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Review of the State of Renal Nerve Ablation for Patients with Severe and Resistant Hypertension

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Abstract

Through modulation of renin secretion, glomerular filtration rate and renal absorption of sodium, the sympathetic innervation of the kidneys plays an important role in the pathogenesis of hypertension. Renal nerve ablation technology is being developed for treatment of drug-treatment resistant hypertension worldwide. Preliminary research with the use of radiofrequency based renal denervation systems have demonstrated encouraging results with significant reduction of blood pressure in patients inadequately controlled despite nearly maximal drug therapy regimens. From work done thus far, the renal denervation procedure has not been associated with serious adverse effects. Long term efficacy and safety still needs to be established for renal nerve ablation. This review focuses on the impact of the renal sympathetic system on blood pressure regulation, the clinical rationale for renal nerve ablation in severe and drug-treatment resistant hypertension and current evidence from the more advanced renal denervation devices.

Keywords

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

Introduction

Inadequate 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 BP, approximately 50% of patients have sub-optimal control of the BP (2). Resistant hypertension has been defined as failure to achieve goal BP 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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Early Experience with Lumbar Sympathectomy for the Treatment of Hypertension

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 β -1 adrenergic receptors) and reduces renal blood flow through vasoconstriction of renal arterioles (mediated by alpha 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).

Clinical Rationale for Renal 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).

Technical Development of Renal Sympathetic Denervation

Sobotka and Esler pioneered the technique of percutaneous renal sympathetic denervation, and performed the first studies of catheter-based renal nerve ablation using radiofrequency energy (23). 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 typical inclusion and exclusion criteria used in present clinical trials of renal denervation for resistant hypertension (24). Of note, the main renal artery length is required to 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 stenosis, calcification or atheromatous plaques and multiple renal arteries supplying the upper and lower poles of the kidney. Figure 1 outlines renal denervation systems undergoing trials and at various stages of development.

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 (25). 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, multi-center study performed in 50 patients out of whom 5 were excluded due to anatomical reasons, who were later used as controls for the analysis (23). 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 (26). 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 (27). Office-based BP measurements in the renal denervation group were decreased significantly by 32 ± 23 / 12 ± 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 ± 21 / 0 ± 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 (28). 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) (29). 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. The Symplicity HTN-4 trial, expected to begin in late 2013, aims to look at the efficacy of the Symplicity renal denervation system in patients with uncontrolled stage 1 hypertension (systolic BP between 140–160 mmHg) and eGFR $> 30\%$ despite treatment with three or more anti-hypertensive medications of different classes.

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/ EnligHTN-1 (Safety and Efficacy Study of Renal Artery Ablation in Resistant Hypertension Patients) trial (30). 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 (31). 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 (32). 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.

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 (33). 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, non-systemically, 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 (34).

Safety Concerns 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. There were 2 procedure-related complications in the initial cohort of Symplicity 1 trial: 1 renal artery dissection related to catheter manipulation, which was treated successfully with renal artery stenting; and 1 femoral artery pseudoaneurysm (23). Procedure-related adverse events in Symplicity HTN-2 trial 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 (27). There were no renal vascular complications on follow-up post procedure imaging studies in both the trials. Similar minor complications of procedure-related hematomas and post procedure bradycardia were noted in 4 and 2 patients respectively, in the EnligHTN-1 study (30).

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 (35). 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 (36). 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 (37). Improvement in both of these independent markers of renal function may suggest long term beneficial effects of renal denervation that needs to be studied in future trials.

Effects of renal denervation in areas outside of hypertension (Table 2)

Heart Failure

The sympathetic nervous system is the driving force behind several compensatory pathophysiologic processes in cardiovascular disorders. For example, neurohumoral activation is a negative prognostic marker in chronic heart failure and the use of beta-blockers significantly reduces cardiovascular morbidity and mortality (38). High renal sympathetic activity in heart failure patients on treatment with beta-adrenergic blockade has shown to predict early death (39). Of interest, studies in animal models of heart failure have shown beneficial effects of renal denervation (40–42). Surgical renal denervations in rat models of heart failure obliterated the sympathetic effect of sodium retention (40), restored the natriuretic effect of atrial natriuretic peptide (41) and have resulted in reduced ventricular filling pressures and improvement in ventricular function (42). In one of the first human heart failure studies, the safety of the procedure was studied in 7 patients with chronic systolic congestive heart failure. Significant improvement in exercise capacity as measured by 6 min walk distance was noted (43) and no untoward hemodynamic findings were seen in the post-ablation period. This safety study paved the way for REACH (REnal Artery Denervation in Chronic Heart Failure), a randomized, double blind, controlled trial of the safety and effectiveness of renal denervation in subjects with chronic systolic heart failure with a focus on symptoms and ventilator responses to exercise and chemoreceptor stimulation (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 (24). Several other trials are underway in patients with systolic heart failure as well as those with preserved ejection fraction heart failure that should clarify the role of renal denervation in these patients.

Regression of left ventricular (LV) hypertrophy with improvement in ejection fraction and diastolic function following renal denervation for resistant hypertension was reported in a small 6-month trial (45). Among the 46 patients who underwent renal denervation, the LV mass index decreased from 112.4 ± 33.9 g/m² at baseline to 94.9 ± 29.8 g/m² at 6 months ($p < 0.001$). The mitral E-wave deceleration time shortened from 227.2 ± 66.5 ms at baseline to 185.2 ± 67.1 ms at 6 months ($p = 0.013$). Of interest, the reductions in left ventricular mass and interventricular septum thickness was independent of the changes in BP suggesting a potential non-hemodynamic effect of renal denervation on cardiac remodeling.

Improvement in central hemodynamics has been observed after renal sympathetic denervation. Significant reduction in aortic pulse pressure with attenuation of pulse wave velocity suggests vascular remodeling (46). Reduced heart rate variability is associated with increased risk of sudden arrhythmic death after myocardial infarction and in heart failure patients (47). The intra-procedure effect of bradycardia during renal artery denervation documented in the SYMPPLICITY trials has also been observed over a longer follow-up periods (26). Even though the role of parasympathetic fibers in kidneys is not well defined, the presumed vagal mediation of bradycardia as suggested by reversal with atropine may suggest uninhibited parasympathetic effects post sympathetic denervation. Heart rate dynamics are significantly improved in patients treated by catheter-based renal denervation (48). 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 BP at maximal exercise was reduced in the treated group compared with that in controls, without compromise of chronotropic competence, cardiac work, or effects on peak oxygen consumption (49). In another study, formal investigation of orthostatic BP changes following renal nerve ablation showed no changes (50).

Arrhythmias

Renal denervation reduces resting heart rate and prolongs PR interval (51). In a porcine model of obstructive sleep apnea, renal denervation displayed antiarrhythmic effects by reducing negative tracheal pressure-induced atrial effective refractory period shortening (52). In patients with refractory atrial fibrillation and resistant hypertension, treatment with renal sympathetic denervation in addition to pulmonary vein isolation has shown to reduce the frequency of the arrhythmia (53). Case reports of successful use of renal denervation in patients with congestive heart failure and treatment-resistant ventricular arrhythmias also support potential anti-arrhythmic effects (54). A pilot study of 14 patients using the EnligHTN system has shown that renal denervation, besides reducing resistant hypertension, produces a favorable effect on atrial and ventricular arrhythmias (55).

Metabolic disorders and obstructive sleep apnea

Sympathetic overactivity is seen in obesity, insulin resistance and metabolic syndrome (56). 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 who underwent renal denervation (57). Fasting glucose levels declined from 118 ± 3.4 mg/dl to 108 ± 3.8 mg/dl after 3 months ($p=0.039$). Increased skeletal muscle blood flow due to reduction in α -1 adrenergic stimulation causing improved glucose uptake may be one of the possible explanations for the benefit of renal denervation on glucose homeostasis (58). Additionally, patients with obstructive sleep apnea have reported improvement of sleep apnea severity and insulin resistance after renal nerve ablation (59). Improvement in insulin resistance was also noted after renal denervation in two patients with polycystic ovary syndrome (60).

Potential Limitations of Renal Denervation

While studies have shown beneficial effects of the procedure, there are no longterm 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. Data from 10 European hypertension clinics within the European network coordinating research on renal denervation (ENCORED), presented at the European Society of Hypertension (ESH) 2013 suggests that the reduction in blood pressure is smaller when systolic blood pressure is assessed using ambulatory blood-pressure monitoring (61). This highlights the importance of appropriate screening of patients for white-coat resistant hypertension. Renal denervation reduces office BP and improves relevant aspects of ABPM in patients with true-treatment resistant hypertension while it only affects office BP in pseudo-resistant hypertension (62).

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 in conditions affecting a single 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. Finally, further 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 a small, but important subset of patients with severe and resistant hypertension. However, the mechanisms governing BP control are complex and multifactorial. 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 well-known complications.

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* Conformité Européenne marked renal denervation systems

Figure 1.
Overview of renal denervation systems at various stages of development

Table 1

Participant entry criteria used recently in clinical trials of renal denervation

Inclusion Criteria
Office-based systolic BP ≤ 160 mmHg (≤ 150 mmHg in diabetes type 2) on ≥ 3 antihypertensive drugs in adequate dosage and combination (including diuretic)
Exclusion Criteria
Known cause of secondary hypertension
Pseudo-resistance determined using ABPM (average BP > 130 mmHg or mean daytime BP > 135 mmHg)
Poor renal function (GFR < 45 ml/min/1.73 m ²)
Presence of renovascular abnormalities: polar or accessory arteries, renal artery stenosis, prior revascularization
Pregnancy
Type 1 Diabetes
Existing permanent pacemaker or implantable cardioverter-defibrillator
Myocardial infarction, unstable angina or cerebrovascular accident in previous 6 months

BP: blood pressure; ABPM: Ambulatory blood pressure monitoring; GFR: glomerular filtration rate

Table 2

Potential effects and benefits of renal denervation in addition to reduction of blood pressure

Cardiac
<i>Heart Failure</i>
Regression of LV hypertrophy
Improvement in diastolic function & ejection fraction
Reduction of arterial stiffness with improved central hemodynamics
Obliteration of sympathetic effects of sodium retention *
Restoration of natriuretic effects of ANP *
Reduction in ventricular filling pressure *
<i>Arrhythmias</i>
Decrease in resting heart rate
Prolongation of PR interval
Improvement in heart rate dynamics
Reduction of BP at maximal exercise on cardiopulmonary testing
Decrease in frequency of atrial and ventricular arrhythmias
Pulmonary
Improvement of sleep apnea severity
Metabolic
Decrease in fasting glucose, insulin and C-peptide levels
Improvement in insulin sensitivity
Renal
Decrease in micro- and macro-albuminuria
Reduction of cystatin C and albumin-to-creatinine ratio

LV: left ventricular; ANP: atrial natriuretic peptide; GFR: glomerular filtration rate;

* Based on animal data only