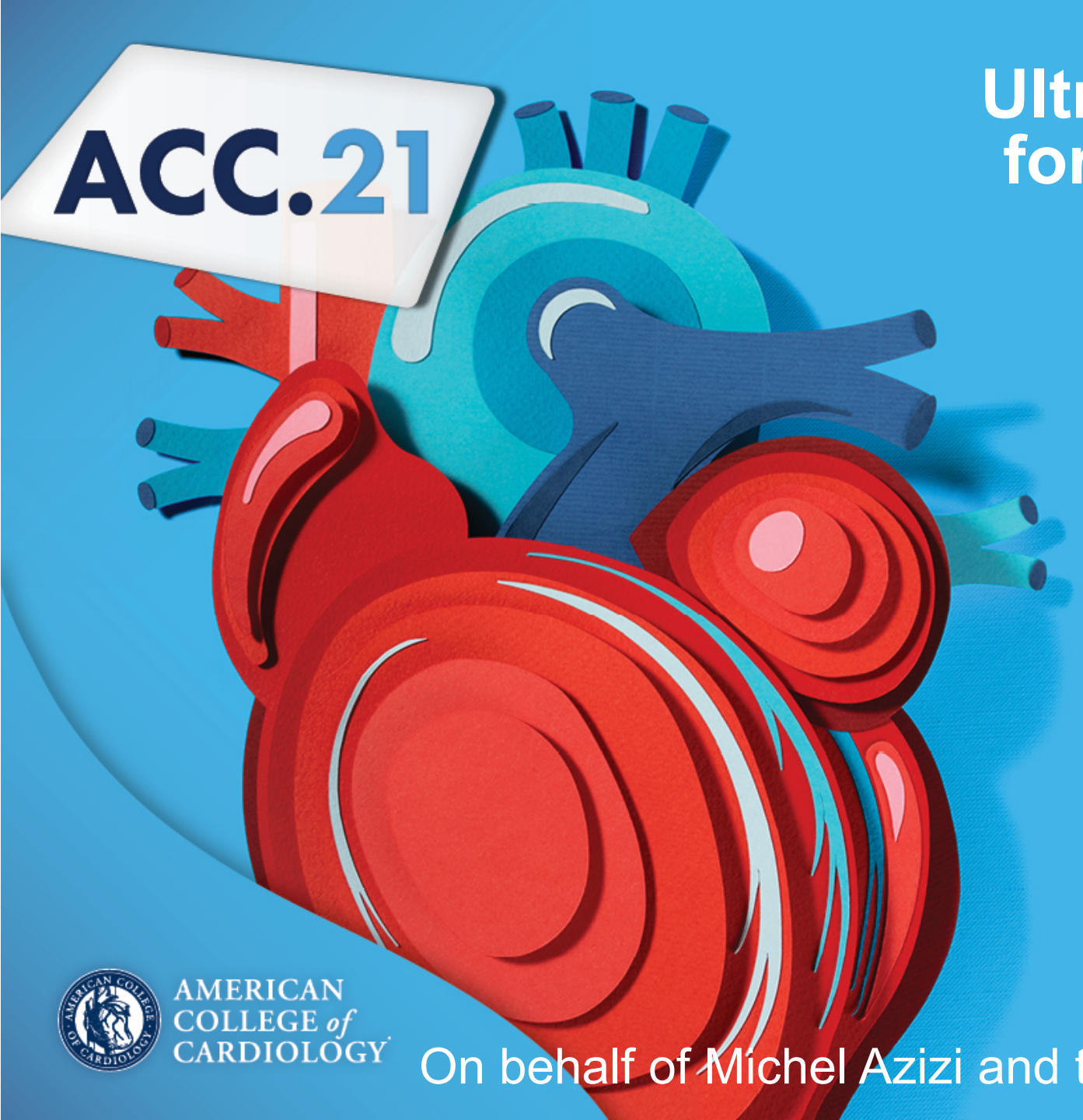


Ultrasound Renal Denervation for Hypertension Resistant to a Triple Medication Pill:

The Randomized Sham Controlled RADIANCE-HTN TRIO Trial

Ajay J. Kirtane, MD, SM
@ajaykirtane

AMERICAN COLLEGE of CARDIOLOGY

On behalf of Michel Azizi and the RADIANCE-HTN TRIO Investigators

Disclosures

- Dr. Kirtane reports Institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical, Neurotronic. In addition to research grants, institutional funding includes fees paid to Columbia University and/or Cardiovascular Research Foundation for consulting/speaking. Personal: Travel Expenses/Meals from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron

Background / Objective

- Endovascular renal denervation reduces blood pressure in patients with mild-moderate hypertension, but its blood pressure-lowering effect has not been previously demonstrated with confidence in patients with resistant hypertension

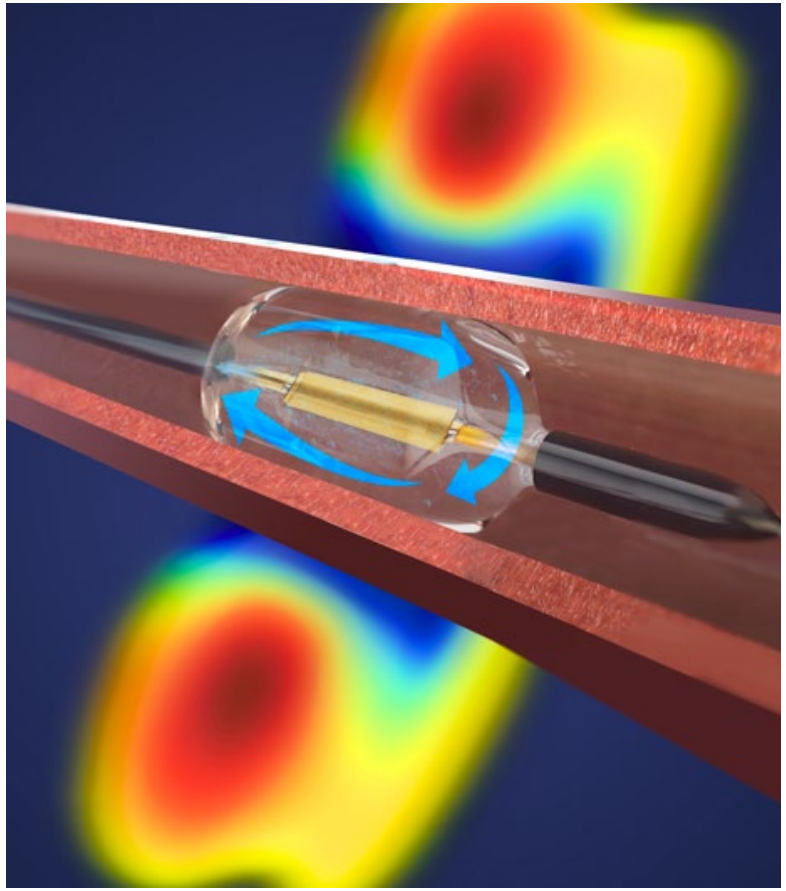
- The study objective was to investigate whether endovascular ultrasound renal denervation reduces daytime ambulatory systolic blood pressure in patients with hypertension resistant to a standardized fixed-dose triple medication pill

Paradise Ultrasound Renal Denervation System

- Ring of ablative energy (depth of 1-6 mm) to interrupt renal nerve traffic
- Arterial wall protected by water circulating through balloon
- 2-3 sonications lasting 7 seconds each are delivered to each main renal artery

Thermal Profile

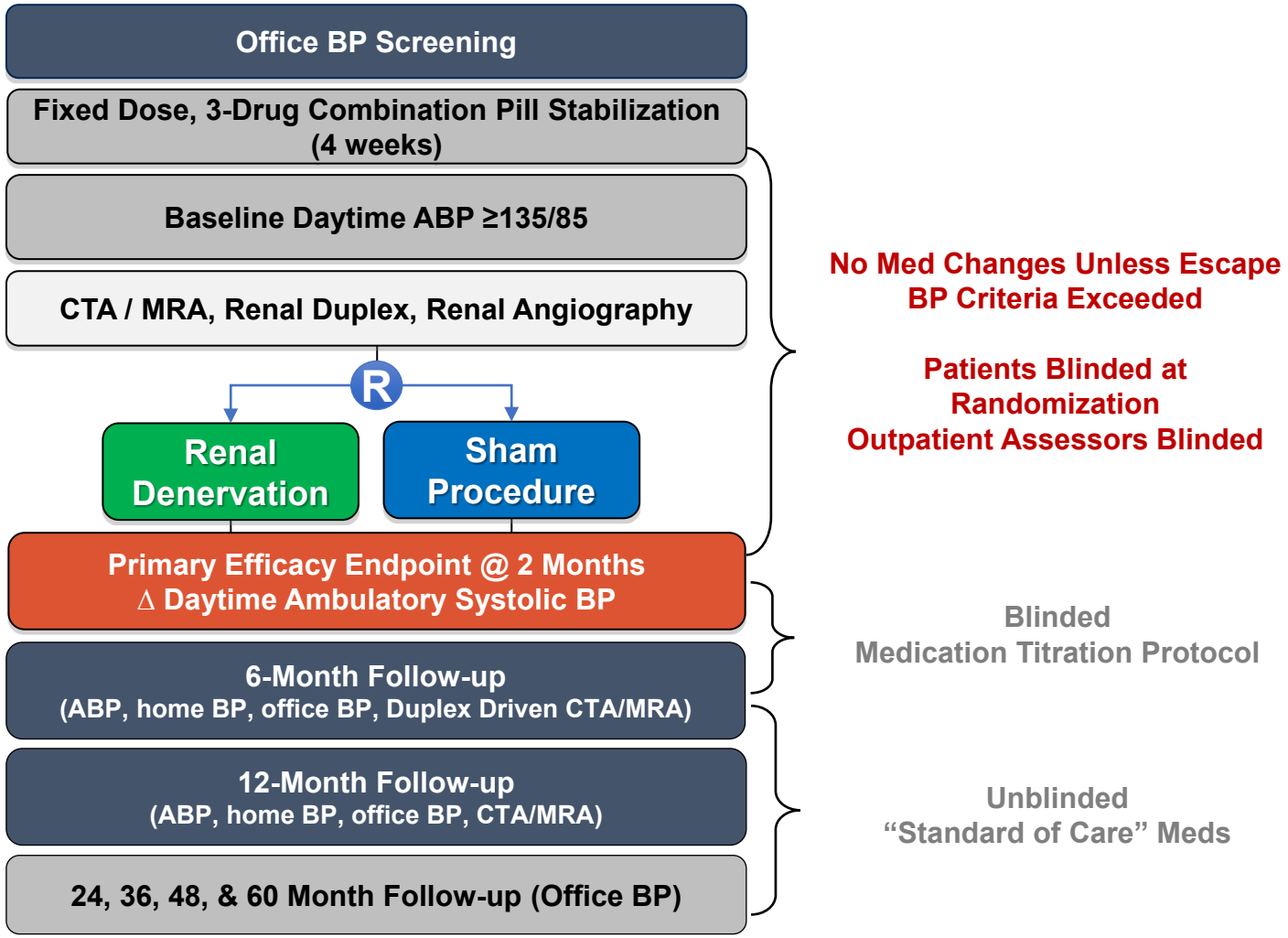
Ultrasonic Heating + Water Cooling



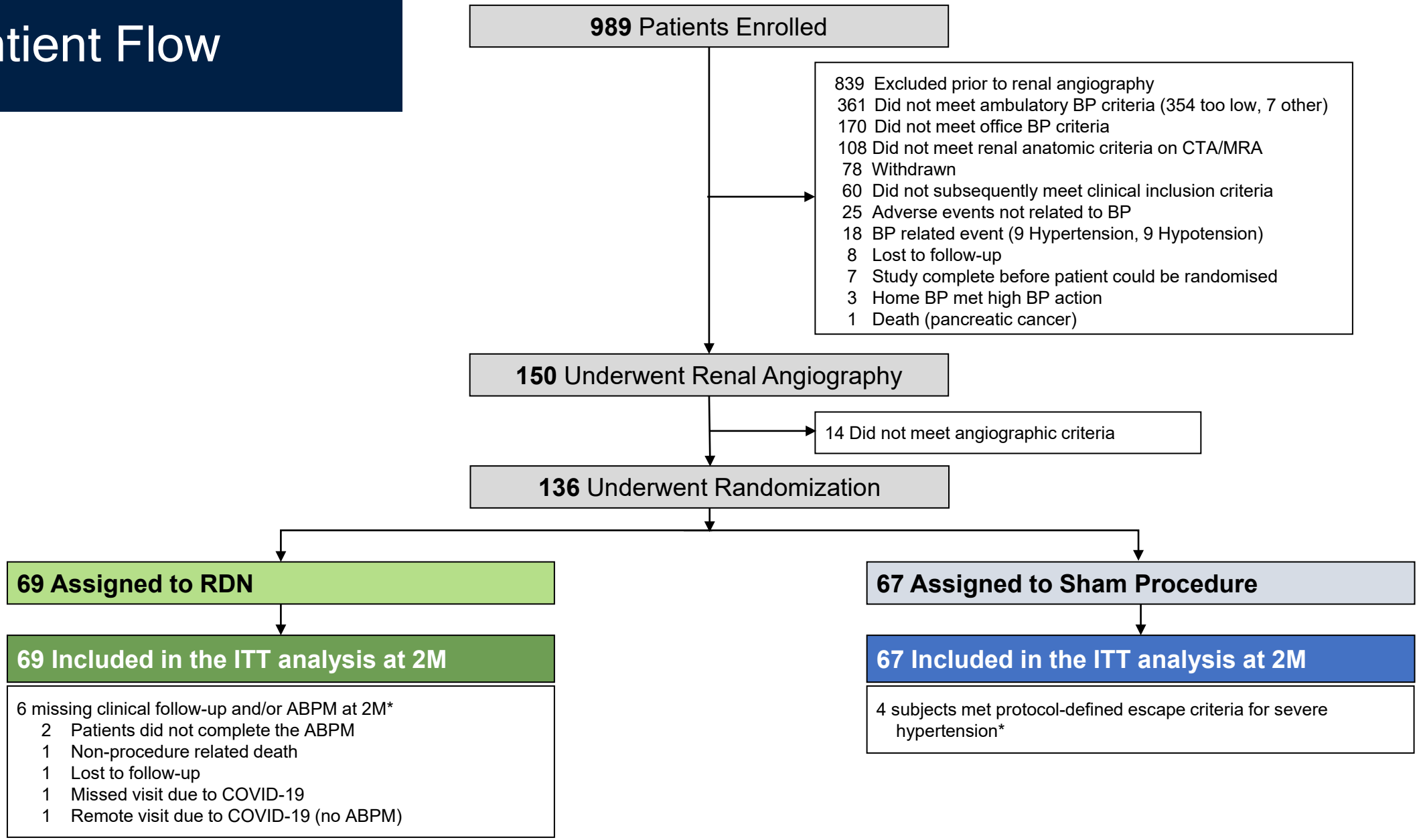
RADIANCE-HTN TRIO Design:
Blinded, Sham-Controlled, Powered to Demonstrate BP Lowering Effectiveness at 2M

Key Entry Criteria:

- Office BP ≥140/90 on 3+ anti-HTN meds
- Daytime ABP ≥135/85 on a fixed-dose, 3-drug combination pill
- Age 18-75 years
- No secondary hypertension aside from OSA
- No CV or cerebrovascular events within the prior 3M
- No Type I or uncontrolled Type II diabetes
- eGFR ≥40 mL/min/m^2
- Eligible renal artery anatomy



Patient Flow



*These subjects had a protocol-specified “0” value imputed for 2M change in ABPM for the Intent-to-Treat analysis

Clinical Characteristics

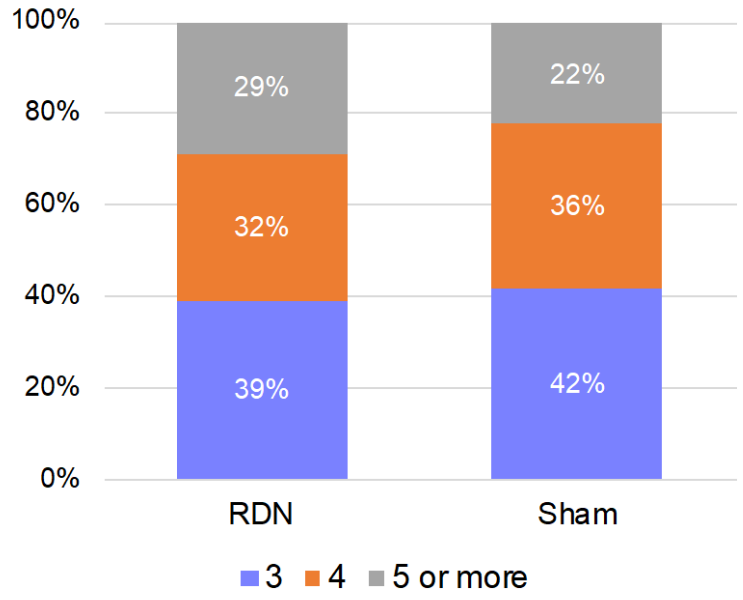
	RDN (N=69)	Sham (N=67)
Age (years)	52.3 ± 7.5	52.8 ± 9.1
Female sex	13/69 (19%)	14/67 (21%)
Race		
White	44/69 (64%)	50/67 (75%)
Black	14/69 (20%)	13/67 (19%)
Other / Unknown *	11/69 (16%)	4/67 (6%)
BMI - kg/m^2	32.8 ± 5.7	32.6 ± 5.4
Abdominal obesity †	54/66 (82%)	55/67 (82%)
eGFR - $mL/min/1.73m^2$ *	86.0 ± 25.2	82.2 ± 19.2
eGFR<60 $mL/min/1.73m^2$ *	8/67 (12%)	7/65 (11%)
Diabetes – Type 2	21/69 (30%)	17/67 (25%)
Sleep apnea	19/69 (28%)	11/67 (16%)
Prior Hospitalization for hypertensive crisis	15/69 (22%)	11/67 (16%)
Prior cardiovascular / cerebrovascular event	8/69 (12%)	9/67 (13%)
History of heart failure	1/69 (1%)	3/67 (4%)

* Two subjects in RDN and 2 subjects in Sham are missing race data. The four subjects with missing race data are not included in eGFR MDRD calculations. Site reported eGFR for these 4 subjects were all greater than 60mL/min/1.73 m^2 at baseline.
† Abdominal obesity defined as a waist circumference greater than 102 cm for men and greater than 88 cm for women.

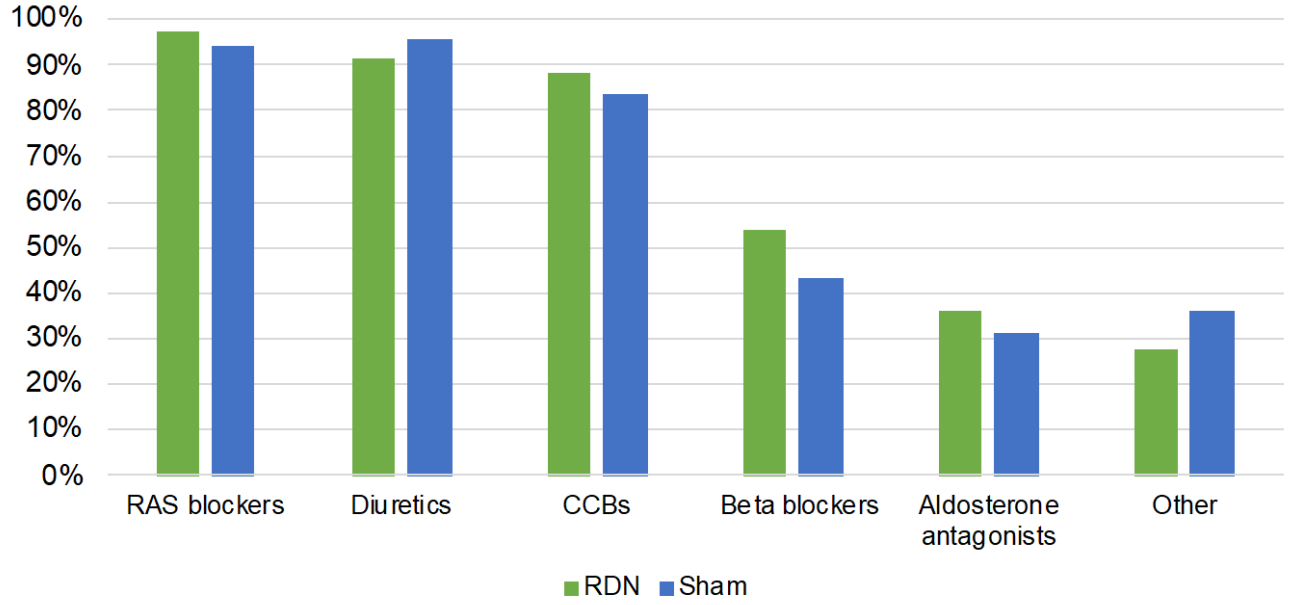
Screening Blood Pressures & Medications

	RDN (N=69)	Sham (N=67)
Blood Pressure		
Office SBP (mmHg)	161.9 ± 15.5	163.6 ± 16.8
Office DBP (mmHg)	105.1 ± 11.6	103.3 ± 12.7
Number of Anti-hypertensive Medications	4.0 ± 1.0	3.9 ± 1.1

Number of Medications at Screening

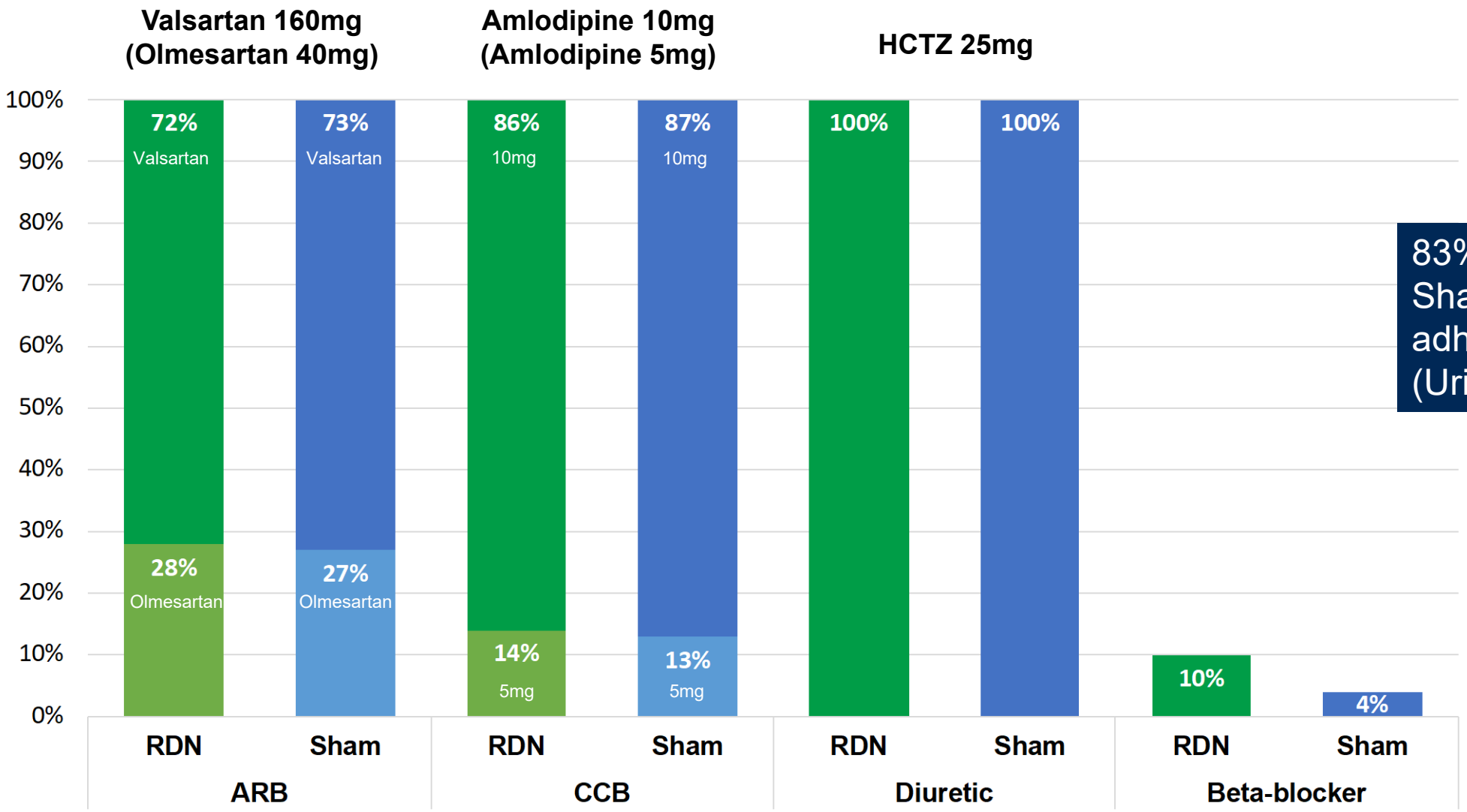


Classes of Anti-HTN Medications at Screening



Baseline Medications

After 4 weeks of Triple Medication Combination Daily Pill



83% of RDN and 76% of Sham patients were fully adherent at baseline (Urine HPLC-MS/MS)

Beta-blocker maintained for compelling indication (CHD, HF)

Baseline Blood Pressures:
After 4 weeks of Triple Medication Combination Daily 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

Procedural Details

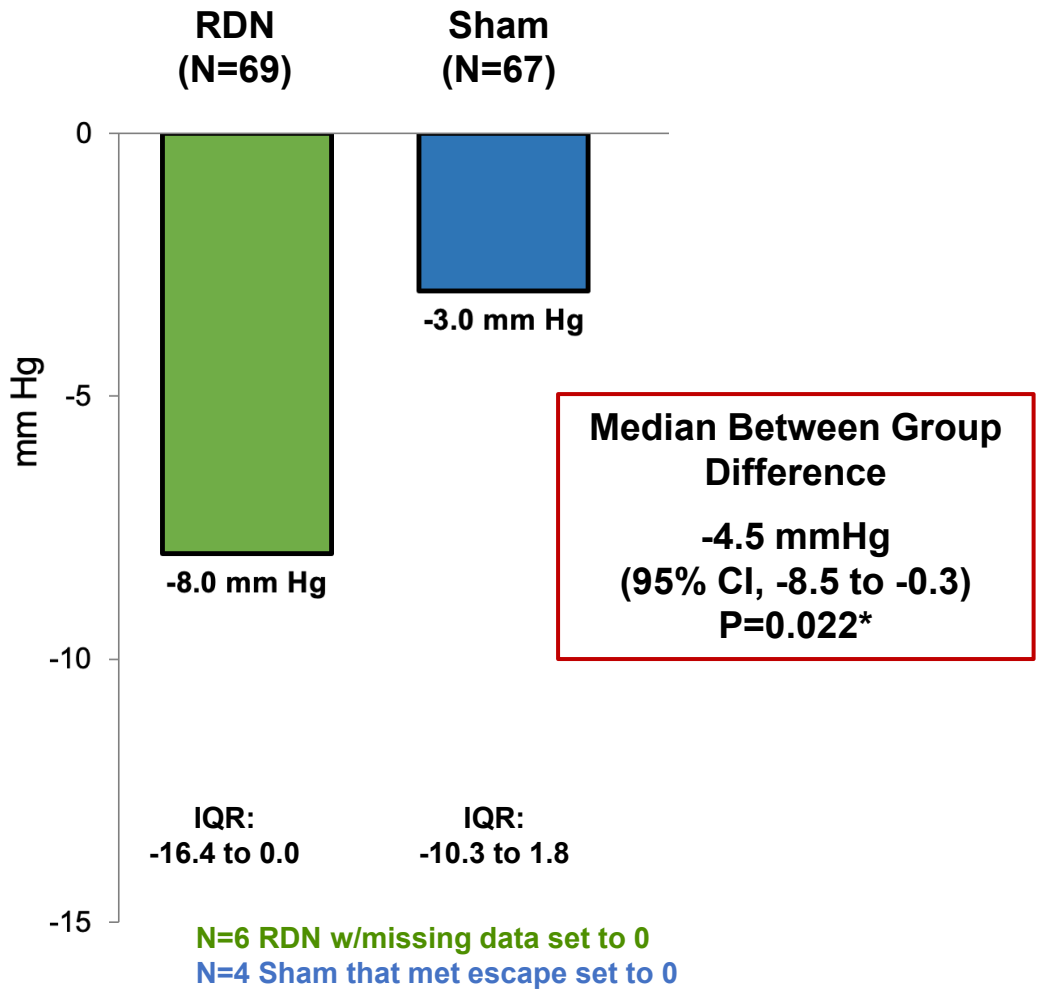
	RDN (N=69)	Sham (N=67)
Procedure time (min)	83.0 [69.0, 99.0]	41.0 [33.0, 50.0]
Sedation		
Conscious Sedation	44/69 (64%)	41/67 (61%)
Monitored Anesthesia Care (e.g. propofol)	17/69 (25%)	16/67 (24%)
General Anesthesia	8/69 (12%)	10/67 (15%)
Contrast volume (cm^3)	176.9 ± 77.0	80.0 ± 40.1
Fluoroscopy time (min)	19.0 ± 11.5	4.1 ± 3.6
Treatment success (≥ 2 bilateral emissions)	67/69 (97%)*	NA
Total Number of Emissions	5.8 ± 1.2	NA
Left Main Renal	2.7 ± 0.5	NA
Right Main Renal	2.7 ± 0.5	NA
Subjects with Treated Accessory Renal Arteries	17/69 (25%)	NA
Total Emission Time (seconds)	40.7 ± 8.1	NA

*1 subject had no treatments on one side; 1 subject had only one treatment on one side

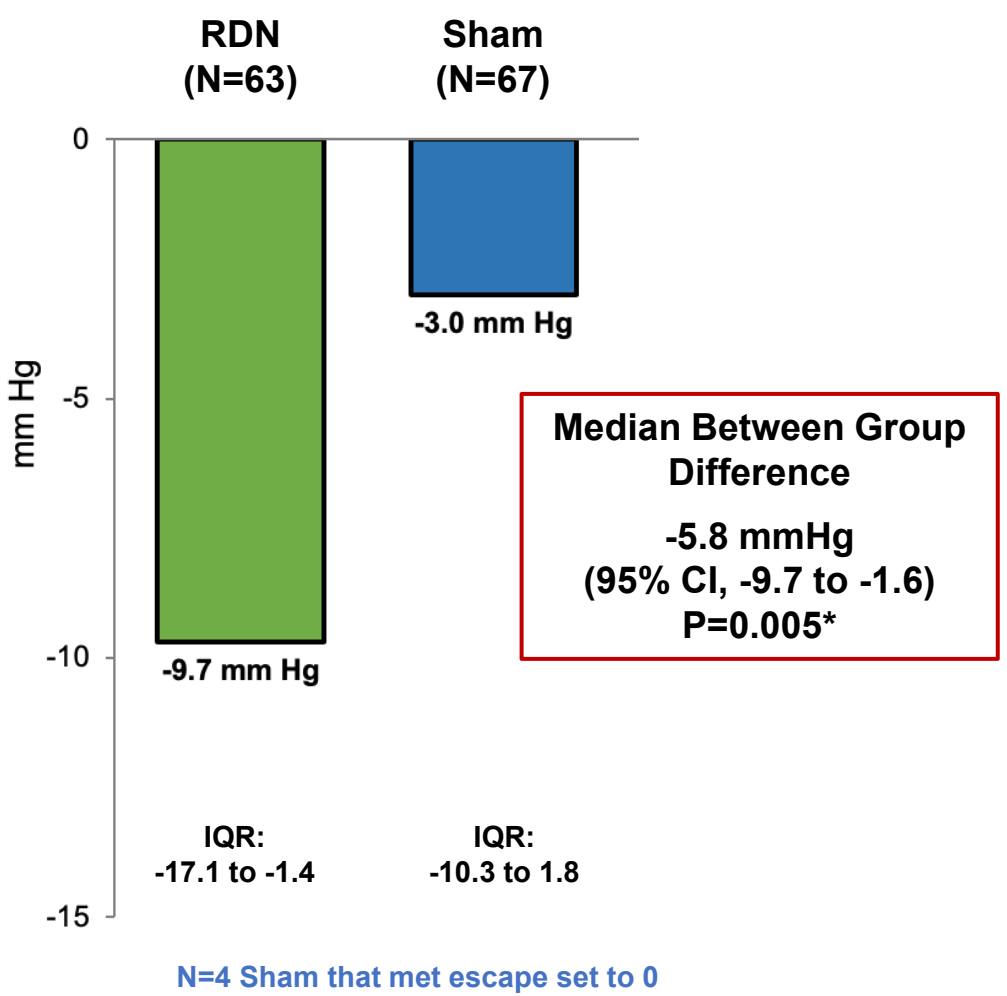
Formal blinding assessments confirmed adequate blinding at discharge and 2-month follow-up

Primary Efficacy Endpoint:
Change in Daytime Ambulatory SBP at 2 Months

Intent-To-Treat Population



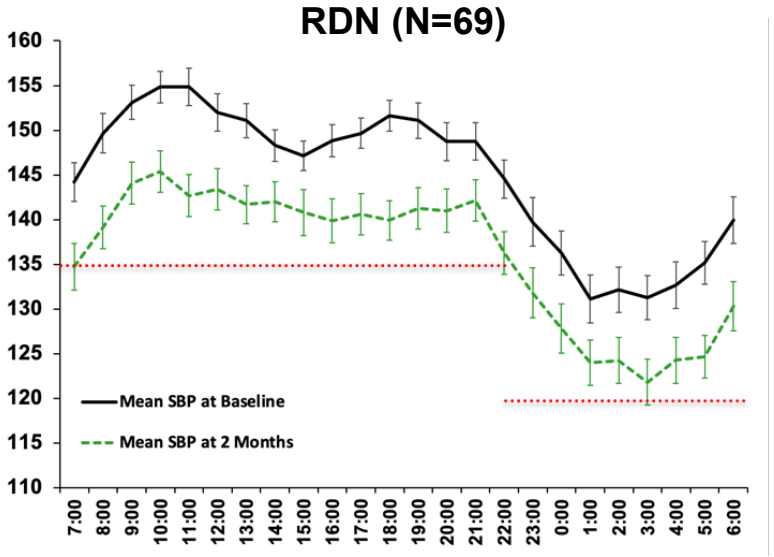
Complete ABPM Population

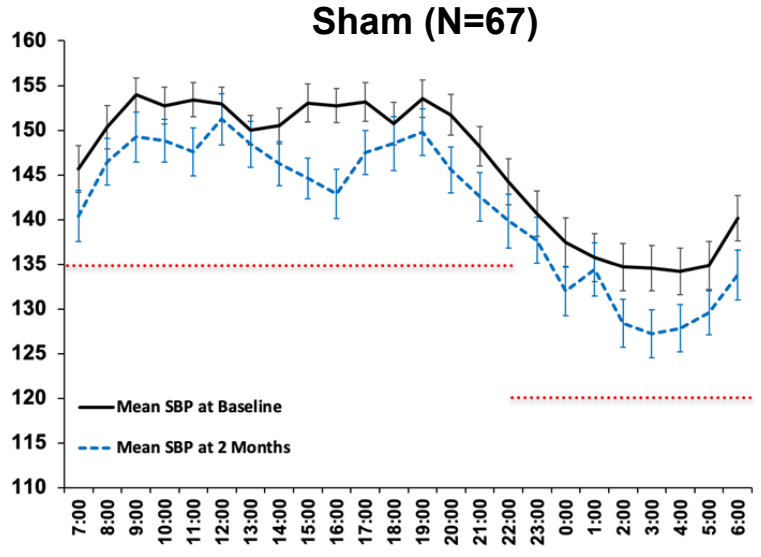


*Baseline-adjusted ANCOVA on the ranks due to non-normality of distribution

ABPM profiles at Baseline and 2 Months

ITT Population
(Imputed Missing and Escape)



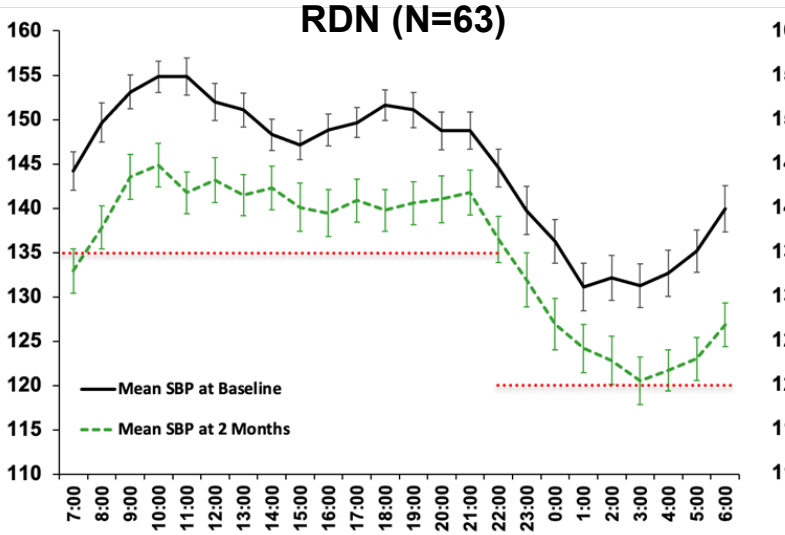


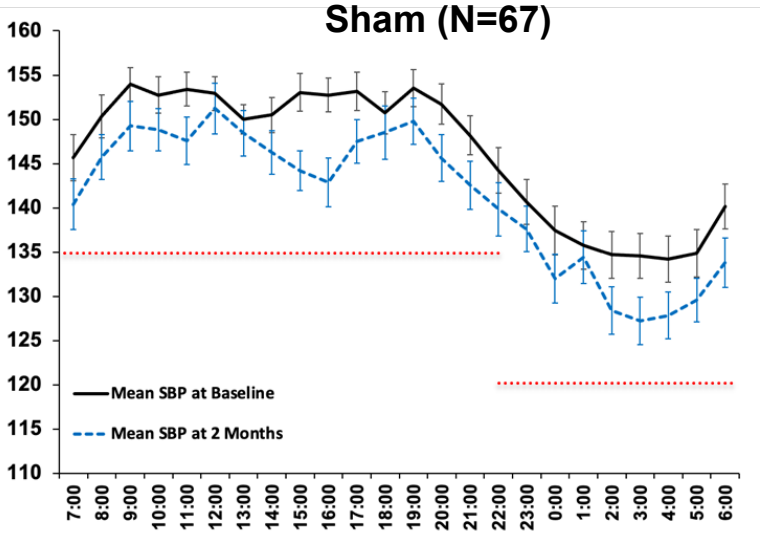
Median Between Group Difference

24h ABPM
-4.2 mmHg
(95% CI, -8.3 to -0.3)
P=0.016*

Nighttime ABPM
-3.9 mmHg
(95% CI, -8.8 to 1.0)
P=0.044*

Complete ABPM Population
(Imputed Escape)





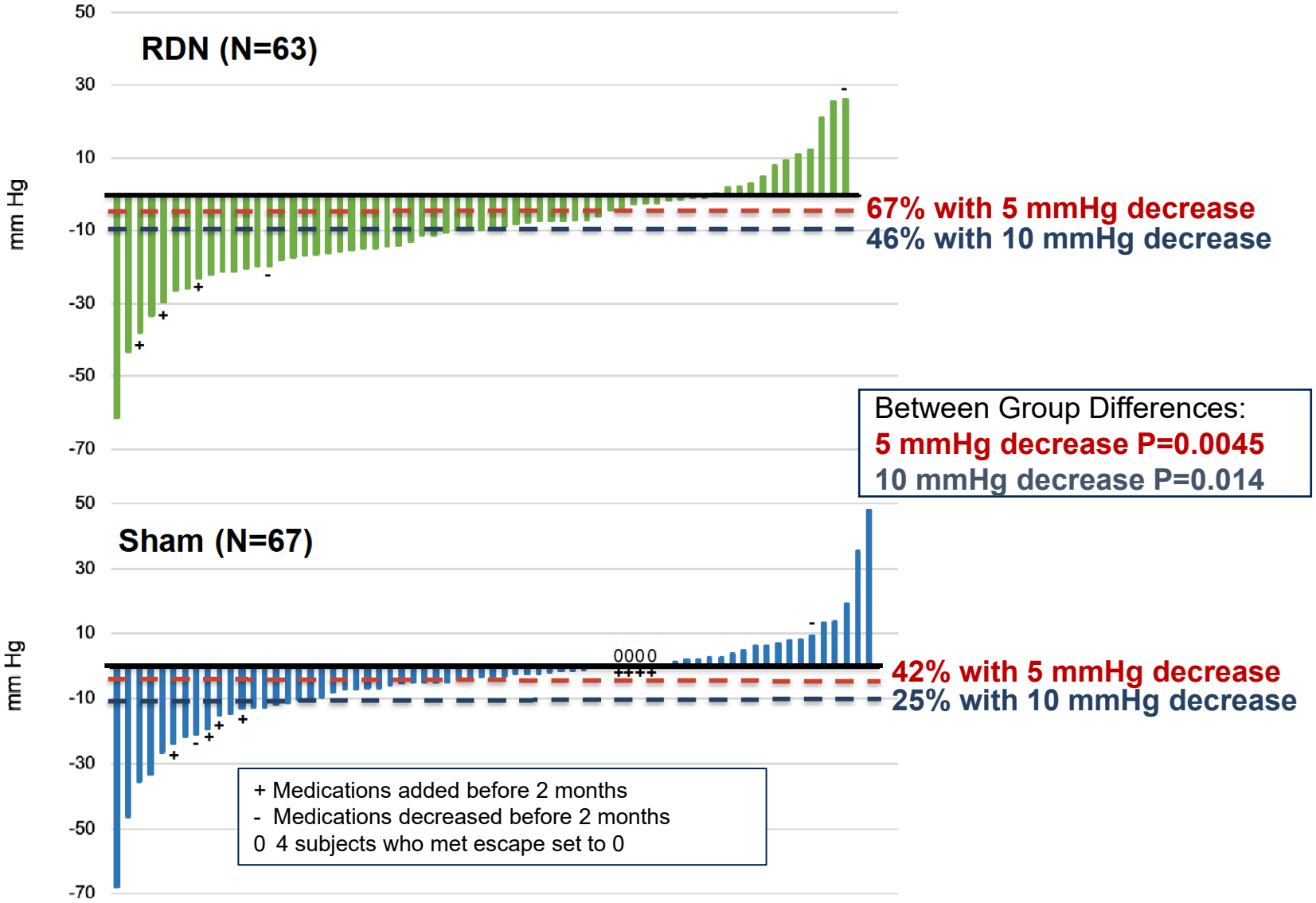
Median Between Group Difference

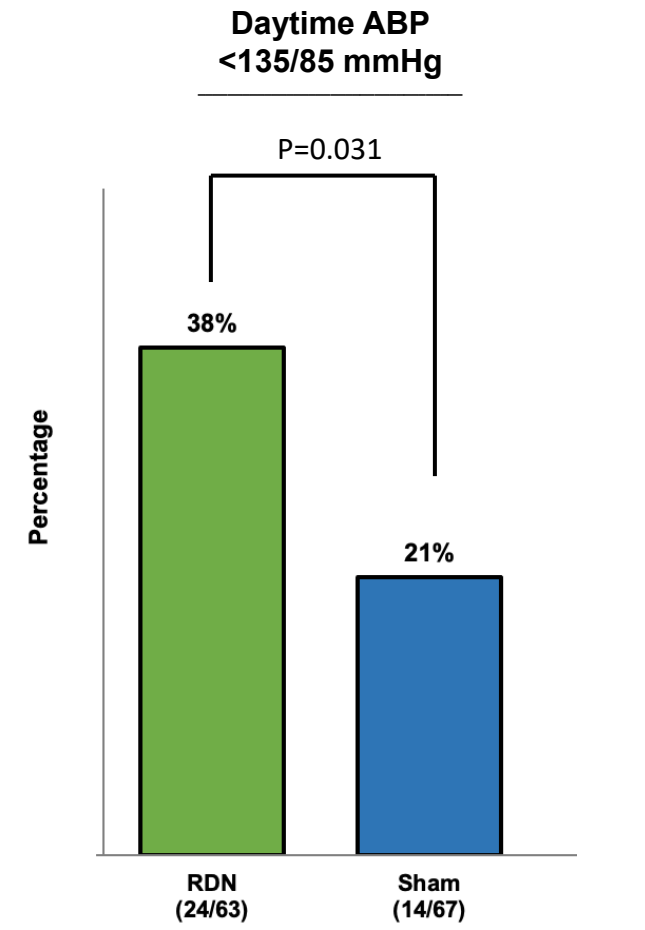
24h ABPM
-5.6 mmHg
(95% CI, -9.5 to -1.3)
P=0.0043*

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

* Baseline-adjusted ANCOVA on the ranks

Individual Patient Responses and % patients with controlled BP:
Change in Daytime Ambulatory SBP at 2 Months (Complete ABPM Population)

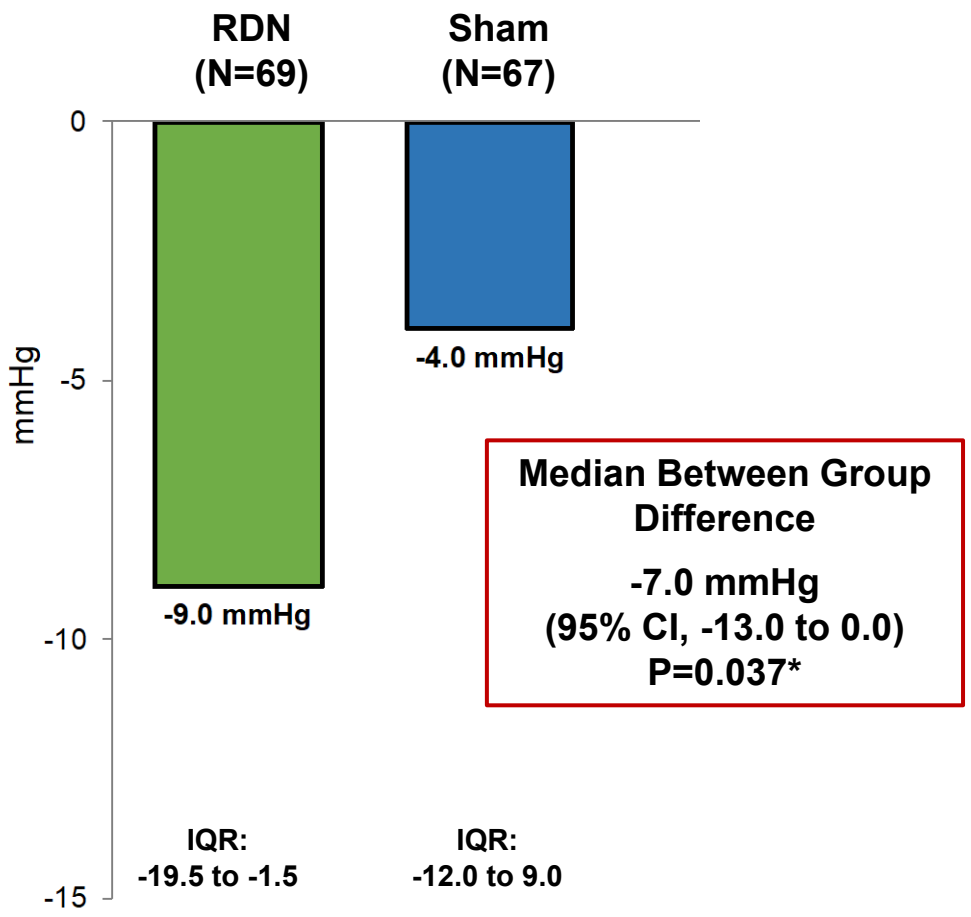




N=4 Sham that met escape set to uncontrolled

Change in Office and Home SBP at 2 Months

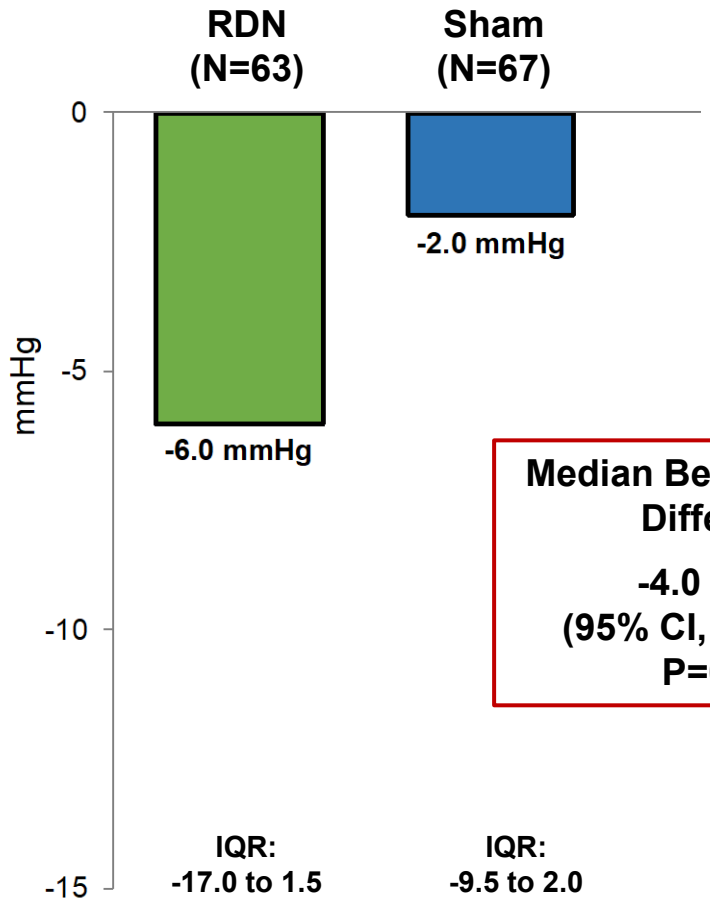
Office SBP



Median Between Group Difference

-7.0 mmHg
(95% CI, -13.0 to 0.0)
P=0.037*

Home SBP



Median Between Group Difference

-4.0 mmHg
(95% CI, -8.0 to 0.0)
P=0.052

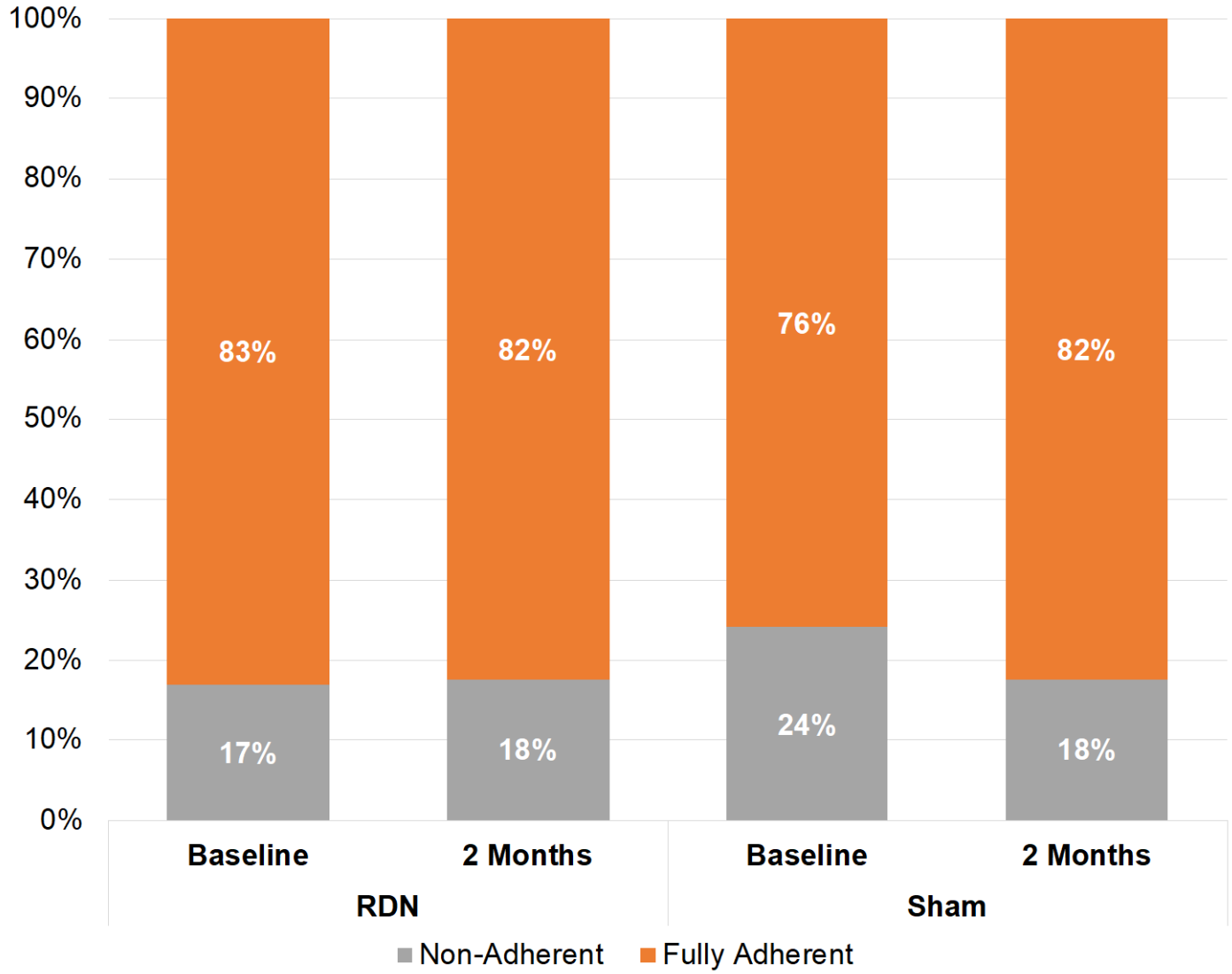
*Baseline-adjusted ANCOVA on the ranks due to non-normality of distribution

Antihypertensive Medication Changes (ITT Population)

Medication Changes	RDN (N=69)	Sham (N=67)	P-value
Additional meds at 2M *	3/69 (4%)	8/67 (12%)	0.10
Protocol defined criteria	0/69 (0%)	4/67 (6%)	0.056
Physician decision/patient preference	3/69 (4%)	4/67 (6%)	0.72
Reduction in meds at 2M	2/69 (3%)	2/67 (3%)	1.0

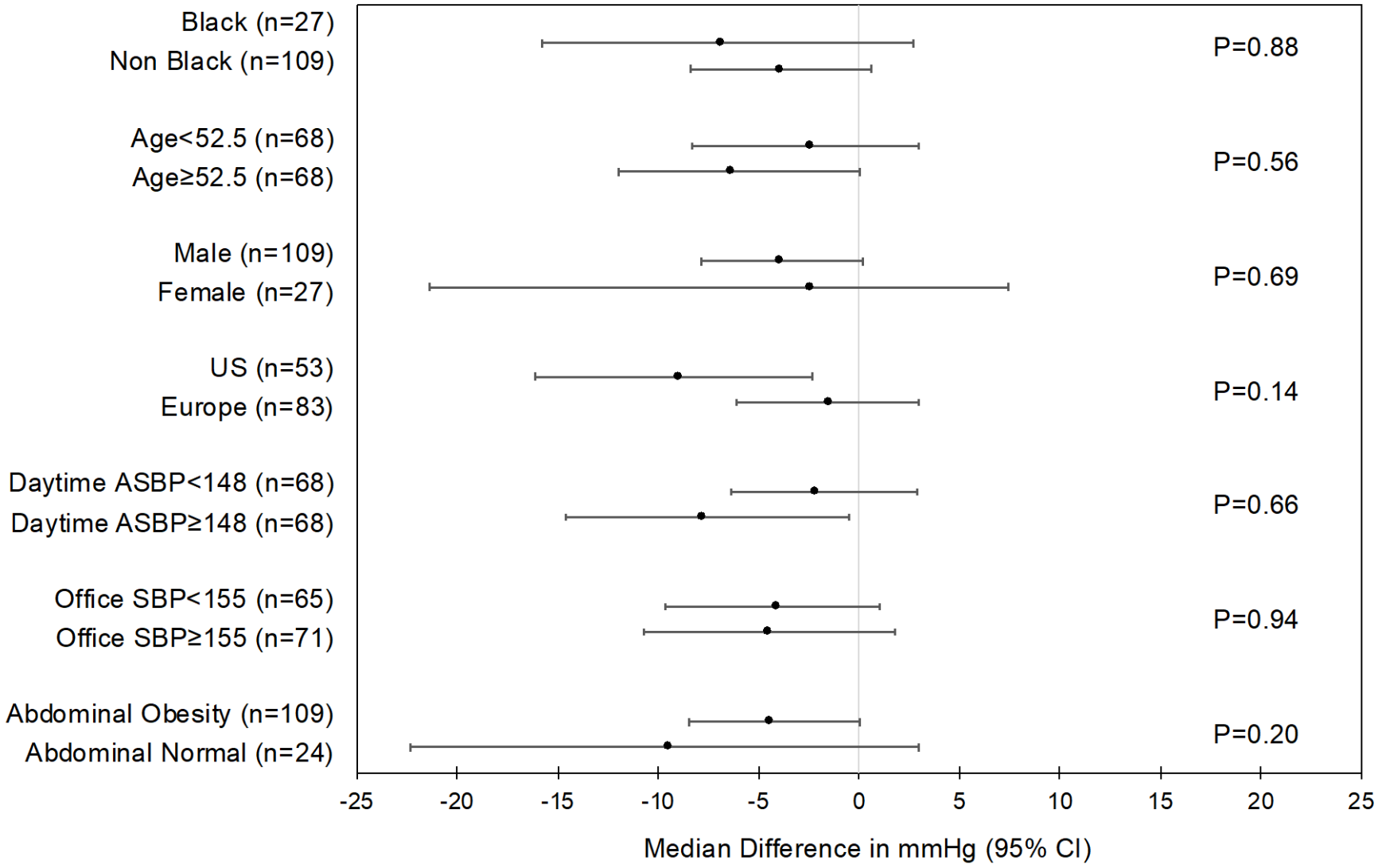
*2 pts of the RDN group were on 25mg spironolactone; 7 pts of the sham group were on spironolactone (2 on 12.5mg, 4 on 25mg and 1 on 50mg)

Medication Adherence as Measured by Urine HPLC-MS/MS

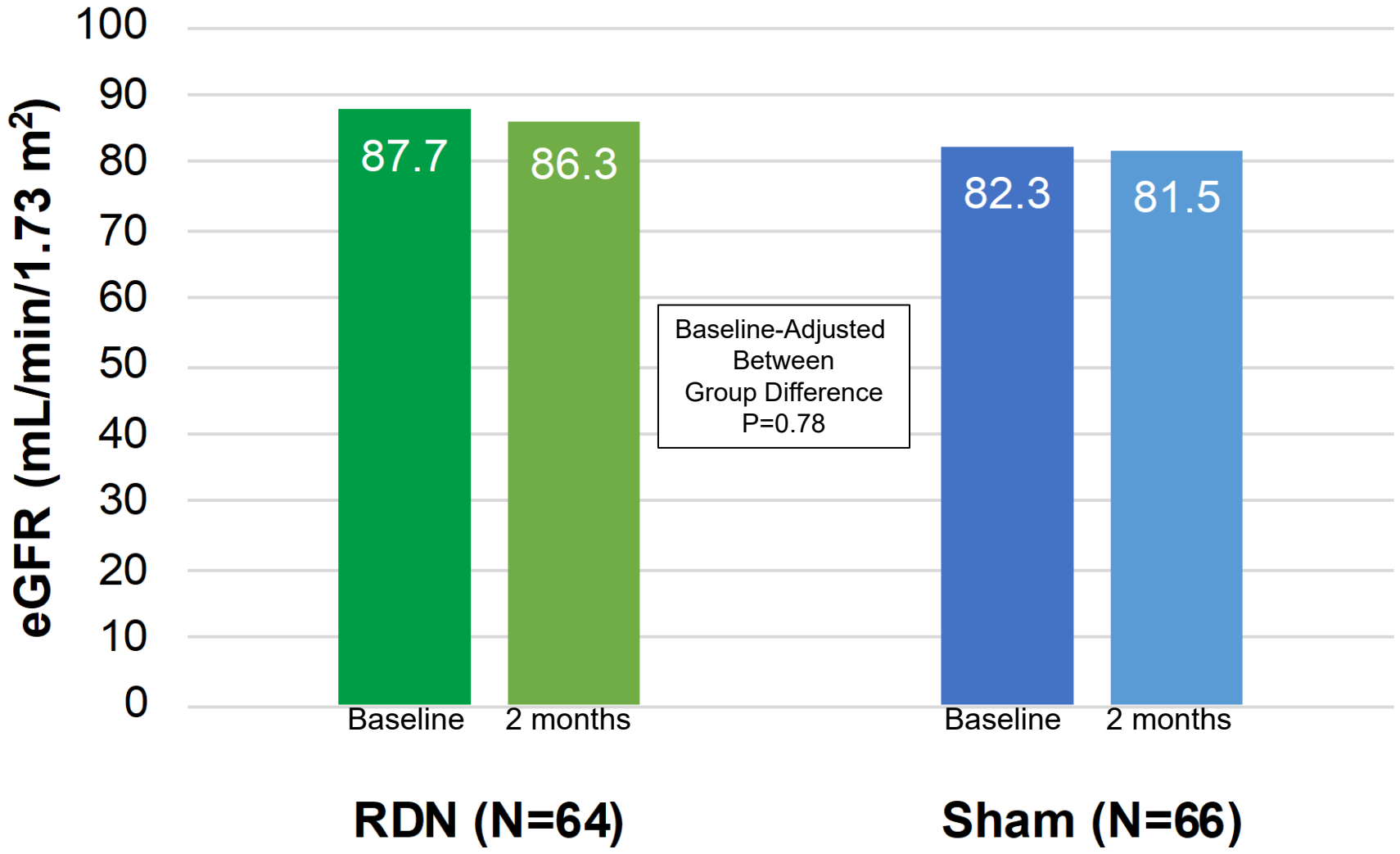


75% of subjects were fully adherent at both Baseline and 2 months

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



eGFR at 2 Months
(Matched data at baseline and 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.

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

Limitations

- Additional follow-up will be required to determine whether the blood pressure lowering effect of ultrasound renal denervation remains safe and durable over time, especially when patients who remain uncontrolled receive additional antihypertensive medications, including the aldosterone antagonist spironolactone

- Without robust pre-procedural predictors of responsiveness and the absence of an intraprocedural marker of denervation success, between-patient variability will continue to be observed

Conclusions

- **In patients with hypertension resistant to guideline-recommended triple combination therapy in a single pill, ultrasound based RDN was associated with a reduction of 8.0 mmHg in daytime ambulatory SBP (a 4.5 mmHg greater decrease than a sham procedure)**
- The greater BP lowering effect of RDN vs. sham was consistent for 24h, nighttime, and office SBP
- These results are concordant with those of RADIANCE-HTN SOLO (patients with mild-to-moderate hypertension), confirming that ultrasound RDN can lower BP across a spectrum of hypertension
- Longer-term assessments for efficacy as well as safety are ongoing

Thank you to all the RADIANCE-HTN TRIO Study Centers!

Europe (N=25)	United States (N=28)
St. Barts Health NHS Trust – M. Saxena	Deborah Heart & Lung Center – K. Sanghvi
Hôpital Saint-André - CHU Bordeaux – P. Gosse	Ochsner Heart and Vascular Institute – J.P. Reilly
Royal Bournemouth Hospital – T. Levy	Vanderbilt University Medical Center – P. Fong
Hôpital Européen Georges-Pompidou – M. Azizi	Stamford Hospital – D. Hsi
Cliniques Universitaires Saint-Luc – A. Persu	NYU Langone Medical Center – S. Bangalore
University Clinic Dusseldorf – L.C. Rump	Medical University of South Carolina – T. Todoran
Clinique Pasteur / GCVI – Toulouse – A. Pathak	Emory University – C. Devireddy
Erasmus MC Rotterdam – J. Daemen	Cedars-Sinai Medical Center – F. Rader
Hôpital de la Croix Rousse, Lyon – P. Lantelme	University of Utah Medical Center – J. Abraham
Royal Devon and Exeter NHS Foundation Trust – A.S.P. Sharp	University of Alabama – D. Calhoun
Institute of Cardiology, Warsaw - A. Witkowski	Columbia University Medical Center – A.J. Kirtane
Sana Kliniken Lübeck GmbH - J. Weil	Massachusetts General Hospital – J. Garasic
University Clinic of Saarland, Homburg – F. Mahfoud	The Cardiac and Vascular Institute, Gainesville – M. Khuddus
The Essex Cardiothoracic Centre – J. Sayer	Minneapolis Heart Institute Foundation – Y. Wang
Leipzig Heart Center – P. Lurz	Drexel University – J. Goldman
Medical University of Gdansk – D. Hering	The Heart Hospital Baylor Plano – S. Potluri
Conquest Hospital, East Sussex NHS Trust – R. Gerber	The Brigham and Women's Hospital – N.D.L. Fisher
University Clinic Erlangen – R.E. Schmieder	University of North Carolina – R. Stouffer
Maastricht University Hospital – A. Kroon	University Hospitals Cleveland Medical Center – D. Zidar
Hammersmith Hospital, Imperial College NHS Trust – J. Davies	Renown Institute for Heart & Vascular Health – M.J. Bloch
Katholisches Klinikum Mainz – S. Genth-Zotz	University of Pennsylvania – D. Cohen
University Medical Center Utrecht – P. Blankestijn	Franciscan Health Indianapolis - A.R. Chugh
CHRU Lille - P. Delsart	Sutter Medical Center, Sacramento – P. Huang
Nottingham University Hospitals NHS Trust – S. Jadhav	Southern Illinois University School of Medicine – J. Flack
Freiburg University – C. von zur Mühlen	Bridgeport Hospital - R. Fishman
	Baptist Health Lexington - M. Jones
	Munson Medical Center - T. Adams
	Cleveland Clinic - C. Bajzer