Renal Denervation: Spyral HTN OFF-MED

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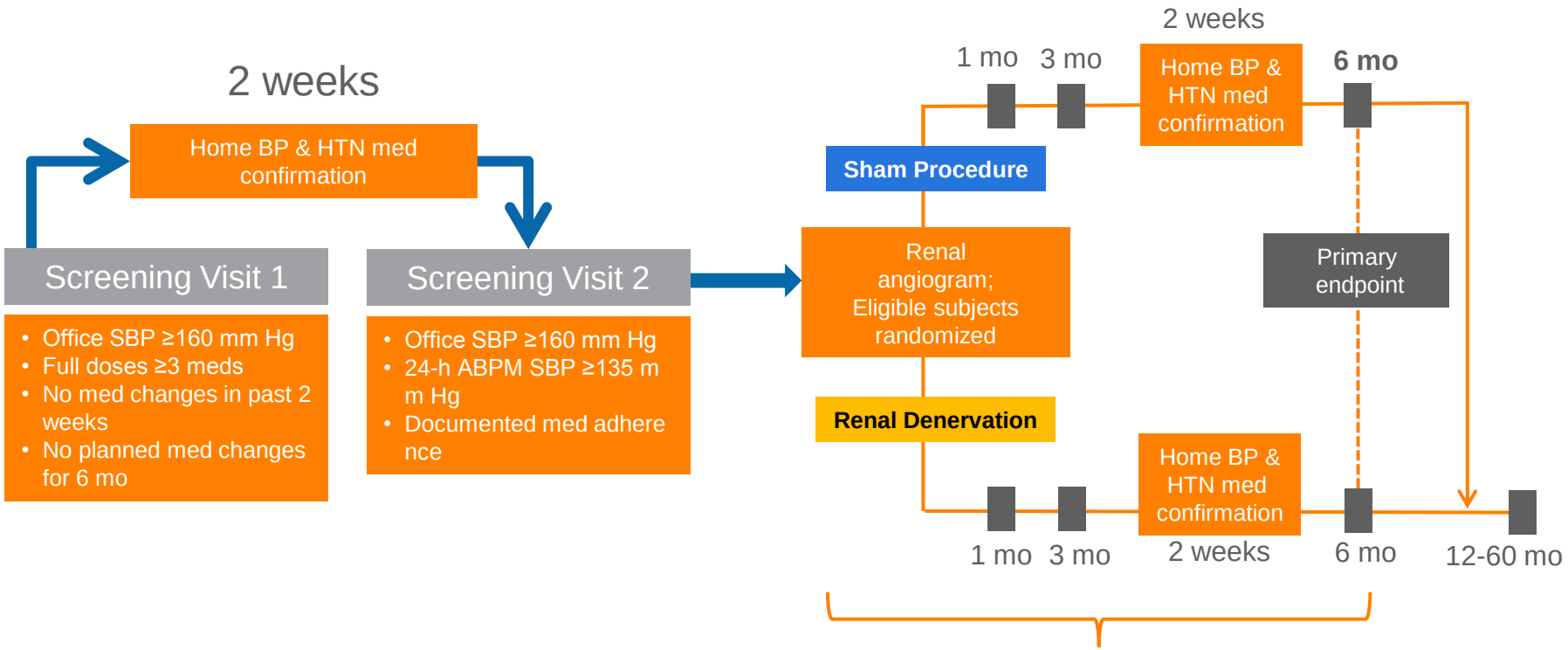
Introduction

- **Up to one-third of adults have hypertension**
  - ✓ Increased risk of cardio and cerebrovascular events
  - ✓ Many patients remain uncontrolled.
- **Renal denervation therapy (RDN) targets the sympathetic nervous system.**
- **Several observational studies demonstrated the efficacy of RDN on reduction of blood pressure.**

SYMPLICITY HTN-3

- 2:1 **randomized, blinded, sham-controlled**
- Sham procedure in control patients that included renal angiogram
- **535 subjects randomized** out of 1441 enrolled (63% screen failure rate)
- 2-week screening process, including maximum tolerated doses of antihypertensives

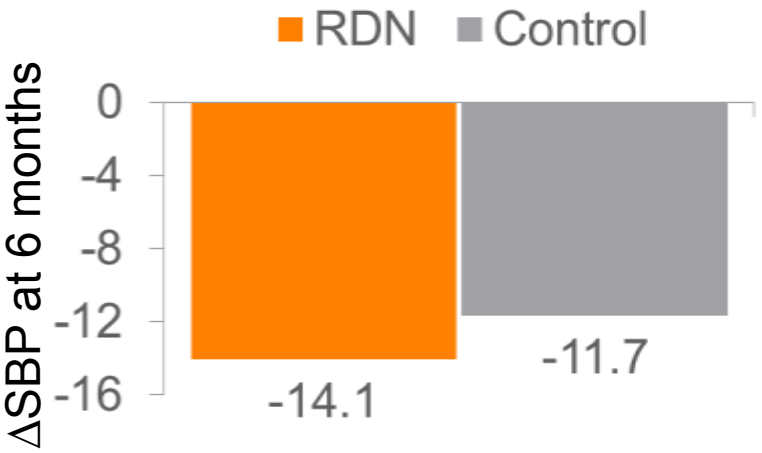


- Patients, BP assessors, and study personnel all blinded to treatment status
- **No changes in medications for 6 M**

N Engl J Med. 2014;370:1393-401

Primary Efficacy Endpoint

Office Systolic Blood Pressure at 6 Months



	RDN	Control	*P* value
Baseline SBP	179.7	180.2	0.765
6 mo SBP	165.6	168.4	0.260
Change	***-14.1*** *P < 0.001*	***-11.7*** *P < 0.001*	***0.255***

-2.39 (-6.89, 2.12), *P* = 0.255 (Primary analysis with **5 mm Hg** superiority margin)

Did not meet primary efficacy endpoint !

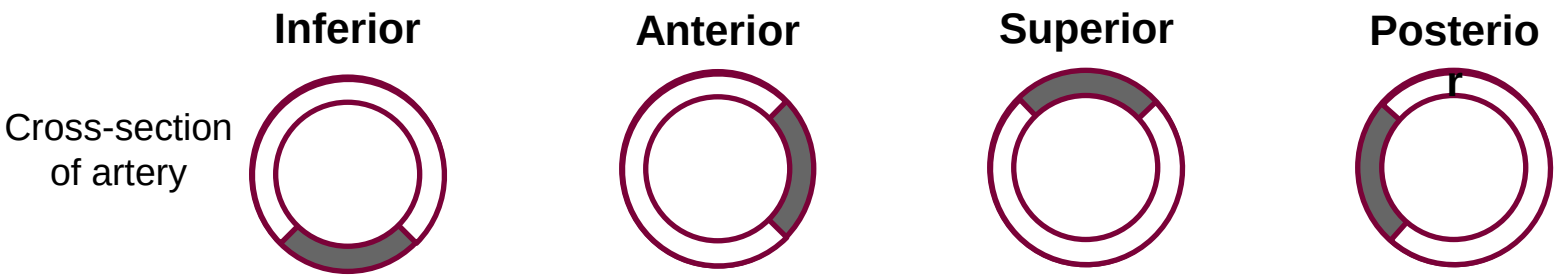
N Engl J Med. 2014;370:1393-401

Why did Symplicity HTN-3 fail ?

- Variation in adherence to medication
- Incomplete renal denervation
- Ine patient included

Procedural variability: Symplicity HTN-3

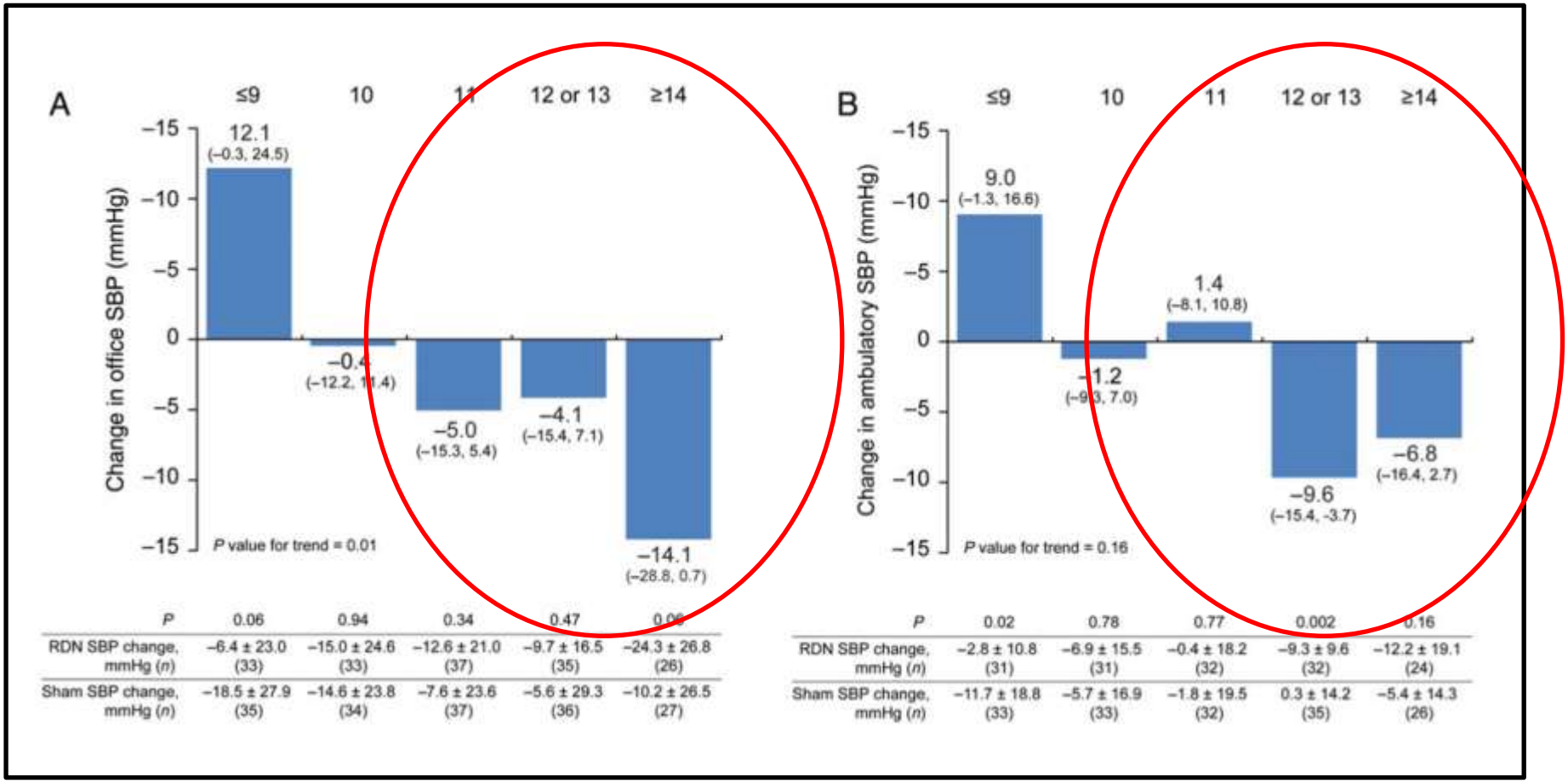
4-quadrant ablation pattern



4 quadrant ablation pattern

0 four quadrant ablation	**N=253 (74%)**
1 four quadrant ablation	**N=68 (20%)**
2 four quadrant ablation	**N=19 (6%)**

Multivariate Predictors of Systolic BP Change at 6 M: Symplicity HTN-3



P	0.06	0.94	0.34	0.47	0.06
RDN SBP change, mmHg (*n*)	−6.4 ± 23.0 (33)	−15.0 ± 24.6 (33)	−12.6 ± 21.0 (37)	−9.7 ± 16.5 (35)	−24.3 ± 26.8 (26)
Sham SBP change, mmHg (*n*)	−18.5 ± 27.9 (35)	−14.6 ± 23.8 (34)	−7.6 ± 23.6 (37)	−5.6 ± 29.3 (36)	−10.2 ± 26.5 (27)

P	0.02	0.78	0.77	0.002	0.16
RDN SBP change, mmHg (*n*)	−2.8 ± 10.8 (31)	−6.9 ± 15.5 (31)	−0.4 ± 18.2 (32)	−9.3 ± 9.6 (32)	−12.2 ± 19.1 (24)
Sham SBP change, mmHg (*n*)	−11.7 ± 18.8 (33)	−5.7 ± 16.9 (33)	−1.8 ± 19.5 (32)	0.3 ± 14.2 (35)	−5.4 ± 14.3 (26)

Larger number of ablations (n =10-13) was associated with significant office and ambulatory BP reduction compared with the sham control group.

EHJ 2015;36:219–27

Hypertensive phenotypes

Young hyperadrenergic hypertensive patient

Obese metabolic hypertensive patient

Elderly hypertensive vascular patient

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Young hyperadrenergic hypertensive patient

Obese metabolic hypertensive patient

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SPYRAL HTN–OFF MED

THE LANCET

Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial

*Raymond R Townsend, Felix Mahfoud, David E Kandzari, Kazuomi Kario, Stuart Pocock, Michael A Weber, Sebastian Ewen, Konstantinos Tsioufis, Dimitrios Tousoulis, Andrew S P Sharp, Anthony F Watkinson, Roland E Schmieder, Axel Schmid, James W Choi, Cara East, Anthony Walton, Ingrid Hopper, Debbie L Cohen, Robert Wilensky, David P Lee, Adrian Ma, Chandan M Devireddy, Janice P Lea, Philipp C Lurz, Karl Fengler, Justin Davies, Neil Chapman, Sidney A Cohen, Vanessa DeBruin, Martin Fahy, Denise E Jones, Martin Rothman, Michael Böhm, on behalf of the SPYRAL HTN-OFF MED trial investigators**

Lancet 2017;390: 2160–70

Background

- **SYMPLICITY HTN-3 trial failed to demonstrate a significant blood pressure lowering effect of RDN**

- **Sub-analysis suggested**:
  - ✓ Variance in medication adherence
  - ✓ Incomplete denervation of the renal arteries
  - ✓ Inclusion of patients with isolated systolic hypertension

- **SPYRAL HTN-OFF MED study**:
  - ✓ Proof of concept trials
  - ✓ **Designed to demonstrate the ability of RDN to influence blood pressure in uncontrolled hypertension**

SPYRAL HTN

Global Trial Center Locations

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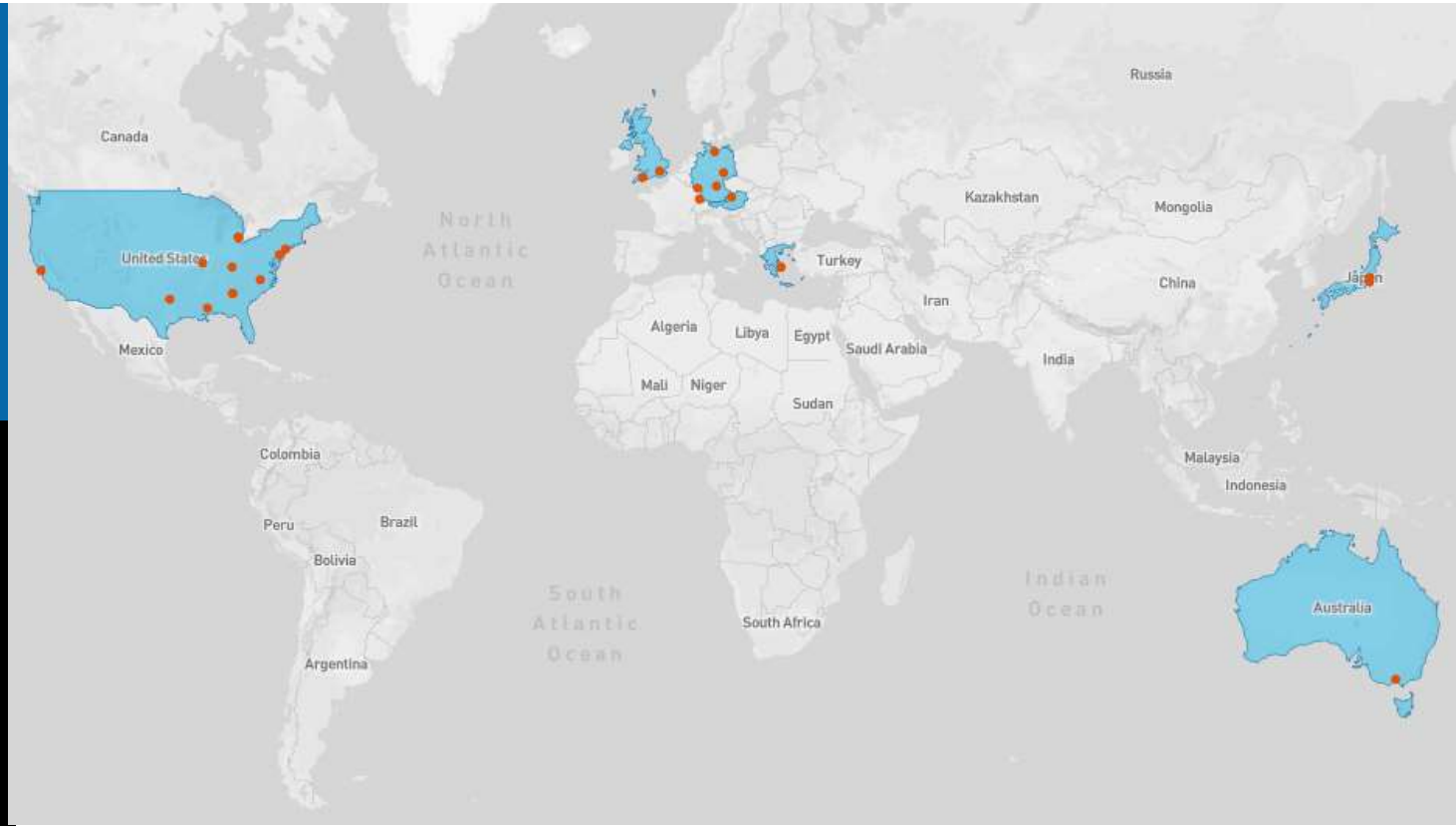
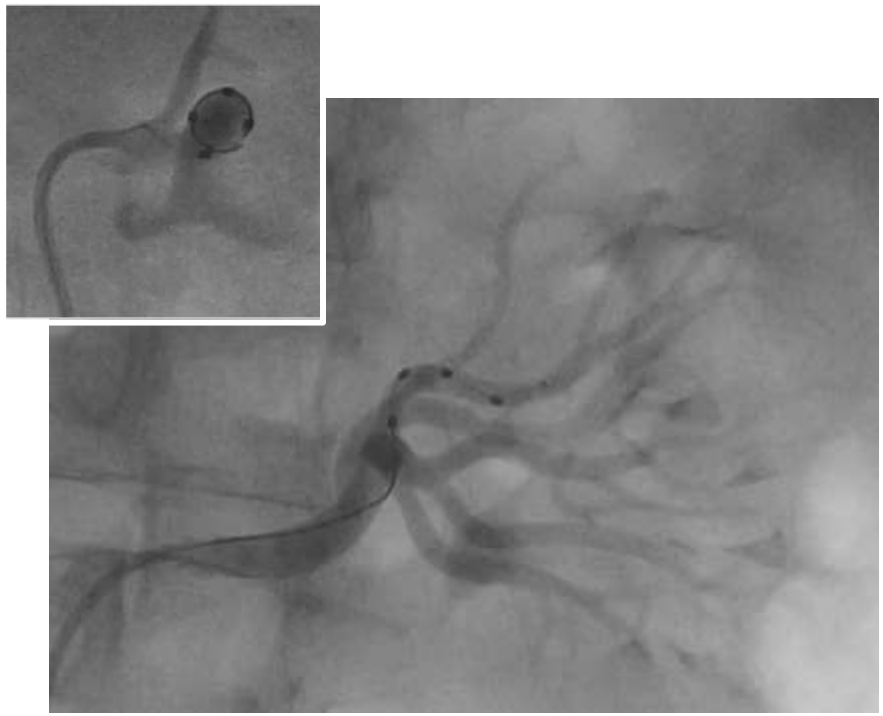
RECRUITING SITES IN:

- USA
- Europe
- Japan
- Australia



Study Device: Symplicity Spyral™ Catheter

- **Multi-electrode catheter** with quadrantic vessel contact for simultaneous ablation in up to 4 electrodes
- 60-second simultaneous energy delivery
- Vessel diameter range: 3–8 mm
- Flexible catheter allows branch treatment
- 6F guiding catheter compatible



SPYRAL HTN–OFF MED

- KEY PATIENT ELIGIBILITY CRITERIA

INCLUSION

1. Patient is either:
- **A. Not on antihypertensive medications, OR**
- **B. Permitting discontinuation of drug therapy**

2. Office SBP ≥ 150 and < 180 mm Hg

3. Office DBP ≥ 90 mm Hg

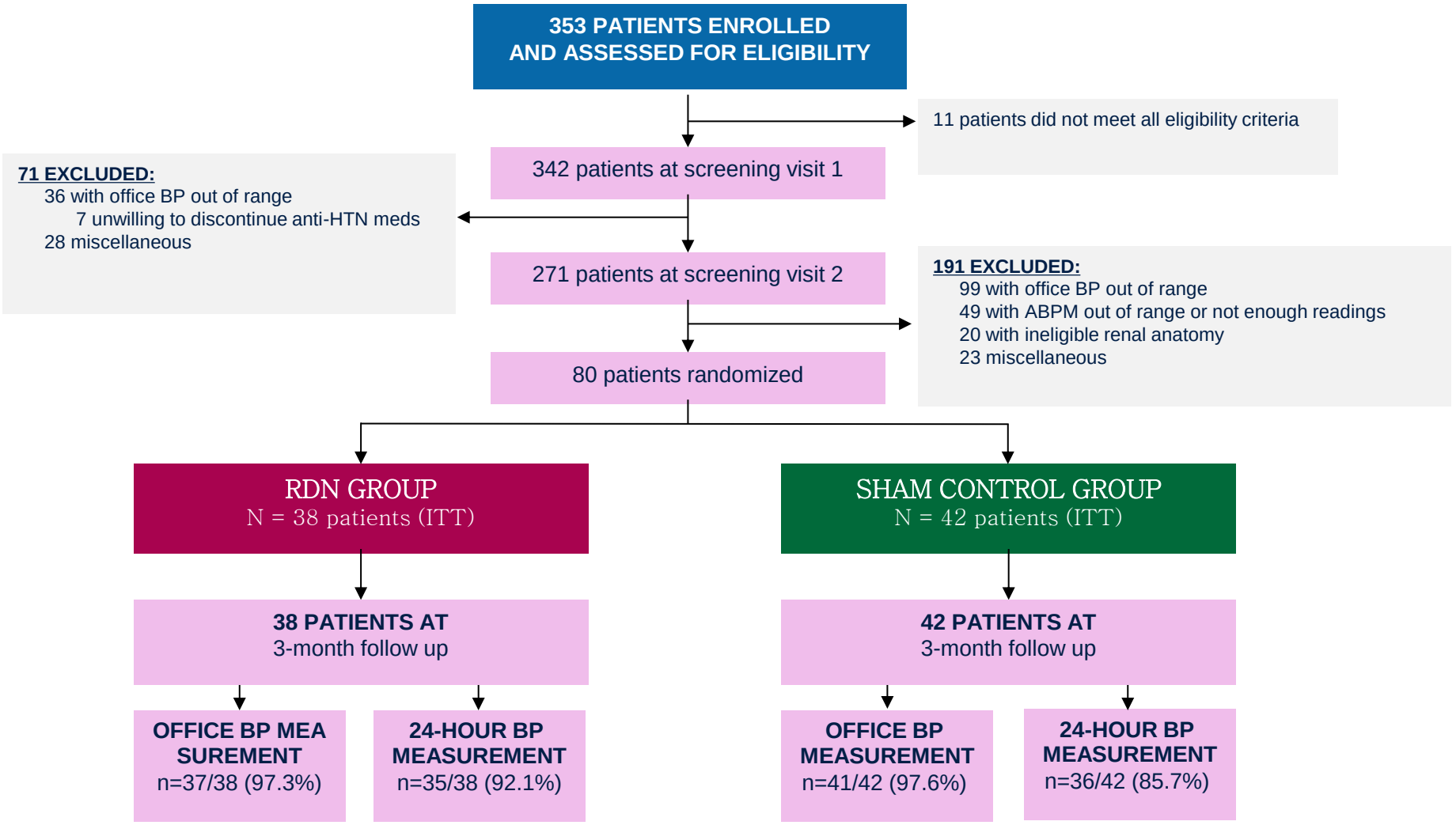
4. Systolic 24-hour mean ABPM ≥ 140 and < 170 mm Hg

EXCLUSION

1. Ineligible renal artery anatomy (accessory arteries allowed)
2. eGFR < 45 mL/min/1.73m^2
3. Type 1 diabetes mellitus or type 2 diabetes mellitus with HbA1C > 8.0%
4. Secondary causes of hypertension

SPYRAL HTN–OFF MED

- Patient Flowchart



Primary efficacy endpoint was BP reduction on ABPM at 3 months

Mean Blood Pressure was lower vs. SYMPLICITY HTN-3

SPYRAL HTN-OFF MED Baseline Blood Pressure

Blood Pressure Measure (mean ± SD)	RDN	Sham Control
Office measurements	N = 38	N = 42
Office SBP (mm Hg)	**162.0 ± 7.6**	**161.4 ± 6.4**
Office DBP (mm Hg)	99.9 ± 6.8	101.5 ± 7.5
Office heart rate (bpm)	71.1 ± 11.0	73.4 ± 9.8
24-hour measurements	N = 37	N = 42
Mean 24-hour SBP (mm Hg)	**153.4 ± 9.0**	**151.6 ± 7.4**
Mean 24-hour DBP (mm Hg)	99.1 ± 7.7	98.7 ± 8.2
Mean 24-hour heart rate (bpm)	72.3 ± 10.9	75.5 ± 11.5

P = NS for differences in all baseline characteristics

RDN was done in Main renal artery plus branches

SPYRAL HTN-OFF MED Procedural Details

Procedural Measure (mean ± SD)	RDN (N = 38)	Sham Control (N = 42)
Number of main renal arteries treated per patient	2.2 ± 0.5	NA
Number of branches treated per patient	5.2 ± 2.5	NA
Total number of ablations per patient	**43.8 ± 13.1**	NA
Main artery ablations	**17.9 ± 10.5**	NA
Branch ablations	**25.9 ± 12.8**	NA
Treatment time (min)	57.1 ± 19.7	NA
Contrast volume used (cc)	251.0 ± 99.4	83.3 ± 38.5

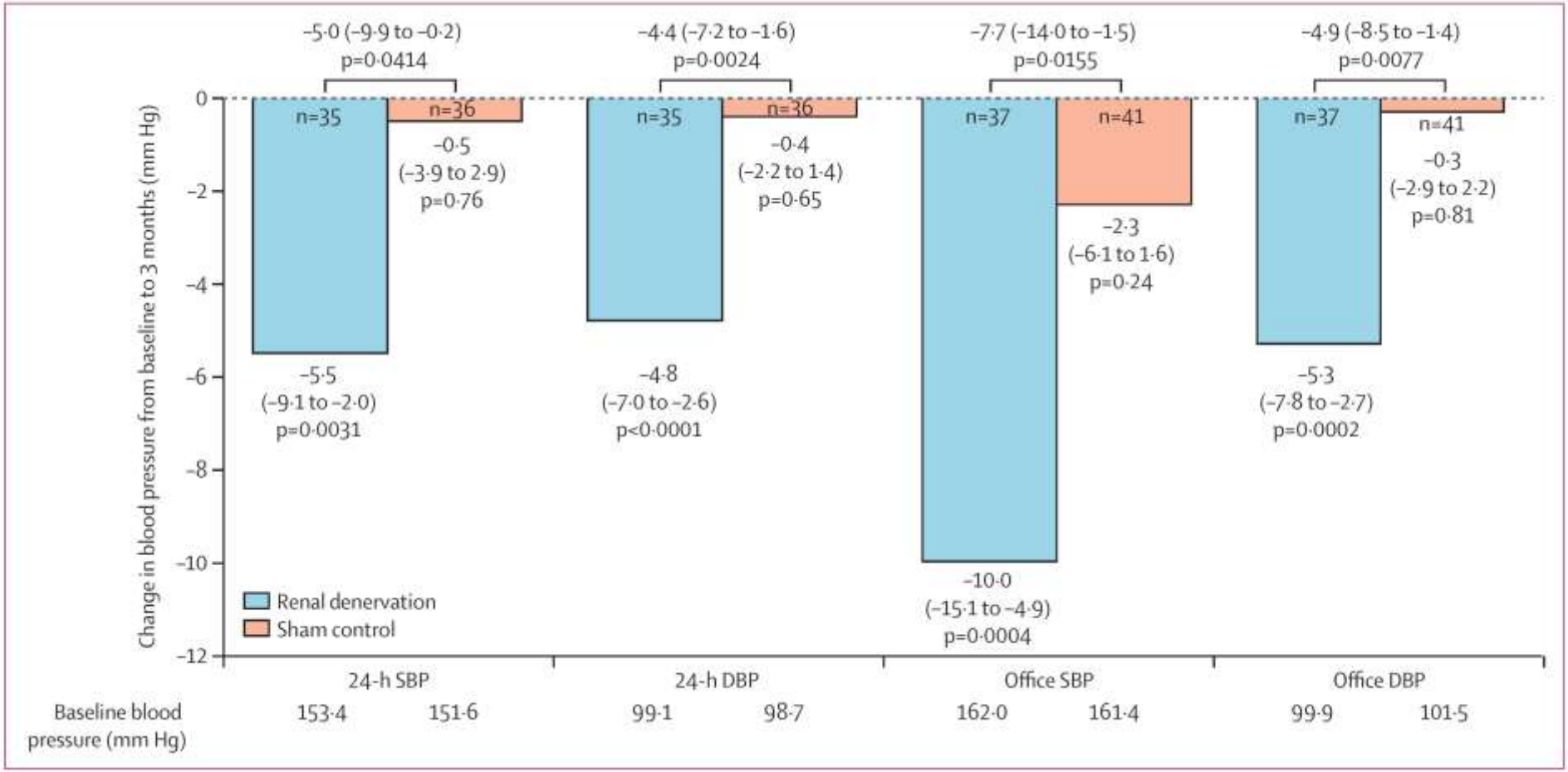
RDN was shown to be safe at 3 months

SPYRAL HTN-OFF MED major adverse events

Adverse event (number of events)	RDN (n = 38)	Sham Control (n = 42)
Death	**0**	0
New myocardial infarction	**0**	0
Major bleeding (TIMI)	**0**	0
New onset end stage renal disease	**0**	0
Serum creatinine elevation >50%	**0**	0
Significant embolic event resulting in end-organ damage	**0**	0
Vascular complications	**0**	0
Hospitalization for hypertensive crisis/emergency	**0**	0
New stroke	**0**	0

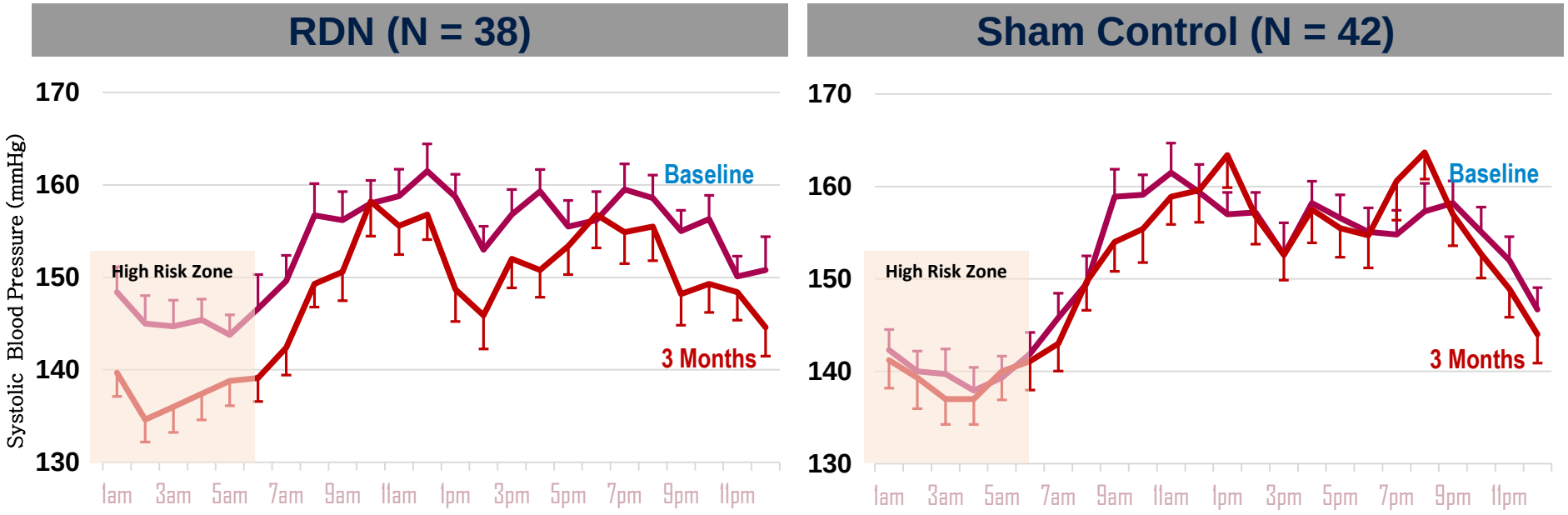
RDN showed a significant reduction in all BP measures at 3 months

SPYRAL HTN-OFF MED Blood pressure change from baseline



24-hour ABPM trend provided further proof of RDN's effect

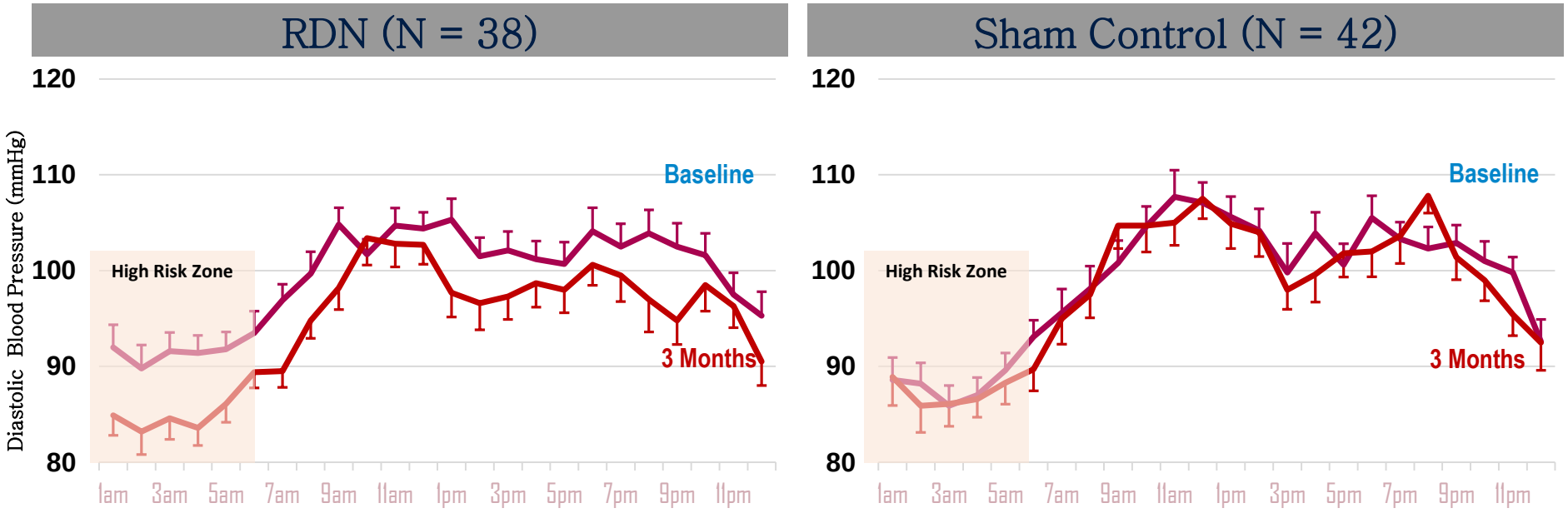
- RDN patients had statistically lower systolic BP in the "high-risk zone[1]" at 3-months



- "High-risk zone" that occurs in the late night/ early morning period is usually associated with increased risk for stroke and cardiovascular events.

24-hour ABPM trend provided further proof of RDN's effect

- RDN patients had statistically lower diastolic BP in the "high-risk zone[1]" at 3-months



- "High-risk zone" that occurs in the late night/ early morning period is usually associated with increased risk for stroke and cardiovascular events.

Renal denervation significantly reduced blood pressure

- **SPYRAL HTN-OFF MED** clinical study showed clinically significant reductions in RDN patients in all blood pressure measurements at 3-months
  - **Office systolic blood pressure declined 10.0 mmHg from baseline (P<0.001)**
  - **24-hour systolic ambulatory blood pressure declined 5.5 mmHg from baseline (P=0.003)**
  - Office diastolic blood pressure declined 5.3 mmHg from baseline (P<0.001)
  - 24-hour diastolic ABPM declined 4.8 mmHg from baseline (P<0.001)

- RDN was shown to be safe, despite a more rigorous procedural approach
  - **Greater total number of ablations** vs. previous RDN trials
  - Ablations were done in the **renal branch and accessory arteries**, as well as main renal artery
  - **No reported cases of renal stenosis**, vascular complications, major adverse events and difference in kidney function

- In previous research, BP reductions of the magnitude reported in SPYRAL HTN-OFF MED have been associated with a **>20% relative risk reduction** of cardiovascular events.

Conclusions

- The **SPYRAL HTN-OFF MED trial** was designed to evaluate the effect of RDN on blood pressure in non-medicated patients with mild to moderate hypertension.
- Patients randomly assigned to RDN had significant reductions in office and 24-h ambulatory blood pressure whereas those in the sham control group had much smaller, non-significant reductions.
- These results provide biological proof of principle for the effect of RDN on blood pressure.
- Results of this proof-of-concept trial will inform the design of a larger, pivotal trial that will be important for establishing the role of renal denervation in treatment of hypertension.

תודה
Dankie
Gracias
Спасибо
شكراً
Merci
Takk
Köszönjük
Terima kasih
Grazie
Dziękujemy
Děkojame
Ďakujeme
Vielen Dank
Paldies
Kiitos
Täname teid
谢谢
Thank You
Tak
感謝您
Obrigado
Teşekkür Ederiz
감사합니다
Σας Ευχαριστούμ
ขอบคุณ
Bedankt
Děkujeme vám
ありがとうございます
Tack

- This novel trial differs substantially from previous renal denervation trials in terms of the hypertensive population enrolled, the renal denervation technique used, and the absence of concomitant antihypertensive medications.
- These data provide biological proof of principle that renal denervation as done in this trial lowers blood pressure in untreated hypertensive patients and these findings support previous data from Esler and colleagues1 about the correlation between reduction in sympathetic tone and blood pressure reduction.
- The standard deviations for blood pressure changes were notably tighter in this trial compared with previous trials, which might be attributed to factors such as removing confounding of blood pressure measurement related to drug adherence, patient selection, proctoring to ensure consistency in implementation of renal denervation, and the addition of branch vessel treatment.
- The choice of 24-h ABPM as the primary endpoint resulted from consensus that this outcome is less prone to bias and, because of the multiple measurements, not only better reflects a patient's blood pressure but also shows less variability of measurement.
- Changes in procedural requirements for renal denervation in the present study could have also contributed to the reduction in blood pressure observed in the treatment group.
- Nevertheless, not all patients responded to renal denervation treatment in this trial, which could be explained by variations in the degree of renal nerve innervation between patients12 or differences in the underlying pathophysiology.

Thank you for attention !