

# The future of renal denervation for uncontrolled hypertension

- By Shawn Moaddeb

## Introduction

The first SYMPLICITY HTN trials generated enthusiasm for catheter-based treatment of hypertension resistant to pharmacotherapy. However, when the treatment arm of SYMPLICITY HTN-3 failed to show significantly lower systolic blood pressure than the control group, some industry observers concluded that the door had been closed on renal denervation. Despite this surprisingly negative result, most industry participants (manufacturers, physicians, etc.) remain optimistic about the future of renal denervation. The sponsor of SYMPLICITY has redesigned its product and refined its trial protocol, while other major medical device manufacturers continue with their own product development in the area. Key physician opinion leaders continue to view renal denervation as a potential hypertension treatment, not least as all clinical trials to date have shown the procedure to be safe. There are several factors driving this enthusiasm:

- **Targeting the renal sympathetic nerves has already proven to be effective in treating hypertension.** Prior to the development of modern antihypertensive medication, the treatment for life-threatening hypertension was renal sympathectomy, which is the surgical removal of sympathetic nerve fibers abutting the renal arteries. Renal sympathectomy significantly reduced blood pressure. However, the morbidity and mortality associated with this invasive surgery, combined with the advent of new drug classes, led to the abandonment of renal sympathectomy as a treatment for hypertension.<sup>1</sup>
- **Renal denervation makes physiological sense.** The kidneys play a critical role in the regulation of blood pressure. When blood pressure becomes elevated, the kidneys increase the amount of salt and water that is excreted from the body and inhibit the release of the enzyme renin, which aid in normalizing blood pressure. The mechanisms for this process stem from the sympathetic nervous system (SNS), which transmits “commands” from the brain through efferent nerves and conveys information from organs and muscles to the brain through afferent nerves. Both types of nerves are located near the outer wall of the renal artery.<sup>2</sup>

Hyperactivity of efferent renal nerves results in retention of sodium, release of renin, and constriction of renal blood flow, all of which lead to hypertension. Hyperactivity of afferent renal nerve signals leads to elevated sympathetic outflow to other regions of the body and increase peripheral vascular resistance, i.e., resistance to blood flow. Thus, by strategically applying electrical energy to the appropriate areas of the renal artery, activity of the efferent and afferent nerve fibers can be suppressed and blood pressure can be normalized.<sup>5,3</sup>

- **Pharmacotherapy does not adequately treat a large number of hypertensive patients.** The World Health Organization (WHO) projects more than 1 billion people worldwide have high blood pressure.<sup>4</sup> Despite lifestyle modification and use of multiple antihypertensive medications, roughly 50% of patients do not meet blood pressure goals. Uncontrolled hypertension is associated with severe consequences, including heart attack, stroke, and heart failure, among others.<sup>5</sup> Given these dire adverse events, it’s not surprising that the economic burden of hypertension is high at \$150 billion in the United States alone.<sup>6</sup> With the aging population and obesity epidemic, it’s expected that the US economic burden will more than double, exceeding \$240 billion, in 2030.<sup>8</sup> Effective treatments are needed to forestall enormous healthcare expenditures related to uncontrolled hypertension.

## Insights from SYMPLICITY

Both the SYMPLICITY HTN-1 and HTN-2 studies demonstrated sustained reduction in blood pressure after renal denervation in patients taking three or more antihypertensive medications.<sup>7,8</sup> Surprisingly, in the randomized SYMPLICITY HTN-3 trial, patients in the renal denervation arm did not have significantly greater reduction in blood pressure compared to the control group. Both cohorts did show significant blood pressure improvement from baseline,<sup>9</sup> leading some to conclude that renal denervation was no better than a sham procedure in lowering blood pressure. There are several variables that may have affected the HTN-3 results:

- **Patient selection.** Unlike the early SIMPLICITY trials, HTN-3 enrolled many African-Americans, who comprised over 26% of the study cohort. African-Americans were more likely to be prescribed a vasodilator than non-African Americans in the trial. Pertaining to the surprisingly good blood pressure reduction in the sham treatment group, African-Americans randomized to control and taking a vasodilator had a substantial improvement in blood pressure whereas other African-Americans assigned to control, but not taking a vasodilator, did not. The reasons for this differential are unclear and require further study.<sup>10</sup> Separately, it is hypothesized that patients resistant to hypertensive medication may also be resistant to other treatments, such as renal denervation. Thus, since HTN-3 results, there has been a redefining of the target patient population to those with uncontrolled hypertension from those with resistant hypertension.
- **Medication regimens.** With 38% of the renal denervation arm and 40% of the control group receiving changes to medical therapy over the course of HTN-3, it's clear that antihypertensive medication wasn't optimized at the outset of the study. Nearly 70% of the medical changes were deemed medically necessary; many adjustments were related to increasing the dosage to the maximally tolerated level. These changes to medical therapy confound the assessment of renal denervation's effect on lowering blood pressure. Of note, there were more medication changes in the control than the treatment group. In addition, patients in the control group were apt to have their medication increased. Comparatively, patients in the renal denervation arm were likely to have their medication *lowered*.<sup>12</sup> These differences in medication changes could be a factor in the treatment group not demonstrating a significant reduction in blood pressure compared to the control arm.
- **Medication adherence.** Investigators in HTN-3 could not confirm patients' adherence to medication regimens, which may have resulted in better-than-expected blood pressure reduction in the control group. It's not uncommon for patients involved in well-controlled clinical trials with frequent follow-up visits to have better adherence to medication regimens than is typical in every day life.<sup>11</sup> Outside of the clinical trial setting, it's been shown that more than half of patients do not comply with antihypertensive treatment regimens.<sup>11</sup> While the effect of medication adherence on HTN-3 results is unknown, it's clear that future renal denervation trial protocols should have a mechanism for confirmation of adherence.
- **Ablation technique.** Ablation technique could have lowered the efficacy shown in the renal denervation arm. A post-hoc analysis showed that less than 25% of patients received the complete ablation pattern, as specified in the HTN-3 protocol. Patients who received the ablation pattern specified in the protocol had an average reduction of 24.3 mmHg in systolic blood pressure compared to a 14.2 mmHg reduction in patients who did not have complete ablations.<sup>12</sup> Further, recent anatomical studies have shown that the number of nerves increases along the renal artery, with the lowest number at the proximal end and the highest number at distal end.<sup>12</sup> This is an important finding for ablation target sites and technique. If sufficient ablation was not performed in the middle and distal parts of the renal artery in HTN-3, it is reasonable to conclude that the treatment group did not achieve the maximum blood pressure reduction possible.
- **Ablation catheter design.** The investigated device was a single electrode catheter, which was difficult to manipulate within the artery and may have been a factor in the failure to perform the complete ablation pattern in the majority of patients.<sup>14</sup> In addition, the catheter used in the SYMPLICITY trials did not give operators feedback on whether ablation (denervation) had been achieved. As a result, the degree of blood pressure reduction in HTN-3's treatment group may have been muted.

## Existing landscape

Several second-generation renal denervation catheters are in various stages of development and clinical trials. The majority of these second-generation devices use multiple electrodes and unipolar radiofrequency to ablate tissue in the renal arteries.<sup>3</sup> The use of multi-electrode catheters is expected to increase efficacy and decrease procedure time.

*Will second-generation catheters make renal denervation "mainstream"?*

Most stakeholders are optimistic that renal denervation will ultimately become an accepted treatment for uncontrolled hypertension. However, it's unlikely that the second-generation catheters currently being studied will have the multiple positive characteristics that are needed to drive widespread adoption. Looking at other break-through medical devices areas such as transcatheter aortic valve implantation/replacement or left ventricular assist devices, it has been the third generation of device iterations that has initiated broader acceptance of these treatments. Third-generation devices generally incorporate designs that allow for greater efficacy, safety, and patient tolerability for the procedure, as well as improved ease of use and reduced procedure times.

### Third-generation catheters for a turnkey procedure

It's likely that this medical device "cycle" will hold true in the renal denervation market. Third-generation renal denervation catheters are expected to enable a turnkey ablation procedure. Renal Dynamics' ReDy Renal Denervation System is one such third-generation product in development. The ReDy Renal Denervation System incorporates sensors and algorithms in a low-profile, multi-electrode catheter to create complete lesion formation from a single position in the renal artery. Predictable lesion formation can be achieved in 60 seconds or less at each denervation site in preclinical studies. With nine electrodes, the ReDy catheter can perform unipolar and bipolar ablation and uses low power RF energy, which may lead to less pain, damage to collateral tissues, and spasms when applied to humans.<sup>13</sup>

The door for renal denervation for uncontrolled hypertension remains open, with learnings from the SYMPPLICITY trials already being effected in new catheter designs and trial protocols. Assuming second-generation systems demonstrate efficacy compared to control groups, it's the third-generation of renal denervation catheters that are likely to provide a turnkey procedure that can be broadly adopted to treat the millions of patients with uncontrolled hypertension.

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### About the author

Shawn Moaddeb is an entrepreneur with over 25 years' experience in the medical device industry. Former VP of RF Technology at Vessix Vascular, Shawn is a named inventor on over 100 issued and pending patents in the areas of RF catheter-based renal denervation, percutaneous mitral valve catheter-based therapy, electrophysiology and cardiac ablation systems, medical laser systems, GI, and implantable pacemaker and defibrillator devices. Mr. Moaddeb is Chief Executive Officer at Renal Dynamics.

