Medtronic

Symplicity Spyral™

Multi-Electrode Renal Denervation Catheter, RDN016

Instructions for Use

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

1 Explanation of symbols on product or package

Applicable symbol standards

- ISO 15223-1:2016 Cor 2017 : Medical Devices — Symbols to be used with medical device labels, labeling and information to be supplied

9.3.1

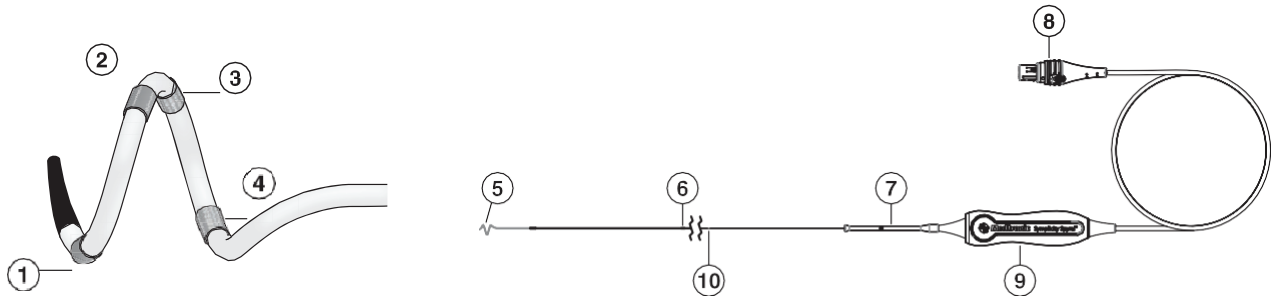
Symbol	Reference	Symbol title	Explanatory text
	ISO 15223-1 Clause 5.1.1	Manufacturer	Indicates the medical device manufacturer.
	Medtronic	Quantity	Indicates the quantity of devices present in the package.
	ISO 15223-1 Clause 5.1.5	Lot number	Indicates the manufacturer's batch code so that the batch or lot can be identified.
	ISO 15223-1 Clause 5.1.4	Use-by date	Indicates the date after which the medical device is not to be used.
	ISO 15223-1 Clause 5.1.3	Date of manufacture	Indicates the date when the medical device was manufactured.
	ISO 15223-1 Clause 5.1.6	Catalog number	Indicates the manufacturer's catalog number so that the medical device can be identified.
	Medtronic	For US audiences only	Indicates the adjacent text/symbology is intended for US audiences only.
	ISO 15223-1 Clause 5.4.3	Consult instructions for use at this website	Indicates the need for the user to consult the instructions for use.
	ISO 15223-1 Clause 5.6.2, 5.6.3	Nonpyrogenic fluid path	Indicates the presence of a fluid path. Indicates a medical device that is nonpyrogenic.
	ISO 15223-1 Clause 5.2.4	Sterilized using irradiation	Indicates a medical device that has been sterilized using irradiation.
	ISO 15223-1 Clause 5.2.6	Do not resterilize	Indicates a medical device that is not to be resterilized.
	ISO 15223-1 Clause 5.4.2	Do not reuse	Indicates a medical device that is intended for one use, or for use on a single patient during a single procedure.
	ISO 15223-1 Clause 5.2.8	Do not use if package is damaged	Indicates a medical device that should not be used if the package has been damaged or opened.
	ISO 15223-1 Clause 5.3.8	Humidity limitation	Indicates the range of humidity to which the medical device can be safely exposed.
	ISO 15223-1 Clause 5.3.9	Atmospheric pressure limitation	Indicates the range of atmospheric pressure to which the medical device can be safely exposed.
	ISO 15223-1 Clause 5.3.7	Temperature limit	Indicates the temperature limits to which the medical device can be safely exposed.
	Medtronic	Guide catheter/minimum inner diameter	Indicates the minimum inner diameter of the guide catheter.
	Medtronic	Maximum guidewire diameter	Indicates the maximum diameter of the guidewire.
	Medtronic	Peel tab to open	Indicates that the packaging should be opened via peel tab.
	Medtronic	Catheter effective length	Indicates the effective length of the catheter.
	Medtronic	Manual control	Indicates that the user should manually open tabs.
	Medtronic	Manufactured in	Indicates the manufacturing site of the device. A manufacturing site is the facility where the product is produced, transformed, or assembled into a medical device.

2 Product description

The Symplicity Spyral multi-electrode renal denervation catheter is designed to be used with the Symplicity G3 ™ renal denervation radiofrequency (RF) generator. The catheter connects to the generator using the integrated cable attached to the catheter handle. The catheter requires the use of a 0.36 mm (0.014 in) guidewire for delivery, preferably without hydrophilic coating. For a straighter electrode array during delivery, Medtronic recommends using an extra support guidewire such as the Medtronic Thunder ™ guidewire. In addition, an adult-sized dispersive electrode (also known as a neutral electrode, return electrode pad, or grounding pad) must be placed on the patient and connected to the generator for the therapy to be delivered (See *Table 3* for compatibility information). Other ancillary devices include: the Symplicity G3 generator, remote control, DVI-D cable, Symplicity G3 generator cart, and optional foot switch (see *Chapter 7* for further information).

The catheter has an effective length of 117 cm and is compatible with a 6 Fr guide catheter. It is designed for treating vessels with diameters ranging from 3 mm to 8 mm. As shown in *Figure 1*, the catheter features 4 gold radiopaque electrodes at the spiral (helical) distal end. The electrodes are deployed into a spiral (helical) shape by partially retracting the guidewire proximal to the spiral section of the catheter. The treatment length (the distance between electrodes 1 and 4) of the catheter is a function of the vessel diameter (*Table 1*). A radiopaque tip marker is located 1 mm proximal to the catheter tip and assists in the positioning of the catheter using fluoroscopic guidance. The catheter also features a straightening tool that facilitates safe insertion of the guidewire into the catheter (*Figure 3*). This tool is located near the handle and slides along the catheter shaft to straighten the distal end.

Figure 1. Symplicity Spyral catheter diagram (right) and deployed electrode configuration (left)



1 Electrode 1 (Distal)
2 Electrode 2
3 Electrode 3
4 Electrode 4 (Proximal)
5 Self-expanding electrode array assembly
6 Rapid exchange port
7 Straightening tool
8 Connector
9 Catheter handle
10 Femoral marker

Table 1. Treatment length

Treatment length: Distance between electrodes 1 and 4 as a function of deployed diameter	
Vessel diameter (mm)	**Treatment length (mm)**
3	21
4	20
5	20
6	19
7	18
8	17

The generator is represented in *Figure 2*. The front panel touch screen shows information such as impedance (as in *Figure 2*), continuous temperature, ablation time, and messages. The front panel also features an RF activation button. Channels on the generator screen correspond to each electrode on the catheter (refer to *Figure 2* and *Figure 1*, respectively). The generator touch screen and remote control allow the user to navigate different options, such as the selection or deselection of channels, viewing previous ablation data sets, or selecting the left or right kidney. The generator uses an automated algorithm to control the power and treatment settings based on real-time temperature and impedance feedback. Refer to the Symplicity G3 generator user manual for further information.

Figure 2. Representative image of the Symplicity G3 generator

Table 2. Specifications

Maximum output voltage	150 V_p
Rated accessory voltage	150 V_p
Maximum permitted length of accessory cords on the catheter connector	Not applicable[1]

[1]The Symplicity G3 generator is only compatible with the Symplicity Spyral catheter. The nominal catheter cord length is 3 m (118 in).

Note: The rated accessory voltage is limited by the generator.

9.3.2 Storage conditions

Temperature	15 °C to 40 °C (59 °F to 104 °F)
Humidity	10% to 90% relative humidity, noncondensing
Pressure	595 hPa to 1060 hPa [~0.595 to 1.05 ATM]

9.3.3 Transit conditions

Temperature	−35 °C to +57 °C (-31 °F to +135 °F)
Humidity	30% to 95% relative humidity, noncondensing
Pressure	595 hPa to 1060 hPa [~0.595 to 1.05 ATM]

Table 3. Compatible components

Component	Model	Symplicity G3 generator model number	Corresponding schematic on generator
Dispersive electrodes	Covidien Valleylab ™ REM ™ Polyhesive Adult Patient Return Electrode, Model E7507	RDNG3A	
	Covidien Valleylab REM Polyhesive Adult Patient Return Electrode, Model E7507DB	RDNG3A	
Foot switch (optional)	Herga Technology Foot Switch ™, Model 6210-0058	RDNG3A	

3 Intended use

The Symplicity G3 Renal Denervation RF Generator when used with the Symplicity Spyral multi-electrode renal denervation catheter is intended to deliver radiofrequency (RF) energy through the wall of the renal artery to denervate the kidney from sympathetic nerve hyper-activity.

4 Indications for use

The Symplicity Spyral Multi-Electrode Renal Denervation Catheter and the Symplicity G3 RF Generator are indicated to reduce blood pressure as an adjunctive treatment in patients with hypertension in whom lifestyle modifications and antihypertensive medications do not adequately control blood pressure.

5 Contraindications

- Renal artery diameter <3mm or >8mm
- Renal artery fibromuscular dysplasia (FMD)
- Stented renal artery (<3 months prior to RDN procedure)
- Renal artery aneurysm
- Renal artery diameter stenosis >50%
- Pregnancy
- Presence of abnormal kidney (or secreting adrenal) tumors
- Iliac/femoral artery stenosis precluding insertion of the catheter

6 Conditions for use

- The catheter is intended for single use only.
- The catheter is intended for use only with the Symplicity G3 renal denervation RF generator.
- The product must be used on or before the use-by date provided on the label.
- Before use, the product should be stored in a cool, dry place. The product should not be exposed to organic solvents, ionizing radiation, or ultraviolet light. Carefully inspect the sterile package for damage before opening. Do not use if the package has been damaged or opened.

7 How supplied

The catheter is contained in a dual tray configuration. The catheter is sterilized using irradiation. The inner tray retains the catheter, while the outer tray with a sealed Tyvek™® lid provides a sterile barrier. The generator and the components provided with it are nonsterile and reusable.

The following system components are compatible with the catheter:

9.3.4 Components available separately

- Symplicity G3 generator, which is provided with the components listed below:
  - Hospital-grade AC power cord
  - Remote control
  - DVI-D cable
- Symplicity G3 generator cart
- Foot switch (see *Table 3* for compatibility information)

The following items are not supplied, but are required to complete the treatment:

- A 0.36 mm (0.014 in) guidewire, preferably without hydrophilic coating
- A dispersive electrode (see *Table 3* for compatibility information)
- A sterile bag to cover the remote control if used in the sterile field
- Other standard items used to aid percutaneous transluminal catheterization in renal arteries

The following accessories are not supplied, but are needed to gain access to the target vessels:

- A 6 Fr guide catheter
- An introducer sheath
- A stopcock sidearm
- A Tuohy-Borst adapter

8 Risks and hazards

Biological hazards include: risks of infection, toxicity, abnormal hematology profile, reaction, hemorrhage, and pyrogenicity.

Environmental hazards are consistent with standard hospital protocols for proper use and disposal of biological wastes.

Radiation hazards are consistent with normal use of x-ray during interventional procedures.

9 Warnings and precautions

9.1 Related to the use of radiofrequency in catheterization laboratories

- Radiofrequency surgery uses high-frequency output. Do not perform procedures if flammable or explosive media are present, such as flammable anesthetics or skin preparation agents.
- Interference produced by the operation of high-frequency surgical equipment may adversely influence the operation of other electronic medical equipment such as monitors and imaging systems.
- Radiofrequency surgery may produce a hazardous electrical output. This equipment is for use only by qualified medical personnel trained in the use of this equipment.

9.2 Related to interventional techniques

- Use caution when accessing the renal vasculature and treating arteries.
- A thorough understanding of the technical principles, clinical applications, and risks associated with vascular access techniques and percutaneous transluminal catheterization in renal

arteries is necessary before using this device. Physicians should be familiar with techniques used to mitigate potential procedural problems that could be encountered while treating renal arteries such as arterial dissection or perforation, or kidney perforation. Ensure that accessories and products that are typically used in such situations are available.

- Ensure that the guide catheter is flushed with heparinized saline between each treatment.
- 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.
- Avoid using ionized contrast agent when performing renal denervation.

9.3 Use in special populations

Information on use of the Symplicity Spyral renal denervation system in certain special patient populations is derived from clinical studies of the Symplicity renal denervation system. See Section 11 – Overview of clinical trials.

The safety and efficacy of the of the Symplicity Spyral system has not been established in patients with isolated systolic hypertension

The safety and efficacy of the of the Symplicity Spyral system has not been established in patients with prior renal artery interventions including renal stents, renal angioplasty, or prior renal denervation.

9.3.1 Pregnancy and Lactation

Careful consideration should be given to the use of the Symplicity Spyral renal denervation system in patients who are pregnant or breastfeeding due to the risk of significant exposure to x-rays and the use of anticoagulation medication during the procedure. The device has not been studied in patients who are pregnant or breastfeeding.

9.3.2 Gender

Clinical studies of the Symplicity Spyral system did not suggest any significant differences in safety and effectiveness for male and female patients.

9.3.3 Ethnicity

Clinical studies of the Symplicity Spyral system did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity.

9.3.4 Pediatric Use

The Symplicity Spyral renal denervation system has not been studied in patients who are less than 18 years old.

9.3.5 Elderly Patients (>65 years of age)

Clinical studies of the Symplicity Spyral system did not suggest any significant differences in safety and effectiveness for patients <65 or ≥65 years of age

9.3.6 Patients with known comorbidities

Diabetes: The Symplicity Spyral system has not been studied in patients with Type I Diabetes Mellitus. Type II diabetes patients in the treatment group comprised 4.4% (8/182) of the patient population studied in the HTN-OFF MED and 10.7% (22/206) of the patient population studied in the HTN-ON MED clinical studies. No safety or effectiveness related differences were observed between the Type II diabetic and non-diabetic population in clinical studies.

Reduced Kidney Function: The Symplicity Spyral system has not been studied in patients with eGFR less than 45 mL/min/1.73m^2. CKD patients (defined as an eGFR of less than 60 mL/min/1.73m^2) in the treatment group comprised 3.8% (7/182) of the patient population studied in the HTN-OFF MED and 6.8% (14/206) of the patient population studied in the HTN-ON MED clinical studies. No safety or effectiveness related differences were observed between the CKD and non-CKD population in clinical studies. .

9.4 Related to patient

- The Symplicity Spyral renal denervation system has not been studied for the treatment of secondary hypertension.
- Careful consideration should be given to use of the Symplicity Spyral renal denervation system in patients with aortic grafts or who have received a renal stent in the last 3 months.
- Avoid use of the catheter in individuals in whom a reduction in blood pressure would be considered hazardous (such as those with hemodynamically significant valvular heart disease).
- Avoid treating in arteries with significant disease or with flow-limiting obstructions. See contraindications for arterial diameter restrictions
- Avoid treating renal arteries inside the renal parenchyma, as identified by fluoroscopy.
- Avoid treating in arteries with a diameter less than 3 mm or greater than 8 mm. See contraindications for arterial diameter restrictions
- Avoid treatment with the Symplicity Spyral catheter within 5 mm of any diseased area or stent.
- Implantable pacemakers (IPGs) and implantable cardioverter defibrillators (ICDs) or other active implants may be adversely affected by RF ablation. Refer to the implantable device's Instructions for Use.
- Safe use of monopolar radiofrequency surgery demands proper attachment of a dispersive electrode to the patient. Follow all of the manufacturer's directions for skin preparation, the placement of the dispersive electrode, and proper insulation between the patient and any metal surfaces. Failure to achieve good skin contact with the entire adhesive surface of the dispersive electrode may result in a burn or high impedance measurements.
- The patient should not come into contact with metal parts that are grounded or have an appreciable capacitance to ground (such as operating table supports, etc). The use of antistatic sheeting is recommended for this purpose.
- The patient's heart rate may drop during the ablation procedure. Consider the administration of medication such as atropine when clinically indicated.
- The patient may experience pain when radiofrequency energy is delivered. Proper pain medication should be administered at least 10 min before ablating renal nerves. Consider pre-treatment with both anxiolytic medications and analgesic medications, such as morphine sulfate or fentanyl (with additional doses timed with ablation treatments as appropriate).

9.5 Related to ablation catheter and generator

- The generator should be powered on and allowed to complete the system self-tests before introducing the catheter to the vasculature.
- The catheter is intended for single patient use only. Do not resterilize or reuse. Reuse, reprocessing or resterilization may compromise device integrity and functionality and may create the risk of transmission of infectious diseases from one patient to another, which may result in injury, illness, or death of the patient.
- Do not advance the catheter against resistance.
- Avoid advancing the guidewire too distally within the renal artery to reduce risk of damaging the kidney. Similarly, guidewires without hydrophilic coating are recommended to prevent unintentional damage to the kidneys or renal arteries.
- Deploy the catheter under fluoroscopic guidance. Avoid torquing the catheter beyond 180 degrees to prevent guidewire entanglement.

9.6 Related to RF treatment

- Remove any guidewires that are not contained within the Symplicity Spyral catheter (such as a buddy wire) from the treatment site before activating the RF output.
- The most distal ablation at the subsequent treatment site should be located approximately 5 mm proximal to the most proximal ablation performed during the preceding ablation.
- Do not ablate if the electrodes are in contact with each other per fluoroscopic observation.
- During RF delivery, avoid occluding blood flow, do not move the catheter or guidewire, and do not inject saline or contrast agent.
- Increased vessel reactivity, such as spasm, may be encountered.
- In the event that the generator stops delivering energy due to high temperature, record an image of the vessel to ensure there is no spasm or occlusion prior to repositioning the catheter in a different section of the artery.
- Do not touch a catheter electrode and the dispersive electrode at the same time during energy delivery as this may result in superficial skin burns.
- Do not allow a catheter electrode or dispersive electrode to come into contact with a metal instrument or surface during energy delivery as this may result in superficial skin burns.

Please consult the generator user manual for additional warnings and precautions.

10 Instructions for use

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

10.1 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 indicator messages or warnings (such as fault or status lights). Following a system self-test, the system is in the STANDBY state and no measurements 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.

10.2 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. For compatible dispersive electrodes, refer to *Table 3*.

   Warning: The dispersive electrode should be placed on the thigh or other nonbony 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 seconds 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.

10.3 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.

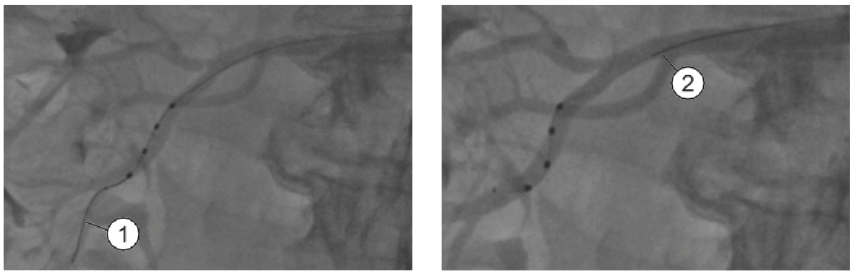
4. Remove the twist-tie clip from the coiled portion of the cable and pass the integrated cable out of the sterile field for an assistant to connect the cable to the appropriate receptacle on the side panel of the generator. The cable should be secured to the table or drape using a towel clamp, hemostats, 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 0.36 mm (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 3*, making sure that approximately 5 mm 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 5*) 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 3. Straightening tool used over the distal portion of the Symplicity Spyral catheter

10.4 Achieving adequate wall contact

Figure 4. 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 5. Making adequate contact with the artery as shown on the Symplicity G3 generator display

1 Adequate wall contact as indicated on the Symplicity G3 generator 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. Under fluoroscopic guidance, advance the catheter until the distal electrode is located in the renal artery (*Figure 4*).
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 4*, 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 5*, image 1).

Note: If wall contact does not appear to be adequate per the two criteria above, it is recommended to slightly adjust electrode positions. To do so, slightly torque the catheter 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.

10.5 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.

10.6 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.

PATIENT SELECTION FOR TREATMENT

In diagnosing and treating hypertension, proper blood pressure measurement techniques are essential to confirm the diagnosis and manage the condition. Medical professional society guidelines (1) provide recommendations regarding accurate and reproducible blood pressure assessment equipment and proper blood pressure measurement methods.

Medical professional society guidelines (2,3) provide target blood pressure goals that reduce end organ damage and cardiovascular risks and blood pressure lowering medication strategies. Lifestyle modifications (e.g., dietary salt restriction, heathy diet, weight loss in overweight individuals, exercise, and limited alcohol intake) and medical therapy are the first-line approaches to lower blood pressure. In hypertensive patients, these interventions reduce the risk of mortality, myocardial infarction, heart failure, stroke, and kidney disease. In general, meta-analyses of randomized hypertension treatment trials show a 2% cardiovascular absolute risk reduction for every 1 mmHg reduction in systolic blood pressure.

In hypertensive patients who are unable to achieve blood pressure goals with lifestyle modifications and an adequate trial of medical therapy, health care providers should consider whether:

- Patients are compliant with prescribed blood pressure medications. Patient counseling and the use of once daily fixed-dose combination antihypertension strategies are among the strategies that can improve medication adherence.
- Blood pressure control may be improved via up-titration of medication dosages or adding antihypertensive medications having a different mechanism of action from the current regimen
- Blood pressure measurements are accurate (e.g., using a proper cuff size)
- Patients are taking agents that can elevate blood pressure (e.g., nonsteroidal anti-inflammatory drugs or stimulants)
- Secondary causes of hypertension are present

Renal denervation with the Symplicity Spyral system is a treatment option in selected patients if blood pressure remains elevated despite: (1) lifestyle modifications and antihypertensive medical therapy; (2) addressing potential factors that may be contributing to inadequate blood pressure control; or (3) strategies to address potential contributing factors are ineffective, not feasible, or not aligned with the patient's interests.

PATIENT COUNSELING

Treatment with the Symplicity Spyral system should be based on a joint decision between the physician and the patient, considering the benefits and risks of the device and following a review of the device indications for use (Section 5), contraindications (Section 6), warnings (Section 8), precautions (Section 9), adverse events (Section 14.2), and clinical study data (Section 14). Patient consultation should include a comprehensive discussion of treatment options, an individualized benefit-risk assessment, and post-procedure follow-up recommendations

11 Overview of clinical trials

Information regarding clinical studies and post-approval studies that are applicable to The Symplicity Spyral Renal Denervation System are available on the Medtronic Manual Library website:

1. Point your browser to www.medtronic.com/manuals.
2. Select the geography and language, and then search by product name for Symplicity Spyral The instructions for use and the clinical data summaries are listed. The clinical study summaries include the following: study name, applicable device, patient population and indication, sample size, and follow-up duration.

If you do not have web access, you can order printed copies of the clinical study summaries from your Medtronic representative or by calling the toll-free number located on the back cover

12 Potential adverse events

Potential adverse events associated with use of the renal denervation device or the interventional procedures include, but are not limited to, the following conditions:

- Allergic reaction to contrast
- Arterial damage, including injury from energy application
- Arterial dissection or perforation
- Arterial spasm
- Arterial stenosis
- Arterio-enteric fistula
- AV fistula
- Bleeding
- Blood clots or embolism
- Bruising
- Cardiopulmonary arrest
- Complications associated with medications commonly utilized during the procedure, such as narcotics, anxiolytics, or other pain or anti-vasospasm medications
- Death
- Deep vein thrombosis
- Edema
- Electrolyte imbalance
- Heart rhythm disturbances, including bradycardia
- Hypotension
- Hypotension causing end organ hypoperfusion
- Hypotension – orthostatic
- Infection
- Kidney damage including renal failure
- Kidney perforation
- Myocardial infarction
- Nausea or vomiting
- Pain or discomfort
- Peripheral ischemia
- Pulmonary embolism
- Proteinuria
- Pseudoaneurysm
- Radiocontrast nephropathy
- Renal artery aneurysm
- Skin burns from a failure of the dispersive electrode pad
- Stroke

- Hematoma
- Hematoma - retroperitoneal
- Hematuria
- Hypertension

There may be other potential adverse events that are unforeseen at this time.

13 Disclaimer of warranty

9.3.7 The warnings contained in the product labeling provide more detailed information and are considered an integral part of this disclaimer of warranty. Although the product has been manufactured under carefully controlled conditions, Medtronic has no control over the conditions under which this product is used. Medtronic, therefore, disclaims all warranties, both express and implied, with respect to the product, including, but not limited to, any implied warranty of merchantability or fitness for a particular purpose. Medtronic shall not be liable to any person or entity for any medical expenses or any direct, incidental, or consequential damages caused by any use, defect, failure, or malfunction of the product, whether a claim for such damages is based upon warranty, contract, tort, or otherwise. No person has any authority to bind Medtronic to any representation or warranty with respect to the product.

The exclusions and limitations set out above are not intended to, and should not be construed so as to, contravene mandatory provisions of applicable law. If any part or term of this disclaimer of warranty is held to be illegal, unenforceable, or in conflict with applicable law by a court of competent jurisdiction, the validity of the remaining portions of this disclaimer of warranty shall not be affected, and all rights and obligations shall be construed and enforced as if this disclaimer of warranty did not contain the particular part or term held to be invalid.

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2022-10-20

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Medtronic

Symplicity Spyral™

Multi-Electrode Renal Denervation Catheter, RDN016

Clinical Study Summary

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

1. Overview of clinical studies

The SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED trials document the safety and effectiveness of renal denervation on blood pressure control in both the presence and the absence of antihypertensive medications, respectively.

The SPYRAL HTN-OFF MED is a global clinical trial of renal denervation with the Symplicity Spyral multi-electrode renal denervation system in patients with uncontrolled hypertension in the absence of antihypertensive medications, which was conducted in the United States, Japan, Canada, Europe and Australia.

The SPYRAL HTN-ON MED is a global clinical trial of renal denervation with the Symplicity Spyral multi-electrode renal denervation system in patients with uncontrolled hypertension in the presence of up to 3 antihypertensive medications. It was conducted in the United States, Japan, Canada, Europe and Australia.

Table 1 summarizes the clinical study designs for the SPYRAL HTN-OFF MED Clinical Study and the SPYRAL HTN-ON MED Clinical Study.

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Table 1. Clinical study designs

	SPYRAL HTN-OFF MED		**SPYRAL HTN-ON MED**	
	SPYRAL HTN-OFF MED Pilot	**SPYRAL HTN-OFF MED**	**SPYRAL HTN-ON MED Pilot**	**SPYRAL HTN-ON MED Expansion**
Study type	Multi-center Prospective Single-blind 1:1 randomization Interventional Sham-controlled	Multi-center Prospectively powered Single-blind 1:1 randomization Interventional Sham-controlled	Multi-center Prospective Single-blind 1:1 randomization Interventional Sham-controlled	Multi-center Prospectively powered Single-blind 2:1 randomization treatment to control (first 26 subjects 1:1) Interventional Sham-controlled
Study site location	United States, Canada, Japan, Europe and Australia		United States, Canada, Japan, Europe and Australia	
Number of subjects enrolled	In the period between June 2015 and August 6, 2015, 314 subjects were screened in order to randomize 80 subjects. 38 subjects were randomized to the rfRDN Group and 42 to the Control Group.	In the period between June 2015 and January 2020, 1629 subjects were screened in order to randomize a total of 366 subjects (80 HTN-OFF MED Pilot subjects, 251 HTN-OFF MED Expansion- Cohort subjects and the 35 subjects randomized after closure of the expansion Cohort and prior to enrollment stop for efficacy), 182 were randomized to undergo renal denervation using the multi-electrode RF catheter and 184 were randomized to receive the sham-controlled procedure.	In the period between June 2015 and May 2017, 467 subjects were screened in order to randomize 80 subjects. 38 subjects were randomized to the rfRDN Group and 42 to the Control Group.	In the period between June 2015 and March 2022, 1780 subjects were enrolled in order to randomize a total of 337 subjects (80 SPYRAL HTN-ON MED Pilot subjects and 257 SPYRAL HTN-ON MED Expansion subjects). 206 were randomized to undergo renal denervation using the multi-electrode RF catheter and 131 were randomized to receive the sham-controlled procedure.
Follow-up Duration	36 months	36 months	36 months	36 months
Status	Complete	Follow-up	Complete	Follow-up
Study rationale and purpose	The purpose of this study was to test the hypothesis that renal denervation decreases blood pressure and is safe when studied in the absence of antihypertensive medication.		The purpose of this study was to test the hypothesis that renal denervation decreases blood pressure and is safe in the presence of up to 3 standard antihypertensive medications.	
Eligibility: Inclusion Criteria	Individual is ≥20 and ≤80 years old at the time of enrollment. Individual has an office systolic blood pressure SBP)≥150 mmHg and <180 mmHg and a diastolic blood pressure (DBP ≥90 mmHg at baseline. Individual has a 24-hour Ambulatory Blood Pressure Monitoring (ABPM) average SBP ≥140 mmHg and <170 mmHg at baseline. Individual is willing to discontinue current antihypertensive medications at Screening Visit 1 through the 3 month post-procedure visit.		Individual is ≥20 and ≤80 years old at the time of enrollment. Individual has an office systolic blood pressure (SBP) ≥150 mmHg and <180 mmHg and a diastolic blood pressure (DBP ≥90 mmHg at baseline when receiving a medication regimen of 1, 2, or 3 antihypertensive medication classes of which at least 1 is ≥50%of the maximum manufacturer's dosage. Individual has a valid 24-hour Ambulatory Blood Pressure Monitoring (ABPM) average SBP ≥140 mmHg and<170 mmHg at baseline after witnessed antihypertensive drug ingestion before applying the ABPM device.	

Eligibility: Exclusion Criteria	• Individual has one or more of the following conditions: stable or unstable angina within 3 months of enrollment, myocardial infarction within 3 months of enrollment; heart failure, cerebrovascular accident or transient ischemic attack, or atrial fibrillation at any time. Patients are permitted to take aspirin or clopidogrel for cardiovascular risk reduction.
	• Patients who received catheter or surgical treatment for Atrial Fibrillation and are in sinus rhythm are not excluded.
	• Individual has undergone prior renal denervation.
	• Individual has renal artery anatomy that is ineligible for treatment including:
	  • Main renal artery for each kidney less than 3mm or greater than 8mm
	  • Lacks a main renal arterial vessel (greater than 3mm and less than 8mm in diameter) for each kidney that does not allow 4 simultaneous quadrantic (4SQ) radio frequency ablations in the main renal artery or equivalent (defined as 4SQ ablations in all branch vessels greater than 3mm and less than 8mm)
	  • Presence of FMD (defined as visible beading of the artery on angiography)
	  • Has >50% stenosis in any treatable vessel
	  • Has a renal artery stent placed <3 months prior to the denervation procedure
	  • Presence of an aneurysm defined as any localized increase in the diameter of the vessel
	• Treatment area within 5mm of a segment in the renal artery which contains any of the following:
	  • Atheroma,
	  • Calcification, or
	  • Renal artery stent
	• Individual has an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73m2, using the 4 variable MDRD calculation (in mL/min per 1.73 m2 = 175 x SerumCr-1.154 x age-0.203 x 1.212 (if patient is black) x 0.742 (if female). (NOTE: an eGFR calculation specific to Japanese patients will be used for subjects enrolled in Japan)			

	• Individual has documented type 1 diabetes mellitus or poorly-controlled type 2 diabetes mellitus with glycosylated hemoglobin greater than 8.0%. • Individual is taking SGLT2 inhibitors or GLP-1 agonists that have been prescribed < 90 days from Screening Visit 1 or who does not plan to remain on these drugs for the duration of the study • Individual has had ≥1 episode(s of orthostatic hypotension not related to medication changes within the past year or reduction of SBP of ≥20 mmHg or DBP of ≥10 mmHg within 3 minutes of standing coupled with symptoms during the screening process (at SV2 . • Individual requires chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea (e.g. CPAP, BiPAP). • Individual who requires more than occasional use (e.g. PRN) of narcotic drugs over the month prior to Screening Visit 1. • Individual has documented primary pulmonary hypertension. • Individual has an untreated secondary cause of hypertension (either known or suspected) or is taking drugs that increase sympathetic tone and could contribute to hypertension. • Individual has frequent intermittent or chronic pain that results in the treatment with non-steroidal anti- inflammatory drugs (NSAIDs) for two or more days per week over the month prior to Screening Visit 2. (patients are permitted to take aspirin or clopidogrel for cardiovascular risk reduction). • Individual with HIV on anti-retroviral drug therapy without documentation that hypertension preceded initiation of anti-retroviral drug treatment. • Individual works night shifts. • Individual has severe cardiac valve stenosis for which, in the opinion of the investigator, a significant reduction of blood pressure is contraindicated. • Individual is pregnant, nursing or planning to become pregnant during the course of the study follow-up. (Female participants of childbearing potential must have a negative serum or urine human chorionic gonadotropin (hCG) pregnancy test prior to angiography.) • Individual is currently taking mineralocorticoid receptor antagonists. (Subjects may be enrolled as long as mineralocorticoid receptor antagonists are weaned off at least 8 weeks prior to Screening Visit 1) • Individual has an active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior six months from consent. • Individual has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions. • Individual has polycystic kidney disease, unilateral kidney, atrophic kidney, or history of renal transplant.
Primary Safety Endpoint	Pooled analysis of first 253 evaluable rfRDN-treated subjects (initial procedure or crossover) from the HTN-OFF MED and HTN-ON MED trials, defined as a patient-level composite of the incidence of the following major adverse events (MAEs): • 1-month post-randomization adjudicated by the clinical events committee • All-cause mortality • End stage renal disease (ESRD) • Significant embolic events resulting in end-organ damage • Renal artery perforation requiring intervention • Renal artery dissection requiring intervention • Vascular complications (e.g., complications that require surgical repair, interventional procedures, thrombin injection or blood transfusion) • Hospitalization for hypertensive crisis not related to non-adherence with BP medications or the study protocol Renal artery stenosis (RAS) at 6 months, as defined as >70% diameter stenosis by angiography confirmed by the angiographic core lab
Primary Effectiveness Endpoint (Powered)	The primary effectiveness endpoints for HTN-OFF MED and HTN-ON MED and the powered secondary effectiveness endpoint (HTN-OFF MED only) were based on difference between randomized groups (rfRDN and Sham, ITT Cohort) using the Bayesian power prior approach methodology • HTN-OFF MED: Change in SBP measured by 24-hour ABPM from baseline to 3-months post-procedure, compared between the rfRDN and Sham groups • HTN-ON MED: Change in SBP measured by 24-hour ABPM from baseline to 6-months post-procedure, compared between the rfRDN and Sham groups Powered Secondary Effectiveness Endpoint for HTN-OFF MED: Change in OSBP from baseline to 3 months post-procedure compared between rfRDN and Sham groups
Secondary Effectiveness Endpoints (Non-Powered)	• Change in SBP from baseline (screening visit 2) to 3, 6, 12, 24, and 36 months post-procedure measured by 24-hour ABPM • Change in office SBP from baseline (screening visit 2) to 1, 3, 6, 12, 24, and 36 months post-procedure • Rate of achieving target OBP (SBP <140 mmHg) at 1, 3, 6, 12, 24, and 36 months post-procedure • Change in office DBP from baseline (screening visit 2) to 1, 3, 6, 12, 24, and 36 months post-procedure • Change in DBP from baseline (screening visit 2) to 3, 6, 12, 24 and 36 months post-procedure measured by 24-hour ABPM • Quality of life (QOL) assessed by EQ5D and SF36 (HTN-OFF MED only) • Antihypertensive medication usage throughout the study, including escape patients and subjects with medication changes within 3-month (OFF MED) and 6-month (ON MED) follow-up. Medication Burden is reported using two indices: o MedIndex 1 is the ratio of prescribed daily doses to maximum recommended daily dose, summed for all prescribed antihypertensive drugs o MedIndex 2 is MedIndex1 multiplied by number of medications
Secondary Safety Endpoints	Acute procedural events at 1-month post-procedure (rfRDN vs. Sham subjects) at 1 month post-procedure: • Significant embolic event resulting in end-organ damage • Renal artery perforation or dissection requiring intervention • Vascular complications • End-stage renal disease • ≥40% decline in eGFR • New MI or stroke • Renal artery re-intervention • Major bleeding per the TIMI definition (intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure) • Increase in serum creatinine >50% from Screening Visit 2 • Renal artery stenosis >70% diameter stenosis) confirmed by angiography and determined by the angiographic core laboratory • Hospitalization for hypertensive crisis not related to non-adherence with BP medications or study protocol Chronic safety endpoints at 3, 6, 12, 24, and 36 months post-procedure (rfRDN vs. Sham subjects) • All-cause mortality • End-stage renal disease • Significant embolic event resulting in end-organ damage • ≥40% decline in eGFR • New MI or stroke • Renal artery re-intervention • Major bleeding per the TIMI definition

	• Increase in serum creatinine >50% vs. screening visit 2 • Renal artery stenosis (>70% diameter stenosis confirmed by angiography and determined by the angiographic core laboratory (at 6 and 12 months only, or if renal artery imaging was performed outside of the protocol-specified windows) • Hospitalization for hypertensive crisis not related to non-adherence with BP medications or the study protocol RAS through 12-month based on CTA/MRA imaging. Sub-study on at least 150 patients who underwent rfRDN (in either HTN-OFF MED or HTN-ON MED studies) to assess extent of renal artery damage, including diameter stenosis <70%.
Product use	The Symplicity Spyral multi- electrode renal denervation catheter (Symplicity Spyral catheter) The Symplicity G3™ renal denervation RF generator (Symplicity G3 generator)

2. Accountability of PMA Cohort

a. HTN-OFF MED

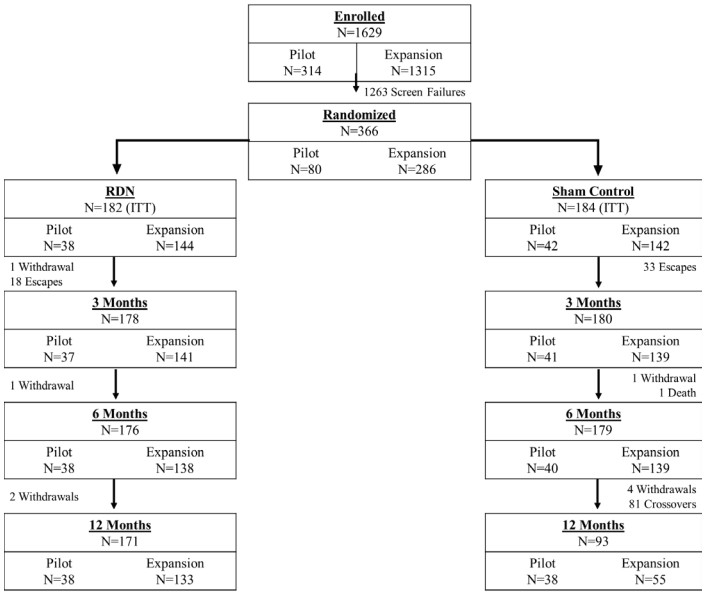


Figure 1: HTN-OFF MED Full Cohort Subject Accountability through 12 Months

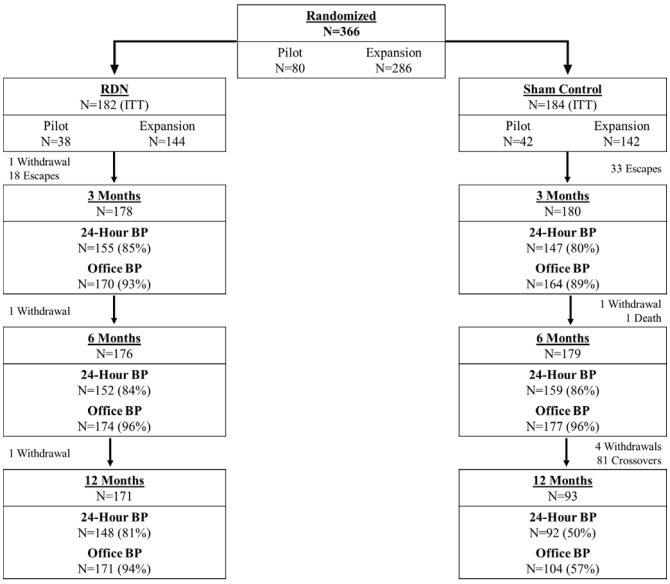


Figure 2: HTN-OFF MED Full Cohort Blood Pressure Endpoint Data Capture through 12 Months

Escape defined as Office SBP ≥180 mmHg OR <115 mmHg associated with symptoms of hypotension or safety concern requiring medication changes.

b. HTN-ON MED

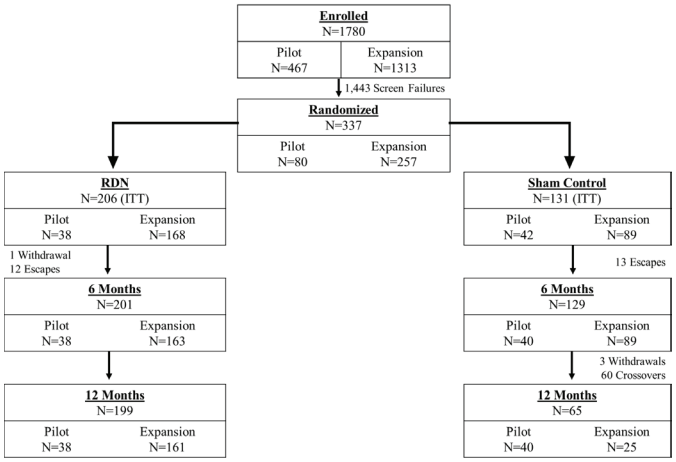


Figure 3: HTN-ON MED Full Cohort Subject Accountability through 12 months

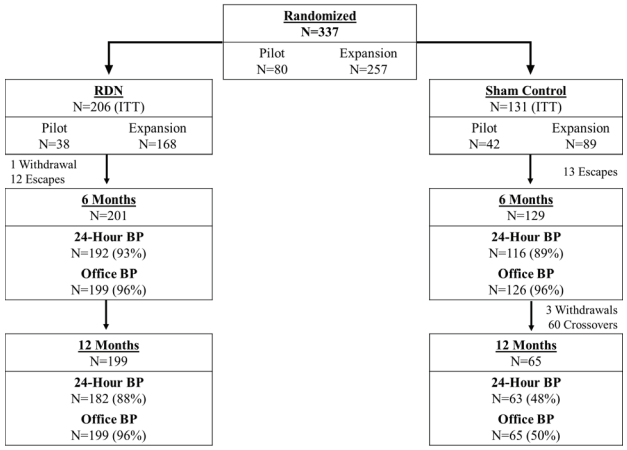


Figure 4: HTN-ON MED Full Cohort Blood pressure endpoint Data Capture through 12 months

Escape defined as Office SBP ≥180 mmHg OR <115 mmHg associated with symptoms of hypotension or safety concern requiring medication changes.

3. Safety Results

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

a. Primary Safety Endpoint Analysis

The primary safety endpoint was the incidence of major adverse events (MAE) at 1 month post-procedure and new renal artery stenosis evaluated at 6 months for the first 253 consecutive patients treated with rfRDN (initial procedure or crossover) in the HTN-OFF and HTN-ON MED studies.

The primary safety endpoint results are shown in Table 15. The primary safety endpoint rate was 0.4% with one-sided upper 95% confidence interval of 1.9%. The 7.1% performance goal was met p-value < 0.001).

b. Additional Safety Analyses

FDA also requested a post-hoc safety analysis on rfRDN-treated subjects from the four studies and all studies pooled using the same endpoint definitions. The results were similar across the studies, as shown in Table 2. There were 2 pseudoaneurysms requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion.

Table 2. Primary Safety Endpoint for the Pooled and Individual Studies (rfRDN Subjects)

	MAE Rate	One-sided upper 95% CI	p-value
Pre-specified Analysis of first 253 evaluable	0.4% 1/253)	1.9%	<0.001
All Studies Pooled	0.4% 2/537)	1.2%	<0.001
HTN-OFF Full Cohort	0.0% (0/182)	--	--
HTN-OFF Crossover	0.0% 0/125)	--	--
HTN-ON Full Cohort	1.0% 2/206)	--	--
HTN-ON Crossover	0.0% 0/24)	--	--

Data displayed as % n/N
p-values not adjusted for with multiplicity

c. Secondary Safety Endpoint Results

The rates of pre-specified MAE through 6 months for the HTN-OFF MED and HTN-ON MED (Full Cohort) studies are shown in Table 3 for the rfRDN and Sham groups. The rates of MAEs were low and similar between the Cohorts and studies.

Table 3. HTN-OFF MED and HTN-ON MED MAEs through 6 months for rfRDN and Sham Subjects

	OFF MED % Subjects with Events (n/N)		HTN-ON MED % Subjects with Events (n/N)	
	rfRDN (n=182) n (%)	Sham (n=184) n (%)	rfRDN (n=206) n (%)	Sham (n=131) n (%)
All-cause mortality	0 0%	0 0%	0 0%	0 0%
New myocardial infarction	0 0%	0 0%	0 0%	0 0%
Major Bleeding	0 0%	2 (1.1%	0 0%	0 0%
Significant embolic events resulting in end organ damage	0 0%	0 0%	0 0%	0 0%
Any renal artery reintervention	0 0%	0 0%	0 0%	0 0%
Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	0 (0%	1 (0.5%	2(1.0%	1 (0.8%
Hypertensive emergency resulting in hospitalization	1 (0.6%	0 0%	0 0%	0 0%
New Stroke	0 (0%	1 (0.5%	0 0%	1 (0.8%
New renal artery stenosis >70% diameter stenosis	0 0%	0 0%	0 0%	0 0%

Data displayed as % n/N

In HTN-OFF MED, 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. SAEs were reported in 8.7% and 11.5% of patients randomized to rfRDN and Sham groups, respectively, in the HTN-ON MED study. The only event that was experienced by more than one patient was vascular access site pseudoaneurysm (Table 4).

Table 4. HTN-OFF MED (24 Months) & HTN-ON MED (6 Months) Serious Adverse Events in > 1 Patient

	HTN-OFF MED (24 Months) % Subjects with Events (n/N)		HTN-ON MED (6 Months) % Subjects with Events (n/N)	
	rfRDN (N=182) n (%)	Sham (N=184) n (%)	rfRDN (N=206) n (%)	Sham (N=131) n (%)
Any Serious Adverse Event	31 17%	27 (14.7%	18 (8.7%	15 (11.5%
Sepsis	2 1.1%	2 1.1%	0 0%	0 0%
Vascular Access Site Haematoma	1 (0.5%	2 (1.1%	2 (1.0%	1 (0.8%
Arthralgia	1 0.5%	5 2.7%	0 0%	0 0%
Vascular Access Site Pseudoaneurysm	0 0%	0 0%	2 (1.0%	1 (0.8%

d. Adverse effects that occurred in the PMA clinical studies

In the OFF MED study, 82% of patients in the rfRDN 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 5). Overall, AEs were balanced across study groups.

Table 5. HTN-OFF MED (12 Months) & HTN-ON MED(6 Months) Pivotal Adverse Events (> 5 % in either arm) - Enrollment to 12 Months (Full Cohort)

	HTN-OFF (12 Months) % Subjects with Events (n/N		HTN-ON (6 Months) % Subjects with Events n/N)	
Events	**rfRDN (N=182) n (%)**	**Sham (N=184) n (%)**	**rfRDN (N=206)** n %	**Sham (N=131)** n %
Any Adverse Event	149 (81.9%	154 83.7%	129 (62.6%	89 67.9%
Headache	32 17.6%	31 16.8%	7 (3.4%	9 (6.9%
Vascular access site hematoma	16 8.8%	22 12.0%	10 4.9%	10 (7.6%
Dizziness	15 8.2%	12 (6.5%	0 0%	0 0%
Back pain	12 6.6%	8 (4.3%	12 5.8%	4 (3.1%
Peripheral edema	12 6.6%	15 (8.2%	6 (2.9%	12 (9.2%
Arthralgia	11 6.0%	13 (7.1%	0 0%	0 0%
Hypertension	11 6.0%	11 (6.0%	0 0%	0 0%
Nasopharyngitis	11 6.0%	14 7.6%	0 0%	0 0%
Hypokalemia	0 0%	0 0%	12 5.8%	8 (6.1%

One renal artery occlusion was reported in the rfRDN group. No dissection was identified by the Investigator during the case. The Angio Core Lab identified dissection in branch L1A that was not denervated. After 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, 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 did not identify a stenosis. The 24-months DUS was diagnostic with no stenosis identified.

In the HTN-ON MED study, AEs were reported for a total of 63% of rfRDN patients and 68% of Sham patients. The most frequently reported AEs in the rfRDN group were back pain, hypokalemia, and vascular access site hematoma (Table 6). The incidence and severity of hematomas was similar between groups and is expected for arterial interventional procedures.

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

Preferred Term	**rfRDN (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 rfRDN patients. One was identified by the angiographic core lab and reported by the site after further review, and 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.

In the HTN-OFF MED study, 1 non-Cardiovascular death occurred in the Sham group through 24 month follow-up. In the HTN-ON MED study, no deaths occurred through the 6-month timepoint.

e. Additional Safety Analyses

i. Assessment of Renal Artery Stenosis

Renal imaging was required in the HTN-OFF MED and HTN-ON MED studies at 6 and 12 months post-procedure. DUS was the first-line imaging modality in the majority of subjects, with repeat imaging via DUS, CTA, or MRA if the initial imaging was non-diagnostic. Renal angiography was required when measured diameter stenosis DS) > 60% when assessed by DUS or > 70% when assessed by CTA or MRA.

Imaging was considered diagnostic if any of following criteria 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
- For rfRDN patients imaging evaluability was assessed only for vessels treated with renal denervation.
- For DUS images, renal flow for accessory main renal arteries and branch vessels was confirmed by visualization of uniform parenchymal flow within segments of the same kidney as well as between kidneys

Of the images evaluated by imaging core laboratories, 100% of angiograms, 89% of DUS, 80% of CTA, and 37% of MRA results met the criteria for being diagnostic. Of 604 rfRDN subjects that had diagnostic baseline angiograms, 519 (86% had diagnostic follow-up imaging (the vast majority via DUS) at 6 months, and 474 85%) had diagnostic follow-up imaging (55% DUS and 45% CTA or MRA at 12 months.

DUS image quality can be highly operator-dependent in the renal vasculature, and this methodology can lack sensitivity to identify non-hemodynamically significant <70% diameter stenoses. HTN-OFF MED and HTN-ON MED studies did not provide data comparing DUS with angiography, CTA, or MRA to correlate imaging sensitivity or accuracy. In addition, the diagnostic imaging rates for CTA and MRA were affected by image quality issues as reported by the CTA/MRA core laboratory. These factors increased the uncertainty of renal artery stenosis assessment.

At 6 months, no potential stenoses of >60% were identified by DUS in either study.

In a separate 12-month analysis of 206 subjects who had diagnostic CTA/MRA, 13 subjects had potential stenosis of >50%. Seven of these subjects had follow-up imaging with angiography, CTA, or MRA that ruled out a stenosis > 70%, though 2 patients had renal angiograms read by the site as "no stenosis," but angiography was of insufficient quality for core lab to calculate diameter stenosis. Four subjects had follow-up imaging with only DUS or refused follow-up imaging. Two subjects had 60% stenosis confirmed by CTA. Carrying forward the results of subjects who did not have adequate follow-up imaging (6) and those with insufficient detail to determine diameter stenosis (2), the rate of renal artery stenosis >50% could be as high as 2.9% (6/206) to 3.9% (8/206) through 12 months.

ii. Renal Function (Estimated Glomerular Filtration Rate, eGFR)

Changes in renal function vs. baseline, assessed by calculating eGFR from serum creatinine (in mL/min per 1.73m2), were pooled for HTN-OFF and HTN-ON. Among 389 rfRDN subjects, 52 (13%) had a >10% decline in eGFR during follow-up. Comparatively, 74/297 (24.9% Sham subjects had a >10% decline in eGFR during follow-up. FDA requested data on the change in eGFR slope for rfRDN and Sham subjects for available follow-up. For this analysis, changes in serum creatinine (SCr) and eGFR from baseline to 3-month follow up for both Cohorts were evaluated by a linear mixed model. The average decline of eGFR in the Sham group was numerically higher vs. the rfRDN group: -1.36 vs. -1.19 mL/min/1.73m2 (p=0.2), but the difference in decline is not clinically-meaningful.

4. SPYRAL HTN-OFF MED

a. SPYRAL HTN-OFF MED Population Overview, Demographics and Baseline Parameters

Baseline characteristics were balanced between the rfRDN and Sham groups and between Pilot and Expansion Cohorts. The majority of patients were male and white, and the median age was 53 years (Table 7). Most patients had hypertension for >5 years, and there was a low incidence of comorbidities such as diabetes and sleep apnea.

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

Table 7. HTN-OFF MED Select Baseline Characteristics

	Pilot Cohort		Expansion Cohort		Full Cohort (Pilot + Expansion + Add'l Subjects)	
Subject Baseline Characteristic (mean ± SD or %)	**rfRDN (N=38 Subjects)**	**Sham (N=42 Subjects)**	**rfRDN (N= 128 Subjects)**	**Sham (N= 123 Subjects)**	**rfRDN (N=182 Subjects)**	**Sham (N=184 Subjects)**
Age (yrs)	55.8 ± 10.1	52.8 ± 11.5	51.4 ± 10.9	52.5 ± 10.0	52.5 ± 10.8	52.7 ± 10.1
Male	68.4% (26/38)	73.8% 31/42)	63.3% (81/128)	66.7% 82/123)	64.3% (117/182)	69.6% (128/184)
Length of hypertension diagnosis >5 yrs	60.5%	42.9%	53.9%	58.5%	56.1% (102/182)	56.0% (103/184)
Geography						
US	34.2% (13/38)	34.2% 13/38)	55.5% (71/128)	52.8% 65/123)	50% 91/182)	46.2% (85/184)
OUS	64.8% (25/38)	64.8% 25/38)	44.5% (57/128)	47.2% 58/123)	50% 91/182)	53.8% (99/184)
Race						
White	26.3% (10/38)	23.8% 10/42)	28.9% (37/128)	32.5% 40/123)	30.8% 56/182)	32.6% (60/184)
Black or African American	13.2% (5/38	11.9% 5/42)	24.2% (31/128)	21.1% 26/123)	20.3% 37/182)	17.4% (32/184)
Asian	2.6% 1/38)	2.4% 1/42)	3.9% 5/128)	0.8% 1/123)	3.8% 7/182)	1.1% 2/184)
Japanese from Japan	5.3% 2/38)	4.8% 2/42)	0.8% 1/128)	0.0% 0/123)	1.6% 3/182)	1.1% 2/184)
Not reportable per local laws or regulations	52.6% (20/38)	57.1% 24/42)	41.4% (53/128)	44.7% 55/123)	42.9% 78/182)	47.3% (87/184)
Other	0.0% 0/38)	0.0% 0/42)	0.8% 1/128)	0.8% 1/123)	0.5% 1/182)	0.5% 1/184)
Hispanic/Latino/Spanish origin						
Yes	2.6% 1/38)	2.4% 1/42)	3.1% 4/128)	1.6% 2/123)	2.7% 5/182)	2.2% 4/184)
No	44.7% (17/38	40.5 (17/42)	54.7% (70/128)	53.7% 66/123)	53.8% 98/182)	50.5% (93/184)
Not reportable per local law or reg	52.6% (20/38)	57.1% 24/42)	41.4% (53/128)	44.7% 55/123)	42.9% 78/182)	47.3% (87/184)
Unknown	0.0% 0/38)	0.0% 0/42)	0.8% 1/128)	0.0% (0/123)	0.5% 1/182)	0.0% 0/184)
BMI	29.8 ± 5.1	30.2 ± 5.1	31.5 ± 6.1	31.1 ± 5.6	31.2 ± 6.0	31.0 ± 5.5
Diabetes Mellitus Type 2	2.6% 1/38)	7.1% 3/42)	3.9% 5/128)	4.9% 6/123)	4.4% 8/182)	6.0% 11/184)
Current Smoker	10.5% (4/38	23.8% 10/42)	18.8% (24/128)	13.8% 17/123)	17.0% 31/182)	15.8% (29/184)
Obstructive sleep apnea	7.9% 3/38)	7.1% 3/42)	8.6% 11/128)	7.3% 9/123)	8.2% 15/182)	7.1% 13/184)
History of coronary artery disease*	0.0% 0/38)	4.8% 2/42)	0.0% 0/128)	4.9% 6/123)	0.0% (0/182)	4.3% 8/184)
History of stroke / transient ischemic attack*	5.3% 2/38)	0.0% 0/42)	0.0% 0/128)	0.0% 0/123)	1.1% 2/182)	0.0% 0/184)
Peripheral Artery Disease	2.6% 1/38)	0.0% 0/42)	0.0% 0/128)	0.0% 0/123)	0.5% 1/182)	0.0% 0/184)

[1]Occurring >3 months before randomization
Data displayed as % (n/N)

Table 8. HTN-OFF MED Baseline Blood Pressures

Subject Baseline Blood Pressure (mmHg)	Pilot Cohort		Expansion Cohort		Full Cohort (Pilot + Expansion + Add'l Subjects)	
	rfRDN (N=38 subjects)	Sham (N=42 subjects)	rfRDN (N=128 Subjects)	Sham (N= 123 Subjects)	rfRDN (N=182)	Sham (N=184)
Office measurements						
Systolic blood pressure	162.0 ± 7.6	161.4 ± 6.4	162.9 ± 7.9	163.4 ± 7.8	162.8 ± 7.8	163.2 ± 7.7
Diastolic blood pressure	99.9 ± 6.8	101.5 ± 7.5	101.6 ± 7.0	102.2 ± 7.0	101.1 ± 7.1	102.2 ± 7.3
24-hour measurements (ABPM)						
Mean systolic blood pressure	153.4 ± 9.0	151.6 ± 7.4	150.8 ± 7.7	150.8 ± 7.5	151.2 ± 7.9	151.3 ± 7.6
Mean diastolic blood pressure	99.1 ± 7.7	98.7 ± 8.2	97.6 ± 7.7	99.2 ± 7.2	97.6 ± 7.9	99.3 ± 7.5

Data displayed as mean ± SD

The mean procedure time, defined as the time from when arterial access was obtained until arterial closure, was 99 minutes in the rfRDN group. The denervation time was approximately 1 hour (Table 9). Pain medication requirements were significantly greater in the rfRDN group.

Table 9: HTN-OFF MED Procedure Characteristics (Full Cohort)

Treatment	rfRDN (N=182)	Sham (N=184)	Crossover (N=125)
Procedure Time (minutes)			
Mean ± SD	99.3 ± 36.2	52.9 ± 16.6	80.2 ± 26.1
Median (min, max)	93.0 (40, 239)	51.5 (25, 128)	77.0 (32, 196)
Amount of Contrast used (cc)	207.8 ± 96.1	74.1 ± 37.4	171.2 ± 75.5
Intra-procedural medication			
Pain Meds	29.7% 54/182)	17.4% (32/184)	24.8% 31/125)
Sedatives/Anxiolytics	100.0% (182/182)	98.4% (181/184)	96.8% 121/125)
Atropine	2.2% 4/182)	0.0% 0/184)	3.2% 4/125)
Hospital Stay (days)	1.0 ± 0.1	1.0 ± 0.2	1.0 ± 0.2
Device Success3	100.0% (181/181)	--	100.0% (125/125)
Procedural Success4	100.0% (181/181)	--	100.0% (125/125)
Denervation Time[34] (minutes)			
Mean ± SD	59.7 ± 24.3	NA	53.1 ± 19.1
Median (min, max)	55.0 (10, 207)		49.0 (20, 135)
Number of Ablation Attempts			
n[15]	181	NA	125
Mean ± SD	46.6 ± 15.3		47.2 ± 16.1
Median (min, max)	45.0 (18, 109)		45.0 (22, 117)
Number of Main Arteries Treated			
n[15]	181	NA	125
Mean ± SD	2.2 ± 0.6		2.3 ± 0.6
Median (min, max)	2.0 (1, 5)		2.0 (2, 4)
Number of Main Arteries Ablations			
n[15]	181	NA	125
Mean ± SD	18.2 ± 9.7		17.8 ± 8.8
Median (min, max)	16.0 (1, 62)		16.0 (5, 60)
Number of Branches Treated			
n[15]	181	NA	125
Mean ± SD	5.8 ± 2.6		6.0 ± 2.5
Median (min, max)	6.0 (0, 17)		6.0 (0, 14)
Number of Branch Ablations			
n[1]	181	NA	125
Mean ± SD	28.4 ± 15.1		29.4 ± 15.5
Median (min, max)	28.0 (0, 94)		27.0 (0, 79)

b. HTN-OFF MED Effectiveness Results

i. HTN-OFF MED Powered Primary and Secondary Endpoint Results

The primary effectiveness endpoint and the powered secondary effectiveness endpoint were based on difference between randomized groups (rfRDN and Sham, ITT Cohort) using the Bayesian power prior methodology.

- *Primary Effectiveness Endpoint:* Change in SBP measured by 24-hour ABPM from baseline to 3-months post-procedure, compared between rfRDN and Sham groups.

- *Powered Secondary Effectiveness Endpoint:* Change in OSBP from baseline to 3-months post-procedure, compared between rfRDN and Sham groups.

Table 10 shows the HTN-OFF MED ITT Cohort Bayesian analysis for the primary and secondary effectiveness endpoints. The power prior parameters were close to 1 for the rfRDN and Sham groups, so a high proportion of Pilot Cohort outcome information was used.
Primary Effectiveness Endpoint: In the rfRDN group, there was an estimated 3.9 mmHg greater reduction in 24-hour ASBP at 3 months vs. the Sham group.
Powered Secondary Effectiveness Endpoint: In the rfRDN group, there was an estimated 6.5 mmHg greater reduction in OSBP at 3 months vs. the Sham group.

For both primary and secondary effectiveness endpoints, the treatment differences in favor of rfRDN met the study success criteria for superiority with posterior probability of superiority >0.999.

Table 10. Powered Primary and Secondary Effectiveness Results at 3 Months – HTN-OFF MED Primary (Bayesian) Analysis

	Power prior parameter	Prior N[b]	N	Bayesian treatment effect[a]	Posterior probability of success
Primary Endpoint: 24-hour SBP					
rfRDN	0.864	30	105	-3.9 mmHg (-6.2 to -1.6)	0.9996
Sham	0.967	34	99		
Secondary Endpoint: Office SBP					
rfRDN	0.980	36	119	-6.5 mmHg (-9.6 to -3.5)	1.000
Sham	0.998	41	109		

[a] Posterior mean and 95% Bayesian credible interval
[b] Effective prior sample size after discounting

Table 11 shows frequentist analyses for the HTN-OFF MED Pilot, Expansion, and Full Cohorts for 24-hour SBP and Office SBP. The treatment differences in favor of rfRDN among the Cohorts were generally similar.

Table 11. Frequentist ANCOVA Analyses for ASBP and OSBP at 3 Months for HTN-OFF MED Cohorts (ITT)

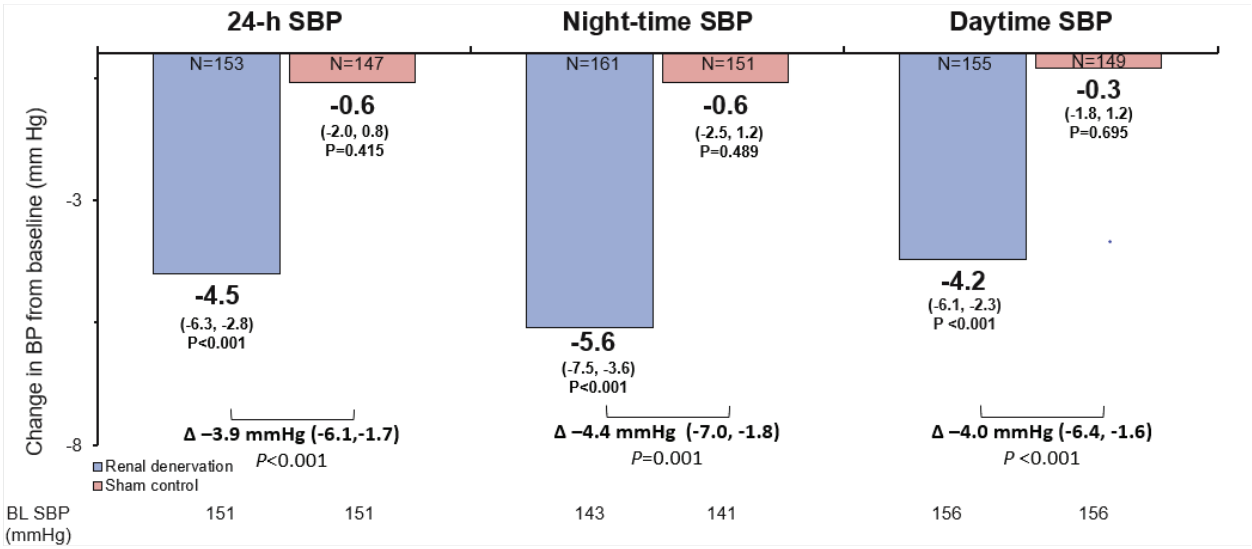
ITT Population	rfRDN	Sham	ANCOVA difference[a]	ANCOVA p-value*
24Hr SBP Change				
HTN-OFF MED Pilot Cohort	-5.5 ± 10.3 (N=35)	-0.1 ± 10.0 (N=35)	-4.9 (-9.6, -0.3)	0.0370
HTN-OFF MED Expansion	-4.4± 10.5 (N=105)	-0.8 ± 8.1 (N=99)	-3.6 (-6.2, -1.0)	0.0065
HTN-OFF MED Full Cohort	-4.5 ± 10.8 (N=153)	-0.6 ± 8.7 (N=147)	-3.9 (-6.1, -1.7)	<0.001
Office SBP Change				
HTN-OFF MED Pilot	-10.0 ± 15.4 (N=37)	-2.3 ± 12.1 (N=41)	-7.1 (-13.2, -1.1)	0.0212
HTN-OFF MED Expansion	-9.2 ± 14.4 (N=119)	-2.6 ± 13.2 (N=109)	-6.6 (-10.2, -3.0)	0.0003
HTN-OFF MED Full Cohort	-9.4 ± 14.8 (N=170)	-2.3 ± 12.7 (N=164)	-7.1 (-10.0, 4.2)	<0.001

[a] Estimated treatment effect and 95% confidence interval
* p-values are not adjusted for multiplicity

ii. HTN-OFF MED Secondary Effectiveness Endpoints

Daytime and Nighttime ASBP
Figure 5 and Figure 6 show the changes in the 24-hour, daytime and nighttime ASBP for the HTN-OFF MED Full Cohort. Daytime was defined as any ABPM readings between 7 am and 10 pm (includes morning ABPM readings between 7 am and 9 am). Nighttime was defined as any ABPM readings between 10 pm to 7 am.

The reduction in SBP at 3 months in favor of rfRDN vs. Sham was significantly greater for all three measures and generally similar across the measures.



p-values not adjusted for multiplicity.
SBP changes are unadjusted absolute drops from baseline.
Differences and p-values are determined from ANCOVA models adjusting for the baseline value

Figure 5. HTN-OFF MED Full Cohort - 24-hour, Night-time, and Daytime ASBP Change at 3 Months –

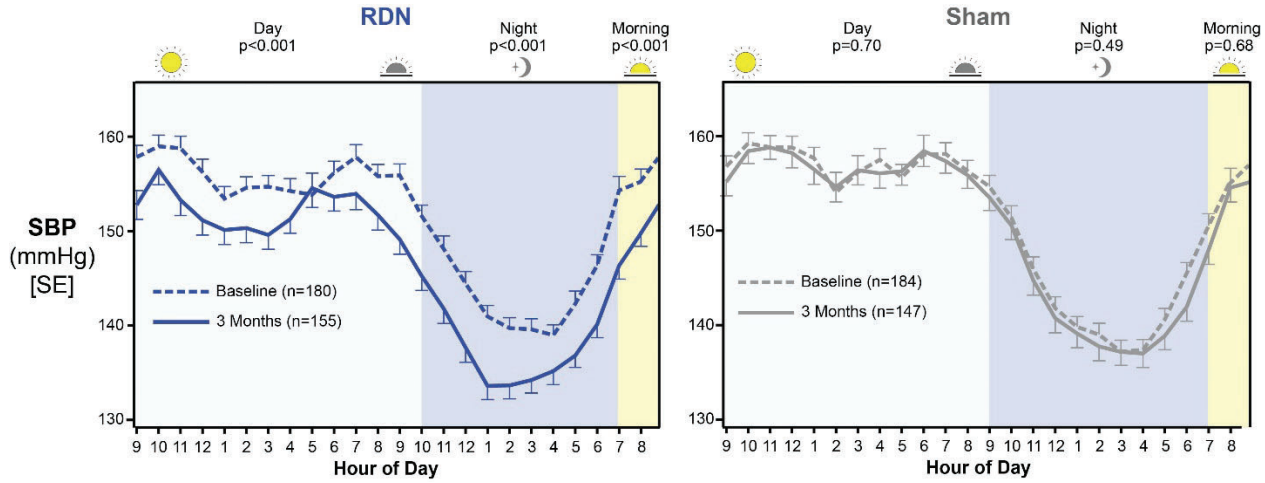


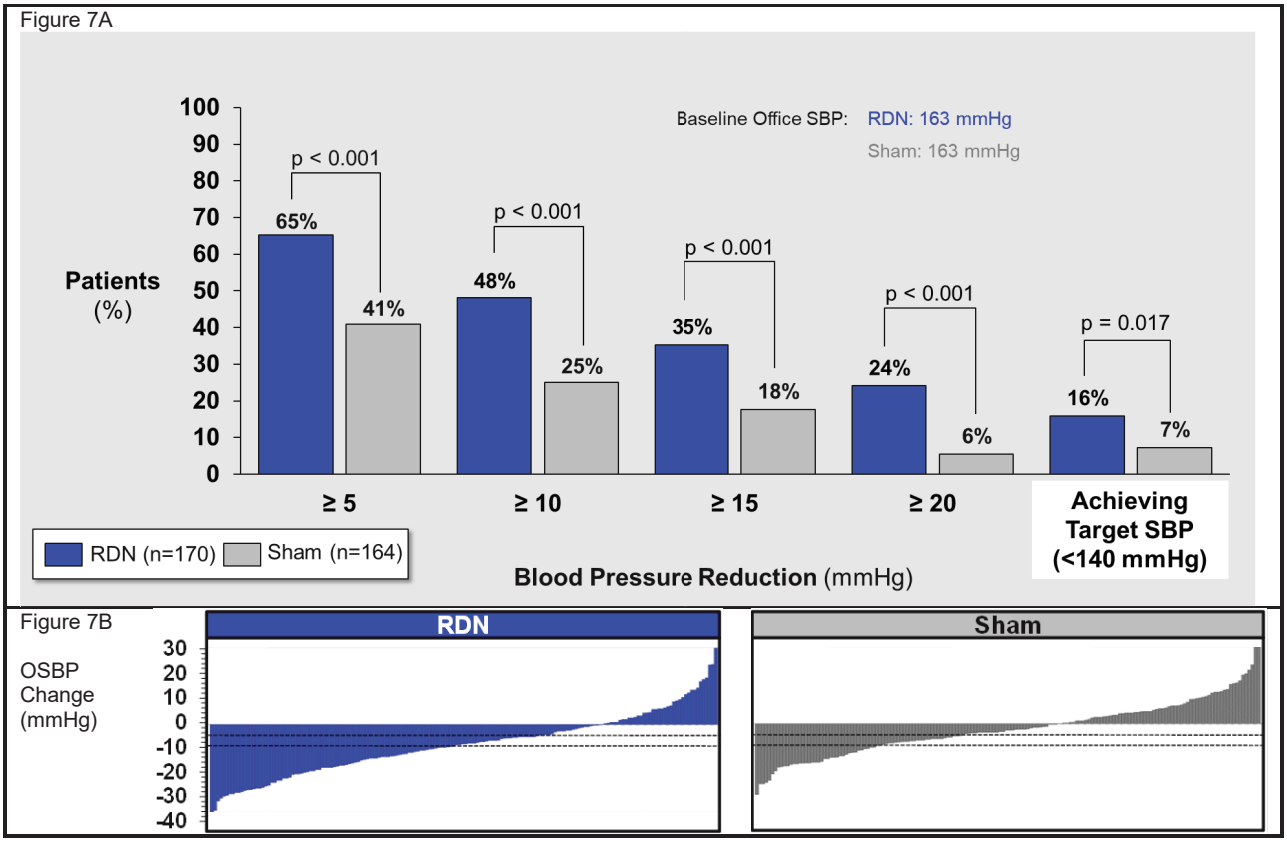
Figure 6. HTN-OFF MED Full Cohort: 24-Hour SBP Baseline vs 3 Months

Distribution of Magnitude of SBP Reduction

Figure 7a and Figure 8 show the proportion of subjects with BP reductions in office and 24-hour SBP, respectively, ≥ 5, 10, 15, and 20 mmHg and patients who achieved goal SBP (<140 mmHg) at 3 months in HTN-OFF MED. Figure 7b shows the waterfall distribution of office SBP change at 3-months in the rfRDN and Sham groups.

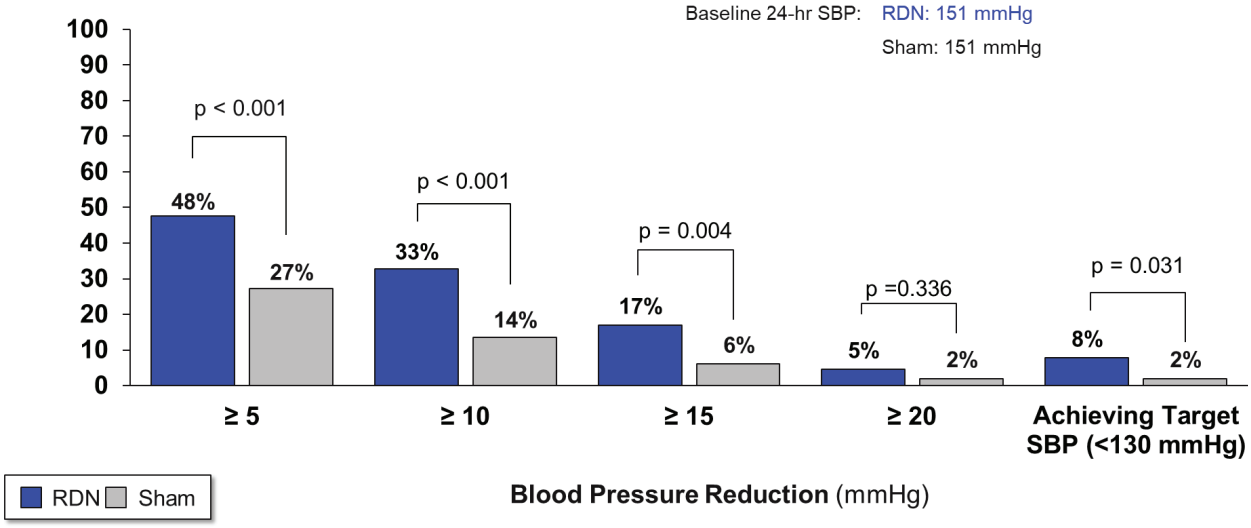
Significantly more rfRDN subjects achieved office SBP reductions than the Sham group (p<0.001 with 65% of rfRDN treated subjects achieving an office SBP reduction of at least 5 mmHg. Subjects treated achieved target office systolic blood pressure (OSBP) <140 mmHg at statistically higher rates than Sham subjects.

An evaluation of progressive reductions measured by 24-hour ambulatory monitoring in HTN-OFF MED (Figure 10) showed similar results to those seen in office SBP for reductions of ≥5, ≥10 and ≥15 mmHg with rfRDN significantly outperforming the Sham group. The proportion of rfRDN subjects with BP reductions of ≥20 mmHg was numerically greater than Sham subjects



p-values not adjusted for multiplicity

Figure 7a) HTN-OFF Full Cohort Tiers of Office SBP Reduction and Achievement of Target SBP at 3 Months, Figure 7b) Waterfall Plots for: HTN-OFF MED Full Cohort: at 3-Months (Prior to Reintroduction of Antihypertensive Medications)



p-values not adjusted for multiplicity

Figure 8. Tiers of 24-Hour SBP Reduction and Achievement of Target SBP: HTN-OFF Full Cohort at 3-Months

Figure 9 and Figure 10 show the proportion of subjects with BP reductions in office and 24-hour SBP, respectively, ⩾5, 10, 15, and 20 mmHg and patients who achieved goal SBP (<140 mmHg) at 6 months in HTN-OFF MED

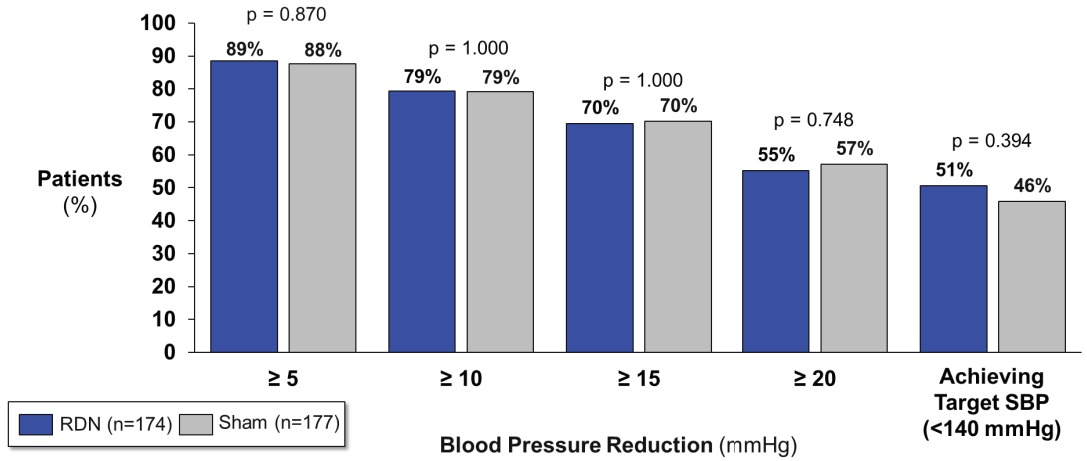


Figure 9. Tiers of Office SBP Reduction and Achievement of Target SBP: HTN-OFF Full Cohort at 6-Months

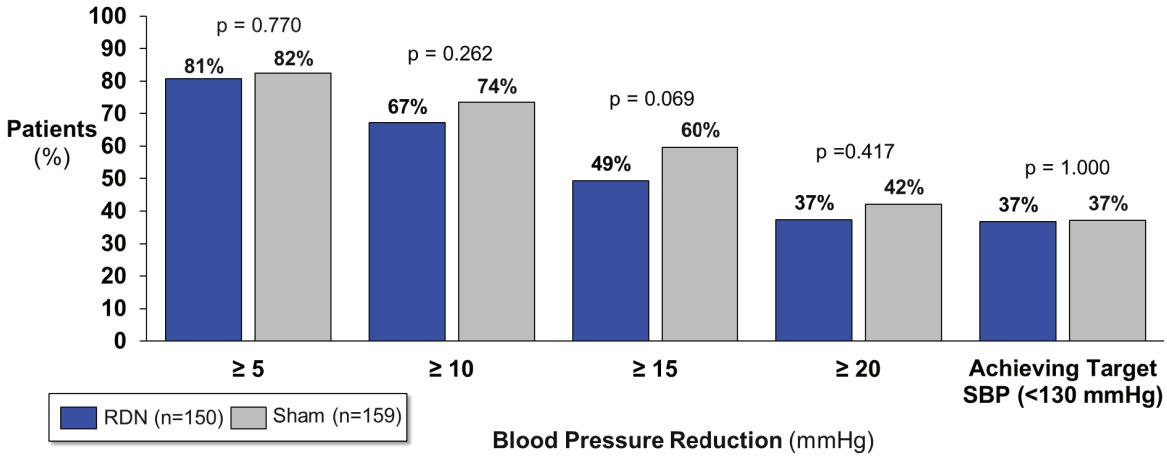


Figure 10. Tiers of 24-Hour SBP Reduction and Achievement of Target SBP: HTN-OFF Full Cohort at 6-Months

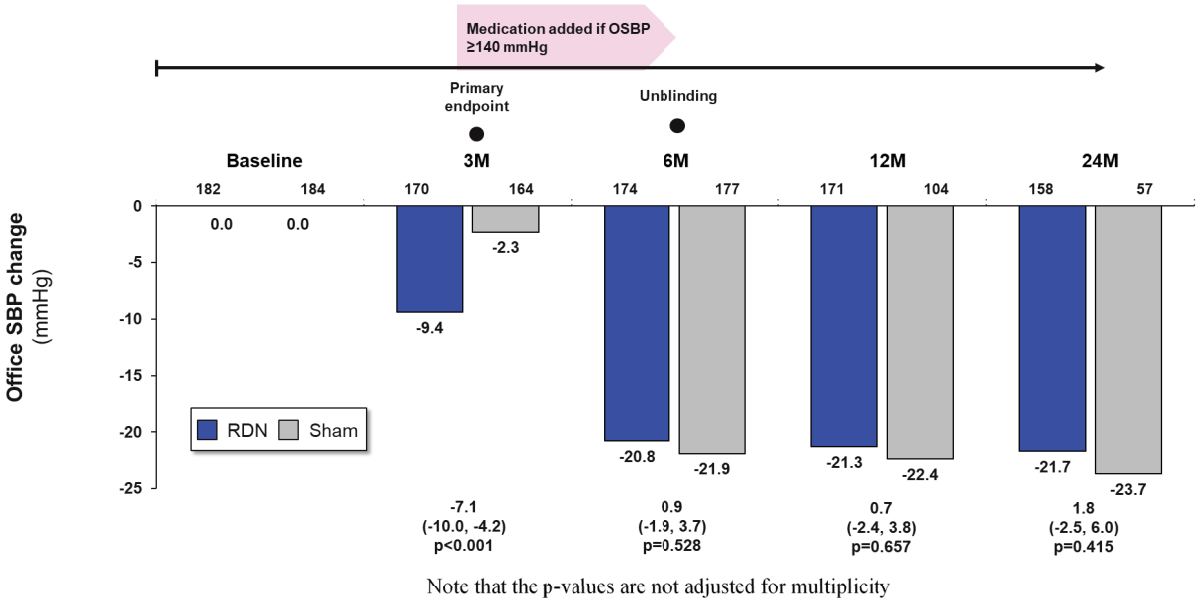
Long-Term Effectiveness Results

The HTN-OFF MED study was not designed to assess the durability of blood pressure reduction, as the effect of rfRDN at later timepoints may be challenging to interpret because of the use and escalation of BP medications beyond after 3 months, unblinding of study subjects to their treatment assignment, and crossover of many Sham subjects to rfRDN treatment.

To assess treatment effectiveness durability, ambulatory and office SBP and medication burden were evaluated. In the HTN-OFF MED protocol, medications were to be withheld (unless escape criteria were met) through 3-month post-procedure and could be restarted after 3 months, with a protocol-driven medication escalation protocol used through 6 months for subjects not at SBP goal (<140 mmHg).

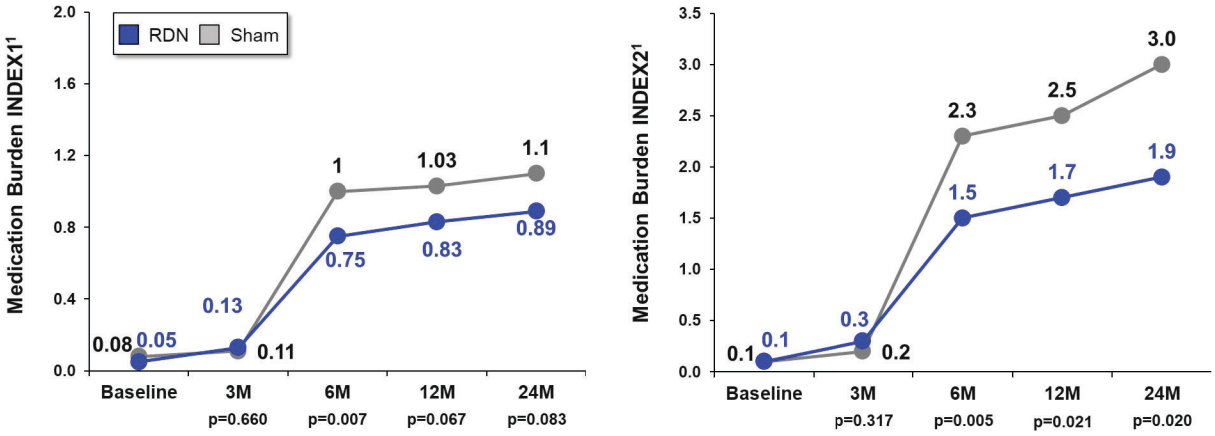
Figure 11 shows the office SBP and medication burden (MedIndex 1 and MedIndex 2 for subjects with available office SBP) through 24 months for the HTN-OFF MED Full Cohort. Figure 12 shows the 24-hour SBP and medication burden (MedIndex 1 and MedIndex 2 for subjects with available 24-hour SBP) through 24 months. Starting at 6 months there was higher BP medication use in the Sham group, and the OSBP and 24 hour SBP reduction vs. baseline was greater in the Sham group.

Interpretation of BP changes between treatment groups at later timepoints is challenging because Sham subject crossover to rfRDN treatment after 6 months reduced the Sham group sample size and resulted in a loss of a randomized comparison.



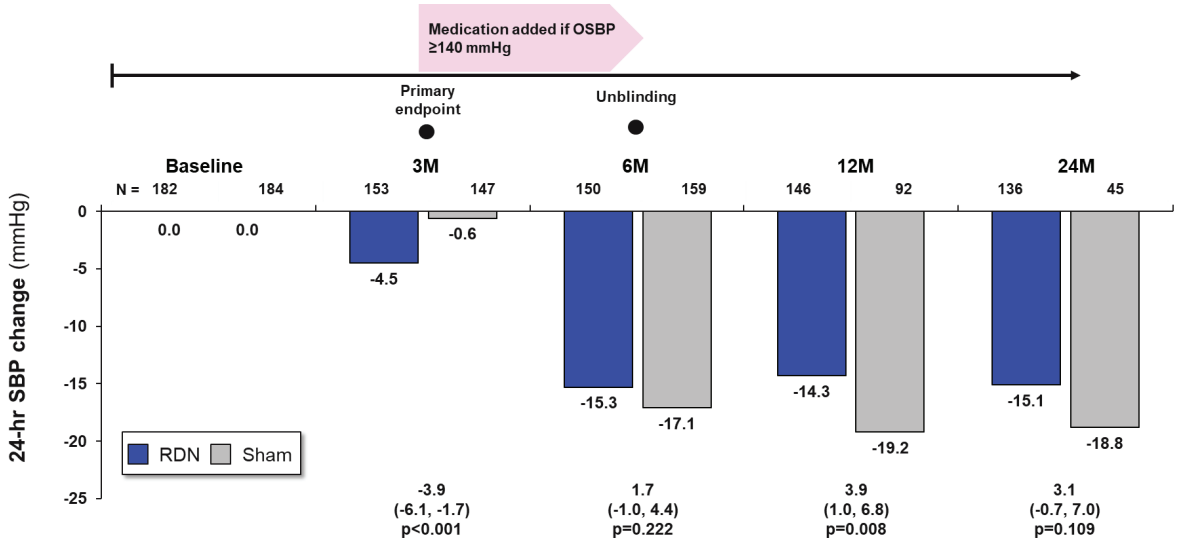
Note that the p-values are not adjusted for multiplicity

Crossovers were allowed starting at 6 months are not included in this analysis.



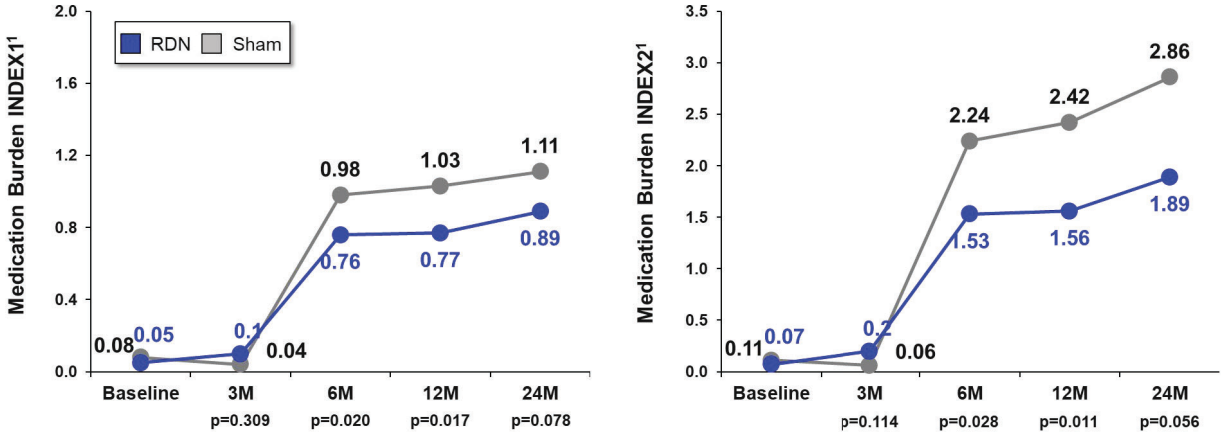
[1]Medication burden INDEX1 and INDEX2 data presented for patients with available office SBP data, and is calculated using drug testing and when unavailable, prescribed medication data. Note that the p-values are not adjusted for multiplicity. Crossovers were allowed starting at 6 months are not included in this analysis.

Figure 11. HTN-OFF MED Full Cohort – Office Systolic Blood Pressure and Medication Burden through 24 Months



Note that the p-values are not adjusted for multiplicity

Crossovers were allowed starting at 6 months are not included in this analysis.



1Medication burden INDEX1 and INDEX2 data presented for patients with available 24-hour SBP data, and is calculated using drug testing and when unavailable, prescribed medication data. Note that the p-values are not adjusted for multiplicity. Crossovers were allowed starting at 6 months are not included in this analysis.

Figure 12. HTN-OFF MED –24-Hour Systolic Blood Pressure and Medication Burden through 24 Months

5. SPYRAL HTN-ON MED

a. SPYRAL HTN-ON MED Population Overview, Demographics and Baseline Parameters

Baseline characteristics were well-balanced between the rfRDN and Sham groups and between Pilot and Expansion Cohorts (Table 14), except there was a slightly higher proportion of US subjects in the Expansion Cohort compared with Pilot Cohort (data not shown).

In the Full Cohort, both the rfRDN and Sham groups were predominantly male 81.1% vs 78.6%) with median ages of 56 and 55 years, respectively. Subjects were mostly white or race not reported. The rate of patients reported as Black or African American was 17.0% and 19.1% in the rfRDN and Sham groups, respectively.

Table 12. HTN-ON MED – Select Baseline Characteristics

	Pilot Cohort		Expansion Cohort		Full Cohort (Pilot + Expansion)	
Subject Baseline Characteristic	**rfRDN (N=38 Subjects)**	**Control (N=42 Subjects)**	**rfRDN (N=168 Subjects)**	**Control (N=89 Subjects)**	**rfRDN (N=206 Subjects)**	**Control (N=131 Subjects)**
Age (yrs)	53.9 ± 8.7	53.0 ± 10.7	55.5 ± 9.0	55.4 ± 8.7	55.2 ± 9.0	54.6 ± 9.4
Male	86.8% 33/38)	81.0% (34/42)	79.8% (134/168)	77.5% 69/89)	81.1% 167/206)	78.6% 103/131)
Length of hypertension diagnosis >5 yrs	60.5% 23/38)	81.0% (34/42)	72.1% (121/168)	82.0% 73/89)	69.9% 144/206)	81.7% 107/131)
Geography						
US	39.5% 15/38)	42.9% (18/42)	45.2% (76/168)	52.8% (47/89)	44.2% 91/206)	49.6% 65/131)
OUS	60.5% 23/38)	57.1% (24/42)	54.8% (92/168)	47.2% 42/89)	55.8% 115/206)	50.4% 66/131)
Race						
White	34.2% 13/38)	35.7% (15/42)	34.5% (58/168)	37.1% 33/89)	34.5% 71/206)	36.6% 48/131)
Black or African American	10.5% 4/38)	11.9% (5/42)	18.5% (31/168)	22.5% 20/89)	17.0% 35/206)	19.1% 25/131)
Asian	0.0% 0/38)	2.4% 1/42)	1.2% 2/168)	3.4% 3/89)	1.0% 2/206)	3.1% 4/131)
Japanese from Japan	7.9% 3/38)	2.4% 1/42)	7.1% 12/168)	5.6% (5/89)	7.3% 15/206)	4.6% 6/131)
Not reportable per local laws or regulations	47.4% 18/38)	47.6% (20/42)	36.9% (62/168)	29.2% 26/89)	38.8% 80/206)	35.1% 46/131)
Other	0.0% 0/38)	0.0% 0/42)	0.0% 0/168)	1.1% 1/89)	0.0% 0/206)	0.8% 1/131)
Hispanic/Latino/Spanish origin						
Yes	0% 0/38)	0% 0/42)	1.8% 3/168)	4.5% 4/89)	1.5% 3/206)	3.1% 4/131)
No	52.6% 20/38)	52.4% (22/42)	60.7% (102/168)	65.2% 58/89)	59.2% 122/206)	61.1% 80/131)
Not reportable per local law or reg	47.4% (18/38)	47.6% (20/42)	36.9% (62/168)	30.3% 27/89)	38.8% 80/206)	35.9% 47.131)
Unknown	0.0% 0/38)	0.0% 0/42)	0.6% 1/168)	0.0% 0/89)	0.5% 1/206)	0.0% 0/131)
BMI	31.4 ± 6.4	32.5 ± 4.6	31.4 ± 6.0	32.0 ± 5.4	31.4 ± 6.0	32.1 ± 5.2
Diabetes Mellitus Type 2	13.2% 5/38)	19.0% (8/42)	10.1% (17/168)	16.9% 15/89)	10.7% 22/206)	17.6% 23/131)
Current Smoker	21.1% 8/38)	26.2% (11/42)	14.3% (24/168)	11.2% 10/89)	15.5% 32/206)	16.0% 21/131)
Obstructive sleep apnea	5.3% 2/38)	23.8% (10/42)	12.5% (21/168)	14.6% 13/89)	11.2% 23/206)	17.6% 23/131)
History of coronary artery disease*	2.6% 1/38)	2.4% 1/42)	6.0% (10/168)	9.0% (8/89)	5.3% 11/206)	6.9% 9/131)
History of stroke / transient ischemic attack*	0.0% 0/38)	2.4% (1/42)	0.6% (1/168)	1.1% (1/89)	0.5% 1/206)	1.5% 2/131)
Peripheral Arterial Disease	0.0% 0/38)	0.0% 0/42)	0.0% 0/168)	0.0% 0/89)	0.0% 0/206)	0.0% 0/131)

*Occurring >3 months before randomization
Data displated as % (n/N)

Baseline systolic and diastolic BPs and rates of comorbidities were similar between groups (Table 15). The majority of patients in the rfRDN and Sham groups had hypertension for> 5 years (69.9% vs 79.4%) (respectively, Table 14).

Table 13. HTN-ON MED – Patient Baseline Blood Pressure

Subject Baseline Blood Pressure(mmHg)	Pilot Cohort		Expansion Cohort		Full Cohort	
	rfRDN N = 38	Sham N = 42	rfRDN N = 168	Sham N = 89	rf RDN N = 206	Sham N = 131
Office measurements						
Systolic blood pressure	164.4 ± 7.0	163.5 ± 7.5	162.6 ± 7.8	162.9 ± 8.2	163.0 ± 7.7	163.1 ± 7.9
Diastolic blood pressure	99.5 ± 6.9	102.7 ± 8.0	101.5 ± 6.9	100.9 ± 6.9	101.2 ± 7.0	101.5 ± 7.3
24-hour measurements (ABPM)						
Mean systolic blood pressure	152.1 ± 7.0	151.3 ± 6.8	149.0 ± 6.8	148.3 ± 6.9	149.6 ± 7.0	149.3 ± 7.0
Mean diastolic blood pressure	97.2 ± 6.9	97.9 ± 8.4	96.5 ± 7.7	94.6 ± 7.2	96.6 ± 7.6	95.7 ± 7.7

Both the rfRDN and Sham groups were prescribed an average of 1.9 anti-hypertensive medication classes at baseline, and drug testing for medication adherence showed that rfRDN patients were taking an average of 1.7 anti-hypertensive medication classes vs. 1.6 in the Sham group (Table 16).

Table 14. HTN-ON MED Full Cohort Baseline Anti-Hypertensive Medications Detected by Drug Testing

Category	Baseline Prescribed Regimen		Medications Detected by Drug Testing at Baseline	
	rfRDN (N=206)	Sham (N=131)	rfRDN (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 a “Heart Disease” indication in addition to 3 other anti-hypertensive medication classes.

Procedure Characteristics
The mean procedure time, defined as the time from when arterial access was obtained until arterial closure, was 91 minutes in the rfRDN group. The denervation time was 54 minutes (Table 17). At the time of the PMA submission, crossover data was only available from 24 subjects in the Pilot Cohort.

Table 15. HTN-ON MED Full Cohort Procedure Characteristics

Treatment	rfRDN (N=206)	Sham (N=131)	Pilot Crossover (N=24)
Procedure Time[1] (minutes)			
Mean ± SD	91.3 ± 31.2	51.2 ± 19.5	82.9 ± 26.9
Median (min, max)	88.5 (33, 210)	48.0 (23, 162)	80.0 (40, 160)
Amount of Contrast used (cc)	204.2 ± 81.4	69.9 ± 35.8	196.0 ± 93.7
Intra-procedural medication			
Pain meds	21.8% 45/206)	17.6% (23/131)	33.3% 8/24)
Sedatives/Anxiolytics	98.5% 203/206)	98.5% (129/131)	95.8% 23/24)
Atropine	2.9% 6/206)	0.0% 0/131)	12.5% 3/24)
Hospital Stay (days)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.0
Device success[2]	100.0% (205/205)	--	100.0% (24/24)
Procedure success[3]	99.5% 204/205)	--	100.0% (24/24)
Denervation Time[4] (minutes)			

Mean ± SD	54.4 ± 19.2	NA	53.1 ± 27.0
Median (min, max)	52.0 (17, 133)		52.0 (0, 141)
Number of Ablation Attempts			
n[5]	205	NA	24
Mean ± SD	47.4 ± 16.5		50.8 ± 21.6
Median (min, max)	44 (16, 107)		45 (17, 115)
Number of Main Arteries Treated			
n[5]	205	NA	24
Mean ± SD	2.3 ± 0.6		2.2 ± 0.4
Median (min, max)	2.0 (1, 5)		2.0 (2, 3)
Number of Main Arteries Ablations			
n[5]	205	NA	24
Mean ± SD	19.4 ± 9.5		18.5 ± 7.8
Median (min, max)	18.0 (5, 82)		18.5 (0, 33)
Number of Branches Treated			
n[5]	205	NA	24
Mean ± SD	5.8 ± 2.7		7.4 ± 4.3
Median (min, max)	6.0 (0, 14)		6.0 (2, 19)
Number of Branch Ablations			
n[5]	205	NA	24
Mean ± SD	28.0 ± 14.6		32.3 ± 18.2
Median (min, max)	25.0 (0, 82)		28.5 (7, 86)

NA: not applicable; SD: standard deviation;
1 Arterial closure - arterial access obtained
2 Final Guide Catheter Removal - Initial Symplicity Spyral Catheter Insertion
3 Successful delivery of any RF
4 Successful delivery of any RF in the absence of in hospital MAE
5 Number of main arteries treated, not number of patients

b. SPYRAL HTN-ON MED Effectiveness Results

i. HTN-ON MED Powered Primary Endpoint Results

The powered primary effectiveness endpoint and the non-powered secondary effectiveness endpoint were based on difference between randomized groups (rfRDN and Sham) using the Bayesian power prior methodology.

- *Primary Effectiveness Endpoint (Powered):* Change in SBP measured by 24-hour ABPM from baseline to 6-months post-procedure, compared between rfRDN and Sham groups
- *Secondary Effectiveness Endpoint (Non-powered):* Change in OSBP from baseline to 6-months post-procedure, compared between rfRDN and Sham groups

Table 18 shows the HTN-ON MED Primary Cohort Bayesian analysis for the primary and secondary effectiveness endpoints. Due to differences in the results for the HTN-ON MED Pilot and HTN-ON MED Expansion Cohorts, much of the Pilot data was discounted (power prior parameter = 0.194 for rfRDN and 0.0002 for Sham) for the 24-hour SBP primary effectiveness endpoint, meaning that little Pilot Cohort blood pressure information was used along with the Expansion Cohort to calculate the treatment effect and posterior probability of success. In contrast, for the OSBP secondary effectiveness endpoint, the results for the HTN-ON MED Pilot and HTN-ON MED Expansion Cohorts were generally more similar such that a higher proportion of Pilot Cohort outcome information was used.

- For the Primary Effectiveness Endpoint of 24-hour ASBP at 6 Months:
  - In the rfRDN group there was an estimated 0.03 mmHg greater reduction in 24-hour ASBP at 6 months vs. the Sham group.
  - The 24-hour ASBP treatment difference did not meet study success criteria for superiority (posterior probability of superiority = 0.51).

- For the Secondary Effectiveness Endpoint of OSBP at 6 Months:
  - In the rfRDN group there was an estimated 4.1 mmHg greater reduction in OSBP at 6 months vs. the Sham group.
  - The OSBP treatment difference had posterior probability of superiority = 0.99 for rfRDN.

Table 16. HTN-ON MED Primary 24-Hour ASBP and Secondary OBP Effectiveness Results at 6 Months: Bayesian Analysis

	Power prior parameter	Prior Nb	N	Bayesian treatment effect	Posterior probability of success
24-hour ASBP Change					
rfRDN	0.194	6.999	156	-0.03 mmHg (-2.82, 2.77)	0.508
Sham	0.0002	0.007	80		
Office SBP Change					
rfRDN	0.999	38	161	-4.095 mmHg (-7.44, -0.75)	0.992
Sham	0.156	6.2	86		

[a] Posterior mean and 95% Bayesian credible interval

[b] Effective prior sample size after discounting

Additional Bayesian sensitivity analyses were performed on the primary endpoint for the ITT population (without adjustment for medication use). Consistent with less discounting of the pilot data than in the primary Bayesian analysis, the estimated treatment effects in the Bayesian sensitivity analyses were similar to the effect estimated from the prespecified frequentist ANCOVA analysis.

ii. Additional Primary and Secondary Effectiveness Analyses

Table 17 shows a frequentist analysis of covariance (ANCOVA) for the baseline BP adjusted treatment effect for the HTN-ON MED Pilot, Expansion, and Full Cohorts.

For 24-hour ASBP, the Pilot Cohort results were discordant with the Expansion Cohort results with a significantly greater reduction in rfRDN treat-subjects vs Sham in the Pilot Cohort and no significant difference between treatment groups in the Expansion Cohort. For OSBP, the Pilot Cohort results were generally similar to the Expansion Cohort results. BP reduction differences were greater in the rfRDN group vs. the Sham group and were significant for all Cohorts (Pilot, Expansion, and Full).

Table 17. Frequentist ANCOVA Analyses for ASBP and OSBP at 6 Months for HTN-ON MED Cohorts

ITT Population	rfRDN	Sham	ANCOVA difference[a]	ANCOVA p-value*
24Hr SBP Change				
HTN-ON MED Pilot Cohort	-9.3 ± 10.9 (N=36)	-1.6 ± 10.7 (N=36)	-7.3 (-12.2, -2.4)	0.0041
HTN-ON MED Expansion Cohort	-5.9 ± 10.6 (N=156)	-5.8 ± 10.0 (N=80)	0.0 (-2.8, 2.9)	0.9735
HTN-ON MED Expansion Cohort (1:1)	-8.2 ± 11.2 (N=13)	-7.4 ± 14.7 (N=9)	-1.3 (-12.5, 9.9)	
HTN-ON MED Expansion Cohort (2:1)	-5.9 ± 10.6 (N=143)	-5.6 ± 9.4 (N=71)	0.0 (-2.9, 3.0)	
HTN-ON MED Expansion Cohort (weighted average)	--	--	-0.1 (-2.9,2.7)	
HTN-ON MED Full Cohort	-6.5 ± 10.7 (192)	-4.5 ± 10.3 (116)	-1.9 (-4.4, 0.5)	0.110
Office SBP Change				
HTN-ON MED Pilot Cohort	-9.2 ± 12.3 (38)	-2.6 ± 12.9 (40)	-6.6 (-12.3, -0.8)	0.0259
HTN-ON MED Expansion Cohort	-10.1 ± 14.3 (161)	-6.2 ± 13.2 (86)	-4.0 (-7.6, -0.4)	0.0280
HTN-ON MED Expansion Cohort (1:1)	-12.3± 10.7 (N=15)	-8.1 ± 10.9 (N=10)	-4.2 (-13.6, 5.1)	
HTN-ON MED Expansion (2:1)	-9.9± 14.6 (N=146)	-6.0 ± 13.5 (N=76)	-4.0 (-7.9, 0.2)	
HTN-ON MED Expansion Cohort (weighted average)	--	--	-4.1 (-7.6,0.5)	
HTN-ON MED Full Cohort	-9.9 ± 13.9 (199)	-5.1 ±13.2 (126)	-4.9 (-7.9, -1.9)	0.001

Data displayed as mean ± SD (N)
[a] Estimated treatment effect and 95% confidence interval
* p-values not adjusted for multiplicity, and the results of HTN-ON MED Expansion and Full Cohorts not adjusted for different randomization ratios

iii. Secondary Effectiveness Results

Figure 13, Figure 14 and Figure 15 show the changes of 24-hour, daytime and nighttime ASBP, and Office SBP at 6 months for the HTN-ON MED Full, Expansion and Pilot Cohorts respectively.

- Daytime was defined as ABPM readings between 7 am and 10 pm.
- Nighttime was defined as ABPM readings between 10 pm to 7 am.

The difference in rfRDN vs. Sham SBP reduction was greater for nighttime SBP (3.7 mmHg) vs. daytime SBP (1.2 mmHg) for the Pilot and Full Cohorts.

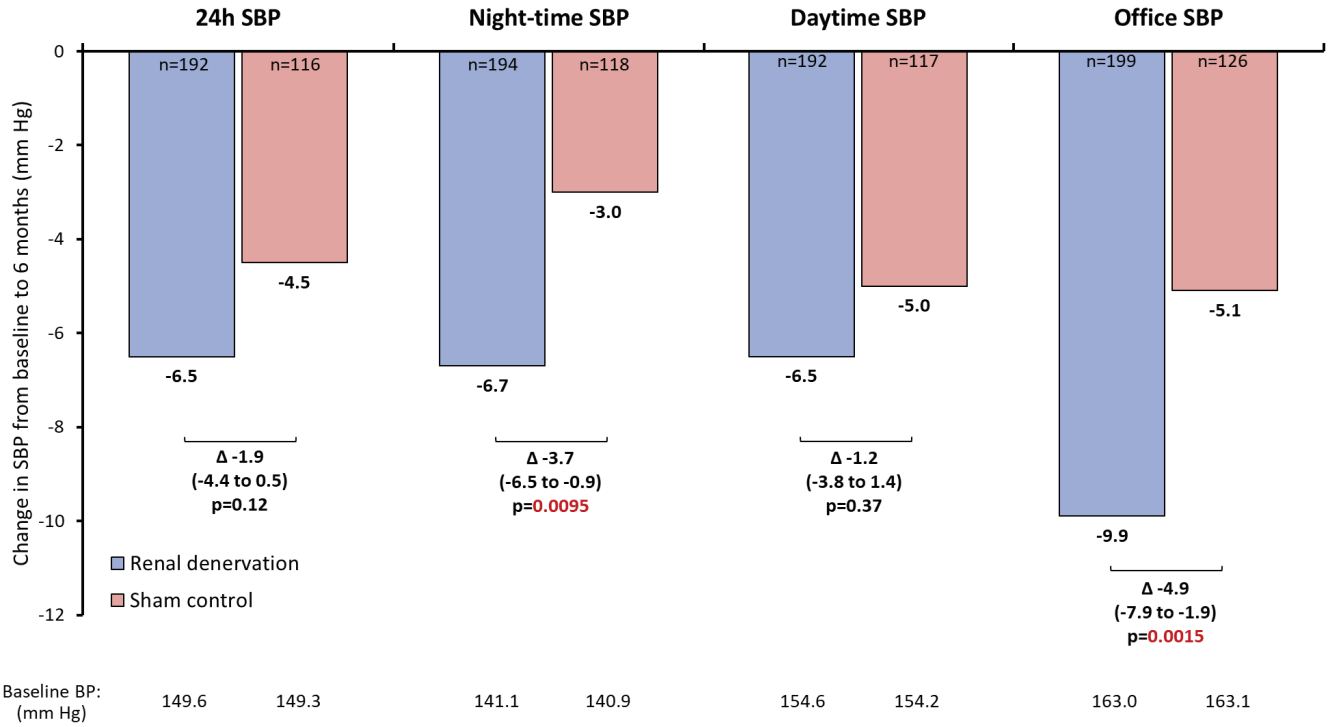


Figure 13. 24-hour, Night-time, and Daytime ASBP and Office SBP Changes at 6 Months – HTN-ON MED Full Cohort

p-values not adjusted for multiplicity
results of HTN-ON MED Full Cohort not adjusted for different randomization ratios.
SBP changes are unadjusted absolute drops from baseline.
Differences and p-values determined from ANCOVA models adjusting for the baseline value

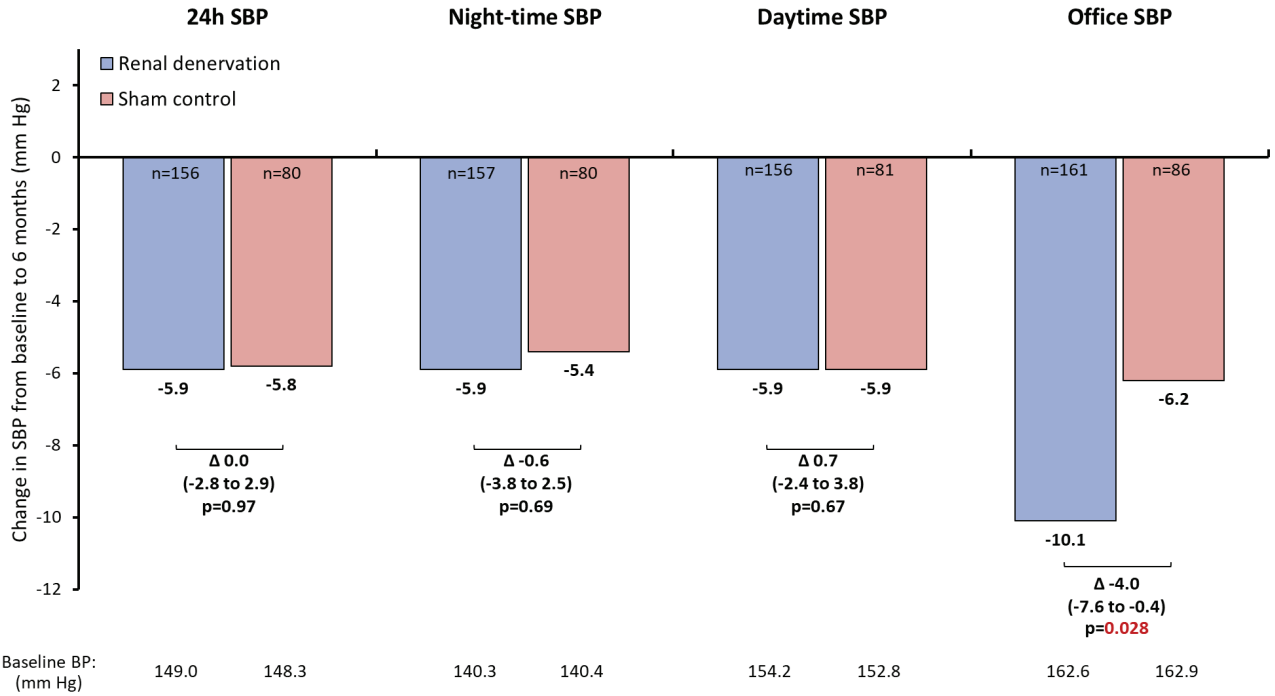


Figure 14. 24-hour, Night-time, and Daytime ASBP and Office SBP Changes at 6 Months – HTN-ON MED Expansion Cohort

p-values not adjusted for multiplicity
results of HTN-ON MED expansion Cohort not adjusted for different randomization ratios.
SBP changes are unadjusted absolute drops from baseline.
Differences and p-values determined from ANCOVA models adjusting for the baseline value

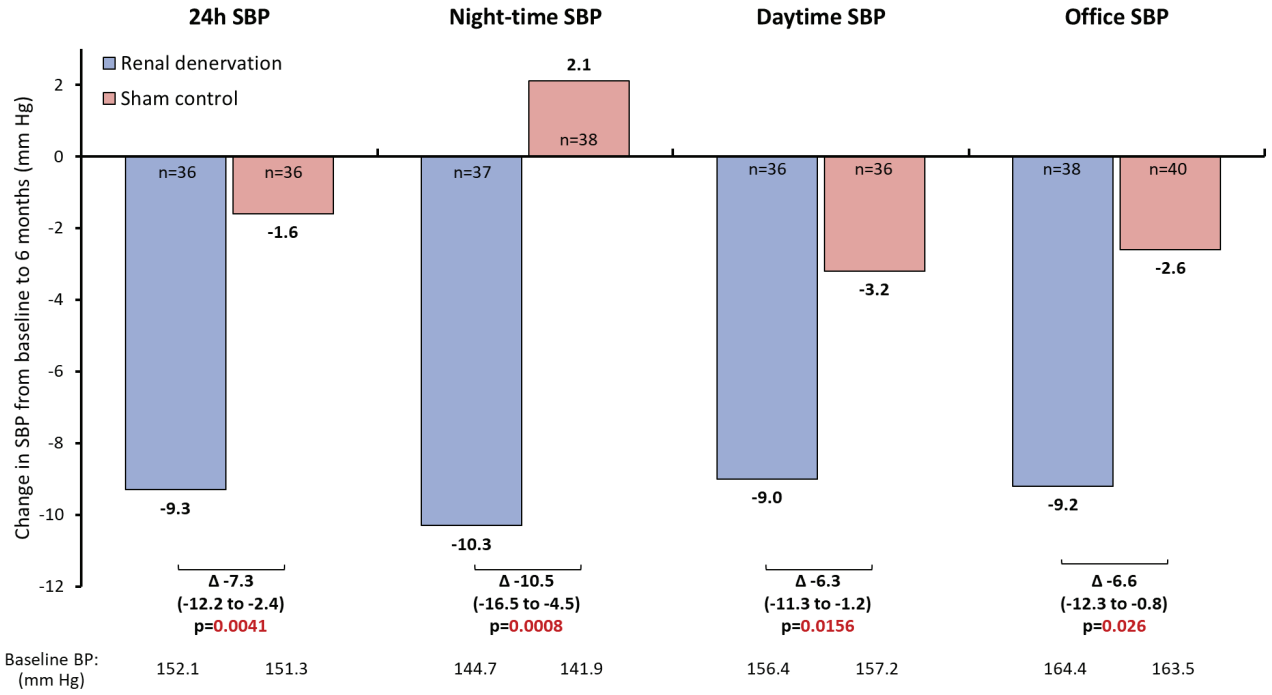


Figure 15. 24-hour, Night-time, and Daytime ASBP and Office SBP Changes at 6 Months – HTN-ON MED Pilot Cohort

p-values not adjusted for multiplicity.
SBP changes unadjusted absolute drops from baseline.
Differences and p-values determined from ANCOVA models adjusting for the baseline value

Distribution of Magnitude of SBP Reduction

Figure 16a and Figure 17 show the proportion of subjects with BP reductions in office and 24-hour SBP, respectively, ≥5, 10, 15, and 20 mmHg and patients who achieved goal at SBP (<140 mmHg) at 6 months. In the HTN-ON MED study, 20% of rfRDN subjects achieved target office SBP compared with 6% of sham subject (p=0.001). Additionally, subjects treated with rfRDN reduced their office SBP by ≥10, ≥15 and ≥20 mmHg at statistically higher rates compared to the Sham group and at numerically higher rates for SBP reductions of ≥5 mmHg.
Waterfall plots demonstrating the distribution of change in office SBP at 6-months in both the rfRDN and sham groups are presented in Figure 16b. Tiers of 24-hour ASBP reduction and the proportion of subjects achieving a SBP <140 mmHg are shown in p-values not **adjusted for multiplicity**
Figure 17.

Figure 16A

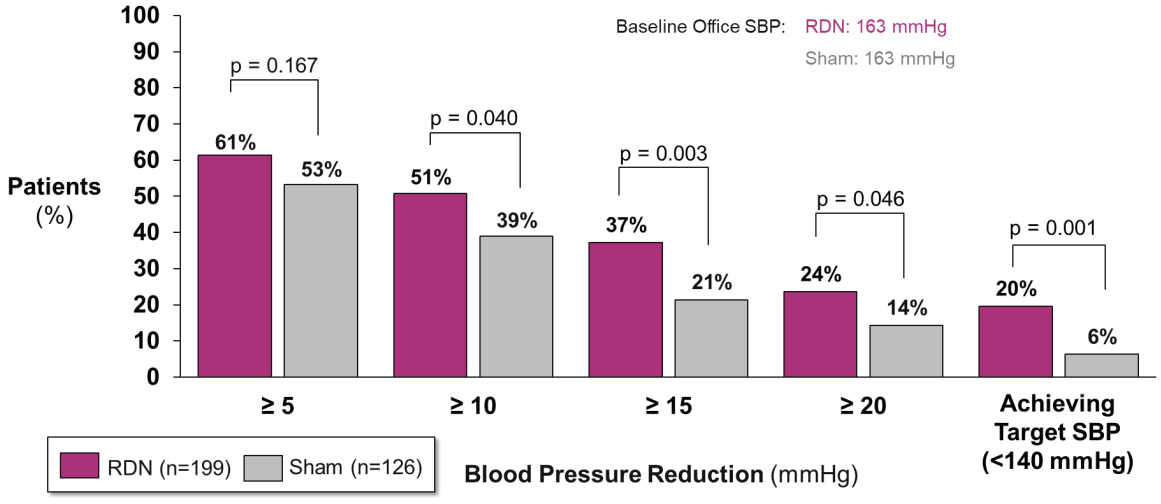


Figure 16B

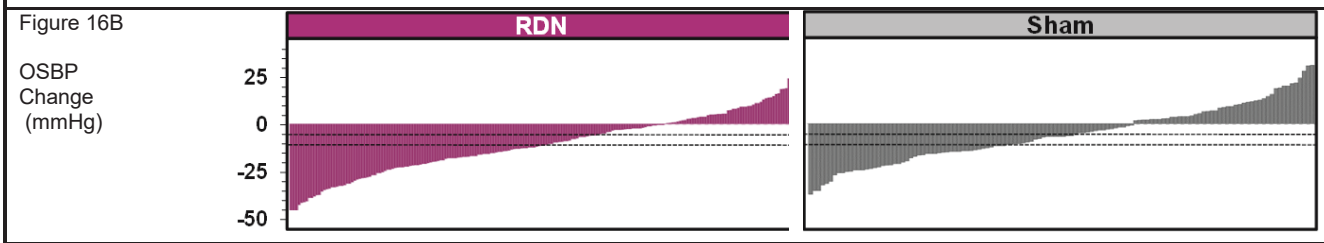
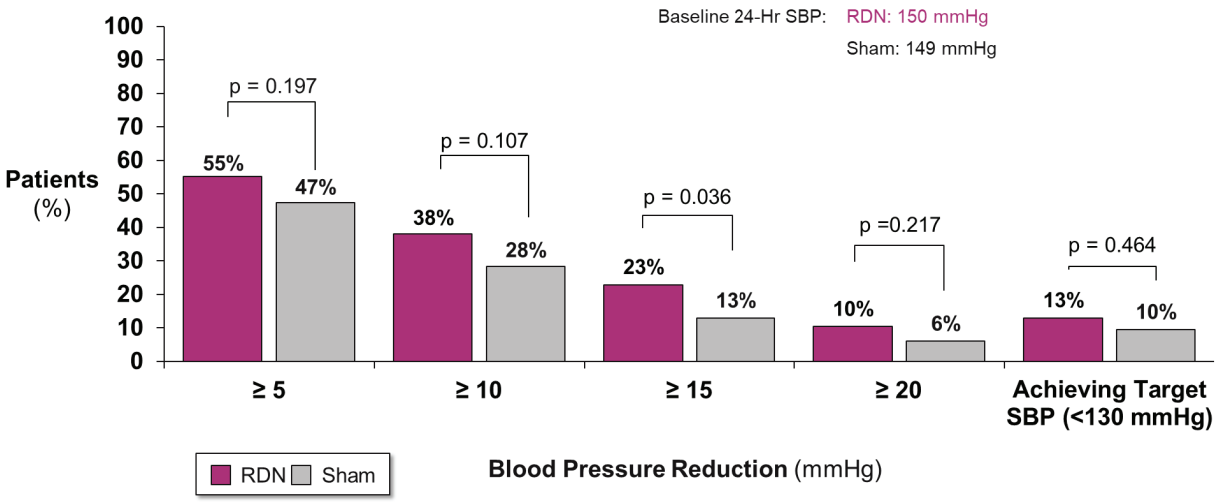


Figure 16a) HTN-ON MED Tiers of Office SBP Reduction and Achievement of Target SBP at 6 Months, Figure 16b) Waterfall Plots for HTN-ON MED Full Cohort Office SBP at 6-Months

p-values not adjusted for multiplicity



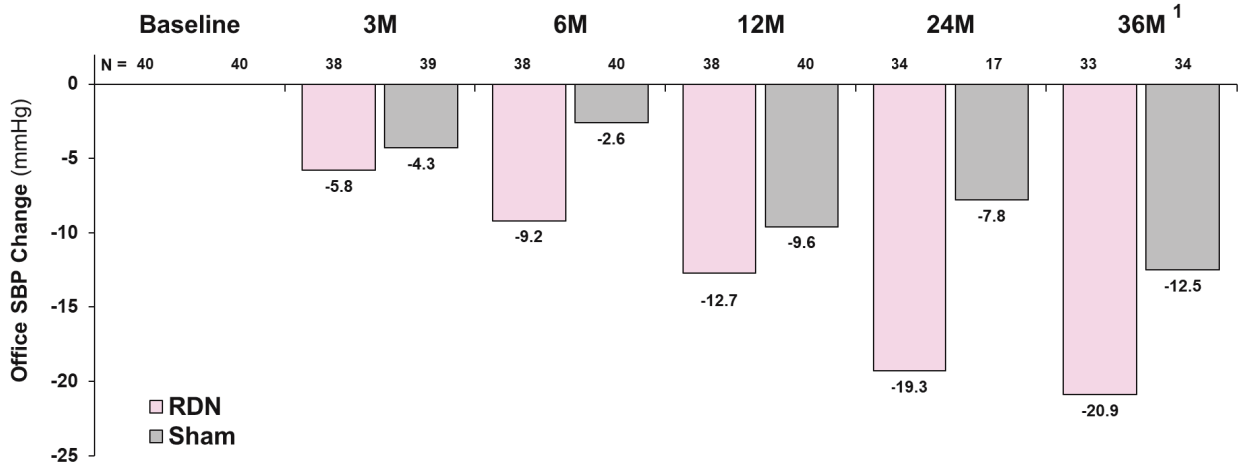
p-values not adjusted for multiplicity

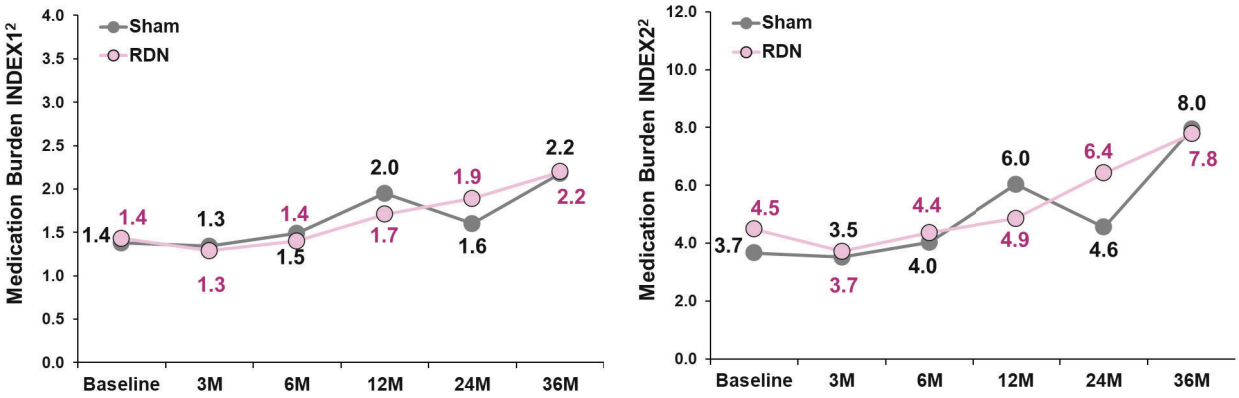
Figure 17. HTN-ON MED Full Cohort Tiers of 24-Hour SBP Reduction and Achievement of Target SBP at 6-Months

HTN-ON MED Long-Term Effectiveness Results

The HTN-ON MED study was not designed to assess the durability of blood pressure reduction, as the effect of rfRDN at later timepoints may be challenging to interpret because of the use and escalation of BP medications after 6 months, unblinding of study subjects to their treatment assignment, and crossover of some Sham subjects to rfRDN treatment (reducing the Sham group size). Additionally, crossover of Sham subjects to rfRDN treatment resulted in a loss of a randomized comparison.

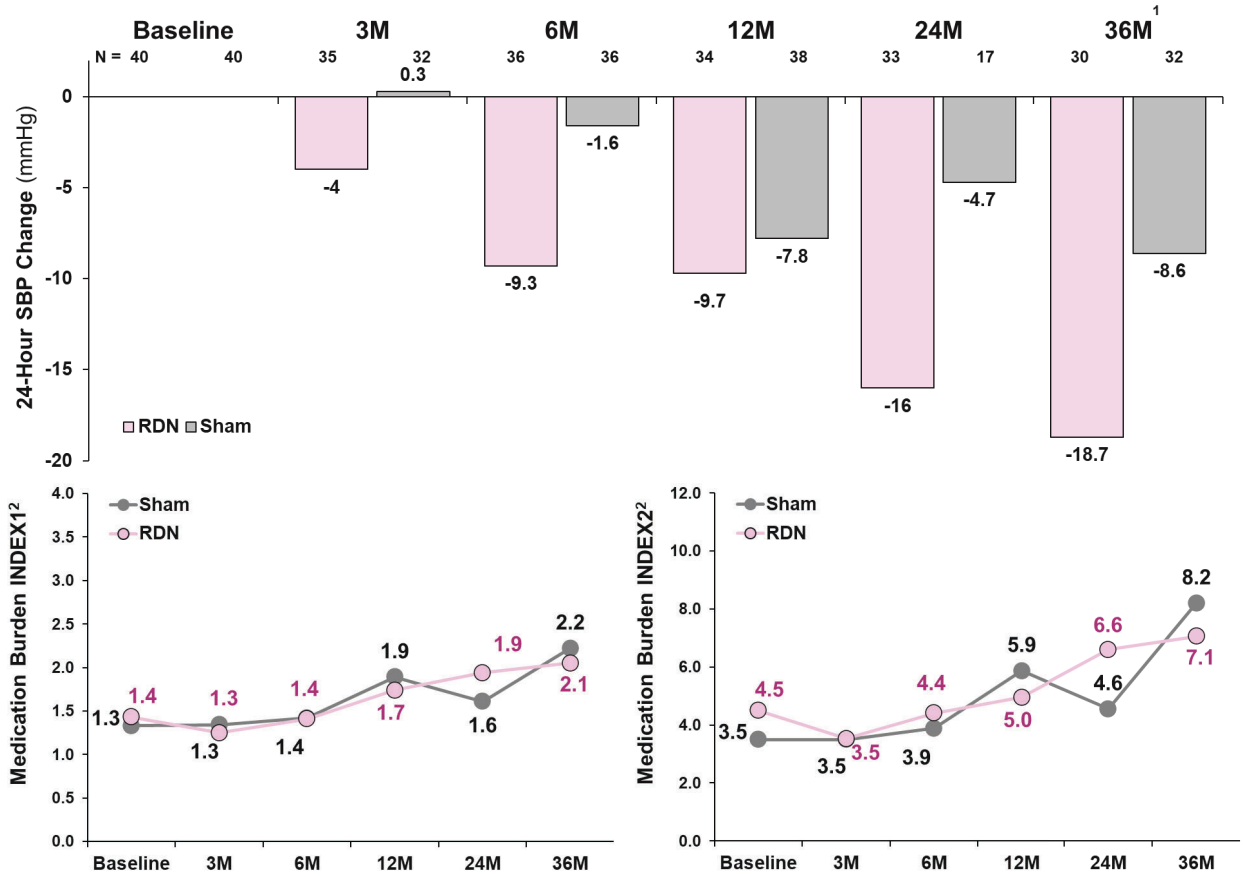
To help assess rfRDN effectiveness durability of, ambulatory and office BP and medication burden were evaluated. BP reduction durability data are not available for the HTN-ON MED Expansion Cohort beyond 6 months, so data beyond 6 months is limited to the HTN-ON MED Pilot Cohort. Figure 18 and Figure 19 show the office SBP and 24-hour ambulatory SBP, respectively, and medication burden (MedIndex 1 and MedIndex 2 in subjects with available SBP) through 36 months for the Pilot Cohort. For patients in the Sham group who crossed over and received rfRDN 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. Office and 24-hour ASBP in both the rfRDN and Sham groups declined after 6 months with larger reductions from baseline in the rfRDN group. Medication burden increased over the course of the study in both groups with no differences between groups.





[1] Last observations of BP measurements and medication burden used to impute 36-month values (note that the extrapolation may be biased)
[2] Medication burden INDEX1 and INDEX2 data presented for patients with available office SBP data, and is calculated using drug testing and when unavailable, prescribed medication data
p-values not adjusted for multiplicity
Crossovers not included in this analysis.

Figure 18. HTN-ON MED Pilot Cohort – Office Systolic Blood Pressure and Medication Burden to 36 Months



[1] Last observations of BP measurements and medication burden used to impute 36-month values (note that the extrapolation may be biased)
[2] Medication burden INDEX1 INDEX2 data presented for patients with available 24-hour SBP data, and is calculated using drug testing and when unavailable, prescribed medication data
p-values not adjusted for multiplicity
Crossovers not included in this analysis.

Figure 19. HTN-ON MED Pilot Cohort –24-Hour Ambulatory Systolic Blood Pressure and Medication Burden to 36 Months

6. HTN-OFF MED and HTN-ON MED Subgroup Analyses

a. Subgroup Analyses by Baseline Characteristics

Figure 20 shows the subgroup analyses for the changes of 24-hour SBP at 3 months for the HTN-OFF Full Cohort. The sample size is small for many subgroups, and some interaction p-values are low (<0.15), but there are no clear trends. The 24-hour SBP reduction trends favoring the rfRDN group was observed for nearly all subgroups.

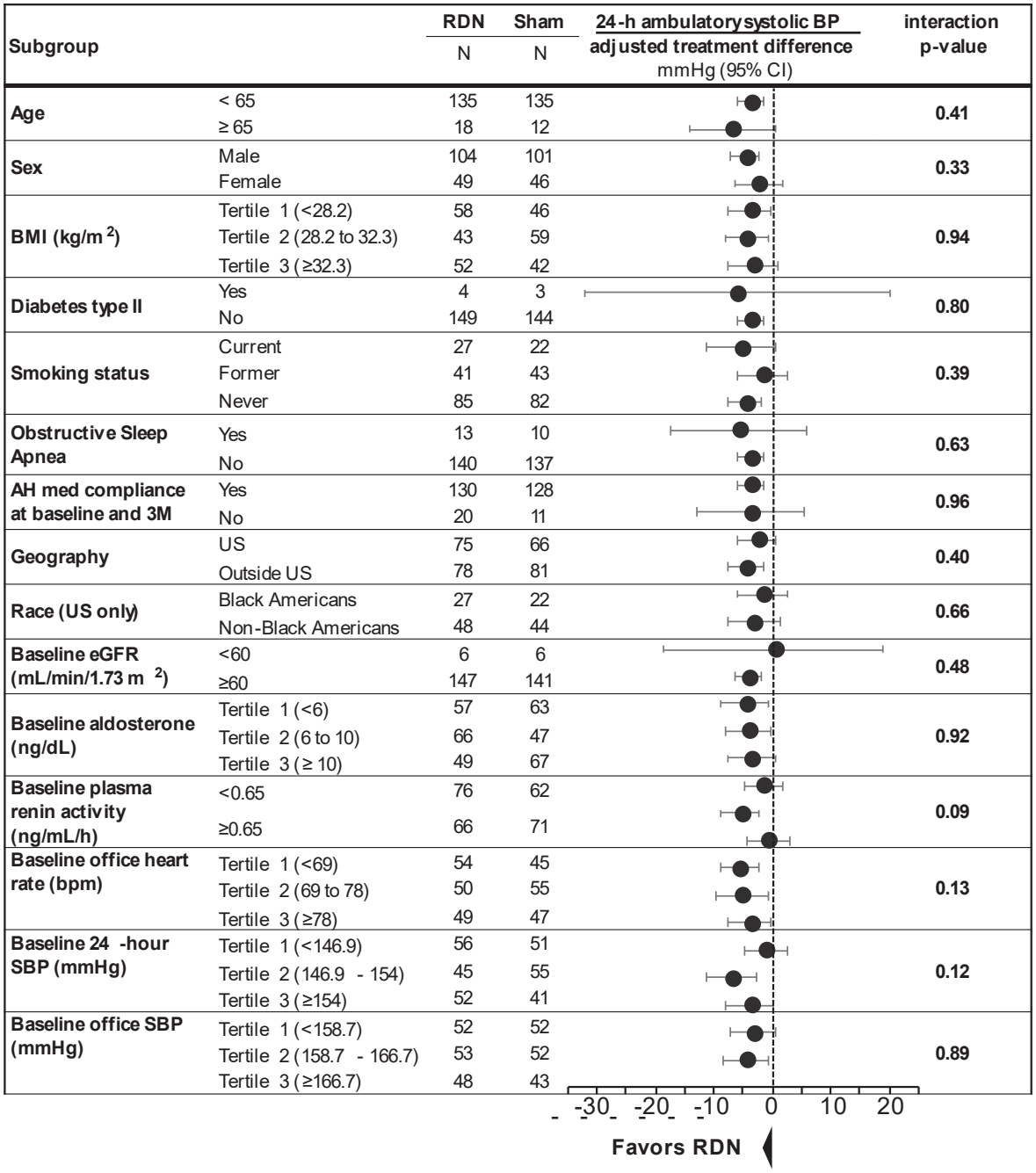


Figure 20. HTN-OFF MED Full Cohort 24-hour Ambulatory SBP Subgroup Analyses at 3 Months –

Figure 21 shows subgroup analyses for the difference of 24-hour SBP at 6 months for the HTN-ON MED Full Cohort. The sample size is small for many of the subgroups, and outcome differences between treatment were generally small.

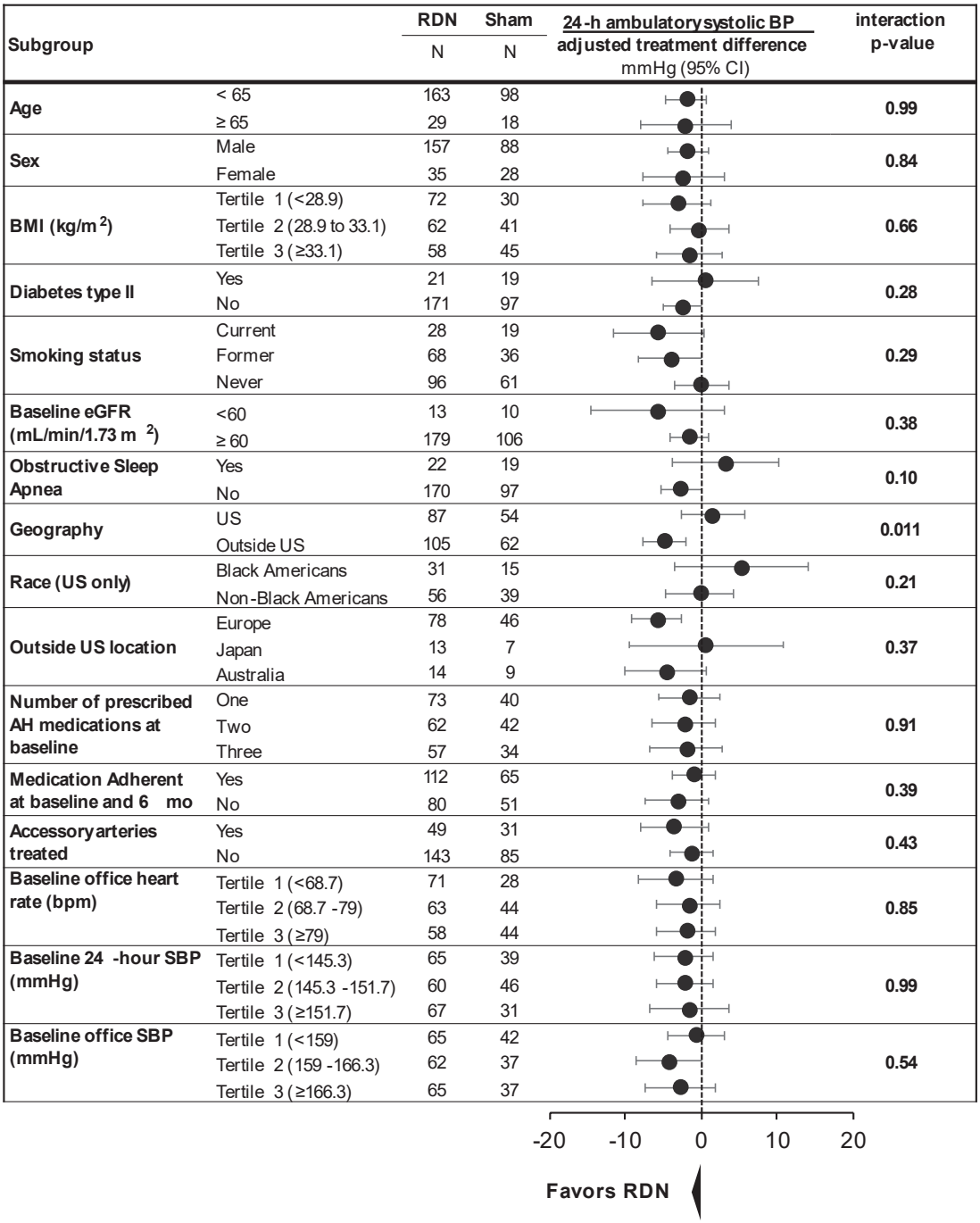


Figure 21. HTN-ON MED Full Cohort 24-hour Ambulatory SBP Subgroup Analyses at 6 Months

HTN-OFF MED and HTN-ON MED were not powered to assess BP responses in subgroups. However, in the HTN-ON MED study, statistically significant differences in 24-hour ASBP were noted in US vs OUS subjects, and the interaction p-value was 0.21 in African Americans vs non-African Americans, which are discussed further below.

US Population

In both the HTN-OFF MED and HTN-ON MED studies, pre-specified 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 help explain these differences. The HTN-OFF MED study, which did not have significant confounding due to medication differences between groups, showed no difference in effectiveness by geographic region (Figure 20).

In the HTN-ON MED study, there was a significant interaction observed between US sites and Non-US for the primary effectiveness endpoint poolability analysis ($p = 0.011$; Figure 21).

Additional post-hoc analyses were performed to analyze the geographic effect. Medication changes were assessed using MedIndex 1 or MedIndex 2. Each patient was categorized by increase, decrease, or no change (results for this categorization were generally consistent for both MedIndices used). Outside the US, antihypertensive medication changes assessed via MedIndex 2 were generally similar between rfRDN and Sham (see Figure 22) and there was a statistically significant 4.8 mmHg 24-hour ASBP reduction difference at 6 months in favor of rfRDN vs. Sham (Figure 22). These results illustrate a potential impact of medication differences on the HTN-ON MED study results.

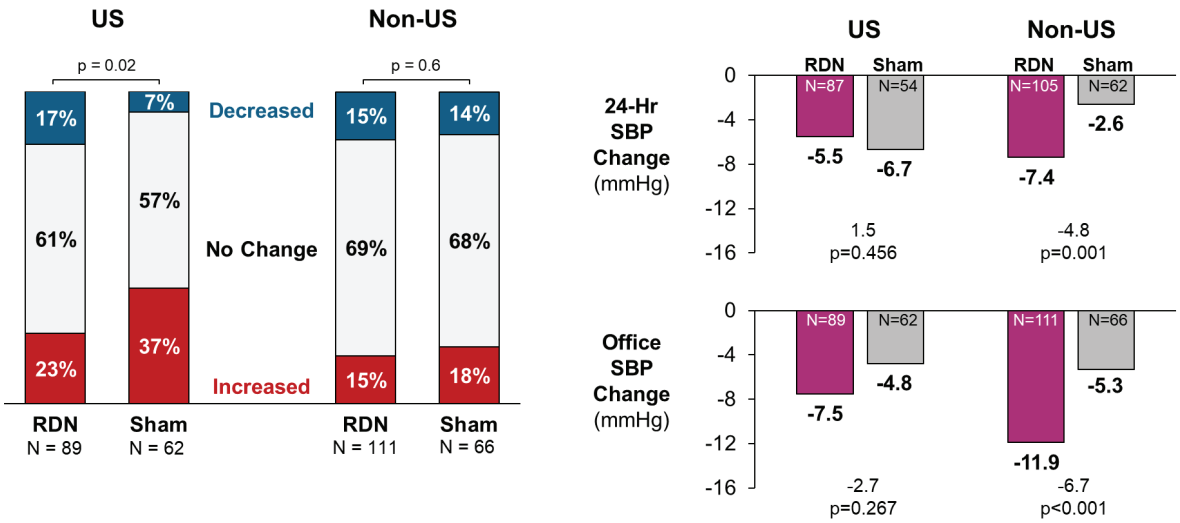


Figure 22. HTN-ON MED Study US and Non-US Subgroups from the Full Cohort: Medication Changes from Baseline to 6 Months and Change in SBP

p-values not adjusted for multiplicity

Black American Population

In the HTN-OFF MED Study, there was no difference in blood pressure results by race (Black Americans (n=49) vs. non-Black Americans (n=92), Figure 20, interaction p=0.66),

In the HTN-ON MED there was a difference in the magnitude of the BP treatment effect. While this difference did not reach statistical significance (Black Americans (n=46) and non-Black Americans (n=95), Figure 21, interaction p-value = 0.21), it was examined further in the following analyses.

Figure 24 and Figure 25 show changes in prescribed BP medication use at 6 months in Black Americans and non-Black Americans:

- Black Americans: The Sham group had a 0.3 MedIndex 1 increase from baseline (corresponding to an average of ~1/3 of a maximal dose of one pill.) vs. no change in the rfRDN group.

- Non-Black Americans: The Sham and rfRDN groups had a 0.1 MedIndex 1 increase from baseline.

The BP medication increase vs. baseline assessed by MedIndex 2 was more pronounced in Black Americans in the Sham group compared with the medication changes assessed with MedIndex 1 method.

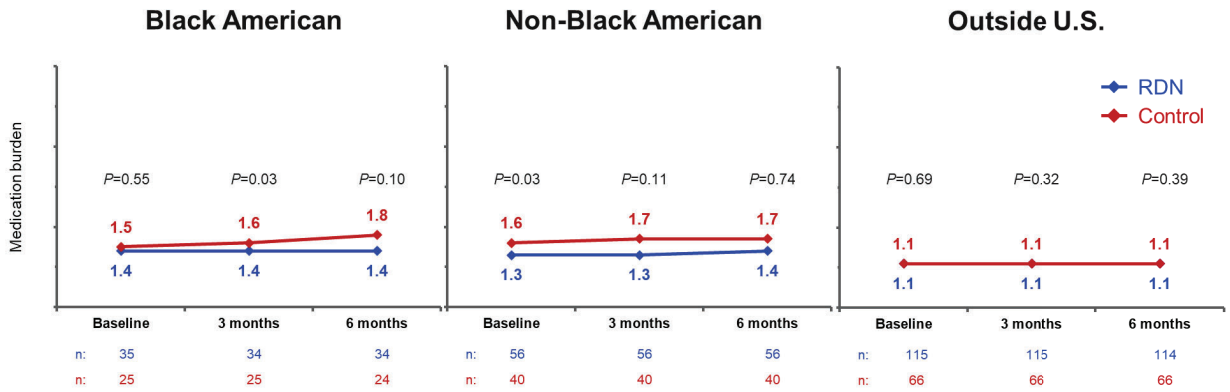


Figure 23. Prescribed BP Medication Changes (MedIndex 1)[1] in Black Americans, Non-Black Americans, and Non-US Subjects at 6 Months – HTN-ON MED Full Cohort[1]

[1] Medication burden based on number, class and dosage, where all medication classes are considered of equivalent potency (Mahfoud et al. Lancet 2022)
P-values at follow-up are ANCOVA adjusted
p-values not adjusted for multiplicity

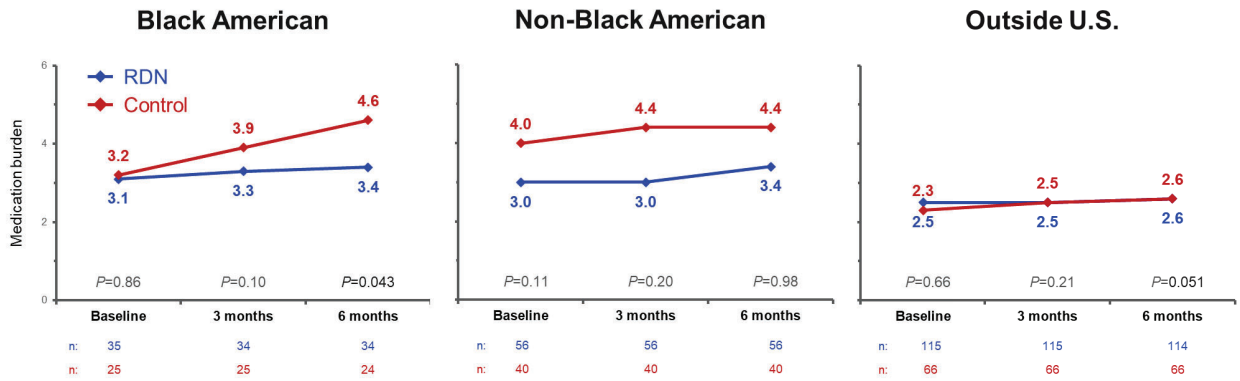
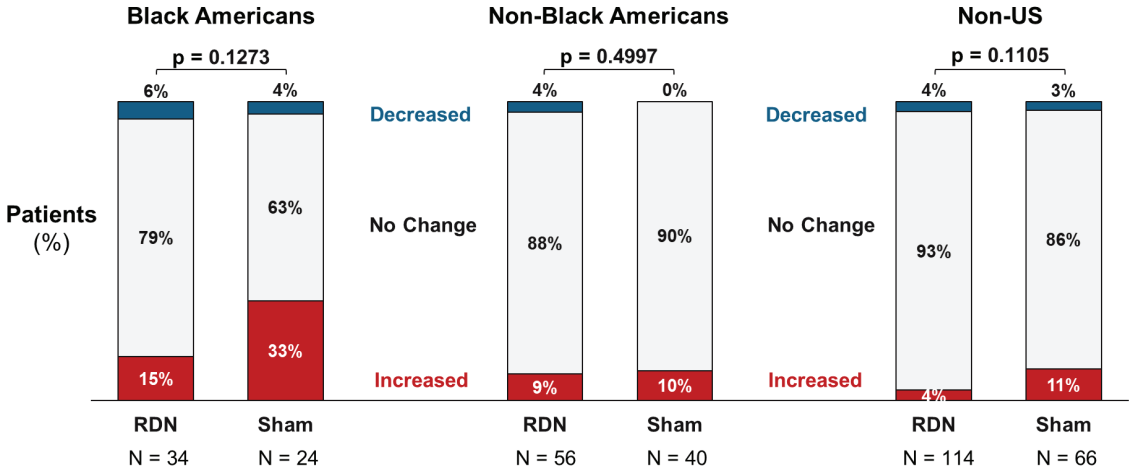


Figure 24. Prescribed BP Medication Changes (MedIndex 2)[1] in Black Americans, Non-Black Americans, and Non-US Subjects at 6 Months – HTN-ON MED Full Cohort

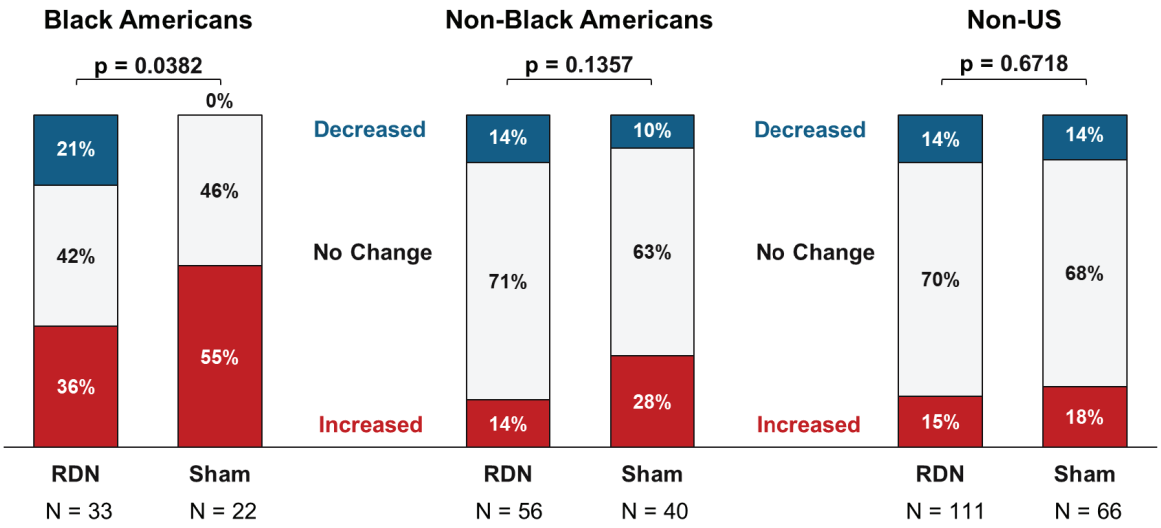
[1] Medication burden based on number, class and dosage, where all medication classes are considered of equivalent potency (Mahfoud et al. Lancet 2022)
P-values at follow-up are ANCOVA adjusted
p-values not adjusted for multiplicity

Figure 26 shows HTN-ON MED prescribed medication changes based on MedIndex 1, and Figure 27 shows these data confirmed by drug testing. A higher proportion of Black Americans in the rfRDN and Sham group increased prescribed BP medications vs. non-Black Americans and non-US subjects. The results are similar using MedIndex 2 (not shown). The BP medication increase was most pronounced in the Black American Sham group.



p-values not adjusted for multiplicity

Figure 25. Prescribed Medication Changes in Black Americans, Non-Black Americans, and Non-US Subjects at 6 Months – HTN-ON MED Full Cohort



p-values not adjusted for multiplicity

Figure 26. Medication Changes Confirmed by Drug Testing in Black Americans, Non-Black Americans, and Non-UUS Subjects at 6 Months – HTN-ON MED Full Cohort

These data suggest that the greater BP reduction noted for Black Americans in the Sham group may have been due to a larger increase in BP medication use vs. the rfRDN group.

The 24-hour SBP response was discordant between Black Americans (N=46) and non-Black Americans (N=95) at 6 months with a greater BP reduction observed in the Sham group in Black Americans (Figure 28). In contrast, the OSBP reduction trend in favor of rfRDN at 6-months was generally similar between Black Americans and non-Black Americans.

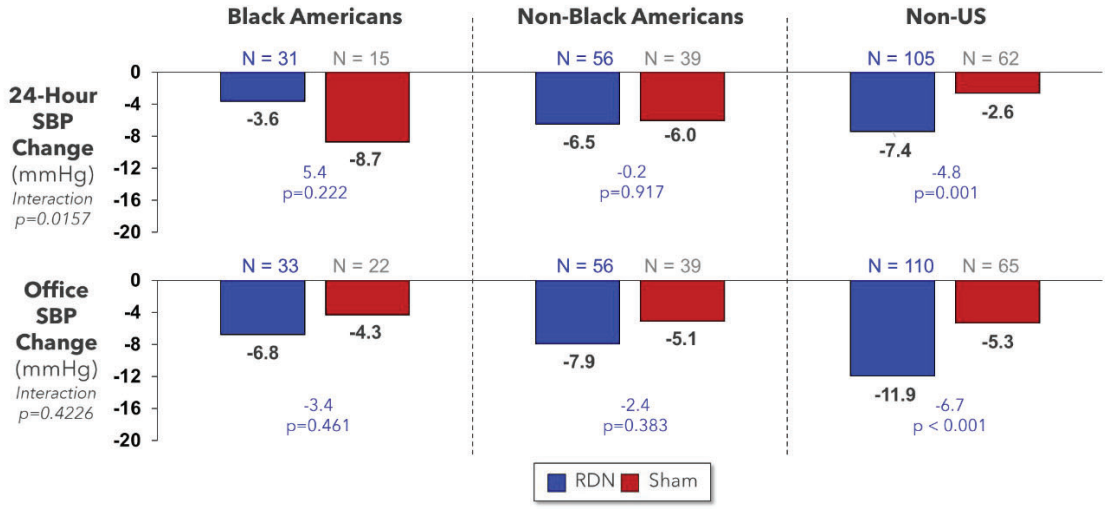


Figure 27. 24-hour SBP Changes for Black Americans, Non-Black Americans, and non-US Subjects at 6 Months – HTN-ON MED Full Cohort

p-values not adjusted for multiplicity
SBP changes are unadjusted absolute drops from baseline. Differences and p-values are determined from ANCOVA models adjusting for the baseline value

BP Tertiles
Figure 29 and Figure 30 show the change of 24-hour and office SBP from baseline to 3 months based on baseline 24-hour ambulatory SBP for the HTN-OFF MED and HTN-ON MED studies (Full Cohorts), respectively. General SBP reduction trends in favor of rfRDN vs. Sham were observed across SBP tertiles in both trials.

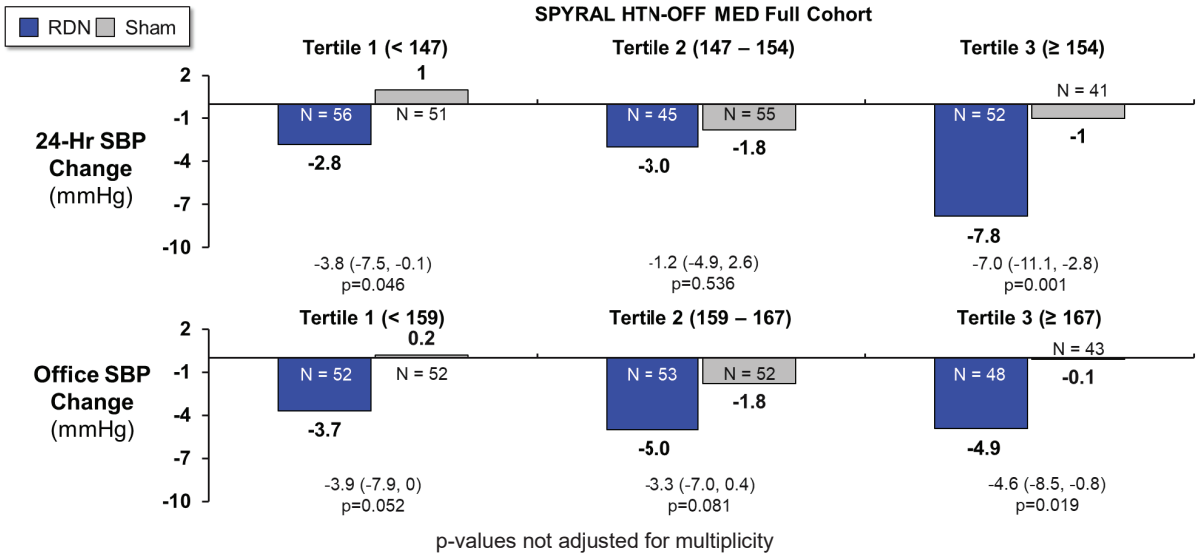


Figure 28. HTN-OFF MED ASBP Change from Baseline to 3 Months by Baseline 24-Hour SBP Tertile

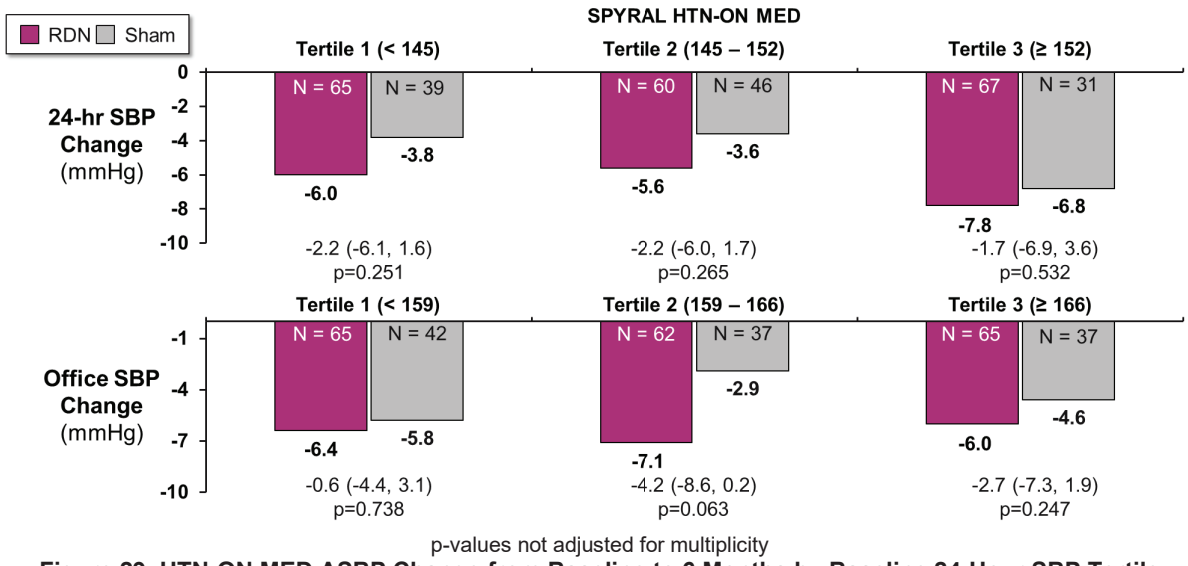


Figure 29. HTN-ON MED ASBP Change from Baseline to 6 Months by Baseline 24-Hour SBP Tertile

7. Summary of Supplementary Clinical Information

b. Global SYMPLICITY Registry (GSR)

The GSR is a prospective, multi-center, single-arm, 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 rfRDN in a real-world patient population.

The GSR includes subjects treated using both the Symplicity Flex (single electrode) and Symplicity Spyral (multi-electrode) catheters and is intended to enroll up to 5000 subjects ≥18 years of age. In the GSR, subjects were included that have different comorbidities vs. the randomized controlled trials, and subgroup analyses were performed.

Subject follow-up is planned at 3, 6, and 12 months and then annually for 3-5 years. However, the actual follow-up visits are based upon the hospital's standard of care for renal denervation.

i. 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 shown in Table 19.

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 the GSR , patient follow up is conducted as a part of routine standard of care. rfRDN 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 18. 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	

ii. GSR Results

Safety Results

Adverse event information collection in the GSR was focused on collecting protocol-specified events only, from consent to 3-5 years follow-up.

Overall, the rfRDN procedure with the Medtronic Symplicity Renal denervation system was not associated with serious adverse events, and there were no unanticipated adverse device effects. No significant embolic events were reported in patients treated with the Symplicity Spyral catheter, while four significant embolic events were reported for patients treated with the Symplicity Flex catheter. Additionally, and in line with other interventional treatments using the groin arterial access site, GSR data show a low rate of vascular complications.

GSR Efficacy Results

In data available for patients treated with the Symplicity Spyral catheter, sustained office and 24-hour SBP reductions are observed for the duration of the 3-year follow-up.

Table 20 shows the office SBP and DBP for the Symplicity Spyral catheter (subject of the current PMA) and the Symplicity Flex catheter. Through the 3-year follow-up period, the mean number of medications (4.85 at baseline, 4.87 at 6 months, 4.86 at 12 months, 4.83 at 24 months, and 4.90 at 3 years) stayed consistent.

Table 19. GSR Office SBP and DBP from Baseline to 36-months in Subjects Treated with the Symplicity Spyral

	Baseline	Change at 6-months	Change at 12-months	Change at 24-months	Change at 36-months
Symplicity Spyral Catheter					
Ambulatory SBP	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
Ambulatory DBP	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
Office SBP	N=792	N=517	N=475	N=331	-18.07 ± 26.76 N=200
Office DBP	91.19 ± 17.44 N=792	-5.52 ± 14.07 N=515	-6.42 ± 14.77 N=473	-7.67 ± 15.06 N=326	-7.79 ± 15.68 N=195

Data displayed as mean ± SD (n); SBP/DBP: Systolic/diastolic blood pressure

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