Patient-Level Pooled Analysis of Endovascular Ultrasound Renal Denervation or a Sham Procedure 6 Months After Medication Escalation: The RADIANCE Clinical Trial Program

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Background:

The randomized, sham-controlled RADIANCE-HTN (A Study of the Recor Medical Paradise System in Clinical Hypertension) SOLO, RADIANCE-HTN TRIO, and RADIANCE II (A Study of the Recor Medical Paradise System in Stage II Hypertension) trials independently met their primary end point of a greater reduction in daytime ambulatory systolic blood pressure (SBP) 2 months after ultrasound renal denervation (uRDN) in patients with hypertension. To characterize the longer-term effectiveness and safety of uRDN versus sham at 6 months, after the blinded addition of antihypertensive treatments (AHTs), we pooled individual patient data across these 3 similarly designed trials.

Methods:

Patients with mild to moderate hypertension who were not on AHT or with hypertension resistant to a standardized combination triple AHT were randomized to uRDN (n=293) versus sham (n=213); they were to remain off of added AHT throughout 2 months of follow-up unless specified blood pressure (BP) criteria were exceeded. In each trial, if monthly home BP was ≥135/85 mm Hg from 2 to 5 months, standardized AHT was sequentially added to target home BP <135/85 mm Hg under blinding to initial treatment assignment. Six-month outcomes included baseline- and AHT-adjusted change in daytime ambulatory, home, and office SBP; change in AHT; and safety. Linear mixed regression models using all BP measurements and change in AHT from baseline through 6 months were used.

Results:

Patients (70% men) were 54.1±9.3 years of age with a baseline daytime ambulatory/home/office SBP of 150.5±9.8/151.0±12.4/155.5±14.4 mm Hg, respectively. From 2 to 6 months, BP decreased in both groups with AHT titration, but fewer uRDN patients were prescribed AHT (P=0.004), and fewer additional AHT were prescribed to uRDN patients versus sham patients (P=0.001). Whereas the unadjusted between-group difference in daytime ambulatory SBP was similar at 6 months, the baseline and medication-adjusted between-group difference at 6 months was −3.0 mm Hg (95% CI, −5.7, −0.2; P=0.033), in favor of uRDN+AHT. For home and office SBP, the adjusted between-group differences in favor of uRDN+AHT over 6 months were −5.4 mm Hg (−6.8, −4.0; P<0.001) and −5.2 mm Hg (−7.1, −3.3; P<0.001), respectively. There was no heterogeneity between trials. Safety outcomes were few and did not differ between groups.

Conclusions:

This individual patient-data analysis of 506 patients included in the RADIANCE trials demonstrates the maintenance of BP-lowering efficacy of uRDN versus sham at 6 months, with fewer added AHTs.

Registration:

URL: https://www.clinicaltrials.gov; Unique identifiers: NCT02649426 and NCT03614260.

Key Words: ablation, catheter ■ antihypertensive drugs ■ blood pressure ■ denervation ■ hypertension ■ hypertension, renal

Nonstandard Abbreviations and Acronyms

AHT

antihypertensive treatment

BP

blood pressure

dASBP

daytime ambulatory systolic blood pressure

eGFR

estimated glomerular filtration rate

IPD

individual patient data

RADIANCE II

A Study of the Recor Medical Paradise System in Stage II Hypertension

RADIANCE-HTN

A Study of the Recor Medical Paradise System in Clinical Hypertension

RDN

renal denervation

SBP

systolic blood pressure

SSAHT

standardized, stepped-care antihypertensive treatment

uRDN

ultrasound renal denervation

Clinical Perspective

What Is New?

- We report the blood pressure (BP)–lowering effects of ultrasound-based renal denervation (n=293) versus sham (n=213) at 6 months in conjunction with monthly addition of standardized antihypertensive treatments (AHTs) at 2, 3, 4, and 5 months, using pooled individual patient-data analysis of RADIANCE-HTN (A Study of the Recor Medical Paradise System in Clinical Hypertension) SOLO (off medications), RADIANCE-HTN TRIO (on medications), and RADIANCE II (A Study of the Recor Medical Paradise System in Stage II Hypertension; off medications).
- A significantly smaller proportion of patients with hypertension randomized to ultrasound-based renal denervation required addition of BP medications to control BP when compared with the sham-treated group at 6-month follow-up.
- Despite more intensified AHT titration in the sham+AHT arm, the baseline and medication-adjusted between-group differences at 6 months favored ultrasound-based renal denervation+AHT for daytime ambulatory, home, and office systolic BP.

What Are the Clinical Implications?

- This individual patient-data analysis demonstrates maintenance of the BP–lowering effect of ultrasound-based renal denervation versus sham at 6 months, with fewer added AHTs.

Hypertension is highly prevalent worldwide and is a major risk factor for cardiovascular, cerebrovascular, and renal morbidity and mortality.[1] Despite the availability of various antihypertensive treatments (AHTs), which reduce hypertension-related complications,[2,3] a large proportion of patients have uncontrolled blood pressure (BP)[4,5] for multiple reasons, including nonadherence to medications and therapeutic inertia.[6,7] In this context, endovascular catheter-based renal denervation (RDN) has emerged as a guideline-recommended BP-lowering treatment in addition to lifestyle changes and pharmacotherapy.[8,9] After inconsistent results from earlier trials,[10,11] subsequent sham-controlled trials with improved study designs, catheter designs, and procedural technique have demonstrated the BP-lowering efficacy and safety of RDN.[12–16]

The multicenter, blinded, randomized, sham-controlled RADIANCE-HTN (A Study of the Recor Medical Paradise System in Clinical Hypertension) SOLO,[12] RADIANCE-HTN TRIO,[16] and RADIANCE II[15] (A Study of the Recor Medical Paradise System in Stage II Hypertension) trials independently met their primary efficacy end point of a greater reduction in daytime ambulatory systolic BP (dASBP) at 2 months after ultrasound-based RDN (uRDN) with the Paradise catheter versus a sham procedure. The decrease in dASBP was on average ≈6 mm Hg greater with uRDN compared with sham in a patient-level pooled analysis of these trials, corresponding to a clinically meaningful decrease in BP.[17] The 3 trials included patients with various degrees of hypertension severity, including patients with true resistant hypertension,[16] in whom AHT were not to be added to the baseline regimen except for escape purposes until ascertainment of the primary outcome at 2 months, thus minimizing the confounding effect of a changing background of AHT.[18]

After assessment of the primary study end point at month 2, in the subsequent 4 months, AHT were sequentially added at monthly office visits in an attempt to achieve BP control under continued blinding to treatment assignment. This protocol therefore allows further assessment of the BP effects of uRDN in conjunction with added medications. We pooled the individual patient data from these 3 trials to present a comprehensive analysis that encompasses a larger sample size of 506 patients, thereby increasing the statistical power to evaluate more precisely the long-term benefits and safety of uRDN in conjunction with AHT.

Methods

Study Design

This patient-level analysis used 6-month pooled data from the 3 aforementioned trials, which have been published previously.[19–21] All trials had comparable designs, primary efficacy end point (dASBP), secondary and observational efficacy end points (all other ambulatory, home, and office BP measurements), data collection, and follow-up procedures at 2 and 6 months. Each study was approved by local ethics committees or institutional review boards and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. For the purposes of reproducing the analysis generated here, the data that support the findings of this study will be available from the corresponding author and study steering committee on reasonable request at the end of the study.

Study Populations

All 3 studies included patients with hypertension between 18 and 75 years of age with an estimated glomerular filtration rate (eGFR) of at least 40 mL/min/1.73 m^2. The proof-of-concept RADIANCE-HTN SOLO enrolled patients with mild to moderate hypertension whose office BP was either controlled (office BP <140/90 mm Hg) with 1 or 2 antihypertensive medications or uncontrolled (office BP ≥140/90 mm Hg) with 0 to 2 antihypertensive medications.[12] The pivotal RADIANCE II enrolled patients with an office BP ≥140/90 mm Hg who were either currently or previously prescribed up to 2 antihypertensive medications.[15] RADIANCE-HTN TRIO enrolled patients with resistant hypertension whose office BP was ≥140/90 mm Hg despite receiving 3 or more antihypertensive medications (Table S1).[16] Despite different populations of patients included in the 3 trials, which differed in some clinical characteristics (as shown in Table 1), similar ambulatory, home, and office BP measurments were achieved at baseline after 4-week medication washout (RADIANCE-HTN SOLO/RADIANCE II) or standardization (RADIANCE-HTN TRIO) before randomization to uRDN or sham procedure.

Table 1. Baseline Clinical Characteristics of the Patients Included in the 3 Trials (Table view)

Measure	RADIANCE II (n=224)	RADIANCE-HTN SOLO (n=146)	RADIANCE-HTN TRIO (n=136)
Age, y	55.0±9.3	54.1±10.1	52.5±8.3
Sex			
Female	160/224 (71.4)	85/146 (58.2)	109/136 (80.2)
Male	64/224 (28.6)	61/146 (41.8)	27/136 (19.9)

Measure	RADIANCE II (n=224)	RADIANCE-HTN SOLO (n=146)	RADIANCE-HTN TRIO (n=136)
Race and ethnicity			
Black	36/224 (16.1)	24/146 (17.1)	27/134 (20.2)
White	170/224 (75.9)	112/146 (76.7)	96/134 (71.6)
Body mass index, kg/m^2*	30.3±5.2	29.5±5.5	32.7±5.6
Abdominal obesity†	136/224 (60.7)	85/145 (58.6)	109/133 (82.0)
eGFR, mL/min/1.73 m^2‡	81.7±14.6	83.8±16.0	84.2±22.4
eGFR <60 mL·min·1.73 m^2	10/224 (4.5)	4/145 (2.8)	15/134 (11.2)
Type II diabetes	14/224 (6.3)	7/146 (4.8)	38/136 (27.9)
Sleep apnea syndrome	34/224 (15.2)	14/146 (9.6)	31/136 (22.8)
Previous hospitalization for hypertensive crisis	12/224 (5.4)	4/146 (2.7)	26/136 (19.1)
Previous myocardial infarction or cerebrovascular event§	0/224 (0.0)	0/146 (0.0)	16/136 (11.8)
History of heart failure	1/210 (0.5)	0/140 (0.0)	4/129 (3.1)
Office BP and heart rate at screening			
SBP, mm Hg	155.3±10.9	143.6±15.3	162.7±16.1
DBP, mm Hg	100.6±6.5	92.9±9.3	104.2±12.1
Heart rate, bpm‖	73.9±11.9	73.2±12.3	76.0±12.0
Number of antihypertensive medications at screening	1.0±0.8	1.2±0.8	4.0±1.1
BP after 4-week medication washout/standardization, mm Hg			
Daytime ambulatory SBP	150.6±8.7	150.2±8.8	150.5±12.2
Daytime ambulatory DBP	93.6±5.3	93.3±5.1	94.2±8.4
24-hour ambulatory SBP#	143.8±9.1	142.9±8.9	144.6±13.7
24-hour ambulatory DBP#	88.4±5.8	87.8±5.2	89.2±8.8

Measure	RADIANCE II (n=224)	RADIANCE-HTN SOLO (n=146)	RADIANCE-HTN TRIO (n=136)
Nighttime ambulatory SBP#	132.8±12.8	131.4±12.8	135.4±18.3
Nighttime ambulatory DBP#	80.1±8.2	79.1±8.1	81.3±11.4
Home SBP**	151.8±9.9	147.6±10.6	153.5±16.5
Home DBP**	97.3±6.9	94.9±7.0	97.0±11.1
Office SBP††	156.7±13.0	154.0±14.1	155.2±16.7
Office DBP††	101.9±7.6	99.4±8.6	100.5±11.3

Data are displayed as mean±SD or n/N (%). BP indicates blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; and uRDN, ultrasound renal denervation.

*

Body mass index was available for 145 participants of RADIANCE-HTN SOLO (A Study of the Recor Medical Paradise System in Clinical Hypertension) and 135 participants of RADIANCE-HTN TRIO.

†

Abdominal obesity was defined as a waist circumference >102 cm for men and >88 cm for women.

‡

eGFR data were available for 145 RADIANCE-HTN SOLO participants and 134 RADIANCE-HTN TRIO participants.

§

RADIANCE-HTN TRIO was the only study that permitted enrollment of patients with previous cardiovascular or cerebrovascular events.

‖

Heart rate was missing for 1 patient in the RADIANCE-HTN SOLO group.

RADIANCE-HTN TRIO was the only study that permitted enrollment of patients taking ≥3 antihypertensive medications.

#One patient in RADIANCE-HTN SOLO was missing 24-hour and nighttime ambulatory SBP and DBP measurements.

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Home SBP and DBP measurements are available for 221 RADIANCE II (A Study of the Recor Medical Paradise System in Stage II Hypertension) participants and for 134 in RADIANCE-HTN TRIO participants.

††

Average of last 2 office BP measurements among 3 measures in the seated position.

Background antihypertensive medications were standardized at enrollment in the 3 studies according to hypertension severity. In both RADIANCE-HTN SOLO and RADIANCE II, all antihypertensive medications were withdrawn for 4 weeks before confirming a daytime ambulatory BP of at least 135/85 mm Hg and <170/105 mm Hg.[12,15] In RADIANCE-HTN TRIO, all patients were switched to a triple-drug, fixed-dose, single combination pill containing a calcium channel blocker, angiotensin receptor blocker, and thiazide diuretic for 4 weeks, before confirming a daytime ambulatory BP of at least 135/85 mm Hg.[16] The baseline characteristics of the patients included in the 3 trials are shown in Table 1.

Participants who met ambulatory BP criteria after a 1-month medication stabilization phase and who had suitable renal artery anatomy on previous computed tomography or magnetic resonance angiography were randomly assigned (1:1 for RADIANCE-HTN SOLO and TRIO; 2:1 for RADIANCE II) to either endovascular uRDN using the Paradise Renal Denervation System (Recor Medical, Inc.) or a sham procedure restricted to renal angiography alone. A minimum of 2 nonoverlapping sonications were delivered in the main right and left renal arteries, and at least one sonication was delivered in accessory arteries according to individual treatment plans developed based on the prerandomization computed tomography or magnetic resonance angiography and after selective renal angiography. Treatable artery sizes in RADIANCE-HTN TRIO and RADIANCE II were ≥3 mm and ≤8 mm. Treatable artery sizes in RADIANCE-HTN SOLO were ≥4 mm and ≤8 mm. The independent randomization process was consistent across all studies. To maintain blinding of the patients, eye covers, headphones, and sedation were used throughout the procedure in all trials. Blinding was to be maintained through 6 months for patients in both RADIANCE-HTN SOLO and TRIO and through 12 months for patients in RADIANCE II. Participants and treating physicians were instructed not to modify their AHT until ascertainment of the primary efficacy outcome of change in dASBP at 2 months, unless safety BP criteria were exceeded.

Monthly follow-up visits included 7-day home BP assessment followed by seated BP and heart rate measurements at an office visit. Twenty-four hour ambulatory BP and heart rate measurements were performed after witnessed medication intake at baseline and at 2 and 6 months. Table 2 shows the different methods of BP measurement in the 3 trials. eGFR determinations were performed at baseline and 2 and 6 months. In each of the 3 trials from the 2nd month through the 5th month, if monthly home BP was ≥135/85 mm Hg, investigators initiated a standardized, stepped-care antihypertensive treatment (SSAHT) protocol in both randomized groups, aiming to achieve BP control, for safety, ethical, and regulatory reasons.

Table 2. Blood Pressure Measurement and Procedural Methods Used in All Studies (Table view)

Setting	Methods
Office	Seated office and home BP was measured according to US and European guidelines[22,23] as previously described.[15,24] After a rest period in the seated position, 3 office BP measurements were taken 1 to 2 minutes apart with a cuff

Setting	Methods
	adapted to the arm circumference, with the last 2 readings averaged and used as the office BP reading.
Home	Participants were requested to measure their BP at home after a 5-minute rest in the sitting position in the morning and the evening (2 BP measurements 1 to 2 minutes apart) during 7 consecutive days before every outpatient visit.
Ambulatory	Serial ambulatory BP measurements were performed to assess initial eligibility and at 2 months after randomization, as previously described.[15,24] BP was recorded every 20 minutes during daytime (7:00 am to 10:00 pm) and every 30 minutes during nighttime (10:00 pm to 7:00 am). The ambulatory BP measurement was repeated if the number of daytime BP measurements was <21. All ambulatory BP recordings were sent to a core laboratory (dabl) with treatment assignment masked.

BP indicates blood pressure.

In both RADIANCE-HTN SOLO and RADIANCE II, the SSAHT included sequential addition of 5 mg per day of amlodipine, a standard dose of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and 12.5 mg per day of hydrochlorothiazide, followed by the sequential uptitration of hydrochlorothiazide (25 mg/day) and amlodipine (10 mg/day).[12,15] In RADIANCE-HTN TRIO, the SSAHT included guideline-recommended sequential addition of: (1) an aldosterone antagonist (preferentially 25 mg/day of spironolactone); (2) a beta-1 blocker (preferentially 10 mg/day of bisoprolol); (3) a central α2-receptor agonist (0.1–0.2 mg/day of clonidine, 1–2 mg/day of rilmenidine, or 0.2–0.4 mg/day of moxonidine); and (4) an α1-receptor blocker (5–10 mg/day of prazosin or 4–8 mg/day of doxazosin).[16]

Outcomes

Prespecified end points at 6 months in each of the studies were: (1) the number of AHTs prescribed; (2) the sum of defined daily dose of each individual antihypertensive medication to assess and compare total drug consumption between the groups[25] and the antihypertensive load index (calculated percentage of the maximum dose of each drug)[26]; and (3) the baseline and covariate-adjusted changes in systolic BP (SBP), as assessed by daytime/nighttime/24-hour ambulatory, home, and office BP measurements. Other prespecified end points included the proportion of patients with controlled out-of-office BP (defined as <135/85 mm Hg for both daytime ambulatory and home SBP and diastolic BP).

Major adverse events, adjudicated by an independent clinical events committee, have been previously reported.[17] In this analysis, a broader set of safety events occurring within 6 months were evaluated according to the definitions used in RADIANCE-HTN.[12,16] These events included all-cause mortality, hypertensive or hypotensive emergency resulting in hospitalization, hospitalization for heart failure, stroke, acute myocardial infarction, coronary revascularization, end-stage renal disease, new-onset renal artery stenosis >50%, or the need for renal artery angioplasty or stenting. In addition, the change in eGFR from baseline though 6 months was assessed.

Statistical Analysis

For the current prespecified analysis, we included all evaluable data based on the initial arm of randomization (intent-to-treat). No imputation was conducted for missing data. Linear mixed models for repeated measures were used to assess baseline and covariate-adjusted changes in BP measures through 6 months after the procedure. Fixed-effects terms included randomized study group (uRDN versus sham), baseline BP, number of AHTs at visit, study, and interaction term (treatment arm*visit). If the treatment arm*visit interaction was significant, only the 6-month estimate was used, rather than the estimate across all time points. An unstructured covariance structure was used in the mixed models, and the clustering of participants within study was accounted for. A similar approach was applied to binary end points with generalized linear mixed models, using log-binomial regression in place of linear regression. *P* values were adjusted for multiple comparisons using the Tukey-Kramer test. Given the limited number of studies, a fixed-effects approach was adopted, and study poolability was assessed using a treatment arm by study interaction term, as well as the calculation of the I^2 statistic in a 2-stage meta-analysis. Of note, no between-study heterogeneity was observed for any of the conducted analyses.

Change in the number of AHTs from baseline to 6 months and defined daily dose at 6 months were assessed using linear mixed models including fixed effects for treatment arm and study. As a result of the 2:1 randomization within RADIANCE II, which enrolled a population of patients with mild to moderate hypertension, pooled comparisons between treatment groups in the total medication burden are confounded because of the imbalance between patients enrolled in each treatment arm. As such, changes in medication burden (rather than absolute numbers) are presented. Subgroup analyses for baseline characteristics were conducted using mean-centered values to prevent ecological bias.[27] Multivariable analyses using linear regression were conducted to identify predictors of BP response to uRDN (Methods in the Supplemental Material). Continuous variables are expressed as mean±SD, unless otherwise specified, and between-group differences are expressed as mean and corresponding 2-sided 95% CIs. Comparisons between groups at baseline and 6 months were made using linear regression adjusted for study for continuous variables and either the Cochran-Mantel-Haenszel test stratified by study or logistic regression adjusted for study for categorical variables.

All analyses were performed using SAS software, version 9.4 (SAS Institute). A *P* value <0.05 (2-sided) was considered statistically significant.

The study principal investigators (M.A., A.J.K.) had full access to all the data in each of the 3 trials and take responsibility for the study integrity and the data analysis.

Results

Among 2830 patients screened for eligibility in the 3 studies, 506 patients were randomized to uRDN (n=293) or sham (n=213).[17] A total of 286 uRDN and 207 sham patients remained in the study at 6 months (Figure S1). The trials included primarily men (354/506 [70.0%]). Patients were 54.1±9.3 years of age with a body mass index of 30.7±5.5 kg/m^2 and an eGFR of 83.0±17.4 mL/min/1.73 m^2, of whom 88/504 (17.5%) were self-described as Black (Table S2). Previous hospitalization for hypertensive crisis and previous cardiovascular or cerebrovascular events were infrequent except in patients with more resistant hypertension included in RADIANCE-HTN TRIO.[16] During screening, the mean±SD office BP was 153.9/99.3±15.6/10.1 mm Hg, and patients were on 1.8±1.6 antihypertensive medications (Table S2). After the 1-month medication stabilization period, daytime ambulatory systolic/diastolic BP was similar at baseline in the uRDN group (150.3/93.6±9.2/5.8 mm Hg) and in the sham group (150.8/93.8±10.5/6.9 mm Hg),

as well as for home and office systolic/diastolic BP values (Table S2). Successful bilateral ablation (total number of sonications, 5.6±1.0) was performed in all but 7 patients (286/293 [97.6%]).[17]

Medication Burden

Fewer patients in the uRDN group had at least 1 antihypertensive medication added from 2 months onward compared with the sham group (189/285 [66.3%] versus 157/204 [77.0%], respectively; *P*=0.002; Table 3). The changes in medication burden indices (defined daily dose and antihypertensive load index) were both smaller in the uRDN+AHT group than in the sham+AHT group at 6 months (Table 3). In linear mixed models, the change in number of AHTs from baseline to 6 months was smaller in the uRDN+AHT group than in the sham+AHT group (*P*=0.0011; Table S3).

Table 3. Number and Type of Antihypertensive Medications, Defined Daily Dose, and Antihypertensive Medication Load at 6 Months (Table view)

Characteristics	uRDN+AHT (n=285)	Sham+AHT (n=204)	*P* value*
Antihypertensive medication change from baseline to 6 months, mean±SD			
Change in number of antihypertensive medications	1.1±1.0	1.3±1.0	0.001
Change in defined daily dose	1.3±1.6	1.6±1.6	0.001
Change in antihypertensive medication load index	0.5±0.6	0.6±0.6	0.001
Antihypertensive medication changes from baseline to 6 months, n/N (%)			
≥1 medication removed or 0 medications added	96/285 (33.7)	47/204 (23.0)	0.002
≥1 medication added	189/285 (66.3)	157/204 (77.0)	
Full adherence to antihypertensive medications†	140/168 (83.3)	88/105 (83.8)	0.47

AHT indicates antihypertensive treatment; and uRDN, ultrasound renal denervation.

*

P value from linear regression adjusted for study for continuous variables and logistic regression adjusted for study for categorical variables comparing treatment arm with sham arm.

†

Adherence to antihypertensive medications by urine drug analysis using liquid chromatography tandem mass spectrometry was done only in RADIANCE-HTN (A Study of the Recor Medical Paradise System in Clinical Hypertension) TRIO and RADIANCE II (A Study of the Recor Medical

Paradise System in Stage II Hypertension). The denominator indicates the number of patients with urine samples available.

Ambulatory BP Changes in the Pooled Population

As expected, given the medication titration at months 2, 3, 4, and 5, BP decreased in both groups at 6 months (from 0–2 months largely reflecting the randomized treatment and from 2–6 months reflecting the medication escalation protocol in addition to randomized treatment). At 6 months, dASBP decreased by −16.3±12.5 mm Hg from baseline, reaching 133.9±13.0 mm Hg in the uRDN+AHT group, and decreased by −15.1±13.9 mm Hg from baseline in the sham+AHT group, reaching 135.5±12.8 mm Hg (Table S4). Reductions were consistent across the 3 included trials (Figure 1), and there was no heterogeneity when tested using a study by treatment arm interaction term by I^2 statistic. The baseline-adjusted decrease in dASBP at 6 months between the uRDN+AHT versus sham+AHT group was −1.9 mm Hg (95% CI, −4.8, 1.0 mm Hg; *P*=0.33; Table 4).

Table 4. Analysis of Daytime Ambulatory Systolic Blood Pressure Using Linear Mixed Model for Repeated Measures in the uRDN+AHT and the Sham+AHT Groups (Table view)

Daytime ambulatory SBP, mm Hg	uRDN+AHT		Sham+AHT		Treatment difference, mean (95% CI)	*P* value
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)		
Model adjusted for baseline						
Overall: Model without treatment arm by visit interaction*	138.1 (136.9, 139.3)	−12.2 (−13.4, −11.1)	141.8 (140.6, 143.1)	−8.5 (−9.8, −7.2)	−3.8 (−5.4, −2.1)	<0.0001
Overall: Model including treatment arm by visit interaction term†	138.1 (137.0, 139.3)	−12.2 (−13.3, −11.1)	141.8 (140.5, 143.1)	−8.5 (−9.8, −7.3)	−3.7 (−5.3, −2.0)	<0.0001
Month 2	142.1 (140.7, 143.6)	−8.2 (−9.6, −6.7)	147.5 (145.9, 149.2)	−2.8 (−4.4, −1.1)	−5.4 (−8.2, −2.7)	<0.0001‖
Month 6	134.1 (132.6, 135.5)	−16.2 (−17.7, −14.8)	136.0 (134.3, 137.7)	−14.3 (−16.0, −12.6)	−1.9 (−4.8, 1.0)	0.33‖
Model adjusted for baseline and number of AHTs						

Daytime ambulatory SBP, mm Hg	uRDN+AHT		Sham+AHT		Treatment difference, mean (95% CI)	*P* value
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)		
Overall: Model without treatment arm by visit interaction‡	138.6 (137.4, 139.8)	−11.7 (−12.9, −10.5)	143.2 (141.9, 144.6)	−7.1 (−8.5, −5.8)	−4.6 (−6.3, −2.9)	<0.0001
Overall: Model including treatment arm by visit interaction term§	138.7 (137.5, 139.9)	−11.6 (−12.8, −10.4)	143.1 (141.8, 144.5)	−7.2 (−8.5, −5.8)	−4.5 (−6.1, −2.8)	<0.0001
Month 2	140.1 (138.6, 141.6)	−10.2 (−11.7, −8.7)	146.1 (144.5, 147.7)	−4.2 (−5.8, −2.6)	−6.0 (−8.6, −3.3)	<0.0001‖
Month 6	137.2 (135.7, 138.8)	−13.1 (−14.6, −11.5)	140.2 (138.3, 142.0)	−10.1 (−12.0, −8.3)	−3.0 (−5.7, −0.2)	0.033‖

AHT indicates antihypertensive treatments; SBP, systolic blood pressure; and uRDN, ultrasound renal denervation.

*

Linear mixed regression model including baseline value, treatment arm, visit, and study as fixed effects.

†

Linear mixed regression model including baseline value, treatment arm, visit, study, and interaction term (treatment arm by visit) as fixed effects. *P* value for interaction (treatment arm by visit)=0.012.

‡

Linear mixed regression model including baseline value, treatment arm, visit, number of AHTs at visit, and study as fixed effects.

§

Linear mixed regression model including baseline value, treatment arm, visit, number of AHTs at visit, study, and interaction term (treatment arm by visit) as fixed effects. *P* value for interaction (treatment arm by visit)=0.016.

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P value adjusted for multiple comparisons (Tukey-Kramer).

Figure 1. **Blood pressure differences between groups. A**, Difference in daytime ambulatory (**top**), home (**middle**), and office (**bottom**) systolic blood pressure (SBP) between the ultrasound renal denervation (uRDN)+antihypertensive treatment (AHT) and the sham+AHT groups for each individual trial at 6 months along with results from a 2-stage meta-analysis without adjustment for medication burden. Individual trial results are from linear mixed models adjusting for baseline value, treatment arm, and visit, with the exception of office SBP in RADIANCE-HTN (A Study of the Recor Medical Paradise System in Clinical Hypertension) SOLO and daytime ambulatory SBP in RADIANCE II (A Study of the Recor Medical Paradise System in Stage II Hypertension). The interaction of treatment arm and visit was significantly associated with office SBP in RADIANCE-HTN SOLO and daytime ambulatory SBP in RADIANCE II, and thus was also included as a covariate in the RADIANCE-HTN SOLO office SBP and RADIANCE II daytime ambulatory SBP linear mixed models. Overall estimates from the linear mixed models are presented when the interaction between treatment arm and visit is not statistically significant; the 6-month specific estimate is presented when the interaction term is statistically significant (eg, RADIANCE-HTN SOLO office SBP and RADIANCE II daytime ambulatory SBP). **B**, Difference in daytime ambulatory (**top**), home (**middle**), and office (**bottom**) SBP between the uRDN+AHT and the sham+AHT groups for each individual trial at 6 months along with results from a 2-stage meta-analysis including adjustment for differences in medication burden. Individual trial results are from linear mixed models adjusting for baseline value, treatment arm, visit, and number of medications at visit, with the exception of daytime ambulatory SBP in RADIANCE II. The interaction of treatment arm and visit was significantly associated with daytime ambulatory SBP in RADIANCE II, and thus was also included as a covariate in the RADIANCE II daytime ambulatory SBP linear mixed model. Similar to results presented in the article, overall estimates from the linear mixed models are presented when the interaction between treatment arm and visit is not statistically significant, whereas the 6-month specific estimate is presented when the interaction term is statistically significant (eg, RADIANCE II daytime ambulatory SBP).

Recognizing that there was a greater increase in medication burden in the sham versus uRDN group, medication burden was used as a covariate in the linear mixed model. After further adjustment for AHT, the baseline-adjusted decrease in dASBP at 6 months was −13.1 mm Hg (95% CI, −14.6, −11.5 mm Hg) in the uRDN+AHT group versus −10.1 mm Hg (95% CI, −12.0 to −8.3 mm Hg) in the sham+AHT group, with a greater fall in the uRDN+AHT group of −3.0 mm Hg (95% CI, −5.7, −0.2 mm Hg; *P*=0.033; Table 4; Figure 2). Individual patient changes in dASBP at 6 months displayed large between-participant variability in both the uRDN+AHT and the sham+AHT groups (Figure S2). The changes in 24-hour and nighttime ambulatory SBP between the 2 groups were consistent with the changes in dASBP (Tables S5 and S6).

Figure 2. **Mean change in blood pressure.** Mean change in daytime ambulatory (**top**), home (**middle**), and office (**bottom**) systolic blood pressure (SBP) from baseline through 6 months in the ultrasound renal denervation group (blue dots and lines) and the sham group (gray dots and lines) as analyzed by linear mixed model (see Statistical Analysis). Error bars represent 95% CI.

Home and Office BP Changes in the Pooled Population

At 6 months (after medication titration at months 2, 3, 4, and 5), home SBP decreased by −17.2±12.8 mm Hg from baseline, reaching 133.9±13.6 mm Hg in the uRDN+AHT group, and decreased by −13.1±12.9 mm Hg from baseline in the sham+AHT group, reaching 136.8±13.8 mm Hg (Table S4). Reductions in home SBP changes were consistent across the 3 included trials (Figure 1), and there was no heterogeneity when tested using a study by treatment arm interaction term by I^2 statistic. In a linear mixed model without adjustment for medications, the difference in baseline-adjusted decrease in BP over 6 months between the uRDN+AHT and sham+AHT groups was −4.5 mm Hg (95% CI, −5.8, −3.2 mm Hg; *P*<0.0001; Table 5).

Table 5. Analysis of Home Systolic Blood Pressure Using Linear Mixed Model for Repeated Measures in the uRDN+AHT and Sham+AHT Groups (Table view)

Home SBP, mm Hg	uRDN+AHT		Sham+AHT		Treatment difference, mean (95% CI)	*P* value
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)		
Model adjusted for baseline						
Overall: Model without treatment arm by visit interaction*	138.1 (137.2, 139.1)	−12.1 (−13.1, −11.2)	142.6 (141.6, 143.7)	−7.6 (−8.7, −6.6)	−4.5 (−5.8, −3.2)	<0.0001
Overall: Model including treatment arm by visit interaction term†	138.1 (137.2, 139.1)	−12.1 (−13.1, −11.1)	142.6 (141.5, 143.7)	−7.6 (−8.7, −6.5)	−4.5 (−5.9, −3.1)	<0.0001
Month 1	143.7 (142.6, 144.8)	−6.5 (−7.6, −5.4)	148.3 (147.0, 149.5)	−2.0 (−3.2, −0.7)	−4.6 (−7.2, −1.9)	<0.000‖
Month 2	142.0 (140.8, 143.2)	−8.3 (−9.5, −7.0)	148.3 (146.9, 149.7)	−2.0 (−3.4, −0.6)	−6.3 (−9.2, −3.3)	<0.000‖
Month 3	138.6 (137.4, 139.8)	−11.7 (−12.9, −10.5)	142.9 (141.5, 144.2)	−7.4 (−8.8, −6.0)	−4.3 (−7.3, −1.3)	0.0002‖

Home SBP, mm Hg	uRDN+AHT		Sham+AHT		Treatment difference, mean (95% CI)	*P* value
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)		
Month 4	136.2 (134.9, 137.4)	−14.1 (−15.4, −12.8)	140.2 (138.7, 141.6)	−10.1 (−11.6, −8.6)	−4.0 (−7.2, −0.8)	0.0023‖
Month 5	134.9 (133.6, 136.2)	−15.3 (−16.6, −14.0)	139.0 (137.4, 140.5)	−11.3 (−12.8, −9.8)	−4.0 (−7.2, −0.8)	0.0027‖
Month 6	133.5 (132.1, 134.8)	−16.9 (−18.4, −15.5)	137.3 (135.7, 138.9)	−13.0 (−14.6, −11.4)	−3.8 (−7.2, −0.5)	0.012‖
Model adjusted for baseline and number of AHTs						
Overall: Model without treatment arm by visit interaction‡	138.7 (137.7, 139.8)	−11.5 (−12.6, −10.5)	144.1 (142.9, 145.3)	−6.2 (−7.3, −5.0)	−5.4 (−6.8, −4.0)	<0.0001
Overall: Model including treatment arm by visit interaction term§	138.6 (137.6, 139.7)	−11.6 (−12.7, −10.6)	144.2 (143.0, 145.4)	−6.0 (−7.2, −4.8)	−5.6 (−7.1, −4.1)	<0.0001
Month 1	141.2 (140.1, 142.3)	−9.1 (−10.2, −7.9)	146.3 (145.0, 147.5)	−4.0 (−5.3, −2.7)	−5.1 (−7.7, −2.4)	<0.000‖
Month 2	139.8 (138.6, 141.1)	−10.4 (−11.7, −9.2)	146.8 (145.4, 148.1)	−3.5 (−4.9, −2.1)	−6.9 (−9.9, −4.0)	<0.000‖
Month 3	138.7 (137.5, 134.0)	−11.5 (−12.8, −10.2)	144.1 (142.7, 145.6)	−6.1 (−7.6, −4.7)	−5.4 (−8.5, −2.4)	<0.000‖
Month 4	137.7 (136.5, 139.0)	−12.5 (−13.8, −11.2)	143.3 (141.7, 144.8)	−7.0 (−8.5, −5.5)	−5.5 (−8.7, −2.4)	<0.000‖

Home SBP, mm Hg	uRDN+AHT		Sham+AHT		Treatment difference, mean (95% CI)	*P* value
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)		
Month 5	137.5 (136.1, 138.8)	−12.8 (−14.1, −11.4)	143.0 (141.4, 144.6)	−7.3 (−8.9, −5.7)	−5.5 (−8.7, −2.4)	<0.0001‖
Month 6	136.8 (135.4, 138.2)	−13.5 (−14.8, −12.1)	142.0 (140.4, 143.7)	−8.2 (−9.9, −6.6)	−5.2 (−8.5, −1.9)	<0.0001‖

AHT indicates antihypertensive treatments; SBP, systolic blood pressure; and uRDN, ultrasound renal denervation.

*

Linear mixed regression model including baseline value, treatment arm, visit, and study as fixed effects.

†

Linear mixed regression model including baseline value, treatment arm, visit, study, and interaction term (treatment arm by visit) as fixed effects. *P* value for interaction (treatment arm by visit)=0.12.

‡

Linear mixed regression model including baseline value, treatment arm, visit, number of AHTs at visit, and study as fixed effects.

§

Linear mixed regression model including baseline value, treatment arm, visit, number of AHTs at visit, study, and interaction term (treatment arm by visit) as fixed effects. *P* value for interaction (treatment arm by visit)=0.11.

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P value adjusted for multiple comparisons (Tukey-Kramer).

In a linear mixed model further adjusting for AHT burden (which was greater in the sham group, especially among those with greater drops in BP, as shown in Table S7), the baseline-adjusted decrease in home SBP across the 6-month follow-up period was −5.4 mm Hg (95% CI, −6.8 to −4.0 mm Hg; *P*<0.0001; Table 5; Figure 2). A higher rate of BP control using a target home BP threshold <135/85 mm Hg was achieved with uRDN+AHT compared with sham+AHT during the 6 months of follow-up (41.5% [n=112/270] versus 26.9% [n=53/197]; *P*=0.004).

Reductions in office SBP changes were consistent across the 3 included trials (Figure 1), and there was no heterogeneity when tested using a study by treatment arm interaction term by

I^2 statistic. The baseline-adjusted decrease in office SBP at 6 months was similar in both groups without adjustment for differences in AHT, but greater with uRDN+AHT compared with sham+AHT in a linear mixed model adjusting for AHT (Table S8; Figure 2).

Subgroup and Multivariable Analyses

The between-group differences for changes in home SBP from baseline to 6 months were consistent across all tested subgroups, with slight variations in some subgroups (Figure S3). The effect of uRDN+AHT versus sham+AHT was robust in multivariable analysis; the only independent correlate of 6-month home SBP changes was higher home SBP at baseline (Table S9).

Safety Outcomes

There were a total of 17 site-reported adverse events of interest occurring within 6 months (8 in the uRDN group and 9 in the sham group; Table S10). These included one death in each group unrelated to procedure. There was one patient in the uRDN group with previously reported progression of unrecognized preexisting stenosis who underwent renal artery stenting before 6 months.[19] eGFR did not significantly change from baseline and was similar in both groups at 6 months (Table S11).

Discussion

Each of the 3 independently powered trials of the RADIANCE-HTN program[17] previously showed that uRDN safely reduced BP at 2 months versus a sham procedure in patients with mild to moderate hypertension off of medications[12,15] or with resistant hypertension on triple-drug fixed-dose combination therapy.[16] The current individual patient data (IPD) analysis further demonstrates that after initiating an SSAHT for hypertension control from the second month after the procedure onward, there was less addition of AHT in the uRDN group compared with sham, and after adjustment for this difference, the BP-lowering effect of uRDN compared with a sham procedure was maintained throughout the 6-month follow-up. Thus, after the initial demonstration of clear efficacy at 2 months in a pure comparison with a sham procedure, the overall magnitude of the BP-lowering effect of uRDN is incremental to and achievable with more medications, if they can be successfully implemented. These data emphasize the adjunctive role of uRDN as an option to lower BP with fewer medications rather than as a primary treatment option for hypertension.

The rationale for conducting a pooled analysis of IPD using repeated-measures analyses was to use all BP data and medication burden indices recorded at each monthly visit during the 6-month follow-up, when AHTs were sequentially added for BP control to characterize the intermediate-term durability of uRDN. The IPD analysis was valuable because it increased the sample size and thus the statistical power to detect smaller between-group differences, especially for dASBP, improved the precision of the estimate of the long-term BP-lowering effect of uRDN at 6 months, and allowed investigation into whether the observed effect of uRDN was consistent across various subgroups. We did not include the REQUIRE trial (Renal Denervation on Quality of 24-hr BP Control by Ultrasound In Resistant Hypertension)[28] on uRDN within this analysis. The lack of blinding of treating physicians, missing standardization of the uRDN procedure, and medication escalation favoring increased adherence in patients within the sham group[28] contributed to the unexpectedly large BP-lowering effect observed within the sham group of the REQUIRE trial.[29,30]

The clinical trial designs used to demonstrate the efficacy of uRDN required a 4-week stabilization of pharmacological therapy before randomization in either “off” medication or “on” medication designs, followed by randomization to either RDN or a sham procedure.[31,32] The evaluation of the primary BP-lowering efficacy end point occurred 2 months after the procedure (ie, 3 months after AHT stabilization), during which no antihypertensive medications were added except for BP escape purposes, to avoid the confounding effect of variable changes in background AHT.[18] In each of the trials, in case of persistence or recurrence of uncontrolled hypertension, a standardized medication escalation protocol was initiated from the second month through the fifth month, for safety, ethical, and regulatory reasons, aiming to control the BP of patients whose BP regimen had remained unchanged for 3 months. Although this trial design prioritizes patient safety and is recommended by consensus statements on trial design,[32] it presents a methodological challenge for demonstrating the durability of the BP-lowering effect of uRDN in conjunction with added AHT. This complexity of these study designs is increased further if there is an imbalance in the medications sequentially added by physicians during follow-up under continuous blinding. Such imbalance occurred in each of the 3 RADIANCE trials[19–21] and was confirmed in the pooled analysis, with a smaller change in AHT in the uRDN group compared with the sham group during 6 months of follow-up. Patients in the sham group with decreases in BP ≥10 mm Hg had even greater increments in medication burden compared with the uRDN group (Table S7). As expected, this imbalanced AHT escalation tended to gradually attenuate the BP difference between the uRDN and sham groups over time.[19–21] Indeed, in each single trial, the reductions of dASBP with uRDN+AHT versus sham+AHT at 6 months were smaller than those observed at 2 months, and no longer significant in RADIANCE-HTN TRIO and RADIANCE II, but they remained significant in RADIANCE-HTN SOLO.[19–21] Of note, in the 3 trials, the reductions of home SBP with uRDN+AHT versus sham+AHT at 6 months were similar to those observed at 2 months.

Both patients and investigators remained blinded to treatment allocation during SSAHT until 6 months. Despite less-intensified medication escalation in the uRDN group, the adjusted reduction in dASBP at 6 months was ≈3 mm Hg greater in the uRDN+AHT group than in the sham+AHT group, and ≈5 mm Hg greater in the uRDN+AHT group by home and office measurements after accounting for differences in number of medications given as AHT. Home BP measurements are known to be more reproducible than 24-hour ambulatory BP measurements,[33] and thus detected with greater accuracy the serial changes in BP in favor of uRDN. Witnessed medication intake immediately at the start of ambulatory BP measurements may have contributed to attenuate the difference in BP between the 2 groups by standardizing exposure to antihypertensive medications, which was not the case for home BP measurements. As per the study protocol, home BP measurements were obtained in the 7 days before an office visit; during the office visit, patients took prescribed AHTs as directly observed by the research teams, and then went home with the ambulatory BP-monitoring device. This greater BP-lowering effect observed in home BP readings led to a greater likelihood of patients achieving out-of-office BP control (<135/85 mm Hg) with uRDN+AHT as assessed with home BP versus ambulatory BP measurements.

Despite a greater sample size with pooling of IPD, multivariable analyses were unable to identify independent predictors of BP response after AHT titration through 6 months other than higher BP at baseline. The BP-lowering effect of uRDN+AHT was consistent across various subgroups of interest, including age, sex, and race. These results collectively confirm the durability of the BP-lowering effect of uRDN in conjunction with AHT.

Waterfall plots displaying individual BP changes across all patients demonstrated large between-subject variability in response to uRDN in conjunction with added AHT, with both uRDN and medications contributing to this variability. Such large between-subject variability in the BP response to uRDN was already present at 2 months for each of the RADIANCE-HTN trials, whether patients were off[12,15] or on[16] medications and may be attributable to variable involvement of prevailing renal sympathetic nerve activity and neural mechanisms to the pathophysiology of hypertension.[34] A similar and large between-subject variability of the BP response to AHT alone was also observed in the sham+AHT group at 6 months. Such variability in response to various antihypertensive medications has been consistently reported[35] and may reflect the variable involvement of the different BP-regulating pathways targeted by these medications or a variable adherence of patients to medications.[6,36]

The pooled IPD analysis from these 3 trials is also reassuring regarding the safety of uRDN. The incidence of safety outcomes, whether related or not to the procedure, remained low and did not increase between 2 and 6 months. No new renal artery stenosis ≥50% was reported. Based on these pooled results, the primary safety concerns surrounding the procedure appear largely related to the site of femoral artery access. Although longer-term safety needs to be established, late safety concerns have not been identified out to 36 months in RADIANCE-HTN SOLO[37] and 24 months in RADIANCE-HTN TRIO.[38] No safety concerns have emerged after >3 years of follow-up in the Global Symplicity Registry with radiofrequency-based RDN.[39]

Limitations

The current IPD analysis only combines data from trials out to 6 months of follow-up, although the maintenance of blinding to this point is an important strength. Additional follow-up from the included trials is planned to determine whether the BP-lowering effect and safety of uRDN continue to be durable in conjunction with additional AHT. Of note, in RADIANCE-HTN SOLO, 12-month BP measurements were no longer significant for dASBP; however, patients in the uRDN group were on fewer medications compared with sham.[40] This pooled analysis benefited from access to the large source of individual participant-level data from RADIANCE trials with standardized protocols, each of which showed a consistent BP-lowering effect of uRDN. However, we did not have access to the IPD of other RDN trials, especially of those of the SPYRAL program. Nonetheless, the SPYRAL trials had different designs; used a different strategy of renal nerve ablation of distal, main, and branches of the renal arteries with radiofrequency energy; did not standardize the background and added antihypertensive medications; and did not use home BP monitoring to assess the effect of RDN.

Next, there is no reliable procedural marker of successful uRDN, and as such, variability in treatment effect will likely affect the results of a uRDN procedure in an individual patient. Another limitation is applicability of the results of this IPD in the real-world setting. The majority of participants in these 3 studies were White or male, and the results may be less applicable to other patients, especially those with non-White race or ethnicity. Moreover, the strict experimental conditions of our blinded trials make it difficult to expand our results to the real-world setting when uRDN will be made available for treating patients routinely without exposing them to randomization to a sham procedure. Real-world data provided by the Global Symplicity Registry for the radiofrequency catheter show persistent BP-lowering effect of RDN for up to 3 years,[39] and the ongoing Global Paradise Registry (URL: https://www.clinicaltrials.gov; Unique identifier: NCT05027685) will provide real-world data for uRDN in the coming years.

Adjustment for medication burden represents adjustment for an after-randomization covariate. However, using all available data in a repeated-measures framework was necessary to try to isolate BP-lowering effects from clear imbalances in the AHT prescribed between the 2 treatment arms.

The results of this IPD analysis of 506 patients who underwent either uRDN or a sham procedure in high-quality blinded trials demonstrate a maintained BP-lowering effect of uRDN at 6 months, together with an added AHT. The protocolized escalation of AHT resulted in a similar dASBP reduction at 6 months in both the uRDN and the sham groups, with fewer additional AHTs required in the uRDN group. uRDN is an additional option to treat patients with uncontrolled hypertension with fewer AHTs rather than as a primary treatment option for hypertension.

Article Information

Supplemental Material

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

Population Definition

Multivariable Analysis

Tables S1–S11

Figures S1–S3

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References

1.

Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1923–1994. doi: 10.1016/S0140-6736(18)32225-6 Crossref. PubMed.

2.

Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957–967. doi: 10.1016/S0140-6736(15)01225-8 Crossref. PubMed.

3.

Rahimi K, Bidel Z, Nazarzadeh M, Copland E, Canoy D, Ramakrishnan R, Pinho-Gomes A-C, Woodward M, Adler A, Agodoa Let al. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet*. 2021;397:1625–1636. doi: 10.1016/S0140-6736(21)00590-0 Crossref. PubMed.

4.

Carey RM, Muntner P, Bosworth HB, Whelton PK. Prevention and control of hypertension: JACC Health Promotion Series. *J Am Coll Cardiol*. 2018;72:1278–1293. doi: 10.1016/j.jacc.2018.07.008 Crossref. PubMed.

5.

Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA, Gregg EW, Bennett JE, Solomon B, Singleton RK, et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. 2021;398:957–980. doi: 10.1016/S0140-6736(21)01330-1 Crossref. PubMed.

6.

Choudhry NK, Kronish IM, Vongpatanasin W, Ferdinand KC, Pavlik VN, Egan BM, Schoenthaler A, Houston Miller N, Hyman DJ; American Heart Association Council on Hypertension; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Medication adherence and blood pressure control: a scientific statement from the American Heart Association. *Hypertension*. 2022;79:e1–e14. doi: 10.1161/HYP.0000000000000203 Crossref. PubMed.

7.

Egan BM, Zhao Y, Li J, Brzezinski WA, Todoran TM, Brook RD, Calhoun DA. Prevalence of optimal treatment regimens in patients with apparent treatment-resistant hypertension based on office blood pressure in a community-based practice network. *Hypertension*. 2013;62:691–697. doi: 10.1161/HYPERTENSIONAHA.113.01448 Crossref. PubMed.

8.

Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, Lorenza Muiesan M, Tsioufis K, Agabiti-Rosei E, Abd Elhady Algharably E, et al. 2023 ESH Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). *J Hypertens*. 2023;41:1874–2071. doi: 10.1097/HJH.0000000000003480 Crossref. PubMed.

9.

Barbato E, Azizi M, Schmieder RE, Lauder L, Böhm M, Brouwers S, Bruno RM, Dudek D, Kahan T, Kandzari DE, et al. Renal denervation in the management of hypertension in adults: a clinical consensus statement of the ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2023;44:1313–1330. doi: 10.1093/eurheartj/ehad054 Crossref. PubMed.

10.

Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, Midulla M, Mounier-Véhier C, Courand P-Y, Lantelme P, et al; Renal Denervation for Hypertension (DENERHTN) investigators. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet*. 2015;385:1957–1965. doi: 10.1016/S0140-6736(14)61942-5 Crossref. PubMed.

11.

Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, et al; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370:1393–1401. doi: 10.1056/NEJMoa1402670 Crossref. PubMed.

12.

Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, Basile J, Kirtane AJ, Wang Y, Lobo MD, et al; RADIANCE-HTN Investigators. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet*. 2018;391:2335–2345. doi: 10.1016/S0140-6736(18)31082-1 Crossref. PubMed.

13.

Böhm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE, Tsioufis K, Pocock S, Konstantinidis D, Choi JW, et al; SPYRAL HTN-OFF MED Pivotal Investigators. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet*. 2020;395:1444–1451. doi: 10.1016/S0140-6736(20)30554-7 Crossref. PubMed.

14.

Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, Tsioufis K, Tousoulis D, Choi JW, East C, et al; SPYRAL HTN-ON MED Trial Investigators. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet*. 2018;391:2346–2355. doi: 10.1016/S0140-6736(18)30951-6 Crossref. PubMed.

15.

Azizi M, Saxena M, Wang Y, Jenkins JS, Devireddy C, Rader F, Fisher NDL, Schmieder RE, Mahfoud F, Lindsey J, et al; RADIANCE II Investigators and Collaborators. Endovascular ultrasound renal denervation to treat hypertension. *JAMA*. 2023;329:651–661. doi: 10.1001/jama.2023.0713 Crossref. PubMed.

16.

Azizi M, Sanghvi K, Saxena M, Gosse P, Reilly JP, Levy T, Rump LC, Persu A, Basile J, Bloch MJ, et al; RADIANCE-HTN investigators. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. *Lancet*. 2021;397:2476–2486. doi: 10.1016/S0140-6736(21)00788-1 Crossref. PubMed.

17.

Kirtane AJ, Sharp ASP, Mahfoud F, Fisher NDL, Schmieder RE, Daemen J, Lobo MD, Lurz P, Basile J, Bloch MJ, et al. Patient-level pooled analysis of ultrasound renal denervation in the sham-controlled RADIANCE II, RADIANCE-HTN SOLO, and RADIANCE-HTN TRIO Trials. *JAMA Cardiol*. 2023;8:464–473. doi: 10.1001/jamacardio.2023.0338 Crossref. PubMed.

18.

Kandzari DE, Mahfoud F, Bhatt DL, Böhm M, Weber MA, Townsend RR, Hettrick DA, Schmieder RE, Tsioufis K, Kario K. Confounding factors in renal denervation trials: Revisiting old and identifying new challenges in trial design of device therapies for hypertension. *Hypertension*. 2020;76:1417. doi: 10.1161/HYPERTENSIONAHA.120.15745 Crossref. PubMed.

19.

Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Lobo MD, Sharp ASP, Bloch MJ, Basile J, Wang Y, et al; RADIANCE-HTN Investigators. Six-month results of treatment-blinded medication titration for hypertension control after randomization to endovascular ultrasound renal denervation or a sham procedure in the RADIANCE-HTN SOLO trial. *Circulation*. 2019;139:2542–2553. doi: 10.1161/CIRCULATIONAHA.119.040451 Crossref. PubMed.

20.

Azizi M, Mahfoud F, Weber MA, Sharp ASP, Schmieder RE, Lurz P, Lobo MD, Fisher NDL, Daemen J, Bloch MJ, et al. Effects of renal denervation vs sham in resistant hypertension after medication escalation: prespecified analysis at 6 months of the RADIANCE-HTN TRIO randomized clinical trial. *JAMA Cardiol*. 2022;7:1244–1252. doi: 10.1001/jamacardio.2022.3904 Crossref. PubMed.

21.

Azizi M, Saxena M, Wang Y, Devireddy C, Jenkins J, Fisher N, Schmieder R, Mahfoud F, Lindsey J, Rader F. Endovascular ultrasound renal denervation to treat uncontrolled hypertension: 6-month results following blinded medication titration in the randomized, sham-controlled RADIANCE II Pivotal Trial. *JACC*. 2023;82(17_Supplement):B159. doi: 10.1016/j.jacc.2023.09.406 Crossref.

22.

Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2018;138:e426–e483. doi: 10.1161/CIR.0000000000000597 Crossref. PubMed.

23.

Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–3104. doi: 10.1093/eurheartj/ehy339 Crossref. PubMed.

24.

Mauri L, Kario K, Basile J, Daemen J, Davies J, Kirtane AJ, Mahfoud F, Schmieder RE, Weber M, Nanto S, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: the RADIANCE-HTN and REQUIRE clinical study designs. *Am Heart J*. 2018;195:115–129. doi: 10.1016/j.ahj.2017.09.006 Crossref. PubMed.

25.

WHO Collaborating Centre for Drug Statistics Methodology. Use of ATC/DDD. Published 2023. Accessed July 30, 2023. https://www.whocc.no/use_of_atc_ddd

26.

Wan S-H, Hart M, Hajjar I. A novel measurement index for antihypertensive medication burden and its use. *Hypertension*. 2009;54:e135–e136. doi: 10.1161/HYPERTENSIONAHA.109.140681 Crossref. PubMed.

27.

Hua H, Burke DL, Crowther MJ, Ensor J, Tudur Smith C, Riley RD. One-stage individual participant data meta-analysis models: estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information. *Stat Med*. 2017;36:772–789. doi: 10.1002/sim.7171 Crossref. PubMed.

28.

Kario K, Yokoi Y, Okamura K, Fujihara M, Ogoyama Y, Yamamoto E, Urata H, Cho J-M, Kim C-J, Choi S-H, et al. Catheter-based ultrasound renal denervation in patients with resistant hypertension: the randomized, controlled REQUIRE trial. *Hypertens Res*. 2022;45:221–231. doi: 10.1038/s41440-021-00754-7 Crossref. PubMed.

29.

Kario K, Kai H, Nanto S, Yokoi H. Anti-hypertensive medication adherence in the REQUIRE trial: post-hoc exploratory evaluation. *Hypertens Res*. 2023;46:2044–2047. doi: 10.1038/s41440-023-01333-8 Crossref. PubMed.

30.

Lauder L, Mahfoud F. Adherence to antihypertensive medication in renal denervation trials: new studies, old problems? *Hypertens Res*. 2023;46:2543–2544. doi: 10.1038/s41440-023-01389-6 Crossref. PubMed.

31.

Mahfoud F, Azizi M, Ewen S, Pathak A, Ukena C, Blankestijn PJ, Böhm M, Burnier M, Chatellier G, Durand Zaleski I, et al. Proceedings from the 3rd European Clinical Consensus Conference for clinical trials in device-based hypertension therapies. *Eur Heart J*. 2020;41:1588–1599. doi: 10.1093/eurheartj/ehaa121 Crossref. PubMed.

32.

Kandzari DE, Mahfoud F, Weber MA, Townsend R, Parati G, Fisher NDL, Lobo MD, Bloch M, Böhm M, Sharp ASP, et al. Clinical trial design principles and outcomes definitions for device-based therapies for hypertension: a consensus document from the Hypertension Academic Research Consortium. *Circulation*. 2022;145:847–863. doi: 10.1161/CIRCULATIONAHA.121.057687 Crossref. PubMed.

33.

Stergiou GS, Palatini P, Parati G, O'Brien E, Januszewicz A, Lurbe E, Persu A, Mancia G, Kreutz R; European Society of Hypertension Council and the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. 2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement. *J Hypertens*. 2021;39:1293–1302. doi: 10.1097/HJH.0000000000002843 Crossref. PubMed.

34.

Esler M. Renal denervation for hypertension: observations and predictions of a founder. *Eur Heart J*. 2014;35:1178–1185. doi: 10.1093/eurheartj/ehu091 Crossref. PubMed.

35.

Sundström J, Lind L, Nowrouzi S, Hagström E, Held C, Lytsy P, Neal B, Marttala K, Östlund O. Heterogeneity in blood pressure response to 4 antihypertensive drugs: a randomized clinical trial. *JAMA*. 2023;329:1160–1169. doi: 10.1001/jama.2023.3322 Crossref. PubMed.

36.

Burnier M, Egan BM. Adherence in hypertension. *Circ Res*. 2019;124:1124–1140. doi: 10.1161/CIRCRESAHA.118.313220 Crossref. PubMed.

37.

Rader F, Kirtane AJ, Wang Y, Daemen J, Lurz P, Sayer J, Saxena M, Levy T, Scicli AP, Thackeray L, et al. Durability of blood pressure reduction after ultrasound renal denervation: three-year follow-up of the treatment arm of the randomised RADIANCE-HTN SOLO trial. *EuroIntervention*. 2022;18:e677–e685. doi: 10.4244/EIJ-D-22-00305 Crossref. PubMed.

38.

Bloch M, Kirtane A, Mahfoud F, Azizi M, Basile J, Daemen J, Saxena M, Godde P, Sanghvi K, Schmeider R. TCT-12 Twenty-four month results in patients with resistant hypertension after endovascular ultrasound renal denervation in the RADIANCE-HTN TRIO trial. *J Am Coll Cardiol*. 2022;80(12 Suppl):B85–B86. Crossref.

39.

Mahfoud F, Böhm M, Schmieder R, Narkiewicz K, Ewen S, Ruilope L, Schlaich M, Williams B, Fahy M, Mancia G. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY registry. *Eur Heart J*. 2019;40:3474–3482. doi: 10.1093/eurheartj/ehz118 Crossref. PubMed.

40.

Azizi M, Daemen J, Lobo MD, Mahfoud F, Sharp ASP, Schmieder RE, Wang Y, Saxena M, Lurz P, Sayer J, et al; RADIANCE-HTN Investigators. 12-Month results from the unblinded phase of the RADIANCE-HTN SOLO trial of ultrasound renal denervation. *JACC Cardiovasc Interv*. 2020;13:2922–2933. doi: 10.1016/j.jcin.2020.09.054 Crossref. PubMed.