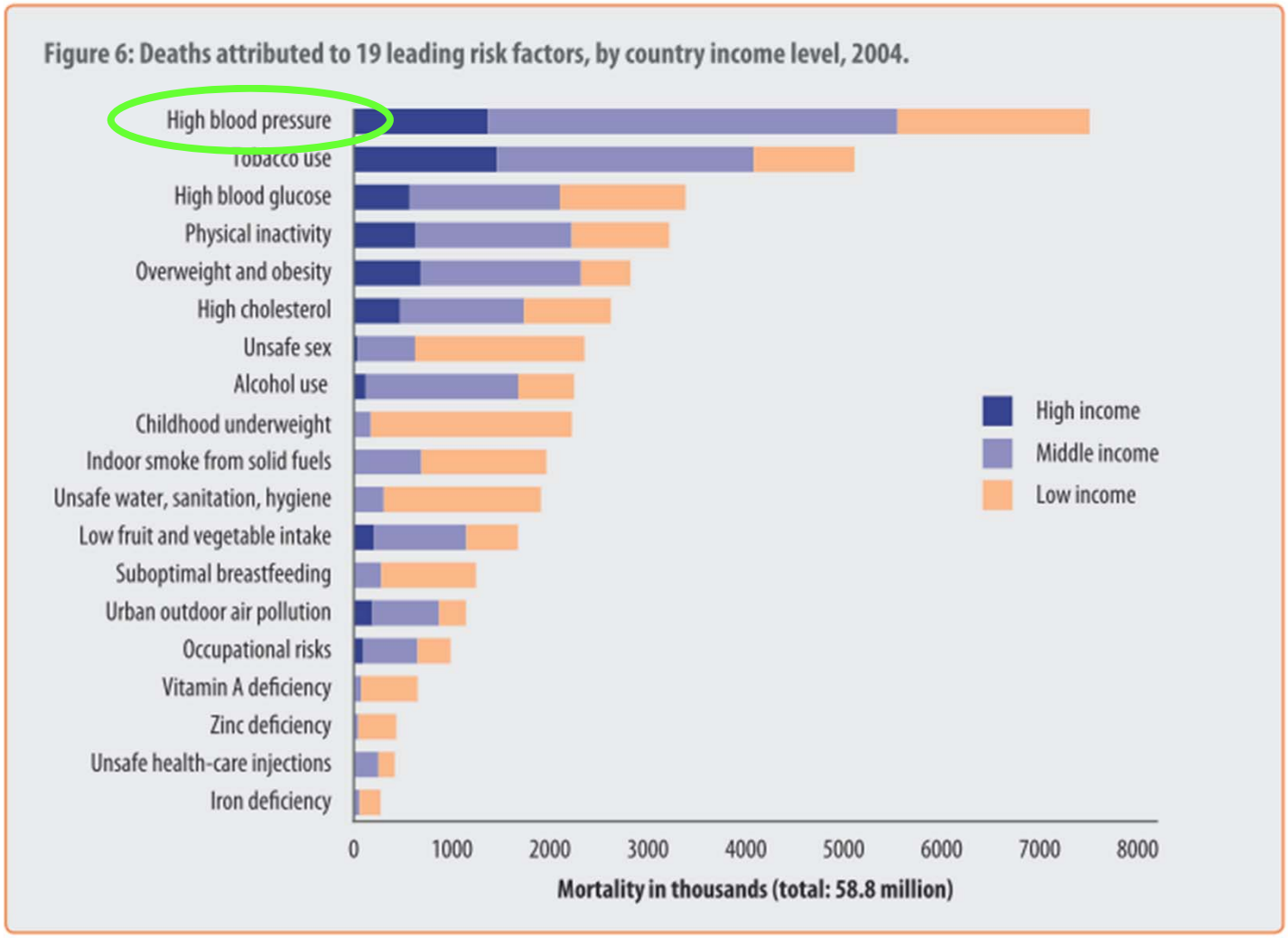
The Management of
Intractable Hypertension

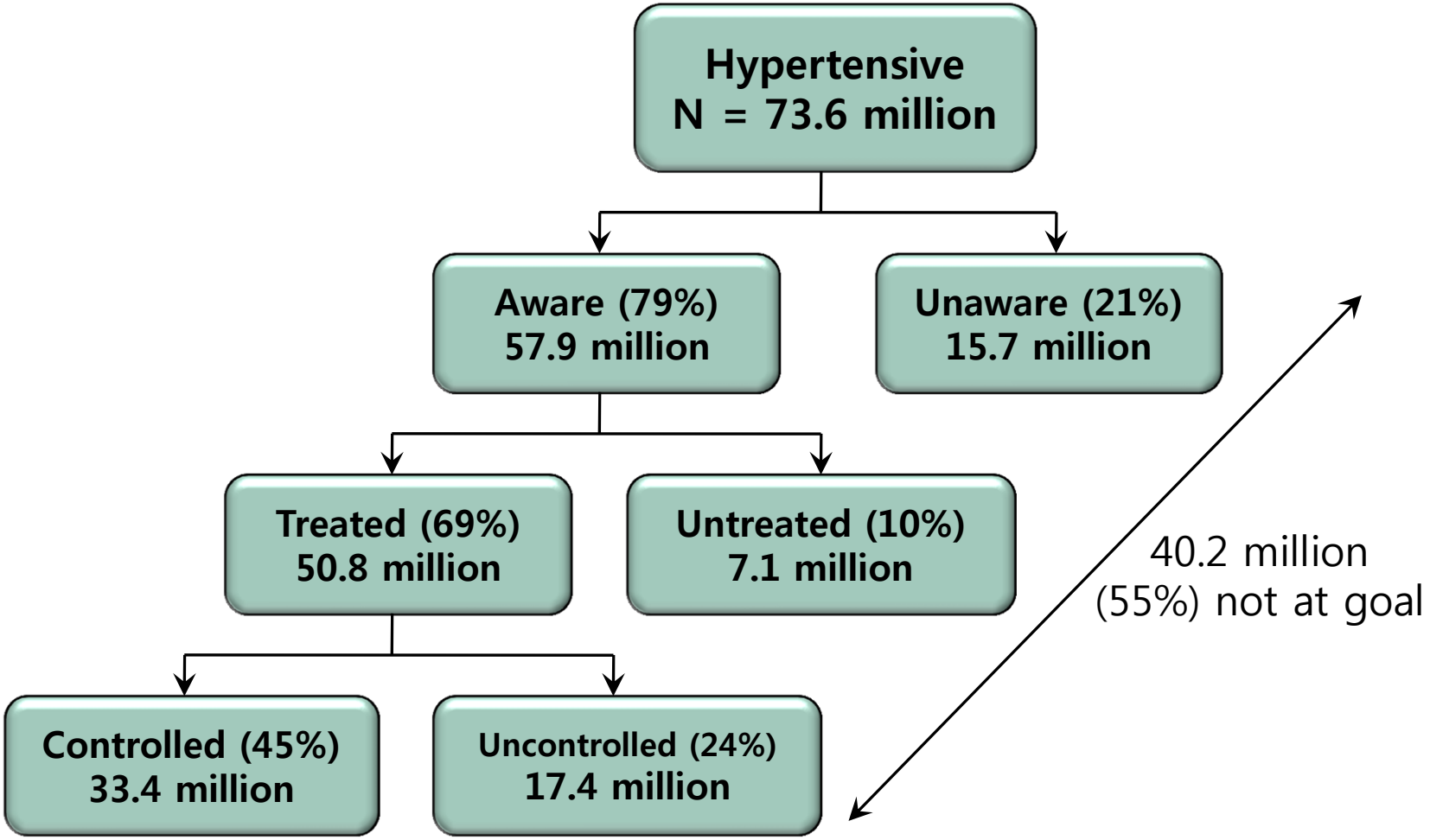
조선의대
정중화

Deaths attributed to 19 leading risk factors



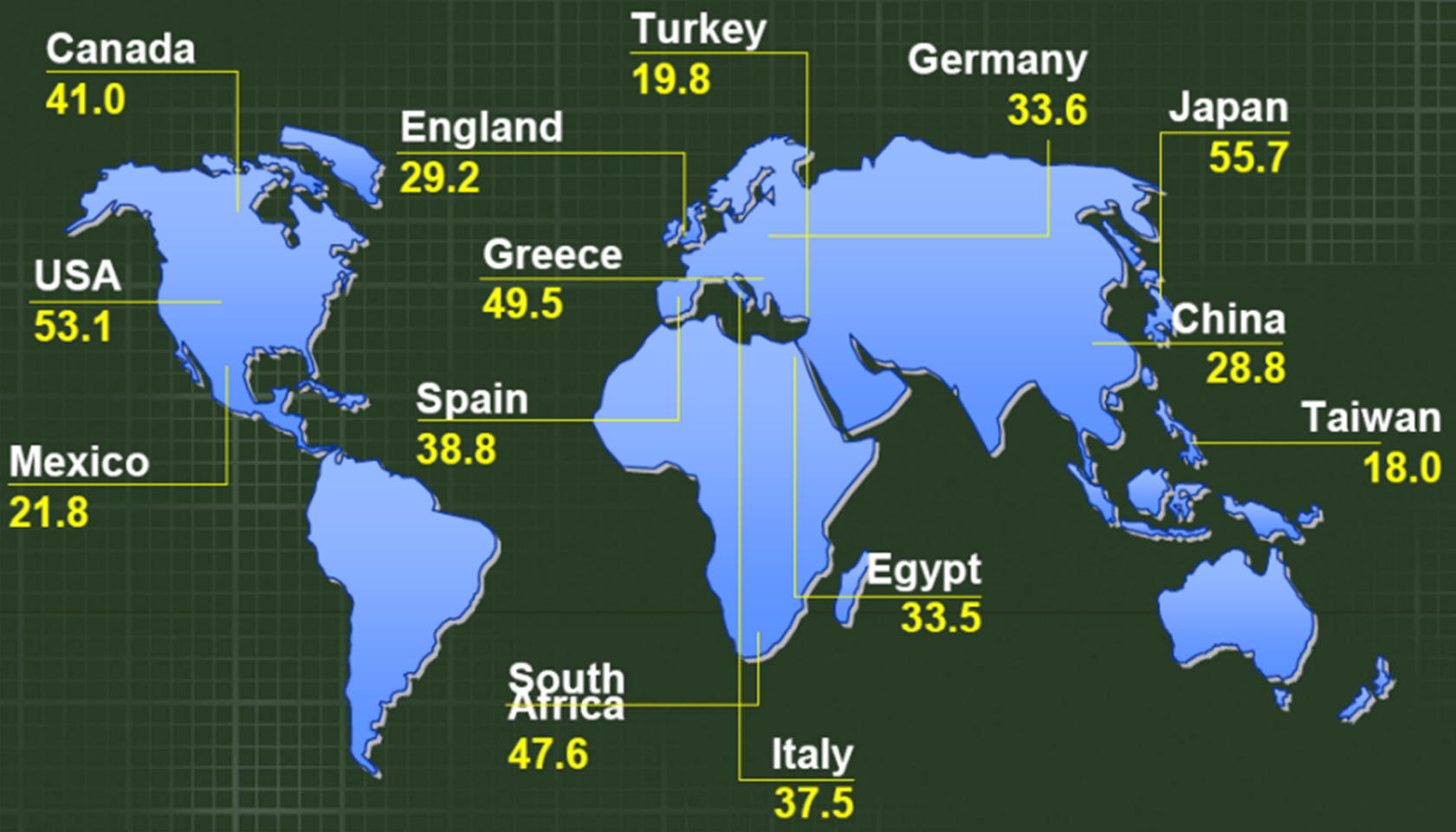
Global helath risks, WHO 2009

Majority of US Hypertensive Patients Not at Systolic BP Goal of < 140 mmHg



Circulation 2009;6:e87-e95.
Based on Data from NHANES/NCHS 2005-2006

Worldwide Blood Pressure Control in Treated Hypertensive Patients



Updated from Kearney et al. J Hypertens 2004; 22: 11-19

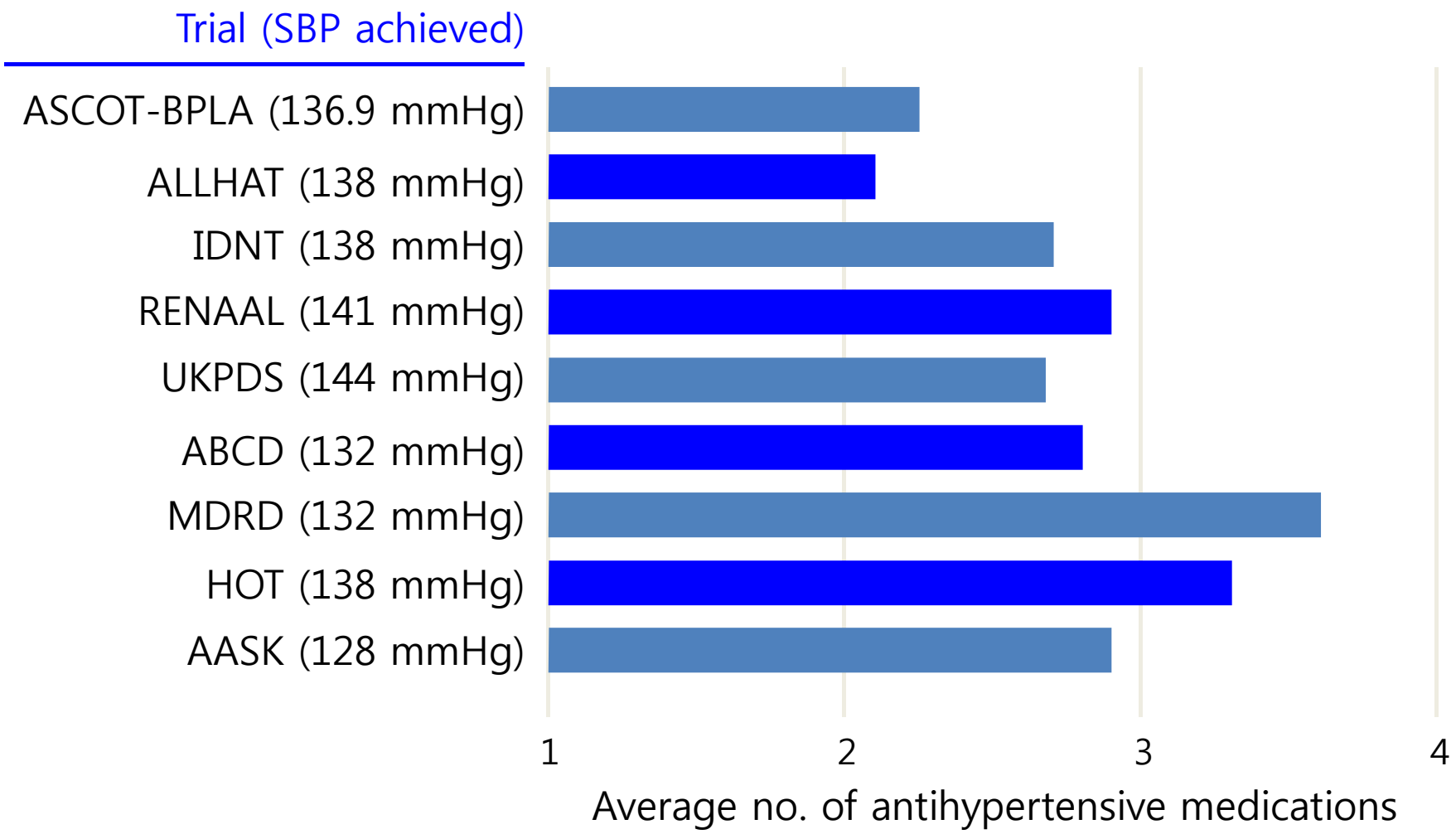
AHA recommendation for high-risk patients

Condition	BP Goal, mm Hg	Preferred Therapy
General CAD prevention	<140/90	Any effective antihypertensive drug or combination
High CAD risk*	<130/80	ACEI, ARB, CCB, or diuretic, or combination
Stable angina	<130/80	BB and ACEI or ARB
UA/NSTEMI	<130/80	BB† and ACEI or ARB
STEMI	<130/80	BB† and ACEI or ARB
Left ventricular dysfunction	<120/80	ACEI or ARB and BB and aldosterone antagonist and thiazide or loop diuretic and hydralazine/isosorbide dinitrate (in black patients)

BP = blood pressure; CAD = coronary artery disease; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; BB = β-blocker; UA = unstable angina; NSTEMI = non–ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.
*Framingham risk score ≥10%.
† If the patient is stable hemodynamically.

AHA Scientific Statement *Circulation.* 2007;115:2761-88.

Multiple Antihypertensive Agents are Needed to Reach BP Goal



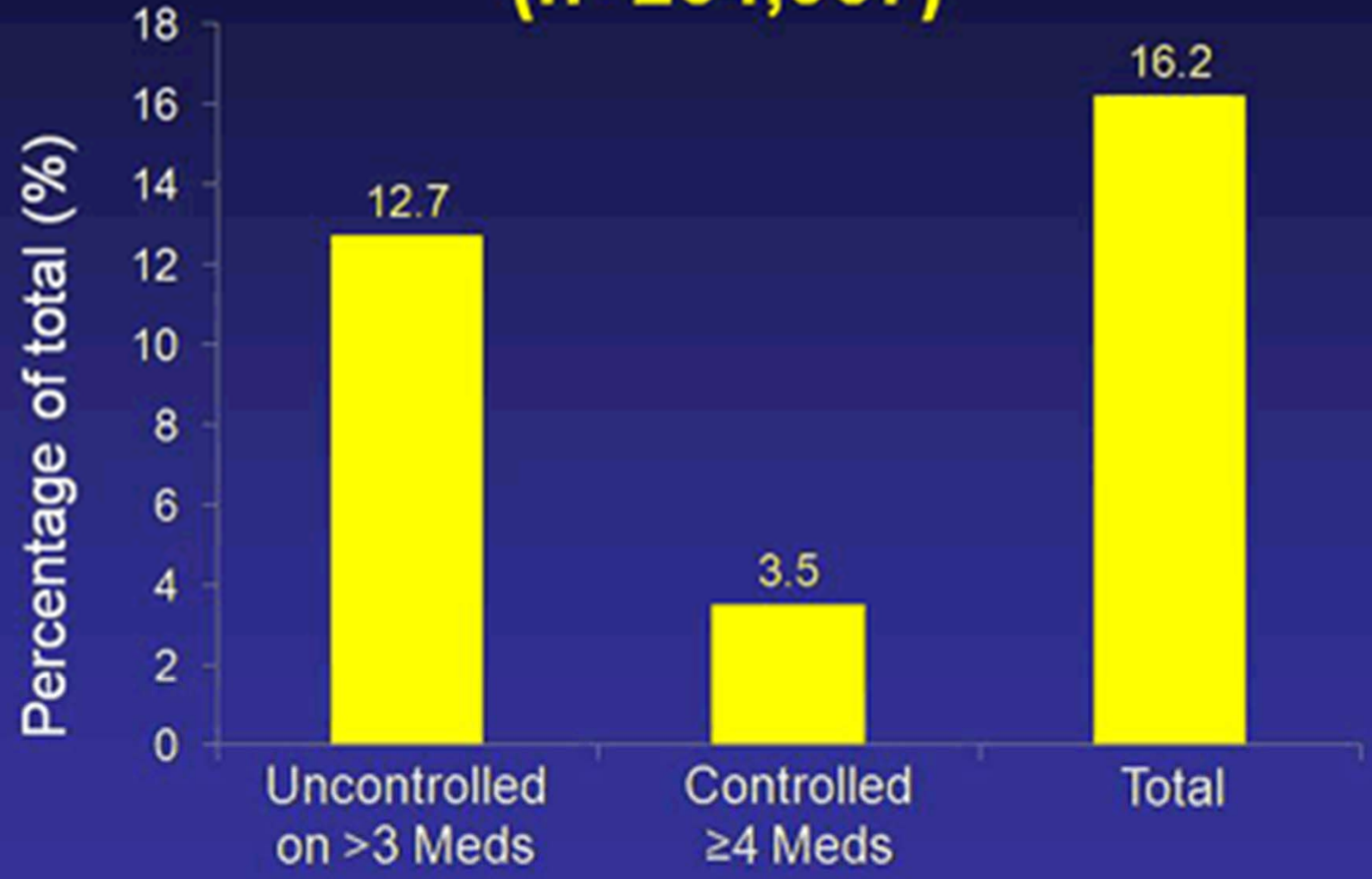
Lancet 2005;366:895–906.

Definition of resistant hypertension

- Resistant hypertension is defined as blood pressure that remains above goal in spite of concurrent use of 3 antihypertensive agents of different classes.
- Ideally, one of the 3 agents should be a diuretic and all agents should be prescribed at optimal dose amounts.
- Patients whose blood pressure is controlled, but required 4 or more medications to do so, should be considered resistant to treatment.

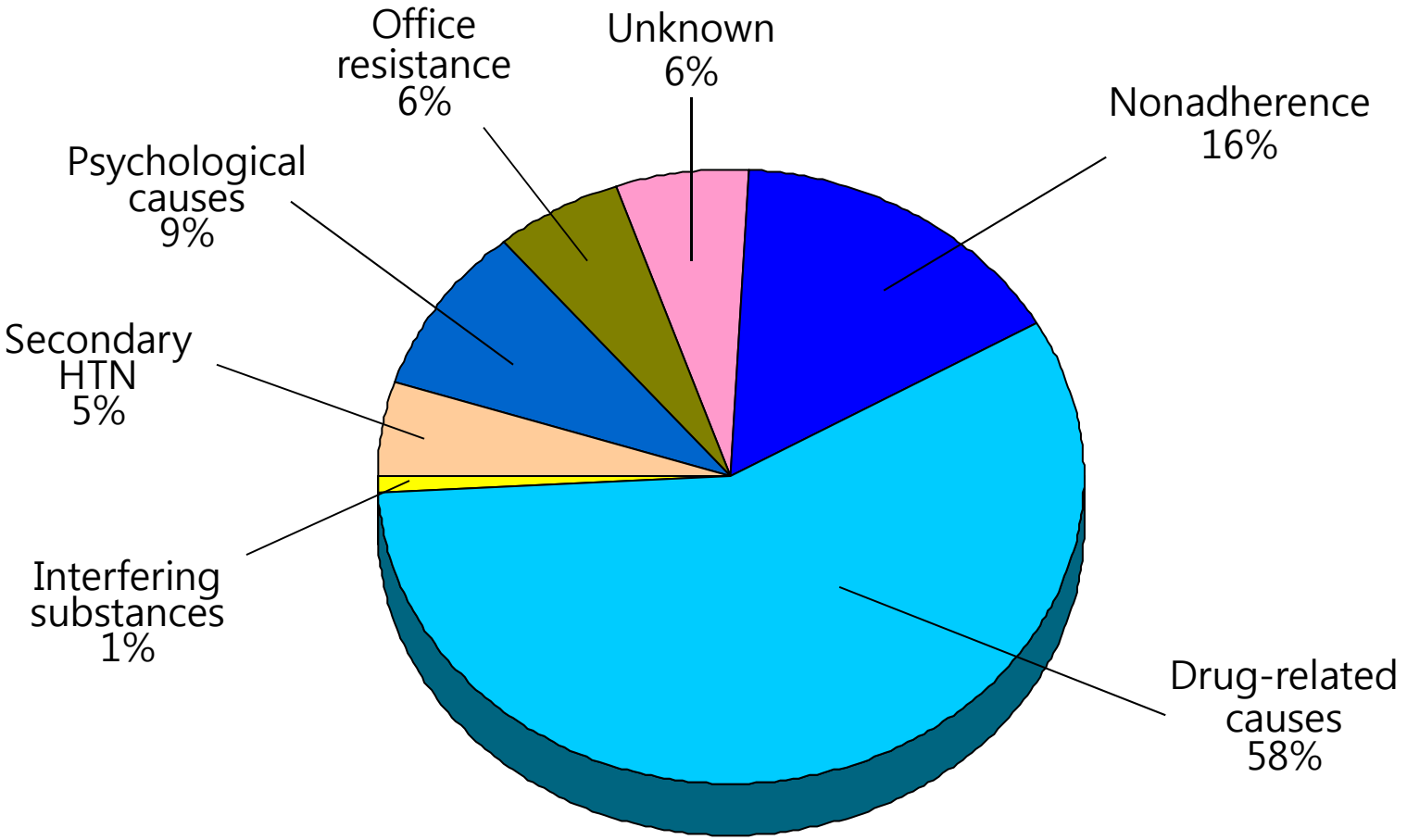
AHA a scientific statement. *Circulation* 2008;117:e513.

Treatment Resistant Hypertension in a Community-Based Practice Network (n=264,967)



Egan et al, J Clin Hypertens 2009, OR-13

Causes of uncontrolled hypertension



Am J Hypertens 2003;16:925-30.

Evaluation objectives

- Confirm true treatment resistance
  - Patient adherent with 3 or more medications
  - Accurate BP measurement
  - Exclude white coat "resistant hypertension"
- Screen for secondary causes of hypertension
  - Primary aldosteronism
  - Renal artery stenosis
  - Obstructive sleep apnea
- Document degree of TOD
  - LVH, retinopathy, CKD, proteinuria

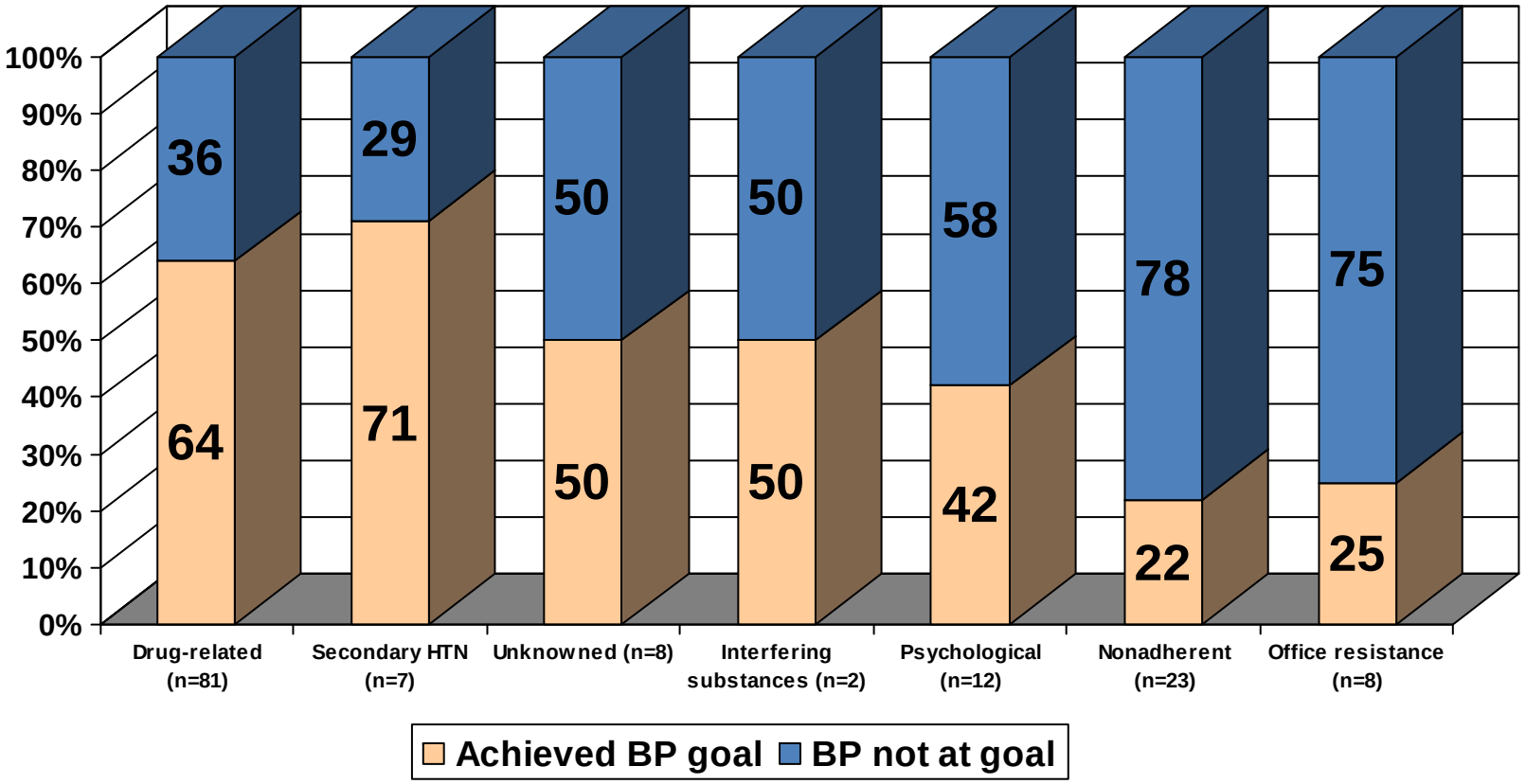
AHA a scientific statement. *Circulation* 2008;117:e510-26.
JACC 2008;52:1749-57.
Int J Hypertens 2011;2011:236-9.

Pseudoresistance

- White-coat hypertension
- Pseudohypertension in the elderly
- Measurement artifact
- Physician inertia
- Poor adherence
- Suboptimal dosing or inappropriate combinations

AHA a scientific statement. *Circulation* 2008;117:e510-26.
JACC 2008;52:1749-57.
Int J Hypertens 2011;2011:236-9.

Achievement of Goal BP by Cause of Resistance



Am J Hypertens 2005;18:619-26.

WCH in resistant hypertension

Parameter	True RH (N=5182)	White-Coat RH (N=3113)	*P*
Age, y	64.0±11.7	65.0±10.9	<0.001
Sex, % men	54.6	46.0	<0.001
BMI, kg/m^2	30.4±4.7	30.5±5.0	0.228
Duration of hypertension, y	11.4±8.7	10.5±8.2	<0.001
Smokers, %	14.8	10.3	<0.001
Diabetics, %	35.1	27.8	<0.001
Creatinine, μmol/L	75 (62 to 89)	72 (61 to 84)	0.006
Total cholesterol, mmol/L	5.23±1.06	5.21±1.06	0.495
HDL cholesterol, mmol/L	1.33±0.37	1.36±0.37	0.022
Triglycerides, mmol/L	1.64±0.93	1.54±0.72	0.005
UAE, mg/g	11.0 (3.4 to 44.5)	7.0 (2.7 to 20.0)	<0.001
UAE >30 mg/g, %	30.1	19.6	<0.001
LVH by ECG, %	18.5	14.4	<0.001
Previous CV disease, %	19.1	16.2	0.001
Treatment with ≥4 AH drugs, %	38.3	34.4	<0.001
Patients taking part of their medication in the evening, %	24.9	25.8	0.319

Parameter	MOR	95% CI	*P*
Age, y	0.99	0.98 to 1.00	0.002
Sex, (males vs females)	1.23	1.02 to 1.49	0.031
Duration of hypertension, y	1.02	1.01 to 1.03	0.001
Smokers (yes vs no)	1.25	1.01 to 1.44	0.041
Diabetics (yes vs no)	1.26	1.10 to 1.39	0.002
Creatinine, μmol/L	1.01	1.00 to 1.02	0.028
HDL cholesterol, mmol/L	NS	NS	0.693
Triglycerides, mmol/L	NS	NS	0.113
LVH by ECG (yes vs no)	1.22	1.02 to 1.38	0.033
Previous CV disease (yes vs no)	1.22	1.02 to 1.38	0.034
Treatment with ≥4 AH drugs (≥4 vs 3)	NS	NS	0.460

MOR indicates multivariate odds ratio; LVH, left ventricular hypertrophy; ECG, electrocardiogram; CV, cardiovascular; AH, antihypertensive; HDL, high-density lipoprotein.

A younger age, a male sex, a longer duration of hypertension, current smoking, diabetes mellitus, elevated plasma creatinine, and a history of previous cardiovascular disease were all associated with true resistant hypertension. (P<0.05)

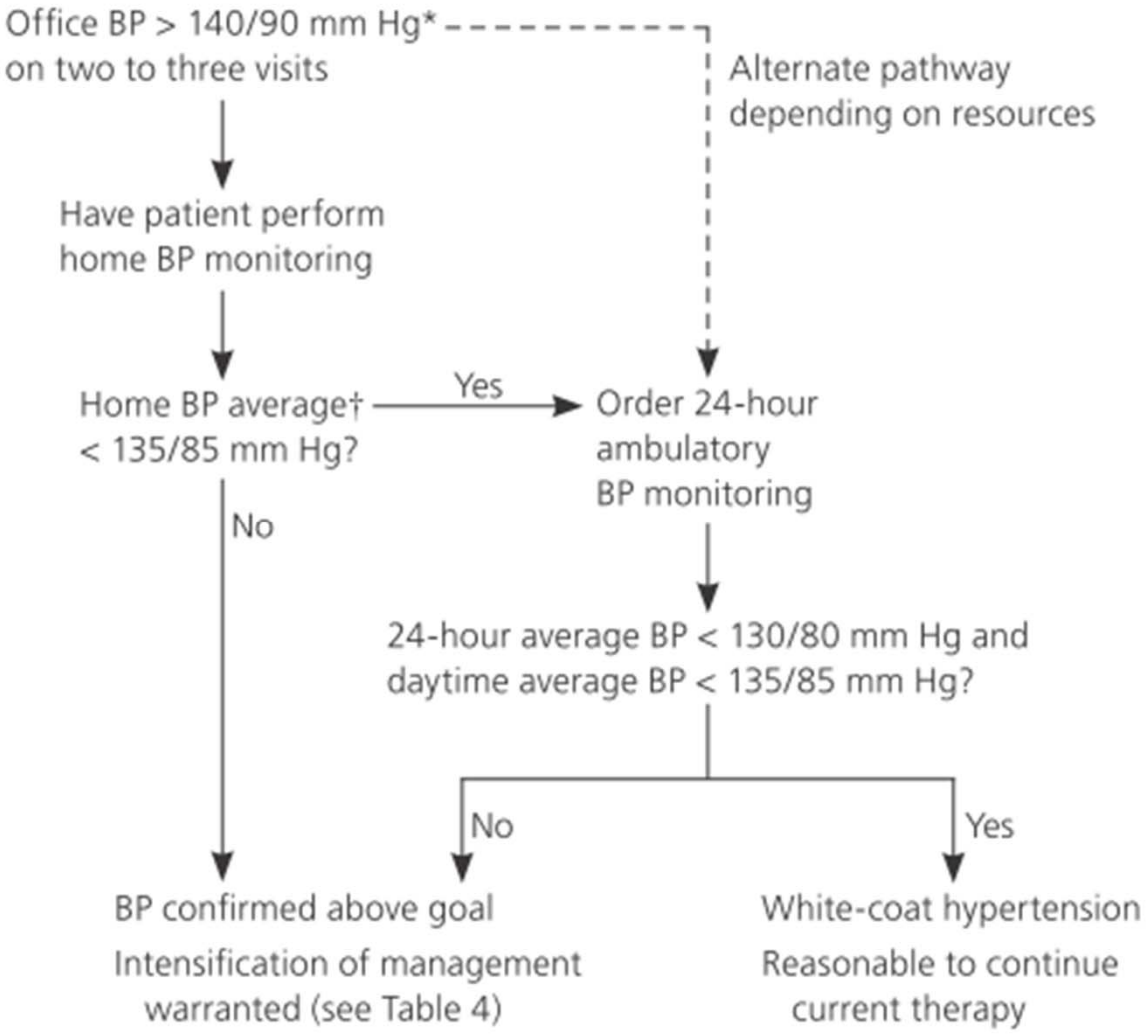
Spanish ABPM Registry. *Hypertension* 2011;57:00-00. Online data supplement

Prognostic influence of office and ambulatory BP in resistant hypertension

	Hazard Ratios (95% Confidence Intervals)[a]					
	Composite End Point (n=109)		All-Cause Mortality (n=70)		Cardiovascular Mortality (n=46)	
BP Measurement	Age and Sex Adjusted	Multivariate Adjusted[b]	Age and Sex Adjusted	Multivariate Adjusted[b]	Age and Sex Adjusted	Multivariate Adjusted[b]
Systolic						
Office	1.08 (0.90-1.30)	1.08 (0.90-1.29)	1.00 (0.79-1.27)	0.99 (0.78-1.25)	1.07 (0.80-1.43)	1.04 (0.79-1.39)
24 h	1.39 (1.15-1.68)[c]	1.32 (1.08-1.60)[d]	1.32 (1.04-1.68)[e]	1.24 (0.97-1.60)	1.39 (1.03-1.86)[e]	1.25 (0.93-1.69)
Daytime	1.33 (1.11-1.61)[d]	1.26 (1.04-1.53)[e]	1.28 (1.01-1.62)[e]	1.21 (0.95-1.54)	1.34 (1.00-1.79)[e]	1.22 (0.91-1.64)
Nighttime	1.44 (1.20-1.73)[c]	1.38 (1.13-1.68)[d]	1.34 (1.05-1.71)[e]	1.27 (0.98-1.64)	1.38 (1.03-1.85)[e]	1.27 (0.93-1.74)
Diastolic						
Office	0.95 (0.77-1.16)	1.03 (0.85-1.26)	0.85 (0.65-1.10)	0.94 (0.73-1.21)	0.83 (0.60-1.15)	0.94 (0.69-1.28)
24 h	1.26 (1.02-1.56)[e]	1.33 (1.06-1.66)[e]	1.13 (0.86-1.48)	1.18 (0.88-1.59)	1.16 (0.83-1.62)	1.18 (0.84-1.68)
Daytime	1.23 (1.00-1.52)	1.31 (1.05-1.63)[e]	1.13 (0.87-1.48)	1.23 (0.93-1.63)	1.16 (0.83-1.60)	1.24 (0.88-1.74)
Nighttime	1.33 (1.09-1.64)[d]	1.36 (1.10-1.69)[d]	1.16 (0.89-1.51)	1.17 (0.87-1.56)	1.19 (0.86-1.65)	1.19 (0.84-1.69)
Pulse pressure						
Office	1.16 (0.96-1.41)	1.09 (0.90-1.32)	1.13 (0.89-1.44)	1.04 (0.81-1.32)	1.26 (0.94-1.70)	1.12 (0.83-1.51)
24 h	1.35 (1.13-1.61)[c]	1.22 (1.00-1.48)[e]	1.34 (1.07-1.67)[e]	1.21 (0.96-1.53)	1.40 (1.07-1.84)[e]	1.21 (0.91-1.60)
Daytime	1.31 (1.09-1.58)[d]	1.17 (0.95-1.44)	1.31 (1.04-1.65)[e]	1.16 (0.90-1.50)	1.38 (1.04-1.84)[e]	1.16 (0.85-1.57)
Nighttime	1.37 (1.14-1.64)[c]	1.27 (1.04-1.55)[e]	1.35 (1.08-1.69)[e]	1.26 (0.98-1.62)	1.37 (1.04-1.81)[e]	1.24 (0.91-1.68)
True RH	2.20 (1.40-3.44)[c]	2.11 (1.34-3.34)[c]	2.13 (1.21-3.73)[d]	2.00 (1.12-3.55)[e]	1.99 (1.01-3.93)[e]	1.88 (0.93-3.80)

Arch Intern Med 2008;168:2340-6.

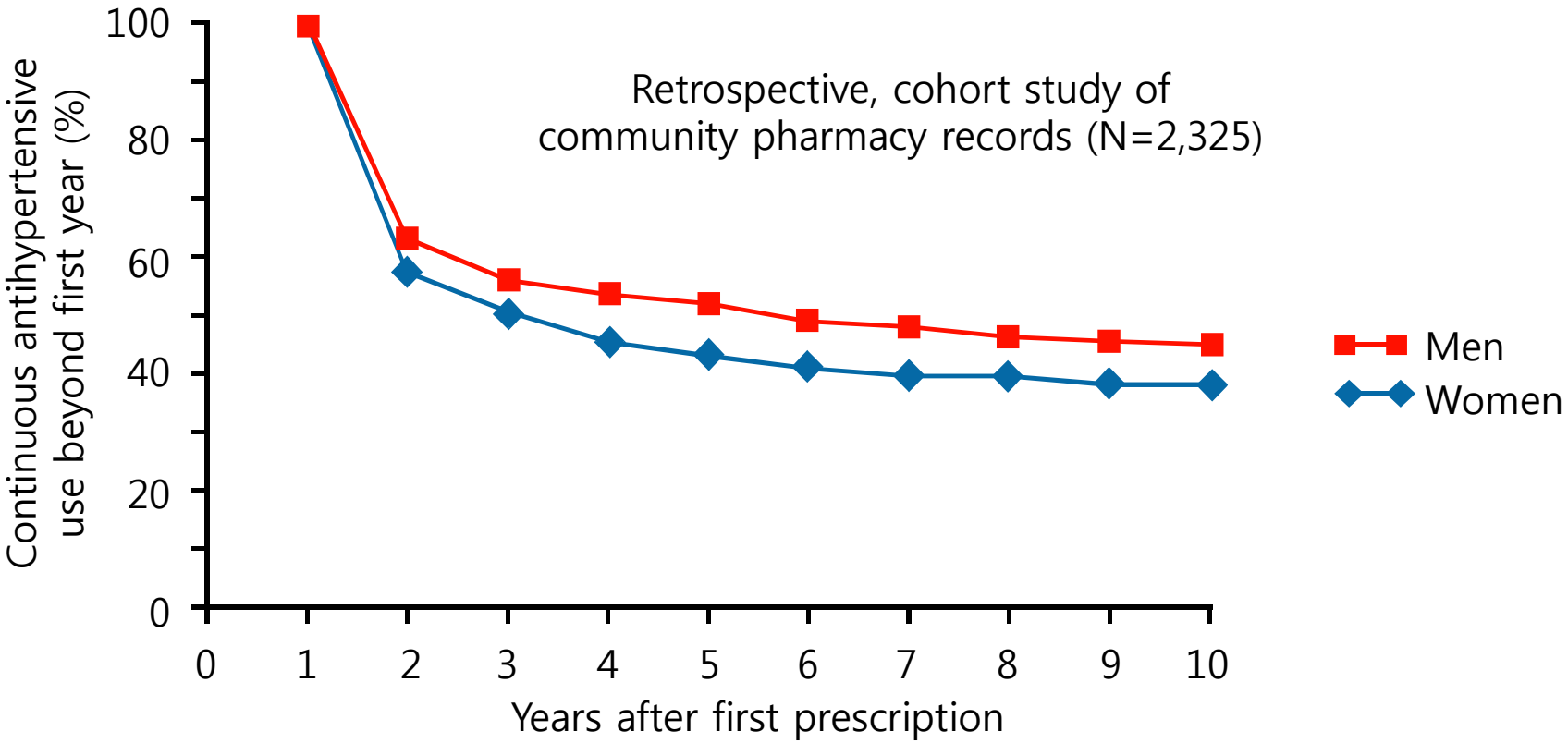
Algorithm for ruling out WCH



ASH position paper. *JASH* 2008;2:122.

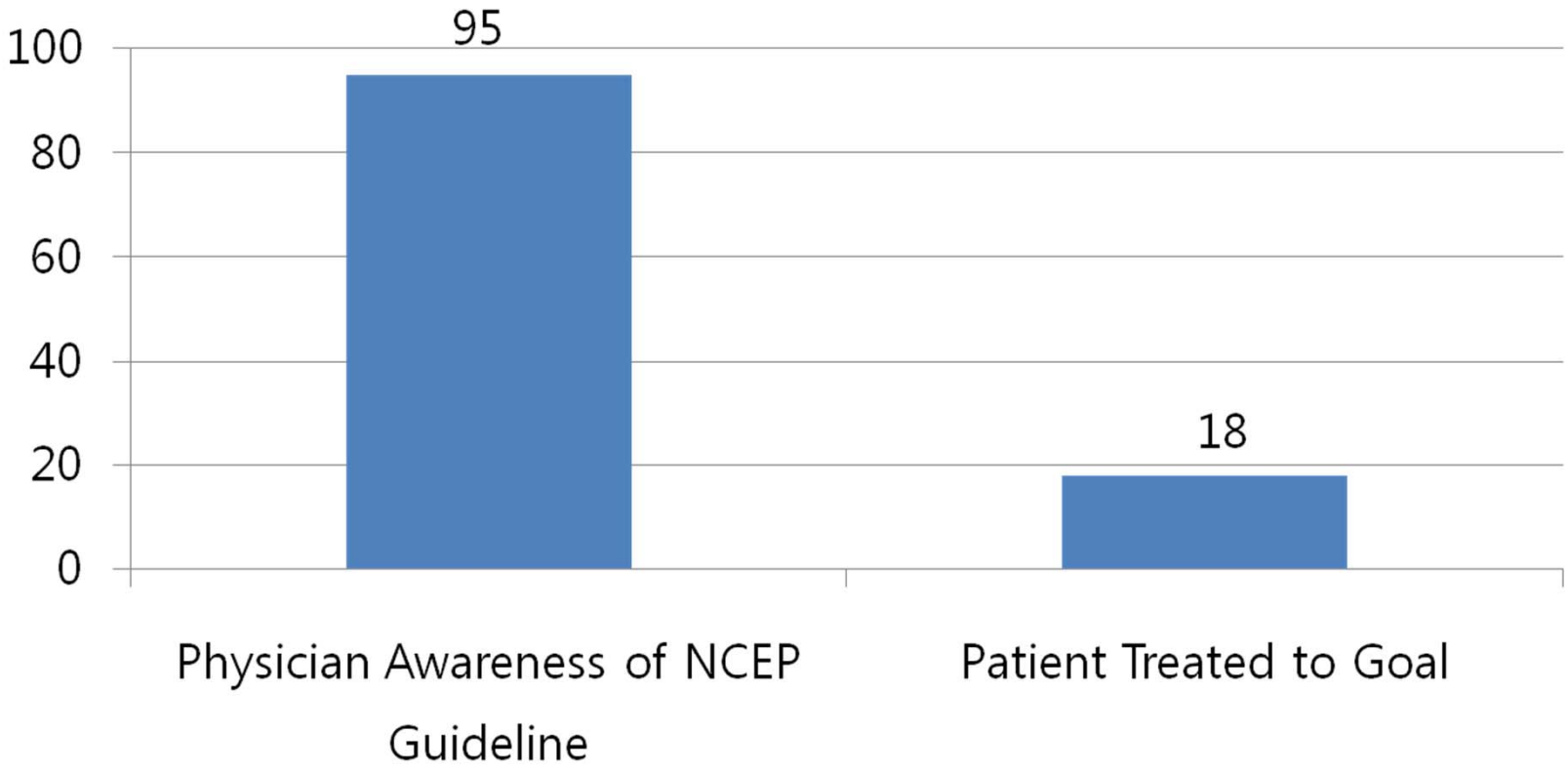
Poor Compliance and Persistence with Antihypertensive Treatment

Among patients receiving therapy after the first year,
~50% stop therapy within the next 2 years



J Hypertens 2005;23:2101–7.

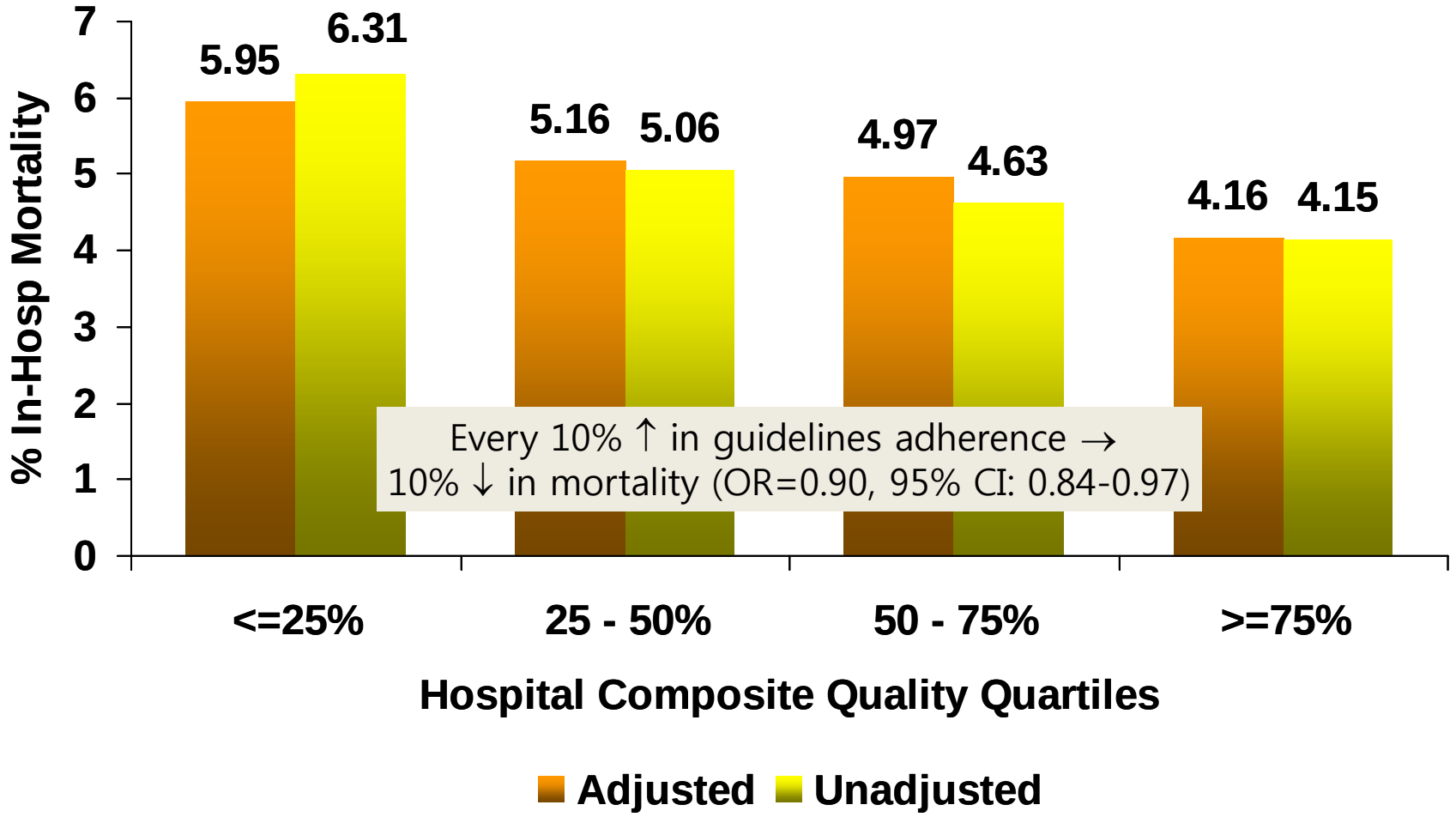
Treatment Gap



Provider awareness does not equal successful implementation

Arch Intern Med 2000;160:459-67.

Hospital Link Between Overall Guidelines Adherence and Mortality



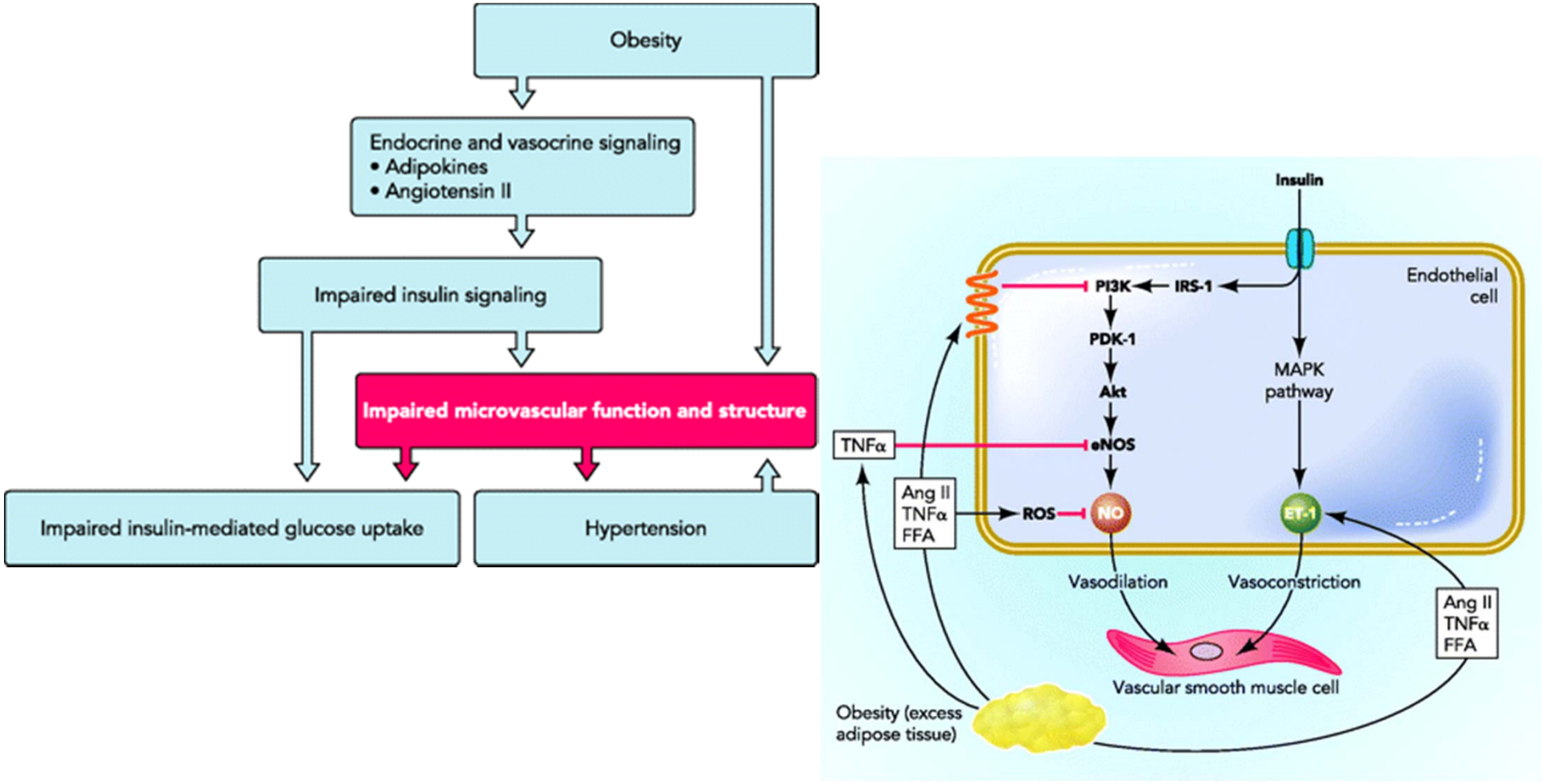
JAMA 2006;295:1863-1912.

Lifestyle factors contributing to resistant hypertension

- Obesity or overweight
- High salt diet
- Physical inactivity
- Ingestion of low-fiber/high-fat diet
- Heavy alcohol ingestion

AHA a scientific statement. *Circulation* 2008;117:e510-26.
JACC 2008;52:1749-57.
Int J Hypertens 2011;2011:236-9.

Obesity, insulin resistance and hypertension



Physiology 2007;22:252-60.

Interfering substances

Common

Alcohol

Nonsteroidal anti-inflammatory drugs (including cyclooxygenase-2 inhibitors)

Oral contraceptives

Some antidepressants (e.g., bupropion [Wellbutrin], tricyclic antidepressants, selective serotonin reuptake inhibitors, venlafaxine [Effexor])

Sympathomimetics (e.g., cocaine, amphetamines, diet pills, decongestants)

Less common

Corticosteroids

Cyclosporine (Sandimmune)

Erythropoietin

Licorice (including some types of chewing tobacco)

Monoamine oxidase inhibitors

Some dietary and herbal supplements (e.g., ginseng, ephedra, ma huang, bitter orange)

Tacrolimus (Prograf)

AHA a scientific statement. *Circulation* 2008;117:e513.

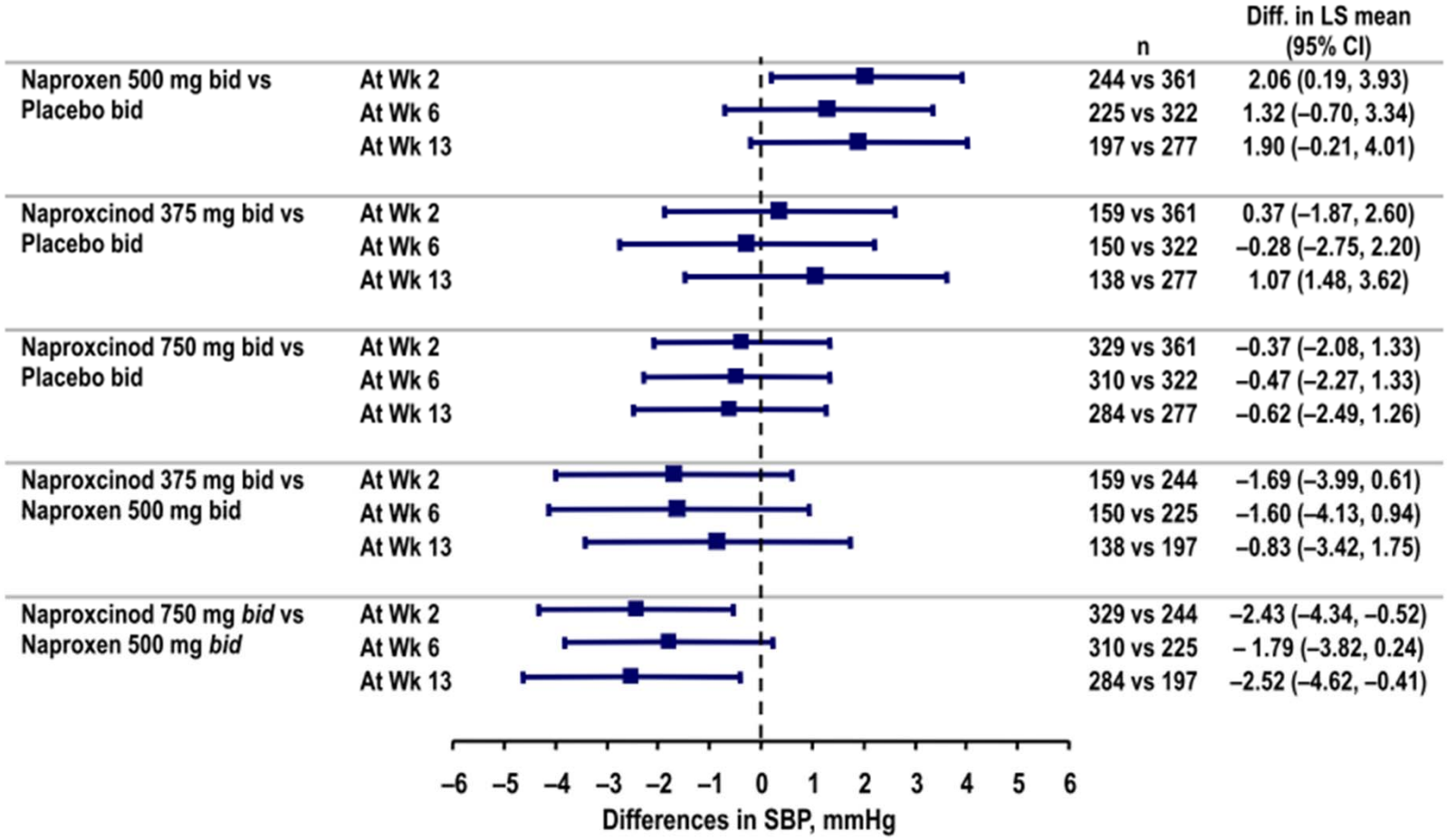
CV phenotypes of COX-isozyme inhibition

COX inhibitor	Platelet TXA_2	Whole Body PGI_2	Cardiovascular phenotype
Aspirin (50–100 mg)	Decreased by >97%	No significant changes	Cardioprotection
Aspirin (650–1,300 mg)	Decreased by >97%	Decreased 60-80%	Cardioprotection(Effects relative to lower doses are uncertain)
Naproxen (500 mg bid)	Decreased by ~95%	Decreased 60-80%	None/cardioprotection?
Other NSAIDs (high doses)	Decreased by 50-90%	Decreased 60-80%	Increased risk of myocardial infarction
Coxibs (high doses)	No significant changes	Decreased 60-80%	Increased risk of myocardial infarction

Mol Interv 2009;9:31-9.

CINODs
(cycloxygenase inhibiting NO donators)

- Naproxcinod



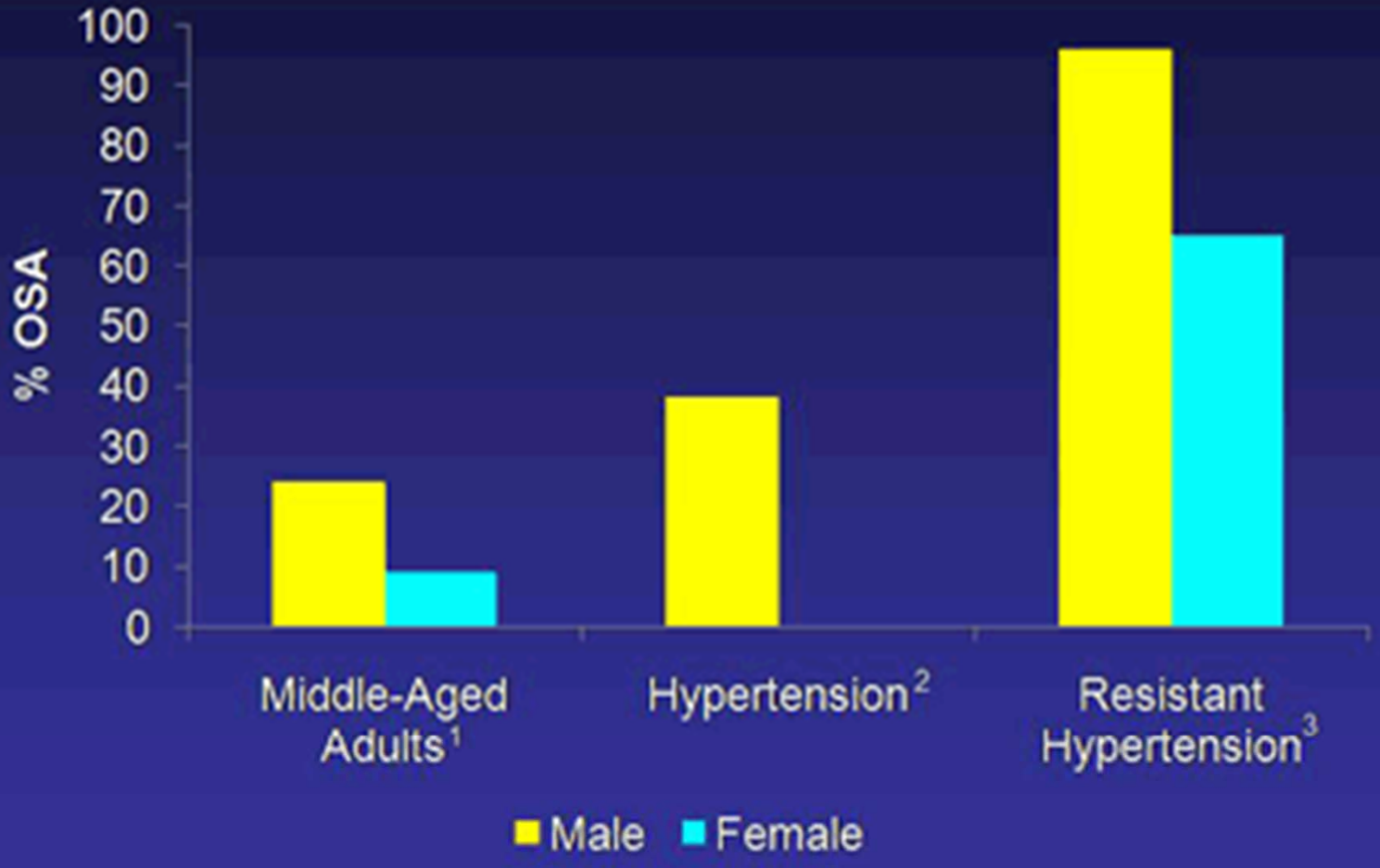
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM212681.pdf

Secondary causes of true resistance

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

AHA a scientific statement. *Circulation* 2008;117:e510-26.
JACC 2008;52:1749-57.
Int J Hypertens 2011;2011:236-9.

Prevalence of OSA



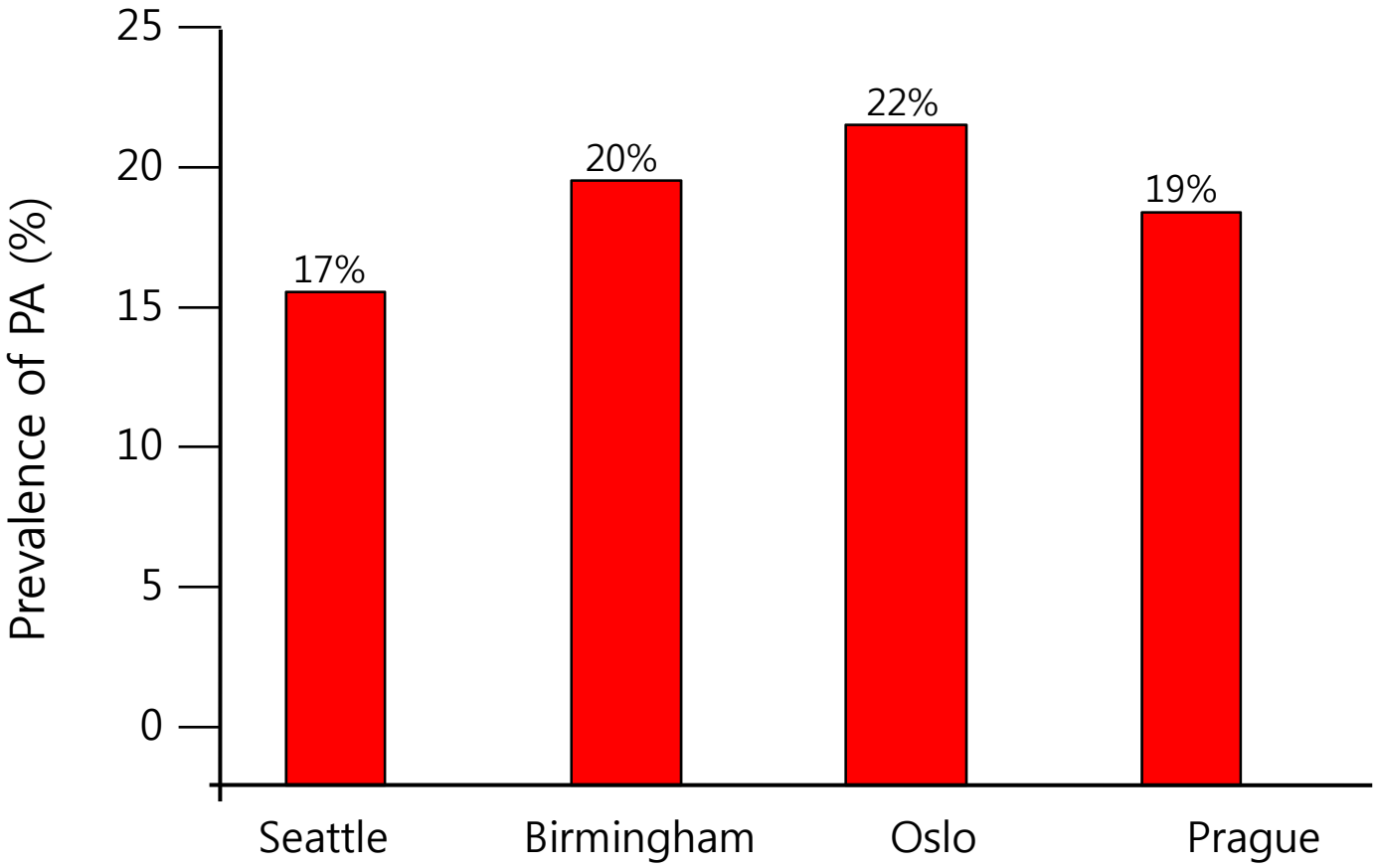
1. Young T, et al. *N Engl J Med*. 1993;328(17):1230-1235. AHI≥5 events/hr.
2. Worsnop CJ, et al. *Am J Respir Crit Care Med*. 1998;157(1):111-115. AHI≥5 events/hr.
3. Logan AG, et al. *J Hypertens*. 2001;19(12):2271-2277. AHI≥10 events/hr.

Obstructive Sleep Apnea

- Associated with resistant hypertension
- Prototype: obese middle age male with large neck
- Pathophysiologic role of sympathetic nervous system and RAAS (renin angiotensin aldosterone system)
- Get sleep study(polysomnography) in resistant hypertension

AHA a scientific statement. *Circulation* 2008;117:e510-26.
JACC 2008;52:1749-57.
Int J Hypertens 2011;2011:236-9.

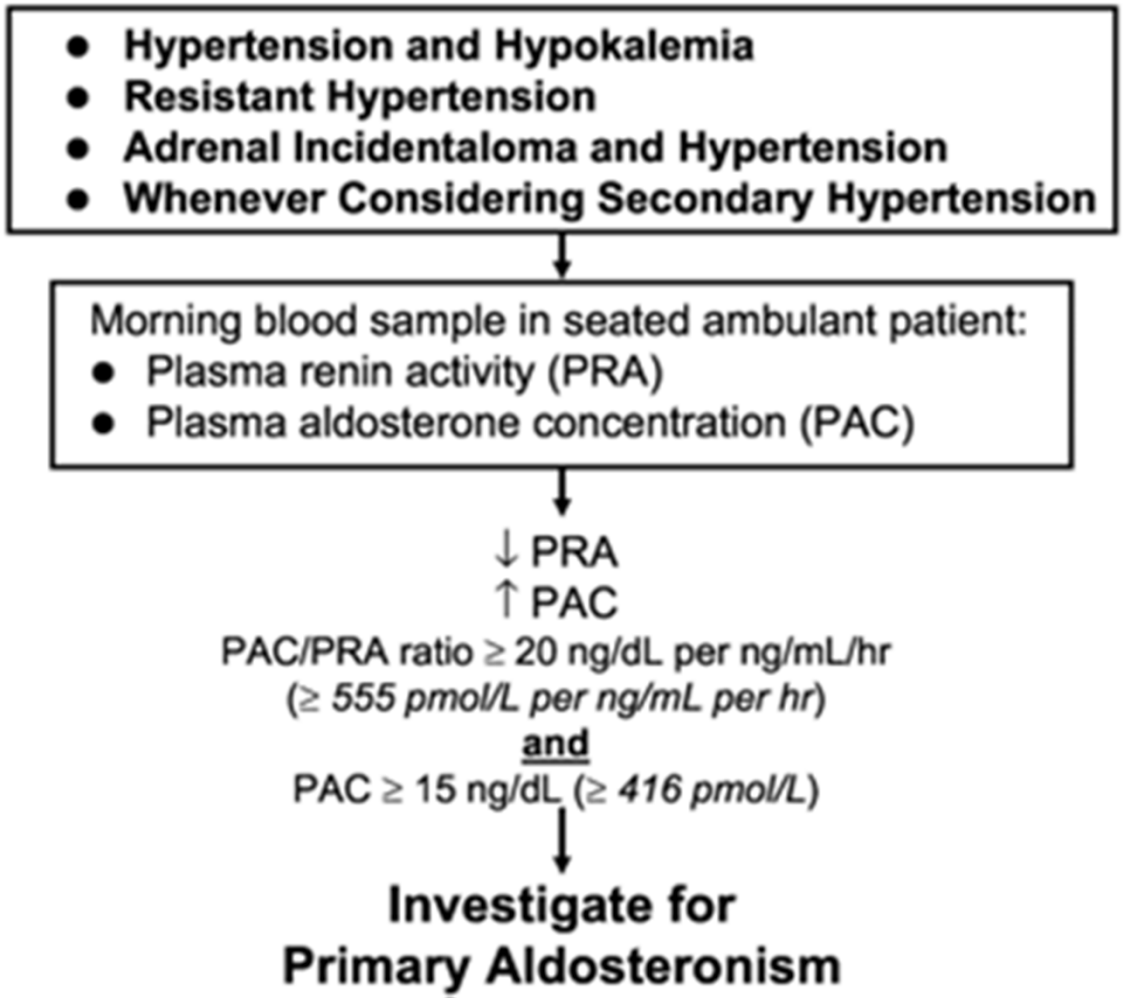
Prevalence of primary aldosteronism in subjects with resistant hypertension



PA = primary aldosteronism

Am J Kidney Dis 2001; 37:699-705
Hypertension 2002; 40:892-896
J Hypertension 2004; 22:2217-2226
J Hum Hypertens 2003; 17:349-352

When to consider screening for primary aldosteronism



J Clin Hypertens (Greenwich) 2008;10:239-44.

Method for predicting RAS

Parameter	Never smoked	Current or former smoker	Score (sum from left side)	Probability of renovascular hypertension (95% CI)
Age (in years)			≥20	≥90 (92–100)
20–29	0	0	19	90 (82–97)
30–39	1	4	18	89 (78–95)
40–49	2	8	17	87 (72–92)
50–59	3	5	16	80 (62–86)
60–69	4	5	15	72 (46–84)
70–79	5	6	14	62 (40–80)
Female gender	2	2	13	47 (28–65)
ASCVD*	1	1	12	37 (18–55)
Hx HTN† ≤2 years	1	1	11	25 (14–40)
BMI <25 kg/m^2	2	2	10	15 (7–28)
Abdominal bruit	3	3	9	11 (5–20)
Serum creatinine (mg/dL)			8	8 (3–12)
0.5–0.75	0	0	7	5 (2–10)
0.75–1.0	1	1	6	3 (1–8)
1.0–1.2	2	2	≤5	<2 (0–5)
1.2–1.65	3	3		
1.7–2.2	6	6		
≥2.3	9	9		
Hypercholesterolemia (>250 mg/dL, or on treatment)	1	1		

Ann Intern Med 1998;129:738-40.

Non-pharmacologic recommendations

- Weight loss
- Ingestion of low-fat, high-fiber diet
- Regular exercise (at least 30 min most days of the week)
- Low dietary salt ingestion
  - (2.4 g of sodium or 6 g of sodium chloride)
- Moderate alcohol ingestion
  - no more than 2 drinks per day for most men and 1 drink per day for women or lighter weight persons
- Treat obstructive sleep apnea if present

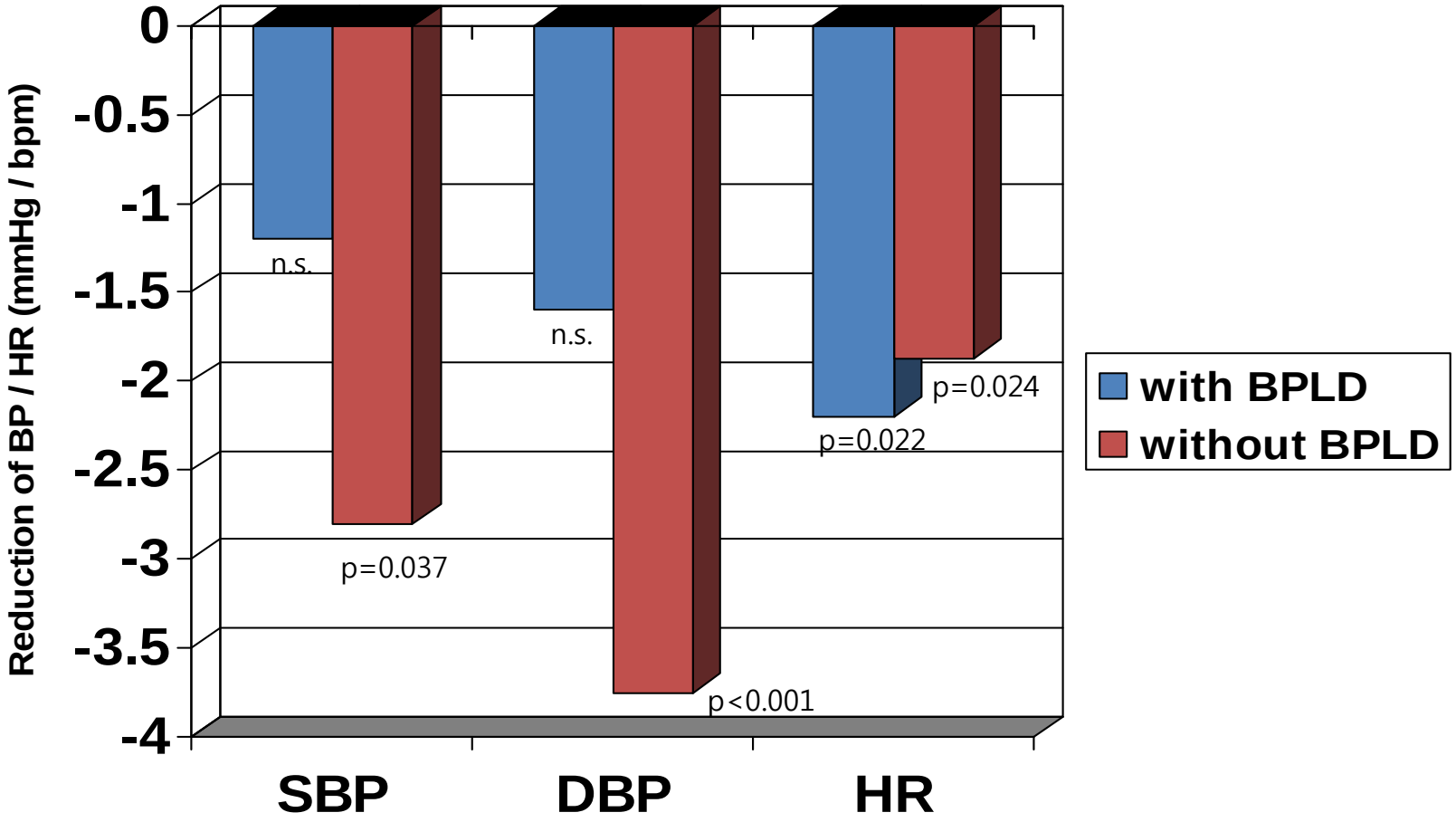
AHA a scientific statement. *Circulation* 2008;117:e510-26.
JACC 2008;52:1749-57.
Int J Hypertens 2011;2011:236-9.

American Heart Association Statement: Proven Lifestyle Modifications

Lifestyle Change	*Recommendation*	*Mean ↓ SBP (mm Hg)*
Weight loss	Goal BMI < 25	4.4
Reduced salt intake	< 65mmol/day (1.5 g)	5.0
DASH type diet	Diet rich in fruits and vegetables, low fat dairy products	5.9
Increased K^+ intake	> 120 mmol/d (4.7 g)	4.4
Moderation of alcohol intake	≤ 2 drinks/day (men) ≤ 1 drink/day (women)	3.3

Hypertension 2006;47:296

CPAP for obstructive sleep apnea



Reduction of blood pressure (BP) and heart rate (HR) after 6 months of bi-level or continuous positive airway pressure treatment in patients taking and not taking BP-lowering drugs (BPLD). SBP = systolic: DBP = diastolic BP.

AJH 2004;17:1081-7.

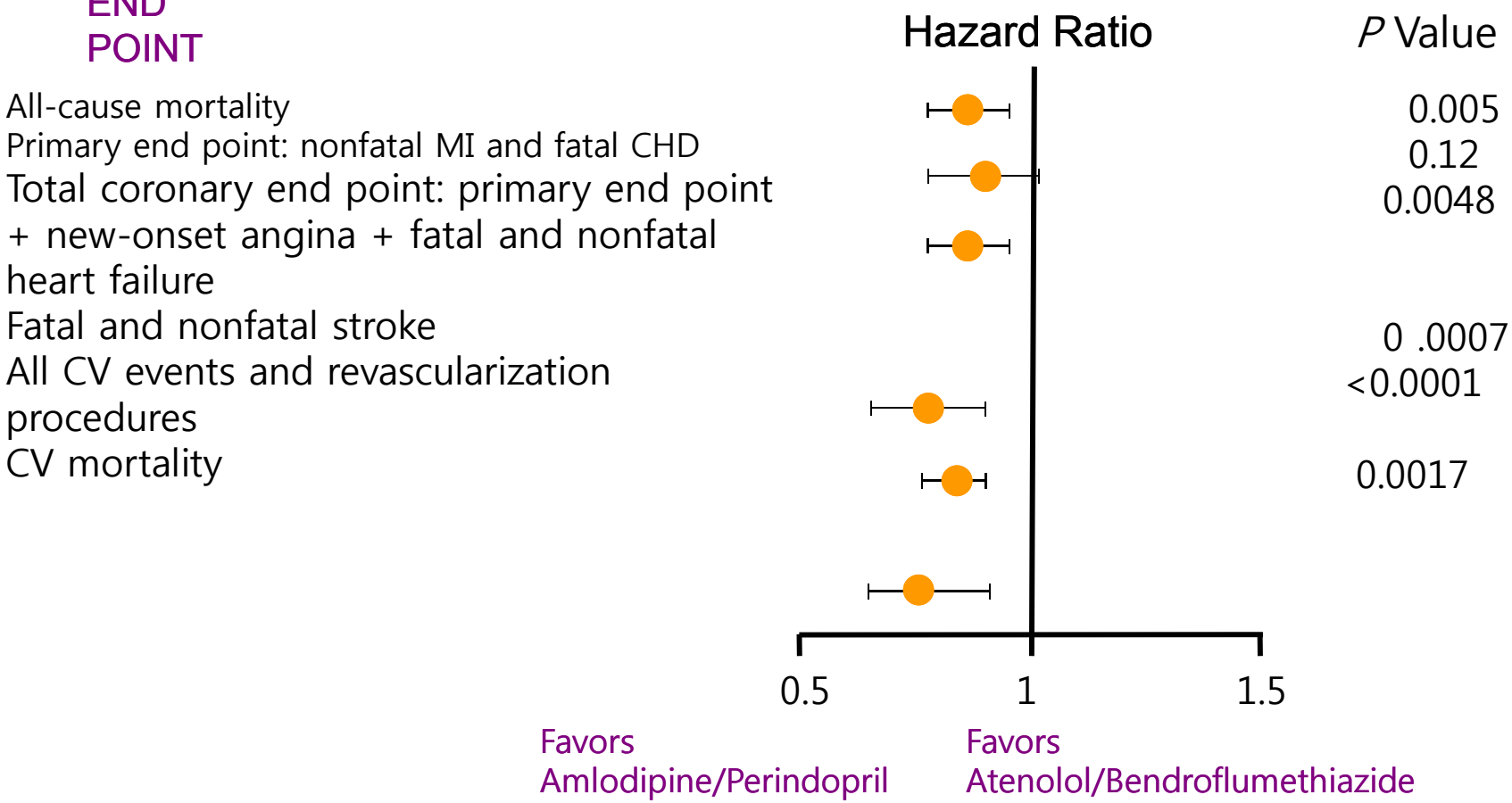
Pharmacologic recommendations

- Withdrawal or down titration of interfering substances as possible
- Use of a long-acting thiazide diuretic, preferable chlorthalidone
- Use of loop diuretic may be necessary in patients with CKD (creatinine clearance < 40 mL/min)
  - At least twice daily due to its limited half-life (1-.15 hour)
- Combine agents with different mechanisms of action
  - Standard triple regimen of ACEI or ARB, diuretics, and long-acting CCB
- Consider use of aldosterone antagonist (spironolactone, amiloride) as fourth drug
- Vasodilating beta-blocker as fifth drug
- Centrally-acting agent as fifth drug (clonidine)
- Vasodilating agents (hydralazine, minoxidil) as last resort

AHA a scientific statement. *Circulation* 2008;117:e510-26.
JACC 2008;52:1749-57.
Int J Hypertens 2011;2011:236-9.

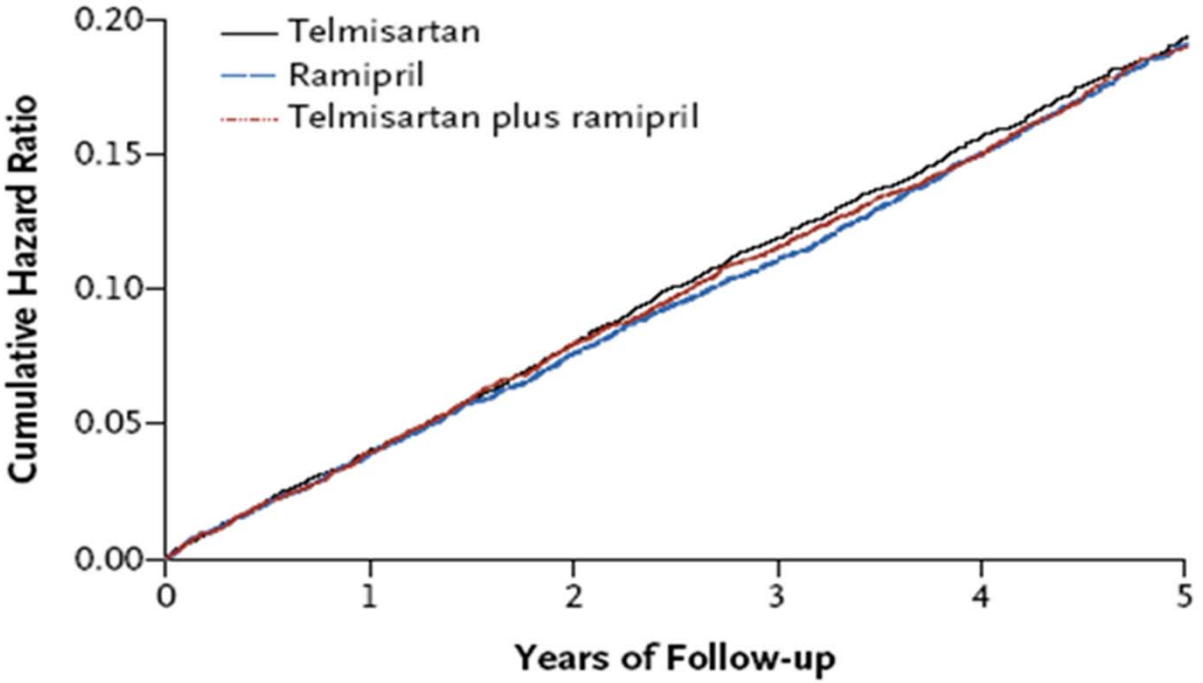
ASCOT: Primary and secondary end points

Amlodipine/Perindopril vs Atenolol/Bendroflumethiazide



Sever PS, Dahlöf B. American College of Cardiology 2005 Scientific Sessions; March 6-9, 2005; Orlando, FL.

Ontarget



No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

NEJM 2008;358:1547-59.

RAAS blockade can be considered a foundation of combination therapy

RAAS Blocker

+ CCB*

- Targets two key mechanisms of action:
  - Pressure
  - Neurohormonal
- Additive efficacy
- Excellent BP reduction in many demographic groups
- Potential safety/ tolerability benefits

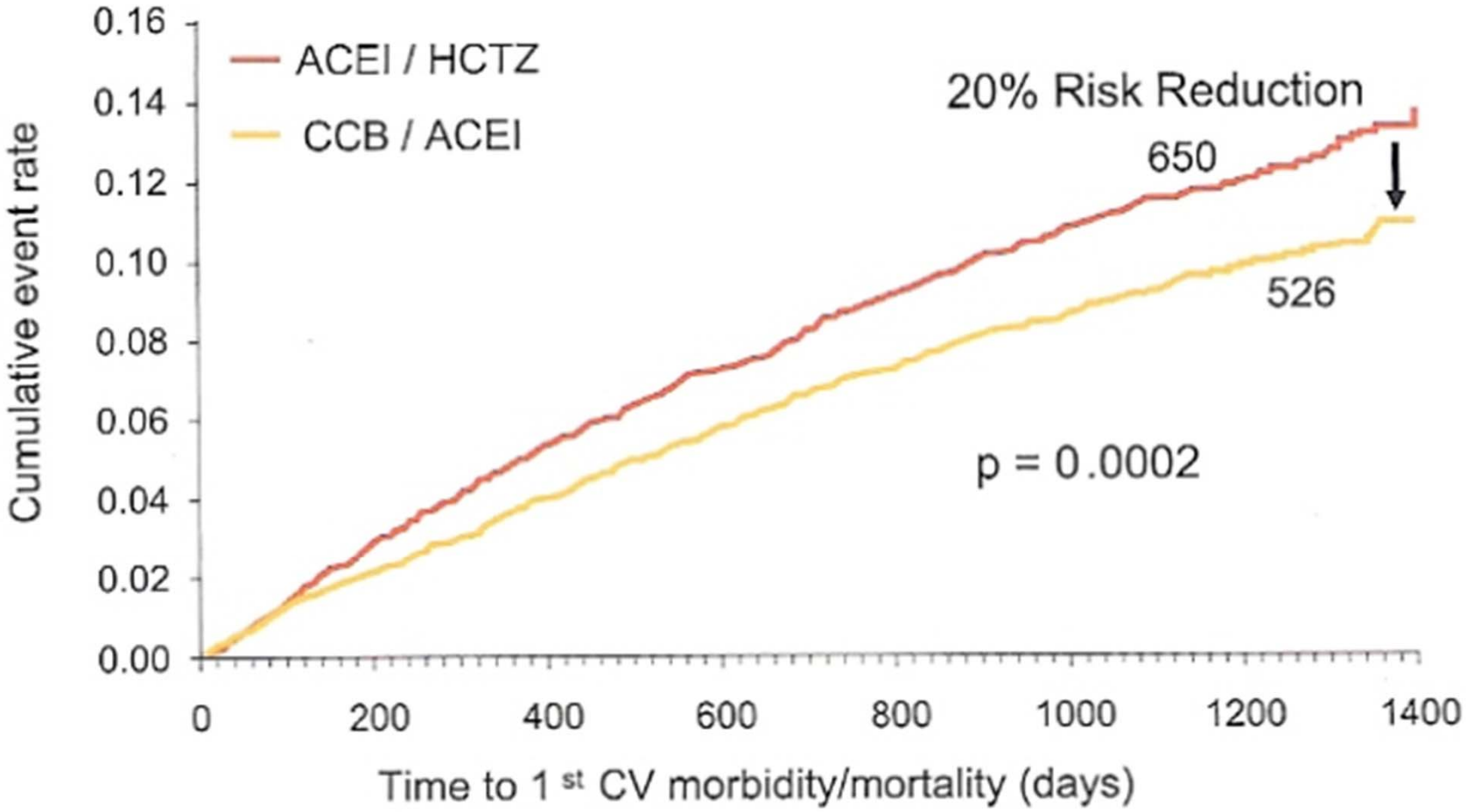
+ Diuretic*

- Targets two key mechanisms of action
  - Salt/volume
  - Neurohormonal
- Additive efficacy
- Excellent BP reduction in many demographic groups
- Potential safety/ tolerability benefits

RAAS=renin-angiotensin-aldosterone system
CCB=calcium channel blocker; BP=blood pressure
*Versus either drug alone

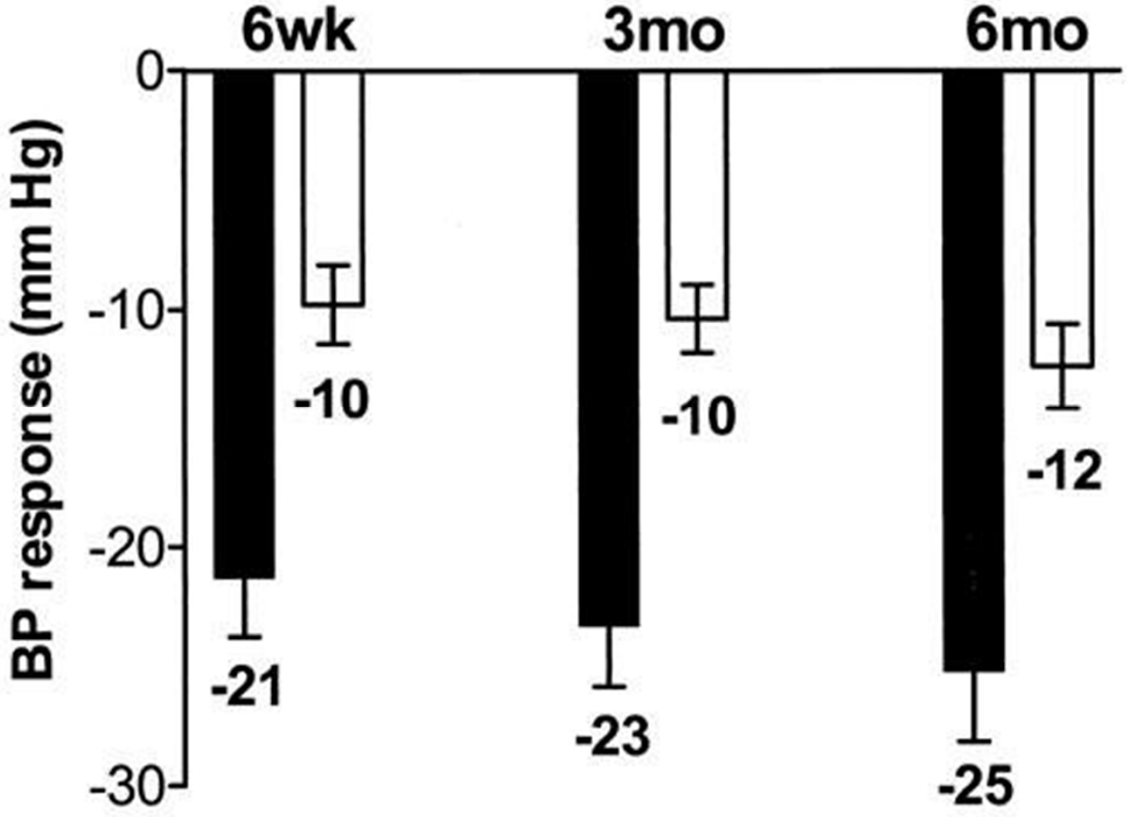
Am J Hypertens 1998;11:163S–9S.

ACCOMPLISH



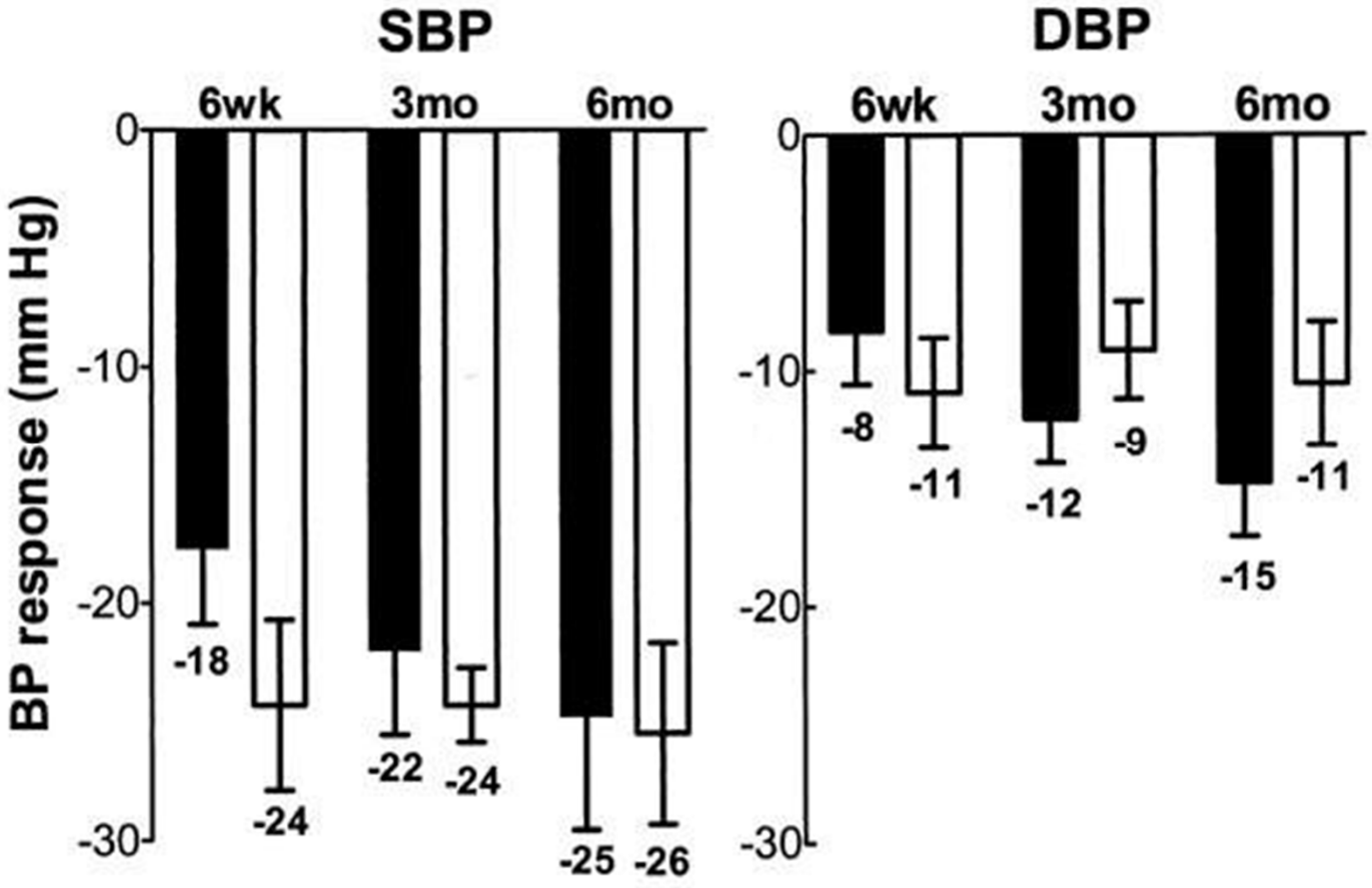
NEJM 2008;359:2417-2428

BP response to spironolactone in patients with resistant hypertension



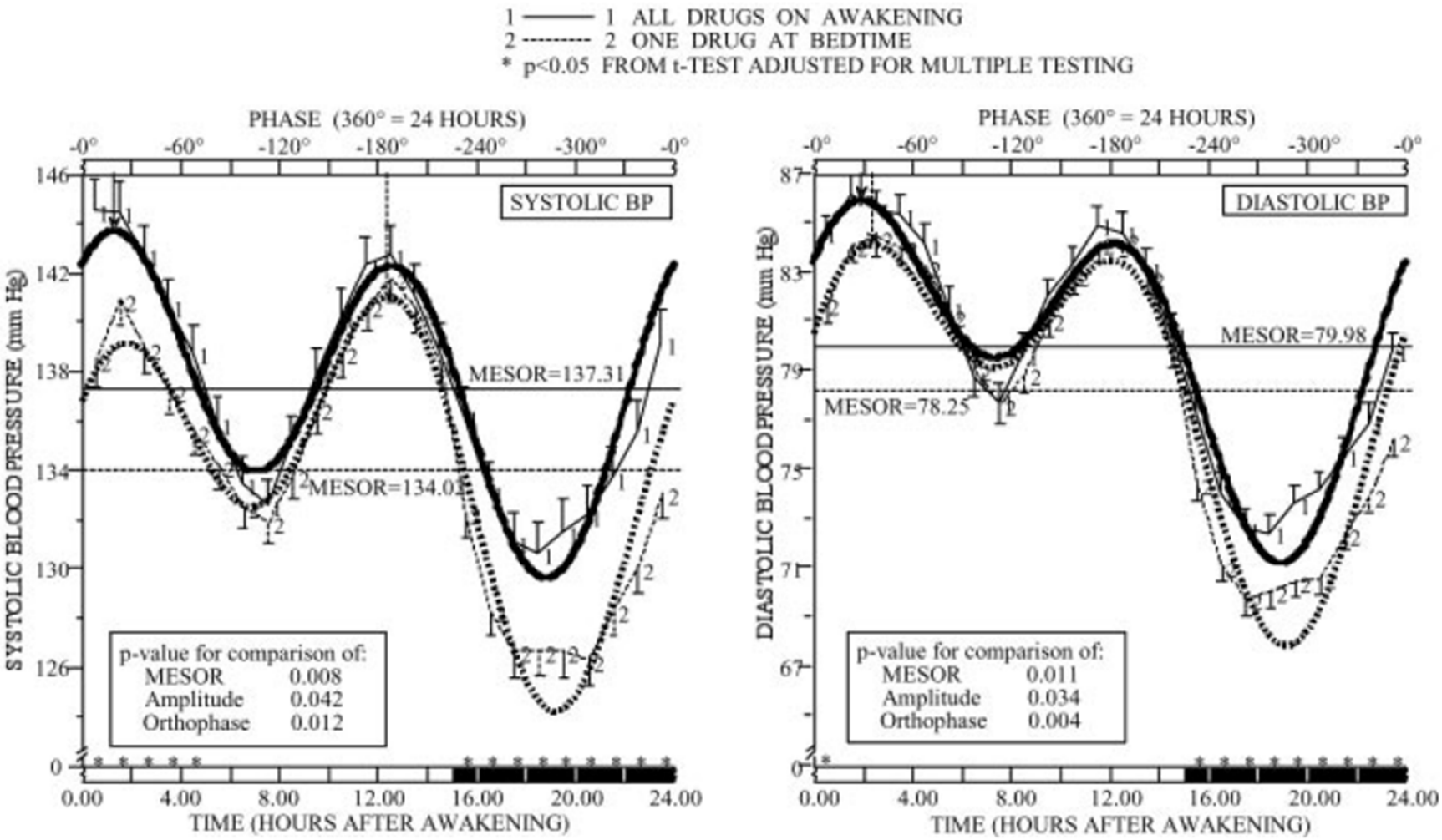
Am J Hypertens 2003;16:925-30.

BP Response to Spironolactone in PA and Non-PA Patients



Am J Hypertens 2003;16:925-30.

Timing of medication administration



Hypertension 2005;46:1053-9.

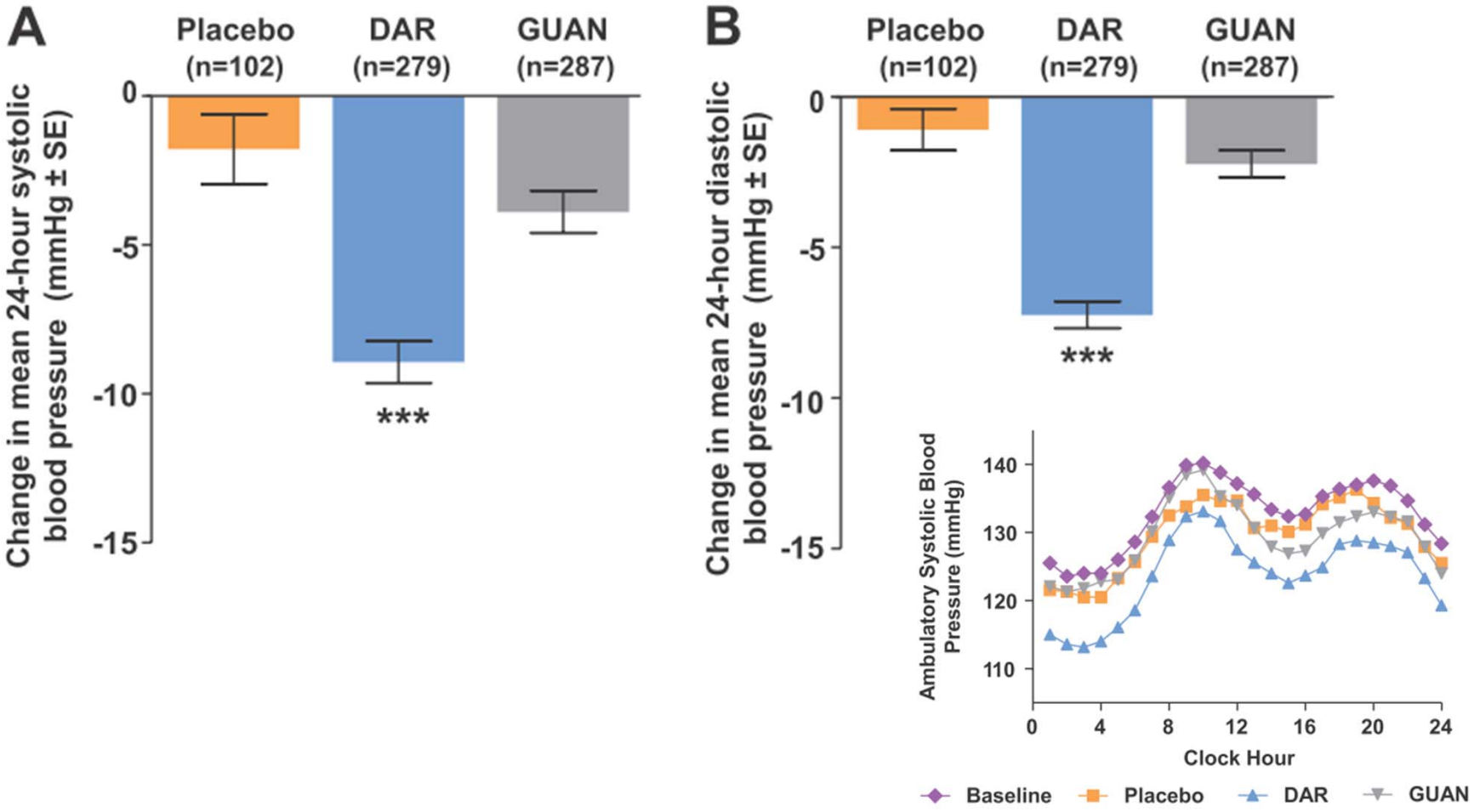
Newer agents

- Endothelin receptor antagonists (ERAs)
  - Darusentan ; type A selective
  - Atrasentan ; type A selective

- Omapatrilat
  - inhibits both neutral endopeptidase (NEP) and angiotensin converting enzyme (ACE).
    NEP inhibition results in elevated natriuretic peptide levels

- Vaccines targeting angiotensin I and II

Darusentan-resistant hypertension trial



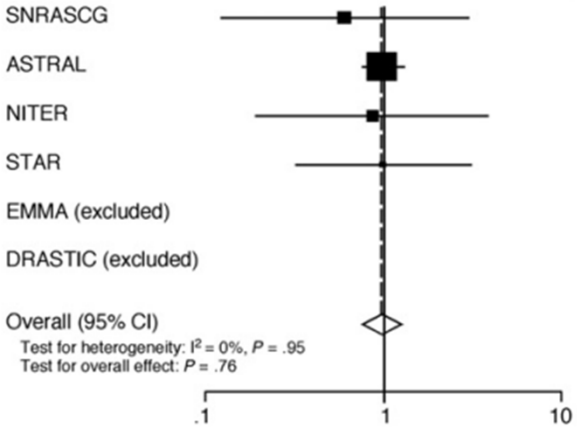
Hypertension 2010;56:824-30.

Interventional strategies

- Percutaneous revascularization (RAS)
- Carotid baroreceptor stimulation
  - Rheos hypertension therapy system by CVRx. Inc., Maple Grove, MN, USA
  - DEBuT-HT trial
- Renal sympathetic denervation
  - Symplicity by Ardian Inc., Palo Alto, CA, USA
  - Simplicity HTN-2 trial

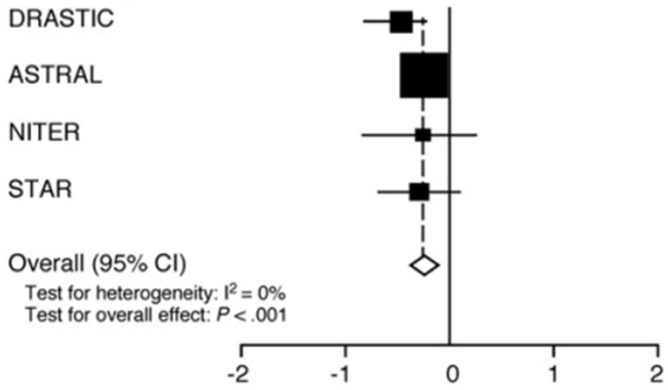
Percutaneous revascularization versus medical management in RAS - A meta-analysis of RCT -

Mortality



	Relative Risk (95% CI)	No. of Events/ Total No. of Participants: Percutaneous Intervention	No. of Events/ Total No. of Participants: Medical Therapy
SNRASCG	0.60 (0.12, 3.01)	2/25	4/30
ASTRAL	0.98 (0.74, 1.29)	79/403	81/403
NITER	0.86 (0.19, 3.86)	3/28	3/24
STAR	0.99 (0.32, 3.09)	5/64	6/76
EMMA (excluded)		0/23	0/26
DRASTIC (excluded)		0/56	0/50
Overall (95% CI)	0.96 (0.74, 1.25)	89/599	94/609

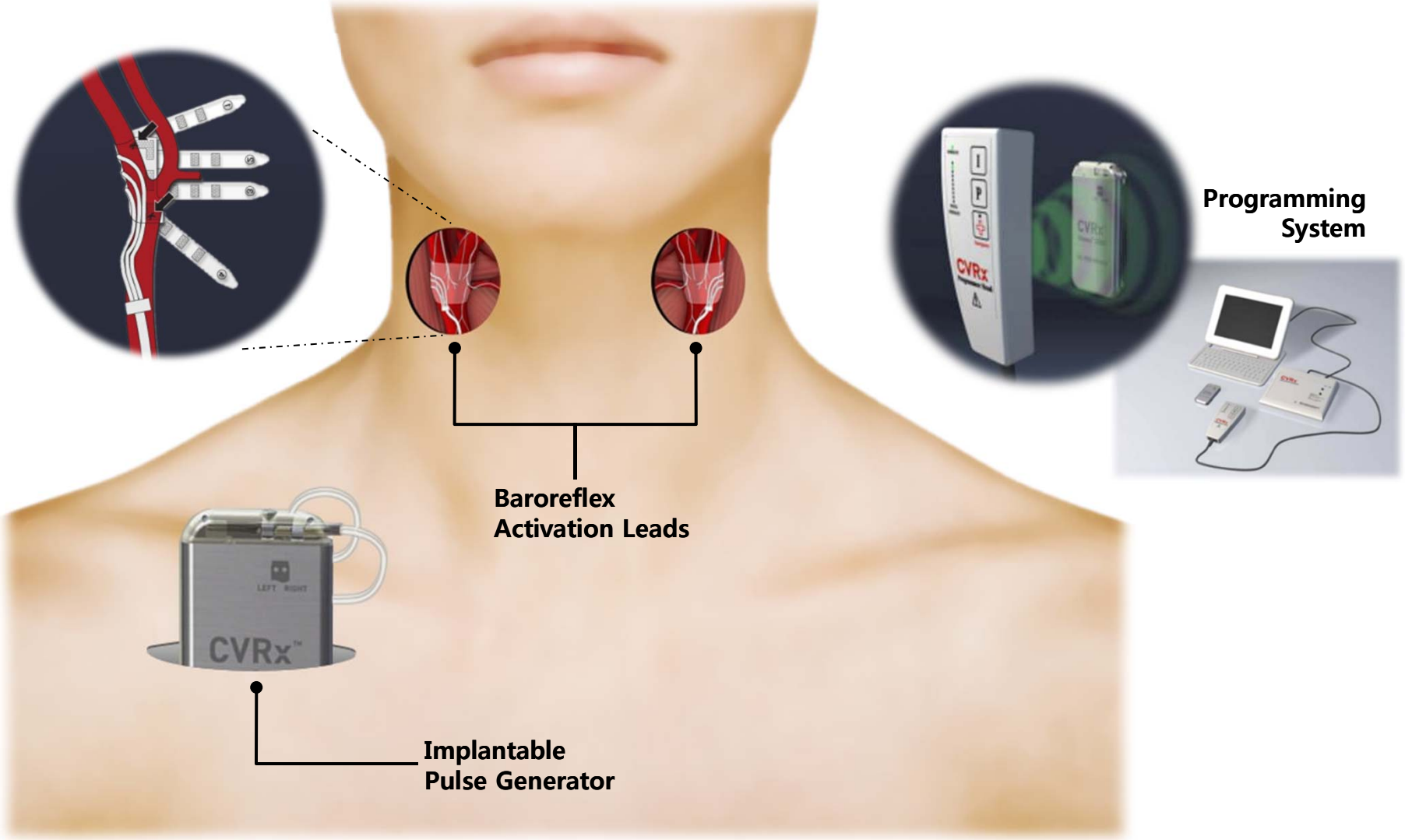
Number of anti-hypertensive medications at end of follow-up



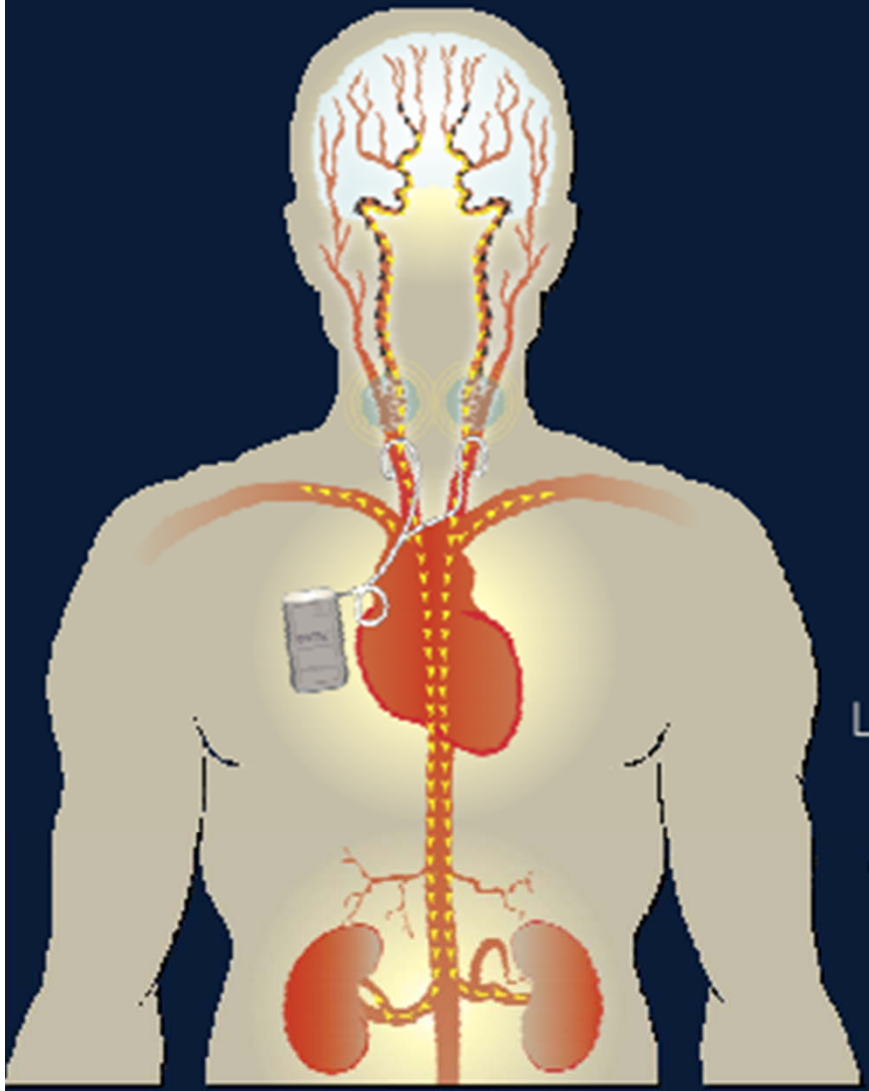
	Weighted Mean Difference (95% CI)	Mean (Standard deviation): Percutaneous Intervention	Mean (Standard deviation): Medical Therapy
DRASTIC	-0.50 (-0.84, -0.16)	1.9 (0.9)	2.4 (0.9)
ASTRAL	-0.20 (-0.36, -0.04)	2.8 (1.2)	3.0 (1.1)
NITER	-0.28 (-0.87, 0.31)	2.9 (1.1)	3.2 (1.1)
STAR	-0.30 (-0.72, 0.12)	2.6 (1.4)	2.9 (1.1)
Overall (95% CI)	-0.26 (-0.39, -0.13)		

Am Heart J 2011;161:622-30.

The CVRx® Rheos System



The Baroreflex as a Therapeutic Target



Carotid Baroreceptor Stimulation

↓

Brain

↓

Autonomic Nervous System
Inhibited sympathetic activity and enhanced parasympathetic activity

Heart	**Vessels**	**Kidneys**
↓ HR	Vasodilation ↓ Stiffness	Diuresis ↓Renin secretion

Reduced excessive blood pressure

Reduced afterload, wave reflections and augmentation

Reduced myocardial work and oxygen consumption

Reduced neurohormonal stimulus

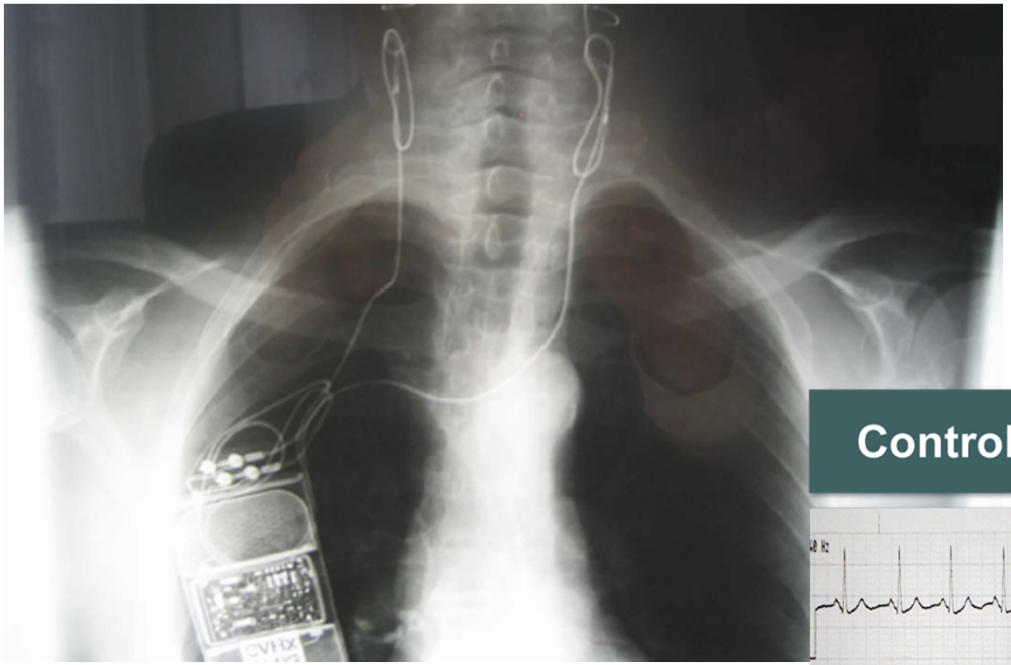
Increased venous capacitance

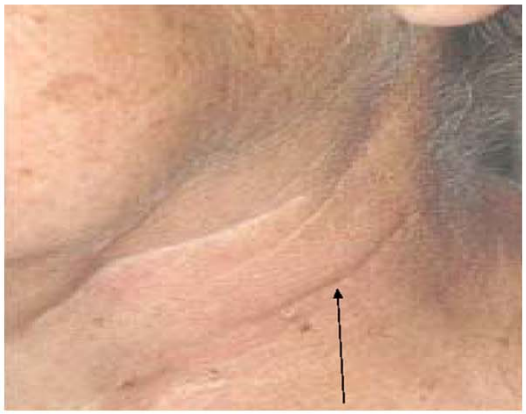
CAUTION: CVRx® Rheos® System is an investigational device and is limited by Federal (or United States) law to investigational use.

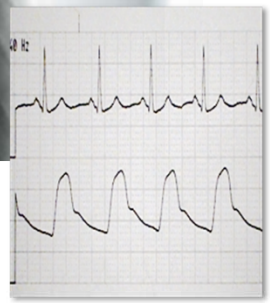
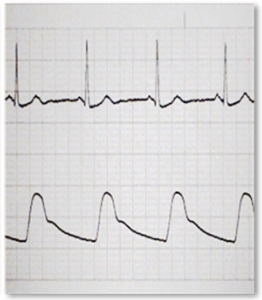
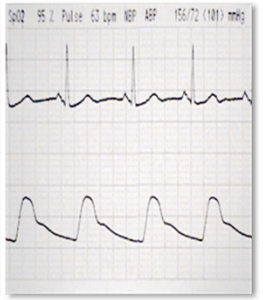
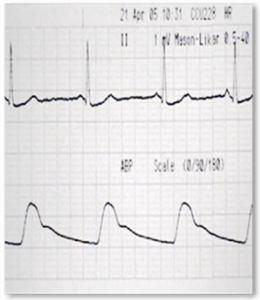
CE The Rheos® System is CE Marked and approved for sale for resistant hypertension.

ISH 2010

Ability to Personalize and Control the Therapy





	Control	1 Volt	2 Volts	3 Volts
				
Heart Rate bpm	71	56	58	50
Blood Pressure mmHg	210 / 96	168 / 73	156 / 72	144 / 66

1-7 V, 480-microsecond pulse width, and 20-Hz frequency

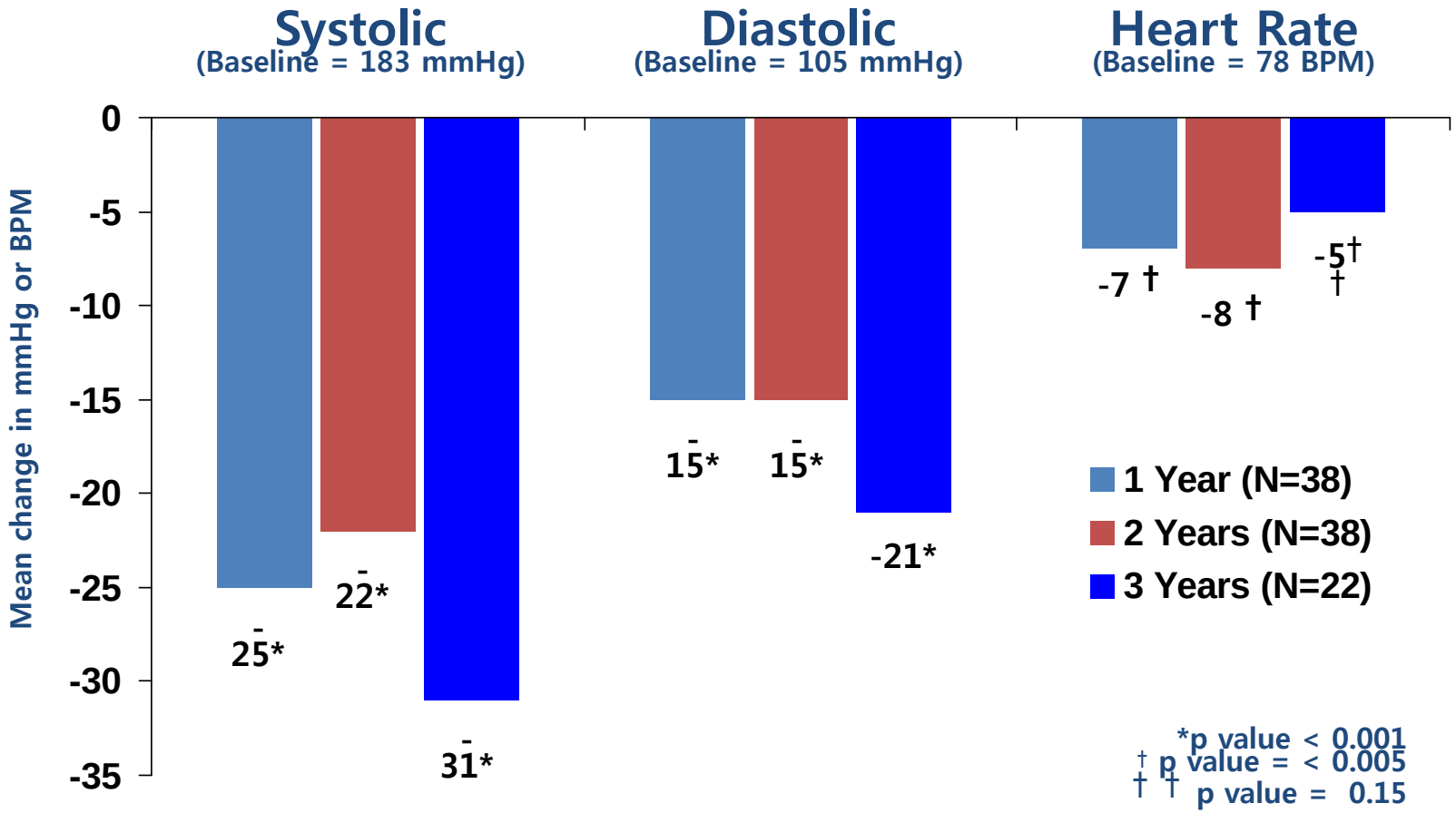
DEBuT-HT trial

- Inclusion criteria
  - Multi-drug resistant systolic hypertension (SBP ≥ 160 mmHg)
  - 3 or more antihypertensive medications with one being a diuretic
  - No treatable secondary cause of hypertension

Location	25 Europe, 13 US
Gender	17 female, 21 male
Race	32 Caucasian, 5 African American
Age (mean years ± sd)	53 ± 11
# Antihypertensive Meds (mean ± sd)	5.1 ± 2
Antihypertensive Therapeutic Index	35.8 ± 17
OC Systolic BP (mean mmHg ± sd)	183 ± 27
OC Diastolic BP (mean mmHg ± sd)	105 ± 21
OC Heart Rate (mean bpm ± sd)	78 ± 12

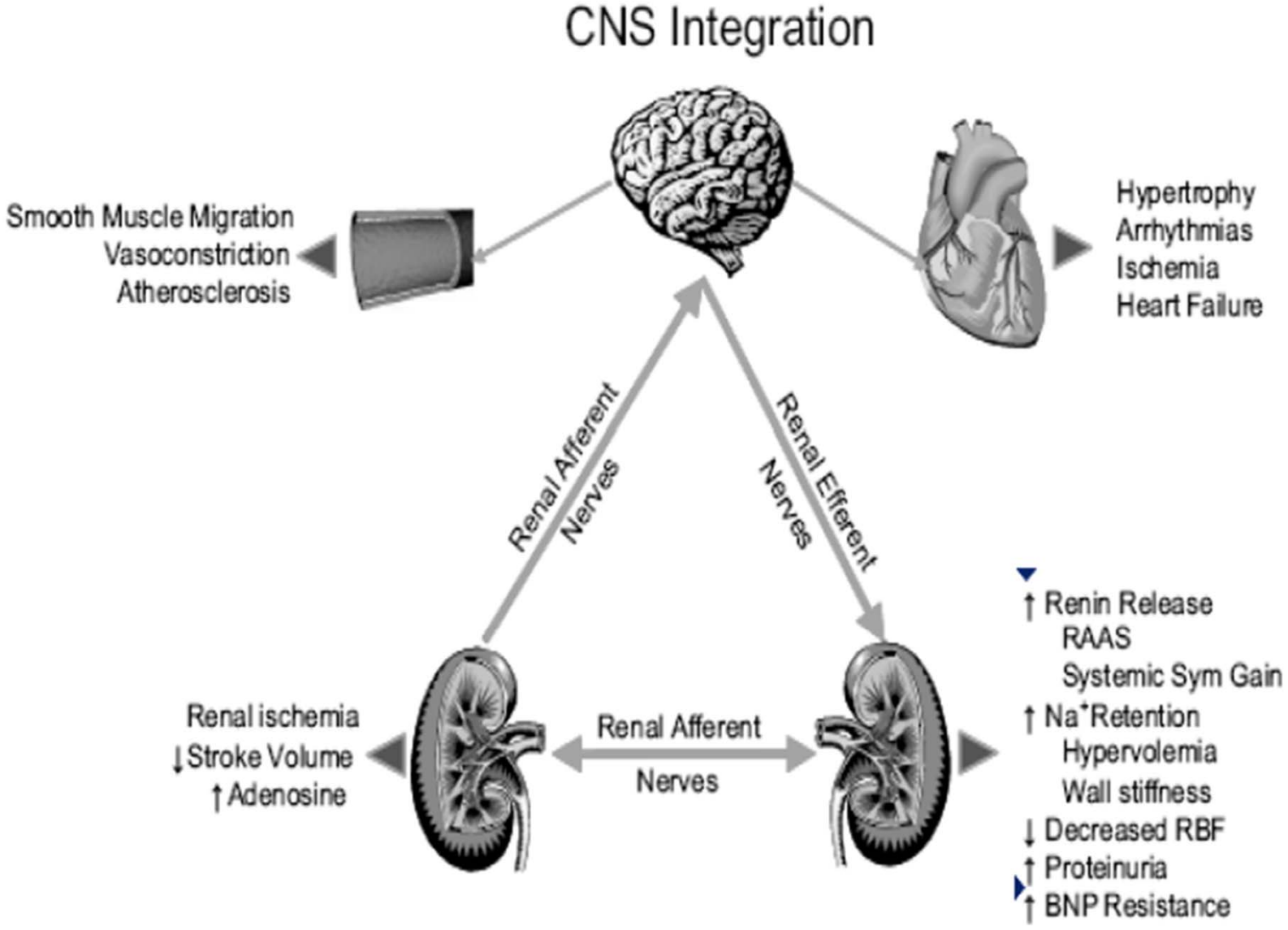
JACC 2010;56:1254-8.

Sustainable reduction of BP over 3 years

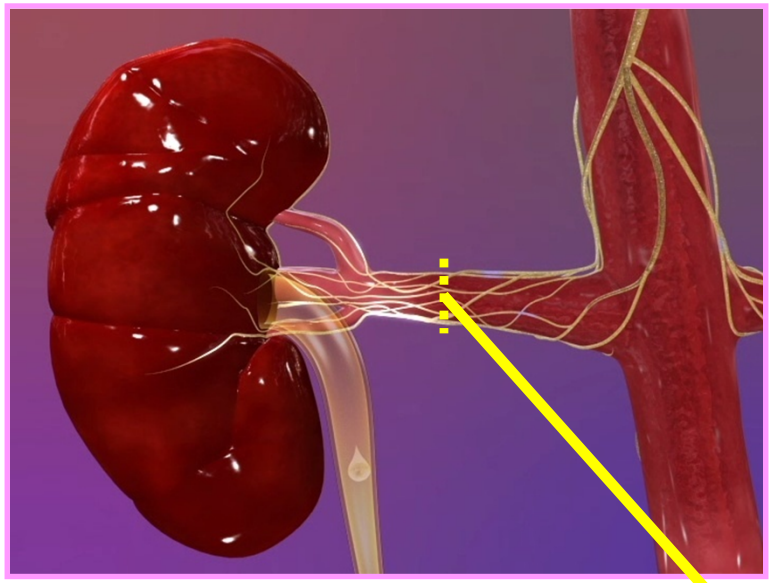


JACC 2010;56:1254-8.

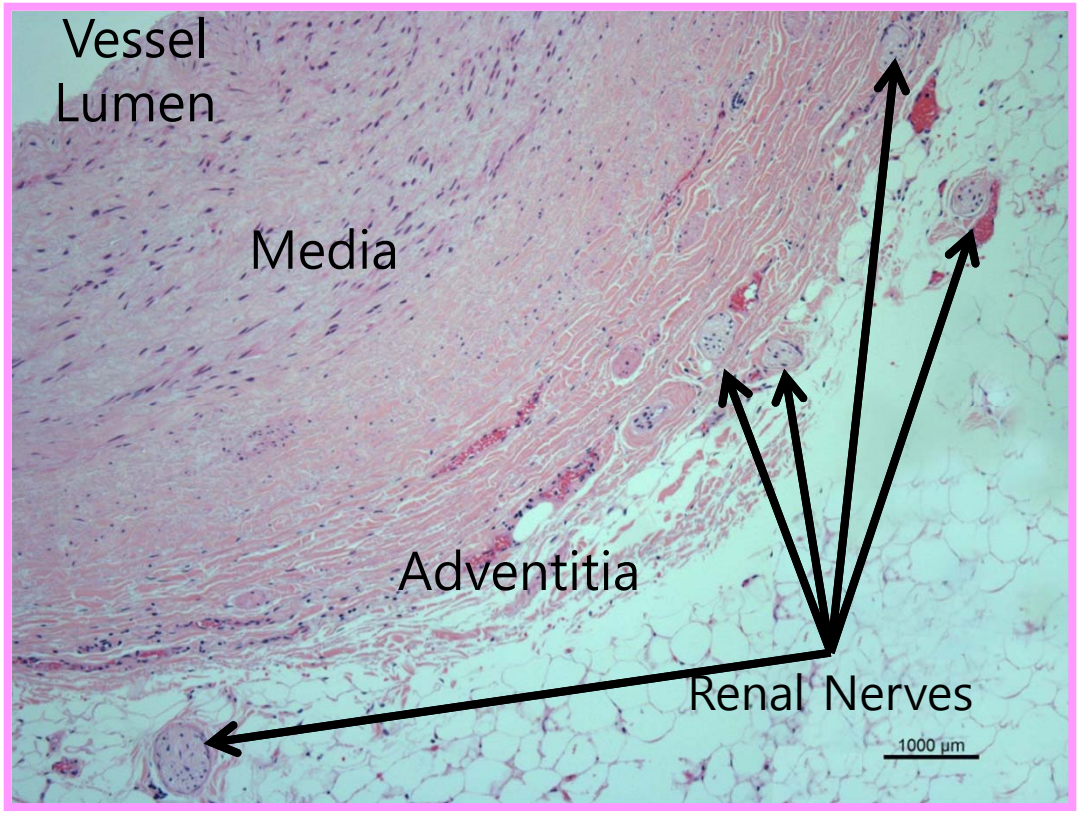
Renal sympathetic nerves



Anatomical Location of Renal Sympathetic Nerves

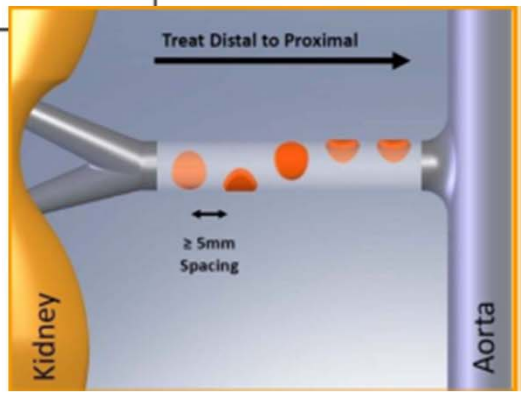


Arise from T10-L1
Follow the renal artery to the kidney
Primarily lie within the adventitia



Symplicity catheter system

- 40-minute catheter-based procedure
- Selectively disable the renal sympathetic afferent and efferent nerves without impairing sympathetic signaling to other organs
- Ramped low power radiofrequency energy delivery (5-8W)
- Blood flow minimizes surface/endothelial injury
- Focal ablations spaced along vessel allows for rapid healing



Symplicity HTN-2 trial (RCT)

- **Purpose: To demonstrate the effectiveness of catheter-based renal denervation for reducing BP in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial**
- **Patients: 106 patients randomized 1:1 to treatment with renal denervation vs. control**
- **Clinical Sites: 24 centers in Europe, Australia, & New Zealand (67% were designated hypertension centers of excellence).**

- **PRIMARY ENDPOINT: Δ Office SBP from baseline to 6 months**
- **SECONDARY ENDPOINTS:**
  - **Safety**
    - **Procedural**
    - **6-month (renovascular & kidney function)**
    - **Composite CV endpoint**
  - **Other measures of BP reduction (e.g. ABPM, % at target, % with 10mmHg response, others)**
  - **LV function (cardiac MRI to assess LV mass)**

Lancet 2010;376:1903-9.

- **Inclusion Criteria:**
  - Office SBP ≥ 160 mmHg (≥ 150 mmHg type II diabetes)
  - ≥ 3 anti-hypertensive meds, no changes within 2 weeks prior to enrollment
  - Age 18-85 years
  - eGFR ≥ 45 mL/min/1.73m^2
- **Exclusion Criteria:**
  - No significant renal artery abnormalities or prior intervention
  - Type I diabetes
  - contraindications to MRI
  - Stenotic valvular heart disease for which ↓BP would be hazardous
  - MI, unstable angina, or CVA in the prior 6 months
  - Pregnancy

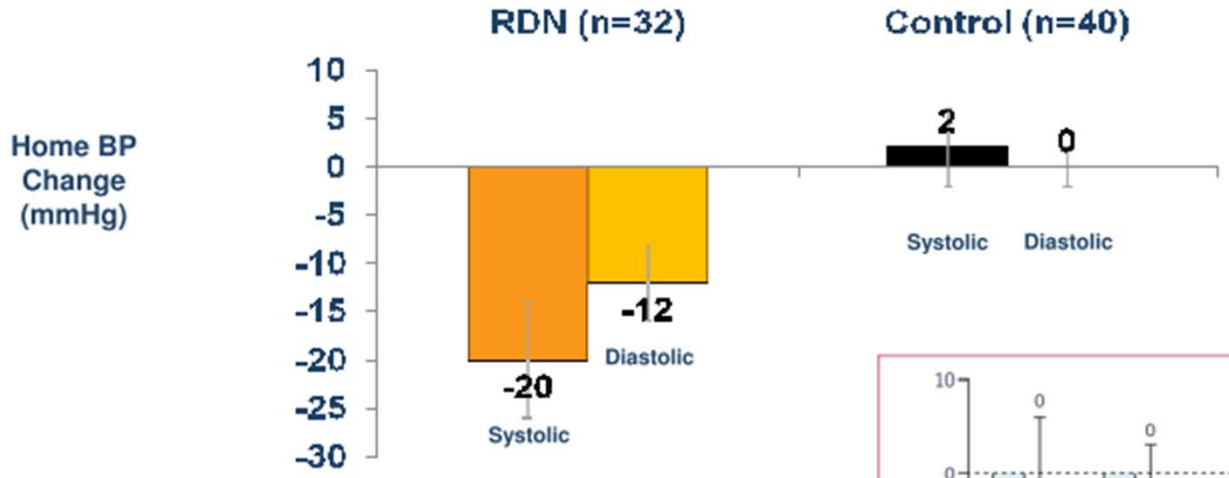
Lancet 2010;376:1903-9.

Baseline characteristics

	RDN (n=52)	Control (n=54)	p-value
Age	58 ± 12	58 ± 12	0.97
Gender (% female)	35%	50%	0.12
Race (% Caucasian)	98%	96%	>0.99
BMI (kg/m^2)	31 ± 5	31 ± 5	0.77
Baseline Systolic BP (mmHg)	**178 ± 18**	**178 ± 16**	**0.97**
Baseline Diastolic BP (mmHg)	**97 ± 16**	**98 ± 17**	**0.80**
Type 2 diabetes	40%	28%	0.22
Coronary Artery Disease	19%	7%	0.09
Hypercholesterolemia	52%	52%	>0.99
eGFR (MDRD, ml/min/1.73m^2)	77 ± 19	86 ± 20	0.013
eGFR 45-60 (% patients)	21%	11%	0.19
Serum Creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.2	0.003
Urine Alb/Creat Ratio (mg/g)†	128 ± 363	109 ± 254	0.64

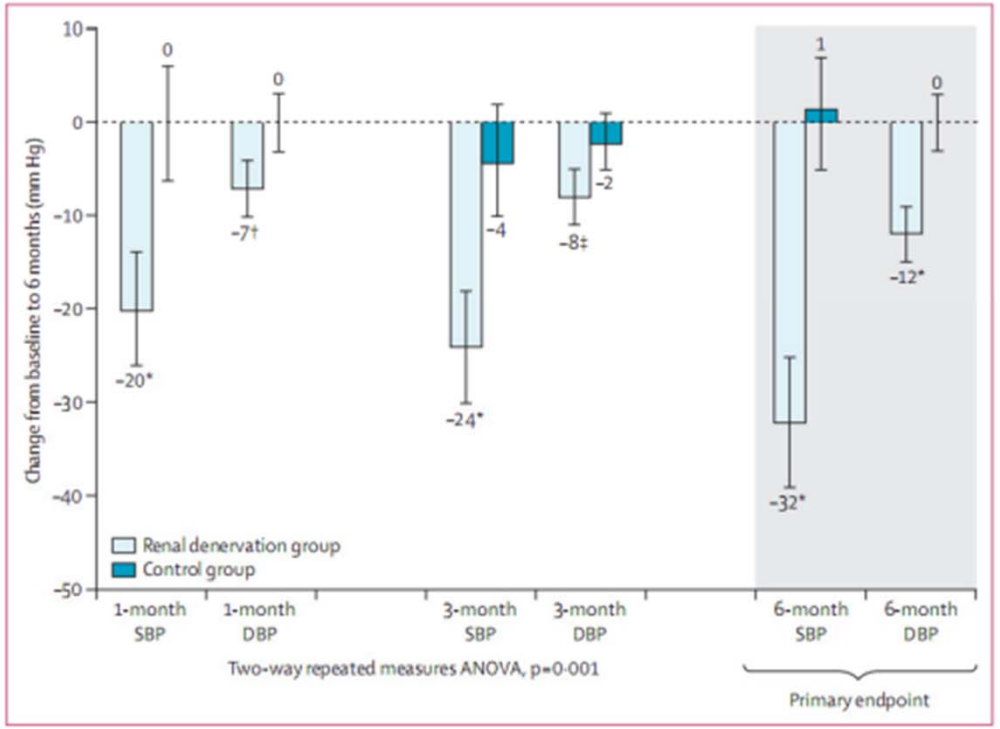
Lancet 2010;376:1903-9.

BP changes



24-h ABPM:

- Analysis on technically sufficient (>70% of readings) paired baseline and 6-m
- RDN (n=20): -11/-7 mmHg (SD 15/11; p=0.006 SBP change, p=0.014 for DB
- Control (n=25): -3/ -1 mmHg (SD 19/12; p=0.51 for systolic, p=0.75 for diasto



Lancet 2010;376:1903-9.

Procedural safety

1. **No serious device or procedure related adverse events (n=52)**

2. **Minor adverse events**

- 1 femoral artery pseudoaneurysm treated with manual compression
- 1 post-procedural drop in BP resulting in a reduction in medication

3. **6-month renal imaging (n=43, 37 Duplex echo, 5 MRI, 5 CT)**

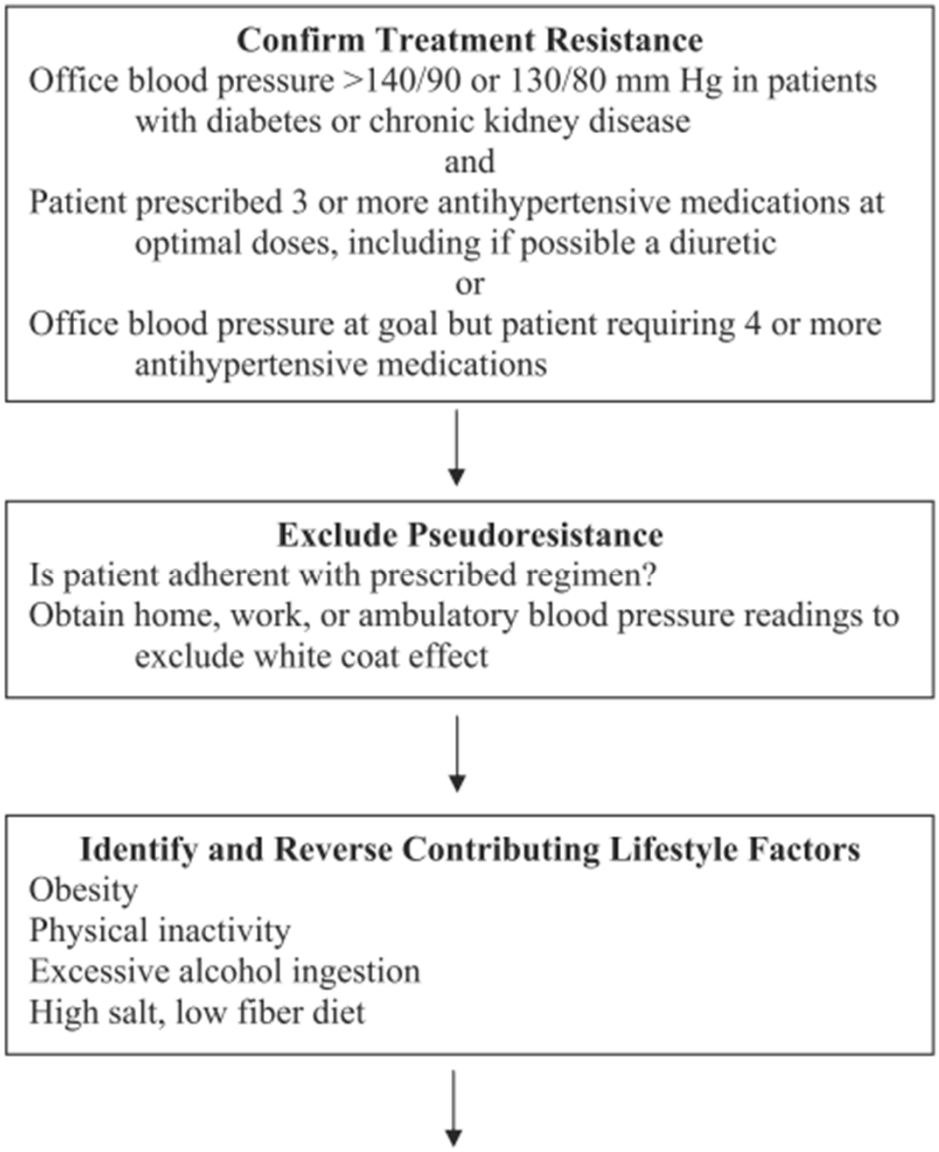
- No vascular abnormality at any RF treatment site
- progression of a pre-existing stenosis unrelated to RF treatment

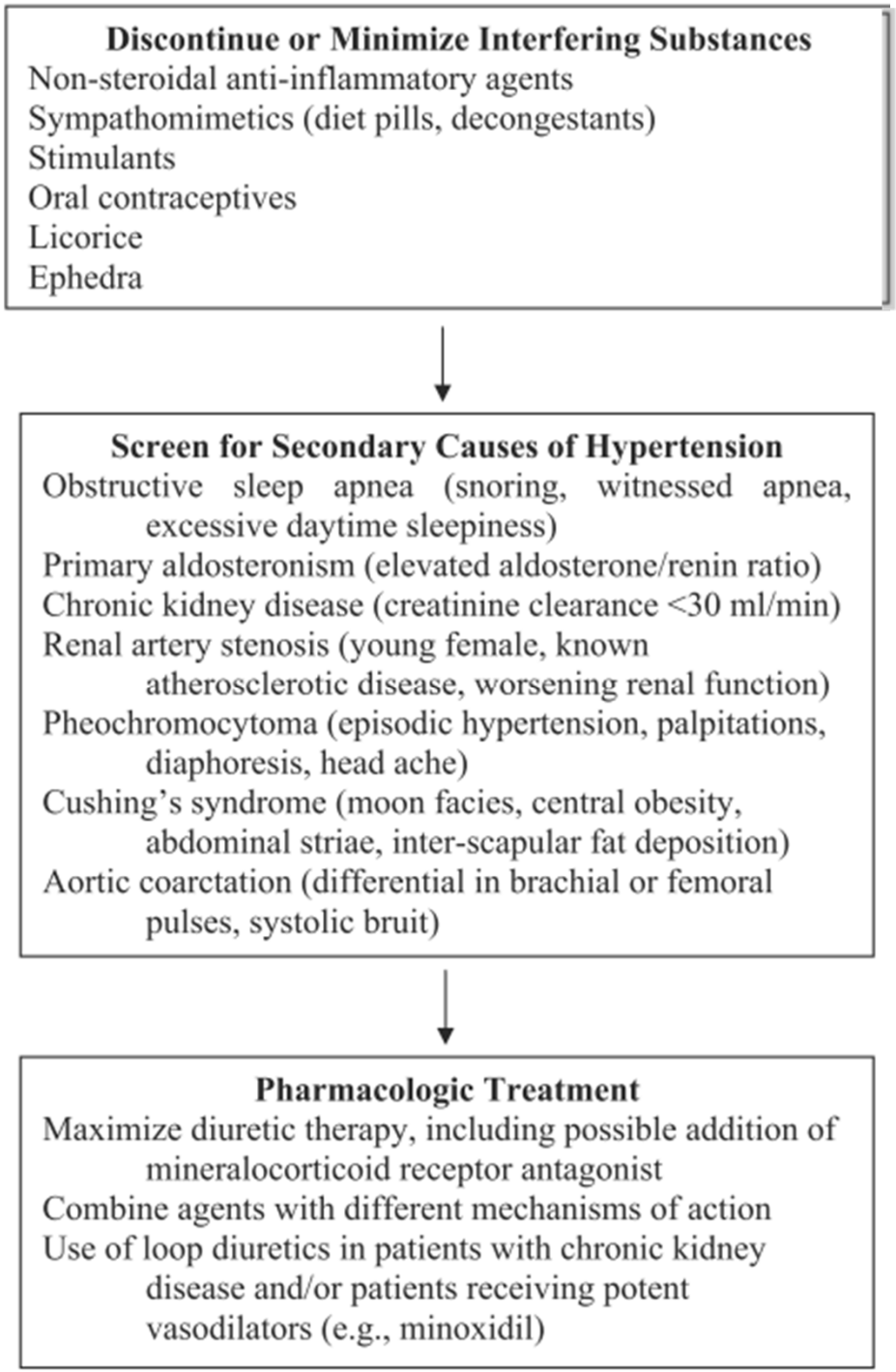
4. **6-month renal function**

- No change

Lancet 2010;376:1903-9.

Summary


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)

경청해 주셔서 감사합니다.