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Resistant hypertension

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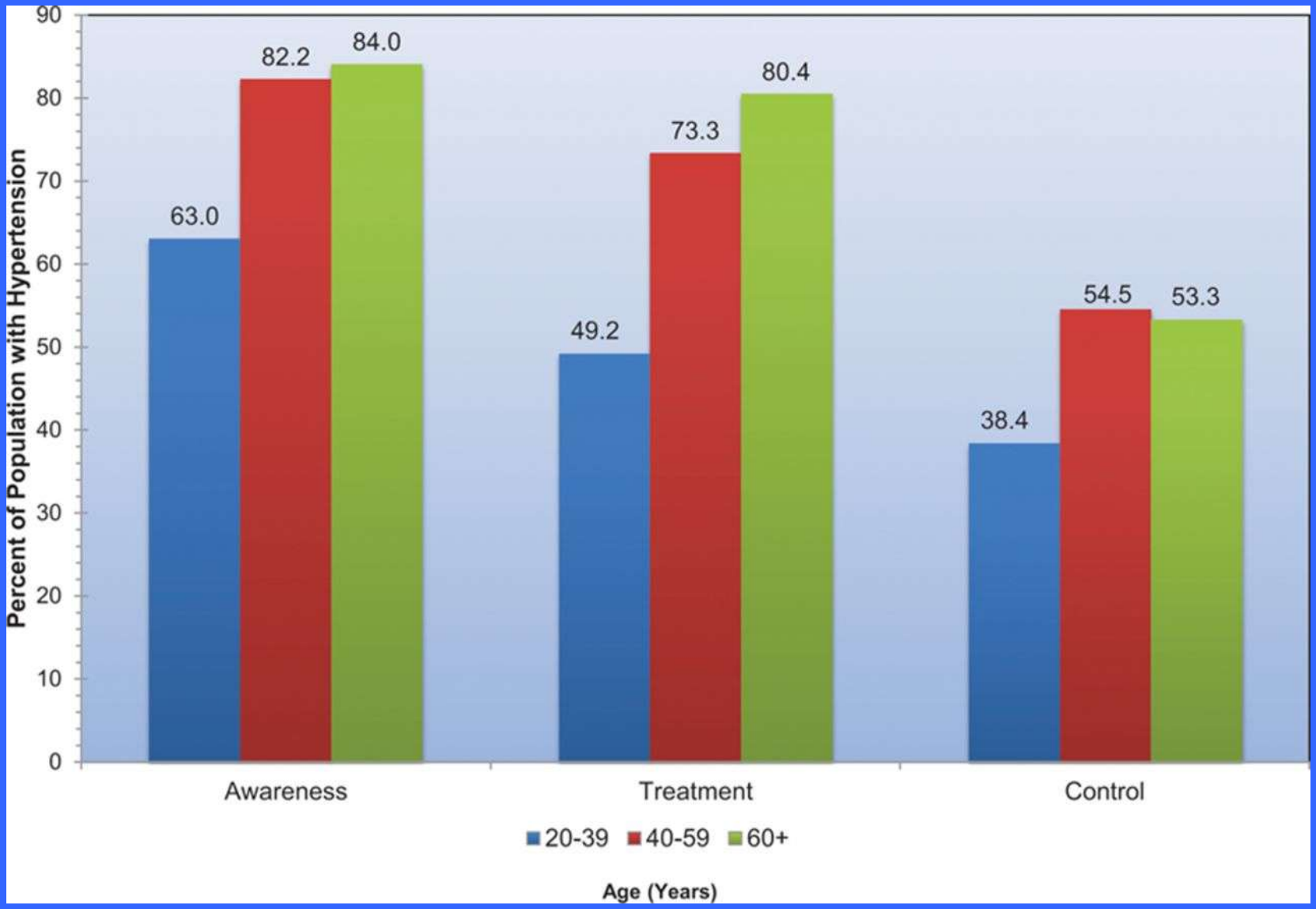
The first Vietnam Congress of Hypertension
Hue, Vietnam, May 2014

Extent of awareness, treatment, and control of high blood pressure by age (National Health and Nutrition Examination Survey: 2007–2010).



Go A et al. Circulation 2014;129:e28-e292

Resistant vs refractory hypertension

Resistant hypertension is hypertension that does not respond to adequate doses of 3 or more antihypertensive drugs.

It represents 10-15% of the general hypertensive population.

Refractory hypertension is defined as BP that remains uncontrolled after 3 visits to a hypertension clinic within a minimum 6-month follow-up period.

Secondary causes of hypertension, obesity, diabetes, sleep disordered breathing and excess salt intake or use of AINS drugs are among some of the findings associated with resistant or refractory hypertension.

Prevalence of resistant hypertension in the United States, 2003-2008 (average of 2 out 3 measures by a physician)

Table 1. Classification of Adults With Hypertension in the United States

Classification	No. of Participants	Among All Hypertensive Adults, % (SE)	Among Drug-Treated Hypertensive Adults, % (SE)
Uncontrolled, no drug treatment	1520	30.7 (1.2)	
Controlled hypertension, ≤3 drugs	2035	40.8 (1.1)	58.9 (1.2)
Uncontrolled hypertension, ≤2 drugs	1136	19.6 (0.8)	28.3 (1.1)
Resistant hypertension, uncontrolled, ≥3 drugs or controlled ≥4 drugs	539	8.9 (0.6)	12.8 (0.9)

Uncontrolled indicates a mean systolic pressure of ≥140 or diastolic ≥90 mm Hg.

Persell SD. Hypertension 2011; 57: 1076-1080.

Clinical features of 8295 patients with resistant hypertension classified on the basis of ABPM

- Prevalence of resistant hypertension in the Spanish ABPM registry
- Resistance defined by BP in office ≥140/90 mmHg and ≥ 3 antihypertensive drugs

- 12.2% of 68,045
- After ABPM: 62.5% were true resistant ≥130/80 mmHg
- After ABPM :55.9% ≥135/85 mmHg

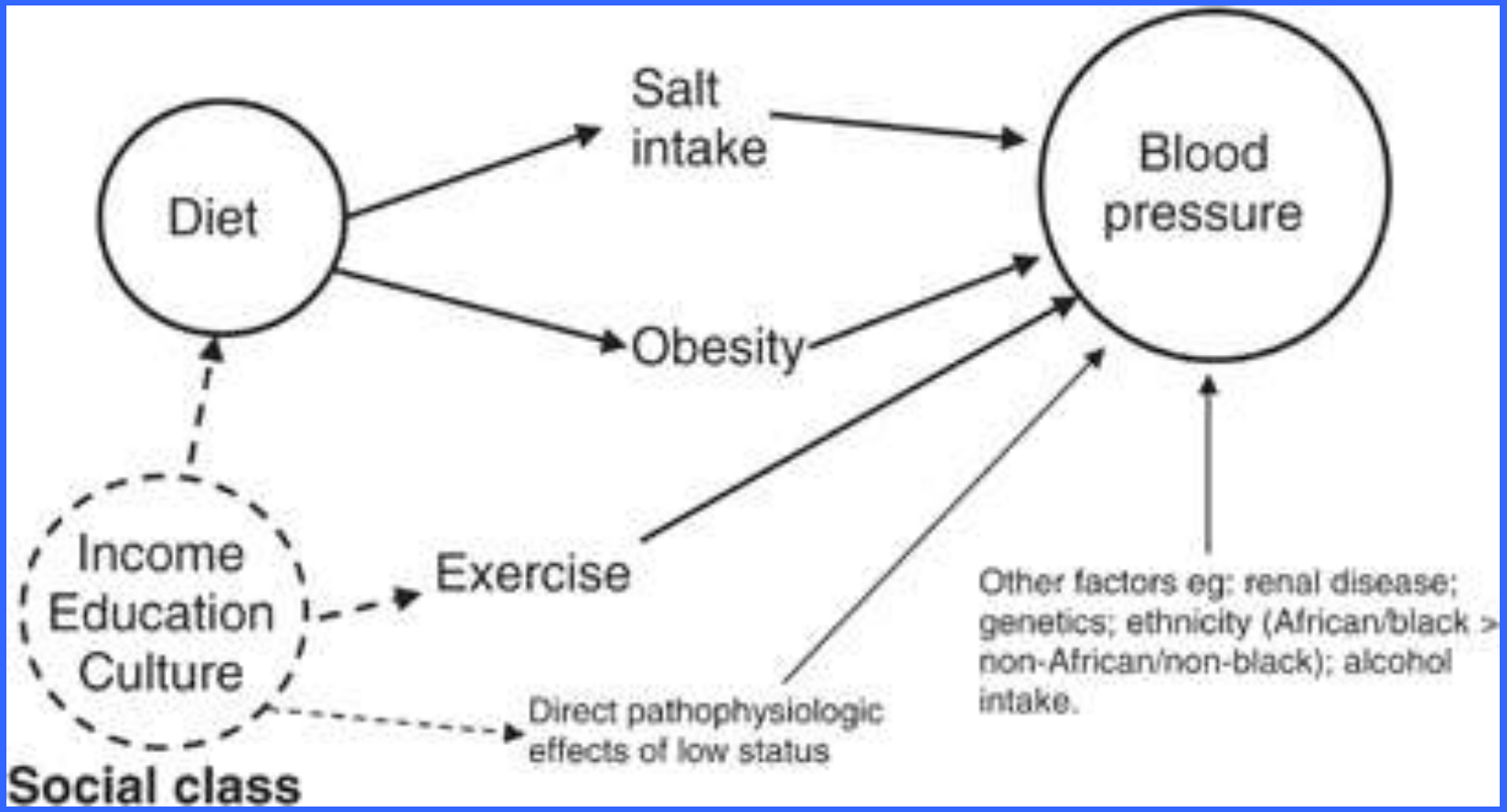
- Selected population

Table 1. Patient Characteristics Associated With Resistant Hypertension

Older age
High baseline blood pressure
Obesity
Excessive dietary salt ingestion
Chronic kidney disease
Diabetes
Left ventricular hypertrophy
Black race
Female sex
Residence in southeastern United States

Calhoun DA et al. Hypertension 2008

Epidemiology and pathophysiology of hypertension in East Asia



The epidemiology of blood pressure in East Asia
W Harrison and T Marshall, *Journal of Human Hypertension* (2006) **20,** 97–99

Comparison Between Western and East Asian Studies According to the Lifestyle in the Hypertension Guidelines

Lifestyle Modification	Epidemiological Findings	Comparison Between Westerners and East Asians
Salt restriction	Reduced salt intake is related to decreasing BP.	Salt intake: Westerners<East Asians Salt sensitivity: Westerners<<East Asians
High consumption of vegetables and fruits	Diets higher in vegetables and fruits may reduce the risk of developing HT.	
Increased intake of fish, reduced content of saturated/total fat, and other type of diet		
Fish	Fish (n-3 PUFA) is a weak but significantly inversely associated with BP.	Westerners, Chinese<Japanese
Soy*	Soy intake reduces risk of CVD and may reduce BP. However, more evidence needs to accumulate.	Westerners, Chinese<Japanese
The DASH diet*†	Salt reduction lowered systolic and diastolic BP.	
The Mediterranean diet*	The Mediterranean diet associated with moderate but significant reduction of systolic and diastolic BP.	
Appropriate weight control	Obesity and overweight are risk factors for CVD and HT.	Obesity: Westerners>>East Asians
Regular physical exercise	Physical inactivity is a risk factor of HT.	
Moderate alcohol consumption	Excessive drinking is a risk factor for increased BP.	Drinking rate: Westerners<Japanese (men), Westerners>East Asians (women) ALDH deficient: Westerners<<East Asians
Quitting smoking		Smoking rate: Westerners<East Asians Population-attributable fraction for CVD: Westerners<East Asians (men)

Kokubo Y. Hypertension 2014; 63: 655-660

Table 2. Medications That Can Interfere With Blood Pressure Control

Nonnarcotic analgesics
Nonsteroidal antiinflammatory agents, including aspirin
Selective COX-2 inhibitors
Sympathomimetic agents (decongestants, diet pills, cocaine)
Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil)
Alcohol
Oral contraceptives
Cyclosporine
Erythropoietin
Natural licorice
Herbal compounds (ephedra or ma huang)

Calhoun DA et al. Hypertension 2008

Table 3. Secondary Causes of Resistant Hypertension

Common
Obstructive sleep apnea
Renal parenchymal disease
Primary aldosteronism
Renal artery stenosis
Uncommon
Pheochromocytoma
Cushing's disease
Hyperparathyroidism
Aortic coarctation
Intracranial tumor

Calhoun DA et al. Hypertension 2008

Confirm Treatment Resistance

Office blood pressure >140/90 or 130/80 mm Hg in patients with diabetes or chronic kidney disease

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

↓

Exclude Pseudoresistance

Is patient adherent with prescribed regimen?

Obtain home, work, or ambulatory blood pressure readings to exclude white coat effect

↓

Identify and Reverse Contributing Lifestyle Factors

Obesity

Physical inactivity

Excessive alcohol ingestion

High salt, low fiber diet

↓

Discontinue or Minimize Interfering Substances

Non-steroidal anti-inflammatory agents

Sympathomimetics (diet pills, decongestants)

Stimulants

Oral contraceptives

Licorice

Ephedra

↓

Screen for Secondary Causes of Hypertension

Obstructive sleep apnea (snoring, witnessed apnea, excessive daytime sleepiness)

Primary aldosteronism (elevated aldosterone/renin ratio)

Chronic kidney disease (creatinine clearance <30 ml/min)

Renal artery stenosis (young female, known atherosclerotic disease, worsening renal function)

Pheochromocytoma (episodic hypertension, palpitations, diaphoresis, head ache)

Cushing's syndrome (moon facies, central obesity, abdominal striae, inter-scapular fat deposition)

Aortic coarctation (differential in brachial or femoral pulses, systolic bruit)

↓

Pharmacologic Treatment

Maximize diuretic therapy, including possible addition of mineralocorticoid receptor antagonist

Combine agents with different mechanisms of action

Use of loop diuretics in patients with chronic kidney disease and/or patients receiving potent vasodilators (e.g., minoxidil)

↓

Refer to Specialist

Refer to appropriate specialist for known or suspected secondary cause(s) of hypertension

Refer to hypertension specialist if blood pressure remains uncontrolled after 6 months of treatment

Calhoun DA et al. Hypertension 2008

Resistant hypertension

- 1- Confirm BP measurement
- 2- Identify life style characteristics
- 3- Identify hypertensive medications and drugs
- 4- Evaluate non-adherence to medications
- 5- Screen for secondary causes of hypertension
- 6- Adjust anti-hypertensive medication
- 7- Referral to specialties

How to approach resistant hypertension

The general treatment approach:

1.adding or titrating diuretic therapy,

2.changing the diuretic class to one appropriate for the patient's kidney function,

3.using medications with complementary mechanisms of action, and

4.adding a mineralocorticoid antagonist to the antihypertensive drug regimen.

How to approach resistant hypertension

1. RAS blocker + diuretic + CCB + MR antagonist with or without a beta-blocker
2. Thiazide diuretics: chlorthalidone @ 25 mg⁄ d, preferred for most patients.
3. CKD: loop diuretic, most commonly furosemide at 20 mg to 40 mg twice daily.
4. Vasodilators, centrally acting antihypertensive agents, and alpha-adrenergic blockers added if failure to control BP.

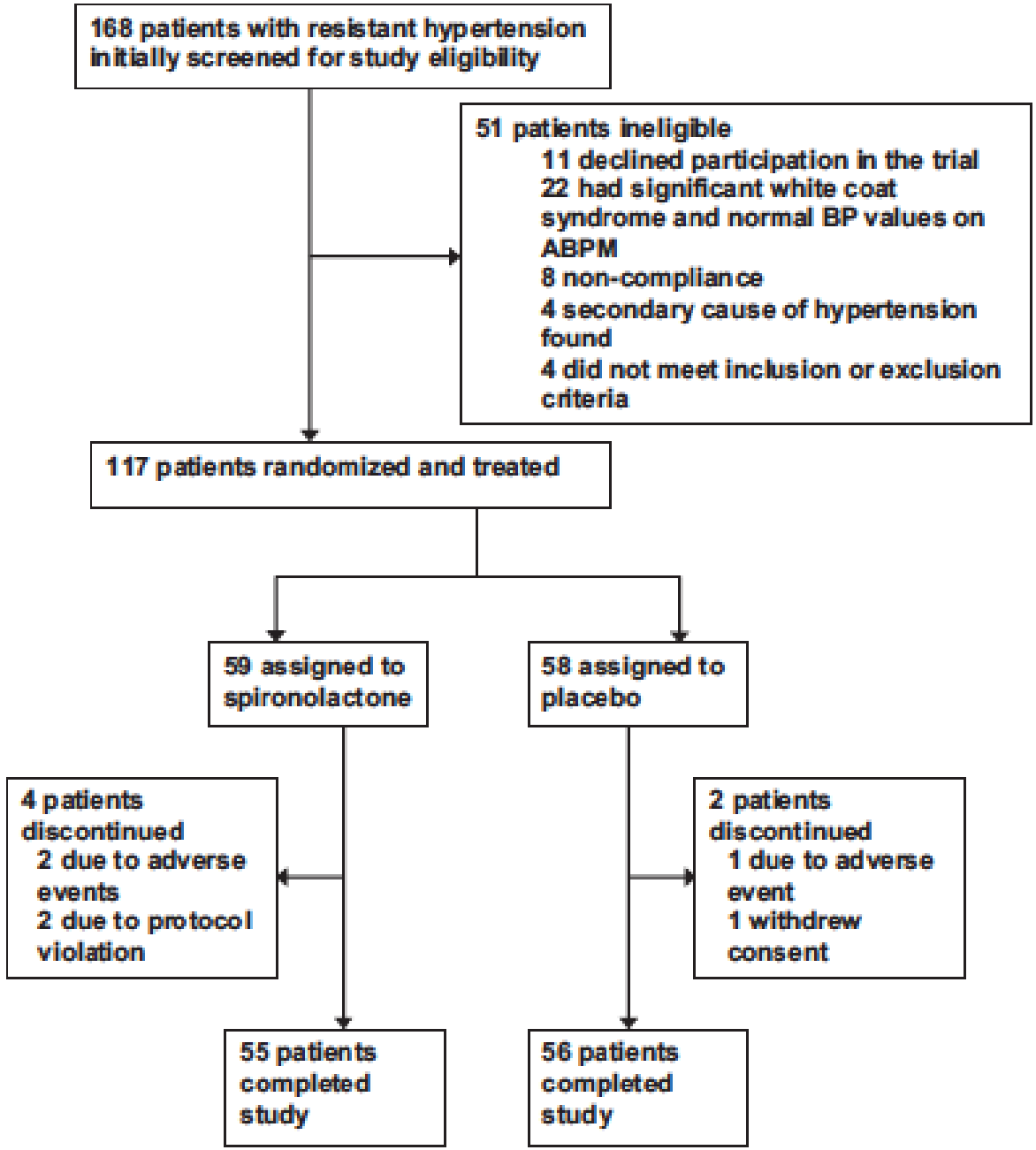
How to approach resistant HTN

- Adherence needs to be assessed by asking the patient about medication use, perceptions about medication efficacy, and presence of adverse effects, if any.
- Patients must be seen every 4 to 8 weeks, with more frequent visits for patients with uncontrolled BP.

Resistant HTN treatment

- Use of a MR antagonist in addition to a diuretic, particularly chlorthalidone, in addition to a full dose of a RAS blocker and a CCB is usually associated with control rates of resistant hypertension >80%.

Spironolactone in Patients With Resistant Arterial Hypertension (ASPIRANT)



Václavík J et al.
***Hypertension*.**
2011;57:1069-1075.

Spironolactone in Resistant Hypertension

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
Other Characteristics				
Weight, kg	0.3 (±1.6)	0.5 (±2.6)	−0.2 (−1.0; 0.6)	0.772
Serum Na, mmol/L	−1 (−6; 3)	−1 (−5; 4)	0.0	0.135
Serum K, mmol/L	0.3 (−0.5; 1.5)	0.0 (−0.8; 0.6)	0.3	<0.001
Serum creatinine, μmol/L	7 (−11; 22)	0 (−11; 18)	7.0	<0.001
Microalbuminuria, mg/day	−4.4 (−257.0;11.0)	0.0 (−87.0; 98.0)	−4.4	0.023
Proteinuria, g/day	0.0 (−0.5; 0.1)	0.0 (−0.3; 1.7)	0.0	0.221

Václavík J et al. *Hypertension*. 2011;57:1069-1075.

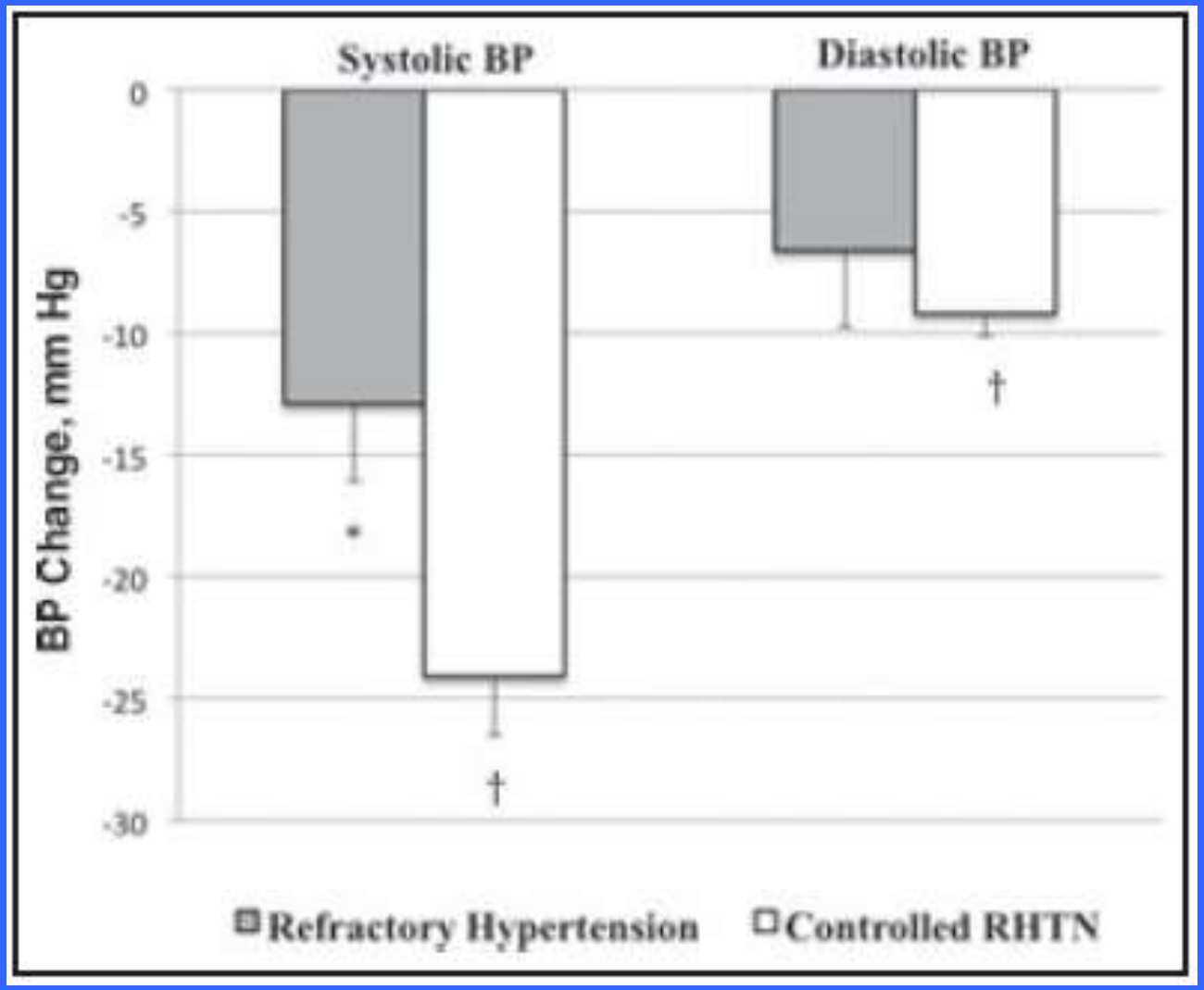
Refractory hypertension

TABLE III. Baseline Biochemical Characteristics in Patients With Refractory and Controlled Resistant Hypertension

Parameter	Refractory Hypertension (n=29)	Controlled RHTN (n=275)	*P* Value
Creatinine, mmol/L	97.2±26.5	88.4±26.5	.89
Plasma aldosterone, pmol/L	379.5±268.7	351.8±246.5	.57
PRA, pmol/L/min	53.8±230.4	49.92±120.3	.93
24-Hour urine aldosterone, nmol/d	37.9±27.4	35.7±29.1	.67
24-Hour urine sodium, mmol/d	173.1±80.9	186.5±89.5	.46

Acelajado MC et al. J Clin Hypert 2012;14:7–12

Response to MR antagonist



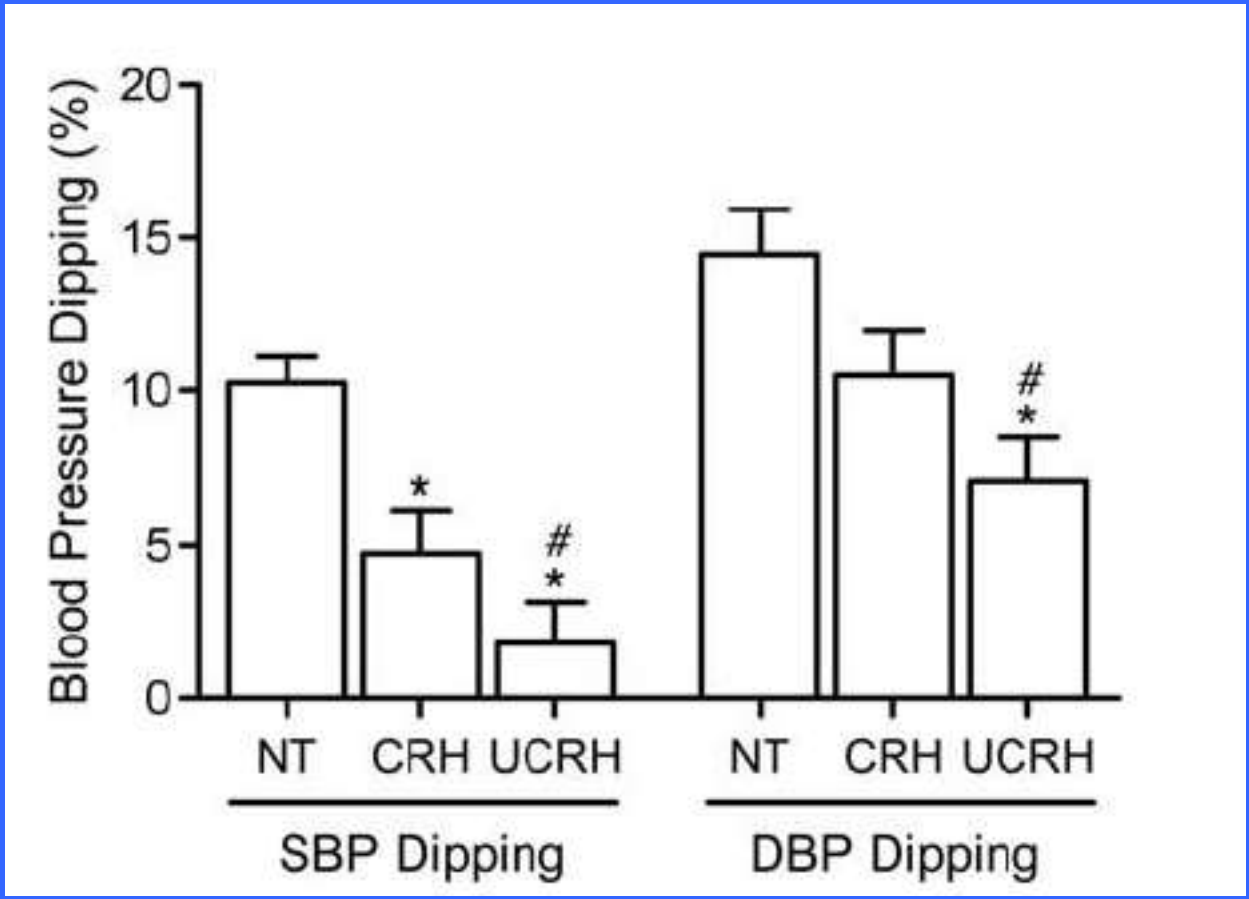
Acelajado MC et al. J Clin Hypert 2012;14:7–12

Refractory hypertension: mechanisms

- No evidence of greater fluid retention in refractory HTN vs controlled resistant HTN since aldosterone or PRA levels not suppressed
- Greater role of increased cardiac output and / or vascular resistance: enhanced sympathetic drive and / or increased peripheral resistance secondary to local or circulating pressor agents?

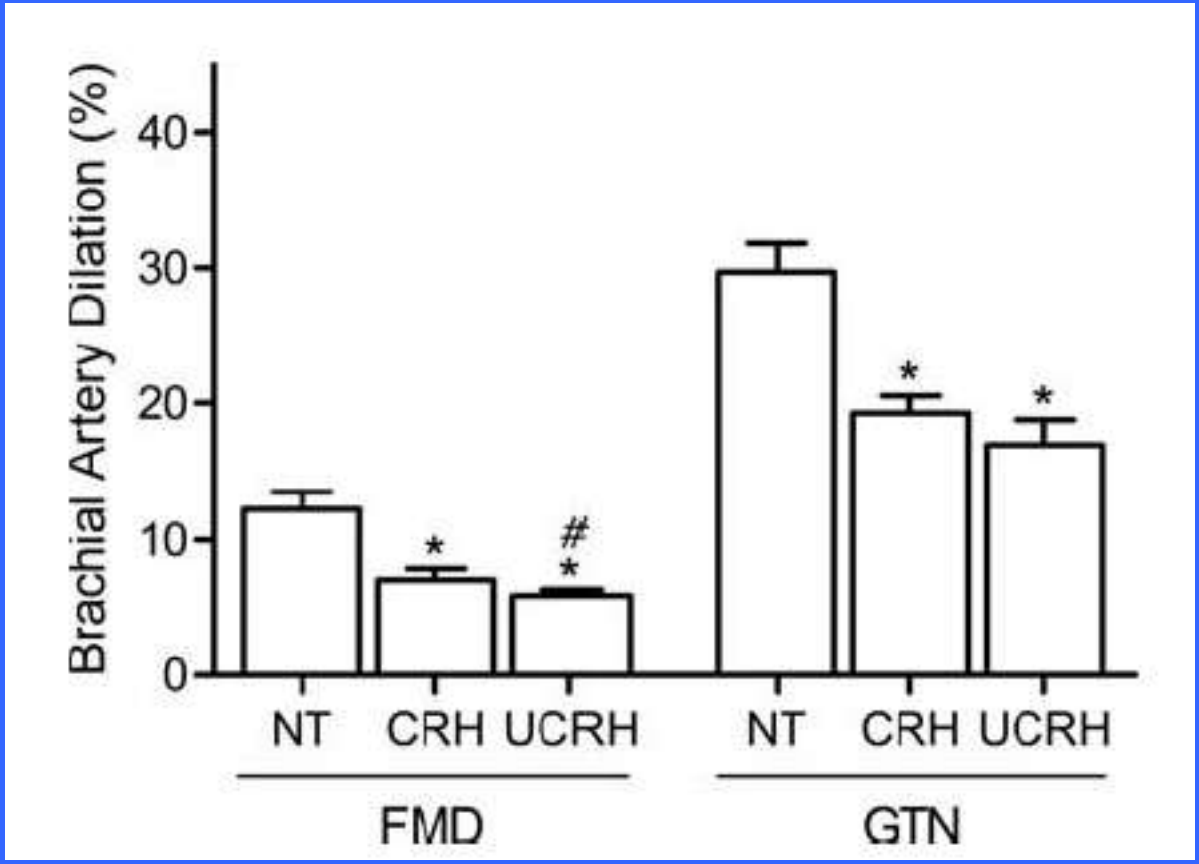
Acelajado MC et al. J Clin Hypert 2012;14:7–12

Non dipping pattern in resistant hypertension



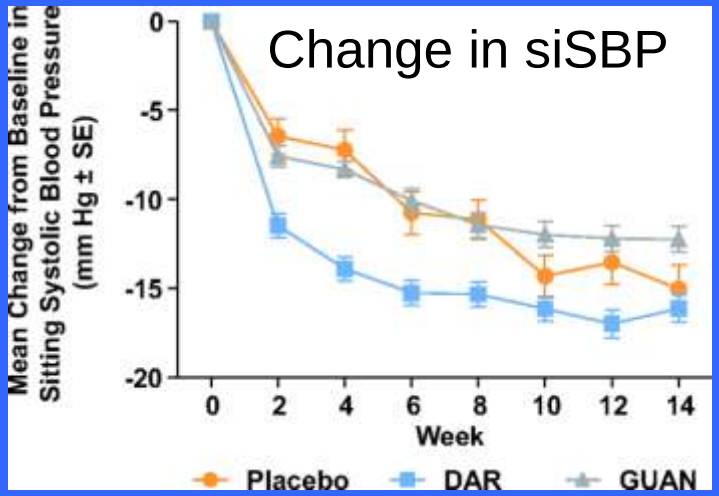
Quinaglia T et al. Journal of Human Hypertension doi:10.1038/jhh.2011.43

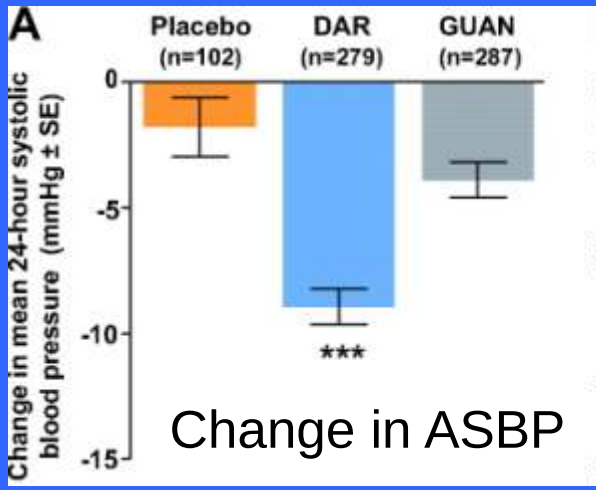
Endothelial dysfunction in resistant hypertension

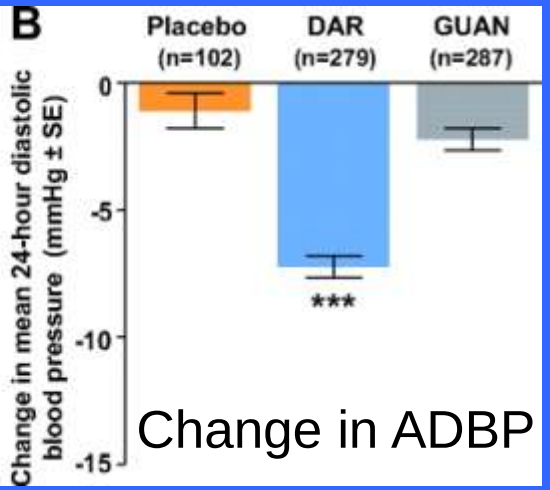


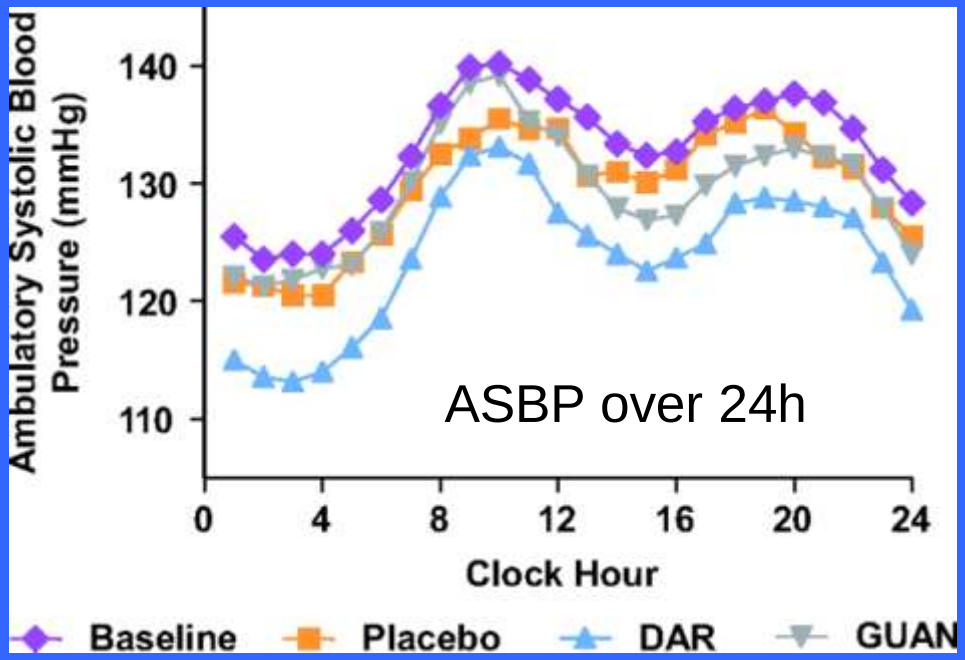
Quinaglia T et al. Journal of Human Hypertension doi:10.1038/jhh.2011.43

BP response to treatment with ET_A antagonist compared to guanfacine









Bakris G L et al. Hypertension 2010;56:824-830.

New approaches to refractory HTN

- Catheter-Based Radiofrequency Renal Sympathetic Denervation
- Baroreceptor stimulation

Symplicity HTN-2 Trial

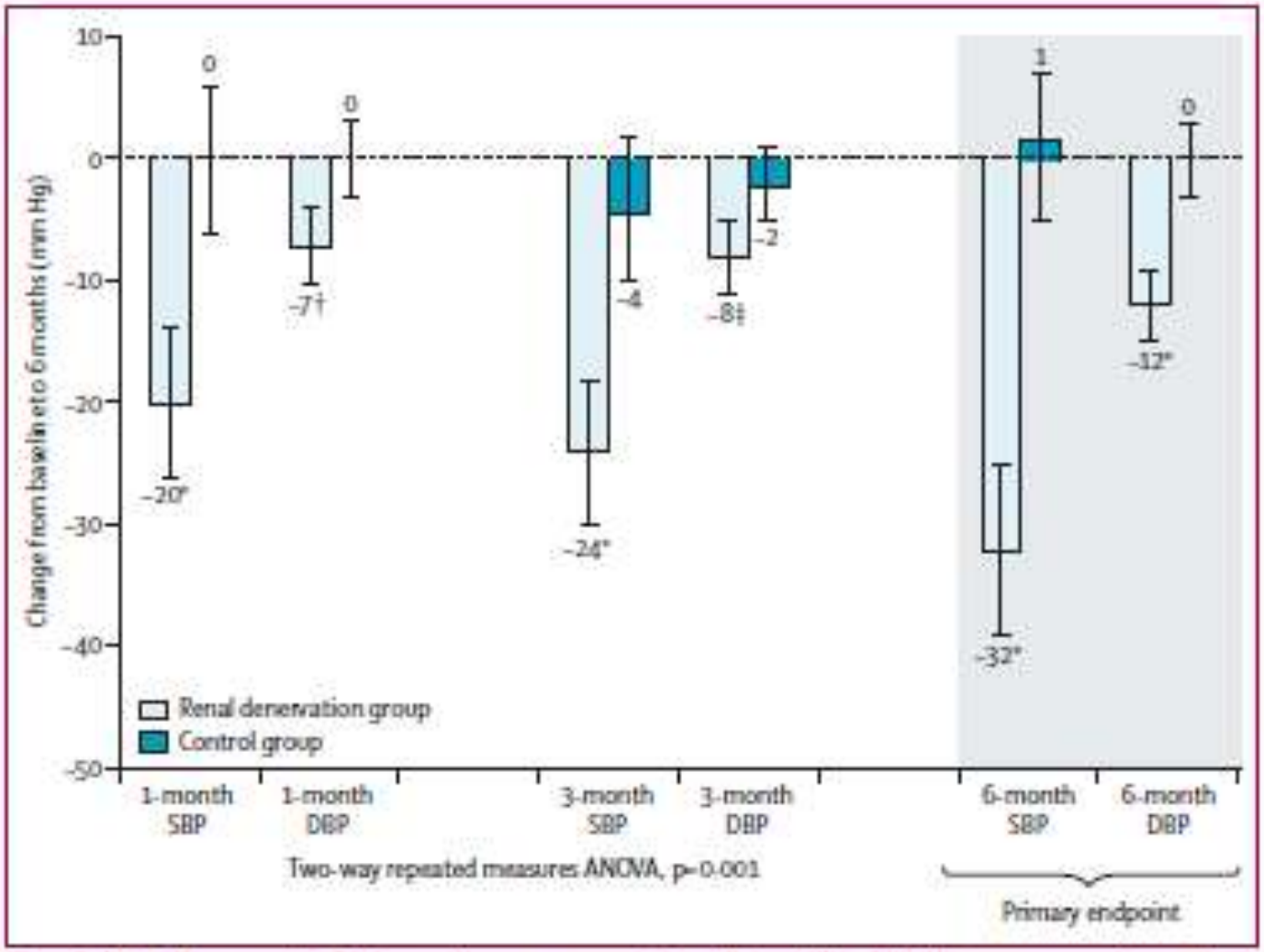


Figure 2: Paired changes in office-based measurements of systolic and diastolic blood pressures at 1 month, 3 months, and 6 months for renal denervation and control groups

Error bars are 95% CI. Multivariable stepwise regression analysis of baseline characteristics, drugs, and treatment assignment was examined for predictors of increased 6-month systolic-blood-pressure response; only variables with p<0·15 on univariate screening were entered into the model with variables with p<0·05 remaining in the final model. Multivariable analysis of baseline characteristics showed that assignment to the renal denervation group (p<0·0001), higher baseline systolic blood pressure (p<0·0001), and slower heart rate (p<0·004) predicted increased 6-month blood-pressure reduction. SBP=systolic blood pressure. DBP=diastolic blood pressure.
*p<0·0001. †p=0·002. ‡p=0·005.

The Lancet 2010;376: 1903-1909

Symplicity HTN-1 Investigators

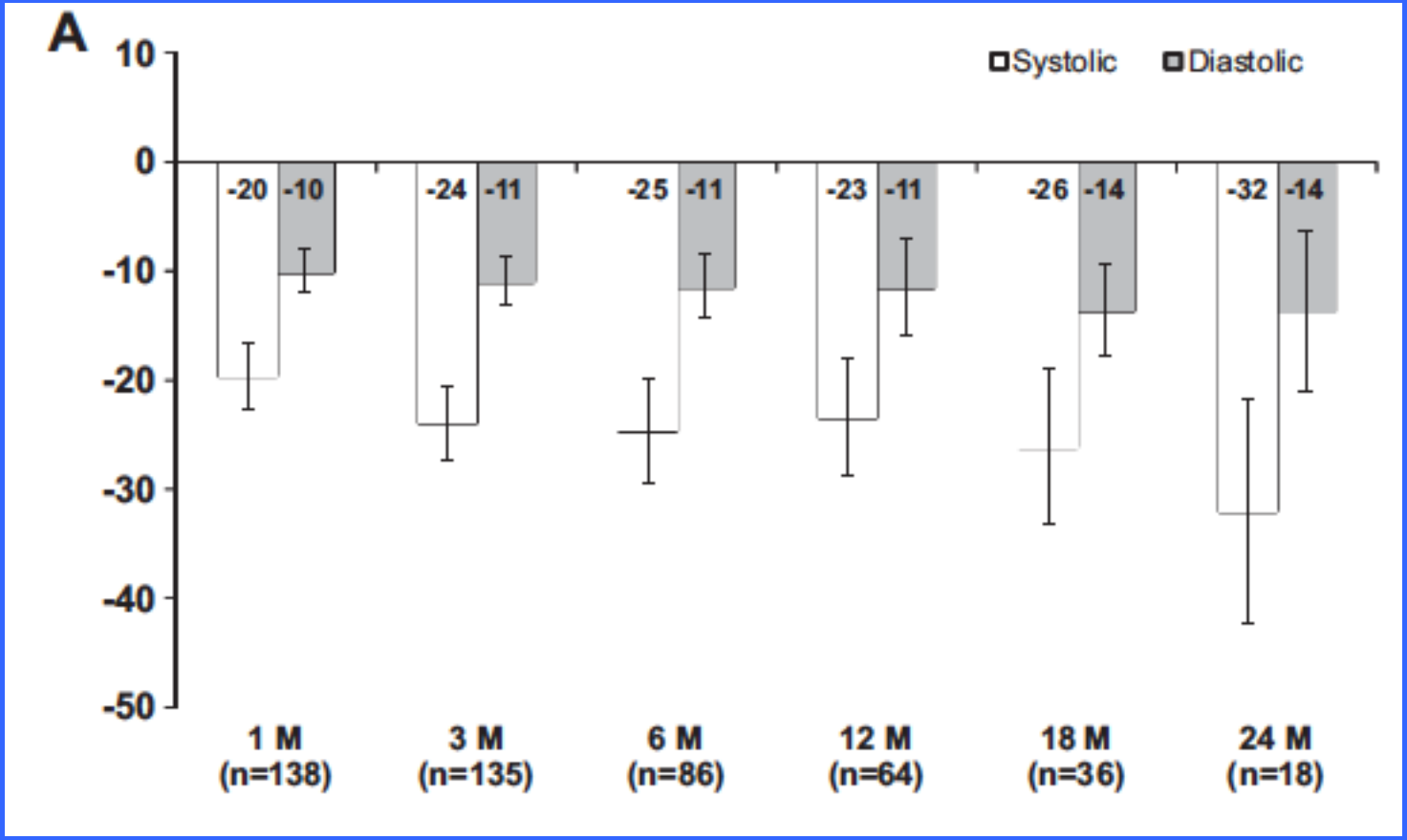
Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension:

Durability of Blood Pressure Reduction Out to 24 Months

153 patients with catheter-based renal sympathetic denervation at 19 centers

Hypertension. 2011;57:911-917.

BP changes after renal sympathetic denervation over 24-months of follow-up

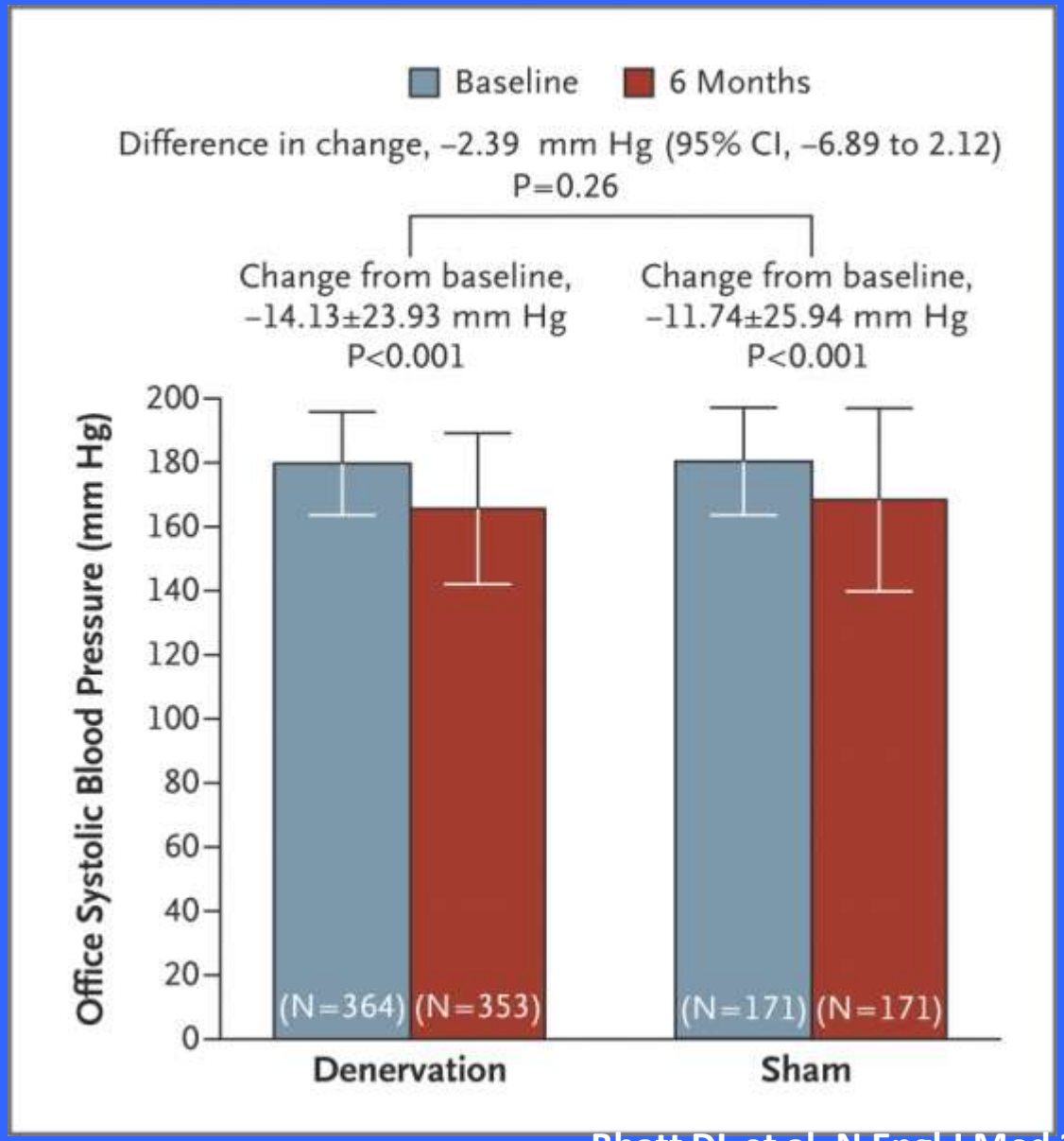


Krum H. et al. *Hypertension*. 2011;57:911-917.

Ongoing and future randomized trials of RDN

Simplicity HTN-3	DEPART	ReSET	MIRT	DENER-HTN	PRAGUE-15	INSPIRED
Simplicity	Simplicity	Simplicity	THERMOCOOL	Simplicity	Simplicity	TBD
530 pts	120 pts	70 pts	150 pts	120 pts	150 pts	230 pts
2013	2014	2012	2012	2014	2013	2015
USA	Belgium	Denmark	Russia	France	Czech Rep.	Europe

Simplicity HTN-3 Trial: Primary Efficacy End Point



Bhatt DL et al. N Engl J Med 2014;370:1393-1401

Requirements for renal denervation in resistant hypertension

Characteristic	Specifications
Experience	Management of resistant hypertension High volume interventional cardiology/radiology
Protocol	Written protocols for diagnostic work-up, procedure and follow-u[Written informed consent Ethics approval Plans for management of complications
Infrastructure	High quality CT/MRI Hemodynamic laboratory
Multidisciplinary team	Hypertension specialists with experience in managing resistant hypertension and interventional cardiologists/radiologists with experience in the denervation procedure Access to Nephrology and Vascular Surgery

Joint UK Societies Consensus on Renal Denervation for Resistant Hypertension

Carotid Baroreceptor Stimulation, Sympathetic activity, Baroreflex function and Blood pressure in Hypertensive Patients

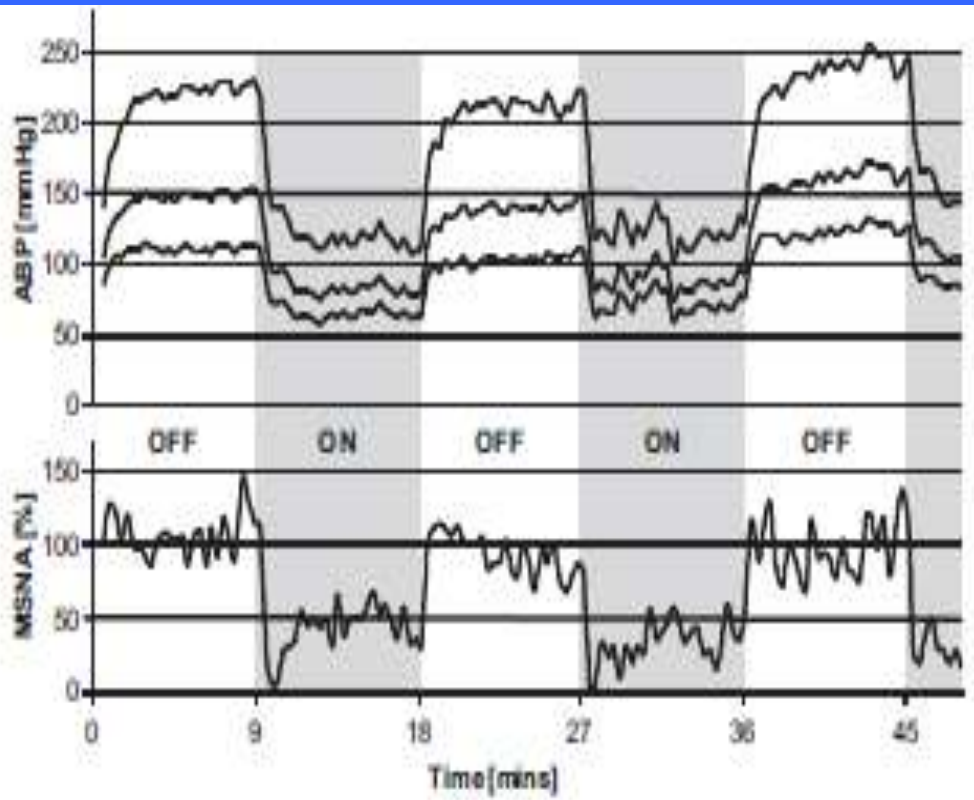


Figure 2. Response repeatability: systolic, mean, and diastolic arterial blood pressure (ABP) and relative total MSNA over time in patient 12. Each time the stimulator was switched on, ABP and MSNA decreased acutely and remained suppressed throughout the stimulation period.

Heusser K et al. Hypertension 2010;55:619-626

Lesson from Japan:

1950s: Salt intake of 26 gm/day
1990s: Gradually reduced to 12 gm/day
SBP reduced by 18 mmHg in both M & F
Stroke rate reduced by 83%

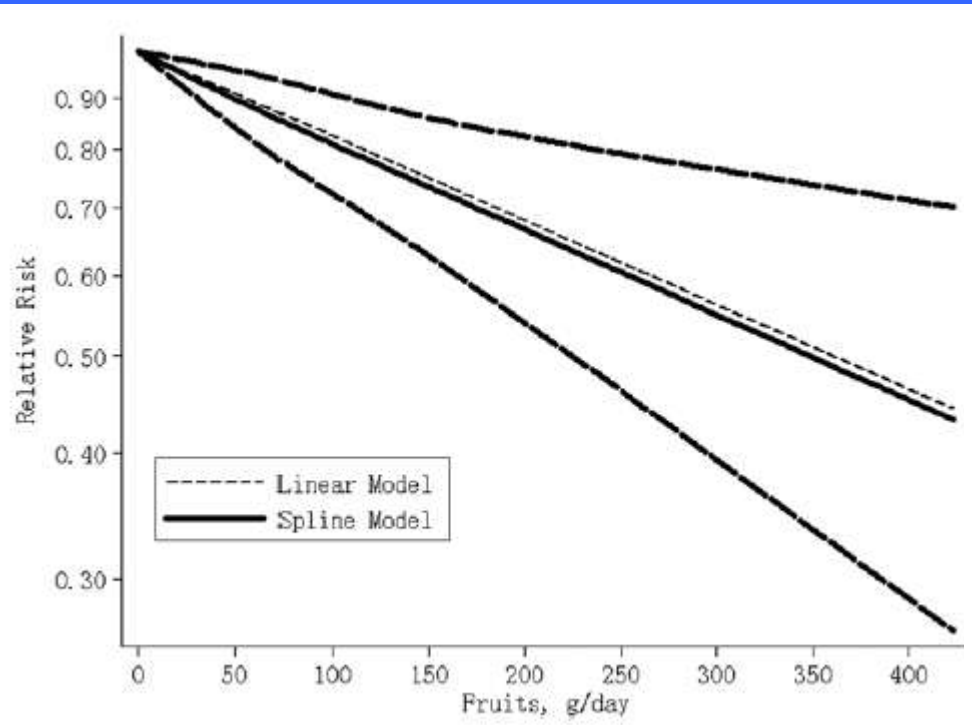
Intensive, sustained public education program
Fresh food delivery system
Refrigeration system
Globalization—exposure to global eating habits
Provision of low salt alternatives

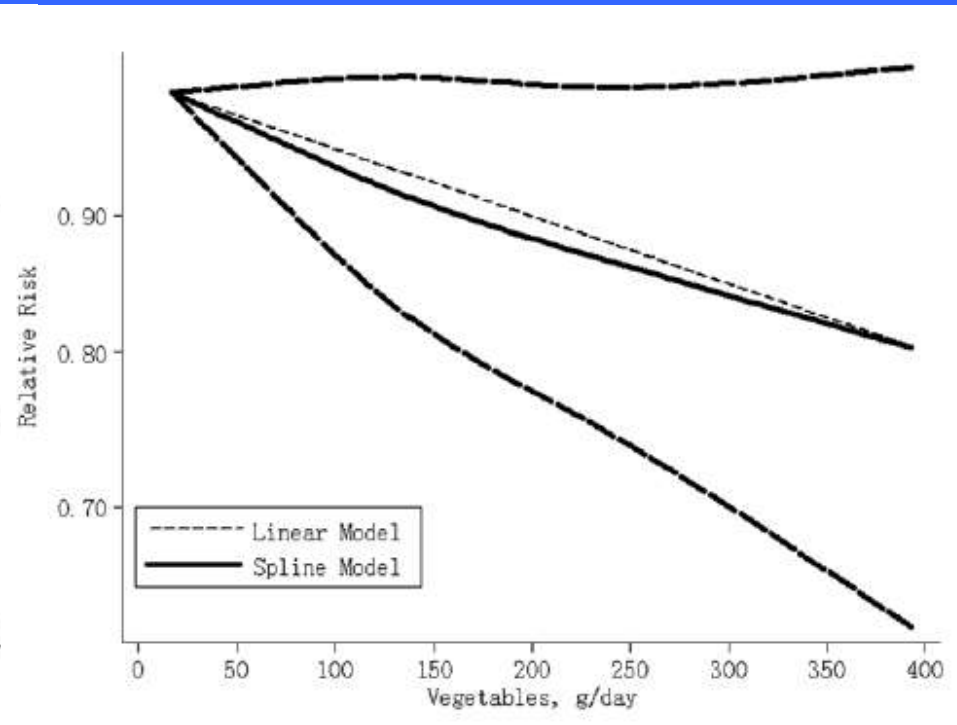
Intensified lifestyle interventions

Reduction of salt intake by 50%

Increased potassium intake, fruits & vegetables
Reduction in saturated fat intake
Increase in physical activity

Fruit and vegetable consumption and risk of stroke





Hu D et al. Stroke. 2014, in press

POLYPILL

Composition?

Safe, inexpensive, requires minimal follow-up, can be easily dispensed

Ideal for high-risk hypertensives as assessed by simple tests

Higher downstream savings than high-tech approaches

Multifaceted Intervention Program for Optimal BP Control

Individual patient education not sufficient

Involvement of community & its leaders, food industry, government (legislation)

Education:
Reduced physician inertia
Interventions to improve long-term patient compliance/adherence