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Overview of the 2018 US Food and Drug Administration Circulatory System Devices Panel Meeting on Device-Based Therapies for hypertension

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1. Introduction

On December 5, 2018, the United States Food and Drug Administration (FDA) convened a meeting of the Circulatory System Devices Panel to discuss and make recommendations regarding issues related to the medical devices used in the management of hypertension [1]. Challenges associated with the design and execution of pre-market clinical trials and post-approval studies, along with indications and labeling of the device-based antihypertensive therapies, were discussed. The panel was asked to make recommendations regarding the target patient population, safety and efficacy endpoints of the trials, and factors important to patients and physicians regarding the benefits and risks associated with these novel devices. The complex physiology associated with blood pressure (BP) control provides an opportunity for the current clinical studies to focus on a variety of therapeutic targets, including renal denervation (with radiofrequency or ultrasound), and carotid baroreceptor amplification or hemodynamic modification, each of which is associated with its own benefit-risk profile.

Hypertension remains the leading preventable cause of myocardial infarction, stroke, and death worldwide [1,2]. Of patients treated for hypertension, over 50% do not achieve their target BP despite readily available drugs. Potential contributing factors include medication non-adherence, resistant hypertension, intolerance, therapeutic inertia, and patient comorbidities [1,2]. Device-based therapies offer these patients an adjunctive strategy to achieve lower BP. The FDA regulatory meeting provided an ideal platform to bring all the stakeholders together and offer a roadmap for future trials involving device-based therapies for hypertension. In this review, we provide highlights of the meeting, outlining the first- and second-generation clinical trials on renal denervation and other anatomical targets, currently available catheter-based technologies from Medtronic, ReCor Medical, ROX Medical, and Vascular Dynamics, for management of hypertension, FDA's questions to the panel, and a summary of the panel members' deliberations (Fig. 1).

2. Manufacturers' presentation of the published data

2.1. Symplicity devices

The Symplicity Spyral multi-electrode catheter (Medtronic, Galway, Ireland) and the Symplicity G3 (Medtronic, Minneapolis, Minnesota, USA) generator utilize four electrodes in spiral configuration delivering radiofrequency energy in a circumferential fashion and target the renal artery and branch vessels. Key Medtronic-sponsored trials assessing renal denervation therapy include Symplicity HTN-1, Symplicity HTN-2, Symplicity HTN-3, SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED [3–7] (Table 1). The Symplicity HTN-1 and Symplicity HTN-2 trials demonstrated significant and durable BP reduction attesting to the efficacy and safety of renal denervation [3,4]. However, Symplicity HTN-3, a sham-controlled trial, did not show a significant reduction of systolic BP in patients with resistant hypertension at 6 months after renal-artery denervation compared to sham control [5]. Subsequent post-hoc analyses of Symplicity HTN-3 from limited patient cohorts revealed several potential confounding factors that could explain the unexpected BP responses in both the sham and the treatment arms. These included patient selection bias, issues with medication adherence, and legitimate concerns as to whether the renal ablation procedure itself was suboptimal [8]. The SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED trials evaluated the safety and efficacy of renal denervation in non-medicated and medicated patients, respectively (with drug adherence testing), with mild to moderate hypertension and demonstrated larger BP reductions in the renal denervation group than in the sham group [6,7]. There were no major adverse events reported in either trial. Long-term data

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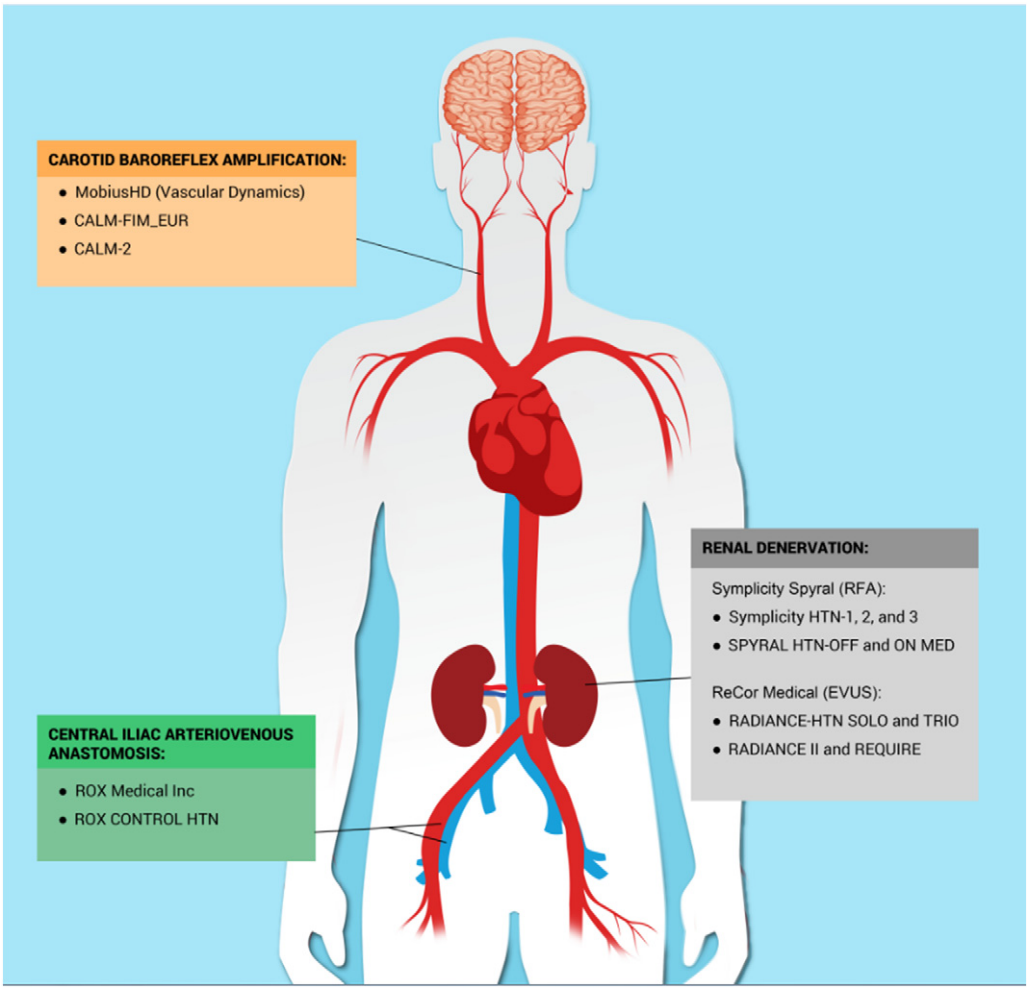

Fig. 1. Anatomical targets for device-based therapies for resistant hypertension with mechanism of action and major published or ongoing clinical trials. RFA: radiofrequency ablation, EVUS: endovascular ultrasound.

from the Global SYMPLICITY Registry (a prospective, open-label registry involving 196 active sites worldwide) have demonstrated safety and efficacy of renal denervation with significant and sustained office and ambulatory BP reductions out to 3 years [9]. The SPYRAL PIVOTAL – SPYRAL HTN-OFF MED Study is an ongoing clinical trial (NCT 02439749) of 433 patients evaluating renal denervation with the Symplicity Spyral multielectrode renal denervation system in patients with uncontrolled hypertension in the absence of antihypertensive medications [10].

2.2. Paradise renal denervation system

The Paradise Renal Denervation System (ReCor Medical, Palo Alto, California, USA) is placed percutaneously within the main renal artery and delivers ultrasound energy to perform targeted circumferential denervation of the renal sympathetic nerves with resultant reduction of BP. A central low-pressure, water-filled cooling balloon protects the renal arteries simultaneously. RADIANCE-HTN SOLO was a randomized sham-controlled trial analyzing the effects of the Paradise system compared to sham in hypertensive patients in the absence of antihypertensive medications [11]. Results demonstrated reduced ambulatory BP at 2 months with endovascular ultrasound renal denervation compared with the sham procedure. Six-month results of the trial demonstrated that the BP-lowering effects of endovascular ultrasound renal denervation were maintained despite fewer prescribed antihypertensive medications in the treatment group than in the sham group [12]. The RADIANCE-HTN TRIO (NCT02649426) (patients on ≥3 medications, n = 146) [13], RADIANCE II (NCT03614260) (US and Europe, n = 225) [14], and REQUIRE (NCT02918305) (Japan and Korea, n = 140) [15] are ongoing sham-controlled trials assessing the Paradise Renal Denervation System (Table 2).

2.3. ROX anastomotic coupler

The ROX Anastomotic Coupler (ROX Medical Inc., San Clemente, California, USA) is a novel nitinol coupler device that acts by the creation of a central iliac arteriovenous anastomosis (between the iliac artery and the vein) resulting in a significant reduction of BP. The ROX CONTROL HTN trial [16] evaluated the safety and efficacy of the device and demonstrated significant reductions in both office and ambulatory systolic and diastolic BP in patients treated with this device plus pharmacotherapy versus pharmacotherapy alone.

2.4. MobiusHD

EndoVascular Baroreflex Amplification (EVBA) lowers BP and may have potential applications for the treatment of resistant hypertension. MobiusHD (Vascular Dynamics, Mountain View, California, USA) is a self-expanding nitinol implant that reshapes the carotid sinus and increases arterial strain augmenting the baroreceptors signals to the central nervous system. The CALM-FIM_EUR study [17] prospectively assessed the impact of MobiusHD devices (implanted unilaterally in the internal carotid artery) in BP reduction in adults with resistant

Table 1
Summary of key clinical trials regarding device-based therapies for hypertension.

Study	Symplicity HTN-1 [3]	Symplicity HTN-2 [4]	Symplicity HTN-3 [5]	SPYRAL HTN-OFF MED [6]	SPYRAL HTN-ON MED [7]	RADIANCE-HTN SOLO [11]	ROX CONTROL HTN [16]	CALM-FIM_EUR [17]
Study design	Open label, cohort	Multicenter, prospective, randomized trial	Prospective, single-blind, randomized, sham-controlled trial	Multicenter, international, single-blind, randomized, sham-controlled trial	Multicenter, International, randomized, single-blind, sham-control trial	Multicenter, international, prospective, single-blind, randomized, sham-controlled trial	Multicenter, international, prospective, open-label randomized study	Multicenter, Prospective, first-in-human, open-label study
Study device	Symplicity (Ardian)	Symplicity (Ardian)	Symplicity (Medtronic)	Symplicity Spyral and Symplicity G3 (Medtronic)	Symplicity Spyral and Symplicity G3 (Medtronic)	Paradise (ReCor Medical)	ROX Anastomotic Coupler (ROX Medical Inc.)	MobiusHD (Vascular Dynamics)
Region	Australia and Europe	Europe, Australia, and New Zealand	United States	United States, Europe, Japan, and Australia	United States, Germany, Japan, United Kingdom, Australia, Austria, and Greece	United States, Europe	Europe	Europe
Year published	2009	2010	2014	2017	2018	2018	2017	2017
Interventional procedure	Renal denervation (RFA)	Renal denervation (RFA)	Renal denervation (RFA)	Renal denervation (RFA)	Renal denervation (RFA)	Renal denervation (EVUS)	Central iliac arteriovenous anastomosis	Carotid baroreflex amplification
Eligibility criteria	SBP ≥160 mm Hg on ≥3 anti-hypertensives (which includes a diuretic)	SBP ≥ 160 mm Hg (≥150 mm Hg in patients with T2DM) on ≥3 anti-hypertensives	SBP ≥160 mm Hg on ≥3 antihypertensives	SBP ≥ 150 mm Hg and <180 mm Hg, DBP ≥ 90 mm Hg, mean ABP (systolic) ≥140 and <170 mm Hg at second screening	SBP 150–180 mm Hg, DBP ≥ 90 mm Hg, 24 h ABP 140–170 mm Hg at second screening, 1–3 antihypertensives for at least 6 weeks	ABP ≥135/85 mm Hg and <170/105 mm Hg after a 4-week discontinuation of up to two antihypertensives	Baseline office SBP ≥140 mm Hg and average daytime ABP ≥135/85 mm Hg	SBP ≥160 mm Hg on ≥3 anti-hypertensives (which includes a diuretic)
Study population	45	106 Renal denervation = 52 Control = 54	535 Renal denervation = 364 Sham = 171	80 Renal denervation = 38 Sham = 42	80 Renal denervation = 38 Sham = 42	146 Renal denervation = 74 Sham = 72	42 in the intention-to-treat analysis at 6 months and 39 at 12 months	30
Primary endpoint	OBP and safety data before and at 1, 3, 6, 9, and 12 months after the procedure	Between-group change in SBP at 6 months	Between-group change in SBP at 6 months	Between-group change in 24 h blood pressure at 3 months	Between-group change in ABP at 6 months compared to the baseline	Between-group change in daytime ABP (systolic) at 2 months in the intention-to-treat population	OBP (systolic/diastolic) and mean 24-hour ABP	Mean OBP and mean ABP at 6 months
Results	Post procedure OBP reduced by −14/−10, −21/−10, −22/−11, −24/−11, and −27/−17 mm Hg at 1, 3, 6, 9, and 12 months, respectively	Between-group differences in blood pressure at 6 months were 33/11 mm Hg ($p < 0{\cdot}0001$)	No significant between-group difference in SBP at 6 months (−2.39 mm Hg difference, $p = 0.26$ for superiority with a margin of 5 mm Hg)	3 months between-group difference in 24 h SBP was −5.0 and −4.4 mm Hg for DBP favoring renal denervation	Between-group 6 months change in SBP (−6.8 mm Hg, $p = 0{\cdot}0205$), 24 h SBP (−7.4 mm Hg, $p = 0{\cdot}0051$), DBP (−3.5 mm Hg, $p = 0{\cdot}0478$), & 24 h DBP (−4.1 mm Hg, $p = 0{\cdot}0292$)	Between-group difference of −6·3 mm Hg, $p = 0{\cdot}0001$ in favor of renal denervation	OBP (systolic/diastolic) reduced by 25.1/20.8 mm Hg ($p < 0.0001$ for both). Mean 24-hour ABP reduced by 12.6/15.3 mm Hg ($p < 0.0001$ for both) post-coupler placement	Mean OBP reduced by 24/12 mm Hg and ABP by 21/12 mm Hg at 6 months
Complications	One renal artery dissection	No serious complications. No difference among groups regarding minor complications	No significant differences in safety between the two groups	No major complications in either group	No major safety events in either group	No major safety events in either group	14 patients (33%) developed ipsilateral venous stenosis; all treated successfully with venous stenting.	Five serious adverse events at 6 months
Device effective	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes

RFA: radiofrequency ablation, SBP: systolic blood pressure, DBP: diastolic blood pressure, OBP: office-based blood pressure, ABP: ambulatory blood pressure, EVUS: endovascular ultrasound.

Table 2
Summary of ongoing clinical trials regarding device-based therapies for hypertension.

Study	SPYRAL PIVOTAL - SPYRAL HTN-OFF MED Study [10]	RADIANCE-HTN TRIO [13]	RADIANCE II [14]	REQUIRE [15]	CALM-2 [18]
Study design	Multicenter, blinded, randomized, sham-controlled trial	Multicenter, blinded, randomized sham-controlled trial	Multicenter, blinded, randomized, sham-controlled trial	Multicenter, blinded, randomized, sham-controlled trial	Multicenter, blinded, randomized, sham-controlled trial
Study device	Symplicity (Metronic)	Paradise (ReCor Medical)	Paradise (ReCor Medical)	Paradise (ReCor Medical)	MobiusHD™ (Vascular Dynamics)
Region	Global	United States and Europe	United States and Europe	Japan and Korea	Global
Interventional procedure	Renal denervation	Renal denervation	Renal denervation	Renal denervation	Carotid baroreceptor amplification
Eligibility criteria	OBP (systolic) ≥150 mm Hg and <180 mm Hg and diastolic ≥90 mm Hg. 24-Hour ABP (systolic) ≥140 mm Hg and <170 mm Hg	OBP ≥ 140/90 mm Hg at screening visit; patient on ≥3 anti-hypertensives (which includes a diuretic)	OBP ≥ 140/90 mm Hg <180/120 mm Hg for at least 4 weeks on 0–2 classes of antihypertensives	OBP ≥ 150/90 mm Hg; patient on ≥3 anti-hypertensives	Mean 24-h ABP (systolic) ≥145 & ≤200 mm Hg for at least 8 weeks on a maximally tolerated GDMT consisting of up to 5 antihypertensives
Study population	433	146	225	140	300
Primary endpoint	Change in ABP (systolic) from baseline to 3-months	Daytime systolic ABP at 2 months	Daytime systolic ABP at 2 months	24-hour systolic ABP at 3 months	Change in mean 24-h ABP (systolic) from baseline to 180-day

OBP: office-based blood pressure, ABP: ambulatory blood pressure, GDMT: guideline directed medical therapy.

hypertension. Results from this study demonstrated substantial BP reduction with an acceptable safety profile. The CALM-2 pivotal study (NCT03179800) [18] is currently ongoing and plans to enroll 300 subjects.

3. FDA questions and panel's responses

The FDA, represented by Mr. Hiren Mistry and Dr. Douglas Silverstein, presented five questions to the panel [1].

3.1. Question 1: indications and labeling of devices

First, the panel was asked about the indications for use and labeling of the emerging medical devices, with a focus on renal denervation therapy for the management of resistant hypertension. Given the evolving definitions of hypertension in different practice guidelines (Seventh and Eighth Joint National Committee guidelines [19,20] and the 2017 American College of Cardiology/American Heart Association guidelines) [2], ethnic disparities in the prior landmark renal denervation trials (such as Symplicity HTN-3) [5], the FDA, moving forward, sought the panel's recommendations to outline a unifying definition of hypertension, therapeutic BP goals, and the target patient population (specific or broad).

3.2. Panel's response

The panel agreed that it would be reasonable to include a broad variety of hypertensive patients (drug-resistant, stage 2 hypertension, and a subset of drug-naïve) in the forthcoming studies. There was less enthusiasm from the panel regarding device-based therapies as the first-line indication for hypertension [1,6]. Data presented by the industry showed that only 20% to 25% of patients achieve adequate BP control with device therapy alone. However, in clinical trials, if some patients achieve optimal BP control with device therapy alone, then it could be considered for first-line therapy in select situations. Sub-analyses to evaluate the impact of device-based therapies across different age groups, genders, ethnicities, races, and socioeconomic factors with integration into pre-market and post-market studies were deemed valuable. It was emphasized that evaluation should include the effects of devices on long-term cardiovascular outcomes.

3.3. Question 2: clinical study design

The second question concerned the optimal clinical trial design needed to inform the sponsors, investigators, and the FDA to unravel this multifaceted field. The feasibility of including a sham group as a rigorous comparator arm while balancing the information it provides versus the risks posed by the sham procedure was addressed. An additional important factor influencing the outcomes of device-based therapies is medication non-adherence, and accordingly, the value of "on" versus "off" medication study designs was also considered. Indeed, the proof-of-concept "on" medication trials (SPYRAL HTN-ON MED and RADIANCE-HTN TRIO) [7,13] and the "off" medication trials (SPYRAL HTN-OFF MED and RADIANCE-HTN SOLO) [6,11] have recently highlighted this important issue in medicated and non-medicated patients, respectively. To support patient enrollment, the option of allowing a crossover of control patients, along with its potential consequences and effects on data interpretability, was also considered.

3.4. Panel's response

Regarding the clinical study design, the panel agreed that a sham-controlled design, whenever ethical and feasible, should be conducted. While comparison with an approved device was deemed appropriate, there was some concern of "noninferiority creep." The panel supported both the on- and off-medication trials given the unique information each provided. Designs with crossover before one year were not supported because of the difficulty with interpretation of the data as well as the need to assess the long-term cardiovascular outcomes with these devices.

3.5. Questions 3 and 4: safety and efficacy endpoint

For questions 3 and 4, the FDA requested the panel's opinion regarding the safety and efficacy endpoint(s) of the devices. The adverse events of antihypertensive catheter-based therapies are affected by the device design, anatomic targets (such as the carotid body or the renal nerve), and the technique applied. The panel was asked to identify important primary and secondary safety endpoints to be considered, the timing of follow-up, imaging modalities that should be used, and the post-market surveillance strategies for monitoring the long-term safety outcomes. In light of the previous pivotal trials and the Center for Devices and Radiological Health (CDRH) recommendations, the

reduction in ambulatory BP is accepted as a primary efficacy endpoint for evaluating novel antihypertension devices. Whether it is acceptable as a surrogate marker for assessing the long-term cardiovascular outcomes remains unknown. The FDA also stressed the importance of defining what constitutes a clinically meaningful reduction in BP and the appropriate statistical comparison for determining effectiveness (superiority, super-superiority, or non-inferiority to a comparator device with a clinically meaningful margin). The potential concern of patients' non-adherence to the medications, how this can be monitored and improved prospectively during the device trials, and how this will affect the final assessment of device efficacy outcomes were also discussed.

3.6. Panel's response

Device safety is an important consideration, and both intra-trial comparison and assessment against a performance goal were advocated. Close monitoring by the Data and Safety Monitoring Board (DSMB) was strongly encouraged for all ongoing and future studies. Nephrologists on the panel were asked to comment on the assessment of safety of renal denervation therapies. They suggested 6- and 12-month follow-up periods with imaging for evaluation of renal artery stenosis (RAS). While duplex ultrasound suffers from low sensitivity for detection of RAS, it was deemed an adequate initial screening tool. Although computed tomography (CT) and magnetic resonance angiography provide superior visualization of the renal vasculature, these modalities are associated with their own risks. It remains unclear what degree of RAS is deemed clinically significant, and in clinical practice, assessment of renal function is more important than the extent of stenosis itself. There are no commercially available biomarkers for RAS. While the estimated glomerular filtration rate (eGFR) is an imperfect tool for renal function assessment, the intra-patient slope of eGFR may provide some information regarding the effects of device therapy on renal function. For carotid device therapies, cerebrovascular imaging with CT and magnetic resonance imaging (MRI) before and at appropriate time intervals after the device therapy were recommended. The reduction in BP was agreed to be a clinically meaningful efficacy endpoint. A reduction of 5 to 7 mm Hg using ambulatory blood pressure monitoring (ABPM) was deemed an appropriate number for a regulatory proposal. While the literature usually reports office-based blood pressure (OBP), which is typically slightly higher than ABPM, the panel recognized that obtaining both values would be helpful to understand the association between OBP and ABPM. Given that the renal denervation therapies may have a delayed reduction in BP, the panel recommended at least a 12-month BP monitoring period to capture any late benefits. The panel noted that even if there is no reduction in BP with the device, some secondary endpoints would still offer valuable information, including a reduction in number, class, and dosage of drugs, nighttime BP, and the impact of patient demographics on BP reduction. Superiority testing between the test and control groups would be sufficient for most devices, with super-superiority employed if the risks are higher. The evaluation of newer devices against already approved devices could be done with non-inferiority testing. The panel advocated medication adherence testing with a minimally invasive and least burdensome method, with pill count deemed an ineffective method.

3.7. Questions 5: patients' perspectives and benefits-risk determination

Question 5 focused on the patient's perspective. Identification of factors that are important to patients (such as patient preference, tolerable risks, the burden of drug adherence, and the impact of adverse events on the quality of life) and incorporation of these factors into the evaluation and appraisal of antihypertension devices are crucial. The value of assessing patient preference information and patient-reported outcomes for antihypertensive therapies, as well as developing surveys to capture these endpoints, was also highlighted. Given the gamut of device designs and anatomical targets (such as sympathetic or parasympathetic stimulation and implanted therapies) each device may carry specific associated risks and benefits; thus, considerations concerning how to evaluate these individual device types were discussed. Lastly, post-market surveillance of devices provides important opportunities to gather supplementary clinical data and real-world evidence to identify long-term safety concerns. Striking a balance between pre-marketing strategies and the post-market analysis of device therapies while considering issues such as medication adherence and patient perspective will help achieve clinical equipoise.

3.8. Panel's response

The panel did not include any patient members but, rather, included a patients' representative. The patients' representative and the other panel members agreed that patients' perspectives need to be incorporated in a shared decision-making process. Written surveys designed to determine how patients decide between medications versus alternative therapies have demonstrated that 38% of patients not on medications would rather choose a single procedure (renal denervation) than drug therapy, whereas 28% on drug therapy would opt for a single procedure (NCT03548623) [21]. Additionally, more men and younger patients preferred a single interventional procedure, and those who preferred invasive therapy were more likely to experience adverse events and less likely to be adherent to their medications. The key challenge is identifying the ideal hypertensive patients who will benefit from device-based antihypertensive therapies, as not all patients are likely to be suitable for this approach. For benefit-risk assessment of the devices, patient preferences and impact on the quality of life are important considerations. Emphasis on the value of post-market studies was made because they can provide insights into the durability of the benefit as well as capture adverse events.

4. Conclusions

After promising outcomes from the earlier smaller trials on renal sympathetic denervation, the surprisingly negative results of the landmark Symplicity HTN-3 sham-controlled trial in 2014 were initially thought to be the nail in the coffin for renal denervation. This prompted discussion about confounding variables and reassessment of the study design and the procedure itself. Subsequently, the recent well-designed trials (SPYRAL HTN-ON MED, SPYRAL HTN-OFF MED, and RADIANCE-HTN SOLO) incorporating improved denervation technology have brought new life to the renal denervation world. Similarly, other novel therapies, including carotid baroreceptor amplification and hemodynamic modulation, have demonstrated encouraging results, prompting the FDA to reconsider device-based therapies for resistant hypertension. The FDA convened an advisory panel meeting to shed light on the previously published data and currently available technologies from the industry and speculate as to the future of this burgeoning technology. The overwhelming response from the panel members was supportive for device-based antihypertensive therapies, with alignment of industry and agency's objectives thus providing a vision for future clinical trials.

Panel members

The 2018 US Food and Drug Administration Circulatory System Devices Panel comprised the following members:

Richard A. Lange, MD; Joaquin Cigarroa, MD; John W. Hirshfeld, Jr., MD; Abdelmonem Afifi, PhD; David J. Slotwiner, MD; David Naftel, PhD; James C. Blankenship, MD; Jeffrey A. Brinker, MD; John C. Somberg, MD; Dan M. Meyer, MD; Karen Griffin, MD; Patrick H. Nachman, MD; Jamie P. Dwyer, Jr., MD; Frederick J. Kaskel, MD; Rachel Brummert; Cynthia Chauhan; Patricio Garcia, MPH, CDR, USPHS.

Declaration of Competing Interest

Toby Rogers: Consultant & Proctor: Medtronic; Proctor: Edwards Lifesciences.

Ron Waksman: Advisory Board: Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips Volcano, Pi-Cardia Ltd.; Consultant: Amgen, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips Volcano, Pi-Cardia Ltd.; Grant Support: AstraZeneca, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance.

All other authors: None.

References

[1] United States Food and Drug Administration Circulatory System Devices Panel Meeting. https://www.fda.gov/advisory-committees/advisory-committee-calendar/december-4-5-2018-circulatory-system-devices-panel-medical-devices-advisory-committee-meeting#event-materials. Accessed July 01, 2019.

[2] Whelton PK, Carey RM, Aronow WS, 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: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;138:e426-e483. 2017 Guidelines.

[3] Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009;373:1275–81.

[4] Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. Symplicity HTN-2 investigators. Lancet 2010;376:1903–9.

[5] Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. Bakris GL; SYMPLICITY HTN-3 investigators. A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014;370:1393–401.

[6] Townsend RR, Mahfoud F, Kandzari DE, 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;390:2160–70.

[7] Kandzari DE, Bohm M, Mahfoud F, 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;391:2346–55.

[8] Kandzari DE, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. Eur Heart J 2015;36:219–27.

[9] Mahfoud F, Böhm M, Schmieder R, et al. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. Eur Heart J 2019 Mar 21. pii: ehz118. doi: https://doi.org/10.1093/eurheartj/ehz118.

[10] SPYRAL PIVOTAL - SPYRAL HTN-OFF MED study. Available from: https://clinicaltrials.gov/ct2/show/NCT02439749. Accessed July 01, 2019.

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

[12] Azizi M, Schmieder RE, Mahfoud F, et al. Six-month results of treatment-blinded medication titration for hypertension control following randomization to endovascular ultrasound renal denervation or a sham procedure in the RADIANCE-HTN SOLO trial. Circulation. RADIANCE-HTN Investigators; 2019 Mar 17. https://doi.org/10.1161/CIRCULATIONAHA.119.040451.

[13] A study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN). https://clinicaltrials.gov/ct2/show/NCT02649426. Accessed July 01, 2019.

[14] The RADIANCE II pivotal study: a study of the ReCor Medical Paradise System in Stage II Hypertension (RADIANCE-II). https://clinicaltrials.gov/ct2/show/NCT03614260. Accessed July 01, 2019.

[15] Renal Denervation on Quality of 24-hr BP Control by Ultrasound In Resistant Hypertension (REQUIRE). https://clinicaltrials.gov/ct2/show/NCT02918305. Accessed July 01, 2019.

[16] Lobo MD, Ott C, Sobotka PA, Saxena M, Stanton A, Cockcroft JR, et al. Central iliac arteriovenous anastomosis for uncontrolled hypertension: one-year results from the ROX CONTROL HTN trial. Hypertension 2017;70:1099–105.

[17] 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;390:2655–61.

[18] Controlling and lowering blood pressure with the MobiusHD™ (CALM-2). https://clinicaltrials.gov/ct2/show/NCT03179800. Accessed July 01, 2019.

[19] Chobanian AV, Bakris GL, Black HR, et al. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206–52. JNC 7.

[20] James PA, Oparil S, Carter BL, 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;311:507–20. JNC 8.

[21] Patient preference in blood pressure therapy. https://clinicaltrials.gov/ct2/show/NCT03548623. Accessed July 01, 2019.