

## Resistant Hypertension Insights on Evaluation and Management in the Post-SPRINT (Systolic Blood Pressure Intervention Trial) Era

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High blood pressure (BP) is the leading risk factor for premature death and disability-adjusted life years in the world.<sup>1</sup> The development of a large pharmaceutical base from which to manage patients with hypertension in addition to many patient years of clinical trial experience have made it possible to successfully manage many of these patients. Nonetheless, many questions remain, particularly with respect to the optimal BP goal in the general population of hypertensive patients, patients with comorbidities like diabetes mellitus, and those with previous target organ damage such as stroke.

Recent meta-analyses confirm that lower systolic and diastolic BP levels are associated with substantial reductions in important health outcomes such as death, coronary heart disease, and stroke in general populations<sup>2,3</sup> and in patients with diabetes mellitus.<sup>4,5</sup> In contrast, the ACCORD study (Action to Control Cardiovascular Risk in Diabetes) failed to support the postulate that lower is better. The ACCORD trial tested a systolic BP goal of 120 mmHg versus 140 mmHg in type 2 diabetics with hypertension<sup>6</sup> and did not find a significant difference in the primary outcome, a composite of death and nonfatal heart attack and stroke. Similarly, the SPS3 trial (Secondary Prevention of Small Subcortical Strokes) evaluated BP goals in patients with a previous lacunar stroke testing a systolic goal of 130 to 149 mmHg versus <130 mmHg.<sup>7</sup> This trial also did not demonstrate significant reductions in ischemic stroke or intracranial hemorrhage in the more intensive-treated group. On the contrary, the SPRINT (Systolic Blood Pressure Intervention Trial) did show a significant improvement in the primary outcome, a pentad of heart attack, stroke, acute coronary syndrome, hospitalized heart failure, and cardiovascular death<sup>8</sup> in the intensive (<120 mmHg) versus standard (<140 mmHg) treatment groups.

Guideline committees have the charge of proposing goal BP values in patients with hypertension, despite the challenges attending the questions of optimal treatment goal, particularly with comorbidities. Irrespective of the proposed goal BP value, there are patients who do not achieve these goals despite usage of substantial amounts of medication. The SPRINT findings are provocative and suggest there is benefit in pursuing lower than currently advocated BP goals. In this review, we will address how SPRINT findings may prompt a re-evaluation of how we define resistant hypertension

(RHTN), how we measure BP in practice, what process are at play in those who do not achieve goal BP values, and what therapies we use to pursue lower BP goals.

### Definitions

Many terms have been used over the past decade to describe aspects of RHTN. The basic definition of drug RHTN consists of office, or clinic, systolic BPs of  $\geq 140$  mmHg, diastolic BPs of  $\geq 90$  mmHg, or an elevation of both, on at least 3 antihypertensive medications from different drug classes.<sup>9-11</sup> Pseudo-RHTN is characterized by patients who fulfill the definition of RHTN above, but have controlled BP by either home or ambulatory monitoring outside the office.<sup>12</sup> Uncontrolled hypertension is characterized by in-office and out-of-office BP values that are above normal.<sup>13</sup> Refractory hypertension is said to be present when patients take  $\geq 5$  antihypertensive and remain uncontrolled after evaluation by a hypertension center or specialist.<sup>14</sup> Optimally, the 3 drugs include a diuretic and all drugs are dosed at least at the midpoint of the dosing range for that drug. With the incorporation of the SPRINT findings into the next set of national guidelines, the definition of RHTN may be revised to a systolic BP of  $>130$  mmHg on 3 drugs. The definition of RHTN becomes more interesting in a patient with controlled BP on  $\geq 4$  antihypertensive agents or who fails to come under control when evaluated by a Hypertension Specialist or at a Hypertension Center. Moreover, if we enter a new era with a lower systolic BP goal, it will be important to review current thinking on process that underlie RHTN and clinical issues that constrain treatment, particularly the risks of hyperkalemia with aldosterone-inhibiting therapies. Terminology associated with RHTN is outlined in Table 1.

### Scope of the Problem

Estimating the prevalence of drug RHTN is fraught with at least 4 obstacles. First is the well-known finding that some people with in-office BPs in excess of 140/90 mmHg on a 3-drug regimen demonstrate ambulatory or in-home BPs that are within the range considered to be controlled. This seems to be the case in up to 12% of hypertensives on 3 drugs.<sup>12</sup> Second is the estimation of drug resistance prevalence using cohort data, where dosing and adherence are unknown, for example, in the National Health and Nutrition Examination Survey data.

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**Table 1. Terminology of Resistant Hypertension**

Term	No. of Antihypertensives	Office Blood Pressures	Comments
Drug resistant hypertension <sup>9</sup>	3–5	>140/>90 mm Hg	Drugs should be from separate classes, preferably including a diuretic
Controlled resistant hypertension <sup>9</sup>	≥4	<140/90 mm Hg	...
Refractory hypertension <sup>67</sup>	>5	>140/>90 mm Hg	Uncontrolled despite evaluation by a hypertension specialist or at a hypertension center
Apparent treatment resistant hypertension <sup>15</sup>	≥3	>140/>90 mm Hg	Assessment made in a cohort study drug dosage and adherence are unknown
Severe drug resistant hypertension <sup>68</sup>	≥3	>160 mm Hg systolic	Drugs should be from separate classes, preferably including a diuretic; confirmed by ABPM
Pseudo-resistant hypertension <sup>12</sup>	≥3	>140/>90 mm Hg	Out-of-office BP controlled as assessed by ABPM

ABPM indicates ambulatory blood pressure monitoring; and BP, blood pressure.

In such cases, the adjective apparent is appended to the term drug RHTN indicating some uncertainty in the prevalence estimate,<sup>15</sup> and estimates here are that up to 16% of hypertensive patients are apparently drug resistant. In other circumstances, particularly those centered in using a population attending a hypertension referral center, recent observations have uncovered substantial nonadherence to the prescribed regimen. For example, the investigation of Jung et al<sup>16</sup> in Germany found that among drug-resistant hypertensives who failed to come under control after optimizing their regimen, and who claimed to be taking their prescriptions, nearly half were nonadherent and of these 1 in 3 were taking nothing and 2 of 3 were taking some but not all of their prescribed medications. Finally, consideration of medication is the nonpersistence. Once prescribed a regimen of antihypertensive therapy, in some cases, people simply do not refill the prescription.<sup>17</sup> Although it is unclear how much white coat effect, insufficient detail on adherence or nonpersistence contributes to the prevalence estimate of true drug RHTN, it seems that between 2% and 5% of patients with hypertension likely fit the current definition.<sup>18,19</sup>

### Role of Measurement Technique

Over the past 15 years, data, mainly from Canada, have emphasized the importance of how, where, and by whom BP is assessed. With the disappearance of mercury-based sphygmomanometers, aneroid and oscillometric methods have risen to take the place of this previous standard. Large studies like SPRINT used an automated oscillometric office BP method that eliminates the need for a human to participate in an actual measurement and also reduces the white coat effect because automated oscillometric office BP does not require an operator to be present when the BP is taken. Compared with a reasonably well-done standard office-based BP, the use of an automated oscillometric office BP method will yield a systolic BP that is 7 to 10 mm Hg lower in the same patient, measured on the same day.<sup>20</sup>

Ambulatory BP monitoring (ABPM), although widely available since the 1980s, remains infrequently used in the United States largely because of reimbursement issues and often the limitation of reimbursement to its use for diagnosing white coat hypertension in an untreated patient whose office-based BP values are in the hypertensive range. ABPM often

differs from the American Heart Association–recommended method of assessment of BP<sup>21</sup> (eg, because it allows antecedent motion, is often done standing upright, may be done with a full bladder, typically uses the nondominant arm) yet it is more predictive of hypertension-related outcomes. The recent United States Preventive Services Task Force recommendation on using ABPM (or another out-of-office method to confirm an elevated BP) may move ABPM into a more frequently used method.<sup>22</sup> Moreover, ABPM is the only way to detect masked hypertension, characterized by BP elevations during daytime hours, or >24 hours, in patients whose in-office values are at goal.<sup>23</sup> Patients with masked hypertension have cardiovascular outcomes that approach those with uncontrolled hypertension<sup>24</sup> although they are currently under-recognized because of the infrequency of ABPM use in treated hypertensive patients.

Home BP measurements continue to gain in popularity. Home BP monitoring allows many more determinations than is possible in a typical office setting. The Call To Action outlined a reasonable plan for how to use home monitoring values to confirm either the presence of hypertension or the lack of control of BP in an outpatient setting.<sup>25</sup> Studies confirm the value of home monitoring to establish control of BP,<sup>26,27</sup> and also to engage the patient more in the management of their chronic condition. The main problems facing home BP measurement are the availability of many BP measuring devices that have never undergone a validation study to ensure that they accurately measure BP,<sup>28</sup> the profusion of apps that purport to measure BP on a smartphone without any cuff-based validation study supporting these claims,<sup>29</sup> and the short-term nature (often <1 year) of most studies that limit inference about relationship to target organ damage.<sup>30</sup>

In a patient with suspected drug RHTN where adherence is likely present, a significant portion will have BP controlled when measured by an out-of-the office technique. Common clinical features of drug RHTN are shown in Table 2. Before further testing is done, it is useful to confirm the presence of truly uncontrolled BP.

### Role of Medication Nonadherence and Nonpersistence

In addition to the study of Jung et al,<sup>16</sup> there is a large literature on nonadherence in hypertension, as is true for many

**Table 2. Salient Clinical Features of Resistant Hypertension**

Resistant hypertension is a common medical disorder, defined as the failure to achieve goal blood pressure despite 3 different antihypertensive medications at full dosages, one of which is a diuretic.
The pathogenesis of true resistant hypertension is multifactorial, but the 2 pivotal factors include volume excess and the myriad effects of aldosterone and MR signaling at the level of the vasculature and the kidney.
MRAs, especially spironolactone, have been demonstrated to be the most effective add-on drug for the treatment of resistant hypertension.
The risk of MRA-induced hyperkalemia is increased in patients with chronic kidney disease, diabetes mellitus, or elderly patients.
Despite their early promise, carotid baroreceptor stimulation, catheter-based renal denervation, and iliac vessel fistulae are not yet ready for clinical application in the management of resistant hypertension.

MR indicates mineralocorticoid receptor; and MRA, mineralocorticoid receptor antagonist.

chronic conditions, such as dyslipidemia<sup>31</sup> and diabetes mellitus.<sup>32</sup> The complexity of the regimens used, the presence of comorbidities that introduce additional pill-burden, and the lack of understanding about the long-term consequences of inadequate treatment for an often asymptomatic condition like hypertension contribute to nonadherence. The recent, comprehensive review by Hyman and Pavlik<sup>33</sup> underscores the remarkable range in the prevalence of nonadherence, ranging from as low as 7 to as high as 66%. At this time, there is little besides a phone call to the pharmacy to verify prescriptions are being filled, and the use of blood and urine sampling to detect analytes of antihypertensive drugs, to address the role of nonadherence or lack of persistence in hypertensive patients. Clinicians also need to be aware of patient behaviors such as taking medications only in the time immediately surrounding an office visit, which can lead to a false impression of controlled BP if the medications are stopped shortly after the clinic visit (Table 3).

### Conspirators in Drug RHTN

#### Aldosterone Excess

Several lines of evidence have demonstrated that aldosterone excess may play a role in the pathogenesis of RHTN. Gaddam et al<sup>34</sup> evaluated the characteristics of 279 consecutive patients with RHTN compared with 53 control subjects (with normotension or hypertension controlled by using 2 antihypertensive medications). They reported that plasma aldosterone, aldosterone:renin ratio, and 24-hour urine aldosterone values were higher, and plasma renin activity and serum potassium values were lower in patients with RHTN versus controls. Their findings implicate aldosterone excess as a common underlying cause of RHTN (Table 2).

#### Primary Aldosteronism and RHTN

Primary aldosteronism is particularly common in patients with RHTN, with a prevalence of 14% to 21%. Among 88 patients who were consecutively referred to the hypertension clinic of the University of Alabama at Birmingham, 18 patients (20%) were confirmed to have primary aldosteronism, based on a high 24-hour urinary aldosterone excretion (>12 µg/24h) paired with a suppressed plasma renin activity level (<1 ng/mL per hour) during a high-sodium diet (urinary sodium excretion >200 mEq/24h).<sup>35</sup> This high prevalence of primary aldosteronism in patients with moderate to severe hypertension has been confirmed in other prospective studies.<sup>36,37</sup>

### Obstructive Sleep Apnea and RHTN

Obstructive sleep apnea (OSA) is common in patients with RHTN.<sup>38,39</sup> In a prospective study on 41 patients with RHTN, 83% were diagnosed with OSA.<sup>40</sup> These results were confirmed by Pratt-Ubunama et al,<sup>41</sup> wherein the prevalence of OSA was determined to be 85% in a study involving 71 patients with RHTN. Increasing severity of OSA also is associated with difficulty to control hypertension. As a corollary, in an observational study on patients with RHTN and OSA, treatment of OSA with continuous positive airway pressure facilitated de-escalation of antihypertensive drug therapy (either by dose reduction or discontinuation of ≥1 drugs) in 71% of the study patients.<sup>42</sup>

Activation of the sympathetic nervous system plays a crucial role in the pathogenesis of hypertension in patients with OSA. OSA causes intermittent hypoxemia and increased upper airway resistance that can increase sympathetic nervous system activity,<sup>43</sup> elevate BP, and increase fluid retention. An open-label study provided preliminary evidence that treatment with a mineralocorticoid receptor antagonist (MRA) substantially reduced the severity of OSA.<sup>44</sup> Importantly, this treatment also reduced the BP of these patients.

Aldosterone seems to be the other significant player in this field. Increased aldosterone levels have been observed in OSA patients with RHTN.<sup>41</sup> The precise relationship of the association between OSA and aldosterone excess remains to be elucidated. Whether OSA results in aldosterone excess or aldosterone excess contributes to OSA, or another underlying

**Table 3. Causes of Resistant Hypertension**

Apparent resistant hypertension
Medication nonadherence
White coat hypertension
Pseudohypertension
True resistant hypertension
Associated factors
Medication and illicit drug use
Weight loss medicines
Herbal medicines
Illicit drugs (cocaine and methamphetamines)
Excessive alcohol consumption
Chronic kidney disease

factor (eg, obesity) promoting both aldosterone excess and OSA has not been clarified.

### Intravascular Volume Expansion

Gaddam et al<sup>34</sup> reported significantly higher brain and atrial natriuretic peptide levels in patients with RHTN compared with controls. These findings of higher brain and atrial natriuretic peptide levels despite widespread diuretic use are consistent with the interpretation that persistent intravascular volume expansion is an important cause of RHTN. This interpretation is consistent with findings by Taler et al<sup>45</sup> who reported that higher intravascular volumes as indexed by thoracic impedance predicted a favorable response to increased diuretic use in patients with RHTN. The Figure summarizes the multiple considerations in the evaluation and management of RHTN.

## Treatment of RHTN

### Lifestyle Changes

Among the standard 4 lifestyle measures recommended to patients with hypertension by JNC 7 (Joint National Committee's Seventh Report),<sup>46</sup> reducing sodium intake is the measure with the most evidence for potential benefit in RHTN. Reducing sodium intake directly influences BP in those with salt-sensitive hypertension, and reducing sodium intake also tends to embellish the effectiveness of most antihypertensive drugs. In the study of Pimenta et al,<sup>47</sup> the reduction of sodium intake from 250 mEq day to 50 mEq daily, for as little as 1 week on the diet, resulted in an office-based reduction of 23 mmHg in systolic BP and 9 mmHg in diastolic BP.

The ongoing TRIUMPH study (Lifestyle Interventions in Treatment-Resistant Hypertension; ClinicalTrials.gov NCT02342808) should provide more information on the use of lifestyle intervention such as exercise training, sodium reduction, and weight loss in RHTN.<sup>48</sup>

### Sleep Apnea

Among the lifestyle changes that do not fall within the categories of exercise, weight loss, sodium restriction, or alcohol reduction, treatment of OSA through the use of positive airway pressure has been used in the RHTN population. The HIPARCO study (Hypertension Arterial Refractaria. Control

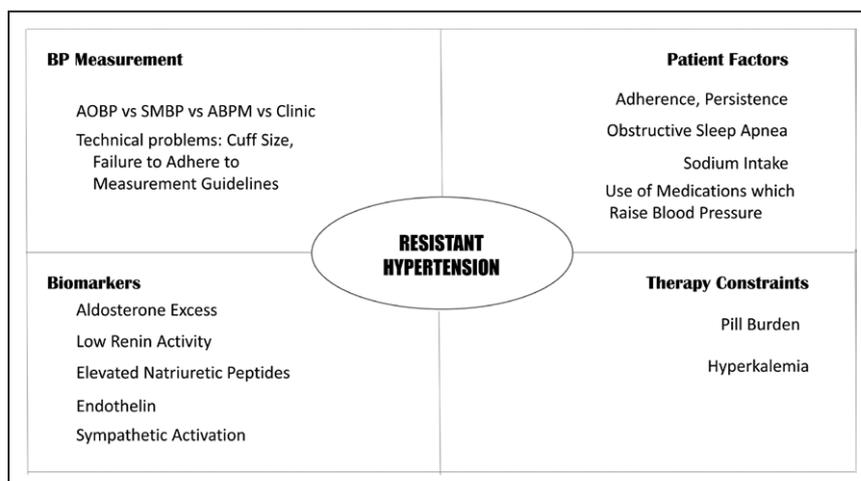
con CPAP) reported by Martinez-Garcia et al<sup>49</sup> noted a reduction in 24-hour mean and diastolic BP after 12 weeks of positive airway pressure, but this was in the range of a 3 mmHg. They also noted that the longer a patient tolerated positive airway pressure treatment, the greater the BP reduction. They did not observe a significant reduction in systolic BP in this study.

### Medication Treatment

In our experience, the majority of patients with RHTN, who are adherent with medication, respond best to changes in diuretic therapy. The SPRINT protocol ([www.sprintrtrial.org](http://www.sprintrtrial.org)) and the experience of many hypertension centers promoted the use of chlorthalidone as it is more potent and longer lasting than hydrochlorothiazide<sup>50</sup> and often add a MRA (covered more extensively below) or the epithelial sodium channel blocking diuretic amiloride.

A reasonable drug regimen in RHTN would include, in addition to a diuretic and an MRA (or amiloride), a drug blocking the renin-angiotensin system such as an angiotensin-converting enzyme-inhibitor or an angiotensin receptor blocking agent, along with a calcium antagonist. In some cases, additional therapy that reduces sympathetic nervous system effect, such as an  $\alpha$ -blocker, a  $\beta$ -blocker, or a drug, that combines both  $\alpha$ - and  $\beta$ -blockade can be useful.

The recent Optimal Treatment of Drug-Resistant Hypertension-PATHWAY2 study is the first randomized controlled trial to compare spironolactone with other BP-lowering drug treatments in patients with RHTN.<sup>51</sup> This double-blind, placebo-controlled, crossover trial randomized patients with seated clinic systolic BP  $\geq 140$  mmHg (or  $\geq 135$  mmHg for patients with diabetes mellitus) and home systolic BP (18 readings  $>4$  days)  $\geq 130$  mmHg, despite treatment for at least 3 months with maximally tolerated doses of 3 drugs. Patients rotated, in a preassigned, randomized order, through 12 weeks of once daily treatment with each of spironolactone (25–50 mg), bisoprolol (5–10 mg), doxazosin modified release (4–8 mg), and placebo, in addition to their baseline BP drugs. After screening, 285 patients received spironolactone, 282 doxazosin, 285 bisoprolol, and 274 placebo; 230 patients completed all treatment cycles. The average reduction in home systolic BP produced by spironolactone was superior to placebo, superior to the mean of the other 2 active treatments (doxazosin



**Figure.** Overview of concerns in resistant hypertension. ABPM indicates ambulatory blood pressure monitoring; AOBP, automated office blood pressure; BP, blood pressure; and SMBP, self-measured (home) blood pressure.

and bisoprolol), and superior when compared with the individual treatments.

Spironolactone was by far the most effective BP-lowering treatment for patients with RHTN. This was true in terms of the magnitude of the BP response, the proportion of patients achieving a stringent measure of BP control (home systolic BP <135 mmHg), and the proportion in whom it was more effective than either of the non-diuretic alternative drugs. The authors interpreted their findings to suggest that the predominant underlying pathophysiological cause of RHTN is sodium retention, despite existing baseline diuretic therapy.

### Mineralocorticoid Receptors and Their Antagonism: Rationale for MRA Treatment in RHTN

It is now widely appreciated that the traditional concepts governing aldosterone and the mineralocorticoid receptor (MR) are incomplete: aldosterone is merely one of the several physiological ligands for the MR, and although the sodium-retaining effects of aldosterone are clearly relevant in maintaining volume homeostasis in the setting of hypovolemia, aldosterone increases BP by diverse actions on the vasculature, the CNS, and by promoting baroreflex dysfunction.<sup>52</sup> A recent review by one of the authors summarizes a newer model for aldosterone and MR signaling, in which several pathways promote hypertension and cardiovascular and renal injury.<sup>53</sup> This model provides a rationale for developing a therapeutic framework encompassing MR antagonism for the management of hypertension, chronic kidney disease, and their attendant cardiovascular complications.

However, there are several caveats. First, the sodium balance of the patient modulates the effects of aldosterone.<sup>54,55</sup> A high sodium state enhances renal and cardiovascular injury and vascular inflammatory effects of MR activation. The presence of a local renal and cardiac autocrine or paracrine aldosterone system suggests that MR blockade could be effective in counteracting adverse cardiovascular effects and BP lowering even in the absence of raised plasma aldosterone.

### Hyperkalemia as a Constraint for Implementing MRA Therapy

The limiting effects of hyperkalemia in terms of use of a mineralocorticoid receptor antagonist (MRA) remain unsettled. Two recent studies have indicated that it is relatively common.<sup>56,57</sup> A recently published, comprehensive, retrospective analysis of a large electronic medical records database encompassing 201 655 patients assessed what happens to prescriptions for renin-angiotensin-aldosterone system (RAAS) inhibitors after hyperkalemia events.<sup>57</sup> A substantive portion of hyperkalemia events (serum potassium  $\geq 5.1$  mEq/L) was followed by discontinuation or downtitration of RAAS inhibitors. Recently, Chang et al<sup>56</sup> evaluated the association of anti-hypertensive medications and the prevalence of hyperkalemia in a large health system over a 3-year time period in 194 456 outpatients. Potassium levels of >5 mEq/L occurred in 10.8% of all patients. The most common medication changes were discontinuation/dose reduction of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. Chronic treatment with the new polymer resin potassium binders have

recently been demonstrated to lower serum potassium sufficiently for periods exceeding 52 weeks, thereby preventing downtitrations/discontinuations of RAAS inhibitors therapy because of hyperkalemia in this RHTN patient cohort.<sup>57</sup> In essence, they are enablers facilitating sustained MRA therapy.

### Device Management

Several devices are currently being studied to delineate their role in the management of hypertension including baroreceptor activation therapy, renal denervation, and an iliac artery-vein fistula.

### Baroreceptor Activation Therapy

Leveraging the carotid baroreceptors to manage hypertension was rekindled by the development of a baroreceptor stimulation system.<sup>58</sup> A large trial with a control group (ie, the device was implanted but not turned on for 6 months in 1 out of 3 participants) was undertaken in 265 patients with RHTN mainly the United States.<sup>59</sup> Although the trial met 3 of 5 end points, the 2 end points not met (superiority in 6-month BP reduction and the 30-day procedure-related safety issue) lead to a halt in US development. The estimated costs for implantation are  $\approx$ \$25 000 US, and practicality of this approach will likely improve with the smaller version (NEO), unilateral lead placement, and simpler electrode attachment.

### Renal Denervation

#### *Fundamental Neuroscience Platform*

The knowledge base for the development of catheter-based renal denervation (RDN) for treatment of RHTN is robust. The physiology and underlying experimental data strongly support RDN as a treatment for RHTN. Sympathetic overactivity clearly has a pivotal role in the pathophysiology of hypertension in both animal models and in patients. As detailed in several recent reviews,<sup>60,61</sup> disruption of the postganglionic efferent sympathetic nerves directed to the kidney modulates several antihypertensive mechanisms, particularly through the reduction of central sympathetic outflow.<sup>62</sup> Consequently, the BP lowering produced by adequate RDN is presumed to represent a summation of the effects of ablation of efferent and afferent renal nerves.

#### *Catheter Technology and Procedural Techniques*

The first-generation RDN catheter was designed to deliver low-level radiofrequency energy from the lumen of the renal arteries with the intent of producing a focal trans-mural burn to ablate the adventitial renal sympathetic nerves. Although the catheter was easy to maneuver, the exact positioning of burns was difficult with conventional fluoroscopic guidance. Other manufacturers resorted to a spiral design from the start with 4 electrodes spatially oriented so that a single activation would produce a 4 quadrant circumferential burn in a corkscrew pattern.<sup>63</sup>

A critical consideration for determining RDN success is the number of applications of radiofrequency energy within the renal arteries and administrations of radiofrequency energy to the distal renal artery, including in the renal artery divisions. A recent observation notes that a larger number of energy applications produces greater BP lowering.<sup>64</sup> The multielectrode denervation systems available now allow 4 ablations to be performed simultaneously with a single short

treatment time for each renal artery, thereby providing more complete ablations.

The costs of RDN are about ≈\$3000 US for the catheter, with additional costs of the catheterization laboratory and a 24-hour hospital stay. The procedure takes less than hour and has been deemed reasonably safe. Practicality will be enhanced if the current off-medication protocols convince clinicians and regulators that the procedure has clear effectiveness over conventional therapies.

Although the initial enthusiasm for RDN has been tempered, device-based treatment strategy remains a viable option worthy of further investigation. Whether RDN is superior to intensified pharmacological treatment remains to be determined. Of interest, Rosa et al<sup>65</sup> have recently published 12-month data from a randomized, multicenter study that compared the relative efficacy of RDN versus pharmacotherapy alone in patients with true RHTN and assessed the effect of spironolactone addition. They concluded that RDN in the settings of true RHTN with confirmed compliance is not superior to intensified pharmacological treatment. We anticipate that future randomized studies comparing RDN versus pharmacotherapy with MRA addition will define the role of RDN in the management of RHTN.

### Iliac Artery–Vein Fistula

Another novel, albeit exploratory, interventional approach to RHTN has been the creation of a 4-mm fistula between the iliac artery and the iliac vein.<sup>66</sup> In the first randomized controlled trial of this technology at 6 months, the intervention group showed a reduction in office systolic BP of 27 mm Hg compared with a fall of 4 mm Hg in the normal care group, corroborated by ABPM. The main adverse effect was unilateral leg edema from venous stenosis that developed 2 to 9 months later in 12 patients (27%) in the intervention group. This was managed successfully with stenting and venoplasty. The coupler device is estimated to cost ≈\$4500 US, along with catheterization unit costs and observation unit costs. It takes less than an hour to place and demonstrates immediate efficacy. Its practicality will likely improve as the procedure is modified to reduce the unilateral iliac vein stenosis.

Baroreflex activation therapy and the creation of the iliac fistula have immediate effects on BP, whereas RDN may take up to 3 months to before BP reduction occurs. Many countries have approved RDN; however, baroreceptor activation therapy and the iliac arteriovenous fistula therapy remain research-only techniques at this time.

### Summary

We have considered how the incorporation of the recently published SPRINT findings into the next set of hypertension guidelines may alter our approach to, and management of RHTN. Conceivably the definition of RHTN may be revised to a lower systolic BP goal while on treatment with 3 drugs. Achieving such a lower target BP is likely to require both optimizing drug therapy and complementary measures including reduction of sodium intake. Additional issues and management challenges raised by SPRINT are summarized in Table 4.

We have focused our discussion on the pathophysiology of RHTN and emphasizing the role of clinical issues that may

**Table 4. Future Questions to Address in Resistant Hypertension Post SPRINT (Systolic Blood Pressure Intervention Trial)**

Will the 3-drug definition move the boundary to 130 mm Hg systolic?
Will the definition of resistant hypertension incorporate the measurement technique?
Will new recommendations focus on lower goal BP in the office, and if so will they emphasize the value of using chlorthalidone and MRA to achieve goal BP?
In getting to a possibly lower goal systolic BP in the future, how much of a deterrent will potassium values in the upper range of normal be to using RAAS-blocking drugs, including MRAs, and will there be a role for using agents that bind potassium to facilitate this?

BP indicates blood pressure; MRA, mineralocorticoid receptor antagonist; and RAAS, renin–angiotensin–aldosterone system.

constitute barriers to treatment. Examples include our consideration of MRA-induced hyperkalemia and the emerging role of newer potassium-binding drugs that may obviate downtitration or discontinuation of RAAS inhibitors. To provide a balanced overview of management approaches, we also review briefly the potential of device-based interventions for lowering BP that are currently undergoing evaluation.

### Disclosures

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## Resistant Hypertension: Insights on Evaluation and Management in the Post-SPRINT (Systolic Blood Pressure Intervention Trial) Era

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