

- Treatment-resistant hypertension

JNC 8

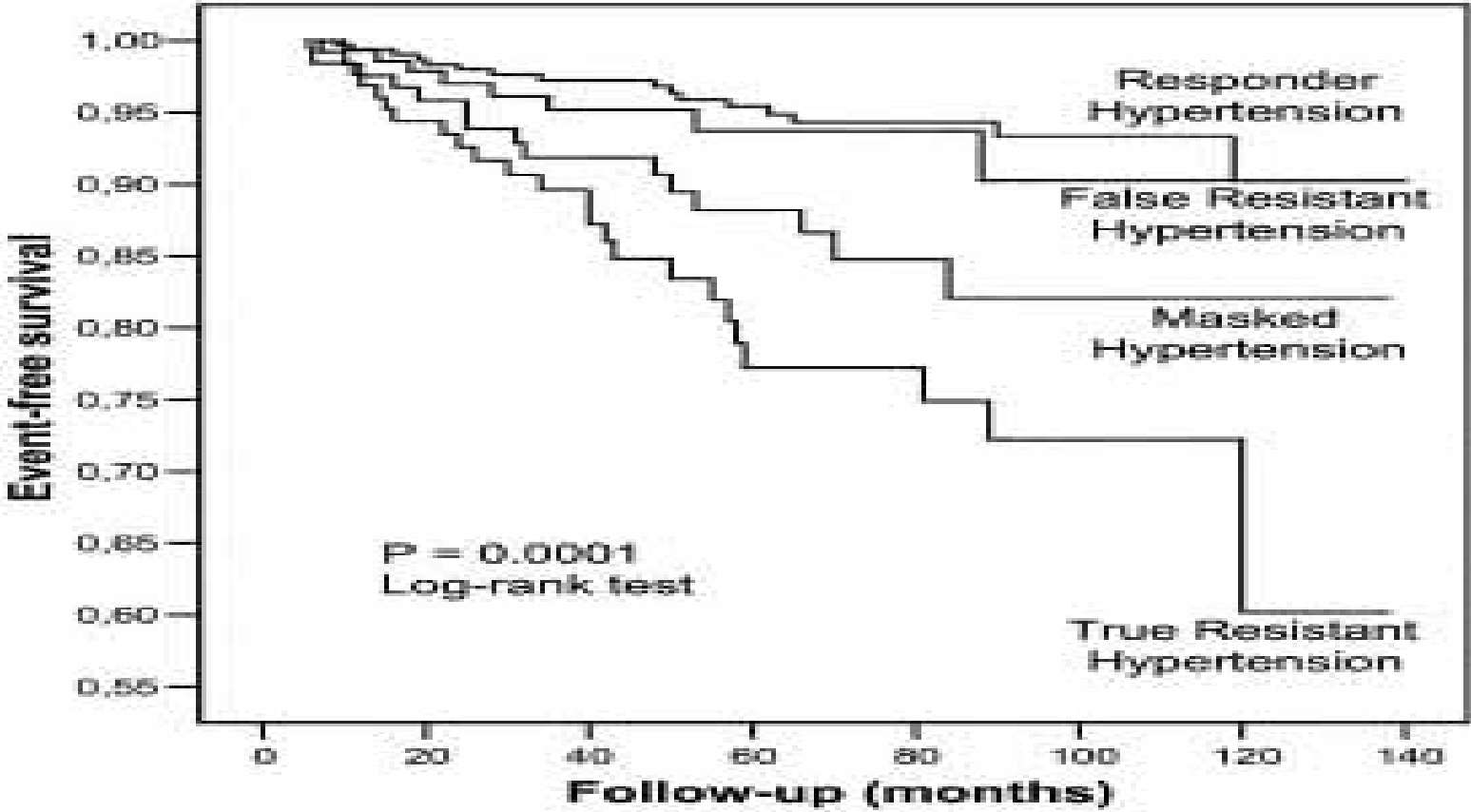
- Everybody has hypertension

Resistant Hypertension

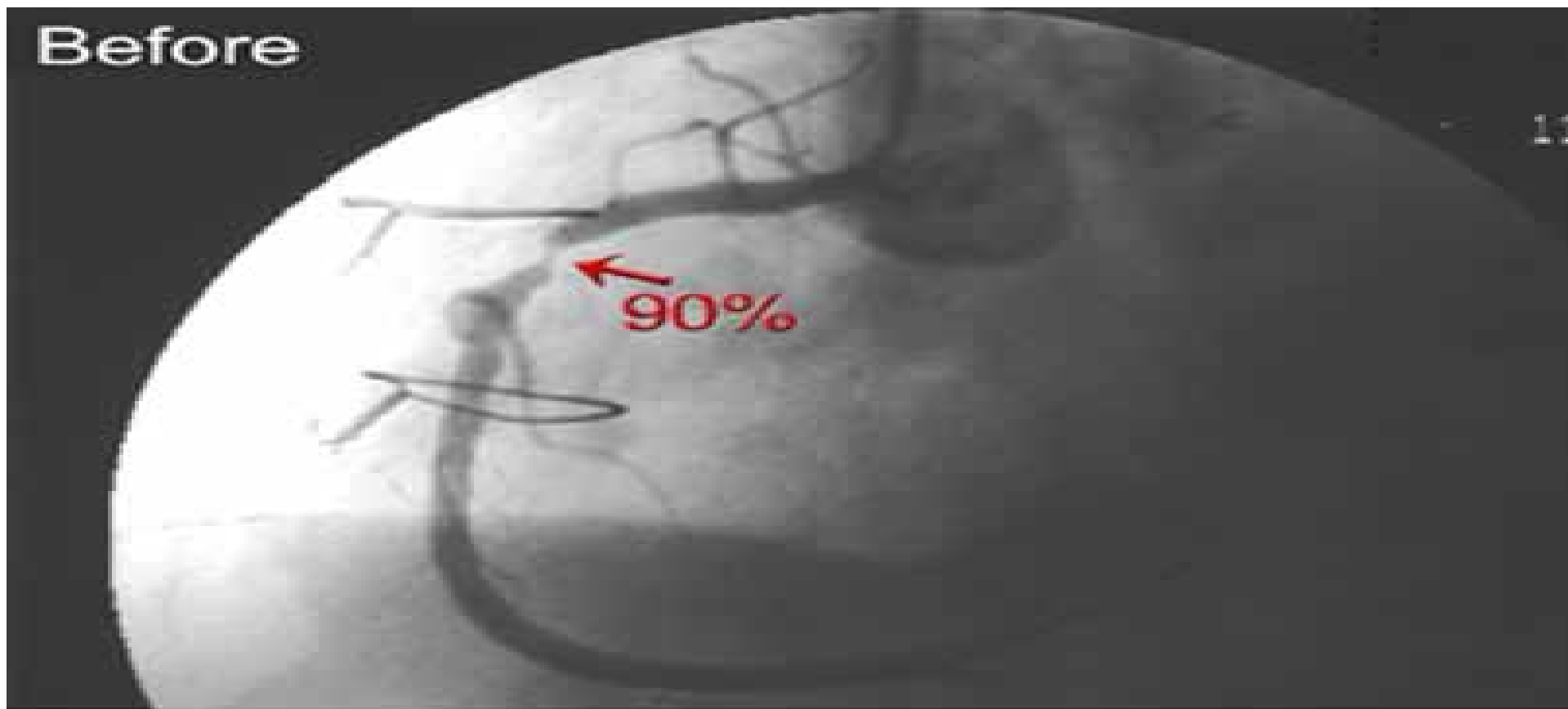
Failure to reach BP goal in spite of three antihypertensive drugs at decent dose, one being a diuretic

> 10 % of hypertensive patients

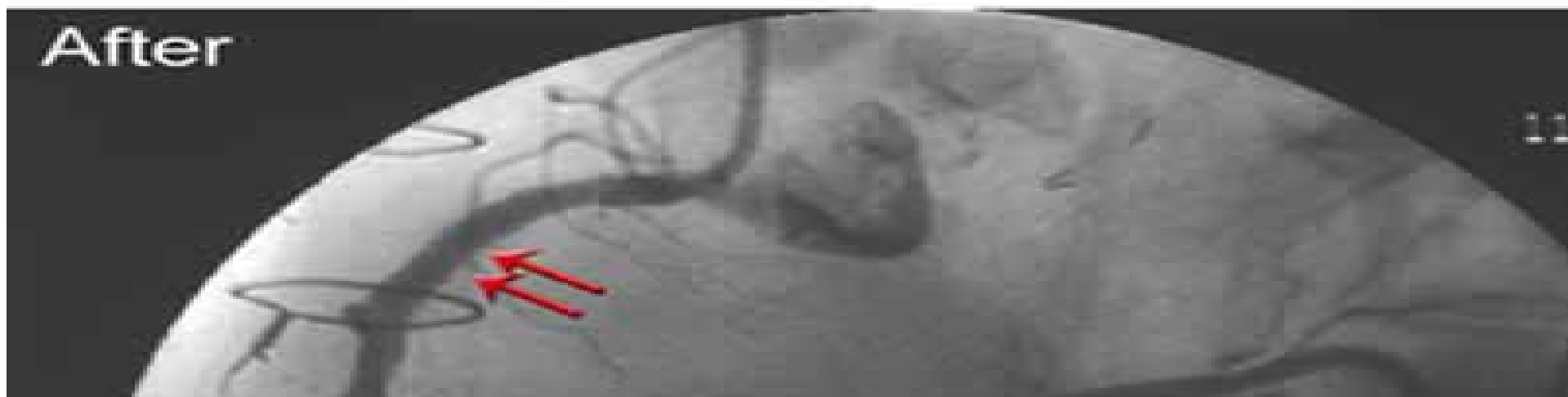
Resistant Hypertension – Unfavorable Prognosis



Before



After



Treatment-resistant hypertension

associated with:

- Obesity
- Sleep-disordered breathing
- CKD
- Diabetes mellitus
- LVH

62 year old retired FBI agent with L hip OA and hypertension. No clinical cardiovascular disease. Feels well. Non-smoker.

Meds: HCTZ 25 mg

Metoprolol 150 mg all once a day

Lisinopril 40 mg

Ibuprofen 600 mg t.i.d.

Viagra, prn

BP readings in office (n=8) average 168/96 mmHg

HR = 56, reg. Rest of exam normal

LDL = 119. Glu= 94 SCr = 1.2 UA neg



Next steps ?

- Consider a secondary cause
- Stop the NSAID ?
- Reinforce lifestyle efforts
- Take 1 of 3 drugs in evening
- Consider 'office' hypertension
- Reassess whether patient taking meds

R E S I S T A N T

REASSESS

SODIUM TWICE A DAY

SECONDARY CAUSE

AMBULATORY MONITOR

IBUPROFEN

NOT TAKING Rx

Secondary causes

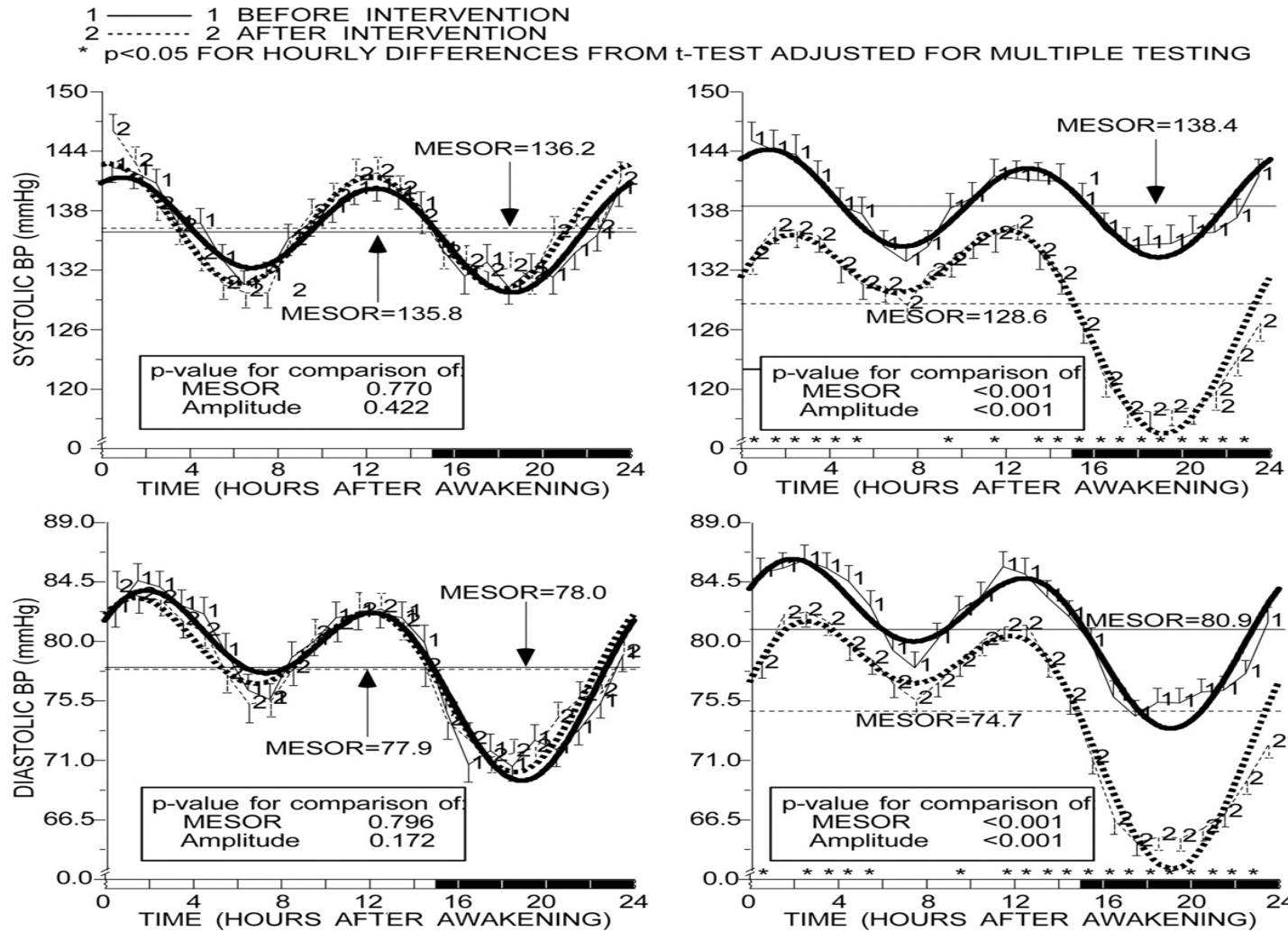
- Sleep apnea
- Primary Aldosteronism
 - ? > 10% cases of RH
 - most have normal K⁺
 - most not APA - medical Rx
 - a.m. Paldo + PRA

DRUGS MAY INTERFERE WITH BP CONTROL

- **NSAIDs**
- **Tricyclics, venlafaxine, OCPs, glucocorticoids, cyclosporine, EPO, sympathomimetics, ethanol**

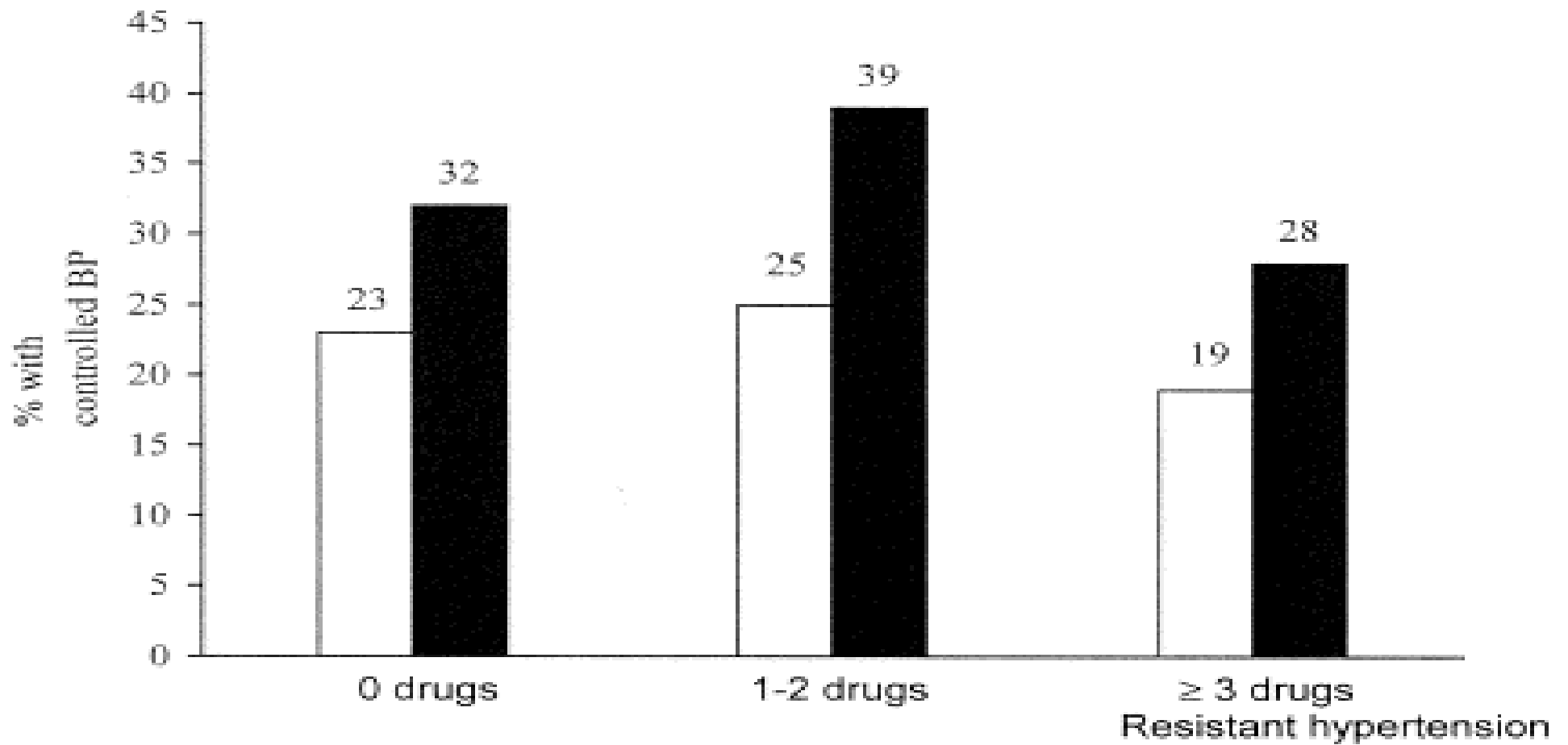


Switching 1 of 3 drugs from a.m. to h.s improves BP control



Hermida, R. C. et al. Hypertension 2008;51:69-76

Up to 1/4 of RH pts have controlled BP at home



- **Non-adherence to therapy**
- Inconvenient dosing schedule
- Side effects
- Cost
- Psychological factors
- Education

R E S I S T A N T

REASSESS

SODIUM TWICE A DAY

SECONDARY CAUSE

AMBULATORY MONITOR

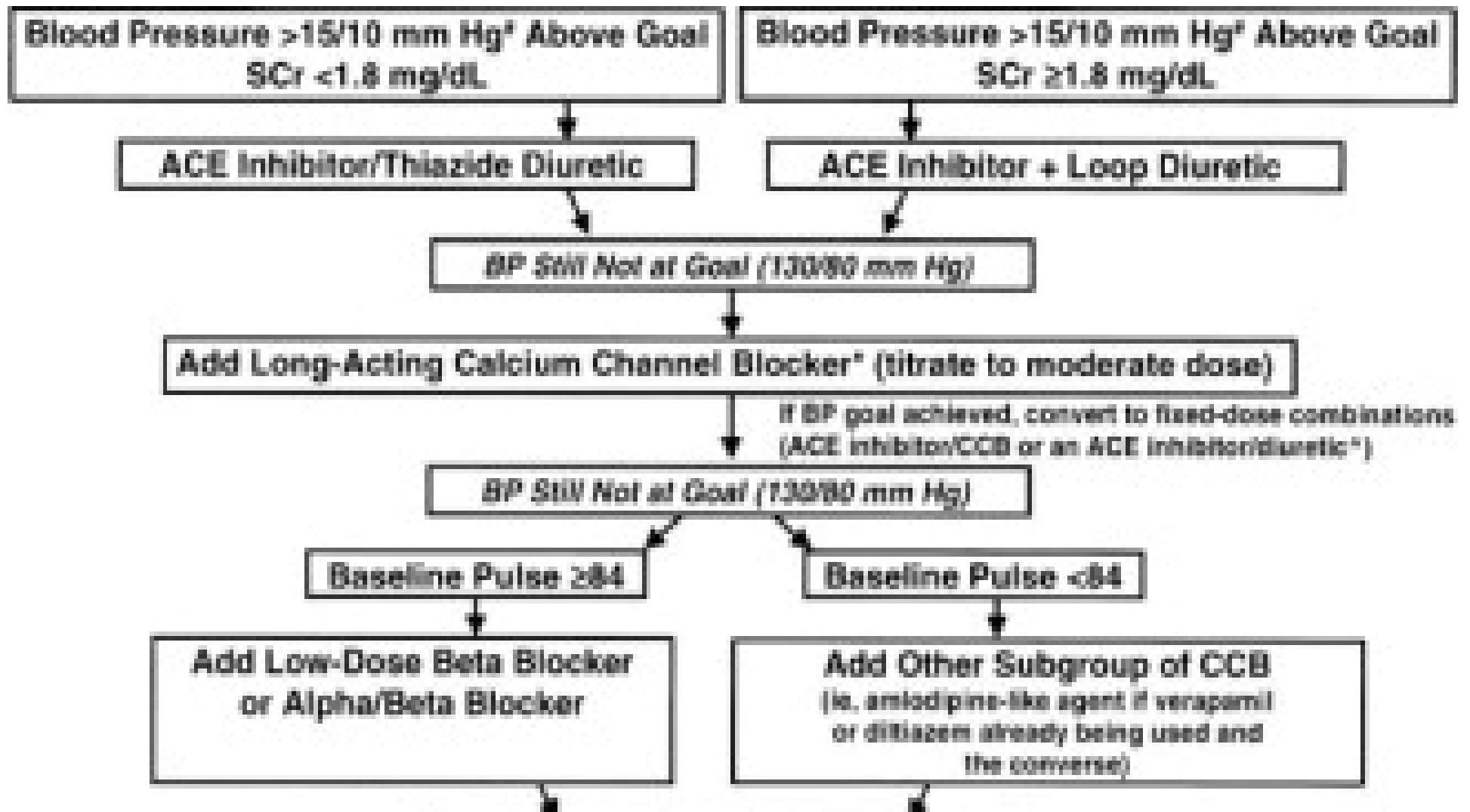
IBUPROFEN

NOT TAKING Rx

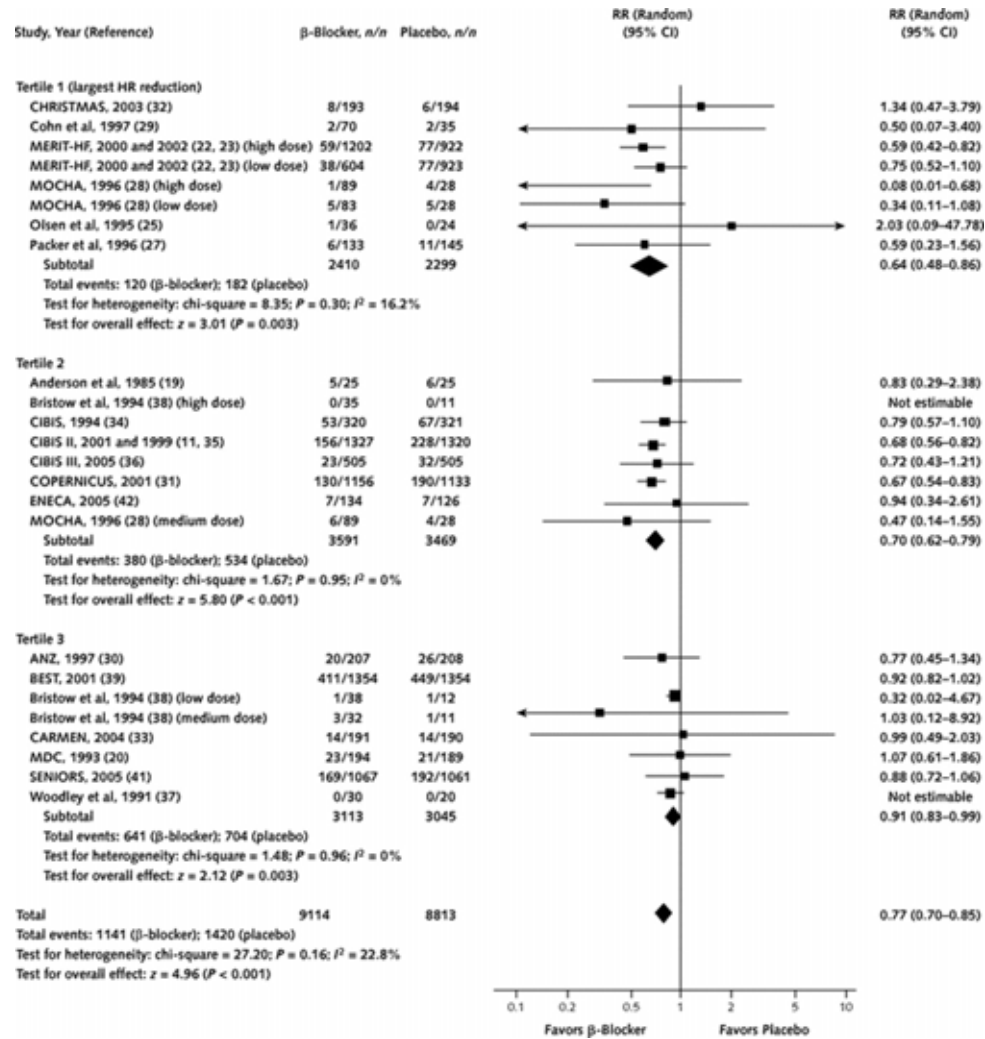
Basic changes in drug regimen

- Substitute new drug for 1 of 3 (not D)
- Maximize doses
- Add 4th drug
- Add BB or increase dose if HR > 84.
- Move 1 of 3 drugs to evening

Beta blockers for patients with HR > 84

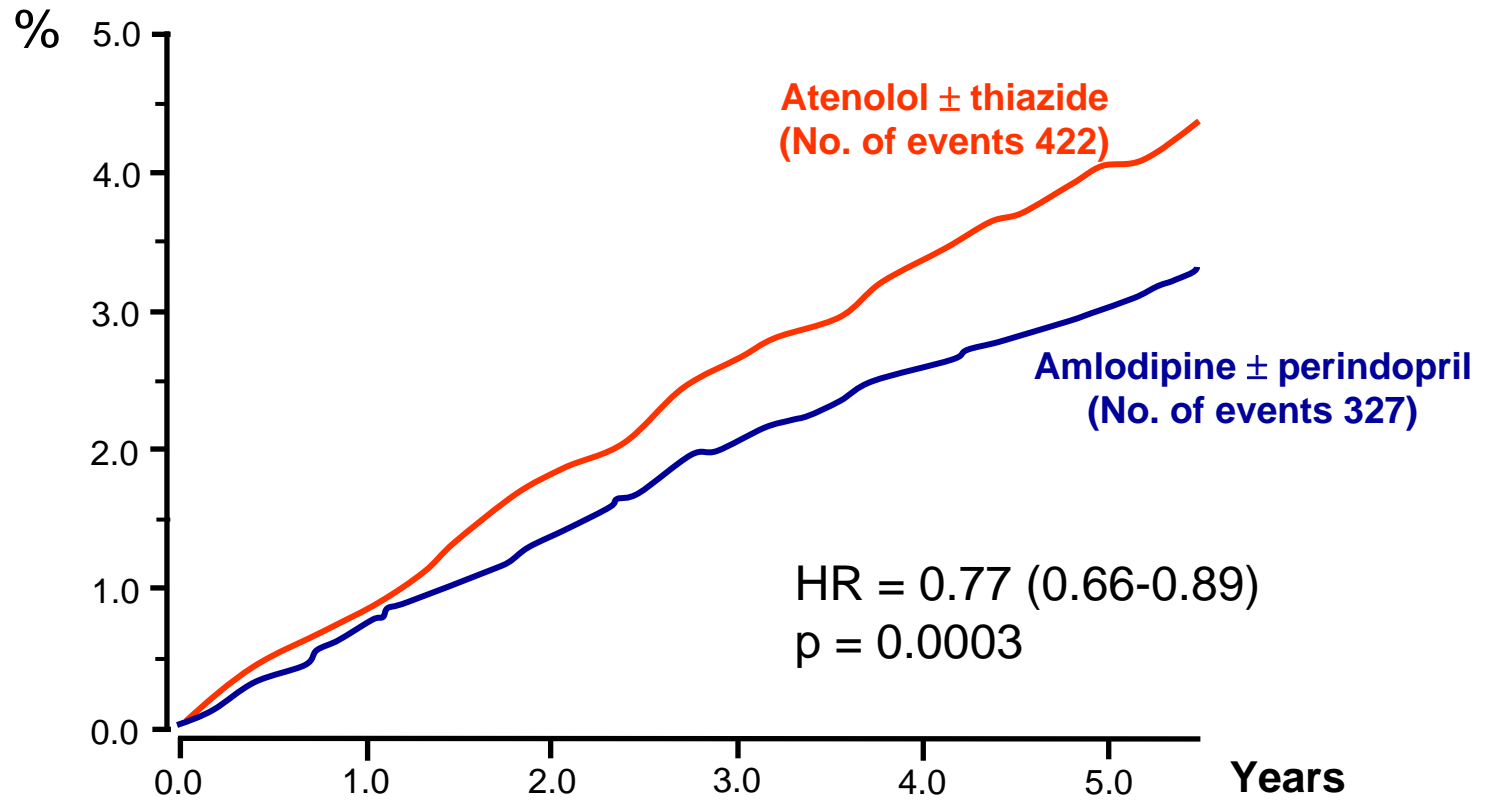


All-cause mortality, by treatment-related HR reduction tertile



McAlister, F. A. et. al. Ann Intern Med 2009;150:784-794

ASCOT ACEi + CCB better at stroke prevention



Number at risk	
Amlodipine ± perindopril	9639 9483 9331 9156 8972 7863
Atenolol ± thiazide	9618 9461 9274 9059 8843 7720

Original Article

Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

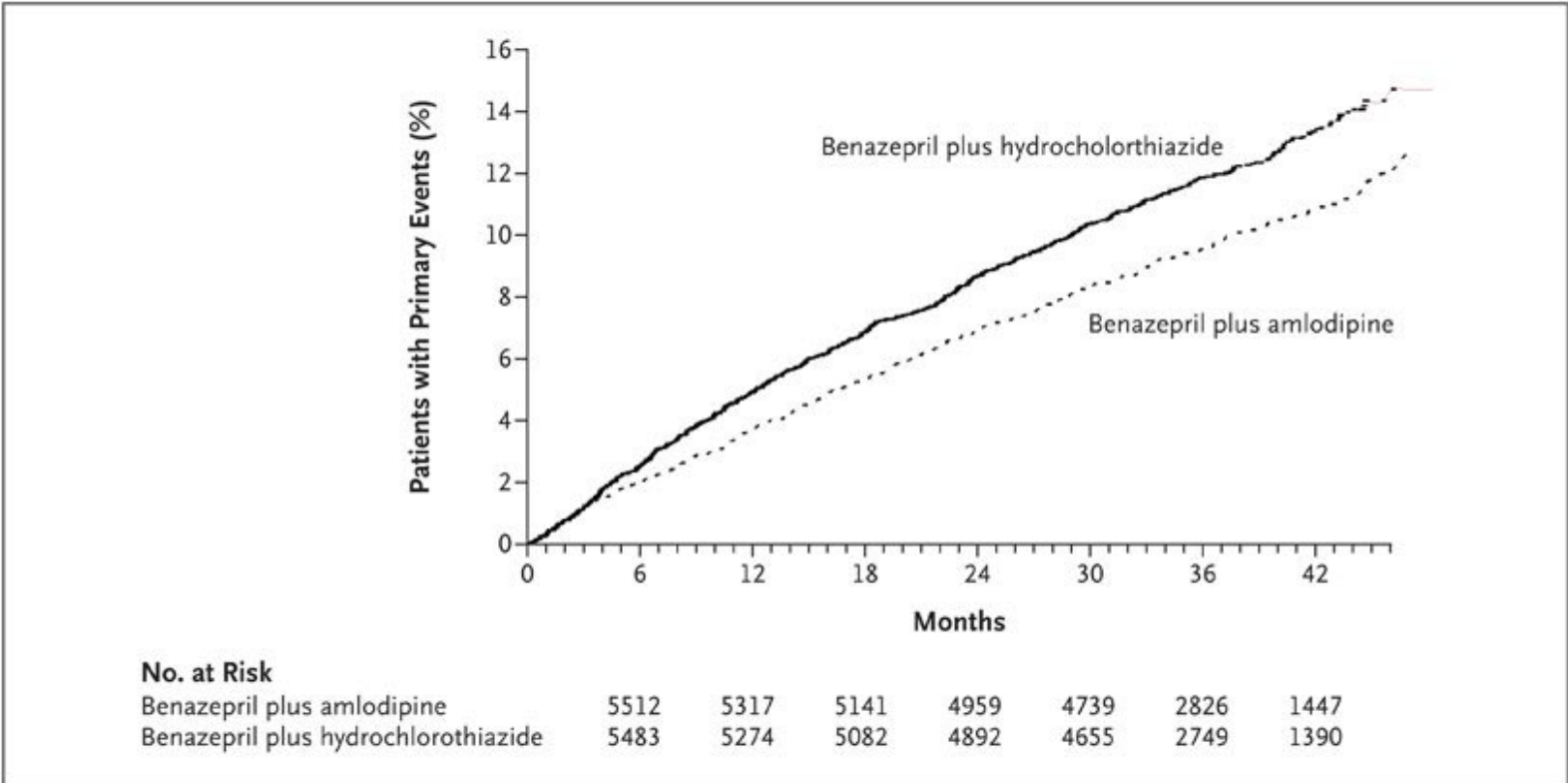
Kenneth Jamerson, M.D., Michael A. Weber, M.D., George L. Bakris, M.D., Björn Dahlöf, M.D., Bertram Pitt, M.D., Victor Shi, M.D., Allen Hester, Ph.D., Jitendra Gupte, M.S., Marjorie Gatlin, M.D., Eric J. Velazquez, M.D., for the ACCOMPLISH Trial Investigators

N Engl J Med
Volume 359(23):2417-2428
December 4, 2008



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Kaplan-Meier Curves for Time to First Primary Composite End Point



Jamerson K et al. N Engl J Med 2008;359:2417-2428

TABLE. Summary of Main Recommendations *AHA Guideline May, 2007*

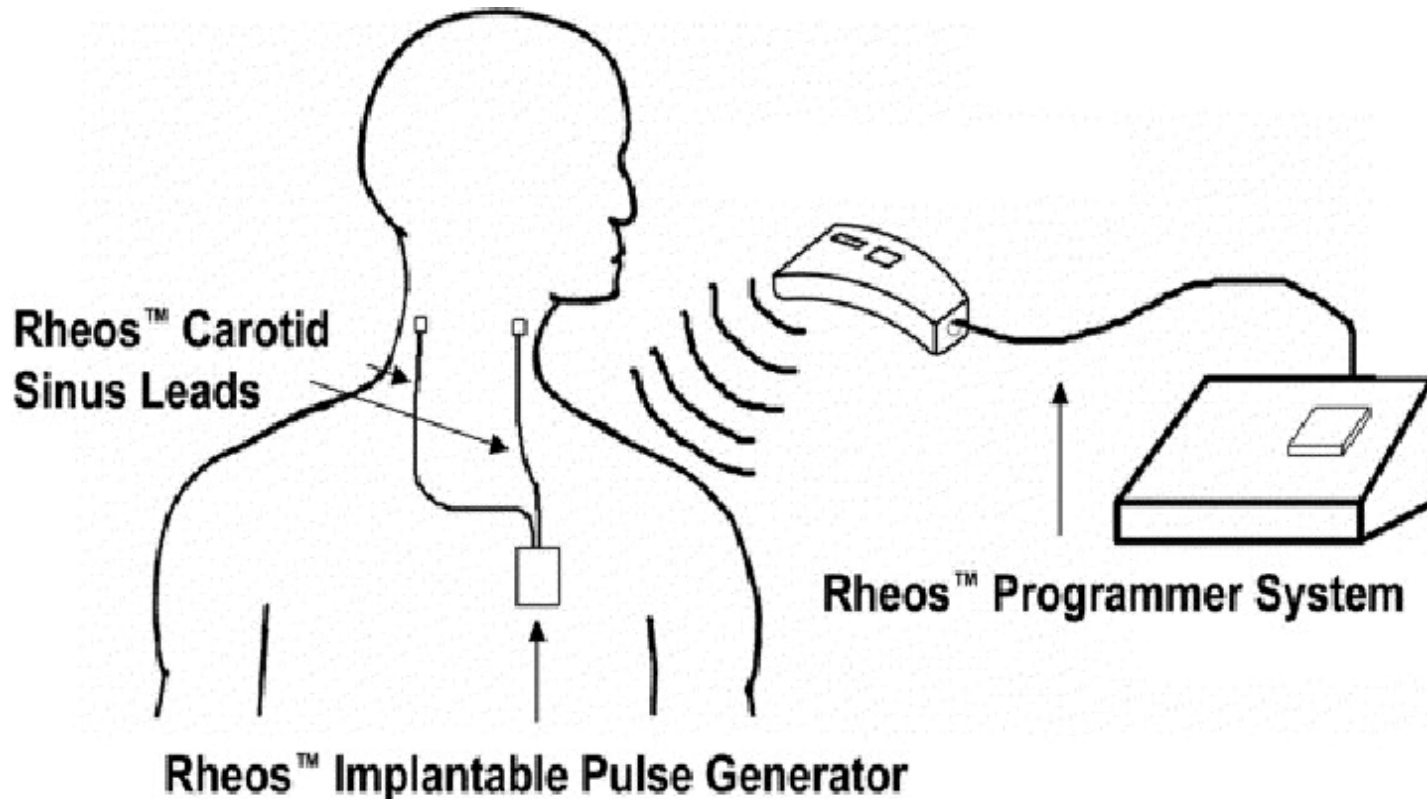
Area of Concern	BP Target, mm Hg	Lifestyle Modification ⁱ	Specific Drug Indications	Comments
General CAD prevention	<140/90	Yes	Any effective antihypertensive drug or combination [†]	If SBP \geq 160 mm Hg or DBP \geq 100 mm Hg, then start with 2 drugs
High CAD risk [*]	<130/80	Yes	ACEI or ARB or CCB or thiazide diuretic or combination	If SBP \geq 160 mm Hg or DBP \geq 100 mm Hg, then start with 2 drugs
Stable angina	<130/80	Yes	β -Blocker and ACEI or ARB	
LVD	<120/80	Yes	ACEI or ARB and β -blocker and aldosterone antagonist [†] and thiazide or loop diuretic and hydralazine/isosorbide dinitrate (blacks)	

^{*}Diabetes mellitus, chronic kidney disease, known CAD or CAD equivalent (carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm), or 10-year Framingham risk score \geq 10% (see Appendix).

[†]Evidence supports ACEI (or ARB), CCB, or thiazide diuretic as first-line therapy.

**Implantable device associated with BP reduction in RH
(5.1 meds) = 24/17 mmHg at 2 years**

ACC 3/30/09



Spironolactone added to 3 drugs for resistant hypertension - results of 4 uncontrolled studies since 2003

- Average drop in SBP and DBP assoc with adding spironolactone ? _____mmHg
- Average increase in serum K⁺ assoc with adding spironolactone ? _____mEq/L
- If spironolactone helpful, but gynecomastia develops, best alternate agent = _____
- Incidence of gynecomastia with this agent same as placebo. True or False

Spironolactone lowers BP by approx 20/10 mmHg in RH patients - uncontrolled trials

AJH 2006; 19:750-755

Efficacy of Add-On Aldosterone Receptor Blocker in Uncontrolled Hypertension

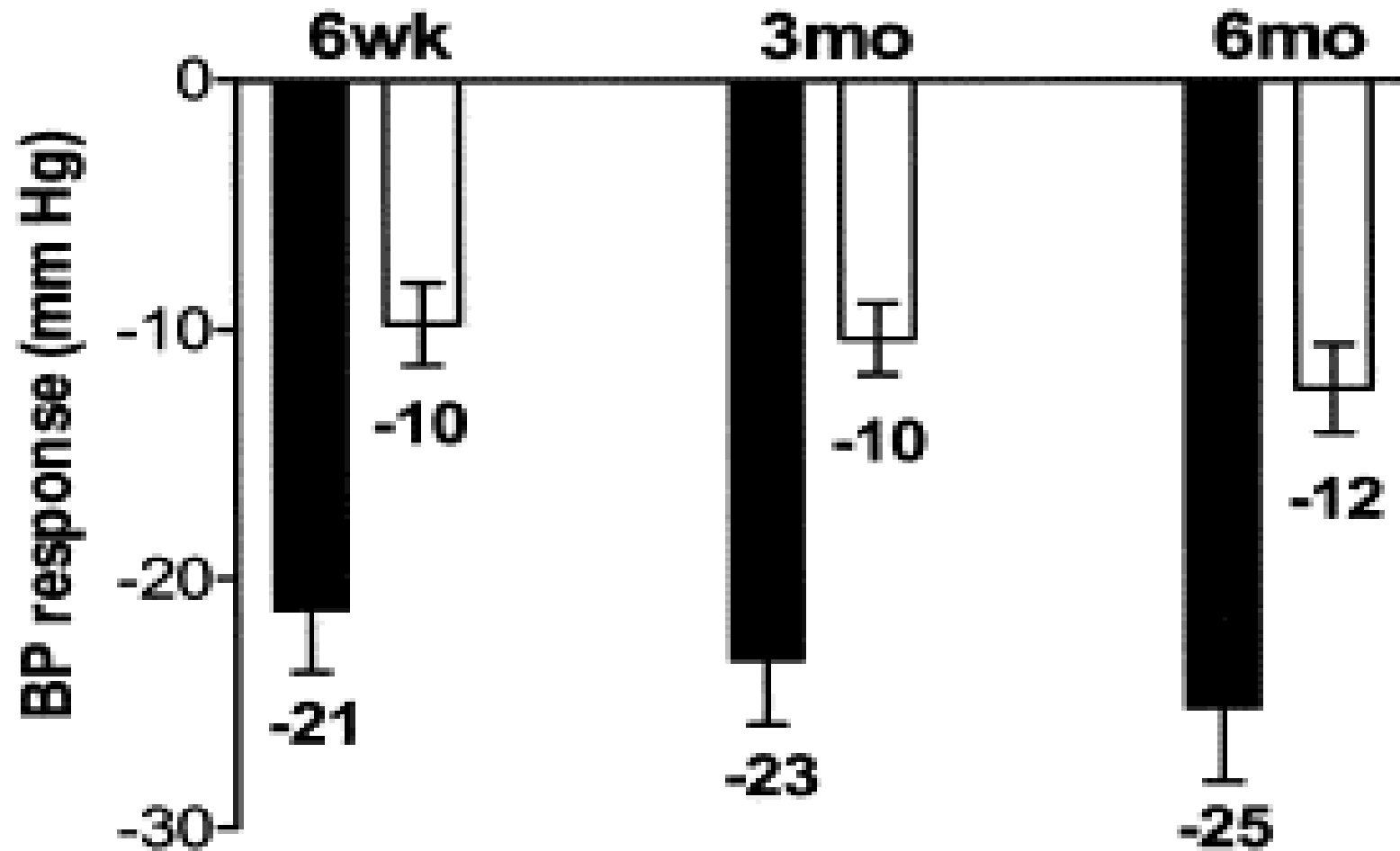
Yehonatan Sharabi, Eldad Adler, Ari Shamis,
Naomi Nussinovitch, Avinoam Markovitz, and Ehud Grossman

Background: Uncontrolled hypertension (UH) may be caused by hyperaldosteronism, and some experts recommend the routine use of aldosterone antagonists in this condition. The purpose of this study was to evaluate the

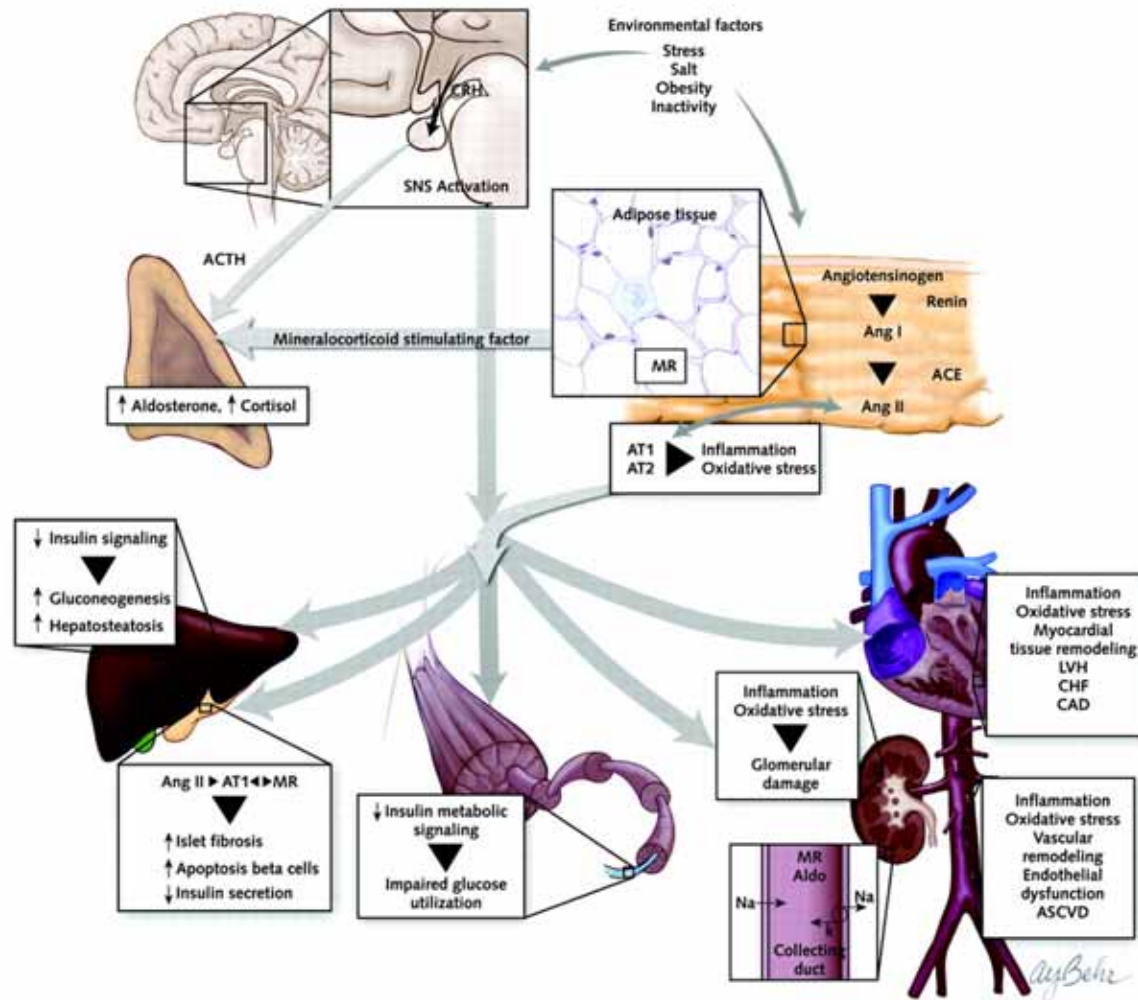
165 ± 27/94 ± 15 to 142 ± 25/81 ± 9 mm Hg, whereas in patients who received other add-on therapy BP decreased by 7.6/5.8 mm Hg from 160 ± 24/91 ± 12 to 152 ± 20/85 ± 11 mm Hg ($P < .05$). Patients who received

Spironolactone lowers BP in resistant patients

University of Alabama



Aldosterone contributes to hypertension and cardiovascular disease



Sowers, J. R. et. al. Ann Intern Med 2009;150:776-783

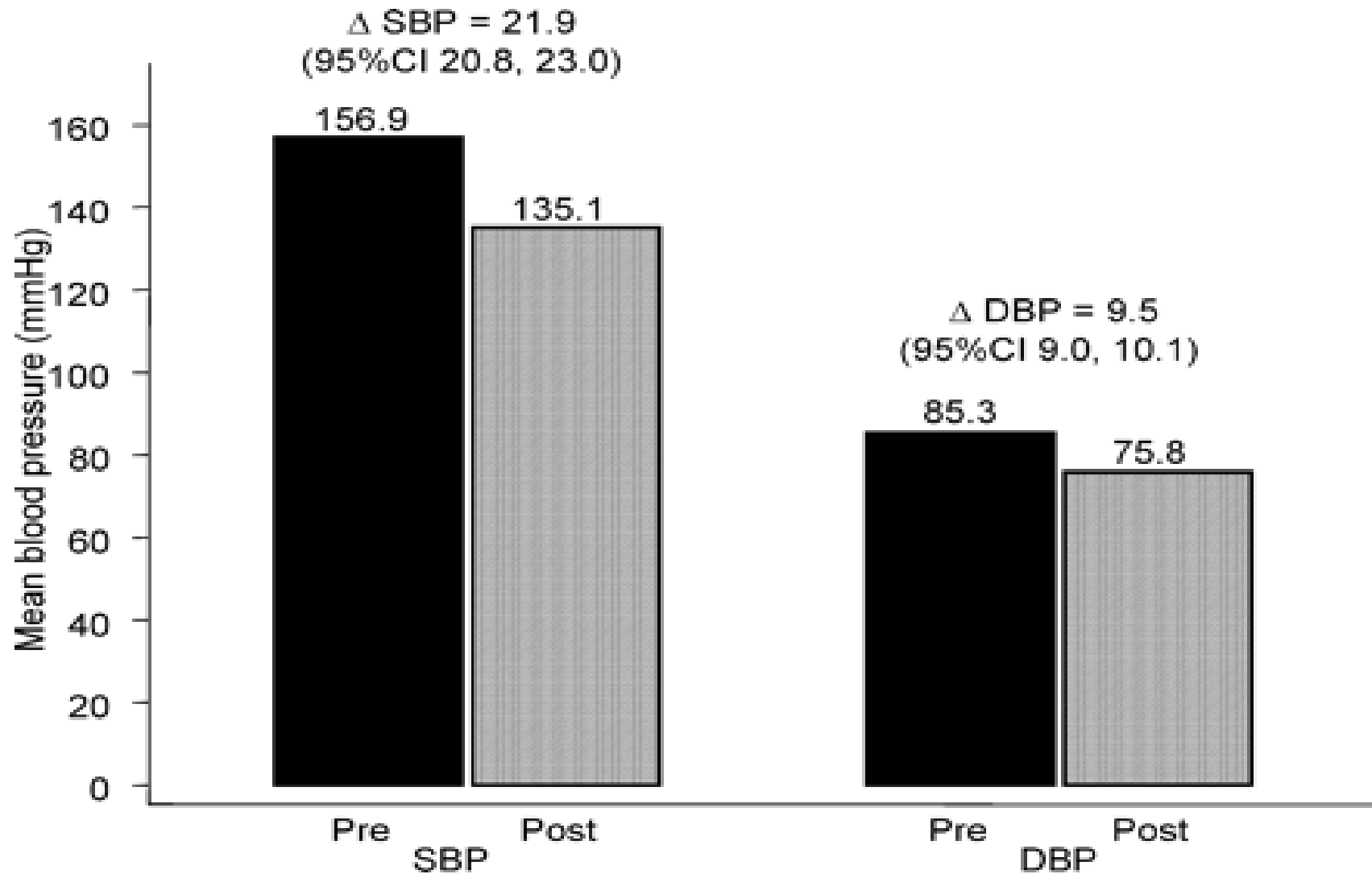
Aldosterone and hypertension

major role beyond primary aldosteronism

- Promotes inflammation and fibrosis
- Vasoconstriction
- Decreased large vessel compliance
- Sodium reabsorption
- LVH
- Albuminuria
- Higher levels in RH patients
- Spironolactone lowers BP independent of ARR
- Greater morbidity for any given BP

Substantial BP Reduction with Spironolactone -ASCOT-

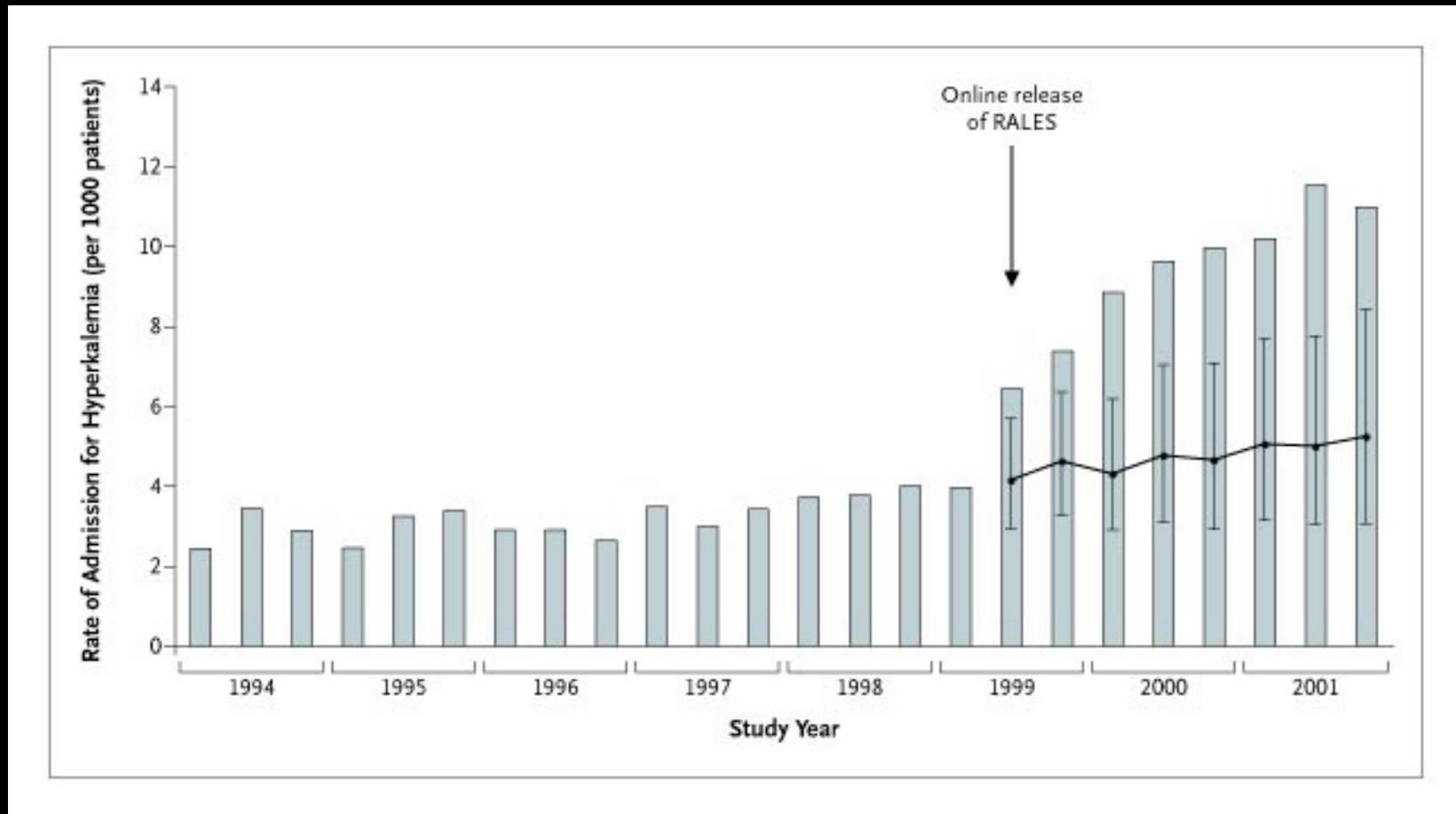
April, 2007



Use Spironolactone in Resistant Hypertension

- If potassium normal or low and creatinine normal
- Start 12.5 – 25 mg/day
- Monitor serum potassium by day 10
- Breast pain / tenderness – 10%

Rate of Hospital Admission for Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors



Juurlink, D. et al. N Engl J Med 2004;351:543-551



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62M on A + B + D BP = 164/94
SCr = 1.2; K⁺ = 4.3

- HCTZ maintained at 25 mg/day
- SPIRONOLACTONE added, 25 MG
- Impressive BP reduction 146 / 84
- Painful gynecomastia

UNIVERSITY OF COLORADO HOSPITAL
UNIVERSITY MEDICINE DENVER
INTERNAL MEDICINE
LAWRENCE FEINBERG, M.D.
360 S GARFIELD ST #500
DENVER, CO 80209
phone 303-372-3000

PHARMACIST may not be able to fill this prescription
if the prescriber's name is not **pre-printed** on the blank
or **printed legibly** in this box.

Name: H.B. PRESSURE Date: 6/24/04

Address: _____ Allergies: _____

DISPENSE AS WRITTEN LABEL INGREDIENTS UNLESS X D

ONE PRESCRIPTION PER FORM

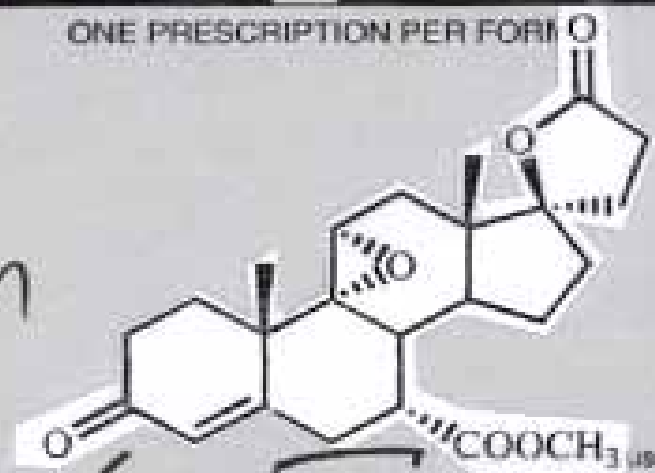
Rx:

Indication:

Signature

DEAN

[Handwritten signature]



tabs
50 mg
\$60
oae, B.I.D.

use Staff #
7 Colo. License #

8732

Prescriptions signed by Physicians without a Colo.
License must be filled at a UCH Outpatient Pharmacy

Refills: two

EPLERENONE

- Selective aldosterone antagonist
- 1/1000th the affinity for androgen receptors
- BP lowering effect = ACEi (monotherapy)

CONTRAINDICATIONS: $K^+ > 5.0$ mEq/L

Creatinine clearance < 50 mL/min (2.0/1.8)

Eplerenone: Hyperkalemia, yes; Gynecomastia, no.

Adverse Event	Eplerenone Group (N=3307)	Placebo Group (N=3301)	P Value
	<i>no. of patients (%)</i>		
≥1 Event	2608 (78.9)	2623 (79.5)	0.57
Cardiovascular disorder*	1606 (48.6)	1661 (50.3)	0.16
Respiratory disorder	729 (22.0)	803 (24.3)	0.03
Cough	167 (5.0)	207 (6.3)	0.03
Dyspnea	243 (7.3)	307 (9.3)	0.004
Gynecomastia	12 (0.5)	14 (0.6)	0.70
Impotence	21 (0.9)	20 (0.9)	1.00
Serious hyperkalemia (serum potassium ≥6 mmol/liter) ¶	180 (5.5)	126 (3.9)	0.002
Serious hypokalemia (serum potassium <3.5 mmol/liter) ¶	273 (8.4)	424 (13.1)	<0.001

59F BP= 158/99 on HCTZ 25 mg
Amlodipine 10 mg
Valsartan 160 b.i.d

Fatigue with Metoprolol

Faintness with Terazosin

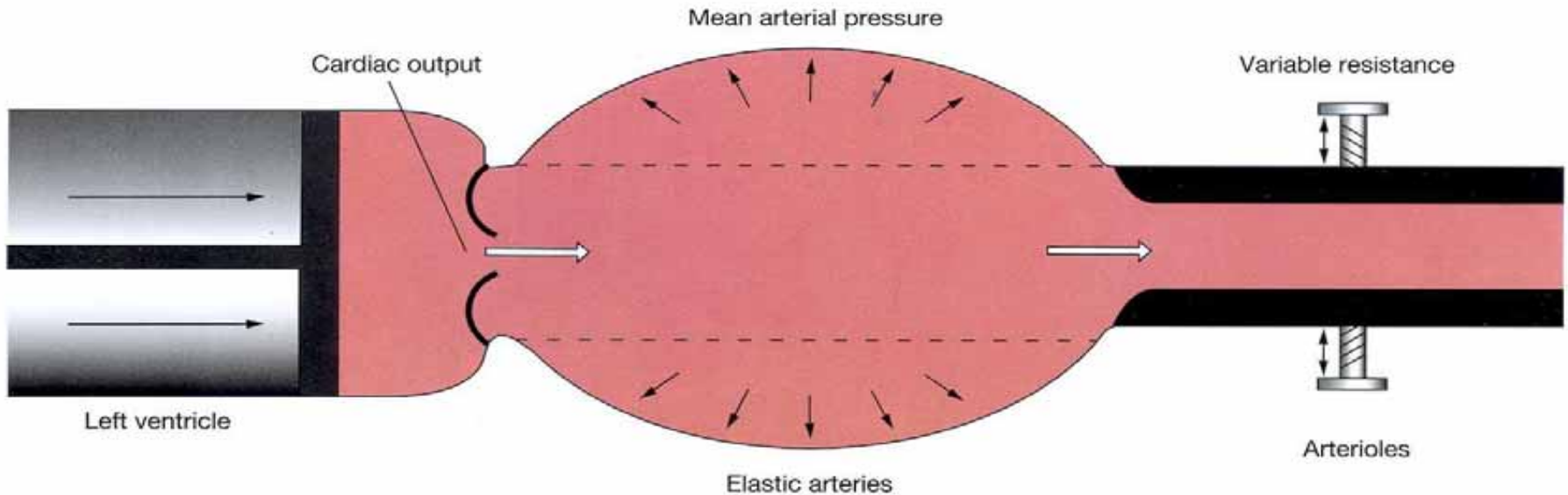
- Creatinine = 1.9 mg/dL; Serum K⁺ = 5.1.
- **Many options.....but NOT spironolactone.**

A loop diuretic deals with volume factor and lowers BP in RH

- 1. Low GFR
- 2. Excess dietary sodium
- 3. Effects of NSAIDs
- 4. Reflex sodium retention in response to antihypertensive Rx
- 5. Genetics
- 6. Hyperaldosteronism

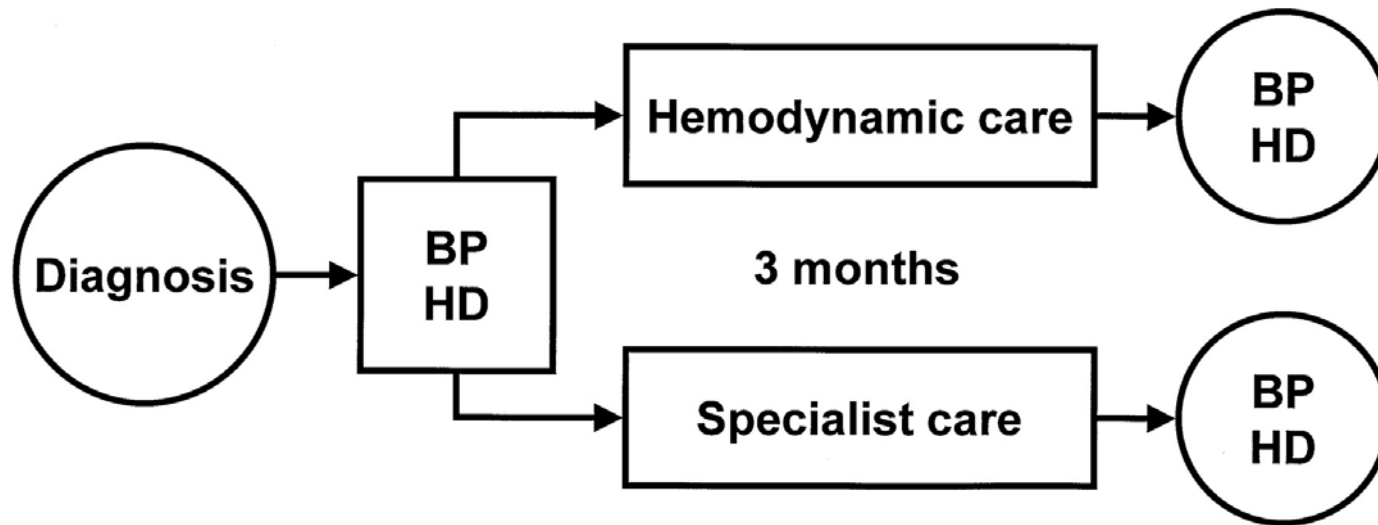


Subclinical volume expansion contributes to resistant hypertension



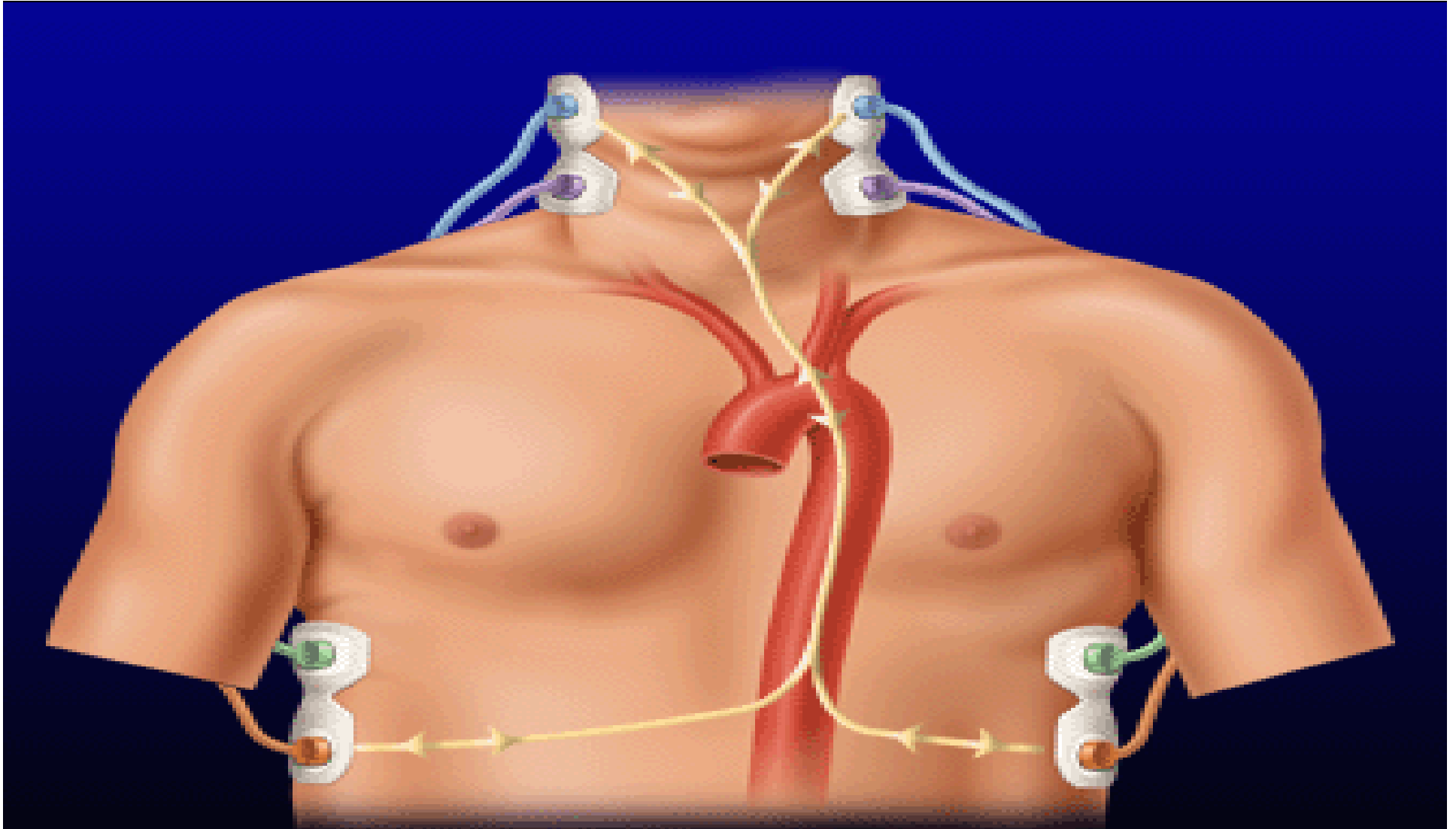
Does attention to 'volume' and use of loop diuretics really improve BP control in RH?

Mayo Clinic



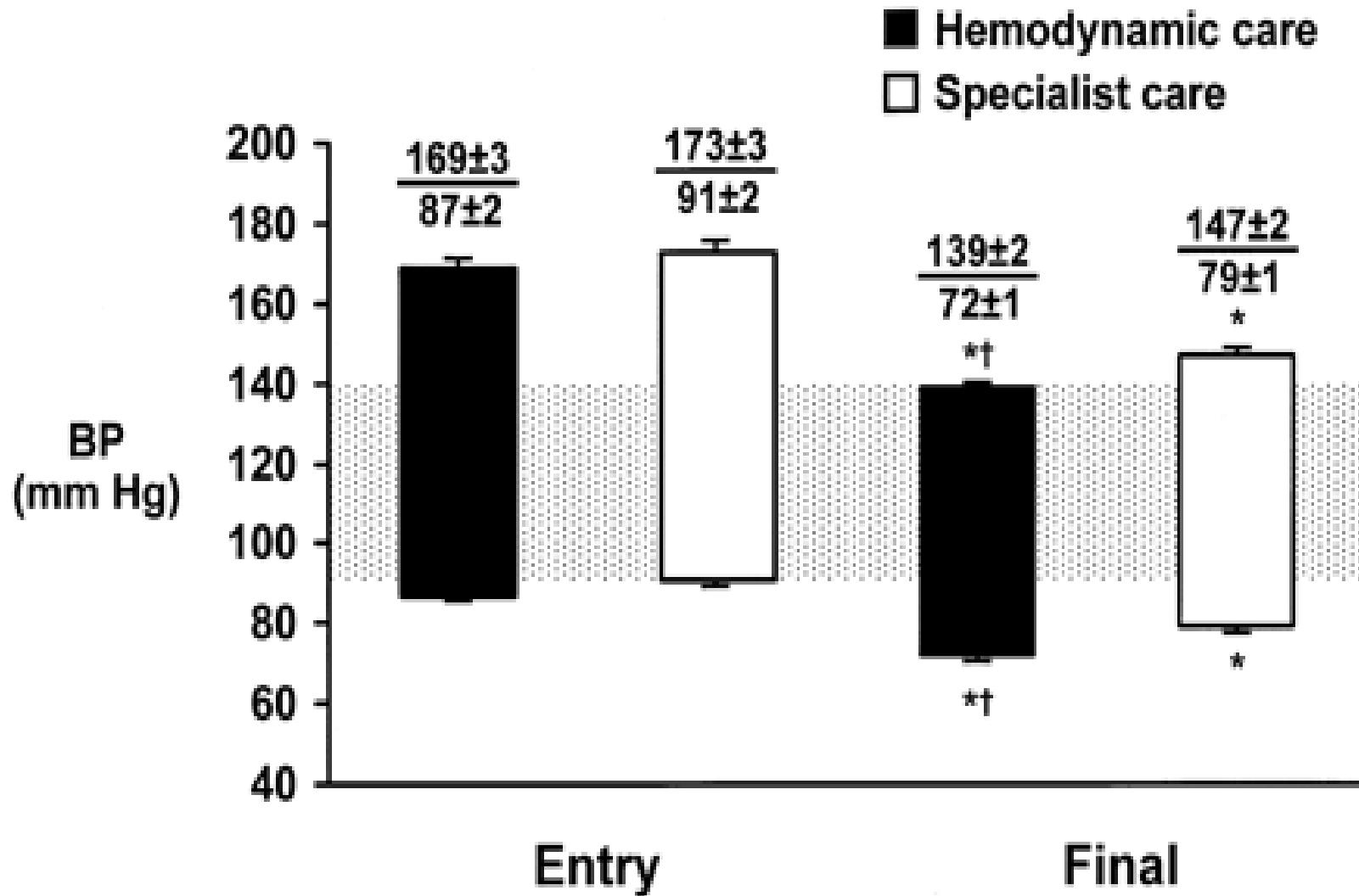
Taler, S. J. et al. Hypertension 2002;39:982-988

Recognition of subclinical volume expansion
guides effective use of loop diuretics in RH
(for those not electrocuted)



ESTIMATES OF BLOOD VOLUME IMPROVE BP LOWERING IN RESISTANT HYPERTENSION

Mayo Clinic experience



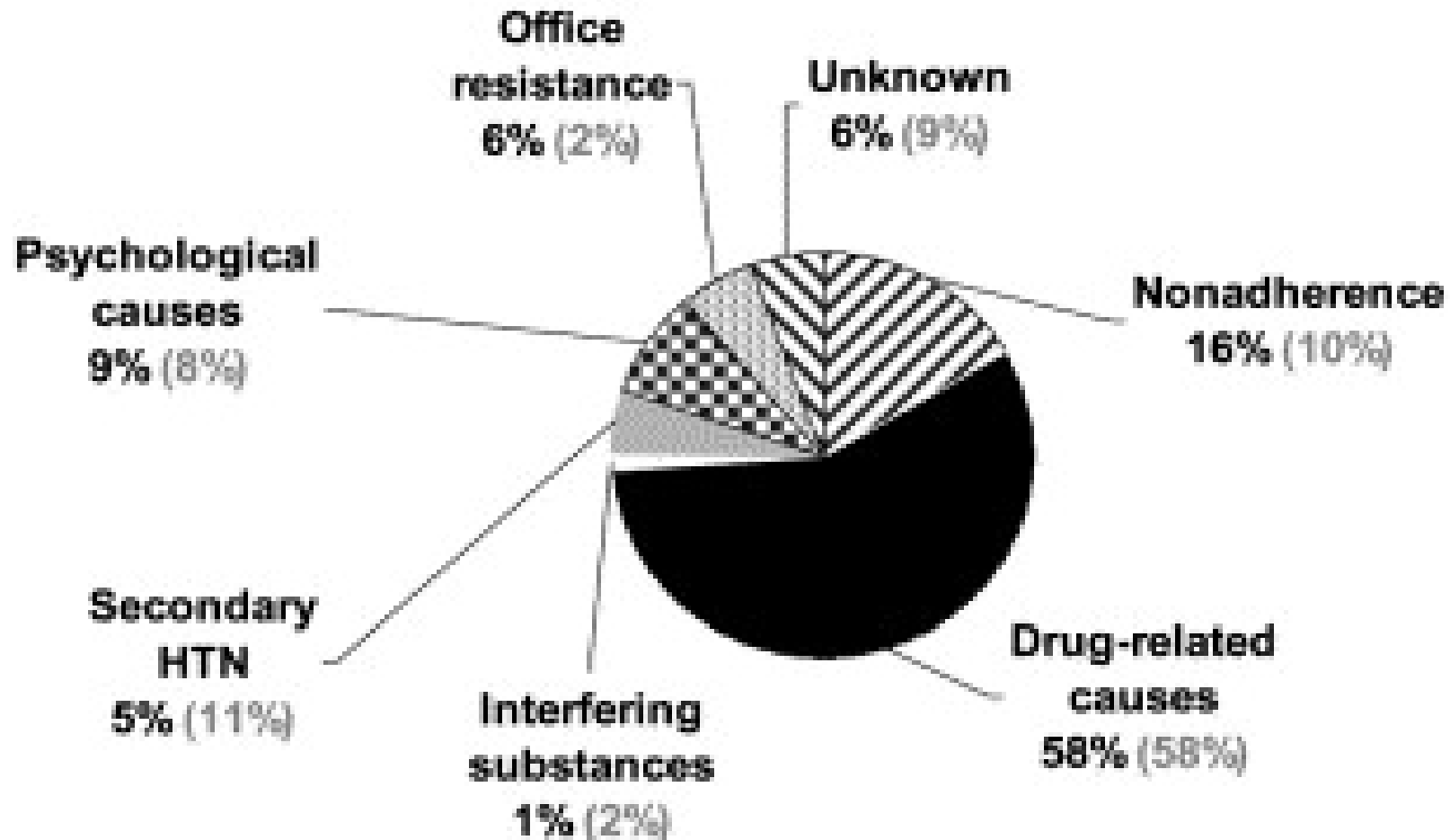
Do other experts think that switching to a loop diuretic is a good idea?

- Rush Medical Center experience - Chicago
- $n = 141$ BP = 169/94 on 3 drugs; age 57
BMI = 32. Scr = 1.2.

Am J Hyper, 2005

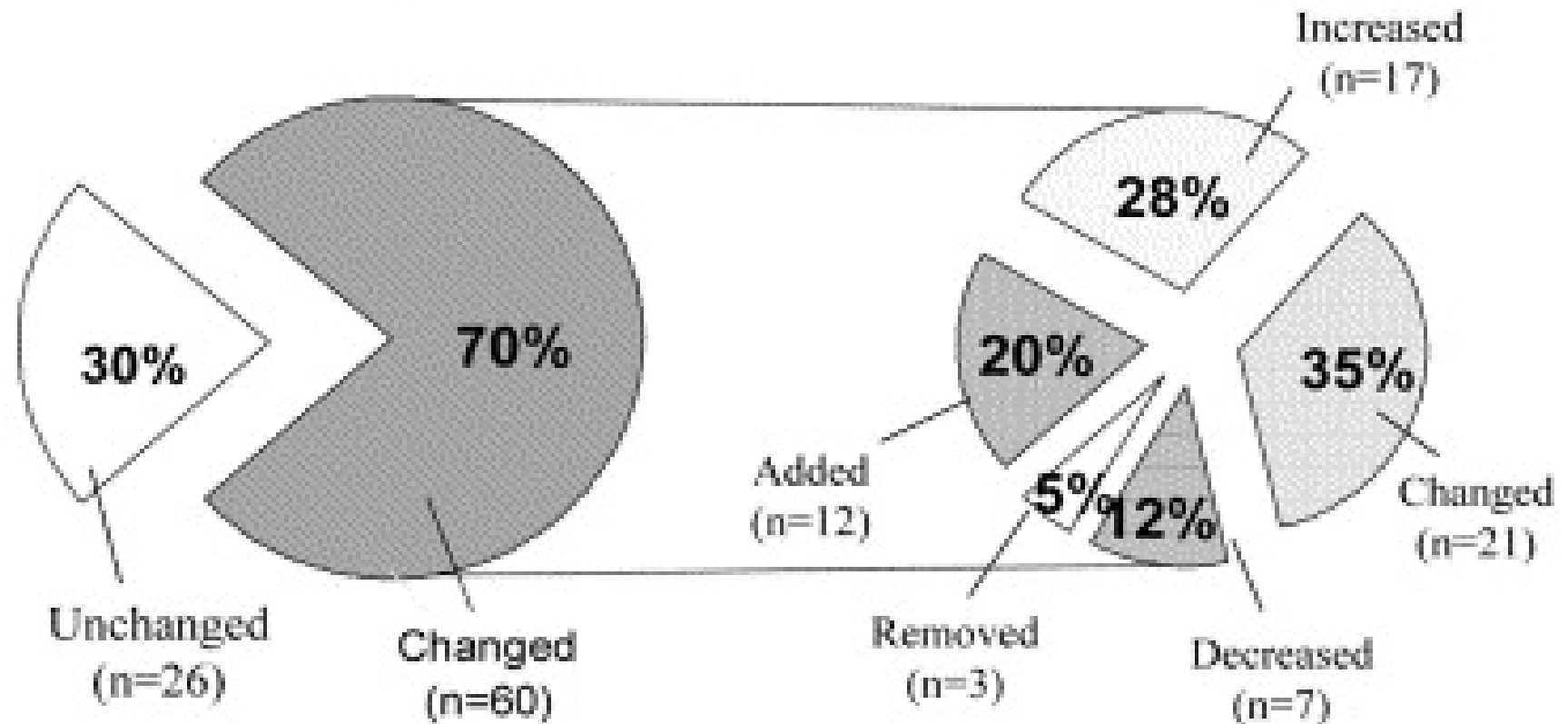
Causes of Resistance

Cause of resistance found in 133/141 - 94% (83/91 - 91%) cases



Diuretic Therapy

Suboptimal Medication Group



n=86

“Because volume overload is common...the most important therapeutic maneuver is...to add or increase diuretic therapy.”

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CLINICAL PRACTICE

Resistant or Difficult-to-Control Hypertension

Marvin Moser, M.D., and John F. Setaro, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 70-year-old woman with a long-standing history of hypertension comes for follow-up. Her medications include atenolol (100 mg daily), hydrochlorothiazide (12.5 mg daily), lisinopril (40 mg daily), and ibuprofen (400 mg twice daily for osteoarthritis). She does not smoke or drink alcohol. Her body-mass index (the weight in kilograms divided by the square of the height in meters) is 32. Her systolic and diastolic blood pressures (measured three times while she was seated) range from 164 to 170 mm Hg and 92 to 96 mm Hg, respectively, and the pulse rate is 72 per minute. Examination of her ocular fundi reveals arteriolar narrowing. The results of cardiovascular examination are normal. There are no abdominal bruits. The serum potassium level is 3.8 meq per liter, and the serum creatinine level is 1.2 mg per deciliter (106 μ mol per liter); there is no microalbuminuria. How should this patient be further evaluated and treated?

THE CLINICAL PROBLEM

Resistant, or refractory, hypertension is defined by a blood pressure of at least 140/90 mm Hg or at least 130/80 mm Hg in patients with diabetes or renal disease (i.e., with a creatinine level of more than 1.5 mg per deciliter [133 μ mol per liter] or urinary protein excretion of more than 300 mg over a 24-hour period), despite adherence to treatment with full doses of at least three antihypertensive medications, including a diuretic.¹ Patients who have recently received a diagnosis of hypertension or who have not yet received treatment should not be considered to have resistant hypertension, regardless of their blood-pressure level.

From the Section of Cardiovascular Medicine and the Cardiovascular Disease Prevention Center, Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn. Address reprint requests to Dr. Moser at the Section of Cardiovascular Medicine, Yale University School of Medicine, Box 338017, 333 Cedar St., New Haven, CT 06520.

Consider Torsemide

1-2 times per day = Furosemide 2-3 X per day

2.5-5 mg = starting dose

Max BP lowering may take six weeks

Resistant Hypertension - management

- Reassessment checklist - R E S I S T A N T
- ACEi/CCB/Diuretic as principal drugs
 - BB for compelling indications; HR > 84
- Many reasonable options, but systematic + aggressive Rx appropriate
- Volume expansion and hyperaldosteronism
- When K⁺+Cr normal, consider **spironolactone**
- When K⁺ or Cr high, consider **loop diuretic**