Supplementary Online Content

Kirtane AJ, Sharp ASP, Mahfoud F, et al; RADIANCE Investigators and Collaborators. Patient-level pooled analysis of ultrasound renal denervation in the sham-controlled RADIANCE II, RADIANCE-HTN SOLO, and RADIANCE-HTN TRIO trials. *JAMA Cardiol*. Published online February 28, 2023. doi:10.1001/jamacardio.2023.0338

eAppendix

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

1. RADIANCE-HTN SOLO, RADIANCE-HTN TRIO, RADIANCE II Organization

1.1. Oversight

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1.2. Funding

RADIANCE-HTN SOLO, RADIANCE-HTN TRIO, and RADIANCE II were funded by ReCor Medical, Inc., Palo Alto, CA.

1.3. Roles and Responsibilities

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Entities that contributed to the design of the study included:

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Data Collection and Analysis

Data collection and analysis was coordinated by ReCor Medical, Inc. The following entities performed independent data and statistical analysis:

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Ajay J. Kirtane, MD, SM and Michel Azizi, MD, PhD jointly wrote the manuscript.

All remaining authors reviewed the manuscript and provided edits and additions. Submission for publication was made by Dr. Kirtane / Dr. Azizi on behalf of the authors.

The sponsor reviewed the manuscript in advance of publication. However, they did not have the right of refusal for any aspects of the writing or publication.

2. Population Definitions

Intention-to-Treat (ITT)

The ITT population was defined as all randomized subjects analyzed according to their original randomization assignment.

There were 293 ultrasound renal denervation (uRDN) and 213 sham patients included in the ITT population.

Multiple imputation was employed for subjects with missing ABP data at 2 months (12 subjects randomized to uRDN and 2 subject randomized to sham). Subjects meeting escape criteria for initiation of anti-hypertensives (5 subjects randomized to uRDN and 13 subjects randomized to sham) were imputed using last observation carried forward.

Complete Ambulatory Blood Pressure (CA)

The CA population was defined as all randomized subjects analyzed according to their original randomization assignment that had ABP values at both baseline and follow-up.

There were 12 uRDN subjects and 2 sham subjects missing ABP values at 2 months. A total of 281 uRDN and 211 sham patients were included in the CA population.

Per-Protocol (PP)

The PP population was defined as all subjects who were randomized, had treatment delivered successfully and were free from major issues which may affect the assessment of the treatment:

- Baseline daytime ABP <135/85 mm Hg or failure to obtain baseline ABP recording
- Renal artery anatomical exclusion deviations
- Failure to obtain 2-month follow-up ABP recording
- Subjects restarting antihypertensive medication, for any reason, prior to the 2-month primary endpoint.

There were 43 subjects excluded from the PP analysis in the uRDN group: 4 with daytime diastolic ABP lower than entry criteria, 12 missing the 2-month ABP, 2 had renal artery anatomy exclusions, 5 added medications prior to 2-months who met the High BP Action criteria, 13 added medications prior to 2-months without meeting the High BP Action criteria, 7 with unsuccessful treatment.

There were 35 subjects excluded from the PP analysis in the Sham group: 2 with daytime diastolic ABP lower than entry criteria, 2 missing the 2-month ABP, 13 added medications prior to 2 months who met the High BP Action criteria, 18 added medications prior to 2 months without meeting the High BP Action criteria.

A total of 250 uRDN and 178 sham patients were included in the PP population.

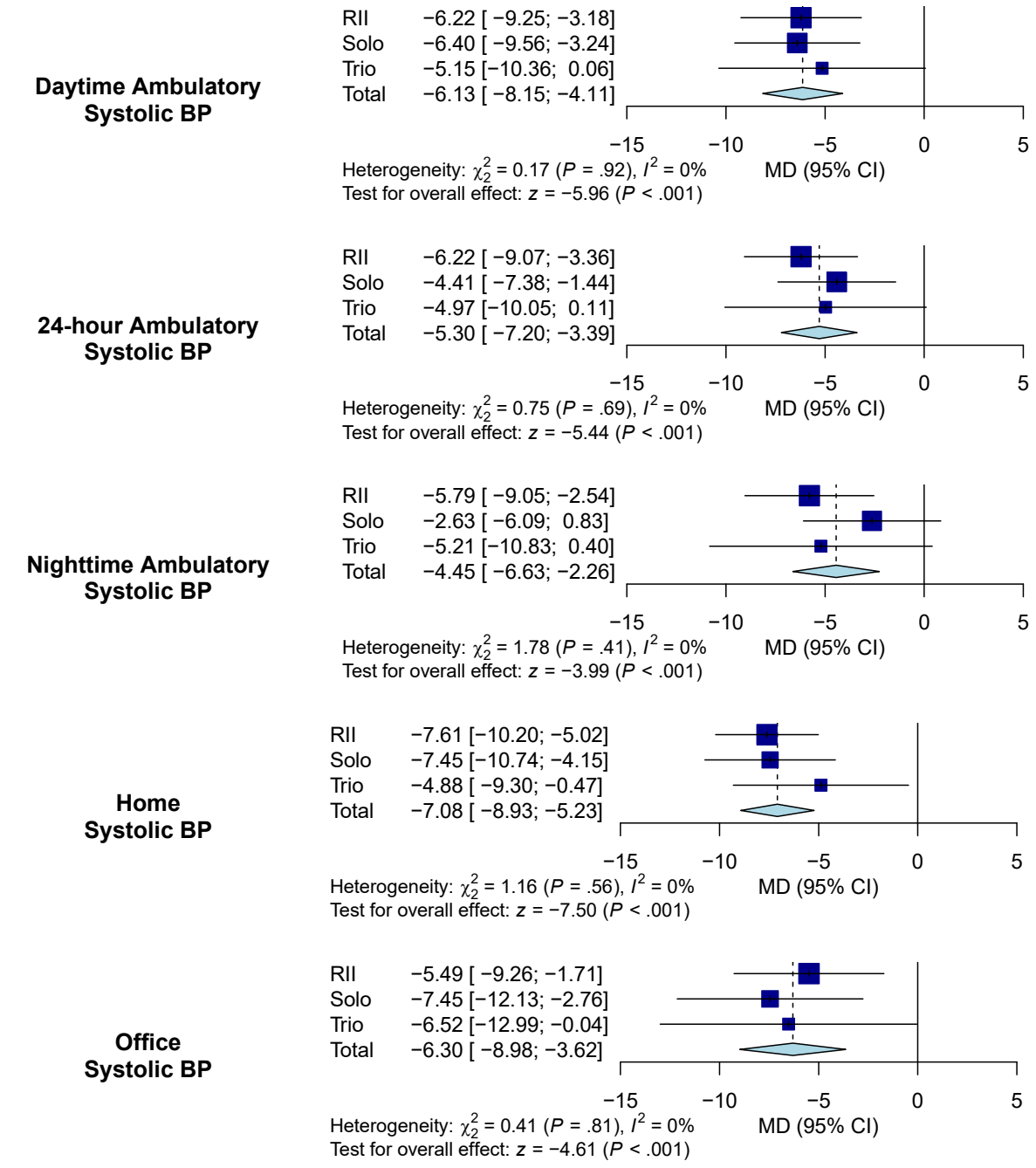
3. Multivariable Analysis

A prespecified multiple linear regression analysis was done to assess change in daytime systolic blood pressure with the following variables independent variables: group, study, sex, race (black vs. non-black), age, baseline daytime ambulatory systolic blood pressure, baseline 24-hour ambulatory heart rate, eGFR, geography, and abdominal obesity.

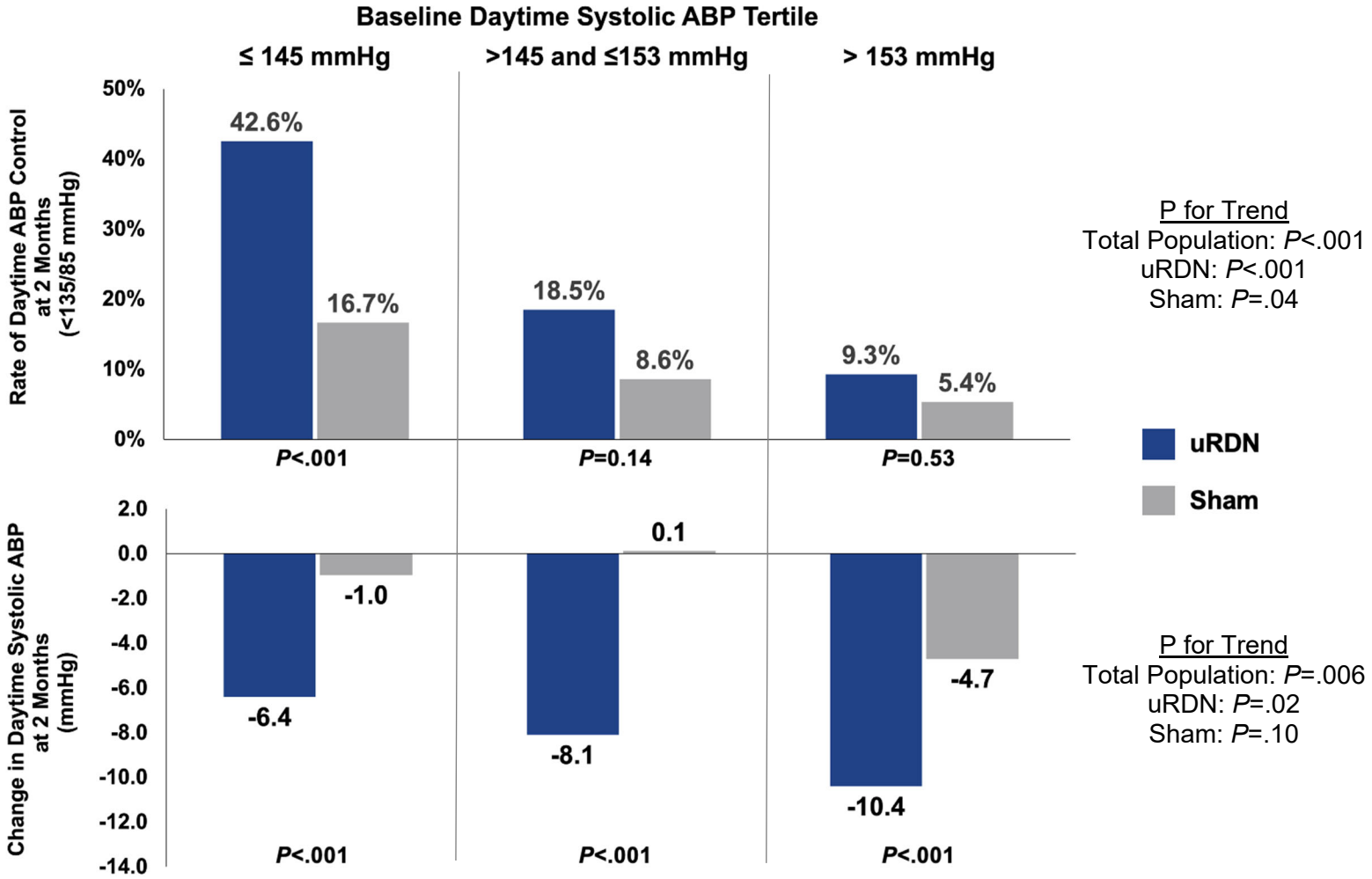
An exploratory multiple linear regression analysis was done to assess change in daytime systolic blood pressure in the uRDN group only with the same independent variables excluding group.

4. Supplemental Figures and Tables

eFigure 1. Two-Stage Meta-analysis Forest Plots Depicting 2-Month Mean Differences (MDs) and 95% CIs Results by Study and in Aggregate for Systolic BPs for Daytime Ambulatory, 24-Hour Ambulatory, Nighttime Ambulatory, Home, and Office Readings



eFigure 2. Daytime Ambulatory BP Control Rates and Daytime Systolic Ambulatory BP Change at 2 Months Stratified by Tertile of Starting Daytime Ambulatory Systolic BP Excluding Patients That Had Additional Antihypertension Medications Prior to 2 Months (uRDN n=261, Sham n=180)



eTable 1. Inclusion/Exclusion Criteria in Each Trial

Inclusion		
RADIANCE-HTN SOLO	**RADIANCE-HTN TRIO**	**RADIANCE II**

• Appropriately signed and dated informed consent
• Age ≥18 and ≤75 years at time of consent
• Documented history of essential hypertension
• Either,
  ○ Average seated office BP <180/110 mm Hg at screening visit (V0) while on a stable regimen of 1 or 2 antihypertensive medications for at least 4 weeks prior to consent or,
  ○ Average seated office BP ≥ 140/90 mm Hg <180/110 mm Hg despite lifestyle measures on no antihypertensive medications
• Documented daytime ABP ≥135/85 mm Hg and <170/105 mm Hg after 4-week washout/run-in period
• Suitable renal anatomy compatible with the renal denervation procedure and documented by renal CTA or MRA of good quality performed within one year prior to consent (a CTA or MRA will be obtained in patients without a recent (≤1 year) renal imaging)
• Able and willing to comply with all study procedures
	• Appropriately signed and dated informed consent
	• Age ≥18 and ≤75 years at time of consent
	• Documented history of hypertension
	• Average seated office BP ≥140/90 mm Hg at screening visit (V0) while on a stable regimen of at least 3 antihypertensive medications of different classes including a diuretic for at least 4 weeks prior to consent
	• Documented daytime ABP ≥ 135/85 mm Hg after 4-week stabilization period
	• Suitable renal anatomy compatible with the renal denervation procedure and documented by renal CTA or MRA of good quality performed within one year prior to consent (a CTA or MRA will be obtained in patients without a recent (≤1 year) renal imaging)
	• Able and willing to comply with all study procedures
		• Appropriately signed and dated informed consent
		• Age ≥18 and ≤75 years at time of consent
		• Documented history of hypertension
		• Previously or currently prescribed antihypertensive therapy
		• Average seated office BP ≥ 140/90 mm Hg <180/120 mm Hg at Screening Visit (V0) while stable for at least 4 weeks on 0-2 anti-hypertensive medications of different classes
		• Able and willing to comply with all study procedures
		• Documented daytime ABP ≥ 135/85 mm Hg and < 170/105 mm Hg at Baseline Visit (V1) after 4-week washout/run-in period
		• Suitable renal anatomy compatible with the renal denervation procedure and documented by renal CTA or MRA of good quality performed within one year prior to consent (a CTA or MRA will be obtained in patients without a recent (≤1 year) cross-sectional renal imaging) confirmed by renal angiogram in subjects that continue to procedure (see Exclusion Criteria)
		• Sinus rhythm at the time of procedure

Exclusion		
RADIANCE-HTN SOLO	**RADIANCE-HTN TRIO**	**RADIANCE II**
• Renal artery anatomy on either side, ineligible for treatment including: ○ Main renal artery diameter < 4 mm and > 8 mm ○ Main renal artery length < 25 mm ○ A single functioning kidney ○ Presence of abnormal kidney (or secreting adrenal) tumors ○ Renal artery with aneurysm ○ Pre-existing renal stent or history of renal artery angioplasty ○ Prior renal denervation procedure ○ Fibromuscular disease of the renal arteries ○ Presence of renal artery stenosis of any origin ≥ 30% ○ Accessory arteries with diameter ≥2mm <4 mm and > 8 mm • Iliac/femoral artery stenosis precluding insertion of the Paradise Catheter • Evidence of active infection within 7 days of procedure • Type I diabetes mellitus or uncontrolled Type II diabetes (defined as a plasma Hb1Ac ≥ 9.0%) • Documented history of chronic active active inflammatory bowel disorders such as Crohn's disease or ulcerative colitis • eGFR of <40 mL/min/1.73 m2 (by Modification of Diet in Renal Disease formula) • Brachial circumference ≥ 42 cm • Any history of cerebrovascular event (e.g. stroke, transient ischemic event, cerebrovascular accident) • Any history of severe cardiovascular event (myocardial infarction, CABG, acute heart failure requiring hospitalization (NYHA III-IV)	• Renal artery anatomy on either side, ineligible for treatment including: ○ Main renal artery diameter < 3 mm or > 8 mm ○ Main renal treatable artery length < 20 mm (may include proximal branching) ○ A single functioning kidney ○ Presence of abnormal kidney tumors ○ Renal artery with aneurysm ○ Pre-existing renal stent or history of renal artery angioplasty ○ Pre-existing aortic stent or history of aortic aneurysm ○ Prior renal denervation procedure ○ Fibromuscular disease of the renal arteries ○ Presence of renal artery stenosis of any origin ≥ 30% ○ Accessory arteries with diameter ≥2mm <3 mm or > 8 mm • Iliac/femoral artery stenosis precluding insertion of the Paradise Catheter • Evidence of active infection within 7 days of procedure • Secondary hypertension not including sleep apnea (documented through clinical work up within the 12 months prior to consent- see Section 7.2.4.1) • Type I diabetes mellitus or uncontrolled Type II diabetes (defined as a plasma Hb1Ac ≥ 9.0%) • Documented history of chronic active inflammatory bowel disorders such as Crohn's disease or ulcerative colitis • eGFR of <40 mL/min/1.73 m^2 (by Modification of Diet in Renal Disease formula) • Brachial circumference ≥ 42 cm	• Renal artery anatomy on either side, ineligible for treatment including: ○ Main renal artery diameter < 3 mm or > 8 mm ○ Main renal treatable artery length < 20 mm (may include proximal branching) ○ A single functioning kidney ○ Presence of abnormal kidney tumors ○ Renal artery with aneurysm ○ Pre-existing renal stent or history of renal artery angioplasty ○ Pre-existing aortic stent or history of aortic aneurysm ○ Prior renal denervation procedure ○ Fibromuscular disease of the renal arteries ○ Presence of renal artery stenosis of any origin ≥ 30% ○ Accessory arteries with diameter ≥2mm <3 mm or > 8 mm • Iliac/femoral artery stenosis precluding insertion of the Paradise Catheter • Known, uncorrected causes of secondary hypertension other than sleep apnea • Evidence of active infection within 7 days of procedure • Type I diabetes mellitus or uncontrolled Type II diabetes (defined as a plasma HbA1c ≥ 9.0%) • Documented history of chronic active inflammatory bowel disorders such as Crohn's disease or ulcerative colitis • eGFR of <40 mL/min/1.73 m2 (by Modification of Diet in Renal Disease formula) • Brachial circumference ≥ 42 cm • Any history of cerebrovascular event (e.g. stroke, transient ischemic event, cerebrovascular accident)

• Documented confirmed episode(s) of stable or unstable angina • Documented repeat (>1) hospitalization for hypertensive crisis within the prior 12 months • Prescribed to any standard antihypertensive of cardiovascular medication (e.g. beta blockers) for other chronic conditions (e.g. ischemic heart disease) such that discontinuation might pose serious risk to health • Documented history of persistent or permanent atrial tachyarrhythmia • Active implantable medical device (e.g. ICD or CRT-D; neuromodulator/spinal stimulator; baroreflex stimulator) • Chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea. • Primary pulmonary hypertension • Documented contraindication or allergy to contrast medium not amenable to treatment • Limited life expectancy of < 1 year at the discretion of the Investigator • Any known, unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or for any reason in the opinion of the investigator, would be unlikely or unable to comply with study protocol requirements or whose participation may result in data analysis confounders (e.g. night shift workers) • Pregnant, nursing or planning to become pregnant (documented negative pregnancy test required documented within a maximum of 7 days prior to procedure for all women of child bearing potential.	• Any history of cerebrovascular event (e.g. stroke, transient ischemic event, cerebrovascular accident) within 3 months prior to consent • Any history of severe cardiovascular event (myocardial infarction, CABG, acute heart failure requiring hospitalization (NYHA III-IV) within 3 months prior to consent • Documented confirmed episode(s) of unstable angina within 3 months prior to consent • Documented intolerance or contraindication for any of the antihypertensive drugs prescribed as a requirement of the study protocol • Documented repeat (>1) hospitalization for hypertensive crisis within the prior 3 months • Prescribed to any standard anti-hypertensive CV medication (other than beta blockers) for other chronic conditions (e.g. ischemic heart disease) such that discontinuation might pose serious risk to health • Documented history of persistent or permanent atrial tachyarrhythmia • Active implantable medical device (e.g. ICD or CRT-D; neuromodulator/spinal stimulator; baroreflex stimulator) • Chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea. • Primary pulmonary hypertension • Documented contraindication or allergy to contrast medium not amenable to treatment • Limited life expectancy of < 1 year at the discretion of the Investigator • Night shift workers	• Any history of severe cardiovascular event (e.g. myocardial infarction, CABG, acute heart failure requiring hospitalization (NYHA III-IV) • Documented confirmed episode(s) of stable or unstable angina within 12 months prior to consent • Documented repeat (>1) hospitalization for hypertensive crisis within the prior 12 months and/or any hospitalization for hypertensive crisis within three (3) months prior to consent • Prescribed to any standard antihypertensive of cardiovascular medication (e.g. beta blockers) for other chronic conditions (e.g. ischemic heart disease) such that discontinuation might pose serious risk to health in the opinion of the investigator • Documented history of persistent or permanent atrial tachyarrhythmia • Active implantable medical device (e.g. ICD or CRT-D; neuromodulator/spinal stimulator; baroreflex stimulator) • Chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea. • Primary pulmonary hypertension • Documented contraindication or allergy to contrast medium not amenable to treatment • Limited life expectancy of < 1 year at the discretion of the Investigator • Night shift workers • Any known, unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or for any reason in the opinion of the investigator, would be unlikely or unable to comply with study

Documentation of effective contraception is also required for women of child bearing potential) • Concurrent enrollment in any other investigational drug or device trial (participation in non-interventional Registries is acceptable)	• Any known, unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or for any reason in the opinion of the investigator, would be unlikely or unable to comply with study protocol requirements or whose participation may result in data analysis confounders • Pregnant, nursing or planning to become pregnant (documented negative pregnancy test required documented within a maximum of 7 days prior to procedure for all women of child bearing potential. Documentation of effective contraception is also required for women of child bearing potential) • Concurrent enrollment in any other investigational drug or device trial (participation in non-interventional Registries is acceptable)	protocol requirements or whose participation may result in data analysis confounders • Pregnant, nursing or planning to become pregnant within 12 months post procedure. Negative pregnancy test required documented within a maximum of 7 days prior to procedure for all women of childbearing potential. Documentation of effective contraception is also required for women of childbearing potential • Concurrent enrollment in any other investigational drug or device trial (participation in non-interventional Registries is acceptable)

eTable 2. Blood Pressure Measurement Methods, Safety Escape Criteria, and Procedural Methods Used in All Studies

Blood Pressure Measurement Methods:
Office: Attended seated office blood pressure and home blood pressure were measured s according to US and European guidelines,[1,2] as previously described.[3,4] After a rest period in the seated position, three office blood pressure measurements were taken one to two minutes apart with an adapted cuff to the arm circumference, with the last two readings averaged and used as the office blood pressure reading.
Home: Subjects were requested to measure their blood pressure at home after a 5-min rest in the sitting position in the morning and the evening (two blood pressure measurements one to two minutes apart) during seven consecutive days before every outpatient visit.
Ambulatory: Serial ambulatory blood pressure measurements were performed to assess initial eligibility and at 2-month post-randomization, as previously described.[3,4] Blood pressure was recorded every 20 minutes during daytime (07:00–22:00 hours) and every 30 minutes during nighttime (22:00–07:00 hours). The ambulatory blood pressure measurement was repeated if the number of daytime blood pressure measurements was less than 21. All ambulatory blood pressure recordings were sent to a core laboratory (dabl Ltd., Dublin, Ireland), with treatment assignment masked.

Safety Escape Criteria:
In RADIANCE-HTN SOLO and RADIANCE-HTN TRIO, escape criteria was met if either Home BP exceeded 170/105 mmHg or Office BP exceeded 180/110 mmHg in conjunction with an adverse event. In RADIANCE II, escape criteria was met if both Home BP exceeded 170/105 mmHg and Office BP exceeded 180/110 mmHg in conjunction with an adverse event. However, if either home or office were not available, the available measurement could be used on its own to make a determination.

Ultrasound Renal Denervation Procedure Methods:
Renal nerve ablation was performed with the Paradise™ endovascular ultrasound renal denervation system (ReCor Medical, Inc., Palo Alto, CA, USA). According to individual treatment plans developed based on the pre-randomization CT- or MR-angiography and following selective renal angiography, a minimum of two non-overlapping sonications were delivered in the main right and left renal arteries and at least one sonication was delivered in accessory arteries. Treatable artery sizes in TRIO and RADIANCE II were ≥3 mm and ≤8 mm. Treatable artery sizes in SOLO were ≥4 mm and ≤8 mm.

eTable 3. Pooled Procedural Data Across Studies

Characteristic	uRDN (n = 293)	Sham (n = 213)
Procedure time (sheath removal – sheath insertion) (min)	78.1 ± 25.8	41.8 ± 15.7
Device time (catheter out - catheter in) (min)[a]	35.3 ± 20.1	NA
Total Emission Time (seconds)[b]	38.9 ± 7.8	NA
Sedation		
Conscious Sedation (e.g. midazolam, fentanyl, and/or morphine)	227/293 (77.4%)	161/212 (75.9%)
Monitored Anesthesia Care (e.g. propofol)	21/293 (7.2%)	13/212 (6.1%)
General Anesthesia (e.g. inhaled anesthetics, muscle relaxants or neuromuscular blocking agents, intubation, and/or ketamine)	45/293 (15.4%)	38/212 (17.9%)
Contrast volume[c] (cm^3)	146.7 ± 71.9	74.2 ± 37.9
Fluoroscopy time[d] (min)	16.2 ± 9.2	4.4 ± 7.9
Total Number of Sonications[b]	5.6 ± 1.1	NA
Left[b]	2.7 ± 0.7	NA
Right[b]	2.9 ± 0.7	NA
Subjects with Treated Renal Accessory or Proximal Side Branch	56/293 (19.1%)	NA
Treatment successfully delivered (minimum 2 emissions bilaterally)	286/293 (97.6%)	NA

Data displayed as either n/N (%) or Mean ± SD.
[a]There were 5 patients in the uRDN group missing device time.
[b]There were two patients in the uRDN group receiving no treatment that were not included.
[c]There were two patients in the uRDN group and two in the sham group missing contrast volume.
[d]There were four patients in the uRDN group and four patients in the sham group missing fluoroscopy time.

eTable 4. Change in Ambulatory, Office, and Home Blood Pressure at 2 Months in the Ultrasound Renal Denervation Group (uRDN) and in the Sham Group in the Intention to Treat Population (n = 293 uRDN, n = 213 sham)

	uRDN			Sham			Study and Baseline Adjusted with Multiple Imputation	
	Randomization	2 months	Difference	Randomization	2 months	Difference	Group Difference (95% CI)[a]	*P* value[c]
SBP Parameters (mm Hg)								
Daytime Ambulatory[e]	150.3 ± 9.3	141.8 ± 13.8	-8.5 ± 11.9	150.8 ± 10.5	147.9 ± 14.6	-2.9 ± 12.1	-5.9 (-8.1, -3.8) -6.2 (-8.0, -4.5)[b]	<.001 <.001[d]
24 Hour Ambulatory[f]	143.3 ± 10.1	135.3 ± 13.5	-7.9 ± 11.1	144.4 ± 11.2	141.3 ± 14.0	-3.1 ± 12.2	-5.3 (-7.4, -3.3) -5.4 (-7.1, -3.6)[b]	<.001 <.001[d]
Nighttime Ambulatory[f]	132.1 ± 14.0	125.4 ± 15.3	-6.7 ± 13.4	134.2 ± 15.4	131.2 ± 15.8	-3.0 ± 14.5	-4.7 (-7.0, -2.4) -4.3 (-6.5, -2.0)[b]	<.001 <.001[d]
Home[g]	151.0 ± 11.3	142.7 ± 13.8	-8.4 ± 11.0	150.1 ± 13.5	148.6 ± 16.0	-1.4 ± 9.4	-6.8 (-8.7, -4.9) -7.1 (-9.0, -5.5)[b]	<.001 <.001[d]
Office[h]	155.9 ± 13.9	145.5 ± 17.1	-10.4 ± 15.0	155.0 ± 15.2	151.6 ± 18.6	-3.4 ± 16.7	-6.4 (-9.1, -3.6) -7.5 (-10.0, -5.0)[b]	<.001 <.001[d]
DBP Parameters (mm Hg)								
Daytime Ambulatory[e]	93.6 ± 5.8	88.2 ± 8.6	-5.5 ± 7.1	93.7 ± 6.9	91.1 ± 9.1	-2.6 ± 7.8	-3.0 (-4.3, -1.7) -3.1 (-4.3, -2.0)[b]	<.001 <.001[d]
24 Hour Ambulatory[f]	88.2 ± 6.3	83.1 ± 8.4	-5.2 ± 6.9	88.6 ± 7.1	86.1 ± 8.7	-2.6 ± 7.8	-2.8 (-4.1, -1.6) -3.0 (-4.0, -1.9)[b]	<.001 <.001[d]
Nighttime Ambulatory[f]	79.7 ± 9.0	75.2 ± 10.1	-4.5 ± 8.8	80.5 ± 9.5	78.4 ± 10.0	-2.0 ± 9.3	-2.9 (-4.4, -1.4) -3.0 (-4.5, -1.5)[b]	<.001 <.001[d]
Home[g]	96.7 ± 7.8	92.1 ± 9.6	-4.6 ± 6.7	95.7 ± 8.8	95.0 ± 10.0	-0.6 ± 5.7	-3.8 (-5.0, -2.6) -4.0 (-5.1, -3.0)[b]	<.001 <.001[d]
Office[h]	101.2 ± 8.8	95.7 ± 11.2	-5.5 ± 10.3	100.0 ± 9.4	98.6 ± 11.7	-1.4 ± 10.4	-3.5 (-5.3, -1.7) -4.0 (-6.0, -2.5)[b]	<.001 <.001[d]

Data displayed as mean ± SD unless otherwise specified. DBP=diastolic blood pressure, SBP=systolic blood pressure

[a]Estimate of treatment difference, from study and baseline adjusted ANCOVA with multiple imputation.

[b]In the event that change from baseline in either cohort is non-normal, the Hodges-Lehmann estimator of location shift and associated 95% confidence interval (observed data) is also provided.

[c]*P* value from study and baseline adjusted ANCOVA with multiple imputation.

[d]In the event that change from baseline in either cohort is non-normal, the P value from a study and baseline adjusted ANCOVA on the ranks (observed data) is also provided.

[e]There were 281 patients in RDN group and 211 patients in the sham group with daytime ambulatory BP measurements.

[f]There were 280 patients in RDN group and 209 patients in the sham group with 24hr ambulatory and nighttime ambulatory BP measurements.

[g]There were 271 patients in RDN group and 205 patients in the sham group with home BP measurements.

[h]There were 275 patients in RDN group and 209 patients in the sham group with office BP measurements.

eTable 5. Change in Ambulatory, Office, and Home Blood Pressure at 2 Months in the Ultrasound Renal Denervation Group (uRDN) and in the Sham Group in the Per-Protocol Population (n = 250 uRDN, n = 178 Sham)

	uRDN			Sham			Study and Baseline Adjusted with Multiple Imputation	
	Randomization	2 months	Difference	Randomization	2 months	Difference	Group Difference (95% CI)[a]	*P* value[c]
SBP Parameters (mm Hg)								
Daytime Ambulatory[e]	150.0 ± 9.2	141.7± 14.0	-8.3 ± 12.0	149.9 ± 10.2	147.9 ± 14.3	-2.0 ± 11.7	-6.5 (-8.8, -4.2) -7.0 (-9.0, -5.1)[b]	<.001 <.001[d]
24 Hour Ambulatory[f]	142.8 ± 9.9	135.1 ± 13.6	-7.7 ± 11.1	143.3 ± 11.0	141.1 ± 13.9	-2.2 ± 11.8	-5.8 (-8.8, -3.7) -6.1 (-8.0, -4.2)[b]	<.001 <.001[d]
Nighttime Ambulatory[f]	131.4 ± 13.7	125.1 ± 15.4	-6.3 ± 13.4	132.9 ± 15.2	130.9 ± 15.8	-2.0 ± 14.5	-5.1 (-7.6, -2.6) -5.0 (-7.3, -2.6)[b]	<.001 <.001[d]
Home[g]	150.5 ± 10.6	142.3 ± 13.8	-8.2 ± 10.8	148.9 ± 13.0	147.7 ± 14.6	-1.2 ± 8.6	-6.7 (-8.7, -4.7) -7.2 (-9.0, -5.4)[b]	<.001 <.001[d]
Office[h]	155.5 ± 14.1	145.4 ± 17.2	-10.1 ± 14.8	154.0 ± 15.3	151.1 ± 17.9	-2.9 ± 16.4	-6.4 (-9.3, -3.5) -8.0 (-11.0, -5.5)[b]	<.001 <.001[d]
DBP Parameters (mm Hg)								
Daytime Ambulatory[e]	93.8 ± 5.6	88.4 ± 8.7	-5.4 ± 7.1	93.5 ± 6.8	91.4 ± 9.0	-2.1 ± 7.8	-3.4 (-4.8, -2.0) -3.7 (-4.9, -2.4)[b]	<.001 <.001[d]
24 Hour Ambulatory[f]	88.3 ± 6.1	83.2 ± 8.5	-5.2 ± 6.9	88.3 ± 7.0	86.2 ± 8.6	-2.1 ± 7.8	-3.2 (-4.6, -1.8) -3.3 (-4.5, -2.1)[b]	<.001 <.001[d]
Nighttime Ambulatory[f]	79.7 ± 8.8	75.1 ± 10.2	-4.5 ± 9.0	80.1 ± 9.3	78.5 ± 9.9	-1.6 ± 9.4	-3.3 (-4.9, -1.6) -3.4 (-5.0, -2.0)[b]	<.001 <.001[d]
Home[g]	96.8 ± 7.7	92.3 ± 9.7	-4.5 ± 6.6	95.3 ± 8.7	94.6 ± 9.6	-0.7 ± 5.3	-3.6 (-4.9, -2.4) -4.0 (-5.1, -3.0)[b]	<.001 <.001[d]
Office[h]	101.3 ± 8.6	95.8 ± 11.0	-5.5 ± 10.0	99.5 ± 9.6	98.5 ± 11.5	-1.0 ± 10.2	-3.6 (-5.5, -1.7) -5.0 (-6.5, -3.0)[b]	<.001 <.001[d]

Data displayed as mean ± SD unless otherwise specified. DBP=diastolic blood pressure, SBP=systolic blood pressure

[a]Estimate of treatment difference, from study and baseline adjusted ANCOVA.

[b]In the event that change from baseline in either cohort is non-normal, the Hodges-Lehmann estimator of location shift and associated 95% confidence interval (observed data) is also provided

[c]*P* value from study and baseline adjusted ANCOVA.

[d]In the event that change from baseline in either cohort is non-normal, the P value from a study and baseline adjusted ANCOVA on the ranks (observed data) is also provided.

[e]There were 250 patients in RDN group and 178 patients in the sham group with daytime ambulatory BP measurements.

[f]There were 249 patients in RDN group and 177 patients in the sham group with 24hr ambulatory and nighttime ambulatory BP measurements.

[g]There were 239 patients in RDN group and 170 patients in the sham group with home blood pressure measurements.

[h]There were 239 patients in RDN group and 175 patients in the sham group with office blood pressure measurements.

eTable 6. Change in Ambulatory, Office, and Home Blood Pressure at 2 Months in the Ultrasound Renal Denervation Group (uRDN) and in the Sham Group in the Complete Ambulatory Blood Pressure Population (n = 281 uRDN, n = 211 sham)

	uRDN			Sham			Study and Baseline Adjusted with Multiple Imputation	
	Randomization	2 months	Difference	Randomization	2 months	Difference	Group Difference (95% CI)[a]	*P* value[c]
SBP Parameters (mm Hg)								
Daytime Ambulatory[e]	150.3 ± 9.3	141.8 ± 13.8	-8.5 ± 11.9	150.8 ± 10.5	147.9 ± 14.6	-2.9 ± 12.1	-6.0 (-8.1, -3.8) -6.2 (-8.0, -4.5)[b]	<.001 <.001[d]
24 Hour Ambulatory[f]	143.3 ± 10.1	135.3 ± 13.5	-7.9 ± 11.1	144.4 ± 11.2	141.3 ± 14.0	-3.1 ± 12.2	-5.3 (-7.4, -3.3) -5.4 (-7.1, -3.6)[b]	<.001 <.001[d]
Nighttime Ambulatory[f]	132.1 ± 14.0	125.4 ± 15.3	-6.7 ± 13.4	134.2 ± 15.4	131.2 ± 15.8	-3.0 ± 14.5	-4.7 (-7.0, -2.4) -4.3 (-6.5, -2.0)[b]	<.001 <.001[d]
Home[g]	151.1 ± 11.3	142.7 ± 13.8	-8.4 ± 10.9	150.0 ± 13.5	148.7 ± 16.0	-1.3 ± 9.2	-7.0 (-8.9, -5.1) -7.3 (-9.0, -5.6)[b]	<.001 <.001[d]
Office[h]	155.9 ± 14.0	145.5 ± 17.2	-10.4 ± 15.1	155.0 ± 15.2	151.7 ± 18.6	-3.4 ± 16.7	-6.5 (-9.3, -3.7) -8.0 (-10.5, -5.0)[b]	<.001 <.001[d]
DBP Parameters (mm Hg)								
Daytime Ambulatory[e]	93.6 ± 5.8	88.2 ± 8.6	-5.5 ± 7.1	93.7 ± 6.9	91.1 ± 9.1	-2.6 ± 7.8	-3.0 (-4.4, -1.7) -3.1 (-4.3, -2.0)[b]	<.001 <.001[d]
24 Hour Ambulatory[f]	88.2 ± 6.3	83.1 ± 8.4	-5.2 ± 6.9	88.6 ± 7.1	86.1 ± 8.7	-2.6 ± 7.8	-2.8 (-4.1, -1.6) -3.0 (-4.0, -1.9)[b]	<.001 <.001[d]
Nighttime Ambulatory[f]	79.7 ± 9.0	75.2 ± 10.1	-4.5 ± 8.8	80.5 ± 9.5	78.4 ± 10.0	-2.0 ± 9.3	-2.9 (-4.4, -1.4) -3.0 (-4.5, -1.5)[b]	<.001 <.001[d]
Home[g]	96.8 ± 7.8	92.2 ± 9.7	-4.6 ± 6.7	95.7 ± 8.8	95.1 ± 10.1	-0.6 ± 5.7	-3.9 (-5.1, -2.7) -4.1 (-5.2, -3.0)[b]	<.001 <.001[d]
Office[h]	101.3 ± 8.8	95.7 ± 11.3	-5.6 ± 10.3	100.0 ± 9.4	98.7 ± 11.7	-1.3 ± 10.4	-3.6 (-5.4, -1.8) -4.5 (-6.0, -3.0)[b]	<.001 <.001[d]

Data displayed as mean ± SD unless otherwise specified. DBP=diastolic blood pressure, SBP=systolic blood pressure

[a]Estimate of treatment difference, from study and baseline adjusted ANCOVA.

[b]In the event that change from baseline in either cohort is non-normal, the Hodges-Lehmann estimator of location shift and associated 95% confidence interval (observed data) is also provided

[c]P value from study and baseline adjusted ANCOVA.

[d]In the event that change from baseline in either cohort is non-normal, the P value from a study and baseline adjusted ANCOVA on the ranks (observed data) is also provided.

[e] There were 281 patients in RDN group and 211 patients in the sham group with daytime ambulatory BP measurements.

[f]There were 280 patients in RDN group and 209 patients in the sham group with 24hr ambulatory and nighttime ambulatory BP measurements.

[g] There were 268 patients in RDN group and 203 patients in the sham group with home BP measurements.
[h] There were 270 patients in RDN group and 208 patients in the sham group with office BP measurements.

eTable 7. Proportion of Patients with Drops in Daytime Ambulatory, 24-Hour Ambulatory, Nighttime Ambulatory, and Home Systolic BP of ≥5, ≥10, ≥15 and ≥20 mm Hg in the Intention-to-Treat Population

Blood Pressure Drop	uRDN (n = 293)	Sham (n=213)	*P* value[b]
Daytime Ambulatory Systolic BP[a]			
≥5 mm Hg	184/281 (65.5%)	77/211 (36.5%)	<.001
≥10 mm Hg	130/281 (46.3%)	42/211 (19.9%)	<.001
≥15 mm Hg	77/281 (27.4%)	25/211 (11.8%)	<.001
≥20 mm Hg	38/281 (13.5%)	17/211 (8.1%)	.04
24-hr Ambulatory Systolic BP[a]			
≥5 mm Hg	172/280 (61.4%)	80/209 (38.3%)	<.001
≥10 mm Hg	123/280 (43.9%)	49/209 (23.4%)	<.001
≥15 mm Hg	71/280 (25.4%)	25/209 (12.0%)	<.001
≥20 mm Hg	31/280 (11.1%)	13/209 (6.2%)	.04
Nighttime Ambulatory Systolic BP[a]			
≥5 mm Hg	160/280 (57.1%)	84/209 (40.2%)	<.001
≥10 mm Hg	113/280 (40.4%)	56/209 (26.8%)	.001
≥15 mm Hg	73/280 (26.1%)	36/209 (17.2%)	.01
≥20 mm Hg	42/280 (15.0%)	22/209 (10.5%)	.12
Home Systolic BP[a]			
≥5 mm Hg	175/271 (64.6%)	65/205 (31.7%)	<.001
≥10 mm Hg	115/271 (42.4%)	34/205 (16.6%)	<.001
≥15 mm Hg	67/271 (24.7%)	16/205 (7.8%)	<.001
≥20 mm Hg	37/271 (13.7%)	10/205 (4.9%)	.001

Data displayed as n/N (%).
[a]Data are cumulative (e.g., subjects included in ≥10 mm Hg row are also included in ≥5 mm Hg row).
[b]*P* value from Cochran-Mantel-Haenszel test, stratified by study.

eTable 8. Hypertension Control Rates at 2 Months

ITT Population			
Definition	**uRDN (n=293)**	**Sham (n=213)**	**P value[a]**
Daytime ambulatory BP <135/85 mmHg	68/281 (24.2%)	26/211 (12.3%)	<.001
24-hour ambulatory BP <130/80 mmHg	74/280 (26.4%)	25/210 (11.9%)	<.001
Home BP <135/85 mmHg	43/274 (15.7%)	13/205 (6.3%)	<.001
Office BP <140/90 mmHg	64/275 (23.3%)	35/209 (16.7%)	.09
ITT Population – Control Rates in the Absence of Additional Antihypertensive Medications			
Definition	**uRDN (n=293)**	**Sham (n=213)**	**P value[a]**
Daytime ambulatory BP <135/85 mmHg	63/281 (22.4%)	19/211 (9.0%)	<.001
24-hour ambulatory BP <130/80 mmHg	69/280 (24.6%)	20/211 (9.5%)	<.001
Home BP <135/85 mmHg	42/275 (15.3%)	8/205 (3.9%)	<.001
Office BP <140/90 mmHg	59/275 (21.5%)	30/209 (14.4%)	.06

Data displayed as % (n/N).
[a]P-value from Chi-square or Fishers exact test, as appropriate, comparing treatment arm to sham arm.

eTable 9. Multivariable Analysis of Daytime Ambulatory Systolic Blood Pressure in the Ultrasound Renal Denervation Group Only in the Intention-to-Treat Population

Independent Variables	Estimate (Standard Error)	*P* value[a]
Study		.17
RII Study (vs TRIO)	3.51 (1.92)	.07
SOLO Study (vs TRIO)	1.92 (2.16)	.37
Female (vs Male)	-1.23 (1.58)	.44
Black (vs non-black)	-0.52 (2.02)	.80
Age, years (1 unit increase)	0.11 (0.08)	.13
Baseline Daytime Ambulatory Systolic Blood Pressure, mmHg (1 unit increase)	-0.25 (0.08)	.001
Baseline 24-hr ABP Heart Rate < 74 (median) (vs. ≥74)	3.62 (1.44)	.01
Baseline eGFR < 60ml/min/1.73 m^2 (vs. ≥60)	-5.76 (3.34)	.09
US (vs. OUS)	-1.68 (1.53)	.27
Abdominal obesity (vs. Normal)	1.49 (1.53)	.33
Orthostatic HTN (vs. No Orthostatic HTN)	-4.41 (1.81)	.02
Sleep Apnea (vs. No Sleep Apnea)	-0.63 (1.97)	.75

[a]*P* value from multiple linear regression. *P* value for 'Study' row is based on the Type 3 *P* value testing across the 3 levels of the variable.

eTable 10. Changes in Kidney Function at 2 Months in Patients With Matched Data at Baseline and 2 Months (n = 273 uRDN and n = 207 Sham)

	uRDN			Sham			Study and Baseline Adjusted Observed	
	Randomization	2 months	Difference	Randomization	2 months	Difference	Group Difference (95% CI)[a]	*P* value[c]
eGFR[e] (mL/min/1.73 m^2)	83.8 ± 18.0	84.4 ± 16.7	0.6 ± 10.8	82.4 ± 16.6	82.9 ± 16.8	0.6 ± 9.5	0.4 (-1.4, 2.2) 0.0 (-1.8, 1.6)[b]	.65 .97[d]
Serum Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2	-0.0 ± 0.1	0.9 ± 0.2	0.9 ± 0.2	0.0 ± 0.1	-0.0 (-0.0, 0.0) -0.0 (-0.0, 0.0)[b]	.34 .80[d]

Data displayed as mean ± SD unless otherwise specified.
[a]Estimate of treatment difference, from study and baseline adjusted ANCOVA.
[b]In the event that change from baseline in either cohort is non-normal, the Hodges-Lehmann estimator of location shift and associated 95% confidence interval (observed data) is also provided.
[c]*P* value from study and baseline adjusted ANCOVA.
[d]In the event that change from baseline in either cohort is non-normal, the p-value from a study and baseline adjusted ANCOVA on the ranks (observed data) is also provided.
[e]Calculated using MDRD formula. There is one subject in the uRDN group and one subject in the sham group that had serum creatinine but are missing eGFR.

5. eReferences

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