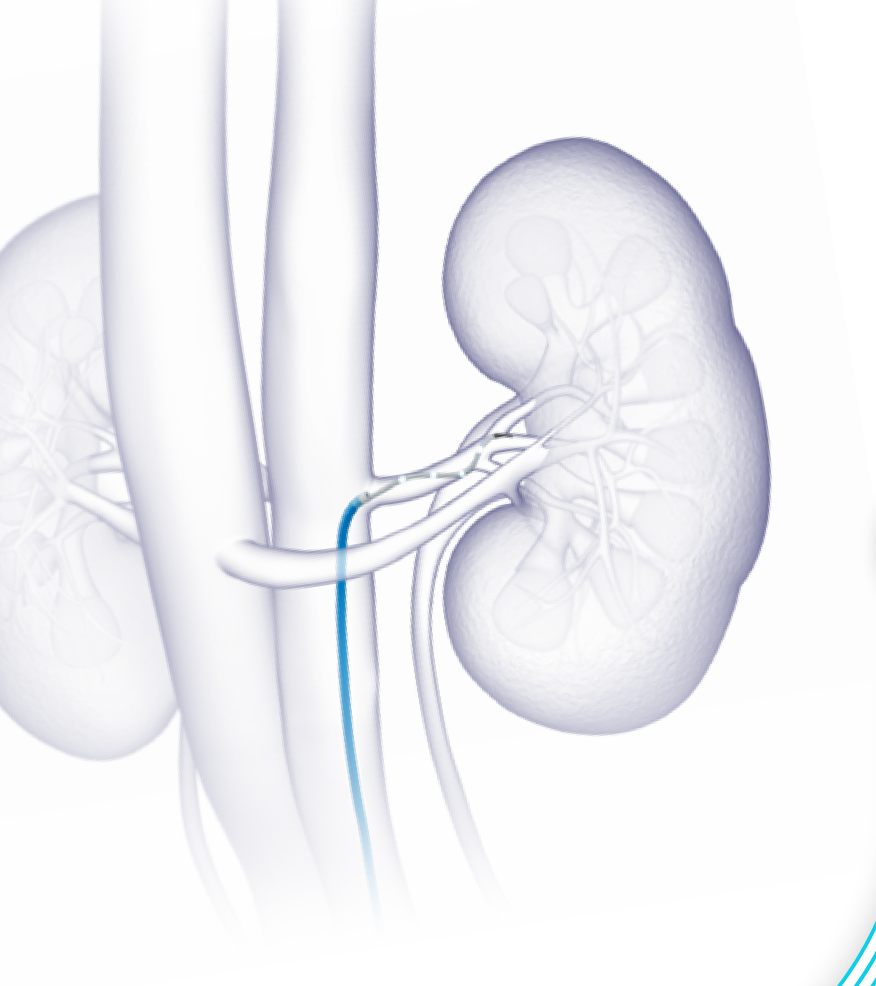
Medtronic

The road to significant, safe, and sustained blood pressure reductions[1–4]

Symplicity Spyral™ renal denervation system

Our commitment to developing a safe, novel, and effective renal denervation (RDN) system never wavered – even with detours along the way. When others gave up, we remained dedicated to:

- Redesigning our clinical studies
- Refining how to perform the procedure
- Advancing our technology



2010

Ardian acquisition

By acquiring the Ardian Symplicity™ renal denervation system, we got to work applying our expertise to further develop a catheter-based procedure for uncontrolled hypertension patients.

Learning from the past to inform our future

While we did not meet the primary endpoint of our HTN-3 trial, it showed:

- A significant difference in nighttime blood pressure (a "high-risk" zone) between the RDN group and the sham group (p = 0.015). We also met our safety endpoint. **These milestones signaled the promising impact of RDN and incentivized us to continue our research and design.**[6]
- Through patient journaling, we saw ~40% of patients had their medications changed during the study. **Because of this, we made sure future studies included a plasma/urine draw to understand medication variance.**[7]

2014

Symplicity HTN-3 trial[5]

Failed to demonstrate superiority of the Symplicity RDN system over a sham procedure and medical therapy in reducing office and ambulatory blood pressure at six months in patients with severe, resistant hypertension.

Peer-reviewed preclinical research showed that combining ablations of the main and branch renal arteries – where the majority of renal nerves converge – resulted in greater and more consistent pre-clinical effects.[8–10]

Preclinical results may not be indicative of clinical performance.

2015

SPYRAL clinical program begins

Spyral HTN-OFF MED trial

Sham-controlled randomized controlled trial (RCT), proving efficacy in the absence of antihypertensive medication[3]

Spyral HTN-ON MED trial

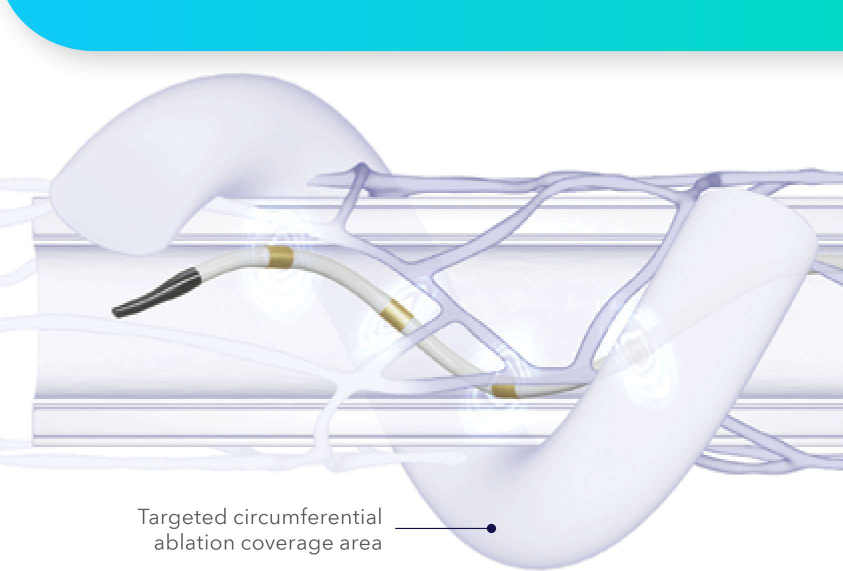
Prospective, sham-controlled RCT proving efficacy in context of background medication[1]

Global SYMPLICITY Registry (GSR)[†,2]

Prospective observational study, documenting real-world acute and long-term safety, effectiveness, and durability of the Symplicity system in over 3,300 patients

With these learnings, we redesigned our catheter into a spiral shape. **Today, the Symplicity Spyral system provides 360-degree ablations, resulting in significant, sustained, and safe blood pressure reductions.**[1-4,11]

Results may vary.



Excellent safety profile

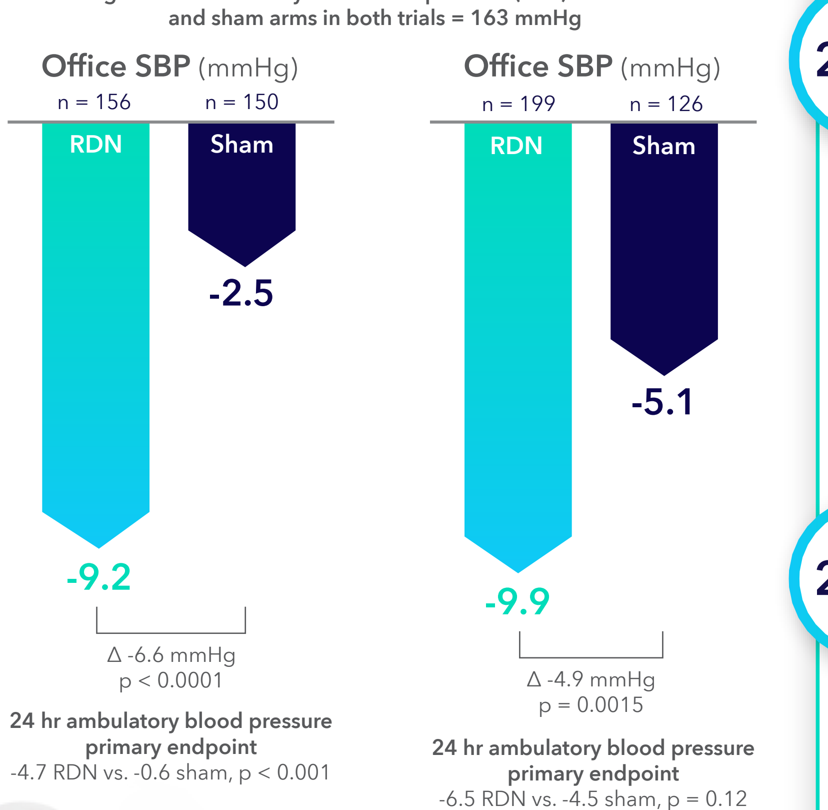
Pooled data from the SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED trials indicated low incidence of procedural related and clinical adverse events.

0.4% major adverse event rate at composite endpoint[4]

2020

SPYRAL HTN-OFF MED pivotal results

Significant blood pressure reductions in the absence of medication at 3 months.[3]



SPYRAL HTN-OFF MED3
Pivotal Trial
Absence of antihypertensive medications
SPYRAL HTN-ON MED4
Full Cohort
Presence of antihypertensive medications
Average baseline office systolic blood pressure (SBP) for both RDN and sham arms in both trials = 163 mmHg
Office SBP (mmHg)
n = 156
n = 150
RDN
Sham
-2.5
-9.2
Δ -6.6 mmHg
p < 0.0001
24 hr ambulatory blood pressure primary endpoint
-4.7 RDN vs. -0.6 sham, p < 0.001
Office SBP (mmHg)
n = 199
n = 126
RDN
Sham
-5.1
-9.9
Δ -4.9 mmHg
p = 0.0015
24 hr ambulatory blood pressure primary endpoint
-6.5 RDN vs. -4.5 sham, p = 0.12

Results may vary.

2021

Clinical evidence expansion begins

SPYRAL AFFIRM Global Clinical Post-approval Study

Single-arm interventional study, evaluating the long-term safety, efficacy, and durability of the Symplicity Spyral system

GSR expansion[†]

2,000 patients added

2022

SPYRAL HTN-ON MED results

Significant blood pressure reductions with 20% lower medication burden at 6 months with RDN (2.9 RDN vs. 3.5 sham, p = 0.04).[4]

2023

FDA approval of the Symplicity Spyral system

† Includes Symplicity Spryal and Flex catheters.

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3. Böhm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet*. May 2, 2020;395(10234):1444–1451.
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5. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial renal denervation for resistant hypertension. *N Engl J Med*. April 10, 2014;370(15):1393–1401.
6. Kario K, Bhatt DL, Brar S, Cohen SA, Fahy M, Bakris GL. Effect of Catheter-Based Renal Denervation on Morning and Nocturnal Blood Pressure: Insights From SYMPLICITY HTN-3 and SYMPLICITY HTN-Japan. *Hypertension*. December 2015;66(6):1130–1137.
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8. García-Touchard A, Maranillo E, Mompeo B, Sañudo JR. Microdissection of the Human Renal Nervous System: Implications for Performing Renal Denervation Procedures. *Hypertension*. October 2020;76(4):1240–1246.
9. García-Touchard A, Sañudo JR. Renal denervation. Importance of knowledge of sympathetic nervous system anatomy in refining the technique. *Rev Esp Cardiol (Engl Ed)*. July 2019;72(7):531–534.
10. Mompeo B, Maranillo E, García-Touchard A, Larkin T, Sañudo J. The gross anatomy of the renal sympathetic nerves revisted. *Clin Anat*. July 2016;29(5):660–664.
11. Coates P, Tunev S, Trudel J, Hettrick DA. Time, Temperature, Power, and Impedance Considerations for Radiofrequency Catheter Renal Denervation. *Cardiovasc Revasc Med*. September 2022;42:171–177.

Indications

The Symplicity Spyral™ renal denervation system is indicated to reduce blood pressure as an adjunctive treatment in patients with hypertension in whom lifestyle modifications and antihypertensive medications do not adequately control blood pressure.

Contraindications

The Symplicity Spyral system is contraindicated in patients with any of the following conditions: • Renal artery diameter < 3 mm or > 8 mm • Renal artery fibromuscular dysplasia (FMD) • Stented renal artery (< 3 months prior to RDN procedure) • Renal artery aneurysm • Renal artery diameter stenosis > 50% • Pregnancy • Presence of abnormal kidney (or secreting adrenal) tumor • Iliac/femoral artery stenosis precluding insertion of the catheter.

Warnings and Precautions

A thorough understanding of the technical principles, clinical applications, and risks associated with vascular access techniques and percutaneous transluminal catheterization in renal arteries is necessary before using this device.

The safety and efficacy of the Symplicity Spyral system has not been established in patients with isolated systolic hypertension or in patients with prior renal artery interventions including renal stents, renal angioplasty, or prior renal denervation. The Symplicity Spyral system has not yet been studied in patients who are breastfeeding, under the age of 18, or with secondary hypertension. • Avoid treatment with the Symplicity Spyral™ catheter within 5 mm of any diseased area or stent. • Implantable pacemakers (IPGs) and implantable cardioverter defibrillators (ICDs) or other active implants may be adversely affected by RF ablation. Refer to the implantable device's *Instructions for Use*. • The patient's heart rate may drop during the ablation procedure. • Proper pain medication should be administered at least 10 min before ablating renal nerves.

Potential Adverse Events

Potential adverse events associated with use of the renal denervation device or the interventional procedures include, but are not limited to, the following conditions: • Allergic reaction to contrast • Arterial damage, including injury from energy application, dissection, or perforation • Arterial spasm or stenosis • Arterio-enteric fistula • AV fistula • Bleeding • Blood clots or embolism • Bruising • Cardiopulmonary arrest • Complications associated with medications commonly utilized during the procedure, such as narcotics, anxiolytics, or other pain or anti-vasospasm medications • Death • Deep vein thrombosis • Edema • Electrolyte imbalance • Heart rhythm disturbances, including bradycardia • Hematoma • Hematoma – retroperitoneal • Hematuria • Hypertension • Hypotension (may cause end organ hypoperfusion) • Infection • Kidney damage including renal failure or perforation • Myocardial infarction • Nausea or vomiting • Pain or discomfort • Peripheral ischemia • Pulmonary embolism • Proteinuria • Pseudoaneurysm • Radiocontrast nephropathy • Renal artery aneurysm • Skin burns from failure of the dispersive electrode pad • Stroke • Other potential adverse events that are unforeseen at this time.

Please reference appropriate product *Instructions for Use* and *User Manual* for more information regarding indications, contraindications, warnings, precautions, and potential adverse events.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

For further information, please call and/or consult Medtronic at 800-633-8766 or the Medtronic website at medtronic.com.

Medtronic

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