Device Therapy and Resistant Hypertension

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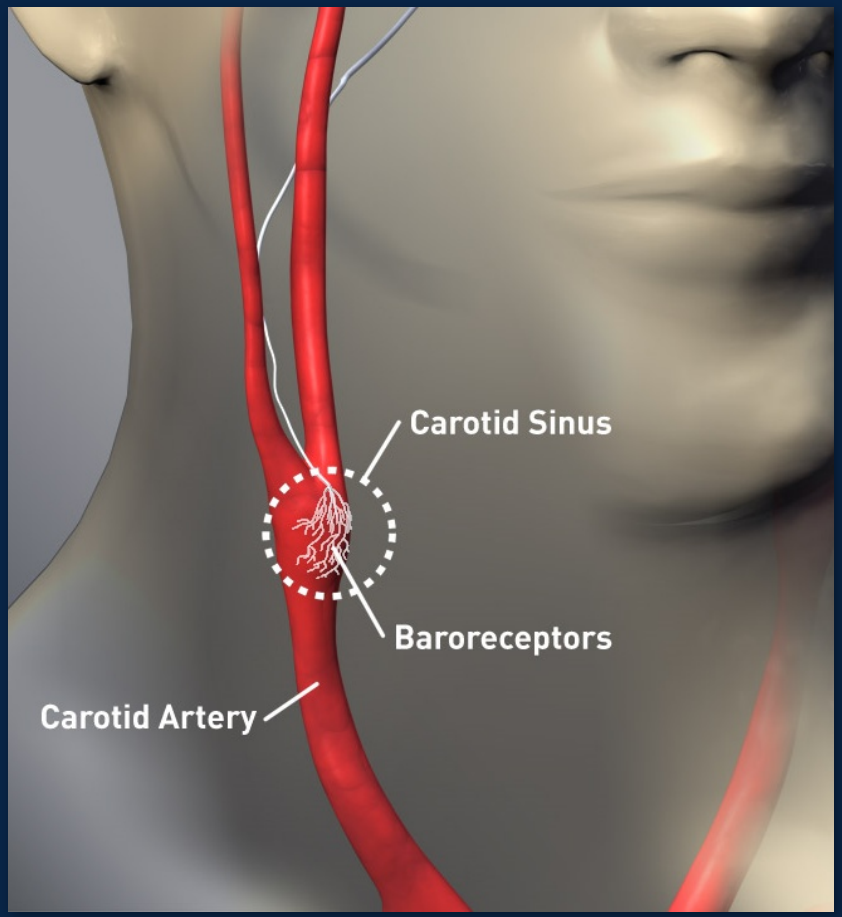
Alternatives to Drug Therapy for Resistant Hypertension: Where Are We?

- Baroreceptor Activation Therapy (BAT)
- Renal Denervation

Resistant Hypertension Treated with Baroreflex Activation (BAT)

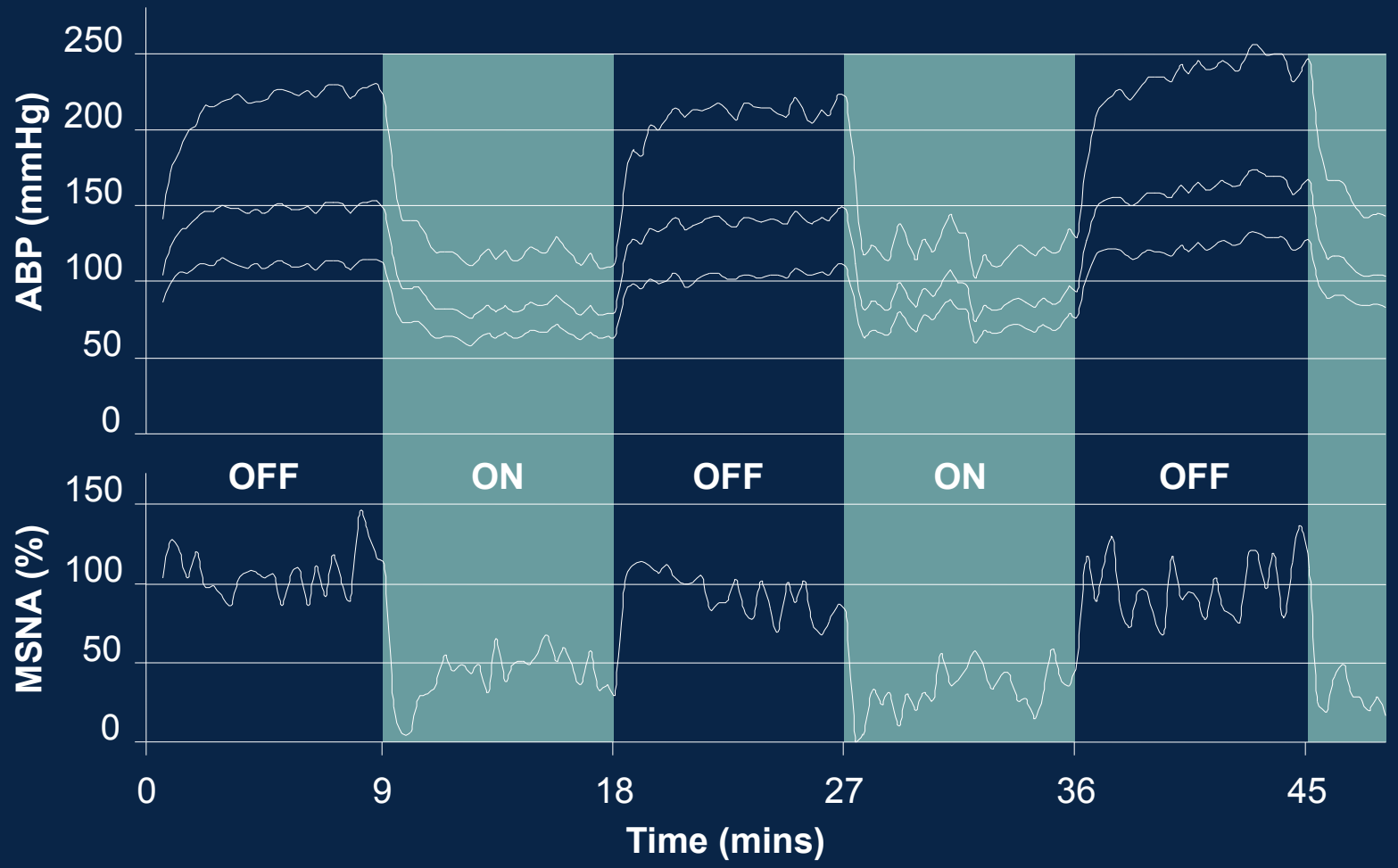


Wireless Programming System

400+ patients treated worldwide

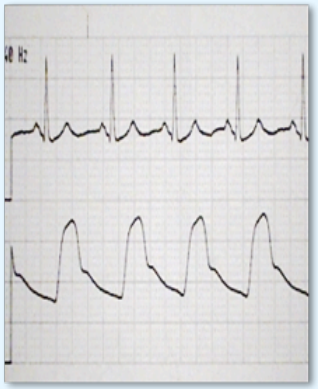
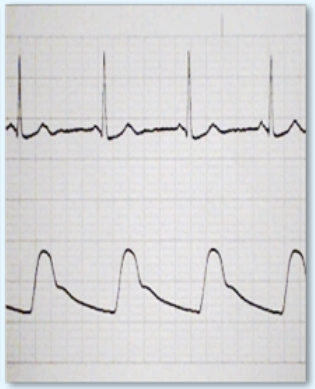
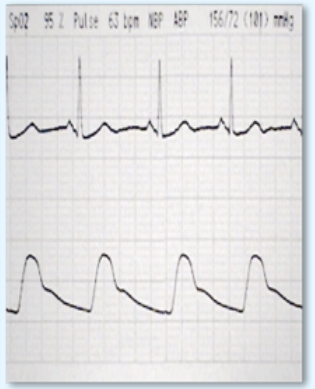
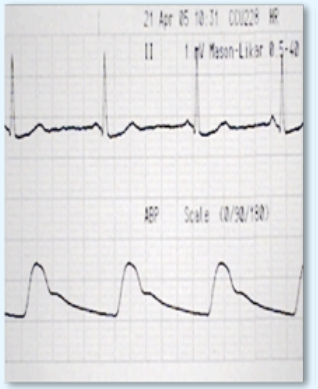
CE *CE Marked for the treatment of resistant hypertension*

Reversible Physiologic Response



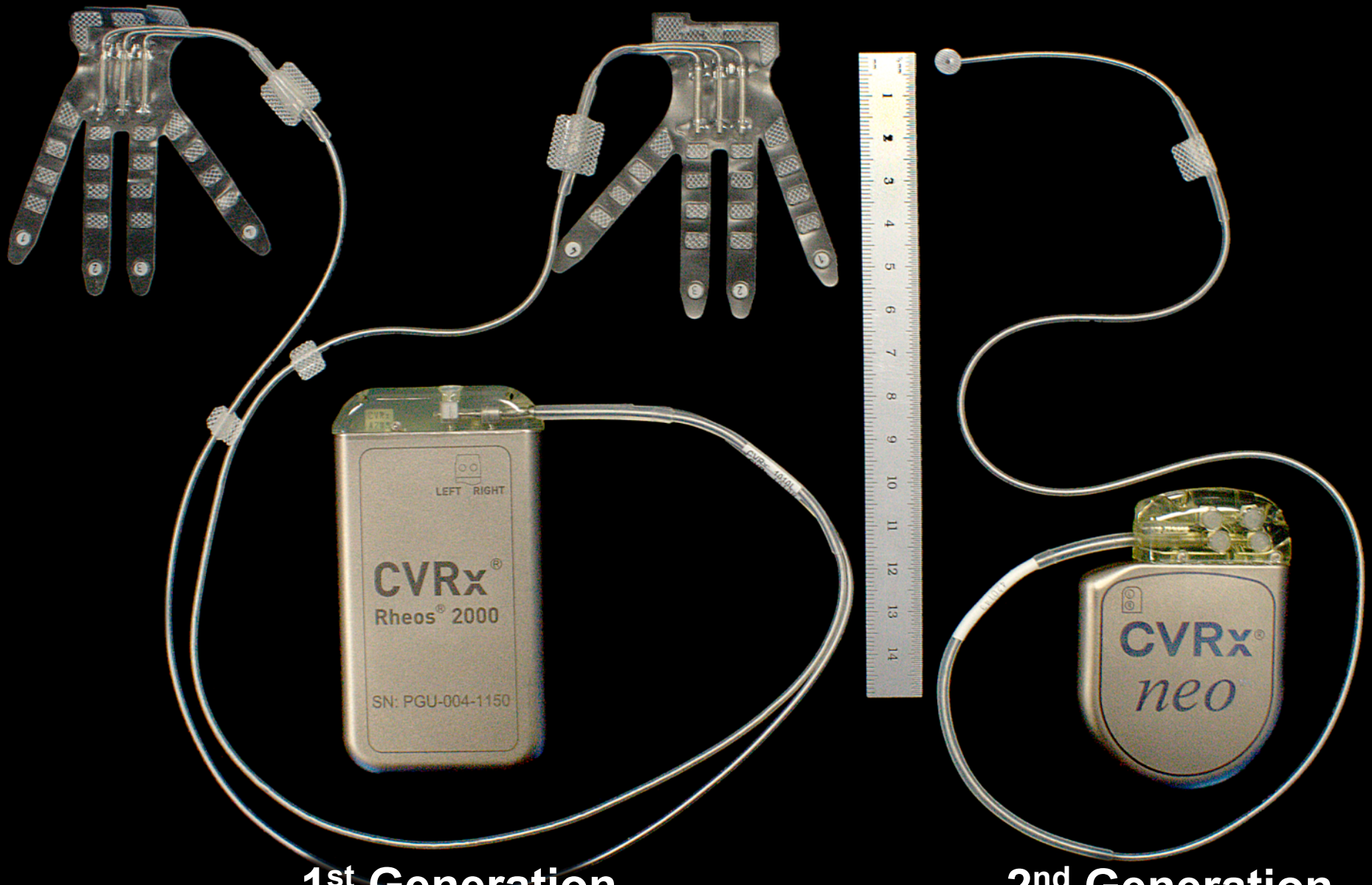
Heusser et al. Hypertension 2010;55:619-26.

Ability to Titrate Device to Meet Individual Patient Need

	Control	1 Volt	2 Volts	3 Volts
				
Heart Rate bpm	71	56	58	50
Blood Pressure mmHg	210 / 96	168 / 73	156 / 72	144 / 66

≈ 4 min

2nd Generation Platform

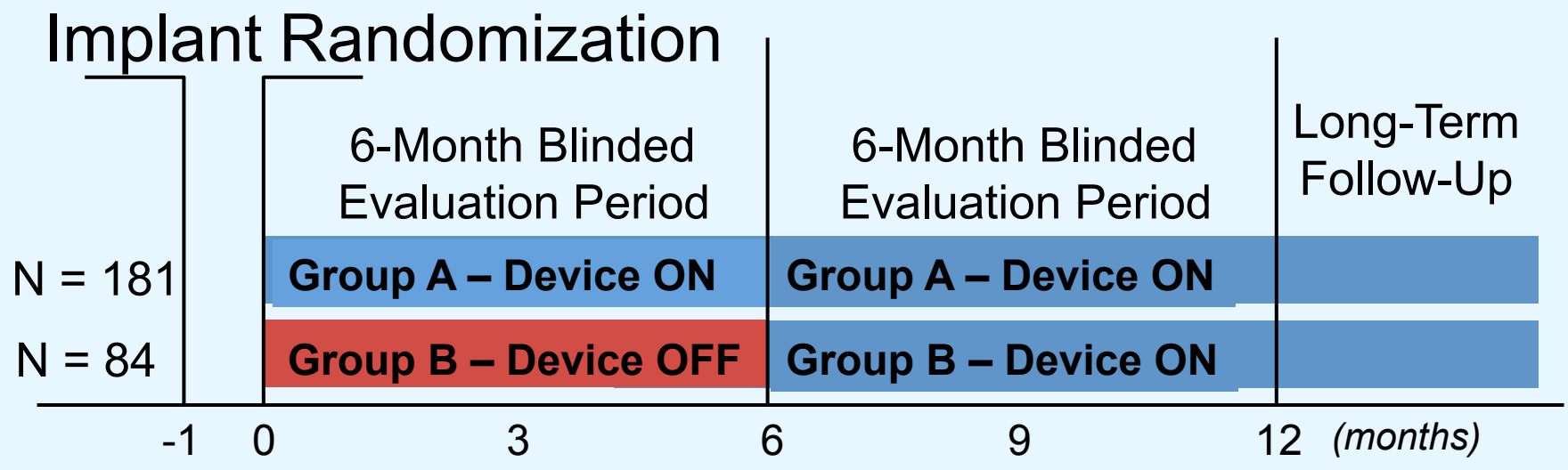


1st Generation

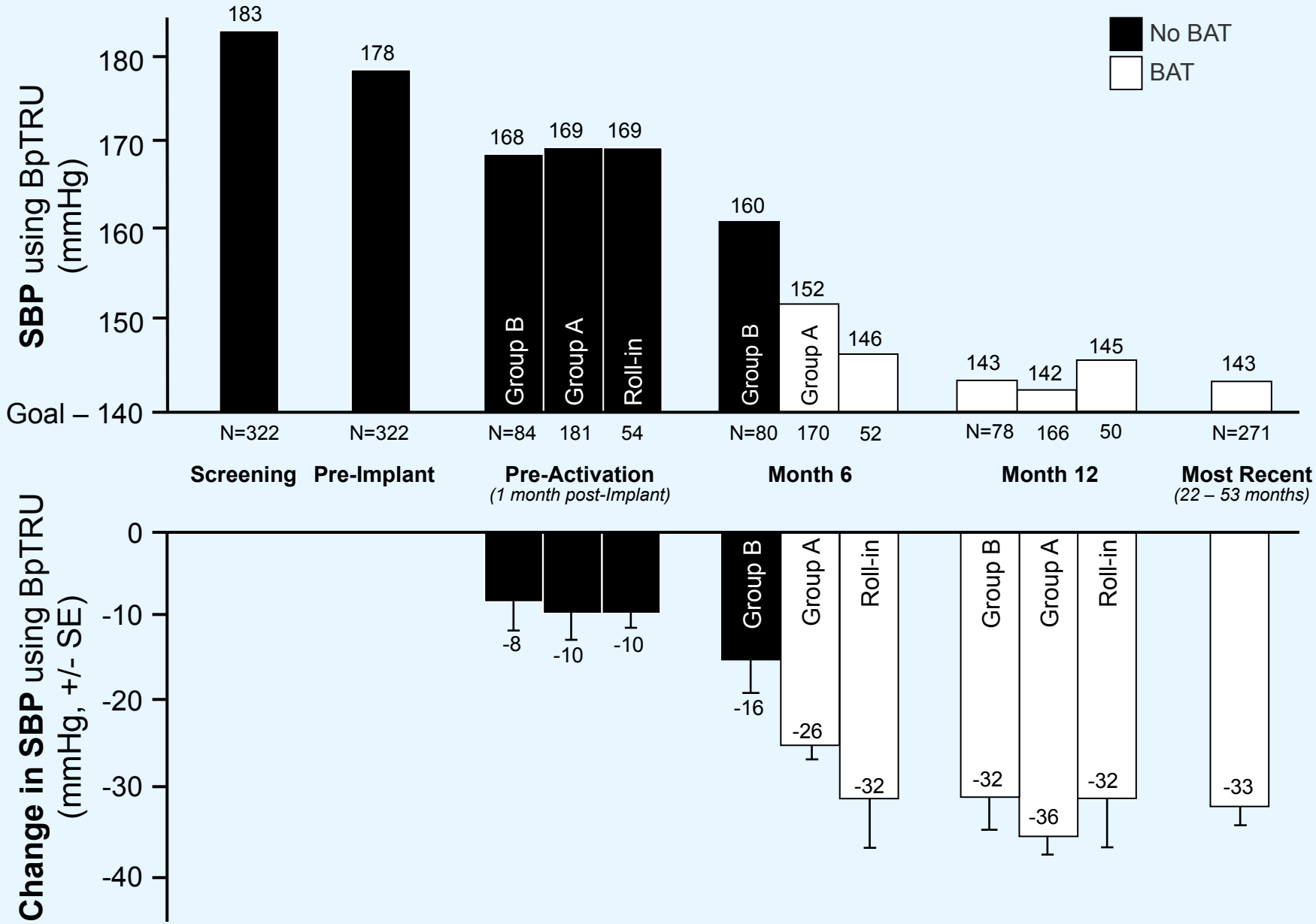
2nd Generation

Rheos Hypertension Pivotal Trial Design

- **Trial Hypothesis**: *Baroreflex Activation Therapy is Safe and Effective for the Treatment of Resistant Hypertension*
- Prospective randomized double-blind trial
  - 322 patients at 49 sites
  - 55 roll-in patients / 265 randomized (2:1)
  - Co-primary endpoints
1. Short-Term Acute Response
2. Long-Term Sustained Response
3. Short-Term Procedural Adverse Events
4. Short-Term Hypertension Therapy Adverse Events
5. Long-Term Device Adverse Events



Long-Term Data in Resistant HTN



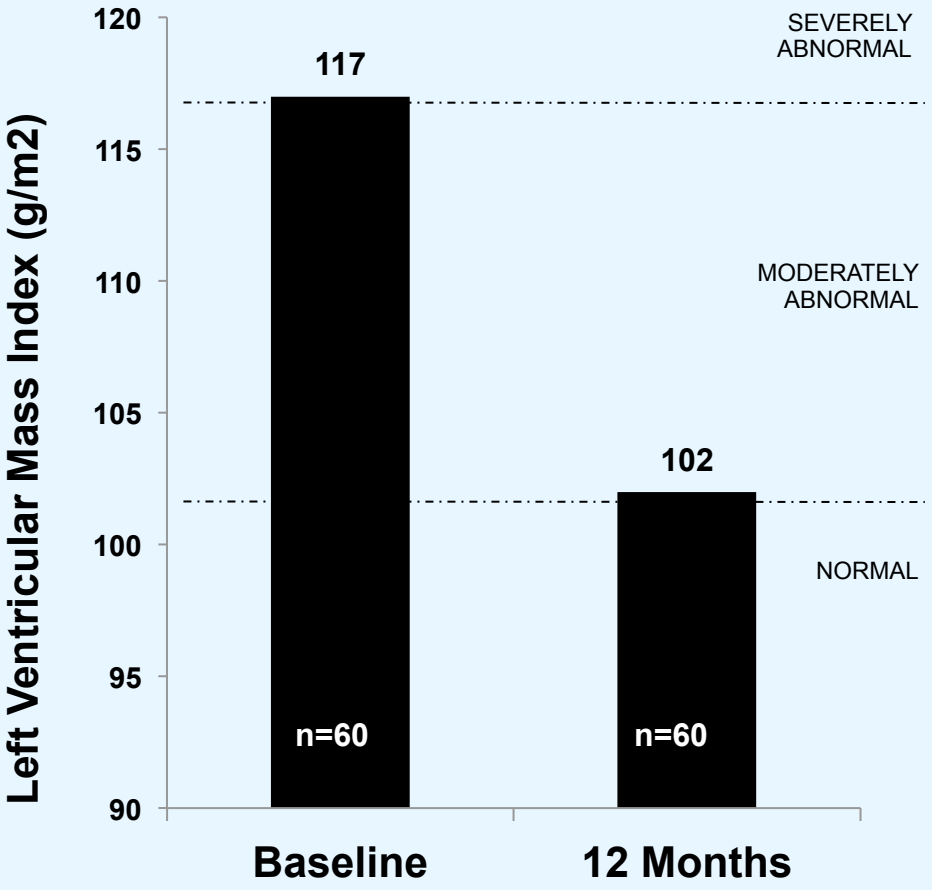
Bakris et al. J Am Soc Hypertens 2012

Barostim Pivotal Trial LV Remodeling

Rheos Study Demonstrated Left Ventricular Reverse Remodeling with BAT

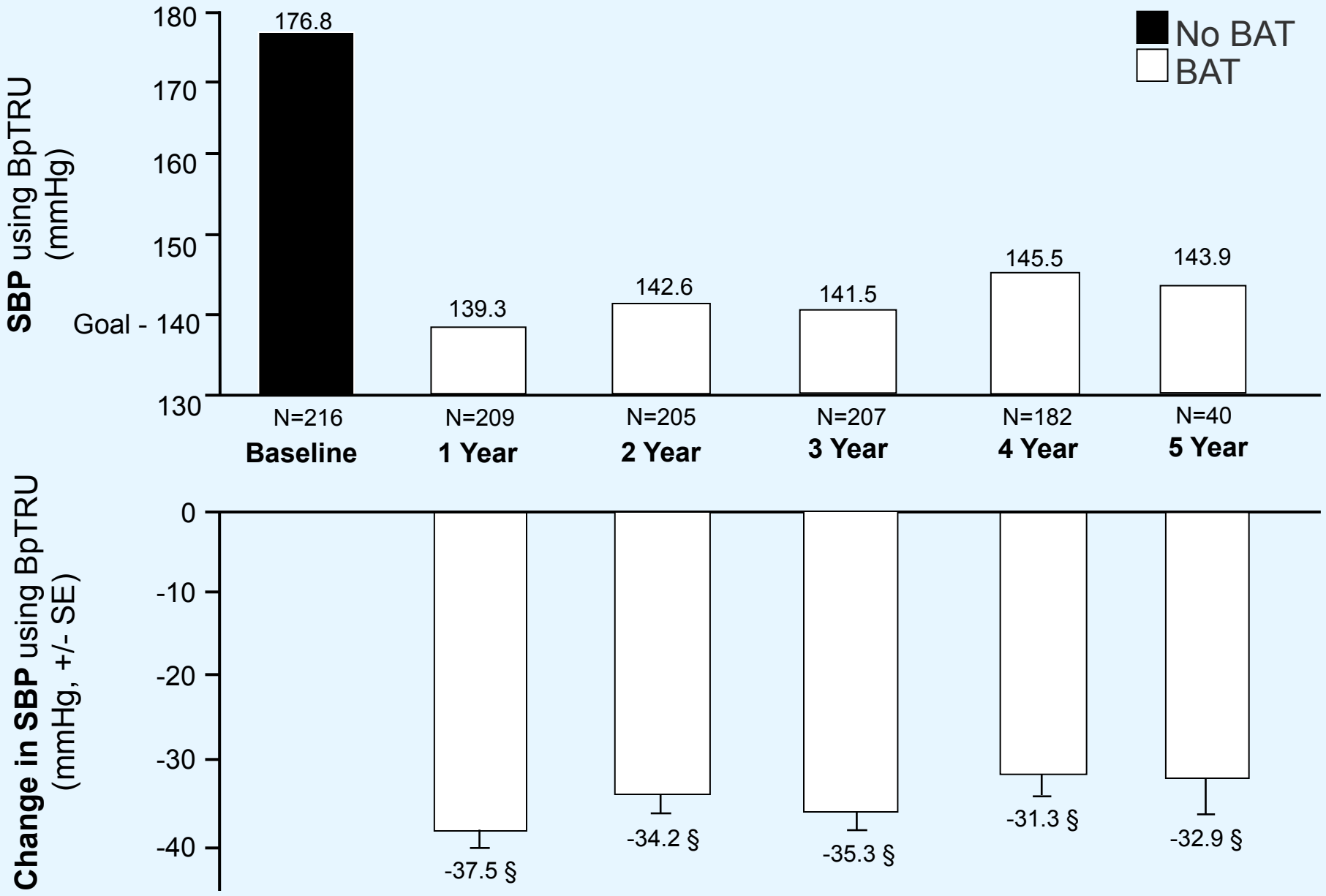
- 60 patients from Rheos study enrolled in echocardiography sub-study
- Study assessed changes in left ventricular mass index (LVMI) after 12 months of active therapy
- LVMI reduction is a strong indicator of effective heart failure therapy
- At 12 months of BAT, average reduction of LVMI was 15 g/m^2

($p < 0.01$) to normal range



Bisognano, et al. J Am Coll Cardiol 2011;58:765-73.

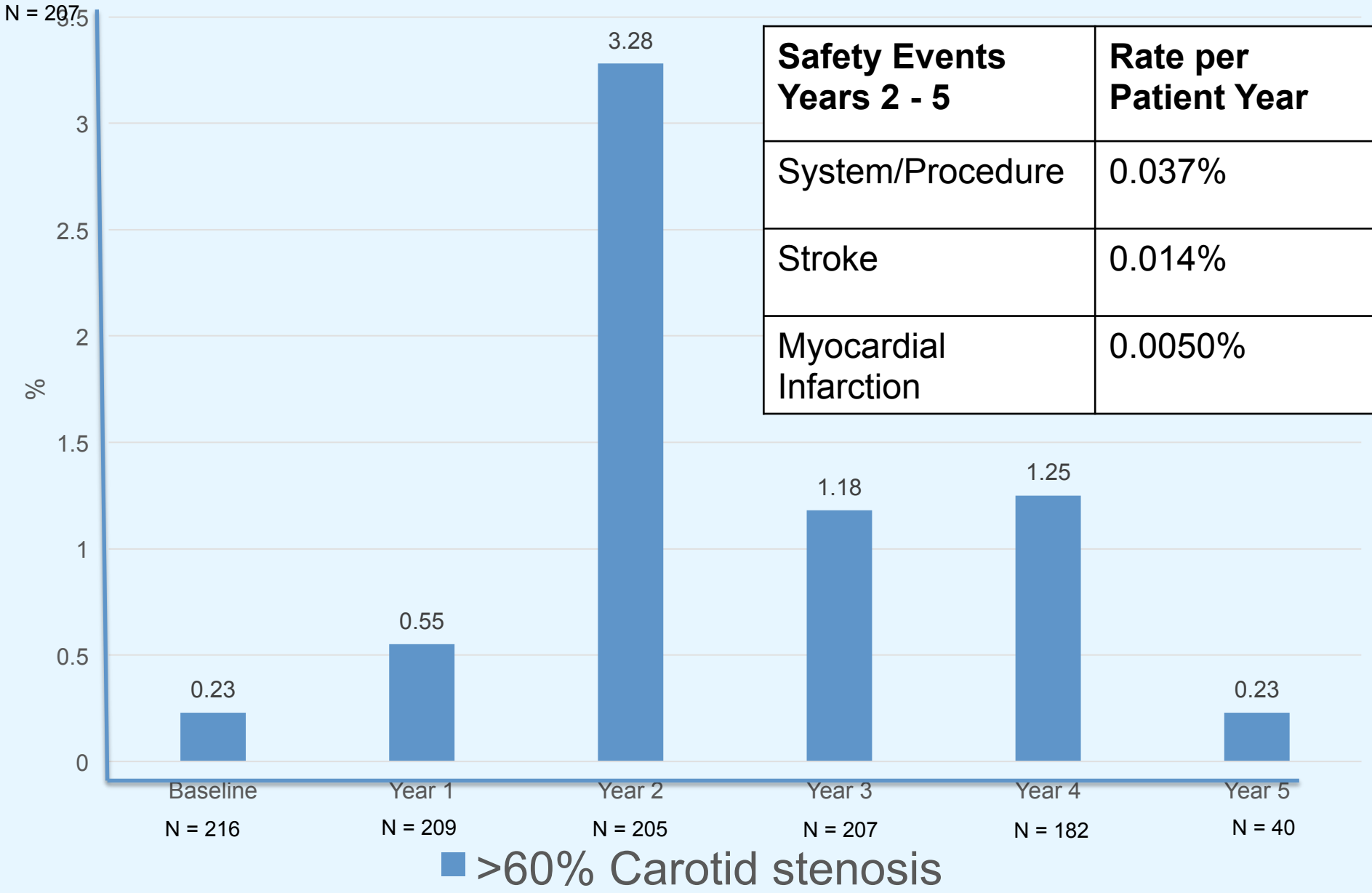
New 5-Year Long-Term SBP Data in Resistant HTN



Bakris et al. ASH 2014

Long-Term Safety of Rheos Implant

(Annual Percent of People with >60% Carotid Stenosis)



Safety Events Years 2 - 5	Rate per Patient Year
System/Procedure	0.037%
Stroke	0.014%
Myocardial Infarction	0.0050%

Catheter-Based Renal Denervation (RDN)
Symplicity HTN Trials

Proof of Principle: Related Changes in Underlying Physiology

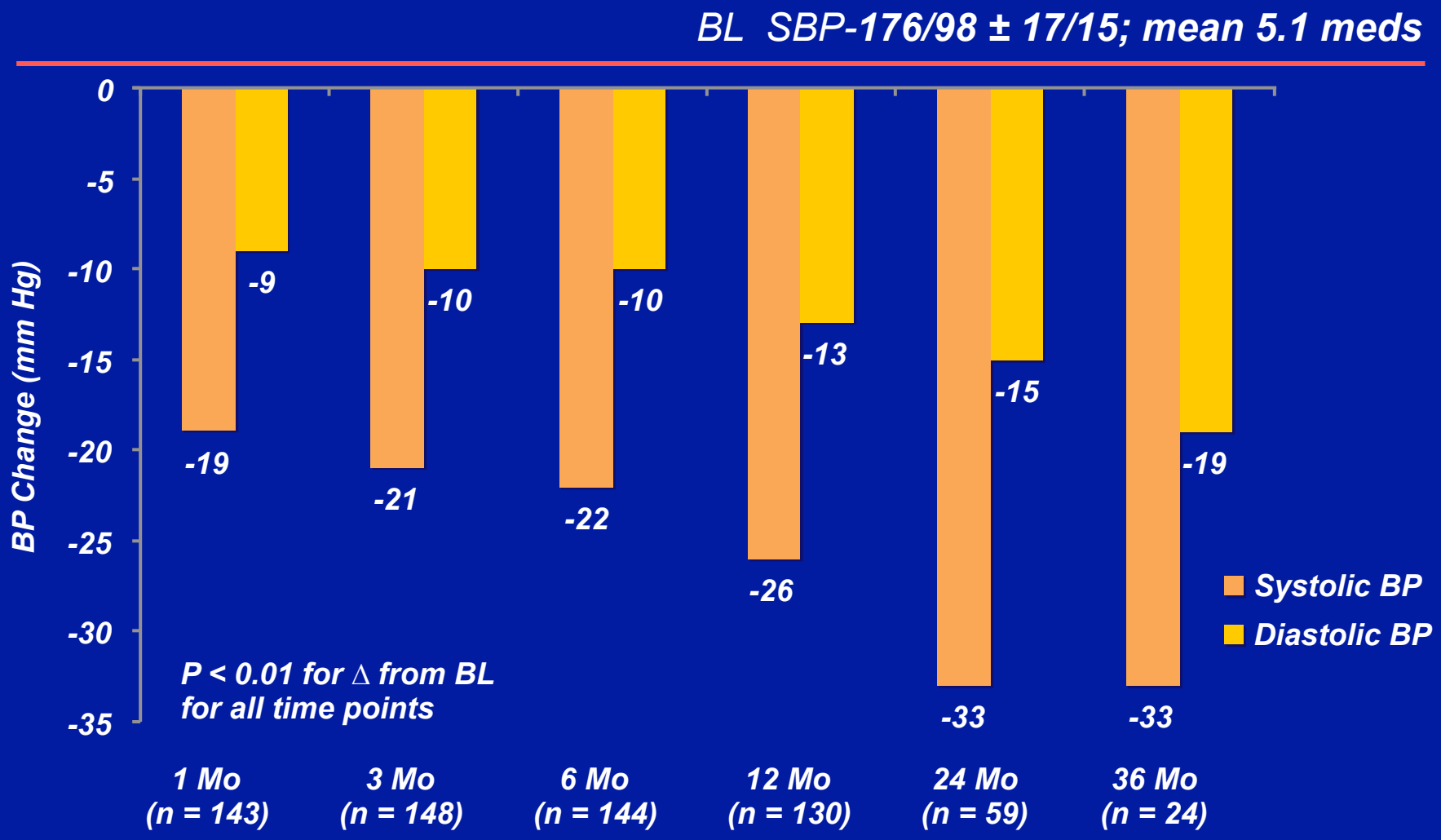
		Baseline	1 mo	Δ
Office BP	(mmHg)	161/107	141/90	
Renal NE spillover	(ng/min)			
- left kidney		72	37	-48%
- right kidney		79	20	-75%
Total body NE spillover	(ng/min)	600	348	-42%
Plasma renin	(µg/l/hr)	0.3	0.15	-50%
Renal plasma flow	(ml/min)	719	1126	57%

LV Mass (cMRI) dropped 7% (from 78.8 to 73.1 g/m^2) from baseline to 12 months

NE=norepinephrine

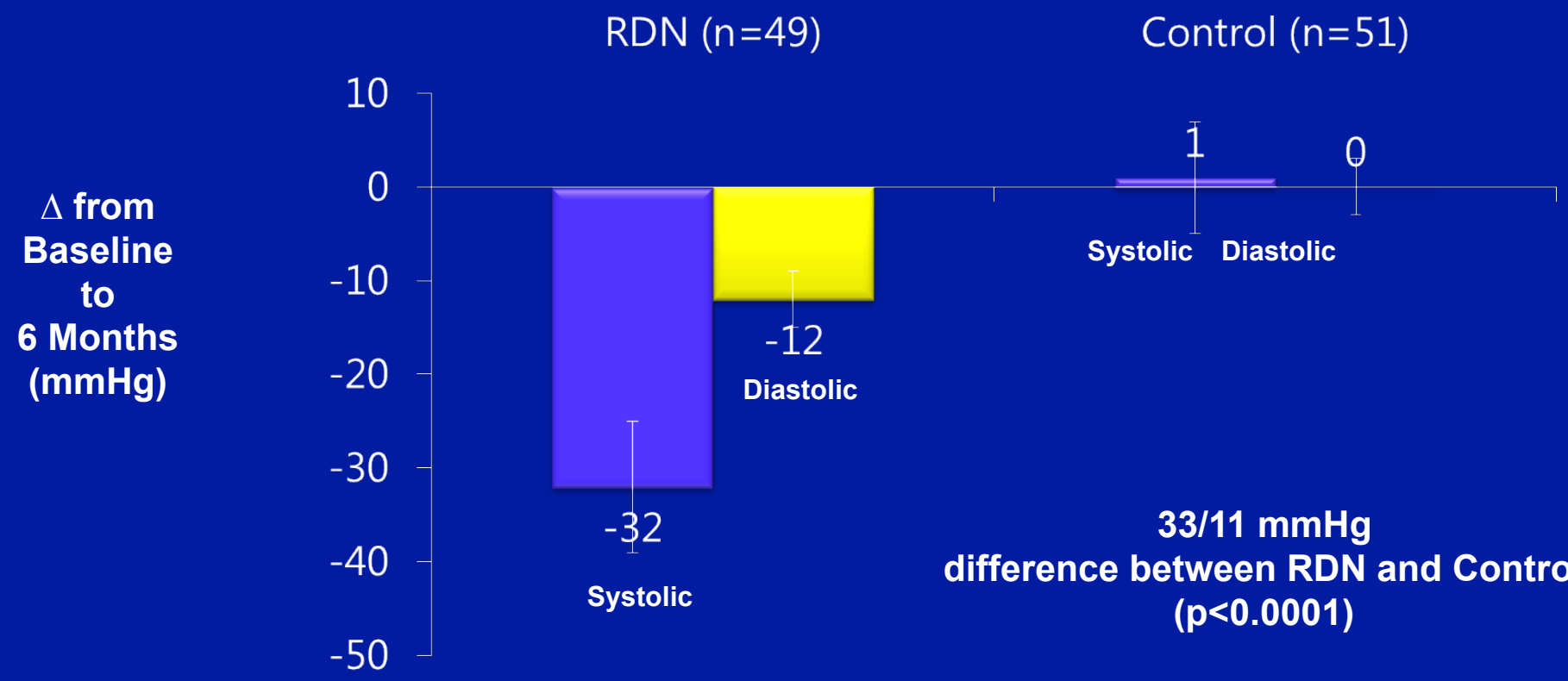
Schlaich et al. NEJM. 2009;36: 932-34.

Symplicity HTN-1 Trial: 36-Month Results



Sobotka. Presented at: ACC.12 61st Annual Scientific Session & Expo; March 25, 2012. Chicago, IL.

SYMPLICITY HTN-2
Primary Endpoint: 6-Month Office BP



- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

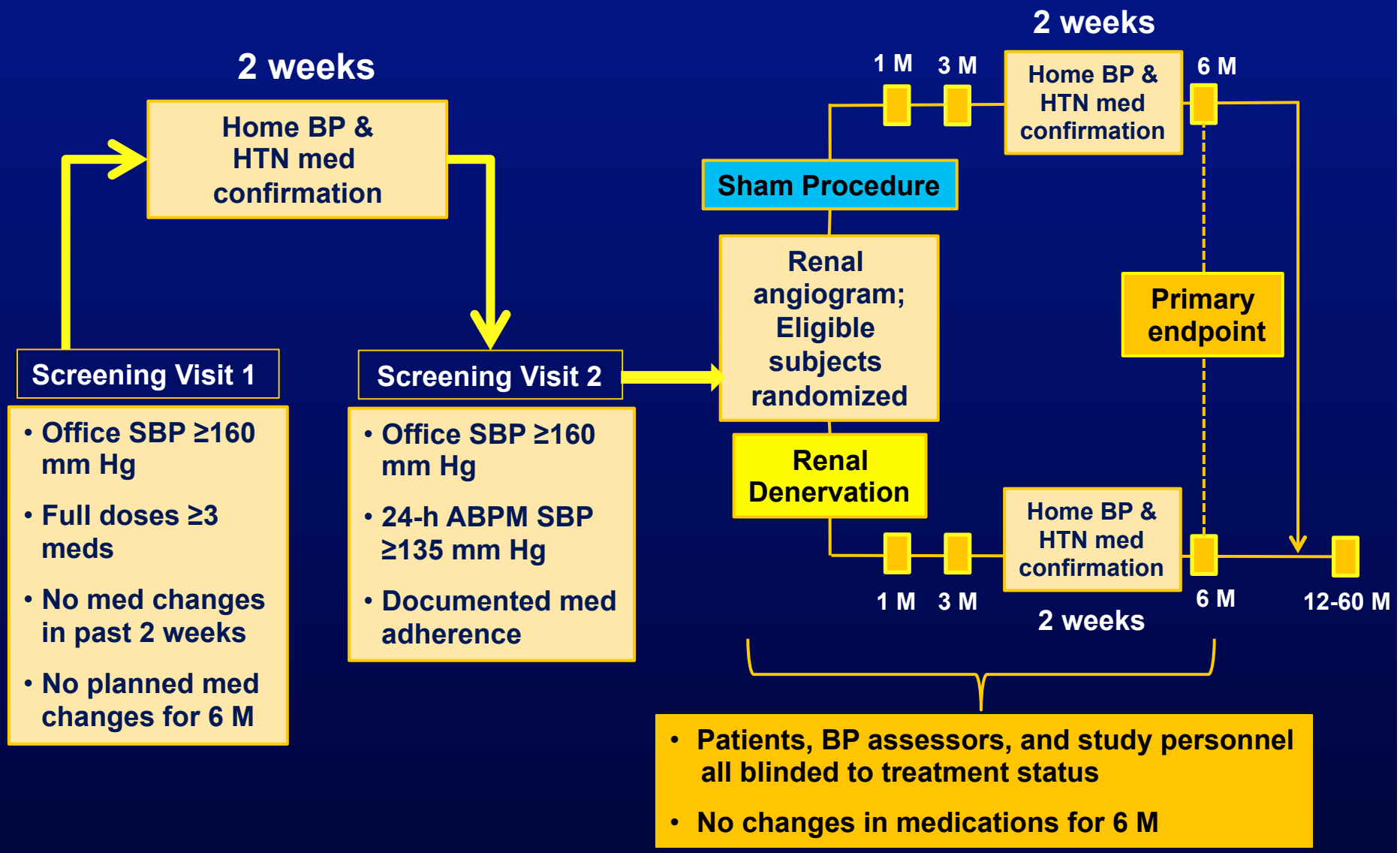
Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-09.

Symplicity HTN-3

- **Purpose:** To provide additional information about a medical device intended to help treat high blood pressure in patients whose blood pressure is not controlled, despite treatment with multiple blood pressure medications
- **Study Design:** multi-center, prospective, single-blind, randomized, controlled study (N=530 randomized patients)-60 US centers
- **Patients:** Ratio 2:1; randomization, treatment to control, after renal angiography confirms anatomy suitable for treatment.
- **Primary Endpoint- Difference in systolic BP between groups at 6 months-**
- **Pre-specified endpoint-change in ABPM at 6 months**
- **Follow-up=3 years**

Kandzari et.al. Clin Cardiol 2012;35:528-35.

SYMPLICITY HTN-3 Trial Design



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

Results: Population Demographics

Symplicity HTN - 3 Clinical Study

Characteristic mean ± SD or %	Renal Denervation (N=364)	Sham Procedure (N=171)	P
Age (years)	57.9 ± 10.4	56.2 ± 11.2	0.09
Male sex (%)	59.1	64.3	0.26
Office systolic blood pressure (mm Hg)	180±16	180±17	0.77
24 hour mean systolic ABPM (mm Hg)	159±13	160±15	0.83
BMI (kg/m^2)	34.2 ± 6.5	33.9 ±6.4	0.56
Race* (%)			0.57
African American	24.8	29.2	
White	73.0	69.6	
Medical history (%)			
Renal insufficiency (eGFR<60 ml/min/1.73m^2)	9.3	9.9	0.88
Renal artery stenosis	1.4	2.3	0.48
Obstructive sleep apnea	25.8	31.6	0.18
Stroke	8.0	11.1	0.26
Type 2 diabetes	47.0	40.9	0.19
Hospitalization for hypertensive crisis	22.8	22.2	0.91
Hyperlipidemia	69.2	64.9	0.32
Current smoking	9.9	12.3	0.45

Race also includes Asian, Native American, or other

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

Baseline Hypertensive Therapy

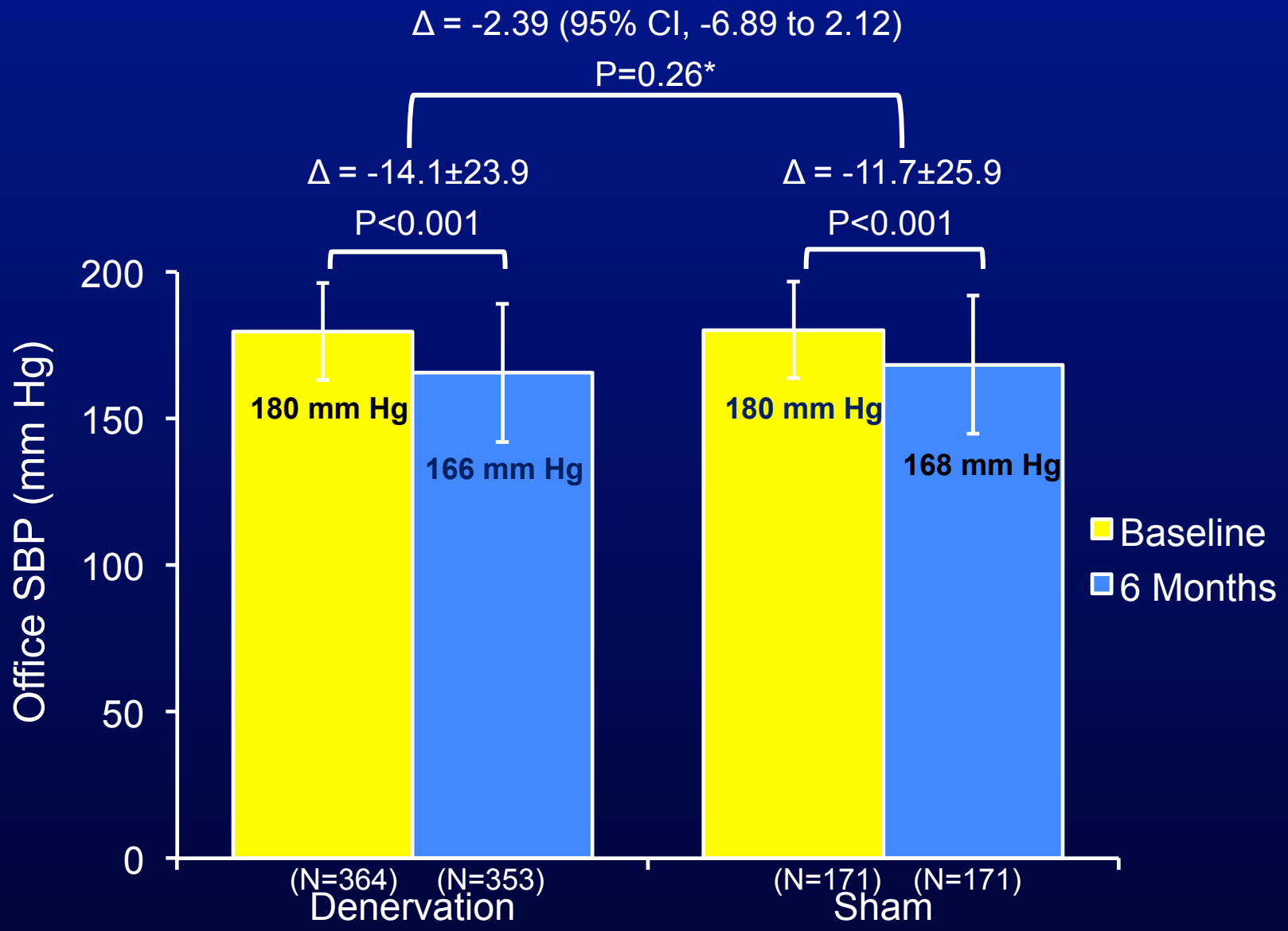
Symplicity HTN - 3 Clinical Study

Characteristic mean ± SD or %	Renal Denervation (N=364)	Sham Procedure (N=171)
No. of antihypertensive medications	5.1 ± 1.4	5.2 ± 1.4
Angiotensin-converting enzyme inhibitors	49.2	41.5
% at max tolerated dose	45.9	37.4
Angiotensin receptor blockers	50.0	53.2
% at max tolerated dose	49.5	51.5
Aldosterone antagonists	22.5	28.7
Alpha-adrenergic blockers	11.0	13.5
Beta blockers	85.2	86.0
Calcium channel blockers	69.8	73.1
% at max tolerated dose	57.1	63.7
Centrally acting sympatholytics	49.2	43.9
Diuretics	99.7	100
% at max tolerated dose	96.4	97.7
Direct renin inhibitors	7.1	7.0
Direct-acting vasodilators	36.8	45.0

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

Primary Efficacy Endpoint

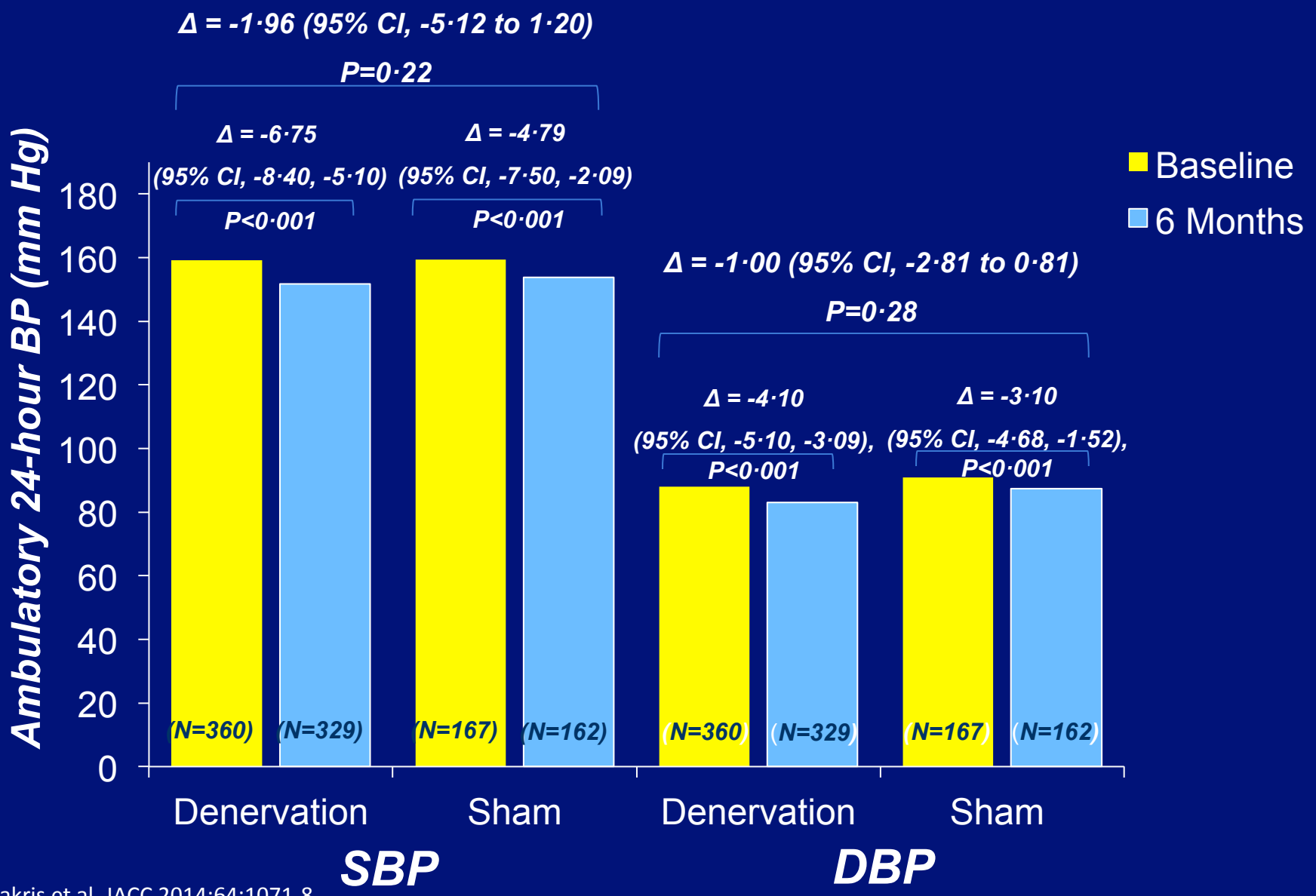
Symplicity HTN - 3 Clinical Study



*P value for superiority with a 5 mm Hg margin; bars denote standard deviations

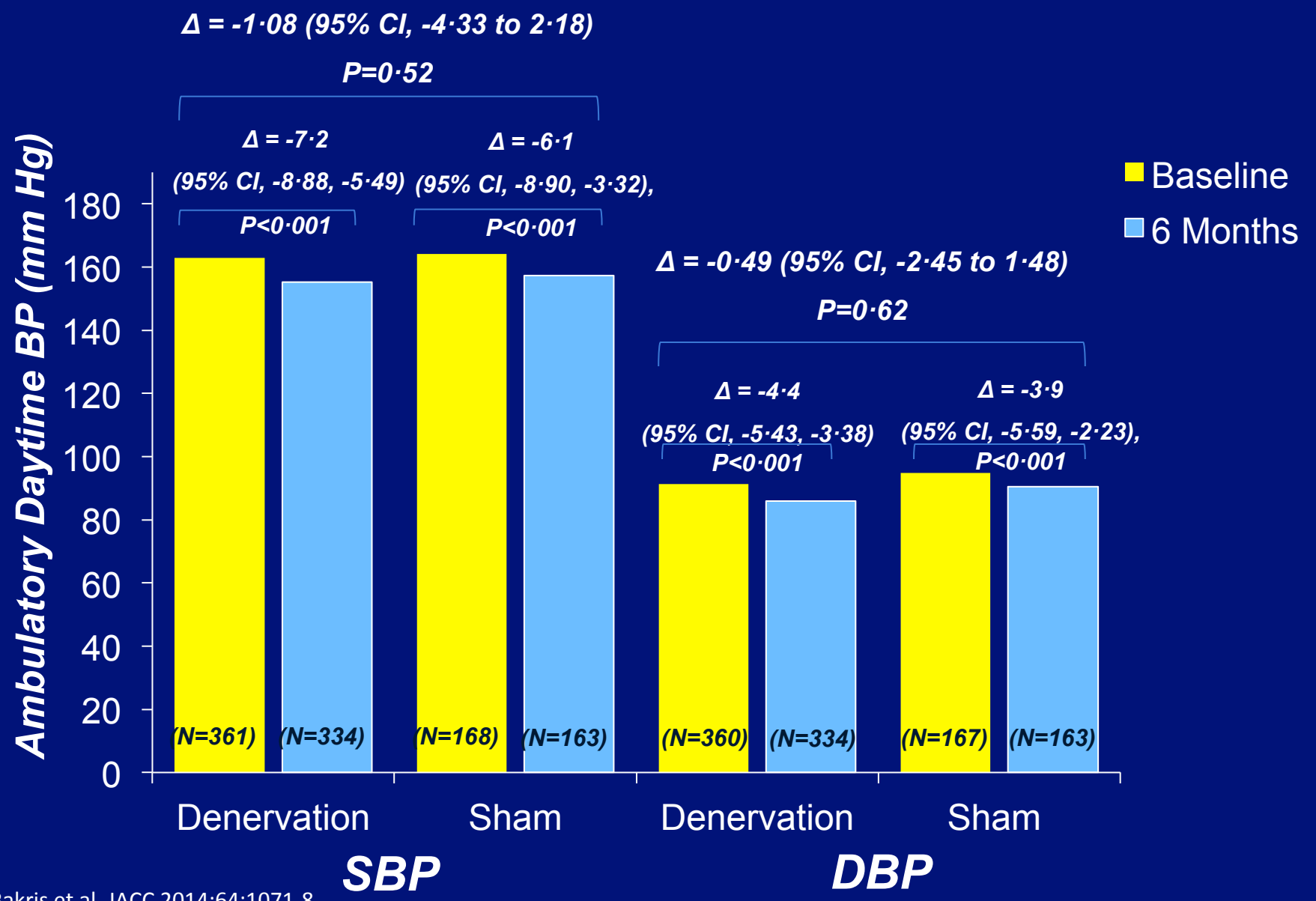
Bhatt et al. N Engl J Med 2014;370:1393-401.

Mean 24-hour ABPM



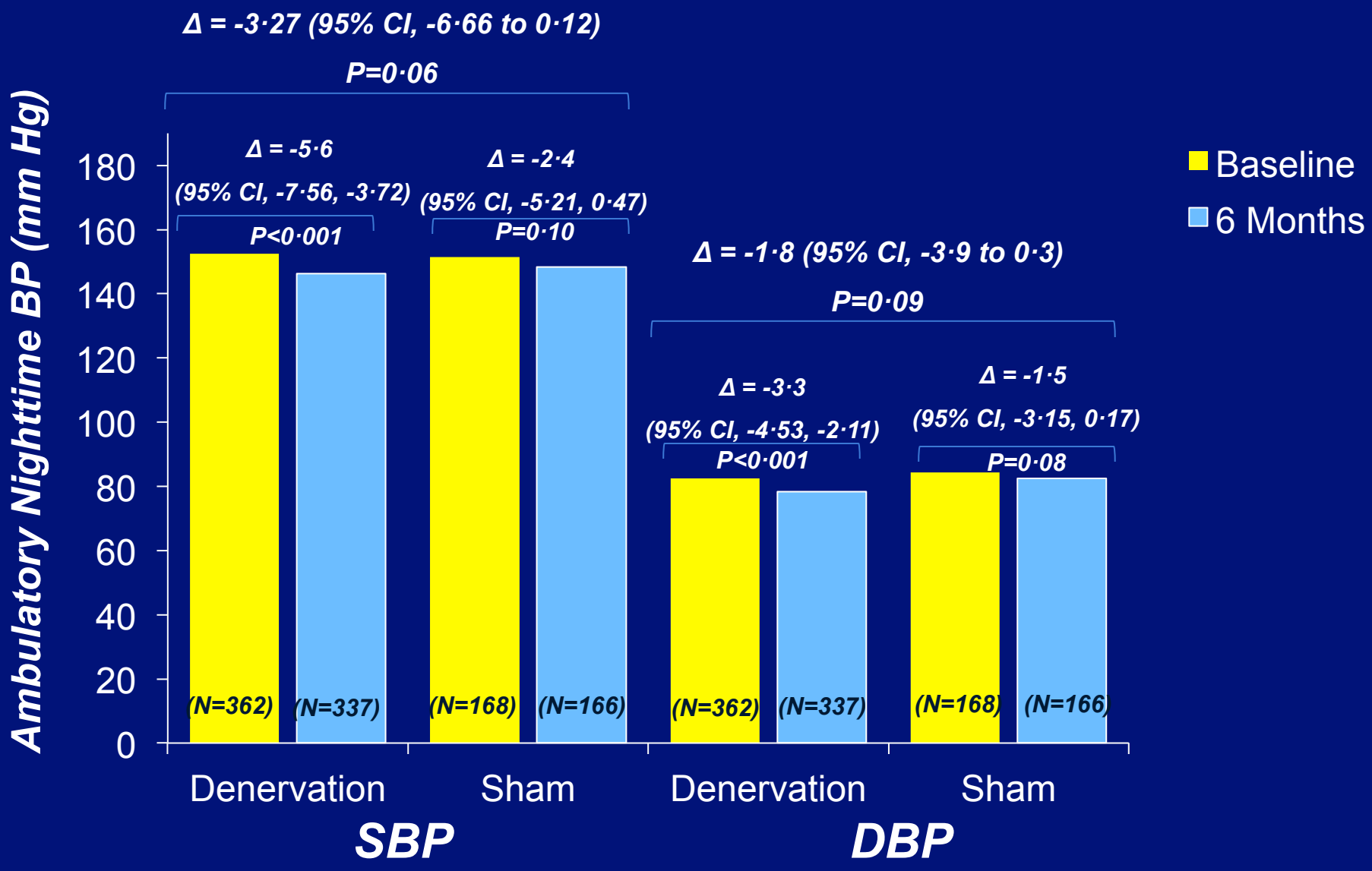
Bakris et al. JACC 2014;64:1071-8.

Mean Daytime ABPM



Bakris et al. JACC 2014;64:1071-8.

Mean Nighttime ABPM

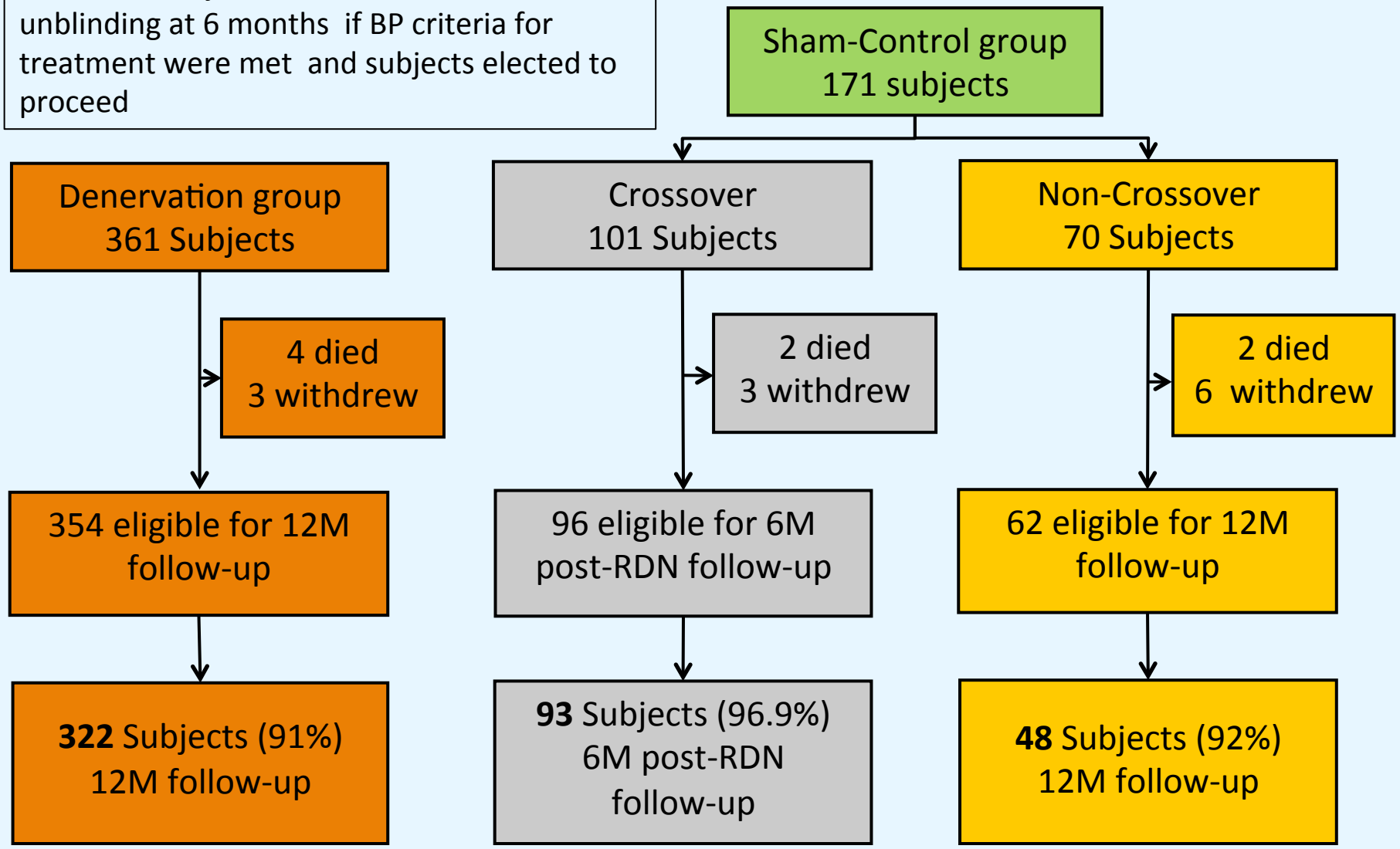


Bakris et al. JACC 2014;64:1071-8.

Patient Disposition: 6 Months to 1 Year

Symplicity® HTN - 3 Clinical Study

Crossover subjects were denervated after unblinding at 6 months if BP criteria for treatment were met and subjects elected to proceed



RDN=renal denervation

Baseline Population Demographics

Symplicity® HTN - 3 Clinical Study

	Denervation (N=364)	Crossover (N=101)	Non-Crossover (N=70)
Age (years)	58 ± 10	55 ± 11	58 ± 12
Male sex (%)	59.1	62.4	67.1
Office Systolic blood pressure (mm Hg)	180 ± 16	184 ± 19	176 ± 15
24-hour mean systolic ABPM (mm Hg)	159 ± 13	163 ± 16	155 ± 15
BMI (kg/m^2)	34.2 ± 6.5	33.0 ± 5.1	35.2 ± 7.8
Race (%)			
White	73.0	71.3	67.1
Black or African American	24.8	27.7	31.4
Medical History (%)			
Renal insufficiency (eGFR <60ml/min/1.73m^2)	9.6	9.9	10.0
Renal artery stenosis	1.4	2.0	2.9
Obstructive Sleep Apnea	25.8	37.6	22.9)
Stroke	8.2	11.9	10.0
Type 2 Diabetes	47.0	37.6	45.7
Hypertensive Crisis	23.1	20.8	24.3
Hyperlipidemia	69.5	63.4	67.1
Current Smoking	9.9	14.9	8.6
Prescribed Anti-Hypertensive Drugs >10 years	68.1	72.3	62.9

Baseline Prescribed Anti-Hypertensive Drugs

Symplicity® HTN - 3 Clinical Study

	Denervation Arm (N=364)	Crossover* (N=101)	Non-Crossover (N=70)
Number of anti-hypertensive medications			
Mean±SD	5.1 ± 1.4	5.2 ± 1.6	5.2 ± 1.4
Number of classes of anti-hypertensive medications			
Mean±SD	4.9 ± 1.2	4.9 ± 1.3	4.9 ± 1.2
Anti-hypertensive medication class (%)			
Aldosterone Antagonist	22.8	28.7	30.0
Alpha 1 Blocker	11.0	10.9	15.7
Alpha 2 Agonist	49.2	41.6	50.0
Angiotensin-Converting Enzyme Inhibitor	49.2	46.5	37.1
Angiotensin Receptor Blocker	50.0	49.5	55.7
Beta Blocker	85.2	87.1	84.3
Calcium Channel Blocker	69.8	75.2	71.4
Diuretic	99.7	99.0	100
Direct Renin Inhibitor	7.1	7.9	7.1
Vasodilator	36.8	43.6	41.4

* “Baseline” is pre-procedure (6 months post-randomization)

Safety to 12 Months

Symplicity® HTN - 3 Clinical Study

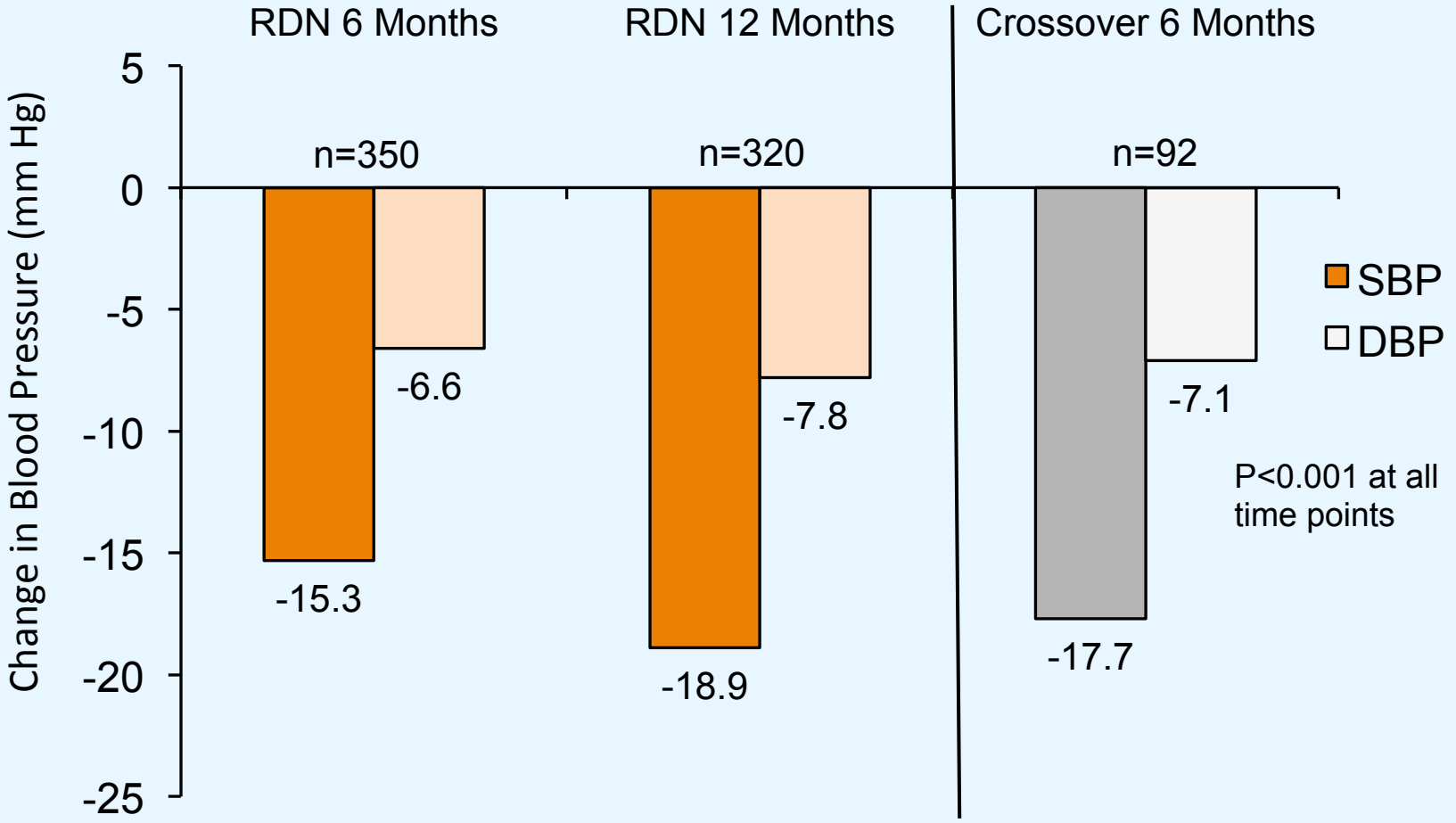
	Denervation (N=364)	Crossover* (N=101)	Non-Crossover (N=70)
Composite Safety to 6M (%)	**3.6 (13/358)**	**5.2 (5/96)**	**2.9 (2/70)**
Death	0.6	2.1	1.4
New onset End Stage Renal Disease	0.0	0.0	0.0
Sig. Embolic Event Resulting in end-organ damage	0.3	0.0	0.0
Vascular Complication	0.3	0.0	0.0
Renal artery re-intervention	0.0	0.0	0.0
Hypertensive crisis/emergency	2.5	3.1	1.4
New renal artery stenosis > 70%	0.0	0.0	0.0
Composite Safety to 12M (%)	**6.8 (24/355)**	**5.3 (5/95)**	**7.2 (5/69)**
Death	1.8	NA	3.6
New onset End Stage Renal Disease	0.3	NA	0.0
Sig. Embolic Event Resulting in end-organ damage	0.3	NA	0.0
Vascular Complication	0.3	NA	0.0
Renal artery re-intervention	0.0	NA	0.0
Hypertensive crisis/emergency	4.8	NA	5.5
New renal artery stenosis >70%	0.0	NA	0.0

**Safety from time of crossover procedure*

Change in Office Blood Pressure Through 12-Months Post-Procedure

Symplicity® HTN - 3 Clinical Study

Same patients being followed

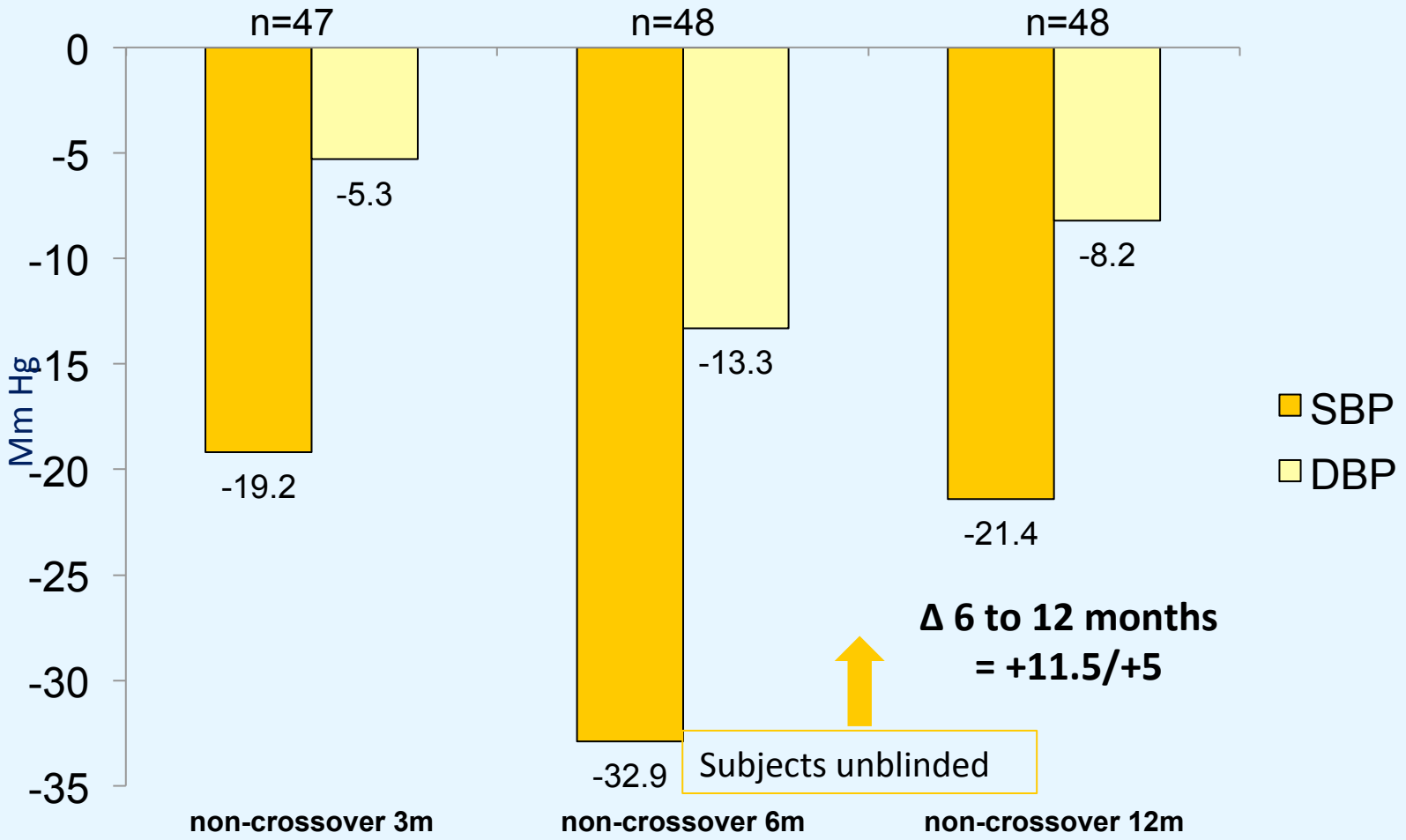


Baseline SBP (mm Hg)	180	179	184*
Baseline DBP (mm Hg)	96	95	102*

*Baseline = time of RDN procedure

Change in Control Non-Crossover Office Blood Pressure Through 12 Months Post-Randomization

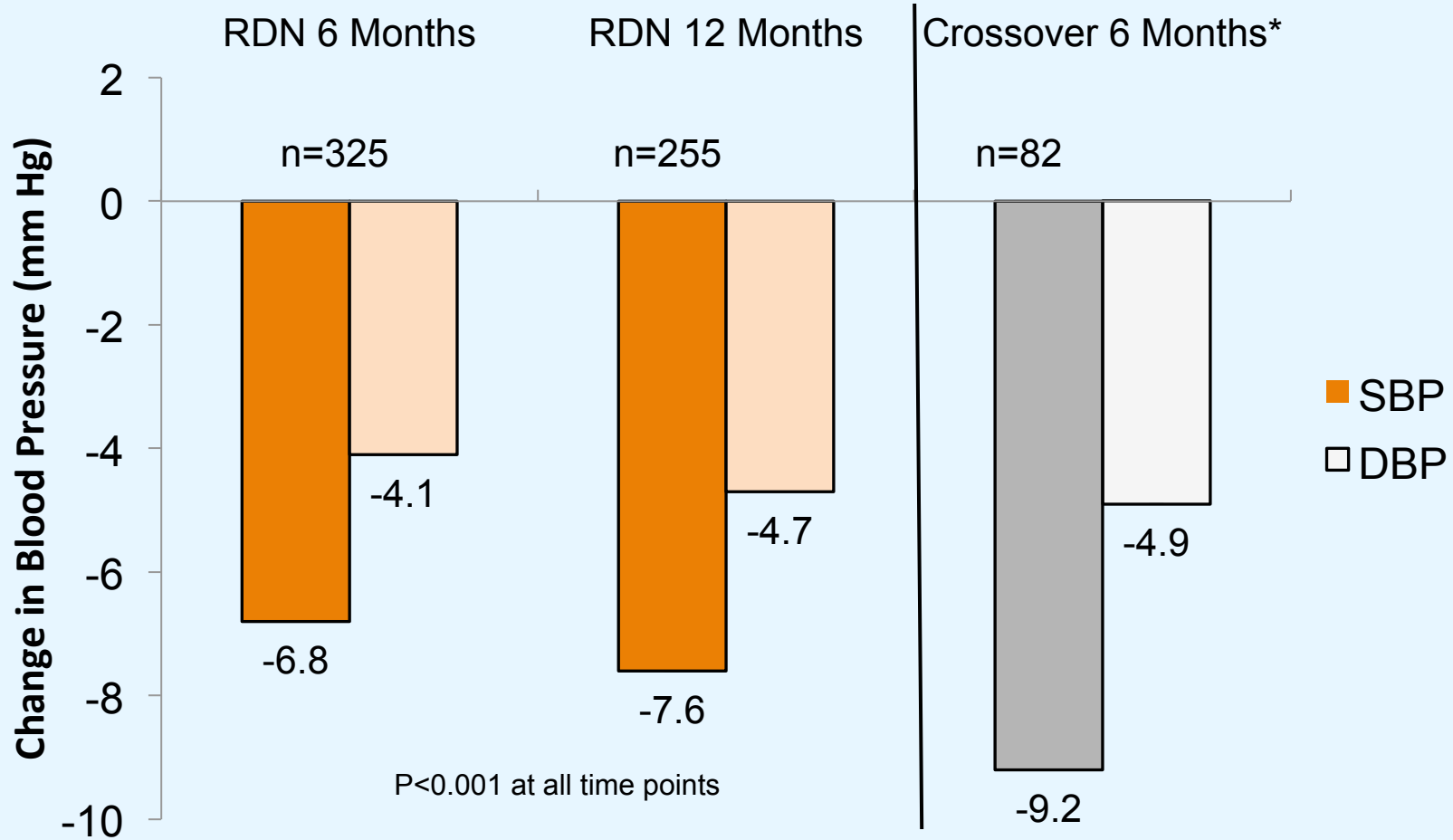
Symplicity® HTN - 3 Clinical Study



BL SBP	175.9
BL DBP	94.1

Change in Mean 24-h Blood Pressure Through 12 Months

Symplicity® HTN - 3 Clinical Study



Baseline SBP (mm Hg)	159	158	163*
Baseline DBP (mm Hg)	87	86	94*

*Baseline = time of RDN procedure

Summary

- Two potentially promising nonpharmacologic approaches exist:
  - BAT
  - Renal Denervation

- Neither is approved in US but BAT was just approved in EU for BP management with heart failure and renal denervation is approved in EU and Australia for resistant hypertension.