

New Perspectives in Diagnosis and Treatment of Resistant Hypertension

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Objectives

- Definition and epidemiology of uncontrolled and resistant hypertension
- Discuss diagnostic algorithm of resistant hypertension
- Overview new therapeutic options for resistant hypertension

CASE PRESENTATION

62 years-old female was referred to you for the evaluation and treatment of difficult to control HTN. Her BP is >140/90 in PCP office for several times while taking daily HCTZ 25 mg, Lisinopril 40 mg, and Amlodipine 10 mg. ROS is + for occasional headaches for which she takes “pain killers”. She works as a manager in a local grocery store. On exam, BMI 35 kg/m², HR 94, BP 164/103. +pitting edema in both ankles. Laboratory findings: glucose 92 mg/dl, K 3.7 mmol/l, Cr 1.0 mg/dL.

What is the next most appropriate step in the management of patient`s hypertenaion?

1. Add metoprolol 50 mg bid
2. Measure 24-hr urine free cortisol
3. Measure morning aldosterone concentration and plasma renin activity
4. Measure fractionated plasma metanephrines
5. Review medication list including OTC meds, advise to reduce Na intake, encourage 5-7% weight loss and exercise 30 mins/day, encourage to take medications daily

Classification of Blood Pressure for Adults

Blood Pressure Classification	SBP mmHg	DBP mmHg
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 Hypertension	140–159	or 90–99
Stage 2 Hypertension	≥160	or ≥100

SBP, systolic blood pressure; DBP, diastolic blood pressure

The 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

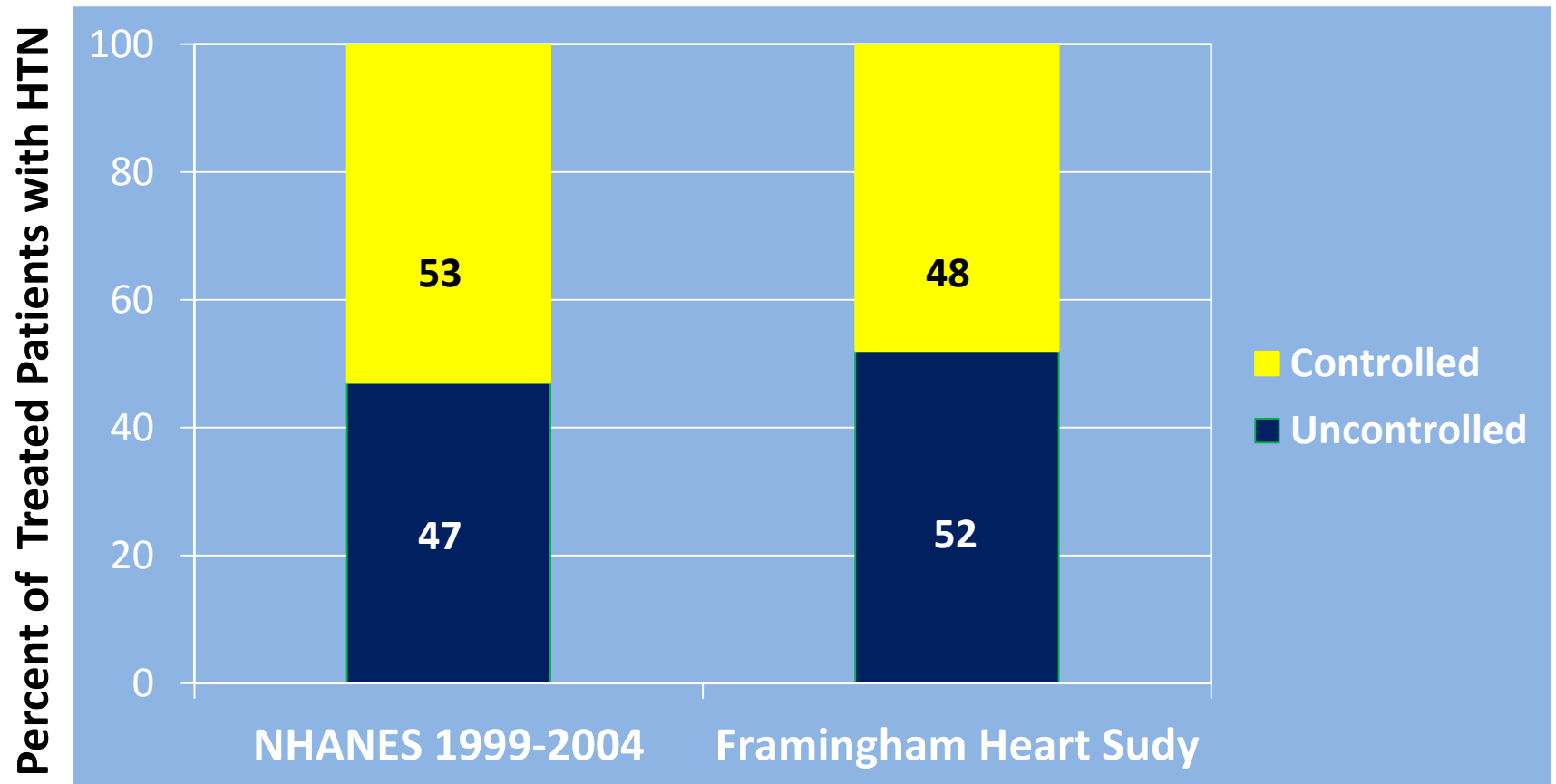
Definition

- **Uncontrolled hypertension:** blood pressure above goal
 - less than 140/90 for the general population (adults age 18 and older)
 - less than 130/80 in patients with diabetes or CKD

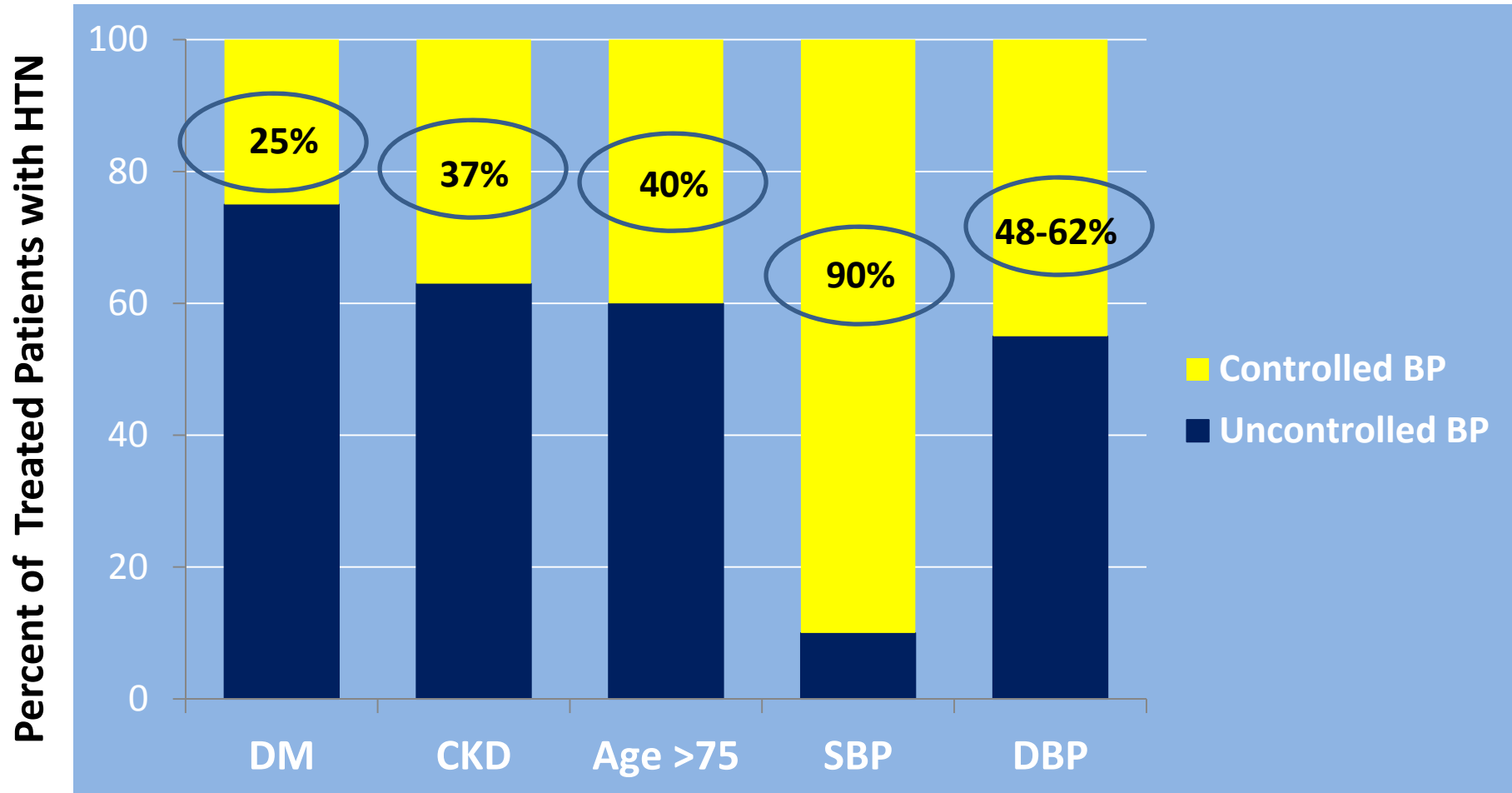
- The 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

- ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly.
Circulation. 2011; 123: 2434-2506

Epidemiology of Uncontrolled HTN



Epidemiology of Uncontrolled Hypertension



NHANES 1999-2004, Framingham Heart Study, ALLHAT
Lloyd-Jones DM, et al. Hypertension. 2000; 36: 594-599

Uncontrolled versus Resistant HTN

- **Uncontrolled hypertension:** blood pressure above goal (<140/90, or 130/80 in patients with DM or CKD)
- **Resistant hypertension:**
 - Office blood pressure that remains above goal (<140/90, or 130/80 in patients with DM or CKD)
 - and**
 - Patient prescribed **3** or more antihypertensive medications **at optimal doses, including if possible a diuretic**
 - or**
 - Office blood pressure at goal but patient requiring 4 or more antihypertensive medications

Why is there a need for definition of resistant hypertension?

“Resistant hypertension is defined in order to identify patients who are at high risk of having reversible causes of hypertension and who may benefit from special diagnostic and therapeutic considerations”.

Epidemiology of Resistant Hypertension

- Largest Data Series from Spain:
 - registry of ~62,000 patients treated for HTN
 - prevalence 12.2% by office BP measurement
(de la Sierra A, et al. *Hypertension*. 57(5): 898–902, 2011)
- 35% in tertiary care center (Hirsch et al, 2007)

Circulation

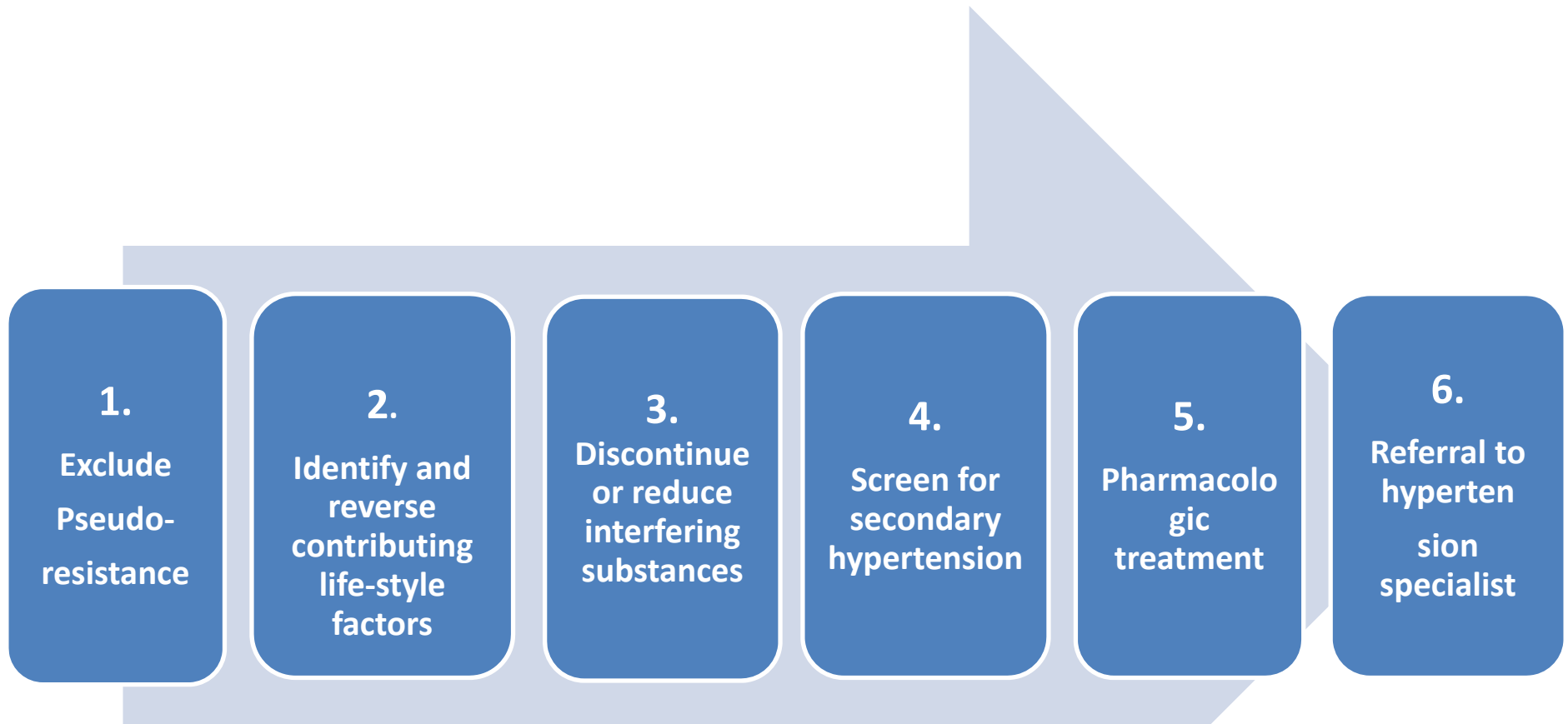
JOURNAL OF THE AMERICAN HEART ASSOCIATION



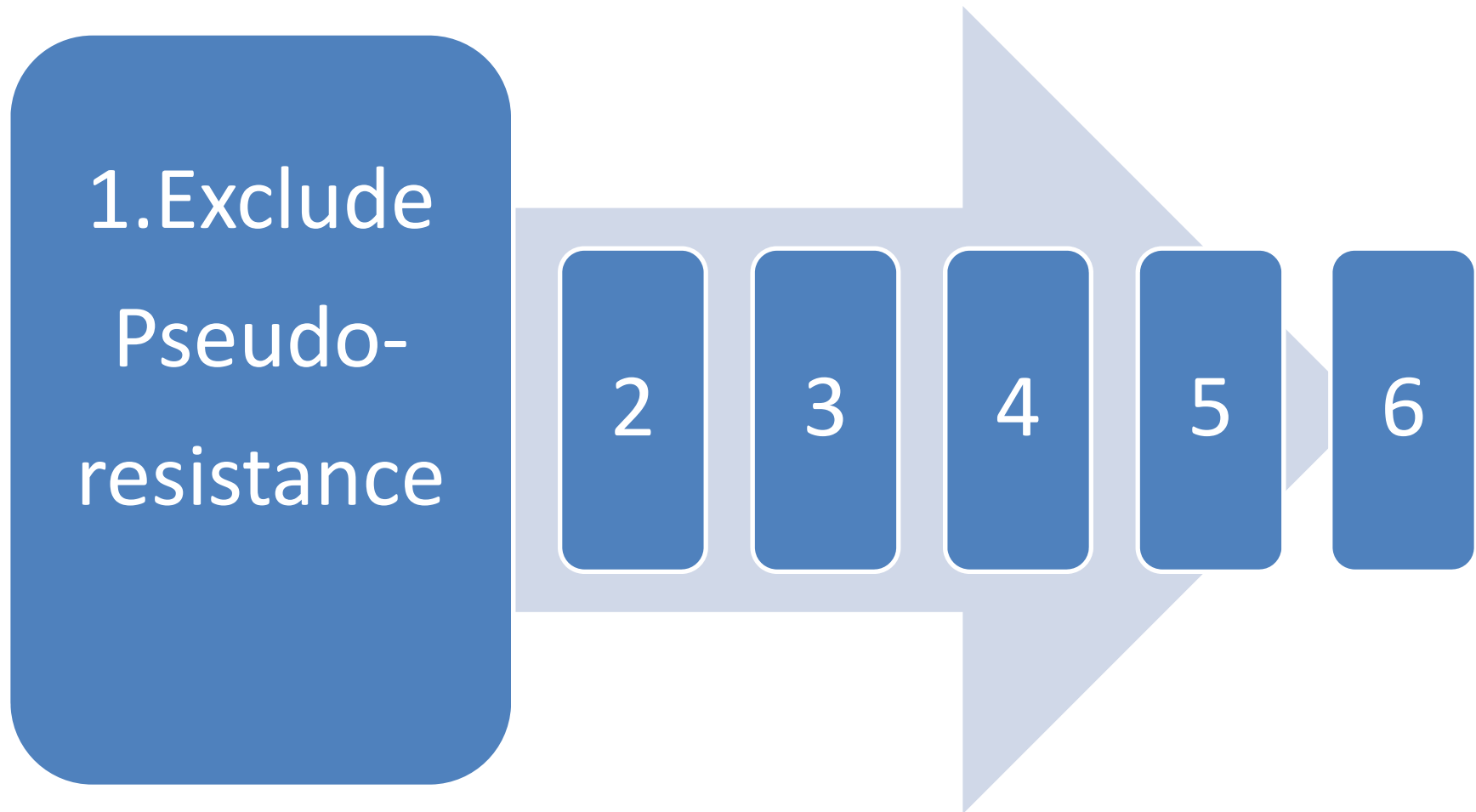
Resistant Hypertension: Diagnosis, Evaluation, and Treatment : A Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research

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

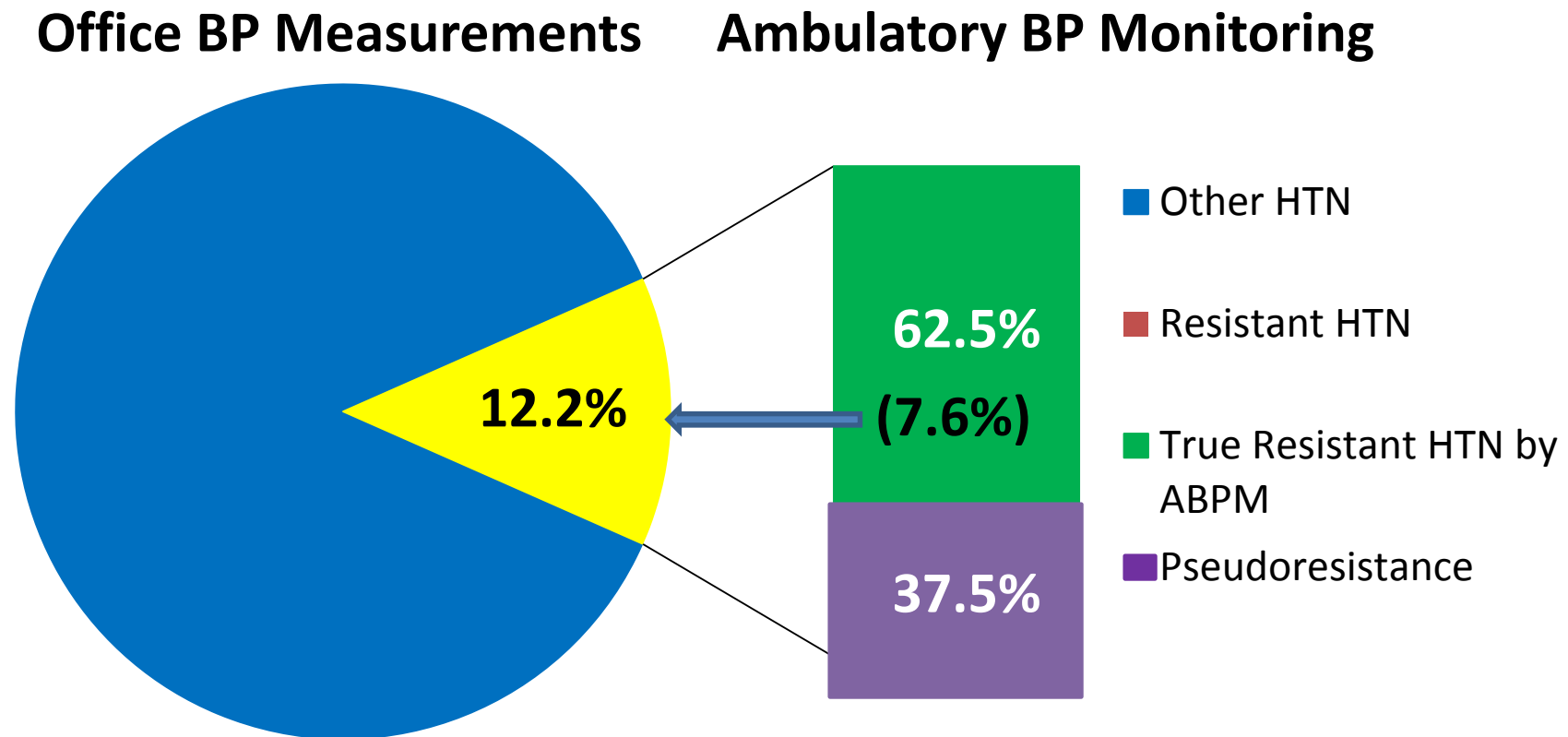
Approach to Resistant Hypertension



Approach to Resistant Hypertension



Prevalence of Pseudoresistance



Pseudoresistance

- Poor blood pressure measuring technique
- Poor adherence
- White coat effect

Poor BP measuring technique

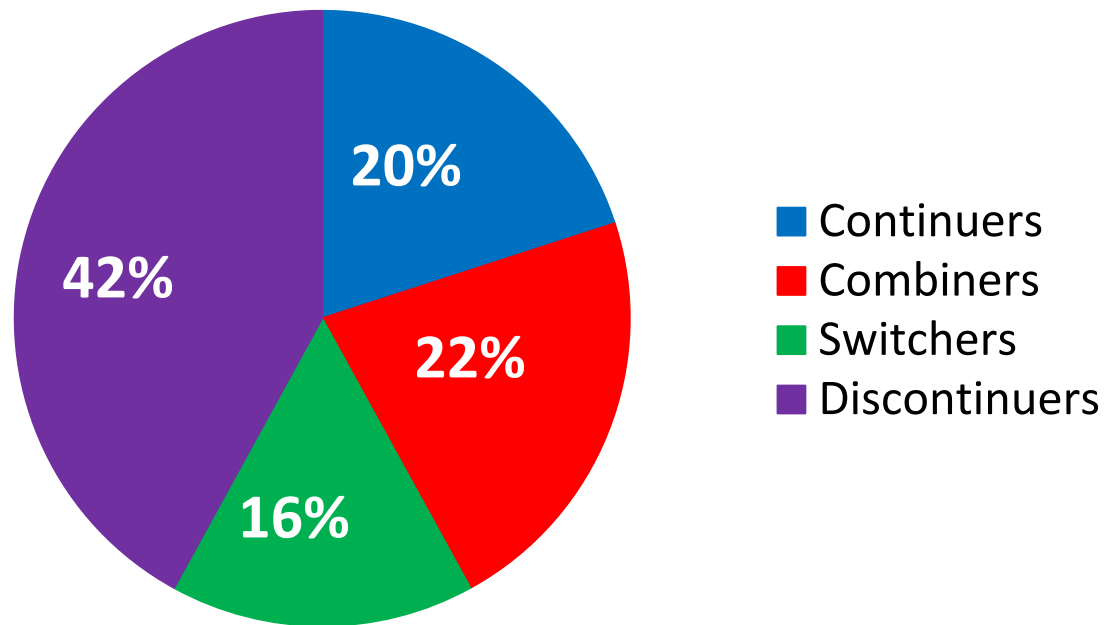
- Train your staff:
 - Average of 2 readings 1 minute apart after 5 minutes of rest with back supported, use appropriate size of cuff, cuff at the level of R atrium
- Common mistakes:
 - measuring BP w/o letting patient to rest
 - too small cuff
- Less common: acute effect of cigarette smoking, acute effect of coffee, wrist monitor

Poor adherence

- Common!!!

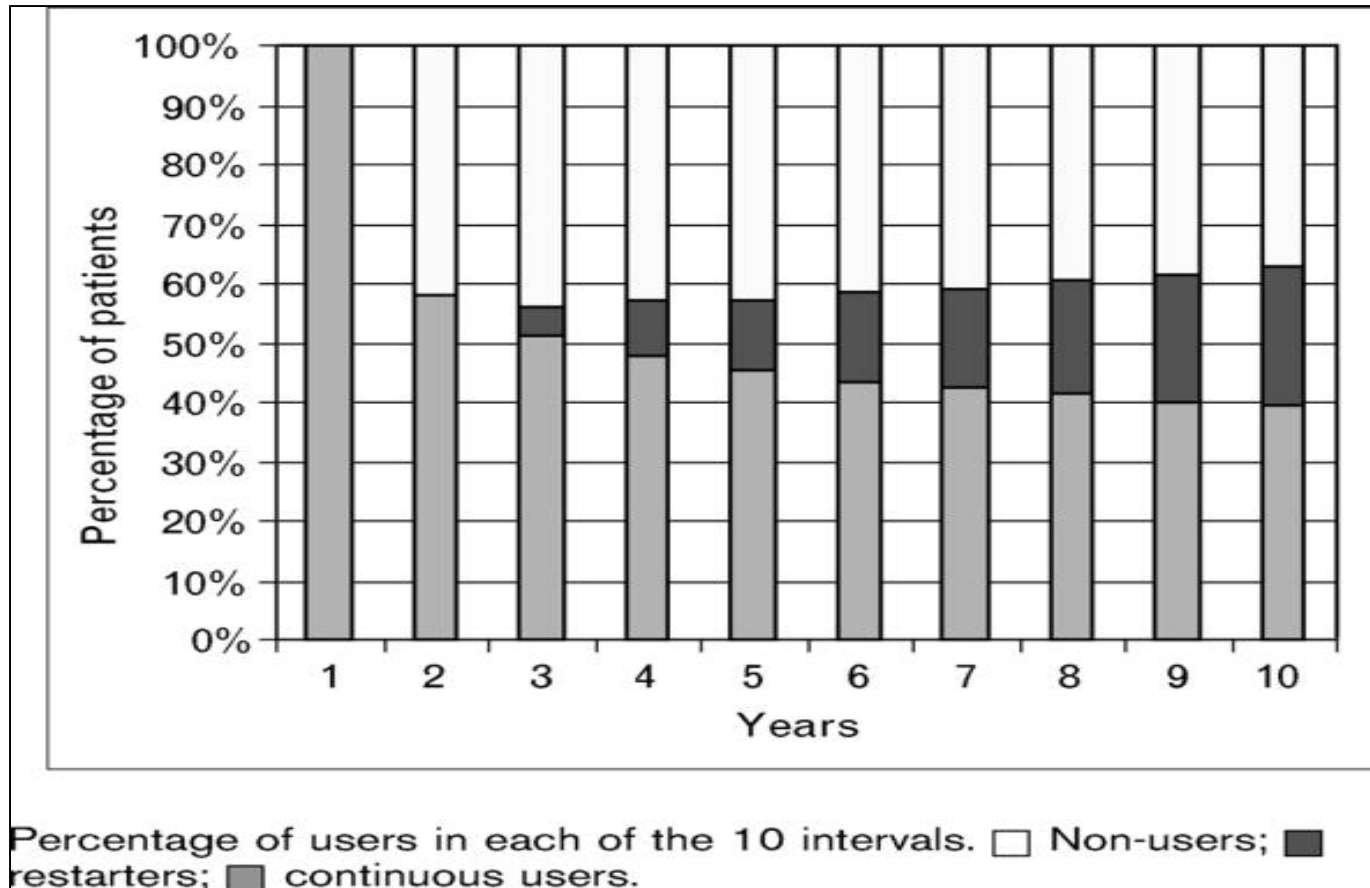
Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients

1-yr Adherence to HTN Drug Therapy



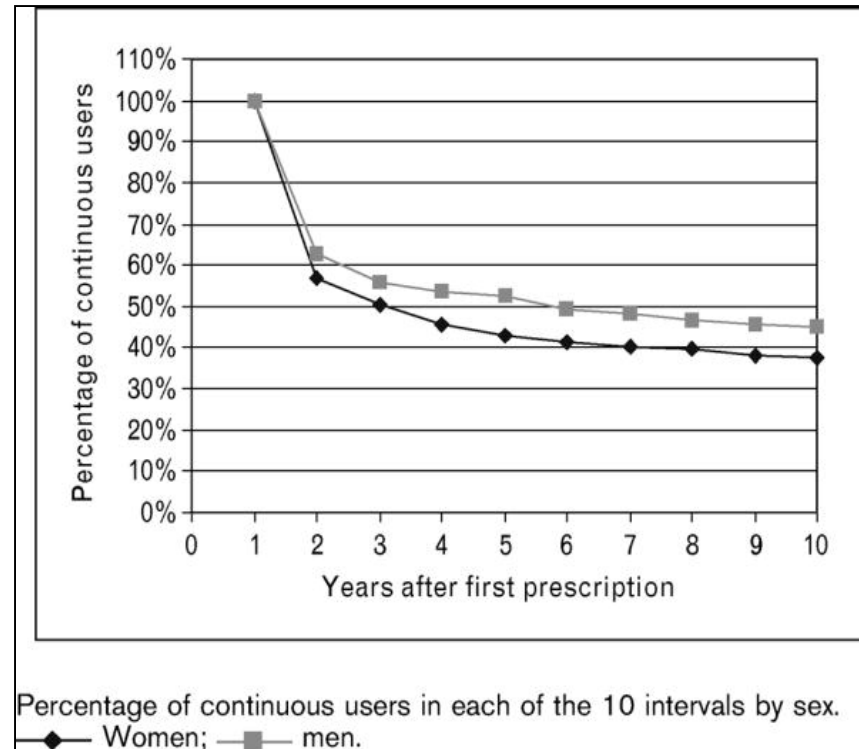
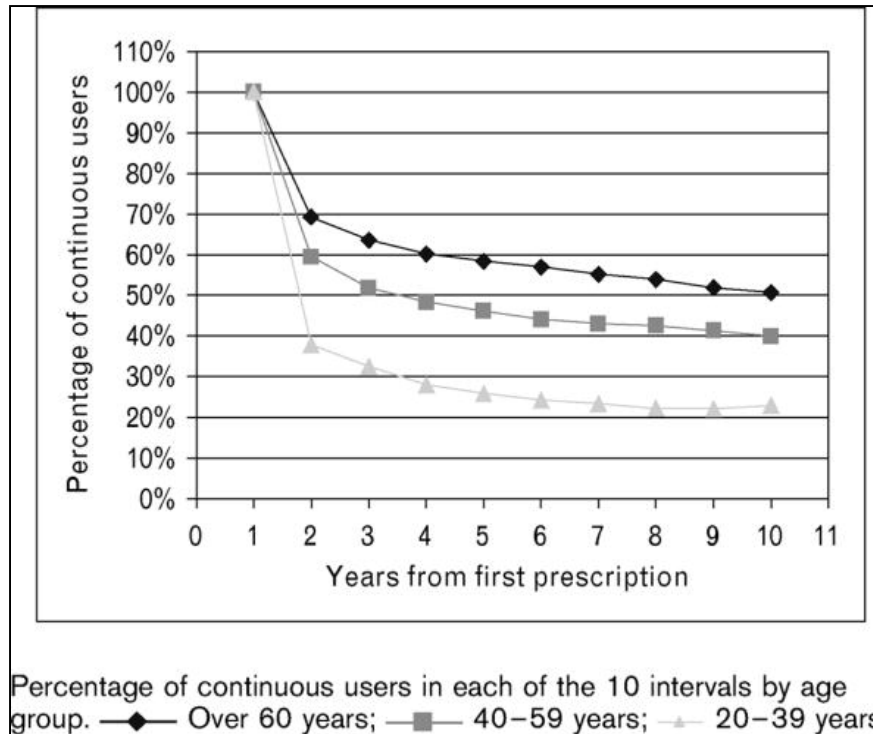
42% patients stopped their BP medications within 1st year after the diagnosis of HTN

Rate and determinants of 10-year persistence with antihypertensive drugs.



~40% patients continue to be non-adherent to BP medications

Rate and determinants of 10-year persistence with antihypertensive drugs.



Compliance:

1. Older patients >> younger
2. Men >> Women

Factors leading to poor adherence

- Cost of treatment
- Complexity of treatment
- Side effects
- Instructions not understood
- Organic brain syndrome (e.g. memory deficit)
- Lack of consistent and continuous primary care

White Coat Effect

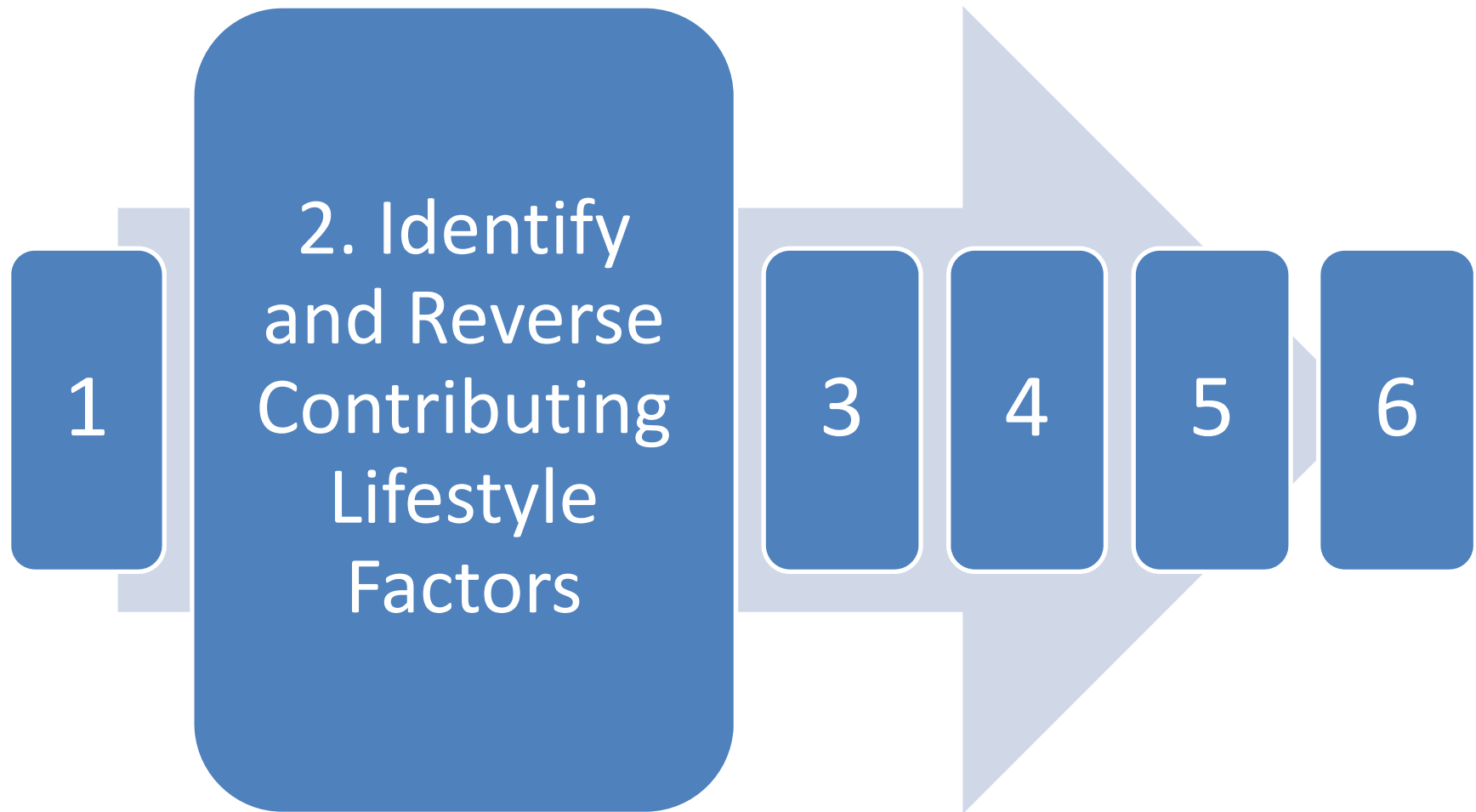
- Office BP is elevated above goal in the office and significantly higher than at home
- When to suspect:
 - uncontrolled HTN in the office with home symptoms of orthostasis/overmedication
- Diagnosis: Home BP monitoring and ABPM
- Medicare pays for ABPM to exclude white coat hypertension (in untreated patients)

Comparison of office, ambulatory, and self (home) blood pressure monitoring

	Office BP Monitoring	ABPM	Self-BP Monitoring
Detects white coat and masked hypertension	No	Yes	Yes (limited)
Evaluation of therapy	Yes	Yes (limited repeat uses)	Yes
Normal limit for average risk patients (mm Hg)	< 140/90	<130/80 (24-hour) <135/85 (awake) <120/75 (sleep)	<135/85
Cost	Low	High	Low
Reimbursement	Yes	Partial	No

-The 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Approach to Resistant Hypertension



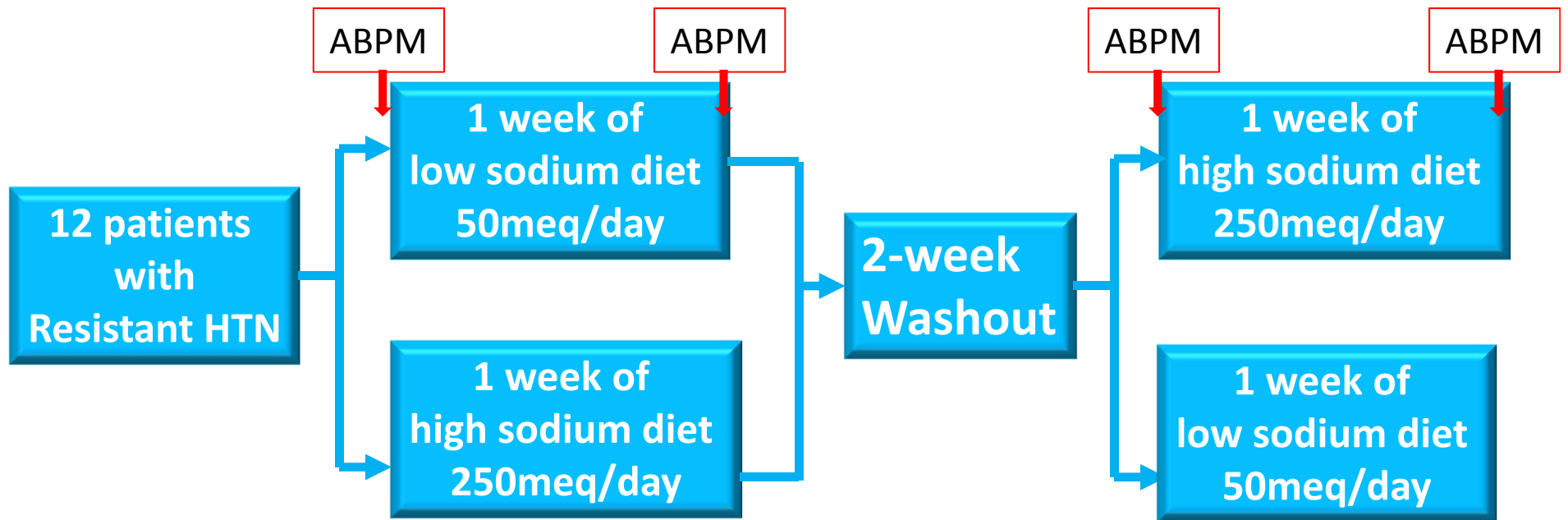
Identify and Reverse Contributing Lifestyle Factors

- **Obesity**
- Physical inactivity
- Excessive alcohol ingestion
- **High salt**
- Low fiber diet

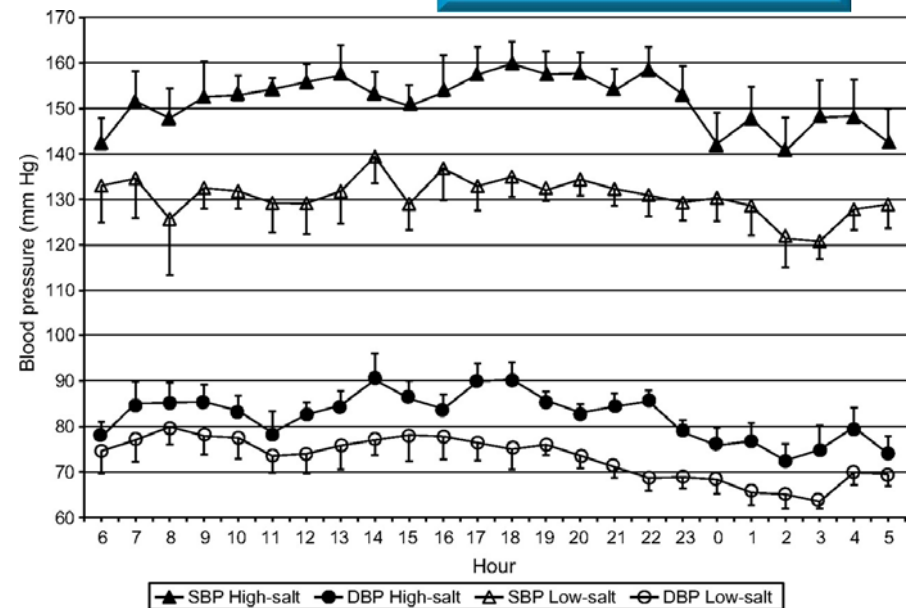
Effect of Weight Loss on BP

Weight Loss kg	SBP mm Hg (95% CI)	DBP mm Hg (95% CI)
~ 5.1	-4.44 (-5.93 to -2.95)	-3.57 (-4.88 to -2.25)
≤ 5	-2.70 (-4.59 to -0.81)	-2.01 (-3.47 to -0.54)
> 5	-6.63 (-8.43 to -4.82)	-5.12 (-6.48 to -3.75)

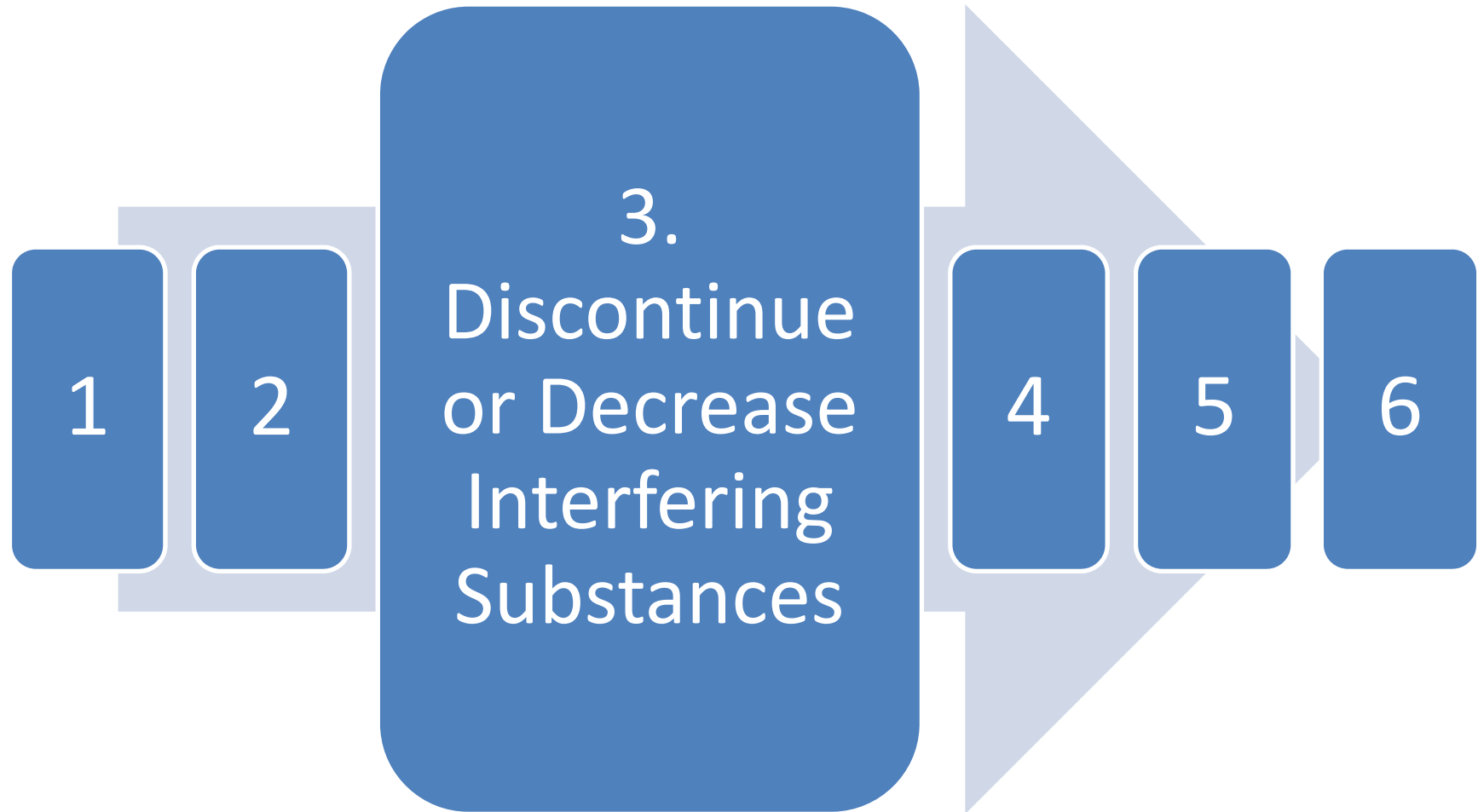
Effect of Salt Restriction on Resistant HTN



Mean office SBP reduced by 22.7 mm Hg (95% CI of 11.8-33.5) and DBP by 9.1 mm Hg (95% CI of 3.1-15.1)



Approach to Resistant Hypertension



Medications That Can Interfere With Blood Pressure Control

Nonnarcotic analgesics

Nonsteroidal anti-inflammatory agents, including aspirin

Selective COX-2 inhibitors, ? acetaminophen

Sympathomimetic agents (decongestants, diet pills, cocaine, caffeine)

Stimulants (methylphenidate, dexamethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil)

Glucocorticosteroids

Alcohol

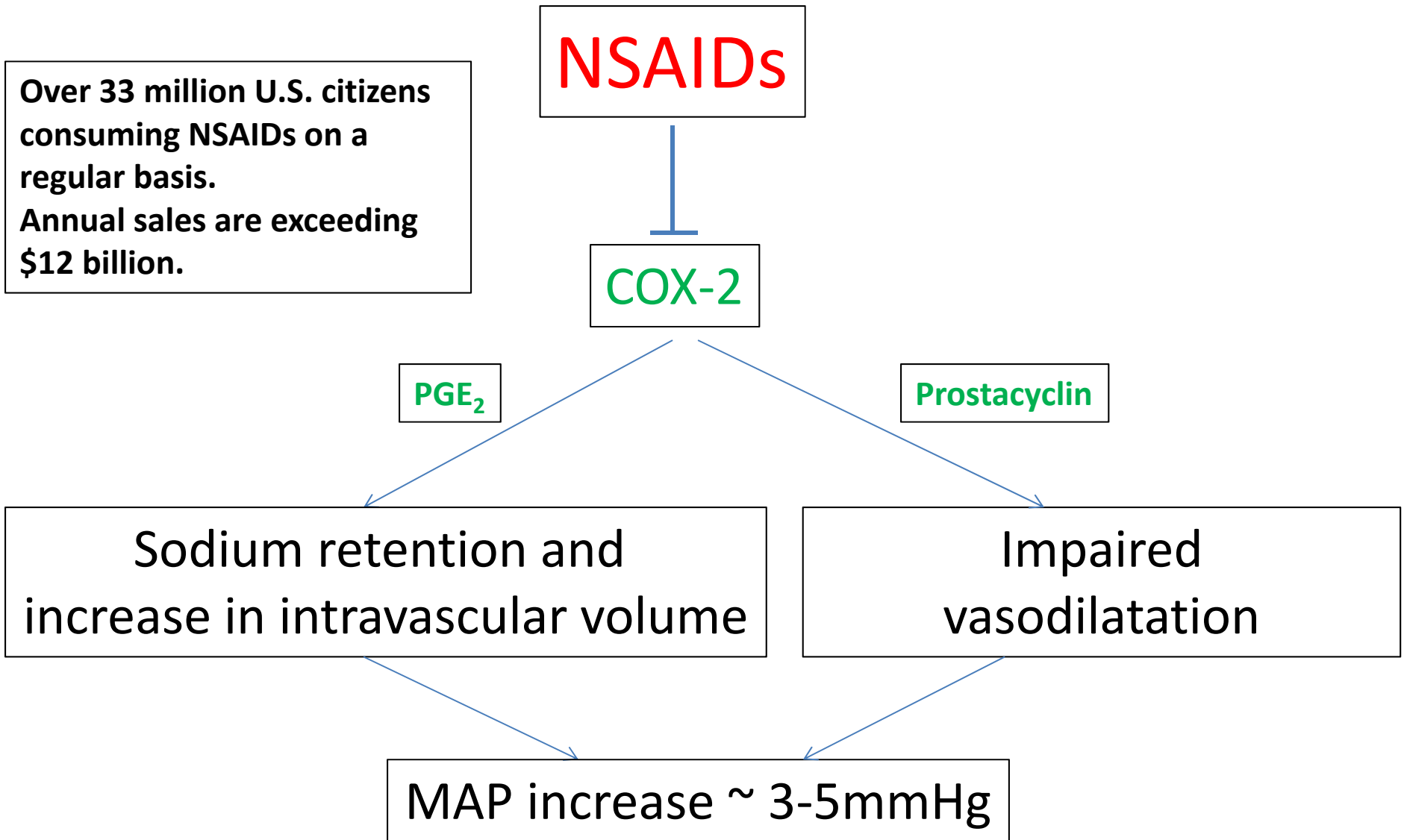
Oral contraceptives

Cyclosporine, tacrolimus

Erythropoietin

Natural licorice

Herbal compounds (ephedra or ma huang)

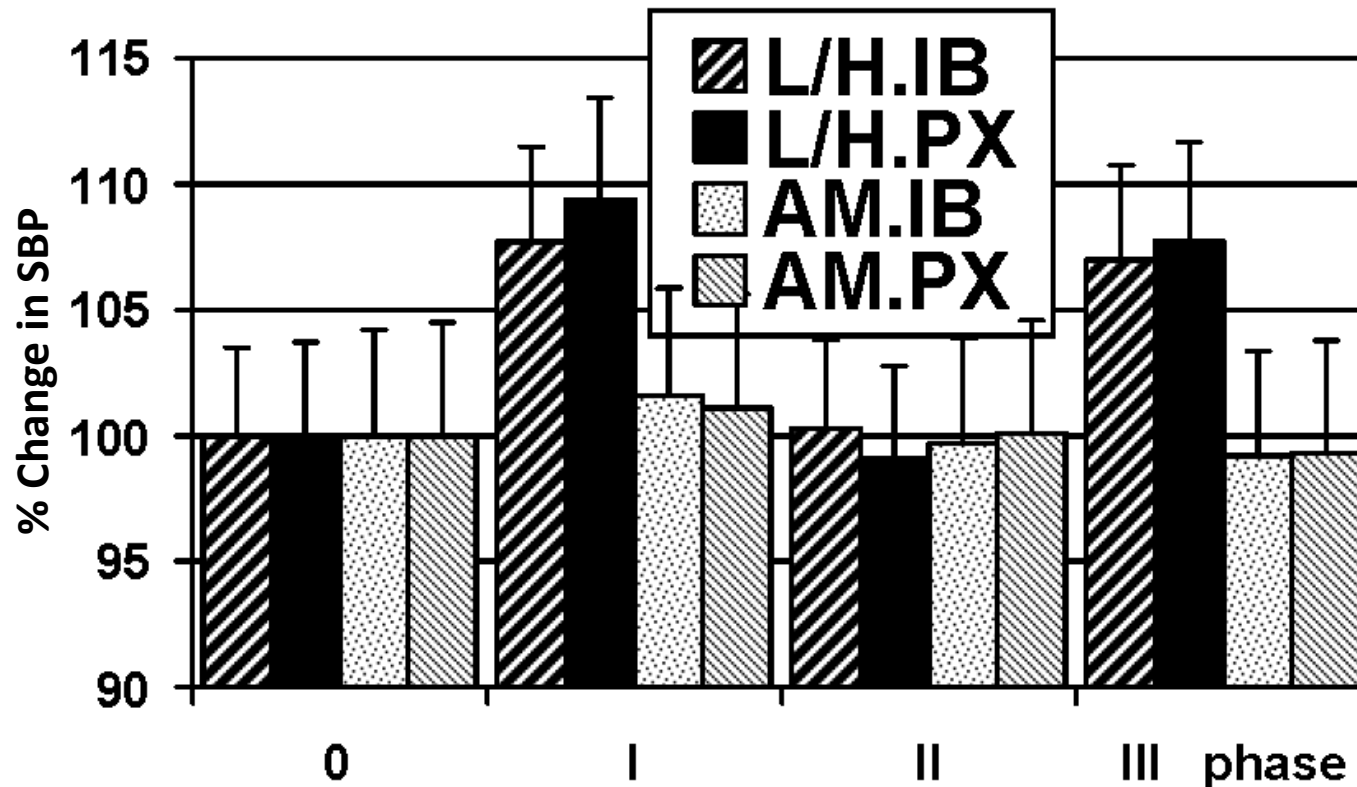


NSAIDs and Blood Pressure

Amlodipine: 5-10mg/day; Lisinopril/HCTZ; (10/6.25-20/12.5 mg o.d.

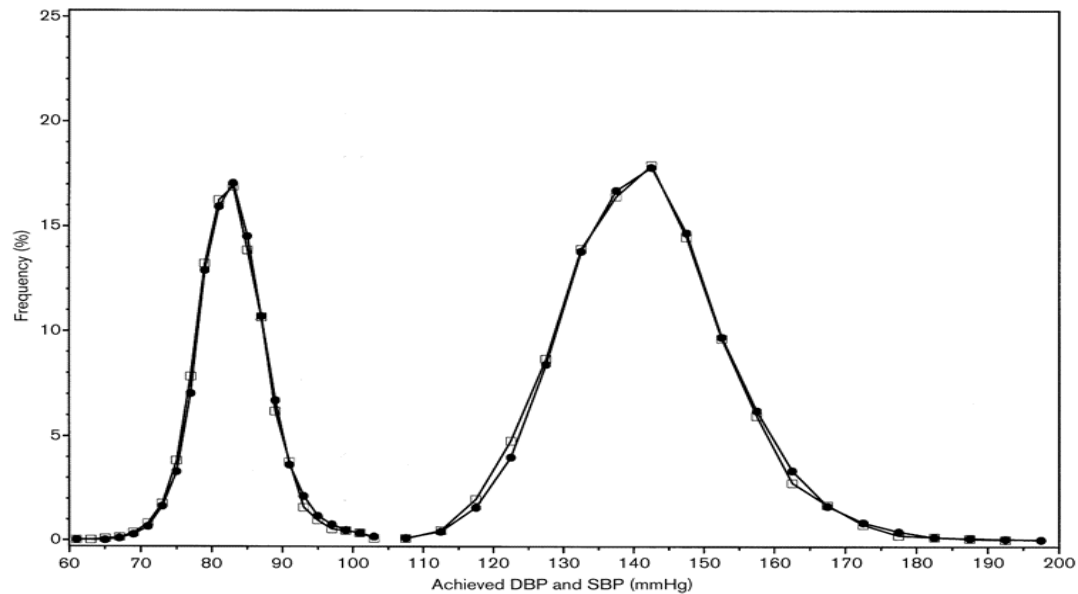
Ibuprofen: 600-800 mg tid; Piroxicam: 10-20 mg/day

Acetaminophen: 1000 mg tid



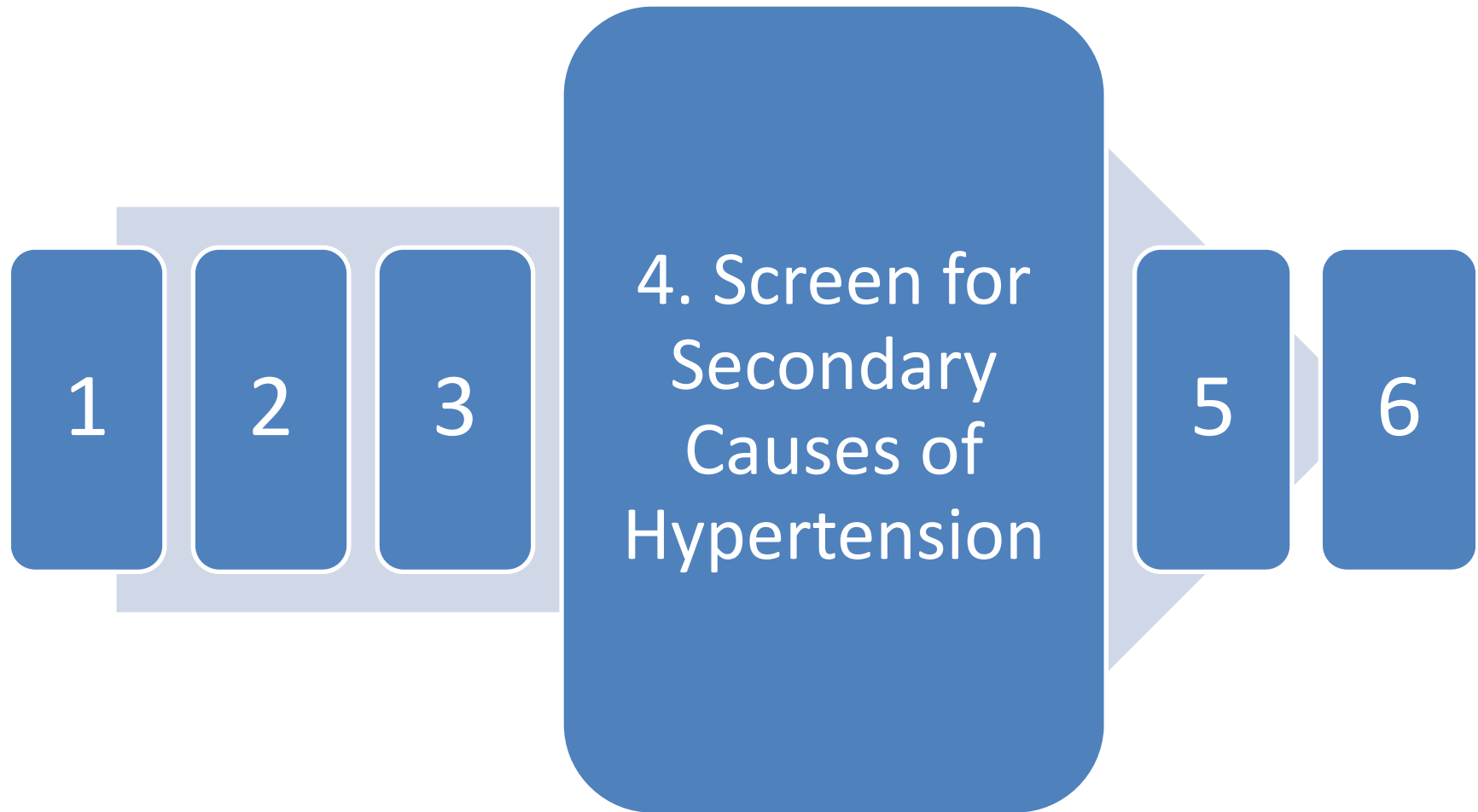
Aspirin and Blood Pressure

Low dose ASA (75mg daily) for CAD prophylaxis was not reported to rise BP in Hypertension Optimal Treatment (HOT) Study (>18,000 patients)



Zanchetti A. *J Hypertens.* 2002;20(5):1015

Approach to Resistant Hypertension



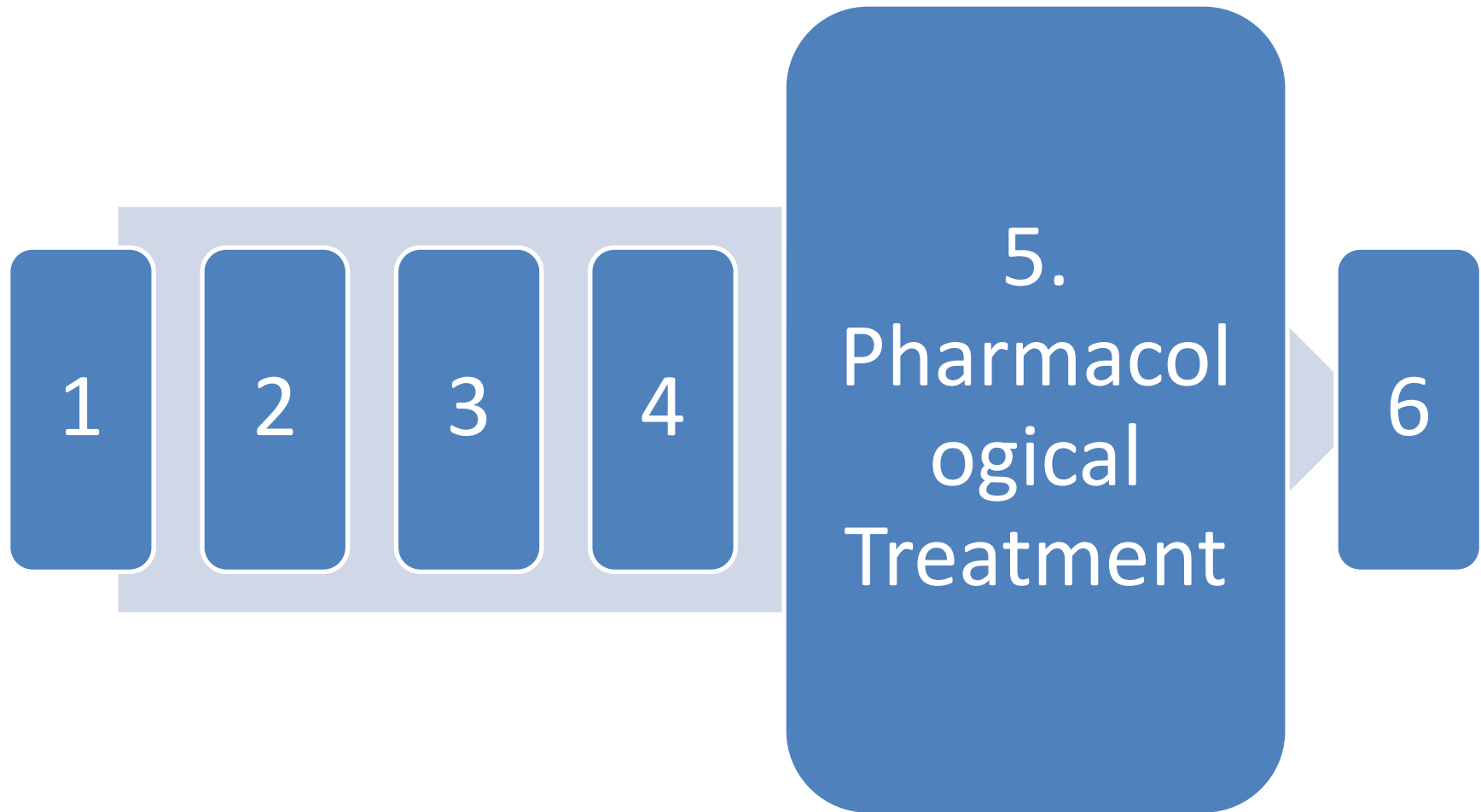
Secondary Causes of Resistant HTN

- Common:
 - Obstructive Sleep Apnea
 - Chronic Kidney Disease
 - Renal Vascular Hypertension
 - Primary Hyperaldosteronism
- Uncommon:
 - Pheochromocytoma
 - Cushing's Syndrome
 - Thyroid Disease
 - Primary hyperparathyroidism
 - Aortic Coarctation
 - Brain Tumors

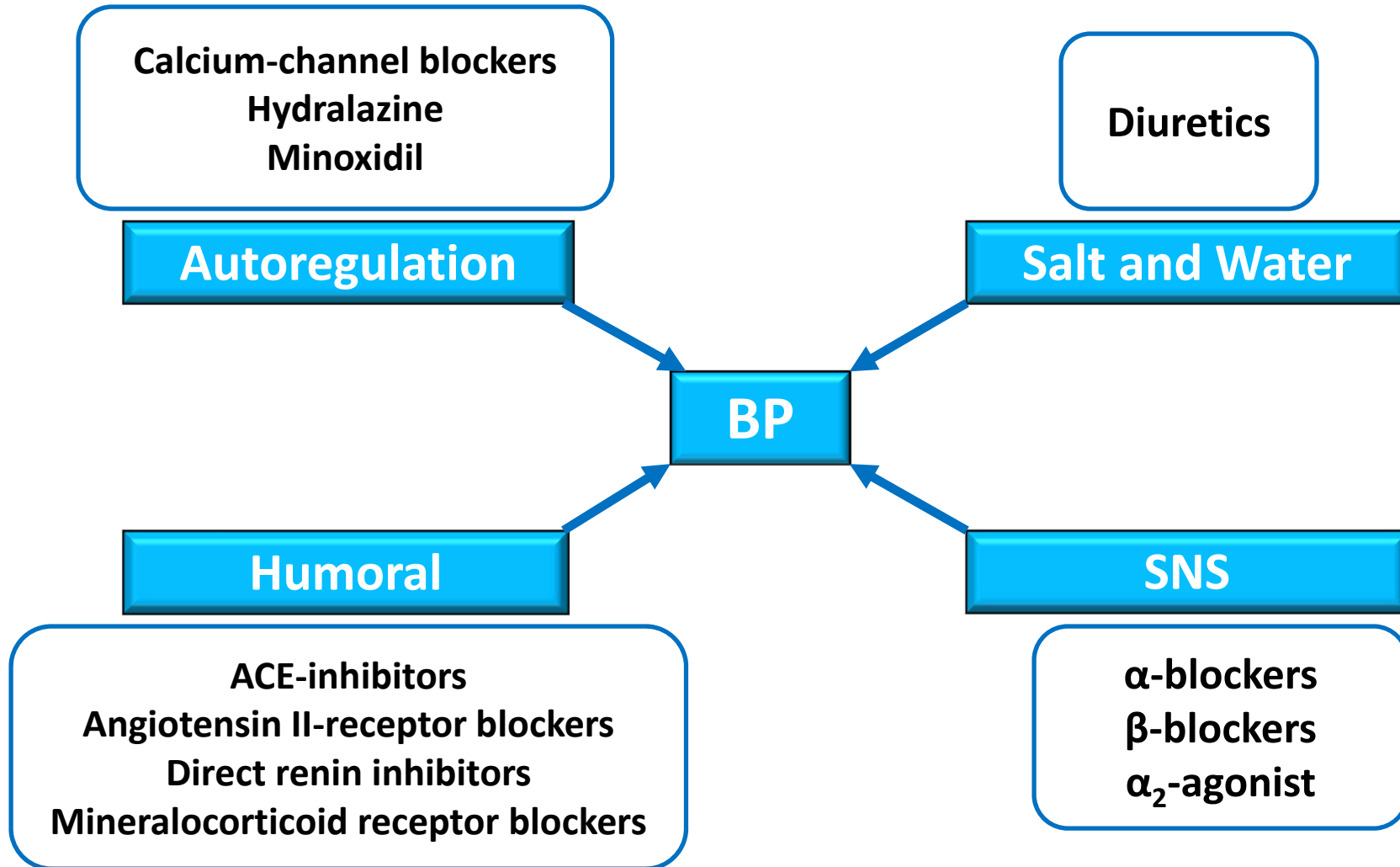
Secondary Causes of Resistant HTN

- Screening for secondary causes should be guided by:
 - clinical history
 - physical examination
 - initial laboratory testing
 - presence of risk factors
- Current guidelines support referral to a **specialist** at this point even without initial screening

Approach to Resistant Hypertension



Antihypertensive Drugs

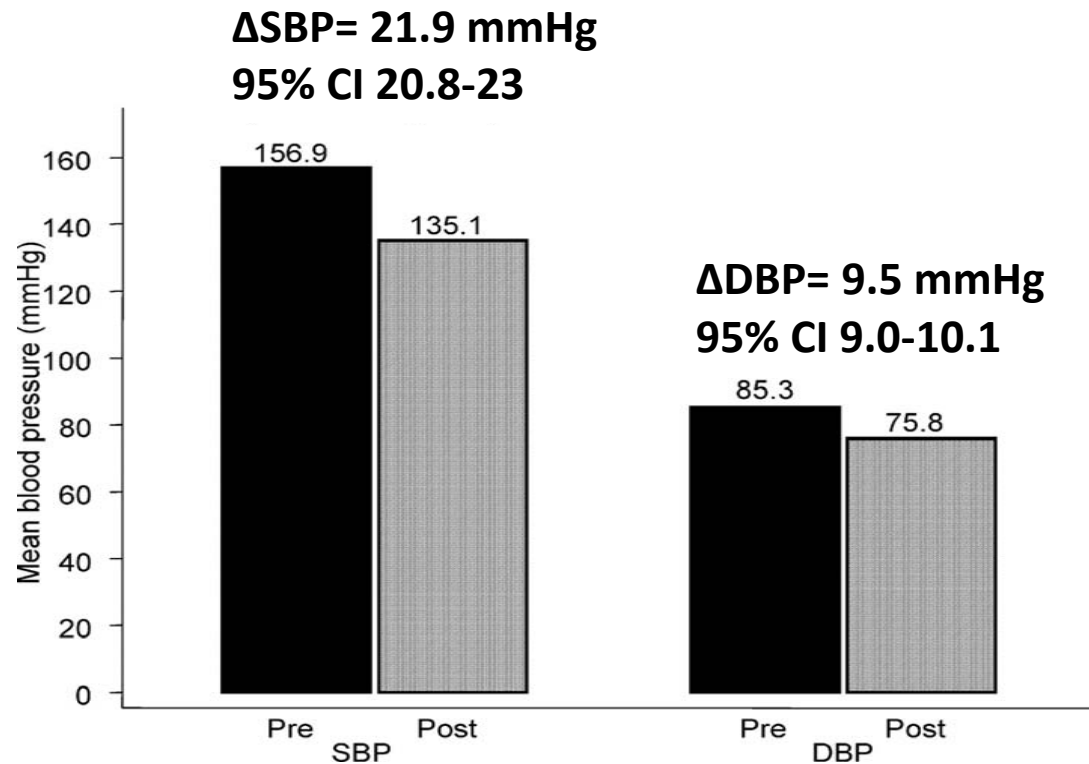
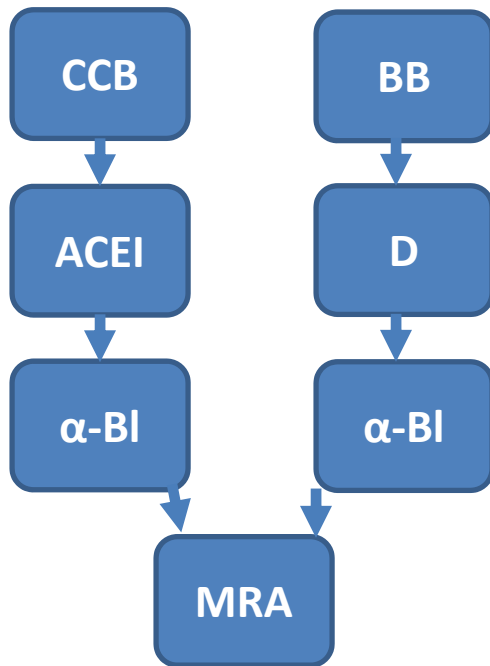


Common Treatment Errors

- Doses too low (failure to titrate to effective dose)
- Inappropriate antihypertensive drug combinations
- Use of short acting drugs
- Failure to utilize diuretics when volume overload is present
 - failure to use furosemide when $eGFR < 40 \text{ ml/min/m}^2$

Anglo-Scandinavian Cardiac Outcomes Trial

Spironolactone 25-50mg



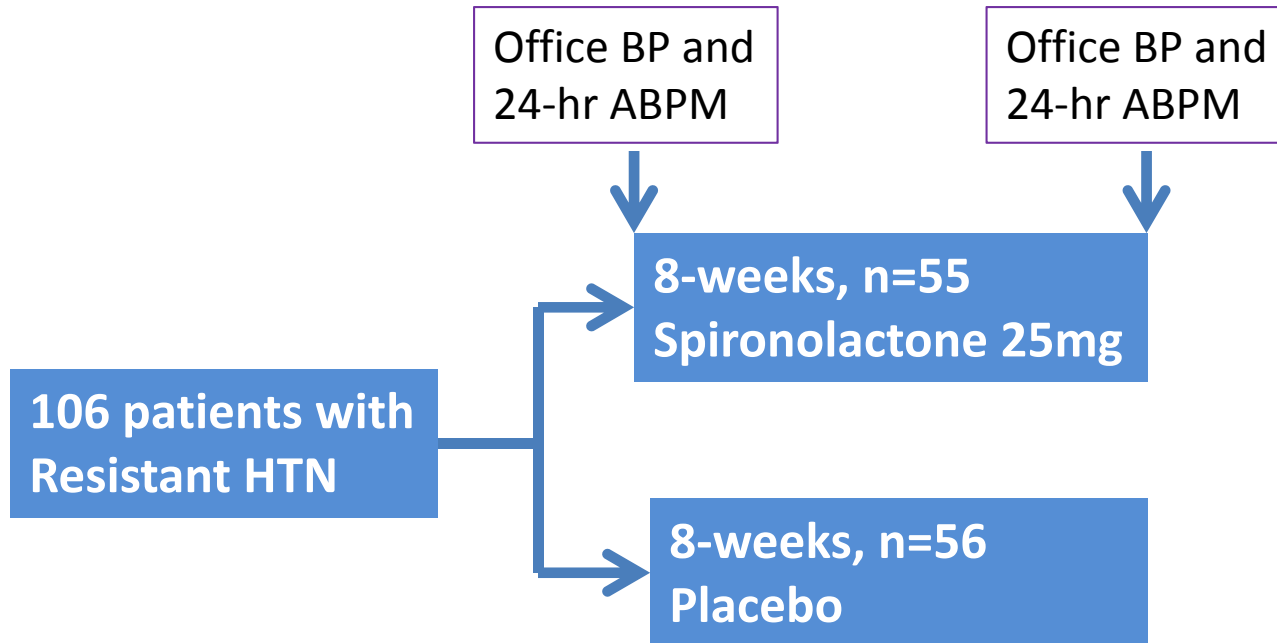
Spironolactone effectively reduced BP when added as 4th line therapy

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

A Randomized, Double-Blind, Placebo-Controlled Trial

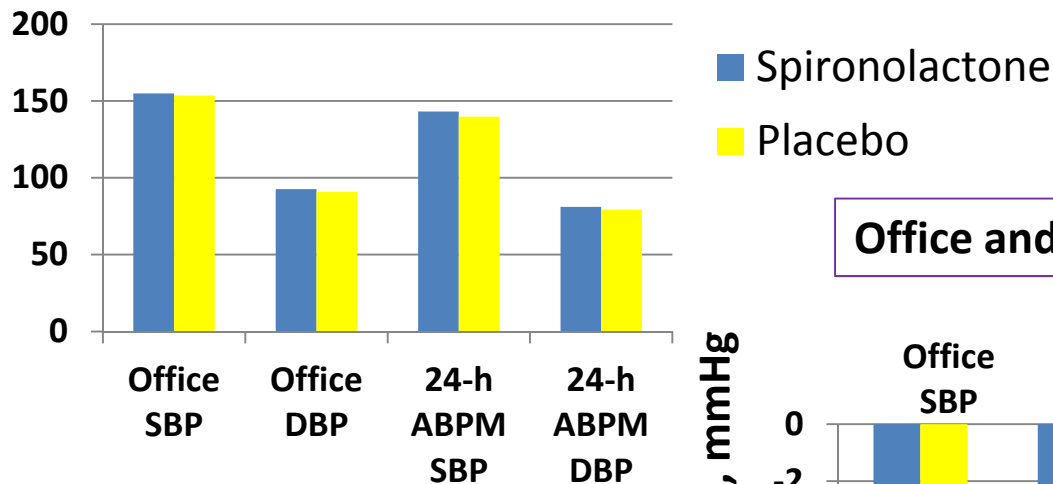
Jan Václavík, Richard Sedlák, Martin Plachý, Karel Navrátil, Jiří Plášek, Jiří Jarkovský,
Tomáš Václavík, Roman Husár, Eva Kociánová, Miloš Táborský

(Hypertension. 2011;57:1069-1075.)

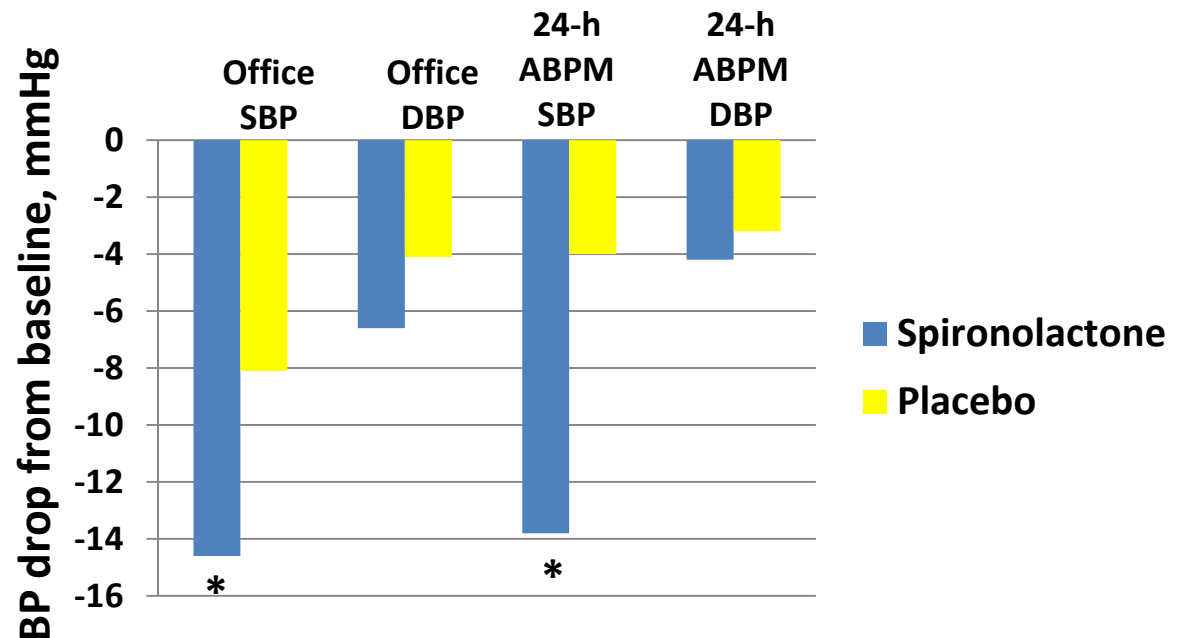


Addition of Spironolactone in treatment of Resistant Hypertension

Office and 24-hr ABPM at the Beginning of study



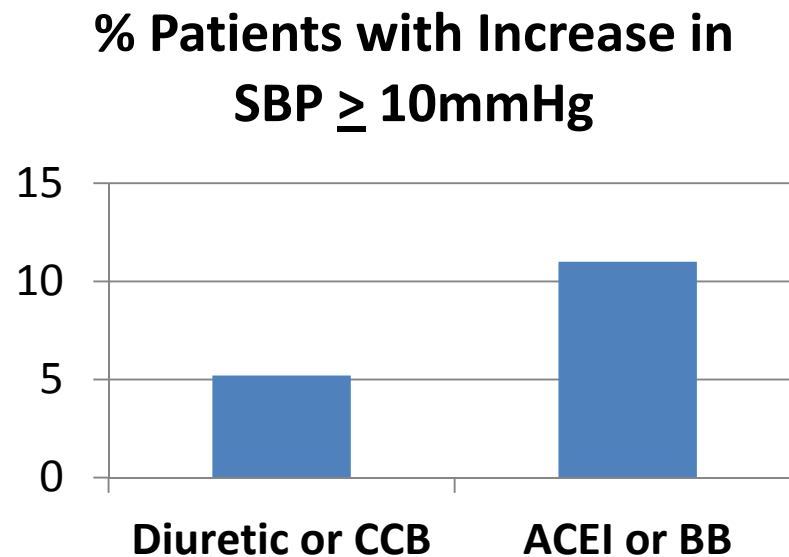
Office and 24-hr ABPM at the beginning of study



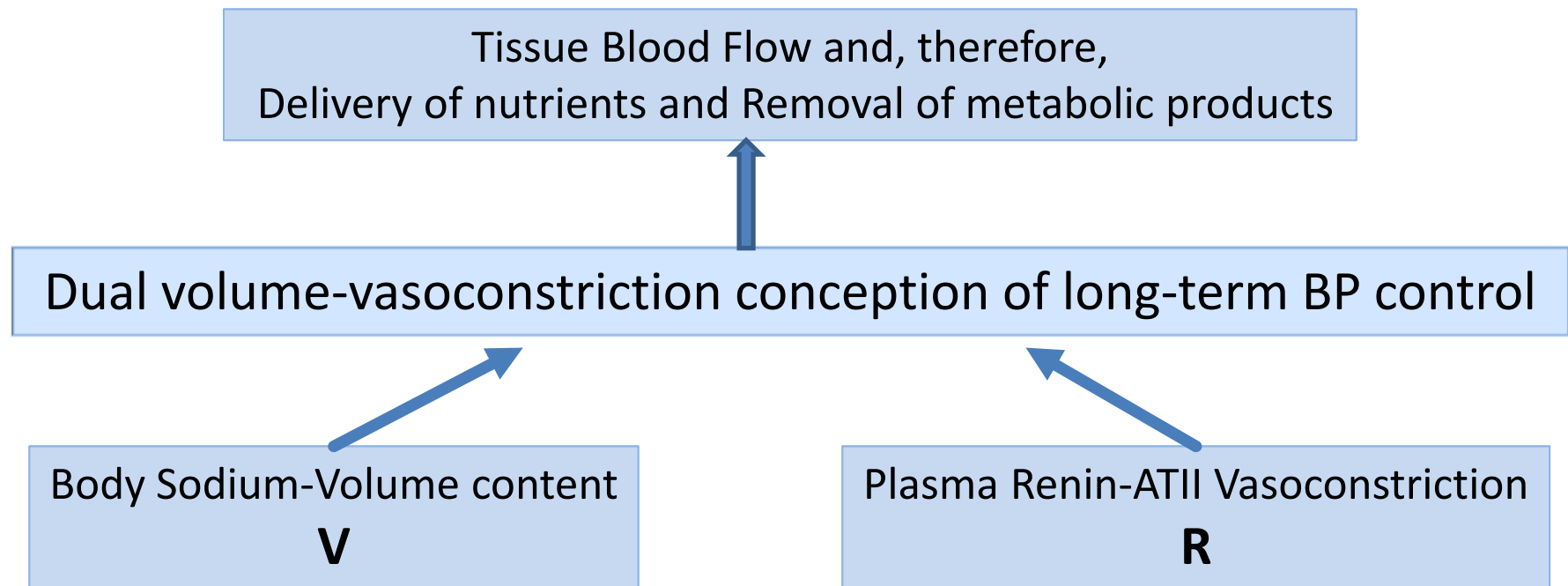
(Hypertension. 2011;57:1069-1075.)

Is there factor(s) related to the treatment itself that contribute to unsuccessful treatment?

- Pressor response to antihypertensive drugs: increase in SBP \geq 10mmHg



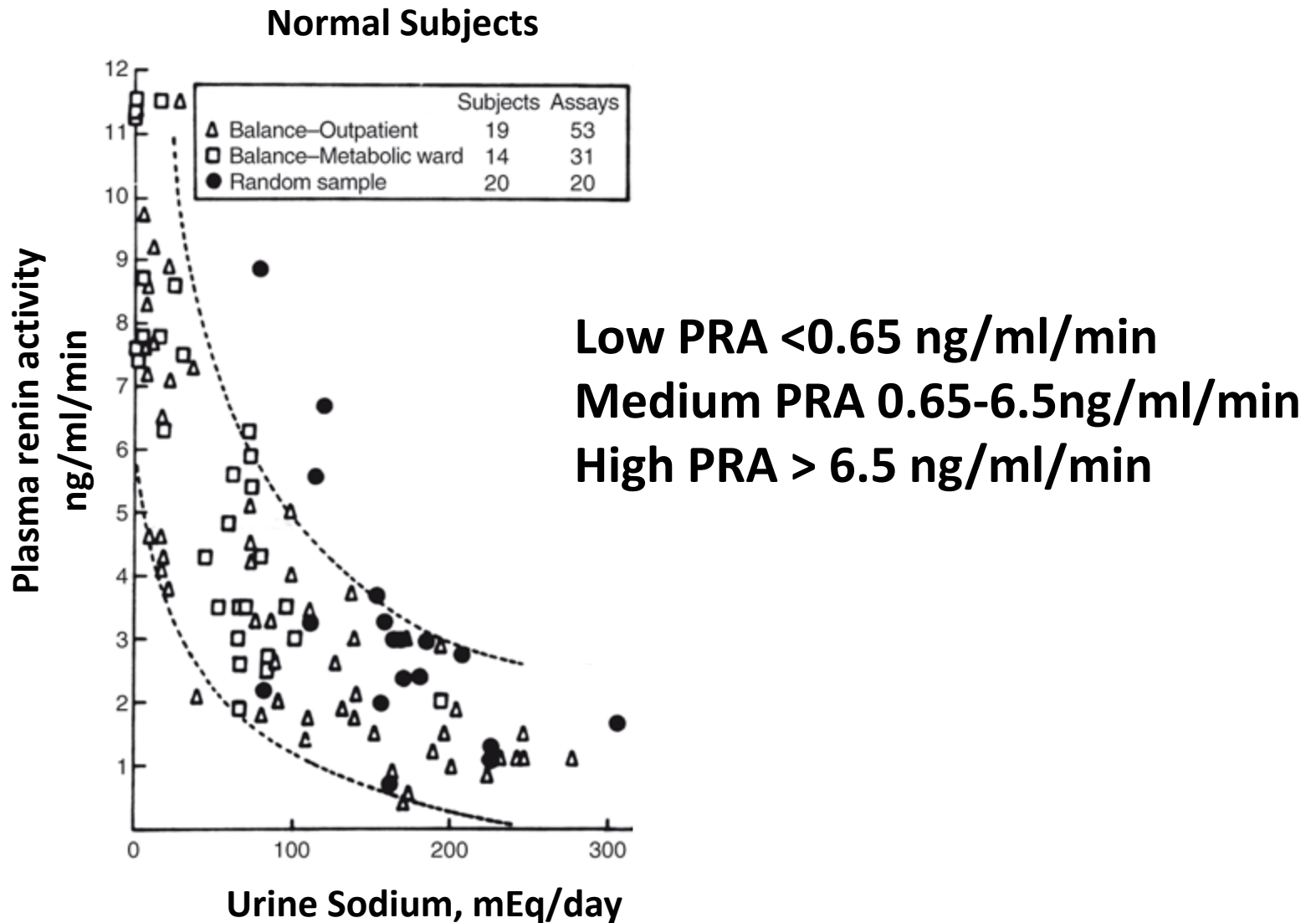
Physiology of Blood Pressure



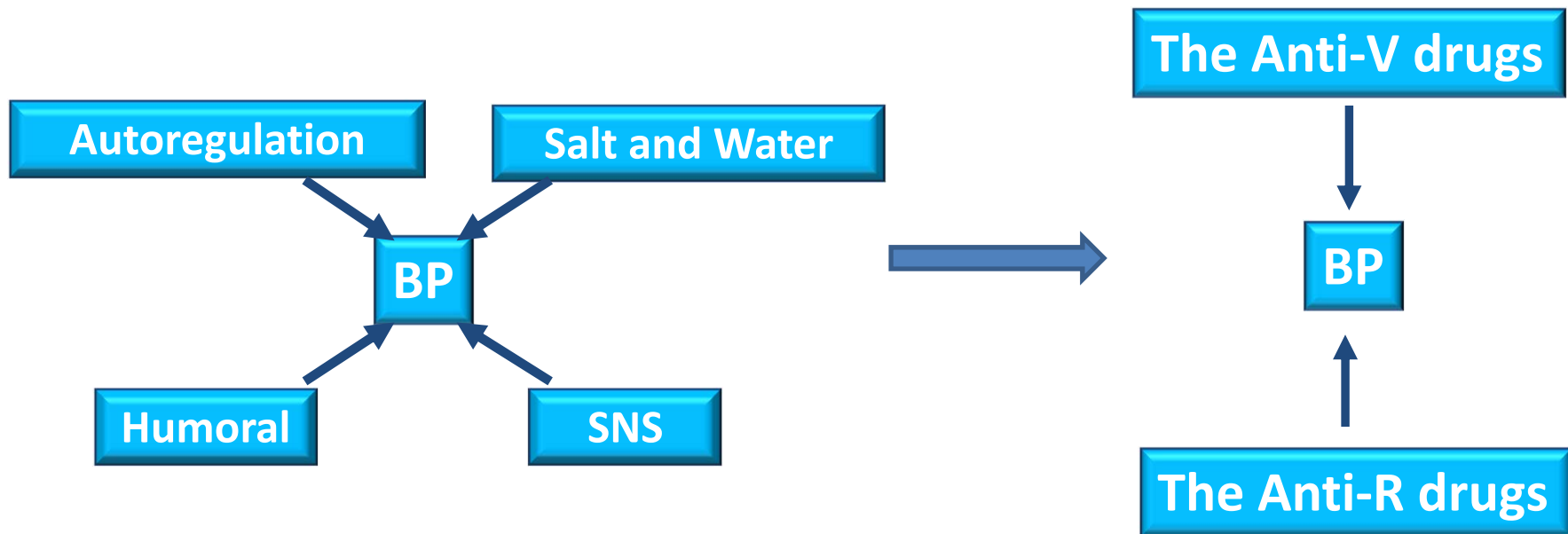
BP and Plasma Renin Activity (PRA)

- Normal BP: any PRA is accompanied by reciprocal changes in V
- Hypertension: kidney fail to reduce PRA in response to an increase in body salt:
 - PRA could be already maximally suppressed (low renin HTN)
 - PRA “too high” (not necessary higher than normal) for the concurrent body salt content (normal and high renin HTN)

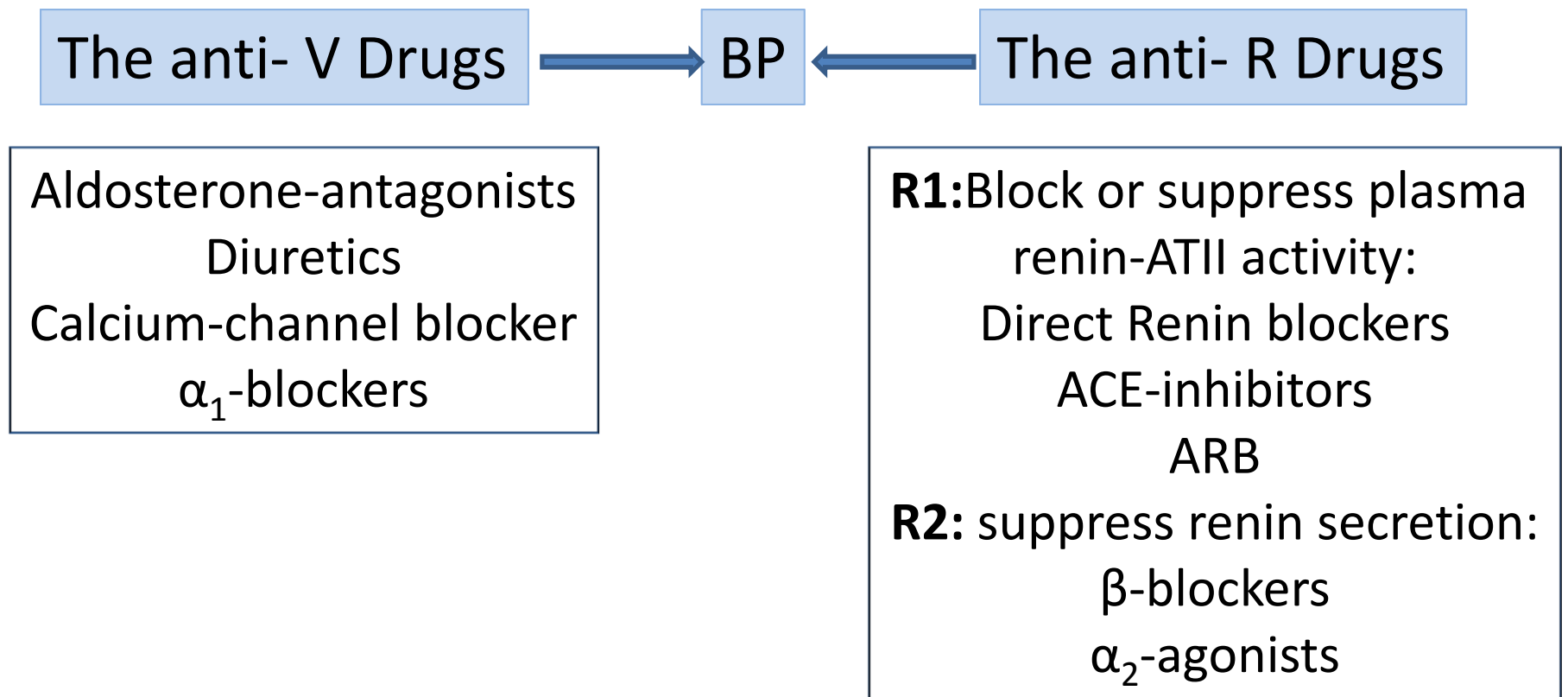
Relationship between PRA and Sodium Intake



Antihypertensive Drugs



$$BP = V \times R$$



BP response based on Plasma Renin Activity and anti-V or -R drug

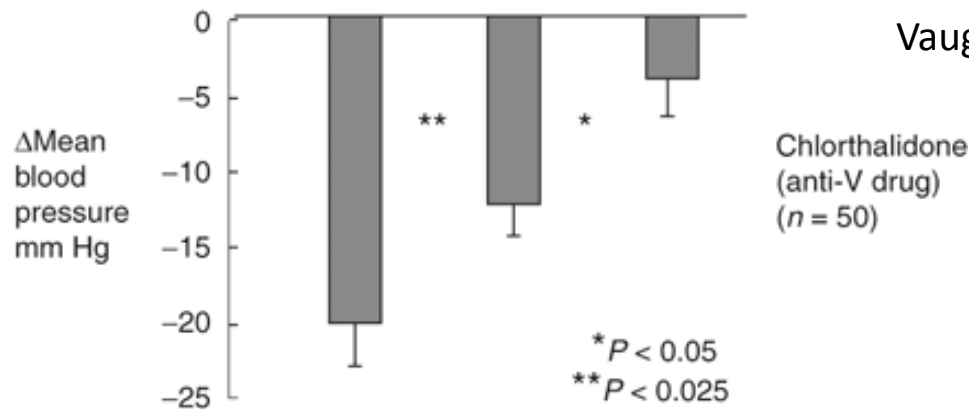
Patient PRA categories

Low renin V Medium renin R High renin R

Buhler ER, et al. *Am J Cardiol.* 32:511-522, 1973

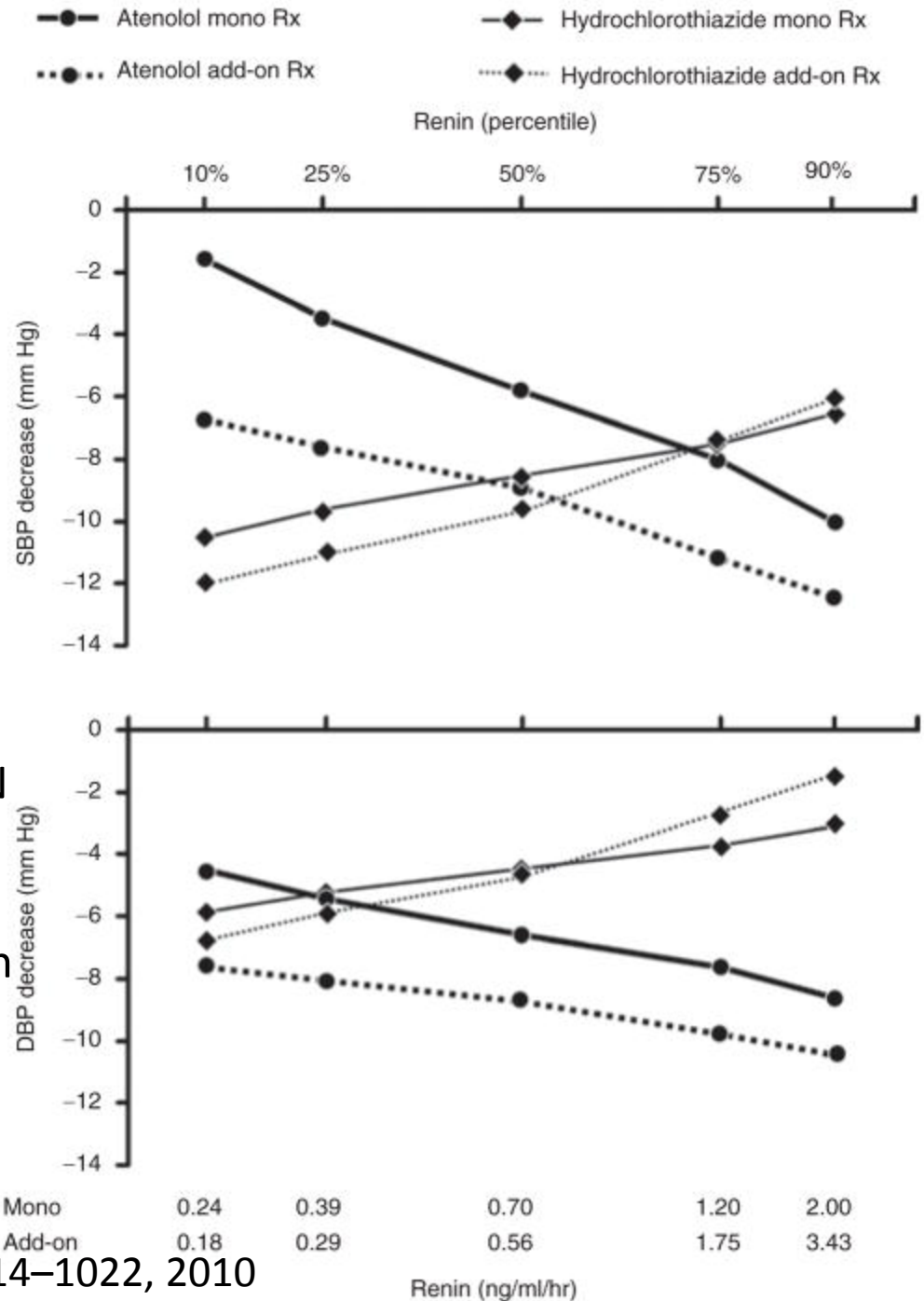


Vaughan ED, et al. *Am J Cardiol.* 32:523-532, 1973

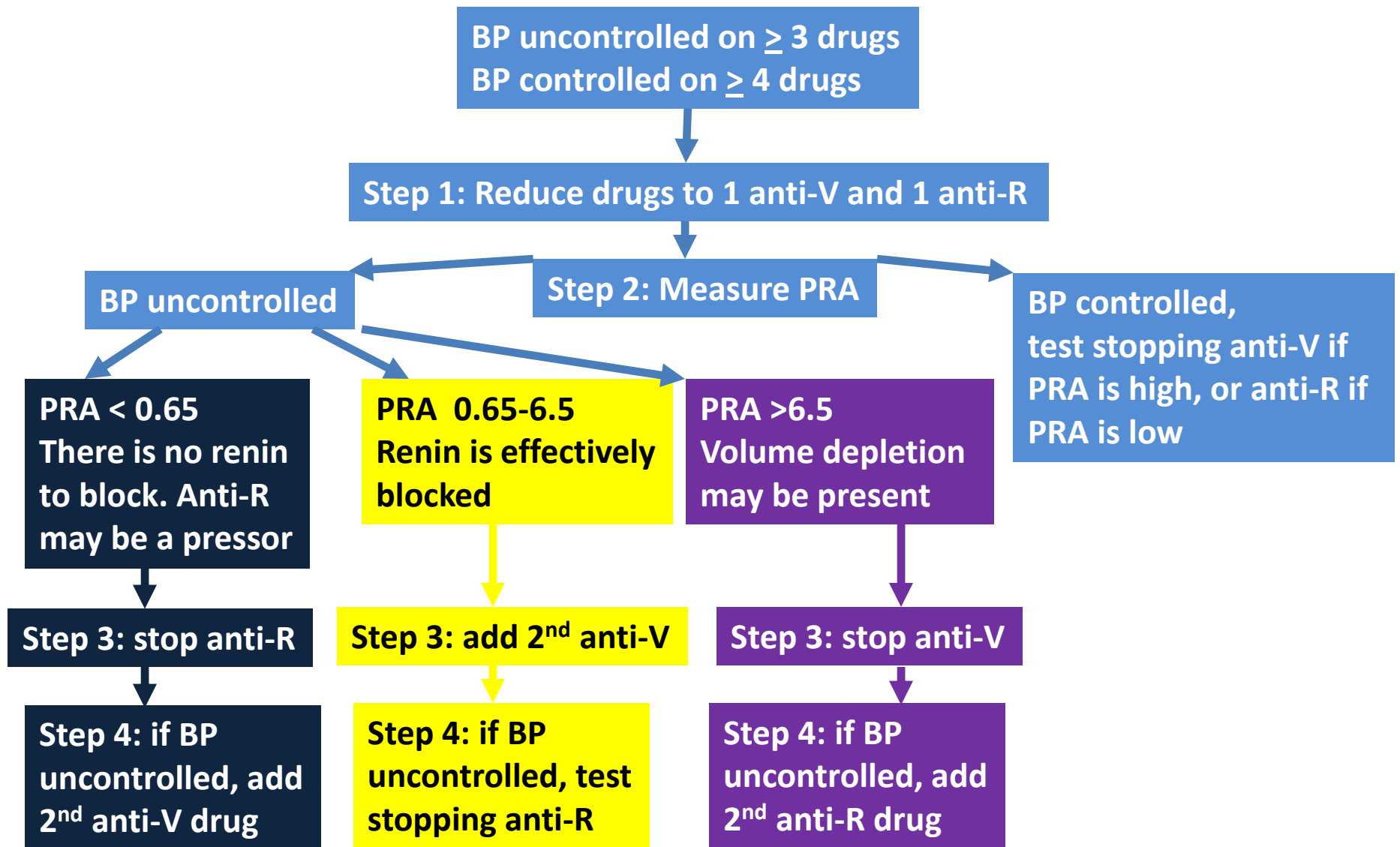


Plasma Renin Activity Predicts Blood Pressure Responses to β -Blocker and Thiazide Diuretic as Monotherapy and Add-On Therapy for Hypertension

- Randomized controlled trial
- 365 participants with stage I-II HTN
- Outcomes:
 1. Home BP averages before and after each drug administration
 2. Predictors of BP response such as age, race, PRA



PRA-guided treatment of resistant hypertension



Plasma Renin Test–Guided Drug Treatment Algorithm for Correcting Patients With Treated but Uncontrolled Hypertension: A Randomized Controlled Trial

Brent M. Egan¹, Jan N. Basile^{1,2}, Shakaib U. Rehman^{1,2}, Phillip B. Davis¹, Curt H. Grob III¹, Jessica Flynn Riehle³, Christine A. Walters³, Daniel T. Lackland^{1,3}, Carmen Merali^{4,6}, Jean E. Sealey⁵ and John H. Laragh⁴

Table 3 | BP and medication number at first and last visits and changes in BP and medication number between the baseline and last visits in RTGT and CHSC patients

	RTGT	CHSC	P value (between groups)
Baseline BP			
SBP, mm Hg	157.0 ± 2.6	153.2 ± 2.3	0.27
DBP, mm Hg	87.1 ± 2.0	91.1 ± 2.0	0.17
BP meds, <i>N</i>	3.1 ± 0.3	2.7 ± 0.2	0.21
Last visit BP			
SBP, mm Hg	127.9 ± 2.3*	134.0 ± 2.8*	0.10
DBP, mm Hg	73.1 ± 1.8*	79.8 ± 1.9*	0.01
BP meds, <i>N</i>	3.1 ± 0.2	3.0 ± 0.2	0.73
Change BP (last–baseline)			
SBP, mm Hg	–29.1 ± 3.2*	–19.2 ± 3.2*	0.03
DBP, mm Hg	–14.1 ± 1.9*	–11.3 ± 2.0*	0.32
BP meds, <i>N</i>	+0.0 ± 0.2	+0.3 ± 0.1	0.25

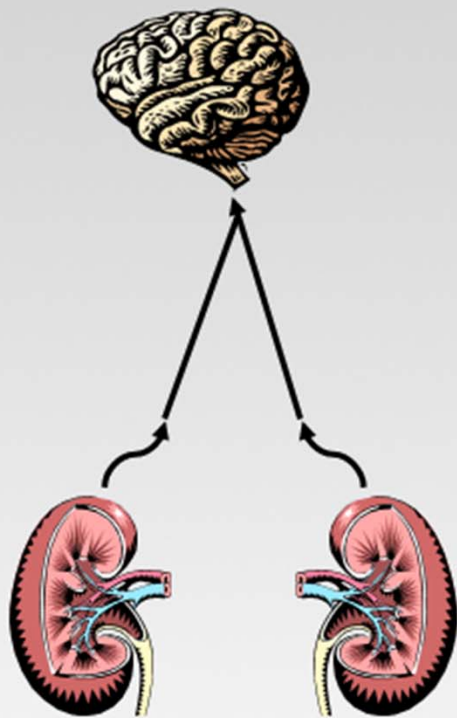
Values = mean ± s.e.m.

Device-Based treatments of Resistant Hypertension

- Renal sympathetic denervation
- Baroreflex sensitization (Carotid baroreceptor stimulation)

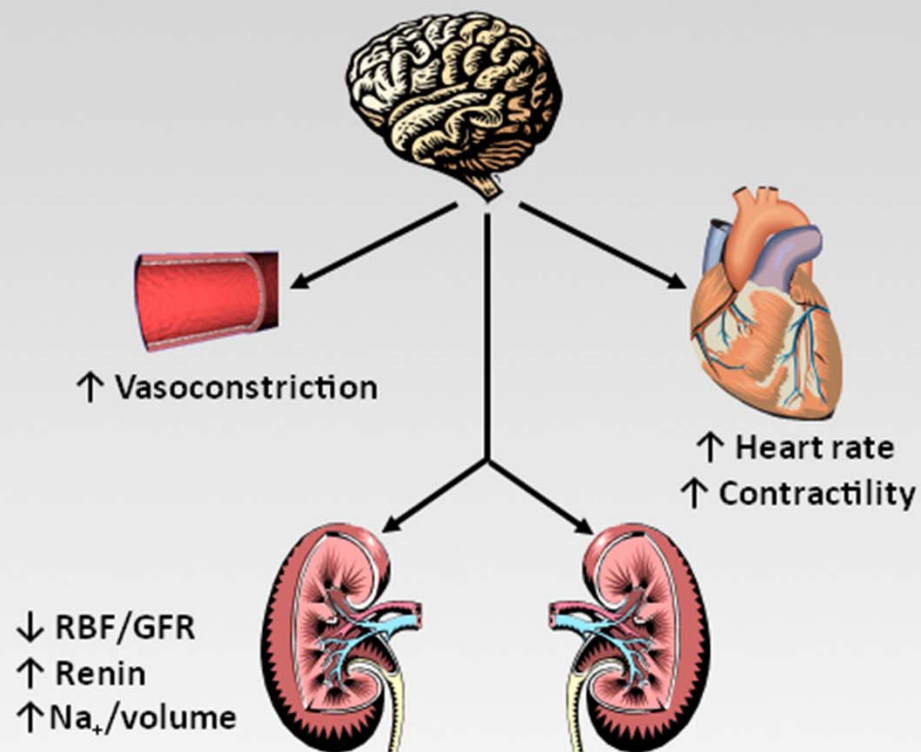
Renal Sympathetic Activation in Hypertension

Renal nerves and the SNS
Afferent renal sympathetics



The kidney is a source of central sympathetic drive in hypertension, heart failure, chronic kidney disease, and ESRD

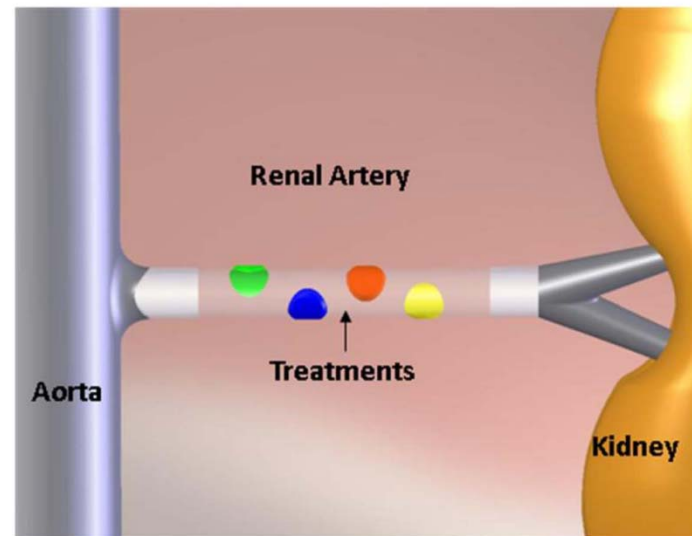
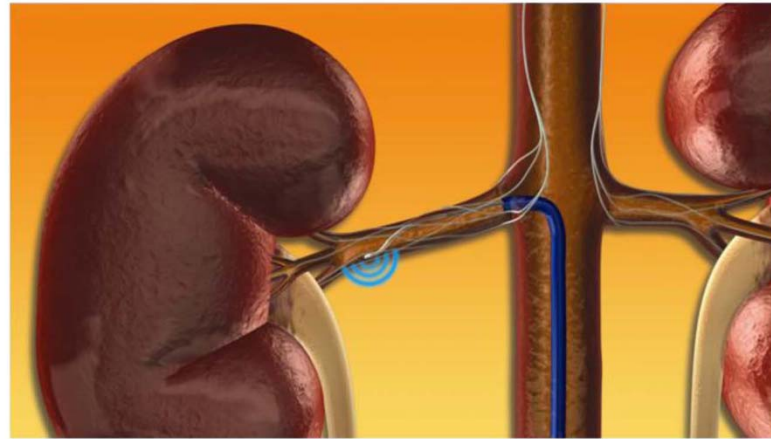
Renal nerves and the SNS
Efferent sympathetic activation



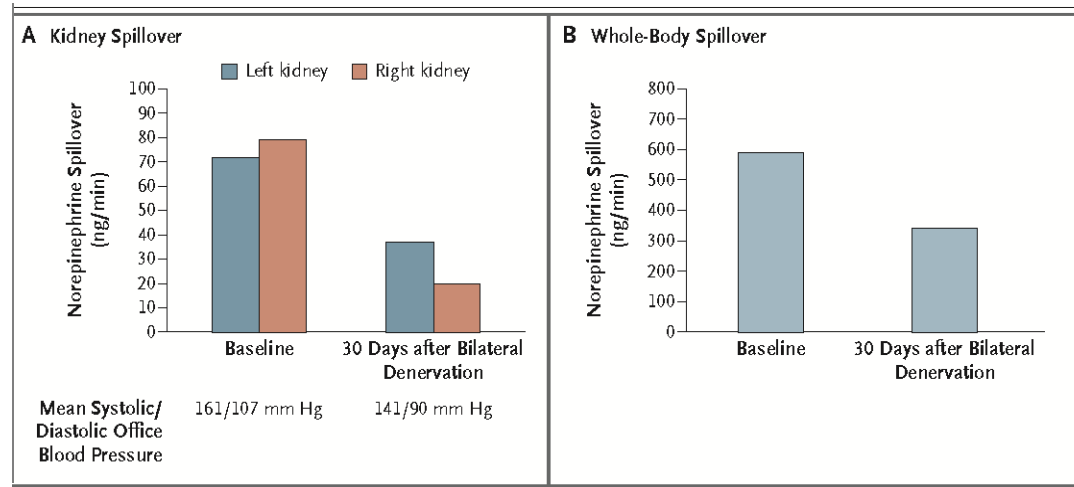
Patients cannot develop and/or maintain elevated blood pressure without renal involvement

ESRD = end-stage renal disease; GFR = glomerular filtration rate; RBF = renal blood flow; SNS = sympathetic nervous system

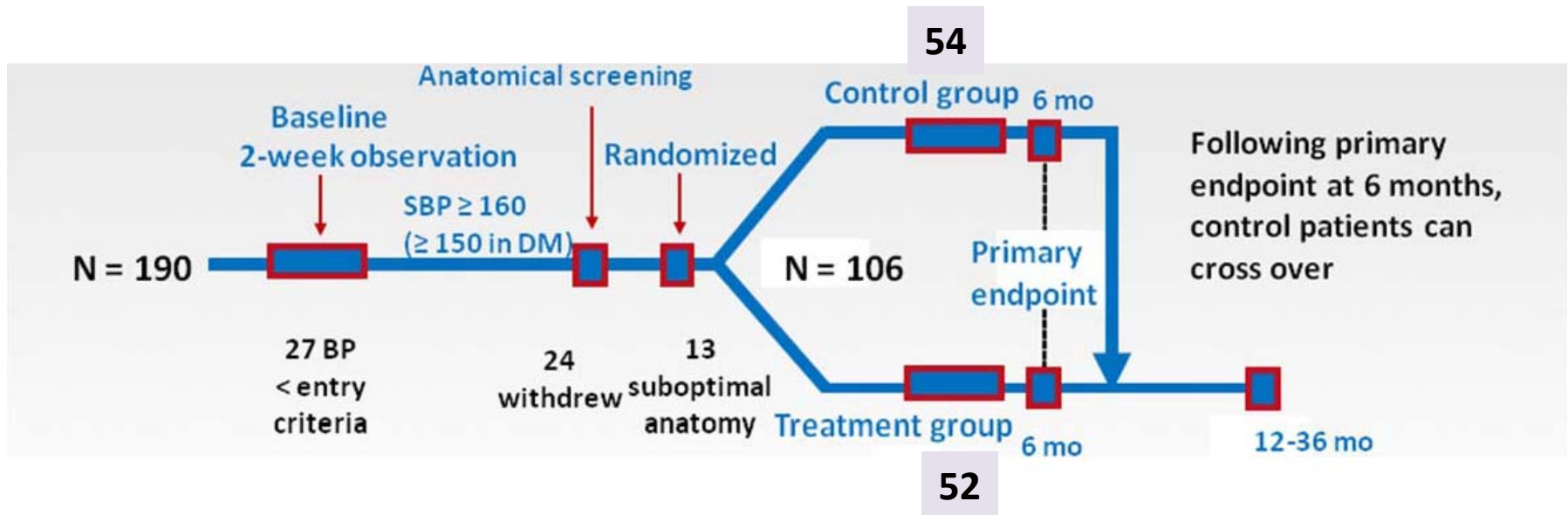
Schematic illustration of the percutaneous catheter-based denervation



Norepinephrine Spillover after Renal-Nerve Ablation



SIMPLICITY HTN-2 Study

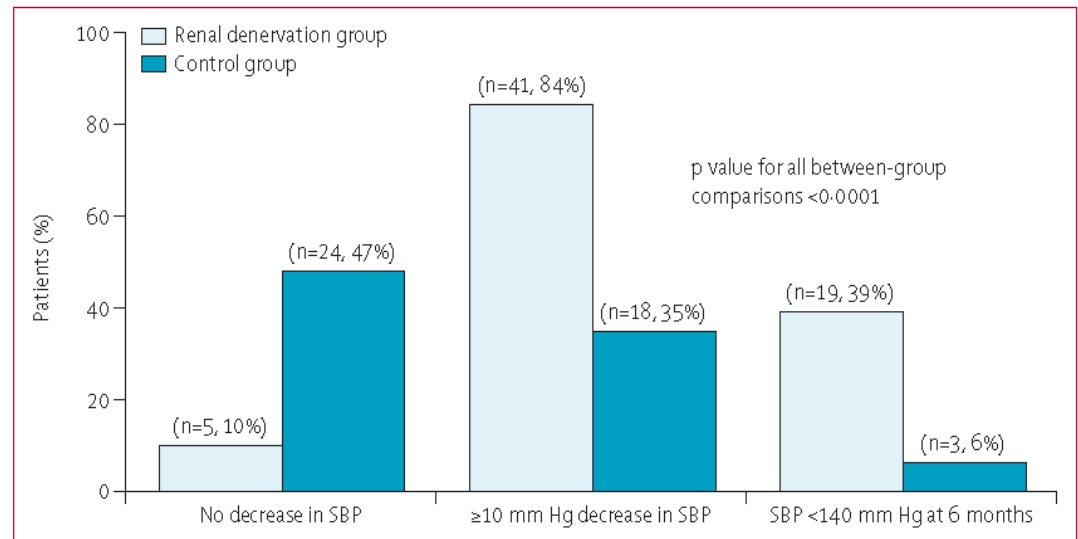
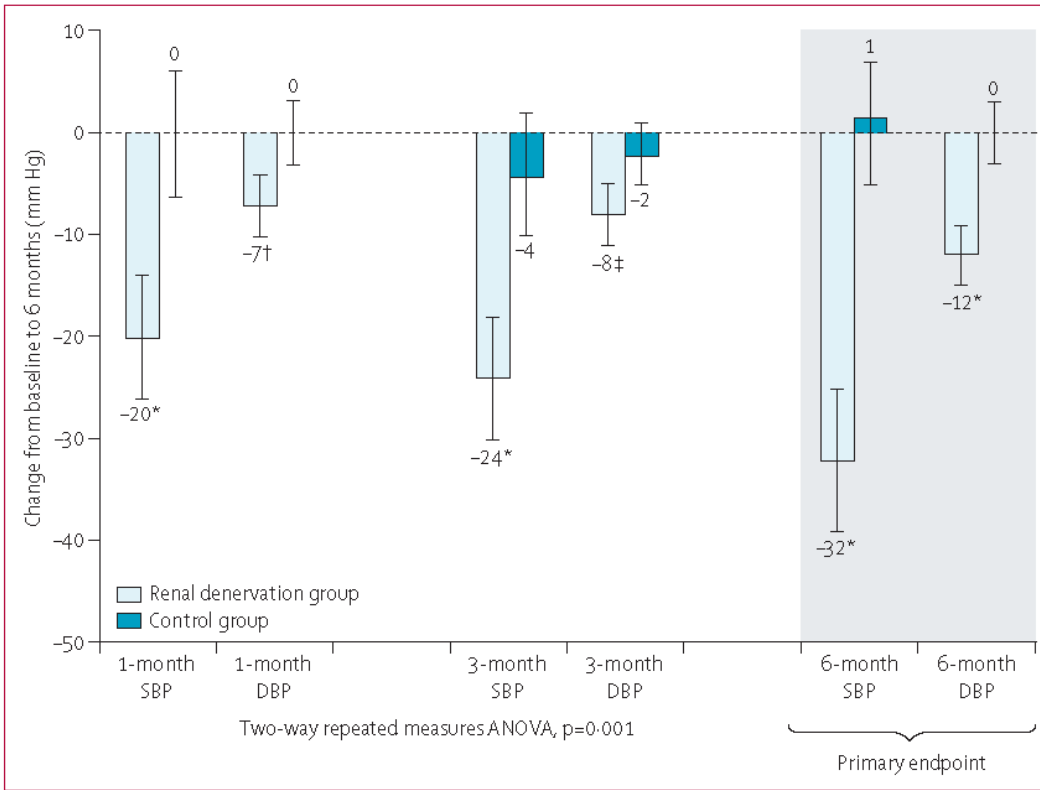


Primary end-point: change in office SBP after 6-months of follow up without changes in BP medications

SIMPLICITY HTN-2 Baseline Characteristics

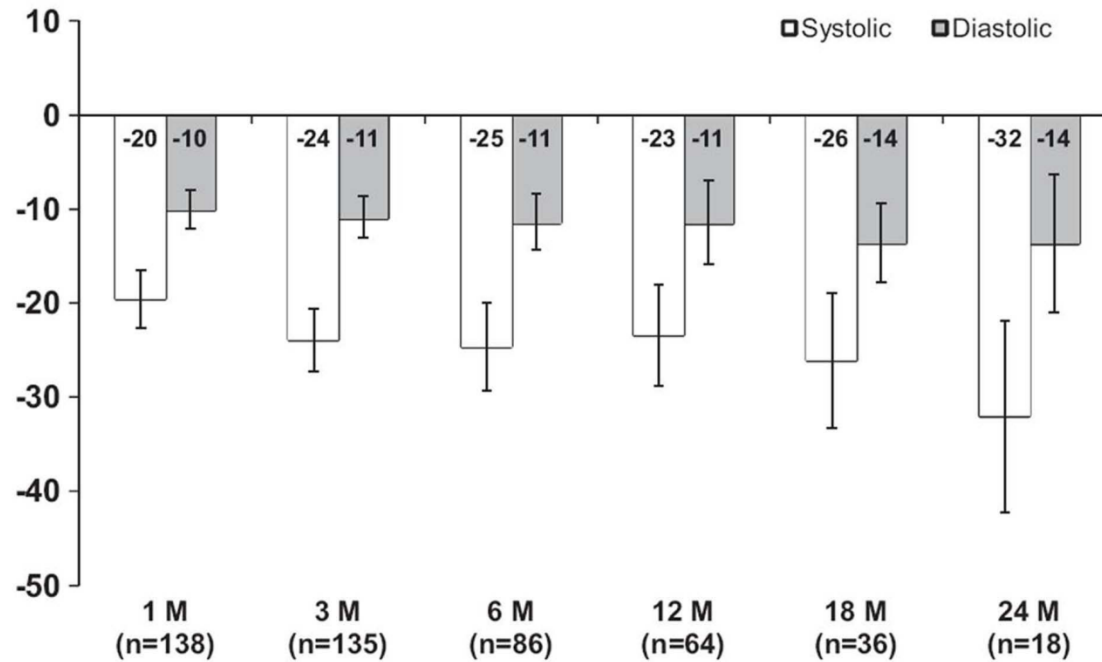
	Renal denervation group (n=52)	Control group (n=54)
Baseline systolic blood pressure (mm Hg)	178 (18)	178 (16)
Baseline diastolic blood pressure (mm Hg)	97 (16)	98 (17)
Age (years)	58 (12)	58 (12)
Sex (female)	18 (35%)	27 (50%)
Race (white)	51 (98%)	52 (96%)
Body-mass index (kg/m ²)	31 (5)	31 (5)
Type 2 diabetes	21 (40%)	15 (28%)
Coronary artery disease	10 (19%)	4 (7%)
Hypercholesterolaemia	27 (52%)	28 (52%)
eGFR* (mL/min per 1.73 m ²)	77 (19)	86 (20)
eGFR* 45–60 mL/min per 1.73 m ²	11 (21%)	6 (11%)
Serum creatinine (µmol/L)	91 (25)	78 (18)
Urine albumin-to-creatinine ratio (mg/g) [†]	128 (363)	109 (254)
Cystatin C (mg/L) [‡]	0.9 (0.2)	0.8 (0.2)
Heart rate (bpm)	75 (15)	71 (15)
Number of antihypertension medications	5.2 (1.5)	5.3 (1.8)
Patients on hypertension medication for more than 5 years	37 (71%)	42 (78%)
Patients on five or more medications	35 (67%)	31 (57%)
Patients receiving (drug class)		
ACE inhibitors/ARBs	50 (96%)	51 (94%)
Direct renin inhibitors	8 (15%)	10 (19%)
β blockers	43 (83%)	37 (69%)
Calcium-channel blockers	41 (79%)	45 (83%)
Diuretics	46 (89%)	49 (91%)
Aldosterone antagonist	9 (17%)	9 (17%)
Vasodilators	8 (15%)	9 (17%)
α-1 blockers	17 (33%)	10 (19%)
Centrally acting sympatholytics	27 (52%)	28 (52%)

SIMPLICITY HTN-2: Outcomes



Simplicity-2. Lancet. 376:1903-1909, 2010

Mean Systolic and diastolic BP changes from baseline after renal denervation with up to 2 yrs of follow up



Krum, H et al. *Hypertension* 57, 911–917.

Carotid Baroreceptor Stimulation

- This method uses a novel implantable device (Rheos System, CVRx, Inc., Minneapolis, Minnesota) that works by electrical stimulation of the carotid sinus
- A nonrandomized prospective study (n=45) to assess whether Rheos therapy could safely lower blood pressure in patients with resistant hypertension

	3 Months	1 Year	2 Years
Office blood pressure	n = 37	n = 26	n = 17
SBP, mm Hg	-21 ± 4 (p < 0.001)	-30 ± 6 (p < 0.001)	-33 ± 8 (p = 0.001)
DBP, mm Hg	-12 ± 2 (p < 0.001)	-20 ± 4 (p < 0.001)	-22 ± 6 (p = 0.002)
HR, beats/min	-8 ± 2 (p < 0.001)	-8 ± 2 (p = 0.001)	-11 ± 4 (p = 0.008)

1

2

3

4

5

6. Refer to
hypertension
specialist

Specialist in Clinical Hypertension

- Certification is offered by American Society of Hypertension
- 3 subspecialties qualify: Cardiology, Nephrology, and Endocrinology
- The specific purpose is to identify and recognize physicians with expert skills and knowledge in the management of clinical hypertension and related disorders.
- These physicians can act as local and regional consultants for the more complex and difficult cases and also assist in advice regarding guidelines and process improvement.
- Specialist Directory: www.ash-us.org

Specialist Referral

- Indications to referral:
 1. Refer to appropriate specialist for known or suspected secondary cause(s) of hypertension
 2. Refer to hypertension specialist if BP remains uncontrolled after 6 months of treatment
- Referral to hypertension specialist improves BP control in over 50% patients with resistant hypertension (Garg JP, et al. *Am J Hypertens.* 18:619–626, 2005).

Conclusions

- Uncontrolled HTN \neq Resistant HTN
- Exclusion of pseudoresistance, implementation of life-style interventions, and discontinuation of interfering substances are initial steps in approaching resistant HTN
- Work up for secondary causes of resistant hypertension should be reserved for patients with appropriate clinical clues
- Referral to hypertension specialists can help to improve BP control

CASE PRESENTATION

62 years-old female was referred to you for the evaluation and treatment of difficult to control HTN. **Her BP is >140/90 in PCP office for several times while taking daily HCTZ 25 mg, Lisinopril 40 mg, and Amlodipine 10 mg.** ROS is + for occasional headaches for which she takes “pain killers”. She works as a manager in a local grocery store. On exam, BMI 35 kg/m², HR 94, **BP 164/103.** +pitting edema in both ankles. Laboratory findings are significant for glucose 92 mg/dl, K 3.7 mmol/l, Cr 1.0 mg/dL.

What is the next most appropriate step in the management of patient`s hypertenaion?

- 1 Add metoprolol 50 mg bid
- 2 Measure 24-hr urine free cortisol
- 3 Measure morning aldosterone concentration and plasma renin activity
- 4 Measure fractionated plasma metanephrines
- 5 Review medication list including OTC meds, advise to reduce Na intake, encourage 5-7% weight loss and exercise 30 mins/day, encourage to take medications daily

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THANK YOU

QUESTIONS?

