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Novel Approaches for the Treatment of the Patient with Resistant Hypertension: Renal Nerve Ablation

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Abstract

Sympathetic innervation of the kidneys plays a major role in the pathogenesis of hypertension through modulation of renin secretion, glomerular filtration rate and renal absorption of sodium. Targeted interventions for renal nerve ablation are being developed for treatment of drug resistant hypertension in the USA and rest of the world. Early studies with the use of radiofrequency based renal denervation systems have shown encouraging results with significant reduction of blood pressure in patients inadequately controlled despite nearly maximal drug therapy regimens. Thus far, the renal denervation procedure has been associated with minimal side effects. Long term efficacy and safety beyond 3 years needs to be determined for renal nerve ablation. This review focuses on the physiology of the renal sympathetic system, the rationale for renal nerve ablation and current evidence in support of the available therapeutic renal denervation systems.

Keywords

resistant hypertension; renal denervation; renal nerve ablation; sympathetic nervous system

Introduction

Sub-optimal blood pressure (BP) control is the most common attributable risk for death worldwide, being responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease (1). Despite the availability of several effective drugs for control of blood pressure, approximately 50% of patients have inadequately controlled blood pressure (2). Resistant hypertension is typically defined as failure to achieve goal blood pressure when a patient adheres to maximum tolerated doses of 3 antihypertensive drugs including a diuretic (3). It is estimated that the prevalence of resistant hypertension in the U.S. varies from 8% to 20% (4, 5). Until recently, therapeutic options for patients with resistant hypertension were limited to drug therapies. However, insights into the pathophysiology of resistant hypertension and understanding of the role of the sympathetic nervous system have led to the development of renal nerve denervation as a potential management option.

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Compliance with Ethics Guidelines

Conflict of Interest

Vinay Gulati declares that he has no conflict of interest.
William B. White is a steering committee member for St. Jude Medical.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Neurogenic Mediated Hypertension and Lumbar Sympathectomy

Recognizing that the sympathetic nervous system played an important role in the pathogenesis of hypertension led to a surgical approach known as radical lumbo-dorsal splanchnicectomy to disrupt catecholamine discharges (6). This technique, developed by Smithwick in 1938, lowered blood pressure and reduced mortality, but at the cost of severe and incapacitating side effects (6,7). Several uncontrolled trials of surgical sympathectomy demonstrated profound improvement in blood pressure control along with reduction in cardiac size, improvement in renal function and lower incidence rates of cerebrovascular events (8–10). However, these beneficial effects were counterbalanced by severe orthostatic hypotension, and with increases in antihypertensive drug development, lumbar sympathectomies were generally discontinued from practice by 1975.

Renal Sympathetic Nervous System

Sympathetic innervation of the kidneys plays a major role in the pathogenesis of hypertension through modulation of renin secretion, glomerular filtration rate and renal absorption of sodium (11, 12). The pre-ganglionic sympathetic neurons originate in the intermediolateral column of the spinal cord at thoracic and lumbar levels (T10 to T12, L1 to L2) and extend via splanchnic nerves to synapse with the post-ganglionic neurons in the pre- and para-vertebral ganglia (13). The renal sympathetic system consists of a dense network of post-ganglionic efferent fibers that run along the renal artery embedded in the adventitia. These filamentous nerves follow the blood vessels and penetrate the cortical and juxtamedullary areas to supply the renal tubular cells, juxtaglomerular apparatus and the vasculature. Efferent fibers increase noradrenaline production and spillover at nerve endings that promotes sodium and water retention, induces renin secretion (mediated by α -1 adrenergic receptors) and reduces renal blood flow through vasoconstriction of renal arterioles (mediated by α adrenergic receptors). These actions stimulate the central nervous system to increase sympathetic tone. Renal norepinephrine spillover is about two to three times greater in both lean and obese patients with primary hypertension relative to individuals with normal BP (14, 15).

Afferent renal sympathetic fibers have an extensive network in the renal pelvis and transmit signals from 2 types of receptors: mechanosensitive receptors that respond to increased hydrostatic pressure and chemosensitive receptors that are activated by hypoxia and renal ischemia. Signals from these receptors travel through the ipsilateral dorsal root ganglia to the central nervous system, in particular the paraventricular nucleus of the hypothalamus. This stimulation of the afferent system increases BP by release of vasopressin and elevation of systemic vascular resistance (16, 17). In addition, afferent fibers communicate with the contralateral kidney balancing unilateral disturbances of salt and water excretion, which has been the basis of the renorenal reflex (18).

Rationale for Renal Nerve Denervation

The concept of renal denervation was initiated from observations made in patients undergoing nephrectomy or renal transplantation and animal models of renal sympathectomy. Increased sympathetic activity has been demonstrated in patients with end stage renal disease requiring dialysis and normalization of that activity following bilateral nephrectomy (19). In contrast, sympathetic overactivity persists in patients whose native diseased kidneys are not removed, further supporting the hypothesis that the kidneys account for the increased sympathetic activity (20). Increased activity of the afferent sympathetic nerve signal is as important as the stimulation of renin-angiotensin system in the genesis and maintenance of hypertension in such patients. This is indicated by studies showing that beta-blocker responsiveness occurs only in those kidney transplant patients whose native kidneys

have not been removed (21). Additionally, central sympatholytic agents induce marked reductions in BP as compared to renin-angiotensin system blockers in patients with end-stage kidney disease (22).

A recent case report of a 59-year old patient with resistant hypertension further elucidated the mechanisms of hypertension control through renal denervation therapy (RDN) (23). In this case, baseline renal norepinephrine spillover from each kidney was about 3 times the normal level, indicating increased renal sympathetic neuronal efferent activity. Bilateral RDN resulted in marked reduction of the BP and decrease of norepinephrine spillover by 48% from the left kidney and 75% from the right kidney associated with a 57% increase in renal plasma flow. Whole-body norepinephrine spillover was reduced by 42%, providing evidence of afferent renal nerve interruption resulting in decreased central sympathetic outflow. Muscle sympathetic nerve activity, assessed by microneurography, decreased toward normal levels at 30 days and 12 months after renal denervation.

Technical Development of Renal Sympathetic Denervation

Sobotka, Krum, and Esler pioneered the technique of percutaneous renal sympathetic denervation, and performed the first studies of catheter-based renal nerve ablation using radiofrequency energy (24). The catheter-based approach was developed to directly target the sympathetic nerves adjacent to the renal artery. The procedure involves insertion of an endovascular catheter under fluoroscopic guidance via the femoral artery using a 6F or 8F guide and advancing it towards the distal renal artery. Ablation of the sympathetic nerves is performed using radiofrequency energy applied via an electrode on the tip of the catheter to the endoluminal surface. The catheter nodes deliver thermal injury selectively to the renal sympathetic nerves without affecting the abdominal, pelvic, or lower-extremity nerves. Multiple radiofrequency treatments are applied circumferentially, initially in the distal renal artery and then proximally on retracting the catheter by increments that depend on the technology. The process is repeated until the entire circumference of the artery has received ablation treatment. The energy delivered is lower than that used for cardiac electrophysiologic procedures and the entire procedure has an average duration of 30–60 minutes.

Selection of the appropriate patient population is essential for clinical trials involving renal nerve ablation. Table 1 outlines the inclusion and exclusion criteria used in clinical trials of renal denervation (25). Of note, the main renal artery length should ideally be 20 mm with a diameter of 4 mm to avoid structural damage to the arterial wall. Relative contraindication to renal nerve ablation also includes renal arteries with visible stenoses, calcification or atheromatous plaques.

Renal nerve ablation procedures should be performed in centers specialized in the management of hypertension with availability of trained interventional cardiologists or radiologists qualified to manage potential complications, such as renal artery dissection by stent implantation. During and for 4 weeks following the procedure, the use of antiplatelet therapy is advised to avoid thrombus formation due to transient local deendothelialization. Monitoring of vital signs should be done continuously during the procedure to avoid potential hypotension. Intraarterial nitroglycerine or verapamil may be required in some patients who develop renal artery edema and/or spasm at the intimal burn sites.

Radiofrequency Ablation (RFA) Technology

Catheter based renal denervation for drug resistant hypertension using a standard electrophysiology catheter has already demonstrated significant reductions in clinic blood pressure in patients resistant to drug therapy (26). These data have paved the way for

development of numerous proprietary systems that are presently undergoing clinical assessment. At present, 4 systems using radiofrequency ablation technology have been approved for phase 3 clinical study programs in the U.S., Europe, and other countries around the world: Medtronic's Symplicity system, St. Jude's EnligHTN system, Boston Scientific's Vessix's V2 system and Covidien's OneShot system.

Symplicity renal denervation system

Initial results have been reported from trials of the Symplicity Renal Denervation System. In the United States, the device (Symplicity Renal Denervation System; Medtronic, Inc., Mountain View, CA) is available only for investigational use while the pivotal safety and efficacy trial is being completed (Symplicity HTN-3).

The first clinical trial with the Symplicity Catheter (Symplicity 1) was an open-label, multicenter study performed in 50 patients out of whom 5 were excluded due to anatomical reasons, who were later used as controls for the analysis (24). The trial was carried out in patients with resistant hypertension (systolic blood pressure ≥ 160 mmHg on 3 or more antihypertensive medications, including a diuretic). Efficacy was assessed in a subgroup of 10 patients by the evaluation of noradrenaline spillover. Reductions in BP at 1-month follow up were 14/10 mmHg. The uncontrolled 36-month follow-up of the cohort showed a reduction in BP of 33/19 mmHg (27). There were 2 procedure-related complications: 1 renal artery dissection related to catheter manipulation and 1 femoral artery pseudoaneurysm. Limitations of this trial included a small number of patients, lack of control group, absence of blinding and a primary outcome of a reduction in office blood pressure (rather than ambulatory blood pressure). The Symplicity HTN-2 (Renal Sympathetic Denervation in Patients with Treatment-Resistant Hypertension) trial is a multicenter, prospective, randomized open-label controlled study in 106 drug-refractory hypertensive patients (28). Office-based BP measurements in the renal denervation group were decreased significantly by $32 \pm 23 / 12 \pm 11$ mmHg ($p < 0.0001$) at 6 months (baseline BP of 178/96 mmHg), whereas they did not differ from baseline in the control (usual care) group (change of $1 \pm 21 / 0 \pm 10$ mmHg, baseline of 178/97 mmHg). Smaller BP reductions were derived from 24-hour ambulatory BP measurements ($11/7 \pm 15/11$ mmHg) however, suggesting that some of the study patients may have had white-coat hypertension at study entry. Sustained blood pressure reductions at 30 months were reported at the American Society of Hypertension meeting in May 2013 (29). Procedure-related adverse events included a single femoral artery pseudoaneurysm treated with manual compression, 1 post-procedural decrease in BP and back pain each, 1 extended hospital stay for paresthesias and one case of urinary tract infection. There were 7 patients (13%) who experienced transient bradycardia requiring atropine but without any sequelae. While Symplicity HTN-2 had superior methodology to Symplicity HTN-1, it was limited by a lack of blinding among data analyzers and absence of a sham procedure in the control group.

To overcome some of the limitations noted in the above-referenced studies with the Symplicity catheter, and to determine longer term efficacy of renal nerve ablation, Symplicity HTN-3 was started in 2011 and is due for completion and reporting of the primary endpoint in 2014; this trial is a randomized, sham-controlled trial in patients with drug-treatment resistant hypertension (clinic SBP > 160 mmHg and 24-hour SBP > 135 mmHg in patients on 3 or more antihypertensive agents) (30). One third of the randomized subjects have been randomized to be in the sham treatment group and a team of blinded investigators and coordinators will assess the longitudinal changes in BP and tolerability.

EnligHTN multielectrode renal denervation system—The EnligHTN renal nerve ablation catheter, developed by St. Jude Medical Inc., St Paul, Minnesota is a

radiofrequency energy delivery device being investigated for patients with drug-resistant hypertension. The multielectrode basket design of the catheter allows simultaneous energy delivery to 4 sites along the endoluminal surface of the artery, thereby reducing the renal denervation procedural time and potentially decreasing the pain associated with the procedure. Preliminary results of the efficacy and safety of this device have been reported from the ARSENAL (Safety and Efficacy Study of Renal Artery Ablation in Resistant Hypertension Patients) trial (31). The trial is a nonrandomized, open-label feasibility study that began enrolling subjects in October 2011 at centers in Australia and Greece. Forty-six patients were treated with the EnligHTN system in the multicenter study. Data reported at various meetings in 2012 and 2013 for the EnligHTN I trial demonstrated that patients with resistant hypertension experienced a mean systolic blood pressure reduction of 28 mmHg after 30 days and that remained stable for up to 12 months after treatment. No serious complications have been reported.

Boston Scientific - Vessix V2 renal denervation system—The V2 renal denervation system (Vessix Vascular Inc., Laguna Hills, California and Boston Scientific, Inc., Minneapolis, MN), consists of the V2 catheter, a patented non-compliant balloon catheter with radio-frequency (RF) electrodes and thermistors mounted on the exterior of the balloon, and the proprietary V2 bipolar RF generator. After insertion into the renal artery, a 30-second inflation/treatment per renal artery delivers simultaneous RF therapy with independent temperature control to all the electrode pairs. The balloon catheter is able to accommodate a smaller renal arterial diameter of 3.0 mm. The shorter RF treatment time should lead to less patient discomfort and allows for lower exposure to radiation and contrast dye. The Vessix V2 balloon catheter is being studied in the REDUCE-HTN (Treatment of Resistant Hypertension Using a Radiofrequency Percutaneous Transluminal Angioplasty Catheter) trial (32). This prospective, non-randomized, open-label feasibility study began enrollment in February 2012 in various centers of Europe and Australia; there is also a 120-patient clinical surveillance study of medication resistant hypertensive patients being conducted through August 2014.

OneShot renal denervation system—The OneShot catheter by Covidien (Dublin, Ireland), features an irrigated balloon-based platform with a helical electrode on its surface to deliver a single RF treatment per artery. The approach should have enhanced consistency of the treatment pattern and avoids the potential for circumferential injury leading to safer and reproducible outcomes. Predictable apposition of the RF electrode to the vessel wall allows for more controlled targeted delivery of the RF energy. In a feasibility study of 8 patients, Covidien's RHAS (Renal Hypertension Ablation System) showed a mean reduction in systolic BP of 42 mmHg at six months (33). The RAPID (Rapid Renal Sympathetic Denervation for Resistant Hypertension) trial is a 50-patient, prospective, open-label, feasibility study that began enrollment in May 2012 and is expected to complete in December 2013.

Other Radio-frequency ablation based renal sympathetic denervation systems

—The Celcius ThermoCool RFA catheter system (Biosense Webster Inc., Diamond Bar, California) ablates the sympathetic nerves using a saline-irrigated catheter. A pilot study done in 10 patients demonstrated decrease in BP by 21/11 mmHg over a period of six months. There was a significant reduction in levels of metanephrines, normetanephrines and aldosterone at 3 months (34). The system is undergoing trials in the SWAN HT (Renal Sympathetic Modification in Patients With Essential Hypertension) study, a nonrandomized open-label safety and efficacy trial in patients with essential hypertension. The study has an anticipated enrollment of 800 patients and is expected completion by August 2016.

The RENABLATE study, started in December 2012 is a prospective, multicenter, non-randomized feasibility study to evaluate the safety and effectiveness of the investigational Celsius® ThermoCool® RD Multi-electrode Ablation Catheter and integrated ablation system to treat resistant hypertension. It has an estimated enrollment of 30 subjects and is expected to complete the data collection for primary outcome measurement by July 2013.

Chilli II irrigated RFA catheter (Boston Scientific Inc., San Jose, California) and Celcius ThermoCool RFA catheter are being evaluated in the long-term safety and efficacy SAVE (Impact of Renal Sympathetic Denervation on Chronic Hypertension) study. The study began in May 2012, has an estimated enrollment of 500 subjects and is expected to be completed by December 2019, though the final data collection for primary outcome measures shall be done by December 2015.

Ultrasonic Ablation Technology

Ultrasound energy consists of high-frequency sound waves that are emitted circumferentially by the cylindrical transducer. These sound waves pass through the surrounding fluids and generate frictional heating of soft tissues, resulting in a temperature increase and nerve damage at depth. It induces a targeted injury pattern to the renal sympathetic nerves within the adventitia of renal artery.

PARADISE catheter system

ReCor Medical, Inc. (Ronkonkoma, NY) has developed a therapeutic, non-focused ultrasound system for performing renal denervation in patients with resistant hypertension. The PARADISE technology (Percutaneous Renal Denervation System) includes a 6-F compatible low-pressure balloon catheter with a cylindrical self-centering transducer that emits ultrasound energy circumferentially, allowing for a more efficient renal denervation procedure. Cool fluid circulating in the balloon cools the endothelial wall and protects it from the frictional heating due to ultrasonic sound waves.

The PARADISE catheter system is being evaluated in the REALISE (Renal Denervation by Ultrasound Transcatheter Emission) study, a single-arm, open –label, first-in-man feasibility study with a primary outcome of acute procedural safety and secondary outcome of 12-month change in ambulatory BP and baseline hypertensive medication intake (35). The parent company ReCor has also started ACHIEVE, a 50-patient, post-market study across multiple sites in Europe with its next-generation PARADISE system.

Therapeutic intravascular ultrasound catheter system (TIVUS)

The TIVUS system (Cardiosonic Ltd., Tel Aviv, Israel) uses high-intensity, non-focused ultrasound to facilitate percutaneous transluminal renal artery denervation. By applying ultrasonic energy, the TIVUS technology enables remote, localized, controlled, and repeatable thermal modulation of the renal vessel wall tissue, resulting in effective renal nerve ablation. The TIVUS system demonstrated significant reduction of 50% on kidney tissue norepinephrine concentration in preclinical studies.

Externally applied focused ultrasound

Almost all current renal denervation devices require the intravascular manipulation of catheters to deliver energy. Invasive techniques have significant limitations including requirement of expertise and resources for establishment of catheterization laboratory. To circumvent these limitations, research is also being focused on external systems to deliver energy to renal nerves. One such system, being developed by Kona Medical Inc. (Bellevue, Washington), is a low-intensity focused ultrasound through an external ultrasound probe,

integrated with an external imaging modality to identify and monitor the treatment area. This system is in the pre-clinical phase of development.

Tissue Directed Pharmacological Ablation Technology

Bullfrog microinfusion catheters

The Mercator Bullfrog microinfusion catheter (Mercator MedSystems Inc., San Leandro, California) is a catheter-guided system designed to inject therapeutic agents directly, nonsystemically, and safely through blood vessel walls into adventitial tissues. It has received US Food and Drug Administration 510(k) clearance. Thus far, the sympatholytic agent guanethidine has been studied for injection in the renal arteries. Given locally, guanethidine induces autonomic denervation directly and through an immune-mediated pathway (36).

Safety Considerations for Renal Nerve Ablation in Humans

All the modalities available for renal sympathetic nerve denervation either approved by European regulatory agencies or in the final stages of development and testing, use intravascular techniques for delivery of energy. Besides any physiological changes occurring due to renal denervation, being an invasive procedure, complications may occur due to the procedure itself. Fortunately, thus far, in the Symplicity and EnligHTN trials there have been no major vascular complications, though rare instances of vasovagal reactions, pseudoaneurysm formation and renal artery dissection have been reported.

Concerns for the long-term effects of renal artery denervation on safety, including renal function should be considered. In the Symplicity HTN-1 trial, the estimated glomerular filtration rate (eGFR) remained stable during the first year of follow up, but was reduced by 16 ml/min/1.73m² in 10 patients whose follow-up data are available at 2 years. In another study of 100 patients, a reduced number of patients with micro- and macro-albuminuria were demonstrated on 6 months after renal denervation, without adversely affecting GFR (37). Patients with severe renal dysfunction (eGFR < 45mL/min/1.73m²) were excluded from the Symplicity trials, though preliminary data from other trials have suggested acceptable safety and efficacy of renal denervation in patients with moderate to severe chronic kidney disease (38). Twelve-month data from the EnligHTN-1 trial show no significant changes in estimated glomerular filtration rate and serum creatinine, while cystatin C declined from 1 mg/L at six months (1.14 mg/L at baseline) to 0.91 mg/L. Similarly, the urine albumin-to-creatinine ratio declined significantly from baseline to 12 months (39).

The effect of renal denervation on the physiological response during cardiopulmonary exercise testing has been tested in a sub-study of Symplicity HTN-2 trial, where it was noted that blood pressure at maximal exercise was reduced in the treated group compared with that in controls, without compromise of chronotropic competence or the work performed. There was also no effect of the procedure on peak oxygen consumption (40). Investigation of orthostatic BP changes following renal nerve ablation showed no changes (41).

Non-blood pressure effects of renal denervation

The sympathetic nervous system is the driving force behind several compensatory physiological states and disease processes in the body. For example neurohumoral activation is a negative prognostic marker in chronic heart failure and the use of betablockers significantly reduces cardiovascular morbidity and mortality (42). High renal sympathetic activity in heart failure patients on treatment with beta-adrenergic blockade has shown to predict early death (43). In a pilot study in patients with chronic heart failure, significant

improvement in 6 min walk distance was seen after renal denervation (44). The ongoing Re-ADAPT-CHF study is a randomized, controlled multi-center trial investigating effects of renal denervation in patients with class II-III chronic heart failure. Regression of left ventricular hypertrophy with improvement in ejection fraction and diastolic function following renal denervation for resistant hypertension was reported in a small trial with 6 month follow up (Figure 1) (45). In fact, the reductions in left ventricular mass and interventricular septum thickness was independent of the changes in blood pressure suggesting a potential non-hemodynamic effect of renal denervation on cardiac remodeling. Treatment with renal sympathetic denervation in addition to pulmonary vein isolation in patients with refractory atrial fibrillation and resistant hypertension has shown to reduce the frequency of arrhythmias (46). Case reports of successful use of renal denervation in patients with congestive heart failure and treatment-resistant ventricular arrhythmias support potential anti-arrhythmic effects (47).

Sympathetic overactivity is seen in obesity, insulin resistance and metabolic syndrome (48). A pilot study by Mahfoud et al showed decreases in fasting glucose, insulin and C-peptide levels and significant improvement in insulin sensitivity in a small group of patients with resistant hypertension undergoing renal denervation (49). Patients with obstructive sleep apnea have reported improvement of sleep apnea severity and insulin resistance after renal nerve ablation (50).

Cost considerations of renal denervation for resistant hypertension

At this point in time, there are too few data to evaluate the cost-benefit of renal nerve ablation in hypertension therapy. A recent study by Geisler et al assessed cost-effectiveness and long-term clinical benefits of renal denervation in resistant hypertensive patients using a state-transition (Markov) model (51). The model indicates that renal denervation would reduce 10 year and lifetime probabilities of stroke, myocardial infarction, all coronary artery disease, heart failure and end stage renal disease. The estimated incremental lifetime cost-effectiveness ratio was \$3071 per quality-adjusted life year and the median survival was 18.4 years for renal denervation compared to 17.1 years for standard of care in patients with severe and resistant hypertension (51).

Limitations of Renal Nerve Denervation

While studies have shown beneficial effects of the procedure, there are no long-term controlled data on the efficacy or sustainability of the procedure. There is also limited data on the impact of renal denervation on out-of-office blood pressure. Data from the Symplicity HTN-2 trial shows that renal denervation might not reduce ambulatory blood pressure nearly as effectively as the doctor's office blood pressure.

Most studies of renal denervation have been performed in non-black patients and findings should not be extrapolated to other ethnicities. The impact of renal denervation on the renorenal reflex particularly in conditions affecting only 1 kidney is also not known. Data on the effect of renal denervation on cardiovascular morbidity and mortality is also lacking and will require further investigation. The recently announced EnLIGHTNment trial is the first large-scale study that will examine the long-term effects of renal denervation in patients with uncontrolled hypertension to evaluate reductions in the risk of major cardiovascular events such as heart attack, stroke and death. With a reported plans to enroll up to 4000 patients, powered to show a 25% reduction in major adverse cardiovascular events, the trial will randomize patients with systolic blood pressures of ≥ 160 mm Hg, uncontrolled on two or more drugs, and with three additional risk factors for CVD. Finally, studies will be needed to determine the effect of renal denervation on conditions associated with sympathetic overdrive including congestive heart failure and metabolic syndromes.

Conclusions

Treatment of drug-resistant hypertension has entered into an interesting historical phase with the emergence of renal nerve ablation therapy. Current evidence from the phase I and 2 clinical trials suggests that the use of catheter based radiofrequency ablation of renal nerves could be successful in an important subset of patients with severe and resistant hypertension. However, the mechanisms governing BP control are complex and multi-factorial. Long-term safety and efficacy data using controlled methodology are forthcoming and necessary to determine where renal nerve ablation therapy will ultimately fit into the treatment of hypertension and its complications.

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FIGURE 1.

Effect of Renal Denervation on Left Ventricle Mass indexed by body mass; panel A shows group data while panel B shows individual changes in the RD group. (RD - Renal Sympathetic Denervation; LVMI - Left Ventricular Mass Index) (Adapted from *J Am Coll Cardiol* 2012;59:901-9. With permission from publisher)

TABLE 1

Patient characteristics that have been used in most clinical trials of renal denervation

Inclusion Criteria
Office-based systolic BP ≥ 160 mmHg (≥ 150 mmHg in diabetes type 2) on ≥ 3 antihypertensive drugs at maximally tolerated dosages (one of which must be a thiazide or loop diuretic)
Exclusion Criteria
Known cause(s) of secondary forms of hypertension
Pseudo-resistance determined by ambulatory BP monitoring (requires 24-hour mean Systolic BP > 130 mmHg and/or mean daytime systolic BP > 135 mmHg)
Moderate to severely reduced renal function (estimated GFR ≤ 45 ml/min/1.73 m ²)
Presence of renovascular abnormalities: polar or accessory arteries, renal artery stenosis, prior revascularization or stent implants
Pregnancy
Type 1 Diabetes Mellitus
Existing permanent pacemaker or implantable cardioverter-defibrillator
Myocardial infarction, unstable angina or cerebrovascular accident in previous 6 months

BP: blood pressure; GFR: glomerular filtration rate