Key Talking Points

SYMPLICITY HTN-3 Trial 6-mo Endpoint Publication in NEJM:
A Controlled Trial of Renal Denervation for Resistant Hypertension

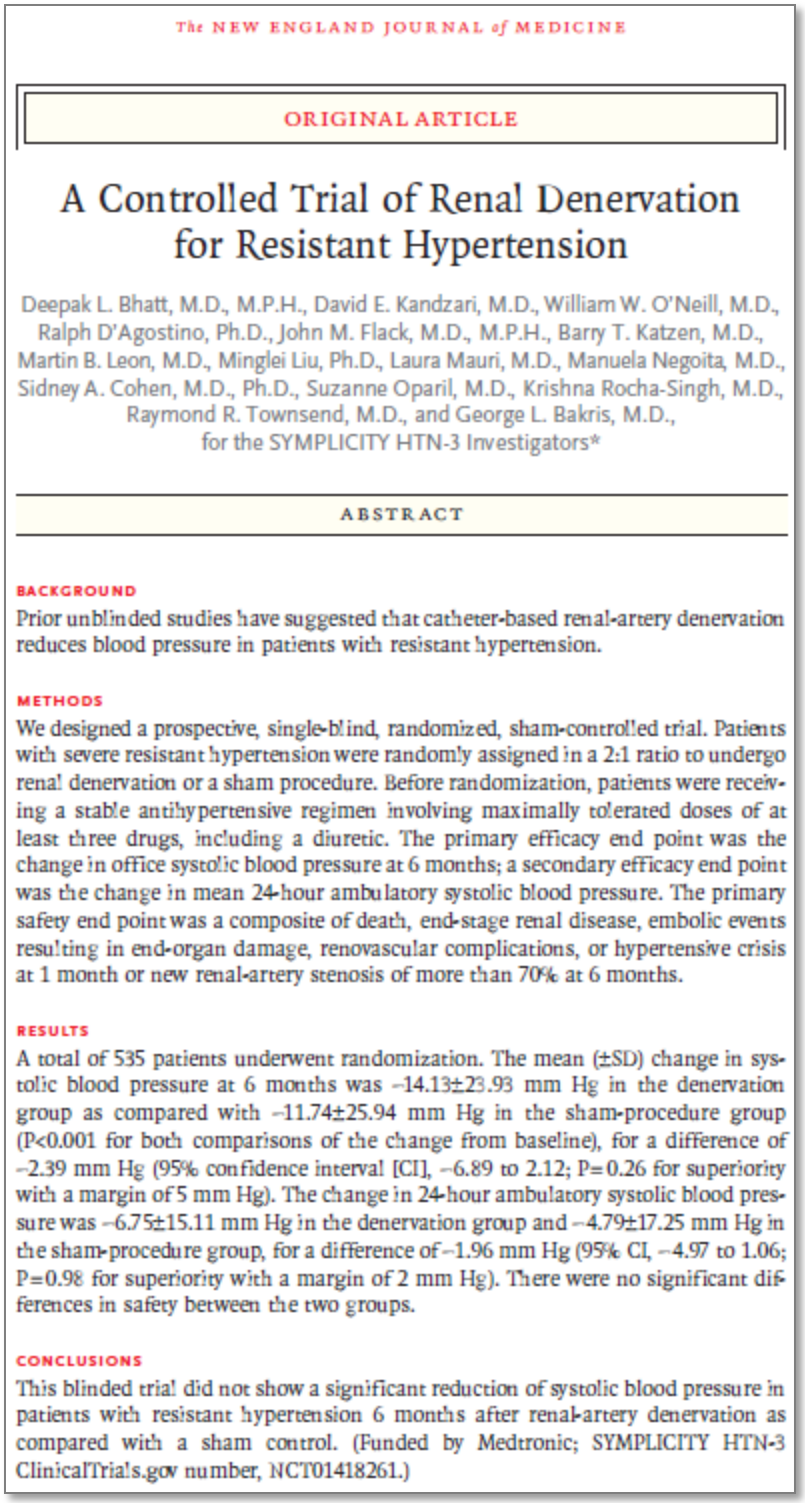
Main Messages

1. SYMPLICITY HTN-3 did not reach the primary or powered secondary efficacy endpoints in this trial. There may be many factors that contributed to the outcome, which we continue to investigate.

2. SYMPLICITY HTN-3 did meet its safety endpoint, which is consistent with all other Symplicity trials, including the Global SYMPLICITY Registry.

3. Based upon our detailed analysis of HTN-3, we believe further clinical investigation is warranted and Medtronic will, in consultation with FDA, pursue a new IDE trial.

4. An unmet need in this uncontrolled hypertension population still exists. Medtronic will continue to provide access to the Symplicity™ system in countries where it has regulatory approval and will continue to support a global hypertension clinical program.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Renal Denervation for Resistant Hypertension

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ABSTRACT

BACKGROUND

Prior unblinded studies have suggested that catheter-based renal-artery denervation reduces blood pressure in patients with resistant hypertension.

METHODS

We designed a prospective, single-blind, randomized, sham-controlled trial. Patients with severe resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure. Before randomization, patients were receiving a stable antihypertensive regimen involving maximally tolerated doses of at least three drugs, including a diuretic. The primary efficacy end point was the change in office systolic blood pressure at 6 months; a secondary efficacy end point was the change in mean 24-hour ambulatory systolic blood pressure. The primary safety end point was a composite of death, end-stage renal disease, embolic events resulting in end-organ damage, renovascular complications, or hypertensive crisis at 1 month or new renal-artery stenosis of more than 70% at 6 months.

RESULTS

A total of 535 patients underwent randomization. The mean (±SD) change in systolic blood pressure at 6 months was −14.13±23.93 mm Hg in the denervation group as compared with −11.74±25.94 mm Hg in the sham-procedure group ($P<0.001$ for both comparisons of the change from baseline), for a difference of −2.39 mm Hg (95% confidence interval [CI], −6.89 to 2.12; $P=0.26$ for superiority with a margin of 5 mm Hg). The change in 24-hour ambulatory systolic blood pressure was −6.75±15.11 mm Hg in the denervation group and −4.79±17.25 mm Hg in the sham-procedure group, for a difference of −1.96 mm Hg (95% CI, −4.97 to 1.06; $P=0.98$ for superiority with a margin of 2 mm Hg). There were no significant differences in safety between the two groups.

CONCLUSIONS

This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPLICITY HTN-3 ClinicalTrials.gov number, NCT01418261.)

Key Differences Between SYMPLICITY HTN-3 and Other SYMPLICITY Studies

Trial Design

SYMPLICITY HTN-3 was an extremely rigorous and novel study design, including a sham procedure for the control arm, where all patients and personnel following up patient care were blinded to treatment status. The study design also imposed great rigor to ensure that maximally-tolerated doses of antihypertensive medications were used, and in some cases that additional medications that may help in resistant hypertension were tried prior to randomization, and that medication regimens were maintained throughout the duration of the six-month primary endpoint.

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Age — yr	56.2±11.2	57.9±10.4
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

Table 1

Patient Population

The population in this study is different from other SYMPLICITY studies because it included an African American population, a higher percentage of diabetics, and higher percentage of population with high BMI. Additionally, vasodilators were used to a greater degree in SYMPLICITY HTN-3 than in previous studies.
(see Tables 1 & 2)

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Type of antihypertensive medication — no. (%)		
ACE inhibitor		
Patients taking medication	179 (49.2)	71 (41.5)
Patients taking maximally tolerated dose	167 (45.9)	64 (37.4)
Angiotensin-receptor blocker		
Patients taking medication	182 (50.0)	91 (53.2)
Patients taking maximally tolerated dose	180 (49.5)	88 (51.5)
Aldosterone antagonist	82 (22.5)	49 (28.7)
Alpha-adrenergic blocker	40 (11.0)	23 (13.5)
Beta-blocker	310 (85.2)	147 (86.0)
Calcium-channel blocker		
Patients taking medication	254 (69.8)	125 (73.1)
Patients taking maximally tolerated dose	208 (57.1)	109 (63.7)
Centrally acting sympatholytic agent	179 (49.2)	75 (43.9)
Direct-acting renin inhibitor	26 (7.1)	12 (7.0)
Direct-acting vasodilator	134 (36.8)	77 (45.0)
Diuretic		
Patients taking medication	363 (99.7)	171 (100)
Patients taking maximally tolerated dose	351 (96.4)	167 (97.7)

Table 2

Renal Denervation with the Symplicity™ RDN System is Safe

The Major Adverse Event rate in SYMPLICITY HTN-3 was 1.4%, significantly lower than the objective performance criterion of 9.8%, indicating that performing renal denervation with the Symplicity™ RDN system is safe. This is consistent with all other Symplicity trials, including the Global SYMPLICITY Registry. (see Figure 1)

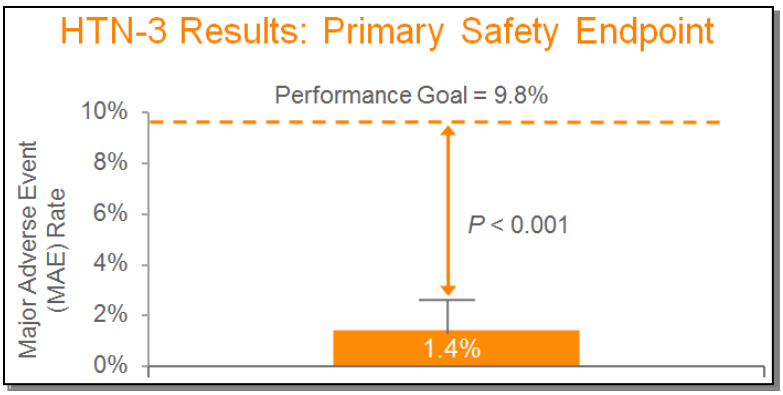
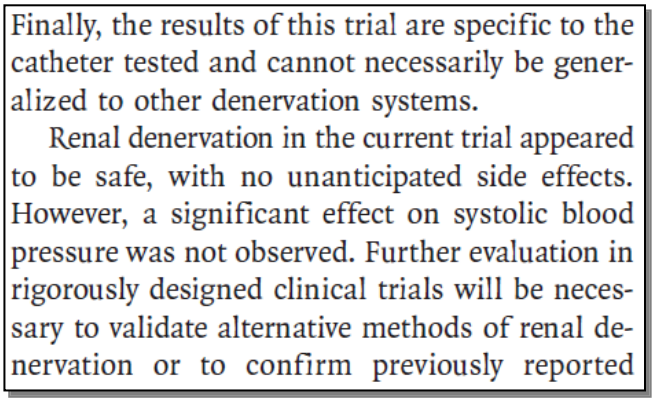


Figure 1

As the authors state in Figure 2, "the results of this trial are specific to the catheter tested and cannot necessarily be generalized to other denervation systems." Consequently, the Symplicity™ RDN system is the only RDN system to be proven safe for renal denervation.



Finally, the results of this trial are specific to the catheter tested and cannot necessarily be generalized to other denervation systems.

Renal denervation in the current trial appeared to be safe, with no unanticipated side effects. However, a significant effect on systolic blood pressure was not observed. Further evaluation in rigorously designed clinical trials will be necessary to validate alternative methods of renal denervation or to confirm previously reported

Figure 2

Q&A Regarding Safety Data

In Table 3, why are there fewer patients assessed for renal artery stenosis (332) than for the other adverse event types (352)?
Assessment of renal artery stenosis requires review of angiograms which were available for 332 of the 352 patients who had a 6-month clinical follow-up.

The 535 pts were randomized to 171 control and 364 therapy, why are those numbers not in this table?
535 patients were enrolled in the study, but not all of them completed a 6-month follow-up. Please refer to the supplement of the NEJM article which includes the flow chart of patients having reached the 6-month follow up.

What caused the stenosis and the embolic event in the denervation group?
The occurrence of 1 stenosis at 6 months in 332 subjects is well within the expected range of spontaneously observed atherosclerotic lesions in hypertensive patients (~1%). This particular case is a progression of a pre-existing stenosis.

The embolic event was a left axillary artery thrombus in the left arm which was treated with thrombectomy. This is a very unusual adverse event, and all indications are that it was not a result of catheter delivery or energy delivery.

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)

Table 3

SYMPLICITY HTN-3 Did Not Meet Its Primary and Secondary Efficacy Endpoints

SYMPLICITY HTN-3 did not meet its powered primary or secondary efficacy endpoints in this trial. (see Figure 3). The RDN group office BP reduction is 14.1mm Hg while the control group's is 11.7mm Hg, a difference of 2.4mm Hg which is less than the 5mm Hg superiority margin required for meeting the primary efficacy endpoint. Similarly, the RDN group ambulatory BP reduction is 6.75mm Hg compared to the control group's 4.79mm Hg, a difference of 1.96mm Hg which is less than the 2mm Hg superiority margin required for meeting the secondary efficacy endpoint.

This is in contrast to the clinical benefit achieved in thousands of patients in the Global SYMPLICITY Registry. There may be many factors that contributed to the outcome in this trial, which we continue to investigate. These may include:

<u>Patient behavior</u>
Due to being enrolled and closely monitored in a clinical trial, as well as blinded to treatment, the patients in SYMPLICITY HTN-3 may have improved or modified their lifestyle and drug adherence.

<u>Study population</u>
The population studied and the requirement for maximum tolerated medication dosage were different from other SYMPLICITY studies.

<u>Procedural experience and variability</u>
SYMPLICITY HTN-3 included a greater number of trial sites and proceduralists compared to SYMPLICITY HTN-1 and HTN-2, which may have led to greater procedural variability. In addition, case proctoring was different and not comparable

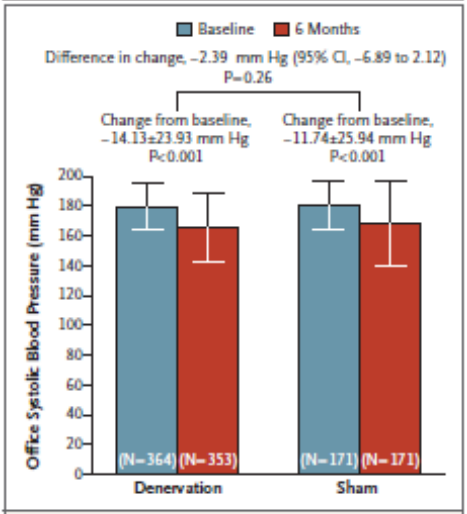


Figure 1. Primary Efficacy End Point.
A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mm Hg. The I bars indicate standard deviations.

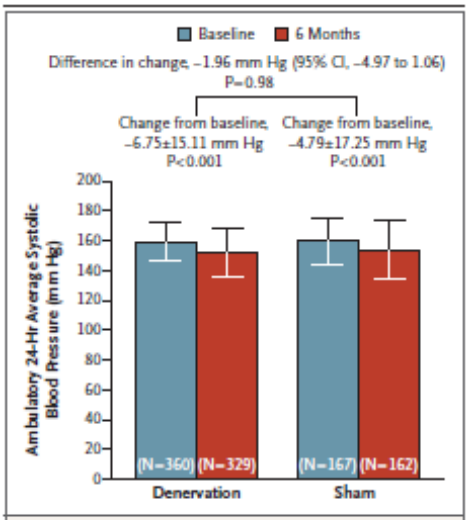


Figure 2. Secondary Efficacy End Point.
A significant change from baseline to 6 months in ambulatory 24-hour average systolic blood pressure was observed in both groups. The between-group difference (the secondary efficacy end point for which the study was powered) did not meet a test of superiority with a margin of 2 mm Hg. The I bars indicate standard deviations.

Figure 3

Q&A Regarding Efficacy Data

According to the efficacy data in Table 4, should we be treating patients with renal denervation who are younger than 65, not of black race, and with healthy kidney function?

SYMPLICITY HTN-3 did not meet its pre-specified primary or secondary efficacy endpoints. Although the analysis of these sub-groups is interesting, it should be used for further clinical investigation.

Does SYMPLICITY HTN-3 show that renal denervation is effective in non-African-Americans, but not African-Americans?

SYMPLICITY HTN-3 did not meet its primary or powered secondary efficacy endpoints. However, interesting results from certain sub populations are currently being explored, as subgroup analysis in a trial that did not meet its primary endpoint and may be a basis for further clinical investigation. There is evidence that African-Americans may respond differently than non-African Americans to certain medications. We recognize that the drop in the control arm for this subgroup was very large and it may be an important area for further study.

Isn't it flawed science to look at subgroups for signs of efficacy with a failed study?

Subgroups are important help identify questions to be addressed in future prospective trials. We are in the process of analyzing the data to determine the most suitable future clinical trial design.

Subgroup	Denervation	Sham	Between-Group Difference in Change in Office Systolic Blood Pressure (95% CI)	P Value	P Value for Interaction
	no. of patients		*mm Hg*		
All patients	353	171	−2.39 (−6.89 to 2.12)	0.26	
Diabetes mellitus					0.82
Yes	169	68	−4.53 (−11.51 to 2.46)	0.20	
No	181	101	−3.46 (−9.55 to 2.62)	0.26	
Sex					0.37
Male	208	108	−2.30 (−7.63 to 3.03)	0.40	
Female	142	61	−6.64 (−14.94 to 1.65)	0.12	
Black race					0.09
Yes	85	49	2.25 (−7.27 to 11.78)	0.64	
No	264	120	−6.63 (−11.81 to −1.44)	0.01	
Body-mass index					0.77
<30	91	42	−2.77 (−11.47 to 5.93)	0.53	
≥30	259	126	−4.36 (−9.76 to 1.03)	0.11	
Receiving aldosterone antagonist at baseline					0.36
Yes	76	47	−8.05 (−17.63 to 1.52)	0.10	
No	274	122	−3.24 (−8.42 to 1.93)	0.22	
Estimated GFR					0.31
<60 ml/min/1.73 m^2	68	38	0.54 (−8.29 to 9.37)	0.90	
≥60 ml/min/1.73 m^2	282	131	−5.22 (−10.51 to 0.06)	0.05	
Age					0.27
<65 yr	246	128	−5.73 (−11.06 to −0.40)	0.04	
≥65 yr	104	41	0.09 (−8.80 to 8.99)	0.99	
Any medication change					0.68
Yes	132	70	−5.41 (−13.49 to 2.67)	0.19	
No	218	99	−3.44 (−8.83 to 1.96)	0.21	

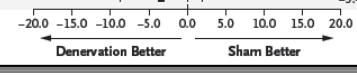


Table 4

Closing

- SYMPLICITY HTN-3 did not reach the primary or powered secondary efficacy endpoints in this trial. There may be many factors that contributed to the outcome, which we continue to investigate.
- SYMPLICITY HTN-3 did meet its safety endpoint, which is consistent with all other Symplicity trials, including the Global SYMPLICITY Registry.
- Based upon our detailed analysis of HTN-3, we believe further clinical investigation is warranted and Medtronic will, in consultation with FDA, pursue a new IDE trial.
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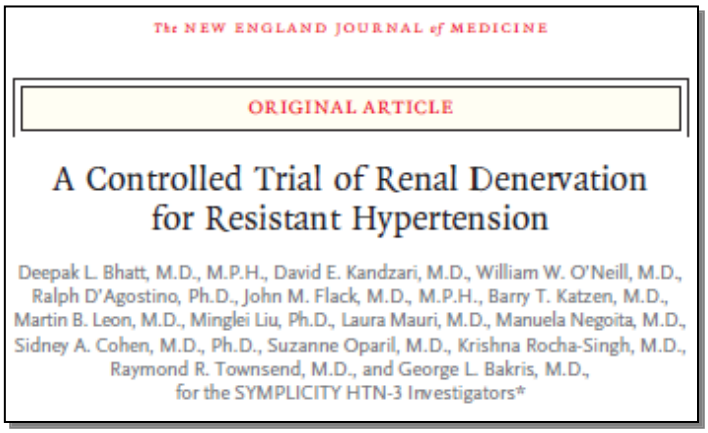
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