

Endovascular Renal Denervation across the Hypertension Spectrum

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Disclosures

Receipt of grants / research supports:

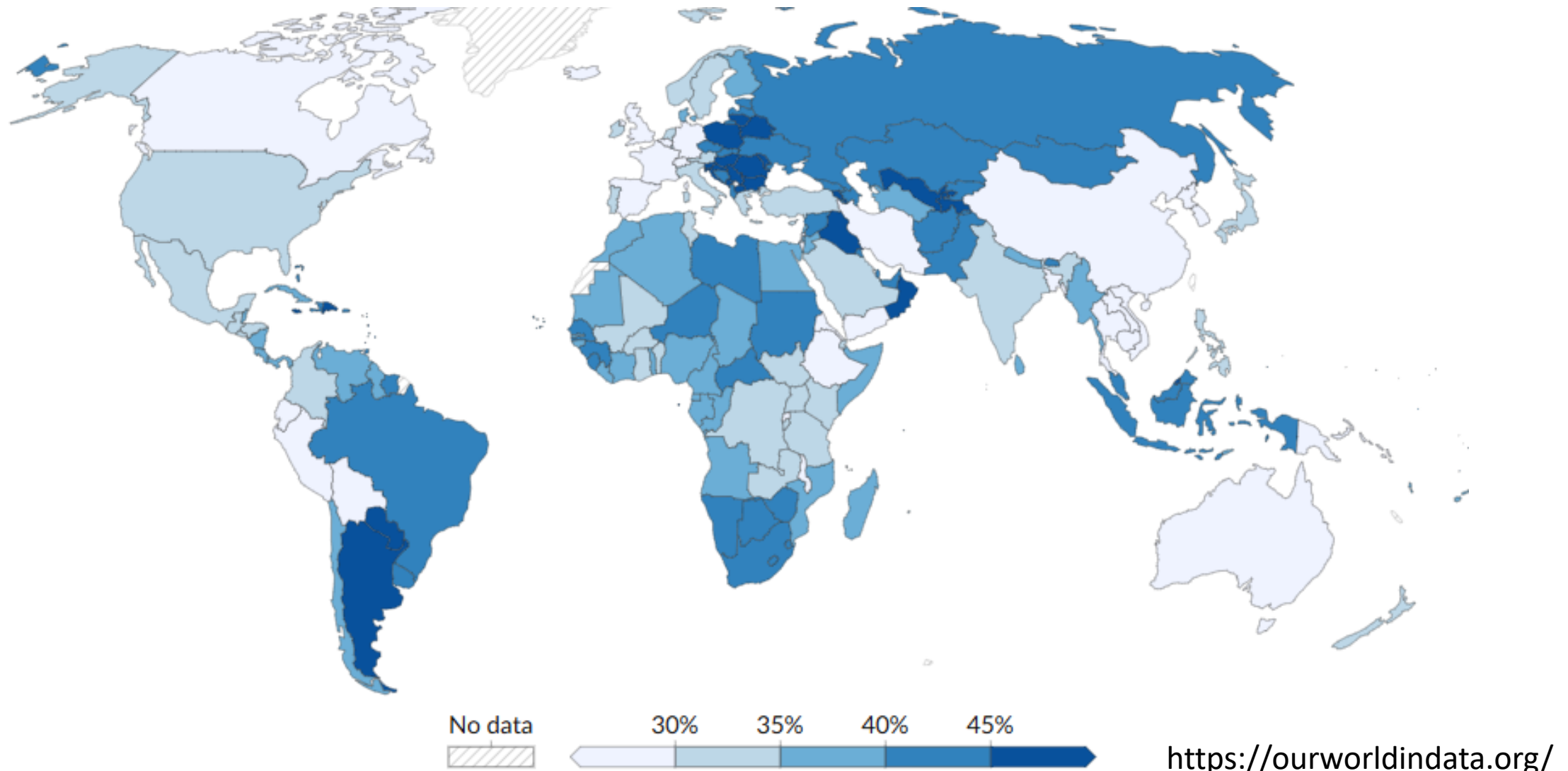
Recor, Novartis, Astra Zeneca, Sonivie

Receipt of honoraria or consultation fees:

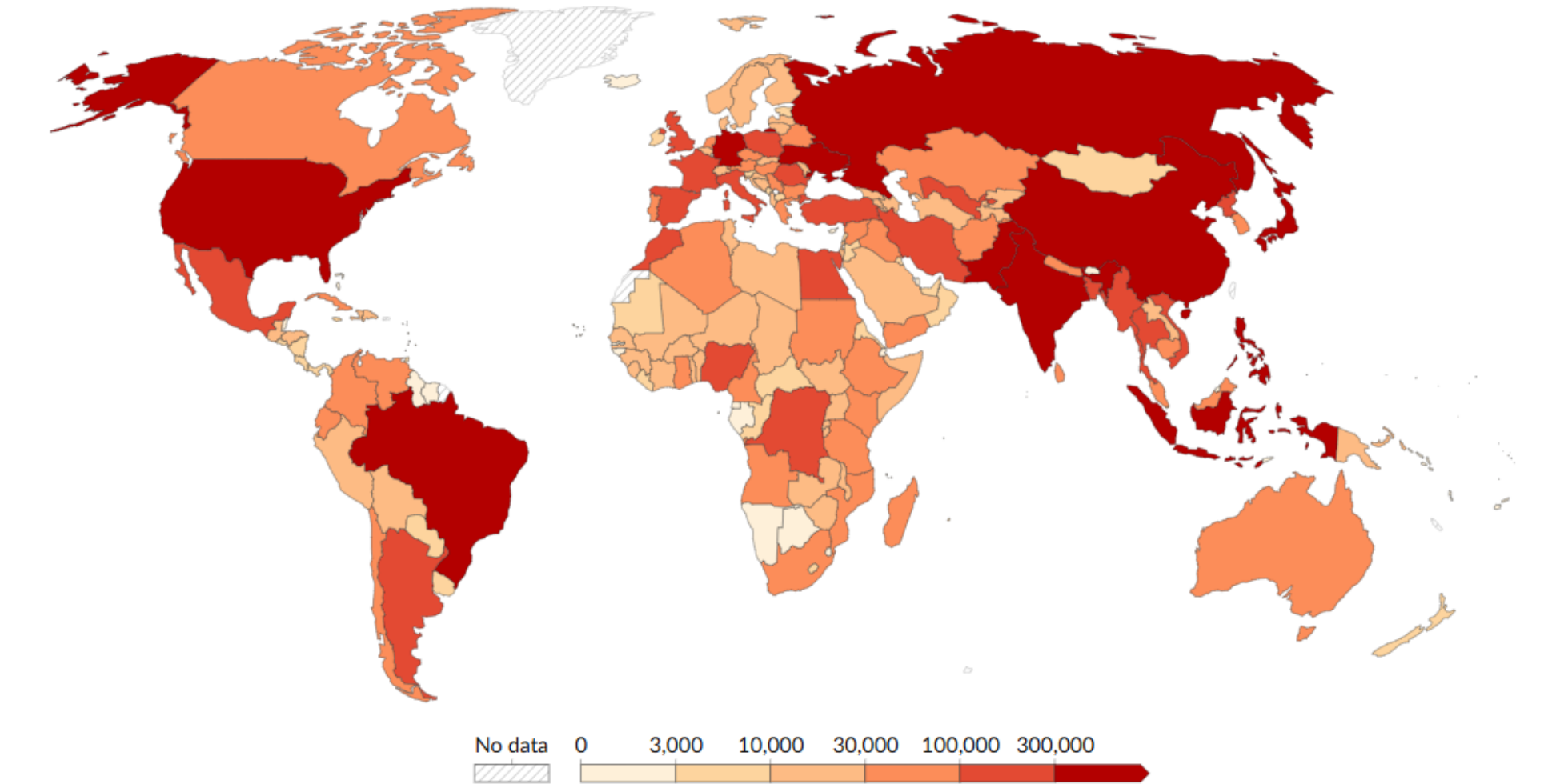
Alnylam, Novartis, Medtronic, Astra Zeneca, Sonivie, Recor,
Boehringer Ingelheim, Servier,

Prevalence rate of hypertension in adults aged 30-79, 2019

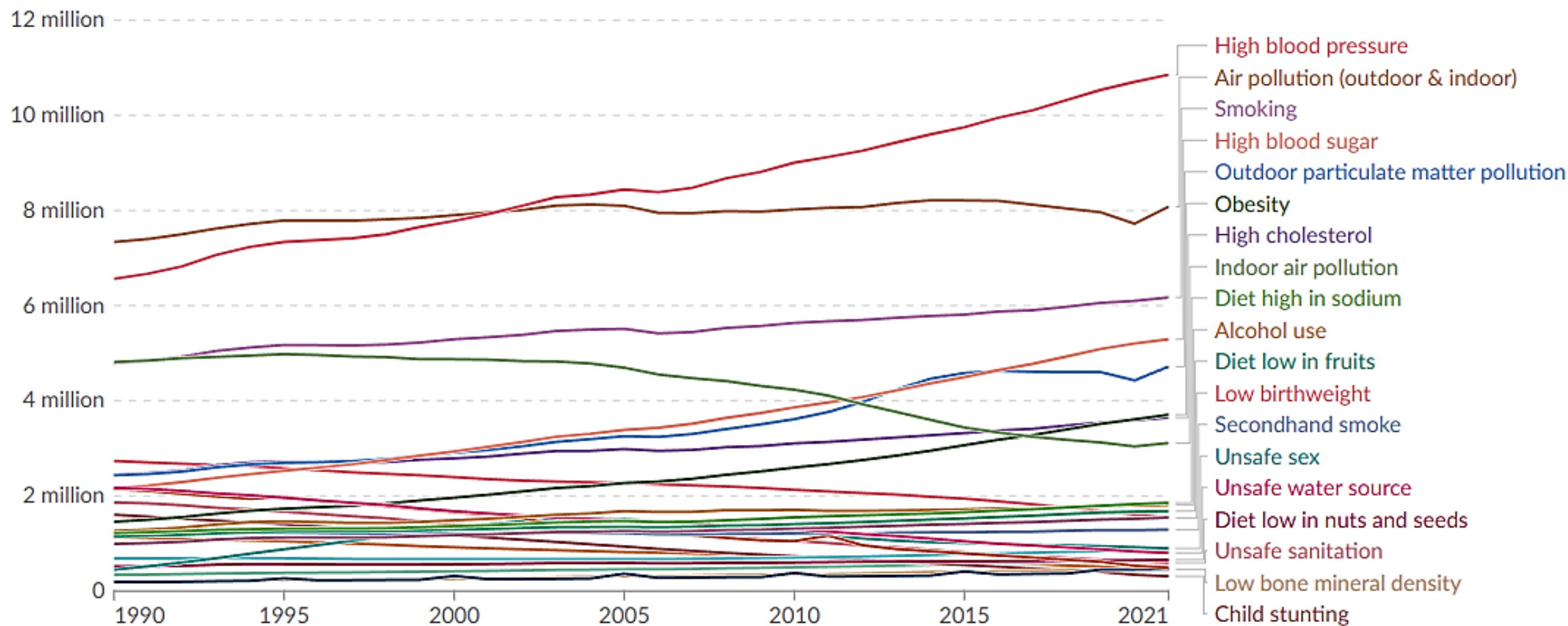
1.4 billion adults (33%) aged 30–79 years worldwide had hypertension in 2024



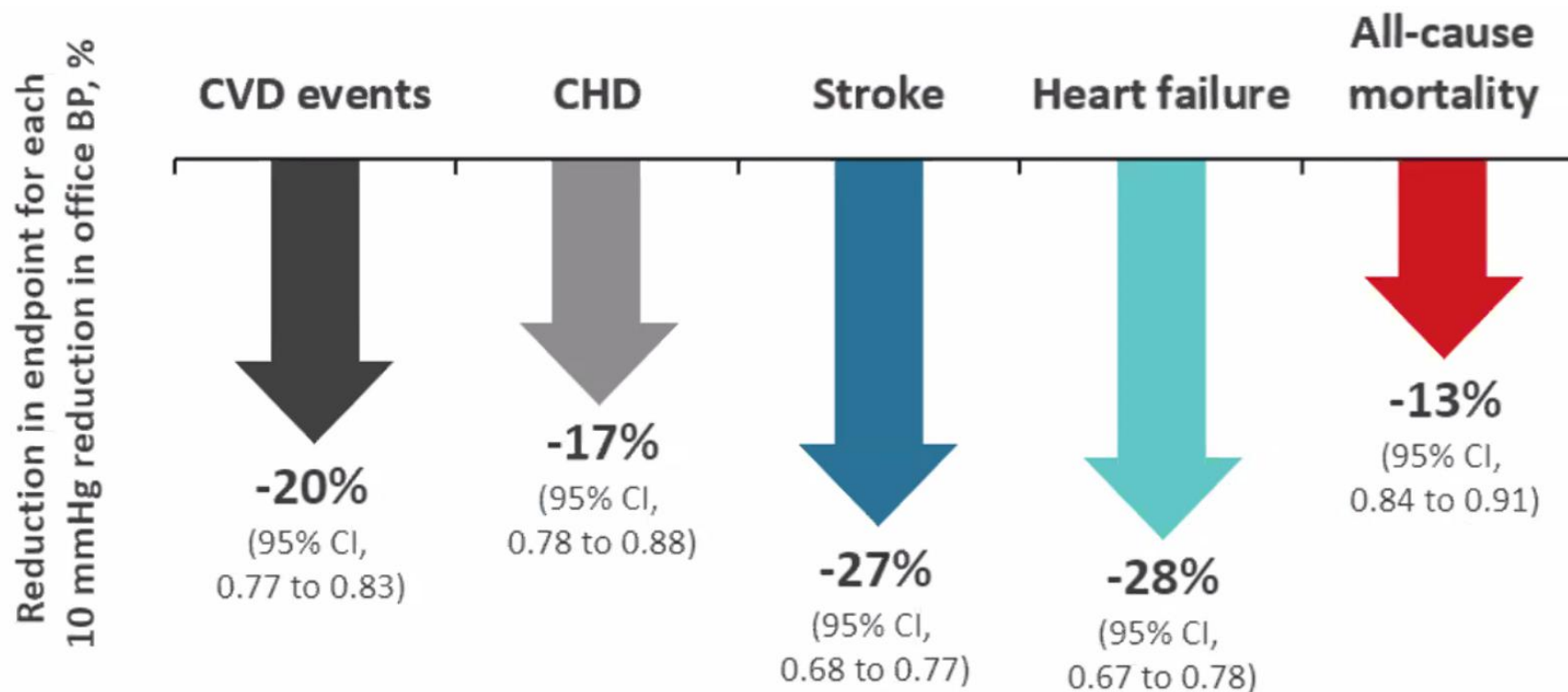
Number of deaths from cardiovascular diseases, 2021



Deaths by risk factor, World, 1990 to 2021



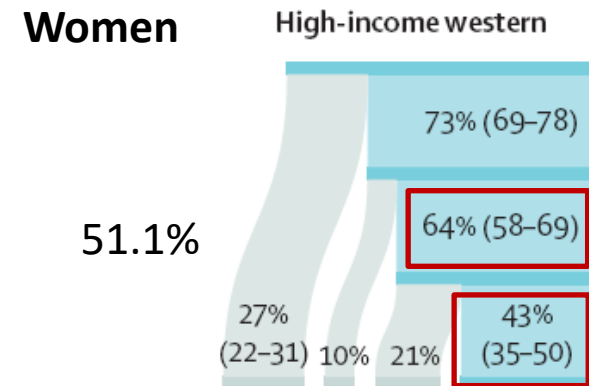
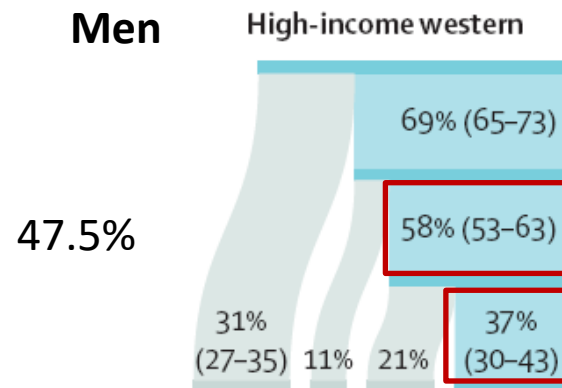
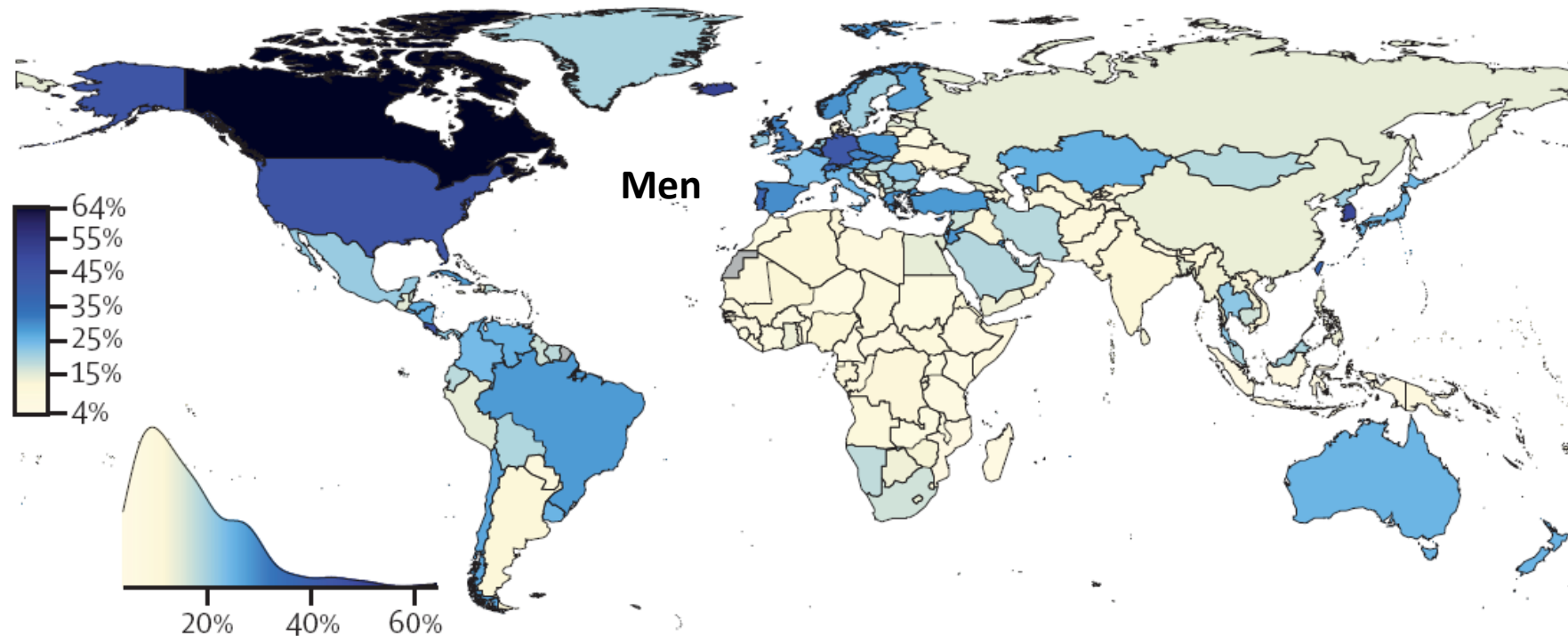
Benefits of SBP reduction



Each reduction in BP of 10 mmHg leads to vascular risk reductions

Systematic review and meta-analysis of large-scale BP-lowering trials, published between January 1, 1966, and July 7, 2015.
BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease.
Adapted from Ettehad D, et al. *Lancet* 2016;387:957-67.

Worldwide control rate of HTN in 2019

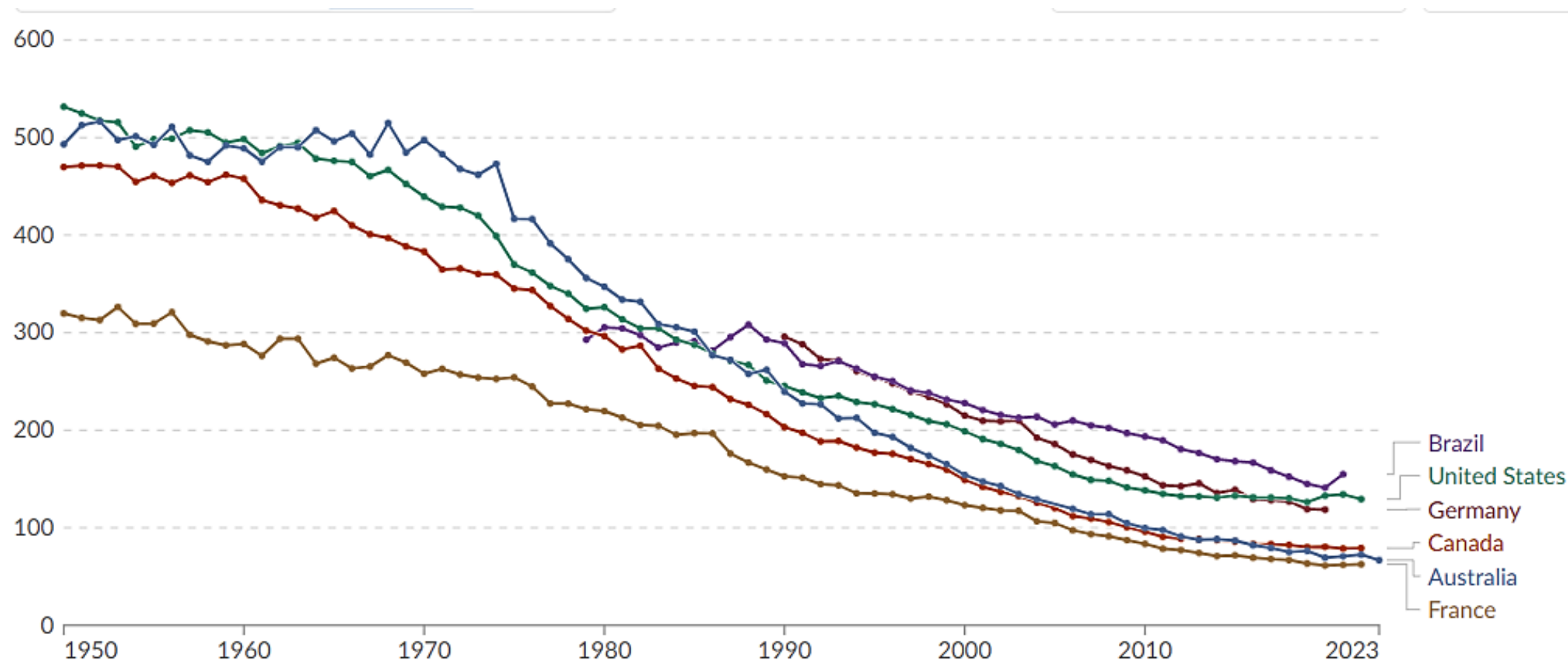


Diagnosed

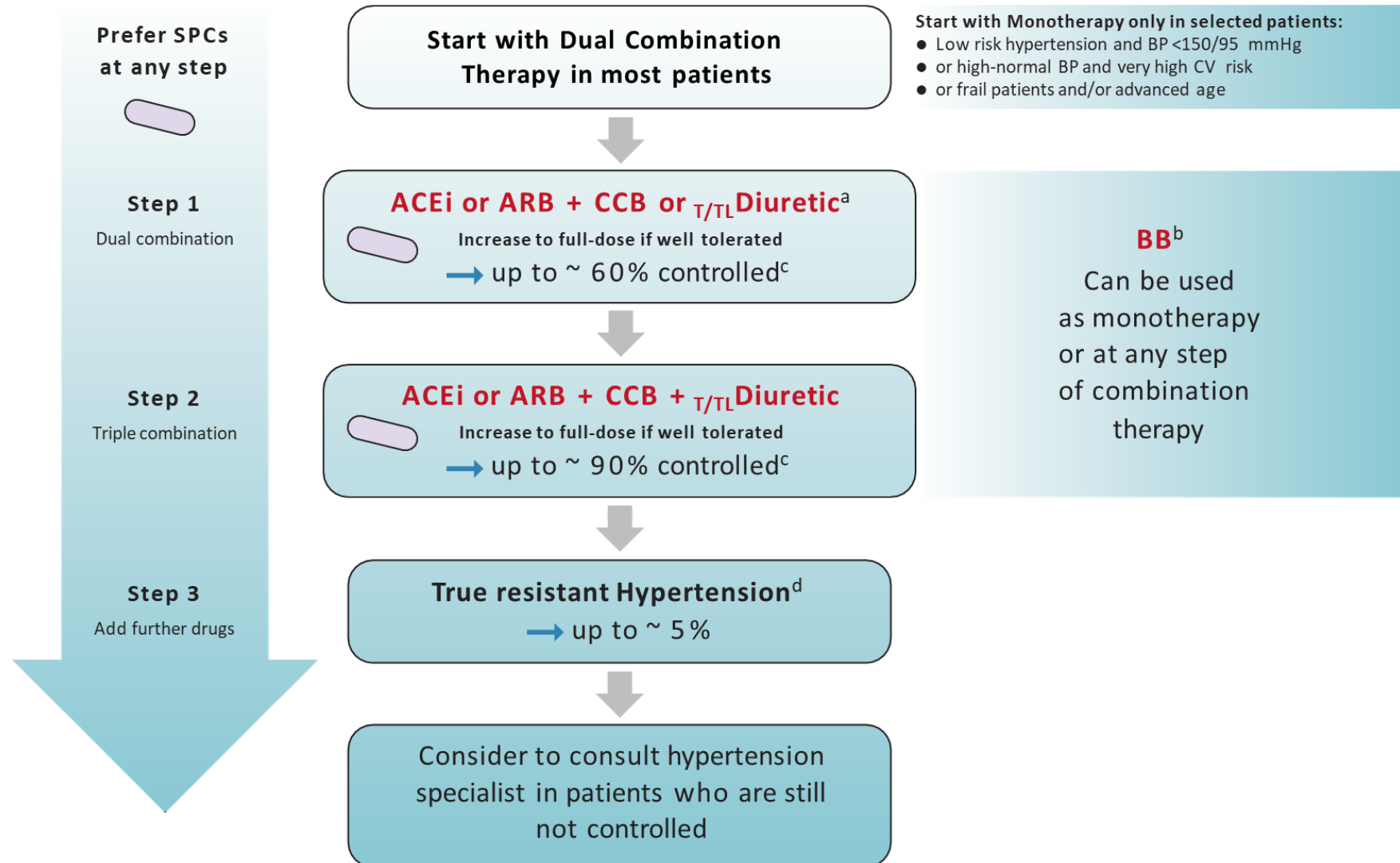
Treated

Controlled

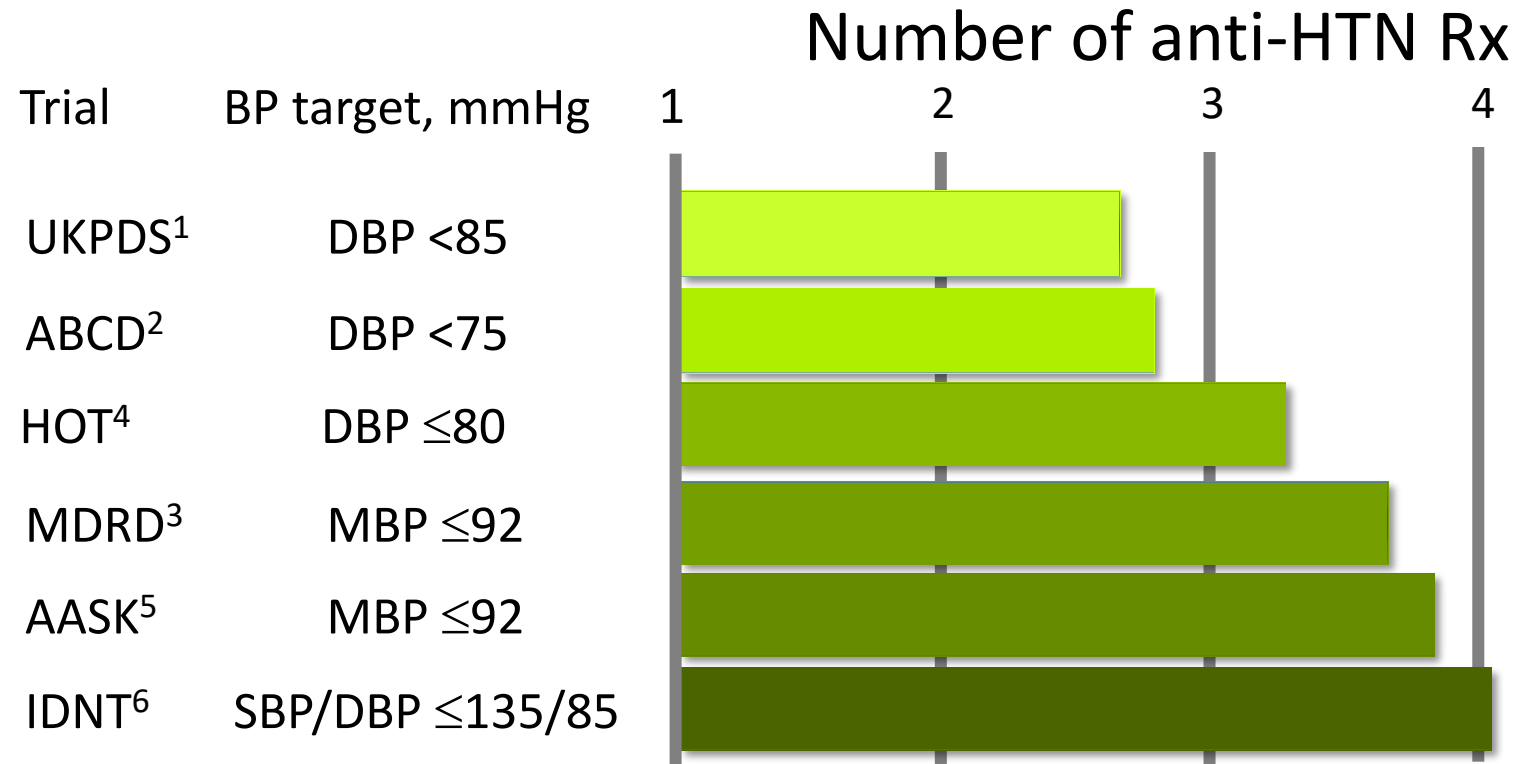
Death rate from cardiovascular diseases, 1950 to 2023



General BP-lowering strategy in patients with hypertension



Multiple antihypertensive drug therapy is necessary to control BP



¹UKPDS, BMJ 1998;317:703

⁴Hansson L, Lancet 1998; 51:1755

²Estacio RO, Am J Cardiol 1998;82:9R

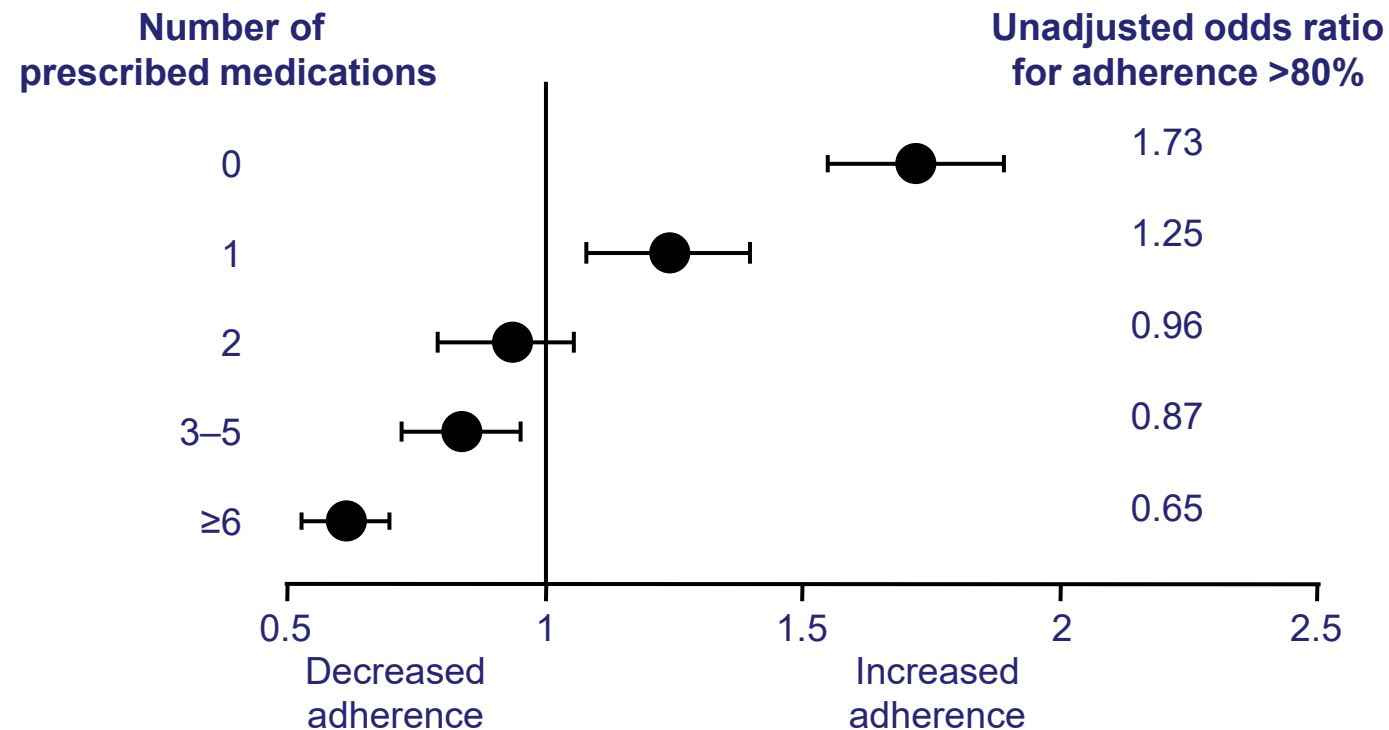
⁵Kusek JW, Control Clin Trials 1996;16:40S

³Lazarus JM, Hypertension 1997;29:6

⁶Lewis EJ, N Engl J Med 2001;345:851

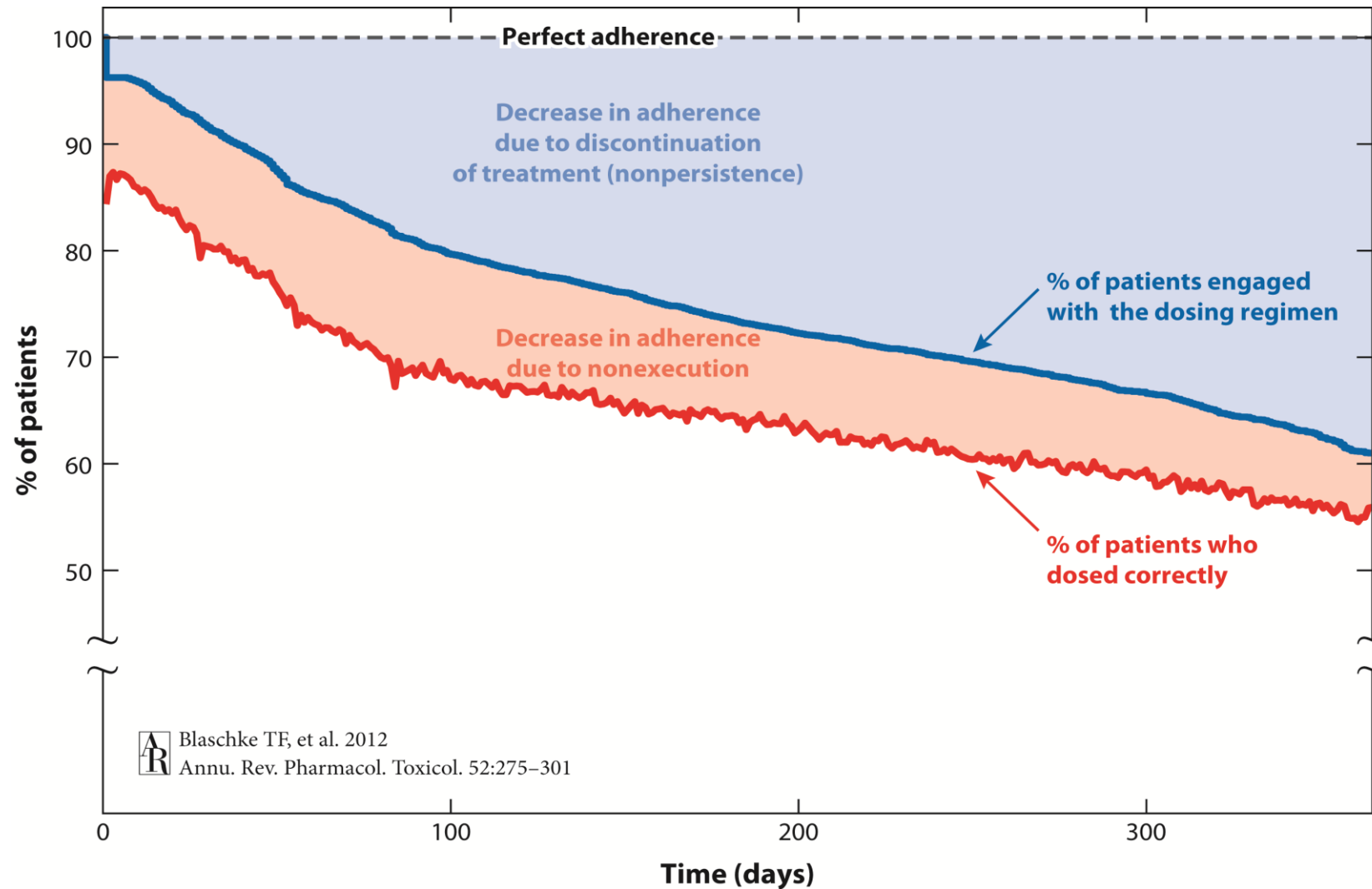
The more you give the less they take !

As the number of prescribed medications increases, the likelihood of adherence decreases

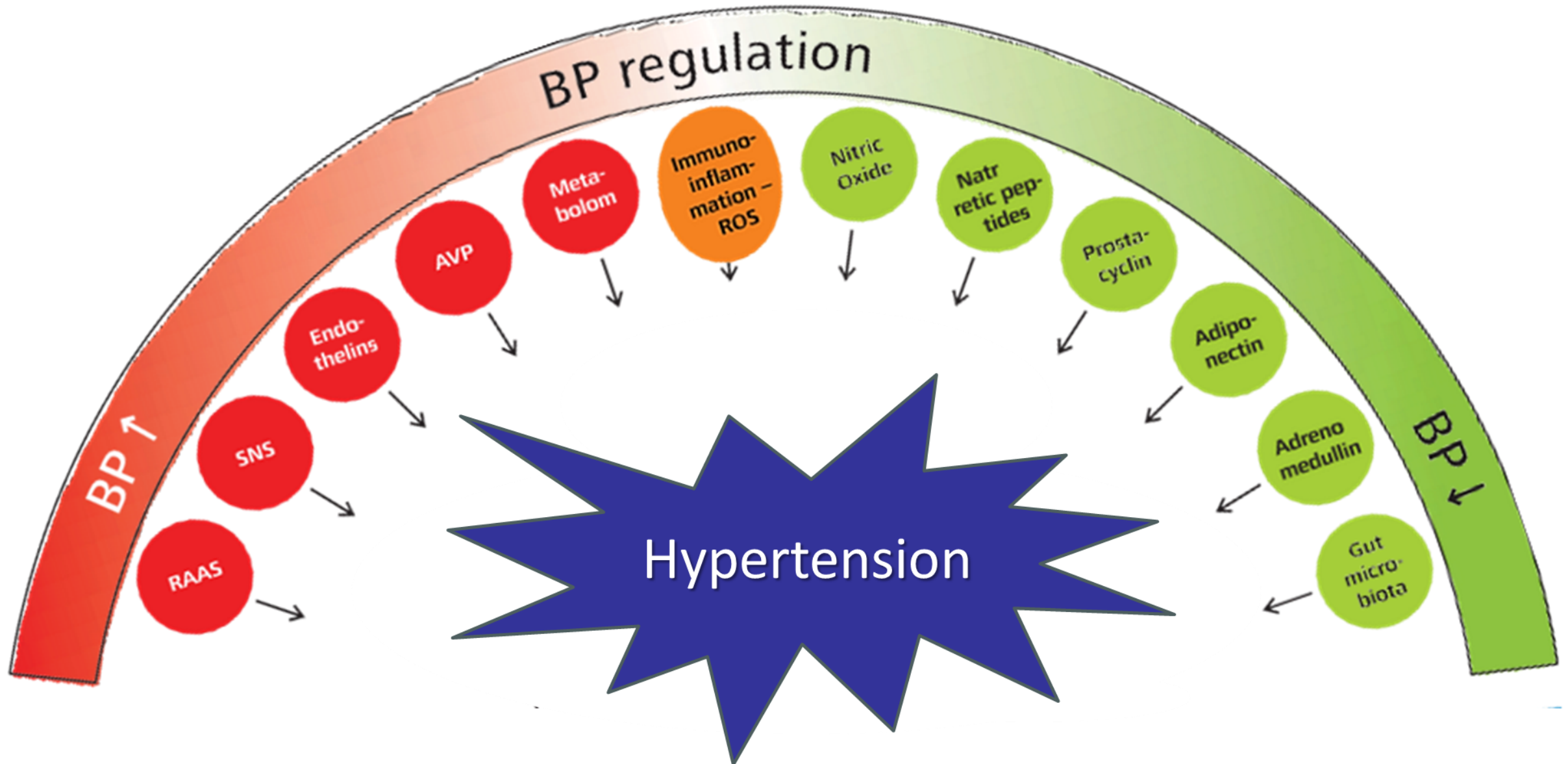


Retrospective study of 8,406 managed care patients with hypertension who added antihypertensive and/or lipid-lowering drugs to existing prescribed meds.

Drug adherence in hypertension: Persistence is more problematic than daily compliance



Mechanisms involved in BP regulation and the pathophysiology of hypertension



Pathophysiology of resistant hypertension

1) RHTN is associated with higher aldosterone levels and intravascular expansion

Gaddam KK et al. Arch Intern Med. 2008;168:1159

2) Salt sensitivity in patients with RHTN

Calhoun DA. Annu. Rev. Med. 2013. 64:233

3) Sympathetic overdrive in conditions associated with RHTN (OSA, MS, CKD)

Mancia G , and Grassi G Circ Res. 2014;114:1804

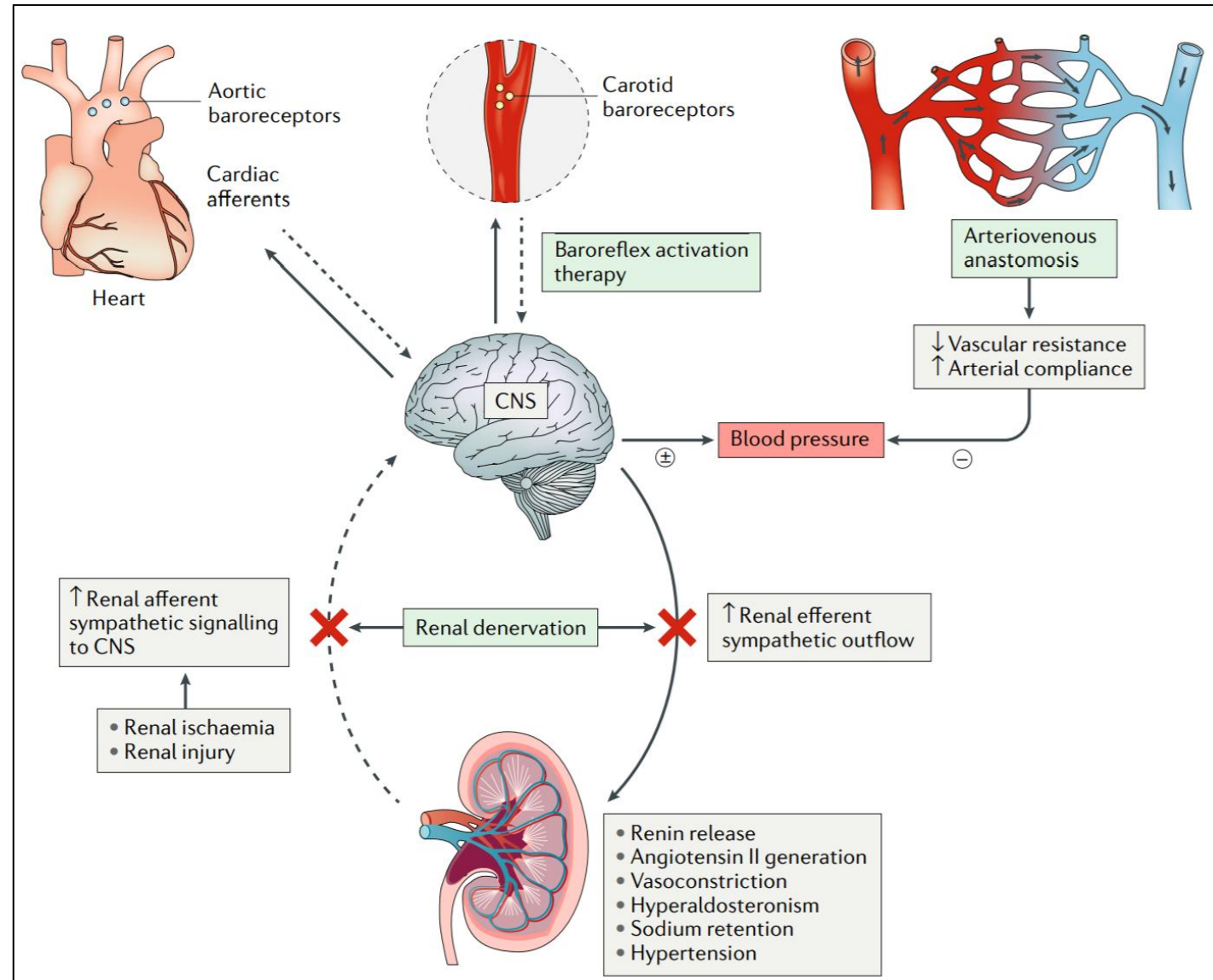
4) Primary central stimulation of AVP release

Mendes M et al. J Hypertens. 2016;34:2458

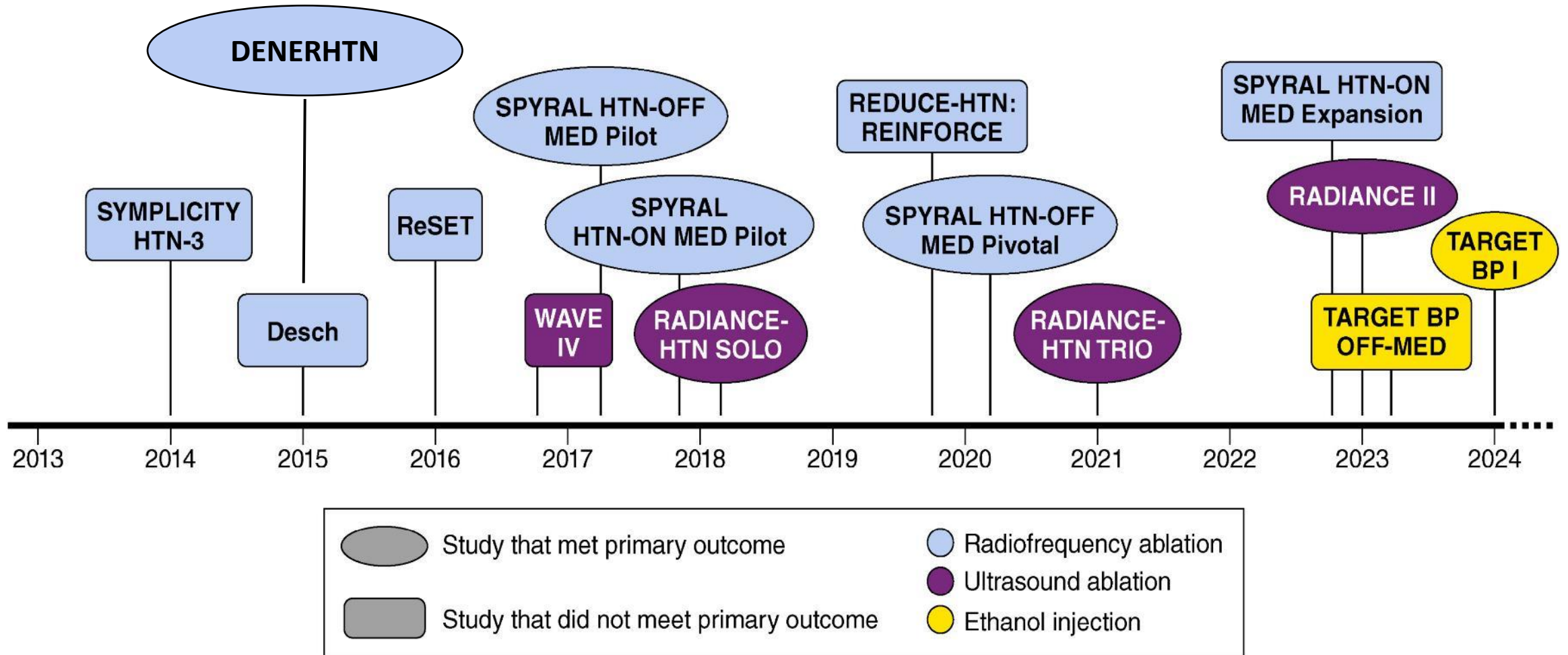
5) Activation of the endothelin system

Weber MA. Lancet 2009; 374: 1423

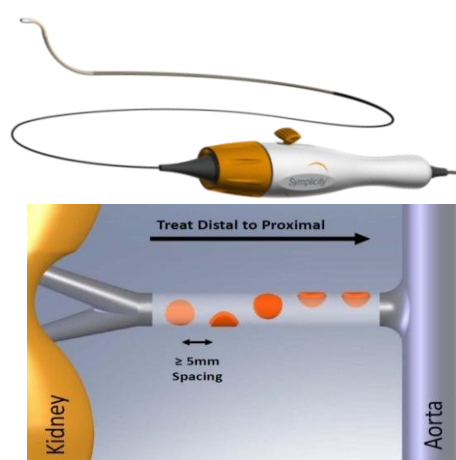
Rationale for use of device therapy in hypertension



Background: Milestones in RDN trials



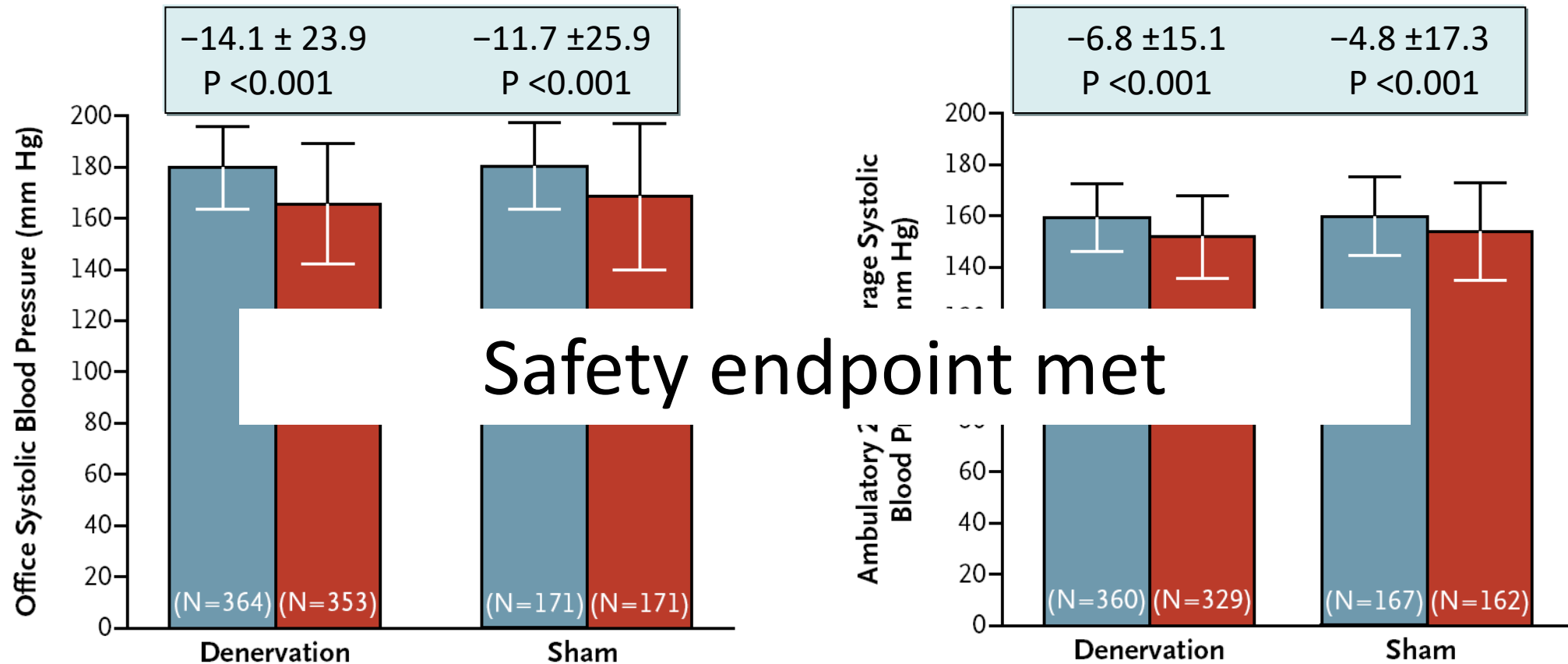
BP decrease at 6 months in Symplicity HTN-2



	RDN (n=52)	Control (n=54)	<i>p</i>
Office BP (mmHg)	-32±23/-12±11 (n=49)	+1±21/0±10 (n=51)	<0.0001
Self BP (mmHg)	-20±17/-12±11 (n=32)	+2±13/0±7 (n=40)	<0.0001
24h-ABPM (mmHg)	-11±15/-7±11 (n=20)	-3±19/-1±12 (n=25)	0.006/0.014
# Med Dose Decrease (%)	10 (20%)	3 (6%)	0.04
# Med Dose Increase (%)	4 (8%)	6(12%)	0.74

SBP < 140 mmHg: 39%

Office and ambulatory SBP decrease at 6 months in Symplicity HTN-3



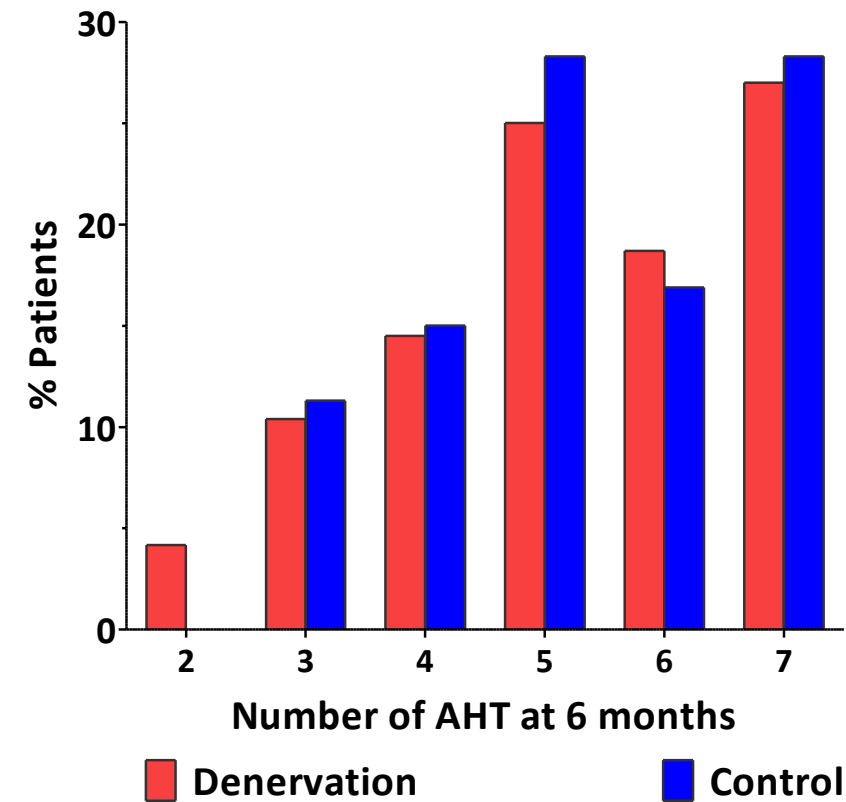
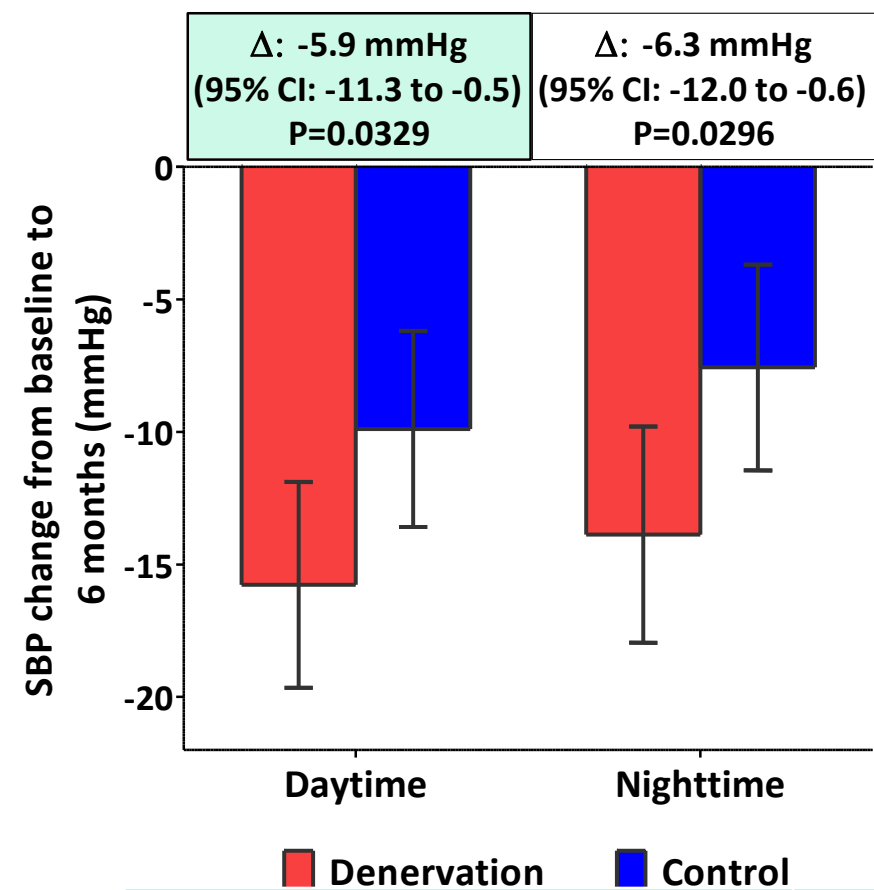
Δ : -2.39 mm Hg (95%CI: -6.89 to 2.12; P =0.26)
Superiority margin: 5 mmHg

Δ : -1.96 mm Hg (95% CI, -4.97 to 1.06); P=0.98)
Superiority margin: 2 mmHg

The French DENERHTN trial: Standardized optimal antihypertensive treatment

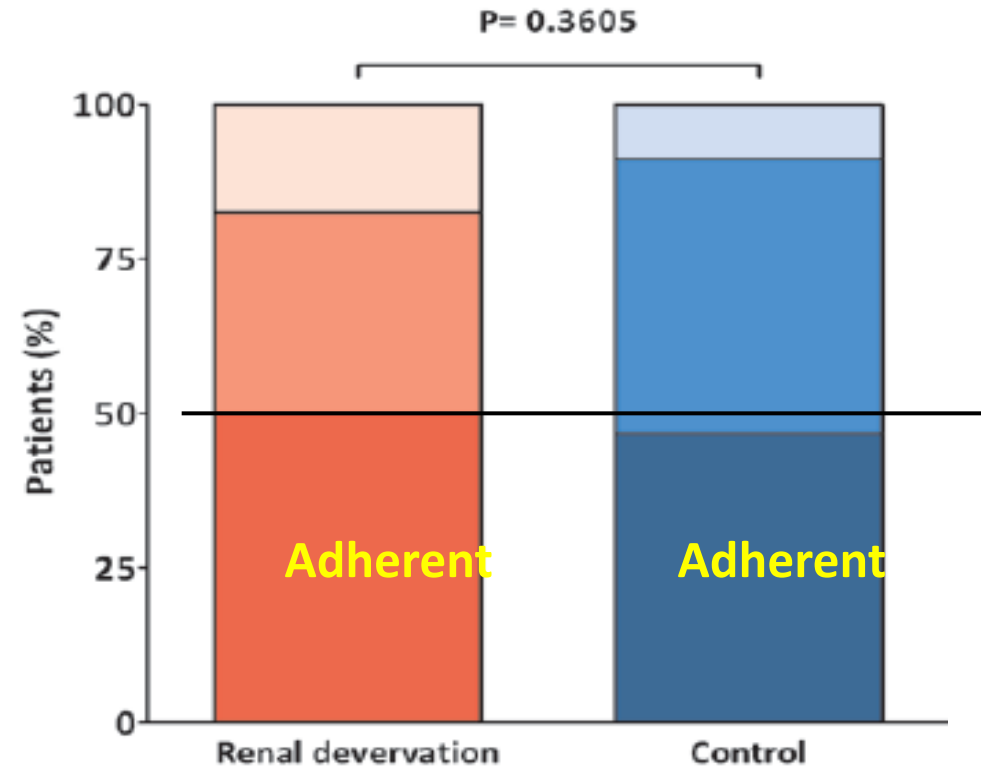
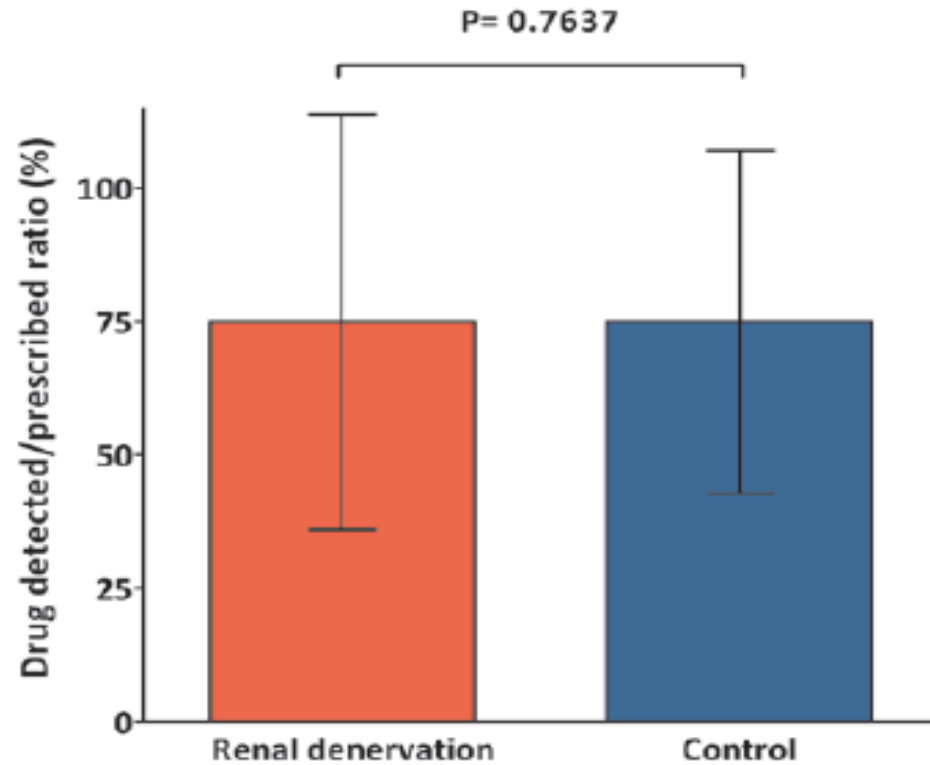
[illegible]

Baseline-adjusted changes (95%CI) in daytime and nighttime ambulatory BP from randomisation to 6 months

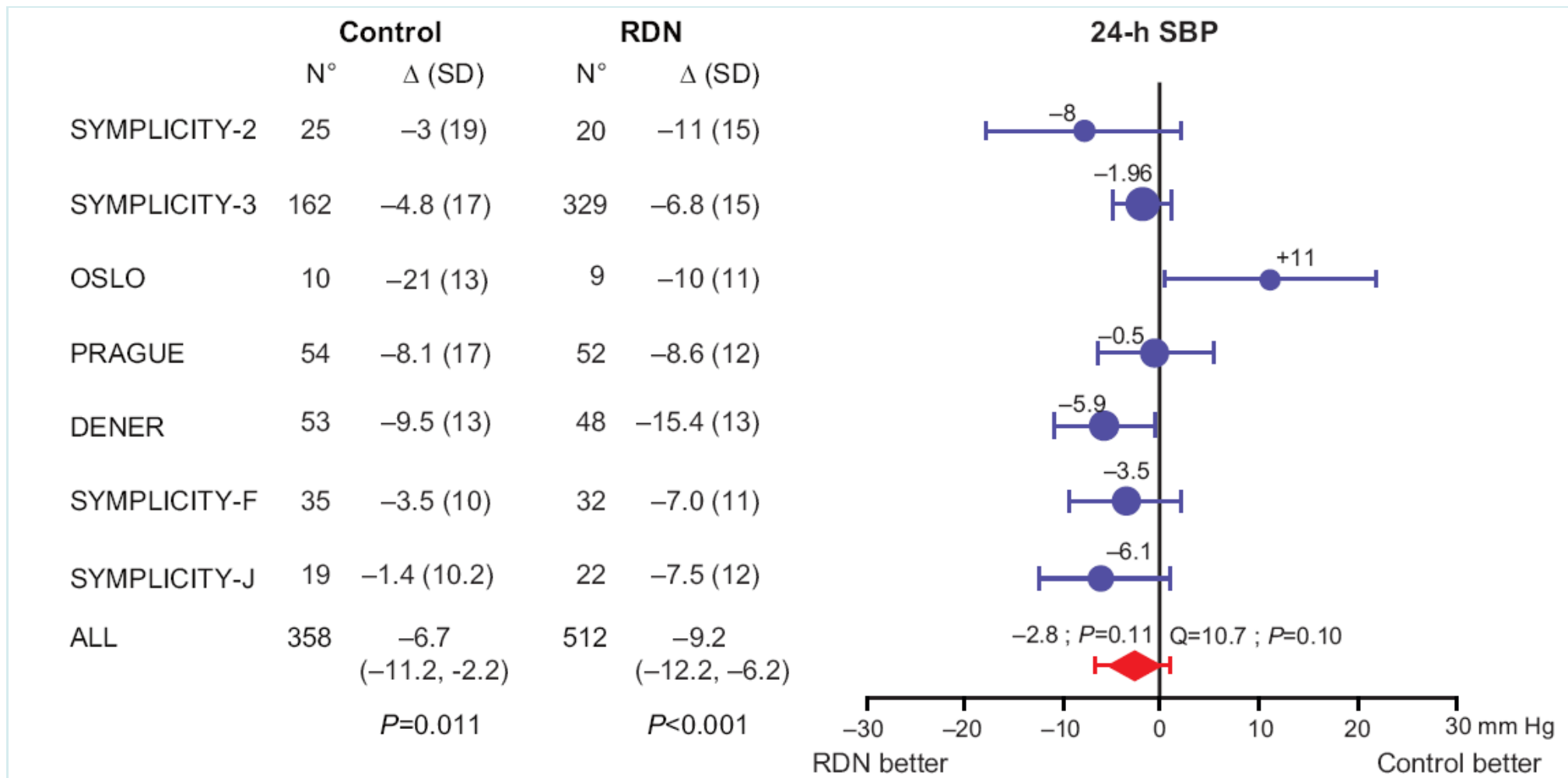


	Renal denervation	Control	P
% patients with 24 h BP < 130/80 mmHg	39.6	18.9	0.0216

Poor adherence to AHT in the DENERHTN trial at 6 months



Metaanalysis of 6-month response of 24 h SBP to unipolar RF-RDN

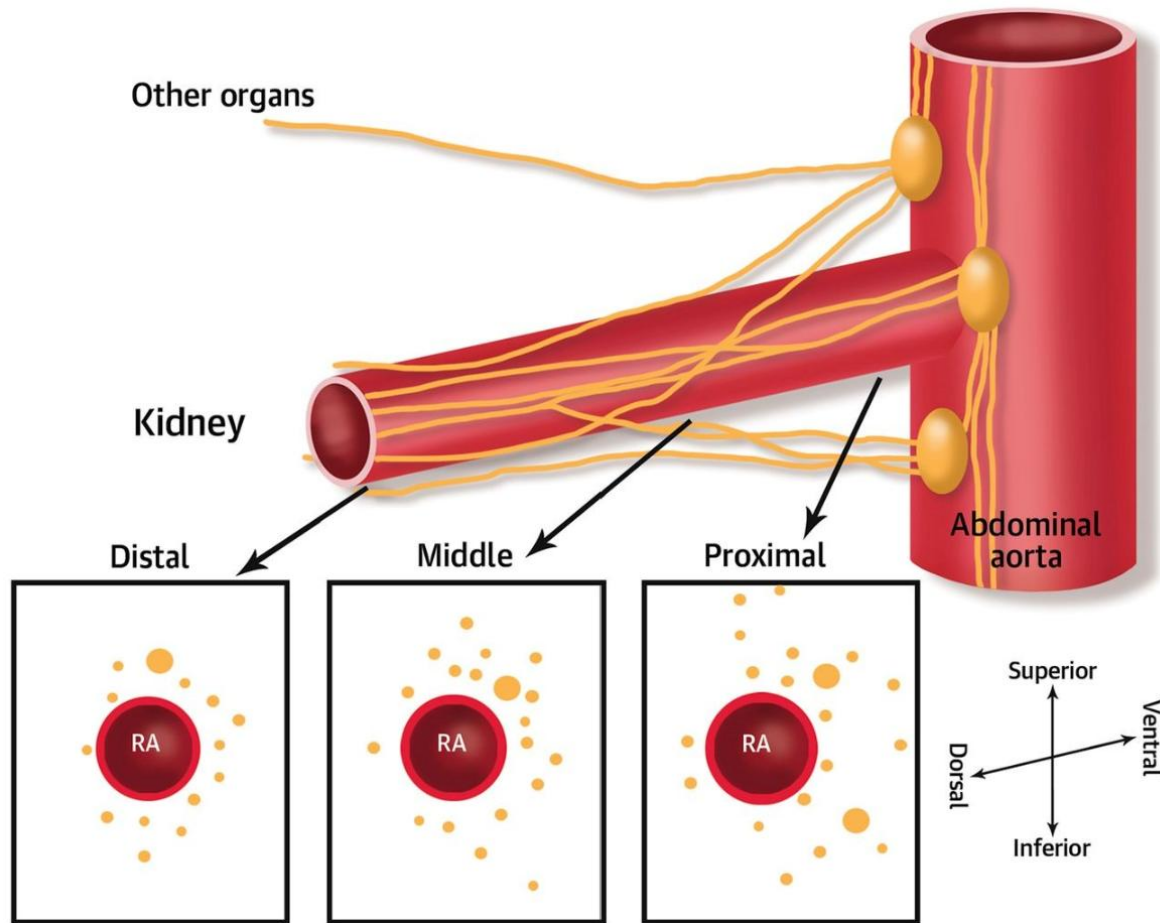


The Path Forward for RDN: Consensus Statement on Trial Design

- **Homogenous HTN patient populations**
- **BP reduction targets (6mmHg ABP/10mmHg OBP)**
- **Primary Endpoint ABPM**
- **Need for Sham**
- **Address medication adherence (Off Drug vs. On Drug)**
- **Consistent Denervation Treatment**

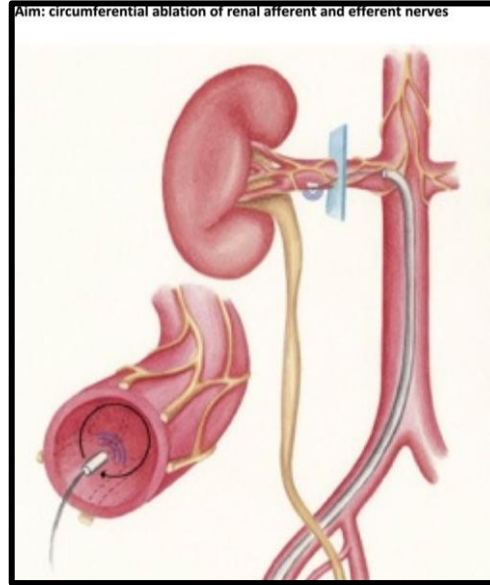
¹Mahfoud F, Bohm M, Azizi M et al. Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: state of the art and considerations for the future. European Heart Journal. 2017;0:1–11

Distribution and Density of Renal Sympathetic Nerves

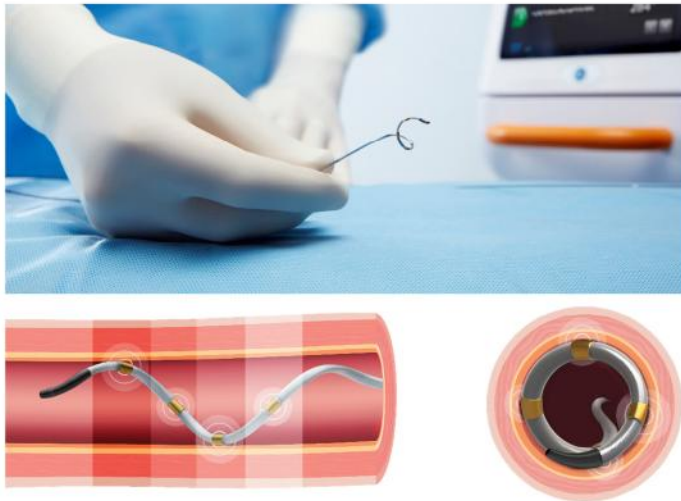


The relationship between the anatomic location of sympathetic nerves within the renal arteries (proximal, middle, or distal and ventral or dorsal) may influence the amount of energy required to achieve catheter-based renal denervation.

Renal denervation systems



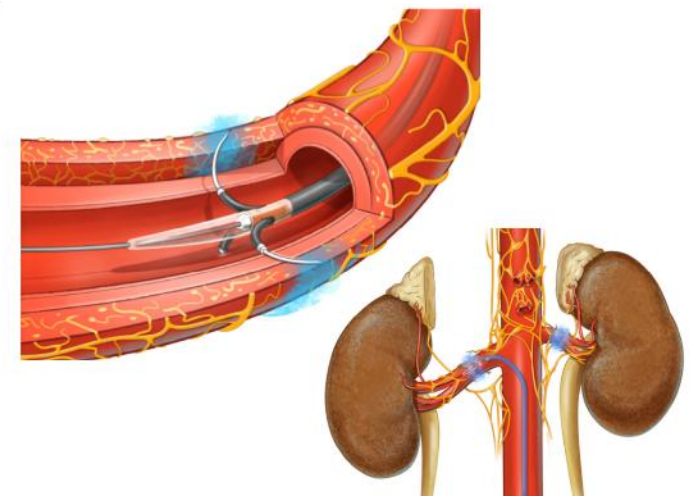
Medtronic Spyral® System



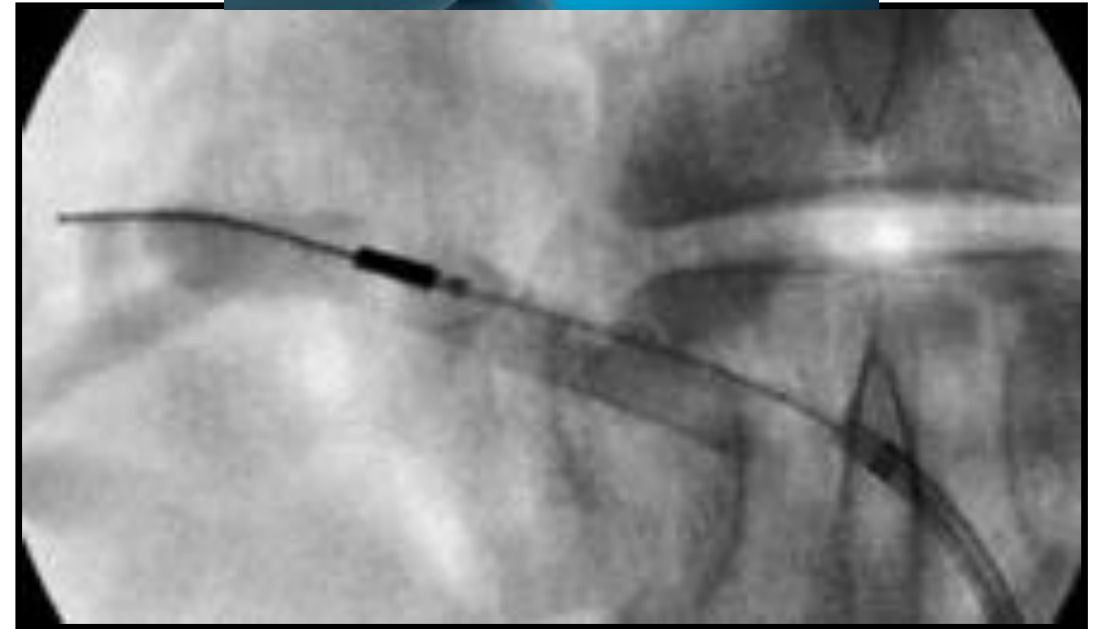
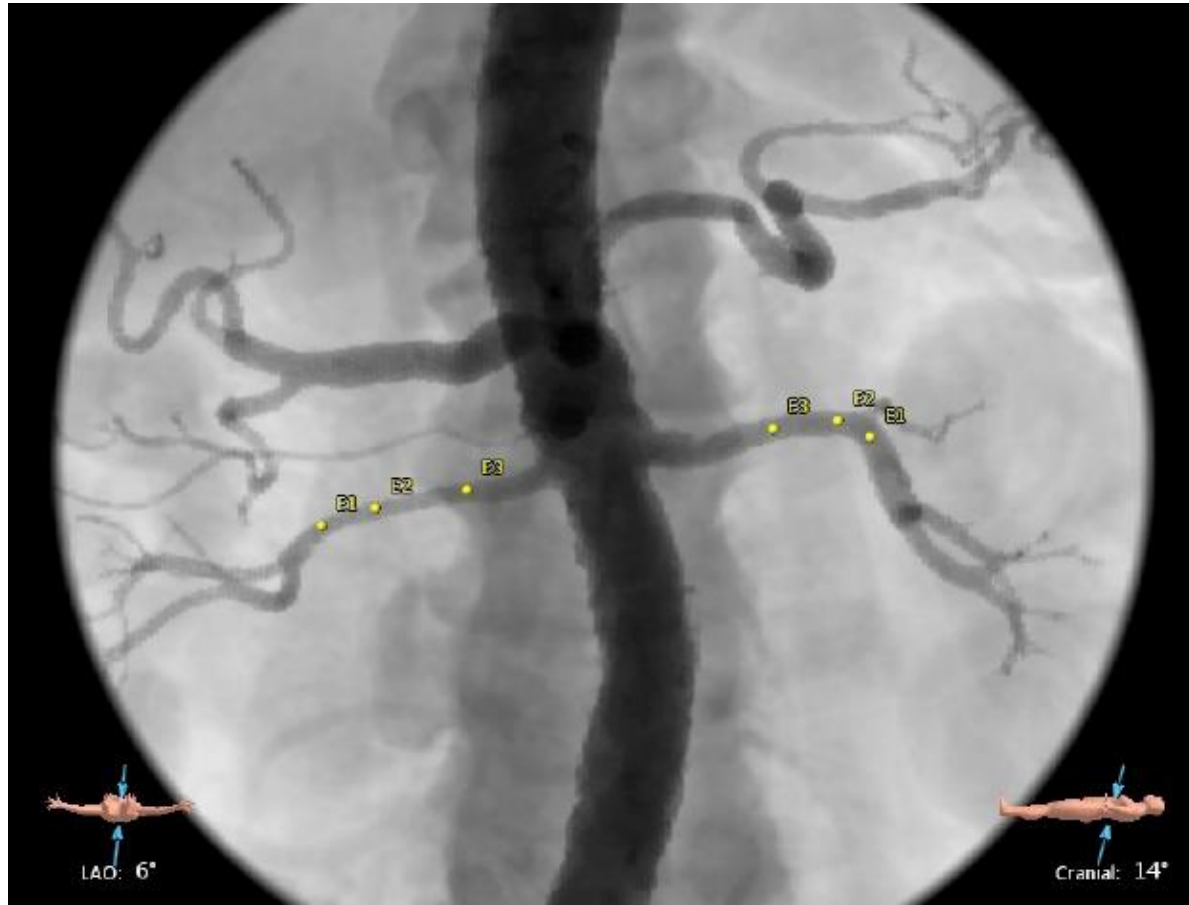
ReCor Paradise® System



Ablative Solutions Peregrine® System



Procedure with the US RDN catheter



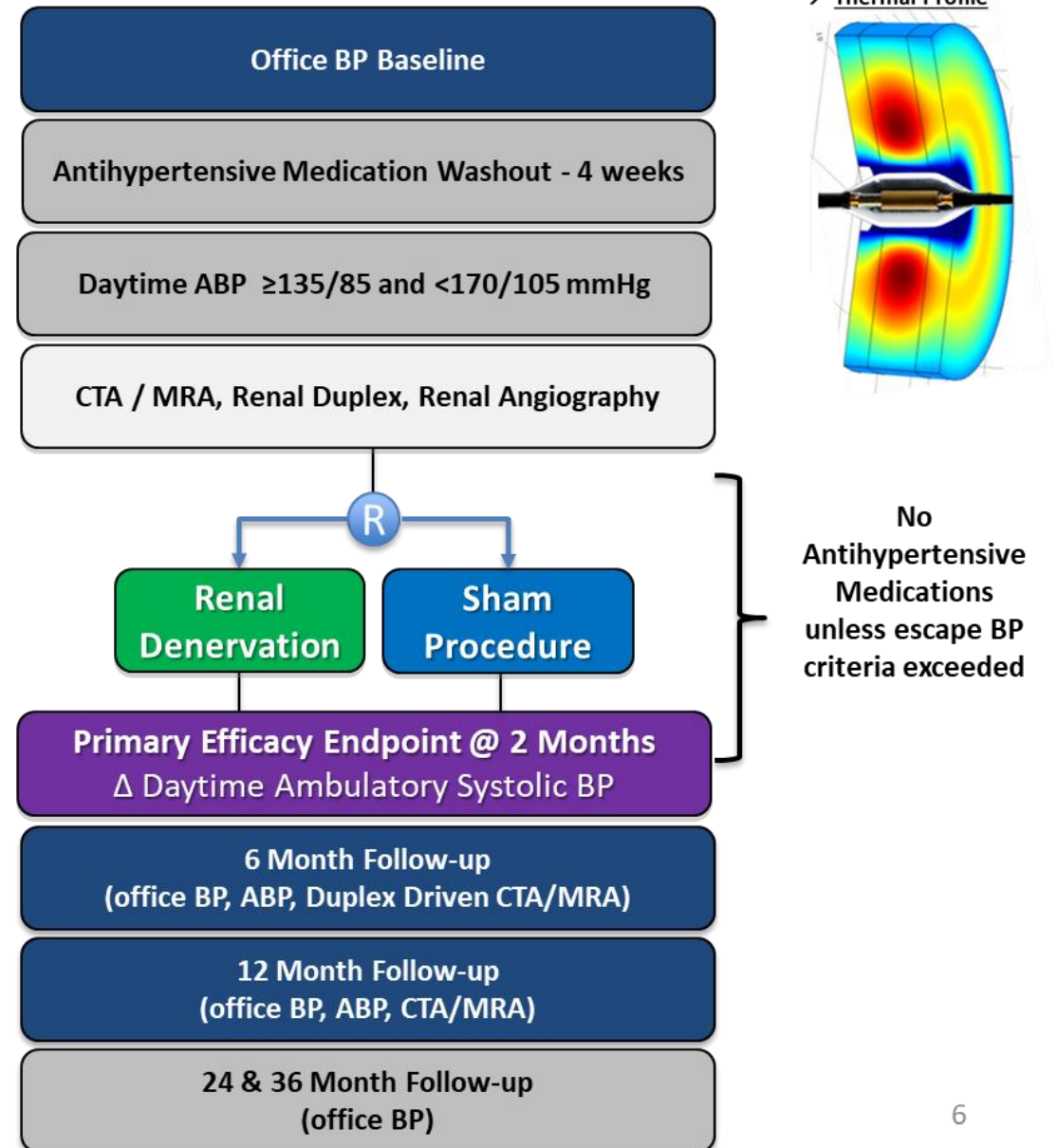
OFF-MED Studies

RADIANCE-HTN SOLO - Study Design

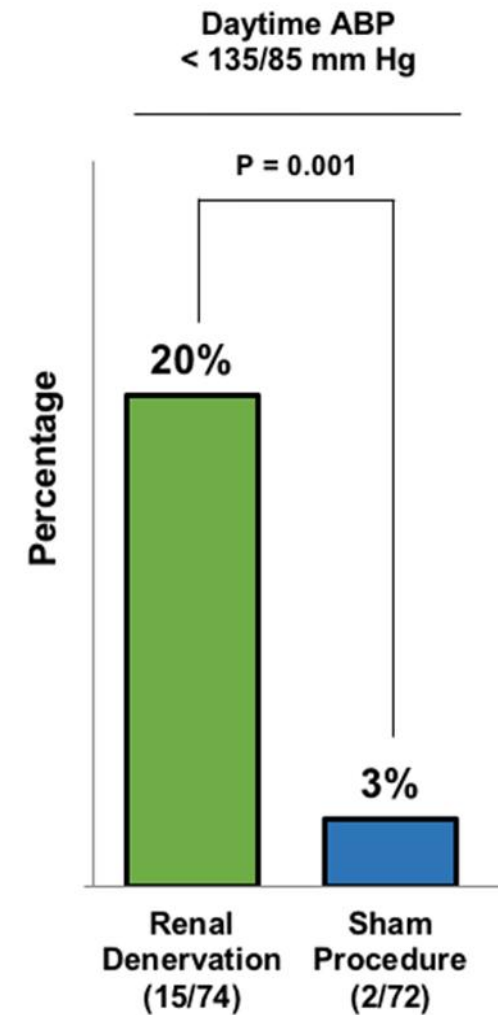
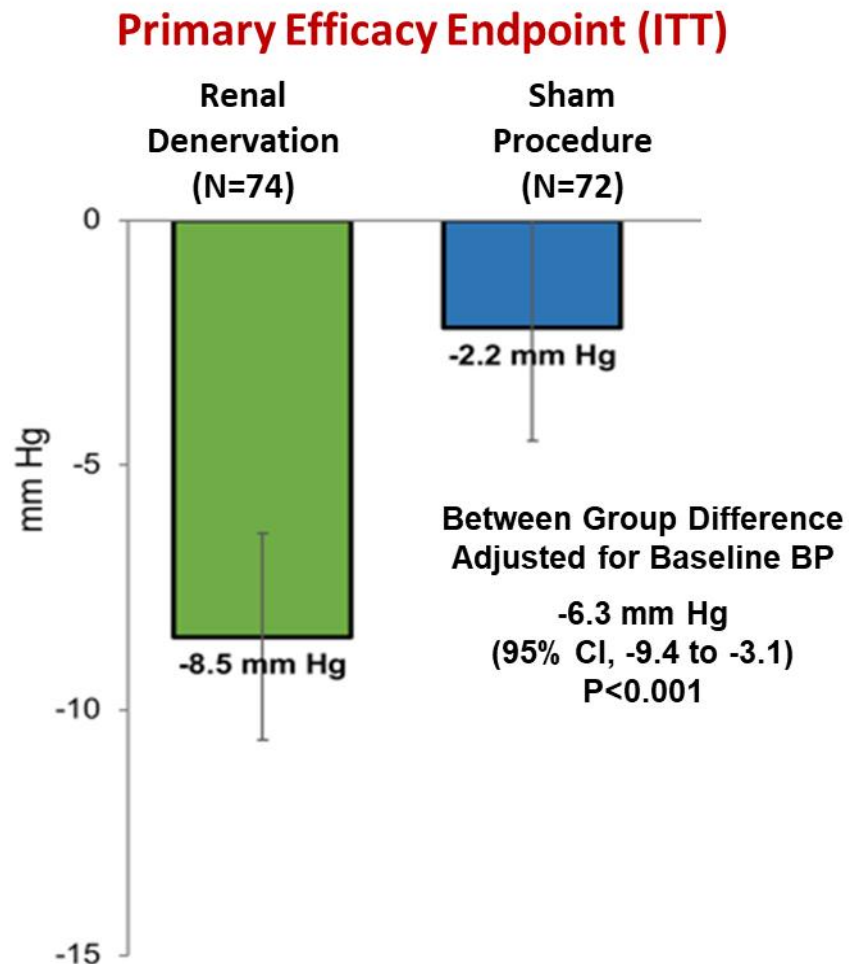
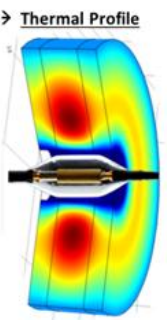
Multicenter, Blinded, Sham-Controlled trial
Powered to Demonstrate BP Lowering Effectiveness at 2M

Key Entry Criteria:

- Hypertension controlled on 1-2 anti-HTN meds or uncontrolled on 0-2 meds
- Off-medication daytime ABP $\geq 135/85$ and $< 170/105$ mmHg
- Age 18-75 years
- No prior cardiovascular or cerebrovascular events
- No Type I or uncontrolled Type II diabetes
- eGFR ≥ 40 mL/min/m²
- Eligible renal artery anatomy (bilateral diameter 4-8mm, length ≥ 25 mm, and no stenosis $\geq 30\%$)



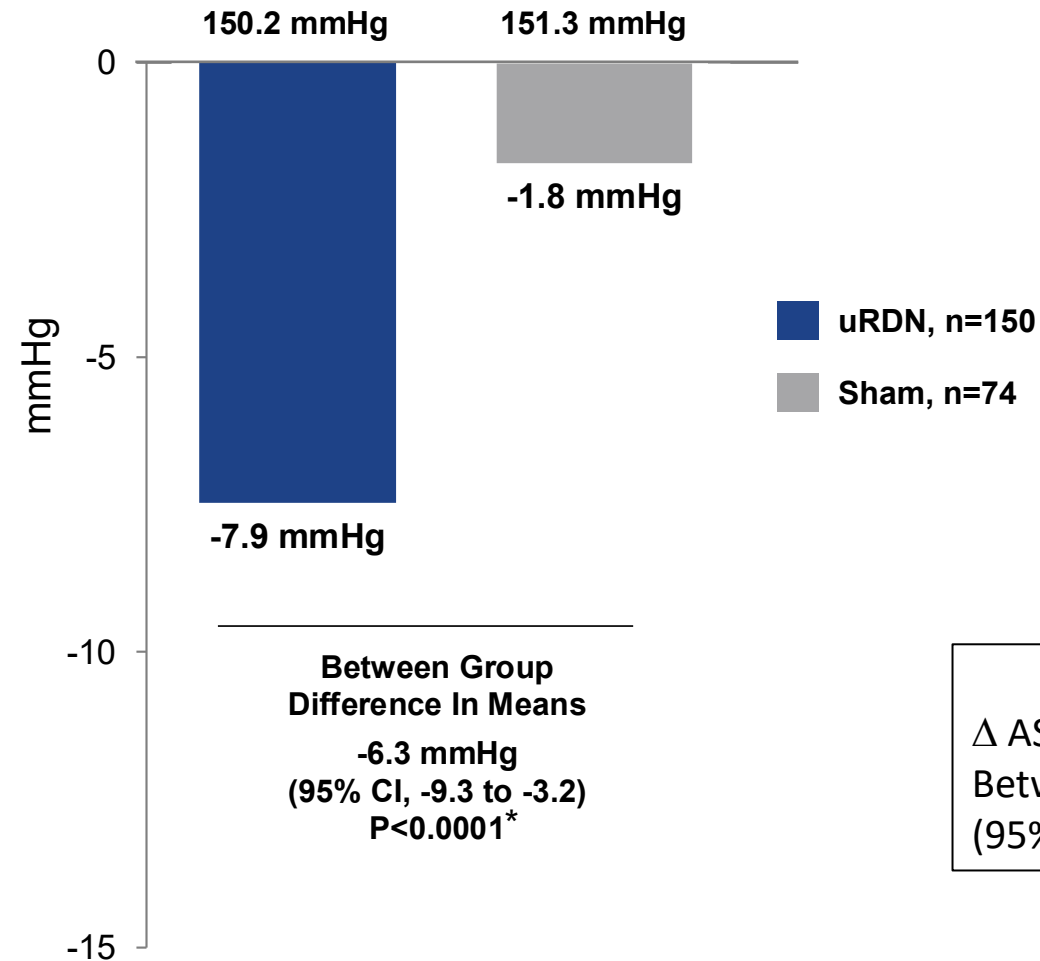
RADIANCE-HTN SOLO : Change in Daytime Ambulatory SBP at 2 Months vs. sham



RADIANCE II PIVOTAL STUDY :

Change in Daytime Ambulatory SBP at 2 Months

Baseline-Adjusted Change in Daytime Ambulatory SBP

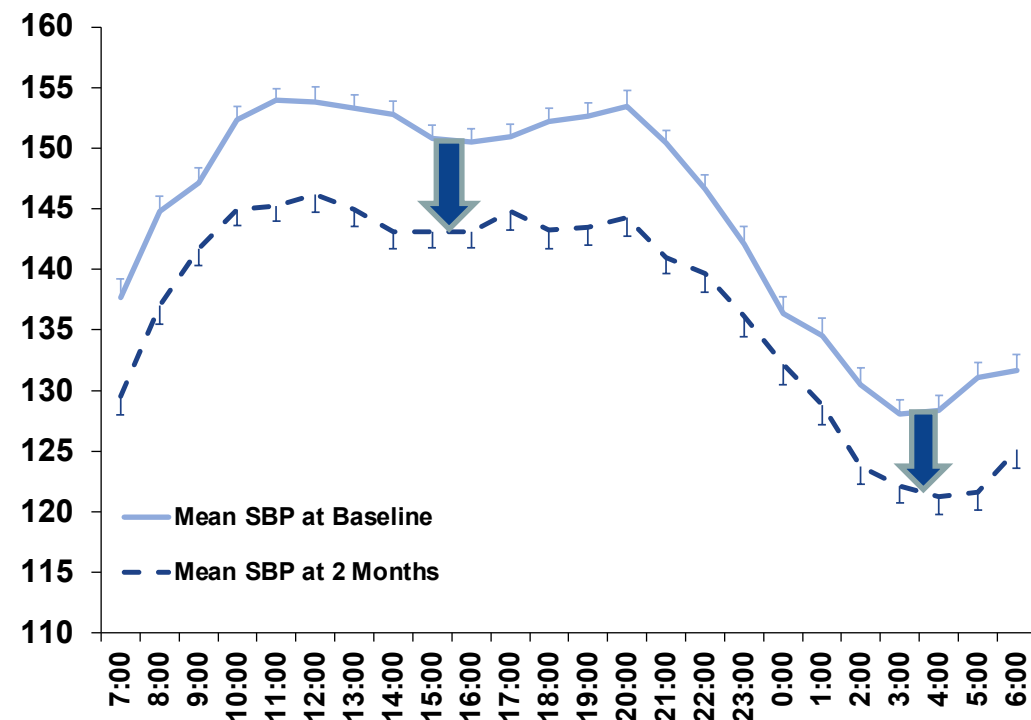


RADIANCE HTN SOLO

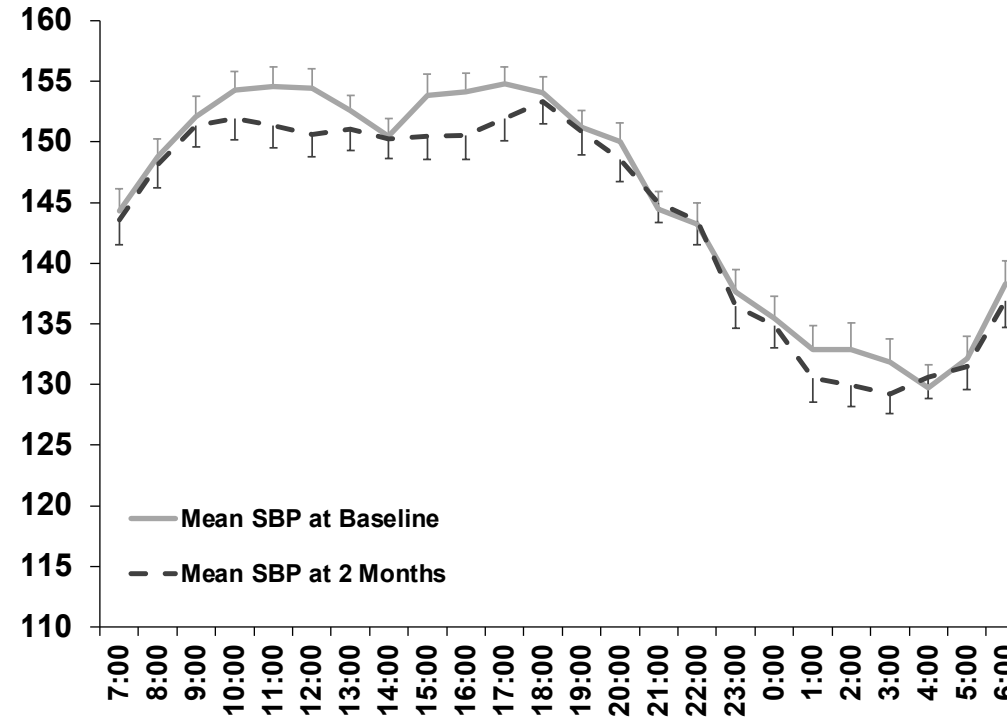
Δ ASBP: -8.5 mm Hg
Between group difference: - 6.3 mmHg
(95%CI: - 9.3 to -3.2 mmHg)

ABPM profiles at Baseline and 2 Months

uRDN (N=145)



Sham (N=73)



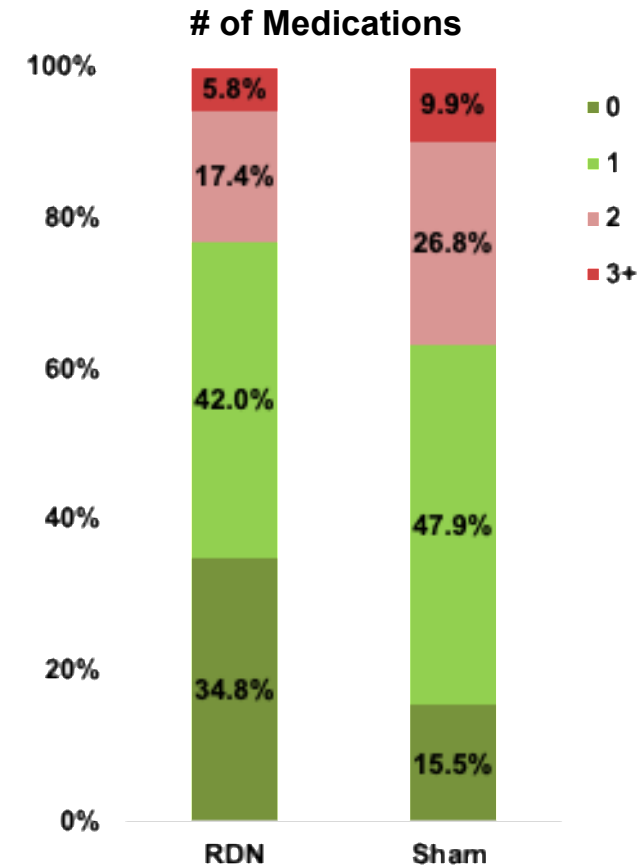
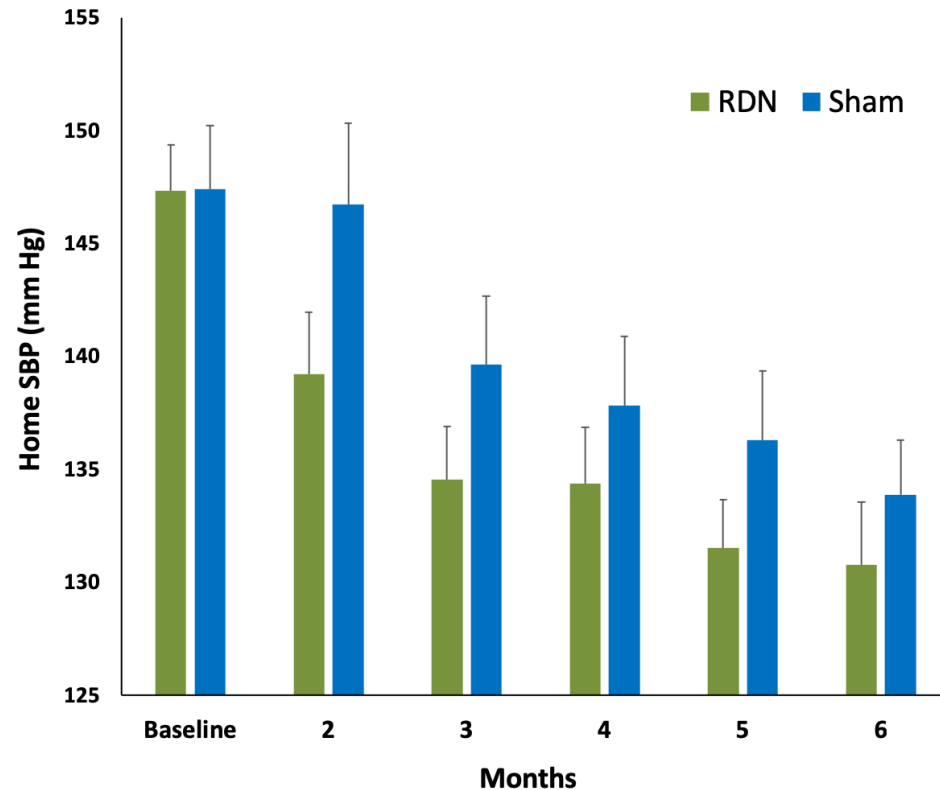
Mean Between Group Difference

24h Ambulatory SBP
-6.2 mmHg
(95% CI, -9.1 to -3.4)
P<0.0001

Nighttime Ambulatory SBP
-5.8 mmHg
(95% CI, -9.0 to -2.6)
P=0.0004

Patients that met escape criteria had baseline values carried forward

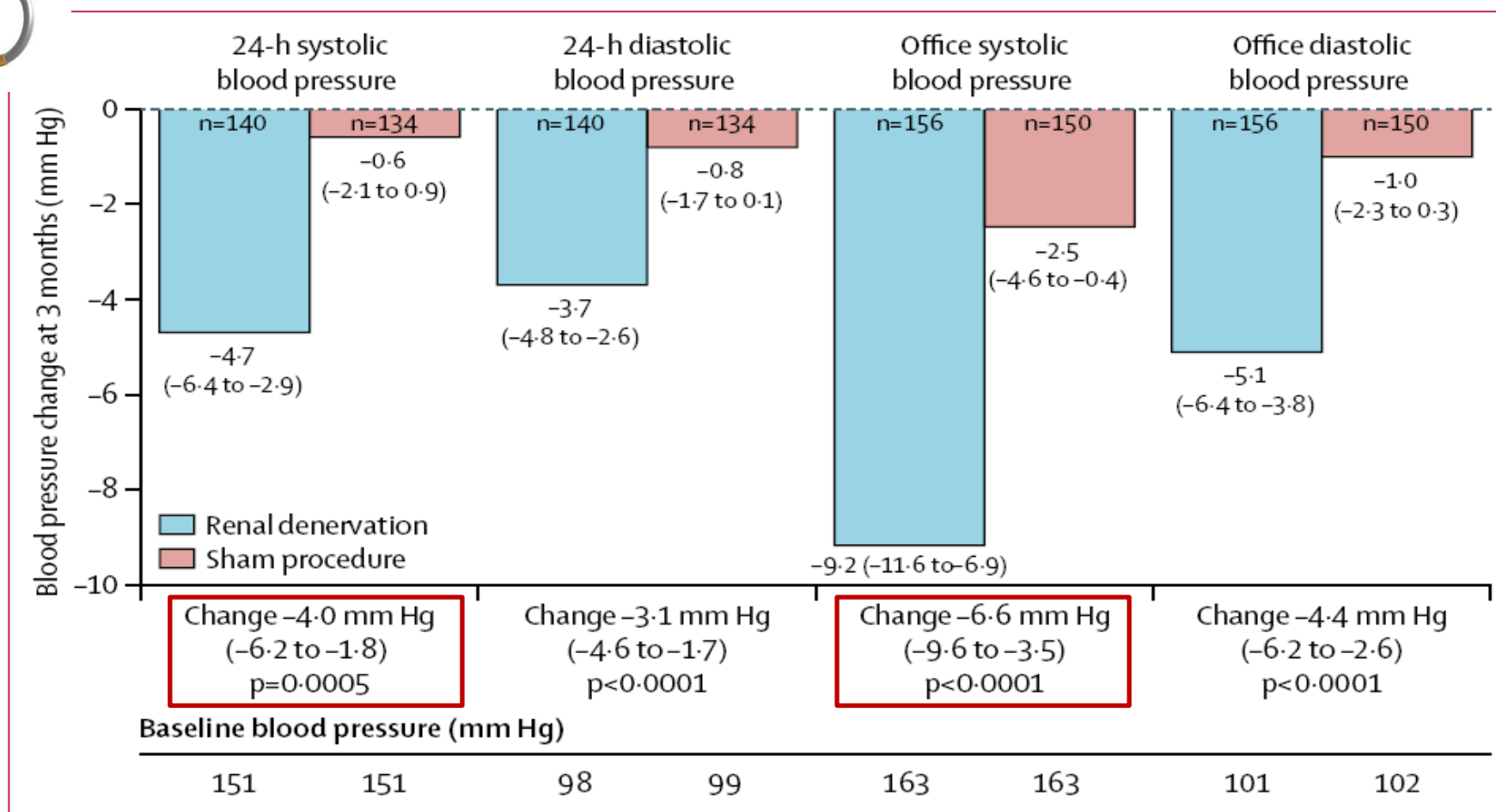
Home Systolic BP Values and Changes from Baseline on medications



P Value for distribution = 0.055
P Value for being on no meds = 0.008

Overall between-group difference -6.9 mm Hg, 95% CI [-9.6,-4.1], $p < 0.001$ from linear mixed model including visit x arm interaction term, adjusted for number of meds

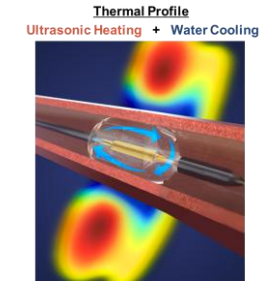
Changes in 24-h and office BP from baseline to 3 months in SPYRAL HTN-OFF MED Pivotal



ON-MED Study

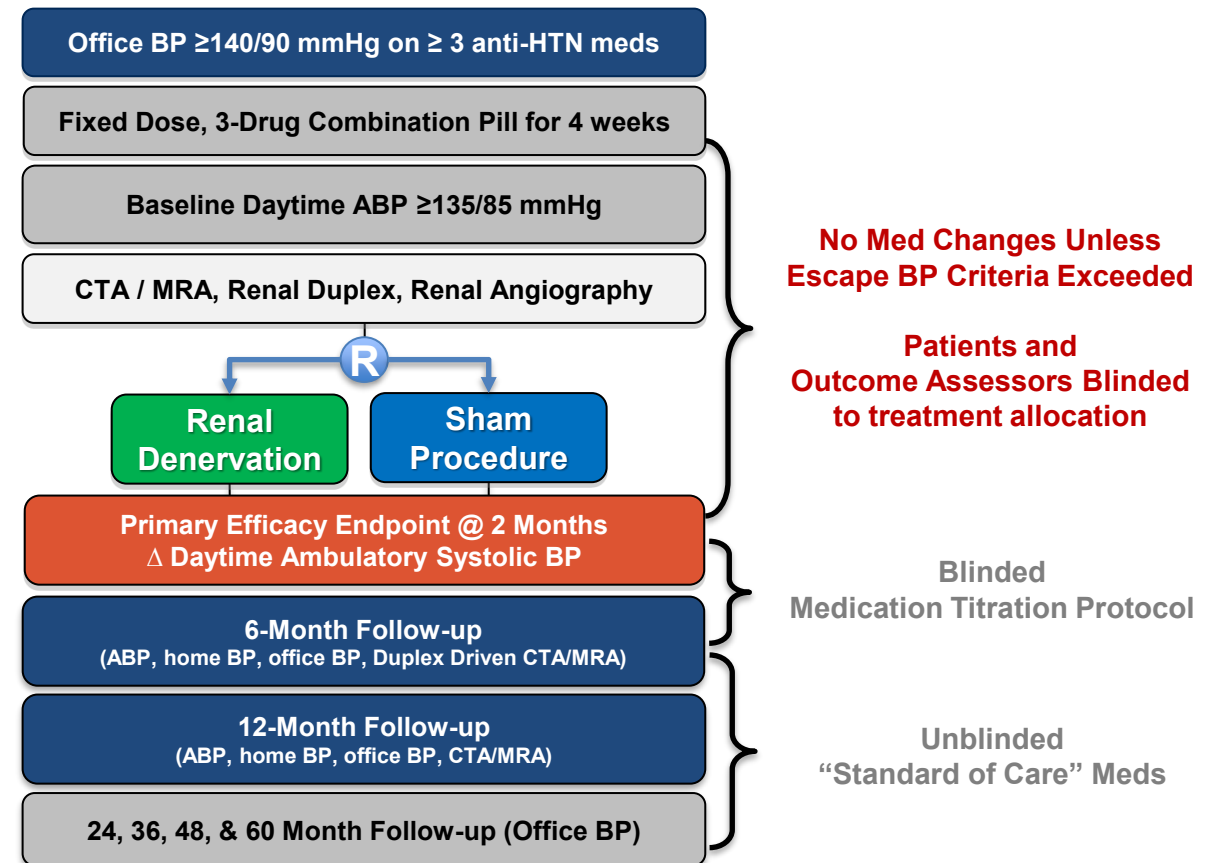
RADIANCE-HTN TRIO

Multicenter, Blinded, Sham-Controlled trial
Powered to Demonstrate BP Lowering Effectiveness at 2M



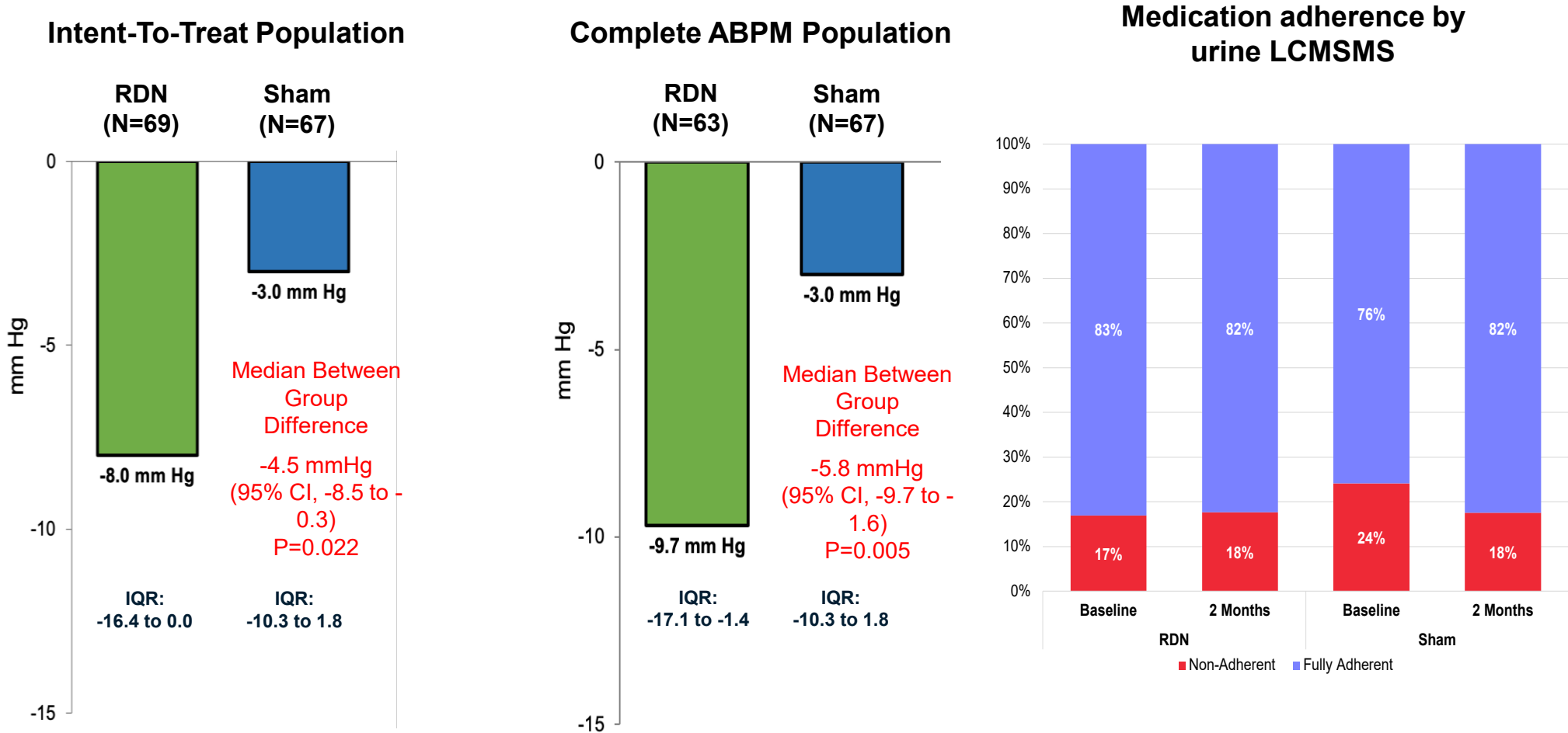
Key Entry Criteria:

- Age 18-75 years
- Office BP $\geq 140/90$ mmHg on ≥ 3 anti-HTN meds
- eGFR ≥ 40 mL/min/m²
- **Daytime ABP $\geq 135/85$ mmHg after 4 weeks on guideline-recommended, fixed-dose, triple combination pill (TZD, ARB, CCB)**
- Suitable renal artery anatomy
- No secondary hypertension aside from OSA
- No CV or cerebrovascular events within prior 3M
- No Type I or uncontrolled Type II diabetes



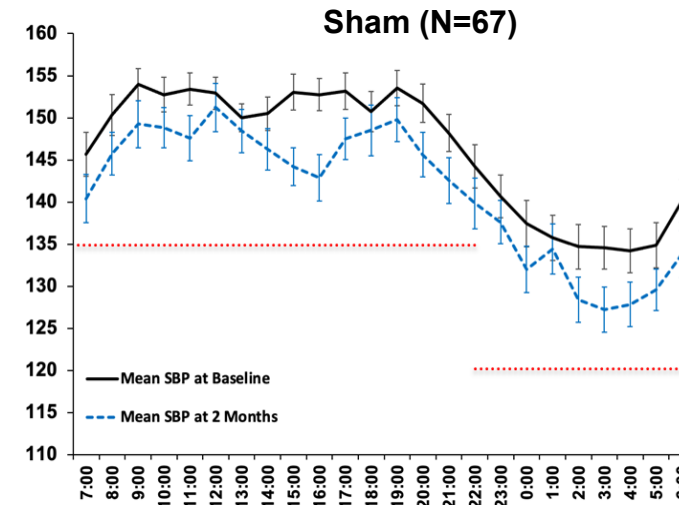
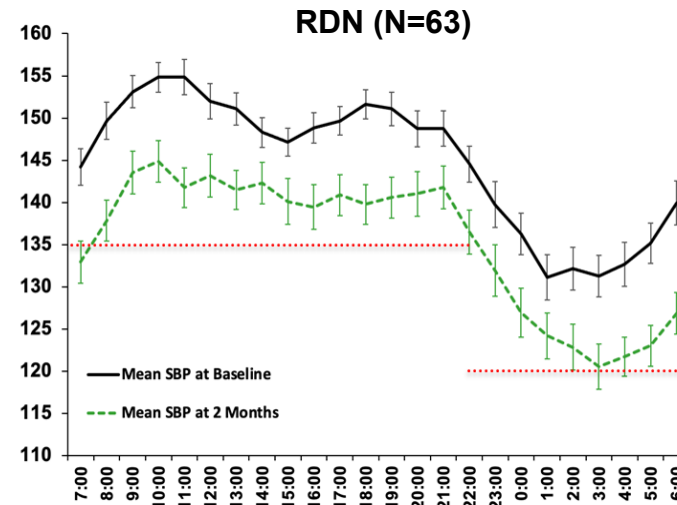
RADIANCE-HTN TRIO Primary Endpoint

Change in Daytime ASBP at 2M



ABPM profiles at Baseline and 2 Months

**Complete ABPM
Population
(Imputed Escape)**



Median Between Group Difference

24h ABPM

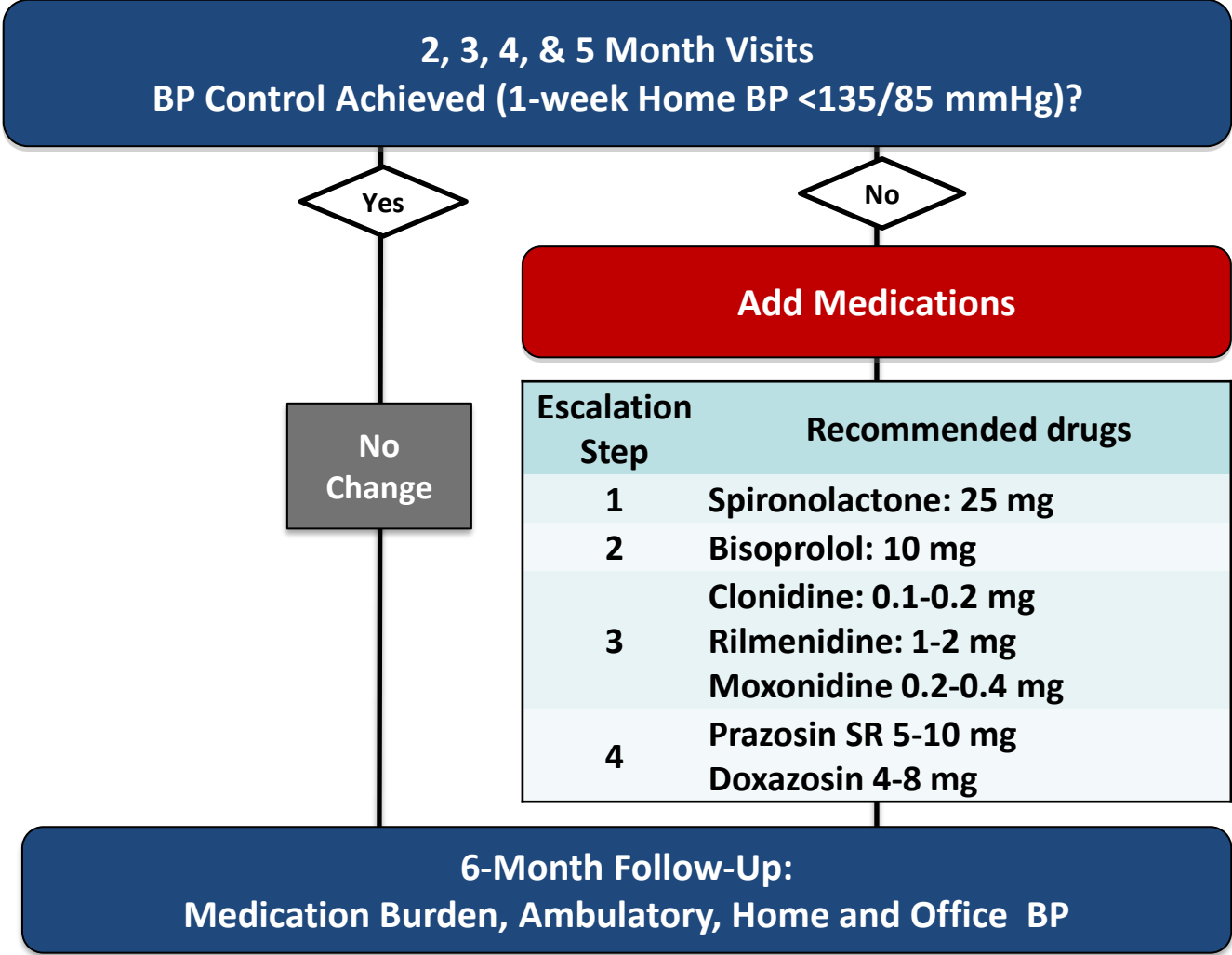
-5.6 mmHg
(95% CI, -9.5 to -1.3)
P=0.0043*

Nighttime ABPM

-5.0 mmHg
(95% CI, -10.1 to 0.5)
P=0.015*

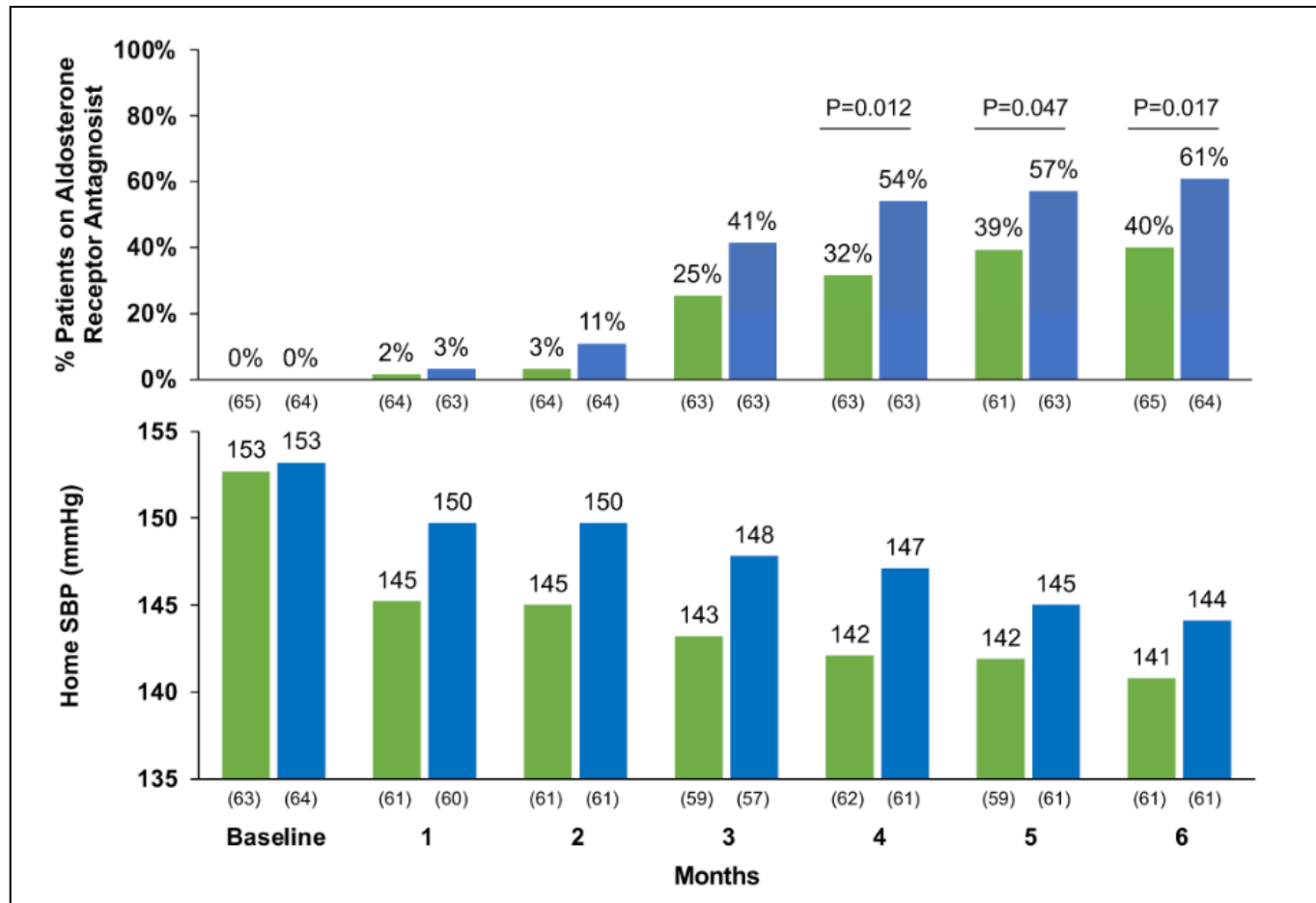
* Baseline-adjusted ANCOVA on the ranks

Blinded Medication Titration Protocol During Months 2-5

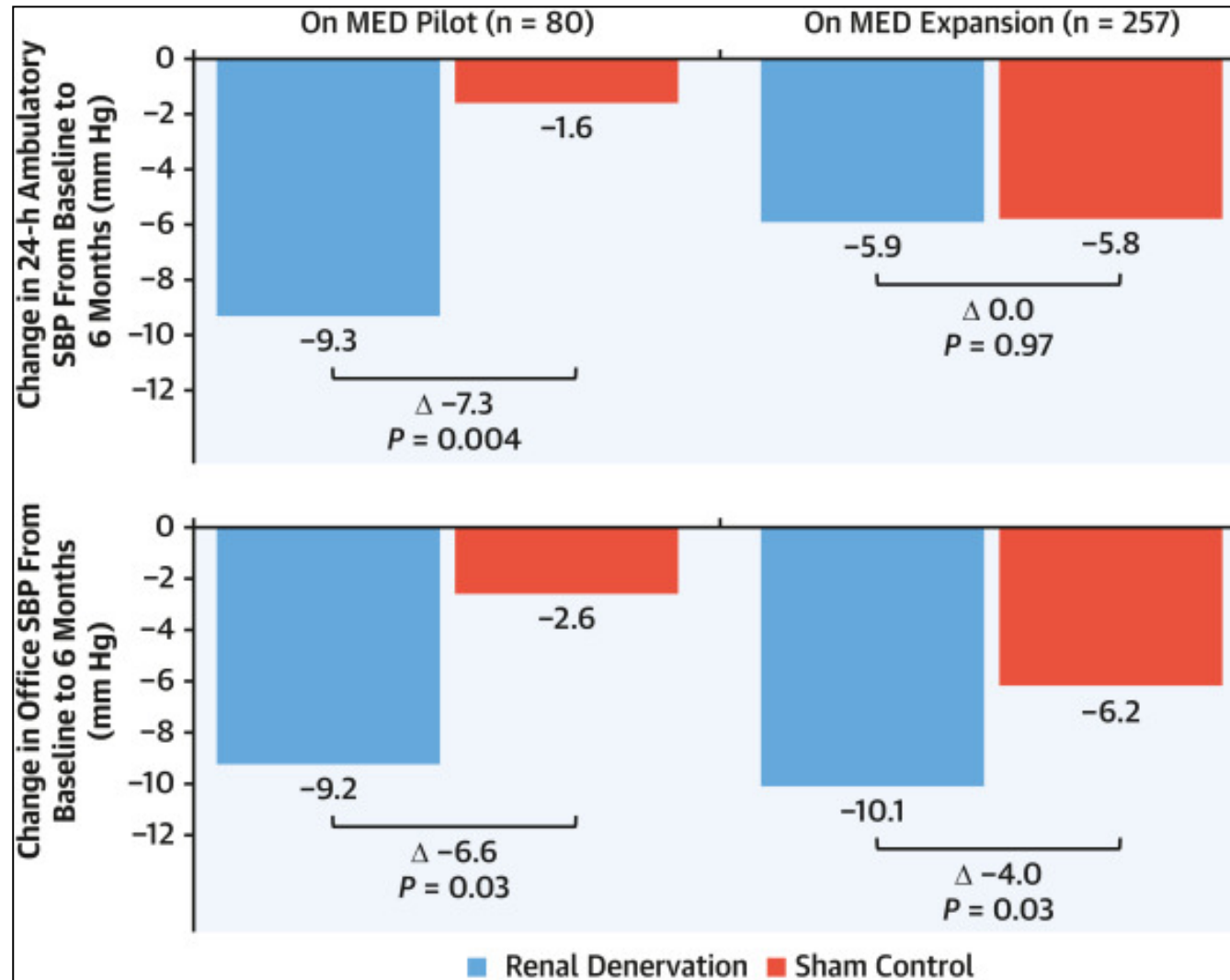


Medications use (aldosterone receptor antagonists) and home BP levels through 6 months

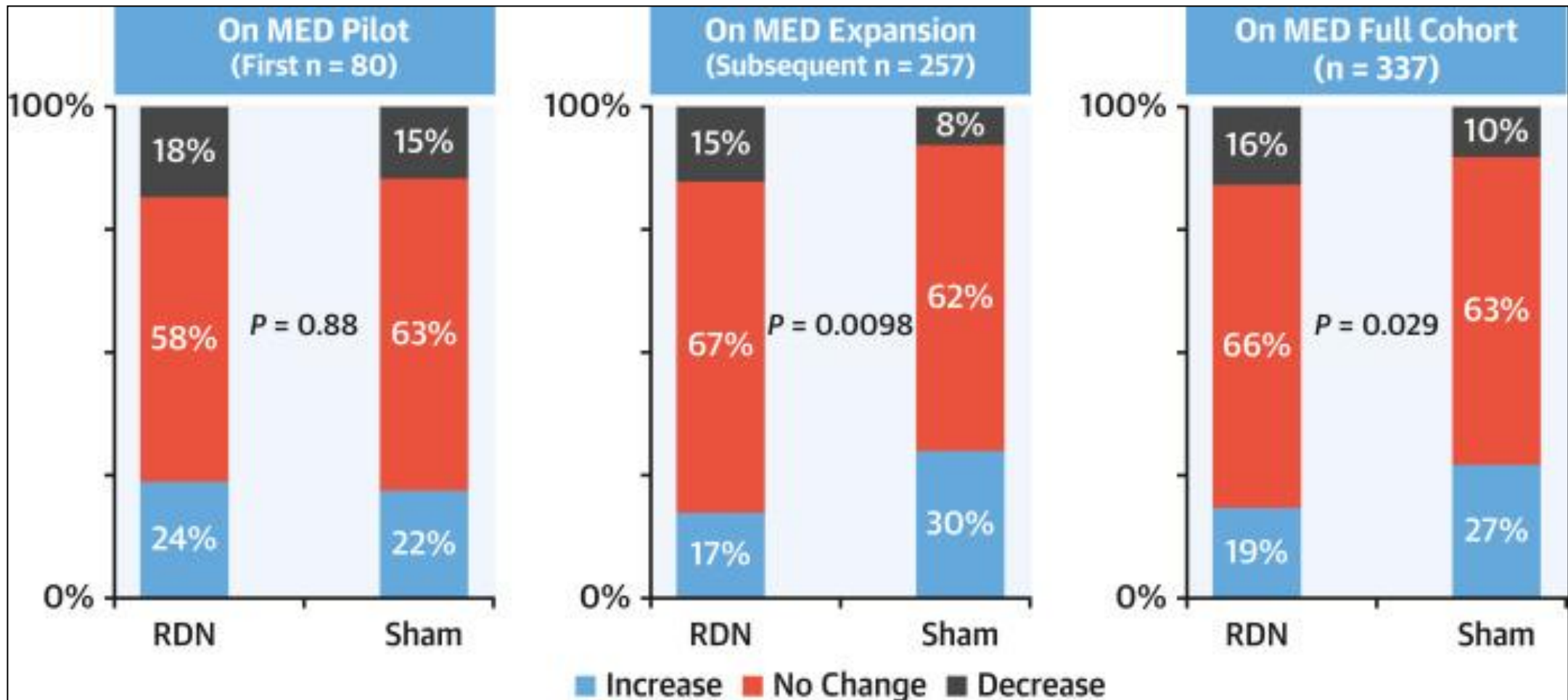
	RDN (n=65)	Sham (n=64)	P-Value
# Anti-HTN Meds at 6 months	3.8 ± 1.0	4.1 ± 1.1	0.078
Change in Anti-HTN Meds from Baseline	0.7 ± 1.0	1.1 ± 1.1	0.045



SBP Change in the Pilot and Expansion Cohorts in SPYRAL on-MED

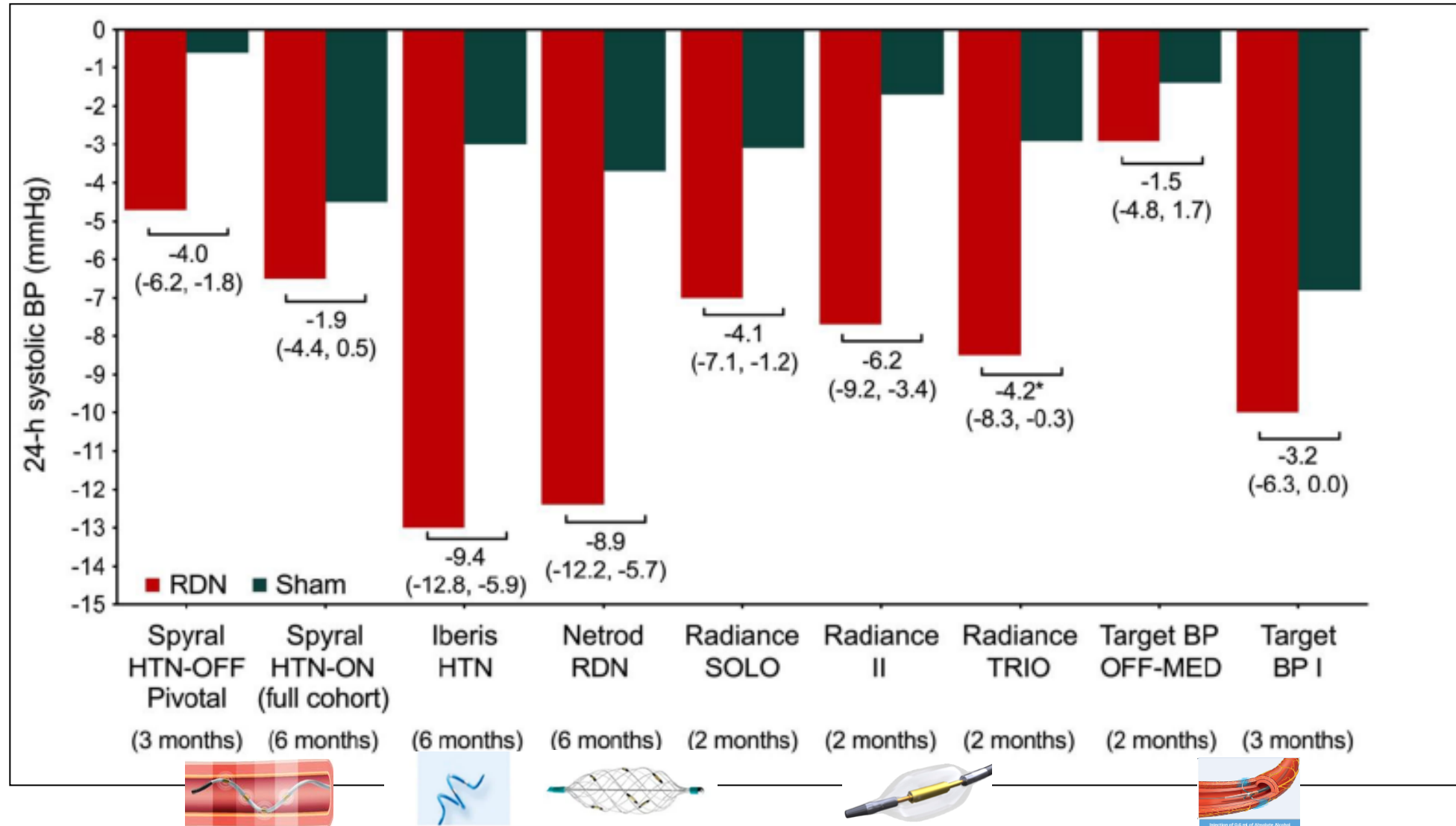


Antihypertensive Medication Burden Change Based on Drug Testing

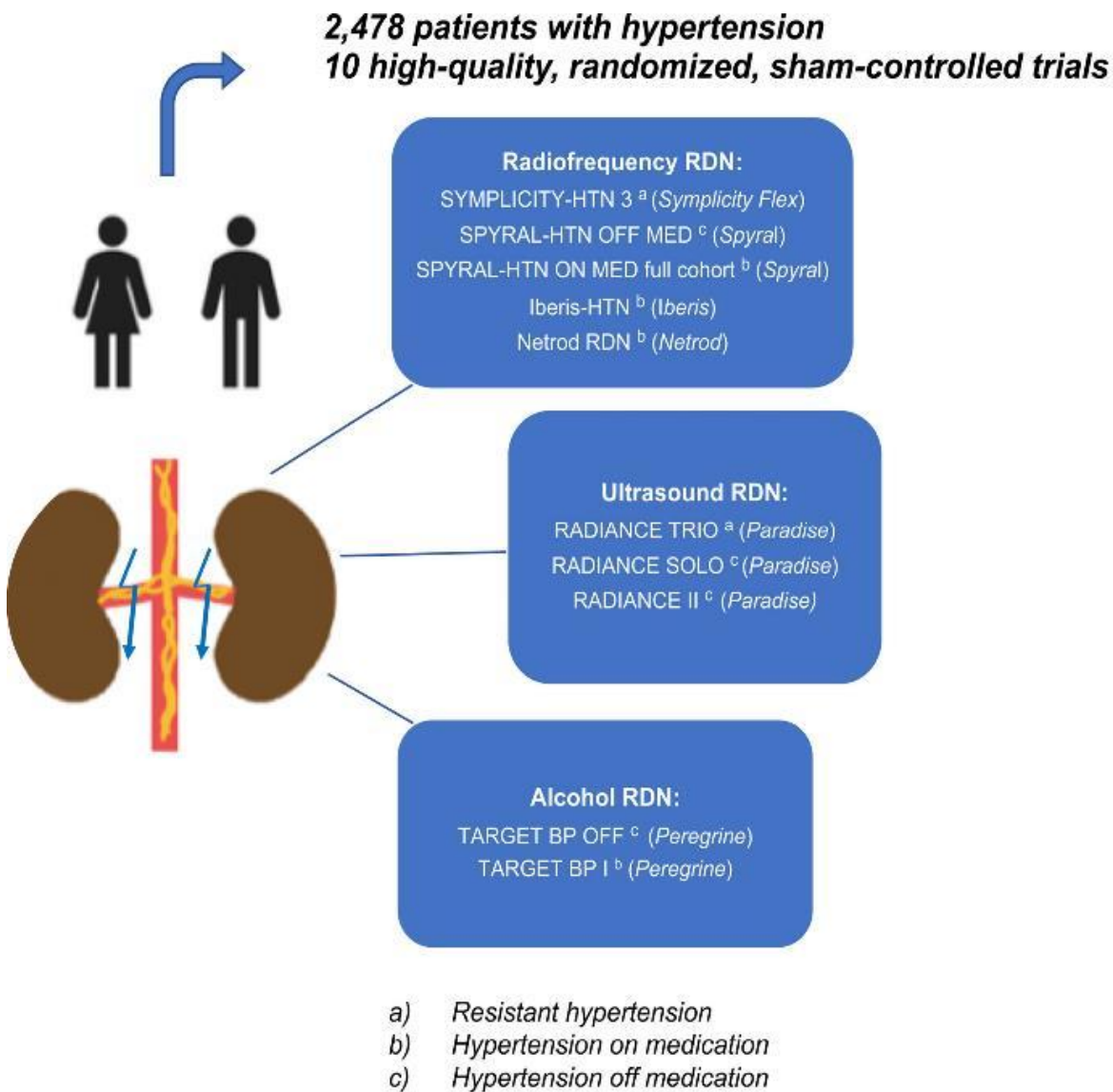


RCT results with other RDN catheters

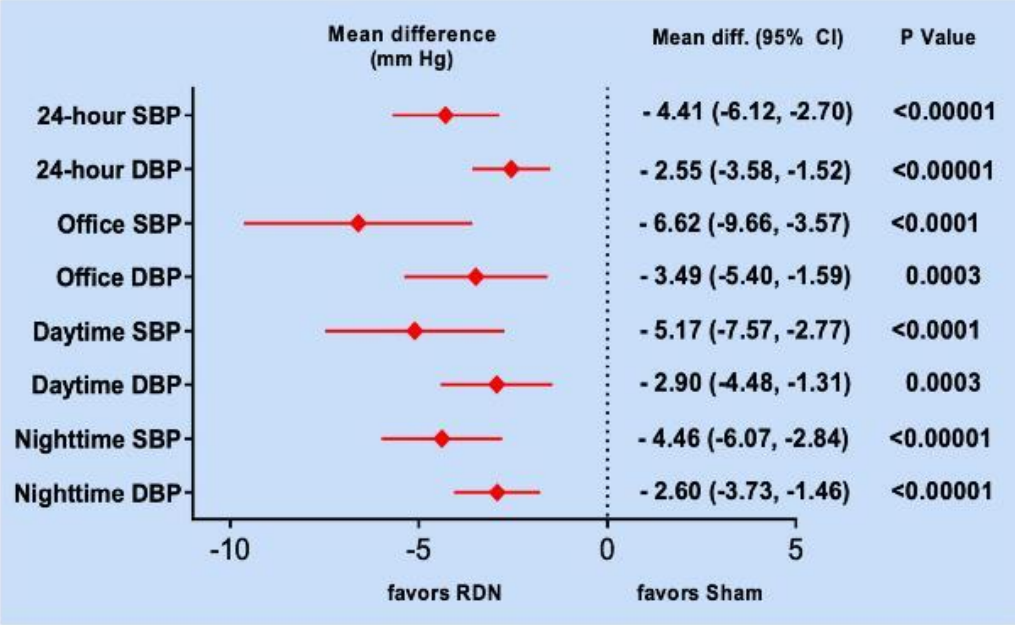
Change in 24-h ambulatory SBP Following RDN in Second-Generation Sham-Controlled Trials



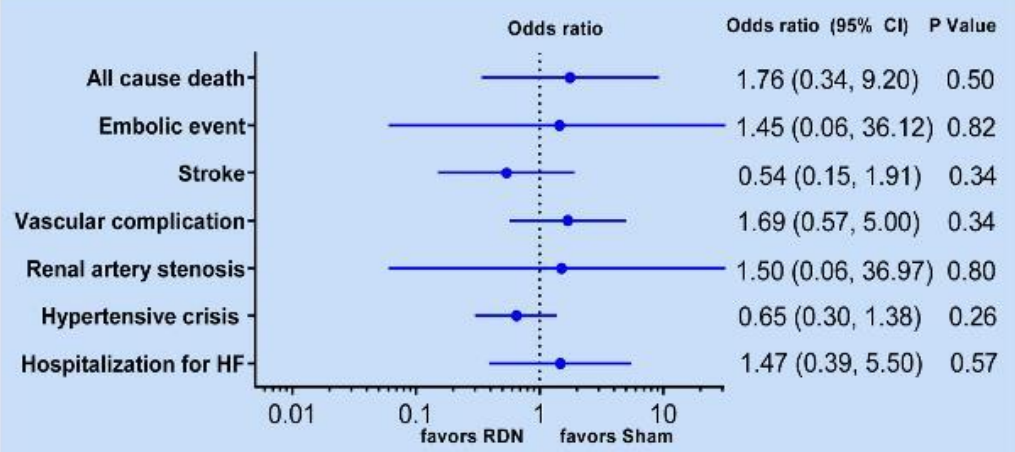
Meta-Analysis of sham-controlled trials on RDN in Hypertension in 2024



Efficacy outcomes



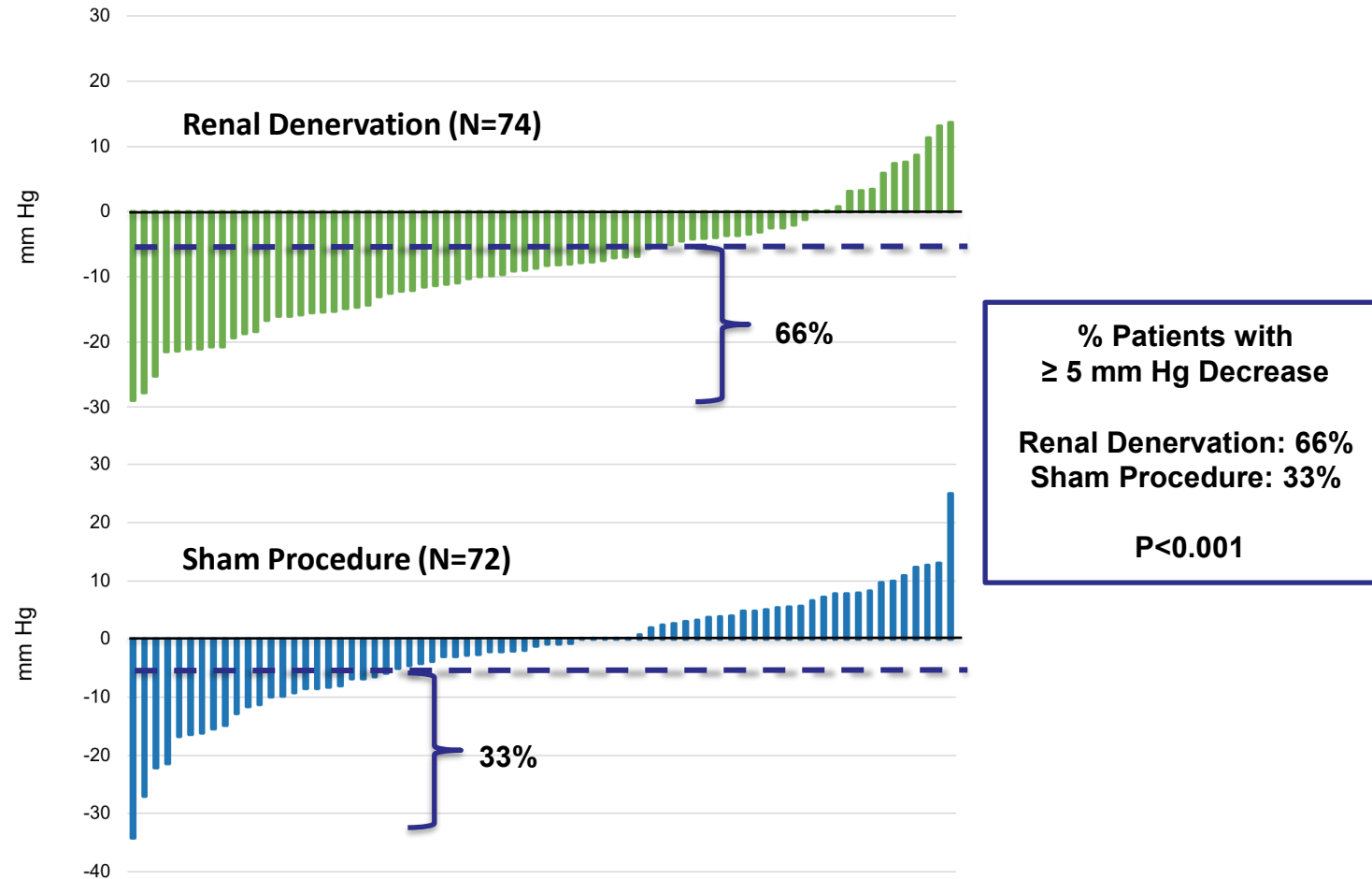
Safety outcomes



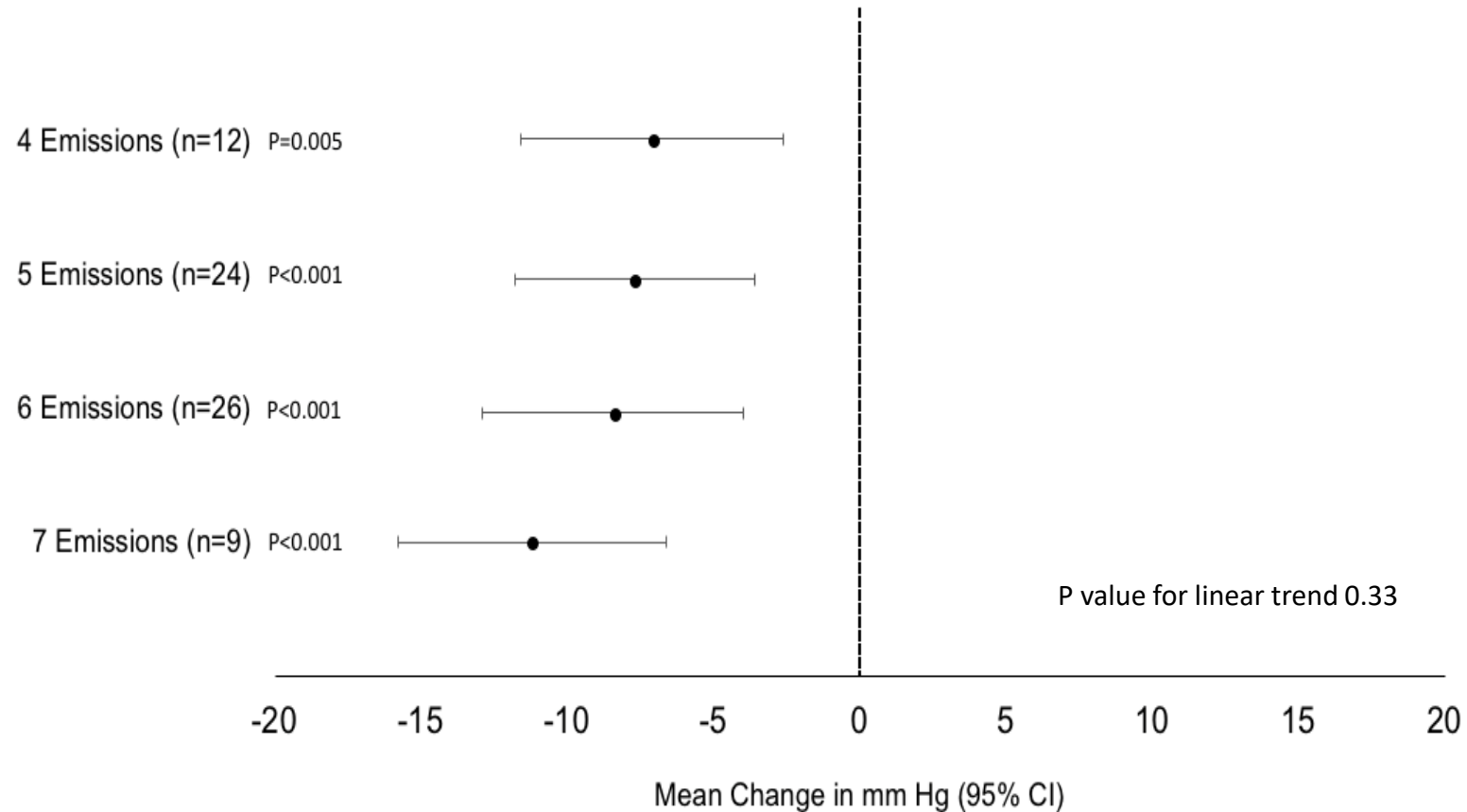
Predictors of BP response to RDN

Individual Patient Response at 2 Months

Change in Daytime Ambulatory Systolic BP at 2 Months (ITT Population)



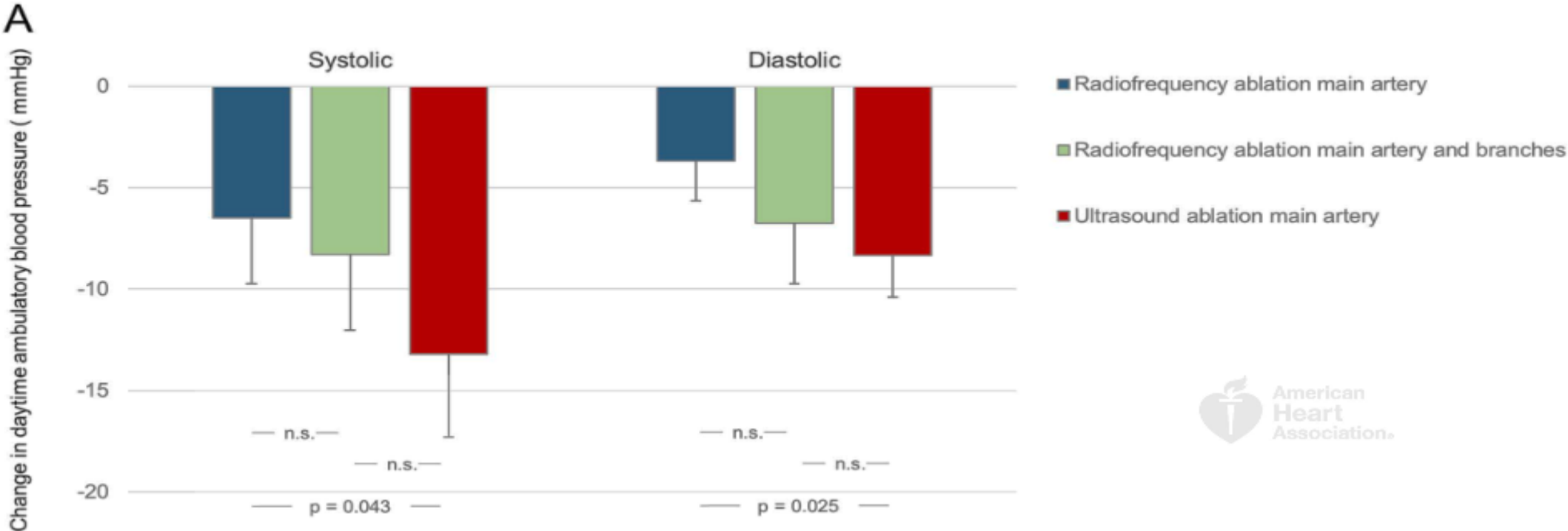
SOLO Trial: 2-Month Change in Daytime Systolic ABP By Total Number of Ultrasound Emissions in RDN Group



**All Numbers of Ablations Were Associated with Significant
Reductions in 2-Month Daytime Systolic ABP**

RADIO SOUND-HTN: RCT of Different of RDN Techniques in Patients with RHTN

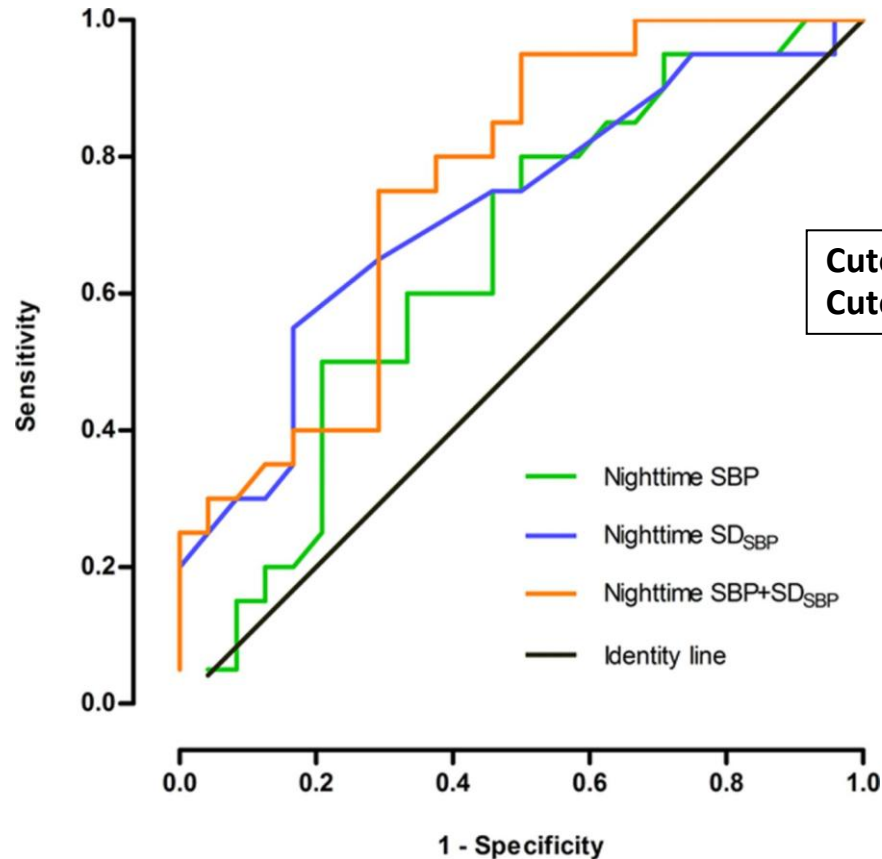
120 pts with RHTN, 1:1 randomization
primary endpoint : change in daytime ambulatory SBP at 3 months.



	All (n = 120)	RF main only (n = 39)	RF branches (n = 39)	US (n = 42)	p-value
Ablation points right renal artery	10.0 ±7.4	9.1 ±3.0	18.3 ±6.1	3.2 ±0.8	<0.001†
Ablation points left renal artery	9.2 ±6.7	8.1 ±2.2	16.8 ±6.0	3.2 ±0.9	<0.001†

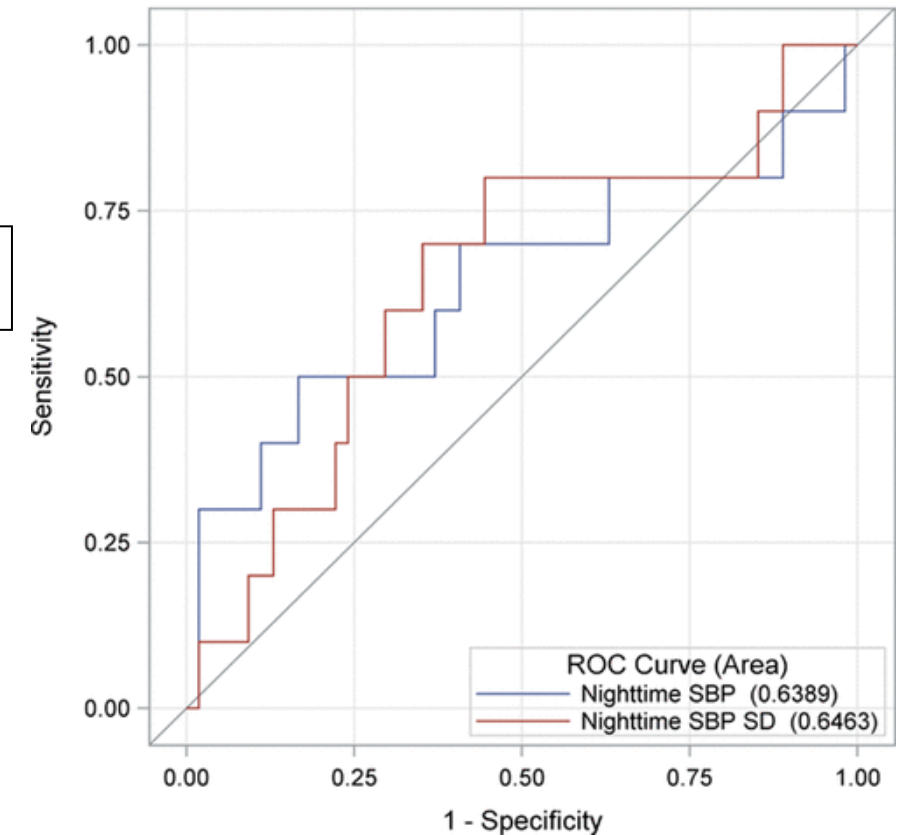
Baseline nighttime SBP and its SD to predict ambulatory BP responders after RDN

DENERHTN

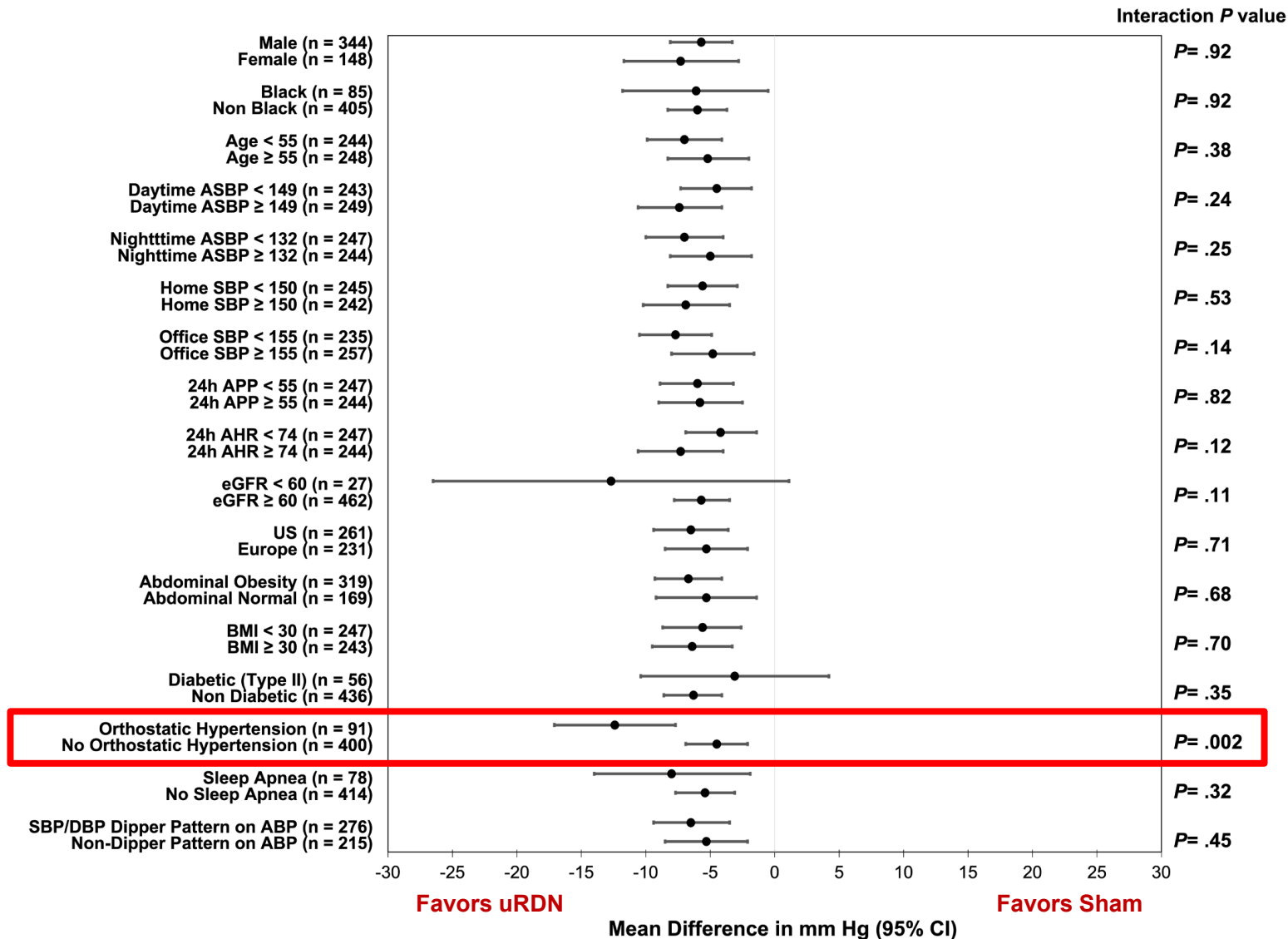


AUC: 0.76 (95%CI: 0.61-0.90)

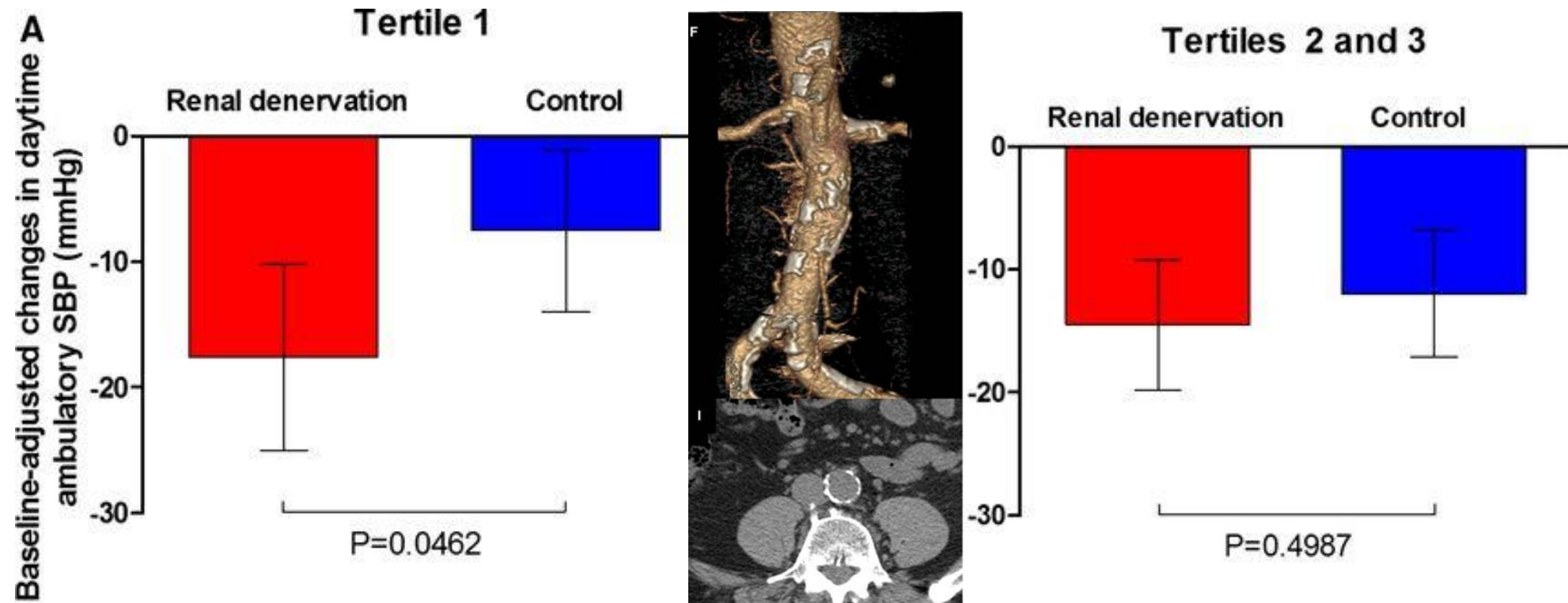
RADIANCE SOLO



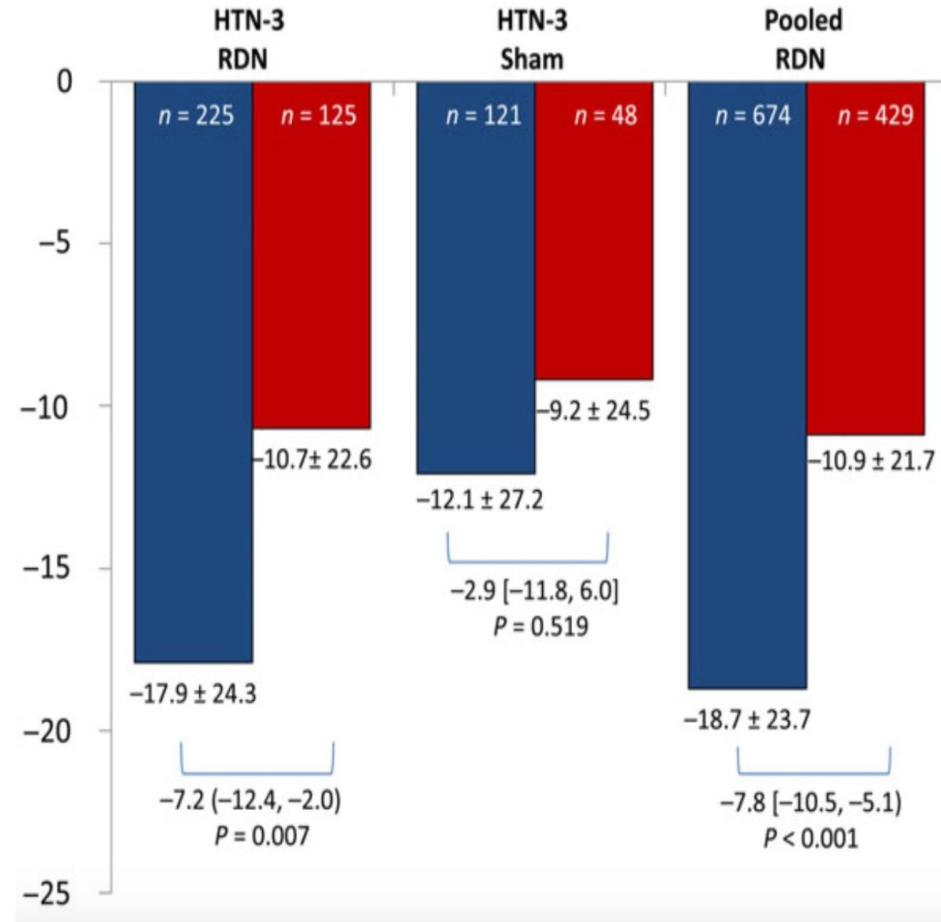
RADIANCE Pooled Analysis: Change in Daytime Ambulatory SBP at 2 Months in Subgroups



Baseline-adjusted changes in daytime ambulatory SBP according to tertiles of AAC



Office SBP changes at 6 months in patients with CH and ISH



Combined hypertension (CH):

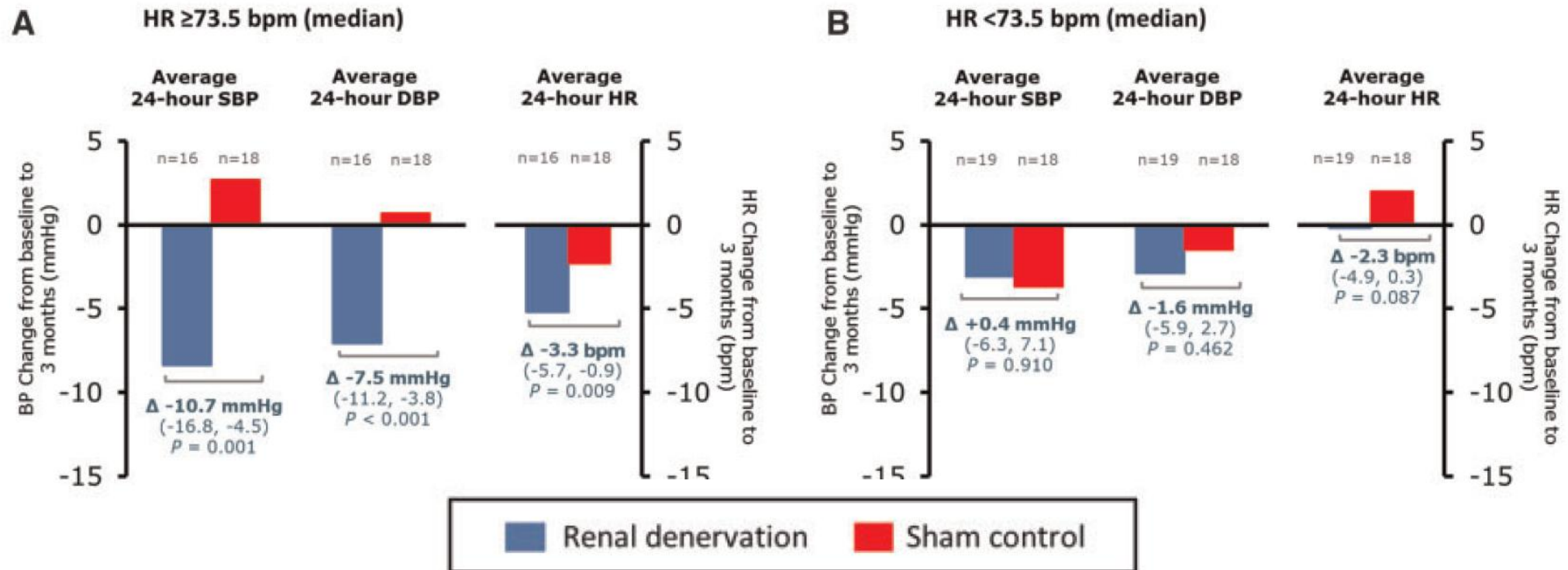
- SBP >140 mmHg, **DBP >90 mmHg**

Isolated systolic hypertension (ISH):

- SBP >140 mmHg, **DBP <90 mmHg**

Baseline 24-h HR : a predictor of changes in BP ?

	Baseline		3 months		Change at 3 months		Mean difference: RDN vs. sham ^a
	RDN (N = 35)	Sham (N = 36)	RDN (N = 35)	Sham (N = 36)	RDN (N = 35)	Sham (N = 36)	
24-h HR (b.p.m.)	72.9 ± 11.0	74.4 ± 11.7	70.4 ± 8.5	74.2 ± 9.6	-2.5 ± 5.3 (-4.3 to -0.7)	-0.2 ± 4.1 (-1.5 to 1.2)	-2.7 (-4.5 to -1.0) P = 0.003



Potential predictors of BP response to RDN



Patient characteristics

- Age
- Ethnicity
- Obesity
- Sleep apnea
- Chronic kidney disease
- Antihypertensive medication
- Poor drug adherence
- Renal artery diameter



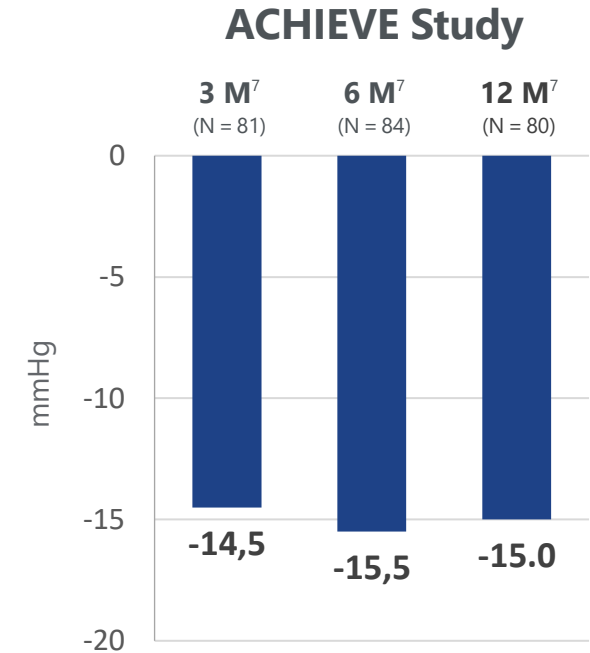
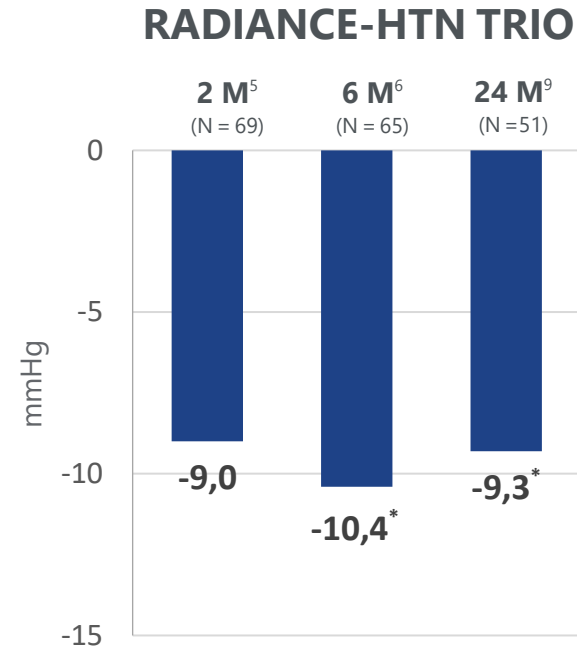
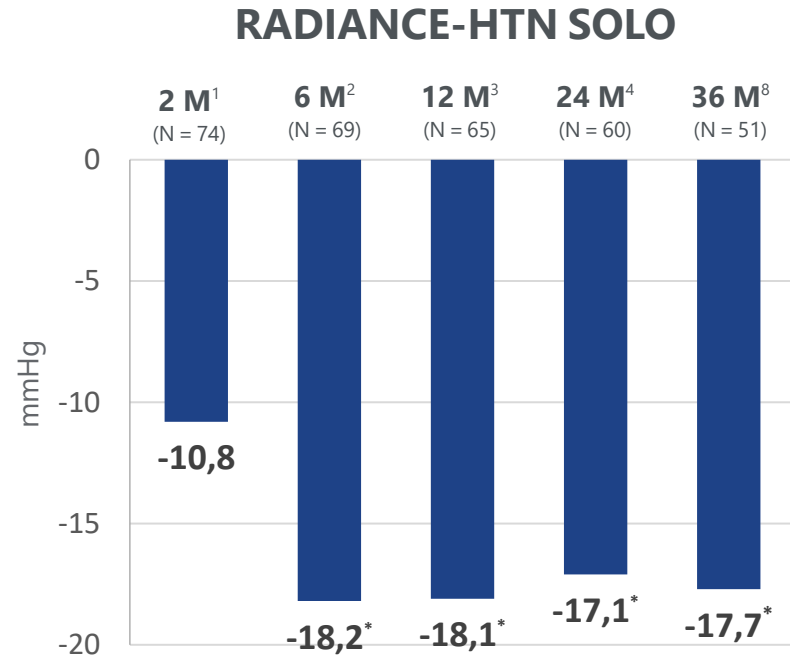
Hemodynamic parameters

- Basal heart rate and heart rate variability
- Nighttime systolic BP and variability
- Pulse wave velocity
- Central pulse pressure
- Aortic calcification
- Baroreceptor sensitivity

Long term efficacy results

RADIANCE-HTN and ACHIEVE Studies:

Office Systolic Blood Pressure up to 36 Months



**Long-term Durability Demonstrated in the
RADIANCE-HTN and ACHIEVE Studies**

* Medication titrated

1. Azizi et al. *Lancet*. 2018 Jun 9;391(10137):2335-2345. 2. Azizi et al. *Circulation*. 2019;139:2542-2553. 3. Azizi et al. *JACC Cardiovasc Interv*. 2020 Dec 28;13(24):2922-2933. 4. Rader et al. TCT 2021 5. Azizi et al. *Lancet*. 2021;397:2476-2486. 6. Kirtane et al. TCT 2021. 7. Daemen et al. *J Hypertens*. 2019 Sep;37(9):1906-1912. _____

24-Month Results From the SPYRAL HTN-ON MED Trial

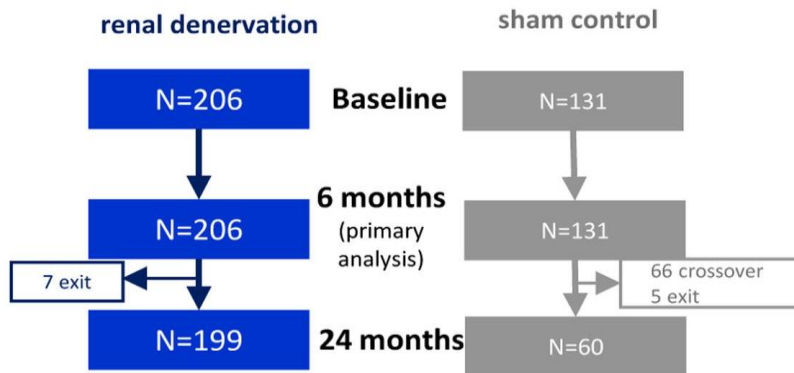
Long-Term Follow-up: SPYRAL HTN-ON MED Trial



TRIAL

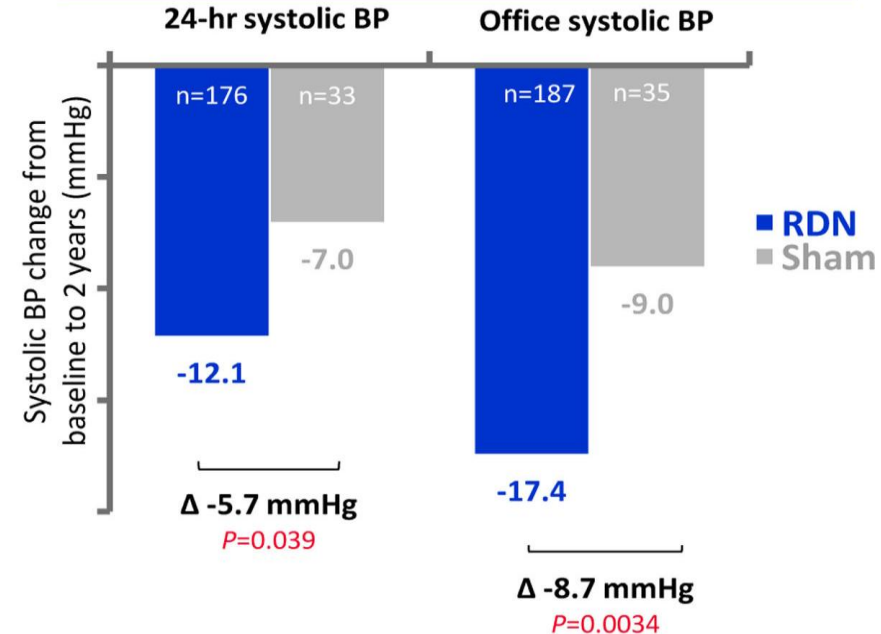
N=337; uncontrolled hypertension patients:

- **Office BP:** systolic 150 -180 / ≥ 90 diastolic mmHg
- **24-hr mean BP:** systolic 140 – 170 mmHg
- **Prescribed 1-3 antihypertensive medications**



- Drug testing suggested more antihypertensive medications in sham control at 2 years
- No renal artery stenosis >70% or reintervention through 2 years

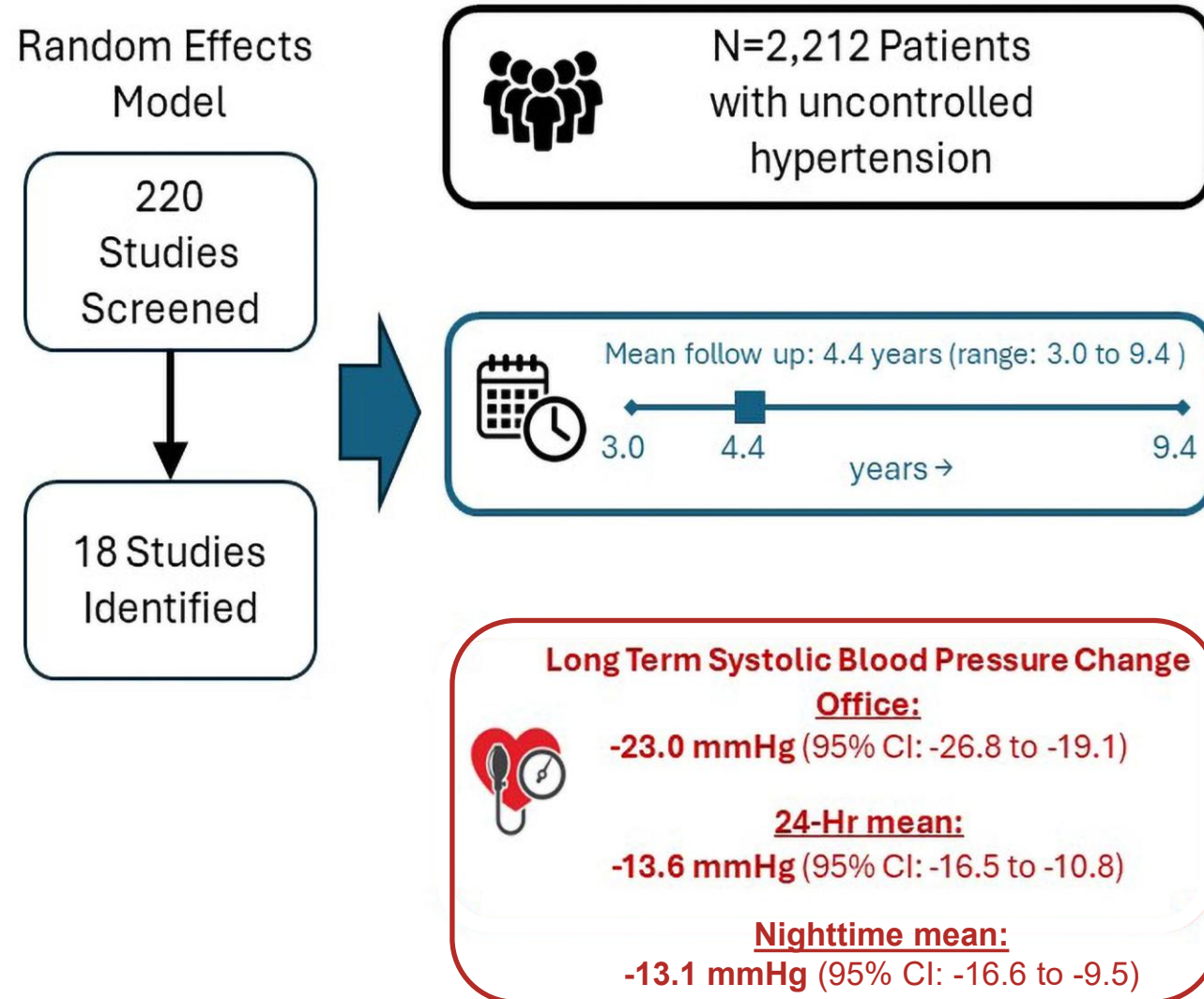
BP Changes at 2 Years



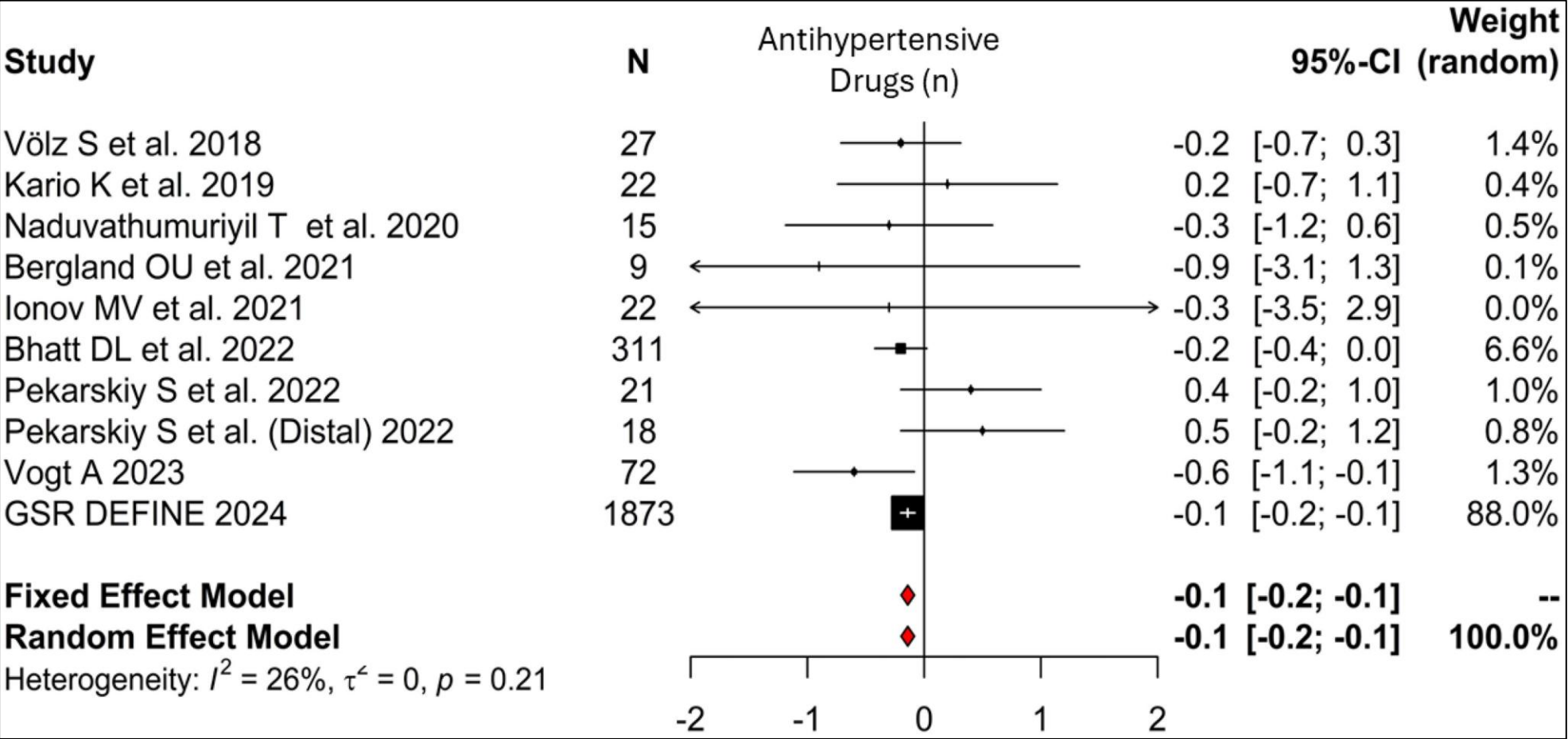
Conclusions

Renal denervation produced greater 24-hr and office systolic BP reductions at 2 years compared with sham control, despite higher medications in sham control.

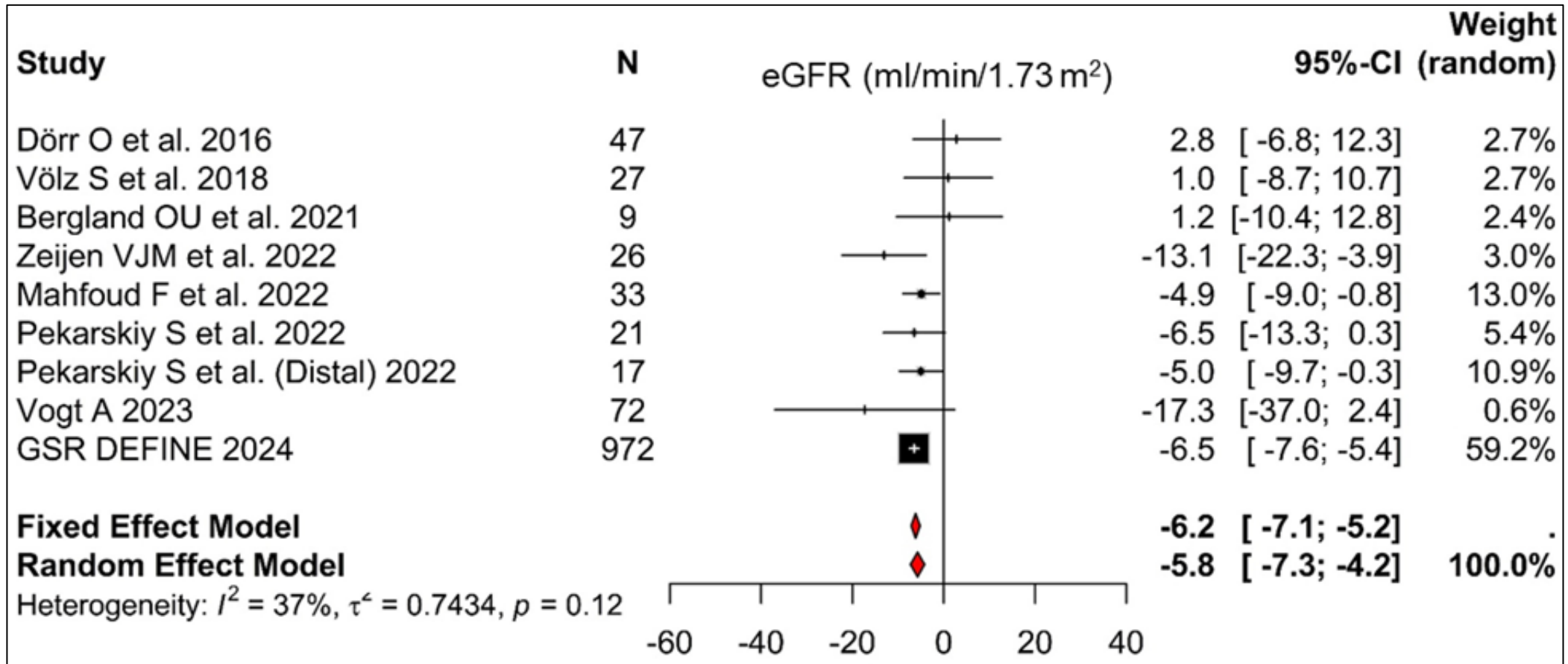
Long-term outcomes following RF-RDN



Long-term changes in the number of prescribed anti-hypertensive drugs



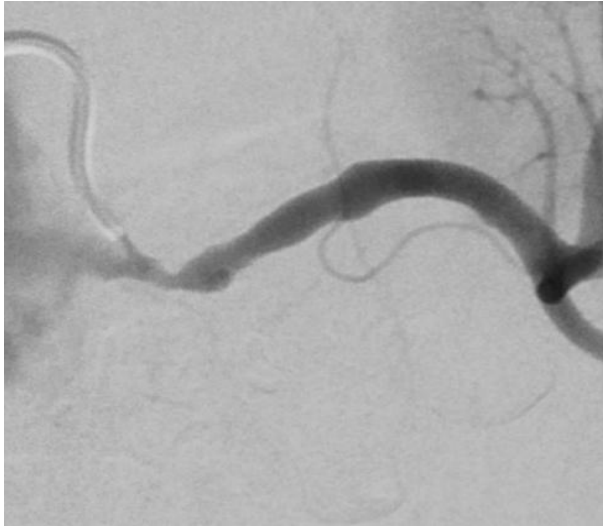
Long-term changes in eGFR



Safety results in the Global Symplivity registry

	6 months (number at risk ^a : 2237)	1 year (number at risk ^a : 2112)	2 years (number at risk ^a : 1917)	3 years (number at risk ^a : 1345)
Death	0.5 (10)	1.3 (28)	2.8 (54)	4.1 (59)
Cardiovascular events				
Cardiovascular death	0.3 (6)	0.8 (16)	1.5 (28)	2.0 (29)
Stroke	0.7 (15)	1.3 (27)	2.1 (41)	3.2 (47)
Hospitalization for new onset heart failure	0.7 (16)	1.1 (24)	2.0 (38)	3.2 (46)
Hospitalization for atrial fibrillation	0.7 (15)	1.5 (32)	2.4 (46)	3.0 (45)
Hospitalization for hypertensive crisis/hypertensive emergency	0.8 (17)	1.1 (24)	1.8 (36)	2.6 (40)
Myocardial infarction	0.7 (16)	1.1 (23)	1.6 (31)	2.2 (33)
Renal events				
New onset end-stage renal disease	0.2 (4)	0.4 (9)	1.0 (19)	1.6 (23)
Serum creatinine elevation >50% mg/dL	0.4 (9)	0.9 (19)	1.2 (24)	1.5 (24)
New artery stenosis (>70% diameter stenosis)	0.05 (1)	0.1 (3)	0.2 (4)	0.3 (4)
Post-procedural events				
Non-cardiovascular death	0.1 (2)	0.3 (7)	1.0 (19)	1.6 (22)
Renal artery reintervention	0.2 (5)	0.4 (8)	0.4 (9)	0.6 (10)

Renal artery stenosis following renal denervation

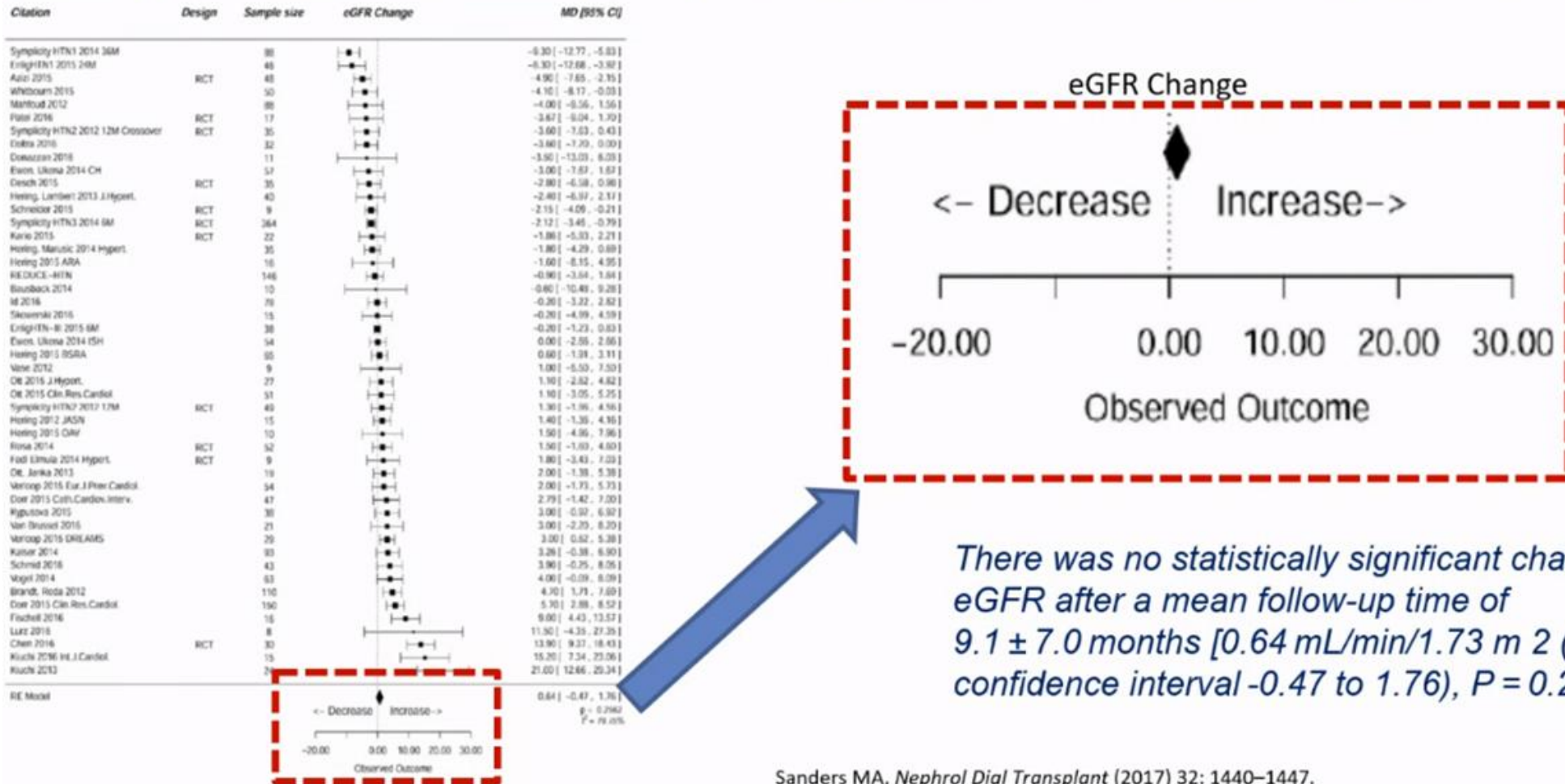


50 published renal denervation (RDN) trials
5,769 subjects with 10,249 patient-years of follow-up

- 26 patients with renal artery stenosis or dissection (0.45%)
- 24 patients(0.41%) renal artery stenting.
- 0.20% pooled annual incidence rate of stent implantation (95% CI: 0.12 to 0.29% per year).
- Median time of occurrence: 5.5 months (0 to 33 months)
- 79% of events occurred within one year of RDN
- Follow-up imaging in 511 subjects : 1 new significant RAS (0.20%) after a median of 11 months post RND

Renal safety of RDN

Forest plot of 48 RDN cohorts, 2381 patients, with information on change in eGFR_{Renal}



There was no statistically significant change in eGFR after a mean follow-up time of 9.1 ± 7.0 months [0.64 mL/min/1.73 m² (95% confidence interval -0.47 to 1.76), $P = 0.26$].

Renal denervation systems



Main indications (2022 ESC/EAPCI clinical consensus statement & 2023 ESH hypertension guidelines):

- Uncontrolled hypertension confirmed by ABPM
- ≥ 3 antihypertensives or < 3 drugs, if treatment elicits serious side effects
- eGFR ≥ 40 ml/min/1.73 m²

Centre qualifications:

- Multidisciplinary hypertension team including hypertension specialists & specifically trained interventionalists

FDA-approved systems:



Paradise
(US, 7 Fr,
CE-marked)



Symplicity Spyral
(RF, 6 Fr,
CE-marked)

Catheter systems under investigation:



Netrod
(RF, 8 Fr,
CE-marked)



Iberis
(RF, 6 Fr,
CE-marked)



SyMapCath
(mapping &
RF, 6-7 Fr,
not CE-marked)



Peregrine
(alcohol-
mediated, 7 Fr,
CE-marked)

Procedural considerations:

- Safe arterial access & closure (e.g., US-guided puncture, use of closure devices)
- Adequate analgesia & sedation
- Start treatment distally and then move proximally
- Standard operating procedures (SOPs) are needed for each device

Current RDN Catheter Systems in Sham-Controlled Trials

	Netrod (Shanghai Golden Leaf MedTec)	Multielectrode (6 electrodes), basket-shaped tip, 120 s per ablation cycle	Uncontrolled hypertension without medication: EuroNetrod (not yet recruiting; NCT06722651) Uncontrolled hypertension despite medication: Netrod RDN (n = 205) ⁶²
	Iberis second-generation (AngioCare)	Multielectrode (4 monopolar electrodes), helical design, over-the-wire catheter, 60 s per ablation cycle, 90-cm catheter length for transfemoral and 160 cm for transradial RDN	Uncontrolled hypertension despite medication: Iberis-HTN (n = 217) ⁶¹
	SyMapCath I (SyMap)	Steerable monoelectrode stimulation and ablation catheter, stimulation time 20-120 s, 120 s per ablation cycle	Uncontrolled hypertension despite medication: SMART (n = 220) ⁸⁷
	TIVUS (SoniVie)	Unidirectional steerable or multidirectional, over-the-wire, 30 s per emission	Uncontrolled hypertension without medication: THRIVE (ongoing; NCT06559891)

Who to treat?

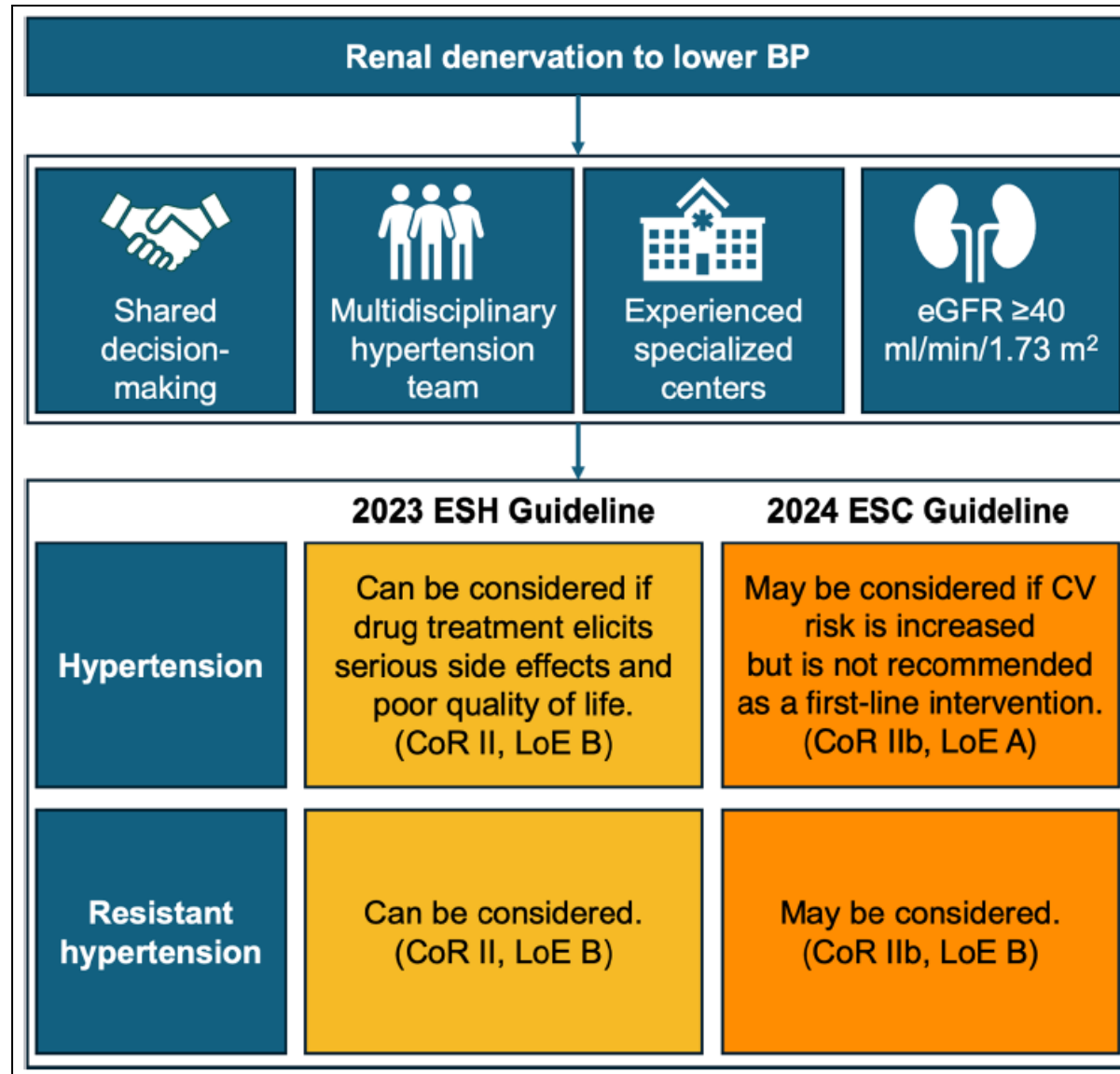
Indications of RDN in international guidelines or consensus statements

Indication	AHA 2025	ESC 2024	AHA 2024	ESH 2023
Uncontrolled hypertension		+	+	+*
Resistant hypertension	+	+	+	+
Intolerant to AHM	+		+	+
Non-adherent to AHM			+	
High CV risk / severe HMOD		+		

* Despite antihypertensive drug combination therapy

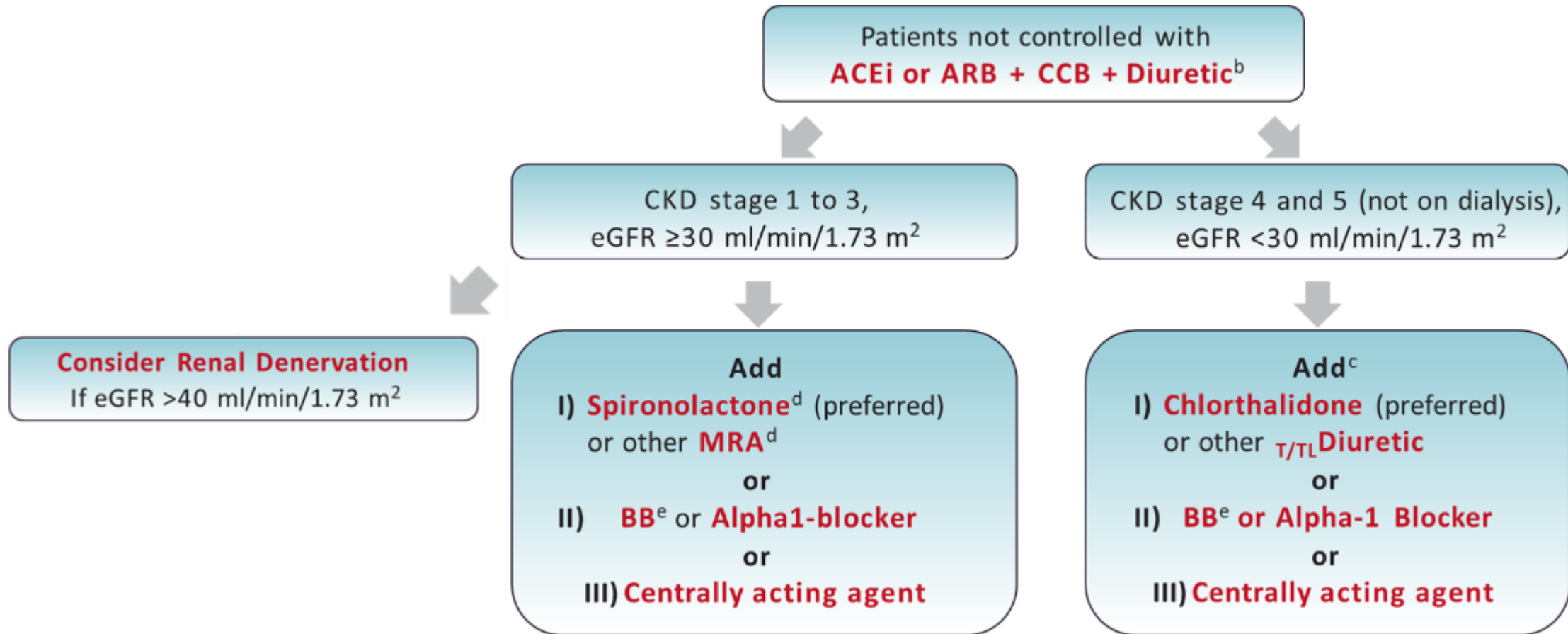
** BP >140 and 90 mm Hg despite taking ≥4 antihypertensive medications at optimal dosages (ACEi/ARB +CCB+thiazide-type diuretics, and MRA)

European Guideline Recommendations for RDN for the Treatment of Patients With Hypertension



Summary

BP-lowering strategy in true resistant hypertension



Preprocedural imaging

1. Non-invasive imaging : abdominal/pelvic CTA or MRA preferentially to duplex ultrasound

- presence of accessory arteries
- anatomical ineligibility criteria
 - inappropriate vessel diameter/ early bifurcation
 - atherosclerotic renal artery stenosis $\geq 30\%$
 - renal artery stenting
 - FMD of renal arteries whatever the degree of stenosis
 - single functional or solitary kidney
 - transplanted kidney
 - extensive abdominal aortic calcifications

2. Selective renal angiography immediately before RDN remains the gold standard since CTA or MRA may miss some renal artery abnormalities such as FMD.

Endovascular interventionalists training and center eligibility

1. The interventionalist cardiologists/radiologists

- should have expertise in access site management, in radiation protection and in specific aspects related to RDN and renal artery catheterization or stenting
- should undergo specific training in RDN procedures in practical and/or simulated sessions, proctored sessions, RDN centre visits, hands-on with commercially available devices.

2. Center eligibility for an RDN program

- Access to inpatient services
- Access to imaging facilities, catheterization room,
- Access to intensive care unit
- Access to vascular surgery services
- Access can be on site or remotely

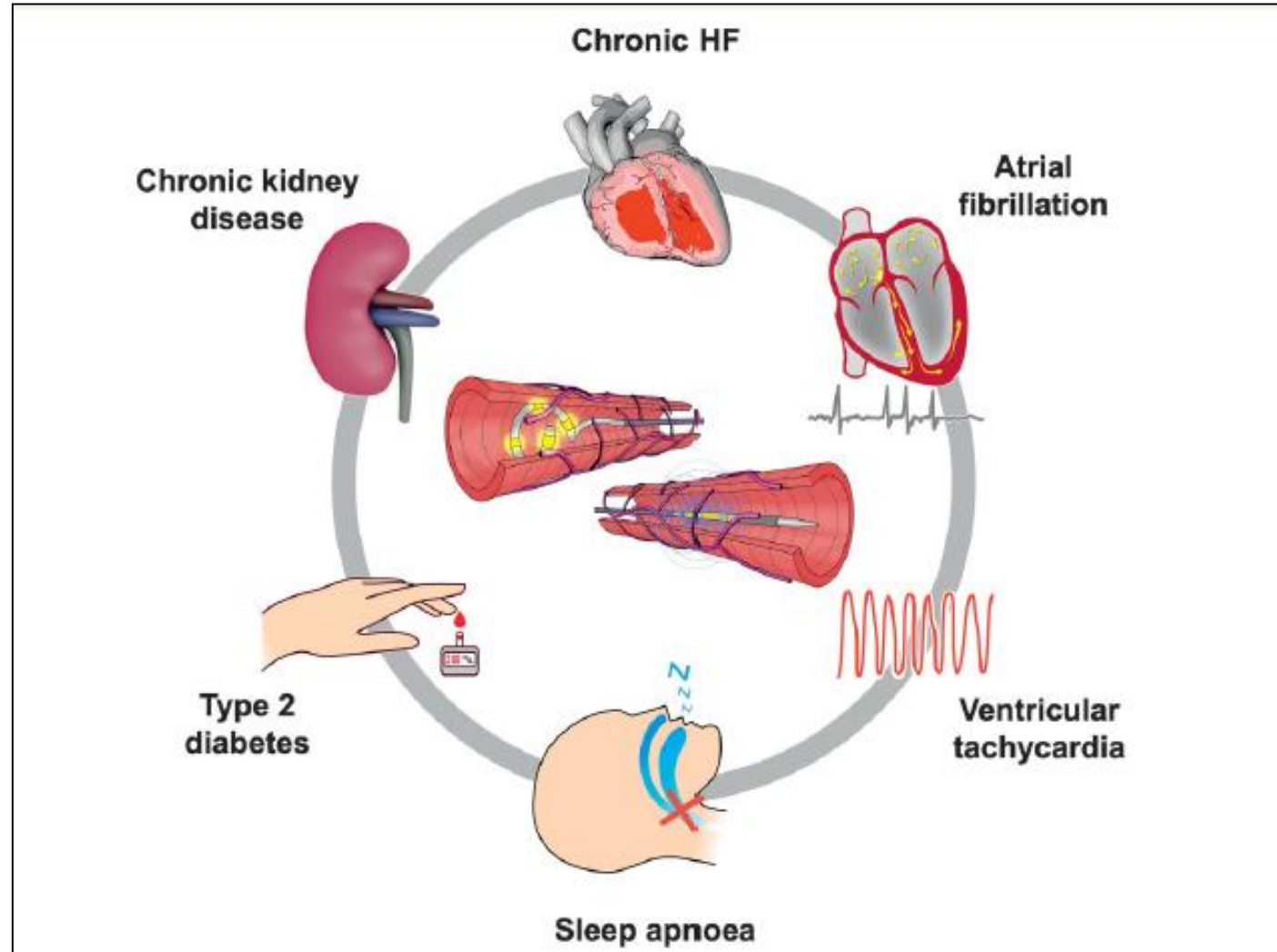
Periprocedural management

- Pre-anaesthesia consultation:
 - RDN is performed under sedation or short general anaesthesia because the procedure is painful.
- Anticoagulant treatments may be temporarily suspended based on the individual risk/benefit balance to limit bleeding complications related to the access site.
- The patient's antihypertensive medications are continued, including on the day of the intervention, unless there is an anaesthetic contraindication.
- The total duration of the procedure is approximately 1 hour and the patient is monitored until the following morning in the hospital.
- Risks of complications at the femoral access site may be minimized using US-guided arterial puncture and arterial closure systems at the end of the procedure
- Aspirin 75–100 mg/d may be given for 1 month after the procedure (low level of evidence)
- Outpatient intervention can be organized, provided clear follow-up instructions are provided to the patient

Follow-up after RDN

1. Optimization of antihypertensive medications after RDN and follow-up of the hypertensive disease.
2. Plasma creatinine can be measured within 30 days, depending on the pre-RDN eGFR and the amount of contrast media injected during RDN.
3. Despite the rarity of renal complications, we suggest performing a renal CTA or Duplex US between 6 months and 1 year after RDN to detect the occurrence of *de novo* renal artery stenosis.
4. BP follow-up with out-of-office BP measurements (HBPM or ABPM) at least at 1–3, 6 and 12 months.
5. HBPM allows the reduction of antihypertensive medication if there is a large decrease in BP and the optimization of therapy in case of persistent uncontrolled BP.

Potential indications of RDN beyond hypertension



Patient considerations and Themes Across Consensus Statements

Universal Patient Consideration themes across Statements



Elevated
BP

Blood pressure (BP) uncontrolled despite attempted hypertensive medications

Merci pour votre attention!