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SGAN
sociedad gallega de nefrología

Manejo diagnóstico y terapéutico de la HTA resistente

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Hospital 12 de Octubre
Madrid

Resistant and Refractory Hypertension: Antihypertensive Treatment Resistance vs Treatment Failure

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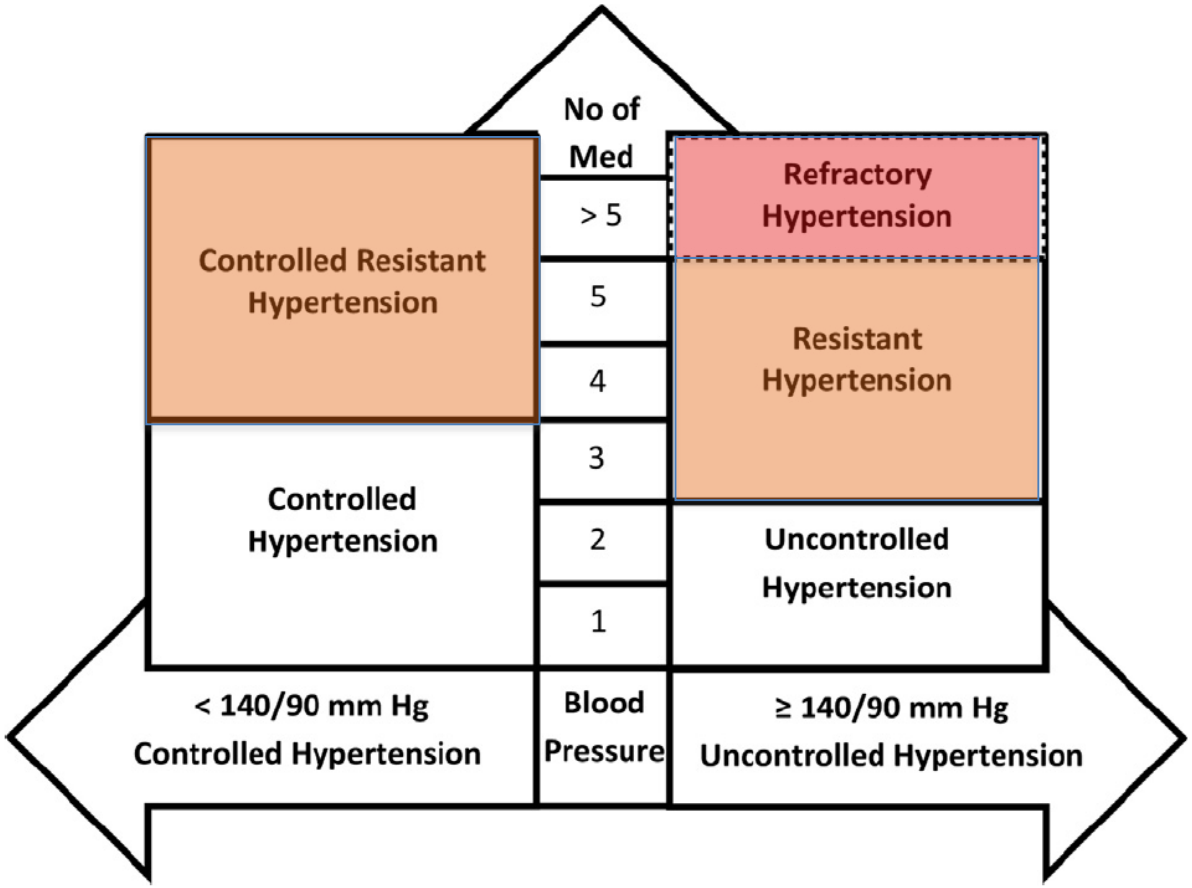


Canadian Journal of Cardiology 32 (2016) 603–606

Resistant Hypertension: Detection, Evaluation, and Management

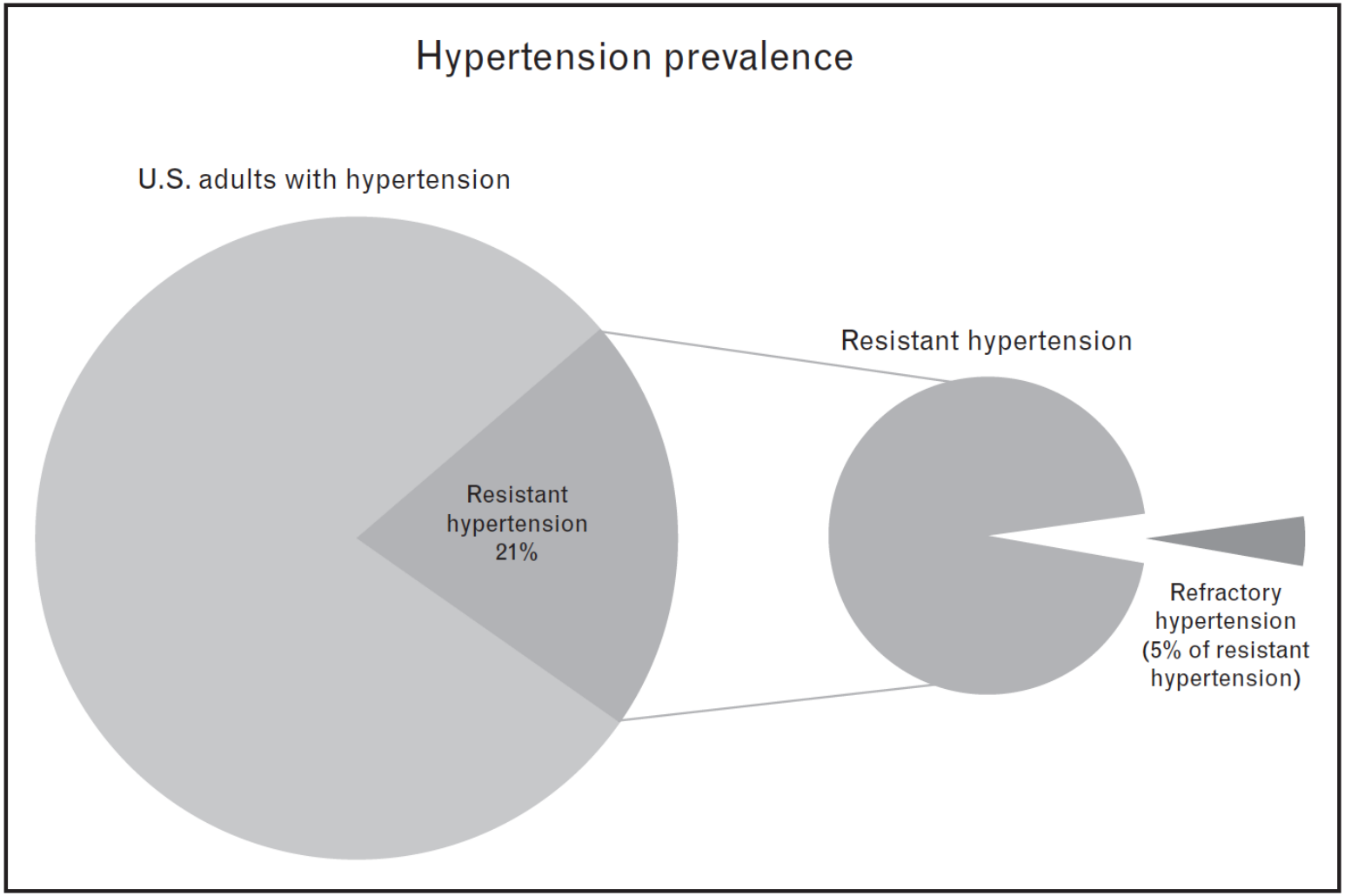
A Scientific Statement From the American Heart Association

Table 1. Prevalence of aTRH in Adults With Treated Hypertension as Reported From Selected Population-, Clinic-, and Intervention-Based Studies

Population Based	Time Period	n	Uncontrolled With ≥3 BP Medications, %	Controlled With ≥4 BP Medications, %	aTRH, %
NHANES[13]	1988–1994	2755	8.3	1.1	9.4
NHANES[13]	1999–2004	3031	8.8	2.9	11.7
NHANES[14]	2003–2008	3710	…	…	12.8
NHANES[13]	2005–2008	2586	9.7	4.8	14.5
REGARDS[15]	2003–2007	14731	9.1	5.0	14.1
REGARDS[16] (CKD)*	2003–2007	3134	…	…	28.1
Clinic based					
EURIKA[17] (diabetes mellitus)	2009–2010	5220	13.0†	3.1	16.1
Spanish ABPM[18]	2004–2009	68045	12.2	2.6	14.8
CRIC (CKD)[19]‡	2003–2008	3939	21.2	19.2	40.4
South Carolina[20]§	2007–2010	468877	9.5	8.4	17.9
Clinical trials					
ALLHAT[21]	1994–2002‖	14684	11.5	1.2	12.7
ASCOT[22]	1998–2005	19527	48.5	…	…
ACCOMPLISH[25]	2003–2006¶	10704	39	…	…
INVEST[26]	1997–2003#	17190	25.1	12.6	37.8

Carey RM et al. Hypertension 2018.

Prevalence of refractory and resistant hypertension



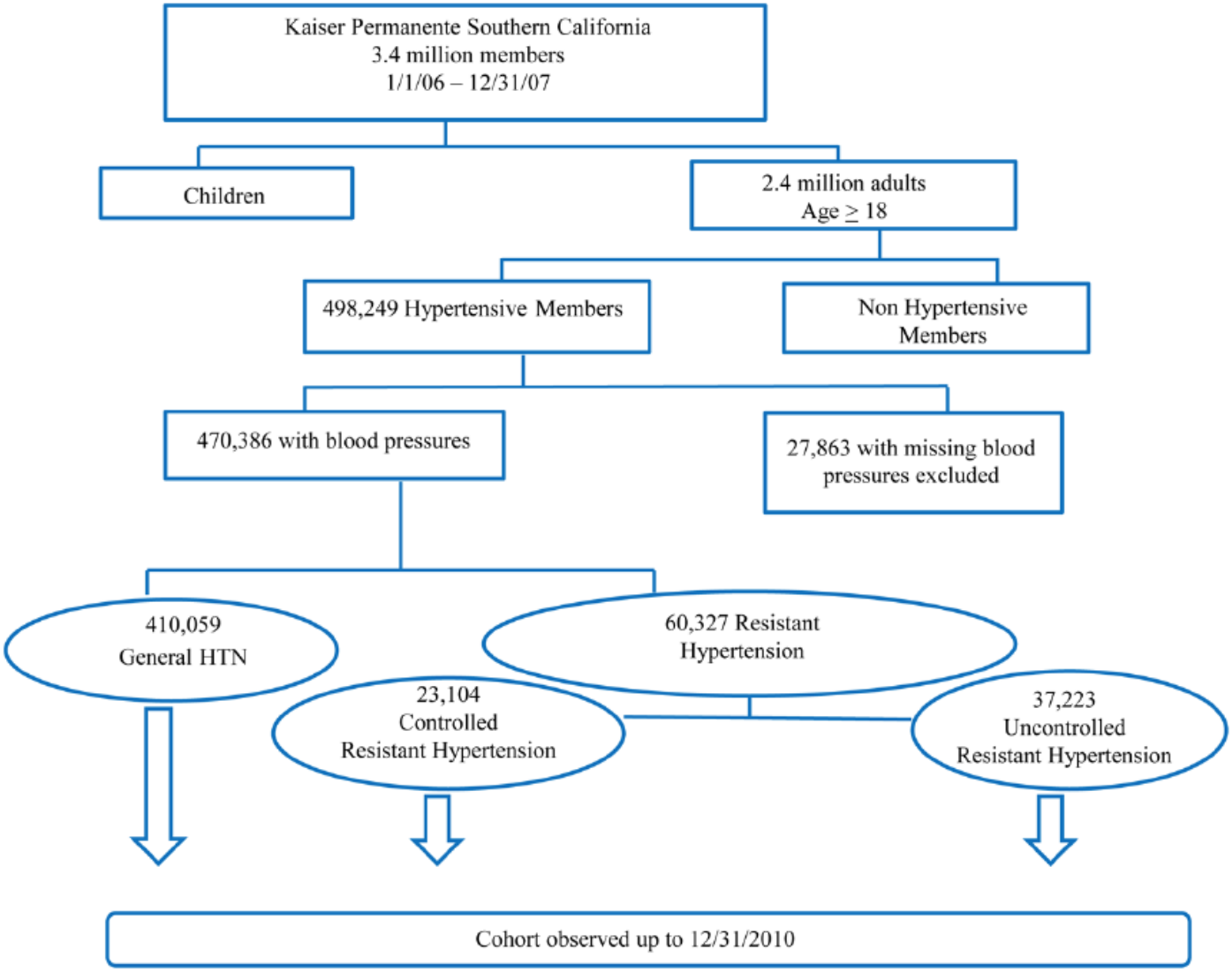
Dudenbostel T, Acelajado MC, Pisoni R, et al. Hypertension 2015; 66:126–133.
Dudenbostel T, Siddiqui M, Oparil S, Calhoun DA. Hypertension 2016; 67:1085–1092.

2018 ESC/ESH Guidelines for the management of arterial hypertension

Characteristics of patients with resistant hypertension	Causes of secondary resistant hypertension	Drugs and substances that may cause raised BP
Demographics • Older age (especially >75 years) • Obesity • More common in black people • Excess dietary sodium intake • High baseline BP and chronicity of uncontrolled hypertension	**More common causes** • Primary hyperaldosteronism • Atherosclerotic renovascular disease • Sleep apnoea • CKD	**Prescribed drugs** • Oral contraceptives • Sympathomimetic agents (e.g. decongestants in proprietary cold remedies) • Non-steroidal anti-inflammatory drugs • Cyclosporin • Erythropoietin • Steroids (e.g. prednisolone and hydrocortisone) • Some cancer therapies
Concomitant disease • HMOD: LVH and/or CKD • Diabetes • Atherosclerotic vascular disease • Aortic stiffening and isolated systolic hypertension	**Uncommon causes** • Phaeochromocytoma • Fibromuscular dysplasia • Aortic coarctation • Cushing's disease • Hyperparathyroidism	**Non-prescription drugs** • Recreational drugs (e.g. cocaine, amphetamines, and anabolic steroids) • Excessive liquorice ingestion • Herbal remedies (e.g. ephedra and ma huang)

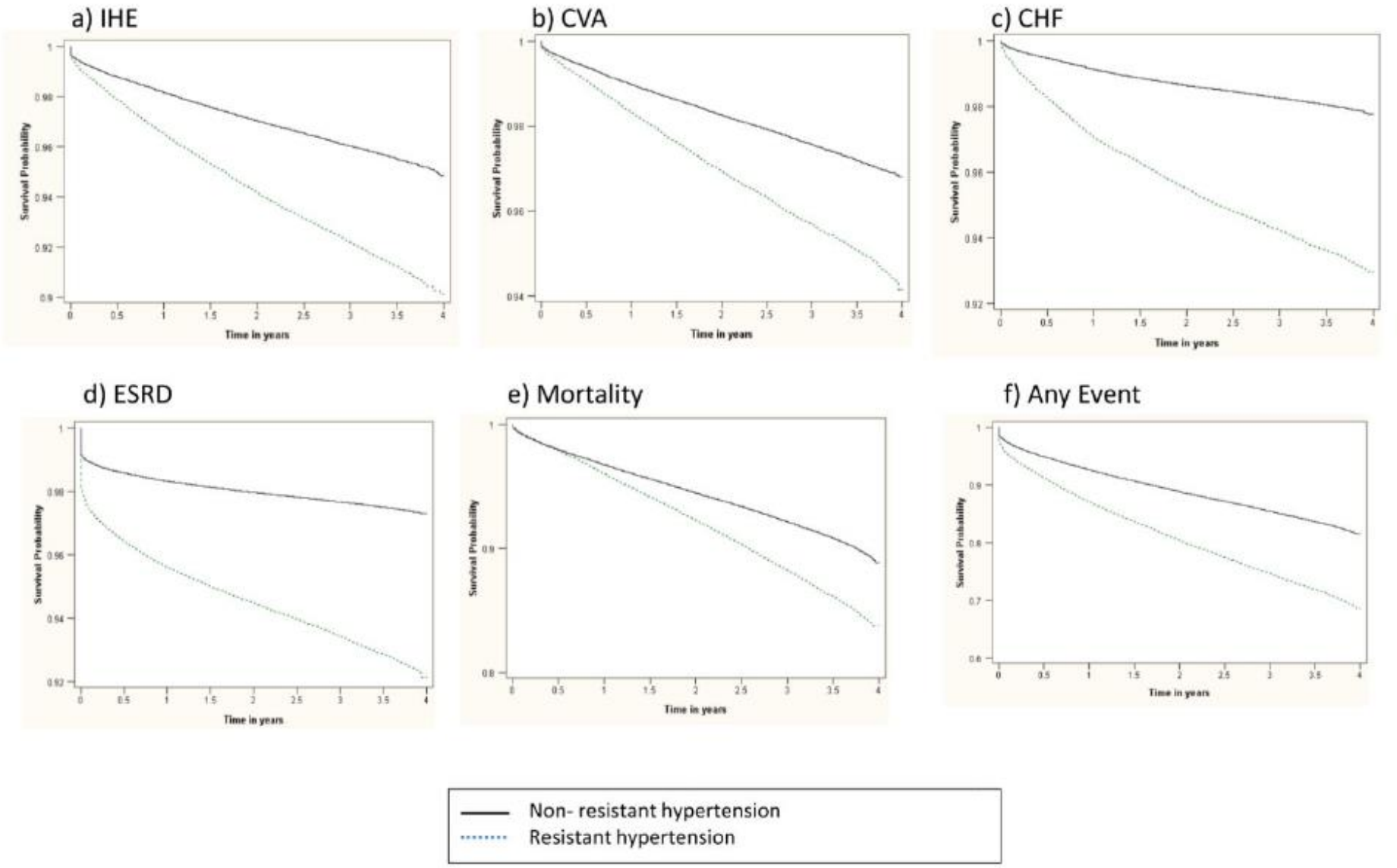
Eur Heart J 2018.

Among approximately 2.4 million adult KPSC members, 470,386 individuals were identified with hypertension. Resistant hypertension was identified in 60,327 (12.8%) with 4.9% controlled resistant hypertension (cRH) and 7.9% uncontrolled resistant hypertension (uRH).



Sim JJ et al. Kidney Int 2015; 88:622–32.

Kaplan Meier survival curves for the primary endpoints (a) ischemic heart event (b) cerebrovascular accident (c) congestive heart failure (d) end stage renal disease (e) all-cause mortality and (f) combined events in patients with non-resistant hypertension (non-RH) and resistant hypertension (RH) which includes both uncontrolled (uRH) and controlled resistant hypertension (cRH).



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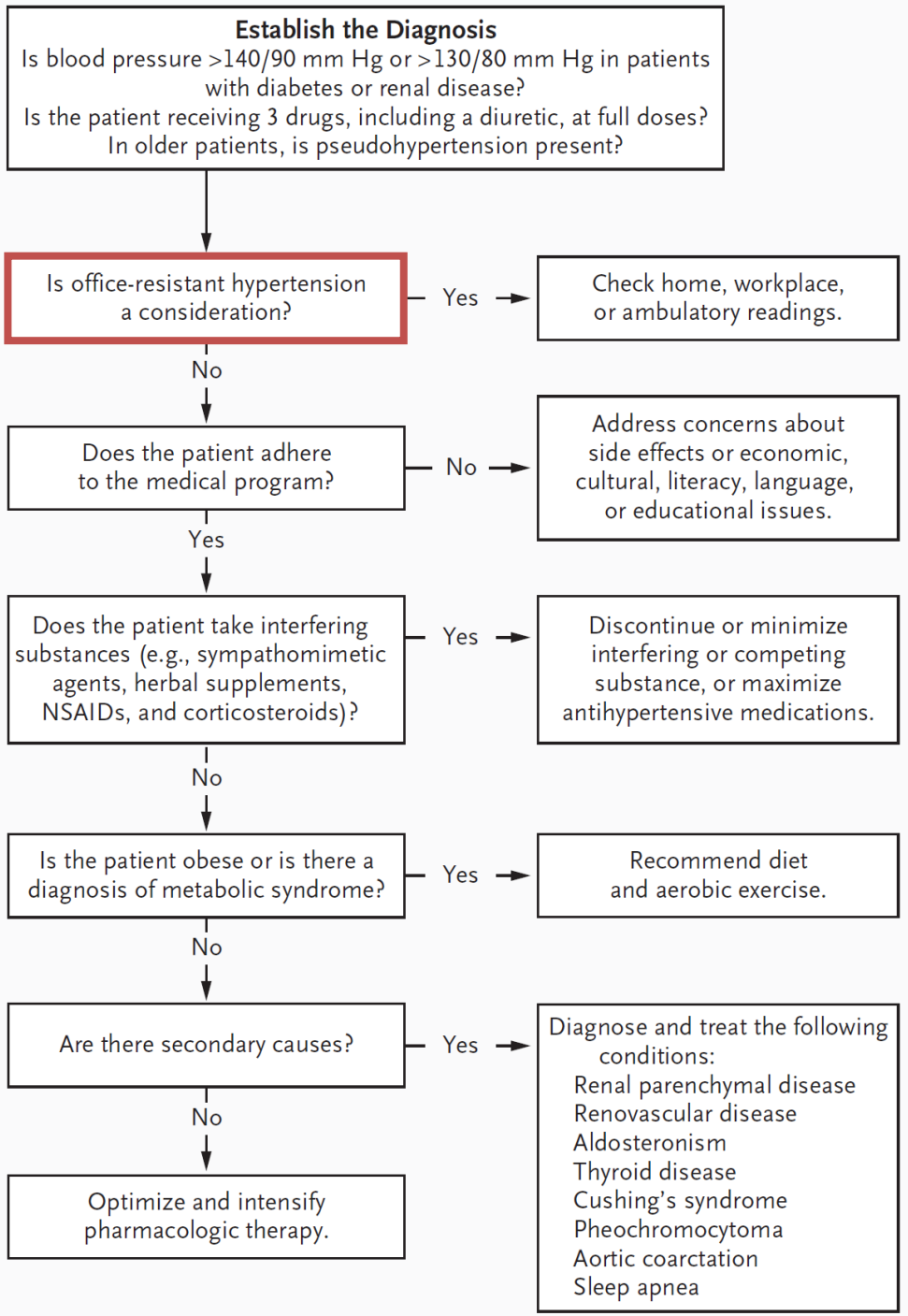
Resistant or Difficult-to-Control Hypertension

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



N Engl J Med 2006;355:385-92.

Clinical Features of 8295 Patients With Resistant Hypertension Classified on the Basis of Ambulatory Blood Pressure Monitoring

Alejandro de la Sierra, Julián Segura, José R. Banegas, Manuel Gorostidi, Juan J. de la Cruz, Pedro Armario, Anna Oliveras, Luis M. Ruilope

Abstract—We aimed to estimate the prevalence of resistant hypertension through both office and ambulatory blood pressure monitoring in a large cohort of treated hypertensive patients from the Spanish Ambulatory Blood Pressure Monitoring Registry. In addition, we also compared clinical features of patients with true or white-coat–resistant hypertension. In December 2009, we identified 68 045 treated patients with complete information for this analysis. Among them, 8295 (12.2% of the database) had resistant hypertension (office blood pressure ≥140 and/or 90 mm Hg while being treated with ≥3 antihypertensive drugs, 1 of them being a diuretic). After ambulatory blood pressure monitoring, 62.5% of patients were classified as true resistant hypertensives, the remaining 37.5% having white-coat resistance. The former group was younger, more frequently men, with a longer duration of hypertension and a worse cardiovascular risk profile. The group included larger proportions of smokers, diabetics, target organ damage (including left ventricular hypertrophy, impaired renal function, and microalbuminuria), and documented cardiovascular disease. Moreover, true resistant hypertensives exhibited in a greater proportion a riser pattern (22% versus 18%; $P<0.001$). In conclusion, this study first reports the prevalence of resistant hypertension in a large cohort of patients in usual daily practice. Resistant hypertension is present in 12% of the treated hypertensive population, but among them more than one third have normal ambulatory blood pressure. A worse risk profile is associated with true resistant hypertension, but this association is weak, thus making it necessary to assess ambulatory blood pressure monitoring for a correct diagnosis and management. (***Hypertension***. **2011;57:898-902.)** • **Online Data Supplement**

Resistant or Difficult-to-Control Hypertension

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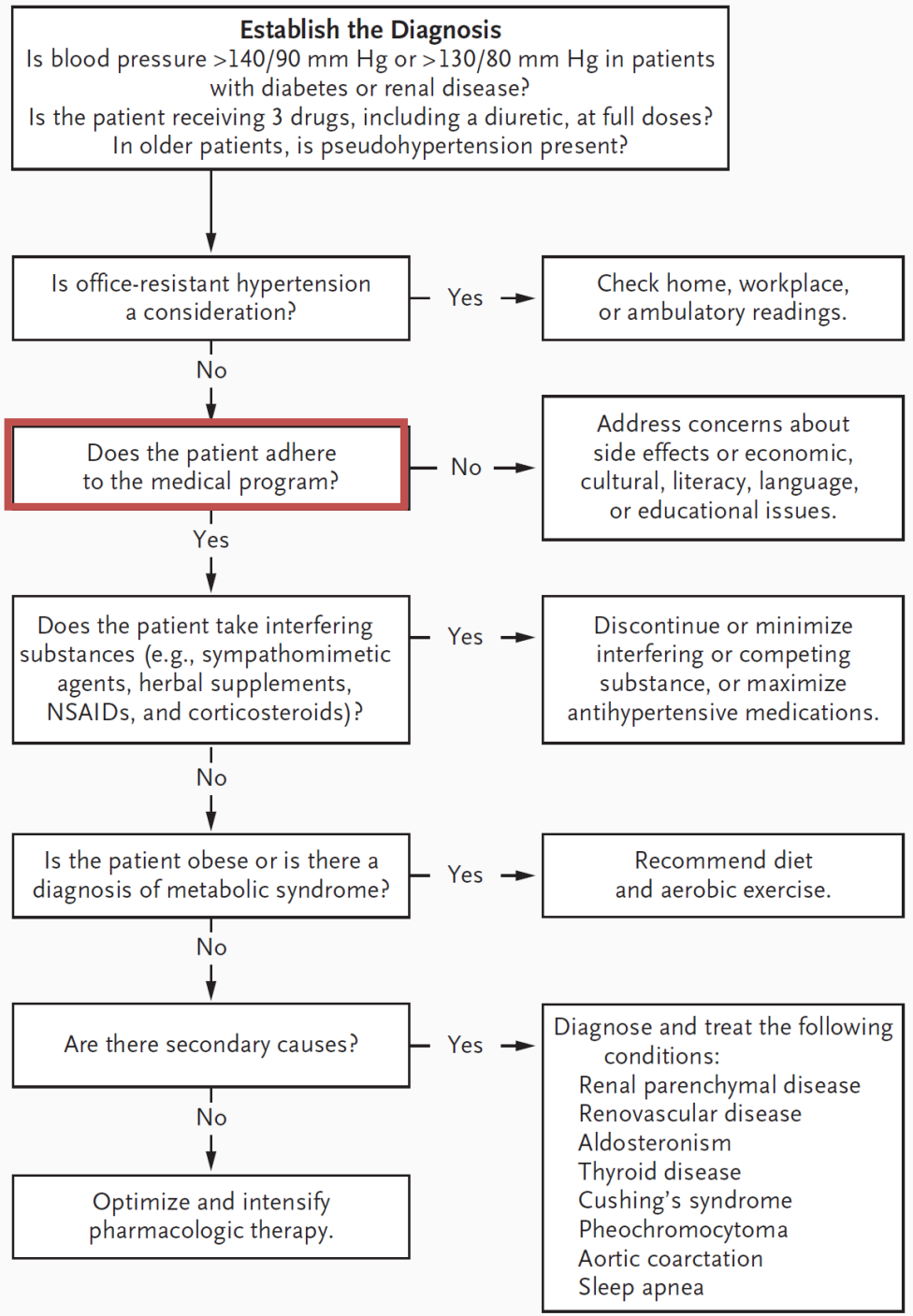
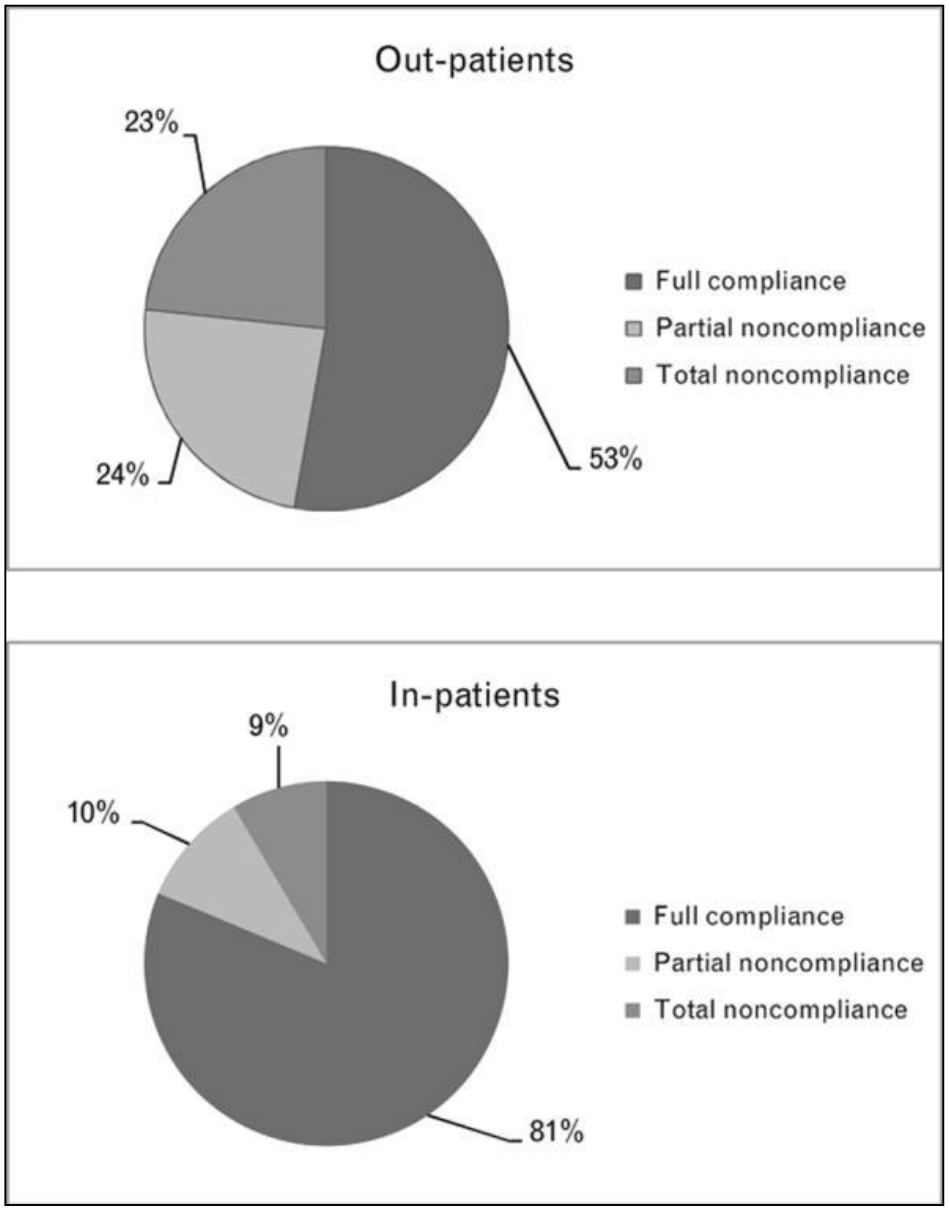


N Engl J Med 2006;355:385-92.



Overview of compliance in out-patients and in-patients in %.

Full compliance = all analyzed drugs positive.

Partial noncompliance = at least one of analyzed drugs negative.

Total noncompliance = all analyzed drugs negative.

J Hypertens 2013; 31: 2455-2461.

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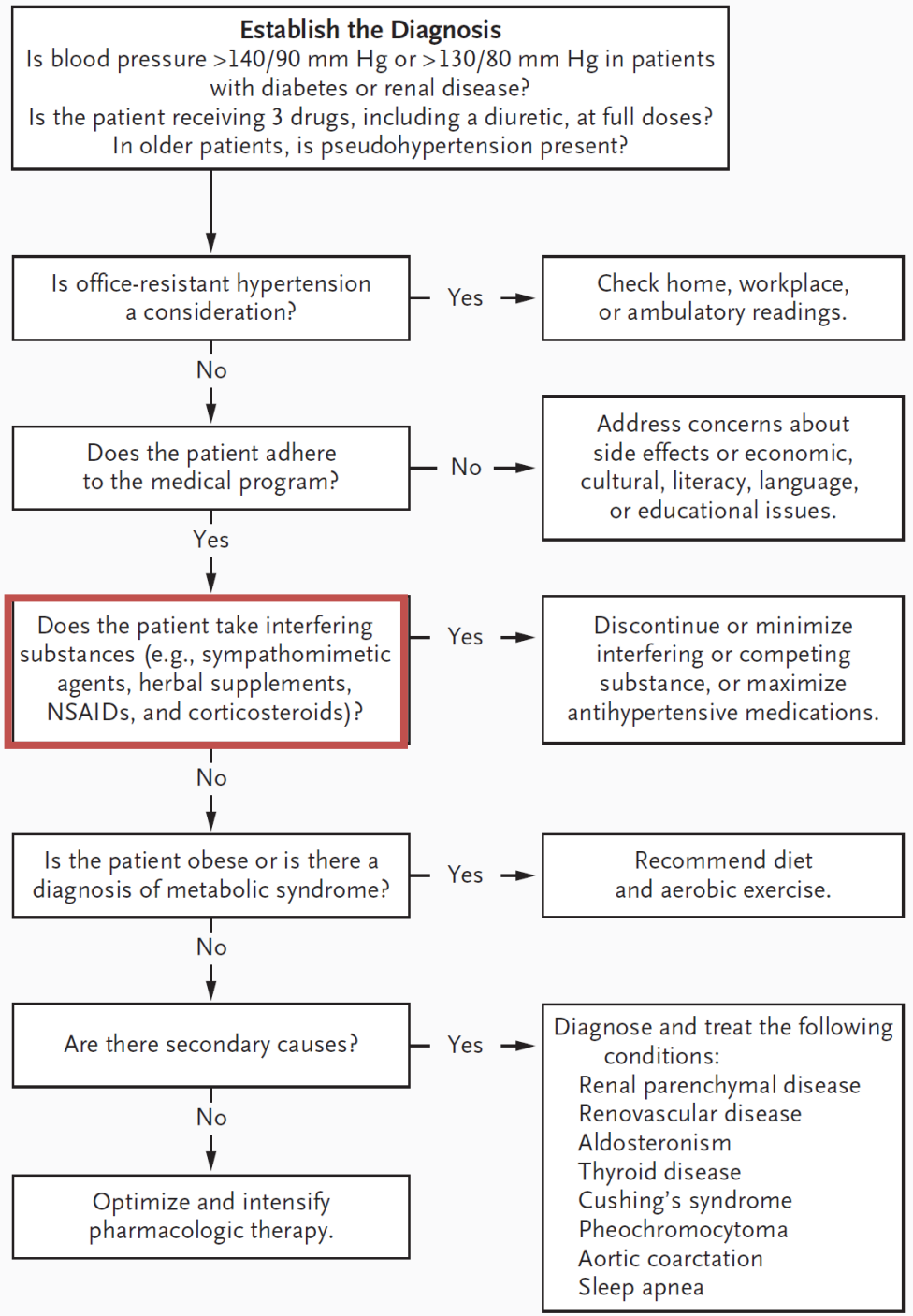

N Engl J Med 2006;355:385-92.

Drug induced hypertension – An unappreciated cause of secondary hypertension

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Chemical compounds studied in this article::
Bevacizumab
Lapatinib
Sunitinib
Sorafenib
Rofecoxib
Celecoxib
Venlafaxine
Prednisone Licorice acid
cyclosporin A

ABSTRACT

Most patients with hypertension have essential hypertension or well-known forms of secondary hypertension, such as renal disease, renal artery stenosis, or common endocrine diseases (hyperaldosteronism or pheochromocytoma). Physicians are less aware of drug induced hypertension. A variety of therapeutic agents or chemical substances may increase blood pressure. When a patient with well controlled hypertension is presented with acute blood pressure elevation, use of drug or chemical substance which increases blood pressure should be suspected. Drug-induced blood pressure increases are usually minor and short-lived, although rare hypertensive emergencies associated with use of certain drugs have been reported. Careful evaluation of prescription and non-prescription medications is crucial in the evaluation of the hypertensive individual and may obviate the need for expensive and unnecessary evaluations. Discontinuation of the offending agent will usually achieve adequate blood pressure control. When use of a chemical agent which increases blood pressure is mandatory, anti-hypertensive therapy may facilitate continued use of this agent.

We summarize the therapeutic agents or chemical substances that elevate blood pressure and their mechanisms of action.

Eur J Pharmacol 2015;763:15–22.

Different drug classes and their effect on blood pressure.

Drug	Clinical use	Notes
Anti cancer agents		
Anti vascular endothelial growth factor (VEGF) signaling	Anti cancer therapy	HTN should be considered as a class effect. The incidence of HTN is dose related and preexisting hypertension, old age ($\geq$ 60 years), and overweight ($\geq$ 25 kg/m^2) are risk factors for anti-VEGF therapy-induced BP elevation
Bevacizumab	Metastatic cancers of the colon, rectum, kidney, breast and glioblastoma multiforme	
Sorafenib	Approved for advanced renal cell carcinoma and hepatocellular carcinoma	
Sunitinib	Advanced gastrointestinal stromal tumor and renal cell carcinoma	
Alkylating agents	Antineoplastic agent	
Paclitaxel	Antineoplastic agent	
Cis-diamminedichloroplatinium	Antineoplastic agent	Only during intra-arterial administration
Analgesic, anti-inflammatory		
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	Analgesic, anti inflammatory	Mild, dose dependent increase in BP. Elderly patients, those with pre-existing hypertension, salt-sensitive patients, patients with renal failure and patients with renovascular HTN are at a higher risk to develop severe HTN. Calcium antagonists are the preferred choice of treatment
Acetaminophen	Analgesic	The effect of acetaminophen on BP is unclear
Psychiatric drugs		
Clozapine	Anti psychotic agent	
Venlafaxine	Antidepressive and anti anxiety agents	At dose above 300 mg/day
Monoamine oxidase inhibitors	antidepressive agents	Mainly with sympathomimetic amines and with certain food containing tyramine. Tranylcypromine is the most hazardous because of its stimulant action, whereas moclobemide and brofaromine are the least likely to induce hypertensive reaction
Tricyclic antidepressants	Antidepressive agent	More common in patients with panic disorders
Buspirone	Anxiolytic agent	Mild dose dependent increase in BP
Fluoxetine	Antidepressive agents	In combination with selegiline
Thioridazine hydrochloride	Psychotic and depressive disorders	Massive overdose may cause severe HTN
Carbamazepine	Bipolar depression and seizures	
Lithium	Manic depressive illness	Acute intoxication can cause severe HTN
Steroids		
Glucocorticoid	Replacement therapy, rheumatic disease collagen disease, dermatologic disease, allergic state, opthalmic disease, inflammatory bowel disease, respiratory disease, hematologic and neoplastic disease, nephropathies	HTN occurs more often in elderly patients and in patients with a positive family history of primary HTN. BP rise is dose-dependent and at low doses cortisol has less effect on BP
Mineralocorticoid		
Liquorice	A flavoring and sweetening agent	Dose dependent, sustained increase in BP characterized by hypokalemia, metabolic alkalosis and suppressed plasma renin activity and aldosterone levels
Carbenoxolone	Ulcer medication	
9-alpha fluoroprednisolone	Skin ointments, antihemorrhoid	
9-Alpha fluorocortisol	Cream	
Ketoconazole	Ophthalmic drops, and nasal sprays Anti mycotic	
Sex hormones Estrogen + Progesterone	Contraception, replacement therapy	Mild, sustained BP elevation, more common in premenopausal women. History of high BP during pregnancy, a family history of HTN, cigarette smoking, obesity, black, diabetes, and renal disease increase the risk of developing HTN. Severe HTN has been reported.
Androgens	Prostate cancer	Mild dose dependent sustained increase in systolic BP. Severe hypertension has been reported
Danazol (semisynthetic androgen)	Anabolic effect Endometriosis, hereditary angioedema	
Immunosuppressive agents		
Cyclosporine A	Immunosuppressive agent, prophylaxis of organ rejection, autoimmune disease,	Dose dependent mild to moderate increase in BP. Presence of HTN before transplantation, elevated creatinine levels and maintenance therapy with corticosteroids, increase the risk of HTN. Severe HTN has been reported

Drug	Clinical use	Notes
	dermatologic disorders	
Tacrolimus	Prophylaxis of organ rejection	Produces less HTN than cyclosporine A
Rapamycin	Prophylaxis of organ rejection	Produces little BP increase
Recombinant human erythropoietin	Anemia of renal failure and of some malignancies	Dose-related mild increasein BP. The risk to develop or worsen HTN is increased in the presence of pre-existing HTN, the presence of native kidneys, a genetic predisposition to HTN, when the initial hematocrit is low and when it increases rapidly. Hypertensive crisis with encephalopathy has been reported
Highly active antiretroviral therapy (HAART)	Anti HIV treatment	Recent studies reported that HTN was associated with traditional cardio metabolic risk factors and was unassociated with the treatment itself
Cocaine	Local anesthetics	Cocaine use is associated with acute but not chronic HTN. Transient severe increase in BP especially when used with β-blockers
Caffeine	Analgesia, vascular headache, beverages	The reaction to caffeine is more pronounced in males, in those with a positive family history of HTN and in African-American subjects. Caffeine may cause persistent BP effects in persons who are regular consumers, even when daily intake is at moderately high levels. Variability in the acute BP response may be partly explained by genetic polymorphisms of the adenosine A2A receptors and alpha(2)-adrenergic receptors.
Alcohol	Beverage	Dose dependent, sustained increase in BP. The BP effects of alcohol are independent from obesity, salt intake, cigarette smoking, and potassium intake.
Anti emetic drugs		
Metoclopramide	Anti emetic	
Alizapride	Anti emetic	
Prochlorperazine	Anti emetic	
Herbal products	Complementary and Alternative medicine	Mainly relate to dietary supplements that contain ephedra alkaloids
Miscellaneous		
Phenylephrine hydrochloride	Upper respiratory decongestant, ophthalmic drops	Dose dependent, sustained increase in BP.
Dipivalyl adrenaline hydrochloride	Opthalmic drops	Severe HTN has been reported
Epinephrine (with β blocker)	Local anesthetic, anaphylactic reaction, bronchodilatation, decongestant, anti hemorrhoidal treatment	
Phenylpropanolamine	Anoretic, upper respiratory decongestant	
Pseudoephedrine hydrochloride	Upper respiratory decongestant	
Tetrahydrozoline hydrochloride	Opthalmic vasoconstrictor drops	
Naphazoline hydrochloride	Opthalmic vasoconstrictor and nasal dec-decongestant drops	
Oxymetazoline hydrochloride	Upper respiratory decongestant drops	
Ketamine hydrochloride	Anesthetic agent	Transient severe increase in BP has been reported
Fentanyl Citrate	Narcotic analgesic and anesthetic agent	
Smokeless tobacoo	Alternative to smoking	
Methylphenidate Demethylphenidate Amphetamine	Attention deficit hyperactivity disorder	
Yohimbine hydrochloride	Impotence	Acute, dose dependent increase in BP
Sibutramine	Weight loss	Mild increase in BP
Glucagon	Prevent bowel spasm	Only in patients with pheochromocytoma.
Selegiline	Used mainly for Parkinsons' disease	
Physostigmine	Reverse anticholinergic syndrome, myasthenia gravis, glaucoma, Alzheimer's disease,	
Ritodrine hydrochloride	Inhibition of pre-term labor	Hypertensive crisis has been reported
Disulfiram	Management of alcoholism	Slight increase in BP. Severe HTN may occur in alcoholic-induced liver disease
Lead	Industry	Also activates the sympathetic nervous system
Scopolamine	Pre-anaesthetic medication, Motion sickness	
Naloxone hydrochloride	Opioid overdose	Transient BP elevation
Cadmium	Industry	The association between cadmium exposure and HTN is equivocal
Arsenic	Industry	
Bromocriptine mesylate	Suppression of lactation, and prolactin inhibition in prolactinoma	Severe HTN with stroke has been reported following the use for suppression of lactation. Patients with pregnancy-induced HTN are at increased risk to develop HTN.
Amphotericin B	Fungal infections	

Resistant or Difficult-to-Control Hypertension

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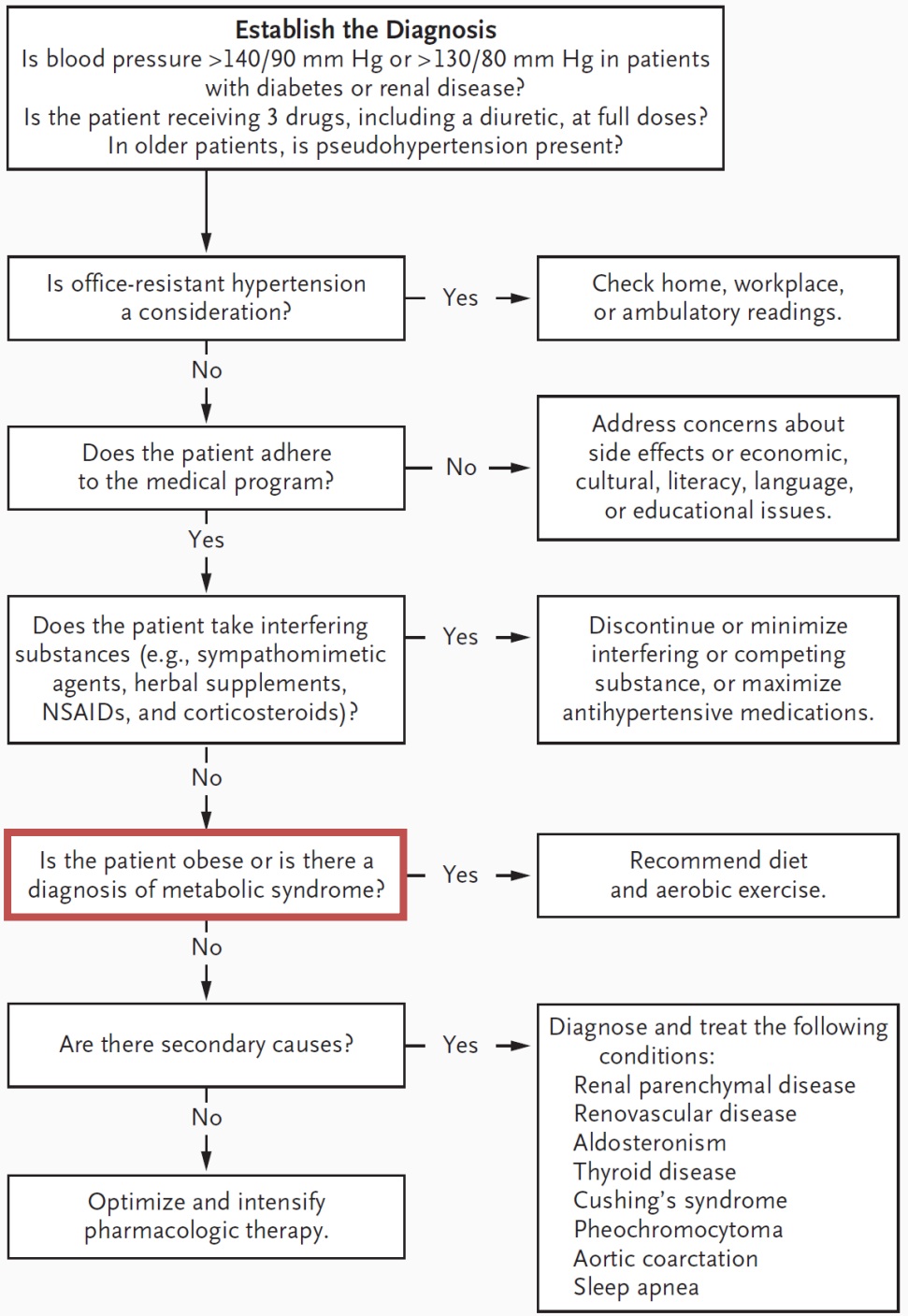

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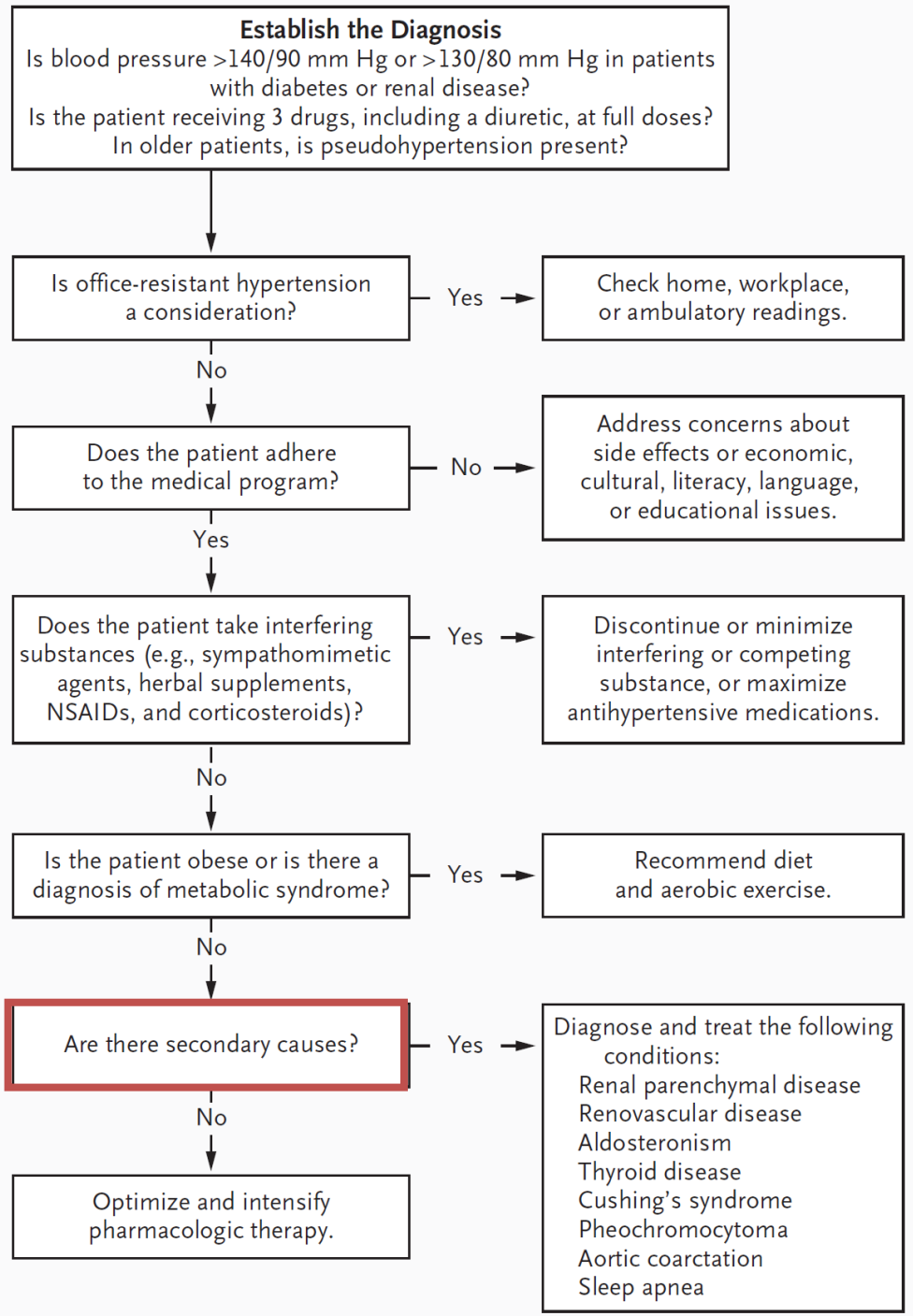

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Secondary cause	Prevalence[a]	Prevalence[b]
Obstructive sleep apnoea	>5–15%	>30%
Renal parenchymal disease	1.6–8.0%	2–10%
Renal artery stenosis	1.0–8.0%	2.5–20%
Primary aldosteronism	1.4–10%	6–23%
Thyroid disease	1–2%	1–3%
Cushing's Syndrome	0.5%	<1.0%
Phaeochromocytoma	0.2–0.5%	<1%
Coarctation of the aorta	<1%	<1%

Table 1 Overview

Secondary cause	Clinical findings	Laboratory findings
Obstructive sleep apnoea	↑ neck circumference; obesity; peripheral oedema	Not specific
Renal parenchymal disease	Peripheral oedema; pallor; loss of muscle mass	↑ Creatinine, proteinuria; ↓ Ca^{2+}, ↑ K^+, ↑ PO_4
Renal artery stenosis	Abdominal bruits; peripheral vascular disease;	Secondary aldosteronism: ARR →; ↓ K^+; ↓ Na^+
Primary aldosteronism	Muscle weakness	↓ K^+; ARR ↑
Thyroid disease	*Hyperthyreodism*: tachycardia, AF; accentuated heart sounds; exophthalmus; *Hypothyreodism*; Bradycardia; muscle weakness; myxoedema	*Hyperthyreodism*: TSH ↓; fT4 and/or fT3 ↑; *Hypothyreodism*: TSH ↑; fT4 ↓; cholesterol ↑
Cushing's Syndrome	Obesity, hirsutism, skin atrophy, Striae rubrae, muscle weakness, osteopenia	24 h urinary; cortisol ↑; Glucose ↑; Cholesterol ↑; K^+ ↓
Phaeochromocytoma	The 5 'Ps'[c]: paroxysmal hypertension; pounding headache; perspiration; palpitations; pallor	metanephrines ↑
Coarctation of the aorta	Different BP (≥20/10 mmHg) between upper–lower extremities and/or between right–left arm; ↓ and delayed femoral pulsations; interscapular ejection murmur; rib notching on chest Rx	Not specific

BP, blood pressure; Ca^{2+}, calc
[a]Prevalence in hypertensive p
[b]Prevalence in patients with r
[c]Kaplan's, Clinical hypertensio

atrial fibrillation; TSH, thyroid-stimulating hormone; fT4, free thyroxine; fT3, free triiodothyronine

European Heart Journal (2014) 35, 1245–1254

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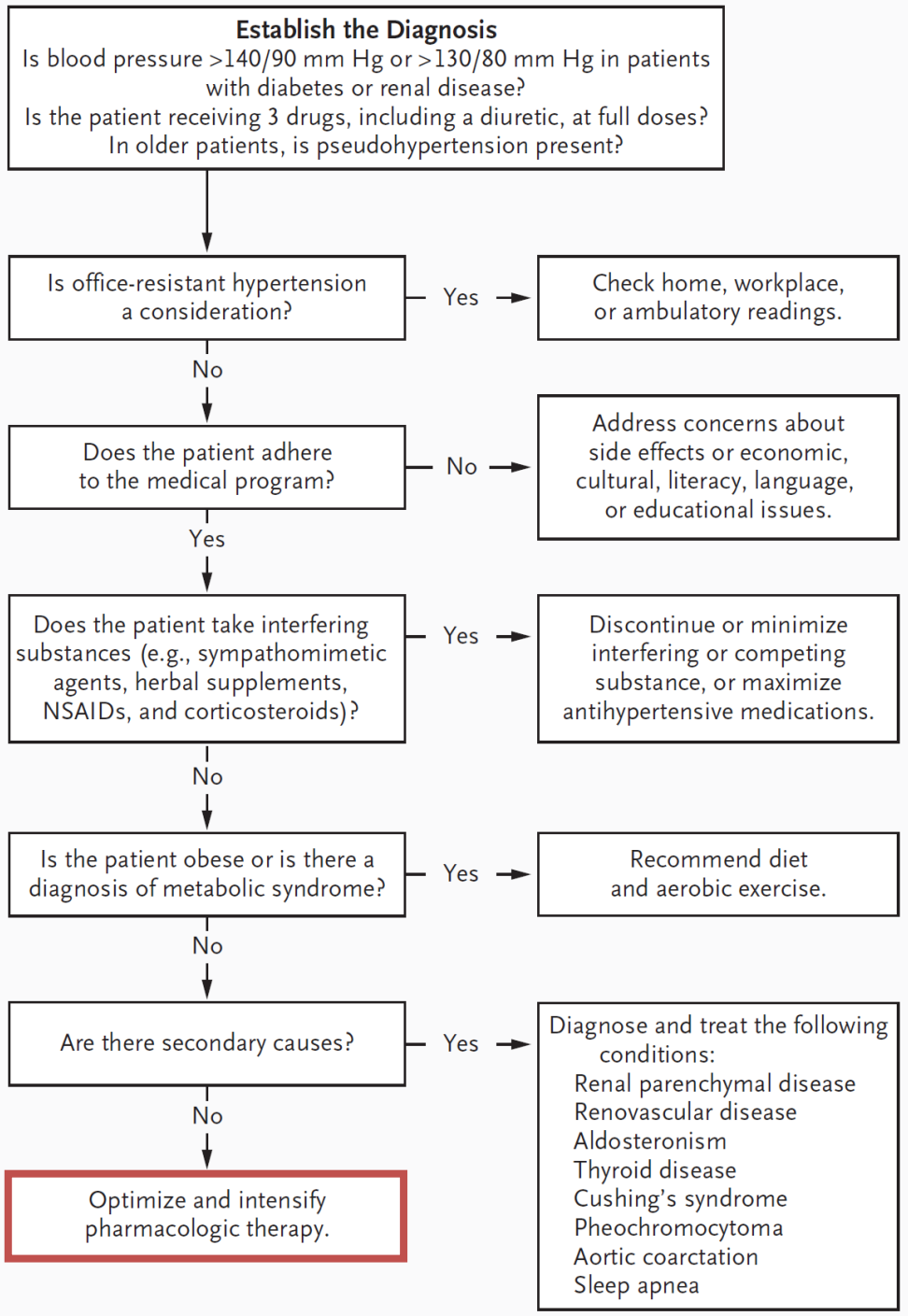

N Engl J Med 2006;355:385-92.

Resistant Hypertension: Detection, Evaluation, and Management

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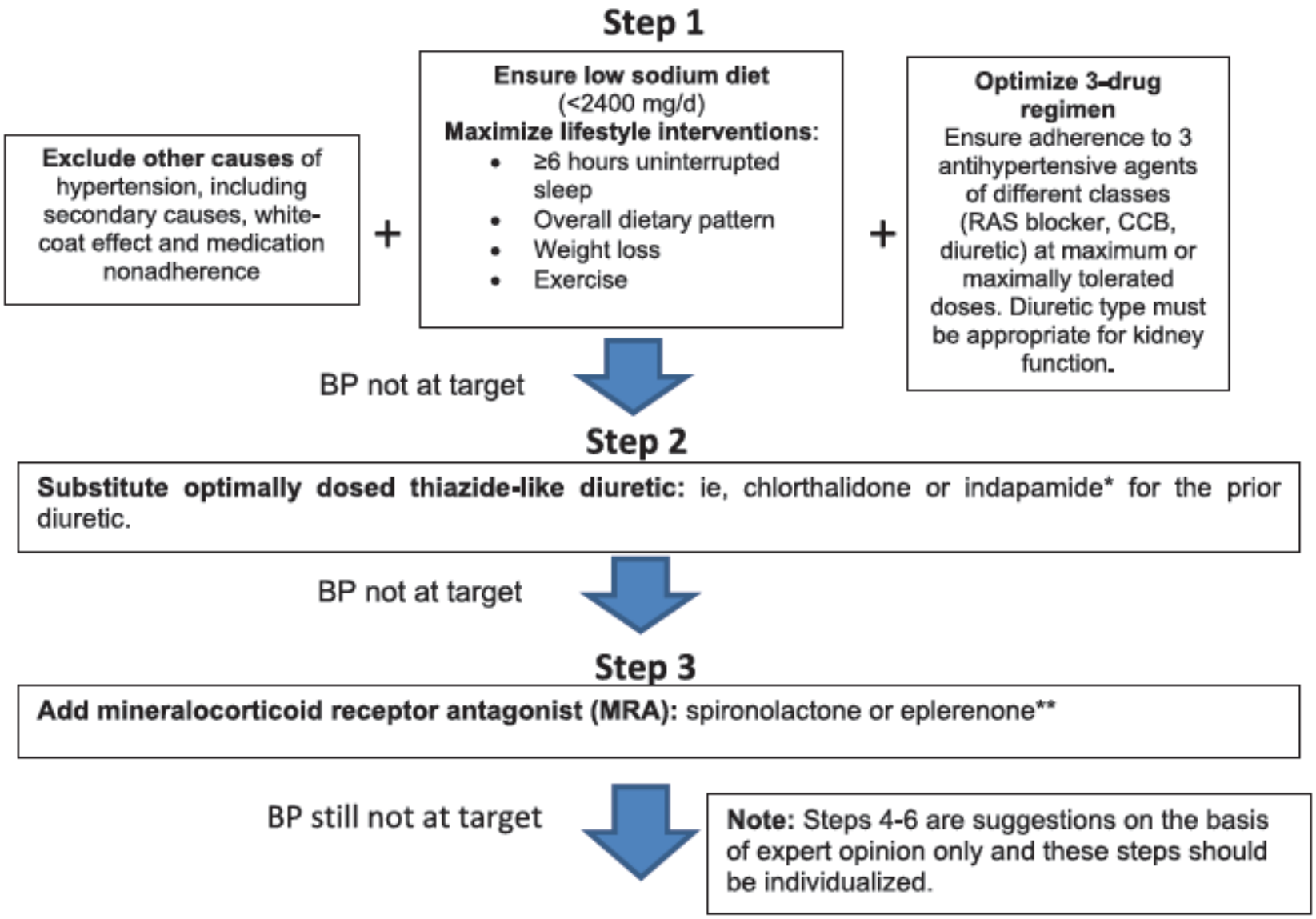
Management of Resistant Hypertension



Carey RM et al. Hypertension 2018.

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

*Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group**

Summary

Background Optimal drug treatment for patients with resistant hypertension is undefined. We aimed to test the hypotheses that resistant hypertension is most often caused by excessive sodium retention, and that spironolactone would therefore be superior to non-diuretic add-on drugs at lowering blood pressure.

Methods In this double-blind, placebo-controlled, crossover trial, we enrolled patients aged 18–79 years with seated clinic systolic blood pressure 140 mm Hg or greater (or ≥135 mm Hg for patients with diabetes) and home systolic blood pressure (18 readings over 4 days) 130 mm Hg or greater, despite treatment for at least 3 months with maximally tolerated doses of three drugs, from 12 secondary and two primary care sites in the UK. Patients rotated, in a preassigned, randomised order, through 12 weeks of once daily treatment with each of spironolactone (25–50 mg), bisoprolol (5–10 mg), doxazosin modified release (4–8 mg), and placebo, in addition to their baseline blood pressure drugs. Random assignment was done via a central computer system. Investigators and patients were masked to the identity of drugs, and to their sequence allocation. The dose was doubled after 6 weeks of each cycle. The hierarchical primary endpoints were the difference in averaged home systolic blood pressure between spironolactone and placebo, followed (if significant) by the difference in home systolic blood pressure between spironolactone and the average of the other two active drugs, followed by the difference in home systolic blood pressure between spironolactone and each of the other two drugs. Analysis was by intention to treat. The trial is registered with EudraCT number 2008-007149-30, and ClinicalTrials.gov number, NCT02369081.

Lancet 2015; 386: 2059–68

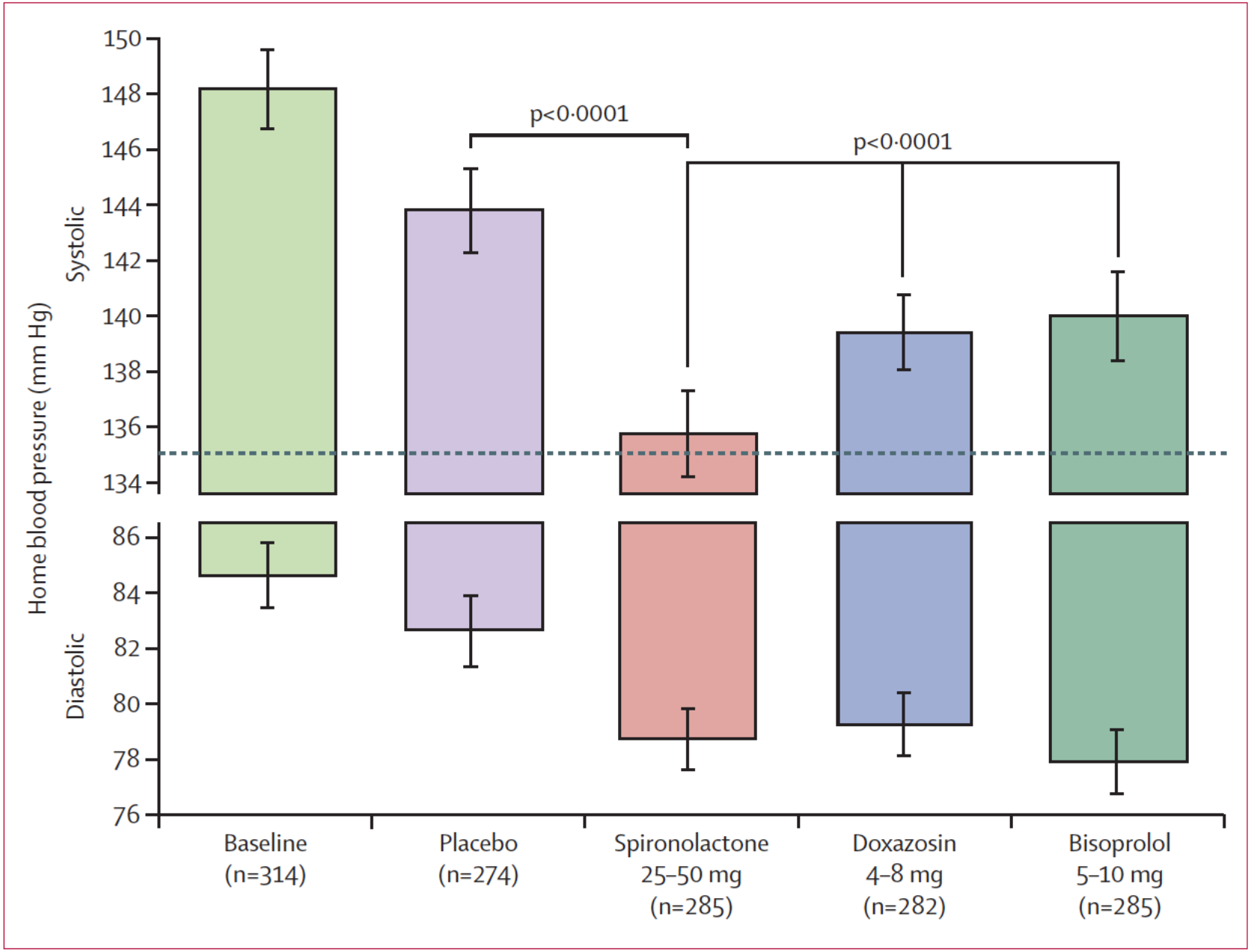


Figure 2: **Home systolic and diastolic blood pressures comparing spironolactone with each of the other cycles**

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Step 4

Check heart rate: unless <70 beats/min, **add β-blocker** (eg, metoprolol succinate, bisoprolol) or combined α-β-blocker (eg, labetalol, carvedilol). If β-blocker is contraindicated, consider central α-agonist (ie, clonidine patch weekly or guanfacine at bedtime). If these are not tolerated, consider once-daily diltiazem.

BP still not at target

Step 5

Add hydralazine* ** 25 mg three times daily and titrate upward to max dose; in patients with congestive heart failure with reduced ejection fraction, hydralazine should be administered on background isosorbide mononitrate 30 mg daily (max dose 90 mg daily).

BP still not at target

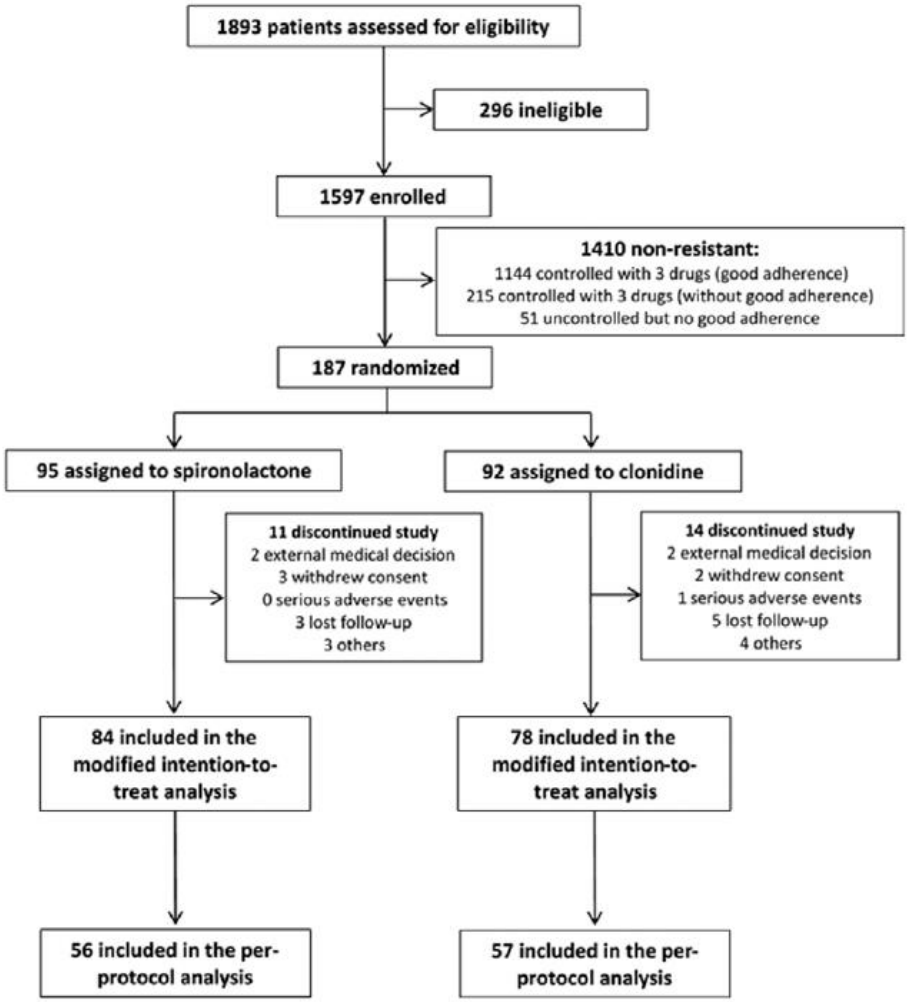
Step 6

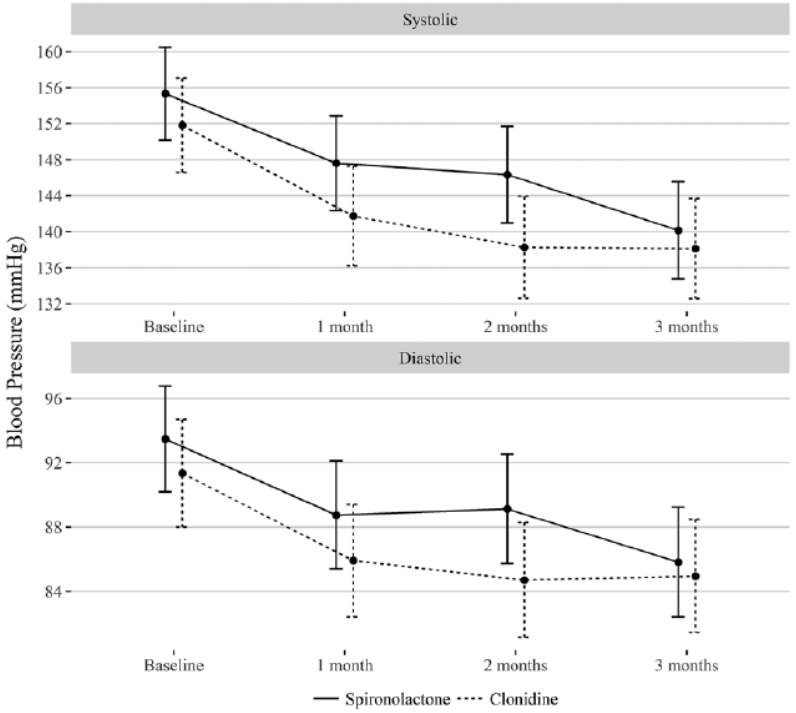
Substitute minoxidil** ** 2.5 mg two to three times daily for hydralazine and titrate upward. If BP still not at target, consider referral to a hypertension specialist and/or for ongoing experimental studies—www.clinicaltrials.gov.

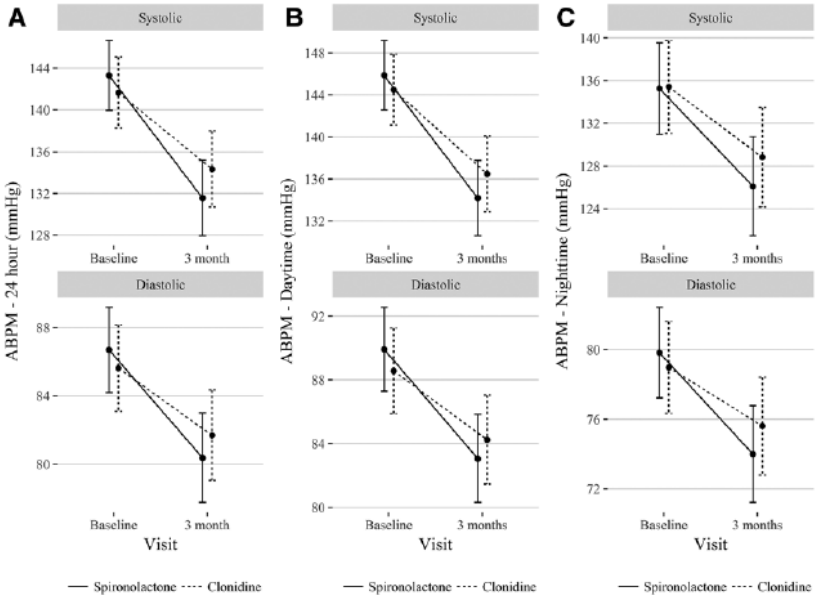
Carey RM et al. Hypertension 2018.

Spironolactone Versus Clonidine as a Fourth-Drug Therapy for Resistant Hypertension

The ReHOT Randomized Study (Resistant Hypertension Optimal Treatment)



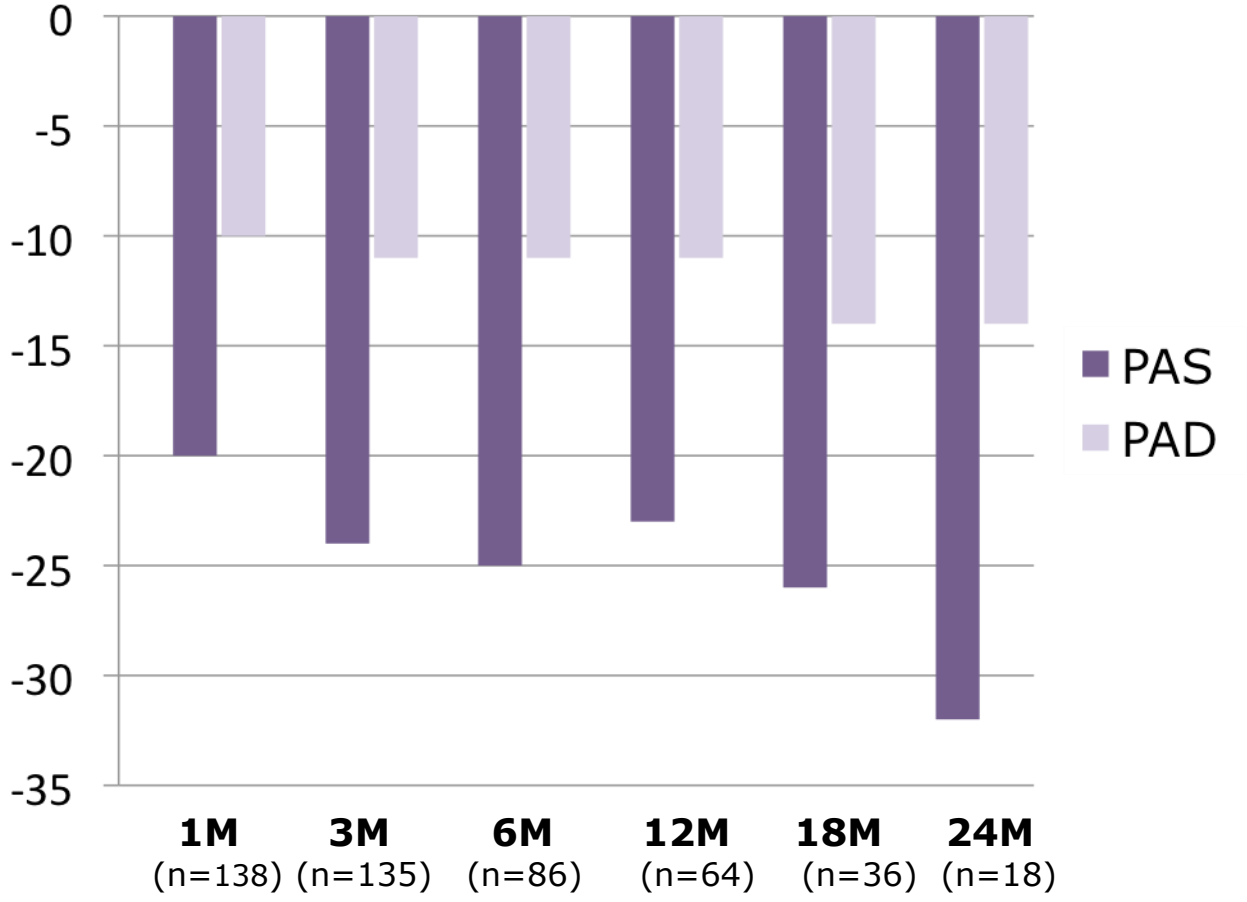




Hypertension. 2018;71:681-690.

Symplicity HTN-1: denervación simpática renal por catéter

- **n = 153** pacientes con HTA resistente
- Mantenimiento de la reducción de PAS a los 24 meses del procedimiento



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

Symplicity HTN-2

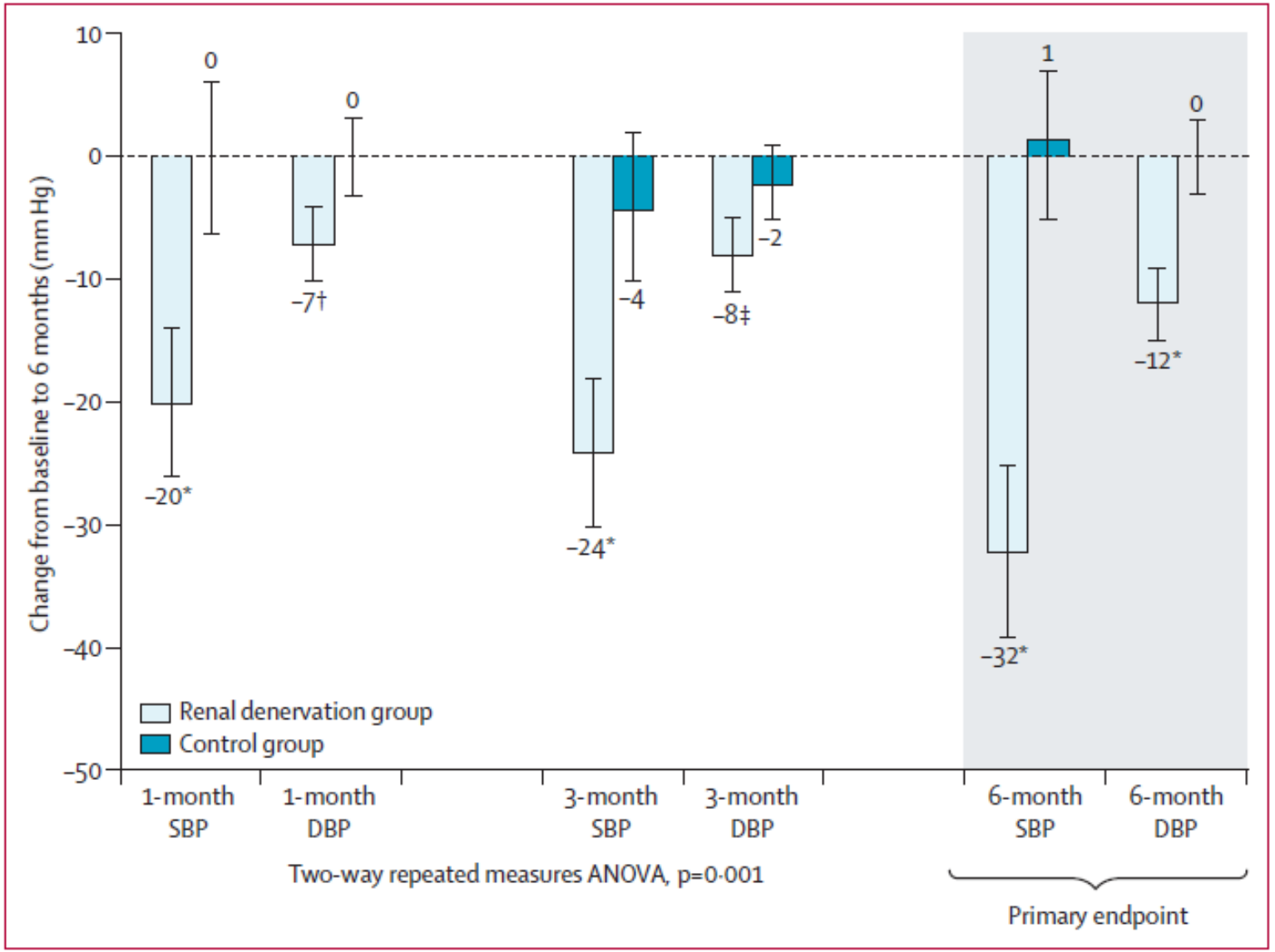
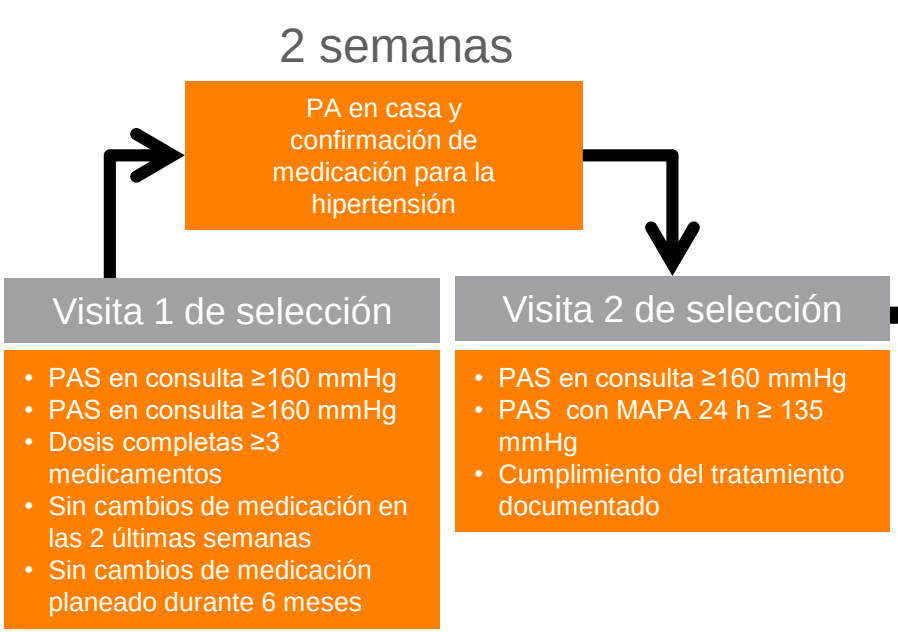


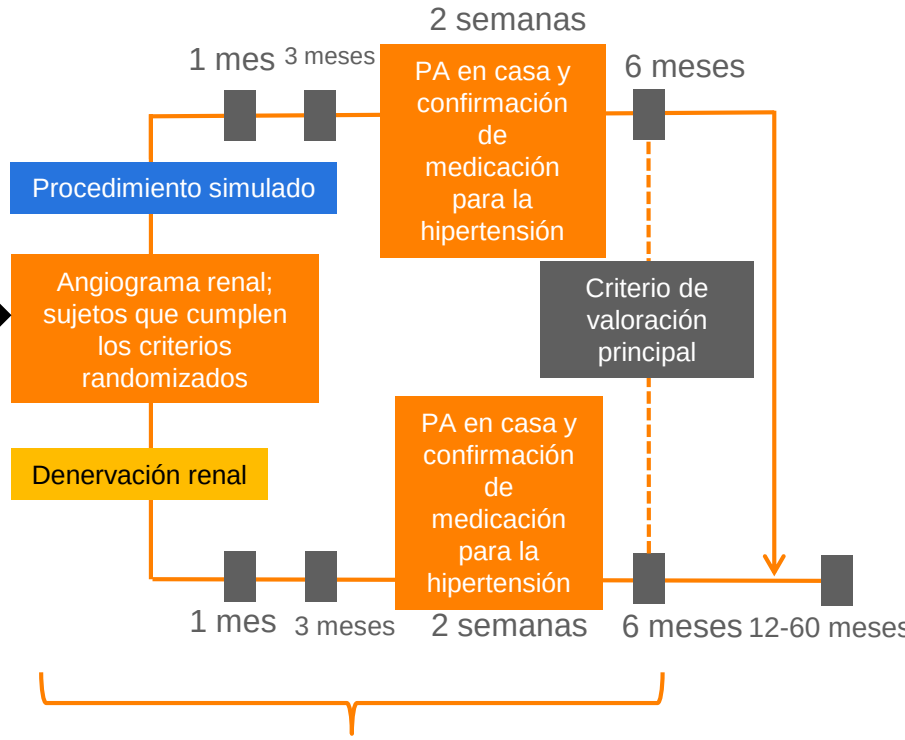
Figure 2: **Paired changes in office-based measurements of systolic and diastolic blood pressures at 1 month, 3 months, and 6 months for renal denervation and control groups**

Lancet 2010; 376: 1903-1909.

SYMPLICITY HTN-3: hipertensión resistente y severa PAS en consulta ≥160 mmHg

- Controlado, ciego y randomizado con proporción 2:1
- Procedimiento simulado en pacientes del grupo control que incluyó angiograma renal
- 535 sujetos randomizados de 1.441 incluidos (tasa de sujetos que no superaron la selección del 63%)
- Proceso de selección de 2 semanas, incluidas dosis máximas toleradas de antihipertensivos



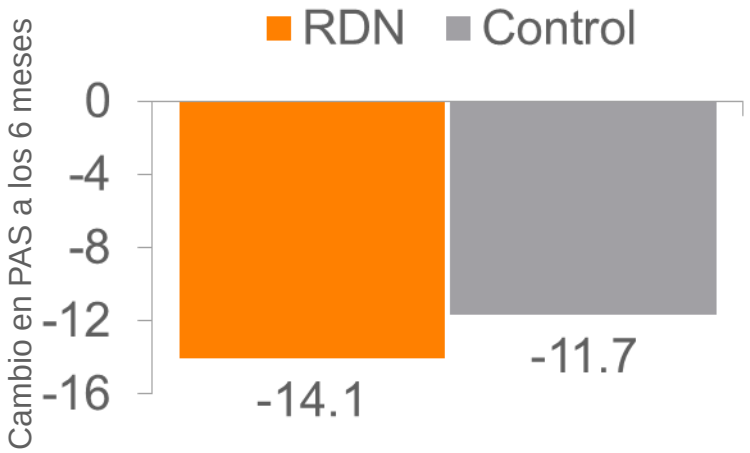


- Ni los pacientes, ni los asesores de PA, ni el personal del estudio conocían el tratamiento asignado
- No se permitieron cambios en la medicación durante 6 meses

Symplicity™
RENAL DENERVATION SYSTEM

Criterio de valoración primario de eficacia

Presión arterial sistólica en consulta a los 6 meses, margen de seguridad de 5 mm



	RDN	Control	Valor *P*
PAS inicial	179,7	180,2	0,765
PAS a los 6 meses	165,6	168,4	0,260
Cambio	*-14,1* *P < 0,001*	*-11,7* *P < 0,001*	*0,255*[1]

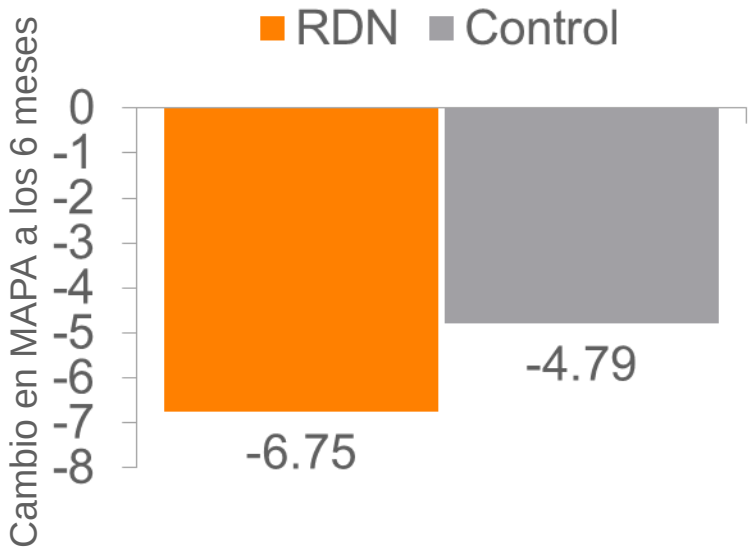
-2,39 (-6,89, 2,12), *P* = 0,255 (análisis principal con margen de seguridad de 5 mmHg)

- No se cumplió el criterio de valoración primario de eficacia

Symplicity™
RENAL DENERVATION SYSTEM

Criterio de valoración secundario de eficacia

Presión arterial sistólica ambulatoria a los 6 meses, margen de superioridad de 2 mm



	RDN	Control	Valor *P*
PAS inicial	158,55	158,85	0,828
PAS a los 6 meses	151,80	154,05	0,201
Cambio	*-6,75* *P < 0,001*	*-4,79* *P < 0,001*	*0,979*

-1,96 (-4,97, 1,06), *P* = 0,979 (análisis ITT con margen de superioridad de 2 mmHg)

- No se cumplió el criterio de valoración secundario de la eficacia

Symplicity™
RENAL DENERVATION SYSTEM

European Heart Journal (2015) **36**, 219–227
doi:10.1093/eurheartj/ehu441

Predictors of blood pressure response in the SYMPLICITY HTN-3 trial

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See page 199 for the editorial comment on this article (doi:10.1093/eurheartj/ehu450)

Aims The SYMPLICITY HTN-3 randomized, blinded, sham-controlled trial confirmed the safety of renal denervation (RDN), but did not meet its primary efficacy endpoint. Prior RDN studies have demonstrated significant and durable reductions in blood pressure. This analysis investigated factors that may help explain these disparate results.

Methods and results Patients with resistant hypertension were randomized 2 : 1 to RDN ($n = 364$) or sham ($n = 171$). The primary endpoint was the difference in office systolic blood pressure (SBP) change at 6 months. A multivariable analysis identified predictors of SBP change. Additional analyses examined the influence of medication changes, results in selected subgroups and procedural factors. Between randomization and the 6-month endpoint, 39% of patients underwent medication changes. Predictors of office SBP reduction at 6 months were baseline office SBP $\geq$180 mmHg, aldosterone antagonist use, and non-use of vasodilators; number of ablations was a predictor in the RDN group. Non-African-American patients receiving RDN had a significantly greater change in office SBP than those receiving sham; -15.2 ± 23.5 vs. -8.6 ± 24.8 mmHg, respectively ($P = 0.012$). Greater reductions in office and ambulatory SBP, and heart rate were observed with a higher number of ablations and energy delivery in a four-quadrant pattern.

Conclusions *Post hoc* analyses, although derived from limited patient cohorts, reveal several potential confounding factors that may partially explain the unexpected blood pressure responses in both the sham control and RDN groups. These hypothesis-generating data further inform the design of subsequent research to evaluate the potential role of RDN in the treatment of resistant hypertension.

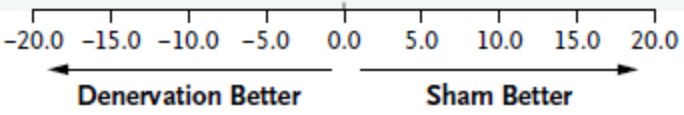
Table 2 **Antihypertensive medication use change analysis**

	RDN group	Sham group
Baseline number of medications	5.1 ± 1.4	5.2 ± 1.4
6-month number of medications	5.0 ± 1.4	5.2 ± 1.6
Medication change SV1 to SV2	18 (4.9%)	13 (7.6%)
Any medication change between baseline and 6 months	139[a] (38.2%)	72[a] (42.1%)
>1 change between baseline and 6 months	119 (32.7%)	60 (35.1%)
Decreased number of medication classes or doses	52 (14.3%)	23 (12.8%)
Increased number of medication classes or doses	31 (8.5%)	17 (9.9%)
Combination of increases and decreases in class and/or dose	56 (15.3%)	32 (18.7%)
Medication change related to an adverse event or symptom change	98 (26.9%)	53 (31.0%)
Medication change related to SBP <115 mmHg	13 (3.6%)	2 (1.2%)
Medication change related to SBP increase >15 mmHg	14 (3.8%)	7 (4.1%)
Other reasons	72 (19.8%)	41 (24.0%)

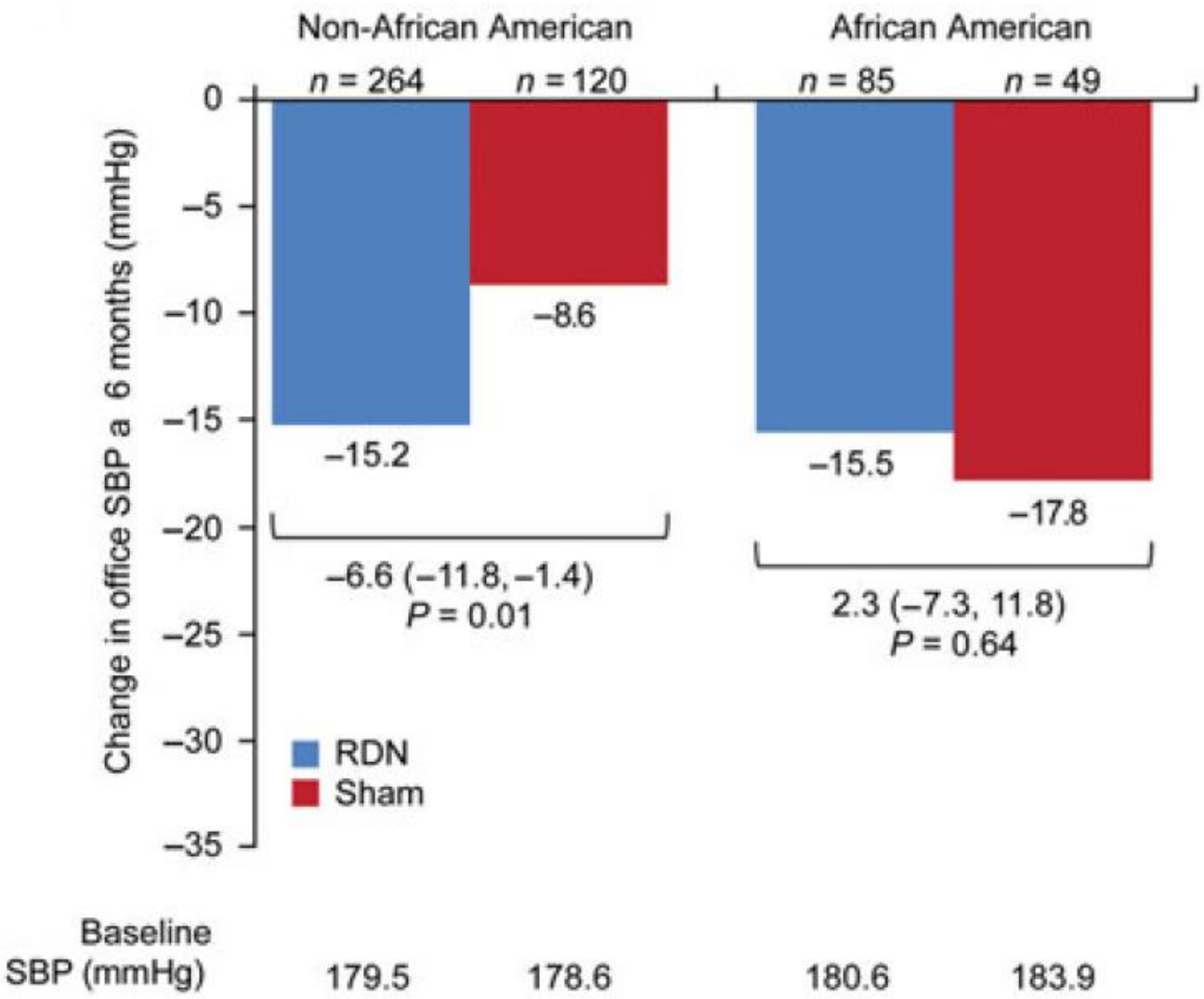
Data is mean (SD) or *n* (%).
SV, screening visit.
[a]Four RDN group patients and two control group patients who had no net change for the 6-month period (i.e. the same medication changed and returned to previous dose).

Change in SBP at 6 Months Within Pre-specified Subgroups

Subgroup	Denervation	Sham	Between-Group Difference in Change in Office Systolic Blood Pressure (95% CI)	P Value	P Value for Interaction
	no. of patients		*mm Hg*		
All patients	353	171	−2.39 (−6.89 to 2.12)	0.26	
Diabetes mellitus					0.82
Yes	169	68	−4.53 (−11.51 to 2.46)	0.20	
No	181	101	−3.46 (−9.55 to 2.62)	0.26	
Sex					0.37
Male	208	108	−2.30 (−7.63 to 3.03)	0.40	
Female	142	61	−6.64 (−14.94 to 1.65)	0.12	
Black race					0.09
Yes	85	49	2.25 (−7.27 to 11.78)	0.64	
No	264	120	−6.63 (−11.81 to −1.44)	0.01	
Body-mass index					0.77
<30	91	42	−2.77 (−11.47 to 5.93)	0.53	
≥30	259	126	−4.36 (−9.76 to 1.03)	0.11	
Receiving aldosterone antagonist at baseline					0.36
Yes	76	47	−8.05 (−17.63 to 1.52)	0.10	
No	274	122	−3.24 (−8.42 to 1.93)	0.22	
Estimated GFR					0.31
<60 ml/min/1.73 m^2	68	38	0.54 (−8.29 to 9.37)	0.90	
≥60 ml/min/1.73 m^2	282	131	−5.22 (−10.51 to 0.06)	0.05	
Age					0.27
<65 yr	246	128	−5.73 (−11.06 to −0.40)	0.04	
≥65 yr	104	41	0.09 (−8.80 to 8.99)	0.99	
Any medication change					0.68
Yes	132	70	−5.41 (−13.49 to 2.67)	0.19	
No	218	99	−3.44 (−8.83 to 1.96)	0.21	



Change in office systolic blood pressure at 6 months for non-African-American and African-American subgroups

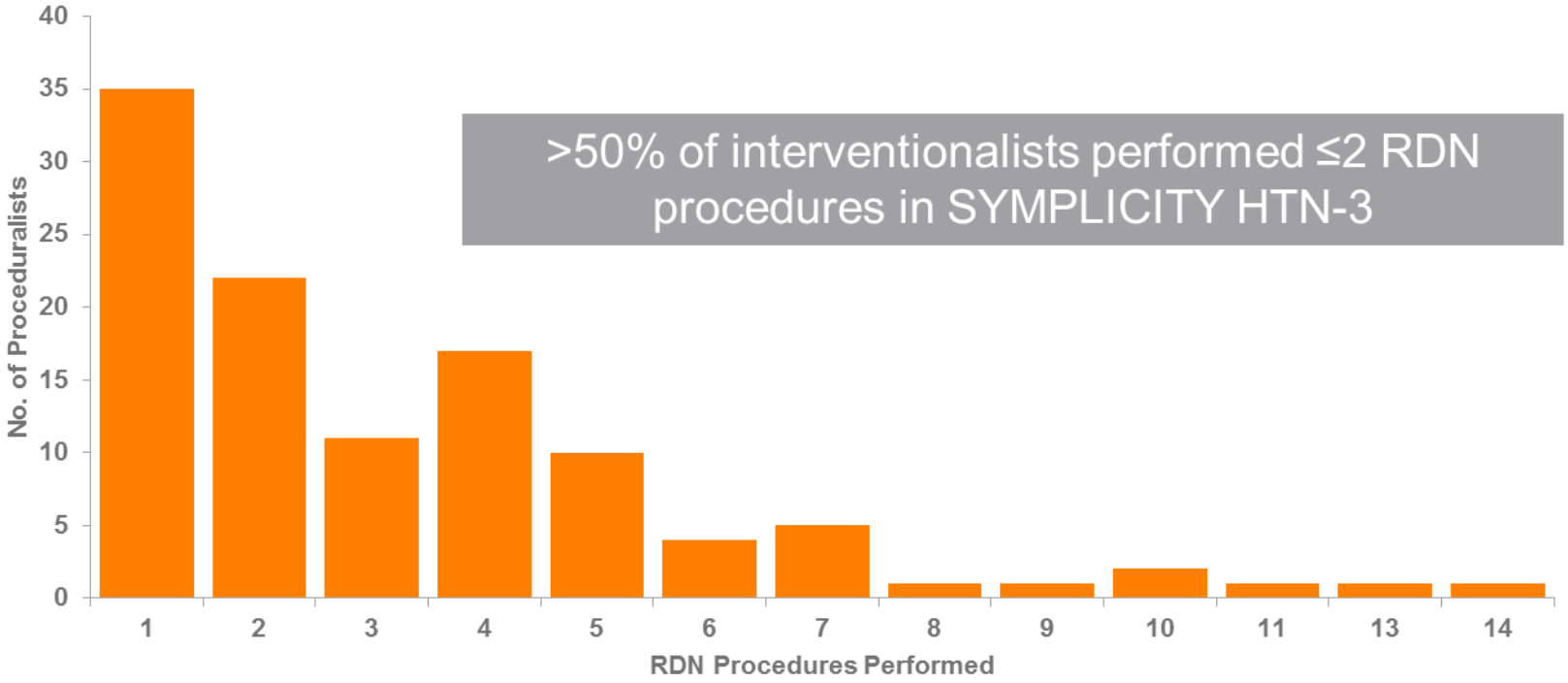


European Heart Journal (2015) **36**, 219–227

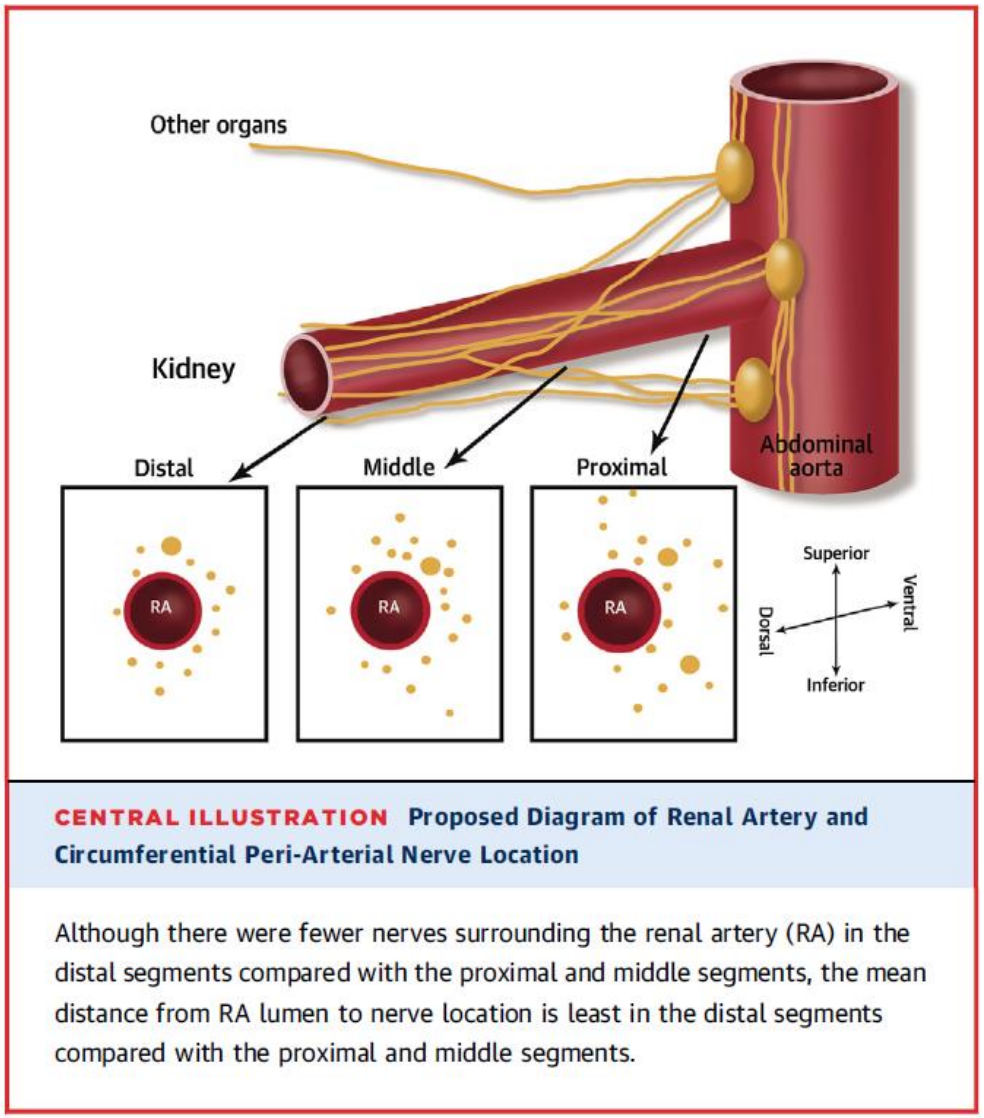
HTN-3: experiencia procedimental

	HTN-1	HTN-3
N.º de operadores	20	112
N.º de procedimientos por operador	6,0	3,3
N.º de procedimientos por centro	8,6	4,7

a) **5 veces más operadores que en HTN-1**
b) **Mayor heterogeneidad de experiencia de operadores que en HTN-1 y HTN-2**
c) **La supervisión de casos fue diferente y no comparable**



Anatomía del SN Simpático Arterias Renales



CENTRAL ILLUSTRATION **Proposed Diagram of Renal Artery and Circumferential Peri-Arterial Nerve Location**

Although there were fewer nerves surrounding the renal artery (RA) in the distal segments compared with the proximal and middle segments, the mean distance from RA lumen to nerve location is least in the distal segments compared with the proximal and middle segments.

Sakakura K et al. JACC 2014;64:635

Anatomía del SN Simpático Arterias Renales

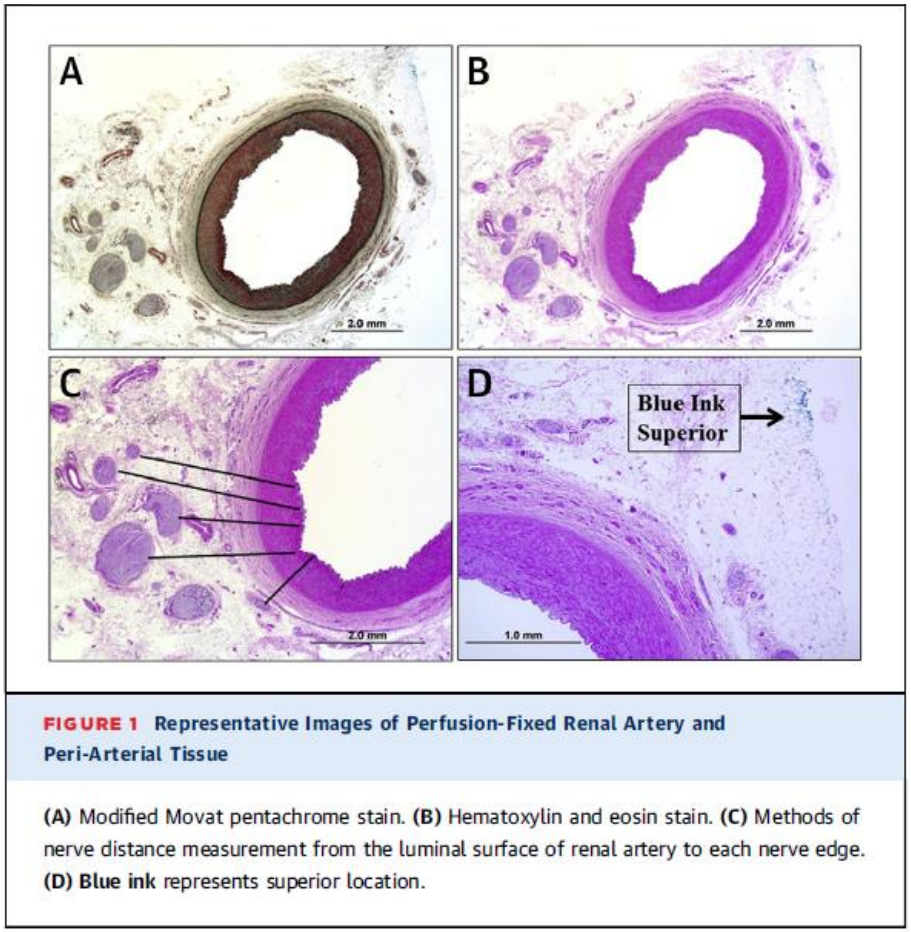


FIGURE 1 **Representative Images of Perfusion-Fixed Renal Artery and Peri-Arterial Tissue**

(A) Modified Movat pentachrome stain. **(B)** Hematoxylin and eosin stain. **(C)** Methods of nerve distance measurement from the luminal surface of renal artery to each nerve edge. **(D) Blue ink** represents superior location.

Sakakura K et al. JACC 2014;64:635

Anatomía del SN Simpático Arterias Renales

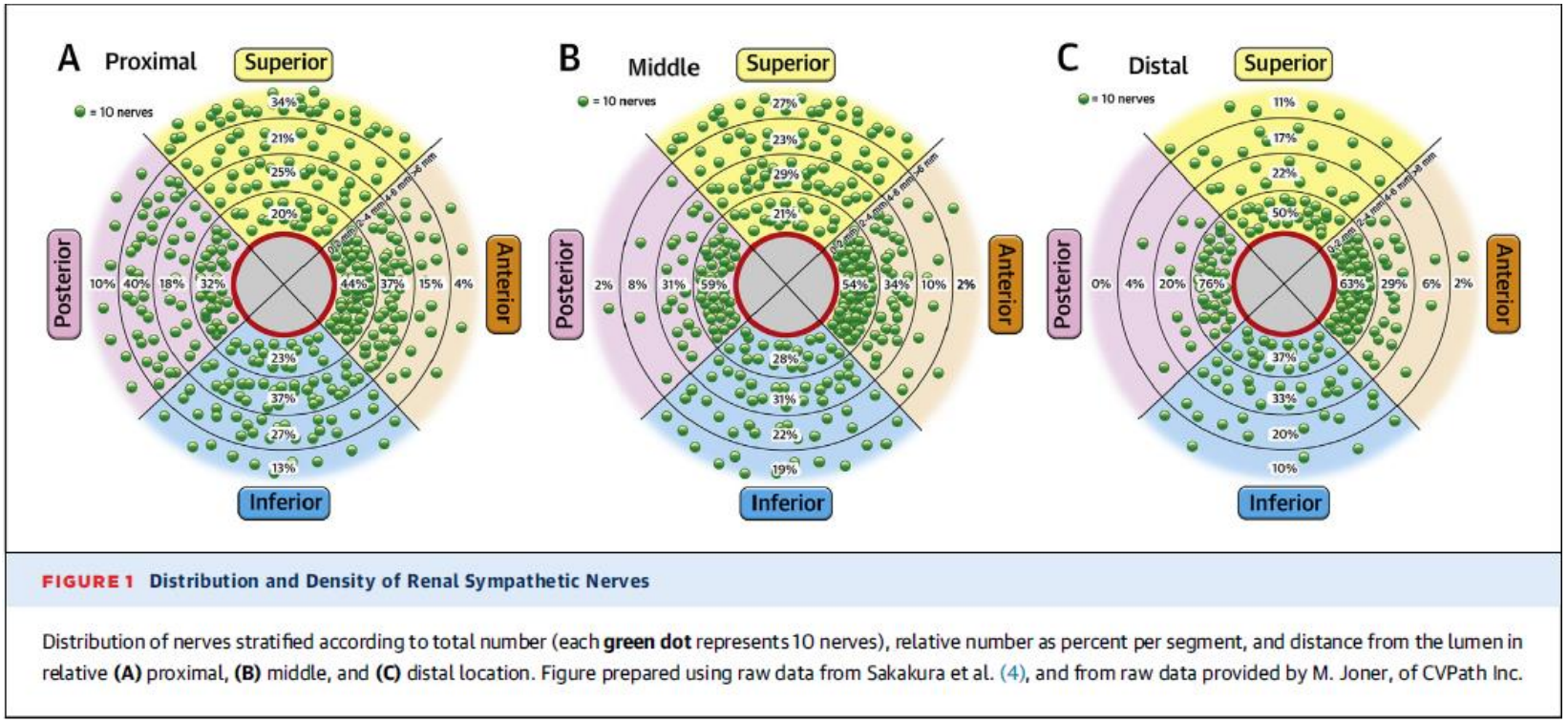
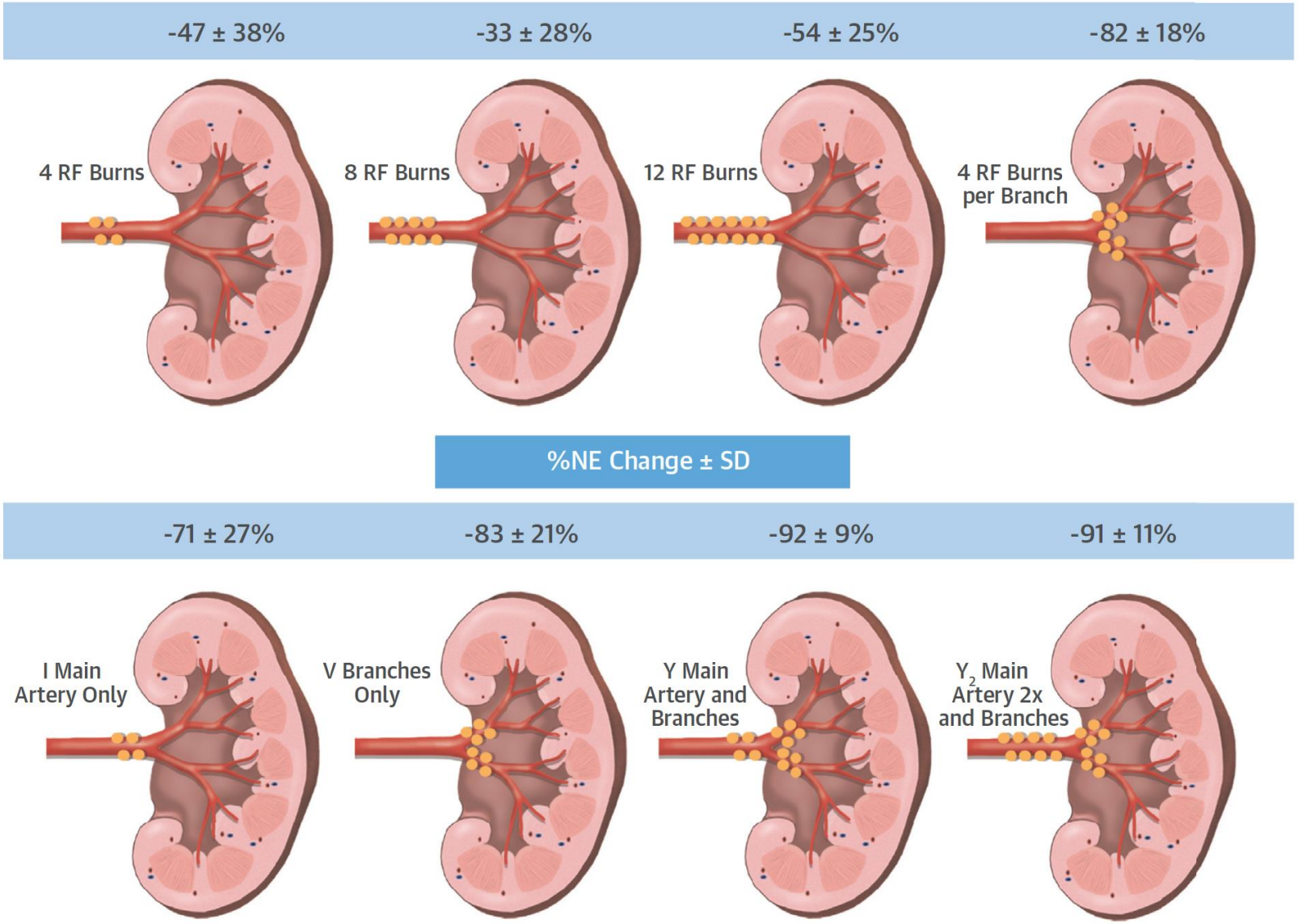


FIGURE 1 **Distribution and Density of Renal Sympathetic Nerves**

Distribution of nerves stratified according to total number (each **green dot** represents 10 nerves), relative number as percent per segment, and distance from the lumen in relative **(A)** proximal, **(B)** middle, and **(C)** distal location. Figure prepared using raw data from Sakakura et al. (4), and from raw data provided by M. Joner, of CVPath Inc.

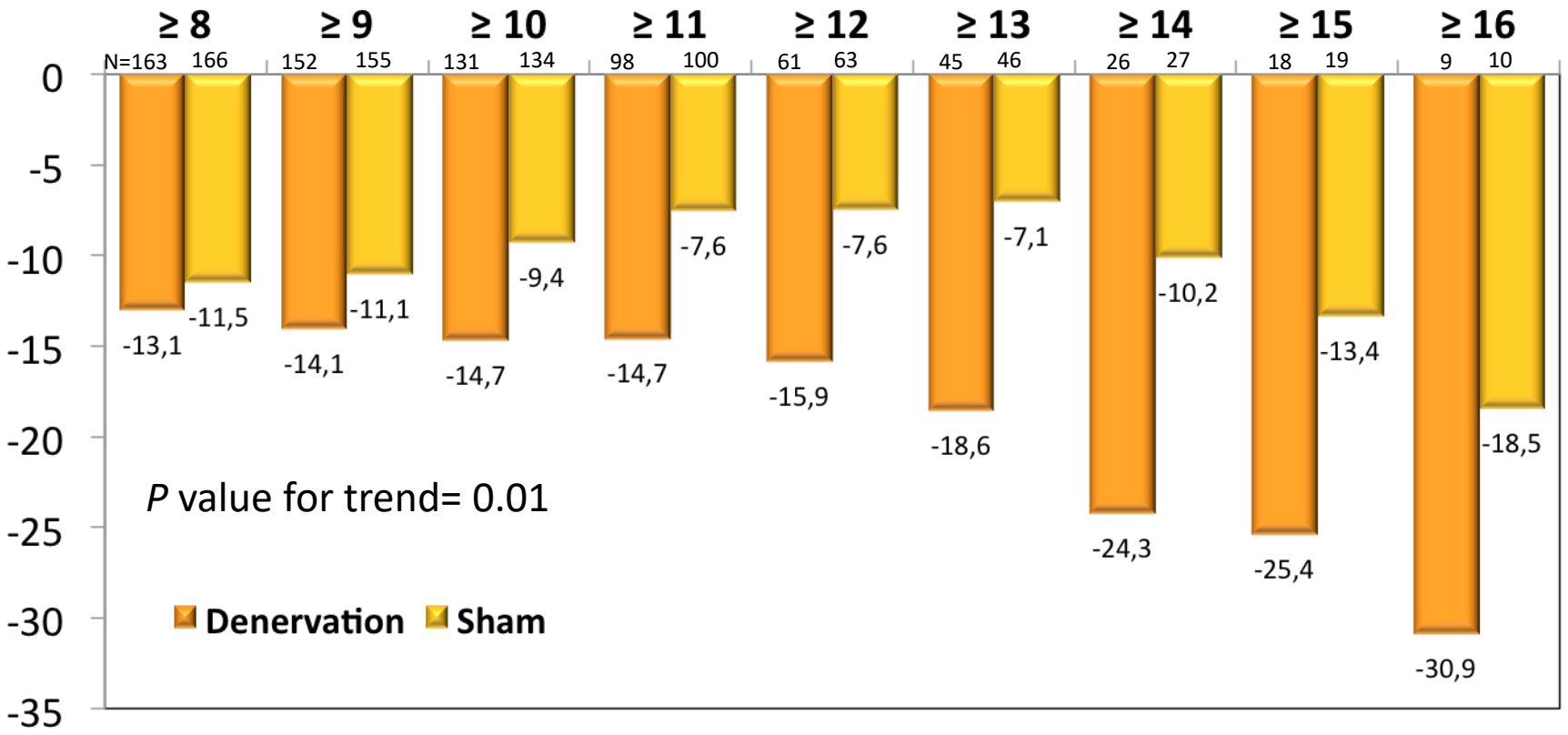
Mahfoud et al. JACC 2014;64:644

Optimized Renal Denervation Techniques
Efficacy of Catheter-Based RadiofrequencyRenal Denervation



Mahfoud, F. et al. J Am Coll Cardiol. 2015; 66(16):1766–75.

Impact of Number of Ablations on Change in Office SBP: Matched Cohort Analysis



	≥ 8	≥ 9	≥ 10	≥ 11	≥ 12	≥ 13	≥ 14	≥ 15	≥ 16
Baseline SBP	178.2 180.1	178.6 180.3	178.2 180.5	179.0 179.4	179.1 179.7	178.3 181.3	181.9 182.3	183.2 182.8	185.4 189.4
95% CI	-1.7(-7.1, 3.7)	-3.1 (-8.6, 2.4)	-5.4 (-11.3, 0.5)	-7.1 (-13.9,-0.3)	-8.4 (-17.4, 0.7)	-11.5 (-21.8,-1.2)	-14.1 (-28.8, 0.7)	-12.0 (-30.0, 5.9)	-12.4 (-44.6, 19.8)
P*	0.54	0.27	0.07	0.04	0.07	0.03	0.06	0.18	0.43

Propensity scores using baseline characteristics as covariates were used to match sham control and denervation patients

*P value change in SBP for RDN compared with sham

Data presented are mean (SD)

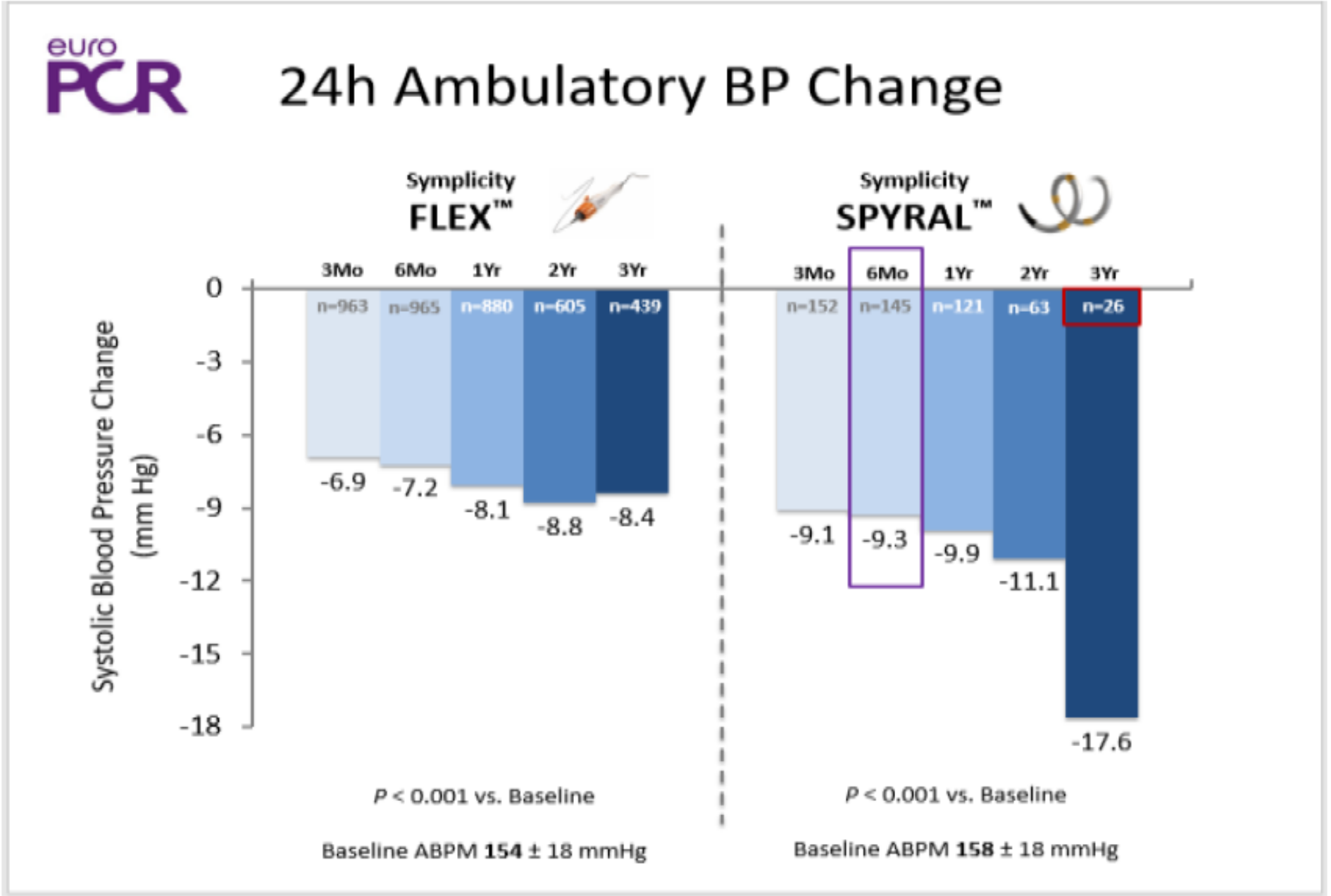


Fig.1: Global SYMPLICITY Registry: *24-Hr ABPM change from baseline to 3-years follow-up - presented at EuroPCR 2018*

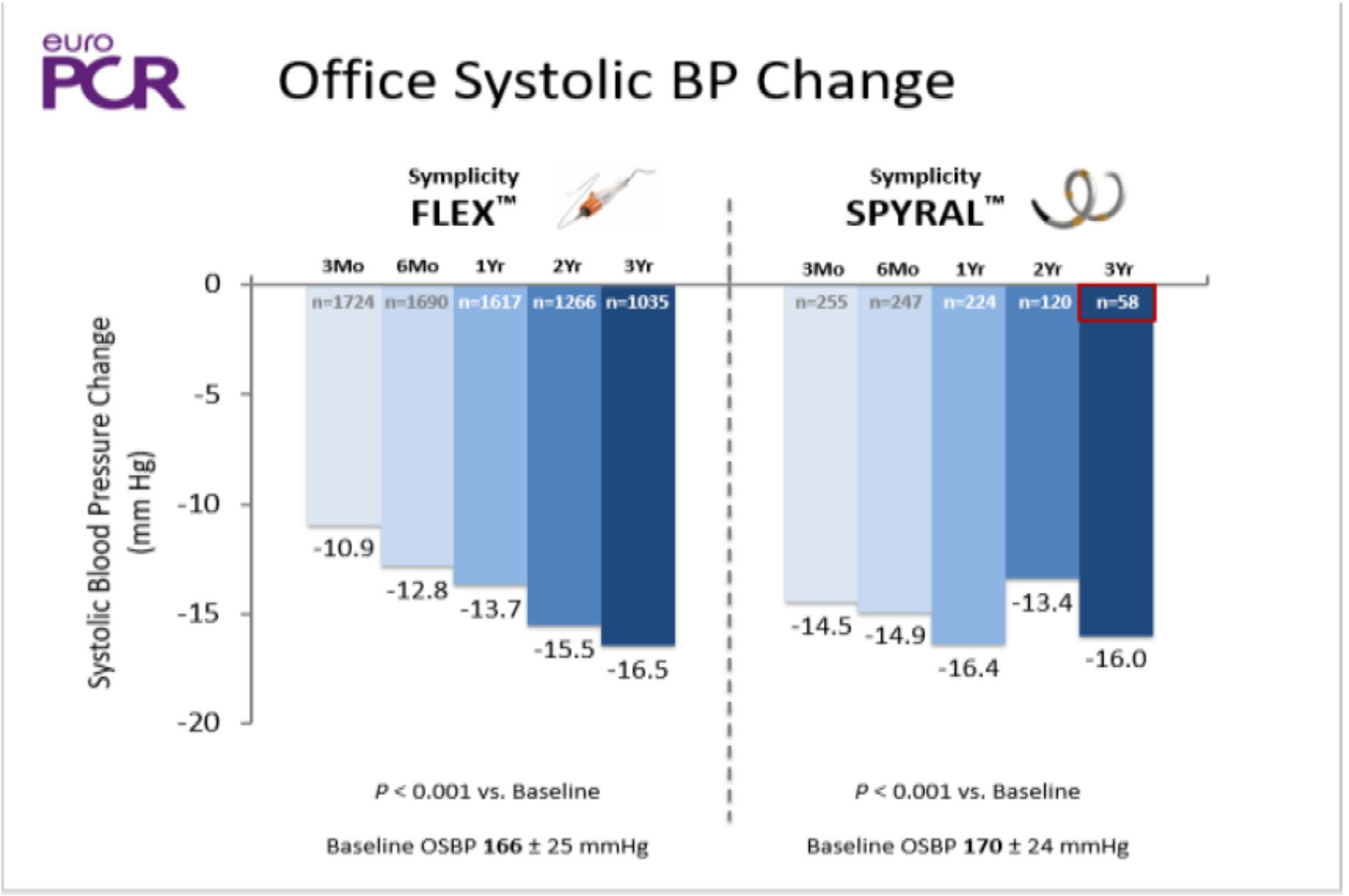


Fig. 2: Global SYMPLICYTY Registry: *OBP change from baseline to 3 years follow-up - presented at EuroPCR 2018*

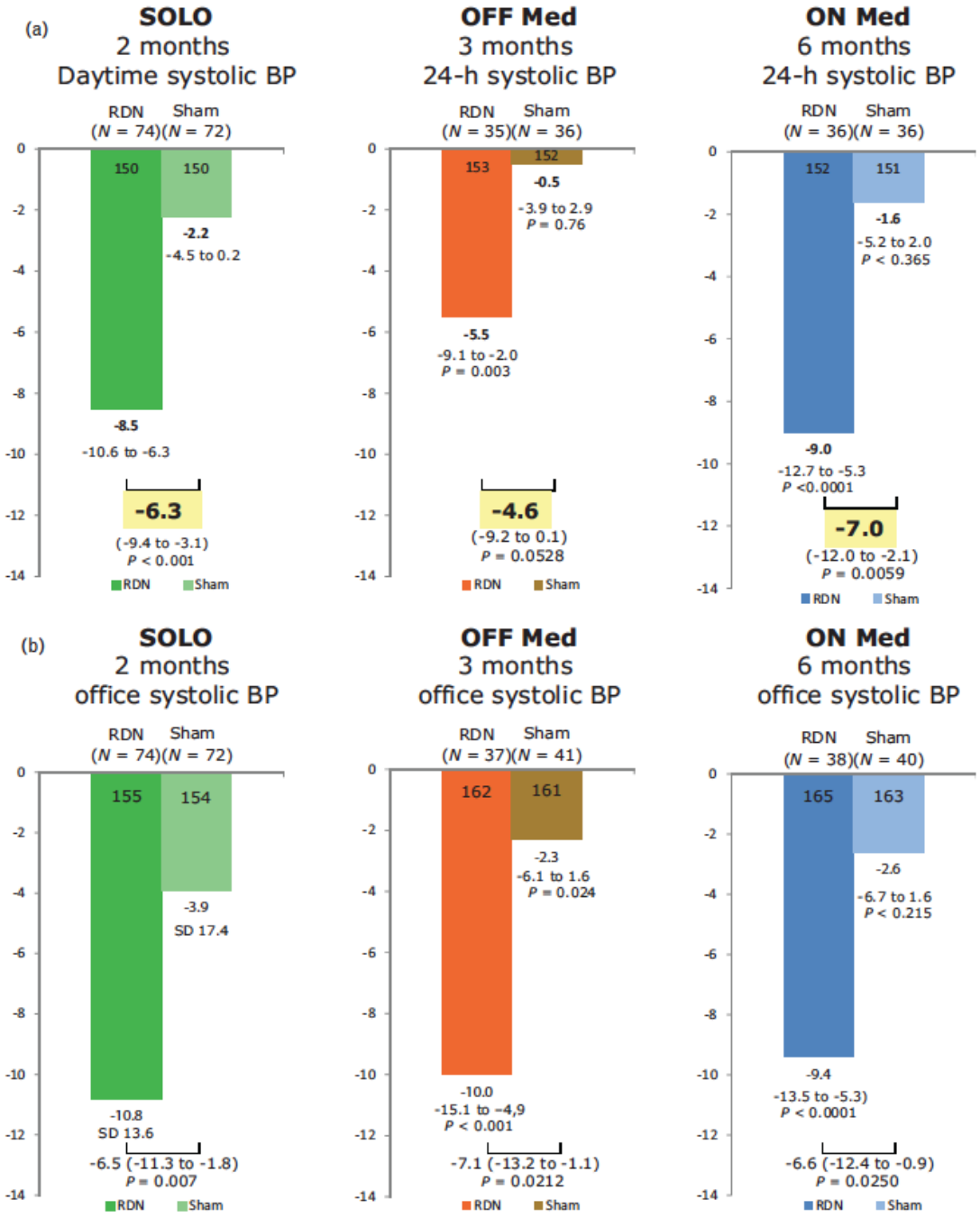


FIGURE 1 (a) Change in ambulatory blood pressure in RADIANCE SOLO, SPYRAL HTN OFF MED and SPYRAL HTN ON MED (baseline adjusted differences of blood pressure between the renal denervation and sham group are given). (b): Change in office blood pressure in RADIANCE SOLO, SPYRAL HTN OFF MED and SPYRAL HTN ON MED (baseline adjusted differences of blood pressure between the renal denervation and Sham group are given).

European Society of Hypertension position paper on renal denervation 2018

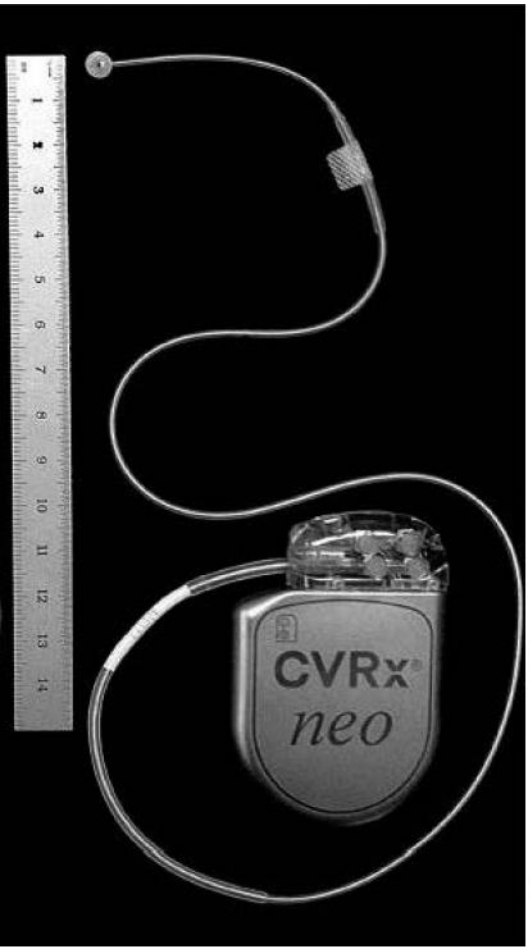
Roland E. Schmieder[a], Felix Mahfoud[b], Michel Azizi[c,d], Atul Pathak[e], Kyriakos Dimitriadis[f], Abraham A. Kroon[g], Christian Ott[a,h], Filippo Scalise[i], Giuseppe Mancia[j], and Costas Tsioufis[k], on behalf of Members of the ESH Working Group on Interventional Treatment of Hypertension

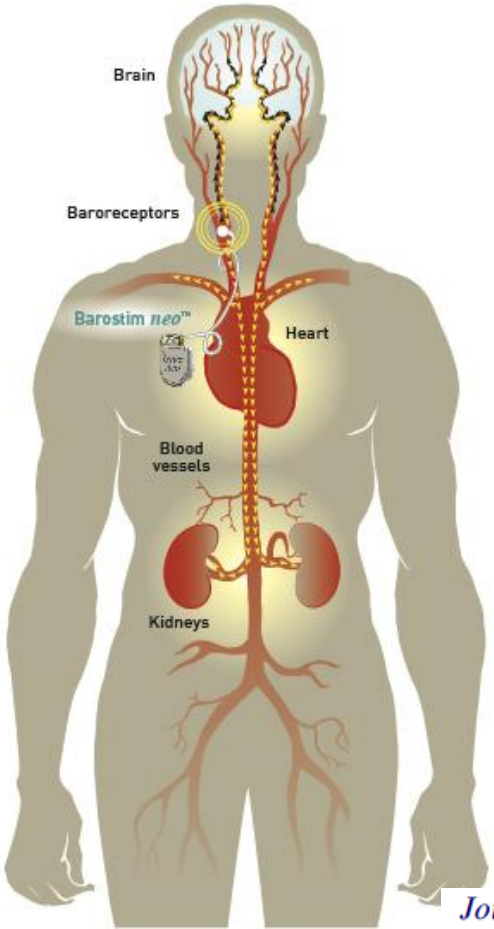
Therefore, despite these promising new results which open widely again the field of RDN, we agree with the current recommendations of the European Guidelines 2018 that 'device based therapies are not recommended *for routine use* in the treatment of HTN at least at the current moment' [5]. However, we recommend to conduct RDN in the framework of 'clinical studies and sham-controlled RCT (to) further provide safety and efficacy in larger set of patients' [5]. So far the number of patients included in the trials is small, the follow-up duration short and several important questions remain unanswered.

Journal of Hypertension 2018, 36:2042–2048

Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim *neo* trial

Results: Thirty patients enrolled from seven centers in Europe and Canada. From a baseline of 171.7 ± 20.2/99.5 ± 13.9 mm Hg, arterial pressure decreased by 26.0 ± 4.4/12.4 ± 2.5 mm Hg at 6 months. In a subset (n = 6) of patients with prior renal nerve ablation, arterial pressure decreased by 22.3 ± 9.8 mm Hg. Background medical therapy for hypertension was unchanged during follow-up. Three minor procedure-related complications occurred within 30 days of implant. All complications resolved without sequelae.





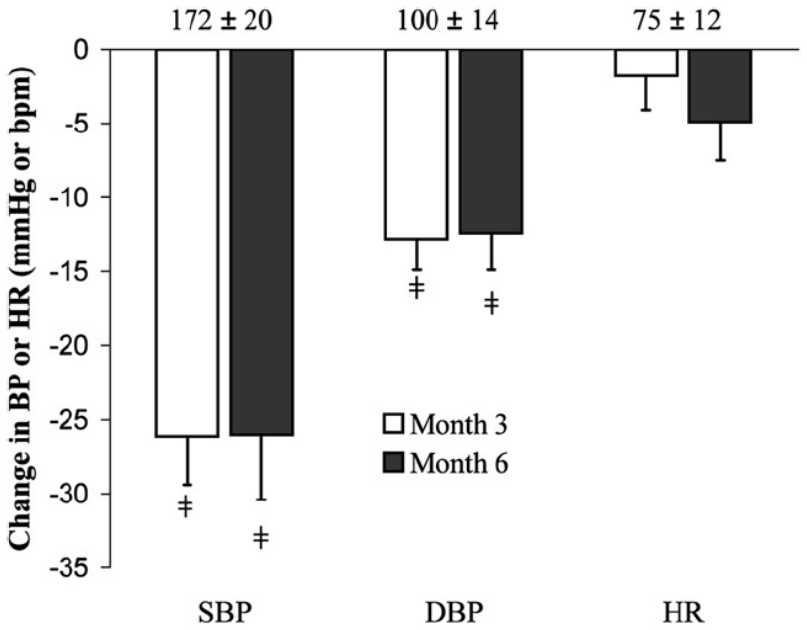


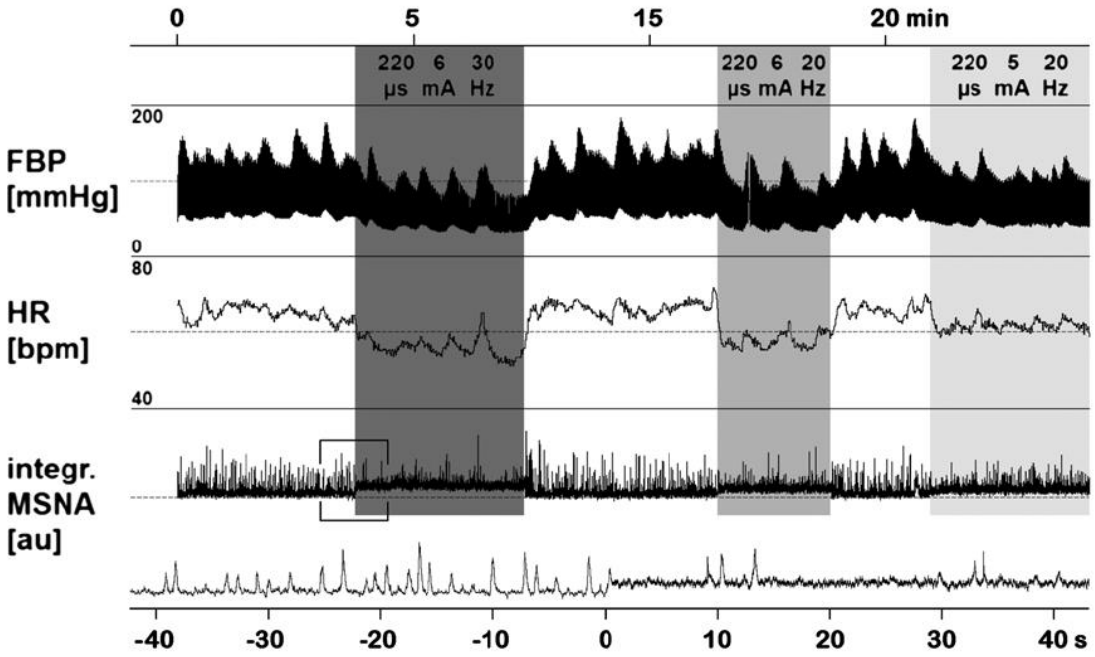
Figure 2. Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) relative to screening averages (average ± standard deviation above columns) at month 3 and month 6. Column height and bars represent average and standard error. ‡$P < .001$.

Acute Response to Unilateral Unipolar Electrical Carotid Sinus Stimulation in Patients With Resistant Arterial Hypertension

Karsten Heusser,* Jens Tank,* Julia Brinkmann, Jan Menne, Jessica Kaufeld, Silvia Linnenweber-Held, Joachim Beige, Mathias Wilhelmi, André Diedrich, Hermann Haller, Jens Jordan

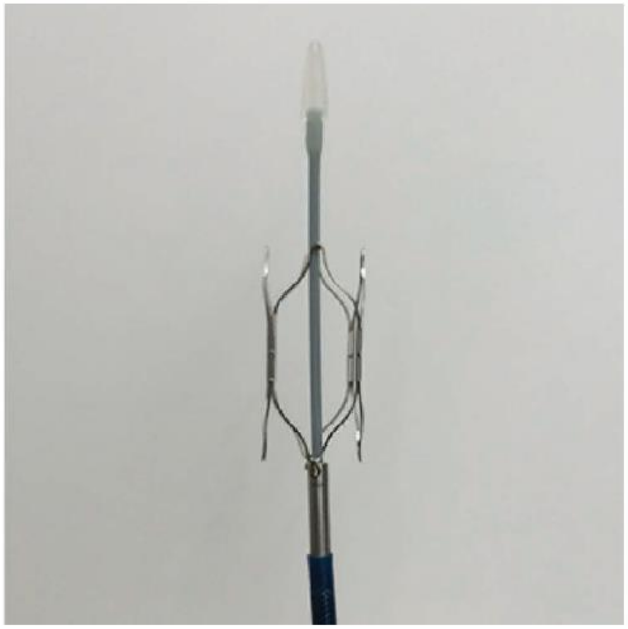
Table 1. Patient Baseline Characteristics (n=18)

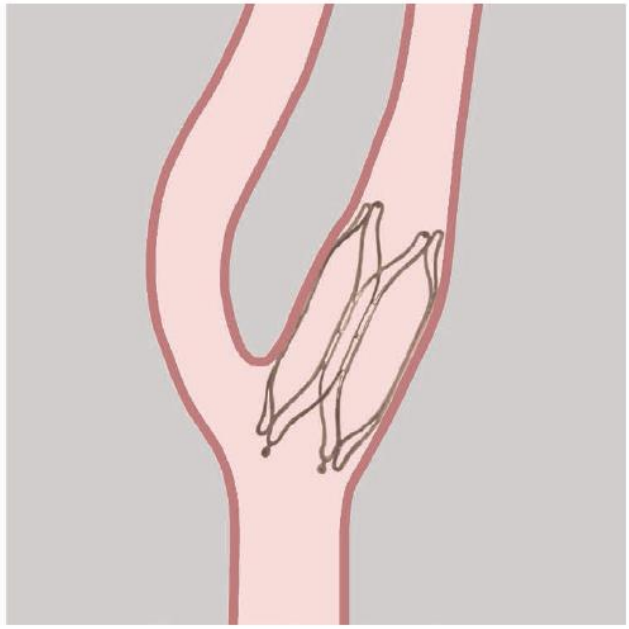
Parameter	Mean±SD
Age, y	53.5±10.6
BMI, kg/m^2	33.4±5.2
SBP, mm Hg	163±22
DBP, mm Hg	93±15
HR, bpm	74.8±15.0
MSNA, bursts/min	51.1±16.4
MSNA, bursts per 100 heart beats	65.2±13.4
MSNA, a.u.	2.99±1.17
Medications	7.1±1.4



Hypertension 2016;67:585-591.

Carotid Nitinol Stent (MobiusHD™)





the MobiusHD™ device (Vascular Dynamics, Inc, Mountain View, CA) was created to target the baroreflex through a different approach. Rather than electrical stimulation, the MobiusHD activates the baroreceptor by causing stretch of the carotid sinus. In contrast to traditional carotid stents used for carotid artery stenosis, this stent has fewer struts and a square shape, which leads to more pulsatile stretch on the carotid bulb and hopefully more long-term reduction in BP. The device is currently enrolling patients in a phase I trial to assess safety in humans.

https://clinicaltrials.gov/ct2/show/results/NCT01831895

Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial

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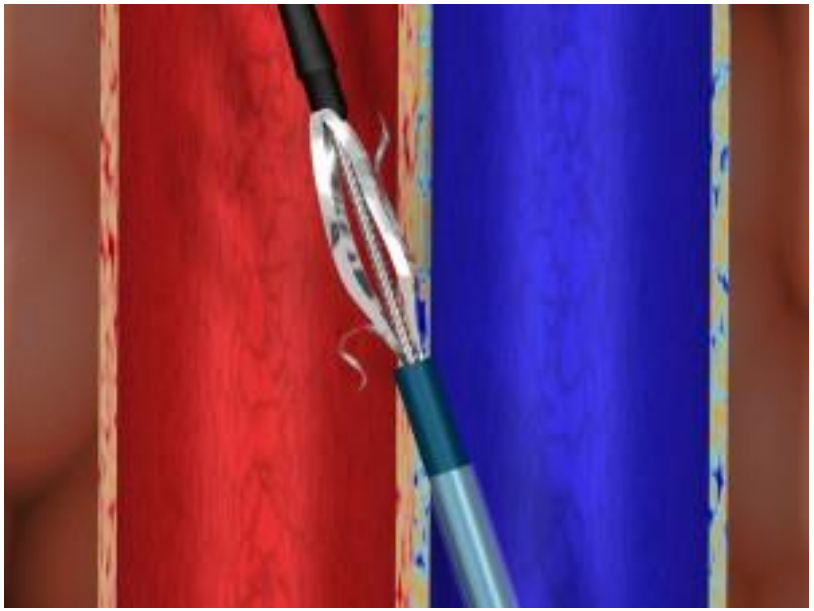
Findings 83 (43%) of 195 patients screened were assigned arteriovenous coupler therapy (n=44) or normal care (n=39). Mean office systolic blood pressure reduced by 26·9 (SD 23·9) mm Hg in the arteriovenous coupler group (p<0·0001) and by 3·7 (21·2) mm Hg in the control group (p=0·31). Mean systolic 24 h ambulatory blood pressure reduced by 13·5 (18·8) mm Hg (p<0·0001) in arteriovenous coupler recipients and by 0·5 (15·8) mm Hg (p=0·86) in controls. Implantation of the arteriovenous coupler was associated with late ipsilateral venous stenosis in 12 (29%) of 42 patients and was treatable with venoplasty or stenting.



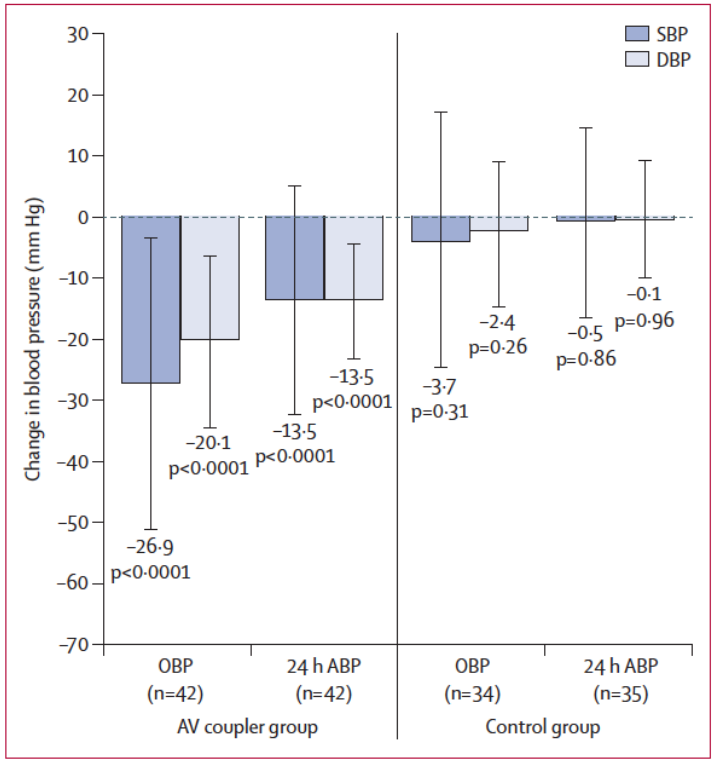


Figure 3: **Change from baseline in blood pressure at 6 months**
Data are mean (SD). SBP=systolic blood pressure. DBP=diastolic blood pressure. OBP=office blood pressure. ABP=ambulatory blood pressure. AV=arteriovenous.

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Conclusiones

- A pesar de los avances terapéuticos, la HTA resistente sigue siendo un reto para los profesionales implicados en su control
- Confirmar diagnóstico mediante MAPA
- Evaluar adherencia terapéutica
- Descartar HTA secundaria
- Optimizar tratamiento farmacológico
- Bloqueo de aldosterona
- En aquellos pacientes con una insuficiente respuesta al tratamiento farmacológico, las terapias intervencionistas pueden ser una opción útil.
- No obstante, la mayoría de ellas siguen siendo motivo de investigación. Queda por confirmar su utilidad a largo plazo y su capacidad para reducir la morbi-mortalidad cardiovascular sin un aumento significativo de los efectos indeseables.