Global Clinical Study of Renal Denervation with the Symplicity Spyral* multi-electrode renal denervation system in Patients with Uncontrolled Hypertension on Standard Medical Therapy

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The objective of this study is to evaluate safety and blood pressure response after renal denervation in patients with uncontrolled hypertension on three standard antihypertensive medications compared to a sham-controlled population. These data, in...

Ethical review	Not approved
Status	Will not start
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON42334

Source
ToetsingOnline

Brief title
SPYRAL HTN-ON MED

Condition

- Vascular hypertensive disorders

Synonym
high blood pressure, uncontrolled hypertension

Research involving

Human

Sponsors and support

Primary sponsor: Medtronic Bakken Research Center B.V.
Source(s) of monetary or material Support: Opdrachtgever van het onderzoek (zie B6)

Intervention

Keyword: Cardiovascular disease, Hypertension, Renal artery, Renal Denervation

Outcome measures

Primary outcome

The following safety endpoints will be evaluated:

* Acute safety up to 30 days post-procedure and chronic safety at 3, 6, 12, 24

and 36 months post-procedure

* Incidence of Major Adverse Events (MAE), defined as a composite of the

following events, compared between groups through 4 weeks post procedure:

* All-cause mortality

* End-stage Renal Disease (ESRD)

* Significant embolic event resulting in end-organ damage

* Renal artery perforation requiring intervention

* Renal artery dissection requiring intervention

* Vascular complications

* Hospitalization for hypertensive crisis not related to confirmed

non-adherence with medications.

* New renal artery stenosis > 70%, confirmed by angiography

* New Myocardial Infarction

* New Stroke

* Renal artery re-intervention

* Major bleeding according to TIMI definition (i.e. intracranial hemorrhage; *5g/dl decrease in hemoglobin concentration; a *15% absolute decrease in hematocrit, or bleeding that results in death within 7 days of procedure)

* Increase in serum creatinine > 50% from Screening Visit 2

The following efficacy endpoints will be evaluated:

* Change in systolic blood pressure from baseline (Screening Visit 2) as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM) at 3, 6, 12, 24 and 36 months post-procedure.

* Change in office systolic blood pressure from baseline (Screening Visit 2) at 1, 3, 6, 12, 24 and 36 months post-procedure.

* Incidence of achieving target office systolic blood pressure (SBP<140 mm Hg or <130 mmHg for patients with diabetes or renal disease) at 1, 3, 6, 12, 24 and 36 months post-procedure.

* Change in office diastolic blood pressure from baseline (Screening Visit 2) at 1, 3, 6, 12, 24 and 36 months post-procedure.

* Change in diastolic blood pressure from baseline (Screening Visit 2) as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM) at 3, 6, 12, 24 and 36 months post-procedure.

Secondary outcome

The following additional analyses will be conducted:

* Antihypertensive medication usage through 36 months.

* Additional procedural characteristics e.g. treatment duration, frequency of

distal renal artery treatment, ablations per vessel, location of ablations,

number of ablations per patient and other characteristics will be analyzed to

assess their impact on blood pressure.

Study description

Background summary

The kidneys are an important regulator of blood pressure and it is thought that in patients whose blood pressure cannot be controlled, there is increased activity in the nervous system between the brain and kidney which results in the kidneys releasing an excessive amount (more than normal) of hormones that raises blood pressure. Medications alone may not be effective in controlling blood pressure. Previous research has shown that disrupting certain nerves may decrease blood pressure in some cases. In the past, one technique that was used to treat severe high blood pressure was a surgical procedure to cut nerves. However, this surgery is no longer commonly performed, because it was a complex invasive procedure.
This clinical research study, named SPYRAL HTN-ON MED, will provide additional information about the safety and effect of renal denervation on blood pressure using the Symplicity Spyral* catheter and G3* generator when combined with 3 blood pressure medications.
These data, in conjunction with the data generated in the companion off medications study (SPYRAL HTN-OFF MED), will help determine whether commonly used antihypertensive medications synergize, antagonize, or have no impact on the effect of renal denervation on elevated blood pressure.

Study objective

The objective of this study is to evaluate safety and blood pressure response after renal denervation in patients with uncontrolled hypertension on three standard antihypertensive medications compared to a sham-controlled population.
These data, in conjunction with the data generated in the companion off medications study (SPYRAL HTN-OFF MED), will help determine whether commonly used antihypertensive medications synergize, antagonize, or have no impact on the effect of renal denervation on elevated blood pressure.

Study design

Multi-center, international, prospective, single blinded, 1:1 randomized, interventional, sham-controlled study.

Intervention

Subjects on three eligible antihypertensive medications for at least six weeks and with an office SBP * 150 mm Hg and < 180 mm Hg and an office DBP * 90 mm Hg will be enrolled and proceed to Screening Visit 1 (SV1). Subjects meeting the eligibility criteria can continue to Screening Visit 2 (SV2) after two weeks, but no later than four weeks. Subjects who continue to meet eligibility criteria after completion of Screening Visit 2 and who have received randomization approval by the sponsor will be randomized and the procedure will occur within a maximum of two weeks from Screening Visit 2, with all efforts undertaken to schedule the procedure within one week.
Following the renal denervation or control procedure, subjects will return for follow-up at 1, 3, 6, and 12 months. Subjects and blinded study personnel will be unblinded to their randomization assignment at 12 months. Subjects randomized to renal denervation will continue to be followed annually through 36 months post-procedure (see table 1 in the protocol). Subjects randomized to the control group will not be required to return annually for office visits, but will be contacted by phone at 24 and 36 months to obtain vital status only.
After the study blinded period (i.e., 12-Month subject follow-up visits are completed), the study sponsor will review preliminary study data. If the outcomes in the Denervation Group are considered to be positive as determined by the study sponsor in consultation with the study Executive Steering Committee and Site Investigator, control subjects may be offered renal denervation therapy (crossover) after meeting key inclusion criteria and no key exclusion criteria. In this case, crossover subjects will need to return for office visits at 1, 6, 12 and 24 months post-renal denervation procedure (see table 2 in the protocol).

Study burden and risks

Standard treatment in The Netherlands is prescribing antihypertensive medication for these hypertensive patients. There is no alternative treatment for patients with uncontrolled hypertension that is reimbursed by the health insurance. Renal denervation is an alternative which is not yet reimbursed in The Netherlands. For this study, patients need to take 3 standard antihypertensive medications.

This study follows the guidelines that have been recommended for the follow up visits/care for the renal denervation. This study adds 1 additional follow up visit at 1 month post procedure to carefully monitor the blood pressure and any possible adverse events.
Additionally, patients will undergo drug adherence tests to see if they are compliant to the medication regimen as well as withnessed pill taking during their hospital visits. In a previous trial the medication intake incompliance of the patients was one of the problems that may have let to insignificant data.

Furthermore, pregnancy tests will be performed to exclude patients that are pregnant prior to the procedure, as it is unclear what the consequences are for the unborn child. Also a quality of life questionnaire needs to be completed, which will not be a big burden for the patient.

There is an extended risk-benefit analysis report available, in which all risks and benefits have been described. See the SPYRAL HTN-ON MED Study Risk Benefit Analysis version 2, 23 April 2015. To summarize:

The risks associated with participation in this study are devided in
1) Anticipated Risks for the Symplicity Spyral Renal Denervation System
2) Procedural risk
3) Study Specific risks

The primary risks of the renal denervation procedure are similar to the risks of all diagnostic procedures requiring catheterization of the arteries of the body. Catheterization risks are considered low with most occurring in less than 1% of patients. Complication rates associated with medications and the catheter insertion site are expected to be higher than 1%, but less than 10%, based on historical precedence.

There are additional risks that could possibly be associated with the denervation procedure/therapy. Procedural risks are low with rates similar to catheterization referenced above.

Renal denervation involves exposure to a small amount of radiation. As part of everyday living, people are exposed to naturally occurring background radiation and receive a dose of about 3 mSv each year. The effective dose from the denervation procedure is about 8 mSv. The dose from this procedure is comparable to that received from many diagnostic medical x-ray and nuclear medicine procedures.

The study may involve unknown or unforeseen side effects or complications other than those mentioned above. If the above complications occur, they may lead to repeat or prolonged hospitalization, repeat procedures, emergency surgery, other emergency procedures, or, in rare
cases, death.

There are additional risks that could possibly be associated with the tests and procedures performed for the clinical study, like risks related to the blood tests required for the study, renal imaging (MRA/CT when no DUS can be made or inconclusive DUS) and risks related to the unborn child.

Patients enrolled in this study did not have controlled blood pressure on entry. Thus, the risks associated with not having a controlled blood pressure during the first 6 months would be present regardless of their participation in the study and may be reduced by the increased medical attention given during

the study compared to usual care and the blood pressure lowering effects of renal denervation.

The detrimental effects of uncontrolled hypertension and the issues of drug adherence to prescribed medications are well established and an alternative treatment is worth of continued study. Renal denervation using the Symplicity SpyralTM catheter and Symplicity G3TM generator is one such alternative. Although there are several theoretical risks that could be associated with the device and procedure, the likelihood of those risks is expected to be low and will be carefully monitored in the study. The potential benefits, including blood pressure reduction in these uncontrolled hypertension patients and the associated beneficial effects of lowered blood pressure in these patients outweigh the risks and justify the investigation of renal denervation in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

1. Individual is * 20 and * 80 years old at time of randomization.
2. Individual has an office systolic blood pressure (SBP) * 150 mm Hg and < 180 mm Hg and an office diastolic blood pressure (DBP) * 90 mm Hg (according to guidelines in Appendix L.7 of the protocol) at Screening Visit 1 and Screening Visit 2 when receiving a medication regimen of three antihypertensive medications on at least 50% of the maximum manufacturer*s dosage; the three anti-hypertensive medications must include a thiazide-type diuretic, a dihydropyridine calcium channel blocker, and an ACE-I/ARB and the subject must be on a stable dose of each medication for at least six weeks prior to Screening Visit 1 and up to Screening Visit 2. Note: In Japan, patients may be prescribed less than 50% of maximum manufacturer*s recommended dosage of a thiazide-type diuretic per standard of care.
3. Individual has a 24-hour ABPM average of SBP * 140 and < 170 mm Hg measured at Screening Visit 2 according to guidelines in Appendix L.7 of the protocol after witnessed antihypertensive drug ingestion prior to applying the ABPM device.
4. Individual agrees to have all study procedures performed, and is competent and willing to provide written, informed consent to participate in this clinical study.

Exclusion criteria

1. Individual has undergone prior renal denervation.
2. Individual has renal artery anatomy that is ineligible for treatment including:
a. Lacks at least one renal arterial vessel for each kidney greater than 3 mm and less than 8 mm in diameter (including accessory, branch, and main renal arteries)
b. Main renal artery which contains renal artery stenosis (> 50%), renal artery aneurysm, fibromuscular dysplasia (FMD), presence of a renal artery stent or calcification which does not allow at least four radio frequency ablations to be delivered in areas free of these abnormalities. FMD is defined as visible beading of the artery on angiography.
c. Unilateral kidney.
3. Individual has an estimated glomerular filtration rate (eGFR) of < 45 mL/min/1.73m2, using the MDRD calculation. (Note: an eGFR calculation specific to Japanese patients will be used for subjects enrolled in Japan)
4. Individual has documented type 1 diabetes mellitus or poorly-controlled type 2 diabetes mellitus with glycosylated hemoglobin greater than 8.0%.
5. Individual has had * 1 episode(s) of orthostatic hypotension not related to medication changes within the past year or has a reduction of SBP of * 20 mm Hg or DBP of *10 mm Hg within 3 minutes of standing coupled with symptoms during the screening process.
6. Individual requires chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea (e.g. CPAP, BiPAP).
7. Individual is being treated chronically (e.g. daily use) with non-steroidal anti-inflammatory drugs (NSAIDs). Aspirin therapy is allowed.
8. Individual has documented primary pulmonary hypertension.
9. Individual has known pheochromocytoma, Cushing*s Disease (adrenal insufficiency),

primary hyperaldosteronism, coarctation of the aorta, untreated hyperthyroidism, untreated hypothyroidism, or primary hyperparathyroidism. (Note: treated hyperthyroidism and treated hypothyroidism are permissible).
10. Individual has experienced a myocardial infarction, unstable angina pectoris, syncope, or a cerebrovascular accident within three months of the screening period, or has widespread atherosclerosis, with documented intravascular thrombosis or unstable plaques.
11. Individual has a scheduled or planned surgery that, in the opinion of the Investigator, may affect study endpoints.
12. Individual has a documented condition that would prohibit or interfere with ability to obtain an accurate blood pressure measurement using the protocol-specified automatic blood pressure monitor (e.g., upper arm circumference outside cuff size ranges available by geography or arrhythmia that interferes with automatic monitor*s pulse sensing and prohibits an accurate measurement).
13. Individual works night shifts.
14. Individual has severe cardiac valve stenosis for which, in the opinion of the investigator, a significant reduction of blood pressure is contraindicated.
15. Individual has a documented confounding medical condition, which in the opinion of the investigator, may adversely affect the safety of the participant (e.g. patients with clinically significant peripheral vascular disease, aortic aneurysm, bleeding disorders such as thrombocytopenia, hemophilia, or significant anemia).
16. Individual is pregnant, nursing or planning to become pregnant during the course of the study follow-up. (Note: Pre-menopausal female participants must have a negative serum or urine human chorionic gonadotropin (hCG) pregnancy test prior to angiography).
17. Individual has a known unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or would be unlikely or unable, in the opinion of the investigator, to comply with study follow-up requirements.
18. Individual is currently enrolled in a concurrent investigational drug or device study, unless approved by the study sponsor. (Note: For the purpose of this protocol, participants involved in extended follow-up studies for products that were investigational but are currently commercially available are not considered enrolled in an investigational study).
19. Individual is currently taking mineralocorticoid drugs.
20. Individual has an active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior six months.
21. Individual has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions.
22. Individual has polycystic kidney disease or history of renal transplant.

Study design

Design

Study type:	Interventional
Intervention model:	Other

Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	24
Type:	Anticipated

Medical products/devices used

Generic name:	The Symplicity renal denervation system composed of the Symplicity Spyral Catheter and the Symplic
Registration:	Yes - CE intended use

Ethics review

Not approved

Date:	08-10-2015
Application type:	First submission
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT02439775
CCMO	NL53264.041.15