

# **Aldosterone, Hypertension and Cardiovascular Risk**

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# Conflicts of Interest in Last 12 Months

- Grant Support: Novartis, NHLBI
- Consultant: Novartis, CVRx
- Off-label Use: None

# Conn's Syndrome

**“...a new clinical syndrome which is designated temporarily as primary aldosteronism. In its fully developed state it is characterized by the presence in the urine of excessive amounts of a sodium-retaining corticoid, by severe hypokalemia, hypernatremia, alkalosis...”**

**Conn JW. Primary aldosteronism, a clinical syndrome. J Lab Clin Med 1955;45:3-17.**

**Historical Prevalence of Primary Aldosteronism:  
1-2% of General Hypertensive Population**

*Hypokalemia in the Hypertensive Patient: With  
Observations on the Incidence of Primary  
Aldosteronism*

Kaplan NM. *Annals Internal Med* 1967;66:1079-1089

*The Incidence Rate of Pheochromocytoma and  
Conn's Syndrome in Denmark, 1977-1981*

Andersen GS, Toftdahl DB, Lund JO, Strandgaard S, Nielson  
PE. *J Human Hypertens* 1988;2:187-189

## **Contemporary Prevalence of Primary Aldosteronism: 10-12% of General Hypertensive Population**

***Evidence that Primary Aldosteronism May Not  
Be Uncommon: 12% Incidence Among  
Antihypertensive Drug Trial Volunteers***

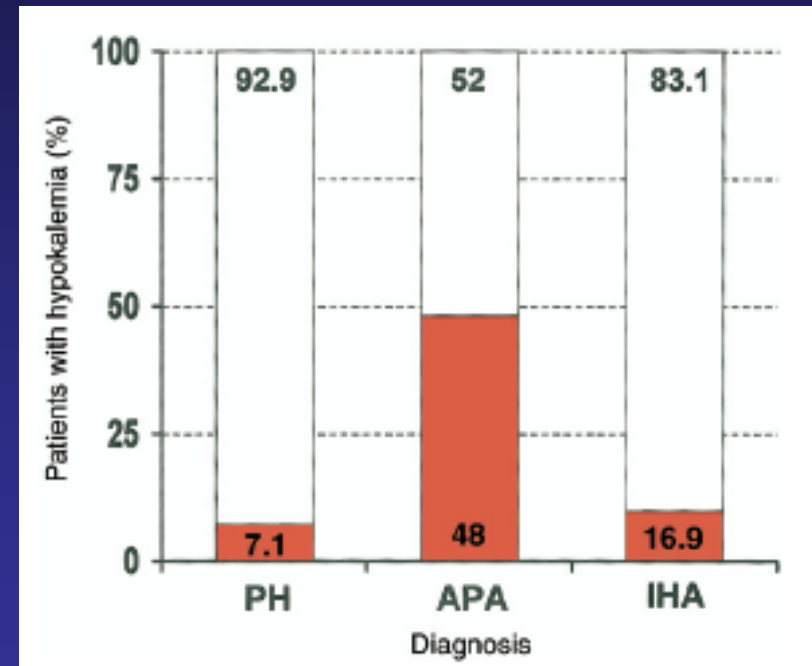
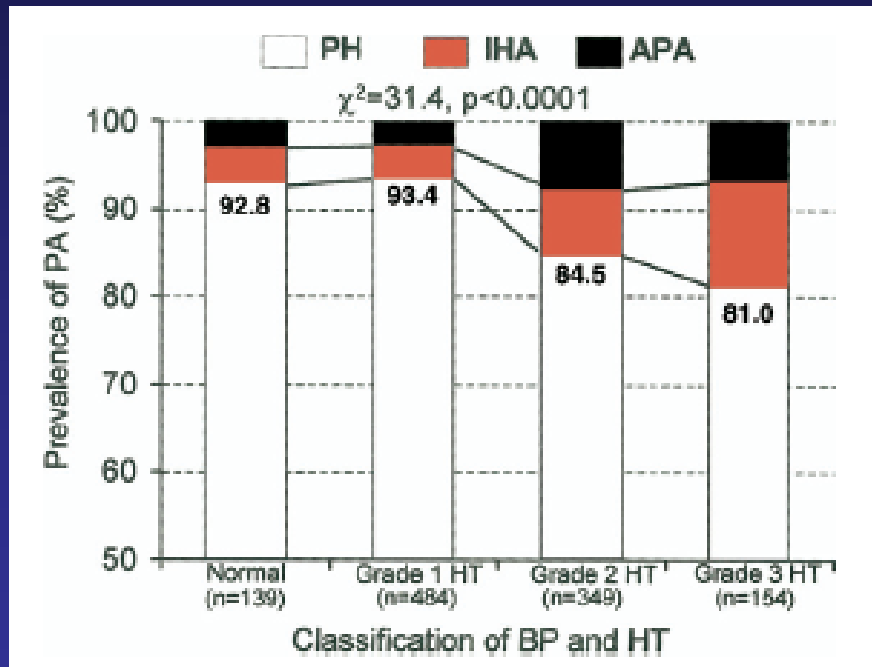
Gordon RD, Ziesak MD, Tunny TJ, Stowasser M, Klemm SA. Clin  
Exp Pharmacol Physiol 1993;20:296-298

***High Incidence of Primary Aldosteronism in 199  
Patients Referred with Hypertension.***

Gordon RD, Stowasser M, Tunny TJ, Klemm SA, Rutherford JC. Clin  
Exp Pharmacol Physiol 1994;21:315-318

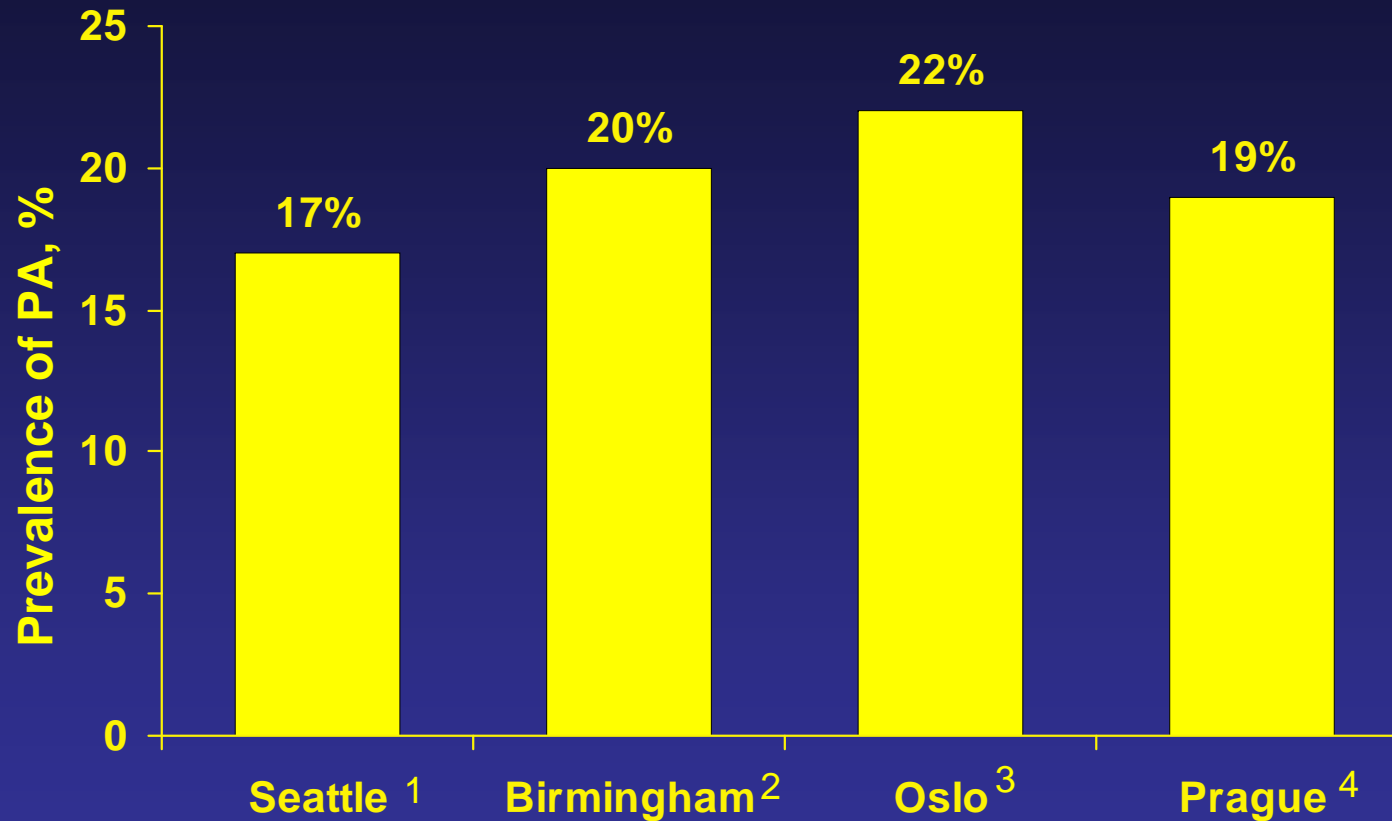
# A Prospective Study of the Prevalence of Primary Aldosteronism in 1,125 Hypertensive Patients

Rossi GP, Bernini G, Caliumi C, et al.



JACC 2006;48:2293-3000

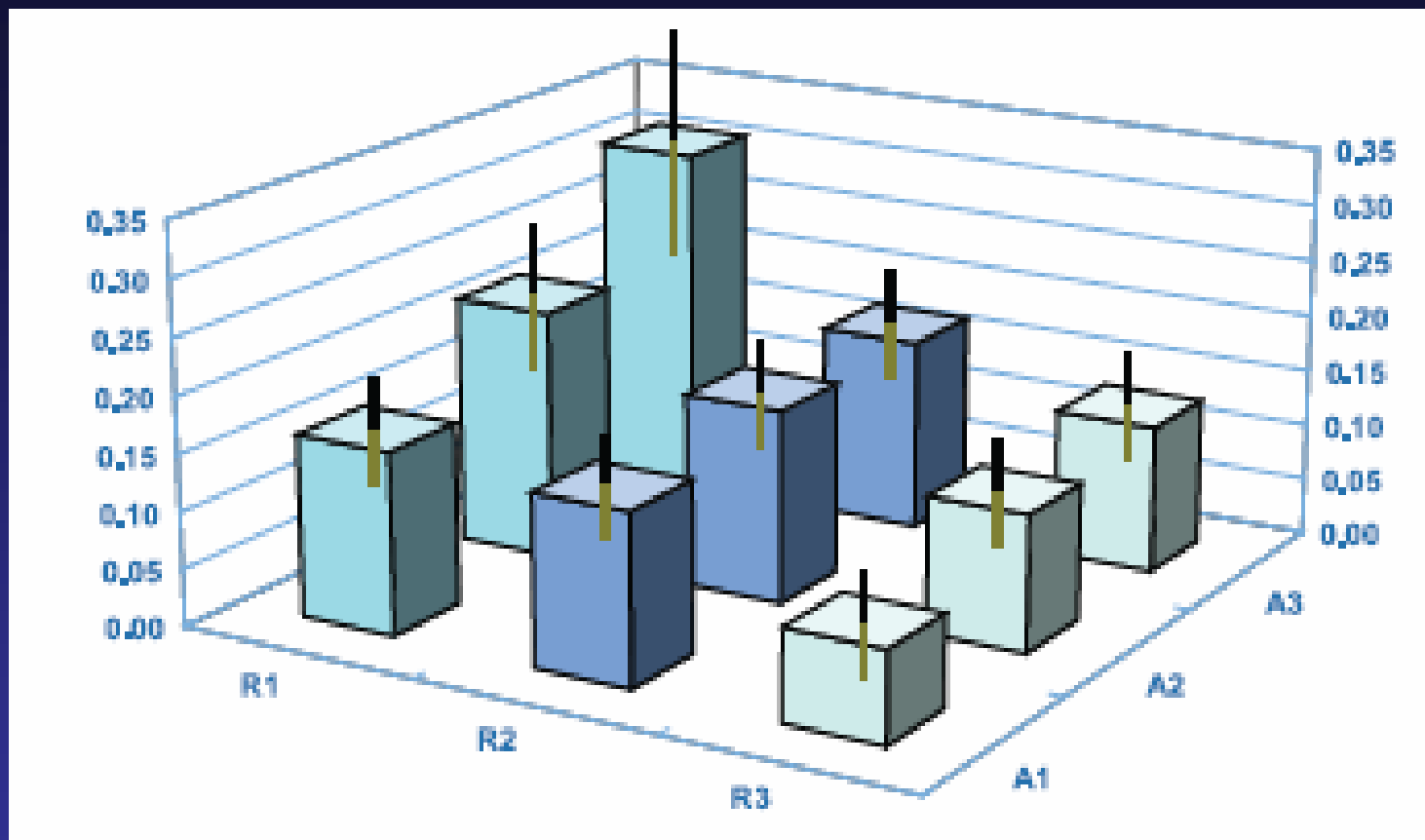
# Prevalence of Primary Aldosteronism in Subjects With Resistant Hypertension



**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.

## Aldosterone/PRA and Risk of Incident Hypertension Framingham



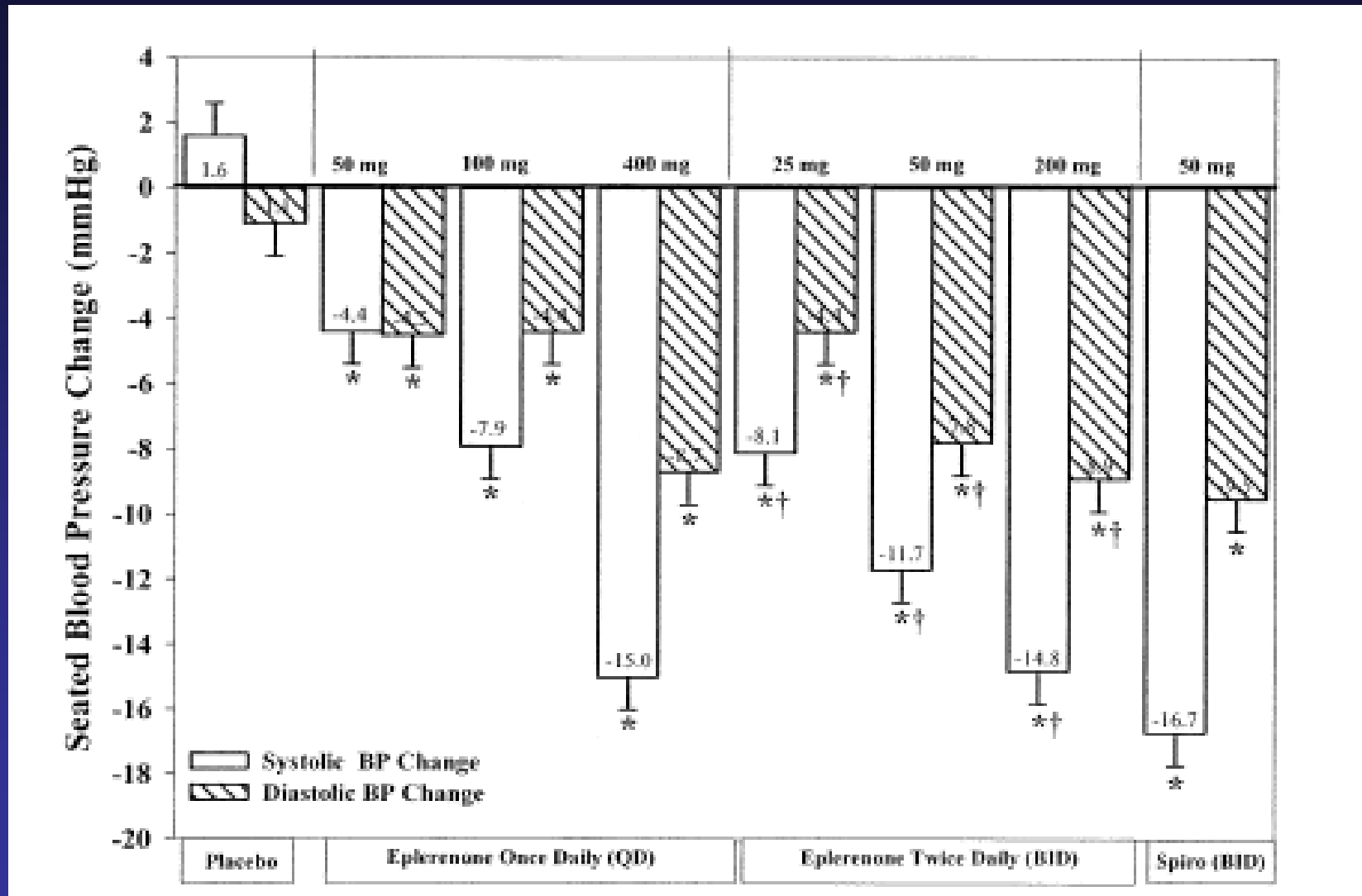
Age- and sex-adjusted incidence rates for incident hypertension a mean of 3 years across tertiles of aldosterone (A1 to A3) and renin (R1 to R3).

Newton-Cheh et al, Hypertension 2007

## **Primary Aldosteronism: Current Considerations**

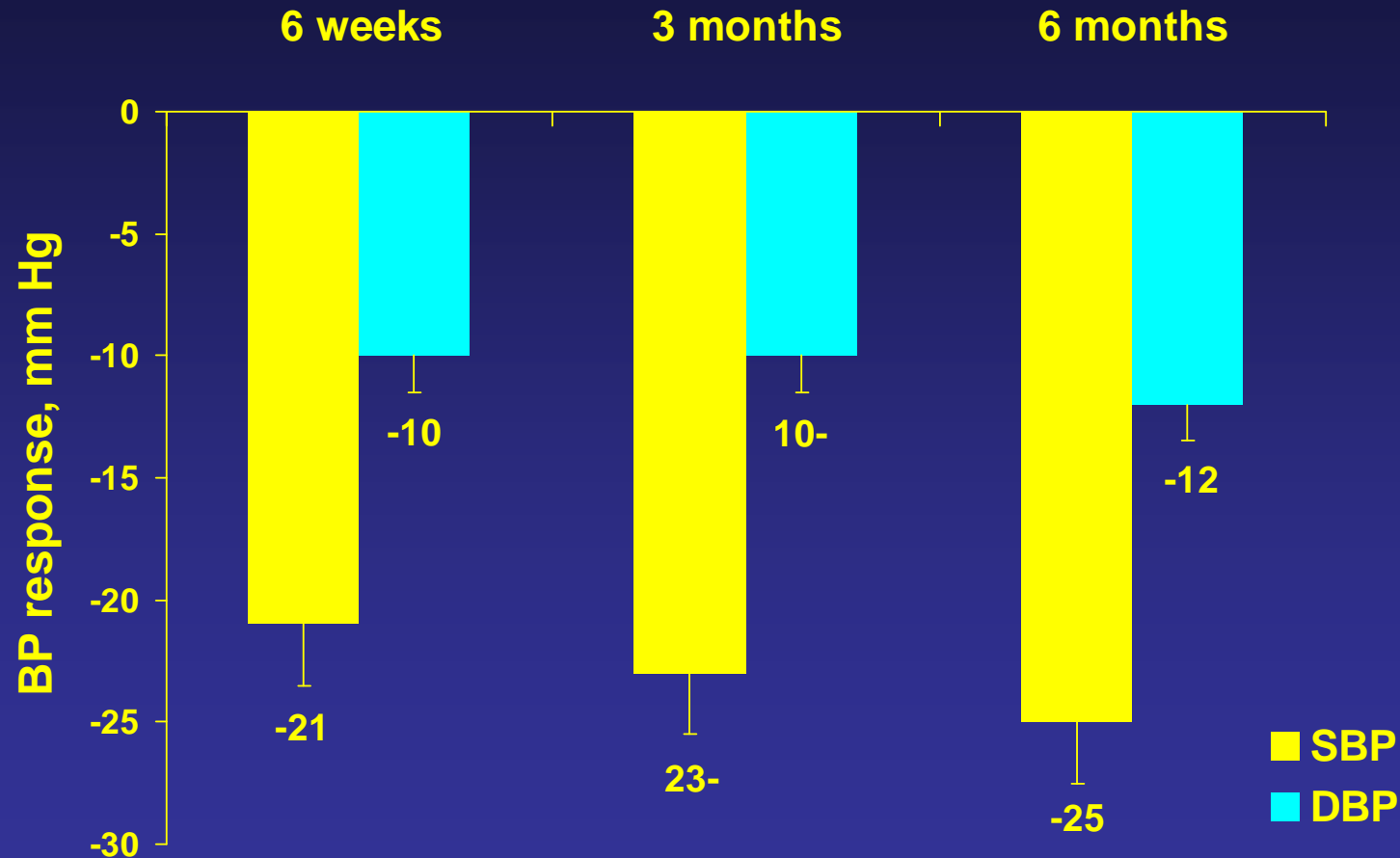
- **More common than that though historically with an estimated prevalence of approximately 10%**
- **Prevalence increases with increasing severity of hypertension and in patients with resistant hypertension (approximately 20%)**
- **Risk of aldosterone-producing-adenoma increased with higher aldosterone levels, occurrence of hypokalemia, and more severe/resistant hypertension**

# BP Response with Eplerenone or Spironolactone in Patients with Mild-Moderate Hypertension



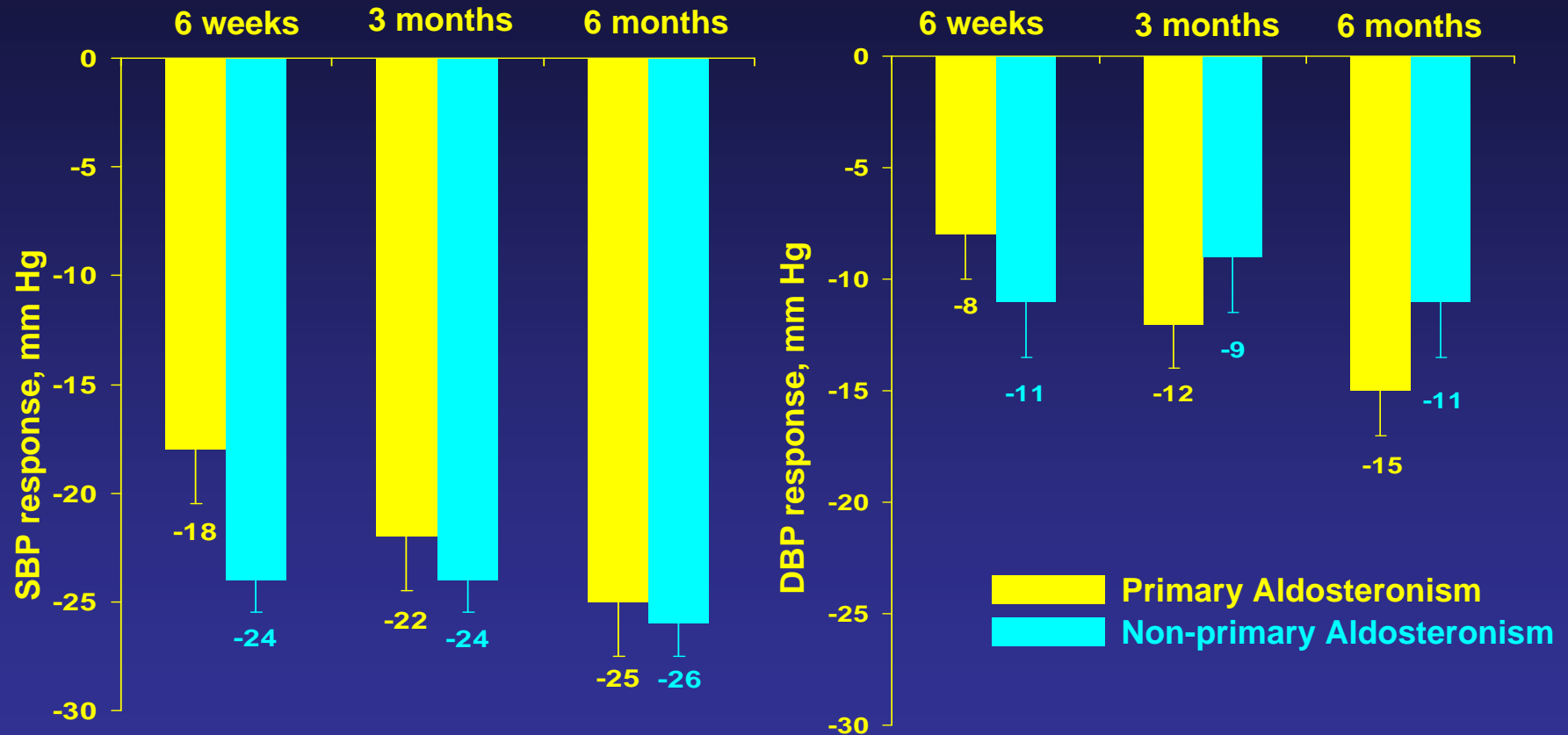
Weinberger et al, Am J Hypertens 2002

# Blood Pressure Response to Spironolactone in Subjects With Resistant Hypertension



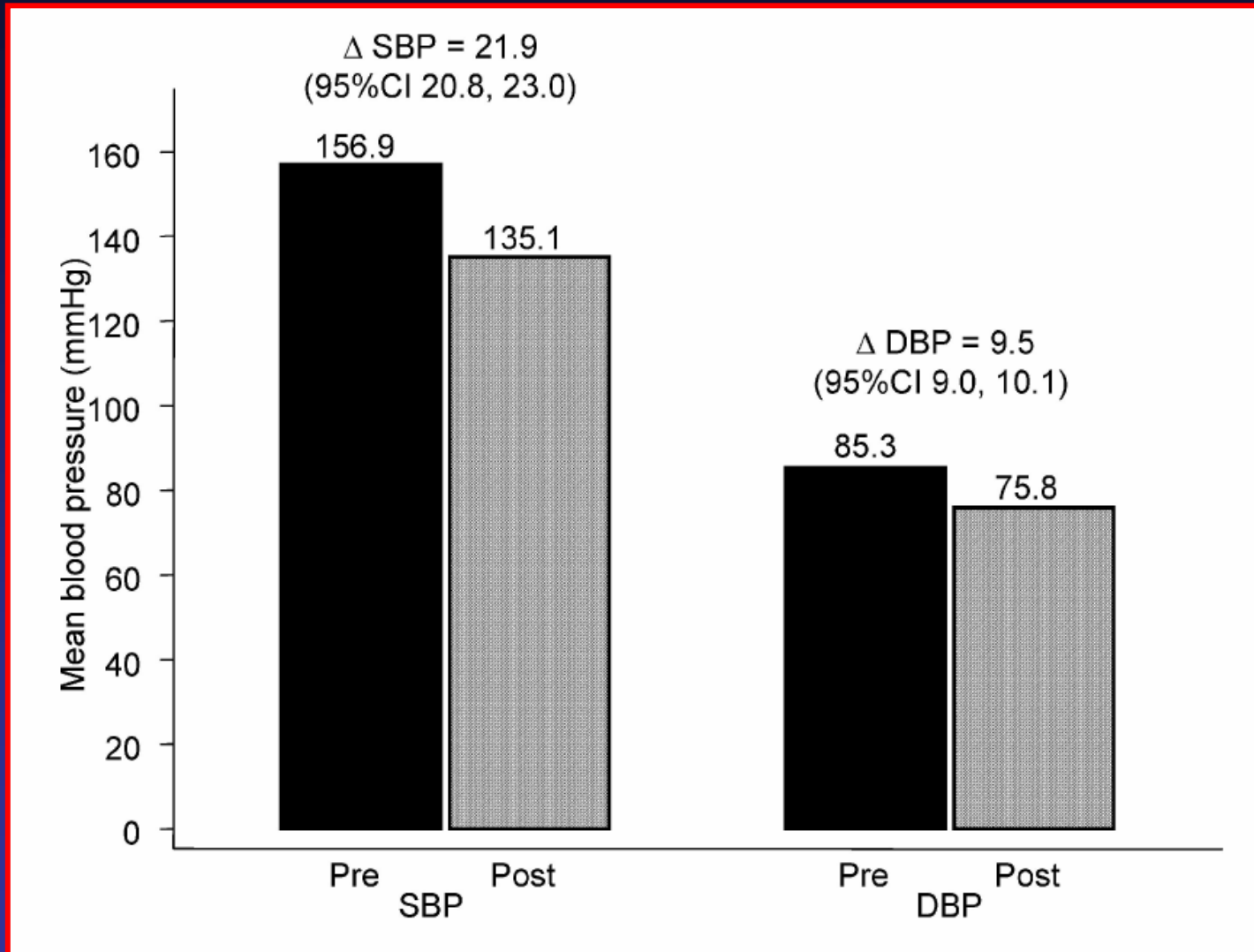
Nishizaka MK, et al. *Am J Hypertens.* 2003;16:925-930.

# 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.

## ASCOT: BP Response to Spironolactone



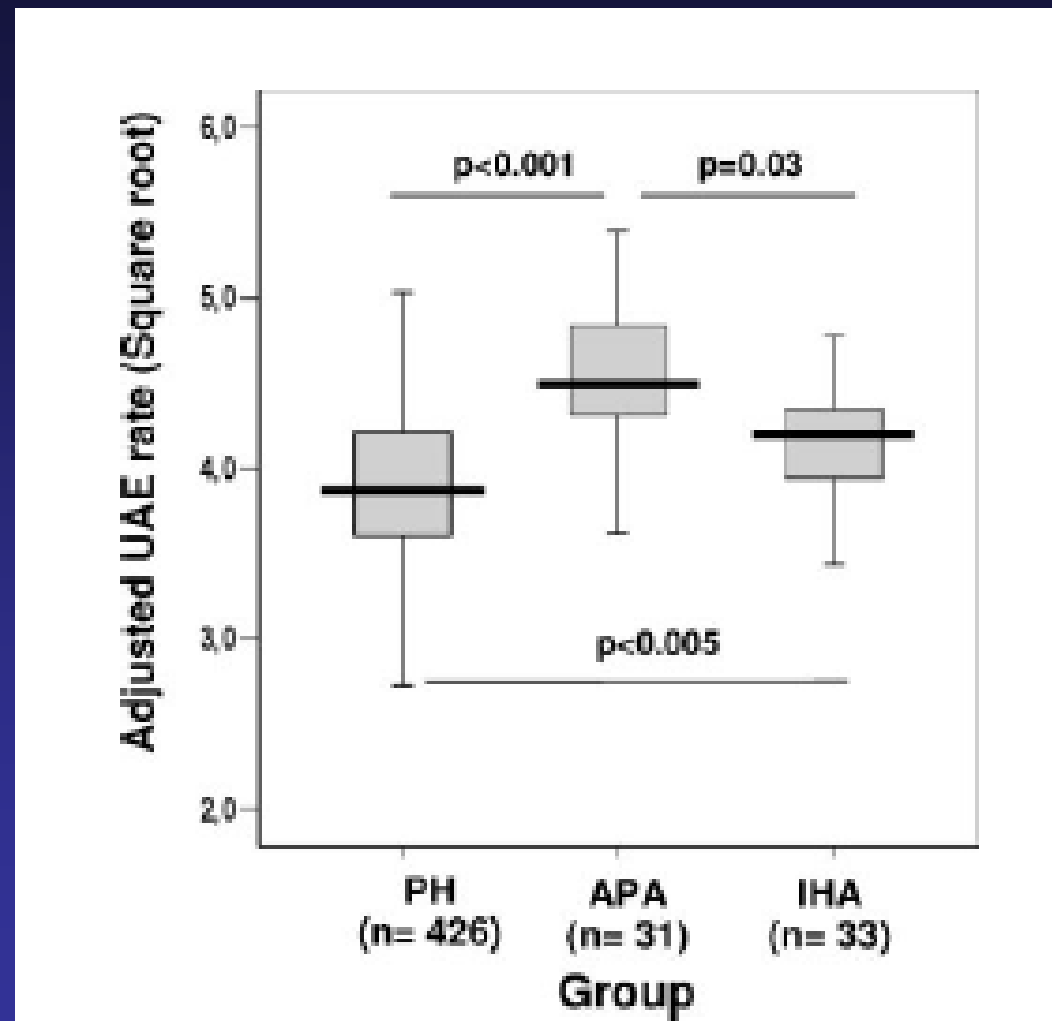
# Primary Aldosteronism and Rates of Cardiovascular Events

	Primary Aldo	Essential HTN	Odds Ratio	P value
	(n = 124)	(n = 465)		
Stroke (%)	12.9	3.4	4.2	<0.001
MI (%)	4.0	0.6	6.5	<0.005
Atrial fib (%)	7.3	0.6	12.1	<0.001
Echo LVH (%)	34	24	1.6	<0.01
ECH LVH (%)	32	14	2.9	<0.001

Melliez et al., JACC 2005

# Renal Damage in Primary Aldosteronism

## Results of the PAPY Study



# Resistant Hypertension and Proteinuria

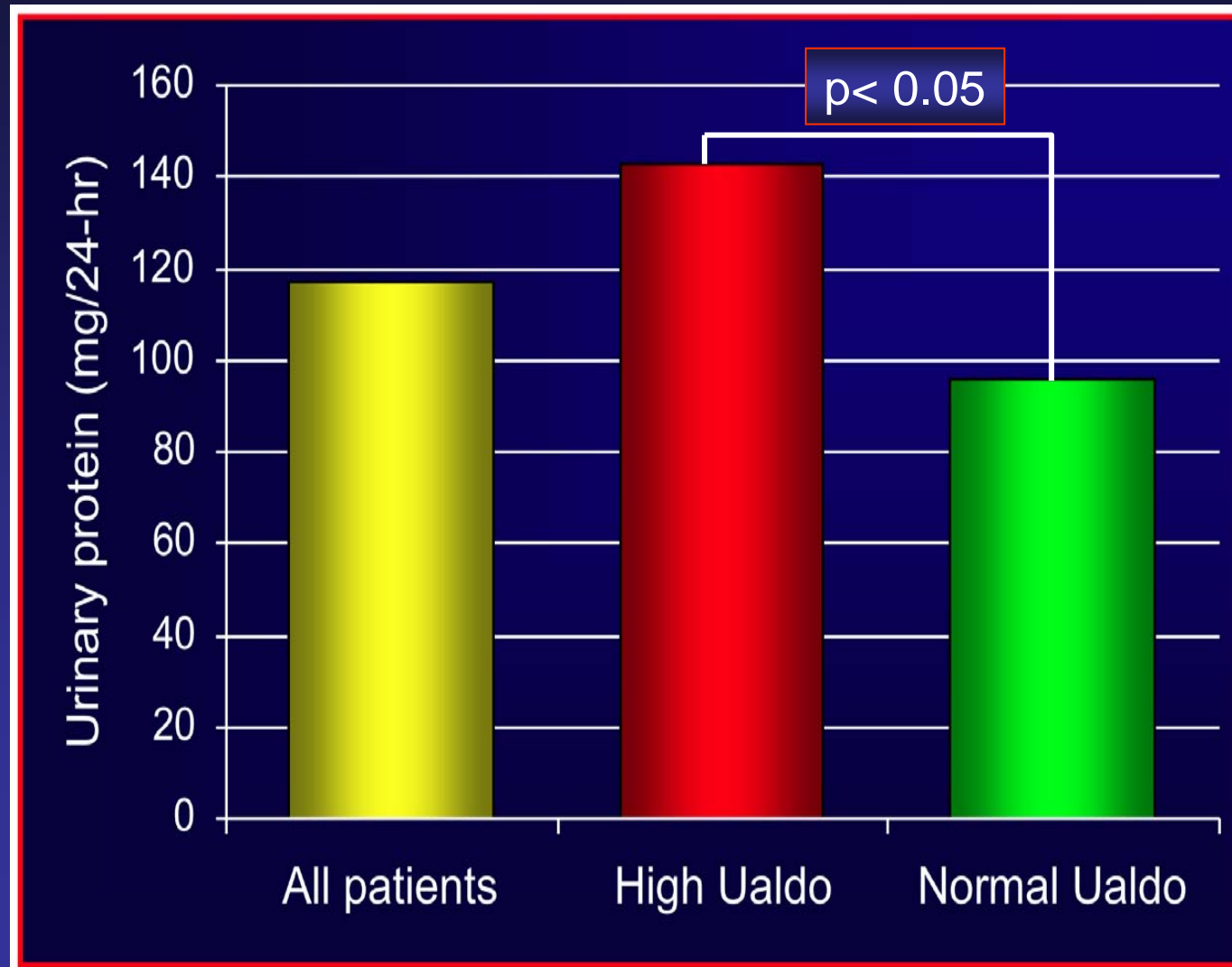
## Biochemical evaluation

	All Patients n = 84	High-Ualdo n = 38	Normal-Ualdo n = 46
Serum potassium (mEq/L)	4.0±0.4	4.0±0.5	4.0±0.3
PAC (ng/dL)	11.1±7.6	14.4±9.0	8.3±4.8**
PRA (ng/mL/h)	3.4±6.5	2.2±3.5	4.4±8.1
ARR	14.1±17.1	15.7±13.6	8.3±8.7*
UNa (mEq/24-hr)	172.3±74.8	177.3±70.2	168.2±78.8
CICr (ml/min)	110.3±31.5	123.4±32.6	100.1±26.8**

\*p<0.01 compared to high-Ualdo; \*\*p<0.001 compared to high-Ualdo.

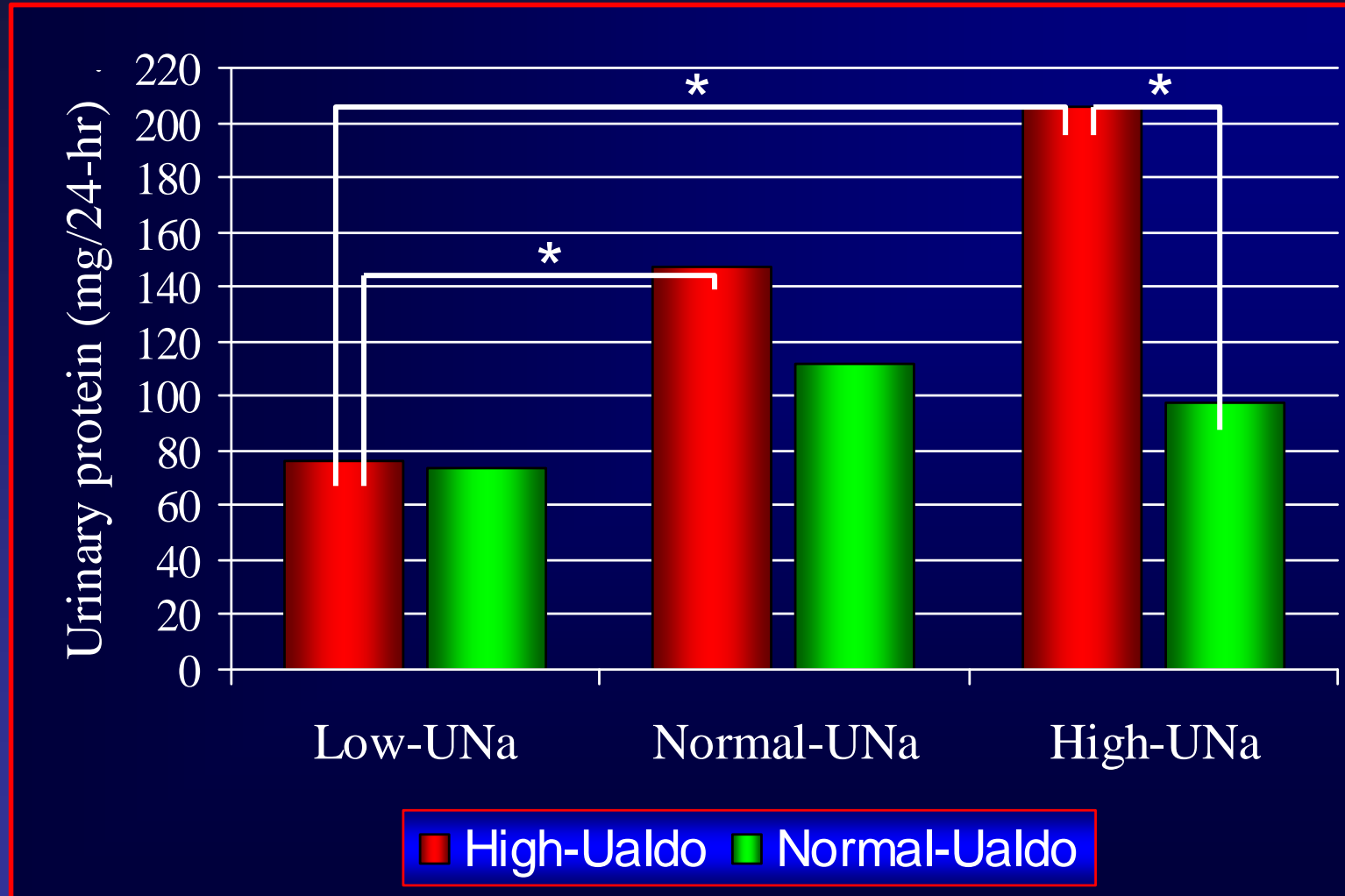
# Results

Urinary protein excretion according aldosterone status



# Results

Urinary protein excretion according aldosterone and salt status



## Spironolactone Reduces Proteinuria in Patients with CKD

Patients (n=42) with mean eGFR of 57 mL/min treated for 8 weeks with spironolactone 25 mg/day in addition to ACEi or ARB.

No change in BP.

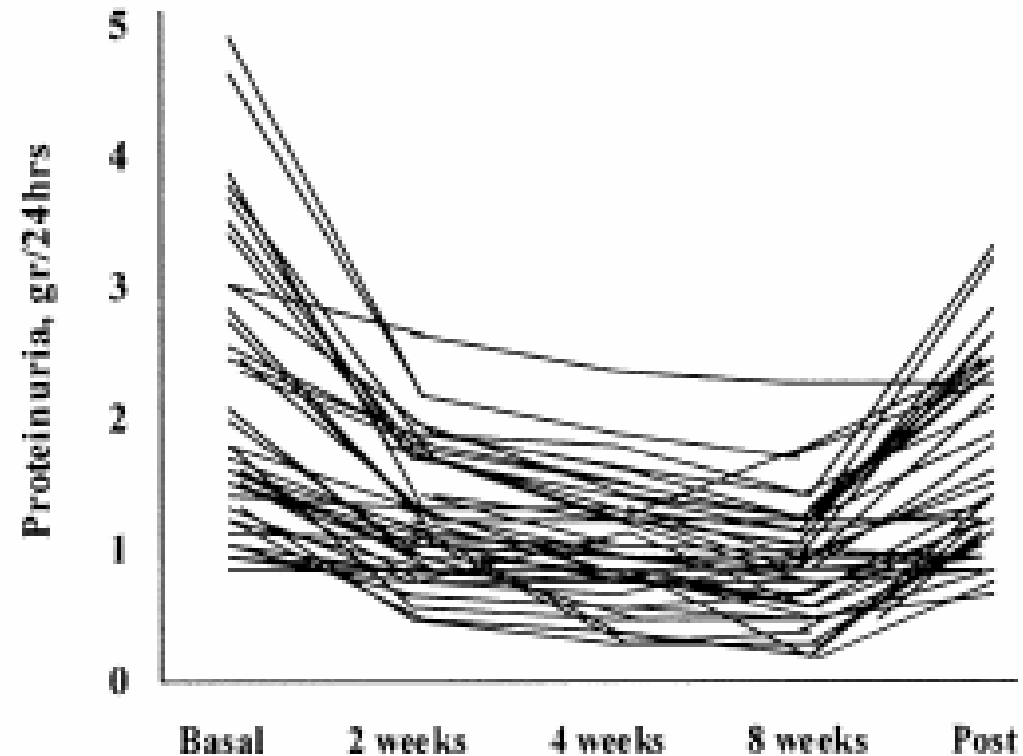


Fig 1. Line graphs show proteinuria levels in all 42 patients at baseline; during treatment with spironolactone, 25 mg/d; and 4 weeks after discontinuation of the drug.

# **Spironolactone and Intracardiac Volumes**

**Resistant Hypertension  
Baseline MRI and Biochemical  
Evaluation**



**Spironolactone 25-50 mg**



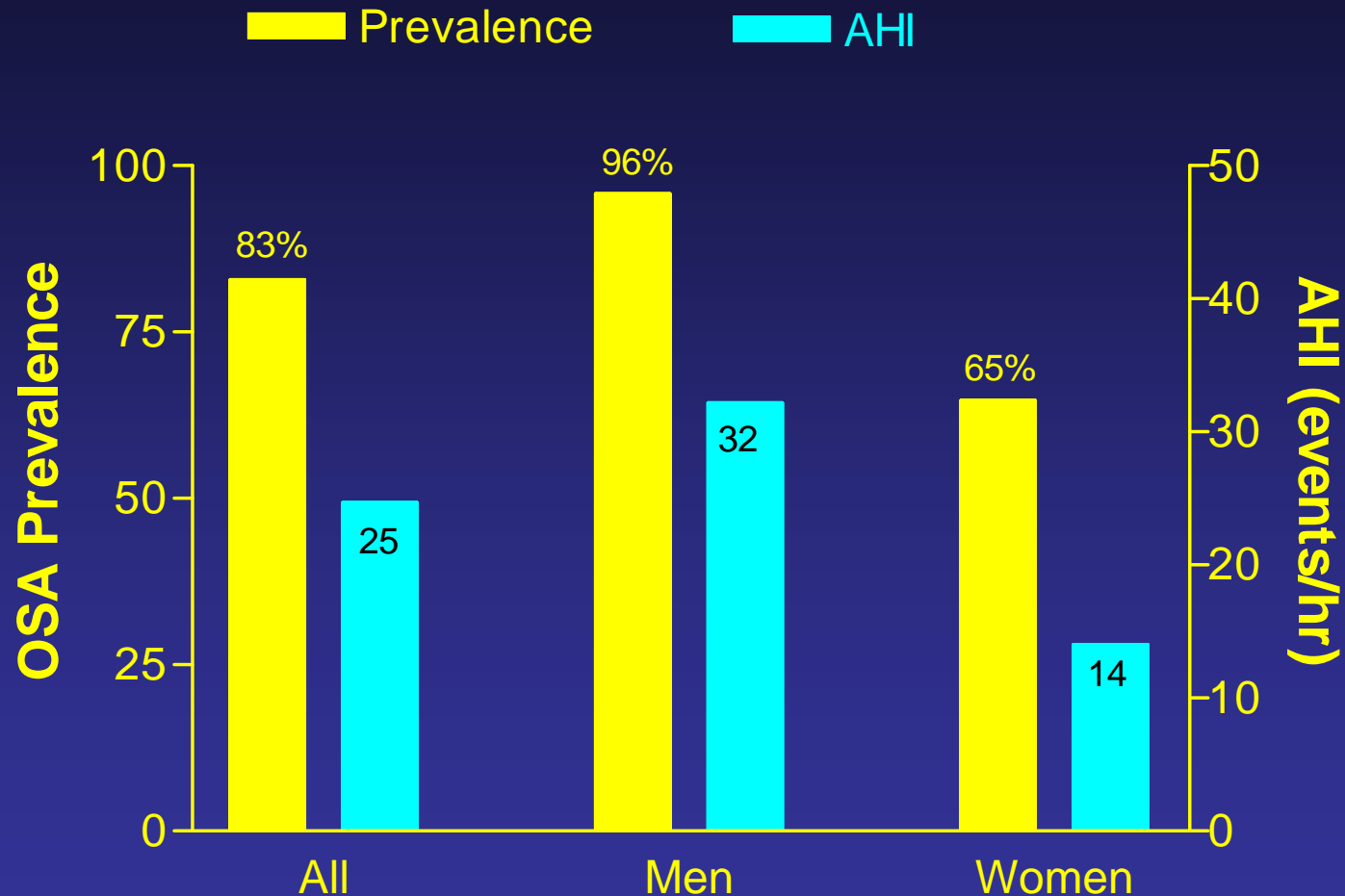
**3 and 6 Months Follow-Up  
Repeat MRI and Biochemical  
Evaluation**

## MRI Changes in High and Normal Aldo Patients after Treatment with Spironolactone 50 mg Daily

	High Aldo (n=19)			Normal Aldo (n=15)		
	Base	3 Mo	6 Mo	Base	3 Mo	6 Mo
<b>BNP</b>	47		-62%*	18		-28%
<b>LVEDVI</b>	77	-9%*	-25%*	68	+5%	+4%
<b>RVEDVI</b>	83	-12%*	-16%*	73	+5%	0%
<b>LAVI</b>	40	-15%*	-18%*	37	-8%	-5%
<b>LVMI</b>	80	-16%*	-22%*	81	-9%*	-12%*
<b>LVEF (%)</b>	67	-3%	0%	68	-3%	0%

\* <0.05 Gaddam et al. Hypertension 2010, in press.

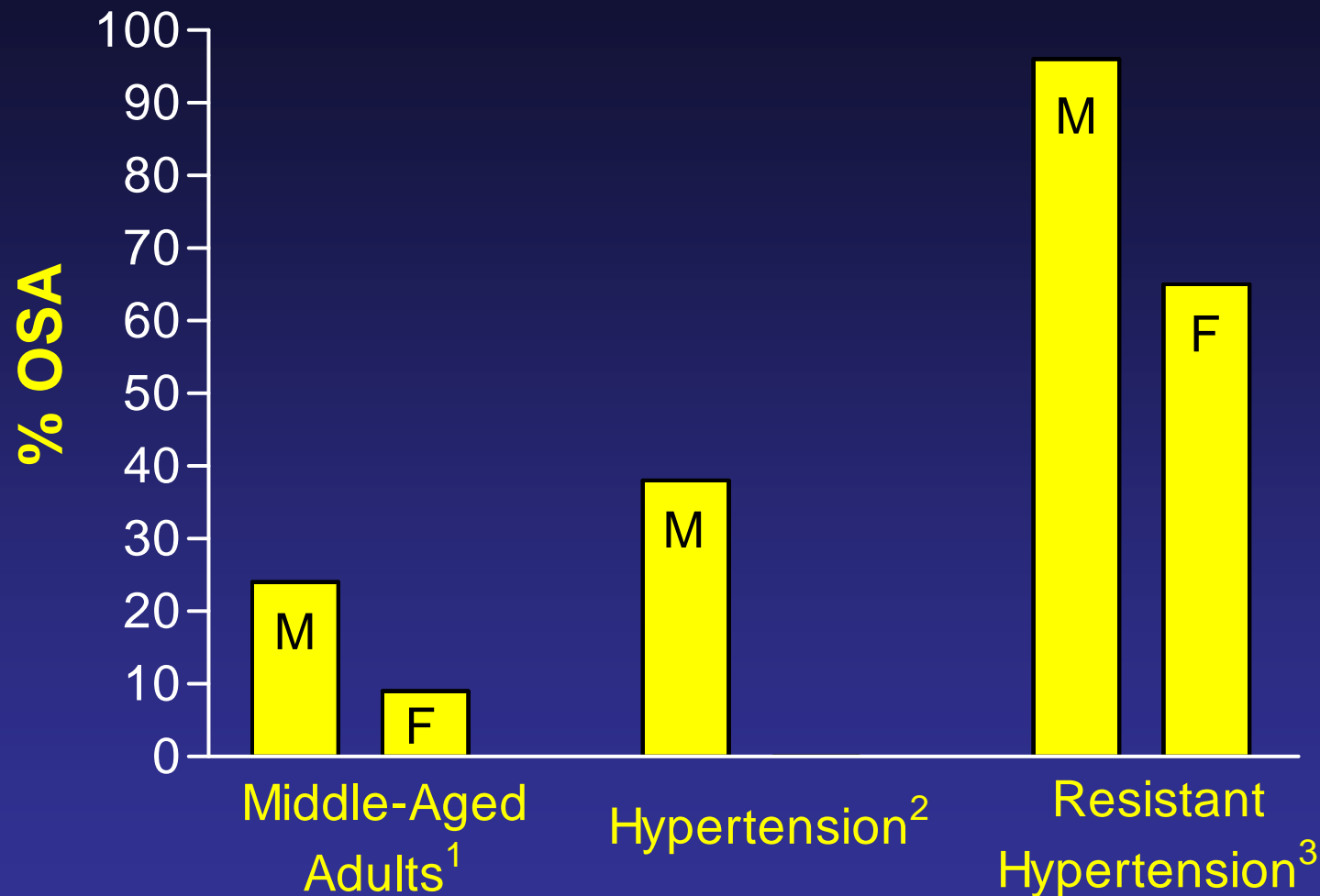
# High Prevalence of Unrecognized Sleep Apnoea\* in Drug-Resistant Hypertension



Logan et al. J Hypertens 2001;19:2271

\* >10 events/hr

# Prevalence of OSA

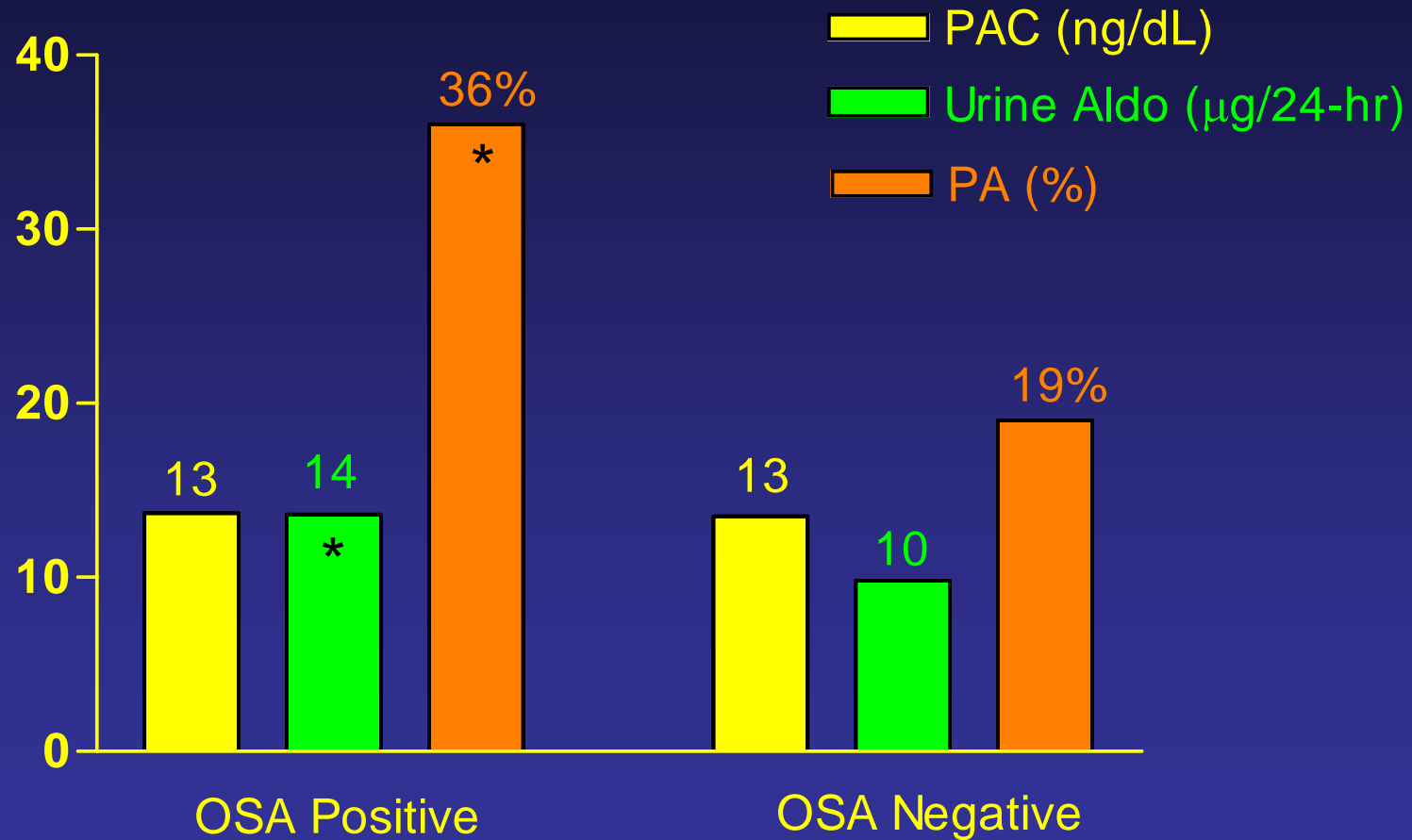


<sup>1</sup>Young et al. NEJM 1993. AHI  $\geq 5$  events/hr.

<sup>2</sup>Worsnop et al. Am J respir Crit Care Med 1998. AHI  $\geq 5$  events/hr.

<sup>3</sup>Logan et al. J Hypertens 2001. AHI  $\geq 10$  events/hr.

## Aldosterone Levels and Risk of OSA in Subjects with Resistant Hypertension



**Biochemical and polysomnography results of evaluated subjects with resistant hypertension (n=71)\* and without resistant hypertension (n=29)\***

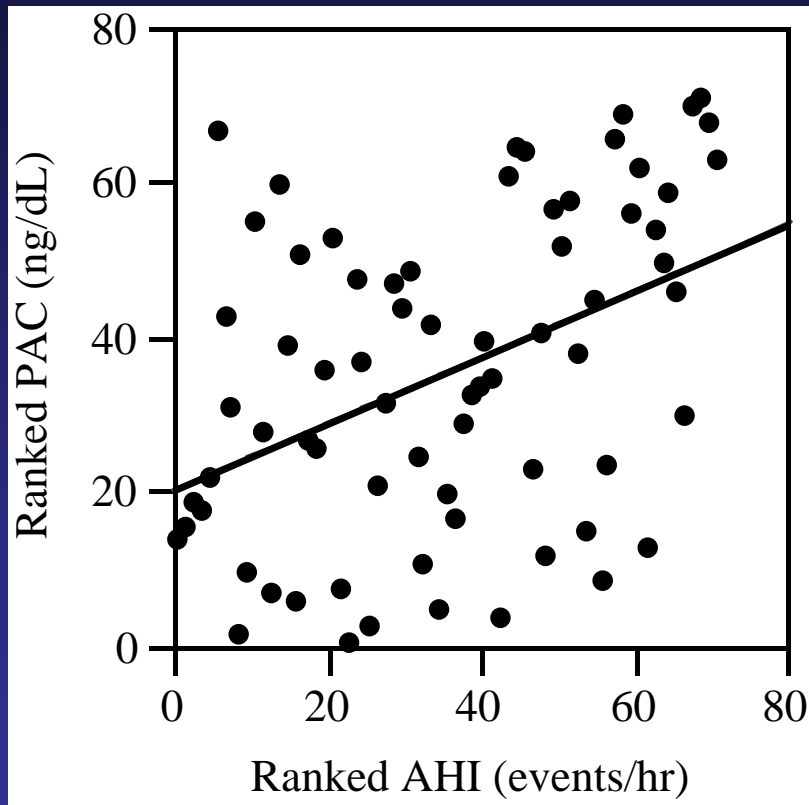
<u>Characteristic</u>	<u>Resistant Hypertension</u>		<u>Control</u>	
	<u>mean ± SD</u>	<u>median</u>	<u>mean ± SD</u>	<u>median</u>
<b>PAC, ng/dL</b>	<b>12.4±7.9</b>	<b>11.0</b>	<b>7.3±3.6</b>	<b>5.5†</b>
<b>PDR, μUnits/mL</b>	<b>21.4 ± 36.0</b>	<b>8.0</b>	<b>27.6±29.7</b>	<b>19.0†</b>
<b>Serum Cr, mg/dL</b>	<b>1.1 ± 0.3</b>	<b>1.0</b>	<b>1.0 ± 0.1</b>	<b>1.0</b>
<b>Serum K, mEq/L</b>	<b>3.8 ± 0.4</b>	<b>3.8</b>	<b>4.3 ± 0.4</b>	<b>4.3</b>
<b>AHI, events/hr</b>	<b>24.1±24.7</b>	<b>15.3</b>	<b>29.0±32.3</b>	<b>14.3</b>
<b>HI, %</b>	<b>7.4±10.9</b>	<b>3.1</b>	<b>2.9±3.8</b>	<b>1.1</b>
<b>OSA Prevalence</b>	<b>85%</b>		<b>83%</b>	

Data are presented as mean ± SD.

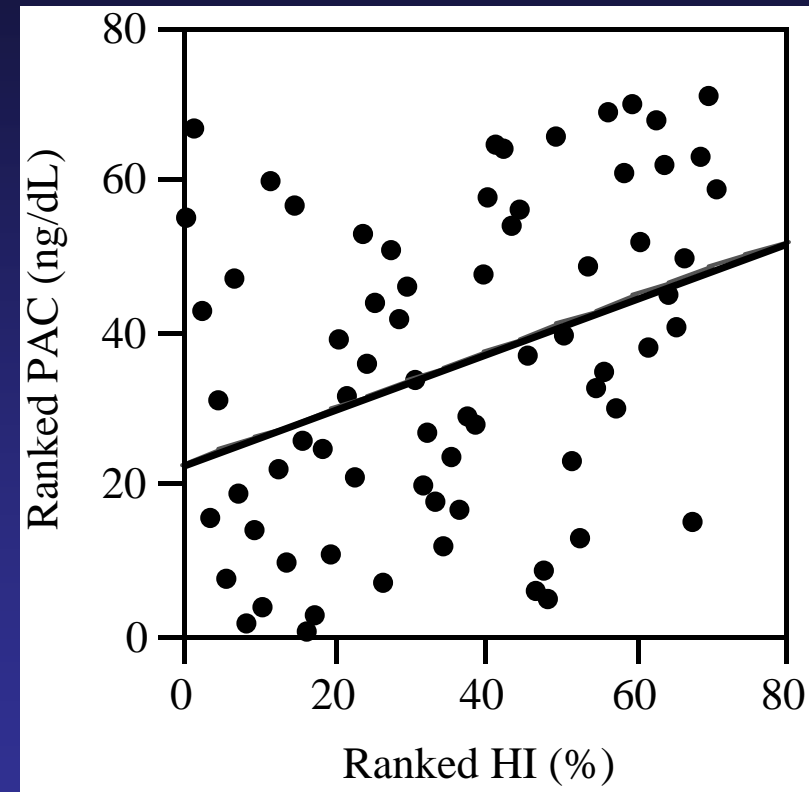
†Different from resistant hypertension subjects (p< 0.05).

# Apnea-hypopnea index and hypoxic index correlates with plasma aldosterone in resistant hypertension subjects

Figure 1



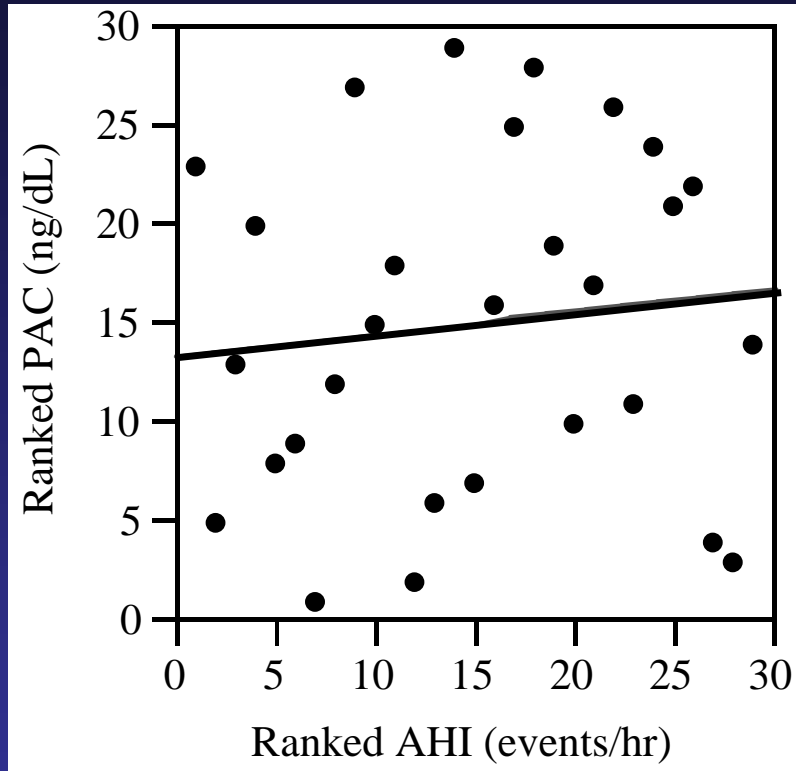
$\text{Rho} = 0.44, p = 0.0002$



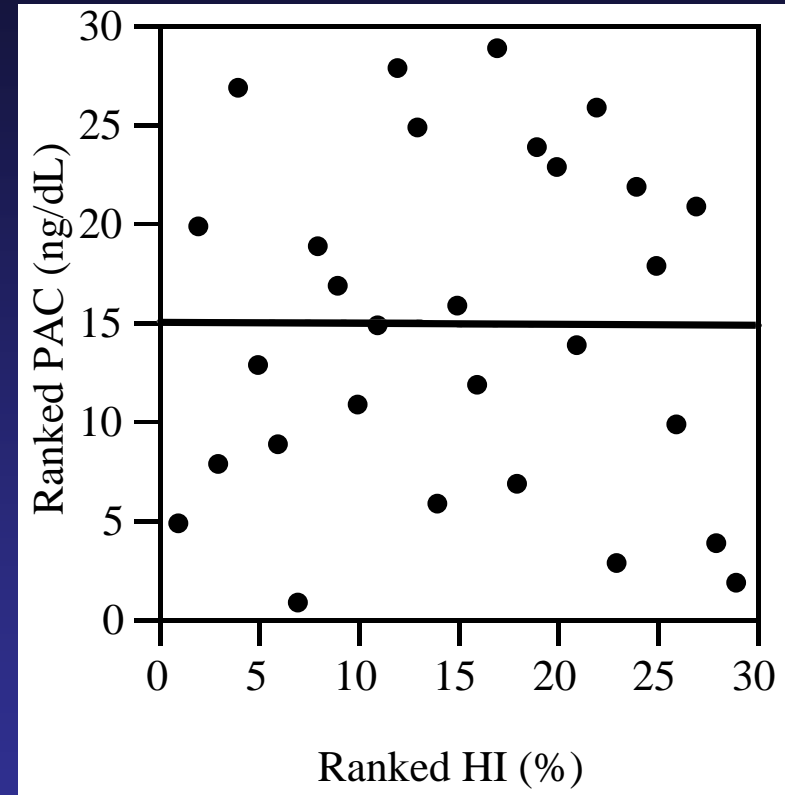
$\text{Rho} = 0.38, p = 0.001$

## Apnea-hypopnea index and hypoxic index does not correlate with plasma aldosterone in control subjects

Figure 2

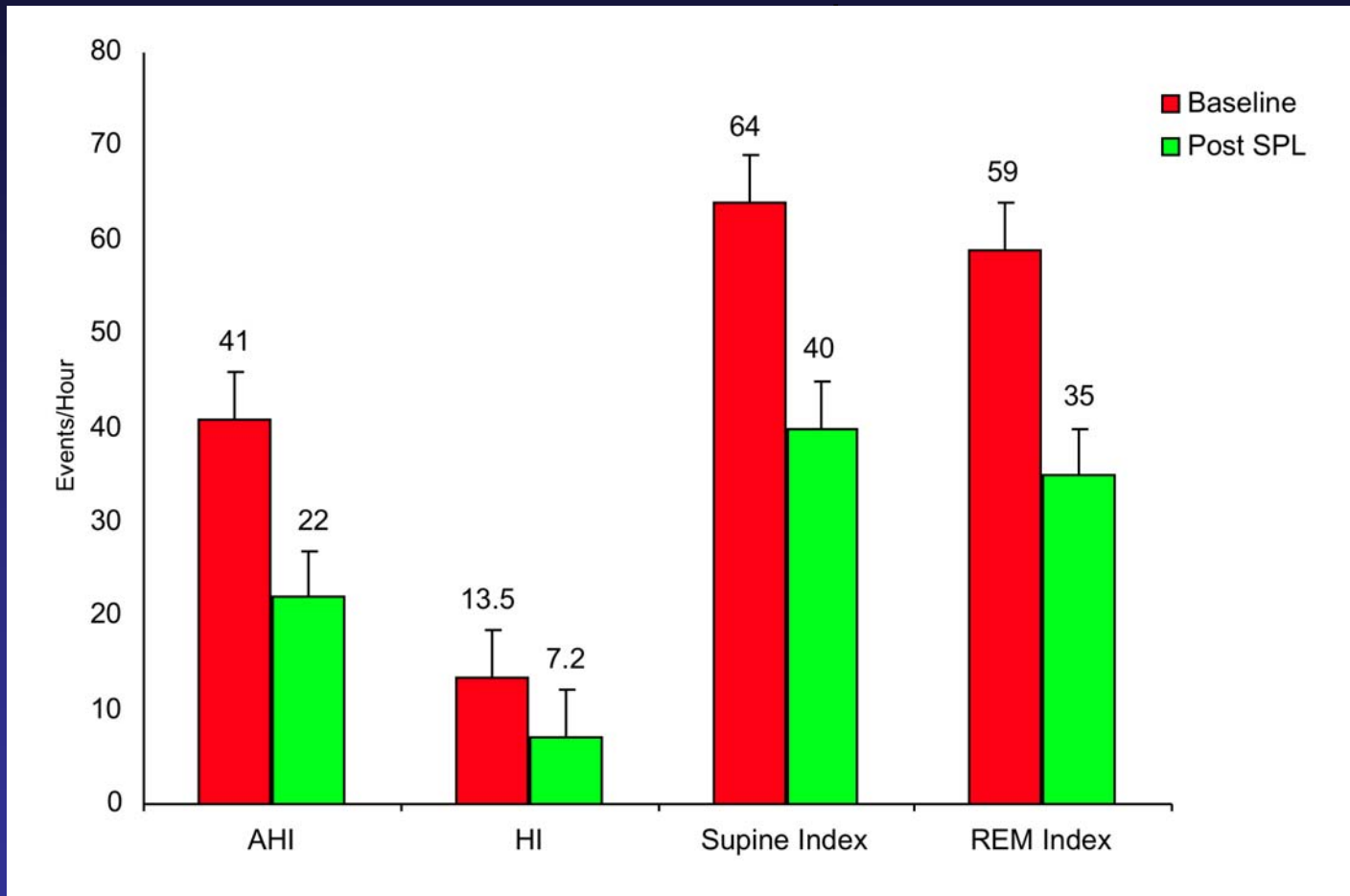


**Rho = 0.12, p = 0.52**



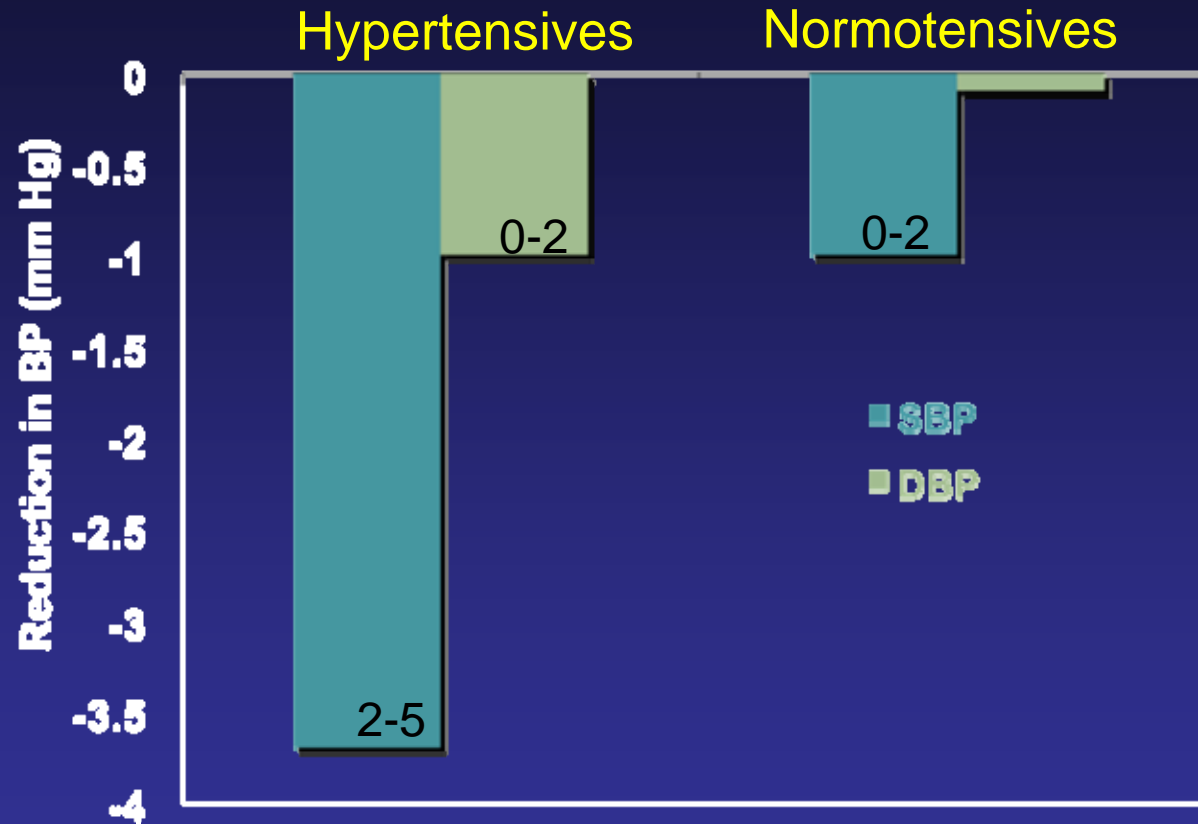
**Rho = 0.002, p = 0.99**

# Results



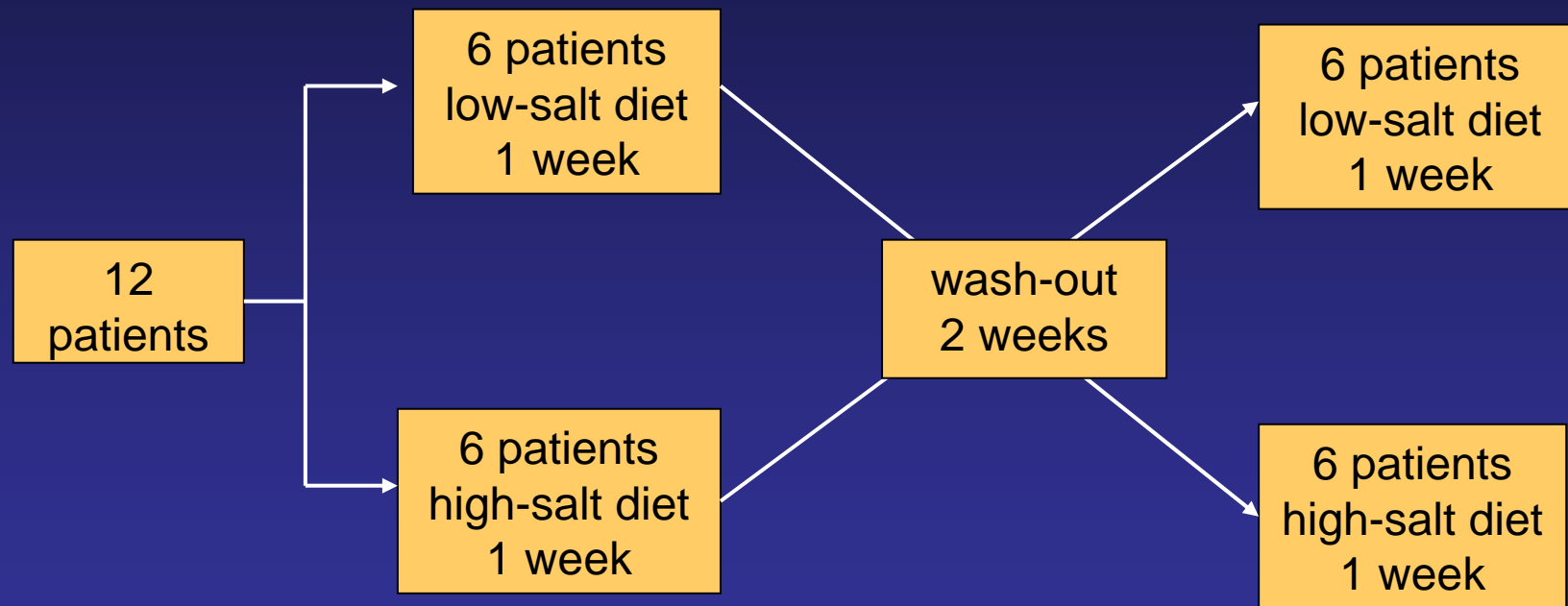
AHI, Apnea-Hypopnea Index; HI, Hypoxic Index; REM, Rapid eye movement sleep;  
\*  $p < 0.05$ .

# Meta-analysis of Salt Restriction Trials



Mean change in BP with 100 meq/day reduction in salt intake

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

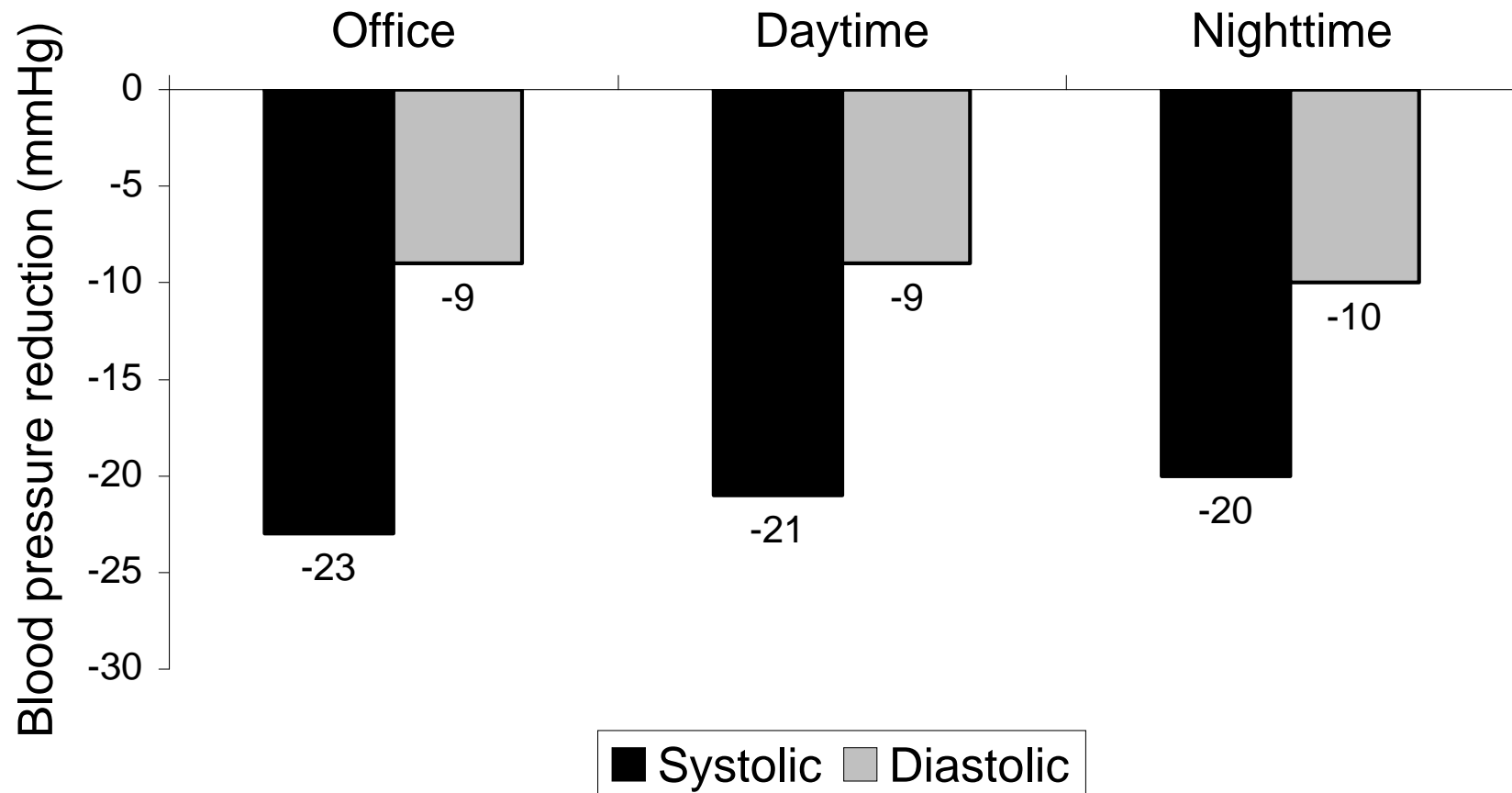


## Results: High-Low Salt Cross-Over

	<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

# Reduction in Blood Pressure High to Low Salt Ingestion



# Conclusion

- **Aldosterone excess contributes importantly to development and severity of hypertension, particularly resistant hypertension**
- **MRA's broadly effective in treating mild-moderate hypertension and resistant hypertension**
- **Aldosterone excess contributes importantly to target organ complications including CKD, LVH, and OSA**
- **Excess dietary salt ingestion is an essential component of these effects**