Symplicity Spyral™ Renal Denervation System to Treat Patients with Hypertension

August 23, 2023

Medtronic

Circulatory System Devices Panel

Introduction

Laura Mauri, MD

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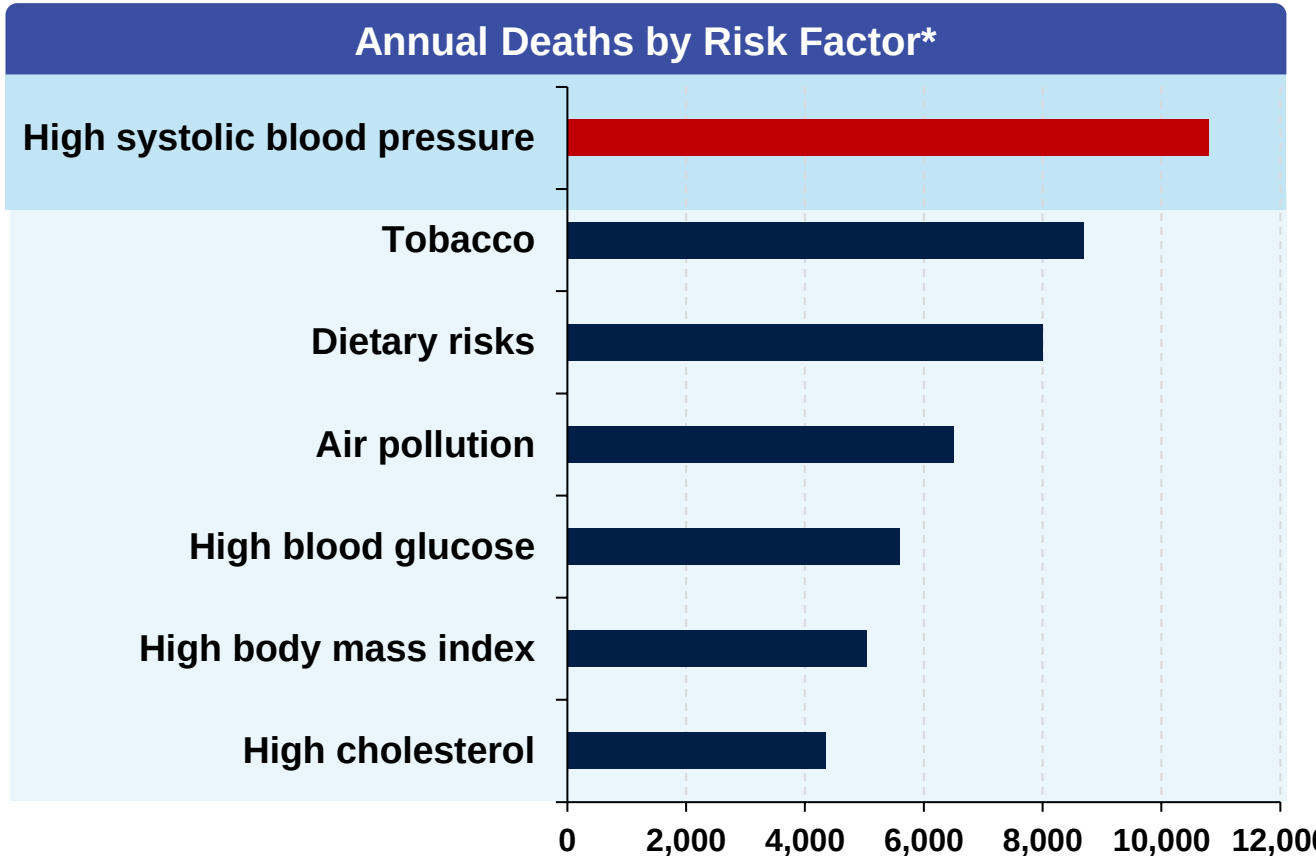
Medtronic

Hypertension is a Global Health Crisis

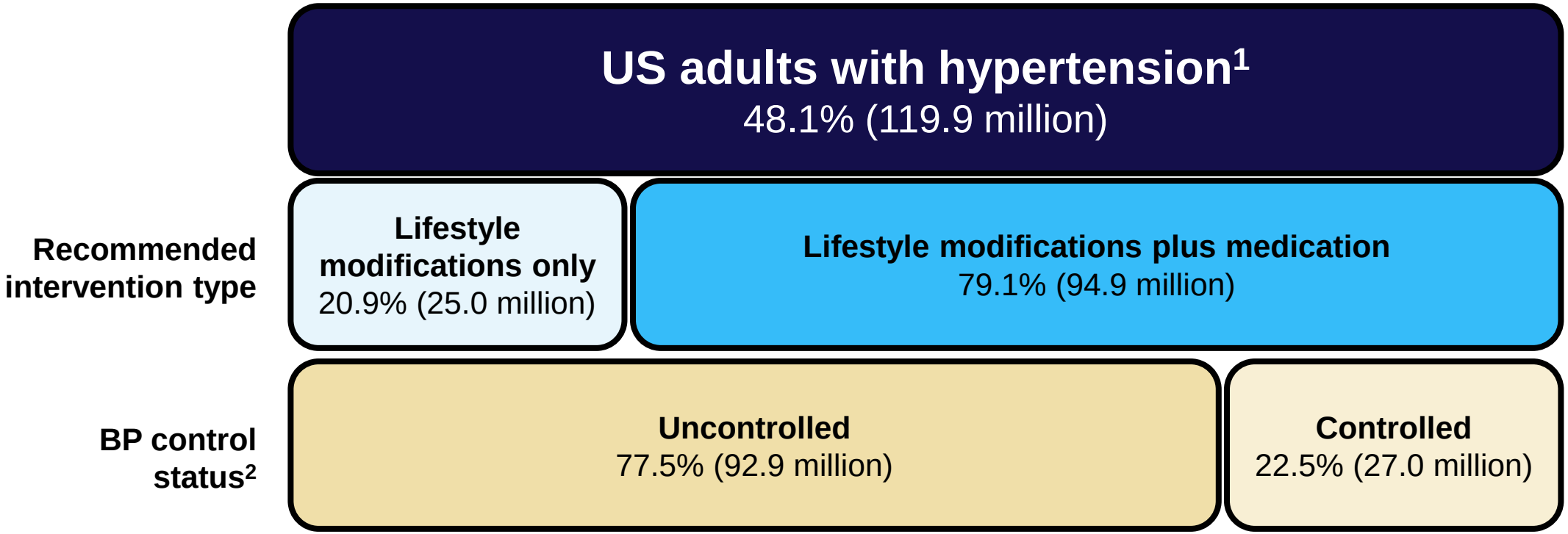
- Leading modifiable risk factor associated with disability and death[1]
- Leads to end organ damage[2]
  - Heart attack
  - Stroke
  - Renal failure
- Impacts underserved communities[3]



1. GBD 2019 Risk Factors Collaborators; *Lancet* 2020
2. Whelton, *Circulation* 2018
3. Whelton, *Hypertension* 2018

Adapted from Lancet 2020
*Including all age groups and both sexes, 2019

Unmet Need for US Patients with Hypertension

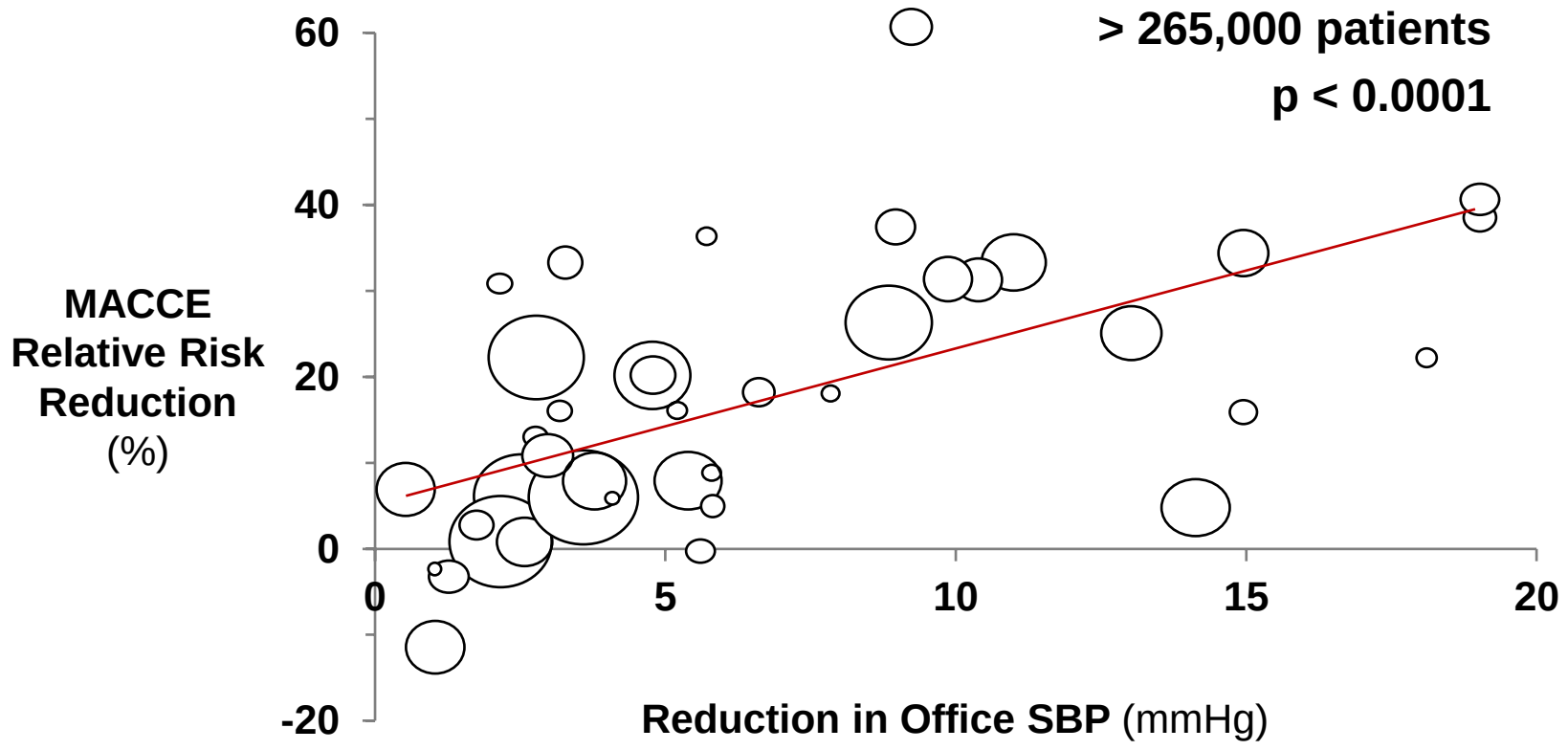


- **Annual Deaths = 700,000** (primary or contributing cause)

CDC (Based on NHANES 2019-2020)
1. BP ≥ 130/80 mmHg or currently using prescription to lower BP; 2. Controlled is defined as having a BP < 130/80 mmHg. All adults recommended lifestyle modifications only are considered uncontrolled as their BP is above the threshold.

Meta-Regression of Drug Trials Shows Lowering Blood Pressure Reduces Cardiovascular Risk

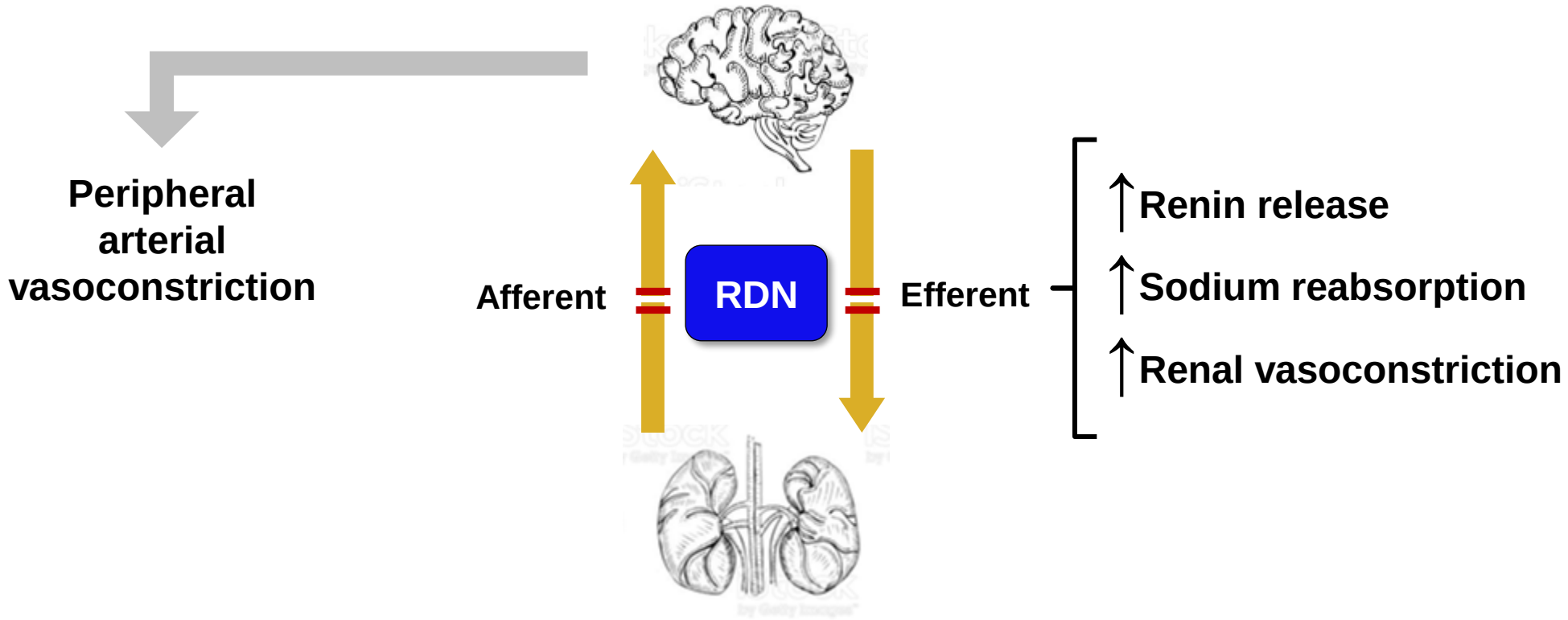
Each 5-mmHg reduction in office SBP corresponds to a 10% reduction in CV events



Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2021; Ettehad D, et al. *Lancet*. 2016
MACCE = fatal and non-fatal myocardial infarction, sudden cardiac death, revascularization, fatal and non-fatal stroke, and fatal and non-fatal heart failure

Mechanism of Renal Denervation

RF RDN modulates renal sympathetic nerve activity to reduce blood pressure. Modulation of renal nerve activity occurs throughout a 24-hour period.



Symplicity Spyral System

Self-expanding
Catheter with
4 Electrodes

G3
Generator

Connector

Straightening
Tool

Wire Exchange Port

Intermediate Bond

Femoral Marker

Catheter Handle

Symplicity Spyral System – Efficient and Simple Method of Performing Renal Denervation

- Consistent deployment
- Responsive power control algorithm using real time temperature and impedance feedback
- 6 French compatible catheter
- Standard 0.014 guidewire
- Conforms to renal artery without occluding blood flow
- Helical ablation pattern
- Treats arteries 3 - 8 mm diameter
- Energy delivery automatically controlled by generator
- Catheter repositioned for contralateral ablation
- Ablation in distal portion of main renal artery and branch segments
- Overall procedure time ~1 hour

SPYRAL HTN Clinical Program Design Considerations

- Designed to assess the safety and BP lowering effect of RDN
- Incorporated device, procedure and trial conduct learnings from HTN-3
- Monitored anti-hypertensive drug use post-randomization
- OFF MED:
  - Enrolled patients not on anti-hypertensive medications at screening or washed out prior to randomization
  - Isolates effect of RDN
  - Consistent with placebo-controlled pharmaceutical trial designs
- ON MED:
  - Confirms impact of RDN in presence of medications
  - Recommendation to keep medications unchanged
- Essential to evaluate totality of data across studies

SPYRAL HTN Global Clinical Program

Randomized, Controlled Studies

Studies in ABSENCE of anti-hypertensive medications

OFF MED Pilot

N = 80

→

OFF MED Pivotal Study

N = 331
(Pilot + Expansion)

Studies in PRESENCE of anti-hypertensive medications

ON MED Pilot

N = 80

→

ON MED Study

N = 337
(Pilot + Expansion)

Additional Evidence

Patient Preference Study

N = 400
Discrete choice experiment

Global SYMPLICITY Registry

N > 3,400 (~800 Spyral)
Real-world evidence on safety and durability

Proposed Indication

The Symplicity Spyral™ multi-electrode renal denervation catheter and the Symplicity G3™ RF Generator are indicated for the reduction of blood pressure in patients with uncontrolled hypertension despite the use of anti-hypertensive medications or in patients in whom blood pressure lowering therapy is poorly tolerated.

Benefit-Risk Profile

Radiofrequency RDN complements established treatment options for hypertension management

Unmet Need

- Hypertension is the leading modifiable risk factor associated with CV events and death
- > 75% of U.S. patients' BP remains uncontrolled
- Many patients are interested in additional treatment options

Efficacy

- Provides clinically meaningful and sustained BP reduction compared to baseline
  - On medication
  - Off medication
- Continuous BP reduction throughout 24-hour period

Safety

- Excellent short and long-term safety, incl:
  - Procedural safety
  - Renal artery patency
  - Maintaining kidney function

Agenda

Unmet Need	**Raymond Townsend, MD** Professor of Medicine and Co-Director of Hypertension Section University of Pennsylvania School of Medicine
Efficacy Results	**David Kandzari, MD** Chief, Piedmont Heart Institute and Cardiovascular Services Director, Interventional Cardiology, Piedmont Heart Institute Chief Scientific Officer, Piedmont Healthcare
Safety and Durability	**Felix Mahfoud, MD** Professor of Medicine and Deputy Director of Cardiology Saarland University Hospital
Clinical Perspective	**Raymond Townsend, MD**
Moderator for Q&A	**Vanessa DeBruin, MS** Senior Director of Clinical Research Medtronic

Additional Experts

Martin Fahy, MS
Senior Principal Biostatistician
Medtronic

Leisa Martinez
Senior Director Regulatory Affairs
Medtronic

Stefan Tunev, DVM
Senior Distinguished Scientist
Medtronic

Tim Hanson, PhD
Distinguished Statistician
Medtronic

Unmet Need

Raymond Townsend, MD

Professor of Medicine

Co-Director of Hypertension Section

University of Pennsylvania School of Medicine

First-Line Therapies for HTN

Lifestyle Modifications

- Healthy diet (DASH)
- Weight loss
- Physical activity
- Limiting alcohol
- Ensuring sufficient sleep

Anti-hypertensive Medications

- ACE inhibitors
- ARBs
- Calcium channel blockers
- Diuretics

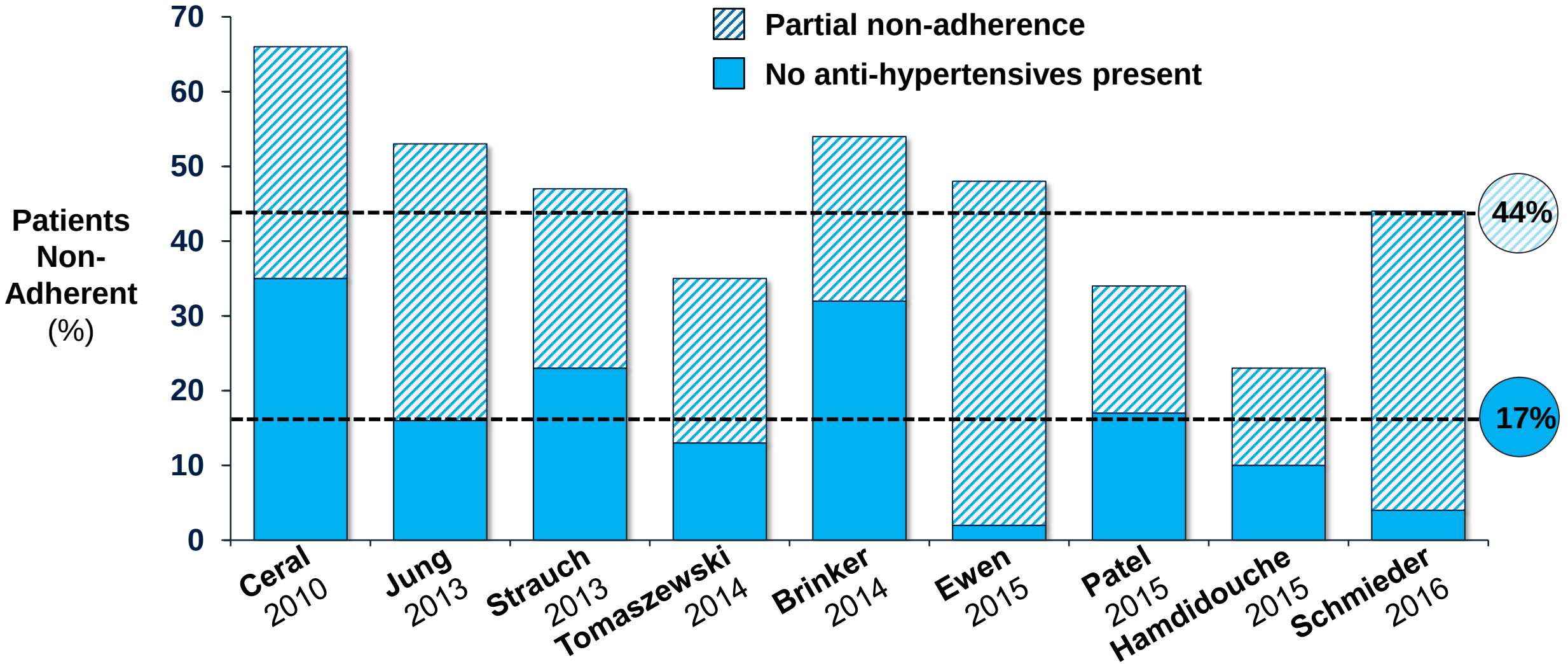
ACE = Angiotensin-converting enzyme, ARBs = Angiotensin receptor blockers

Whelton, *Circulation* 2018

Limitations of Anti-hypertensive Medications

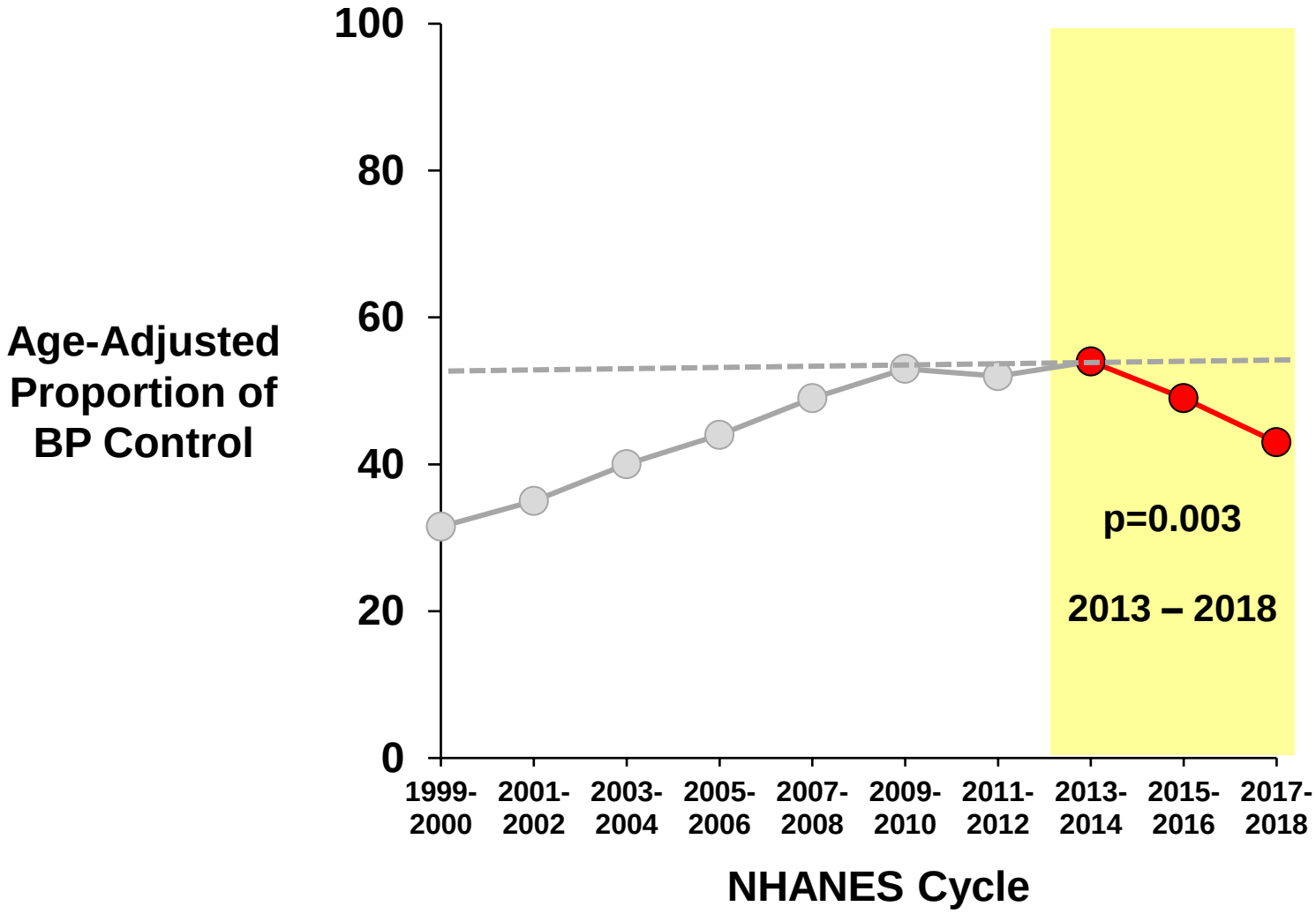
- Suboptimal and dynamic adherence
  - Strict adherence difficult to maintain long term
  - Drug side effects (cough, fatigue, impotence, ankle swelling, polyuria)
- Inability to predict responders
- Modest BP changes for added drugs

Medication Adherence is Low



Berra, *Hypertension* 2016

Hypertension Control Rates in United States are Declining Since 2013



Muntner, *JAMA* 2020

NHANES = National Health and Nutrition Examination Survey

Medtronic Patient Preference Study

Randomized, Controlled Studies

Studies in ABSENCE of anti-hypertensive medications

OFF MED Pilot	OFF MED Pivotal Study
N = 80	N = 331 (Pilot + Expansion)

Studies in PRESENCE of anti-hypertensive medications

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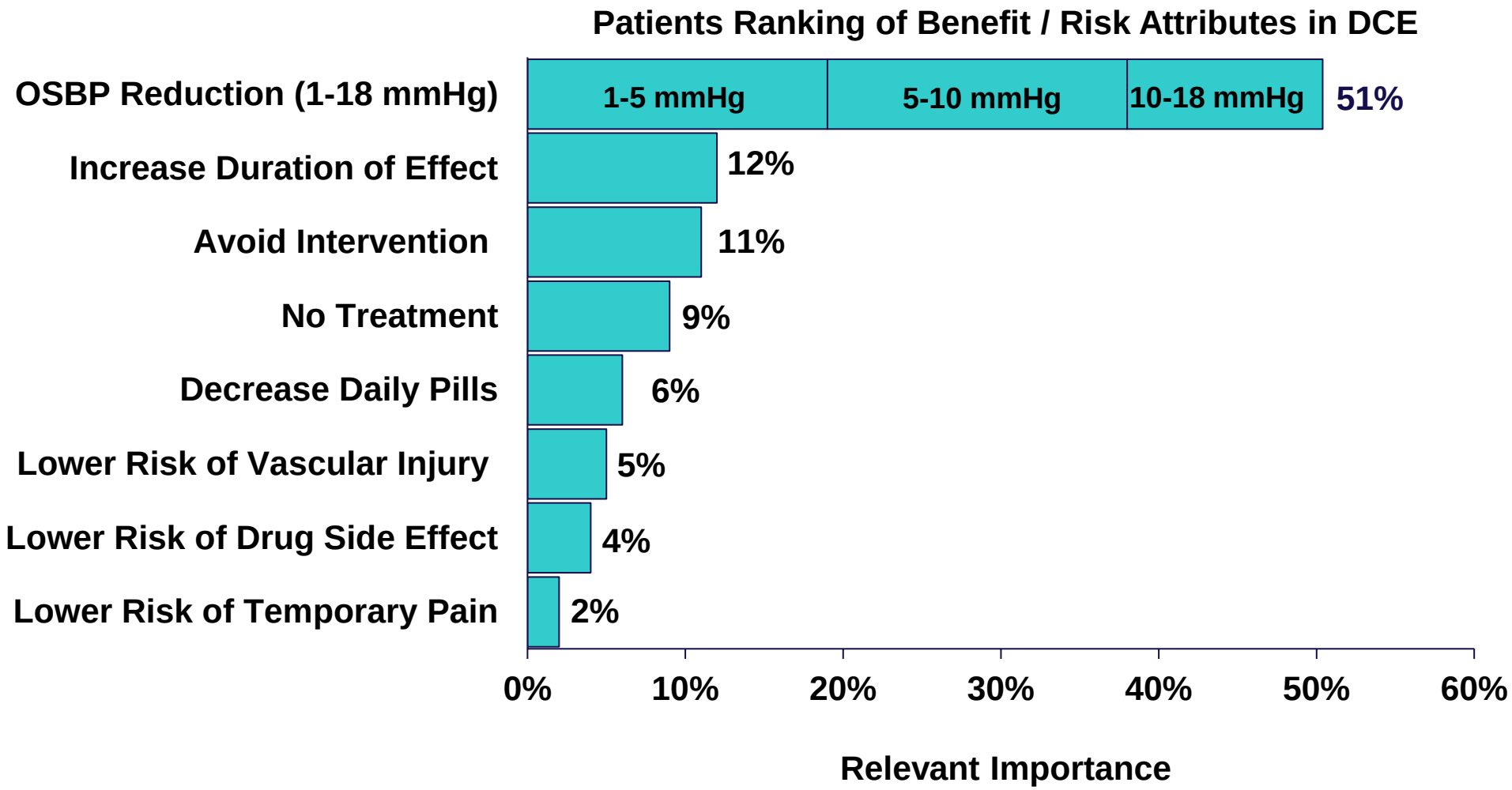
Medtronic Patient Preference Study to Assess Patient Perspective

- Discrete Choice Experiment (DCE) to quantify patient preferences for key treatment attributes of pharmaceutical and interventional treatments for HTN
- 400 US patients on 0-3 meds with physician-confirmed HTN from non-SPYRAL HTN study sites
- Quantify weights for attributes relating to treatment method, efficacy and safety
- Applied weights to different HTN profiles (eg, ON MED, OFF MED) to model patient preference for RDN

Patient Preference Study Results: BP Reduction Most Important



Kandzari, *Circ Cardiovasc Qual Outcomes* 2023

Patient Preference Study: Key Findings

- BP reduction was the most important driver of patient preference for treating hypertension
- Model was developed to predict percent of patients who would choose one treatment over another
- Applying BP reductions and risks from OFF and ON MED studies, up to 31% of patients would choose interventional treatment to manage hypertension

Kandzari, *Circ Cardiovasc Qual Outcomes* 2023

Unmet Need Conclusions

- Current treatment options are inadequate as many patients remain uncontrolled
- Patients are interested in complementary solutions
- BP reduction was the most important driver of patient preference
- Up to 31% of patients likely to select interventional treatment to help manage hypertension (eg, RDN)

Efficacy

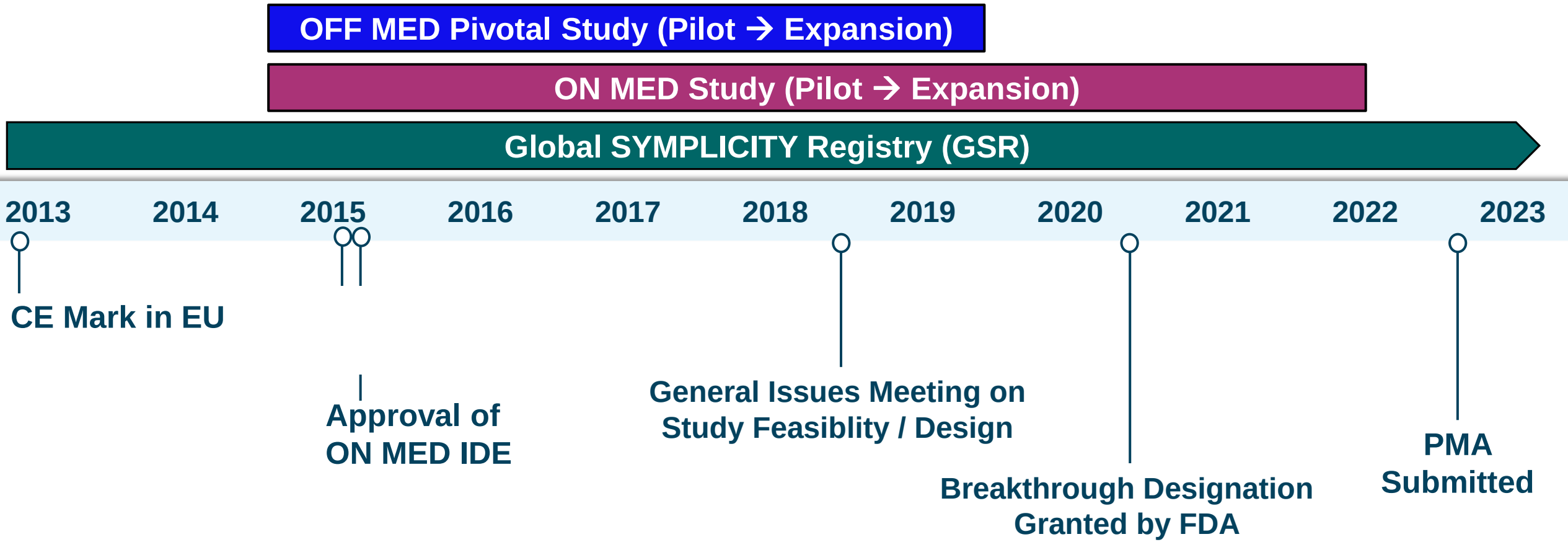
David Kandzari, MD, FACC, FSCAI

Chief, Piedmont Heart Institute and Cardiovascular Services

Director, Interventional Cardiology, Piedmont Heart Institute

Chief Scientific Officer, Piedmont Healthcare

Symplicity Spyral Program History



Approved, used, and considered clinically in continuum of care in 70 total countries worldwide

SPYRAL HTN-OFF MED Pivotal Study

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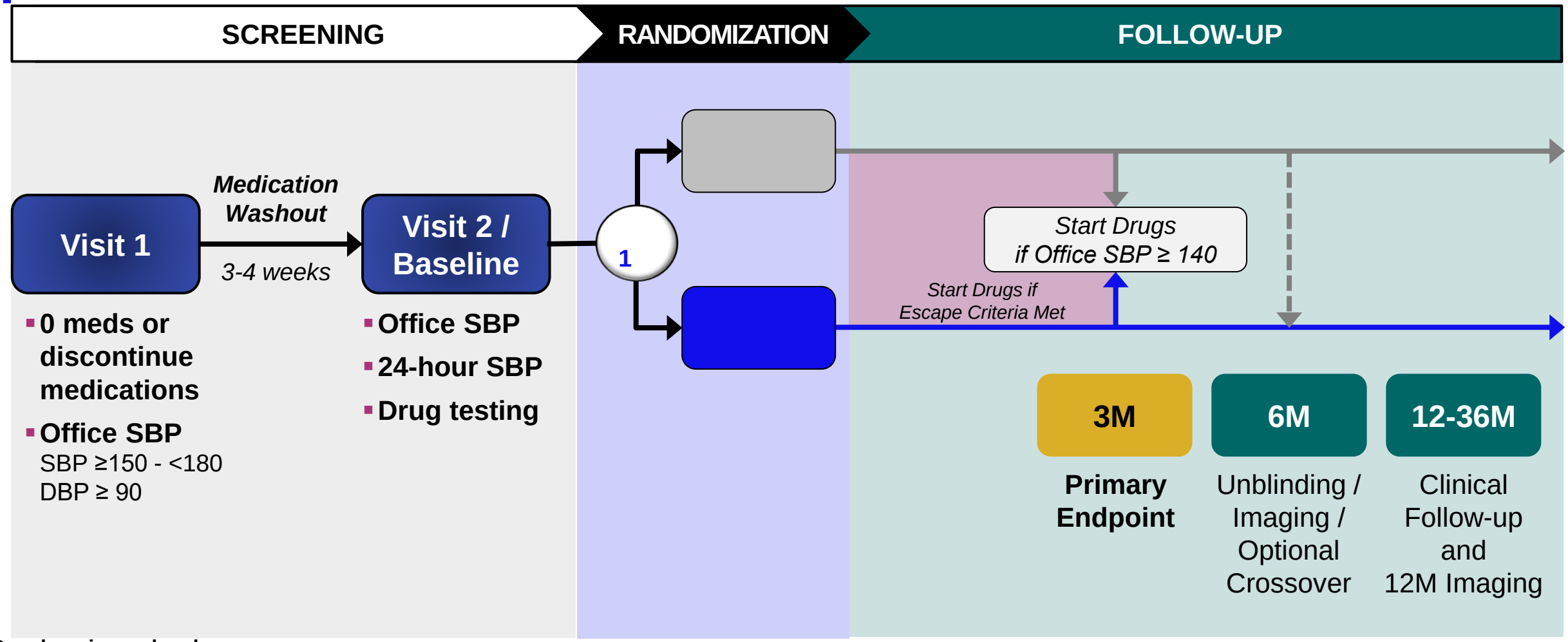
OFF MED Study Design



*Renal angiography alone
SBP: systolic blood pressure; DBP: diastolic blood pressure
Escape criteria = Office SBP ≥ 180 or safety concern

OFF MED Pivotal Study: Key Entry Criteria

Inclusion Criteria

- Not taking or discontinued antihypertensive medications
- Office SBP ≥ 150 to < 180 mmHg
- DBP ≥ 90 mmHg
- Mean 24-hour SBP ≥ 140 to < 170 mmHg

Exclusion Criteria

- Ineligible renal artery anatomy
- eGFR < 45mL/min/1.73m^2
- Type 2 Diabetes with A1C > 8% or Type 1 Diabetes
- Secondary causes of hypertension

SBP = systolic blood pressure; DBP = diastolic blood pressure
eGFR = estimated glomerular filtration rate; NSAID = non-steroidal anti-inflammatory drug

OFF MED Pivotal Study: Efficacy Endpoints

Primary Endpoint

Change from baseline in 24-hour SBP at 3 months post procedure*

Powered Secondary Endpoint

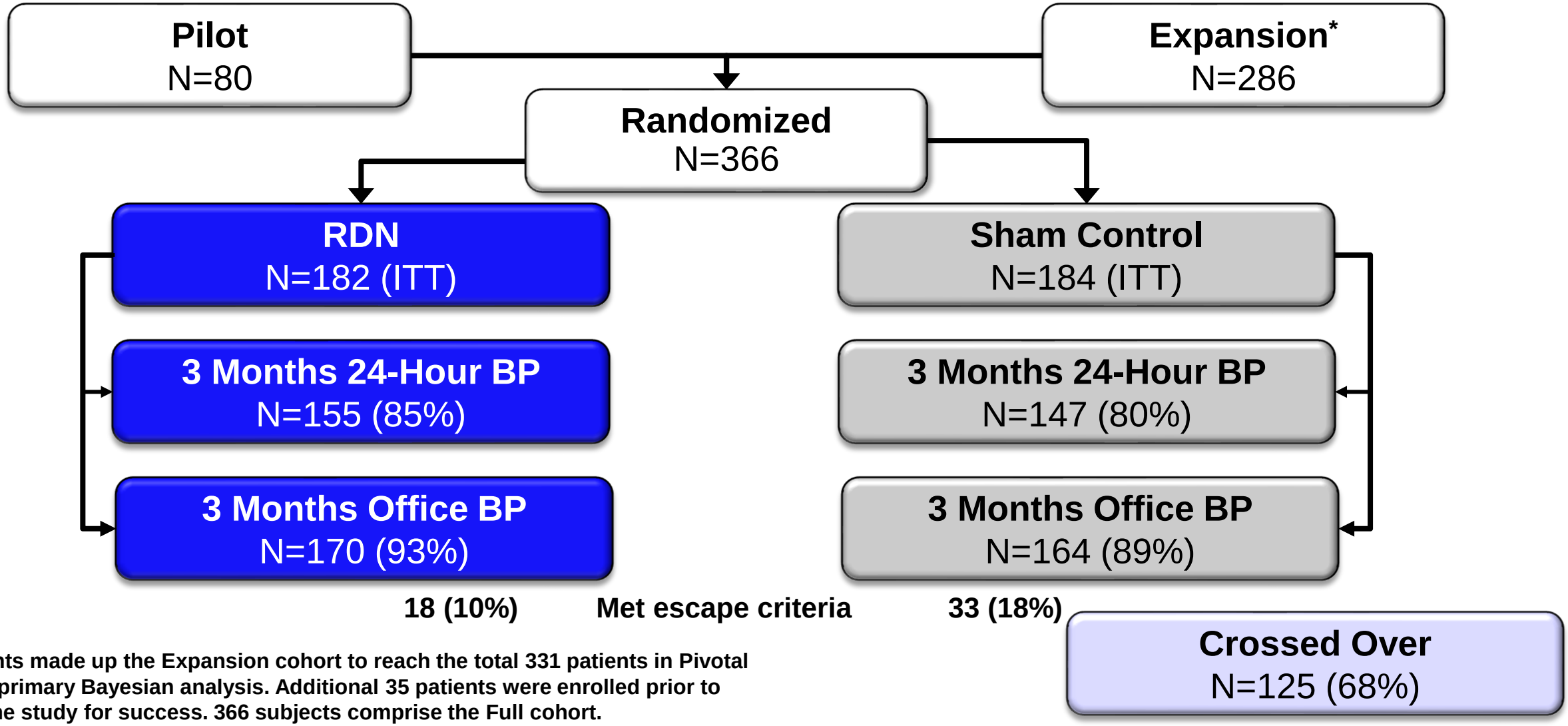
Change from baseline in office SBP at 3 months post procedure*

Key Secondary and Other Analyses

- Change from baseline in 24-hour and SBP and DBP assessed at 3, 6, 12, 24, and 36 months
- Medication abstinence evaluated using drug testing

Note that for pilot study, endpoints shown were not powered
***Adjusted for baseline blood pressure**

OFF MED Full Cohort: Patient Disposition



* 251 patients made up the Expansion cohort to reach the total 331 patients in Pivotal Cohort for primary Bayesian analysis. Additional 35 patients were enrolled prior to stopping the study for success. 366 subjects comprise the Full cohort.

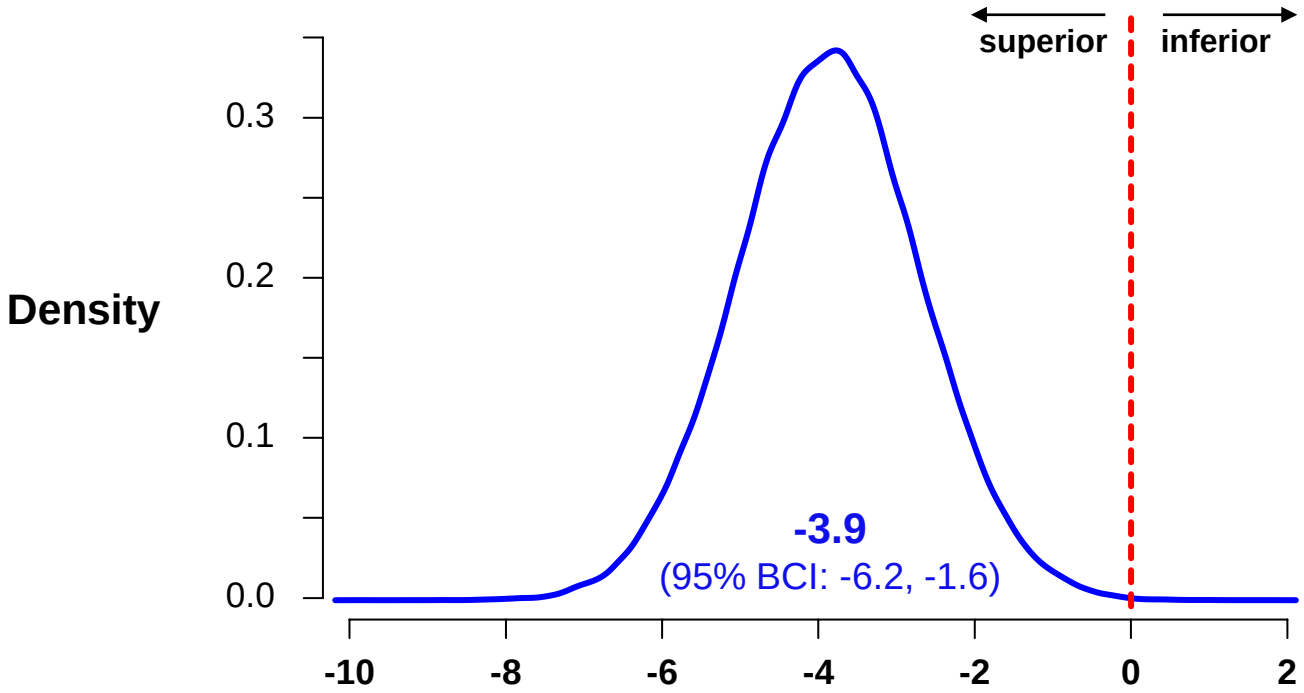
OFF MED Full Cohort: Demographics

	RDN N = 182	Sham N = 184
Age, mean (years)	52.5	52.7
Male	64%	70%
Race		
White	31%	33%
Black American	20%	17%
Asian	5%	2%
Not reportable per local laws or regulations	43%	47%
Region		
US	50%	46%
Non-US	50%	54%

OFF MED Full Cohort: Baseline Characteristics Balanced Between Groups

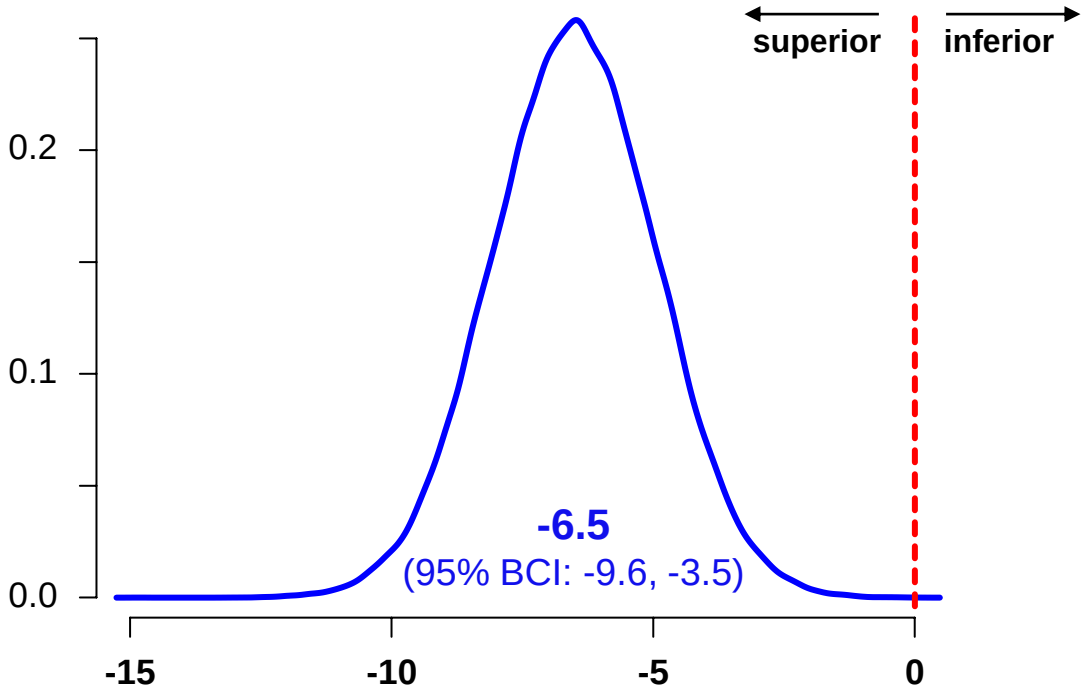
	RDN N = 182	Sham N = 184
Length of Hypertension		
0-5 years	**44%**	**44%**
6-10 years	**19%**	**16%**
> 10 years	**37%**	**40%**
Diabetes	**4%**	**6%**
Coronary Artery Disease	**0%**	**4%**
Obstructive Sleep Apnea	**8%**	**7%**

OFF MED Pivotal Study: Met Both Primary and Secondary Efficacy Endpoints



24-hr SBP Difference from Baseline (mmHg)

> 99.9% probability of superiority

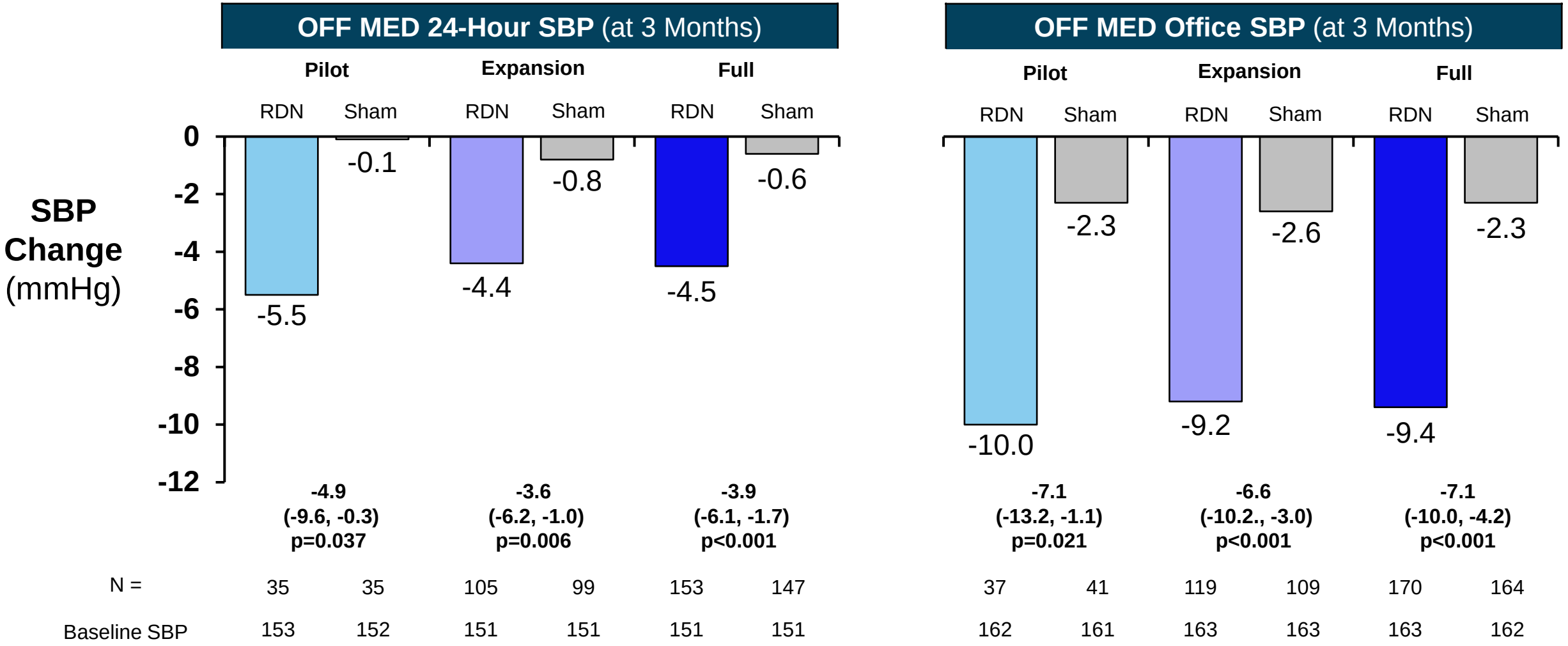


Office SBP Difference from Baseline (mmHg)

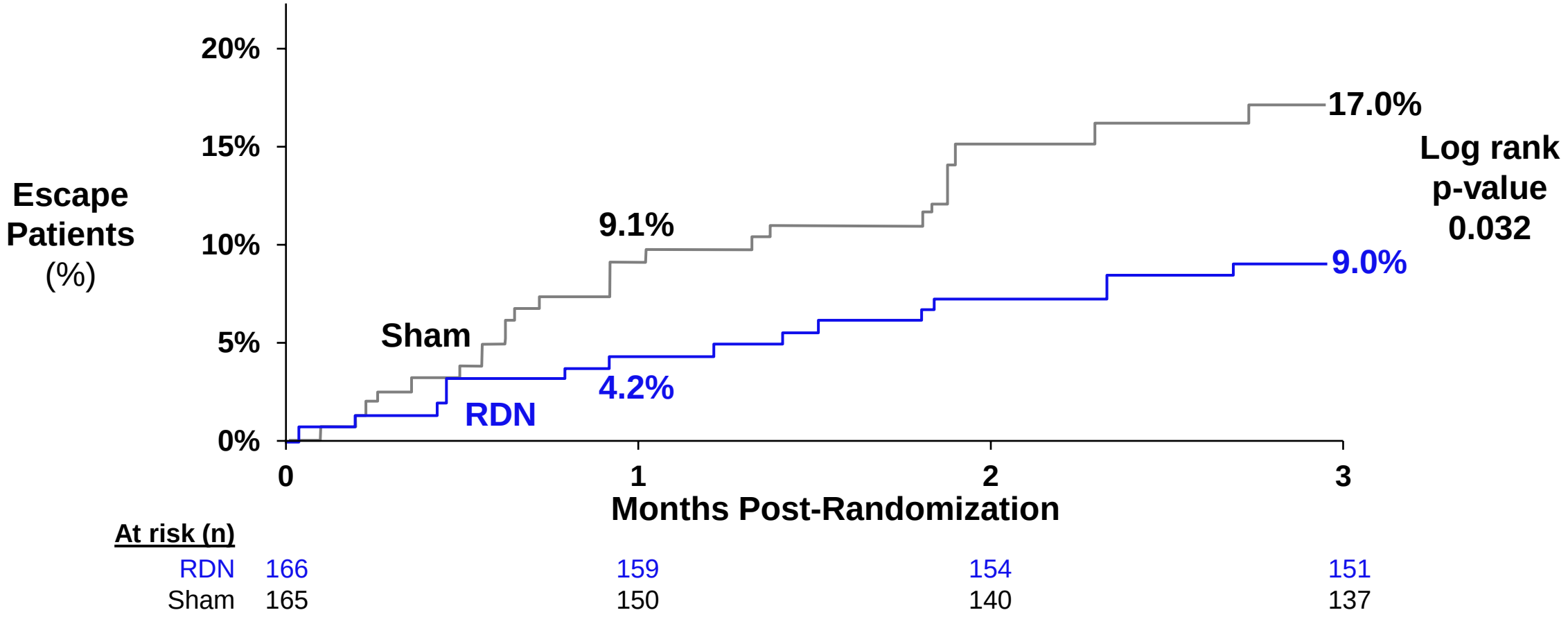
> 99.9% probability of superiority

BCI = Bayesian credible interval

OFF MED Full Cohort: Consistent Reductions in SBP Observed in Both Pilot and Expansion Cohorts (ITT)



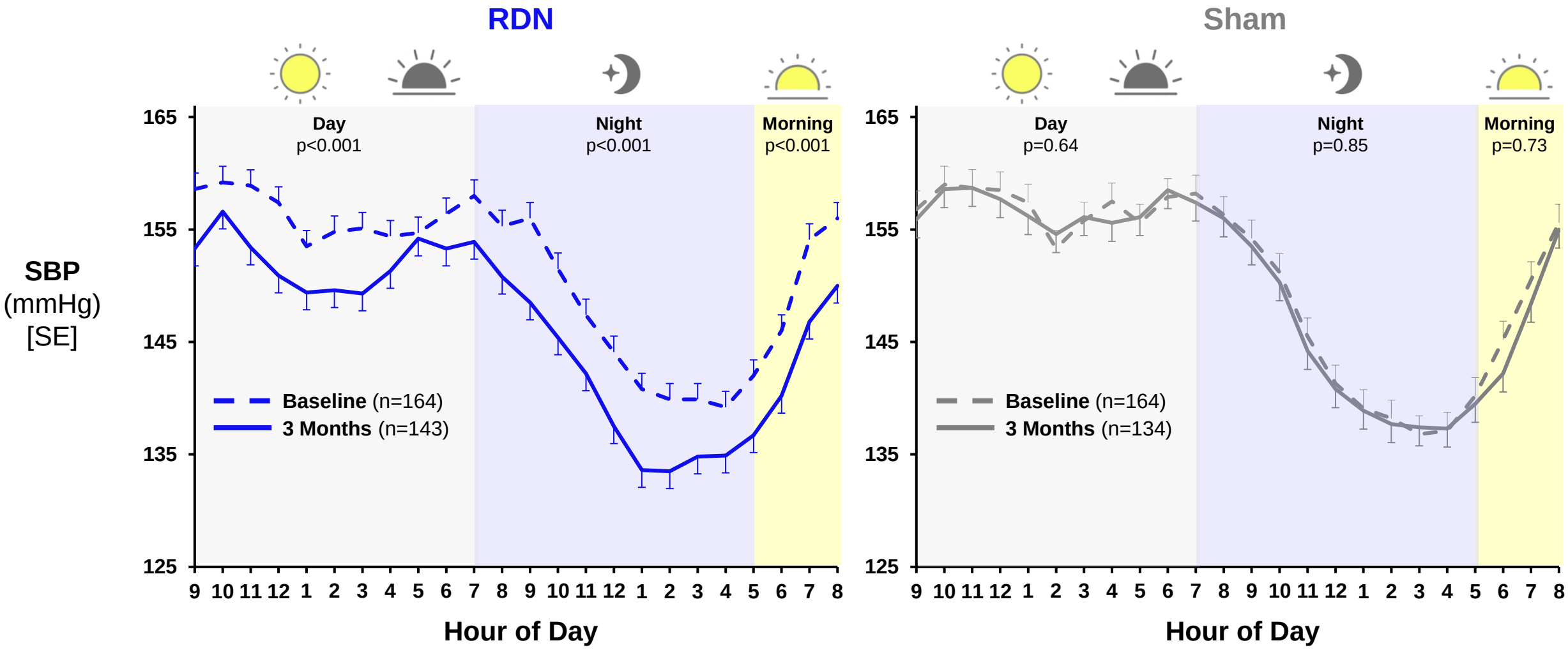
OFF MED Pivotal Study: Significantly Fewer Patie ated with RDN Met Escape Criteria



Pivotal = Pilot + Expansion

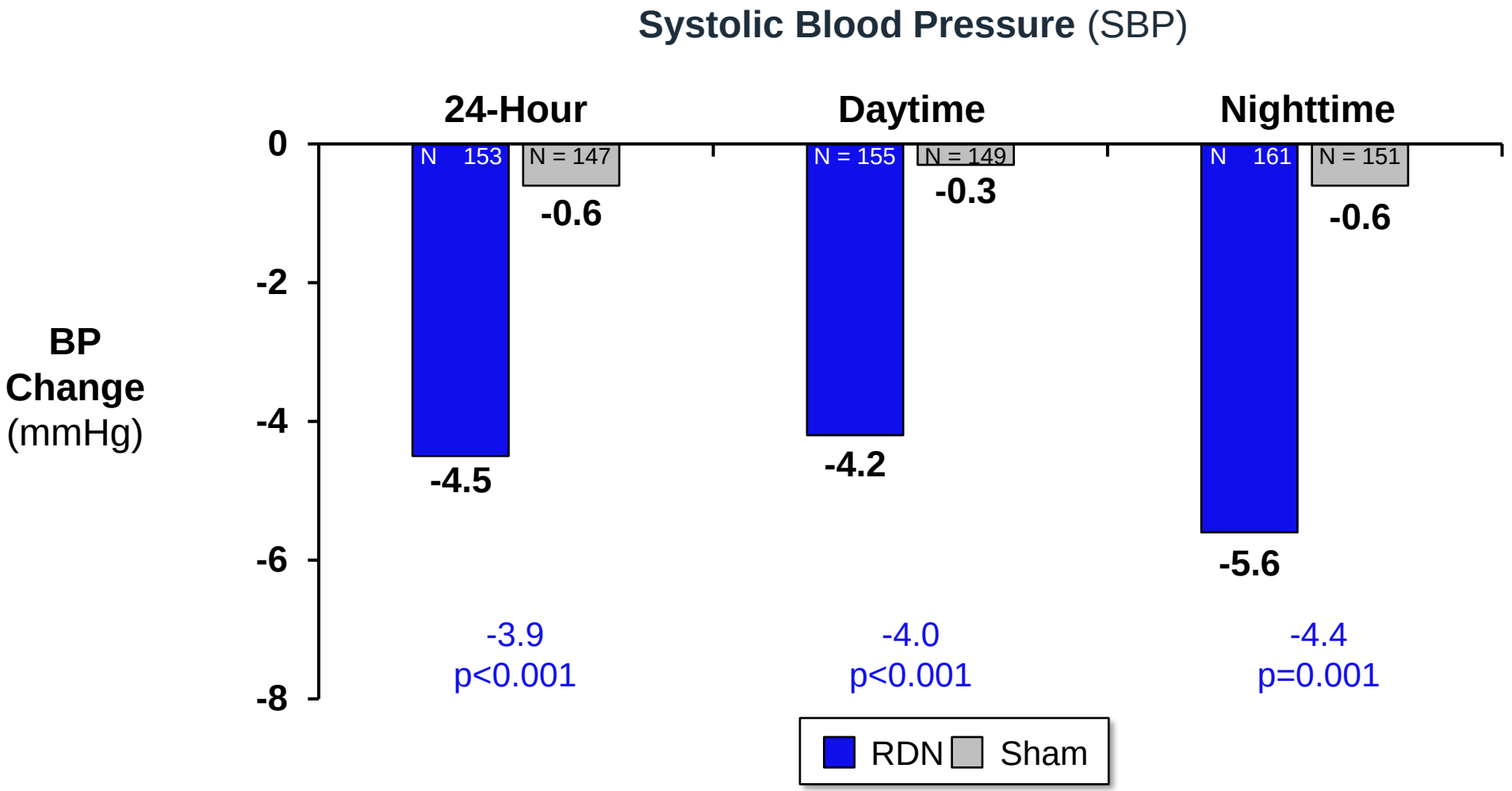
Figure A, Weber et al. *Clin Res Cardiol* 2022

OFF MED Pivotal Study: Continuous Reductions in 24-Hour Blood Pressure (ITT)



Pivotal = Pilot + Expansion

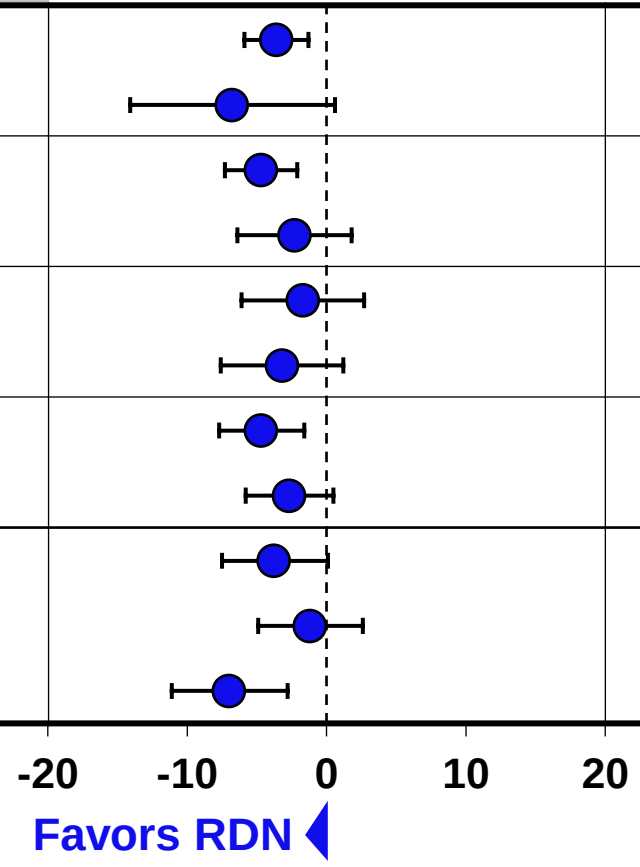
OFF MED Full Cohort: Daytime and Nighttime SBP Significantly Lower for RDN Patients (ITT)



p-values are ANCOVA adjusted; Daytime = 7am to 10pm; Nighttime = 10pm to 7am

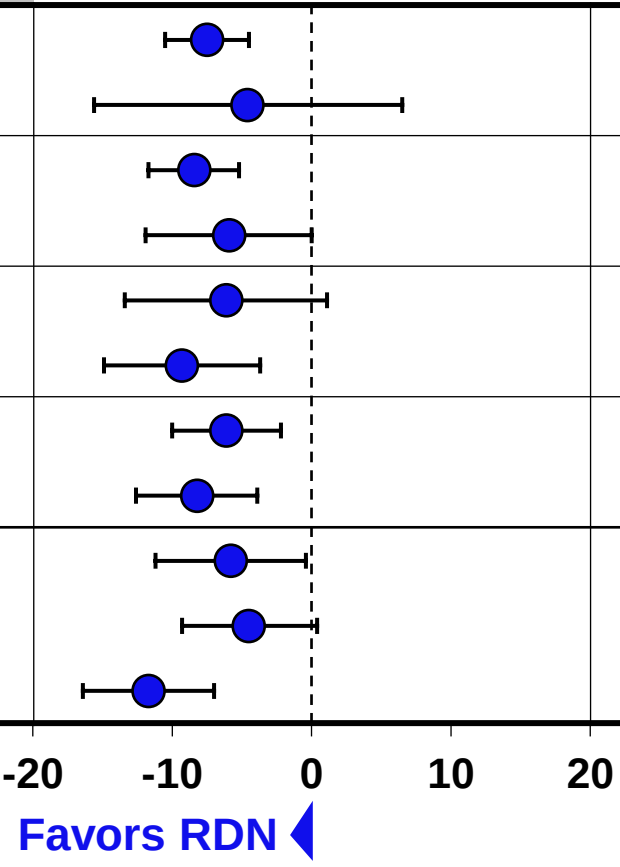
OFF MED Full Cohort: 24-Hour SBP Reductions Consistent Across Subgroups (ITT)

		Change in 24-Hour SBP (at 3 months)				ANCOVA Treatment Difference (95% CI)	Interaction p-value
		RDN		Sham			
		N	Δ	N	Δ		
Age	< 65	135	**-4.3 ± 10.7**	135	**-0.7 ± 9.0**		**0.410**
	≥ 65	18	**-5.9 ± 11.6**	12	**0.9 ± 4.5**		
Sex	Male	104	**-4.5 ± 10.3**	101	**0.2 ± 8.5**		**0.331**
	Female	49	**-4.5 ± 11.8**	46	**-2.3 ± 9.0**		
Race	Black American	27	**-2.9 ± 9.3**	22	**-0.7 ± 6.5**		**0.655**
	Non-Black Americans	48	**-4.0 ± 12.8**	44	**-0.0 ± 8.2**		
Geography	Non-US	78	**-5.5 ± 9.9**	81	**-0.9 ± 9.5**		**0.401**
	US	75	**-3.6 ± 11.6**	66	**-0.3 ± 7.6**		
Baseline 24-Hour SBP by Tertiles	1: < 147	56	**-2.8 ± 11.2**	51	**1.0 ± 7.9**		**0.122**
	2: 147 – 154	45	**-3.0 ± 10.7**	55	**-1.8 ± 8.1**		
	3: ≥ 154	52	**-7.8 ± 9.7**	41	**-1.0 ± 10.1**		



OFF MED Full Cohort: Office SBP Reductions Consistent Across Subgroups (ITT)

		Change in Office SBP (at 3 months)				ANCOVA Treatment Difference (95% CI)	Interaction p-value
		RDN		Sham			
		N	Δ	N	Δ		
Age	< 65	149	**-9.8 ± 14.3**	151	**-2.4 ± 12.8**		**0.604**
	≥ 65	21	**-6.6 ± 17.7**	13	**-1.1 ± 11.0**		
Sex	Male	111	**-10.8 ± 12.9**	110	**-2.1 ± 11.4**		**0.311**
	Female	59	**-6.9 ± 17.6**	54	**-2.7 ± 15.0**		
Race	Black American	33	**-6.5 ± 14.2**	29	**-0.6 ± 14.3**		**0.498**
	Non-Black American	52	**-10.0 ± 15.6**	49	**-0.1 ± 13.6**		
Geography	Non-US	85	**-10.2 ± 14.5**	86	**-4.2 ± 11.3**		**0.462**
	US	85	**-8.7 ± 15.1**	78	**-0.3 ± 13.8**		
Baseline OSBP by Tertiles	1: < 159	61	**-4.9 ± 15.5**	56	**0.8 ± 14.3**		**0.078**
	2: 159 – 167	58	**-9.8 ± 14.5**	59	**-5.6 ± 11.5**		
	3: ≥ 167	51	**-14.4 ± 12.6**	49	**-2.0 ± 11.2**		



OSBP = Office SBP

OFF MED Pivotal Study Demonstrated Reductions in BP in Absence of Medication

Statistically significant and clinically meaningful systolic and diastolic BP reductions:

- ✓ Office
- ✓ 24-hour mean
- ✓ Daytime
- ✓ Nighttime

SPYRAL HTN-ON MED Study

Randomized, Controlled Studies

Studies in ABSENCE of anti-hypertensive medications

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N = 80

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OFF MED Pivotal Study

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(Pilot + Expansion)

Studies in PRESENCE of anti-hypertensive medications

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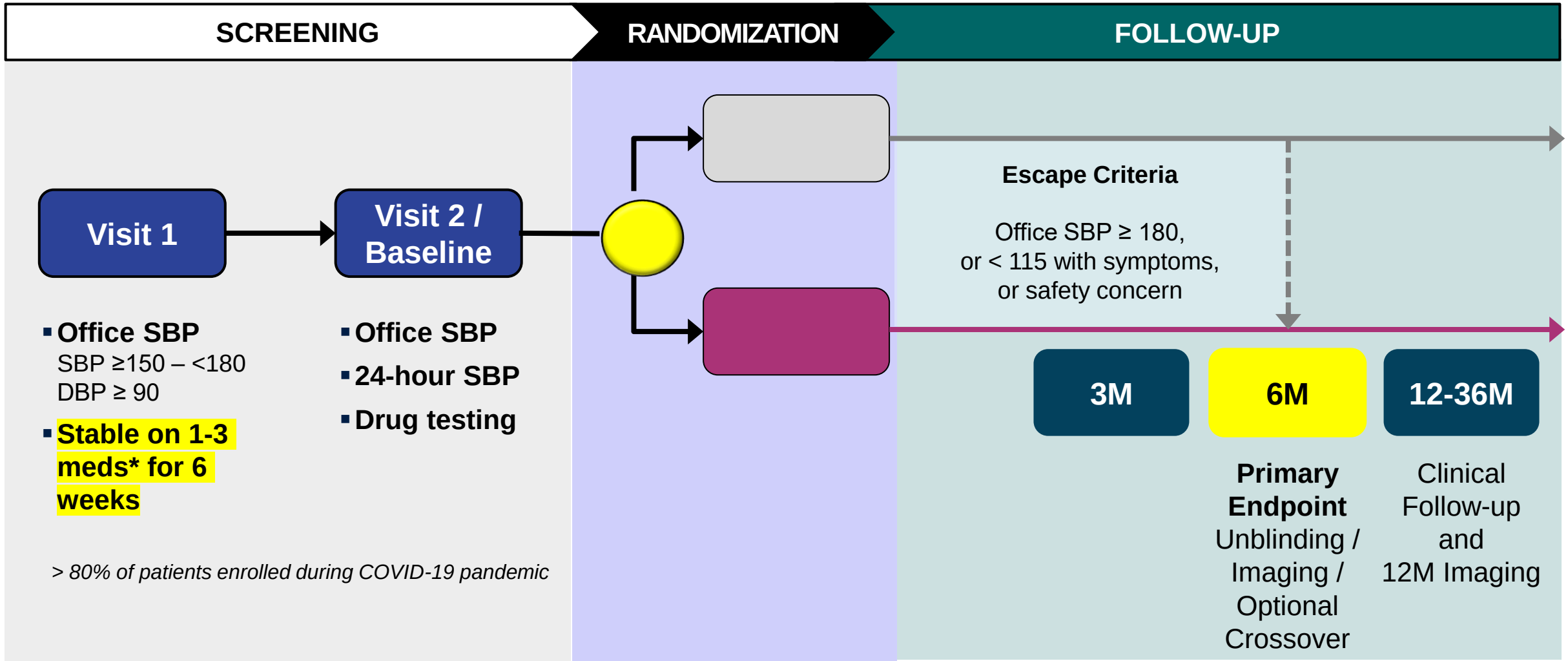
ON MED Study Design



*Thiazide diuretic, ACE/ARB, Calcium Channel Blocker, Beta Blocker; ** First 106 patients randomized 1:1

SBP: systolic blood pressure; DBP: diastolic blood pressure

ON MED Study: Key Entry Criteria

Inclusion Criteria

- **On stable regimen of 1-3 anti-hypertensive medications**
- Office SBP ≥ 150 to < 180 mmHg
- DBP ≥ 90 mmHg
- Mean 24-hour SBP ≥ 140 to < 170 mmHg

Exclusion Criteria

- Ineligible renal artery anatomy
- eGFR < 45mL/min/1.73m^2
- Type 2 Diabetes with A1C > 8% or Type 1 Diabetes
- Secondary causes of hypertension

SBP = systolic blood pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; NSAID = non-steroidal anti-inflammatory drugs

ON MED Study: Efficacy Endpoints

Primary Endpoint

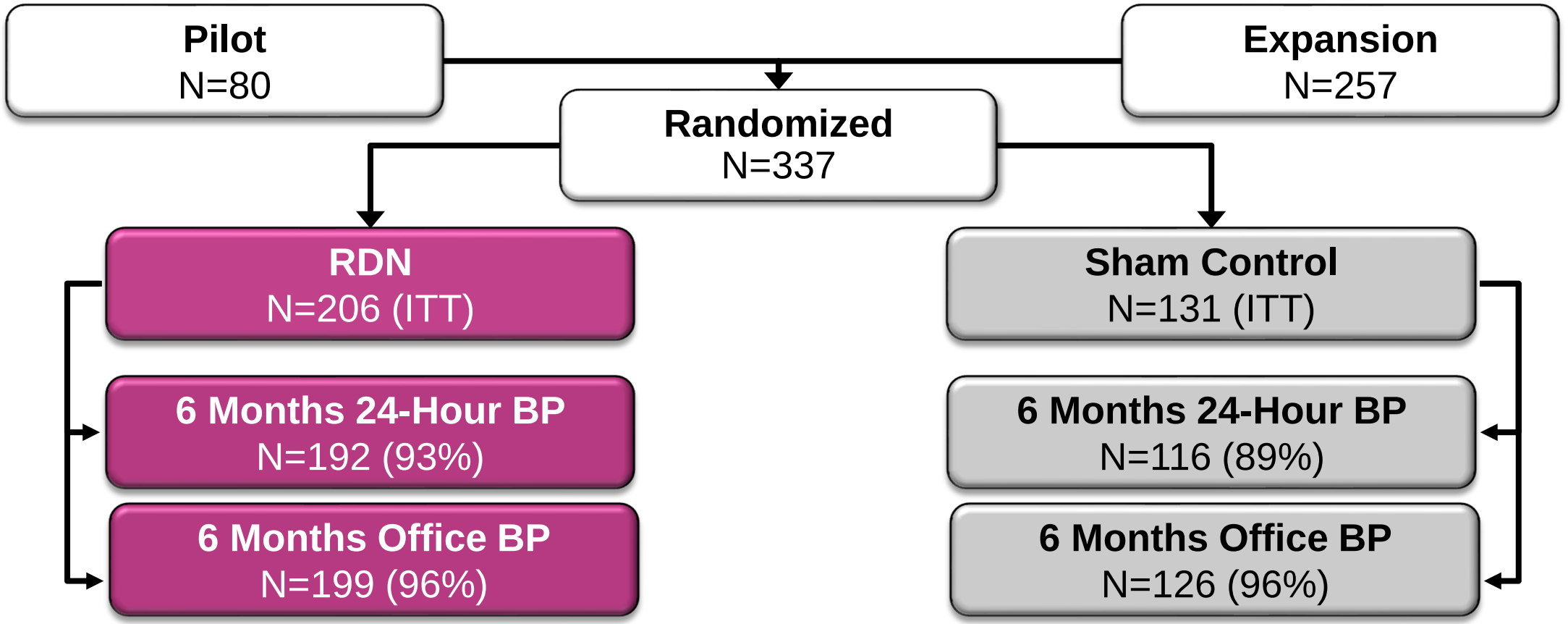
Change from baseline in 24-Hour SBP at 6-months post-procedure*

Key Secondary and Additional Endpoints

- Change from baseline in 24-hour and SBP and DBP assessed at 3, 6, 12, 24, and 36 months
- Nighttime SBP at 6-months post-procedure
- Medication adherence using results from drug testing

*Adjusted for baseline blood pressure

ON MED Study: Patient Disposition



First 106 patients randomized 1:1, remaining randomized 2:1

ON MED Full Cohort: Demographics

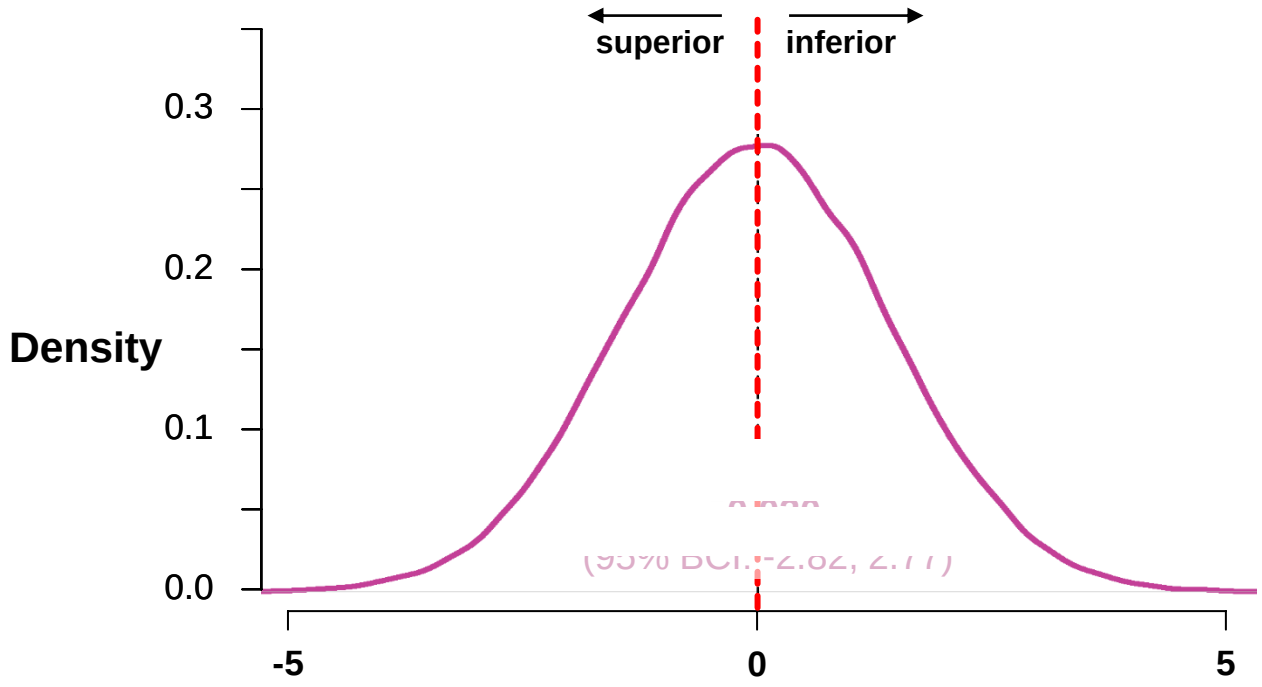
	RDN N=206	Sham N=131
Age, Mean (years)	55.2	54.6
Male	81%	79%
Race		
White	35%	37%
Black American	17%	19%
Asian	8%	8%
Not reportable per local laws or regulations	39%	35%
Geography		
US	44%	50%
Non-US	56%	50%

ON MED Full Cohort: Key Baseline Characteristics

	RDN N=206	Sham N=131
Length of hypertension		
0–5 years	30%	18%
6–10 years	18%	21%
> 10 years	52%	61%
Number of medication classes		
1	39%	36%
2	33%	36%
3	28%	27%
4	>1%	>1%
Diabetes	11%	18%
Coronary artery disease	5%	7%
Obstructive sleep apnea	11%	18%

ON MED Study: Primary Efficacy Endpoint Not Met

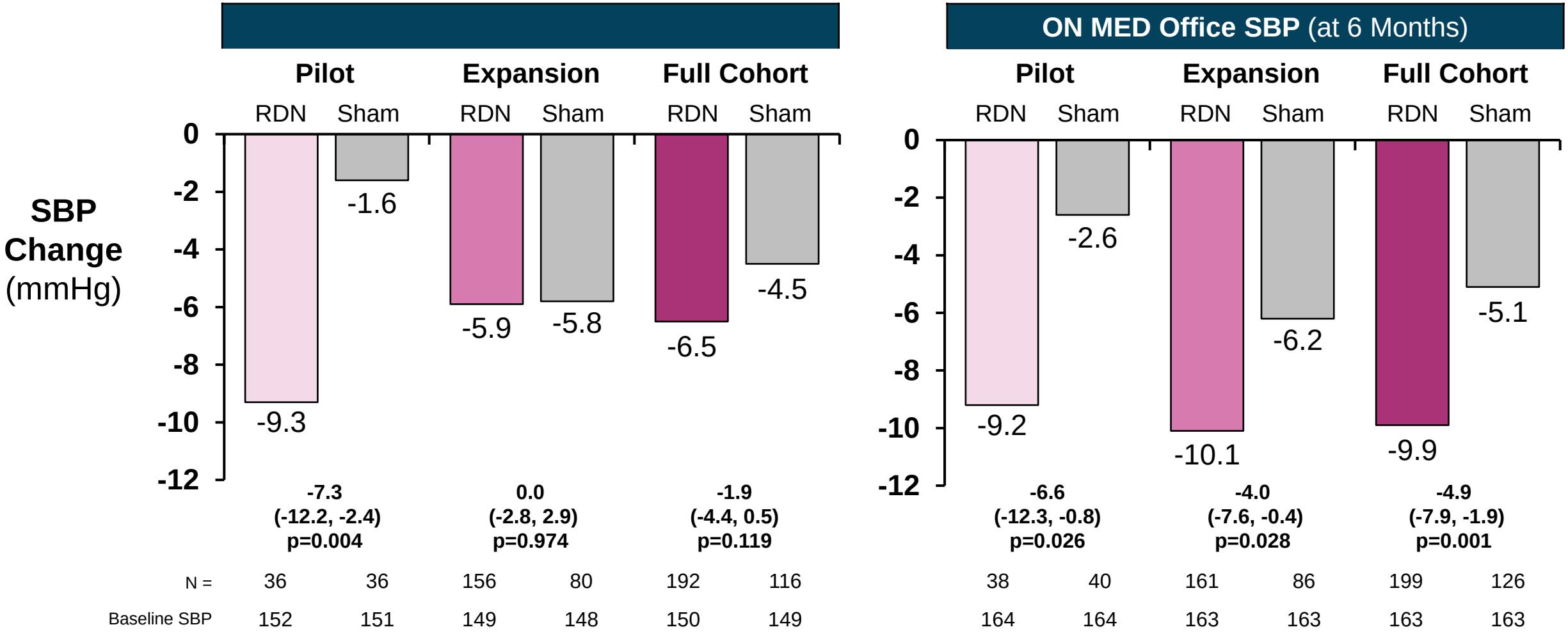
- Primary efficacy endpoint used Bayesian design
- Pilot data to be incorporated as long as 24-hour SBP data aligned with expansion phase
- Due to differences in 24-hour SBP at 6 months, limited pilot data could be used for primary efficacy analysis
  - ~20% RDN and 0% sham



> 50.8% probability of superiority

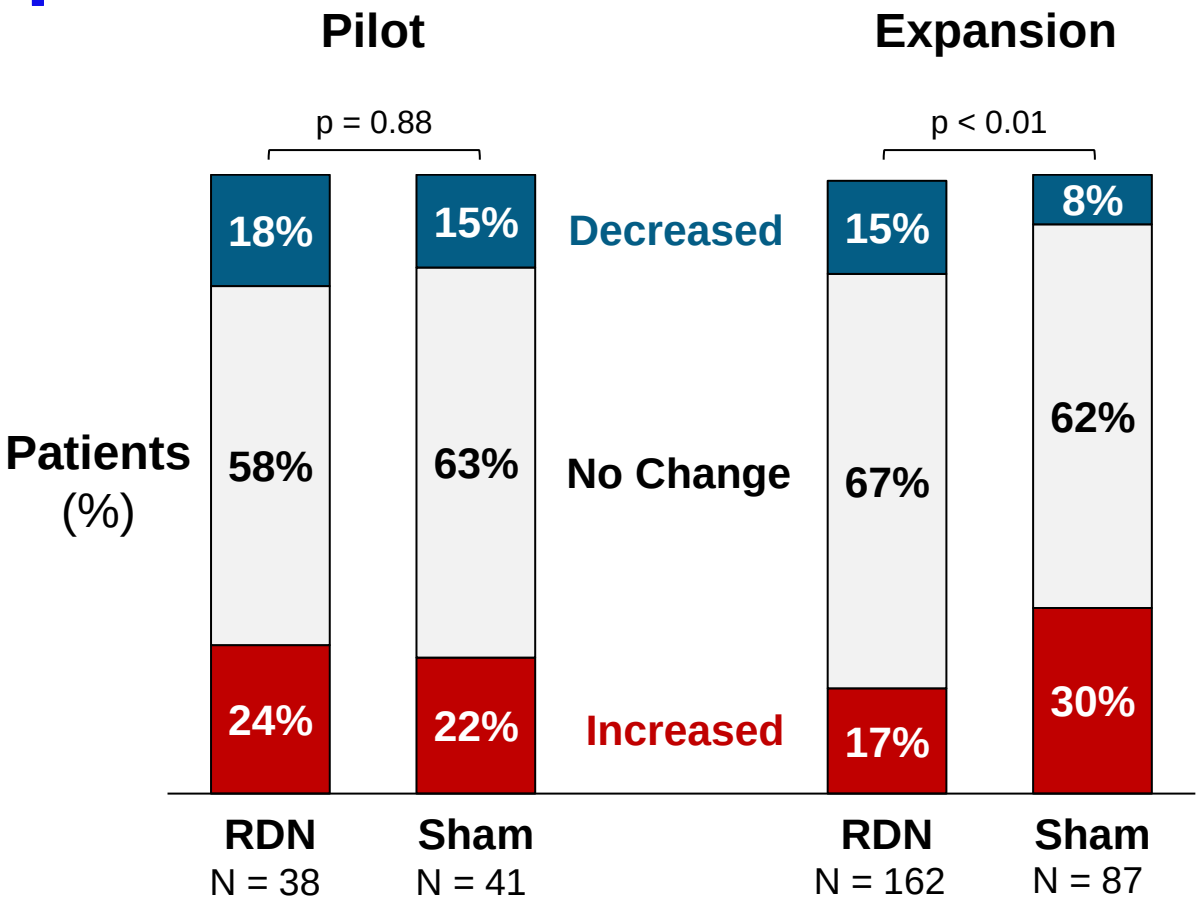
BCI = Bayesian credible interval

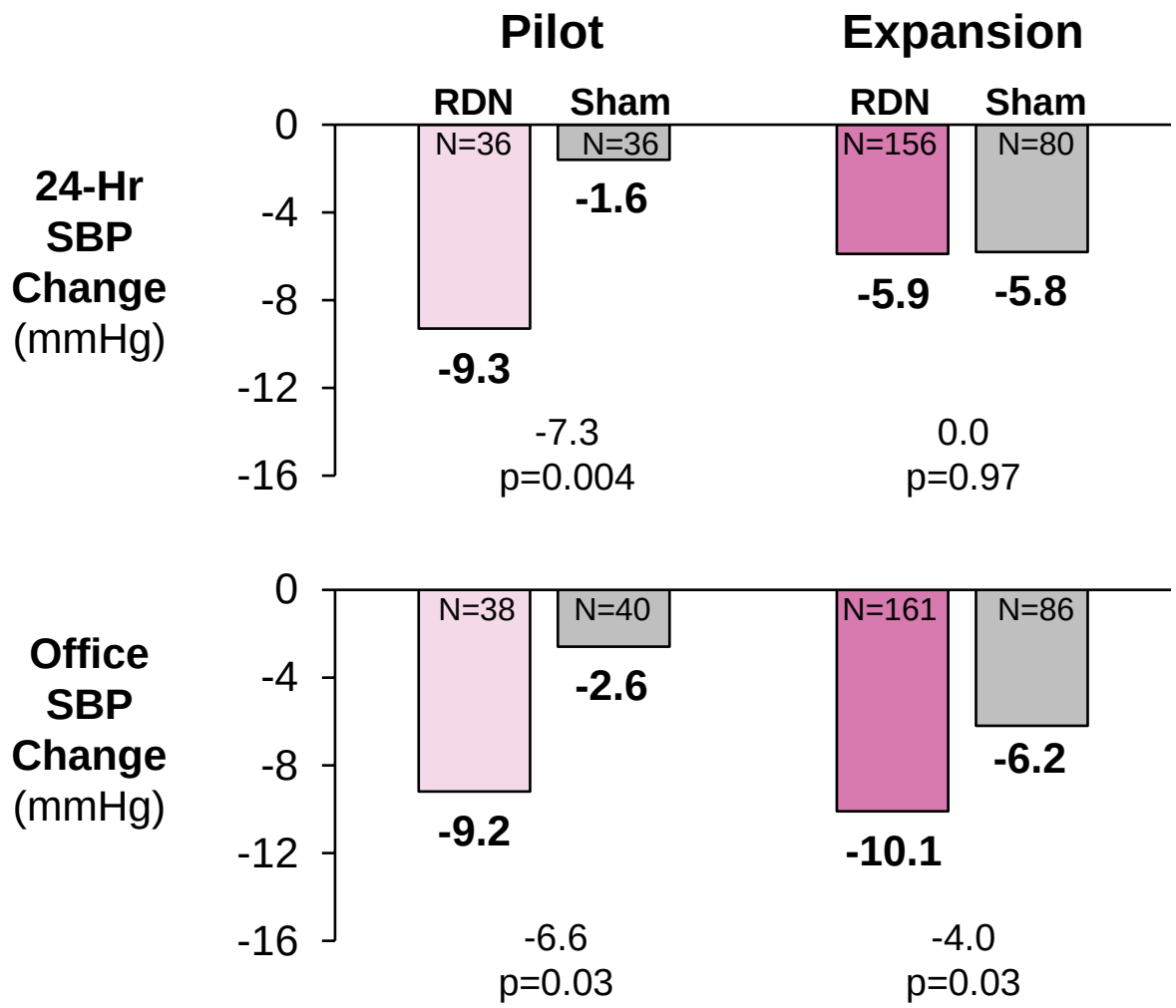
ON MED Study: Consistent Reductions in SBP Observed with RDN (ITT)



Full Cohort = Pilot + Expansion

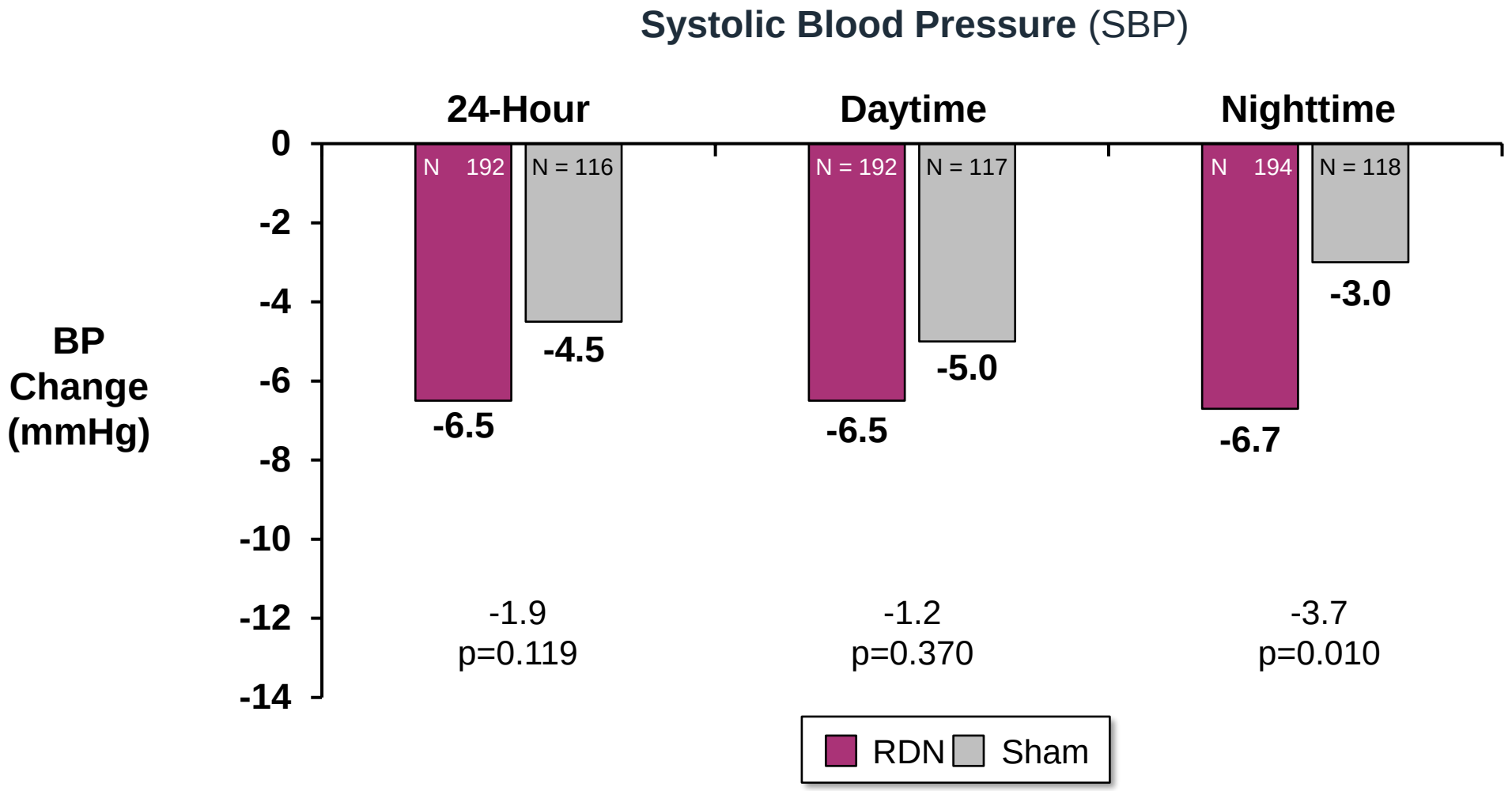
ON MED Study Expansion: Disproportionate Detected Medication Increases in Sham Group





Medication burden was based on number, dose, and class of anti-hypertensive medications as determined by urine and blood analysis.

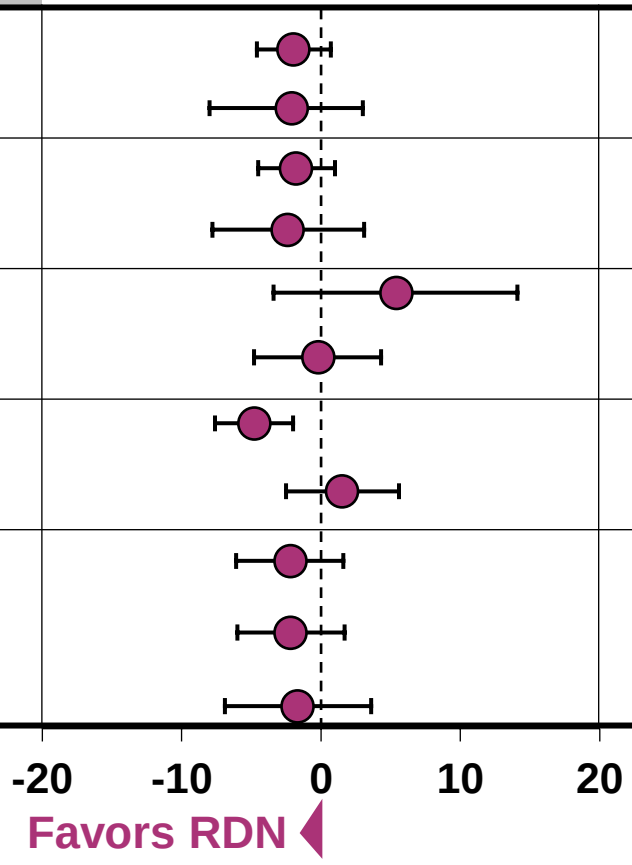
ON MED Study: Treatment Effect Largest at Night When Medication Effect is Lower (ITT)



p-values are ANCOVA adjusted; Daytime = 7am to 10pm; Nighttime = 10pm to 7am

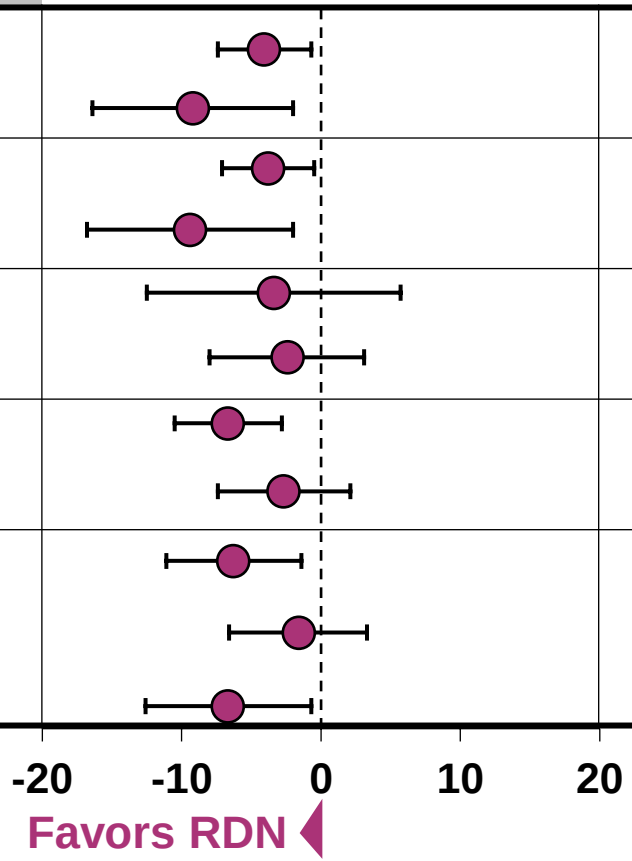
ON MED Study: Change in 24-Hour SBP at 6 Months by Subgroups (ITT)

		Change in 24-Hour SBP (at 6 months)				ANCOVA Treatment Difference (95% CI)	Interaction p-value
		RDN		Sham			
		N	Δ	N	Δ		
Age	< 65	163	**-6.4 ± 10.9**	98	**-4.4 ± 10.4**		**0.994**
	≥ 65	29	**-7.0 ± 9.7**	18	**-5.3 ± 10.5**		
Sex	Male	157	**-6.6 ± 10.6**	88	**-4.7 ± 10.3**		**0.837**
	Female	35	**-6.2 ± 11.3**	28	**-3.8 ± 10.7**		
Race	Black American	31	**-3.6 ± 15.0**	15	**-8.7 ± 10.8**		**0.214**
	Non-Black American	56	**-6.5 ± 11.3**	39	**-6.0 ± 11.0**		
Geography	Non-US	105	**-7.4 ± 8.6**	62	**-2.6 ± 9.5**		**0.011**
	US	87	**-5.5 ± 12.8**	54	**-6.7 ± 10.9**		
Baseline 24-Hour SBP by Tertiles	1: < 145	65	**-6.0 ± 9.4**	39	**-3.8 ± 9.6**		**0.986**
	2: 145 – 152	60	**-5.6 ± 10.2**	46	**-3.6 ± 9.7**		
	3: ≥ 152	67	**-7.8 ± 12.3**	31	**-6.8 ± 12.0**		



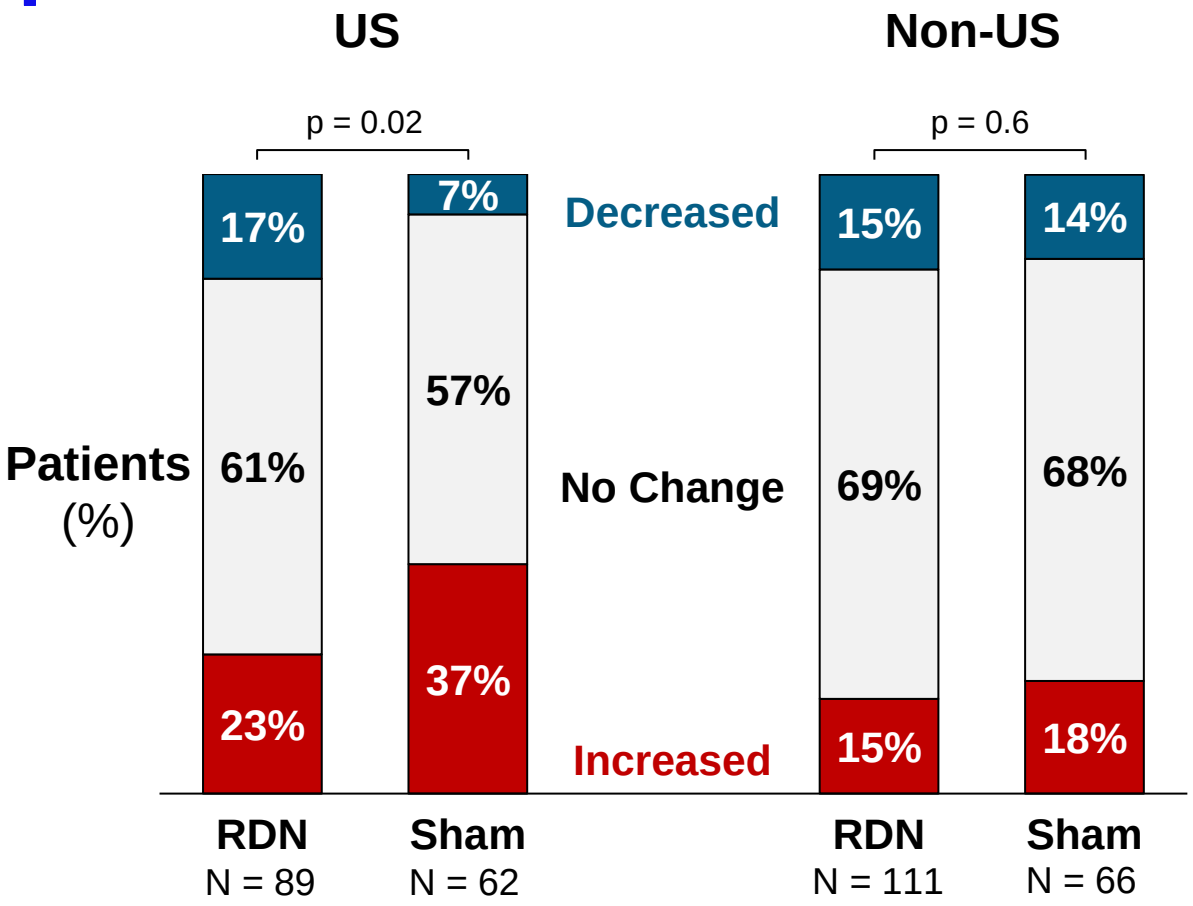
ON MED Study: Change in Office SBP at 6 Months by Subgroups (ITT)

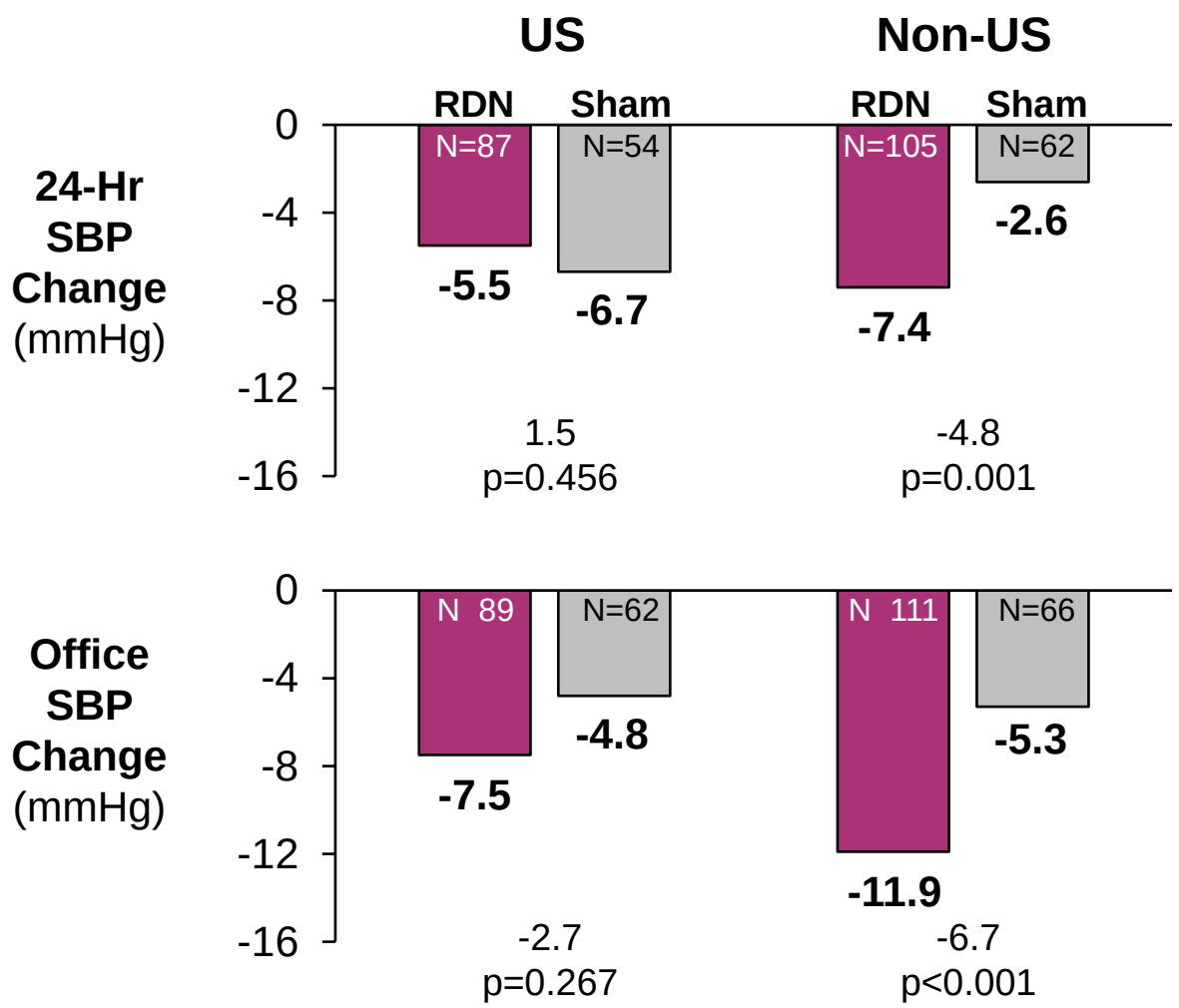
		Change in Office SBP (at 6 months)				ANCOVA Treatment Difference (95% CI)	Interaction p-value
		RDN		Sham			
		N	Δ	N	Δ		
Age	< 65	168	**-9.3 ± 13.9**	107	**-5.3 ± 13.5**		**0.208**
	≥ 65	31	**-13.6 ± 13.5**	19	**-3.8 ± 11.6**		
Sex	Male	162	**-9.7 ± 13.8**	98	**-5.8 ± 12.3**		**0.176**
	Female	37	**-10.8 ± 14.4**	28	**-2.6 ± 15.8**		
Race	Black American	33	**-6.8 ± 18.1**	22	**-4.3 ± 14.0**		**0.869**
	Non-Black American	56	**-7.9 ± 14.2**	39	**-5.1 ± 12.2**		
Geography	Non-US	110	**-11.9 ± 12.0**	65	**-5.3 ± 13.6**		**0.191**
	US	89	**-7.5 ± 15.7**	61	**-4.8 ± 12.8**		
Baseline OSBP by Tertiles	1: < 159	68	**-8.4 ± 11.9**	45	**-2.3 ± 14.6**		**0.371**
	2: 159 – 166	63	**-7.9 ± 13.3**	40	**-6.2 ± 10.6**		
	3: ≥ 166	68	**-13.3 ± 15.8**	41	**-7.0 ± 13.6**		



OSBP = Office SBP

ON MED Medication Burden Changes Show Disproportionate Changes Geographically

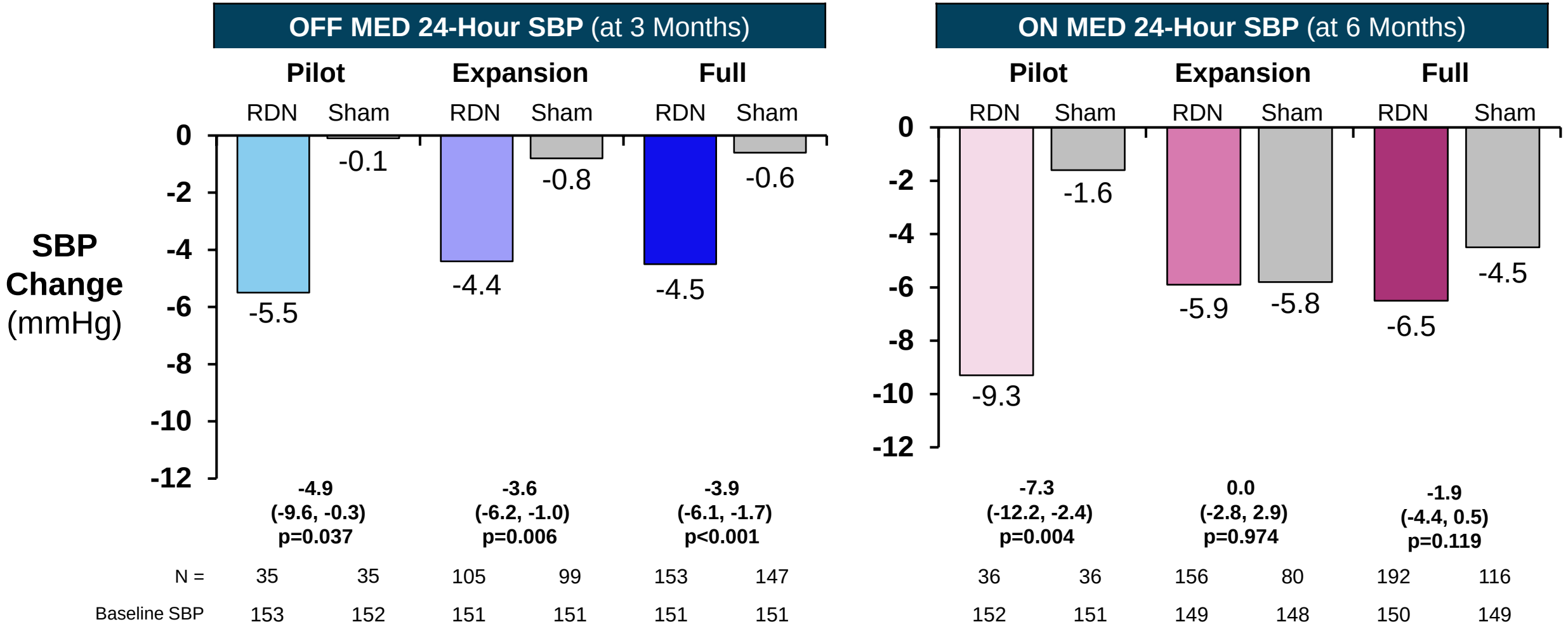




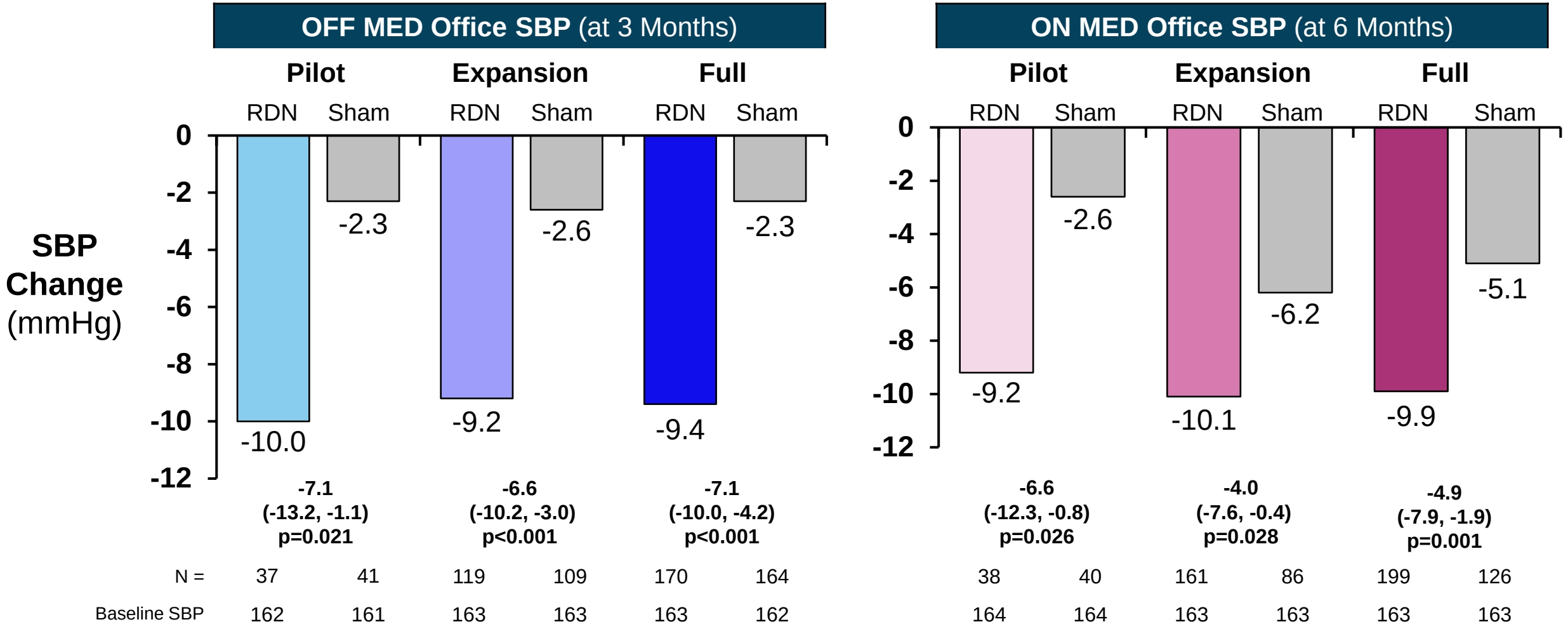
Medication burden was based on number, dose, and class of anti-hypertensive medications as determined by urine and blood analysis.

Overall Efficacy Results

Consistent Reductions in 24-Hour SBP Observed with RDN (ITT)



Consistent Reductions in Office SBP Observed with RDN (ITT)



Clinically Meaningful BP Reduction in Both Presence or Absence of Medications

- Continuous BP reductions over 24-hour period
- OFF MED:
  - Primary Endpoint met – significant reductions in 24-hour and Office SBP compared to Sham
- ON MED:
  - Significant reductions in 24-hour and Office SBP compared to Sham in Pilot cohort
  - Primary Endpoint for Full Cohort not met
    - Differential medication changes post-randomization attenuated treatment effect
    - Significant reductions in Office and nighttime SBP compared to Sham
- Consistent reductions from baseline in RDN-treated patients across all studies

Safety and Durability

Felix Mahfoud, MD, MA

Professor of Medicine and Deputy Director of Cardiology

Saarland University Hospital

Primary Safety Endpoint Cohort Comprises Data from OFF MED and ON MED Studies

		Sample Size N = 253
Pilot	OFF MED	31
	ON MED	95
Expansion	OFF MED	35
	ON MED	24
Crossover	OFF MED	51
	ON MED	17

Clinical Events Committee (CEC) Adjudicated Safety Events

- External, independent CEC to review and adjudicate all protocol-defined reportable events
- Comprised multiple clinicians
  - Pertinent expertise
  - Not participating in studies
  - No potential conflicts of interest
- Independent DSMB also reviewed reported safety events

30-Day Major Adverse Events Primary Safety Endpoint Met

	RDN N = 253	Upper 95% CI	Performance Goal	p-value
Major Adverse Events	**1 (0.4%)**	**1.9%**	**7.1%**	**< 0.001**
Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	**1 (0.4%)**			
All-cause mortality	**0**			
End stage renal disease	**0**			
Significant embolic event resulting in end-organ damage	**0**			
Renal artery perforation requiring re-intervention	**0**			
Renal artery dissection requiring re-intervention	**0**			
Hospitalization for hypertensive crisis not related to confirmed nonadherence with medication or protocol	**0**			
New renal artery stenosis > 70%	**0**			

Low Incidence of MAEs Through 3 and 6 Months in OFF MED and ON MED Studies

	OFF MED (to 3 months)		ON MED (to 6 Months)	
	RDN N = 180	**Sham** N = 184	**RDN** N = 206	**Sham** N = 131
MAE	**1 (0.6%)**	**1 (0.5%)**	**2 (1.0%)**	**1 (0.8%)**
Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	0	1 (0.5%)	2 (1.0%)	1 (0.8%)
Hospitalization for hypertensive crisis / emergency	1 (0.6%)	0	0	0
New stroke	0	1 (0.5%)	0	0

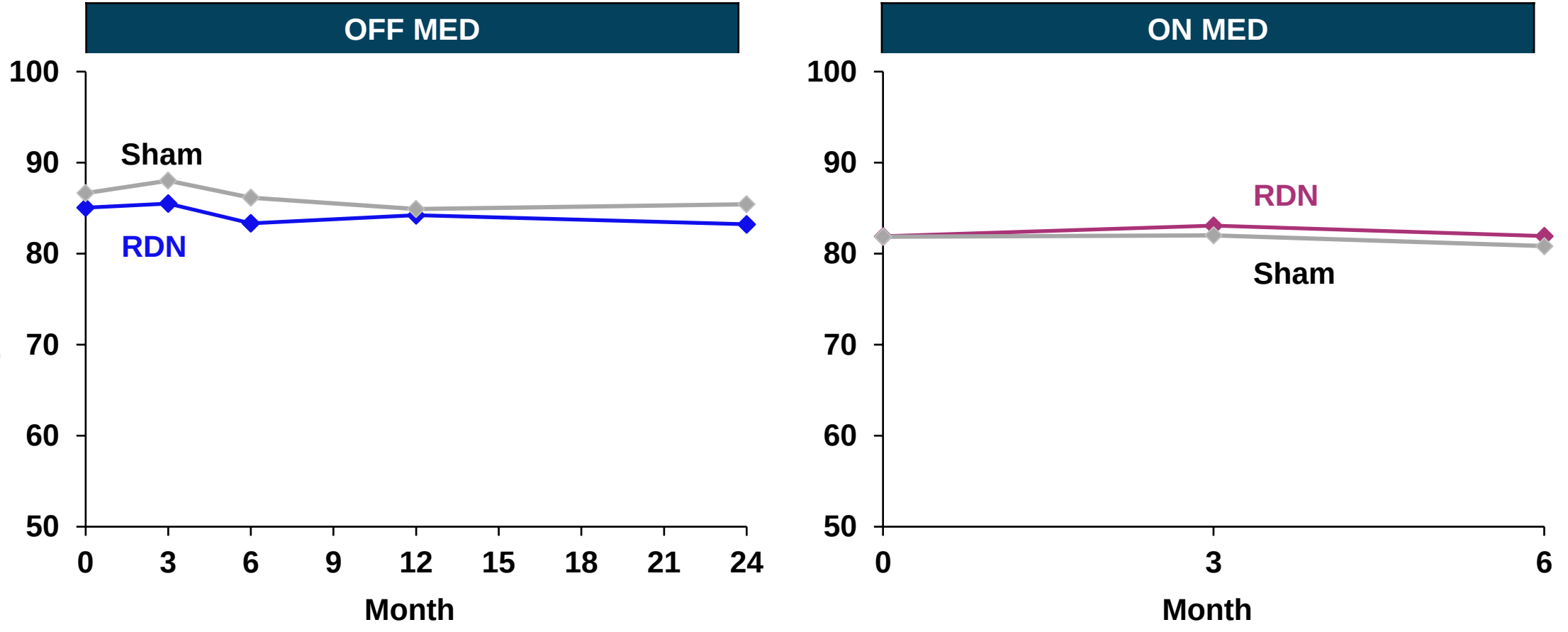
Safety measures with events at primary assessment

Stenosis via Imaging in OFF MED and ON MED Studies

- Clinically significant renal artery stenosis was defined as >70%
- 474 patients with long-term imaging at 12 months or later
  - 1 patient with renal stenosis (> 70%) in accessory renal artery
    - Identified on MRA 1,106 days post-procedure and patient exited trial prior to follow-up imaging
    - No deterioration in renal function
- Rate of stenosis **in ON/OFF MED** = 0.2% (1/474)
- Comparable yearly incidence: 0.5 to 5% per year[1-4]

1. Expert Panels on Urologic Imaging and Vascular Imaging, *J Am. Coll. Radiol.* 2017
2. Kalra, *Kidney International* 2005
3. Crowley, *Am. Heart J.* 1998
4. Zierler, *J of Vascular Surgery* 1994

Changes in eGFR Following RDN Consistent with Natural Progression



RDN (N)	182	165	156	158	147	206	198	201
Sham (N)	184	149	163	95	48	131	125	128

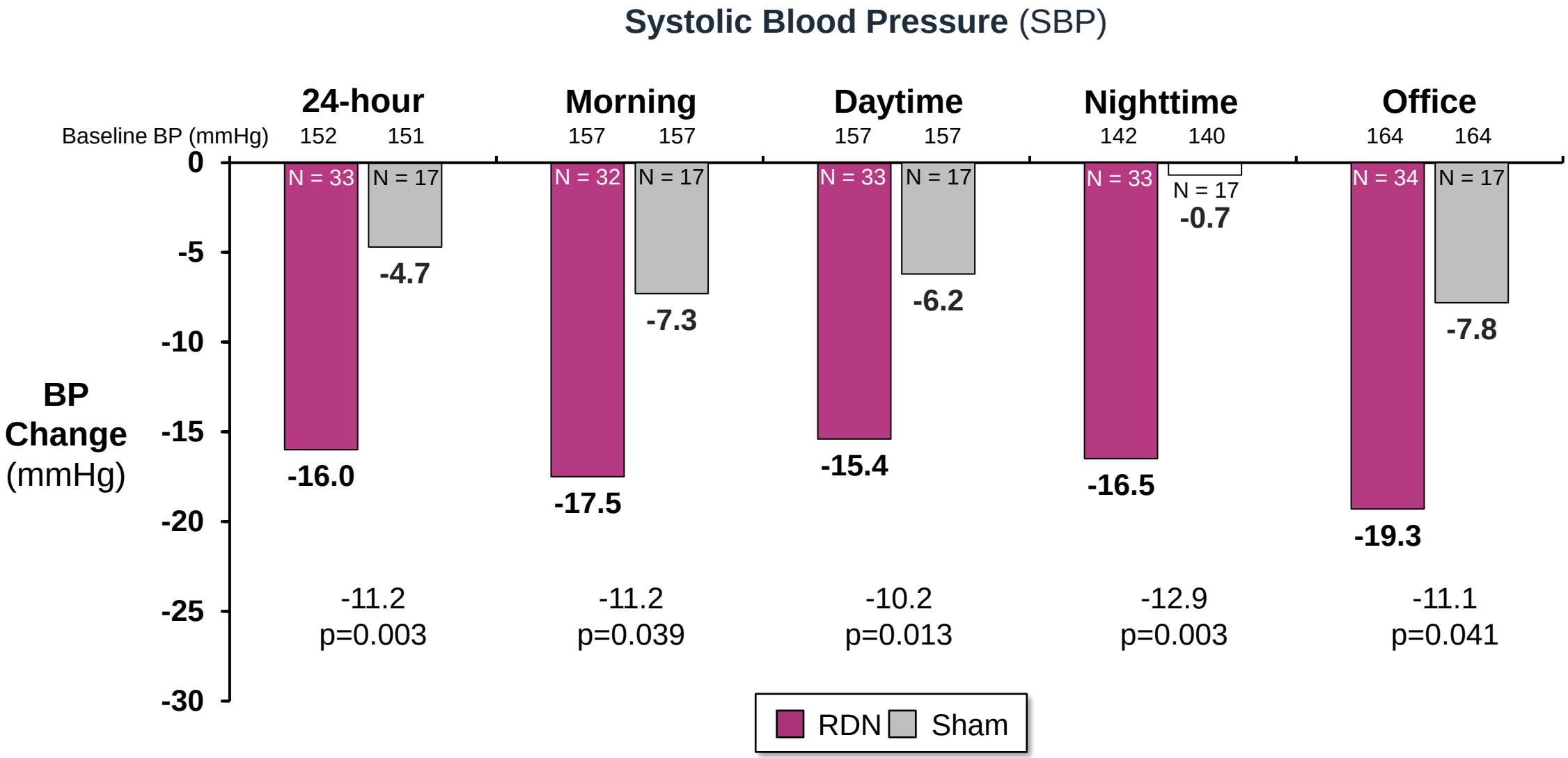
eGFR calculated using Modification of Diet in Renal Disease (MDRD) equation

Safety Summary

- Pooled primary safety endpoint was met with low rate of MAEs
- No major device-related and low rate of procedure-related safety events observed
- No increased risk of RDN-associated renal artery stenosis
- Sustained renal function

Durability of Effect and Long-Term Safety

ON MED Pilot SBP Changes at 24 Months



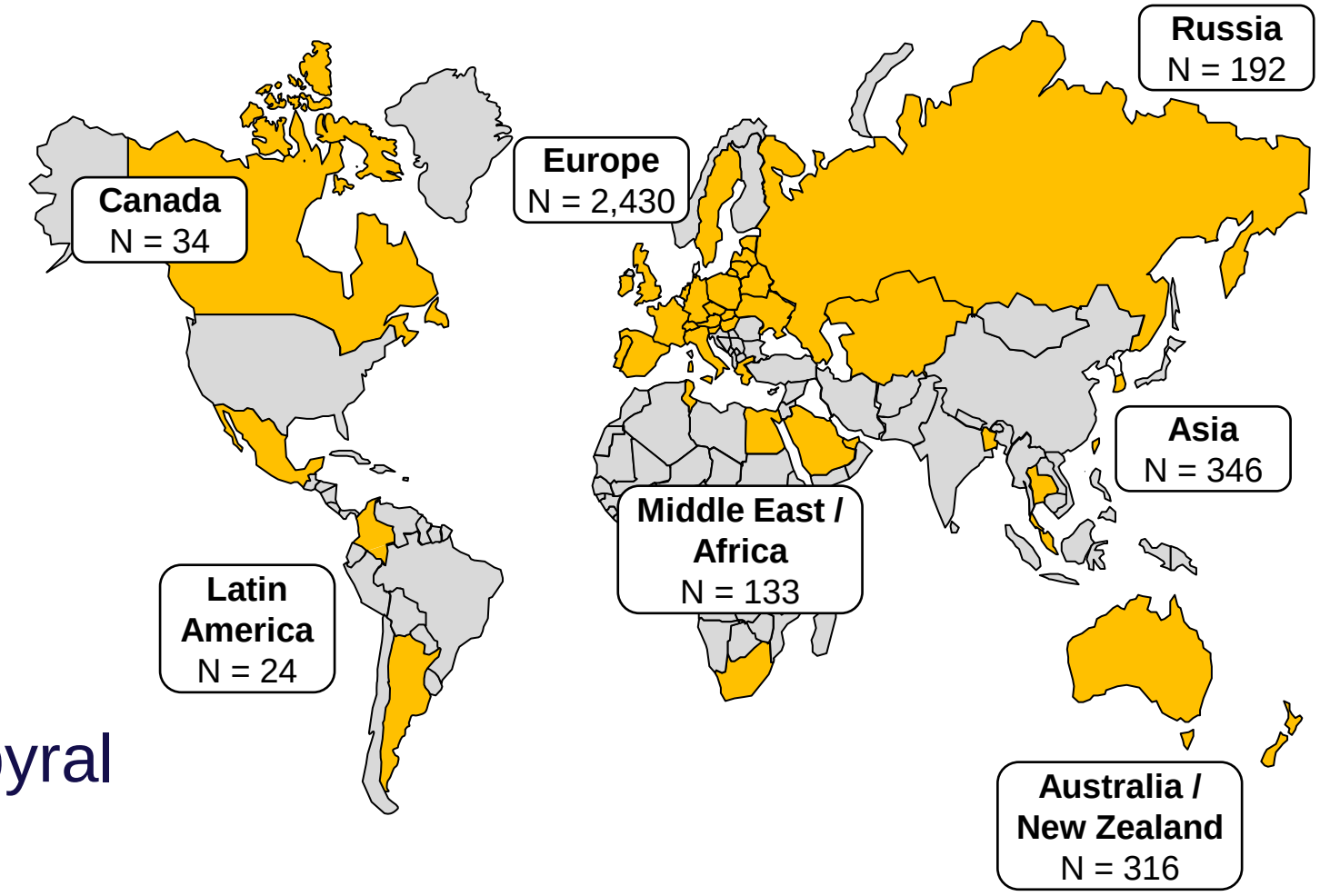
Long-Term Safety from ON MED and OFF MED Studies

- Low incidence of reported AEs, rates similar to control
- Data continue to show that reduction in eGFR following RDN is consistent with decline seen in patients not treated with RDN, per their natural disease course
- Suspected renal artery stenosis within range reported in literature for hypertensive patients
- Long-term safety results continue to support device use; raise no new concerns

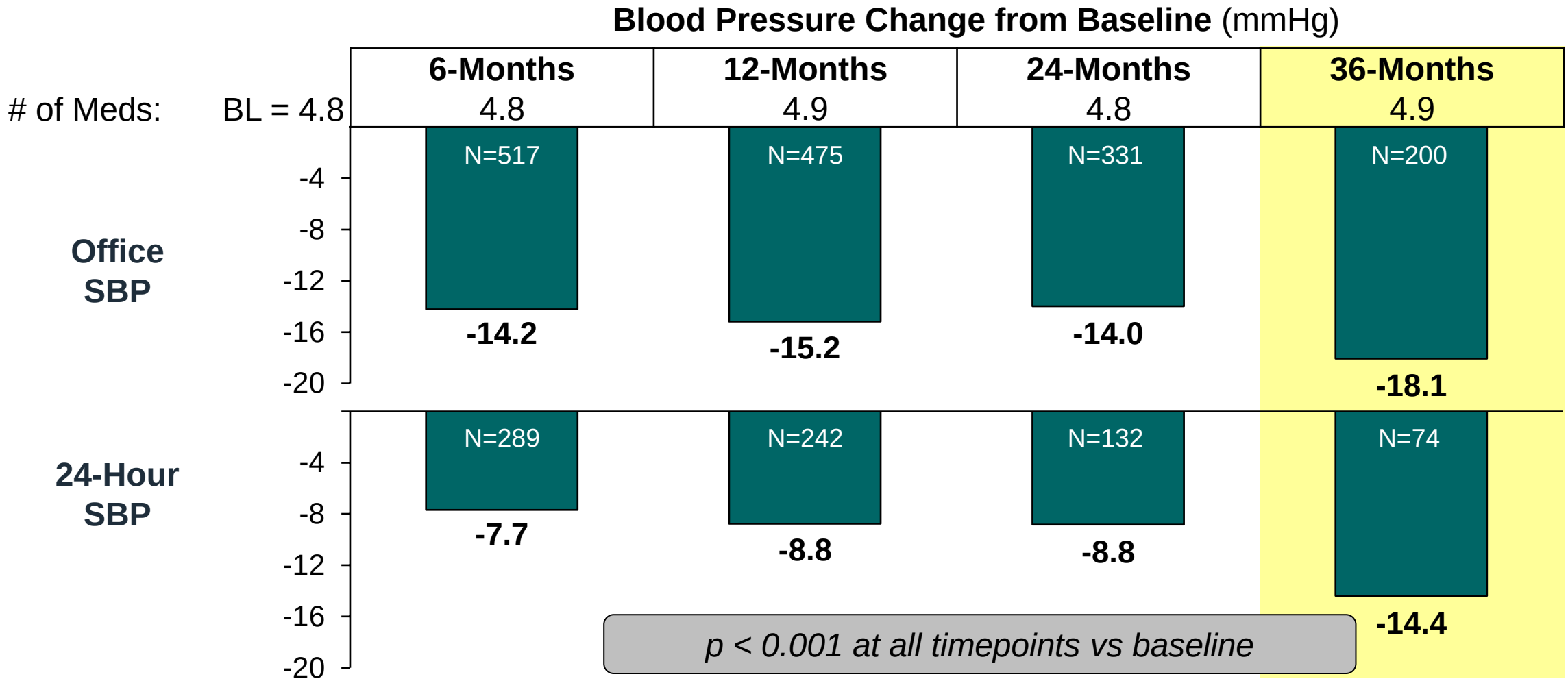
Global SYMPLICITY Registry (GSR) Durability and Long-Term Safety

GSR Designed to Capture Long-Term Safety and Efficacy in Real-World Setting

- Prospective, open-label registry conducted at 245 sites worldwide
- Began enrollment in 2012
- Enrolled > 3,400 patients
- > 7,000 patient-years of follow-up
- Includes ~800 patients treated with Symplicity Spyral

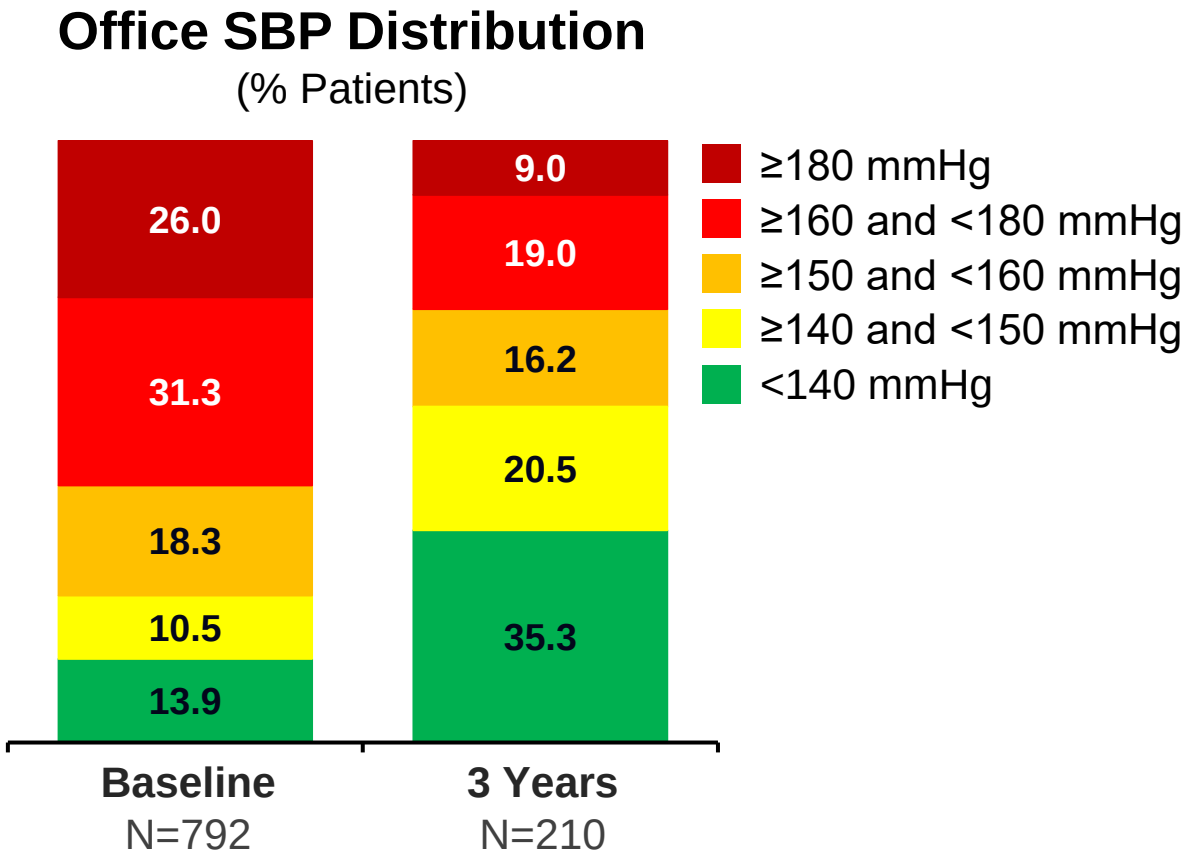


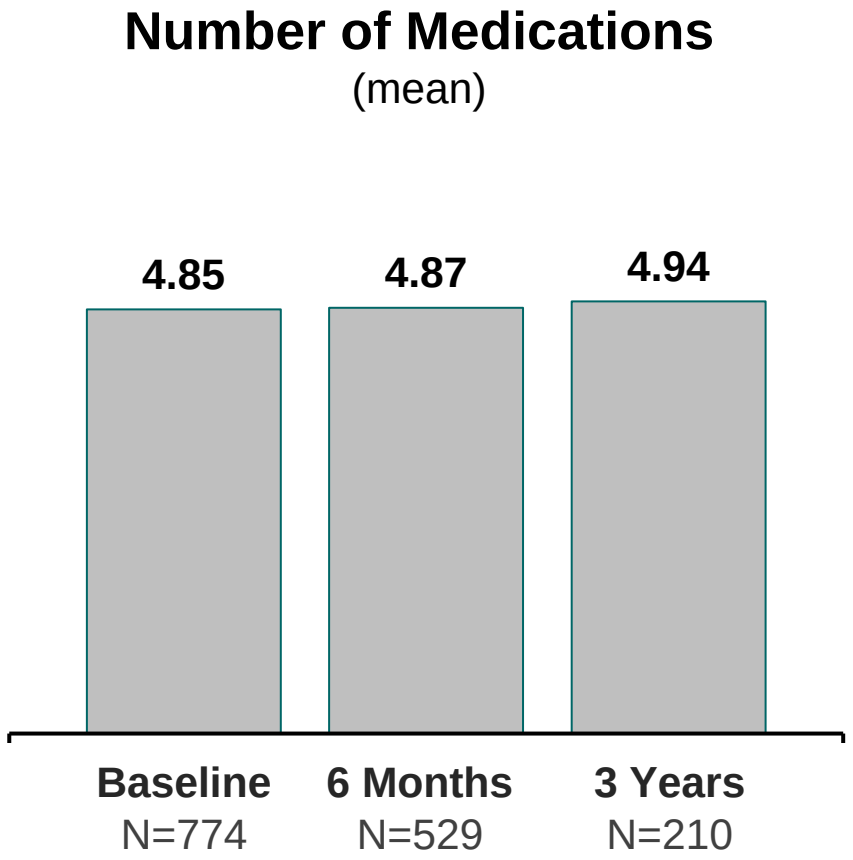
GSR Demonstrates Sustained Blood Pressure Reductions Over 3 Years with Symplicity Spyral



Baseline OSBP = 165.8 ± 24.8 | 24-Hr SBP = 155.2 ± 20.1

GSR Demonstrates RDN Decreased BP Without Increasing Medications at 3 years



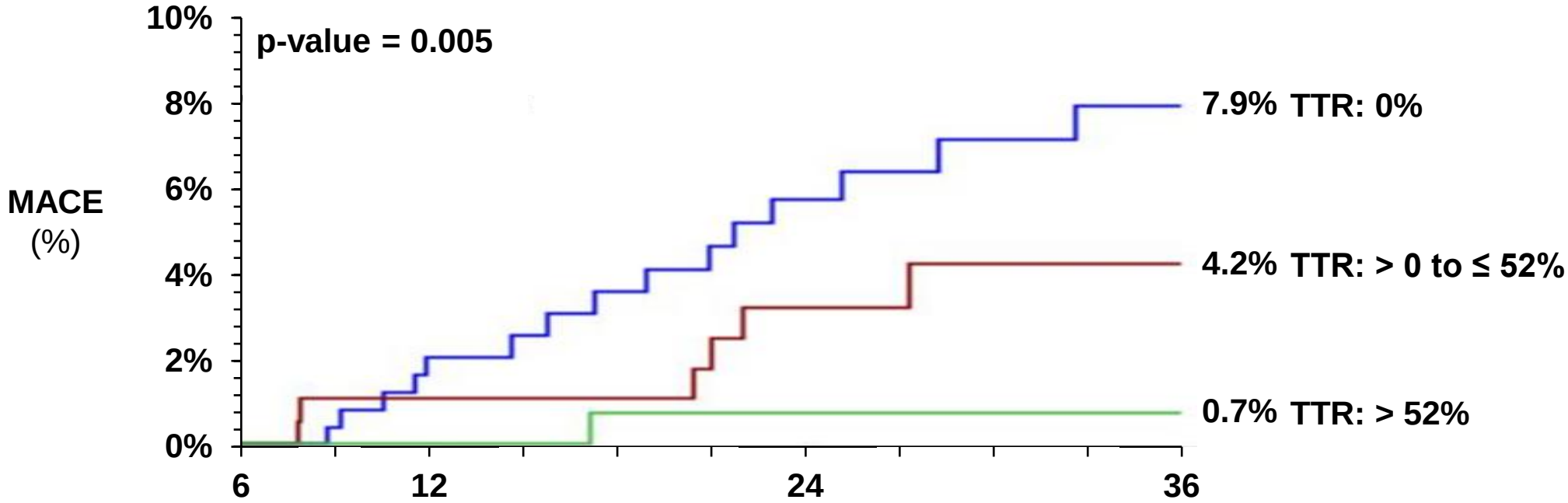


GSR: Time in Target Range (TTR) is Independent Predictor of Cardiovascular Events

- TTR estimate based on successive SBP measurements from baseline through follow-up were linearly interpolated
- Time spent under target SBP was calculated using maximum value of office SBP ≤ 140 or 24-hour SBP ≤ 130 mmHg
- TTR from baseline to 6 months used to inform logistic regression model to predict how TTR affects MACE rates between 6–36 months
- TTR is an independent predictor of cardiovascular events

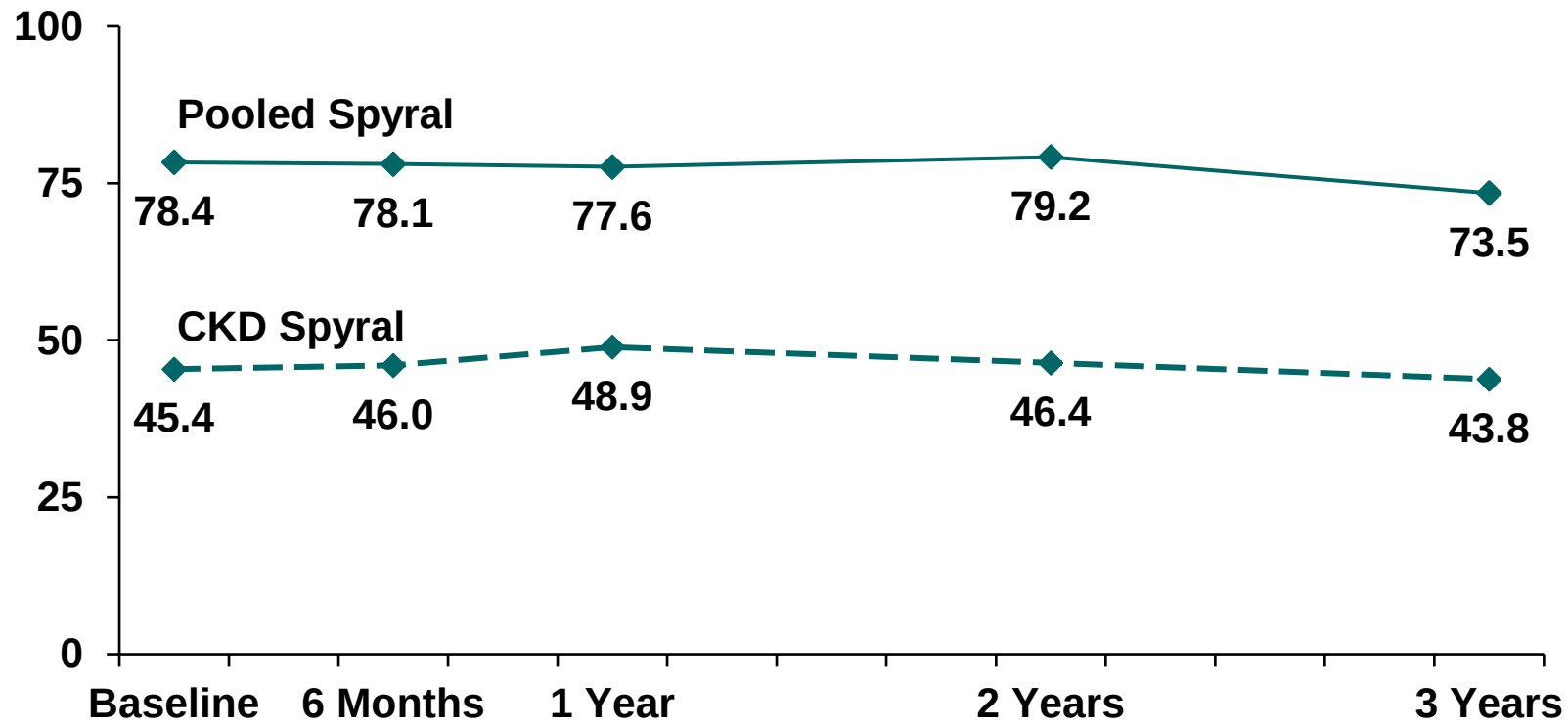
Fatani, *JACC* 2021

GSR Spyral Outcomes
Increased TTR, Decreased MACE



At Risk				
TTR: 0%	266	237	169	95
TTR: > 0 to ≤ 52%	200	172	123	60
TTR: > 52%	195	176	120	64

Stable Renal Function Through 3 Years in Pooled Data Using Spyral



eGFR (calculated by creatinine, mL/min/1.73m^2)

	Baseline	6 Months	1 Year	2 Years	3 Years
Pooled Spyral (N)	1,472	972	881	595	282
CKD Spyral (N)	275	142	125	87	50

Data pooled from Symplicity Spyral treated patients in GSR, proof of concept study, OFF MED and ON MED
CKD defined as eGFR < 60 mL/min/1.73m^2

GSR: Safety With Symplicity Spyral Demonstrated Through 3 Years

- GSR data support safety results from the clinical trials in the Spyral cohort
- Sustained renal function following RDN
- No events of renal artery stenosis, dissections, or renal artery reinterventions (0 / 846)

Durability and Long-Term Safety Demonstrated

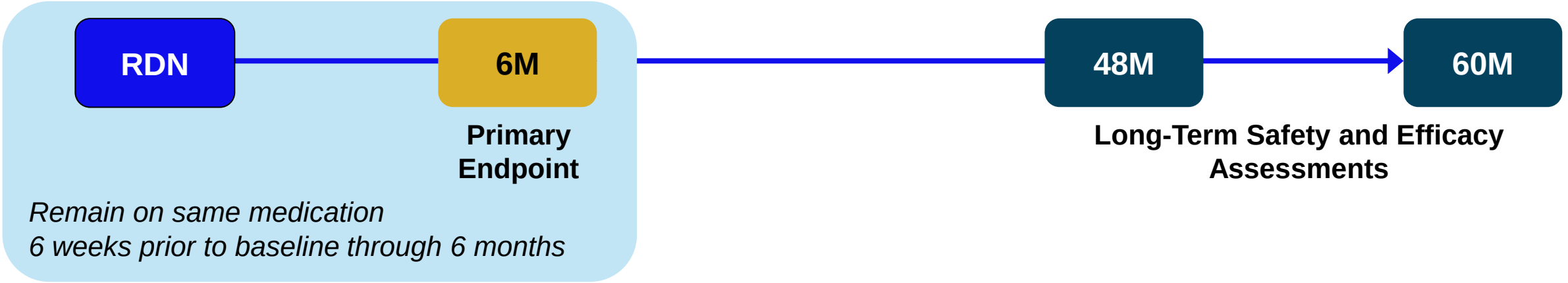
- BP reductions sustained through 3 years
- Real-world population office and 24-hour BP reductions comparable to sham-controlled trials
- Significant reductions in office and 24-hour BP
- Fewer CV events in patients with greater time in target range
- Long-term safety established

Renal denervation is a safe, minimally invasive procedure that can help patients manage their hypertension over time

AFFIRM Study

Ongoing AFFIRM Study: International, Multi-Center, Prospective, Single-Arm Study

- To evaluate safety, efficacy, and durability in real-world setting
- Patients with diabetes, isolated systolic hypertension, and CKD
- Actively enrolling up to 1,200 patients



Clinical Perspective

Raymond Townsend, MD

Co-Director of Hypertension Section

University of Pennsylvania School of Medicine

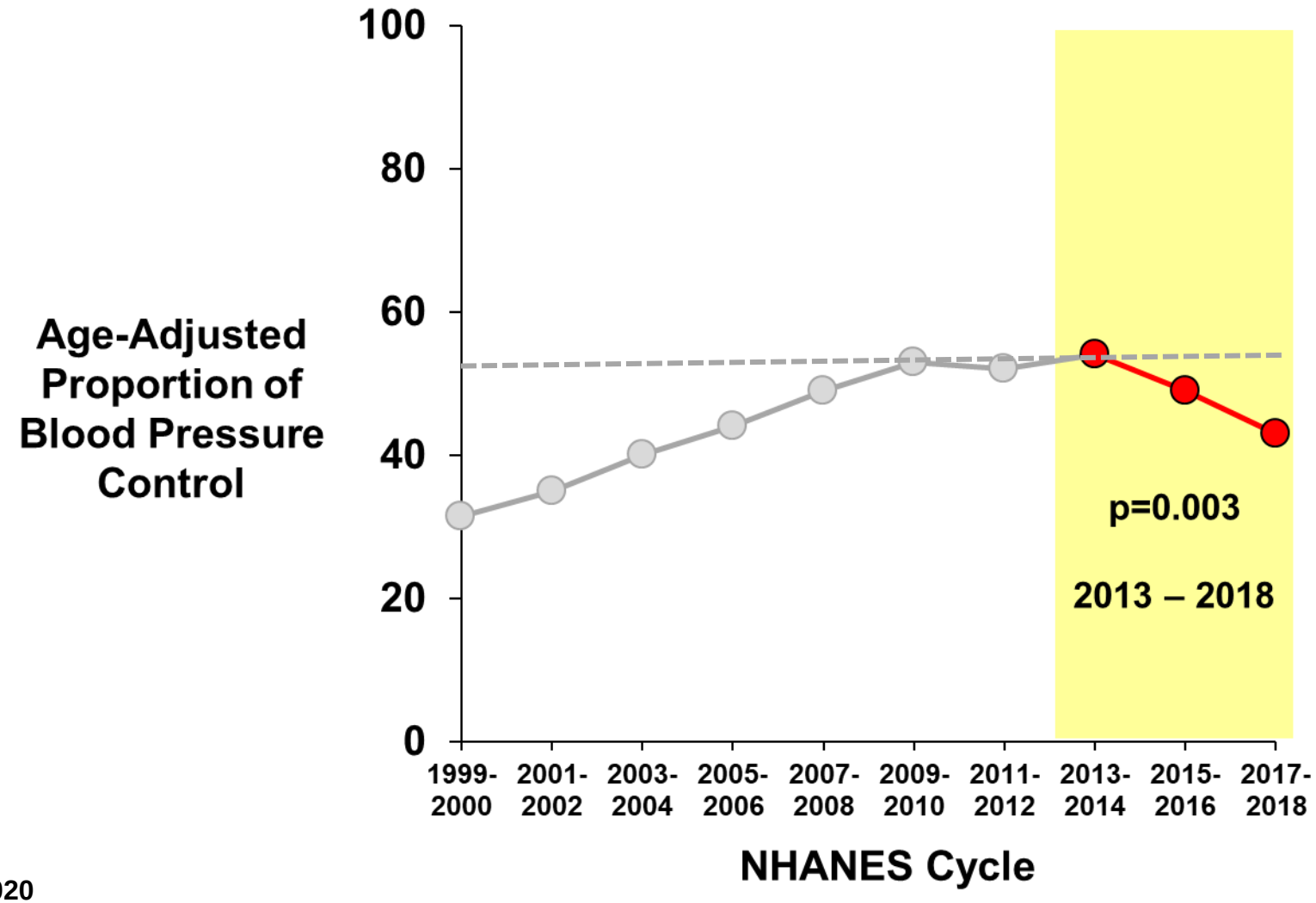
Many Patients Remain Uncontrolled Due to Sub-Optimal Adherence to Medication and/or Lifestyle Changes

Initial Conversations with Patients

Lifestyle Modifications

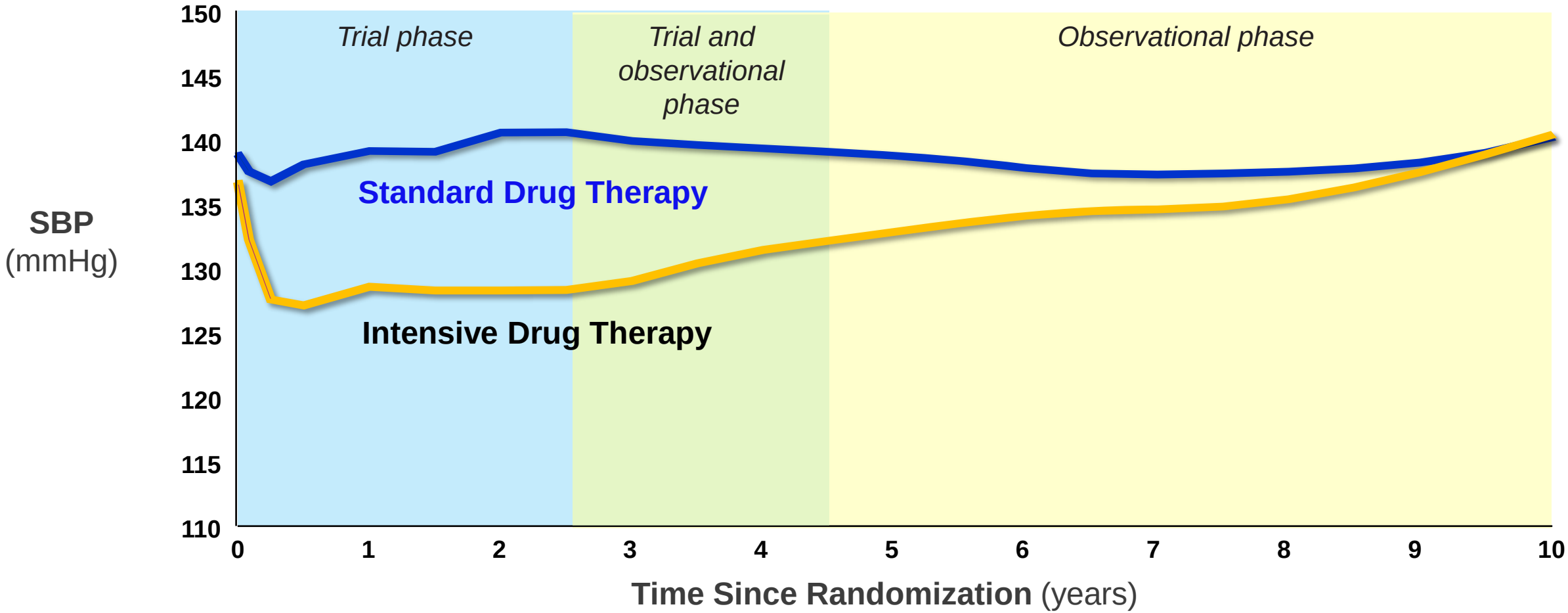
Anti-hypertensive Medications

Hypertension Control Rates in United States are Declining Since 2013



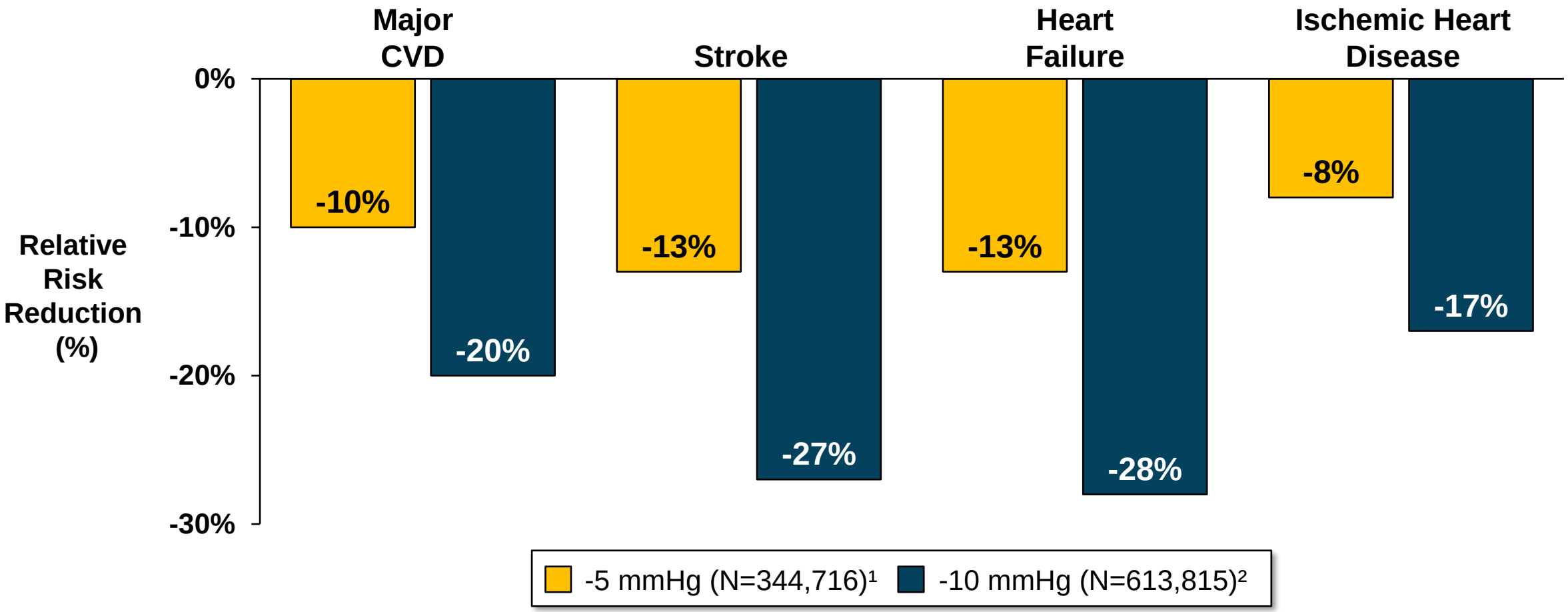
Muntner, *JAMA* 2020
NHANES = National Health and Nutrition Examination Survey

Long-Term Attenuation of Antihypertensive Medication Benefit in SPRINT



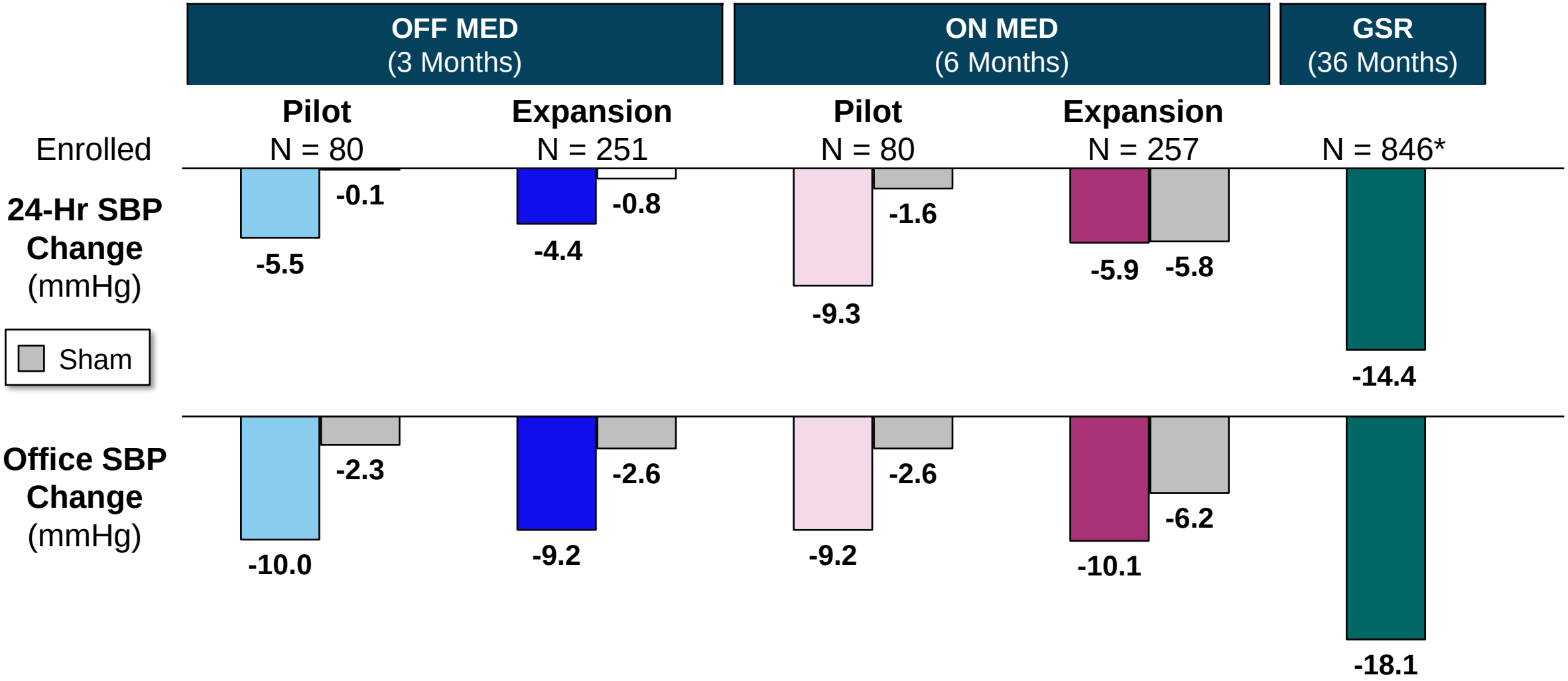
Adapted from Jaeger et al. *JAMA Cardiol*, 2022

Every 5 mmHg Reduction in Office SBP Translates to 10% Reduction in MACE



1. Blood pressure lowering treatment trialists' collaboration, *Lancet* 2021
2. Ettehad, *Lancet* 2016

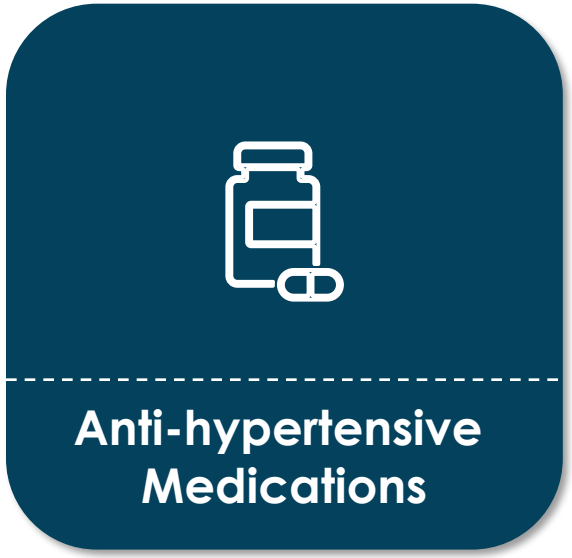
Consistent 24-Hour and Office SBP Reductions Across Medtronic RDN Spyral Studies



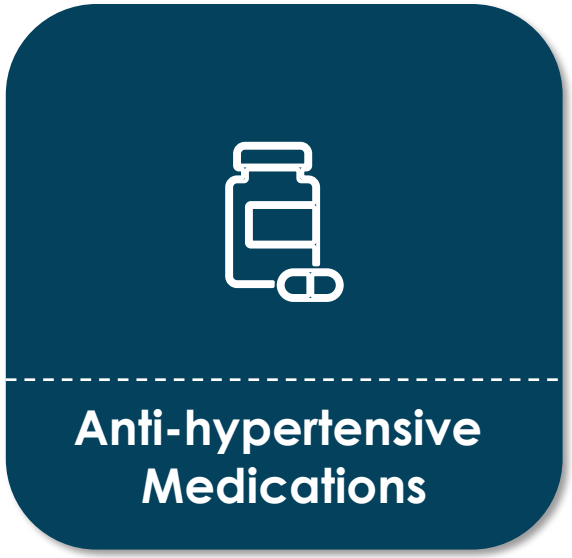
* 274 patients evaluable at 36 months

RDN Should be an Option for Patients Who Remain Uncontrolled

- Uncontrolled despite use of anti-hypertensive medications
- Uncontrolled and poorly tolerate BP lowering therapy



Conversations with Patients About Treatment Options Should Include RDN



- Complementary to medication
- Non-drug intervention
- Lower BP, continuously over 24 hrs
- Results durable for ≥ 3 years
- Favorable procedural and long-term safety

Evidence Provides Reasonable Assurance of Positive Benefit-Risk

FDA Guidance	SPYRAL Clinical Program Study Results
"The device fills an unmet medical need or niche for more effective treatment of life-threatening or irreversibly debilitating human disease/conditions"	• Breakthrough device designation received for the treatment of uncontrolled hypertension. • Symplicity Spyral is one of the first device options for uncontrolled HTN
"[What are] the adverse events (AEs) or outcomes related to the device itself?"	• Low rate of MAEs • No major device-related and low rate of procedure-related safety events observed • No increased risk of RDN-associated renal artery stenosis • Sustained renal function through 3 years
"Favorable change in at least 1 clinical assessment that is equal to or greater than seen in the control group [whether or not the results are statistically significant]"	• OFF and ON MED studies showed a clinically meaningful reduction in blood pressure that is equal to or greater than that seen in the control (sham) in all endpoints.

FDA Guidance: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

Positive Benefit-Risk Profile Supports Approval of Symplicity Spyral System

- Uncontrolled BP is highly prevalent, with drug adherence as a challenge
- Patients are open to complementary treatment options
- Totality of data support safety and efficacy of RDN to treat patients with hypertension
  - Reduces BP continuously over 24-hour period
  - Durable BP reductions compared to baseline to 3 years, including in real world populations
- Favorable risk-benefit profile established in clinical trials of over 1800 patients

Moderator for Q&A

Vanessa DeBruin, MS

Senior Director of Clinical Research

Medtronic

Symplicity Spyral™ Renal Denervation System to Treat Patients with Hypertension

August 23, 2023

Medtronic

Circulatory System Devices Panel