A Controlled Trial of Renal Denervation for Resistant Hypertension

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#NephJC
Tuesday, May 27
9 pm Eastern

Topic 1

- SYMPLICITY HTN 3 (S3) results differ, to put it mildly, from SYMPLICITY 1 and SYMPLICITY 2. Was it because of more robust study design?

Topic 2

- S3 results may be different from previous trial due to other factors: eg more use of spironolactone? Technical issues: operator dependent procedural aspects?

Topic 3

- What happens now?
  - Another trial?
  - Different population?
  - Different indication?
  - Different device?
  - Throw this away?

Article Summary

- Symplicity HTN 1 was proof of concept, uncontrolled (before-after data) showing renal sympathetic denervation was effective in reducing office BP by ~ 30 mm. First report (Lancet 2009) reported 45 patients; last one (Lancet 2014) reported data on 88 additional patients. Total reported: 153 patients.

- Symplicity HTN 2 was an open label, unblinded RCT, n of 106, which showed similar results. Interestingly, the control group had no change in BP (1/0).

- EnligHTN was another uncontrolled study with a different catheter. n of 46, and similar impressive drop in office (-26 mm) and ABPM (-10) in SBP.

SYMPLICITY HTN-3

- single-blind, randomized, sham-controlled trial
- patients randomized 2:1 ratio to undergo renal denervation or a sham procedure
- primary efficacy end point was the change in office systolic blood pressure at 6 months

- 535 patients underwent randomization
- change in SBP at 6 months:
  - Denervation: −14.1±23.9 mm Hg
  - Sham: −11.7±25.9 mm Hg
  - Difference of −2.39 mm Hg

- The change in 24-hour ambulatory systolic blood pressure was
  - Denervation: −6.8±15.1 mm Hg
  - Sham: −4.8±17.3 mm Hg
  - Difference: 2.0 mm Hg

- resistant hypertension defined as systolic blood pressure of 140 mmHg or higher despite adherence to 3 antihypertensives at maximum doses including a diuretic

- about 10% of patients with hypertension

inclusion criteria

- age 18-80
- resistant hypertension
  - SBP ≥ 160 office blood pressure (average of 3 measurements)
  - maximally tolerated doses of ≥ 3 antihypertensive medications of complementary classes, one of which had to be an appropriately dosed diuretic

- For the next 2 weeks, patients recorded their blood pressure at home in the morning and the evening and kept a diary indicating their adherence to medical therapy.

- After 2 weeks there was a confirmatory screening visit where systolic blood pressure ≥ 160 mm Hg was confirmed.

- Adherence to medications was documented, and automated 24-hour ambulatory blood-pressure monitoring was performed to ensure a systolic blood pressure ≥ 135 mm Hg

exclusion criteria

- >1 hospitalization for hypertensive emergency in the previous year
- secondary hypertension
- RAS > 50%
- renal artery aneurism
- prior renal artery interventipn
- multiple renal arteries
- renal artery less than 4 mm diameter
- treatable segment less than 20 mm in length

Primary end point

- mean change in office systolic blood pressure from baseline to 6 months
- Secondary end point
  - change in mean 24-hour ambulatory systolic blood pressure at 6 months

primary safety end point: composite of major adverse events

- death from any cause
- end-stage renal disease
- embolic event resulting in end-organ damage
- renal-artery or other vascular complications
- hypertensive crisis within 30 days
- new renal-artery stenosis > 70% within 6 months

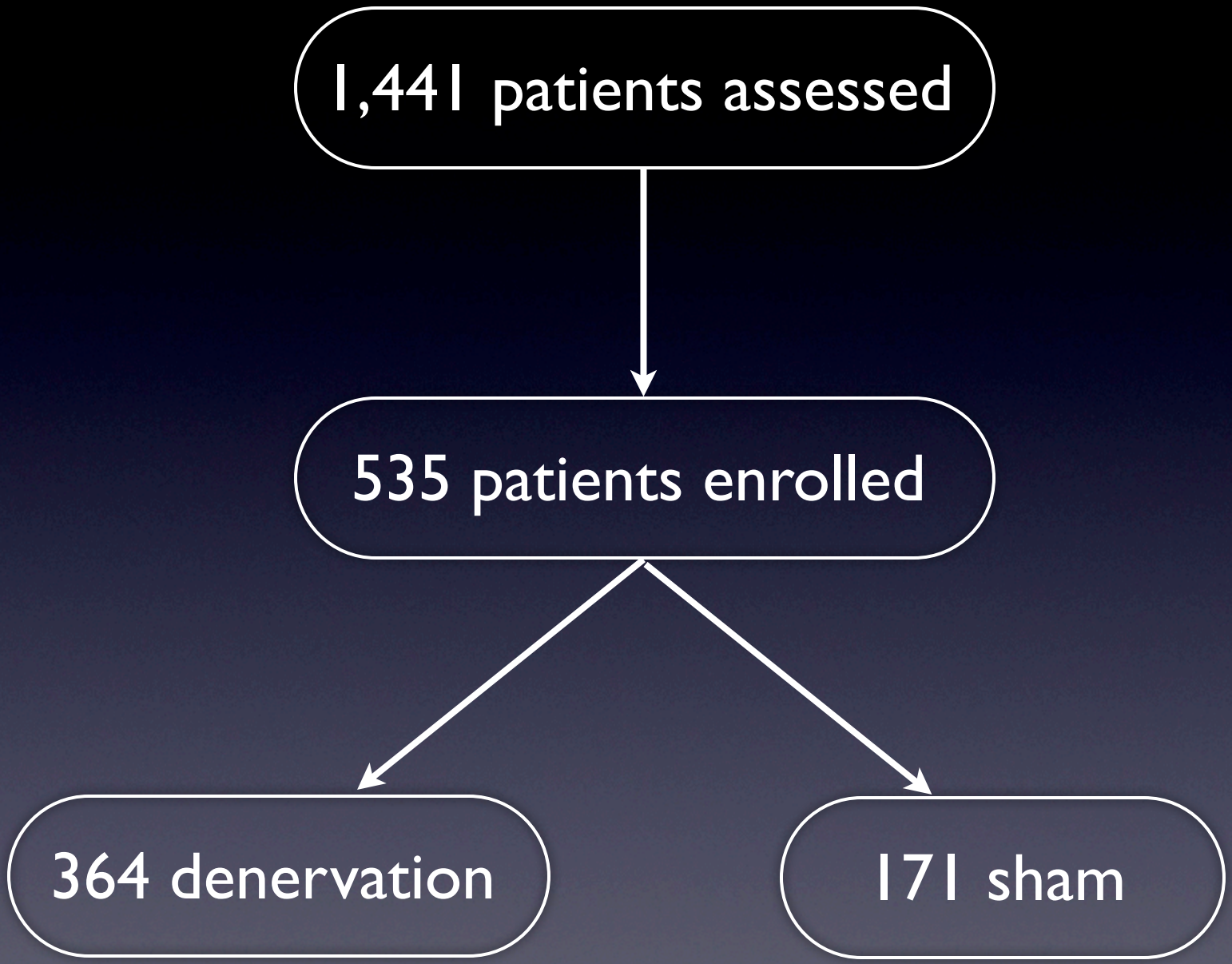
1,441 patients assessed
535 patients enrolled
364 denervation
171 sham

Table 1. Baseline Characteristics of the Study Population.*

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Age — yr	57.9±10.4	56.2±11.2
Male sex — no. (%)	215 (59.1)	110 (64.3)
Body-mass index†	34.2±6.5	33.9±6.4
Race — no./total no. (%)‡		
Black	90/363 (24.8)	50/171 (29.2)
White	265/363 (73.0)	119/171 (69.6)
Asian	2/363 (0.6)	0/171
Other	6/363 (1.7)	2/171 (1.2)
Medical history — no. (%)		
Renal insufficiency§	34 (9.3)	17 (9.9)
Renal-artery stenosis	5 (1.4)	4 (2.3)
Obstructive sleep apnea	94 (25.8)	54 (31.6)
Stroke	29 (8.0)	19 (11.1)
Transient ischemic attack	28 (7.7)	13 (7.6)
Peripheral artery disease	19 (5.2)	5 (2.9)
Cardiac disease		
Coronary artery disease	101 (27.7)	43 (25.1)
Myocardial infarction	32 (8.8)	11 (6.4)
Diabetes		
Type 1	0	0
Type 2	171 (47.0)	70 (40.9)
Hyperlipidemia — no. (%)	252 (69.2)	111 (64.9)
Current smoker — no. (%)	36 (9.9)	21 (12.3)
Family history of hypertension — no./total no. (%)	305/361 (84.5)	140/170 (82.4)
Hypertension history — no. (%)		
Hospitalization for hypertensive crisis	83 (22.8)	38 (22.2)
Hospitalization for hypotension	8 (2.2)	4 (2.3)
No. of antihypertensive medications	5.1±1.4	5.2±1.4

- 5 anti-hypertensive medications per patient
  - 4 at maximum tolerated doses
  - majority receiving HCTZ

- blinding index was great erthan 0.5 indicated successful blinding.

Table S4. Blinding Index*

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 greater than 0.5, indicating that there is sufficient evidence for blinding.

- There was no significant between-group difference in the change in office blood pressure at 6 months
  - denervation −14.13±23.93 mm Hg
  - sham −11.74±25.94 mm Hg
  - difference of −2.39 mm Hg (95% CI, −6.89 to 2.12; P=0.26 with a superiority margin of 5 mm Hg).

- The change in ambulatory blood pressure at 6 months was
  - denervation −6.75±15.11 mm Hg
  - sham −4.79±17.25 mm Hg
  - difference of −1.96 mm Hg (95% CI, −4.97 to 1.06); P = 0.98 with a superiority margin of 2 mm Hg)

The proportions of patients with a reduction in office systolic or diastolic blood pressure of at least 5 mm Hg or at least 10 mm Hg are shown in Table S6 in the Supplementary Appendix. The responses with regard to systolic and diastolic blood pressure were significantly greater in the denervation group than in the sham-procedure group.

Table S6. Systolic and Diastolic Blood Pressure Response Based on ≥5 mm Hg and ≥10 mm Hg Reduction From Baseline at 6 Months

Effectiveness Measures	Renal Denervation Group (N = 364 Patients)	Sham-Procedure Group (N = 171 Patients)	P-Value
Reduction in Office SBP at 6 months			
≥ 5 mm Hg	66.9% (234/350)	55.6% (94/169)	0.02
≥ 10 mm Hg	58.3% (204/350)	48.5% (82/169)	0.04
Reduction in Office DBP at 6 months			
≥ 5 mm Hg	55.1% (193/350)	43.8% (74/169)	0.02
≥ 10 mm Hg	37.7% (132/350)	28.4% (48/169)	0.04

pre-specified subgroup analysis found significant reductions in office SBP in:

- Not black
- GFR > 60 ml/min
- age < 65

The differences were not significant with the use of a superiority margin of 5 mm Hg *or after adjustment for multiple comparisons*

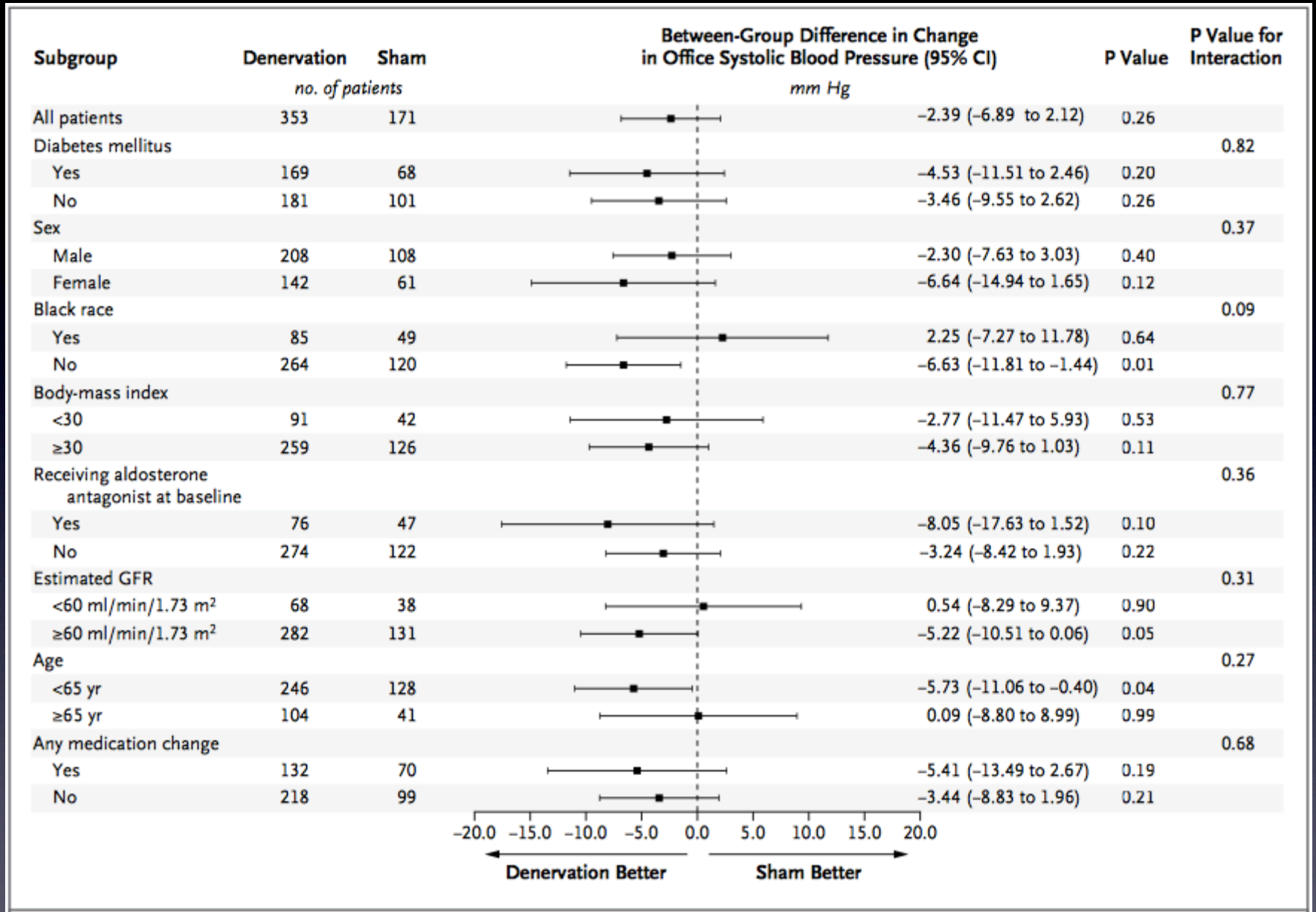

Figure 3. Selected Subgroup Analyses.

Shown are between-group differences in the change in office systolic blood pressure from baseline to 6 months in selected subgroups. The body-mass index is the weight in kilograms divided by the square of the height in meters. GFR denotes glomerular filtration rate.

no safety signal

Table 2. Safety End Points.*

End point	Renal-Denervation Group	Sham-Procedure Group	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		
Major adverse event†	5/361 (1.4)	1/171 (0.6)	0.8 (–0.9 to 2.5)
Composite safety end point at 6 mo‡	14/354 (4.0)	10/171 (5.8)	–1.9 (–6.0 to 2.2)
Specific event within 6 mo			
Death	2/352 (0.6)	1/171 (0.6)	0.0 (–1.4 to 1.4)
Myocardial infarction	6/352 (1.7)	3/171 (1.8)	0.0 (–2.4 to 2.3)
New-onset end-stage renal disease	0/352	0/171	—
Increase in serum creatinine of >50% from baseline	5/352 (1.4)	1/171 (0.6)	0.8 (–0.8 to 2.5)
Embolic event resulting in end-organ damage	1/352 (0.3)	0/171	0.3 (–0.3 to 0.8)
Renal-artery intervention	0/352	0/171	—
Vascular complication requiring treatment	1/352 (0.3)	0/171	0.3 (–0.3 to 0.8)
Hypertensive crisis or emergency	9/352 (2.6)	9/171 (5.3)	–2.7 (–6.4 to 1.0)
Stroke	4/352 (1.1)	2/171 (1.2)	0.0 (–2.0 to 1.9)
Hospitalization for new-onset heart failure	9/352 (2.6)	3/171 (1.8)	0.8 (–1.8 to 3.4)
Hospitalization for atrial fibrillation	5/352 (1.4)	1/171 (0.6)	0.8 (–0.8 to 2.5)
New renal-artery stenosis of >70%	1/332 (0.3)	0/165	0.3 (–0.3 to 0.9)