REDUCE-HTN: REINFORCE Study

Renal Denervation Using the Vessix **Reduce**™ Catheter and Vessix™ Generator for the Treatment of **H**yper**T**ensio**N: REINFORCE**

CLINICAL PROTOCOL

IDE G130240

Sponsored By

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Version AG: October 29, 2018 (Not implemented)

Version AH: January 23, 2019

2. Revision History

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
AA	7-Nov-2014	N/A	N/A	Initial Release
AB	6-Jul-2015	Synopsis	Updated Clinical Contact Information	To reflect current contact information
		Synopsis	Corrected rescue medication language	To ensure consistency within the protocol
		Table 11.1-1/ 11.4.5 / 11.9 / 11.11	Added Laboratory Assessments: Renin, Aldosterone	To allow for assessment of renal denervation's effect on the angiotensin system
		11.11	Corrected 6-month follow up window	To ensure consistency within the protocol
		Figure 12.2-1	Updated Addition of Medications Algorithm	To ensure patient safety
		13.1.1.1	Corrected null and alternate hypothesis	To ensure consistency within the protocol
		14.3 / 14.3.4	Added central laboratory	To allow for central analysis of selected serum assessments

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
AC	14-Jan-2016	Synopsis / 8.1	Increase number of centers to 20	To help facilitate timely enrollment
		Synopsis / 7.3	Update Additional Assessments	To ensure consistency with changes to Medication Addition Algorithm
		Synopsis / 11.10 / 12.2	Updated Medication Addition Process	To clarify intent of protocol
		Figure 8.1-1	Updated Study Design Figure	To allow an ABPM one time optional rescreen
		11.5.1 Table 11.18-1	Removed Timeline Requirement	To ensure consistent assessment windows
		12.2	Added Laboratory Source Documentation Requirements	To document data disposition
			Updated Medication Addition Process	To allow investigator discretion when prescribing anti-hypertensive medications
AD	10-Jan-2018	N/A	N/A	Changes proposed to FDA, not approved/not implemented.
AE/AF	N/A	N/A	N/A	Document control system administrative changes only. No content changes.
AG	29-Oct-2018	N/A	N/A	Changes proposed to FDA, not approved/not implemented.

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
AH	23-Jan-2019	Contact Information	Update sponsor contact	Reflect current study contact
		Synopsis / 9.1 / 12.1 / Table 12.1-1 / 12.14-12.17	Updated minimum follow-up visit/assessment requirements to 24 months and added DUS at 24 months	To reduce subject and site effort and collect only the necessary data post enrollment termination of pilot study to ensure subject safety
		Synopsis / 14.1	Updated statistical methods with removal of the primary efficacy statistical hypothesis testing	Due to enrollment termination, insufficient power to make a statistically meaningful conclusion.
		19.4 /19.4.1 / 26.0	Updated confidentiality language	To ensure consistent with current requirements

3. Protocol Synopsis

REDUCE-HTN: REINFORCE	
Objective(s)	To assess safety and efficacy of the Vessix™ Renal Denervation System for the treatment of uncontrolled hypertension [off-treatment office systolic blood pressure (OSBP) ≥150 mmHg and ≤180 mmHg]
Test Device	Vessix Renal Denervation System: • Vessix Reduce™ Catheter (4.0, 5.0, 6.0 and 7.0 mm) • Vessix™ Generator (bipolar radio frequency)
Control Therapy	Masked procedure (renal angiogram)
Device Sizes	The Vessix Reduce Catheter is available in balloon diameters of 4.0 mm, 5.0 mm, 6.0 mm and 7.0 mm with a balloon length of 25 mm and a total catheter working length of approximately 90 cm. The number of electrodes on each balloon varies from 4 to 6 bipolar electrodes, depending on balloon diameter. The catheter is compatible with a 7F guide sheath.
Study Design	Prospective, multicenter, single blinded, randomized, controlled, pilot study
Planned Number of Subjects	Up to 100 randomized subjects
Planned Number of Centers / Countries	Up to 20 centers in the US
Primary Efficacy Assessment	Mean reduction in average 24-hour ambulatory systolic blood pressure (ASBP) at 8 weeks post randomization Due to enrollment termination (51 subjects randomized), the primary efficacy statistical hypothesis testing will not be conducted. All assessments will be observational.
Safety Assessments	<u>Safety Assessments analyzed at all follow-up time points:</u> • All-cause death • Renal failure • Hospitalization for hypertensive crisis • Hospitalization due to severe hypotension/syncope

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	Safety Assessments analyzed at 4 weeks: • Significant embolic event resulting in end-organ damage or intervention to prevent it • Renal artery dissection or perforation requiring intervention • Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion Safety Assessments analyzed at 6 months: • Significant new renal artery stenosis assessed by duplex ultrasound (DUS) and confirmed by the angiographic core laboratory [>70% stenosis by computed tomographic angiography (CTA) or digital subtraction angiography (DSA)] through 6 months post randomization Note: All Safety Assessments will be adjudicated by an independent Clinical Events Committee (CEC).
Additional Assessments	Additional Assessments analyzed at all follow-up time points: • Mean reduction in office-based systolic blood pressure (OSBP) from baseline • Mean reduction in office-based diastolic blood pressure (ODBP) from baseline • Percent of subjects at target blood pressure • Episodes of Congestive Heart Failure (CHF) • Stroke • Myocardial Infarction (MI) Additional Assessments analyzed at 3 and 6 months: • Anti-hypertensive medications Additional Assessments analyzed at 6 and 12 months: • Mean reduction in average 24-hour ambulatory systolic blood pressure (ASBP) from baseline Mean reduction in average 24-hour ambulatory diastolic blood pressure (ADBP) from baseline
Randomization	2:1 (Test:Control) • **Test:** Renal Denervation • **Control:** Masked Procedure (renal angiogram)

REDUCE-HTN: REINFORCE	
Method of Assigning Patients to Treatment	Subjects meeting the eligibility criteria will be randomized at index procedure using an Interactive Randomization System
Follow-up Schedule	All enrolled subjects will be evaluated at 2 (14 ±7 days), 4 (28 ±7 days) and 8 (56±7 days) weeks post randomization. Subjects will be further evaluated at 3 (90±14 days), 4 (120 ±14 days), 5 (150 ±14 days), 6 (180 ±14 days), 12 (365 ±30 days), 18 (545 ±30 days), 24 (730±30 days), 30 (910±30 days), and 36 (1095 ±30 days) months post randomization. All subjects are required to complete follow up through the 24-month time point. After approval of protocol version AH, no further follow up will be required for subjects who have completed at least 24 months of follow up post randomization. Subjects not yet through the 24-month follow up time point will be required to complete follow up through the 24-month visit and will undergo a DUS at the 24-month follow up time point.
Study Duration	It is estimated that it will take approximately 4 years to complete this study.
Medication Wash-out Phase and Medication Additions	After signing the study Informed Consent Form, patients receiving pharmacotherapy for their hypertension will be discontinued from current antihypertensive medications. These patients will be required to complete a 4-week wash-out phase prior to randomization. If a patient is not on antihypertensive medication at the time of Informed Consent, the wash-out period is not applicable. Subjects will remain off antihypertensive medications through the primary efficacy assessment (8 weeks post randomization) unless rescue changes are required. Investigators have ultimate discretion regarding the type of antihypertensive medication and timing of adding rescue medications to ensure subject safety. If subjects are not at target (target defined as OSBP <140 mmHg) from the time of the primary efficacy assessment (8 weeks post randomization) through the 6-month assessment, medications will be added and doses escalated as described in Section 13.3.
Key Inclusion Criteria	• Age ≥18 and ≤75 years

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	• OSBP ≥150 mmHg and ≤180 mmHg based on an average of 3 office-based blood pressure measurements • Average 24-hour ASBP ≥135 mmHg and ≤170 mmHg • For each kidney, a main renal artery, with or without accessory renal arteries, with diameter ≥3.0 mm and ≤7.0 mm and length ≥20.0 mm • Agrees to have all study procedures performed, and is competent and willing to provide written, informed consent
Key Exclusion Criteria	• Previous renal artery intervention or clinically significant renal artery abnormalities that would interfere with safe cannulation of the renal artery • Stenosis >30% or renal artery aneurysm in either renal artery • Fibromuscular dysplasia (FMD) • Platelet count of <90,000 or >500,000 per microliter (μL) of blood or history of bleeding diathesis • Known causes of secondary HTN • Type 1 diabetes mellitus • eGFR <40 mL/min/1.73m^2, as calculated using the MDRD (Modification of Diet in Renal Disease) methodology[1] • Only one kidney or prior transplantation • Contraindicated for anticoagulant therapy and other recommended study medications • Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated • Pregnant or planning to become pregnant • History of myocardial infarction (MI), unstable angina pectoris, hypertensive crisis, or a cerebrovascular accident (CVA) in the previous 3 months • Known ejection fraction of <30% or heart failure that required hospitalization in the previous 6 months • Scheduled for or has planned surgery or cardiovascular (CV) intervention in the next 6 months

REDUCE-HTN: REINFORCE	
	• ≥1 episode(s) of orthostatic hypotension not related to medication changes, coupled with symptoms, within the past year or identified during screening • Severe valvular heart disease • History of any serious medical condition, which in the opinion of the investigator, may adversely affect the safety of the participant and/or the scientific integrity of the study • Active implantable device [e.g., implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy defibrillator (CRT-D), spinal cord stimulators, cochlear implants] • Current participation in another drug or device trial
Multiple Interventions During Index Procedure	There are no concomitant procedures allowed immediately prior to or during the renal denervation procedure.
Statistical Methods	Due to enrollment termination (51 subjects randomized), the primary efficacy statistical hypothesis testing will not be conducted. Descriptive analysis will be performed for data review purposes.

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5. Introduction

5.1. *Hypertension and the Evolution of Renal Denervation*

Management of patients with resistant hypertension continues to be a significant clinical challenge for the health care field and is a major global public health burden. Hypertension is a leading attributable cause of mortality worldwide, causing 7.5 million deaths annually.[2,3,4,5,6] _ENREF_1

As early as the 1930s, surgical procedures of splanchnicectomy and radical sympathectomy were conducted to reduce blood pressure in patients. This research demonstrated that procedures targeted at reducing sympathetic nerve activity achieved blood pressure reductions in the treated patients, demonstrating improved long-term outcomes.[7,8] However, these methods were abandoned because they were associated with high perioperative morbidity and mortality and long-term complications.[2,3,8,9] Radio frequency[9] current has been used for decades in the operating room to safely and effectively create surgical lesions and to facilitate hemostasis.[10,11] The technique of catheter based RF ablation to treat arrhythmias was developed as an adaptation of electrosurgical cautery.

In the late 1990s, the connection between hypertension and the sympathetic nervous system, specifically the renal nerves, was reconfirmed._ENREF_12 Shortly thereafter, catheter-based RF ablation was applied to renal nerves as a hypertension treatment.[12] Clinical evidence continues to confirm that the renal efferent sympathetic nerves and afferent sensory nerves that lie within and immediately adjacent to the wall of the renal artery are crucial for initiation and maintenance of systemic hypertension.[2,3,12] Renal sympathetic efferent nerve activity participates in renin release, sodium retention and reduced blood flow which in turn, contributes to the development and maintenance of hypertension .[4] Renal sympathetic afferents are recognized as seminal in conveying central sympathetic drive in patients with both chronic kidney disease and end-stage renal disease.[4] Thus, inhibition of the renal sympathetic efferent or afferent nerves (or both) represents an attractive treatment of established hypertension.

Today, despite the availability of numerous antihypertensive drugs, dietary and lifestyle changes, hypertension remains an issue in a considerable number of patients. New innovative therapeutic approaches such as renal nerve ablation may be particularly relevant for these patients as their hypertensive state puts them at high risk of major cardiovascular events.[2] A recent article by Kostis et al. reported that in hypertensive patients being treated by medication, each month of active treatment was associated with approximately 1 day of life expectancy gain.[13] Renal ablation has the potential to provide a long term effect on hypertension which could increase the patient's life expectancy and reduce the economic burden of a progressive disease state.

5.2. *Clinical Study Summary*

5.2.1. Vessix Vascular, Inc. REDUCE-HTN

The REDUCE-HTN study (NCT 01541865) was initiated by Vessix Vascular, Inc. Laguna Hills, CA in February 2012.

REDUCE-HTN is a prospective, non-randomized, single arm, multicenter study evaluating the safety and feasibility of renal denervation using the Vessix Renal Denervation System in subjects with medication resistant hypertension. The first in man (FIM) cohort enrolled 18 subjects at six centers in Europe (5) and Australia (1) between February 22, 2012 and May 10, 2012. Subjects considered for enrollment had office-based systolic blood pressure (OSBP) ≥160 mmHg while maintaining compliance with a stable drug regimen of ≥3 antihypertensive medications, including one diuretic (unless intolerance was documented), at maximally tolerated doses for a minimum of two weeks prior to enrollment. Subjects were required to have single main renal arteries of diameters ≥3.5 mm and ≤7.0 mm and lengths ≥20.0 mm without significant stenosis (<30% via angiography) or abnormalities to be eligible for enrollment. Subjects with eGFR <45 mL/min/1.73m^2, Type I diabetes mellitus, known/diagnosed secondary hypertension, prior renal artery intervention, or accessory renal arteries >2 mm in diameter that supplied >20% perfusion to the kidney were excluded.

Following CE marking of the Vessix Renal Denervation System, the REDUCE-HTN protocol was amended to allow expanded enrollment in the Post Market Study (PMS). Key protocol modifications for the PMS included enrollment of subjects with renal artery length ≥15 mm or accessory renal arteries, clarification of the exclusion criterion related to abnormal electrocardiogram ("clinically significant") and substitution of the 1-month renal artery duplex ultrasound (DUS) requirement with a 6-month DUS requirement.

Subject recruitment in the REDUCE-HTN Post Market Study was completed on April 8, 2013, with a total of 146 subjects enrolled and treated at 23 centers in Europe (17), Australia (4), and New Zealand (2), including continued follow-up on the 18 subjects in the FIM cohort and 128 newly enrolled post-market study subjects.

All subjects will be followed at 2 weeks and 1, 3, 6, 12, 18 and 24 months. Follow-up assessments will include office blood pressure measurement, blood assays and urinalysis for renal function, renal DUS at 6 months, and ambulatory blood pressure monitoring (ABPM) at 6 and 12-months. Subjects are required to maintain compliance with all antihypertensive medications throughout the follow-up period.

At 6 months, the mean office SBP was 157.5±23.5 mmHg, a reduction of 24.7±22.1 mmHg compared with baseline (P<.0001), thus met the efficacy primary endpoint for the study. Twenty four-hour ambulatory SBP was reduced by 8.4±14.4 mmHg at 6 months (P<.0001). No pre-specified acute safety events occurred. However, one subject (0.7%) was hospitalized for a hypertensive emergency unrelated to medication and/or non-compliance within 1 month of the procedure. One subject (0.7%) had renal artery stenosis which required an intervention. Three other subjects had flow-limiting stenosis in the renal artery at 6 months which did not require intervention. [14]

Subject follow-up in the REDUCE-HTN Study continues and data monitoring activities are ongoing through 2 years post procedure.

5.2.1. Competitive Studies

5.2.1.1. Symplicity™ HTN-1, HTN-2 and HTN-3

In a proof of concept study (Simplicity HTN-1)[6], 50 subjects were enrolled at five European and Australian centers between June 2007 and November of 2008 with follow-up surveillance occurring at 1, 3, 6, 9 and-12-months. Of these enrolled subjects, 45 received bilateral percutaneous RF ablative treatments to the renal sympathetic nervous system. All subjects were followed with office blood pressure measurements, renal angiography between 14-30 days post procedure and magnetic resonance angiography (MRA) at 6 months; blood assays for renal function were collected at each follow-up. A subgroup of 10 subjects was assessed for a reduction of noradrenaline spillover as a measurement of effectiveness of the renal denervation procedure.

HTN-1 clinical outcomes for treated subjects demonstrated a sustained reduction of office blood pressure of -14/-10, -21/-10, -22/-11, -24/-11 and -27/-17 mmHg at 1, 3, 6, 9 and 12 months, respectively. In those subjects assessed for noradrenaline spillover, a mean reduction of 47% (95% CI 28-65%) was observed. For the 5 non-treated subjects, a mean rise in office based blood pressure of +3/-2, +2/+3, +14/+9 and +26/+17 mmHg was observed at 1, 3, 6 and 9 months, respectively. Long term 36-month follow-up data from the Symplicity HTN-1 trial demonstrated a sustained effect of blood pressure reduction on the original treatment cohort.[5,15]

HTN-1 safety outcomes were satisfactory with one occurrence of an intraprocedural renal artery dissection occurring before RF energy delivery without further sequelae. There were no other renovascular complications or serious adverse events reported.

Building upon previous studies, the two and three year durability of blood pressure reduction via renal sympathetic renal nerve ablation was reported by Krum et al.[5,15] _ENREF_2 A total of 153 patients with resistant hypertension were enrolled in the open label study. Follow-up assessments occurred at 1, 3, 6, 12, 18, 24 and 36 months. Renal nerve ablation resulted in highly significant blood pressure reductions that were maintained over the 3-year follow-up period.

The mean blood pressure reductions reached 32 mmHg for systolic and 14 mmHg for diastolic at 36 months. Ninety-three percent of the patients had an office blood pressure reduction of ≥10 mmHg. The changes in both systolic and diastolic blood pressures were highly significant for all time points post procedure. Blood pressures were reduced on average by 21/10, 24/11, 26/11, 27/12, 26/14, 30/13 and 32/14 mmHg at 1, 3, 6, 12, 18, 24 and 36 months respectively.[15]

The procedure was without complication in 97% of patients (149/153). Complications included renal artery dissection, pseudoaneurysm/hematomas at the femoral access site, minor spasm or edema, progression of a preexisting renal artery stenosis and flank pain. Renal function remained stable during the first year of follow-up with a mean eGFR reduction of 2.9 ml/min/1.73 m2 (95% CI -6.2 to +0.3) for the 64 patients who were available

at 12 months. However, in the ten patients who completed the 24-month follow-up, there was a drop of 16 ml/min/1.73 m2 in eGFR values. The two and three-year durability study demonstrates that significant blood pressure reductions were sustained out to 24 and 36 months which supports the durability of reduction in blood pressure due to renal nerve ablation. The procedure is well tolerated and generally safe.

Based on the positive outcomes observed in HTN-1, a larger randomized trial (HTN-2) was conducted. Simplicity HTN-2[16] was a multicenter prospective randomized trial designed to assess the effectiveness and safety of catheter-based renal denervation to produce a reduction in blood pressure in subjects with 'treatment resistant hypertension'. Of the 190 subjects screened for eligibility, 106 were randomly allocated to renal denervation (n=52) or control (n=54) groups between June 9, 2009 and January 15, 2010. The primary efficacy endpoint consisted of the change in seated office-based measurement of systolic blood pressure at 6 months. The 6-month primary endpoint was assessed in 49 of the 52 subjects who underwent renal denervation and 51 of 54 controls. Office based blood pressure in the renal denervation group reduced by -32/-12 mmHg (baseline of 178/96 mmHg), whereas blood pressures did not differ from baseline in the control group (+1/0 mmHg, baseline of 178/97 mmHg).

After the primary endpoint was met, 46 control patients (cross over group) underwent renal denervation. Esler et al[17] _ENREF_18 reported that the 6-month follow up of the cross over group showed a significant drop in blood pressure (190.0/99.9 mmHg to 166.3/91.5 mmHg). The one-year follow-up of the initial RDN group continued to show significantly lower blood pressure when compared to baseline office BP; although BP at 12 months was slightly elevated from the 6-month average (-31.7/-11.7 at 6 months compared to -28.1/-9.7 at 12 months).

As with HTN-1, a favorable safety profile was observed in HTN-2. Safety outcomes for HTN-2 demonstrated no serious procedure or device related complications or elevated occurrence rates of adverse events. In the treatment group, one subject had a possible progression of an underlying atherosclerotic lesion but required no further treatment.

The Simplicity HTN-3[18] trial is a pivotal study designed as a prospective, randomized, masked procedure, single-blind trial evaluating the safety and effectiveness of catheter-based bilateral renal denervation for the treatment of resistant hypertension despite compliance with at least 3 antihypertensive medications of different classes at maximal tolerable doses. Bhatt et al[19] report 535 patients were enrolled into the trial; 2 treatment : 1control (masked procedure). The primary efficacy endpoint of mean change at 6 months in systolic office blood pressure was not met. The reduction for the treatment group was -14.13±23.93 mmHg and for the control was -11.74±25.94 mmHg; P=0.26. The study continued to demonstrate safety of the technology with a 1.4% major adverse event rate for the renal denervation group and 0.6% for the masked procedure group. Ongoing discussions continue as to why these results do not replicate those of previous trials. Medication compliance and adjustments are thought to have played a role.[20]

5.2.1.2. EnligHTN™ FIM

The first-in-human, prospective, multi-center, non-randomized study to evaluate the safety and efficacy of the EnligHTN multi-electrode system to interrupt the renal sympathetic nerve

fibers in patients with drug-resistant hypertension was conducted in 46 patients (67% male, mean age 60 years, and mean baseline office blood pressure 176/96 mmHg) with drug-resistant hypertension. The primary efficacy objective was change in office blood pressure from baseline to 6 months. Safety measures included all adverse events with a focus on the renal artery and other vascular complications and changes in renal function. Renal artery denervation, using the EnligHTN system significantly reduced the office blood pressure from baseline to 1, 3, 6 and 12 months by -28/10, -27/10, -26/10 mmHg and -27/-11, respectively (P=0.0001). No acute renal artery injury or other serious vascular complications occurred. Three patients had device and/or procedural related adverse events through the 12-month follow-up. The events were hypotension, progression of renal artery stenosis and progression of hypertensive renal artery disease. Small, non-clinically relevant, changes in average estimated glomerular filtration rate were reported from baseline (87±19 mL/min/1.73 m^2) to 6 months post-procedure (82±20 mL/min/1.73 m^2) and 12 months post-procedure (86±21 mL/min/1.73 m^2).[21,22]

6. Device Description

The Vessix Renal Denervation System consists of the Vessix Reduce Catheter, a non-compliant balloon catheter with bipolar electrodes mounted on the exterior of the balloon, the Vessix Generator (including power supply), and an optional patient extension cable. Study sites will also be provided with Vessix Guide Sheaths and a mobile roll cart for transporting the Vessix Generator.

The Vessix Renal Denervation System is designed to deliver radio frequency (RF) energy to create precisely located and defined local lesions in the renal artery in order to inactivate the sympathetic nerves located in the adventitial layer of the renal artery.

The Vessix Renal Denervation System is CE-marked, TGA-approved and approved for use in other regions, but is investigational in the US.

6.1. *Vessix Reduce Catheter*

The Vessix Reduce Catheter is a sterile, single use, over-the-wire percutaneous transluminal balloon catheter designed to transmit RF energy via surface-mounted electrodes to treat resistant hypertension. The balloon exterior surface carries bipolar electrodes that deliver RF energy to the renal arteries after low pressure (3 ATM) inflation via standard balloon angioplasty techniques. The electrodes are centered axially on a noncompliant PET balloon and are gold for radiopacity, thereby facilitating fluoroscopic visualization (see Figure 6.1-1). The number of electrodes on each balloon varies from 4 to 6 bipolar electrodes, depending on balloon diameter.

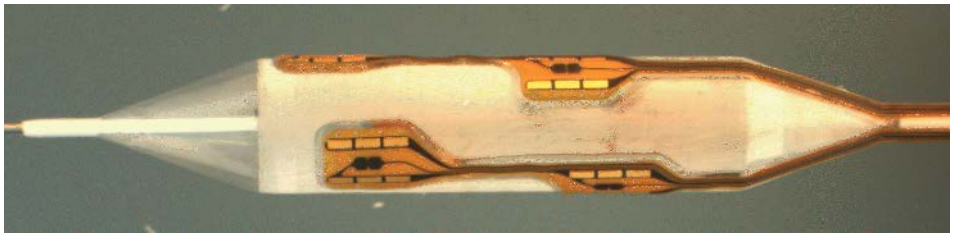

Figure 6.1-1 Vessix Reduce Catheter with Bi-Polar Electrodes

The Vessix Reduce Catheter is available in balloon diameters of 4.0 mm, 5.0 mm, 6.0 mm and 7.0 mm, with a balloon length of 25 mm and a total catheter working length of approximately 90 cm.

The catheter design incorporates standard angioplasty balloon features and is compatible with conventional interventional devices. The balloon is inflated to maximize electrode contact with the artery wall and temporarily occludes blood flow through the renal artery for optimal RF energy conduction. A mix of saline and contrast media is administered through a separate lumen in the catheter shaft by connecting an off-the-shelf inflation device to the Luer lock fitting on the catheter hub.

Concentric to the balloon is a guidewire lumen which extends from the atraumatic distal tip axially to the proximal Luer lock hub port. The guidewire lumen enables the device to be advanced and retracted over a standard, off-the-shelf 0.014-inch or 0.018-inch guidewire. The overall diameter of the catheter shaft is compatible with 7F internal diameter guide sheaths and associated hemostatic control devices. All the fluid connection ports have a Luer lock and allow use of off-the-shelf inflation and hemostasis devices. The catheter is sterilized via E-Beam radiation.

The key dimensional features of the Vessix Reduce Catheter are listed in Table 6.1-1 and the catheter components are illustrated in Figure 6.1-2.

Table 6.1-1 Vessix Reduce Catheter Dimensional Features

Attribute	**Vessix Reduce Catheter**	
Balloon Diameters	4.0 mm, 5.0 mm, 6.0 mm, or 7.0 mm	
Balloon Length	25 mm	
Electrode Treatment Length	21 mm	
Bipolar Electrode Length	4 mm	
Number of Bipolar Electrodes	4.0 mm diameter	4
	5.0 mm, 6.0 mm and 7.0 mm diameter	6
Nominal Balloon Pressure	3 ATM	
Rated Burst Pressure	5 ATM	
Catheter Working Length	90 cm	
Connector Cable Length	145 cm	
Guidewire Compatibility	0.014” and 0.018”	
Guide Sheath Compatibility	7 French	

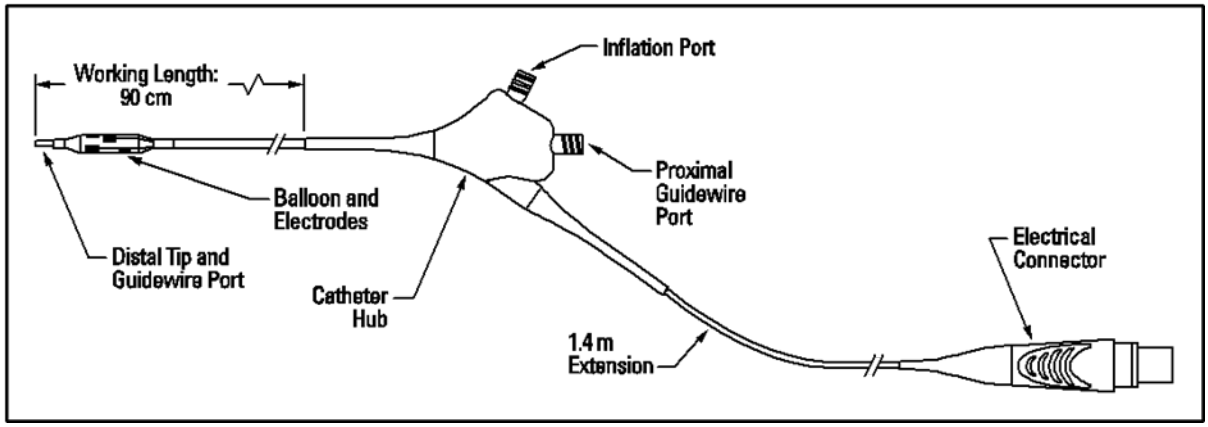

Figure 6.1-2 Vessix Reduce Catheter Components

6.2. *Vessix Generator*

The Vessix generator is a portable bipolar RF generator which interfaces with the catheter to deliver low-power (typically 0.5-2 watts per electrode) RF energy into the renal artery at a treatment frequency of 480 kHz. The generator consists of a bright 9" diagonal LCD screen, minimalistic and user-friendly graphical user interface (GUI), and an assortment of indicator lights (LEDs) and physical buttons.

The generator is classified as a Type BF applied part per ANSI/ASMI IS 60601-1:2009 3rd Edition.

The catheter is connected to the generator either directly or via an intermediate accessory 3 meter patient extension cable. The generator is pole-mounted to a mobile roll stand and does not reside within the sterile field.

6.3. *Patient Extension Cable*

The patient extension cable is a 3 meter cable that connects the Vessix Reduce Catheter to the Vessix Generator and allows for the RF equipment to be located outside the sterile field. Use of the patient extension cable is optional.

6.4. *Power Supply*

A medically-certified power supply will convert wall mains AC to local 15 VDC to power the Vessix Generator. The power supply is not an investigational device.

6.5. *Roll Cart*

The Vessix Generator is mounted onto the top of a mobile roll cart. A bracket is also mounted onto the roll cart in order to secure the Vessix Generator power supply (external power supply brick). A basket is mounted below the Vessix Generator for holding non-sterile items and spooling up the patient extension cable. The roll cart is not an investigational device.

6.6. *Guide Sheath*

The Vessix Guide Sheath will be provided to study sites, along with the system components outlined above. The Vessix Guide Sheath has an inner diameter of 0.10 inch (2.5 mm), Model # H749RDNDCR14500 (RDC) or H749RDNDCL14500 (LIMA). The Vessix Guide Sheath is not an investigational device. It is recommended that the Vessix Reduce Catheter be used with the Vessix Guide Sheath.

6.7. *Device Labeling*

The Vessix Reduce Catheter Directions for Use (DFU), Operator's Manual (OM) and packaging are labeled as investigational. Use of these devices outside of this clinical study is strictly prohibited. A copy of the DFUs and OM will be provided in the local language and are included in the study Manual of Operations. The catheter packaging will include peelable, self-adhesive labels for each unit shipped. The labeling will include the following information in English.

- Product Name
- Universal Part Number (UPN)
- Serial or tracking identification number
- Lot number
- Product dimensions
- Expiration (use by) date

7. Objectives

The objective of the REDUCE-HTN: REINFORCE Clinical Study is to assess safety and efficacy of the Vessix™ Renal Denervation System for the treatment of uncontrolled hypertension [off-treatment office systolic blood pressure (OSBP) ≥150 mmHg and ≤180 mmHg].

8. Endpoints

The endpoints of the study are based upon the safety and efficacy of the Vessix Renal Denervation System.

8.1. *Primary Efficacy Assessment*

The primary efficacy assessment is the mean reduction in average 24-hour ambulatory systolic blood pressure (ASBP) at 8 weeks post randomization.

8.2. *Safety Assessments*

Safety Assessments analyzed at all follow-up time points:

- All-cause death
- Renal failure
- Hospitalization for hypertensive crisis
- Hospitalization due to severe hypotension/syncope

Safety Assessments analyzed at 4 weeks:

- Significant embolic event resulting in end-organ damage or intervention to prevent it
- Renal artery dissection or perforation requiring intervention
- Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion

Safety Assessments analyzed at 6 months:

- Significant new renal artery stenosis assessed by duplex ultrasound (DUS) and confirmed by the angiographic core laboratory [>70% stenosis by computed tomographic angiography (CTA) or digital subtraction angiography (DSA)] through 6 months post randomization
    - Subjects will be required to have a 6-month duplex ultrasound to assess for evidence of significant stenosis, defined as ≥60% as reported by the duplex ultrasound (DUS) core laboratory. A significant stenosis (≥60%) detected by DUS will trigger the performance of a confirmatory CTA or DSA.
    - If a diagnostic duplex ultrasound cannot be adequately achieved at the 6-month follow-up, then a CTA or DSA must be conducted.

NOTE: All Safety Assessments will be adjudicated by an independent Clinical Events Committee (CEC)

8.3. *Secondary Assessments*

Additional Assessments analyzed at all follow-up time points:

- Mean reduction in office-based systolic blood pressure (OSBP) from baseline
- Mean reduction in office-based diastolic blood pressure (ODBP) from baseline
- Percent of subjects at target blood pressure
- Episodes of Congestive Heart Failure (CHF)
- Stroke
- Myocardial Infarction (MI)

Additional Assessments analyzed at 3 and 6 months:

- Anti-hypertensive medications

Additional Assessments analyzed at 6 and 12 months:

- Mean reduction in average 24-hour ambulatory systolic blood pressure (ASBP) from baseline
- Mean reduction in average 24-hour ambulatory diastolic blood pressure (ADBP) from baseline

9. Design

The REDUCE-HTN: REINFORCE Clinical Study is a prospective, single blinded, multicenter, randomized, controlled, pilot study.

9.1. *Scale and Duration*

The REDUCE-HTN: REINFORCE Clinical Study will enroll up to 100 subjects. This study will be conducted at up to 20 study centers in the United States. The expected duration of this clinical study is anticipated to be approximately 4 years. Figure 9.1-1 below outlines the study screening and treatment flow.

After approval of protocol version AH, subjects will be required to complete a minimum of 24 months follow up post randomization.

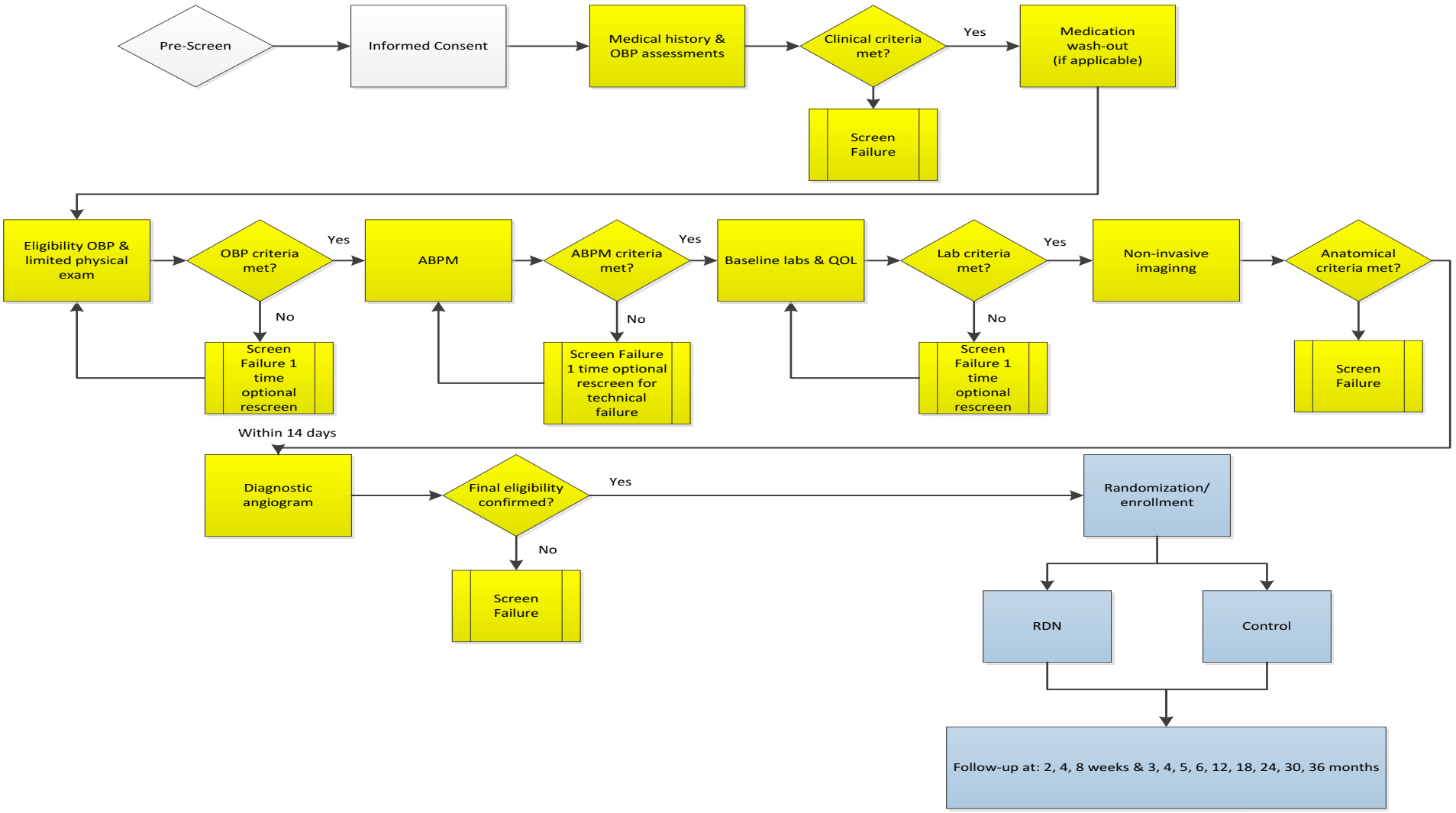

Figure 9.1-1: REDUCE-HTN: REINFORCE Study Design

9.2. *Treatment Assignment*

The REDUCE-HTN: REINFORCE Clinical Study is a randomized study with treatment arm assignments. Subjects who meet all the inclusion criteria and do not meet any exclusion criteria will be assigned to treatment in a 2:1 (Treatment:Control) scheme.

Randomization will be accomplished using an Interactive Randomization System. Subjects will be considered enrolled at the time of randomization.

9.2.1. Treatment and Control

9.2.1.1. Treatment

The device to be evaluated will consist of the Vessix Renal Denervation System:

- Vessix Reduce Catheter (4.0, 5.0, 6.0 and 7.0 mm)
- Vessix Generator (bipolar radio frequency)

9.2.1.2. Control

The control for the primary efficacy assessment is a masked procedure.

9.2.2. Target and Non-target Arteries

For each kidney, main renal arteries and accessory renal arteries (as applicable) which meet all the inclusion criteria and do not meet any of the exclusion criteria will be treated in this study.

9.3. *Justification for the Study Design*

The REDUCE-HTN: REINFORCE Clinical Study is intended to demonstrate the effects of renal denervation in the absence of potentially confounding antihypertensive medications. The design, including an antihypertensive medication wash-out phase, is similar to pharmaceutical study designs looking at early efficacy of compounds. The number of safety events in patients off therapy during the primary efficacy assessment period is low in the pharmaceutical studies.[23,24]

A masked procedure will be used as the control for this study. Subjects and study personnel obtaining OBP will be blinded to treatment assignment. The primary efficacy endpoint will be evaluated using ABPM which minimizes any placebo effect[25]. Subject blinding, the blinded blood pressure assessor and the utilization of ABPM will provide unbiased data in support of efficacy.

Because REDUCE-HTN: REINFORCE Clinical Study is the first study to evaluate the Vessix Renal Denervation System in this off medication population, actions will be taken throughout the course of the study to minimize risks to enrolled subjects. These risk minimization efforts are summarized in Section 21.2.

10. Subject Selection

10.1. *Study Population and Eligibility*

The subject population for this clinical study will be drawn from the Investigators' general or professional referral population. The inclusion and exclusion criteria are included, respectively, in Sections 10.2 and 10.3 below.

10.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 10.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 10.3) is met.

Table 10.2-1: Inclusion Criteria

- Age ≥18 and ≤75 years
- OSBP ≥150 mmHg and ≤180 mmHg based on an average of 3 office-based blood pressure measurements
- Average 24-hour ASBP ≥135 mmHg and ≤170 mmHg
- For each kidney, a main renal artery, with or without accessory renal arteries, with diameter ≥3.0 mm and ≤7.0 mm and length ≥20.0 mm
- Agrees to have all study procedures performed, and is competent and willing to provide written, informed consent

10.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 10.3-1) will be excluded from this clinical study.

Table 10.3-1: Exclusion Criteria

Exclusion Criteria	• Previous renal artery intervention or clinically significant renal artery abnormalities that would interfere with safe cannulation of the renal artery • Stenosis >30% or renal artery aneurysm in either renal artery • Fibromuscular dysplasia (FMD) • Platelet count of <90,000 or >500,000 per microliter (µL) of blood or history of bleeding diathesis • Known causes of secondary HTN • Type 1 diabetes mellitus • eGFR <40 mL/min/1.73m^2, as calculated using the MDRD (Modification of Diet in Renal Disease) methodology[1] • Only one kidney or prior transplantation • Contraindicated for anticoagulant therapy and other recommended study medications • Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated • Pregnant or planning to become pregnant • History of myocardial infarction (MI), unstable angina pectoris, hypertensive crisis, or a cerebrovascular accident (CVA) in the previous 3 months • Known ejection fraction of <30% or heart failure that required hospitalization in the previous 6 months • Scheduled for or has planned surgery or cardiovascular (CV) intervention in the next 6 months • ≥1 episode(s) of orthostatic hypotension not related to medication changes, coupled with symptoms, within the past year or identified during screening • Severe valvular heart disease • History of any serious medical condition, which in the opinion of the investigator, may adversely affect the safety of the participant and/or the scientific integrity of the study • Active implantable device [e.g., implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy defibrillator (CRT-D), spinal cord stimulators, cochlear implants] • Current participation in another drug or device trial

11. Subject Accountability

11.1. *Informed Consent*

All subjects will be required to sign an informed consent form prior to the conduct of any study specific tests or procedures that are not standard of care. No study specific data will be collected without first obtaining written consent for study participation.

11.2. *Point of Enrollment*

Once a subject has signed the IRB approved study informed consent form, and has met all clinical inclusion and no clinical exclusion criteria, the subject will be considered eligible to be enrolled in the trial. If a subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be enrolled. If the subject is found to meet the inclusion criteria during the diagnostic angiographic phase of the procedure, he/she should be randomized to Treatment or Control using the Interactive Randomization System at which time the subject is considered enrolled in the study.

11.3. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal may include but are not limited to:

- Physician discretion
- Subject choice to withdraw consent
- Lost to follow-up or death

While study withdrawal is discouraged, subjects may withdraw from the study at any time with or without reason, and without prejudice to further treatment.

Additional data may not be collected after the point at which the subject has been withdrawn from the study, or withdraws his/her consent. All open adverse events should be closed or documented as chronic (ongoing). Data collected up to the point of subject withdrawal may be used.

11.4. *Subject Status and Classification*

Subjects will be classified in the study based upon subject conditions that relate to the subject selection process/consent process or further procedures. The definitions are:

Screen Failure: A subject who has signed the informed consent and undergoes screening evaluation(s), but is found to not meet the eligibility criteria.

Intent: A subject who has signed the informed consent and is randomized/enrolled in the study.

Per-protocol: A subject who meets the eligibility criteria and is randomized/enrolled in the study and received the assigned treatment (renal denervation or masked procedure).

12. Study Methods

12.1. *Data Collection*

The visit and data collection schedule for the REDUCE-HTN: REINFORCE Study is provided in Table 12.1-1. Subjects may be followed for up to 36 months but are only required to complete follow up through the 24 month visit.

Table 12.1-1: REDUCE-HTN: REINFORCE Study Data Collection for Scheduled Visits

	Screening / Baseline	RDN and Masked Procedure	Hospital Discharge	2 Wks (14±7 days)	4 Wks (28±7 days)	8 Wks (56 ±7 days)	3 Mon (90 ±14 days)	4 Mon (120 ±14 days)	5 Mon (150 ±14 days)	6 Mon (180 ±14 days)	12 Mon (365 ±30 days)	18 Mon (540 ±30 days)	24 Mon (730 ±30 days)	30 Mon (900 ±30 days)	36 Mon (1095 ±30 days)
Office Seated BP x 3; Standing BP; Heart Rate; Height & Weight; Limited Physical Exam	X		X	X	X	X	X	X	X	X	X	X	X	X[3]	X[3]
24-hour Ambulatory BP	X				X	X				X	X				
Quality of Life (PGWBI)	X					X				X	X		X		X[3]
Renin[2]	X					X				X					
Aldosterone[2]	X					X				X					
Serum Creatinine	X		X			X				X	X		X		X[3]
CBC with platelets, BMP, HbA1c	X		X			X				X	X		X		X[3]
Pregnancy Test (as applicable)	X	X													
CTA	X									X[1]			X[4]		
Renal Angiogram (DSA)		X								X[1]			X[4]		
Renal Duplex Ultrasound (DUS)										X			X[4]		
Adverse events assessment		X	X	X	X	X	X	X	X	X	X	X	X	X[3]	X[3]
Blinding Index Assessment			X			X				X					

[1] A Renal DUS is required for subjects who receive treatment. If DUS shows a ≥60% stenosis per the core laboratory or is inconclusive per the core laboratory after repeat DUS, CTA or DSA are required.

[2] Renin and Aldosterone Serum tests will be collected at screening/baseline, 8 weeks and 6 months post-randomization. Subjects that are enrolled/randomized prior to the implementation of protocol version AB will not undergo Renin or Aldosterone testing

[3] Visit/assessment not required after approval of protocol version AH.

[4] Only subjects who received treatment and reach the 24 month follow up after approval of protocol version AH will be required to undergo a DUS at 24 months. If the DUS shows a ≥60% stenosis per the core laboratory or is inconclusive per the core laboratory after repeat DUS, a CTA or DSA is required.

12.1.1. Medical Equipment Description

12.1.1.1. Office-based Blood Pressure Monitoring

Office-based blood pressure (OBP) measurements will be collected during screening, at hospital discharge and each study follow-up visit with an automatic oscillometric Omron HEM-705CP-II monitor (Omron Healthcare, Vernon Hills, IL, USA) with a printer for documentation. Blood pressure will be measured according to the Standard Joint National Committee VII[26] and the European Society of Cardiology and European Society of Hypertension[27] recommendations. The devices should be properly maintained and regularly calibrated according to the manufacturer's recommendations.

Office-based blood pressure must be obtained by study personnel that are blinded to treatment assignment through the 6-month follow-up visit. Site blinding guidelines are described in the Manual of Operations.

Refer to the instruction manual for the OBP monitor for set up and care information, and instructions for preparing the subject for blood pressure (BP) measurements, applying the BP cuff, taking the BP measurements and using the monitor in special conditions (i.e., SBP >220mmHg).

NOTE: A properly sized BP cuff should be selected based upon the subject's arm circumference.

During subject preparation the subject should:

- avoid smoking, eating or vigorous exercise for 30 minutes prior to the BP measurements
- sit quietly for 5 minutes prior to the measurements
- sit in a chair with feet flat on the floor
- rest arm on a table so that the cuff is at the same level as the heart
- avoid talking during the measurements

NOTE: The BP should be measured in both upper arms at the screening visit to detect possible differences in the measurements. The arm with the higher values should be used for baseline and all subsequent measurements. It is recommended to obtain follow-up BP measurements at the same time of day as the baseline measurements are obtained.

Three (3) BP measurements will be obtained using the same arm at least 2-3 minutes apart during a single visit. The provided monitor must be used for all OBP measurements. If the lowest and highest systolic BP (SBP) measurements are more than 15 mmHg apart, additional readings should be performed. The last 3 consecutive consistent SBP measurements will be averaged to determine the final value to be used to assess eligibility. If the lowest and highest SBP measurements are more than 20 mmHg apart after a total of six measurements, the measurements will not be used to assess study eligibility, but the subject's OBP may be reassessed for study eligibility at a subsequent time point. If the lowest and

highest SBP values remain more than 20 mmHg apart after 6 measurements at a subsequent assessment, the patient will be excluded from the study.

To assess for orthostatic hypotension during screening and follow-up, a standing BP measurement must be obtained within 3 minutes of assuming a standing position using the standardized equipment provided for the study.

NOTE: The heart rate will be recorded at the same time as all blood pressure measurements.

12.1.1.2. 24-Hour Ambulatory Blood Pressure Monitoring

24-hour ambulatory blood pressure monitoring (ABPM) will be performed at screening, the 4 and 8-week, and 6 and 12-month follow-up visits post randomization. A qualified ABPM core laboratory will be utilized. The core laboratory will provide validated ABPM equipment to all study sites.

The ABPM measurements will be collected with the Microlife® Watch BP-03 (Microlife Intellectual Property GMBH, Great Neck, NY, USA) with readings taken as described in ABPM Core Laboratory Manual and overall 24-hour averages calculated for each subject. Minimum acceptance criteria, as described in the Manual of Operations, are required for inclusion of the ABPM data. If the minimum acceptance criteria are not met, the ABPM procedure may be repeated if the study visit window allows.

ABPM data will be transmitted to, reviewed and managed by the core laboratory, and reported to Boston Scientific Corporation (BSC) or delegate for analysis purposes.

The ABP monitor set up, care information, instructions for preparing the subject for ABPM measurements, applying the ABPM cuff, fitting the ABP monitor and transmitting the ABPM data are outlined in the ABPM Core Laboratory Manual.

12.2. *Study Candidate Screening*

Subjects will be pre-screened for participation in the study through a review of medical records and attainment of clinical data to support the eligibility criteria (inclusion and exclusion criteria) through normal standard of care procedures.

12.3. *Informed Consent*

All subjects who appear to meet the eligibility criteria based on pre-screening will have the study explained to them. They will be provided a copy of the written informed consent form (ICF) and extended an invitation to sign the form to allow further assessments to be conducted to determine their eligibility to participate in the study.

Study personnel should explain to the subject that even if the subject agrees to participate in the study and signs the ICF, screening assessments prior to randomization/enrollment, including the diagnostic angiogram, may demonstrate that the subject is not a suitable candidate for the study.

12.3.1. Post-Consent Eligibility Validation

Participation in the study begins with signing the informed consent as described in Section 11.1. During the screening period (see Section 12.4) eligibility for the study is assessed. If the subject does not meet the eligibility criteria, the subject will be considered a screen failure and no further follow-up will be required.

12.4. *Screening*

All screening assessments are to be conducted at the study site by the study staff. The tests required at screening are summarized in Table 12.1-1 and described in Sections 12.4 to 12.4.7.

If the subject is found to not meet study eligibility criteria during the screening period, including during diagnostic angiography, the subject will be considered a screen failure and should not be randomized/enrolled. A Screening Log will be maintained in the EDC system to document selected information about subjects who fail to meet the REDUCE-HTN: REINFORCE Clinical study eligibility, including the reason for screen failure.

12.4.1. Demographics and Medical History (within 50 or 21 days prior to randomization)

Demographic data (age, gender, race, etc.) will be collected within 50 days (for patients requiring wash-out) or 21 days (for patients not requiring wash-out) of randomization. A comprehensive medical history will be collected to verify inclusion/exclusion criteria.

12.4.2. Medication Wash-Out Period [a minimum of 4 weeks (28 days) prior to randomization]

All patients that meet medical history requirements and sign the study Informed Consent Form will be discontinued from current antihypertensive medications, as applicable. There will be a 4-week wash-out phase prior to randomization. If a patient is not on antihypertensive medication at the time of Informed Consent, the wash-out period is not applicable.

12.4.3. Limited Physical Examination (within 21 days prior to randomization)

A limited physical examination, including weight and height will be conducted.

12.4.4. Blood Pressure Monitoring (within 21 days prior to randomization)

12.4.4.1. Office-Based BP and Heart Rate

Office-based blood pressure measurements collected during the screening period will be used to determine whether or not the subject meets the inclusion criteria. Office-based blood pressures will be measured using an electronic sphygmomanometer (Omron HEM-705CP-II monitor (Omron Healthcare, Vernon Hills, IL, USA) according to the instructions in Section 12.1.1.1. A heart rate will be recorded at the time of each blood pressure measurement. The

office-based blood pressure measurements documenting study eligibility must be performed after the medication wash-out period if applicable and within 21 days prior to randomization.

12.4.4.2. 24-Hour Ambulatory BP Monitoring

24-hour Ambulatory BP Monitoring, during the screening period, will be used to determine whether or not subjects meet the study inclusion criteria. 24-Hour Ambulatory Blood Pressure Monitoring will be performed as outlined in the Ambulatory Blood Pressure Monitoring Core Laboratory Manual. The ABP measurement documenting eligibility must be performed after the medication wash-out period if applicable and within 21 days prior to randomization.

12.4.5. Laboratory Assessments and Calculations (within 21 days prior to randomization/enrollment)

All subjects will have screening blood assays conducted including basic metabolic panel (BMP) of sodium, potassium, calcium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN) and serum creatinine. The serum creatinine (plus demographic, height and weight data) will be used to calculate an estimated glomerular filtration rate (eGFR). In addition, renin, aldosterone, HbA1c and complete blood count (CBC) with platelet count will be collected.

A urine or serum pregnancy test will be performed on all prospective female subjects of child-bearing potential within 24 hours of randomization.

12.4.5.1. eGFR Calculation

The Modification of Diet in Renal Disease (MDRD) Study[1] equation will be used to calculate the eGFR for all subjects enrolled in the study. The MDRD calculation utilizes the serum creatinine reported in mg/dL and is normalized to a 1.73 m^2 body surface area, which is an accepted average adult body surface area. See the definition and formula in Table 27.2-1: Definitions Table 27.2-1.

12.4.6. Non-Invasive Imaging (within 6 months prior to informed consent)

12.4.6.1. Computed Tomographic Angiography (CTA)

A computed tomographic angiography (CTA) of the kidneys must be performed using standard techniques to confirm that all anatomical inclusion criteria have been met, and that none of the exclusion criteria have been met. The CTA may have been performed within 6 months of the patient signing Informed Consent. If a CTA has not been previously performed, it is recommended that the CTA be performed once office and ambulatory BP eligibility has been confirmed.

Visual assessment will be used to determine if criteria are met. This initial anatomic assessment should be recorded in the subject medical records to document that study eligibility criteria have been met. CTA images must be sent to the angiographic core laboratory for evaluation.

NOTE: Final anatomic eligibility will be confirmed during diagnostic angiography (see Section 12.5.1.1).

12.4.7. Quality of Life Assessment (within 7 days prior to randomization)

Quality of Life (QOL) Survey: Psychological General Well-Being Index (PGWBI)[28] will be administered to the subject within seven (7) days prior to randomization.

12.5. *Treatment Period*

For the REDUCE-HTN: REINFORCE Clinical Study, subjects will be randomized to either the control group, who will receive a masked procedure or to the treatment group, who will receive renal denervation. All subjects will be washed out from antihypertensive medications and remain off medications through the primary efficacy assessment at 8 weeks post randomization unless rescue medication is required as described in Section 13.1.

12.5.1. Diagnostic Renal Angiogram, Masked Procedure and Renal Denervation Procedure

Patients meeting all clinical eligibility and anatomic eligibility based on non-invasive imaging will undergo diagnostic renal angiography. If anatomic eligibility is confirmed during the diagnostic angiogram, the patient will be immediately randomized and enrolled to the control or to the renal denervation treatment.

12.5.1.1. Diagnostic Renal Angiogram

A diagnostic aortogram should be performed to obtain visual confirmation of all renal arteries. A selective arteriogram will be performed on each renal artery using a diagnostic catheter in order to confirm anatomic eligibility is met.

NOTE: If new anatomical exclusion criteria are identified during the angiogram the patient should not be randomized.

Upon catheter/sheath removal, either manual compression or commercialized closure devices can be used to achieve hemostasis at the puncture site. Standard-of-care post-intervention monitoring procedures should be followed.

Angiographic images must be sent to the angiographic core laboratory for evaluation.

12.5.1.1.1 Diagnostic Angiogram Medications

Investigators should prescribe procedural medications consistent with current clinical practice for renal endovascular procedures. Consider pre-treatment with anxiolytic medications. Subjects must be sedated. Intra-arterial vasodilators may be administered during angiogram to prevent spasm.

Investigators should ensure close monitoring of the amount of contrast for subjects with low baseline eGFRs.

12.5.1.2. Masked Procedure

The masked procedure will consist of the diagnostic renal angiogram performed to confirm anatomic eligibility (see Section 12.5.1.1).

12.5.1.2.1 Masked Procedure Medications

Investigators should prescribe procedural medications as described for the diagnostic angiogram in Section 12.5.1.1.1.

12.5.1.3. Renal Denervation Procedure

Investigators should practice standard of care for procedures not defined in the protocol, Vessix Reduce Catheter Directions for Use (DFU) or Vessix Generator Operators Manual (OM). The DFU and OM contain more detailed Vessix Reduce Catheter preparation, Vessix Generator operation, cable connections, power algorithms and trouble-shooting instructions.

Investigators should consider placement of a Foley catheter and make additional allowances for appropriate analgesic.

12.5.1.3.1 Renal Denervation Procedure Medications

Investigators should prescribe procedural medications consistent with current clinical practice for subjects randomized to renal denervation treatment. Anti-coagulation therapy administered during the procedure should be consistent with current clinical practice for renal endovascular procedures. There is no protocol requirement for heparin reversal or antiplatelet therapy post-procedure. Investigators may consider a low dose aspirin regimen if they feel that prophylactic platelet anti-aggregation is warranted.

There is no clinical evidence to date suggesting the need for anticoagulant/ antiplatelet medications post-treatment.

Subject must be able to tolerate analgesics during the treatment. Consider pre-treatment with both anxiolytic medications and analgesic medications, such as morphine sulfate or fentanyl. Subjects must be sedated. Intra-arterial vasodilators may be administered during the procedure or prior to final angiogram after completing the procedure to prevent spasm.

Investigators should ensure close monitoring of the amount of contrast for subjects with low baseline eGFRs.

12.5.1.3.2 Renal Artery Access

- Use a femoral puncture technique to insert an appropriately sized (5 or 6F) introducer sheath. An activated clotting time (ACT) of >200 seconds is recommended prior to the initiation of the renal denervation procedure.
- The appropriate Vessix Reduce Catheter to be used for the treatment should be identified from the information in Table 12.5-1 below.

Table 12.5-1: Vessix Reduce Catheter Sizing

Recommended Catheter Sizing Table	
Artery Size	**Balloon Size**
3.0 - 4.0 mm	4.0 mm
3.8 - 5.0 mm	5.0 mm
4.7 - 6.0 mm	6.0 mm
5.6 - 7.0 mm	7.0 mm

- The short sheath should be exchanged for the recommended 7F guide sheath (Vessix Guide Sheath).
- Introduce a 0.014 inch or 0.018 inch guide wire into the renal vasculature via the guide sheath. The wire should be placed beyond the bifurcation. Once access is secured, the Vessix Reduce Catheter should be prepared for treatment.

12.5.1.3.3 Placement of Vessix Reduce Catheter

- Insert the Vessix Reduce Catheter over the guide wire through the sheath. If resistance is encountered, do not force passage. Resistance may indicate a problem and may result in damage to the balloon circuitry if it is forced. If significant resistance is encountered, remove and replace the Vessix Reduce Catheter.
- Advance the Vessix Reduce Catheter over the guide wire until the balloon is fully inside the renal artery, and the distal electrode is located 3 - 5 mm proximally to the first bifurcation, using direct fluoroscopic visualization. Do not torque the Vessix Reduce Catheter during insertion or placement.
- Utilize the proximal and distal electrodes on the balloon as a reference to optimally position the Vessix Reduce Catheter.

  NOTE: Due to the length of the balloon catheter and average length of the renal artery, no more than two non-overlapping treatments per artery are expected.

12.5.1.3.4 Vessix Reduce Catheter Activation and RF Treatment

- Once connection to the Vessix Generator is confirmed, the Vessix Reduce Catheter can be inflated moving in 0.5 ATM increments up to a pressure of 3.0 ATM.
- When proper apposition is confirmed by the Vessix Generator upon balloon inflation, fluoroscopy should be used to demonstrate that the catheter is at the optimal position and that blood flow is occluded. Discontinue use of the Vessix Reduce Catheter if excessive pressure is required to inflate the balloon.
- Perform the denervation treatment. (See Vessix Generator Operators Manual).
- Initiate the treatment by pressing the Treat Button on the front of the Vessix Generator. (See the Vessix Generator Operators Manual).
- If the more proximal portion of the artery needs to be denervated to achieve treatment of the full length of the renal artery, avoid overlap of treatment zones. It is

recommended that the gap between treatment zones is approximately 5mm. (**NOTE:** To allow for a partial treatment it is acceptable for the balloon to be located partially outside of the renal artery in the aorta).

- Upon completion of the treatment, deflate the balloon by 0.5 ATM decrements and carefully retract the balloon back into the guide sheath, preferably in a coaxial manner. If resistance is encountered, advance the balloon 5 to 10 mm back into the renal artery, and carefully retract the balloon again into the sheath with care to avoid drawing the sheath into the artery. The guide wire should remain in the renal artery until a selective renal arteriogram has been completed.
- Perform post procedural imaging on the treated renal artery.
- Treat the contralateral renal artery at this time if the Vessix Reduce Catheter is appropriately-sized. If treatment of the contralateral renal artery requires a different balloon size, remove the Vessix Reduce Catheter, and insert an appropriately sized catheter.
- Treat accessory renal arteries at this time if study anatomical criteria are met. Ensure the Vessix Reduce Catheter is appropriately-sized. If treatment of the accessory renal artery requires a different balloon size, remove the Vessix Reduce Catheter, and insert an appropriately sized catheter.

12.5.1.3.5 Vessix Reduce Catheter Deflation and Removal

- Slowly deflate the balloon to negative pressure.
- Carefully retract the Vessix Reduce Catheter through the guide sheath and out of the body.
- Upon guide sheath removal, either manual compression or commercialized closure devices can be used to achieve hemostasis at the puncture site. Standard-of-care post-intervention monitoring procedures should be followed.

Angiographic images must be sent to the angiographic core laboratory for evaluation.

NOTE: Re-treatment with renal denervation is not allowed through the protocol follow-up period.

12.5.2. Data Collection

The following data will be collected during and after the procedure.

- Procedural times
- Device usage data
- Generator display data, including the number of electrodes activated
- Renal anatomical measurements
- Medications
- ACT – should be therapeutic at > 200 seconds once the femoral access is in place prior to the introduction of the investigational device
- Adverse events

12.6. *Hospital Discharge*

Prior to hospital discharge, the following will be reviewed and documented:

- Limited physical examination including height and weight
- Blood assays (serum creatinine, CBC and platelets, BMP and HbA1c)
- Office-based sitting and standing blood pressure (obtained by blinded study personnel) and heart rate
- Medications administered since last visit including medications administered during the hospitalization
- Adverse events
- Blinding index assessment

Subjects should be made familiar with the follow-up study visit schedule and instructed to report any unusual pain or symptomology, medication changes, etc. to the study Investigator between study follow-up visits. Antihypertensive medications should only be added and/or adjusted by study Investigators as described in Figure 13.2-1.

12.7. *Follow-up Visit Week 2 (14 ±7 days)*

The 2-week follow-up office visit (14 ±7 days) will include the following assessments:

- Limited physical exam including height and weight
- Office-based sitting and standing blood pressure (obtained by blinded study personnel) and heart rate
- Medications administered since last visit
- Adverse events

12.8. *Follow-up Visit Week 4 (28 ±7 days)*

The 4-week follow-up office visit (28 ±7 days) will include the following assessments:

- 24-Hour Ambulatory BP Monitoring
- Limited physical exam including height and weight
- Office-based sitting and standing blood pressure (obtained by blinded study personnel in the US) and heart rate
- Medications administered since last visit
- Adverse events

12.9. *Follow-up Visit Week 8 (56 ±7 days)*

The 8-week follow-up office visit (56 ±7 days) will include the following assessments:

- 24-Hour Ambulatory BP Monitoring

- Limited physical exam including height and weight
- Quality of Life Assessment
- Blood assays (serum creatinine, CBC and platelets, renin, aldosterone, BMP and HbA1c)
- Office-based sitting and standing blood pressure (obtained by blinded study personnel in the US) and heart rate
- Medications administered since last visit
- Adverse events
- Blinding index assessment

After completion of the 8-week follow-up assessments, subjects not at target (target defined as OSBP <140 mmHg) will have antihypertensive medications reintroduced as described in Section Medication Additions13.

12.10. *Follow-up Visits Months 3, 4 and 5 (90 ±14 days, 120 ±14 days, 150 ±14 days)*

The 3-month (90 ±14 days), 4-month (120 ±14 days) and 5-month (150 ±14 days) follow-up visits will include the following assessments:

- Limited physical exam including height and weight
- Office-based sitting and standing blood pressure (obtained by blinded study personnel in the US) and heart rate
- Medications administered since last visit
- Adverse events

After completion of the 3, 4 and 5-month OBP follow-up assessments, subjects not at target (target defined as OSBP <140 mmHg) will have antihypertensive medications adjusted or reintroduced as described in Section 13.2.

12.11. *Follow-up Visit Month 6 (180 ±14days)*

The 6-month follow-up office visit (180 ±14 days) will include the following assessments:

- 24-Hour Ambulatory BP Monitoring
- Limited physical exam including height and weight
- Quality of Life Assessment
- Blood assays (serum creatinine, CBC and platelets, renin, aldosterone, BMP and HbA1c)
- Office-based blood sitting and standing pressure (obtained by blinded study personnel) and heart rate
- Medications administered since last visit

- Renal Duplex Ultrasound (DUS) - for subjects who received renal denervation treatment
    - Subjects will be required to have a 6-month duplex ultrasound to assess for evidence of significant stenosis, defined as ≥60% as reported by the duplex ultrasound (DUS) core laboratory. A significant stenosis (≥60%) detected by DUS will trigger the performance of a confirmatory CTA or DSA.
    - If a diagnostic duplex ultrasound cannot be adequately achieved at the 6-month follow-up, then a CTA or DSA must be conducted.
- Adverse events
- Blinding index assessment

NOTE: Control subjects do not require a duplex ultrasound. Unblinding should occur after all other 6-month follow-up assessments are completed.

12.12. *Follow-up Visit Month 12 (365 ±30 days)*

The 12-month follow-up office visit (365 ±30 days) will include the following assessments:

- 24-Hour Ambulatory BP Monitoring
- Limited physical exam including height and weight
- Quality of Life Assessment
- Blood assays (serum creatinine, CBC and platelets, BMP and HbA1c)
- Office-based sitting and standing blood pressure and heart rate
- Medications administered since last visit
- Adverse events

12.13. *Follow-up Visit Month 18 (540 ±30 days)*

The Month 18 follow-up office visit (540 ±30 days) will include the following assessments:

- Limited physical exam including height and weight
- Office-based sitting and standing blood pressure and heart rate
- Medications administered since last visit
- Adverse events

12.14. *Follow-up Visit Month 24 (730 ±30 days)*

The 24-month follow-up office visit (730 ±30 days) will include the following assessments:

- Limited physical exam including height and weight
- Quality of Life Assessment

- Blood assays (serum creatinine, CBC and platelets, BMP and HbA1c)
- Office-based sitting and standing blood pressure and heart rate
- Medications administered since last visit
- Renal Duplex Ultrasound (DUS) - for subjects who received renal denervation treatment and reached the 24-month follow-up visit following approval of protocol version AH:
    - Subjects will be required to have duplex ultrasound to assess for evidence of significant stenosis, defined as ≥60% as reported by the duplex ultrasound (DUS) core laboratory. A significant stenosis (≥60%) detected by DUS will trigger the performance of a confirmatory CTA or DSA.
    - If a diagnostic duplex ultrasound cannot be adequately achieved at the 24-month follow-up, then a CTA or DSA must be conducted.
- Adverse events

12.15. *Follow-up Visit Month 30 (900 ±30 days) [Visit/Assessments Not Required After Approval of Protocol vAH]*

The 30-month follow-up office visit (900 ±30 days) will include the following assessments:

- Limited physical exam including height and weight
- Office-based sitting and standing blood pressure and heart rate
- Medications administered since last visit
- Adverse events

12.16. *Follow-up Visit Month 36 (1095 ±30 days) [Visit/Assessments Not Required After Approval of Protocol vAH]*

The 36-month follow-up office visit (1095 ±30 days) will include the following assessments:

- Limited physical exam including height and weight
- Quality of Life Assessment
- Blood assays (serum creatinine, CBC and platelets, BMP and HbA1c)
- Office-based sitting and standing blood pressure and heart rate
- Medications administered since last visit
- Adverse events

12.17. *Study Completion*

All subjects, independent of group to which they were randomized will be followed through a minimum of 24 months post randomization. BSC will notify the study sites when the follow-up period has ended for all subjects.

12.18. *Source Documents*

Table 12.18-1 includes, but is not limited to, a summary of source document requirements. Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document. Data documented in the eCRF relevant to device deficiencies, relationship of AE to study device(s), may be considered source data for the study.

Table 12.18-1: Source Documentation Requirements

Requirement	Disposition
Written Informed Consent	Retain at study site
24-hour Ambulatory BP Monitor Report	Retain at study site
Medical visit information (vital signs, medication administration, physical exam, etc.) gathered in the clinic/hospital	Retain at study site
Laboratory Test Results and Calculated eGFR	Retain at study site
Renal Duplex Ultrasound (DUS) report	Retain at Core Laboratory
Angiography Reports for Digital Subtraction Angiography (DSA) and Computed Tomographic Angiography (CTA)	Retain at Core Laboratory
Renin and Aldosterone Test Results	Retain at Core Laboratory

Abbreviations: BP=Blood Pressure; eGFR=Estimated Glomerular Filtration Rate

13. Medication Additions

13.1. *Rescue Medications*

Subjects will remain off antihypertensive medications through the primary efficacy assessment (8 weeks post randomization) unless rescue changes are required. Rescue medications will be introduced if a subject's OSBP is ≥180mmHg at two consecutive visits. The OBP recheck visit must occur within 3 days of the initial elevated reading. The recheck OBP should be measured according to the methodology described in Section 12.1.1.1. If rescue medications are required, the investigator should initiate therapy immediately with appropriate agents (typically a 2-drug antihypertensive combination) and it is also

recommended that the Investigator consults with the Study HTN Coordinating Principal Investigator.

NOTE: Investigators have ultimate discretion regarding the type of antihypertensive medication and timing of adding rescue medications to ensure subject safety.

13.2. *Medications for Subjects Not at Target*

If subjects are not at target from the time of the primary efficacy assessment (8 weeks post randomization) through the 6-month assessment, antihypertensive medications will be added and doses escalated. Target blood pressure is defined as OSBP <140 mmHg.

Note: At the 8 week follow up time point, the investigator may use ABPM data, along with OSBP data, to determine the need for anti-hypertensive medications.

Medications and dose escalation must continue until target BP is reached and throughout the 6-month follow-up period. After anti-hypertension medications are introduced and a subject reaches target, no additional medication additions or adjustments should be made prior to the 6-month follow-up assessment other than for rescue of excessively high blood pressures or for symptomatic hypotension.

The recommended medication addition and adjustment protocol is described in Figure 13.2-1. The type and dose of antihypertensive medication is based on Investigator discretion. The recommended algorithm is suggested through the 6-month follow-up visit.

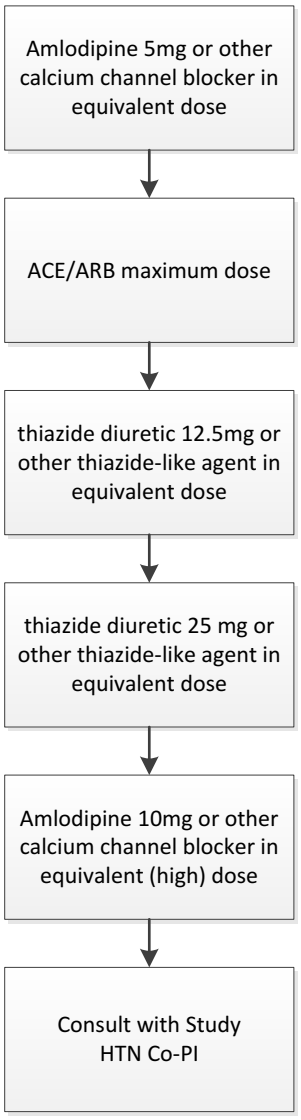

Figure 13.2-1 Addition of Medications Algorithm

13.3. *Medication Adjustment Visits*

Subjects requiring medication additions or adjustments will require a follow-up visit 2 weeks after the antihypertensive drug has been introduced or the dose modified. Investigators must obtain OBP according to the details in Section 12.1.1.1 during the 2-week follow-up visit. Two-week follow-up visits and medication additions/adjustments should continue until blood pressure reaches target.

14. Statistical Considerations

14.1. *Endpoints*

14.1.1. Primary Efficacy Assessment

Due to enrollment termination with approximately half of the planned subjects randomized, the primary efficacy assessment will be observational only. No formal tests of hypotheses will be performed.

The primary efficacy assessment for the study is mean reduction in average 24-hour ASBP through 8 weeks post randomization in subjects treated with renal denervation (Test) and subjects treated with masked procedure (Control).

14.2. *General Statistical Methods*

14.2.1. Analysis Sets

The primary and pre-specified additional assessments will be analyzed on an intent-to-treat (ITT) basis and on a per-protocol basis. For the ITT analysis, all subjects who sign the written ICF and are randomized in the study will be included in the analysis population, regardless of whether the subjects receive the assigned treatment. For the per-protocol analysis, only randomized subjects who meet the eligibility criteria and receive the assigned treatment will be included in the analysis population.

The ITT population will be the primary analysis set for the purpose of assessing superiority of Test to Control for 8-week average 24-hour ASBP reduction. All other endpoint analyses will be based on ITT population.

14.2.2. Randomization Scheme

Randomization to treatment will be stratified by study site. A computer generated list of random treatment allocations (i.e., a randomization schedule) will be used to assign subjects to treatments in a 2:1 ratio of Test to Control. This list will be specific to the subject's site. Random permuted blocks of varying sizes will be employed to ensure approximate balance of treatment allocation within each site.

14.2.3. Control of Systematic Error/Bias

Selection of subjects will be made from the Investigators' general or professional referral population. All subjects meeting the inclusion/exclusion criteria and having signed the ICF will be eligible to enroll in the study. Consecutively eligible subjects should be enrolled into the study to minimize selection bias. Study subjects will be randomly assigned to a treatment group within the investigational site. In determining subject eligibility for the study, the investigator's assessment of imaging will be used. However, the Angiographic Core Laboratory will independently analyze the angiograms for all renal denervation procedures and the data obtained from the core laboratory will be used for analyses in order to control

for inter-observer variability. An independent CEC composed of medical experts will adjudicate safety assessments, as defined in the CEC Charter.

14.2.4. Number of Subjects per Study Site

Study sites will not be allowed to randomize more than 10 subjects without prior approval from the Sponsor (10% of the total number of randomized subjects). No center will be allowed to enroll more than 20 subjects (20% of the total number of randomized subjects).

14.3. *Data Analyses*

Baseline data will be summarized by treatment group for the randomized study. Subject demographics, clinical history, procedure assessment, and medication compliance will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables. The analysis unit may be (but will not be limited to) by subject, catheter, or treatment.

Test and Control in the randomized study will be compared as needed with a Chi-square test or a Fisher exact test for discrete variables and a Student t-Test for continuous variables. The differences between Test and Control in the randomized study and their 95% confidence intervals will be presented as needed.

14.3.1. Additional Assessments/Measurements

No formal tests of hypotheses will be performed for additional assessments. Statistical comparisons may be performed for exploratory purposes. No inferences are planned on the additional assessments and therefore alpha-adjustments for multiple comparisons will not be used.

Blinding index measures will be collected prior to discharge and at 8 weeks and 6 months post-randomization to assess whether the blinding efforts are ultimately successful.

14.3.2. Interim Analyses

One interim analysis was pre-specified in the Statistical Analysis Plan.

14.3.3. Subgroup Analyses

No formal tests of hypotheses will be performed for subgroup analyses. All subgroup analyses will be observational.

14.3.4. Analysis Software

All statistical analyses will be performed using the Statistical Analysis Software (SAS), version 9.2 or later (Copyright © 2002-2010 by SAS Institute Inc., Cary, North Carolina 27513, USA. All rights reserved).

14.3.5. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

15. Data Management

15.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (BSC) or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

15.2. *Data Retention*

The Investigator or Investigational site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

15.3. *Core and Central Laboratories*

Core and central laboratories will be established for the central assessment of key data collected during this clinical study. Detailed guidelines for the collection, analysis and interpretation of the following data will be provided in the Renal Duplex Ultrasound Core Laboratory Manual of Operations, the Angiographic Core Laboratory Manual of Operations, the Ambulatory Blood Pressure Monitoring Core Laboratory Manual of Operations, and the Central Laboratory Manual of Operations. The following core laboratories have been assigned for this study:

15.3.1. Renal Duplex Ultrasound

A renal duplex ultrasound core laboratory has been established to assess renal duplex ultrasounds performed at 6 months and 24 months* following renal denervation treatment during the follow-up period.

*Note: The 24 month DUS will be completed only for subjects who received renal denervation and reached the 24 month follow up after approval of protocol version AH.

15.3.2. Angiography

An angiographic core laboratory has been established to provide quantitative and qualitative analysis of the following tests:

- Computed Tomographic Angiography (CTA) – screening and at 6 months and 24 months*, if renal duplex ultrasound core laboratory results indicate a stenosis ≥60% or are inconclusive when repeated at the recommendation of the core laboratory
- Renal Angiogram (DSA) – renal denervation procedure; review of clinical events; and at 6 months and 24 months*, if renal duplex ultrasound results indicate a stenosis ≥60% or are inconclusive when repeated at the recommendation of the core laboratory

*Note: The 24 month CTA or DSA only applies to subjects who received renal denervation and reached the 24 month follow up after approval of protocol version AH.

15.3.3. Ambulatory Blood Pressure Monitoring

A core laboratory has been established to manage the ABPM system and software setup, ABPM device configuration, study site and BSC personnel/representative training, and data processing of ABPM data including downloads, interpretation and reporting to BSC and study sites. Subjects will undergo ABPM at screening and at 4 and 8 weeks, and 6 and 12 months post randomization.

15.3.4. Serum Analysis

A central laboratory has been established to manage selected laboratory assessments (including Renin and Aldosterone). Subjects will undergo serum testing at screening, 8 weeks and 6 months post randomization.

16. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/FDA) of the revised protocol must be obtained prior to implementation.

17. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using EDC. Sites may also be required to report deviations to the IRB, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) will be put into place by the sponsor.

18. Device/Equipment Accountability

The investigational devices/equipment shall be securely maintained, controlled, and used only in this clinical study. Device accountability records for all investigational devices must be maintained at the study site. The quantity of devices received by the study site, those returned to the supplier, and those used at the study site will be recorded in the device accountability record. The Investigator must explain in writing the reasons for any discrepancy noted in device accountability.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.

Records shall be kept by the investigator to document the physical location and conditions of storage of all investigational devices/equipment.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices/equipment, which shall include the following

- Date of receipt
- Identification of each investigational device/piece of equipment (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the investigational device/piece of equipment was returned or destroyed, as applicable
- Date of return of unused, expired, or malfunctioning investigational devices/equipment, if applicable.

Written procedures may be required by national regulations.

19. Compliance

19.1. *Statement of Compliance*

This study will be conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

19.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following:

- Prior to beginning the study, sign the Investigator Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of

interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency.
- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency

treatment, including decoding procedures for blinded/masked clinical investigations, as needed.

- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

19.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

19.3. *Institutional Review Board*

Prior to gaining Approval-to-Enroll status, the investigational center will provide to the sponsor documentation verifying that their IRB is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB requirements. Copies of the Investigator's reports and the IRB continuance of approval must be provided to the sponsor.

19.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subject name.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

19.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

19.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

20. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

21. Potential Risks and Benefits

21.1. *Anticipated Adverse Events*

Anticipated adverse events that could possibly occur during the study include, but are not limited to:

- Ablation or thermal injury to vessel, adjacent tissue or other structures from energy application
- Allergic reaction (drug, contrast, device or other)
- Arrhythmia
- Arteriovenous (AV) or arterioenteric fistula
- Cardiopulmonary arrest
- Death
- Embolism (air, plaque, thrombus, device or other)
- Hematoma
- Hematuria
- Hemorrhage
- Hypertension
- Hypotension
- Infection and/or Sepsis
- Myocardial infarction (MI)
- Pain
- Pseudoaneurysm

- Renal artery aneurysm
- Renal artery stenosis or acceleration of atherosclerotic disease
- Renal failure or renal insufficiency
- Renal infarction (including due to embolization of plaque or coagulated/charred blood or tissue)
- Transient ischemic attack (TIA) and/or Cerebrovascular accident (CVA)
- Vasospasm
- Vessel trauma (perforation, dissection, or rupture)
- Vessel thrombosis or occlusion

21.2. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

21.3. *Anticipated Benefits*

Subjects participating in this study may experience a similar therapy response as subjects treated with other devices marketed for renal denervation treatment for resistant hypertension. Some potential advantages of the Vessix renal denervation procedure may include shorter treatment times and reduced pain.

21.4. *Risk to Benefit Rationale*

The published data to date for renal denervation treatment for resistant hypertension have demonstrated Major Adverse Event rates as low as 1.4% in the treated cohort.[19] Long-term 24-month data has also demonstrated a sustained reduction of SBP to support the efficacy of renal denervation therapy.[5] Risks associated with the renal denervation procedure are expected to be similar to those related with renal stenting, and the benefits of the treatment have been shown to outweigh the risks.

22. Safety Reporting

22.1. *Definitions and Classification*

Adverse event definitions are provided in Table 22.1-1. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 12/2010.

Table 22.1-1: Safety Reporting Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious

Table 22.1-1: Safety Reporting Definitions

Term	Definition
Note: For US IDE studies only, otherwise remove UADE from table	problem associated with a device that relates to the rights, safety, or welfare of subjects.
Device Deficiency *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. For centers in Austria cancer must always be reported as a Serious Adverse Event. Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see Table 22.1-1 for AE definitions).

Any AE experienced by the study subject after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF.

Refer to Section 21 for the known risks associated with the study device(s).

22.2. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device as related or unrelated. See criteria in Table 22.2-1:

Table 22.2-1: Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

22.3. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 22.3-1. Relevant source documents (de-identified) for specific events must be provided to BSC as described in the Manual or Operations.

Table 22.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect **Note:** UADE is for US IDE studies only, otherwise remove UADE from the table	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
Serious Adverse Event including Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete device deficiency eCRF with all available new and updated information.	• Within 2 business days of first becoming aware of the event and as per local/regional regulations. • Reporting required through the end of the study
Adverse Event	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner after becoming aware of the information • Reporting required through the end of study for CEC AEs • Reporting required through 1-year post randomization for non-CEC AEs

Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect

22.4. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to BSC. If

possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded on the appropriate eCRF.

And any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

22.5. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

BSC is responsible for reporting adverse event information to all participating investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB, and regulatory authorities of UADE and SAE as required by local/regional regulations.

23. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by BSC or its delegate (e.g. CRO), the center's IRB, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's IRB. Any modification requires approval from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,

- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB. The new version of the ICF must be approved by the IRB. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB. The IRB will determine the subject population to be re-consented.

Study personnel should explain to the subject that even if the subject agrees to participate in the study and signs the ICF, screening assessment prior to randomization may demonstrate that the subject is not a suitable candidate for the study. A Screening/Enrollment Log will be maintained to document select information about candidates who fail to meet entry criteria.

24. Committees

24.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Data Monitoring Committee, Clinical Events Committee and BSC Medical Monitor will provide evaluations of safety events. Success of

this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through BSC's safety team, which is responsible for coordinating the collection of information for the subject dossier from the centers and core laboratories. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

24.2. *Data Monitoring Committee*

The independent Data Monitoring Committee (DMC) is responsible for the oversight review of all AEs. The DMC will include leading experts in peripheral interventions or interventional cardiology, hypertension, and biostatistics who are not participating in the study and who have no affiliation with BSC. During the course of the study, the DMC will review accumulating safety data to monitor the incidence of CEC events and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership and committee procedures are outlined in the DMC Charter.

Interim data will be analyzed by the independent DMC statistician. Any DMC recommendations for study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to the BSC. In consultation with the Study Coordinating Principal Investigators, BSC will evaluate the recommendation and make a final decision. However, if the DMC at any time determines that a potentially serious risk exists to subjects in this study, the DMC chairman will immediately notify BSC.

24.3. *Clinical Events Committee*

An independent Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that reviews and adjudicates important endpoints and relevant adverse events reported by study investigators. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites, depending on event timing for, reported case of renal failure, embolic event, vascular complications, renal dissection, renal stenosis, hypertensive crisis, severe hypotension/syncope and death.

Committee membership will include practitioners of peripheral interventions or interventional cardiology, and hypertension as well as other experts with necessary therapeutic and subject matter expertise to adjudicate the event categories outlined above. CEC responsibilities, qualifications, membership and committee procedures are outlined in the CEC Charter.

24.4. *Steering Committee*

A Steering Committee composed of the Sponsor's Clinical Management, the study Co-Principal Investigators and interventional radiologists, interventional cardiologists, vascular surgeons and hypertension specialists will be convened. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee

members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission. As appropriate, the Steering Committee may request participation of REDUCE-HTN: REINFORCE Study Investigators on the Committee.

25. Suspension or Termination

25.1. *Premature Termination of the Study*

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

25.1.1. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

25.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB Approval*

Any investigator or IRB in the REDUCE-HTN: REINFORCE Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

25.3. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating centers by Boston Scientific. The IRB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB terminates participation in the study, participating investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The investigator must return all documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

25.4. *Criteria for Suspending/Terminating a Study Center*

Boston Scientific reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the center will continue to be followed. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.

26. Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. In accordance with the Corporate Policy for the Conduct of Human Subject Research, BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.

- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

27. Abbreviations and Definitions

27.1. *Abbreviations*

Abbreviations are shown in Table 27.1-1.

Table 27.1-1: Abbreviations

Abbreviation/Acronym	Term
ABPM	Ambulatory Blood Pressure Monitoring
ACT	Activated Clotting Time
ADBP	Ambulatory Diastolic Blood Pressure
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
ASBP	Ambulatory Systolic Blood Pressure
ATM	Atmospheres
AV	Arteriovenous
BMP	Basic Metabolic Panel
BP	Blood Pressure
BSC	Boston Scientific Corporation
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CEC	Clinical Events Committee
CHF	Congestive Heart Failure
CI	Confidence Interval
CM	Centimeters
CRO	Contract Research Organization
CRT-D	Cardiac Resynchronization Therapy-Defibrillator
CTA	Computed Tomographic Angiography
CV	Cardiovascular
CVA	Cerebrovascular Accident
DBP	Diastolic Blood Pressure
DFU	Directions For Use
DMC	Data Monitoring Committee
DSA	Digital Subtraction Angiography
DUS	Duplex Ultrasound
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate

Table 27.1-1: Abbreviations

Abbreviation/Acronym	Term
F	French
FDA	Food and Drug Administration
FIM	First in Man
FMD	Fibromuscular Dysplasia
GCP	Good Clinical Practices
HbA1c	Hemoglobin A1c
HCP	Healthcare Professional
HTN	Hypertension
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
kHz	Kilohertz
LCD	Liquid-crystal Display
LED	Light-emitting Diode
M	Meters
MAE	Major Adverse Event
MAOI	Monoamine Oxidase Inhibitor
MDRD	Modification of Diet in Renal Disease
MEDDEV	Medical Device Directives
µL	Microliters
MI	Myocardial Infarction
MM	Millimeters
MRA	Magnetic Resonance Angiography
NSAID	Non-steroidal Anti-inflammatory Drug
OBP	Office-based Blood Pressure
ODBP	Office-based Diastolic Blood Pressure
OM	Operators Manual
OSBP	Office-based Systolic Blood Pressure
PGWBI	Psychological General Well-Being Index
PMS	Post Market Study
RDN	Renal Denervation
RF	Radio Frequency
SADE	Serious Adverse Device Effect

Table 27.1-1: Abbreviations

Abbreviation/Acronym	Term
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VDC	Volts Direct Current

27.2. *Definitions*

Terms are defined in Table 27.2-1.

Table 27.2-1: Definitions

Term	Definition
Congestive Heart Failure Episode	Defined as overnight hospital stay or prolongation of an existing hospitalization for signs and symptoms of heart failure with the use of IV diuretics and/or inotropes
Death	*Cardiac death* - defined as death due to any of the following: 1. Acute myocardial infarction. 2. Cardiac perforation/pericardial tamponade. 3. Arrhythmia or conduction abnormality. 4. Cerebrovascular accident through hospital discharge or cerebrovascular accident suspected of being related to the procedure. 5. Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery. 6. Any death in which a cardiac cause cannot be excluded. *Non-cardiac death* - defined as a death not due to cardiac causes (as defined above). **NOTE:** See Major Adverse Event definition.
Embolic Event	An embolic event causing end-organ damage (unanticipated kidney/bowel infarct, lower extremity ulceration or gangrene, or loss of kidney function). **NOTE:** For Embolic Event, loss of kidney function is defined as Serum Creatinine increased to more than 200% to 300% (>2- to 3-fold) from baseline.[29] **NOTE:** See Major Adverse Event definition.
Estimated Glomerular Filtration Rate	eGFR (mL/min/1.73 m^2) = $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) $\times$ (1.212 if African American/Black) (conventional units)[1]
Known Causes of Secondary Hypertension	Include but are not limited to:

Table 27.2-1: Definitions

Term	Definition
	• Renal disorders (advanced chronic kidney disease, renal artery stenosis, polycystic kidney(s), urinary tract infection, hematuria, analgesic abuse) • Endocrine disorders (pheochromocytoma, hyperaldosteronism, Cushing's syndrome, acromegaly, hyperparathyroidism, hyperthyroidism or hypothyroidism) • Drug/Substance Intake such as certain antidepressants, carbenoxolone (UK), cyclosporine, erythropoietin, hormonal contraceptives, buspirone, carbamazepine, bromocriptine, clozapine, estrogens, NSAIDS, ethanol, nasal decongestants with adrenergic effects, MAOIs, adrenoceptor stimulants, gluco- and mineralocorticosteroids, nicotine use, cocaine, amphetamines, and black liquorice when consumed in excess • Other causes such as neurological disorders, obstructive sleep apnea, scleroderma, neurofibromatosis, pregnancy, cancers, aortic coarctation, bradycardia or ischemia
Hypertensive Crisis	Hypertensive crisis includes hypertensive emergencies and hypertensive urgencies. Hypertensive emergencies are characterized by severe elevations in BP (180/120 mm Hg) complicated by evidence of impending or progressive target organ dysfunction.[26] They require immediate BP reduction (not necessarily to normal) to prevent or limit target organ damage. Examples include hypertensive encephalopathy, intracerebral hemorrhage, acute myocardial infarction, acute left ventricular failure with pulmonary edema or unstable angina pectoris. Hypertensive urgencies are those situations associated with severe elevations in BP without progressive target organ dysfunction. **NOTE:** See Major Adverse Event definition.
Investigational Devices	Vessix Renal Denervation System • Vessix Reduce Catheter (4.0, 5.0, 6.0 and 7.0 mm) • Vessix Generator (bipolar radio frequency)
Major Adverse Event	Through 4 weeks post randomization: • All-cause death • Renal failure

Table 27.2-1: Definitions

Term	Definition
	• Hospitalization for hypertensive crisis • Hospitalization due to severe hypotension/syncope • Significant embolic event resulting in end-organ damage or intervention to prevent it • Renal artery dissection or perforation requiring intervention • Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion Through 6 months post randomization: • Significant new renal artery stenosis >70% assessed by duplex ultrasound (DUS) and confirmed by the angiographic core laboratory [computed tomographic angiography (CTA) or digital subtraction angiography (DSA)]
Orthostatic Hypotension	A fall in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg (as compared to sitting blood pressure measurement) within 3 minutes of assuming a standing position[22]
Renal Artery Dissection (NHLBI Grade Types)	Type A - Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material. Type B - Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles. Type C - Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material. Type D - Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow. Type E - Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen. Type F - Filling defect accompanied by total vessel occlusion. **NOTE:** See Major Adverse Event definition.

Table 27.2-1: Definitions

Term	Definition
Renal Artery Perforation	*Angiographic perforation*: perforation detected by clinical site or the Angiographic Core Laboratory at any point during the procedure. *Clinical perforation*: perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant hemodynamic compromise, abrupt closure, or death. **NOTE:** Only clinical perforations will be considered endpoint events. **NOTE:** See Major Adverse Event definition.
Renal Artery Stenosis	>70% narrowing in the renal artery as confirmed by CTA or DSA. **NOTE:** See Major Adverse Event definition.
Renal Failure	Serum Creatinine increased to more than 300% (>3-fold) from baseline, or more than or equal to 4.0 mg/dL (354 μmol/l) with an acute increase of at least 0.5 mg/dl (44 μmol/L) or on renal replacement therapy.[29] **NOTE:** See Major Adverse Event definition.
Source Data	All information in original records of clinical findings, observation or other activities in a clinical investigation necessary for the reconstruction and evaluation of the clinical investigation
Source Document	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation
Stroke	A new focal neurological deficit or loss of brain function with presumed vascular origin persisting more than 24 hours and with a neuro-imaging study that does not indicate a different etiology. The 24-hour criterion is not applicable if the subject undergoes cerebrovascular surgery or expires secondary to a stroke within the first 24 hours following the onset of the symptoms. It includes subjects presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. It does not include stroke events in cases of

Table 27.2-1: Definitions

Term	Definition
	blood disorders such as leukemia and excludes subjects with a history of stroke secondary to trauma.
Target Blood Pressure	OSBP <140mmHg
Vascular Complications	Clinically significant groin hematoma, arteriovenous fistula, pseudoaneurysm, or excessive bleeding requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion (requiring more than 2 units of packed red blood cells within any 24 hour period during the first 7 days post-renal denervation treatment). **NOTE:** See Major Adverse Event definition.

Abbreviations are defined in Table 27.1-1.

28. Bibliography

[1] Levey AS, Coresh J, Greene T, et al. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-54.
[2] Gewirtz JR, Bisognano JD. Catheter-based renal sympathetic denervation: A targeted approach to resistant hypertension. Cardiology Journal. 2011;18(1):97-102.
[3] Uder M, Schmid A, Titze S, et al. Renal artery denervation for the treatment of hypertension: Opening up new horizons. CardioVascular and Interventional Radiology. 2011;34(3):442-444.
[4] Krum H, Schlaich M, Sobotka P, et al. Novel procedure- and device-based strategies in the management of systemic hypertension. European Heart Journal. 2011;32(5):537-544.
[5] Krum H. Catheter-based renal sympathetic denervation for resistant hypertension: Durability of blood pressure reduction out to 24 months. Hypertension. 2011;57(5):911-917.
[6] 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. The Lancet. 2009;373(9671):1275-1281.
[7] Schlaich MP, Krum H, Sobotka PA. Renal sympathetic nerve ablation: The new frontier in the treatment of hypertension. Current Hypertension Reports. 2010;12(1):39-46.
[8] Schlaich MP, Krum H, Sobotka PA, et al. Renal denervation and hypertension. American Journal of Hypertension. 2011;24(6):635-642.
[9] Kaltenbach B, Id D, Franke JC, et al. Renal artery stenosis after renal sympathetic denervation. J. Am. Coll. Cardiol. 25 2012;60(25):2694-2695.
[10] Zipes D. Therapy: Pulmonary Vein Isolation for Artrial Fibrillation. Cardiac Electrophysiology: From Cell to Bedside. 3 ed2003:1045-1059.
[11] Miller J. Management of the Patient with Cardiac Arrhythmias. Heart Disease: A Textbook of Cardiovascular Medicine. 6 ed2007.
[12] DiBona GF, Kopp UC. Neural control of renal function. Physiol Rev. Jan 1997;77(1):75-197.
[13] Kostis JB, Cabrera J, Cheng JQ, et al. Association between chlorthalidone treatment of systolic hypertension and long-term survival. JAMA. 2011;306(23):2588-2593.
[14] Sievert H, Schofer J, Ormiston J, et al. Renal denervation with a percutaneous bipolar radiofrequency balloon catheter in patients with resistant hypertension: 6-month results from the REDUCE-HTN clinical study. EuroIntervention. 2014; in press.
[15] Krum H, Schlaich MP, Bohm M, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet. 2014; 383(9917):622-9.
[16] Symplicity HTN-2 Investigators, 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.
[17] Esler MD, Krum H, Schlaich M, et al. Renal sympathetic denervation for treatment of drug-resistant hypertension: One-year results from the symplicity htn-2 randomized, controlled trial. Circulation. 18 2012;126(25):2976-2982.

[18] Kandzari DE, Bhatt DL, Sobotka PA, et al. Catheter-based renal denervation for resistant hypertension: rationale and design of the SYMPLICITY HTN-3 Trial. Clin Cardiol. 2012;35(9):528-35.
[19] Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled Trial of renal denervation for resistant hypertension. NEJM. 2014; 370(15): 1393-401.
[20] Bakris GL, Townsend RR, Liu M, et al. Impact of renal denervation on 24-hour ambulatory blood pressure. JACC. 2014; 64(11) : 1071-78.
[21] Worthley SG, Tsioufis CP, Worthley MI, et al. Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial. Eur Heart J. 2013; 34(28):2132-40.
[22] Papademtriou, V, Tsioufis CP, Sinhal A, et al. Catheter-based renal denervation for resistant hypertension 12-month results of the EnligHTN I First-in-Human Study using multielectrode ablation system. Hypertension. 2014;64(3):565-72.
[23] McGill JB and Reilly PA. Telmisartan plus hydrochlorothiazide versus telmisartan or hydrochlorothiazide monotherapy in patients with mild to moderate hypertension: a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. Clin Ther. 2001;23(6):833-50.
[24] White WB, Weber MA, Sica D, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. Hypertension. 2011;57(3):413-20.
[25] Lacourcière Y, Lefebvre J, Poirier L et al. Treatment of ambulatory hypertensives with nebivolol or hydrochlorothiazide alone and in combination. A randomized, double-blind, placebo-controlled, factorial-design trial. Am J Hypertens. 1994;7:137-145.
[26] Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42: 1206–52.
[27] 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). J Hypertens. 2013;31(7):1281-357.
[28] Lundgren-Nilsson A, Jonsdottir I, Ahlborg G, et al. Construct validity of the psychological general well-being index (PGWBI) in a sample of patients undergoing treatment for stress-related exhaustion: a rasch analysis. Health and Quality of Life Outcomes 2013, 11:2.
[29] Ostermann M, Chang R; Riyadh ICU Program Users Group. Correlation between the AKI classification and outcome. Crit Care. 2008;12(6):R144.