

CADTH Horizon Scan

# Renal Denervation for People With Hypertension

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**ISSN:** 2563-6596

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**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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## Table of Contents

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Key Messages .....	5
Symlicity Spyrax: A Renal Denervation System for Hypertension .....	5
How It Works .....	5
Who Might Benefit? .....	6
Current Practice.....	7
What Is the Evidence? .....	8
Safety .....	9
Availability in Canada .....	9
What Does It Cost? .....	9
Related Developments.....	10
Looking Ahead.....	10
References .....	12

List of Figures

---

Figure 1: Flexible, Multielectrode Catheter Component of the Simplicity Spyral Renal Denervation System..... 6  
Figure 2: Simplicity G3 Generator That Delivers Radiofrequency Pulses to the Treatment Location ..... 7

## Key Messages

- Horizon scan reports provide brief summaries of information regarding new and emerging health technologies; Health Technology Update articles typically focus on a single device or intervention.
- These technologies are identified through the CADTH Horizon Scanning Service as topics of potential interest to health care decision-makers in Canada.
- This Horizon Scan summarizes the available information regarding an emerging technology – Symplicity Spyral – a renal denervation system for the treatment of uncontrolled hypertension.

## Symplicity Spyral: A Renal Denervation System for Hypertension

As an alternative or adjunct treatment to pharmacological therapy, Symplicity Spyral is a second-generation renal denervation (RDN) system designed to reduce blood pressure (BP) in people with uncontrolled hypertension.

## How It Works

The sympathetic nervous system, which is in charge of regulating the body's fight-or-flight response, innervates several organ systems, including major structural components of the kidneys. Increased activity of the renal sympathetic nervous system is known to be 1 of the possible mechanisms of hypertension.<sup>1</sup> Sympathetic nerve fibres may be overactivated in patients with hypertension, which, through a chain of pathophysiological changes, results in increased volume of blood in the circulatory system as well as increased resistance of blood vessels.<sup>1</sup> These factors subsequently increase BP. RDN is a minimally invasive procedure that reverses the activation of sympathetic nerves in the renal artery using radiofrequency pulses to decrease their activity, which can in turn lower BP.<sup>1</sup>

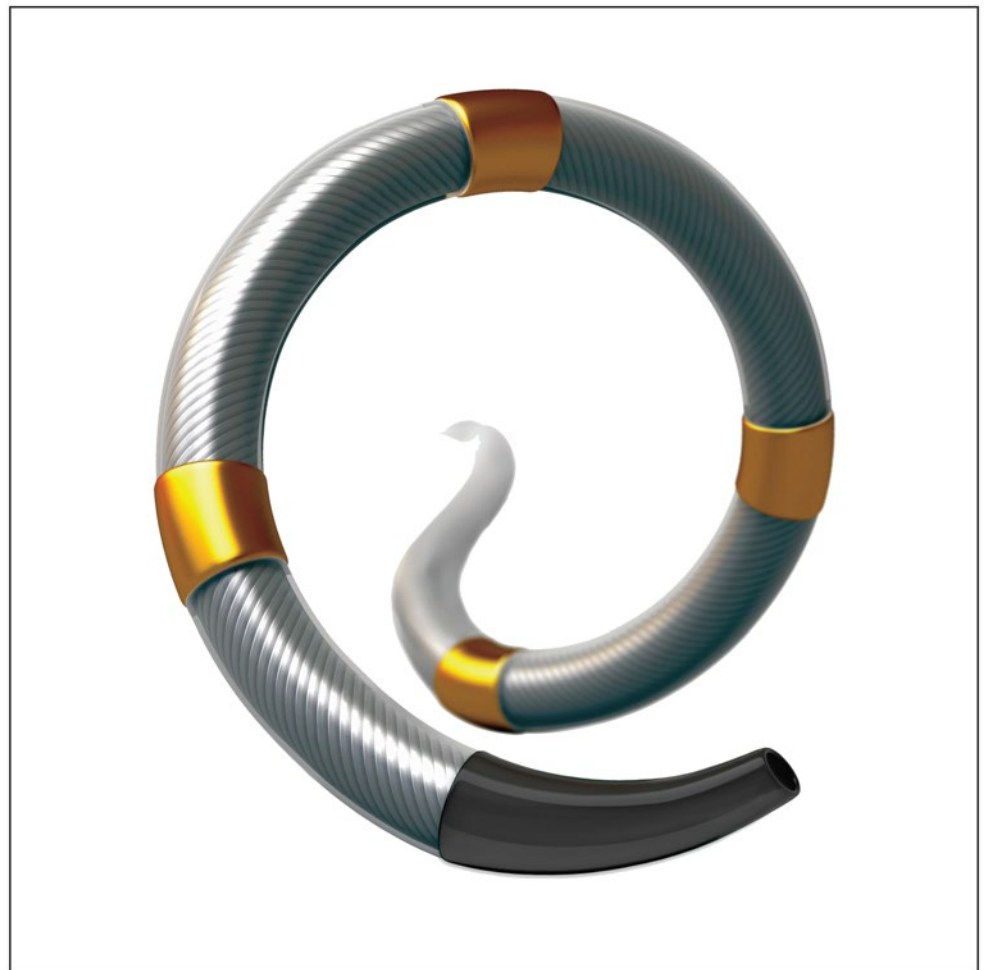
Medtronic's Symplicity Spyral RDN system consists of 2 main components: a flexible, multielectrode catheter that is used to reach the treatment location in the patient's renal artery wall (Figure 1) and a radiofrequency generator that delivers controlled, low-power pulses of energy according to a programmed treatment algorithm (Figure 2).<sup>2,3</sup> The procedure begins by introducing a catheter into the femoral artery through a small incision in the groin.<sup>4</sup> Under fluoroscopic control, the catheter is then advanced into the renal artery, where it delivers low-power pulses of radiofrequency energy produced by the generator.<sup>4</sup> The pulses ablate renal sympathetic nerves in multiple locations, which reduces nerve activity, with the subsequent goal of decreasing BP.<sup>4</sup> This procedure is performed bilaterally, on both kidneys, during the treatment session.<sup>4</sup>

## Who Might Benefit?

Hypertension affects approximately 1.28 billion adults worldwide, and only 1 in 5 of those adults achieve the target BP necessary to control the condition.<sup>5</sup> In the Canadian context, 23% of Canadian adults were reported to have been diagnosed with hypertension in the 2016 to 2019 Canadian Health Measures Survey.<sup>6</sup> The prevalence of poorly controlled hypertension both in Canada and worldwide can be attributed to a variety of reasons, including cost of medications, side effects, lack of patient education, and therapeutic inertia, in which health care providers do not to initiate or intensify therapy when goals are not reached.<sup>7,8</sup>

Patients with resistant hypertension, which is defined as BP above target despite 3 or more BP-lowering drugs at optimal doses, form an estimated 10% to 30% of the population of people with hypertension.<sup>9</sup> Large epidemiological studies have found that patients with resistant hypertension are at greater risk of experiencing major adverse cardiovascular events and developing chronic kidney disease.<sup>9</sup> In addition, barriers to pharmacological treatment

**Figure 1: Flexible, Multielectrode Catheter Component of the Simplicity Spyral Renal Denervation System**



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adherence are prevalent among patients with resistant hypertension.<sup>10</sup> Therefore, this subgroup may benefit from a nonpharmacological intervention such as RDN. Other people who might benefit from RDN include patients who prefer nonpharmacological approaches to antihypertensive treatment and those who are intolerant or experience severe side effects due to their current medication regimen.

## Current Practice

The current approach to managing hypertension in Canada consists of lifestyle modifications and pharmacological therapy. According to 2020 guidelines from Hypertension Canada, first-line intervention for hypertension involves health behaviour change, with recommendations including weight reduction, physical exercise, and decreasing alcohol and sodium intake.<sup>11</sup>

**Figure 2: Simplicity G3 Generator That Delivers Radiofrequency Pulses to the Treatment Location**



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Medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and longer-acting thiazide-like diuretic are considered for adults with uncomplicated hypertension.<sup>11</sup> Hypertension Canada recommends that patients with resistant hypertension be administered agents such as spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine in addition to their baseline regimen.<sup>11</sup> Evidence supporting the use of device-based interventions such as renal sympathetic denervation is considered inconclusive by the Hypertension Canada Guidelines Committee.<sup>9</sup>

Similarly, 2018 joint guidelines from the European Society of Cardiology and the European Society of Hypertension recommend that device-based therapies not be used for the routine treatment of hypertension except in the context of clinical studies.<sup>12</sup> In an updated position statement, the European Society of Hypertension deems RDN a safe and evidence-based alternative or additive therapeutic option that can be incorporated into a patient's treatment plan, with consideration to their preferences, stage of hypertensive disease, and comorbidities.<sup>13</sup>

## What Is the Evidence?

Results published in 2020 from the SPYRAL HTN-OFF MED pivotal trial show that in the absence of antihypertensive medications, participants in the treatment group experienced a statistically significant reduction in 24-hour ambulatory systolic BP as well as office systolic BP from baseline to 3 months after the procedure.<sup>14</sup> The SPYRAL HTN-ON MED proof-of-concept trial investigated the efficacy and safety of the RDN system in patients with uncontrolled hypertension on antihypertensive medications.<sup>15</sup> Similarly, participants who underwent the procedure experienced a statistically significant reduction in office and 24-hour ambulatory BP from baseline to 6 months compared with those in the sham control group.<sup>15</sup> Ambulatory BP monitoring involves several recordings from a device worn continuously over a 24- or 48-hour period and is used to confirm or rule out the effect of white coat hypertension, a phenomenon in which a patient's BP is temporarily inflated due to anxiety caused by being in a clinical setting.<sup>16</sup> Patients with white coat hypertension are not considered candidates for RDN. Hypertension can be a chronic condition; therefore, a limitation of these trials is the short 3-month and 6-month follow-up periods, which may not be long enough to elucidate the true treatment effect of RDN.

The Global SYMPLICITY Registry, with 2,600 enrolled participants, evaluates long-term outcomes associated with Symplicity Spyral and first-generation Symplicity Flex; a 3-year follow-up analysis found that participants who underwent the intervention sustained a statistically significant reduction in office and 24-hour ambulatory systolic BP as well as a reduction in the use of some antihypertensive medication classes.<sup>17</sup> A limitation of the single-arm registry is the lack of control or sham group for comparison.<sup>17</sup>

The earlier sham-controlled SYMPLICITY HTN-3 trial investigated the efficacy of the first-generation Symplicity system in patients with uncontrolled hypertension.<sup>18</sup> Similar to the SPYRAL HTN-ON MED trial, participants stayed on their prescribed medication regimen for the duration of the study.<sup>15,18</sup> However, the selection criteria for SYMPLICITY HTN-3 was more restrictive because only participants with severe resistant hypertension on 3 or more antihypertensive medications of different classes, of which 1 had to be a diuretic, were enrolled.<sup>18</sup> However, SPYRAL HTN-ON MED included participants who were on a regimen of



1, 2, or 3 antihypertensive medication classes.<sup>15</sup> Ultimately, both the intervention and sham control groups in the SYMPLICITY HTN-3 trial experienced reductions in office and 24-hour ambulatory systolic BP, but the study did not show a significant reduction of systolic BP after renal artery denervation compared with a sham control.<sup>18</sup>

## Safety

No major safety events related to the device or study were observed during the SPYRAL HTN-OFF MED or SPYRAL HTN-ON MED trials.<sup>14,15</sup> No long-term safety concerns were observed following the procedure in the Global SYMPLICITY Registry analysis, which contained data from those treated with the older Symplicity Flex catheter.<sup>17</sup> However, data derived from the use of the older, single-electrode Symplicity Flex catheter may not be as relevant when evaluating the safety profile of the newer, multielectrode Symplicity Spyral model.<sup>17</sup> Medtronic states that there are some uncommon risks associated with RDN: nausea or vomiting, temporary complications when using pain or anxiety medication during or following the procedure, and complications such as pain or bruising at the catheter insertion site.<sup>19</sup> These risks are similar to those of other diagnostic and treatment procedures that involve arterial catheterization.<sup>19</sup>

## Availability in Canada

Renal sympathetic denervation systems and device-based interventions for hypertension in general have not yet been approved for use in Canada.<sup>9</sup> The Symplicity Spyral RDN system is limited to clinical investigational use as of the writing of this report.<sup>20</sup> According to Medtronic, the procedure is approved for commercial use in more than 60 countries around the world.<sup>21</sup>

## What Does It Cost?

The anticipated cost of the Symplicity Spyral RDN system in Canada was not identified. Symplicity Spyral is designed to be used either an alternative or adjunctive surgical intervention to standard pharmacological therapy, with the main economic and planning considerations for implementation being operating room resources, time for the operating physician to learn and set up the generator for treatment, and the cost of the system itself. In the recent SPYRAL HTN-OFF MED trial, the average procedure time was approximately 100 minutes.<sup>14</sup> The catheter component, along with the additional guidewire used to deliver the catheter to the renal artery, is single use and intended for 1 bilateral procedure.<sup>4</sup>

Using findings from the SYMPLICITY HTN-3 trial and thresholds recommended by Australian reimbursement authorities, a 2018 economic evaluation found that RDN is a cost-effective intervention for treatment-resistant hypertension compared with standard care alone, with the condition that it is targeted to patients whose 10-year predicted cardiovascular risk was at least 13.2% initially.<sup>22</sup> Although RDN systems have a higher upfront cost compared with most antihypertensive medications, the long-term costs associated with hospitalizations and

complications due to poorly controlled hypertension must be considered when evaluating the cost-effectiveness of devices like Simplicity Spyral.

## Related Developments

Another RDN system, Paradise by ReCor Medical, uses ultrasound instead of radiofrequency waves to decrease the activity of the renal sympathetic nervous system. Investigators of the ongoing RADIANCE-HTN randomized controlled trial found that among patients in the mild-to-moderate hypertension cohort, participants who underwent RDN experienced a statistically significant reduction in daytime ambulatory systolic BP compared with those assigned to the sham procedure.<sup>23</sup> Participants discontinued antihypertensive medications 4 weeks before the recording of baseline measurements and stayed off of them throughout the study.<sup>23</sup> The BP-lowering effect was observed after they restarted antihypertensive medications.<sup>24</sup> Recent results from another sham-controlled trial in patients resistant to 3 or more antihypertensive medications show that participants who underwent ultrasound RDN experienced statistically significant reductions in office and ambulatory systolic BP.<sup>25</sup> Lastly, in a head-to-head randomized trial, ultrasound-based RDN was found to be similar to radiofrequency-based RDN (of the main arteries, accessories, and side branches) among patients with resistant hypertension.<sup>26</sup>

RDN has the potential to treat other conditions that are linked to sympathetic nerve activation, such as heart failure, atrial fibrillation, and chronic kidney disease.<sup>1</sup> A first-in-person study investigated the efficacy and safety of RDN in participants with chronic systolic heart failure.<sup>27</sup> Although participants symptomatically improved with no complications following the procedure, they did not experience a significant reduction in BP.<sup>27</sup> Authors of the ERADICATE-AF trial found that RDN in conjunction with catheter ablation increased the likelihood of freedom from atrial fibrillation compared with catheter ablation alone.<sup>28</sup> Catheter ablation is a standard procedure for patients who do not respond to pharmacological treatments for atrial fibrillation.<sup>28</sup> In terms of limitations, the trial lacked a formal sham control for RDN and excluded participants who did not have comorbid hypertension; therefore, the results cannot be extrapolated to all patients with atrial fibrillation.<sup>28</sup>

## Looking Ahead

Hypertension is a global condition, so there is a strong rationale for developing and adopting nonpharmacological treatments to offer alternative therapeutic options to people with uncontrolled hypertension. Several past iterations of RDN systems, including the previous generation manufactured by Medtronic, have failed to demonstrate efficacy in sham-controlled trials.<sup>29</sup> In contrast, recent trials for Simplicity Spyral have shown more promising results.

As more long-term efficacy and safety data for devices like Simplicity Spyral emerge, there may be a revision in recommendations regarding device-based therapies for the management of hypertension. For example, the National Institute for Health and Care Excellence is currently updating their guidance on renal sympathetic denervation for resistant

hypertension.<sup>30</sup> The high level of interest in this modality of hypertension management may increase the pace of technological development. However, factors such as cost — especially when compared to low-cost standard care options like angiotensin-converting enzyme inhibitors — can be barriers to the rapid uptake of RDN systems even as more robust clinical data become available. Further evaluation of how RDN may mitigate the long-term complications and health care utilization costs associated with uncontrolled hypertension would aid in decision-making.

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