Individual Patient-Data Pooled Analysis of Endovascular Ultrasound Renal Denervation or a Sham Procedure at 6 Months in the RADIANCE Clinical Trial Program

Ajay J. Kirtane, MD, SM
Columbia University Irving Medical Center
NewYork-Presbyterian Hospital

on behalf of Michel Azizi and the RADIANCE Investigators

CRF TCT

Disclosure of Relevant Financial Relationships

- Dr. Kirtane reports Institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Amgen, CSI, Philips, ReCor Medical, Neurotronic, Biotronik, Chiesi, Bolt Medical, Magenta Medical, Canon, SoniVie, Shockwave Medical, and Merck. In addition to research grants, institutional funding includes fees paid to Columbia University and/or Cardiovascular Research Foundation for consulting and/or speaking engagements in which Dr. Kirtane controlled the content. Personal: Consulting from IMDS; Travel Expenses/Meals from Medtronic, Boston Scientific, Abbott Vascular, CSI, Concept Medical, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron.
- The PARADISE™ System is Limited by US Federal Law to Investigational Use Only in the United States.

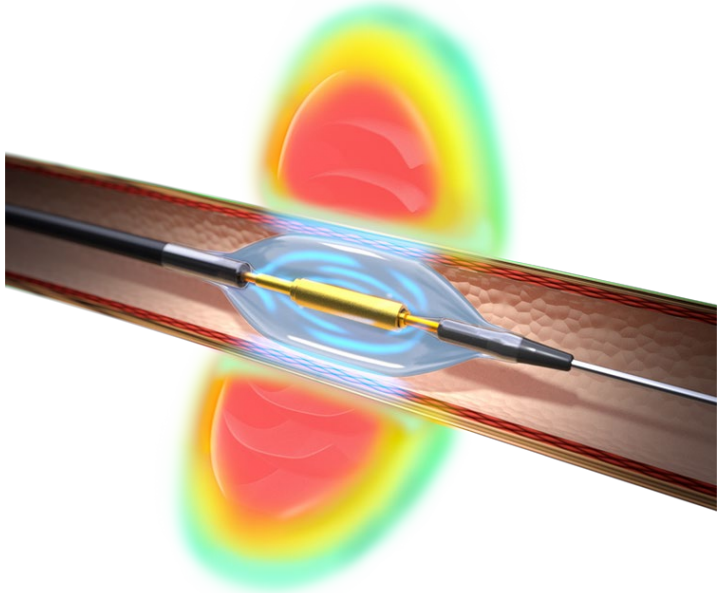
All Relevant Financial Relationships have been mitigated.
Faculty disclosure information can be found on the app

Paradise Ultrasound Renal Denervation System

- Circumferential ring of ablative energy (depth of 1-6 mm) to interrupt renal nerve signaling
- Arterial wall protected by water circulating through balloon
- 2-3 sonications each lasting 7 seconds are delivered to appropriately sized renal arteries

Thermal Profile

Ultrasonic Heating + Water Cooling

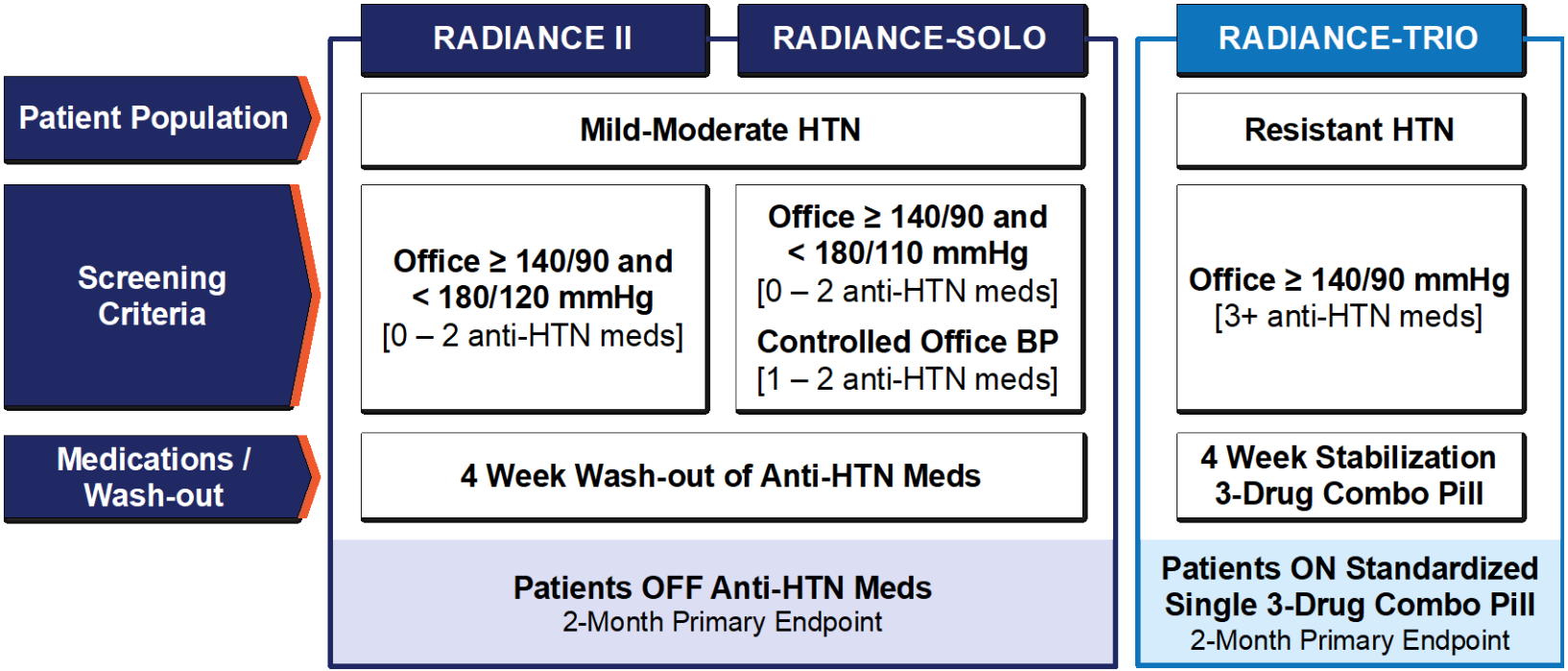


Background and Methods

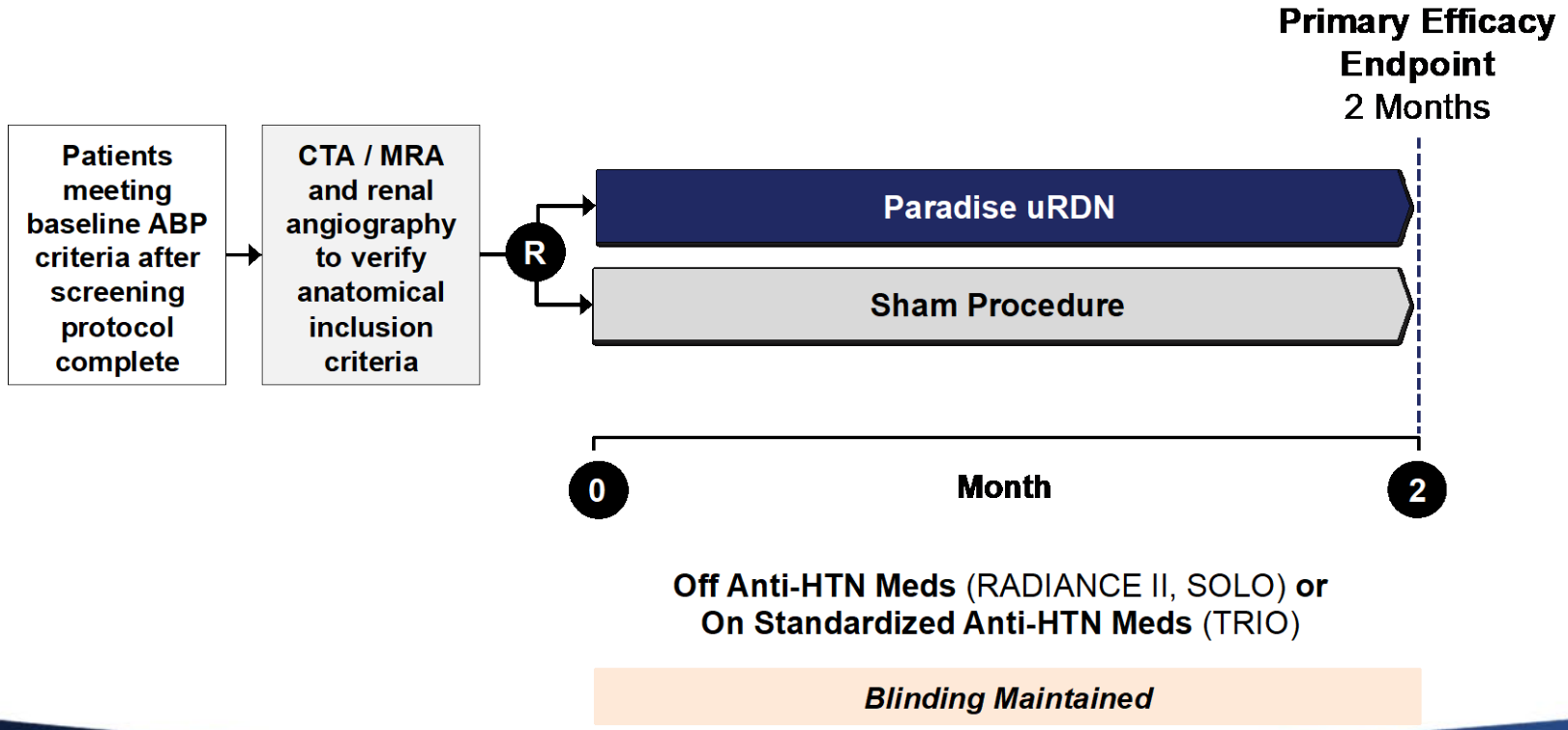
- Endovascular ultrasound renal denervation (uRDN) lowered blood pressure at 2 months in patients with both mild-moderate hypertension and hypertension resistant to a triple combination pill in the sham-controlled RADIANCE II, RADIANCE HTN-SOLO, and RADIANCE HTN-TRIO trials
- We performed an individual patient-data pooled analysis to characterize the 6-month effectiveness and safety of uRDN vs. sham in conjunction with escalating medical antihypertensive therapy for hypertension control
  - Linear mixed models (repeated measures) were used to assess differences between randomized groups in medication changes and BP over time

RADIANCE Study Designs (RADIANCE II, SOLO, and TRIO)

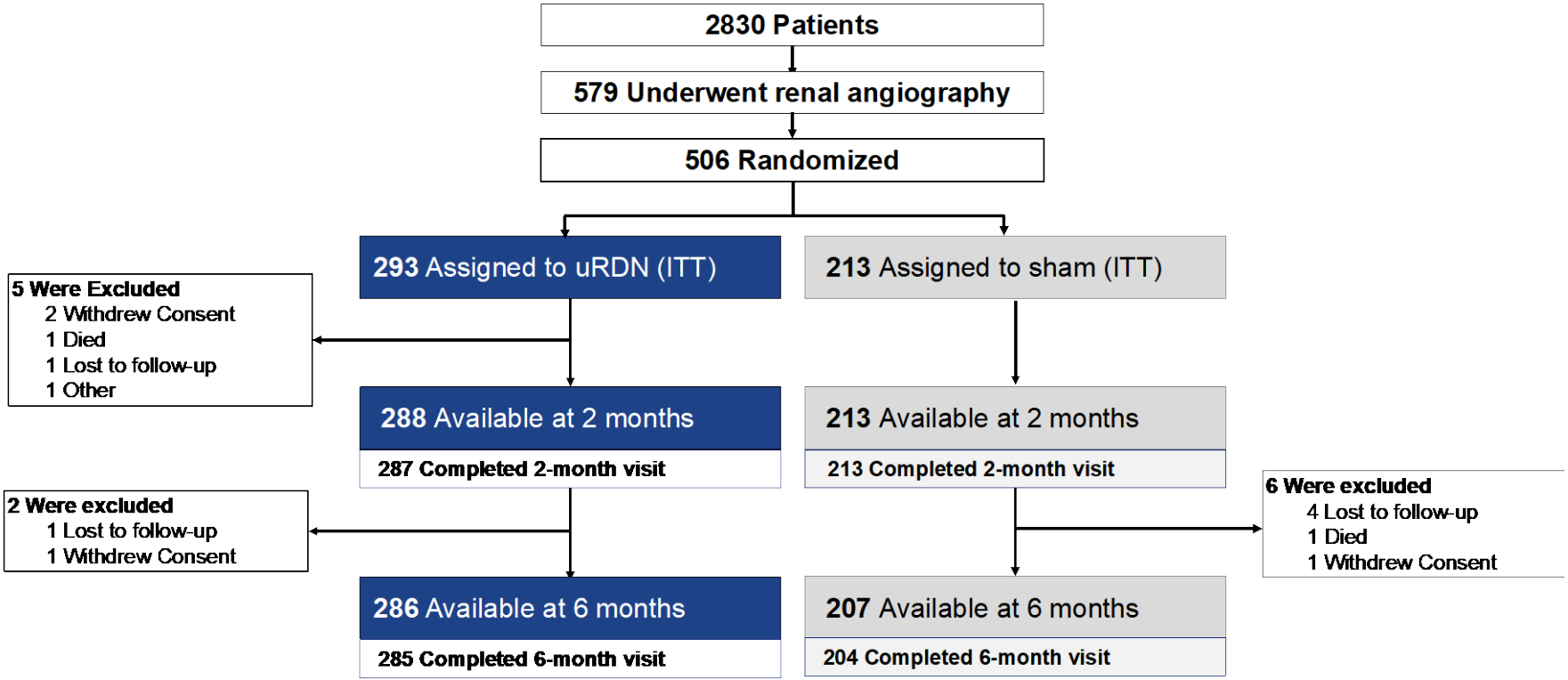
Blinded, Sham-Controlled, Individually Powered Trials to Demonstrate BP Lowering



Primary Efficacy Endpoint of Daytime Ambulatory Blood Pressure (ABP) Ascertained at 2 Months



RADIANCE Pooled Analysis: Flow Diagram



Baseline Characteristics Upon Enrollment

Measure	uRDN (N=293)	Sham (N=213)
Age (years)	54.2 ± 9.5	53.9 ± 9.0
Female sex	30.0% (88/293)	30.0% (64/213)
Race		
White	75.0% (219/292)	75.0% (159/212)
Black	16.1% (47/292)	19.3% (41/212)
Other	8.9% (26/292)	5.7% (12/212)
Body mass index - kg/m^2 *	30.7 ± 5.6	30.7 ± 5.4
eGFR - $ml/min/1.73m^2$ †	83.3 ± 17.9	82.5 ± 16.6
Type II diabetes	10.9% (32/293)	12.7% (27/213)
Sleep apnea	16.0% (47/293)	15.0% (32/213)
Prior hospitalization for hypertensive crisis	8.9% (26/293)	7.5% (16/213)
Prior MI or cerebrovascular event	2.7% (8/293)	3.8% (8/213)
History of heart failure	0.7% (2/293)	1.4% (3/213)

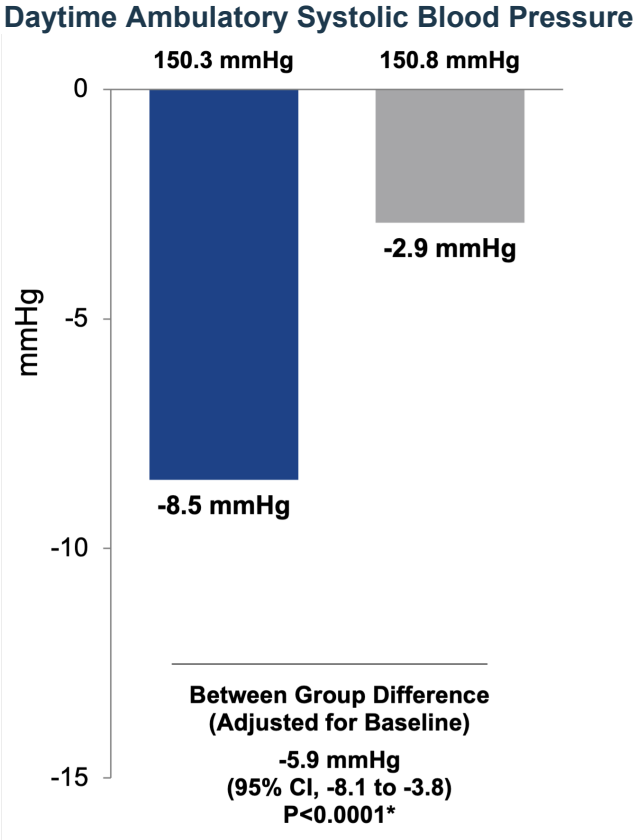
** BMI is available for N=291 in the uRDN Group and N=213 in the Sham group*
† eGFR data is available for N=292 in the uRDN group and N=211 in the Sham group

Screening and Baseline Blood Pressures

Measure	uRDN (N=293)	Sham (N=213)
Screening Office BP	153.9/99.9 ± 14.9/10.1	153.9/98.6 ± 16.4/10.0
Baseline Blood Pressures (Following medication washout)		
Daytime Ambulatory	150.3/93.6 ± 9.2/5.8	150.8/93.8 ± 10.5/6.9
24-hour Ambulatory*	143.3/88.3 ± 9.9/6.2	144.4/88.7 ± 11.2/7.1
Nighttime Ambulatory*	132.3/79.8 ± 13.9/8.8	134.3/80.6 ± 15.3/9.6
Office	155.9/101.4 ± 13.9/8.8	155.0/99.9 ± 15.1/9.3
Home†	151.6/97.1 ± 11.5/7.9	150.3/95.8 ± 13.6/8.8

** 24-hour and nighttime ambulatory systolic and diastolic BPs are available for n = 293 in the uRDN group and n = 212 in the Sham group*
† Home systolic and diastolic BPs are available for n = 289 in the uRDN group and n = 212 in the Sham group

Change in Daytime Ambulatory Systolic Blood Pressure at 2 Months



Individual group changes are means based on observed values (uRDN – N=281; Sham – N=211)
Between group difference includes multiple imputation for missing values

**P<0.0001 using either observed values or multiple imputation*

Study by treatment interaction p=0.92 demonstrating consistency of effect

Kirtane et al, JAMA Cardiology 2023

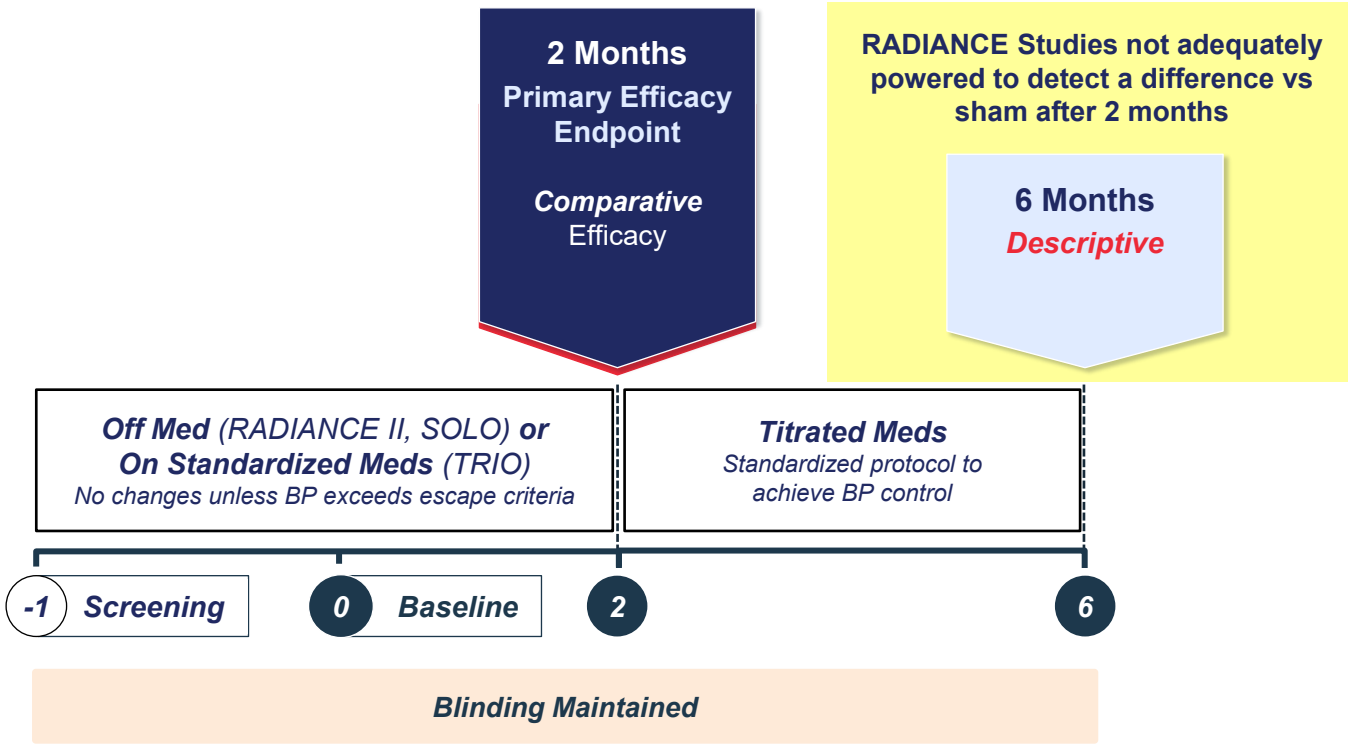
Month 2-6 Medication Titration Protocol

Patients recorded home BP monthly between months 2-6

If home BP ≥135/85 mmHg and Office BP ≥140/90 mmHg, study protocols recommended one pre-specified medication be added per month *with goal of achieving BP control*

Step	SOLO / RADIANCE II (medication washout)	TRIO (initially studied in presence of amlodipine, ARB, and thiazide)
1	Long acting dihydropyridine CCB: mid dose	Aldosterone antagonist
2	ARB or ACEi: full dose	Long acting, cardioselective Beta-1 receptor blocker: full dose
3	Thiazide diuretic: low dose	Central Alpha-2 receptor agonist: full dose
4	Thiazide diuretic: full dose	Long acting Alpha-1 receptor blocker: full dose
5	Long acting dihydropyridine CCB: full dose	

RADIANCE Studies Designed to Demonstrate Effects of uRDN on BP Lowering at 2 Months Compared with Sham



Anti-hypertensive medication changes at 6 months

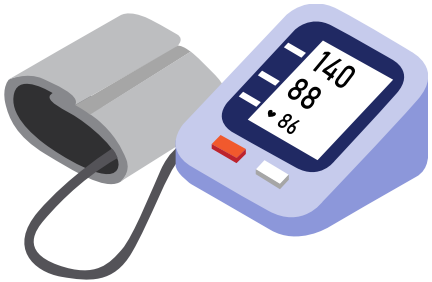
Characteristic	uRDN+AHT (n=285)	Sham + AHT (n=204)	P value*
Full adherence to antihypertensive medications†	140/168 (83.3%)	88/105 (83.8%)	0.47
Anti-hypertensive medication change from baseline to 6 months			
Change in number of antihypertensive medications	+1.1	+1.3	0.001
Change in Defined Daily Dose	+1.3	+1.6	0.001
Change in antihypertensive medication load index	+0.5	+0.6	0.001
Patients with antihypertensive medication changes			
≥ 1 Medication added	189/285 (66.3%)	157/204 (77.0%)	0.002
Medication remained the same or decreased	96/285 (33.7%)	47/204 (23.0%)	

** P value from linear regression adjusted for study for continuous variables and logistic regression adjusted for study for categorical variables comparing treatment arm to sham arm*
† Adherence to antihypertensive medications by urine drug analysis using liquid chromatography tandem mass spectrometry was done only in RADIANCE-HTN TRIO and RADIANCE II studies. The denominator indicates the number of patients with urine sample available.

Blood Pressure Measurements at Follow-up Visits

Home BP

7 Consecutive Days Prior to Office Visit



Office BP

Recommended
8:00 –10:00 AM

1. **Med Adherence (urine) Testing***
2. **Office BP Measurement**
3. **Anti-HTN Pills (Directly Observed)**

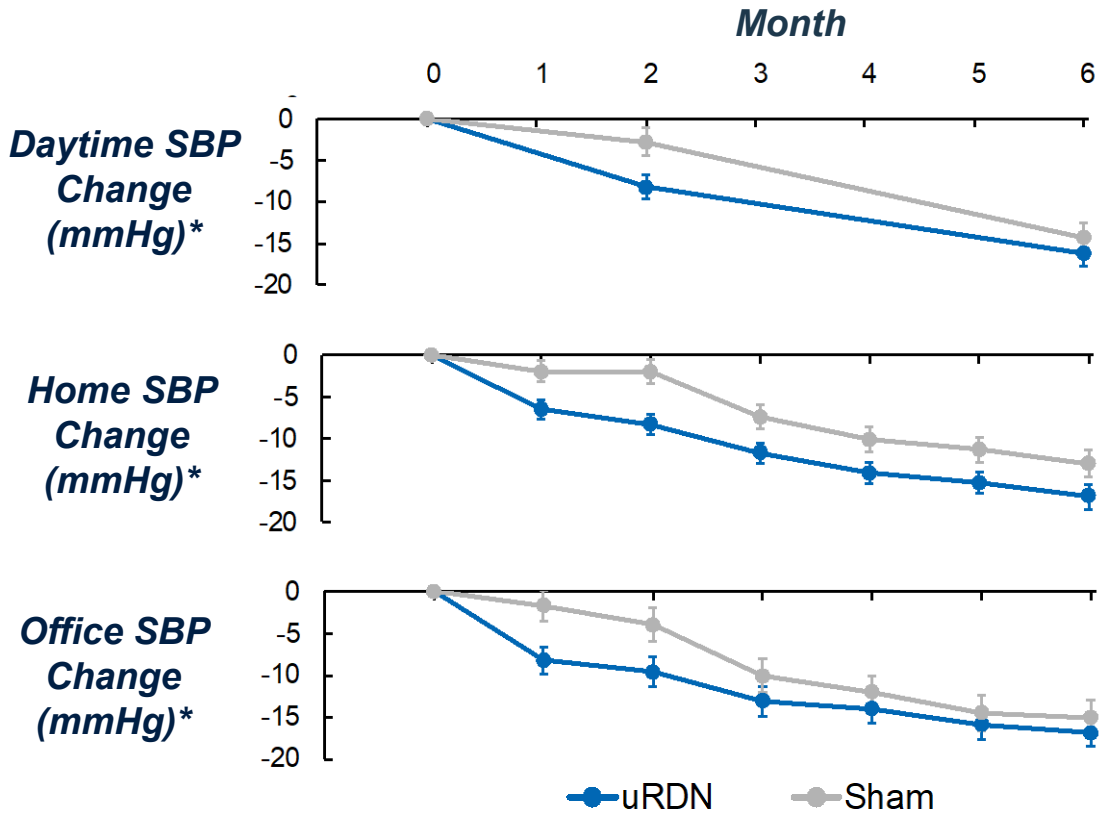
Ambulatory BP Monitoring*

Placed in Office

2 – 6 Months

*Done at Baseline, 2M, and 6M Visits

Baseline-Adjusted SBP over Time



6-Month Mean difference (95% CI)*	P value
-1.9 (-4.8, 1.0)	**0.33**

Overall Model Mean difference (95% CI)**	P value
-4.5 (-5.8, -3.2)	**<0.0001**

6-Month Mean difference (95% CI)*	P value
-1.8 (-6.1, 2.6)	**0.97**

*Linear mixed regression model including baseline value, treatment arm, visit, cohort and interaction term as fixed effects.
**Linear mixed regression model including baseline value, treatment arm, visit, and cohort as fixed effects.

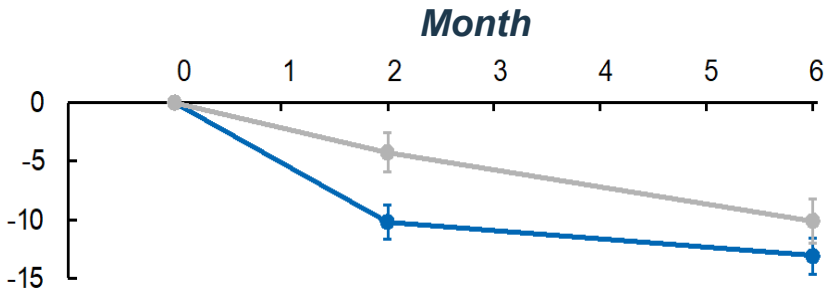
Medication Changes at 6M in Patients with Drop in Home SBP ≥ 10 mmHg

Characteristic, mean ± SD	uRDN N = 203	Sham N = 113	P value*
Change in Number of anti-HTN meds at 6 Months from Baseline	**+1.2**	**+1.7**	**<0.0001**
Change in Medication dose burden at 6 Months from Baseline			
Change in Defined Daily Dose	**+1.5**	**+2.2**	**<0.0001**
Change in Antihypertensive medication load index	**+0.6**	**+0.9**	**<0.0001**

* *P value from linear regression adjusted for study comparing treatment arm to sham arm*

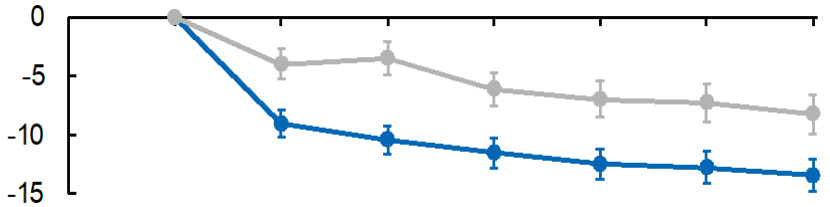
Baseline-adjusted SBP over Time (adjusting for medications)

Daytime SBP Change (mmHg)*



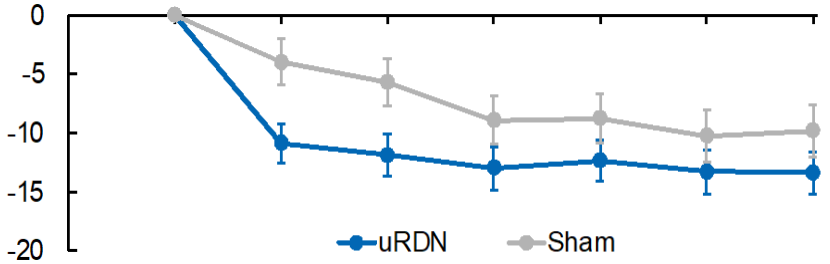
6-Month Mean difference (95% CI)*	P value
-3.0 (-5.7, -0.2)	**0.033**

Home SBP Change (mmHg)*



Overall Model Mean difference (95% CI)**	P value
-5.4 (-6.8, -4.0)	**<0.0001**

Office SBP Change (mmHg)*



Overall Model Mean difference (95% CI)**	P value
-5.2 (-7.1, -3.3)	**<0.0001**

*Linear mixed regression model including baseline value, treatment arm, visit, number of medications at visit, cohort and interaction term as fixed effects.
**Linear mixed regression model including baseline value, treatment arm, visit, number of medications at visit, and cohort as fixed effects.

RADIANCE Pooled Safety Events Through 6 Months

	uRDN (n=293)	Sham (n=213)
All-cause mortality	1 (0.34%)	1 (0.47%)
Hypertensive emergency resulting in hospitalization	1 (0.34%)	3 (1.41%)
Hypotensive emergency resulting in hospitalization	0 (0.00%)	0 (0.00%)
Hospitalization for heart failure	0 (0.00%)	0 (0.00%)
Stroke, transient ischemic attack, cerebrovascular accident	0 (0.00%)	3 (1.41%)
Acute myocardial infarction (STEMI/non-STEMI)	1 (0.34%)	1 (0.47%)
Any coronary revascularization	1 (0.34%)	1 (0.47%)
End stage renal disease, the need for permanent renal replacement therapy; doubling of plasma creatinine	2 (0.34%)	0 (0.00%)
Significant (>50%) new onset renal stenosis confirmed by renal CTA/MRA	1 (0.34%)*	0 (0.00%)
Need for renal artery angioplasty or stenting	1 (0.34%)*	0 (0.00%)

Data presented as number of events (% of patients with event)
* The renal artery stenosis led to renal artery stenting in the same patient

Limitations

- The active (and asymmetric) medication titration protocol in both treatment groups precludes a “pure comparison” of the effect of RDN vs. sham at 6 months
  - This was done for safety, especially for patients in the sham group, who were untreated for three months (one prior to randomization, and two following it)
- The adjustment for medication burden represents adjustment for a post-randomization covariate, but is an attempt to try to separate BP effects from randomized treatment from those related to medications
- Somewhat limited applicability of the results of this analysis in the real world setting (with less frequent follow-up and intensity of medication changes), and in patient populations with more diverse ethnicities

Conclusions

- Each of the three independently powered trials of the RADIANCE-HTN program previously showed that uRDN with the Paradise system safely reduced BP at 2 months vs. a sham procedure in patients with mild to moderate hypertension off-medications or with resistant hypertension on triple-drug fixed dose combination therapy
- The present individual patient data analysis demonstrates that after initiating standardized medication regimen for hypertension control from the 2nd month post-procedure onwards, there was less addition of these medications in the uRDN group compared with sham, and after adjustment for this difference, the BP lowering effect of uRDN vs. sham was maintained throughout the 6-month follow-up