Interventional treatment of hypertension: Back again?

Michel Azizi,
Université Paris Cité,
Hypertension Unit,
Hopital Européen Georges Pompidou
CIC INSERM
Paris, France

Disclosures

Receipt of grants / research supports:

Recor, Idorsia, Quantum genomics, French Ministry of Health, European Horizon 2020 programme

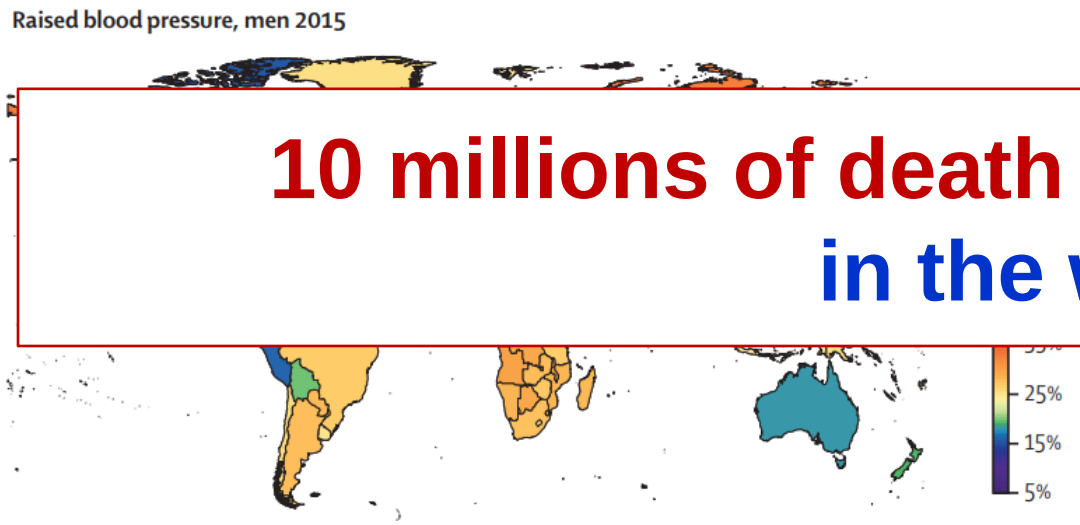
Receipt of honoraria or consultation fees:

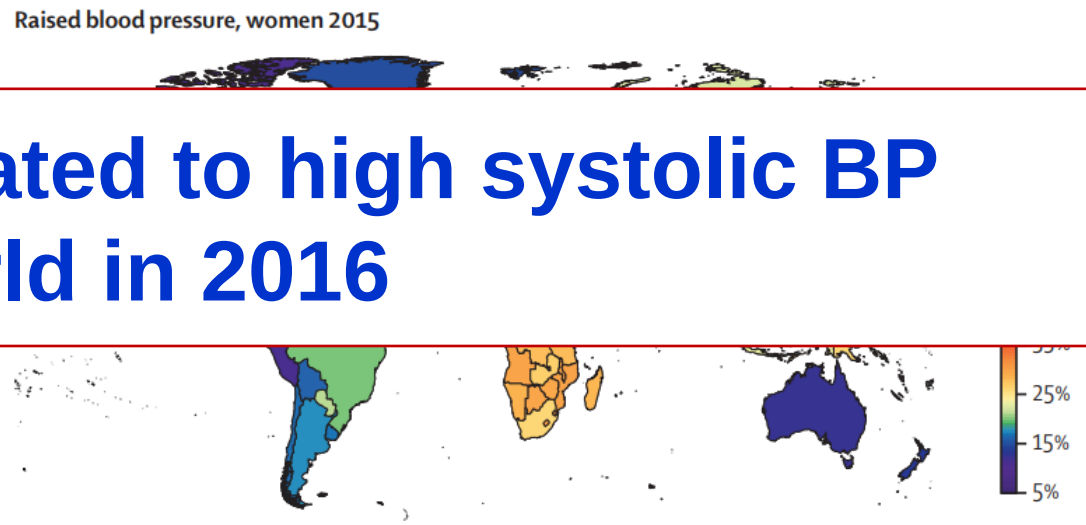
Alnylam, Poxel, Astra Zeneca, CVRx, Novartis, Medtronic

The number of adults with raised BP increased from 594 M in 1975 to 1.13 B in 2015

Prevalence of raised BP in men in 2015
24·1% (21·4–27·1)

Prevalence of raised BP in women in 2015
20·1% (17·8–22·5)



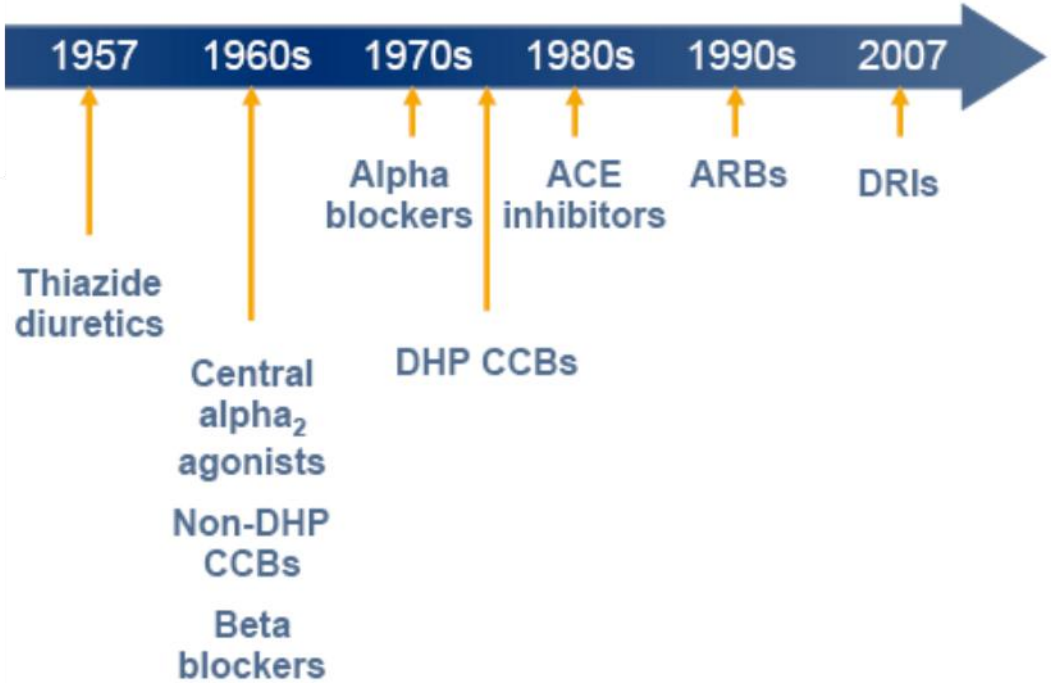


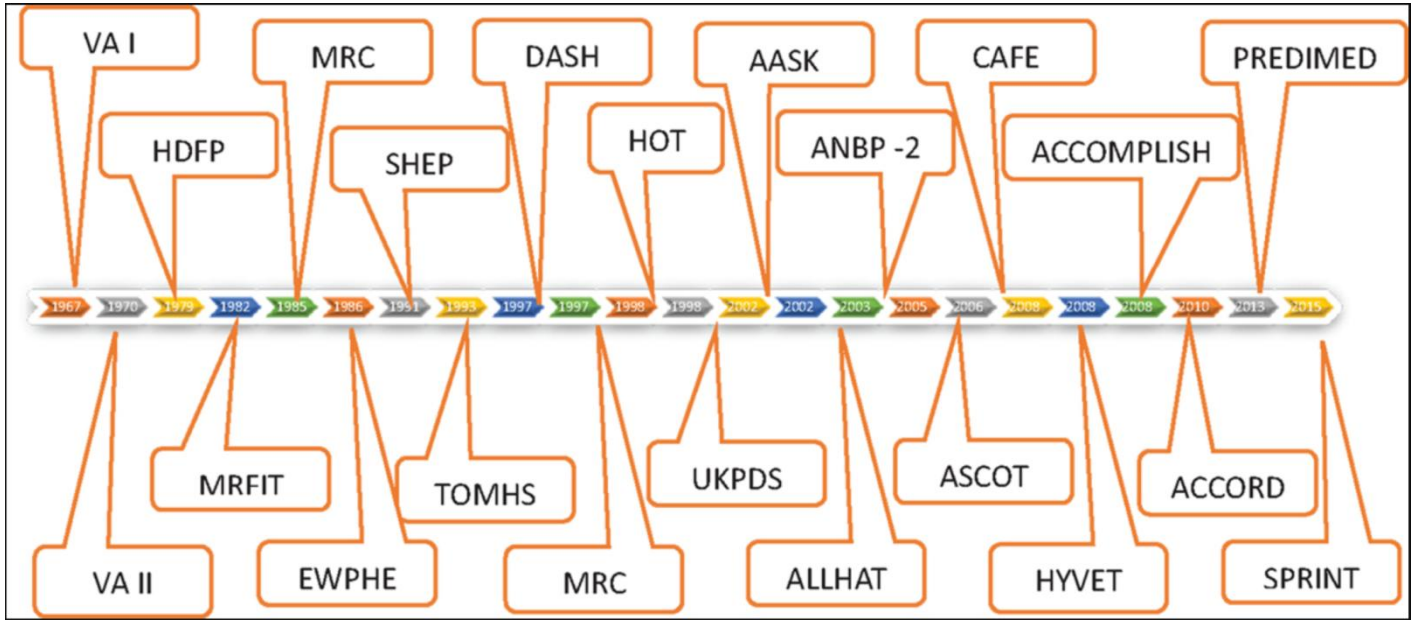
10 millions of death related to high systolic BP in the world in 2016

increase largely in low-income and middle-income countries.

NCD Risk. Lancet 2017; 389: 37–55

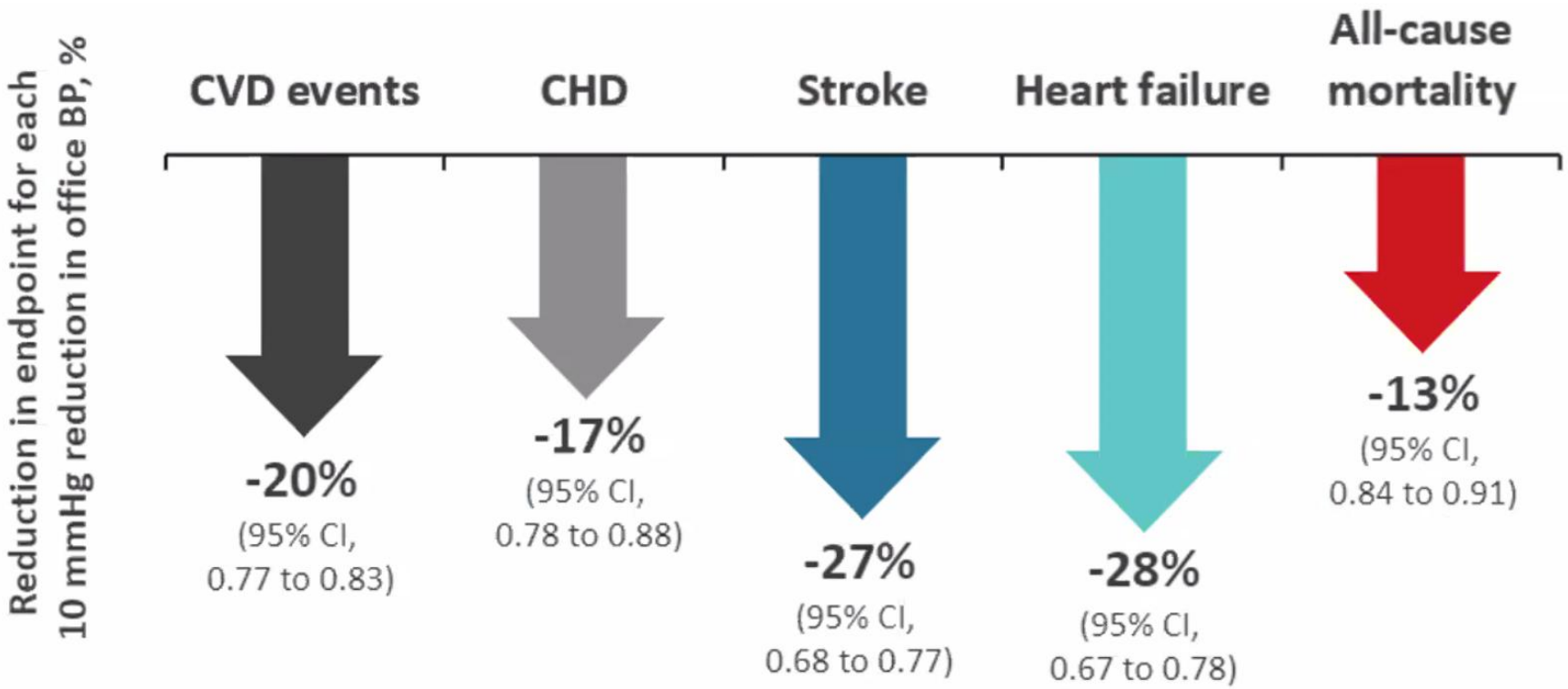
Timeline of RCT of Hypertension Treatment





Saklayen MG Front. Cardiovasc. Med. 2016; 3:3.

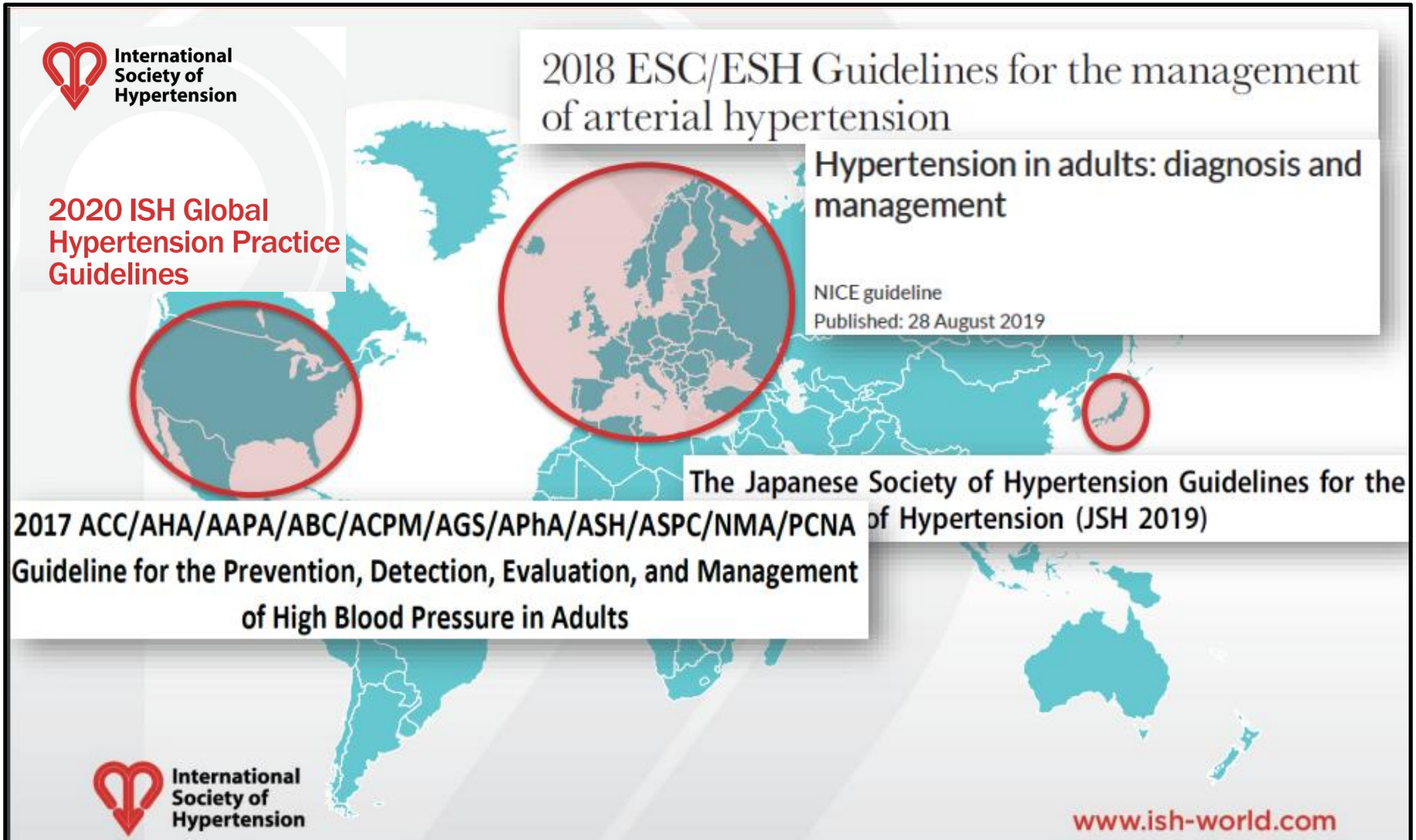
Benefits of SBP reduction



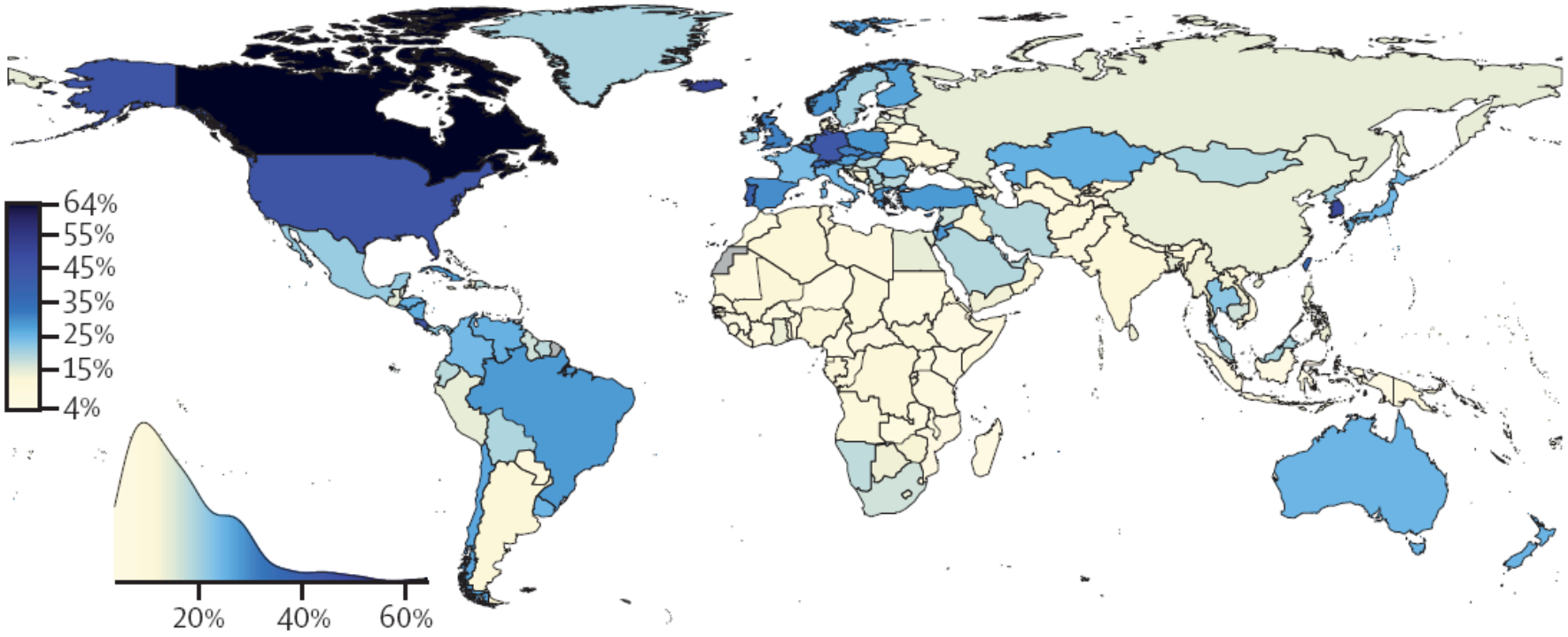
Each reduction in BP of 10 mmHg leads to vascular risk reductions

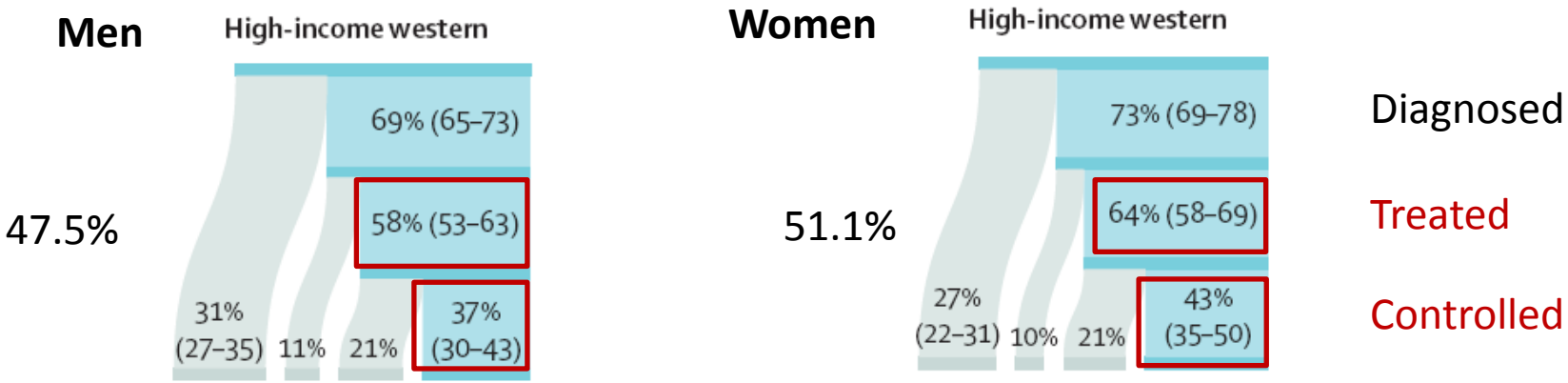
Systematic review and meta-analysis of large-scale BP-lowering trials, published between January 1, 1966, and July 7, 2015.
BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease.
Adapted from Ettehad D, et al. *Lancet* 2016;387:957-67.

Hundreds of pages of guidelines



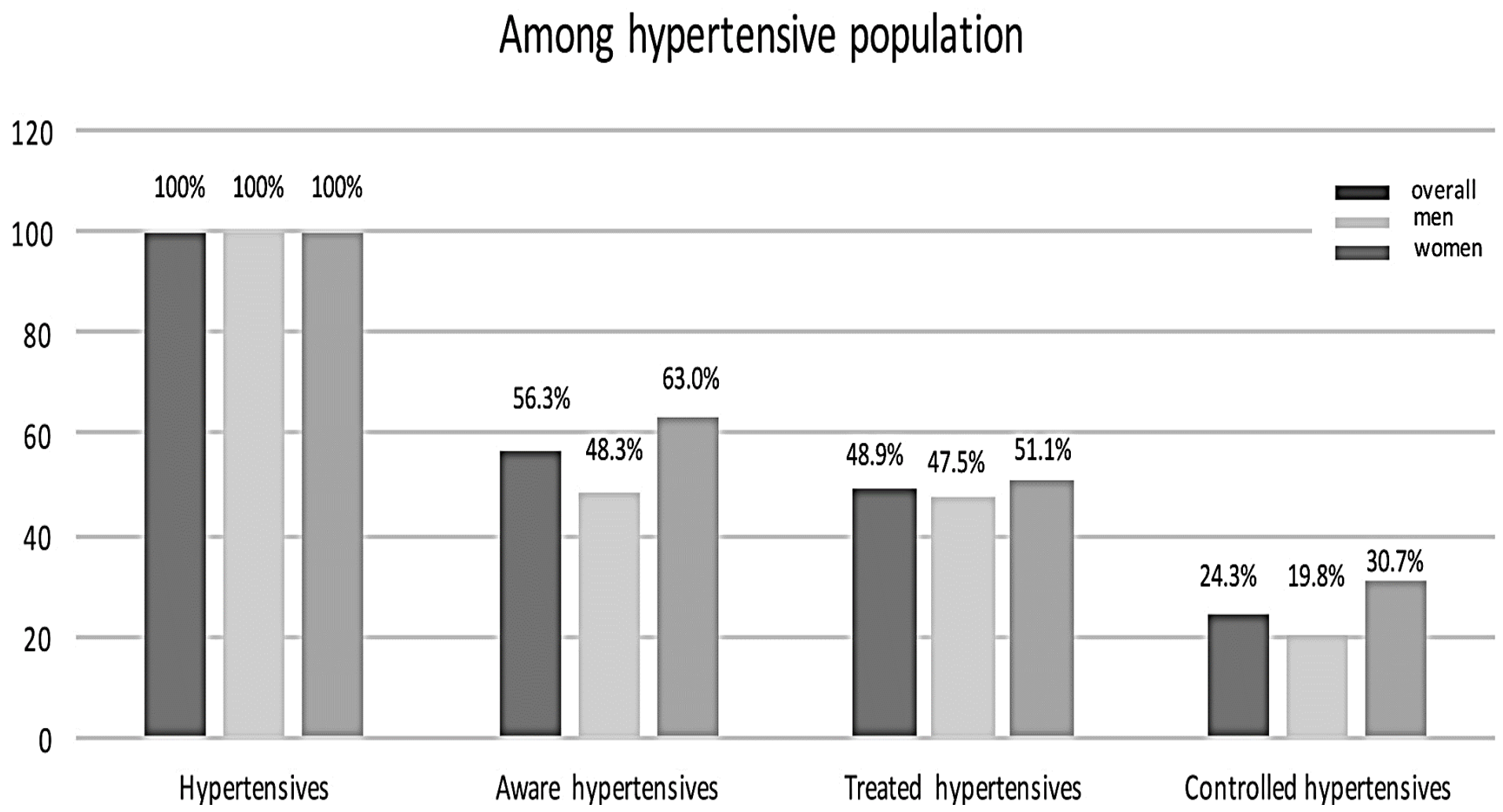
Worldwide control rate of HTN in 2019





NCD-RisC. . Lancet. 2021;398:957

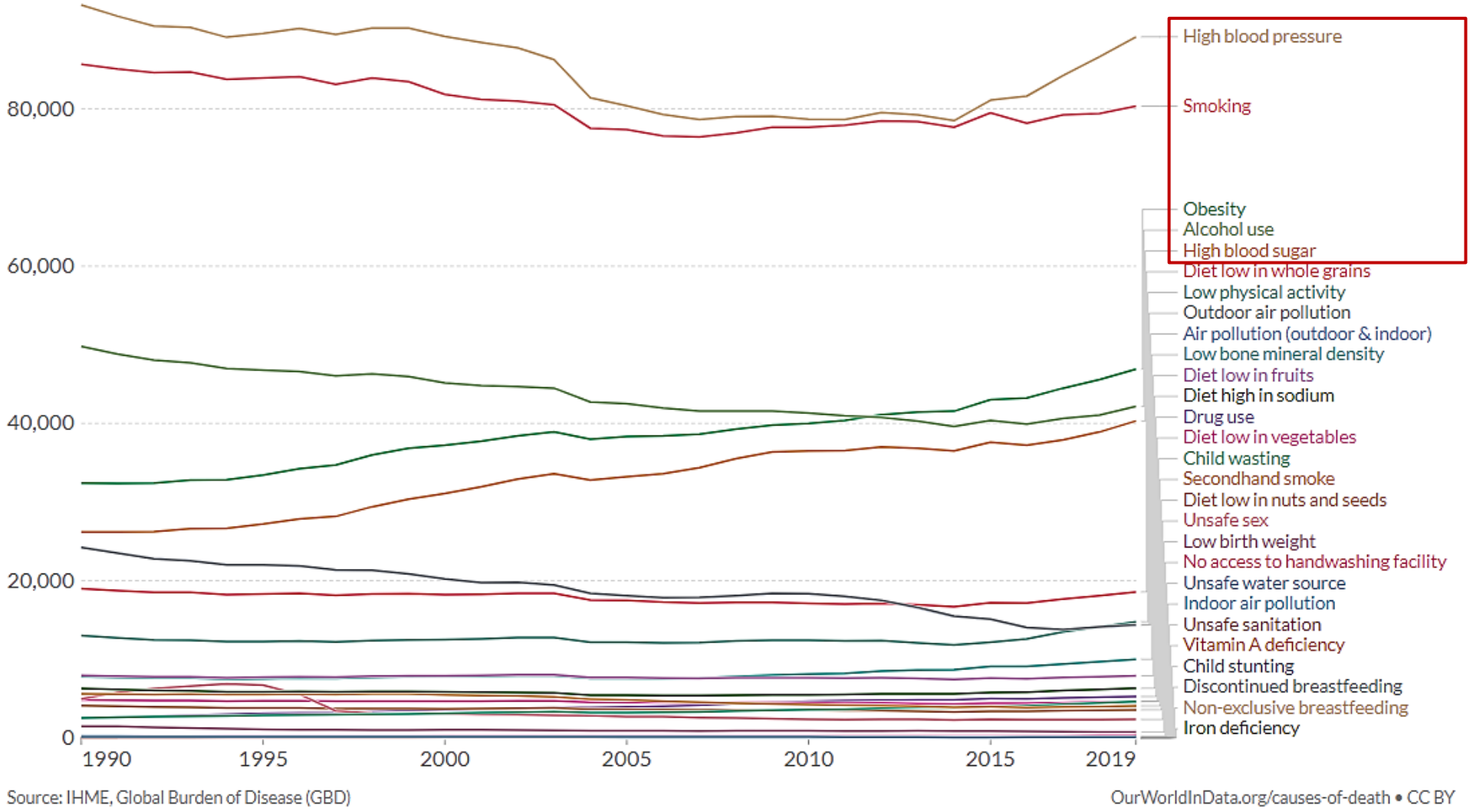
Patterns of hypertension management in France in 2015: The ESTEBAN survey



Vallée A. J Clin Hypertens. 2020 Apr;22(4):663

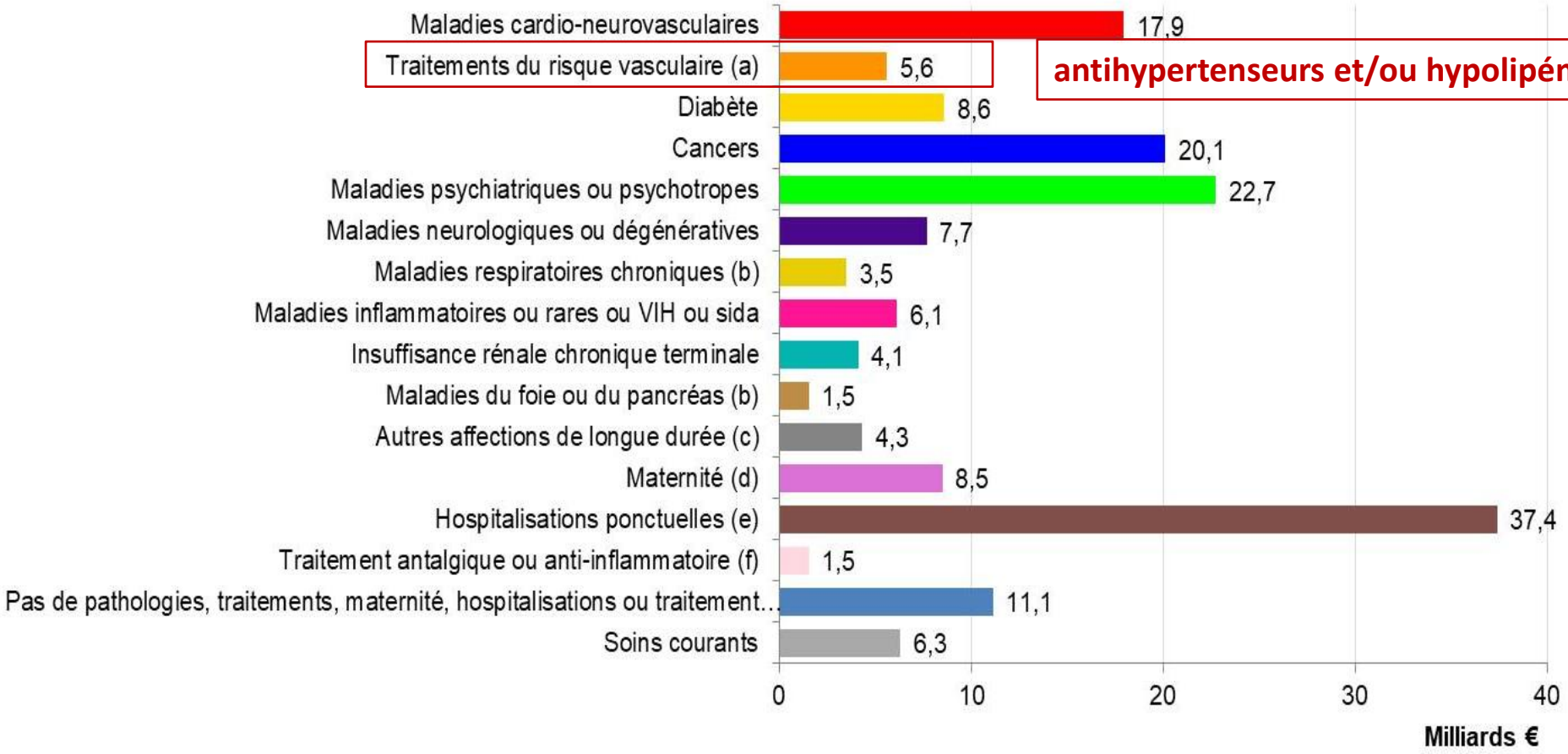
Number of deaths by risk factor, France, 1990 to 2019

Our World in Data



https://ourworldindata.org/

2019 – dépenses par catégorie de pathologies, traitements chroniques et épisodes de soins



antihypertenseurs et/ou hypolipémiants (3%, 661 €/ patient)

Total
167 Milliards €

(a) hors pathologies
(b) hors mucoviscidose
(c) dont 31 et 32
(d) avec ou sans pathologies
(e) avec ou sans pathologies, traitements ou maternité
(f) hors pathologies, traitements, maternité ou hospitalisations

CNAM-Dr RIO B-14-09-21

Champ : tous régimes, dépenses remboursées - France entière
Source : Cnam (cartographie version de juillet 2021)

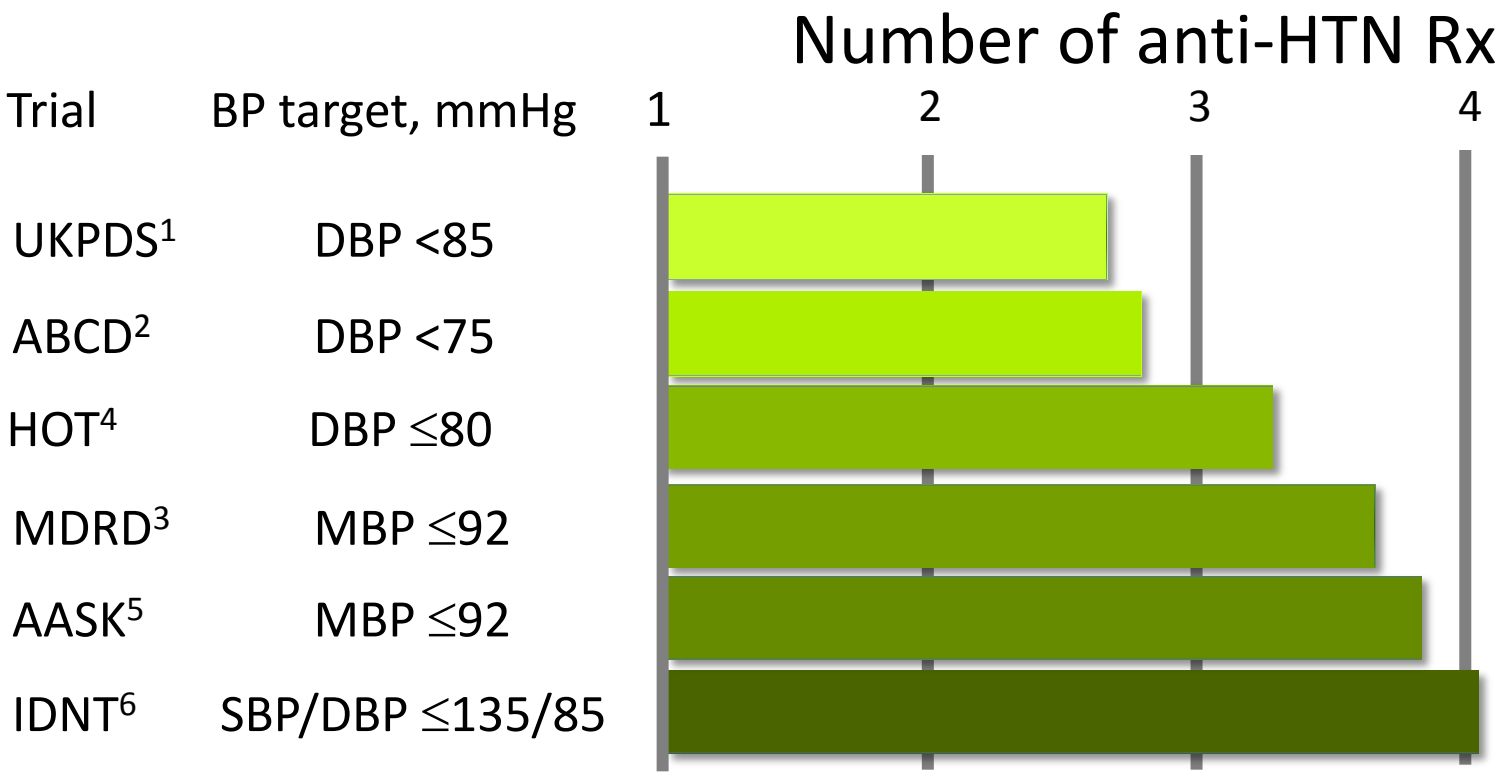
BP can be controlled but other factors affect the rate of control

The 2018 ESH−ESC guidelines have identified key factors involved in suboptimal BP control:

- Therapeutic/physician inertia
- Low patient adherence to treatment
- Deficiencies of healthcare systems in their approach to chronic diseases

Williams B et al *Eur Heart J 2018*

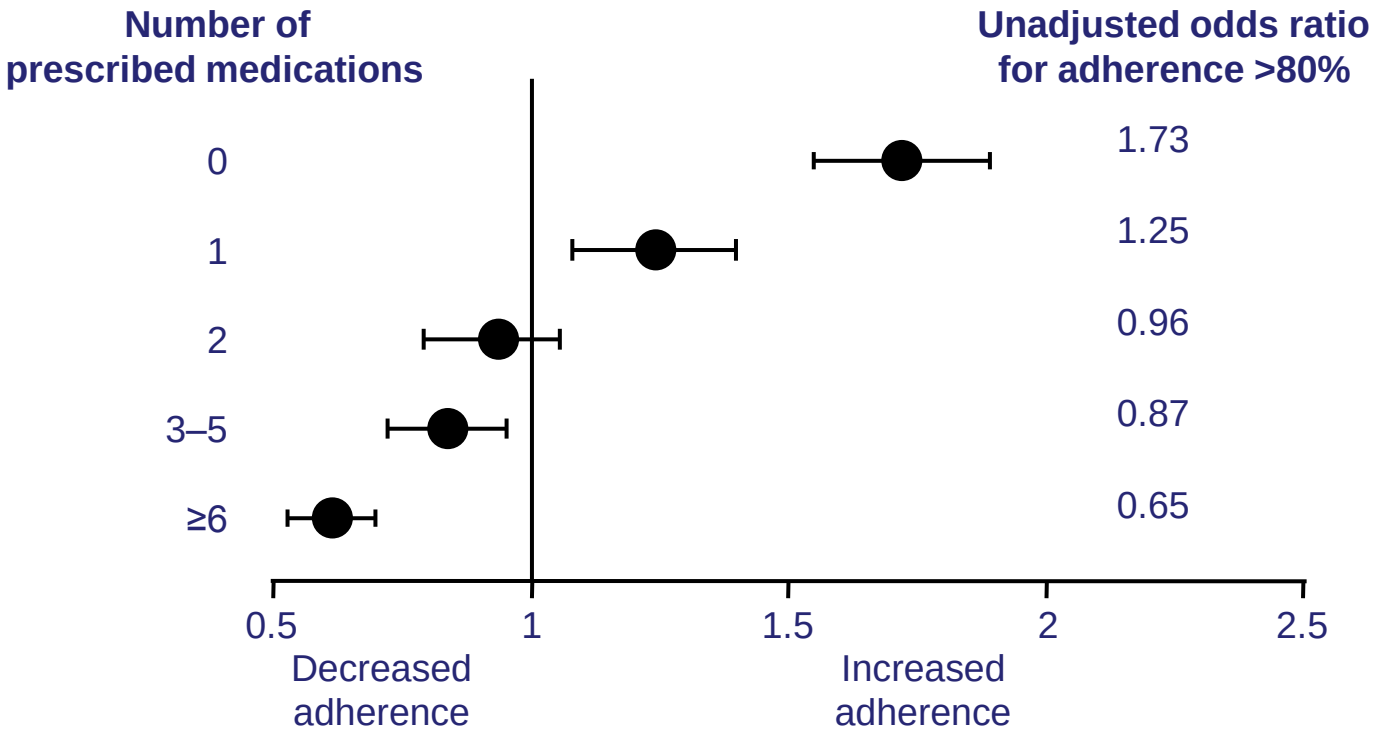
Multiple antihypertensive drug therapy is necessary to control BP



[1]UKPDS, BMJ 1998;317:703
[2]Estacio RO, Am J Cardiol 1998;82:9R
[3]Lazarus JM, Hypertension 1997;29:6
[4]Hansson L, Lancet 1998; 51:1755
[5]Kusek JW, Control Clin Trials1996;16:40S
[6]Lewis EJ, N Engl J Med 2001;345:851

The more you give the less they take !

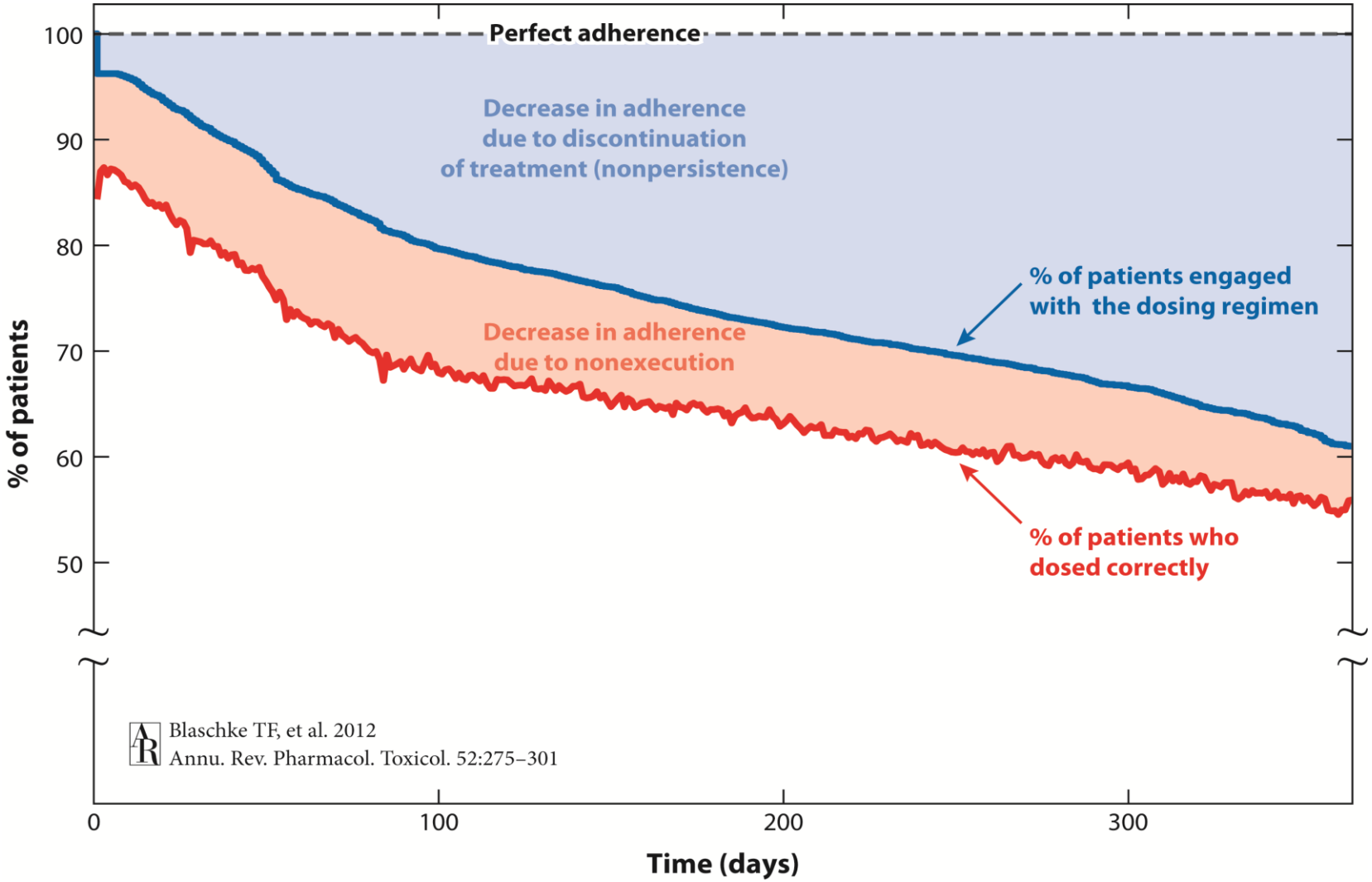
As the number of prescribed medications increases, the likelihood of adherence decreases



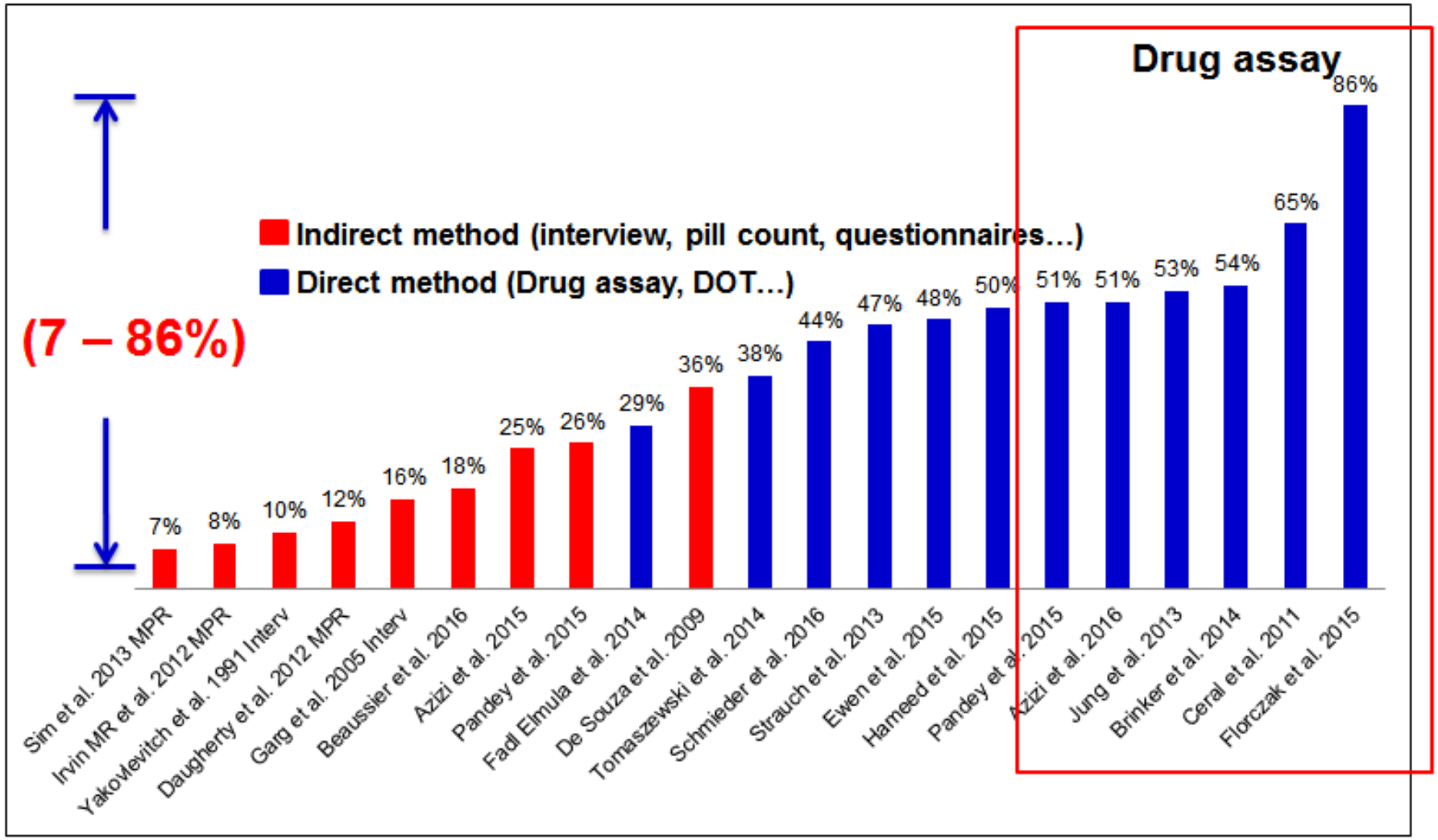
Retrospective study of 8,406 managed care patients with hypertension who added antihypertensive and/or lipid-lowering drugs to existing prescribed meds.

Chapman RH, et al. *Arch Intern Med* 2005;165:1147–52

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



Prevalence of non-adherence in apparent resistant hypertension



Lay perspectives on hypertension and drug adherence

1. Patients often actively decide to avoid drugs without consulting their doctor

2. Patients often rely on the presence of stress or symptoms to determine whether their BP was raised
   - many reduce or stop drugs in response to fewer symptoms or less stress

3. Patients dislike treatment and its side effects and fear addiction.

Marshall IJ. BMJ. 2012; 345: e3953.

- **8.2% of adults would give up 2 years of their life to avoid adding one daily pill!**
- **Up to 30% of Adults Would Rather Die Early than Submit to Lifelong Polypharmacy !**

Hutchins et al. *Circ Cardiovasc Qual Outcomes*. 2015;8.

Apparent Resistant hypertension

1. Estimated Prevalence : 5 to 25% in tertiary Hypertension Clinics
   > 50 % in patients with CKD*
   8-12 % in general population

2. Incidence: 0.7 cases per 100 person-years follow-up
   (≈ 1/50 pts develop aTRH within 1.5 yrs)

2. Associated with TOD and high cardiovascular risk

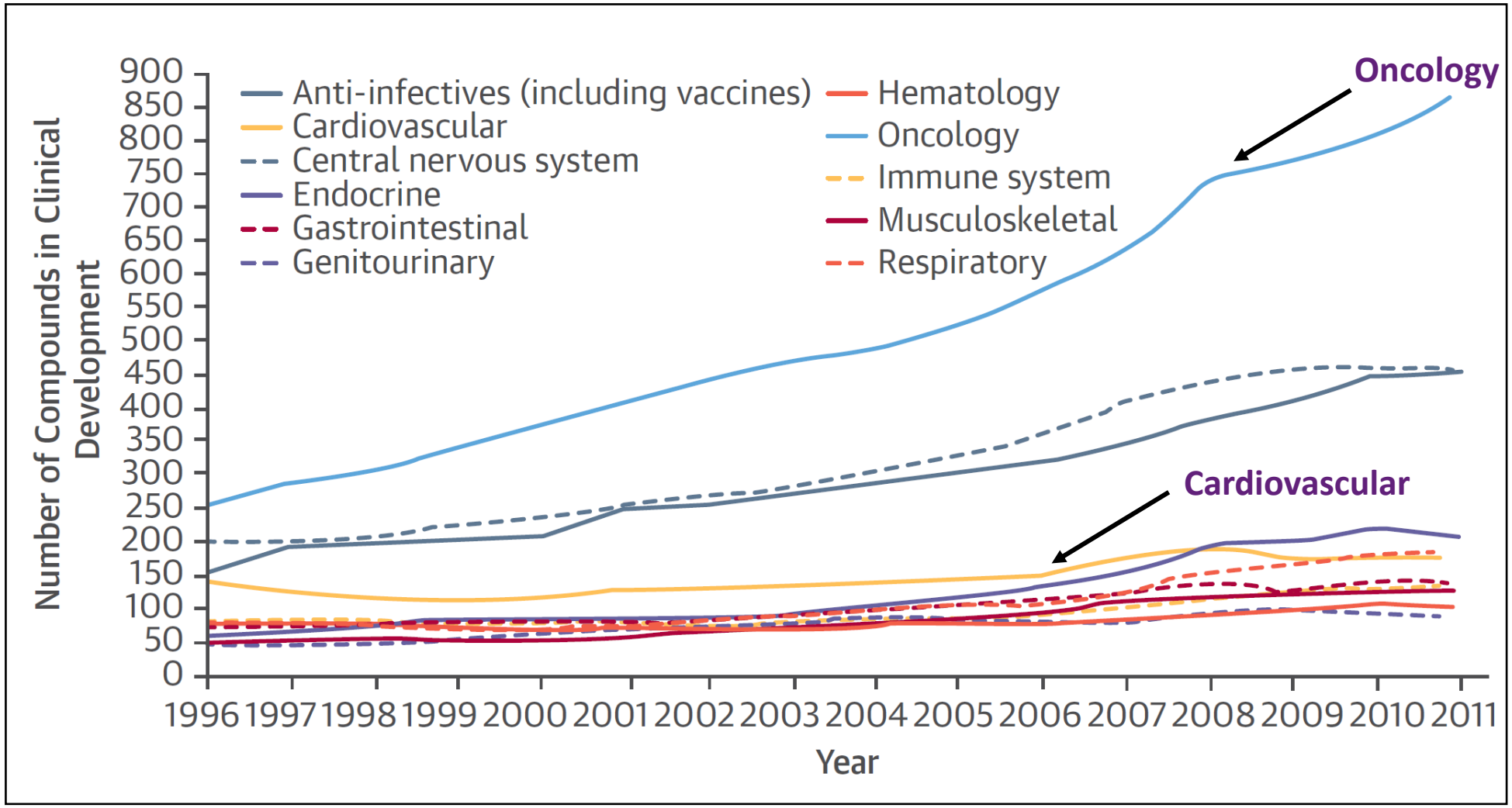
3. Associated with increased CV morbidity and mortality

Calhoun et al Circulation 2008;117:e510
de la Sierra A et al. Hypertension. 2011;57:898

Persell SD. Hypertension. 2011;57
Daugherty SL et al. Circulation 2012, 125:1635
Tanner RM et al. CJASN 2013;8:1583

Any new treatments?

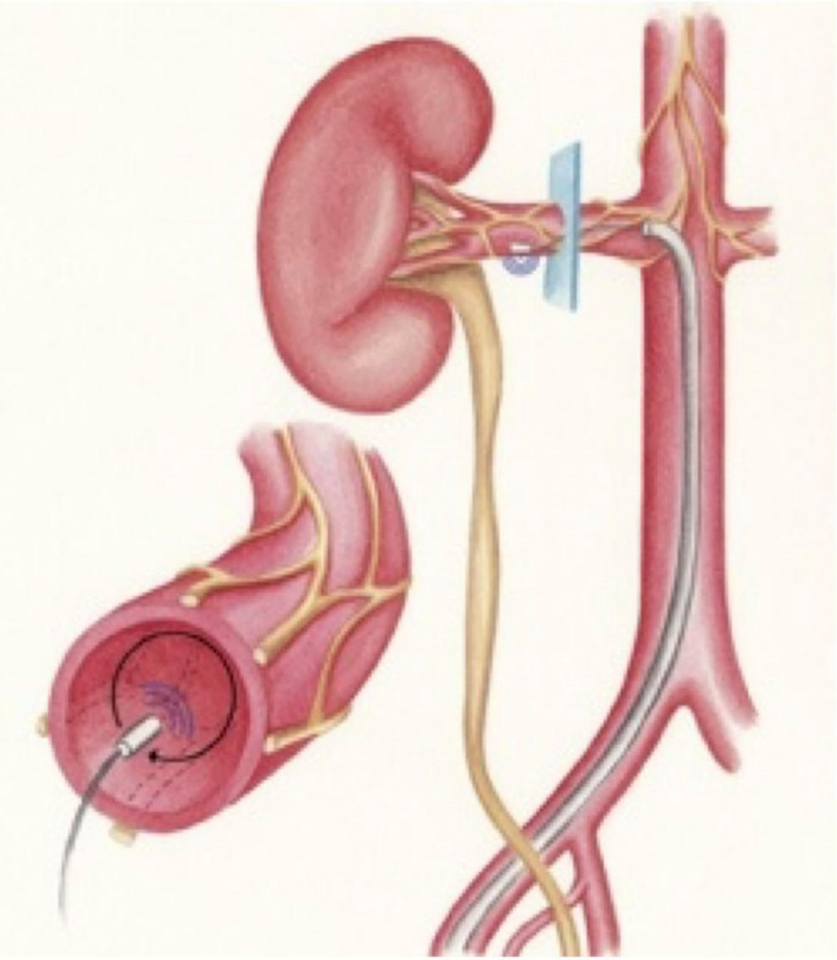
Innovative Compounds Between Phase I and III Development Over Time



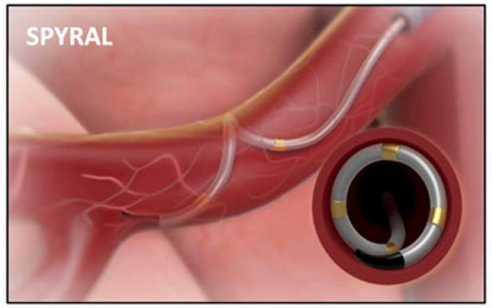
Fordyce CB J Am Coll Cardiol 2015;65:1567

Renal denervation systems

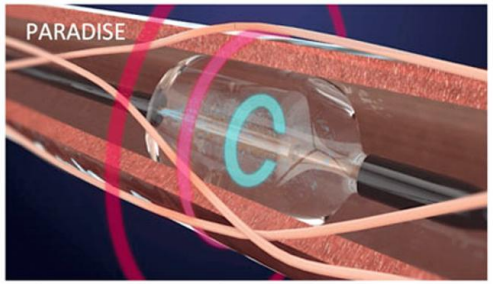
Aim: circumferential ablation of renal afferent and efferent nerves



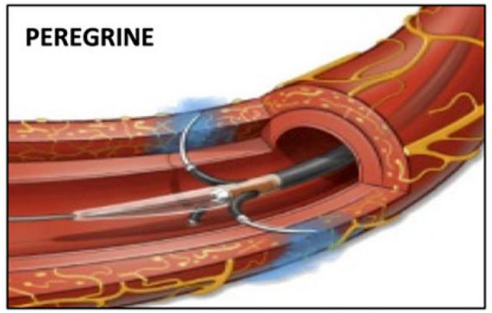
Approaches:



Multi-electrode radiofrequency ablation



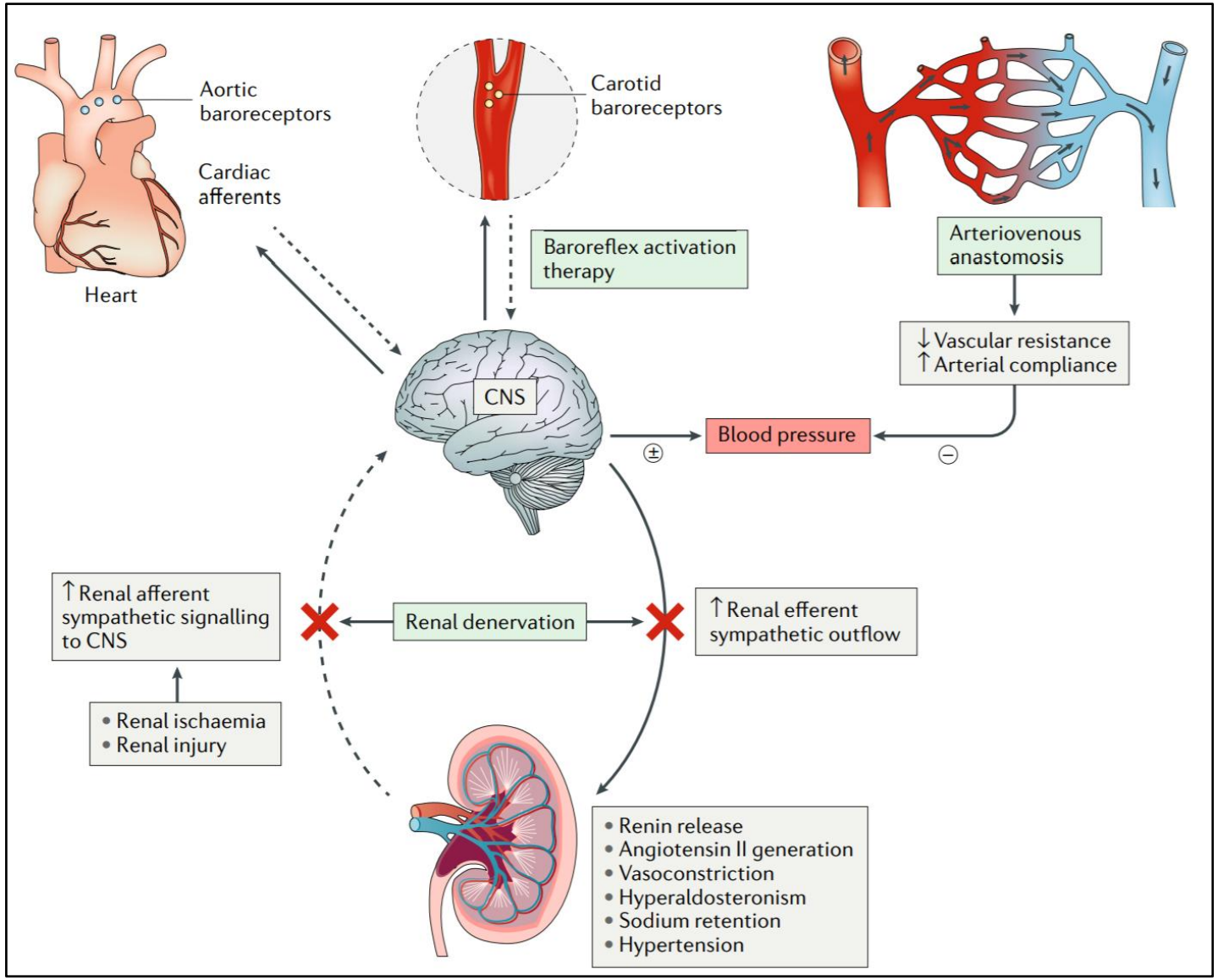
Ultrasound-based nerve ablation



Alcohol-mediated perivascular denervation

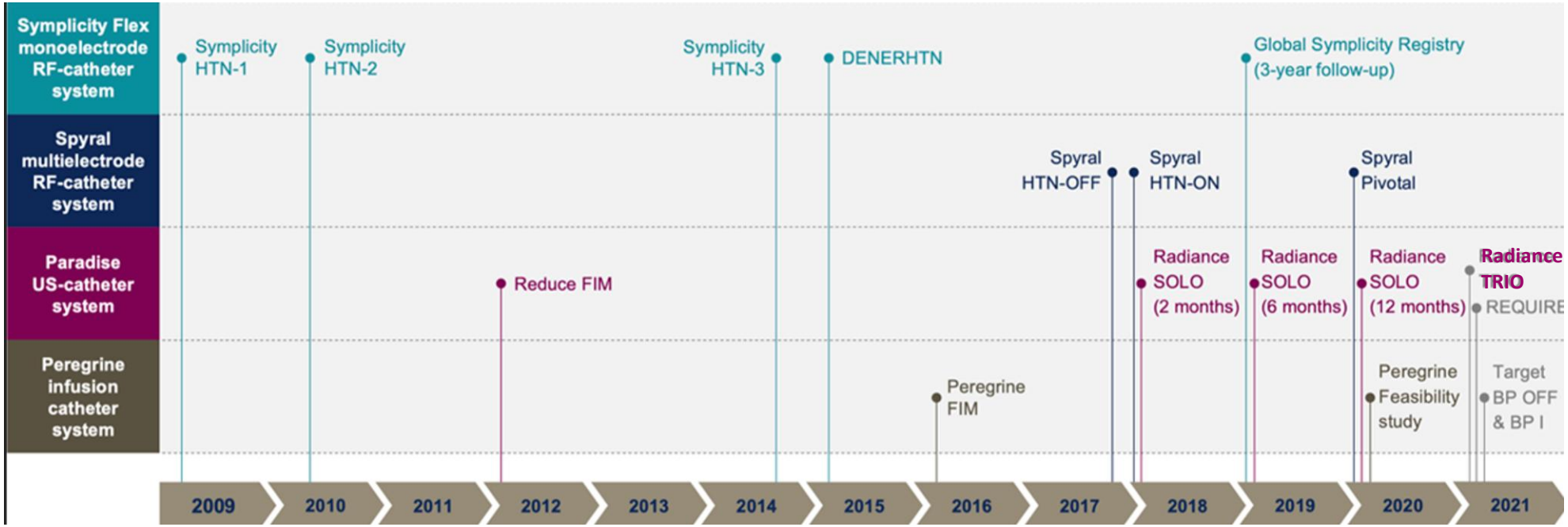
Mahfoud F Circ Res. 2021 Apr 2;128(7):1080

Rationale for use of device therapy in hypertension



Wei FF Nature Reviews | Nephrology, 2018

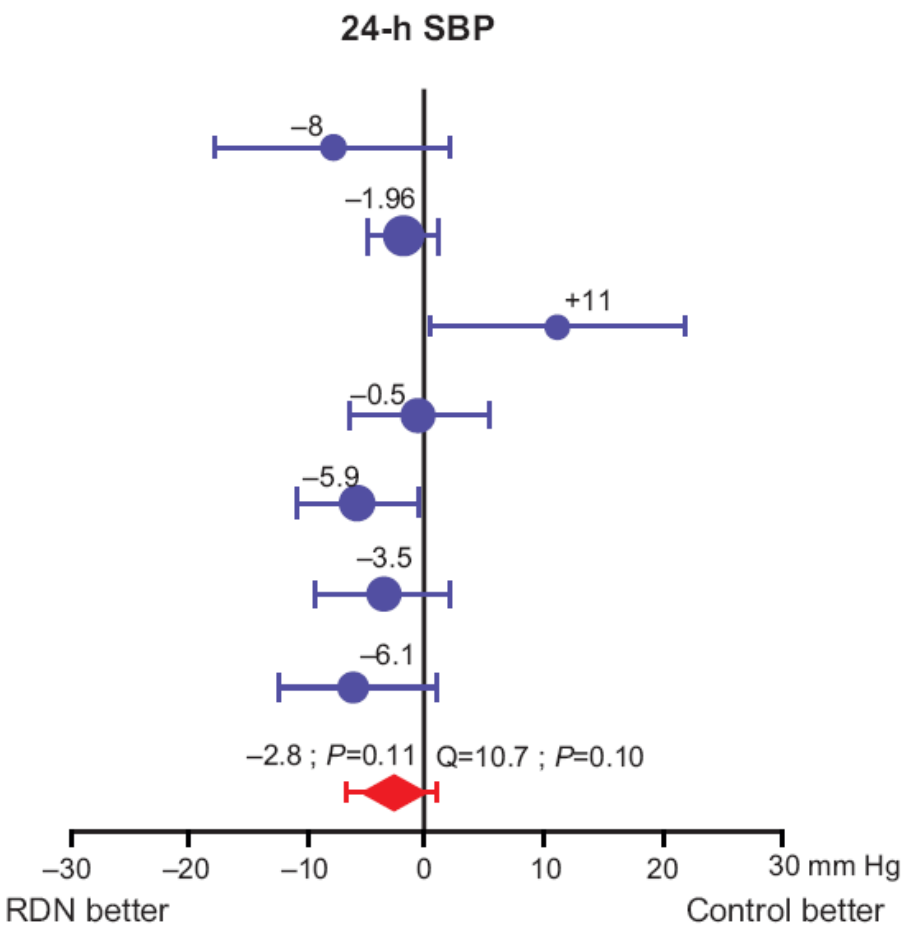
Milestones in RDN-based treatment of hypertension



Mahfoud F Circ Res. 2021 Apr 2;128(7):1080

Metaanalysis of 6-month response of 24 h SBP to renal denervation

	Control		RDN	
	N°	Δ (SD)	N°	Δ (SD)
SYMPLICITY-2	25	–3 (19)	20	–11 (15)
SYMPLICITY-3	162	–4.8 (17)	329	–6.8 (15)
OSLO	10	–21 (13)	9	–10 (11)
PRAGUE	54	–8.1 (17)	52	–8.6 (12)
DENER	53	–9.5 (13)	48	–15.4 (13)
SYMPLICITY-F	35	–3.5 (10)	32	–7.0 (11)
SYMPLICITY-J	19	–1.4 (10.2)	22	–7.5 (12)
ALL	358	–6.7 (–11.2, -2.2)	512	–9.2 (–12.2, –6.2)
		P=0.011		*P*<0.001



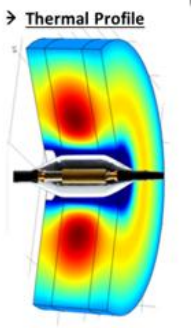
Fald Elmula FE. Blood Press. 2015 Oct;24(5):263-74.

The Path Forward for RDN: Consensus Statement on Trial Design[1]

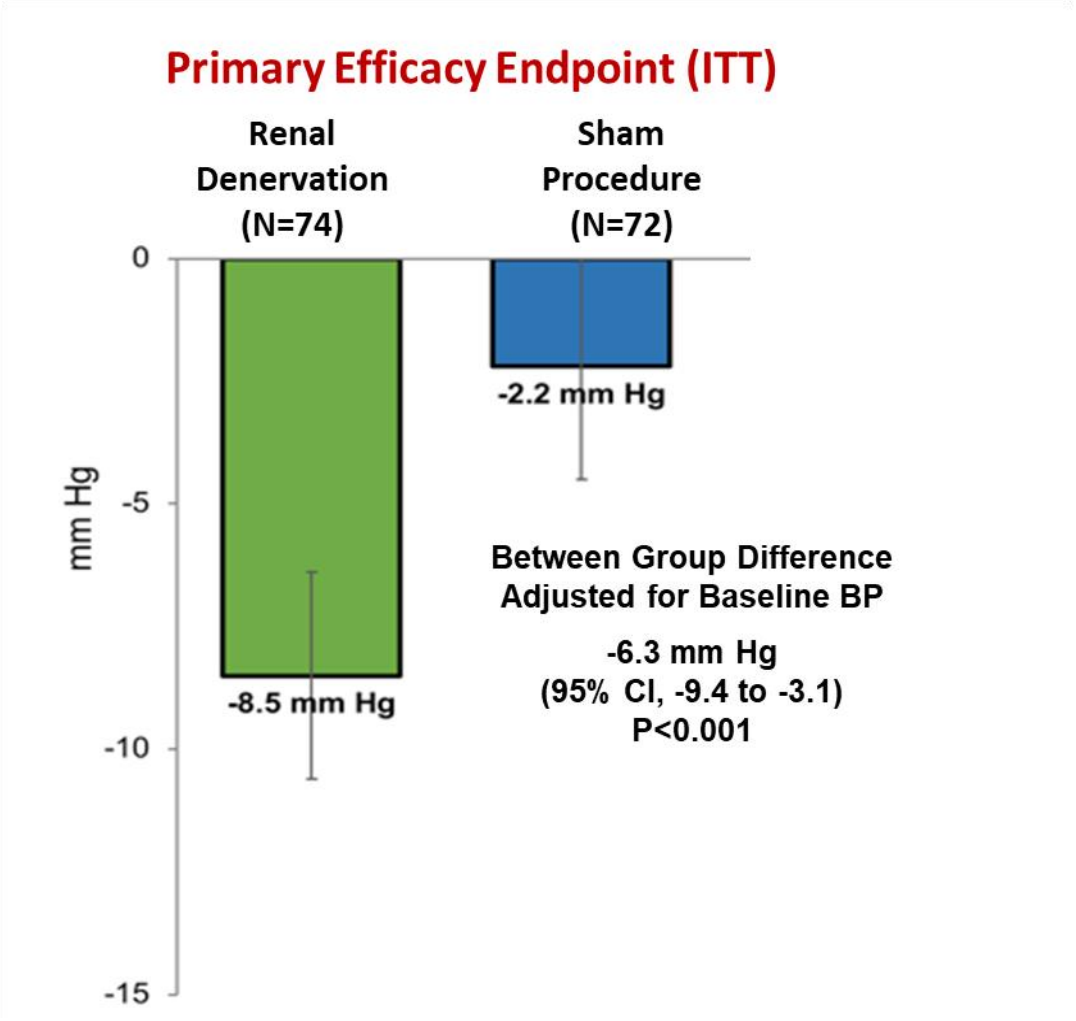
- Homogenous HTN patient populations
- BP reduction targets (6mmHg ABP/10mmHg OBP)
- Primary Endpoint ABPM
- Need for Sham
- Address medication adherence (Off Drug vs. On Drug)
- Consistent Denervation Treatment

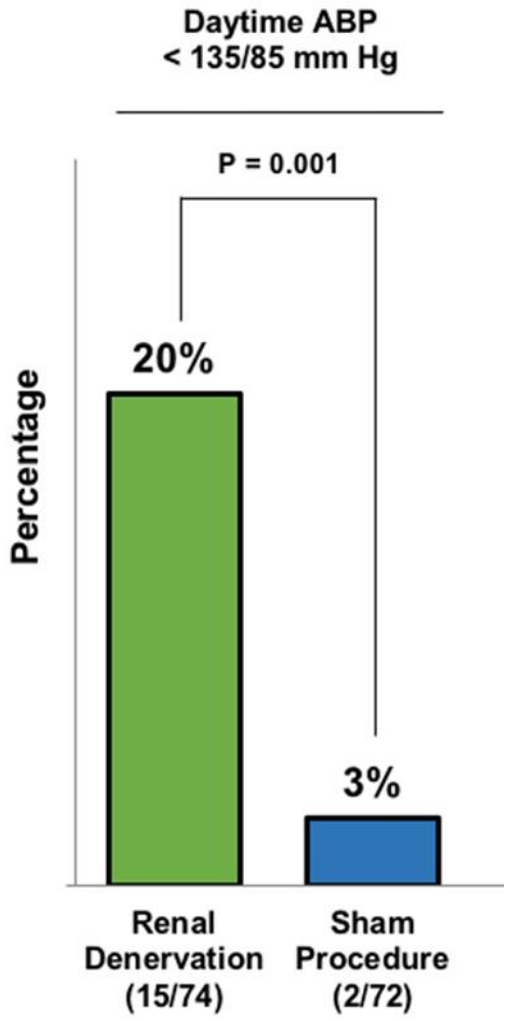
[1]Mahfoud F, Bohm M, Azizi M et al. Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: state of the art and considerations for the future. European Heart Journal. 2017;0:1–11

OFF-MED Studies



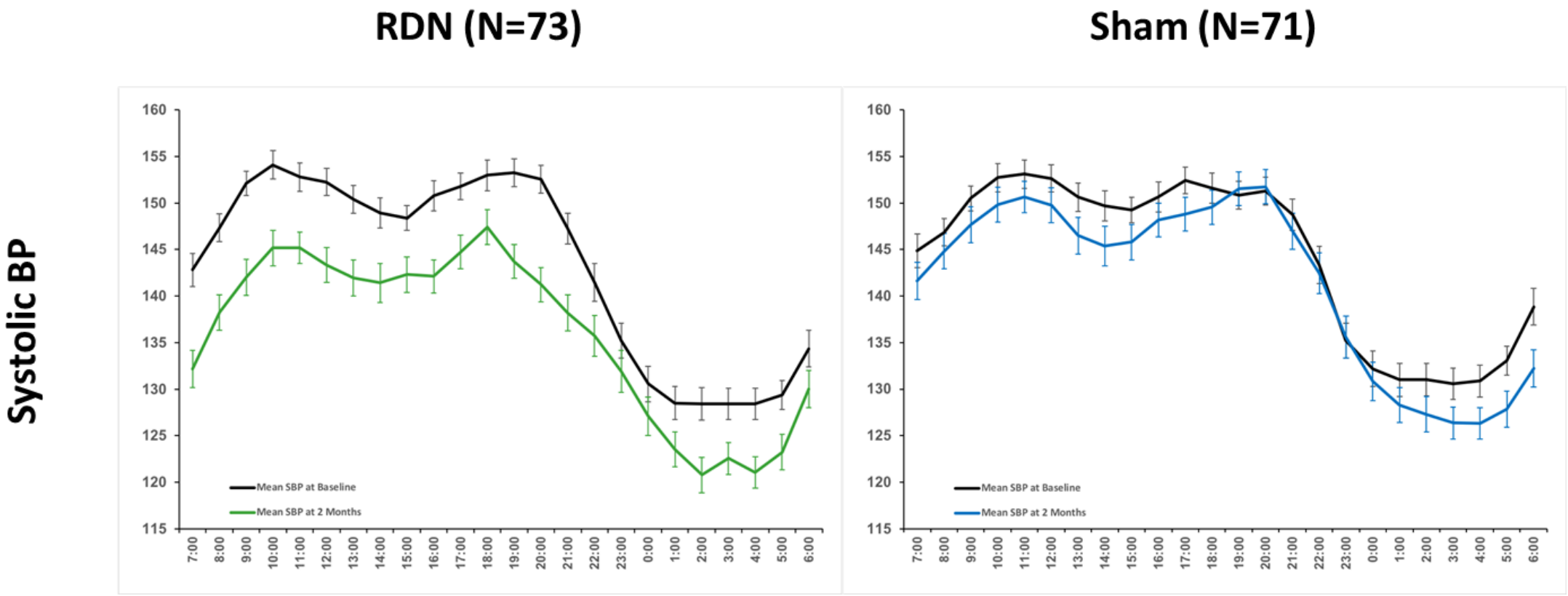
RADIANCE-HTN SOLO : Change in Daytime Ambulatory SBP at 2 Months vs. sham



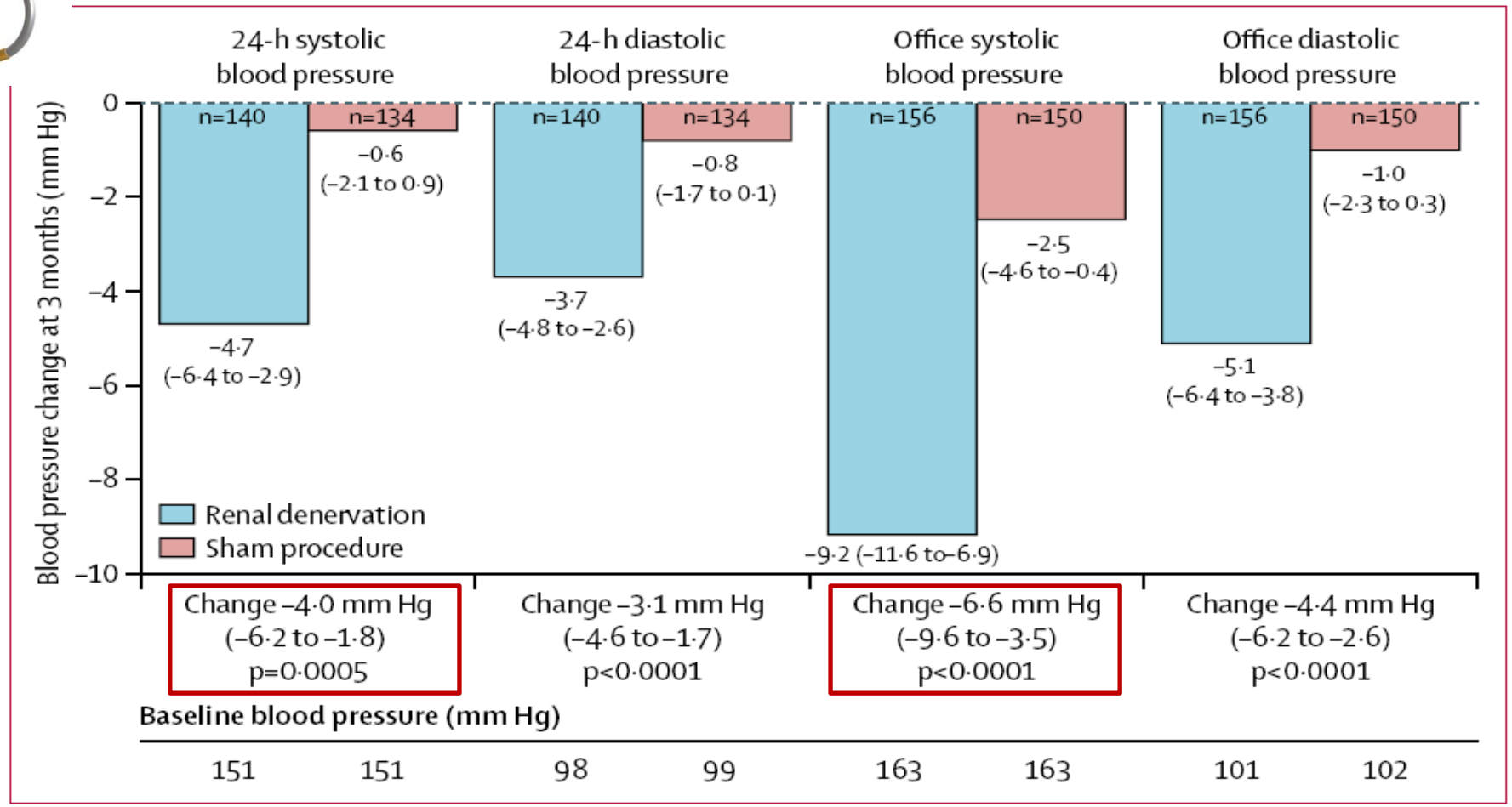


Azizi et al. Lancet. 2018 Jun 9;391(10137):2335-2345.

Average Hourly BP at Baseline and 2 Months



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



Böhm M et al. Lancet 2020;395:1444-1451.

RADIANCE-HTN SOLO:
Blinded Medication Titration Protocol During Months 2-5

2, 3, 4, & 5 Month Visits
BP Control Achieved (1-week Home BP <135/85)?

Yes → **No Change**

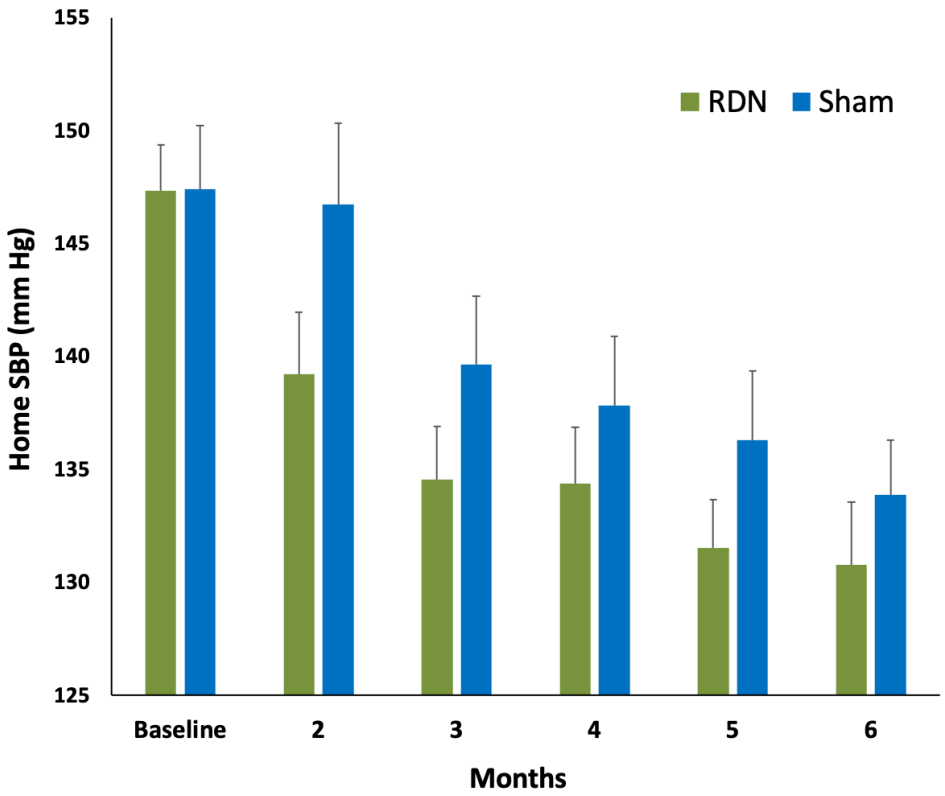
No → **Add Medications**

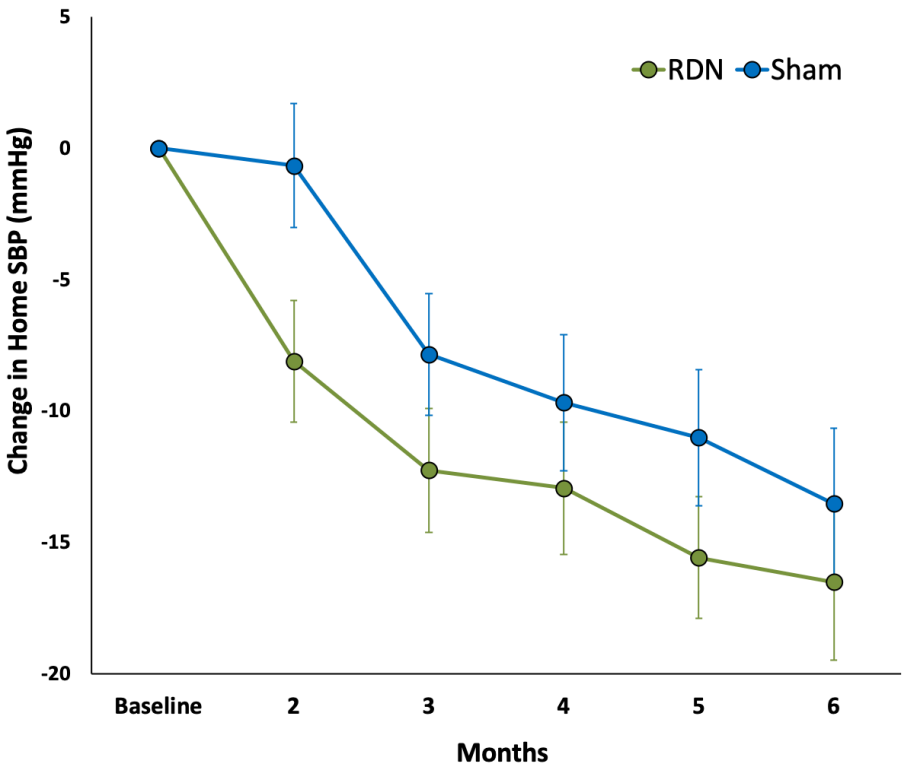
Escalation Step	Recommended drugs
0	NA
1	Amlodipine: 5 mg
2	ARB: Valsartan 160-320 mg; Olmesartan 20-40 mg ACEi: Ramipril 10-20 mg; Lisinopril 20-40 mg
3	HCTZ 12.5 mg
4	HCTZ 25 mg
5	Amlodipine 10 mg

6-Month Follow-Up:
Medication Burden, Ambulatory, Home, and Office BP

Azizi M. Circulation 2019;139:2542–2553

Home Systolic BP Values and Changes from Baseline on medications

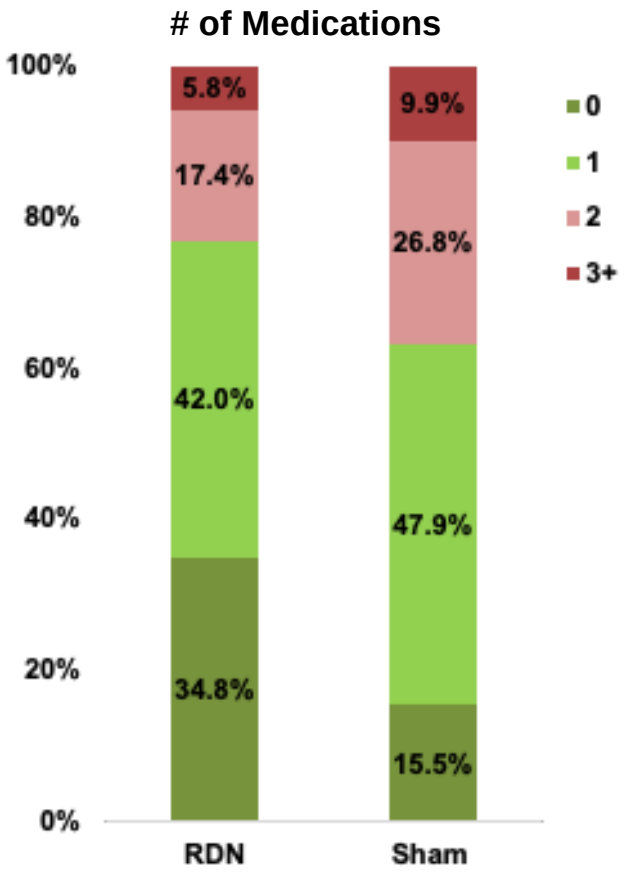




Overall between-group difference -6.9 mm Hg, 95% CI [-9.6,-4.1], p<0.001
from linear mixed model including visit x arm interaction term, adjusted for number of meds

Azizi M. Circulation 2019;139:2542–2553

Medication Burden at 6 Months



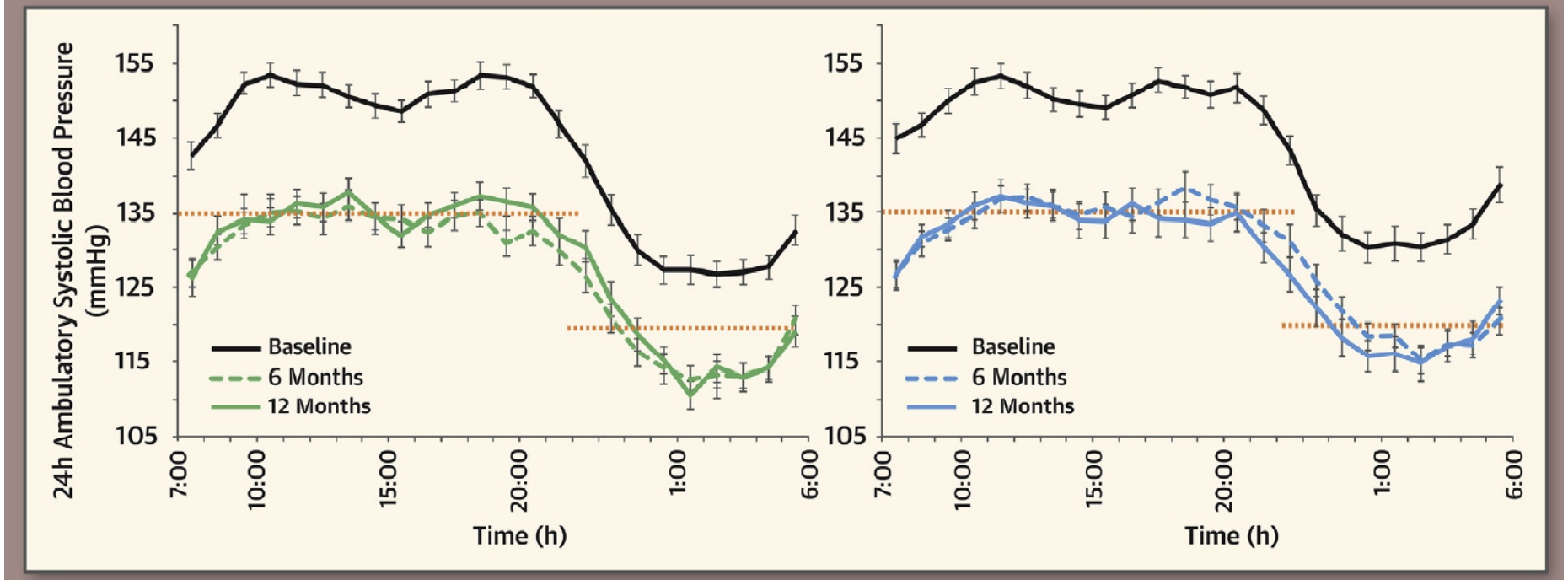
P Value for distribution = 0.055
P Value for being on no meds = 0.008

	RDN (n=69)	Sham (n=71)	P Value
# Anti-HTN Meds	0.9 ± 0.9	1.3 ± 0.9	0.010
Defined Daily Dose	1.4 ± 1.5	2.0 ± 1.8	0.018
Anti-HTN Med Load Index	0.5 ± 0.5	0.7 ± 0.6	0.014
Patients on Meds	**45 (65%)**	**60 (84.5%)**	
CCB	73%	83%	0.234
RAS blockers	51%	47%	0.696
Diuretic	20%	20%	1
Beta blocker	0%	1.7%	1
Aldosterone antagonist	0%	5.0%	0.258

Azizi M. Circulation 2019;139:2542–2553

Medication Burden and ABPM profiles at 12 months in Radiance SOLO

Medication Burden	Renal Denervation			12M Between-group p Value	Sham		
	Randomization	6M	12M		Randomization	6M	12M
Number of Antihypertensive Medications (mean)	0.0	0.9	1.0	0.015	0.0	1.3	1.4
Defined Daily Dose (mean)	0.0	1.4	1.4	0.007	0.0	2.1	2.2



Azizi, M. et al. J Am Coll Cardiol Intv. 2020;13(24):2922–33.

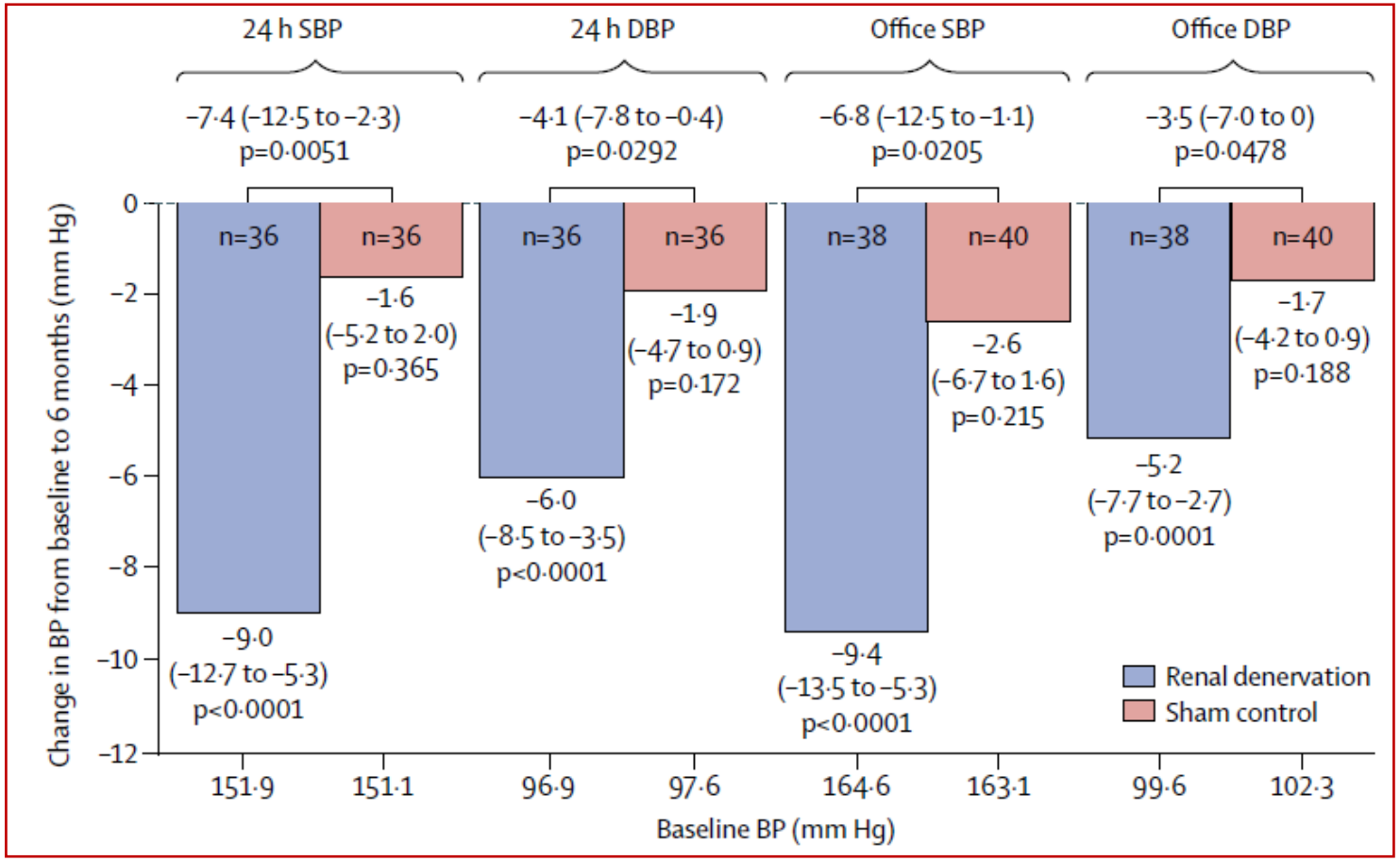
Safety Events at 6 Months (complete cohort)

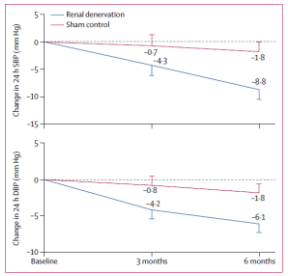
Endpoint	RDN (n= 73)	Sham (n=71)
Major adverse event within 30 days and through 6 months	0	0
Death	0	0
Acute renal failure	0	0
Embolic event resulting in end-organ damage	0	0
Renal artery or other vascular complication requiring intervention	0	0
Hypertensive crisis	0	0
New renal artery stenosis of more than 70% within 6 months†	0	0
Safety Events Through 6 Months		
Hypotensive emergency	0	0
Hospitalization for HF	0	0
Stroke, TIA	0	1
Acute myocardial infarction (STEMI/non-STEMI)	0	0
Any coronary revascularization	0	0
New onset renal stenosis of greater than 50%	0	0
Need for renal artery angioplasty or stenting	1*	0
New orthostatic hypotension (transient)	2†	0

* One patient in the renal denervation group had unrecognized pre-existing renal artery stenosis of 44% and underwent stenting for the lesion which measured 57% prior to stent placement at 6 months.
† One patient had a vasovagal episode that is not counted here.

ON-MED Studies

BP results in the SPYRAL ON MED trial

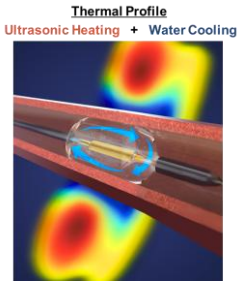




Kandzari DE Lancet. 2018; May 23

RADIANCE-HTN TRIO

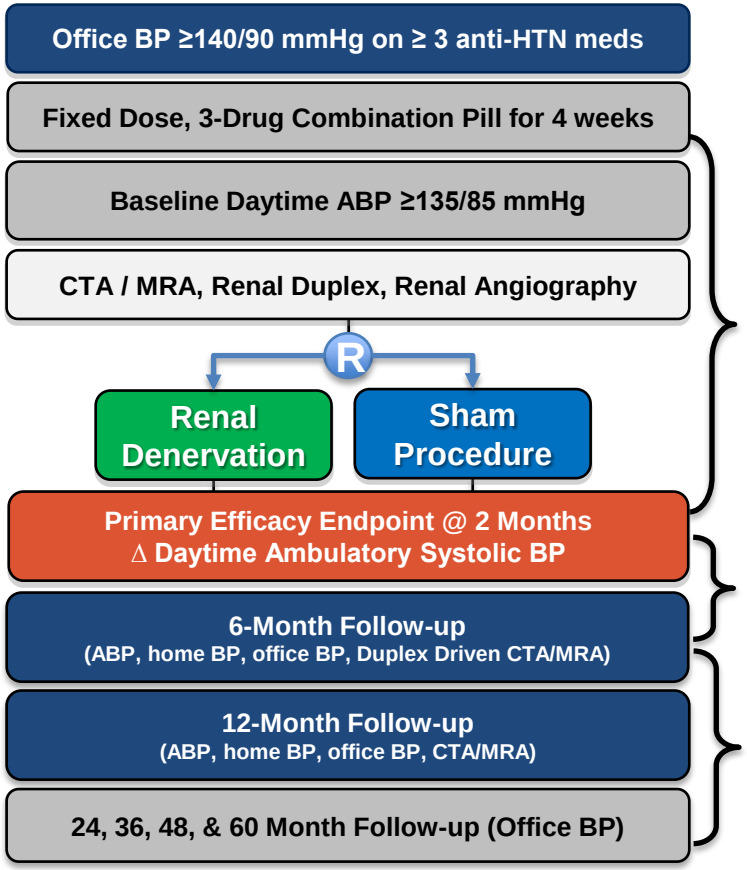
Multicenter, Blinded, Sham-Controlled trial
Powered to Demonstrate BP Lowering Effectiveness at 2M



Key Entry Criteria:

- Age 18-75 years
- Office BP ≥140/90 mmHg on ≥ 3 anti-HTN meds
- eGFR ≥ 40 mL/min/m^2
- Daytime ABP ≥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



No Med Changes Unless Escape BP Criteria Exceeded

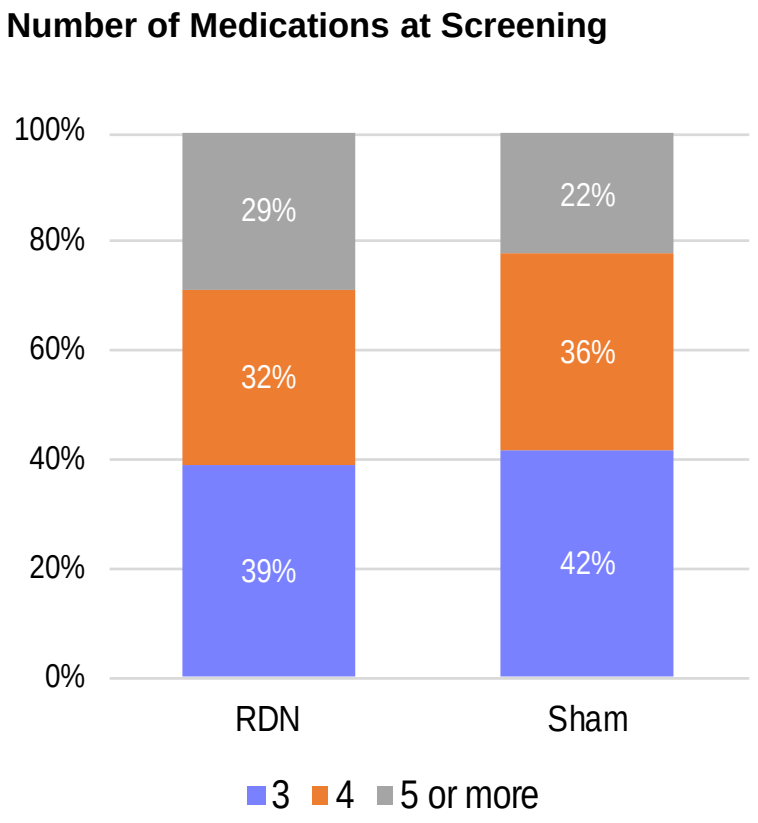
Patients and Outcome Assessors Blinded to treatment allocation

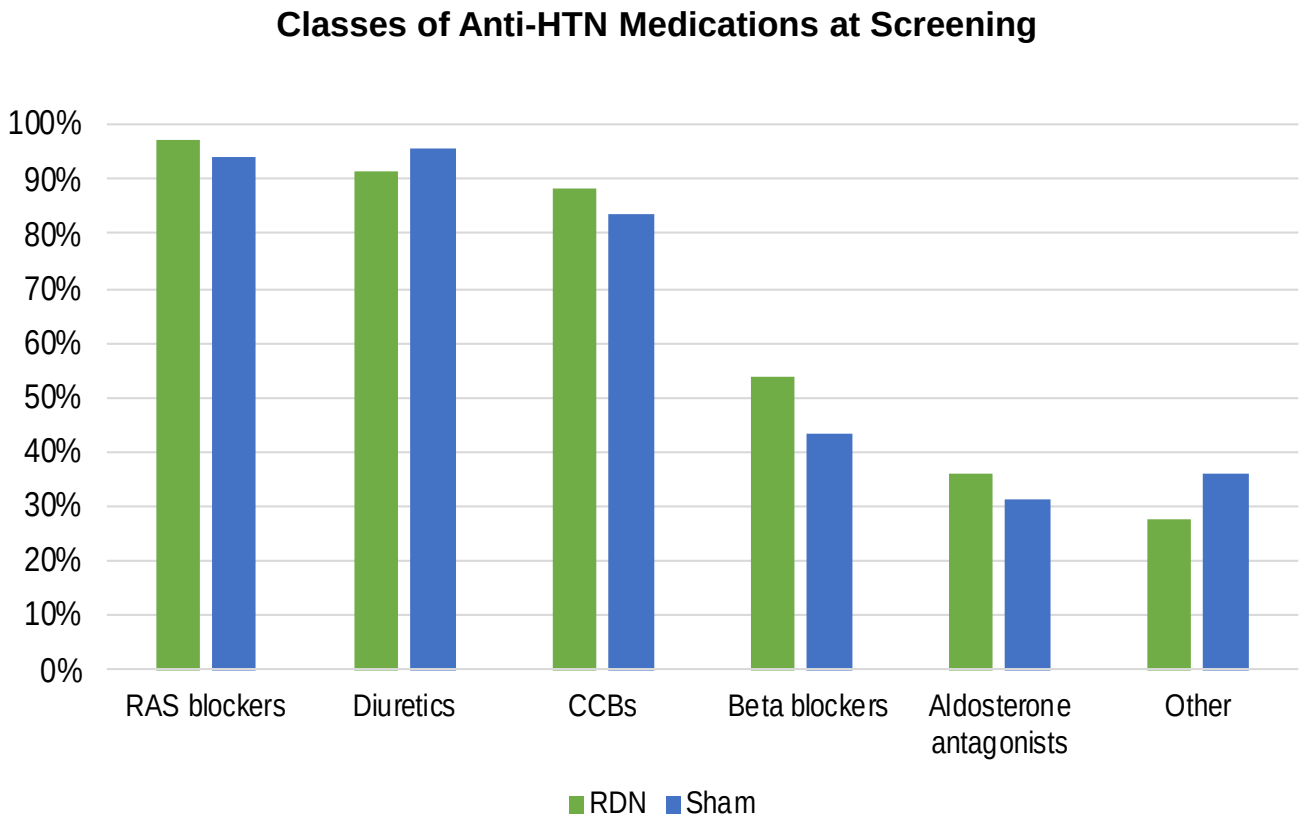
Blinded Medication Titration Protocol

Unblinded "Standard of Care" Meds

Azizi M et al. Lancet. 2021 Jun 26;397:2476-86

Screening AHT Medications





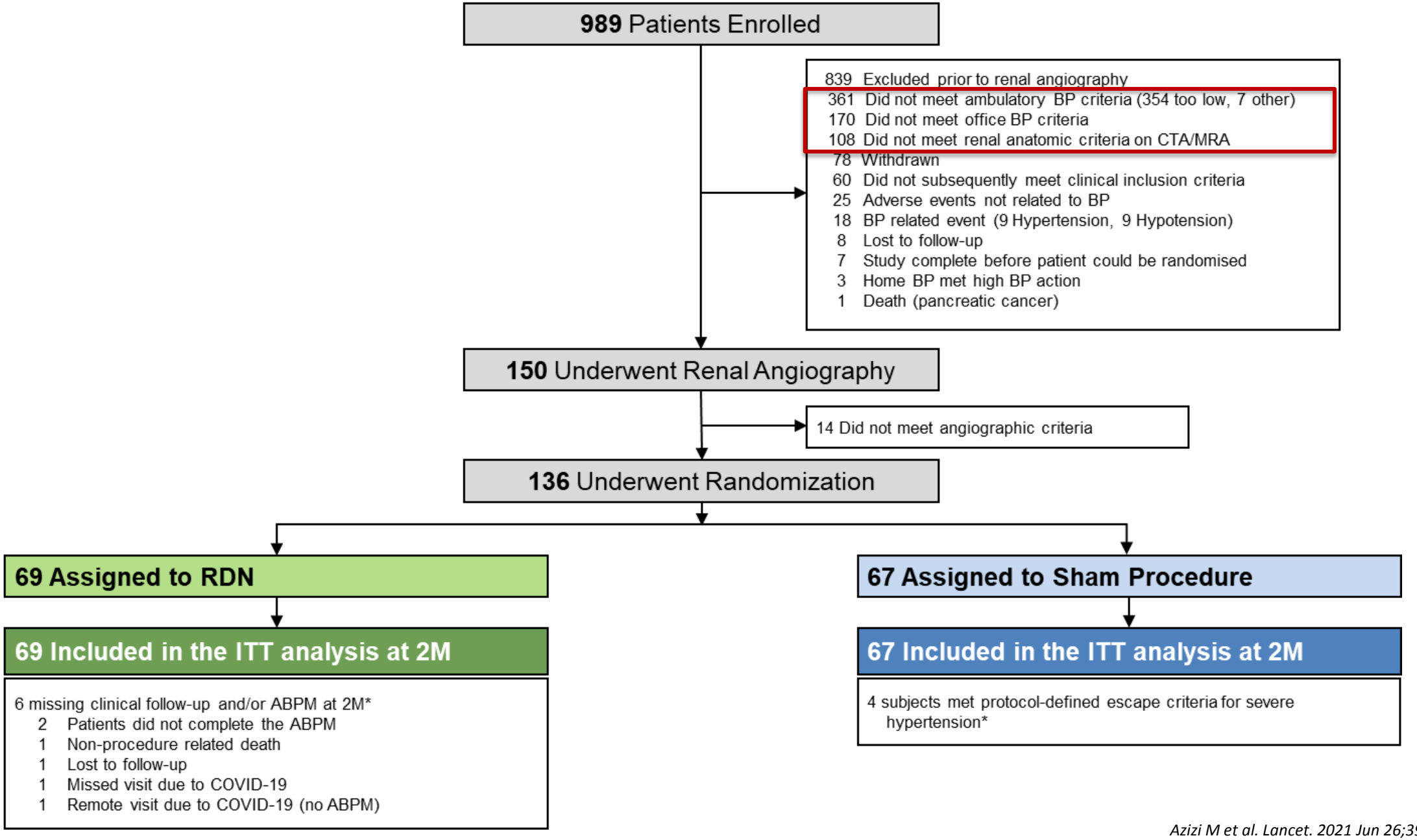
Azizi M et al. Lancet. 2021 Jun 26;397:2476-86

Baseline Blood Pressure:
After 4 weeks of Triple Medication Combination Pill

	RDN (N=69)	Sham (N=67)
ABPM		
Daytime SBP (mmHg)	150.0 ± 11.9	151.1 ± 12.6
Daytime DBP (mmHg)	93.8 ± 7.7	94.6 ± 9.1
Nighttime SBP (mmHg)	134.4 ± 18.0	136.4 ± 18.6
Nighttime DBP (mmHg)	81.3 ± 10.7	81.3 ± 12.1
24-h SBP (mmHg)	143.9 ± 13.4	145.4 ± 14.0
24-h DBP (mmHg)	88.9 ± 8.2	89.5 ± 9.5
Home BP		
SBP (mmHg)	153.6 ± 16.2	153.4 ± 17.0
DBP (mmHg)	97.1 ± 10.9	96.9 ± 11.3
Office BP		
SBP (mmHg)	155.2 ± 16.8	155.1 ± 16.8
DBP (mmHg)	101.3 ± 11.7	99.6 ± 10.9

Azizi M et al. Lancet. 2021 Jun 26;397:2476-86

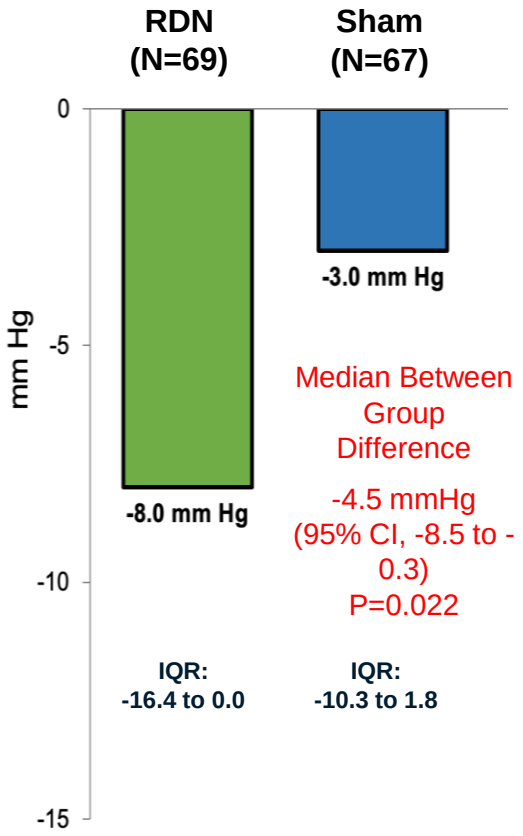
Patient Flow



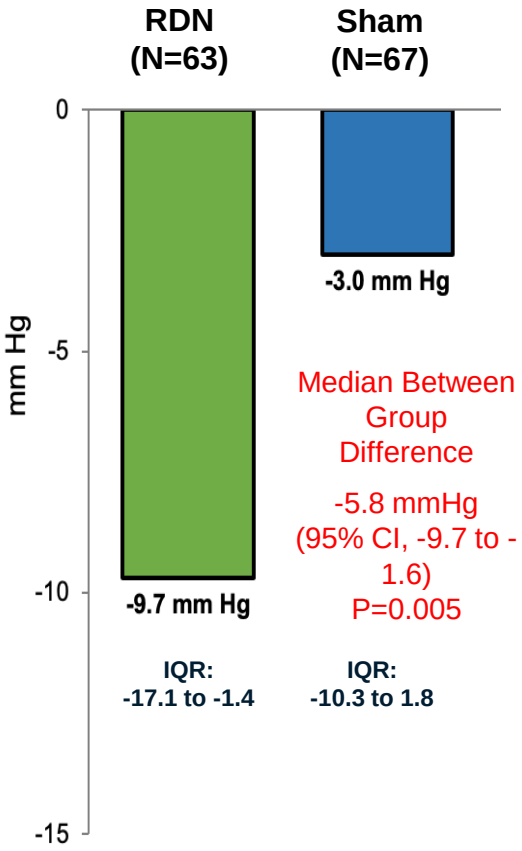
Azizi M et al. Lancet. 2021 Jun 26;397:2476-86

RADIANCE-HTN TRIO Primary Endpoint
Change in Daytime ASBP at 2M

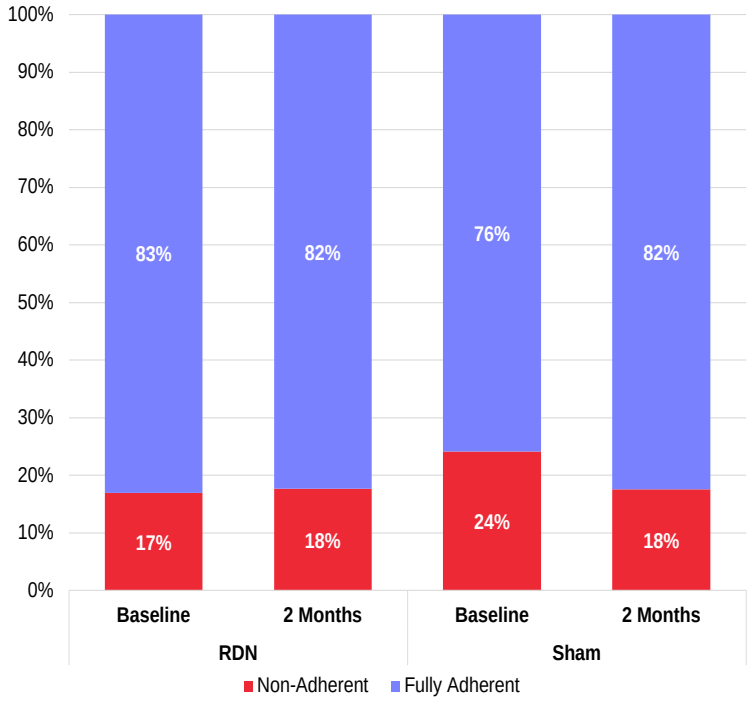
Intent-To-Treat Population



Complete ABPM Population



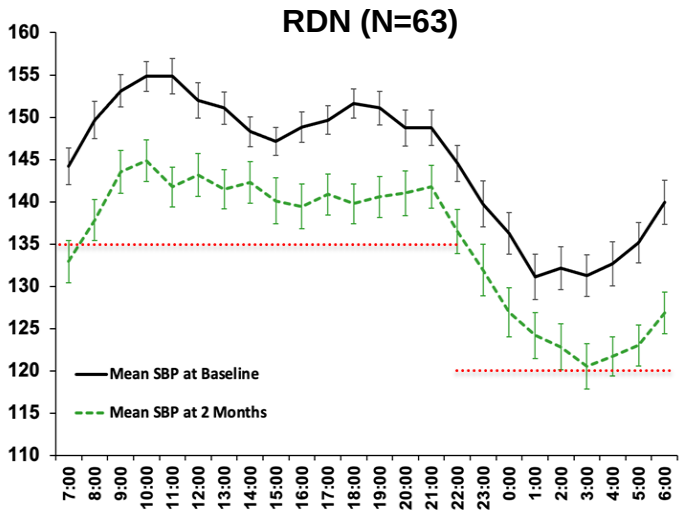
Medication adherence by urine LCMSMS

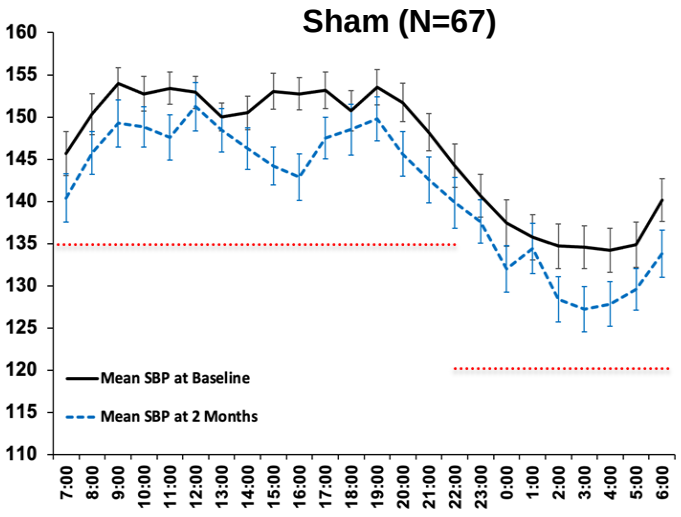


Azizi M et al. Lancet. 2021;397:2476

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*

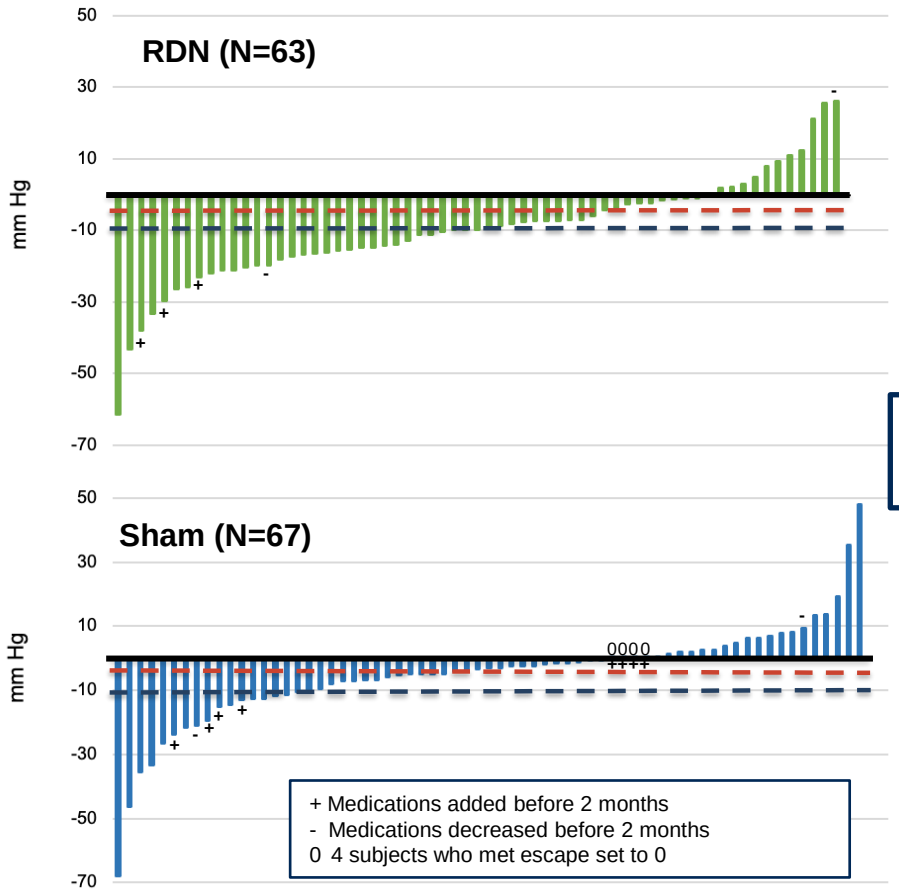
Nighttime ABPM
-5.0 mmHg
(95% CI, -10.1 to 0.5)
P=0.015*

* Baseline-adjusted ANCOVA on the ranks

Azizi M et al. Lancet. 2021 Jun 26;397:2476-86

Individual Patient Responses

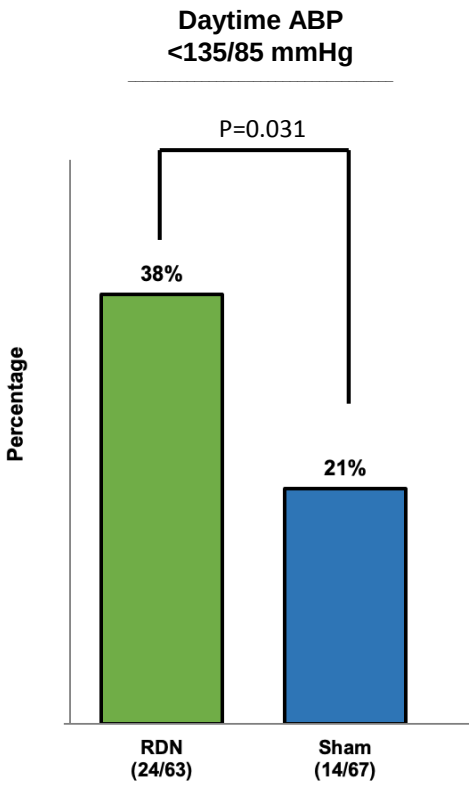
Change in Daytime Ambulatory SBP at 2 Months (Complete ABPM Population)



67% with 5 mmHg decrease
46% with 10 mmHg decrease

Between Group Differences:
5 mmHg decrease P=0.0045
10 mmHg decrease P=0.014

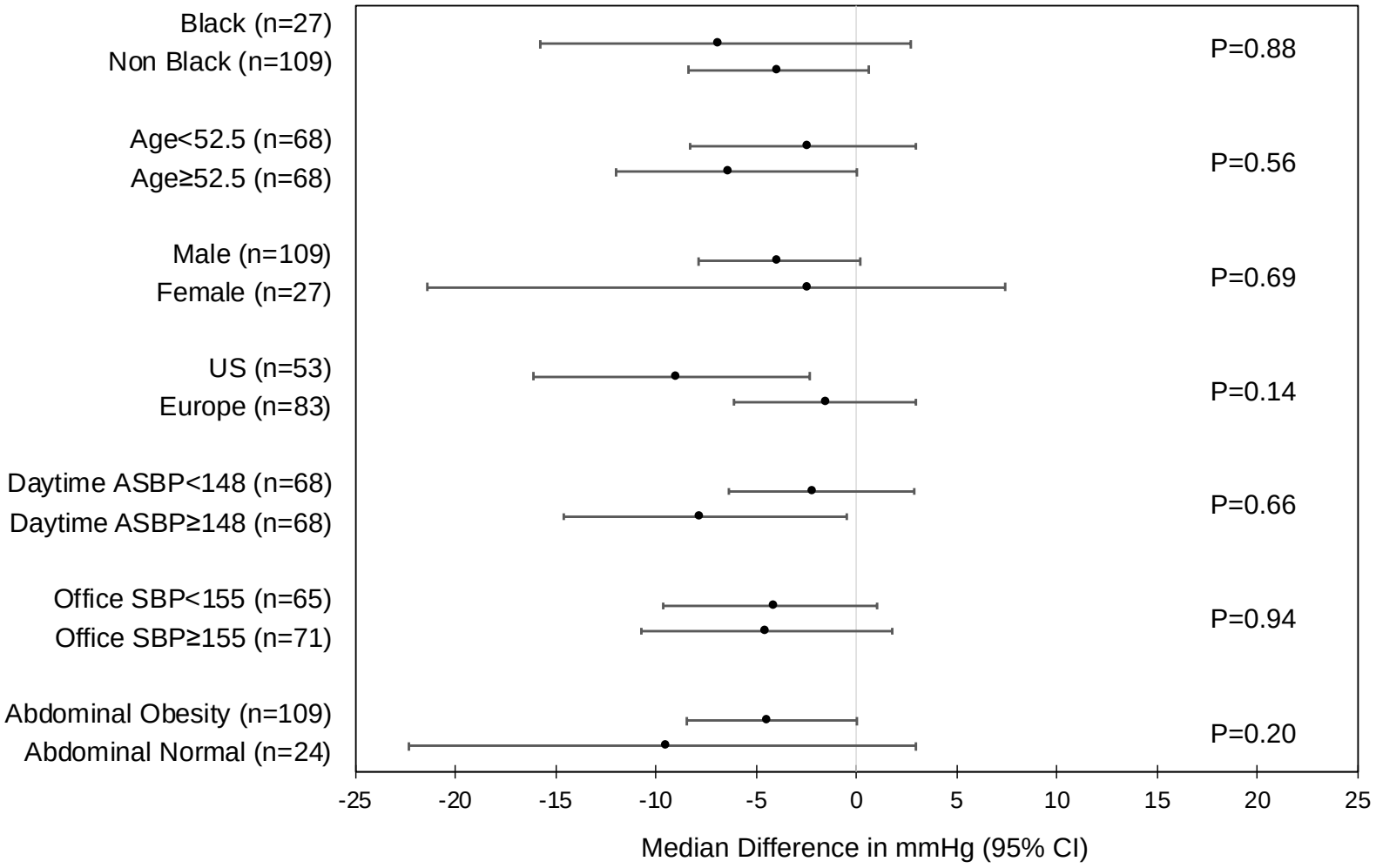
42% with 5 mmHg decrease
25% with 10 mmHg decrease



N=4 Sham that met escape set to uncontrolled

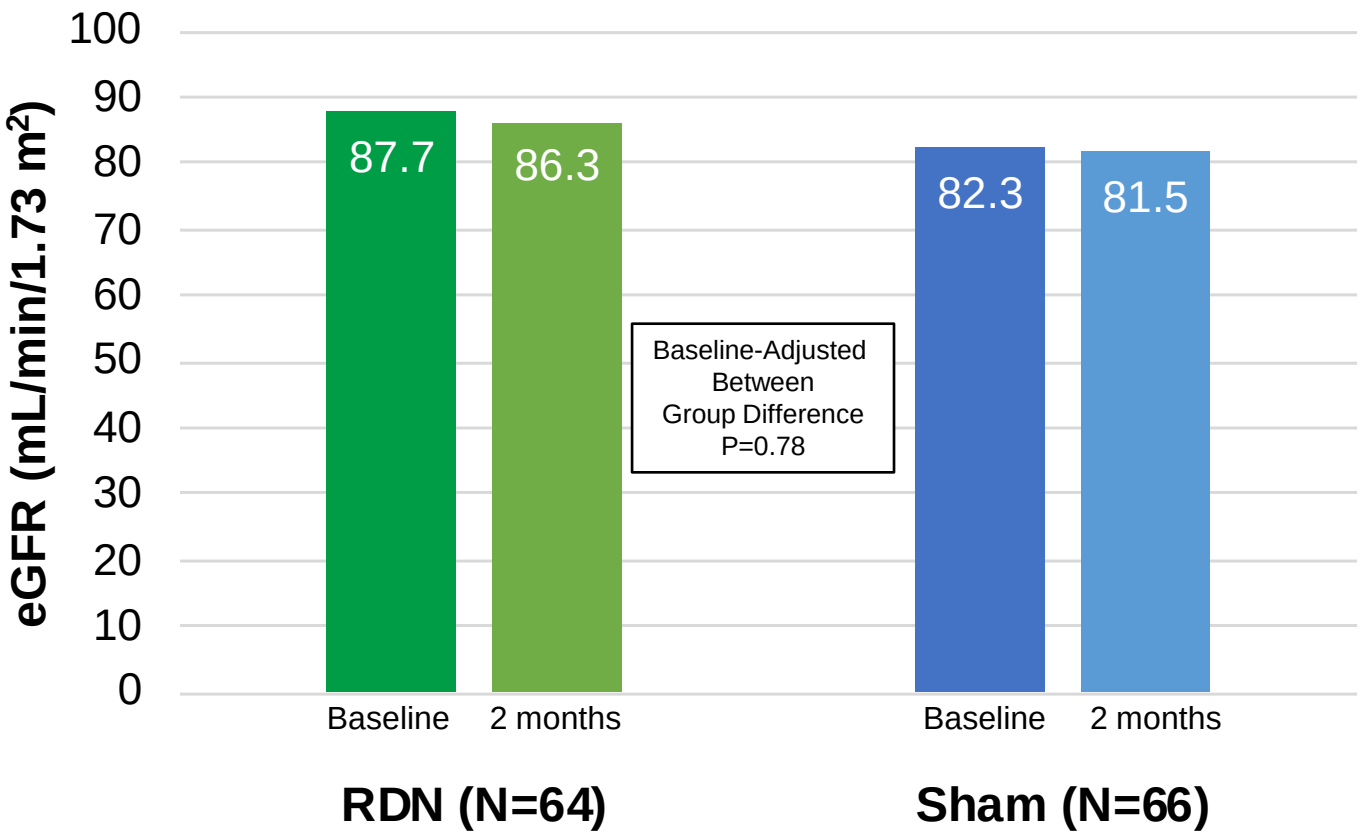
Azizi M et al. Lancet. 2021 Jun 26;397:2476-86

Subgroup Analysis: Between Group Difference in 2-month Change in Daytime Ambulatory SBP



Azizi M et al. Lancet. 2021 Jun 26;397:2476-86

eGFR at 2 Months



Note: Two subjects in the renal denervation group and two subjects in the sham group are missing race data and therefore not included in the eGFR calculations.

Azizi M et al. Lancet. 2021 Jun 26;397:2476-86

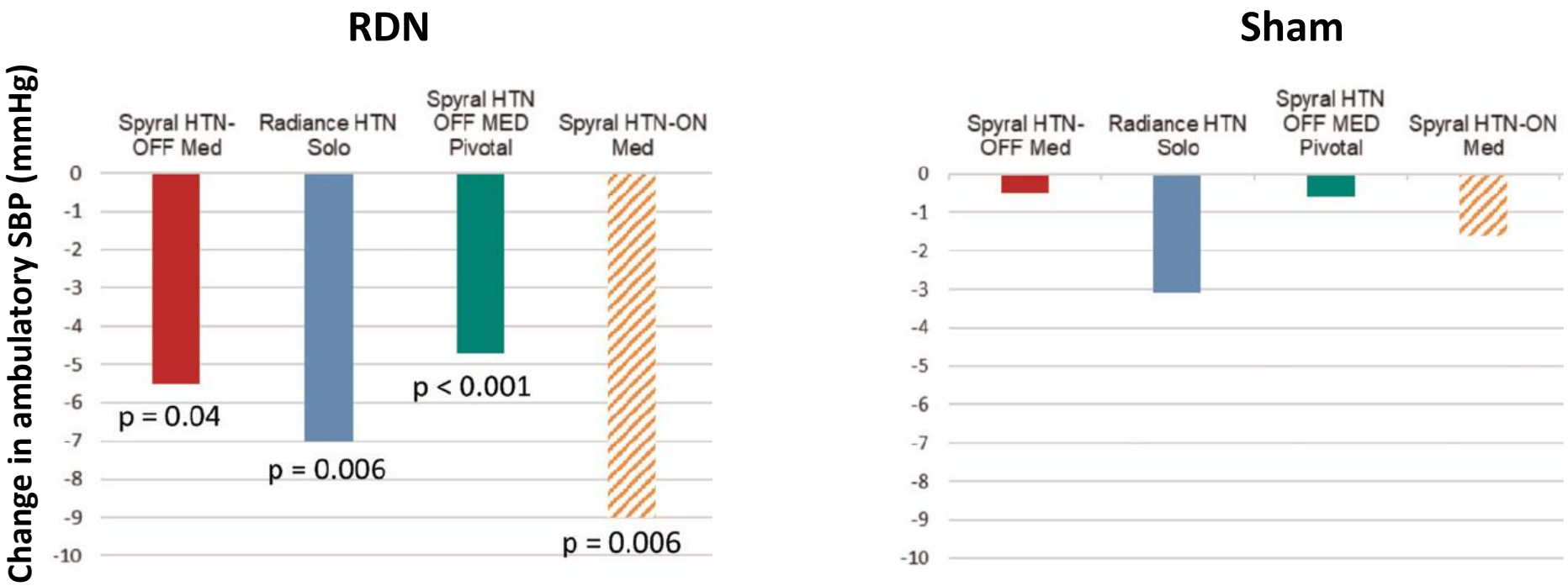
Major Adverse Events

Major Adverse Events	RDN (N=69)	Sham (N=67)
30-Day Major Adverse Events		
Death	1 (1%)[1]	0 (0%)
End stage renal disease, the need for permanent renal replacement therapy	0 (0%)	0 (0%)
Doubling of plasma creatinine	1 (1%)[2]	0 (0%)
Embolic event resulting in end organ damage	0 (0%)	0 (0%)
Renal artery complication requiring intervention	0 (0%)	0 (0%)
Major access site complications requiring intervention	1 (1%)[3]	0 (0%)
Hypertensive emergency resulting in hospitalization	0 (0%)	0 (0%)
Other Major Adverse Events Measured Through 2 Months		
New onset renal artery stenosis of greater than 70%	0 (0%)	0 (0%)

[1] Sudden death unrelated to device or procedure 21 days post-procedure
[2] Transient acute renal injury 25 days post-procedure associated with spironolactone use and resolved upon discontinuation of spironolactone
[3] Femoral access site pseudoaneurysm post-procedure resolved with thrombin injection

Azizi M et al. Lancet. 2021 Jun 26;397:2476-86

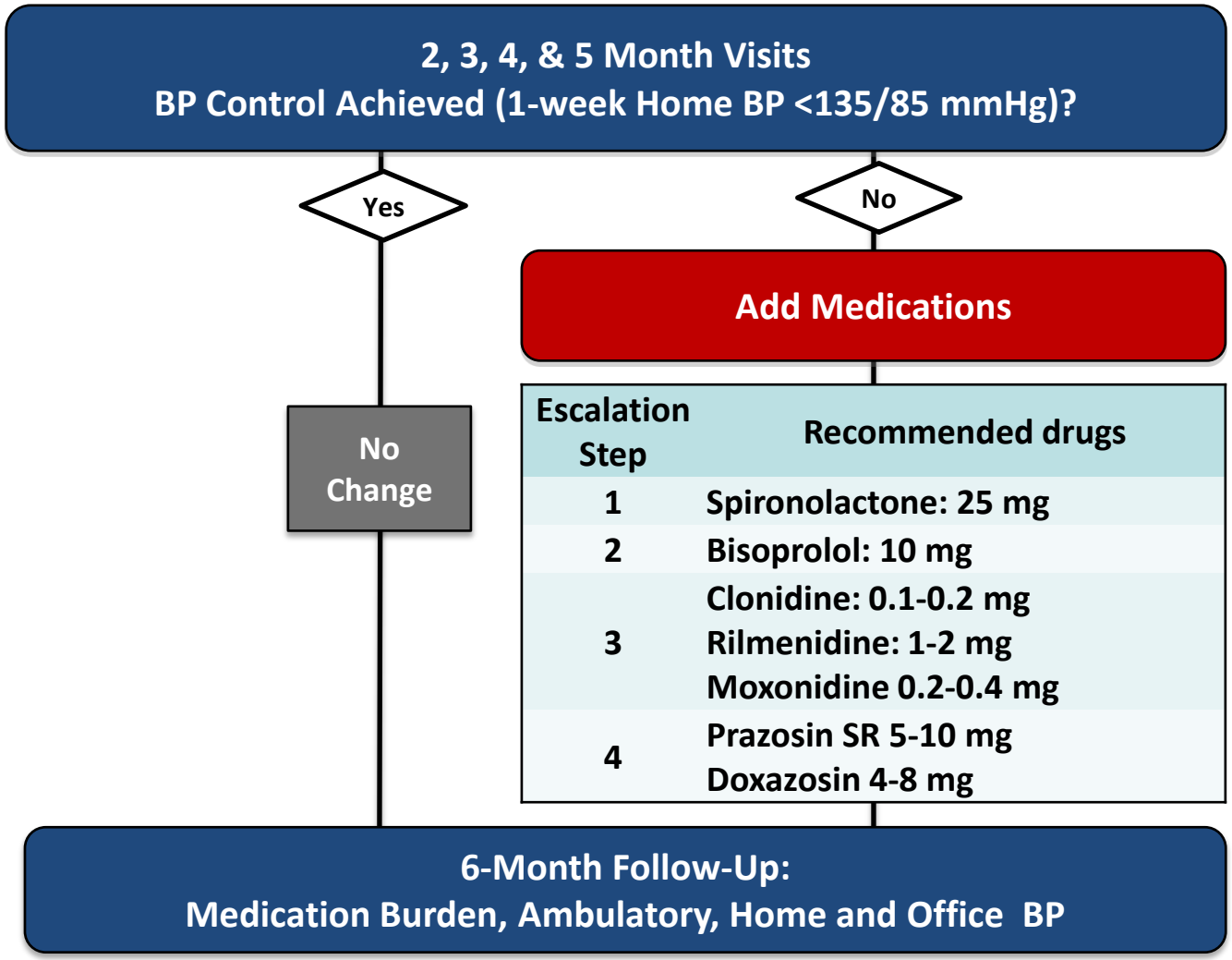
RADIANCE HTN TRIO results are concordant with those of observed in patients with less severe hypertension



Schmieder RE. J Hypertens. 2021 Jul 13.

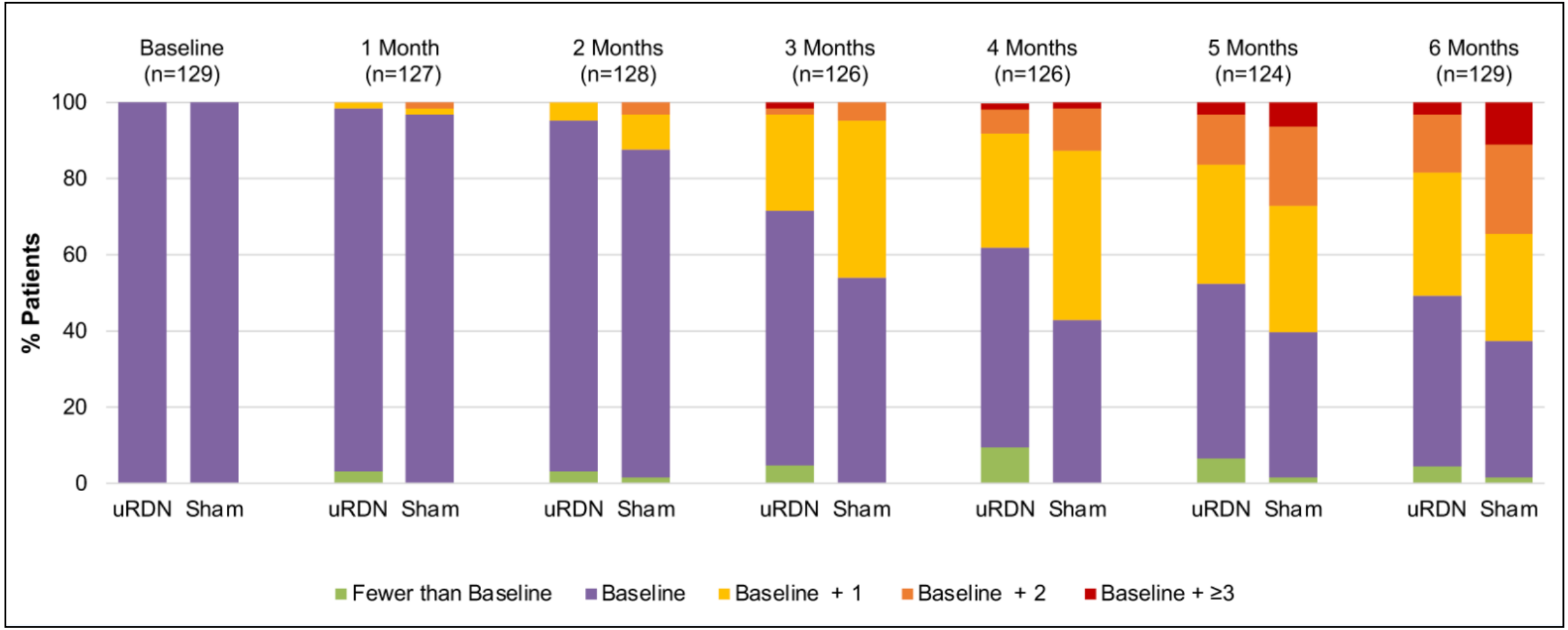
Lauder L, Azizi M. Nat Rev Cardiol. 2020 Oct;17:614

Blinded Medication Titration Protocol During Months 2-5



Escalation Step	Recommended drugs
1	Spironolactone: 25 mg
2	Bisoprolol: 10 mg
3	Clonidine: 0.1-0.2 mg Rilmenidine: 1-2 mg Moxonidine 0.2-0.4 mg
4	Prazosin SR 5-10 mg Doxazosin 4-8 mg

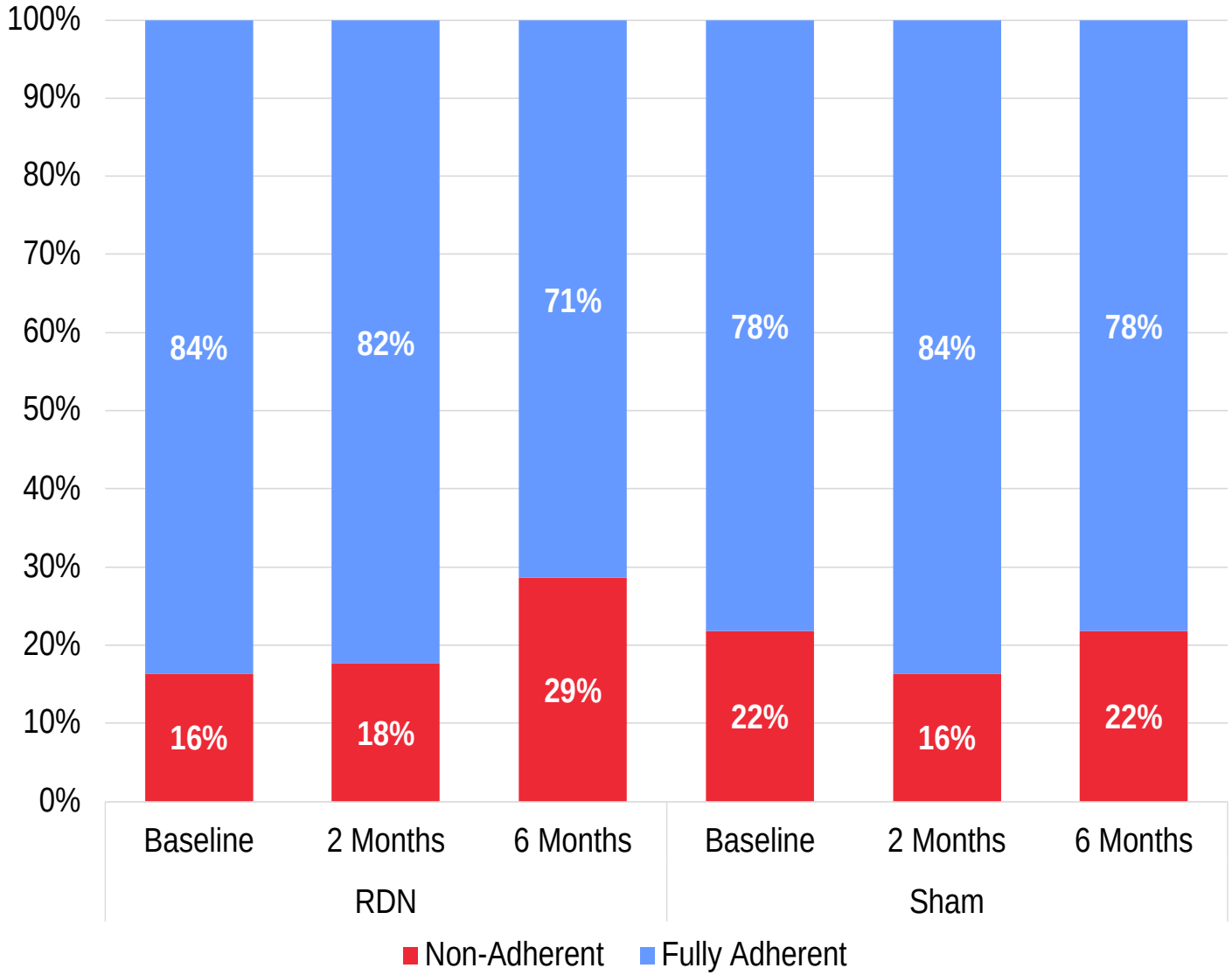
Changes in antihypertensive medications



Antihypertensive Medications at 6 Months

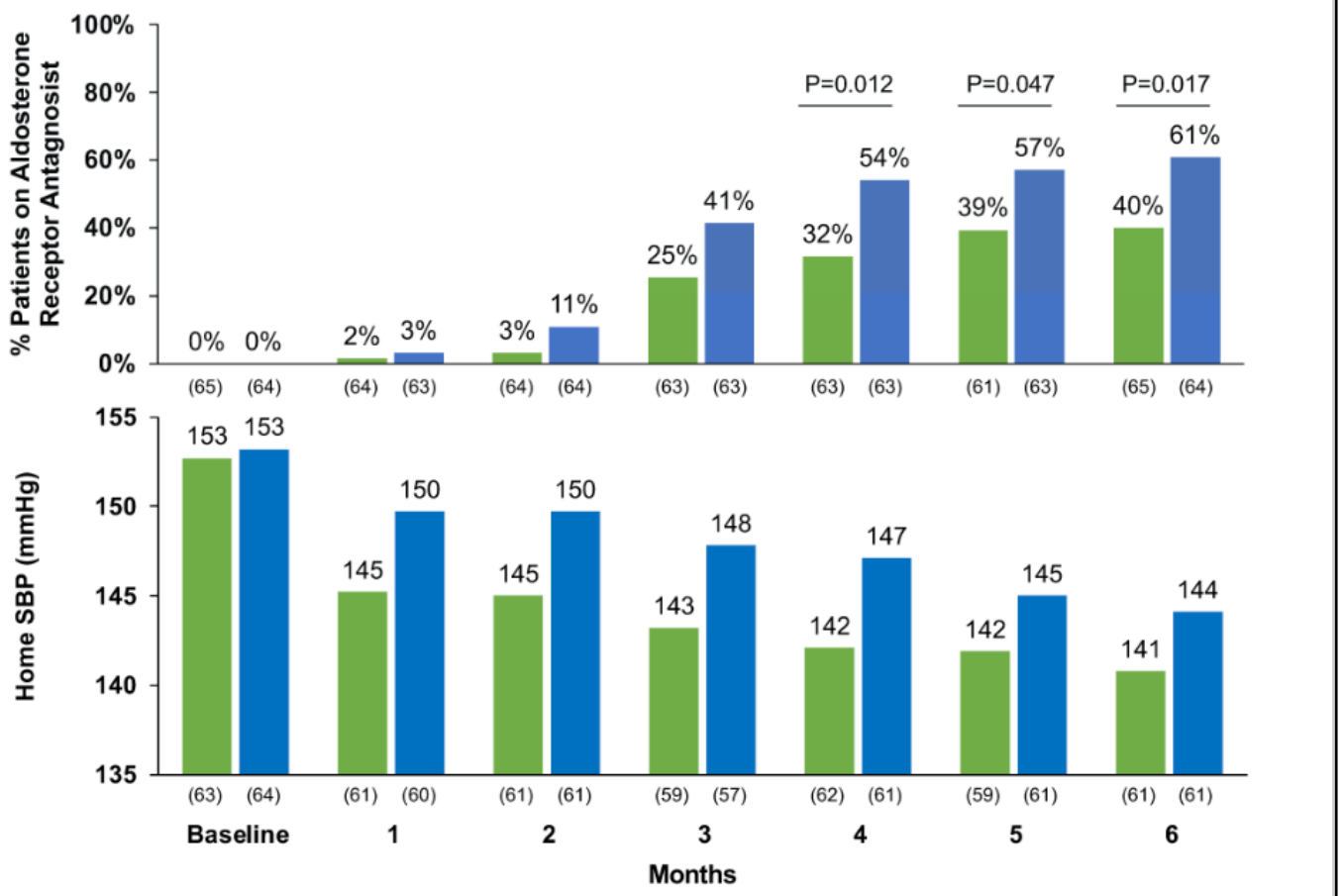
	RDN (n=65)	Sham (n=64)	P-Value
# Anti-HTN Meds at 6 months	3.8 ± 1.0	4.1 ± 1.1	0.078
Change in Anti-HTN Meds from Baseline	0.7 ± 1.0	1.1 ± 1.1	0.045
Medication Class			
CCB	98.5% (64/65)	98.4% (63/64)	1.000
RAS blockers	96.9% (63/65)	100% (64/64)	0.496
Diuretic	95.4% (62/65)	95.3% (61/64)	1.000
Aldosterone antagonist	40.0% (26/65)	60.9% (39/64)	0.017
Beta blocker	33.8% (22/65)	39.1% (25/64)	0.538
Centrally acting drug	4.6% (3/65)	9.4% (6/64)	0.324
Alpha receptor blocker or vasodilator	6.2% (4/65)	6.3% (4/64)	1.000

Medication Adherence through 6 months



Comparison Between Groups	
Baseline	P=0.47
2 Months	P=0.86
6 Months	P=0.41

Aldosterone receptor antagonists use and home BP levels through 6 months

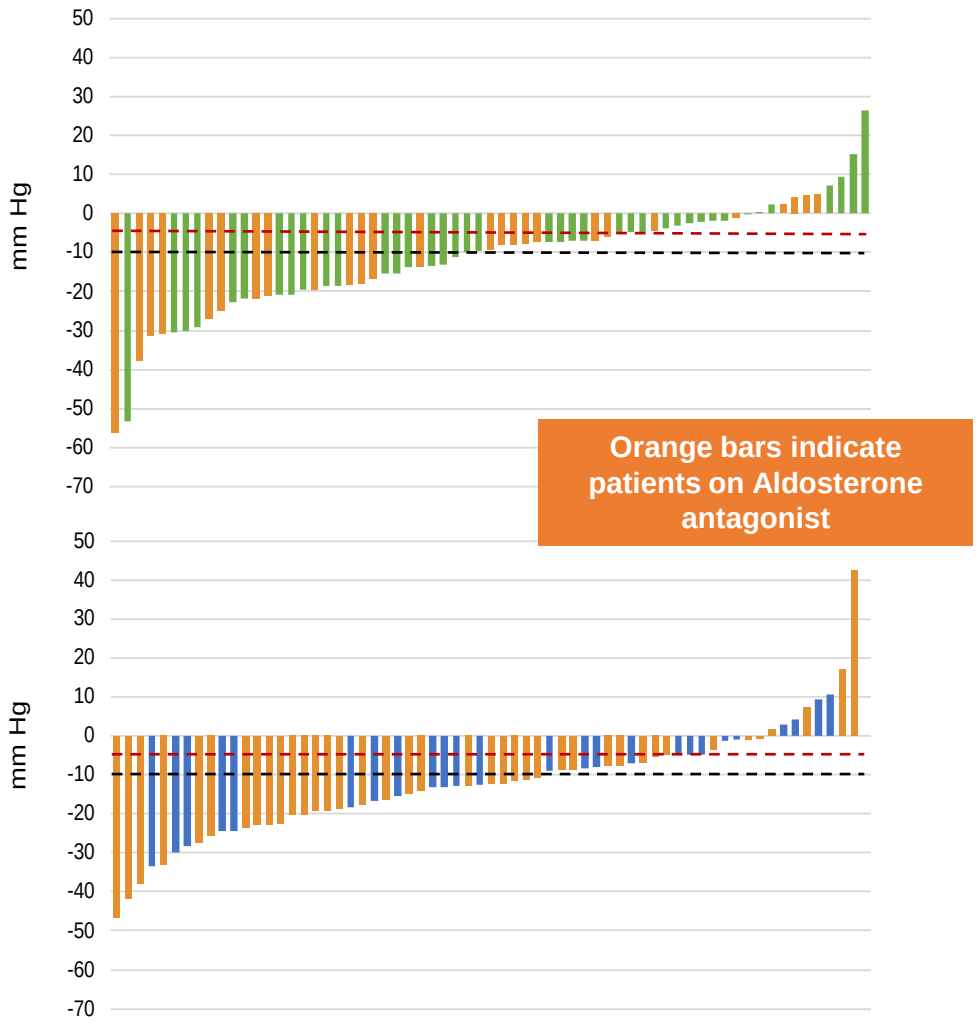


- ✓ An aldosterone receptor antagonist was much less frequently added at each monthly visit in the uRDN group by physicians blinded to the randomization compared with the sham group though 6 months (overall odds ratio [OR]: 0.4 (95%CI: 0.2, 0.7), absolute risk difference: -15.1% (95%CI: -23.9%, -6.2%), p<0.001).
- ✓ The overall decrease in home SBP from baseline to 1, 2, 3, 4, 5, and 6 months was greater in the uRDN group than in the sham group (estimated overall between-group difference: -4.3 mmHg; 95% CI, -8.1 to -0.5 mmHg; p=0.027 in a mixed linear model adjusting for baseline and medications added).

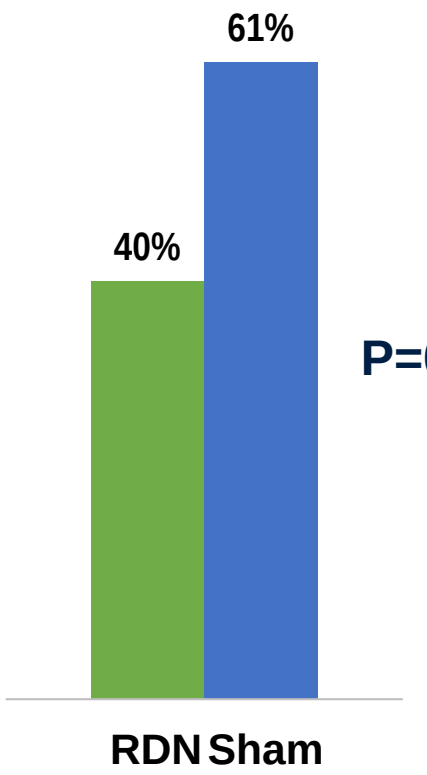
Individual Patient Responses
Change in Daytime Ambulatory SBP at 6 Months

RDN
(N=65)

SHAM
(N=64)

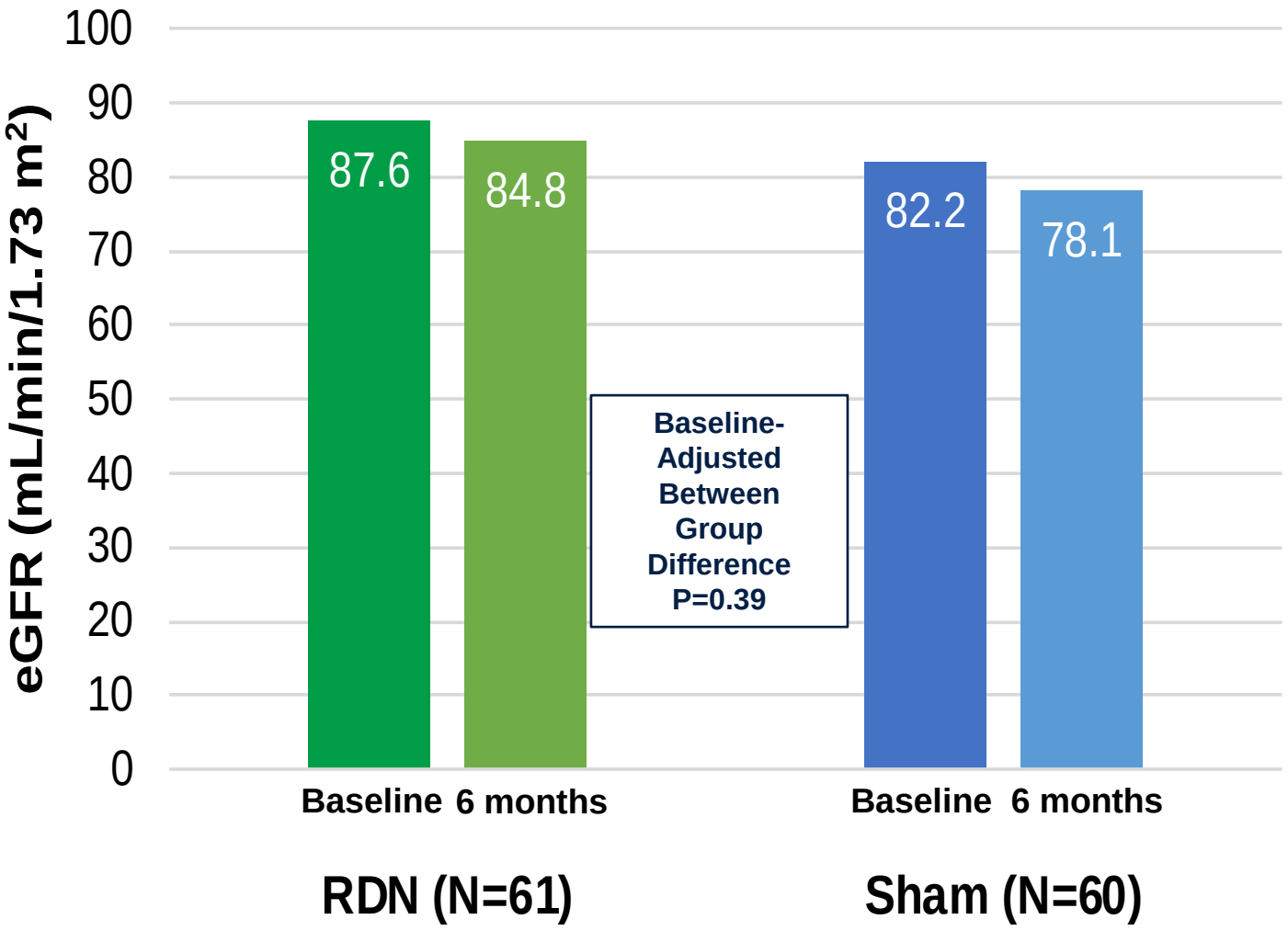


Aldosterone Antagonist use at 6M

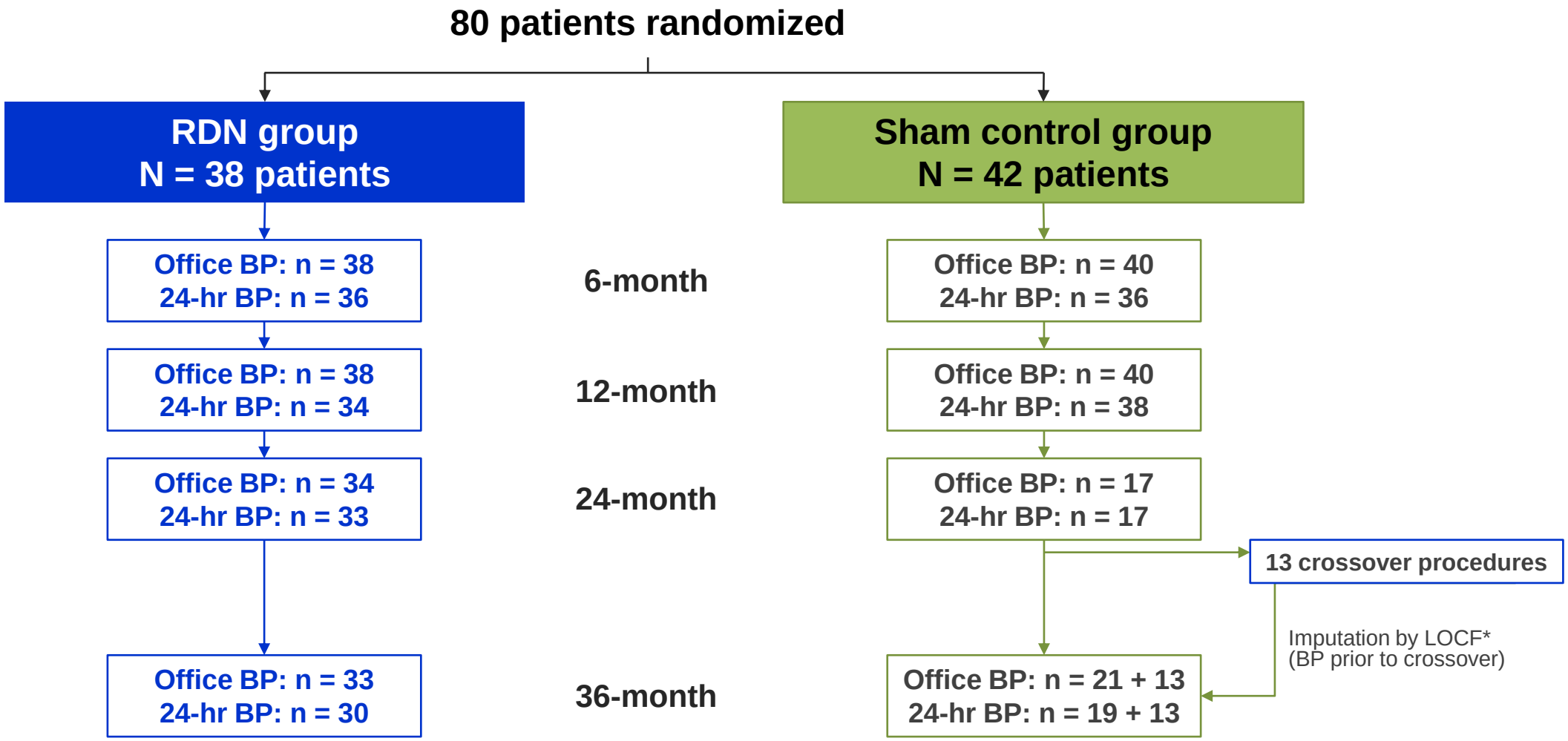


P=0.017

eGFR at 6 Months
(Matched data at baseline and 6 months)



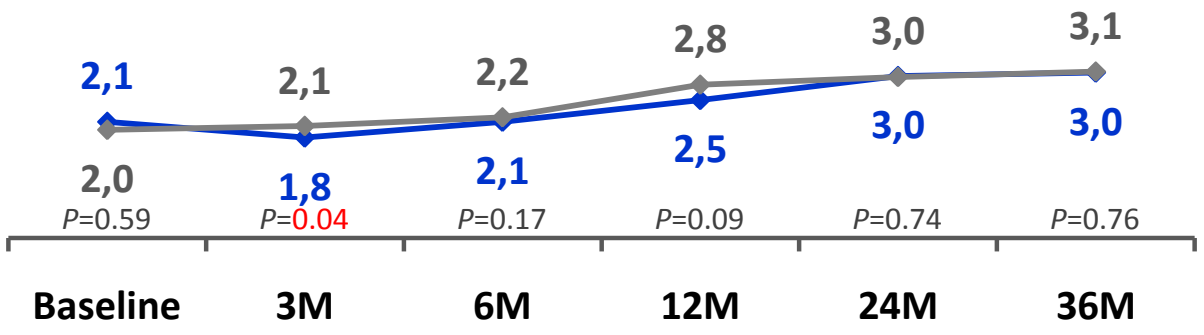
SPYRAL HTN – ON MED Study : 36-month results



Antihypertensive Medications

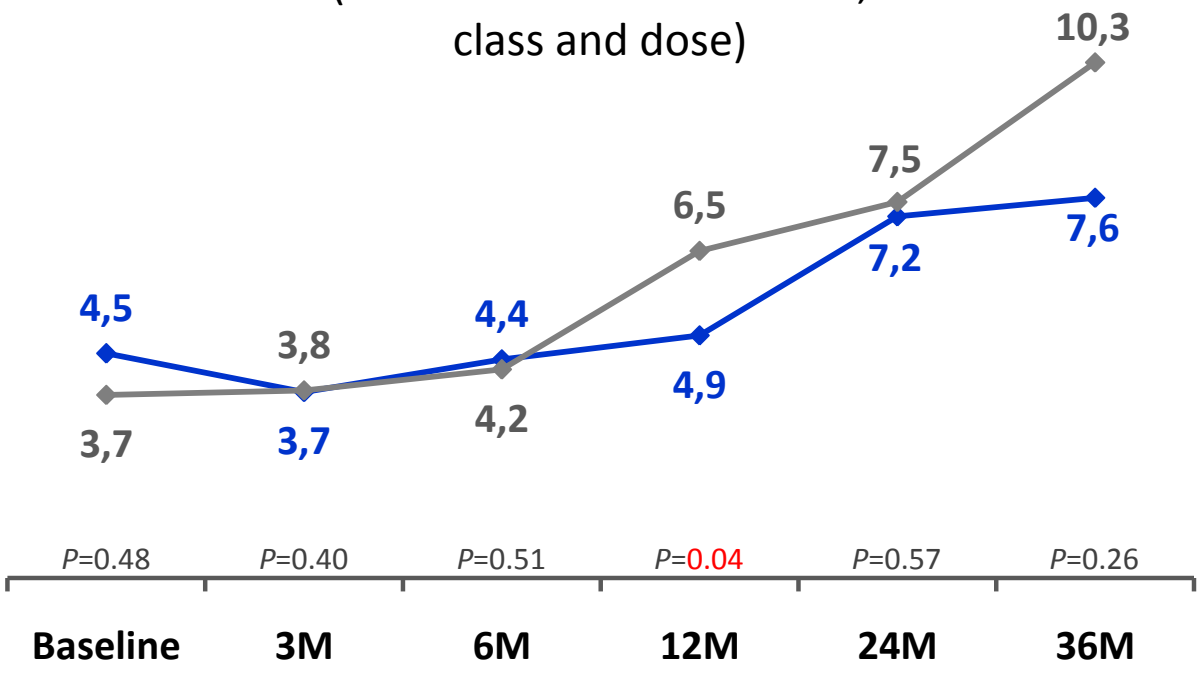
Number of medications[1]

Med. adherence at 36 months:
RDN 77%, Sham 93%



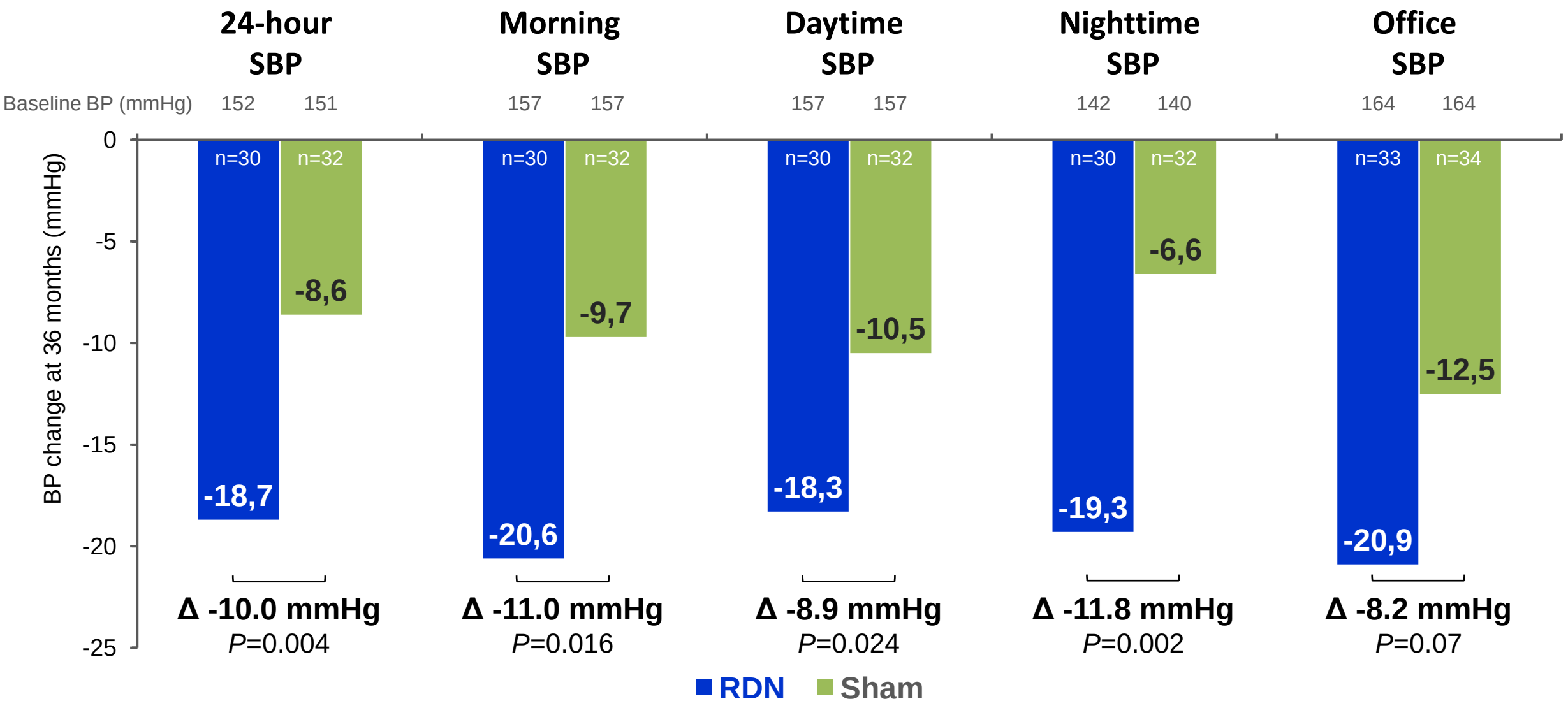
Medication burden[1,2]

(based on number of meds, class and dose)



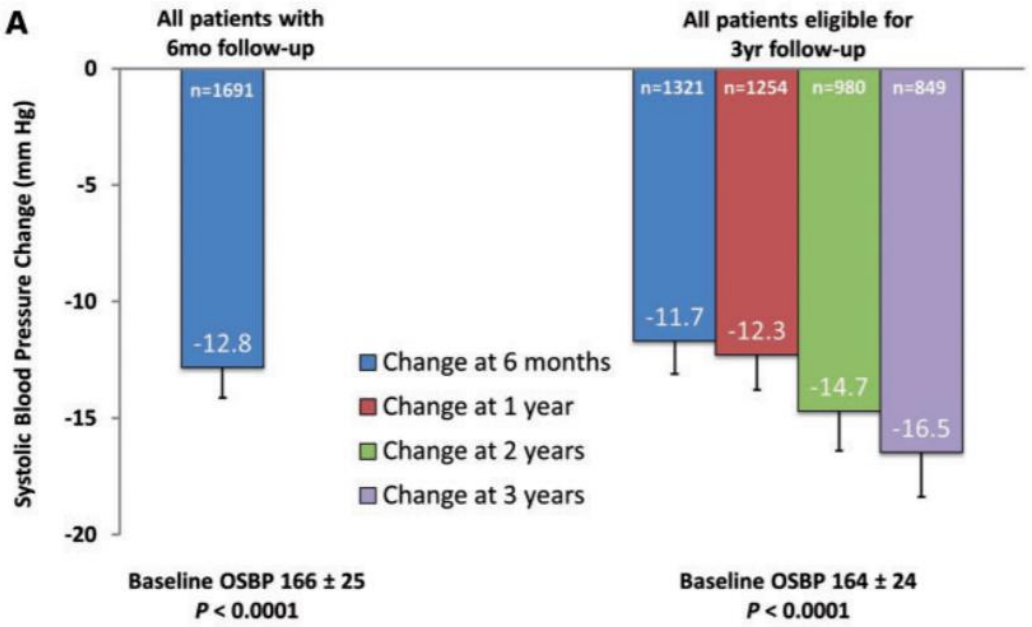
RDN Sham

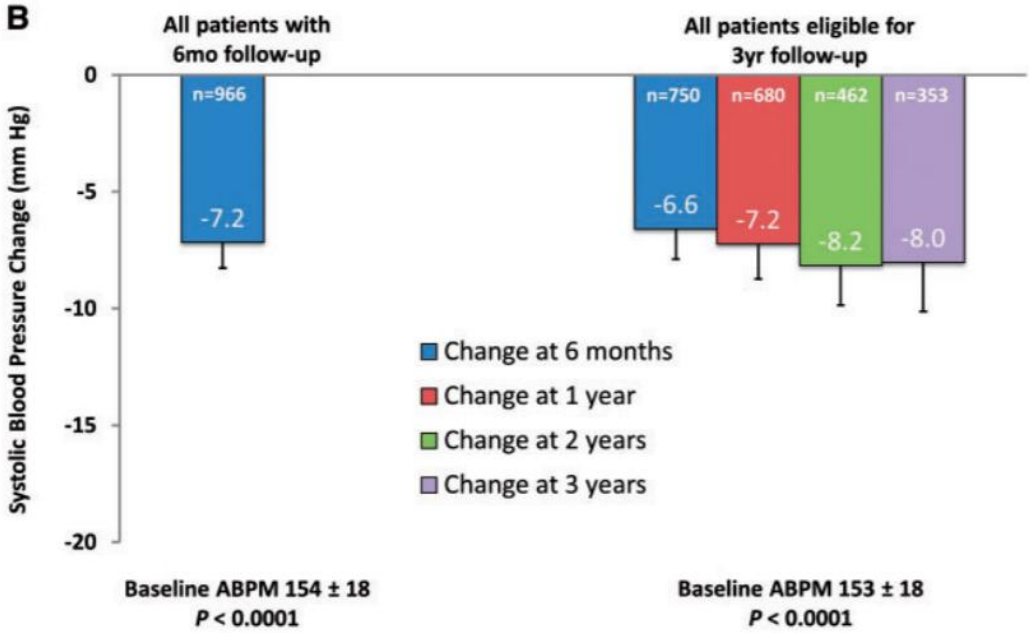
Systolic BP Changes from Baseline to 36 Months



Long-term BP effects : Global Symplicity registry

	Baseline (n = 1721)	1 year (n = 1729)	2 years (n = 1729)	3 years (n = 1730)	*P*-value
Antihypertensive medication classes	4.5 ± 1.4	4.4 ± 1.4	4.4 ± 1.5	4.4 ± 1.5	<0.001

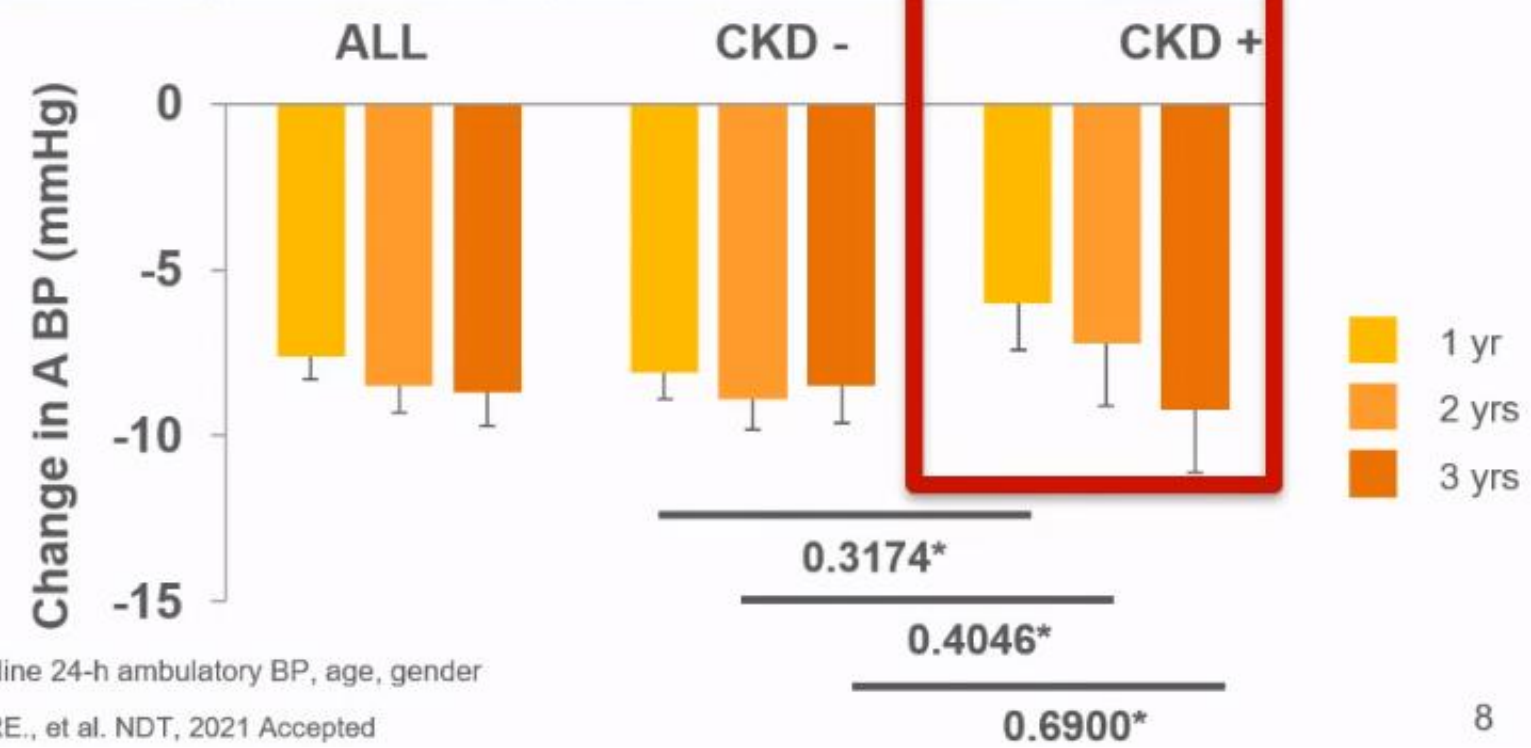




Mahfoud F. Eur Heart J. 2019 Mar 21. pii: ehz118.

BP reduction in CKD patients in GSR

Parameter	ALL (N=1980)	CKD - (N=1505)	CKD + (N=475)
Age (yrs)	61 ± 12	60 ± 12	65 ± 11
% Male (n)	58%	60%	52%
# Med classes	4.6 ± 1.3	4.5 ± 1.3	4.8 ± 1.3
eGFR at Baseline	77 ± 24	87 ± 19	47 ± 10
Baseline ABP (mmHg)	154/86 ± 18/14	154/88 ± 18/14	154/82 ± 19/14



*adjusted for baseline 24-h ambulatory BP, age, gender

Ott,C., Schmieder, RE., et al. NDT, 2021 Accepted

BP Changes With RDN Versus Sham First- vs. Second-Generation Trials

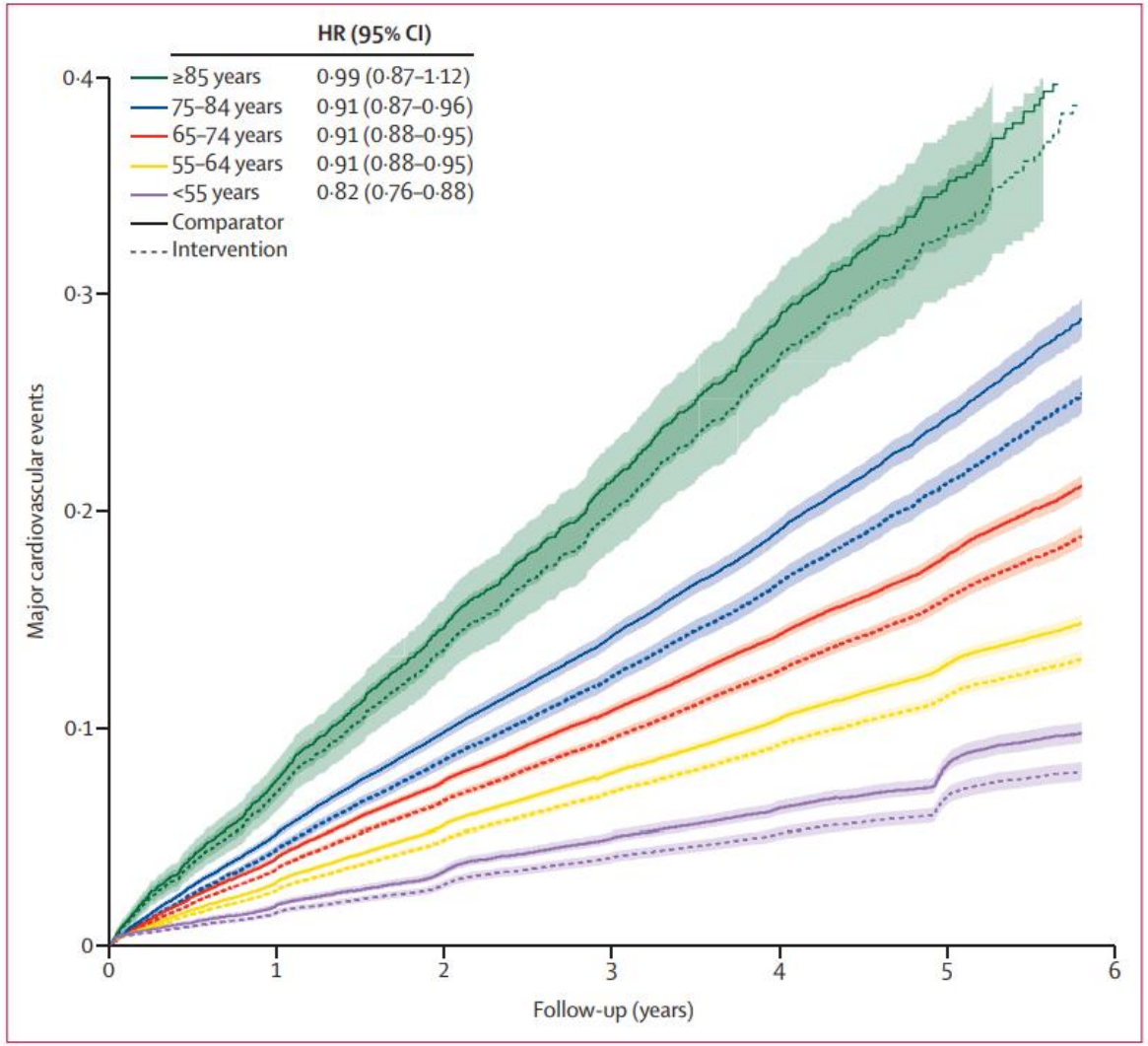
Outcome of Interest	Weighted Mean Difference (95% Confidence Interval)	
	First-Generation RSD Trials	Second-Generation RSD Trials
24-h ambulatory systolic blood pressure	−2.23 (−4.70 to 0.25)	−4.85 (−7.12 to −2.58)
24-h ambulatory diastolic blood pressure	−0.66 (−2.07 to 0.75)	−2.98 (−5.10 to −0.86)
Daytime ambulatory diastolic blood pressure	−0.72 (−2.24 to 0.80)	−2.72 (−4.50 to −0.95)
Night-time ambulatory systolic blood pressure	−1.86 (−4.70 to 0.98)	−6.49 (−16.47 to 3.49)
Night-time ambulatory diastolic blood pressure	−0.24 (−2.73 to 2.26)	−2.74 (−7.59 to 2.11)
Change in glomerular filtration rate	−0.40 (−2.65 to 1.85)	−0.02 (−2.64 to 2.61)

Metaanalysis of RCT, 11 457 pts, at least 3 weeks treatment:
Triple compared with dual therapy : ΔSBP by 5.4 mmHg (95% CI 4.6–6.3)

Salam A et al. J Hypertens 2019. ePub

Sardar P. J Am Coll Cardiol 2019;73:1633

Rate of MACE per 5 mmHg reduction in SBP stratified by treatment allocation and age categories at baseline



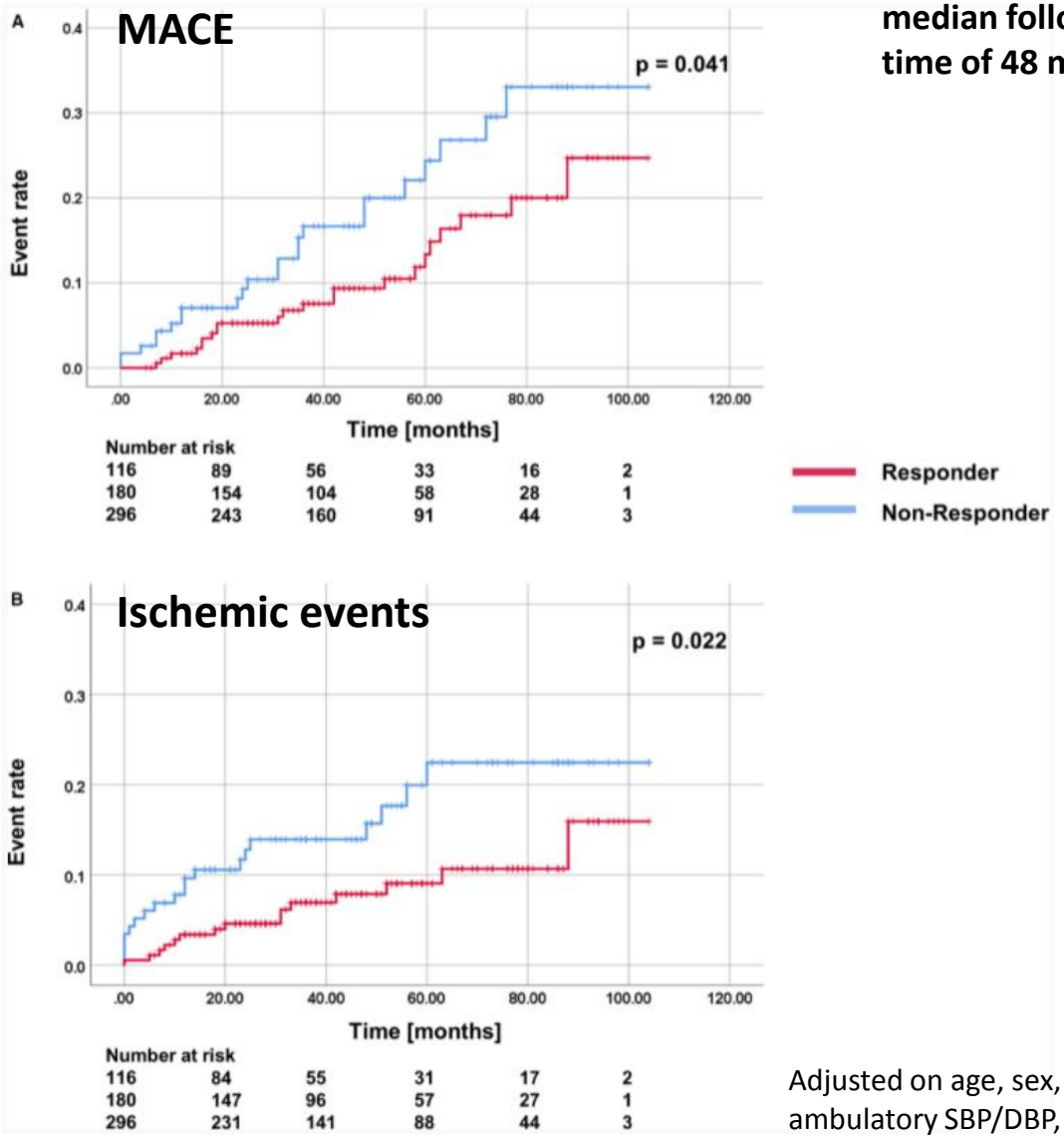
Major cardiovascular events: composite of fatal or non-fatal stroke, fatal or non-fatal MI or IHD , or HF causing death or requiring hospital admission.

BPLTT Collaboration. Lancet. 2021;398:1053

Long-Term Outcomes for Responders vs. Non-Responders to RDN in Resistant Hypertension: An observational study

BP responders (≥5 mmHg 24-hour ABP reduction)

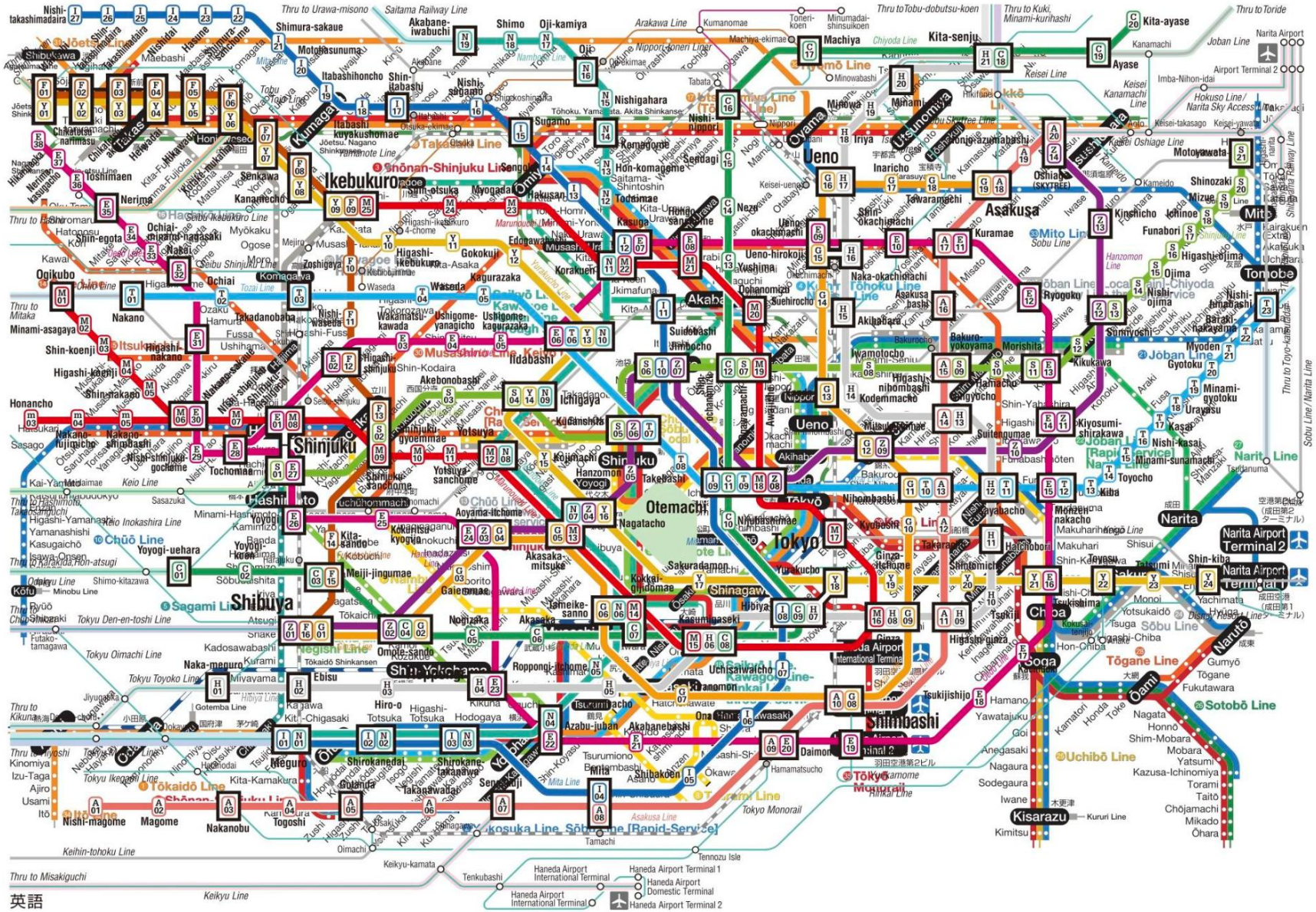
SBP response (mmHg)	6 months	12 months
Responders (n=180)	12.1±12.8	2.8±13.8
Non-responders (n=116)	11.7±12.0	2.0±10.7



median follow-up time of 48 months

Adjusted on age, sex, baseline ambulatory SBP/DBP, ISH, past stroke

Where is the ideal patient?



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

Biomarkers

- Ghrelin, MR-proadrenomedullin, neuropeptide-Y, intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1 (VCAM)
- Micro-RNA
- Muscle SNA

Hemodynamic parameters

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

Lauder L, Prog Cardiovasc Dis. 2021;65:76

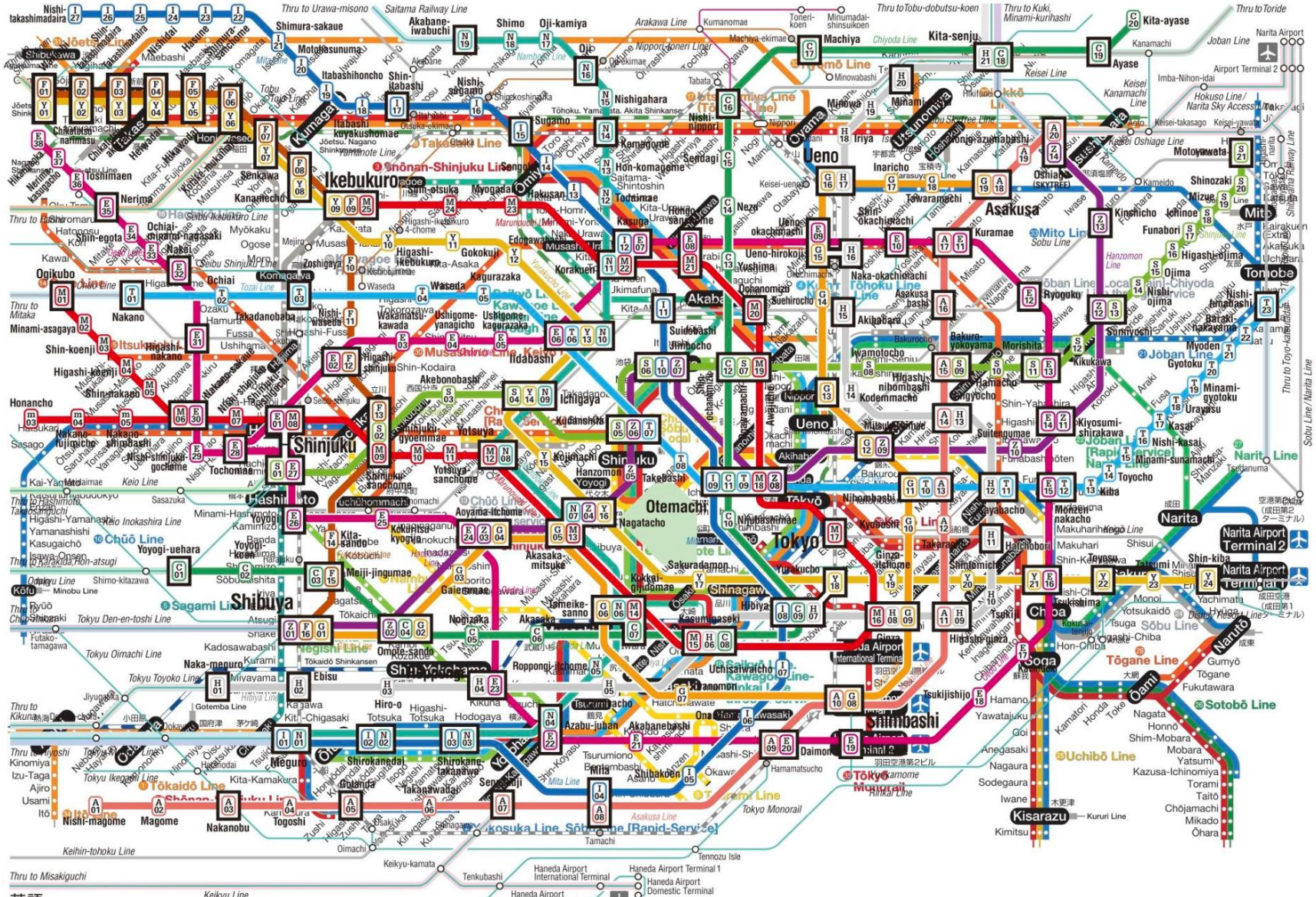
Conclusion

- 4 sham-controlled RCT of the 2.0 generation yielded now similarity in the average BP decrease following RDN:
  - Reduction of ABP of ≈ 5 to 7 mmHg and of OBP of ≈ 10 mmHg.
  - Such a decrease in BP by pharmacologic therapy has been found to be associated with lower incidence of cardiovascular events (heart failure and stroke) by ≈ 25%.

- Questions left:
  - heterogeneity of the BP-lowering response point to the clinical need to identify predictors for efficacy,
  - long-term efficacy and durability
  - Long term safety

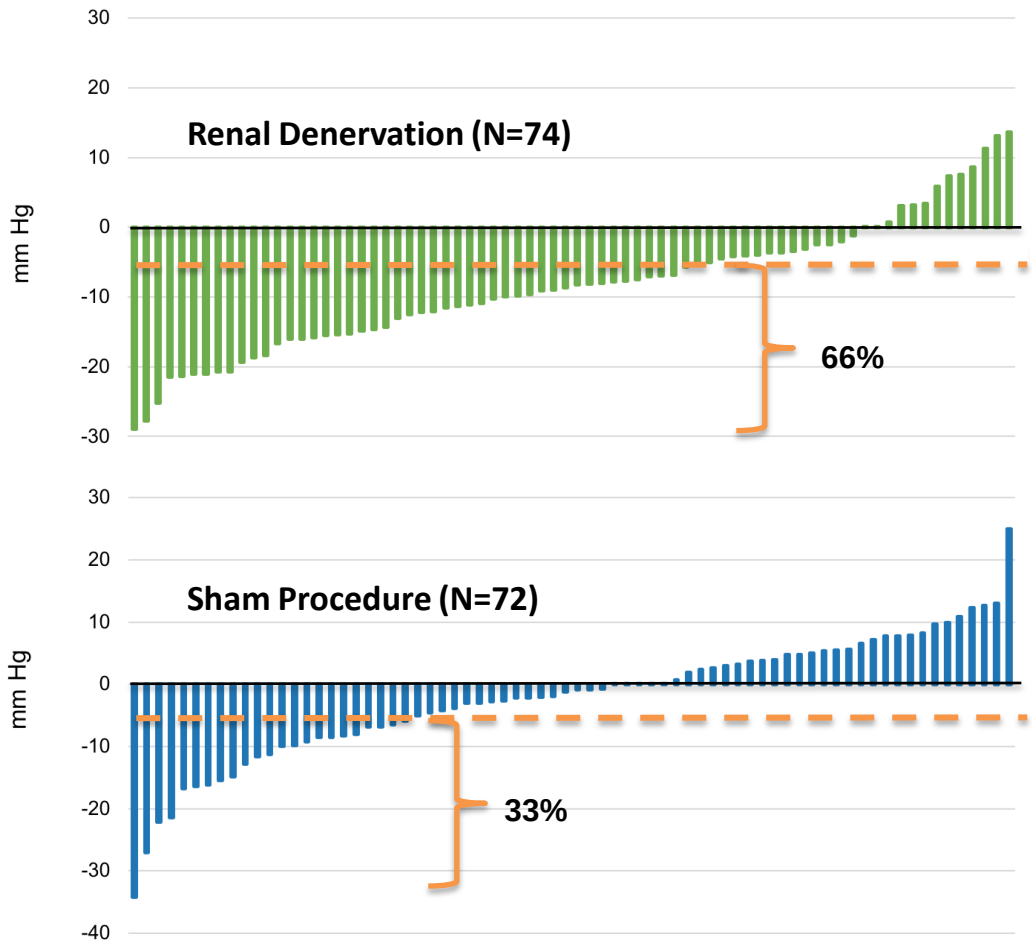
Predictors of BP response to RDN

Where is our ideal patient?



Individual Patient Response at 2 Months

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



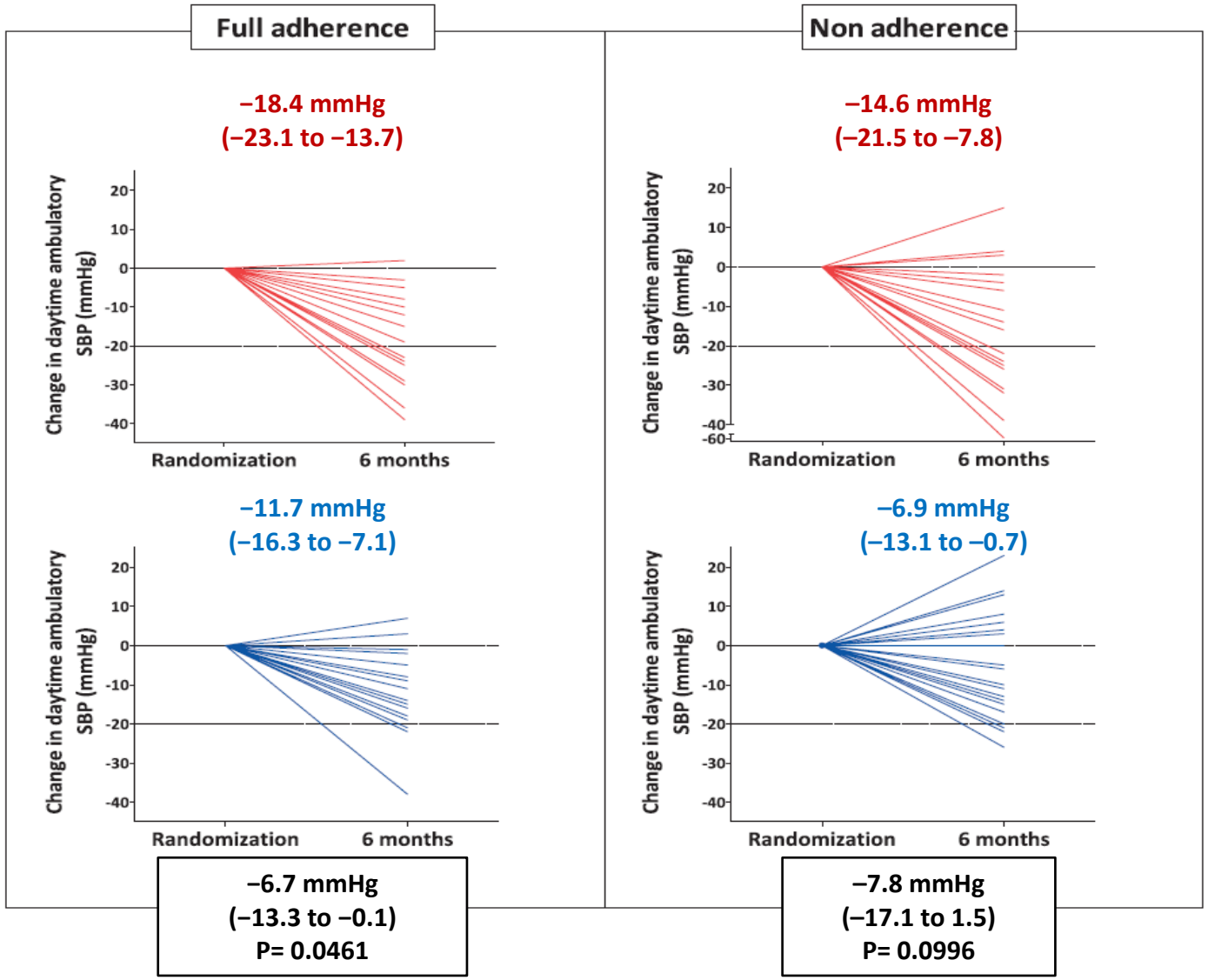
% Patients with ≥ 5 mm Hg Decrease

Renal Denervation: 66%
Sham Procedure: 33%

P<0.001

BP response to RDN and SSAHT in adherent and nonadherent patients

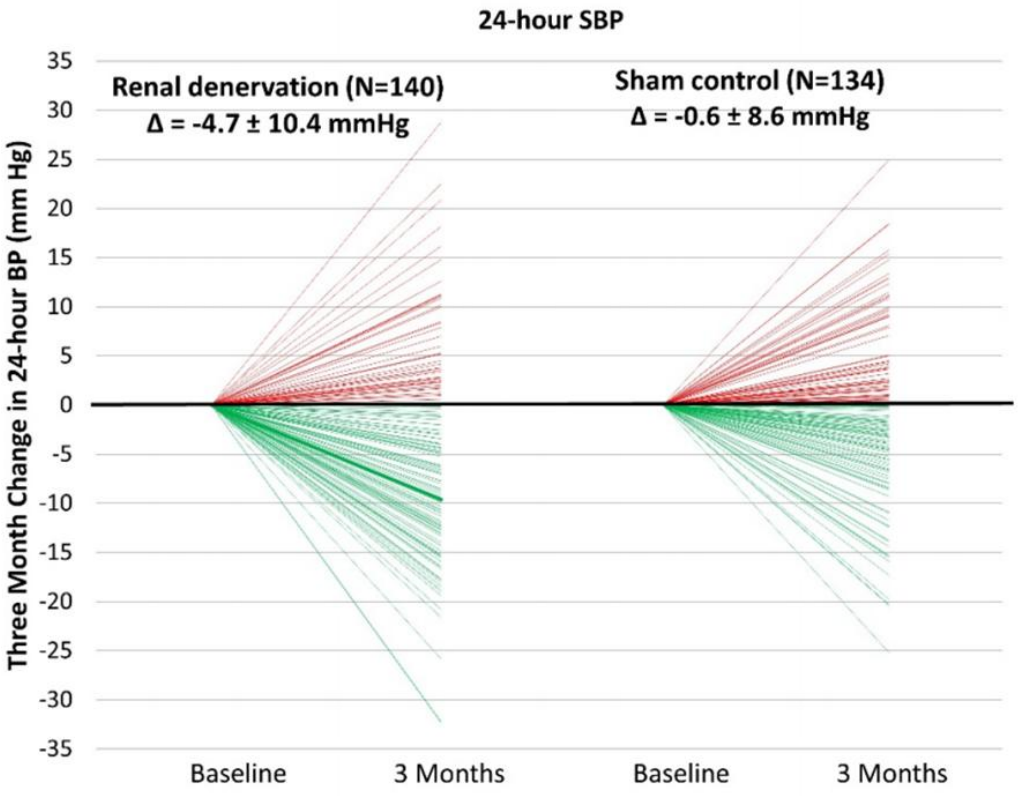
11 RF ablations, main



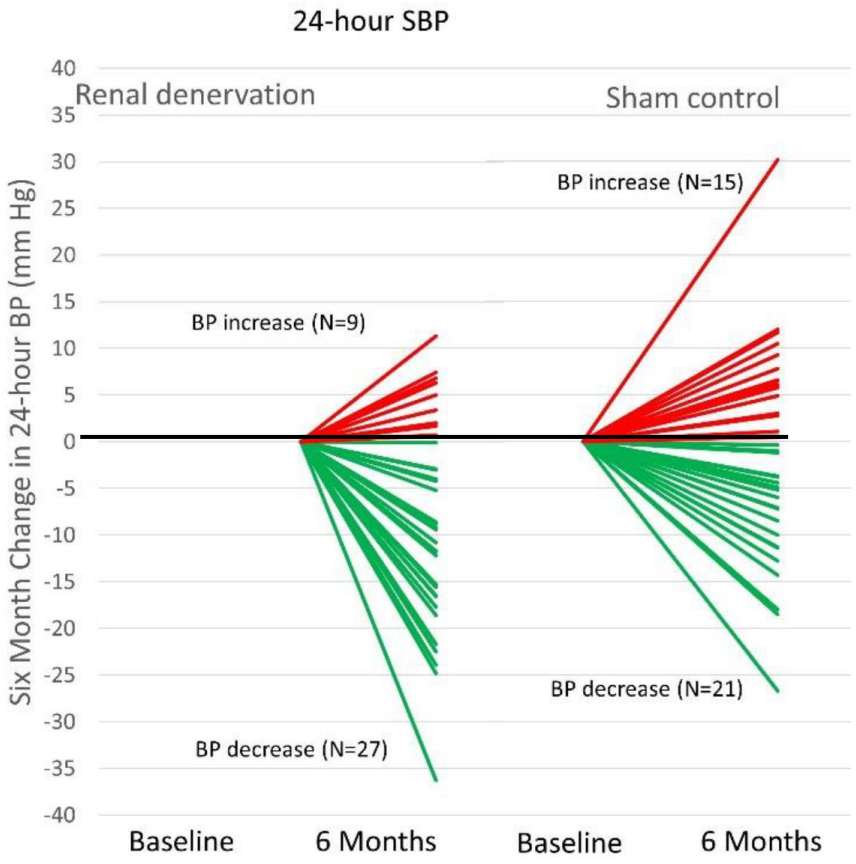
Large between-patient variability in the ABP response to RDN and sham procedure

> 40 RF ablations, distal, branch

Off-MED



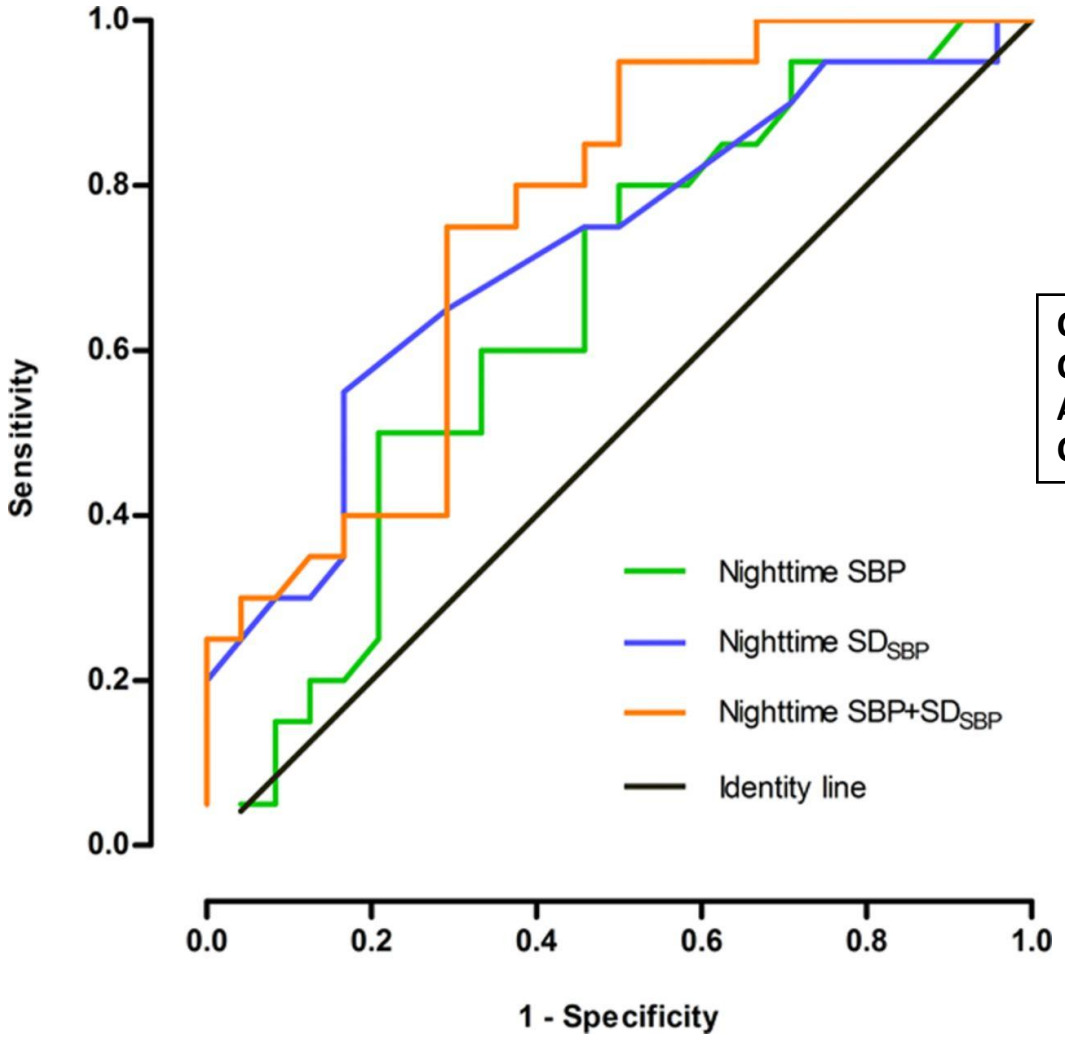
On-MED



Böhm M et al. Lancet 2020;395:1444-1451.

Kandzari DE Lancet. 2018; May 23

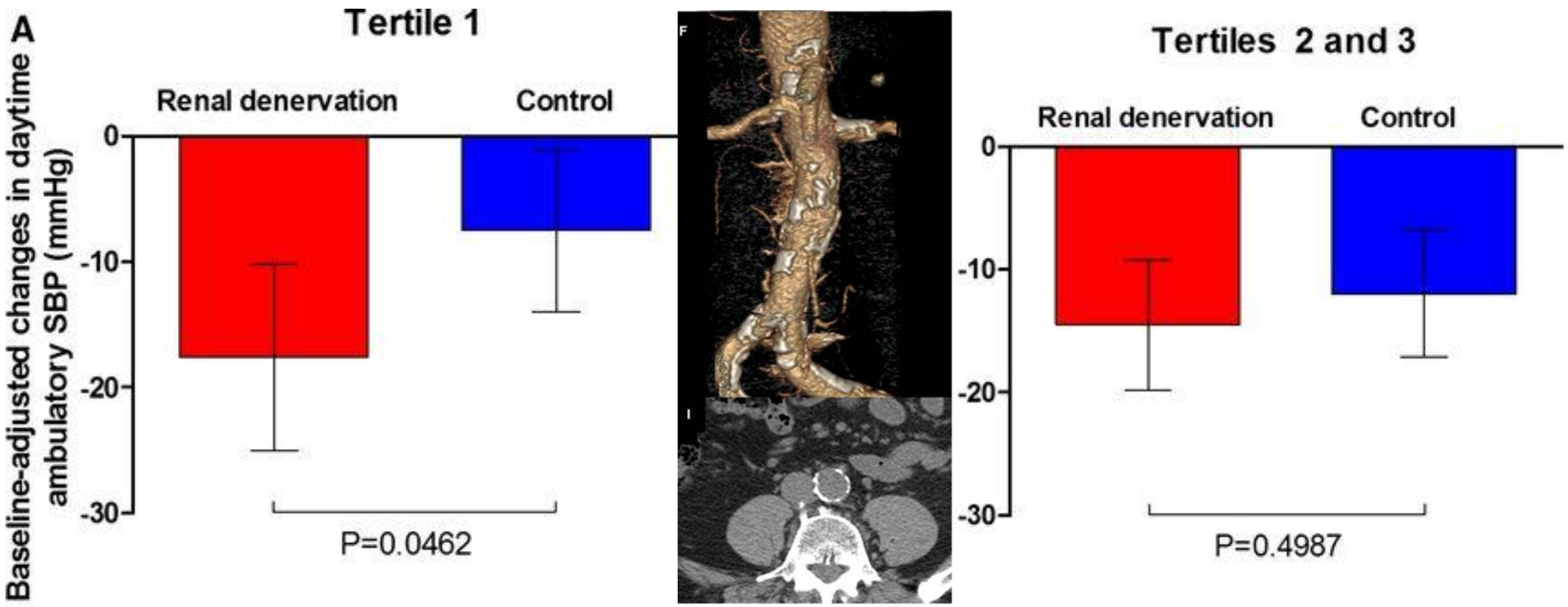
ROC curves of baseline nighttime SBP and nighttime SD_{SBP} to predict responders to RDN (daytime SBP decrease ≥ 20 mmHg)



Cutoff baseline nighttime SBP: 136 mm Hg
Cutoff nighttime SD_{SBP} :12 mm Hg
AUC: 0.76 (95%CI: 0.61-0.90)
Correct prediction of responders to RDN: 70%

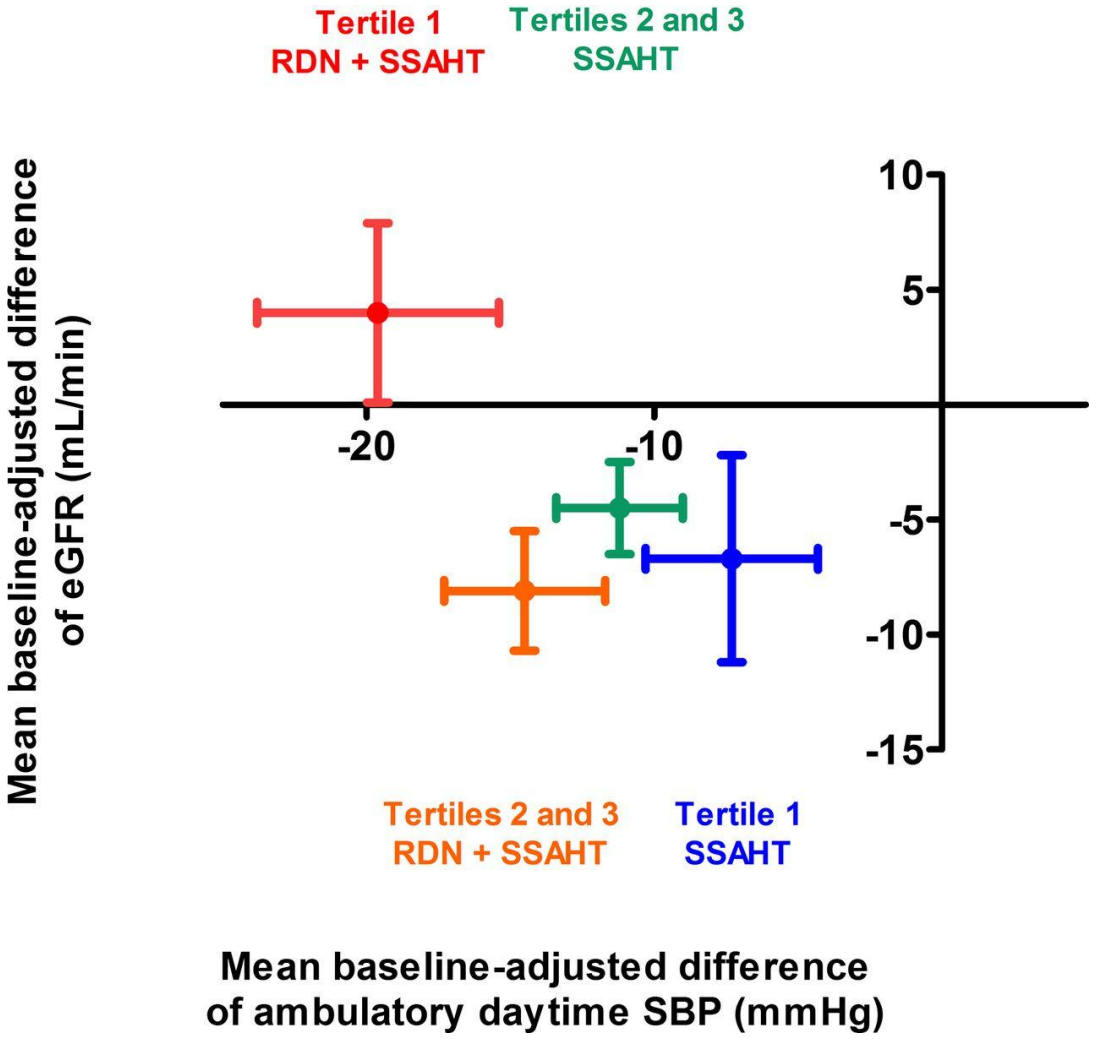
Philippe Gosse et al. Hypertension. 2017;69:494-500

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



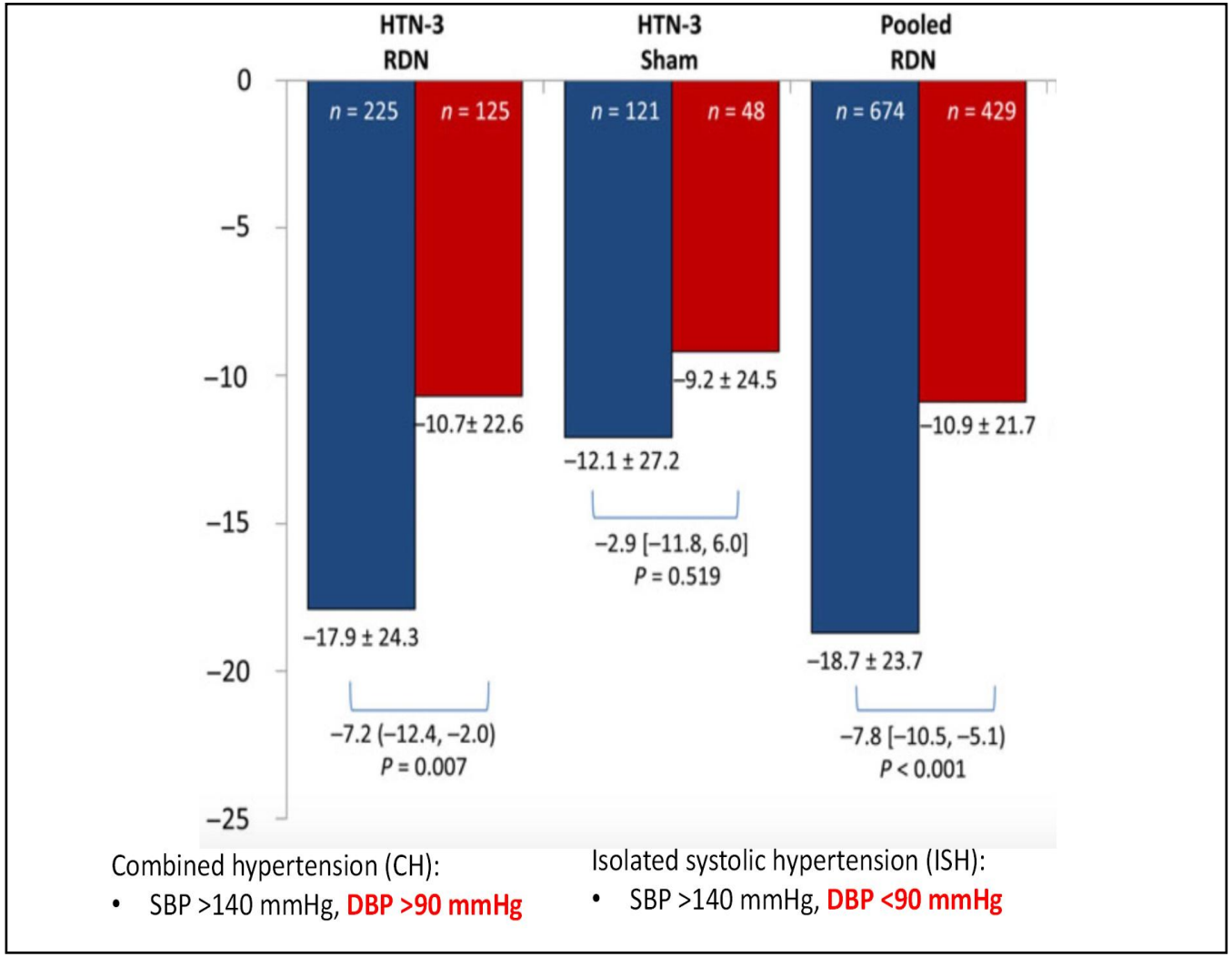
Pierre-Yves Courand et al. J Am Heart Assoc 2017;6:e007062

Relationship between the changes from baseline to 6 months in mean baseline-adjusted eGFR and daytime ambulatory SBP according to tertiles of AAC



Pierre-Yves Courand et al. J Am Heart Assoc 2017;6:e007062

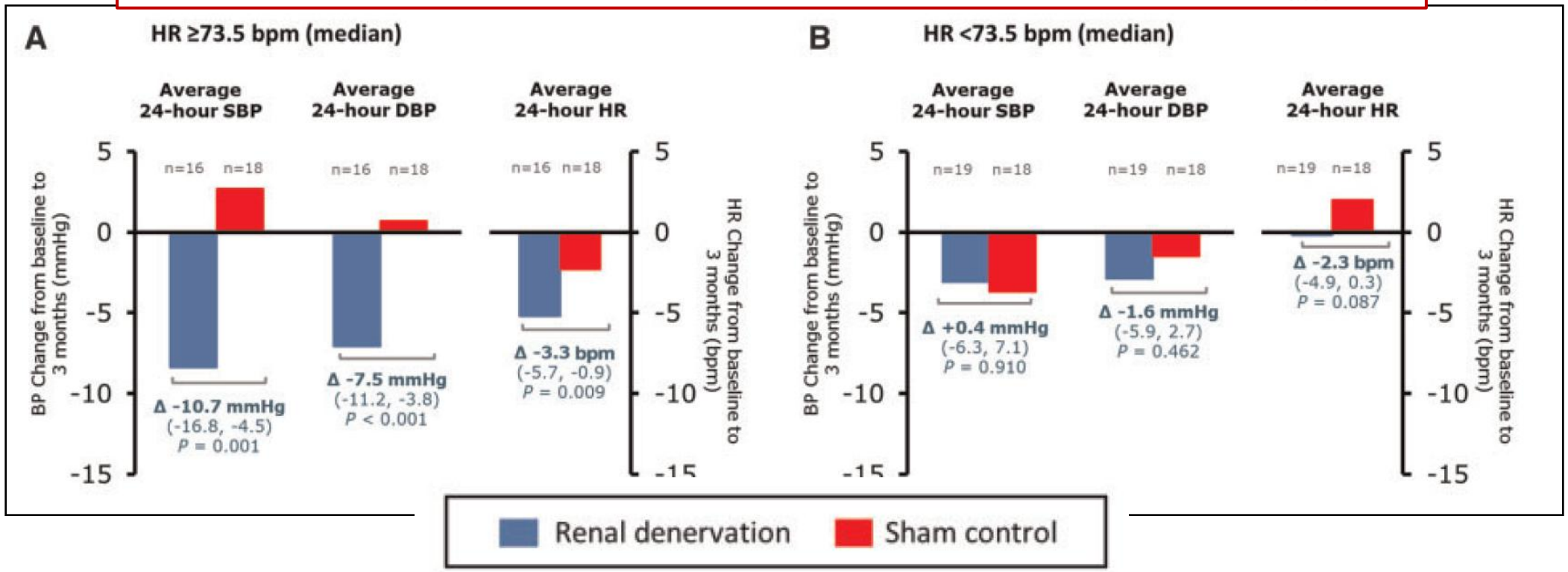
Office SBP changes at 6 months in patients with CH and ISH



Mahfoud F et al. Eur Heart J 2016

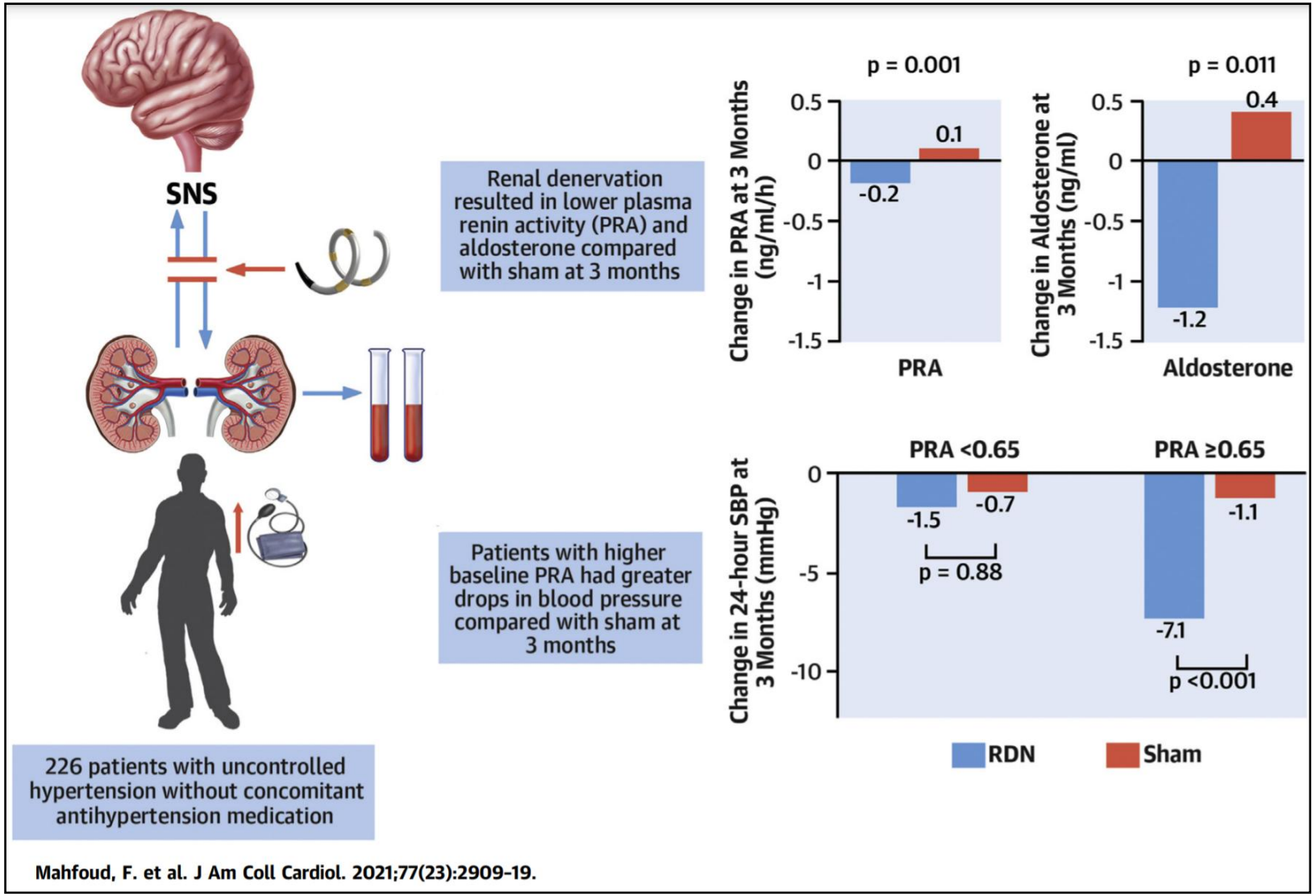
Baseline 24-h HR : a predictor of changes in BP ?

	Baseline		3 months		Change at 3 months		
	RDN (*N* = 35)	Sham (*N* = 36)	RDN (*N* = 35)	Sham (*N* = 36)	RDN (*N* = 35)	Sham (*N* = 36)	Mean difference: RDN vs. sham[a]
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



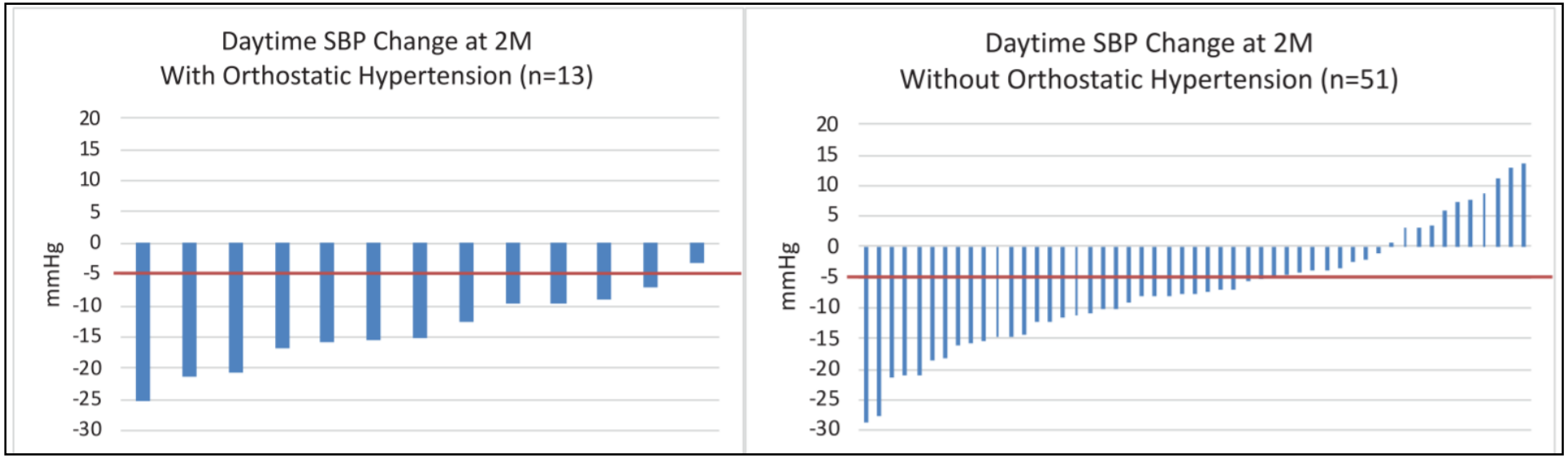
Bohm M. Eur Heart J 2019; 40: 743

Impact of RDN on Plasma Renin Activity, Aldosterone, and BP Reduction at 3 Months



Mahfoud, F. et al. J Am Coll Cardiol. 2021;77(23):2909-19.

Change in ASBP after RDN in patients with or without orthostatic HTN in RADIANCE SOLO

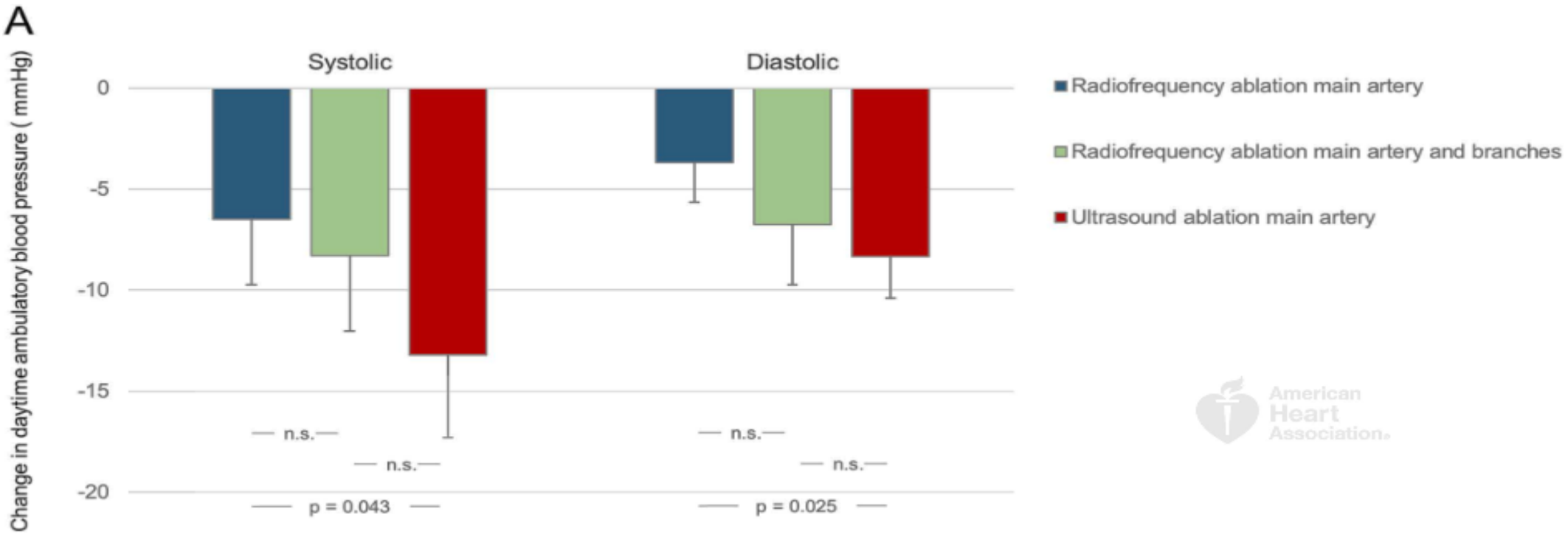


Parameters	With orthostatic hypertension ($N = 13$)	Without orthostatic hypertension ($N = 51$)	p value
Change from baseline to 2 months			
Daytime SBP (mmHg)	-14.00 ± 6.26	-7.05 ± 9.82	0.022
Daytime DBP (mmHg)	-8.92 ± 5.10	-4.47 ± 5.88	0.025
Nighttime SBP (mmHg)	-7.07 ± 11.75	-4.24 ± 12.32	0.641
Nighttime DBP (mmHg)	-5.28 ± 8.18	-3.13 ± 9.00	0.488
24-H SBP (mmHg)	-10.98 ± 7.68	-6.01 ± 9.04	0.094
24-H DBP (mmHg)	-7.28 ± 5.55	-3.93 ± 6.01	0.111
24-H HR (bpm)	0.55 ± 4.52	1.24 ± 4.68	0.700

Saxena M. J Hum Hypertens. 2021 May 24.

RADIOSOUND-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.

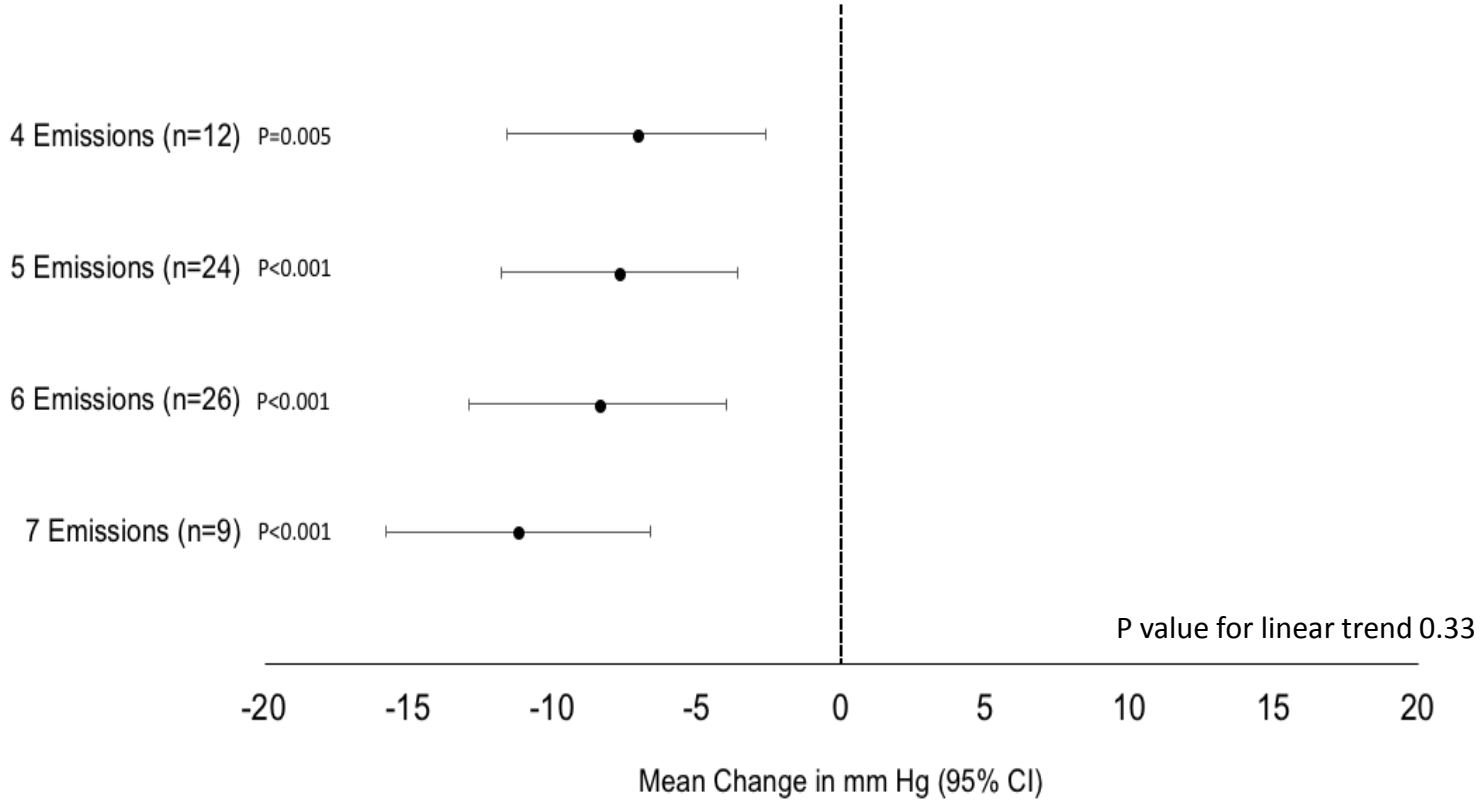


	All (n = 120)	RF main only (n = 39)	RF branches (n = 39)	US (n = 42)	*p*-value
Ablation points right renal artery	10.0 ±7.4	9.1 ±3.0	18.3 ±6.1	3.2 ±0.8	<0.001†
Ablation points left renal artery	9.2 ±6.7	8.1 ±2.2	16.8 ±6.0	3.2 ±0.9	<0.001†

Fengler et al. Circulation 2018 epub

SOLO Trial: 2-Month Change in Daytime Systolic ABP

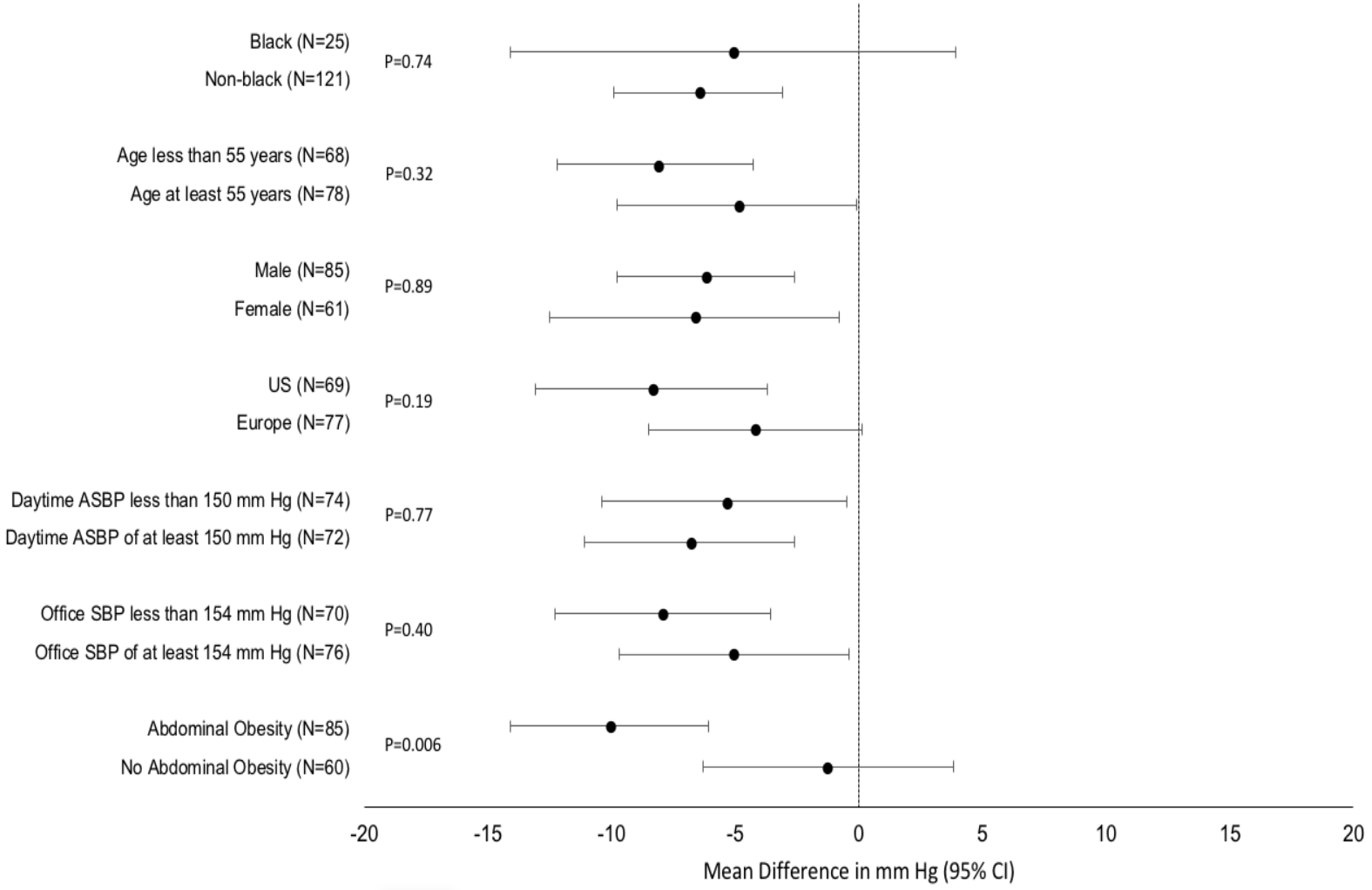
By Total Number of Ultrasound Emissions in RDN Group



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

Prespecified Subgroup Analysis:

Between Group Difference in 2-Month Daytime Systolic ABP Change



Potential predictors of response to RDN

Baseline characteristics

- **Systolic blood pressure**
- **Amplitude**
- **Variability**
- **Combined versus ISH**
- **Pulse wave velocity**
- **Heart rate**
- **Variability**
- **Antihypertensive medications**
- **Poor drug adherence**
- **Ethnicity**
- **Risk factors**
- **Obstructive sleep apnoea**
- **Chronic kidney disease**
- **Obesity**
- **PRA but not PRC**

Procedural variables

- Number of ablations, Anatomic site
- Distal branch vessels for RF; accessory RA;
- RA diameter

Biomarkers

- Ghrelin, proADM, NPY, BDNF, ICAM-1, VCAM-1
- microRNA
- MSNA

Invasive/provocative testing

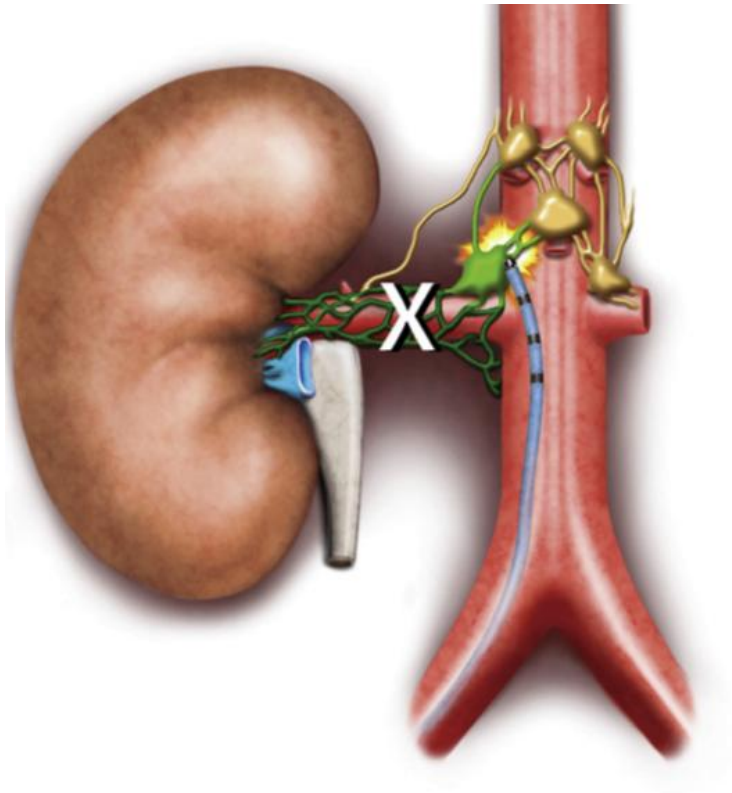
- Renal resistance and wave speed
- Drug challenge (e.g. clonidine)
- Baroreceptor sensitivity
- BP response to orthostasis
- Electrical renal nerve stimulation

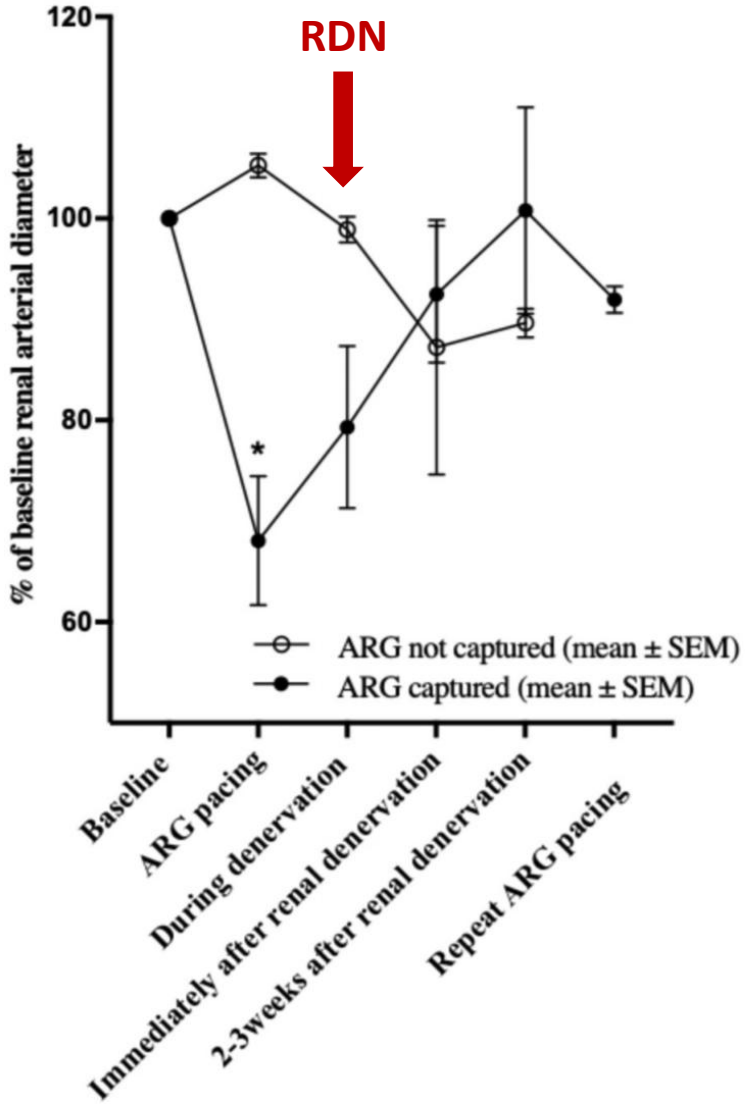
Imaging

- MIBG (kidney/heart)

Mahfoud F, Azizi M. Eur Heart J 2020; 41: 1588

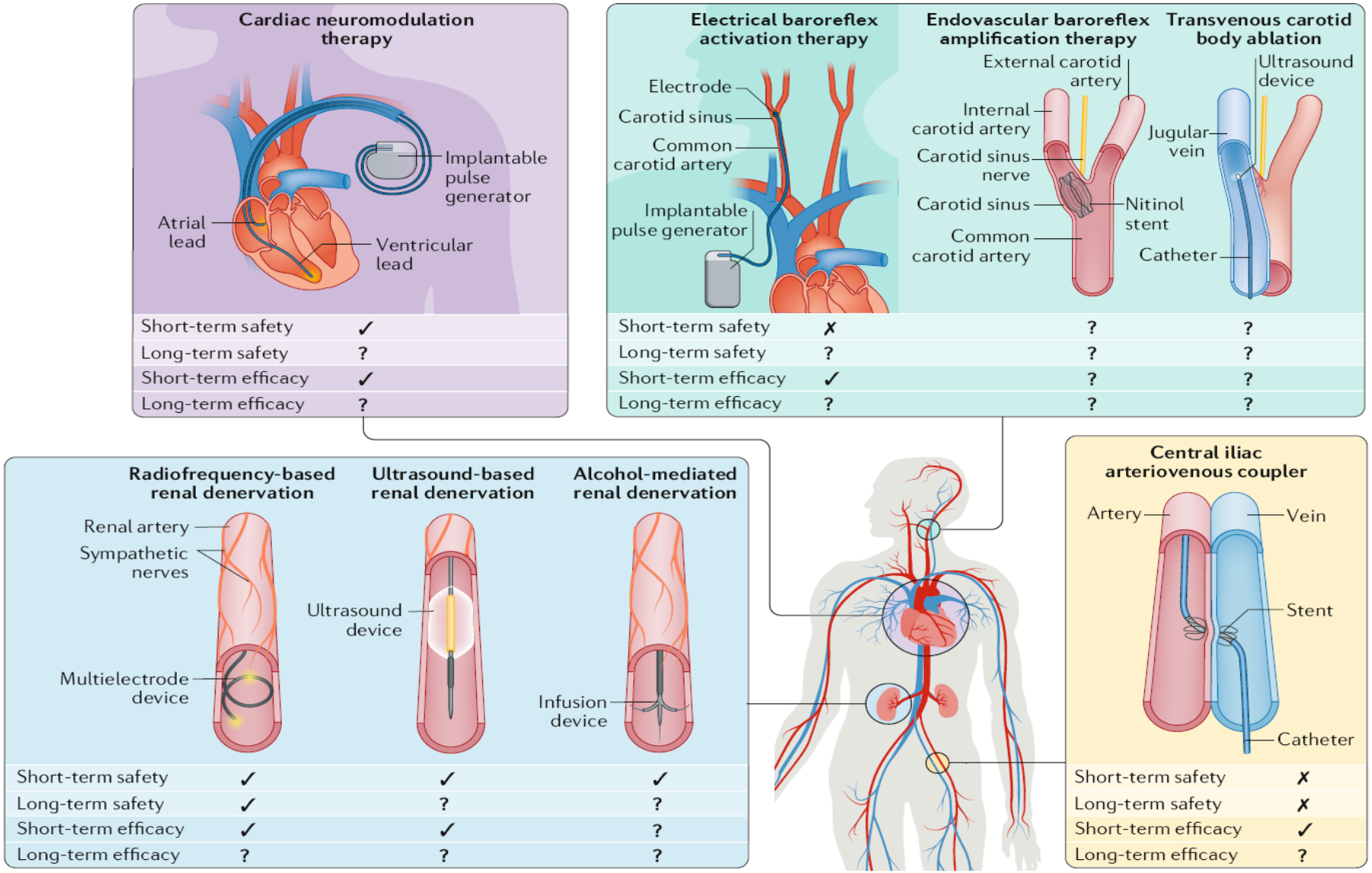
Abolition of aorticorenal ganglion pacing- induced renal arterial vasoconstriction : a procedural endpoint for RDN ?





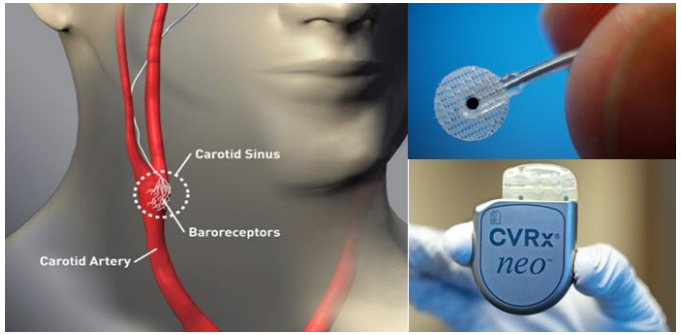
Quian PC. J Am Coll Cardiol Intv 2019;12:1109–20

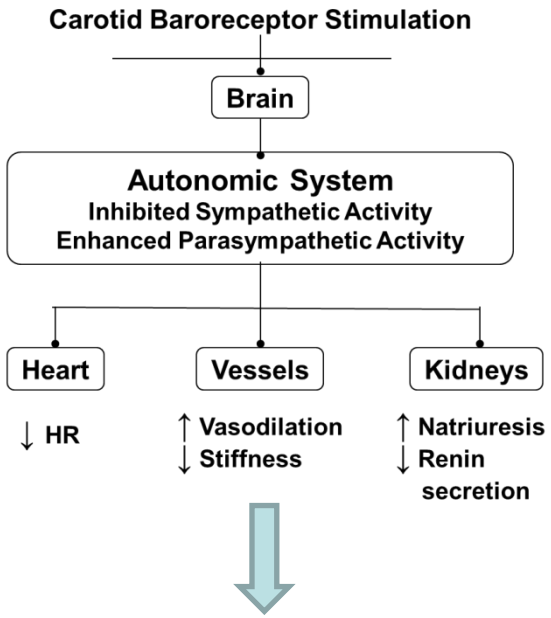
Device-based therapies for arterial hypertension



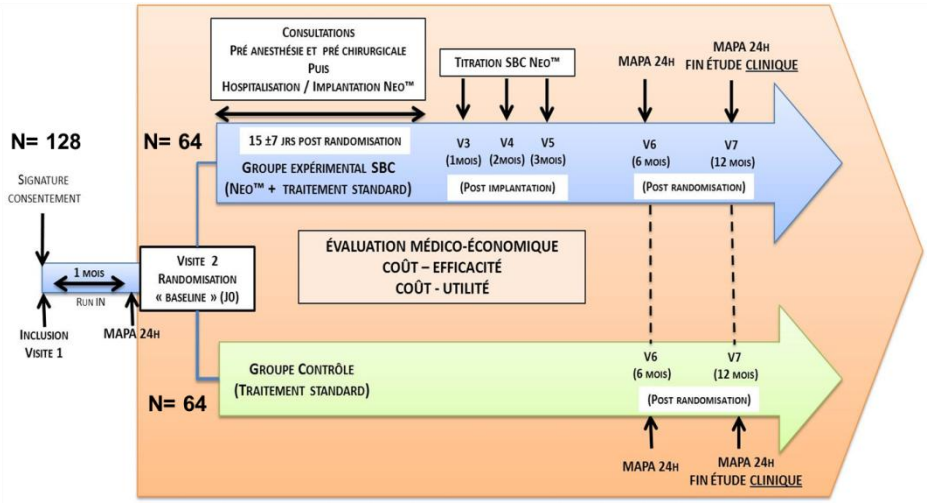
Lauder L, Azizi M. Nat Rev Cardiol. 2020 ahead of print

Baroreflex activation therapy

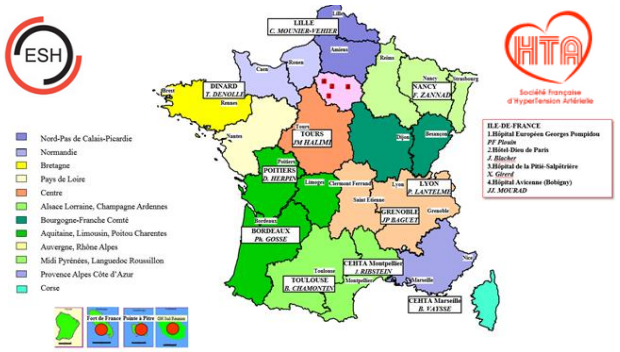




ESTIM-rHTN

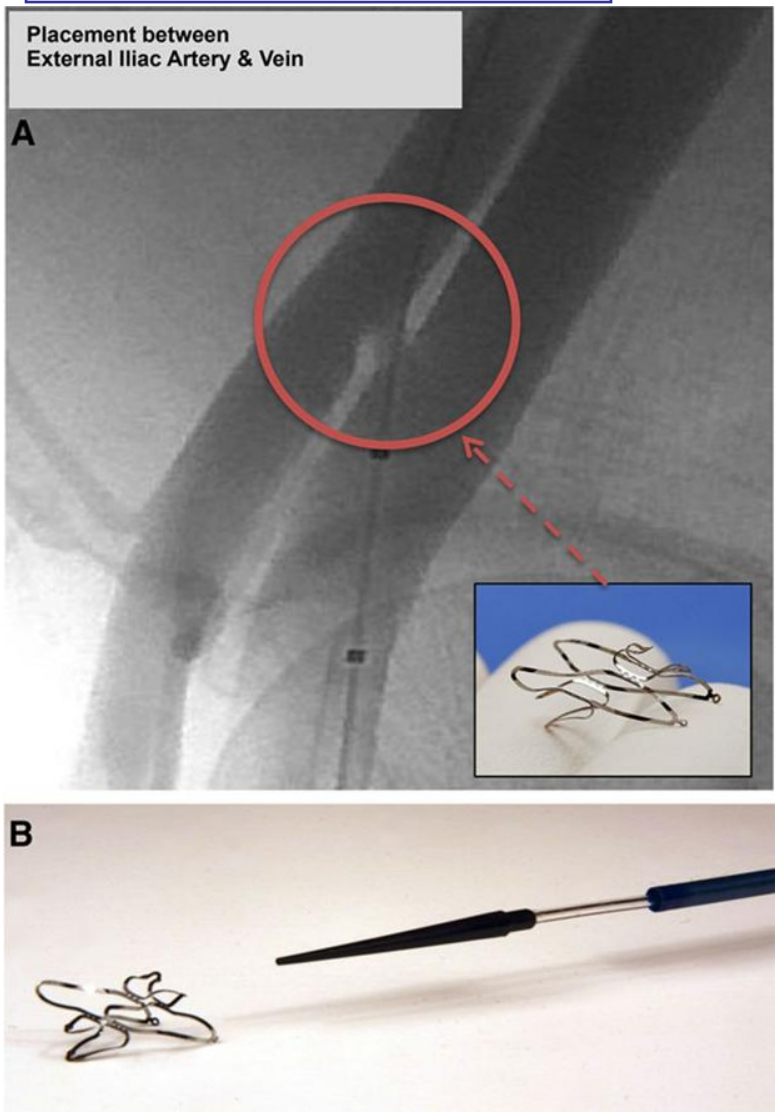


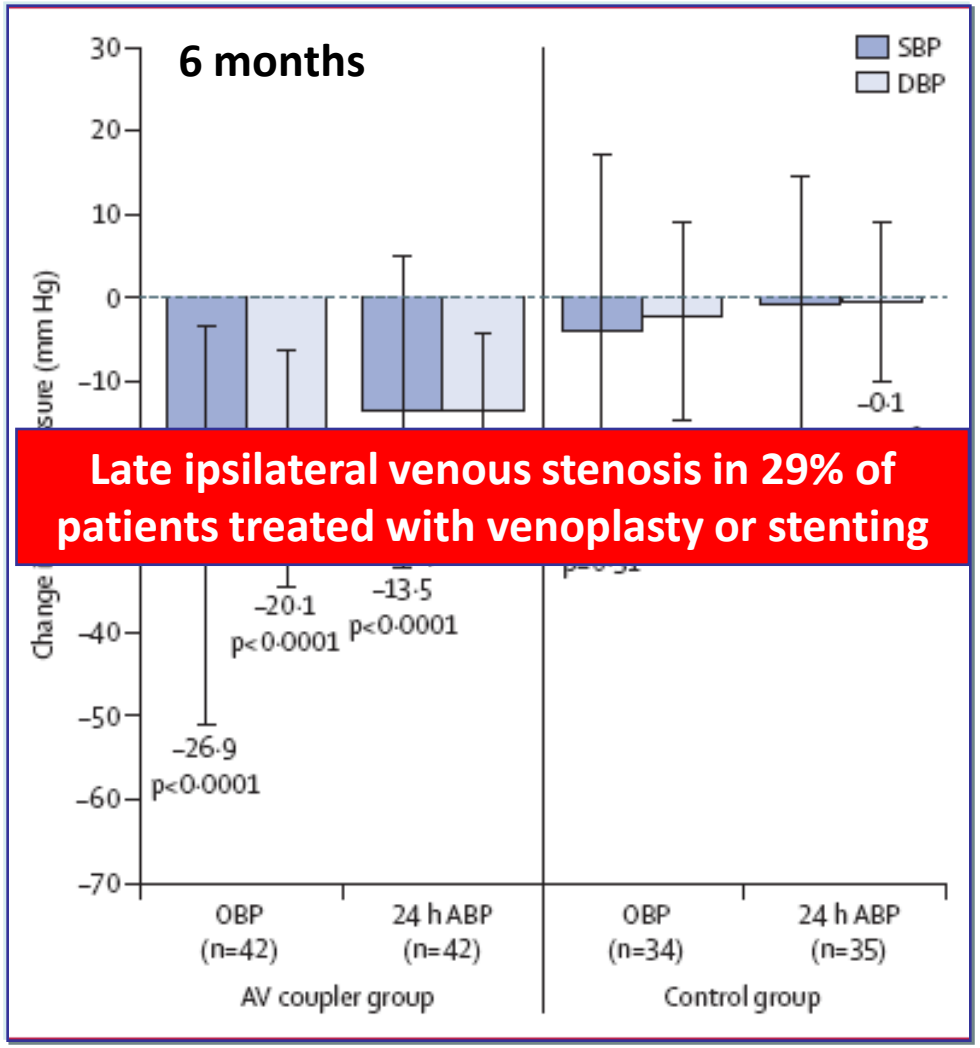
IP: M Azizi, HEGP; P Rossignol, Nancy
Financement: PRME



Central arteriovenous anastomosis for the treatment of patients with RHTN

ROX arteriovenous coupler



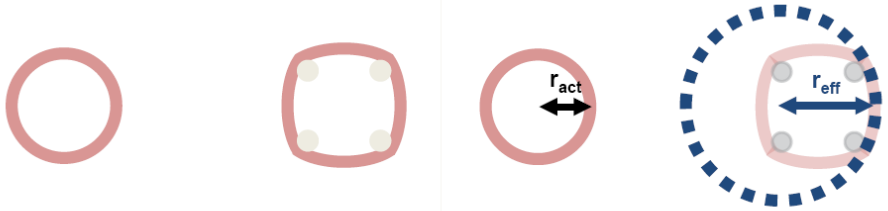


Late ipsilateral venous stenosis in 29% of patients treated with venoplasty or stenting

Lobo MD Lancet 2015; 385: 1634–41

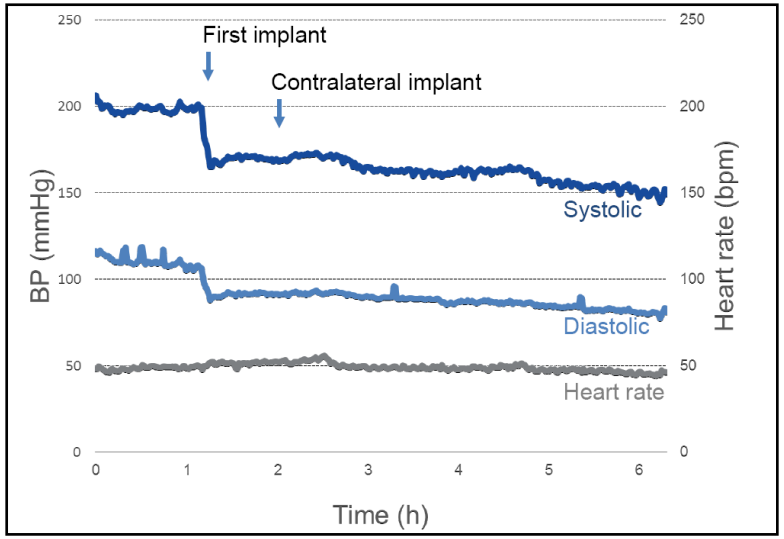
Endovascular baroreflex amplification

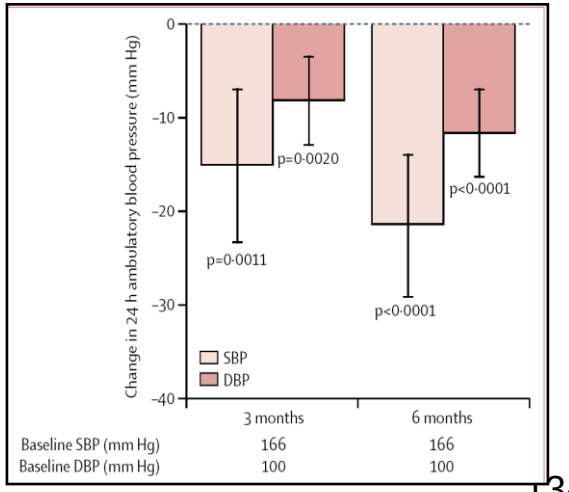
- Baroreceptors are activated by pulsatile strech
- MobiusHD™ : a passive endovascular implant which reshapes the carotid sinus carotidien



MobiusHD™ changes the shape of the carotid sinus **in the diastolic phase**

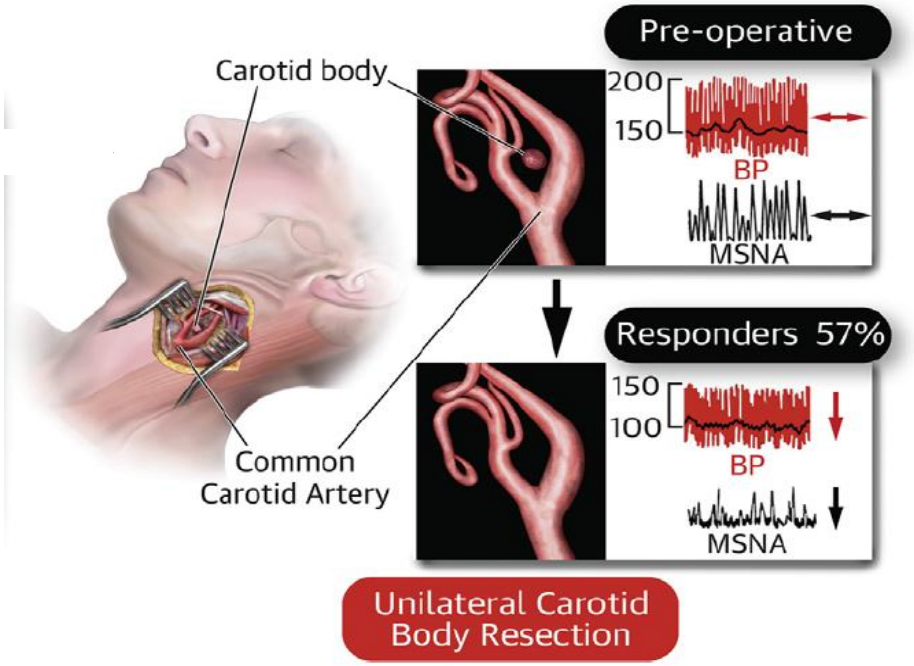
The **effective** radius of the reshaped vessel is much larger than the **actual** radius of the untreated vessel

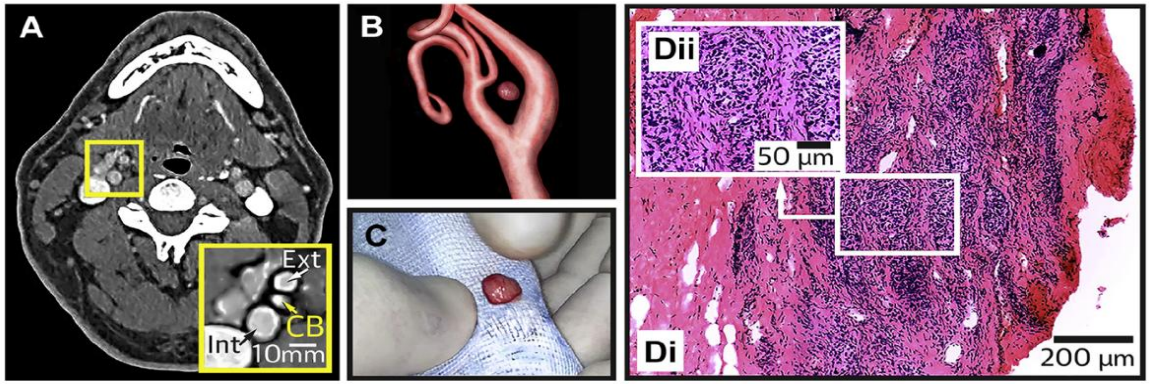




Spiering W. Published online September 1, 2017

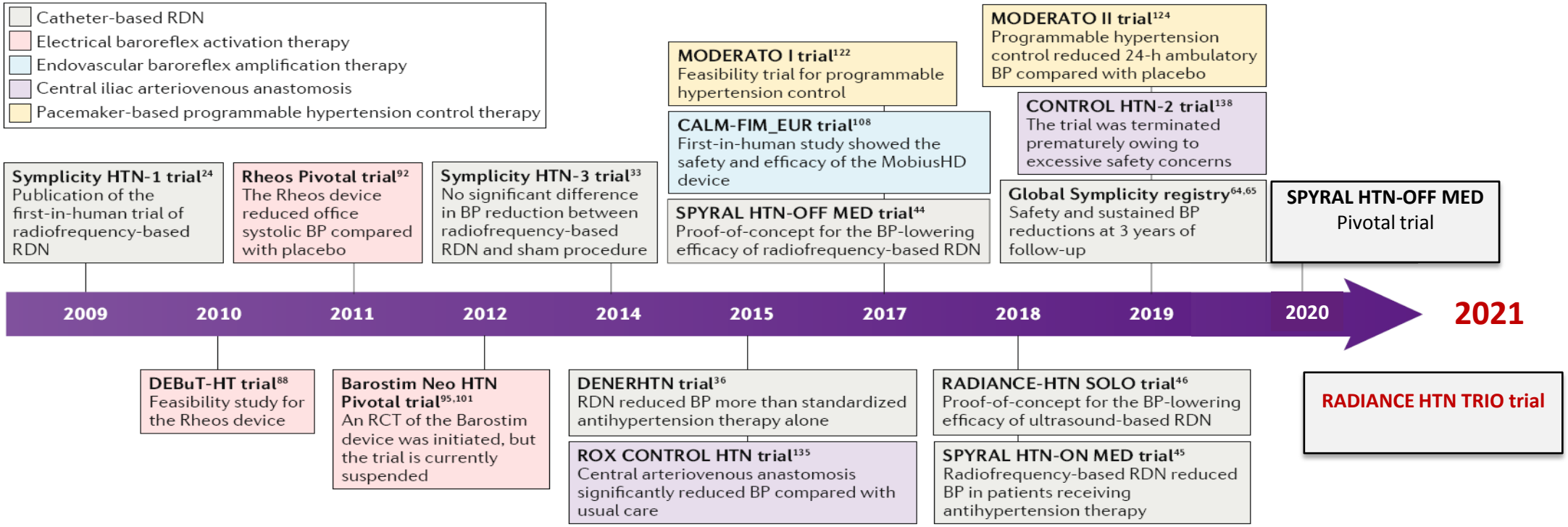
Unilateral Carotid Body Surgical Resection in Resistant Hypertension





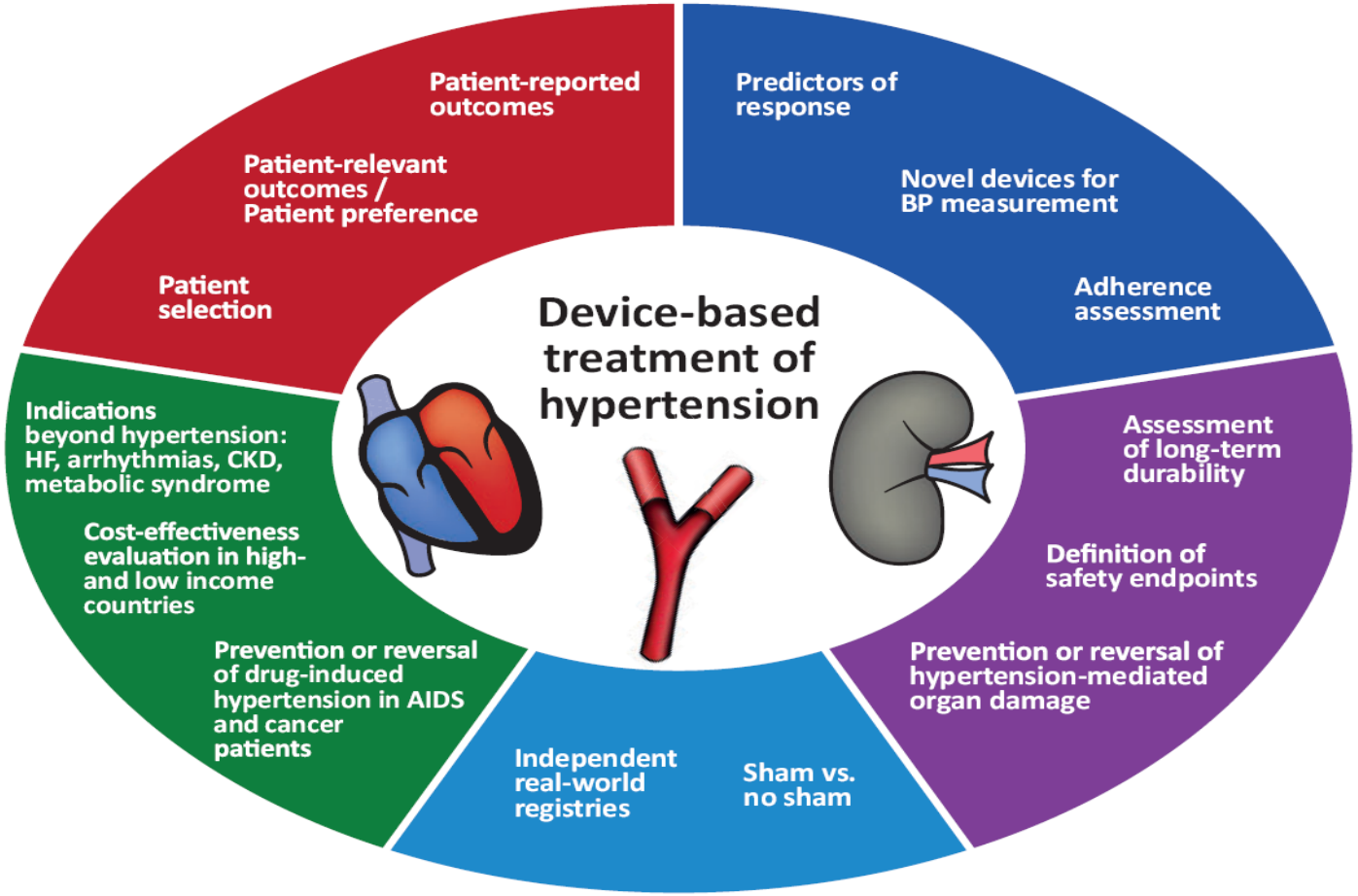
Narkiewicz, K. et al. J Am Coll Cardiol Basic Trans Science. 2016;1(5):313–24.

Milestones in device-based treatment of arterial hypertension



Lauder L, Azizi M. Nat Rev Cardiol. 2020 ahead of print

Research and development challenges in device-based hypertension treatment



Mahfoud F, Azizi M. Eur Heart J 2020; 41: 1588