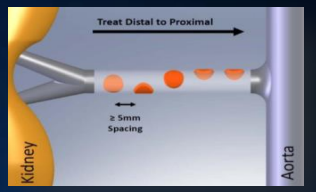
Recent Update of Renal Denervation Therapy

Byeong-Keuk Kim, MD, PhD

Division of Cardiology, Severance Cardiovascular Hospital
Yonsei University College of Medicine, Seoul, Korea

Renal denervation therapy for resistant hypertension



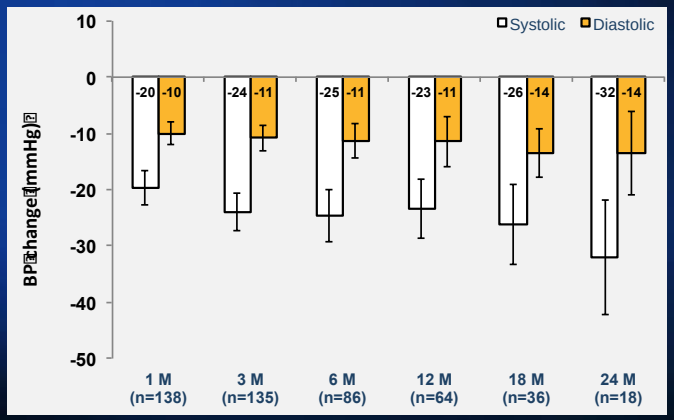
- **Catheter-based renal sympathetic denervation has shown remarkable and durable BP reduction in patients with resistant hypertension through the staged clinical studies.**

First-in-Man
↓
Series of Pilot studies
↓
Symplicity HTN-2 ✓
EU/AU Randomized Clinical Trial

Symplicity HTN-1 & extended

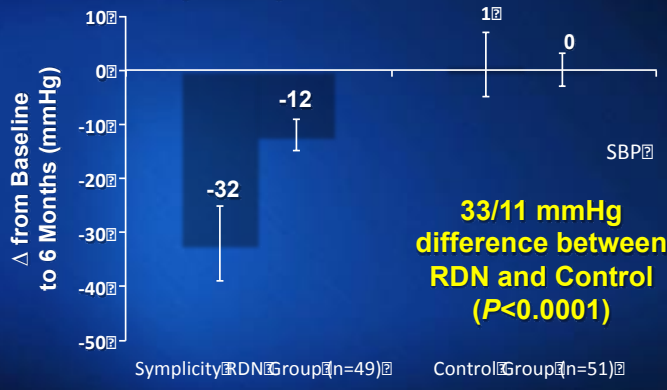
Symplicity HTN-1, Cohort Study

Significant BP reduction started at 1 month
... Sustained at 12 & 24 months



Symplicity HTN-2 Trial

Primary Endpoint: 6-Month Office BP



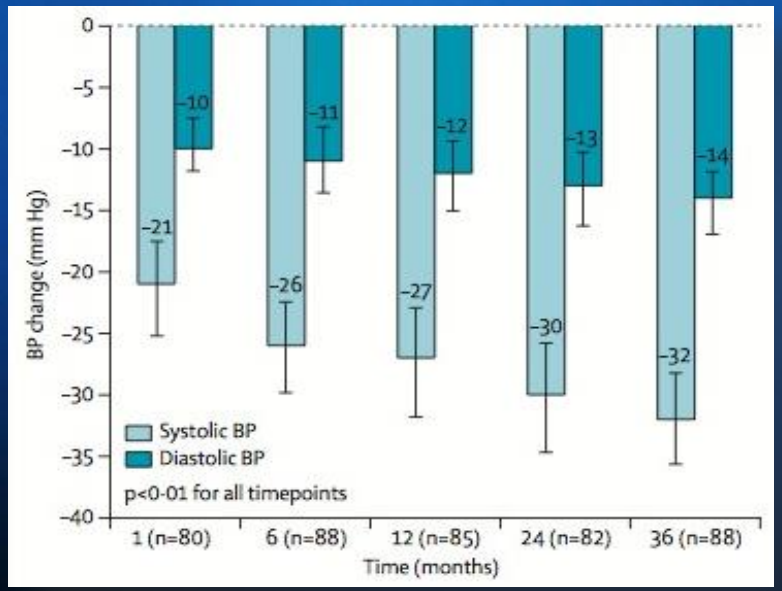
33/11 mmHg difference between RDN and Control (*P*<0.0001)

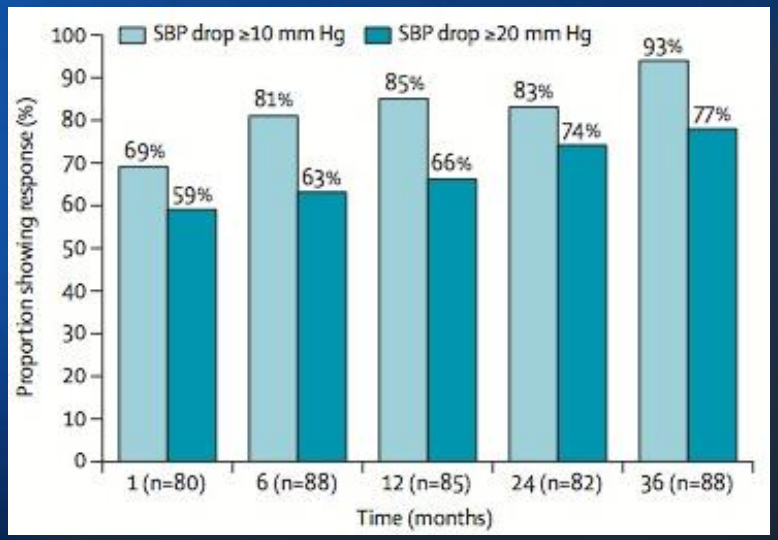
✓ **84% of RDN patients had ≥ 10 mmHg reduction in SBP**

Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study

Henry Krum, Markus P Schlaich, Paul A Sobotka, Michael Böhm, Felix Mahfoud, Krishna Rocha-Singh, Richard Katholi, Murray D Esler

- ✓ 153 patients with resistant hypertension were enrolled in the Symplicity HTN-1 study, of whom **88 patients** had complete data at **36 months**.
- ✓ At 36 months, significant BP changes; **SBP (–32.0 mm Hg), DBP (–14·4 mm Hg)**
- ✓ Rates of **SBP-drop ≥10 mm Hg**;
  - 1, 6, 12, 24, and 36 months, 69%, 81%, 85%, 83%, and 93%





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Fri May 02, 2014

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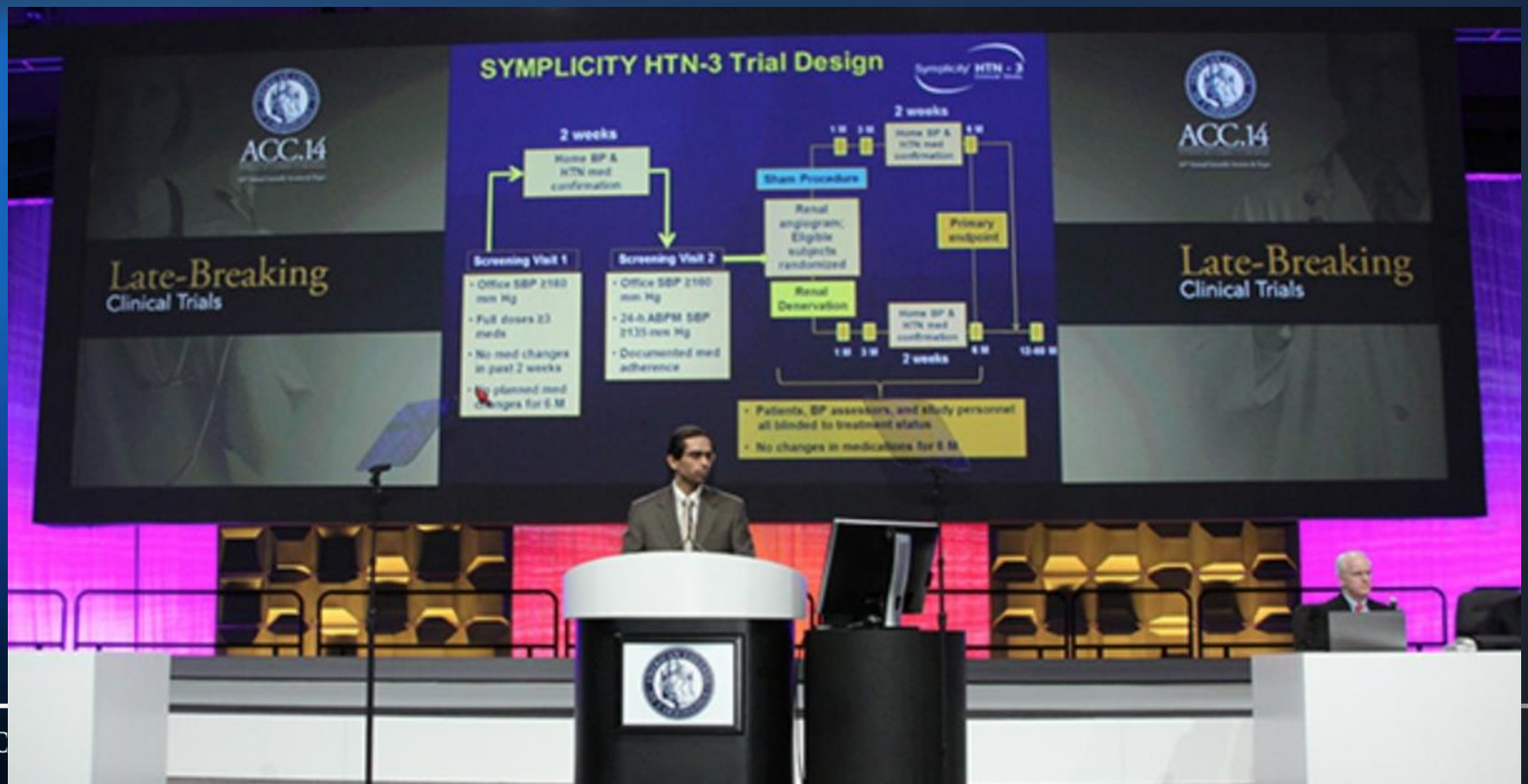
Home > News/Media > Cardiology Magazine > 2014 > 03 > SYMPLICITY HTN-3: Renal Artery Denervation Fails for Resistant HTN

SYMPLICITY HTN-3: Renal Artery Denervation Fails for Resistant HTN

March 29, 2014

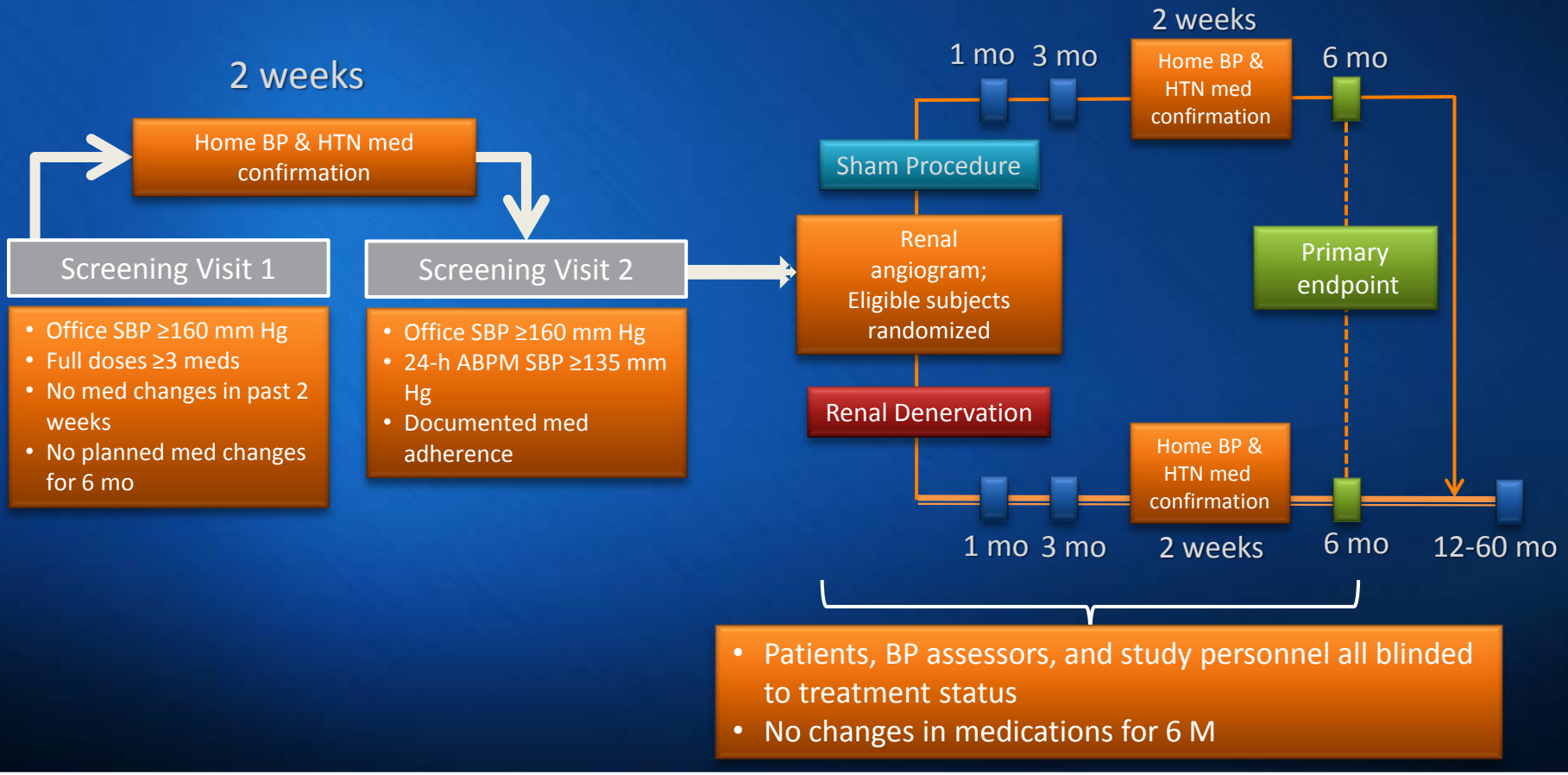
Prospective, single-blind, randomized, sham-controlled trial.



SEVERANCE C

Trial Design

- 2:1 randomization, blinded and sham-controlled
- 535 subjects randomized out of 1441 enrolled at 88 sites in US (63% screen failure rate)
- 2-week screening process, including maximum tolerated doses of antihypertensive medications



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Renal Denervation

Deepak L
Ralph D
Martin B.
Sidney A.

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CONCLUSIONS
This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPLICITY HTN-3 ClinicalTrials.gov number, NCT01418261.)

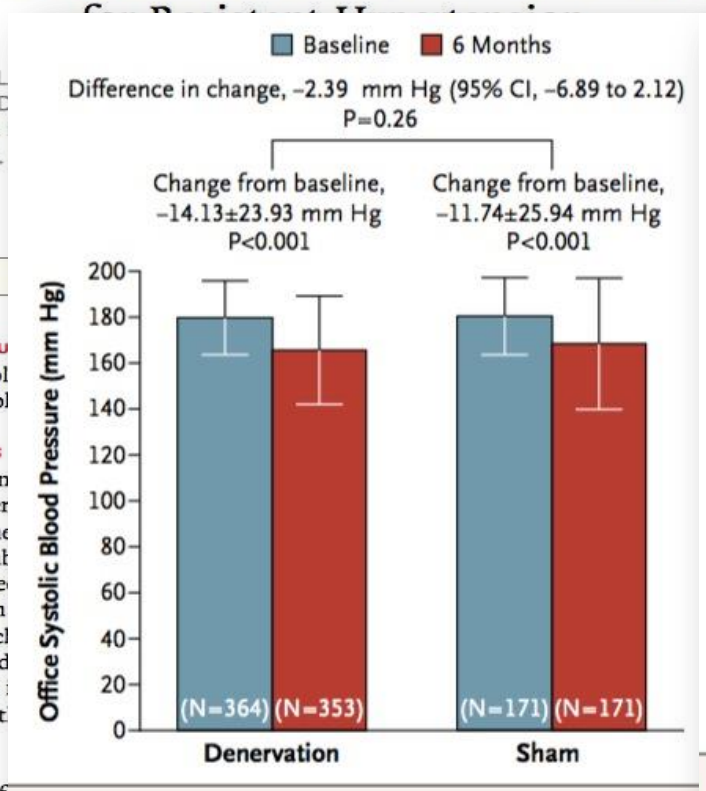

Figure 1. Primary Efficacy End Point.

A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mm Hg. The I bars indicate standard deviations.

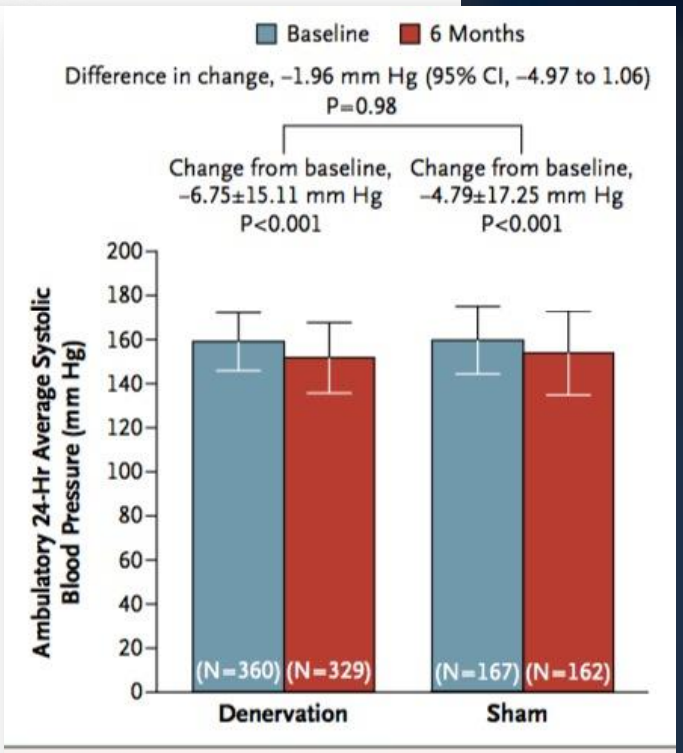

Figure 2. Secondary Efficacy End Point.

A significant change from baseline to 6 months in ambulatory 24-hour average systolic blood pressure was observed in both groups. The between-group difference (the secondary efficacy end point for which the study was powered) did not meet a test of superiority with a margin of 2 mm Hg. The I bars indicate standard deviations.

N Engl J Med 2014;370:1393-401.
DOI: 10.1056/NEJMoa1402670

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin
Sidney

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This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPLICITY HTN-3 ClinicalTrials.gov number, NCT01418261.)

N Engl J Med 2014;370:1393-401.
DOI: 10.1056/NEJMoa1402670

After SYM-3 publication

From 2014 EuroPCR meeting

European Heart Journal Advance Access published November 16, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu441

FASTTRACK CLINICAL RESEARCH
Hypertension

Predictors of blood pressure response in the SYMPLICITY HTN-3 trial

David E. Kandzari[1]*, Deepak L. Bhatt[2], Sandeep Brar[3], Chandan M. Devireddy[4], Murray Esler[5], Martin Fahy[3], John M. Flack[6], Barry T. Katzen[7], Janice Lea[4], David P. Lee[8], Martin B. Leon[9], Adrian Ma[8], Joseph Massaro[10], Laura Mauri[2,10], Suzanne Oparil[11], William W. O'Neill[12], Manesh R. Patel[13], Krishna Rocha-Singh[14], Paul A. Sobotka[15], Laura Svetkey[13], Raymond R. Townsend[16], and George L. Bakris[17]

[1]Piedmont Heart Institute, Atlanta, GA, USA; [2]Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA, USA; [3]Medtronic, Inc., Santa Rosa, CA, USA; [4]Emory University School of Medicine, Atlanta, GA, USA; [5]Baker IDI Heart and Diabetes Institute, Monash University, Melbourne, Australia; [6]Wayne State University and the Detroit Medical Center, Detroit, MI, USA; [7]Baptist Cardiac and Vascular Institute, Miami, FL, USA; [8]Stanford Hospital and Clinics, Palo Alto, CA, USA; [9]New York Presbyterian Hospital, Columbia University Medical Center and Cardiovascular Research Foundation, New York, NY, USA; [10]Harvard Clinical Research Institute, Boston, MA, USA; [11]University of Alabama at Birmingham, Birmingham, AL, USA; [12]Division of Cardiology, Henry Ford Hospital, Detroit, MI, USA; [13]Duke University Medical Center, Durham, NC, USA; [14]Prairie Heart Institute, Springfield, IL, USA; [15]The Ohio State University, Columbus, OH, USA; [16]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; and [17]The University of Chicago Medicine, Chicago, IL, USA

Received 29 August 2014; revised 9 October 2014; accepted 18 October 2014

Background & Objective

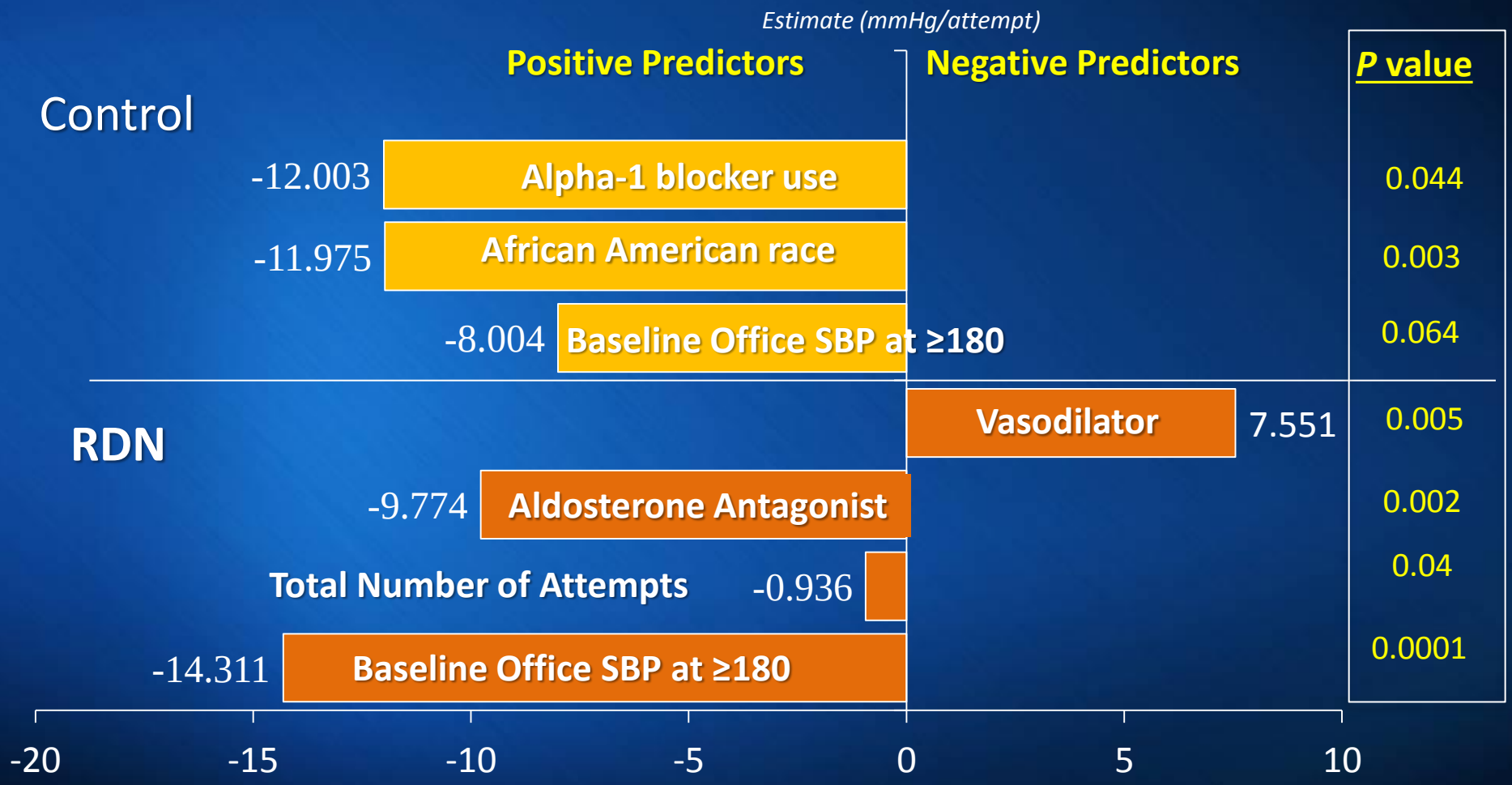
- ***Key factors,*** **for** the **greater than expected BP-drop after sham-procedure** and the **less than expected BP-drop after RDN**

- Based on the results of ***multivariable analysis for the predictors of SBP change,*** and ***analysis of pre-specified and post hoc subgroups*** to ***identify "potential confounding factors" that may have affected the trial results***, three areas of investigation were pursued:

  i. **outcomes in selected subgroups, and**

  ii. **detailed assessment of procedural data that may have impacted the delivery of effective RDN.**

Multivariable predictors of SBP reduction at 6 months

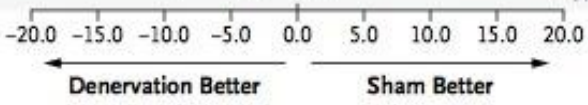


Univariate P <0.2 required to enter the model

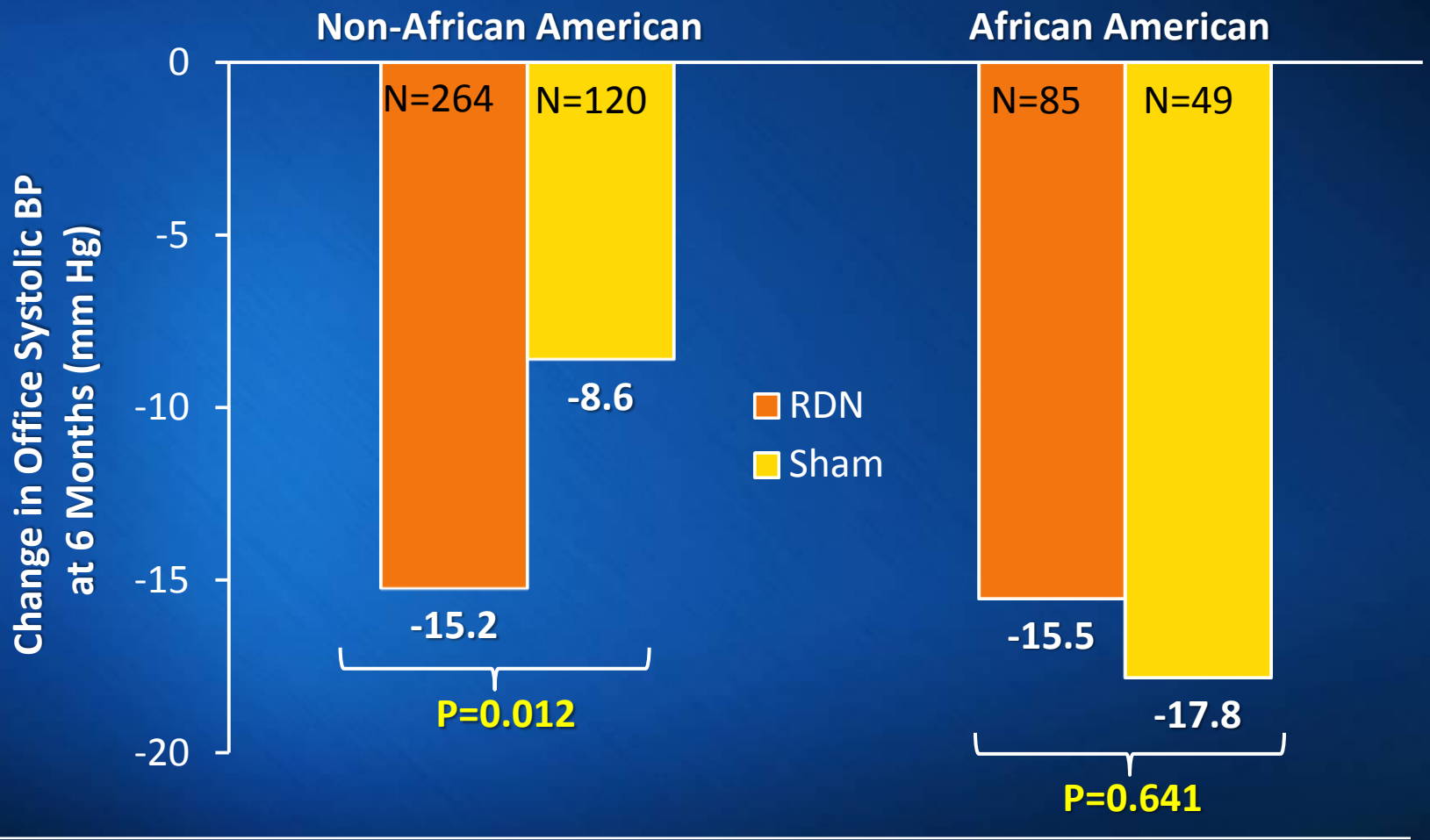
Sub-group analysis of SYMPLICITY HTN-3

Unlike previous SYMPLICITY trials, SYMPLICITY HTN-3 enrolled a substantial number of African-American patients who represent a significant proportion of hypertensive patients in U.S.

Subgroup	Denervation	Sham	Between-Group Difference in Change in Office Systolic Blood Pressure (95% CI)	P Value	P Value for Interaction
	no. of patients		*mm Hg*		
All patients	353	171	−2.39 (−6.89 to 2.12)	0.26	
Diabetes mellitus					0.82
Yes	169	68	−4.53 (−11.51 to 2.46)	0.20	
No	181	101	−3.46 (−9.55 to 2.62)	0.26	
Sex					0.37
Male	208	108	−2.30 (−7.63 to 3.03)	0.40	
Female	142	61	−6.64 (−14.94 to 1.65)	0.12	
Black race					0.09
Yes	85	49	2.25 (−7.27 to 11.78)	0.64	
No	264	120	−6.63 (−11.81 to −1.44)	0.01	
Body-mass index					0.77
<30	91	42	−2.77 (−11.47 to 5.93)	0.53	
≥30	259	126	−4.36 (−9.76 to 1.03)	0.11	
Receiving aldosterone antagonist at baseline					0.36
Yes	76	47	−8.05 (−17.63 to 1.52)	0.10	
No	274	122	−3.24 (−8.42 to 1.93)	0.22	
Estimated GFR					0.31
<60 ml/min/1.73 m²	68	38	0.54 (−8.29 to 9.37)	0.90	
≥60 ml/min/1.73 m²	282	131	−5.22 (−10.51 to 0.06)	0.05	
Age					0.27
<65 yr	246	128	−5.73 (−11.06 to −0.40)	0.04	
≥65 yr	104	41	0.09 (−8.80 to 8.99)	0.99	
Any medication change					0.68
Yes	132	70	−5.41 (−13.49 to 2.67)	0.19	
No	218	99	−3.44 (−8.83 to 1.96)	0.21	



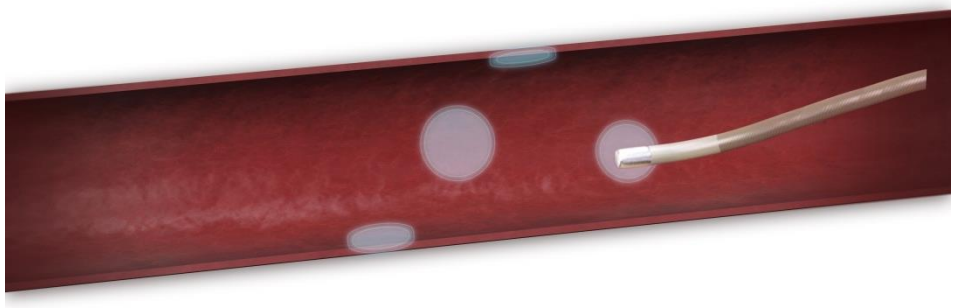
Change in Office SBP at 6 Months for Non-African American and African American Subgroups



Baseline SBP, mm Hg	179.5	178.6	180.6	183.9

Procedural Variability

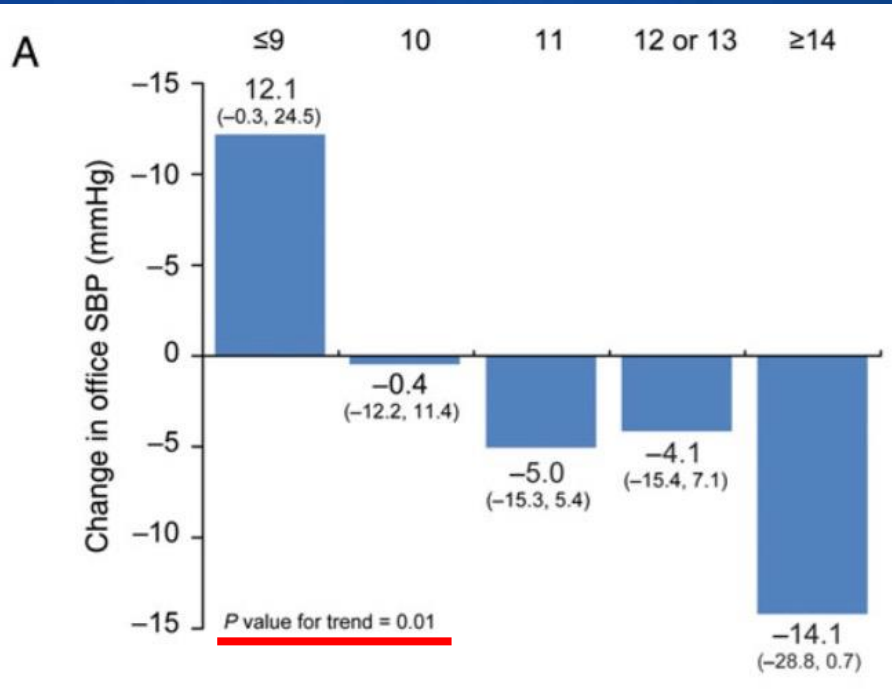
- Correlation with **# of ablations ?**
- Correlation with **4-quadrant ablation pattern ?**



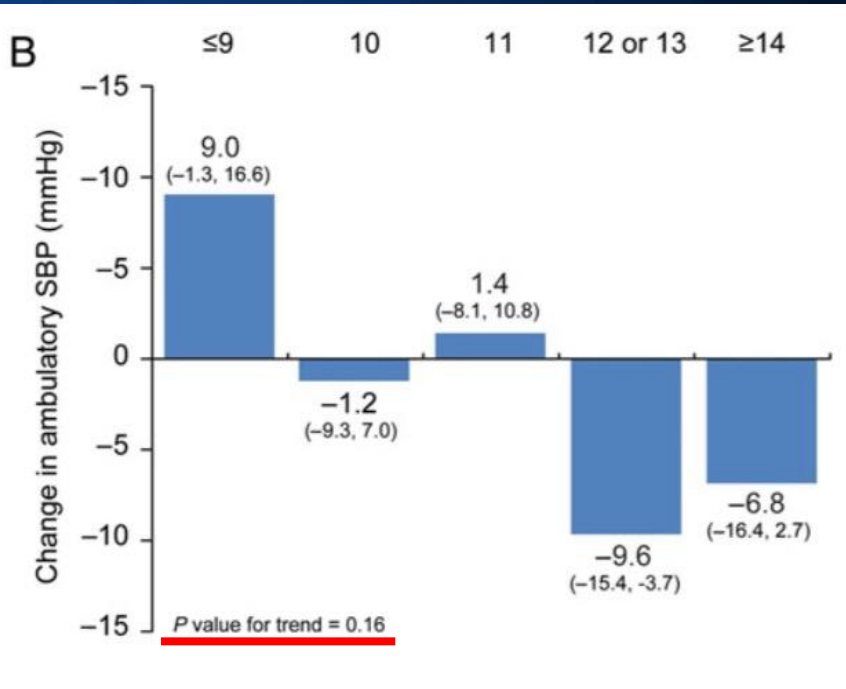
4 quadrant ablation pattern

Patients were categorized by delivery of 4-quadrant ablations into 1) **2 Four-quadrant ablation pattern** (both sides), 2) **1 Four-quadrant ablation pattern** (either right or left), or 3) **0 Four-quadrant ablation**.

Impact of "number of ablation attempts" on difference in 6-month change in office SBP (A) and 24-h ABPM, SBP (B) after propensity scored matching



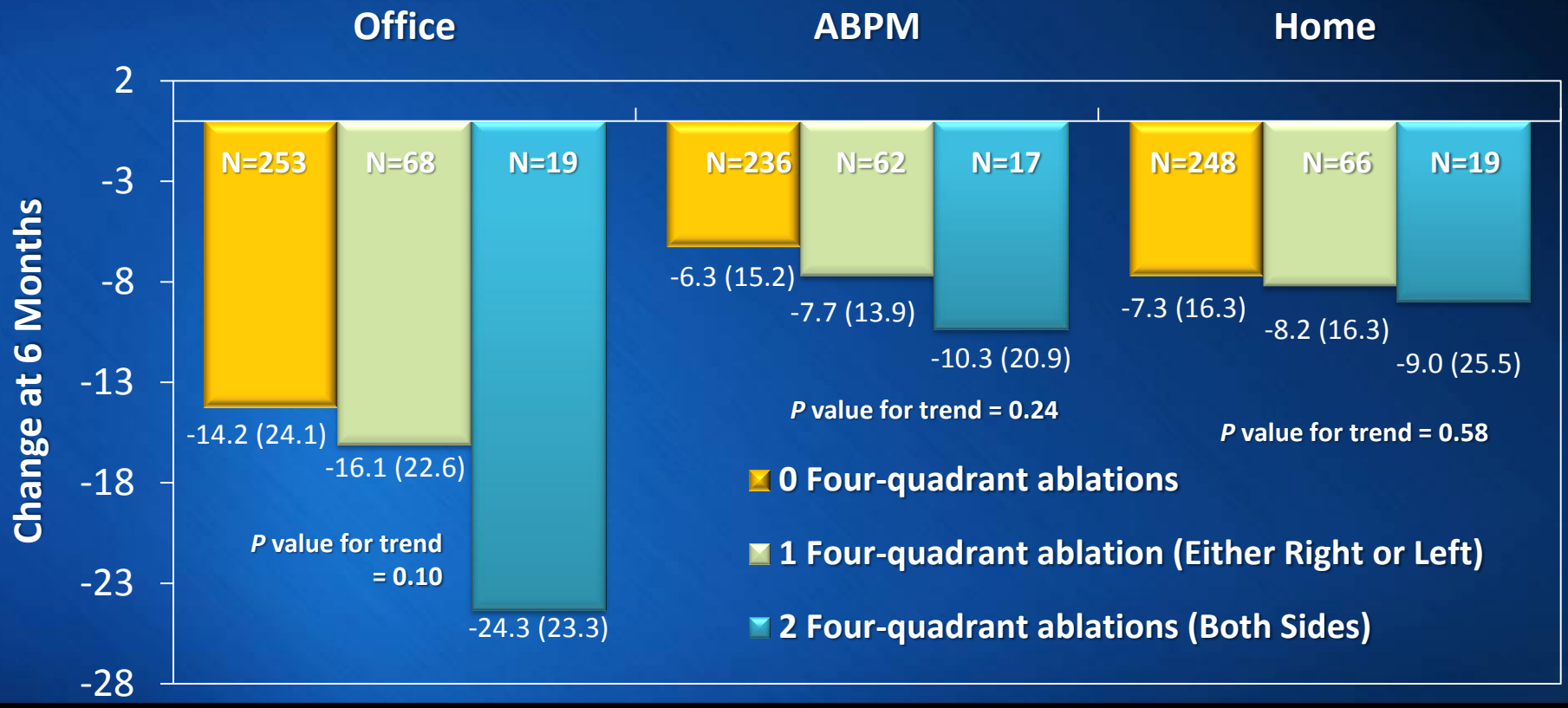
	≤9	10	11	12 or 13	≥14
P	0.06	0.94	0.34	0.47	0.06
RDN SBP change, mmHg (*n*)	−6.4 ± 23.0 (33)	−15.0 ± 24.6 (33)	−12.6 ± 21.0 (37)	−9.7 ± 16.5 (35)	−24.3 ± 26.8 (26)
Sham SBP change, mmHg (*n*)	−18.5 ± 27.9 (35)	−14.6 ± 23.8 (34)	−7.6 ± 23.6 (37)	−5.6 ± 29.3 (36)	−10.2 ± 26.5 (27)



	≤9	10	11	12 or 13	≥14
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)

✓ **There was no increase in safety events corresponding to the increasing number of renal artery ablations (no MAEs occurred in patients receiving ≥13 ablations).**

Systolic BP Change at 6 Months According to the Ablation Pattern



Baseline SBP Measurements (mm Hg)			
0 four-quadrant tx*	179.6	158.7	168.5
1 Four-quadrant tx	178.8	161.2	171.3
2 four-quadrant tx	186.9	159.9	170.4

*1 superior, 1 inferior and 2 anterior/ posterior

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EDITORIAL COMMENT

Catheter-Based Renal Denervation Is No Simple Matter

Lessons to Be Learned From Our Anatomy?*

Felix Mahfoud, MD,† Elazer R. Edelman, MD, PhD,‡§ Michael Böhm, MD†

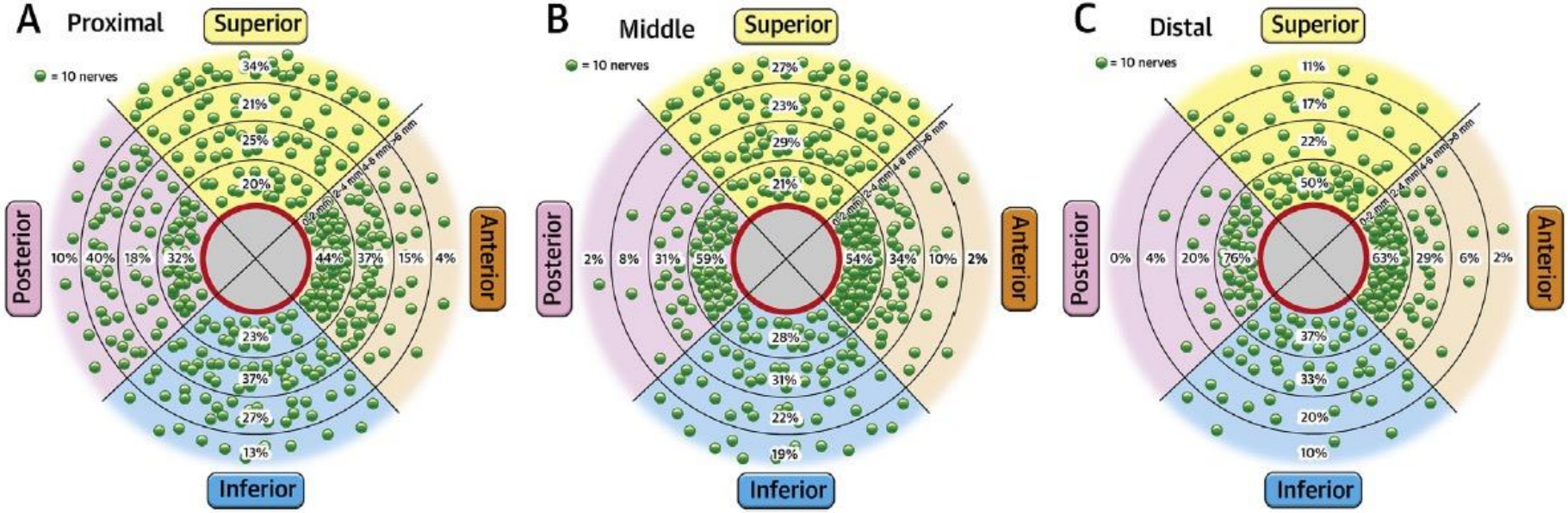


FIGURE 1 **Distribution and Density of Renal Sympathetic Nerves**

Distribution of nerves stratified according to total number (each **green dot** represents 10 nerves), relative number as percent per segment, and distance from the lumen in relative **(A)** proximal, **(B)** middle, and **(C)** distal location. Figure prepared using raw data from Sakakura et al. (4), and from raw data provided by M. Joner, of CVPath Inc.

Predictors of nonresponse to renal denervation in a real world population of patients with uncontrolled hypertension: Analysis of the Global SYMPLICITY Registry

non-response to RDN defined as **Office SBP** reduction <**10 mm Hg** from baseline

Felix Mahfoud, MD

on behalf of the GSR Investigators

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

Global SYMPLICITY Registry

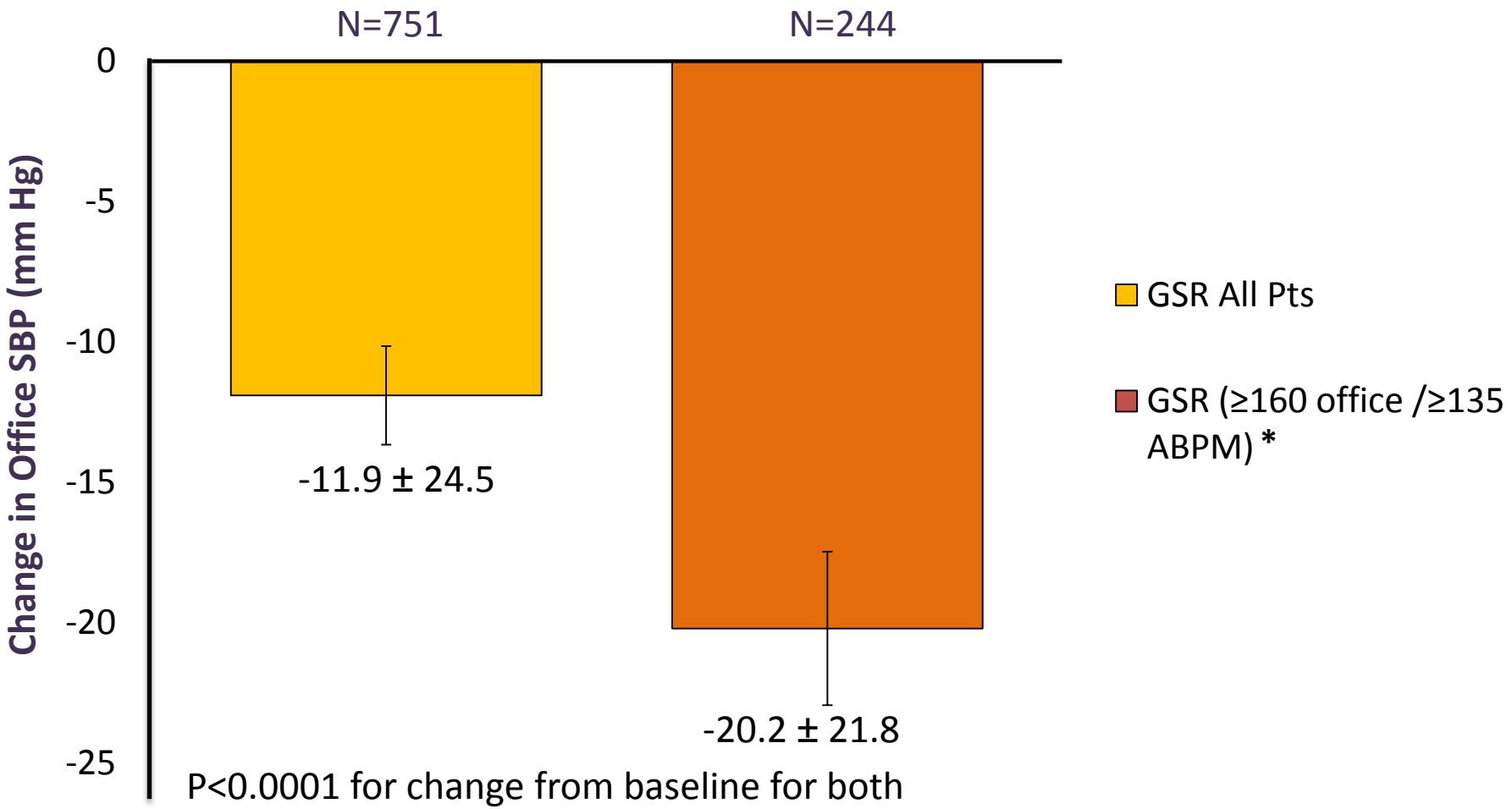
Consecutive patients treated in real world population 5000 patients

- **GREAT Registry N=1000** ✓
- **Korea Registry* N=102** ✓
- **South Africa Registry* N=400**
- **Canada and Mexico***
- **Rest of GSR N~3500**

231 international sites in 37 countries
40% randomly assigned to 100% monitoring

Follow-up schedule

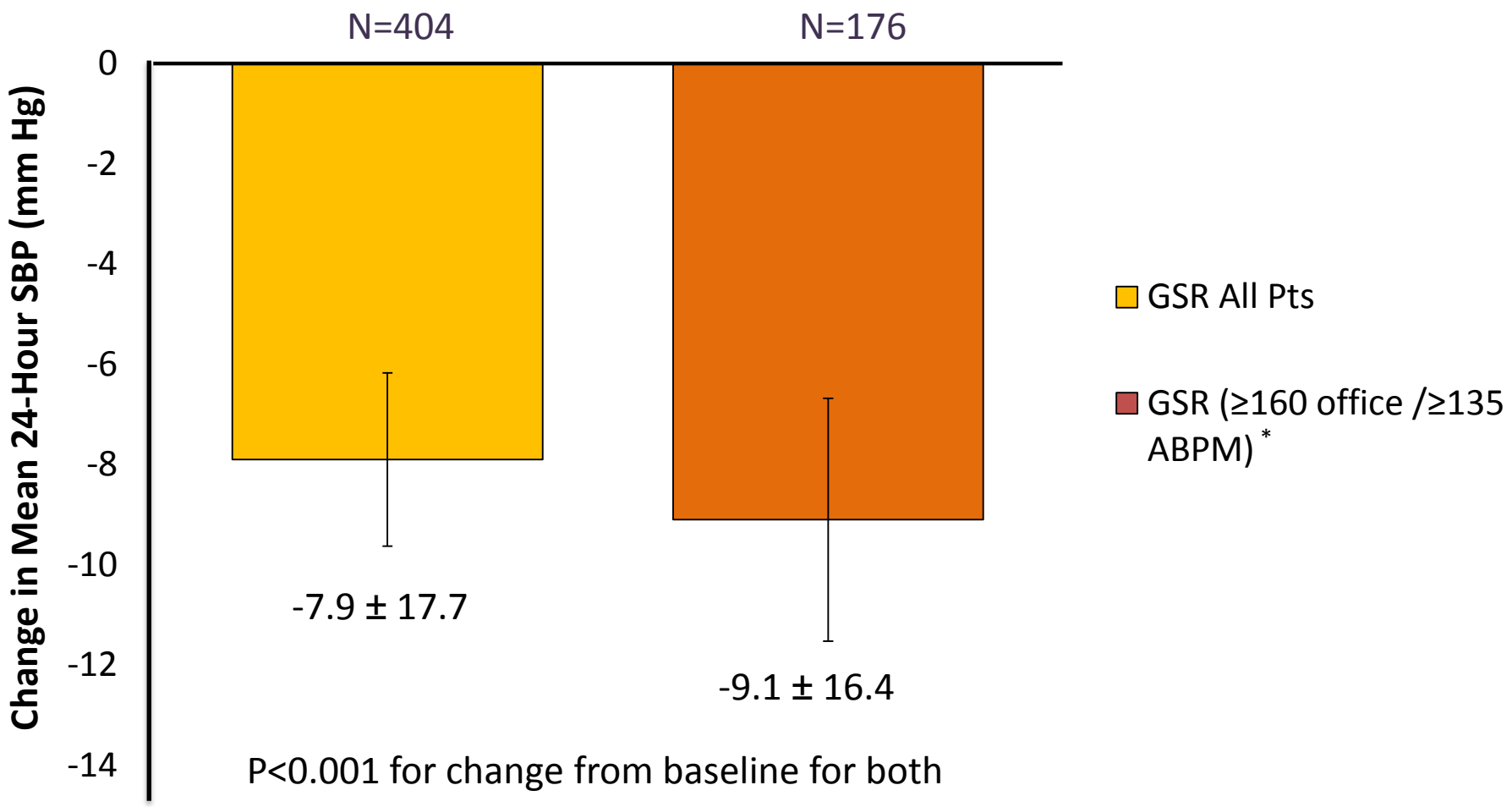
Change in Office SBP at 6 Months



***with ≥3 antihypertensive medication classes**

Error bar is ± 1.96 SE

Change in Ambulatory SBP at 6 Months



*with ≥3 antihypertensive medication classes
Error bar is ± 1.96 SE

Predictors of non-response in office systolic BP: all patients

Variable	Odds Ratio (95% CI)	P-value
342 non-responders/ 408 responders in both models		
Baseline office SBP (mm Hg)	0.95 [0.94, 0.96]	<0.0001
2 or more comorbidities	0.69 [0.50, 0.97]	0.03

- **Higher baseline office SBP** and **presence of 2 or more comorbidities** was associated with a response to renal denervation.

✓ **Relatively lower baseline SBP** and **lower risks** was associated with non-response.

Predictors of non-response in office systolic BP: HTN-3 like cohort

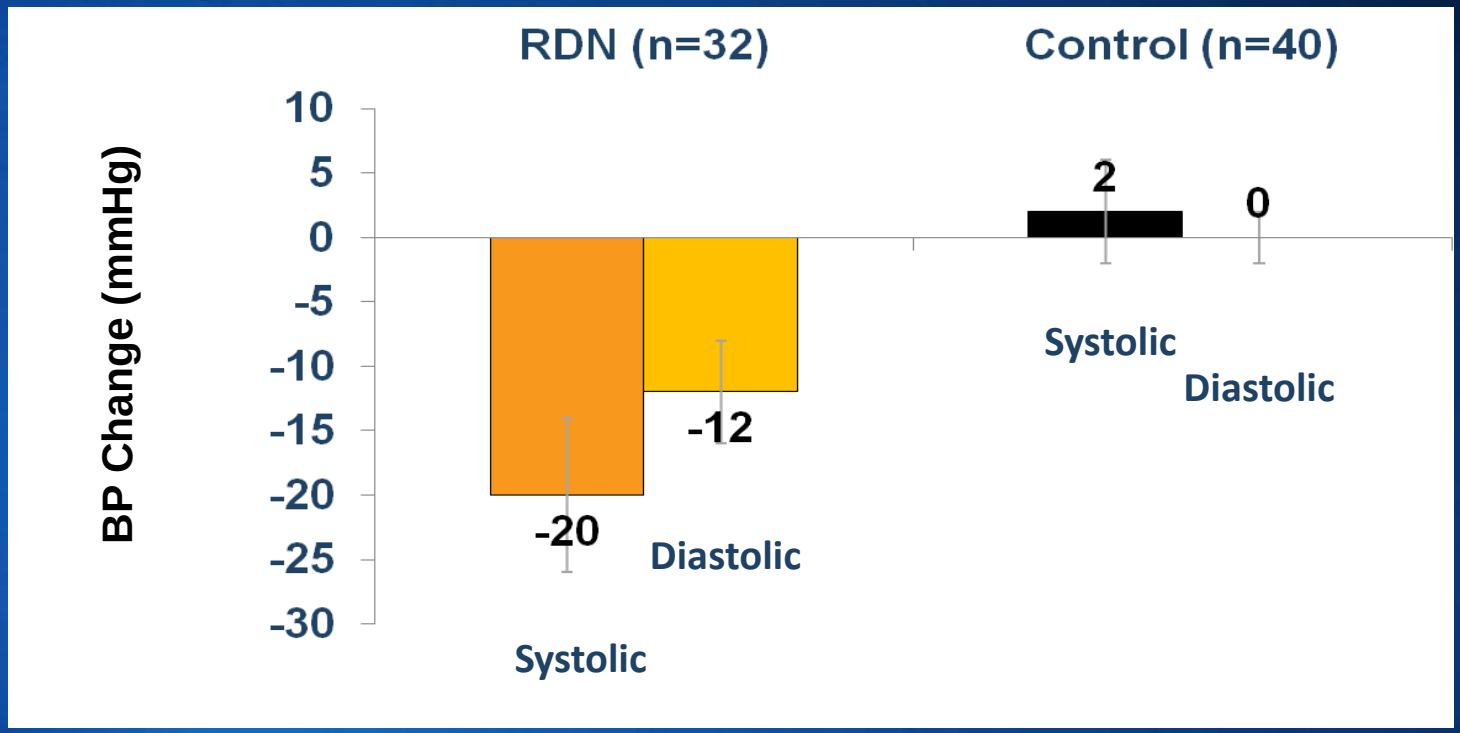
Variable	Odds Ratio (95% CI)	P-value
77 non-responders/ 167 responders in model with standard covariates		
Number of attempts	0.91 [0.84, 0.99]	0.032
Male sex	0.46 [0.24, 0.87]	0.018
Baseline office SBP	0.94 [0.91, 0.96]	<0.0001
Number of anti-HTN drugs	1.26 [0.97, 1.63]	0.078

- **Higher baseline office SBP**, **male sex** and **increasing number of ablation attempts** were associated with a response to renal denervation.
- **Number of anti-hypertensive medications at baseline** was associated with non-response.

Changes of Ambulatory BP

Home BP & 24-Hr Ambulatory BP

Home BP change



 # 24-h ABPM: Analysis on technically sufficient (>70% of readings) paired baseline & 6-month

- **RDN (n=20): -11 / -7 mmHg**
  (SD 15/11; p=0.006 SBP change, p=0.014 for DBP change)
- **Control (n=25): -3 / -1 mmHg**
  (SD 19/12; p=0.51 for systolic, p=0.75 for diastolic)

Ambulatory Blood Pressure Changes After Renal Sympathetic Denervation in Patients With Resistant Hypertension

Felix Mahfoud, MD; Christian Ukena, MD; Roland E. Schmieder, MD; Bodo Cremers, MD; Lars C. Rump, MD; Oliver Vonend, MD; Joachim Weil, MD; Martin Schmidt, MD; Uta C. Hoppe, MD; Thomas Zeller, MD; Axel Bauer, MD; Christian Ott, MD; Erwin Blessin

Background—Cathet
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Methods and Results
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Conclusions—RDN
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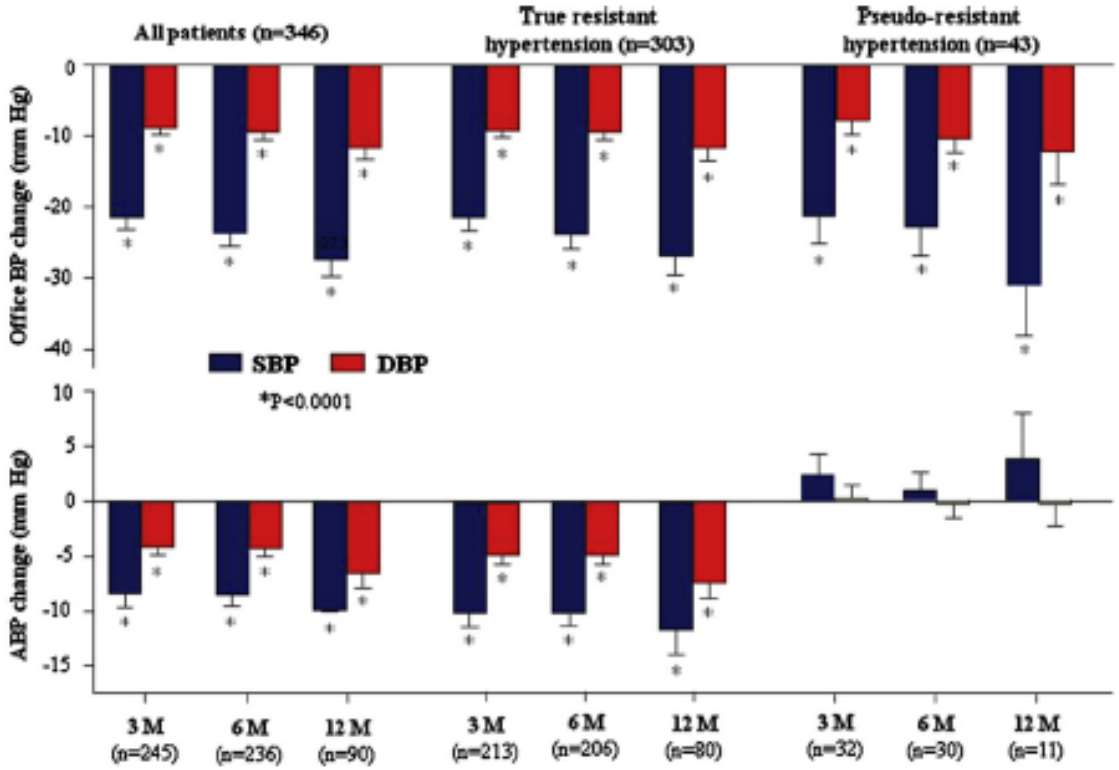

Changes in Office DBP and SBP and ABP in Patients With True Treatment-Resistant Hypertension and Those With Pseudoresistant Hypertension

- **Pseudo-resistan**

Circulation. 2013;128:132-40.

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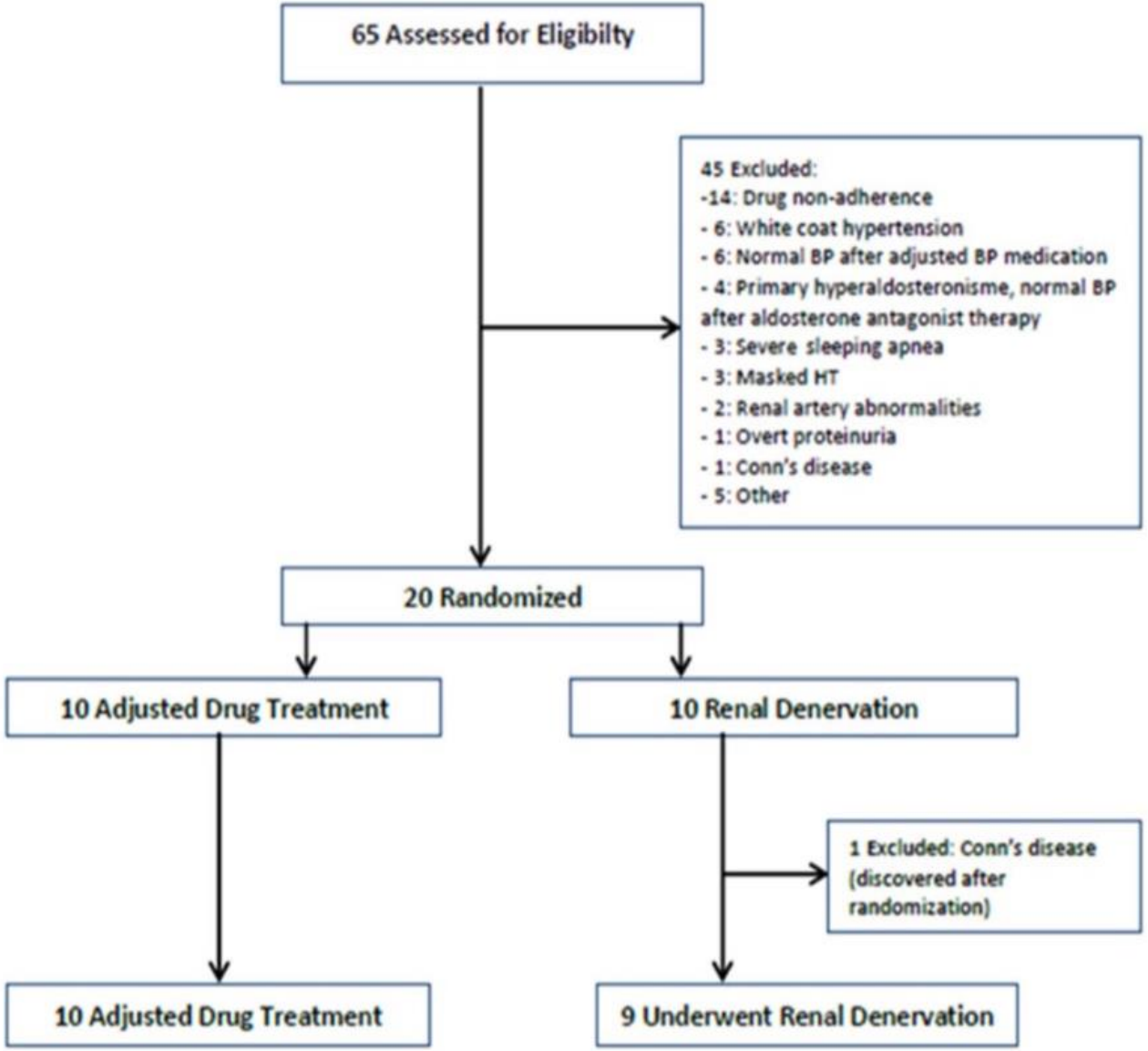
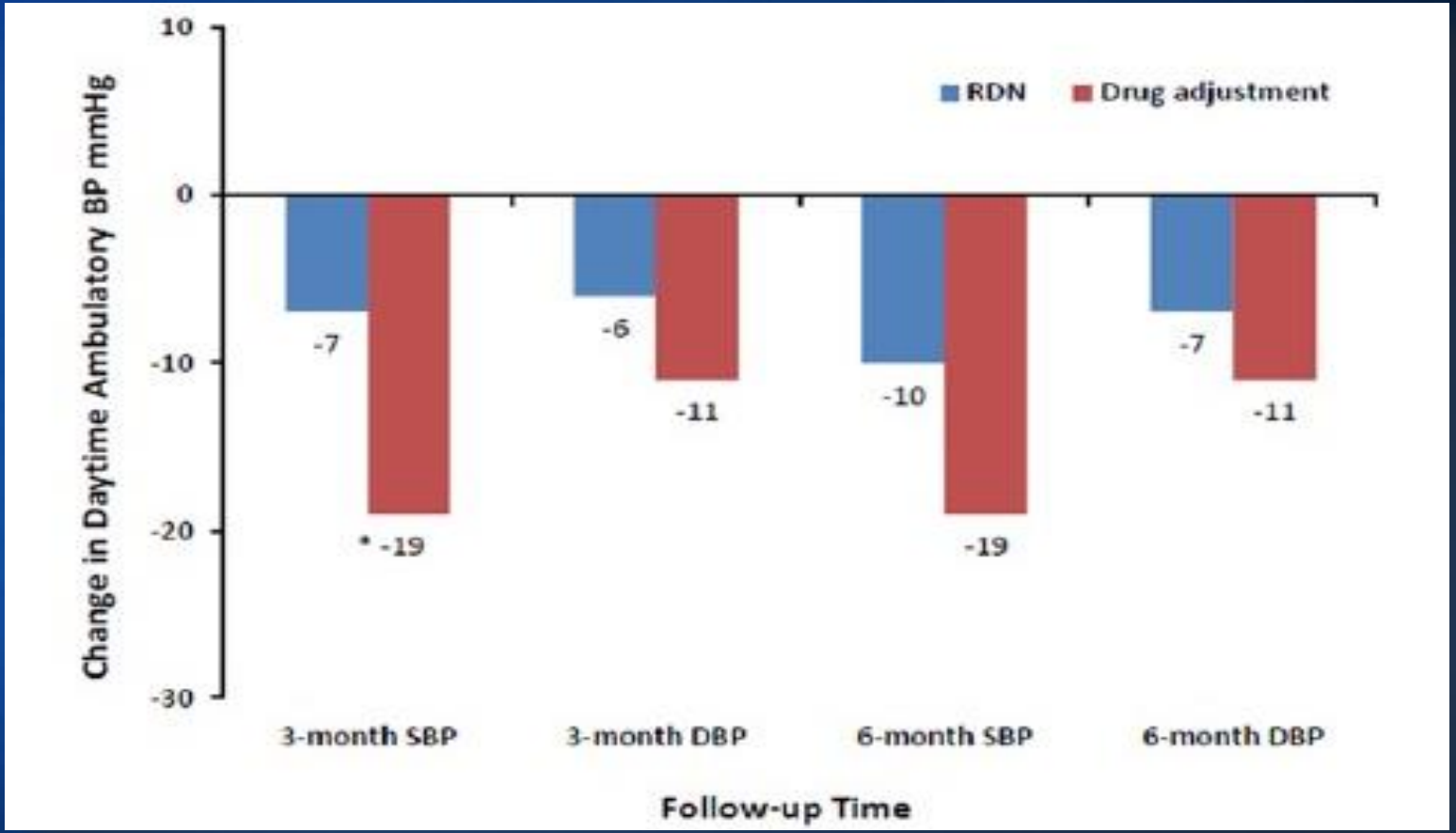


Figure 2. Illustration shows the flow chart of the present study. BP indicates blood pressure.

OSLO RDN trial



Our data suggest that **adjusted drug treatment has superior BP lowering effects** compared with RDN in patients with true TRH.

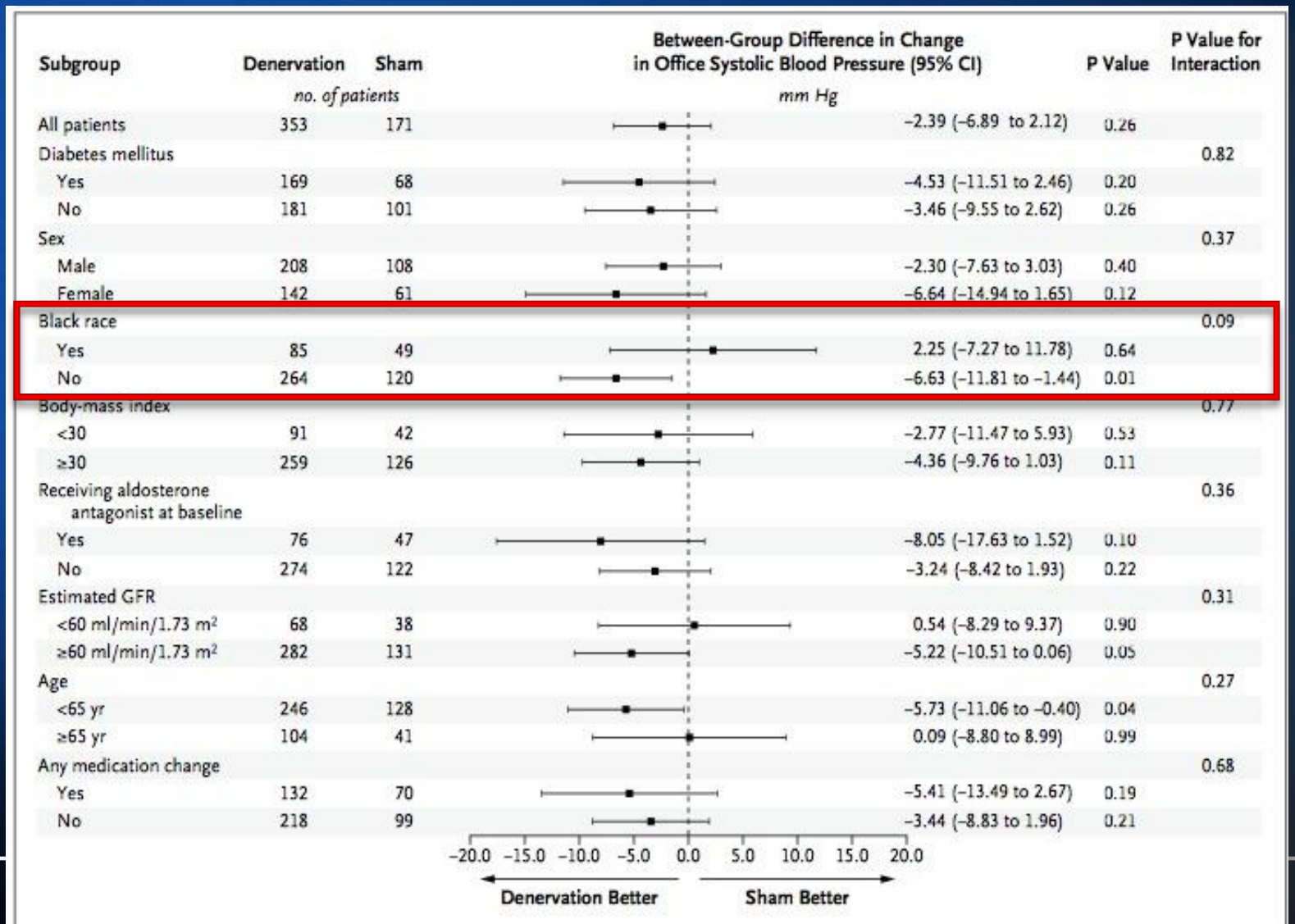
Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label,

	Renal denervation group			Control group			Mean baseline-adjusted difference (95% CI) between the two groups at 6 months	p value
	Randomisation (mean ± SD)	6 months (mean ± SD)	Mean baseline-adjusted difference (95% CI)	Randomisation (mean ± SD)	6 months (mean ± SD)	Mean baseline-adjusted difference (95% CI)		
ABP, mm Hg	n=48	n=48		n=53	n=53			
Daytime								
SBP	155·5±16·1	139·1±17·8	−15·8 (−19·7 to −11·9)	151·0±16·0	141·7±17·5	−9·9 (−13·6 to −6·2)	−5·9 (−11·3 to −0·5)	0·0329
DBP	92·9±15·0	82·9±13·7	−9·9 (−12·5 to −7·3)	92·0±10·8	85·4±13·2	−6·8 (−9·3 to −4·3)	−3·1 (−6·7 to 0·5)	0·0922
Night-time								
SBP	141·4±17·3	126·7±18·5	−13·9 (−18·0 to −9·8)	135·5±14·3	128·6±17·9	−7·6 (−11·4 to −3·7)	−6·3 (−12·0 to −0·6)	0·0296
DBP	82·0±16·1	73·1±13·3	−8·5 (−10·8 to −6·2)	79·4±10·5	74·5±11·5	−5·3 (−7·5 to −3·1)	−3·2 (−6·4 to 0·0)	0·0510
24 h								
SBP	151·6±16·2	135·5±17·6	−15·4 (−19·1 to −11·7)	146·8±15·2	137·9±16·4	−9·5 (−13·0 to −6·0)	−5·9 (−11·0 to −0·8)	0·0238
DBP	90·0±15·2	80·1±13·0	−9·7 (−12·0 to −7·4)	88·8±10·6	82·3±12·0	−6·6 (−8·8 to −4·4)	−3·1 (−6·3 to 0·05)	0·0538

The randomisation sequence was generated by computer, and stratified by centres. For SSAHT, after randomisation, spironolactone 25 mg per day, bisoprolol 10 mg per day, prazosin 5 mg per day, and rilmenidine 1 mg per day were sequentially added from months two to five in both groups if home blood pressure was more than or equal to 135/85 mm Hg. The primary endpoint was the mean change in daytime systolic blood pressure from baseline to 6 months as assessed by ambulatory blood pressure monitoring. The primary endpoint was analysed blindly. The safety outcomes were the incidence of acute adverse events of the renal denervation procedure and the change in estimated glomerular filtration rate from baseline to 6 months. This trial is registered with ClinicalTrials.gov, number NCT01570777.

Sub-group analysis of SYMPLICITY HTN-3

Unlike previous SYMPLICITY trials, SYMPLICITY HTN-3 enrolled a substantial number of African-American patients who represent a significant proportion of hypertensive patients in U.S.

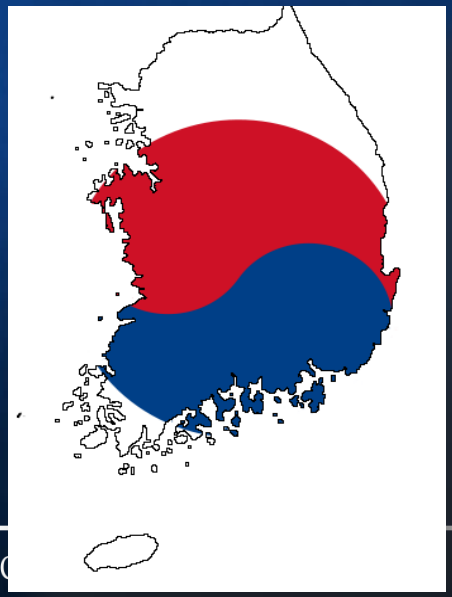


Subgroup	Denervation	Sham	Between-Group Difference in Change in Office Systolic Blood Pressure (95% CI)	P Value	P Value for Interaction
	no. of patients		*mm Hg*		
All patients	353	171	−2.39 (−6.89 to 2.12)	0.26	
Diabetes mellitus					0.82
Yes	169	68	−4.53 (−11.51 to 2.46)	0.20	
No	181	101	−3.46 (−9.55 to 2.62)	0.26	
Sex					0.37
Male	208	108	−2.30 (−7.63 to 3.03)	0.40	
Female	142	61	−6.64 (−14.94 to 1.65)	0.12	
Black race					0.09
Yes	85	49	2.25 (−7.27 to 11.78)	0.64	
No	264	120	−6.63 (−11.81 to −1.44)	0.01	
Body-mass index					0.77
<30	91	42	−2.77 (−11.47 to 5.93)	0.53	
≥30	259	126	−4.36 (−9.76 to 1.03)	0.11	
Receiving aldosterone antagonist at baseline					0.36
Yes	76	47	−8.05 (−17.63 to 1.52)	0.10	
No	274	122	−3.24 (−8.42 to 1.93)	0.22	
Estimated GFR					0.31
<60 ml/min/1.73 m²	68	38	0.54 (−8.29 to 9.37)	0.90	
≥60 ml/min/1.73 m²	282	131	−5.22 (−10.51 to 0.06)	0.05	
Age					0.27
<65 yr	246	128	−5.73 (−11.06 to −0.40)	0.04	
≥65 yr	104	41	0.09 (−8.80 to 8.99)	0.99	
Any medication change					0.68
Yes	132	70	−5.41 (−13.49 to 2.67)	0.19	
No	218	99	−3.44 (−8.83 to 1.96)	0.21	

How about the treatment Outcome after RDN in Asian population?

Outcomes of Korean population

Data of Global Symplicity Korean registry



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Renal Sympathetic Denervation for Treatment of Drug-Resistant Hypertension in an Asian Population: Results from the Global SYMPLICITY Registry in South Korea (GSR Korea)

Byeong-Keuk Kim*, Michael Boehm, Felix Mahfoud, Giuseppe Mancia, Sungha Park, Myeong-Ki Hong, Hyo-Soo Kim, Seung-Jung Park, Chang Gyu Park, Ki Bae Seung, Hyeon-Cheol Gwon, Dong-Ju Choi, Tae Hoon Ahn, Chong Jin Kim, Hyuck Moon Kwon, Murray Esler, Yangsoo Jang

***Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea**

Global Symplicity Registry

Clinical Trial Design

Prospective, open-label, single-arm, all-comer observational registry

5000 consecutive "real-world" patients treated with Symplicity™ renal denervation system for uncontrolled hypertension and/or conditions associated with sympathetic nervous system activation

- **GREAT Registry** N=1000
- **Korea Registry[1]** N=102
- **South Africa Registry[1]** N=400
- **Canada & Mexico[1]**
- **Rest of GSR** N≈3500

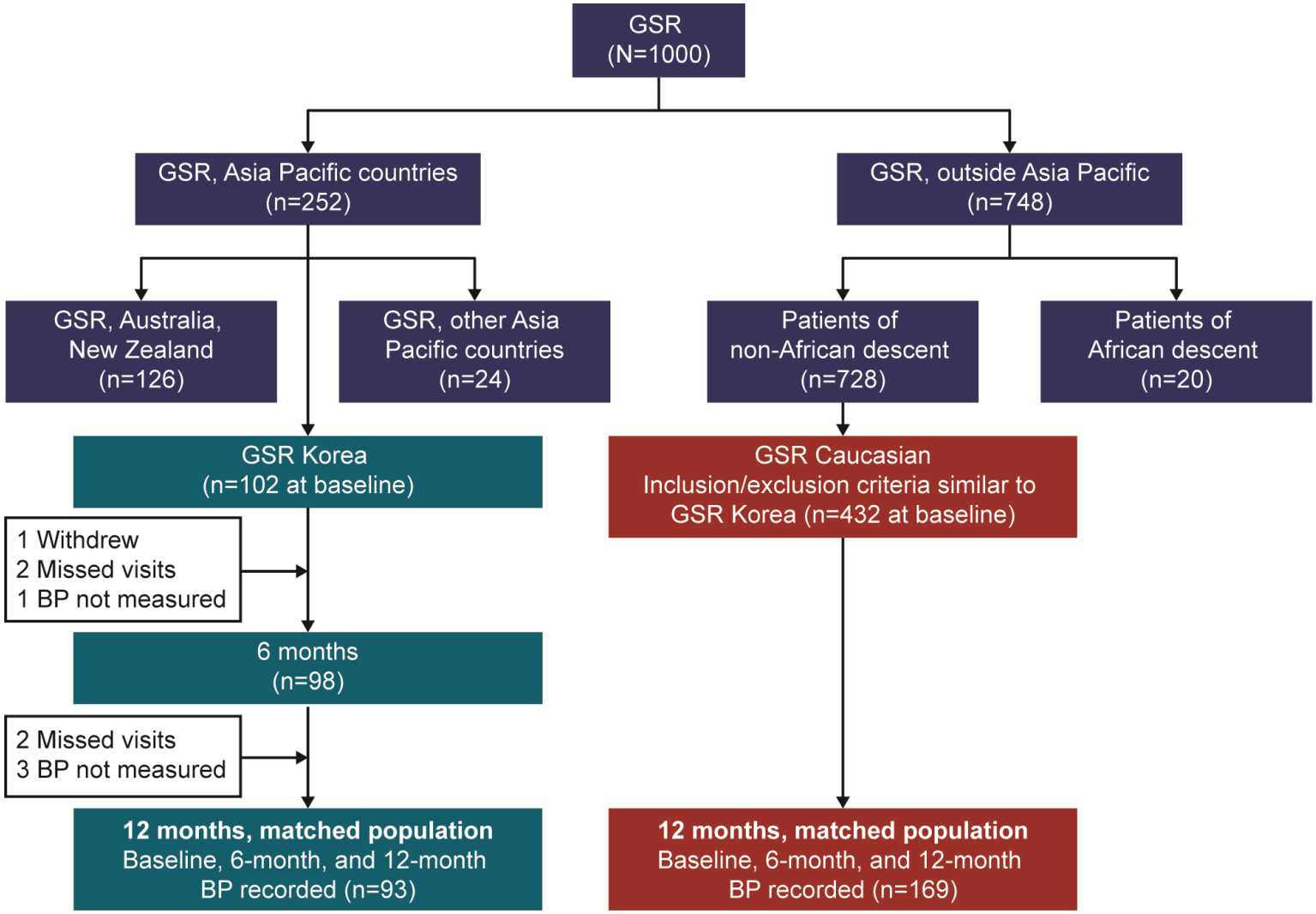
- **Primary objective:** assess peri-procedural and long-term safety of RDN in a real world population
- **Min. 10% randomly assigned to 100% monitoring**
- **Key GSR inclusion criteria**: any candidate for renal denervation by the Symplicity™ catheter
- **Key GSR-Korea inclusion criteria**: office systolic BP ≥160 mmHg (or ≥150 mmHg for diabetes mellitus type-2) while receiving ≥3 antihypertensive medications
- **Key GSR-Korea exclusion criteria**: prior renal artery intervention, main renal artery diameter <4mm or length <20mm, hemodynamically or anatomically significant renal artery abnormalities

[1] Limited to resistant hypertension only

NCT01534299

Böhm,M, et al. *Hypertension*. 2015; online ahead of print. doi: 10.1161/HYPERTENSIONAHA.114.05010

Patient Flowchart



Baseline Patient Characteristics

% or mean ± SD	GSR Korea (N=93)	GSR Caucasian (N=169)	*P*-value
Office systolic blood pressure, mm Hg	168.3 ± 13.9	176.1 ± 15.6	< 0.001
Office diastolic blood pressure, mm Hg	95.5 ± 12.8	94.5 ± 14.5	0.403
Age, years	55.9 ± 13.4	61.8 ± 10.8	< 0.001
Male gender	72.0	62.7	0.127
Body mass index, kg/m^2	27.5 ± 4.3	31.2 ± 5.1	< 0.001
Obesity (≥ 30 kg/m^2)	10.8	38.5	< 0.001
Diabetes mellitus type 2	46.2	36.3	0.117
eGFR, ml/min/1.73 m^2	88.9 ± 25.3	80.9 ± 18.2	0.011
Renal insufficiency (eGFR <60 ml/min/1.73 m^2)	5.4	13.6	0.039
History of atrial fibrillation	5.4	11.3	0.112
History of sleep apnea	2.2	21.9	< 0.001
Heart rate (beats per minute)	72.3 ± 11.5	69.0 ± 14.2	0.016
Heart failure	2.2	3.0	> 0.999

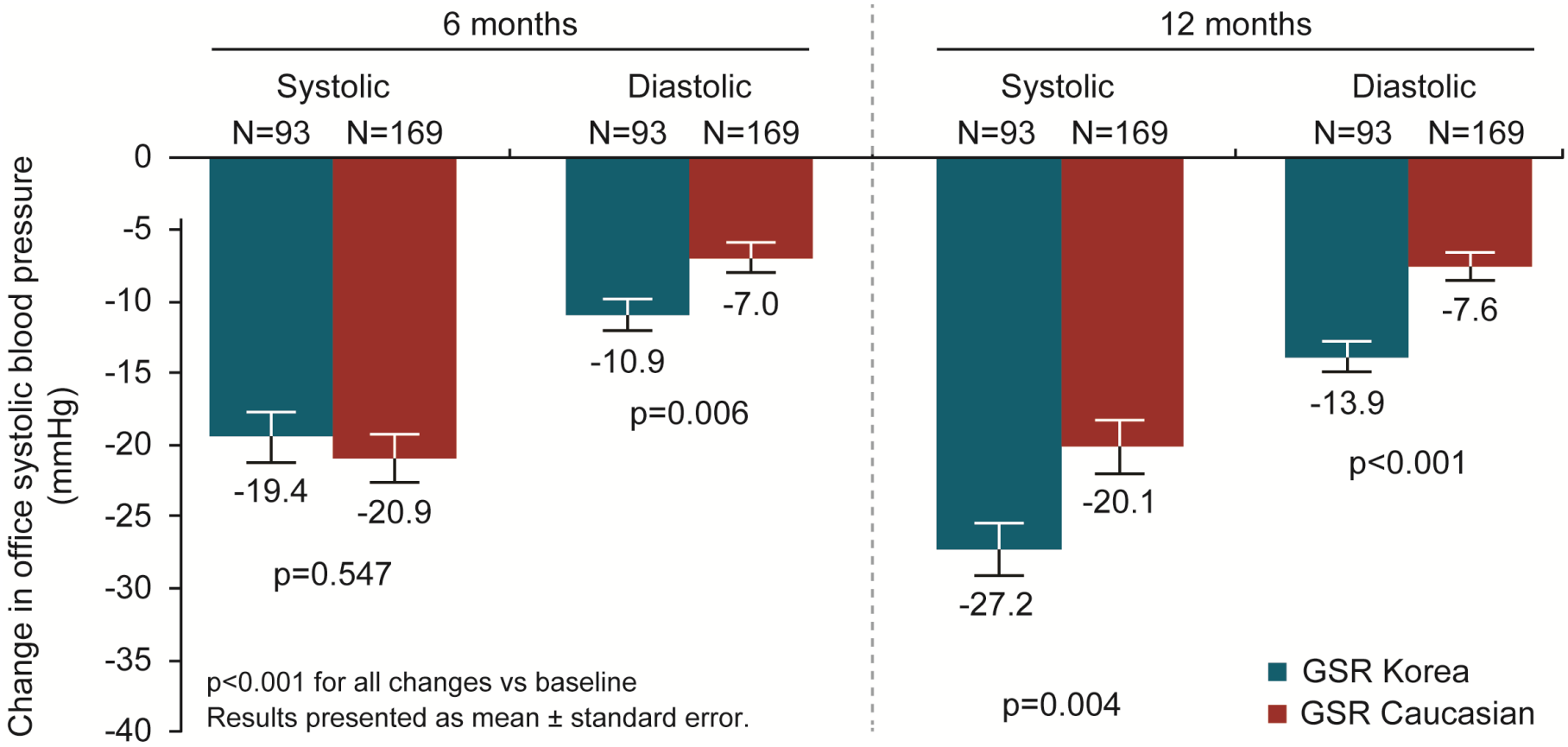
Antihypertensive Medications

Baseline

% (n)	GSR Korea (N=93)	GSR Caucasian (N=169)	*P*-value
No. of anti-hypertensive medication classes	3.7 ± 0.9	4.7 ± 1.2	< 0.001
ACE inhibitors	8.6 (8)	38.5 (65)	< 0.001
Angiotensin receptor blockers	88.2 (82)	69.2 (117)	< 0.001
Calcium channel blockers	84.9 (79)	78.1 (132)	0.18
Diuretics	83.9 (78)	78.1 (132)	0.26
Aldosterone antagonists	8.6 (8)	18.3 (31)	0.03
Direct renin inhibitors	0.0 (0)	12.4 (21)	< 0.001
Beta blockers	79.6 (74)	79.9 (135)	0.95
Alpha-adrenergic blocker	11.8 (11)	37.3 (63)	< 0.001
Direct-acting vasodilators	4.3 (4)	16.6 (28)	0.004

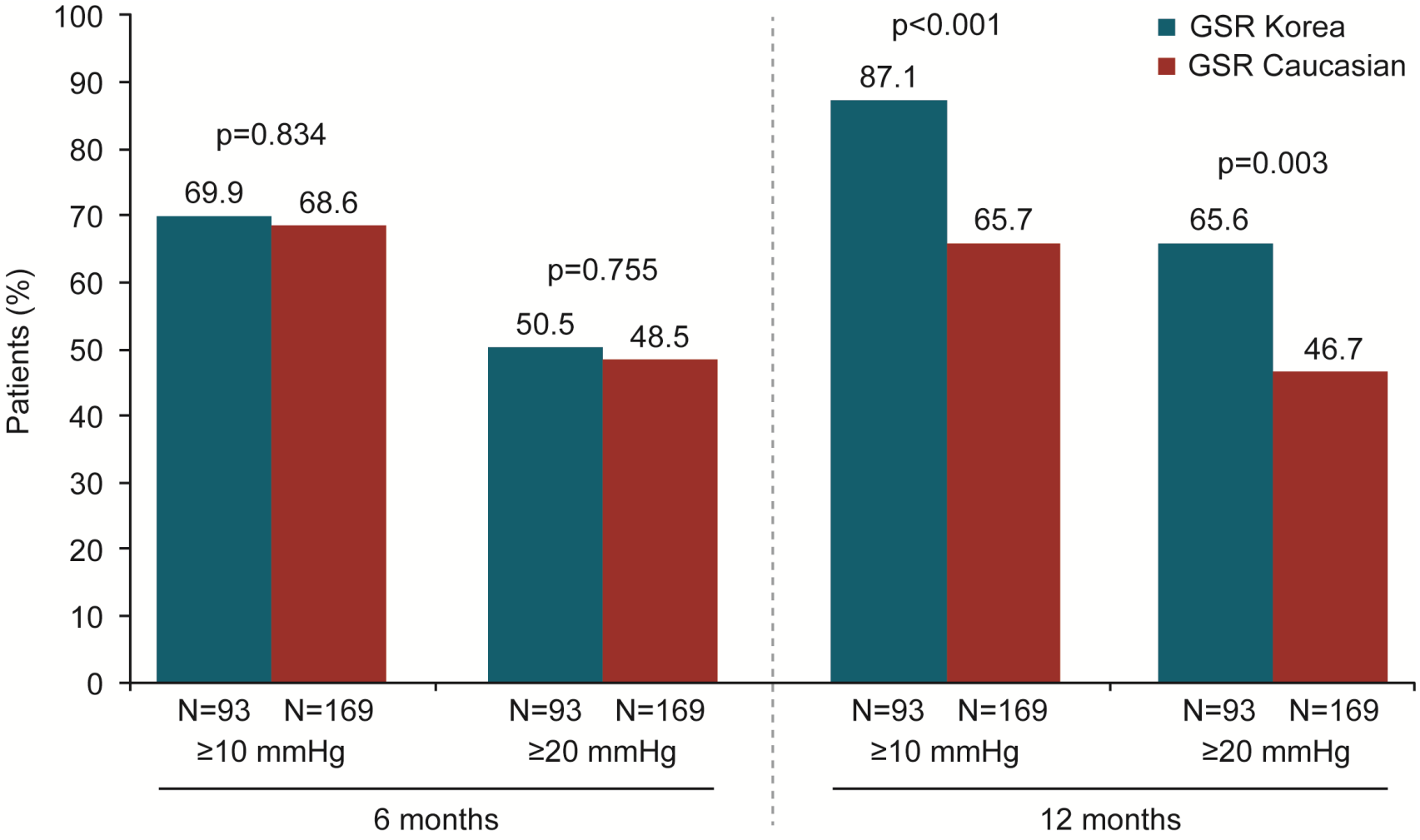
Office BP Change

6- and 12 Months



Office Systolic BP

≥ 10- and 20 mmHG Reduction



Determinants for Office Systolic BP Change

Multivariate Analysis

6 Months	Estimate	95% CI	p-value
Korean (vs Caucasian)	-2.4	(-7.14, 2.29)	0.315

12 Months	Estimate	95% CI	p-value
Korean (vs Caucasian)	-11.8	(-16.85, -6.73)	**<0.001**

Safety Outcomes at 12 Months

%	GSR Korea (n = 93/93)	GSR Caucasian (n=165/169)	*P*-value
Procedure-related vascular complications	0.0	0.0 [1]	[3]
Death	0.0	0.0 [2]	[3]
Spontaneous myocardial infarction	0.0	0.6	1.00
Serum creatinine elevation > 50%	0.0	0.0 [1]	[3]
Renal failure	1.1	0.0	0.36
Atrial fibrillation requiring hospitalization	2.2	0.6	0.29
Stroke	2.2	0.6	0.29
Hypertensive crisis requiring hospitalization	1.1	1.2	1.00
Vascular complication	0.0	1.2	0.54

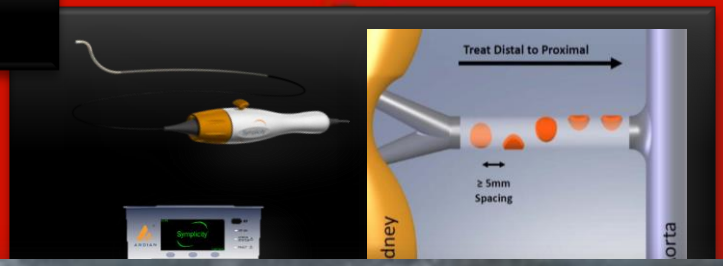
[1] For vascular complications and serum creatinine elevation >50%, 12-month data available on all 169 matched patients
[2] There was no deaths in the total GSR population (N=432)
[3] *P*-value cannot be calculated when there are no events in both arms

Conclusions

- ✓ RDN in the GSR Korea substudy provided a **significant reduction** in **office systolic BP** at 6 and 12 months compared to baseline.
- ✓ As compared to the GSR Caucasian subset, the reduction in systolic BP in GSR Korea was **similar at 6 months but higher at 12 months** (fewer medications and a lower systolic BP in baseline; contrary to prior studies that consistently indicated a relationship between baseline systolic BP and RDN BP-lowering response).
- ✓ In multivariate analysis, **Korean patients** remained **more likely** to have a **larger reduction** in 12-month **systolic BP**

  → A larger role of **Sympathetic tone** in the pathogenesis of hypertension of **Asian patients** compared to Caucasian patients ? **Ethnic difference** by RDN?
- ✓ Finally, RDN with the **Symplicity™** still showed **favorable safety results**.

RDN is not dead…



OPTIMISTIC

Why could RDN be optimistic?

- ✓ A large and significant unmet need remains for patients with uncontrolled hypertension.
  Other definite methods for uncontrolled true resistant hypertension?
- ✓ The safety profile for current catheter-based RDN
- ✓ Pre-clinical data and post-hoc analyses from HTN-3 continue to instill new confidence in the therapy
- ✓ Therapeutic roles of RDN are not confined to the treatment of resistant hypertension. Beyond BP-lowering effects of RDN.

For the successful RDN therapy for resistant hypertension

1. "Proper patients-selection" will be the most important.

- Before the selection of patients for RDN, the following factors first should be met.

1) ABPM for excluding pseudo-resistant hypertension
2) Proper full doses medications including diuretics, especially aldosterone antagonists
3) Good drug-adherence

For the successful RDN therapy for resistant hypertension

2.

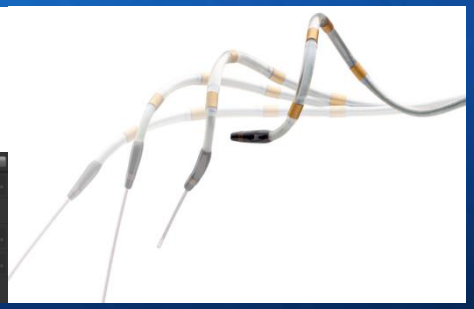
- As for technical issues …

“Grater No. of ablation” and “Even ablations of 4-quadrants of renal artery” will be important.

Upcoming "Next-generation RDN device"

; *Multi-electrode system, one shot system*

- **EnligHTN™ Ablation Catheter**; designed with an expandable electrode basket with four Platinum–Iridium (Pt–Ir) ablation electrodes.



- **Symplicity Spyral™ Multi-Electrode Renal Denervation Catheter**

European Heart Journal Advance Access published June 19, 2013

European Heart Journal
doi:10.1093/eurheartj/eht197

CLINICAL RESEARCH

Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial

Stephen G. Worthley[1]*, Costas P. Tsioufis[2], Matthew I. Worthley[1], Ajay Sinhal[3], Derek P. Chew[3], Ian T. Meredith[4], Yuvi Malaiapan[4], and Vasilios Papademetriou[2,5]

[1]Cardiovascular Research Centre, c/o The Cardiovascular Investigational Unit, Level 6 Theatre Block, University of Adelaide, Royal Adelaide Hospital, Adelaide 5000, Australia; [2]The First Cardiology Clinic, University of Athens, Hippokration Hospital, Athens, Greece; [3]The Department of Cardiology, Flinders University, Bedford Park, Australia; [4]The Monash Heart and Monash University, Melbourne, Australia; and [5]VA and Georgetown University Medical Centers, Washington, DC, USA

Received 26 February 2013; revised 15 May 2013; accepted 16 May 2013

Aims Catheter-based renal artery sympathetic denervation has emerged as a novel therapy for treatment of patients with drug-resistant hypertension. Initial studies were performed using a single electrode radiofrequency catheter, but recent advances in catheter design have allowed the development of multi-electrode systems that can deliver lesions with a pre-determined pattern. This study was designed to evaluate the safety and efficacy of the EnligHTN™ multi-electrode system.

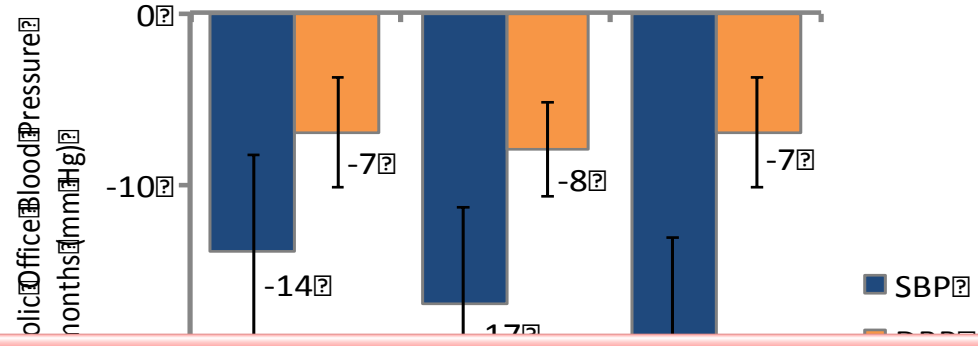
Methods and results We conducted the first-in-human, prospective, multi-centre, non-randomized study in 46 patients (67% male, mean age 60 years, and mean baseline office blood pressure 176/96 mmHg) with drug-resistant hypertension. The primary efficacy objective was change in office blood pressure from baseline to 6 months. Safety measures included all adverse events with a focus on the renal artery and other vascular complications and changes in renal function. Renal artery denervation, using the EnligHTN™ system significantly reduced the office blood pressure from baseline to 1, 3, and 6 months by −28/10, −27/10 and −26/10 mmHg, respectively ($P < 0.0001$). No acute renal artery injury or other serious vascular complications occurred. Small, non-clinically relevant, changes in average estimated glomerular filtration rate were reported from baseline (87 ± 19 mL/min/1.73 m^2) to 6 months post-procedure (82 ± 20 mL/min/1.73 m^2).

Conclusion Renal sympathetic denervation, using the EnligHTN™ multi-electrode catheter results in a rapid and significant office blood pressure reduction that was sustained through 6 months. The EnligHTN™ system delivers a promising therapy for the treatment of drug-resistant hypertension.

Renal artery denervation with a new simultaneous multi-electrode catheter for treatment of resistant hypertension: 6-month safety results from the SYMPLICITY Spyral FIM Study

euro PCR 2014

Symplicity Spyral Feasibility Study: Change in Office BP through 6 months



→ Preparing for sham-controlled clinical study (already submitted to FDA)

P<0.001 for all values compared to baseline
Error bars: +/- 1.96 SE

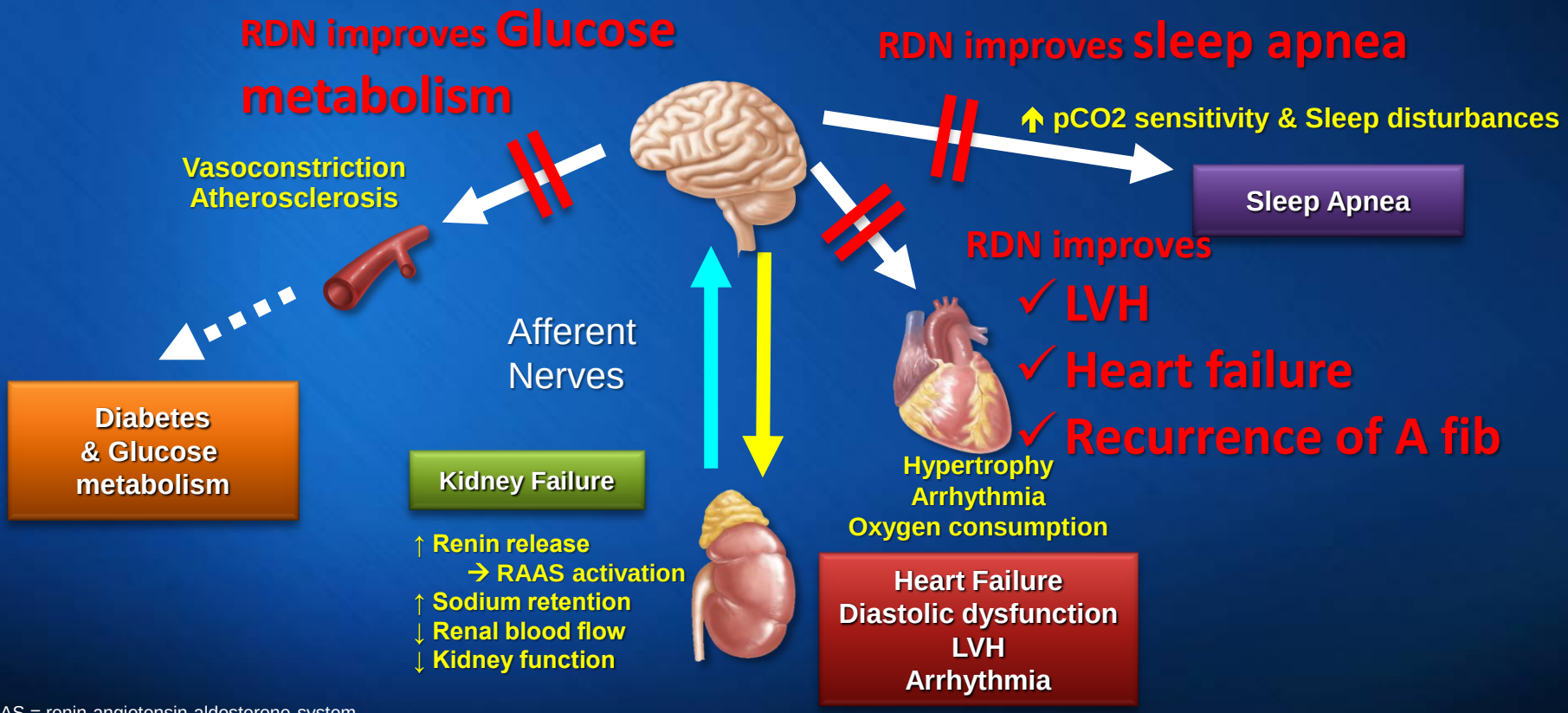
For the successful RDN therapy for resistant hypertension

3.

- BP reduction have been shown even with controversies after SYMPLICITY HTN-3.
- … outcome data on hard CV endpoints are missing !

→ the game will be over **if the clinical outcomes following RDN could be improved** irrespective of BP reduction.

4. Never forget the proven roles of RDN beyond BP lowering! … Can Sham-group do these?



RAAS = renin-angiotensin-aldosterone system.

1. Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.
2. Blankestijn PJ, et al. *Nephrol Dial Transplant*. 2011;26:2732-2734.

Conclusion

- ✓ RDN therapy is "not the End" … However, we need a more concrete data … we should await future studies…


Thank you for your attention