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Renal denervation: What happened, and why?

ABSTRACT

Despite promising results in initial trials, renal denervation failed to achieve its efficacy end points as a treatment for resistant hypertension in the SYMPLICITY HTN-3 trial, the largest trial of this treatment to date (N Engl J Med 2014; 370:1393–1401). Is renal denervation dead, or will future trials and newer technology revive it?

KEY POINTS

Renal denervation consists of passing a catheter into the renal arteries and ablating their sympathetic nerves using radiofrequency energy. In theory, it should lower blood pressure and be an attractive option for treating resistant hypertension.

SYMPLICITY HTN-3 was a blinded trial in which patients with resistant hypertension were randomized to undergo real or sham renal denervation.

At 6 months, office systolic blood pressure had failed to fall more in the renal denervation group than in the sham denervation group by a margin of at least 5 mm Hg, the primary efficacy end point of the trial.

Methodologic and technical shortcomings may explain the negative results of the SYMPLICITY HTN-3 trial, but most device manufacturers have put the brakes on future research into this novel therapy.

Today, renal denervation is not available in the United States but is available for routine care in Europe and Australia.

MANY PATIENTS, clinicians, and researchers had hoped that renal denervation would help control resistant hypertension. However, in the SYMPLICITY HTN-3 trial,¹ named for the catheter-based system used in the study (Symplicity RDN, Medtronic, Dublin, Ireland), this endovascular procedure failed to meet its primary and secondary efficacy end points, although it was found to be safe. These results were surprising, especially given the results of an earlier randomized trial (SYMPLICITY HTN-2),² which showed larger reductions in blood pressures 6 months after denervation than in the current trial.

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Here, we discuss the results of the SYMPLICITY HTN-3 trial and offer possible explanations for its negative outcomes.

LEAD-UP TO SYMPLICITY HTN-3

Renal denervation consists of passing a catheter through the femoral artery into the renal arteries and ablating their sympathetic nerves using radiofrequency energy. In theory, this should interrupt efferent sympathetic communication between the brain and renal arteries, reducing muscular contraction of these arteries, increasing renal blood flow, reducing activation of the renin-angiotensin-aldosterone system, thus reducing sodium retention, reducing afferent sympathetic communication between the kidneys and brain, and in turn reducing further sympathetic activity elsewhere in the body, such as in the heart. Blood pressure should fall.³

The results of the SYMPLICITY HTN-1 and 2 trials were discussed in an earlier article in this *Journal*,³ and the Medtronic-Ardian re-

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nal denervation system has been available in Europe and Australia for clinical use for over 2 years.⁴ Indeed, after the SYMPPLICITY HTN-2 results were published in 2010, Boston Scientific's Vessix, St. Jude Medical's EnligHTN, and Covidien's OneShot radiofrequency renal denervation devices—albeit each with some modifications—received a *Conformité Européenne* (CE) mark and became available in Europe and Australia for clinical use. These devices are not available for clinical use or research in the United States.^{3,5}

Therefore, SYMPPLICITY HTN-3, sponsored by Medtronic, was designed to obtain US Food and Drug Administration approval in the United States.⁶

■ SYMPPLICITY HTN-3 DESIGN

Inclusion criteria were similar to those in the earlier SYMPPLICITY trials. Patients had to have resistant hypertension, defined as a systolic blood pressure ≥ 160 mm Hg despite taking at least 3 blood pressure medications at maximum tolerated doses. Patients were excluded if they had a glomerular filtration rate of less than 45 mL/min/1.73 m², renal artery stenosis, or known secondary hypertension.

A total of 1,441 patients were enrolled, of whom 364 were eventually randomized to undergo renal denervation, and 171 were randomized to undergo a sham procedure. The mean systolic blood pressure at baseline was 188 mm Hg in each group. Most patients were taking maximum doses of blood pressure medications, and almost one-fourth were taking an aldosterone antagonist. Patients in both groups were taking an average of 5 medications.

The 2 groups were well matched for important covariates, including obstructive sleep apnea, diabetes mellitus, and renal insufficiency. Most of the patients were white; 25% of the renal denervation group and 29% of the sham procedure group were black.

The physicians conducting the follow-up appointments did not know which procedure the patients underwent, and neither did the patients. Medications were closely monitored, and patients had close follow-up. The catheter (Symplicity RDS, Medtronic) was of the same

design that was used in the earlier SYMPPLICITY trials and in clinical practice in countries where renal denervation was available.

Researchers expected that the systolic blood pressure, as measured in the office, would fall in both groups, but they hoped it would fall farther in the denervation group—at least 5 mm Hg farther, the primary end point of the trial. The secondary effectiveness end point was a 2-mm Hg greater reduction in 24-hour ambulatory systolic blood pressure.

■ SYMPPLICITY HTN-3 RESULTS

No statistically significant difference in safety was observed between the denervation and control groups. However, the procedure was associated with 1 embolic event and 1 case of renal artery stenosis.

Blood pressure fell in both groups. However, at 6 months, office systolic pressure had fallen by a mean of 14.13 mm Hg in the denervation group and 11.74 mm Hg in the sham procedure group, a difference of only 2.39 mm Hg. The mean ambulatory systolic blood pressure had fallen by 6.75 vs 4.79 mm Hg, a difference of only 1.96 mm Hg. Neither difference was statistically significant.

A number of prespecified subgroup analyses were conducted, but the benefit of the procedure was statistically significant in only 3 subgroups: patients who were not black ($P = .01$), patients who were less than 65 years old ($P = .04$), and patients who had an estimated glomerular filtration rate of 60 mL/min/1.73 m² or higher ($P = .05$).

■ WHAT WENT WRONG?

The results of SYMPPLICITY HTN-3 were disappointing and led companies that were developing renal denervation devices to discontinue or reevaluate their programs.

Although the results were surprising, many observers (including our group) raised concerns about the initial enthusiasm surrounding renal denervation.³⁻⁷ Indeed, in 2010, we had concerns about the discrepancy between office-based blood pressure measurements (the primary end point of all renal denervation trials) and ambulatory blood pressure measurements in SYMPPLICITY HTN-2.⁷

Baseline mean systolic pressure was 188 mm Hg on 5 medications

The enthusiasm surrounding this procedure led to the publication of 2 consensus documents on this novel therapy based on only 1 small randomized controlled study (SYMPPLICITY HTN-2).^{8,9} Renal denervation was even reported to be useful in other conditions involving the sympathorenal axis, including diabetes mellitus, metabolic syndrome, and obstructive sleep apnea, and also as a potential treatment adjunct in atrial fibrillation and other arrhythmias.⁵

What went wrong?

Shortcomings in trial design?

The trial was well designed. Both patients and operators were blinded to the procedure, and 24-hour ambulatory blood pressure monitoring was used. We presume that appropriate patients with resistant hypertension were enrolled—the mean baseline systolic blood pressure was 188 mm Hg, and patients in each group were taking an average of 5 medications.

On the other hand, true medication adherence is difficult to ascertain. Further, the term maximal “tolerated” doses of medications is vague, and we cannot rule out the possibility that some patients were enrolled who did not truly have resistant hypertension—they simply did not want to take medications.

Patients were required to be on a stable medication regimen before enrollment and, ideally, to not have any medication changes during the course of the study, but at least 40% of patients did require medication changes during the study. Additionally, it is unclear whether all patients underwent specific testing to rule out secondary hypertension, as this was done at the discretion of the treating physician.

First-generation catheters?

The same type of catheter was used as in the earlier SYMPPLICITY trials, and it had been used in many patients in clinical practice in countries where the catheter is routinely available. It is unknown, however, whether newer multisite denervation devices would yield better results than the first-generation devices used in SYMPPLICITY HTN-3. But even this would not explain the discrepancies in data between earlier trials and this trial.

Operator inexperience?

It has been suggested that operator inexperience may have played a role, but an analysis of operator volume did not find any association between this variable and the outcomes. Each procedure was supervised by at least 1 and in most cases 2 certified Medtronic representatives, who made certain that meticulous attention was paid to procedure details and that no shortcuts were taken during the procedure.

Inadequate ablation?

While we can assume that the correct technique was followed in most cases, renal denervation is still a “blind” procedure, and there is no nerve mapping to ascertain the degree of ablation achieved. Notably, patients who had the most ablations reportedly had a greater average drop in systolic ambulatory blood pressure than those who received fewer ablations. Sympathetic nervous system activity is a potential marker of adequacy of ablation, but it was not routinely assessed in the SYMPPLICITY HTN-3 trial. Techniques to assess sympathetic nerve activity such as norepinephrine spillover and muscle sympathetic nerve activity are highly specialized and available only at a few research centers, and are not available for routine clinical use.

While these points may explain the negative findings of this trial, they fail to account for the discrepant results between this study and previous trials that used exactly the same definitions and techniques.

Patient demographics?

Is it possible that renal denervation has a differential effect according to race? All previous renal denervation studies were conducted in Europe or Australia; therefore, few data are available on the efficacy of the procedure in other racial groups, such as black Americans. Most of the patients in this trial were white, but approximately 25% were black—a good representation. There was a statistically significant benefit favoring renal denervation in nonblack (mostly white) patients, but not in black patients. This may be related to racial differences in the pathophysiology of hypertension or possibly due to chance alone.

At 6 months, systolic pressure had fallen by 14.13 mm Hg in the denervation group and 11.74 mm Hg in the sham procedure group

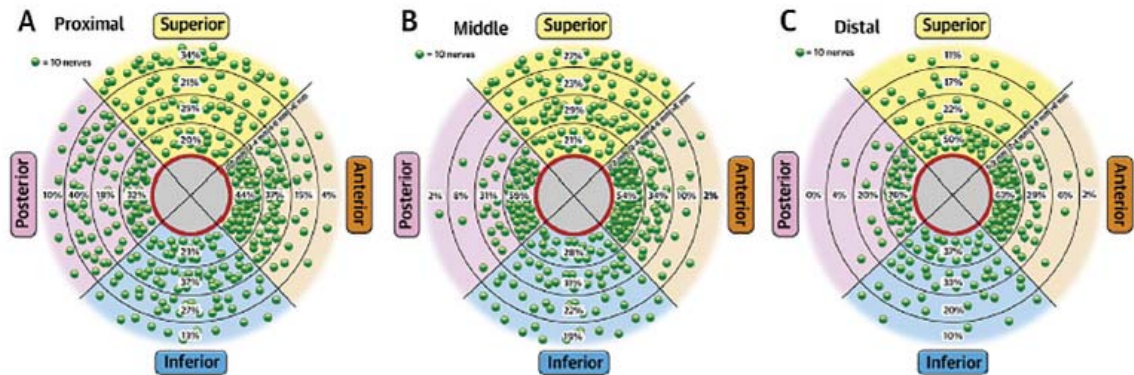


FIGURE 1. Distribution and density of renal sympathetic nerves. Distribution of nerves stratified according to total number (each green dot represents 10 nerves), relative number as percent per segment, and distance from the lumen in the proximal (A), middle (B), and distal (C) location.

Reprinted from Mahfoud F, Edelman ER, Bohm M. Catheter-based renal denervation is no simple matter: lessons to be learned from our anatomy? *J Am Coll Cardiol* 2014; 64:644–646; based on data in Sakakura K, Ladich E, Cheng Q, et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol* 2014; 64:635–643 and from raw data provided by M. Joner, of CVPath Inc.

A Hawthorne effect?

A Hawthorne effect (patients being more compliant because physicians are paying more attention to them) is unlikely, since the renal denervation arm did not have any reduction in blood pressure medications. At 6 months, both the sham group and the procedure group were still on an average of 5 medications.

Additionally, while the blood pressure reduction in both treatment groups was significant, the systolic blood pressure at 6 months was still 166 mm Hg in the denervation group and 168 mm Hg in the sham group. If denervation was effective, one would have expected a greater reduction in blood pressure or at least a decrease in the number of medications needed, eg, 1 to 2 fewer medications in the denervation group compared with the sham procedure group.

Regression to the mean?

It is unknown whether the results represent a statistical error such as regression to the mean. But given the run-in period and the confirmatory data from 24-hour ambulatory blood pressure, this would be unlikely.

WHAT NOW?

Is renal denervation dead? SYMPPLICITY HTN-3 is only a single trial with multiple shortcomings and lessons to learn from. Since its publication, there have been updates from 2 prospective, randomized, open-label tri-

als concerning the efficacy of catheter-based renal denervation in lowering blood pressure.^{10,11}

DENERHTN (Renal Denervation for Hypertension)¹⁰ studied patients with ambulatory systolic blood pressure higher than 135 mm Hg, diastolic blood pressure higher than 80 mm Hg, or both (after excluding secondary etiologies), despite 4 weeks of standardized triple-drug treatment including a diuretic. Patients were randomized to standardized stepped-care antihypertensive treatment alone (control group) or standard care plus renal denervation. The latter resulted in a significant further reduction in ambulatory blood pressure at 6 months.

The Prague-15 trial¹¹ studied patients with resistant hypertension. Secondary etiologies were excluded and adherence to therapy was confirmed by measuring plasma medication levels. It showed that renal denervation along with optimal antihypertensive medical therapy (unchanged after randomization) resulted in a significant reduction in ambulatory blood pressure that was comparable to the effect of intensified antihypertensive medical therapy including spironolactone. (Studies have shown that spironolactone is effective when added on as a fourth-line medication in resistant hypertension.¹²) At 6 months, patients in the intensive medical therapy group were using an average of 0.3 more an-

The results were disappointing, and companies have either discontinued or are reevaluating their programs

ti hypertensive medications than those in the procedure group.

These two trials addressed some of the drawbacks of the SYMPPLICITY HTN-3 trial. However, both have many limitations including and not limited to being open-label and nonblinded, lacking a sham procedure, using a lower blood pressure threshold than SYMPPLICITY HTN-3 did to define resistant hypertension, and using the same catheter as in the SYMPPLICITY trials.

Better technology is coming

Sakakura et al and Mahfoud et al showed that the concentration of sympathetic periarterial renal nerves is higher in the proximal and ventral areas but closer to the lumen in the distal segment (**Figure 1**).^{13,14} Moreover, Id et al¹⁵ found that ablating nerves in the renal arteries without addressing accessory arteries resulted in less-optimal blood pressure reduction. Thus, the technical aspects of the procedure are highly important.

Advanced renal denervation catheters are needed that are multielectrode, smaller, easier to manipulate, and capable of providing simultaneous, circumferential, more-intense, and deeper ablations. The ongoing Investigator-Steered Project on Intravascular Renal Denervation for Management of Drug-Resistant Hypertension (INSPIRED)¹⁶ and Renal Denervation Using the Vessix Renal Denervation System for the Treatment of Hypertension (REDUCE-HTN: REINFORCE)¹⁷ trials are using contemporary innovative ablation catheters to address the limitations of the first-generation Symplicity catheter.

Further, Fischell et al¹⁸ reported encouraging results of renal denervation performed by injecting ethanol into the adventitial space of the renal arteries. This is still an invasive procedure; however, ethanol can spread out in all directions and reach all targeted nerves, potentially resulting in a more complete renal artery sympathetic ablation.

As technology advances, the WAVE IV trial¹⁹ is examining renal denervation performed from the outside through the skin using high-intensity focused ultrasound, which eliminates the need for femoral arterial catheterization, a promising noninvasive approach.

Proposals for future trials

The European Clinical Consensus Conference for Renal Denervation²⁰ proposed that future trials of renal denervation include patients with moderate rather than resistant hypertension, reflecting the pathogenic importance of sympathetic activity in earlier stages of hypertension. The conference also proposed excluding patients with stiff large arteries, a cause of isolated systolic hypertension. Other proposals included standardizing concomitant antihypertensive therapy, preferably treating all patients with the combination of a renin-angiotensin system blocker, calcium channel blocker, and diuretic in the run-in period; monitoring drug adherence through the use of pill counts, electronic pill dispensers, and drug blood tests; and using change in ambulatory blood pressure as the primary efficacy end point and change in office blood pressure as a secondary end point.

Trials ongoing

To possibly address the limitations posed by the SYMPPLICITY HTN-3 trial and to answer other important questions, several sham-controlled clinical trials of renal denervation are currently being conducted:

- INSPIRED¹⁶
- REDUCE-HTN: REINFORCE¹⁷
- Spyral HTN-Off Med²¹
- Spyral HTN-On Med²¹
- Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN).²²

We hope these new studies can more clearly identify subsets of patients who would benefit from this technology, determine predictors of blood pressure reduction in such patients, and lead to newer devices that may provide more complete ablation.

Obviously, we also need better ways to identify the exact location of these sympathetic nerves within the renal artery and have a clearer sense of procedural success.

Until then, our colleagues in Europe and Australia continue to treat patients with this technology as we appropriately and patiently wait for level 1 clinical evidence of its efficacy. ■

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Renal denervation is still a 'blind' procedure, with no nerve mapping to ascertain the degree of ablation

REFERENCES

1. Bhatt DL, Kandzari DE, O'Neill WW, et al, for the SYMPPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; 370:1393–1401.
2. Symplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. *Lancet* 2010; 376:1903–1909.
3. Bunte MC, Infante de Oliveira E, Shishehbor MH. Endovascular treatment of resistant and uncontrolled hypertension: therapies on the horizon. *JACC Cardiovasc Interv* 2013; 6:1–9.
4. Thomas G, Shishehbor MH, Bravo EL, Nally JV. Renal denervation to treat resistant hypertension: guarded optimism. *Cleve Clin J Med* 2012; 79:501–510.
5. Shishehbor MH, Bunte MC. Anatomical exclusion for renal denervation: are we putting the cart before the horse? *JACC Cardiovasc Interv* 2014; 7:193–194.
6. Bhatt DL, Bakris GL. The promise of renal denervation. *Cleve Clin J Med* 2012; 79:498–500.
7. Bunte MC. Renal sympathetic denervation for refractory hypertension. *Lancet* 2011; 377:1074; author reply 1075.
8. Mahfoud F, Luscher TF, Andersson B, et al; European Society of Cardiology. Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. *Eur Heart J* 2013; 34:2149–2157.
9. Schlaich MP, Schmieder RE, Bakris G, et al. International expert consensus statement: percutaneous transluminal renal denervation for the treatment of resistant hypertension. *J Am Coll Cardiol* 2013; 62:2031–2045.
10. Azizi M, Sapoval M, Gosse P, et al; Renal Denervation for Hypertension (DENERHTN) investigators. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 2015; 385:1957–1965.
11. Rosa J, Widimsky P, Tousek P, et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension* 2015; 65:407–413.
12. Williams B, MacDonald TM, Morant S, et al; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015; 386:2059–2068.
13. Sakakura K, Ladich E, Cheng Q, et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol* 2014; 64:635–643.
14. Mahfoud F, Edelman ER, Bohm M. Catheter-based renal denervation is no simple matter: lessons to be learned from our anatomy? *J Am Coll Cardiol* 2014; 64:644–646.
15. Id D, Kaltenbach B, Bertog SC, et al. Does the presence of accessory renal arteries affect the efficacy of renal denervation? *JACC Cardiovasc Interv* 2013; 6:1085–1091.
16. Jin Y, Jacobs L, Baelen M, et al; Investigator-Steered Project on Intravascular Renal Denervation for Management of Drug-Resistant Hypertension (Inspired) Investigators. Rationale and design of the Investigator-Steered Project on Intravascular Renal Denervation for Management of Drug-Resistant Hypertension (INSPIRED) trial. *Blood Press* 2014; 23:138–146.
17. ClinicalTrials.gov. Renal Denervation Using the Vessix Renal Denervation System for the Treatment of Hypertension (REDUCE HTN: REINFORCE). <https://clinicaltrials.gov/ct2/show/NCT02392351?term=REDUCE-HTN%3A+REINFORCE&rank=1>. Accessed August 3, 2017.
18. Fischell TA, Ebner A, Gallo S, et al. Transcatheter alcohol-mediated perivascular renal denervation with the peregrine system: first-in-human experience. *JACC Cardiovasc Interv* 2016; 9:589–598.
19. ClinicalTrials.gov. Sham controlled study of renal denervation for subjects with uncontrolled hypertension (WAVE_IV) (NCT02029885). <https://clinicaltrials.gov/ct2/show/results/NCT02029885>. Accessed August 3, 2017.
20. Mahfoud F, Bohm M, Azizi M, et al. Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design. *Eur Heart J* 2015; 36:2219–2227.
21. Kandzari DE, Kario K, Mahfoud F, et al. The SPYRAL HTN Global Clinical Trial Program: rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications. *Am Heart J* 2016; 171:82–91.
22. ClinicalTrials.gov. A Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN). <https://clinicaltrials.gov/ct2/show/NCT02649426?term=RADIANCE&rank=3>. Accessed August 3, 2017.

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