

# **Resistant Hypertension: Diagnosis and Treatment**

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Today's speaker has no conflict of interest to disclose.

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# Conflicts of Interest During Prior 12 Months

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- Off-Label Use: None

## **AHA Scientific Statement**

### **Resistant Hypertension: Diagnosis, Evaluation, and Treatment**

#### **A Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research**

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# Definition

- Resistant hypertension is defined as blood pressure that remains above goal in spite of concurrent use of 3 antihypertensive agents of different classes.
- Ideally, one of the 3 agents should be a diuretic and all agents should be prescribed at optimal dose amounts.
- As defined, resistant hypertension includes patients whose blood pressure is controlled with use of more than 3 medications. That is, patients whose blood pressure is controlled, but required 4 or more medications to do so, should be considered resistant to treatment.

**AHA Scientific Statement *Hypertension* 2008**

Simplified definition: blood pressure requiring use of 4 antihypertensive agents, whether controlled or uncontrolled.

# RATIONALE FOR A SCIENTIFIC STATEMENT

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- Common medical problem that is increasing in prevalence.
- Group of patients at high cardiovascular risk.
- High occurrence of curable causes of hypertension, including secondary hypertension.
- Identification of patients that may benefit from special therapeutic and diagnostic considerations.
- Practical definition that can be applied both for clinical and research applications.

# UNCONTROLLED BLOOD PRESSURE

## PSEUDORESISTANCE

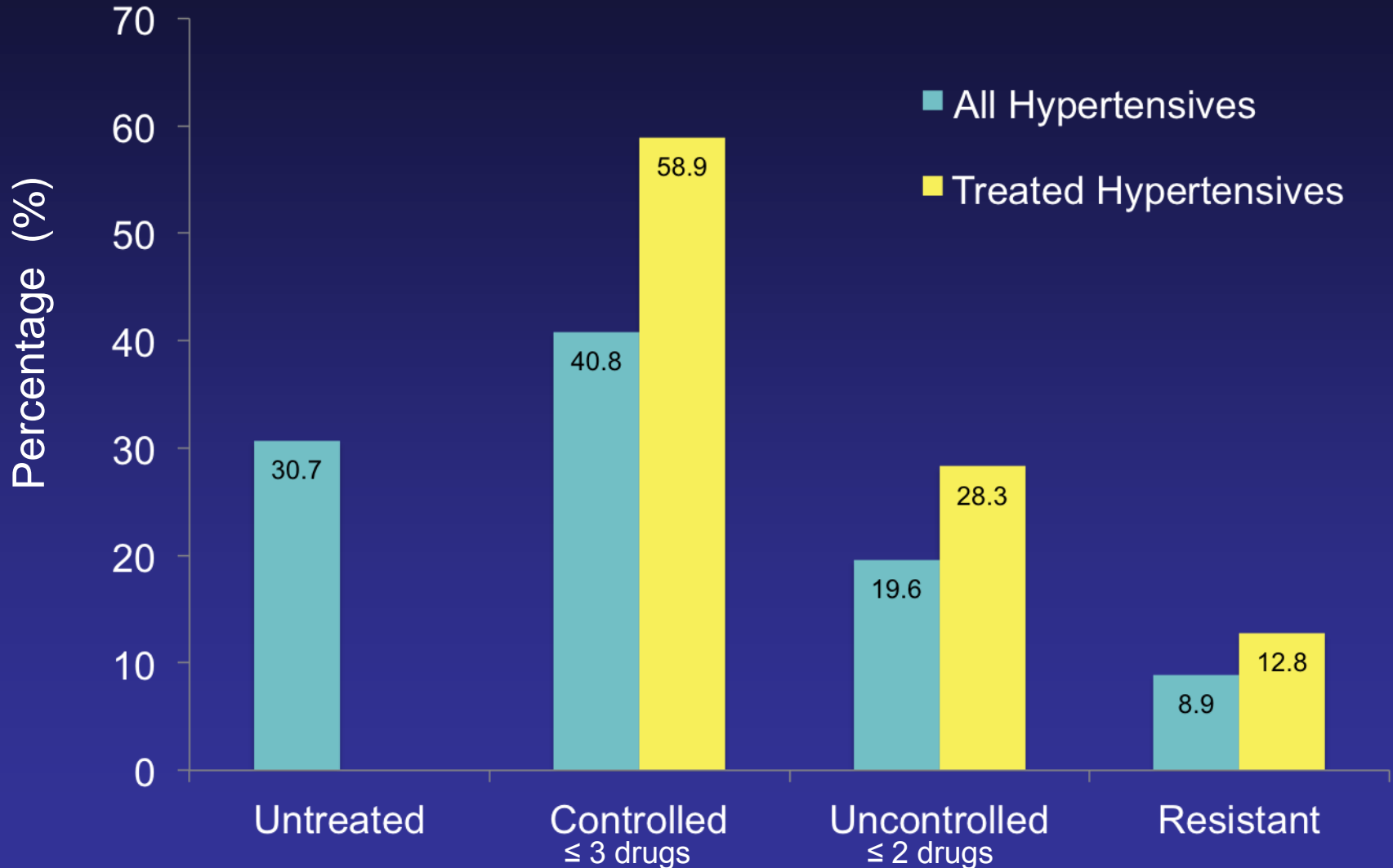
- poor BP technique
- poor adherence
- whitecoat effect

## RESISTANT HYPERTENSION

# Prevalence of Resistant Hypertension in the US

NHANES 2003-2008

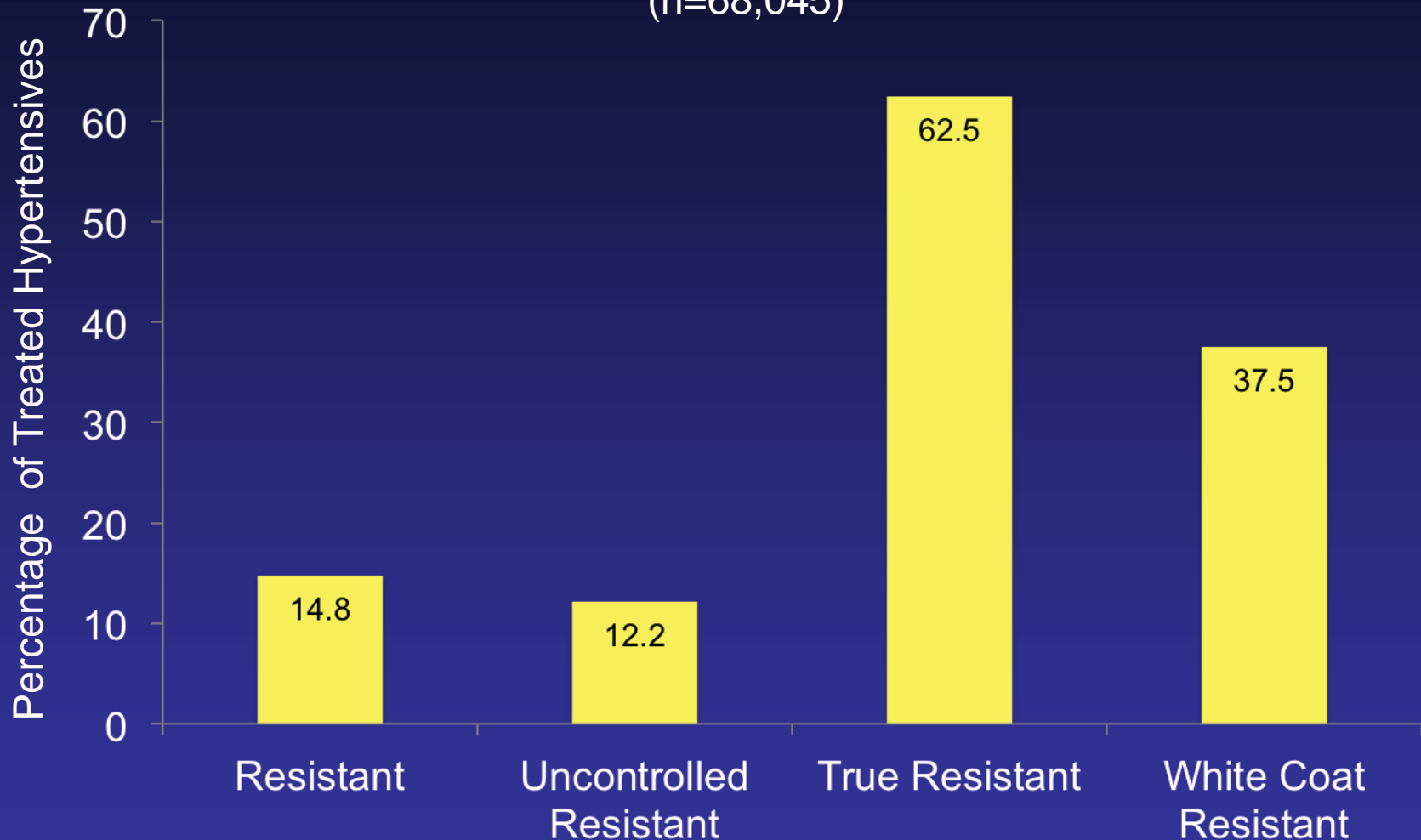
(n=5,230)



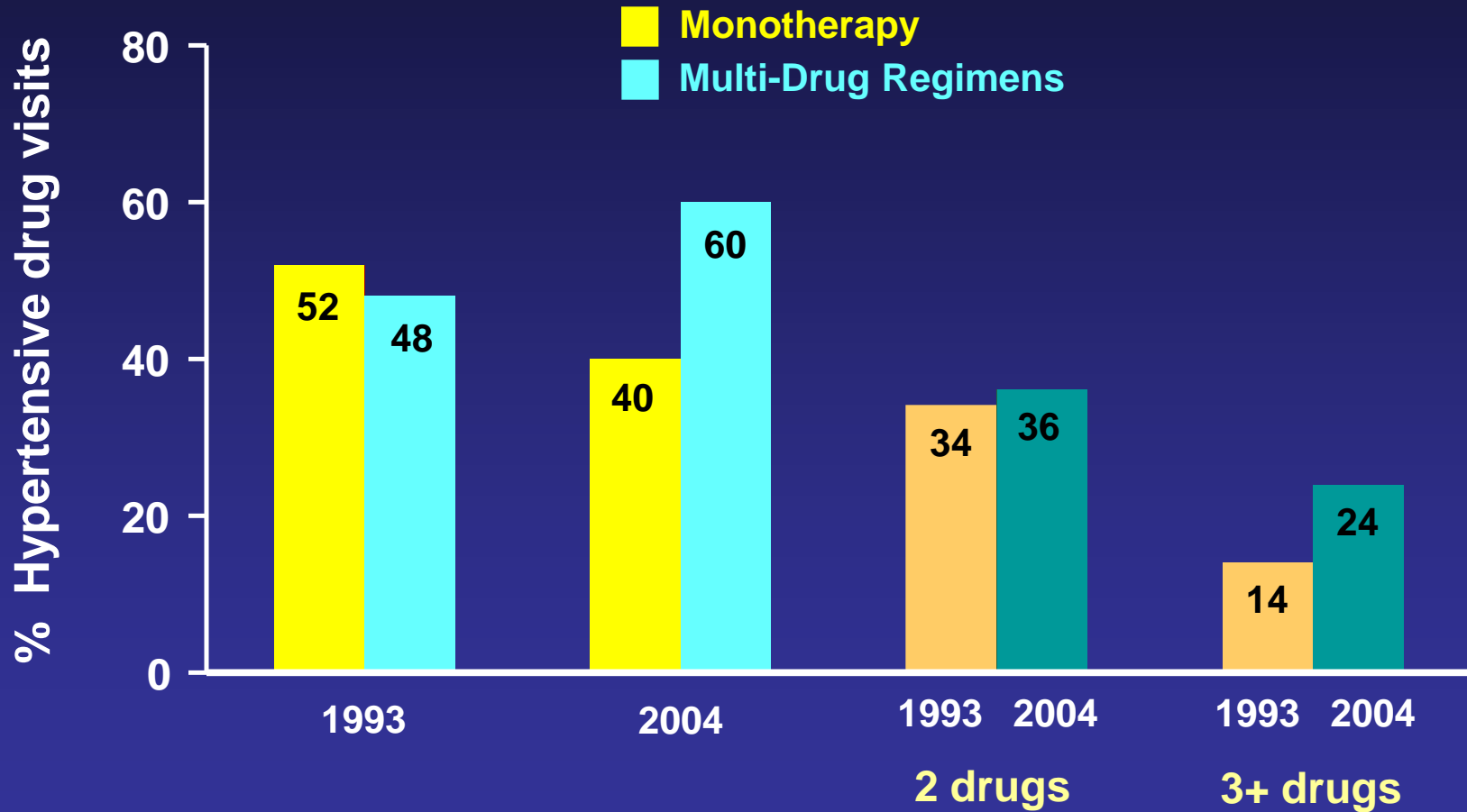
# Prevalence of Resistant Hypertension in Spain

Spanish APBM Registry 2009

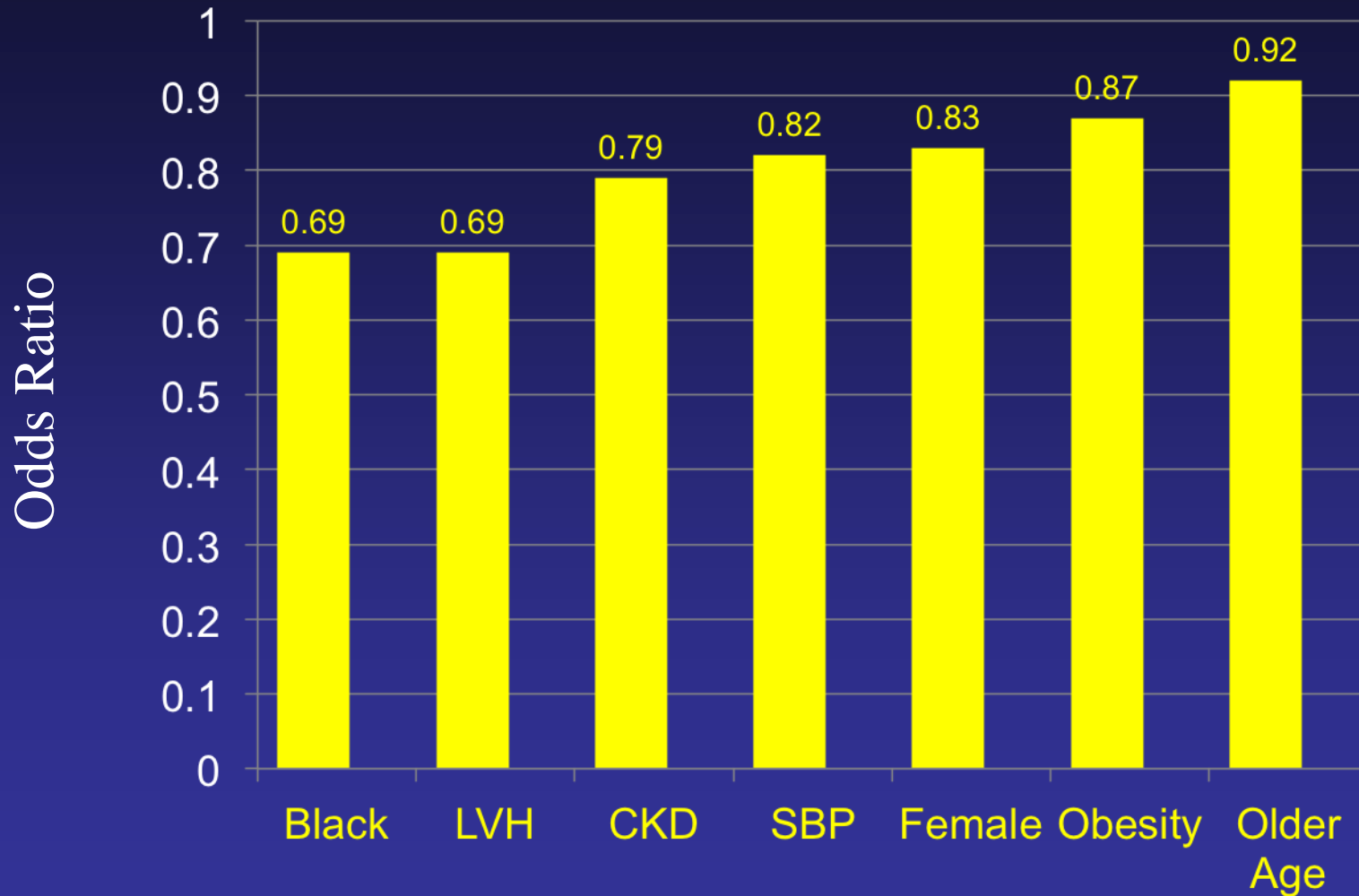
(n=68,045)



# Multi-Drug Treatment Trends 1993-2004



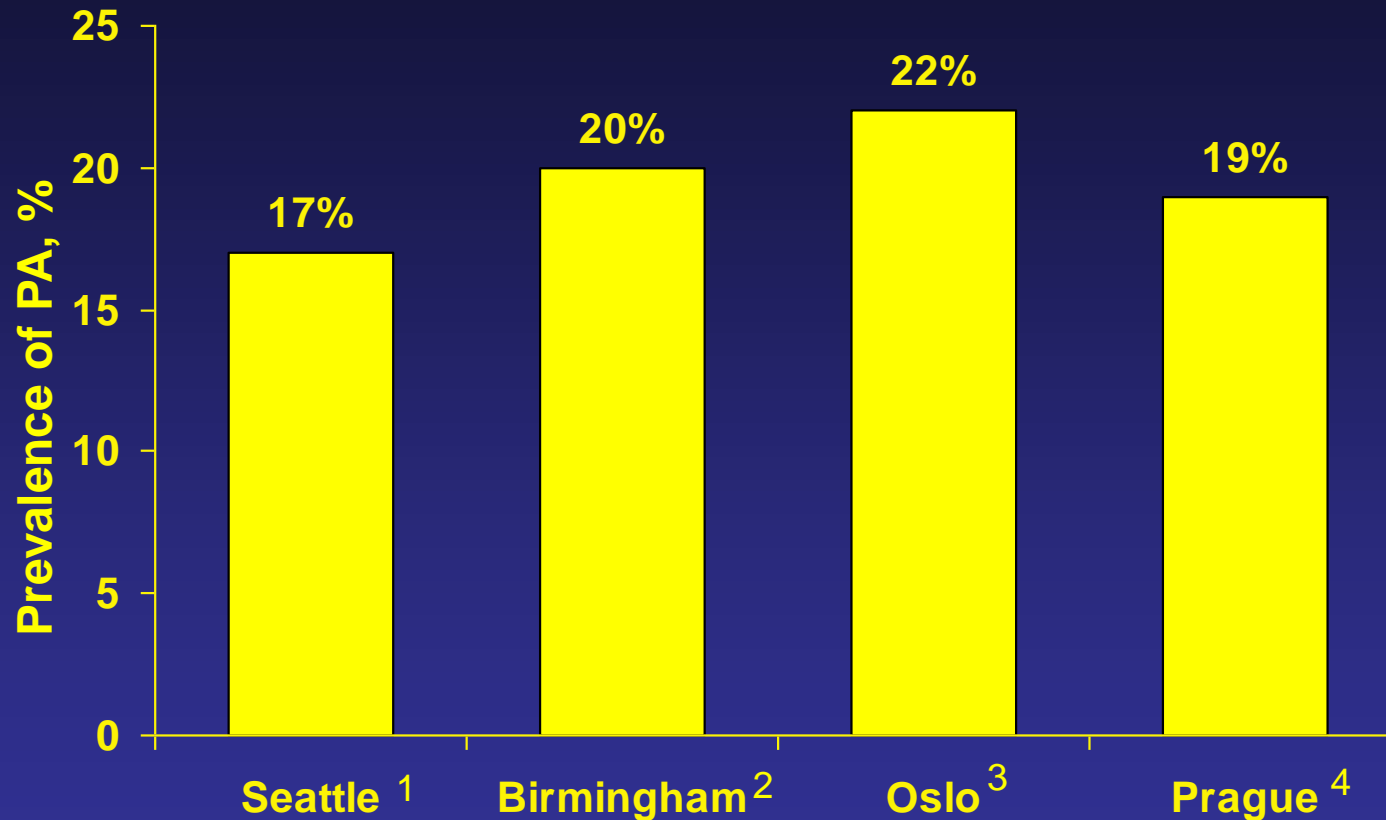
# Predictors of Lack of Blood Pressure Control in ALLHAT



# Evaluation Objectives

- **Confirm true treatment resistance**
  - Patient adherent with 3 or more medications
  - Accurate BP measurement
  - Exclude white coat “resistant hypertension”
- **Screen for secondary causes of hypertension**
  - Primary aldosteronism
  - Renal artery stenosis
  - Obstructive sleep apnea
- **Document degree of target-organ damage**
  - LVH, retinopathy, CKD, proteinuria

# Prevalence of Primary Aldosteronism in Subjects With Resistant Hypertension



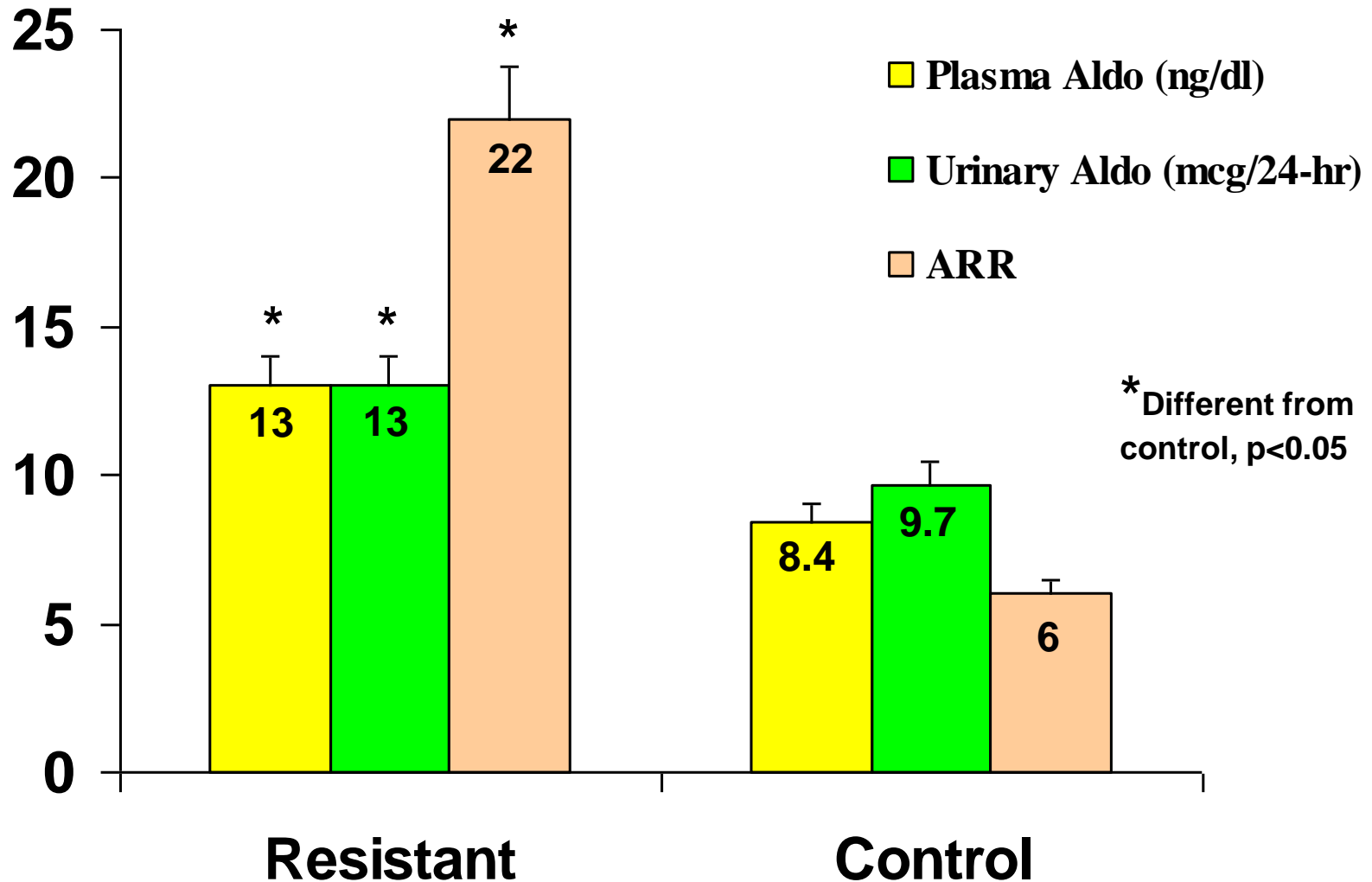
PA = Primary aldosteronism.

1. Gallay BJ, et al. *Am J Kidney Dis.* 2001;37:699-705.
2. Calhoun DA, et al. *Hypertension.* 2002;40:892-896.
3. Eide IK, et al. *J Hypertens.* 2004;22:2217-2226.
4. Strauch B, et al. *J Hum Hypertens.* 2003;17:349-352.

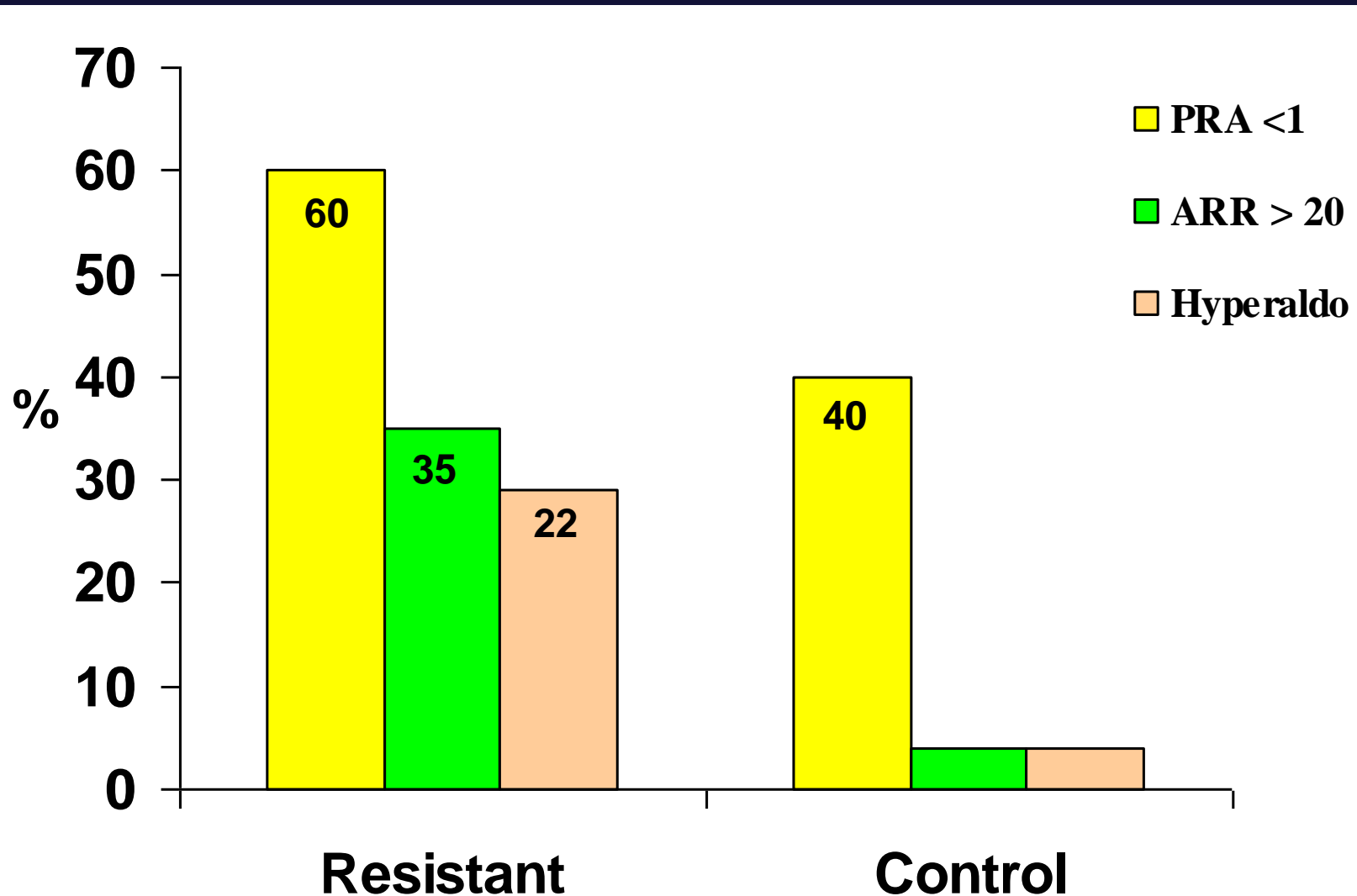
# Comparison of Patients with Resistant Hypertension vs. Control Subjects

	Resistant Hypertension	Controls
<b>N</b>	<b>279</b>	<b>53</b>
<b>Age (years)</b>	<b>54 ± 0.7*</b>	<b>50 ± 1.4</b>
<b>BMI (kg/m )</b>	<b>33.0 ± 0.4</b>	<b>33.9 ± 0.9</b>
<b>Clinic BP (mm Hg)</b>	<b>146 ± 1.2/86 ± 0.9*</b>	<b>125 ± 1.4/79 ± 1.0</b>
<b>Number of BP Meds</b>	<b>4.1 ± 0.1*</b>	<b>0.5 ± 0.1</b>
<b>Potassium (mEq/L)</b>	<b>3.9 ± 0.1*</b>	<b>4.3 ± 0.1</b>

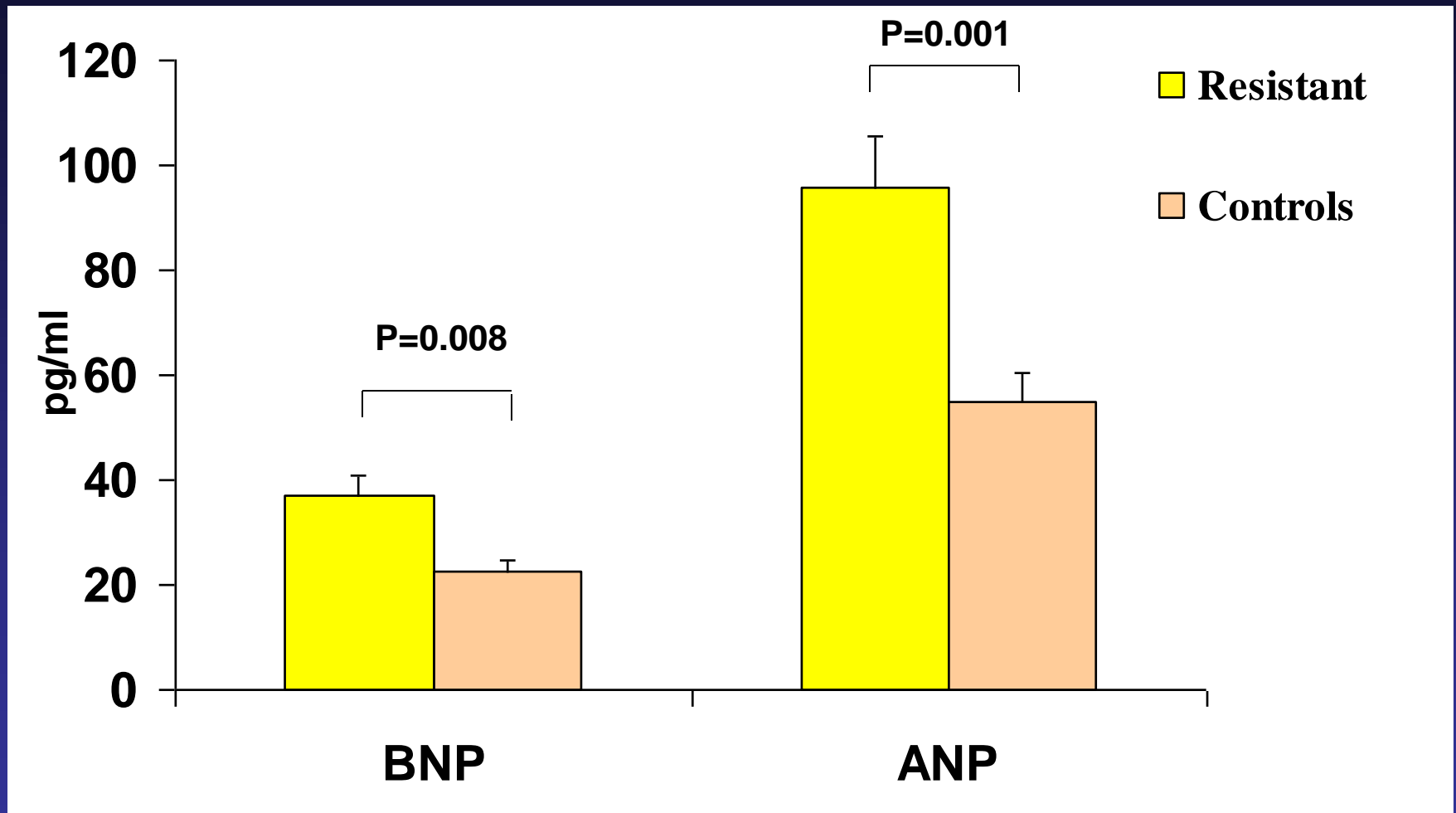
# Plasma and Urinary Aldosterone and ARR in Patients with Resistant Hypertensive Patients vs. Controls



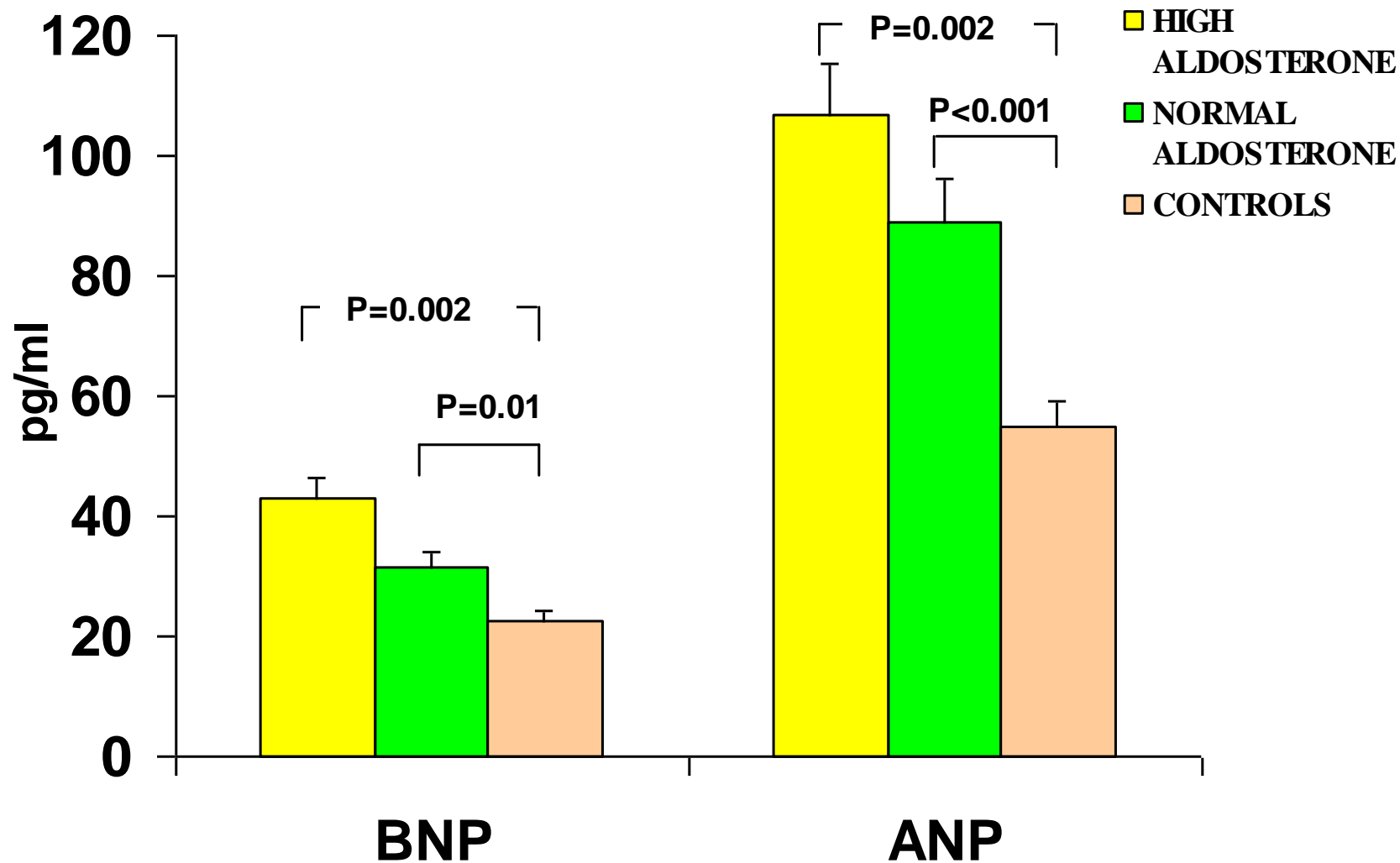
# Percent suppressed PRA, high ARR, and High Aldo in Resistant Hypertension vs. Controls



# BNP and ANP Levels in Patients with Resistant Hypertension vs. Control Subjects



# BNP and ANP Levels in Patients with High and Normal Aldosterone and Resistant Hypertension vs. Control Subjects



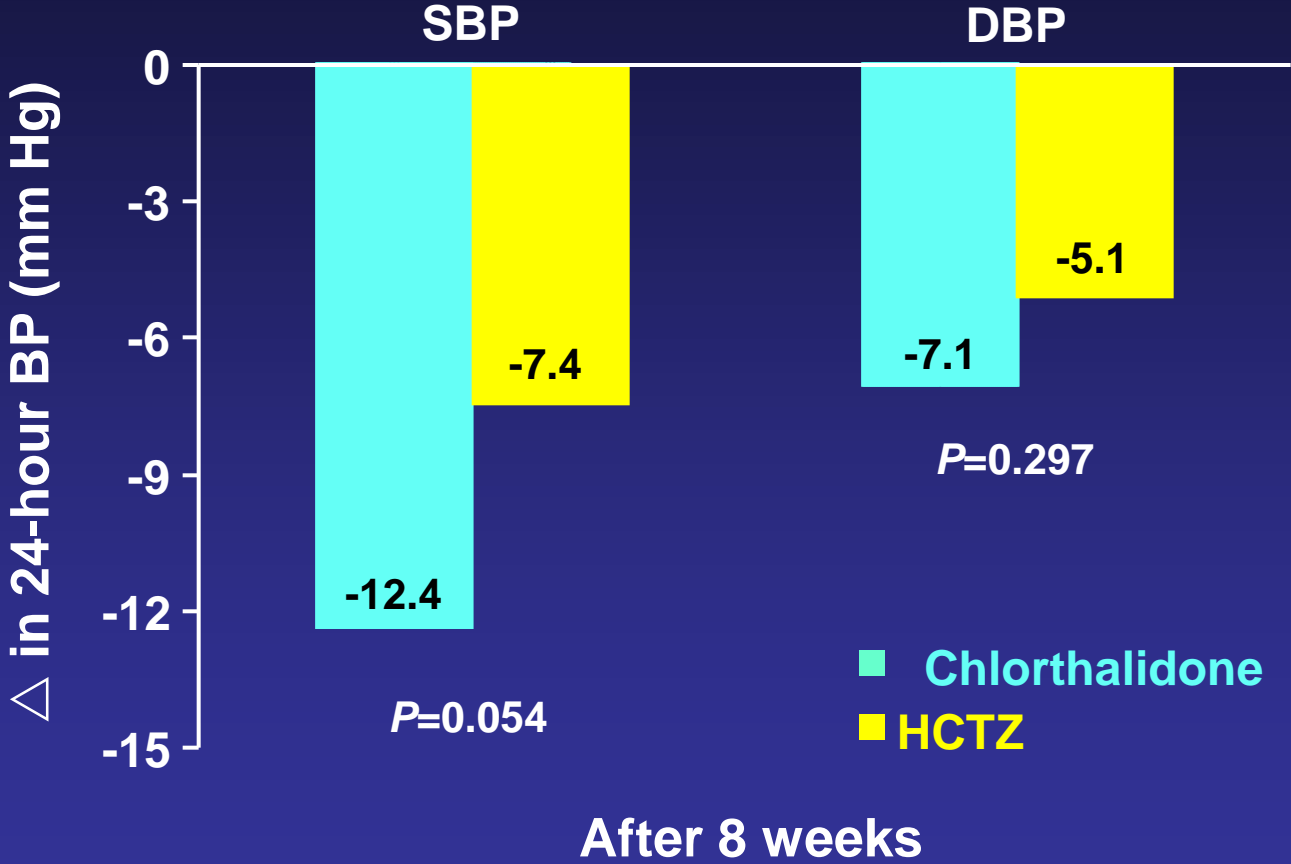
# Potential Mechanisms of Refractory Fluid Retention in Patients with Resistant Hypertension

- Hyperaldosteronism
- Obesity
- African American race
- Chronic kidney disease
- High dietary salt intake

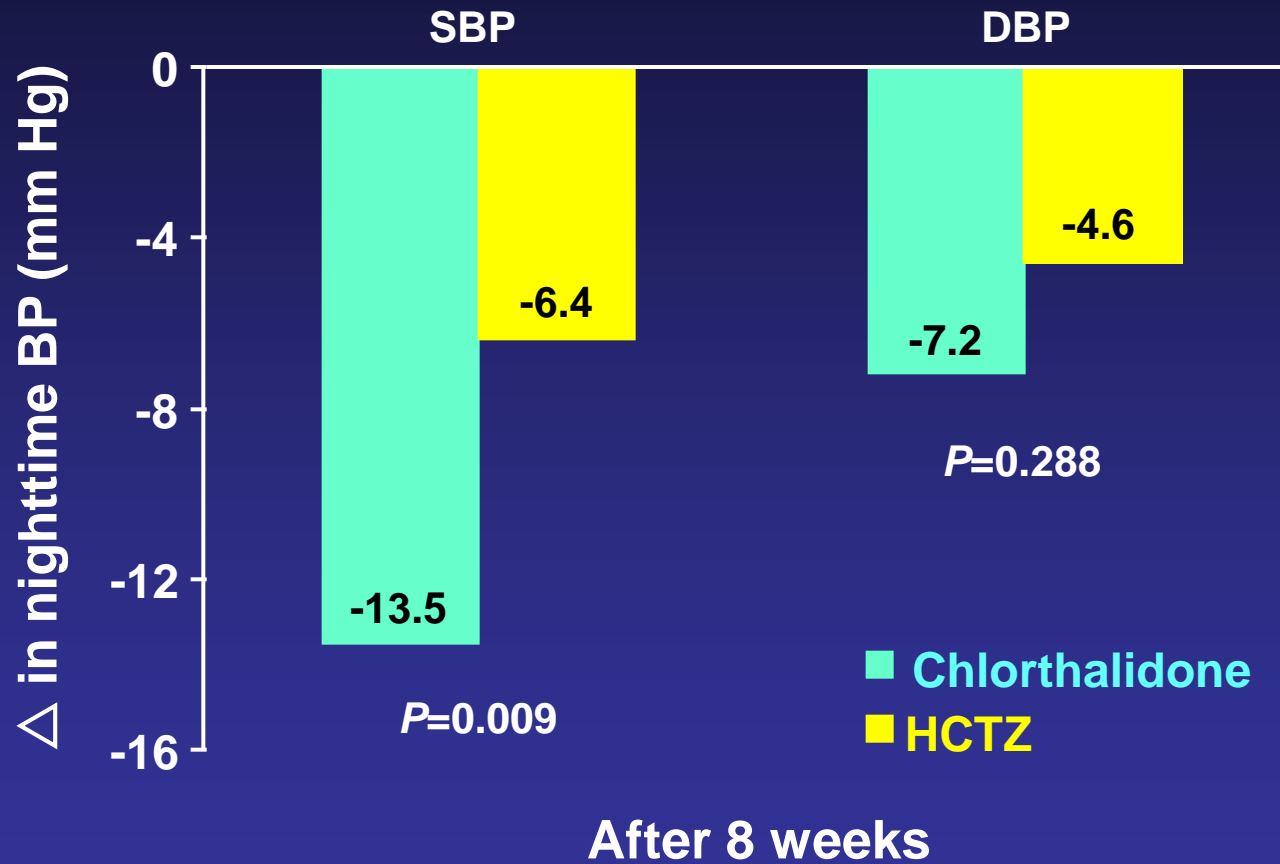
# Generalized Treatment Recommendations

- Life style modifications (weight loss, exercise, low-salt/high fiber diet)
- Standard triple regimen of ACE inhibitor or ARB, thiazide diuretic, and long-acting calcium channel blocker
- Preferential use of chlorthalidone
- Consider use of aldosterone antagonist (spironolactone, eplerenone, amiloride) as fourth drug
- Vasodilating beta-blocker as fifth drug
- Centrally-acting agent as fifth drug (clonidine, guanfacine)
- Vasodilating agents (hydralazine, minoxidil) as last resort

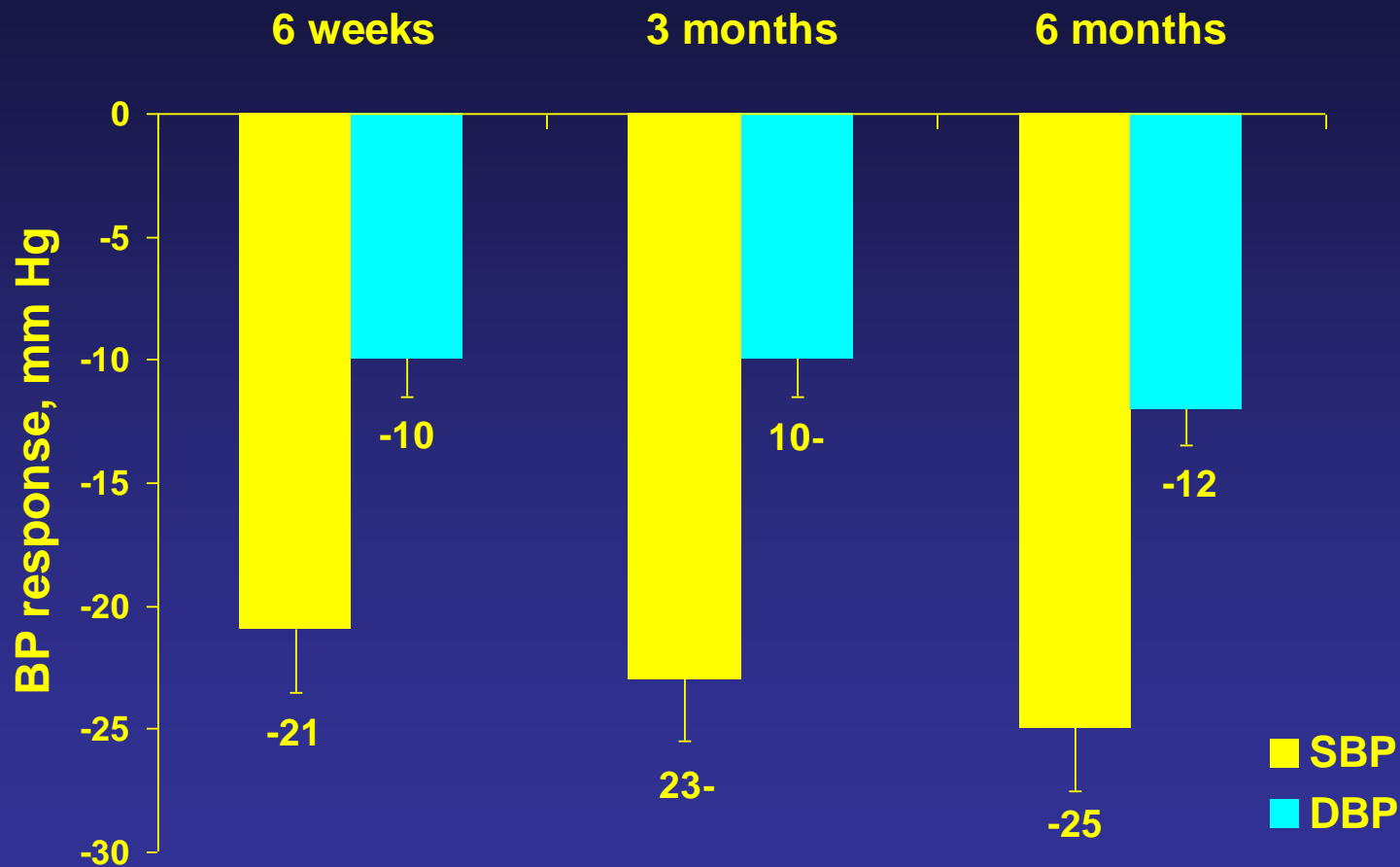
# Chlorthalidone 25 mg vs. HCTZ 50 mg daily



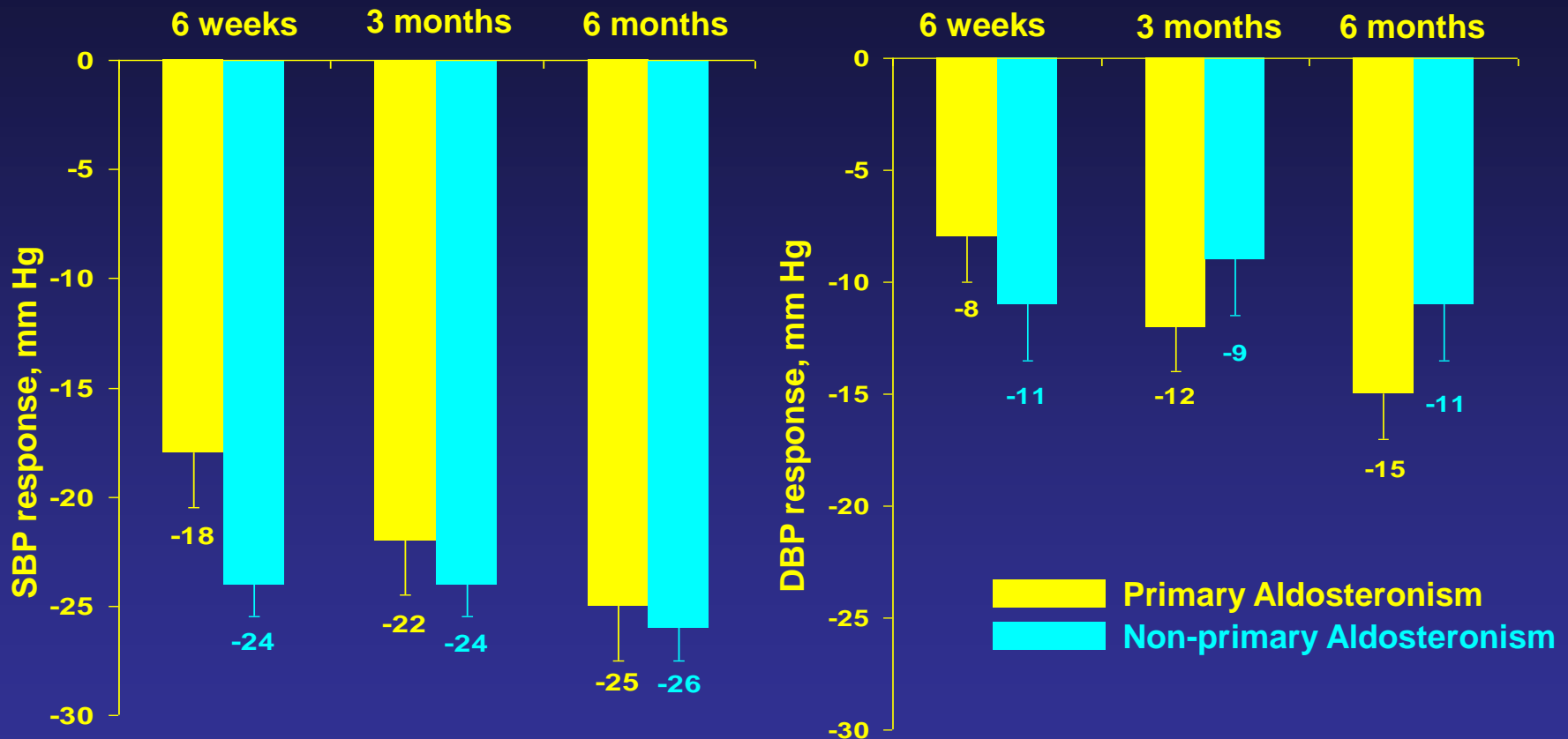
# Chlorthalidone 25 mg vs. HCTZ 50 mg daily



# Blood Pressure Response to Spironolactone in Subjects With Resistant Hypertension

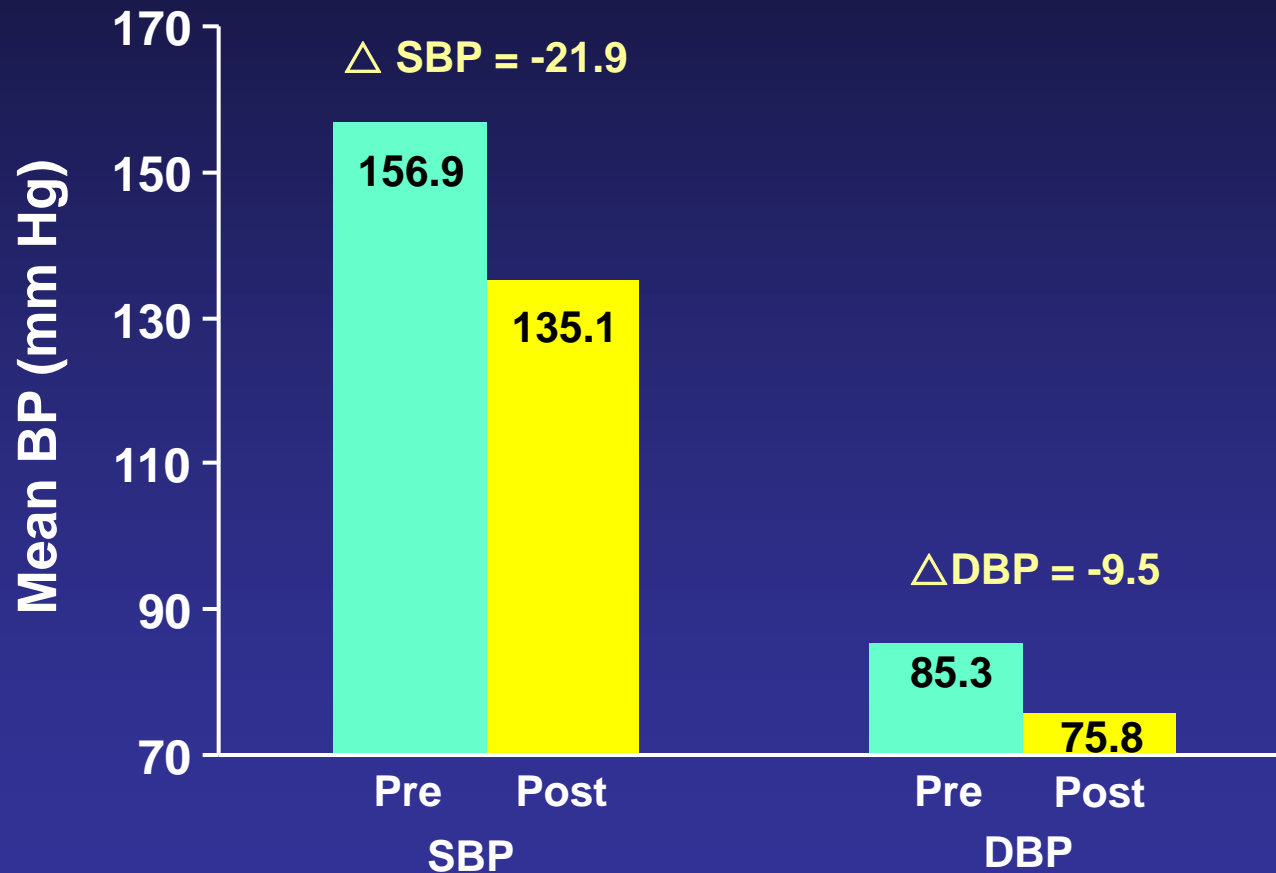


# BP Response to Spironolactone in PA and Non-PA Subjects

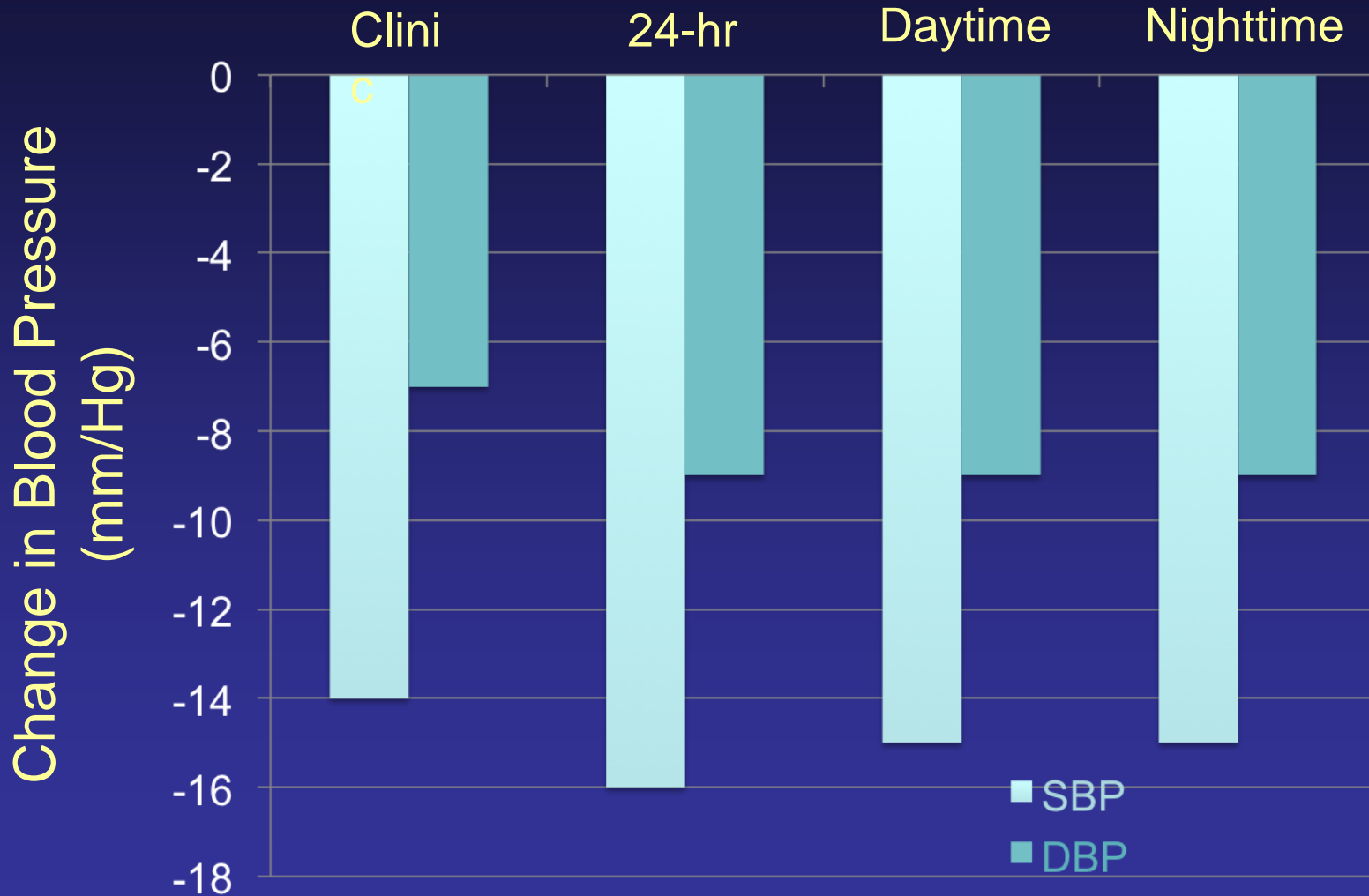


SBP = systolic blood pressure; DBP = diastolic blood pressure  
Nishizaka MK et al. *Am J Hypertens* 2003;16:925-930

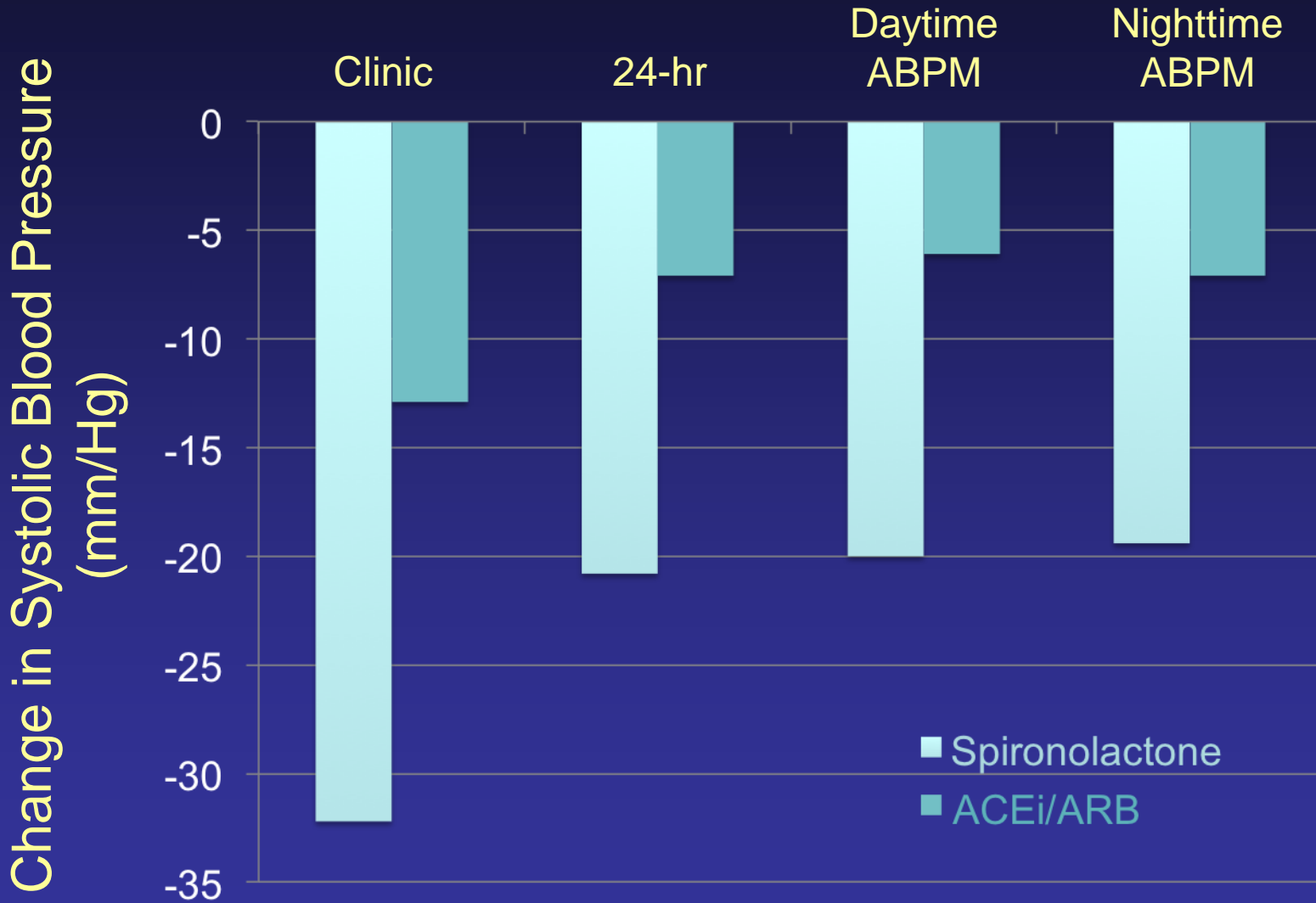
# BP Response with Spironolactone 25-50 mg ASCOT Results



# Change in ABPM Levels with Spironolactone in Patients with True Resistant Hypertension



# Change in SBP with Spironolactone vs. ACEi/ARB in Patients with True Resistant Hypertension



# Diuretic Use: Practical Considerations

- **Chlorthalidone**

- Dosing 12.5-25 mg daily
- Metabolic complications worse, especially hypokalemia
- We typically dose with spironolactone

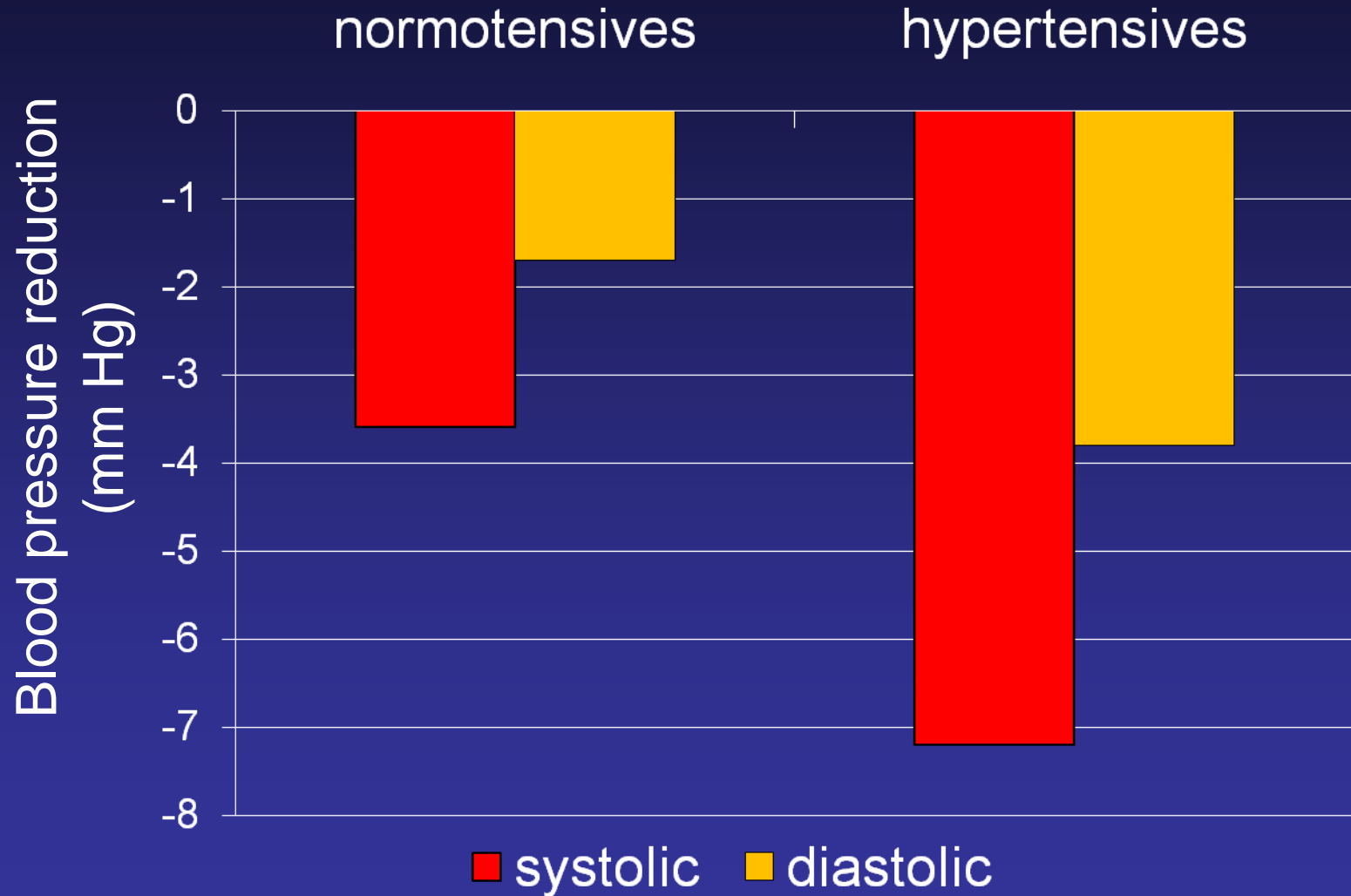
- **Spironolactone**

- Dosing 12.5 -100 mg daily
- Hyperkalemia uncommon if good renal function
- CKD, ACEi/ARB, renin inhibitor, NSAID's increase risk
- Generally well tolerated up to 25 mg
- Breast tenderness/gynecomastia dose dependent

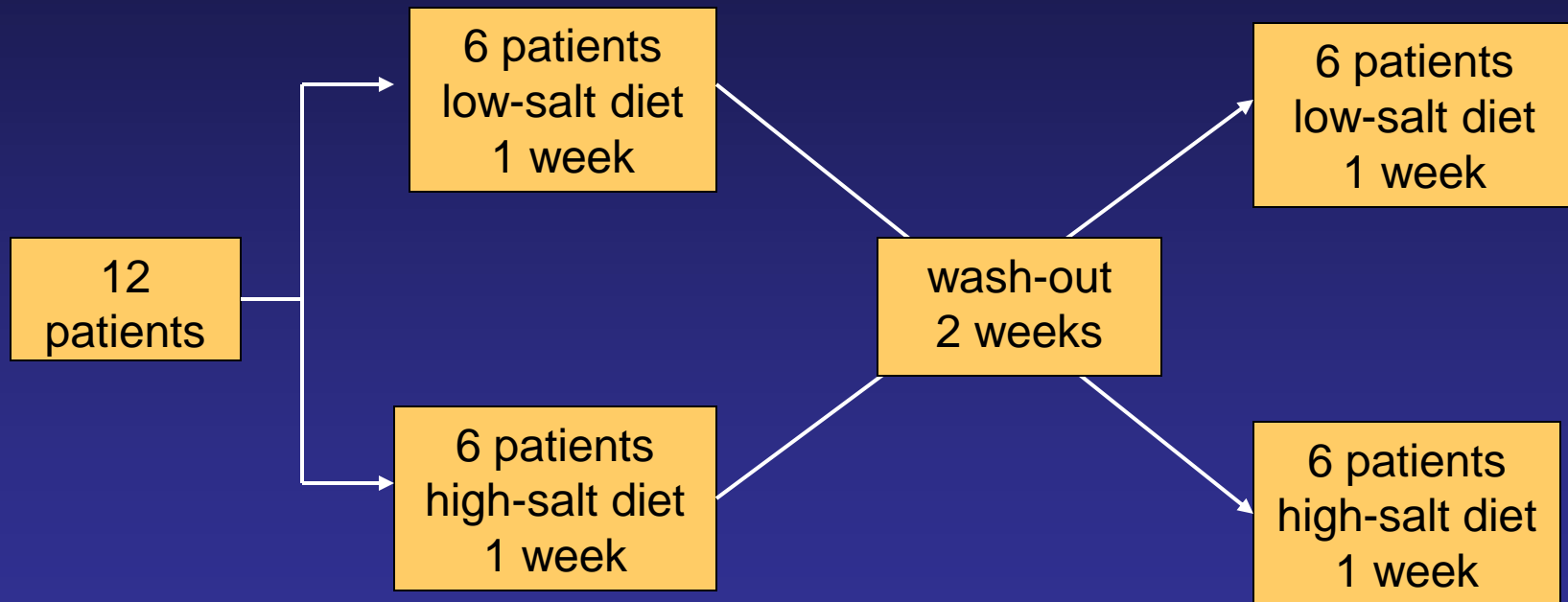
- **Loop diuretics**

- Usually not needed until GFR < 30
- Use with minoxidil or hydralazine
- Long acting agent or twice daily dosing of furosemide

# EFFECTS OF SALT REDUCTION (6 g/day)



# Resistant Hypertension High/Low Dietary Salt Cross-Over Evaluation



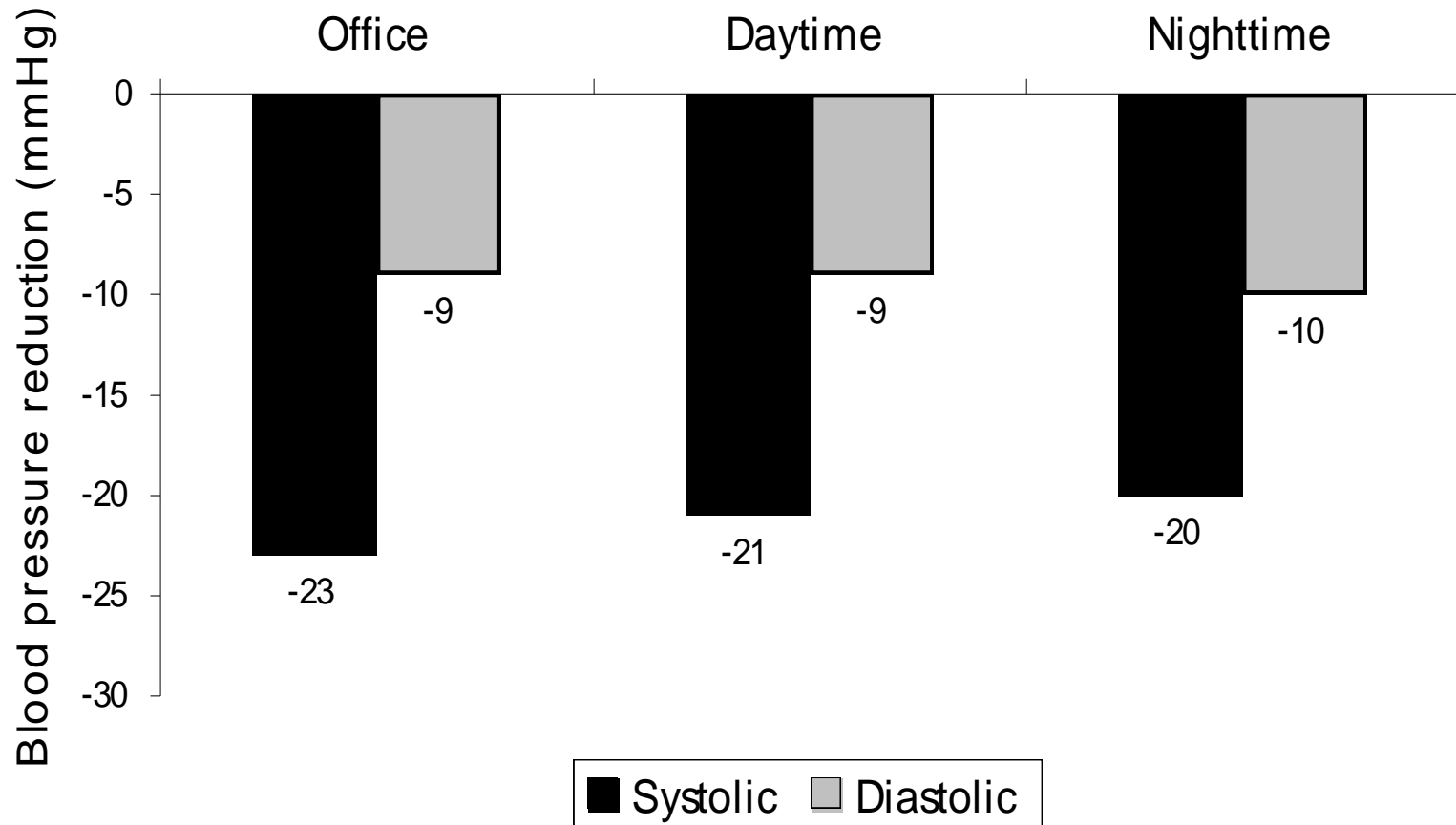
# Results: High-Low Salt Cross-Over

	<b>High-salt (n=12)</b>	<b>Low-salt (n=12)</b>
<b>Weight (kg)</b>	<b>94.3 ± 18.6</b>	<b>92.7 ± 17.6*</b>
<b>BNP (pg/mL)</b>	<b>35.1 ± 32.1</b>	<b>12.5 ± 10.8*</b>
<b>Serum K (mEq/L)</b>	<b>3.8 ± 0.3</b>	<b>4.1 ± 0.5</b>
<b>PAC (ng/dL)</b>	<b>11.1 ± 4.8</b>	<b>15.5 ± 9.3*</b>
<b>PRA (ng/mL/h)</b>	<b>0.9 ± 0.5</b>	<b>14.3 ± 32.6</b>
<b>Ualdo (mcg/24-hr)</b>	<b>11.7 ± 5.1</b>	<b>18.6 ± 11.2*</b>
<b>UK (mEq/24-hr)</b>	<b>56.9 ± 21.8</b>	<b>69.2 ± 27.7*</b>
<b>UNa (mEq/24-hr)</b>	<b>261.5 ± 70.4</b>	<b>48.6 ± 27.2*</b>
<b>TFC (kohms<sup>-1</sup>)</b>	<b>29.3 ± 3.7</b>	<b>26.5 ± 3.5</b>

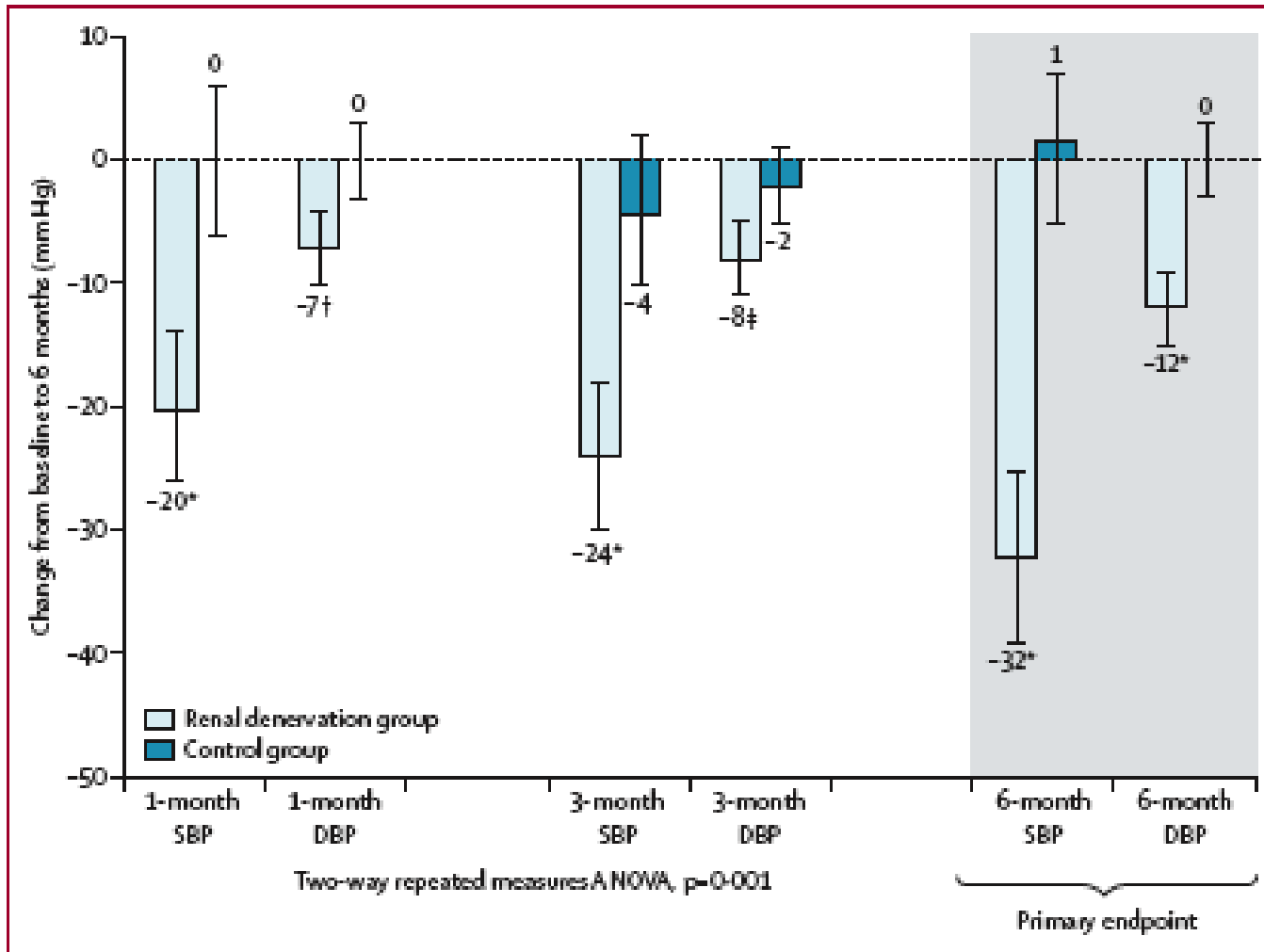
\* Different from high-salt, p<0.05

Pimenta et al. Hypertension 2009

# Reduction in Blood Pressure High to Low Salt Ingestion



# Simplicity Study: Renal Nerve Ablation for Resistant Hypertension



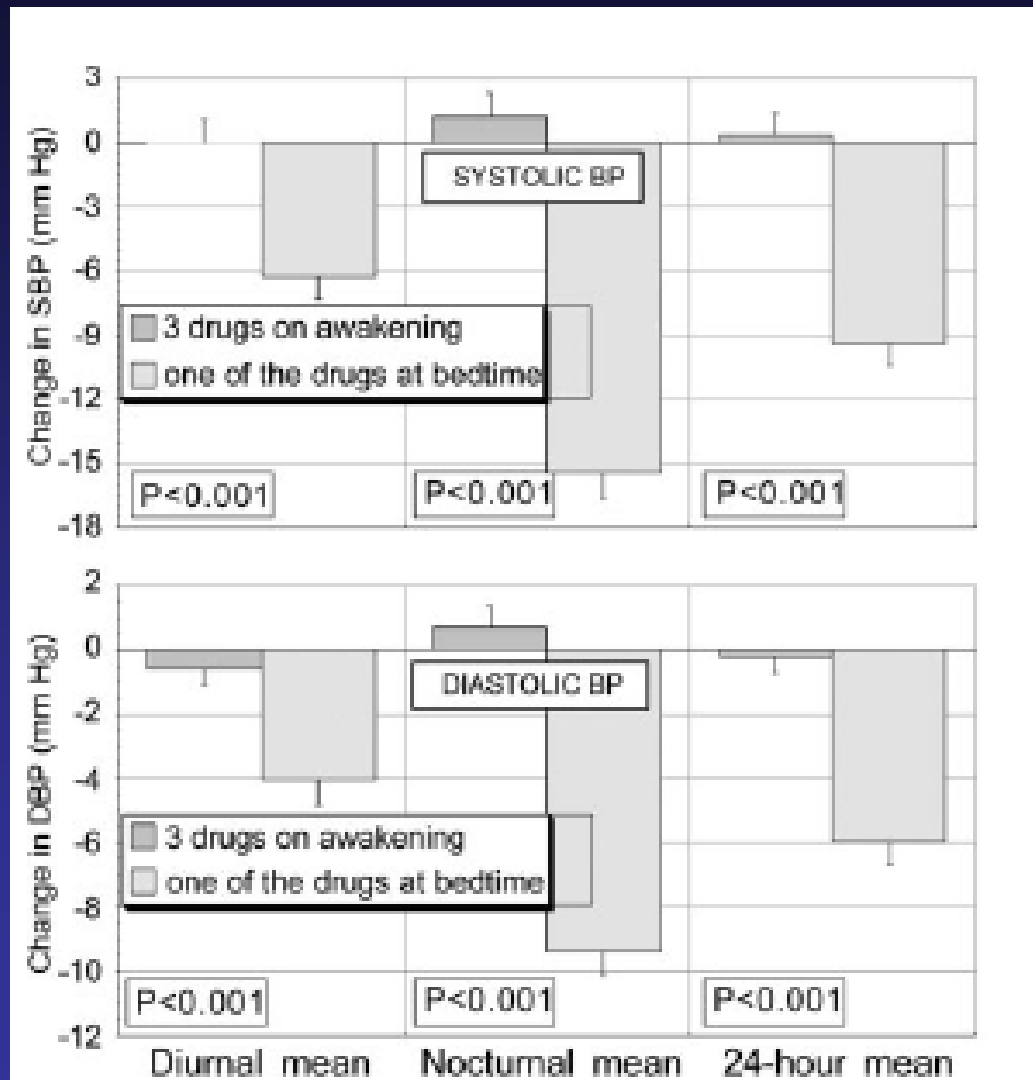
# Open-label Assessment of Carotid Sinus Stimulation for Resistant HTN

**Table 2**

**Blood Pressure Results, Mean Change ( $\Delta$ )  
Presented for Office and Ambulatory Readings**

	$\Delta$ 3 Months	$\Delta$ 1 Year	$\Delta$ 2 Years
<b>Office blood pressure</b>	<b>n = 37</b>	<b>n = 26</b>	<b>n = 17</b>
SBP, mm Hg	$-21 \pm 4$ (p < 0.001)	$-30 \pm 6$ (p < 0.001)	$-33 \pm 8$ (p = 0.001)
DBP, mm Hg	$-12 \pm 2$ (p < 0.001)	$-20 \pm 4$ (p < 0.001)	$-22 \pm 6$ (p = 0.002)
HR, beats/min	$-8 \pm 2$ (p < 0.001)	$-8 \pm 2$ (p = 0.001)	$-11 \pm 4$ (p = 0.008)
<b>Ambulatory blood pressure</b>	<b>n = 26</b>	<b>n = 15</b>	<b>n = 8</b>
SBP, mm Hg	$-6 \pm 3$ (p = 0.102)	$-13 \pm 3$ (p < 0.001)	$-24 \pm 8$ (p = 0.017)
DBP, mm Hg	$-4 \pm 2$ (p = 0.041)	$-8 \pm 2$ (p = 0.001)	$-13 \pm 5$ (p = 0.049)
HR, beats/min	$-5 \pm 2$ (p = 0.001)	$-6 \pm 2$ (p = 0.012)	$-11 \pm 34$ (p = 0.005)

# Bedtime dosing of one BP medication in Resistant Hypertension



# Summary

- Resistant hypertension is a common medical problem that is increasing in prevalence.
- Mechanisms are multiple, but aldosterone excess and high dietary salt ingestion contributing to persistent intravascular fluid retention appears to be an important underlying factor.
- Treatment predicated upon lifestyle changes, combining agents from different classes, effective use of diuretics