RENAL DENERVATION FOR HTN

Sina Salehi Omran, MD
Structural Heart Disease Fellow
Gates Vascular Institute

DISCLOSURES

Vijay Iyer MD PhD FACC FSCAI

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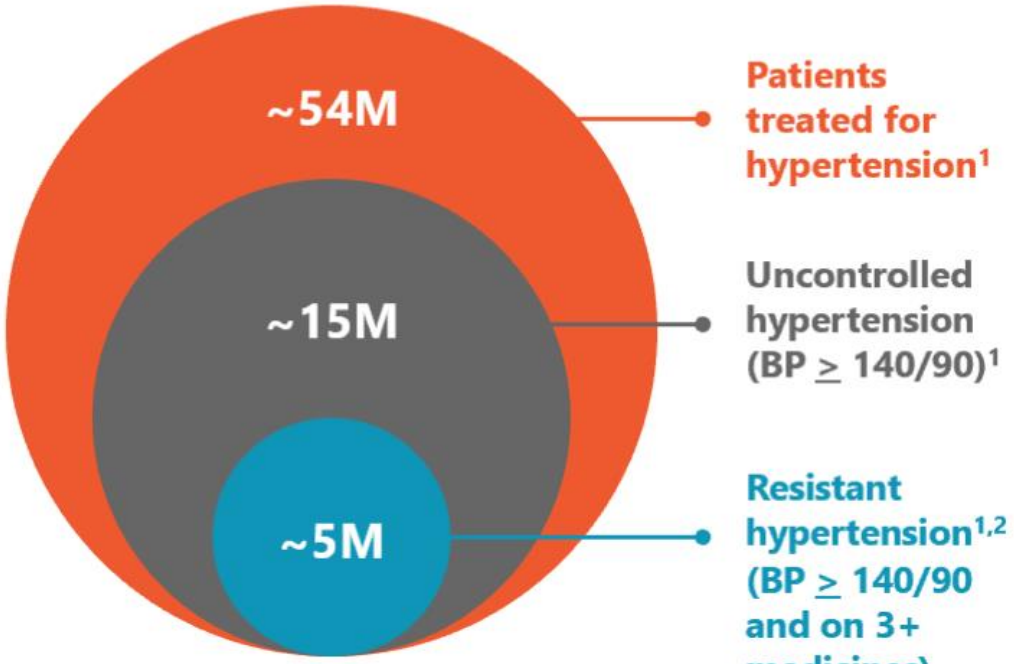
Significant number of treated hypertension patients have resistant and/or uncontrolled hypertension



Left undetected or untreated over time, hypertension can lead to:

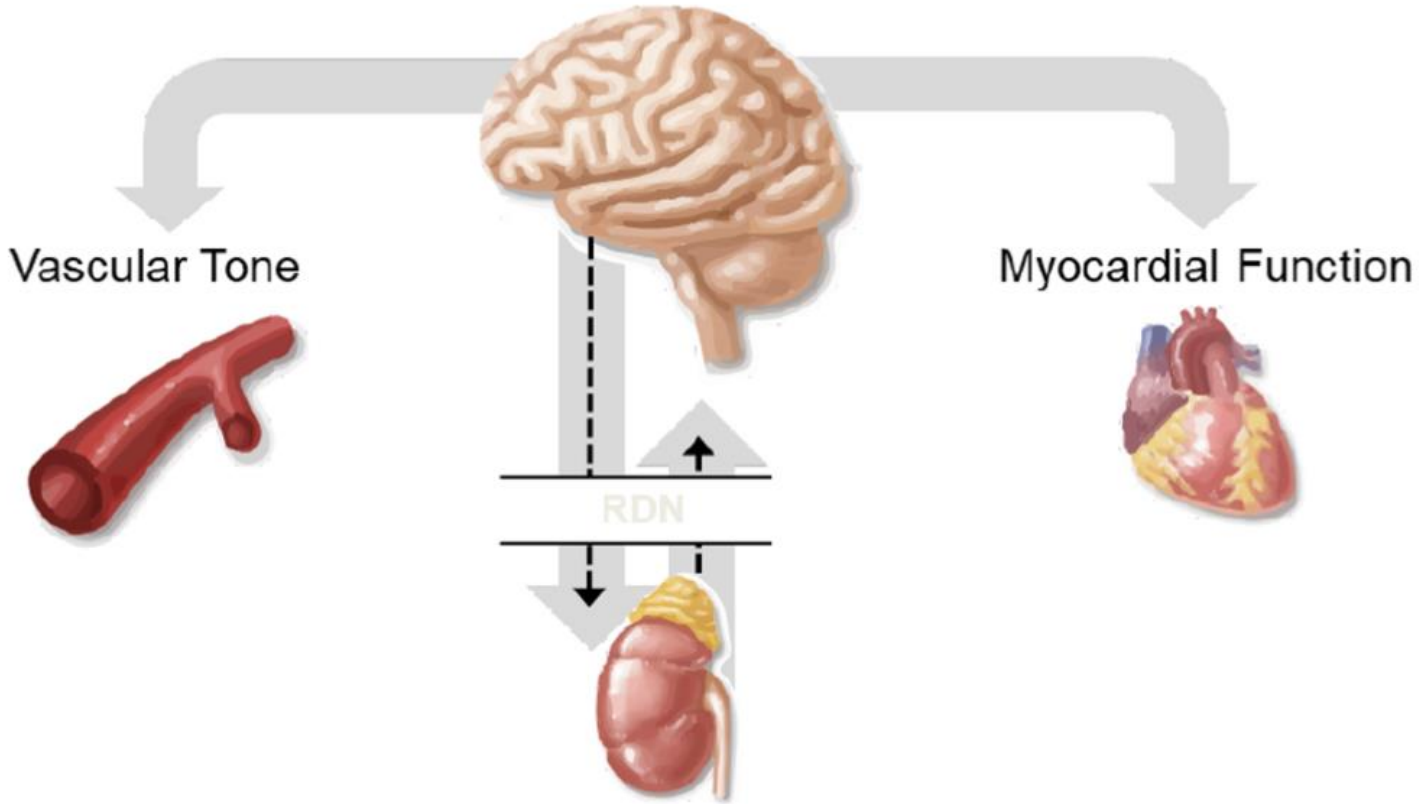
- **Ischemic heart disease**, including myocardial infarction
- **Stroke**
- **Heart failure**
- **Chronic renal failure**
- **Cognitive decline**

Hypertension is associated with **5 years reduced life expectancy**[3]

1. Zhang et al. *Hypertension*. 2017 Oct;70(4):736-742. Online Supplement - 2013-14 Data.Carey et al. Hypertension. 2019 Feb;73(2):424-431
2. Carey et al. *Hypertension*. 2019 Feb;73(2):424-431.
3. Stroke and High Blood pressure correlation – AHA - High Blood Pressure and Stroke Infographic | American Stroke Association

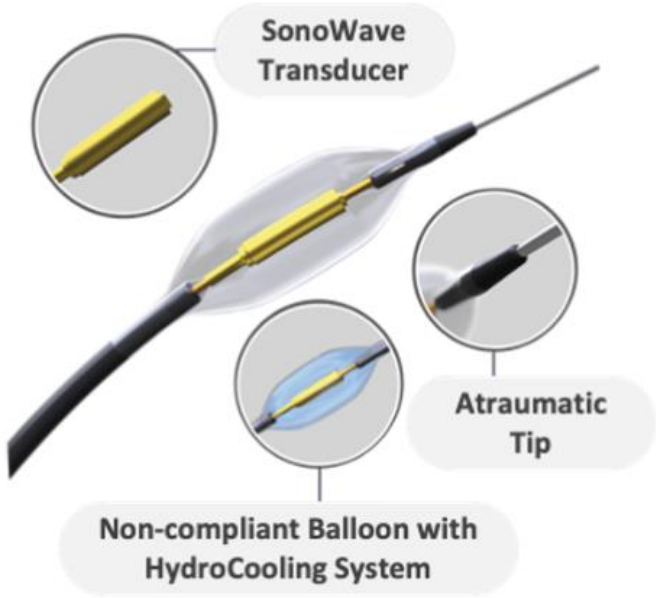
Renal Denervation is a Minimally Invasive Option to Treat Hypertension

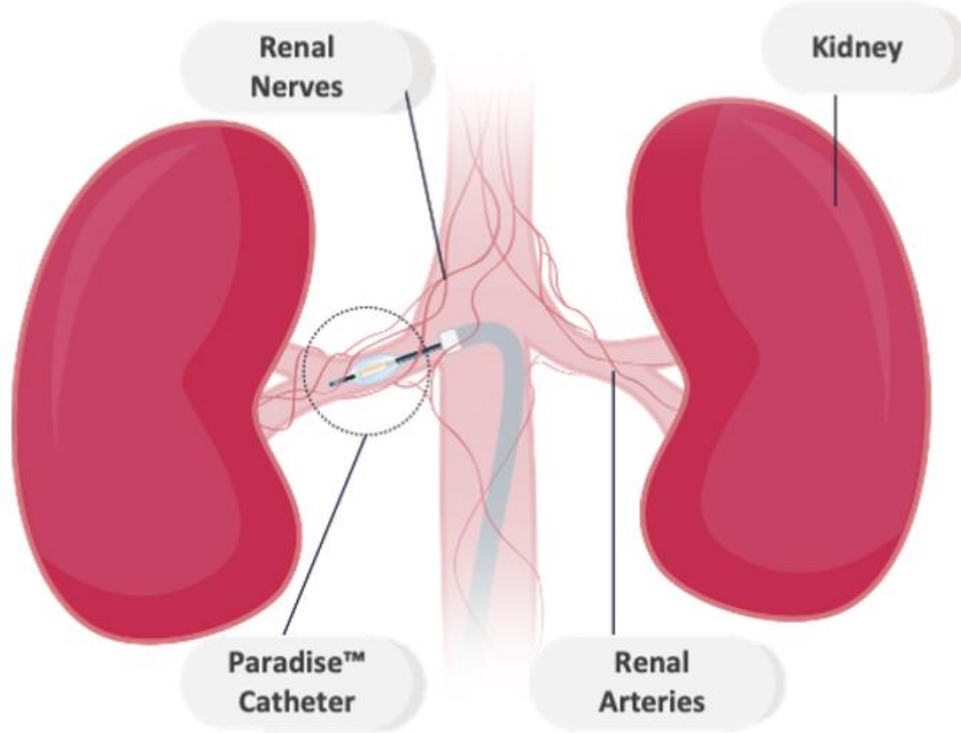
Interrupts Sympathetic Neural Activity Between Brain and Kidneys



Efferent sympathetic signals from the CNS to the kidney and afferent sensory feedback from the kidney to the CNS modulate renal function and overall sympathetic activity.

The Paradise® Ultrasound Renal Denervation system



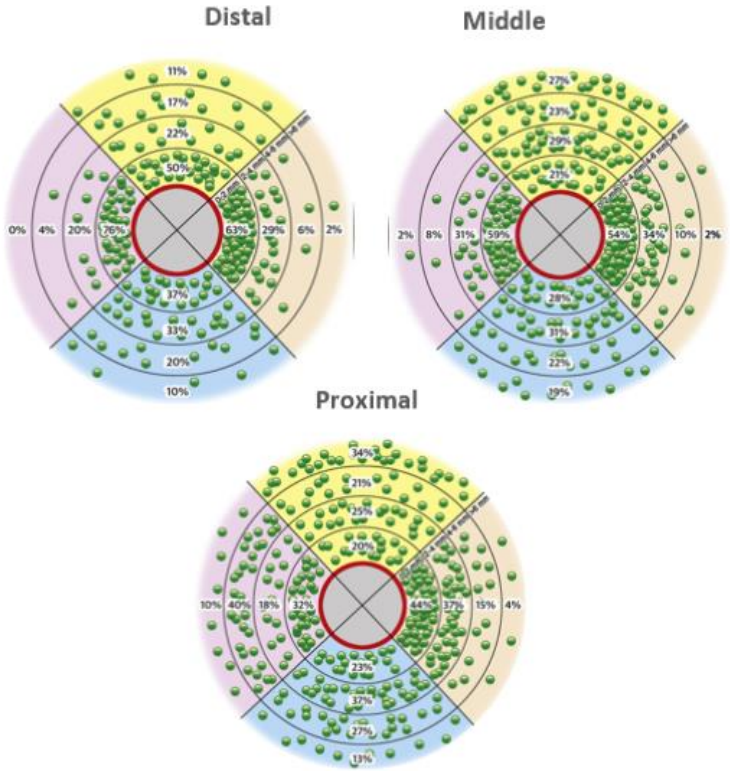


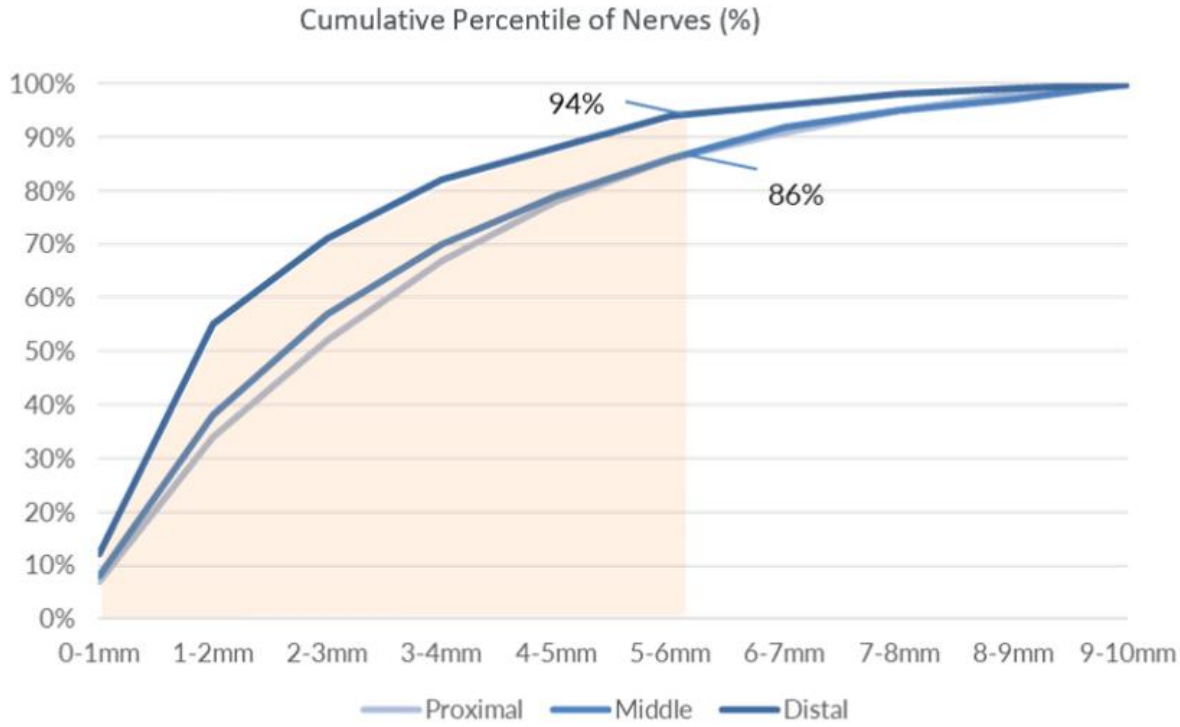
Paradise® Catheter

Paradise® Generator

Nerve distribution along renal arteries

Nerve Distribution by Renal Artery Sections (n=8030 nerves)[1]

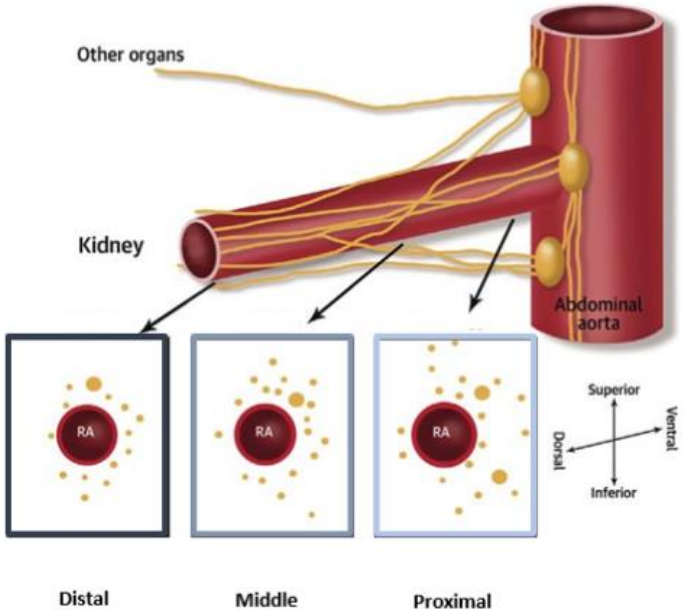




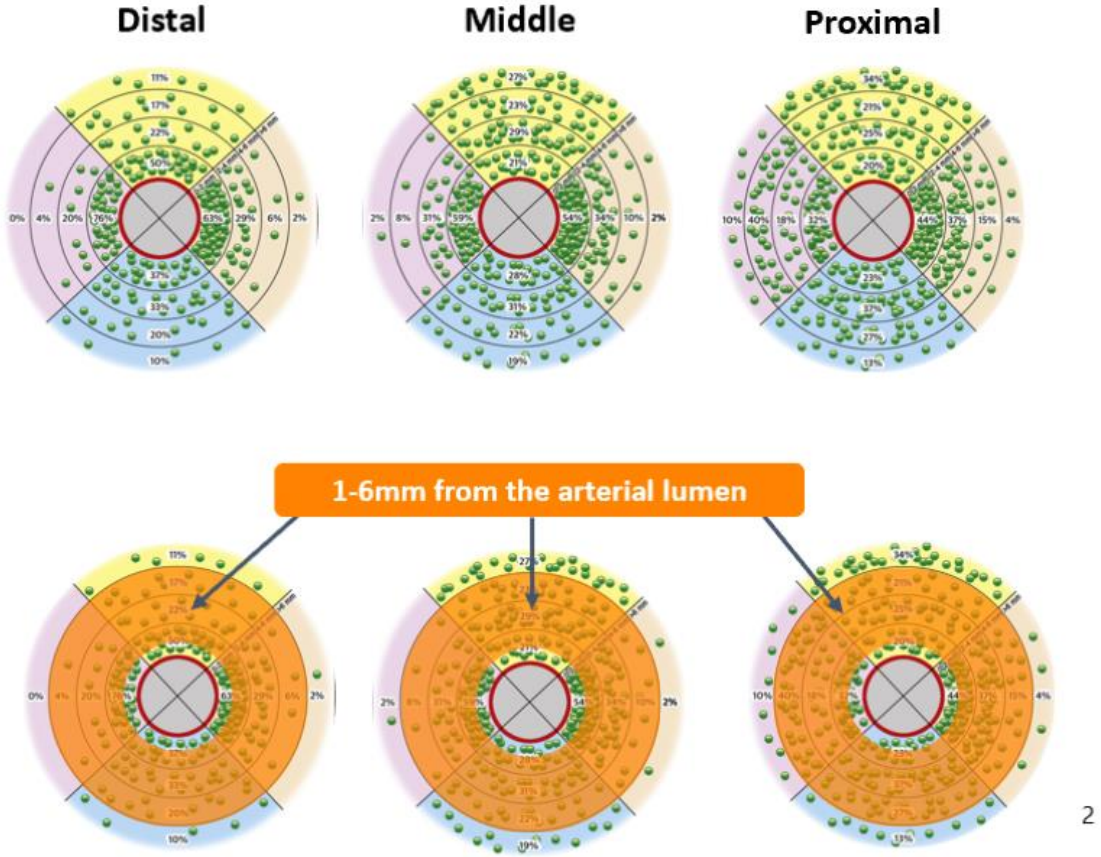
Majority of renal nerves along the main renal artery are within depths of 1-6 mm[1]

1. Sakakura et al. *JACC*. 2014; 64(7):635–643.

Impact of 360° sonication



Renal Artery Sections[1]

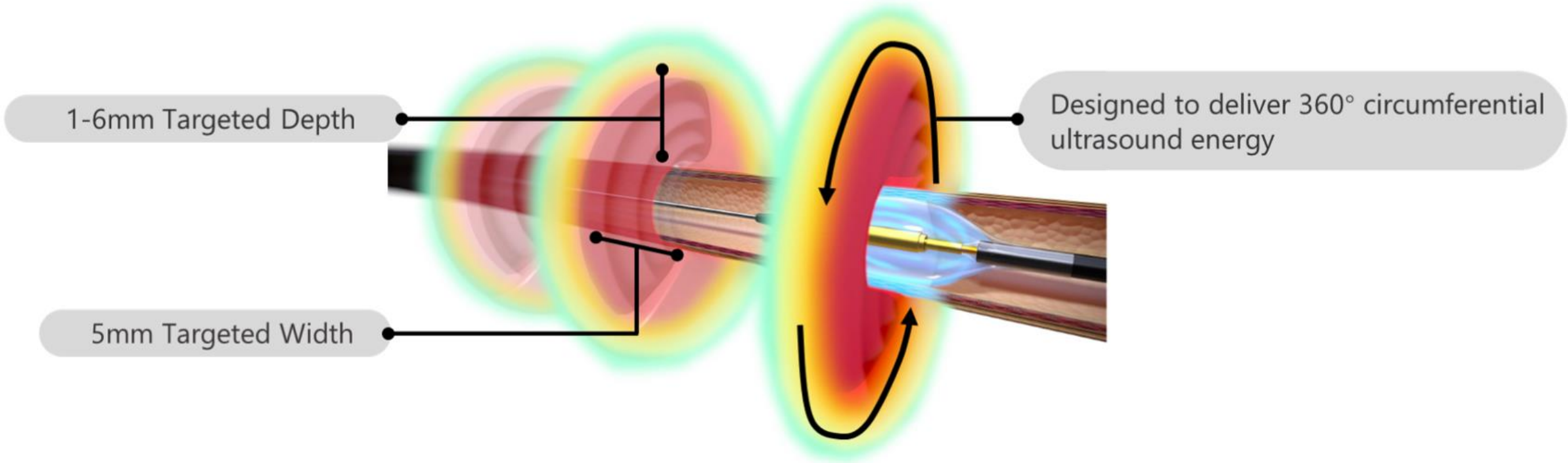


2

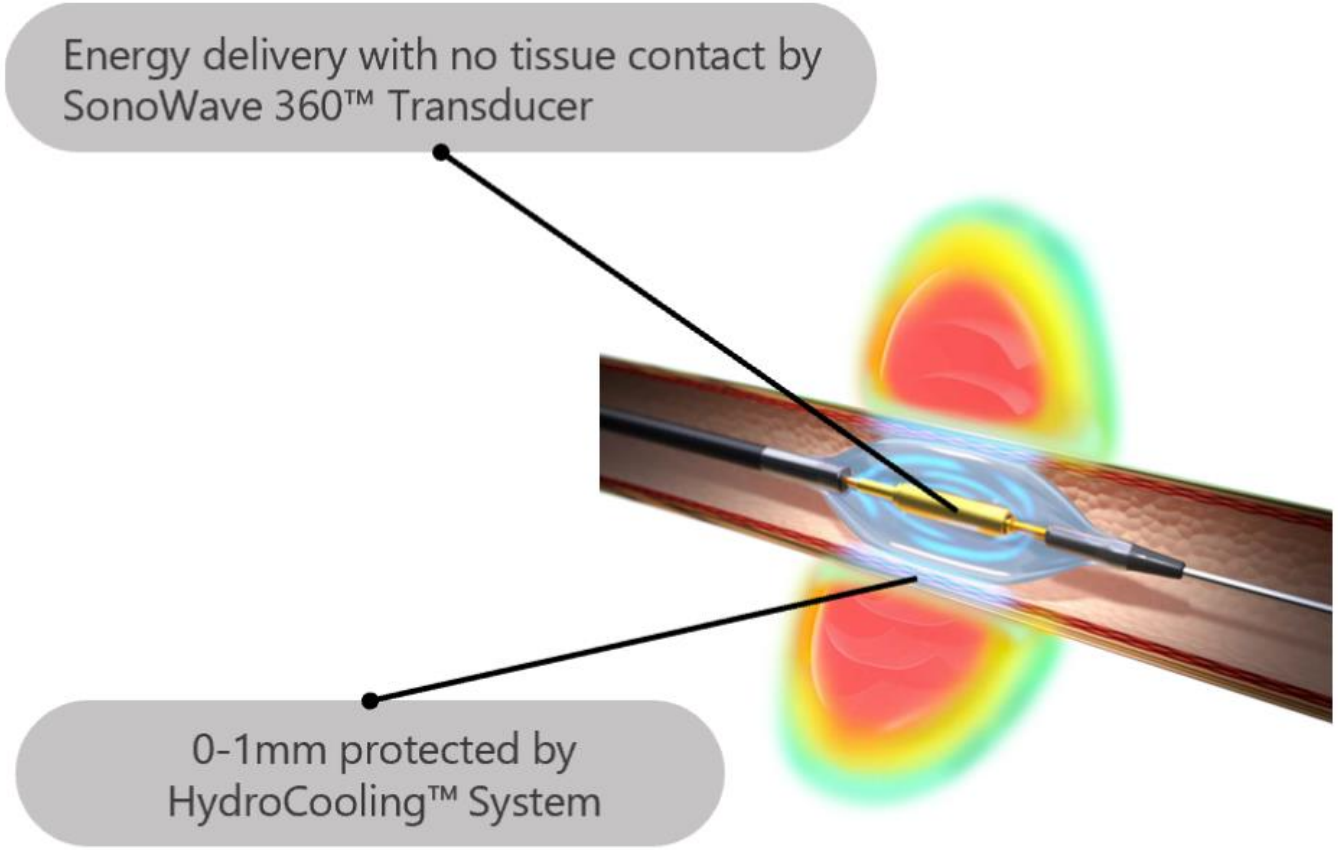
Approximately 80% of renal nerves are targeted by 360° circumferential sonication (1-6mm in depth)[1,2]

1.Sakakura et al. JACC. 2014; 64(7):635–643. 2. Mahfoud et al. JACC. 2014; 64(7):644-646.

Designed to deliver 360° circumferential energy



Actively helps protect arterial wall with simultaneous heating & cooling



RADIANCE program highlights

Recor Global Clinical Trial Program

Completed Studies	RADIANCE-HTN Prospectively Powered RCTs	New Programs Registries and New Indications
REDUCE & REALISE[1] (N = 35)	RADIANCE-HTN SOLO[3] (Off Meds → Med Titration) Mild to Moderate HTN (N = 146)	Global Paradise System (GPS) Registry (N up to 3,000)
ACHIEVE[2] (N = 96)	RADIANCE-HTN TRIO[4] (On-Meds) Resistant HTN (N = 136)	RADIANCE CAP (Continued Access Protocol, US)
REQUIRE[5] (N = 140)	RADIANCE II Pivotal[6] (Off Meds → Med Titration) Mild to Moderate HTN (N = 224)	Additional Indications CKD | Arrhythmia | Heart Failure
RADIANCE PREFER[7] (N = 300, US)	RADIANCE-HTN DUO (On-Meds) Moderate HTN (N = 154)	

1. Mabin et al. *EuroIntervention* 2012;8:57-61. 2. Daemen et al. *J Hypertens*. 2019 Sep;37(9):1906-1912. 3. Azizi et al. *Lancet*. 2018 Jun 9;391(10137):2335-2345. 4. Azizi et al. *Lancet* 2021; 26: 2476-2486.
5. Kario et at. *Hypertens Res*. 2022 Feb;45(2):221-231. 6. Azizi et al. 2023. *JAMA*, 329(8), 651. 7. Fisher et al. *AHA Hypertension 2023*.

RADIANCE trial design (SOLO, RADIANCE II and TRIO)

Blinded, sham-controlled, individually powered trials to demonstrate BP lowering effectiveness by ABPM at 2 months

	SOLO[1]	RADIANCE II[2]	TRIO[3]
Screening BP, Age, med and eGFR criteria	• Age ≥ 18 and ≤ 75 • Office BP ≥140/90 on 0-2 anti-HTN meds or controlled on 1-2 meds • eGFR ≥ 40 mL/min/1.72m^2	• Age ≥ 18 and ≤ 75 • Office BP ≥140/90 on 0-2 anti-HTN meds • eGFR ≥ 40 mL/min/1.72m^2	• Age ≥ 18 and ≤ 75 • Office BP ≥140/90 on 3+ anti-HTN meds • eGFR ≥ 40 mL/min/1.72m^2
4-week medicine washout/standardization	Anti-HTN medication washout	Anti-HTN medication washout	Fixed dose, 3-drug combination pill stabilization
ABPM criteria at baseline	Daytime ABP ≥135/85 & <170/105 mmHg	Daytime ABP ≥135/85 & <170/105 mmHg	Daytime ABP ≥135/85 mmHg

CTA / MRA, Renal Duplex, Renal Angiography

Ultrasound RDN (N=293)

SOLO (N=74) | RADIANCE II (N=150) TRIO (N=69) |

Sham (N=213)

SOLO (N=72) | RADIANCE II (N=74) | TRIO (N=67)

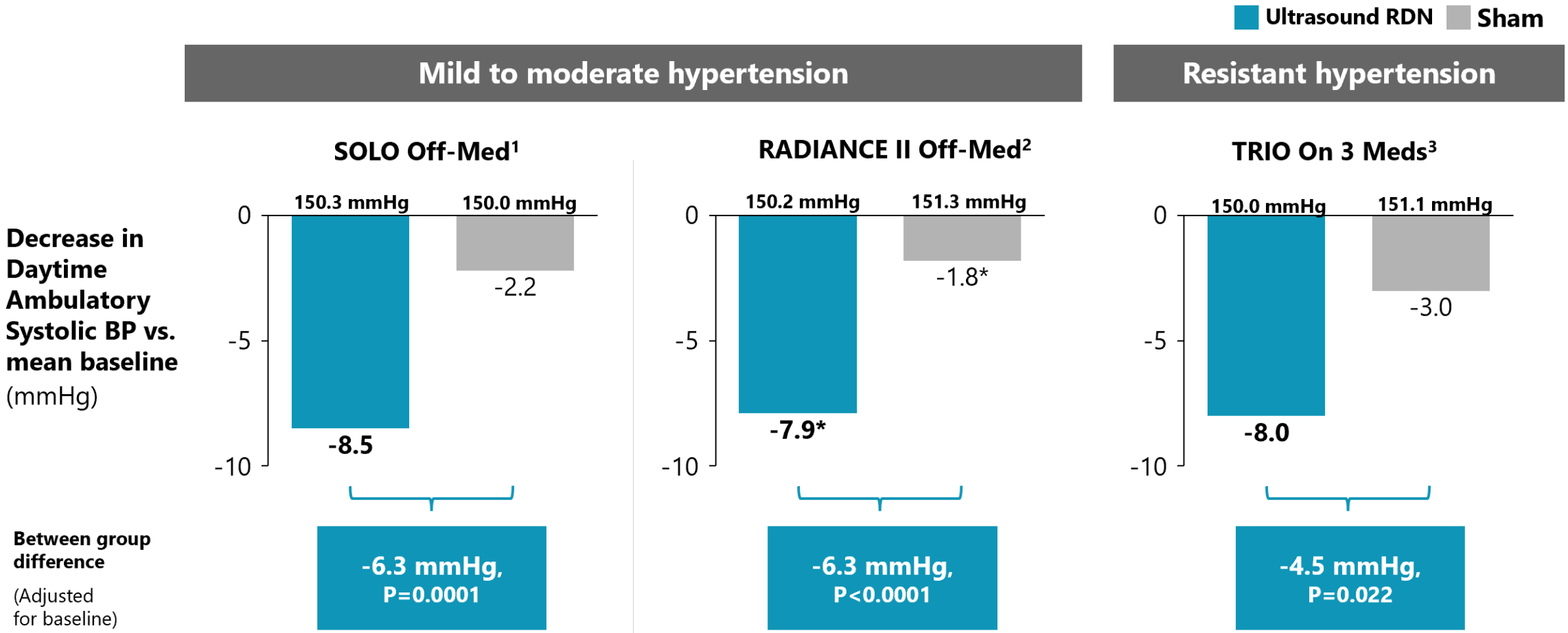
Primary efficacy endpoint @ 2 Months
Δ Daytime ambulatory systolic BP

No med changes unless escape BP criteria exceeded

Patients, following physicians, and output assessors blinded at randomization

1. Azizi et al. *Lancet*. 2018 Jun 9;391(10137):2335-2345.; 2. Azizi et al. *JAMA*. 2023 Feb 28;329(8):651-661. 3. Azizi et al. *Lancet*. 2021 Jun 26;397(10293):2476-2486.

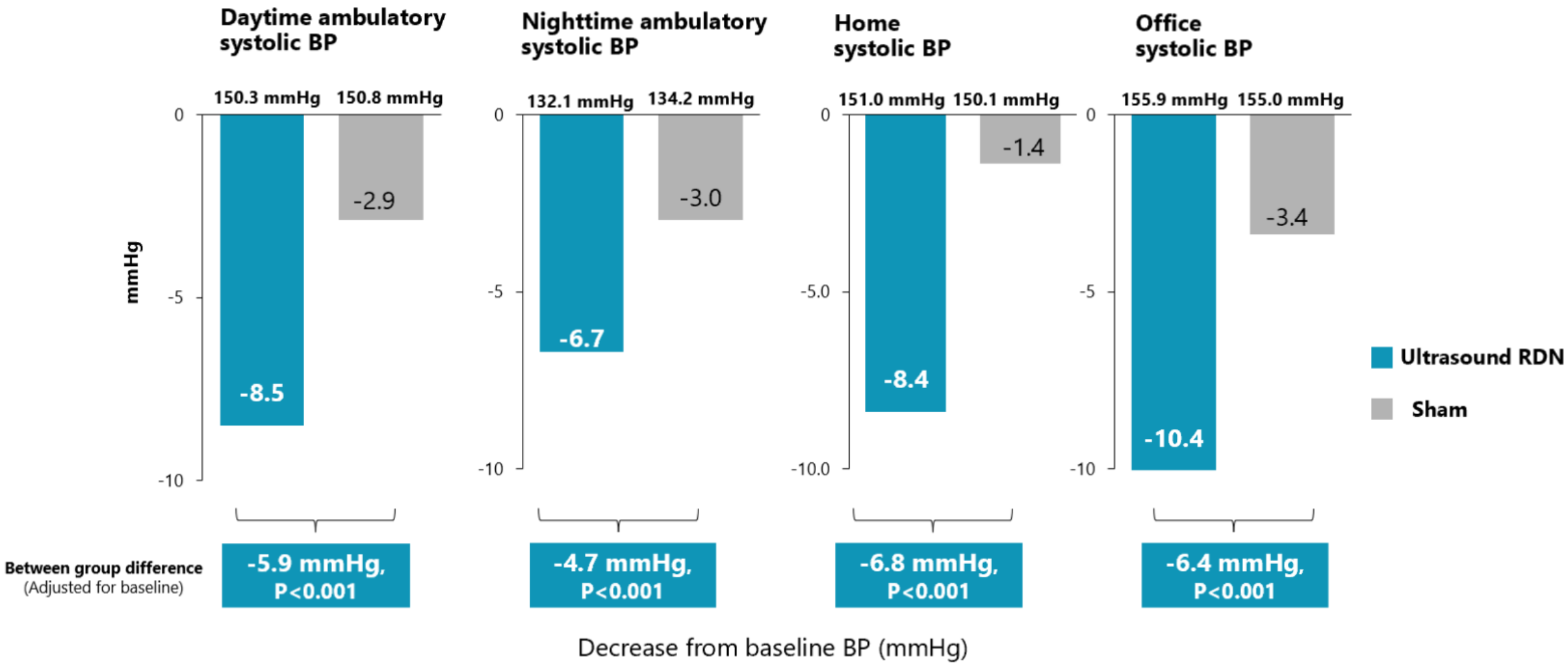
Ultrasound RDN met its primary efficacy endpoint at 2 months in 3/3 US randomized controlled trials



*individual group changes are based on observed values ultrasound RDN n=145 and sham control n=73

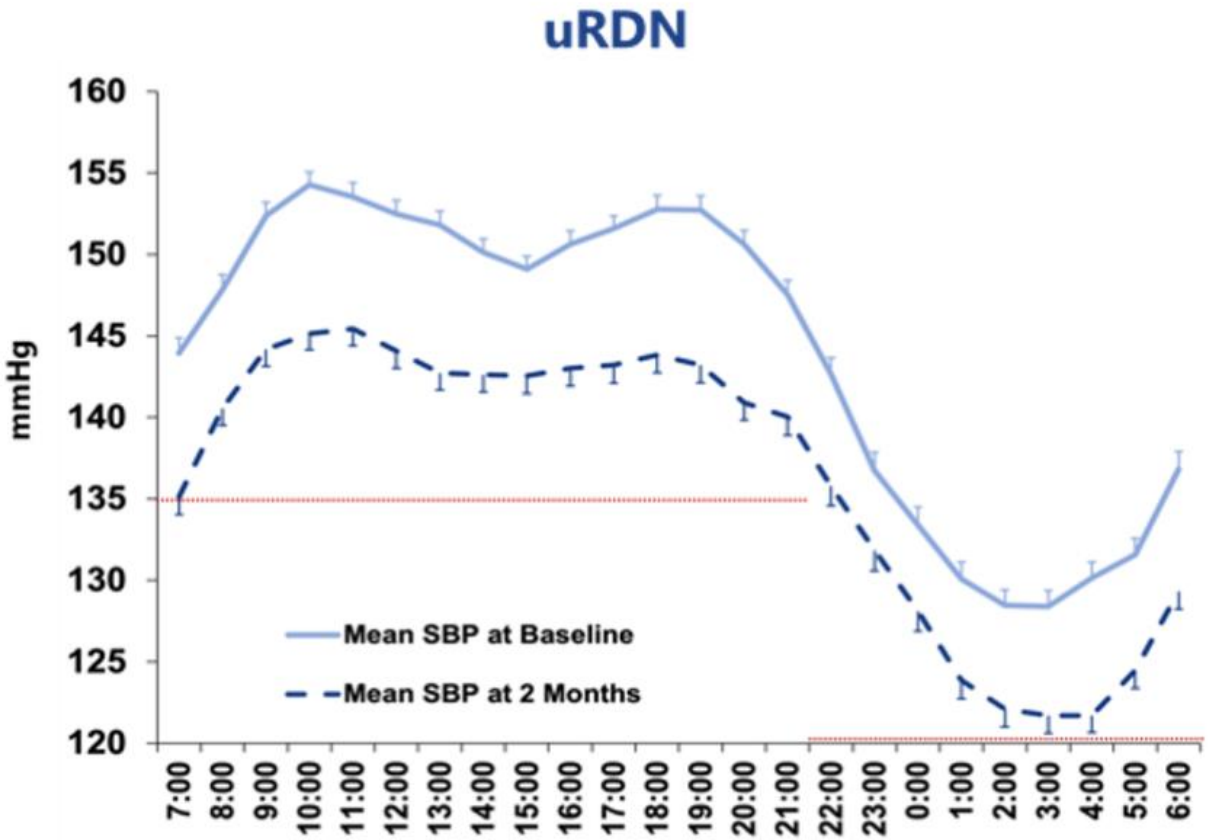
1 Azizi et al. *Lancet*. 2018 Jun 9;391(10137):2335-2345. 2. Azizi et al. *JAMA*. 2023 Feb 28;329(8):651-661. 3. Azizi et al. *Lancet*. 2021 Jun 26;397(10293):2476-2486.

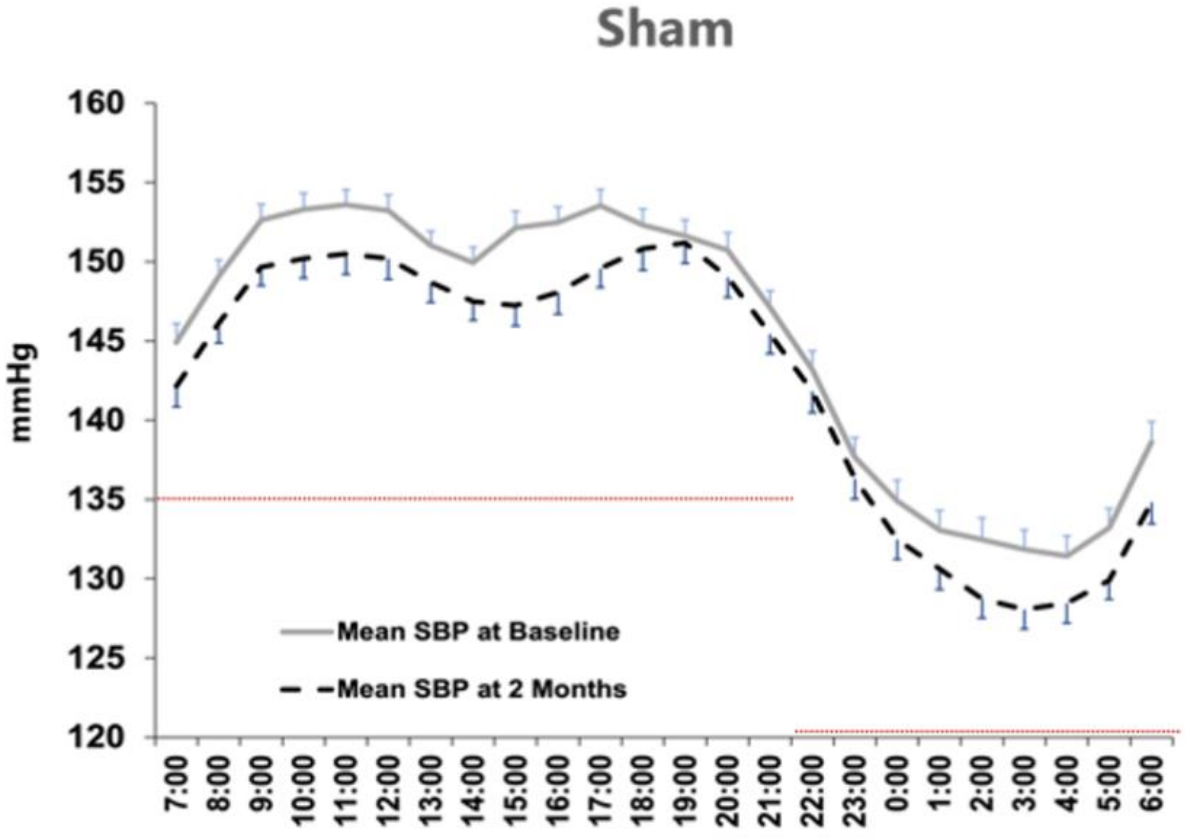
Ultrasound RDN led to a consistent ambulatory, home and office SBP decrease from baseline at 2 months in the individual data pooled analysis from 3 randomized trials



Kirtane et al. *JAMA Cardiol.* 2023;8(5):464-473.

Pooled Analysis of RADIANCE Trials: Lower Ambulatory BP throughout 24-hr period





Patients that met escape criteria had baseline values carried forward

Kirtane et al. AHA2022.

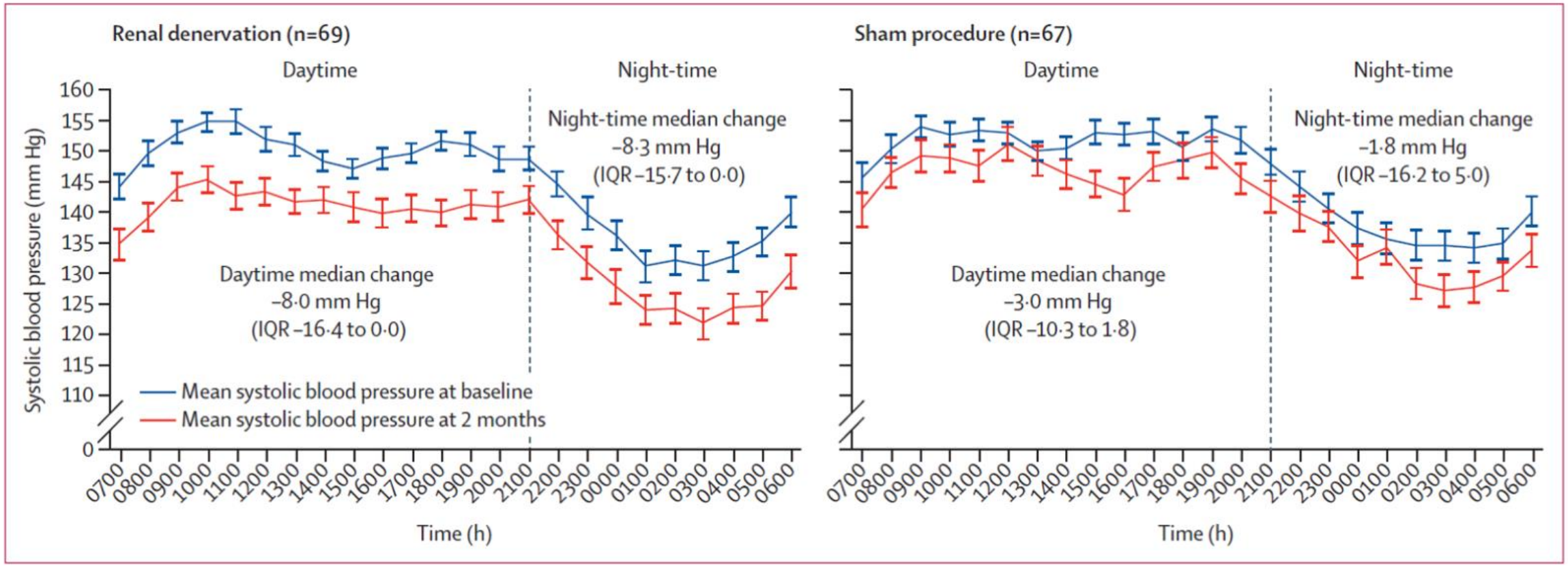
24h Ambulatory SBP

Between Group = -5.3 mmHg
P<0.0001

Nighttime Ambulatory SBP

Between Group = -4.7 mmHg
P<0.0001

RADIANCE-HTN TRIO 24-hr Ambulatory Systolic BP Drop



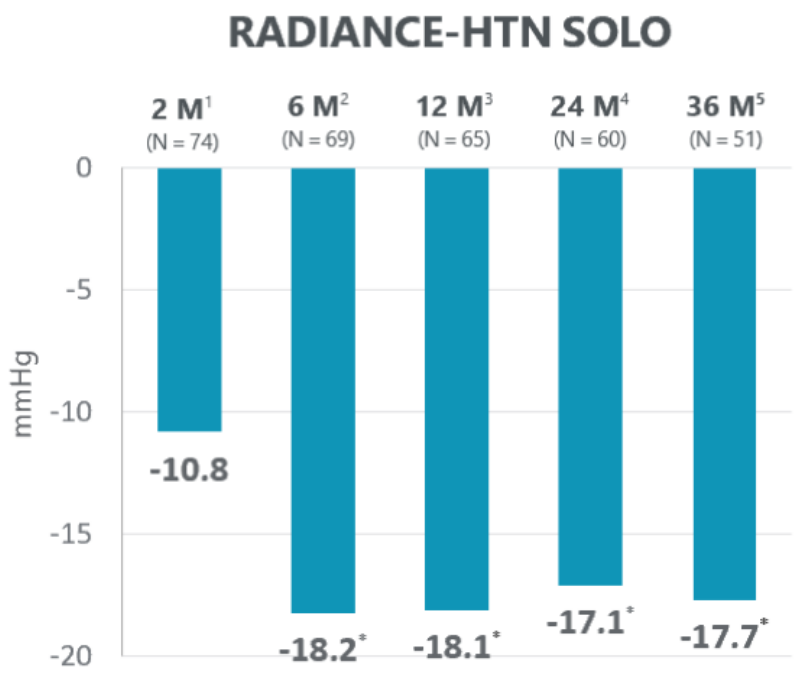
<u>24-hr ambulatory SBP</u>
Between group = -4.2mmHg
p< 0.016

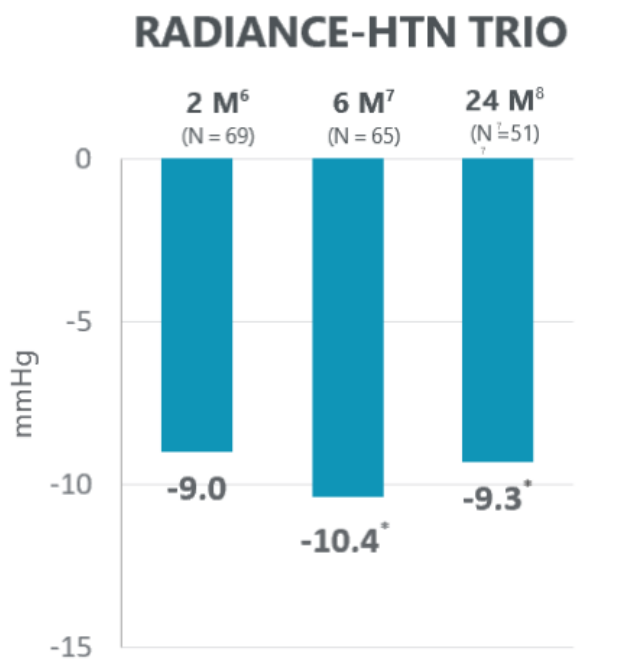
<u>Night-time ambulatory SBP</u>
Between group = -3.9mmHg
p< 0.044

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

The Paradise ® System is approved for use in the United States and countries that accept CE mark. For investigational use in Japan.

RADIANCE SOLO and TRIO: office SBP reduction up to 36 months





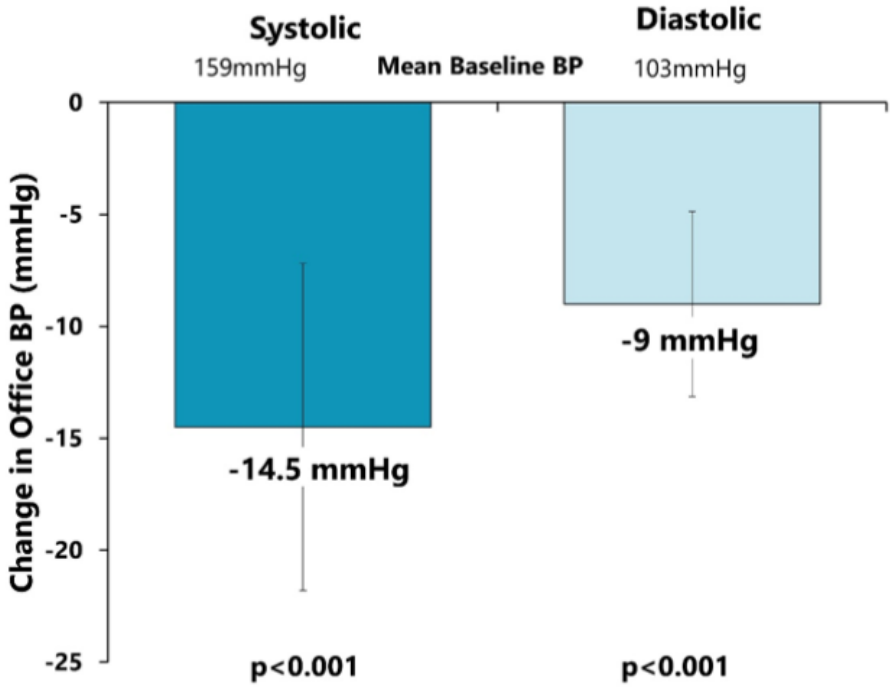
Reduction of Office BP by 10 mmHg Leads to 20% Reduction in Risk of CV Events[9]

* 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. Rader et al. *EuroIntervention* 2022;18-online
  6. Azizi et al. *Lancet*. 2021;397:2476-2486 7. Azizi et al. *JAMA Cardiol*. 2022;7(12):1244-1252.. 8. Schmieder et al. TCT 2022. 9. Ettehad et al. *Lancet* 2016; 387: 957–67

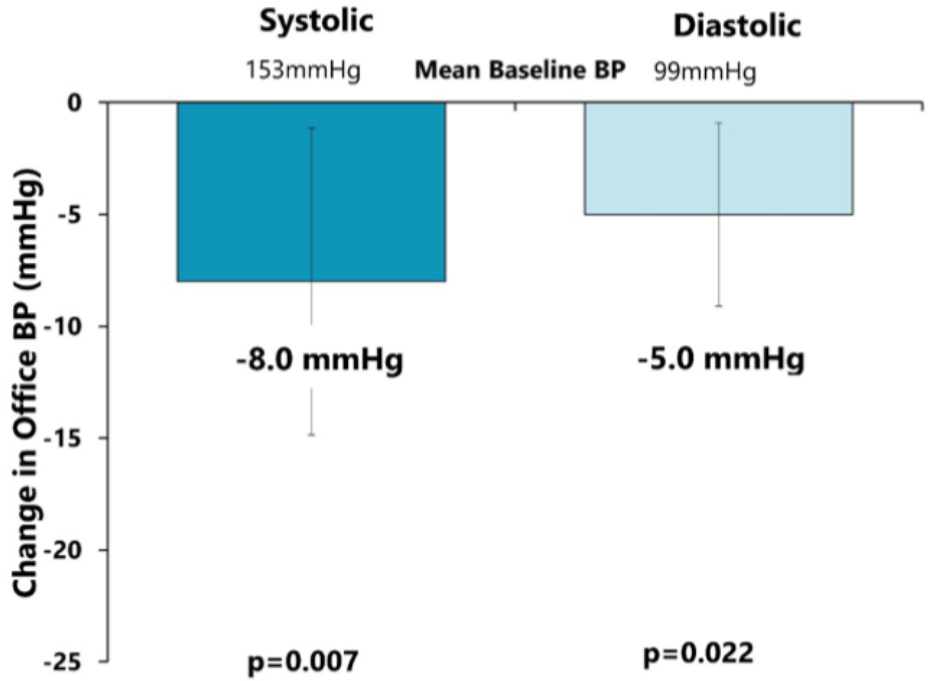
RADIANCE TRIO: office SBP reduction up to 36 months

Screening to 36M (n=49)



	Screening	36 Mo	Δ Screening to 36M	p value
# of meds	3.9 ± 1.0	3.7 ± 1.3	-0.2 ± 1.3	p=0.130

Baseline to 36M (n=49)



	Baseline*	36 Mo	Δ Baseline to 36M	p value
# of meds	3.1 ± 0.3	3.7± 1.3	0.6 ± 1.3	p=0.004

*Baseline measurement occurred following 4-week standardization on a 3-drug single-pill

Bloch et al. *AHA 2023*

RADIANCE pooled major adverse event rates (patient-level, non-hierarchical)

	uRDN (N=293)	Sham (N=213)
30-day events		
All-cause mortality*	1 (0.3%)	0 (0.0%)
New onset ESRD (eGFR<15 mL/min/m^2 or need for renal replacement therapy)	0 (0.0%)	0 (0.0%)
Significant embolic event resulting in end-organ damage	0 (0.0%)	0 (0.0%)
Renal artery perforation or dissection requiring an invasive intervention	0 (0.0%)	0 (0.0%)
Major vascular complication requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	1 (0.3%)	0 (0.0%)
Hospitalization for hypertensive or hypotensive crisis	1 (0.3%)	0 (0.0%)
Hospitalization for major cardiovascular or hemodynamic related events	1 (0.3%)	0 (0.0%)
New onset stroke	0 (0.0%)	0 (0.0%)
New onset myocardial infarction	0 (0.0%)	0 (0.0%)
6-month events		
New onset renal artery stenosis >70%	0 (0.0%)	0 (0.0%)

5 Major Adverse Events occurred in 3/293 patients (1.0%) in the uRDN arm. Multiple events occurred in a single patient: 2 vascular complications and a hospitalization for hypotension

* Death was unrelated to the procedure

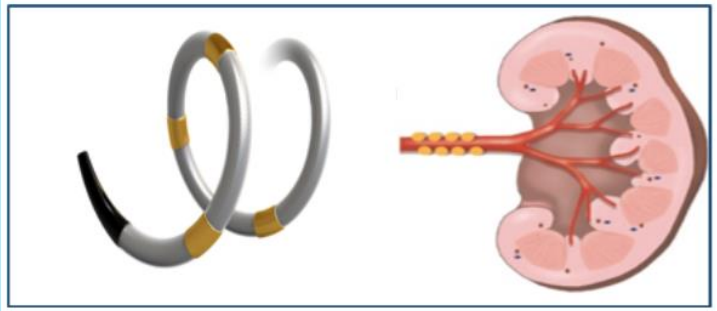
Kirtane et al. *JAMA Cardiol.* 2023;8(5):464-473.

ACHIEVE and RADIOSOUND-HTN study update

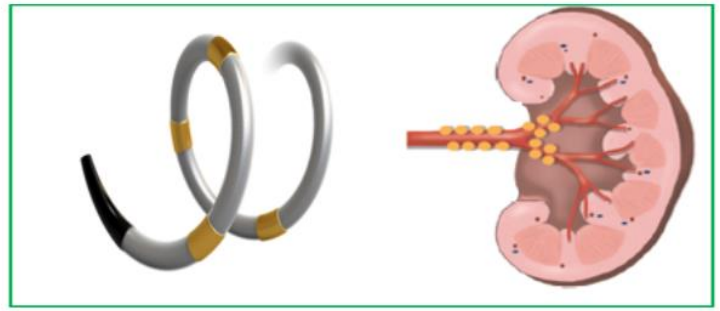
RADIOSOUND-HTN - Design

Comparison of effect of Renal Denervation with:

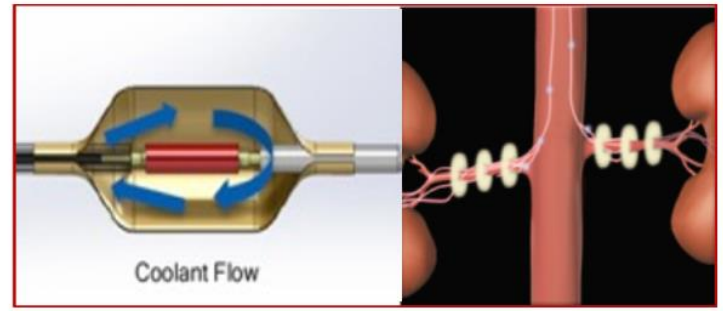
1: radio frequency ablation of the main renal artery



2: radio frequency ablation of main renal artery and side branches



Ultrasound ablation of the main renal artery



In patients with therapy-resistant arterial hypertension

Lurz, P. RADIOSOUND-HTN study update. TCT 2023.

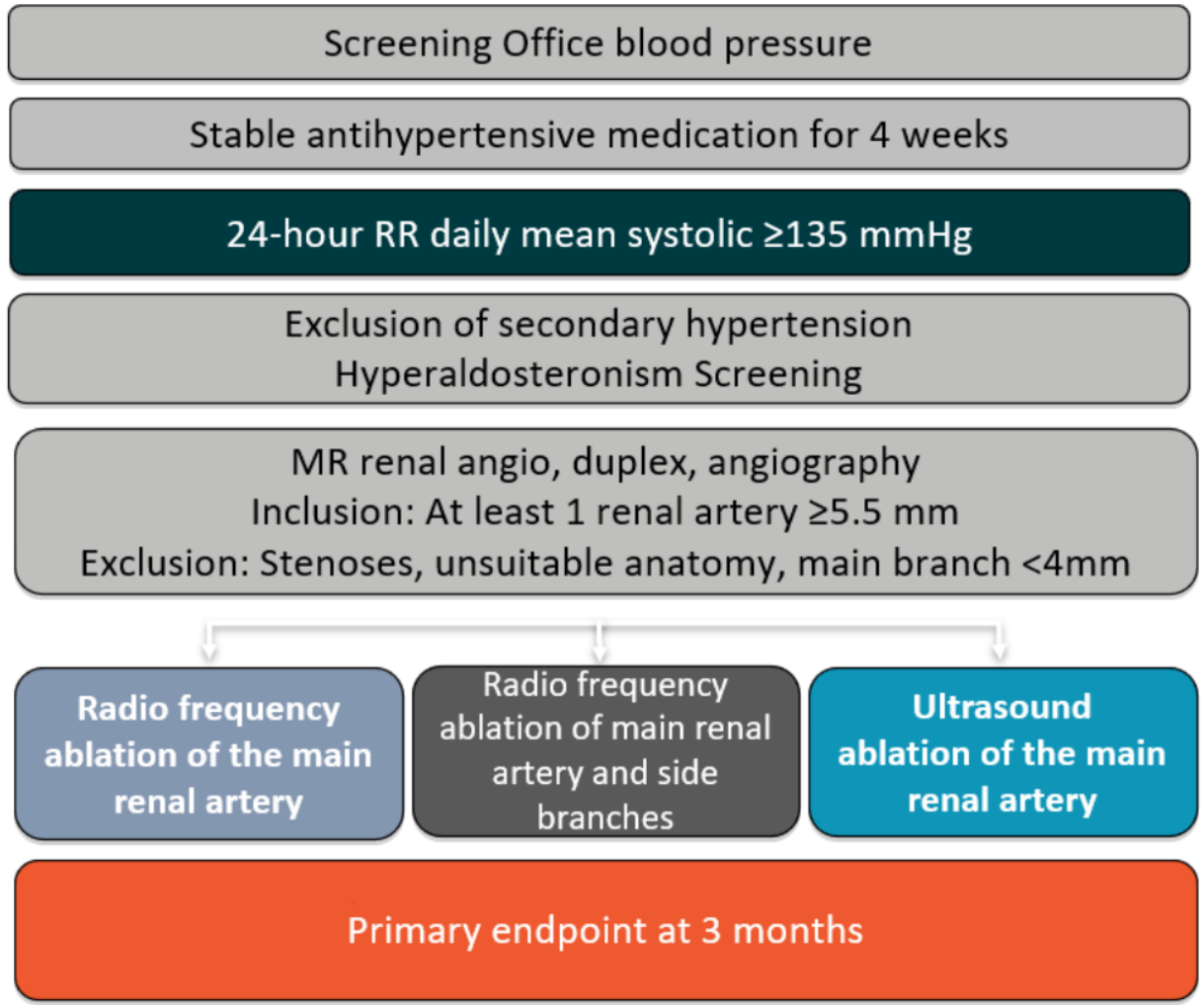
RADIOSOUND-HTN - Design

Design

Prospective, blinded, single-centre, randomized study (1:1:1)

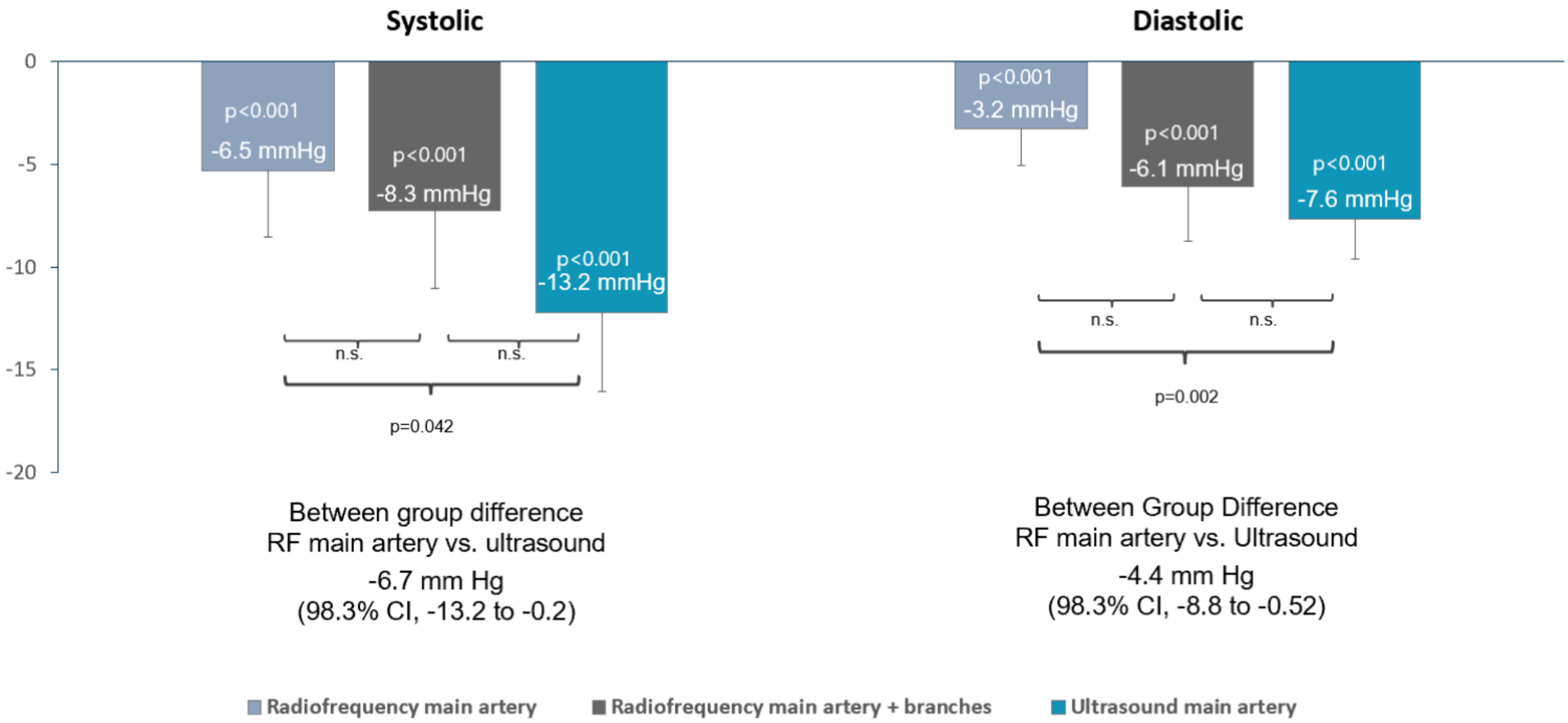
Population: Patients between >18 and <75 years with resistant hypertension despite therapy with ≥3 drug classes including diuretics.

Primary endpoint: daily mean from 24-hour RR after 3 months



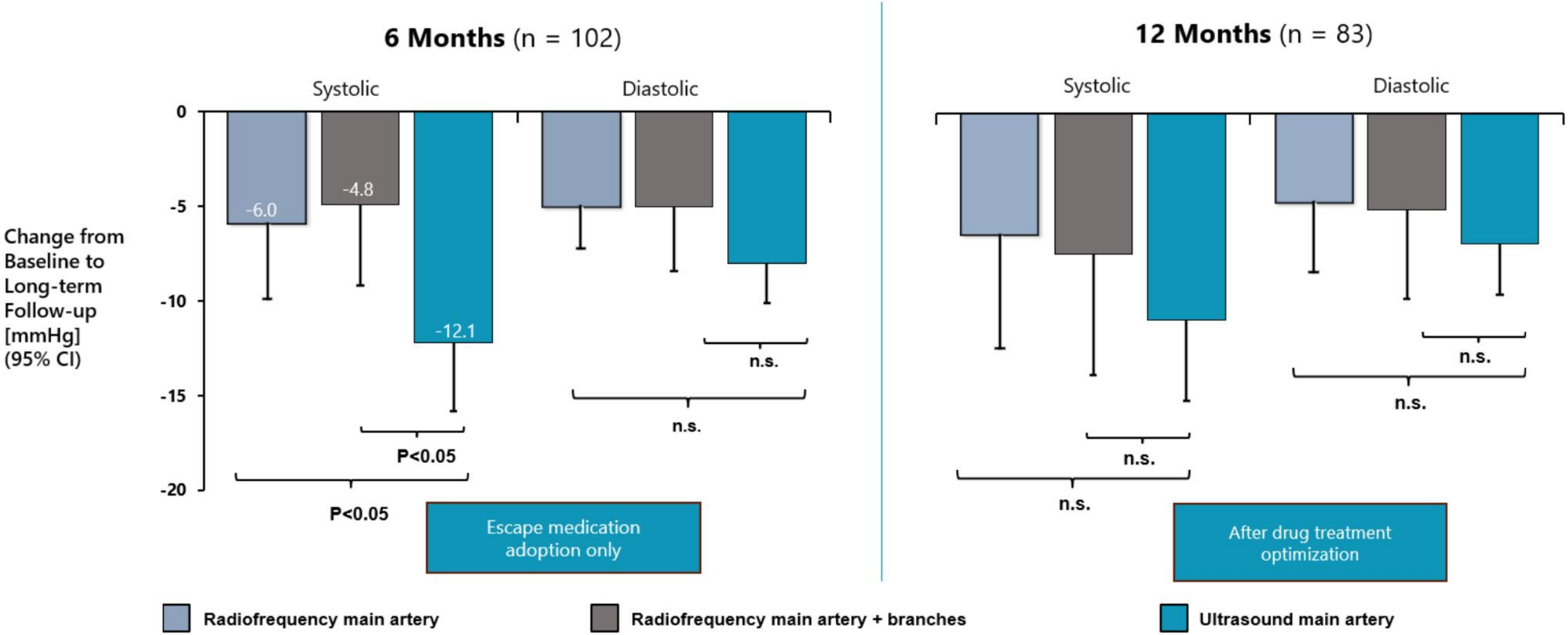
Fengler et al. *JACC: Cardiovascular Interventions*. Vol 16. No. 3. 2023: 359-369.
Fengler et al. *Circulation*. 2019 Jan 29;139(5):590-600.

RADIOSOUND-HTN – Primary results at 3 months



Fengler et al. *Circulation*. 2018

RADIOSOUND-HTN: Change in 24 hrs. ABP from baseline through 6- and 12-month follow-up



Fengler et al. *JACC Cardiovasc Interv*. 2023 Feb 13;16(3):367-369.

8 years results from ACHIEVE Study – Presented at TCT 2023

Erasmus MC

Long-term Safety and Efficacy of Endovascular Ultrasound Renal Denervation in Resistant Hypertension: 8-year Results from the ACHIEVE Study

Victor J.M. Zeijen, BSc

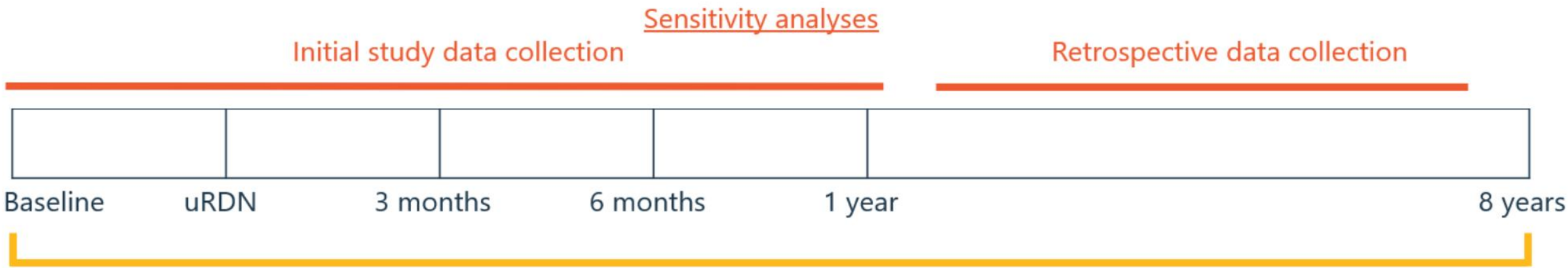
On behalf of: Sebastian Völz, MD PhD; Thomas Zeller, MD PhD; Felix Mahfoud, MD MA; Michael Kunz, MD; Karl-Heinz Kuck, MD PhD; Bert Andersson, MD PhD; Tobias Graf, MD PhD; Horst Sievert, MD PhD; Philipp Kahlert, MD PhD; Meital Horesh-Bar, BA; Mattie J. Lenzen, PhD; Isabella Kardys, MD PhD; Joost Daemen, MD PhD

Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam (NL)

Wednesday October 25th, 2023; 9:18 – 9:27 AM PDT

CRF TCT

ACHIEVE STUDY – methods & outcomes



Primary efficacy outcome

Primary efficacy outcome

- 8-year change in mean 24h ambulatory SBP

Primary safety outcome (composite)

- All-cause mortality
- Myocardial infarction
- Stroke
- Renal failure
- Renal artery stenosis ≥ 70%
- Hypertensive crisis

Zeijen, Z. ACHIEVE study update. TCT 2023.

Results – baseline characteristics

	Prospective efficacy cohort (n=27)	Safety cohort (n=96)
Age (years)	62.6 ± 9.3	64.0 ± 10.3
Female sex, n (%)	10 (37.0)	39 (40.6)
Diabetes, n (%)	9 (33.3)	38 (39.6)
Coronary artery disease, n (%)	9 (33.3)	30 (31.3)
Stroke, n (%)	1 (3.7)	10 (10.4)
eGFR (ml/min/1.73m^2)	81.0 ± 17.3	76.7 ± 18.8
24h ambulatory BP (mmHg)	151.9/84.1 ± 11.5/11.1	156.2/88.4 ± 15.4/12.7
Office BP (mmHg)	178.1/93.1 ± 18.0/13.3	176.5/95.2 ± 20.7/15.7
Antihypertensive drug DDDs	5.0 [4.3-7.0]	5.4 [4.1-7.4]
Antihypertensive drug classes	4 [3-4]	4 [3-5]

Zeijen, Z. ACHIEVE study update. TCT 2023.

Results – efficacy outcomes

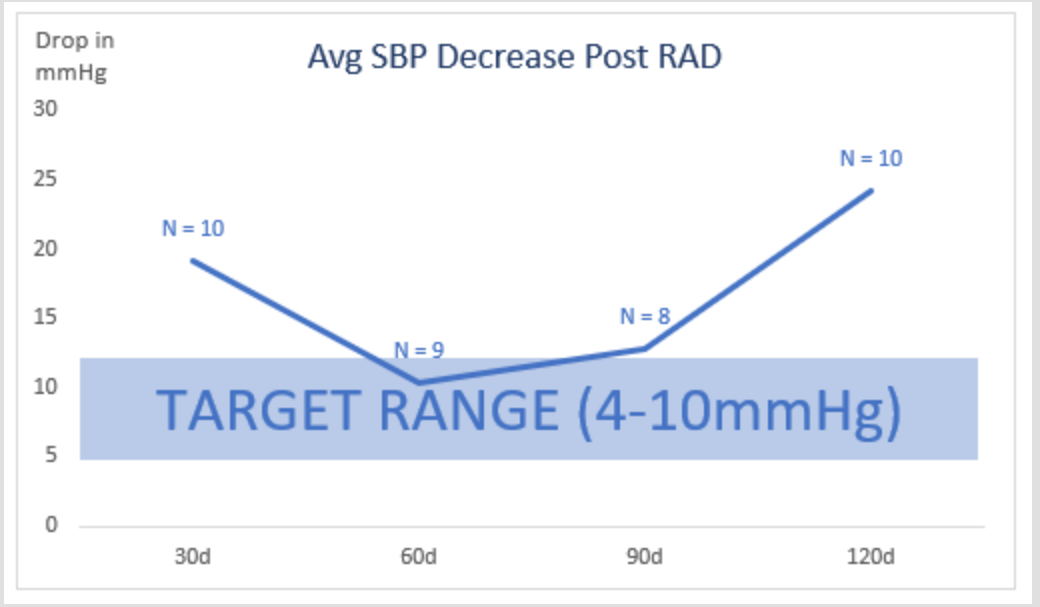
	Effect estimate	95% CI	P-value
Blood pressure			
24h ambulatory SBP (mmHg)	-19.5	-26.7, -12.4	<0.001
24h ambulatory DBP (mmHg)	-9.5	-14.5, -4.4	0.001
Office SBP (mmHg)	-22.1	-34.3, -9.8	0.001
Office DBP (mmHg)	-11.2	-16.9, -5.5	0.001

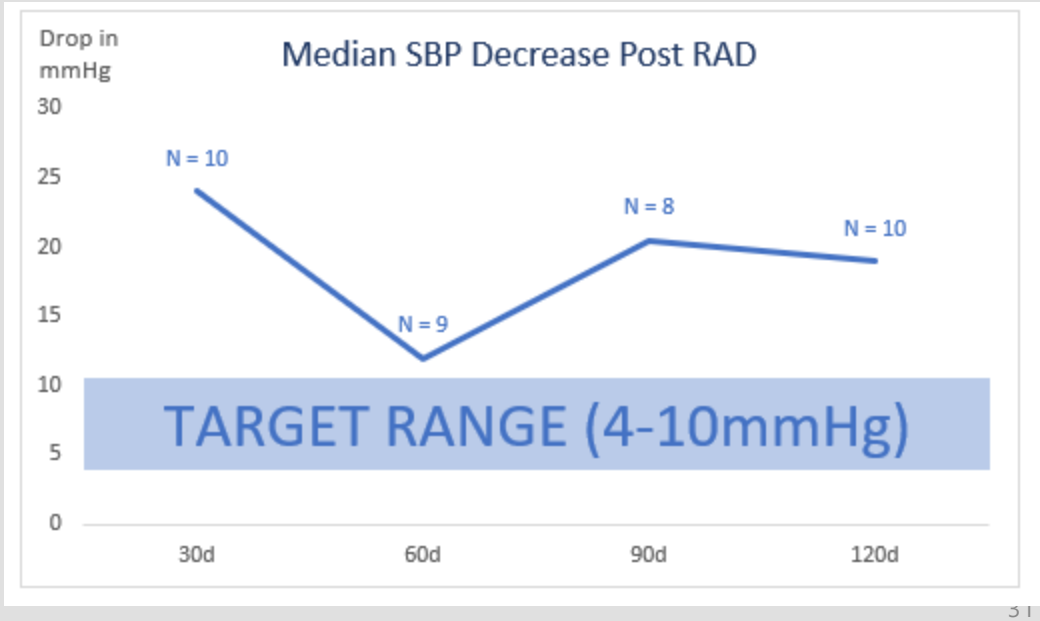
The 8-year change in the number of DDDs was –1.7 [95% CI: –2.8, –0.6] (*P* = 0.003).

Zeijen, Z. ACHIEVE study update. TCT 2023.

Updated RDN Results GVI/BGMC

Dec mmHg	Average	Median	N Patients	N Inc	N Dec <10
30d	19	24	10	1	1
60d	10	12	9	2	4
90d	13	20.5	8	2	2
120d	24	19	10	0	0
Average	17	18.875			





PATIENT 1

53/M

HTN, Obese, OSA on CPAP, HLD, Small infrarenal AAA, Non obstructive CAD

Current Meds: Amlodipine, Carvedilol, HCTZ, Losartan

Ambulatory BP and home reading >140/90

Compliant with meds and CPAP

REFERRAL AND WORK UP

Referral from Primary Cardiologist

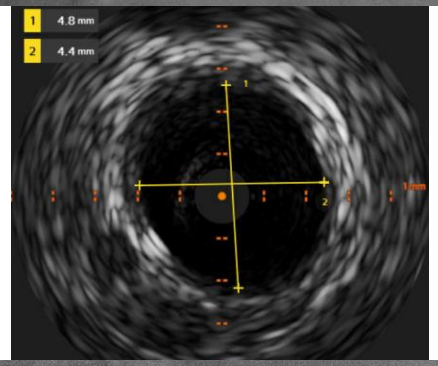
Program APP received referral, **chart review** undertaken, patient within group allowed for easy access to prior testing in office BPs and documentation of screening for secondary causes hypertension. **APP met with the patient virtually** reviewed both his in office blood pressures as well as his home blood pressures**. Realistic outcomes range of BP reduction 4mmHg-10mmHg reviewed with patient.**

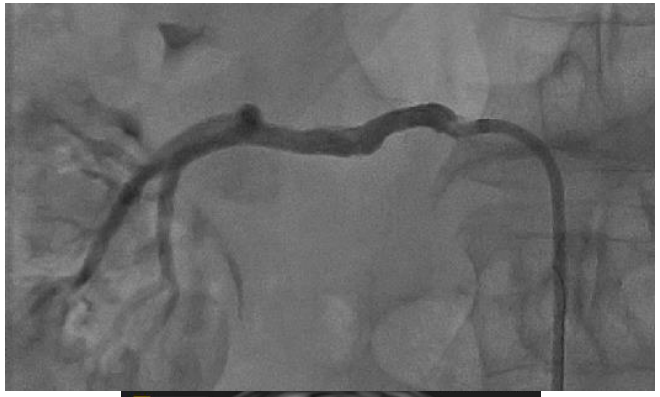
Continuation of present antihypertensives, CPAP and ongoing lifestyle modifications discussed. Providing access to printed and electronic information on RDN provided.

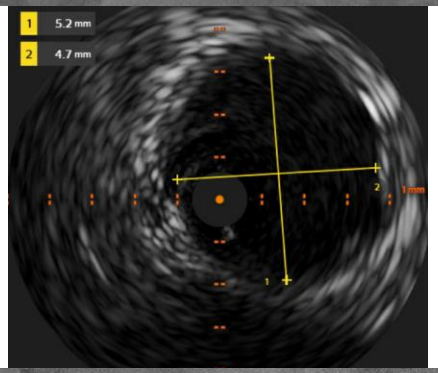
PROCEDURAL DETAILS

- Groin Access: Ultrasound and micropuncture
- 7 Fr Sheath
- 7Fr IMA Guide
- Non selective Abdominal Aortogram with 5 Fr Pigtail
- Run through wire in renal arteries
- IVUS for balloon sizing and Angio correlation
- URDN as per protocol

URDN: IVUS BASED SIZING







Results

Virtual FUP with RDN program completed on 04/04/2024.

Since procedure date documented BPs <140/80, consistently.

He is following closely with his primary cardiologist as he had some episodes of lightheadedness and dizziness with position change. Readings less than 110 systolic are becoming more consistent

Pre uRDN BP >140/90

Post URDN BP ~110/76

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AMBULATORY BLOOD PRESSURE MONITORING

WHO IS A CANDIDATE FOR RDN?

Uncontrolled HTN or poorly controlled HTN on 2 or more medications

Adequate compliance

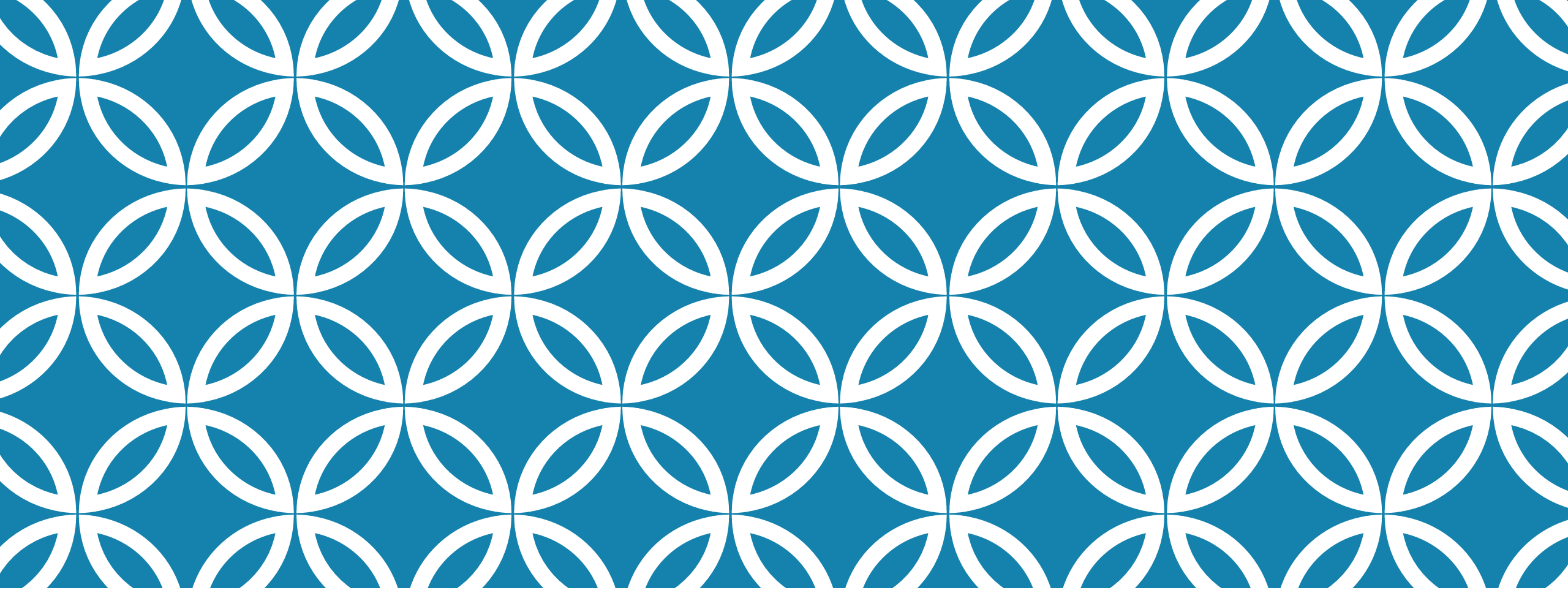
Evidence of or high risk for end-organ damage

All secondary causes of HTN have been excluded

HOW DO I REFER FOR CONSIDERATION FOR RDN?

Contact (Hypercare) Vijay Iyer MD or Adele Whited APP

716-725-4797
vsiyer@buffalo.edu



QUESTIONS