HIGH TECH MARSEILLE

ÉDITION 2023

1·2·3 FÉVRIER

MARSEILLE•PALAIS DU PHARO

Les études qui pourraient changer la pratique

RADIANCE II / HTN3

B.Honton - MD
Clinique Pasteur -Toulouse

How to devellop … ?

Phase 1	FIM / Pathophysiology	*Understand*
Phase 2	Small Trials	*Redefine*
Phase 3	RCT	*Prove*
Phase 4	Registry	*Expand*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Fleck, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Mingkei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators*

ABSTRACT

BACKGROUND

Prior unblinded studies have suggested that catheter-based renal-artery denervation reduces blood pressure in patients with resistant hypertension.

METHODS

We designed a prospective, single-blind, randomized, sham-controlled trial. Patients with severe resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure. Before randomization, patients were receiving a stable antihypertensive regimen involving maximally tolerated doses of at least three drugs, including a diuretic. The primary efficacy end point was the change in office systolic blood pressure at 6 months; a secondary efficacy end point was the change in mean 24-hour ambulatory systolic blood pressure. The primary safety end point was a composite of death, end-stage renal disease, embolic events resulting in end-organ damage, renovascular complications, or hypertensive crisis at 1 month or new renal-artery stenosis of more than 70% at 6 months.

RESULTS

A total of 535 patients underwent randomization. The mean (±SD) change in systolic blood pressure at 6 months was −14.13±23.93 mm Hg in the denervation group as compared with −11.74±25.94 mm Hg in the sham-procedure group (P<0.001 for both comparisons of the change from baseline), for a difference of −2.39 mm Hg (95% confidence interval [CI], −6.89 to 2.12; P=0.26 for superiority with a margin of 5 mm Hg). The change in 24-hour ambulatory systolic blood pressure was −6.75±15.11 mm Hg in the denervation group and −4.79±17.25 mm Hg in the sham-procedure group, for a difference of −1.96 mm Hg (95% CI, −4.97 to 1.06; P=0.98 for superiority with a margin of 2 mm Hg). There were no significant differences in safety between the two groups.

CONCLUSIONS

This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPLICITY HTN-3 ClinicalTrials.gov number, NCT01418261.)

From Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School (D.L.B., L.M.), Boston University School of Public Health (R.D.), and Harvard Clinical Research Institute (R.D., L.M.) — all in Boston; Piedmont Heart Institute, Atlanta (D.E.K.); the Division of Cardiology, Henry Ford Hospital (W.W.O.), and Wayne State University and the Detroit Medical Center (J.M.F.) — all in Detroit; Baptist Cardiac and Vascular Institute, Miami (B.T.K.); New York Presbyterian Hospital, Columbia University Medical Center, and Cardiovascular Research Foundation, New York (M.B.L.); Medtronic Cardiovascular, Santa Rosa, CA (M.L., M.N., S.A.C.); University of Alabama at Birmingham, Birmingham (S.O.); Prairie Heart Institute, Springfield, IL (K.R.-S.); Perelman School of Medicine, University of Pennsylvania, Philadelphia (S.A.C., R.R.T.); and University of Chicago Medicine, Chicago (G.L.B.). Address reprint requests to Dr. Bhatt at Brigham and Women's Hospital Heart and Vascular Center, 75 Francis St., Boston, MA 02115, or at dlbhattmd@post.harvard.edu.

*A complete list of investigators in the SYMPLICITY HTN-3 trial is provided in the Supplementary Appendix, available at NEJM.org.

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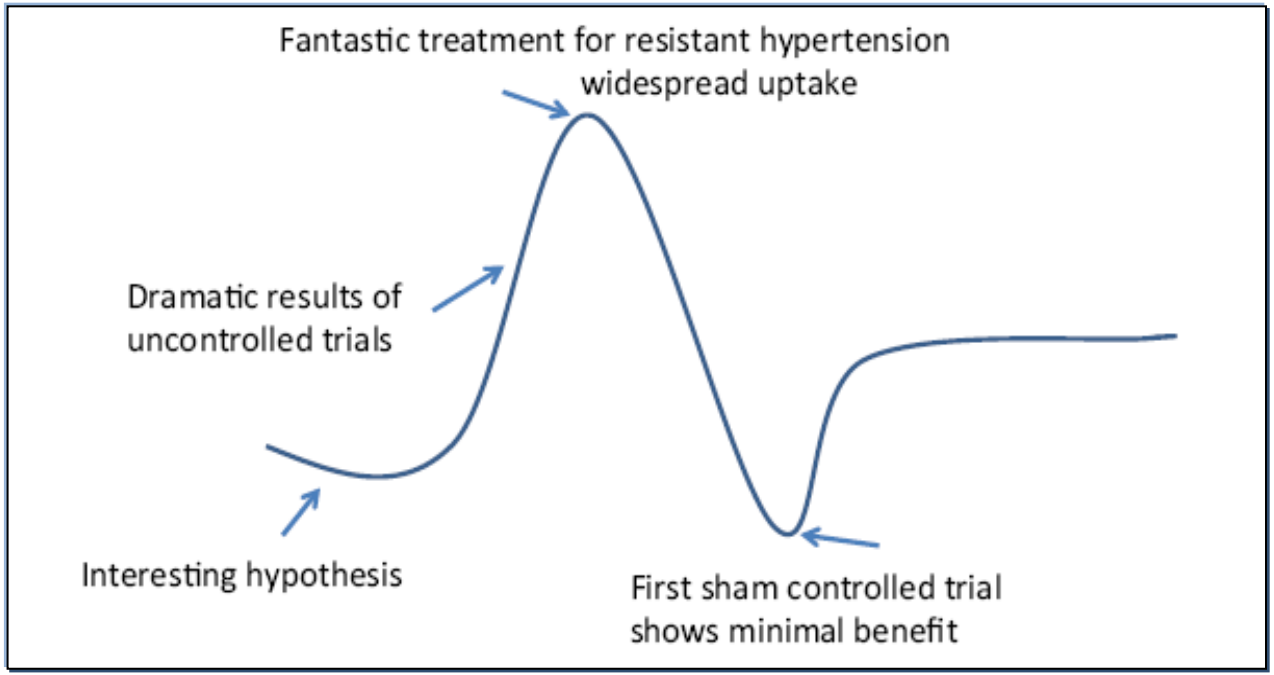
Bhatt et al. *NEJM* 2014

How to (re)PROVE … ?



PHASE HYBRIDE 1-3 RCT TO UNDERSTAND

How to (re)PROVE … ?

HIGH TECH MARSEILLE

Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial

Michael Böhm, Kazuomi Kario, David E Kandzari, Felix Mahfoud, Michael A Weber, Roland E Schmieder, Konstantinos Tsioufis, Stuart Pocock, Dimitris Konstantinidis, James W Choi, Cara East, David P Lee, Adrian Ma, Sebastian Ewen, Debbie L Cohen, Robert Wilensky, Chandan M Devireddy, Janice Lea, Axel Schmid, Joachim Weil, Tolga Agdirlioglu, Denise Reedus, Brian K Jefferson, David Reyes, Richard D'Souza, Andrew S P Sharp, Faisal Sharif, Martin Fahy, Vanessa DeBruin, Sidney A Cohen, Sandeep Brar, Raymond R Townsend, on behalf of the SPYRAL HTN-OFF MED Pivotal Investigators*

Summary

Background Catheter-based renal denervation has significantly reduced blood pressure in previous studies. Following a positive pilot trial, the SPYRAL HTN-OFF MED (SPYRAL Pivotal) trial was designed to assess the efficacy of renal denervation in the absence of antihypertensive medications.

Methods In this international, prospective, single-blinded, sham-controlled trial, done at 44 study sites in Australia, Austria, Canada, Germany, Greece, Ireland, Japan, the UK, and the USA, hypertensive patients with office systolic blood pressure of 150 mm Hg to less than 180 mm Hg were randomly assigned 1:1 to either a renal denervation or sham procedure. The primary efficacy endpoint was baseline-adjusted change in 24-h systolic blood pressure and the secondary efficacy endpoint was baseline-adjusted change in office systolic blood pressure from baseline to 3 months after the procedure. We used a Bayesian design with an informative prior, so the primary analysis combines evidence from the pilot and Pivotal trials. The primary efficacy and safety analyses were done in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, NCT02439749.

Findings From June 25, 2015, to Oct 15, 2019, 331 patients were randomly assigned to either renal denervation (n=166) or a sham procedure (n=165). The primary and secondary efficacy endpoints were met, with posterior probability of superiority more than 0·999 for both. The treatment difference between the two groups for 24-h systolic blood pressure was –3·9 mm Hg (Bayesian 95% credible interval –6·2 to –1·6) and for office systolic blood pressure the difference was –6·5 mm Hg (–9·6 to –3·5). No major device-related or procedural-related safety events occurred up to 3 months.

Interpretation SPYRAL Pivotal showed the superiority of catheter-based renal denervation compared with a sham procedure to safely lower blood pressure in the absence of antihypertensive medications.

Funding Medtronic.

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*Investigators are listed in the appendix pp 4–9

Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Homburg (Saar), Germany (Prof M Böhm MD, Prof F Mahfoud MD, S Ewen MD); Jichi Medical University School of Medicine, Tochigi, Japan (Prof K Kario MD); Piedmont Heart Institute, Atlanta, GA, USA (D E Kandzari MD, D Reedus DNP); Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA (Prof F Mahfoud); SUNY Downstate College of Medicine, Brooklyn, NY, USA (Prof M A Weber MD); Universitätsklinikum Erlangen, Erlangen, Germany (Prof R E Schmieder MD, A Schmid MD); National and Kapodistrian University of Athens, Hippocratio Hospital, Athens, Greece (K Tsioufis MD, D Konstantinidis MD); London School of Hygiene & Tropical Medicine, London, UK (S Pocock PhD); Baylor Scott and White Heart and Vascular Hospital, Dallas, TX, USA (J W Choi MD, C East MD); Stanford Hospital and Clinics, Stanford, CA, USA (D P Lee MD, A Ma MD); Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA (D L Cohen MD, R Wilensky MD, S A Cohen MD, Prof R R Townsend MD); Emory University School of Medicine, Atlanta, GA, USA (C M Devireddy MD, J Lea MD); Sana Cardiomed Heart Center, Lübeck, Germany

Introduction

Catheter-based renal denervation is intended to lower blood pressure by reducing sympathetic activity through renal nerve ablation.[1] Although significant blood pressure reductions were observed in early proof of concept studies,[2,3] the results from the randomised, sham-controlled trial Symplicity HTN-3 in patients with uncontrolled hypertension despite multidrug treatment regimens showed significant blood pressure reduction in both the treatment and control groups versus baseline, but no significant difference between groups.[4] Analysis of the trial data indicated that variations in procedural methods as well as changes in medication use after randomisation might have diminished the ability of the trial to distinguish the effects of renal denervation.[5] To address these concerns, smaller sham-controlled, randomised trials were designed to assess whether catheter-based renal denervation is effective in hypertensive patients with and without antihypertensive medications.[6] Results from these trials showed proof of concept of catheter-based renal denervation to reduce blood pressure in the absence and presence of antihypertensive medications.[7,8]

The SPYRAL HTN-OFF MED (SPYRAL Pivotal) trial is a randomised, sham-controlled trial statistically powered to assess the efficacy of catheter-based renal denervation in the absence of antihypertensive medications.[9] This analysis uses a Bayesian study design to combine data from this trial (n=251) with an informative prior from the previous randomised pilot trial (n=80) to constitute the overall primary analysis population of 331 randomly assigned patients.

Methods

Study design

The SPYRAL Pivotal trial is a multicentre, international, prospective, single-blind, randomised, sham-controlled

Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial

Michel Azizi*, Roland E Schmieder, Felix Mahfoud, Michael A Weber, Joost Daemen, Justin Davies, Jan Basile, Ajay J Kirtane, Yale Wang, Melvin D Lobo, Manish Saxena, Lida Feyz, Florian Rader, Philipp Lurz, Jeremy Sayer, Marc Sapoval, Terry Levy, Kintur Sanghvi, Josephine Abraham, Andrew S P Sharp, Naomi D L Fisher, Michael J Bloch, Helen Reeve-Stoffer, Leslie Coleman, Christopher Mullin, Laura Mauri*, on behalf of the RADIANCE-HTN Investigators†

Summary

Background Early studies suggest that radiofrequency-based renal denervation reduces blood pressure in patients with moderate hypertension. We investigated whether an alternative technology using endovascular ultrasound renal denervation reduces ambulatory blood pressure in patients with hypertension in the absence of antihypertensive medications.

Methods RADIANCE-HTN SOLO was a multicentre, international, single-blind, randomised, sham-controlled trial done at 21 centres in the USA and 18 in Europe. Patients with combined systolic–diastolic hypertension aged 18–75 years were eligible if they had ambulatory blood pressure greater than or equal to 135/85 mm Hg and less than 170/105 mm Hg after a 4-week discontinuation of up to two antihypertensive medications and had suitable renal artery anatomy. Patients were randomised (1:1) to undergo renal denervation with the Paradise system (ReCor Medical, Palo Alto, CA, USA) or a sham procedure consisting of renal angiography only. The randomisation sequence was computer generated and stratified by centres with randomised blocks of four or six and permutation of treatments within each block. Patients and outcome assessors were blinded to randomisation. The primary effectiveness endpoint was the change in daytime ambulatory systolic blood pressure at 2 months in the intention-to-treat population. Patients were to remain off antihypertensive medications throughout the 2 months of follow-up unless specified blood pressure criteria were exceeded. Major adverse events included all-cause mortality, renal failure, an embolic event with end-organ damage, renal artery or other major vascular complications requiring intervention, or admission to hospital for hypertensive crisis within 30 days and new renal artery stenosis within 6 months. This study is registered with ClinicalTrials.gov, number NCT02649426.

Findings Between March 28, 2016, and Dec 28, 2017, 803 patients were screened for eligibility and 146 were randomised to undergo renal denervation (n=74) or a sham procedure (n=72). The reduction in daytime ambulatory systolic blood pressure was greater with renal denervation (–8·5 mm Hg, SD 9·3) than with the sham procedure (–2·2 mm Hg, SD 10·0; baseline-adjusted difference between groups: –6·3 mm Hg, 95% CI –9·4 to –3·1, p=0·0001). No major adverse events were reported in either group.

Interpretation Compared with a sham procedure, endovascular ultrasound renal denervation reduced ambulatory blood pressure at 2 months in patients with combined systolic–diastolic hypertension in the absence of medications.

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See Comment page 2298

*Contributed equally

†The complete list of study investigators and study committee members is available in the appendix

Université Paris-Descartes, Paris, France (Prof M Azizi MD, Prof M Sapoval MD); Hypertension Department and DHU PARC (Prof M Azizi) and Vascular and Oncological Interventional Radiology Department (Prof M Sapoval), Hôpital Européen Georges-Pompidou, AP-HP, Paris, France; INSERM CIC1418, Paris, France (Prof M Azizi); Nephrology and Hypertension, University Hospital Erlangen, Friedrich Alexander University, Erlangen, Germany (Prof R E Schmieder MD); Klinik für Innere Medizin III, Saarland University Hospital, Homburg, Germany (Prof F Mahfoud MD); Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA (Prof F Mahfoud); Division of Cardiovascular Medicine, State University of New York, Downstate Medical Center, New York, NY, USA (Prof M A Weber MD); Erasmus MC Thoraxcenter, Rotterdam, NL, Netherlands (J Daemen MD, L Feyz MD); Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK (J Davies MBBS); Seinsheimer Cardiovascular Health Program, Medical University of South Carolina,

Introduction

Targeted endovascular catheter-based denervation of the renal efferent and afferent nerves with minimally invasive approaches has been investigated as a novel blood pressure lowering treatment for resistant hypertension.[1] Although in initial randomised trials, catheter-directed radiofrequency ablation was associated with blood pressure reduction,[2,3] a subsequent sham-controlled study did not show improvement in blood pressure control.[4]

Several features of this sham-controlled trial might have limited its ability to show blood pressure reduction following renal denervation.[5] These include uncertainty regarding the completeness of denervation, variable adherence to antihypertensive medications among patients during follow-up, and a population including patients with isolated systolic hypertension or substantial vascular stiffness that might be difficult to reverse.[6,7] Subsequently, trials have been designed with more attention to procedural technique and the inclusion of patients with less severe hypertension in order to examine the blood pressure lowering efficacy of catheter-based renal denervation in the absence of antihypertensive medications.[5,8] The results of one such study support the ability of renal denervation with a multielectrode radiofrequency ablation device to reduce blood pressure.[9]

How to expand : RADIANCE II - Pivotal Trial

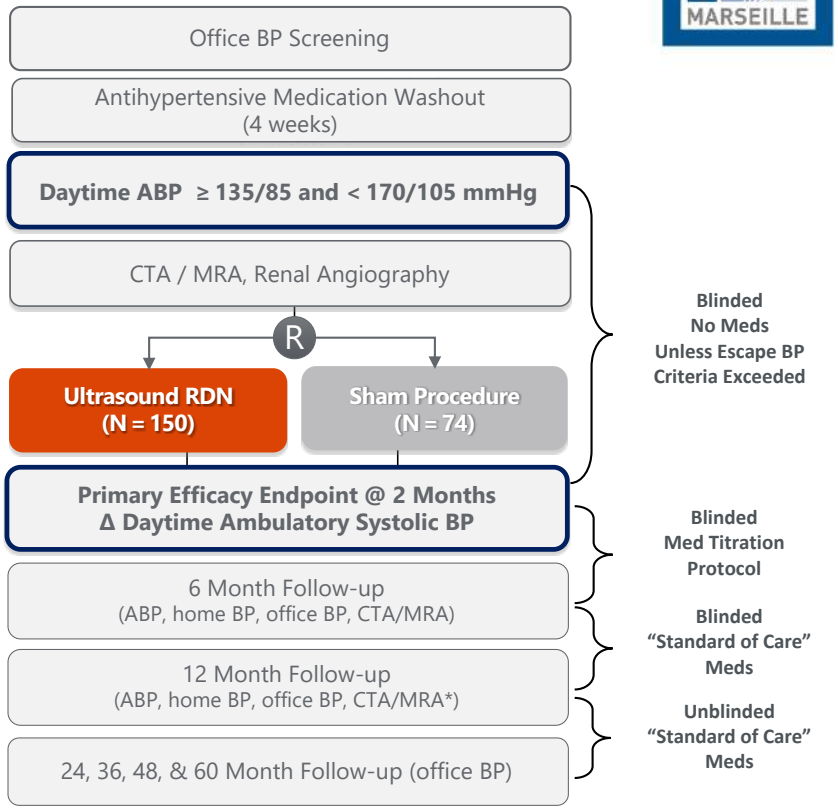
Blinded, 2:1 randomized, sham-controlled study

Objective:
Demonstrate the effectiveness and safety of the Paradise™ Ultrasound RDN System in subjects with Stage 2 hypertension on 0-2 anti-hypertensive medications of different classes at the time of consent. Prior to randomization, subjects will be hypertensive in the absence of hypertension medication.

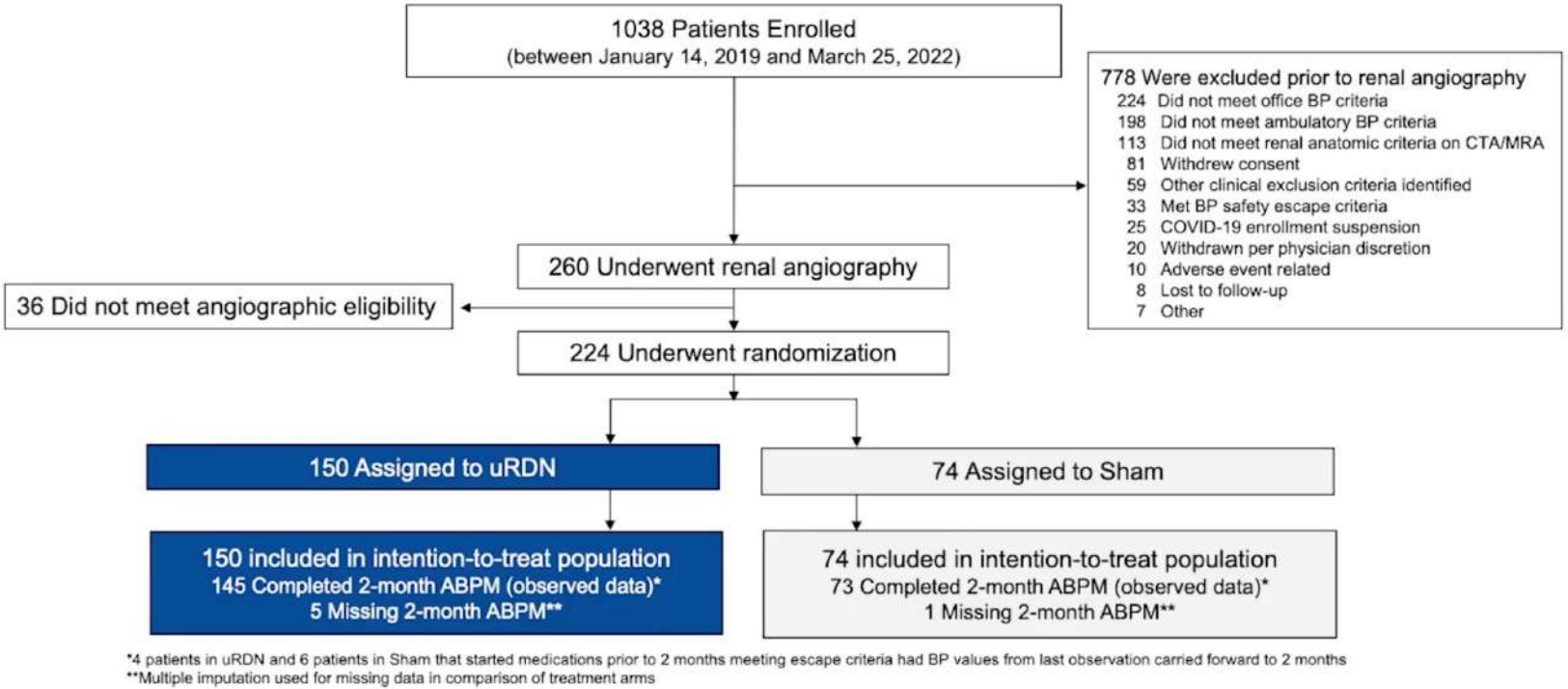
Key Entry Criteria:

- Uncontrolled hypertension on 0-2 anti-HTN meds with a history of medication treatment
- Off-medication daytime ABP ≥ 135/85 and < 170/105 mmHg
- Age 18-75 years
- No prior cardiovascular or cerebrovascular events
- No Type I or uncontrolled Type II diabetes
- eGFR ≥ 40mL/min/m^2
- Eligible renal artery anatomy

Escape BP criteria:
- Home BP≥170/105 mmHg / Office BP≥180/110 mmHg with clinical symptoms



RADIANCE II : Patient Flow

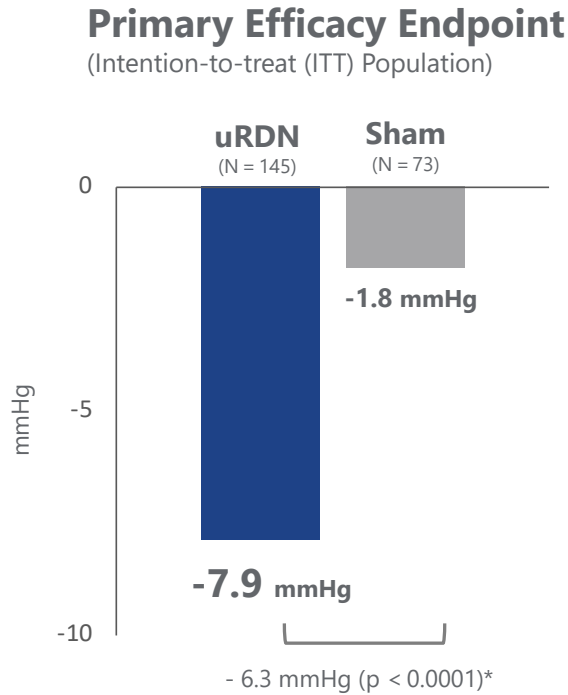


*4 patients in uRDN and 6 patients in Sham that started medications prior to 2 months meeting escape criteria had BP values from last observation carried forward to 2 months
**Multiple imputation used for missing data in comparison of treatment arms

RADIANCE II : Baseline characteritics

	uRDN (N=150)	Sham (N=74)
Age (years)	55.1 ± 9.9	54.9 ± 7.9
Female sex, % (N)	31.3% (47)	23.0% (17)
Race, % (N)		
White	76.0% (114)	75.7% (56)
Black	14.0% (21)	20.3% (15)
Other	10.0% (15)	4.1% (3)
Body mass index - kg/m^2	30.1 ± 5.2	30.6 ± 5.2
eGFR - $ml/min/1.73m^2$	81.4 ± 14.4	82.3 ± 14.9
Type 2 Diabetes, % (N)	6.0% (9)	6.8% (5)
Sleep apnea, % (N)	14.0% (21)	17.6% (13)
Prior Hospitalization for hypertensive crisis, % (N)	6.0% (9)	4.1% (3)
Office Blood Pressure		
SBP (mmHg)	155.8 ± 11.1	154.3 ± 10.6
DBP (mmHg)	101.3 ± 6.7	99.1 ± 5.6
Number of Anti-hypertensive Medications	0.9 ± 0.8	1.1 ± 0.9

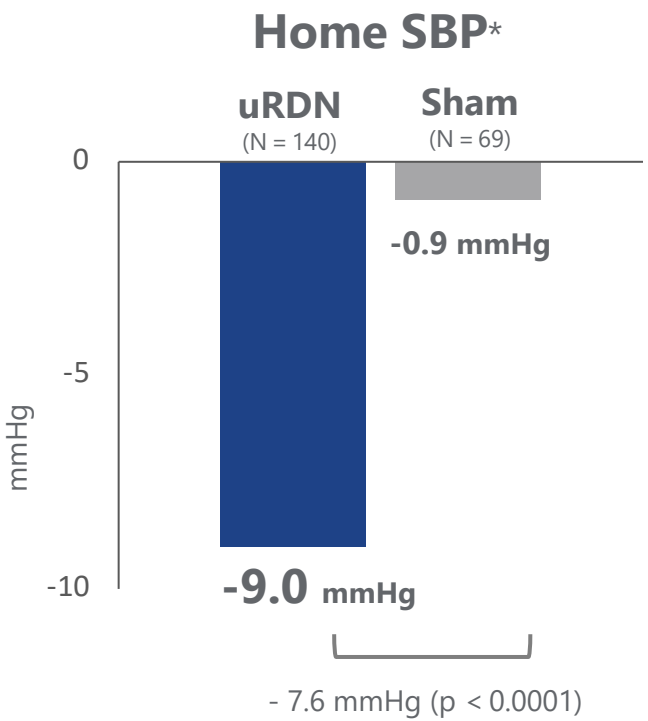
RADIANCE II : Primary efficacy Endpoint Systolic BP ABPM

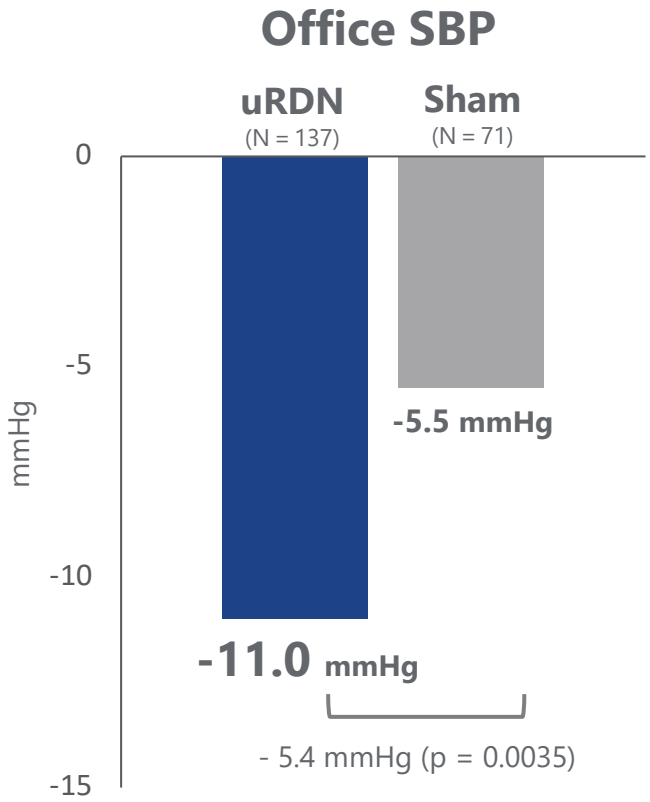


Achieved Significant Blood Pressure Reductions in Patients with Mild-to-Moderate Hypertension

* P<0.0001 using observed values or multiple imputation
The individual group changes are based on observed values and the between group difference includes multiple imputations for missing values (uRDN N=150, Sham N=74).

RADIANCE II : Secondary Endpoint



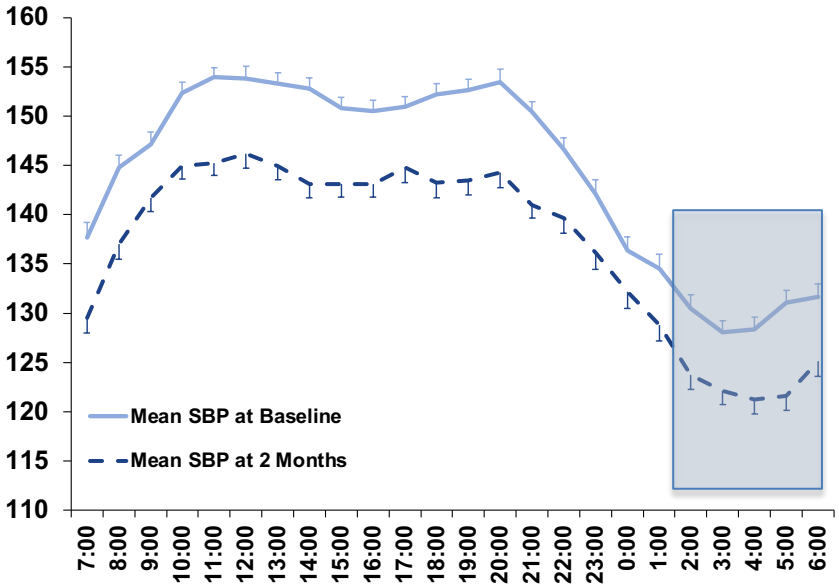


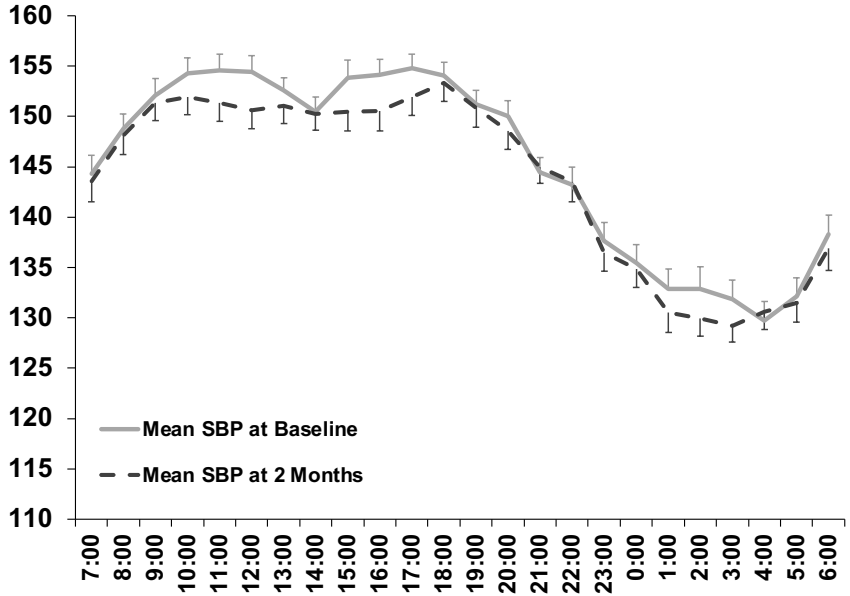
RADIANCE II : ABPM profile

Mean Between Group Difference

24h Ambulatory SBP
-6.2 mmHg
P<0.0001

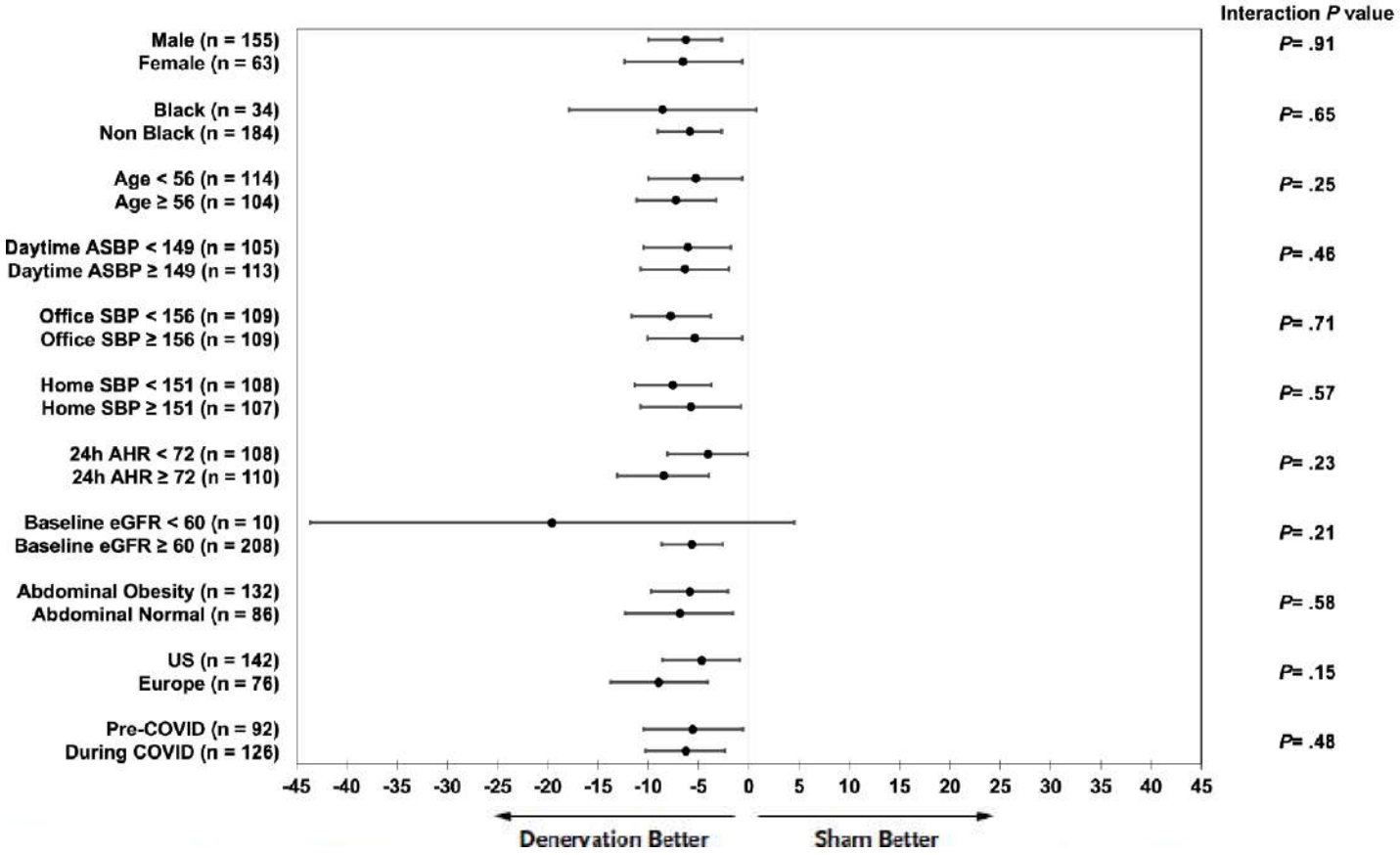
Nighttime Ambulatory SBP
-5.8 mmHg
P=0.0004



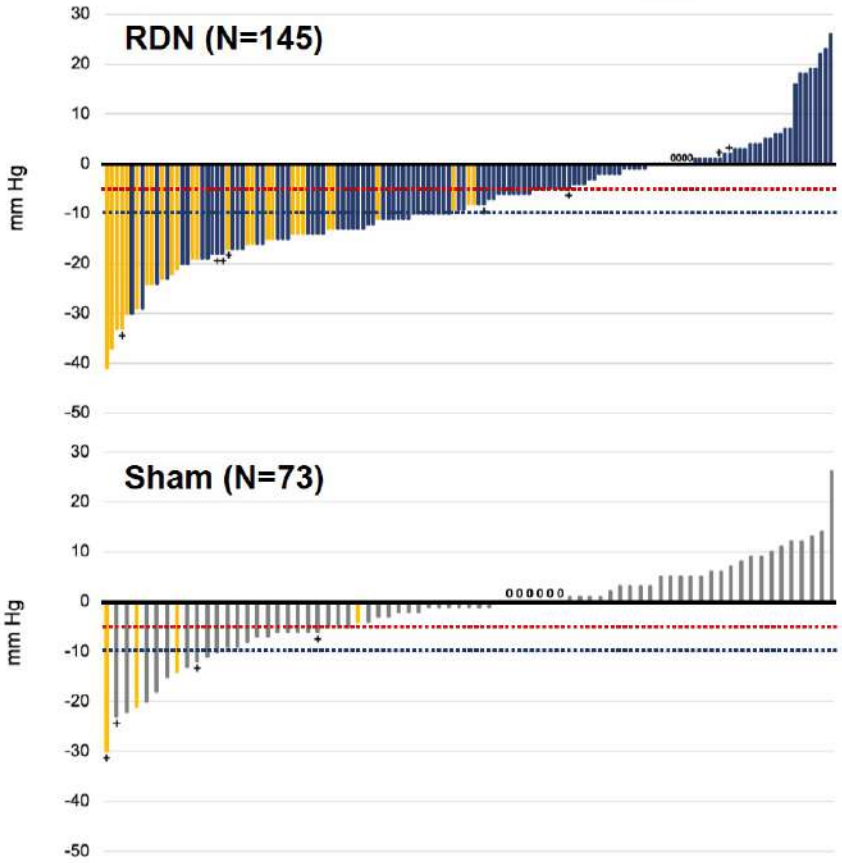


Morning Surge

RADIANCE II : Subgroup analysis



RADIANCE II : Individual responses and controlled proportion patient

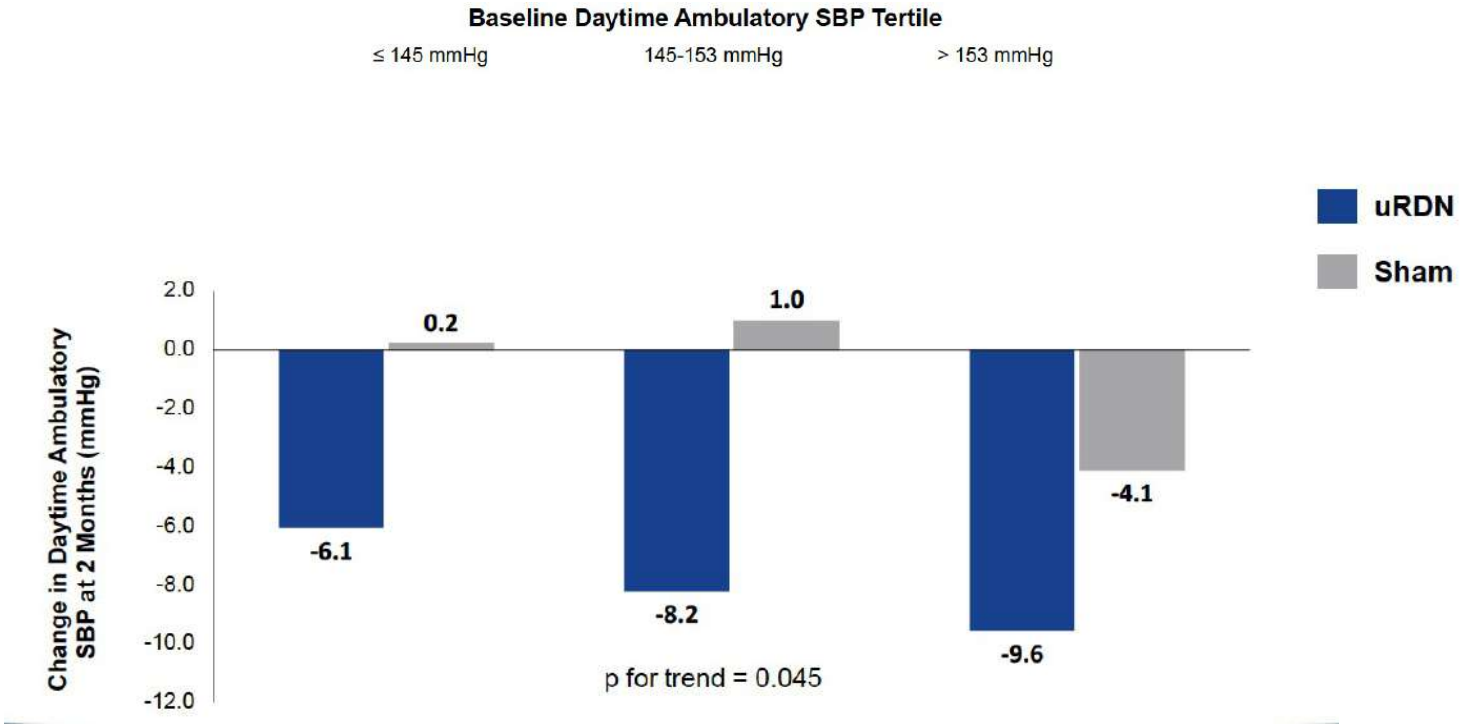


64% with 5 mmHg decrease
48% with 10 mmHg decrease

Between Group Differences:
5 mmHg decrease P<0.0001
10 mmHg decrease P<0.0001

34% with 5 mmHg decrease
16% with 10 mmHg decrease

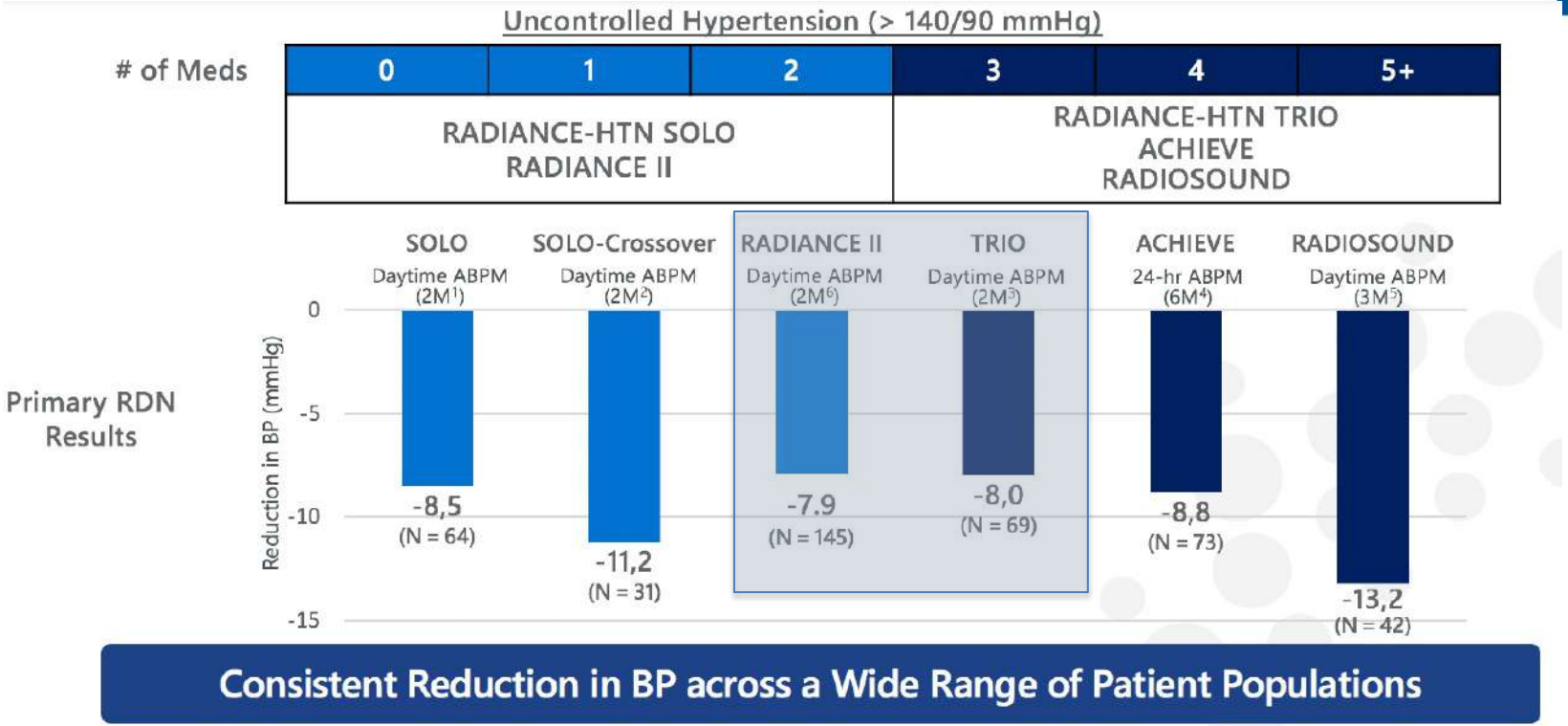
RADIANCE II : DAYTIME SBP modifications according to baseline SBP



RADIANCE II : Safety issue

30-day Events	uRDN (N=150)	Sham (N=74)
All-cause mortality	0 (0.0%)	0 (0.0%)
New onset end-stage renal disease (eGFR<15 mL/min/m^2 or need for renal replacement therapy)	0 (0.0%)	0 (0.0%)
Significant embolic event resulting in end-organ damage	0 (0.0%)	0 (0.0%)
Renal artery perforation requiring an invasive intervention	0 (0.0%)	0 (0.0%)
Renal artery dissection requiring an invasive intervention	0 (0.0%)	0 (0.0%)
Major vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	0 (0.0%)	0 (0.0%)
Hospitalization for hypertensive or hypotensive crisis	0 (0.0%)	0 (0.0%)
Hospitalization for major cardiovascular or hemodynamic related events	0 (0.0%)	0 (0.0%)
New onset stroke	0 (0.0%)	0 (0.0%)
New onset myocardial infarction	0 (0.0%)	0 (0.0%)

RADIANCE II : Pivotal Trial



HTN 3 – 36 month FU

Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 Trial

Deepak L Bhatt, Mathiah Vaduganathan, David E Kandzari, Martin B Leon, Krishna Rocha-Singh, Raymond R Townsend, Barry T Katzen, Suzanne Oparil, Sandeep Brar, Vanessa DeBruin, Martin Fahy, George L Bakris for the SYMPLICITY HTN-3 Steering Committee and Investigators

Summary

Background The SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) trial showed the safety but not efficacy of the Symplicity system (Medtronic, Santa Rosa, CA, USA) at 6 months follow-up in patients with treatment-resistant hypertension. This final report presents the 36-month follow-up results.

Methods SYMPLICITY HTN-3 was a single-blind, multicentre, sham-controlled, randomised clinical trial, done in 88 centres in the USA. Adults aged 18–80 years, with treatment-resistant hypertension on stable, maximally tolerated doses of three or more drugs including a diuretic, who had a seated office systolic blood pressure of 160 mm Hg or more and 24 h ambulatory systolic blood pressure of 135 mm Hg or more were randomly assigned (2:1) to receive renal artery denervation using the single electrode (Flex) catheter or a sham control. The original primary endpoint was the change in office systolic blood pressure from baseline to 6 months for the renal artery denervation group compared with the sham control group. Patients were unmasked after the primary endpoint assessment at 6 months, at which point eligible patients in the sham control group who met the inclusion criteria (office blood pressure ≥160 mm Hg, 24 h ambulatory systolic blood pressure ≥135 mm Hg, and still prescribed three or more antihypertensive medications) could cross over to receive renal artery denervation. Changes in blood pressure up to 36 months were analysed in patients in the original renal artery denervation group and sham control group, including those who underwent renal artery denervation after 6 months (crossover group) and those who did not (non-crossover group). For comparisons between the renal artery denervation and sham control groups, follow-up blood pressure values were imputed for patients in the crossover group using their most recent pre-crossover masked blood pressure value. We report long-term blood pressure changes in renal artery denervation and sham control groups, and investigate blood pressure control in both groups using time in therapeutic blood pressure range analysis. The primary safety endpoint was the incidence of all-cause mortality, end stage renal disease, significant embolic event, renal artery perforation or dissection requiring intervention, vascular complications, hospitalisation for hypertensive crisis unrelated to non-adherence to medications, or new renal artery stenosis of more than 70% within 6 months. The trial is registered with ClinicalTrials.gov, NCT01418261.

Findings From Sep 29, 2011, to May 6, 2013, 1442 patients were screened, of whom 535 (37%: 210 [39%] women and 325 [61%] men; mean age 57·9 years [SD 10·7]) were randomly assigned: 364 (68%) patients received renal artery denervation (mean age 57·9 years [10·4]) and 171 (32%) received the sham control (mean age 56·2 years [11·2]). 36-month follow-up data were available for 219 patients (original renal artery denervation group), 63 patients (crossover group), and 33 patients (non-crossover group). At 36 months, the change in office systolic blood pressure was −26·4 mm Hg (SD 25·9) in the renal artery denervation group and −5·7 mm Hg (24·4) in the sham control group (adjusted treatment difference −22·1 mm Hg [95% CI −27·2 to −17·0]; p≤0·0001). The change in 24 h ambulatory systolic blood pressure at 36 months was −15·6 mm Hg (SD 20·8) in the renal artery denervation group and −0·3 mm Hg (15·1) in the sham control group (adjusted treatment difference −16·5 mm Hg [95% CI −20·5 to −12·5]; p≤0·0001). Without imputation, the renal artery denervation group spent a significantly longer time in therapeutic blood pressure range (ie, better blood pressure control) than patients in the sham control group (18% [SD 25·0] for the renal artery denervation group vs 9% [SD 18·8] for the sham control group; p≤0·0001) despite a similar medication burden, with consistent and significant results with imputation. Rates of adverse events were similar across treatment groups, with no evidence of late-emerging complications from renal artery denervation. The rate of the composite safety endpoint to 48 months, including all-cause death, new-onset end-stage renal disease, significant embolic event resulting in end-organ damage, vascular complication, renal artery re-intervention, and hypertensive emergency was 15% (54 of 352 patients) for the renal artery denervation group, 14% (13 of 96 patients) for the crossover group, and 14% (10 of 69 patients) for the non-crossover group.

Interpretation This final report of the SYMPLICITY HTN-3 trial adds to the totality of evidence supporting the safety of renal artery denervation to 36 months after the procedure. From 12 months to 36 months after the procedure, patients

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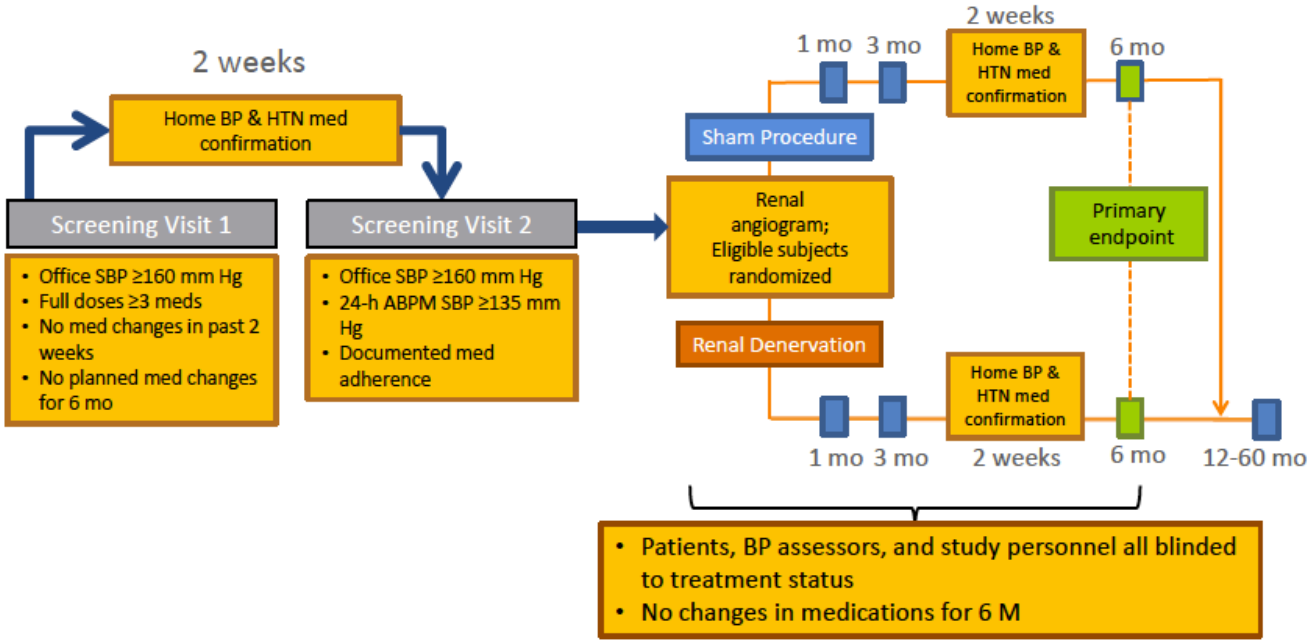
Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA, USA (Prof Dr. Bhatt MD); M Vaduganathan MD); Piedmont Heart Institute, Atlanta, GA, USA (D E Kandzari MD); New York Presbyterian Hospital, Columbia University Medical Center, and Cardiovascular Research Foundation, New York, NY, USA (Prof M B Leon MD); Prairie Heart Institute, Springfield, IL, USA (Prof K Rocha Singh MD); Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA (Prof R R Townsend MD); Miami Cardiac Vascular Institute, Miami, FL, USA (Prof B T Katzen MD); University of Alabama at Birmingham, Birmingham, AL, USA (Prof S Oparil MD); Medtronic, Santa Rosa, CA, USA (S Brar MD, V DeBruin MS, M Fahy MS); University of Chicago Medicine, Chicago, IL, USA (Prof G L Bakris MD)

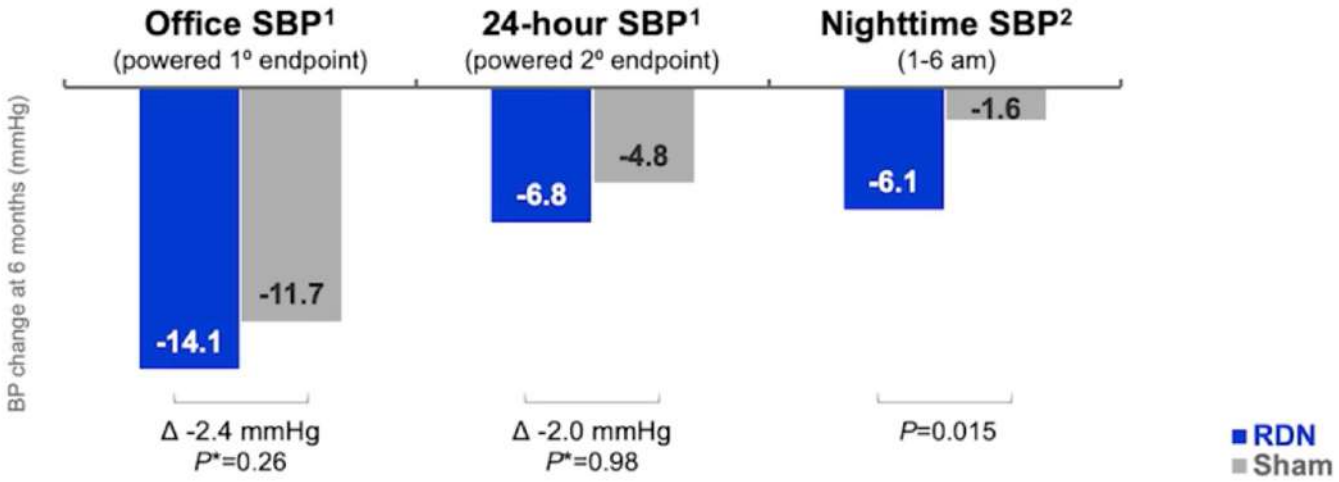
Correspondence to: Prof Deepak L Bhatt, Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA 02115, USA dlbhattmd@post.harvard.edu

HTN 3 – 36 month FU

- 2:1 randomization, blinded and controlled
- Sham procedure in control patients that included renal angiogram
- 535 subjects randomized out of 1441 enrolled at 88 sites in US (63% screen failure rate)
- 2-week screening process, including <u>maximum</u> tolerated doses of antihypertensive medications

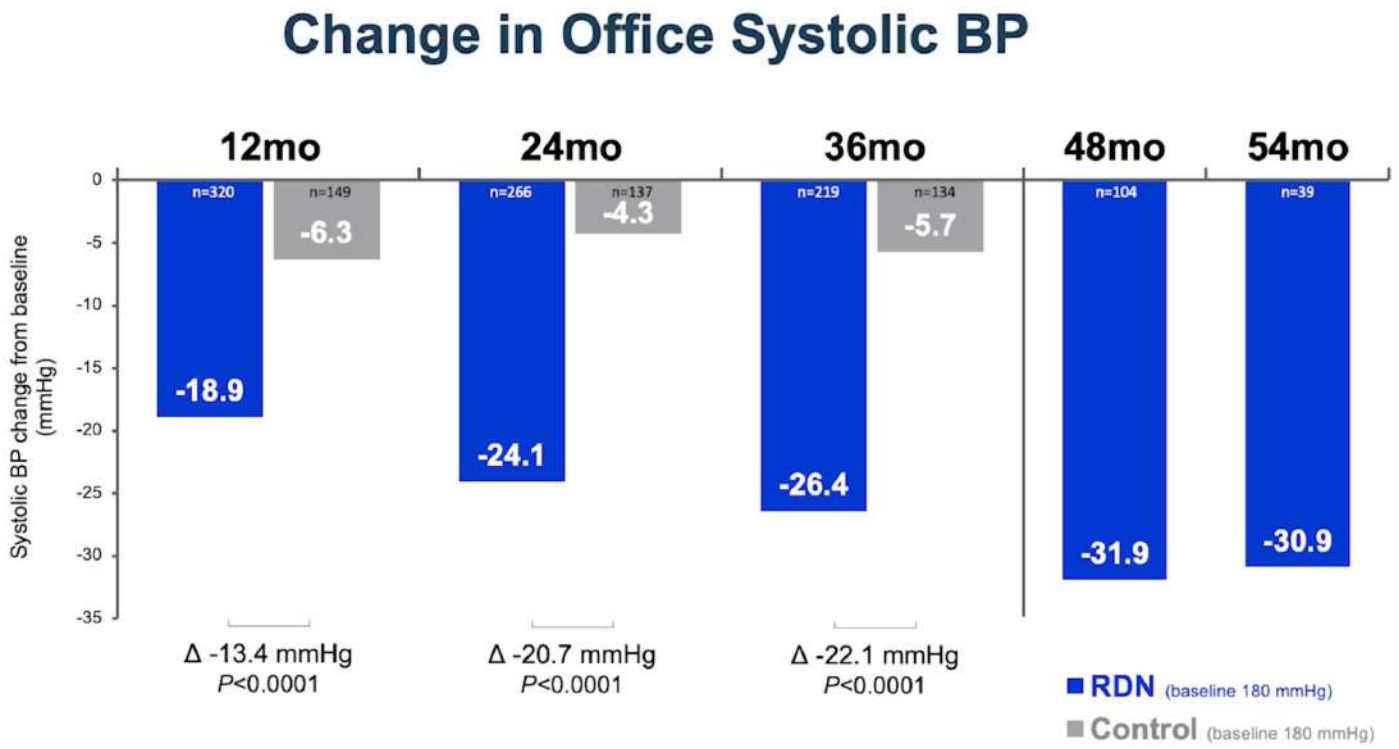


Endpoints at 6 Months

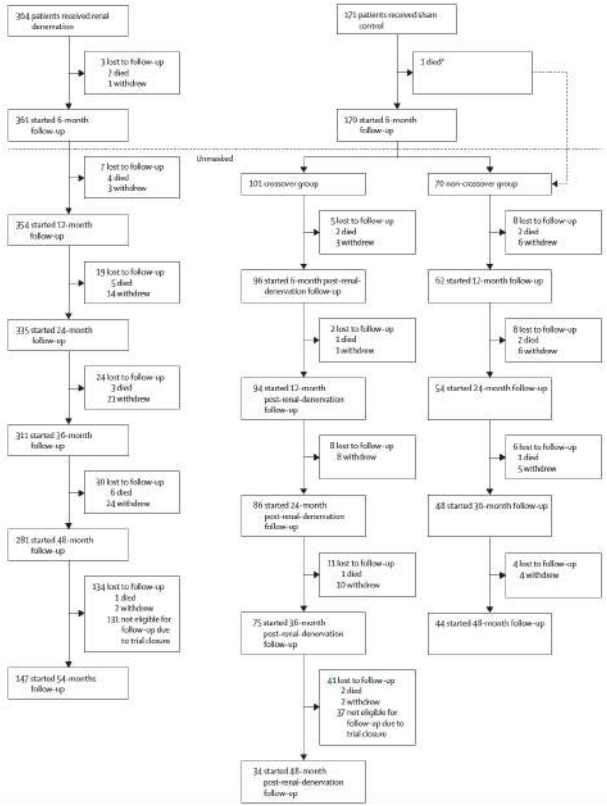


Met primary safety endpoint:[1] Major adverse event (MAE) 1.4% observed vs 9.8% performance goal; *P*<0.001

HTN 3 – 36 month FU



HTN 3 – 36 month FU



Etude negative sur l'endpoint

Lost in the FU +++

Observationnel en ouvert

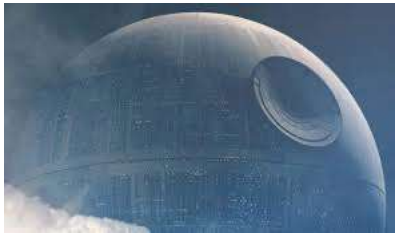
Stratégie statistique

IA RDN / medicament ne peut être exclue

Indique un signal – resultats exploratoires

Safety Outcomes

% (n)	RDN	Crossover*	Non-Crossover
To 36 Months	**(n=290)**	**(n=68)**	**(n=46)**
Composite Safety Endpoint to 36 months**	12.4%	12.4%	14.5%
Death	4.1% (12)	5.9% (4)	10.9% (5)
New-onset end-stage renal disease	3.4% (10)	0	0
Sig. embolic event resulting in end-organ damage	0.3% (1)	0	0
Vascular complication	0.3% (1)	0	0
Renal artery re-intervention	1.0% (3)	0	0
Hypertensive crisis/emergency	10.7% (31)	11.8% (8)	10.9% (5)
To 48 Months	**(n=217)**	**(n=35)**	**(n=33)**
Composite Safety Endpoint to 48 months**	15.3%	13.5%	14.5%
Death	8.3% (18)	17.1% (6)	15.2% (5)
New-onset end-stage renal disease	5.1% (11)	0	0
Sig. embolic event resulting in end-organ damage	0.5% (1)	0	0
Vascular complication	0.5% (1)	0	0
Renal artery re-intervention	1.4% (3)	0	0
Hypertensive crisis/emergency	16.6% (36)	22.9% (8)	15.2% (5)



RENAL DENERVATION IN THE PRESENCE OF ANTI-HYPERTENSIVE MEDICATIONS: SIX-MONTH RESULTS FROM THE RANDOMIZED, BLINDED, SHAM-CONTROLLED SPYRAL HTN – ON MED TRIAL

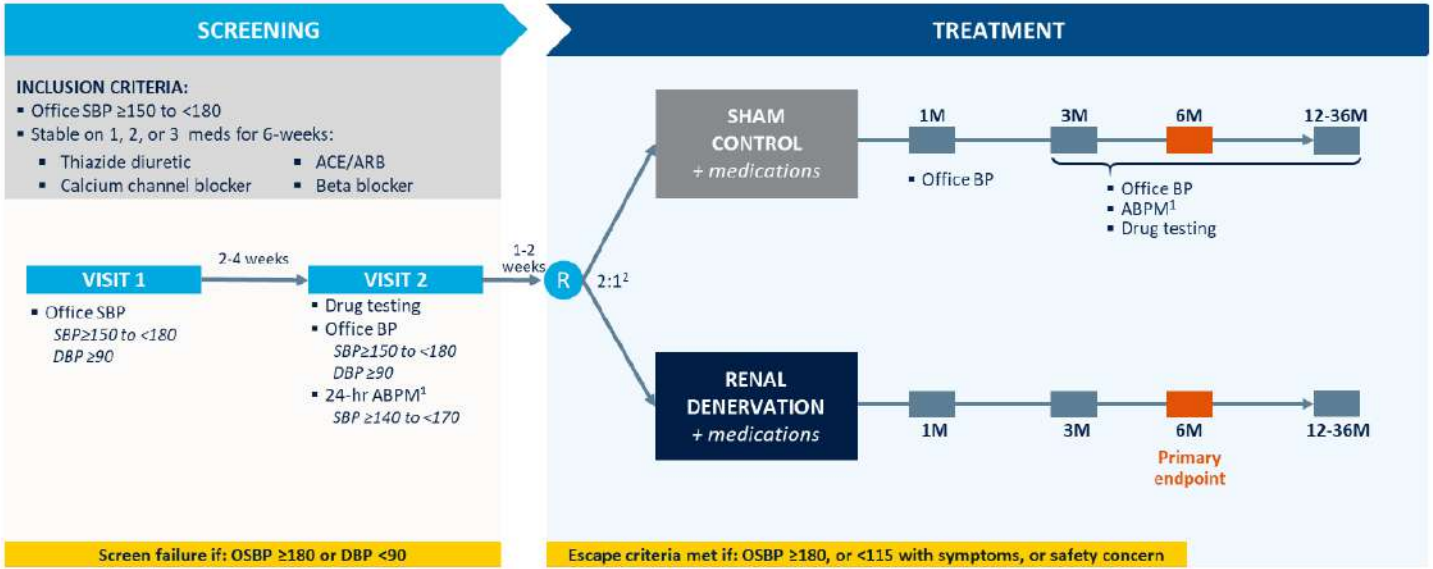
SPYRAL HTN ON MED FULL COHORT

Primary EFFICACY Endpoint

Change in 24-hr Systolic ABPM at 6 months
(Bayesian analysis, 97.5% threshold for success)

PILOT Cohort	EXPANSION Cohort
N=80 patients	N=257 patients[3]

FULL Cohort: N = 337 randomized patients



SPYRAL HTN ON MED – 6 month Primary Endpoint

Conclusion

Complexe …

RDN : Diminue la pression artérielle

RDN : Diminue le nombre de medicament

US vs RF ?

SELECTION PATIENT / SUCCES PROCEDURAL ?