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Renal Denervation: What Is on the Horizon?

A look at the background of renal denervation studies and the future directions of this therapy for patients with hypertension.

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What does the total body of preclinical and clinical evidence suggest about the effectiveness of renal denervation for the treatment of hypertension?

Prior to the emergence of percutaneous radiofrequency-based therapy for renal denervation, considerable preclinical and clinical experience reinforced the importance of afferent and efferent renal sympathetic nerve activity in the initiation and maintenance of severe hypertension. In the mid-1950s, surgical thoracic sympathectomy and splanchnicectomy successfully controlled severe, resistant hypertension. Unfortunately, although the procedure was successful in treating blood pressure, it resulted in considerable morbidity and adverse clinical events, including debilitating orthostatic hypotension and incontinence. Nevertheless, the successful surgical interruption of renal sympathetic nerves confirmed their essential role in the maintenance of resistant hypertension and bolstered the preclinical animal model work of Drs. Richard Katholi, Gerald DiBona, and others. This body of work established that renal sympathetic nerve activation results in renin release, which promotes renal tubular reabsorption of sodium, increases renal vasoconstriction, and reduces renal blood flow, all of which potentially elevate blood pressure.

More recent contributions by Dr. Murray Esler in humans with resistant hypertension demonstrated the variable yet clear increase in renal norepinephrine spillover to plasma—a biomarker of increased renal sympathetic activation—when compared to normotensive volunteers. These essential preclinical and clinical paradigms, the role of renal nerves in the underlying pathophysiology of hypertension, and the observation that surgical renal sympathectomy improved hypertension control have lead us to the consideration of a percutaneous approach to renal sympathetic denervation for control of resistant hypertension.

However, as suggested by more recent work by investigators at CBSET, Inc. and others, the microanatomic location of these renal nerves and the appropriate application of radiofrequency energy to the renal intimal surface, sufficient to ablate nerves without causing renal injury, remains a significant challenge.

The rapid evolution in our understanding of both the human renal nerve microanatomy and appreciation of the ideal technique for the safe application of radiofrequency technology leading to successful renal nerve ablation may, in part, explain the variable clinical results witnessed in the series of SYMPLICITY HTN trials, which date back to 2007. Nonetheless, this evolving preclinical science continues to reinforce our interest in renal denervation as a therapeutic modality to treat resistant hypertension.

What were the potential causes for the failure of SYMPLICITY HTN-3?

The potential causes for SYMPLICITY HTN-3 to fail to meet its primary effectiveness endpoint are multiple and have been the subject of substantial speculation in the medical literature. A detailed assessment of the potential reasons for failure of SYMPLICITY HTN-3 centers around several essential themes: trial design issues that required randomized patients to be on "maximum tolerable" medical therapy, the possible effect of patient compliance with their hypertension regimen, the catheter technology used in SYMPLICITY HTN-1 and -2 (the Arch catheter) versus SYMPLICITY HTN-3 (the Flex catheter), poor investigator experience with the renal nerve ablation technique, and the marked variability in the number and location of radiofrequency ablation sites within the renal artery. These numerous potential causes, taken separately or together, may have resulted in the failure of SYMPLICITY HTN-3.

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How do you reconcile the positive results seen in the early renal denervation studies with the negative results seen in SYMPLICITY HTN-3?

This question reflects on the importance and impact of the clinical trial design and its many ramifications. The essential differences in the trial designs between SYMPLICITY HTN-1 and -2 and the pivotal SYMPLICITY HTN-3 demonstrate the potential effect of investigator patient selection bias, the inclusion and exclusion criteria as it affected the patient cohort studied, the appropriate method by which serial blood pressure measurements were performed (office blood pressure vs ambulatory blood pressure measurements), and evolution of the various techniques and technologies for the application of radiofrequency energy.

However, the differences between the series of SYMPLICITY trials go well beyond issues of trial design. Differences in operator experience in SYMPLICITY HTN-1 and -2 versus SYMPLICITY HTN-3, in which the typical investigator performed only three procedures with specific pretrial "hands-on" training with the technique, and the differences in patient referral patterns to European and Australian hypertension centers of excellence may have also influenced the trial results. These issues not withstanding, the randomized sham-controlled trial design and trial execution of SYMPLICITY HTN-3 must be considered a central element in the discrepant results.

Have the hypertension and interventional physician communities taken any steps to understand the factors that resulted in the failure of SYMPLICITY HTN-3?

Since Medtronic announced that SYMPLICITY HTN-3 failed to meet its primary efficacy endpoint on January 9, 2014 (with full results presented at the ACC meeting on March 29, 2014), there has been considerable debate and reflection within and among the hypertension and interventional communities. As previously noted, there have been questions as to the discrepancy of the trial design, the influence of the requirement of prescribed use of "maximal tolerable" medical therapy and its impact on patient behavior and compliance, and the hypothesis that physician device use training, when taken together, contributed to substantial "noise" that may have masked any actual impact of renal denervation.

The debate has also focused on the mercurial nature of the blood pressure and its assessment as a trial endpoint. Debate regarding the multiple potential reasons for the failure of SYMPLICITY HTN-3 has refocused the physician communities to consider a more "pharma-like" phase II trial design, which is reflected in the upcoming REDUCE-HTN: REINFORCE study. The design of this randomized 100-patient investigation is an attempt to remove, as much as possible, the overlying confounding variables and isolate the potential direct effect of renal denervation in the absence of medical therapies and the associated change in medical therapies. This trial design, approved in collaboration with the American Society of Hypertension and the US Food and Drug Administration (FDA), is an important step to refocus attention on the fundamentals of radiofrequency-based renal denervation.

What has the medical community learned about the resistant hypertensive patient population, and the challenges in studying it, from SYMPLICITY HTN-3 and its disparity from previous trials?

Appropriately, attention has focused on patient selection and patient behavior prior to and during the treatment phase of these trials. There are multiple influences on patient behavior and its potential impact on trial results; specifically, simply going through the informed consent phase, coupled with a potential Hawthorne effect, whereby a patient's behavior may change simply by being observed in a clinical trial setting, may affect trial results. The subsequent trial designs will center on the mitigating influences that may mask an underlying beneficial hypertensive effect. Importantly, one of the collateral benefits from the failure of SYMPLICITY HTN-3 is the increased awareness now paid to this previously relatively neglected patient cohort. Many patients who were screen failures in SYMPLICITY HTN-3 are now, hopefully, receiving increased medical attention.

The use of office blood pressure values as opposed to ambulatory blood pressure measurements has been another topic of ongoing debate. Although the majority of investigators believe that ambulatory blood pressure is a more accurate assessment of a patient's blood pressure throughout the day, this technique has traditionally not been used by general internists but more by hypertensive specialists. The fact that this technology is not reimbursed by the Centers for Medicare & Medicaid Services has also made the transition from a clinical trial into clinical practice potentially problematic.

Finally, the devices, which by their design reduce the variability of the application of radiofrequency energy, have evolved. The newer devices are potentially able to provide a more uniform application of radiofrequency energy throughout the length of the renal artery; unfortunately, however, the simple fact remains that the denervation procedure remains a "black box" relative to understanding the in–cath lab procedural endpoint. This issue will persist in newer device designs to be employed in the trials using the Vessix (Boston Scientific Corporation) and Spyral (Medtronic) catheters.

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Should the focus change for future studies? If so, why? And, to what?

As more clinical data from various registries are reported, we will have additional insight into the appropriate patient cohorts that should be considered for denervation as an adjunct to their medical therapy. Emerging evidence seems to suggest that older hypertensive patients with isolated systolic hypertension may not be ideal candidates for renal denervation. I suspect we will evolve to the understanding that based on both patient hypertension "phenotypes" and renal artery anatomy, one size does not fit all.

Regardless, the intermediate step in performing a phase II trial whereby drugs are "washed out" will be a very challenging trial design because the patient cohort selected to partake in such a trial may be very different from the cohort involved in a pivotal trial. Ultimately, any pivotal clinical trial design will have to address aspects of variable patient behaviors and compliance. In this regard, assessments of patient compliance with random urine testing, pill counts, assessment of pharmacy records, etc. has been discussed. These rather excessive design elements may be impractical in a larger pivotal cohort. Rather, I believe the solution is to focus on the appropriate hypertensive patient cohort with the appropriate anatomy and clinical indications. Recall that in the advent of the SYMPLICITY trials, we were led to believe that patients with resistant hypertension numbered in the billions. Clearly, that estimate has been overstated; the screen failure rate of approximately 65% witnessed in SYMPLICITY HTN-3 has taught us otherwise.

What are likely to be the most appropriate pivotal trial designs for future device trials on hypertension?

Future trial designs for radiofrequency-based renal denervation should focus on specific patient populations. Including larger hypertension cohorts may be impractical and again result in substantial "noise." Rather, trials to specifically address the African American cohort may be appropriate and thereby test this therapy in a more homogenous population. Other trial designs should consider renal denervation in patients undergoing atrial fibrillation ablation as an important adjunct to reduce its recurrence. Additionally, understanding the underlying pathophysiology related to sympathetic modulation in those patients with underlying systolic heart failure may be a more focused patient group. As such, incremental trial designs that are more narrowly focused on specific cohorts may be the best way to advance the clinical spectrum of where this important therapy is best suited.

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Based on your review of SYMPLICITY HTN-3 and its failure to meet its primary endpoint, what role did the Ardian technology play in the failure, and what role did operator variability play?

The SYMPLICITY HTN-3 trial failed for a multitude of reasons. Many of these, such as very inconsistent antihypertensive therapy and highly variable baseline blood pressure recordings, had nothing to do with the limitations of the Symplicity renal denervation system (Ardian, Inc., acquired by Medtronic in 2010).[1] The lack of efficacy related to the Symplicity device may be related more to operator performance than to the technology itself. The Symplicity Flex catheter used in HTN-3 differs in some ways from the original device known as the Symplicity Arch catheter used in the successful predicate studies HTN-1 and HTN-2.

Both devices have single electrodes located at their tips, but the newer version requires the operator to actively appose the catheter tip to the artery wall by manually deflecting the tip with a lever on the handle. Although seemingly a subtle difference, it translates into more variability in terms of contact between the catheter tip and the artery wall. Insufficient wall contact will compromise lesion creation in the artery wall and thus limit efficacy, as adequate artery wall apposition is a critical determinant of a successful ablation. The single human postmortem specimen reported with the Symplicity Flex catheter showed very shallow tissue penetration with minimal nerve injury, likely reflecting poor contact between the catheter and the artery wall.[2]

The Symplicity generator offers some feedback to the operator regarding the tissue contact of the catheter; it records both temperature at the catheter tip and impedance of the tissue. A stable baseline impedance, drop in impedance with energy delivery, and rise in tissue temperature during ablation all suggest effective artery wall apposition. Still, these variables require some operator judgment for interpretation. The procedural requirements pertain to each contact point for ablation, and multiple contact points with Symplicity Flex have to be positioned by the operator in order to create a circumferential injury pattern thought to be necessary for effective renal nerve injury. Despite HTN-3 using a different catheter than in HTN-1 and HTN-2, the technology is the same—a single-point radiofrequency ablation device. The difference, however,

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is that the technique and operator experience with this technique differs greatly between these studies. On average, the number of ablations per patient in HTN-3 (9.2) was less than the average number of ablations performed by much more experienced operators in the severe hypertension cohort of the SYMPLICITY global registry (13.7).[1,3] Furthermore, a post hoc analysis of the HTN-3 study showed that a greater number of renal artery ablations led to a more pronounced blood pressure drop.

Also, in the HTN-3 study, only 19 of 364 patients treated with Symplicity Flex underwent a four-quadrant injury pattern in both renal arteries. This multiquadrant injury pattern more effectively targets the renal nerves distributed around the artery, showing a trend toward greater blood pressure lowering in this group.[1] So, it seems that technical rather than technological issues may have compromised the performance of SYMPLICITY in HTN-3. The recently published DENER-HTN trial using the same Flex catheter but with experienced operators is a well-designed, randomized, sham-controlled trial. Its clinical success, in stark contrast to HTN-3, highlights the technical and/or operator issues that may have plagued the earlier study.[4]

What does the medical community know about renal neuroanatomy that impacts the success or failure of renal denervation, and what still remains to be studied?

Atherton et al first reported the renal nerve distribution pattern in a human postmortem study of nine renal arteries.[5] The study was limited by relatively shallow sampling into the artery wall. Still, the number of nerves increased along the length of the artery and became closer to the lumen as the nerves approached the kidney. Sakakura et al confirmed that the nerves have a shallower depth distally, averaging 2.6 ± 0.77 mm.[6] The more shallow the nerves, the more susceptible they are to injury via various renal artery ablation techniques. Nerves have been found as far as 10 mm away from the renal artery, but it is unclear whether these nerves are actually traveling to the kidney.

There is also some asymmetry in terms of nerve distribution around the artery, favoring the ventral surface, but a significant number of nerves occupy each quadrant of the renal artery wall.[7] These anatomic considerations suggest that the optimal renal nerve target injury zone may be the most distal aspect of the renal artery or in fact into the renal artery branches where the nerves are closer to the catheter tip. Preclinical studies with both the Symplicity catheter and the EnligHTN catheter (St. Jude Medical, Inc.) indicate more effective nerve injury occurs when more distal ablation is performed.[8,9]

It remains unknown whether all renal nerve fibers must be ablated for successful blood pressure lowering or if there is some critical threshold effect. Furthermore, it is unclear whether it is more important to interrupt the efferent or afferent nerve traffic. Because these nerves travel together, they are injured simultaneously with the current renal ablation techniques.

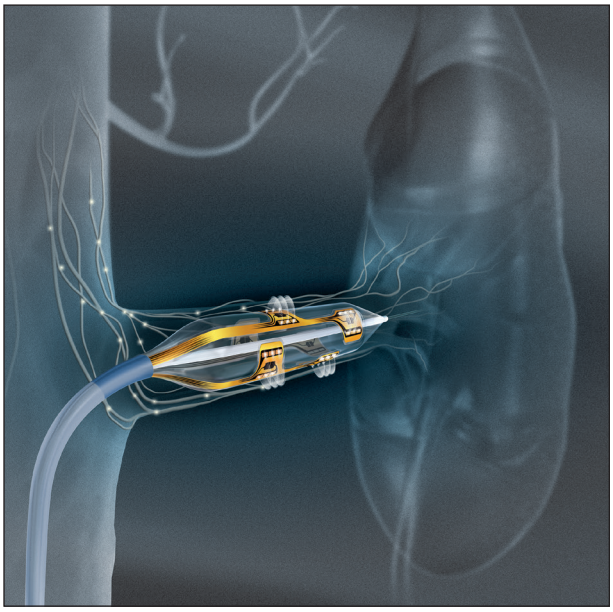

Figure 1. Overview of the mechanisms of the Vessix system.

Do you think the Vessix system avoids the technical and operator issues experienced in SYMPLICITY HTN-3?

The Vessix renal denervation system overcomes many of the technical challenges that plagued the Symplicity device in HTN-3. The Vessix system is composed of a balloon catheter with a helical array of electrodes mounted on its surface, with thermistors positioned in between each electrode pair (Figure 1). The balloon actively apposes the electrodes to the artery wall, ensuring sufficient tissue contact that is confirmed by internal measurements made by the generator and recorded on a display. The generator uses a temperature-control algorithm to deliver energy at 68°C to the electrode surface, creating a consistent ablation lesion approximately 4 mm deep into the artery wall. The helical electrode array creates a multiquadrant injury pattern independent of operator positioning of the catheter.

The system also uses bipolar electrodes to deliver radiofrequency energy more efficiently into the tissue. The design features of the Vessix system have been optimized based upon renal nerve anatomy and should minimize or eliminate the technical and operator limitations experienced with the Symplicity Flex catheter in HTN-3.

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What is the aim of the REDUCE-HTN: REINFORCE study?

The aim of this study is to try to clearly answer the question of whether renal denervation can actually reduce blood pressure. For many who are in the field, this is often taken as a given. However, considering the mixed results of previous trials, we have to critically assess the current state of the evidence, as this concept has not yet been definitely proven.

Can you provide an overview of the study protocol?

The trial will examine the efficacy and safety of the Vessix system compared with a masked (sham) procedure in patients who have uncontrolled (but not unstable) hypertension when off medications. Patients who are stable but with elevated blood pressures off medications are candidates for this study, as are patients on a limited number of medications who have elevated blood pressures when off these medications. Please see Table 1 for further details of the study.

TABLE 1. REDUCE-HTN: REINFORCE STUDY DETAILS

Randomization	2:1 (test: control) • Test: renal denervation • Control: masked procedure (renal angiogram)
Key inclusion criteria	• ≥ 18 and ≤ 75 years of age • Office systolic blood pressure ≥ 150 mm Hg and ≤ 180 mm Hg based on an average of three office-based blood pressure measurements • Average 24-h ambulatory systolic blood pressure ≥ 135 mm Hg and ≤ 170 mm Hg • For each kidney, a main renal artery, with or without accessory renal arteries, with diameter ≥ 3 mm and ≤ 7 mm and length ≥ 20 mm
Primary efficacy assessment	• Mean reduction in average 24-h ambulatory systolic blood pressure at 8 weeks postrandomization
Safety assessments*	Safety assessments analyzed at all follow-up time points: • All-cause death • Renal failure • Hospitalization for hypertensive crisis • Hospitalization due to severe hypotension/syncope Safety assessments analyzed at 4 weeks: • Significant embolic event resulting in end-organ damage or intervention to prevent it • Renal artery dissection or perforation requiring intervention • Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion Safety assessments analyzed at 6 months: • Significant new renal artery stenosis assessed by duplex ultrasound and confirmed by the angiographic core laboratory

**All safety assessments will be adjudicated by an independent clinical events committee.*

Does this new study design address the questions raised by SYMPLICITY HTN-3?

By restricting the study population to one that is off medication, some of the variability in previous trials (eg, dose changes of medications, etc) can be reduced (Figure 1). Additionally, the use of ambulatory blood pressure for enrollment and endpoint assessment should

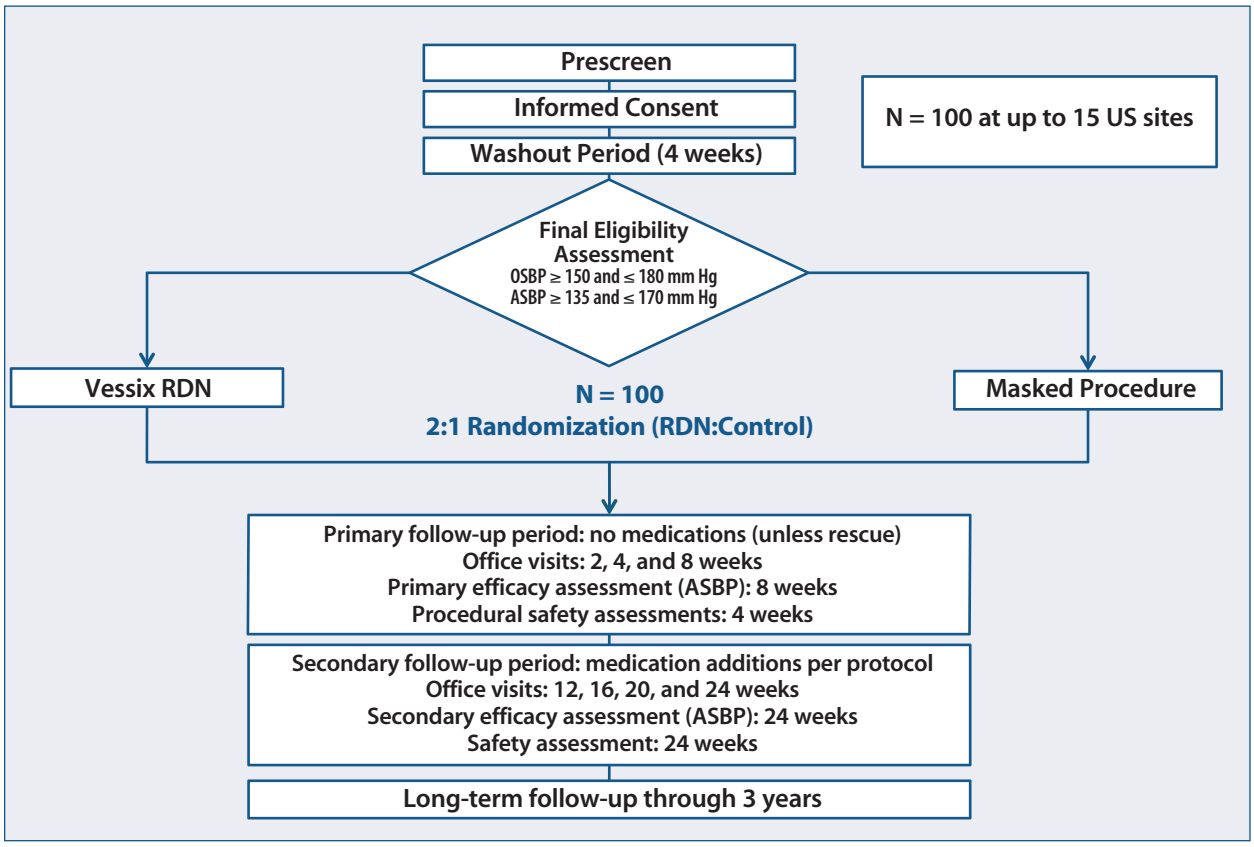

Figure 1. REDUCE-HTN: REINFORCE study overview. ASBP = ambulatory systolic blood pressure; OSBP = office systolic blood pressure.

helpfully reduce the variability in measuring blood pressure within the trial. Additionally, the Vessix catheter (like other newer renal denervation systems) has the ability to provide stable denervation procedures covering the full length of the renal artery (including accessory arteries), which we think should decrease the variability of the procedure.

Why doesn't this study target resistant hypertensive patients?

Sometimes, targeting a therapy to the most resistant or hardest-to-treat patients is more challenging. These patients may be resistant to many therapies (not just denervation, but by definition to medications, as well), and issues of variable adherence to medications also arise. Fundamentally, the REDUCE-HTN: REINFORCE study aims to start out by asking the simple question of the impact of renal denervation on blood pressure. By taking the medications out of the equation, there should be a cleaner "signal" to assess.

Are there any ethical considerations in taking hypertensive patients off their medications for a period of time?

Patient safety is of course paramount in any clinical study. This particular issue is something that the study investigators, FDA, and sponsors have thought about very carefully. First, there is a very short period of time that patients are off medications (3 months). Second, this is a commonly used design among trials of pharmaceutical antihypertensives, which is endorsed by the FDA, which has studied and published on this type of design and has not found it to be associated with increased rates of worrisome outcomes. Third, if there are any adverse clinical sequelae of this approach, patients should of course be treated, and this is specified in the investigational plan.

Does the hypertension community support this new study design?

Because of the similarity of this approach to pharmaceutical studies of new antihypertensives, I think that this design should be more familiar to the hypertension community. The American Society of Hypertension was integrally involved in two think tank meetings with the FDA and other stakeholders, and ultimately, the recommendation for this type of study design is what came out of those meetings. The treatment of hypertension is a multidisciplinary endeavor, and we're thrilled to have their guidance and input into the study. ■

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