



HAL
open science

A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs

Laura Mauri, Kazuomi Kario, Jan Basile, Joost Daemen, Justin Davies, Ajay J Kirtane, Felix Mahfoud, Roland E Schmieder, Michael Weber, Shinsuke Nanto, et al.

► To cite this version:

Laura Mauri, Kazuomi Kario, Jan Basile, Joost Daemen, Justin Davies, et al.. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs. American Heart Journal, 2018, 195, pp.115-129. 10.1016/j.ahj.2017.09.006 . hal-04050430

HAL Id: hal-04050430

<https://hal.science/hal-04050430v1>

Submitted on 30 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License



A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs

Laura Mauri, MD, MSc,^a Kazuomi Kario, MD,^b Jan Basile, MD,^c Joost Daemen, MD,^d Justin Davies, MBBS, MRCP, PhD,^e Ajay J. Kirtane, MD,^f Felix Mahfoud, MD,^{g,h} Roland E. Schmieder, MD,ⁱ Michael Weber, MD,^j Shinsuke Nanto, MD,^k and Michel Azizi, MD, PhD^{l,m,n} *Boston, MA; Tochigi, Hyogo, Japan; Charleston, SC; NL, the Netherlands; London, UK; New York, NY; Homburg/Saar, Erlangen, Germany; Cambridge, MA; and Paris, France*

Catheter-based renal denervation is a new approach to treat hypertension via modulation of the renal sympathetic nerves. Although nonrandomized and small, open-label randomized studies resulted in significant reductions in office blood pressure 6 months after renal denervation with monopolar radiofrequency catheters, the first prospective, randomized, sham-controlled study (Symplicity HTN-3) failed to meet its blood pressure efficacy end point. New clinical trials with new catheters have since been designed to address the limitations of earlier studies. Accordingly, the RADIANCE-HTN and REQUIRE studies are multicenter, blinded, randomized, sham-controlled trials designed to assess the blood pressure-lowering efficacy of the ultrasound-based renal denervation system (Paradise) in patients with established hypertension either on or off antihypertensive medications, is designed to evaluate patients in 2 cohorts—SOLO and TRIO, in the United States and Europe. The SOLO cohort includes patients with essential hypertension, at low cardiovascular risk, and either controlled on 1 to 2 antihypertensive medications or uncontrolled on 0 to 2 antihypertensive medications. Patients undergo a 4-week medication washout period before randomization to renal denervation (treatment) or renal angiogram (sham). The TRIO cohort includes patients with hypertension resistant to at least 3 antihypertensive drugs including a diuretic. Patients will be stabilized on a single-pill, triple-antihypertensive-drug combination for 4 weeks before randomization to treatment or sham. Reduction in daytime ambulatory systolic blood pressure (primary end point) will be assessed at 2 months in both cohorts. A predefined medication escalation protocol, as needed for blood pressure control, is implemented between 2 and 6 months in both cohorts by a study staff member blinded to the randomization process. At 6 months, daytime ambulatory blood pressure and antihypertensive treatment score will be assessed. REQUIRE is designed to evaluate patients with resistant hypertension on standard of care medication in Japan and Korea. Reduction in 24-hour ambulatory systolic blood pressure will be assessed at 3 months (primary end point). Both studies are enrolling patients, and their results are expected in 2018. (*Am Heart J* 2018;195:115-29.)

Reduction in blood pressure (BP) with orally active antihypertensive treatments (AHTs) is associated with lower cardiovascular morbidity and mortality.^{1,2} Despite the well-documented ability of antihypertensive drugs to reduce BP, particularly in combination,³ hypertension

remains uncontrolled in more than 50% of patients in the United States, Europe, and Japan.^{4,5} Uncontrolled hypertension may be caused by multiple factors, including clinician reluctance to intensify treatment, inappropriate combination of treatments, interfering substances or

From the ^aBrigham and Women's Hospital, Boston, MA, ^bDivision of Cardiovascular Medicine, School of Medicine, Jichi Medical University, Shimotsuke, Tochigi, Japan, ^cSeinsheimer Cardiovascular Health Program, Medical University of South Carolina, Ralph H Johnson VA Medical Center, Charleston, SC, ^dErasmus MC Thoraxcenter, ^eS Gravendijkwal 230, Rotterdam, NL, the Netherlands, ^fHammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK, ^gColumbia University Medical Center/NewYork-Presbyterian Hospital and the Cardiovascular Research Foundation, New York, NY, ^hKlinik für Innere Medizin III, Saarland University Hospital, Homburg/Saar, Germany, ⁱInstitute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, ^jNephrology and Hypertension, University Hospital Erlangen, Erlangen, Germany, ^kDivision of Cardiovascular Medicine, State University of New York, Downstate Medical Center, New York, NY, ^lNishinomiya Hospital Affairs, Nishinomiya

Municipal Central Hospital, Nishinomiya, Hyogo, Japan, ^mUniversité Paris-Descartes, Paris, France, ⁿAPHP, Hôpital Européen Georges-Pompidou, Hypertension Department and DHU PARC, Paris, France, and ^oINSERM, CIC1418, Paris, France.

RCT Nos. NCT02649426 and NCT02918305

Submitted April 28, 2017; accepted September 6, 2017.

Reprint requests: Laura Mauri, MD, MSc, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115.

E-mail: lmauri1@partners.org

0002-8703

© 2017 Elsevier Inc. All rights reserved.

<http://dx.doi.org/10.1016/j.ahj.2017.09.006>

illicit drugs of abuse, undiagnosed secondary hypertension, or poor medication adherence.^{6,7} In a subset of patients, hypertension is truly resistant to combination therapy of 3 medications or more, including a diuretic at optimal doses (office BP above target goal of 140/90 mm Hg).⁸ For patients with resistant hypertension (RHTN), current guidelines recommend the addition of several AHTs, including spironolactone, further increasing the risk of adverse effects and nonadherence to treatment.⁹ The absence of novel antihypertensive drugs and the limitations of purely pharmacologic approaches for patients with RHTN have prompted investigation of interventional approaches to provide complementary treatments.^{10,11}

In the past 10 years, catheter-based renal denervation has emerged as an investigational approach to treat patients with RHTN. Targeted denervation of the renal efferent and afferent nerves may lead to a decrease in renal and central sympathetic activity resulting in a reduction in arterial BP.¹²⁻¹⁵ Catheter-based renal denervation is founded on the proof of concept demonstrated by surgical splanchnicectomy (sympathectomy), performed in the early- to mid-20th century. This intervention had an unacceptable risk profile and limited long-term benefits¹⁶⁻¹⁸ and was abandoned at the end of the 1960s with the availability of improved orally AHT. Nonetheless, surgical sympathectomy set the stage for less invasive catheter-based interventions with its more targeted approach to sympathetic denervation and its potentially more favorable risk profile.

The initial clinical experience with catheter-based renal denervation using radiofrequency (RF) ablation demonstrated marked reductions in office BP, with an acceptable safety profile, albeit in either single-arm, nonrandomized clinical trials or open-label randomized clinical trials versus standard medical care.^{19,20} The Symplicity HTN-3 clinical trial was the first prospective, randomized, sham-controlled study to evaluate the effectiveness and safety of single-electrode RF renal denervation.²¹ This study failed to meet its primary office BP-lowering efficacy end point but met its safety end point. The SYMPPLICITY HTN-Japan, a prospective, open-label, randomized, controlled trial comparing renal denervation with standard pharmacotherapy for treatment of RHTN, was discontinued before completion when SYMPPLICITY HTN-3 failed.²² Various reasons for the neutral outcome have been extensively discussed.²³ Among them, substantial variation in AHT prescription after randomization, inconsistent adherence to antihypertensive drugs after randomization, and variation in the procedural technique may have been important factors contributing to the lack of BP-lowering efficacy of renal denervation.

In early 2015, the results of DENERHTN study, a multicenter, open-label, randomized controlled clinical trial with blinded end point evaluation investigating renal

denervation plus standardized stepped-care AHT (SSAHT) versus SSAHT alone in 106 subjects with RHTN, demonstrated an additional decrease of 5.9 mm Hg in daytime ambulatory systolic BP (ASBP) at 6 months in the renal denervation group. Furthermore, the rate of controlled HTN was greater in the renal denervation group.²⁴ These data suggested that renal denervation can lower ambulatory BP in patients with RHTN in a well-controlled clinical setting managed by hypertension specialists. Importantly, adherence to medication among the 2 groups (renal denervation + SSAHT and SSAHT alone) was similar and therefore determined not to have influenced the outcome. Interestingly, medication adherence was overall low (50% of patients took less medication than prescribed or no medication at all), despite management at hypertensive centers.²⁵ This suggests that even when patients are managed closely by hypertension experts, medication adherence continues to be a contributing factor to ineffective BP control.

Furthermore, there is evidence that renal denervation may be effective in lowering BP in hypertensive patients who are not taking any BP-lowering drugs, suggesting further exploration in this patient population.²⁶

Subsequently, considerations surrounding optimal study designs and procedural techniques to improve the efficacy of renal denervation have been discussed, including methods to achieve more comprehensive ablation.^{27,28} Indeed, human and animal renal neural anatomy studies have demonstrated that most nerves are located within 6 mm of the renal arterial lumen, distributed circumferentially and closer to the lumen in the distal part of the main renal arteries. Therefore, improved understanding of anatomy has led to improved technologies that deliver energy circumferentially at defined locations along the renal artery to potentially achieve more effective nerve ablation. Several new denervation catheters have been designed to achieve this more comprehensive approach to denervation and are currently under clinical investigation.

The ongoing clinical evaluation of renal denervation as a potential treatment of hypertension is supported by US, European, and Japanese regulatory bodies, among others. Several Scientific Statements²⁹ and consensus documents^{30,31} published in 2015 support continuing the evaluation of renal denervation, provided strict guidelines are followed.

The learnings from both Symplicity HTN-3 and DENERHTN have been incorporated into a multinational clinical plan to evaluate the Paradise Renal Denervation System (ReCor Medical, Palo Alto, CA) in the RADIANCE-HTN Clinical Study (United States and Europe) and the REQUIRE Clinical Study (Japan and Korea). The RADIANCE-HTN and REQUIRE Clinical studies are blinded, randomized, sham-controlled studies fulfilling the recommendations made by the consensus guidelines³²

The Paradise Renal Denervation System

The Paradise Renal Denervation System is a catheter-based system that delivers ultrasound energy circumferentially to thermally ablate the renal sympathetic nerves. It includes a single-use 6F catheter and an automated, portable, customized generator. The catheter consists of a through-lumen shaft with a cylindrical piezoelectric ceramic transducer located at the distal end of the catheter. The catheter has a distal balloon, which is pressurized by the generator to a range of 1.5 to 2.0 atm using sterile circulating water. The device's ultrasound transducer converts electrical energy to acoustic energy, which is then delivered radially through the cooling balloon into the renal artery. The pressurized balloon centers the ultrasound transducer within the artery, and the circulation of fluid serves as coolant to protect the endothelial and medial layers of the renal arterial wall. Each catheter has an embedded chip that communicates directly with the generator and specifies the power settings to be applied.

Nonclinical evaluation of the Paradise system

The Paradise System dose settings were selected based on computer simulations and an *ex vivo* thermal gel model, and subsequently confirmed in a normotensive porcine model to achieve a target circumferential ablation of the renal sympathetic nerves, which run in a plexus at varying depths of 1 to 6 mm in the periadventitia region. Circumferential lesions with marked renal nerve injury of nerve bundles of varying sizes are induced at each ablation site. These lesions are associated with marked decreases in kidney norepinephrine content.³³ Histopathology has confirmed that the integrity of the renal artery is protected with rare to minimal focal medial injury, and no endothelial injury has been observed at 7 days,³⁴ 28 days, or 90 days.

Clinical evaluation of the Paradise System

The preliminary safety and BP-lowering efficacy of the Paradise System have been evaluated in a total of 131 patients with RHTN in single-arm observational studies (first in human feasibility REDUCE study, *n* = 15 patients³⁵; REALISE, *n* = 20 patients, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01529372) identifier NCT01529372; ACHIEVE, *n* = 96 patients, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01789918) identifier NCT01789918). A clinically significant reduction in both office and 24-hour ASBP was observed 6 months after RDN in all 3 clinical studies (data on file). The number of serious adverse events was low and decreased over time (data on file). In the REDUCE study, the first version of the Paradise catheter induced thermal renal-artery injury due to insufficient cooling of the flow rate at the tip of the catheter and led to renal artery stenosis that required renal artery

stenting in 3 cases. A change to the cooling flow rate and other design changes were therefore implemented for the subsequent version of the catheter used in the REALISE and ACHIEVE studies, in which there were no reports of renal artery injury. The most common adverse event reported was lumbar or nonspecific abdominal pain, which resolved spontaneously. Overall, the safety profile of the Paradise System is consistent with other renal denervation systems.³⁶

RADIANCE-HTN and REQUIRE clinical study designs

The RADIANCE-HTN ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02649426) identifier NCT02649426) and REQUIRE ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02918305) identifier NCT02918305) clinical studies are designed to assess the BP-lowering efficacy of the Paradise Renal Denervation System in adult patients with hypertension in the United States, Europe, Japan, and Korea. These studies are funded by Otsuka Holdings Co, Ltd, and ReCor Medical, Inc. Leslie Coleman, DVM, MS, DACLAM, an employee of ReCor Medical, helped with the writing, editing, and formatting of this article.

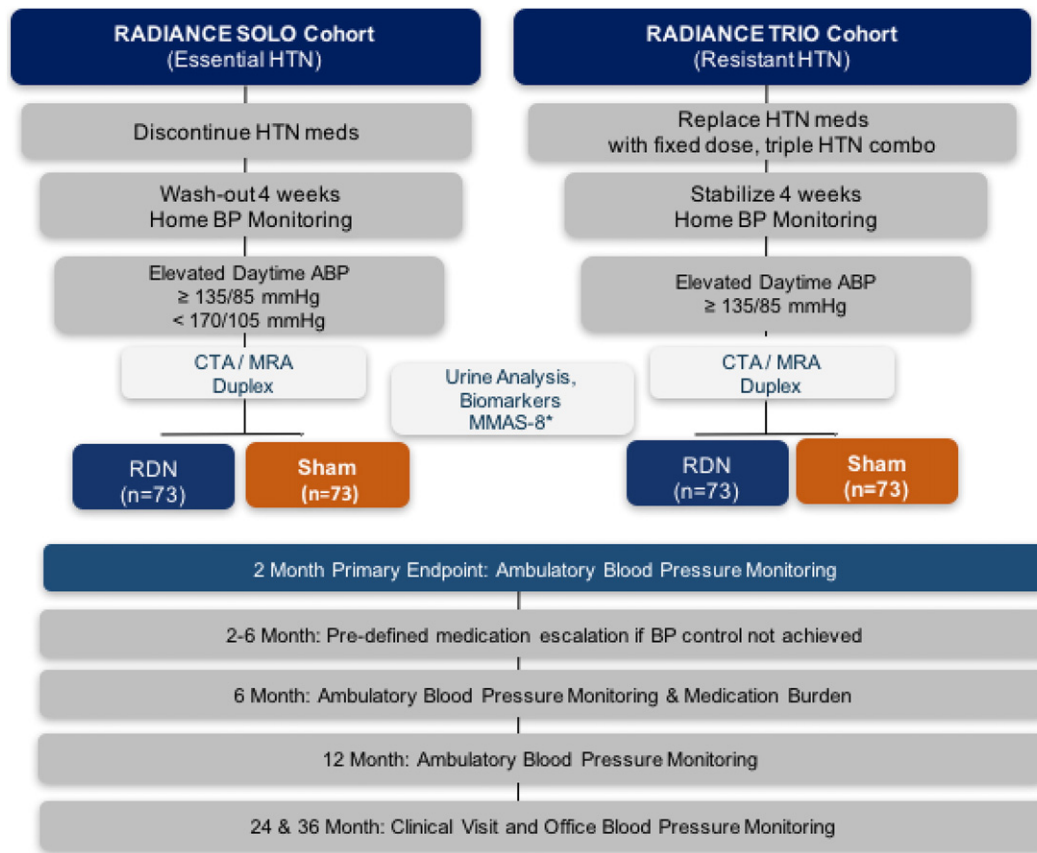
RADIANCE-HTN

RADIANCE-HTN is a multicenter, randomized, double-blind, sham-controlled, 2-cohort (off-medication SOLO cohort and on-medication TRIO cohort, see below) superiority trial conducted in the United States (22 centers) and in Europe (17 centers in France, Germany, the Netherlands, and United Kingdom) (Figure 1).

The primary objective of the study is to evaluate whether renal denervation with the Paradise System can significantly and safely reduce daytime ASBP at 2 months compared with a sham procedure in the 2 separate SOLO and TRIO cohorts. Secondary end points will include mean changes in all other BP variables from baseline to 2, 6, and 12 months as assessed by ambulatory, home, and office BP; proportion of patients with controlled BP at 2, 6, and 12 months (<135/85 mm Hg by daytime, <120/70 mm Hg by nighttime, and <130/80 mm Hg by 24-hour ambulatory BP monitoring); adherence to antihypertensive medication assessed by liquid chromatography-tandem mass spectrometry (TRIO cohort only); antihypertensive medication score at 6 and 12 months; mean changes in estimated glomerular filtration rate from baseline to 2, 6, and 12 months; incidence of acute adverse events of the renal denervation procedure; incidence of all adverse events from baseline to 2, 6, 12, 24, and 36 months; and mean changes in plasma biomarkers from baseline to 2 and 6 months (SOLO cohort only).

For each cohort, we calculated that 64 patients should be randomly assigned to each treatment arm to detect a 6-mm Hg difference in daytime ASBP from baseline to 2 months between renal denervation and the sham procedure, assuming a common SD of 12 mm Hg (80%

Figure 1



RADIANCE-HTN study design.

power, 5% type I error). To account for an expected premature withdrawal of 10% of the patients until measurement of ASBP at 2 months after procedure, 146 patients will be included in each cohort of the study.

SOLO cohort

The SOLO cohort will include patients with essential hypertension either controlled on 1 to 2 antihypertensive medications (average seated office BP $< 140/90$ mm Hg) or uncontrolled on 0 to 2 hypertensive medications (average seated office BP $\geq 140/90$ mm Hg but $< 180/110$ mm Hg) with low cardiovascular risk and no history of cardiovascular or cerebrovascular events (see full inclusion/exclusion criteria in [Appendix A](#)). After a 4-week washout period during which antihypertensive drugs will be discontinued, subjects with daytime ASBP $\geq 135/85$ mm Hg will continue to be eligible for the study.

TRIO cohort

The TRIO cohort will include patients with essential RHTN (average seated office BP $\geq 140/90$ mm Hg despite use of at least 3 hypertensive medications of different drug classes,

including a diuretic) who will have their current hypertensive regimen replaced with a single-pill, fixed-dose, triple-antihypertensive-drug combination of a calcium channel blocker, angiotensin II receptor blocker, and hydrochlorothiazide diuretic. Secondary causes of hypertension will be excluded before inclusion (see full inclusion/exclusion criteria in [Appendix A](#)). After a 4-week stabilization period on the single combination pill, patients with daytime ASBP $\geq 135/85$ mm Hg will continue to be eligible for the study.

All patients in both cohorts who meet ambulatory BP eligibility criteria after the 4-week washout/stabilization period will have a computed tomography (CT) or magnetic resonance (MR) angiogram to assess renal artery anatomy before randomization. Patients who meet anatomical eligibility requirements are eligible for the procedure. Key medical and anatomical exclusion criteria are provided in [Table I](#). Patients will first undergo a renal angiogram for confirmation of renal anatomy and balloon sizing requirements and then will be randomized in a 1:1 ratio during the procedure to renal denervation with the Paradise catheter or to a sham procedure (renal angiogram only). Patients will be blinded during the

Table I. Key exclusion criteria for SOLO (essential hypertension patients) and TRIO/REQUIRE (resistant HTN patients)

Medical history	SOLO	TRIO/REQUIRE
Secondary hypertension (not including sleep apnea)	n/a	Exclusion
Renal function	eGFR <40 mL/min per 1.73 m ²	eGFR <40 mL/min per 1.73 m ²
History of cerebrovascular event	Any history	Events within 3 mo before procedure
History of myocardial infarction, coronary artery bypass procedure, NYHA class III-IV heart failure	Any history	Events within 3 mo before procedure
Hospitalization for hypertensive crisis	>1 hospitalization within 12 mo before procedure	n/a
Type 1 diabetes mellitus or uncontrolled type 2 diabetes	Exclusion	Exclusion
Renal artery anatomy		Main renal artery diameter <4 or >8 mm Accessory renal artery diameter ≥2 and <4 mm or >8 mm Presence of renal artery stenosis ≥30%
Preexisting renal stent or history of renal artery angioplasty	Exclusion	Exclusion
Prior renal denervation procedure	Exclusion	Exclusion

CABG, Coronary artery bypass graft; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; n/a, not applicable; NYHA, New York Heart Association.

Table II. Antihypertension treatment escalation protocol in the RADIANCE-HTN trial

	SOLO cohort	TRIO cohort
Step 1 (2 mo after randomization)	Add mid-dose long-acting dihydropyridine calcium-channel blocker (preferentially amlodipine 5 mg)	Add spironolactone (25-50 mg)
Step 2 (3 mo after randomization)	Add full dose of long-acting angiotensin receptor blocker (preferentially valsartan 160-320 mg or olmesartan 20-40 mg) or ACEi (preferentially ramipril 10-20 mg or lisinopril 20-40 mg)	Add full dose of long-acting, cardioselective β-1 receptor blocker (preferentially bisoprolol 10 mg)
Step 3 (4 mo after randomization)	Add low dose of hydrochlorothiazide (12.5 mg)	Add full dose of central α-2 receptor agonist (preferentially clonidine 0.1-0.2 mg, rilmenidine 1-2 mg, or moxonidine 0.2-0.4 mg)
Step 4 (5 mo after randomization)	Increase dose of hydrochlorothiazide (25 mg)	Add full dose of long-acting α-1 receptor blocker (preferentially slow release prazosin 5-10 mg or doxazosin 4-8 mg)
Step 5 (6 mo after randomization)	Increase long-acting dihydropyridine calcium-channel blocker to full dose (eg, amlodipine 10 mg)	—

ACEi, Angiotensin-converting enzyme inhibitor.

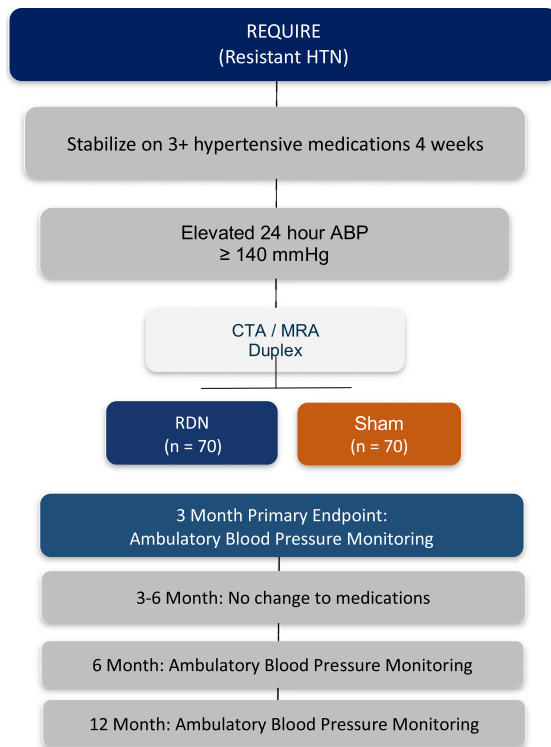
procedure by ensuring that sedation occurs before randomization. Other measures to ensure adequate subject blinding include the use of headphones and eye covers during the procedure, standardization of length of time spent in catheterization laboratory, and the use of deep conscious sedation and/or general anesthesia. All patients and study personnel responsible for follow-up assessments, including the measurement of BP after randomization, will be blinded until the 6-month follow-up visit. A blinding index³⁷ will be used to evaluate the success of subject blinding after procedure but before discharge and at 2 and 6 months.

Follow-up and primary efficacy and safety assessments

SOLO cohort subjects will be maintained off all hypertensive medication through the 2-month primary

efficacy end point (daytime ASBP). TRIO cohort subjects will be maintained on the single-pill, fixed-dose, triple-antihypertensive-drug combination through the 2-month primary efficacy end point (daytime ASBP).

Between the 2- and 6-month follow-up visits after randomization, antihypertensive drugs will be sequentially added if the BP measured monthly at home is ≥135 mm Hg (systolic BP) or ≥85 mm Hg (diastolic BP) in both cohorts according to different escalation protocols (Table II). Safeguards exist for subjects who experience a hypotensive episode or a hypertensive crisis with predefined recommended medication adjustments, as needed. From 6 months onward, the AHT can be modified at the physician's discretion. In addition, patients randomized to the sham group may cross over and receive renal denervation with the Paradise System if

Figure 2

A multicenter, randomized, double-blind, sham-controlled, superiority trial designed to demonstrate the safety and BP-lowering effectiveness of the Paradise Renal Denervation System in patients with RHTN in Japan and Korea.

the following conditions are met: (1) the primary efficacy end point has been met in that particular patient's cohort; (2) the data safety monitoring board has not stopped the study due to safety concerns, indicated an increased safety risk associated with the treatment, or recommended stopping the trial due to futility; (3) daytime ambulatory BP remains ≥ 135 mm Hg (systolic) or ≥ 85 mm Hg (diastolic), documented at the 6-month follow-up; and (4) the subject agrees to the procedure.

Medication adherence will be monitored by urine drug determination using liquid chromatography-tandem mass spectrometry (TRIO cohort only) and by the Morisky Medication Adherence Scale (both cohorts).

All randomized subjects will undergo a safety-driven renal duplex ultrasound at 2 and 6 months. In addition, subjects randomized to renal denervation will undergo a safety-driven renal CT angiogram at 12 months to assess renal artery anatomy, with continued monitoring of renal artery anatomy by duplex ultrasound at 24 and 36 months. All subjects will be followed up for 3 years; all safety data will be collected for 3 years (see [Appendix C](#) for safety assessments).

BP measurements

Seated office and home BP, with appropriate cuff size and using the same dedicated and validated semiautomatic device (Omron M10-IT; Omron Co, Kyoto, Japan) across study centers, will be measured according to international guidelines⁸ monthly for the first 6 months after procedure and every 6 months thereafter. All measurements will be obtained in the seated position using the same arm throughout the study. Ambulatory BP monitoring will be performed with an appropriate cuff size, using a validated device (Microlife WatchBP 03; Microlife, Taipei, Taiwan) before the procedure and at 2, 6, and 12 months after procedure. Blood pressure will be measured every 20 minutes during the daytime (0700-2200 hours) and every 30 minutes overnight (2200-0700 hours). Only ambulatory BP recordings with a minimum of 21 measurements during the daytime period will be considered valid. In the case of a nonvalid measurement, a new ambulatory BP recording can be performed the next day. All recordings will be sent to a central, independent, and blinded core laboratory for validation and analysis.

REQUIRE

REQUIRE is a multicenter, randomized, double-blind, sham-controlled, superiority trial designed to demonstrate the safety and BP-lowering effectiveness of the Paradise Renal Denervation System in patients with RHTN in Japan and Korea ([Figure 2](#)). The primary end point of the study will be the reduction in 24-hour ASBP from baseline to 3 months. Hypothesizing a 6-mm Hg treatment effect (lowering) of renal denervation with an SD of 12 mm Hg, the number of patients required to detect a difference between the study group (renal denervation) and the control group (sham treatment) at a 5% 2-sided significance level and a power of 80%, is 64 for each arm (total 128). Anticipating that approximately 10% of patients will discontinue the study before the measurement of ASBP at 3 months after procedure, the planned number of patients is 70 for each arm (total 140).

The REQUIRE study will include patients with RHTN (average seated office BP $\geq 150/90$ mm Hg) uncontrolled on a stable regimen of at least 3 hypertensive medications, at maximal tolerated dosages, of different drug classes, including a diuretic. Patients with 24-hour ASBP ≥ 140 mm Hg within 4 weeks of the renal denervation procedure will continue to be eligible for the study, pending final confirmation of renal artery anatomy eligibility based on CT or MR angiogram. Key medical and anatomical inclusion/exclusion criteria are provided in [Table I](#) (see full inclusion/exclusion criteria in [Appendix B](#)). A total of 140 patients will be randomized in a 1:1 ratio to renal denervation or sham (renal angiogram) during the procedure. All patients will be

Table III. Study design comparison

	RADIANCE-HTN SOLO	RADIANCE-HTN TRIO	REQUIRE
Age (y)	≥18 and ≤75	≥18 and ≤75	≥20 and ≤75
Medications at screening	Essential HTN—0, 1, 2 meds	RHTN on ≥3 meds	RHTN on ≥3 meds
Seated office BP (mm Hg)	≥140/90 and <180/110 if on no meds <180/110 if on 1-2 meds	≥140/90	≥150/90
Medication after consent	None	Single-pill, fixed-dose, triple-drug combination	Standard of care
Ambulatory BP (mm Hg)	Daytime ≥135/85 after 4-wk wash-out	Daytime ≥135/85 after 4-wk stabilization on single-pill, fixed-dose, triple-drug combination	24-h BP ≥140 systolic within at most 4 wk of procedure (no predefined diastolic criteria)
CTA/MRA preprocedure	Yes	Yes	Yes
Randomization	1:1	1:1	1:1
Treatment (Paradise System)	Bilateral ultrasound emissions—minimum of 2 per artery	Bilateral ultrasound emissions—minimum of 2 per artery	Bilateral ultrasound emissions—minimum of 2 per artery
Sham (renal angiogram)	Yes	Yes	Yes
Primary end point	Reduction in the mean daytime systolic ABP from baseline to 2 mo after procedure	Reduction in the mean daytime systolic ABP from baseline to 2 mo after procedure	Reduction in the mean 24-h systolic ABP from baseline to 3 mo after procedure
Sample size	146	146	140
Medications to primary end point	None	Single-pill, fixed-dose, triple-drug combination	Standard of care
Medications after primary end point	Prescribed recommended medication escalation 2-6 mo	Prescribed recommended medication escalation 2-6 mo	Recommend no change between 3 and 6 mo
Follow-up	3 y	3 y	12 mo
Status	Enrolling	Enrolling	Enrolling

ABP, Ambulatory BP; CTA, CT angiogram; HTN, hypertension; MRA, MR angiogram.

maintained on their preprocedure medication regimen through 3 months, with no changes permitted.

BP measurements

Office BP monitoring will be conducted using a validated automated device (Omron HEM-907), monthly for the first 6 months after procedure and at 12 months. Blood pressure measurement techniques will be standardized. All measurements will be obtained in the seated position using the same arm throughout the study. Ambulatory BP monitoring will be performed using a validated portable automated device (TM-243 series; A&D, Corp, Tokyo, Japan) before the procedure and at 3, 6, and 12 months after procedure. Blood pressure will be measured every 30 minutes throughout the day. All subjects will remain blinded through 6 months. All subjects will be followed up for 12 months; all safety data will be collected for 12 months (see Appendix D for safety assessments).

Comparison between the RADIANCE and REQUIRE studies

Both studies are sham-designed studies using ambulatory BP monitoring as the primary end point (Table III). RADIANCE-HTN SOLO will include patients off-medication, whereas RADIANCE-HTN TRIO and REQUIRE will both include patients with RHTN on medication taking different therapeutic regimens (Table III). TRIO subjects will be maintained on a single-pill, fixed-dose, triple-antihypertensive

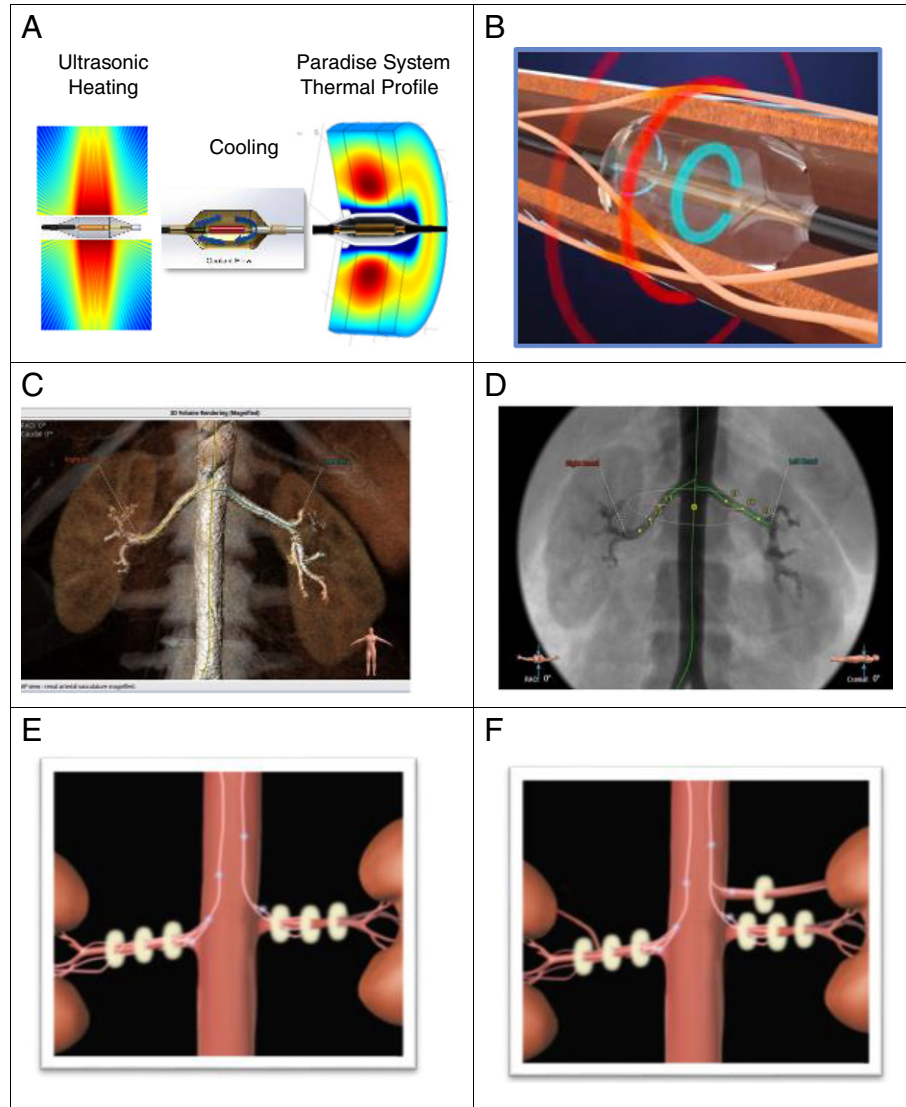
drug combination from enrollment through the 2-month primary end point with a recommended predefined stepwise medication escalation protocol between 2 and 6 months, whereas REQUIRE subjects will be maintained on a stable regimen of at least 3 antihypertensive medications of different classes including a diuretic at maximal tolerated dose through the 3-month primary end point with no change allowed for 6 months.

Renal denervation procedure

A consistent renal denervation procedure will be used for all subjects enrolled in the RADIANCE-HTN and REQUIRE studies. Two to 4 circumferential ultrasound emissions of 7-second duration will be delivered within the main renal artery bilaterally. At least one emission will be delivered proximal to radiographically visible side branches. At least one emission will be delivered within accessory arteries ≥4 mm diameter (Figure 3).

Discussion

The RADIANCE-HTN and REQUIRE clinical studies are designed to evaluate the potential effectiveness of ultrasound-based renal denervation with the Paradise System in patients with essential hypertension, either resistant or not, and either treated or not treated with concomitant

Figure 3

The treatment includes Paradise System thermal profile (A), Paradise System cooling (blue) arterial wall and heating (red) nerves (B), CT angiogram renal anatomy (C), fluoro simulation of Paradise treatment (D), and bilateral treatment of renal arteries with Paradise System (E) and of accessory artery (F).

antihypertensive drugs. The RADIANCE-HTN and REQUIRE studies were designed to be parallel, although with differences in subject populations, ambulatory BP inclusion criteria, primary end point, and use of a predefined medication escalation protocol between 2 and 6 months to achieve BP target in RADIANCE-HTN.

The advantage of the use of a single-pill, triple-combination antihypertensive therapy in the RADIANCE TRIO cohort is a likely improvement in treatment adherence rates and hence may be associated with an increased probability of controlling BP in patients who are not truly resistant. Although this may

require a larger screening population to enroll the required number of subjects, it is expected that the enrolled cohort will represent patients who continue to have uncontrolled hypertension despite receiving 3 antihypertensive drugs. There is also some evidence that patients with increased incidence of endothelial dysfunction, inflammation and extreme arterial stiffness may not be suitable for renal denervation control of BP.³⁸⁻⁴⁰ With that in mind, the inclusion/exclusion criteria of these studies have been designed to minimize inclusion of subjects with substantial arterial stiffness, excluding elderly patients (>75 years) with isolated systolic hypertension.

The RADIANCE SOLO cohort will include patients with milder forms of essential hypertension who are not taking any medications for 3 months. Indeed, some younger hypertensive patients may have greater sympathetic nervous system activity than patients with more severe RHTN and thus might be more likely to respond positively to renal denervation. In addition, the arterial wall may be more responsive to renal denervation-induced changes in sympathetic tone because vascular remodeling may still be in a reversible state in younger, less severely hypertensive patients. Indeed, the high prevalence of target organ damage in patients with RHTN, including renal fibrosis and vascular stiffness, both of which are difficult to reverse, renders BP control difficult to achieve regardless of the methods used. Consequently, this study design allows for an investigation of the true BP-lowering efficacy of renal denervation compared with a sham procedure as primary treatment of hypertension, as it is conducted upon a background of no antihypertensive therapy, similar to the design of placebo-controlled studies testing the efficacy of pharmacologic antihypertensive agents. It will also provide data on predictive factors of the BP response to renal denervation without the confounding influence of drugs, both from a pharmacologic perspective and a patient-adherence perspective.

To minimize risk of cardiovascular events including stroke, RADIANCE SOLO cohort patients will not take their antihypertensive medications during a very limited period of 12 weeks (4 weeks before and 8 weeks after randomization), similar to the short-term study designs typically used to evaluate new antihypertensive therapy against placebo control.⁴¹ Indeed, the Placebo in Hypertension Adverse Reaction Meta-analysis Project showed that the risk of serious adverse events including death, stroke, and myocardial infarction associated with placebo-controlled studies of short-term duration is low and equally distributed between the placebo and the active treatment groups. In addition, the good immediate-, mid-, and long-term vascular safety thus far documented from more than 3000 renal denervation procedures performed worldwide with RF catheters and from more than 200 procedures with the Paradise Catheter provide confidence in the safety of this procedure. These trials will allow us to test the hypothesis that renal denervation can not only reduce BP in hypertensive patients, but may also reduce the need for antihypertensive medications.

Enrollment for both the RADIANCE-HTN and REQUIRE studies started in 2016. Initial results are expected in 2018.

Funding

The RADIANCE-HTN study is funded by ReCor Medical, Inc. The REQUIRE study is funded by JIMRO Co, Ltd.

Author contributions

Study concept and design: Drs Mauri, Kario, and Azizi
Drafting of the manuscript: Drs Mauri, Kario, and Azizi

Critical revision of the manuscript for important intellectual content: Drs Mauri, Kario, Basile, Daemen, Davies, Francis, Kirtane, Mahfoud, Schemieder, Weber, Nanto, and Azizi

Disclosure

Dr Mauri reports grants to institution from Amgen, Abbott, Boston Scientific, Boehringer Ingelheim, Biotronik, and Corvia, and consulting fees from Amgen, Eli Lilly, St. Jude Medical, ReCor, and Corvia. Dr Kario reports grants from Teijin Pharma Limited, Omron Healthcare Co, Ltd, FUKUDA DENSHI, Bayer Yakuhin Ltd, A&D Co, Ltd, Daiichi Sankyo Company, Ltd, Mochida Pharmaceutical Co, Ltd, EA pharma, Otsuka Pharmaceutical Co, Ltd, Boehringer Ingelheim Japan Inc, Mitsubishi Tanabe Pharma Corporation, Medtronic Japan Co, Ltd, and Takeda Pharmaceutical Company Ltd, and personal fees from Takeda Pharmaceutical Company Ltd, Daiichi Sankyo Company, Ltd, and Omron Healthcare Co, Ltd, outside the submitted work. Dr Basile has received grant support from the NHLBI (SPRINT), Eli-Lilly (REWIND), and Re-Cor (RADIANCE-HTN); is a consultant/advisory board for Novartis, Medtronic, and Up-to-Date; and has received speakers' honoraria from Amgen, Arbor, and Janssen. Dr Daemen reports research grants from ReCor Medical, St Jude, Medtronic, Boston Scientific, Acist, and Biotronik. Dr Davies has received consultancy payments and research support from Medtronic and ReCor. Dr Kirtane reports institutional research grants to Columbia University and the Cardiovascular Research Foundation from Boston Scientific, Medtronic, ReCor Medical, and Abott Vascular. Dr Mahfoud is supported by Deutsche Hochdruckliga and Deutsche Gesellschaft für Kardiologie and has received speaker honoraria and consultancy fees from Medtronic and ReCor. Dr Schemieder has received speaker fees, consultancy and advisory board fees, and other from Kona Medical, Medtronic, and ReCor. The University Hospital has received research funding from Ablative Solutions, Medtronic, Roxmedical, KONA, and ReCor. Dr Weber reports research support from Boston Scientific, Medtronic, and ReCor; consulting fees for Novartis and Daiichi Sankyo; and speaking fees for Menarini and Merck. Dr Nanto reports no conflict of interest with respect to this work. Dr Azizi has received honoraria for advisory board meetings from Vessix, Boston Scientific Corporation, Cordis (all these are 6 years ago), and Actelion; has received speakers' honoraria from CVRx and Servier; was involved as an investigator in the Symplicity HTN-2 (Ardian/Medtronic) and REDUCE-HTN (Vessix/Boston Scientific Corporation) trials; is involved as an investigator in the RADIANCE-HTN trial; and has received a research grant from Servier, Novartis, and ReCor.

Acknowledgments

Leslie Coleman, DVM, MS, DACLAM, an employee of ReCor Medical, helped with the writing, editing, and formatting of this article. She was compensated by ReCor Medical for her work.

Appendix A. Inclusion/exclusion criteria—RADIANCE-HTN

	SOLO cohort	TRIO cohort
Inclusion criteria	<ul style="list-style-type: none"> • Signed informed consent • Age ≥ 18 and ≤ 75 y at the time of consent • Documented history of essential HTN • Either <ul style="list-style-type: none"> ◦ average seated office BP $< 180/110$ mm Hg at screening visit (V0) while on a stable regimen of 1 or 2 antihypertensive medications for at least 4 wk before consent or ◦ average seated office BP $\geq 140/90$ mm Hg $< 180/110$ mm Hg despite lifestyle measures on no antihypertensive medications • Documented daytime ABP $\geq 135/85$ and $< 170/105$ mm Hg after 4-wk washout/run-in period • Suitable renal anatomy compatible with the renal denervation procedure and documented by renal CTA or MRA of good quality performed within 1 y before consent (a CTA or an MRA will be obtained in patients without a recent [≤ 1 y] renal imaging) • Renal artery anatomy on either side, ineligible for treatment including the following: <ul style="list-style-type: none"> ◦ Main renal artery diameter < 4 and > 8 mm ◦ Main renal artery length < 25 mm ◦ A single functioning kidney ◦ Presence of abnormal kidney (or secreting adrenal) tumors ◦ Renal artery with aneurysm ◦ Preexisting renal stent or history of renal artery angioplasty ◦ Prior renal denervation procedure ◦ Fibromuscular disease of the renal arteries ◦ Presence of renal artery stenosis of any origin $\geq 30\%$ ◦ Accessory arteries with diameter ≥ 2, < 4, and > 8 mm • Iliac/femoral artery stenosis precluding insertion of the Paradise catheter 	<ul style="list-style-type: none"> • Signed informed consent • Age ≥ 18 and ≤ 75 y at the time of consent • Documented history of HTN • Average seated office BP $\geq 140/90$ mm Hg at screening visit (V0) while on a stable regimen of at least 3 antihypertensive medications of different classes including a diuretic for at least 4 wk before consent • Documented daytime ABP $\geq 135/85$ mm Hg after 4-wk stabilization period on single-pill, fixed-dose, triple-drug combination • Suitable renal anatomy compatible with the renal denervation procedure and documented by renal CTA or MRA of good quality performed within 1 y before consent (a CTA or an MRA will be obtained in patients without a recent [≤ 1 y] renal imaging)
Exclusion criteria	<ul style="list-style-type: none"> • Evidence of active infection within 7 d of procedure • Type 1 diabetes mellitus or uncontrolled type 2 diabetes (defined as a plasma Hb1Ac $\geq 9.0\%$) • Documented history of chronic active inflammatory bowel disorders such as Crohn disease or ulcerative colitis • eGFR < 40 mL/min per 1.73 m² (by Modification of Diet in Renal Disease formula) • Brachial circumference ≥ 42 cm • Any history of cerebrovascular event (eg, stroke, transient ischemic event, and cerebrovascular accident) • Any history of severe cardiovascular event (MI, CABG, acute heart failure requiring hospitalization [NYHA III-IV]) • Documented confirmed episode(s) of stable or unstable angina • Documented repeat (> 1) hospitalization for hypertensive crisis within the prior 12 months • Prescribed to any standard antihypertensive of cardiovascular medication (eg, β-blockers) for other chronic conditions (eg, ischemic heart disease) such that discontinuation might pose serious risk to health • Documented history of persistent or permanent atrial tachyarrhythmia 	<p>Renal artery anatomy on either side, ineligible for treatment including the following:</p> <ul style="list-style-type: none"> ◦ Main renal artery diameter < 4 and > 8 mm ◦ Main renal artery length < 25 mm ◦ A single functioning kidney ◦ Presence of abnormal kidney (or secreting adrenal) tumors ◦ Renal artery with aneurysm ◦ Preexisting renal stent or history of renal artery angioplasty ◦ Prior renal denervation procedure ◦ Fibromuscular disease of the renal arteries ◦ Presence of renal artery stenosis of any origin $\geq 30\%$ ◦ Accessory arteries with diameter ≥ 2, < 4, and > 8 mm <ul style="list-style-type: none"> • Iliac/femoral artery stenosis precluding insertion of the Paradise catheter • Evidence of active infection within 7 d of procedure • Secondary HTN not including sleep apnea (documented through clinical workup within the 12 mo before consent) • Type 1 diabetes mellitus or uncontrolled type 2 diabetes (defined as a plasma Hb1Ac $\geq 9.0\%$) • Documented history of chronic active inflammatory bowel disorders such as Crohn disease or ulcerative colitis • eGFR < 40 mL/min per 1.73 m² (by Modification of Diet in Renal Disease formula) • Brachial circumference ≥ 42 cm • Any history of cerebrovascular event (eg, stroke, transient ischemic event, and cerebrovascular accident) within 3 mo before consent • Any history of severe cardiovascular event (MI, CABG, acute heart failure requiring hospitalization [NYHA III-IV]) within 3 mo before consent • Documented confirmed episode(s) of unstable angina within 3 mo before consent • Documented intolerance or contraindication for any of the antihypertensive drugs prescribed as a requirement of the study protocol • Prescribed to any standard antihypertensive medication (other than β-blockers) for other chronic conditions (eg, ischemic heart disease) such that discontinuation might pose serious risk to health • Documented history of persistent or permanent atrial

(continued)

SOLO cohort	TRIO cohort
<ul style="list-style-type: none"> • Active implantable medical device (eg, ICD or CRT-D, neuromodulator/spinal stimulator, baroreflex stimulator) • Chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea • Primary pulmonary HTN • Documented contraindication or allergy to contrast medium not amenable to treatment • Limited life expectancy of <1 y at the discretion of the investigator • Any known, unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or for any reason in the opinion of the investigator, would be unlikely or unable to comply with study protocol requirements or whose participation may result in data analysis confounders (eg, night shift workers) • Pregnant, nursing, or planning to become pregnant (documented negative pregnancy test result required documented within a maximum of 7 d before procedure for all women of child bearing potential. Documentation of effective contraception is also required for women of child bearing potential) • Concurrent enrollment in any other investigational drug or device trial (participation in noninterventional registries is acceptable) 	<p>tachyarrhythmia</p> <ul style="list-style-type: none"> • Active implantable medical device (ICD or CRT-D, neuromodulator/spinal stimulator, baroreflex stimulator) • Chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea. • Primary pulmonary HTN • Documented contraindication or allergy to contrast medium not amenable to treatment • Limited life expectancy of <1 y at the discretion of the investigator • Any known, unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or for any reason in the opinion of the investigator, would be unlikely or unable to comply with study protocol requirements or whose participation may result in data analysis confounders (eg, night shift workers) • Pregnant, nursing, or planning to become pregnant (documented negative pregnancy test result required documented within a maximum of 7 d before procedure for all women of childbearing potential. Documentation of effective contraception is also required for women of childbearing potential) • Concurrent enrollment in any other investigational drug or device trial (participation in noninterventional registries is acceptable)

ABP, Ambulatory blood pressure; BP, blood pressure; CABG, coronary artery bypass graft; CRT-D, cardiac resynchronization therapy device; CTA, computed tomography angiogram; eGFR, estimated glomerular filtration rate; HTN, hypertension; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; MRA, magnetic resonance angiogram; NYHA, New York Heart Association.

Appendix B. Inclusion/exclusion criteria—REQUIRE

Inclusion criteria	<ul style="list-style-type: none"> • Written informed consent • Age ≥ 20 and ≤ 75 y • Documented history of hypertension • Antihypertensive treatment with a stable regimen, using doses including the maximal tolerated dose, of at least 3 antihypertensive medications of different classes including a diuretic for at least 4 wk before consent <ul style="list-style-type: none"> ◦ A combination drug is counted for each effective active ingredient. When a dosing regimen of the respective drug is not changed, changes from single to combination drug or from combination to single drug are permitted. • Patients meeting the following criteria <ul style="list-style-type: none"> ◦ Before informed consent ◦ Seated office BP $\geq 150/90$ mm Hg measured within 4 wk before informed consent ◦ After informed consent ◦ Both 2 measurements of seated office BP in at least a 4-wk interval are $\geq 150/90$ mm Hg. For BP, an average of intraday triplicate measurements will be used. ◦ Within at most 4 wk before the study procedure ◦ In addition to the above (1) and (2), the mean 24-h systolic ambulatory BP monitoring of ≥ 140 mm Hg within at most 4 wk before the study procedure • Suitable renal anatomy compatible with the renal denervation procedure documented by renal CTA or MRA within 1 y before obtaining consent. For patients without a renal imaging within 1 y before obtaining consent, a CTA or an MRA will be obtained, and compatibility with the renal denervation procedure will be confirmed within a period between informed consent and before the study procedure.
Exclusion criteria	<ul style="list-style-type: none"> • Subjects with any of the following findings that disqualify patients from participation in the study. <ul style="list-style-type: none"> ◦ Diameter of the main renal artery in the region to be treated with the procedure is <4 or >8 mm

(continued on next page)

(continued)

- Main renal artery length of <25 mm
- The region to be treated with the procedure meets any of the following:
 - Presence of renal artery stenosis of any origin $\geq 30\%$
 - Renal artery with aneurysm/fibromuscular lesion or severe calcification
 - Preexisting renal stent or history of renal artery angioplasty or renal denervation
- Presence of kidney or adrenal tumors
- A single functioning kidney
- Accessory renal arteries with diameter ≥ 2 and < 4 mm or > 8 mm
- Iliac/femoral artery stenosis precluding insertion of PRDS-001 (catheter)
- Secondary hypertension (patients with sleep apnea syndrome are eligible)
- Type 1 diabetes mellitus or type 2 diabetes inadequate control (defined as HbA1c $\geq 8.4\%$)
- Documented history or complication of chronic active inflammatory bowel disorders (eg, Crohn disease and ulcerative colitis)
- eGFR of < 40 mL/min per 1.73 m² (based on the predictive equation by the Japanese Society of Nephrology)
- Unavailable or having difficulty with determination of BP using an automatic manometer specified for the study
- Any history of severe cardiovascular event (eg, myocardial infarction, CABG, and acute heart failure requiring hospitalization) or severe cerebrovascular event (eg, stroke, transient ischemic event, and cerebrovascular accident) within 3 mo before informed consent
- Documented confirmed episode(s) of unstable angina within 3 mo before informed consent
- Evidence of active infection within 1 wk before the study procedure
- Planned PCI or surgery for ischemic heart disease within 8 mo after informed consent
- Complication with persistent atrial fibrillation
- Active implantable medical device (eg, ICD or CRT-D, neuromodulator/spinal stimulator, and baroreflex stimulator)
- Any notable aorta irregularity or aneurysm for which the investigator or subinvestigator deems inappropriate to participate in the trial
- Chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea
- Primary pulmonary hypertension
- Documented contraindication, unacceptable anaphylactic reaction, or uncontrolled allergy to contrast medium not amenable to treatment
- Limited life expectancy of < 1 y at the discretion of the investigator
- Any notable psychiatric disorder, unresolved history of drug use, or alcohol dependency
- Pregnant, nursing, or planning to become pregnant. (A documented negative pregnancy test result is required between informed consent and before study procedure for all women of childbearing potential.)
- Any factor that may affect the result of study assessment (eg, nighttime workers)
- Concurrent enrollment in any other studies and clinical research (Participation in studies of approved products, including medical device, drugs, and regenerative medicine, is acceptable.)
- Other factor for which the investigator or subinvestigator deemed inappropriate for the study subject

BP, blood pressure; CABG, coronary artery bypass graft; CRT-D, cardiac resynchronization therapy device; CTA, computed tomography angiogram; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; MRA, magnetic resonance angiogram; PCI, percutaneous coronary intervention.

Appendix C. Safety assessments—RADIANCE-HTN

Safety events reported throughout study

- All-cause mortality
- Hypertensive emergency resulting in hospitalization
- Hypotensive emergency resulting in hospitalization
- Hospitalization for heart failure
- Stroke, transient ischemic attack, cerebrovascular accident
- Acute myocardial infarction (STEMI/non-STEMI)
- Any coronary revascularization
- End-stage renal disease, the need for permanent renal replacement therapy (ie, the need for dialysis); doubling of plasma creatinine
- Any renal artery complication requiring intervention (eg, dissection and perforation)
- Major access site complications requiring intervention
- Significant embolic events resulting in end-organ damage
- Procedure-related pain lasting for > 2 d
- Acute renal injury, defined as follows:
 - Increase in plasma/serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) within 48 h of the procedure or
 - Increase in serum/plasma creatinine to ≥ 1.5 times baseline known to have occurred during 7 d after procedure or
 - Urine volume < 0.5 mL $\text{kg}^{-1} \text{h}^{-1}$ for 6 h

(continued)

30-d safety events rates	<ul style="list-style-type: none"> • Significant (>50%) and severe (>75%) new-onset renal stenosis as diagnosed by duplex ultrasound and confirmed by renal CTA/MRA or as diagnosed/confirmed by renal CTA/MRA • Need for renal artery angioplasty or stenting • Any renal artery complication requiring intervention (eg, dissection and perforation) • Major access site complications requiring intervention • Significant embolic events resulting in end organ damage • Procedure-related pain lasting for >2 d • Acute renal failure, defined as follows: <ul style="list-style-type: none"> ◦ Increase in plasma/serum creatinine ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) within 48 h of the procedure or ◦ Increase in serum/plasma creatinine to ≥ 1.5 times baseline known to have occurred during 7 d after procedure or ◦ Urine volume < 0.5 mL kg^{-1} h^{-1} for 6 h
6-, 12-, 24, and 36-mo safety event rates	<ul style="list-style-type: none"> • Significant (>50%) and severe (>75%) new-onset renal stenosis as diagnosed by duplex ultrasound and confirmed by renal CTA/MRA or as diagnosed/confirmed by renal CTA/MRA • Need for renal artery angioplasty or stenting • Level of postprocedural pain as determined by the use of a visual analog scale <ul style="list-style-type: none"> ◦ Incidence of severe procedural pain defined as a score of ≥ 8 on the visual analog scale
Additional safety reporting	<ul style="list-style-type: none"> • Incidence of new-onset orthostatic hypotension after procedure • Change (reductions) from baseline in mean eGFR at 2, 6, and 12 mo after procedure • Change (increases) from baseline in mean plasma creatinine at 2, 6, and 12 mo after procedure

CTA, Computed tomography angiogram; eGFR, estimated glomerular filtration rate; MRA, magnetic resonance angiogram; STEMI, ST-elevation myocardial infarction.

Appendix D. Safety assessments—REQUIRE

Safety events reported throughout study	<ul style="list-style-type: none"> • All-cause mortality • Hypertensive episode resulting in hospitalization • Hypotensive episode resulting in hospitalization • Hospitalization for heart failure • Cerebrovascular disorder, transient ischemic attack, cerebrovascular accident • Acute myocardial infarction (STEMI/non-STEMI) • End-stage renal disease, permanent renal replacement therapy (ie, dialysis, renal transplant), doubling of plasma creatinine • Any renal artery complication requiring intervention (eg, dissection and perforation) • Complications in inguinal or femoral region, iliac artery, or ventral aorta requiring intervention • Significant embolic events resulting in end-organ damage • Procedure-related pain lasting for >2 d • Acute renal failure • Bleeding requiring blood transfusion or surgery • False aneurysm • Significant (>50%) and severe (>75%) new-onset renal artery stenosis • Any coronary revascularization • Need for renal artery stenting or angioplasty
30-d safety events rates	<ul style="list-style-type: none"> • Any renal artery complication requiring intervention (eg, dissection and perforation) • Complications in inguinal or femoral region, iliac artery, or ventral aorta requiring intervention • Significant embolic events resulting in end-organ damage • Procedure-related pain lasting for >2 d • Acute renal failure • Bleeding requiring blood transfusion or surgery • False aneurysm
6- and 12-mo event rates	<ul style="list-style-type: none"> • Significant (>50%) and severe (>75%) new-onset renal artery stenosis • Need for renal artery stenting or angioplasty
Additional safety reporting	<ul style="list-style-type: none"> • Incidence of severe procedure-related pain (defined as a score of ≥ 8 by the pain perception evaluation) • Incidence of newly occurred orthostatic hypotension after the procedure • Changes (reductions) in mean eGFR from baseline to 3, 6, and 12 mo after procedure • Changes (increases) in mean creatinine from baseline to 3, 6, and 12 mo after procedure

eGFR, estimated glomerular filtration rate; STEMI, ST-elevation myocardial infarction.

References

1. Franco OH, Peeters A, Bonneux L, et al. Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women. Life course analysis. *Hypertension* 2005;46:280-6.
2. Staessen JA, Li Y, Thijs L, et al. Blood pressure reduction and cardiovascular prevention; an update including the 2003-2004 secondary prevention trials. *Hypertens Res* 2005;28:385-407.
3. Epstein BJ, Shah NK, Borja-Hart NL. Management of hypertension with fixed dose triple combination treatments. *Ther Adv Cardiovasc Dis* 2013;7:246-59.
4. Rahimi K, Emdin CA, MacMahon S. The epidemiology of blood pressure and its worldwide management. *Circ Res* 2015;116:925-36.
5. Miura K, Nagai M, Ohkubo T. Epidemiology of hypertension in Japan. Where are we now? *Circ J* 2013;77:2226-31.
6. Baroletti S, Dell'Orfano H. Medication adherence in cardiovascular disease. *Circulation* 2010;121:1455-8.
7. Burnier M, Wuerzner G, Struijker-Boudier H. Measuring, analyzing and managing drug adherence in resistant hypertension. *Hypertension* 2013;62:218-25.
8. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;34:2159-219.
9. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008;117:e510-26.
10. White WB, Turner JR, Sica DA, et al. Detection, evaluation, and treatment of severe and resistant hypertension: proceedings from an American Society of Hypertension Interactive Forum held in Bethesda, MD, USA, October 10th 2013. *J Am Soc Hypertens* 2014;8:743-57.
11. Schmieder RE, Redon J, Grassi G, et al. Updated ESH position paper on interventional therapy of resistant hypertension. *EuroIntervention* 2013;9:R58-6.
12. Mancia G, Grassi G, Giannattasio C, et al. Sympathetic activation in the pathogenesis of hypertension and progression of organ damage. *Hypertension* 1999;34:724-8.
13. Grisk O, Rettig R. Interactions between the sympathetic nervous system and the kidneys in arterial hypertension. *Cardiovasc Res* 2004;61:238-46.
14. Schlaich MP, Lambert E, Kaye DM, et al. Sympathetic augmentation in hypertension. Role of nerve firing, norepinephrine reuptake, and angiotensin neuromodulation. *Hypertension* 2004;43:169-75.
15. Sobotka PA, Mahfoud F, Schlaich MP, et al. Sympatho-renal axis in chronic disease. *Clin Res Cardiol* 2011;100:1049-57.
16. Evelyn KA, Singh MM, Chapman WP, et al. Effect of thoracolumbar sympathectomy on the clinical course of primary (essential) hypertension. A ten-year study of 100 sympathectomized patients compared with individually matched symptomatically treated control subjects. *Am J Med* 1960;28:188-221.
17. Smithwick RH, Thompson JE. Splanchnicectomy for essential hypertension. *JAMA* 1953;152:1501.
18. Hoobler SW, Manning JT, Paine WG, et al. The effects of splanchnicectomy on the blood pressure in hypertension. A controlled study. *Circulation* 1951;4:173-83.
19. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009;373:1275-81.
20. Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. *Lancet* 2010;376:1903-9.
21. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *NEJM* 2014;370:1393-401.
22. Kario K, Ogawa H, Okumura K, et al. SYMPLICITY HTN-Japan—first randomized controlled trial of catheter-based renal denervation in Asian patients. *Circ J* 2015;79(6):1222-9.
23. Persu A, Kjeldsen S, Staessen JA, et al. Renal denervation for treatment of hypertension: a second start and new challenges. *Curr Hypertens Rep* 2016;18(1):6.
24. Azizi M, Sapoval M, Gosse P, et al. Optimum and Stepped Care Standardised Antihypertensive Treatment with or without Renal Denervation for Resistant Hypertension (DENERHTN): a multi-centre, open-label, randomised controlled trial. *Lancet* 2015;6736:1-9.
25. Azizi M, Pereira H, Hamdidouche I, et al. Adherence to Antihypertensive Treatment and the Blood Pressure Lowering Effects of Renal Denervation in the Renal Denervation for Hypertension (DENERHTN) trial. *Circulation* 2016;134:847-57.
26. De Jager RL, Sanders MF, Bots ML, et al. Renal denervation in hypertensive patients not on blood pressure lowering drugs. *Clin Res Cardiol* 2016;105:755-62.
27. Esler M. Illusions of truths in the Symplicity HTN-3 Trial: generic design strengths but neuroscience failings. *J Am Soc Hypertens* 2014;8:593-8.
28. Epstein M, de Marchena E. Is the failure of Symplicity HTN-3 trial to meet its efficacy endpoint the "end of the road" for renal denervation? *J Am Soc Hypertens* 2015;9:140-9.
29. White WB, Galis ZS, Henegar J, et al. Renal denervation therapy for hypertension: pathways for moving development forward. *J Am Soc Hypertens* 2015;9:341-50.
30. Weber MA, Kirtane A, Mauri L, et al. Renal denervation for the treatment of hypertension: making a new start, getting it right. *J Clin Hypertens* 2015;17:743-50.
31. Mahfoud F, Böhm M, Azizi M, et al. Proceedings from the European Clinical Consensus Conference for Renal Denervation: considerations on future clinical trial design. *Eur Heart J* 2015;36:2219-27.
32. Zannad F, Stough WG, Mahfoud F, et al. Design considerations for clinical trials of autonomic modulation therapies targeting hypertension and heart failure. *Hypertension* 2015;65:5-15.
33. Pathak A, Coleman L, Roth A, et al. Renal sympathetic nerve denervation using intraluminal ultrasound within a cooling balloon preserves the arterial wall and reduces sympathetic nerve activity. *EuroIntervention* 2015;11:477-84.
34. Sakakura K, Roth A, Ladich E, et al. Controlled circumferential renal sympathetic denervation with preservation of the renal arterial wall using intraluminal ultrasound: a next-generation approach for treating sympathetic overactivity. *EuroIntervention* 2015;10:1230-8.
35. Mabin T, Sapoval M, Cabane V, et al. First experience with endovascular ultrasound renal denervation for the treatment of resistant hypertension. *EuroIntervention* 2012;8:57-61.
36. Böhm M, Mahfoud F, Ukena C, et al. First report of the Global SYMPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. *Hypertension* 2015;65:766-74.
37. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004;25:143-56.
38. Dörr O, Liebetrau C, Möllmann H, et al. Soluble fms-like tyrosine kinase-1 and endothelial adhesion molecules (intercellular cell adhesion molecule-1 and vascular cell adhesion molecule-1) as

- predictive markers for blood pressure reduction after renal sympathetic denervation. *Hypertension* 2014;63:984-90.
39. Mahfoud F, Bakris G, Bhatt DL, et al. Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: data from SYMPLICITY HTN-3 and the Global SYMPLICITY Registry. *Eur Heart J* 2017;38:93-100.
 40. Ewen S, Ukena C, Linz D, et al. Reduced effect of percutaneous renal denervation on blood pressure in patients with isolated systolic hypertension. *Hypertension* 2015;65:193-9.
 41. DeFelice A, Willard J, Lawrence J, et al. The risks associated with short-term placebo-controlled antihypertensive clinical trials: a descriptive meta-analysis. *J Hum Hypertens* 2008;22:659-68.