

Renal Denervation Next Steps

Evolution of Evidence and Future Directions

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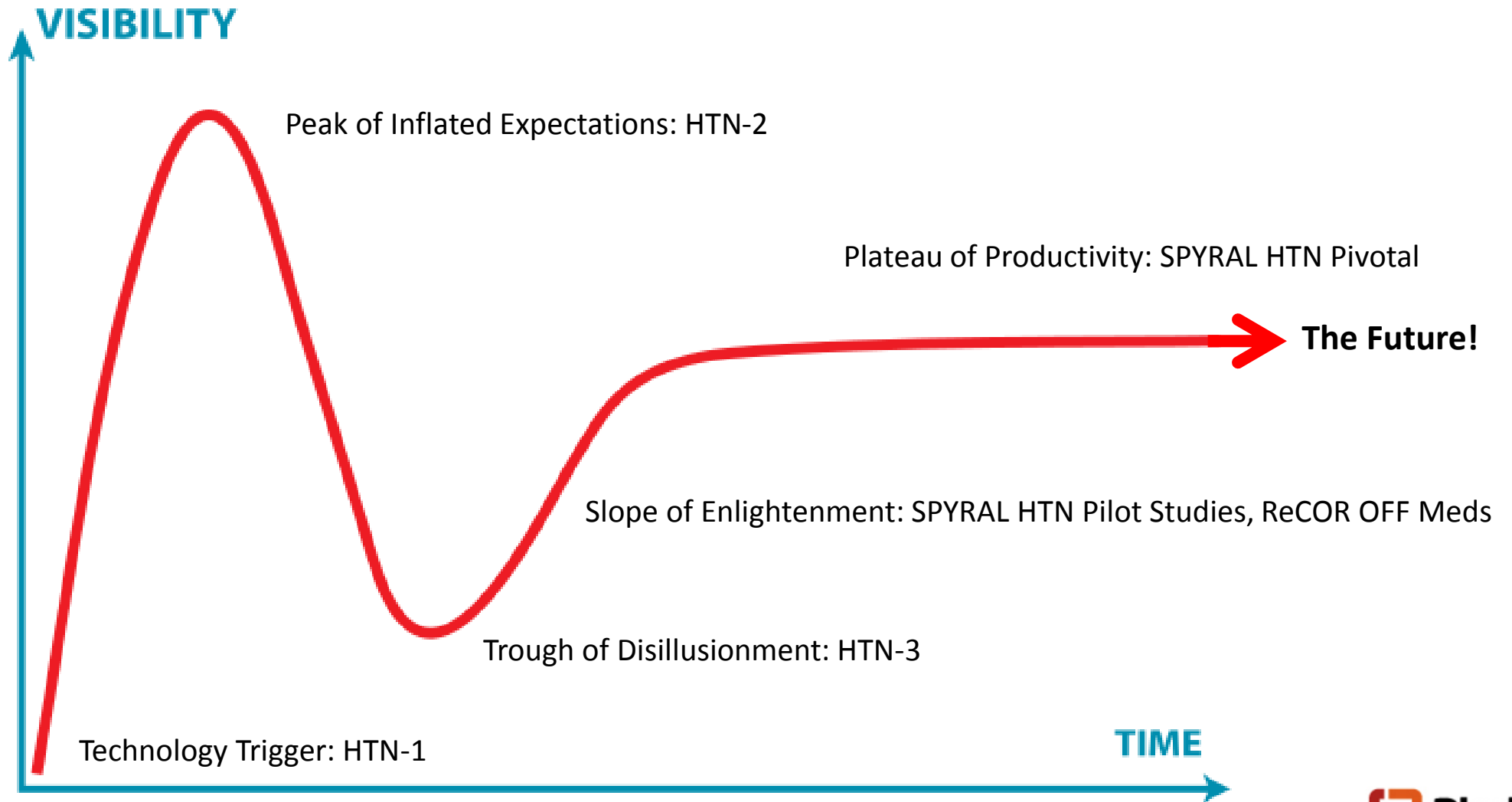
Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

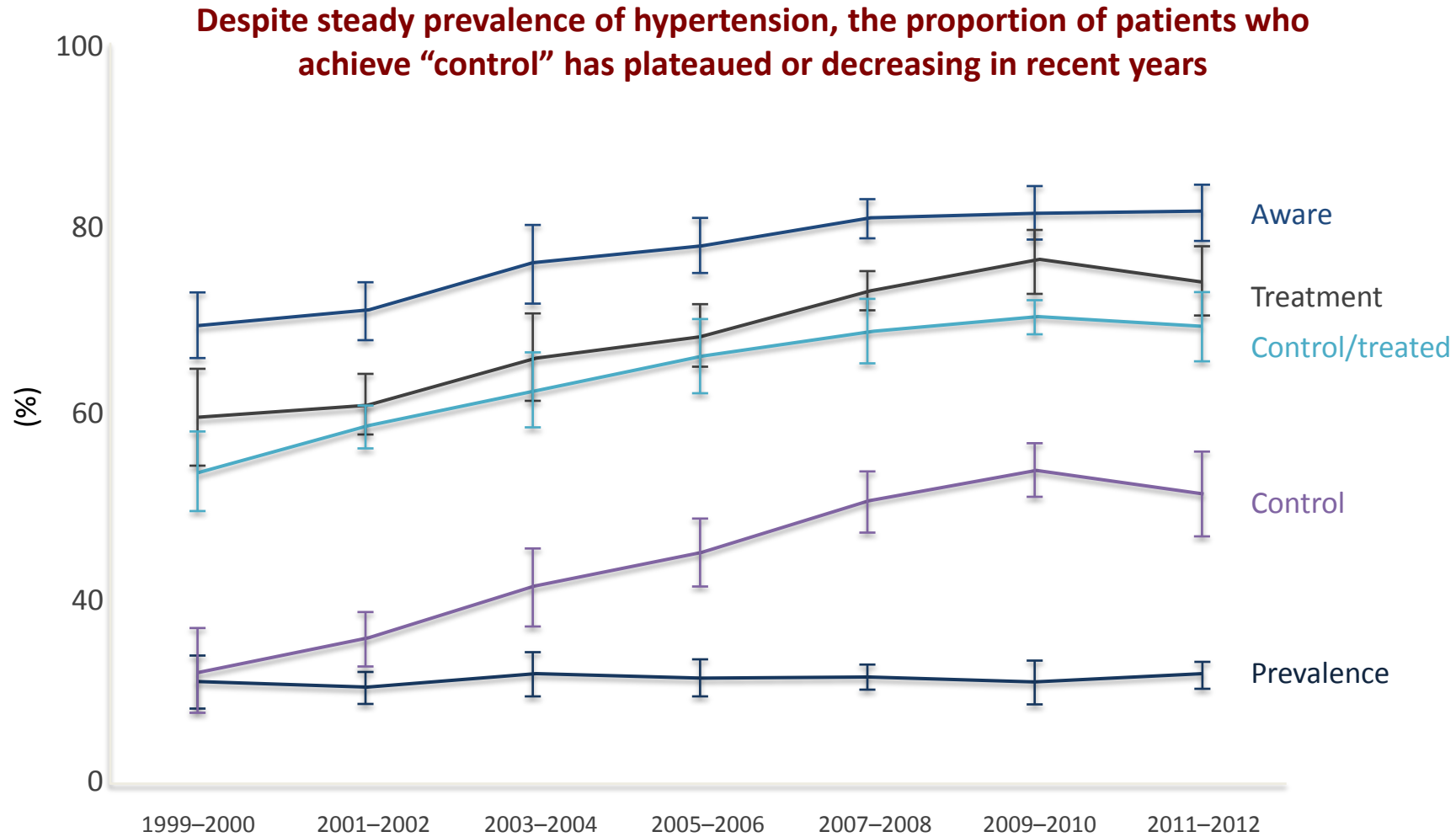
<u>Affiliation/Financial Relationship</u>	<u>Company</u>
Grant/Research Support	Biotronik, Boston Scientific, Medtronic CardioVascular, Medinol, Orbus Neich
Consulting Fees/Honoraria	Biotronik, Boston Scientific Corporation, Medtronic CardioVascular
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

Clinical Development of Renal Denervation Therapy

A Storied Path


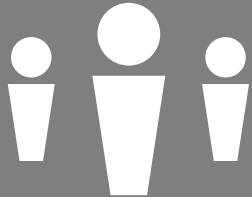
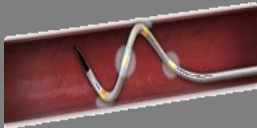


Polypharmacy Strategy Is Failing to Achieve Goals for Hypertension Control

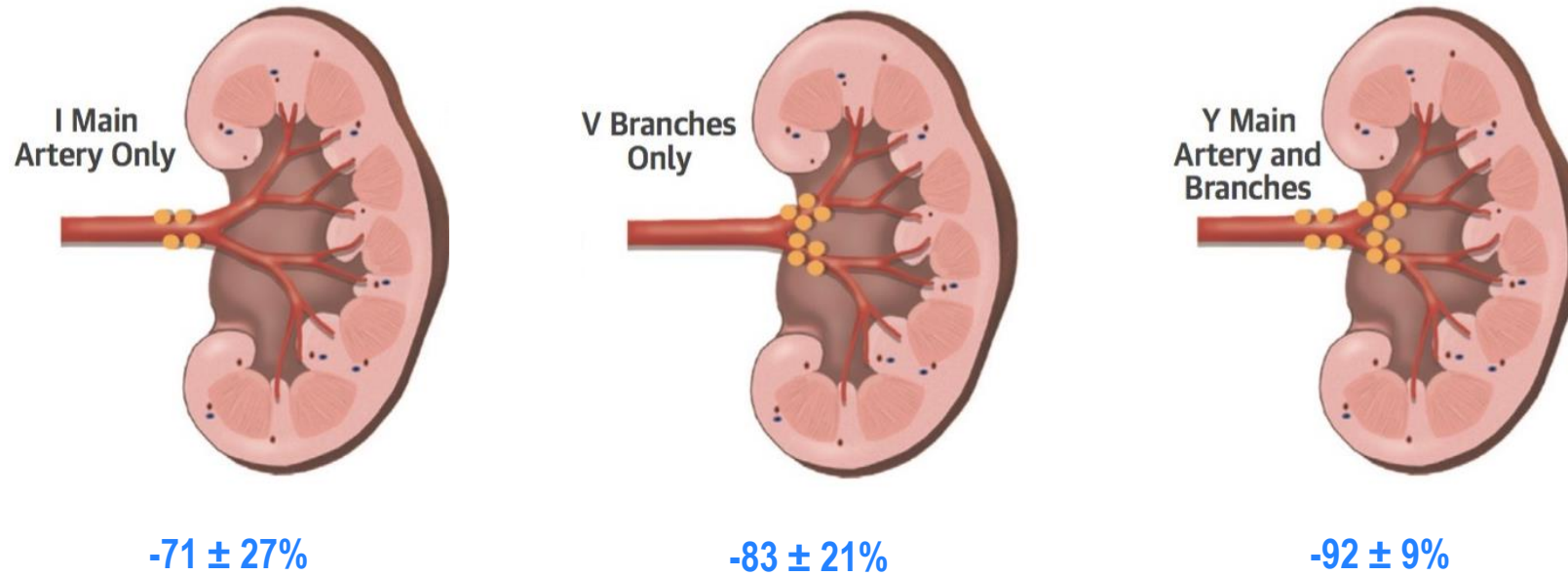


ADVANCES OF SPYRAL HTN COMPARED TO SYMPLICITY HTN-3

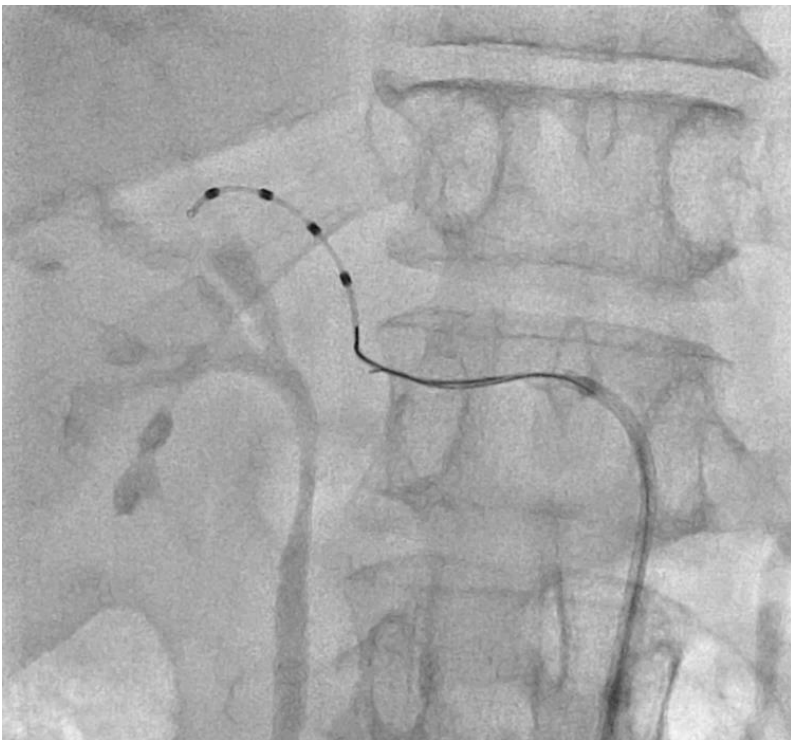
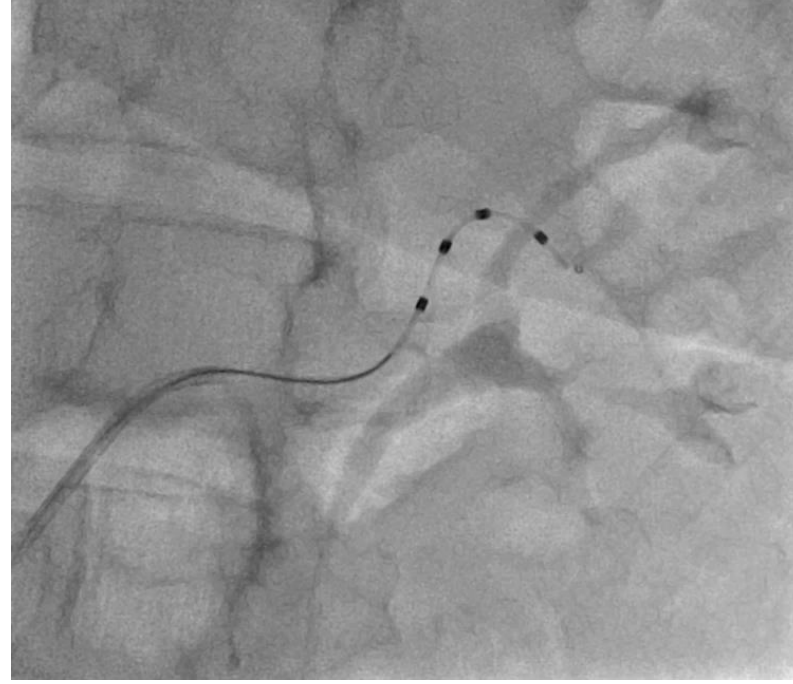
EVOLUTION OF CLINICAL TRIAL DESIGN, CONDUCT, INDICATION AND METHODS

	 Medications	 Patients/Endpoints	 Procedure
SYMPLICITY HTN-3	<ul style="list-style-type: none">▪ 5.1 prescribed anti-HTN drugs at randomization▪ No drug testing	<ul style="list-style-type: none">▪ Resistant hypertension patients (OSBP 180±16)▪ No diastolic cutoff▪ Office SBP endpoint	<ul style="list-style-type: none">▪ Mono-electrode, sequential ablation system▪ Mostly inexperienced operators without proctoring▪ Main artery RDN only▪ Ablations per pt: 11.2 ± 2.8
SPYRAL HTN	<ul style="list-style-type: none">▪ No anti-HTN drugs at time of randomization▪ Drug testing	<ul style="list-style-type: none">▪ Moderate hypertension patients (OSBP 162±7)▪ Excluding ISH patients (ODBP 101±7)▪ 24 hr ABPM endpoint	<ul style="list-style-type: none">▪ Four-electrode, simultaneous ablation system▪ Highly experienced operators with proctoring▪ Main + branches RDN▪ Ablations/pt: 43.8 ± 13.1

IVY Pre Clinical Trial: Combined Treatment in Main Artery and Branch Vessels in Porcine Model

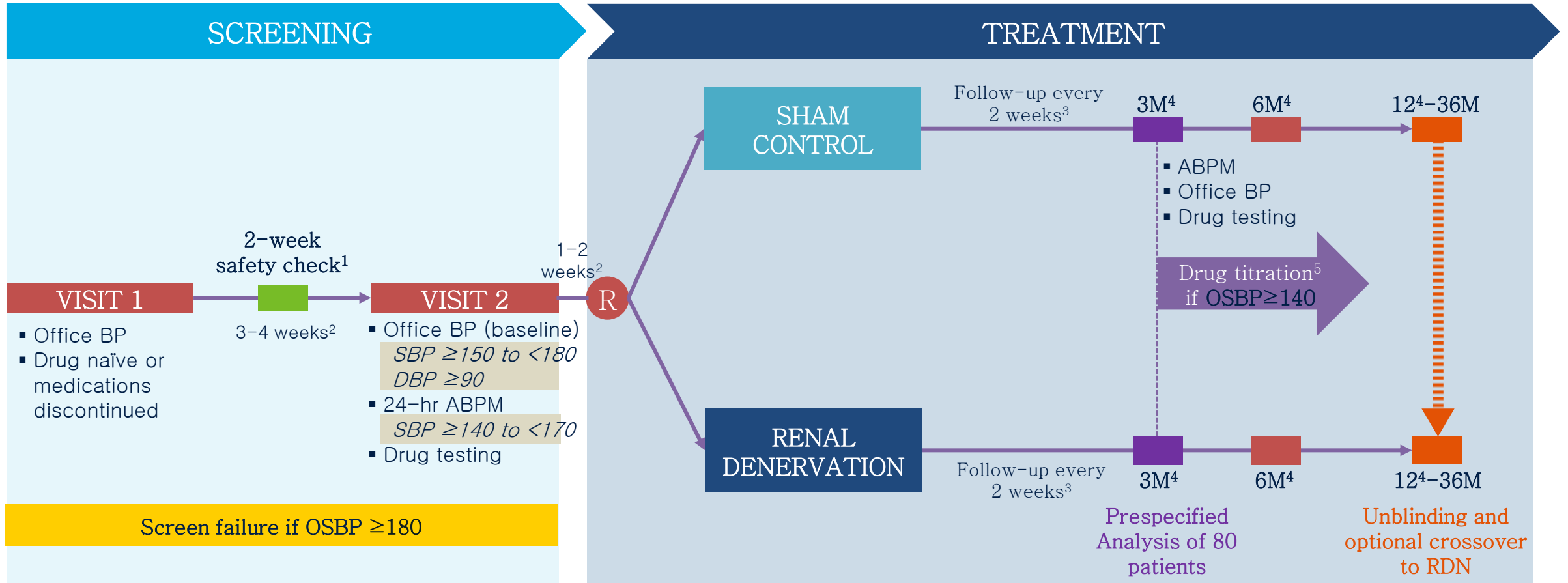


Pre-clinical porcine data show significantly greater reductions in renal sympathetic activity with combined proximal and distal therapy application.



SPYRAL HTN – OFF MED

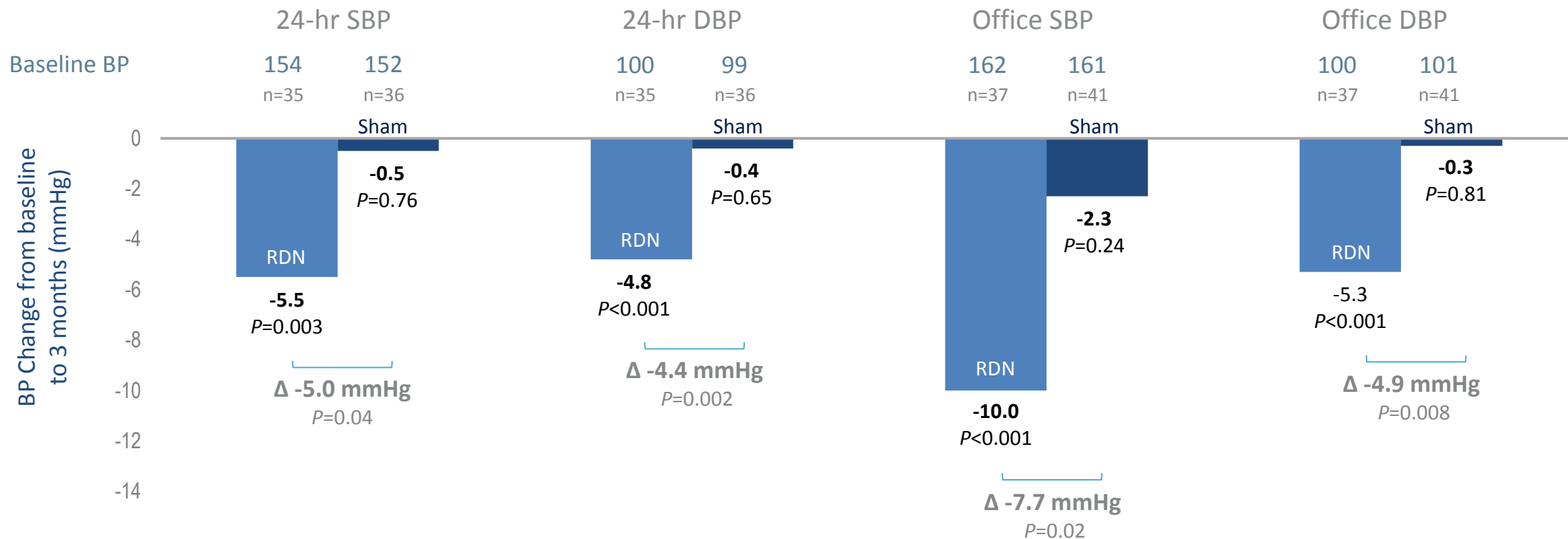
RANDOMIZED, SHAM-CONTROLLED TRIAL



¹Only for patients discontinuing anti-hypertensive medications. ²According to scheduling. ³Phone follow-up is required at 6 and 10 week visits. ⁴Drug testing. ⁵Med titration every 2 weeks until OSBP < 140
Kandzari D, et al. Am Heart J. 2016;171:82-91

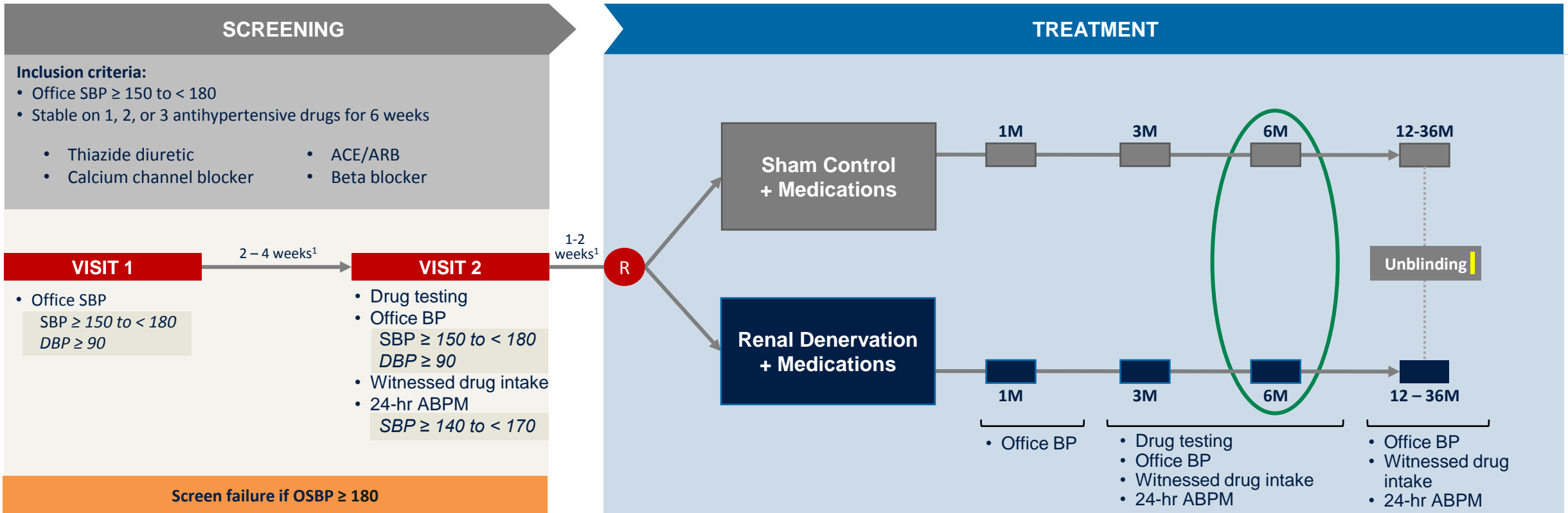
RDN ASSOCIATED WITH SIGNIFICANT REDUCTION IN ALL BP MEASURES AT 3-MONTHS

SPYRAL HTN-OFF MED BLOOD PRESSURE CHANGE FROM BASELINE



SPYRAL HTN ON MEDS STUDY DESIGN

- Randomized, sham-controlled, (patient and assessor) blinded, proof-of-concept trial
- 25 sites in Germany, UK, Austria, Greece, Japan, Australia and USA



¹According to scheduling
 Clinicaltrials.gov NCT02439775
 Kandzari D, et al. *Am Heart J.* 2016;171:82-91

SPYRAL HTN ON MEDS BASELINE BLOOD PRESSURE

Mean ± SD	RDN (N = 38)	Sham Control (N = 42)
Office measurements		
Office SBP (mm Hg)	164.6 ± 7.1	163.5 ± 7.5
Office DBP (mm Hg)	99.6 ± 6.9	102.7 ± 8.0
Office heart rate (bpm)	75.6 ± 11.8	73.5 ± 10.4
24-hour measurements		
Mean 24-hour SBP (mm Hg)	152.1 ± 7.0	151.3 ± 6.8
Mean 24-hour DBP (mm Hg)	97.2 ± 6.9	97.9 ± 8.4
Mean 24-hour heart rate (bpm)	75.3 ± 11.3	75.6 ± 10.7

P = NS for differences in all baseline measurements

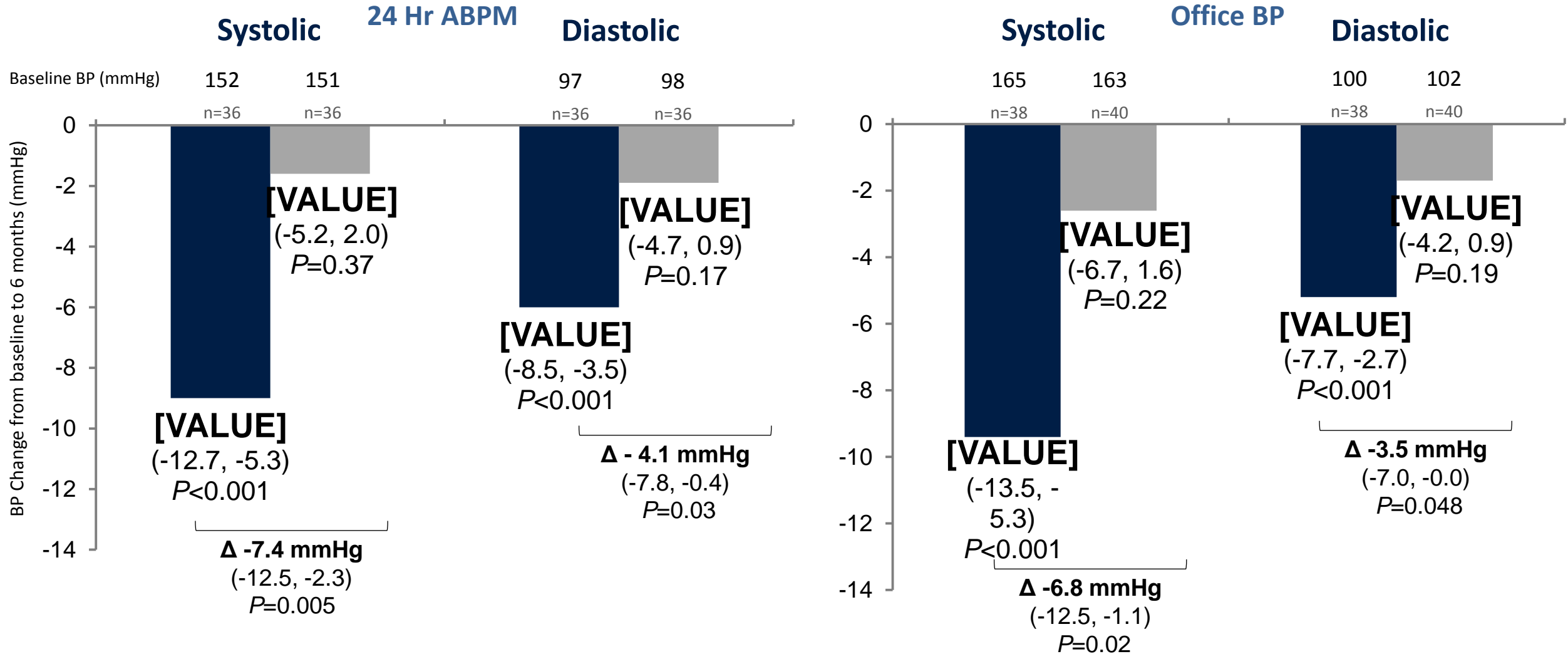
SPYRAL HTN ON MEDS BASELINE MEDICATIONS

	RDN (N = 38)	Sham Control (N = 42)
Number of anti-hypertensive medication classes		
Mean ± SD	2.2 ± 0.9	2.3 ± 0.8
Prescribed medication classes		
1	28.9 (11)	21.4 (9)
2	18.4 (7)	26.2 (11)
3	52.6 (20)	52.4 (22)
Medication class		
Thiazide diuretic	57.9 (22)	59.5 (25)
Calcium channel blocker	71.1 (27)	73.8 (31)
ACE-I/ARB	81.6 (31)	83.3 (35)
Beta blocker	10.5 (4)	14.3 (6)

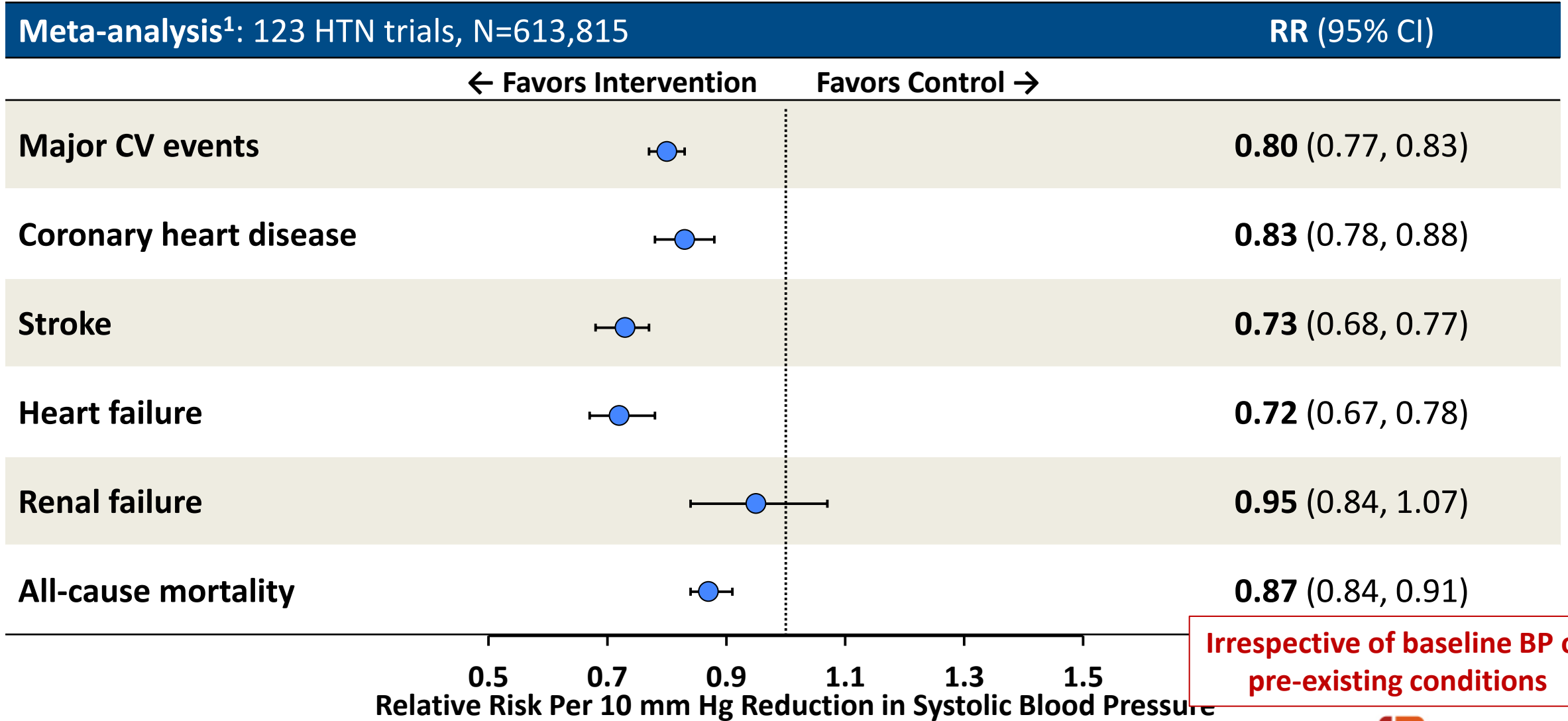
P = NS for differences in all baseline medications

SPYRAL HTN ON MEDS

24 HR AND OFFICE BLOOD PRESSURE CHANGE

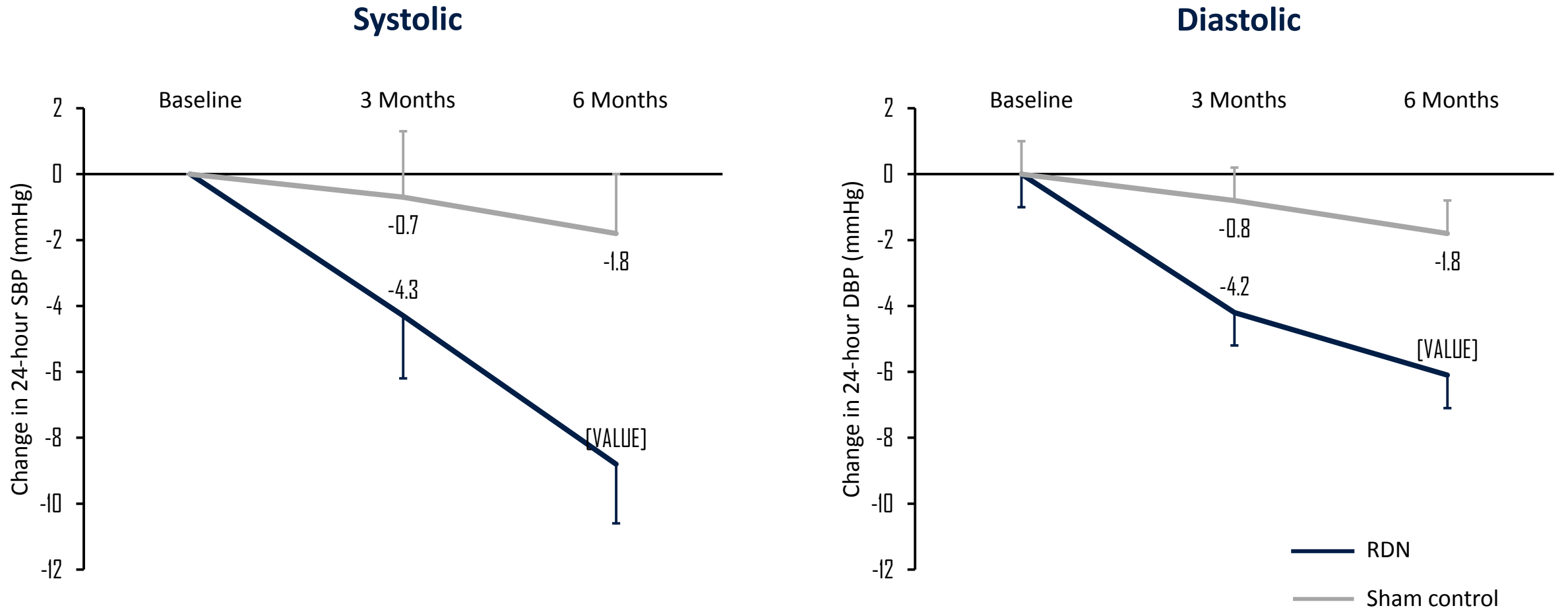


RISK REDUCTION FOR A 10 MM HG FALL IN OFFICE SYSTOLIC BLOOD PRESSURE



SPYRAL HTN ON MEDS

24 Hr ABPM Progressive Decline from Baseline to 6 Months

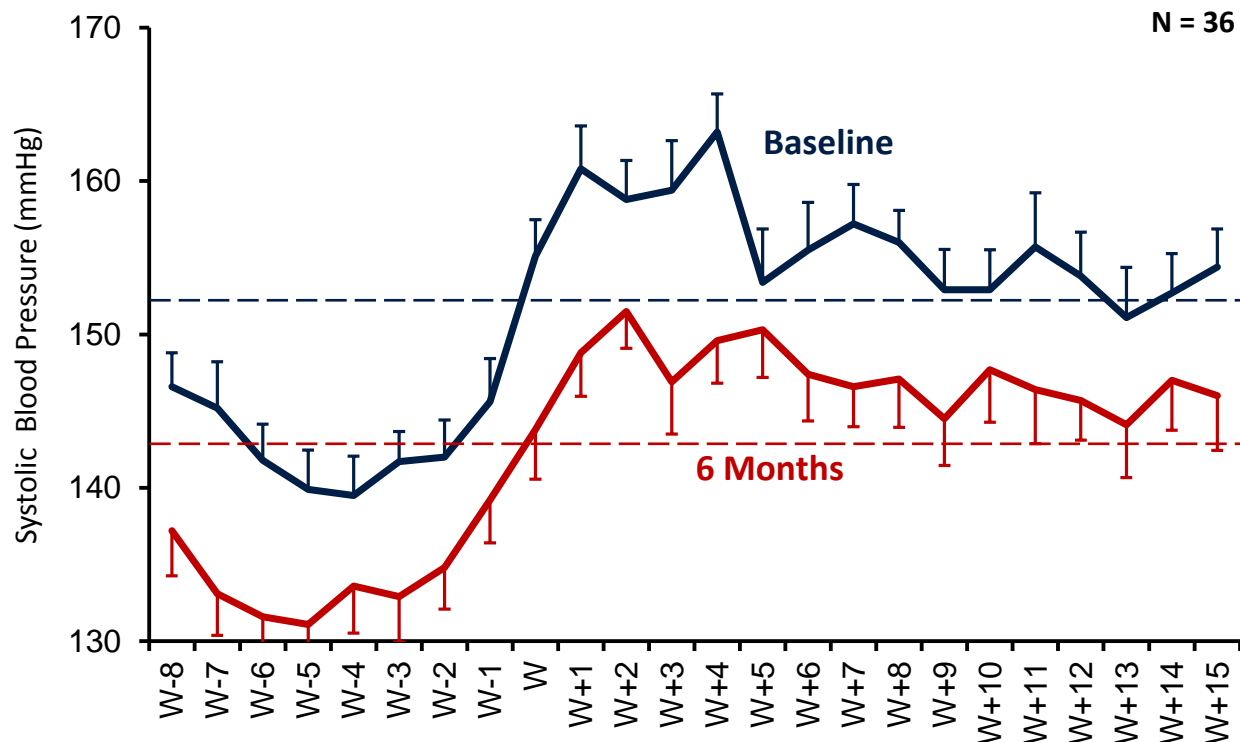


ANCOVA adjusted analysis

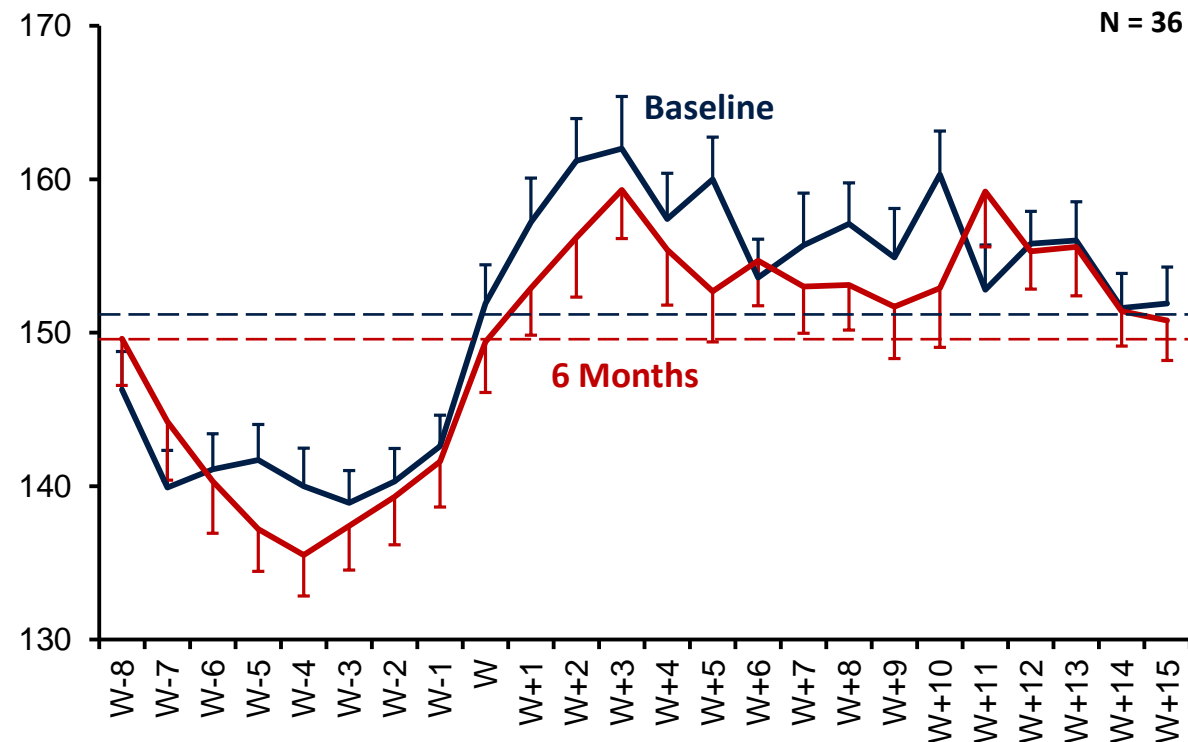
SPYRAL HTN ON MEDS

24 Hr ABPM

RDN



Sham Control



Dashed line represents the 24-hr mean at baseline (blue) and 6 months (red)
 W = Self reported wake time or 7:00 AM if not reported

RDN SAFETY: SPYRAL ON and OFF MEDS

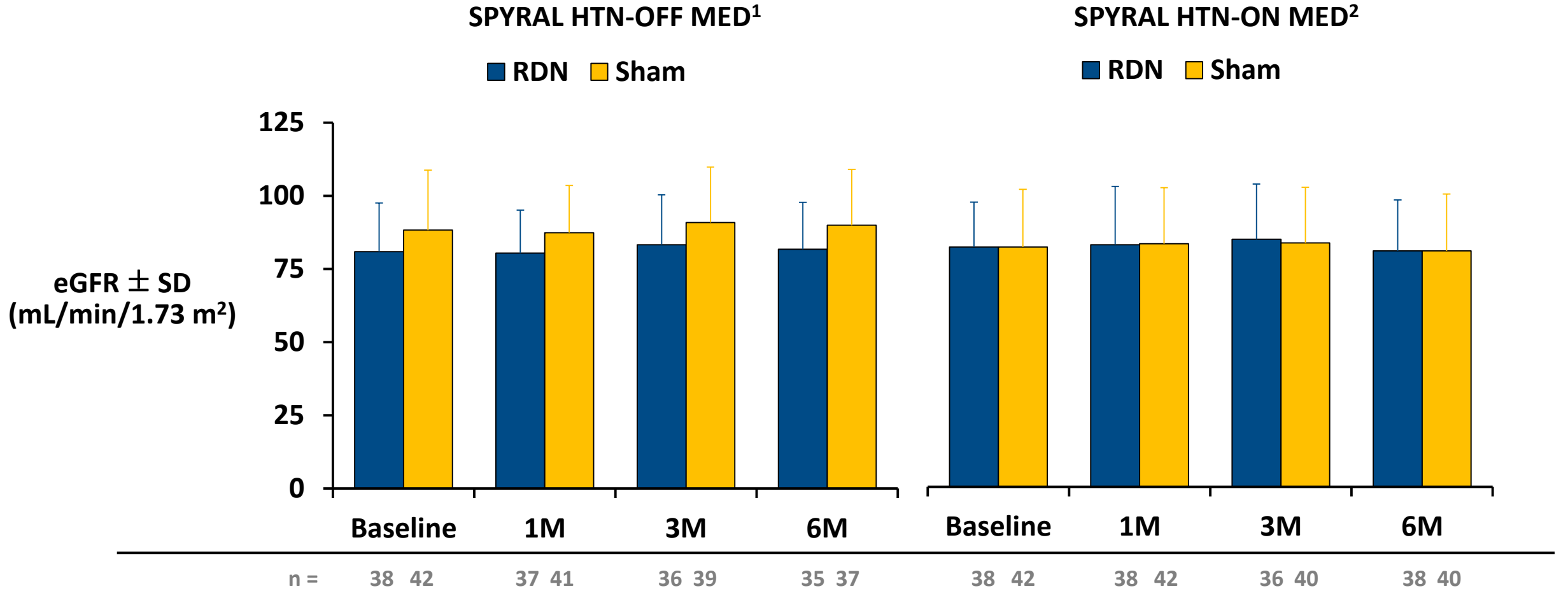
NO MAJOR ADVERSE EVENTS IN TWO PILOT TRIALS

	OFF MED PILOT STUDY 3M POST-PROCEDURE		ON MED PILOT STUDY 3M & 6M POST-PROCEDURE	
Major Adverse Events (%)	RDN (n = 38)	Sham Control (n = 42)	RDN (n = 38)	Sham Control (n = 42)
Death	0	0	0	0
New myocardial infarction	0	0	0	0
Major bleeding (TIMI ¹)	0	0	0	0
New onset end stage renal disease	0	0	0	0
Serum creatinine elevation >50%	0	0	0	0
Significant embolic event resulting in end-organ damage	0	0	0	0
Vascular complications	0	0	0	0
Hospitalization for hypertensive crisis/emergency	0	0	0	0
New stroke	0	0	0	0
New renal artery stenosis > 70%			0	0

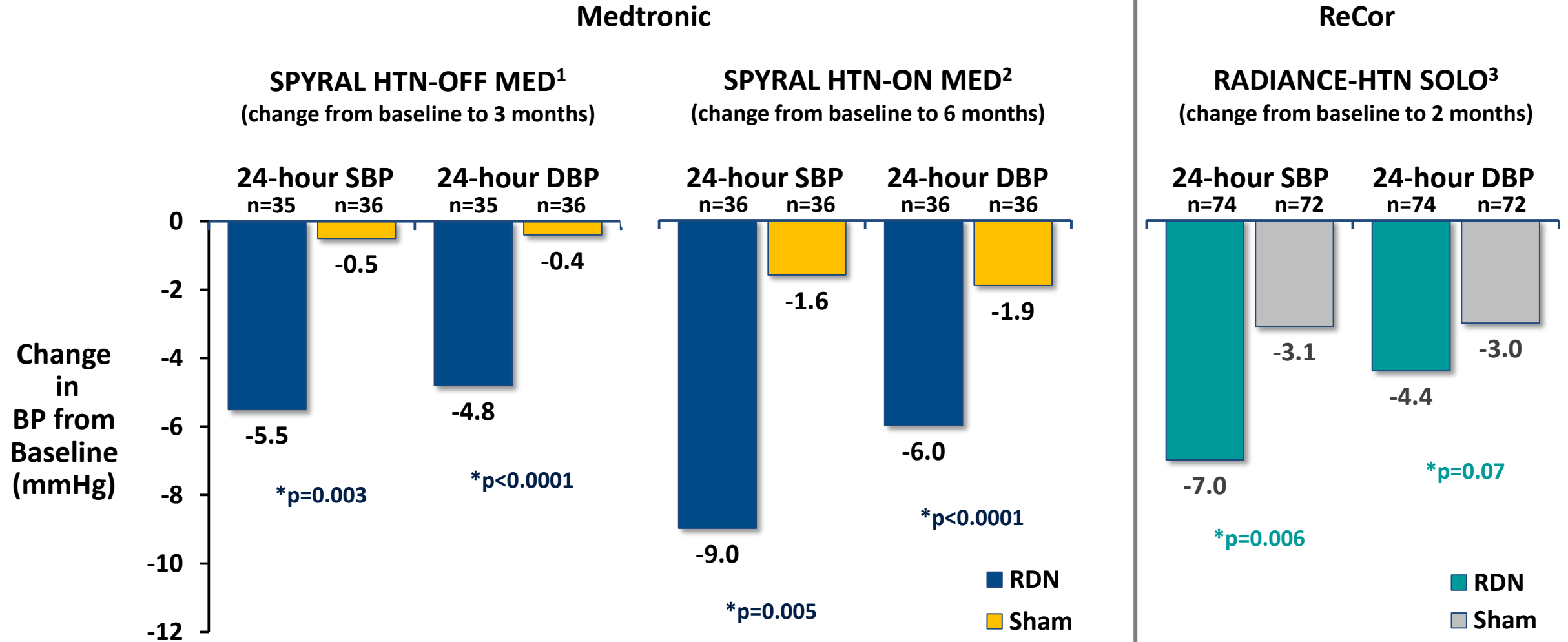
1. Townsend R, et al. Lancet. 2017;390:2160-2170; 2. Kandzari D, et al. Lancet. 2018;391:2346-2355

3. 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 procedure.

No Difference in Renal Function Difference through 6 Months



Blood Pressure Reduction in 3 Sham-Controlled Studies



* Between group difference

1. Townsend R, et al. Lancet. 2017;390:2160-2170; 2. Kandzari D, et al. Lancet. 2018;391:2346-2355 3. Azizi M, et al. Lancet. 2018;391:2335-2345

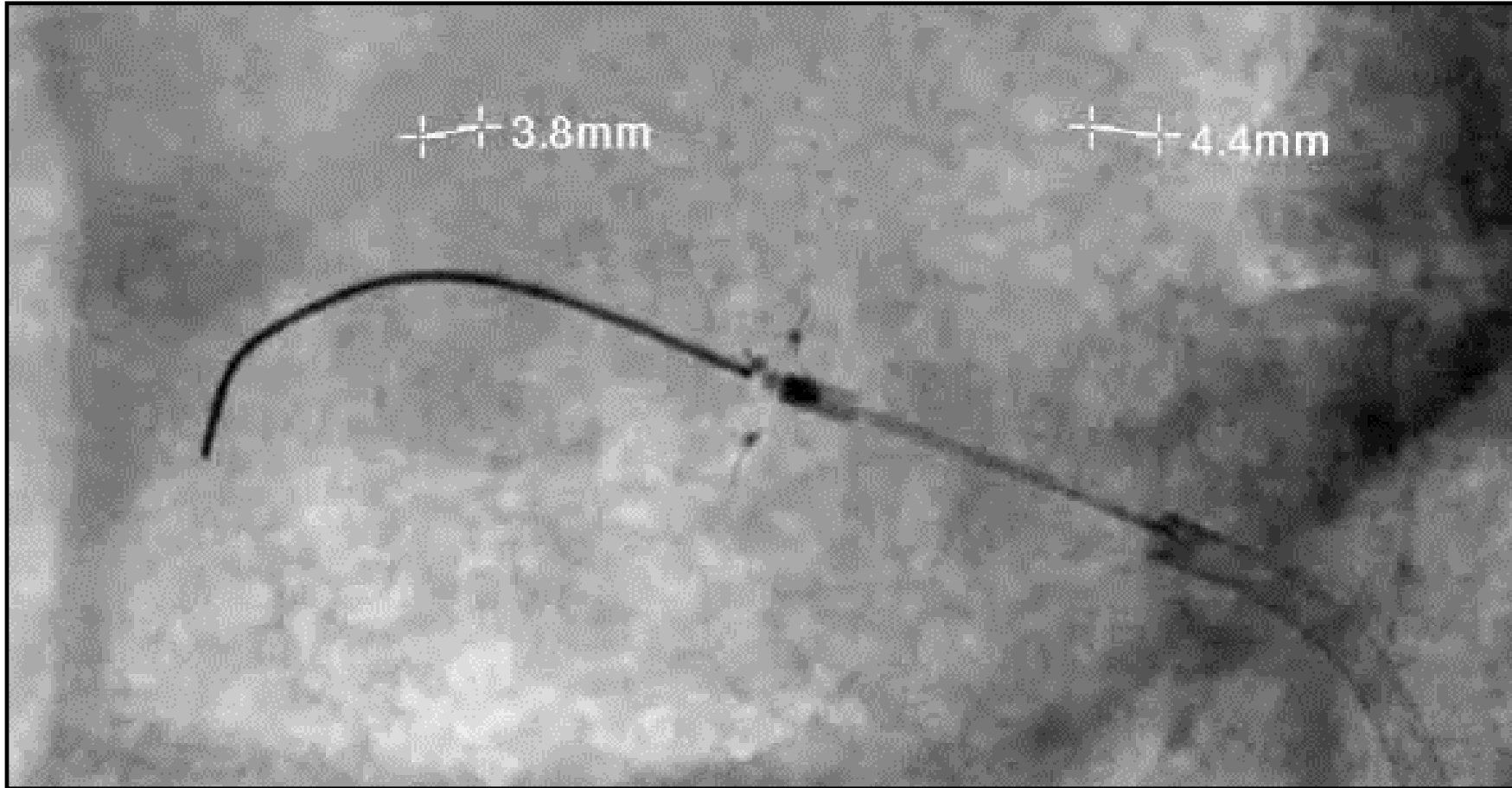
Ablative Solutions

Alcohol Delivery Using The Peregrine Catheter in the Renal Artery Perivascular Space



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Alcohol Delivery Using The Peregrine Catheter in the Renal Artery Perivascular Space



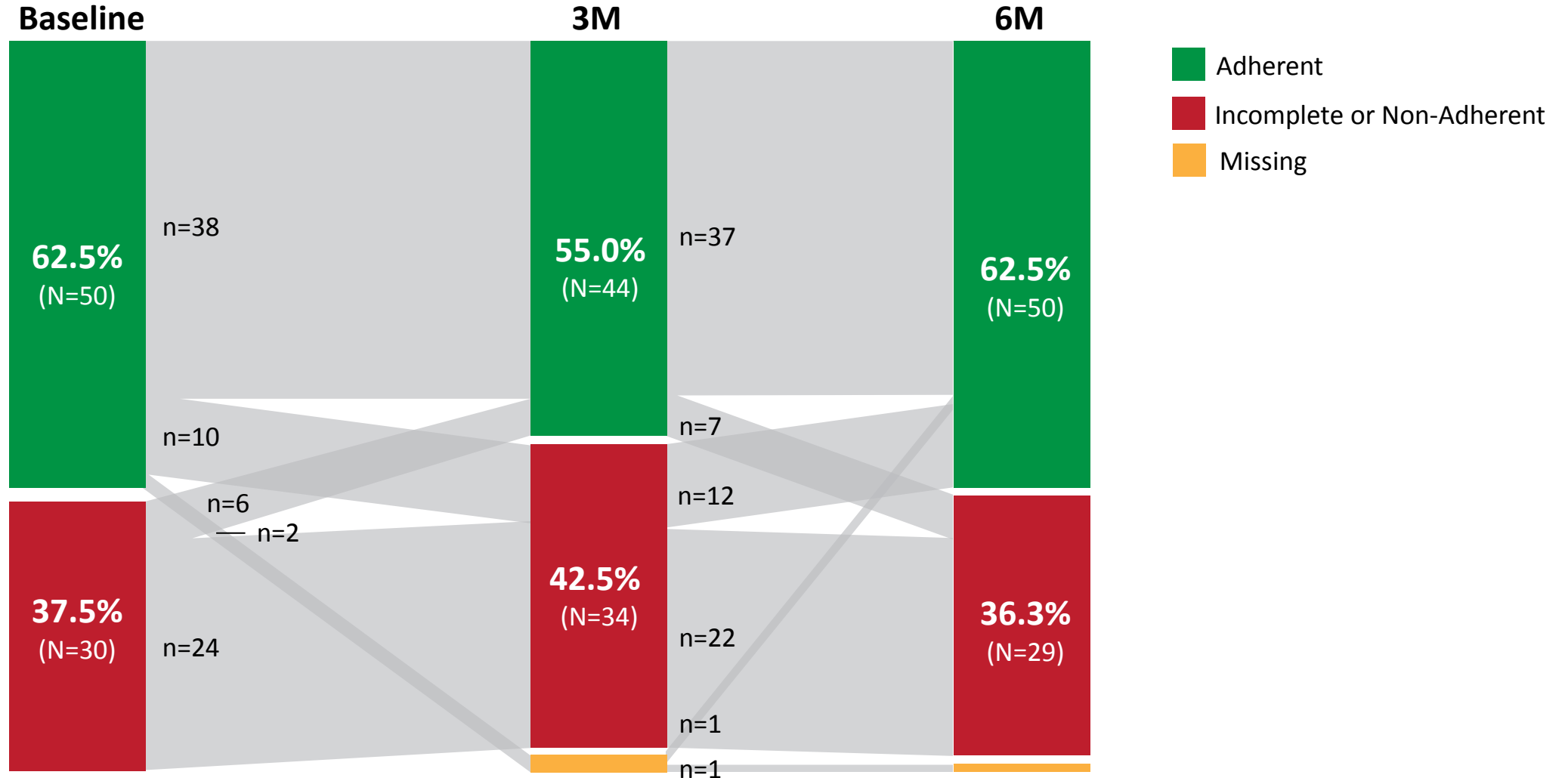


“...there are also unknown unknowns—the ones we know we don’t know. And if one looks throughout history...it is the latter category that tend to be the difficult ones.”

— Donald Rumsfeld

SPYRAL HTN ON MEDS

MEDICATION ADHERENCE

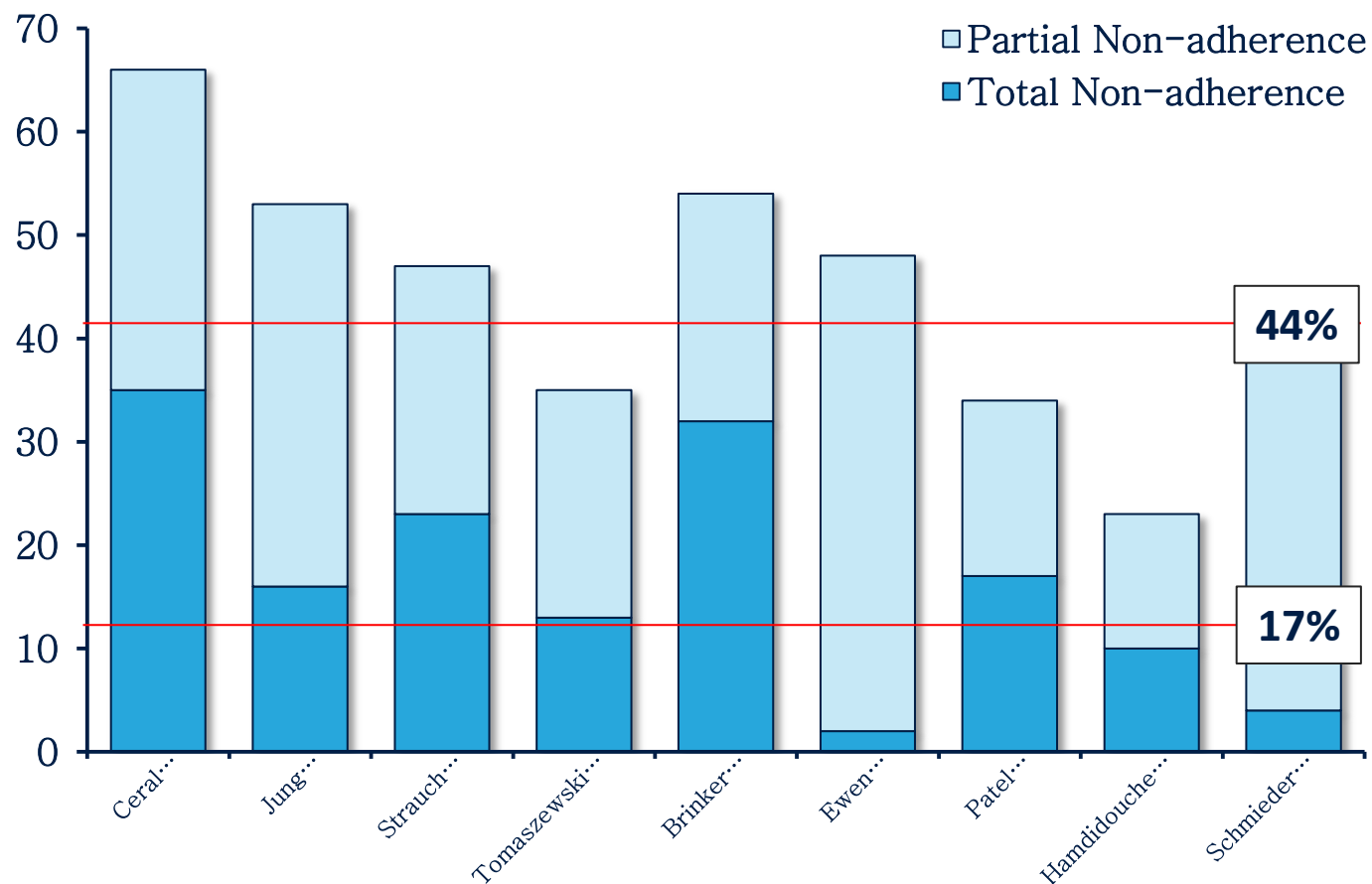
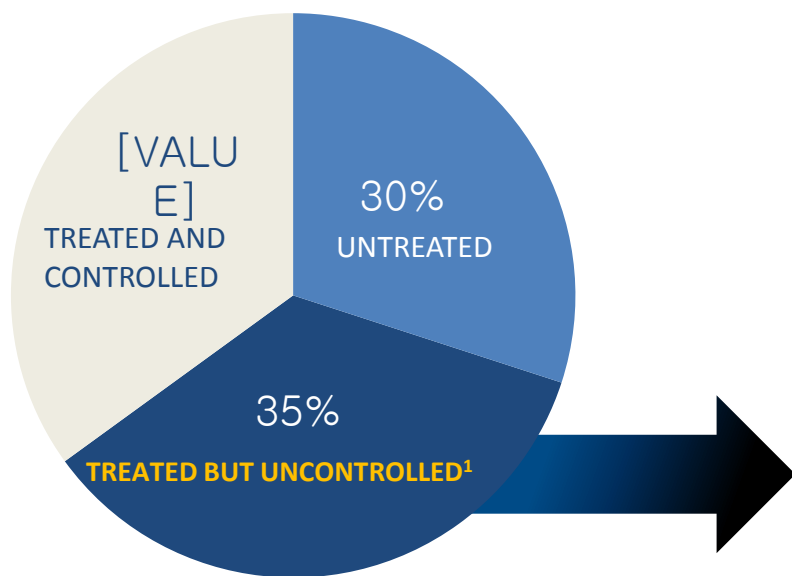


Drug testing of urine and serum by tandem HPLC and mass spectroscopy. Medication adherence defined as detectable levels of all prescribed antihypertensive medications at each follow-up visit and includes cases in which an extra antihypertensive medication was also detected.

TREATMENT RESISTANT OR RESISTANT TO TREATMENT?

~50% ARE PARTIALLY ADHERENT WITHIN FIRST YEAR OF TREATMENT

Even with combination pills, studies show patients become non-adherent



Elena Berra et al. Hypertension. 2016;68:297-306
Bangalore et al. Am J Med. 2007 Aug;120(8):713-9.

Patient Preference For Pill vs Renal Denervation

Suppose your blood pressure is still too high, even though you have been taking medication for a long time. Your doctor advises you therefore to an additional treatment of your hypertension. *What would you rather choose, even if you have to continue to take all the tablets as before?*

	N=1011 Patients
I would rather take an additional tablet for the high blood pressure	71.8 %
I would opt for a single medical procedure using a catheter (ablation treatment) and not to have to take even more drugs	28.2 %

Patient Preference Study



US-based trial



Up to 300 participants from approximately 15 non-SPYRAL HTN study sites



MDT is partnering with an external expert in the construct and conduct of patient preference studies



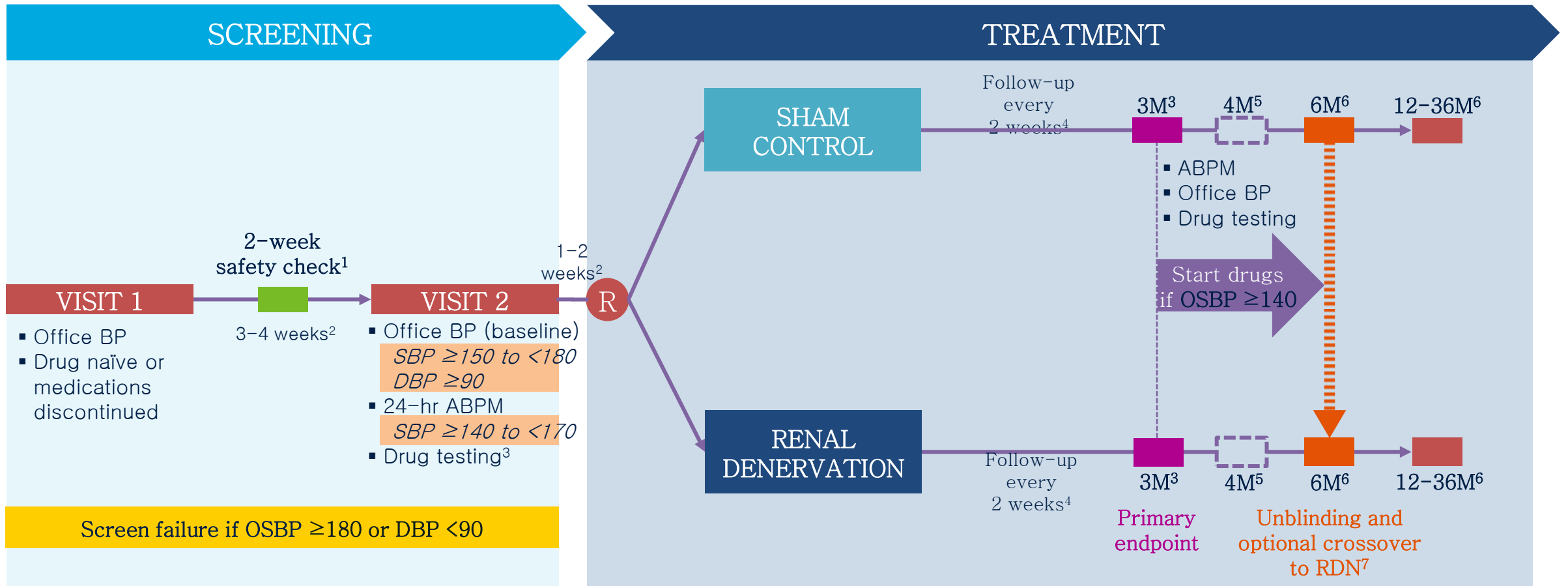
Patient population aligns similarly with the SPYRAL HTN trials



Conducted via an online questionnaire of discrete choices leading to answer-identified attributes, in a manner to avoid bias to one treatment option over the other

SPYRAL HTN PIVOTAL

RANDOMIZED, SHAM-CONTROLLED TRIAL



¹Only for patients discontinuing anti-hypertensive medications. ²According to scheduling. ³Drug testing to ensure no medications are present. ⁴Optional follow up at weeks 6 and/or 10 if the patient is not controlled. ⁵Only for patients with BP ≥ 140 mmHg at 3M. ⁶Drug testing to ensure prescribed medications are present (if on drug). ⁷6 and 12 month renal imaging.

SPYRAL HTN-ON MED RCT

Study Design

	ON-MED Feasibility	ON-MED RCT
Geography Expansion	25 sites max. in US, Europe, Australia, Japan	55 sites in US, Europe, Australia, Japan and Canada
Sample Size	Up to 110 Randomized/700 enrolled	Up to 340 Randomized/1600 enrolled
Primary Endpoints	ABPM and secondary OBP efficacy endpoints	Powered for ABPM
Randomisation	1:1 Randomization	2:1 Randomization
Crossover	Unblinding @ 12 months	Unblinding and Crossover @ 6 months
Renal Imaging	Duplex ultrasound imaging (6 months)	Duplex Ultrasound imaging (6 months) renal artery CTA or MRA imaging (12 months) <i>(min 50 and up to 340 subjects)</i>

Global SYMPLICITY Registry (GSR)

Clinical Trial Design

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



Follow-up	3M	6M	1Y	2Y	3Y
Follow-up eligible to date:					
Patients treated with Flex catheter		2232	2227	2204	2139
Patients treated with Spyral catheter		351	327	231	132

* Limited to resistant hypertension only

10% of patients are randomly assigned to 100% monitoring

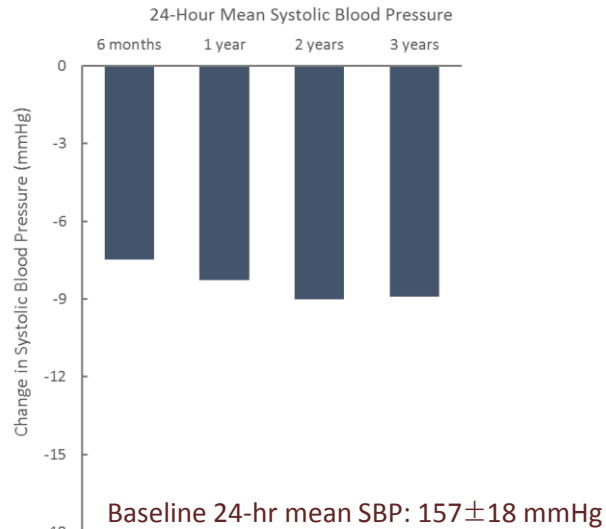
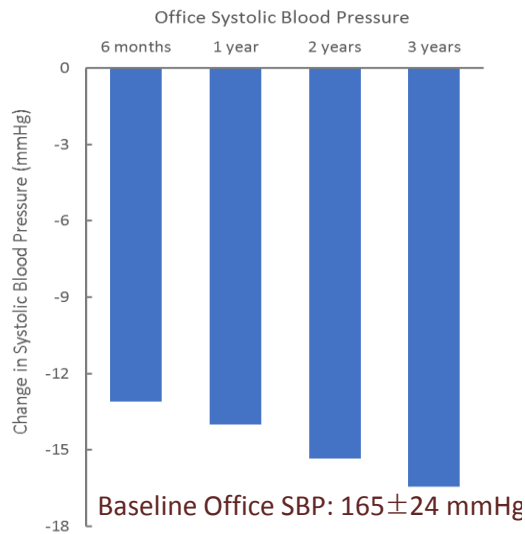
NCT01534299

Böhm M, Hypertension 2015

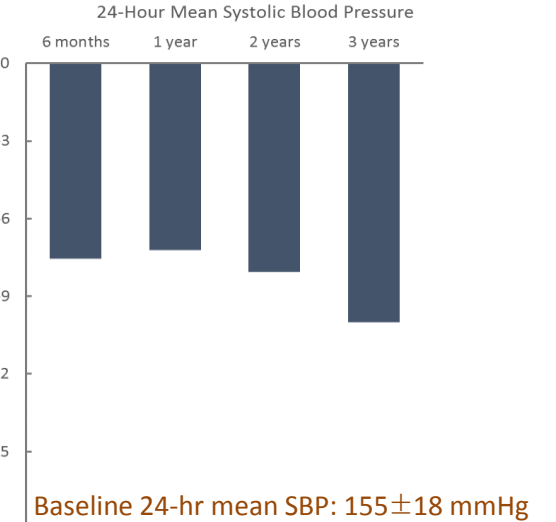
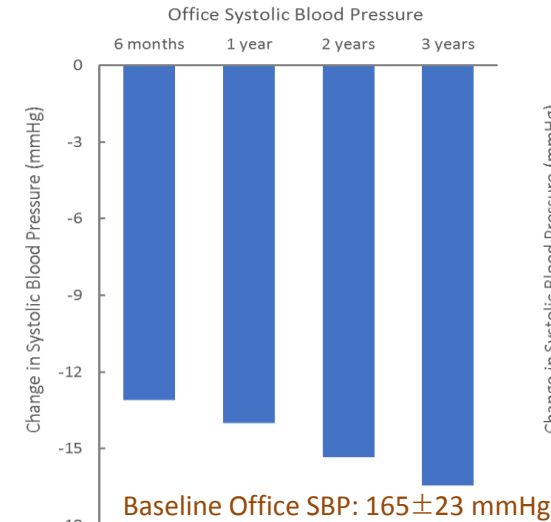
Renal Denervation Therapy: Formulating a Reimbursement Model

Global Symplicity Registry: Real World and High Risk Experience and Durability

Overall: N=2,583

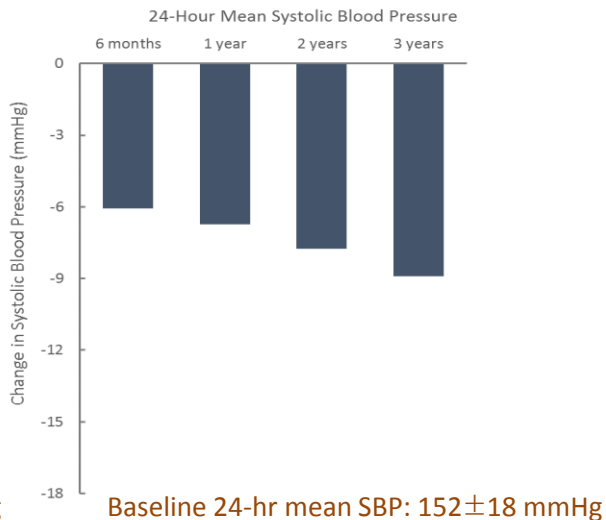
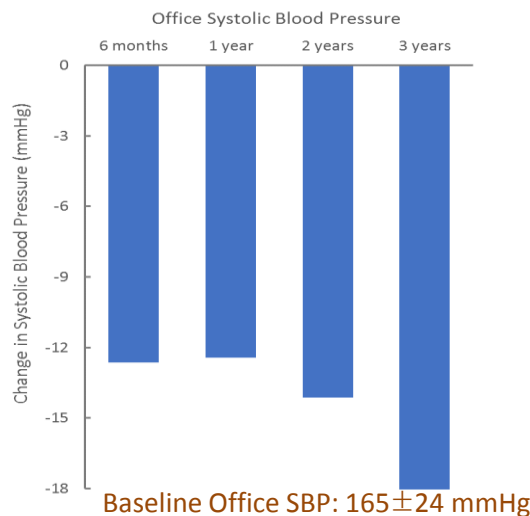


Type 2 Diabetes: N=985

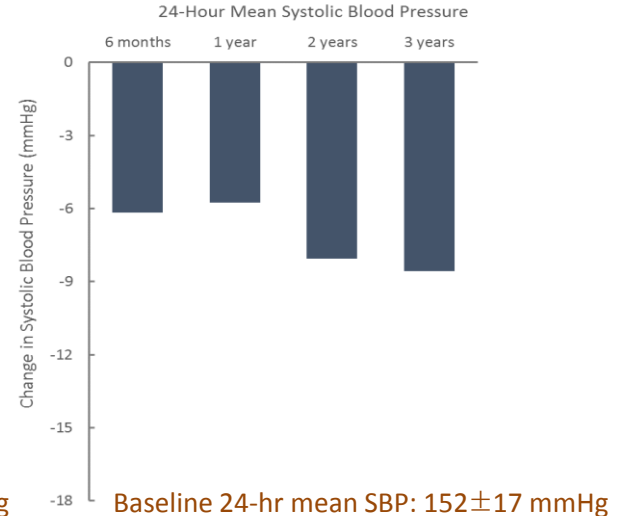
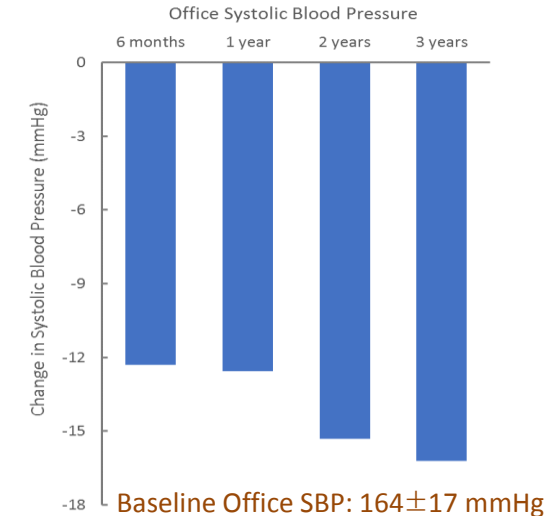


$P < 0.001$ for all vs. Baseline

Age ≥ 65 years: N=1,073



ISH: N=969



Next Steps in RDN Trials

Is RDN Ready for Clinical Practice?

- New US blood pressure guidelines motivated by increasing awareness of benefit with more intensive blood pressure control, abysmal levels of hypertension control, and epidemic non-adherence to antihypertensive medications identify the need for non-drug treatment options
- Renal denervation results in **statistically significant and clinically relevant blood pressure reductions** at 6 months
 - In **uncontrolled hypertensive** patients compared with sham control
 - In the **absence and presence** of commonly prescribed anti-hypertensive medications
- Blood pressure after renal denervation **continued to decrease** between 3 and 6 months
- Blood pressure reductions following renal denervation were present **throughout the day and night** (“always on” effect)
- **No major safety events across studies** despite a more complete denervation procedure that includes extension into renal artery branch vessels
- **SPYRAL HTN PIVOTAL trial in an OFF MEDS population in addition to ON MEDS trial are underway**
 - Trials will further inform the safety and effectiveness of RDN modalities for the treatment of uncontrolled hypertension
 - Future directions include patient reported health status and preference and continued real world surveillance