Catheter-Based Renal Denervation for Treatment-Resistant Hypertension

Summary

✓ Renal denervation is a minimally invasive treatment that uses low-level radio frequency energy to disrupt the renal sympathetic nerves in order to reduce blood pressure. The Symplicity Renal Denervation System (Medtronic Inc.) is the first licensed renal denervation device in Canada for treatment-resistant hypertension.

✓ Clinical data to support the use of the Symplicity Renal Denervation System in treatment-resistant hypertension have been reported in two clinical studies. Symplicity HTN-1 (a multi-centre, open-label, pooled analysis of non-randomized pilot studies) showed that office-based blood pressures were statistically significantly reduced from baseline measurements at six months, and that these reductions were sustained at 36 months after the procedure. Symplicity HTN-2 (a multi-centre, open-label, randomized controlled trial) showed a statistically significant reduction in office-based blood pressure at six months following the procedure, which was sustained at 24 months. Office-based blood pressure did not change in the control group receiving antihypertensive therapy only.

✓ Ambulatory blood pressure measurements were not consistently reported during the trials. The use of office-based blood pressure measurements as a primary end point may have overestimated the true treatment effect of renal denervation.

✓ Few procedural complications were noted in the two trials. These included hematomas at the femoral access site and renal artery dissections that were treated without any subsequent complication.

✓ Symplicity HTN-3 is an ongoing, multi-centre, single-blinded, randomized controlled trial assessing the safety and efficacy of renal denervation for treatment-resistant hypertension. Results are anticipated in March 2013.

✓ The long-term safety and efficacy of the procedure in a real-world setting, markers for the extent of renal sympathetic nerve ablation, predictors of blood pressure response to guide patient selection, and the effect on cardiovascular morbidity and mortality will have to be clarified to determine the extent of uptake of renal denervation into clinical practice.

The Technology

Treatment-resistant hypertension is defined as persistently high blood pressure despite receiving optimal or best-tolerated doses of at least three different classes of antihypertensive drugs, one of which is a diuretic.¹ Research has shown that overactivity of the sympathetic nervous system, including the afferent and efferent renal nerves, may contribute to treatment-resistant hypertension.²,³ Renal denervation is a minimally invasive treatment that uses low-level radio frequency energy to disrupt the renal sympathetic nerves without affecting other abdominal, pelvic, or lower extremity nerves.⁴ The Symplicity Renal Denervation System (Medtronic Inc., Mountain View, California) consists of a radiofrequency generator and a flexible catheter.⁵ The catheter is introduced through the femoral artery and threaded up into the renal artery lumen. Once in place, a series of 4 to 6 radio frequency treatments are applied within each renal artery to ablate the sympathetic nerves coursing along the outside of the artery. The procedure takes about 40 minutes and is performed in a catheterization laboratory under analgesic or conscious sedation. The Symplicity Renal Denervation System is the first renal denervation device to be launched commercially.⁶ Other companies, including St. Jude Medical, Covidien, Boston Scientific, and Biosense Webster have renal denervation systems under development.⁷

Regulatory Status

Health Canada issued a Class IV Licence to Medtronic Inc. for the Symplicity Renal Denervation System in March 2012.⁸ It is the first licensed device in Canada for treatment-resistant hypertension. The license was issued with conditions of post-market follow-up to monitor for rare adverse events and to ensure sustained safety and effectiveness. The procedure has been performed by cardiologists and radiologists in more than 30 patients at hypertension centres in Toronto, Montreal, Ottawa, and Edmonton.⁹,¹⁰ The Symplicity Renal Denervation System has been approved in several European countries and in Australia but has not been approved by the United States (US) Food and Drug Administration (FDA).¹¹

The Canadian Agency for Drugs and Technologies in Health (CADTH) is funded by Canadian federal, provincial, and territorial governments. (www.cadth.ca)
Patient Group

An estimated 7.3 million Canadians aged 20 years or older are currently living with diagnosed hypertension. Estimates of the proportion of patients with hypertension who are treatment-resistant range between 5% and 30% in different studies. In clinical practice, the estimate for treatment-resistant hypertension is less than 5% after the exclusion of patients with other reasons for poor response to therapy including antihypertensive medication non-adherence, suboptimal treatment, or secondary causes of hypertension. Patients with resistant hypertension are at a greater risk of stroke, myocardial infarction, heart failure, and chronic kidney disease compared with patients who have controlled hypertension. Mortality rates have been estimated to be between 34% and 44% higher for Canadians diagnosed with hypertension compared with the general population. A significant portion of health care budgets in Canada are used for the treatment of hypertension and its associated cardiovascular, renal, and cerebrovascular complications. In 2003, more than C$2.3 billion was spent for hypertension-related physician, medication, and laboratory costs.

Current Practice

The initial assessment of treatment-resistant hypertension involves a standard diagnostic workup to exclude other reasons for poor response to therapy such as non-adherence, secondary causes of hypertension (e.g., interacting drug therapy, primary aldosteronism, chronic kidney disease, and obstructive sleep apnea), lifestyle factors (e.g., excessive salt intake), and the white coat effect (an elevation of blood pressure by virtue of being in a clinical setting). Recommendations for the pharmacological treatment of resistant hypertension are largely empiric due to the absence of studies evaluating three or four drug combinations. First-line antihypertensive drugs, to be used alone or in combination, include a thiazide diuretic, a long-acting calcium channel blocker, an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, and a beta-blocker in patients younger than 60 years of age. The Canadian Hypertension Education Program recommends adding other classes of antihypertensive drugs if uncomplicated hypertension is not controlled using three antihypertensives. Aldosterone antagonists (e.g., spironolactone) are the most commonly used agents. The guidelines also recommend alpha-adrenergic blockers (e.g., terazosin) or centrally acting agents (e.g., guanfacine or clonidine). However, the addition of other drug classes to antihypertensive combinations may require extra monitoring and increase the frequency of adverse events.

Methods

Literature Search Strategy

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and The Cochrane Library (2012, Issue 11). Grey literature was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters). No methodological filters were applied. The search was limited to English language documents published between January 1, 2007 and November 23, 2012. Regular alerts were established to update the search until the publication of this bulletin. Conference abstracts were excluded from the search results.

Study Selection Criteria

Studies evaluating the clinical efficacy and safety of renal denervation for the treatment of hypertension in a minimum of 50 participants were considered for inclusion in the evidence section of this bulletin. Unpublished long-term data from the selected published studies were also included. All other unpublished data, case reports, editorials, letters, and narrative literature reviews were excluded.

The Evidence

Clinical data to support the use of the Symplicity Renal Denervation System in treatment-resistant hypertension have been reported in the Symplicity HTN-1 and Symplicity HTN-2 clinical trials. The results from these two clinical studies are summarized in Table 1. Symplicity HTN-3 is an ongoing trial designed to meet the US FDA regulatory requirements for evaluating the safety and efficacy of the Symplicity Renal Denervation System for treatment-resistant hypertension.

Symplicity HTN-1 was a non-randomized, open-label, proof-of-principle study that assessed the feasibility and safety of the Symplicity Renal Denervation System in 50 patients. Results from this initial cohort were pooled with other non-randomized phase 1 studies conducted at 19 centres in Australia, Europe, and the US. Patients 18 years of age or older were enrolled in the study if they had an office-based systolic blood pressure of 160 mmHg or greater despite treatment with three or more antihypertensive medications at a target or maximal tolerated dose, one of which was a diuretic.
Patients with moderate or severe chronic kidney disease, type 1 diabetes mellitus, renal artery abnormalities, or a known secondary cause of hypertension (other than sleep apnea or chronic kidney disease) were excluded. The primary outcome was the average change in office-based systolic blood pressure. The proportion of patients achieving a systolic blood pressure reduction of 10 mmHg or greater was assessed as a secondary outcome. Physicians were encouraged not to alter antihypertensive drug therapy, unless necessary, for clinical reasons.

A total of 153 participants (mean age of 57 ± 11 years and a mean baseline office-based blood pressure of 176/98 ± 17/15 mmHg) were evaluated in the expanded Symplicity HTN cohort. Patients were taking an average of 5.1 ± 1.4 antihypertensive medications. Of the 145 patients (95%) receiving treatment with a diuretic, 34 patients (22%) were using an aldosterone antagonist. Statistically significant within-patient changes from baseline were shown in both systolic and diastolic office-based blood pressure measurements up to 36 months (P < 0.01 for all time points). The proportion of patients achieving a systolic blood pressure reduction of 10 mmHg or greater increased during the course of the trial (69% at one month, 82% at 24 months, 94% at 36 months). Several limitations in the study design of HTN-1 must be considered in the interpretation of these results. Due to the absence of a control group, confounding factors such as the Hawthorne effect (modification of the patient’s behaviour in response to the study context) and regression to the mean may have influenced the treatment effect. Investigators who performed blood pressure measurements were unblinded to treatment allocation. Hence, a placebo effect and observer bias cannot be excluded.

The Symplicity HTN-2 trial is an ongoing, multi-centre, open-label, randomized controlled trial of the safety and effectiveness of renal denervation in patients with treatment-resistant hypertension. Patients were enrolled at 24 centres in Europe, Australia, and New Zealand. To be eligible for the study, patients had to be aged 18 to 85 years, compliant with three or more antihypertensive medications over a two-week period, and still have a systolic blood pressure of 160 mmHg or greater (150 mmHg or greater in patients with type 2 diabetes mellitus). It is not clear whether any attempt was made to ascertain adherence to antihypertensive therapy during the trial or follow-up period. Patients with previous renal artery interventions, renal artery abnormalities, moderate or severe kidney disease, type 1 diabetes mellitus, stenotic valvular disease, or recent acute coronary syndromes were excluded. Patients who were pregnant or planning to be pregnant during the study were also excluded.

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Table 1: Summary of Symplicity HTN-1 & HTN-2 Trial Results

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>18 Months</th>
<th>24 Months</th>
<th>36 Months</th>
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</thead>
<tbody>
<tr>
<td>RDN Office BP (mmHg)</td>
<td>−19/-9 (n = 143)</td>
<td>−21/-10 (n = 148)</td>
<td>−22/-10 (n = 144)</td>
<td>−27/-14 (n = 132)</td>
<td>NR</td>
<td>−29/-14 (n = 105)</td>
<td>−31/-16 (n = 34)</td>
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<tr>
<td>RDN ABPM (mmHg)</td>
<td>NR</td>
<td>NR</td>
<td>−11/-7 (n = 20)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Control Office BP (mmHg)</td>
<td>0/0 (n = 51)</td>
<td>−4/-2 (n = 51)</td>
<td>+1/0 (n = 51)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Control ABPM (mmHg)</td>
<td>NR</td>
<td>NR</td>
<td>−3/-1 (n = 25)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Crossover Office BP (mmHg)</td>
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<td>NR</td>
<td>−24/-8 (n = 35)</td>
<td>−24/-10 (n = 33)</td>
<td>−28/-11 (n = 31)</td>
<td>−35/-13 (n = 26)</td>
<td>NR</td>
</tr>
</tbody>
</table>

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; NR = not reported; RDN = renal denervation.

The Canadian Agency for Drugs and Technologies in Health (CADTH) is funded by Canadian federal, provincial, and territorial governments. (www.cadth.ca)
Participants selected for study inclusion were randomly allocated to a renal denervation group (n = 52) or a control group (n = 54). Both groups were maintained on their antihypertensive medications, and changes to baseline doses were not permitted unless medically necessary. The primary outcome was the between-group change in average office-based systolic blood pressure from baseline to six months. Secondary end points included 24-hour ambulatory blood pressure measurement at six months post-procedure, the proportion of patients achieving a reduction in systolic blood pressure of 10 mmHg or greater, procedural safety, and a composite cardiovascular end point. The mean blood pressure at baseline was 178/97 ± 18/16 mmHg for the renal denervation group and 178/98 ± 16/17 mmHg for the control group, despite both receiving an average daily regimen of five antihypertensive medications. The two groups had a comparable distribution of antihypertensive medications at baseline. The average age of the patient cohort was 58 ± 12 years. Some clinical differences were identified between the renal denervation and control groups at baseline: higher rates of type 2 diabetes (40% versus 28% respectively), coronary artery disease (19% versus 7% respectively), and lower renal function (77 mL/min per 1.73m² versus 86 mL/min per 1.73m² respectively). No adjustments were made for these between-group baseline clinical differences. Diuretics were being used for treatment in 95 patients (90%), and 18 patients (17%) were being treated with an aldosterone antagonist.

Six months after randomization, office-based measurements of blood pressure in the renal denervation group were statistically significantly reduced compared with baseline (P < 0.0001 for systolic and diastolic blood pressure). In contrast, office-based measurements of blood pressure in the control group did not change from baseline (P ≥ 0.77 for systolic and diastolic blood pressure). The between-group difference in the office-based blood pressure averaged 33/11 mmHg (P < 0.0001 for both systolic and diastolic blood pressure). Ambulatory blood pressure monitoring results were available for 20 patients (41%) in the renal denervation group and 25 patients (49%) in the control group. Changes in ambulatory blood pressure measurements from baseline in the renal denervation group were statistically significant (P = 0.006 for systolic blood pressure and P = 0.014 for diastolic pressure). However, the reduction in ambulatory blood pressure was substantially smaller when compared with office-based blood pressure measurements, with a between-group difference of 8/6 mmHg.

Forty-one patients (84%) who underwent renal denervation had reductions in systolic blood pressure greater than 10 mmHg compared with 18 controls (35%; P < 0.0001). The proportion of patients who did not show a reduction in systolic blood pressure from baseline was lower in the renal denervation group compared with the control group (10% versus 47% respectively; P < 0.0001). Twelve-month results showed a sustained office-based blood pressure reduction from baseline (P < 0.001), with no significant difference from the previously reported six-month follow-up result (P = 0.16). Thirty-seven patients (79%) in the renal denervation group maintained a reduction in systolic blood pressure of at least 10 mmHg at 12 months.

After the assessment of the six-month primary end point was complete, 35 patients in the control group who had a systolic blood pressure of 160 mmHg or greater crossed over to receive the renal denervation procedure. Before the renal denervation procedure, patients in the crossover group had a mean 7/1 mmHg increase in office-based blood pressure compared with baseline values (P = 0.026 for systolic blood pressure and P = 0.066 for diastolic blood pressure). The crossover patients also showed a statistically significant reduction in both systolic and diastolic office-based blood pressure from the pre-procedure measurement (P < 0.001), which was similar to findings at six months in the initial renal denervation group (P = 0.15). Twenty-two patients (63%) in the crossover group achieved a reduction in systolic blood pressure of at least 10 mmHg six months after the procedure. Statistically significant reductions in both systolic and diastolic office-based blood pressures from baseline have been shown to be sustained in both the initial renal denervation group and the crossover group at 18 months and 24 months (P < 0.01 for both groups). The findings of the Symplicity HTN-2 trial should be interpreted with caution because of the small number of participants and the 24-month follow-up period, which may not have allowed for the detection of rare adverse events. The trial was performed by hypertension experts in a highly selected patient population. Hence, efficacy in a real-world clinical practice setting requires assessment. The use of office-based blood pressure measurements as the primary end point may have overestimated the true treatment effect. Compared with office-based blood pressure measurements, ambulatory blood pressure measurements are taken at regular intervals over 24 hours to provide a better estimate of a patient’s blood pressure and cardiovascular prognosis. Ambulatory blood pressure measurements also minimize the elevation in blood pressure observed with the white coat effect. Since
the white coat effect is thought to be mediated by the sympathetic nervous system, these elevations in blood pressure may have been diminished after renal denervation. Ambulatory blood pressure measurements were not consistently reported and only half of the cohort was evaluated. The observed reduction in ambulatory blood pressure was one-third the magnitude of the reduction in office-based blood pressure, suggesting the possibility that a substantial portion of the blood pressure response reported for the primary end point reflects a decrease in the white coat effect. However, since the investigators did not report the baseline values of ambulatory blood pressure, the prevalence of the white coat effect cannot be assessed. Furthermore, secondary causes of hypertension were not defined as exclusion criteria. This may have led to an overestimation of the treatment effect if the underlying cause of hypertension (such as interacting drug therapy or lifestyle factors) was treated during the course of the trial. Lack of double-blinding with a sham operation makes it difficult to ascertain whether a placebo effect on blood pressure might have occurred. In addition, investigators were not blinded, which may have introduced observer bias in blood pressure measurements, particularly as they were instructed to take three or more readings until consistent readings were obtained and then record three of these consistent readings on the case report forms. The total number of readings taken for each patient and the difference between the readings that were and were not selected were not reported.

HTN-3 is an ongoing multi-centre, single-blind, randomized controlled trial that will evaluate the safety and effectiveness of the Symplicity Renal Denervation System in patients with treatment-resistant hypertension. The study is expected to enroll 530 participants across 87 medical centres in the US. All patients and hypertension follow-up assessors will be blinded to the randomization assignments. Control patients will undergo a sham procedure of screening renal angiography alone. The primary outcome is the change in office-based systolic blood pressure from baseline to six months. The change in the 24-hour ambulatory systolic blood pressure from baseline to six months will be assessed more consistently as a secondary outcome to help clarify current discrepancies between ambulatory and office-based readings. The primary safety end point is the incidence of major adverse events at one month following randomization or a new renal artery stenosis greater than 70% within six months following randomization. All study patients will be followed for three years following randomization. The expected completion date is March 2013.

Adverse Events

No immediate serious complications occurred related to the device or procedure during the Symplicity trials. Minor procedural complications were reported that were treated without any subsequent complications. These included hematomas at the femoral artery access site (three patients in HTN-1 and one patient in HTN-2). Renal artery dissections occurring upon catheter placement before the delivery of radiofrequency energy (one patient in HTN-1 and one patient in the crossover group during HTN-2) were managed with renal artery stenting. Six-month renal vascular imaging identified one case of progression of a pre-existing renal artery stenosis during HTN-1 and one case of progression of an underlying atherosclerotic lesion during HTN-2. Both cases occurred at a location unrelated to the site of radiofrequency energy application. No stenoses, aneurysms, or new atherosclerotic lesions were observed at the radiofrequency energy delivery sites. No late procedure-related safety events or vascular complications were reported during follow-up in either Symplicity trial.

Other minor adverse events occurring during the Symplicity HTN-2 trial in the renal denervation group included one post-procedural drop in blood pressure resulting in a reduction in medication, one urinary tract infection, one prolonged hospitalization for investigation of paresthesia, and one case of back pain that resolved with an analgesic. Seven patients in the renal denervation group had transient bradycardia during the procedure, which resolved with atropine treatment. Five hospital admissions for hypertensive emergency occurred that were unrelated to non-adherence with antihypertensive therapy (three patients in the initial renal denervation group and two controls), which required adjustment of antihypertensive therapy. During the 18-month follow-up period, five new hospitalizations due to hypertensive events were reported (three patients who underwent initial renal denervation and two patients in the crossover group), which required adjustment of antihypertensive therapy. One hypotensive episode occurred in the crossover group, which resolved with adjustment of medication. No additional adverse events were reported at the 24-month follow-up.
Renal function did not appear to deteriorate acutely after the denervation procedure in either Symplicity trial. There was no decline in renal function during the first year of follow-up during HTN-1. Data were available from 10 patients at the two-year follow-up in HTN-1. In these 10 patients, estimated glomerular filtration rate (eGFR) decreased by 16.0 mL/min per 1.73m². Five of these patients had spironolactone or another diuretic added after the first year of follow-up, which may have worsened renal function. In patients without a newly added diuretic, eGFR decreased by 7.8 mL/mL/min per 1.73m². None of these patients experienced a doubling of serum creatinine, developed class IV chronic kidney disease, or progressed to dialysis.\(^{20}\) Renal function did not change from baseline to six months in either group during HTN-2. In addition, no patients experienced a decrease in eGFR greater than 50\%, although two renal denervation patients and three controls experienced a more than 25\% decrease in eGFR. No significant decline in kidney function was reported in either the initial renal denervation treatment group or the crossover group at the 12-month and 24-month follow-up.\(^{23,25}\)

Results from two independent studies provide evidence that renal function is not adversely impacted by renal denervation.\(^{33,34}\) In a case-control study, the effect of renal denervation on renal hemodynamics and renal function were studied in 100 consecutive patients.\(^{33}\) Eighty-eight patients underwent renal denervation and 12 served as the control group. Six months after renal denervation, no renal artery stenosis, dissections, or aneurysms were observed. Renal resistive index (a measure of renal hemodynamics and arterial compliance) decreased significantly from baseline to the six-month follow-up in patients who underwent renal denervation. Renal function remained unchanged after the procedure. In addition, the number of patients with albuminuria decreased. A prospective cohort study assessed biomarkers of acute renal injury to identify if any structural kidney damage during the early post-procedural period occurred in 62 consecutive patients with treatment-resistant hypertension.\(^{34}\) Patients with moderate or severe kidney disease (eGFR < 45 mL/min per 1.73m²) were included in the study population. Results showed no evidence of renal denervation-related functional or structural kidney damage or decreases in renal function two days after the procedure and after a three-month follow-up.

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**Cost**

The manufacturer’s price for the Symplicity Renal Denervation System in Canada is currently unavailable.

**Renal Denervation Devices**

Medtronic is currently investigating a next-generation Symplicity system designed to reduce treatment time.\(^{35}\) Several other radiofrequency renal denervation devices are also being developed to increase the consistency of energy delivery for more reliable denervation, shortened procedure time, and increased safety.\(^{6,7}\) These include EnligHTN (St. Jude Medical Inc., St. Paul, Minnesota),\(^{26}\) OneShot (Covidien, Dublin, Ireland),\(^{37}\) the V2 Renal Denervation System (Boston Scientific Inc., San Jose, California; formerly Vessix Vascular Inc., Laguna Hills, California),\(^{38}\) and THERMOCOOL Irrigated Tip Catheter and Integrated Ablation System ( Biosense Webster Inc., Diamond Bar, California).\(^{39}\) St. Jude has announced that a large-scale, multi-centre, randomized controlled trial will evaluate the efficacy of EnligHTN for reducing the risk of major cardiovascular events in patients with uncontrolled hypertension.\(^{40}\) The trial is expected to take five years to complete.

Ultrasound is being investigated as an alternative to radiofrequency energy to provide more targeted nerve ablation without the need for direct vessel contact.\(^{6,7}\) Ultrasound devices currently under development include PARADISE (ReCor Medical Inc., Menlo Park, California)\(^{41}\) and a device being developed by Kona Medical Inc. (Bellevue, Washington) that may offer the first potentially non-invasive method of renal denervation through focused ultrasound.\(^{42}\) Catheters designed to inject therapeutic agents directly and non-systemically through the renal artery wall, such as the Cricket and Bullfrog Micro-Infusion Catheters, (Mercator MedSystems Inc., San Leandro, California) are also in development.\(^{33}\)

**Baroreflex Activation Therapy**

The Rheos System (CVRx, Minneapolis, Minnesota) is a pacemaker-like device designed to electrically decrease blood pressure by activating the baroreflex that is also involved in the regulation of the sympathetic nervous system.\(^{44}\) Unlike renal denervation, the procedure involves a permanent implant, and several complications including nerve injury, general surgery complications, and surgical wound infections have been reported.\(^{44}\)
Furthermore, results for blood pressure reduction have been mixed. A clinical trial is currently underway to evaluate a smaller second-generation device (Barostim neo System, also CVRx) that has been developed to reduce procedural invasiveness and improve safety. Baroreflex activation therapy devices have not received FDA approval for sale in the US.

**Pharmacological Therapy**

Several new pharmacological therapies for hypertension are being investigated in phase 2 and 3 clinical trials including drugs with new pharmacological targets (such as dual vasopeptidase inhibitors, a dual-acting angiotensin receptor-neprilysin inhibitor, endothelin antagonists, nitric oxide donors, and angiotensin vaccines) and novel, fixed-dose combination drug products.

**Rate of Technology Diffusion**

In addition to hypertension, elevated sympathetic nervous activity has been linked to other conditions, such as heart failure, obstructive sleep apnea, insulin resistance, arrhythmias, and chronic kidney disease. There is preliminary evidence that renal denervation may have beneficial effects on the comorbidities associated with treatment-resistant hypertension. Effects include decreasing left ventricular mass and improving cardiac function in patients with left ventricular hypertrophy, improving glucose metabolism in patients with insulin resistance, reducing atrial fibrillation occurrence, and reducing obstructive sleep apnea severity. A pilot study has also shown that renal denervation may potentially improve symptoms and exercise capacity in patients with chronic systolic heart failure. Preliminary results from a case series also suggest that renal denervation may be safe to use in patients with moderate-to-severe chronic kidney disease.

Several research initiatives are currently being undertaken by Medtronic to evaluate the effectiveness of the Symplicity Renal Denervation System for mild refractory hypertension, obstructive sleep apnea, heart failure with renal impairment, and insulin resistance. A post-market, open-label registry will enrol 5,000 patients globally to evaluate the long-term safety and effectiveness of the Symplicity Renal Denervation System in a real-world patient population with hypertension. The registry will also gather data for other diseases characterized by sympathetic overactivity, such as type 2 diabetes, heart failure, and renal insufficiency. Several biological variables will also be evaluated to study the effect of using the Symplicity Renal Denervation System on heart and kidney function. Additional studies will evaluate renal denervation for atrial fibrillation, stroke, and coronary artery disease.

**Implementation Issues**

There is evidence that the Symplicity renal denervation procedure significantly decreases blood pressure in patients with treatment-resistant hypertension and that this reduction can be sustained up to three years. Although these results are promising, further studies are required to clarify several knowledge gaps. The long-term efficacy and safety of the renal denervation procedure beyond three years in a larger patient population in a real-world clinical practice setting has yet to be determined. It is possible that sympathetic nerve regrowth over a period of months to years could diminish long-term blood pressure reduction. More studies are required to ascertain the need for repeat procedures and the requirement for the continuation of antihypertensive combination therapy. Although follow-up imaging to date has not shown any evidence of renal artery stenosis, aneurysms, new atherosclerotic lesions, or other damage that appears to be directly related to the renal denervation procedure, the long-term impact on renal function and renal artery structure requires further investigation. A small number of patients in the Symplicity HTN-1 and Symplicity HTN-2 clinical trials did not experience a reduction in blood pressure after the renal denervation procedure. The reasons for this variability in response need to be determined. No imaging or functional marker for the extent of renal sympathetic nerve ablation after the procedure is currently available. Furthermore, neither of the Symplicity trials identified specific predictors of blood pressure reduction after the procedure. In order to ensure appropriate patient selection, more research is needed to identify parameters that may predict the response to renal denervation.

The mechanisms by which renal artery denervation reduces blood pressure are not completely understood. There is some evidence to suggest that, in addition to lowering efferent renal sympathetic nerve activity (signals from the brain to the kidneys involved in sodium and water regulation), renal denervation may reduce centrally generated sympathetic activity by lowering renal afferent nerve activity (signals from the kidney to the brain that subsequently regulate the cardiovascular system). Preliminary evidence suggests that measuring central sympathetic nerve
activity (blood pressure, heart rate, and serum catecholamines) following electrical stimulation of the renal nerves before and after ablation of the renal artery may provide a method to assess the technical success of the procedure and monitor efficacy of renal denervation over time.\textsuperscript{65,66} The effect of renal denervation on the regulation and function of other organs, such as the heart, also requires investigation. There is evidence that renal denervation does not affect responses in heart rate and oxygen uptake during exercise.\textsuperscript{67} However, the effect on blood pressure response in various clinical situations, such as sepsis, hemorrhage, trauma, or shock is unknown.

In Canada, renal denervation is currently being performed at specialized hypertension centres in patients carefully selected after a thorough diagnostic workup for treatment-resistant hypertension. Renal denervation is currently used as an adjunct to available therapies for hypertension. It is associated with additional health care resources in terms of the cost of the device, the training of specialist staff, and the use of hospital radiology services during the procedure. This cost must be weighed against the potential health care resource benefits from reducing the morbidity associated with hypertension. Whether the reductions in blood pressure reported in clinical trials translate into clinically meaningful reductions in cardiovascular morbidity and mortality remains an important question that will have to be evaluated with much larger and longer clinical trials. Comparing renal denervation with a hypertension expert-guided treatment program that performs a comprehensive assessment for secondary causes, optimizes non-pharmacological treatment, and uses more than three agents at maximal doses would help establish the benefit of renal denervation over optimal therapy. Confirmatory evidence to support procedural safety, patient selection, and therapeutic durability will determine the uptake of renal denervation into clinical practice for treatment-resistant hypertension.

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