Renal Denervation in Patients with Uncontrolled Hypertension: Results of the SYMPLICITY HTN 3 Trial

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Disclosure

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

Affiliation/Financial Relationship	*Company*
Grant/Research Support	*Boston Scientific Corporation, Medtronic CardioVascular*
Consulting Fees/Honoraria	*Boston Scientific Corporation, Medtronic CardioVascular*
Major Stock Shareholder/Equity	*None*
Royalty Income	*None*
Ownership/Founder	*None*
Intellectual Property Rights	*None*

Background

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- Due to aging of the population and greater trends towards obesity, hypertension is growing in prevalence worldwide.
- Approximately 10% of patients with diagnosed hypertension have “resistant” hypertension.
- The sympathetic nervous system appears to play an important role in resistant hypertension.
- Prior non-blinded studies have suggested that catheter-based renal artery denervation reduces blood pressure in resistant hypertension.

Trial Objectives

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- SYMPLICITY HTN-3 is the first prospective, multi-center, randomized, blinded, sham controlled study to evaluate both the safety and efficacy of percutaneous renal artery denervation in patients with severe treatment-resistant hypertension.
- The trial included 535 patients enrolled by 88 participating US centers.

Participating Sites

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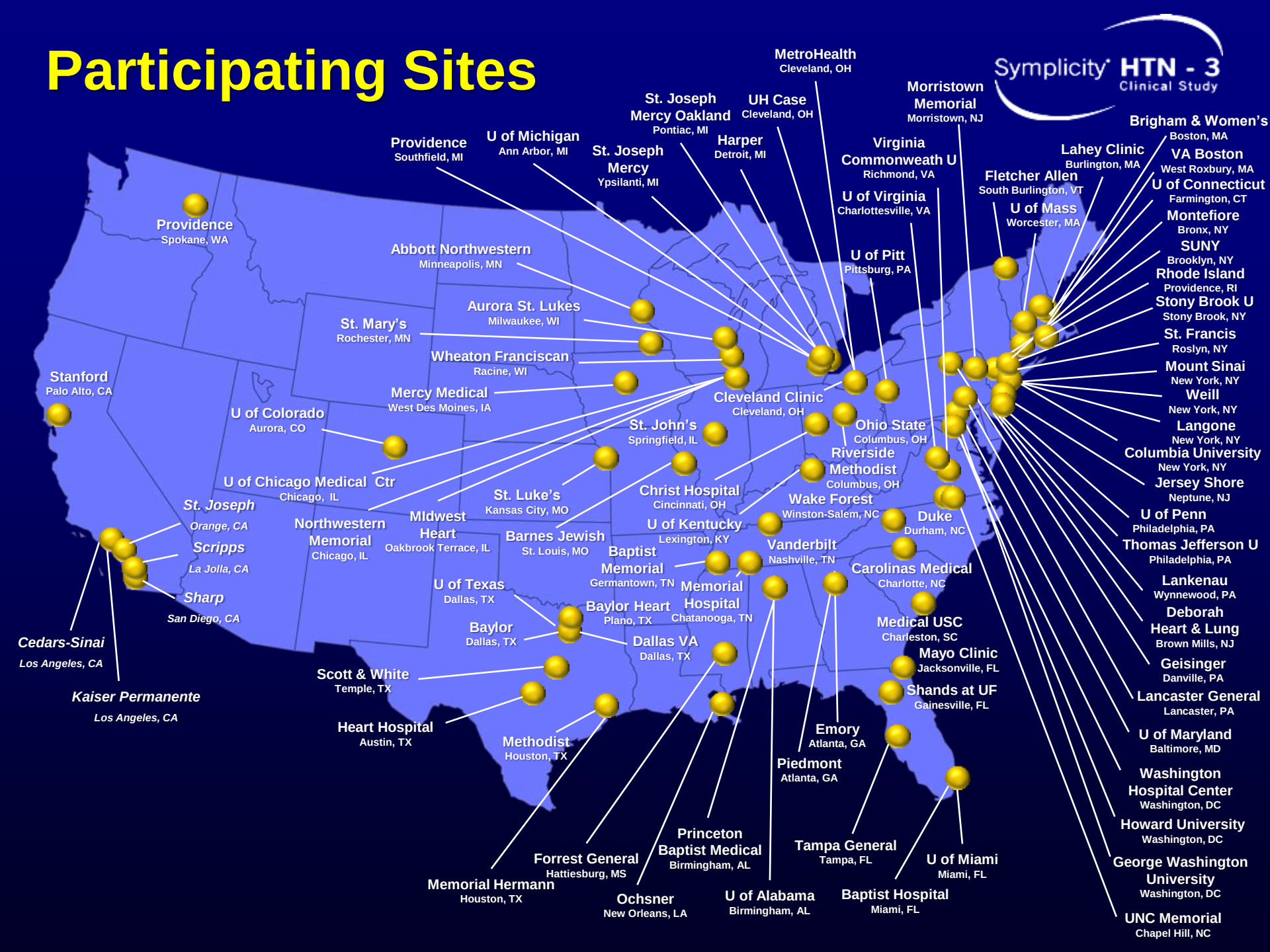

Key Inclusion/Exclusion Criteria

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Inclusion

- Stable medication regimen including full tolerated doses of 3+ antiHTN meds of different classes, including a diuretic

- Office SBP ≥160 mm Hg based on an average of 3 blood pressure readings measured at both an initial and a confirmatory screening visit

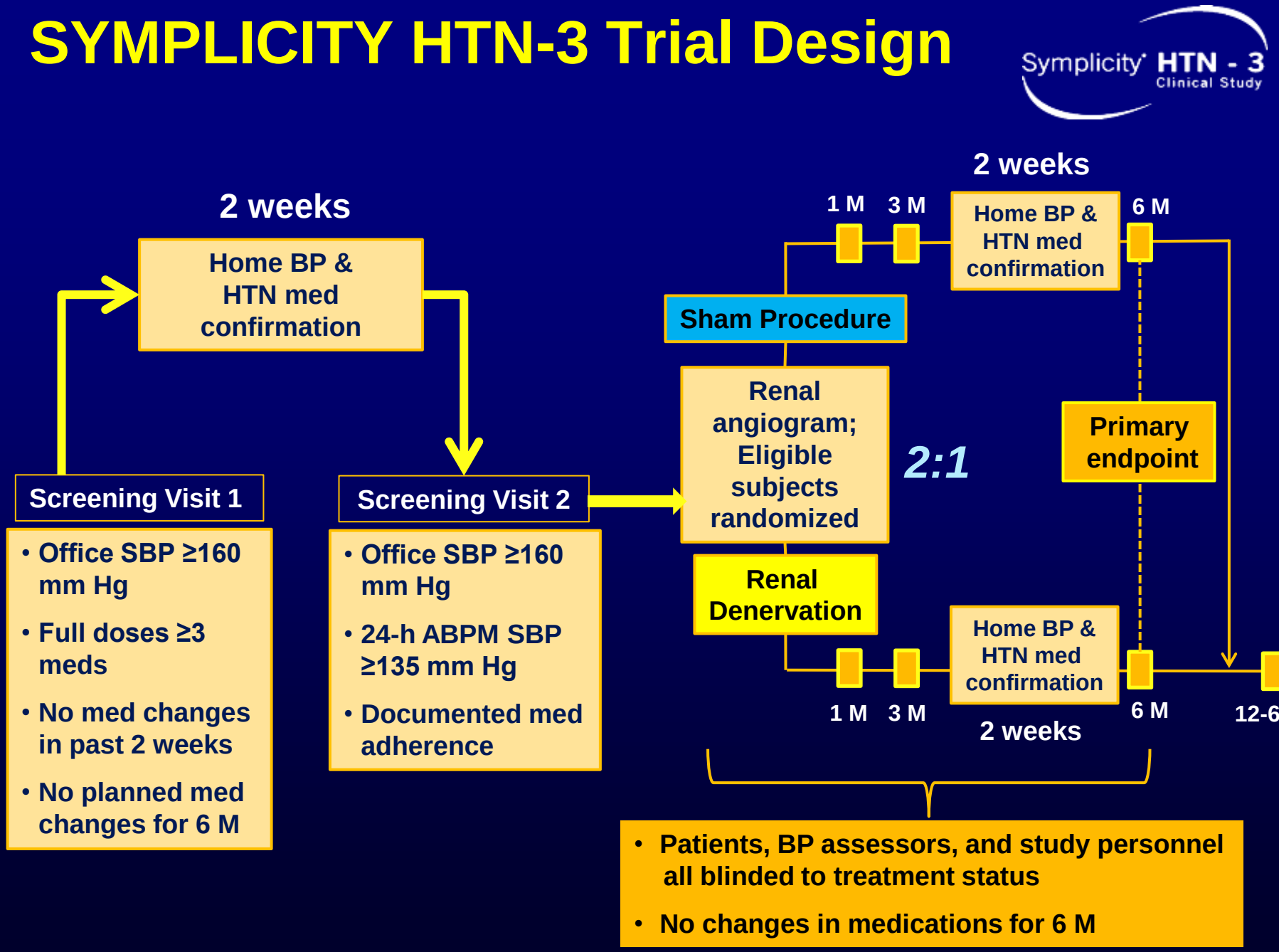
Exclusion

- ABPM 24 hour average SBP <135 mm Hg

- eGFR of <45 mL/min/1.73 m^2

- Main renal arteries <4 mm diameter or <20 mm treatable length

SYMPLICITY HTN-3 Trial Design



Primary Safety Endpoint

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- The rate of Major Adverse Events (MAE) in the treatment group compared with an Objective Performance Criterion (OPC)
- OPC = 9.8% (derived from historical data)
- MAE was defined as all-cause mortality, end-stage renal disease, embolic event resulting in end-organ damage, renal artery or other vascular complication, hypertensive crisis through 30 days, or new renal artery stenosis within six months

Efficacy Endpoints

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Primary Effectiveness Endpoint:

- Comparison of office SBP change from baseline to 6 months in RDN arm compared with change from baseline to 6 months in control arm

$$\text{Endpoint} = (SBP_{\text{RDN 6 month}} - SBP_{\text{RDN Baseline}}) - (SBP_{\text{CTL 6 month}} - SBP_{\text{CTL Baseline}})$$

- *Superiority margin of 5 mm Hg*

Powered Secondary Effectiveness Endpoint:

- Comparison of mean 24-hour ambulatory (ABPM) SBP change from baseline to 6 months in RDN arm compared with change from baseline to 6 months in control arm

- *Superiority margin of 2 mm Hg*

Patient Disposition

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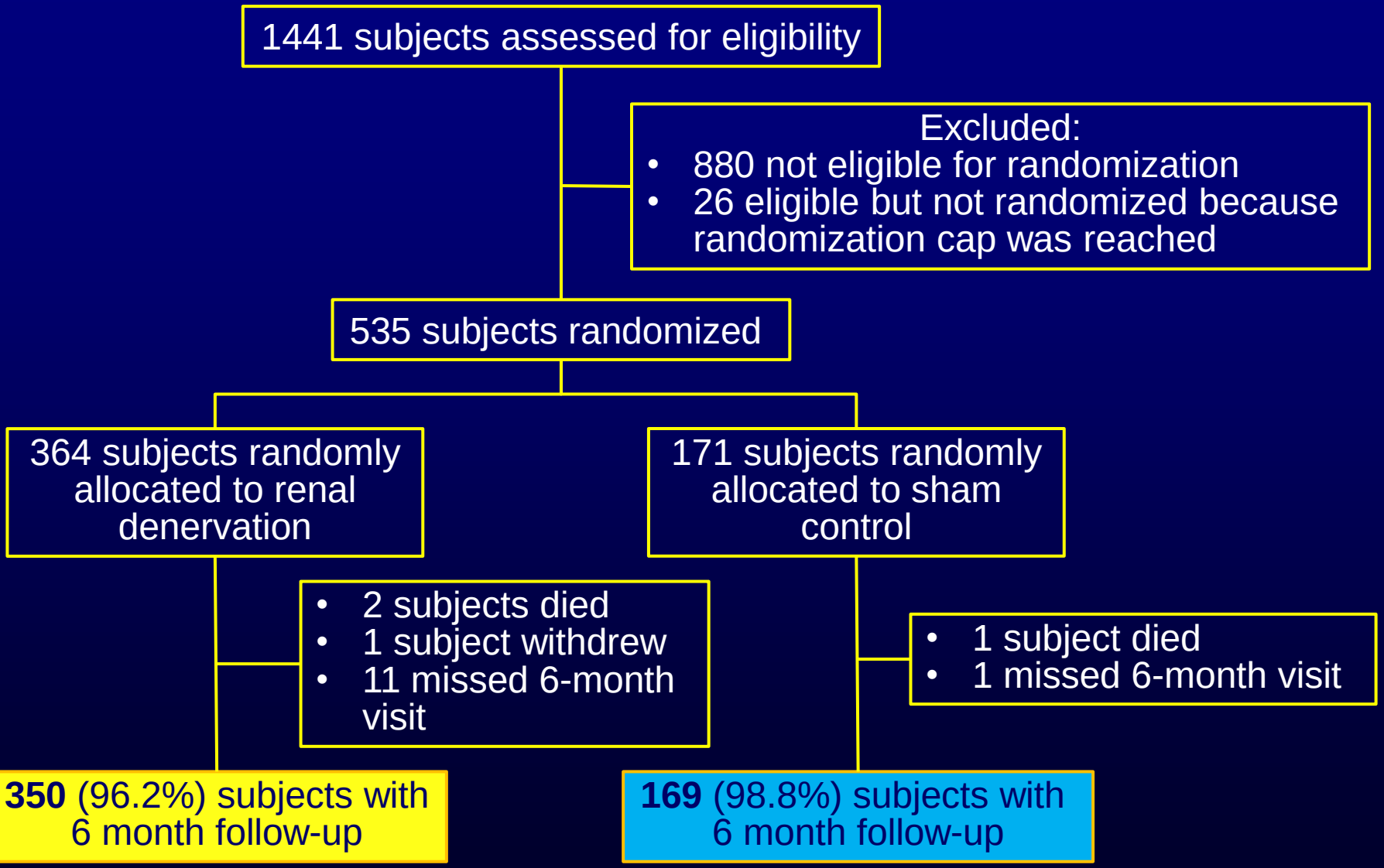

Results: Population Demographics

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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

Baseline Hypertensive Therapy

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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

Blinding Efficacy

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Blinding Procedure:

- All patients underwent renal angiography
- Conscious sedation
- Sensory isolation (e.g., blindfold and music)
- Lack of familiarity with procedural details and expected duration
- Assessed by questionnaire at discharge and 6 months (before unblinding)

Time	Blinding Index*	95% CI
Discharge	0.68	(0.64, 0.72)
6 Months	0.77	(0.74, 0.81)

*The lower boundaries of the confidence intervals of the blinding index are both > 0.5, indicating sufficient evidence of blinding.

Primary Safety Endpoint

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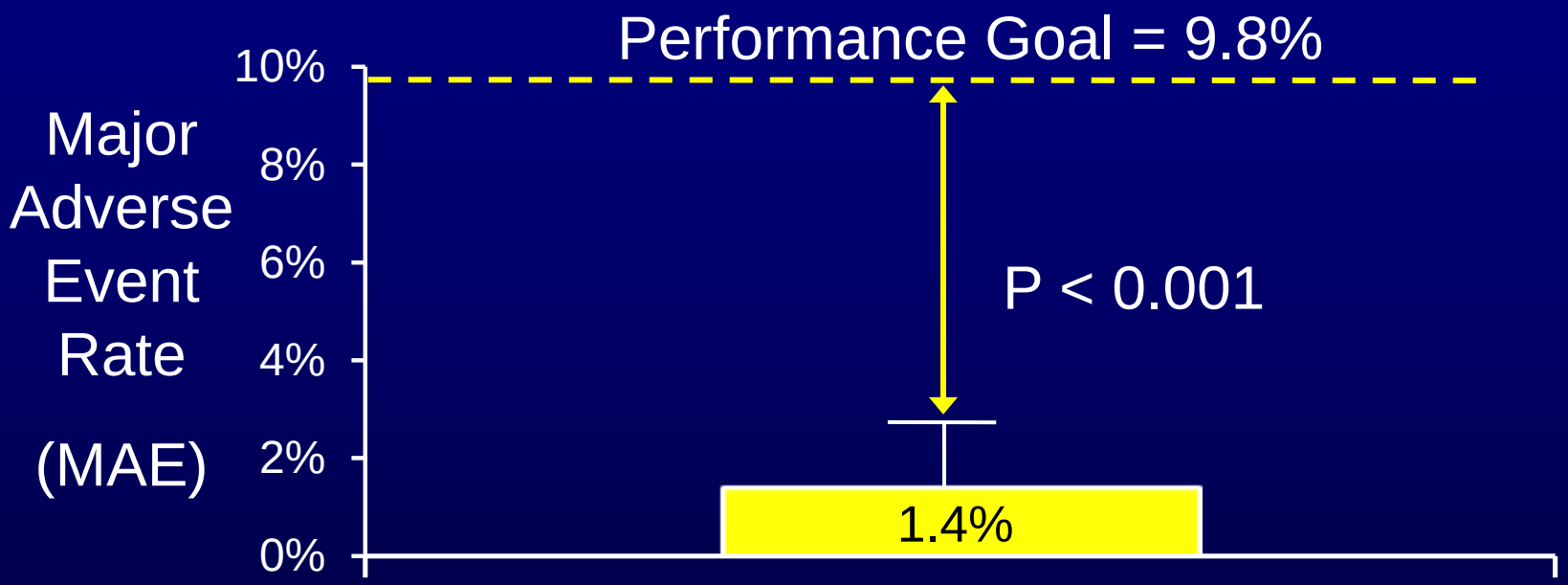

	Renal Denervation (N=364)	Sham Procedure (N=171)	Difference [95% CI]	P*
MAE	1.4% (5/361)	0.6% (1/171)	0.8% [-0.9%, 2.5%]	0.67

*comparison of MAE to control group

Safety Event Rate

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Safety Measures (%)	Renal Denervation (N=364)	Sham Procedure (N=171)	Difference (95% CI)	P
Major Adverse Events To 6 Months	1.4	0.6	0.8 (-0.9, 2.5)	0.67
6-Month Composite Safety	4.0	5.8	-1.9 (-6.0, 2.2)	0.37
Death	0.6	0.6	0.0 (-1.4, 1.4)	1.00
Myocardial infarction	1.7	1.8	0.0 (-2.4, 2.3)	1.00
New onset ESRD	0	0	-	-
Serum creatinine elevation >50%	1.4	0.6	0.8 (-0.8, 2.5)	0.67
Embolic event resulting in end-organ damage	0.3	0	0.3 (-0.3, 0.8)	1.00
Renal artery intervention	0	0	-	-
Vascular complication requiring treatment	0.3	0	0.3 (-0.3, 0.8)	1.00
Hypertensive crisis/emergency	2.6	5.3	-2.7 (-6.4, 1.0)	0.13
Stroke	1.1	1.2	0.0 (-2.0, 1.9)	1.00
Hospitalization for new onset heart failure	2.6	1.8	0.8 (-1.8, 3.4)	0.76
Hospitalization for atrial fibrillation	1.4	0.6	0.8 (-0.8, 2.5)	0.67
New renal artery stenosis >70%	0.3	0	0.3 (-0.3, 0.9)	1.00

Primary Efficacy Endpoint

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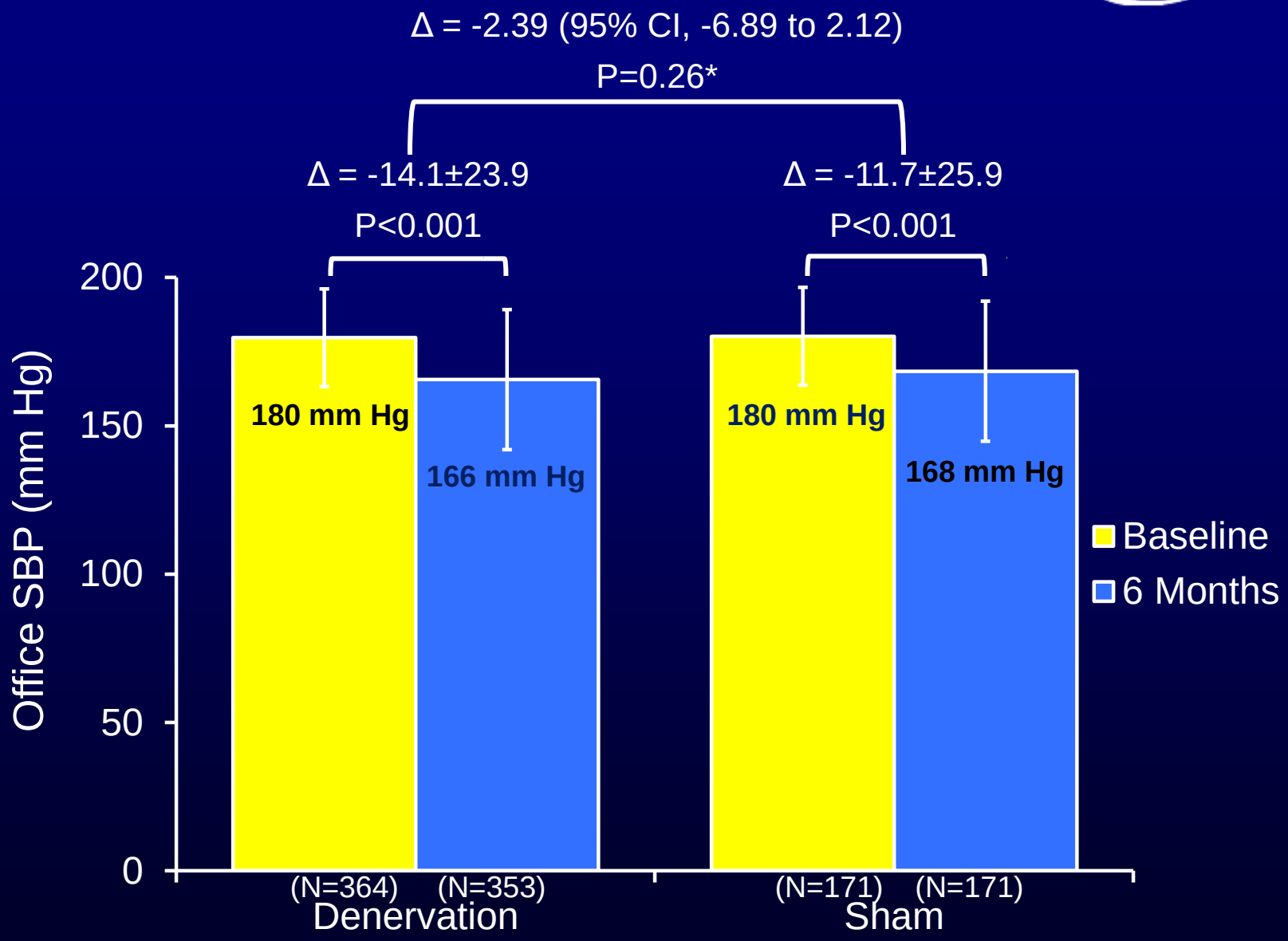

**P value for superiority with a 5 mm Hg margin; bars denote standard deviations*

Would the trial have met the primary endpoint if there had been no 5 mm Hg superiority margin?

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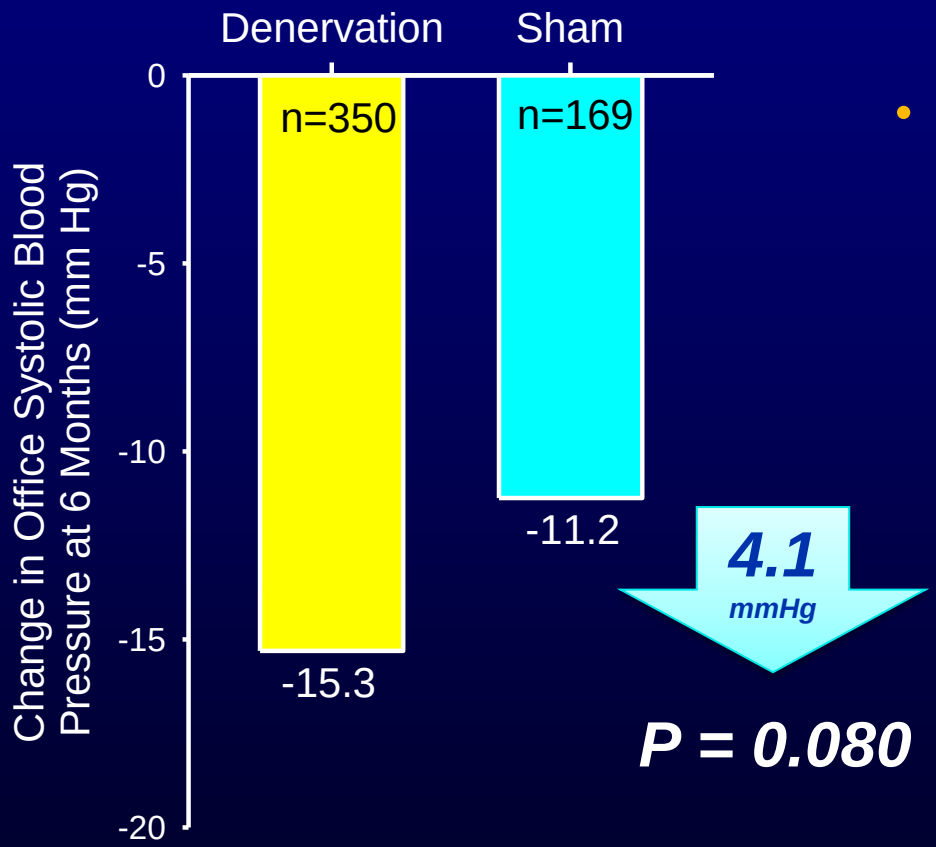

- *No Superiority Margin*
- *Intention to Treat*

ABPM: -6.8 vs -4.8, p=0.223

Home: -7.4 vs -6.1, p=0.413

Medtronic Data on File

Powered Secondary Efficacy Endpoint

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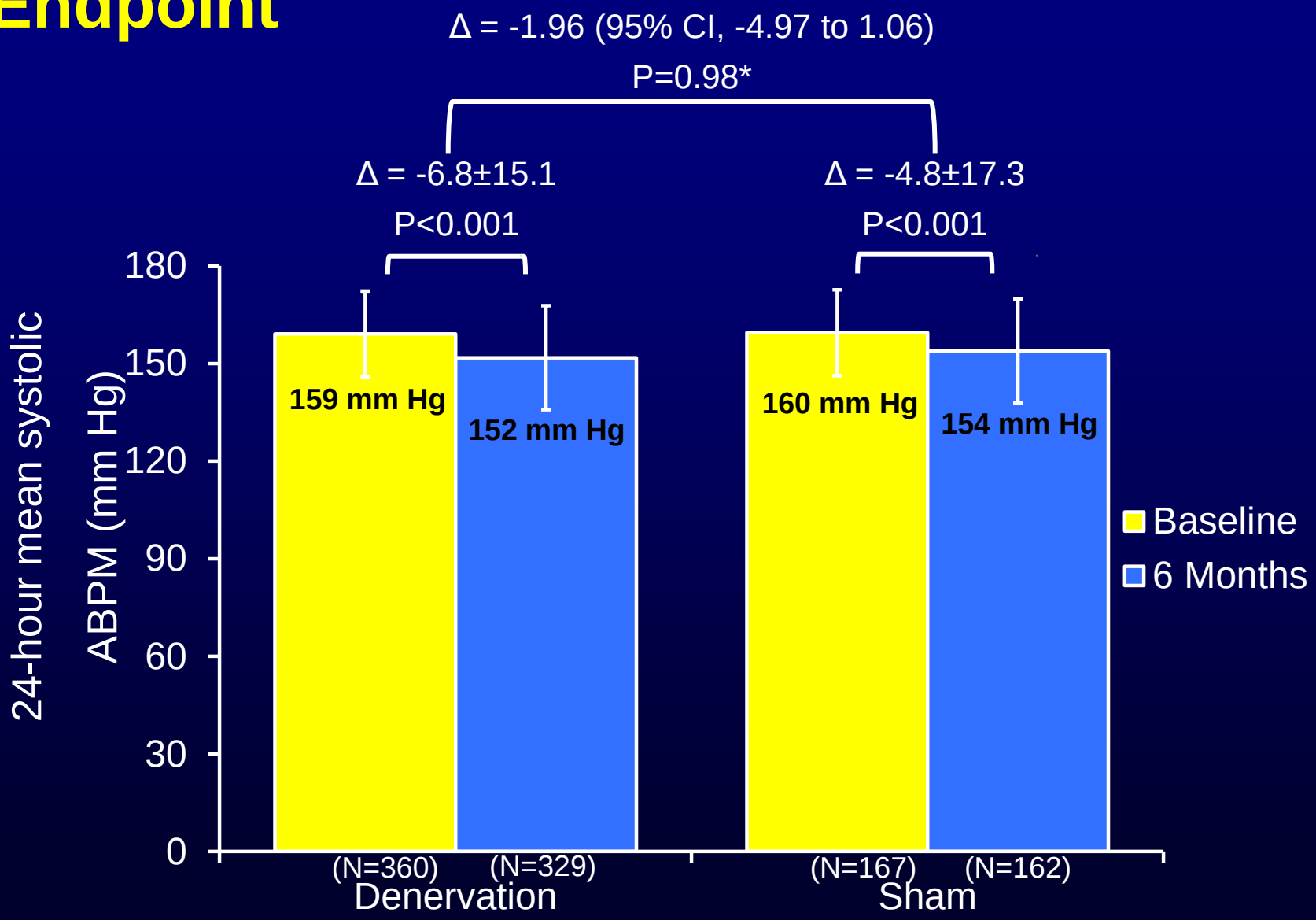

**P value for superiority with a 2 mm Hg margin; bars denote standard deviations*

Change in Office SBP by Tertile of Baseline Office SBP

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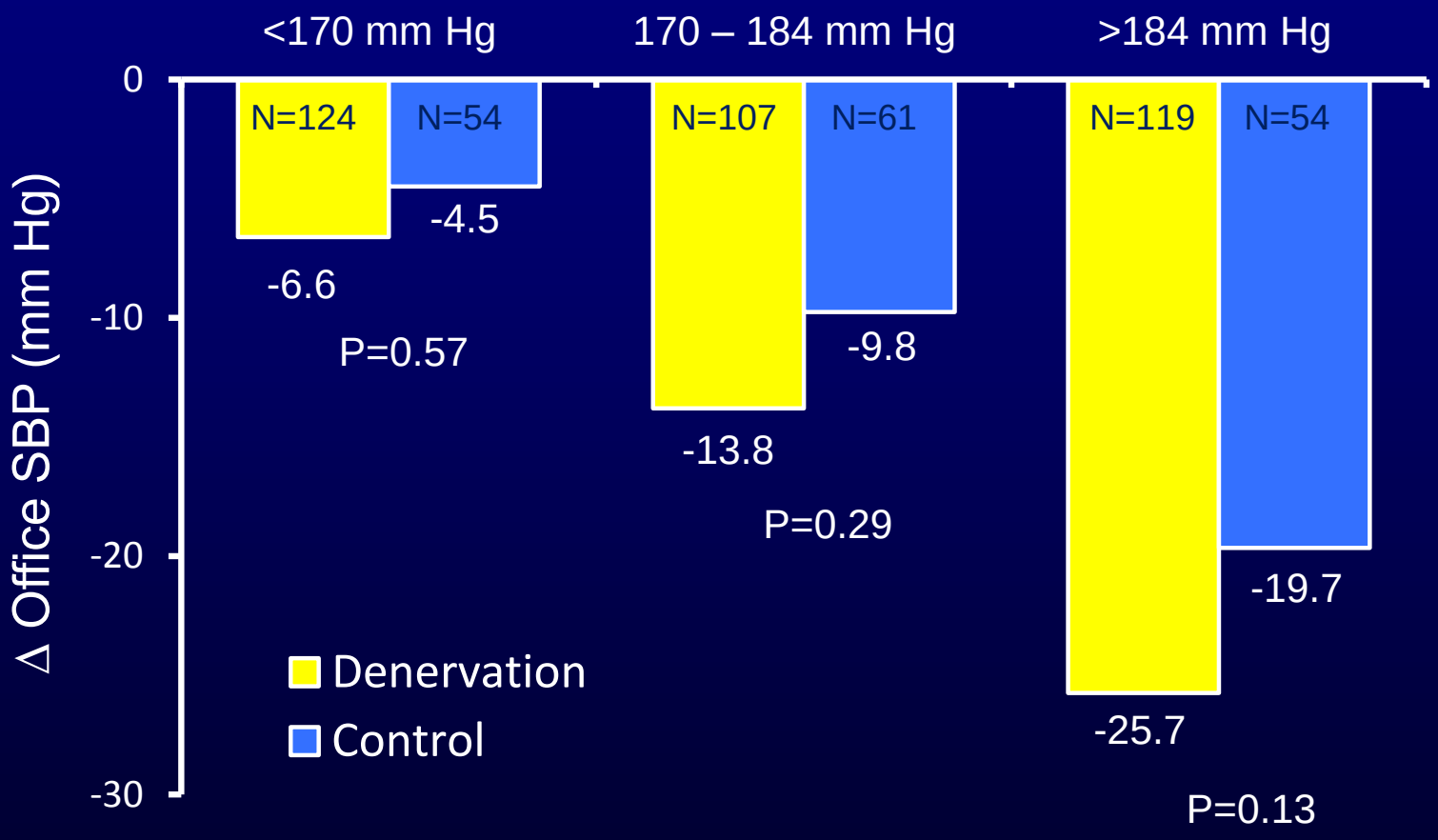

Results: Prespecified Subgroup Analyses

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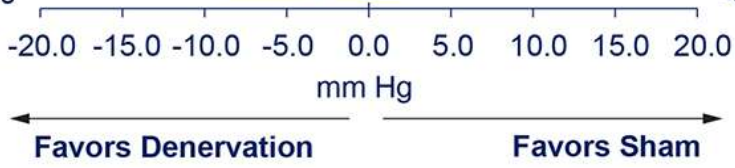
	No. of Patients		Difference (95% CI) mm Hg	P Value	Interaction P Value
	Denervation	Sham			
All patients	353	171	-2.39 (-6.89 – 2.12)	0.26 *	
Diabetes mellitus					0.82
Yes	169	68	-4.53 (-11.51 – 2.46)	0.20	
No	181	101	-3.46 (-9.55 – 2.62)	0.26	
Sex					0.37
Male	208	108	-2.30 (-7.63 – 3.03)	0.40	
Female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



** P value for superiority with margin of 5 mm Hg*

Potential Limitations

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- Drug adherence not measured by blood levels, but adherence was measured by patient diaries at baseline and 6 months.
- Medication changes did occur, but results unchanged even when these patients were censored.
- Duration of primary endpoint may have been too short, but prior studies had found benefit by 6 months.
- Operator learning curve is always a possibility, but we found no relationship with procedural volume in the trial.
- Biological confirmation of denervation did not occur, as there is no accepted measure, but appropriate energy delivery was confirmed.

Conclusions

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- In a prospective, multicenter, randomized, blinded, sham controlled trial of patients with uncontrolled resistant hypertension, percutaneous renal denervation was safe but not associated with significant additional reductions in office or ambulatory blood pressure

- These results underscore the importance of blinding and sham controls in evaluations of new devices

- Additional analyses are underway to further detail confounders related to medications, patient subgroups and procedural technique

- Further study in rigorously designed clinical trials will be necessary to confirm previously reported benefits of renal denervation in patients with resistant hypertension or to validate alternate methods of renal denervation