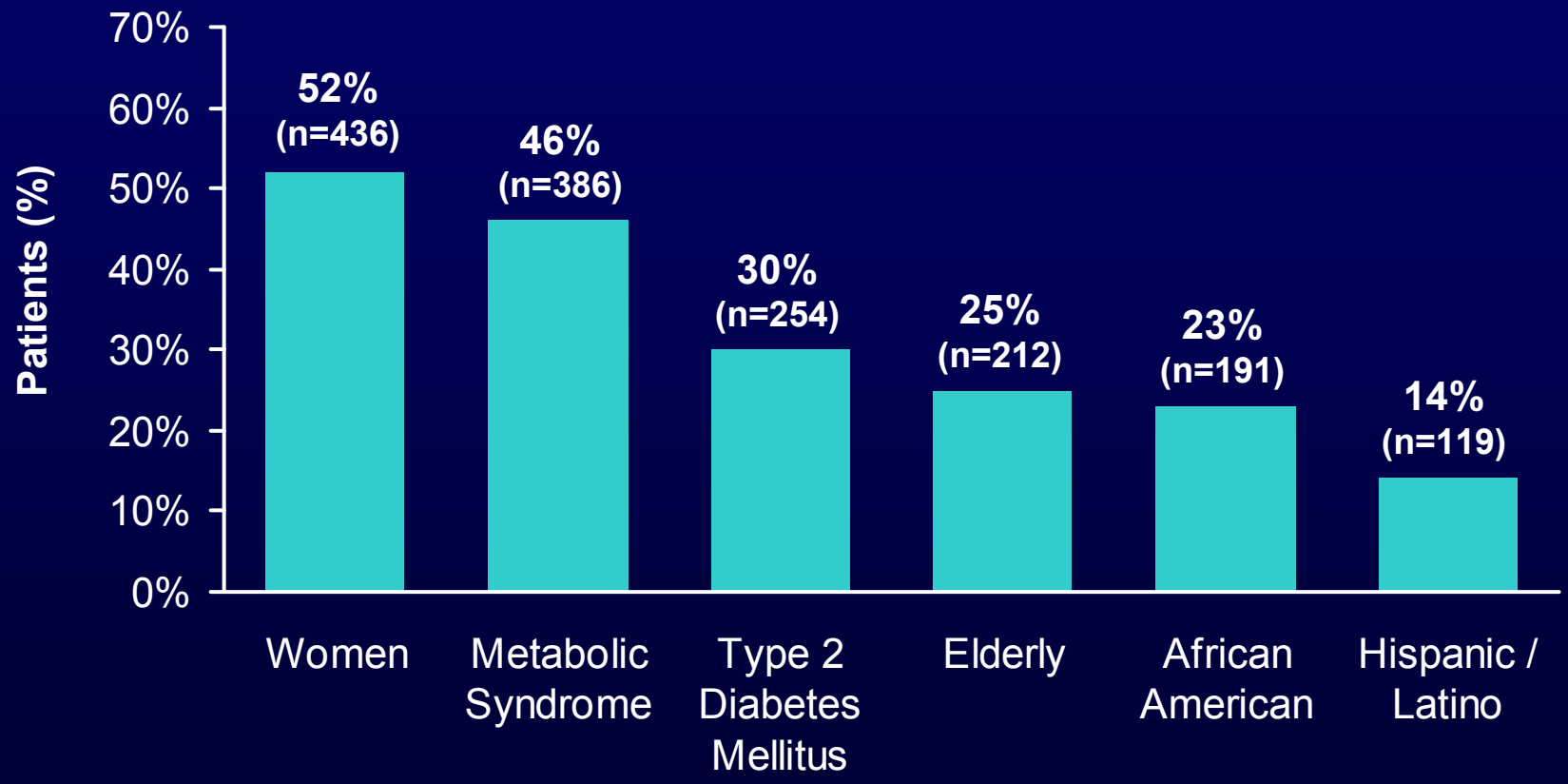
Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

Patient Baseline Demographics

Characteristic	Total Patients Enrolled at Week 0 (n=844)
Age, years	
Mean ± SD	57.3 ± 11.2
Min, Max	24, 90
<65 years, n (%)	632 (75%)
≥65 years, n (%)	212 (25%)
Women, n (%)	436 (52%)
SBP, mmHg	
Mean ± SD	**154.0** ± 10.3
Min, Max	130, 179
DBP, mmHg	
Mean ± SD	**91.3** ± 8.8
Min, Max	63, 109

Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

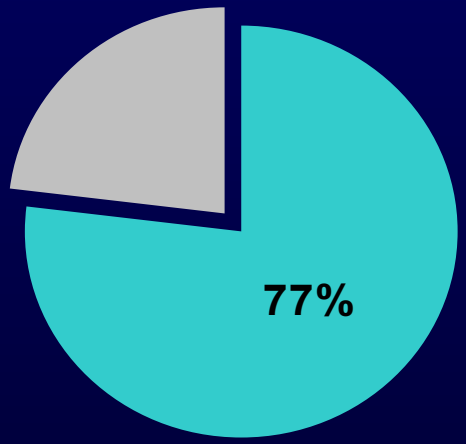
Demographics



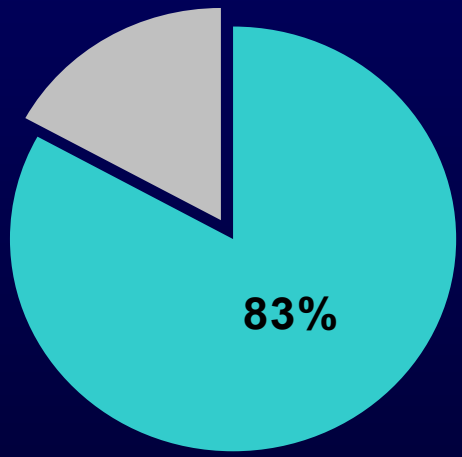
Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

Blood Pressure Goal Attainment With Irbesartan/HCTZ at Week 18

SBP Goal

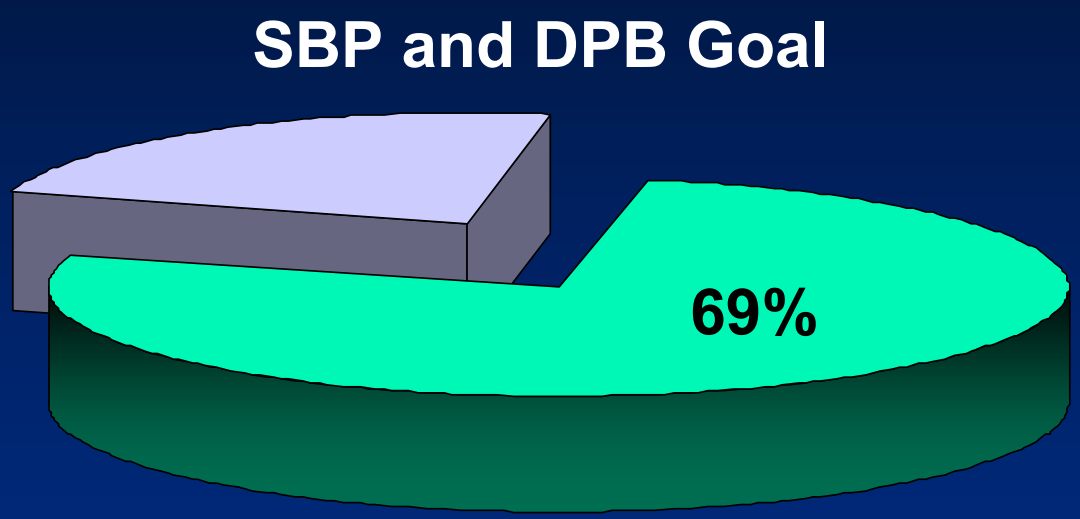


DBP Goal



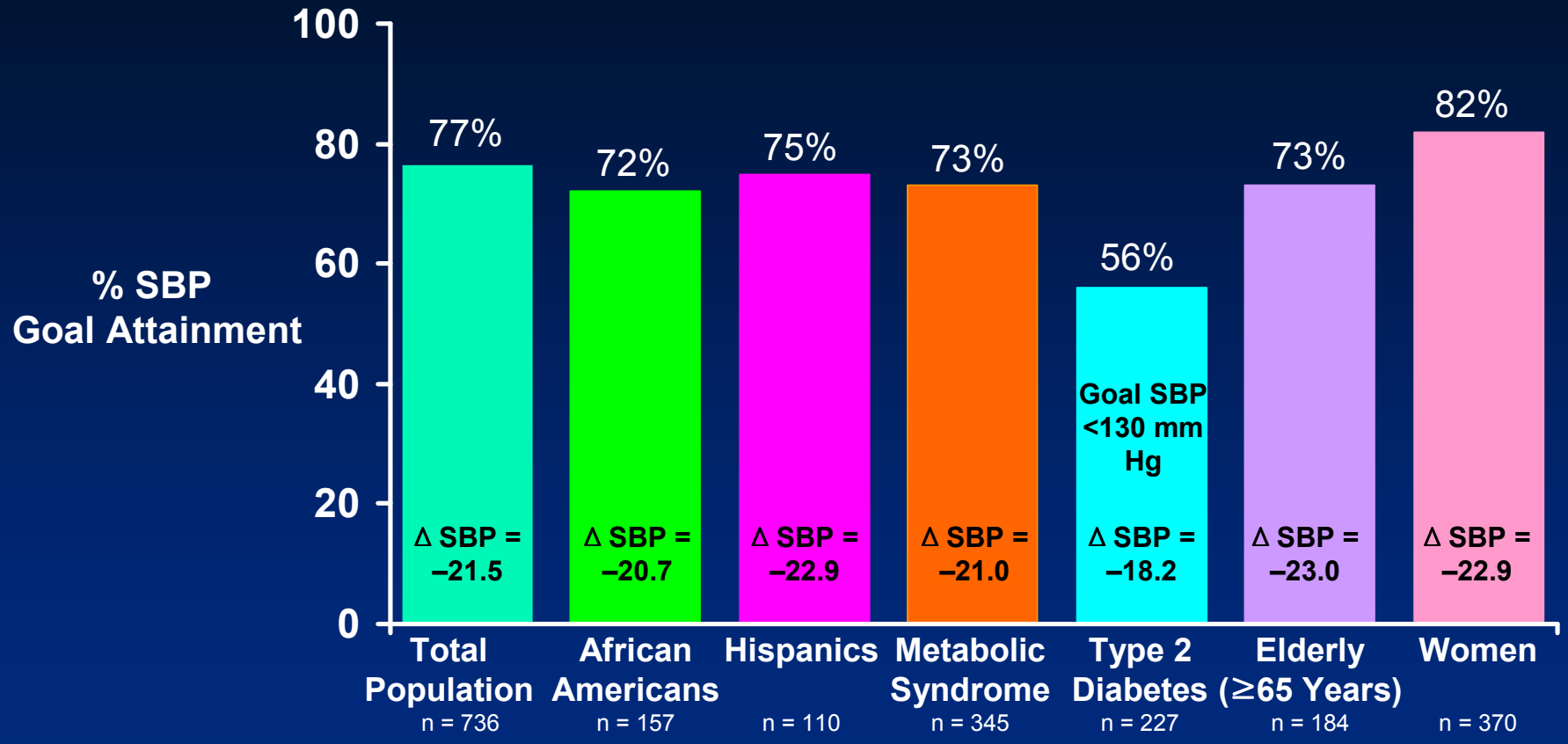
Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

Overall BP Goal* Attainment With Irbesartan/HCTZ at Week 18



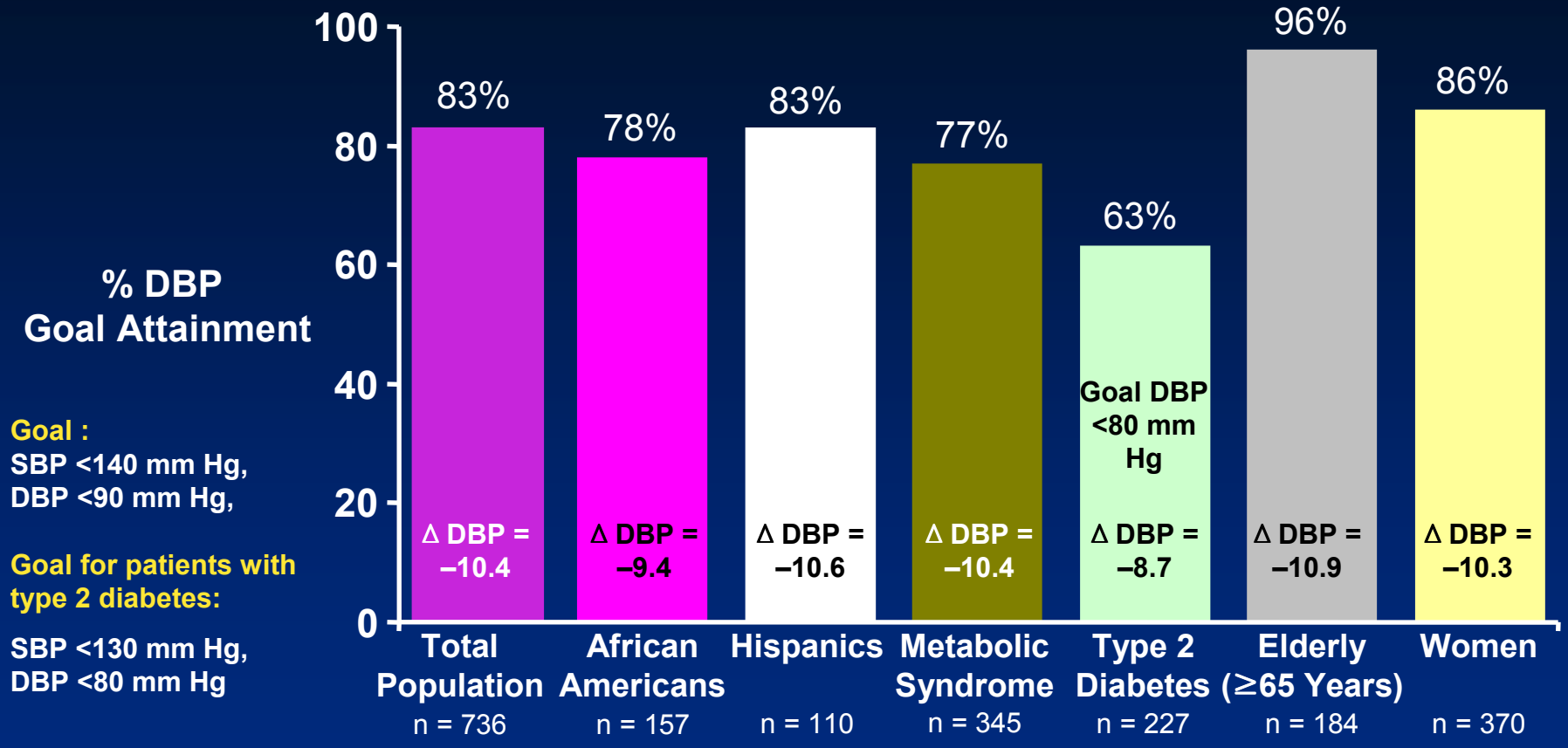
Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

SBP Goal Attainment Subpopulations



Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

DBP Goal Attainment Subpopulations



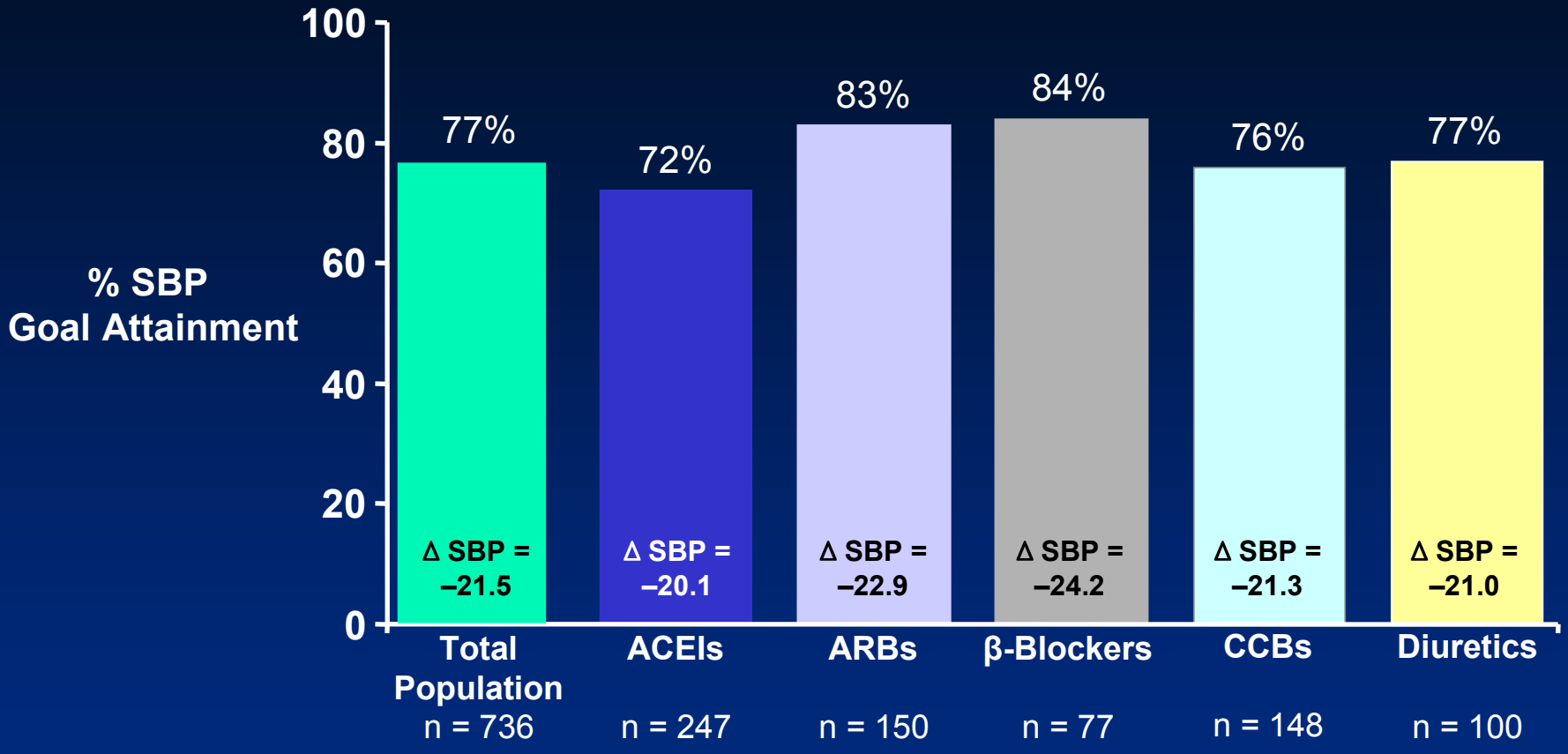
Goal :
SBP <140 mm Hg,
DBP <90 mm Hg,

Goal for patients with type 2 diabetes:

SBP <130 mm Hg,
DBP <80 mm Hg

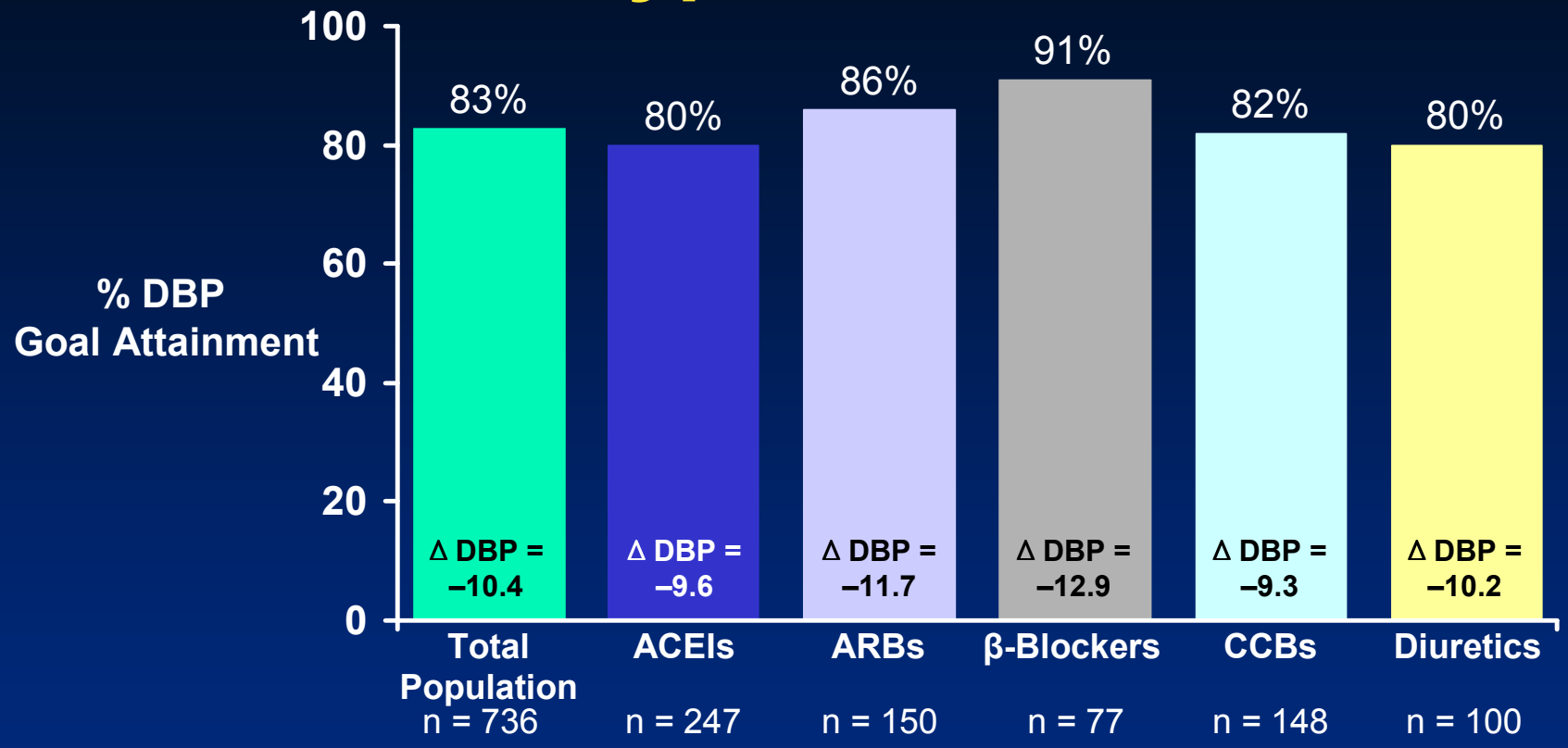
Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

SBP Goal Attainment
Previous Antihypertensive Treatments



Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

DBP Goal Attainment
Previous Antihypertensive Treatments



Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

Laboratory Parameters
Total Population

	Baseline	Week 18 (Avalide 300/25 mg)
BUN, mg/dL		
Mean ± SD	15.7 ± 4.4 (n=736)	18.6 ± 6.0 (n=574)
Creatinine, mg/dL		
Mean ± SD	1.09 ± 0.18 (n=736)	1.14 ± 0.21 (n=574)
Glucose, mg/dL		
Mean ± SD	110.9 ± 27.9 (n=736)	116.3 ± 36.5 (n=574)
Potassium, mmol/L		
Mean ± SD	4.41 ± 0.46 (n=736)	4.28 ± 0.44 (n=574)
Microalbumin, mg/L		
Mean ± SD	48.5 ± 169.9 (n=475)	33.74 ± 90.3 (n=387)

Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

Lipid Parameters
Total Population

	Baseline	Week 18 (Avalide 300/25 mg)
Cholesterol, mg/dL Mean ± SD	198.8 ± 36.8 (n=732)	198.4 ± 38.2 (n=574)
HDL-C, mg/dL Mean ± SD	52.2 ± 13.5 (n=732)	50.0 ± 12.9 (n=574)
LDL-C, mg/dL Mean ± SD	116.1 ± 30.7 (n=709)	115.6 ± 33.2 (n=551)
Triglycerides, mg/dL Mean ± SD	159.4 ± 112.4 (n=732)	175.7 ± 123.1 (n=574)

Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

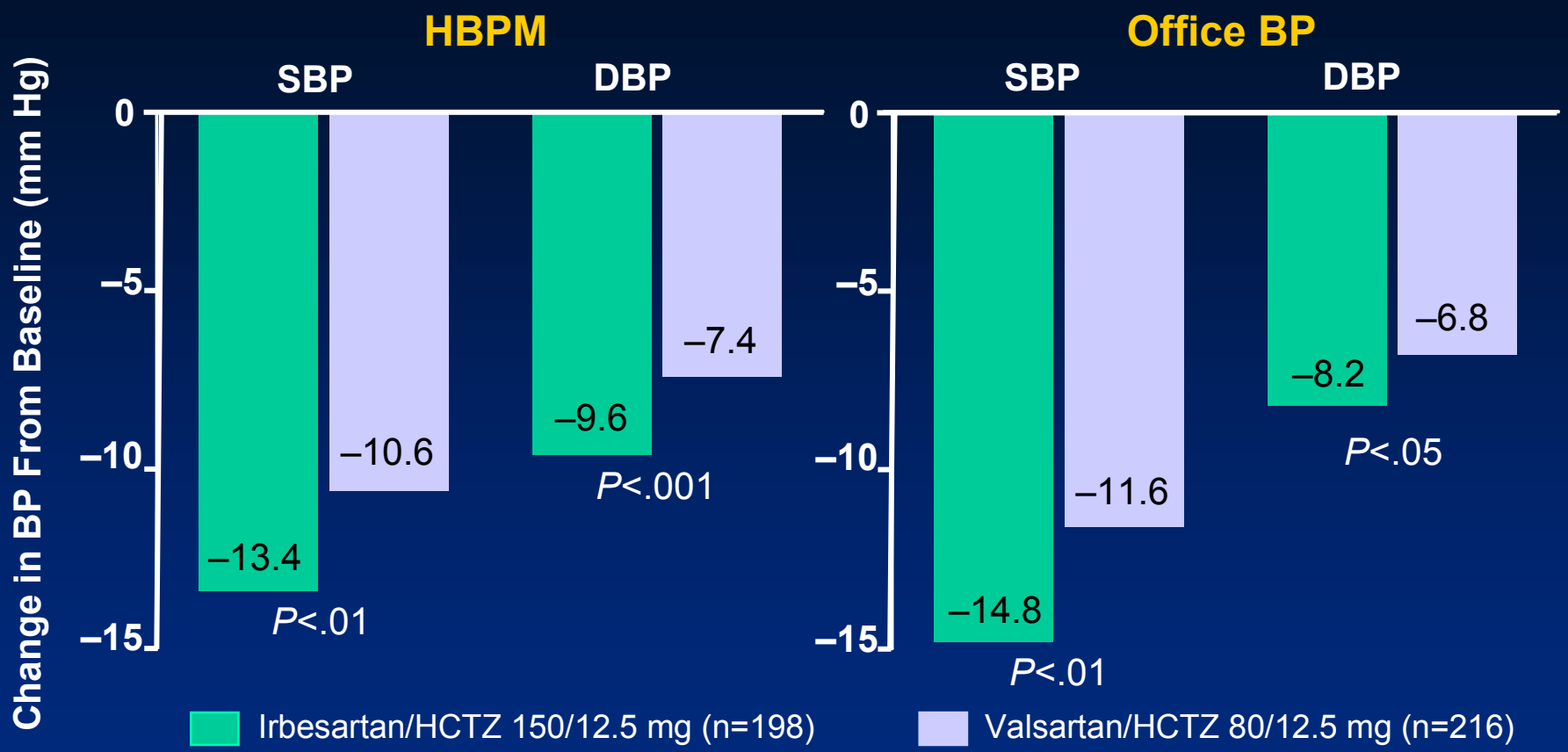
Drug-Related Adverse Events Occurring ≥1% During Any Treatment Period

	Placebo Washout	HCTZ 12.5 mg	Week 18 Irbesartan/HCTZ 150/12.5 mg	Week 18 Irbesartan/HCTZ 300/25 mg	Total*
Patients with drug-related AE†, (%)	1	3	6	8	14
Dizziness, (%)	<1	1	1	2	3
Fatigue, (%)	<1	<1	1	1	1
Hypotension, (%)	0	0	<1	1	<1

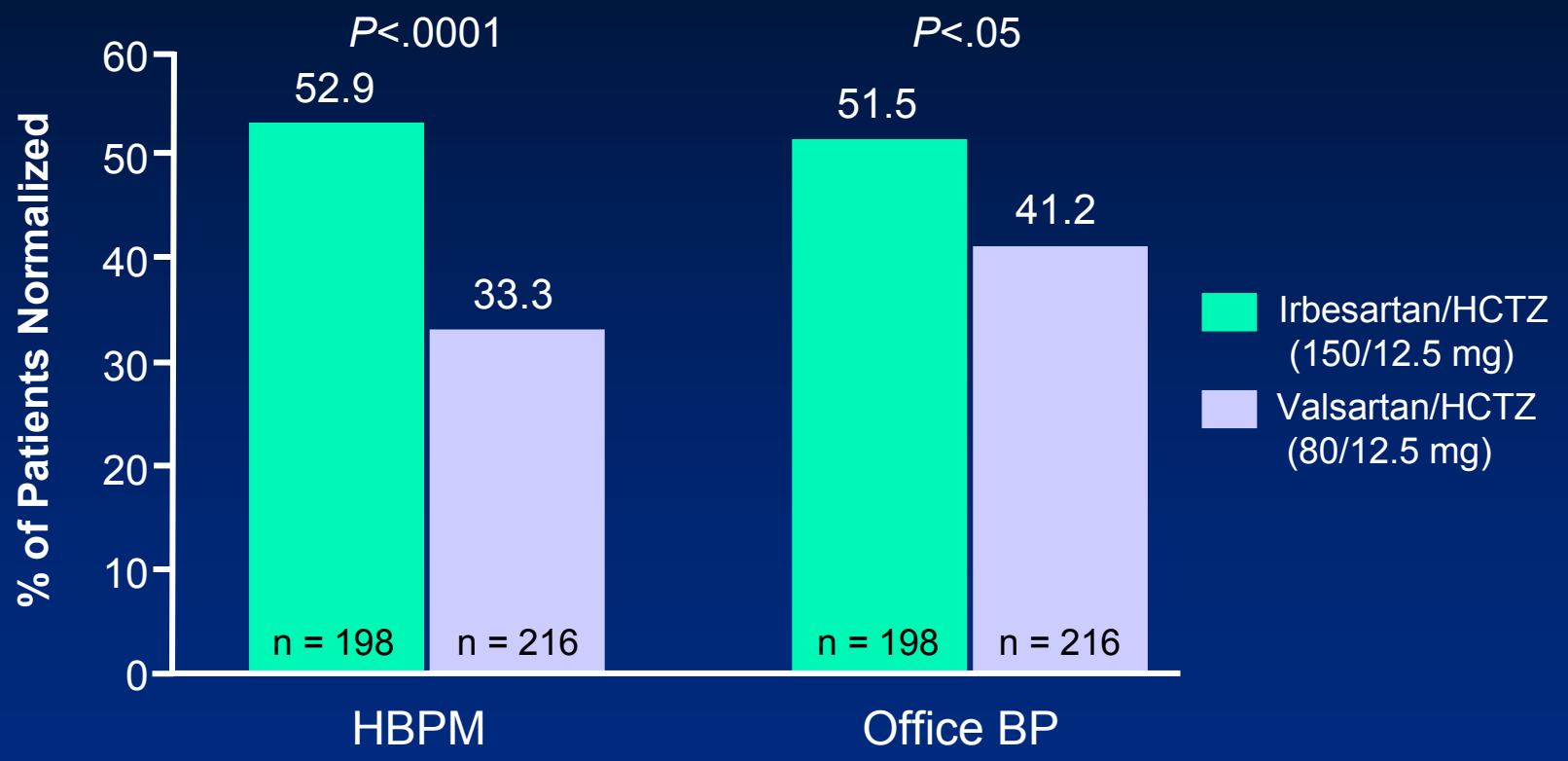
*Includes all safety patients from placebo administration onward; n = 1,005.
†Total AEs reported, with a possible, probable, or definite relationship to study drug.
AE = adverse event.
Most common adverse experiences reported in AVALIDE-vs.-placebo clinical trials: fatigue (7% vs. 3%), musculoskeletal pain (7% vs. 5%), dizziness (8% vs. 4%), and nausea/vomiting (3% vs. 0%).

Neutel JM et al. *J Clin Hypertens*. 2005;7:578-586.

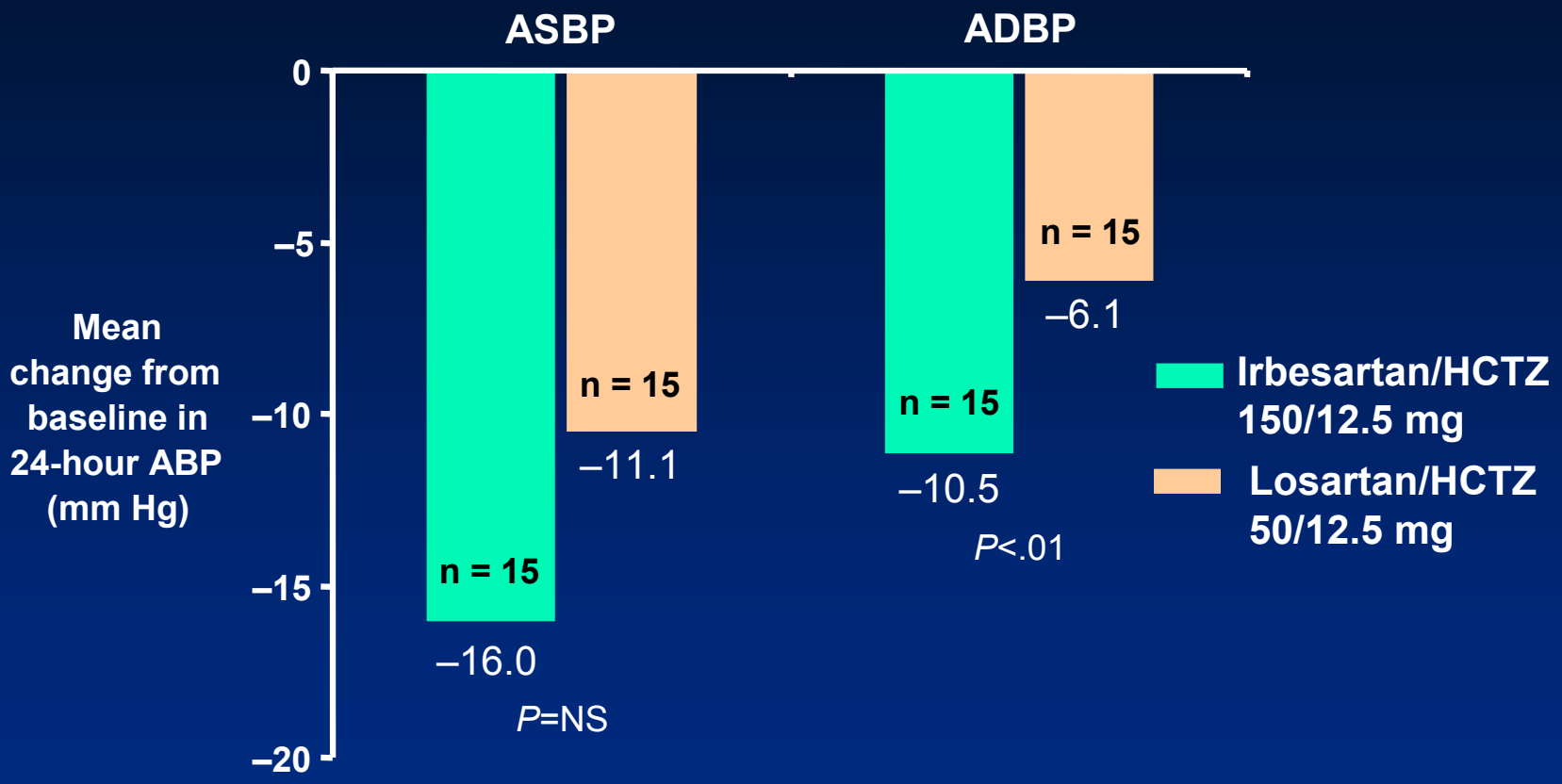
Irbesartan/HCTZ vs Valsartan/HCTZ: Change From Baseline in HBPM and Office BP



Irbesartan/HCTZ vs Valsartan/HCTZ: Normalization of HBPM and Office BP

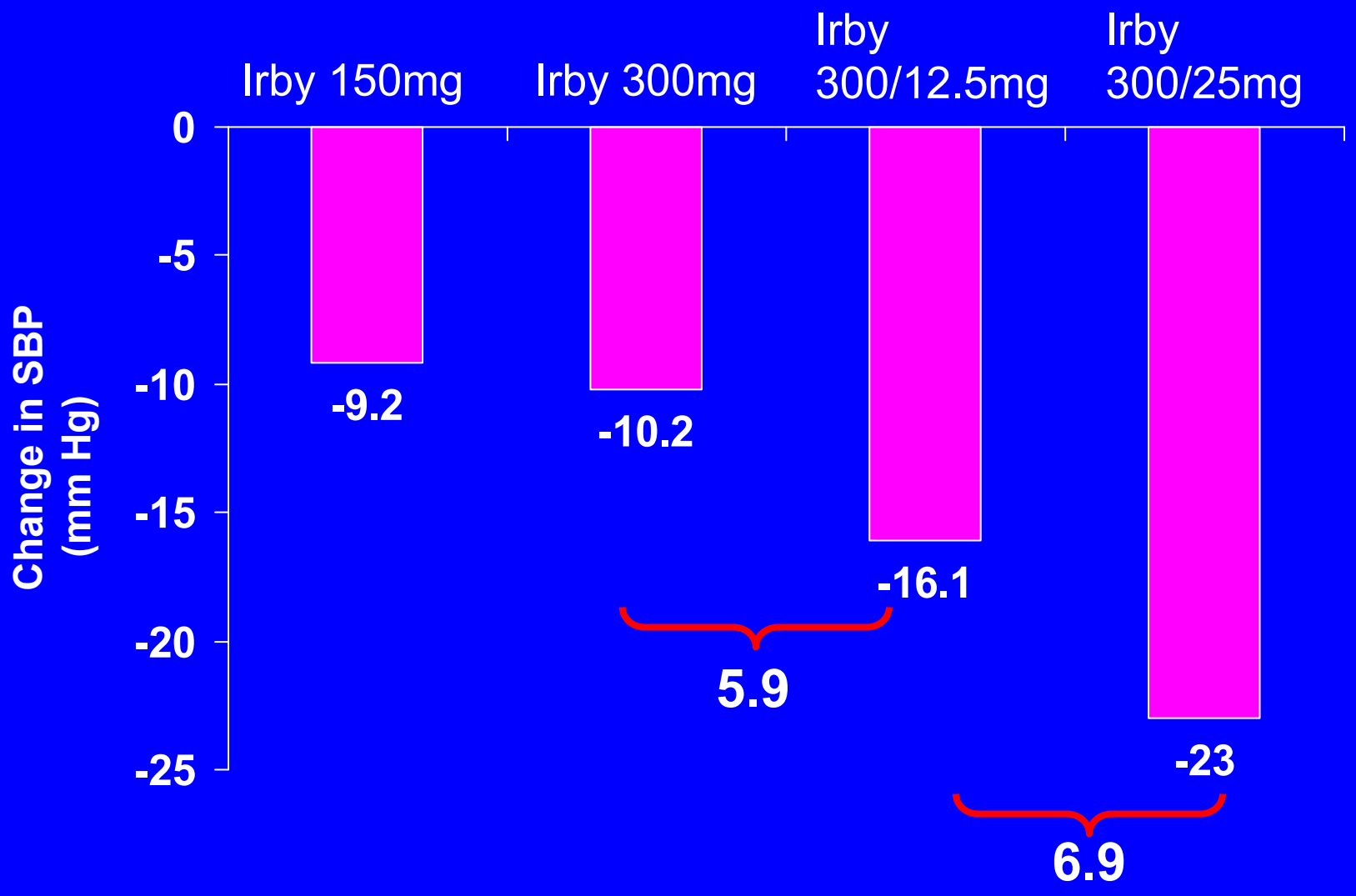


Irbesartan/HCTZ vs Losartan/HCTZ
Mean Reduction in 24-Hour Ambulatory BP



AVALIDE FAQ slide

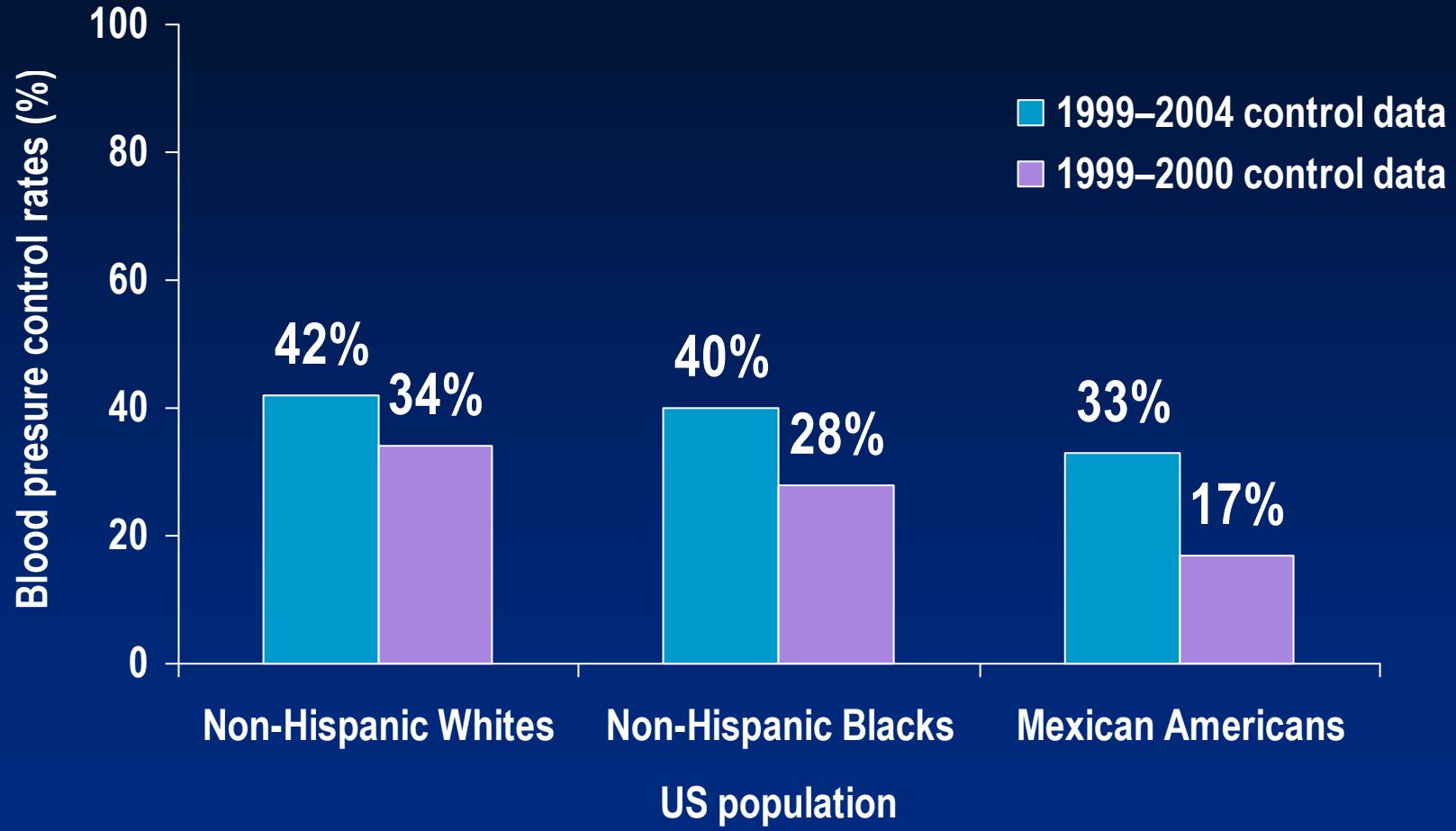
SBP Response to HCTZ 12.5mg Vs HCTZ 25mg in Combination with ARB's



Adverse Events: HCTZ 25mg vs ARB + HCTZ 25mg

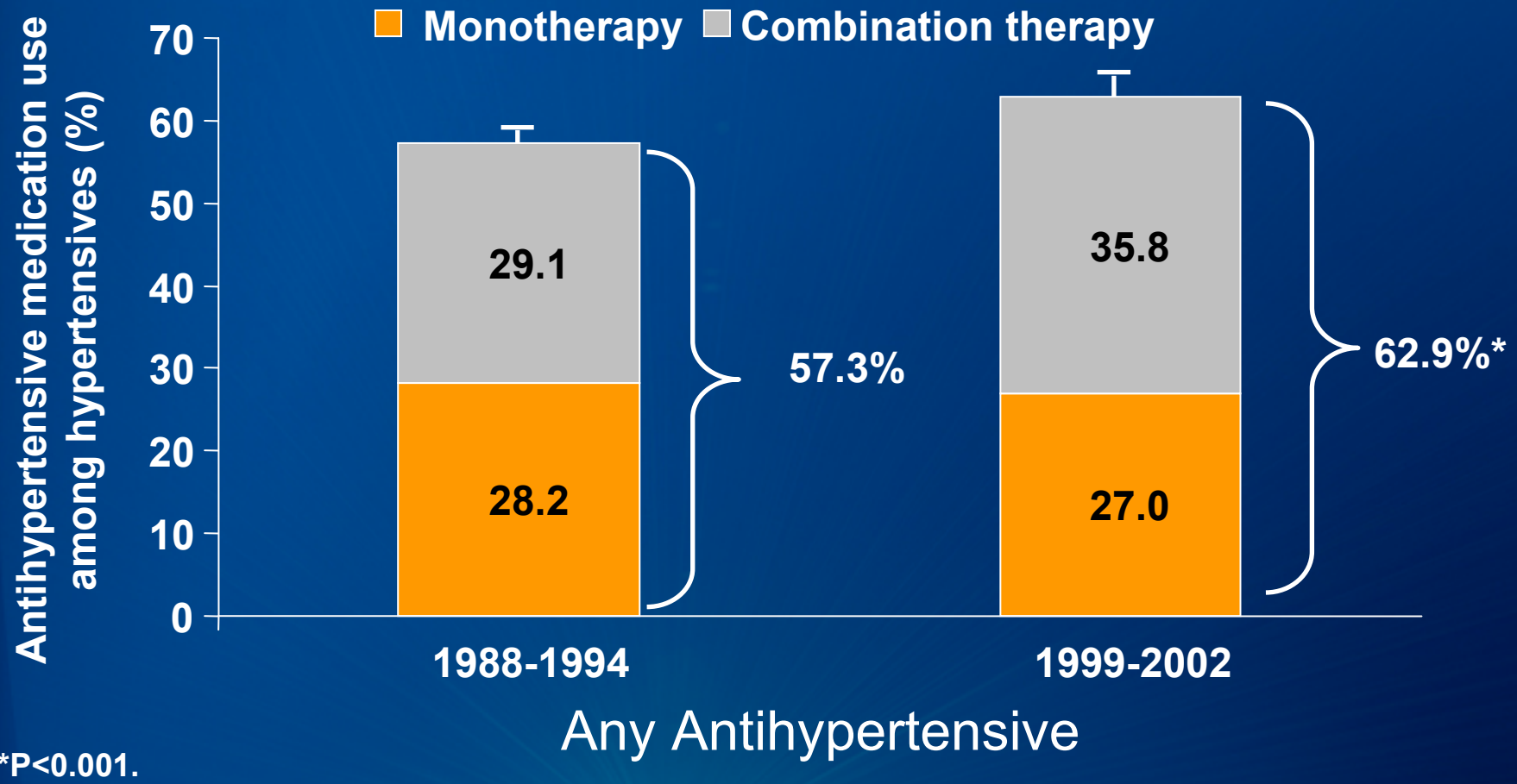
	HCTZ	ARB + HCTZ
Potassium	↓	+/-
Insulin	↑	+/-
Glucose	↑	+/-
Lipids	↑	+/-
Uric Acid	↑	+/-
Adverse events	↑	+/-
Impotence	↑	+/-

Prevalence, Awareness, Treatment and Control of Hypertension: NHANES 1999–2004



Adapted Cheung BM, et al. *Circulation*. 2006;114:II-867.

Antihypertensive Drug Use Among U.S. Adults With Hypertension

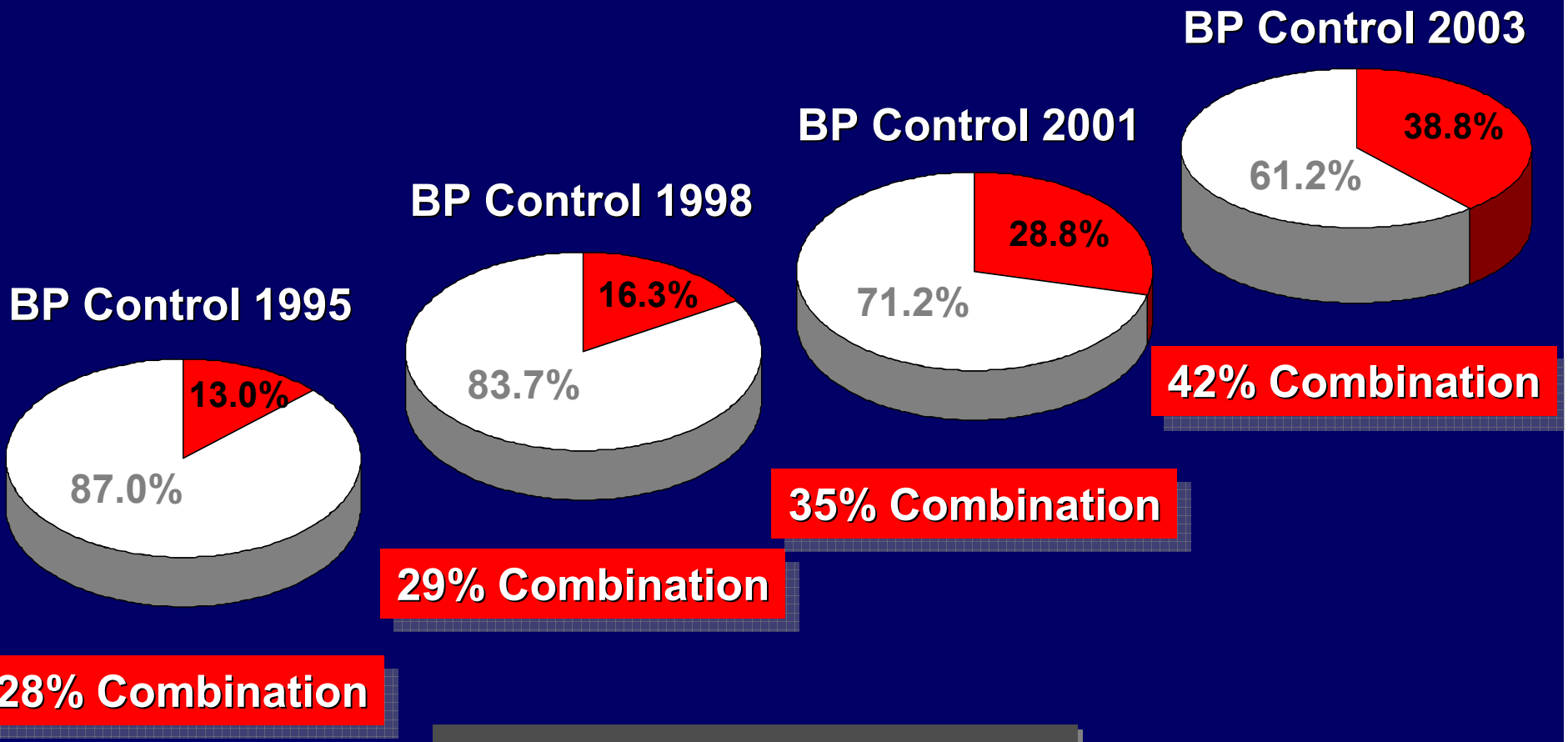


*P<0.001.

Gu Q. et al. *Circulation*. 2006;113:213-221.

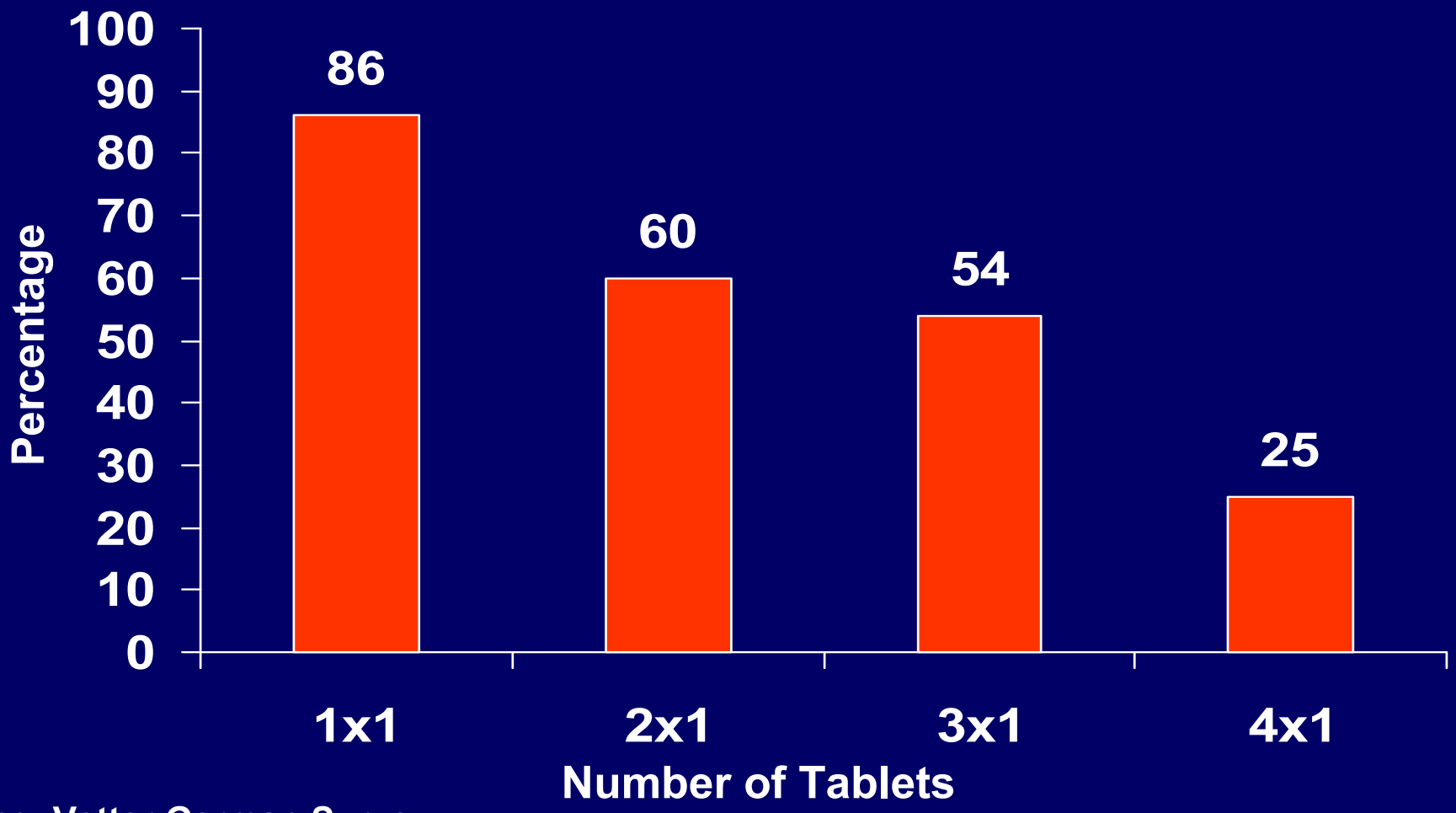
Blood Pressure Control in Hypertensive Patients Treated by GPs in Spain

Use of Combination Therapy



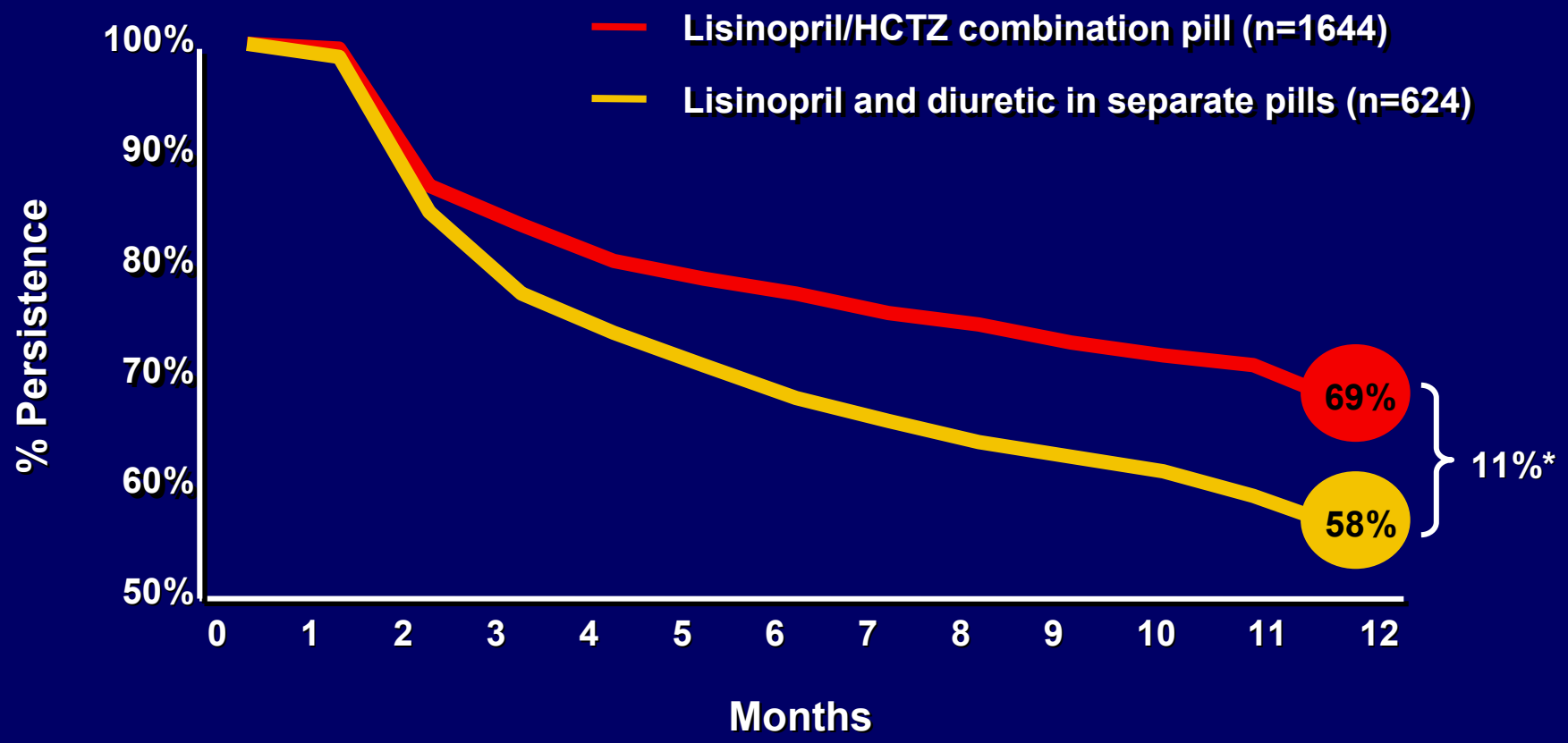
Coca A. Hipertension 2005; 22: 5-1

Compliance in the Treatment of Hypertension



During, Vetter German Survey

Two HTN Agents in One Pill Enhances Adherence

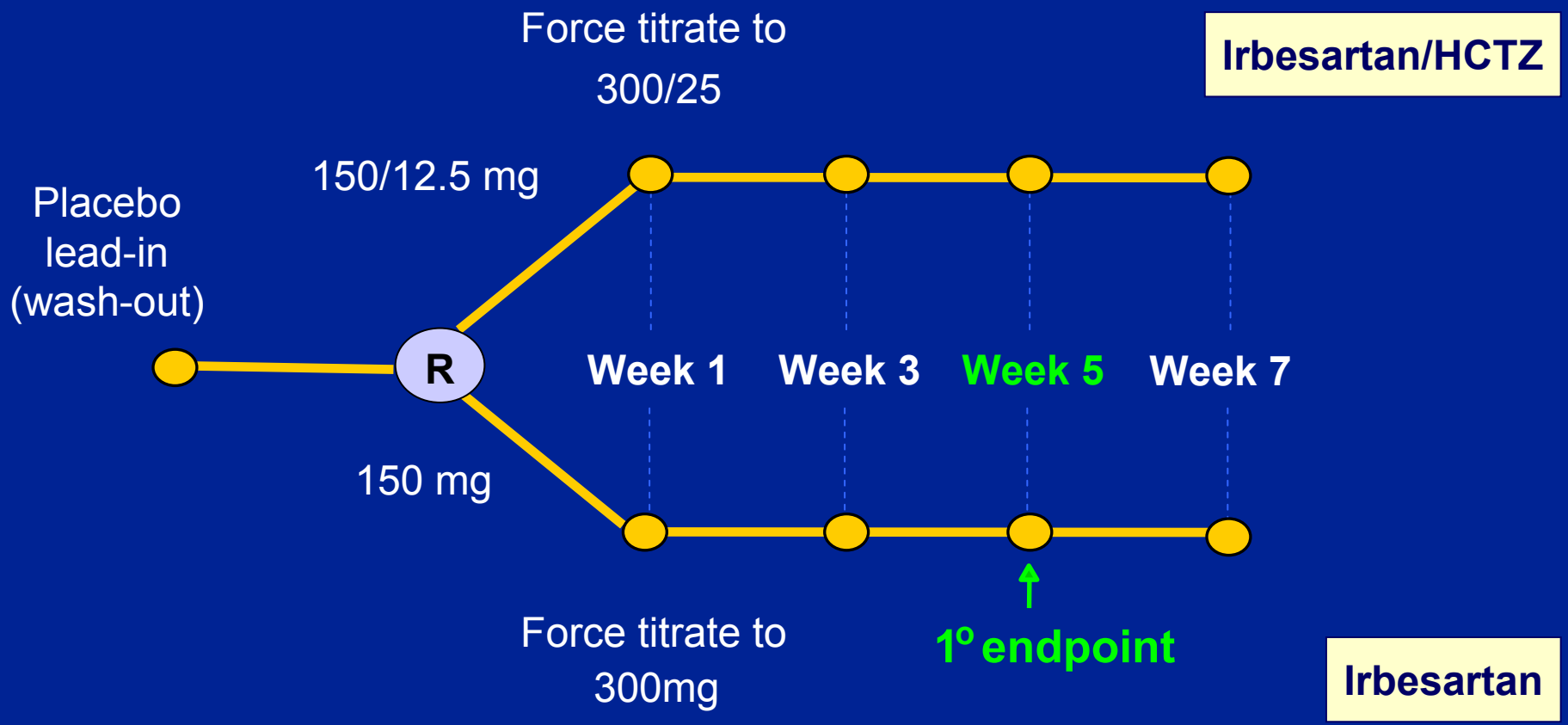


*p<0.05 vs fixed-dose combination

Source: Dezii C. *Managed Care*. 2000;9:S2.

The Future-
Which is Now

First-Line Severe: Study Design



Multicenter, randomized, double-blind, active-controlled, 7-week, parallel arm study

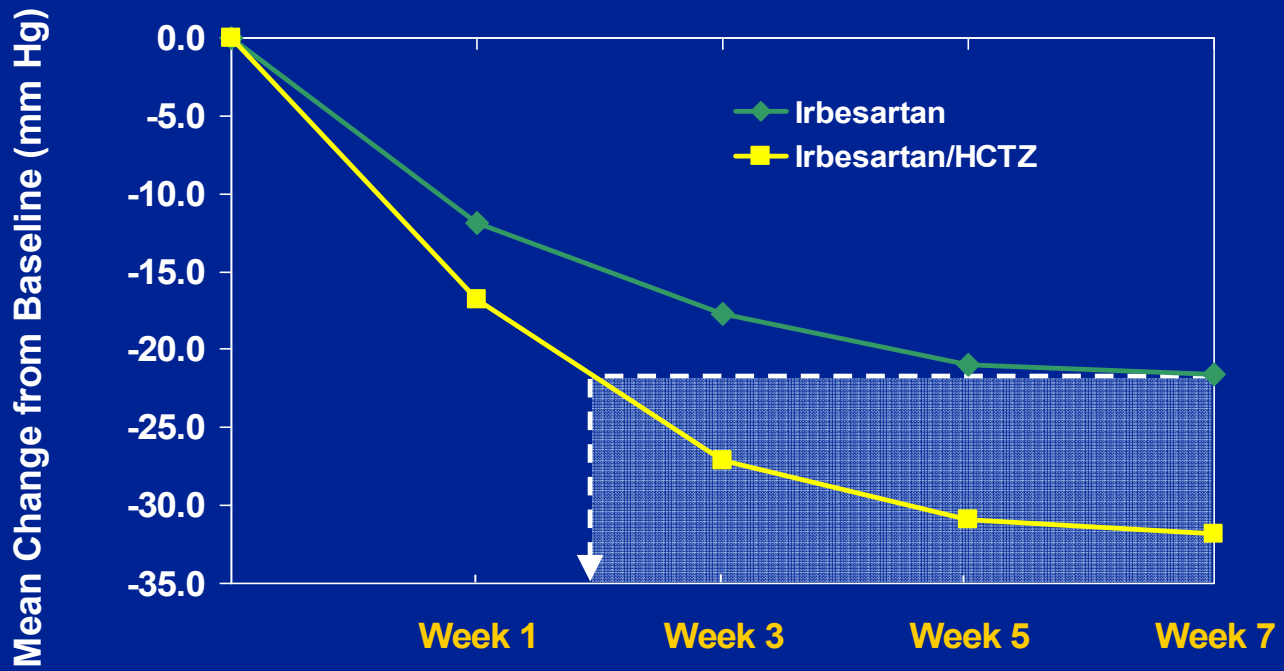
First-Line Severe: Baseline Characteristics

	Irbesartan n=229	Irbesartan/HCTZ n=468
Age (mean)	52.9	52.2
Gender		
male (%)	54.1	59.2
Ethnicity		
white (%)	83.8	84.4
black (%)	14.8	14.3
Weight (kg)	91.8	89.7
Baseline BP (mm Hg)	172/113	171/113

ASH MAY 2006

First-Line Severe: Systolic Blood Pressure

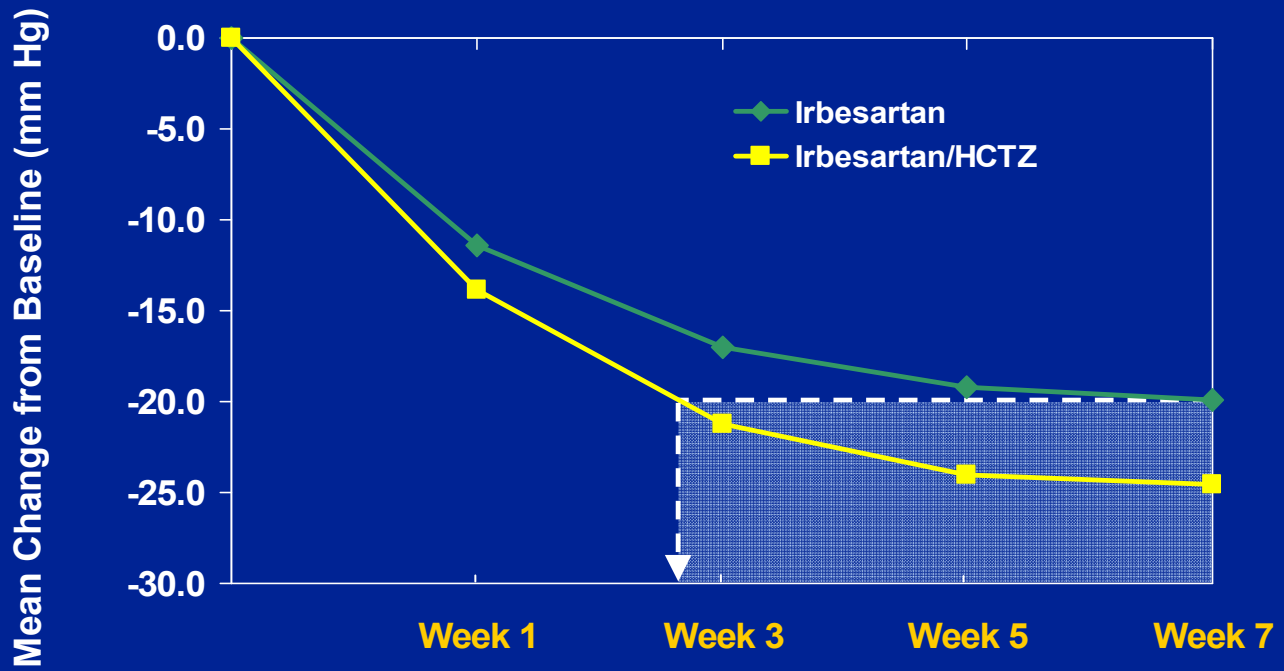
Change in Seated SBP from Baseline



ASH MAY 2006

First-Line Severe: Diastolic Blood Pressure

Change in Seated DBP from Baseline



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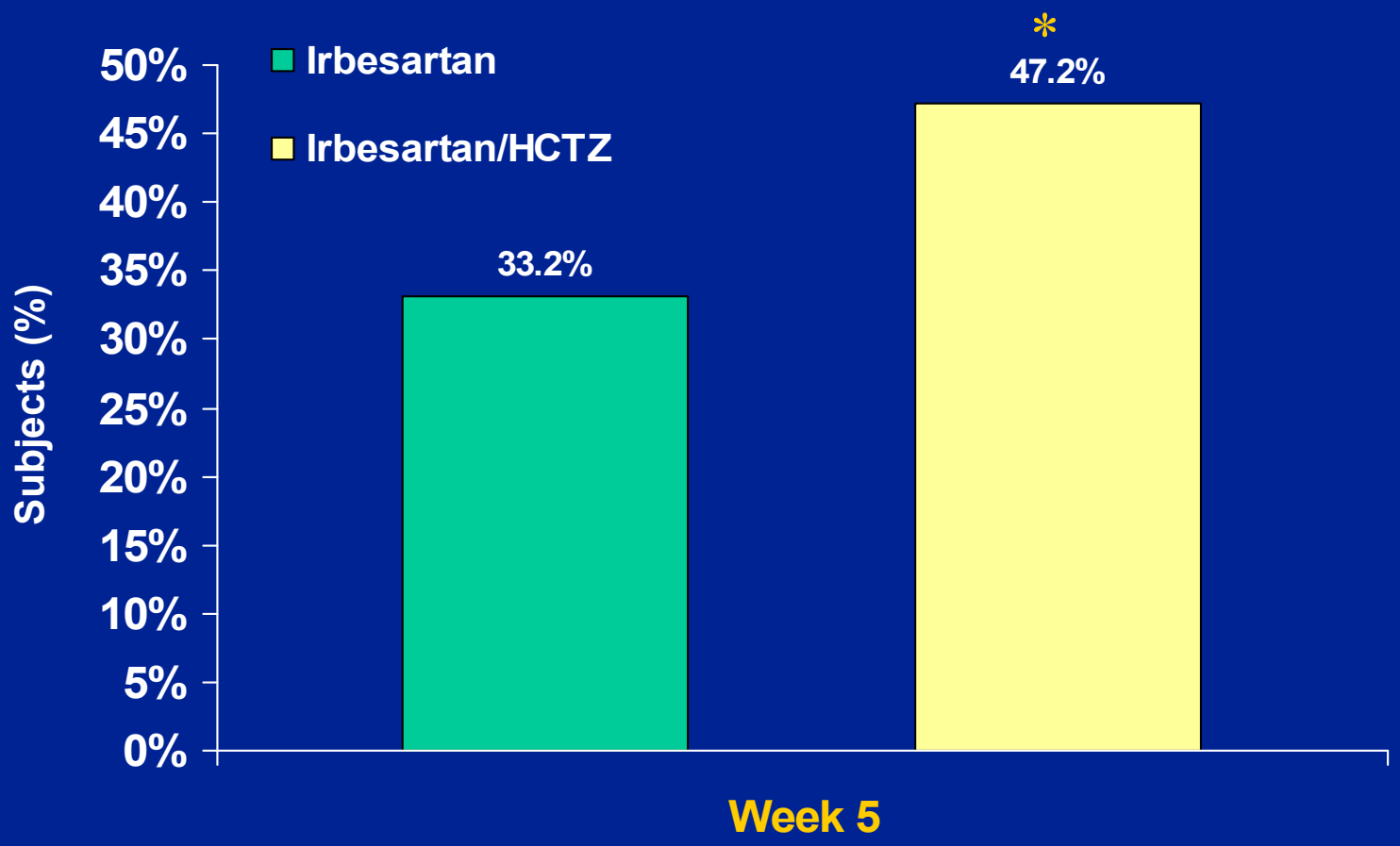
First-Line Severe: Primary Endpoint

DBP Goal Rate: < 90 mm Hg



*Significant difference; Week 5: *P*<.001

ASH MAY 2006

First-Line Severe: Safety/Tolerability

*Overall Adverse Events**

	Irbesartan n=227	Irbesartan/HCTZ n=468
Adverse Event, n (%)	82 (36.1)	140 (29.9)
Treatment-Related AE	23 (10.1)	53 (11.3)
Serious AEs	1 (0.4)	1 (0.2)
Discontinuations due to AE	5 (2.2)	9 (1.9)
Deaths	0	0

*all adverse events included (drug-related and non-drug-related)

One subject in each group experienced a serious adverse event; both events were deemed unrelated to study therapy.

First-Line Severe: Safety/Tolerability

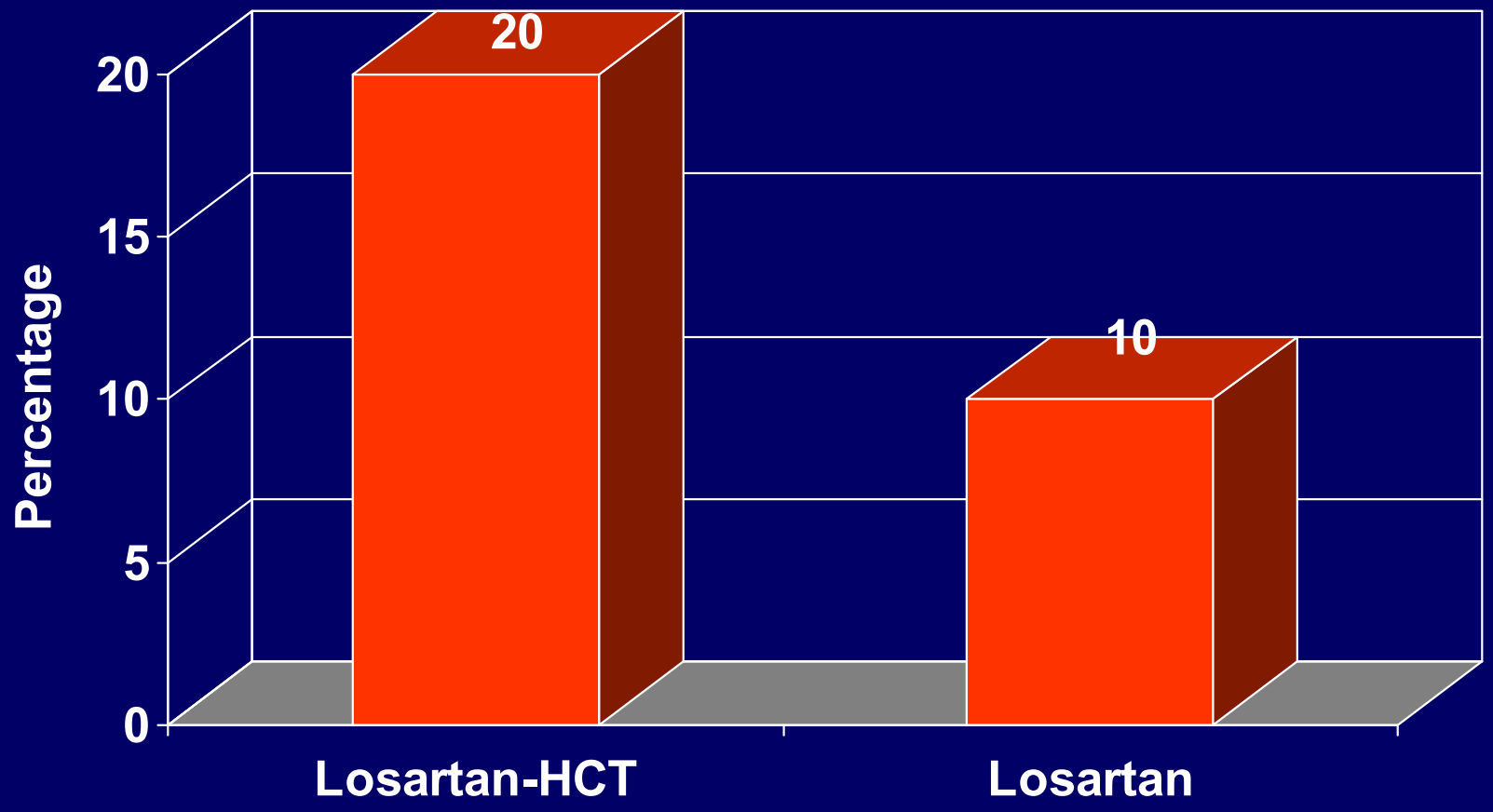
*Pre-specified Adverse Events**

	Irbesartan n=227	Irbesartan/HCTZ n=468
Pre-specified Adverse Events	**11.5**	**8.8**
Dizziness	**4.0**	**3.6**
Headache	**6.6**	**4.3**
Hyperkalemia	**0**	**0.2**
Hypokalemia	**0.4**	**0.6**
Hypotension	**0**	**0.6**
Syncope	**0**	**0**

*all adverse events included (drug-related and non-drug-related)

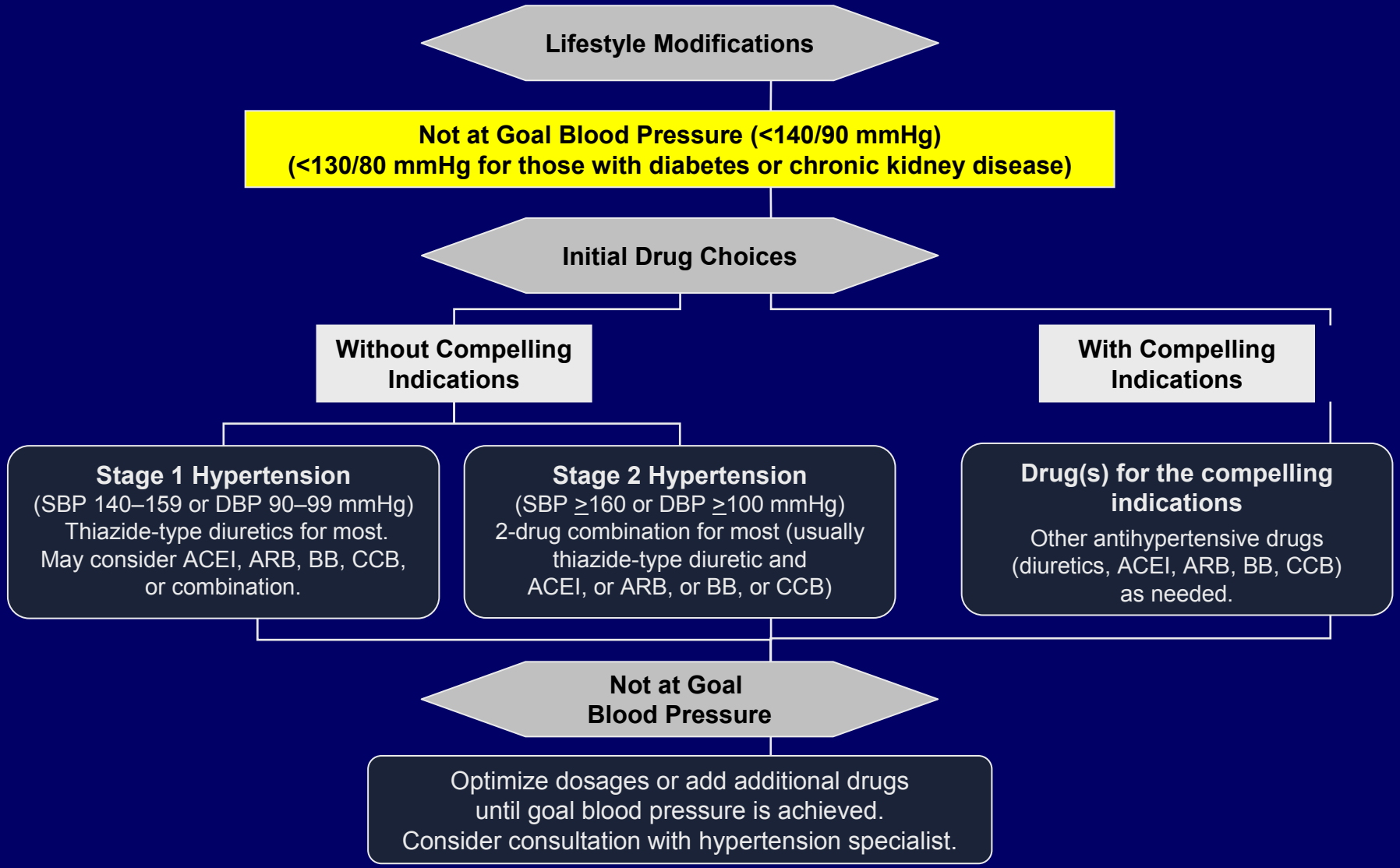
One subject in each group experienced a serious adverse event; both events were deemed unrelated to study therapy.

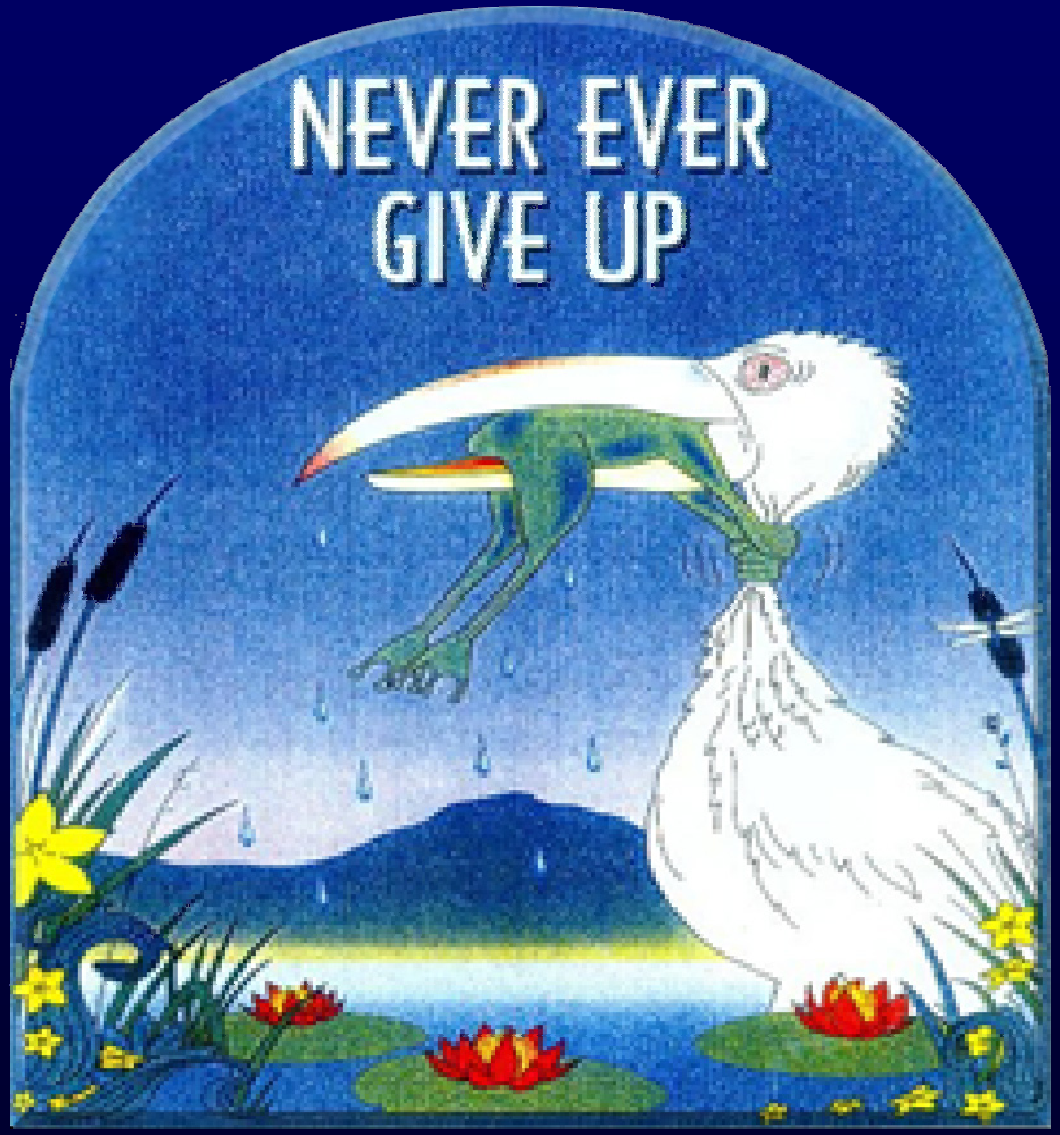
Losartan-HCT First-Line Severe Study Percentage Achieving a DBP < 90mm Hg



Salerno. *J Clin Hypertens.* 2004;6:614–620.

Algorithm for Treatment of Hypertension JNC 7




NEVER EVER
GIVE UP