Hypertension: Are there "Treatment Resistant" Patients?

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Case

- John Smith presents to clinic for routine follow-up. He has no new symptoms or changes in his history since his last visit 6 months ago. He faithfully takes all of his medicatons each morning, including 3 medications for hypertension: enalapril 20 mg daily, amlodipine 5 mg daily, and HCTZ 25 mg daily.
- His exam is unremarkable except for a BP of 160/95, which is repeated 5 minutes later at 155/95.

Case

- John Smith presents to clinic for routine follow-up. He has no new symptoms or changes in his hist
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- His
160/95, which is repeated 5 minutes later at 155/95.

Does he have resistant HTN?

A. Yes

B. No

C. Undecided

Definitions

- Secondary hypertension → identifiable, underlying, etiologic condition
  - Correct the etiology → *reverse* HTN
  - Secondary HTN = rare
- Resistant hypertension = BP ≥ 140/90 mm Hg on 3 antihypertensive medications, including a diuretic
  - Address the etiology → *improve* BP control
  - Resistant HTN = up to 40% of hypertensive patients

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association.

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
David A. Calhoun, Daniel Jones, Stephen Textor, David C. Goff, Timothy P. Murphy, Robert D. Toto, Anthony White, William C. Cushman, William White, Domenic Sica, Keith Ferdinand, Thomas D. Giles, Bonita Falkner and Robert M. Carey

First rule out “pseudo-resistance”

Cause	Example
Improper blood pressure measurement	Inappropriately sized cuff
White-coat hypertension	Persistently lower home blood pressures
Difficult to compress heavily calcified or sclerotic arteries	Very elderly patients
Poor patient adherence	Complicated dosing schedules, high costs of medications
Inadequate antihypertensive medication	Inappropriate combinations, insufficient doses
Physician inertia	Failure to change or increase dose regimens

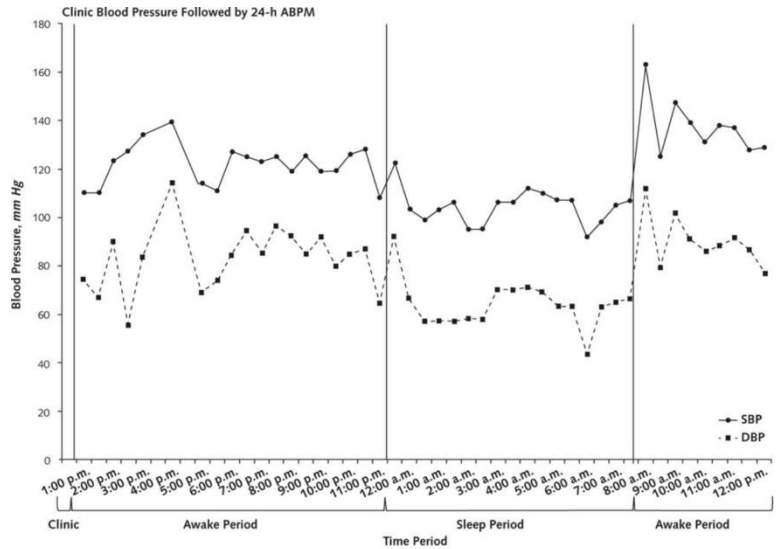
Bomback AS, Bakris GL. *Chronic Kidney Disease and Hypertension Essentials*. Boston, Massachusetts: Jones and Bartlett Publishers, 2010.

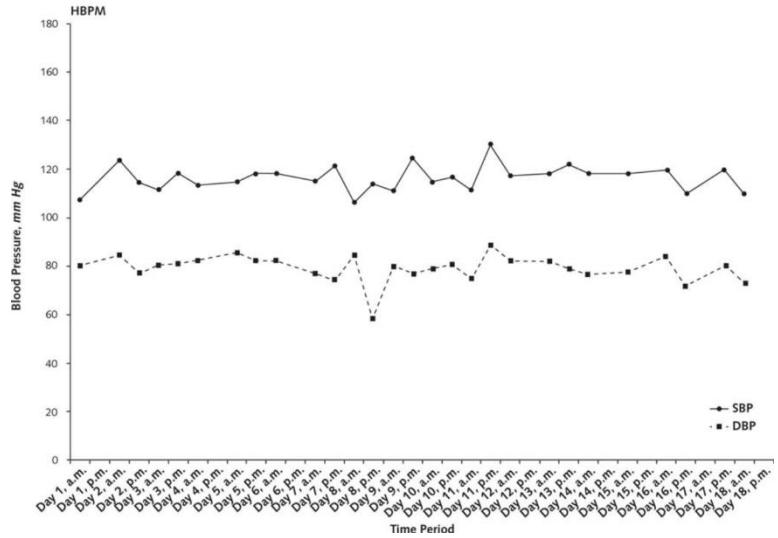
Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Role of Ambulatory and Home Blood Pressure Monitoring in Clinical Practice: A Narrative Review

Daichi Shimbo, MD; Marwah Abdalla, MD; Louise Falzon; Raymond R. Townsend, MD; and Paul Muntner, PhD

Ann Intern Med. 2015;163(9):691-700

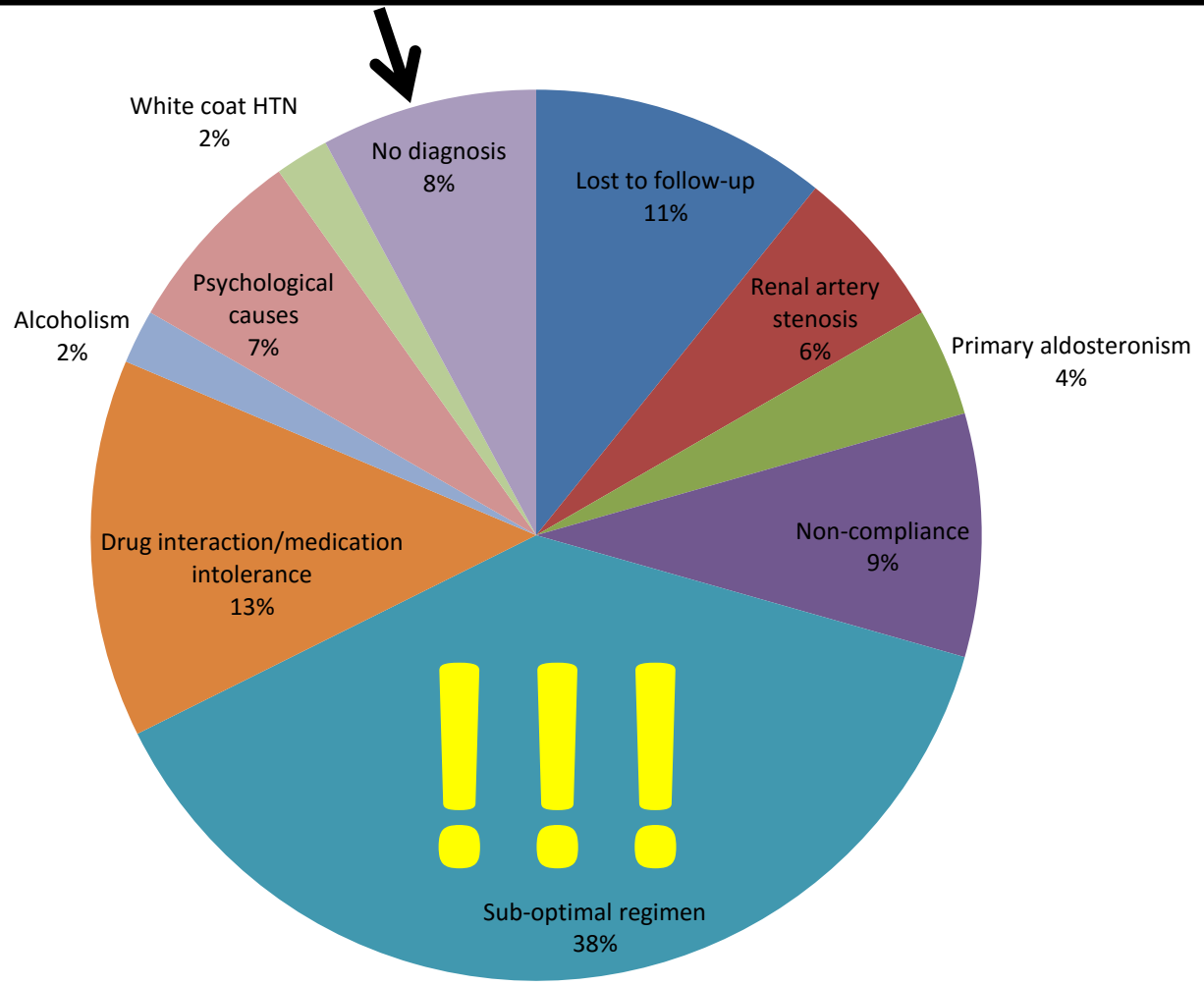




The prevalence of **white coat hypertension** ranges from 5-65% among participants with elevated clinic blood pressure

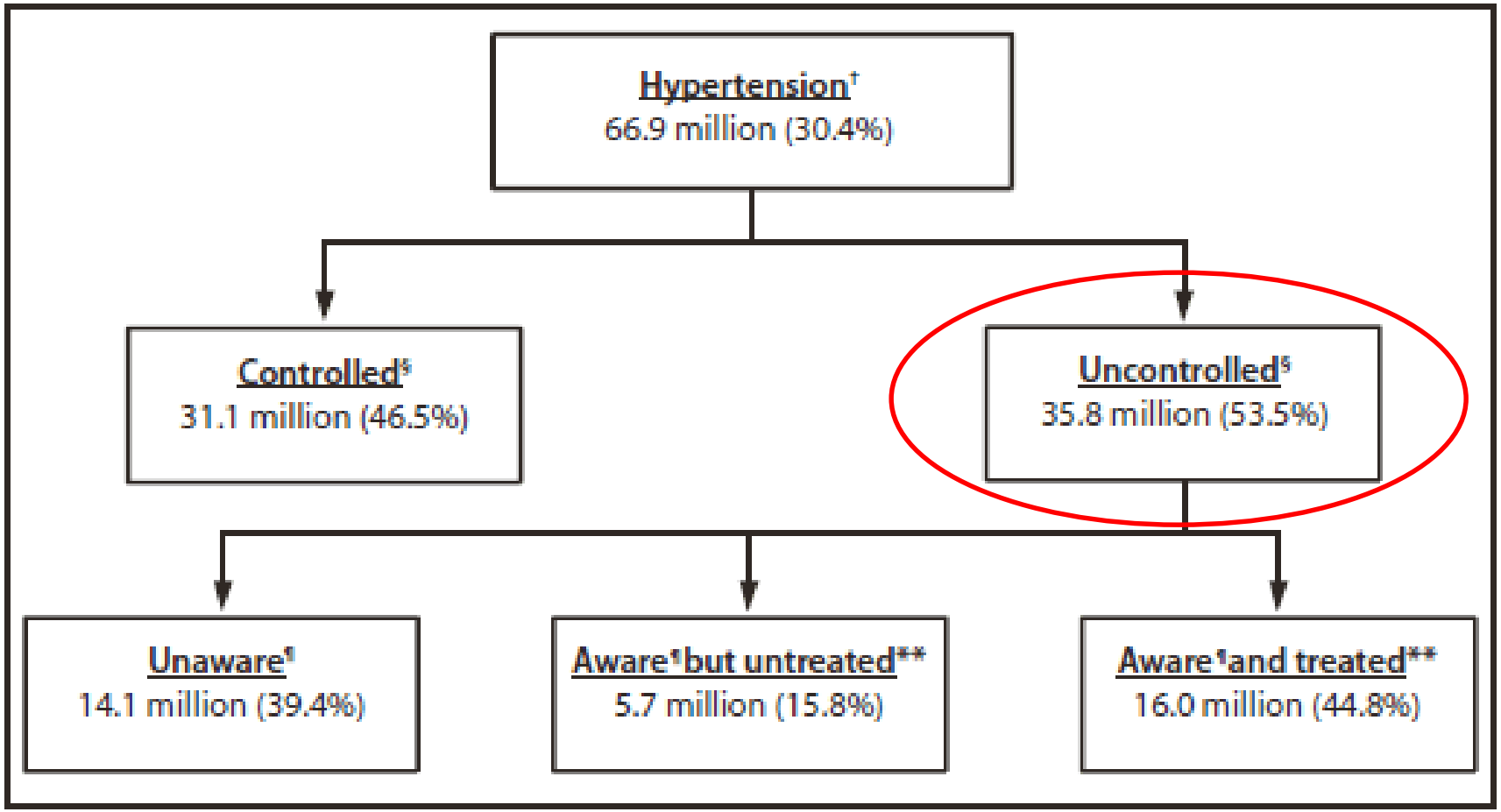
The prevalence of **masked hypertension** ranged from 14-30% among participants without elevated clinic blood pressure

Of 102 patients with resistant HTN in a tertiary care clinic, only 8% were eventually deemed “resistant”



Arch Intern Med. 1991 Sep;151(9):1786-92.
Resistant hypertension in a tertiary care clinic.
Yakovlevitch M, Black HR.

CDC Report (9/4/12): Awareness and Treatment of Uncontrolled Hypertension Among US Adults, 2003-2010



MMWR Sep 2012; 61(35):703-709

Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: JNC 7

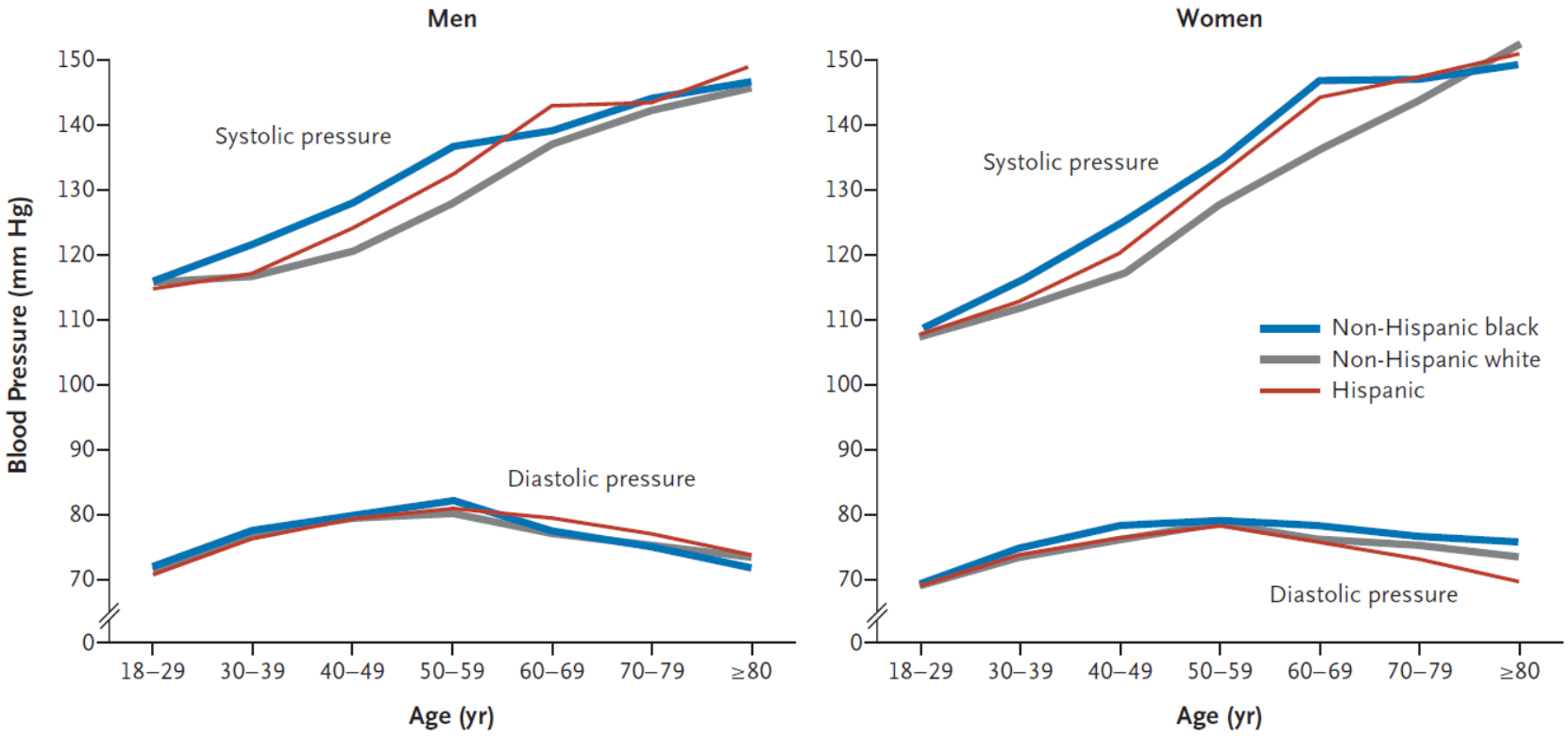
Classification of Blood Pressure (BP)*			
Category	SBP mmHg		DBP mmHg
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Hypertension, Stage 1	140–159	or	90–99
Hypertension, Stage 2	≥160	or	≥100

Chobanian, A. V. et al. JAMA 2003;289:2560-2571

When do the guidelines recommend starting medication?

JAMA. 2014;311(5):538

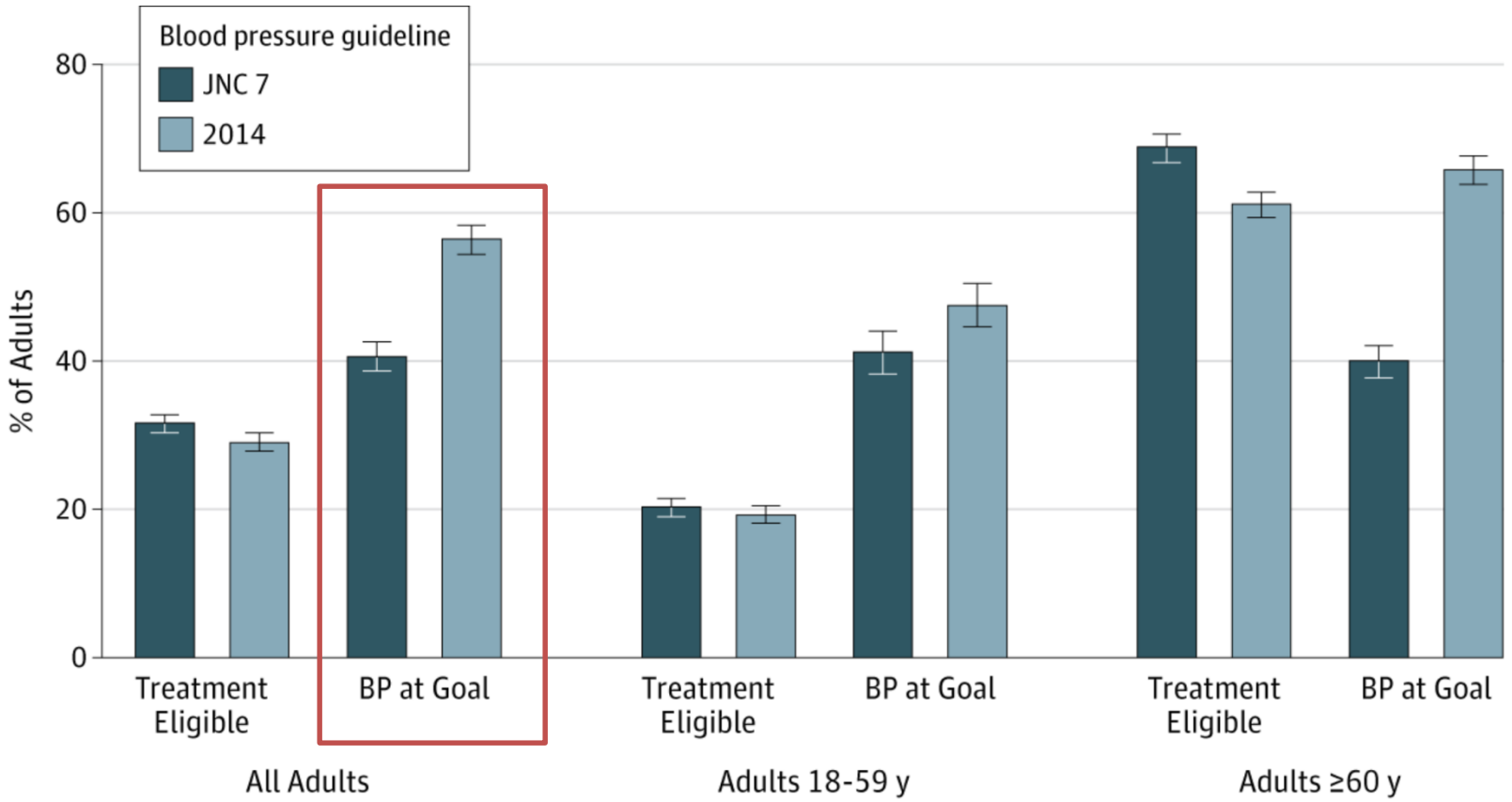
Isolated systolic hypertension in the elderly



Chobanian AV. *N Engl J Med.* Aug 23 2007;357(8):789-796.

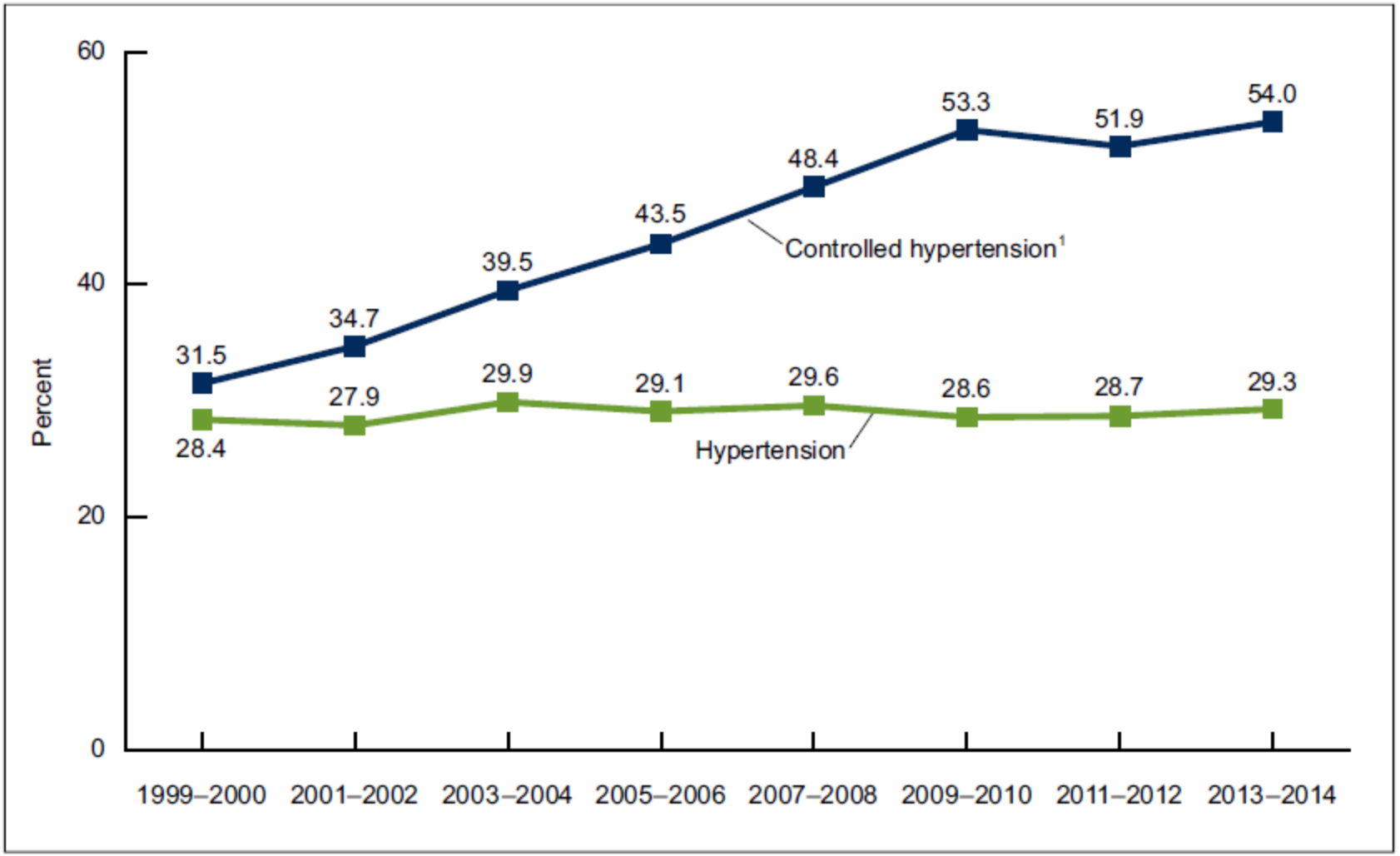
From: **Proportion of US Adults Potentially Affected by the 2014 Hypertension Guideline**

JAMA. 2014;311(14):1424-1429. doi:10.1001/jama.2014.2531



NHANES participants												
No. in category	5982	5448	2292	3080	2218	2109	859	943	3764	3339	1433	2137
Total No.	16372	16372	5982	5448	11076	11076	2218	2109	5296	5296	3764	3339

Figure 5. Age-adjusted trends in hypertension and controlled hypertension among adults aged 18 and over: United States, 1999–2014



[1]Significant increasing linear trend, $p < 0.0001$.

NOTES: Hypertension estimates are age-adjusted by the direct method to the 2000 U.S. census population using age groups 18–39, 40–59, and 60 and over; see reference 9. Controlled hypertension estimates are age-adjusted by the direct method using computed weights based on the subpopulation of persons with hypertension in the 2007–2008 National Health and Nutrition Examination Survey; see reference 7.

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2011–2014.

SPECIAL ARTICLE

Cost-Effectiveness of Hypertension Therapy According to 2014 Guidelines

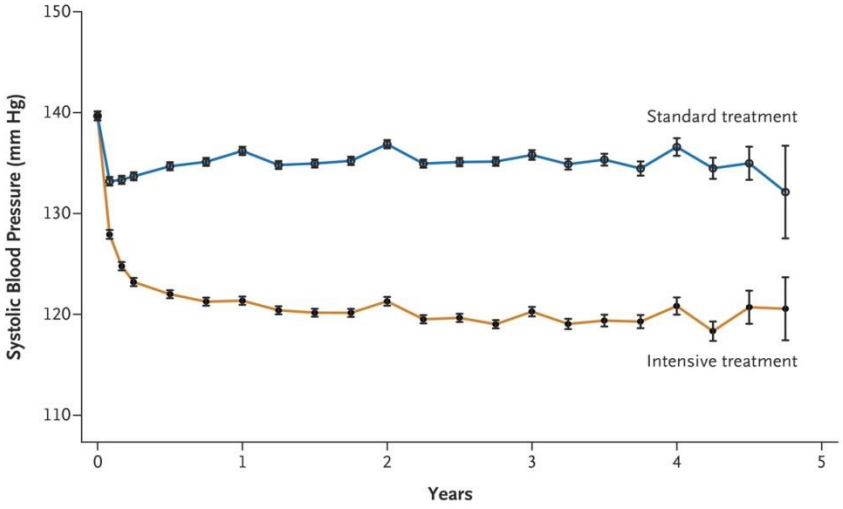
Andrew E. Moran, M.D., M.P.H., Michelle C. Odden, Ph.D., Anusorn Thanataveerat, M.P.H., Keane Y. Tzong, M.P.H., Petra W. Rasmussen, M.P.H., David Guzman, M.S.P.H., Lawrence Williams, M.S., Kirsten Bibbins-Domingo, Ph.D., M.D., Pamela G. Coxson, Ph.D., and Lee Goldman, M.D., M.P.H.

The full implementation of the 2014 HTN Guidelines would result in approximately

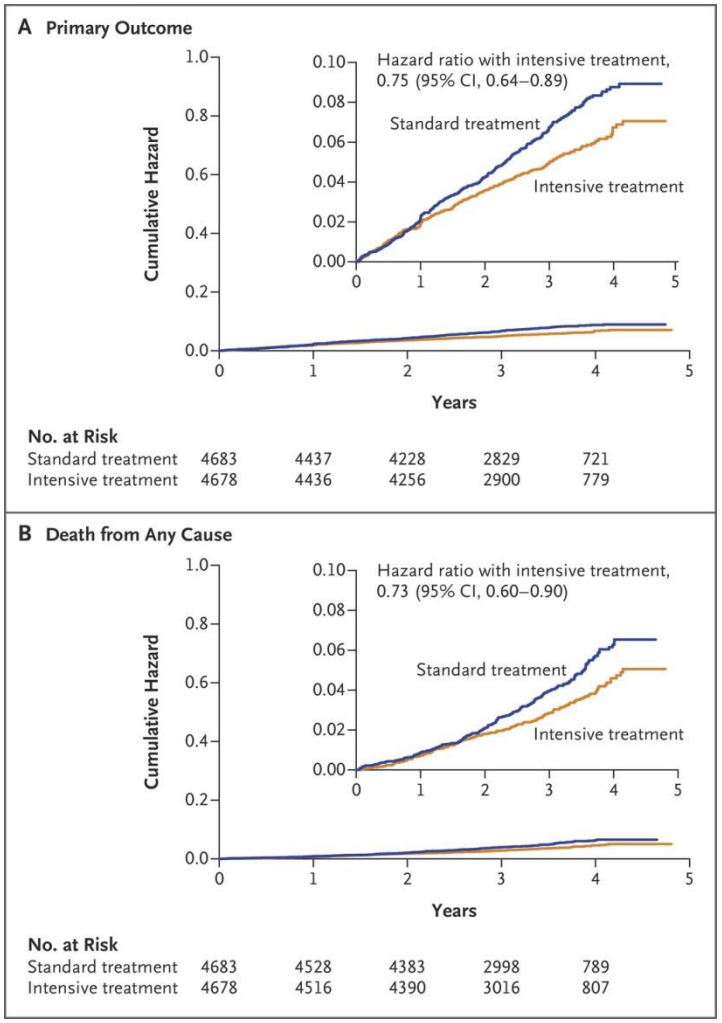
- **56,000 fewer CV events/year**
- **13,000 fewer deaths from CV causes/year**

N Engl J Med 2015;372:447-55.

SPRINT TRIAL: New BP Goals?



No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286
Mean No. of Medications										
Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	3.0



The SPRINT Research Group. N Engl J Med 2015;373:2103-2116.

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. **Baseline Characteristics of the Study Participants.***

Characteristic	Intensive Treatment (N=4678)	Standard Treatment (N=4683)
Criterion for increased cardiovascular risk — no. (%)†		
Age ≥75 yr	1317 (28.2)	1319 (28.2)
Chronic kidney disease‡	1330 (28.4)	1316 (28.1)
Cardiovascular disease	940 (20.1)	937 (20.0)
Clinical	779 (16.7)	783 (16.7)
Subclinical	247 (5.3)	246 (5.3)
Framingham 10-yr cardiovascular disease risk score ≥15%	2870 (61.4)	2867 (61.2)
Female sex — no. (%)	1684 (36.0)	1648 (35.2)
Age — yr		
Overall	67.9±9.4	67.9±9.5
Among those ≥75 yr of age	79.8±3.9	79.9±4.1
Race or ethnic group — no. (%)§		
Non-Hispanic black	1379 (29.5)	1423 (30.4)
Hispanic	503 (10.8)	481 (10.3)
Non-Hispanic white	2698 (57.7)	2701 (57.7)
Other	98 (2.1)	78 (1.7)
Black race¶	1454 (31.1)	1493 (31.9)
Baseline blood pressure — mm Hg		
Systolic	139.7±15.8	139.7±15.4
Diastolic	78.2±11.9	78.0±12.0
Distribution of systolic blood pressure — no. (%)		
≤132 mm Hg	1583 (33.8)	1553 (33.2)
>132 mm Hg to <145 mm Hg	1489 (31.8)	1549 (33.1)
≥145 mm Hg	1606 (34.3)	1581 (33.8)
Serum creatinine — mg/dl	1.07±0.34	1.08±0.34
Estimated GFR — ml/min/1.73 m^2		
Among all participants	71.8±20.7	71.7±20.5
Among those with estimated GFR ≥60 ml/min/1.73 m^2	81.3±15.5	81.1±15.5
Among those with estimated GFR <60 ml/min/1.73 m^2	47.8±9.5	47.9±9.5
Ratio of urinary albumin (mg) to creatinine (g)	44.1±178.7	41.1±152.9
Fasting total cholesterol — mg/dl	190.2±41.4	190.0±40.9
Fasting HDL cholesterol — mg/dl	52.9±14.3	52.8±14.6
Fasting total triglycerides — mg/dl	124.8±85.8	127.1±95.0
Fasting plasma glucose — mg/dl	98.8±13.7	98.8±13.4
Statin use — no./total no. (%)	1978/4645 (42.6)	2076/4640 (44.7)
Aspirin use — no./total no. (%)	2406/4661 (51.6)	2350/4666 (50.4)
Smoking status — no. (%)		
Never smoked	2050 (43.8)	2072 (44.2)
Former smoker	1977 (42.3)	1996 (42.6)
Current smoker	639 (13.7)	601 (12.8)
Missing data	12 (0.3)	14 (0.3)
Framingham 10-yr cardiovascular disease risk score — %	20.1±10.9	20.1±10.8
Body-mass index‖	29.9±5.8	29.8±5.7
Antihypertensive agents — no./patient	1.8±1.0	1.8±1.0
Not using antihypertensive agents — no. (%)	432 (9.2)	450 (9.6)

* Plus–minus values are means ±SD. There were no significant differences (P<0.05) between the two groups except for statin use (P=0.04). To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551. GFR denotes glomerular filtration rate, and HDL high-density lipoprotein.
† Increased cardiovascular risk was one of the inclusion criteria.
‡ Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area.
§ Race and ethnic group were self-reported.
¶ Black race includes Hispanic black and black as part of a multiracial identification.
‖ The body-mass index is the weight in kilograms divided by the square of the height in meters.

SPRINT participants:

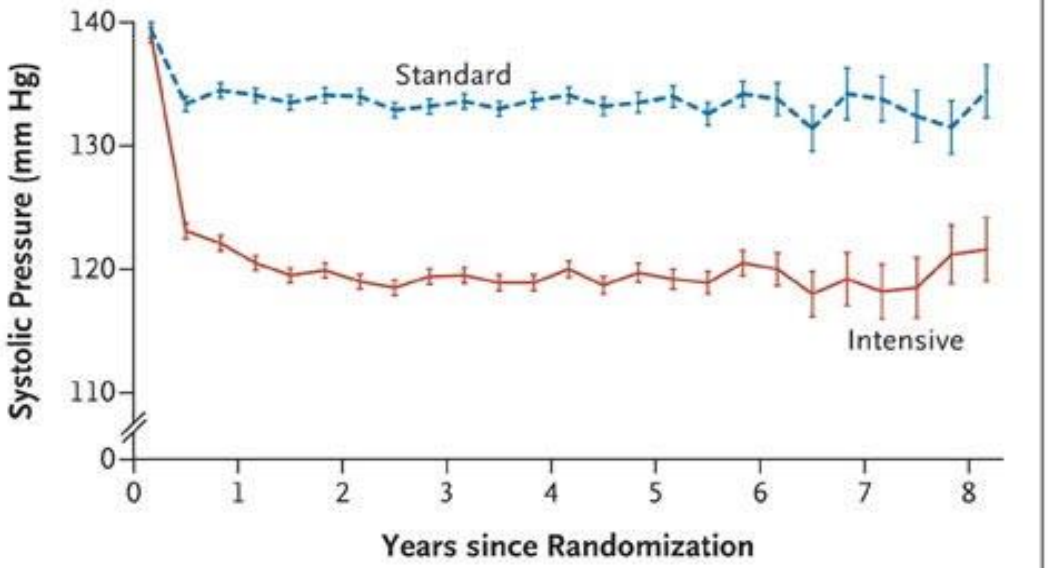
- **aged ≥50 years**
- **SBP 130-180**

  and
- **≥ 1 of the following CV risk factors**
  - **age ≥ 75 years**
  - **clinically evident CV disease (i.e. previously documented CAD, PAD, or CVD)**
  - **subclinical CV disease (i.e. ↑ coronary artery calcification score by CT scan, LVH, or an ABI <0.9)**
  - **eGFR 20-59 mL/min/1.73 m^2**
  - **10-year Framingham Risk Score ≥ 15%**

SPRINT excluded: DM, symptomatic CHF, CVA history, proteinuria ≥ 1 g/day, and nursing home residents

SPRINT used automated oscillometric blood pressure (AOBP), which averages multiple consecutive readings with the patient resting alone in a room. In general, systolic pressure readings are 5-10 mmHg lower with AOBP than with manual measurement

ACCORD TRIAL: Mean Systolic BP Levels at Each Study Visit in Diabetics



Mean No. of Medications Prescribed								
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
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

The ACCORD Study Group. N Engl J Med 2010;362:1575-1585.

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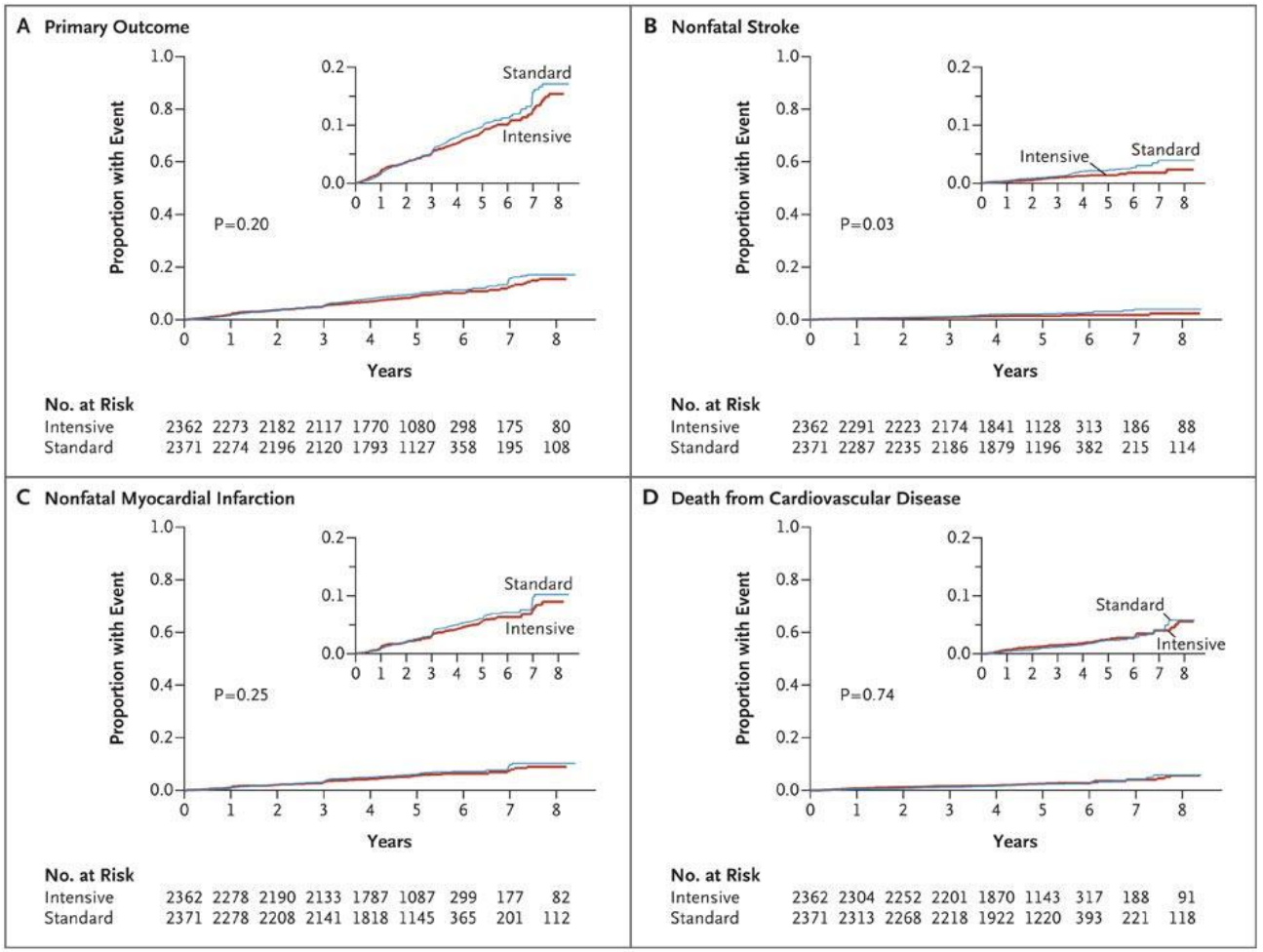
ACCORD TRIAL: Kaplan–Meier Analyses of Selected Outcomes



The ACCORD Study Group. N Engl J Med 2010;362:1575-1585.

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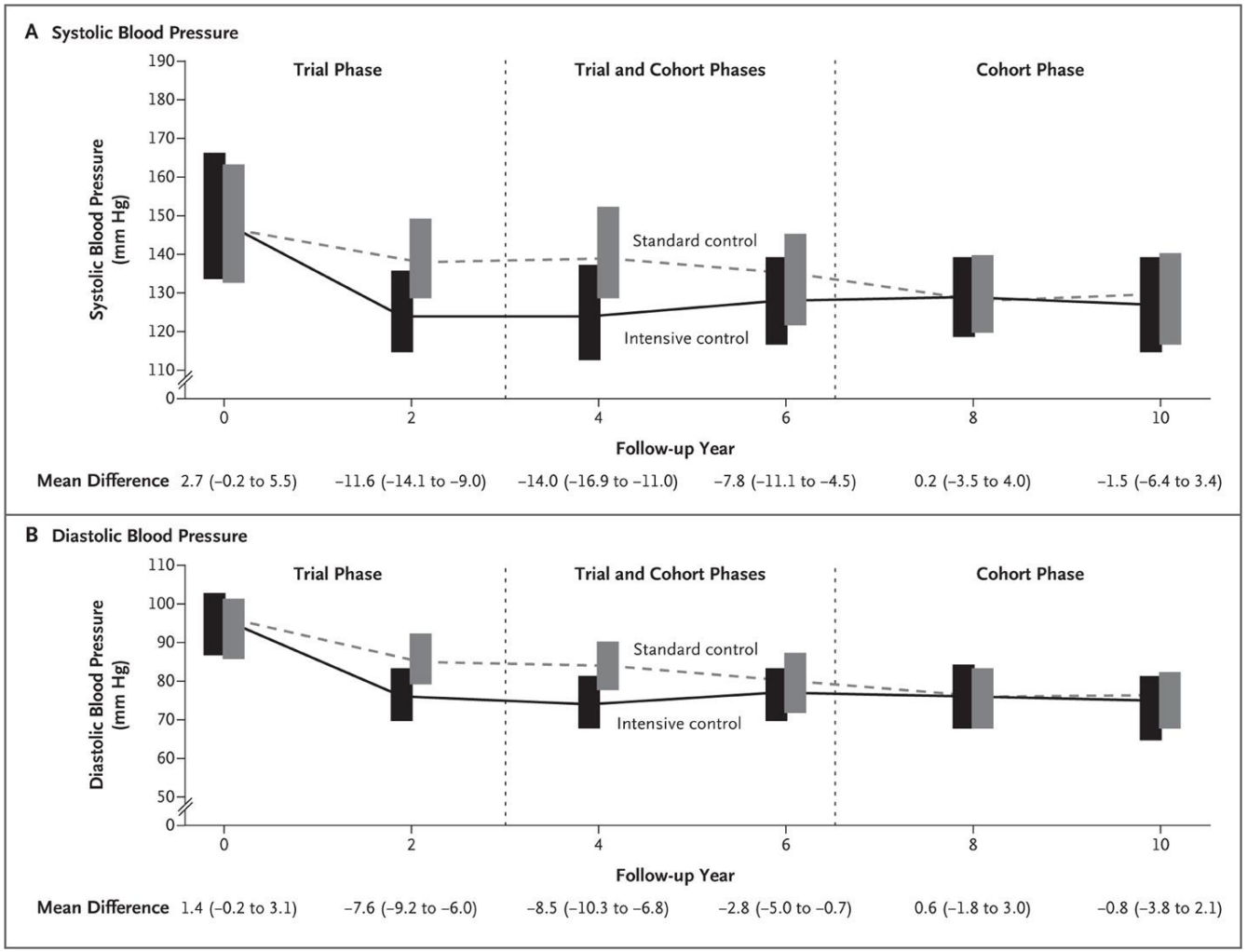
AASK: Blood-Pressure Levels in Patients with Chronic Kidney Disease



Appel LJ et al. N Engl J Med 2010;363:918-929.

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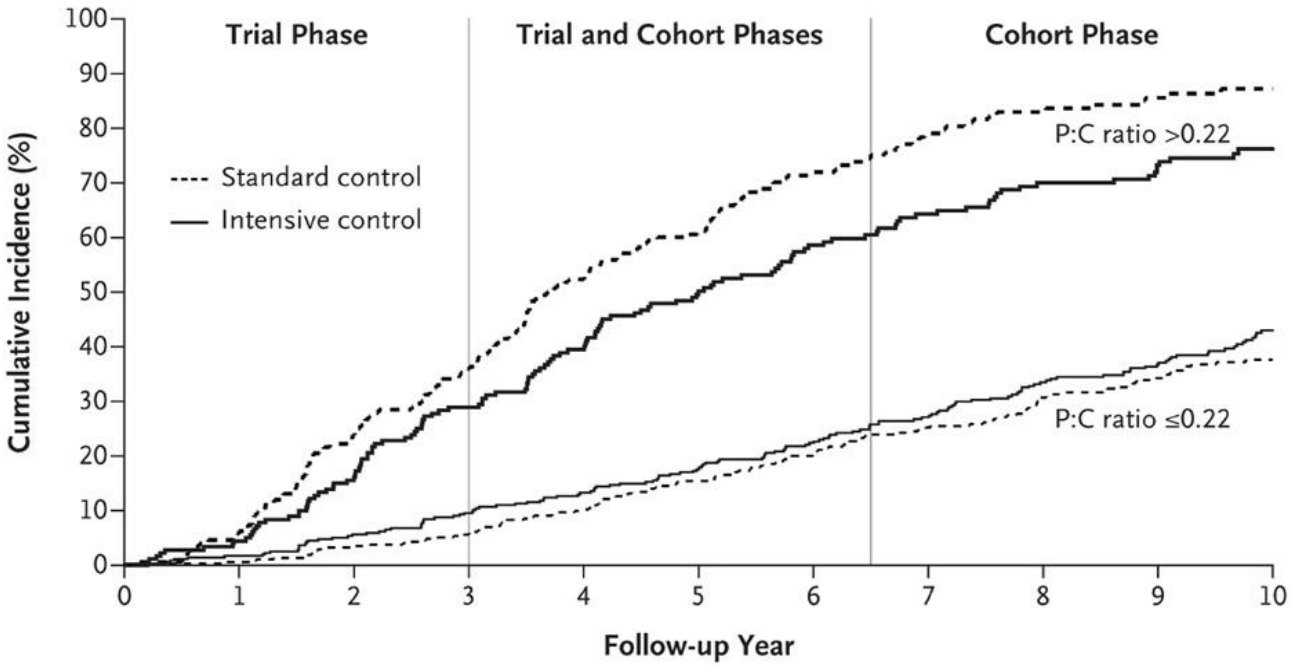
AASK: Event rates for primary and secondary outcomes

Variable	Intensive Control		Standard Control		Hazard Ratio (95% CI)	P Value
	no./total no.	*rate per 100 person-yr*	*no./total no.*	*rate per 100 person-yr*		
All patients						
Doubling of serum creatinine level, ESRD, or death						
Trial phase	159/540	7.0	169/554	7.3	0.88 (0.71–1.09)	0.24
Cohort phase	123/377	7.9	116/382	7.7	0.95 (0.74–1.23)	0.70
Both phases	282/540	7.3	285/554	7.5	0.91 (0.77–1.08)	0.27
Doubling of serum creatinine level or ESRD						
Trial phase	121/540	5.3	125/554	5.4	0.91 (0.71–1.18)	0.49
Cohort phase	92/377	5.9	84/382	5.5	0.99 (0.73–1.33)	0.95
Both phases	213/540	5.5	209/554	5.5	0.95 (0.78–1.15)	0.59
ESRD or death						
Trial phase	124/540	5.3	140/554	5.9	0.84 (0.66–1.07)	0.16
Cohort phase	114/412	6.4	116/411	6.9	0.86 (0.67–1.12)	0.27
Both phases	238/540	5.8	256/554	6.3	0.85 (0.71–1.02)	0.08

The NEW ENGLAND JOURNAL of MEDICINE

Appel LJ et al. N Engl J Med 2010;363:918-929.

AASK: Incidence of the composite primary outcome (doubling of Scr, ESRD, or death) according to baseline proteinuria



P:C Ratio >0.22											
Standard control	176	165	134	113	81	66	45	32	26	22	13
Intensive control	181	172	151	128	109	87	67	56	47	40	25
P:C Ratio ≤0.22											
Standard control	376	373	362	353	332	302	267	234	214	196	128
Intensive control	357	350	335	321	306	282	254	228	206	189	128

Appel LJ et al. N Engl J Med 2010;363:918-929.

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True/false: 120/80 is the currently recommended blood pressure goal for patients with hypertension and concomitant chronic kidney disease.

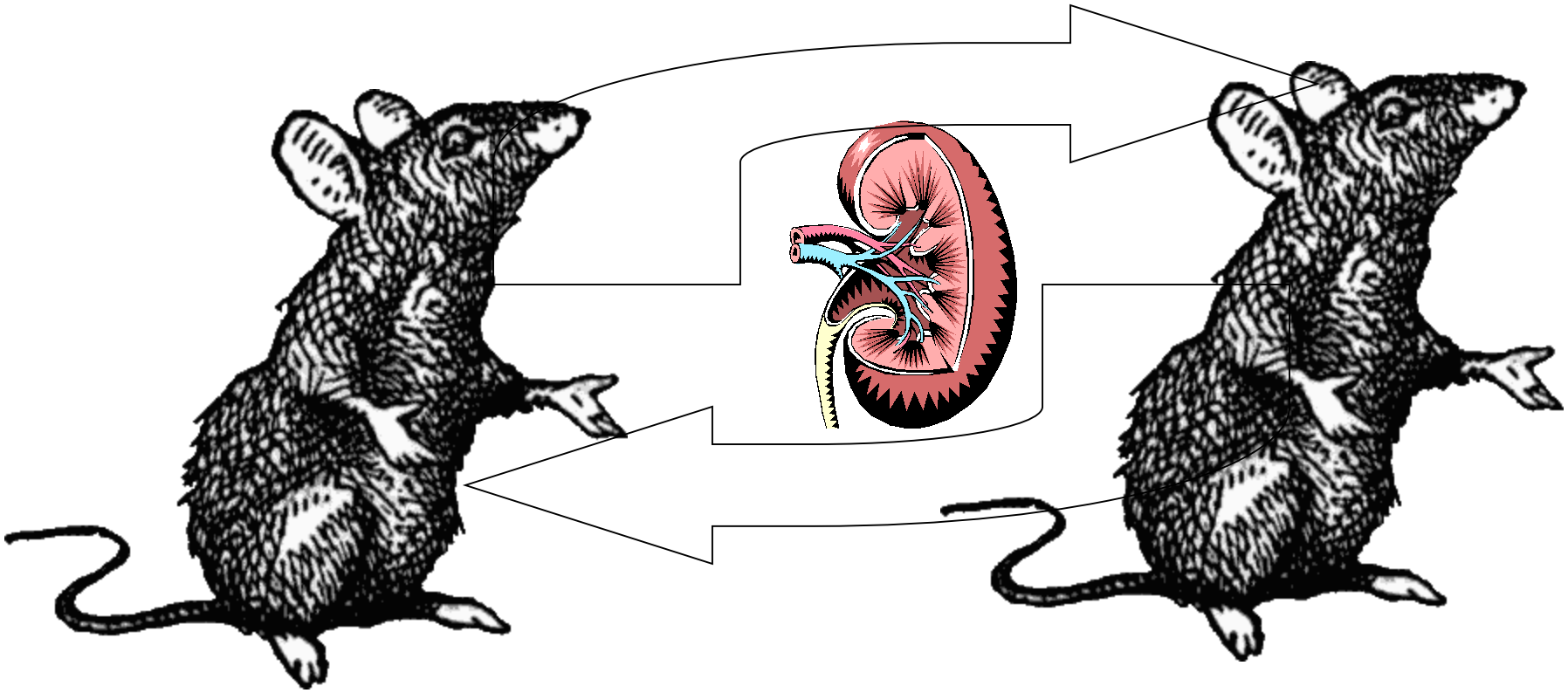
A.True
B.False

Can Hypertension Really Be Resistant?

- Are we addressing volume status sufficiently?
  - Salt restriction and getting away from HCTZ 25 mg QD
- Are we prescribing medications at optimal levels?
  - More effectively blocking the RAAS
- Are we prescribing medications at optimal schedules?
  - Chronotherapy – not what, but *when*

Are we addressing volume status sufficiently?

Blood Pressure Follows the Kidney



genetically hypertension-prone rat

normotensive rat

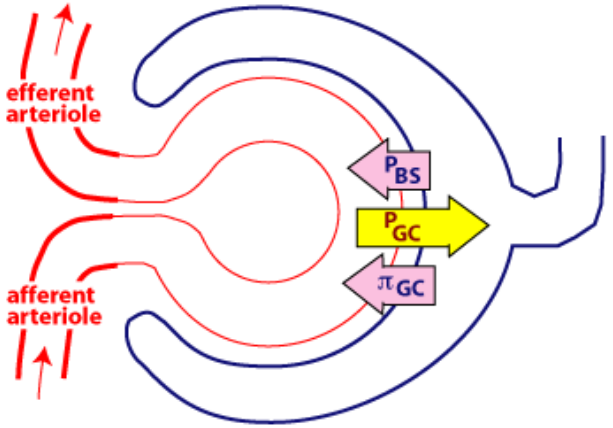
Blood Pressure Follows the Kidney

- The human version of the experiment

LEFT: Bill Evans (publicist, kidney donor, friend)
RIGHT: Neil Simon (playwright, kidney recipient, friend)

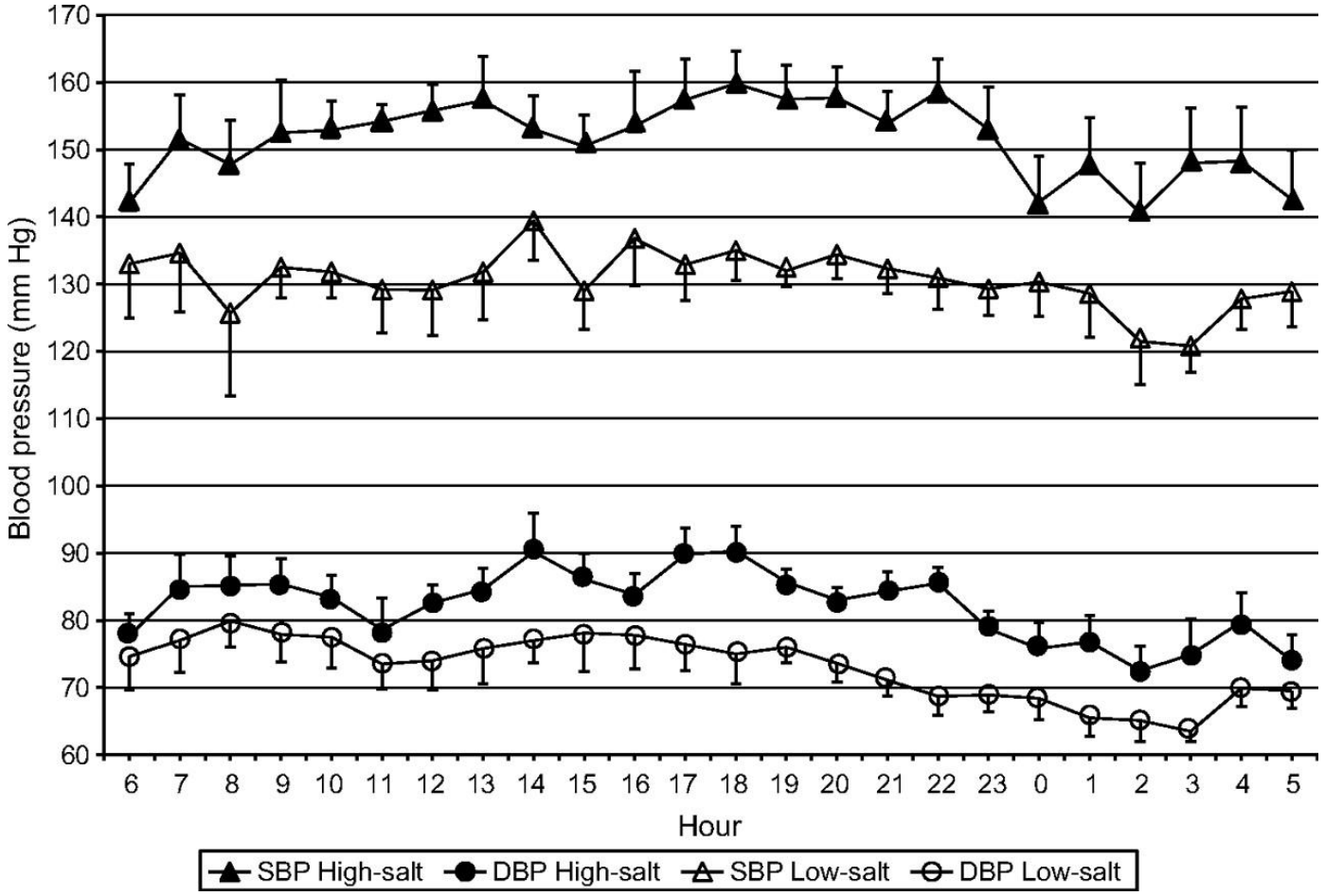
“Pressure-natriuresis” theory

- Renal handling of sodium is the ultimate determinant of blood pressure
  - Normal renal function → effectively excrete Na loads
  - **Impaired renal function *(<u>overt</u> or <u>occult</u>)* → must raise BP to efficiently excrete Na and stay in steady state**



- Most patients with elevated blood pressure are, at root, suffering from a natriuretic handicap
  - Salt restriction and/or diuretics can help overcome this handicap

Randomized, cross-over evaluation of 12 obese subjects with resistant HTN on low (1.2 g/day) and high sodium diets (5.8 g/day)



Pimenta, E. et al. Hypertension 2009;54:475-481

Effect of Dietary Sodium Reduction is Greatest in Patients with Resistant Hypertension

	Dietary Na^+ (mg)	BP effect
[1]Non-hypertensives	1800	↓ 2.0/1.0
[2]Hypertensives	1800	↓5.0/2.7
[3]Resistant hypertensives	1800	↓22.7/9.1

[1]He FJ and MacGregor GA. J Human Hypertens 2002; 16:761
[2]Pimenta E. Hypertension 54:475
[3]Bray GA. Am J Cardiol. 2004; 94:222

TABLE 1. Prevalence of U.S. population aged ≥2 years with us sodium intake in excess of *2015–2020 Dietary Guidelines for Americ* limits, by sex, age group, and racial/ethnic subpopulation* — Natic Health and Nutrition Examination Survey, 2009–2012

Subpopulation (limit)	No. in sample (unweighted)	% with intake ≥limit (95% CI)
Age 2–3 yrs (1,500 mg)	**793**	**93.5 (87.4–99.6)**
Male	403	95.4 (90.0–100)
Female	390	91.4 (84.1–98.8)
White, non-Hispanic	219	93.9 (87.6–100)
Black, non-Hispanic	190	96.1 (91.0–100)
Hispanic	273	92.0 (83.2–100)
Age 4–8 yrs (1,900 mg)	**1,639**	**92.2 (88.6–95.7)**
Male	861	95.1 (92.4–97.8)
Female	778	89.0 (83.4–94.5)
White, non-Hispanic	470	91.8 (86.9–96.6)
Black, non-Hispanic	367	94.3 (90.3–98.4)
Hispanic	595	91.6 (87.2–95.9)
Age 9–13 yrs (2,200 mg)	**1,526**	**93.7 (89.9–97.6)**
Male	742	97.0 (93.6–100)
Female	784	90.7 (85.8–95.7)
White, non-Hispanic	443	93.4 (89.1–97.7)
Black, non-Hispanic	364	92.0 (85.5–98.4)
Hispanic	536	94.5 (89.5–99.6)
Age 14–18 yrs (2,300 mg)	**1,330**	**92.8 (86.8–98.8)**
Male	682	99.0 (97.1–100)
Female	648	87.1 (76.8–97.4)
White, non-Hispanic	378	94.6 (89.0–100)
Black, non-Hispanic	345	86.6 (76.2–97.0)
Hispanic	438	91.9 (83.2–100)
Age ≥19 yrs (2,300 mg)	**9,440**	**89.0 (87.0–90.9)**
Male†	4,613	98.4 (97.6–99.2)
Female	4,827	79.9 (76.7–83.0)
White, non-Hispanic§	4,210	89.8 (87.9–91.8)
Black, non-Hispanic	2,061	84.6 (80.9–88.3)
Hispanic	2,266	88.6 (84.5–92.8)
Age 19–50 yrs (2,300 mg)	**5,025**	**92.1 (89.4–94.7)**
Male	2,459	99.3 (98.5–100)
Female	2,566	84.5 (79.8–89.2)
White, non-Hispanic	2,037	93.1 (90.7–95.5)
Black, non-Hispanic	1,049	88.1 (82.6–93.5)
Hispanic	1,338	91.3 (86.8–95.8)
Age ≥51 yrs (2,300 mg)	**4,415**	**85.0 (82.2–87.9)**
Male	2,154	96.6 (95.0–98.2)
Female	2,261	74.8 (70.2–79.4)
White, non-Hispanic	2,173	86.2 (83.1–89.3)
Black, non-Hispanic	1,012	78.3 (72.8–83.8)
Hispanic	928	80.5 (73.8–87.3)

Subpopulation	Mean sodium intake, mg/day (SE)
Age 19–50 yrs	**3,744 (35.8)**
Male	4,374 (67.1)
Female	3,090 (37.9)
White, non-Hispanic	3,816 (47.5)
Black, non-Hispanic	3,480 (91.7)
Hispanic	3,674 (98.1)
Hypertensive	3,793 (87.7)
Prehypertensive	3,932 (40.6)
Normotensive	3,628 (39.4)
Age ≥51 yrs	**3,293 (48.3)**
Male	3,812 (76.6)
Female	2,837 (46.4)
White, non-Hispanic	3,346 (61.5)
Black, non-Hispanic	3,057 (79.8)
Hispanic	3,129 (117.5)
Hypertensive	3,228 (52.5)
Prehypertensive	3,411 (71.1)
Normotensive	3,350 (67.5)

MMWR Morb Mortal Wkly Rep. 2016 Jan 8;64(52):1393-1397
Prevalence of Excess Sodium Intake in the United States - NHANES, 2009-2012.
Jackson SL, King SM, Zhao L, Cogswell ME.

Table 2. Drug-Treated Hypertension Among Adults in the 2003–2008 National Health and Nutrition Examination Survey

Characteristic	Resistant Hypertension, Uncontrolled, ≥3 Drugs or Controlled ≥4 Drugs (N= 539)	Uncontrolled Hypertension, ≤2 Drugs (N=1136)	*P**	Controlled Hypertension, ≤3 Drugs (N=2035)	*P**
Age in y, mean	66.4 (0.9)	64.7 (0.5)	0.1	59.5 (0.5)	<0.001
Women, %	53.8 (2.4)	59.2 (1.8)	0.07	53.8 (1.3)	0.9
Race/ethnicity, %			0.02		0.002
Mexican American	1.9 (0.6)	4.4 (1.1)		3.5 (0.7)	
White, non-Hispanic	72.6 (2.8)	75.9 (2.9)		77.8 (1.9)	
Black, non-Hispanic	18.5 (2.3)	13.7 (2.0)		12.6 (1.5)	
Other/multiracial	7.1 (1.7)	6.0 (0.9)		6.0 (0.9)	
Body mass index in kg/m^2, mean†	32.4 (0.5)	29.7 (0.2)	<0.001	31.0 (0.2)	0.01
Estimated GFR in mL/min, mean‡	69.1 (1.5)	78.9 (0.9)	<0.001	80.2 (0.7)	<0.001
Estimated GFR <60 mL/min, %‡	33.7 (2.6)	19.4 (1.6)	<0.001	16.5 (0.9)	<0.001
Serum potassium, mmol/L, %‡	4.03 (0.02)	4.00 (0.01)	0.4	4.00 (0.01)	0.4
Albumin:creatinine ratio, %§			<0.001		<0.001
<30 mg/g	61.0 (2.1)	75.8 (1.5)		86.8 (0.8)	
30 to 300 mg/g	26.2 (2.3)	20.1 (1.4)		11.3 (0.8)	
>300 mg/g	12.8 (2.2)	4.1 (0.7)		1.9 (0.3)	
Coronary heart disease, %	22.0 (2.6)	12.1 (1.6)	<0.001	9.4 (1.2)	<0.001
Heart failure, %	10.0 (2.0)	3.9 (0.8)	<0.001	4.1 (0.5)	<0.001
Diabetes mellitus, %	35.2 (2.6)	20.2 (1.1)	<0.001	20.0 (1.0)	<0.001
Stroke, %	10.1 (1.7)	5.8 (0.8)	0.02	3.8 (0.5)	<0.001

Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension. 2011 Jun;57(6):1076-80.

True/false: A rise in BUN, creatinine, and/or uric acid level is an indication that a hypertensive patient is on too strong a dose of diuretics.

A.True
B.False

Table II. Clinical and Biochemical Clues Suggesting the Need for a More Potent Diuretic Regimen
High sodium intake
Size of patient
Presence of edema
Low plasma renin activity
Absence of increase in blood urea nitrogen, creatinine, and uric acid levels
Chronic renal disease

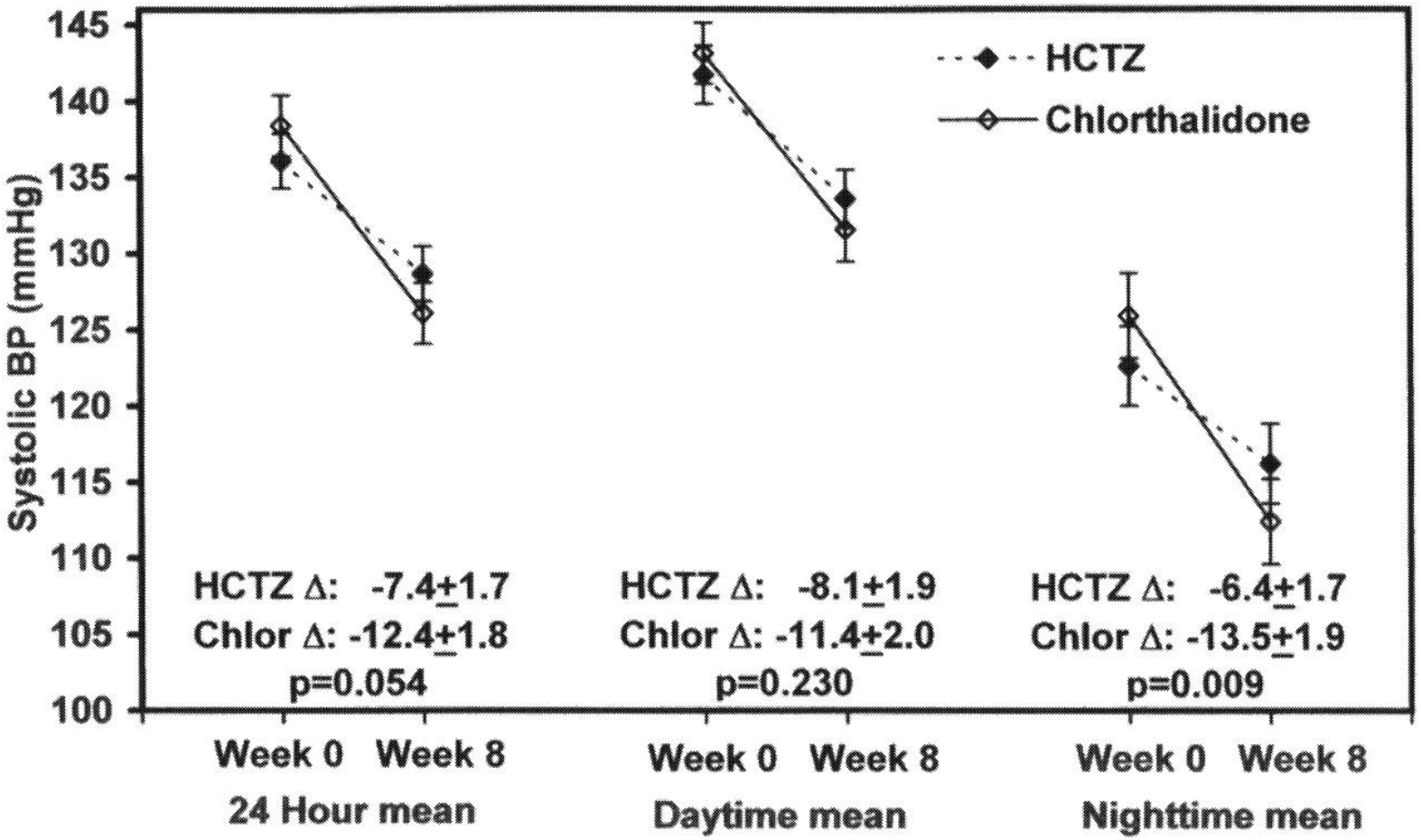
Drug therapy for resistant hypertension: simplifying the approach.
Mann SJ.
J Clin Hypertens (Greenwich). 2011 Feb;13(2):120-30.

Table III. Options for Increasing the Diuretic Regimen When 25 mg of HCTZ Is Ineffective

Increase hydrochlorothiazide (HCTZ) dose to 37.5 mg or 50 mg (probably add a potassium-sparing agent)
Maintain 25 mg of HCTZ and add spironolactone, amiloride, or eplerenone
Switch to chlorthalidone 25 mg (±potassium-sparing agent)
Switch to a loop diuretic (especially patients with reduced renal function)
Combine a loop diuretic with thiazide (in advanced renal insufficiency)

Drug therapy for resistant hypertension: simplifying the approach.
Mann SJ.
J Clin Hypertens (Greenwich). 2011 Feb;13(2):120-30.

Choice of diuretic



Khosla N, Chua DY, Elliott WJ, Bakris GL. *J Clin Hypertens (Greenwich).* Jun 2005;7(6):354-356

Table 4. Type of Antihypertensive Medications Used in the Past Month Among Adults With Resistant Hypertension

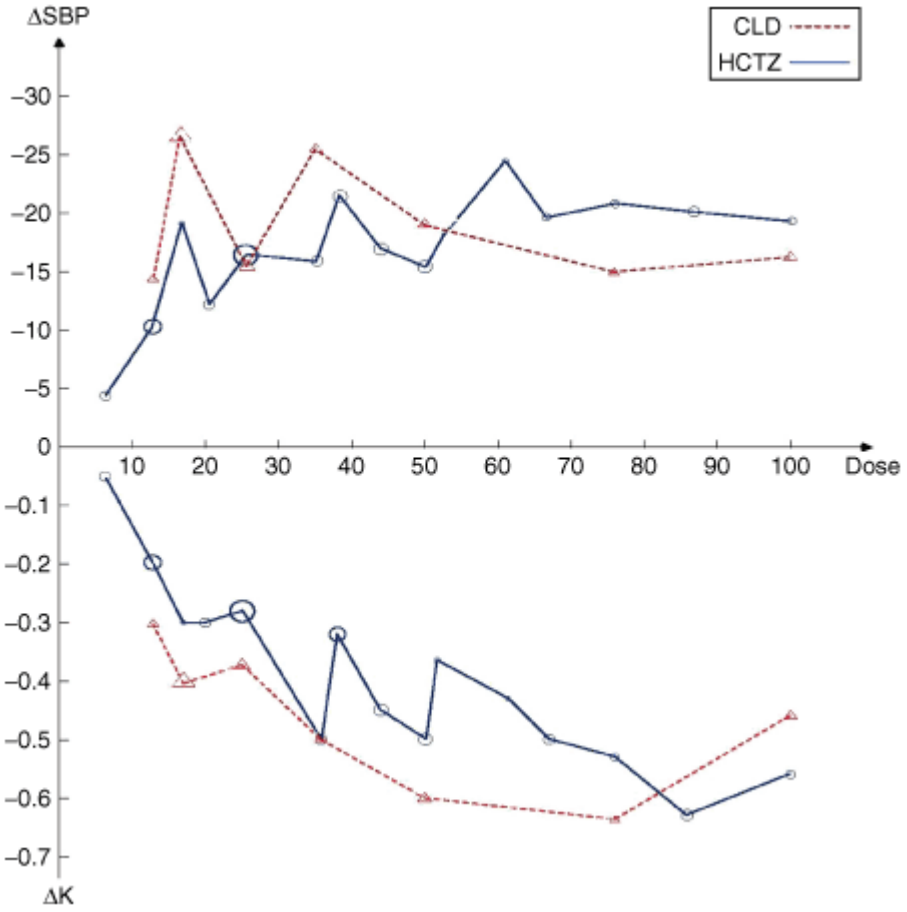
Antihypertensive Medication Class	Subclass	Number	Percentage (SE)
ACE inhibitor		317	57.0 (2.8)
ARB		209	40.9 (2.8)
β-blocker		402	75.5 (2.1)
Calcium channel blocker		354	66.5 (2.4)
	Dihydropyridine	272	50.7 (2.4)
	Nondihydropyridine	88	17.0 (2.5)
Diuretic		458	85.6 (2.4)
	Thiazide like	300	58.5 (3.3)
	HCTZ	279	55.1 (3.3)
	Loop	176	30.4 (3.1)
	Potassium sparing	57	12.5 (2.0)
	Aldosterone antagonist	20	3.0 (0.8)
α-Adrenergic receptor antagonist		108	17.7 (1.7)
Central-acting and other antiadrenergic drugs		58	10.0 (1.4)
Direct vasodilator		32	4.7 (0.9)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HCTZ, hydrochlorothiazide.

Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension. 2011 Jun;57(6):1076-80.

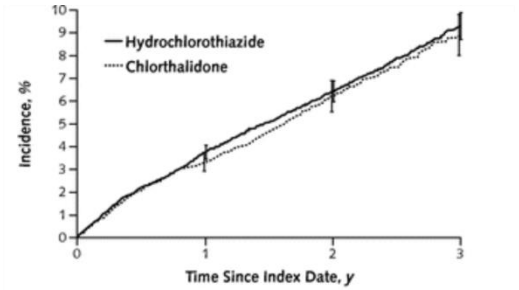
Meta-Analysis of Dose–Response Characteristics of Hydrochlorothiazide and Chlorthalidone: Effects on Systolic Blood Pressure and Potassium

Michael E. Ernst, Barry L. Carter, Shimin Zheng and Richard H. Grimm Jr



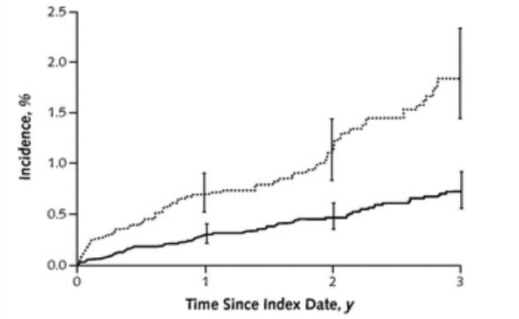
American Journal of Hypertension 2010; **23** 4, 440–446

Chlorthalidone Versus HCTZ for the Treatment of HTN in Older Adults



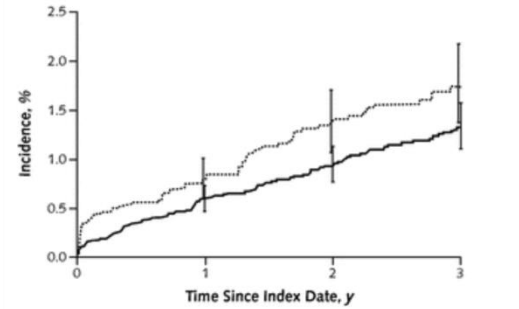
Drug	Patients at Risk, *n*		
	End of Year 1	End of Year 2	End of Year 3
Chlorthalidone	4385	2940	2062
Hydrochlorothiazide	10 032	7361	5568

Primary outcome: composite of death or hospitalization for heart failure, stroke, or myocardial infarction



Drug	Patients at Risk, *n*		
	End of Year 1	End of Year 2	End of Year 3
Chlorthalidone	4406	2953	2078
Hydrochlorothiazide	10 115	7446	5641

Hospitalization with hypokalemia



Drug	Patients at Risk, *n*		
	End of Year 1	End of Year 2	End of Year 3
Chlorthalidone	4401	2957	2080
Hydrochlorothiazide	10 105	7440	5639

Hospitalization with hyponatremia

Ann Intern Med. 2013;158(6):447-455. doi:10.7326/0003-4819-158-6-201303190-00004

Risk of Thiazide-Induced Metabolic Adverse Events in Older Adults
Mean Age = 74 +/- 6 years

Outcome	1060 Matched Thiazide Users	1060 Matched Nonusers	Number Needed to Harm (95% CI)	Relative Risk (95% CI)	*P*-Value
	n (%)				
AE (Na<135, K<3.5, eGFR drop of >25%)	152 (14.3)	64 (6.0)	12 (9–17)	2.61 (1.91–3.55)	<.001
Hyponatremia	68 (6.5)	21 (2.0)	22 (15–40)	3.40 (1.95–5.93)	<.001
Hypokalemia	47 (4.5)	15 (1.4)	33 (22–70)	3.21 (1.85–5.60)	<.001
>25% decrease in eGFR	50 (5.5)	29 (3.2)	43 (24–229)	1.76 (1.11–2.79)	.015
Severe AE (Na<130, K<3.0, eGFR drop of >50%)	19 (1.8)	6 (0.6)	82 (47–326)	3.21 (1.36–7.55)	.008
Emergency department visit or hospitalization for AE	40 (3.8)	21 (2.0)	56 (31–323)	1.94 (1.11–3.39)	.02

J Am Geriatr Soc. 2014 Jun;62(6):1039-45

Are we prescribing medications at optimal levels?

Blockade of the RAAS

- Lowers blood pressure
- Decreases morbidity and mortality in CHF pts
- Decreases proteinuria and may slow the rate of GFR decline in patients with CKD
- Particularly applicable to pts with resistant hypertension +/- CKD

How much RAAS blockade is enough?

- Significant numbers of patients with chronic heart and kidney disease continue to progress at a higher than predicted rate despite standard therapy with ACE-I or ARB
  - e.g. current treatment regimens that include an ACE-I or ARB have not been proven to halt kidney disease progression in most adult patients over the long term
- ***Incomplete blockade of the RAAS at recommended doses may be one explanation for this observation***

Toto R, Palmer BF. Rationale for combination angiotensin receptor blocker and angiotensin-converting enzyme inhibitor treatment and end-organ protection in patients with chronic kidney disease. *Am J Nephrol.* 2008;28(3):372-380.
Jorde UP, Ennezat PV, Lisker J, et al. Maximally recommended doses of angiotensin-converting enzyme (ACE) inhibitors do not completely prevent ACE-mediated formation of angiotensin II in chronic heart failure. *Circulation.* Feb 29 2000;101(8):844-846.

Ultrahigh doses of ACE-Is or ARBs

- Counters potentially incomplete RAAS blockade
- In small, short-term clinical studies, ultrahigh doses yield better reductions in surrogate outcomes, such as BP and proteinuria reduction, than conventional doses of ACE-Is or ARBs
- Supporters of this ultrahigh therapy contend that the FDA-recommended doses of ACE-Is and ARBs used in routine practice are inadequate

Berl T. Maximizing inhibition of the renin-angiotensin system with high doses of converting enzyme inhibitors or angiotensin receptor blockers. *Nephrol Dial Transplant.* Aug 2008;23(8):2443-2447

2-month treatment periods on various doses of ACE-I

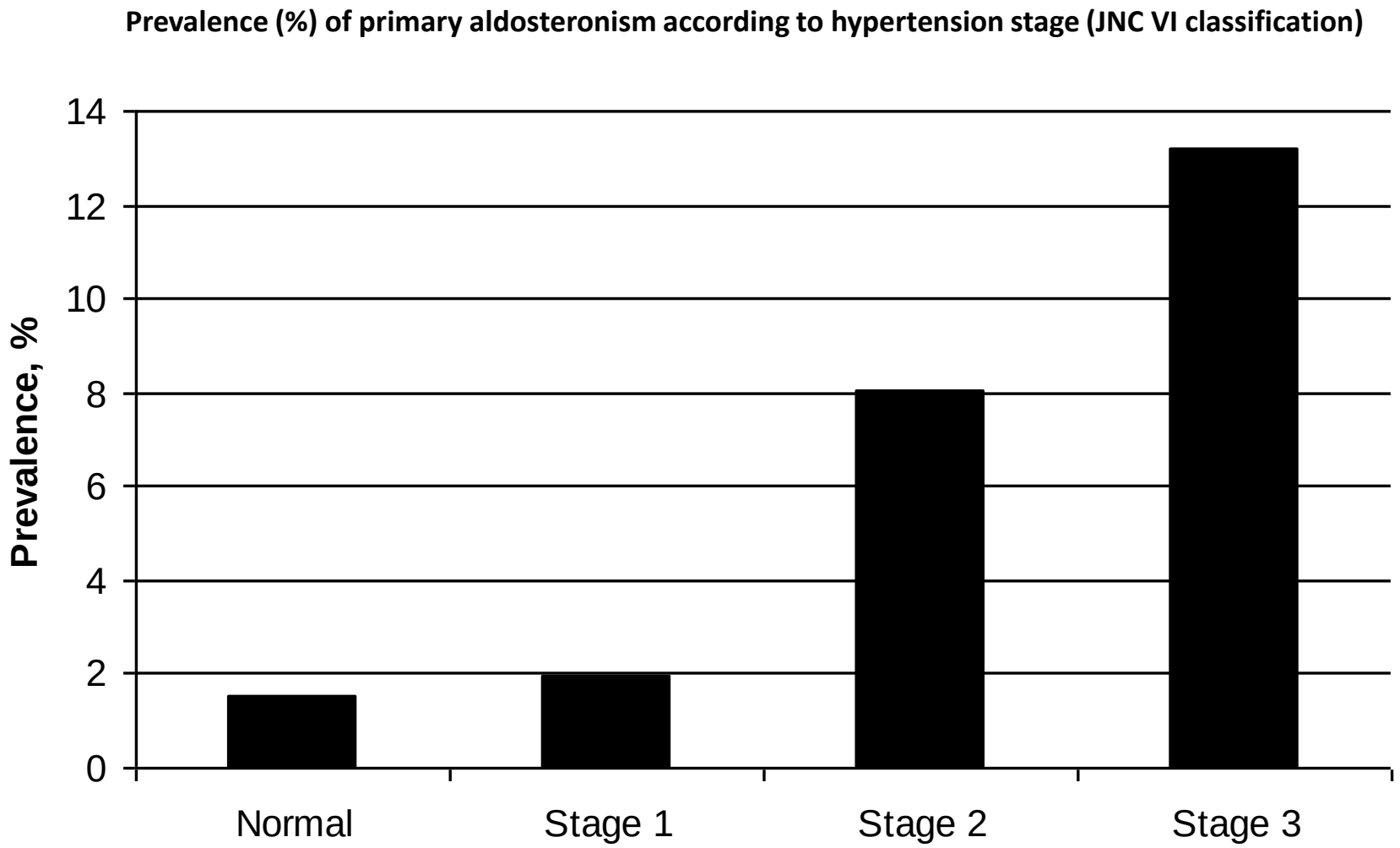
Table 2 Laboratory data during treatment with lisinopril 20, 40 and 60 mg in random order compared with baseline in 49 type 1 diabetic patients with DN

Characteristic	Baseline	Lisinopril (mg)		
		20	40	60
UAER[a] (mg/24 h)	362 (240–545)	121 (85–172)[b]	100 (68–147)[b,c]	103 (69–154)[b,c]
24 h ABP (mmHg)	142 (2)/74 (1)	131 (2)[b] /67 (1)[b]	128 (2)[b] /66 (1)[b,c]	130 (2)[b] /66 (1)[b]
Estimated GFR (ml $min^{-1}1.73\ m^{-2}$)	75 (4)	69 (4)[b]	68 (4)[b]	67 (4)[b]
P-potassium (mmol/l)	3.9 (0.1)	4.3 (0.1)[b]	4.4 (0.1)[b]	4.4 (0.1)[b]
HbA_{1c} (%)	8.6 (0.1)	8.7 (0.2)	8.8 (0.2)	8.9 (0.1)[b]
B-Haemoglobin (mmol/l)	8.3 (0.1)	8.0 (0.1)[b]	7.8 (0.1)[b,c]	7.9 (0.1)[b,c]
P-total cholesterol (mmol/l)	4.5 (0.1)	4.2 (0.1)[b]	4.1 (0.1)[b]	4.2 (0.1)[b]
P-renin activity (ng angiotensin I $ml^{-1}\ h^{-1}$)	6 (5–7)	22 (17–31)[b]	26 (20–34)[b]	35 (26–47)[b,d]
P-ACE activity (U)	51 (44–58)	4.4 (3.5–5.6)[b]	3.0 (2.3–3.8)[b,c]	2.7 (2.3–3.2)[b,c]
P-angiotensin I (pmol/l)	25 (21–29)	130 (95–179)[b]	134 (102–177)[b]	192 (142–260)[b,d]
P-angiotensin II (pmol/l)	11 (8–14)	4.1 (2.9–5.9)[b]	2.9 (1.9–4.3)[b,c]	3.2 (2.2–4.6)[b]
P-aldosterone (pg/ml)	66 (51–86)	26 (17–41)[b]	22 (15–32)[b]	19 (12–30)[b]

Data are mean (SE) or [a] geometric mean (95% CI)
[b] $p<0.05$ vs baseline, [c] $p<0.05$ vs 20 mg, [d] $p<0.05$ vs 20 mg and 40 mg. Friedman test for several related samples was used followed by paired samples *t* test if significant
B, blood; P, plasma

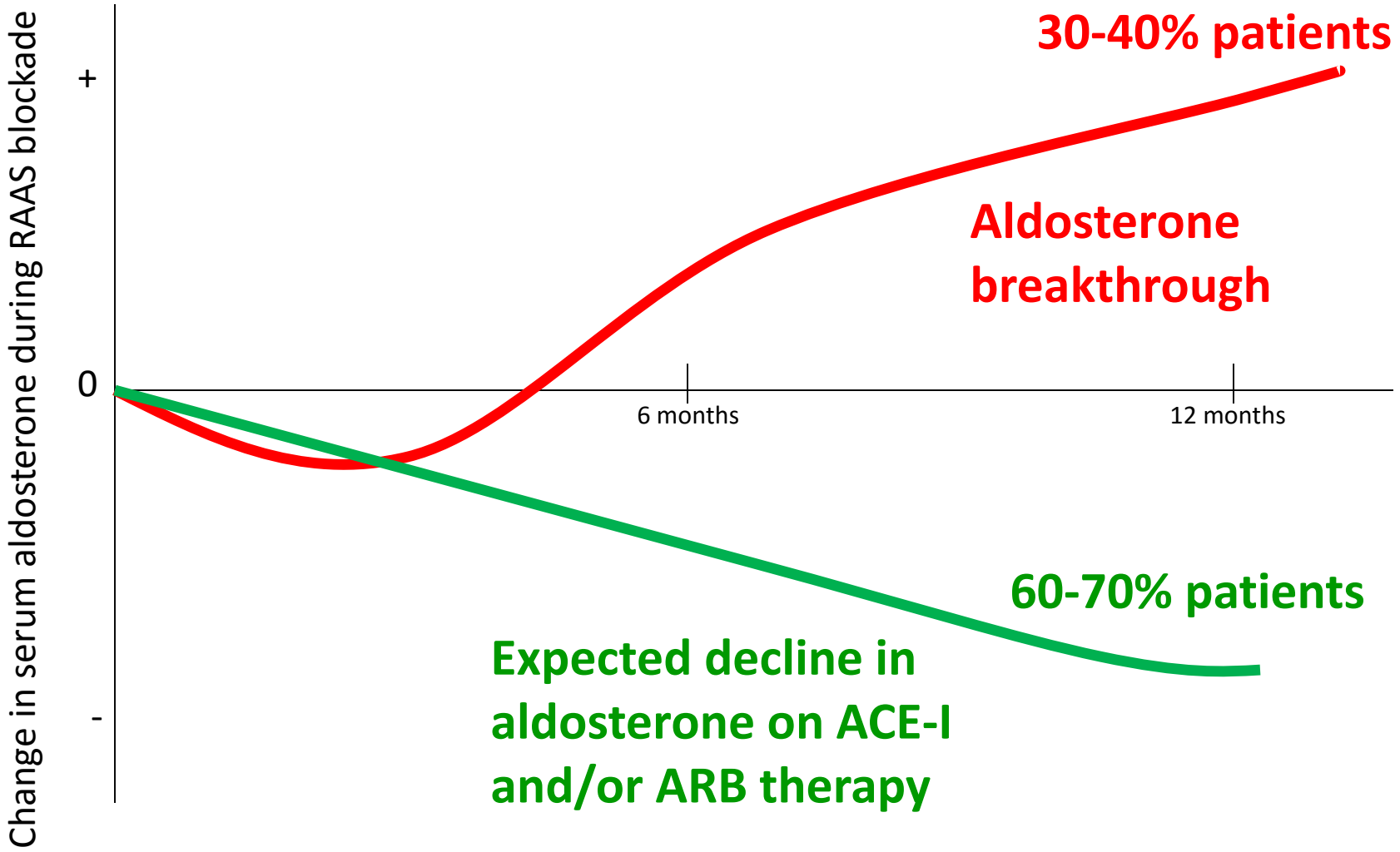
Schjoedt KJ, Astrup AS, Persson F, et al. Optimal dose of lisinopril for renoprotection in type 1 diabetic patients with diabetic nephropathy: a randomised crossover trial. *Diabetologia.* Jan 2009;52(1):46-49

Address the RAAS



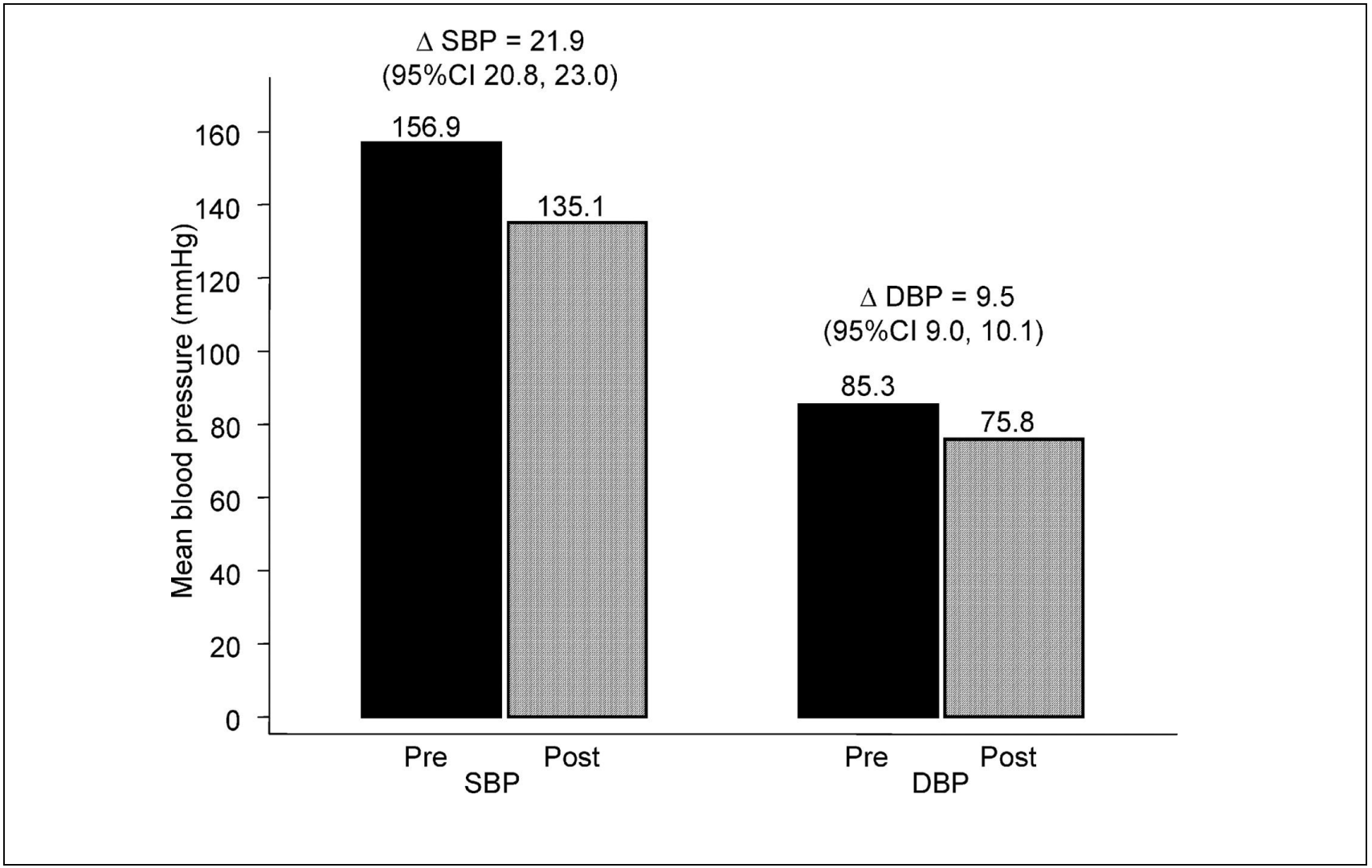
Mosso L, Carvajal C, Gonzalez A, et al. Primary aldosteronism and hypertensive disease. *Hypertension.* Aug 2003;42(2):161-165.

Aldosterone Breakthrough



Bomback AS, Klemmer PJ. *Nat Clin Pract Nephrol*. 2007;3(9):486-92

ASCOT: Use of spironolactone for resistant hypertension in 1411 subjects



Chapman N, Dobson J, Wilson S, et al. *Hypertension.* Apr 2007;49(4):839-845.

Addition of Spironolactone in Patients With Resistant Arterial Hypertension (ASPIRANT)

A Randomized, Double-Blind, Placebo-Controlled Trial

Jan Václavík, Richard Sedlák, Martin Plachý, Karel Navrátil, Jiří Plášek, Jiří Jarkovský, Tomáš Václavík, Roman Husár, Eva Kociánová, Miloš Táborský

Table 2. Change of Patient Characteristics at 8 Weeks Compared to Baseline

Patient Characteristics	Spironolactone (n=55)	Placebo (n=56)	Between-Group Difference*	P†
Systolic BP				
ABPM daytime systolic BP, mm Hg	−9.3 (±12.6)	−3.9 (±12.1)	−5.4 (−10.0; −0.8)	0.024
ABPM nighttime systolic BP, mm Hg	−11.2 (±17.6)	−2.6 (±17.7)	−8.6 (−15.2; −2.0)	0.011
24-h ABPM systolic BP, mm Hg	−13.8 (±11.8)	−4.0 (±12.7)	−9.8 (−14.4; −5.2)	0.004
Office systolic BP, mm Hg‡	−14.6 (±15.6)	−8.1 (±14.8)	−6.5 (−12.2; −0.8)	0.011
Diastolic BP				
ABPM daytime diastolic BP, mm Hg	−4.2 (±8.0)	−3.2 (±8.2)	−1.0 (−4.0; 2.0)	0.358
ABPM nighttime diastolic BP, mm Hg	−5.6 (±10.5)	−2.6 (±11.0)	−3.0 (−7.0; 1.0)	0.079
24-h ABPM diastolic BP, mm Hg	−4.2 (±7.0)	−3.2 (±7.7)	−1.0 (−3.7; 1.7)	0.405
Office diastolic BP, mm Hg‡	−6.6 (±9.6)	−4.1 (±8.6)	−2.5 (−5.9; 0.9)	0.079
Pulse Pressure§				
ABPM daytime pulse pressure, mm Hg	−5.1 (±8.4)	−0.7 (±8.3)	−4.4 (−7.5; −1.3)	0.007
ABPM nighttime pulse pressure, mm Hg	−5.6 (±12.9)	0.0 (±10.4)	−5.6 (−10.0; −1.2)	0.005
24-h ABPM pulse pressure, mm Hg	−6.5 (±7.2)	−0.8 (±7.6)	−5.7 (−8.5; −2.9)	<0.001
Office pulse pressure, mm Hg‡	−8.0 (±11.2)	−4.0 (±11.8)	−4.0 (−8.3; 0.3)	0.056

Hypertension 2011; 57(6): 1069-1075

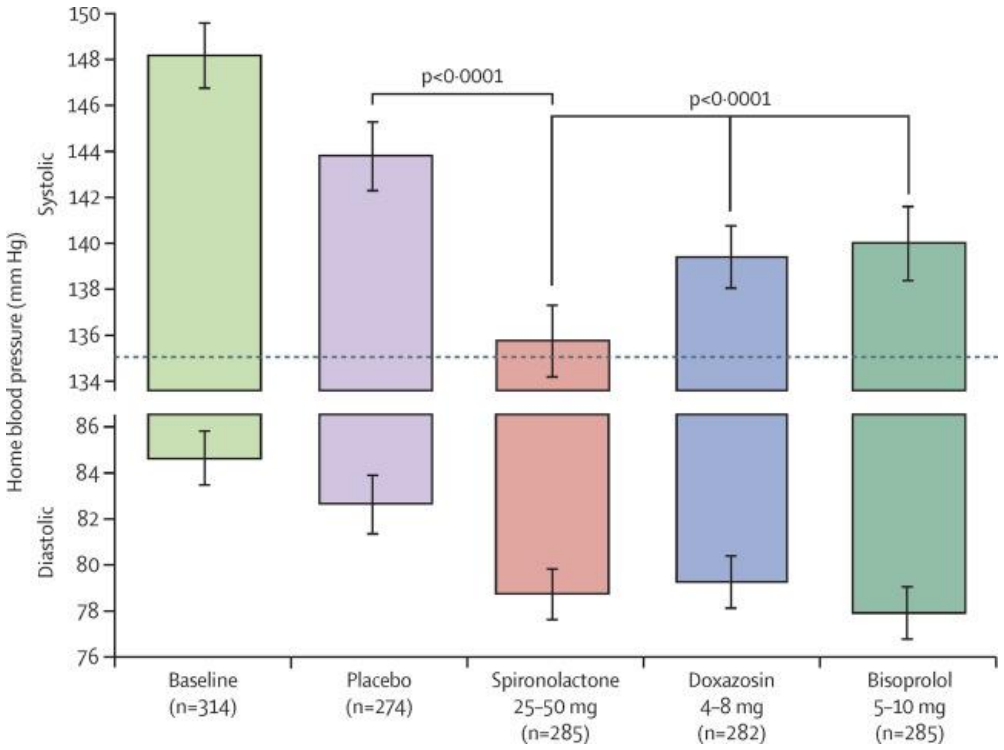


Figure 2. Home systolic and diastolic blood pressures comparing spironolactone with placebo, doxazosin, and bisoprolol

	Blood pressure (mm Hg)	Change from baseline (mm Hg)
Mean		
Spironolactone	133·5 (132·3 to 134·8)	−14·4 (−15·6 to −13·1)
Doxazosin	138·8 (137·6 to 140·1)	−9·1 (−10·3 to −7·8)
Bisoprolol	139·5 (138·2 to 140·8)	−8·4 (−9·7 to −7·1)
Placebo	143·7 (142·5 to 145·0)	−4·2 (−5·4 to −2·9)
Mean differences		
Spironolactone *vs* placebo	−10·2 (−11·7 to −8·74)	p<0·0001
Spironolactone *vs* mean bisoprolol and doxazosin	−5·64 (−6·91 to −4·36)	p<0·0001
Spironactone *vs* doxazosin	−5·30 (−6·77 to −3·83)	p<0·0001
Spironolactone *vs* bisoprolol	−5·98 (−7·45 to −4·51)	p<0·0001

Data are mean (95% CI). Sensitivity analysis using only the mean home systolic blood pressure at the final visit of each cycle (week 12).

***Table 3*: Home systolic blood pressure at final visit of each cycle**

Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

LANCET 2015; Volume 386: 2059–2068

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Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension. 2011 Jun;57(6):1076-80.

Are we prescribing medications at optimal schedules?

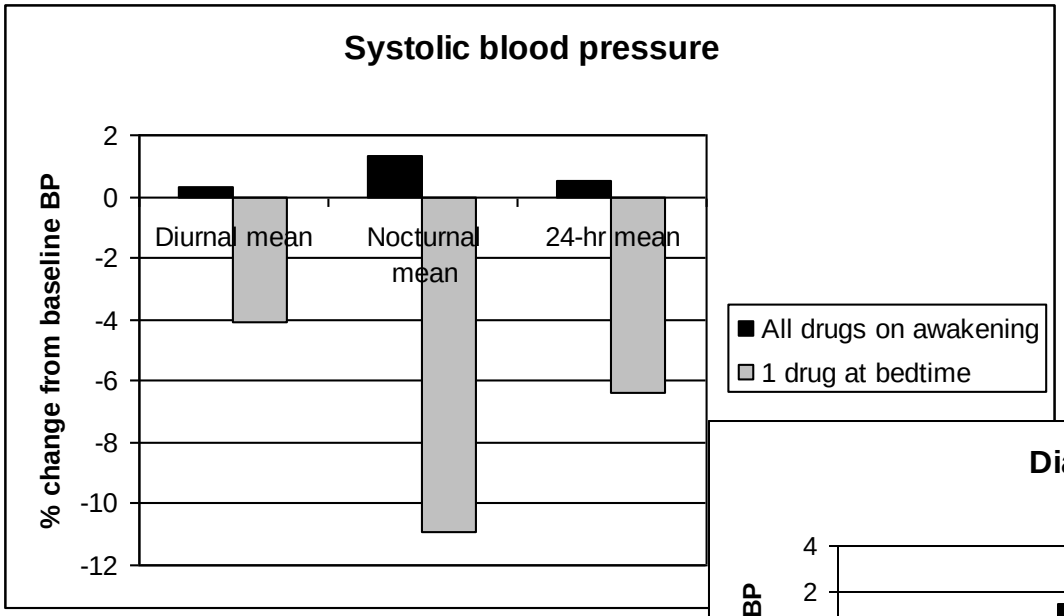
Rationale for chronotherapy

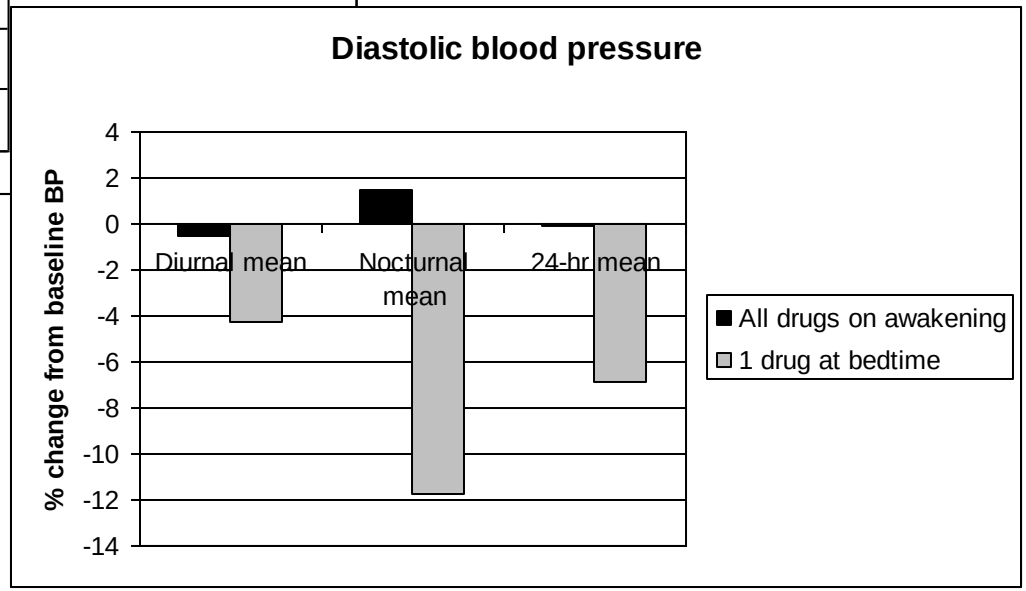
- Many, if not all, specific human physiological functions are under the control of a circadian timing system
  - includes kidney function and, by extension, the control of blood pressure
  - most obvious example of circadian rhythmicity of renal function is the well-recognized difference in urine volume formation and excretion between daytime and nighttime

- Urinary excretion of all major solutes – ***including sodium*** – also follows a circadian pattern; when this pattern is impaired, disease may ensue
  - Abnormal circadian rhythm for renal sodium reabsorption is considered one of the major factors leading to the loss of nocturnal blood pressure dipping

Burnier M, Coltamai L, Maillard M, Bochud M. *Semin Nephrol.* Sep 2007;27(5):565-571.
Bankir L, Bochud M, Maillard M, Bovet P, Gabriel A, Burnier M. *Hypertension.* Apr 2008;51(4):891-898.

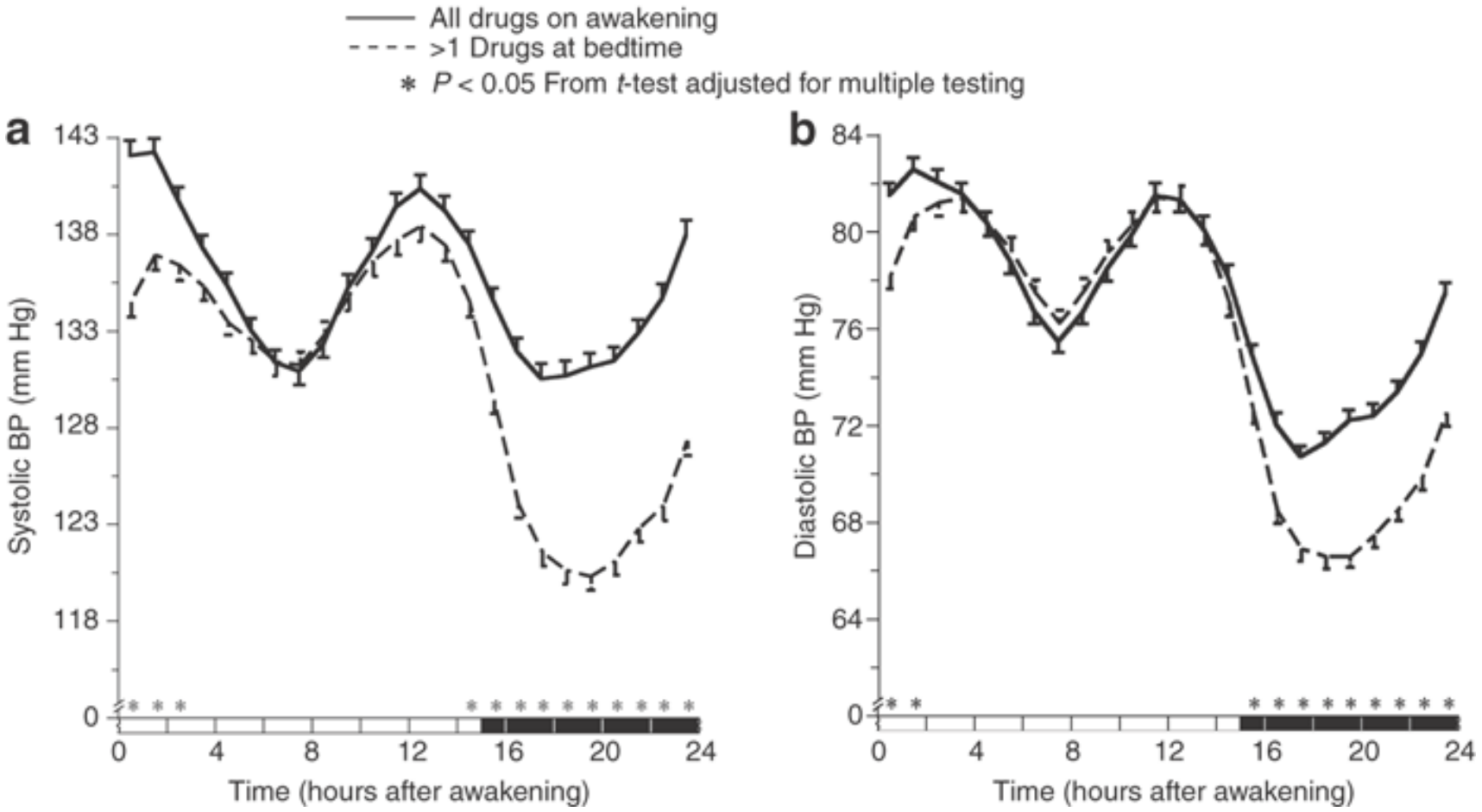
Timing of drugs in resistant HTN





Hermida RC, Ayala DE, Fernandez JR, Calvo C. *Hypertension* 2008;51(1):69-76.

Chronotherapy in 1794 subjects with “true” resistant HTN



Am J Hypertens. 2010 Apr;23(4):432-9.

Effects of time of antihypertensive treatment on ambulatory blood pressure and clinical characteristics of subjects with resistant hypertension.

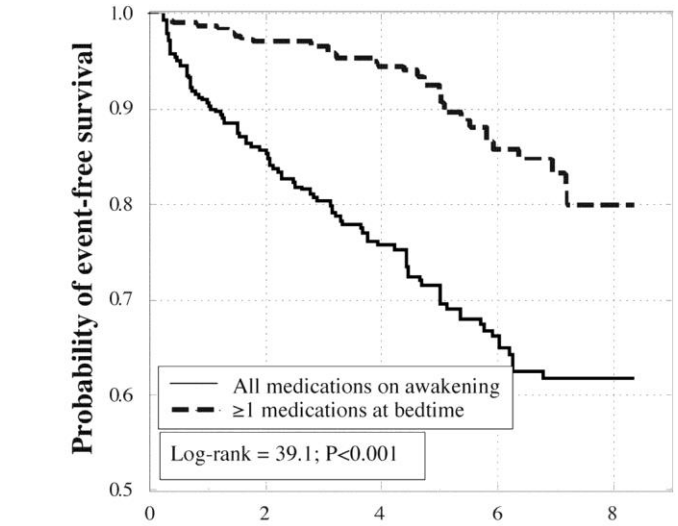
Hermida RC, Ayala DE, Mojón A, Fernández JR.

True/false: Chronotherapy, the use of nighttime dosing of blood pressure medications, has been shown to improve nocturnal blood pressure control but has not been associated with improved daytime blood pressure control or a reduction in cardiovascular outcomes.

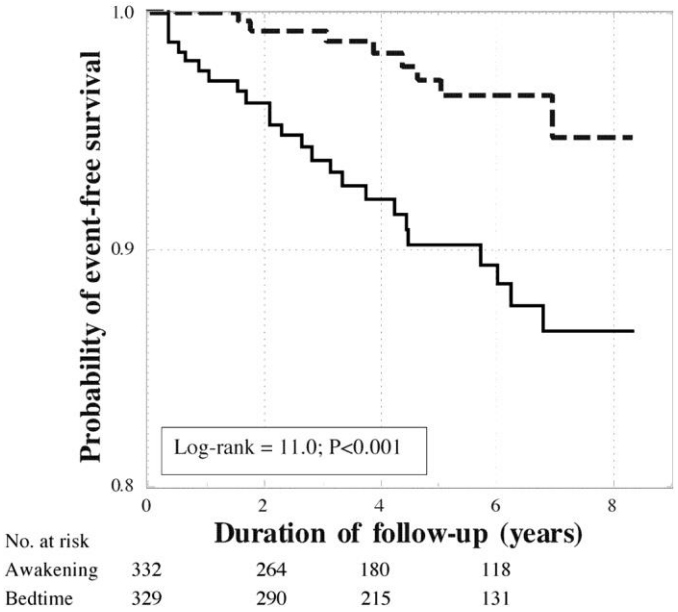
A.True

B.False

Survival curves as a function of time-of-day of hypertension treatment in CKD patients



Total CV events



Major CVD events = cardiovascular deaths, MI, ischemic CVA, and hemorrhagic CVA

Hermida R C et al. JASN 2011;22:2313-2321

Case

- John Smith presents to clinic for routine follow-up. He has no new symptoms or changes in his history since his last visit 6 months ago. He faithfully takes all of his medicatons each morning, including 3 medications for hypertension: enalapril 20 mg daily, amlodipine 5 mg daily, and HCTZ 25 mg daily.
- His exam is unremarkable except for a BP of 160/95, which is repeated 5 minutes later at 155/95.

Case

- John Smith presents to clinic for routine follow-up. He has no new symptoms or changes in his history since his last visit 6 months ago. He faithfully takes all of his medications every morning, including 3 medications for hypertension: enalapril 20 mg daily, amlodipine 5 mg daily, and HCTZ 25 mg daily.
- His exam is unremarkable except for a systolic BP of 160/95, which is repeated 5 minutes later at 155/95.
- ***Does he have resistant hypertension?***

Is volume status adequately addressed?

Is volume status

Case

- John Smith presents to clinic for routine follow-up. He has no new [illegible] changes in his history since his [illegible] go. He faithfully takes all [illegible] each morning, including 3 medications for hypertension: enalapril 20 mg daily, amlodipine 5 mg daily, and HCTZ 25 mg daily.
- His exam is unremarkable except for a systolic BP of 160/95, which is repeated 5 minutes later at 155/95.
- ***Does he have resistant hypertension?***

Are RAAS blockers optimally dosed?

Case

- John Smith presents to clinic for routine follow-up. He has no new symptoms or changes in his history since his last visit 6 months ago. He faithfully takes all of his medications every morning, including 3 medications for his hypertension: enalapril 20 mg daily, amlodipine 5 mg daily, and HCTZ 25 mg daily.
- His exam is unremarkable except for a systolic BP of 160/95, which is repeated 5 minutes later at 155/95.
- ***Does he have resistant hypertension?***

Has chronotherapy been utilized?

Case

- John Smith presents to clinic for routine follow-up. He has no new symptoms or changes in his history since his last visit 6 months ago. He faith
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- ***Does he have resistant hypertension?***

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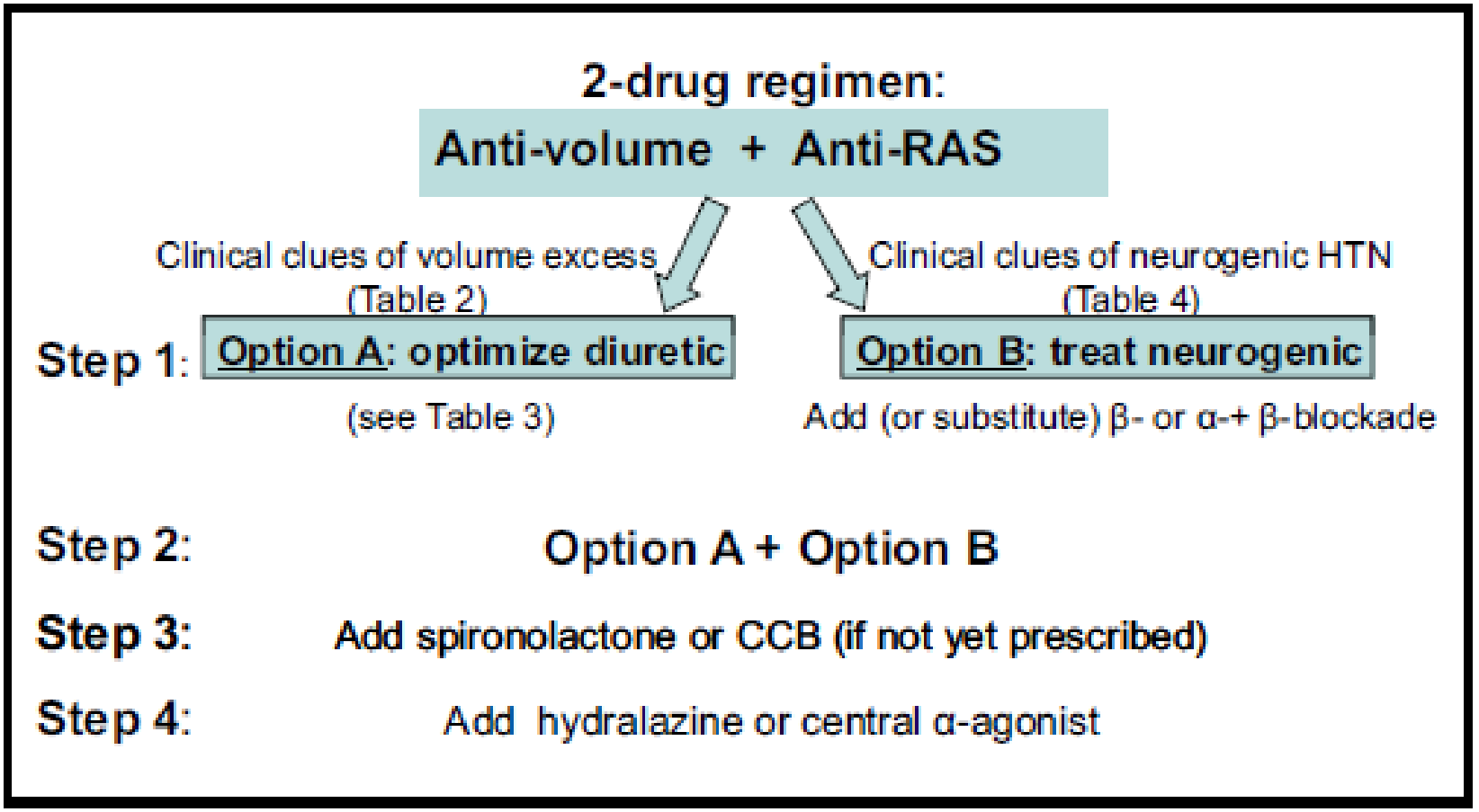
1. **Change amlodipine to 5 mg PM**
2. **Change HCTZ 25 mg daily to chlorthalidone 25 mg daily**
3. **Increase enalapril to 20 mg bid *or* add spironolactone 25 mg daily**



Drug therapy for resistant hypertension: simplifying the approach.
Mann SJ.
J Clin Hypertens (Greenwich). 2011 Feb;13(2):120-30.

A Simplified Mechanistic Algorithm for Treating Resistant Hypertension: Efficacy in a Retrospective Study

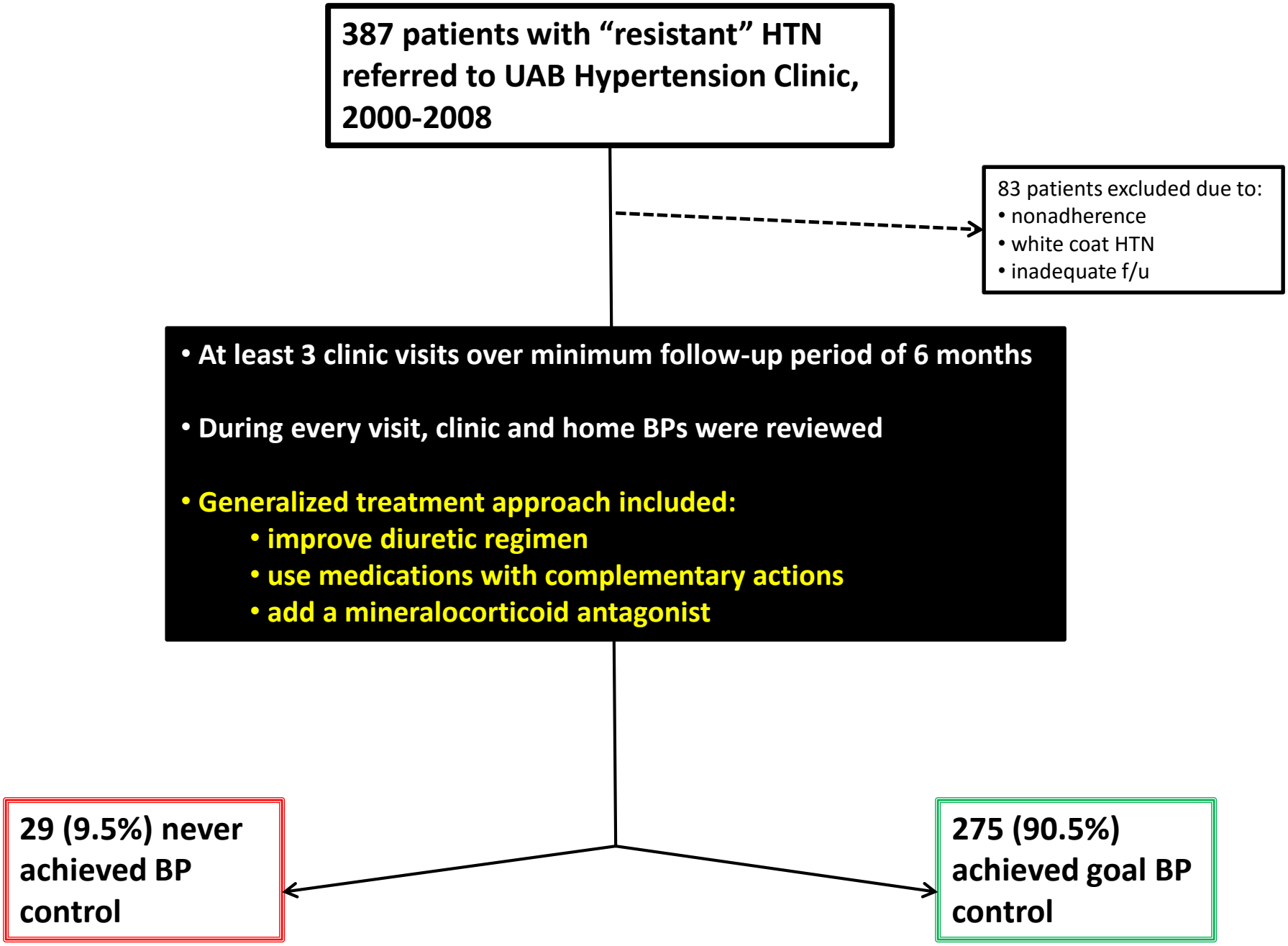
TABLE III. Initial and Final Office Blood Pressure

Patient group	Initial Blood Pressure	Final Blood Pressure
All patients (n=27)	149.6±15.7	125.9±14.4
	89.4±15.6	80.2±9.7
Initial systolic BP ≥160 (n=10)	166.7±7.1	129.8±15.8
	99.1±18.5	83.7±12.3

TABLE V. BP Outcomes and Treatment Options Employed

	All Patients		Patients With Initial SBP ≥160 mm Hg	
Outcome	N=27	Percent	N=10	Percent
BP controlled	24	88.9	8	80
Option A only: strengthen diuretic	13	54.1	5	62.5
Option B only: α-blocker+ nonmetabolized β-blocker	6	25.0	1	12.5
Both option A+option B	5	20.8	2	25.0
Total				
Option A employed	18		7	
Option B employed	11		3	
BP not controlled	3	11.1	2	20.0

J Clin Hypertens (Greenwich). 2012 Apr;14(4):191-7
A simplified mechanistic algorithm for treating resistant hypertension: efficacy in a retrospective study.
Mann SJ, Parikh NS.



J Clin Hypertens (Greenwich). 2012 Jan;14(1):7-12.
Refractory hypertension: definition, prevalence, and patient characteristics.
Acelajado MC, Pisoni R, Dudenbostel T, Dell'Italia LJ, Cartmill F, Zhang B, Cofield SS, Oparil S, Calhoun DA.

Resistant Hypertension: Key Points

- Common → up to 40% of hypertensives
- Most patients with "resistant" HTN can be controlled with medications when prescribed *physiologically*
- Optimize volume control
  - Salt restriction
  - Better diuretic regimen → move away from HCTZ 25 mg daily
- Maximize RAAS inhibition
  - Higher doses of ACE-Is or ARBs
  - Spironolactone
- Employ chronotherapy in *every* patient on >1 anti-HTN med
- Use clinical clues to decide whether volume, RAAS, or neurogenic etiology of HTN is most important for individual patient

Questions?

"I'm going to take your blood pressure, so try to relax and not think about what a high reading might mean for your chances of living a long, healthy life."