Medtronic

SYMPLICITY SPYRAL™ RENAL DENERVATION SYSTEM

SPONSOR EXECUTIVE SUMMARY

CIRCULATORY SYSTEM DEVICES PANEL

MEETING DATE: 23 AUGUST 2023

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations

Abbreviation	Definition
ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
AE	adverse event
ANCOVA	analysis of covariance
ARB	angiotensin II receptor blockers
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CEC	Clinical Events Committee
CI	confidence interval
CKD	Chronic kidney disease
CTA	computed tomography angiography
CV	Cardiovascular
DBP	diastolic blood pressure
DCE	discrete choice experiment
DSMB	data safety monitoring board
DUS	duplex ultrasound
eGFR	estimated glomerular filtration rate
ERA	European Renal Association
ESH	European Society Hypertension
EU	European Union
FDA	Food and Drug Administration
GSR	Global SYMPLICITY Registry
HARC	Hypertension Academic Research Consortium
ISH	isolated systolic hypertension
ISPOR	The Professional Society for Health Economics and Outcomes Research
ITT	intent-to-treat
LOCF	last observation carried forward
MAB	minimal acceptable benefit
MAE	major adverse events
MAR	maximum acceptable risk
MDIC	Medical Device Innovative Consortium
MRA	magnetic resonance angiography
NHANES	National Health and Nutrition Examination Survey

PG	performance goal
PMA	Premarket Approval Application
PSV	peak systolic velocity
RAR	Renal/Aorta Ratio
RDN	renal denervation
RF	radiofrequency
SAE	serious adverse event
SBP	systolic blood pressure
SNS	sympathetic nervous system
TTR	time in target range
TIMI	thrombolysis in myocardial infarction
US	United States

Cohort Definitions

OFF MED Pivotal Patient Cohorts

Term	Definition
Pilot Cohort	First consecutively randomized 80 patients in OFF MED
Expansion Cohort	Next 251 patients consecutively randomized in OFF MED (N=251)
Pivotal Cohort	First consecutively randomized 80 patients + next 251 consecutively randomized patients (N=331)
Full Cohort	First consecutively randomized 80 patients + next 251 consecutively randomized patients + next 35 randomized patients prior to stopping enrollment for success = 366 total
Denervation Group	Patients randomized to renal denervation
Sham Group	Patients randomized to sham control
Crossover Group	Patients randomized to Sham, who elected to crossover to the renal denervation procedure following completion of the primary endpoint in the study
Non-Crossover Group	Patients randomized to Sham who did not elect for the renal denervation procedure

ON MED Patient Cohorts

Term	Definition
Pilot Cohort	First 80 patients randomized in ON MED (N=80)
Expansion Cohort	Next 257 patients consecutively randomized in ON MED (N=257)
Full Cohort	Pilot + Expansion (N=337)
Denervation Group	Patients randomized to renal denervation
Sham Group	Patients randomized to Sham control

1 Synopsis

1.1 Introduction

Medtronic is seeking approval of the Symplicity Spyral Renal Denervation System (Symplicity Spyral System), which provides a catheter-based approach to denervate the renal arteries using radiofrequency (RF) energy. The proposed indication of the Symplicity Spyral System is for reduction of blood pressure (BP) in patients with uncontrolled hypertension, despite the use of anti-hypertensive medications or in patients in whom blood pressure lowering therapy is poorly tolerated. Evidence in support of this proposal and indication including data from prospective, randomized trials as well as a real-world registry are provided here.

RF renal denervation (RDN) is a minimally invasive procedure designed to permanently interrupt nerve signaling between the brain and kidney that may contribute to hypertension. Excellent short and long-term safety suggest the procedure would complement established treatment options for the management of hypertension. To date, the scientific evidence demonstrates clinically meaningful and sustained BP reduction in patients with hypertension, either alone or in combination with other BP lowering therapies.

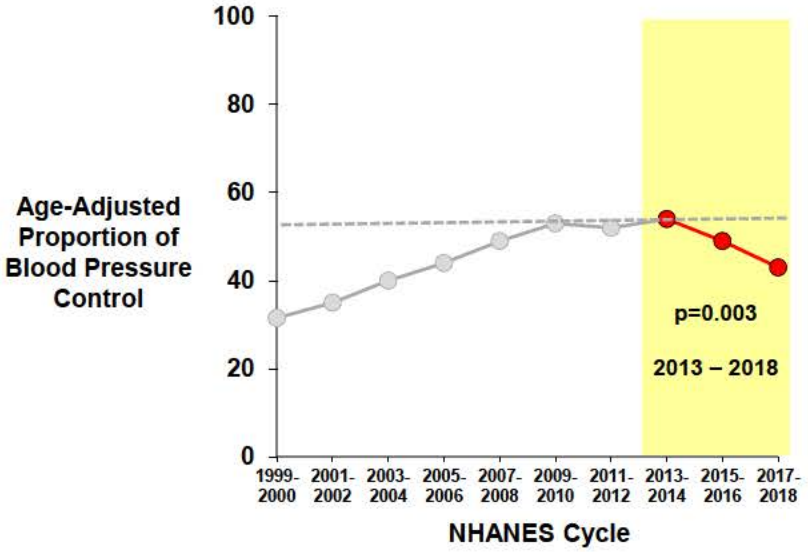
1.2 Background and Unmet Need

The global prevalence of hypertension, defined as systolic BP (SBP) greater than 140 mmHg, is estimated to be over 30% (Muntner et al 2018). Less than 20% of these patients have their BP adequately controlled. Hypertension is the most prevalent risk factor for stroke, and major risk factor for other cardiovascular (CV) diseases such as coronary artery disease, heart failure, and chronic kidney disease, accounting for 9.4 million deaths worldwide every year (WHO 2015). Hence, hypertension remains the leading modifiable cause of death globally.

Hypertension statistics in the United States (US) reflect the global data. According to the current American College of Cardiology and the American Heart Association guidelines, which define hypertension as an office SBP of *130 mmHg* or higher (Whelton et al 2018), the prevalence of hypertension among US adults is approximately 48% (CDC 2023).

Current US treatment guidelines recommend lifestyle modifications followed by anti-hypertensive medications for patients with primary hypertension (Whelton et al 2018). Hypertension control rates within the US are also low and have been decreasing over recent time. Indeed, the proportion of US patients with controlled BP decreased significantly from approximately 54% over the period from 2013–2014 to 44% in 2017–2018 (Figure 1).

Figure 1: Blood Pressure Control Over Time (1999–2018)



NHANES: National Health and Nutrition Examination Survey
Source: Muntner et al 2020

BP reduction is strongly associated with reduced CV risk. Meta-regression analysis of placebo-controlled BP lowering trials demonstrated a continuous linear reduction in relative risk of major cerebral-cardiovascular events that was independent of baseline BP and comorbidities (see Figure 13). This evidence also supports the validity of BP reduction as a surrogate clinical trial outcome and has been utilized as the primary measure of effectiveness for pharmaceutical trials as shown in the product insert for various antihypertensive agents (Merck Sharp & Dohme Corp 2018; Pfizer Laboratories 2019).

Low global and US hypertension control rates are due in part to widespread non-adherence to prescribed medications. A review of recent reports of adherence objectively quantified with plasma and urine analysis indicated that approximately 44% of treated uncontrolled hypertensive patients were not taking all their anti-hypertensive medications, and approximately 17% were found to be not taking any anti-hypertensive medications (Berra et al 2016). The probability of drug non-adherence is proportional to the number of anti-hypertensive medications prescribed and going from 2 to 3 anti-hypertensive agents doubles the likelihood of non-adherence (Gupta et al 2017b). Non-adherence to newly prescribed medication has been shown to progressively increase over time, especially within the first year of prescription (Vrijens et al 2008).

1.3 Product Description

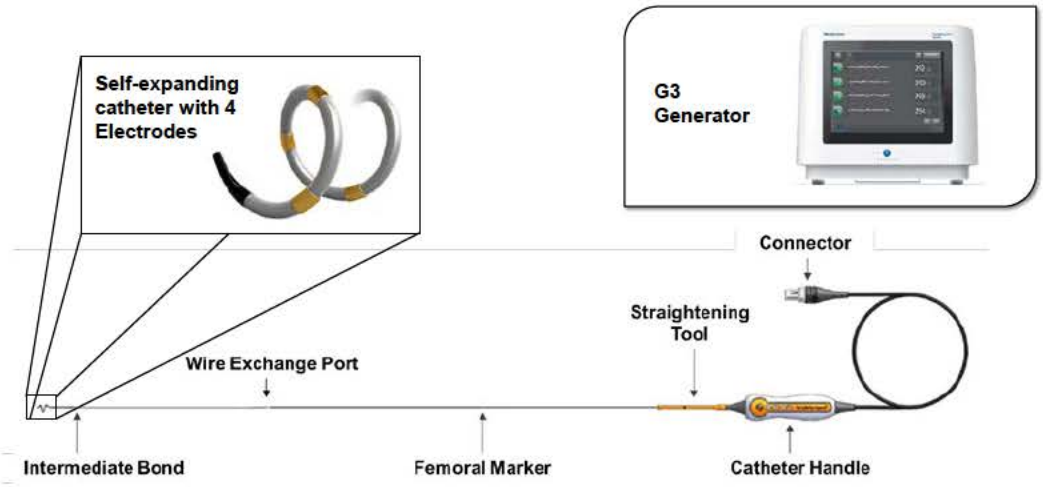
The Symplicity Spyral System offers a catheter-based RDN procedure to modulate renal efferent and afferent autonomic pathways, which both play critical roles in the regulation of BP (see Section 3.2.1).

RF RDN was first approved for commercial use outside the United States in 2010 using the predicate Symplicity Flex system. The Symplicity Spyral System, the subject of this Premarket Approval Application (PMA), was first CE Marked in the European Union (EU) on 15 October 2013 and is commercially available in 70 countries. It is supported as a treatment option for uncontrolled hypertension by multiple society statements worldwide, including most recently the European Society Hypertension (ESH) guidelines, which are additionally endorsed by the European Renal Association (ERA) and the International Society of Hypertension (Mancia et al 2023).

The system includes the Symplicity Spyral™ multi-electrode RF RDN catheter and the Symplicity G3™ RF generator (Figure 2). The Symplicity Spyral catheter consists of a distal, self-expanding array onto which four cylindrical gold electrodes are mounted in a helical configuration, allowing for denervation along 4 quadrants covering the circumference of the vessel lumen. To minimize the thermal effects on the renal artery wall, the non-occlusive design allows for continuous blood flow throughout the treatment, thus cooling the arterial wall and the electrodes during treatment.

The generator provides a safe and effective means of delivering RF energy to the catheter. Each of the four electrodes on the distal end of the Symplicity Spyral catheter are independently controlled by 4 RF output channels on the generator. Real-time temperature and electrode impedance feedback are used to automatically adjust the delivered power independently to each electrode (Coates et al 2022).

Figure 2: Symplicity Spyral System



Principles of operation are fully described in Section 3.2. Briefly, the single-use catheter is inserted using vascular access and guided to the renal artery via the abdominal aorta through a standard 6F guide catheter and over a standard 0.014" guidewire. Once the catheter is positioned at a desired treatment location in the renal artery, the guidewire is retracted to deploy the catheter, which naturally conforms to the patient's anatomy. Each of the 4 electrodes delivers RF energy simultaneously for 60 seconds; the catheter is then repositioned to include treatment of branches and accessory arteries

located outside the renal parenchyma, if present. The duration of the interventional procedure is approximately one hour, similar to a routine percutaneous coronary interventional procedure.

1.4 Development Program

Medtronic has engaged the Food and Drug Administration (FDA) throughout the development and conduct of the RDN clinical program; utilizing the pre-submission process to align on critical elements of the program. RDN using a catheter-based approach has been evaluated in clinical studies performed by Medtronic over more than 10 years in more than 4,000 patients. Specifically, the current generation Symplicity Spyral System, for which the approval is being sought here, has been studied in over 1,800 patients.

1.4.1 Historical Perspective

Early studies with a first generation, single electrode version of the device (Symplicity Flex™ Catheter), including the SYMPLICITY HTN-1, -2, and -3 studies, supported the long-term durability and safety of renal denervation, but presented opportunities to improve the device, study designs, and procedural technique. HTN-3, a sham-controlled trial, enrolled 535 patients with severe resistant hypertension on a maximum tolerated dose of 3+ medications (Kandzari et al 2015).

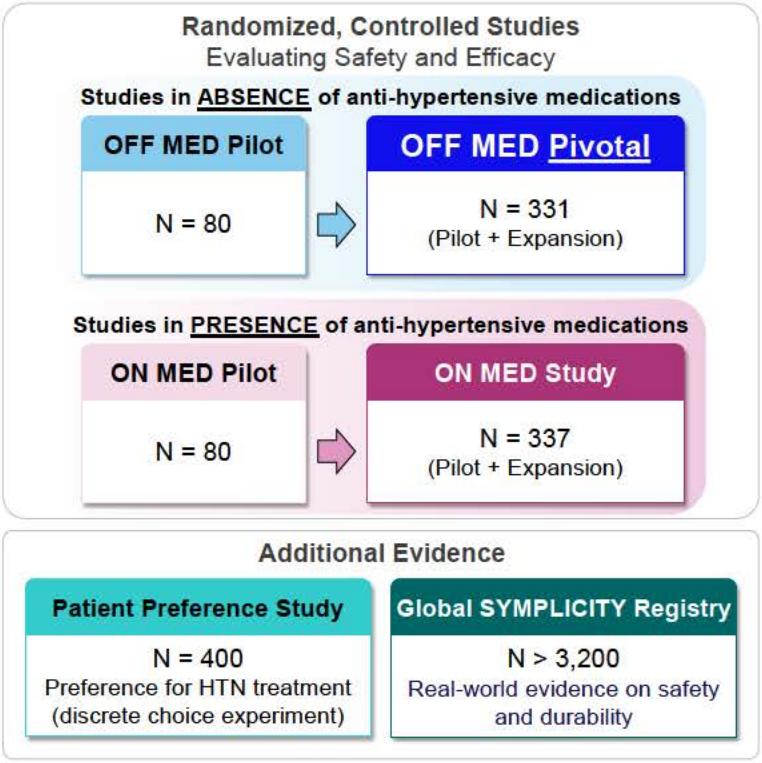
HTN-3 met its primary safety endpoint and failed to meet its primary efficacy endpoint of change in office SBP at 6 months compared with control. Analysis of the HTN-3 study results led to improvements in the device design to the current Symplicity Spyral catheter to enable circumferential ablation as well as improvements in the procedural technique and updates to the study population as incorporated in the SPYRAL HTN clinical program (see Appendix 3: Clinical History of Renal Denervation).

1.4.2 SPYRAL HTN Clinical Program (Subject of PMA)

Both the OFF MED and ON MED studies were initiated as pilot cohorts and based on positive safety and efficacy results, were each expanded to include an Expansion cohort. To limit the potential confounding impact of changes in prescribed medication after randomization, which was one factor that affected the HTN-3 study results, the current SPYRAL HTN clinical program included an OFF MED study which was designed to isolate the effects of the Symplicity Spyral System in the absence of other anti-hypertensive drug therapies, an approach similar to that used to support pharmaceutical approval of anti-hypertensive medications. ON MED was designed to supplement the OFF MED Pivotal data by examining device efficacy in the presence of commonly prescribed anti-hypertension medications (eg, the most common clinical application of the procedure) (Figure 3). The pilot and the expansion cohorts for each of the OFF MED and ON MED studies were designed to be combined prospectively, using Bayesian methods for the powered primary endpoint assessments, as outlined in the statistical analysis plan. These Bayesian methods for combining data put stronger

weight on data from the pilot cohort depending on the similarity of the result in the pilot vs the expansion cohorts, and lesser weight for divergent data.

Figure 3: Symplicity Spyral System Key Clinical Studies



HTN: hypertension

1.4.3 Patient Preference Study

In addition to these studies, Medtronic consulted with the FDA on the design and execution of a patient preference study to understand patient prioritization of safety and efficacy variables when considering an interventional treatment compared to current standard of care.

1.4.4 Global SYMPLICITY Registry

Additionally, the Global SYMPLICITY Registry (GSR) is an ongoing study outside the US, designed to gather safety and durability data on the RF RDN procedure in a wide range of patients reflecting real-world use conditions.

1.5 Efficacy Findings

1.5.1 OFF MED

Study Design

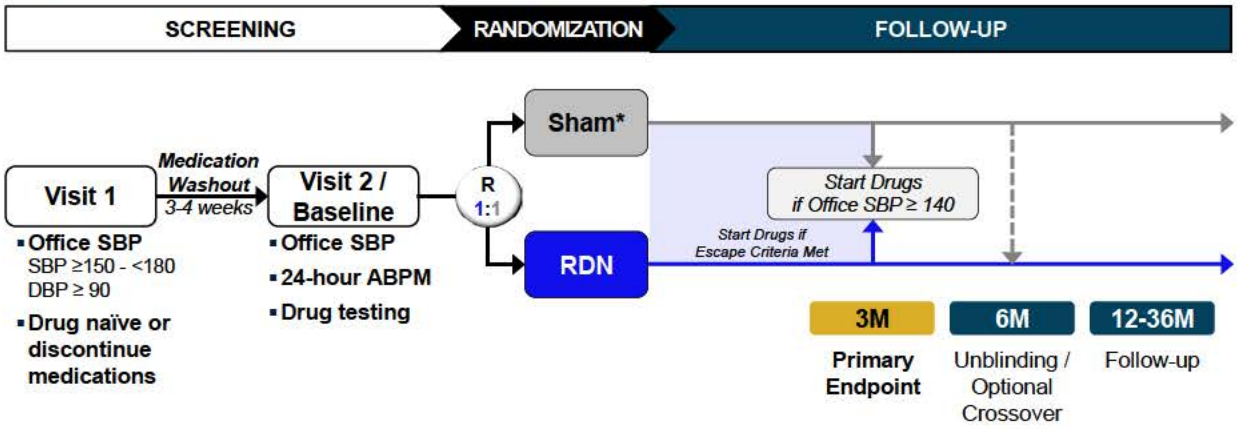
The OFF MED design was implemented to evaluate the safety and efficacy of RDN in patients with uncontrolled hypertension compared to a sham-controlled population, in the absence of anti-hypertensive medications. This design was intended to isolate the effects of the Symplicity Spyral System and avoid confounding effects of medications following an approach commonly applied in anti-hypertension drug approval trials (Kandzari et al 2016). OFF MED Pivotal was conducted in two cohorts: an initial pilot cohort to determine the feasibility of the design (described in Section 5.1.1) and the second prospectively powered cohort, that continued via an adaptive Bayesian design (refer to Appendix 1: Bayesian Approach used in OFF MED and ON MED for additional details about Bayesian design).

Key inclusion criteria were baseline office SBP 150–180 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, and 24-hour mean SBP 140–170 mmHg. Patients were either drug naïve or discontinued anti-hypertensive medications in the 3–4 weeks prior to randomization. Key exclusion criteria included ineligible renal artery anatomy, estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m^2, Type 2 diabetes with HbA1C above 8% or Type 1 diabetes, and patients with secondary causes of hypertension (see Section 5.1.1.2).

The participants were randomized 1:1 to denervation with the Symplicity Spyral System (Denervation group) or sham control (Sham group; Figure 4). Unless patients met prespecified escape criteria (office SBP ≥ 180, or safety concern), the protocol required that patients remain off medications through the 3-month visit for analysis of the primary efficacy endpoint. Unblinding occurred at 6 months, and patients in the Sham group could opt to crossover to receive the renal denervation procedure, if they met the anatomical and kidney function criteria for the treatment procedure.

Denervation patients and Sham patients were followed through 36 months. Crossover patients are followed through 24 months post RDN procedure.

Figure 4: OFF MED Pivotal Study Design



ABPM: ambulatory blood pressure measurement; DBP: diastolic blood pressure; M: month; R: randomization; RDN: renal denervation SBP: systolic blood pressure
*renal angiography alone
Escape criteria = Office SBP ≥ 180 or safety concern

The primary efficacy endpoint in OFF MED was the baseline-adjusted change in 24-hour SBP from baseline to 3-months. While Bayesian design discounts prior data based on the dissimilarity of the BP results to the expansion data, key secondary analyses utilizing an analysis of covariance (ANCOVA) approach include all patients. The powered secondary efficacy endpoint was the baseline-adjusted change in office SBP at 3 months. Key secondary analyses included daytime and nighttime SBP and DBP at 3 months and change from baseline in SBP and DBP measured via 24-hour BP at 3, 6, 12, 24, and 36 months. Additional endpoints are described in Section 5.1.1.7.

Participants

OFF MED pilot randomized 80 patients. After initial positive feasibility was established, an additional 251 patients were treated in an Expansion cohort to reach the total 331 patients included in OFF MED Pivotal Cohort for the primary Bayesian analysis. An additional 35 patients were enrolled prior to stopping the study for success to reach the total 366 subjects comprising the Full cohort. Overall, 182 patients were randomized to the Denervation group and 184 to the Sham group to form the Full Cohort.

A total of 190 (52%) patients were enrolled from outside of the US. Key baseline characteristics were balanced between groups (Table 1). Complete demographics and baseline characteristics are described in Section 5.1.3.

Table 1: OFF MED Key Baseline Characteristics (Full Cohort)

	Denervation N=182	Sham N=184	P-Value
Length of Hypertension			0.822
0–5 years	44.0% (80/182)	44.0% (81/184)	
6–10 years	18.7% (34/182)	16.3% (30/184)	
> 10 years	37.4% (68/182)	39.7% (73/184)	
Systolic BP [mean ± SD, mmHg]			
Office	162.8 ± 7.8	163.2 ± 7.7	0.604
24-Hour	151.2 ± 7.9	151.3 ± 7.6	0.967
Diastolic BP [mean ± SD, mmHg]			
Office	101.1 ± 7.1	102.2 ± 7.3	0.174
24-Hour	97.6 ± 7.9	99.3 ± 7.5	0.041
Diabetes	4.4% (8/182)	6.0% (11/184)	0.639
Coronary Artery Disease	0.0% (0/182)	4.3% (8/184)	0.007
Chronic Kidney Disease*	3.8% (7/182)	4.3% (8/184)	1.000
Obstructive Sleep Apnea	8.2% (15/182)	7.1% (13/184)	0.699

BP: blood pressure; eGFR: estimated glomerular filtration rate; SD: standard deviation
*Defined as baseline eGFR <60 mL/min/1.73m^2

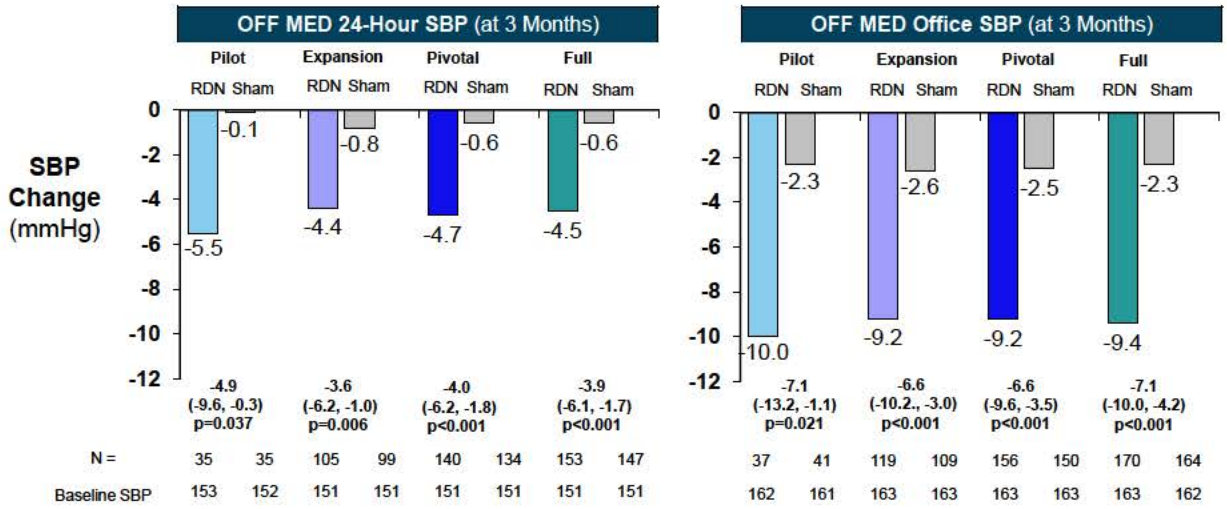
Results

As shown in Figure 5, in the OFF MED pilot study, 24-hour SBP decreased from baseline to 3 months in the Denervation group by −5·5 mmHg (p = 0.028) and Office SBP decreased from baseline to 3 months by −10.0 mmHg (p = 0.016), respectively. No significant changes were seen in the Sham group. The mean difference between the Denervation and the Sham groups favored RDN in both 24-hour SBP and office BP from baseline to 3 months of −4.9 mmHg (p = 0.037) and −7.1 mmHg (p = 0.021), respectively.

In the OFF MED Pivotal study, the primary 24-hour SBP and secondary office SBP Bayesian endpoints were met, with posterior probability of superiority > 0.999 for both endpoints. The mean treatment difference between the Denervation and Sham groups for 24-hour SBP was −3.9 mmHg (Bayesian 95% credible interval −6.2 to −1.6) and −6.5 mmHg (−9.6 to −3.5) for office SBP. In the secondary efficacy frequentist ANCOVA, statistically significant between-group differences in favor of the Denervation group from baseline to 3 months of −3.9 mmHg and −7.1 mmHg were observed for 24-hour and office SBP, respectively (both p < 0.001; Figure 5). The reduction in 24-hour mean SBP in the Denervation group was maintained throughout the 24-hour measurement period (Figure 6), including the nighttime and early morning hours where CV risk has been shown to be greatest (Staplin et al 2023; Yang et al 2019a).

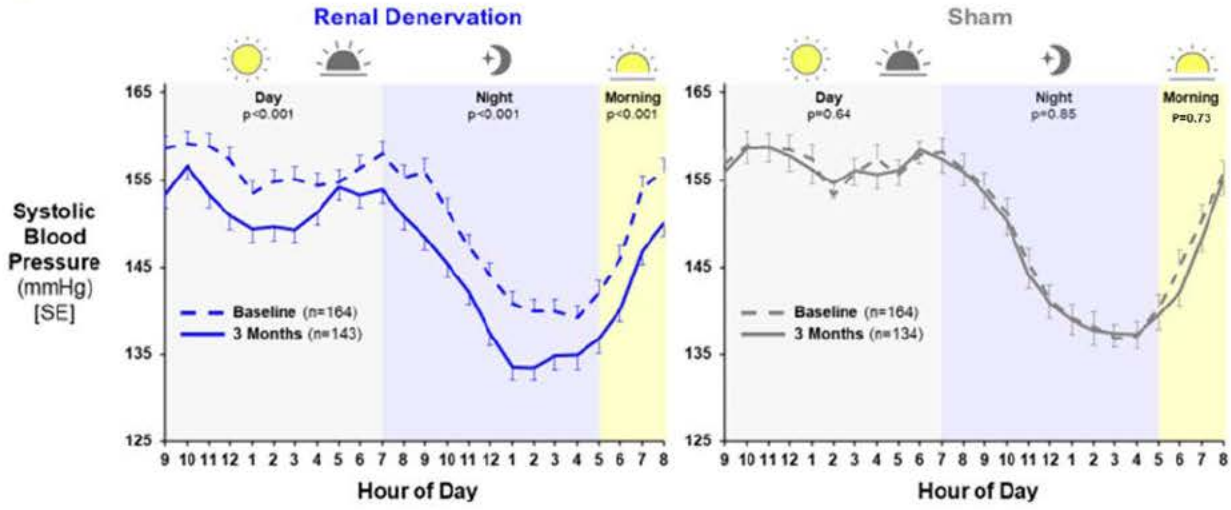
Additional results from OFF MED are presented in Section 5.1.6.

Figure 5: OFF MED All Cohorts Change in 24-Hour and Office Systolic Blood Pressures (ITT Population)



BP: blood pressure; RDN: renal denervation; SBP: systolic blood pressure

Figure 6: OFF MED Pivotal Cohort Hourly Change in Systolic Blood Pressure (ITT Population)



SE: standard error

1.5.2 ON MED

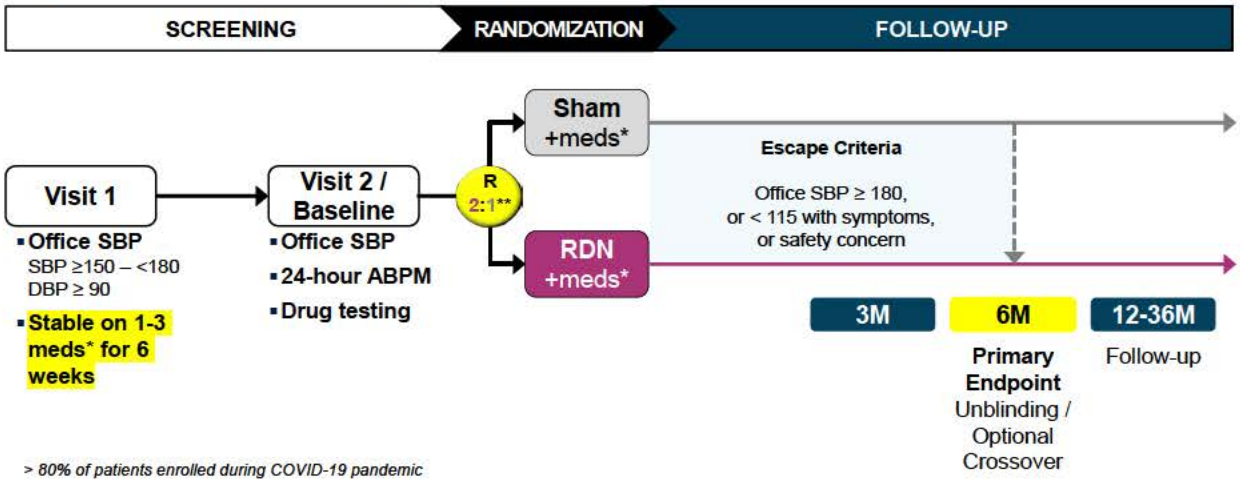
While OFF MED Pivotal was designed to isolate the treatment effect of the Symplicity Spyral System and avoid the confounding effects of anti-hypertensive medications, additional complementary studies were also performed to understand RDN used

adjunctively with medications. The ON MED design evaluated safety and efficacy of RDN in patients with uncontrolled hypertension compared to a sham-controlled population, in the presence of anti-hypertensive medications.

Like OFF MED, ON MED was conducted in two cohorts; an initial pilot cohort to determine the feasibility of the study design and a second expansion cohort that continued the study via an adaptive Bayesian design. Eligible patients had uncontrolled BP (office SBP 150 to < 180 mmHg; DBP ≥ 90 mmHg; average 24-hour SBP 140 to < 170 mmHg) and were on 1–3 standard anti-hypertensive medications at baseline. Key exclusion criteria were ineligible renal artery anatomy, eGFR at or below 45 mL/min/1.73 m^2, Type 2 diabetes with HbA1C above 8% or Type 1 diabetes, and patients with secondary causes of hypertension were excluded from the study (see Section 5.2.1.2).

Patients were randomized 1:1 in the pilot study and 2:1 in the expansion study, (Denervation or Sham) (Figure 7). Note that the first 26 subjects in the HTN-ON Expansion cohort was randomized based on 1:1 fashion. Patients in both groups were required to be prescribed a stable course of commonly prescribed standardized anti-hypertensive medication classes (thiazide diuretic, angiotensin-converting enzyme [ACE]/ angiotensin II receptor blockers [ARB], calcium channel blocker, beta blocker). Changes to medications were not permitted through the 6-month follow-up visit unless pre-specified escape safety criteria were met (office SBP ≥ 180 or < 115 with symptoms, or safety concern). At the completion of the 6-month visit, patients were unblinded and those in the Sham group could opt to crossover and receive the RDN procedure. Follow-up extends through 36-months post-procedure.

Figure 7: ON MED Study Design



ABPM: ambulatory blood pressure monitoring; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; DBP: diastolic blood pressure; M: month; R: randomized; RDN: renal denervation; SBP: systolic blood pressures; Yellow highlight represents differences from OFF MED
*Thiazide diuretic, ACE/ARB, Calcium Channel Blocker, Beta Blocker
** First 106 patients randomized 1:1

The primary efficacy endpoint of ON MED was the change in 24-hour SBP from baseline to 6 months using a Bayesian analyses approach. While Bayesian design discounts prior data based on the dissimilarity of the BP results to the expansion data, key secondary analyses utilizing an ANCOVA approach include all patients. These secondary analyses included change from baseline in office SBP, 24-hour SBP and DBP at 6 months, day and nighttime SBP and DBP at 6 months, and a win ratio analysis to determine the impact that changes in medication had on blood pressure. Additional endpoints are described in Section 5.2.1.7.

Participants

ON MED Pilot randomized 80 patients. After initial positive feasibility was established, an additional 257 patients were enrolled in an expansion cohort to reach the total 337 patients forming the Full Cohort. Overall, 206 patients were randomized to the Denervation group and 131 to the Sham group.

A total of 181 (54%) patients were enrolled from outside of the US. Baseline systolic and DBP was similar between groups, as was the incidence of comorbidities and co-existing illnesses such as coronary artery disease (Table 2).

Notably, 80% of patient follow-up visits for the ON MED Expansion cohort occurred during the Covid-19 pandemic.

Complete demographics and baseline characteristics are described in Section 5.2.3.

Table 2: ON MED Key Baseline Characteristics (Full Cohort)

	Denervation N=206	Sham N=131	P-values
Length of Hypertension			0.038
0–5 years	30.1% (62/206)	18.3% (24/131)	
6–10 years	18.0% (37/206)	20.6% (27/131)	
> 10 years	51.9% (107/206)	61.1% (80/131)	
Systolic BP [mean ± SD, mmHg]			
Office	163.0 ± 7.7	163.1 ± 7.9	0.871
24-Hour	149.6 ± 7.0	149.3 ± 7.0	0.703
Diastolic BP [mean ± SD, mmHg]			
Office	101.2 ± 7.0	101.5 ± 7.3	0.712
24-Hour	96.6 ± 7.6	95.7 ± 7.7	0.277
Diabetes	10.7% (22/206)	17.6% (23/131)	0.074
Coronary Artery Disease	5.3% (11/206)	6.9% (9/131)	0.638
Chronic Kidney Disease*	6.8% (14/206)	8.4% (11/131)	0.671
Obstructive Sleep Apnea	11.2% (23/206)	17.6% (23/131)	0.105

BP: blood pressure; eGFR: estimated glomerular filtration rate; SD: standard deviation
*Defined as baseline eGFR < 60 mL/min/1.73m^2

Results

As shown in Figure 8, in the ON MED pilot study, 24-hour and office SBP decreased significantly from baseline to 6 months ($p < 0.001$) in the Denervation group by −9.3 mmHg in 24-hour SBP and −9.2 mmHg in office SBP. No significant changes were seen in the Sham group.

The mean difference between the groups favored RDN for 6-month change in both 24-hour and office SBP from baseline of −7.3 mmHg ($p = 0.004$) and −6.6 mmHg ($p = 0.026$), respectively (Figure 8).

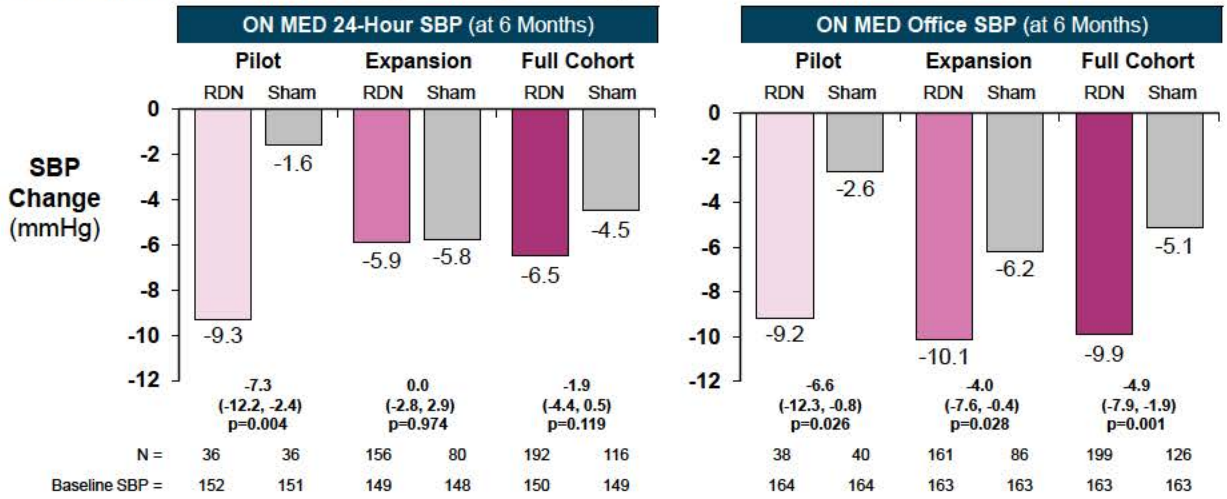
In the ON MED Full Cohort (pilot plus expansion), the primary Bayesian efficacy endpoint was not met due to a larger than expected Sham group 24-hour SBP reduction and a lower than expected RDN group 24-hour SBP reduction. The difference between the Denervation and Sham groups was −0.030 mmHg (Bayesian 95% credible interval: −2.82, 2.77). For the Bayesian analyses that utilized both pilot and expansion, approximately 80% of the pilot Denervation BP data and all of the pilot Sham BP data were excluded from the primary efficacy endpoint analysis (see Section 5.2.1.7.4) due to dissimilarity in 24-hour SBP results between the Pilot and Expansion cohorts.

Using the frequentist ANCOVA analysis of all patients in the ON MED Full Cohort, a between-group difference in 24-hour SBP in favor of the Denervation group from baseline to 6 months of −1.9 mmHg was observed (−6.5 mmHg in the Denervation group and −4.5 mmHg in the Sham group; $p = 0.119$; Figure 8). The reduction in daytime SBP was similar between groups (−6.5 mmHg for Denervation group and −5.0 mmHg for Sham group; $p=0.370$). However, nighttime SBP reductions were significantly greater in the Denervation vs Sham group with reductions of 6.7 and

3.0 mmHg, respectively (between-group difference of −3.7 mmHg, p = 0.010; Section 5.2.7.2.2).

In addition, office SBP reductions were greater in the Denervation group (−9.9 mmHg) than the Sham group (−5.1 mmHg) (between-group difference: −4.9 mmHg, p = 0.001). The absolute changes in 24 hour and office SBP from baseline were statistically significant and clinically meaningful for patients receiving RDN and consistent with the pilot study.

Figure 8: ON MED Study 24 hour and Office Systolic Blood Pressure Change from Baseline to 6 Months (ITT Population)



RDN: renal denervation; SBP: systolic blood pressure

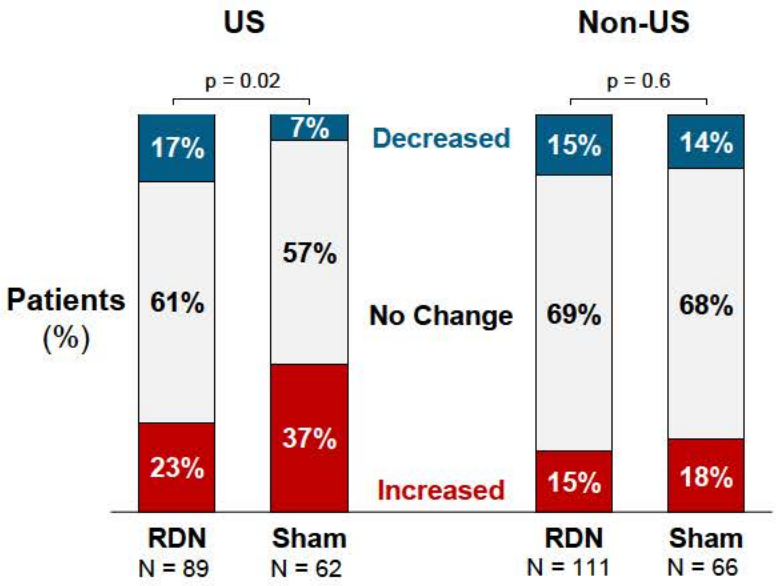
Additional analyses were performed to understand the discordance between the sham-adjusted changes in office and 24-hour SBP at 6 months as well as the discordance between 24-hour SBP results between the Pilot and Expansion cohorts. These analyses identified additional factors including medication changes and missing ambulatory blood pressure monitoring (ABPM) data that disproportionately impacted the Sham group and may have biased the primary endpoint toward the null. Significant medication changes between baseline and the 6-month follow-up assessment were observed in the Expansion cohort (p<0.03). A higher percentage of patients in the Sham group increased their medications (27%) while more patients in the Denervation group decreased their medications (16%) as determined by drug testing.

Furthermore, a greater percentage of patients in the Sham group (11.5% Sham vs 6.8% RDN) were missing their 24-hour BP data due to more Sham patients meeting the 'escape' criteria and not having the recommended ABPM obtained prior to medication increases. For these patients with missing 24-hour BP, but available office SBP data (N = 17), the corresponding office SBP data showed an increase of 2.1 mmHg for the Sham group (N = 10) and a reduction of 14 mmHg for the Denervation group (N = 7) (−16.5 mmHg between-group difference, p = 0.03). Therefore, absence of these ABPM readings biases the primary endpoint to the null.

Importantly, pre-specified subgroup analyses highlight the potential impact of confounding factors on ABPM. As shown in Figure 9, medications identified by drug testing increased disproportionately in the US Sham group, while medications decreased more often in the US Denervation group, resulting in a between-group BP reduction that was not statistically significant in the US cohort. In the Non-US population, where medication changes were balanced across study arms, significant 24-hour SBP changes favored RDN with a treatment difference −4.8 mmHg (−7.4 mmHg for the Denervation group, −2.6 mmHg for the Sham group, p = 0.001; see Figure 43). These results were similar to those reported in the ON MED pilot study where medication changes were not disproportionate between treatment groups. Additionally, results from the OFF MED Pivotal study, which is not confounded by medication changes, identified no significant differences between US and Non-US subgroups.

As a method to consider the combined impact of reduction in BP and reduction in medication use, win ratio analysis (Pocock et al 2012; Redfors et al 2020) were applied in a hierarchical composite endpoint to include the medication changes and 24-hour SBP reduction at 6 months. Using a threshold of 5 mmHg for the 24-hour SBP and a threshold of 0 (any change) for the medication burden component based on drug testing, the win ratio was 1.49 (95% confidence interval [CI]: 1.13 to 2.00; p = 0.005) in favor of Denervation (Table 25). This win ratio represents a 1.49 × greater likelihood of reducing BP or medication with RDN therapy than with sham treatment.

Figure 9: ON MED Comparison of US and Non-US Changes from Baseline in 6-Month Medication Burden (ITT Population)



RDN: renal denervation; US: United States

1.5.3 Durability of Blood Pressure Reduction

Data from pre-clinical studies, randomized controlled trials and real-world clinical registries support the durability of blood pressure reduction following RDN. Though literature on regeneration and reinnervation is mixed with some suggesting functional efferent and afferent reinnervation of the renal vasculature within weeks after surgical RDN in normal rats (Foss et al 2015; Kline and Mercer 1980; Mulder et al 2013); this morphological evidence of sympathetic regrowth was not accompanied by recovery in renal NE content (Rodionova et al 2016). Both anatomical and functional re-innervation were demonstrated 11-months after RF RDN in normotensive sheep via histological staining and response to stimulation, respectively (Booth et al 2015). However, the same group subsequently reported results from an ovine model of chronic kidney disease demonstrating sustained reductions in BP with cardio- and reno-protection at 30 months following RF RDN, despite partial functional recovery (Singh et al 2019). Some regeneration of renal nerve fibers was reported within a year following nephrectomy and transplant in humans (Mauriello et al 2017; Shannon et al 1998). However, contradictory analysis has shown no evidence of functional efferent reinnervation after 2 months and 2 years (Hansen et al 1994).

Sustained natriuresis and suppressed renin release reported one year after surgical denervation in dogs, suggest lack of functional renal nerve recovery (Nomura et al 1972). Similarly, reductions in renal norepinephrine, cortical axon density and downstream axonal loss following denervation with the Symplicity Spyral device in pigs persisted through 180 days post-renal denervation. These data suggest that functional

nerve regrowth after RF renal denervation is also unlikely in the clinical settingF (Sharp et al 2022). This may be due to a combination of sustained fibrosis around the ablated lesion and non-myelination of postganglionic renal sympathetic nerves. This lack of myelination is an important characteristic that does not allow for reinnervation following ablation. A comparable analysis in healthy swine identified neuromatous tangles with disorganized architecture and distal axonal loss at 90 days following RDN with RF energy, making functional regenerative activity unlikely (Rousselle et al 2015). These data, while mixed, provide evidence that functional nerve regrowth after RF renal denervation is unlikely.

OFF MED and ON MED Long-Term Efficacy Data

Due to the unblinding of participants to their randomization assignment after the primary endpoint and large number of Sham patients opting to cross over to receive the RDN procedure (OFF MED: 68%; ON MED: 74%), sham control comparisons are confounded. Further, medication optimization in patients was permitted after primary endpoint ascertainment and as a result, similar BP reductions were expected. Therefore, beyond the primary endpoint, it is important to look at the totality of results including medication changes. Results from the OFF MED Pivotal study through 24 months and following unblinding showed a consistent and sustained reduction in BP in Denervation patients (office SBP reduction of −21.5 mmHg; 24-hour SBP reduction of −15.5 mmHg). Long-term 36-month office SBP and 24-hour SBP results from the ON MED pilot study demonstrate BP reductions that are durable and clinically meaningful in Denervation patients (office SBP reduction of −20.9 mmHg [N = 33]; 24-hour SBP reduction of −18.7 mmHg [N = 30]).

Global SYMPLICITY Registry Long-Term Efficacy Data

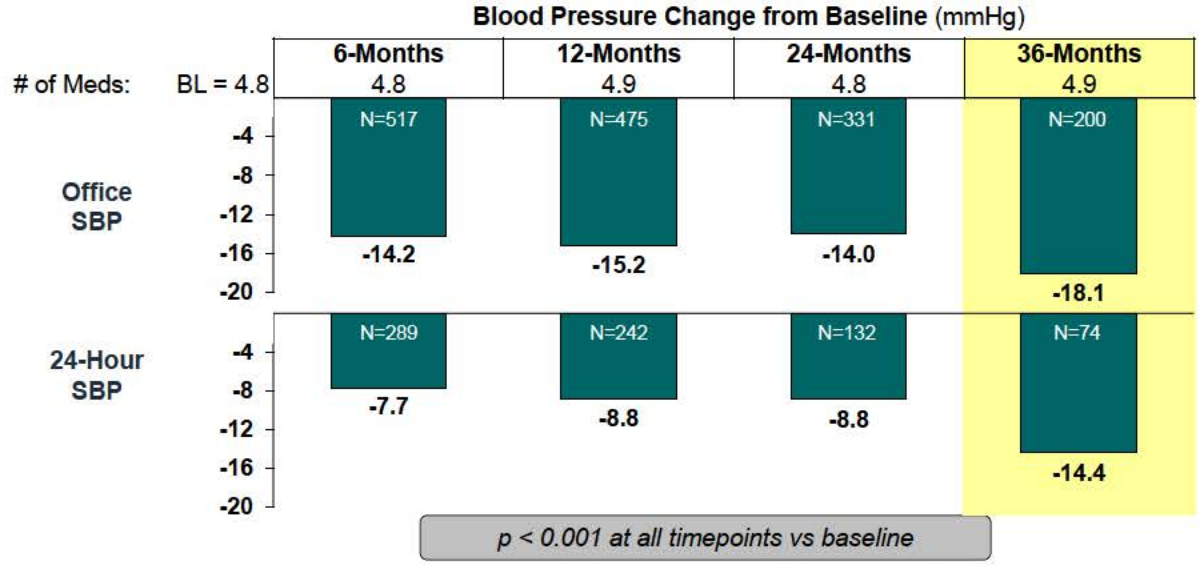
The GSR is a prospective, multi-center, single-arm, non-interventional and open label registry. The GSR aims to include a patient population that resembles real-world clinical practice. The primary objective of the registry is to document the long-term safety and effectiveness of renal denervation in a real-world patient population.

A total of 3,077 patients, including 846 patients treated using the Symplicity Spyral catheter (subject of this PMA) have been enrolled in GSR. Prior to availability of the Symplicity Spyral catheter, patients in the GSR were treated with a single electrode version, the Symplicity Flex catheter. The results described in this Executive Summary are from the Symplicity Spyral patient cohort only.

For patients treated with the Symplicity Spyral catheter, 6-month follow-up data are available for 724 patients, 12-months follow-up data for 642 patients, 24-months follow-up data for 485 patients and 36 months follow-up data for 328 patients.

Sustained significant office and 24-hour BP reductions following RDN out to 3 years are demonstrated independent of medication changes (Figure 10).

Figure 10: Global SYMPLICITY Registry (Symplicity Spyral Cohort Only) Change from Baseline in Systolic Blood Pressure (6 Month to 3 Years)



BL: baseline; OSBP: office systolic blood pressure monitoring; OBP: office; SBP: systolic blood pressure Baseline OSBP=165.8 ± 24.8 | 24-hour SBP=155.2 ± 20.1

1.6 Safety Findings

Safety was evaluated in the pre-specified pooled safety population, which included the first 253 consecutive patients treated with RDN in the OFF and ON MED studies. Safety evaluations were also performed for the individual studies comparing Denervation to Sham and independently adjudicated by each study's Clinical Events Committee (CEC).

Acute Safety to 6-Months

The primary safety endpoint was the incidence of major adverse events (MAE) at 1-month post-procedure (renal artery stenosis evaluated at 6 months) for the pooled safety population (N = 253, first 253 consecutive patients treated with RDN in the OFF and ON MED studies inclusive of both US and non-US subjects). The performance goal (PG), derived from literature for renal interventions including renal stenting was established at 7.1% (Bax et al 2009; Bersin et al 2013; Bradaric et al 2017; Cooper et al 2014; Investigators et al 2009; Jaff et al 2012; Laird et al 2010; Rocha-Singh et al 2005; van Jaarsveld et al 2000).

The primary safety endpoint was met, with an MAE rate of 0.4% (upper 95% confidence bound 1.9%) in patients treated with RDN (Table 3). Importantly, there were no deaths reported in either study in patients treated with RDN.

Table 3: MAE Safety Endpoint Analysis (Pooled Safety Population)

	Denervation N=253	Upper 95% CI	PG	p-value
MAE	**0.4%** (1/253)	**1.9%**	**7.1%**	**< 0.001**
All-cause mortality	0			
End stage renal disease	0			
Significant embolic event resulting in end-organ damage	0			
Renal artery perforation requiring re-intervention	0			
Renal artery dissection requiring re-intervention	0			
Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	0.4% (1/253)			
Hospitalization for hypertensive crisis not related to confirmed non-adherence with medication or the protocol	0			
New renal artery stenosis > 70%	0			

CI: confidence interval; MAE: major adverse events; PG: performance goal

In the OFF MED Pivotal study at 3 months, the MAE rate was 0.6% in the Denervation group and 0.5% in the Sham group (Table 4). In the ON MED study, the incidence of MAE from enrollment to 6-months was 1.0% and 0.8% in the Denervation and Sham groups, respectively.

Table 4: MAE Rates in OFF MED (3 Months) and ON MED (6 Months)

	OFF MED (3 months)		ON MED (6 months)	
	Denervation N=180	Sham N=184	Denervation N=206	Sham N=131
MAE	0.6% (1/180)	0.5% (1/184)	1.0% (2/206)	0.8% (1/131)
All-cause mortality	0	0	0	0
End stage renal disease	0	0	0	0
Significant embolic event resulting in end-organ damage	0	0	0	0
Renal artery perforation requiring re-intervention	0	0	0	0
Renal artery dissection requiring re-intervention	0	0	0	0
Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	0	0.5% (1/184)	1.0% (2/206)	0.8% (1/131)
Hospitalization for hypertensive crisis/emergency	0.6% (1/180)	0	0	0
New renal artery stenosis > 70%	0	0	0	0

MAE: major adverse events

Analysis of device and procedure-related events were pre-defined in the study protocols. No catheter, generator or therapy-related safety events were detected in the OFF and ON MED studies, and procedure-related events were very low. In OFF MED,

there were 0 (zero) procedure-related events adjudicated by the CEC. In ON MED, there were 4 events in 3 patients within 6-months (2 Denervation patients and 1 Sham patient) adjudicated as procedure-related and resolved without sequelae.

Long-Term Safety

Long-term safety data, up to 3 years, from the OFF and ON MED studies demonstrate low incidence of reported adverse events (AEs) for patients treated with Denervation. Renal function over time, as assessed by eGFR, was stable in Denervation patients, showing small decreases consistent with those expected for patients with hypertension and consistent with the Sham group. Long-term safety results from the GSR also support the continued safe use of the Symplicity Spyral System and raise no new concerns.

Renal Artery Imaging

Renal artery imaging (duplex ultrasound [DUS]/computed tomography angiography [CTA]/magnetic resonance angiography [MRA] or Angio, if renal artery stenosis suspected) was performed at the 6-month and 12-month post-procedure visit to assess for any potential renal artery stenosis. In Denervation patients from OFF MED and ON MED, the rate of possible stenosis ≥ 70% was 0.17% (1/604) identified by MRA, but not confirmed by angiography due to subject refusal and exiting the study. The rate of possible stenosis ≥ 50% when only taking into account patients with a diagnostic CTA or MRA at 12 months is 0.63% (3/474), but were not confirmed by angiography. The rate of possible stenosis ≥ 50% is similar to the reported rate in both published safety meta-analysis of RF RDN trials and with the natural incidence of renal artery stenosis in hypertensive patients of 0.36%-5% per year (Townsend et al 2020).

Additional safety analyses are presented in Section 6.

1.7 Patient Preference

Patient preference and shared decision making have been identified as critical components of developing a hypertension care plan including the RDN procedure. Medtronic executed a prospective US study, further described in Section 7, using discrete choice methodology to quantify patients' preferences for the benefits and risks of an interventional treatment with or without pills compared with pills only for the treatment of hypertension (Kandzari et al 2023). The study design followed FDA guidelines for Patient Preference Information studies conducted for benefit-risk assessment, as well as guidelines prepared by the International Society for Pharmacoeconomics and Outcomes Research (Bridges et al 2011; FDA 2016; Hauber et al 2016; Reed Johnson et al 2013).

The results of this patient preference study conducted in adults with physician-confirmed uncontrolled hypertension indicated that BP reduction was the most influential driver of treatment choices and was more influential on choice than the risk of treatment-related side effects. The risk tolerance estimates indicated that patients

would be willing to accept higher risks of drug side effects and vascular injury than have been observed in the ON MED and OFF MED studies in exchange for modest office SBP reductions. When presented with an interventional treatment with BP reduction and potential risks in line with those of RDN, 15%–31% of respondents were likely to select the interventional treatment.

This study supports patient interest in an interventional procedure such as RDN (in the presence and absence of anti-hypertensive drugs) and highlights specific real-world clinical scenarios where a procedure such as RDN would be an important addition to options available for the treatment of hypertension.

1.8 Benefit-Risk Summary

Hypertension remains the leading modifiable risk factor associated with CV events and death. Current treatment strategies include lifestyle modifications and pharmacotherapy but there is still an increasing trend of hypertension related morbidity and mortality in the last two decades. Uncontrolled BP is highly prevalent, driven by challenges with medication adherence. Based on patient preference research, patients are open to seeking safe and effective complementary treatment options to help address this unmet need.

RF RDN can complement pharmacotherapy in the treatment of uncontrolled hypertension, as well as for patients who poorly tolerate pharmacotherapy. The Symplicity Spyral System provides a safe and effective BP lowering therapy in the in the presence and absence of antihypertensive medications.

The OFF MED Pivotal design minimized the confounding influence of antihypertensive medications on outcomes by utilizing an approach similar to pharmaceutical approval trials that are conducted in patients off their medications for primary endpoint assessment. The OFF MED pilot cohort randomized 80 patients. After initial positive feasibility was established, an additional 251 patients were enrolled in an expansion cohort to reach the total 331 patients included in OFF MED Pivotal. OFF MED Pivotal showed that RF RDN significantly lowers BP in patients with hypertension, in the absence of medication. These reductions were clinically meaningful for 24-hour and office SBP compared to Sham at 3 months post-procedure. The average treatment differences were −3.9 mmHg (Bayesian 95% credible interval: −6.2 to −1.6) in 24-hour SBP and −6.5 mmHg (−9.6 to −3.5) in office SBP between groups. In addition, RDN provided persistent, sustained reductions in BP over a 24-hour period which includes the nighttime BP which has been associated as the highest risk factor for CV events. These reductions were durable and sustained through 24 months with a lower medication burden for Denervation compared to Sham.

The ON MED design was performed to understand the effect of RF RDN in the presence of antihypertensive medications. ON MED Pilot randomized 80 patients. After initial positive feasibility was established, an additional 257 patients were enrolled in an expansion cohort to reach the total 337 patients forming the Full Cohort. The

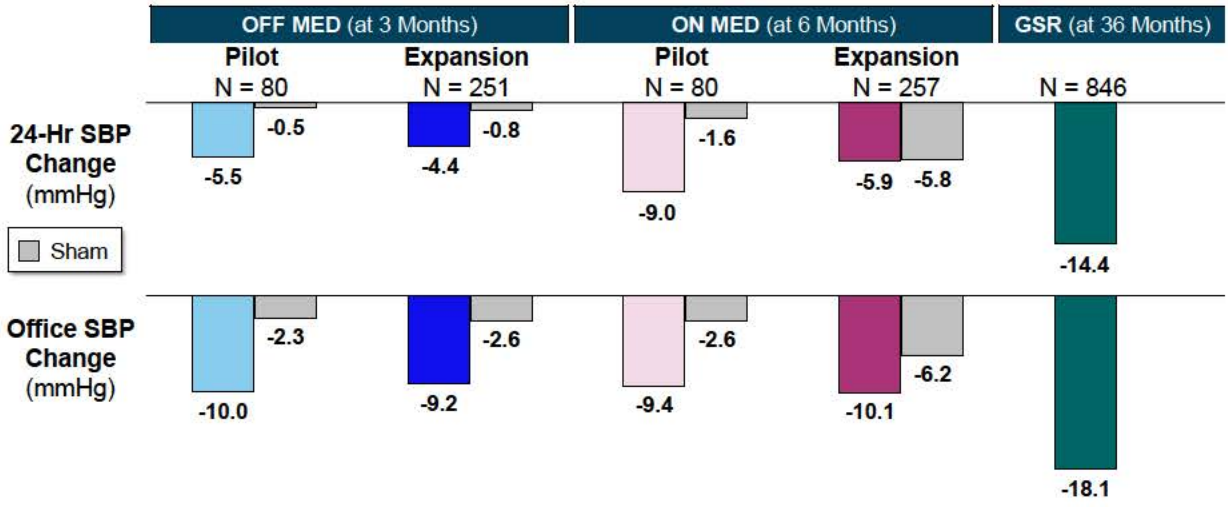
prospectively powered primary endpoint analysis of the Full Cohort did not reach statistical significance due to a higher proportion of anti-hypertension medication increases and a higher proportion of missing ABPMs in Sham which disproportionately impacted the 24-hour SBP measurement, biasing the result towards null with a larger than expected reduction in 24-hour SBP in the Sham group. The nighttime BP appeared to be less impacted by the medication changes and showed a significant difference in favor of RDN (Denervation −6.7 ± 12.3 mmHg, Sham −3.0 ± 12.6 mmHg, treatment difference −3.7 mmHg, p = 0.010). Notably, the secondary endpoint of office SBP was significantly different in favor of RDN (Denervation −9.9 ± 13.9 mmHg, Sham −5.1 ± 13.2 mmHg, treatment difference −4.9 mmHg, p = 0.002).

Additional data from the real-world GSR as well as the ON MED pilot study show sustained significant office and 24-hour BP reductions following RDN out to 3 years independent of medication changes.

In addition to the ON and OFF MED Randomized clinical studies conducted to support approval of RDN in the US, it is important to consider the totality of data collected to date on the Symplicity Spyral System which includes over 1,800 procedures and demonstrates consistent and clinically meaningful reductions in BP across multiple studies and timepoints (Figure 11).

OFF MED and ON MED both demonstrated the excellent safety profile of RDN with the Symplicity Spyral System. The pooled primary safety endpoint was met with a low rate of MAE. There were no device-related events and a low rate of procedure-related safety events observed without an increase in the risk of denervation-associated renal artery stenosis. These findings add to the already established safety profile of catheter-based RF RDN and support a positive risk/benefit assessment for RDN as an additional option for physicians treating patients with uncontrolled hypertension.

Figure 11: 24-Hour and Office SBP RDN Reductions Across SPYRAL Program



GSR: Global SYMPLICITY Registry; RDN: renal denervation; SBP: systolic blood pressure

Finally, a DCE patient preference study demonstrated that 15-31% of patients would choose an interventional procedure to help manage hypertension.

Using FDA's guidance document for factors to consider when making benefit-risk determinations in medical device pre-market approvals, the broad totality of evidence presented for the Symplicity Spyral System provides a reasonable assurance of a positive benefit-risk ratio. The Symplicity Spyral System fills an unmet medical need for the more effective treatment of uncontrolled hypertension to compliment the current strategies available to physicians in the US. The device has a low rate of MAEs with no major device-related events and a low rate of procedure-related safety events observed. There is no increased risk of RDN-associated renal artery stenosis and sustained renal function is demonstrated through 3 years. In addition, there is a clinically meaningful reduction in BP that is equal to or greater than that seen in the Sham group in all endpoints.

2 Background on Hypertension

Summary

- Hypertension is the most prevalent risk factor for other CV diseases such as coronary artery disease, heart failure, stroke, and chronic kidney disease, accounting for 9.4 million deaths worldwide every year (WHO 2019).
- Treatment guidelines recommend lifestyle modifications followed by anti-hypertensive medications for patients with primary hypertension (Whelton et al 2018).
- A reduction in office SBP of 5 mmHg reduces the risk of myocardial infarction, stroke, kidney disease, and death (Blood Pressure Lowering Treatment Trialists 2021a). Sustained 24-hour BP reductions also serve to reduce risks of CV events during the night and early morning, when patients are most vulnerable.
- Despite the availability of safe and effective treatments for hypertension for several decades, control rates are still low due in part to low adherence: ~40% of patients do not take their medicines as prescribed.
- Patients would benefit from a simplified regimen including an alternative or adjunctive approach to managing their BP.

2.1 Overview of Hypertension

2.1.1 Hypertension Epidemiology

The estimated global prevalence of hypertension, defined as SBP greater than 140 mmHg, is estimated to be over 30% (Mills et al 2020). Control rates are low and less than 20% of hypertension patients are controlled worldwide. Hence, hypertension remains the leading global modifiable cause of death. Complications from hypertension, primarily including stroke, acute coronary syndromes and chronic kidney disease, account for 9.4 million deaths worldwide every year (WHO 2019).

US hypertension statistics reflect the global data. The current American College of Cardiology and the American Heart Association guidelines define hypertension as an office SBP of *130 mmHg* or higher or office DBP above 80 mmHg (Table 5) (Whelton et al 2018). Latest epidemiologic data from the Centers for Disease Control and Prevention (CDC), based on National Health and Nutrition Examination Survey (NHANES) 2019–2020 data, indicate that nearly 120 million Americans, or about 48% of the US adult population, have hypertension. Among US patients with hypertension, about 77% have uncontrolled BP. Hence, in 2021, hypertension was a primary or contributing cause of nearly 700,000 deaths in the US (CDC 2023).

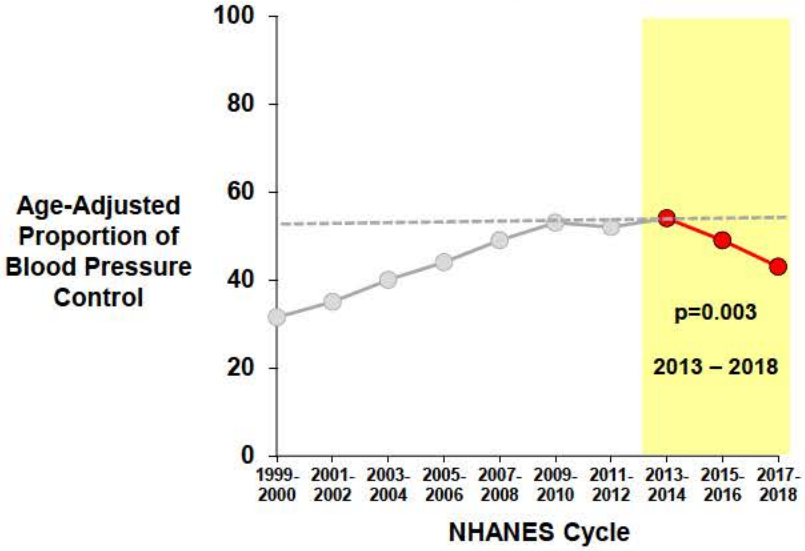
Table 5: Blood Pressure Categories and Stages of Hypertension in Adults

Category	Systolic Blood Pressure		Diastolic Blood Pressure
Normal	< 120 mmHg	and	< 80 mmHg
Elevated	120–129 mmHg	and	< 80 mmHg
Hypertension			
Stage 1	130–139 mmHg	or	80–89 mmHg
Stage 2	≥ 140 mmHg	or	≥ 90 mmHg

Source: Whelton et al 2018

Hypertension control rates within the US are also low and appear to be decreasing over time. Indeed, the proportion of US patients with controlled BP decreased significantly from approximately 54% over the period from 2013–2014 to 44% in 2017–2018 (Figure 12). These reductions were primarily driven by decreasing control rates among women and non-Hispanic Blacks (Muntner et al 2020).

Figure 12: Blood Pressure Control Over Time (1999–2018)



NHANES: National Health and Nutrition Examination Survey
Source: Muntner et al 2020

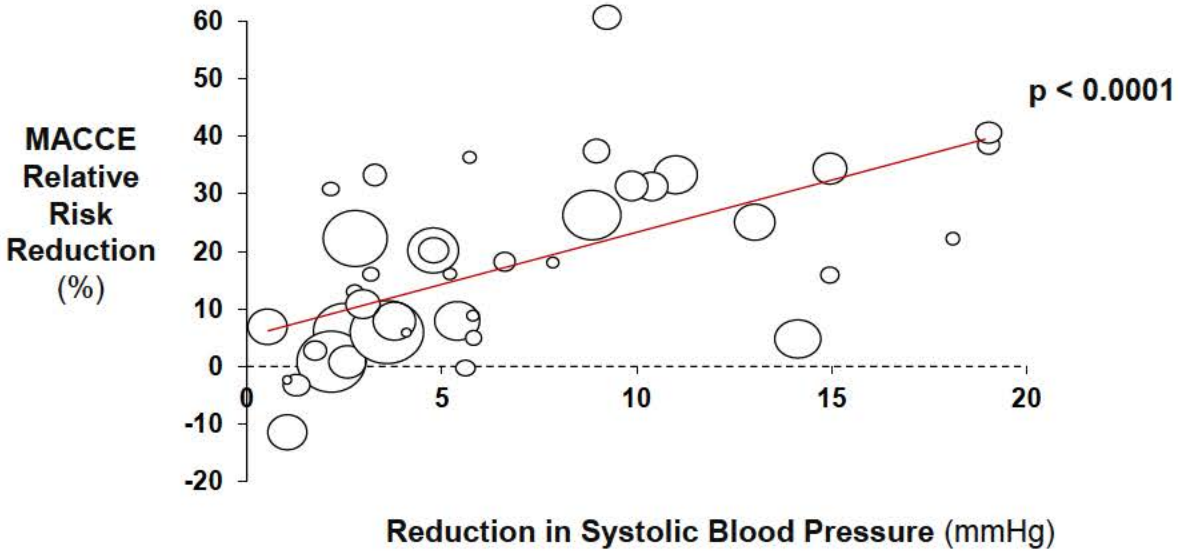
Factors associated with increased risk for hypertension include increased age, family history, unhealthy lifestyle habits, and obesity. In addition, males, Black Americans, and Hispanics are also at increased risk.

2.1.2 Clinical Outcomes and Consequences

BP reduction is strongly associated with reduced CV risk. Meta-regression analysis of placebo-controlled BP trials demonstrate a continuous linear reduction in relative risk of major cerebral-cardiovascular events that is independent of baseline pressure and

comorbidities (Figure 13) (Ettehad et al 2016). This strong association also supports the validity of BP reduction as a surrogate clinical trial outcome.

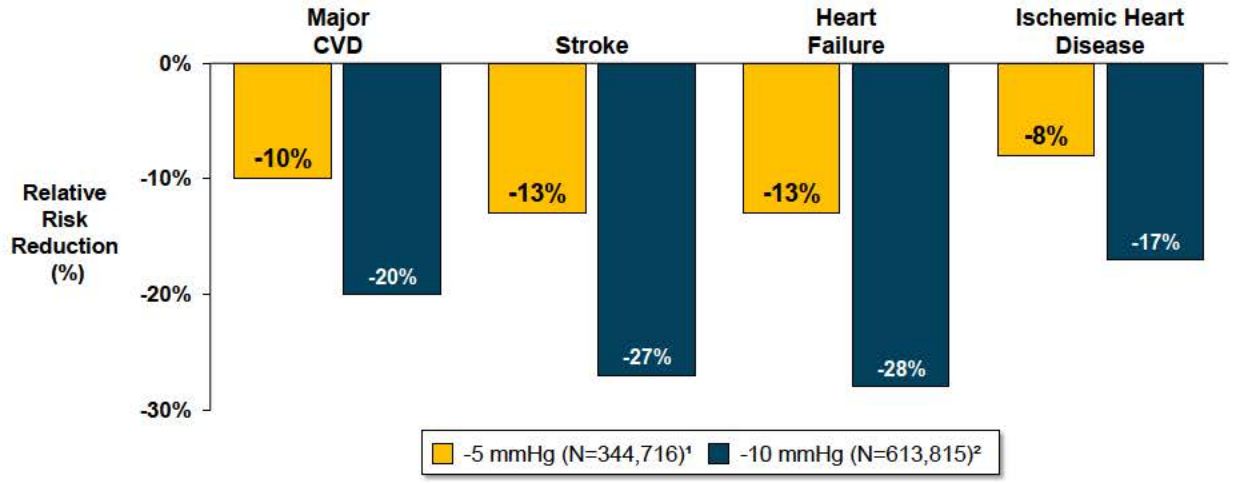
Figure 13: Meta-regression Plot of MACCE Relative Risk Reduction and Reduction in Systolic Blood Pressure



MACCE=fatal and non-fatal myocardial infarction, sudden cardiac death, revascularization, fatal and non-fatal stroke, and fatal and non-fatal heart failure
Source: Ettehad et al 2016

These meta-regression data further indicate that relatively modest reductions in BP are associated with substantial reductions in CV risk. For example, a reduction in office BP of 5 mmHg (based on patient level data) or 10 mmHg (based on trial level data) are associated with 10 and 20% relative risk reduction, respectively, in major cerebral-CV AEs (Figure 14).

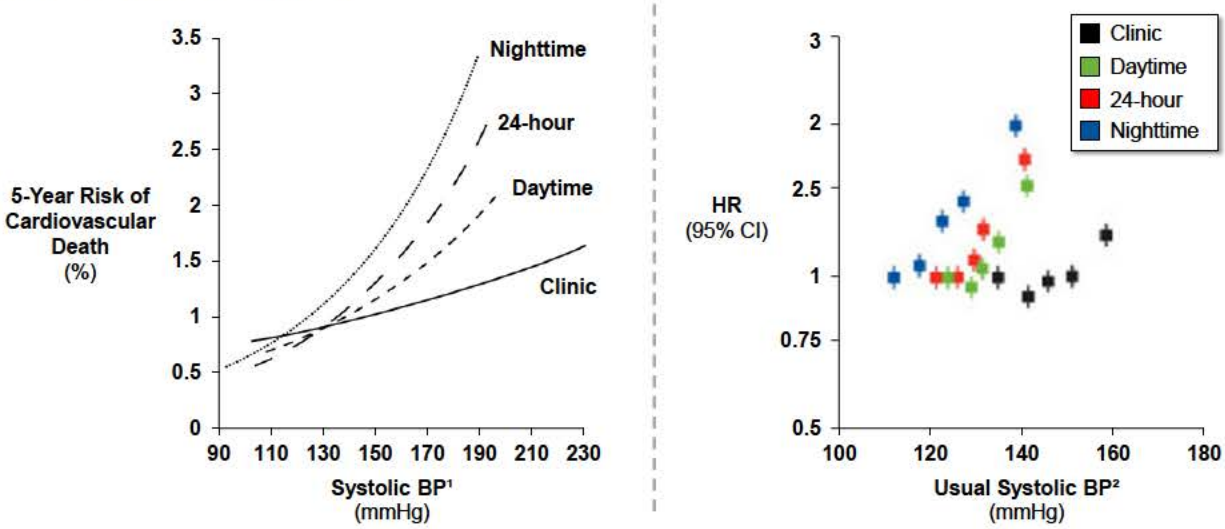
Figure 14 Risk Reduction in Cardiovascular Risk with Lower Blood Pressure



CVD: cardiovascular disease
1 Blood pressure lowering treatment trialists' collaboration 2021. 2 Ettehad et al 2016

Importantly, the risks associated with hypertension are disproportionately distributed throughout the 24-hour circadian cycle. Hence, nighttime BP is associated with greater CV risk reduction than similar reductions in overall 24-hour BP or daytime office BP (Figure 15).

Figure 15: Nighttime Blood Pressure Reductions Are More Strongly Associated with CV Risk Reduction



BP: blood pressure; CI: confidence interval; CV: cardiovascular; HR: heart rate
1. Dolan et al 2005 2. Staplin et al 2023

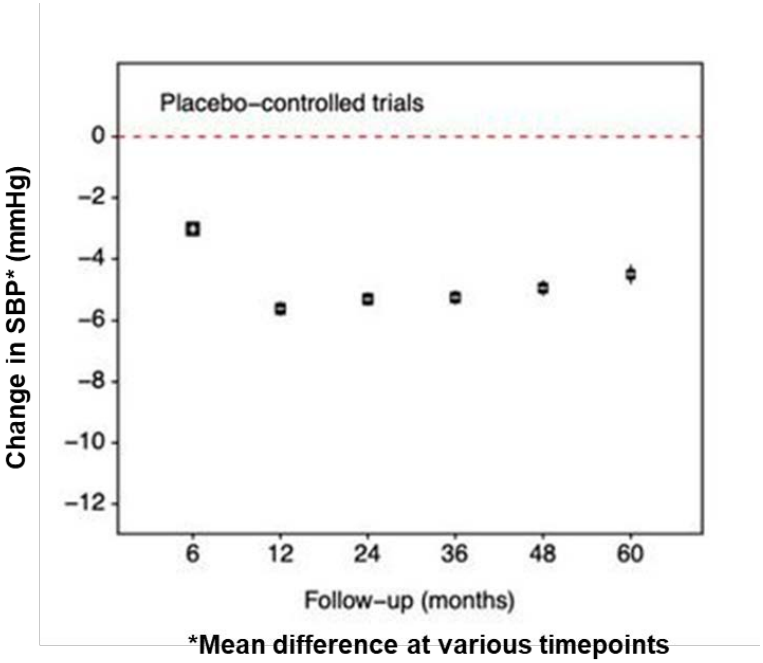
2.2 Current Treatment Options

2.2.1 Standard of Care

Current US treatment guidelines recommend lifestyle modifications followed by anti-hypertensive medications for patients with primary hypertension (Whelton et al 2018). Initial pharmacologic therapy may include 1 or 2 drug classes and, if control is not achieved, dosages or the number of classes are increased with no upper limit to the number of classes prescribed. In fact, about 28% of US-treated patients with hypertension are prescribed 3 or more drug classes (Carey et al 2019).

A recently reported meta-regression of clinical trials showed average placebo-adjusted difference in office SBP of roughly −3 mmHg following drug initiation. This reduction plateaued to roughly −5 mmHg at 60 months follow-up (Figure 16) (Canoy et al 2022).

Figure 16: Average Systolic Blood Pressure Reduction Over Time with Anti-hypertensive Drugs



SBP: systolic blood pressure
Source: Canoy 2022

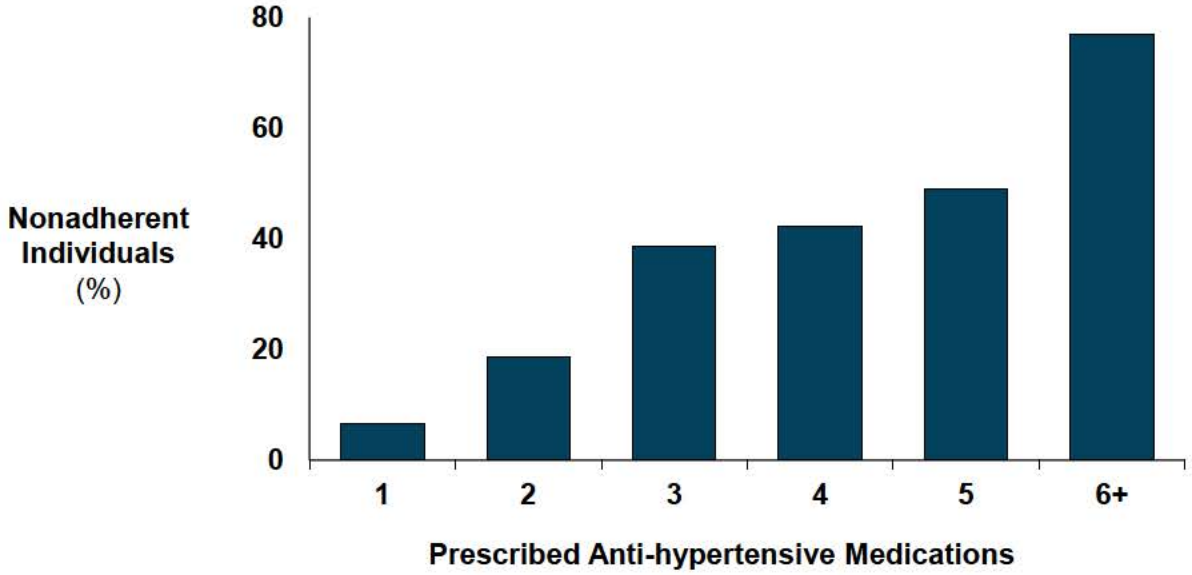
Similarly, another meta-analysis reported incremental reductions in office SBP of −7.5 mmHg, when adding a second drug at standard dose (Salam et al 2019b), but the reduction reported for adding a third drug was just −5.4 mmHg (Salam et al 2019a).

2.2.2 Limitations of Available Treatment Options

Low global and US hypertension control rates are due in part to widespread non-adherence to prescribed medications. A review of recent reports of adherence objectively quantified with plasma and urine analysis indicated that approximately 44%

of treated uncontrolled hypertensive patients were not taking all their anti-hypertensive medication and approximately 17% were found to be not taking any anti-hypertensive medications (Berra et al 2016). The probability of drug non-adherence is proportional to the number of antihypertensive drugs prescribed (Figure 17) and going from 2 to 3 anti-hypertensive agents doubles the likelihood of non-adherence (Gupta et al 2017b). Non-adherence to prescription of a new drug has been shown to progressively increase over time, especially within the first year of drug prescription (Vrijens and Urquhart 2014).

Figure 17: Anti-Hypertensive Medication Adherence Worsens With Increasing Drug Burden



Adapted from Gupta et al 2017a

Barriers to medication adherence are multidimensional and include economic, psychological, and social influences (WHO 2003). Clinicians tend to overestimate patient's adherence (Jung et al 2013). Non-adherence is independently associated with increased CV risk (Chowdhury et al 2013; Corrao et al 2011; Jaeger et al 2022; Zeller et al 2008) and higher levels of non-adherence to anti-hypertensive medications are associated with significantly higher healthcare costs (Sokol et al 2005). The emergency, hospital, and outpatient visits attributable to non-adherence is estimated to have added $18.6 billion in costs to the US health care system alone (IMS Institute for Healthcare Informatics 2013).

2.3 Patient Unmet Medical Need

Despite long time availability of effective lifestyle and chronic drug therapy treatments, hypertension within the US remains widely prevalent and poorly controlled. This combination is directly associated with increased morbidity, especially acute coronary syndromes heart attack and stroke, as well as increased mortality. Medication non-

adherence is likely a primary contributor to increasingly poor US BP control rates. The high rates of non-adherence also suggest patient preferences for treatment alternatives. Therefore, a complementary treatment approach that does not require lifelong daily adherence could augment existing therapy strategies leading to improved BP control.

3 Product Description

Summary

- The proposed indication of the Symplicity Spyral Renal Denervation System is for the reduction of BP in patients with uncontrolled hypertension, despite the use of anti-hypertensive medications or in patients in whom BP lowering therapy is poorly tolerated.
- The system uses a catheter-based approach to denervate the renal arteries to lower BP.
- RDN interrupts both afferent and efferent renal sympathetic nerves, which results in BP reduction.

3.1 Proposed Indication

As proposed, the Symplicity Spyral multi-electrode renal denervation catheter and Symplicity G3 renal denervation RF generator are indicated for the reduction of blood pressure in patients with uncontrolled hypertension, despite the use of anti-hypertensive medications or in patients in whom blood pressure lowering therapy is poorly tolerated.

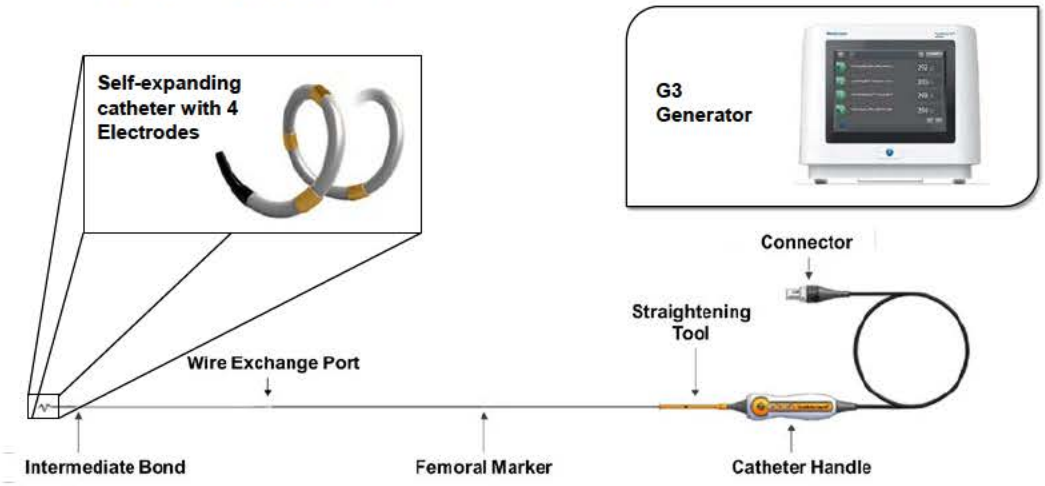
3.1.1 Symplicity Spyral Renal Denervation System Product Overview

The Symplicity Spyral System is designed to provide a catheter-based approach to modulate renal efferent and afferent autonomic pathways with the intent of lowering BP. As shown in Figure 18, the Symplicity Spyral System comprises:

- a single-use, disposable catheter (Symplicity Spyral catheter), and
- a reusable RF generator (Symplicity G3 RF generator).

The Symplicity Spyral catheter and the Symplicity G3 generator are designed to be used together for the ablation of the renal arteries via RF energy. Additional detail on Symplicity Spyral System use is provided in Appendix 2: Symplicity Spyral™ Multi-Electrode Renal Denervation Catheter Instructions for Use.

Figure 18: Symplicity Spyral System



RF RDN was first approved for commercial use outside the US in 2010 using the predicate Symplicity Flex system. The Symplicity Spyral System, the subject of this PMA, was first CE Marked in the European Union on 15 October 2013. As of July 2023, the Symplicity Spyral Renal Denervation System is commercially available in the 70 countries listed in Table 6.

Table 6: Countries Where Symplicity Spyral System Is Commercially Available

Australia	Dominican Republic,	Kazakhstan	Romania
Argentina	Ecuador	Kuwait	Russia
Austria	Egypt	Latvia	Saudi Arabia
Bangladesh	El Salvador	Liechtenstein	Singapore
Bahamas	Estonia	Lithuania	Slovakia
Belgium	Finland	Luxembourg	Slovenia
Brazil	France	Malaysia	South Africa
Brunei	Germany	Malta	South Korea
Bulgaria	Greece	Mexico	Spain
Cayman Islands	Guatemala	Netherlands	Sweden
Chile	Hong Kong	New Zealand	Switzerland
Colombia	Hungary	Nicaragua	Taiwan
Costa Rica	Iceland	Norway	Thailand
Croatia	India	Panama	Turkey
Curacao	Indonesia	Peru	United Kingdom
Cyprus	Ireland	Philippines	Venezuela
Czech Republic	Israel	Poland	
Denmark	Italy	Portugal	

RDN is supported as a treatment option for uncontrolled hypertension by multiple society statements worldwide, including most recently the ESH guidelines, which are additionally endorsed by the ERA and the International Society of Hypertension (Mancia et al 2023).

3.1.2 Symplicity Spyral Catheter

The Symplicity Spyral catheter, when used with the Symplicity G3 generator, allows for ablation of sympathetic nerves surrounding the renal arteries by simultaneously delivering RF energy to four electrodes. The Symplicity Spyral catheter is single use and consists of a distal, self-expanding catheter onto which four gold electrodes are mounted in a helical configuration, allowing for denervation along 4 quadrants covering the circumference of the vessel lumen. To minimize the thermal effects on the renal artery wall, the design allows for continuous blood flow throughout the treatment, thus cooling the arterial wall and electrodes during treatment.

The catheter has an effective working length of 117 cm and is compatible with a 6 Fr guide catheter. A radiopaque marker is embedded in the catheter tip, approximately 1 mm proximal from the distal end of the Symplicity Spyral Catheter to assist in the positioning of the catheter using fluoroscopic guidance. The self-expanding electrode array consists of nitinol stranded tubing, which maintains the helical shape-set and guidewire lumen integrity during the procedure. The gold electrodes are connected to individual, insulated bi-filar wires that deliver the RF energy and measure temperature.

3.1.3 Symplicity G3 Generator and Treatment Algorithm

The Symplicity G3 generator is intended to provide a safe and effective means of delivering RF energy to the Symplicity Spyral catheter for ablation of renal artery nerves.

The Symplicity G3 generator has been designed with automated safety algorithms to ensure safe RF energy delivery and stoppage. The algorithm is based on preclinical data, which demonstrated significant denervation to renal nerves with minimal damage to collateral tissues (Sato et al 2023). RF energy is delivered for up to 60 seconds to each electrode via a temperature-controlled power delivery algorithm, and power shutoff at a prespecified upper temperature threshold. The treatment algorithm for RF ablation is a fixed algorithm within the main software system controller and cannot be adjusted by a user.

RF energy delivery for each electrode is independently controlled. Temperature and impedance values are monitored at each electrode before and during RF energy delivery. Real-time temperature and electrode impedance feedback are used to automatically adjust the delivered power independently to each electrode (Coates et al 2022). The algorithm will not allow RF energy delivery to start or will turn RF power off to one or more electrodes if safety thresholds are exceeded.

The Symplicity G3 generator was designed to control each of the four electrodes on the distal end of the Symplicity Spyral catheter via four independently controlled RF output channels. The electrodes can be selected or de-selected for treatment via the touch screen interface on the generator or via the wired remote control accessory.

3.2 Principles of Operation

3.2.1 Renal Denervation Overview and Mechanism of Action

Chronic over-activation of the sympathetic nervous system (SNS) has been identified by preclinical and clinical literature as a common and key factor in disease states such as hypertension, heart failure, and chronic kidney disease (Charkoudian and Rabbitts 2009; Joles and Koomans 2004; Mancia et al 1999). The renal nerves are a major contributor to the complex pathophysiology of elevated SNS activity and hypertension.

Therapeutic RDN, which is the deliberate disruption of the autonomic signaling between the renovascular and the higher autonomic centers has been shown to be an effective means of modulating elevated SNS activity — both by reducing the sympathetic control of renal function (renin release, sodium excretion and renal blood flow) and by removing the renal afferent contribution to central sympathetic elevation (Krum et al 2009). Compared with pharmacological treatment of hypertension, RDN provides an adjunctive treatment non-reliant on patient adherence to medications and provides a sustained BP reduction throughout the day and night.

The renal nerves play a complex and critical role in the regulation of BP. Activation of renal sympathetic efferent nerves results in decreased renal blood flow, decreased tubular secretion of salt and water and increased renin release from the kidney and thus has a direct effect on the renin angiotensin aldosterone system (DiBona and Kopp 1997; Osborn and Foss 2017). The net result is increased arterial BP. Likewise, renal afferent nerve signaling is also important in the regulation of BP (Figure 19). Renal afferent nerve activation can cause a reflex increase in sympathetic activity in the kidneys as well as other organs, including constrictions of peripheral arterial vessels, resulting in increased BP (Kopp 2015).

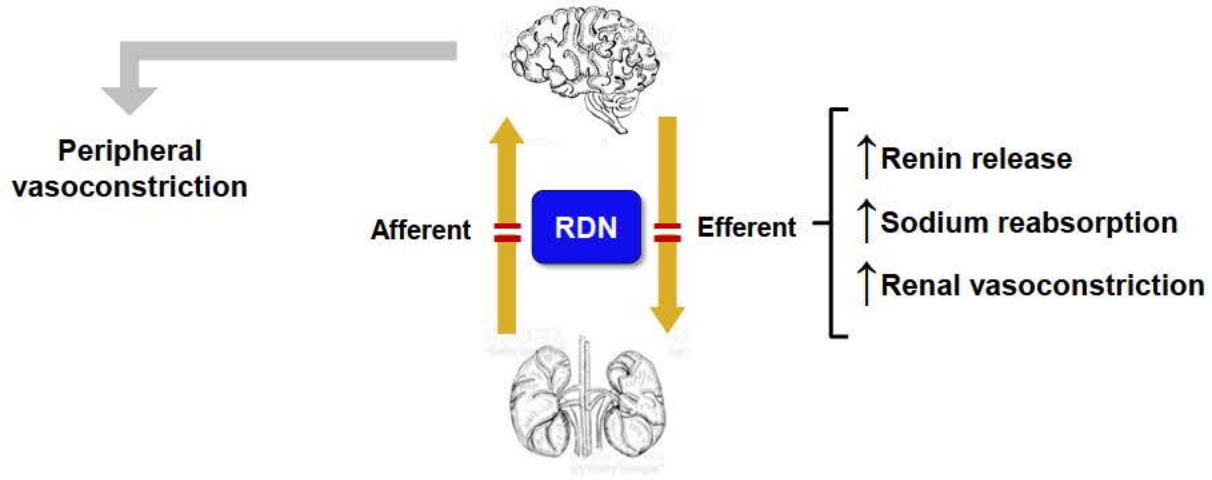
Renal sympathetic efferent activation alters BP regulation by the kidney, whereas activation of some types of renal afferent nerves can cause a global reflex increase in sympathetic tone and elevation of BP. RDN interrupts both afferent and efferent neural pathways.

The renal sympathetic innervation that is the target of the RDN therapy constitutes of multiple nerve bundles running along the renal artery and its branches. Each of these nerve bundles is unmyelinated and contains numerous sympathetic axons. Upon investigation by Sakakura et al it was determined by immunofluorescence labeling that most of the axons in these nerve bundles are efferent and a small portion of the axons are afferent. There are no distinct nerve bundles comprised entirely of afferent axons. Instead, the afferent axons are haphazardly and unpredictably admixed with the efferent axons in each nerve bundle.

Symplicity Spyral RDN targets and ablates renal nerve bundles around the renal artery in their entirety. The neuropathological result of this ablation is axonal loss, nerve bundle reduction in size and terminal fibrosis. These processes affect both efferent and

afferent axons indiscriminately and the sum effect of this ablation is that both afferent and efferent axons are effectively ablated.

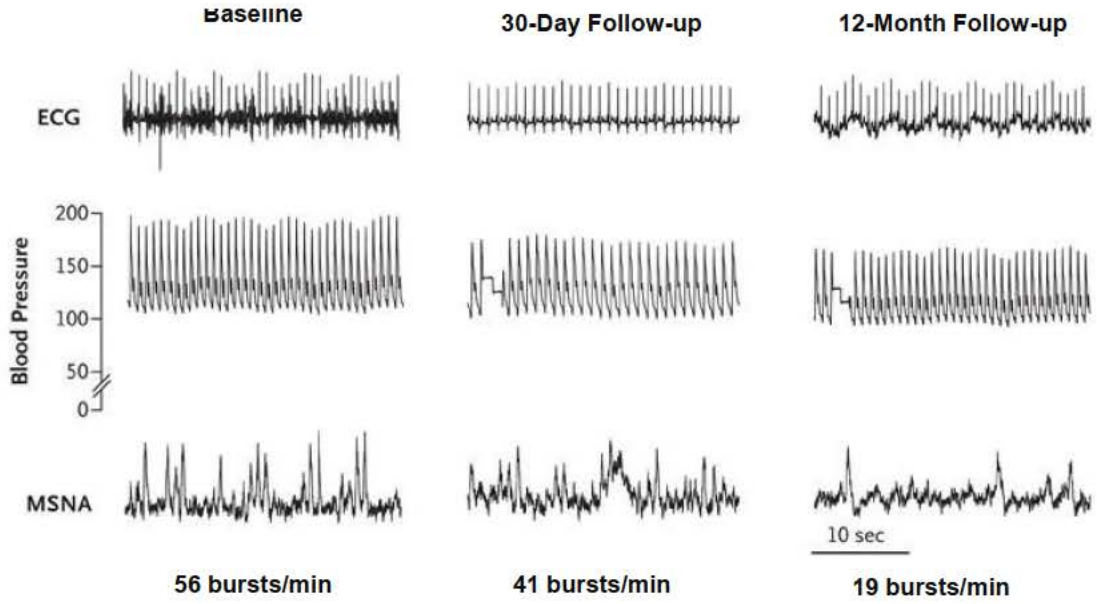
Figure 19: Efferent and Afferent Innervation of the Kidney



RDN: renal denervation

Renal afferent activation normally occurs in response to stress such as ischemia or inflammation and may cause a reflex increase in sympathetic tone to the peripheral vasculature in patients with hypertension. This evidence is based on nerve recordings of sympathetic activity from a microelectrode inserted subcutaneously into the peroneal nerve (a nerve that innervates blood vessels in skeletal muscle). Figure 20 shows the effect of catheter-based RDN on muscle sympathetic nerve activity recorded from the peroneal nerve in a 59-year-old male who had a history of obstructive sleep apnea and a BP of 161/107 mmHg despite treatment with seven different anti-hypertensive drugs (Schlaich et al 2009). There was a dramatic reduction in both BP and muscle sympathetic nerve activity at 30 days after catheter-based RDN, with further reductions in both parameters at 12 months. The changes in muscle sympathetic nerve activity shown in Figure 20 were confirmed in 25 patients with uncontrolled hypertension who had nerve recordings before and at 3 months after catheter-based RDN (Hering et al 2013). Furthermore, these reductions in muscle sympathetic nerve activity were sustained for at least 1 year after RDN (Hering et al 2014).

Figure 20: Muscle Sympathetic Nerve Activity Before and After Catheter-Based RDN



ECG: electrocardiogram; MSNA: Muscle Sympathetic Nerve Activity; RDN: renal denervation

3.2.2 Symplicity Spyral Renal Denervation Procedure

The Symplicity Spyral Catheter used in conjunction with the Symplicity G3 generator requires the use of standard interventional technique to achieve vascular access. The renal artery is cannulated with a guide catheter placed in the renal artery ostium.

To begin the RDN procedure, the Symplicity Spyral catheter is advanced to the treatment site by tracking through a standard 6F guide catheter and over a 0.014" guidewire using a rapid exchange technique. Once the catheter is positioned at a desired treatment location in the renal artery, the guidewire is retracted to deploy the catheter, which naturally conforms to the patient's anatomy. Each of the 4 electrodes delivers RF energy simultaneously for 60 seconds, the catheter is then repositioned to include treatment of branches and accessory arteries located outside the renal parenchyma if present. The duration of the interventional procedure is approximately one hour, similar to a routine percutaneous coronary interventional procedure.

The catheter is designed to attain acceptable electrode-vessel positioning and wall contact with minimal manipulation and/or interpretation. Assessment of the quality of the catheter electrode contact is made by observing the radiographic image and the stability of the impedance values for each electrode. Minor adjustments to the Symplicity Spyral catheter may be achieved by torquing the catheter clockwise or moving it forward. If repositioning is required, this can be achieved by retraction or repositioning to ensure good artery wall contact with the electrodes.

Treatments are initiated by an operator using a button on the front of the Symplicity G3 generator or the remote control and may also be manually stopped by the operator using these same methods. The generator is pre-programmed with an automated algorithm to provide the intended power level for the duration of treatment. Temperature and impedance values are monitored at each electrode to provide input to the algorithm to ensure safe energy delivery. The default treatment parameters cannot be changed by the operator.

The RDN procedure consists of multiple treatments. After each treatment, the guidewire can be advanced distally to straighten the electrode array and facilitate repositioning of the catheter for additional treatment, or for removal from the vessel into the guide catheter for placement into the contra-lateral renal artery.

4 Regulatory and Clinical Program Development Overview

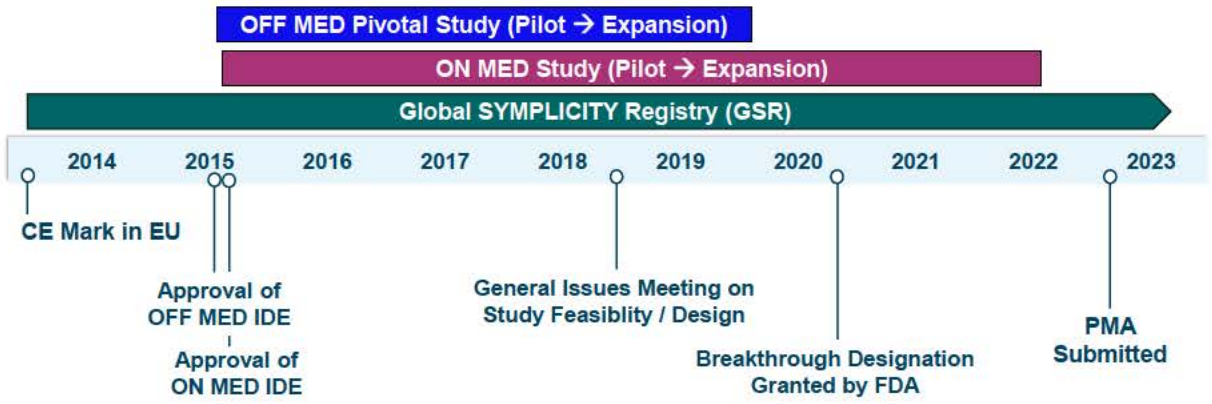
Summary

- FDA granted designation as a Breakthrough Device for the Symplicity Spyral Renal Denervation System in March 2020.
- OFF MED Pivotal evaluated the Symplicity Spyral System in the absence of other anti-hypertensive therapies – a design that best isolates the mechanistic effect of the device and treatment.
- ON MED was designed to examine device efficacy in the presence of anti-hypertensive medications, eg, the most common clinical application of the procedure.
- Global SYMPLICITY Registry (GSR) is an ongoing study outside the US, designed to gather safety and durability data on the RF RDN procedure in a wide range of patients reflecting real-world use conditions.
- Primary safety data are derived by pooling Denervation patients from the OFF MED and ON MED pilot and prospectively powered studies. Primary effectiveness data are derived from OFF MED Pivotal and supportive data are provided by ON MED.

4.1 Regulatory Milestones

Medtronic has engaged the FDA throughout the development and conduct of the SPYRAL HTN clinical program utilizing the pre-submission process to align on critical elements along the way. Key regulatory milestones are shown in Figure 21, with additional detail provided in Appendix 3: Clinical History of Renal Denervation. The Symplicity Spyral Renal Denervation System was granted designation as a Breakthrough Device by the FDA in March 2020.

Figure 21: Key Regulatory Milestones and Interactions



EU: European Union; FDA: Food and Drug Administration; IDE: investigational device exemption; PMA: pre-market approval application

4.1.1 2018 Circulatory System Devices Panel General Issues Meeting

A general issues Circulatory System Devices Panel meeting was held on 5 December 2018 to discuss device-based therapies for hypertension. At this time Medtronic's OFF MED Pivotal study and supportive ON MED Expansion study were already enrolling. The FDA requested panel input regarding the potential indications and labeling for devices intended to treat hypertension and optimal study designs needed to evaluate the potential benefits and risks while considering issues such as medication adherence, patient perspective, and appropriate study controls.

Key conclusions from panel's discussion are highlighted below. Although most of these were already part of the ongoing Medtronic SPYRAL HTN Clinical program, additional design modifications were made where possible:

- **General Study Design**
    - Diverse population: resistant hypertension, Stage 2 hypertension, and drug naïve patients
    - Recommended sham control
    - On- and off-medication trials each provide unique information to support a premarket application
- **Safety**
    - Include comparison between trial groups and against a PG
    - Renal artery stenosis evaluation at 6 months in all patients and in subset with imaging at a later timepoint
- **Efficacy**
    - Reduction in BP of 5–7 mmHg between groups using ABPM would be adequate
    - Reduction in medications and improvement in nighttime ABPM could be clinically meaningful
    - Long-term durability should be evaluated, possibly as part of a post-market study
- **Benefit-Risk**
    - Patient preference information should be formally assessed and incorporated into the evaluation and review of the device

4.2 History of Symplicity Global Clinical Program

Catheter-based RDN is a novel approach intended to provide physicians with additional options for the treatment of hypertension and has been evaluated in clinical studies performed by Medtronic over more than 10 years in over 4,000 patients. Specifically,

the current generation Symplicity Spyral System, for which the approval is being sought here, has been studied in over 1,800 patients (Table 7).

Early studies with a previous, single electrode version of the device (Flex Catheter), including the SYMPLICITY HTN-1, -2, and -3 studies, supported the long-term durability and safety of RDN, but presented opportunities to improve the device, study designs, and procedural technique. HTN-3, a sham-controlled trial, enrolled 535 patients with severe resistant hypertension on a maximum tolerated dose of 3+ medications (Kandzari et al 2015).

HTN-3 met its primary safety endpoint and failed to meet its primary efficacy endpoint of change in office SBP at 6 months compared with control. Analysis of the HTN-3 study results led to improvements in the device design to the current Symplicity Spyral catheter to enable circumferential ablation as well as improvements in the procedural technique and updates to the study population as incorporated in the SPYRAL HTN clinical program (see Appendix 3: Clinical History of Renal Denervation).

To limit the potential confounding impact of changes in prescribed medication after randomization, which was one factor that affected the HTN-3 study results, the current SPYRAL HTN clinical program included an OFF MED study which was designed to isolate the effects of the Symplicity Spyral System in the absence of other anti-hypertensive drug therapies, an approach similar to that used to support pharmaceutical approval of anti-hypertensive medications. ON MED was designed to supplement OFF MED Pivotal data by examining device efficacy in the presence of commonly prescribed anti-hypertensive medications, eg, the most common clinical application of the procedure. Conducting a randomized controlled trial in the presence of anti-hypertensive medications introduces significant complexity in study conduct and ability to interpret results given patient behaviors including changes in medications following randomization. Despite efforts to strictly manage medications prescribed and consumed under the rigor of blinded, sham-controlled studies, patients may monitor their BP at home and if so inclined, can adjust their anti-hypertensive medication either on their own or by seeing their primary care physician, thereby confounding the results of these rigorously controlled studies. In addition, patients in a clinical study have a heightened awareness of their high BP and thinking about the associated risks can lead to changes in patient behavior.

Both the OFF MED and ON MED studies started with non-prospectively powered pilot cohorts and based on positive safety and efficacy results from the pilot were expanded in accordance with prespecified statistical analysis plans. To enable the inclusion of the pilot population into the overall powered analyses for OFF MED Pivotal and ON MED studies, Bayesian analyses approach was utilized for the primary endpoint analyses. The primary effectiveness endpoint in the studies was the change from baseline in 24-hour SBP at 3 months (OFF MED) and at 6 months (ON MED). The prespecified primary safety endpoint was based on the pooled MAE rate from both the OFF MED

and ON MED studies compared with a pre-defined performance criterion derived from literature for renal interventions including renal stenting.

In addition to these studies, Medtronic consulted with FDA on the design and execution of a patient preference study to understand patient prioritization of safety and efficacy variables when considering an interventional treatment compared to current standard of care. Additionally, the GSR is an ongoing study outside the US, designed to gather safety and durability data on the RF RDN procedure in a wide range of patients reflecting real-world use conditions.

Table 7: SPYRAL HTN Clinical Program Overview

Study Name	N	Primary Effectiveness Endpoint	Primary Safety Endpoint	Status	Follow-up Duration
SPYRAL HTN-OFF MED Pilot	80	Change from baseline in 24-hour SBP at 3 months post-procedure	Pooled ON & OFF MED MAE (PG=7.1%)	Complete	36 months
SPYRAL HTN-OFF MED Pivotal – Primary Endpoint Cohort	251			Follow-up through 24 months	36 months
SPYRAL HTN-OFF MED Pivotal – Full Cohort	35				
SPYRAL HTN-ON MED Pilot	80	Change from baseline in 24-hour SBP at 6 months post-procedure		Complete	36 months
SPYRAL HTN-ON MED Expansion	257			Follow-up through 6 months	36 months
Global SYMPLICITY Registry (GSR)	846*	N/A	N/A	Enrolling	60 months**
Patient Preference	400	N/A	N/A	Complete	N/A

MAE: major adverse events; N/A: not applicable; PG: performance goal; pts: patients; SBP: systolic blood pressure
*Number of patients treated with Symplicity Spyral System; full registry also incorporates 2,231 patients treated with previous generation Symplicity Flex System
**3 years up to 3,000 patients, retrospective Symplicity Spyral pts to 5 years. New pts enrolled to 5 years

5 Clinical Efficacy

Summary

- The Symplicity Spyral System provides clinically meaningful and sustained BP reductions as compared to sham, both in the presence and absence of medications as well as sustained short and long term reductions in BP compared to baseline.
- Reductions in BP were achieved continuously throughout the 24-hour period.

OFF MED Pivotal Study

- Primary and secondary endpoints were met with a > 99.9% probability of superiority vs Sham at 3 months:
    - 24-hour SBP: −4.6 mmHg reduction in the Denervation group vs − 0.6 mmHg in the Sham group (treatment difference of −4.0 mmHg)
    - Office SBP: −9.4 mmHg reduction in the Denervation group vs − 2.5 mmHg in Sham group (treatment difference of −6.7 mmHg)
- RDN consistently reduced BP at night when CV risk is highest.
- Results through 24 months showed consistent and sustained reductions in BP and lowered medication burden compared to Sham.

ON MED Expansion Study

- The ON MED trial did not demonstrate statistically significant reductions in 24-hour SBP compared to Sham.
    - Both the Denervation and Sham groups demonstrated significant reductions in 24-hour SBP from baseline to 6 months.
    - Unexpected between-group bias was observed due to unanticipated anti-hypertensive drug changes (significantly higher prescribed medications in the Sham group) and more missing 24-hour SBP prior to medication changes in the Sham group.
- Significant reductions in office SBP and nighttime BP were observed with denervation compared to Sham.
- Data from the ON MED Pilot study demonstrates the durability of RDN treatment with both 24-hour and office BP reductions from baseline on the order of 20 mmHg through 36 months.

Global SYMPLICITY Registry

- This real-world population with multiple comorbidities and antihypertensive medications showed office and 24-hour SBP reductions comparable to the SPYRAL HTN-ON and -OFF MED sham-controlled-trials.

- Reductions in BP were sustained out to 3 years without increasing medications.

5.1 OFF MED Pilot and Pivotal Study

5.1.1 Study Design

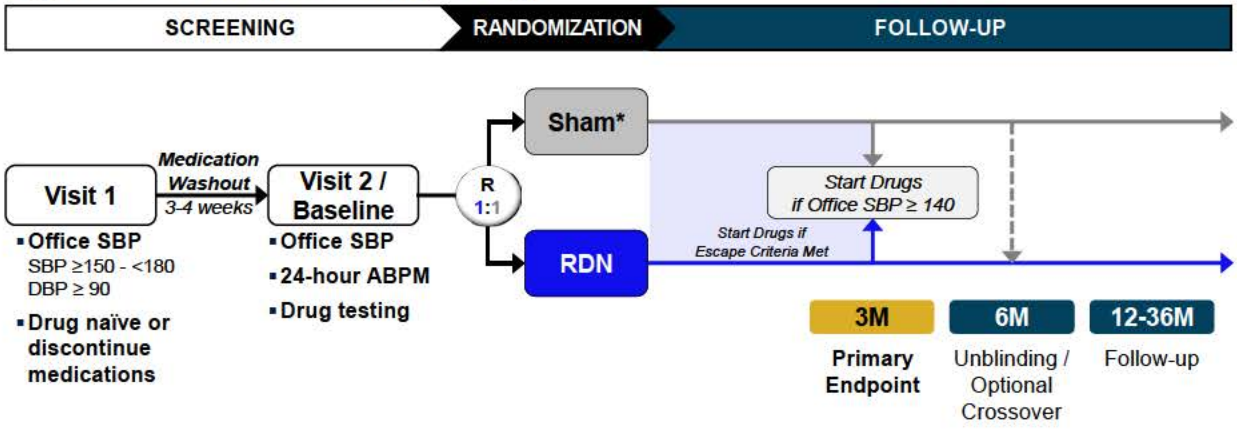
5.1.1.1 Overview

OFF MED was designed to evaluate safety and efficacy of RDN in patients with uncontrolled hypertension compared to a sham-controlled population, in the absence of anti-hypertensive medications. This design isolated the effects of the Symplicity Spyral System and avoided confounding effects of medications following the approach commonly applied in anti-hypertension drug approval trials (Kandzari et al 2016).

OFF MED Pivotal was conducted in two cohorts: an initial pilot cohort to determine the feasibility of the study design and a second prospectively powered expansion cohort that expanded the study via an adaptive Bayesian design (refer to Appendix 1 for additional details about Bayesian design).

Pilot and Expansion cohorts were designed as a multi-center, international, prospective, single blinded, randomized, interventional, sham-controlled cohorts (Figure 22). In both cohorts, patients were randomized to Denervation or Sham in a 1:1 fashion.

Figure 22: OFF MED Study Design



ABPM: ambulatory blood pressure monitoring; DBP: diastolic blood pressure; M: month; R: randomization; RDN: renal denervation; SBP: systolic blood pressure
*Renal angiography alone

Patients returned for office follow-up visits at weeks 2, 4, 8 (± 3 days) post-procedure. Phone call follow-ups were conducted at weeks 6 and 10 (± 3 days) post-procedure. Additional follow-up visits occurred at 3- and 6-months post-procedure with visits conducted at ±14 days from the procedure date.

After patients were unblinded at the completion of their 6-month visits, those who were randomized to the Sham group could opt to crossover to receive the RDN procedure if

they continued to meet the required anatomy and eGFR exclusionary criteria. Denervation group patients and the Sham group patients who did not wish to crossover are being followed through 36 months post-randomization. Crossover patients are being followed through 24 months post RDN procedure.

Drug Testing

To ensure patients were not taking anti-hypertensive medication through the 3-month visit, drug testing was completed by an outside core lab by analyzing urine and blood sample collected at study visits. Anti-hypertensive medication drug testing results were only shared with Medtronic and not with the investigational sites nor patients so as not to influence patient behavior or practice of medicine at the research site.

5.1.1.2 Enrollment Criteria

Patients with uncontrolled hypertension were enrolled in accordance with the following Inclusion and Exclusion criteria:

BP inclusion criteria included:

- Office SBP ≥ 150 mmHg and < 180 mmHg
- Office DBP ≥ 90 mmHg
- 24-hour average SBP ≥ 140 mmHg to < 170 mmHg

Key study exclusion criteria included:

- Ineligible renal artery anatomy, including:
  - Main renal artery for each kidney less than 3 mm or greater than 8 mm
  - Lacking a main renal arterial vessel that does not allow 4 simultaneous quadrantic RF ablations in the main renal artery or equivalent
- eGFR < 45 mL/min/1.73m^2
- Type 1 Diabetes Mellitus or Type 2 Diabetes Mellitus with HbA1C > 8.0%
- Secondary causes of hypertension

5.1.1.3 Study Treatment/Procedure

Study participants received either renal angiography followed by RDN with the Symplicity Spyral System or renal angiography alone (sham control).

5.1.1.4 Blinding

The study was blinded to prevent potential bias.

All study staff and necessary hospital personnel were instructed that participants were not to be informed of their randomization assignments and appropriate measures should be taken to minimize the risk of premature unblinding.

The Investigator performing the catheterization lab procedures and his/her designated study staff were blinded to a participant's randomization group up until the angiography was completed and inclusion/exclusion confirmed. Investigators performing study follow-up visits and the participant's referring/managing physicians were not proactively informed of a participant's treatment assignment to minimize potential bias in the participant's care decisions. Furthermore, to specifically minimize potential bias in the measurement of office BP and 24-hour BP, each investigational site specified several designated "blinded" members of their study staff that were not informed of the participant's group assignments and were responsible for performing the office BP measurements, conducting 24-hour BP measurement preparation, and printing results upon a patient completing the ABPM.

Participants were blinded during the renal angiogram by a combination of conscious sedation, sensory isolation (eg, blindfold and music), and lack of familiarity to the procedural details and duration (ie, participants did not know the difference between the renal angiography procedure alone and the renal angiography and denervation procedure). Participants only interacted with blinded site personnel through the 6-month follow-up visit post-procedure. All participants were unblinded after the completion of their required 6-month follow-up testing.

The effect of the blind was assessed using the James blinding index which ranges from 0 (all patients correctly guessed their study-group assignments) to 1 (all patients did not know their study-group assignments), with values greater than 0.5 indicating successful blinding. All indices assessed indicate blinding was successful at each timepoint.

5.1.1.5 Clinical Events Committee/Adjudication

An independent CEC adjudicated all safety endpoint events. The CEC comprised physicians with experience in clinical trials in hypertension and/or CV indications. The members of the CEC were not investigators in the study.

5.1.1.6 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) assessed the differences in safety between Denervation and Sham groups, monitored for excessive occurrence of AEs and made recommendations to Medtronic regarding safety issues and risks to research participants. Additionally, they had the unique responsibility for conducting confidential reviews of effectiveness data, to which the sponsor was blinded, at prespecified interim analyses. Members of the DSMB were qualified in their area of specialty as well as in clinical trial conduct and were not members of the CEC nor participating investigators.

5.1.1.7 Endpoints

OFF MED included both efficacy and safety endpoints. The efficacy endpoints are described below; the safety endpoints are described in Section 6.

5.1.1.7.1 Primary Endpoint
The primary efficacy endpoint was the baseline-adjusted (ANCOVA) change in 24-hour SBP from baseline to 3-months post-procedure. This endpoint was only prospectively powered in the pivotal cohort.

5.1.1.7.2 Secondary Endpoints
The secondary powered efficacy endpoint of the pivotal cohort was the baseline-adjusted change in office SBP from baseline to 3-months post-procedure, compared between treatment groups.

Other secondary efficacy endpoints included:

- Change in 24-hour SBP and DBP from baseline at 3, 6, 12, 24, and 36 months post-procedure
- Change in office SBP and DBP from baseline at 1, 3, 6, 12, 24, and 36 months post-procedure
- Incidence of achieving target office SBP < 140 mmHg at 1, 3, 6, 12, 24, and 36 months post-procedure

5.1.1.7.3 Time in Target Range (TTR)
Time in target range (TTR) analyses calculate the percentage of time that a subject's BP is within pre-specified BP ranges. To be included in this analysis, subjects had to have a minimum of 2 BP measurements within the time interval presented. TTR is calculated by performing linear interpolation over the days between successive BP measurements and summarizing over the entire follow-up time period. Office SBP TTR was evaluated using a range of ≤ 140 mmHg and 24-hour SBP TTR was evaluated using a range of ≤ 130 mmHg.

TTR is a secondary analysis added to the statistical analysis plan after the completion of the pilot study.

5.1.2 Statistical Analysis Methods

5.1.2.1 Sample Size Calculation

To account for potential screen failures, it was anticipated that approximately 1,800 patients would be enrolled to randomize up to approximately 433 patients (including the first 80 consecutively randomized to the pilot cohort) in the adaptive Bayesian design with an informative prior comprised of OFF MED pilot patients (Gelman 2004; Ibrahim and Chen 2000).

The Bayesian adaptive design allowed the possibility of stopping early upon efficacy futility or success at the first or second prespecified interim analysis. Based on 15% attrition rate, the interim analyses would take place after the 210th and 240th patients had completed 3-month follow-up, with a maximum size of 300 patients with 3-month follow-up if the study did not stop at either interim look. The actual rate of attrition dictated the available sample size for analyses.

The prior data consists of the first consecutively randomized 80 patients in the OFF MED pilot cohort; results from these 80 patients have been analyzed and published (Kandzari et al 2018). The weight of the prior data was adjusted using a discount function, which scales from 0 to 1, according to the similarity of the prior and pivotal data. This discount function adjusts the amount of weight the prior receives. This discount function approach was proposed by the Medical Device Innovative Consortium (MDIC) working group and is a collaborative effort between FDA and industry through the MDIC (Haddad et al 2017; Medical Device Innovation Consortium).

5.1.2.2 Analysis Population

The primary analysis population was the intent-to-treat (ITT), which included all randomized patients analyzed according to their randomized treatment. Patients who met the anti-hypertensive medication escape criteria (office SBP > 180 [hypertensive urgency] or safety reasons) were analyzed using last observation carried forward (LOCF) for their BP measurements. If a LOCF was not available, the patients who met escape criteria were excluded from the ITT analysis.

Patient cohort definitions are provided in Table 8.

Table 8: OFF MED Pivotal Patient Cohorts

Term	Definition
Pilot Cohort	First consecutively randomized 80 patients
Expansion Cohort	Next 251 patients consecutively randomized in OFF MED (N=251)
Pivotal Cohort	First consecutively randomized 80 patients + next 251 consecutively randomized patients (N=331)
Full Cohort	First consecutively randomized 80 patients + next 251 consecutively randomized patients + next 35 randomized patients prior to stopping enrollment for success = 366 total
Denervation Group	Patients randomized to renal denervation
Sham Group	Patients randomized to sham control
Crossover Group	Patients randomized to Sham, who elected to crossover to the renal denervation procedure following completion of the primary endpoint in the study
Non-Crossover Group	Patients randomized to Sham who did not elect for the renal denervation procedure

5.1.2.3 Endpoint Analyses

The primary 24-hour SBP and the powered secondary office SBP efficacy endpoints were analyzed using a Bayesian method that allowed for prespecified interim analyses with predetermined stopping rules for efficacy or futility. The pilot cohort (N = 80), done under similar enrollment and treatment criteria, provided data for the informative prior in

the Bayesian power prior method. Simulations verified that overall type 1 error was preserved in the sequential evaluation of the primary endpoint. Weighting of the pilot study data was established by the degree of similarity between the pilot and pivotal 24-hour SBP datasets.

The first interim analysis took place when 251 patients had been randomized which resulted in 204 patients with evaluable baseline and 3-month follow-up data for the primary efficacy endpoint of 24-hour SBP and 228 patients for the secondary powered efficacy endpoint of office SBP. The efficacy stopping criteria were met during the first interim look and study enrollment was stopped at the first interim analysis. The interim analysis and Bayesian analysis were performed by an independent organization and reviewed by the DSMB. Medtronic personnel were blinded to the results until the DSMB reviewed the blinded primary endpoint results and implemented the prespecified stopping rule whereby Medtronic was notified of efficacy success.

The primary and secondary Bayesian efficacy endpoints, defined in Sections 5.1.1.7.1 and 5.1.1.7.2 above, were met if the posterior probabilities of superiority were more than 0.975. Treatment differences were presented with Bayesian 95% credible intervals.

BP changes between treatment arms at 3 months were made using ANCOVA models which adjust for the baseline BP. Statistical comparisons between treatment groups were made using the independent samples t-test for continuous outcomes and Fisher's exact test for categorical outcomes. Paired tests were used to compare changes from baseline to follow-up within each treatment group. Unless otherwise specified, a two-sided 0.05 level of significance was used to declare statistical significance.

5.1.2.4 Handling of Missing Data

For the primary and secondary efficacy endpoint analyses, patients with missing data were excluded from the analyses.

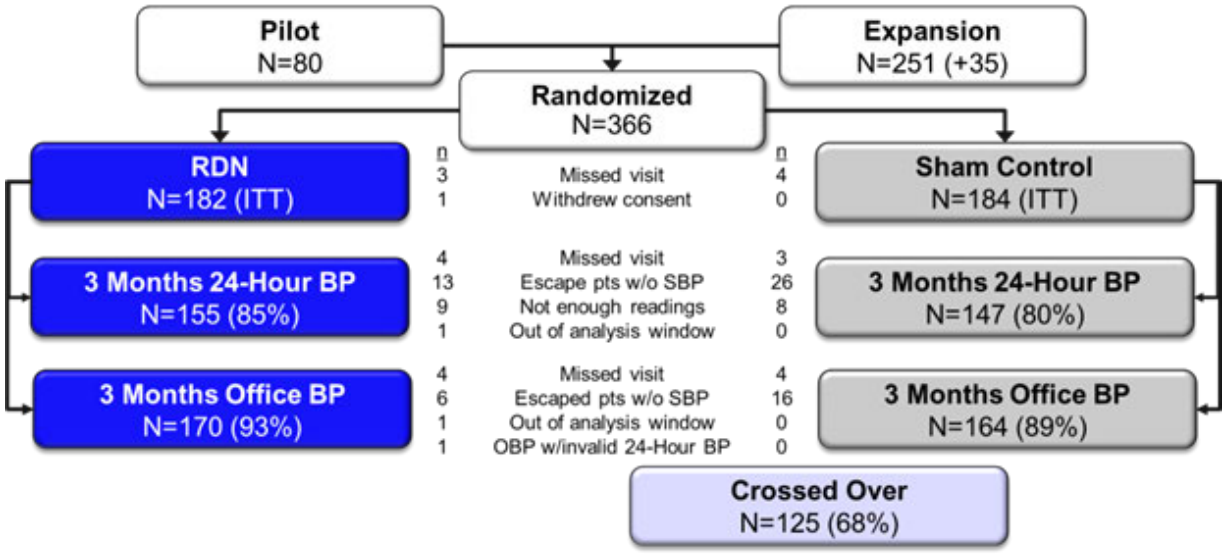
5.1.3 OFF MED Study Participants

5.1.3.1 Disposition

Of the first 80 randomized patients in the study, 38 were randomized to the Denervation group and 42 to the Sham group. These patients formed the Pilot Cohort.

In the Expansion Cohort, 251 additional patients were randomized for a total of 331 patients comprising the Pivotal cohort (166 patients to Denervation and 165 patients to Sham). An additional 35 patients were randomized prior to stopping enrollment for success (182 Denervation and 184 Sham= 366 total) comprising the Full cohort (Figure 23). Most patients completed the 3-month follow-up period. After 6 months, patients were unblinded and Sham patients were given the option to receive RDN procedure (cross over), if they met the anatomical and kidney function criteria for the treatment procedure. Over 75% of Sham patients opted to crossover to receive RDN.

Figure 23: OFF MED Pivotal Study: Patient Disposition (ITT Population)



ABPM: ambulatory blood pressure measurement; BL: baseline; BP: blood pressure; ITT: Intent-to-Treat; OSBP: office systolic blood pressure; RDN: renal denervation; SBP: systolic blood pressure
Escape – OSBP ≥ 180 mmHg or safety reason

5.1.3.2 Demographics

In the Pivotal Study, key baseline characteristics were balanced between groups. The majority of patients were male and white, and the median age was 53 years (Table 9).

Table 9: OFF MED Pivotal Study Patient Baseline Demographics (Full Cohort)

Characteristic	Denervation (N=182)	Sham (N=184)	P-value
Age (years)			
Mean ± SD	52.5 ± 10.8	52.7 ± 10.1	0.862
Median (Min, Max)	53.0 (23, 78)	53.5 (23, 78)	
Male	117 (64.3%)	128 (69.6%)	0.318
Race, n (%)			0.557
White	56 (30.8%)	60 (32.6%)	
Black or African American	37 (20.3%)	32 (17.4%)	
Asian	10 (5.5%)	4 (2.2%)	
Other	1 (0.5%)	1 (0.5%)	
Not reportable per local laws or regulations	78 (42.9%)	87 (47.3%)	
Ethnicity, n (%)			0.633
Hispanic/Latino/Spanish origin	5 (2.7%)	4 (2.2%)	
Not Hispanic/Latino/Spanish origin	98 (53.8%)	93 (50.5%)	
Not reportable per local laws or regulations/ Patient refuses to answer/Unknown	78 (42.9%)	87 (47.3%)	
BMI			
Mean ± SD	31.2 ± 6.0	31.0 ± 5.5	0.759
Median (Min, Max)	30.0 (22, 59)	30.0 (18, 54)	

BMI: body mass index; SD: standard deviation

5.1.3.3 Baseline Characteristics

Most patients in the OFF MED Pivotal study had hypertension for more than 5 years, and there were low incidences of comorbidities such as diabetes and sleep apnea (Table 10).

Coronary artery disease was the only characteristic that was significantly different ($p = 0.007$) between the two treatment groups (0% in the Denervation group; 4.3% (8/184) in the Sham group).

Table 10: OFF MED Pivotal Study Patient Baseline Characteristics (Full Cohort)

Characteristic	Denervation (N=182)	Sham (N=184)	P-value
Systolic Blood Pressure [mean (SD), mmHg]			
Office	162.8 ± 7.8	163.2 ± 7.7	
24-hour	151.2 ± 7.9	151.3 ± 7.6	
Diastolic Blood Pressure [mean (SD), mmHg]			
Office	101.1 ± 7.1	102.2 ± 7.3	
24-hour	97.6 ± 7.9	99.3 ± 7.5	
Length of hypertension diagnosis, n (%)			0.822
0–5 years	80 (44.0%)	81 (44.0%)	
6–10 years	34 (18.7%)	30 (16.3%)	
> 10 Years	68 (37.4%)	73 (39.7%)	
Cardiovascular Diagnosis, n (%)			
Congenital Heart Disease	0	1 (0.5%)	1.000
Left Ventricular Hypertrophy	9 (4.9%)	11 (6.0%)	0.819
Myocardial Infarction/ACS	0	3 (1.6%)	0.248
Coronary Artery Disease, n (%)	0	8 (4.3%)	0.007
Peripheral Artery Disease, n (%)	1 (0.5%)	0	0.497
Stroke, n (%)			
Hemorrhagic	1 (0.5%)	0	0.497
Transient Ischemic Attack	1 (0.5%)	0	0.497
Atrial Fibrillation, n (%)	1 (0.5%)	1 (0.5%)	1.000
Receiving drug for heart rate control, n (%)	0	1 (0.5%)	1.000
Type 2 Diabetes Mellitus, n (%)	8 (4.4%)	11 (6.0%)	0.639
Hyperthyroidism, n (%)	1 (0.5%)	2 (1.1%)	1.000
Hypothyroidism, n (%)	12 (6.6%)	10 (5.4%)	0.667
History of Sleep Apnea, n (%)			
Obstructive	15 (8.2%)	13 (7.1%)	0.699
Unknown	3 (1.6%)	6 (3.3%)	0.502
Smoking/Tobacco Use, n (%)			
Former	49 (26.9%)	55 (29.9%)	0.563
Current	31 (17.0%)	29 (15.8%)	0.779
Previous Surgical/PercutaneousInterventions, n (%)			
Renal Intervention (excluding renal denervation)	0	1 (0.5%)	1.000
Coronary balloonangioplasty/Stent	0	3 (1.6%)	0.248
Coronary artery bypass grafting	0	1 (0.5%)	1.000

ACS: acute coronary syndrome; SD: standard deviation

5.1.4 Procedure Metrics

The mean procedure time, defined as the time from when arterial access was obtained until arterial closure, was 99 minutes in the Denervation group; denervation time was approximately 1 hour (Table 11).

Table 11: OFF MED Pivotal Procedure Characteristics (Full Cohort)

Treatment	Denervation (N=182)	Sham (N=184)
Procedure Time[2] (minutes)		
Mean ± SD	99.3 ± 36.2	52.9 ± 16.6
Median (min, max)	93.0 (40, 239)	51.5 (25, 128)
Denervation Time[3] (minutes)		
Mean ± SD	59.7 ± 24.3	
Median (min, max)	55.0 (10, 207)	
Number of Ablation Attempts		
n[1]	181	NA
Mean ± SD	46.6 ± 15.3	
Median (min, max)	45.0 (18, 109)	
Number of Main Arteries Treated		
n[1]	181	NA
Mean ± SD	2.2 ± 0.6	
Median (min, max)	2.0 (1, 5)	
Number of Main Arteries Ablations		
n[1]	181	NA
Mean ± SD	18.2 ± 9.7	
Median (min, max)	16.0 (1, 62)	
Number of Branches Treated		
n[1]	181	NA
Mean ± SD	5.8 ± 2.6	
Median (min, max)	6.0 (0, 17)	
Number of Branch Ablations		
n[1]	181	NA
Mean ± SD	28.4 ± 15.1	
Median (min, max)	28.0 (0, 94)	

NA: not applicable; SD: standard deviation
1 Number of main arteries treated, not number of patients
2 Arterial closure - arterial access obtained
3 Final Guide Catheter Removal - Initial Symplicity Spyral Catheter Insertion

5.1.5 Blinding Assessment

Blinding assessments in the pivotal study were performed at discharge and 3 Months. All indices reflect an upper bound CI of > 0.5 indicating the blinding was successful at each timepoint (Table 12).

Table 12: Blinding Index Results for OFF MED Pivotal Study

	Patient Blinding Index[1] (95% CI)	Assessor Blinding Index[1] (95% CI)
Discharge	0.66 (0.61, 0.71)	0.82 (0.78, 0.86)
3-Months	0.53 (0.48, 0.59)	0.73 (0.68, 0.78)

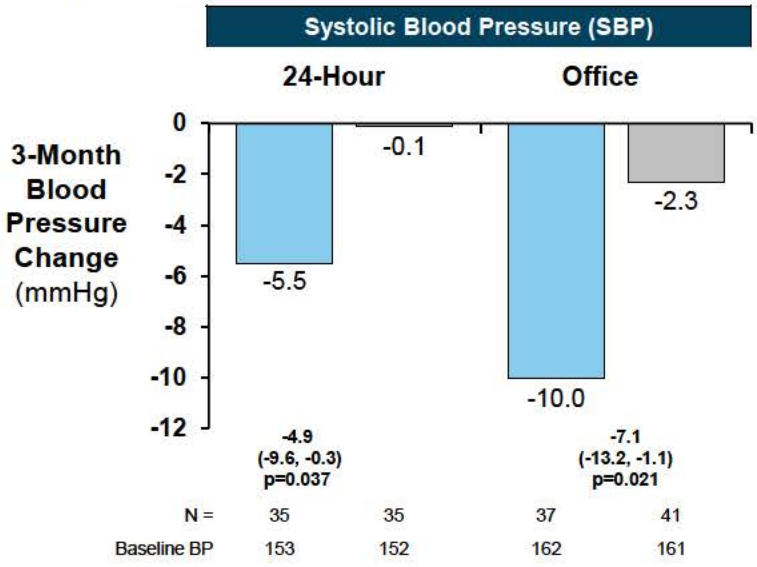
CI: confidence interval
1. James blinding index
The blinding index ranges from 0 (all patients correctly guessed their study-group assignments) to 1 (all patients did not know their study-group assignments), with values greater than 0.5 indicating successful blinding.

5.1.6 OFF MED Efficacy Results

5.1.6.1 Pilot Study Results

Comparison of 3-month changes, adjusted for baseline measures using ANCOVA, showed significantly greater reductions in office SBP and DBP, 24-hour SBP and DBP in the Denervation group compared to the Sham group for the pilot study (Figure 24).

Figure 24: OFF MED Pilot Study Office and Ambulatory Systolic Blood Pressure Changes at 3 Months (ITT Population)



ANCOVA: analysis of covariance; BP: blood pressure; ITT: Intent-to-Treat; SBP: systolic blood pressure
ANCOVA differences and p-values adjusted for baseline blood pressure

Evaluation of changes in 24-hour SBP and DBP at the 3-month endpoint showed statistically significant BP reductions for the Denervation group.

5.1.6.2 Pivotal Cohort Primary Endpoint

The primary effectiveness endpoint of the pivotal cohort, defined as the baseline adjusted (analysis of covariance/ANCOVA) change in SBP from baseline (Screening

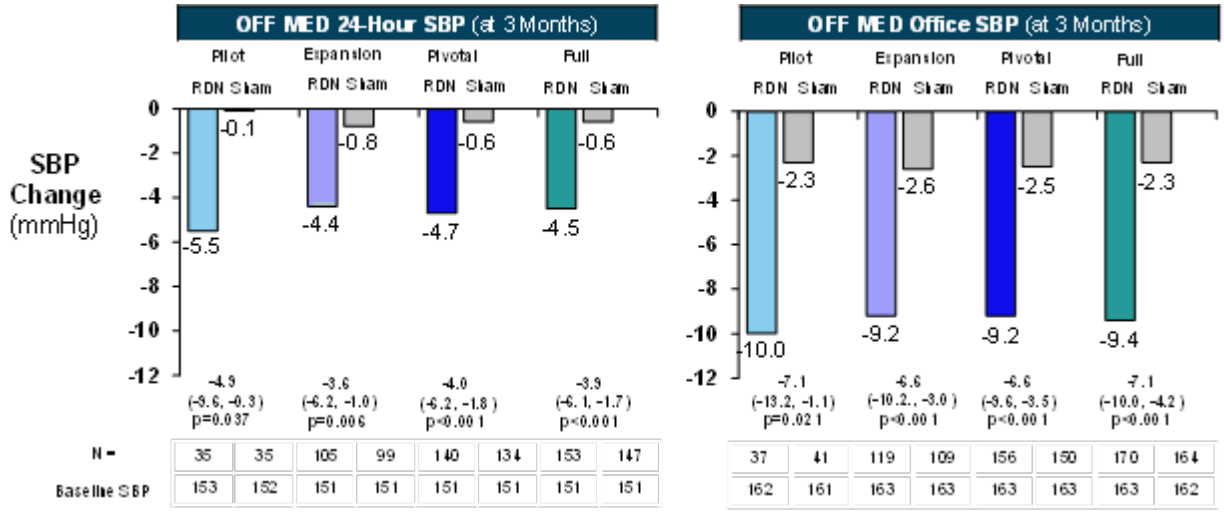
Visit 2) to 3-months post-procedure as measured by 24-hour ABPM was met, with posterior probability of superiority > 0.999. The treatment difference was −3.9 mmHg (Bayesian 95% credible interval: −6.2 to −1.6) in 24-hour SBP between groups. A Bayesian power prior approach in conjunction with a discount function was used to incorporate prior data. The discount function reduces the strength of the prior data if disagreements are observed with the current data. For the Bayesian analyses that utilized both pilot and expansion, nearly all of the pilot Denervation BP data and nearly all of the pilot Sham BP data were included in the primary efficacy endpoint analysis due to similarity in 24-hour SBP results between the Pilot and Expansion cohorts.

5.1.6.3 Powered Secondary Endpoint

The secondary efficacy endpoint was met, with posterior probability of superiority > 0.999. The between-group treatment difference in office SBP was −6.5 mmHg (−9.6 to −3.5).

Figure 25 summarizes the changes in 24-hour and office SBP from baseline to 3 months for the Denervation and Sham groups using the frequentist ANCOVA analysis, adjusting for the baseline BP value, for the ITT population in the Pivotal Cohort. Between-group differences were statistically significant for 24-hour and office SBP reductions in the Pilot, Expansion, Pivotal and Full cohorts of OFF MED. 24-hour and office DBP reductions were significant for all cohorts as well.

Figure 25: OFF MED All Cohorts: Change in 24-Hour and Office Systolic Blood Pressure at 3 Months (ITT Population)



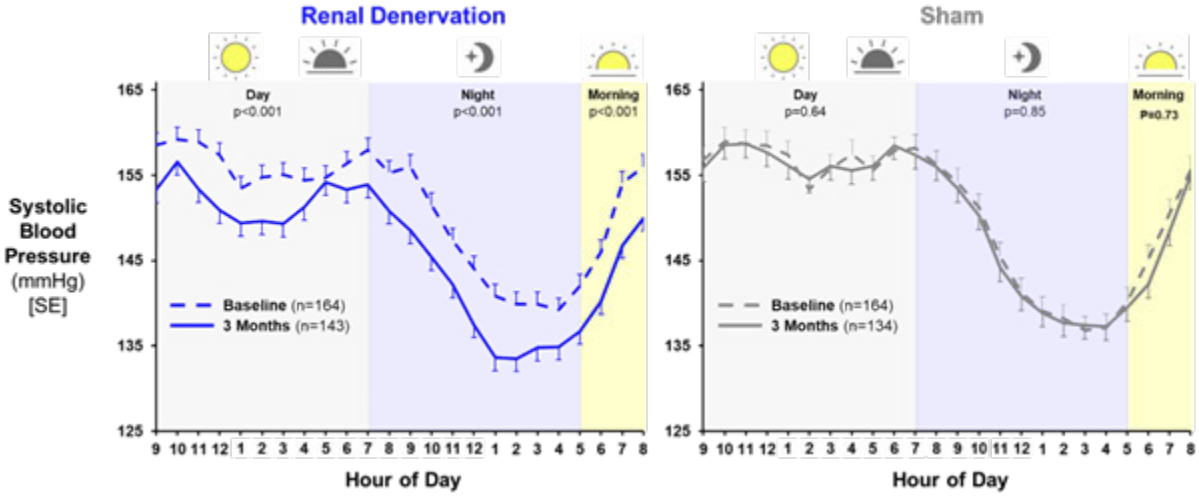
ANCOVA: analysis of covariance; BL: baseline; BP: blood pressure; ITT: Intent-to-Treat; RDN: renal denervation; SBP: systolic blood pressure
Pivotal = Pilot + Expansion
Note: frequentist ANCOVA analysis, adjusting for the baseline BP value

5.1.6.4 Additional Secondary Endpoints

In contrast to the Sham group, the Denervation group had a consistent reduction from baseline in both SBP (Figure 26) and DBP across 24 hours. Notably, these constant

reductions were also observed in the early morning hours when patients are at higher risk for CV events (Ettehad et al 2016; Sega et al 2005). It is important to note that ABPM results are only reported for patients with evaluable ABPM, which is defined as a minimum of 21 daytime readings and 12 nighttime readings over a 24-hour period.

Figure 26: OFF MED Pivotal Study: 24-Hour SBP Baseline vs 3 Months (ITT Population)

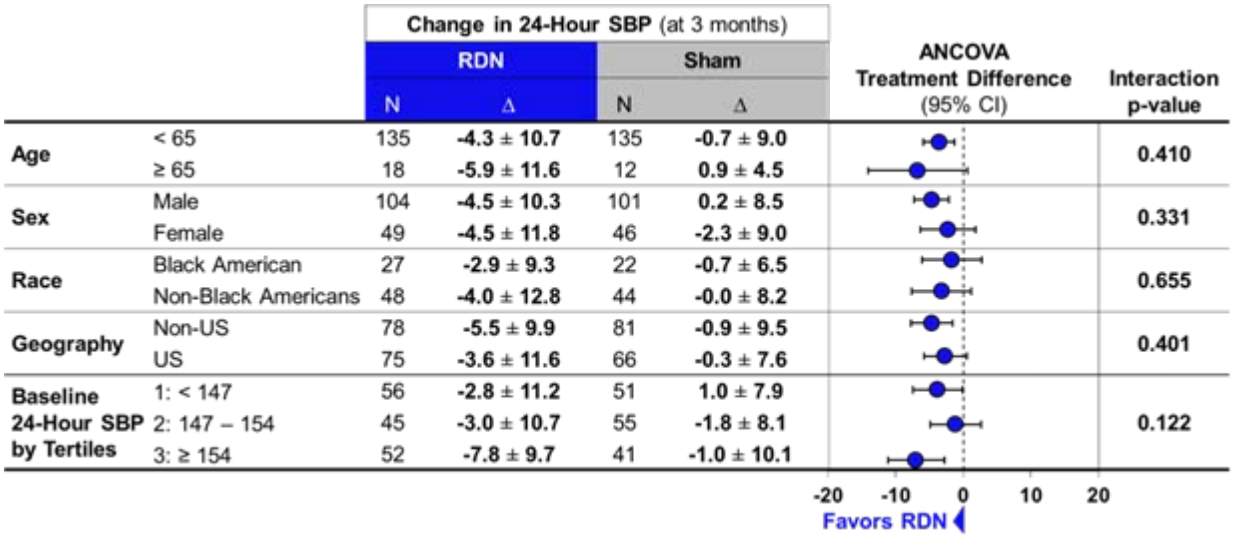


SE: standard error; SBP: systolic blood pressure

5.1.6.5 Subgroup Efficacy Analyses

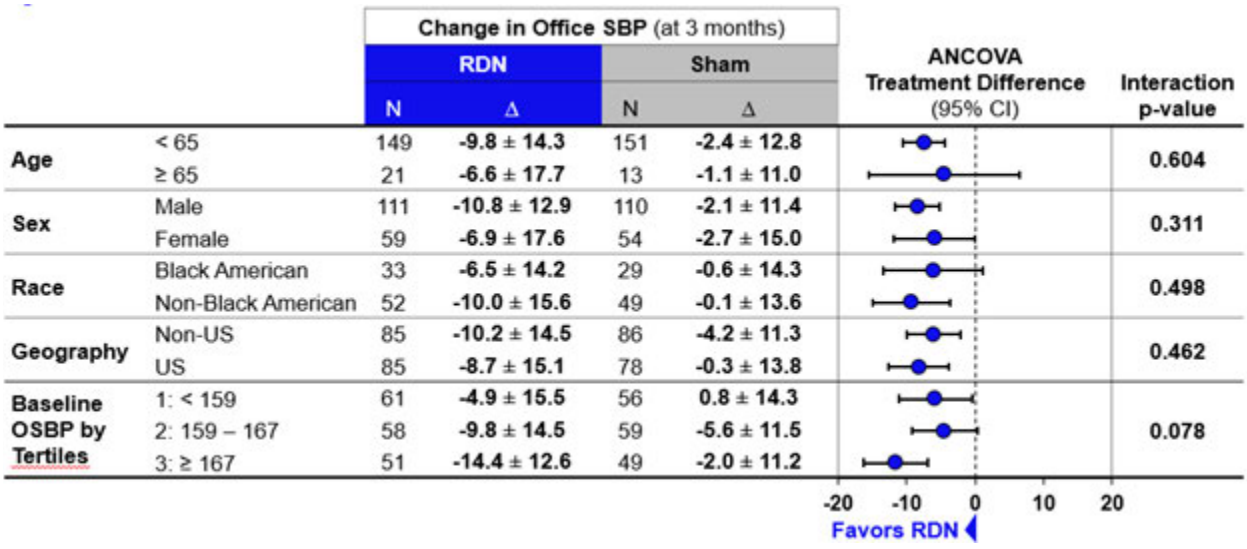
Subgroup analyses were prespecified to assess safety and efficacy in specific patients, and to evaluate whether any subgroup responded more than another. Subgroup analyses presented below are for the full cohort. No significant differences were observed among any subgroups for 24-hour SBP (Figure 27) or office SBP (Figure 28).

Figure 27: OFF MED Full Cohort: 24-Hour SBP Subgroup Analysis (ITT Population)



ANCOVA: analysis of covariance CI: confidence interval; RDN: renal denervation; SBP: systolic blood pressure; US: United States

Figure 28: OFF MED Full Cohort: Office SBP Subgroup Analysis (ITT Population)



ANCOVA: analysis of covariance CI: confidence interval; OSBP: office systolic blood pressure; RDN: renal denervation; SBP: systolic blood pressure; US: United States

5.1.6.6 Escape Patient Analysis

In the event a patient's office SBP was ≥ 180 mmHg, indicating hypertensive urgency, or there was a safety concern from randomization to 3-month follow-up, the patient would be seen a second time within 72 hours for a repeat office BP. If the patient's

office SBP remained ≥ 180 mmHg at this second reading, the patient was put back on medication and met escape criteria.

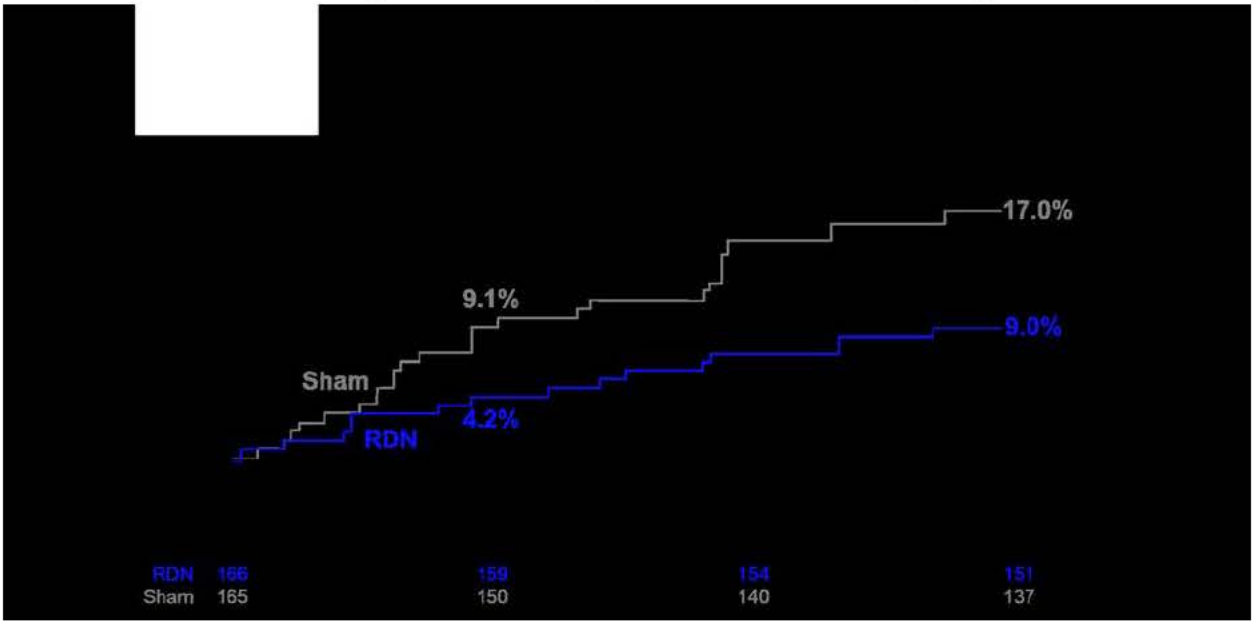
In the Pivotal Cohort, 16/166 (10%) patients in the Denervation group and 28/165 (17%) patients in the Sham group met the escape criteria due to SBP ≥ 180 mmHg or site reported safety concern between randomization and 3-months (Table 13 and Figure 29).

Table 13: OFF MED Pivotal Study Patients Meeting "Escape" Criteria - Primary Bayesian Dataset

Criteria	Denervation N=166 n (%)	Sham N=165 n (%)
Patients meeting escape criteria*	16 (10%)	28 (17%)
Escape criterion		
SBP ≥ 180 mmHg (hypertensive urgency)	5 (31%)	15 (54%)
Site-reported safety concern	11 (69%)	13 (46%)

SBP: Systolic blood pressure
* There were significantly more escape patients in the Sham group compared to the Denervation group (p = 0·032).

Figure 29: Kaplan–Meier Estimate of Rate of Patients Meeting Escape Criteria for RDN and Sham Groups for All Escape Patients in Primary Bayesian Dataset



RDN: renal denervation
Source: Weber et al 2022

5.1.6.7 Medication Adherence

Both groups showed similar adherence to the off-medication protocol requirement through 3 months as determined by drug testing at baseline and 3 months (Table 14).

Table 14: OFF MED Full Cohort Medication Adherence to 3 Months

Adherence (no anti-hypertensive medications identified), %	Denervation N = 182	Sham N = 184	p-Value
Baseline	91.7%	88.6%	0.381
Month 3	91.5%	95.3%	0.258
Both Baseline and 3 months	85.8%	90.5%	0.223

5.1.6.8 OFF MED Time in Target Range

Target ranges of office SBP ≤ 140 mmHg or 24-hour BSP ≤ 130 mmHg were used to calculate TTR through 24 months. Time in target range in both office and 24-hour ambulatory SBP for subjects treated with RDN at different time points is shown in Table 15. The Denervation group spent significantly more time in the target SBP range and had significantly lower medication burden as compared to the Sham group at 6, 12, and 24 months.

Table 15: Percent Time in Target Range (%TTR) – OFF MED Full Cohort

	Denervation (%)	Sham (%)	p-value
Office SBP TTR% (≤ 140 mmHg)[1]			
TTR 0-3 months	11.7 ± 23.7 (180)	4.7 ± 14.0 (180)	0.002
TTR 0-6 months	18.5 ± 25.8 (182)	12.7 ± 18.7 (184)	0.091
TTR 0-12 months	31.7 ± 30.2 (182)	23.1 ± 26.4 (184)	0.003
TTR 0-24 months	38.7 ± 33.3 (182)	25.6 ± 29.5 (184)	<0.001
24hr SBP TTR% (≤ 130 mmHg)[1]			
TTR 0-3 months	2.0 ± 8.3 (153)	0.1 ± 0.8 (146)	0.007
TTR 0-6 months	7.8 ± 15.2 (165)	6.3 ± 11.2 (168)	0.713
TTR 0-12 months	17.6 ± 23.8 (166)	13.6 ± 20.3 (175)	0.193
TTR 0-24 months	22.1 ± 27.9 (167)	15.7 ± 23.2 (176)	0.019
Combined OSBP and 24hr TTR[2]			
Max (OSBP/140 TTR, ASBP/130 TTR) 0-3M	12.4 ± 24.1 (180)	4.8 ± 14.0 (180)	<0.001
Max (OSBP/140 TTR, ASBP/130 TTR) 0-6M	20.8 ± 26.1 (182)	15.3 ± 19.4 (184)	0.109
Max (OSBP/140 TTR, ASBP/130 TTR) 0-12M	36.1 ± 29.7 (182)	26.9 ± 26.7 (184)	0.001
Max (OSBP/140 TTR, ASBP/130 TTR) 0-24M	43.2 ± 32.4 (182)	30.2 ± 30.2 (184)	<0.001

OSBP: office systolic blood pressure; SBP: systolic blood pressure; TTR: time in target range
Data displayed as mean ± SD (n)
[1] Analyses use all non-missing BP data from BL, 2W, 4W, 8W, 3M, 6M, 12M, 24M within time ranges p-values from non-parametric Kruskal-Wallis test
[2] The maximum value of Office TTR and 24-Hour TTR within each time period is used in combined analysis P-values from non-parametric Kruskal-Wallis test
Note that all p-values are not adjusted with multiplicity

5.1.7 OFF MED Pivotal Efficacy Conclusions

The powered primary and powered secondary efficacy endpoints were both met in OFF MED Pivotal. Reductions in BP after RDN were consistent throughout 24-hour measurement periods, with significant differences in nighttime and daytime BP from baseline to 3 months. Treatment differences for 24-hour and office SBP in key subgroup measurements demonstrated no significant difference between subgroups.

5.2 ON MED Pilot and Expansion Study

5.2.1 Study Design

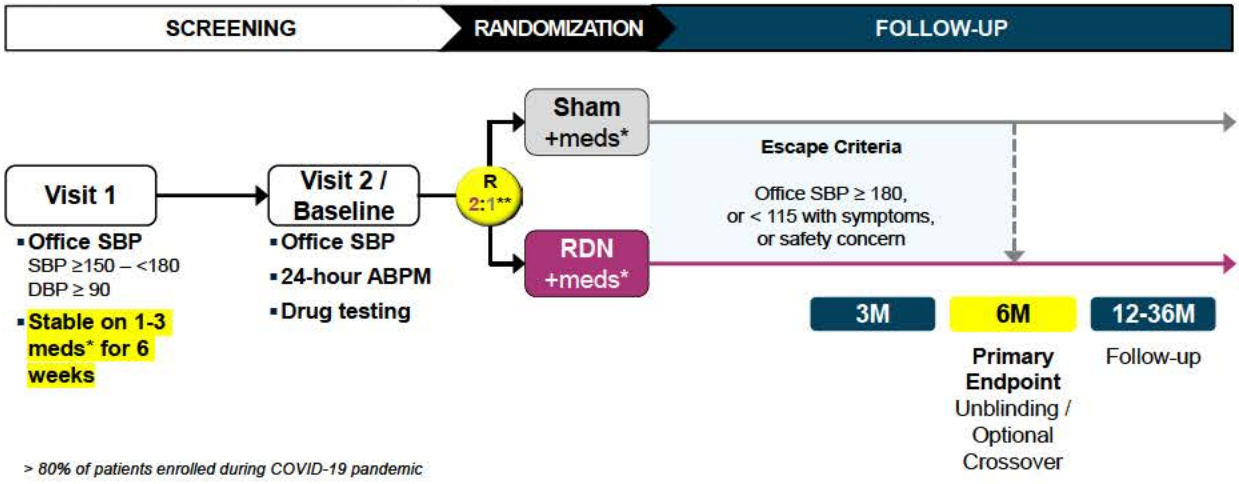
5.2.1.1 Overview

ON MED was designed to evaluate safety and efficacy of RDN in patients with uncontrolled hypertension compared to a sham-controlled population, in the presence of anti-hypertensive medications. Like OFF MED, ON MED was conducted in two cohorts, an initial pilot cohort and a second prospectively powered expansion cohort that continued via an adaptive Bayesian design. Patients were not to have their anti-

hypertensive medications changed between baseline and the 6-month primary endpoint, unless they met specific escape criteria (described in Figure 30). Eligible patients had uncontrolled BP (office SBP 150 to < 180 mmHg; DBP ≥ 90 mmHg; average 24-hour SBP 140 to < 170 mmHg) and were on 1–3 standard anti-hypertensive medication classes on at least 50% of the maximum manufacturer's dose. The medication classes were to include a thiazide-type diuretic, a dihydropyridine calcium channel blocker, an ACE-I/ ARB, or a beta blocker.

Given ongoing recruitment during the trial expansion process, the first 26 patients in the prospectively powered Expansion Cohort (patients 81–106) were randomized in a 1:1 ratio, while patients 107 onward were randomized in a 1:2 ratio to Sham or denervation treatment (Figure 30). The randomization scheme was changed to allow for more safety data to be collected to contribute to the primary safety endpoint.

Figure 30: ON MED Study Design



ABPM: ambulatory blood pressure monitoring; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; DBP: diastolic blood pressure; M: month; R: randomization; RDN: renal denervation; SBP: systolic blood pressure
Yellow highlight represents differences from OFF MED
*Thiazide diuretic, ACE/ARB, Calcium Channel Blocker, Beta Blocker
** First 106 patients randomized 1:1

After patients were unblinded at the completion of their 6-month visits, those who were randomized to the Sham group were given the opportunity to crossover and receive the RDN procedure if they continued to meet the required anatomy and eGFR exclusionary criteria. Denervation patients were followed through 36-months post-randomization. Sham patients who did not crossover were followed through 12-months post-randomization with vital status updates at 24-months and 36-months unless the patient was reconsented under a later protocol version which would require in-person follow-up visits at 24-months and 36-months. Crossover patients were followed through 24-months post RDN procedure unless the patient was reconsented under a later

protocol version which would require an in-person follow-up visit at 36-months post-RDN.

Drug Testing

To ensure patients were not taking anti-hypertensive medication unless prescribed by a physician, drug testing was completed by an outside core lab by analyzing urine and blood samples collected at study visits. Drug testing results were only shared with Medtronic and not with the investigational sites nor patients so as not to influence patient behavior or practice of medicine at the research site.

5.2.1.2 Enrollment Criteria

BP inclusion criteria included:

- Office SBP ≥ 150 mmHg and < 180 mmHg
- Office DBP ≥ 90 mmHg
- 24-hour average SBP ≥ 140 mmHg to < 170 mmHg

Key study exclusion criteria included:

- Ineligible renal artery anatomy, including:
    - Main renal artery for each kidney less than 3 mm or greater than 8 mm
    - Lacking a main renal arterial vessel that does not allow 4 simultaneous quadrantic RF ablations in the main renal artery or equivalent
- eGFR < 45 mL/min/1.73 m^2
- Type 1 Diabetes Mellitus or Type 2 Diabetes Mellitus with HbA1C > 8.0%
- Secondary causes of hypertension

5.2.1.3 Study Treatment

Study participants received either renal angiography followed by RDN with the Symplicity Spyral System or renal angiography alone (sham).

5.2.1.4 Blinding

In addition to patients being blinded to their randomization assignment, sponsor and site personnel involved in the measurement of office BP were also blinded to study patients' randomization assignment through 6 months post-procedure to prevent potential bias of results.

The effect of the blind was assessed using the James blinding index which ranges from 0 (all patients correctly guessed their study-group assignments) to 1 (all patients did not know their study-group assignments), with values greater than 0.5 indicating successful blinding. All indices assessed indicate blinding was successful at each timepoint.

5.2.1.5 Clinical Events Committee/Adjudication

An independent CEC adjudicated all safety endpoint events. The CEC comprised physicians with experience in clinical trials in hypertension and/or CV indications. The members of the CEC were not investigators in the study.

5.2.1.6 Data Safety Monitoring Board

The DSMB assessed the differences in safety between Denervation and Sham groups, monitored for excessive occurrence of AEs and made recommendations to Medtronic regarding safety issues and risks to research participants. Additionally, they had the unique responsibility for conducting confidential reviews of effectiveness data, to which the sponsor was blinded, at prespecified interim analyses. Members of the DSMB were qualified in their area of specialty as well as in clinical trial conduct and were not members of the CEC nor participating investigators.

5.2.1.7 Endpoints

5.2.1.7.1 Primary Endpoint

The primary efficacy endpoint was the baseline-adjusted change (using ANCOVA) in 24-hour SBP from baseline to 6-months post-procedure.

5.2.1.7.2 Secondary Endpoints

The secondary efficacy endpoints were:

- Change in 24-hour SBP and DBP from baseline at 3-, 6-, 12-, 24- and 36-months post-procedure
- Change in office SBP and DBP from baseline at 1-, 3-, 6-, 12-, 24- and 36-months post-procedure
- Incidence of achieving target office SBP< 140 mmHg at 1-, 3-, 6-,12-, 24- and 36-months post-procedure

5.2.1.7.3 Win Ratio

A win ratio analysis was used to analyze the BP and medication data at 6-months.

The following endpoints were included in the hierarchical composite endpoint comparison:

1. 24-hour SBP change from baseline to 6 months using a threshold of 5 mmHg
2. Medication burden change from baseline to 6 months using a threshold of zero

Win Ratio is a method implemented in randomized clinical trials to combine different types of endpoints into a single composite endpoint to evaluate treatment effect (Redfors et al 2020).

Win ratio is a secondary analysis added to the statistical analysis plan after the completion of the pilot study and after the ON MED first interim analysis.

5.2.1.7.4 ON MED Time in Target Range

TTR analyses calculate the percentage of time that a subject's BP is within prespecified BP ranges. To be included in this analysis, subjects had to have a minimum of 2 BP measurements within the time interval presented. TTR is calculated by performing linear interpolation over the days between successive BP measurements and summarizing over the entire follow-up time period. Office SBP TTR was evaluated using a range of ≤ 140 mmHg and 24-hour SBP TTR was evaluated using a range of ≤ 130 mmHg.

TTR is a secondary analysis added to the statistical analysis plan after the completion of the pilot study and after the ON MED first interim analysis.

5.2.2 Statistical Analysis Methods

5.2.2.1 Sample Size Calculation

ON MED was planned to enroll approximately 1,600 patients in order to randomize up to 340 patients, including 80 patients in the pilot cohort, at up to 55 study centers globally. The first 106 patients were randomized 1:1 and the remaining patients were randomized 2:1 to denervation vs Sham for the reasons discussed in Section 5.2.1.1.

Bayesian adaptive design allowed the possibility of stopping early upon efficacy futility or success at the first or second prespecified interim analyses. Based on expected 15% attrition rate at 6 months, the interim analyses would take place after the 110th and 149th patients had completed 6-month follow-up, with a maximum study size of 221 patients with 6-month data if the study did not stop at either interim analysis. The actual rate of attrition dictated the available sample size for analyses.

5.2.2.2 Analysis Populations

ON MED patient cohort definitions are provided in Table 16.

Table 16: ON MED Patient Cohorts

Term	Definition
Pilot Cohort	First 80 patients randomized in ON MED (N=80)
Expansion Cohort	Next 257 patients consecutively randomized in ON MED (N=257)
Full Cohort	Pilot + Expansion (N=337)
Denervation Group	Patients randomized to renal denervation
Sham Group	Patients randomized to sham control

5.2.2.3 Endpoint Analyses

The Expansion cohort primary efficacy endpoint analysis used a Bayesian design incorporating the pilot data as an informative prior. The Bayesian posterior treatment effects were determined along with the 95% Bayesian credible interval. The prespecified threshold for success was a probability > 0.975.

5.2.2.4 *Handling of Missing Data*

For the primary and secondary efficacy endpoint analyses, patients with missing data were excluded from the analyses.

5.2.3 *ON MED Study Participants*

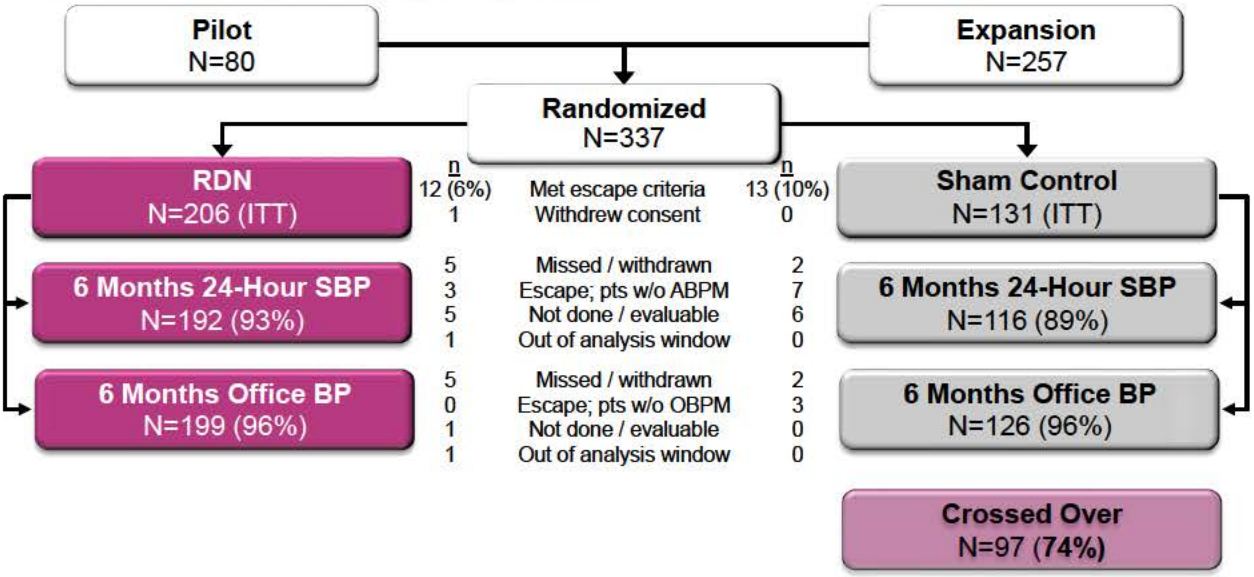
5.2.3.1 *Disposition*

Of the first 80 randomized patients, 38 were randomized to the Denervation group and 42 to the Sham group. These patients formed the Pilot Cohort.

An additional 257 patients were randomized in the Expansion Cohort for a total of 337 patients forming the Full Cohort (Figure 31) (206 patients in the Denervation group and 131 in the Sham group). A total of 181 (54%) patients were enrolled from outside the US.

At the 6-month timepoint, 192 patients in the Denervation group and 116 patients in the Sham group completed an evaluable 24-hour BP assessment. Notably, 80% of patient follow-up visits for the ON MED Expansion cohort occurred during the Covid-19 pandemic.

Figure 31: ON MED Patient Disposition



ABPM: ambulatory blood pressure monitoring; BP: blood pressure; ITT: intent-to-treat; LOCF: last observation carried forward; OBP OBPM: office blood pressure monitoring; OSBP: office systolic blood pressure; RDN: renal denervation; SBP: systolic blood pressure
Escape – OSBP ≥ 180 mmHg or safety reason

5.2.3.2 *Demographics*

Within the Full Cohort, both the Denervation and Sham groups were predominantly male (81.1% vs 78.6%) with median ages of 56 and 55 years, respectively (Table 17).

While these groups were largely reported to be white or race not reported, there was a notable rate of patients who were black or African American (17.0% vs 19.1%).

Table 17: ON MED Patient Demographics (Full Cohort)

Characteristic	Denervation (N=206)	Sham (N=131)	P-Value
Age (years)			
Mean ± SD	55.2 ± 9.0	54.6 ± 9.4	0.566
Median	56.0	55.0	
Min, Max	25, 76	32, 76	
Male, n (%)	167 (81.1%)	103 (78.6%)	0.579
Race, n (%)			0.492
White	71 (34.5%)	48 (36.6%)	
Black or African American	35 (17.0%)	25 (19.1%)	
Asian	17 (8.3%)	10 (7.6%)	
Multi-racial / Bi-racial	2 (1.0%)	0	
Other/ Patient refuses to answer / Unknown	1 (0.5%)	2 (1.5%)	
Not reportable per local laws or regulations	80 (38.8%)	46 (35.1%)	
Hispanic/Latino/Spanish origin, n (%)			0.605
Yes	3 (1.5%)	4 (3.1%)	
No	122 (59.2%)	80 (61.1%)	
Not reportable per local laws or regulations/ Patient refuses to answer/Unknown	81 (39.3%)	47 (35.9%)	
BMI			
Mean ± SD	31.4 ± 6.0	32.1 ± 5.2	0.223
Median	30.1	31.4	
Min, Max	17, 53	20, 49	

BMI: body mass index; SD: standard deviation

5.2.3.3 Baseline Medical History

Baseline systolic and diastolic BP was similar between groups, as was the incidence of comorbidities and co-existing illnesses such as coronary artery disease. The majority of patients in the Denervation and Sham groups presented with a longstanding history (> 5 years) of hypertension (69.9% vs 79.4%) (Table 18).

Table 18: ON MED Patient Baseline Characteristics (Full Cohort)

Characteristic	Denervation (N=206)	Sham (N=131)	p-values
Systolic Blood Pressure [mean (SD), mmHg]			
Office	163.0 ± 7.7	163.1 ± 7.9	0.871
24-hour	149.6 ± 7.0	149.3 ± 7.0	0.703
Diastolic Blood Pressure [mean (SD), mmHg]			
Office	101.2 ± 7.0	101.5 ± 7.3	0.712
24-hour	96.6 ± 7.6	95.7 ± 7.7	0.277
Length of hypertension diagnosis, n (%)			0.038
0–5 years	62 (30.1%)	24 (18.3%)	
6–10 years	37 (18.0%)	27 (20.6%)	
> 10 Years	107 (51.9%)	80 (61.1%)	
Cardiovascular Diagnosis, n (%)			
Congenital Heart Disease	1 (0.5%)	0	1.000
Left Ventricular Hypertrophy	15 (7.3%)	9 (6.9%)	1.000
Myocardial Infarction/ACS	4 (1.9%)	4 (3.1%)	0.716
Cardiomyopathy	2 (1.0%)	2 (1.5%)	0.644
Congestive Heart Failure, n (%)	0	1 (0.8%)	0.389
Coronary Artery Disease, n (%)	11 (5.3%)	9 (6.9%)	0.638
Stroke, n (%)	0	2 (1.5%)	0.150
Transient Ischemic Attack, n (%)	1 (0.5%)	0	1.000
Atrial Fibrillation, n (%)	5 (2.4%)	5 (3.8%)	0.519
Type 2 Diabetes Mellitus, n (%)	22 (10.7%)	23 (17.6%)	0.074
Hyperthyroidism, n (%)	0	1 (0.8%)	0.389
Hypothyroidism, n (%)	8 (3.9%)	12 (9.2%)	0.058
Renal Artery Stenosis, n (%)	1 (0.5%)	1 (0.8%)	1.000
History of Sleep Apnea - Obstructive	23 (11.2%)	23 (17.6%)	0.105
Smoking/Tobacco Use, n (%)			
Former	73 (35.4%)	38 (29.0%)	0.236
Current	32 (15.5%)	21 (16.0%)	1.000
Previous Surgical/Percutaneous Interventions, n (%)			
Renal Intervention (including renal denervation)[2]	1 (0.5%)	1 (0.8%)	1.000
Coronary balloon angioplasty / Stent	8 (3.9%)	2 (3.1%)	0.772
Coronary artery bypass grafting	1 (0.5%)	0	1.000
Peripheral PTA/Stent/Bypass	0	2 (1.5%)	0.150

ACS: acute coronary syndrome; PTA: peripheral transluminal angioplasty; SD: standard deviation

5.2.3.4 *Medication Adherence*

Although both the Denervation and Sham groups were prescribed an average of 1.9 anti-hypertensive medication classes at baseline, drug testing for adherence revealed that Denervation patients were taking an average of 1.7 anti-hypertensive medication classes compared to 1.6 in the Sham group (Table 19).

Table 19: ON MED Baseline Anti-Hypertensive Medications As Detected by Drug Testing (Full Cohort)

	Baseline Prescribed Regimen		Medications Detected by Drug Testing at Baseline	
Category	**Denervation (N=206)**	**Sham (N=131)**	**Denervation (N=206)**	**Sham (N=131)**
Number of anti-hypertensive medication classes				
Mean ± SD	1.9 ± 0.8	1.9 ± 0.8	1.7 ± 0.9	1.6 ± 0.9
Median	2.0	2.0	2.0	1.0
Min, Max	1, 4	1, 4	0, 5	0, 5
Number of medication classes, n (%)				
1	80 (38.8%)	47 (35.9%)	80 (38.8%)	57 (43.5%)
2	67 (32.5%)	47 (35.9%)	78 (37.9%)	41 (31.3%)
3	58 (28.2%)	36 (27.5%)	29 (14.1%)	20 (15.3%)
4**	1 (0.5%)	1 (0.8%)	6 (2.9%)	2 (1.5%)
Medication class, n (%)				
Diuretic	84 (40.8%)	57 (43.5%)	49 (23.8%)	34 (26.0%)
Calcium Channel Blocker	110 (53.4%)	73 (55.7%)	106 (51.5%)	59 (45.0%)
ACE-I/ARB	158 (76.7%)	99 (75.6%)	145 (70.4%)	87 (66.4%)
Beta Blocker	37 (18.0%)	24 (18.3%)	38 (18.4%)	26 (19.8%)
Other	1* (0.5%)	0	9 (4.4%)	2 (1.5%)

ACE-I: angiotensin-converting enzyme inhibitor; ARB; angiotensin receptor blocker; SD: standard deviation
*Vasodilator
**One patient was prescribed Metoprolol at baseline for an indication of "Heart Disease" in addition to three other medication anti-hypertensive medication classes. A query is with the site for the other patient to determine if this is a data entry error.

5.2.4 Procedure Metrics

The mean procedure time, defined as the time from when arterial access was obtained until arterial closure, was 91 minutes in the Denervation group; denervation time was 54 minutes (Table 20).

Table 20: ON MED Procedure Characteristics (Full Cohort)

Treatment	Denervation (N=206)	Sham (N=131)
Procedure Time[2] (minutes)		
Mean ± SD	91.3 ± 31.2	51.2 ± 19.5
Median (min, max)	88.5 (33, 210)	48.0 (23, 162)
Denervation Time[3] (minutes)		
Mean ± SD	54.4 ± 19.2	
Median (min, max)	52.0 (17, 133)	
Number of Ablation Attempts		
n[1]	205	NA
Mean ± SD	47.4 ± 16.5	
Median (min, max)	44 (16, 107)	
Number of Main Arteries Treated		
n[1]	205	NA
Mean ± SD	2.3 ± 0.6	
Median (min, max)	2.0 (1, 5)	
Number of Main Arteries Ablations		
n[1]	205	NA
Mean ± SD	19.4 ± 9.5	
Median (min, max)	18.0 (5, 82)	
Number of Branches Treated		
n[1]	205	NA
Mean ± SD	5.8 ± 2.7	
Median (min, max)	6.0 (0, 14)	
Number of Branch Ablations		
n[1]	205	NA
Mean ± SD	28.0 ± 14.6	
Median (min, max)	25.0 (0, 82)	

NA: not applicable; SD: standard deviation;
1 Number of main arteries treated, not number of patients
2 Arterial closure - arterial access obtained
3 Final Guide Catheter Removal - Initial Symplicity Spyral Catheter Insertion

5.2.5 Blinding Assessment

Blinding assessments in the Expansion cohort were performed at discharge, 3 Months and 6 Months. All indices reflect an upper bound CI of > 0.5 indicating the blinding was successful at each timepoint (Table 21).

Table 21: Blinding Index Results for ON MED Full Cohort

	Patient Blinding Index[1] (95% CI)	Assessor Blinding Index[1] (95% CI)
Discharge	0.68 (0.63, 0.73)	0.82 (0.78, 0.87)
3-Months	0.58 (0.53, 0.63)	0.75 (0.70, 0.79)
6-Months	0.58 (0.53, 0.63)	0.73 (0.68, 0.78)

CI: confidence interval
1. James blinding index
The blinding index ranges from 0 (all patients correctly guessed their study-group assignments) to 1 (all patients did not know their study-group assignments), with values greater than 0.5 indicating successful blinding.

5.2.6 ON MED Pilot Cohort Results

In the ON MED Pilot cohort, 24-hour and office SBP decreased significantly (both $p < 0.001$) from baseline to 6 months in the Denervation group by −9.3 in 24-hour SBP and −9.2 mmHg in OSBP (Figure 32). Similar significant reductions were seen for 24-hour and office DBP. Moreover, no significant changes were seen in the Sham group.

The mean difference between the groups favored Denervation for 6-month change in both 24-hour and office BP from baseline of −7.3 mmHg ($p = 0.004$) and −6.6 mmHg ($p = 0.026$), respectively (Figure 32).

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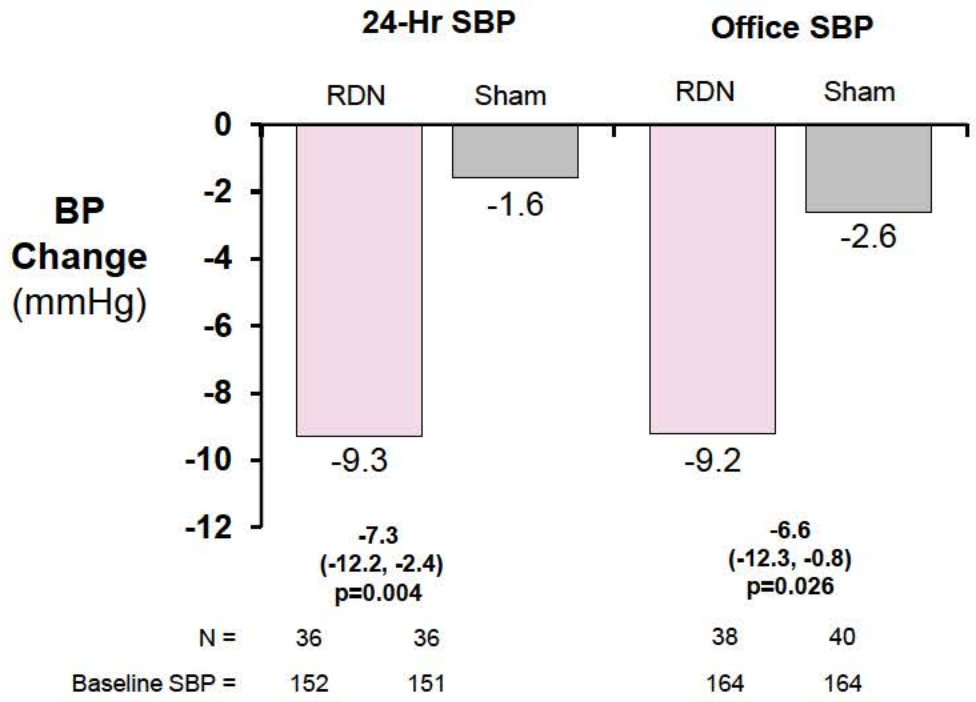
Figure 32: ON MED 24-Hour and Office SBP Changes at 6-Months Post-Procedure in the Denervation and Sham Groups (Pilot Cohort, ITT Population)



BP: blood pressure; RDN: renal denervation; SBP: systolic blood pressure

5.2.7 ON MED Full Cohort Efficacy Results

Results below are presented for the Full Cohort, which includes patients from both the Pilot and Expansion cohorts.

5.2.7.1 Primary Efficacy Endpoint

The primary Bayesian efficacy endpoint, defined as the baseline-adjusted change (using ANCOVA) in SBP from baseline (Screening Visit 2) to 6-months post-procedure as measured by 24-hour ABPM, was not met due to a larger than expected Sham group 24-hour SBP reduction and a lower than expected RDN group 24-hour SBP reduction. The difference between the Denervation and Sham groups was −0.030 mmHg (Bayesian 95% credible interval: −2.82, 2.77). A Bayesian power prior approach, in conjunction with a discount function was used to incorporate prior data. The discount function reduces the strength of the prior data if disagreements are observed with the current data. For the Bayesian analyses that utilized both pilot and expansion, approximately 80% of the pilot Denervation BP data and all of the pilot Sham BP data were excluded from the primary efficacy endpoint analysis (see Section 5.2.1.7.4) due to dissimilarity in 24-hour SBP results between the Pilot and Expansion cohorts.

5.2.7.2 Secondary Efficacy Endpoints

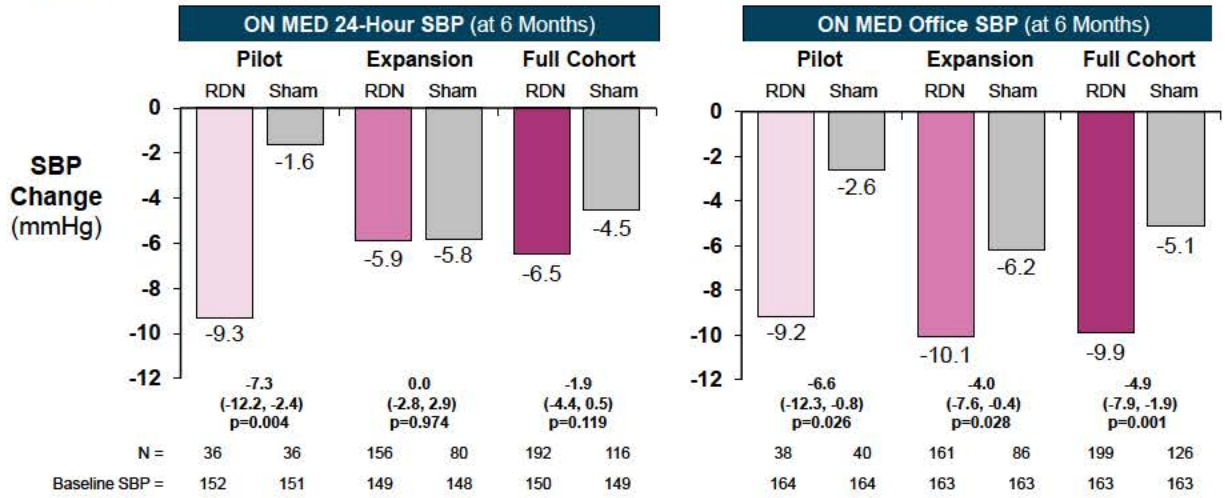
Secondary analyses were performed using frequentist ANCOVA methods which included all data from the Pilot and Expansion cohorts (unlike the primary endpoint which excluded most pilot data based on the Bayesian approach).

5.2.7.2.1 6-month Change in Office BP and 24-hour BP

At the 6-month follow-up, statistically significant changes from baseline between treatment groups were observed in the office SBP (ANCOVA Difference −4.9 mmHg; p = 0.002; Figure 33) and office DBP (ANCOVA Difference −2.0 mmHg; p = 0.04).

Changes in 24-hour SBP (ANCOVA Difference −1.9 mmHg, p = 0.119) and 24-hour DBP (ANCOVA Difference −0.8 mmHg, p = 0.369) were numerically greater in the Denervation group compared to the Sham group although these changes did not reach statistical significance (Figure 33).

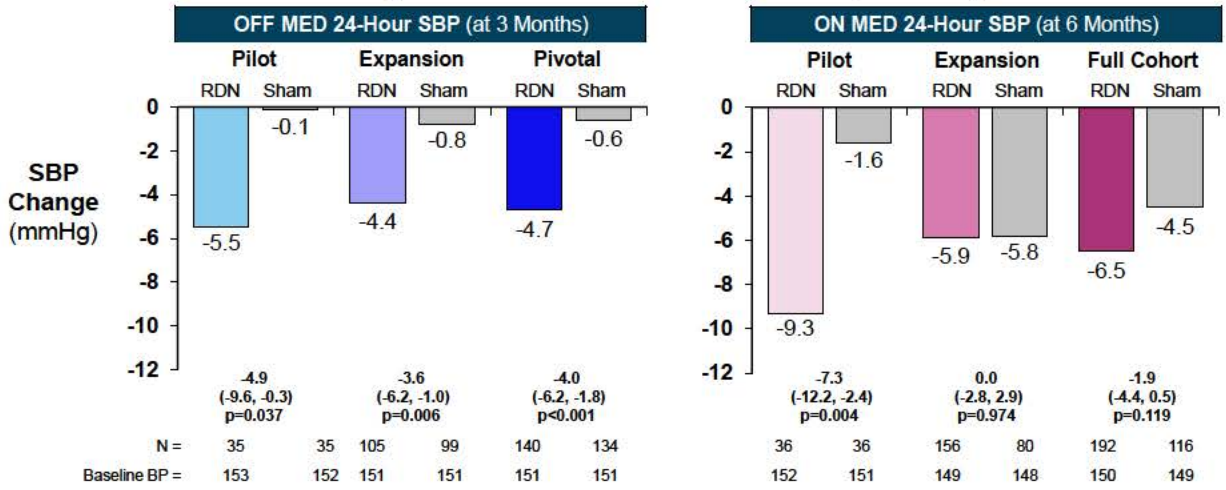
Figure 33: ON MED Study Changes in 24-Hour and Office SBP through 6-Months using Frequentist ANCOVA Analyses Adjusting for Baseline Blood Pressure (Pilot, Expansion, and Full Cohorts, ITT Population)



ANCOVA: analysis of covariance; ITT: intent-to-treat; RDN: renal denervation; SBP: systolic blood pressure

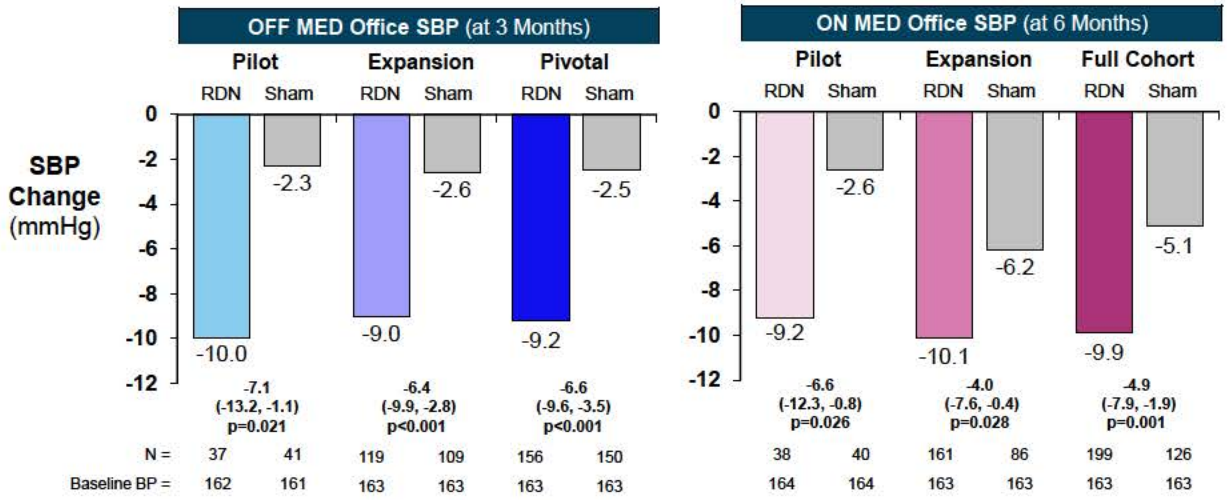
Looking at these results in contrast with the OFF MED Pivotal results, similar BP reductions are observed for the Denervation groups, while the Sham group results are markedly different between OFF and ON MED (Figure 34 and Figure 35).

Figure 34: OFF MED and ON MED Study Blood Pressure Reductions: Change from Baseline in 24-Hour Systolic Blood Pressure (ITT Population)



BP: blood pressure; RDN: renal denervation; SBP: systolic blood pressure

Figure 35: OFF MED and ON MED Study Blood Pressure Reductions: Change from Baseline in Office Systolic Blood Pressure (ITT Population)

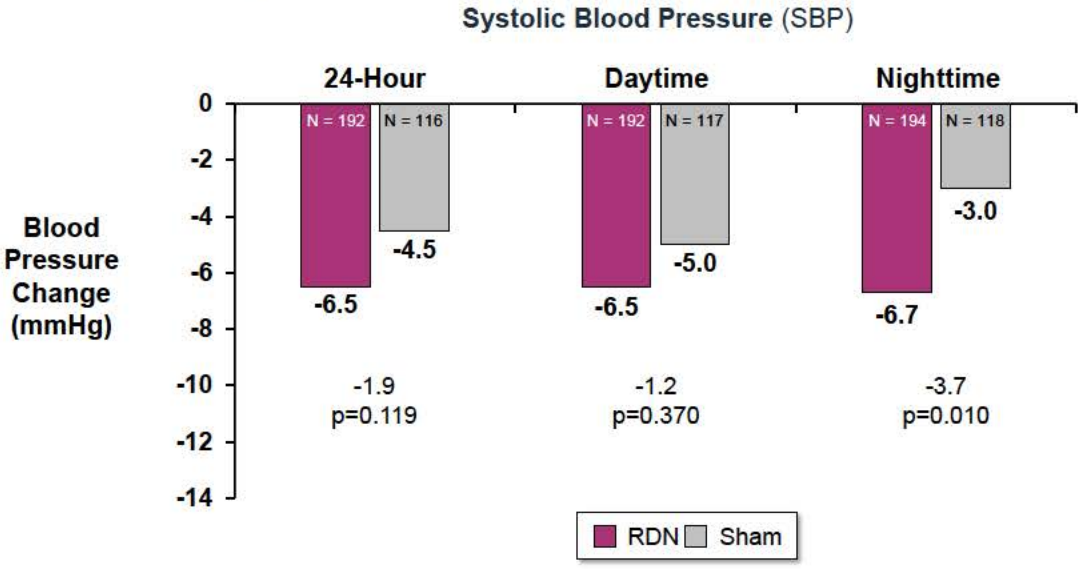


BP: blood pressure; RDN: renal denervation; SBP: systolic blood pressure

5.2.7.2.2 Daytime and Nighttime SBP at 6 Months

Results of the daytime and nighttime components of 24-hour SBP were discordant. The reduction in daytime SBP was similar between groups (−6.5 mmHg for Denervation group and −5.0 mmHg for Sham group; p = 0.370; Figure 36). However, nighttime SBP reductions were significantly greater in the Denervation vs Sham group with reductions of 6.7 and 3.0 mmHg, respectively (between-group difference of −3.7 mmHg, p = 0.010)

Figure 36: ON MED Study Change in Daytime and Nighttime Systolic Blood Pressure at 6-Months (Full Cohort, ITT Population)



ANCOVA: analysis of covariance; RDN: renal denervation
p-values are ANCOVA adjusted; Daytime = 7am to 10pm; Nighttime = 10pm to 7am

5.2.7.3 Escape

Anti-hypertensive medication changes were not permitted per protocol through the 6-month follow-up visit unless escape criteria were met (Office SBP ≥ 180 mmHg or < 115 mmHg associated with symptoms of hypotension or safety concern requiring medication changes). Patients who met escape criteria were evaluated using LOCF (where available).

Denervation patients experienced a lower rate of escape (5.8%) compared to those in the Sham group (9.9%; Table 22). A total of 25 randomized patients met escape criteria for SBP ≥ 180 mmHg (n = 9) or a safety concern (n = 16), and no patients escaped due to office SBP < 115 associated with symptoms of hypotension.

Table 22: ON MED Study Patients Meeting Escape Criteria (Full Cohort)

	Denervation N=206 n (%)	Sham N=131 n (%)
Total Escapes	12 (5.8%)	13 (9.9%)
Safety Concern[1]	8 (3.9%)	8 (6.1%)
SBP ≥ 180 mmHg	4 (1.9%)	5 (3.8%)

SBP: systolic blood pressure
[1]Safety concern escape reasons were not protocol defined and were assessed by the site Investigator. Safety concern escape reasons were variable.

5.2.7.4 Prescribed Medication

From baseline to 6-months, there was a small increase in number of medications prescribed in the Denervation group, which started at an average of 1.91 and had an average of 1.95 medications at 6 months. The number of medications prescribed with the Sham group increased from a baseline average of 1.94 to an average of 2.08 anti-hypertensive medications; the difference in changes between groups was statistically significant (0.02 vs 0.14, ANCOVA Difference −0.12; p = 0.0085).

5.2.7.5 Medication Adherence

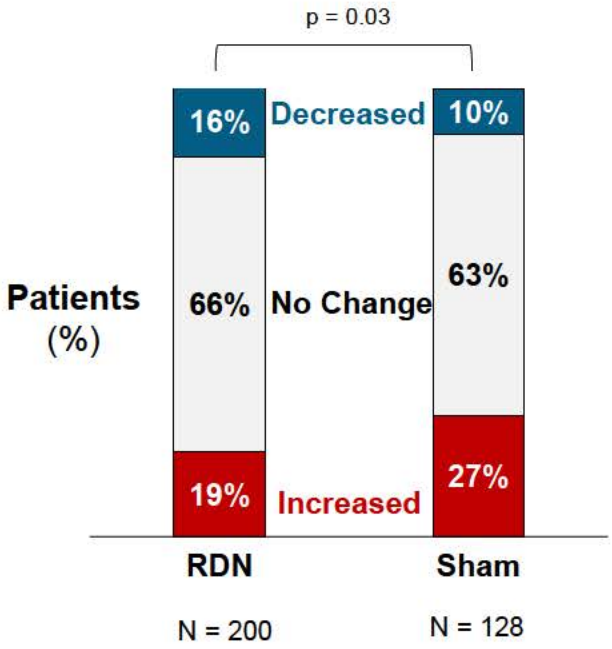
At each of the timepoints assessed, approximately 30% of patients were not adherent with their prescribed medication regimen. Adherence by individuals in both groups was dynamic at different time points during follow up with only 47.5% (160/337) of total patients adherent to their baseline medications per drug testing at baseline, 3 months and 6 months.

At 6 months, there were significant (p=0.03) differences in medication adherence between Denervation and Sham groups. 19% of patients in the Denervation group had an increase in medication burden from baseline compared with 27% in the Sham group (Figure 37). At the same time a greater proportion of patients in the Denervation group had reduced medication burden from baseline than in the Sham group (16% vs 10%) which favored a BP reduction in the Sham group.

5.2.7.5.1 Medication Adherence Analyses

Subjects fully adherent with their medication regimen in OFF and ON MED studies are summarized below. The OFF MED Pivotal compliant subgroup is defined as subjects on no antihypertensive medications at baseline and 3M follow-up by drug testing and the ON MED compliant subgroup is defined as subjects with definite antihypertensive compliance assessed by drug testing at both baseline and 6 months. The p-values shown are ANCOVA adjusted.

Figure 37: ON MED Study Medication Changes Detected by Drug Testing from Baseline to 6-Months (Full Cohort)

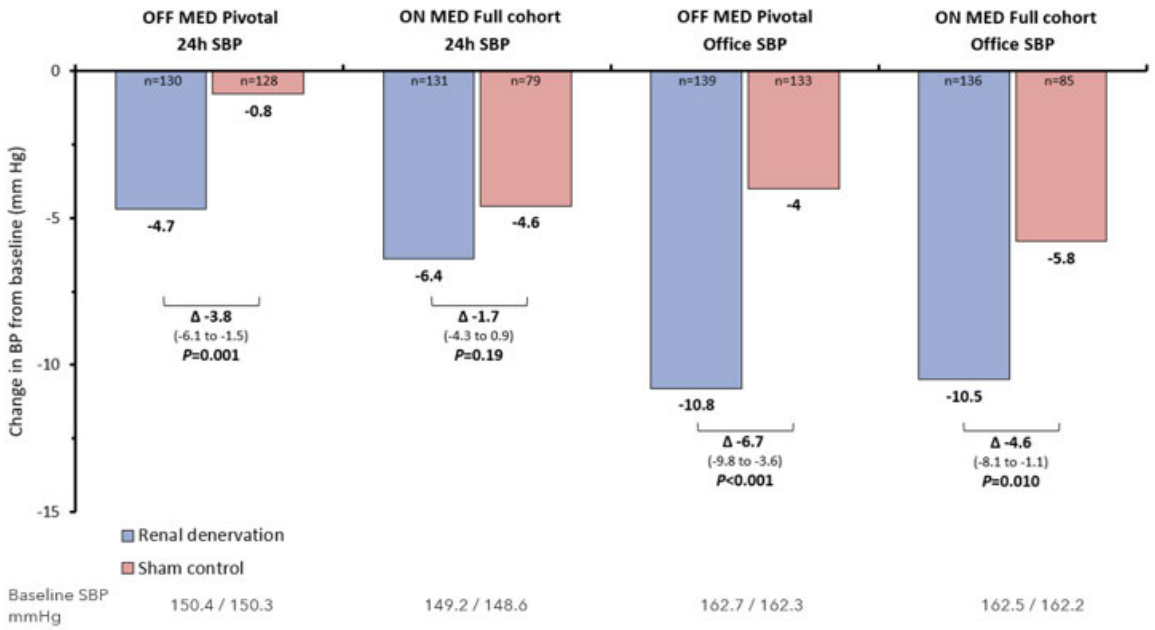


RDN: renal denervation

5.2.7.5.2 Medication Adherence Analyses

Data from subjects fully adherent with their medication regimen in OFF and ON MED studies are summarized in Figure 38. The OFF MED Pivotal compliant subgroup is defined as subjects on no anti-hypertensive medications at baseline and 3-month follow-up by drug testing and the ON MED compliant subgroup is defined as subjects with definite anti-hypertensive compliance assessed by drug testing at both baseline and 6 months. The p-values shown are ANCOVA adjusted. This analysis of the ON MED Full Cohort did not adjust for the greater proportion of sham control patients in the expansion phase who increased their antihypertensive medications, and conversely a greater proportion of RDN patients who decreased medications, nor the greater number of patients in the Sham group meeting 'escape' criteria, missing their 24-hour SBP data and not having the recommended SBP obtained prior to medication increases. These disparities bias toward a null result and are described in Section 5.2.7.6.

Figure 38: 3-Month OFF MED Pivotal Office BP and 24-Hour Reductions for Compliant Subgroup. 6-Month ON MED Full Cohort office BP and 24-Hour Reductions for Med Compliant Subgroup



P-values are ANCOVA adjusted

ANCOVA: analysis of covariance; BP: blood pressure; SBP: systolic blood pressure

5.2.7.6 ON MED Comparison of Pilot and Expansion Cohort Results

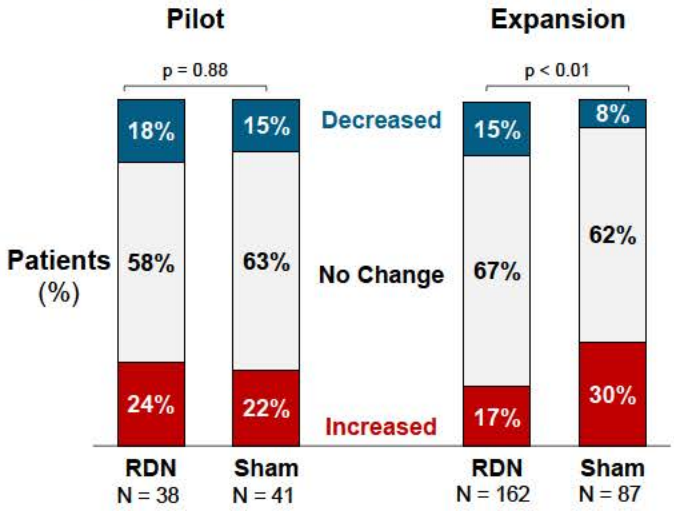
As described in Section 5.2.7.1, in the primary endpoint Bayesian analysis, Pilot 24-hour SBP data were discounted based on the level of discordance with Expansion 24-hour SBP data which resulted in approximately 80% of the Pilot Denervation and all of the Pilot Sham groups being excluded from the analysis. This indicated a high degree of discordance between these two cohorts.

The difference in medication utilization, as determined by drug testing, was more pronounced in the Expansion cohort than in the Pilot cohort. Figure 39 shows changes in medication burden in the Denervation and Sham groups. In the Pilot cohort, these were relatively balanced with the Denervation group having 24% of patients with an increase in medication burden vs. 22% in the Sham group, and 18% of patients in the Denervation group with a decrease in medication burden vs 15% in the Sham group. Furthermore, the denervation group showed greater BP reductions than the Sham group at 6-months.

A different pattern in medication burden emerges in the Expansion cohort (Figure 39). The Denervation group and Sham groups had different changes in medication burden at

6 months. In the Denervation group, 17% of patients had an increase in medication burden vs. 30% in the Sham group, and 15% of patients in the Denervation group had a decrease in medication burden vs 8% in the Sham group. The change observed in medication burden between groups was highly significant and in favor of BP reduction in the Sham group and a lower than expected SBP reduction in the RDN group.

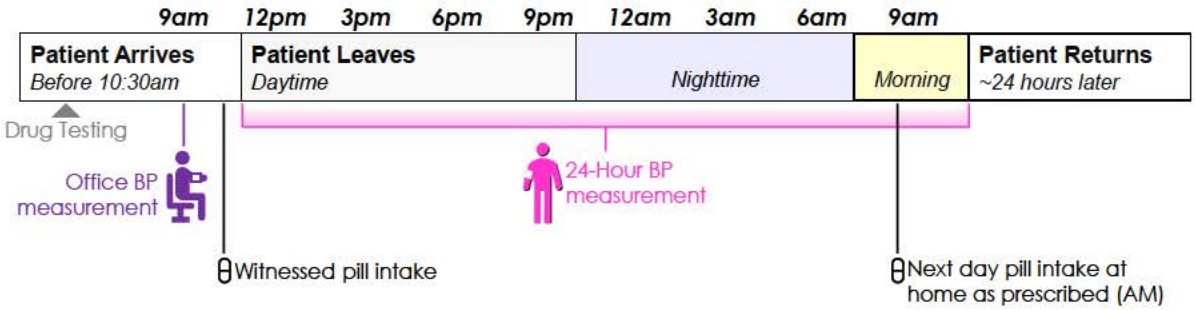
Figure 39: ON MED Medication Changes Detected by Drug Testing from Baseline to 6-Months (Pilot vs. Expansion Cohorts)



RDN: renal denervation; SBP: systolic blood pressure

The differences in medication burden between Denervation and Sham groups across the Pilot and Expansion cohorts likely exacerbated the different patterns in BP changes measured using 24-hour SBP compared to Office SBP. Based on the procedure for collection of 24-hour BP, patients took anti-hypertensive medications twice during a specific 24-hour period (Figure 40). Patients were scheduled to arrive for their appointment before 10:30 am on the morning of the study visit, with instructions to avoid activities and compounds impacting BP (e.g., exercise, coffee, nicotine) and to bring but not take their anti-hypertensive medications the morning of the visit. Upon arrival, they provided their first morning urine (which may have been collected at home) and had labs drawn for anti-hypertensive drug analysis. At this time, patients would also complete the office BP measurement process following protocol required measurement criteria. Patients were then instructed to ingest their medications as witnessed by blinded site personnel and initiate the 24-hour BP measurement. The patient continued to wear the ABPM device overnight and resumed their usual anti-hypertension medication regimen the following morning, before returning to the office to return the ambulatory BP measurement device.

Figure 40: Timing of Office and ABPM Assessments



ABPM: ambulatory blood pressure monitoring; BP: blood pressure

Taking anti-hypertensive medications twice within the 24-hour BP assessment should not produce a disproportionate response if the prescribed medications and medication changes were similar and balanced between the Denervation and Sham groups (as seen in the Pilot cohort) but can doubly confound the 24-hour BP results within the 24-hour period when the medication changes disproportionally favor the Sham group (as seen in the Expansion cohort). These greater increases in medication burden in the Expansion Sham group (beyond those who qualified for escape) introduced bias to both 24-hour and office SBP to null, with greater null bias for 24-hour SBP due to the timing of witnessed pill intake. Post hoc analyses evaluating noon to 6 am timeframe which limits the impact of a second potential pill showed no difference between 2 groups with ANCOVA difference of −1.9 mm Hg for overall ITT cohort. Following the peak effect, the impact of medications starts to wane, the night-time (10 pm to 7 am) time-frame is likely less impacted by the medications and shows significant treatment difference of −3.7 mm Hg in favor of RDN for the ITT cohort highlighting the impact of medication changes on the overall ITT cohort (Table 23).

Table 23: ON MED Full Cohort 24-Hour SBP noon – 6 am and Nighttime (10 pm – 7 am) (ITT Population)

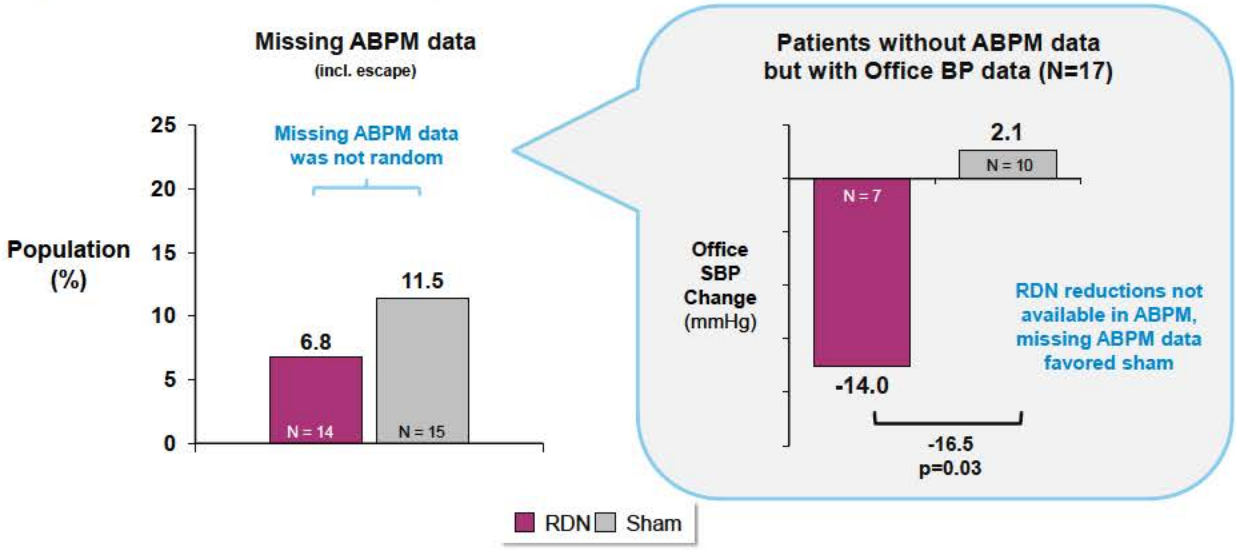
ON MED - ITT Population	RDN	CONTROL	ANCOVA DIFFERENCE (Baseline to 6M)	ANCOVA P-VALUE
Average SBP noon to 6am	-6.4 ± 11.4 (N=192)	-4.4 ± 11.1 (N=116)	-1.9 (-4.5, 0.6)	0.1373
Average SBP 10pm-7am (Nighttime)	-6.7 ± 12.3 (N=194)	-3.0 ± 12.6 (N=118)	-3.7 (-6.5, -0.9)	0.0095

ANCOVA: analysis of covariance; RDN: renal denervation; SBP: systolic blood pressure

Another confounding factor is related to missing data for the primary analysis. Subjects are excluded from the primary analysis ITT population if they do not have an evaluable 6-month ABPM. Reasons for non-evaluable 6-month ABPM include escape with no

LOCF (n = 10), visit not complete (n = 10), invalid number of ABPM readings per protocol (n = 7), visit completed outside the analysis window (n = 1). One additional subject was excluded from the primary efficacy endpoint analysis ITT population due to an invalid number of ABPM readings at Screening Visit 2. Measurements of 24-hour SBP at 6 months were missing for 6.8% (14/206) of patients in the Denervation group and 11.5% (15/131) of patients in the Sham group. For those patients with missing 24-hour BP, but who had office SBP data available at this timepoint, there was a significant difference in the Office SBP reduction; the corresponding office SBP data showed an increase of 2.1 mmHg for the Sham group and a reduction of −14 mmHg for the Denervation group (−16.5 mmHg between-group difference, p = 0.03) as shown in Figure 41. These data show that the missingness was not random between groups, absence of these ABPM readings biases the primary endpoint to the null.

Figure 41: ON MED Missing Data

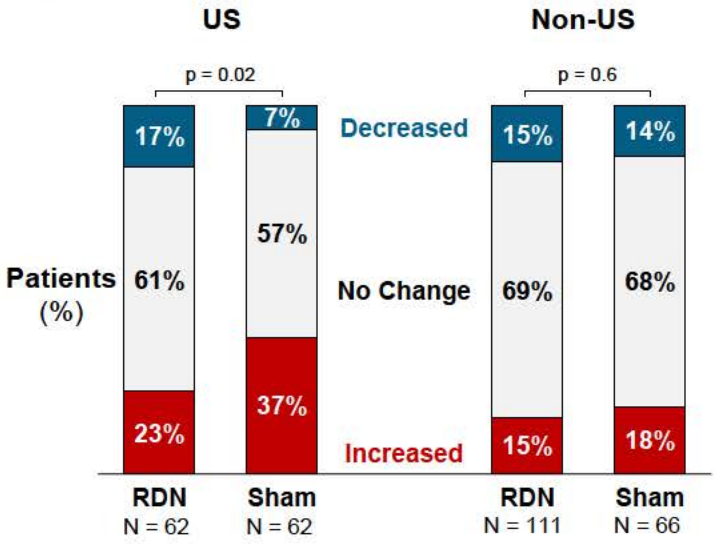


ABPM: ambulatory blood pressure monitoring; BP: blood pressure; RDN: renal denervation; SBP: systolic blood pressure

Looking at a per protocol or other analysis to address the confounding of medication changes would reduce the population by half, removing a disproportionate number of Denervation patients with BP decrease and Sham patients with increasing BP. A more appropriate way to understand the expected BP reductions without imbalances in medication burden is to look at subgroups with consistent medication burden changes across Denervation and Sham.

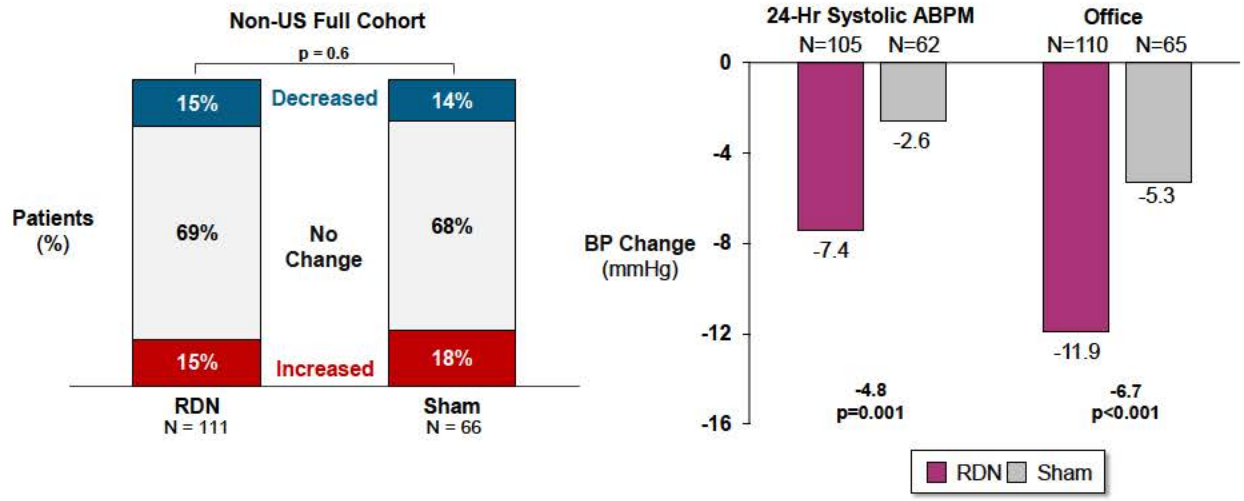
Outside the US, medication changes were similar in both groups (see Figure 42), which led to a statistically significant 6 months 24-hour SBP treatment difference of −4.8 mmHg in favor of Denervation over Sham (Figure 43). These results illustrate the potential impact of medication differences on the ON MED study results.

Figure 42: ON MED Comparison of US and Non-US Medication Changes Detected by Drug Testing from Baseline to 6 Months



RDN: renal denervation; US: United States

Figure 43: ON MED Study Non-US Subgroup: Medication Changes from Baseline to 6 Months and Change in SBP



ABPM: ambulatory blood pressure monitoring; BP: blood pressure; RDN: renal denervation; SBP: systolic blood pressure; US: United States

5.2.7.7 *Poolability*

Analyses were performed to evaluate the poolability of data from different groups. If the resulting tests were significant at the 0.15 level, further exploratory analyses were conducted to identify covariates that may explain these differences.

There was a significant interaction observed between sites within the US and Non-US on the primary effectiveness endpoint poolability (p = 0.011; Table 24).

Table 24: ON MED Efficacy Poolability Analysis - US vs Non-US

Predictors of 24-hour SBP Change at 6-Months	P-Value
Baseline 24-hour SBP (mmHg)	0.010
Treatment Arm (Denervation vs Sham)	0.173
US/Non-US	0.545
Treatment Arm X US/Non-US Interaction	0.011

SBP: systolic blood pressure; US: United States
Statistical interaction significant at 0.15

As previously described and shown in Figure 42, medication burden differences, based on urine and blood analysis, between patients in the US and Non-US likely account for the resulting difference in 24-hour SBP changes. This imbalance disproportionately impacted Sham patients within the US and thus, contributed to the differences observed, as demonstrated by the significant poolability interaction, in the 24-hour SBP BP outcomes between the US and Non-US populations. Despite the differences in medication burden, baseline demographics and characteristics were similar between patients from the US and outside the US indicating that the data from outside the US remain relevant to the US population. Of note, the OFF MED Study, which did not have significant confounding due to medication differences between groups, showed no difference in efficacy by geographic region.

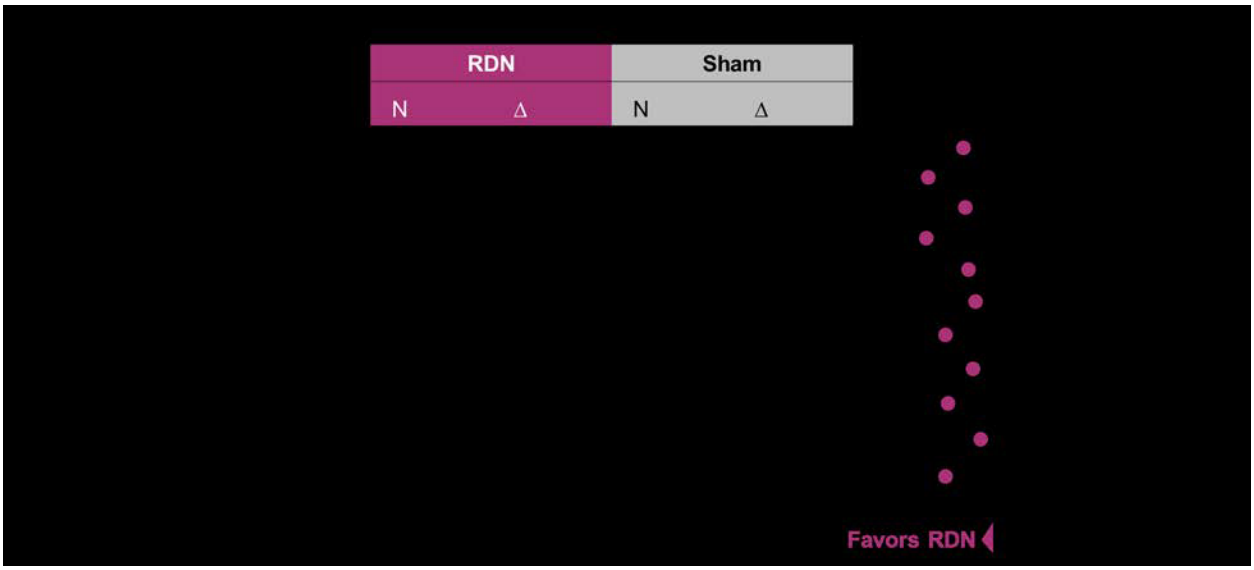
5.2.7.8 *Subgroup Efficacy Analyses*

No significant differences were observed among any subgroups for 24-hour SBP (Figure 44) or office SBP (Figure 45), with the exception of geographic region, which were also clearly observed in the prespecified test for poolability described above in Section 5.2.7.7.

Figure 44: ON MED Change in 24-Hour SBP Subgroup Analysis (ITT Population)

ANCOVA: analysis of covariance; CI: confidence interval; RDN: renal denervation; SBP: systolic blood pressure
US: United States

Figure 45: ON MED Change in Office SBP Subgroup Analysis (ITT Population)



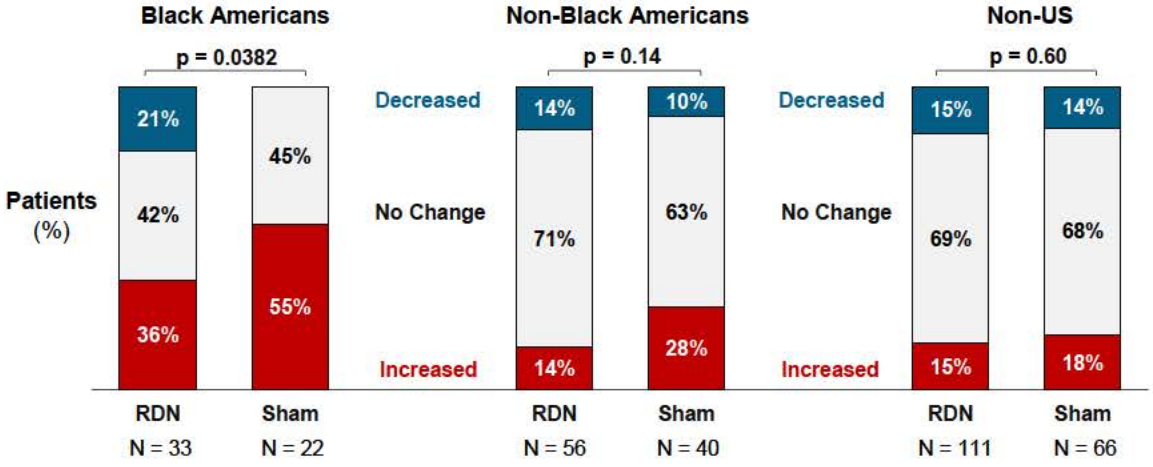
ANCOVA: analysis of covariance; CI: confidence interval; OSBP: office systolic blood pressure; RDN: renal denervation; SBP: systolic blood pressure; US: United States

While not statistically significant, the sham-adjusted treatment difference in Black American (24-Hour = 5.4 (−3.4, 14.1); Office = −3.4 (−12.5, 5.7)) patients was less than that of Non-Black American patients (24-Hour = −0.2 (−4.8, 4.3); Office = −2.4 (−8.0,

3.1)) and other subgroups (see Figure 44). The sham-adjusted treatment difference in US patients (24-Hour = 1.5 (−2.5, 5.6); Office = −2.7 (−7.4, 2.1)) was less than that of Non-US patients (24-Hour = −4.8 (−7.6, −2.0); Office = −6.7 (−10.5, −2.8)) (see Figure 45).

Changes in medication burden, shown in Figure 46, follow the same pattern observed in the comparisons of Pilot vs Expansion and US vs Non-US, where the medication burden in the Black American Sham group was notably increased over the 6-month primary evaluation period. This medication burden difference is useful in interpreting the observed BP reductions for the different subgroups. Note that the study was not powered to detect differences between subgroups.

Figure 46: ON MED Change in Medications Detected by Drug Testing from Baseline to 6 Months; Subgroup Analyses for Black Americans, Non-Black Americans, and Non-US Patients



RDN: renal denervation; US: United States

5.2.7.9 Win Ratio

As a method to consider the combined impact of reduction in BP and reduction in medication use, win ratio analysis enables evaluation of clinical benefit based on multiple clinically relevant variables in a hierarchical composite endpoint. This method has been widely applied in clinical research (Pocock et al 2012; Redfors et al 2020). Win Ratio analyses were applied to include the medication changes and BP since 24-hour SBP reduction and medication reduction are both important to patients and clinicians.

In the win ratio analysis, 26,986 pairs (206 Denervation × 131 Sham) were constructed, each consisting of 1 Denervation and 1 Sham patient. The primary win ratio analysis used a threshold of 5 mmHg for the 24-hour SBP component and a threshold of 0 for the medication burden component based on drug testing. Every Denervation/Sham subject pair is analyzed as follows:

a) For every pair:

   i. Calculate the change in the first endpoint (24-hour SBP) from screening visit 2 to 6-months for the Denervation subject (ΔRDN) and the Sham control subject (ΔCON)

   ii. Calculate the pairwise treatment effect for the pair: ΔP=ΔRDN -ΔCON

   iii. Compare ΔP to the specified threshold (5 mmHg)

   iv. If the Denervation subject has a better outcome compared to control subject using this threshold (ΔP ≤ -5) then this results in a "win" for the Denervation subject. Stop analyzing this pair and move on to the next

   v. if the Sham control subject has a better outcome compared to the Denervation subject (ΔP ≥ +5) then this results in a "loss" for the RDN subject. We stop analyzing this pair and move on to the next

   vi. if the pairwise treatment effect is smaller than the threshold (-5 < ΔP < +5) or if either subject has missing data, then this pair results in a "tie"

b) Only pairs classified as ties for the first endpoint (24-hour SBP) proceed to the second hierarchical endpoint of medication burden change and we repeat step a) above using their medication burden change data and a threshold of zero.

After every pair has been analyzed, the win ratio statistic is calculated as the total number of wins divided by the total number of losses from both endpoints.

The win ratio was 1.49 (95% CI: 1.13 to 2.00; p = 0.005) in favor of denervation (Table 25). This win ratio represents a 1.49 × greater likelihood of reducing blood pressure or medication with renal denervation therapy than with sham treatment.

Table 25: ON MED Study Win Ratio Analysis at 6 Month Timepoint (Full Cohort)

N= 206 × 131 = 26,986 pairs	Threshold	% Pairs Win	% Pairs Lose	% Pairs Tied	WR	WR 95%CI	P-Value
1. Δ 24-hour SBP	5.0	34.8%	25.8%	39.4%			
2. Δ Medication Burden	0.0	13.2%	6.5%	19.7%	1.49	[1.13, 2.00]	0.005

CI: confidence interval; SBP: systolic blood pressure; WR: win ratio
Medication Burden Calculated based on Medication Index 2, using drug testing data, which is a composite index based on the class numbers and doses of medication (see Appendix 4: Medication Burden Analysis Method)

5.2.7.10 Time in Target Range

Target ranges of office SBP ≤ 140 mmHg, 24-hour BSP ≤ 130 mmHg, and office SBP ≤ 140 mmHg or ABSP ≤ 130 mmHg were used to calculate TTR through 6 months and are shown in Table 26. The Denervation group spent significantly more time in the target SBP range using the target ranges of office SBP ≤ 140 mmHg and office

SBP ≤ 140 mmHg or ABSP ≤ 130 mmHg compared to the Sham group at 3 and 6 months.

Table 26: Percent Time in Target Range (%TTR) – ON MED Full Cohort

	Denervation % ± SD (N)	Sham % ± SD (N)	p-value
OFFICE SBP TTR% (≤140 mmHg)[1]			
TTR 0-3 months	11.8 ± 22.6 (206)	5.8 ± 17.7 (128)	0.0004
TTR 0-6 months	13.8 ± 24.7 (206)	5.9 ± 16.5 (129)	0.0001
24hr SBP TTR% (≤130 mmHg)[1]			
TTR 0-3 months	2.6 ± 9.6 (189)	1.4 ± 5.0 (113)	0.8471
TTR 0-6 months	5.8 ± 16.5 (196)	4.0 ± 12.8 (121)	0.3368
COMBINED OFFICE & 24HR TTR[2]			
Max (OSBP-140, ASBP-130) 0-3M	12.5 ± 22.9 (206)	6.8 ± 17.9 (129)	0.0073
Max (OSBP-140, ASBP-130) 0-6M	16.0 ± 26.3 (206)	8.5 ± 19.1 (129)	0.0012

OSBP: office systolic blood pressure; SBP: systolic blood pressure: SD: standard deviation; TTR: time in target range
Data displayed as mean ± SD (N)
[1] Analyses use all non-missing BP data from BL, 1M, 3M, 6M within time ranges
[2] The maximum value of Office TTR and 24-Hour TTR within each time period is used in combined analysis p-values from non-parametric Kruskal-Wallis test
Note that all p-values are not adjusted with multiplicity

5.2.8 ON MED Efficacy Discussion

Although the ON MED trial did not meet its pre-specified primary endpoint for 24-hour SBP, there were several important confounding factors that may have impacted the results. In the absence of disproportionate medication changes between groups, the ON MED Pilot showed a significant 6-month 24-hour SBP treatment difference (see details in Section 5.2.6). 24-hour BP can often be a more accurate representation of patient's average BP throughout the day, but in cases such as in ON MED where there were significant confounding factors such as both imbalanced prescribed and detected medication changes, office BP is equally important. Office BP is established in guidelines as a recommended measure in the management of hypertension, and large randomized controlled trials evaluating long-term CV risk are based on continuous office SBP reductions. The ON MED trial showed a significant treatment difference in the office SBP, despite the confounding medication changes favoring Sham over denervation. Denervation significantly reduced BP from baseline consistently across all SPYRAL HTN trials in the presence and absence of medications. This totality of evidence demonstrates that RDN meets the Panel recommendations to provide a clinically meaningful treatment for patients with uncontrolled hypertension.

5.2.9 ON MED Efficacy Conclusions

The ON MED Full Cohort did not achieve its primary endpoint and was impacted by higher medication burden in the Sham group. Nonetheless, ON MED showed clinically relevant reductions in 24-hour SBP compared to baseline and a statistically significant reduction in office BP and nighttime 24-hour BP compared to baseline as well as to Sham. Win ratio analyses in favor of RDN therapy support the observation that RDN therapy provided effective treatment for hypertension without the necessity of the medication increases observed in the Sham group.

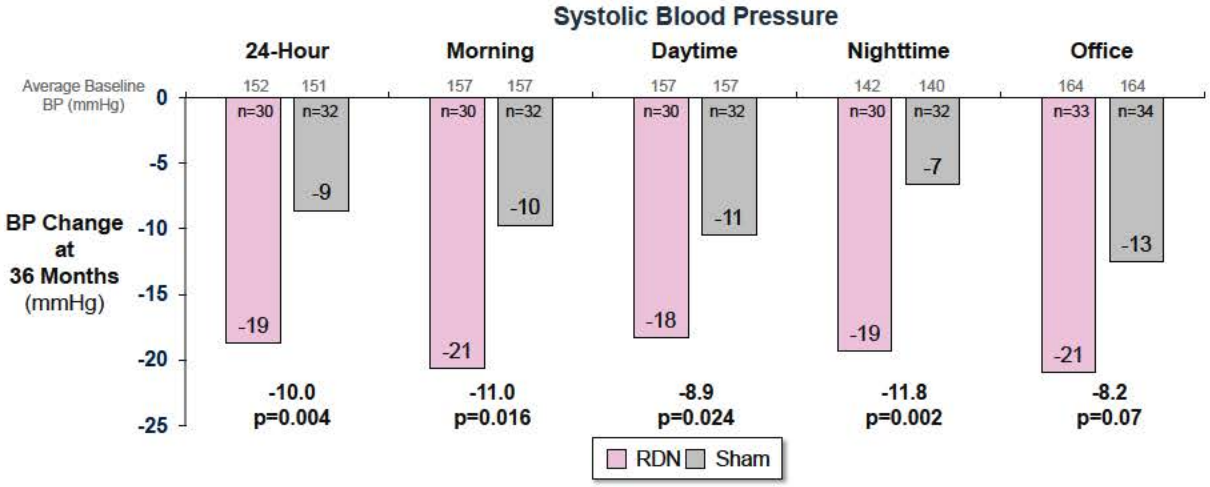
5.3 Durability of Effect

5.3.1 Durability in ON MED and OFF MED

Durability is defined as the long-term sustained drops in BP over time, reduction in anti-hypertensive medication burden, and/or increased time for BP to stay within TTR following RDN. The durability of the Symplicity Spyral System is supported by Medtronic-sponsored studies and independent clinical studies.

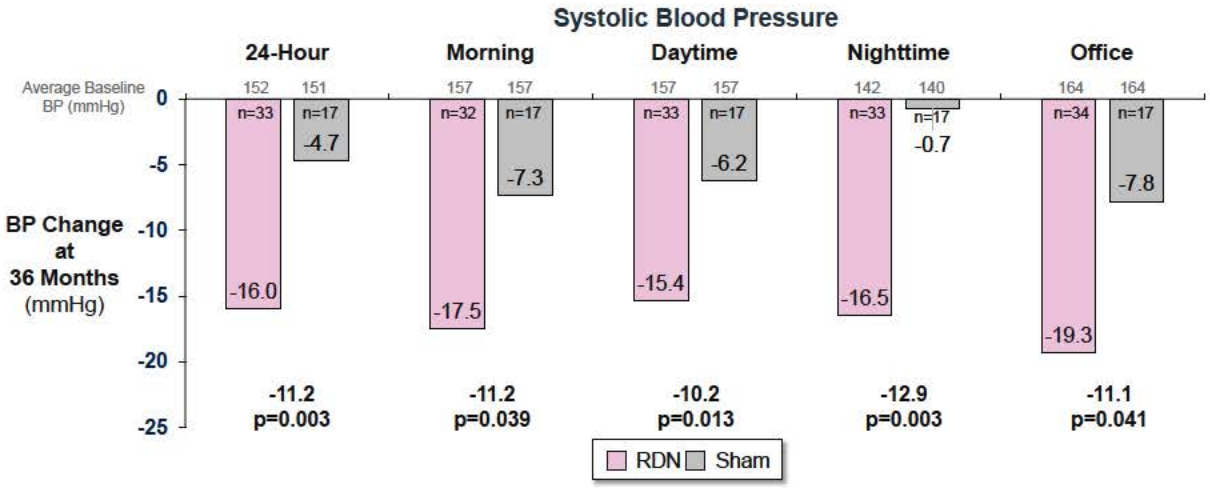
Specifically, statistically significant and clinically meaningful reductions in both office and 24-hour SBP to 36 months in the ON MED Pilot cohort demonstrate durability in patients who are also taking anti-hypertensive medications (Figure 47). For patients in the Sham group who crossed over and received RDN between the 24-month and 36-month follow-up visit, the last observations of BP measurements and medication burden were used to impute their 36-month values. The 24-month data without crossover imputation is consistent with the 36-month data (Figure 48).

Figure 47: ON MED Pilot Cohort – Change in Blood Pressure to 36 Months



BP: blood pressure; RDN: renal denervation

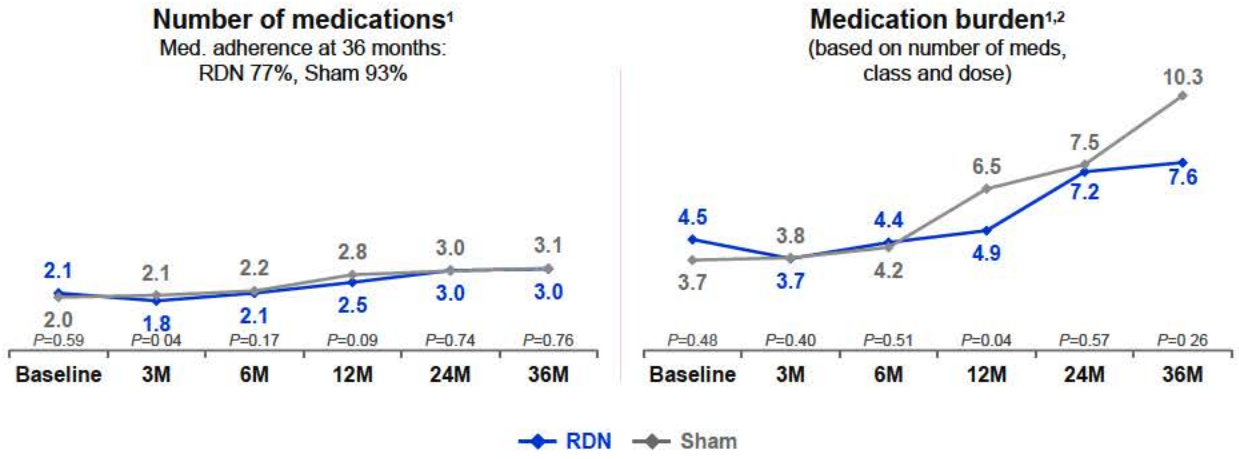
Figure 48: ON MED Pilot Cohort – Change in Blood Pressure to 24 Months



BP: blood pressure; RDN: renal denervation

The durability of effect is assessed using ON MED Pilot medication burden data to 36 months and is presented in Figure 49. The number of medications was similar between Denervation and Sham during long term follow-up. However, when also accounting for number of medications and dosage (med index 2), comparison of medication indices at 12 months found significantly greater anti-hypertensive medication burden for Sham patients at 12 months.

Figure 49: ON MED Pilot-Medication Burden to 36 Months



M: month; RDN: renal denervation

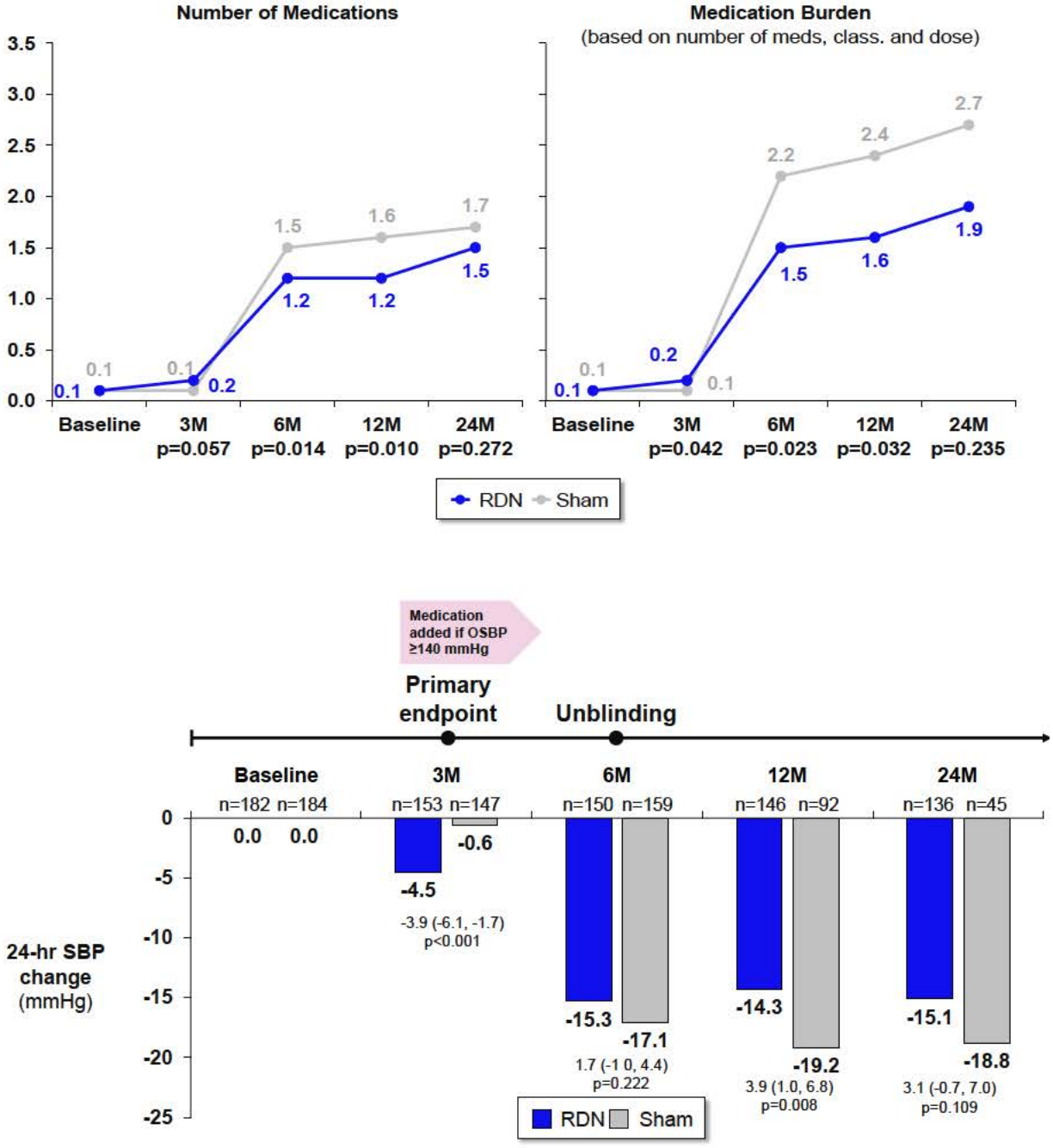
1 Based on available drug testing (blood / urine) and prescribed medications.

2 Medication burden INDEX2 based on number and dosage

P-values are ANCOVA adjusted. For sham control patients who crossed over to RDN before their 3-year follow-up (N=13), the most recent data prior to crossover was imputed.

Although the primary purpose of OFF MED Pivotal was to isolate the effects of RDN therapy without the confounding effects of medication, longer-term follow-up data also support the assessment of the durability of effect on BP control which can be achieved by either a reduction in BP or medication burden. The OFF MED Pivotal cohort demonstrated durability with a significant reduction in medication burden through 24 months in the Denervation group as compared to the Sham group (Figure 50) supporting long-term durability of the RDN.

Figure 50: OFF MED Pivotal – Medication Burden and 24 hour Systolic Blood Pressure to 24 Months



M: month; OSBP: office systolic blood pressure; RDN: renal denervation; SBP: systolic blood pressure
RDN and Sham baseline 24-hour SBP=151 mmHg

5.3.2 Global SYMPLICITY Registry – Additional Clinical Study

5.3.2.1 Overview

The GSR is a prospective, multi-center, single-arm, non-interventional and open label registry. The GSR aims to include a patient population that resembles real-world clinical practice. The primary objective of the registry is to document the long-term safety and effectiveness of RDN in a real-world patient population.

5.3.2.2 Enrolled Patients

A total of 3,077 patients, including 846 patients treated using the Symplicity Spyral catheter have been enrolled in GSR. Prior to availability of the Symplicity Spyral catheter, patients were treated with a single electrode version, the Symplicity Flex catheter. Key characteristics of the Symplicity Spyral patients are presented in Table 27.

For patients treated with the Symplicity Spyral catheter, 6-month follow-up data are available for 724 patients, 12-months follow-up data for 642 patients, 24-months follow-up data for 485 patients and 36 months follow-up data for 328 patients.

In GSR with commercially available product, patient follow up is conducted as a part of routine standard of care. RDN procedures were performed per the commercial (non-US) Instructions for Use which indicate that ablations should occur in all vessels 3-8 mm in size. Physician discretion was utilized for the number and depth of branch vessels treated. Branch treatment was performed in 63.2% of patients. Overall, 100% of patient informed consents and 34% of patient data were monitored.

Table 27: GSR Demographics, Medical History and Risk Factors for Patients Treated with Symplicity Spyral Catheter

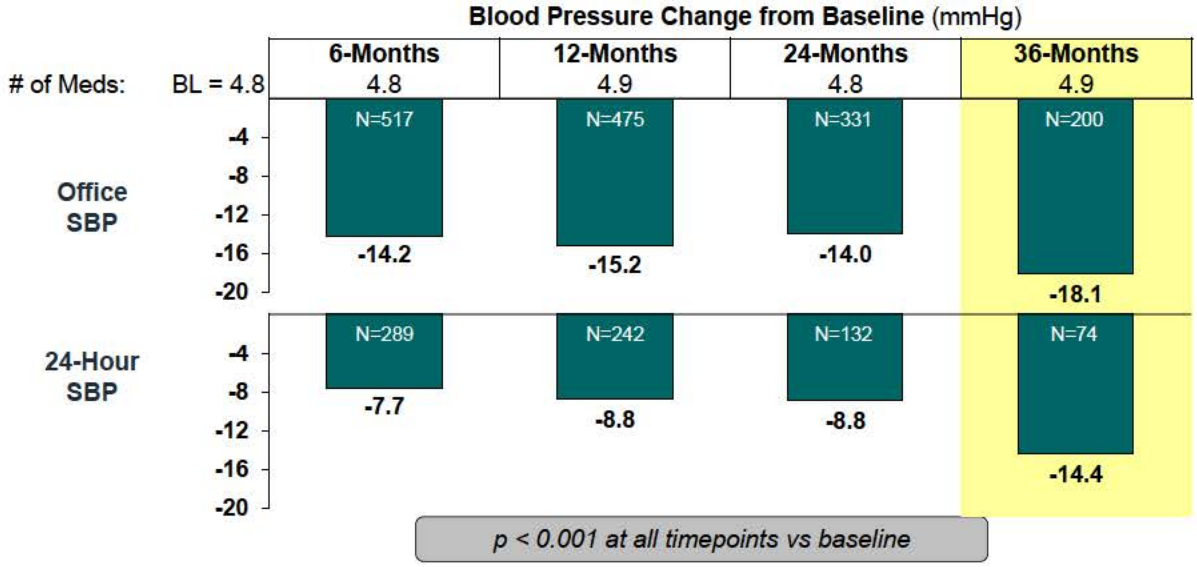
Characteristic	GSR Spyral
Age (Years)	59.59 ± 12.87 (n=846)
Sex (Male)	57.3 % (485/846)
BMI (kg/m^2)	30.93 ± 7.31 (n=838)
Blood pressure (mmHg)	165.83/91.19 ± 24.82/17.44 (n=792)
Heart rate (bpm)	71.46 ± 13.46 (n=761)
Renal insufficiency (eGFR < 60)	20.7% (175/845)
Sleep Apnea	21.3 % (169/795)
History of diabetes mellitus (Type 1 + Type 2) (%)	40.6 % (343/844)
Type 1 Diabetes Mellitus – insulin dependent	2.7% (23/844)
Type 2 Diabetes Mellitus – insulin independent	37.9% (320/844)
Atrial fibrillation	11.1% (93/841)
Hypercholesterolemia (%)	35.5% (299/842)
Smoking, current	11.0% (93/842)

BMI: body mass index; eGFR: estimated glomerular filtration rate; GSR: Global SYMPLICITY Registry

5.3.2.3 Efficacy Results

In patients treated with the Symplicity Spyral catheter, an overall office SBP reduction of 14.23 ± 25.76 mmHg at 6 months was achieved. An overview of the office and 24-hour BP reduction out to 3 years is provided in Figure 51.

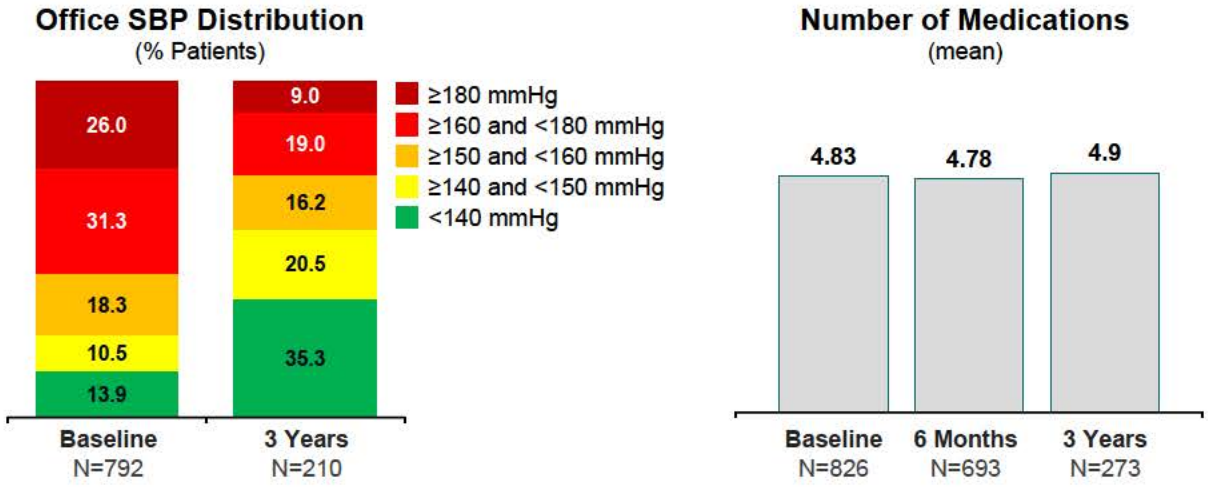
Figure 51: Global SYMPLICITY Registry – Office SBP and 24 hour SBP to 3 years – Spyral Cohort



BL: baseline; SBP: systolic blood pressure

Importantly, these reductions translated into more patients meeting the target range of SBP below 140 mmHg, significantly increasing from 13% at baseline to 35% at 3 years (Figure 52). This improvement cannot be credited to medication changes as the number of medication classes remained constant over the same time period.

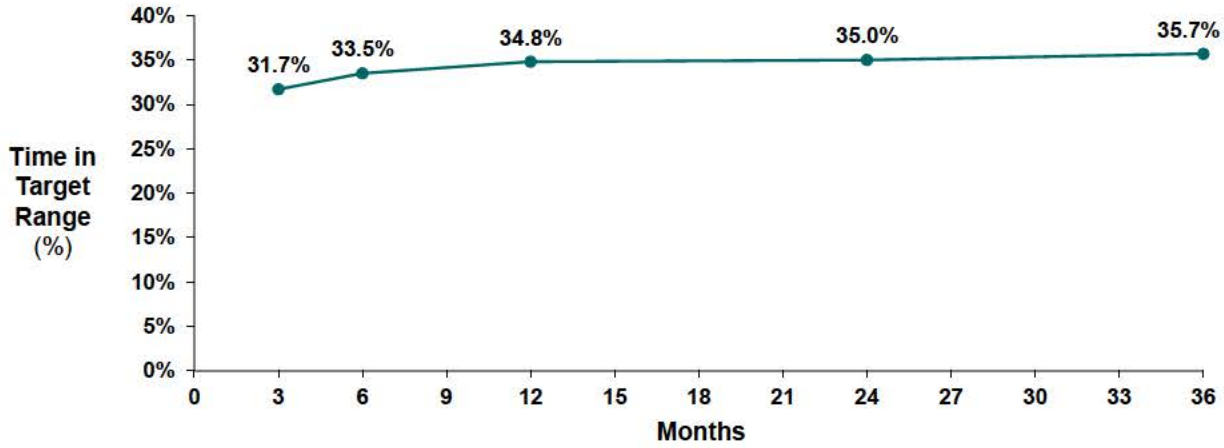
Figure 52: Global SYMPLICITY Registry Distribution of Office SBP and Number of Medications



SBP: systolic blood pressure Includes data from Spyral only

Durability is demonstrated in a real-world setting in the aforementioned Global SYMPLICITY Registry, which showed statistically significant and clinically meaningful reductions in both office and ambulatory SBP and DBP. Estimated TTR also increased with time following RDN therapy (Figure 53).

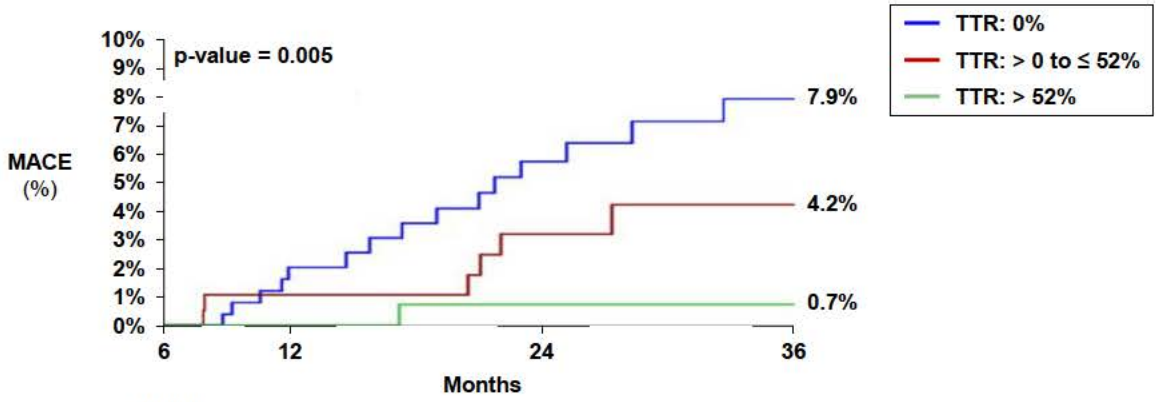
Figure 53: GSR Spyral patients - Time in Target Range to 36 months



ASBP: ambulatory systolic blood pressure; GSR: Global SYMPLICITY Registry; OSBP: office systolic blood pressure; SBP: systolic blood pressure; TTR: time in target range
N=846TTR calculated as target SBP range OSBP ≤ 140 mmHg and/or ASBP ≤ 130 mmHg; includes data from Spyral patients only

Independent studies demonstrate that time spent in SBP target range is an independent predictor of major adverse CV event risk and associated with renal and CV events (Buckley et al 2023; Fatani et al 2021). A TTR analysis was conducted for the GSR population, using the estimated TTR based on data over 6 months. This analysis suggested that even modest increases in TTR are associated with significant risk reductions related to CV events, including stroke. The comparison of TTR and the rate of MACE events using 3-year results from the GSR suggest that reductions in BP after RDN correlate with a significant reduction in AEs, CV death, myocardial infarction, and stroke (Figure 54). The mean number of medications was 4.9 at baseline and 4.8 at 3 years.

Figure 54: GSR Spyral Patients: Relationship Between TTR and Cardiovascular Events



At Risk				
TTR: 0%	266	237	169	95
TTR: > 0 to ≤ 52%	200	172	123	60
TTR: > 52%	195	176	120	64

GSR: Global SYMPLICITY Registry; MACE: major adverse cardiac events; MI: myocardial infarction; TTR: time in target range

It is also important to note that significant reductions in nighttime and early morning ambulatory BP at 24 months and 36 months could translate into clinically important reductions in CV events. If anti-hypertensive medication adherence is low, medical therapy may not provide sustained BP reduction when compared to RDN.

5.3.2.4 Additional Efficacy Results: Symplicity Spyral & Symplicity Flex

The GSR includes subjects treated using both the Symplicity Flex (single electrode) and Symplicity Spyral (multi-electrode) catheters. Office and 24-hour SBP and DBP changes for all GSR subjects are summarized in Table 28 and Table 29 below and show consistent results among the Flex- and Spyral-treated cohorts.

Table 28: GSR Office SBP and DBP from Baseline to 36-months in Subjects Treated with the Spyral and Flex Catheters

	Baseline	Change at 6-months	Change at 12-months	Change at 24-months	Change at 36-months
Spyral Catheter					
Systolic OBP	165.83 ± 24.82 (792)	-14.23 ± 25.76 (517)	-15.18 ± 26.54 (475)	-13.99 ± 27.59 (331)	-18.07 ± 26.76 (200)
Diastolic OBP	91.19 ± 17.44 (792)	-5.52 ± 14.07 (515)	-6.42 ± 14.77 (473)	-7.67 ± 15.06 (326)	-7.79 ± 15.68 (195)
Flex Catheter					
Systolic OBP	165.48 ± 24.81 (2169)	-12.85 ± 26.20 (1691)	-13.68 ± 26.67 (1617)	-15.62 ± 27.52 (1275)	-16.42 ± 28.69 (1068)
Diastolic OBP	89.79 ± 16.51 (2170)	-4.55 ± 14.31 (1686)	-5.12 ± 15.01 (1616)	-6.21 ±16.00 (1273)	-6.13 ± 16.18 (1064)

DBP: diastolic blood pressure; OBP: office blood pressure; SBP: systolic blood pressure

Table 29: GSR Ambulatory SBP and DBP from Baseline to 36-months in Subjects Treated with the Spyral and Flex Catheters

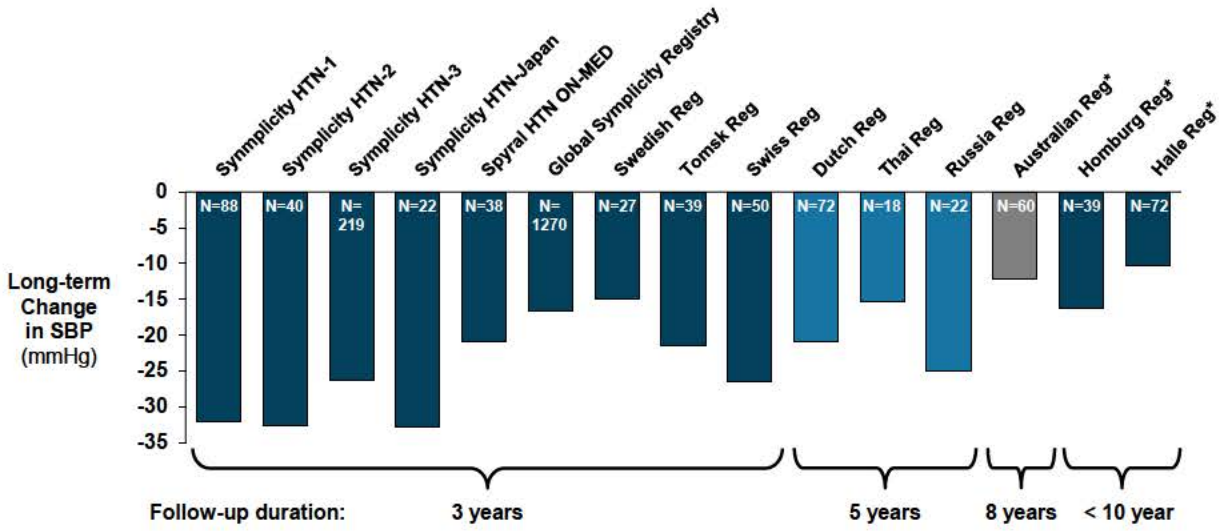
	Baseline	Change at 6-months	Change at 12-months	Change at 24-months	Change at 36-months
Spyral Catheter					
Systolic ABP	155.20 ± 20.10, N=542	-7.69 ± 18.72, N=289	-8.77 ± 18.04, N=242	-8.83 ± 17.96, N=132	-14.39 ± 21.93, N=74
Diastolic ABP	88.10 ± 15.18, N=542	-4.88 ± 10.76, N=289	-4.90 ± 10.62, N=242	-4.42 ± 10.05, N=132	-6.12 ± 12.33, N=74
Flex Catheter					
Systolic ABP	153.99 ± 18.18, N=1554	-7.21 ± 17.76, N=965	-8.06 ± 18.87, N=880	-8.89 ± 19.83, N=609	-8.13 ± 19.83, N=459
Diastolic ABP	86.51 ± 14.17, N=1555	-4.21 ± 10.45, N=966	-4.47 ± 11.66, N=881	-4.88 ± 11.42, N=610	-4.30 ± 12.05, N=460

ABP: ambulatory blood pressure; DBP:

5.3.3 Durability Across Medtronic and Independent Studies - Supplementary

Durability to over nine years has been consistently observed across a range of Sponsor and independent-initiated studies separate from ON and OFF MED, summarized in Figure 55. Appendix 6: Registries Demonstrating RDN Durability provides reference to all non-Medtronic studies listed for durability.

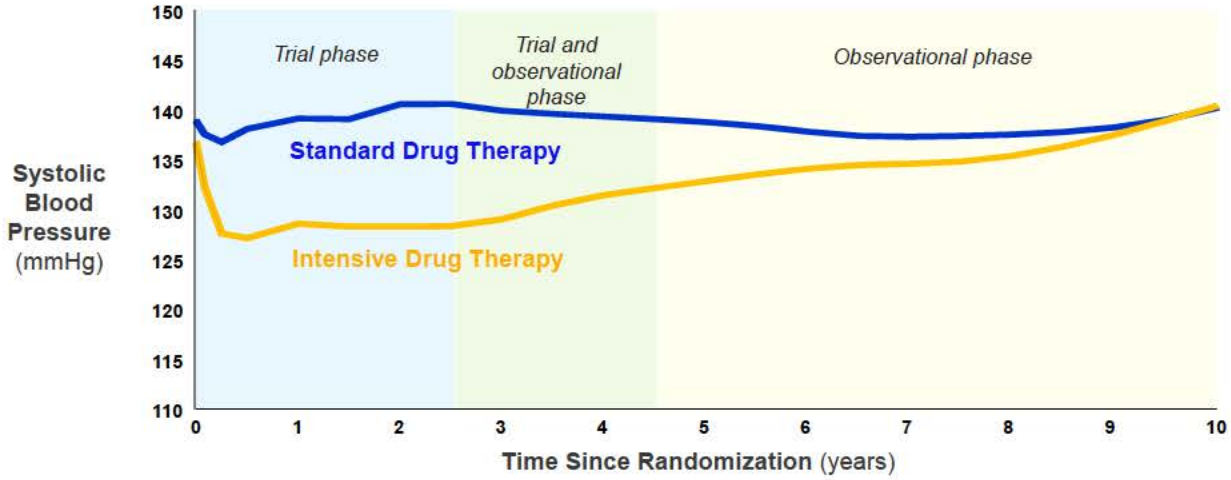
Figure 55: Renal Denervation Studies (Office SBP Durability 3 Year to > 8 Years)



BP: blood pressure; SBP: systolic blood pressure
*24-hour BP
Sources: Al Ghorani et al 2023; Bhatt et al 2022; Esler et al 2014; Ionov et al 2021; Kario et al 2019; Krum et al 2014; Mahfoud et al 2022; Naduvathumuriyil et al 2020; Panchavinnin et al 2022; Pekarskiy et al 2022; Sesa-Ashton et al 2023; Vogt et al 2023; Völz et al 2018; Zeijen et al 2022

These results contrast with the longer-term results recently reported from the SPRINT trial. SPRINT is a multicenter US clinical trial randomizing high-risk hypertensive patient to standard medication treatment or intensive hypertensive treatment. Initial results demonstrated both decreased BP and decreased CV risk in the intensive drug therapy group (Figure 56). However, recently reported long-term follow-up data indicated attenuation of both the BP and outcome benefit within a few years following the conclusion of the study follow-up period. Indeed, the attained mortality benefit experienced by the intensive therapy group was no longer detectable within 5.6 years following randomization. These results imply that the benefits of intensified drug therapy may not persist, and that durable alternatives to polypharmacy are an unmet clinical need.

Figure 56: SPRINT Results: Mean Systolic Blood Pressures by Treatment Group Comparing Trial Measurements With Outpatient Readings From the Electronic Health Record

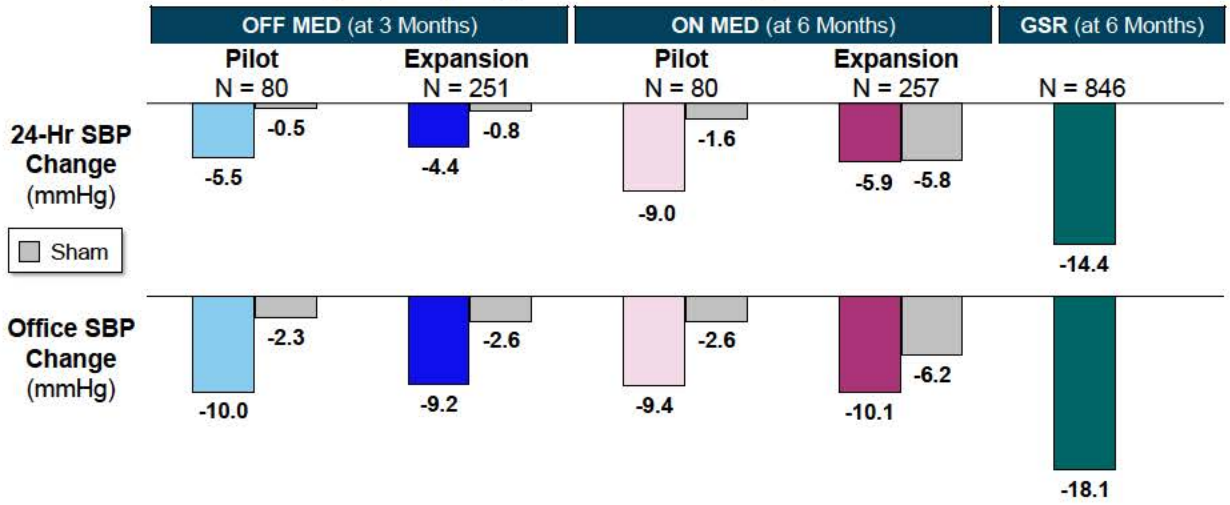


Source: Adapted from Jaeger et al. 2022

5.4 Efficacy Conclusions

Efficacy of the Symplicity Spyral System has been demonstrated in the OFF MED Pivotal and ON MED studies with data evaluating use in both the absence and presence of medications. Statistical significance for absolute BP reduction has been met across the SPYRAL HTN program, but it is also important to consider the clinical significance of the magnitude of BP reduction. Since those discussions in 2018, highly consistent BP responses to RDN were reported, especially in randomized, sham-controlled trials with “off-med” designs. At the HARC meeting in 2020, hypertension experts discussed that a reduction in mean 24-hour ambulatory SBP of ≥ 5 mmHg relative to baseline can be considered a clinically meaningful response to RDN. The proceedings of the 2020 European Clinical Consensus statement for clinical trials in device-based hypertension therapies, considered a 10 mmHg reduction in office SBP or 6–7 mmHg in daytime or 24-hour SBP as clinically meaningful (Mahfoud et al 2020a). The 24-hour SBP reductions in the denervation-treated patients in the ON and OFF MED studies were −6.5 and −4.7 mmHg, at 6 and 3 months, respectively. For office SBP, the ON and OFF MED studies demonstrated a reduction of −9.2 and −9.9 mmHg at 6 and 3 months respectively. As shown in Figure 57, the BP reductions are consistent across the SPYRAL HTN Clinical Program. Results for both office BP and 24-hour SBP are in line with the previously mentioned recommendations.

Figure 57: Absolute Reductions in Office SBP and 24-hr ASBP Following Renal Denervation Across Symplicity Spyral Clinical Program



The between-group difference for the ON MED Full Cohort contrasts with the OFF MED Pivotal results due to the larger than expected BP reduction in the Sham group and a lower than expected BP reduction in the RDN group. This larger than anticipated BP reduction in the ON MED Full Cohort Sham group -may be attributed to confounding factors including, but not limited to: increased medication burden in prescribed medications and more medications detected in the Sham group as well as missing 24 hour SBP in the Sham group, particularly for escape patients.

Efficacy – Nighttime Blood Pressure Reduction

RDN significantly and persistently reduced 24-hour BP including nighttime, providing a more uniform BP control over a 24-hour period, compared to medications that achieve a nadir in the pre-morning period prior to waking due to pharmacokinetics. This is particularly relevant as elevated nighttime BP is associated with increased CV events, including myocardial infarction and stroke (Ben-Dov et al 2007; Dolan et al 2005; Fujiwara et al 2020; Hoshide et al 2021; Kario 2018; Sega et al 2005; Yang et al 2019b).

Efficacy – Comparison to Anti-hypertensive Drug Therapy Alone

Considering the totality of efficacy data available, RF RDN performed with the Symplicity Spyral System provided for improvement in key secondary endpoints across the Medtronic SPYRAL HTN Clinical program as indicated by each of the check marks in Table 30.

Table 30: Overview of Clinically Relevant Secondary Endpoints* in the Medtronic SPYRAL HTN Clinical Program

	OFF MED Pilot (n=80)	OFF MED Pivotal (Pooled) (n=331)	OFF MED Full (n=366)	ON MED Pilot (n=80)	ON MED Pooled (n=337)	GSR Spyral (n=846)
Secondary endpoints (not powered, between groups)						
Δ 24 hr SBP from baseline	✓	✓	✓	✓	x	✓
Δ 24 hr DBP from baseline	✓	✓	✓	✓	x	✓
Δ Nighttime ASBP from baseline	✓	✓	✓	✓	✓	✓
Δ OSBP from baseline	✓	✓	✓	✓	✓	✓
Δ ODBP from baseline	✓	✓	✓	✓	✓	✓
OSBP < 140 mmHg (Target BP)	✓	✓	✓	✓	✓	✓

ASBP: ambulatory systolic blood pressure; BP: blood pressure; DBP: diastolic blood pressure; GSR: Global SYMPLICITY Registry; ODBP: office diastolic blood pressure; OSBP: office systolic blood pressure; SBP: systolic blood pressure

*For the ON MED Pooled results, the medication changes, medications, and medication burden were higher in the control group

According to Whelton et al, in the 2017 American College of Cardiology and American Heart Association Clinical practice guidelines, initiation of anti-hypertensive drug therapy is recommended for adults with stage 2 hypertension, which is the population included in the OFF and ON MED studies (Whelton et al 2018). The average BP reduction seen in the Symplicity Spyral clinical program is similar to anti-hypertensive drug therapy recommended by these clinical guidelines (Julius et al 2003; Ontarget Investigators et al 2008). Additionally, in the successful OFF MED study BP reduction was consistent with the treatment benefit demonstrated for pharmacological therapies. Importantly, RDN has an additional benefit over anti-hypertensive drug therapy as it is not dependent on patient adherence to a medication regime and/ or lifestyle changes.

Efficacy - Durability

Durability of the Symplicity Spyral System is supported by Medtronic-sponsored studies and independent clinical studies, which show long-term sustained drops in BP over time, reductions in anti-hypertensive medication burden, and increased TTR following RDN therapy. The totality of data supports the conclusion that the RDN procedure provides a clinically meaningful benefit over a 24-hour time frame to aid in the treatment of hypertension. At 24 months in the OFF MED Pivotal cohort, durability was demonstrated with a significant reduction in medication burden through 24 months in the Denervation group as compared to the Sham group. The significant and clinically meaningful reductions in both office and 24-hour BP seen out to 36 months in the ON MED pilot cohort demonstrate the durability of effect. Further, the durability in a real-world setting is demonstrated through data from the Global SYMPLICITY Registry, including patients in high-risk subgroups.

Cardiovascular Event Reduction

Data from patients treated with RDN pooled from Medtronic-sponsored studies at 36 month follow-up which shows significant reductions in both office and 24-hour BP with no change in anti-hypertensive medications. It is also important to note that significant reductions in nighttime and early morning ambulatory BP at 24 months and 36 months could translate into clinically important reductions in CV events. The sustained nature of 24-hour BP reduction with RDN may provide additional benefits beyond those associated with anti-hypertensive drugs which are often challenges associated with non-adherence.

6 Clinical Safety

Summary

- RDN performed with the Symplicity Spyral System is minimally invasive with an excellent short and long-term safety profile.
- Pooled primary safety endpoint was met with an MAE rate of 0.4% ($p < 0.001$), significantly lower than the prespecified PG of 7.1% derived from literature for renal interventions.
- In OFF MED Pivotal, at 24 months, the MAE rate was 0.6% in the Denervation group and 2.5% in the Sham group.
- In ON MED, MAE incidence at 6 months was comparable between groups (1.0% in Denervation group and 0.8% in the Sham group).
- No angiographically confirmed renal arterial stenoses > 70% were reported in Denervation patients.
- Across studies, no device-related safety events and a low rate of procedure-related events have been detected.

6.1 Primary Safety Endpoint Analysis

The safety of the Symplicity Spyral System was evaluated in patients from the OFF and ON MED Pilot and Expansion studies, all of whom received the same RDN procedure and treatment approach, including treatment in the branch renal arteries. The first 253 consecutively randomized patients treated with the Symplicity Spyral catheter with evaluable safety data were used to perform the primary safety endpoint analysis (Table 31). These patients were either included in the original treatment group or were crossover patients.

Table 31: Distribution of Patients Comprising Primary Safety Endpoint Cohort

Study		Sample Size N=253
Pilot	OFF MED	31
	ON MED	95
Expansion	Pivotal OFF MED	35
	Supportive ON MED	24
Crossover	OFF MED	51
	ON MED	17

The primary safety endpoint was defined as the incidence of MAE (a composite of key events), through one-month post-randomization (6 months for new renal artery

stenosis). The PG, derived from literature for renal interventions including renal stenting, was 7.1% (Bax et al 2009; Bersin et al 2013; Bradaric et al 2017; Cooper et al 2014; Investigators et al 2009; Jaff et al 2012; Laird et al 2010; Rocha-Singh et al 2005; van Jaarsveld et al 2000).

The primary safety endpoint was met, with an MAE rate of 0.4% (upper 95% confidence bound 1.9%), significantly ($p < 0.001$) less than the prespecified PG of 7.1% (Table 32).

Table 32: MAE Safety Endpoint Analysis (Pooled Safety Population)

	Denervation N=253	Upper 95% CI	PG	p-value
MAE	**1 (0.4)**	**1.9%**	**7.1%**	**< 0.001**
All-cause mortality	0			
End stage renal disease	0			
Significant embolic event resulting in end-organ damage	0			
Renal artery perforation requiring re-intervention	0			
Renal artery dissection requiring re-intervention	0			
Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	1 (0.4)			
Hospitalization for hypertensive crisis not related to confirmed non-adherence with medication or the protocol	0			
New renal artery stenosis > 70%	0			

CI: confidence interval; MAE: major adverse events; PG: performance goal;

6.2 Secondary Safety Endpoints

Acute procedural (1-month) and chronic (3, 6, 12, 24, 36-month) safety event rates were compared between groups in the OFF and ON MED studies.

6.2.1 OFF MED

At 1 month, the composite safety endpoint was 0 in the Denervation group and 0.5% (1/184) in the Sham group using all available data from the Full Cohort (Table 33).

At 24 months, the composite safety endpoint was 0.6% (1/169) in the Denervation group and 2.5% (4/162) in the Sham group in the Full Cohort (Table 33). In the Denervation group, 1 patient had Hospitalization for hypertensive crisis/emergency. In the Sham group, 4 patients experienced 9 events; 1 case of non-CV death, 2 cases of major bleeding (thrombolysis in myocardial infarction [TIMI]), 1 case of hematoma, 2 cases of hospitalization for hypertensive crisis/emergency, and 3 cases of new stroke.

Table 33: OFF MED Secondary Safety Analysis Results (Full Cohort, ITT Population)

Safety Measures	Denervation (N=182)	Sham (N=184)	p-value
MAE[1]	**0.0% (0/182)**	**0.5% (1/184)**	**1.000**
To 1 Month			
Death	0	0	
Cardiovascular Death	0	0	
Non-cardiovascular Death	0	0	
New MI	0	0	
Major Bleeding (TIMI)	0	0	
End Stage Renal Disease	0	0	
Renal artery re-intervention	0	0	
Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	0	0.5% (1/184)	1.000
Vascular Complication, hematoma	0	0.5% (1/184)	1.000
Hospitalization for hypertensive crisis/emergency	0	0	
New Stroke	0	0	
To 24 Months			
Composite Safety Endpoint[2]	**0.6% (1/169)**	**2.5% (4/162)**	**0.206**
Death	0	0.6% (1/162)	0.489
Cardiovascular Death	0	0	--
Non-cardiovascular Death	0	0.6% (1/162)	0.489
New MI	0	0	--
Major Bleeding (TIMI)	0	1.2% (2/162)	0.239
End Stage Renal Disease	0	0	--
Renal artery re-intervention	0	0	--
Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	0	0.6% (1/162)	0.489
Vascular Complication, hematoma	0	0.6% (1/162)	0.489
Hospitalization for hypertensive crisis/emergency	0.6% (1/169)	1.2% (2/162)	0.616
New Stroke	0	1.9% (3/162)	0.116
New Renal Artery Stenosis > 70%	0	0	--

MAE: major adverse events; MI: myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction definition

6.2.2 ON MED

The incidence of MAE occurring in the Full Cohort from enrollment to 6-months was 1.0% (2/204) and 0.8% (1/130) in the Denervation and Sham groups, respectively (Table 34). All 3 events were pseudoaneurysms; one required surgical repair (Denervation) and 2 required thrombin injection (Denervation and Sham). Each of these events were resolved without sequelae.

Table 34: ON MED Secondary Safety Analysis Results 6 Months (ITT Population)

Safety Measures	Denervation (N=206)	Sham (N=131)	P-Value
MAE[1]			
To 6 Months			
Composite Safety Endpoint[2]	1.0% (2/204)	0.8% (1/130)	1.000
Death	0	0	--
Cardiovascular Death	0	0	--
Non-cardiovascular Death	0	0	--
New MI	0	0	--
Major Bleeding (TIMI)	0	0	--
End Stage Renal Disease	0	0	--
Renal artery re-intervention	0	0	--
Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	1.0% (2/202)	0.8% (1/130)	1.000
Vascular Complication, pseudoaneurysm	1.0% (2/202)	0.8% (1/130)	1.000
Hospitalization for hypertensive crisis/emergency	0	0	--
New Stroke	0	0.8% (1/130)	0.392
New Renal Artery Stenosis > 70%	0	0	--

ITT: Intent-to-Treat; MAE: major adverse events; MI: myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction definition

6.3 Overall Adverse Events

6.3.1 OFF MED

In the OFF MED study, 82% of patients in the Denervation group and 84% of patients in the Sham group experienced an AE. The most common types of AEs reported were headache and vascular access site hematoma (Table 35). Overall, AEs were balanced across study groups.

Table 35: OFF MED Pivotal Adverse Events (> 5 % in either arm) - Enrollment to 12 Months (Full Cohort)

Events	Denervation (N=182) n (%)	Sham (N=184) n (%)
Any Adverse Event	149 (81.9%)	154 (83.7%)
Headache	32 (17.6%)	31 (16.8%)
Vascular access site hematoma	16 (8.8%)	22 (12.0%)
Dizziness	15 (8.2%)	12 (6.5%)
Back pain	12 (6.6%)	8 (4.3%)
Peripheral edema	12 (6.6%)	15 (8.2%)
Arthralgia	11 (6.0%)	13 (7.1%)
Hypertension	11 (6.0%)	11 (6.0%)
Nasopharyngitis	11 (6.0%)	14 (7.6%)

One renal artery occlusion was reported in the Denervation group. No dissection was identified by the Investigator during the case. The Angio Core Lab identified dissection in branch L1A during their analysis; this branch was not denervated. By reviewing the angiography and the procedure, the site concluded that the vascular damage was in a small peripheral renal branch (estimated diameter, 1 mm) of the left accessory artery. According to the site's common practice, the insertion of the guide wire and the pullback afterwards caused the vascular complication and consequently was not related with the study device. Six-month duplex ultrasound was non-diagnostic, a repeat CTA was conducted that did not identify any stenosis. 24-months DUS was diagnostic with no stenosis identified.

6.3.2 ON MED

In the ON MED study, AEs were reported for a total of 63% of Denervation patients and 68% of Sham patients. The most frequently reported AEs in the Denervation group were back pain, hypokalemia, and vascular access site hematoma (Table 36).

Table 36: ON MED Adverse Events (> 5 % in either arm) - Enrollment to 6 Months (Full Cohort, ITT Population)

Preferred Term	Denervation (N=206) n (%)	Sham (N=131) n (%)
Any Adverse Event	129 (62.6%)	89 (67.9%)
Back pain	12 (5.8%)	4 (3.1%)
Hypokalemia	12 (5.8%)	8 (6.1%)
Vascular access site hematoma	10 (4.9%)	10 (7.6%)
Headache	7 (3.4%)	9 (6.9%)
Peripheral edema	6 (2.9%)	12 (9.2%)

There were 2 renal dissection events reported in Denervation patients. One was identified by the angiographic core lab and reported by the site after further review, another was identified and reported by the site. These events did not meet the criteria to be reported as "serious adverse events" and did not require intervention.

6.4 Serious Adverse Events

6.4.1 OFF MED

In the OFF MED study, the incidence of serious AEs (SAEs) was similar between treatment groups and the majority of events were only experienced by one patient. The only SAEs that occurred in more than one patient were sepsis, vascular site hematoma, and arthralgia (Table 37).

Table 37: OFF MED Pivotal Serious Adverse Events in > 1 Patient Enrollment to 24 Months (Full Cohort)

Preferred Term	Denervation (N=182) n (%)	Sham (N=184) n (%)
Any Serious Adverse Event	31 (17%)	27 (14.7%)
Sepsis	2 (1.1%)	2 (1.1%)
Vascular Access Site Haematoma	1 (0.5%)	2 (1.1%)
Arthralgia	1 (0.5%)	5 (2.7%)

6.4.2 ON MED

SAEs were reported in 8.7% and 11.5% of patients randomized to Denervation and Sham groups, respectively, in the ON MED study. The only event that was experienced by more than one patient was vascular access site pseudoaneurysm (Table 38).

Table 38: ON MED Serious Adverse Events in > 1 Patient Enrollment to 6 Months (Full Cohort, ITT Population)

Preferred Term	Denervation (N=206) n %	Sham (N=131) n %
Any Serious Adverse Event	**18 (8.7%)**	**15 (11.5%)**
Vascular Access Site Pseudoaneurysm	2 (1.0%)	1 (0.8%)

6.5 Deaths

In the OFF MED Pivotal study, 1 non-CV death occurred in the Sham group through 24-month follow-up.

In the ON MED study, no deaths occurred through the 6-month timepoint.

6.6 Long-Term Safety

6.6.1 OFF MED and ON MED Studies

Long-term safety data, up to 3 years, from the OFF and ON MED studies demonstrate low incidence of reported AEs for patients treated with Denervation, with rates similar to Sham. Renal function over time, as assessed by eGFR, was stable in Denervation patients, showing small decreases consistent with those expected for patients with hypertension and consistent with the Sham group. Long-term safety results from the GSR also support the continued safe use of the Symplicity Spyral System and raise no new concerns.

6.6.2 Global SYMPLICITY Registry

AE information collection in the GSR was focused on collecting protocol-specified events only, from consent up to 3 years follow-up. These events are summarized in Table 39.

Consistent with other studies of the Medtronic Symplicity Renal denervation system, there was no significant change in measured renal function from baseline to 36 months demonstrated in GSR. Patients receiving the RDN procedure experienced extremely low rates of renal artery stenosis and changes in eGFR comparable to changes expected as a result of natural aging.

Overall, the RDN procedure with the Medtronic Symplicity Renal denervation system was associated with minimal complications and no unanticipated adverse device effects. No significant embolic events were reported in patients treated with the Symplicity Spyral catheter, while 4 significant embolic events were reported for patients treated with the Symplicity Flex catheter. Additionally, and in line with other interventional treatments using the groin access site, GSR data show a low rate of vascular complications.

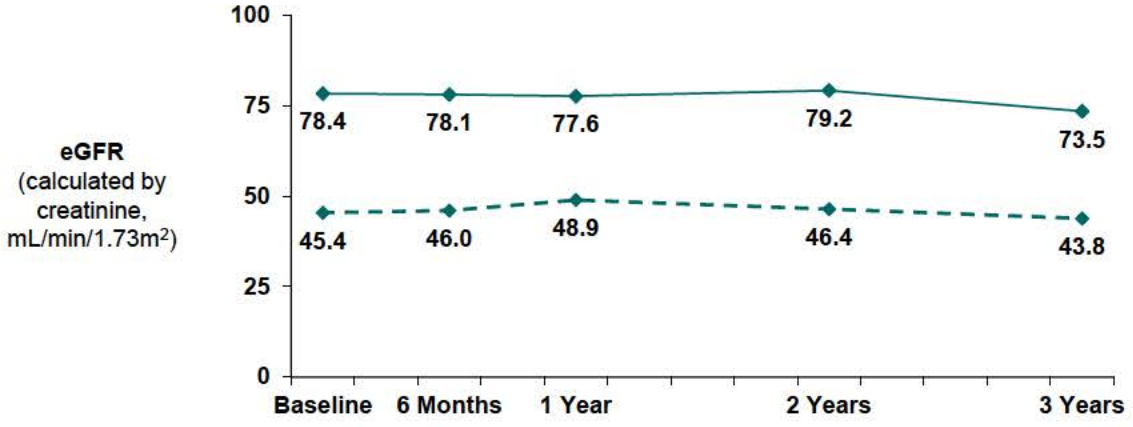
Table 39: Overview of Safety Events in Global SYMPLICITY Registry

Event, n (%)	6 months N=724	12 months N=642	24 months N=485	36 months N=328
Death	3 (0.4%)	8 (1.2%)	21 (4.3%)	26 (7.9%)
Cardiovascular death	1 (0.1%)	4 (0.6%)	8 (1.6%)	8 (2.4%)
Cardiovascular death, secondary to renal failure	0	0	0	0
Non-cardiovascular death	2 (0.3%)	3 (0.5%)	11 (2.3%)	16 (4.9%)
Unknown death	0	1 (0.2%)	2 (0.4%)	2 (0.6%)
Spontaneous MI	0	0	3 (0.6%)	4 (1.2%)
New onset end stage renal disease	2 (0.3%)	4 (0.6%)	6 (1.2%)	9 (2.7%)
Serum creatinine elevation > 25%	4 (0.6%)	4 (0.6%)	4 (0.8%)	4 (1.2%)
Serum creatinine elevation > 50%	0	0	0	0
Significant embolic event resulting in end-organ damage	0	0	0	0
Renal artery re-intervention	0	0	0	0
Renal artery re-intervention due to perforation	0	0	0	0
Renal artery re-intervention due to dissection	0	0	0	0
Renal artery re-intervention (ballooning/stenting) for reasons other than perforation, dissection, other	0	0	0	0
Renal artery re-intervention, other	0	0	0	0
New renal artery stenosis > 70%	0	0	0	0
New renal artery stenosis >70%, treated	0	0	0	0
New renal artery stenosis >70%, untreated	0	0	0	0
Vascular complication	4 (0.6%)	4 (0.6%)	4 (0.8%)	4 (1.2%)
Vascular complication,retroperitoneal bleed	0	0	0	0
Vascular complication,pseudoaneurysm	4 (0.6%)	4 (0.6%)	4 (0.8%)	4 (1.2%)
Vascular complication, AV fistula	0	0	0	0
Vascular complication, hematoma	0	0	0	0

AV: arteriovenous; MI: myocardial infarction

Figure 58 shows the change in eGFR over time, pooled across patients treated with the Symplicity Spyral System in the GSR, the original proof of concept study which included 50 patients, and the OFF and ON MED studies. These pooled long-term results are similar to that observed the clinical studies: renal function over time shows a small decrease in eGFR, which consistent with those expected in patients with hypertension as they age. When looking at patients with pre-existing chronic kidney disease, defined as an eGFR below 60 mL/min, a small decrease in eGFR is also observed, which is again consistent with the natural progression of the disease.

Figure 58: Renal Function Through 3 Years in Pooled Data



	Baseline	6 Months	1 Year	2 Years	3 Years
Pooled Spyral (N)	1,472	972	881	595	282
CKD Spyral (N)	275	142	125	87	50

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; GSR: Global SYMPLICITY Registry
Data pooled from Symplicity Spyral treated patients in GSR, proof of concept study, OFF MED and ON MED
CKD defined as eGFR < 60 mL/min/1.73m^2

6.7 Safety Topics of Interest

6.7.1 Device-Related Adverse Events

No device-related safety events were detected in the OFF and ON MED studies, and procedure-related events were very low.

6.7.2 Procedure-Related Adverse Events

The only event in the OFF MED study adjudicated by CEC to be related to study procedure was from the Sham group (hematoma at procedure access site).

In the ON MED study, there were 5 events in 4 patients that were relevant to clinical safety endpoints within 6-months; four of these events were adjudicated as procedure related but not catheter, generator or therapy-related and have been reported by the site to be resolved without sequelae. The fifth event, a new stroke in a Sham patient was adjudicated as not related to the catheter, generator, therapy or procedure and the site has reported that the patient was continuing with treatment.

6.7.3 Renal Artery Stenosis via Imaging

Medtronic executed a renal artery imaging protocol which provided data from a total of 1,623 follow-up imaging studies in 703 randomized patients as of 27 Feb 2023. Of the 703 patients, 604 underwent treatment with RDN. Denervation patients had 1,019 follow-up imaging studies obtained 6 or more months following randomization that were

determined to be diagnostic by the respective core laboratories. An image was considered diagnostic if any of the following were met:

- Initial imaging study provided complete visualization and ability to evaluate patency for all treated renal artery segments
- Repeat imaging with either the same or an alternate imaging modality provided complete visualization of treated vessel segments that were not evaluable in the initial non-invasive imaging study
- Non-invasive imaging was not evaluable only in a vessel that did not receive renal denervation

For DUS images, renal flow for accessory main renal arteries and branch vessels were confirmed by visualization of uniform parenchymal flow within segments of the same kidney as well as both kidneys.

Diagnostic images for Denervation subjects included 11 angiograms, 773 DUS, 179 CTA, and 58 MRA studies which are broken down by time point in Table 40.

Table 40: Images Determined to be Diagnostic for Denervation Subjects Only

Imaging Timepoints and Days Post Procedure	ANGIO	DUS	CTA	MRA	TOTALS
6M window (DAY 136-270)	0	493	15	11	519
>12M window (DAY 271-study exit)	11	280	164	47	500
TOTALS	11	773	179	58	1,623

CTA: computed tomography angiography; DUS: duplex ultrasound; M: month; MRA: magnetic resonance angiography

Below is a summary of the evaluable 6-month imaging as of 27 Feb 2023 and a description of how it was calculated.

6 Month

Numerator = Subjects with Diagnostic imaging (519)

Denominator = Total RDN subjects those subjects pending initial imaging – Exits prior to visit = Expected (610 – 3 – 3 = 604 subjects)

In summary, 86% of the eligible subjects had diagnostic imaging at 6 months.

12 Month

Imaging that occurred at > 12-month or > 12-month crossover has been collected for 527 subjects and 474 subjects had diagnostic imaging. Additionally, 53 subjects had non-diagnostic imaging and due to the long follow-up period to obtain imaging (Day 270–end of study), there are 25 subjects that are pending repeat imaging. As long as the subject remains in the trial, then the sponsor requests that the site continue to try

and get at least 1 diagnostic imaging study during the > 12-month time period. Early versions of the consents didn't require imaging past the 6-month visit and 14 subjects exited without consenting to ≥ 12-month imaging.

Numerator = Subjects with Diagnostic imaging (474)

Denominator = Total RDN subjects – subjects pending initial imaging – subjects that exited prior to visit – subjects that did not consent to later imaging = Expected (610 – 33 – 7 – 14= 556)

85% of the eligible subjects had diagnostic imaging at > 12 months.

Table 41: Imaging Status for Denervation Subjects Only

	6 Month / 6 Month Crossover	12 Month / 12 Month Crossover
N	610	610
Pending imaging	**0.5% (3/610)**	**5% (33/610)**
Exits prior to visit	**0.5% (3/610)**	**1% (7/610)**
Did not consent to long term imaging	.	**2% (14/610)**
Eligible for imaging	**99% (604/610)**	**91% (556/610)**
Imaging completed	**93% (564/604)**	**95% (527/556)**
Diagnostic (% of eligible)	86% (519/604)	85% (474/556)
Diagnostic (% of imaging completed)	92% (519/564)	90% (474/527)
Non-diagnostic (% of imaging completed)	8% (45/564)	10% (53/610)
Pending repeat imaging	0% (0/45)	47% (25/53)
Imaging not done within window	100% (45/45)	53% (28/53)
Imaging not completed	**7% (40/604)**	**5% (29/556)**

The criteria used to categorize the various categories of stenosis by imaging modality are as follows:

- DUS: patent, 60–99%, totally occluded
- MRA/CTA: patent, 1–25%, 26–50%, 51–75%, 76–100%
- Angiogram – patent or calculated percent diameter stenosis

The DUS core laboratory evaluated renal artery anatomy, renal artery flow and aortic flow for any signs of renal artery stenosis. Direct visualization of the subject's kidneys allows comparison of the size, symmetry, and uniformity between the two kidneys. Hemodynamic evaluation of flow in the aorta, main renal artery, branch arteries, and cortical branches allows assessment of peak systolic velocity (PSV), Renal/Aorta Ratio (RAR), acceleration time, resistive index and end diastolic velocity.

Ultrasound criteria for accessory renal artery stenosis fall into two categories: direct assessment with findings at the site of the stenosis (RAR and/or elevated PSV) and indirect findings which occur distal to the area of the stenosis. Indirect criteria for subjects include symmetrical findings between the right and left kidney, uniform stable velocities and waveform pattern throughout the entire kidney, and normal acceleration time of < 0.07 seconds (< 70 ms). The normal waveform pattern is a low resistive index with rapid systolic upstroke from all areas of the kidney from the hilum to the cortex. Direct findings that are diagnostic criteria for significant renal artery stenosis include renal artery to aorta peak systolic velocity (taken at the level of the superior mesenteric artery) ratio (RAR) of > 3.5, peak systolic velocity > 200 cm/sec, and presence of post-stenotic turbulence (PST) (Hansen et al 1990). Flow changes detected in the presence of a > 60% stenosis include the presence of post stenotic turbulence immediately distal to the stenosis, and a tardus parvus waveform (delayed systolic upstroke) in the renal hilum (Cohen et al 2021; Mahfoud et al 2012; Olin et al 1995). Indirect findings that are diagnostic for assessing branch vessel disease utilized Doppler interrogation of renal parenchyma flow. Patency in branch vessels was evaluated by identifying normal waveforms throughout all segments of the same kidney as well as symmetry of waveforms between the right and left kidney (Hansen et al 1990). Indirect assessment also includes evaluating the absence (no stenosis) or presence (indicating stenosis) of a tardus parvus waveform in the renal hilum.

Definition of stenosis using these measurements does not provide continuous values of % diameter stenosis, but rather defines stenosis dichotomously as either present (> 60%) or absent. If the duplex ultrasound resulted in a finding of 60-99%, an angiogram was requested. If the duplex ultrasound was read as non-diagnostic, a repeat CTA/MRA or DUS was requested.

Of the follow-up imaging obtained, there were only 14 subjects across both arms (13 Denervation, 1 Sham) of the OFF MED and ON MED studies that had suspected stenosis of > 50%. A key finding is that there were no angiographically confirmed stenoses > 70%.

Of the 13 Denervation subjects, one subject was suspected to have a stenosis of > 70% and refused any additional follow-up imaging to confirm this stenosis.

The remaining 12 subjects either had repeat imaging that ruled out significant stenosis or did not meet the 70% threshold that as per the Clinical Investigation Plan required confirmatory imaging. Thus, these data provide a possible stenosis rate for > 70% stenosis of 0.17% (1/604) in the patients treated with RDN. Including patients with > 50% stenoses, a rate of 0.7% (4/604) is obtained. It should be noted that none of these stenoses were confirmed via angiography.

Table 42 summarizes the imaging modalities used and imaging study results for the 14 subjects that had suspected stenosis of > 50%.

Table 42: Subjects with a Possible Stenosis of > 50% Identified on Follow-up Imaging and Outcomes

Study	Randomization Assignment	6 Month Imaging (days post baseline procedure)	Stenosis identified at 6 Month Imaging	Imaging Modality (days post baseline procedure)	Location of Stenosis Identified on First Imaging Modality	Confirmatory Imaging Modality and Days Post Baseline Procedure	Final Outcome
On Med	Denervation	DUS (190)	No	CTA (455)	Stenosis of 76-99% detected in right and left main	Angiogram (546)	Angiogram – right main 9.28%, Left main reported as patent by site*1
On Med	Control (crossover)	DUS (175)	No	CTA (1034, 404*2)	Stenosis of 76-99% detected in right main	Angiogram (1050, 420*2)	Angiogram – reported as patent by site*3
Off Med	Denervation	DUS (188) DUS (244)	No No	MRA (363)	Stenosis of 51-75% in left main	DUS (1069)*4	DUS- no stenosis found
Off Med	Denervation	DUS (176) CTA (229)	No No	CTA (357)	Stenosis of 76-99% detected in left branch artery	DUS (629)	DUS- Patent, no stenosis found
On Med	Denervation	DUS (174)	No	CTA (383)	Stenosis of 51-75% in left renal main	Angiogram (420)	Angio confirmed 20% on the right and 41% on the left. This is consistent with baseline and no treatment was completed in these areas.
On Med	Denervation	DUS (215)	No	CTA (348)	Stenosis of 51-75% in left branch artery	NA	CTA confirmed stenosis was 60%. No additional imaging required.
On Med	Denervation	DUS (189)	No	CTA (368)	Stenosis of 76-99% detected in left main	Angiogram (658)	Angiogram – Left main 32%, consistent with Baseline stenosis (29%)
Off Med	Denervation	Missed due to Covid	NA	MRA (339)	Stenosis of 76-99% detected in right branch	Angiogram (854)	Angiogram – no stenosis found
Off Med	Denervation	DUS (191)	No	MRA (303)	Stenosis of 76-99%	CTA (383) MRA (1112)	CTA- no stenosis found

Study	Randomization Assignment	6 Month Imaging (days post baseline procedure)	Stenosis identified at 6 Month Imaging	Imaging Modality (days post baseline procedure)	Location of Stenosis Identified on First Imaging Modality	Confirmatory Imaging Modality and Days Post Baseline Procedure	Final Outcome
					detected in left branch		MRA – no stenosis found
Off Med	Control	DUS (184)	No	MRA (332)	Stenosis of 76-99% detected in left branch	Angiogram (401)	Angiogram – left branch 6.30%*5
Off Med	Denervation	DUS (181)	No	MRA (379)	Stenosis of 76-99% detected in right branch	Angiogram (482)	Angiogram – right branch 5.37%*6
On Med	Control (crossover)	DUS (1063,169*2)	No	MRA (1649, 755*2)	Stenosis of 51-75% in right branch	DUS (1891, 997*2)	DUS- Patent, no stenosis found
On Med	Denervation	DUS (166)	No	MRA (1106)	Stenosis of 76-99% detected in treated left proximal renal accessory main	Subject refused imaging and exited	Subject refused imaging and exited
On Med	Denervation	DUS (175)	No	MRA (215)	Stenosis of 51-75% in untreated right main	CTA (343)	60% stenosis in MRA and CTA.- Baseline stenosis of 44% noted in the proximal right main. No additional imaging required

*1 The angio core laboratory reported image quality was insufficient to calculate stenosis in the left main renal artery; site interventionist reported no stenosis.
*2 First number is the days post baseline procedure, and second number is days post crossover procedure
*3 The angio core laboratory reported image quality was insufficient to calculate the stenosis on the right main artery; site Interventionalist reported no stenosis
*4 This subject had a pre-existing stenosis of close to 50% identified at baseline angiogram and 6-month follow-up imaging did not meet the 70% threshold required for angiogram. Long term imaging was not initially required for this subject per protocol. Later the subject was consented to a protocol that required additional long-term imaging. This explains the delay between imaging timepoints.
*5 In the database the angio core laboratory does not calculate the stenosis in branch vessels but does provide the information needed to. Calculations based on data provided.
*6 In the database the angio core laboratory does not calculate the stenosis in branch vessels but does provide the information needed to. Calculations based on data provided.

These are exceptionally low rates and are similar to the reported rate of stenosis > 50% in both published safety meta-analysis of Medtronic RDN trials and with the natural incidence of renal artery stenosis in hypertensive patients of 0.36%–5% per year (Townsend et al 2020).

Importantly, there has been no confirmed accelerated progression of disease identified when comparing baseline evaluations to follow-up imaging.

6.7.4 Estimated Glomerular Filtration Rate Findings

Both FDA and the 2018 Circulatory Systems Devices Panel had a specific interest in understanding long-term renal function in patients following RDN. Consequently, in addition to the robust reporting of AEs, particular endpoints related to renal function (via eGFR) and Renal Artery Stenosis are presented.

eGFR is the primary tool for assessing functional changes in the kidney and is typically the only tool for examining kidney function since kidney biopsy and kidney imaging are not typically justified in routine patient care. Pooled safety analyses provide confirmation that any reduction in eGFR in denervation-treated patients is consistent with the decline seen in patients not treated with RDN, per their natural or disease course. Accounting for all risk factors at baseline (hypertension, diabetes, obesity, chronic kidney disease), the reduction in eGFR following denervation treatment is within the expected ranges for a normal progression of eGFR. In the ON and OFF MED studies, < 1% of patients experienced a decline of ≥ 40% of eGFR. In both studies (with available data out to 24 months), the slope of eGFR decline was not significantly different between the Denervation and Sham groups out to 24-months.

6.8 Safety Conclusions

In summary, the OFF MED and ON MED studies both demonstrate the positive safety profile of RDN with the Symplicity Spyral System. The pooled primary safety endpoint was met with a low rate of MAE. There were no major device-related or procedure-related safety events observed and no increase in the risk of RDN-associated renal artery stenosis.

7 Patient Preference

7.1 Overview

Patient preference information has been defined as “qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions” (FDA 2020). Patient preference and shared decision making have been identified as critical components of developing a hypertension care plan including the RDN procedure (Barbato et al 2023; Kandzari et al 2021).

Medtronic US Discrete Choice Experiment Study

Medtronic executed a prospective US study using established, rigorous Discrete Choice Experiment (DCE) methodology to quantify patients’ preferences for the benefits and risks of an interventional treatment (based on the Symplicity Spyral Renal Denervation System) with or without pills compared with pills only (standard of care) for the treatment of hypertension (Kandzari et al 2023). DCE modelling assumes that individuals will choose the option of maximal benefit when confronted with a discrete set of options. The study design followed FDA guidelines for Patient Preference Information studies conducted for benefit-risk assessment, as well as guidelines prepared by the ISPOR - The Professional Society for Health Economics and Outcomes Research (formerly, the International Society for Pharmacoeconomics and Outcomes Research) (Bridges et al 2011; FDA 2016; Hauber et al 2016; Reed Johnson et al 2013).

The primary objective was to measure US hypertensive patients’ preferences for attribute levels associated with interventional treatments for hypertension with or without pills compared to pills only.

The set of attributes evaluated included the treatment type (ie, interventional treatment and number of oral anti-hypertensive pills per day), effectiveness (reduction in office SBP and duration of effect) and AEs associated with oral and interventional anti-hypertensive treatments. The final study was informed by the findings from survey pretest interviews conducted via 28 interviews with adults with uncontrolled hypertension. The final survey was administered online.

7.2 Patient Demographics and Characteristics

In total, 346 (86.5%) individuals were recruited through physicians, and 54 (13.5%) individuals were recruited via online panels or social media (Table 43).

Overall, the average age, average number of classes of oral anti-hypertensive medications, and proportion of the sample by sex, race, and ethnicity were similar to the broader US population with hypertension (Bress et al 2016; Muntner et al 2018).

Table 43: Participant Demographics and Characteristics

	Participants N=400
Age, mean (SD), years	59.2 (13.0)
Min, max	25, 79
Sex	
Male	194 (48.5%)
Female	206 (51.5%)
Race	
White	269 (67.3%)
Black American	59 (14.8%)
Hispanic or Latino	36 (9.0%)
Asian	20 (5.0%)
Other	16 (4.0%)
Length of Hypertension (years)	
0–5	171 (42.8%)
6–10	111 (27.8%)
> 10	118 (29.5%)
On prescribed HTN medication (%, mean #)	89%, 1.8
Office SBP, mean mmHg	155.1 ± 12.3
Office DBP, mean mmHg	95.2±5.3

DBP: diastolic blood pressure; HTN: hypertension; SBP: systolic blood pressure; SD: standard deviation

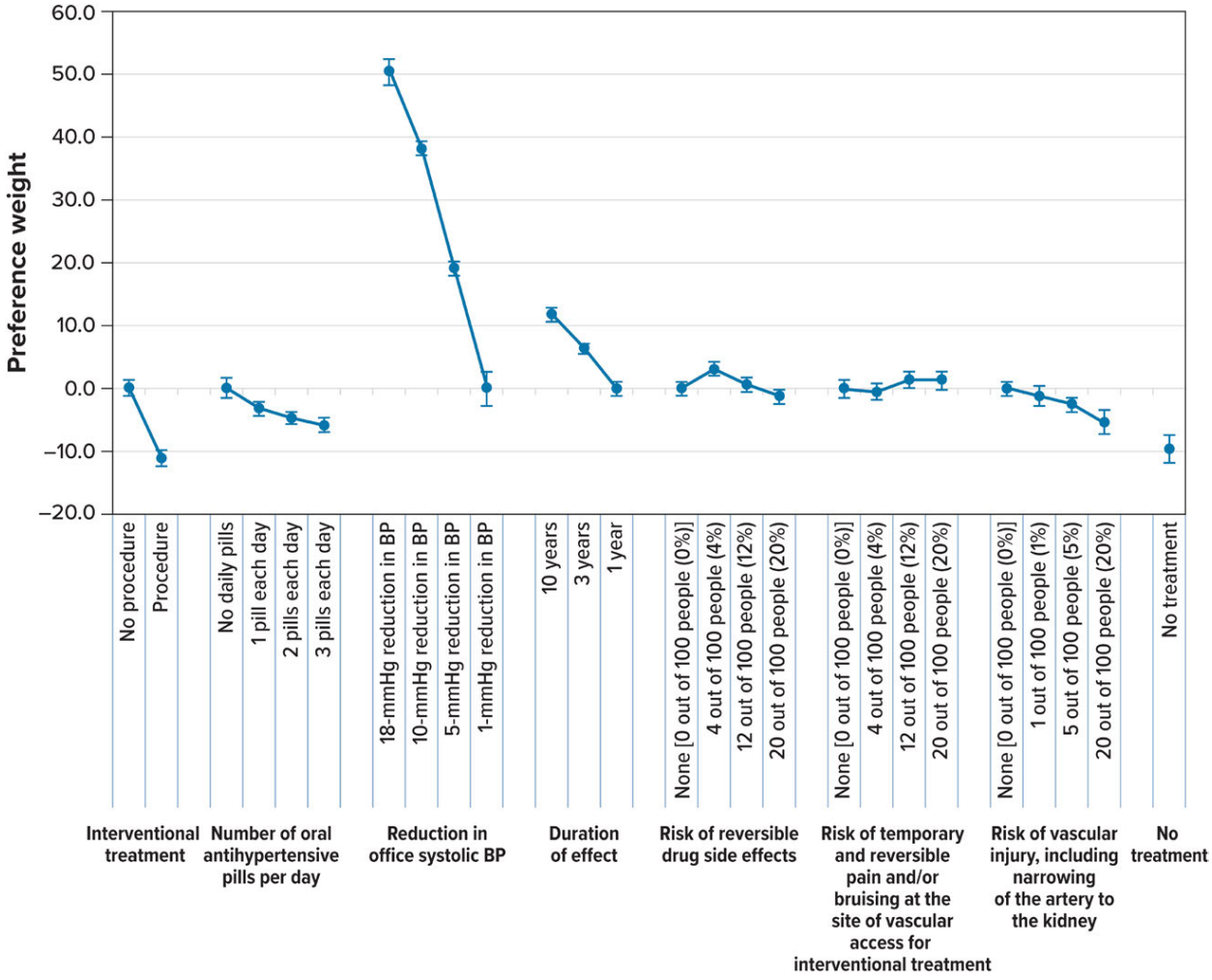
7.3 Results

Among respondents currently on medication treatment for high BP, treatment satisfaction was relatively high, with an average score of 3.8 out of 5 (where 5 was "Extremely satisfied"), even though the average office SBP of the sample was 155 mmHg with a range of 140 to 197 mmHg. Most of the sample (84.0%) considered reducing the risk of death, heart attack, stroke, or kidney damage as one of the most important goals of treatment for hypertension. Approximately one in 5 respondents in the study would not be interested at all in an interventional treatment for hypertension when all else is equal.

Figure 59 summarizes the estimates of the mean preference weights (and 95% CIs) which are the primary endpoints describing the relative preferences for all attribute levels in the study. Attribute levels with larger preference weights are preferred to attribute levels with smaller preference weights. Thus, the results indicate that the preferences are well-ordered for the following naturally ordered treatment attributes: number of daily pills, reduction in office SBP, duration of effect, and risk of vascular injury. On average, respondents preferred the treatments in the survey to no treatment and preferred a longer duration of effect to a shorter duration of effect. Of note,

respondents preferred no procedure to receiving a procedure. Interestingly, the respondents had similar preference for different levels of drug and interventional AEs.

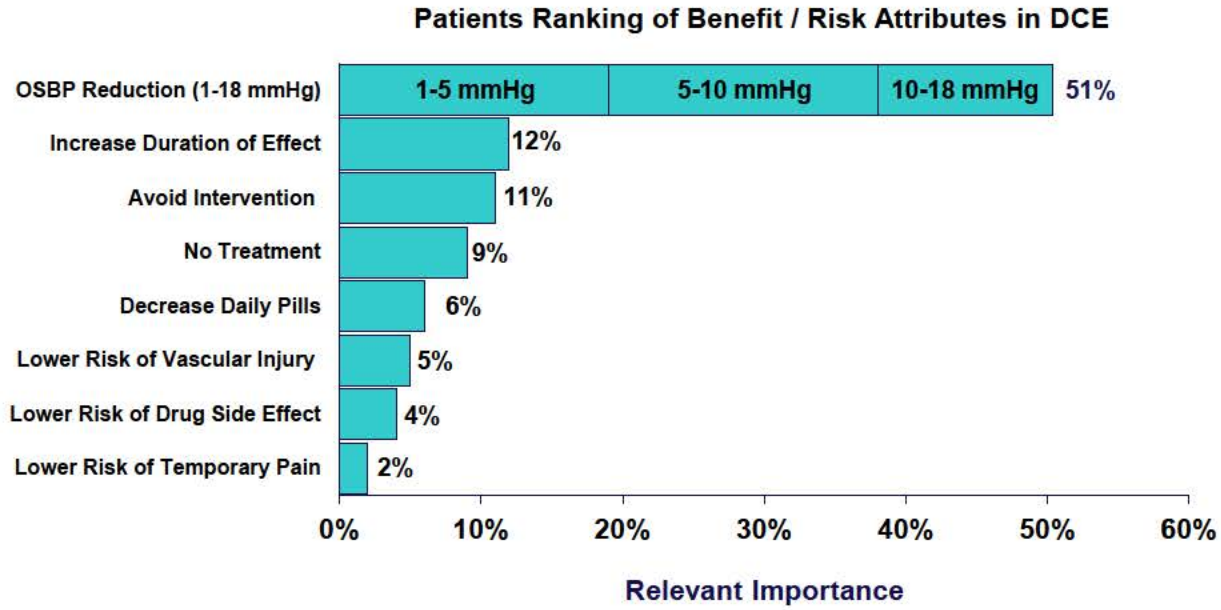
Figure 59: Preference Weights for Treatment Attributes



Most notably, patients' choices in the survey revealed that BP reduction was more important than other attributes, including procedural risk. Also, the relative importance of BP reduction increased as the magnitude of BP reduction increased (Figure 60). This preference was further demonstrated using "Minimal Acceptable Benefit" (MAB) and "Maximum Acceptable Risk" (MAR) calculated using the modelled preference weights. For MAB, respondents would require that treatment reduce office SBP by any amount > 0 mmHg in exchange for bearing an increase in the risks of drug-related side effects by 20% and 1.1 mmHg (95% CI: 0.6–1.6) in exchange for bearing an increase in the risks of vascular injury by 20% (assuming all other attributes were held constant). If all other attributes were equal, respondents would prefer to avoid interventional treatments

for hypertension, yet only a 2.3 mmHg reduction in office SBP, on average (95% CI: 1.7–2.9), was required to offset this preference.[1]

Figure 60: Relevant Importance of Benefit/Risk Attributes

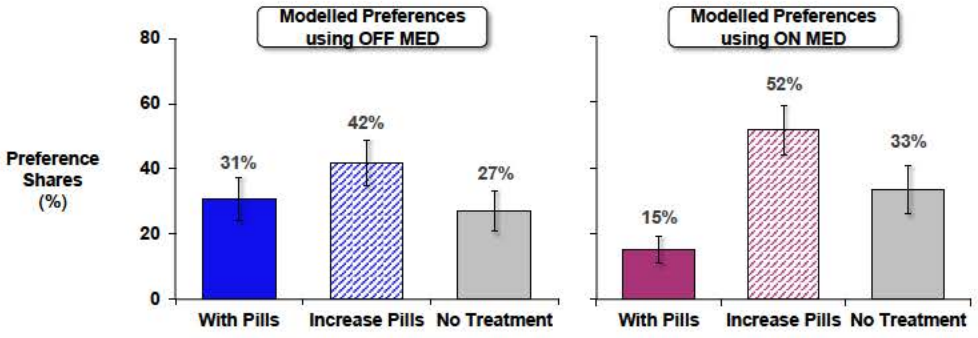


DCE: Discrete Choice Experiment; OSBP: office systolic blood pressure
Source: Kandzari et al 2023

Application of the resultant modelled preferences to clinically observed treatment outcomes in the OFF MED Pivotal and ON MED studies suggests that 15% to 31% of patients would likely select an interventional treatment (Figure 61). This percentage increased in clinical scenarios representing an inability or unwillingness to take oral anti-hypertensive drugs, or representing conditions where drug non-adherence led to reduced clinical benefit, and representing increased treatment effect due to greater duration as reported with the 3-year follow-up in several RDN studies (Bhatt et al 2022; Mahfoud et al 2022; Mahfoud et al 2020b).

[1]Each estimate of MAB calculated should be interpreted as being in addition to a 1-mmHg reduction, which is the minimum level of office SBP reduction evaluated for this attribute." So, 2.3 is the minimum acceptable ***increase*** in benefit. Thus, the average MAB would be 3.3 mmHg reduction in OSBP

Figure 61: Modelled Preferences Using OFF MED Pivotal and ON MED Studies



Intervention treatment	Yes	No	No treatment	Yes	No	No treatment
Change in number of oral antihypertensive pills per day	No change	Increase		No change	Increase	
Reduction in office SBP (mmHg)	6.8	5.1		4.9	5.1	
Duration of effect	1 year	1 year		1 year	1 year	
Risk of reversible drug side effects	10%	10%		10%	10%	
Risk of temporary and reversible pain and/or bruising	13%	0%		13%	0%	
Risk of vascular injury	0.3%	0%		0.3%	0%	
Average predicted likelihood of selecting treatment profile (95% CI)	30.93% (24.40, 37.45)	41 9% (34.86, 48.94)	27.18% (20.89, 33.46)	15.09% (11.02, 19.16)	51 5% (44.09, 58.92)	33.41% (26.07, 40.75)

7.4 Conclusions

The Medtronic Patient Preference study utilized rigorous DCE methodology to assess preferences for attributes in adults with physician-confirmed uncontrolled hypertension. The results indicated that BP reduction was the most influential driver of treatment choices and was more influential on choice than the risk of treatment-related side effects. Thus, real-world RDN candidates understand the risk-benefit trade off and based on the DCE, 15-31% would choose an interventional procedure to help manage hypertension.

8 Post-Approval Study

8.1 Study Design Overview

The SPYRAL AFFIRM study is a multi-center, international, prospective, interventional, single-arm study designed to evaluate RDN in a broader patient population with a focus on collecting safety, efficacy, and durability of the procedure in patients with varying severity of hypertension and associated comorbidities. The study is intended to meet the post-market data collection requirements, powered subgroup analyses are planned for patients with chronic kidney disease (CKD), isolated systolic hypertension (ISH), and Type 2 Diabetes Mellitus. AFFIRM will continue to follow patients previously enrolled in the OFF and ON MED studies for an additional 24 months, bringing the total follow-up period for select patients to 5 years further expanding the data available supporting long-term safety, efficacy and durability of renal denervation utilizing Symplicity Spyral catheter.

8.2 Population

The study will enroll up to 1,200 patients at up to 100 study sites with greater than 50% of sites in the US. Study participants will be followed for 36 months post procedure. In addition, up to 200 participants treated with RDN in the OFF MED and ON MED clinical studies, upon completion and exit from those trials, may be eligible to participate in the AFFIRM study, and continue follow-up through 60 months post RDN procedure.

The study consists of two cohorts:

Main Cohort: all patients consented to the AFFIRM study who undergo the RDN procedure once enrolled.

Continuation Cohort: patients who also participated in the OFF MED or ON MED, initially randomized to the treatment arm and successfully treated via the RDN procedure for continued follow-up through 60 months after the RDN procedure.

8.3 Enrollment Criteria

The key inclusion criteria include the following but is not limited to:

- Office SBP ≥ 140 mmHg (no upper threshold)
- No office DBP requirements
- Obtain ≥ 7 days of valid home BP readings within 30 days prior to the procedure

The key exclusion criteria include the following but is not limited to:

- Renal anatomy requirements
- Untreated secondary cause of hypertension (either known or suspected)
- eGFR < 30 mL/min/1.73m^2, using the 4 variable Modification of Diet in Renal Disease calculation (in mL/min per1.73m^2 = 175 x SerumCr $^{1.154}$ x age $^{0.203}$ x 1.212)

8.4 Endpoints

Efficacy objectives will be evaluated at each follow-up visit based on patient cohort assignment. The Main Cohort will be followed for 36-months post procedure. Baseline data for patients in the Continuation Cohort will be pulled from OFF MED and ON MED and patients will be evaluated out to 48 and 60-months post index procedure as a secondary cohort only. Endpoints include:

- Change in office SBP from baseline at 3, 6, 12, 24, 36, 48 and 60-months post-procedure
  - Prespecified comparison will be made for the following subgroups at 6 months:
    - ISH (baseline office SBP > 140 mmHg and DBP < 90 mmHg)
    - CKD (eGFR < 60 mL/min/1.73m^2)
    - Type 2 Diabetes Mellitus
- Change in home BP from baseline at 3, 6, 12, 24, 36 months post-procedure (*Main Cohort only)*
- Change in 24-hour BP from baseline (*ABPM Subset & Continuation Cohort*) at 3, 6, 12, 24, 36, 48 and 60-months post-procedure
- Change in office BP, home BP and 24-hour BP from baseline will be assessed ineach of the following subgroups as applicable:
  - Severe hypertension (baseline office SBP ≥ 150 mmHg, despite the prescription of ≥ 3 anti-hypertensive medications)
  - Age ≥ 65 years
  - ISH (baseline office SBP $\geq$ 140 mmHg and DBP < 90 mmHg)
  - CKD (eGFR < 60 mL/min/1.73m^2)
  - Atrial fibrillation

8.5 Powered Subgroup Analyses

The following three subgroups will be analyzed with pre-specified hypotheses. Key objectives related to RDN efficacy, safety and durability in those subgroups will be presented. To ensure desired subgroup sizes are obtained to meet the statistical needs, the study sponsor may pause enrollment of any subgroup at any time.

- ISH
- CKD
- Type 2 Diabetes Mellitus

9 Benefit-Risk Conclusions

Hypertension is one of the most important risk factors for ischemic heart disease, stroke, heart failure and other CV diseases. It remains the leading cause for premature deaths worldwide. Currently treatment strategies include lifestyle modifications and long standing availability of pharmacotherapy but there is still an increasing trend of hypertension related morbidity and mortality in the last two decades. Adherence to these therapies continues to be poor, and this trend urgently calls for a new and definitive therapy to help the diverse population of patients with uncontrolled BP. Based on patient preference research, patients are open to seeking safe and effective complementary treatment options.

The renal sympathetic nervous system is key in the pathophysiology of hypertension. The renal nerves and their proximity to the renal artery wall allows for a safe and effective way to target the renal nerves percutaneously. RF RDN allows for permanent renal nerve abolition without reinnervation, with durable BP reduction over time. Furthermore, RF RDN complements other treatment strategies for uncontrolled BP and offers an alternative strategy for BP reduction in the presence and absence of medication treatment.

Clinically meaningful reductions in BP with RF RDN have been demonstrated through prospective, randomized sham-controlled studies, including the OFF MED and ON MED studies. OFF MED first demonstrated a selective benefit of RF RDN in both 24-hour and office BP, in the absence of antihypertensive medications. This was critical in understanding the true mechanism of RF RDN without potential confounding factors such as the effect of medications. Importantly, an “always on” effect of RF RDN was observed with sustained BP reductions throughout the 24-hour period, which overcomes the limitations of medications by not relying on medication adherence, dosing and their pharmacokinetic profiles to prevent large swings of BP throughout the day. This may be particularly helpful for patients who have nocturnal or early morning hypertension, who have higher CV risk.

Subsequently, ON MED evaluated the effects of RF RDN in the presence of antihypertensive medications and did not show a significant treatment difference in the overall 24-hour BP reduction between the two treatment groups at 6 months. There were two main possible confounders for this outcome: 1) the sham procedure had larger than expected reduction in 24-hour SBP due to disproportionately increased anti-hypertensive medications compared to the Denervation group, 2) more 24-hour SBP measurements were missing in the Sham group and their corresponding office BP had actually increased during follow-up.

However, the nighttime BP in ON MED at 6 months showed a significant treatment difference in favor of RF RDN (Denervation −6.7 mmHg, Sham −3.0 mmHg; treatment difference −3.7 mmHg; p = 0.010). Furthermore, there was a significant treatment difference in the office BP, favoring RF RDN over the sham procedure as well (Denervation −9.9 ± 13.9 mmHg, Sham −5.1 ± 13.2 mmHg; treatment difference

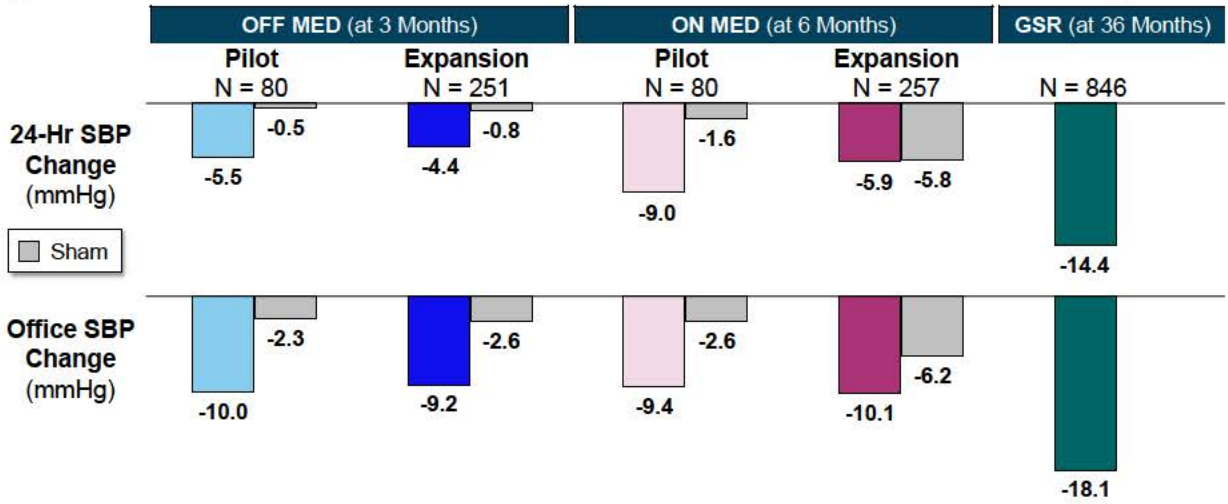
−4.9 mmHg, p = 0.002). The nighttime and office BP reductions are still clinically relevant and important measures that have strong correlation with improvement in long-term CV outcomes.

In ON MED, a prespecified Win Ratio analysis enabled the evaluation of the clinical benefit of RF RDN based on multiple clinically relevant variables including 24-hour SBP reduction and medication burden reduction, both important endpoints for patients and clinicians. The Win Ratio was 1.49 (95% CI: 1.13 to 2.00; p = 0.005) in favor of RF denervation. This represented a 1.49 × greater likelihood of reducing BP or medication with RF RDN than with sham procedure.

In addition to the ON and OFF MED studies, it is important to consider the totality of evidence collected to date to evaluate the safety and efficacy of the Symplicity Spyral System. Data from over 1,800 procedures demonstrates consistent and clinically meaningful reductions in BP across multiple studies and timepoints, applicable to a wide range of patients in the presence and absence of antihypertensive medications (Figure 62).

An excellent safety profile was demonstrated with the Symplicity Spyral system and RF RDN. The pooled primary safety endpoint was met with a low rate of MAE. There were no device-related events and a low rate of procedure-related safety events observed without an increase in the risk of denervation-associated renal artery stenosis.

Figure 62: 24-Hour and Office SBP RDN Reductions Across SPYRAL Program



GSR: Global SYMPLICITY Registry; RDN: renal denervation; SBP: systolic blood pressure

Lastly, Medtronic's patient preference study demonstrated a patient's willingness to accept alternative BP therapies based on the clinical risks and benefits associated with an interventional procedure.

Using FDA's guidance document for factors to consider when making benefit-risk determinations in medical device pre-market approvals, the broad totality of evidence

presented for the Symplicity Spyral System provides a reasonable assurance of a positive benefit-risk ratio (Table 44). The Symplicity Spyral system fills an unmet medical need for the more effective treatment of uncontrolled hypertension to compliment the current strategies used in the US. The device has a low rate of MAEs with no major device-related events and a low rate of procedure-related safety events observed. There is no increased risk of RDN-associated renal artery stenosis and sustained renal function is demonstrated through 3 years. In addition, there is a clinically meaningful reduction in BP that is equal to or greater than that seen in the sham in all endpoints.

Table 44: FDA Guidance Summary: Factors to Consider when Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

FDA Guidance[1]	SPYRAL Clinical Program Study Results
"The device fills an unmet medical need or niche for more effective treatment of life-threatening or irreversibly debilitating human disease/conditions"	• Breakthrough device designation received for the treatment of uncontrolled hypertension. • Symplicity Spyral is one of the first device options for uncontrolled HTN
"[What are] the adverse events (AEs) or outcomes related to the device itself?"	• Low rate of MAEs • No major device-related and low rate of procedure-related safety events observed • No increase risk of RDN-associated renal artery stenosis • Sustained renal function through 3 years
"Favorable change in at least 1 clinical assessment that is equal to or greater than seen in the control group [whether or not the results are statistically significant]"	• OFF and ON MED studies showed a clinically meaningful reduction in blood pressure that is equal to or greater than that seen in the control (sham) in all endpoints.

HTN: hypertension; MAE: major adverse events; RDN: renal denervation
1. FDA Guidance: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications (FDA 2019)

In conclusion, the totality of evidence when considered in parallel with studies conducted on patient preference support a positive risk/ benefit assessment for RDN. The Symplicity Spyral System offers a minimally invasive, safe and effective strategy to reduce BP for patients and compliments the current strategies used to manage hypertension in the US (Figure 63).

Figure 63: Symplicity Spyral System Positive Benefit-Risk Profile

Unmet Need	Efficacy	Safety

▪ Hypertension is the leading modifiable risk factor associated with CV events and death
▪ Up to half of all patients' BP remains uncontrolled
▪ Many patients are interested in additional treatment options
	▪ Provides clinically meaningful and sustained BP reduction compared to baseline,
	  ▪ On medication
	  ▪ Off medication
	▪ Continuous BP reduction throughout 24-hour period
		▪ Excellent short and long-term safety, incl:
		  ▪ Procedural safety
		  ▪ Renal artery patency
		  ▪ Maintaining kidney function

BP: blood pressure; CV: cardiovascular; US: United States

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Appendix 1: Bayesian Approach used in OFF MED and ON MED

Parametric statistics involve a probability model and associated data. For example, in a one-sample t-test the assumption is that the data are normal with unknown mean μ and variance σ^2, ie, $y_1, \ldots, y_n \sim N(\mu, \sigma^2)$. Here $\boldsymbol{y} = (y_1, \ldots, y_n)$ are the observed data and $\boldsymbol{\theta} = (\mu, \sigma^2)$ are the model parameters. The probability model provides the joint density $f(\boldsymbol{y}|\boldsymbol{\theta})$ of the data $\boldsymbol{y}$ governing probabilities about the data $\boldsymbol{y}$. Likelihood-based statistics use the joint density $f(\boldsymbol{y}|\boldsymbol{\theta})$ directly, but as a function of $\boldsymbol{\theta}$, renaming it the 'likelihood.' For example, maximum likelihood maximizes $f(\boldsymbol{y}|\boldsymbol{\theta})$ as a function of $\boldsymbol{\theta}$ only, keeping $\boldsymbol{y}$ fixed at the observed values. Likelihood-based based inference considers $\boldsymbol{\theta}$ fixed and unknown, and estimators of $\boldsymbol{\theta}$ are based on criteria such as unbiasedness and mean squared error. A Bayesian parametric approach also uses the likelihood, but treats $\boldsymbol{\theta}$ as random and specifies a distribution $\pi(\boldsymbol{\theta})$ of plausible values termed the 'prior.' Bayes' rule combines all information giving the joint 'posterior' distribution of $\boldsymbol{\theta}$ given data $\boldsymbol{y}$, model, and prior $\pi(\boldsymbol{\theta})$: namely $\pi(\boldsymbol{\theta}|\boldsymbol{y}) \propto f(\boldsymbol{y}|\boldsymbol{\theta})\pi(\boldsymbol{\theta})$, where $\propto$ denotes proportionality. Bayesian estimates of $\boldsymbol{\theta}$ include the posterior mean, posterior median, and posterior maximum (MAP). Under a flat prior, the Bayesian MAP estimator corresponds to the maximum likelihood estimator. For both OFF MED and ON MED pilot data were used to construct an informative prior $\pi(\boldsymbol{\theta})$ on the treatment effect, which was then used to down-weight pilot data information in the pivotal analyses.

The power prior (Ibrahim et al 2015) assumes the same probability model for both pilot and pivotal data, and essentially uses the pilot data likelihood raised to the power α, where $0 \leq \alpha \leq 1$, as a prior for the pivotal analysis. The RDN and sham arms have different weights, say α_t and α_c for treatment and control arms, and the probability model used for both the 24-hour ambulatory and office BP primary analysis is a baseline-adjusted ANCOVA model. Note that $\alpha = 0$ implies that the pilot data are not used at all (eg, the ON MED sham arm for 24-hour BP) and $\alpha = 1$ implies that the pilot data are essentially pooled with the pivotal data with no down-weighting (eg, the ON MED RDN arm for office BP). Values of α between 0 and 1 indicate the degree of borrowing. If the pilot data has sample size n, then the effective sample size being added to the pivotal analysis through the power prior is $\alpha \times n$.

The discount power prior used for both OFF and ON MED essentially down-weights the pilot data more the further apart the treatment effects are in the pilot and pivotal data. The discount prior can be viewed as a Bayesian "test-then-pool" approach that down-weights on a continuum instead of a discrete hard threshold.

Appendix 2: Symplicity Spyral™ Multi-Electrode Renal Denervation Catheter Instructions for Use

Draft instructions for using the Symplicity Spyral System are as follows:

Closely follow these Instructions for Use and consult the generator user manual for additional instructions for use.

Equipment and procedure preparation

1. Install the generator on a cart or table.

   Warning: For proper equipment ventilation, position the generator more than 30 cm (12 in) away from a wall and do not cover the generator while in use.

2. If the use of a remote control and/or foot switch is desired, connect the remote control and/or foot switch into the respective receptacles on the rear panel of the generator. If desired, the information displayed on the touch screen can also be projected on a cathlab monitor by connecting the DVI-D cable between the rear panel of the generator and the cathlab monitor.

   Note: If the remote control is being used, insert it into a sterile bag and place it within the sterile field using standard aseptic techniques.

3. Plug the power cable into the back panel of the generator and turn it on by pressing the on/off switch also located on the back panel. Make sure that no catheter is connected to the generator while the generator is being turned on.

4. Check for any system indicatormessages orwarnings (such as fault or status lights). Following a system self-test, the system is in the STANDBY state and nomeasurements are possible. After a successful self-test, the front panel will display a screen prompting the user to connect a catheter to the generator.

5. Gather the accessories needed for the procedure, such as dispersive electrode, 6 Fr guide catheter, introducer sheath, 0.36 mm (0.014 in) guidewire, stopcock sidearm, Tuohy-Borst adapter, as well as any other standard items used to aid percutaneous transluminal catheterization in renal arteries.

6. Gather the medications needed for the procedure, such as pain medications, atropine, nitroglycerine, and heparin.

Patient preparation

1. Prepare the patient using standard techniques for electrosurgery and catheterization. Ensure the patient’s entire body, including extremities, is insulated from contact with grounded metal parts. Closely follow instructions provided by the manufacturer of the dispersive electrode.

   Warning: The dispersive electrode should be placed on the thigh or other non-bony area of the body and should be outside of the angiographic field of view. Shave the placement area if necessary for good contact between the dispersive electrode and the skin. Failure to achieve good skin contact by the entire adhesive surface of the

dispersive electrode may result in a burn or high impedance measurements. Do not apply the dispersive electrode where fluid may pool.

2. Connect the dispersive electrode to the generator using the receptacle located on the side panel.
3. Ensure that the patient has intravenous (IV) access for drug administration during the procedure. Prior to starting the procedure, administer appropriate systemic anticoagulation (such as heparin) to the patient. An activated clotting time (ACT) of at least 250 s should be maintained during the procedure.
4. Administer pain medication at least 10 minutes prior to ablation. Check vital signs throughout the procedure.
5. Prepare the patient for catheter placement using standard interventional techniques.
6. Advance the guide catheter to the renal arteries.
7. Under fluoroscopy, inject diluted contrast (1:1) in both renal arteries to assess anatomy.
8. Determine whether the arteries are suitable for treatment.

Catheter insertion in renal artery

1. Using aseptic technique, carefully remove the seal on the outer tray and place the inner tray containing the catheter into the sterile field.
2. Once the tray containing the catheter is in the sterile field, carefully remove the lid by pulling on the lid's pull tab to gain access to the catheter and integrated cable.
3. Remove the coiled cable from the tray and place on a stable sterile surface. Grip the catheter handle with one hand and the hoop with the other hand. Carefully remove the handle and hoop from the tray and place on the stable sterile surface next to the coiled cable.
4. Remove the twist-tie clip from the coiled portion of the cable and pass the integrated cable out of the sterile field for an assistant to connect the cable to the appropriate receptacle on the side panel of the generator. The cable should be secured to the table or drape using a towel clamp, hemostats, or equivalent to help prevent movement of the catheter and handle.
5. An assistant outside the sterile field must perform patient selection on the touch screen (new patient or same patient).
6. Advance a 0.36mm (0.014 in) guidewire into the target vessel.
    - It is recommended to use only guidewires with a flexible distal tip that are not hydrophilic coated to avoid kidney perforation.
7. Remove the catheter from the hoop; ensure that the straightening tool stays with the handle when pulling the catheter out of the hoop. Inspect the catheter for damage.
    - If the catheter is damaged, do not use.

- Do not advance the catheter into the hoop after full or partial removal from the hoop. If advanced, fully remove the catheter from the hoop and inspect for damage. If damaged, replace the catheter.
- Prior to use, do not flush the catheter lumen or the catheter while in the hoop. Do not wipe the spiral section of the catheter.

8. Slide the straightening tool over the spiral portion of the catheter as illustrated in Figure 1A, making sure that approximately 5mm of the catheter tip still protrudes from the distal end of the straightening tool.
   - If excessive resistance is felt while advancing the straightening tool over the spiral section of the catheter, stop, retract the straightening tool, and assess for damage.
   - If the electrodes or the distal end of the catheter are damaged, replace the catheter.
9. Squeeze the distal flare of the tool to secure the catheter. Carefully insert the proximal end of the guidewire through the tip of the catheter. Continue to pass the guidewire through the catheter until the guidewire exits through the rapid exchange port. This exit port is located 30 cm proximal to the distal tip of the catheter.
   - If the guidewire does not exit from the rapid exchange port, remove the guidewire from the catheter and reinsert the guidewire while assessing for device breaches.
   - If the catheter is breached or damaged, replace the catheter and guidewire.
10. Once the guidewire has exited the rapid exchange port, return the straightening tool by the handle to prevent interference with the guidewire.
11. Administer nitroglycerine before advancing the catheter in the artery to reduce risk of arterial spasm, if not contraindicated.
12. Advance the catheter over the guidewire through the guide catheter.
    - If using a 55 cm guide catheter, the catheter tip will exit the guide catheter when the shaft marker enters the rotating hemostatic valve.
13. When all four electrodes exit the guide catheter, the impedance monitoring screen (Figure 3A) will then be displayed.

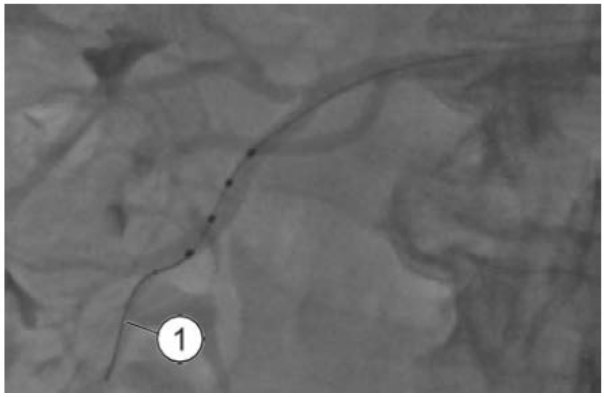
    Note: If the display does not continue to the impedance monitoring screen, follow these steps:

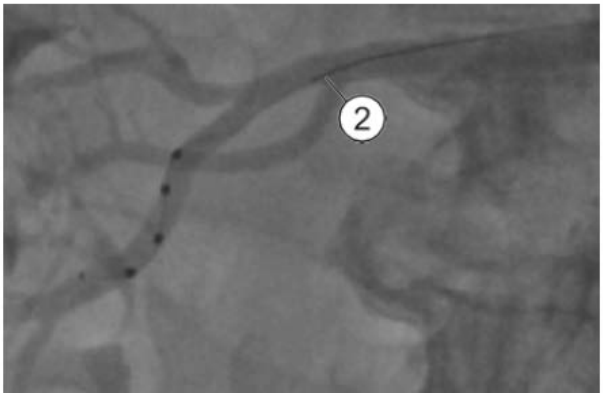
    a. Check the catheter position and ensure that all 4 electrodes are outside of the guide catheter.
    b. Verify appropriate dispersive electrode connection and contact with patient.
    c. If the previous steps do not result in the display of the impedance monitoring screen, try moving the dispersive electrode to the patient's flank. If needed, replace the dispersive electrode.

Figure 1A. Straightening tool used over the distal portion of the Symplicity Spyral catheter

Achieving adequate wall contact

Figure 2A. Device placement within the renal artery





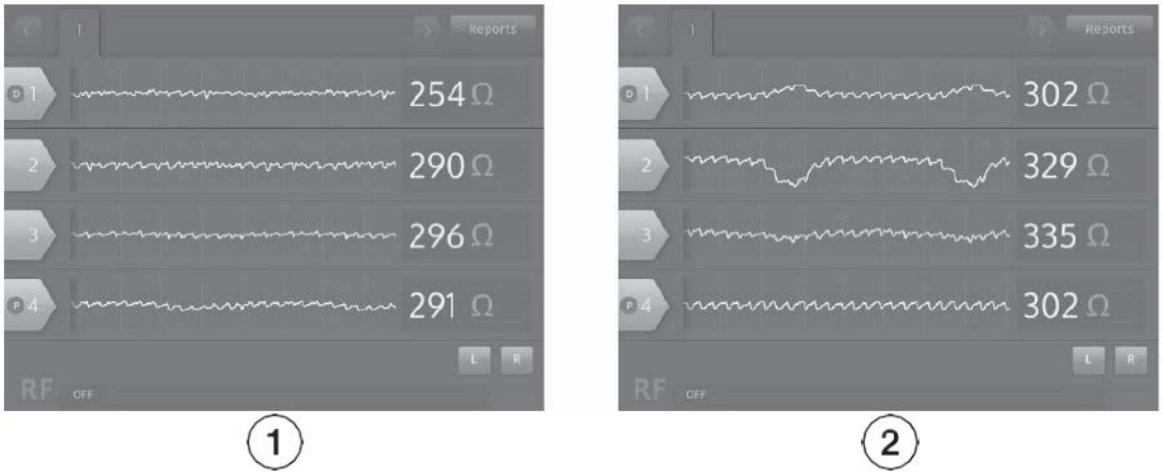
1 Guidewire inserted beyond the distal tip (spiral not deployed).

2 Guidewire retracted proximal to the proximal most electrode (spiral deployed).

Figure 3A. Making adequate contact with the artery as shown on the Symplicity G3 generator display

1 Adequate wall contact as indicated on the Symplicity G3generator display. All 4 electrode impedance values are stable, as shown by an overall linear impedance tracing at all electrodes.

2 Inadequate wall contact as indicated on the Symplicity G3 generator display. Cyclic, large amplitude tracing is observed on electrode 2, in particular, and on electrode 1. Catheter adjustments are necessary to achieve adequate wall contact.



1 2

1. Under fluoroscopic guidance, advance the catheter until the distal electrode is located in the renal artery (Figure 2A).
2. Under fluoroscopic guidance, deploy the Symplicity Spyral catheter by retracting the guidewire into the device until the guidewire tip is proximal to electrode 4 (Figure 2A, image 2).Make sure the guidewire does not completely exit the rapid exchange port.
3. Adequate wall contact is assessed by the physician and is achieved when the following two conditions are met:
    a. Deployment of the distal end appears adequate when observed angiographically.
    b. Impedance values at each electrode are stable through at least one respiratory cycle (Figure 3A, image 1). clockwise and/or slightly move the catheter forward. These small maneuvers should improve electrode apposition against the vessel wall.

Note: If these small adjustments do not improve wall contact, reinsert the guidewire in the distal end of the catheter and change the device location in the artery.

4. If an electrode is not located within the renal artery, or if any electrode deploys in an unsuitable location (such as the ostium of a small vessel or an adrenal gland feeder), deselect (turn off) these electrodes by pressing the electrode number button on the remote control or on the generator touch screen. By deselecting these individual electrodes, RF energy will not be delivered to these electrodes when RF is activated.

Note: Deselection must happen when all electrodes are outside the guide catheter and are displaying impedance values.

5. If desired, for annotation purposes, the left or right kidney can be annotated for the treatment by pressing the icons on the generator touch screen or by depressing the kidney button on the remote control. Pressing the button on the remote control will alternate between the left and right kidney selection.

Performing ablation procedure

1. Once electrodes are well apposed angiographically and impedance values and tracings are stable, RF energy can be delivered to the treatment site. This is done by pressing any of the following: the RF button on the generator front panel, the RF button on the remote control, or an optional foot switch. The generator delivers power for a target duration of 60 s using an automated algorithm and will cease power delivery upon completion of the treatment after 60 s. The timer begins counting up and the LED indicator remains illuminated while RF energy is being delivered. At any point during the procedure, delivery of RF energy can be stopped by pressing the RF button on the generator front panel, pressing the RF button on the remote control, or depressing an optional footswitch.

   Note: If the ablation does not initiate due to high-impedance values, first check the catheter position, then check the contact of the dispersive electrode, and finally try moving the dispersive electrode to the patient's flank.

2. If the generator stops delivering RF energy to one or more electrodes before reaching the 60 s treatment duration, an additional RF ablation may be performed from the electrode(s) that did not complete treatment at the same location. First, image the artery to ensure that it is safe to perform an ablation. Using the touchscreen, deselect electrodes that completed a 60 s cycle. If needed, perform a slight adjustment to the catheter to ensure proper wall contact, then initiate ablation again.

   Note: The generator may automatically stop delivering RF energy if certain conditions are detected. A system indicator message or code will appear on the display (see the generator user manual). In the case of a hardware fault condition, the generator will activate an LED indicator light, emit an audio alert, and display a fault code, if applicable (see the generator user manual for more information about indicator messages and codes).

3. If multiple treatments are to be performed in one artery, move the catheter proximally by pulling it back while taking care to avoid diseased or calcified areas of the vessel. A slight clockwise rotation while pulling back can be applied to ease the motion. All treatments should be located at least 5 mm proximal to any prior treatment location.
4. Once the treatment is completed on one side, advance the guidewire carefully out the tip of the catheter to straighten the spiral distal end. Retract the straightened catheter into the guide catheter and obtain an image of the artery.
5. If treating another vessel, reposition the guide catheter within the next vessel. Repeat the procedure for positioning the catheter and delivering treatments.
   - If excessive resistance is felt between the guide catheter and electrodes while retracting, consider adjusting the guide catheter position in the vessel to align the catheter coaxially with the guide catheter tip.

- Ensure that the guide catheter is flushed with heparinized saline periodically, or, at a minimum, between each treatment. Whenever flushing the guide catheter, wait at least 3 s to allow the temperature and impedance measurements on the Symplicity G3 generator display to stabilize before initiating the next treatment.

Post procedure

1. Upon completion of all treatments, straighten the distal end by advancing the guidewire, and then withdraw both the guidewire and the straightened catheter completely from the guide catheter.
2. Retract the guide catheter from the sheath.
3. Remove the introducer sheath from the artery and use standard of care procedures to achieve hemostasis at the puncture site.
4. Dispose of the devices in accordance with local hospital, administrative, and/or other government policies.

Appendix 3: Clinical History of Renal Denervation

Renal denervation as a treatment for hypertension has been commercially available outside the US for over 10 years with extensive peer-reviewed literature supporting the ongoing safety and utilization of Medtronic's Symplicity renal denervation system.

Medtronic's first series of studies on renal denervation used the first generation single electrode Symplicity (Flex) catheter. A change in the catheter design in later studies transitioned from a single electrode catheter to a multi-electrode catheter to drive greater consistency in therapy delivery. The predetermined safety algorithm controlling energy delivery and the mode of utilizing RF are identical.

Symplicity HTN-1

In 2009, Krum and colleagues reported the results of the first proof-of-principle multicenter study in which 45 patients with uncontrolled ("treatment resistant") hypertension underwent percutaneous renal denervation using the Symplicity™ RF ablation system (Flex). The inclusion criteria were office SBP ≥ 160 mmHg and prescription of at least 3 anti-hypertensive drugs including a diuretic or confirmed intolerance to medications. Patients were excluded if they had impaired renal function, type 1 diabetes or a known secondary cause of hypertension other than sleep apnea or chronic kidney disease. The average BP at enrollment was 177/101 mmHg and patients were prescribed an average of 4.7 anti-hypertensive drugs. At the primary follow-up endpoint of 6 months after renal denervation, the mean reduction in office SBP/DBP was −21/−10 mmHg.

The patients enrolled in this proof-of-principle trial formed part of the larger total single-armed cohort included in the SYMPLICITY HTN-1 trial (n=153). Upon expansion of the initial proof-of-principle study, the follow-up duration was increased to up to 3 years. The SYMPLICITY HTN-1 trial enrolled patients at 19 centers in Australia, Europe and the United States. The mean baseline office BP in the expanded cohort was 176/98 mmHg while patients were on an average of 5.1 anti-hypertensive drugs. The mean reductions in office BP were sustained over 36 months of follow-up after renal denervation (−32.0 [95% CI: −35.7 to −28.2] / −14.4 [−16.9 to −11.9] mmHg).

Study limitations which led to the development of SYMPLICITY HTN-2 include:

- SYMPLICITY HTN-1 did not include mandatory 24-hour ambulatory BP monitoring.
- SYMPLICITY HTN-1 did not include a control group for comparison.

SYMPLICITY HTN-2

The multicenter randomized controlled SYMPLICITY HTN-2 trial was initiated to advance and further test the findings from the SYMPLICITY HTN-1 trial. The SYMPLICITY HTN-2 trial enrolled patients at 24 centers in Europe, Australia and New Zealand. The inclusion criteria were similar to SYMPLICITY HTN-1 and included an office SBP ≥ 160 mmHg (≥ 150 mmHg in patients with DMT2) despite the use of

≥ 3 anti-hypertensive drugs including a diuretic, and an eGFR > 45 mL/min/1.73 m^2. As part of the screening process, patients were required to record twice daily home BP measurements using an automated device and to document their drug compliance for 2 weeks. Patients with an office BP that was below the enrollment criteria when they returned to the clinic after 2 weeks were excluded. Office BP measurements were performed with an automated device, and the average of three measurements was reported.

There were 106 patients with uncontrolled hypertension on stable prescribed drug therapy randomized to either the denervation group (n=52) or the control group (n=54). Control group patients were instructed to maintain their current drug treatment regime and were aware of their randomization. The mean number of anti-hypertensive medications at baseline was 5.2 ± 1.5 in the denervation group and 5.3 ± 1.8 in the control group. The mean baseline office BP was 178/97 mmHg in the denervation group and 178/98 mmHg in the control group. Office BP fell by an average of −32/−12 mmHg in the denervation group at 6 months (SD 23/11, p < 0.0001), compared with a nominal increase of 1/0 mmHg in the control group (p=0.77 systolic and p=0.83 diastolic). The between-group difference in the change in BP favored denervation by −33/−11 mmHg, and the differences in both SBP and DBP were significant (p < 0.0001).

A subgroup of 20 patients in the denervation group and 25 in the control group also had 24-hour ambulatory BP monitoring before and 6 months after denervation. The ambulatory BP was recorded every 15 min during the daytime and every 30 min during the nighttime. The average 24-hour ambulatory BP decreased significantly by −11/−7 mmHg in the denervation group (SD 15/11; p=0.006 for SBP change, p=0.014 for DBP change), whereas the decrease in the control group (–3/–1 mmHg) was not significant ([19/12];p=0.51 for systolic, p=0.75 for diastolic). The between-group difference in 24-hour ambulatory SBP favored denervation by −8/−6 mmHg (p < 0.05).

After 6 months, 35 patients in the control group crossed over to undergo denervation, and these patients had a significant drop in office BP similar to that observed in the initial denervation group. The changes in office BP after denervation were sustained out to 3 years.

SYMPLICITY HTN-3

Following the positive results of SYMPLICITY HTN-1 and 2, a multicenter randomized trial (SYMPLICITY HTN-3) was conducted using the Symplicity (Flex) RF ablation system. This was the first RDN trial to incorporate a blinded sham-controlled design. Patients were enrolled from 88 centers in the US and met the following inclusion criteria:

- Office SBP ≥ 160 mmHg on an initial screening visit as well as a confirmatory Screening Visit 2 weeks later;
- Prescribed use of ≥ 3 anti-hypertensive medications including a diuretic at maximal tolerated doses (with no changes for at least 2 weeks prior to screening);

- eGFR > 45 mL/min/1.73 m^2.

Patients were excluded if they had an average 24-hour ambulatory SBP < 135 mmHg at the second screening visit. All patients underwent renal angiography before randomization, and patients with renal artery stenosis > 50%, renal artery aneurysm, prior renal artery intervention, multiple renal arteries, a renal artery of < 4 mm in diameter or a treatable segment < 20 mm in length were excluded. Of 1,455 patients screened, 535 were randomized in a 2:1 ratio to either RDN or sham treatment. All patients were blinded to randomization using sedation, sensory isolation and lack of familiarity with the procedure. In addition, those individuals who performed BP measurements were blinded to the patients' randomization assignments. The primary efficacy endpoint was the change in office SBP at 6 months between the denervation and sham groups; changes in the 24-hour BP between the two groups served as a secondary endpoint. Office BP measurements were performed with an automated device, and the average of three measurements within 15 mmHg was reported. Ambulatory BP was measured every 30 minutes over 24 hours. After 6 months of follow up, patients in the sham-control group could crossover to the denervation group if they continued to meet baseline enrollment criteria.

Baseline office BP averaged 180/97 mmHg for the denervation group and 180/99 mmHg for the sham group. Patients were prescribed an average of 5 anti-hypertensive drug classes. The average number of ablations was 11.2 ± 2.8 in both renal arteries combined (the protocol required 4–6 per renal artery). After 6 months, the mean decrease in office BP was −14.1 ±23.9/6.6 ± 11.9 mmHg in the denervation group and −11.7 ± 25.9/4.6 ± 13.6 mmHg in the sham group. Although the decreases in office SBP from baseline were significant in both groups, there was no significant difference in the primary efficacy endpoint of BP change (−2.39 mmHg, 95% CI: −6.89 to 2.12), p = 0.26) between the two groups as compared to a prespecified superiority margin of 5 mmHg. BP decreases from baseline were significant in both treatment groups; however, the between-group differences in changes in office and ambulatory SBP were not significant (Bhatt et al 2014). The average decrease in 24-hour SBP was −6.8 ± 15.1 mmHg in the denervation group and −4.8 ± 17.2 mmHg in the sham group, and both changes were significantly different from baseline; however, there was no significant difference in the BP change (−1.96 mmHg [95% CI: −4.97 to 1.06]; p=0.98) between the two groups.

The safety of renal denervation was also evaluated in SYMPLICITY HTN-3. The rate of MAEs at 6 months was 1.4% in the denervation group and not statistically different from the rate of 0.6% in the sham-control group. This rate was also significantly lower than the prespecified performance metric of 9% and thus the trial achieved its primary safety endpoint. The rate of all-cause death was 0.6% in both groups. The rate of a hypertensive crisis/emergency that required hospitalization was 2.6% in the denervation group and 5.3% in the sham group (p=NS). The rate of renal artery stenosis > 70% was 0.3% in the denervation group and 0% in the sham group.

A larger than expected decrease in office and ambulatory SBP occurred in the control group of SYMPLICITY HTN-3 suggesting that other factors impacting BP were not controlled in this study. Additional analyses explored the inability of renal denervation to significantly reduce BP compared to sham group reductions and the possibility for biased patient behavior, despite sham control. Notably, changes in prescribed medication were documented in 39% of patients during the study period, despite the protocol mandating no medication changes. Adherence to prescribed medications was not objectively monitored by blood or urine testing as part of the study protocol. Therefore, the actual rates of drug adherence and potential changes in drug adherence between baseline and primary endpoint assessment are unknown in HTN-3 and could have been different between groups.

Incomplete or insufficient denervation may also have confounded the results of HTN-3 at the 6 month endpoint. Post hoc review of fluoroscopic images recorded during the trial revealed that only 6% of patients in the denervation group received a complete circumferential ablation pattern in both renal arteries as was recommended in the protocol.

In evaluating the outcomes of SYMPLICITY HTN-3, several confounding factors were identified that are believed to have contributed to the neutral outcomes of that study. These include the incompleteness of the renal denervation procedure, the study population, and the anti-hypertensive drug regimen required by the protocol. The design features of the OFF MED and ON MED studies incorporate design elements derived from these investigations.

Specific changes in study protocols derived from prior learnings:

A key difference relates to the denervation procedure. Available data provide strong evidence that both greater uniformity and extent of renal denervation occurs when ablations are performed not only in a circumferential pattern but also more distal in the renal arterial tree than was done in SYMPLICITY HTN-3, namely by including additional ablations in the branch vessels where the renal nerves are closer to the vessel lumen. The use of the Symplicity Spyral catheter and the updated denervation procedure used in the OFF MED and ON MED studies specifically address this issue.

A change in approach to both the population under study and the management of anti-hypertensive agents was determined by careful review of the development pathway for pharmaceutical drugs approved for use as anti-hypertensive agents. It became clear from this review that the severe resistant hypertension population chosen for the SYMPLICITY HTN-3 clinical study was very different from the participants commonly studied for drug approval. Further, Medtronic learned that the severe resistant hypertension population contributed a number of undesirable confounders to clinical study design, study execution, and, ultimately, the study outcomes. Given these learnings, the population proposed for evaluation in both the OFF MED and ON MED studies more closely matches the typical populations used in hypertension regulatory studies.

And finally, the approach for the design of the SPYRAL HTN clinical program was designed to be consistent with studies required to support regulatory approvals for pharmaceuticals. Specifically, Medtronic focused on OFF MED being conducted in the absence of anti-hypertensive medications to demonstrate pure reductions in BP without impact/ interference of medications (proof-of-principle). ON MED, in the presence of anti-hypertensive medications was intended to be supplementary data to evaluate the efficacy of RDN in parallel with drugs to determine any interaction and reflect how the device is likely to be used clinically.

Learnings from HTN-3 were shared with 2018 Circulatory System Devices Panel and study designs for the OFF MED and ON MED studies were also consistent with panel recommendations (see Section 4.1.1).

Appendix 4: Medication Burden Analysis Method

Medication Index 2 (Medication Burden)	A composite index based on the doses of medications but multiplies this result by the number of prescribed medications. Medication burden is calculated for all antihypertensive medications at study specified follow-up visits for each patient and added to yield a single, summative score. All classes of drug are considered equivalent in potency so the "class weight" is set a "1" for all antihypertensive medications (Law et al 2003). $MedIndex2 = no.of\ meds \sum_{n=1}^{\infty} \left(class\ weight\ \frac{prescribed\ dose}{standard\ dose} \right)$ Class weight = 1 Standard dose = JNC 7 max daily recommended dose

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Appendix 6: Registries Demonstrating RDN Durability

Registry Name/ Geography	Study Design	Device Used	Number of Subjects	F/up duration (yrs)	Citation
Swedish Reg	Prospective Multi Center Registry	Symplicity Flex Symplicity Spyral Others	252	3	J Hypertens. 2018 Jan;36(1):151-158. doi: 10.1097/HJH.0000000000001517.
Russian (Tomsk)	Prospective Registry Single Center	Symplicity Flex	55	3	Heliyon 2022 https://doi.org/10.1016/j.heliyon.2022.e08747
Swiss Reg	Retrospective Analysis of outcomes Single center	Multiple	17	3	J Clin Hypertens. 2020 DOI: 10.1111/jch.14005
Dutch Reg	Prospective Registry Single Center	Symplicity Flex, Symplicity Spyral, others	29	3.5	Zeijen Clin Res Cardiol 2022. https://doi.org/10.1007/s00392-022-02056-5
Thai Reg	Prospective Registry Single Center	Symplicity Flex	18	1-9	Hypertension Research (2022) 45:962–966 https://doi.org/10.1038/s41440-022-00910-7
Russian (St. Petersburg)	Prospective Registry Single Center	Symplicity Flex	22	1-5	Артериальная Гипертензия 2021;27(3):318–332
Australian Reg	Retrospective Registry Single Center	Symplicity Flex	66	8.8	Hypertension. 2023 Apr;80(4):811-819. doi: 10.1161/HYPERTENSIONAHA.122.20853. Epub 2023 Feb 10.
Homburg Reg	Retrospective Registry Single Center	Symplicity Flex	39	9.4	J Am Coll Cardiol. 2023 Feb 7;81(5):517-519. doi: 10.1016/j.jacc.2022.11.038.
Halle Reg	Retrospective Registry Single Center	Symplicity Flex	72	9.3	Front Cardiovasc Med. 2023 Jun 19;10:1210801. doi: 10.3389/fcvm.2023.1210801.