Investigation of catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications: Three-month results from the randomized, sham-controlled, proof of concept SPYRAL HTN-OFF MED Trial

Prof. Dr. Michael Böhm

Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany

and

David Kandzari, Raymond Townsend, Felix Mahfoud, Kazuomi Kario, Stuart Pocock, Michael Weber, Sebastian Ewen, Konstantinos Tsioufis, Dimitrios Tousoulis, Andrew Sharp, Tony Watkinson, Roland Schmieder, Axel Schmid, James Choi, Cara East, Anthony Walton, Ingrid Hopper, Debbie Cohen, Robert Wilensky, David Lee, Adrian Ma, Chandan Devireddy, Janice Lea, Philipp Lurz, Karl Fengler, Justin Davies, Neil Chapman

on behalf of the SPYRAL HTN-OFF MED Trial Investigators

Disclosures

- **Consultant** – Abbott/St. Jude, Astra, Medtronic, Servier, Vifor
- **Grant support** – Medtronic, Servier, German Research Foundation (DFG)

SPYRAL HTN – OFF MED
Study Organization

Executive Committee	Data Safety Monitoring Board
PI: Michael Böhm, MD (Homburg/Saar, Germany)	Chairman: Bernard J. Gersh, MB, ChB, DPhil, FRCP (Rochester, MN, USA)
PI: David E. Kandzari, MD (Atlanta, GA, USA)	John A. Ambrose, MD (Fresno, CA, USA)
PI: Kazuomi Kario, MD (Tochigi, Japan)	Phyllis August, MD, MPH (New York, NY, USA)
PI: Raymond R. Townsend, MD (Philadelphia, PA, USA)	Michael Parides, BSC, MSc, PhD (New York, NY, USA)
Felix Mahfoud, MD (Homburg/Saar, Germany)	
Stuart Pocock, PhD (London, United Kingdom)	**Clinical Event Committee**
Michael A. Weber, MD (Brooklyn, NY, USA)	Chairman: Clive Rosendorff, MD, FRCP, FACC (Bronx, NY, USA)
	Ladan Golestaneh, MD (Bronx, NY, USA)
Study Sponsor	Steven Marx, MD (New York, NY, USA)
Medtronic	Michele H. Morkrzycki, MD (Bronx, NY, USA)
	Joel Neugarten, MD, PhD, DSc (Bronx, NY, USA)

SPYRAL HTN Clinical Program
Background

- Up to one-third of adults have hypertension
  - Increased risk of cardiovascular events and stroke
  - Many patients remain uncontrolled
- Renal denervation therapy (RDN) targets the sympathetic nervous system
- SYMPLICITY HTN-3 trial failed to demonstrate a significant blood pressure lowering effect of RDN
- Sub-analyses suggested:
  - Variance in medication adherence
  - Incomplete denervation of the renal arteries
  - Inclusion of patients with isolated systolic hypertension

SPYRAL HTN Clinical Program
Background

SPYRAL HTN-ON MED and SPYRAL HTN-OFF MED studies:

- Proof of concept trials
- Designed to demonstrate the ability of RDN to influence blood pressure in uncontrolled hypertension

Kandzari D, et al. *Am Heart J*. 2016;171:82-91.

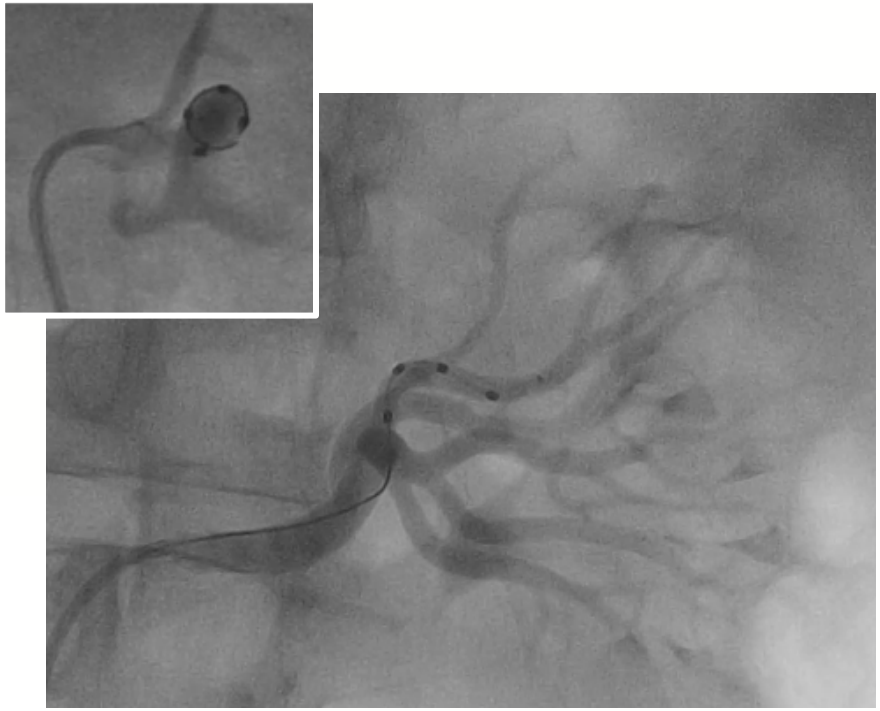
SPYRAL HTN
Global Trial Center Locations

21 Recruiting Sites in:

- USA
- Europe
- Japan
- Australia

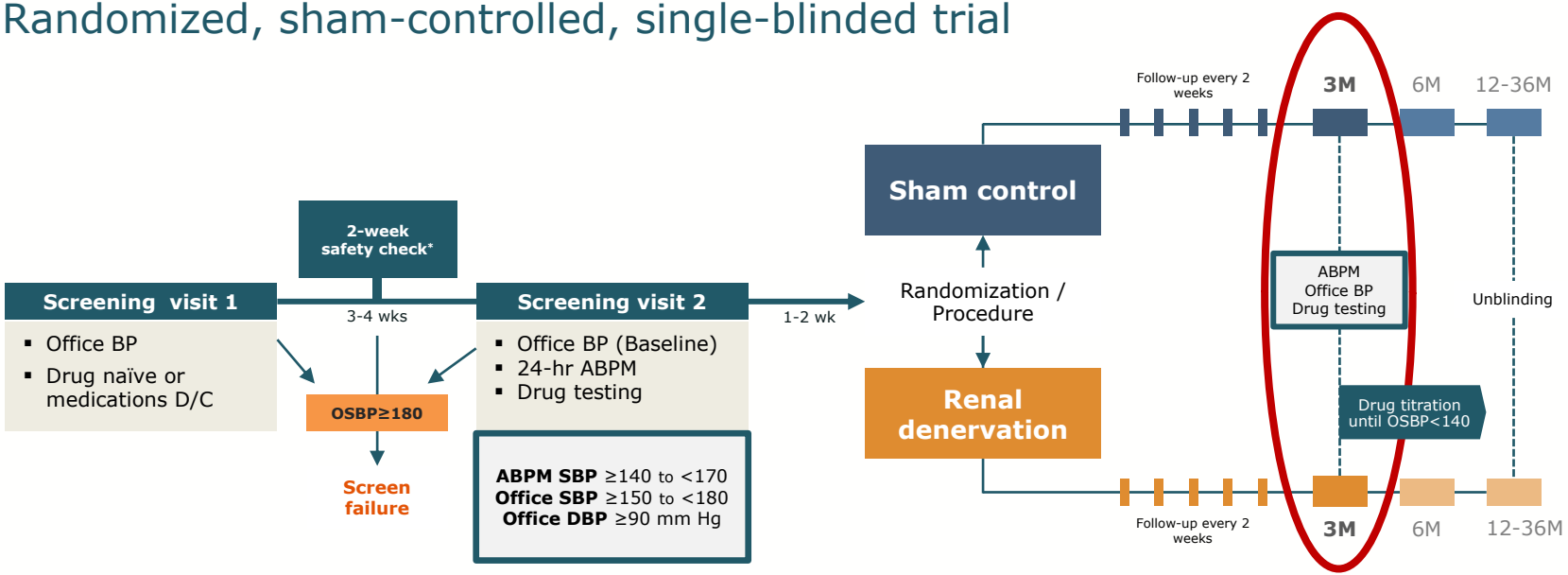
SPYRAL HTN Clinical Program
Study Device: Symplicity Spyral™ Catheter

- 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
Study Design

Randomized, sham-controlled, single-blinded trial



*Only for patients discontinuing anti-hypertensive medications
Kandzari D, et al. *Am Heart J*. 2016;171:82-91.

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**

Kandzari D, et al. *Am Heart J*. 2016;171:82-91.

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Blinding Procedure & Efficacy

- All patients underwent renal angiography
- Conscious sedation
- Sensory isolation (e.g., blindfold and music)
- Lack of familiarity with procedural details and expected duration
- Assessed by blinding questionnaire at discharge and 3 months:

Time	Blinding Index	95% CI
Discharge	0.65	(0.56, 0.75)
3 Months	0.59	(0.49, 0.70)

Blinding Index >0.5 indicates successful blinding.

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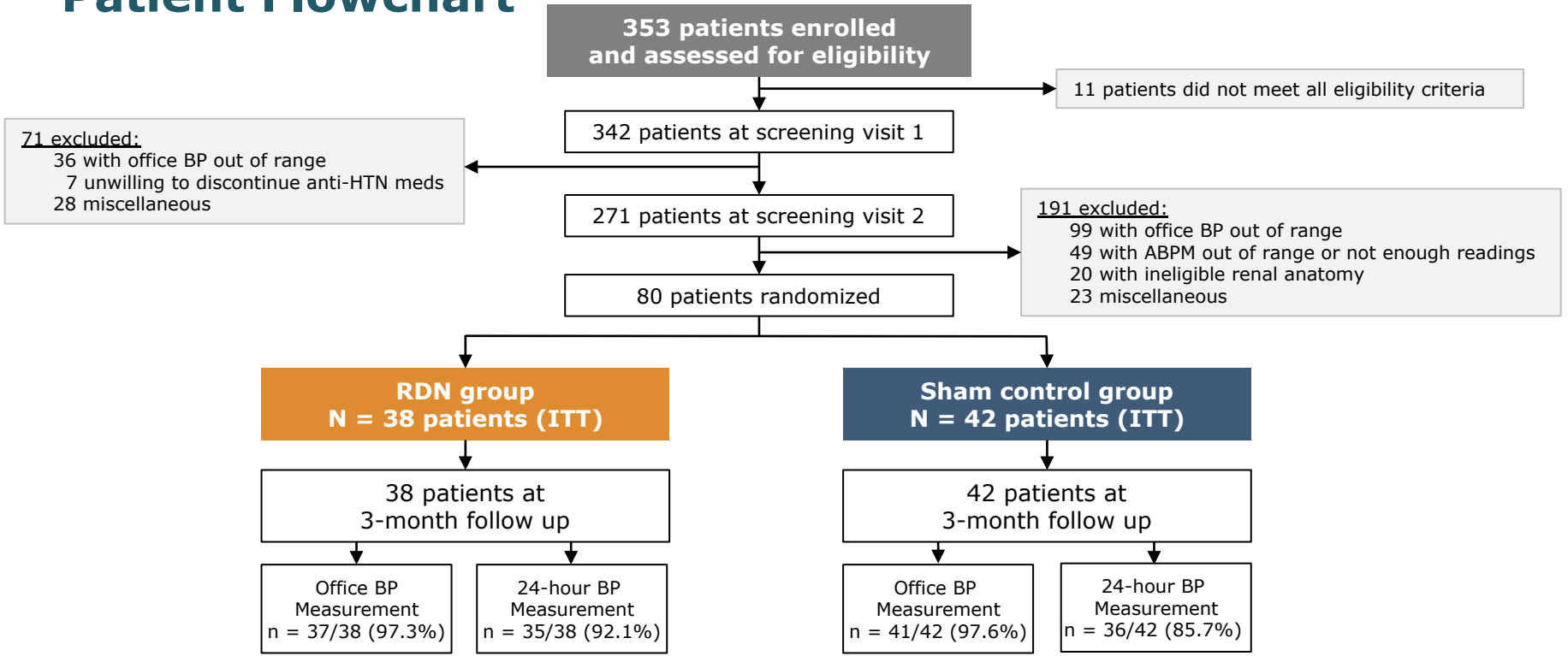
Patient Flowchart



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Patient Baseline Characteristics

Mean ± SD or % (N)	RDN (N = 38)	Sham Control (N = 42)
Age (years)	55.8 ± 10.1	52.8 ± 11.5
Male	68.4% (26/38)	73.8% (31/42)
BMI (kg/m^2)	29.8 ± 5.1	30.2 ± 5.1
Body weight (kg)	88.8 ± 16.6	90.9 ± 19.1
Diabetes (type 2)	2.6% (1/38)	7.1% (3/42)
Current smoker	10.5% (4/38)	23.8% (10/42)
Obstructive sleep apnea	7.9% (3/38)	7.1% (3/42)
Peripheral artery disease	2.6% (1/38)	0% (0/42)
Coronary artery disease†	0% (0/38)	4.8% (2/42)
Stroke and transient ischemic attack†	2.6% (1/38)	0% (0/42)
Myocardial infarction / acute coronary syndrome†	0% (0/38)	2.4% (1/42)

†These events occurred >3 months before randomization.
P = NS for differences in all baseline characteristics.

SPYRAL HTN – OFF MED
Baseline Blood Pressure

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.

SPYRAL HTN – OFF MED
Procedural Details

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

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Medication Adherence

% (n)	RDN	Sham Control	*P*
No anti-HTN drug identified by drug testing:			
At baseline	92.1% (35/38)	88.1% (37/42)	0.72
At 3 months	94.3% (33/35)	92.7% (38/41)	1.00
At baseline and 3 months	88.6% (31/35)	82.9% (34/41)	0.53
Patients meeting escape criteria (n)	2	4	

Drug testing of Urine and Serum by tandem HPLC and Mass Spectroscopy.

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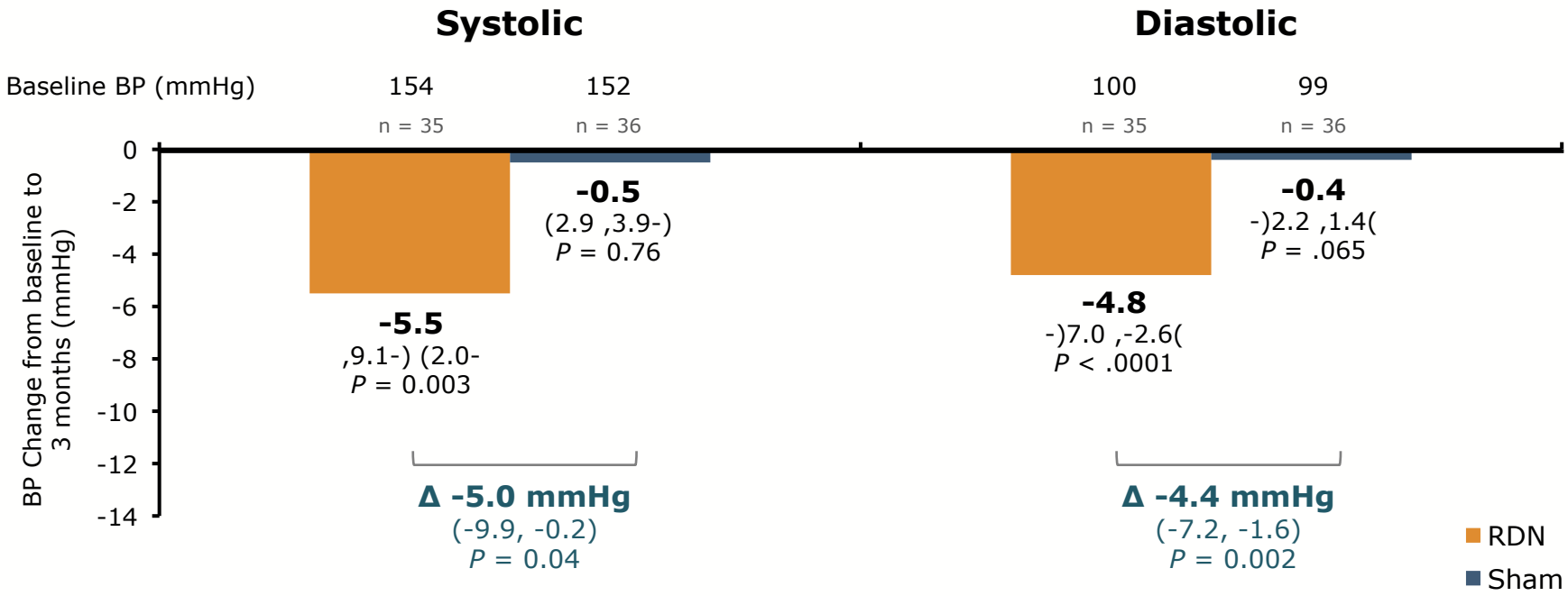
Blood Pressure Change from Baseline to 3 Months: 24-Hr ABPM



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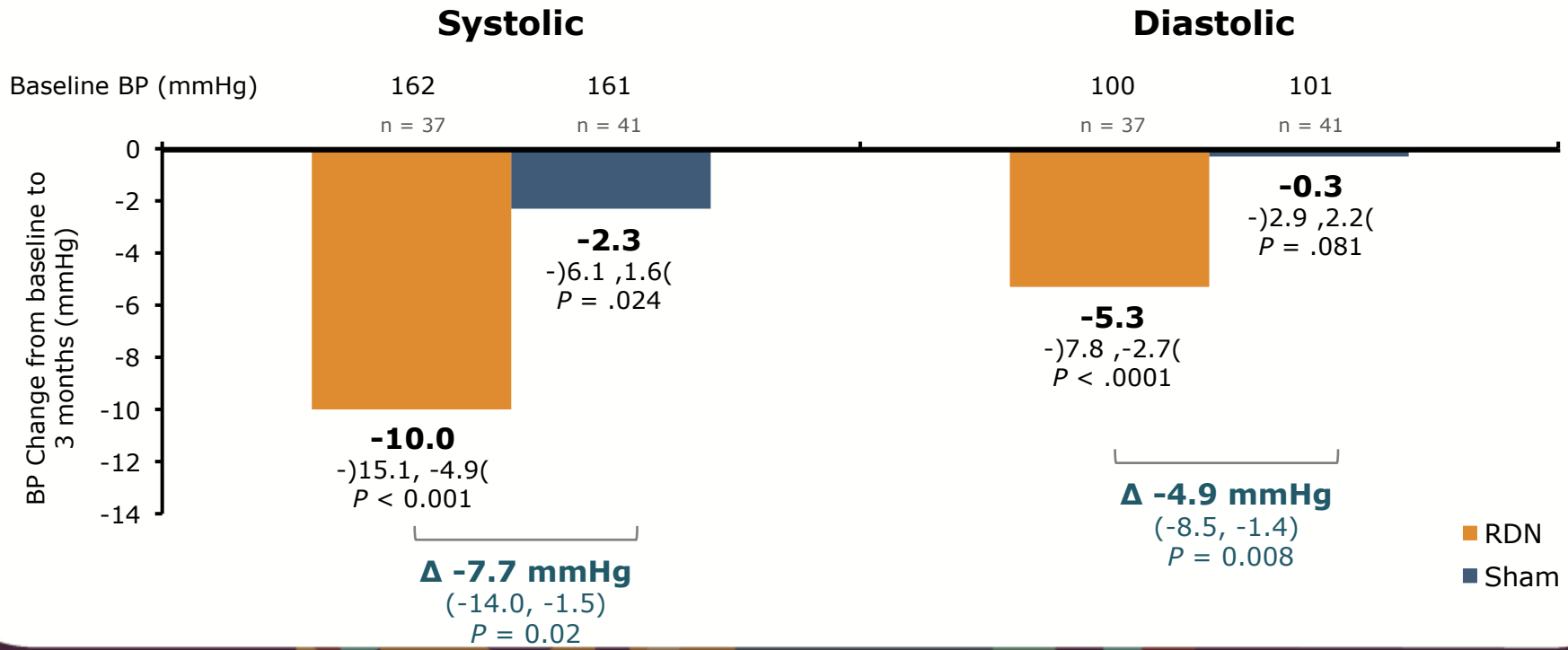
Blood Pressure Change from Baseline to 3 Months: Office BP



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Safety Results at 3 Months

%	RDN (n = 38)	Sham Control (n = 42)
Death	0	0
New myocardial infarction	0	0
Major bleeding (TIMI[1])	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

[1]TIMI definition: intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure.

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Limitations

- Proof of concept trial, not prospectively powered for statistical significance
- Antihypertensive drugs were detected in the blood/urine of some patients despite off-med protocol
  - Results in the modified ITT and PP populations were consistent
  - Similar results observed after adjustment for baseline blood pressure (ANCOVA) in all groups
- No practical methods to verify nerve destruction
- Results may not be generalizable to other RDN technologies

SPYRAL HTN Clinical Program

Advances of SPYRAL HTN Compared to SYMPLICITY HTN-3

	Medications	Patients	Procedure
SYMPLICITY HTN -3	▪ 5.1 prescribed anti-HTN drugs at randomization ▪ No drug adherence testing	▪ Resistant hypertension patients (OSBP 180 ± 16) ▪ No diastolic cutoff	▪ Mono-electrode, sequential ablation system ▪ Mostly inexperienced operators without proctoring ▪ Main artery RDN only ▪ Ablations per pt: 11.2 ± 2.8
SPYRAL HTN OFF MED	▪ No anti-HTN drugs at time of randomization ▪ Drug adherence testing by serum and urine	▪ Moderate hypertension patients (OSBP 162 ± 7) ▪ Excluding ISH patients (ODBP 101 ± 7)	▪ Four-electrode, simultaneous ablation system ▪ Highly experienced operators with proctoring ▪ Main + branches RDN ▪ Ablations/pt: 43.8 ± 13.1

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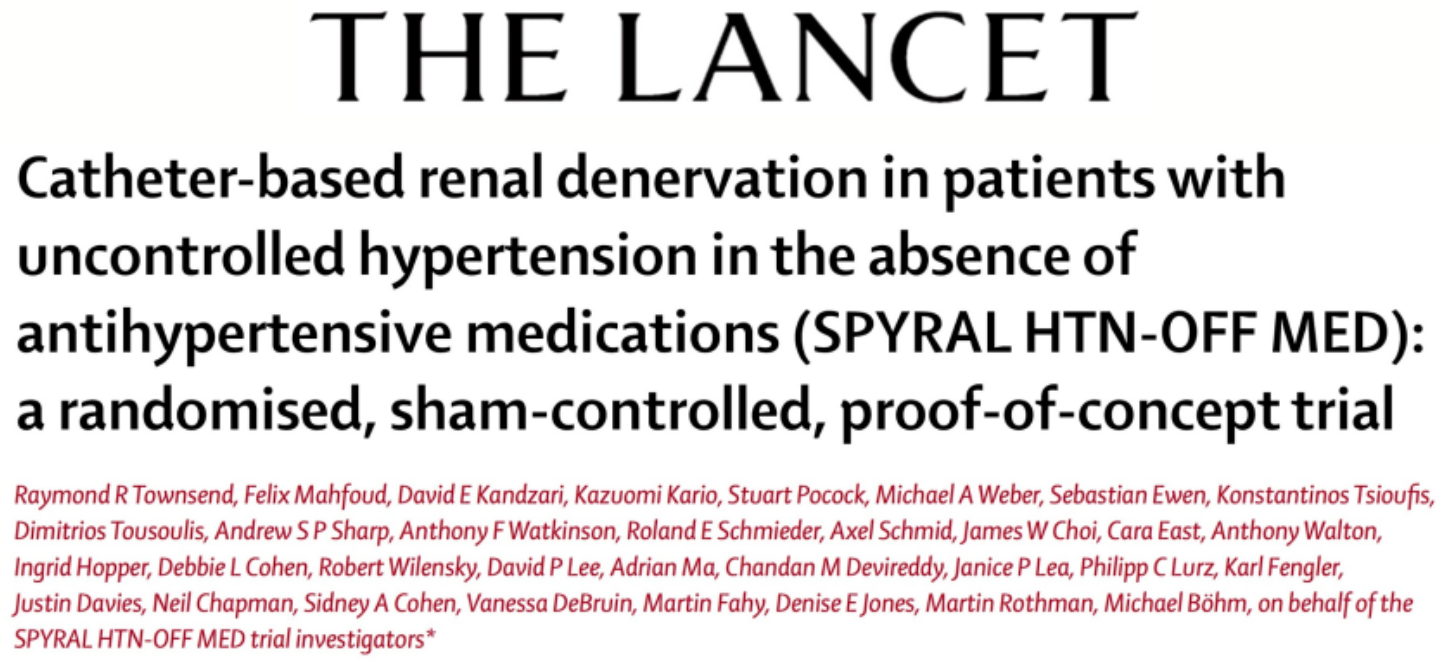
Conclusions

- **Biologic proof of principle** for the efficacy of renal denervation
- **Clinically meaningful blood pressure reductions** at 3 months
  - In mild to moderate hypertensive patients treated with RDN
  - In the absence of anti-hypertensive medications compared to sham control
- **No major safety events**
  - Despite a more complete denervation procedure that extended into renal artery branch vessels
- **The results of this feasibility study will inform the design of a larger pivotal trial**

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**

Townsend et al, *Lancet*. Published online 28 Aug 2017

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We thank patients, investigators, committee members and staff for their outstanding contribution!

Thank you for your attention!

SPYRAL HTN – OFF MED
Participating Centers – I

Principal Investigator	Sub-Investigator	Centre	Location	Patients Randomized
Michael Böhm, MD	Felix Mahfoud, MD	Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes	Homburg/Saar, Germany	14
Konstantinos Tsioufis, MD	Dimitrios Tousoulis, MD	University of Athens, Hippokration Hospital	Athens, Greece	10
Roland Schmieder, MD	Axel Schmid, MD	Universitätsklinikum Erlangen	Erlangen, Germany	8
James W. Choi, MD	Cara East, MD	Baylor Jack and Jane Hamilton Heart and Vascular Hospital	Dallas, TX, USA	6
Debbie L. Cohen, MD	Robert Wilensky, MD	Hospital of the University of Pennsylvania	Philadelphia, PA, USA	6
Anthony Walton, MD	Ingrid Hopper, PhD	The Alfred Hospital and Monash University	Melbourne, Australia	6
David P. Lee, MD	Adrian Ma, MD	Stanford Hospital & Clinics	Stanford, CA, USA	5
Philipp C. Lurz, MD	Karl Fengler, MD	University of Leipzig - Heart Center	Leipzig, Germany	4
Justin Davies, MD	Neil Chapman, MD	Imperial College Healthcare Trust	London, United Kingdom	3
Kazuomi Kario, MD	Satoshi Hoshide, MD	Jichi Medical University Hospital	Tochigi, Japan	3
Joachim Weil, MD	Tolga Agdirlioglu, MD	Sana Cardiomed Heart Center	Lübeck, Germany	3