FDA Executive Summary

Circulatory System Devices Panel Meeting

December 5, 2018

General Issues Panel

Clinical Evaluation of Anti-Hypertensive Devices

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1   Introduction

This is an Executive Summary for the General Issues Panel Meeting on Clinical Evaluation of Device-Based Hypertension Therapies. This panel is being held for the Committee to discuss and make recommendation on the pre-market clinical trial design, post-approval study (PAS) design, indications and labeling for device-based hypertension treatments. Specifically, the Committee will be asked to make recommendation on the patient population, clinical trial safety and effectiveness endpoints and margins, and factors important to patients and clinicians regarding the potential benefits and risks associated with these technologies.

The Executive Summary provides a discussion of the general history of hypertension treatments, publicly available clinical data on device-based therapies, specific considerations regarding the clinical trial design and endpoints, and current thinking from the Food and Drug Administration (FDA or "the Agency") on this information. The Panel's review and discussion of the information will inform the Agency's recommendations in terms of appropriate clinical trial design, benefit-risk profile, post-approval requirements, and device labeling.

2   Overview of Hypertension

The study, diagnosis and treatment of hypertension (HTN) gained attention as observational studies conducted over the last century have demonstrated associations between high blood pressure and the long-term risks of cardiovascular disease. While the effects of hypertension were initially theorized after review of surgical sympathectomies in the 1930s and 40s, the analysis of the large scale observational NIH Framingham Heart Study launched in 1948 provided additional evidence of the negative impacts of high blood pressure.[1] The resulting analyses from the Framingham study, as well as other large scale observational studies, have continued to demonstrate evidence that high blood pressure maintains a continuous graded association with an increased risk of fatal and nonfatal stroke, ischemic heart disease, heart failure, and noncardiac vascular disease.[2] Specifically, a 2002 meta-analysis demonstrated that a 20 mmHg higher systolic blood pressure and 10 mmHg higher diastolic blood pressure are associated with doubling of the lifetime risk of death from stroke, heart disease, other vascular disease.[3,4] A 2014 observational study analyzed the data from 1.25 million adult patients ≥30 years of age to determine associations of increased clinically-measured blood pressure with 12 acute and chronic cardiovascular diseases and lifetime risks.[5] The authors explain that higher systolic blood pressures and diastolic pressures were associated with an increased risk of

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[1] Dawber TR. The Framingham Study: The Epidemiology of Atherosclerotic Disease. Cambridge, MA: Harvard University Press; 1980.

[2] Carey RM, et al. Prevention and Control of Hypertension: JACC Health Promotion Series. J Am Coll Cardiol. 2018;72(11):1278-93

[3] Lewington S, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.

[4] Whelton PK, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;138(17):e484-e594.

[5] Rapsomaniki E, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet. 2014;383(9932):1899-911.

cardiovascular disease incidence and angina, myocardial infarction, heart failure, stroke, peripheral artery disease, and abdominal aortic aneurysm, each evaluated separately.

Hypertension has a high prevalence in the U.S., in which the National Health and Nutrition Examination Survey (NHANES) collected between 2011-2014 estimated that 31.3% of the population 18 years old or over has hypertension using a cut-off pressure of ≥140/90 mm.[6] Similarly, the latest NHANES data collected over a two-year period from 2015-2016 also report a high prevalence of 32.1%.[7] However, the new 2017 American College of Cardiology (ACC)/American Heart Association (AHA) hypertension clinical practice guidelines have modified the definition of hypertension to a lower cut-off pressure of ≥130/80 mm, which is expected to increase the prevalence to 45.6% (103.3 million people).[4,8]

2.1 Defining Hypertension

Practice guidelines continue to be developed and revised every few years in order to provide awareness, prevention recommendations, and treatment strategies to control high blood pressure. As discussed above, the new 2017 ACC/AHA practice guidelines have reclassified the definition of high blood pressure as compared to the previous guidelines established in the 2003 JNC7 and 2014 JNC8 reports.[9,10] The new ACC/AHA guidelines continue to stratify blood pressure into four levels on the basis of average systolic and diastolic blood pressures (SBP and DBP) measured in a healthcare setting (office pressures): normal, elevated, and Stage 1 or 2 hypertension as detailed in Table 1 below.[4,9,10]

Table 1: Comparison of Guideline Classification of Blood Pressure in Adults[4,9,10]

AHA/ACC Category	SBP		DBP	JNC 7 / JNC 8 Category	SBP		DBP
Normal	< 120 mmHg	AND	< 80 mmHg	Normal	< 120 mmHg	AND	< 80 mmHg
Elevated	120-129 mmHg	AND	< 80 mmHg	Pre-Hypertension	120-139 mmHg	OR	80-89 mmHg
Hypertension				Hypertension			
Stage 1	130-139 mmHg	OR	80-89 mmHg	Stage 1	140-159 mmHg	OR	90-99 mmHg
Stage 2	≥ 140 mmHg	OR	≥ 90 mmHg	Stage 2	≥ 160 mmHg	OR	≥ 100 mmHg

According to the cited 2011-2014 NHANES survey, while prevalence of hypertension remains high, at least half of the adults with hypertension are considered controlled, in which the systolic blood pressure is less than 140 mmHg and diastolic blood pressure is less than 90 mmHg among those with hypertension.[6] Historically, the prevalence of controlled hypertension measured by the NHANES surveys increased from 31.5% for 1999–2000 to 53.3% for 2009–2010 but has not significantly changed during the more recent period from 2013-2014 or from 2015-2016.[7]

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[6] Yoon SS, et al. Hypertension prevalence and control among adults: United States, 2011–2014. NCHS data brief, no 220. Hyattsville, MD: National Center for Health Statistics. 2015.

[7] Fryar CD, et al. Hypertension prevalence and control among adults: United States, 2015–2016. NCHS data brief, no 289. Hyattsville, MD: National Center for Health Statistics. 2017

[8] Muntner P, et al. Potential US Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. Circulation. 2018;137(2):109-18.

[9] Chobanian AV, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42(6):1206-52.

[10] James PA, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20.

The 2017 ACC/AHA blood pressure guidelines recommend pharmacological antihypertensive treatment based on a combination of high blood pressure and absolute risk of cardiovascular disease (CVD), defined as coronary heart disease (CHD), heart failure (HF), and stroke. Pharmacological treatment is recommended for adults with SBP between 130-139 mmHg or DBP between 80-89 mmHg if they have a history of CVD, diabetes, and chronic kidney disease, or a 10-year predicted CVD risk ≥10% or age ≥65 years. [4] Additionally, pharmacological treatment is recommended for adults with SBP ≥140 mmHg or DBP ≥90 mmHg, even if the patients have no history of CVD, and an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk <10%.[4]

While the new 2017 ACC/AHA guidelines have increased the proportion of adults in the U.S. that are considered hypertensive, the number of patients who are recommended pharmacological antihypertensive treatment is only expected to increase by 1.9% as compared to JNC7 guidelines and 5.1% as compared to JNC8.[8] A comparison of the blood pressure levels in the 2017 ACC/AHA, JNC7, and JNC8 guidelines used to define hypertension, recommend antihypertensive medication, and define the treatment goal is provided in Table 2 below.[8]

Table 2: Comparison of ACC/AHA 2017, JNC7, and JNC8 Blood Pressure Levels Used to Define Hypertension and Treatment Approach[8]

	2017 ACC/AHA	JNC7	JNC8 panel member report
	Guideline – Definition of hypertension		
Systolic blood pressure, mm Hg			
General population	≥ 130	≥ 140	≥ 140
≥60 years of age without diabetes or CKD			≥ 150
Diastolic blood pressure, mm Hg			
General population	≥ 80	≥ 90	≥ 90
	Guideline – Recommended antihypertensive medication		
Systolic blood pressure, mm Hg			
General population	≥ 140	≥ 140	≥ 140
Diabetes or CKD	≥ 130	≥ 130	≥ 140
High cardiovascular disease risk†	≥ 130		
Age ≥ 65 years	≥ 130		
≥60 years of age without diabetes or CKD			≥ 150
Diastolic blood pressure, mm Hg			
General population	≥ 90	≥ 90	≥ 90
Diabetes or CKD	≥ 80	≥ 80	
High cardiovascular disease risk†	≥ 80		
	Guideline – Treatment goal among those taking antihypertensive medication		
Systolic blood pressure, mm Hg			
General population	< 130	< 140	< 140
Age ≥ 65 years	< 130		
Diabetes or CKD		< 130	< 140
≥60 years of age without diabetes or CKD			< 150
Diastolic blood pressure, mm Hg			
General population	< 80	< 90	<90
Diabetes or CKD	< 80	< 80	

No specific blood pressure threshold is provided in the guideline for this population. The other thresholds listed from the guideline should be applied, as appropriate.

The American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) have provided statements explaining that they have not endorsed the new ACC/AHA Guidelines.[11,12] While the ACP acknowledges the emphasis placed on blood pressure measurement technique and lifestyle modifications, they are concerned regarding the expansion of the hypertensive definition, particularly the initiation of pharmacologic therapy in hypertensive and pre-hypertensive patients in a broad population of older adults.[11] The ACP explains that there is a lack of consistent evidence of benefit for treating older adults to achieve the 130 mmHg SBP target, including those with diabetes or kidney disease; the trial findings used to support the recommendations may overestimate the benefits and underestimate the harms of treating the broader primary care population to the lower blood pressure target; there is a lack of evidence from randomized clinical trials (RCTs) to support targeting DBP < 80 mmHg; and that the lower SBP targets should coincide with clinical practice which allows for physician discretion to consider a patient's risk profile, susceptibility to adverse effects, and treatment preferences.[11] The AAFP continues to support the JNC8 guidelines, as they are concerned that the development of the over 100 recommendations in the 2017 ACC/AHA guidelines only used a systematic review of the evidence for four of the key questions.[12] Although the systematic review used by the guidelines suggested a small benefit for lower treatment targets for reducing cardiovascular events, the AAFP and ACP expressed concern that there was no benefit observed in all-cause mortality, cardiovascular disease mortality, myocardial infarction, and renal events.[12] As such, the AAFP and ACP recommend considering treatment to lower targets for some patients in the context of shared decision-making.[12] Specifically, the ACP and AAFP have released 2018 hypertension guidelines focusing on the treatment of hypertension in adults aged 60 years or older, in which the core recommendation for this patient population is initiation of treatment in those with persistent SBP at or above 150 mmHg to achieve a target SBP < 150 mmHg to reduce the risk of mortality, stroke and cardiac events. [13]

The majority of the differences between the guidelines are related to the definition of hypertension and the treatment goals for the population. Antihypertensive pharmacotherapy continues to be an important treatment method. A variety of clinical studies in the 1990s were designed to evaluate the effects of various types of antihypertensive medications on mortality and major cardiovascular morbidity in several populations. In efforts to align these studies, in 1995 a collaboration formed between principal investigators of major trials of antihypertensive medications, called the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC), in which they agreed to prospectively plan to analyze the combined results from individual studies to provide sufficient statistical power to detect differences in the effects of various antihypertensive medications on major cardiovascular outcomes.[14] The resulting series of analyses were presented in a series of publications; the first cycle published in 2000 included

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[11] Wilt TJ, et al. Hypertension Limbo: Balancing Benefits, Harms, and Patient Preferences Before We Lower the Bar on Blood Pressure. Ann Intern Med. 2018;168(5):369-70.
[12] Crawford C. AAFP Decides to Not Endorse AHA/ACC Hypertension Guideline. 2018.
[13] Qaseem A, et al. Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2017;166(6):430-7.
[14] Protocol for prospective collaborative overviews of major randomized trials of blood-pressure-lowering treatments. World Health Organization-International Society of Hypertension Blood Pressure Lowering Treatment Trialists' Collaboration. J Hypertens. 1998;16(2):127-37.

analysis of data from n=74,696 patients in 15 studies, while the second cycle published in 2003 analyzed data from n=162,341 patients in 29 studies.[15,16] Overall, these analyses demonstrated that the relative risks of total major cardiovascular events were reduced by the antihypertensive medication regimens, with no significant differences in events between drug classes, including angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, or diuretics or beta blockers.

More recent analyses by the collaboration have aimed to analyze whether the magnitude of cardiovascular major event risk reduction by blood pressure lowering varies according to baseline blood pressures or baseline cardiovascular risk.[17,18] The most recent 2018 analysis by the collaborative effort has compared the outcomes from blood pressure-lowering treatment strategy based on predicted cardiovascular risk with one based on SBP level.[19] Using data collected from the collaboration from 1995 to 2013, spanning 11 trials consisting of 47,872 participants, the authors noted that the use of the cardiovascular risk approach resulted in more avoidance of cardiovascular events over a 5-year period as compared with the SBP strategy; specifically for participants with SBP between 150 to 170 mmHg or a 5-year CVD risk between 7.5% to 15%. However, the authors continue to support further study of this approach as they acknowledge that the analysis was limited by the short duration of the studies and the specific risk algorithm used.[19]

The ongoing evolution of the clinical definition of hypertension and the guidelines for treatment based on new information can be an important factor when designing clinical studies evaluating hypertension treatments and comparing results across studies. Despite any such changes over time, there is a consistently accepted view that blood pressure above the normal physiological range increases the risk for cardiovascular events.

2.2 Etiology and Current Treatment

Hypertension has a complex and varied etiology. The majority of hypertension cases are termed primary (essential) hypertension and may originate from a combination of genetic, environmental, and social determinants.[2,4] Hypertension has been found to be a complex polygenic disorder as a variety of genes or gene combinations influence the occurrence of high blood pressure.[2] Currently, the collective effect of all blood pressure genetic variants identified through genome-wide association studies accounts for only a small proportion of phenotypic variation, and as such, additional studies are needed to better link genetic expression to the

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[15] Neal B, et al. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet. 2000;356(9246):1955-64.

[16] Turnbull F, et al. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003;362(9395):1527-35.

[17] Czernichow S, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. J Hypertens. 2011;29(1):4-16.

[18] Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014;384(9943):591-8.

[19] Karmali KN, et al. Blood pressure-lowering treatment strategies based on cardiovascular risk versus blood pressure: A meta-analysis of individual participant data. PLoS medicine. 2018;15(3):e1002538-e.

variation of the disease and disease risk.[4] Environmental risk factors compose well-known lifestyle behaviors that promote blood pressure elevation and hypertension, such as an unhealthy diet, weight gain leading to overweight/obesity, poor physical activity, and excessive alcohol consumption.[4] Social determinants include the socioeconomic factors that may affect cardiovascular health, including the circumstances in which people live and the systems used to diagnose, treat, and prevent illness.[20] In the U.S., a strong association exists between social determinants of health and hypertension, especially in minority populations, economically deprived neighborhoods, and in certain geographic areas such as in the Southeast.[2,21,22] Overall, these factors are important considerations towards the study and diagnosis of the hypertension diseases as well as for creating a suitable treatment plan for the patients.

While the majority of cases of hypertension are considered primary, the disease can be attributed to a specific, sometimes remediable cause for approximately 10% of adults with hypertension.[4] There are a variety of causes for secondary hypertension, in which the most common causes include renal parenchymal disease, renovascular disease, primary aldosteronism, obstructive sleep apnea, and drug/alcohol induced disease. However, these causes are linked to specific recommended diagnostic screening tests and may treatable to achieve blood pressure control or normalization of the blood pressure.[4,2]

The most common medication therapies used for hypertension include thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs). Although numerous medication classes exist, these medications are considered "primary agents" and preferentially used as they have demonstrated the ability to reduce clinical events.[4] Secondary agents may also be used in the treatment of patients; however, it remains unclear whether these agents reduce cardiovascular events to an extent similar to that of the primary agents or may have safety or tolerability concerns that preclude their primary use.[4] Clinical determination of a treatment regimen is typically based on the etiology of the patients hypertension, as well as their comorbidities and previous medical history.

For initial treatment of high blood pressure, consideration of strategies includes selection of the class of medications as well as determining whether combination therapy with multiple agents should be employed. Patient specific factors including age, concurrent medications, drug interactions, the overall treatment regimen, out-of-pocket costs, and comorbidities may also be considered as part of the selection of the treatment strategy.[4] Additional factors that may affect a patient's treatment choice may also include the negative impact of their medication regimen due to side effects or dislike of pills that may lead to poor adherence, which is defined by the 2017 ACC/AHA guidelines as not following recommended medical or health advice, including failure to "persist" with medications.[4] Therefore, a device-based solution may provide added benefit in these patients.

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[20] Havranek EP, et al. Social Determinants of Risk and Outcomes for Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2015;132(9):873-98.

[21] Rodriguez F, et al. Hypertension in minority populations: new guidelines and emerging concepts. Adv Chronic Kidney Dis. 2015;22(2):145-53.

[22] Kershaw KN, et al. Geographic variation in hypertension prevalence among blacks and whites: the multi-ethnic study of atherosclerosis. Am J Hypertens. 2010;23(1):46-53.

3   Device Targets to Treat Hypertension

Based on the complex physiology associated with controlling blood pressure, current clinical studies for devices have focused on a variety of treatment targets—reducing or attenuating sympathetic activity (e.g., renal nerves, carotid body), stimulating parasympathetic activity (e.g. carotid baroreceptor), or modifying hemodynamics, as shown in Figure 1.[23,24] Each paradigm or device design has its own specific advantages and risks. These will be discussed further in this section and below under clinical trial design. A comparative summary of the emerging device technologies is also provided after a description of these technologies in Table 3 below.[23]

Figure 1: Graphical Illustration of Sympathetic Contribution to Hypertension[24]

Nature Reviews | Cardiology
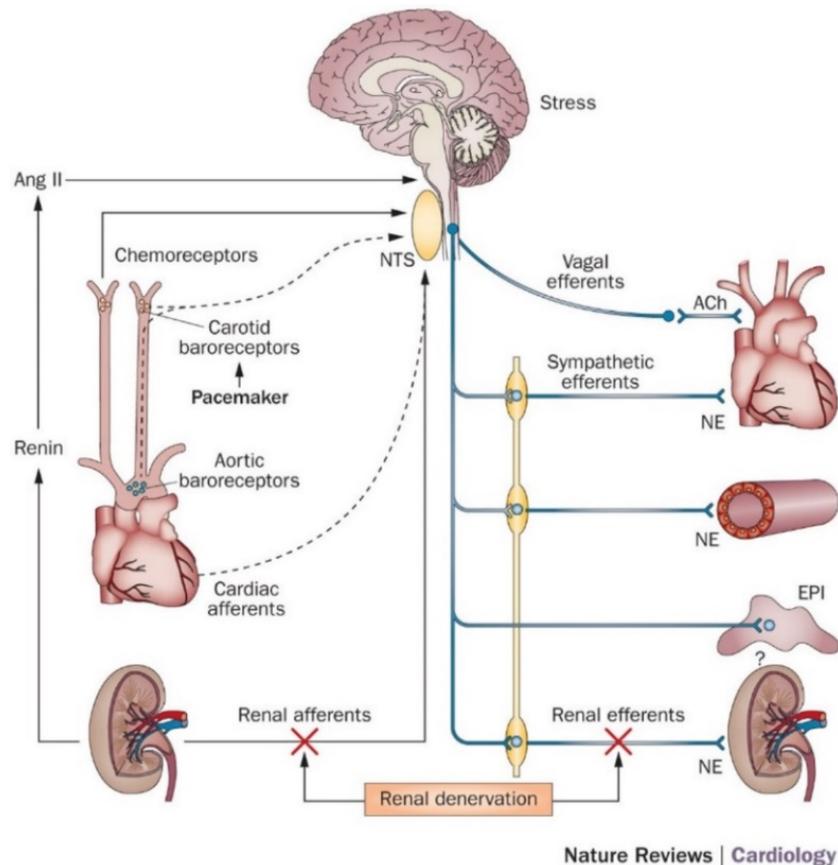
3.1 Surgical Sympathectomy and Renal Denervation

3.1.1   Lessons from Surgical Sympathectomy

Sympathetic afferent fibers originate in the kidneys and travel to the midbrain, regulating sympathetic outflow and stimulating the sympathetic nervous system (SNS) in response to renal injury. Efferent sympathetic renal nerves arise in the brain, travel down the spinal cord and reach the kidneys by coursing through the sympathetic ganglia. From there the efferent fibers reach the

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[23] Ng FL, et al. Device-based Therapy for Hypertension. Curr Hypertens Rep. 2016;18(8):61.

[24] Victor RG. Carotid baroreflex activation therapy for resistant hypertension. Nat Rev Cardiol. 2015;12(8):451-63.

kidneys via nerves that run on the adventitia of the renal arteries and in the adjacent peri-adventitial tissues of the retroperitoneum. Stimulation of the renal efferent fibers produce renal vasoconstriction, directing releasing norepinephrine, which causes the renal epithelial cells to retain sodium and water. In addition, adrenergic mediated hemodynamic changes also elevate the blood pressure. Stimulation of the renal efferent sympathetic fibers acts conversely, to reduce the blood pressure.

Mayo clinic neurosurgeon A.W. Adson was the first to treat malignant hypertension by bilateral renal surgical denervation in 1925. The therapeutic effect for his first patient was minimal, but the case demonstrated that renal function was not adversely impacted. As experience with surgical sympathectomy was acquired, the pioneering surgeons of that era realized that renal denervation (RDN) done via renal decapsulation or resection of tissue along the renal arteries alone had a relatively modest and short-lived effect. More radical forms of surgical sympathectomy were developed. In the early 1930's neurosurgeon Max Peet at the University of Michigan described and popularized the procedure of thoraco-lumbar or supradiaphragmatic splanchnicectomy.[25] The dorsal sympathetic ganglion from T9 to T12 were removed via synchronous, extrapleural exposures through the bed of the 11th ribs. If the anatomy was favorable, sometimes surgeons could resect the upper two lumbar ganglia and the T8 ganglia as well.

For the several decades, bilateral thoracolumbar sympathectomy became the treatment of choice for thousands of patients with severe hypertension who failed to respond to a salt restricted diet and the very limited pharmacologic options of the times. Well-documented large case series from the hypertension centers of excellence of that day resulted in number of key observations and lessons learned. Hoobler *et al*. reported on the 10 to 18-month follow-up of 338 hypertensive subjects treated with bilateral splanchnicectomy and 79 similar subjects who declined intervention.[26] The operative mortality was 3.4%. Roughly a third of the surgical patients had a decrease in DBP of over 20 mmHg, a third had DBP reductions of 0 to 20 mm, and BP increased in the remaining third of subjects. The results indicated that while 67% of treated subjects had reduction in DBP of 20mm or more at 9 days post-op, that rate fell to 32% at one year.

In 1953, Smithwick and Thompson reported on the outcomes of 1266 cases treated with a more extensive two stage transdiaphragmatic thoracolumbar splanchnicectomy (T8/9 through L1/2) who had between 5 and 14 years of follow-up.[27] Overall, operative mortality was 2.5%. The surgical group was compared to a simultaneous group of 467 subjects who declined the operation. Patients were analyzed in four subgroups, depending on the severity of their hypertension. Overall, the mortality at 5 years was 54% for those treated medically and 19% in the sympathectomy group. Mortality was significantly less in all four subgroups for the patients who opted for surgery with Chi-squared analysis, though the most advanced group had the least benefit. Approximately 45% of living operated patients had a significant lowering of basal blood

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[25] Isberg EM, Peet MM. The role of surgical treatment in the management of hypertension. South Med J. 1946;39(12):966-70.

[26] Hoobler SW, et al. The effects of splanchnicectomy on the blood pressure in hypertension; a controlled study. Circulation. 1951;4(2):173-83.

[27]Smithwick RH, et al. Splanchnicectomy for essential hypertension; results in 1,266 cases. J Am Med Assoc. 1953;152(16):1501-4.

pressure in years 1 through 5, while the other 55% had no change or an increase in blood pressure.

The lessons learned and the uncertainties arising from the historical experience with surgical sympathectomy for hypertension are important to remember as contemporary efforts focus on accomplishing renal denervation in a variety of less invasive ways. While these early studies suggest potential benefits in a complex patient population for both decreased blood pressure and improved mortality, the results also suggest that it is challenging to predict in advance which patients may benefit from renal sympathectomy. Variations in the extent of denervation achieved did appear to affect the procedural outcome. Patients with impaired renal function, macrovascular occlusive disease, and significant heart failure did not benefit from renal denervation. Additionally, the durability of the benefit remains unclear as many subjects experienced only a temporary drop in blood pressure.

3.1.2 Renal Denervation

Renal denervation has emerged as an interventional approach to applying the lessons learned from the historical surgical sympathectomy experience. The procedure is designed to attenuate the kidney's sympathetic activity by ablating the peri-arterial adventitial afferent and efferent renal nerves outside the renal artery using various methods such as radiofrequency or ultrasonic energy, or chemical neurotoxins (e.g., ethanol, guanethidine).[23] The currently published technologies utilize intraarterial catheters to deliver the energy through the arterial wall, catheters to deliver neurotoxins in the peri-vascular space containing the nerves, transurethral catheters designed to ablate the renal pelvis, or external devices focusing the energy around the renal artery. By reducing sympathetic nerve signaling, these technologies aim to reduce renin secretion, as well as initiate renal vasodilatation and sodium excretion.[23] Considering the location of the target nerves, these technologies pose the risk of potential damage to the kidney, tissues surrounding the renal artery, or the renal artery itself.

The initial proof of concept study for renal denervation was an open-label clinical study conducted in Australia and Europe, SYMPLICITY HTN-1, in which percutaneous radio-frequency ablation applied by a unipolar intravascular catheter was delivered to 50 subjects with hypertension, with a baseline mean office blood pressure (OBP) of 177/101 mmHg and who were receiving a mean 4.7 antihypertensive medications. The results demonstrated a mean reduction in OBP of 22/10 mmHg.[28] The subsequent SYMPLICITY HTN-2 study was a larger randomized open-label study, in which renal denervation was compared against the control group who maintained their antihypertensive medication regimen. The 6-month results demonstrated that the 52 subjects who received the renal denervation procedure achieved improvements in OBP by 33/11 mmHg as compared to the 54 control subjects.[29] The effects of the denervation appeared to be durable, in which a fall of 33/14 mmHg in OBP was observed at 36 months post-procedure.[30]

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[28] Krum H, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;373(9671):1275-81.

[29] Esler MD, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 2010;376(9756):1903-9.

[30] Esler MD, et al. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. Eur Heart J. 2014;35(26):1752-9

As reports of the success of the renal denervation procedure emerged, additional catheter designs were developed and studied, demonstrating similar results from initial open-label studies. The 12-month results from the first-in-man open-label EnligHTN I study using a multielectrode radiofrequency catheter demonstrated a 12-month reduction in OBP of 27/11 mmHg for 46 subjects with a mean baseline OBP of 176/96 mmHg and taking a mean 4.7 antihypertensive medications.[31] The 6-months results from the single-arm REDUCE-HTN study using a percutaneous bipolar radiofrequency balloon catheter demonstrated a reduction in OBP of 24.7/10.3 mmHg.[32] Devices that employ ultrasound as the energy source for the ablation were also developed and evaluated; the 12-month results from the singe-arm ACHIEVE study demonstrated that a percutaneous balloon catheter delivering targeted circumferential ultrasound energy achieved an office SBP reduction of 15 mmHg for 96 subjects with a baseline office SBP of 176 mmHg.[33] Another modality considered for achieving denervation is the periadventitial infusion of ethanol; a first-in-man study conducted in 18 subjects demonstrated a reduction of 24 mmHg for office SBP at 6 months.[34] In addition to the intravascular approaches, externally focused ultrasound delivered to the renal sympathetic nerves was studied in 69 subjects over 3 consecutive single-arm studies, in which OBP decreased by 23.8/10.3 mmHg after 12 months follow-up.[35]

While these initial reports provided promising results renal denervation technologies, these studies were all open-label and criticized in that the invasive nature of the therapy may have contributed to a substantial placebo effect and treatment biases.[23] In response, the SYMPLICITY HTN-3 study was designed to be randomized and sham controlled to minimize potential biases and confounders from the open-label studies. The results reported in 2014 demonstrated that at 6 months the reduction in OBP of 14/7mmHg in the treatment group was comparable to the 12/5 mmHg reduction found in the sham control group which only received renal angiography, and the comparison between 24-hour ambulatory blood pressure measurements (ABPM) also found a lack of a statistically-significant difference between groups.[36,37] Additional analyses from the study identified potential confounders that may have contributed to the negative study results,

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[31] Papademetriou V, et al. Catheter-based renal denervation for resistant hypertension: 12-month results of the EnligHTN I first-in-human study using a multielectrode ablation system. Hypertension. 2014;64(3):565-72.

[32] Sievert H, et al. Renal denervation with a percutaneous bipolar radiofrequency balloon catheter in patients with resistant hypertension: 6-month results from the REDUCE-HTN clinical study. EuroIntervention. 2015;10(10):1213-20.

[33] Daemen J, et al. CRT-200.22 Safety And Efficacy Of Renal Sympathetic Denervation Using Circumferential Ultrasound: 12-month Results of the ACHIEVE Study. JACC: Cardiovascular Interventions. 2018;11(4 Supplement):S33.

[34] Fischell TA, et al. Transcatheter Alcohol-Mediated Perivascular Renal Denervation With the Peregrine System: First-in-Human Experience. JACC Cardiovasc Interv. 2016;9(6):589-98.

[35] Neuzil P, et al. Externally Delivered Focused Ultrasound for Renal Denervation. JACC Cardiovasc Interv. 2016;9(12):1292-9

[36] Bhatt DL, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393-401.

[37] Bakris GL, et al. 12-month blood pressure results of catheter-based renal artery denervation for resistant hypertension: the SYMPLICITY HTN-3 trial. J Am Coll Cardiol. 2015;65(13):1314-21.

including 1) medication changes by study participants in both arms and 2) delivery of bilateral complete circumferential denervation in only a small (5%) proportion of study subjects.[23,38]

As a result of this study, additional research was conducted to understand the anatomic distribution of sympathetic perirenal nerves to further refine renal denervation procedures and therapies. These postmortem exams found that the distance from artery lumen to renal nerves was shortest in the distal renal artery as compared with proximal and middle regions of the artery, implying that it may be more effective to ablate nerves in the distal renal artery rather than closer to the renal ostium, as shown in Figure 2.[39,40]

Figure 2: Graphical Illustration of Renal Artery and Circumferential Peri-Arterial Nerve Location[39]
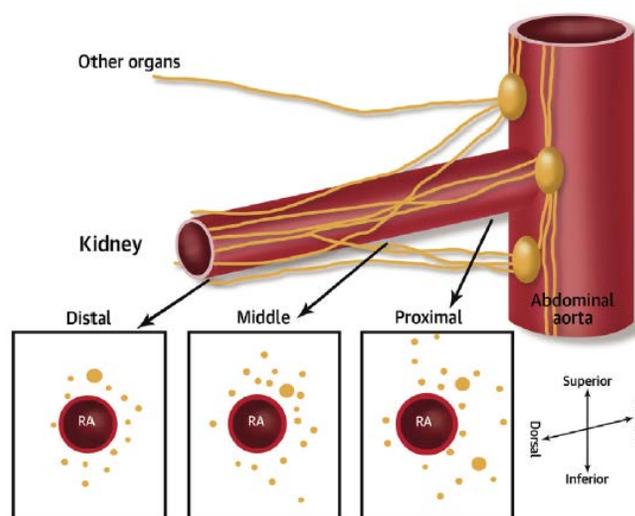
In parallel, the American Society of Hypertension (ASH) convened a multi-stakeholder forum of representatives from academia, cardiovascular societies, industry, and regulatory agencies to identify optimal clinical trial design strategies to evaluate the safety and effectiveness of renal denervation therapies. [40] The discussion included design of proof-of-concept trials in hypertension subjects not confounded by medication therapy followed by pivotal trials in severe and/or drug-resistant hypertensive subjects. Following these recommendations and the lessons learned from the initial renal denervation studies, subsequent proof–of–concept clinical trials for multiple devices have emerged in efforts to determine a signal of effectiveness and safety prior towards initiation of a larger complex pivotal study. In order to quickly and efficiently and adequately evaluate the safety and effectiveness of the technologies, the forum recommended clinical trials designed as small, prospective, double–blind, randomized, sham–controlled studies of the device incorporating a run-in period, medication washout, and evaluations of medication

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[38] Kandzari DE, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. Eur Heart J. 2015;36(4):219-27.

[39] Sakakura K, et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. J Am Coll Cardiol. 2014;64(7):635-43.

[40] White WB, et al. Renal denervation therapy for hypertension: pathways for moving development forward. J Am Soc Hypertens. 2015;9(5):341-50.

therapy compliance, as discussed further below.[40] Following these recommendations and the lessons learned from the initial renal denervation studies, subsequent proof–of–concept clinical trials for multiple devices have emerged in efforts to determine a signal of effectiveness and safety prior towards initiation of a larger complex pivotal study. The trial populations included subjects with primary hypertension with stable office SBP between either lower limits of 150 or 160 mmHg and an upper limit of 180 mmHg in the untreated state. Subjects were either newly diagnosed and untreated or could tolerate the washout of antihypertensive medications as part of participation in the study.

Due to the confounders noted in previous studies related to biases and potential placebo effects, it is important to study these devices in clinical trial subjects in the presence and absence of medication. The "OFF" medication studies isolate the effects of the device by reducing confounders related to medication use (e.g., regimen variability, poor patient medication adherence/compliance), and the "ON" medication studies ascertain how the device may function in a real-world setting with patients on medication. Data from both study designs are valuable for regulatory and clinical decision-making. As two examples, the SPYRAL HTN-OFF MED and RADIANCE-HTN SOLO feasibility studies evaluating Medtronic's Symplicity Spyral RDN catheter and ReCor Medical's Paradise RDN catheter, respectively, have recently published their initial results from the early endpoints set at 2 or 3 months to detect an early effectiveness signal following medication washout.[41,42]

The SPYRAL HTN-OFF MED was a multicenter, international, single-blind, 1:1 randomized, sham-controlled study involving 21 centers in the U.S., Europe, Japan, and Australia. The trial enrolled subjects aged 20-80 years, who were drug naïve or able to discontinue existing pharmacologic therapy, with mild to moderate hypertension (defined as OBP ≥150/90 mmHg and <180 mmHg, and a mean 24-h ambulatory SBP ≥140 mmHg and <170 mmHg) after 3-4 weeks of medication washout.[41] Subjects were excluded if they had an estimated glomerular filtration rate (eGFR) < 45 mL/min per 1.73 m^2, a history of cardiovascular or cerebrovascular events, ineligible renal anatomies, presence of stenosis >50% in the main renal artery, presence of a renal artery stent for <3 months or treatment within 5 mm of a stent in place >3 months, or prior renal denervation. [43] The primary effectiveness endpoint of a change in 24-hour ABPM at 3 months was compared between the treatment and sham control groups. The overall study design is provided in Figure 3 below.

Similarly, the RADIANCE-HTN SOLO was a multicenter, international, single-blind, randomized, sham-controlled trial conducted at centers in the U.S. and Europe. The trial enrolled subjects aged 18–75 years, with hypertension either uncontrolled on 0-2 antihypertensive medications (defined as OBP ≥140/90 mmHg and <180/110 mmHg) or controlled on 1-2

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[41] Townsend RR, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet. 2017;390(10108):2160-70.

[42] Azizi M, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet. 2018;391(10137):2335-45.

[43] Kandzari DE, 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(1):82-91.

antihypertensive medications (defined as OBP <140/90 mmHg). Subjects were enrolled if their daytime ABPM > 135/85 mmHg and < 170/105 mmHg after a 4-week medication washout. Subjects were excluded if they had an eGFR < 40 mL/min per 1.73 m^2, a history of cardiovascular or cerebrovascular events, ineligible renal anatomies, presence of renal artery stenosis ≥ 30%, preexisting renal stent or prior renal artery angioplasty, or prior renal denervation.[44] The overall study design is provided in Figure 4 below.

The results from the SPYRAL HTN-OFF Med study showed that blood pressure decreased significantly from baseline to 3 months in the renal denervation group with no significant changes in the sham-control group.[41] The difference in these results as compared to the SYMPLICITY HTN-3 has been attributed to catheter redesign, distal treatment target, and a well-controlled clinical protocol that includes a longer run-in period to generate a more accurate baseline and reduce regression to the mean.[41] For the RADIANCE SOLO study, the results for the primary effectiveness endpoint of change in daytime ambulatory SBP at 2 months compared between the treatment and sham control groups showed that the reduction in daytime ambulatory SBP was significantly greater with renal denervation than with the sham procedure.[42] Key results from these published studies are shown in Figures 5 and 6 below.

Two examples of "ON" medication trials are the SPYRAL HTN-ON MED and RADIANCE HTN-TRIO clinical studies, in which the effects of the renal denervation procedure are being studied in the presence of antihypertensive medications.[43,44] These subjects continue their prescribed medication regimen and do not undergo medication washout. The SPYRAL HTN-ON MED is an international, randomized, single-blind, sham-control, proof-of-concept trial in centers in U.S., Germany, Japan, UK, Australia, Austria, and Greece. An overview can be visualized in Figure 7. The trial enrolled subjects aged 20-80 years, who were on 1-3 antihypertensive medications at stable doses for 6 weeks and with mild to moderate hypertension (defined as OBP ≥150/90 mmHg and <180 mmHg, and a mean 24-h ambulatory SBP ≥140 mmHg and <170 mmHg). Subjects were excluded with the same criteria previously discussed as part of the description of the SPYRAL HTN-OFF MED provided above. The primary effectiveness endpoint of blood pressure reduction from baseline based on ABPM was assessed at 6 months, as compared between treatment groups. The results demonstrated that the reduction in blood pressure was significantly greater at 6 months in the renal denervation group than the sham-control group for OBPM, as well as 24-hour ABPM.[45] The RADIANCE HTN-TRIO is also a multicenter, blinded, randomized, sham-controlled trial that is currently ongoing (clinicaltrials.gov: NCT02649426). The trial is enrolling subjects aged 18–75 years on a stable regimen of at least 3 antihypertensive medications of difference classes including a diuretic for at least 4 weeks, and with an OBP ≥140/90 mmHg as well as ABPM > 135/85 mmHg and < 170/105 mmHg. Subjects are excluded using the same criteria previously discussed as part of the description of the RADIANCE HTN-SOLO study above.[44]

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[44] Mauri L, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs. Am Heart J. 2018;195:115-29.
[45] Kandzari DE, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet. 2018;391(10137):2346-55.

Figure 3: Overview of the SPYRAL HTN OFF-MED Design[43]
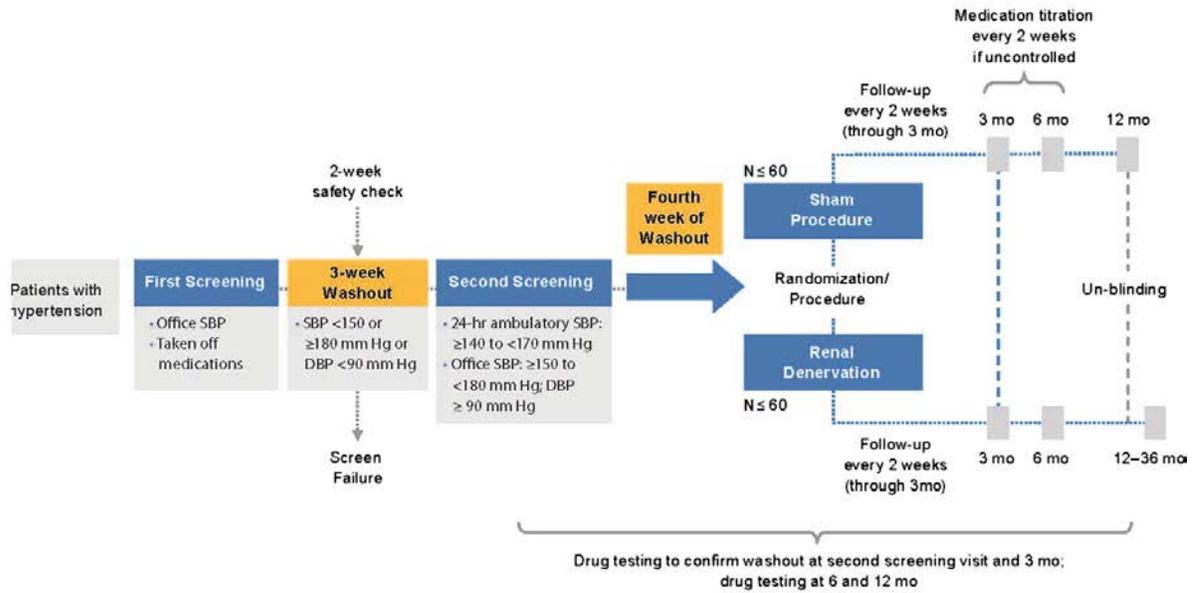

Figure 4: Overview of the RADIANCE HTN SOLO and TRIO Designs[44]
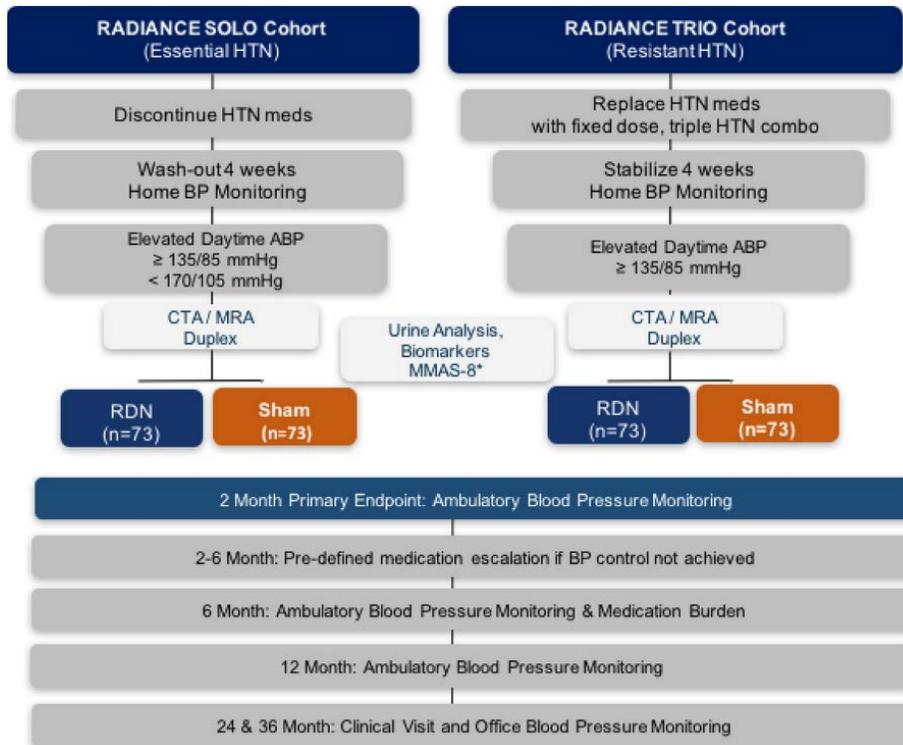
Figure 5: SPYRAL HTN-OFF MED Office and Ambulatory BP Results at 3 Months[41]

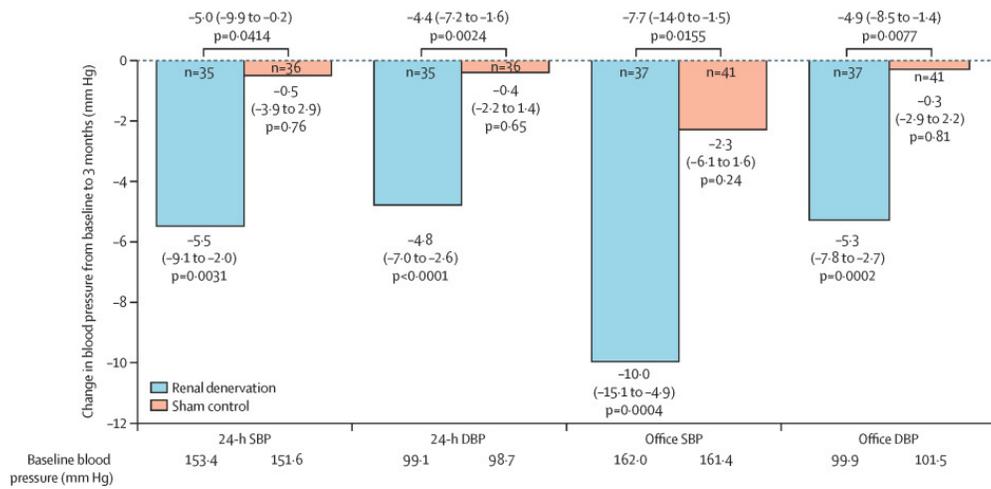

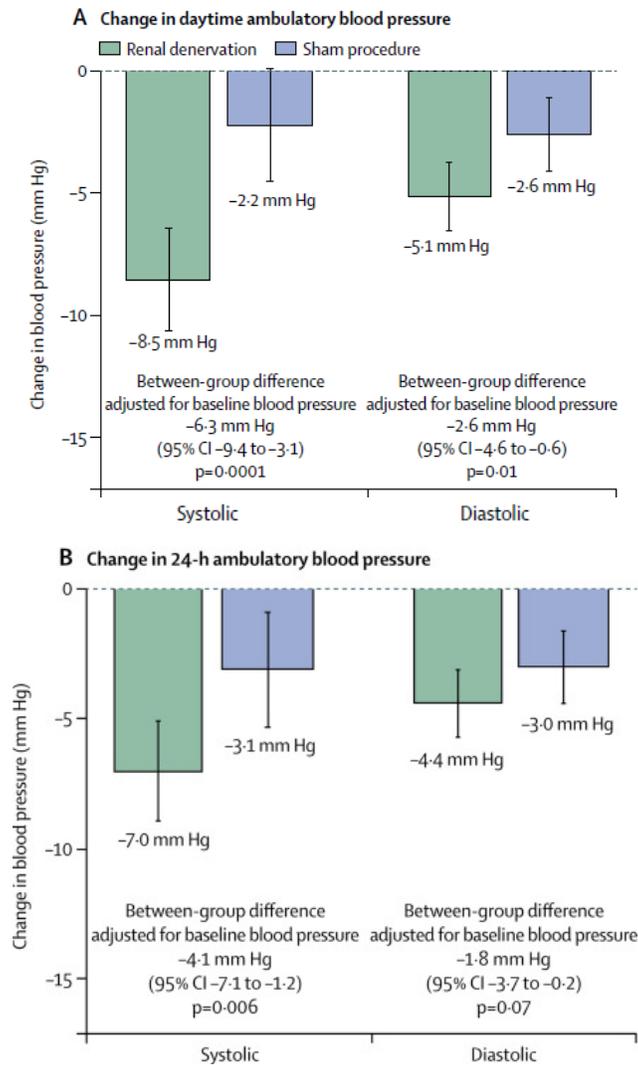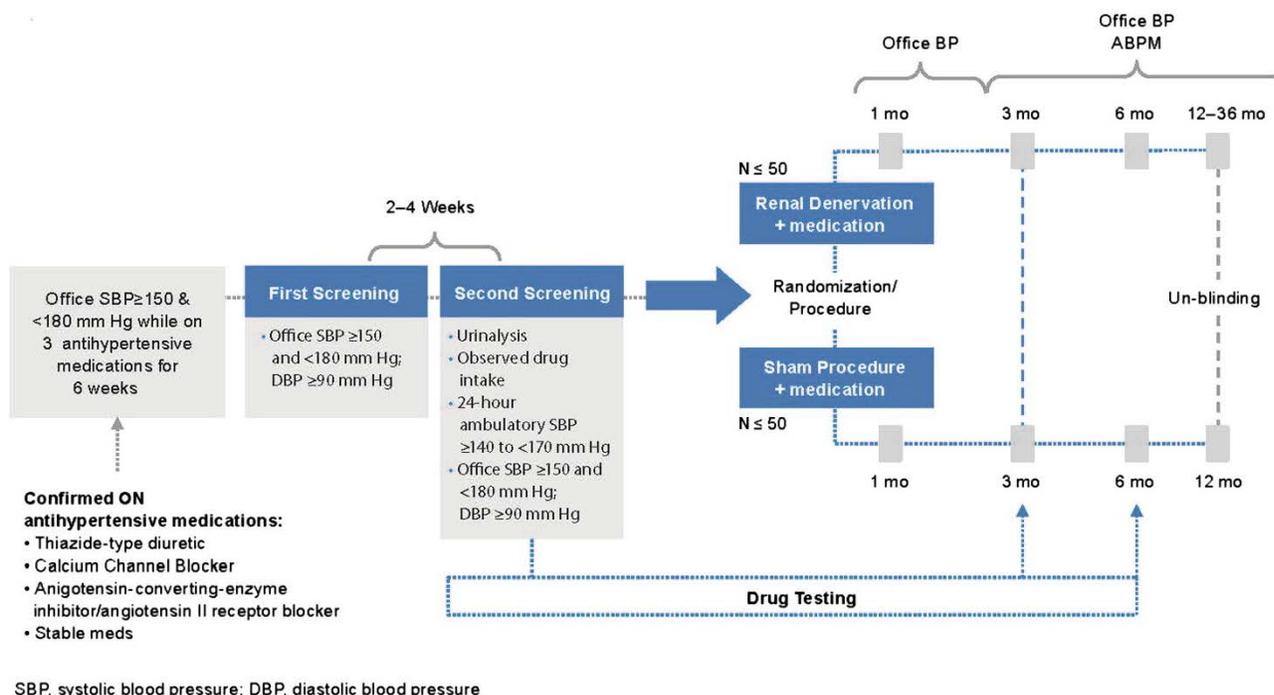**Figure 6: RADIANCE HTN SOLO Ambulatory BP Results at 2 Months**[42]

Figure 7: Overview of the SPYRAL HTN ON-MED Design[43]

SBP, systolic blood pressure; DBP, diastolic blood pressure

3.2 Carotid Body Ablation

The carotid body is a peripheral chemoreceptor located in the bifurcation of each common carotid artery into the main and external carotid arteries. The carotid body helps to regulate sympathetic tone and respiratory minute ventilation in response to stimuli such as hypoxia, hypercapnia, hypoglycemia, and acidosis.[23] Specifically, this receptor contributes towards a chemoreflex mechanism, in which increased afferent signaling from the carotid body stimulates the sympathetic nervous system resulting in an increase in blood pressure while suppression of the signal reverses the effect.[23,46] Therefore, the carotid body is thought to be a potential therapeutic target for those with a hypersensitive chemoreflex.[46] A recent pilot study evaluated the effects of unilateral carotid body resection in patients who had evidence of increased baseline carotid baroreceptor activity. Following treatment, eight out of 15 subjects demonstrated significant reductions in daytime ambulatory SBP at 3 months.[47] Additionally, a trend was noted in a reduction in both the number of medications and the medication classes among responders compared to non-responders. Although not detected in this pilot study, the potential risks associated with devices that target the carotid therapies include damage to the carotid artery and surrounding tissue as well as release of emboli leading to cerebral ischemia.

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[46] Paton JF, et al. The carotid body as a therapeutic target for the treatment of sympathetically mediated diseases. Hypertension. 2013;61(1):5– 13. doi:10.1161/HYPERTENSIONAHA.111.00064.

[47] Narkiewicz K, et al. Unilateral Carotid Body Resection in Resistant Hypertension: A Safety and Feasibility Trial. JACC. Basic to translational science. 2016;1(5):313-24.

3.3 Carotid Baroreceptor

These stretch receptors are activated by carotid sinus and aortic arch distension in response to rises in arterial BP during systole.[23] Activation sends afferent nerve impulses into the nucleus tractus solitarius in the central nervous system, decreasing the efferent sympathetic nervous system signals to the heart, peripheral vasculature and kidneys as well as increasing parasympathetic outflow; this results in decreased heart contraction, vasodilation and reduced renin secretion.[23] As these effects lead to a decrease in blood pressure, devices have emerged to stimulate the carotid baroreceptor directly with an electrical lead or mechanically stimulate the carotid baroreceptor by implanting a stent-like device in the internal carotid artery to increase the stretch sensitivity of the baroreceptor. These technologies pose risks due to the sensitive location of the intended therapy, as the carotid baroreceptor is surrounded by critical nervous tissue and intervention in the carotid arteries risks carotid stenosis or the formation of emboli or debris that can travel downstream to the cerebral vasculature.

The initial non-randomized DEBuT-HT open-label trial evaluated the Rheos device, which implanted electrodes bilaterally against the carotid baroreceptors in 45 patients. The feasibility study observed an average OBP reduction of 21/12 mmHg at 3 months and 33/22 mmHg at 2 years.[23,48] The subsequent Rheos pivotal trial randomized 265 patients to early (1-month post-implantation) or delayed (6 months post-implantation) device activation. Although no significant difference in the primary effectiveness endpoint of ≥10 mmHg reduction in SBP after 6-month follow-up was detected, 42% of participants in the early group vs 24 % of the delayed group achieved SBP <140 mmHg at 6 months.[49] Additionally, SBP reductions of 30 mmHg were sustained at 53 months.[50] However, the trial did not meet the endpoints for acute responders or procedural safety, and some patients developed transient (4.4%) or permanent (4.8%) facial nerve injury.[49] The newer-generation BAROSTIM NEO system utilizes a smaller generator and smaller single-lead for carotid sinus stimulation. The initial studies for this version demonstrated blood pressure reductions of 26/12 mmHg at 6 months as well as shorter implantation times, and less immediate procedure-related complications[51,52] The BAROSTIM Hypertension Pivotal Trial (clinicaltrials.gov: NCT01679132) is currently in progress.

The initial CALM FIM study evaluated the MobiusHD endovascular implant designed to reshape the carotid sinus in order to increase wall strain and stimulate the carotid baroreceptors. The CALM-FIM EUR was a prospective, first-in-human, open-label study conducted at six European centers. The mean OBP for 30 subjects was reduced by 24/12 mmHg at 6 months from a mean

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[48] Scheffers IJ, et al. Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. J Am Coll Cardiol. 2010;56(15):1254–8. doi:10.1016/j. jacc.2010.03.089.

[49] Bisognano JD, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the doubleblind, randomized, placebo-controlled rheos pivotal trial. J Am Coll Cardiol. 2011;58(7):765–73. doi:10.1016/j.jacc.2011.06.008.

[50] Bakris GL, et al. Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: results of long-term follow-up in the Rheos Pivotal Trial. J Am Soc Hypertens. 2012;6(2):152–8. doi:10.1016/j.jash.2012.01.003.

[51] Gassler JP, Bisognano JD. Baroreflex activation therapy in hypertension. J Hum Hypertens. 2014;28(8):469-74.

[52]Hoppe UC, et al. Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim neo trial. J Am Soc Hypertens. 2012;6(4):270-6.

baseline OBPM of 184/109 mmHg.[53] The CALM-2 pivotal study is currently in progress (clinicaltrials.gov: NCT03179800).

3.4 Hemodynamic Modulation

In contrast to the neurological modulation based treatment pathways described above, the use of a central iliac arterio-venous (AV) anastomosis intends to reduce effective arterial volume, systemic vascular resistance (SVR) and cardiac afterload to reduce blood pressure.[23] The ROX AV coupler is a nitinol stent-like device which creates a 4-mm conduit between the external iliac artery and vein. By diverting 0.8 to 1.0 L/min of arterial blood through the conduit into the proximal large capacitance venous circuit, a reduction of systemic vascular resistance and blood pressure is noted immediately. The device aims restore the Windkessel function of the central circulation which may especially help patients with reduced vascular compliance due to arterial stiffening. [23,54] A sympathomodulatory effect is thought to also contribute to the blood pressure lowering effect through increasing venous oxygenation and increasing right heart stretch through increased pre-load.[23,55]

While initial studies evaluated the device in patients with COPD, this device was studied in hypertensive patients as part of the ROX CONTROL HTN study, a randomized controlled, open-label trial in which 83 patients were randomized to either standard care or insertion of AV coupler in addition to standard care.[56] At 6 months, the subjects which received the device reduced OBP by 27/20 mmHg and ABPM by 14/14mmHg, while no significant changes were observed in the control group. Reductions in hospitalizations for hypertensive urgencies and a decrease in medication use were also observed for those that received the device. The main complication reported in the coupler group was a 29% incidence of ipsilateral venous stenosis. [23] A pivotal study of the ROX coupler is currently in progress (clinicaltrials.gov: NCT02895386).

3.5 Additional Therapies

Other additional therapies are developing early clinical evidence, including the use of deep-brain stimulation as a treatment for hypertension, the stimulation of the median nerve by an implantable subcutaneous neurostimulator placed in the forearm, as well as methods to stimulate the vagus nerve in efforts to increase parasympathetic activation. [23]

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[53] Spiering W, et al. Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle clinical study. Lancet. 2017;390(10113):2655-61.

[54] Foran JP, et al. The ROX coupler: creation of a fixed iliac arteriovenous anastomosis for the treatment of uncontrolled systemic arterial hypertension, exploiting the physical properties of the arterial vasculature. Catheter Cardiovasc Interv. 2015;85(5):880–6.

[55] Burchell AE, et al Arteriovenous anastomosis: is this the way to control hypertension? Hypertension 2014;64(1): 6–12.doi:10.1161/HYPERTENSIONAHA.114.02925.

[56] Lobo MD, et al. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial. Lancet. 2015;385(9978):1634-41.

Table 3 : Comparative Summary of Device Based Therapies for Hypertension, adapted[23]

	Strength of evidence	Sham trial	Verifiable technical success	Reversible	Patient selection	Specific advantage	Potential adverse events
Renal denervation	Large sham-controlled RCT, no clear effect but potential confounders. Supportive registry data.	Yes	No	No	Younger patients, non-African Americans, preserved renal function	Multiple approaches to achieve denervation	Diffuse arterial injury (from endovascular approach) with thermal energy
Baroreflex activation therapy	Large RCT for first-generation device completed. Ongoing large RCT (optimal medical therapy as control) for new-generation device.	Not yet	Yes	Yes. All electrical neuromodulation is reversible by switching off	Not enough experience	Potentially titratable activation with future iterations of device.	Potential nerve damage, although risk thought to be reduced with smaller, single-lead next-generation device. Battery replacement needed at 3–5-year intervals, generator failure possible. Open loop system—cannot titrate therapy to ambient BP levels
Carotid body ablation	Ongoing observational feasibility study	Not yet	Yes (surgical resection)	No	Patients with high carotid body tone, although difficult to measure	Verifiable surgical resection	Not enough experience
Central iliac arteriovenous anastamosis	Small RCT (standard medical care as control) completed. Ongoing global registry study	Not easily achieved	Yes	Yes	Nearly all patients respond but may best suit older patients with arterial stiffness/isolated systolic hypertension	Verifiable procedural success with immediate BP reduction. Targets mechanical aspects of the circulation rather than sympathetic drive	30 % incidence of ipsilateral venous stenosis, increased cardiac output
Deep brain stimulation	No registered trials, only observational data from non-blood pressure indications available	Not yet	Yes	Yes. All electrical neuromodulation is reversible by switching off	Not enough experience	Not enough experience	Not enough experience. Generator failure possible and battery replacement needed every 3–5 years. Open loop system - cannot titrate therapy to ambient BP levels
Median nerve stimulation	Ongoing sham-controlled RCT	In progress	Not enough experience	Yes. All electrical neuromodulation is reversible by switching off	Not enough experience	Minimally invasive procedure, inexpensive. Potentially titratable activation with future iterations of device.	Not enough experience. Battery replacement needed every 3–5 years. Open loop system—cannot titrate therapy to ambient BP levels
Vagal nerve stimulation	Animal model data and human case report available	Not yet	Not enough experience	Yes. All electrical neuromodulation is reversible by switching off	Not enough experience	Acts on parasympathetic system. Frequency- and current-dependent—facilitates titratable stimulation with future devices.	Battery replacement needed every 3–5 years. Open loop system—cannot titrate therapy to ambient BP levels

4 Clinical Evaluation of Anti-Hypertensive Devices

As discussed as part of the ASH multi-stakeholder forum, it is important to use lessons from previous clinical experience in the hypertensive patient population to design a comparative clinical trial while minimizing bias and reducing potential confounders to yield meaningful data to support clinical and regulatory decision-making. Key important factors include determining the appropriate patient population, utilizing a sham control, limiting potential confounders related to medication usage, and determining the appropriate safety and effectiveness endpoints. FDA considers both the benefits and the risks when making regulatory determinations in a least burdensome way, meaning FDA will consider balancing the collection of data in the pre- and post-market settings to bring safe and effective treatments to the U.S. market in an efficient manner.

4.1 Patient Demographics

Hypertension has a complex etiology resulting in variable pathophysiology and clinical response to therapies, and the role of the device treatment targets (e.g., sympathetic and parasympathetic nervous system) on the long-term impact of hypertension is uncertain. Additional challenges in this patient population include the wide variety in medication regimens and poor patient medication adherence/compliance and potential resistance. Clinical determination of a treatment regimen is typically based on a patient's etiology, comorbidities, and previous medical history. Additional factors that may affect a patient's treatment choice may also include the negative impact of their medication regimen due to side effects or dislike of pills that may lead to poor adherence. These latter factors that affect patient preference may be difficult to control for in a clinical study and will be discussed later.

The specific patient population who may benefit from device-based therapies is currently unknown, and therefore, evaluating both general and specific patient demographics in clinical studies is important. Additionally, the target anatomy for the device may play a role in the effectiveness in a particular patient demographic due to specific pathophysiology. Eligible patients for device trials for the treatment of hypertension may include those with varying etiologies and degrees of hypertension. Typically, but not exclusively, eligible patients for device trials are those that are either inadequately responsive to or intolerant of prescribed anti-hypertensive therapy. These patients with drug-intolerances or -resistances may be willing to accept the potential risks of a chronic therapy and may, therefore, be a good patient population to evaluate first in feasibility studies before expanding to a larger population.

Multiple factors determine the appropriate patient population for a clinical trial, including the benefit-risk profile and specificity of the indications. Points to consider regarding potential categories of patient populations include the level of hypertension, drug-resistance or -intolerance, and drug naivety, as described below:

1) Level of Hypertension: As detailed above in Section 2.2, the 2017 ACC/AHA guidelines for the detection, prevention, management and treatment of high blood pressure recommend earlier treatment with lifestyle changes, and, in some patients, medication therapy for blood pressures ≥130/80 mmHg.[4] These modified and updated guidelines of the 2003 "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment

of High Blood Pressure" (JNC7), are based on the potential advantage of earlier diagnosis and therapy. These guidelines differ slightly from those provided by the European Society of Cardiology (ESC)/European Society of Hypertension (ESH), which established a treatment threshold for "high normal" blood pressure of 130-139/85-89 mmHg.[57] The potential overall benefits of lowering blood pressure earlier are based on current knowledge based on population data using medication therapies which suggests improvements in overall cardiovascular morbidity and mortality. Whether these benefits across the range of disease will also apply to device-based treatments is currently unknown.

2) <u>Resistant Hypertension or Uncontrolled Hypertension:</u> The current definition of resistant hypertension is blood pressure that remains above goal despite optimal doses of three antihypertensive agents of different classes, with one medication being a diuretic. Patients achieving blood pressure control with the addition of a fourth antihypertensive agent also meet the definition of resistant hypertension. [4,58] Patients defined as having true resistant hypertension are those who do not have secondary hypertension and in whom lifestyle modification does not result in significant blood pressure reduction. Depending on the etiology of the disease, device-based therapies may be valuable for these patients.

3) <u>Drug Naivety:</u> As noted above, the benefits and risks of current therapies (e.g., lifestyle changes, medication) are well-understood, while device-based treatments are relatively novel. One consideration is that patients with resistant hypertension may represent a patient population that could receive the greatest benefit relative to the potential risks. However, companies may have challenges with patient enrollment in clinical trials limited to this patient population and the results may lack generalizability. Additionally, it may be difficult to minimize the confounding effects of variations in medication adherence/compliance in a study of this patient population, as withholding multiple medications from these subjects may impractical and unsafe. Therefore, industry may choose to enroll less hypertensive patients or drug naïve patients. Due the limited data for device-based treatments, there are currently no consistent effectiveness or safety data to demonstrate whether previously-treated patients have different outcomes than those who are drug naïve. The SYMPLICITY HTN-3 study results showed that the strongest predictors of improvement in blood pressures were observed in patients with entry SBP ≥180 mmHg, baseline estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2, and those being treated with aldosterone antagonists, suggesting that "a pivotal Phase III trial with RDN as the device therapy might be more likely to succeed if the population were enriched with more severely hypertensive participants."[40]

It may not be possible at the time of marketing approval to fully understand the long-term durability and safety of these therapies, the potential interactions with medication, and the generalizability to the broad hypertensive patient population. FDA anticipates the collection of important safety and effectiveness information through completion of post-approval studies. However, it would not be in the best interest of the public health to delay approval and

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[57] Williams B, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36(10):1953-2041.
[58] Carey RM, et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. Hypertension. 2018;72(5):e53-e90..

potentially prevent patient access to these devices for this reason. In such circumstances, a notation in the labeling can indicate the limits of current data collection and understanding of these issues, pending completion of post-approval data collection. It is expected, therefore, that labeling will be modified over time as a result of successfully collected post-approval data.

4.2 Clinical Study Design

4.2.1   Randomized and Controls

There have been many large clinical trials evaluating medication therapies for patients with hypertension, including ALLHAT and INVEST.[59,60] The double-blinded ALLHAT and open-label INVEST trials were prospective, multi-center, international studies used to evaluate the rates of adverse outcomes for common classes of antihypertensive medications. The main advantages of RCTs are allowing direct comparison between treatment arms while minimizing biases, such as those related to patient selection and allocation, and minimizing confounders resulting from the variability of the patient population and other sources (e.g., placebo effect, poor drug adherence/compliance). In these types of studies, the "control" subjects continue to receive standard of care (SOC) treatment, which provided an effective comparator to patients in the "treatment," "study" or "experimental" arm. While FDA will strongly consider the contribution of clinical evidence derived from real-world data or clinical literature to develop performance goals, studies that provide optimal interpretability are generally controlled designs that allow for direct comparison to the SOC using a recognized meaningful endpoint. This is particularly true for approval of first-of-a-kind indications for use where the potential for bias, patient variability, and other confounders is high.

The current recommendation from FDA's Center for Drug Evaluation and Research (CDER) for evaluating antihypertensive pharmaceuticals is the use of RCTs comparing the pharmaceutical to a placebo or another drug, as discussed in the 2000 draft guidance document titled International Conference on Harmonization - E12A Principles for Clinical Evaluation of New Antihypertensive Drugs.[61] However, the typically large RCTs associated with evaluating drugs in the general hypertension patient population to demonstrate a reduction in stroke or mortality may be untenable in a more limited patient population (e.g., resistant or uncontrolled hypertension) being evaluated for device-based therapies. In fact, as discussed as part of a June 15, 2005 Cardiovascular and Renal Drugs Advisory Committee panel meeting regarding class labeling for cardiovascular outcome claims for anti-hypertension drugs and in the subsequent 2011 guidance document titled Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims, CDER accepts reduction in blood pressure as a surrogate endpoint for new anti-hypertensive drug approval.[62]

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[59] Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Jama. 2002;288(23):2981-97.

[60] Pepine CJ, et al. Rationale and design of the International Verapamil SR/Trandolapril Study (INVEST): an Internet-based randomized trial in coronary artery disease patients with hypertension. J Am Coll Cardiol. 1998;32(5):1228–1237.

[61] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073147.pdf

[62] https://www.fda.gov/downloads/Drugs/.../Guidances/ucm075072.pdf

RCTs have proven valuable to evaluate devices compared to current medical practice or another device, and a sham control is often the best way to maintain blinding to patients and investigators in order to reduce potential assessment bias. This type of control is particularly valuable in trials in which the effectiveness endpoint is subjective and vulnerable to interpretation and circumstances, as when evaluating medication and device-based therapies in hypertensive patients. As noted above, one example study that employed a sham control is the SYMPLICITY HTN-3 study in which the sham group received renal angiography but did not undergo renal denervation. While the lack of difference in blood pressure reduction between the two groups may have resulted from a variety of sources (e.g., suboptimal procedural technique, electrode design), the addition of a sham control allowed researchers and clinicians to better understand the physiology of renal denervation from this sham-controlled trial as compared to the positive results from previous single-arm trials. However, the sham procedure and device are not without potential risks to the patient. This differs from placebo drug trials in which the "sham" does not confer any patient risks, other than potentially delayed therapy. Sutherland provided a rational argument for the inclusion of sham controls in device trials: "The absence in clinical trials [of] a placebo (or sham) procedural control failed to account for multiple factors that can lead to inaccurate conclusions regarding efficacy. Notable examples include surgical treatments such as internal mammary artery ligation for angina pectoris, cervical glomectomy for the treatment of bronchial asthma, and fetal nigral cell transplantation for the treatment of Parkinson's Disease, all adopted as procedures thought to be efficacious on the basis of uncontrolled studies and then later shown not to be beneficial."[63]

An alternative viewpoint of the value of sham-controlled RDN device trials for patients with hypertension was posed by Elmula *et al.*[64] They conducted a meta-analysis of ten (3 sham, 7 no sham) RCTs and otherwise controlled studies and found that while the overall effect of the devices for blood pressure reduction was small and statistically non-significant, the sham design may not have provided unique results as compared to previous meta-analyses of multiple studies. Rather, Elmula *et al.* posited that assessment of 24-hour ABPM alone reduces the impact of biases and the Hawthorne effect (alteration of subject behavior due to being observed) for evaluating RDN devices in hypertensive patients.

In a scientific statement provided by the American Society of Hypertension (ASH), FDA and NHLBI, "It was agreed that the most appropriate Phase III device therapy trial for an indication of treating hypertension remains a blinded, sham–procedure controlled, randomized study that includes rigorous screening for participants correctly meeting the inclusion criteria. While sham– procedure control is not equivalent to optimal clinical care of severe or uncontrolled hypertension, it is necessary since both a 'placebo–like' effect and changes in individuals' behavior during the course of the follow–up period are expected in a hypertension trial."[40]

4.2.2 Medication Use

As noted above, there are numerous treatments available for hypertensive patients, and many patients may be taking more than one medication to control their blood pressure effectively. Due

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[63] Sutherland ER. Sham procedure versus usual care as the control in clinical trials of devices: which is better? Proc Am Thorac Soc. 2007;4(7):574-6.

[64] Fadl Elmula FEM, et al. Sham or no sham control: that is the question in trials of renal denervation for resistant hypertension. A systematic meta-analysis. Blood Press. 2017;26(4):195-203.

to these concerns noted in previous single-arm device trials, it is important to design the clinical trial to isolate the effects of the device therapy and limit potential confounders related to medication use. Three trial design considerations for "ON" and "OFF" medication studies are incorporating a run-in period, medication washout, evaluation of drug adherence/compliance, and control over concomitant medication during the trial, particularly prior to the endpoints.

1) Run-in Period: To reduce variability and potential regression to the mean (e.g., the tendency for a quantitative variable that is extreme on the first measurement to become less extreme on subsequent measurements), one approach is include a run-in period before the trial in which a patient in on a stable medication regimen and multiple blood pressure measurements are captured over a specified period. Pocock *et al*. evaluated data from SYMPLICITY HTN-3 and determined that designing the clinical and statistical protocols to correct for the influence of regression to the mean is particularly valuable to evaluate blood pressure changes in hypertension patients.[65]

2) Medication washout: For trials in which the entry participants are receiving pharmaco-therapy, the ideal mechanism to assess the independent effect of the device is to include in the protocol a medication washout period. As opposed to a run-in period, which occurs before the trial begins, the washout period transpires after enrollment. During this period, patients are exposed to the risks of hypertension. Literature suggests that this washout period should be limited to 8-12 weeks to reduce the risks to the patient.[40] Examples of trials using a washout period in a device trial is the SPYRAL HTN-OFF MED study, and the RADIANCE HTN-SOLO study. In these studies, the safety and effectiveness of renal nerve denervation was evaluated in patients with hypertension who were either drug naïve or agreed to discontinue their medication regimen for three to four weeks. During the washout period, the patients' blood pressures were continually monitored to ensure the patients did not exhibit negative symptoms.

3) Medication Adherence and Compliance: Poor medication adherence and compliance are well-known for hypertensive patients and is a major contributing factor to uncontrolled blood pressure. Methods to measure medication adherence and compliance can include indirect approaches such as physician assessment, patient self-reporting, pill counting, prescription refill, or pharmacodynamic parameters (e.g., heart rate for β-blockers, acetyl-SDKP measurements for ACE inhibitors) as well as direct methods such as witnessed drug intake or serum/urine drug monitoring.[66] Up to 25% of patients do not fill their initial prescription for antihypertensive therapy.[2,4] A retrospective analysis of medication adherence in older U.S. adults was performed by collecting a random 5% sample of data from U.S. Medicare beneficiaries between 2007-2012, totaling 41,135 adults aged $\geq$ 65 years.[67] The authors found that 21.3% of the adults discontinued treatment in 90 days of the first year of treatment. Additionally, medication adherence, defined as having medication available to

[65] Pocock SJ, et al. Regression to the Mean in SYMPLICITY HTN-3: Implications for Design and Reporting of Future Trials. J Am Coll Cardiol. 2016;68(18):2016-25.

[66] Berra E, et al. Evaluation of Adherence Should Become an Integral Part of Assessment of Patients With Apparently Treatment-Resistant Hypertension. Hypertension. 2016;68(2):297-306.

[67] G.S. Tajeu, et al. Incident cardiovascular disease among adults with blood pressure <140/90 mm Hg Circulation, 136 (2017), pp. 798-812

take for <80% of days in the year after initiation of treatment, decreased overall from 37.4% in 2007 to 31.7% in 2012.

4) <u>Concomitant Use of Medications During the Trial:</u> The study design may permit continuation or re-introduction of anti-hypertensive medications during the trial. Medication use may be necessary to ensure patient safety if the blood pressure is not adequately controlled after the device therapy. However, the concomitant use of a drug and device can confound the ability to discern the device effect. Studies with crossover design may be provide additional insight by allowing the period of participation in the sham control arm to serve as a comparison for after the patient crosses over. Yet, it is recommended that the statistical plan include some provision for analysis of effectiveness in patients who receive supplemental medications after device therapy.

4.2.3 Interim Analyses

To reduce the potential burden and time of a clinical trial, interim analyses may be conducted to evaluate futility, determine early success, and/or modify the sample size based on the information gathered thus far. If an interim analysis is proposed in the statistical plan, FDA recommends that the process for conducting an interim analysis be pre-specified with clinical and statistical considerations (e.g., alpha-spending techniques) and blinded to reduce the likelihood of false-positive results, while preserving the integrity of the trial. This proposal is consistent with that discussed as part of the ASH multi-stakeholder forum. [40] It is noteworthy that an interim analysis can assist in reducing unnecessary exposure of patients to harm if the device under study is resulting in either minimal benefit or safety concerns.

4.2.4 Patient crossover

One limitation of a RCT may be slow patient enrollment (i.e., patients choose not to enroll because they do not want a chance of being treated with a control). Therefore, one method to overcome this obstacle is to allow control patients to crossover to the treatment group after a particular time period. It is noteworthy that, in order to maintain equipoise for the study, crossover should be allowed once analysis of the data shows the device to be of potential benefit. However, crossover may reduce the number of subjects available, leading to reduced statistical power, to evaluate longer-term safety and durability of effectiveness. Additionally, without an adequate number of control patients, effects noted in the treatment group may be attributed to the treatment when actually due to the natural progression of disease. Therefore, it is important to weigh the advantages and disadvantages of patient crossover when designing a clinical study.

4.3 Clinical Study Endpoints

There are typically two "phases" of device studies: feasibility and pivotal. Feasibility studies typically contain a small number of patients and may be first-in-human studies. Feasibility studies are valuable to evaluate the initial safety and potentially the effectiveness of a device and to inform design of a larger pivotal trial to conclusively evaluate safety and effectiveness. For anti-hypertensive device trials, the general effectiveness endpoint may be based on blood pressure measurements, and the safety endpoint will be determined by the particular risks associated with the device, as discussed further below.

4.3.1 Safety Endpoints

Safety endpoints are generally based on adverse events (AE) that are observed during the clinical study. While the FDA will strongly consider the contribution of published literature (i.e., real world evidence, or RWE) in support of a marketing application, one common limitation of RWE is the suboptimal, prospective surveillance and collection of AE information. Therefore, many marketing applications that include clinical data use prospective studies to assess AE severity and rates. Similar to studies of anti-hypertensive medications, the types of AE collected vary according to the device type, and it is important to identify AE related to the procedure (access site infections, bleeding) or the device (e.g., perforation, fracture). For example, the types of AE one may observe with devices that perform RDN may be very dissimilar to AE typically seen with devices that interrupt the carotid body. Therefore, FDA encourages companies and investigators to prospectively determine the types of AE that are most likely to occur in a clinical trial. While all AE are collected in a trial and provide valuable information, particular focus on certain potentially severe AE (e.g., renal artery stenosis for RDN devices) is recommended.

Typically, in a RCT, safety can be evaluated through comparisons of AE severity and rates between the control and experimental groups. However, in a sham-controlled trial, this comparison may not adequately incorporate AE related to the procedure, and it may be challenging to develop a pre-specified AE rate comparison (including the identification of an appropriate margin) to demonstrate a reasonable assurance of safety. Therefore, a performance goal may be valuable to evaluate the acute and chronic safety of the procedure and/or implantation. The determination of safety is dependent on a variety of factors, including assessment of the most severe events. For trials involving RDN, the major safety events can be divided into acute (generally procedural, e.g., bleeding, pain, vascular injury, thrombosis, hematoma) and chronic (e.g., renal artery stenosis, venous stenosis). In addition to determining which AE are the most relevant in a device trial for hypertension, another consideration is what period (e.g., 6 versus 24 months) is most appropriate to adequately assess the occurrence of AE. A composite performance goal based on the available safety data from comparable patient populations for alternative treatments may be valuable to evaluate safety while also taking the comparison between the treatment and controls groups in consideration.

Potential risks will depend on the device technology and the anatomical target. As there is currently more adverse event information in the literature for therapies targeting the renal arteries or the carotid arteries, these will be discussed as examples below.

Adverse events associated with RDN. Although more information on RDN appears to be publicly available than other device-based hypertension treatments, current literature suggests that evidence related to procedural and chronic complications remain unclear or unknown. The Cochrane Database study by Coppolino *et al*. evaluated RDN studies in patients with resistant hypertension and determined that the quality of the evidence was low for cardiovascular outcomes and adverse events and moderate for lack of effect on blood pressure and renal function with limited or no data available for all-cause mortality, hospitalization, fatal cardiovascular events, quality of life, atrial fibrillation episodes, left ventricular hypertrophy, sleep apnea severity, need for renal replacement therapy, and metabolic profile.[68] Patel *et al*.

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[68] Coppolino G, et al. Renal denervation for resistant hypertension. Cochrane Database Syst Rev. 2017;2:Cd011499.

found a relatively low composite complication rate of 1.5% among 55 studies of RDN in patients with resistant hypertension which included vascular access site complications, renal artery injury (dissection, stenosis) and renal dysfunction (defined as >50% change in renal function).[69] Despite the low rates of AE, the authors conclude that the burden and progression of chronic complications cannot be conclusively determined due to the study designs (e.g., single-arm, lack of systematic renal artery imaging, short timepoints) and may not be generalizable due to more than 90% of the published data attributed to the Symplicity catheter. The authors also report a small study in this series using optical coherence tomography immediately after RDN found differences in the extent of vascular damage between balloon and non-balloon-based catheter systems. Other potential but less commonly observed complications of RDN, as reported in the SYMPLICITY HTN-1 trial, include renal artery spasm or dissection, post-procedural flank pain, infection, and pseudoaneurysms at the puncture site.[28]

Renal artery stenosis (RAS) is a significant adverse event that occasionally occurs after treatment in the renal arteries and, as such, may occur following RDN. As stated above, the true incidence of RAS following RDN is difficult to ascertain since many study designs only require imaging studies for 6-12 months post-procedure. While it is commonly presumed that the majority of new-onset RAS events occur in the first 12 months after RDN, that assumption is based on trials that typically rely on performing duplex ultrasound (DUS) opposed to more accurate studies such as computed tomography angiography (CTA) or magnetic resonance angiography (MRA). Although DUS is a common screening tool used for RAS, it is highly operator dependent and depends on adequate visualization of the stenotic segment which may be obscured by patient body type, prescience of bowel gas, dense atherosclerotic plaque or accessory renal arteries; as such, MRI or CT modalities may be more reliable.[70] A meta-analysis compared CTA, MRA, ultrasonography, and captopril renal scintigraphy for diagnostic accuracy for RAS in the general population.[71] They found that the areas under the summary ROC curves were 0.99 for CTA, 0.99 for gadolinium-enhanced MRA, 0.97 for non-gadolinium-enhanced MRA, 0.93 for ultrasonography, and 0.92 for captopril renal scintigraphy. A study by Hashemi Jazi *et al.* found that the sensitivity and positive predictive values for RAS with MRA were 100% and 25% compared to 67% and 67% for ultrasonography.[72] Eriksson *et al.* performed CTA, MRA, contrast-enhanced Doppler ultrasound, and captopril renography in 47 consecutive patients with moderately impaired renal function and a clinical suspicion of RAS using a reference standard of >50% stenosis of the vessel diameter on CTA.[73] They found that the frequency of positive findings was 70% for CTA, 60% for MRA, 53% for ultrasound and 30% for captopril renography.

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[69] Patel HC, et al. Renal denervation for the management of resistant hypertension. Integrated blood pressure control. 2015;8:57-69.

[70] Harvin HJ, Verma N, Nikolaidis P, Hanley M, Dogra VS, Goldfarb S, et al. ACR Appropriateness Criteria((R)) Renovascular Hypertension. J Am Coll Radiol. 2017;14(11s):S540-s9.

[71] Vasbinder GB, et al. Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. Ann Intern Med. 2001;135(6):401-11.

[72] Hashemi Jazi M, et al. Comparing Diagnostic Techniques of Magnetic Resonance Angiography (MRA) and Doppler Ultrasonography in Determining Severity of Renal Artery Stenosis. ARYA Atheroscler. 2011;7(2):58-62.

[73] Eriksson P, et al. Non-invasive investigations of potential renal artery stenosis in renal insufficiency. Nephrol Dial Transplant. 2010;25(11):3607-14.

Another issue is the extent of renal artery narrowing that defines new-onset RAS. The National Kidney Foundation KDOQI Guidelines define anatomical RAS as >50% narrowing of the lumen by angiography while the stenosis is considered hemodynamically significant if the narrowing is ≥75%, in which renovascular hypertension or ischemic nephropathy may result.[74] However, the threshold value for clinically-significant narrowing of the renal artery is debatable and has been variably determined to be between 50 and 70% reduction of the internal diameter, albeit depending on the imaging modality used to assess the degree of stenosis.[75, 9,76,77,78,79] In a comparison of various imaging modalities for the diagnosis of RAS in 58 patients with suspected renovascular HTN, Rountas *et al*. found that the sensitivity, specificity, and positive and negative predictive values were all significantly higher for CTA or MRA compared to DUS.[80] The sensitivity values were: 94% for CTA, 90% for MRA, and 75% for DUS.

One final issue related to the risk of developing new-onset RAS after RDN is the type of procedure performed for denervation. The results from the previously cited postmortem anatomical studies suggest that ablation of nerves in the distal renal arteries may be more effective.[39,40] However, rates of RAS have only been assessed in patients prior to recent modifications in the device design and target location (i.e., main renal artery versus branches), it is uncertain how prior data are relevant to newer iterations of the devices and changes in the procedure. Additionally, it remains unclear how to best evaluate for RAS in the distal renal arteries; while DUS may provide indirect assessment proximal stenosis by use of the parvus-tardus intrarenal waveform, high-spatial-resolution small-field-of-view contrast-enhanced MRA techniques may allow distal stenosis to be evaluated while CTA may provide better depiction of branch renal arteries.[70] Therefore, the choice of imaging techniques should be carefully considered and pre-specified to identify potential risks associated with the device therapy.

Adverse Events associated with carotid body devices. Devices that involve percutaneous delivery and/or implantation in or near the carotid artery to alter the carotid baroreceptor activity may induce AE similar to those observed after RDN, but there are also some unique AE to be considered. While less studied than RDN devices, potential AE in these devices include cerebrovascular accidents (e.g., stroke, TIA), hypotension, hypertensive crisis, bradycardia, nerve injury, heart rate or rhythm abnormality, and carotid stenosis. Some of these AE, such as procedural hypotension, may be acute whereas other AE may develop later such as clinical-significant carotid stenosis. As with studies evaluating therapies that target the renal arteries, the timing and modality of imaging is an important consideration to pre-specify.

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[74] K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43(5 Suppl 1):S101.

[75] Bosmans JL, et al. Renovascular hypertension: diagnostic and therapeutic challenges. JBR-BTR. 2004;87(1):32-5.

[76] Dworkin LD,et al. Clinical practice. Renal-artery stenosis. The New England journal of medicine. 2009;361(20):1972-8.

[77] Vasbinder GB, et al. Accuracy of computed tomographic angiography and magnetic resonance angiography for diagnosing renal artery stenosis. Ann Intern Med. 2004;141(9):674-82; discussion 82.

[78] Zhang HL, et al. Renal artery stenosis: imaging options, pitfalls, and concerns. Prog Cardiovasc Dis. 2009;52(3):209-19.

[79] Drieghe B, et al. Assessment of renal artery stenosis: side-by-side comparison of angiography and duplex ultrasound with pressure gradient measurements. Eur Heart J. 2008;29(4):517-24.

[80] Rountas C, et al. Imaging modalities for renal artery stenosis in suspected renovascular hypertension: prospective intraindividual comparison of color Doppler US, CT angiography, GD-enhanced MR angiography, and digital substraction angiography. Ren Fail. 2007;29(3):295-302.

4.3.2 Effectiveness Endpoints

Assessment of clinically meaningful or "direct" (e.g., mortality, cardiovascular events) endpoints is preferred in device clinical trials. The Systolic Blood Pressure Intervention Trial (SPRINT) was a multicenter, randomized trial designed to assess the outcomes of reducing SBP to a lower blood pressure level than typically recommended on cardiovascular (CV) risk. The efficacy endpoints included clinical-meaningful endpoint of occurrence of a myocardial infarction (MI), acute coronary syndrome (ACS), stroke, heart failure (HF), or CV death. The secondary outcomes included mortality, renal function, dementia, decline in cognitive function, and small vessel cerebral ischemic disease.

While clinically meaningful effectiveness endpoints are ideal, FDA is cognizant that there may be circumstances where requiring clinically meaningful endpoints may be overly burdensome and therefore can potentially hinder successful trial completion due to low observation rates or long time to event, or other factors. In these cases, any proposed surrogate endpoint should be objective, validated, and established to correlate, directly reflect, or predict a clinically meaningful outcome. Surrogate endpoints can include clinical findings, laboratory results, or other outcomes. For example, if a 10 mmHg reduction in SBP has been shown to correlate with a reduction of major adverse cardiovascular events (MACE), blood pressure reduction can be proposed as the primary effectiveness endpoint. In the hypertensive patient population, the surrogate endpoint of blood pressure may be appropriate because the trial design may not allow for an adequate sample size or time period of observation to assess certain clinically meaningful outcomes, such as MACE. In such cases, the surrogate endpoint may permit a shorter observation period while the results can still provide a meaningful outcome. Important considerations for this surrogate primary endpoint include determination of what constitutes a clinically meaningful blood pressure reduction, the appropriate time point to predict short- and long-term effectiveness, the method of measurement, and the statistical comparison.

Clinically meaningful blood pressure reduction. The recommendations for hypertension treatment to control blood pressure as well as determination of the optimum target pressure for a patient have evolved over time as well as may differ between practice guidelines. However, both of the recent AAFP/ACP and ACC/AHA guidelines recommend nonpharmacologic interventions for all adults, in which the most important are considered to be weight loss, increased physical activity and dietary changes such as use of the DASH diet (Dietary Approaches to Stop Hypertension), reduced intake of dietary sodium, enhanced intake of dietary potassium and moderation of alcohol intake.[4,13] These guidelines and literature studies provide perspective on the approximate blood pressure reduction for common therapies, including life-style changes and medications, as detailed below. The degree to which blood pressure is lowered as a result of these changes can provide perspective as to the potential health benefits of blood pressure reduction after device-based treatment. However, many of these studies use office or home blood pressure measurements as opposed to the recommended ABPM for device studies, so any comparisons may be limited.

As summarized below and detailed in Table 3 reproduced from the 2017 ACC/AHA Guidelines, nonpharmaceutical lifestyle changes have demonstrated to be effective in lowering blood pressure and are recommended to prevent hypertension, achieve blood pressure goal for Stage 1 hypertension, and are essential components for the treatment plan of Stage 2 hypertension.[4] Weight loss is recommended to be achieved through both reduced calorie intake and increased physical activity in which there is an apparent dose–response relationship of about 1 mmHg per kilogram of weight loss. Physical activity, including dynamic aerobic exercise, dynamic resistance training, and static isometric exercise have demonstrated in numerous clinical studies to have blood pressure lowering effects, and may reduce blood pressure from 4 to 8 mmHg for hypertensive patients or 2 to 4 mmHg in normotensive patients. Regarding dietary considerations, the DASH diet is considered the most effective for lowering blood pressure and has produced overall reductions in SBP of approximately 11 mmHg in hypertensive patients and 3 mmHg in normotensive patients. The guidelines explain that sodium reduction by 1,000 mg/day can reduce systolic blood pressure by 2-3 mmHg in normotensive patients, but this blood pressure reduction may more than double for those patients with hypertension, susceptible to sodium, following the DASH diet, or losing weight.

In efforts to aid the creation of an antihypertensive medication regimen, Wu *et al*. conducted a meta-analysis of clinical trials conducted between 1969-2003 and summarized the effects of blood pressure lowering medications.[81] The authors collected information from 137 clinical trials with monodrug therapies and 28 clinical trials of combination drug therapies with a total of 11,739 participants. They analyzed six major classes/groups of antihypertensive medications for effects and categorized the results by ethnicity, including ACE inhibitors, alpha1-blockers, cardioselective beta-blockers, CCBs, thiazide and thiazide-like diuretics, and loop diuretics. The weighted average effects of monodrug therapy including clinical trials using sitting or supine blood pressures are provided in Table 5 below.[81] Such analyses of the blood pressure lowering effects may help provide physicians perspective towards how device-based therapies could be utilized as part of the treatment regimen for a hypertensive patient.

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[81] Wu J, et al. A summary of the effects of antihypertensive medications on measured blood pressure. Am J Hypertens. 2005;18(7):935-42.

Table 4: ACC/AHA 2017 Guideline Recommended Best Proven Nonpharmacological Interventions for Prevention and Treatment of Hypertension[4]

	Nonpharmacological Intervention	Dose	Approximate Impact on SBP		
			Hypertension	Normotension	Reference
Weight loss	Weight/body fat	Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.	-5 mm Hg	-2/3 mm Hg	(1)
Healthy diet	DASH dietary pattern	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	-11 mm Hg	-3 mm Hg	(6, 7)
Reduced intake of dietary sodium	Dietary sodium	Optimal goal is <1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults.	-5/6 mm Hg	-2/3 mm Hg	(9, 10)
Enhanced intake of dietary potassium	Dietary potassium	Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium.	-4/5 mm Hg	-2 mm Hg	(13)
Physical activity	Aerobic	• 90–150 min/wk • 65%–75% heart rate reserve	-5/8 mm Hg	-2/4 mm Hg	(18, 22)
	Dynamic resistance	• 90–150 min/wk • 50%–80% 1 rep maximum • 6 exercises, 3 sets/exercise, 10 repetitions/set	-4 mm Hg	-2 mm Hg	(18)
	Isometric resistance	• 4 × 2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk • 8–10 wk	-5 mm Hg	-4 mm Hg	(19, 31)
Moderation in alcohol intake	Alcohol consumption	In individuals who drink alcohol, reduce alcohol† to: • Men: ≤2 drinks daily • Women: ≤1 drink	-4 mm Hg	-3 mm Hg	(22-24)

Table 5: Comparison of Effect Size of Common Antihypertensive Medication Classes[81]

Table 1. Weighted average effects of antihypertensives as monodrug therapy by ethnicity for sitting or supine BP

Medication*	African Americans			Non-African Americans			All		
	No. of Trials	No. of Pts	Average Effect ± SD (SBP/DBP in mm Hg)	No. of Trials	No. of Pts	Average Effect ± SD (SBP/DBP in mm Hg)	No. of Trials	No. of Pts	Average Effect ± SD (SBP/DBP in mm Hg)
ACE	10	446	6.8 ± 2.4/6.6 ± 2.5	23	1221	14.3 ± 4.4/10.4 ± 3.2	36	1898	12.5 ± 5.3/9.5 ± 3.4
α_1-Blockers	2	805	17.9 ± 2.6/12.0 ± 0.9	5	275	18.6 ± 7.0/12.5 ± 1.3	15	1849	15.5 ± 4.8/11.7 ± 1.3
β_1-Blockers	2	190	9.1 ± 0.8/10.5 ± 0.4	11	495	14.6 ± 4.1/12.1 ± 3.4	18	908	14.8 ± 4.9/12.2 ± 2.2
Calcium blockers	7	554	17.6 ± 4.0/13.0 ± 1.8	16	2214	16.9 ± 4.1/10.6 ± 2.8	34	3727	15.3 ± 5.0/10.5 ± 2.8
Dihydropyradine	3	286	20.2 ± 3.8/13.0 ± 2.1	14	2084	17.1 ± 4.4/10.4 ± 3.2	26	3169	15.5 ± 5.3/10.2 ± 2.8
Non-Dihydropyradine	4	268	14.8 ± 3.2/13.1 ± 1.3	2	130	13.9 ± 4.6/14.6 ± 4.2	8	558	14.2 ± 2.5/12.5 ± 3.1
Thiazides	5	449	19.1 ± 4.1/12.4 ± 2.2	8	578	15.0 ± 1.6/9.5 ± 2.2	18	1657	15.3 ± 5.4/9.8 ± 3.6
Loop diuretics	1	16	26.7 ± 2.4/10.1 ± 2.3	8	215	12.3 ± 6.9/6.1 ± 4.4	17	366	15.8 ± 7.8/8.2 ± 4.7
Average	27	2460	15.4 ± 4.8/11.2 ± 2.3	71	4998	15.7 ± 1.5/10.5 ± 1.2	137	10405	14.8 ± 1.1/10.5 ± 1.0

ACE = angiotensin-converting enzyme inhibitors; SBP = systolic blood pressure; DBP = diastolic blood pressure.
  * Lists the class or group of antihypertensive medications along with an Appendix table (in parentheses) that provides the details of individual clinical trials. For example, see Table A2 in the Appendix A for ACE inhibitors.

Blood Pressure Measurement Method. An important consideration for evaluating blood pressure is the mechanism (e.g., office, daytime, home, ambulatory) of how blood pressure is measured in a trial. However, the method of measuring blood pressure varies in literature and in the above tables. As summarized by Mahfoud *et al*., there is convincing evidence that compared to OBPM, ABPM is a more sensitive and specific method to assess blood pressure, measure CV risk, and reduces potential variability due to White Coat hypertension, that may occur due to increased stress in a doctor's office. [82,83,84,85] Moreover, OBPM suffers from the lack of inclusion of nighttime blood pressure evaluation which may better predict CV morbidity and mortality.[85] The main reason why daytime or OBPM is generally considered inferior to ABPM is that blood pressure varies throughout the day (due to activity) and night with a circadian pattern. Blood pressures typically declines during nighttime sleeping, and as a result, daytime (or office) blood pressure assessments may not accurately reflect diurnal variations. For these reasons, practice guidelines endorse ABPM to assess blood pressure in clinical trials.[86] However, one limitation associated with ABPM is that patients may not tolerate wearing the equipment which may result in missing data. Yet, the benefits of assessing ABPM for the primary endpoint outweigh the potential risks of missing data.

Primary endpoint timepoint. Full assessment of the benefit-risk fit ratio of novel devices currently being developed requires scientific evidence that the therapy has some degree of durability. Device use today appears targeted to subjects with less severe blood pressure elevation than those subjects with advanced or malignant hypertension previously treated surgically, subjects who do have a plethora of available pharmacologic options. While short-term benefit of varying degrees has been demonstrated in the recent feasibility studies of RDN, the

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[82] Mahfoud F, et al. Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. Circulation. 2013;128(2):132-40.

[83] Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. N Engl J Med. 2006;354(22):2368-74.

[84] Ohkubo T, et al. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. J Hypertens. 1997;15(4):357-64.

[85] Fagard RH, et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. Hypertension. 2008;51(1):55-61.

[86] Mancia G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2007;25(6):1105-87.

sustained durability of such benefit remains to be reproducibly established. Durability is especially important considering that studies relating the surrogate endpoint of blood pressure reduction to lifetime cardiovascular events are based on a sustained reductive effect.[3,5] Assessing duration of treatment effect should be an important consideration in the design of clinical investigation of devices intended to treat hypertension.

Studies with a short-term (3-9 month) observation period for the primary effectiveness endpoint may provide some evidence of a benefit but may not necessarily predict long-term success. In drug therapy studies, the durability may abate due to non-adherence or physiological adaptation to the drug mechanism. Such limitations may be less likely to occur in device trials, especially those employing implantable devices, depending on the type of device and mechanism of action. Despite the inherent challenges of conducting long-term intervention studies, a longer duration of blood pressure reduction is more likely to predict greater long-term reduction of CV events. While the PREMIER trial was a lifestyle modification and not a drug or device intervention trial, the primary efficacy outcome assessment occurred at 6 months.[87] However, in the device trials, patients may be taking concomitant medication by 6 months, which may confound the treatment effect of the device. One option is to evaluate the primary effectiveness of blood pressure reduction at the end of the washout period prior to returning medication while also considering endpoints at later timepoints to include reductions in blood pressure and medication types/dosages. Although medications changes may be challenging to quantitatively or qualitatively assess, these endpoints may be valuable to patients.

Statistical Comparison. For RCTs, comparison of effectiveness between the control and treatment arms is appropriate, and comparison with the sham control is valuable as potential confounders related to the procedure and any placebo effect should be reduced. From a statistical perspective, these comparisons can be based on non-inferiority, equivalence, or superiority, and clinically meaningful margins can be pre-specified. In clinical trials evaluating anti-hypertensive devices, it is important to demonstrate that the device provides a clinically meaningful reduction in blood pressure, and therefore, a test for super-superiority (i.e., the lower bound of the confidence interval for the treatment effect is greater than the upper bound for the control by a pre-specified amount) may be important to demonstrate effectiveness rather than using a simple superiority test.

5   Benefit-Risk Determination

FDA considers both the benefits and risks for regulatory decision-making. Factors that are considered include the extent of the probable benefits and risks, including the type, magnitude/severity, probability, and duration; the uncertainty surrounding these factors; whether alternative treatment exist; the patient's perspective, and the public health need. Identifying these factors early during development can help to guide the intended patient population and clinical trial design. For example, patients with drug-resistant hypertension may have few other options available and therefore may be more willing to accept a reduced benefit or greater risk compared to the general population.

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[87] Appel LJ, et al. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. Jama. 2003;289(16):2083-93.

5.1 Patient Preference

FDA values the experience and perspectives of patients. This kind of input is important to consider during FDA's decision-making on these devices. Patient perspectives refer to patient input, including information relating to patients' experience with a disease or condition and its management and the patients' willingness to tolerate risks for a given benefit. Patient perspective information (PPI) can be especially important when multiple treatment option exists with varying degrees of benefits and risks.

One option for incorporating patient perspectives in the assessment of anti-hypertension devices is to include patient-reported outcomes (PROs) in the study design. PROs are defined by FDA (Patient Reported Outcomes in Assessing Effects of Medical Devices) as "a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else." The PRO must be scientifically designed and validated. PROs can be included as primary or secondary effectiveness or safety endpoints. Studies on patients with cardiovascular disease may be ideally suited for inclusion of PROs as endpoints. FDA states: "In chronic conditions such as heart failure, PROs can play an important role in quantifying the impact on a patient's health status, in addition to the traditional clinical endpoints of hospitalizations and mortality. Deficiencies in heart function coincide with a significant detriment to various aspects of a patient's quality of life and everyday function". However, there are not currently any validated questionnaires or surveys to collect for PPI or PRO related to hypertension.

6   Conclusion

Device-based therapies for treatment of hypertension are potentially very important new ways to treat a disease that is a major cause of morbidity and mortality in the U.S. However, careful consideration must be given to clinical trial design given the variability in trial results that have been observed so far and the many questions regarding device mechanism of action that remain unanswered. The Panel will be asked to provide specific comments on many important areas of clinical trial design to help guide sponsors, investigators and FDA in sorting out this complex field. The major questions to be posed to the panel are below. The Panel will be asked to discuss other key aspects of this field that they find relevant. Special attention should be focused on trying to define a reasonable pre-/post-market device investigational paradigm so that U.S. patients are afforded timely access to safe and effective devices for treatment of hypertension while at the same time encouraging further important investigational work in the device hypertension field.

7   FDA Questions

QUESTION #1. Indications and Labeling

   A. There is variability in the clinical etiology, hypertension definitions, and proposed patient demographics included in clinical studies of anti-hypertension devices. Please comment on the patient population that should be evaluated in these studies (e.g., resistant

hypertension, drug naïve). Please comment on whether the indications for use and labeling for approved devices should only reflect the studied population or include a broader population that may potentially benefit. For example, potential strategies for stratification could include specification of blood pressure goals or degree of medical hypertension control. Please also comment on the potential for post-market evaluation, including new enrollment trials and registries, to study clinically meaningful sub-populations that are not well-represented in the pivotal study.

B. Antihypertensive drugs are currently indicated for management of hypertension as sole therapeutic agents and/or in combination with other antihypertensive drugs for more severe forms of hypertension. Please discuss the role for device-based therapies (e.g., first-line or adjunctive therapy) for patients with hypertension, and how this should be reflected in the indications for use.

QUESTION #2. Clinical Study Design

A. Please discuss the necessity of including a sham group, with specific attention to balancing the type of information gained versus the potential risks of a sham procedure. Additionally, please comment on whether other control groups should be considered, particularly after the initial marketing approval for an anti-hypertensive device.

B. Please discuss the value of the "ON" and "OFF" medication studies to support an approval determination. Please comment on whether both study designs are needed after the proof-of-concept for that technology has been established and the first such device is approved.

C. To support enrollment, one option is to allow crossover of control patients to be treated with the device. However, crossover may reduce the ability to evaluate longer-term safety and durability of effectiveness of the device in comparison to the control. Please discuss the potential consequences of patient crossover, including the appropriate crossover time point and any effects on data interpretability.

QUESTION #3. Safety Endpoints

A. Although each device and treatment modality has its own specific risks, please identify the important adverse events that should be included as part of the primary and secondary safety endpoint(s), including the time of follow-up that balances capturing important safety information while maintaining a least burdensome approach. As part of your response, please also discuss the timing and modality for imaging studies to detect new-onset RAS for renal-directed therapies, and for major cardiovascular or neurovascular events for devices that target the carotid anatomy. Currently, FDA is recommending imaging at 12 months to evaluate RAS for renal therapies and at least 12 months to evaluate ipsilateral carotid stenosis and cerebral ischemia for therapies that target the carotid anatomy.

B. Please discuss the appropriate statistical methodology to evaluate the frequency and severity of adverse events, such as non-inferiority between trial arms or establishing a performance goal for the safety endpoint.

C. Please comment on any additional long-term safety endpoints that should be collected postmarket.

QUESTION #4. Effectiveness Endpoints

A. Currently, CDRH accepts a primary effectiveness endpoint of a reduction in ambulatory blood pressure for trials evaluating anti-HTN devices. Please discuss the acceptability of this surrogate endpoint and if the results from the cited BPLTTC series of prospective analyses are applicable to device-based treatments such that a reduction in blood pressure may be sufficiently correlated to long-term cardiovascular measures. Please also identify any additional clinically important endpoints that should be collected premarket and/or during the post-market period.

B. For trials in which reduction in blood pressure is the primary effectiveness endpoint, please address the following:
   i. Please discuss what constitutes a clinically meaningful magnitude of blood pressure reduction and time period necessary to support the durability of the device performance to establish a reasonable assurance of effectiveness to support a marketing application, while considering the ability to discern the device effect from concurrent antihypertensive medication use (e.g., after washout at 2-3 months post-treatment, at 12 months).
   ii. Given the clinically meaningful magnitude specified, please discuss the appropriate statistical comparison for effectiveness (e.g., super or simple superiority margin) as well as comment on how the recommendation comparisons would change after approval of the first anti-hypertension device (e.g., superiority or non-inferiority to a comparator device).
   iii. If no significant blood pressure drop is determined, please comment on the value of decreased drug number, type, and dose, and indicate potential statistical analysis methods to consider the impact of medication usage.

C. Considering observed issues with patient adherence to medication regimens, please discuss how adherence can be practically monitored during a device therapy trial. Please also discuss how to consider the impact of adherence in the final assessment of effectiveness.

QUESTION #5. Benefit-Risk Profile

A. Please identify additional factors important to patients (i.e., patient preference, tolerable risks) and how these should be incorporated into the evaluation and review of anti-hypertension devices. As part of the discussion, please consider the burden of drug adherence and the impact of side effects associated with current antihypertensive medications.

B. Please comment on the value of evaluating patient preference information (PPI) and patient-reported outcomes (PRO) for therapies for hypertension. Please identify important surveys or endpoints that may be used to capture PPI and PRO.

C. As particular device designs, procedures, and anatomical targets may carry specific associated risks and benefits, please identify any additional considerations to evaluate the listed device types:
   a. Sympathetic ablation
   b. Parasympathetic stimulation
   c. Implanted therapy
   d. Temporary wellness therapy

D. Please discuss any other issues that you think should be considered when designing and interpreting clinical studies involving evaluation of device-based hypertension treatment.

8 Recommended Literature

A. White WB, Galis ZS, Henegar J, Kandzari DE, Victor R, Sica D, et al. Renal denervation therapy for hypertension: pathways for moving development forward. J Am Soc Hypertens. 2015;9(5):341-50.

B. Ng FL, Saxena M, Mahfoud F, Pathak A, Lobo MD. Device-based Therapy for Hypertension. Curr Hypertens Rep. 2016;18(8):61.

C. Kandzari DE, Kario K, Mahfoud F, Cohen SA, Pilcher G, Pocock S, 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(1):82-91.

D. Mauri L, Kario K, Basile J, Daemen J, Davies J, Kirtane AJ, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs. Am Heart J. 2018;195:115-29.

E. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet. 2017;390(10108):2160-70.

F. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet. 2018;391(10137):2335-45.

G. Kandzari DE, Bohm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet. 2018;391(10137):2346-55.

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I. Kapil V, Sobotka PA, Lobo MD, Schmieder RE. Central arteriovenous anastomosis to treat resistant hypertension. Curr Opin Nephrol Hypertens. 2018;27(1):8-15.

J. Spiering W, Williams B, Van der Heyden J, van Kleef M, Lo R, Versmissen J, et al. Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle clinical study. Lancet. 2017;390(10113):2655-61.

K. Gassler JP, Bisognano JD. Baroreflex activation therapy in hypertension. J Hum Hypertens. 2014;28(8):469-74.