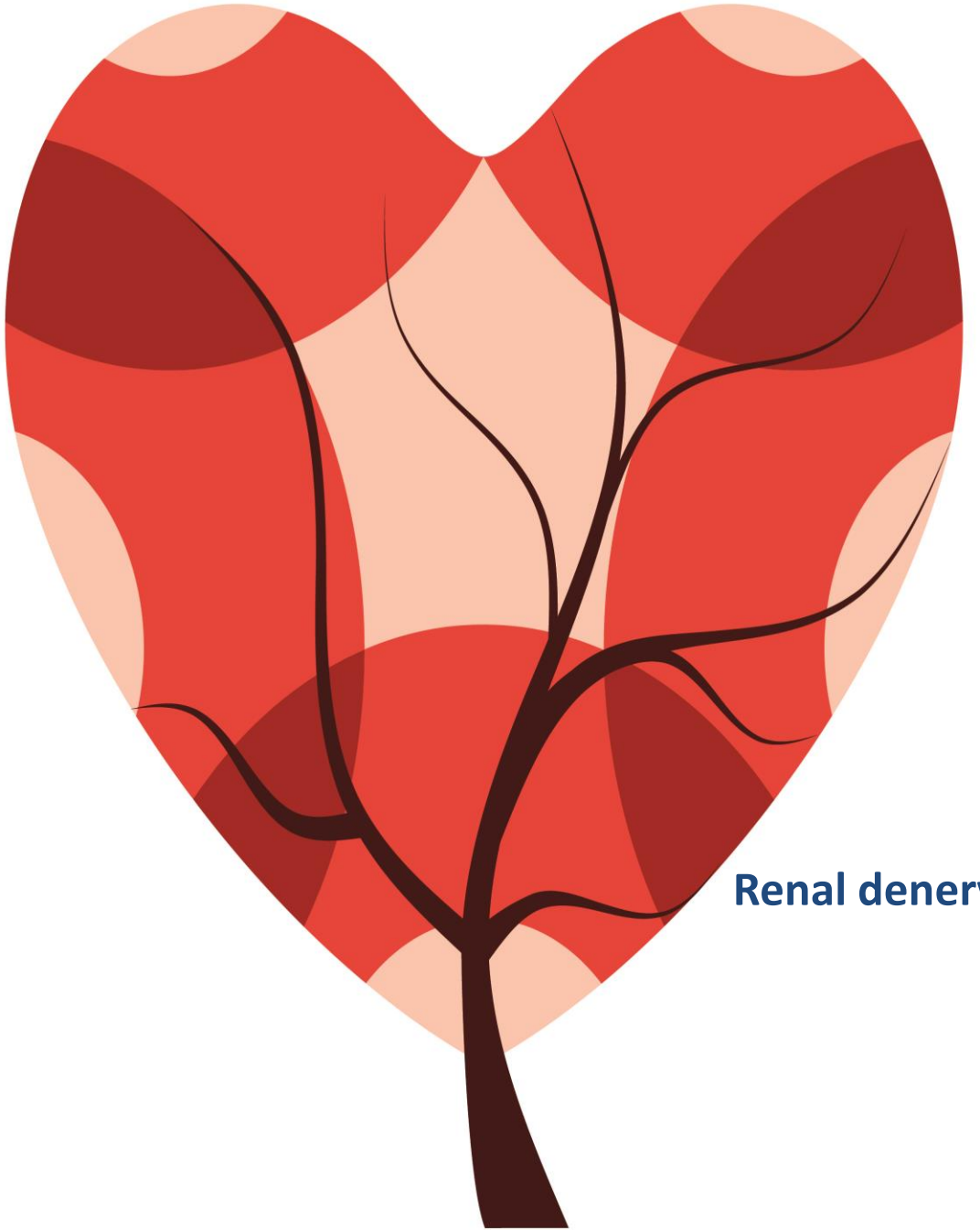

8th CHALLENGES in CARDIOLOGY

July 2018
6th, 7th
Palace Hotel Monte Real

Renal denervation in uncontrolled hypertension: the story continues to unfold

José A. García-Donaire
Nephrologist. Hypertension Unit
Hospital Clínico San Carlos
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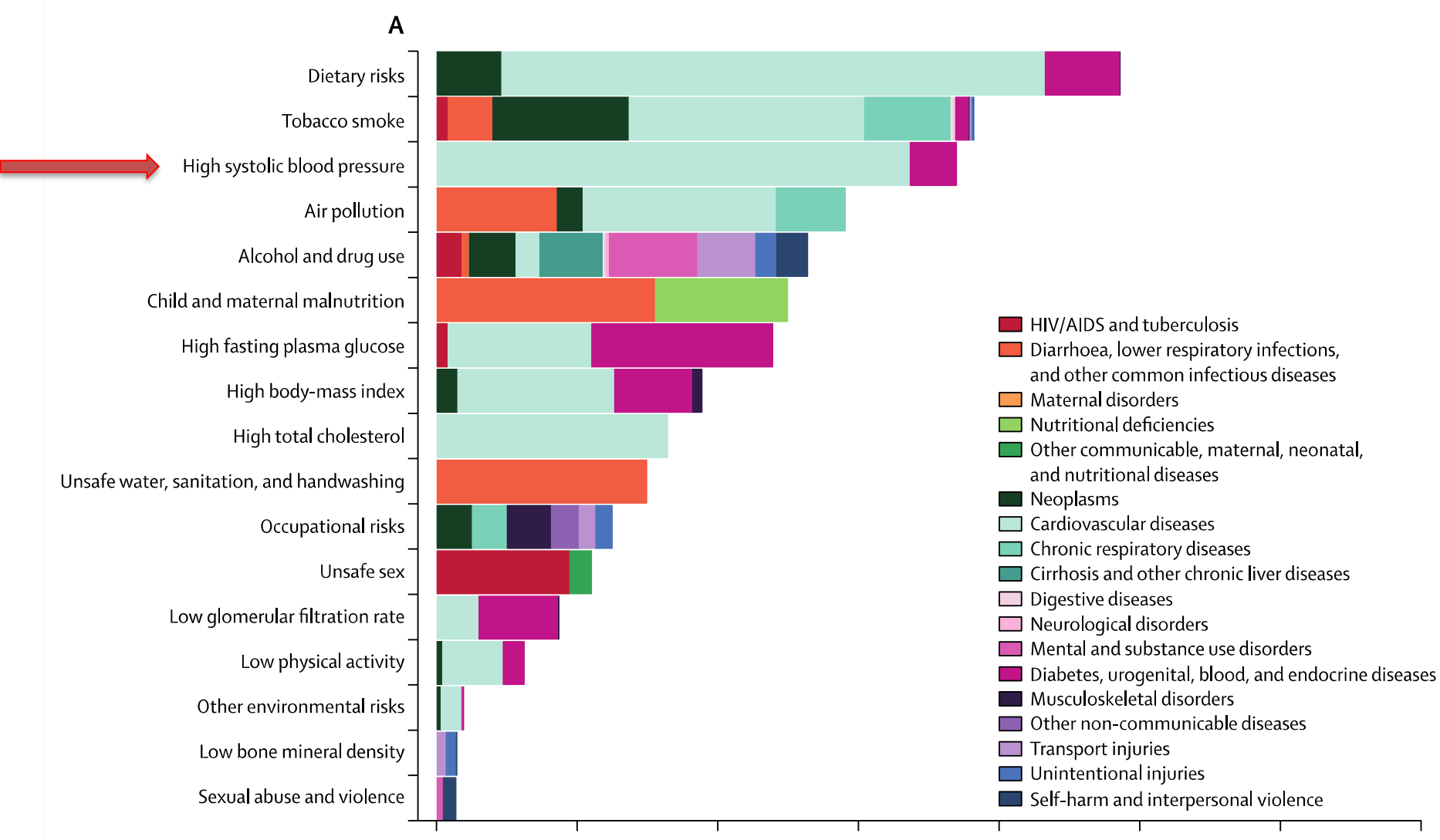
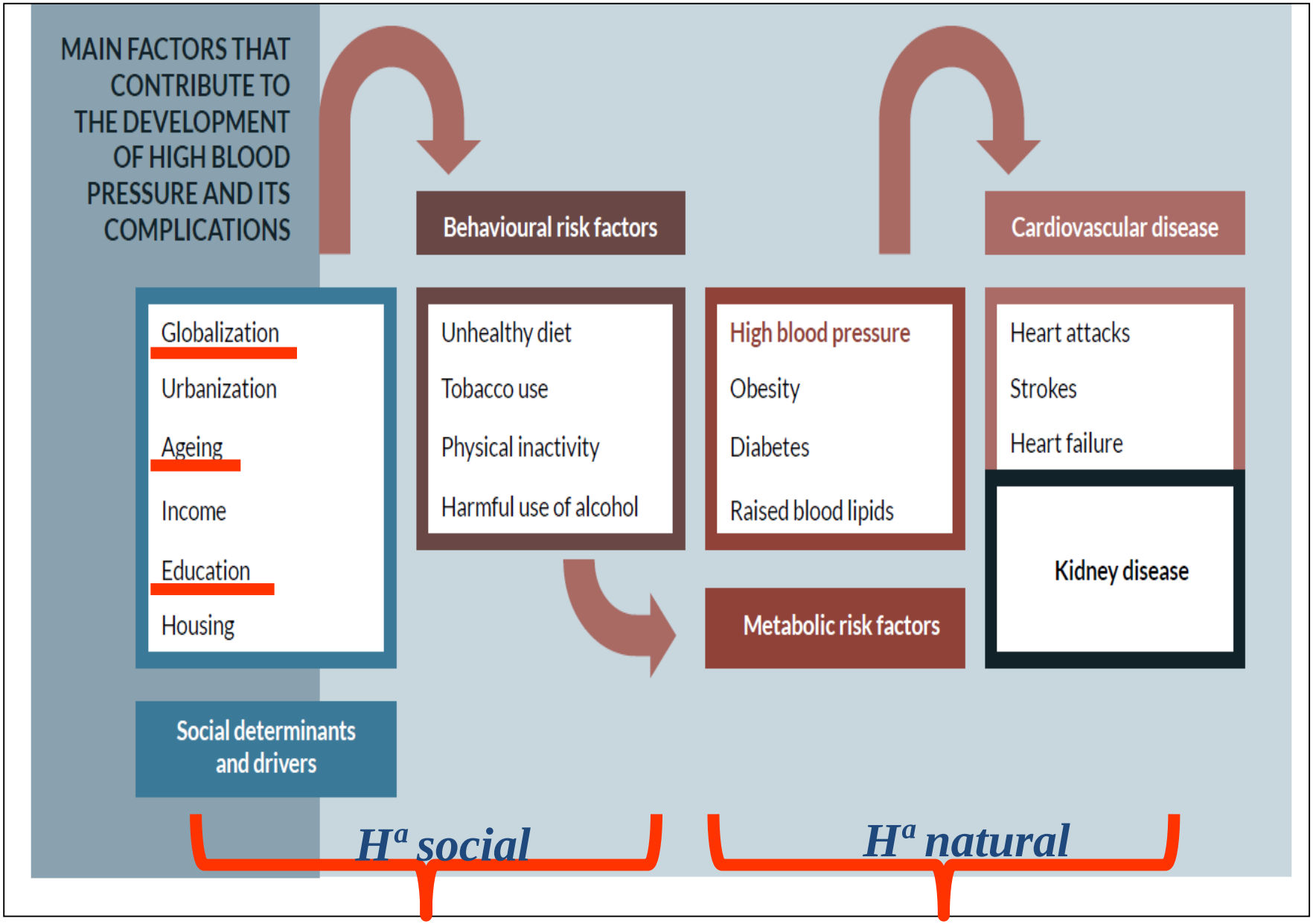
Global DALYs attributable to RF

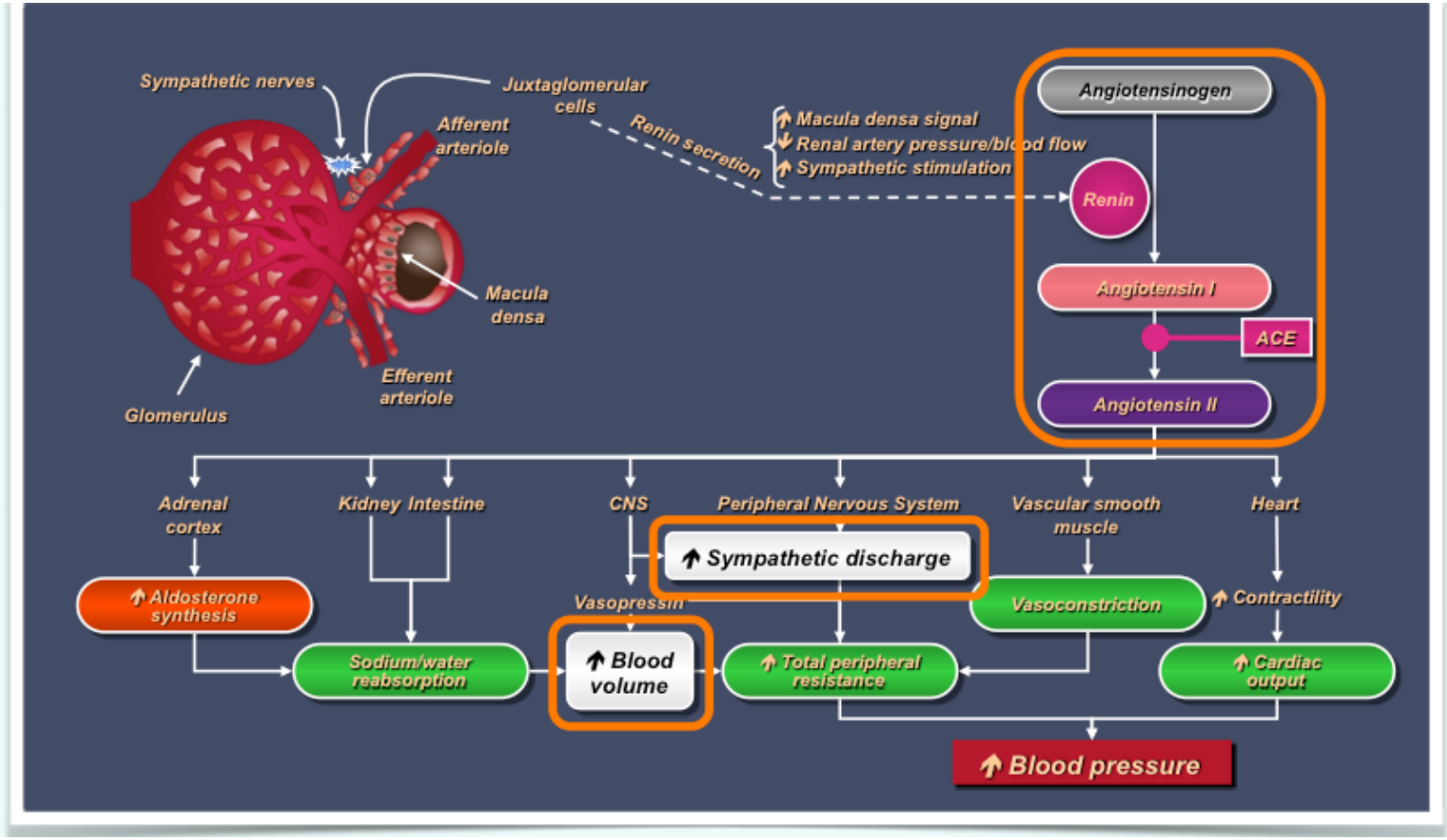


GBD 2015 RF Collaboration. Lancet 2016; 388: 1659–724

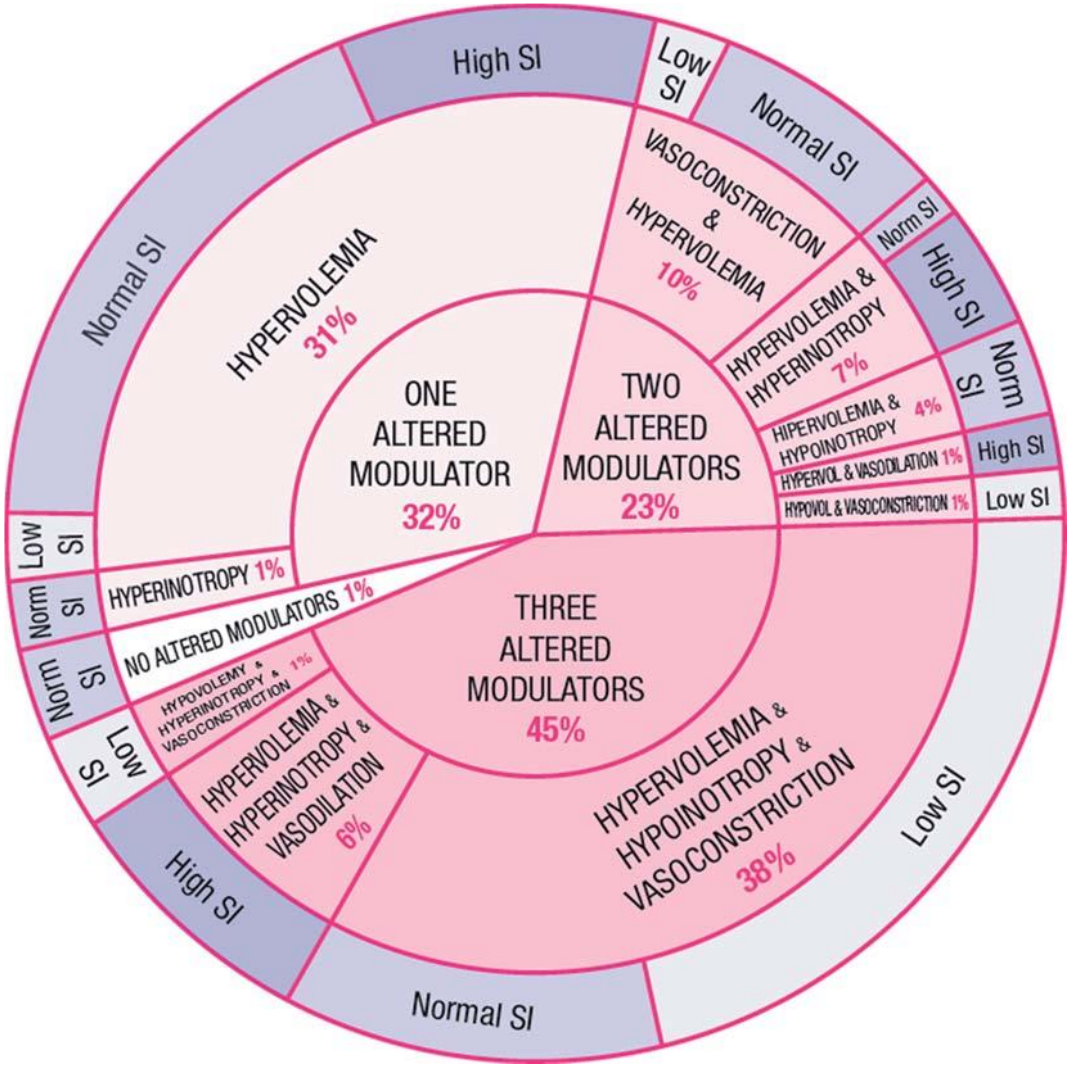
¿What factors affect HTN?



¿What factors affect HTN?



Do haemodynamic mechanisms matter?



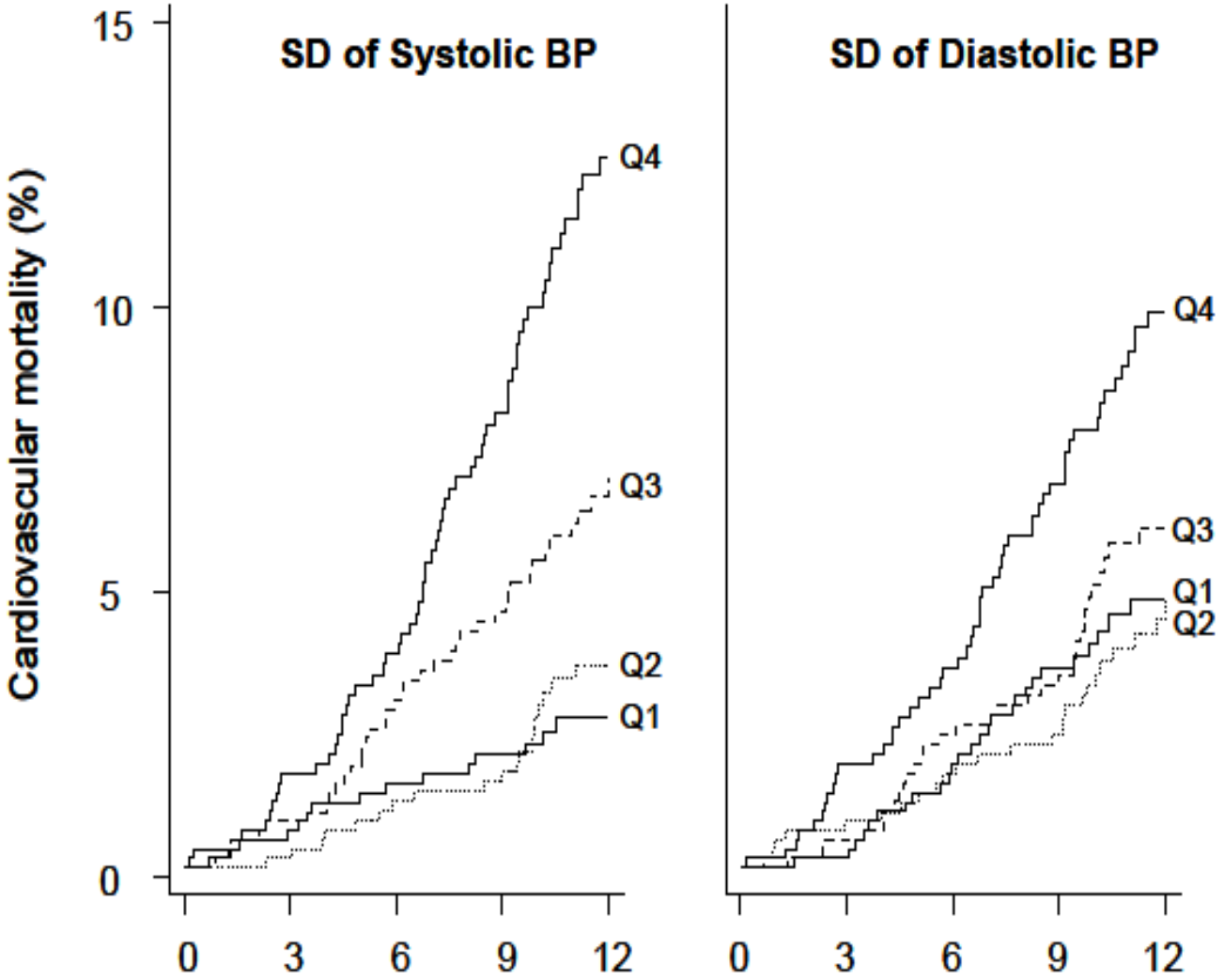
ViIgimaa et al. Blood Press. 2013; 22: 362-70

What % of hypertensives reach control?

	Prevalence [% (95% CI)][a]				
	Hypertension	Awareness	Treatment	Control[b]	Control[c]
Developed countries					
Men	40.2 (36.6–43.8)	48.4 (44.1–52.7)	28.8 (24.9–32.6)	33.1 (27.7–38.6)	10.6 (7.2–14.0)
Women	32.2 (29.0–35.4)	61.1 (57.3–65.0)	40.5 (36.2–44.9)	38.5 (32.6–44.3)	17.3 (13.1–21.5)
Developing countries					
Men	33.4 (30.5–36.4)	42.1 (35.0–49.1)	29.9 (24.4–35.3)	29.7 (25.0–34.4)	10.2 (6.9–13.5)
Women	32.0 (28.5–35.4)	53.6 (44.5–62.8)	40.6 (32.4–48.7)	33.8 (27.9–39.6)	16.2 (10.9–21.4)
North America					
Men	33.7 (30.7–36.6)	66.1 (58.3–73.9)	46.3 (40.3–52.3)	50.1 (39.5–60.8)	24.9 (18.0–31.8)
Women	30.6 (25.7–35.4)	70.1 (65.3–75.0)	53.3 (42.4–64.1)	55.9 (46.0–65.8)	31.0 (21.0–41.0)
Central, South America and Caribbean					
Men	33.1 (25.4–40.8)	61.1 (46.6–75.6)	38.4 (28.3–48.6)	37.9 (24.8–50.9)	15.9 (7.6–24.2)
Women	33.5 (25.2–41.8)	73.6 (56.1–91.0)	62.5 (48.8–76.2)	50.4 (37.5–63.3)	33.2 (18.6–47.8)
Africa					
Men	40.5 (31.5–49.6)	39.4 (20.1–58.6)	34.5 (15.6–53.4)	21.3 (17.0–25.6)	8.6 (1.9–15.2)
Women	40.3 (38.7–42.0)	55.8 (35.7–76.0)	49.0 (24.9–73.2)	24.7 (9.6–39.8)	14.6 (0–30.2)
Eastern Asia					
Men	33.6 (31.3–36.0)	37.7 (24.9–50.6)	24.1 (10.0–38.2)	25.3 (19.7–31.0)	5.7 (2.0–9.4)
Women	26.9 (25.0–28.8)	47.5 (36.8–58.2)	34.7 (23.9–45.5)	30.4 (23.2–37.5)	10.5 (7.6–13.4)
South-eastern, South-central and Western Asia					
Men	31.3 (25.1–37.6)	35.3 (32.0–38.6)	27.1 (24.4–29.7)	31.8 (29.6–34.0)	10.6 (6.4–14.9)
Women	32.6 (27.9––37.2)	46.4 (34.4–58.5)	30.6 (28.1–33.0)	30.3 (24.7–35.8)	11.8 (8.7–15.0)
Southern Europe					
Men	37.3 (28.5–46.0)	47.3 (43.0–51.5)	23.6 (20.4–26.7)	31.4 (20.5–42.2)	7.3 (3.4–11.1)
Women	32.1 (24.4–39.8)	59.0 (49.7–68.3)	38.1 (32.7–43.5)	29.5 (21.0–38.0)	12.2 (7.0–17.3)
Northern Europe					
Men	45.8 (37.7–53.9)	40.7 (33.0–48.4)	24.7 (19.8–29.6)	29.0 (19.5–38.4)	8.0 (3.7–12.3)
Women	34.9 (27.5–42.3)	52.1 (47.2–57.0)	29.9 (22.6–37.2)	31.9 (24.4–39.4)	10.0 (5.4–14.6)
Western Europe					
Men	42.4 (37.4–47.4)	46.4 (40.6–52.2)	27.1 (24.8–29.4)	29.7 (20.3–39.1)	9.5 (5.1–13.9)
Women	29.3 (24.2–34.5)	63.0 (59.1–66.9)	42.7 (38.7–46.8)	44.5 (36.3–52.7)	22.2 (16.6–27.7)
Central and Eastern Europe					
Men	41.2 (34.1–48.2)	53.7 (44.6–62.8)	34.5 (26.4–42.5)	29.1 (23.3–35.0)	10.1 (4.3–15.9)
Women	38.4 (27.2–49.7)	70.8 (67.8–73.9)	50.6 (43.1–58.0)	34.4 (21.3–47.5)	17.9 (9.7–26.1)
Australia/New Zealand					
Men	30.2 (20.3–40.0)	54.0 (44.6–63.4)	33.2 (28.6–37.8)	50.9 (45.3–56.4)	16.7 (14.5–18.9)
Women	23.8 (18.4–29.2)	67.1 (60.4–73.8)	38.2 (30.2–46.2)	52.7 (44.3–61.0)	19.6 (16.8–22.3)

Pereira M et al. J Hypertens 2009; 27:963-75

Should BP variability be included among objectives?



Kikuya et al. Hypertension. 2008

Hipertensión resistente
PA consulta > 140/90 mmHg
Recibiendo 3 anti HTA (incl. diuréticos)

Excluir Pseudorresistancia

Identificar y revertir factores de estilo de vida perjudiciales

Suspender o minimizar sustancias que interfieren con el control de la PA

Buscar causas de HTA secundaria

Aprox. farmacológica:
adherencia
combinación de fármacos

Aprox. intervencionista

Denervación renal

Schmieder RE et al Eurointervention 2013

WHAT HAVE WE LEARNT?

- Poor adherence affects BP variability
- BP measurements must be standardized
- SHAM is quite important
- Human anatomy is a key-point to optimize the results of RDN
- Patient selection is critical

WHAT DO WE BELIEVE TO KNOW?

- Prevalence and pathophysiology of HTN (resistant?)
- Morbidity and mortality associated with HTN (resistant?)
- HTN control is deficient
- Protocols of patients flows and paths are necessary

WHAT DO WE BELIEVE TO KNOW (II)?

- Patients with Isolated Systolic Hypertension may not respond as well to RDN

- Medication adherence likely modulates or masks the effect of RDN

- Patient preference is strong – almost half the patients self-referred for SPYRAL HTN trials

WHAT DO WE WANT TO KNOW (#1)?

- Is the same patient that under 3 vs 7 drugs?
- 24h-ABPM has been evaluated in clinical trials?
- Have secondary causes of HTN been reasonably withdrawn?
- Concept of optimal dosage? Which anti-HTN drugs?
- Should all the hypertensives be treated with drugs?
- Biomarker of successful denervation?

WHAT DO WE WANT TO KNOW (#2)?

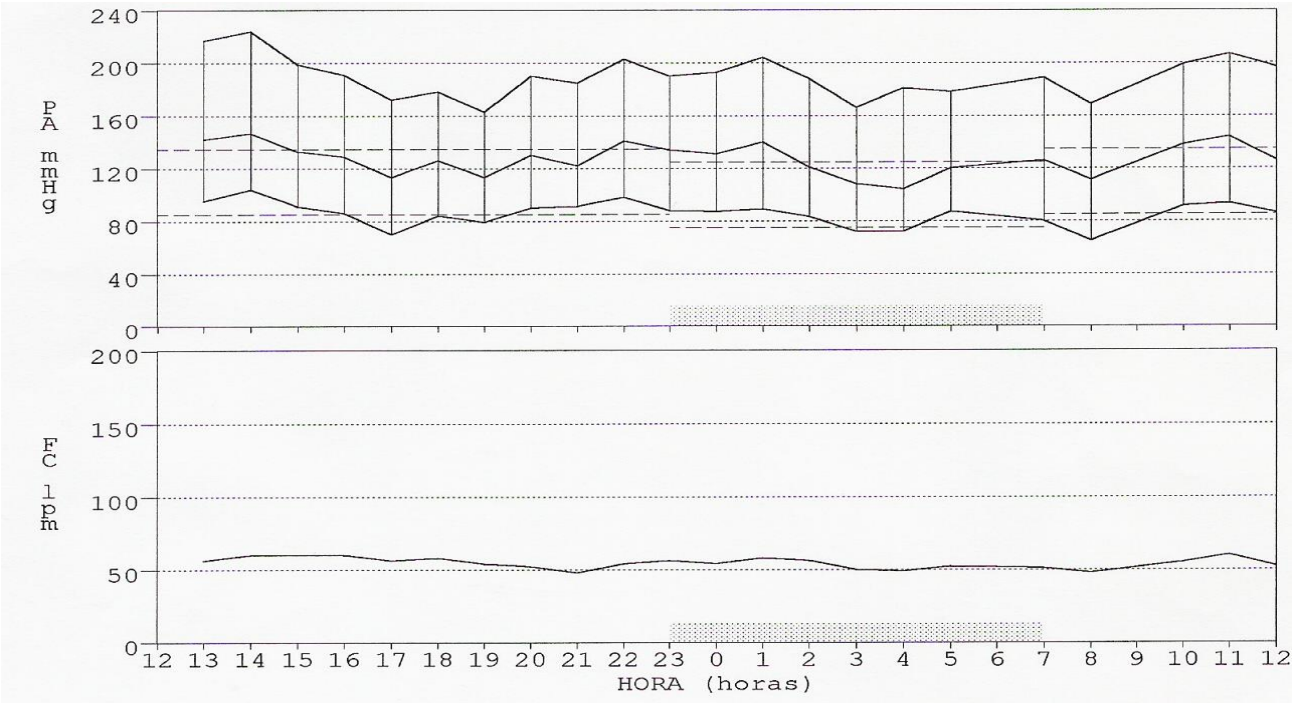
- What is the best patient to be treated with RDN?
- Is RDN safe in the long-term?
- What arteries should be preferable to be treated?
- How do patients with the highest expectable sympathetic activity (OSA, CKD, HF…) respond to RDN?

CASE REPORT

- Female, 44 yo.
- Resistant HTN. Diagnosed at 32 yo. LVH and albuminuria.
  Ckecked adherence
  - Valsartan/Amlodipine/Hctz 320/10/25mg
  - Spironolactone 100mg
  - Bisoprolol 10mg

- Type 2 DM since 2010, metformin
- Dyslipidemia since 2010, statins
- Obesity since childhood

Case report. 24h ABPM



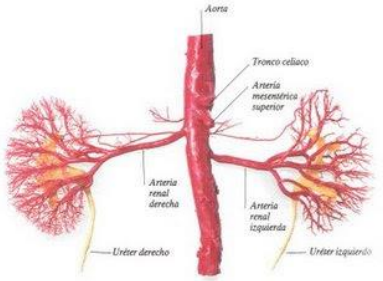
24 h	191/96 mmHg
Activity	193/97 mmHg
Night	185/92 mmHg

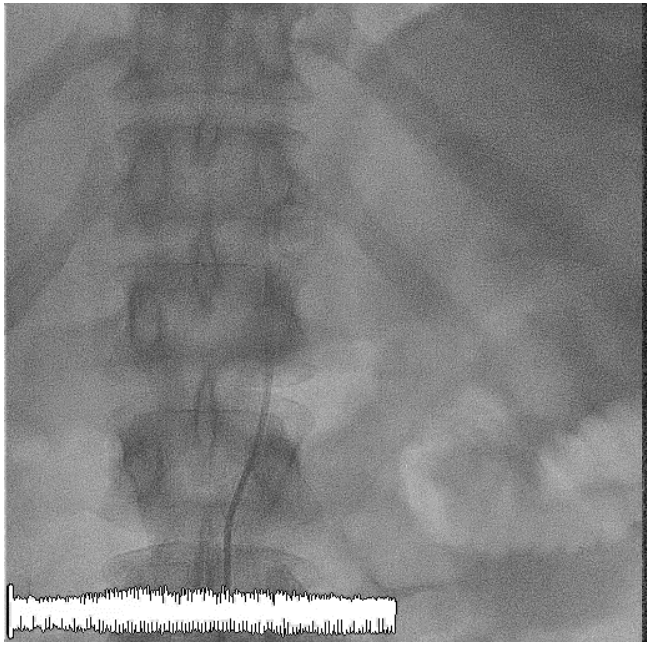
Case report. Withdrawn of causes of 2ª HTN

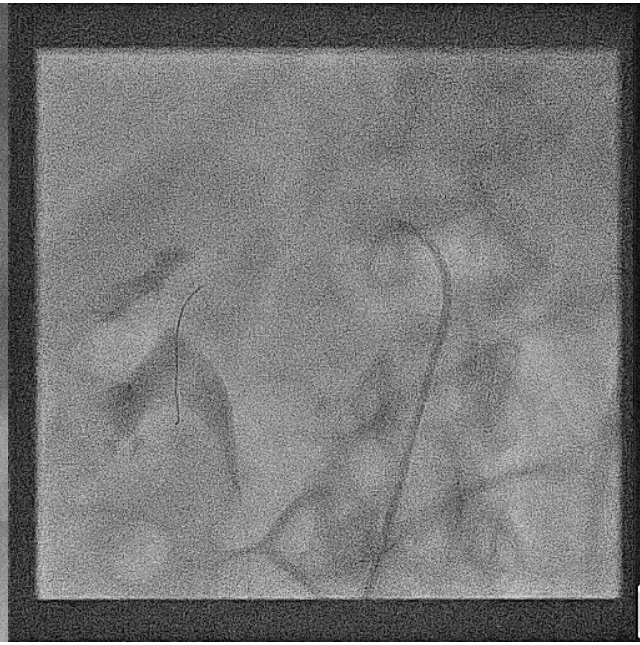
ABCD
A: Apnea, Aldosteronism
B: Bruits, Bad kidneys
C: Catecholamines, Coarctation, Cushing's Syndrome
D: Drugs, Diet

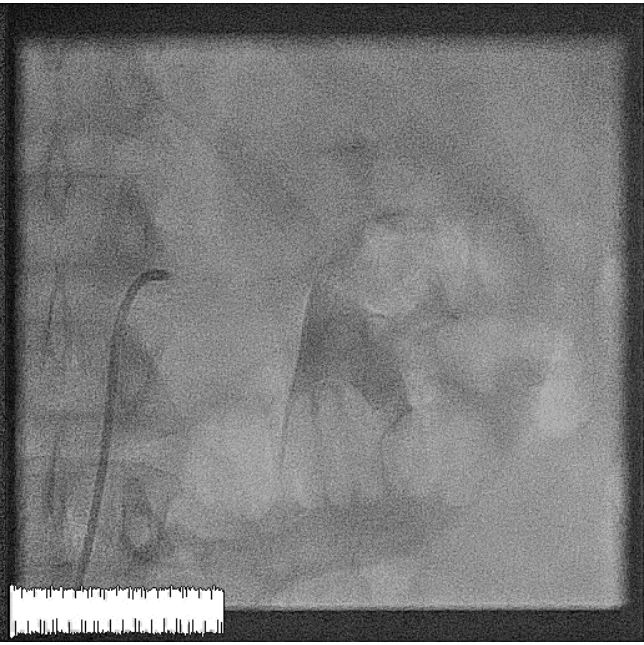
Onusko E. *Am Fam Physician*. 2003;67:67-74.

Case report. RDN

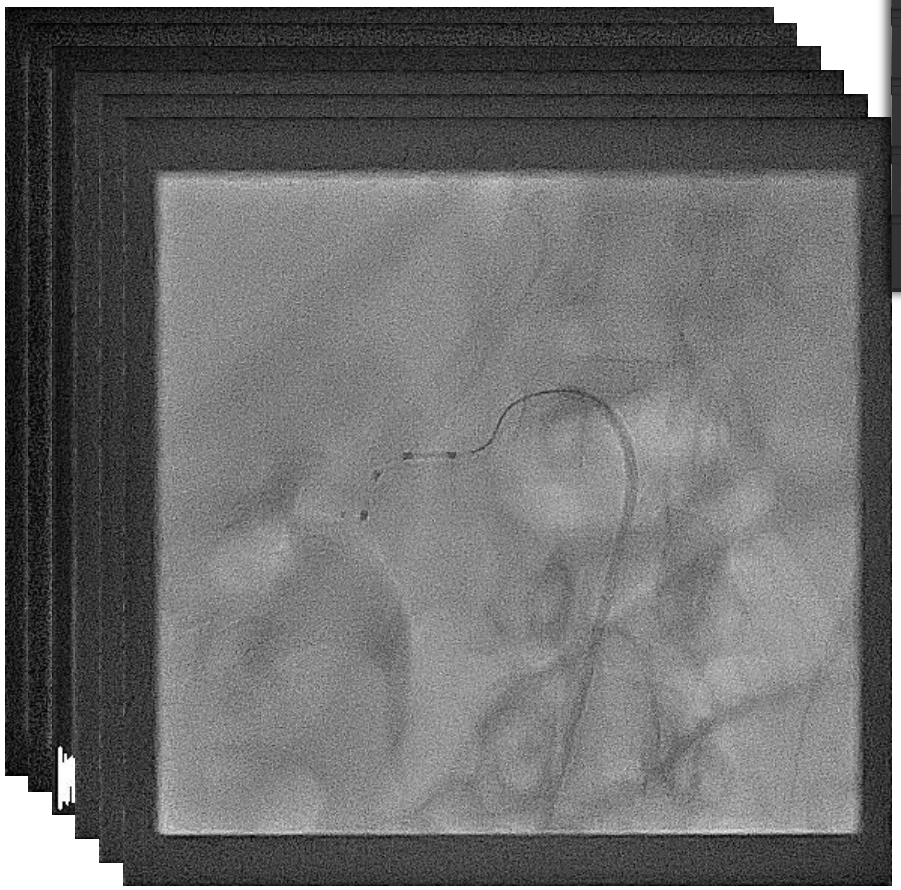


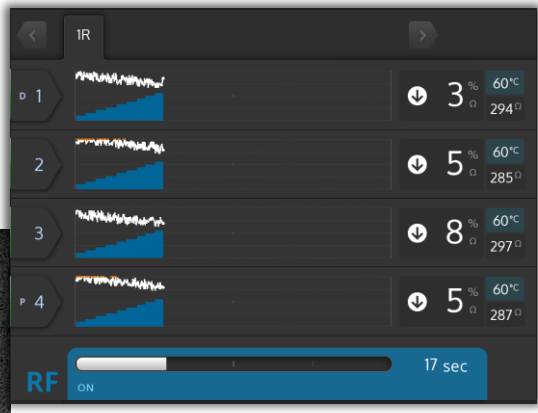




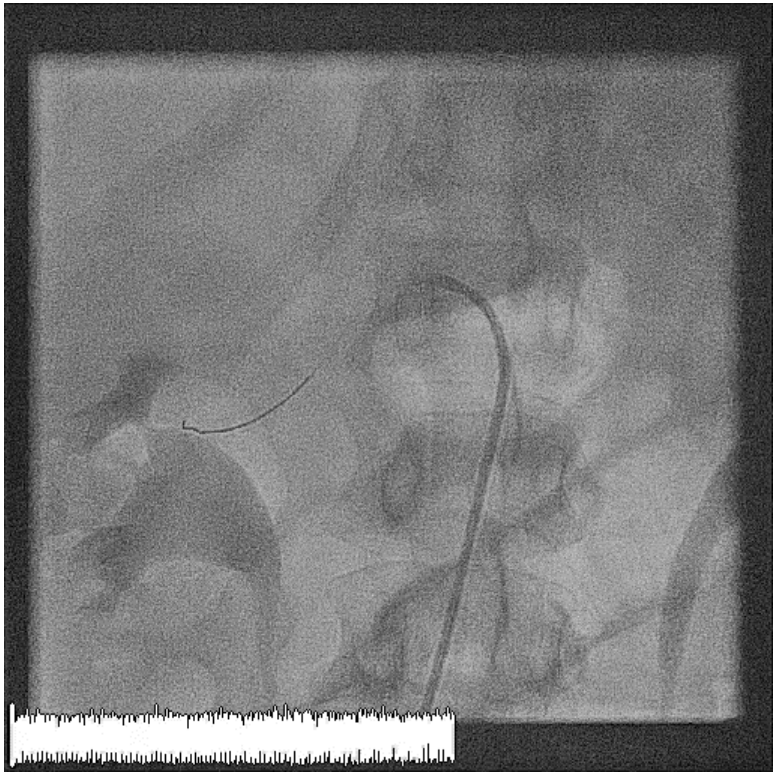


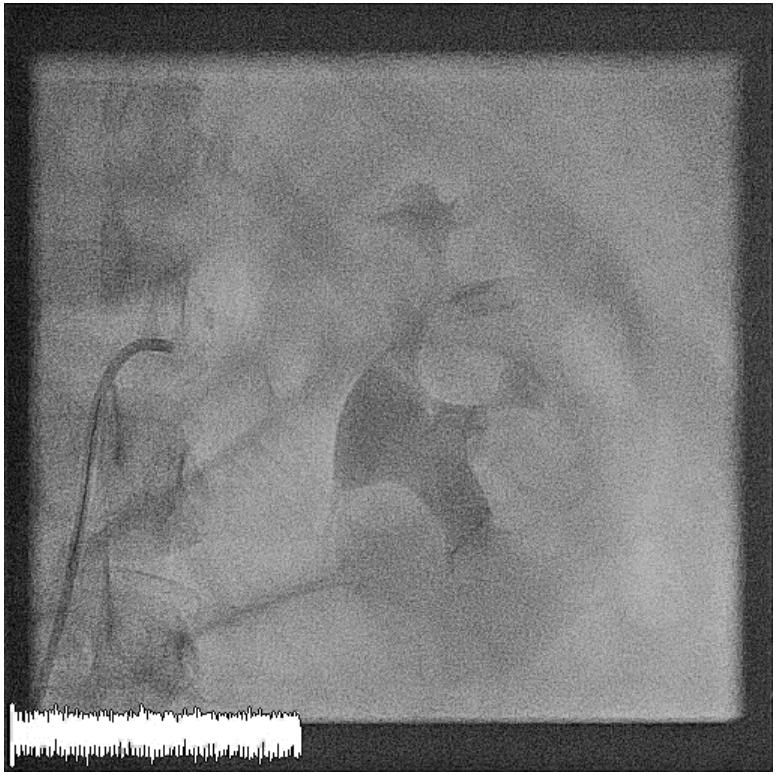
Case report. RDN



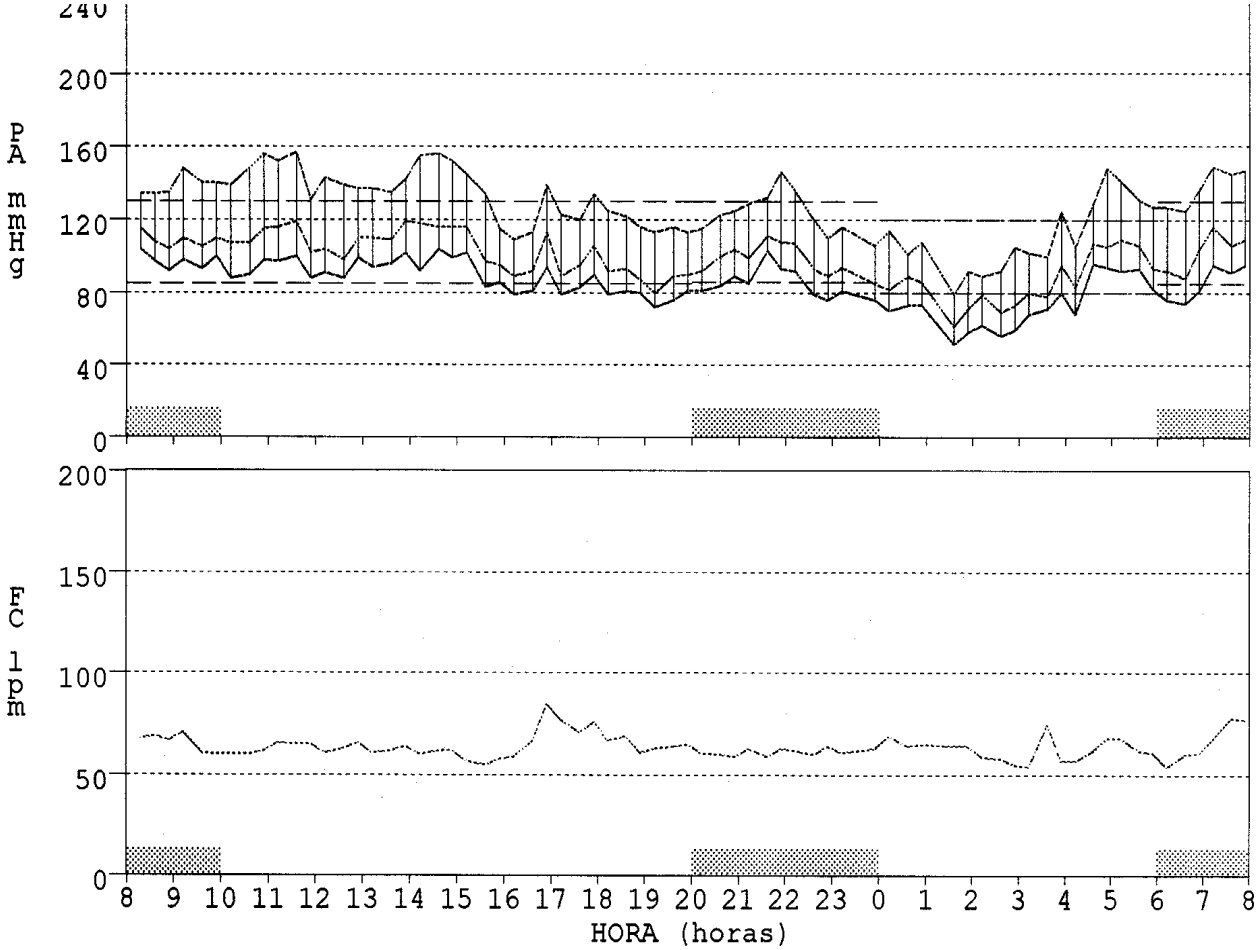


Case report. RDN



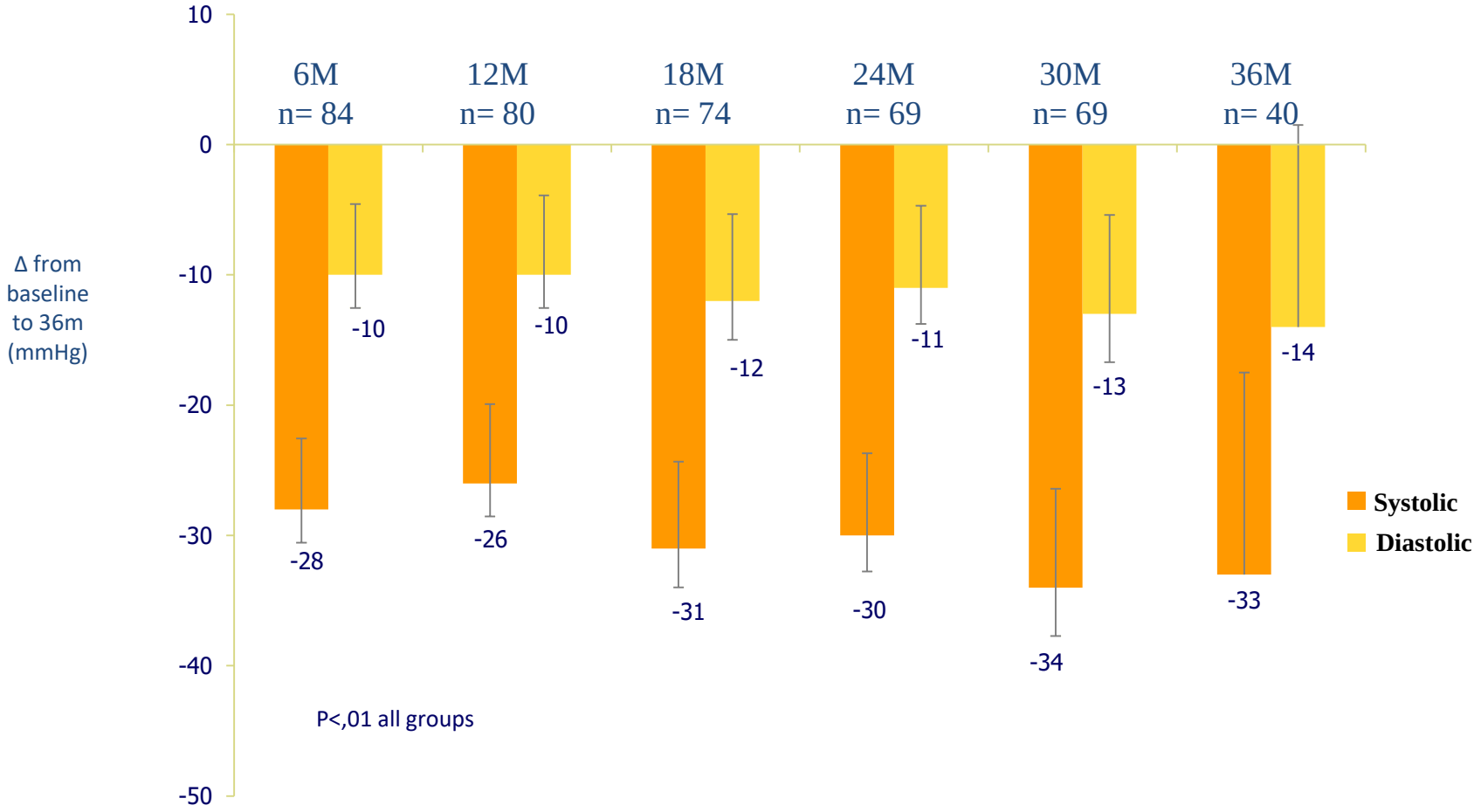


Case report. 3 months later 24h ABPM



24 h	152/87 mmHg
Activity	154/89 mmHg
Night	148/85 mmHg

Symplicity HTN-2 at 36 months



Esler M et al. Eur Heart J 2014 Jun 4. PMID: 24898552

DNR en pacientes con ERC

Renal denervation in moderate to severe CKD.

Hering D, **Mahfoud F**, **Walton AS**, Krum H, Lambert GW, Lambert EA, Sobotka PA, Böhm M, Cremers B, Esler MD, Schlaich MP.

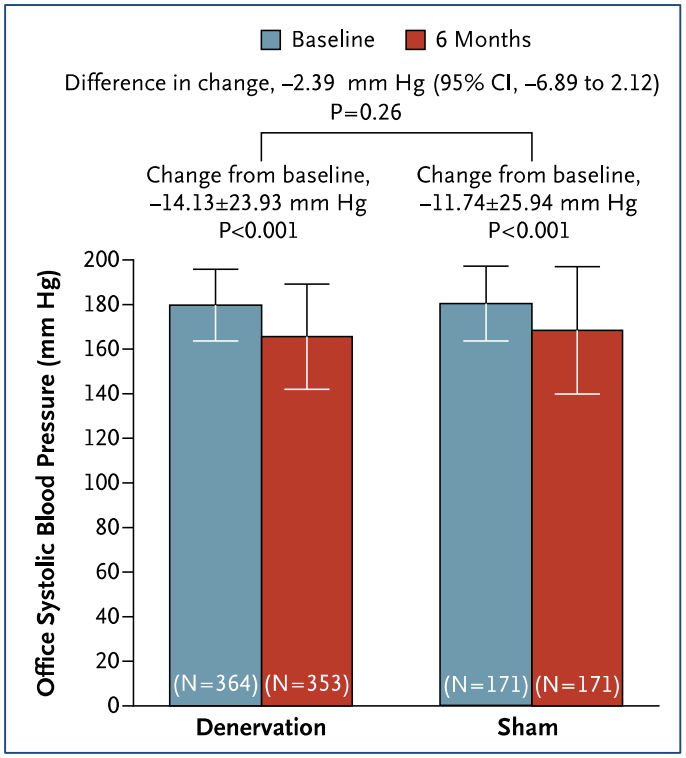
Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia.

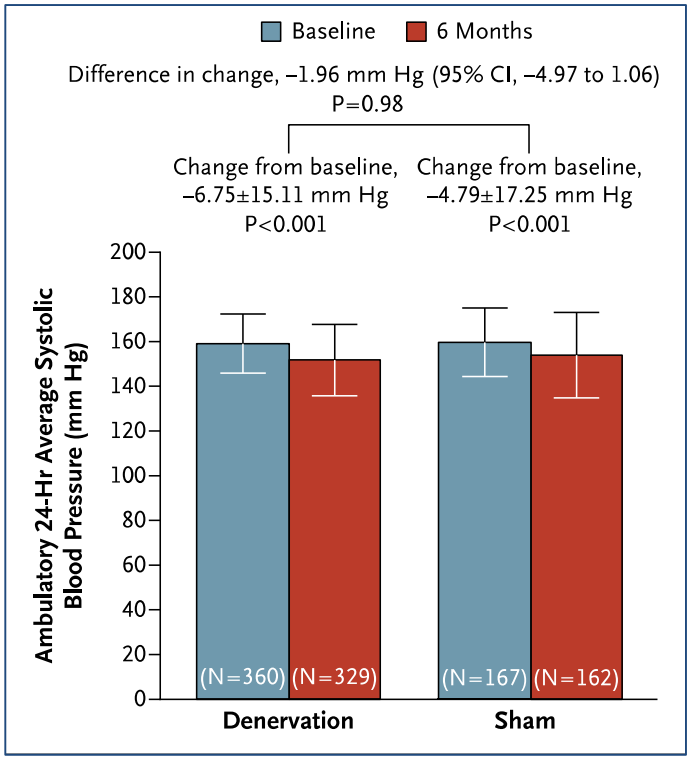
Abstract

Sympathetic activation contributes to the progression of CKD and is associated with adverse cardiovascular outcomes. Ablation of renal sympathetic nerves reduces sympathetic nerve activity and BP in patients with resistant hypertension and preserved renal function, but whether this approach is safe and effective in patients with an estimated GFR (eGFR) < 45 ml/min per 1.73 m(2) is unknown. We performed bilateral renal denervation in 15 patients with resistant hypertension and stage 3-4 CKD (mean eGFR, 31 ml/min per 1.73 m(2)). We used CO(2) angiography in six patients to minimize exposure to contrast agents. Estimated GFR remained unchanged after the procedure, irrespective of the use of CO(2) angiography. Mean baseline BP ± SD was 174 ± 22/91 ± 16 mmHg despite the use of 5.6 ± 1.3 antihypertensive drugs. Mean changes in office systolic and diastolic BP at 1, 3, 6, and 12 months were -34/-14, -25/-11, -32/-15, and -33/-19 mmHg, respectively. Night-time ambulatory BP significantly decreased (P<0.05), restoring a more physiologic dipping pattern. In conclusion, this study suggests a favorable short-term safety profile and beneficial BP effects of catheter-based renal nerve ablation in patients with stage 3-4 CKD and resistant hypertension.

J Am Soc Nephrol. **2012** Jul;23(7):1250-7.

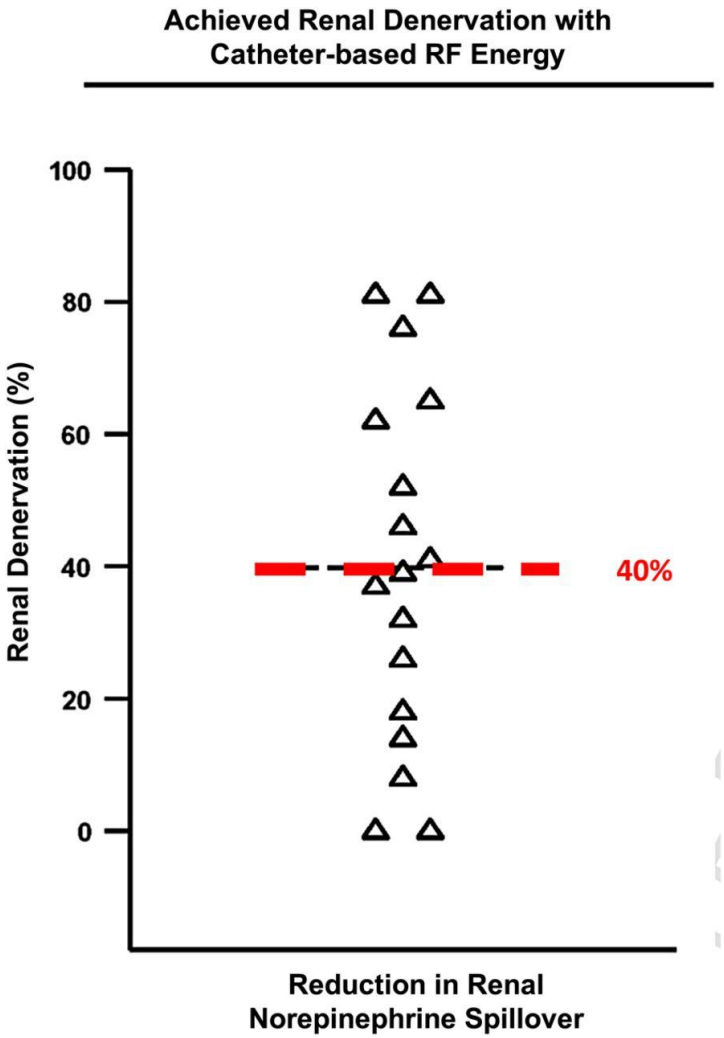
Symplicity HTN-3 a 6 meses





Bhatt D et al. NEJM 2014;370: 1393-01

Possible explanations: variability

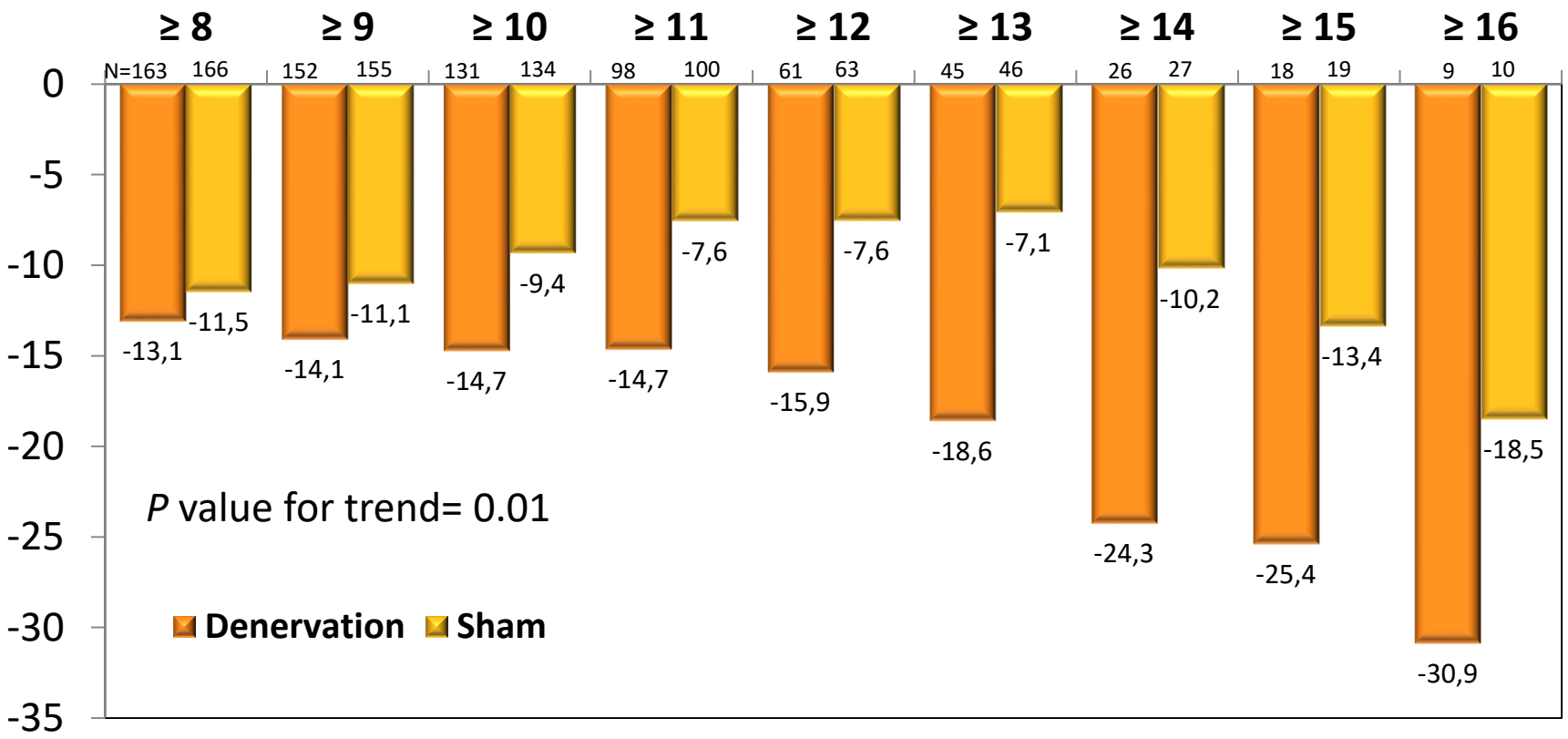


Effectiveness and variability of catheter-based renal denervation 30 days after the procedure measured by renal norepinephrine (NE) spillover (n = 17).

Felix Mahfoud, and Thomas Felix Lüscher Eur Heart J 2015;36:199-202

European Heart Journal

Possible explanations: expertise



	≥ 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

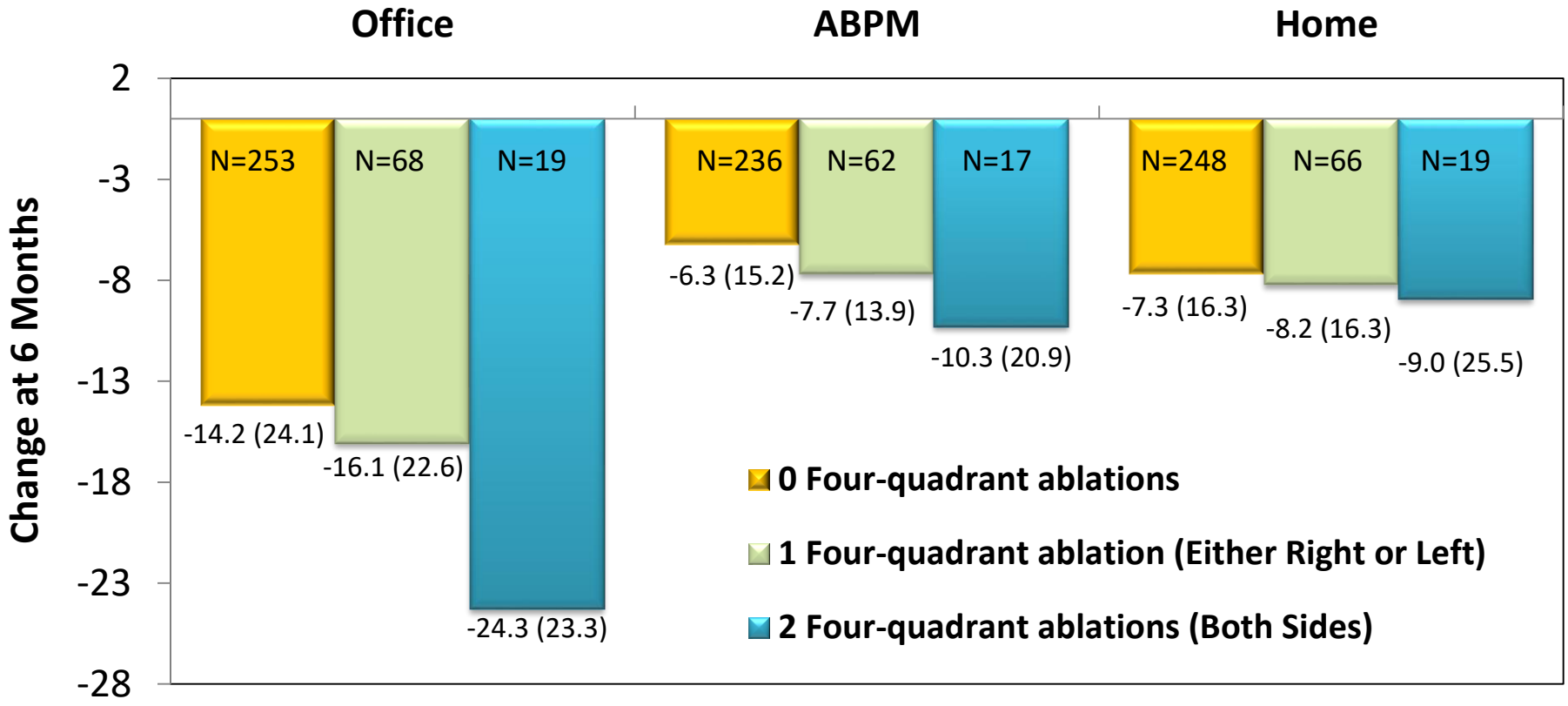
Propensity scores using baseline characteristics as covariates were used to match sham control and denervation patients

*P value change in SBP for RDN compared with sham

Data presented are mean (SD)

Bhatt D et al. NEJM 2014;370: 1393-01

Possible explanations: technique



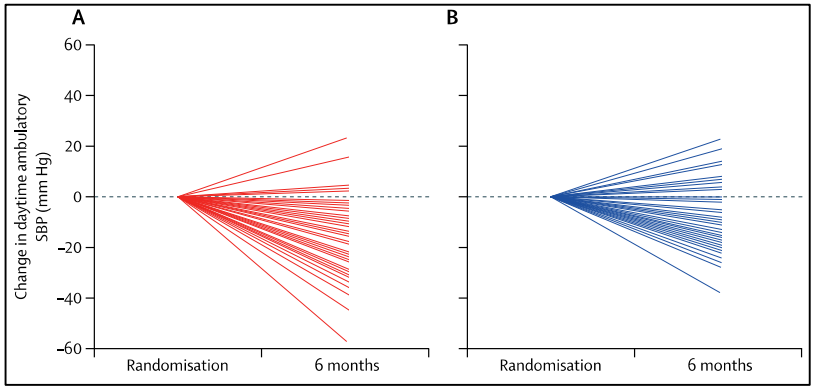
Baseline SBP Measurements (mm Hg)

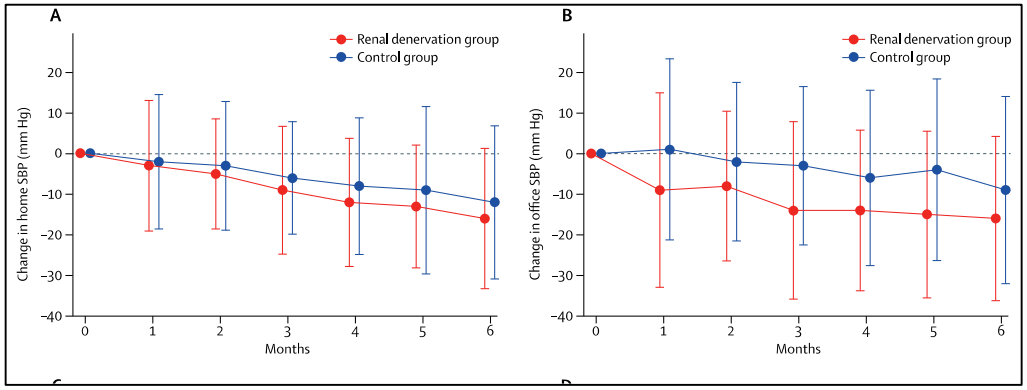
0 four-quadrant tx*	179.6	158.7	168.5
1 Four-quadrant tx	178.8	161.2	171.3
2 four-quadrant tx	186.9	159.9	170.4

*1 superior, 1 inferior and 2 anterior/ posterior

Bhatt D et al. NEJM 2014;370: 1393-01

Possible explanations: drug effect



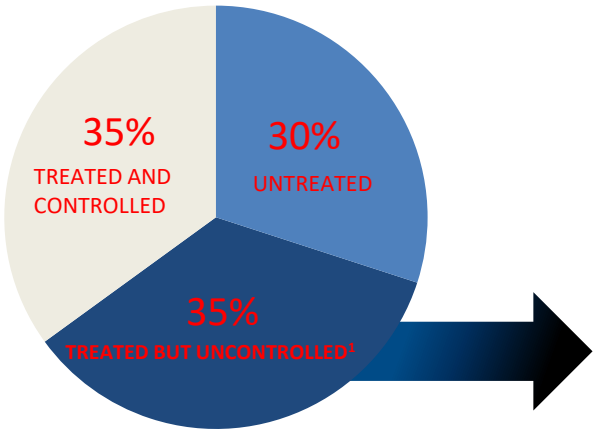


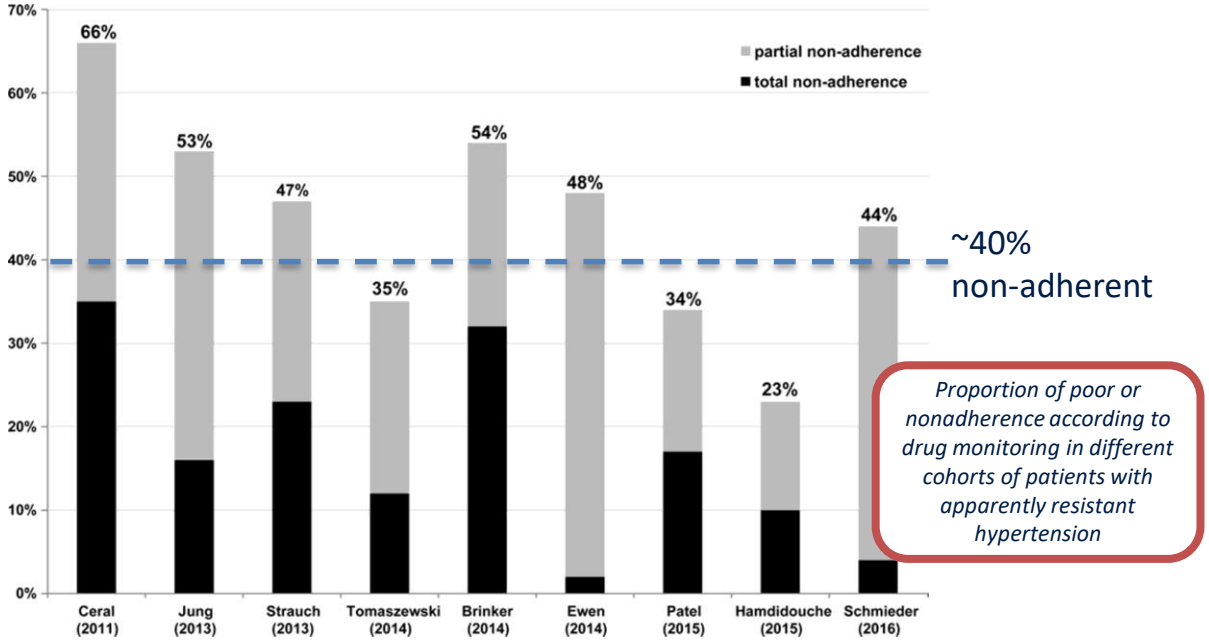
	Renal denervation group			Control group			Mean baseline-adjusted difference (95% CI) between the two groups at 6 months	p value
	Randomisation (mean ± SD)	6 months (mean ± SD)	Mean baseline-adjusted difference (95% CI)	Randomisation (mean ± SD)	6 months (mean ± SD)	Mean baseline-adjusted difference (95% CI)		
ABP, mm Hg	n=48	n=48		n=53	n=53			
Daytime								
SBP	155·5±16·1	139·1±17·8	−15·8 (−19·7 to −11·9)	151·0±16·0	141·7±17·5	−9·9 (−13·6 to −6·2)	−5·9 (−11·3 to −0·5)	0·0329
DBP	92·9±15·0	82·9±13·7	−9·9 (−12·5 to −7·3)	92·0±10·8	85·4±13·2	−6·8 (−9·3 to −4·3)	−3·1 (−6·7 to 0·5)	0·0922
Night-time								

www.thelancet.com Published online January 26, 2015 http://dx.doi.org/10.1016/S0140-6736(14)61942-5

Possible explanations: adherence

- Even with combination pills for high BP, studies show patients become non-adherent
- ~50% of patients show episodes of drug non-adherence within 1-year of initial drug treatment





Possible explanations: adherence (II)

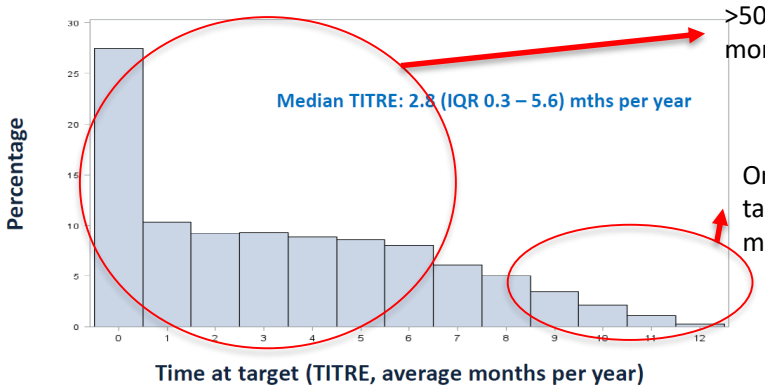
PATIENTS ARE RARELY AT BP TARGET FOR SUSTAINED PERIOD OF TIME

TITRE: average TIme per year spent by newly-identified hypertensive patients at BP care TaRgEt

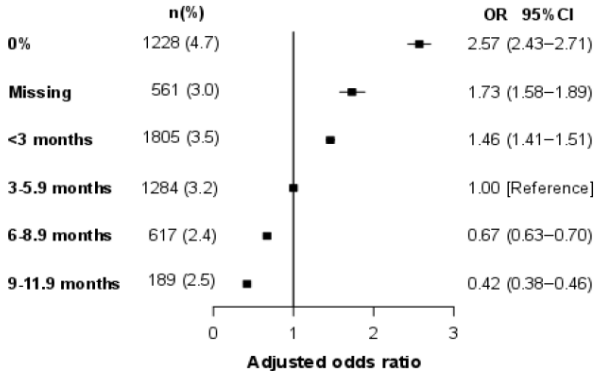
- Few patients sustained complete, year-round on-target BP over time

- A higher time at target was associated with a lower risk of incident CVDs, independent of widely-used BP control indicators

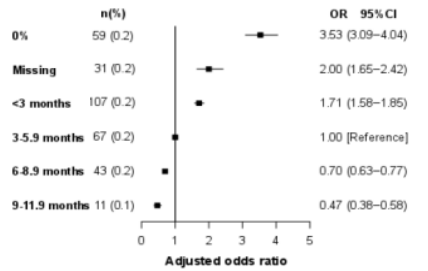
Time at target (TITRE) distribution (N=150,130)



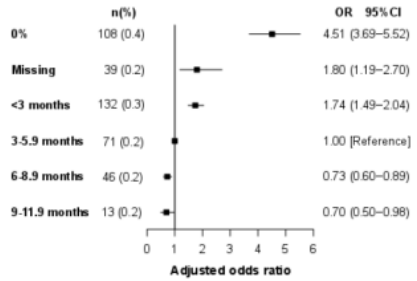
Any CVD and death



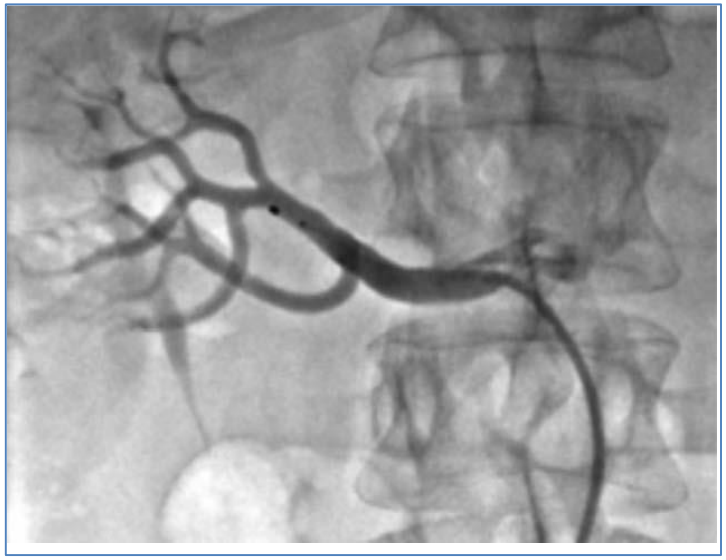
Heart failure

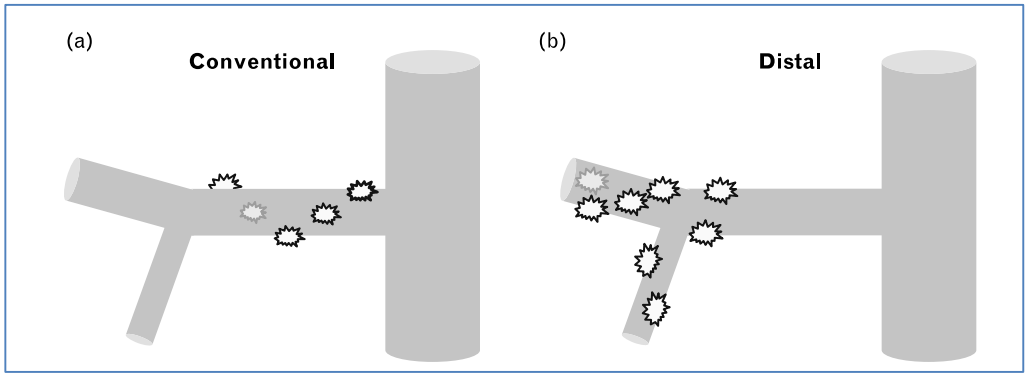


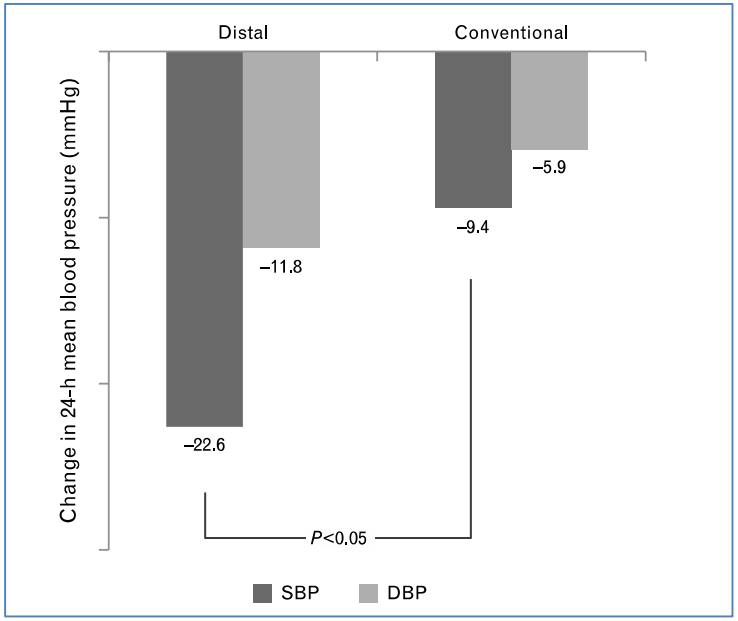
CVD composite



Possible explanations: anatomy

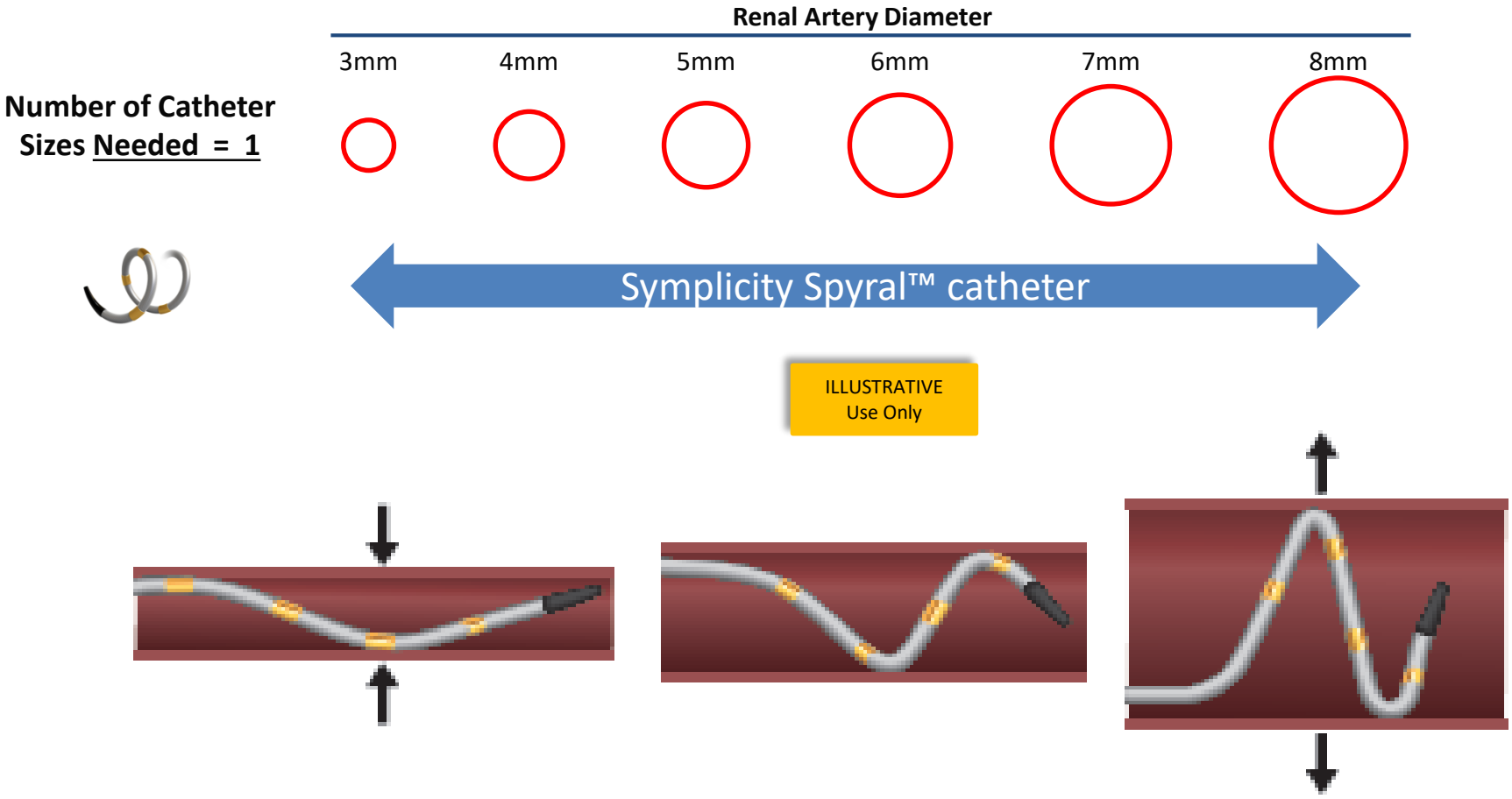




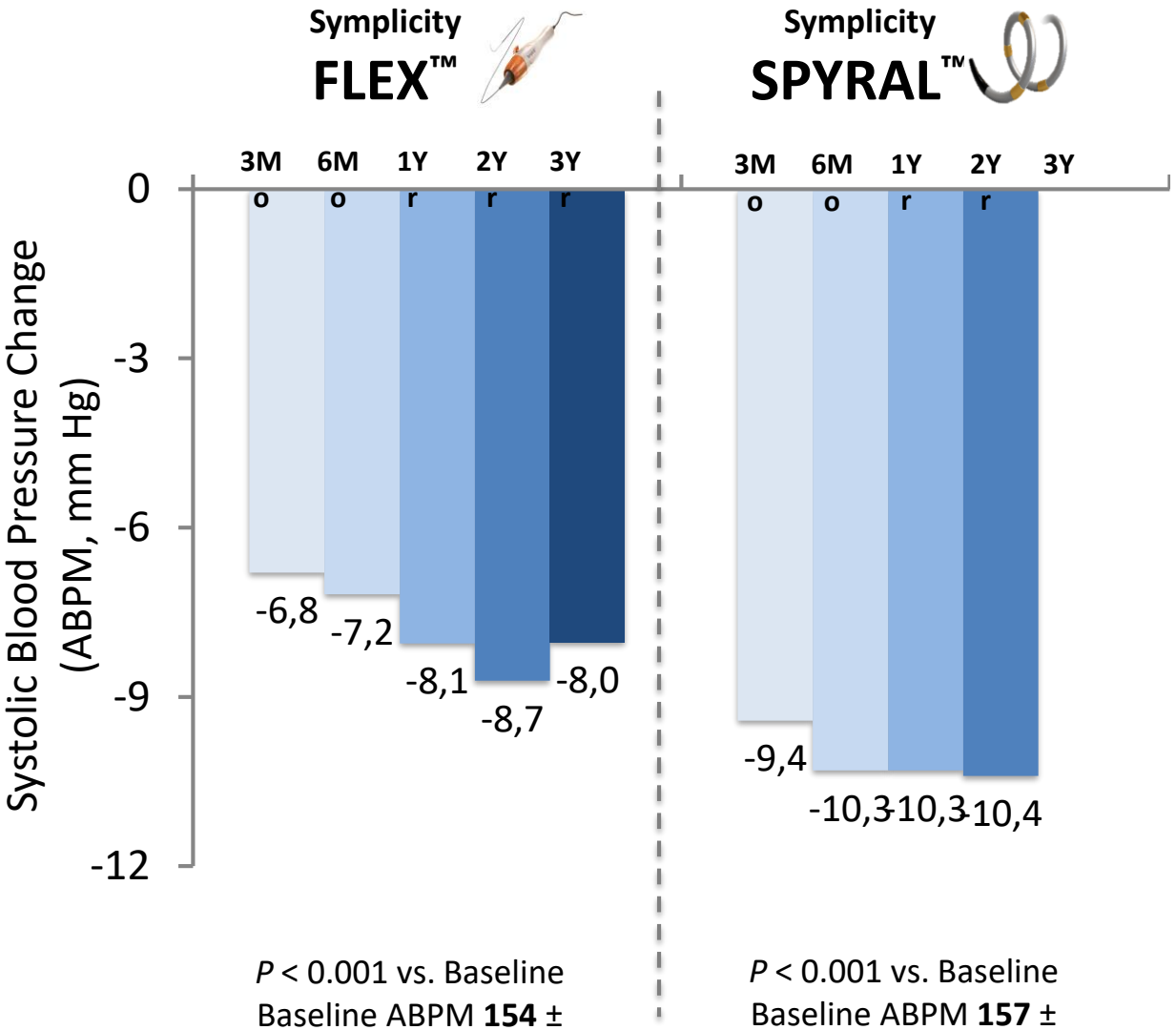


Journal of Hypertension 2017, 35:369–375

Possible explanations: catheter



RDN data in real clinical practice



P < 0.001 vs. Baseline
Baseline ABPM **154** ± 18 mmHg

P < 0.001 vs. Baseline
Baseline ABPM **157** ± 18 mmHg

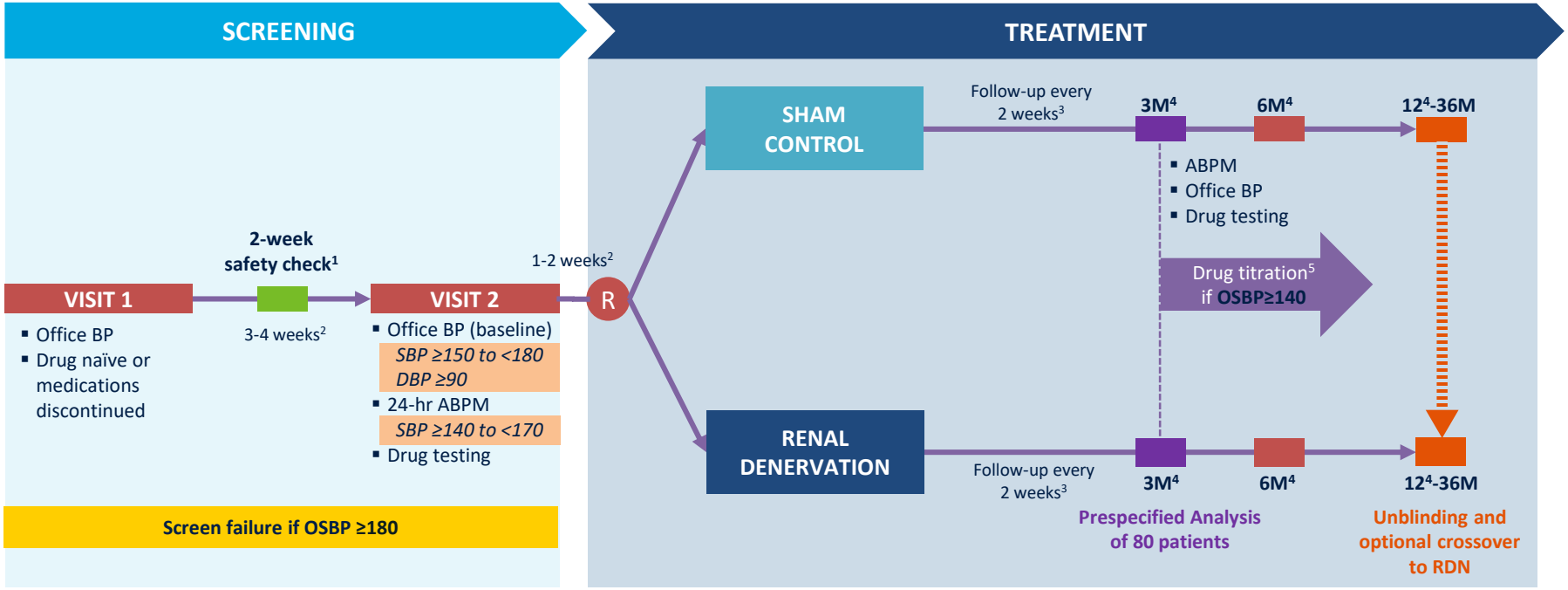
Böhm M, et al. data presented at PCR 2017
24 hour ABMP measurements shown

Publications with Spyral and "real" patients

Published Reports on Safety and Efficacy of Symplicity Spyral				
Trial	**Author**	**Reference**	**N**	**Geography**
SPYRAL FIM	Whitbourn et al.	*EuroIntervention* . 2015;11:104-9.	50	Australia
GLOBAL SYMPLICITY REGISTRY	Mahfoud et al.	EuroPCR 2017	258	Global
RESISTANCE	Davies et al.	EuroPCR 2016 (Euro16A-OP0228)*	16	United Kingdom
UK Registry	Sharp et al.	*Clin Res Cardiol* . 2016;105:544-52.	10	United Kingdom
CO2 Case series	Renton et al.	Br J Radiol, 2016 20160311	11	UK
TREND Registry	Zweiker et al.	PLoS ONE. 2016;11(8): e0161250	11	Austria
Spyral Radial Access Case	Heradien et al.	*Cardiovasc J Afr* . 2016;27:53-5.	2	South Africa
First in Man Case Series	Plehn et al.	*Confluence* . 2014;1(8):18-21.	7	Germany
Distal vs. Main Ablation	Fengler et al.	J Amer Heart Assoc. 2017	50	Germany
SPYRAL HTN-OFF MED	Townsend	Lancet 2017	38	Global
Repeat Procedure Case	Ribichini et al.	EuroPCR 2015	1	Italy
Main vs. Distal Ablation	Beeftink et al.	*J Clin Hypertens* . 2017 doi: 10.1111/jch.12989	10	Netherlands
		Total	**464**	

RDN effect without BP-lowering drugs

SPYRAL HTN – OFF MED. RANDOMIZED, SHAM-CONTROLLED TRIAL



[1]Only for patients discontinuing anti-hypertensive medications. [2]According to scheduling.[3]Phone follow-up is required at 6 and 10 week visits. [4]Drug testing. [5]Med titration every 2 weeks until OSBP < 140 Kandzari D, et al. Am Heart J. 2016;171:82-91

RDN effect without BP-lowering drugs

RDN WAS DONE IN MAIN RENAL ARTERY PLUS BRANCHES

SPYRAL HTN-OFF MED PROCEDURAL DETAILS

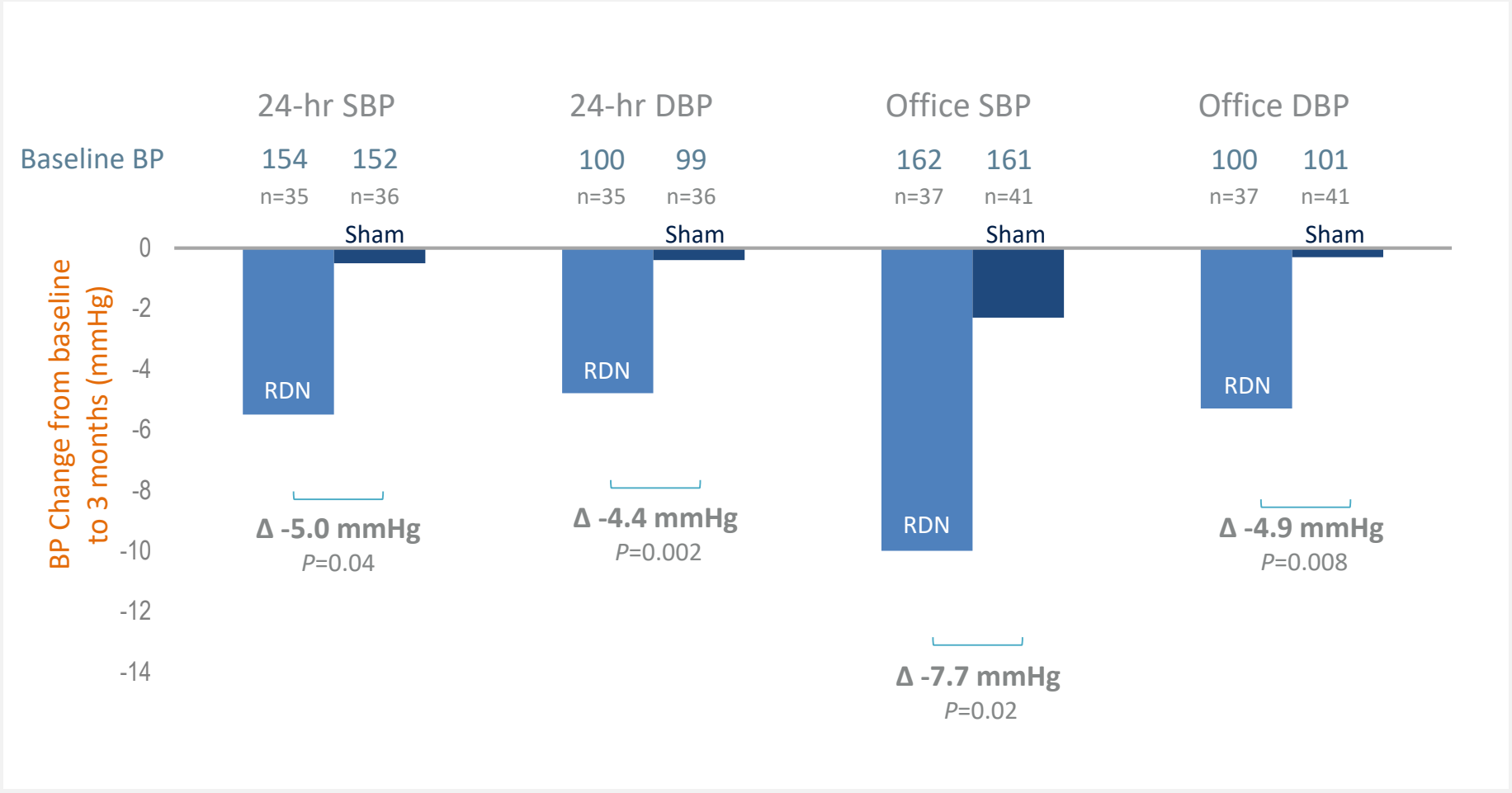
Procedural Measure (mean ± SD)	RDN (N = 38)	Sham Control (N = 42)
Number of main renal arteries treated per patient	2.2 ± 0.5	NA
Number of branches treated per patient	5.2 ± 2.5	NA
Total number of ablations per patient	43.8 ± 13.1	NA
Main artery ablations	17.9 ± 10.5	NA
Branch ablations	25.9 ± 12.8	NA
Treatment time (min)	57.1 ± 19.7	NA
Contrast volume used (cc)	251.0 ± 99.4	83.3 ± 38.5

RDN effect without BP-lowering drugs

Adverse event (number of events)	RDN (n = 38)	Sham Control (n = 42)
Death	0	0
New myocardial infarction	0	0
Major bleeding (TIMI)	0	0
New onset end stage renal disease	0	0
Serum creatinine elevation >50%	0	0
Significant embolic event resulting in end-organ damage	0	0
Vascular complications	0	0
Hospitalization for hypertensive crisis/emergency	0	0
New stroke	0	0

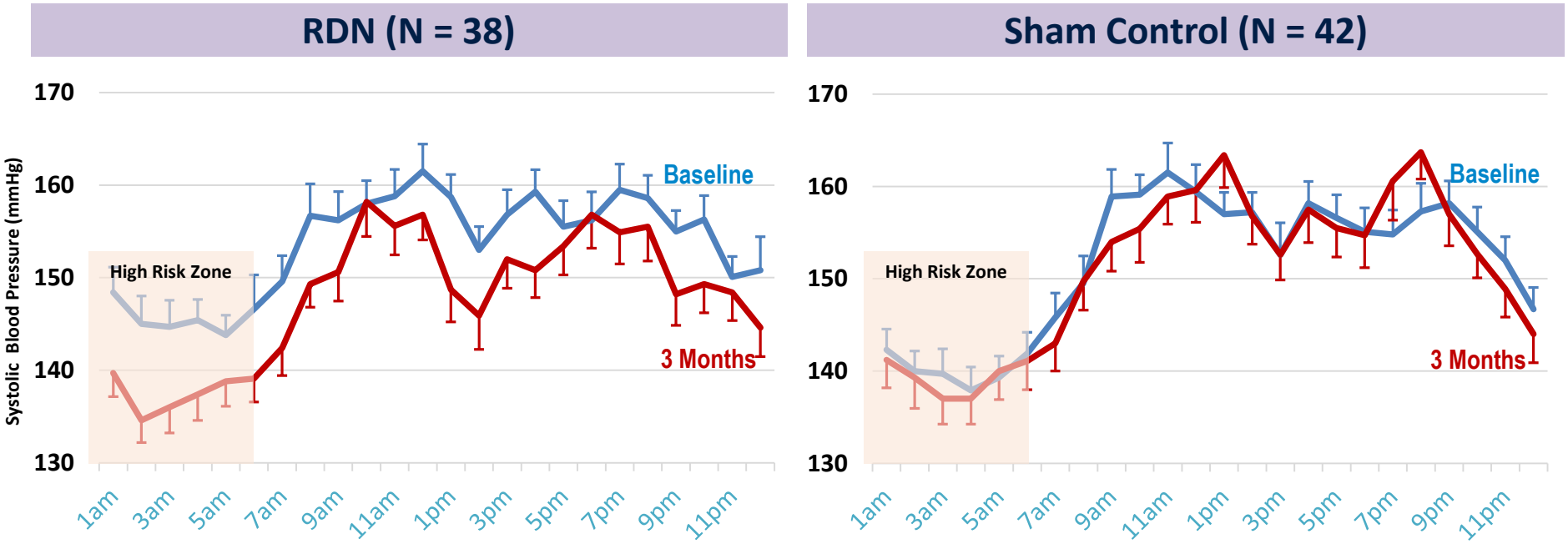
RDN effect without BP-lowering drugs

SPYRAL HTN-OFF MED BLOOD PRESSURE CHANGE FROM BASELINE



RDN effect without BP-lowering drugs

RDN PATIENTS HAD STATISTICALLY LOWER SYSTOLIC BP IN THE "HIGH-RISK ZONE[1]" AT 3-MONTHS

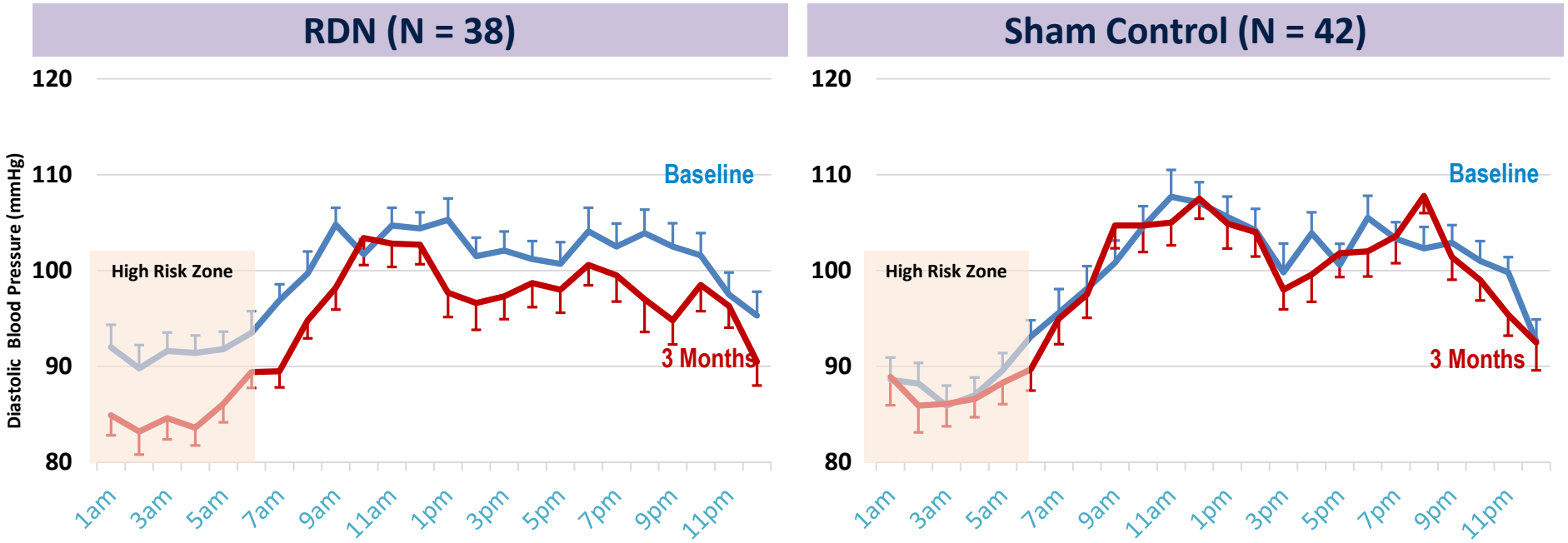


- "High-risk zone" that occurs in the late night/ early morning period is usually associated with increased risk for stroke and cardiovascular events[2,3]

1. Kario K et al, ACC 2018
2. Amodeo C, Blood Pressure Monit, 2014
3. Boggia J, The Lancet, 2007

RDN effect without BP-lowering drugs

RDN PATIENTS HAD STATISTICALLY LOWER DIASTOLIC BP IN THE "HIGH-RISK ZONE[1]" AT 3-MONTHS

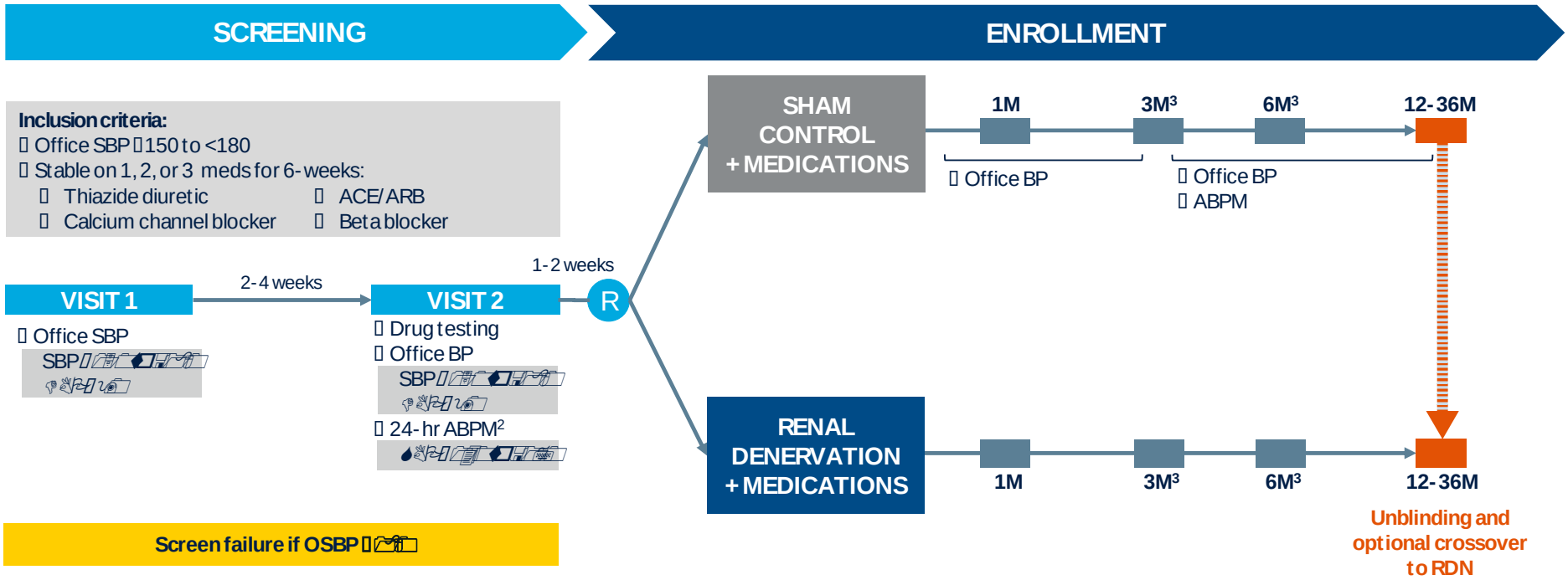


- "High-risk zone" that occurs in the late night/ early morning period is usually associated with increased risk for stroke and cardiovascular events[2,3]

1. Kario K et al, ACC 2018
2. Amodeo C, Blood Pressure Monit, 2014
3. Boggia J, The Lancet, 2007

RDN effect with BP-lowering drugs

SPYRAL HTN ON MED
RANDOMIZED, SHAM-CONTROLLED TRIAL[1]



[1]Kandzari D, et al. Am Heart J. 2016;171:82-91 and NCT02439775
[2]Measurement started after witnessed drug ingestion
[3]Drug testing

Kandzari D et al. http://dx.doi.org/10.1016/ S0140-6736(18)30951-6

RDN effect with BP-lowering drugs

	Renal denervation (N=38)	Sham procedure (N=42)
Age (years)	53·9 (8·7)	53·0 (10·7)
Male	33 (87%)	34 (81%)
BMI (kg/m²)	31·4 (6·4)	32·5 (4·6)
Race		
White	13 (34%)	15 (36%)
Black or African American	4 (11%)	5 (12%)
Asian	0	1 (2%)
Not reportable per local laws or regulations	18 (47%)	20 (48%)
Diabetes (all type 2)	5 (13%)	8 (19%)
Current smoker	8 (21%)	11 (26%)
Obstructive sleep apnoea	2 (5%)	10 (24%)
Peripheral artery disease	0	0
Coronary artery disease*	1 (3%)	1 (2%)
Stroke and transient ischaemic attack*	0	1 (2%)
Myocardial infarction or acute coronary syndrome	0	0
Office SBP (mm Hg)	164·6 (7·1)	163·5 (7·5)
Office DBP (mm Hg)	99·6 (6·9)	102·7 (8·0)
Mean 24 h SBP (mm Hg)	152·1 (7·0)	151·3 (6·8)
Mean 24 h DBP (mm Hg)	97·2 (6·9)	97·9 (8·4)
Office heart rate (bpm)	75·6 (11·8)	73·5 (10·4)
24 h heart rate (bpm)	75·3 (11·3)	75·6 (10·7)
Mean number of antihypertensive drug classes	2·2 (0·9)	2·3 (0·8)
Median number of antihypertensive drug classes	3·0 (1·0–3·0)	3·0 (1·0–3·0)
Prescribed drug classes		
1	11 (29%)	9 (21%)
2	7 (18%)	11 (26%)
3	20 (53%)	22 (52%)
Drug class		
Diuretic	22 (58%)	25 (60%)
Calcium channel blocker	27 (71%)	31 (74%)
ACE-I/ARB	31 (82%)	35 (83%)
Beta blocker	4 (11%)	6 (14%)

Data are mean (SD), n (%), or median (Q1–Q3). All comparisons of baseline drugs between renal denervation and sham control groups were non-significant. BMI=body-mass index. SBP=systolic blood pressure. DBP=diastolic blood pressure. bpm=beats per minute. ACE-I=angiotensin converting enzyme inhibitors. ARB=angiotensin-receptor blockers. *These events occurred more than 6 months before randomisation.

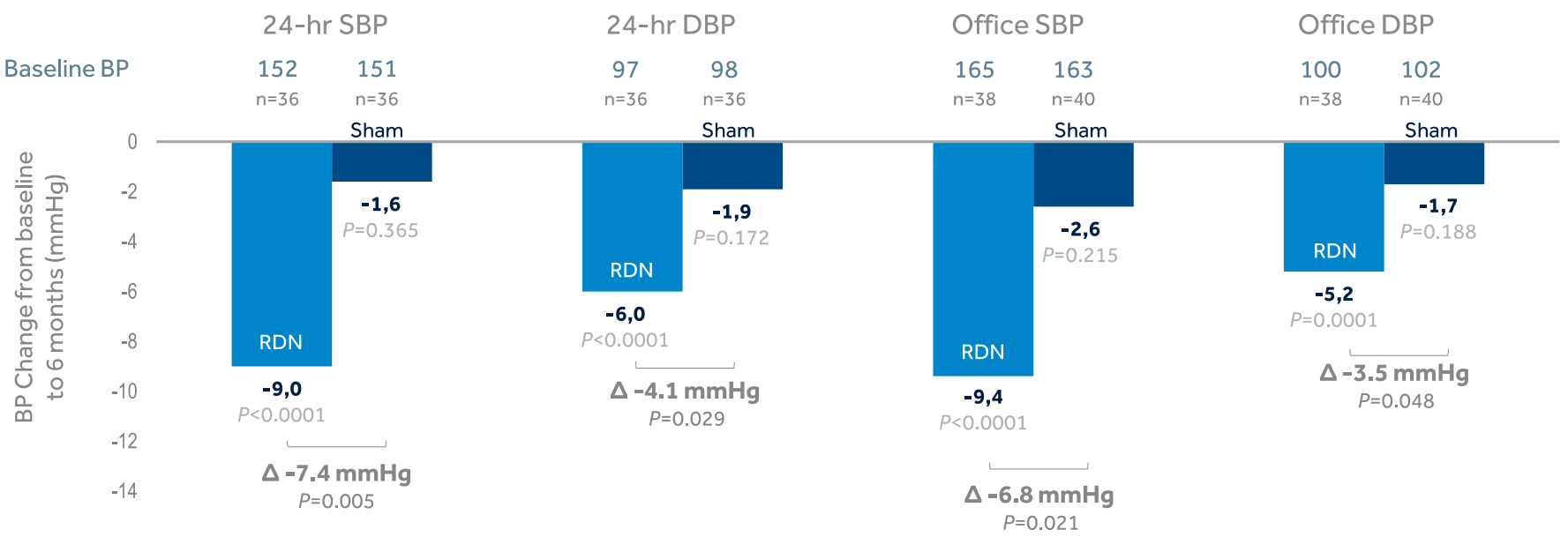
Table 1: **Baseline characteristics**

Kandzari D et al.
http://dx.doi.org/10.1016/ S0140-6736(18)30951-6

RDN effect with BP-lowering drugs

RDN SHOWED A SIGNIFICANT REDUCTION IN ALL BP MEASURES AT 6-MONTHS

SPYRAL HTN-ON MED BLOOD PRESSURE CHANGE FROM BASELINE

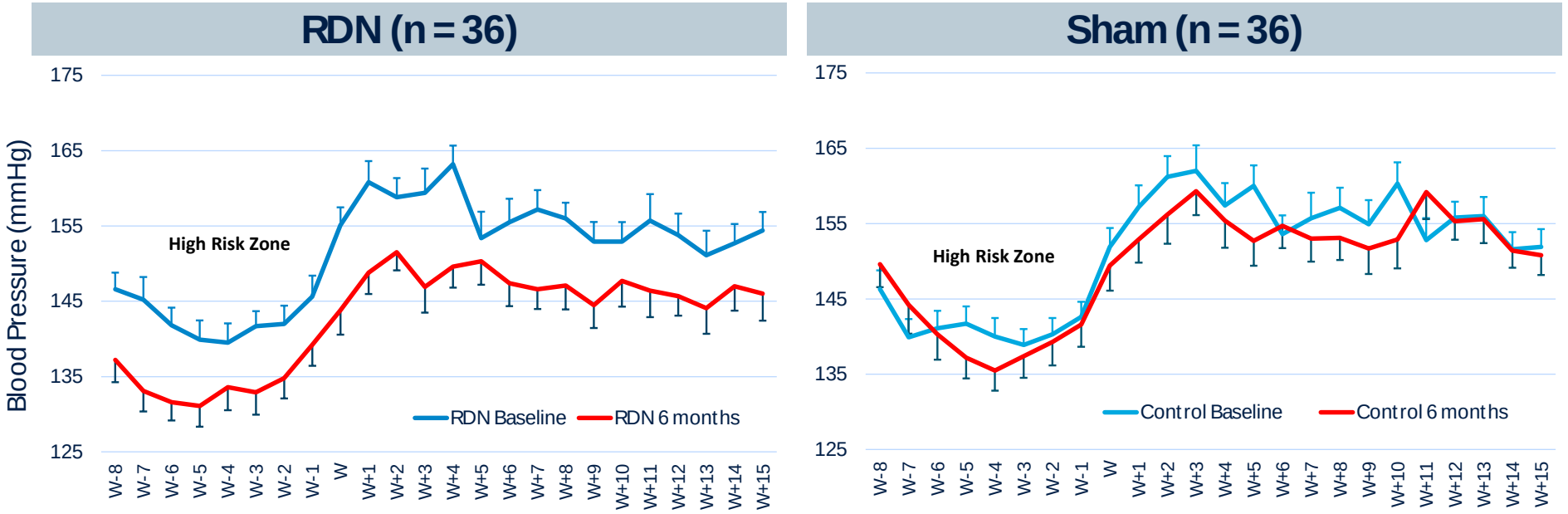


Kandzari D et al. http://dx.doi.org/10.1016/ S0140-6736(18)30951-6

RDN effect with BP-lowering drugs

24-HOUR ABPM TREND PROVIDED FURTHER PROOF OF RDN'S EFFECT

SPYRAL HTN-ON MED RDN PATIENTS SHOWED LOWER 24-HOUR SYSTOLIC BP, INCLUDING IN THE HIGH-RISK ZONE[1]



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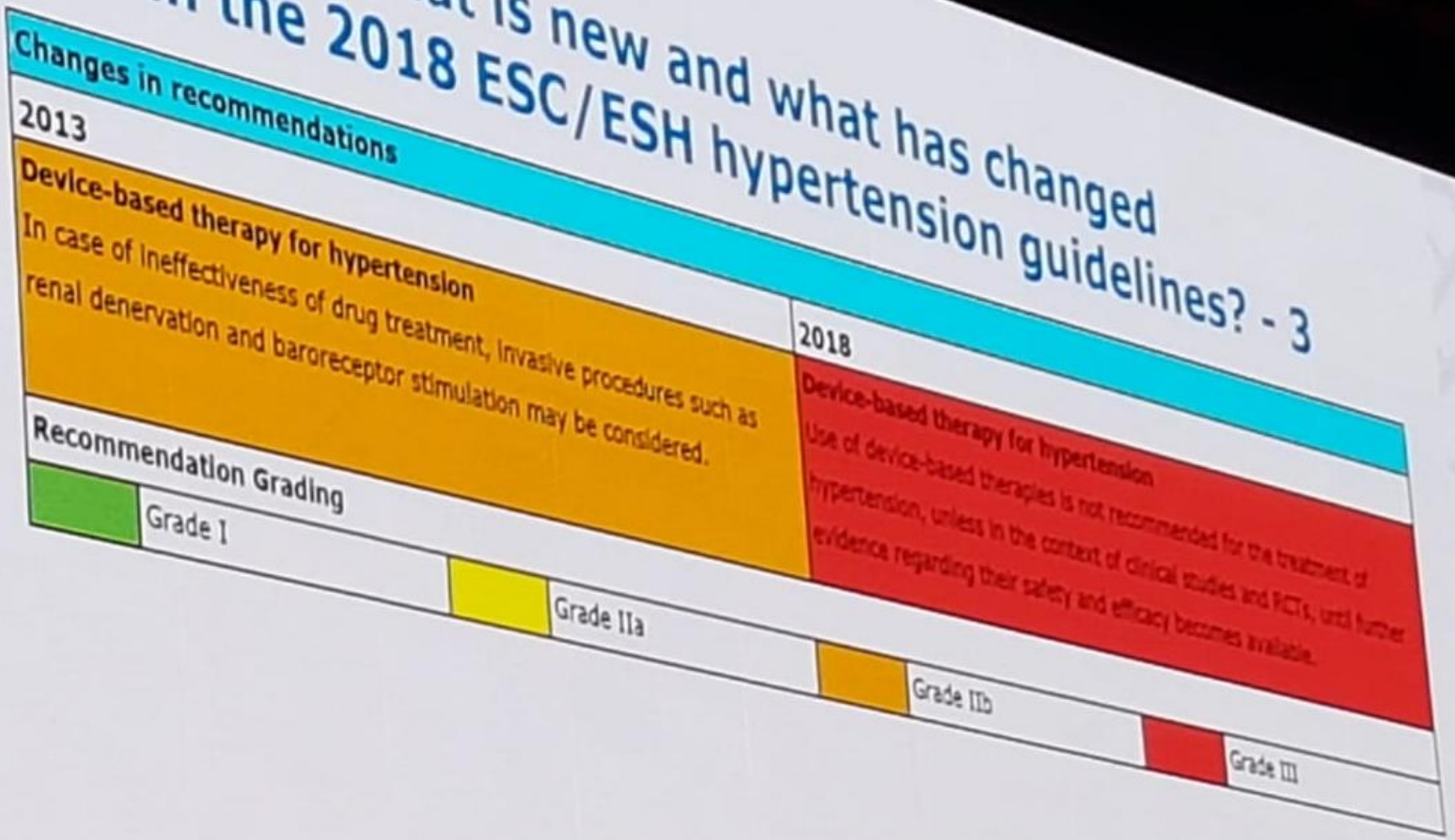
Kandzari D et al. http://dx.doi.org/10.1016/ S0140-6736(18)30951-6

What is new and what has changed in the 2018 ESC/ESH hypertension guidelines? - 3



Proposal of improvement for RDN

STAGES OF THE REFERRERS JOURNEY

FRAMEWORK AND DESIRED RESPONSE FROM THE REFERRER AT EACH POINT

Awareness | Consideration | Initial Referrals | Regular Referring

Need to address Barriers at each stage

Can take specific Actions that lead to success at each stage

Key Success Factors for this transition

- Carefully selecting patients that will “respond”
- Maximizing positive patient experience
- Communicating closely with the Referral physician

Conclusions

- Patients with RHTN has an increased mortality and current percentage of controlled population is not acceptable.
- Sympathetic hyperactivity in HTN is directly related to vascular damage.
- RDN technique is effective as if the patient is correctly selected.

Conclusions

- RDN is a *blind* technique. There are no easy-to use diagnostic tets to measure sympathetic activity in real practice. Neither to evalute successful results.

- Challenges:

  - Assure and confirm safety and cost-effectiveness.

  - Vascular anatomy and catheter/device design.

  - Clinical practice: Who is the optimal candidate? We do have hypertensives (high CV-risk) with few therapeutical options. Is it needed to treat every patients with drugs?

Obrigado. Thank you. Gracias