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Renal Denervation: A case for foundational understanding of macro-level disease dynamics

Summary

Following the publication of the initial Symplicity studies several years ago, the medtech community met the emergence of renal denervation for treatment of drug resistant hypertension with excitement and optimism. Those initial studies demonstrated significant reductions in blood pressure among those taking greater than three antihypertensive medications. However, the third-phase trial results showed no significant difference in blood pressure reduction between the treatment and sham arms. Why? What changed from trial to trial? A lack of understanding about population level disease dynamics likely was a major factor. This white paper shares insight on the critical importance of population level disease dynamics, and how they inform patient selection and clinical trial design, define market opportunity and ultimately help determine an emerging technology's full market potential.

Researchers exhaust brain power, time, energy and budget to invent and vet potentially effective new drugs and treatments. As such, it's unfortunate – and costly – when preventable, knowable variables hinder progress. Case in point, the Symplicity HTN-3 trial. These mixed results recently caused much debate and scrutiny in the medical technology community about how best to conduct clinical trials.

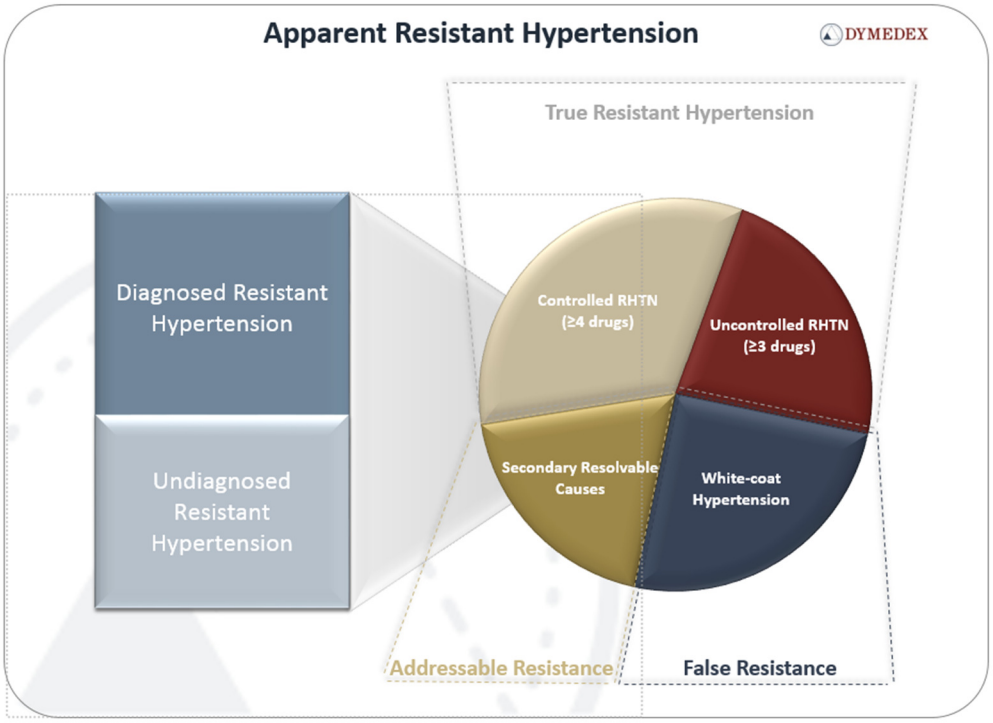
Following the publication of the initial Symplicity studies several years ago, the medtech community met the emergence of renal denervation for treatment of drug resistant hypertension with excitement and optimism. Those initial studies demonstrated significant reductions in blood pressure among those taking more than three antihypertensive medications. Symplicity HTN-3 then targeted a subset of particularly high-risk hypertension patients, specifically those resistant to traditional antihypertension drug classes and who might benefit from specialized care. But the trial results, published in 2014, showed no significant difference in blood pressure reduction between the treatment and sham arms.

Symplicity HTN-3 was the first blinded, randomized, controlled trial designed to evaluate the safety and effectiveness of renal denervation with the investigational system in patients with treatment-resistant hypertension and systolic blood pressure higher than 160 mmHg in the United States. While Symplicity HTN-3 met its primary ***safety*** endpoint, it failed to achieve its primary ***efficacy*** endpoint.

Published commentaries and editorials critique several aspects of the clinical trial design, ranging from inadequate operator experience to inappropriate patient selection. While multiple factors certainly contributed to the conflicting results, a dominant factor likely is appropriate patient selection, given the complex nature of the resistant hypertension population.

1. A Controlled Trial of Renal Denervation for Resistant Hypertension

Accurately identifying and selecting patients for clinical trials



Differentiating between those who have true drug resistant hypertension and those who simply *appear* resistant is critical to trial results. Resistant hypertension currently is defined as a lack of response to antihypertensive medications, and is diagnostically ambiguous. While this diagnosis highlights a group of hypertensive patients with elevated risk for cardiovascular comorbidity and mortality, it also includes several heterogeneous subgroups that do not truly have resistance to traditional antihypertensive medications despite meeting the current classification criteria. This "pseudo resistant" subgroup includes individuals with white-coat hypersensitivity, which elevates in-office blood pressure measurement, as well as distinct secondary causes, which have potentially resolvable etiologies. This subgroup also includes patients who fail to comply with antihypertensive medication regimes, which causes the appearance of resistance, and patients with incorrectly measured blood pressure.

As a result, differentiating between those who have true drug resistant hypertension and those who only *appear* resistant is challenging. Further, among the three major renal denervation trials, the exclusion of patients with white coat hypertension was not uniformly performed, the elimination of patients with resolvable secondary causes was not consistently outlined, and robust screening for medication compliance was not included in the selection criteria or controlled for during the study duration of any of these trials. Consequently, variability in patient selection and enrollment criteria have likely led to non-uniform study populations with different proportions of true resistant hypertension relative to pseudo resistant hypertension.

Future trial design needs for emerging technologies

In order for the true utility of renal denervation or any potential neuromodulation therapy to be assessed for the treatment of resistant hypertension, future trials need to outline more stringent enrollment criteria to ensure appropriate and consistent patient selection. Trials should include only those patients with true resistance to traditional antihypertensive medications and a response profile that showcases the effects of the technology.

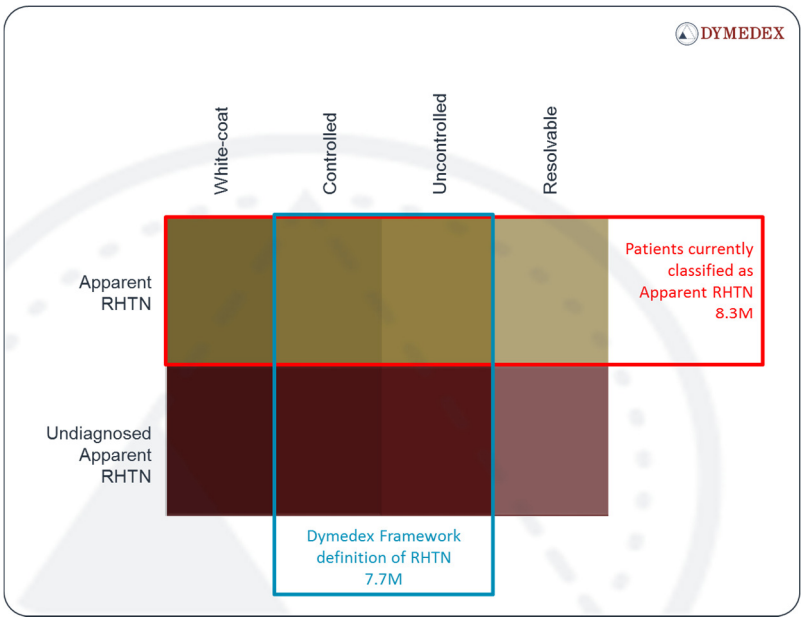
Based on the results of the Symplicity trial phases to date, it is too early to disregard renal denervation as a potential treatment for drug resistant hypertension, especially given that a demonstrable and quantifiable benefit likely exists for appropriately and stringently defined patient subsegments.

2. Dymedex Disease Dynamics Report
3. Doumas M, Douma S. Renal sympathetic denervation: the jury is still out. Lancet 2010;376:1878-1880.

However, further work will be required to delineate what age ranges, comorbidities, or other patient factors characterize the spectrum of response for such emerging therapies. Knowing the number of patient segments with white coat hypertension or resolvable secondary causes, the rates across different ethnicities, the presence or overlap between major comorbidities and the status of diagnosis or blood pressure control at a population-wide level is critical for informing the clinical trial design, increasing the probability of success, and helping ensure the validity and efficacy of findings. It also will help inform which patient subgroups receive the greatest benefit from the treatment.

Appropriate selection and segmentation of a patient population for any technology begins with a foundational understanding of the macro-level dynamics of a given disease. Furthermore, beyond patient care, a better understanding of the population level disease dynamics will help establish the real market opportunity size, and guide strategies and investments for market development.

Currently, approximately 8.3 million patients meet the diagnostic criteria for resistant hypertension, but only a fraction of these patients are *truly* resistant to antihypertensive medications and are candidates for alternative therapies, according to the Dymedex report "Hypertension and Resistant Hypertension: Understanding the complex landscape and epidemiology of the disease". In addition, a substantial number of patients with treated hypertension is outside the diagnostic criteria for resistant hypertension and is under-titrated on one-to-two drugs.



To learn more about the distinct and overlapping subsegments and characteristics of hypertension and resistant hypertension, download the Dymedex report, "Hypertension and Resistant Hypertension: Understanding the complex landscape and epidemiology of the disease," which synthesizes the body of clinical and epidemiologic hypertension literature, and provides unique insights into the market opportunity, underlying denominator for emerging therapies targeting true resistant hypertension, as well as perspective on how this is likely to evolve through 2024.

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