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STATE-OF-THE-ART PAPER

CME

Endovascular Treatment of Resistant and Uncontrolled Hypertension

Therapies on the Horizon

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CME Objective for This Article: At the end of this activity the reader should be able to: 1) discuss the epidemiology of uncontrolled and resistant hypertension; 2) explain the mechanism(s) for resistant hypertension; 3) list available endovascular technologies for treatment of resistant hypertension; 4) Outline the limitations of the current renal denervation technology (SYMPLICITY catheter).

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Endovascular Treatment of Resistant and Uncontrolled Hypertension

Therapies on the Horizon

The treatment of resistant hypertension has undergone remarkable advancements in recent years. Endovascular radio frequency renal sympathetic denervation (RSD) has shown initial success in treating resistant hypertension by targeting the connection between the brain and renal sympathetic nerves. However, the encouraging results of first-generation RSD have been tempered by important procedural limitations and a need for long-term results of safety and efficacy. In an effort to build on early clinical success, several second-generation RSD technologies are now being developed that may improve procedural safety and efficacy. Preliminary evidence for some of the latest technologies is now available. In this review, we summarize the current evidence in support of RSD and consider unique features of several new technologies that are likely to refine the endovascular treatment of resistant hypertension. (J Am Coll Cardiol Intv 2013;6:1–9) © 2013 by the American College of Cardiology Foundation

Among the estimated 76 million Americans with hypertension, over one-half have inadequately controlled blood pressure (BP) (1). This looming problem persists despite national public health efforts promoting awareness and achieving improved treatment rates (1). Over the past decade, new therapeutic options for uncontrolled and resistant hypertension (RH) that target the autonomic nervous system have become the focus of considerable medical interest. Renal sympathetic denervation (RSD) has stood out as an intriguing and potentially viable treatment option for RH, as was expertly reviewed in a previous issue of *JACC: Cardiovascular Interventions* (2). However, important limitations with available RSD treatments have provided an opportunity for novel technologies to improve on already impressive BP-lowering results.

Here we briefly review the societal impact of RH, elaborate on the evolution of treatment favoring use of autonomic modulation for RH, and explore various endovascular strategies that may strengthen therapeutic options against RH.

Scope of Resistant Hypertension

Resistant hypertension is defined as persistent elevation of BP above goal despite concurrent use of 3 antihypertensive agents, each of unique class with a diuretic included among the treatment regimen, and with all drugs at target dose (3). Hypertension that is controlled to goal levels using 4 or more medications is also considered resistant to treatment (3). From the 2003 to 2008 National Health and Nutrition Examination survey cycles, 12.8% of the U.S. adult hypertensive population met the strict definition for RH (4).

Even though RH accounts for a minor proportion of the overall hypertensive population, it serves as an alarming marker of increasingly more difficult BP control (5). Among adult Americans taking at least 3 medications, the rate of uncontrolled hypertension has risen from 15.9% (1988 to 1994) to 28.0% (2005 to 2008) (6), mirroring the rising prevalence of obesity from 23% (1988 to 1994) to 34% (2007 to 2008) (7). As the epidemic of obesity and diabetes grows, the prevalence of RH, and its associated costs are sure to rise. Whereas cost-effectiveness and durability of new RH therapies has yet to be determined, the concept of successful BP reduction among high-risk populations has garnered considerable enthusiasm for patients and providers.

Splanchnicectomy and the Basis for Renal Sympathetic Denervation

The basis for targeting the autonomic nervous system to treat RH was established decades ago. In 1938, hypertension had a 25% prevalence among Americans and carried a clear association with cardiovascular disease (8). Treatment was limited to a small number of sedative and antihypertensive drugs and radical surgeries, such as nephrectomy and surgical lysis of the autonomic nerves. Thoracolumbar splanchnicectomy was introduced as a treatment for hypertension, a particularly invasive surgical procedure involving resection of splanchnic innervation to the kidneys (9). The benefits of splanchnicectomy were confirmed in a large nonrandomized clinical trial that spanned nearly a decade from 1938 to 1947. The dramatic results of surgery were clear; for those treated surgically (n = 1,266) versus those declined for surgery and treated medically (n = 467), 5-year mortality rates were 19% and 54%, respectively (9). Furthermore, the BP-lowering result after surgery was durable. After a successful operation, some patients enjoyed BP-lowering results that extended up to 10 years or more. Nevertheless, as

medical treatments became increasingly available and effective, adverse surgical side effects and procedural risks relegated surgical splanchnicectomy out of favor.

Over the next 50 years, considerable research efforts contributed to a more refined understanding of the benefits of autonomic renal nerve modification. The kidneys are richly innervated with post-ganglionic sympathetic efferent fibers that associate with efferent and afferent renal arterioles, the juxtaglomerular apparatus, and the renal tubular system (10). Acute increase in efferent sympathetic nerve activity from the brain to the kidney results in renal vasoconstriction, renin release, and sodium retention (Fig. 1). When unchecked, excessive renal sympathetic efferent tone from the brain contributes to pathological hypertension through these mechanisms (Fig. 2) (11).

With recent advancements in technology, the concept of severing the brain-kidney connection to treat poorly controlled hypertension has undergone a revival. RSD targets the renal efferent and afferent sympathetic nerves, which lie in the adventitia of the arterial wall and are locally injured during the procedure, thereby reducing brain-kidney crosstalk and systolic BP. RSD has evolved into 3 unique strategies: radiofrequency ablation (RFA); ultrasonic ablation; and tissue-directed pharmacological ablation (Table 1). Most RSD technologies have been investigated among the RH population, although contemporary clinical studies have expanded application to a population with less-severe BP elevation that does not meet the strict definition of RH. Emerging preliminary results from small clinical trials provide encouraging signs that RSD for RH is rapidly advancing.

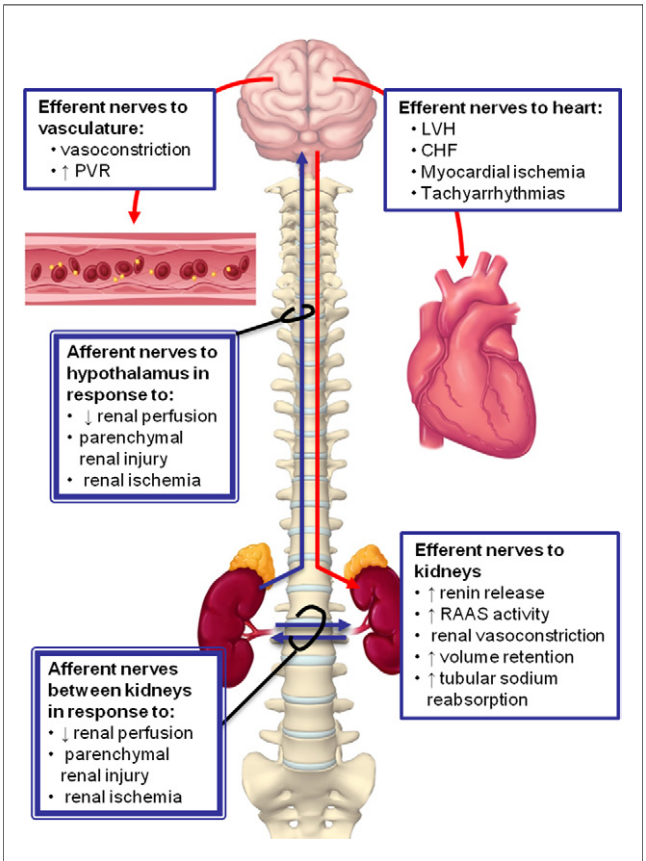

Figure 1. Pathways of Sympathetic Activity Leading to Hypertension

↑ = increased; ↓ = decreased; CHF = chronic heart failure; LVH = left ventricular hypertrophy; PVR = peripheral vascular resistance; RAAS = renin-angiotensin-aldosterone system.

Radiofrequency Ablation Technology

The feasibility of RFA for the renal nerves using a standard electrophysiology catheter has been applied and proven successful (12). However, proprietary systems specifically designed for RSD are most likely to maximize patient comfort, procedural safety, and efficacy, if not at greater costs. Several variations of RFA technology designed for RSD are under clinical study or are in development.

Symplicity renal denervation system. The Symplicity catheter system (Medtronic Inc., Minneapolis, Minnesota) uses a novel percutaneous single-electrode RFA catheter inserted sequentially into each renal artery that delivers ablative energy to the endoluminal surface. The Symplicity catheter system received CE (Conformité Européene) Mark approval in Europe (2010), although it remains investigational in the United States. The SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) trial is currently under way and will be pivotal for potential U.S. Food and Drug Administration approval of the device.

Abbreviations and Acronyms

BP = blood pressure
CE = Conformité Européene
EuroPCR = European Association for Percutaneous Cardiovascular Interventions
RFA = radiofrequency ablation
RH = resistant hypertension
RSD = renal sympathetic denervation

The SYMPLICITY HTN-1 (SYMPLICITY I: One-Year Results Following Sympathetic Renal Denervation in Refractory Hypertension) (13) and SYMPLICITY HTN-2 (Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension) (14) clinical trials evaluated the safety and effectiveness of RSD among an international cohort of patients with RH. The SYMPLICITY HTN-1 trial was a proof-of-principle, open-label, multicenter study of procedural safety and efficacy for RSD among patients with RH (13). The SYMPLICITY HTN-2 trial was a larger, randomized, efficacy study that built on the impressive results from SYMPLICITY HTN-1 (14). The results of these trials have been extensively reviewed elsewhere (2,15–18) and are summarized in Table 2. Important limitations of the Symplicity catheter system have provided opportunities for further improvement of RSD

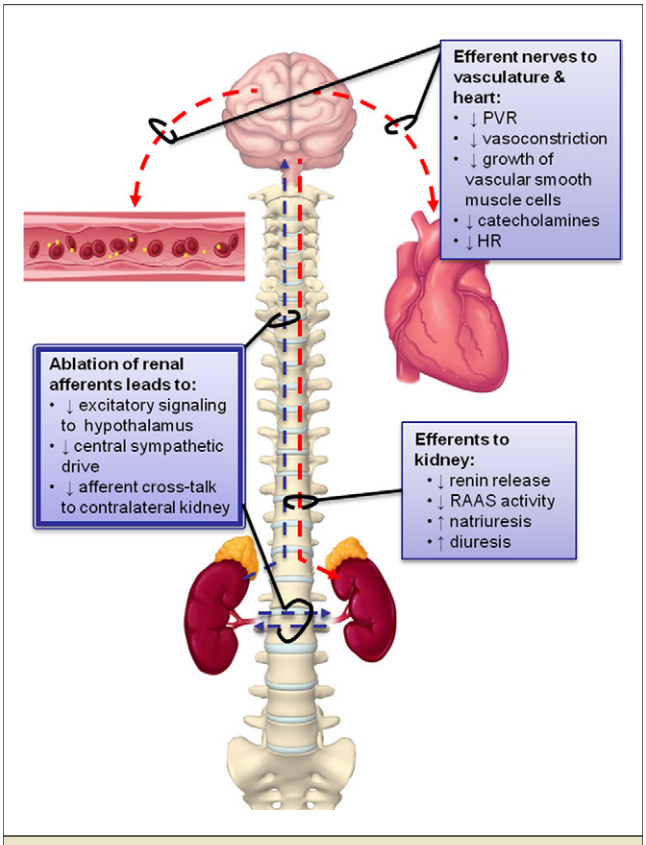

Figure 2. Proposed Pathways of Therapeutic Benefit of RSD

HR = heart rate; other abbreviations as in Figure 1.

application. These opportunities now drive emerging technologies focused on advancing the application of RSD.

Limitations of the SYMPLICITY HTN-1 and HTN-2 trials. Although the Symplicity catheter system has proven itself as an acceptably safe and effective treatment for RH, several aspects of the RSD procedure are likely to undergo optimization in the near future. Reducing procedural duration and exposure to painful endovascular RFA is a priority. Smaller delivery systems might expand application to a broader spectrum of patients; currently, the Symplicity catheter is not recommended for renal arteries <4 mm in diameter or those with <20 mm of longitudinal endoluminal surface accessible for ablation. Mapping of pre- and post-procedural renal nerve activity may provide confirmation of procedural success, thereby enhancing effectiveness and durability of RSD.

Periprocedural sedation is required for diffuse, visceral, nonradiating abdominal pain during denervation. The Symplicity procedure involves a series of 2-min ablations along the endoluminal surface of the artery (19). The initial procedure time reported in the SYMPLICITY HTN-1 trial was estimated at 40 min, although as experience has grown, procedural time continues to shrink. Reducing procedural time and exposure to painful ablation has been an important advance in newer technologies.

The Symplicity catheter system requires femoral arterial access to place a guiding catheter in the renal arteries through which the Symplicity catheter is advanced. In the SYMPLICITY HTN-1 trial, a single patient suffered renal artery dissection due to manipulation of the guiding catheter. Another patient developed a femoral pseudoaneurysm. From the SYMPLICITY HTN-2 trial, procedure-related adverse events included a single femoral artery pseudoaneurysm. Radial arterial access has become increasing popular for endovascular procedures owing to reduced rates of vascular complications. Radial access RSD may also facilitate cannulation of the renal arteries and improve procedural safety. Further advancements that might eliminate the need for a guiding catheter, which can have more aggressive angulations than the treatment catheter itself, might reduce procedure-related renal artery dissection.

Other acute, procedural complications that have been reported include intraprocedural bradycardia requiring atropine and post-procedural hypotension. Whereas these dramatic consequences of RSD likely indicate the abrupt effect of the procedure, the ablation of renal nerves might be best tolerated with a graded, gradual ablative effect. New technologies that provide biochemical ablation might enable such a strategy.

The short-term BP-lowering results from SYMPLICITY HTN-1 and HTN-2 are encouraging, although further evidence is needed to confirm the durability and long-term effectiveness of RSD. Among a small cohort of nonrandomized patients in the original SYMPLICITY HTN-1 cohort, 2- and 3-year results suggest the technology offers durable BP-lowering. Mean reduction in office-based BP at 2 years (n = 18) was −32/−14 mm Hg (20) and at 3 years (n = 24) was −33/−19 mm Hg (21). Nevertheless, 13% of SYMPLICITY HTN-1 patients had systolic BP reductions <10 mm Hg and were deemed nonresponders (13). Similarly, 10% of intervention patients had no decline in systolic BP in the SYMPLICITY HTN-2 trial (14). The ability to measure procedural success, perhaps via renal nerve monitoring, might enable identification of nonresponders to RSD. Such an alert might enable additional treatment acutely, or suggest alternative modalities to treat RH. Treatment of RH is likely to be advanced by further research that elaborates on appropriate patient selection and post-procedural indicators of efficacy.

EnligHTN multielectrode renal denervation system. The multielectrode basket design of the EnligHTN catheter (St. Jude Medical Inc., St. Paul, Minnesota) allows for simultaneous energy delivery to 4 sites along the endoluminal surface of the artery, with a potential benefit of reducing renal denervation procedural time. Shorter treatment time offers less RFA time and thereby reduced procedural pain for the patient, a known and common side effect of RSD as

Table 1. Overview of Clinical Trials Enrolling Hypertensive Patients for Endovascular Renal Nerve Ablation

Product Name	Product Design	Clinical Trial Name	Hypertension Type Studied	Trial Status	Clinical Trial ID	Sponsor
Radiofrequency ablation						
Symplicity RFA catheter	Single-electrode RFA catheter	SYMPLICITY HTN-1	Resistant	Active, not recruiting	NCT00664638	Medtronic Inc.
		SYMPLICITY HTN-2	Resistant	Active, not recruiting	NCT00888433	
		SYMPLICITY HTN-3	Resistant	Recruiting	NCT01418261	
		Effect of renal denervation on biological variables	Resistant	Recruiting	NCT01427049	
		Renal nerve ablation in CKD patients	Resistant, with Stage 3–5 CKD	Recruiting	NCT01442883	
		PRAGUE-15	Uncontrolled	Recruiting	NCT01560312	
		Renal denervation in patients with RH and OSA	Uncontrolled, with OSA	Recruiting	NCT01366625	
EnligHTN RFA catheter	Multielectrode RFA catheter	ARSENAL	Resistant	Active, not recruiting	NCT01438229	St. Jude, Inc.
Vessix V2 RFA catheter	Balloon-mounted RFA catheter	REDUCE-HTN	Resistant	Recruiting	NCT01541865	Vessix Vascular Inc.
OneShot RFA catheter	Irrigated, balloon-mounted RFA catheter	RAPID	Resistant	Recruiting	NCT01520506	Maya Medical Inc.
ThermoCool cryoablative catheter	Irrigated RFA catheter	SWAN HT	Uncontrolled	Recruiting	NCT01417221	Biosense Webster Inc.
		SAVE	Uncontrolled	Recruiting	NCT01628198	
		RELIEF	Uncontrolled	Recruiting	NCT01628172	
Chilli II cryoablative catheter	Irrigated RFA catheter	SAVE	Uncontrolled	Recruiting	NCT01628198	Boston Scientific Inc.
Ultrasonic ablation						
PARADISE ultrasonic catheter	Ultrasonic balloon catheter	REALISE	Resistant	Recruiting	NCT01529372	ReCor Medical Inc.
TIVUS ultrasonic catheter	Ultrasonic autoregulating balloon catheter	In development				Cardiosonic Ltd.
Kona medical ultrasonic system	Low-intensity external ultrasonic ablation system	In development				Kona Medical Inc.
Tissue-directed pharmacological ablation						
Bullfrog microinfusion catheter	Microneedle-equipped balloon catheter	In development				Mercator MedSystems Inc.

ARSENAL = Safety and Efficacy Study of Renal Artery Ablation in Resistant Hypertension Patients trial; CKD = chronic kidney disease; HTN = hypertension; OSA = obstructive sleep apnea; PARADISE = ReCor Percutaneous Renal Denervation System catheter; PRAGUE-15 = Renal Denervation in Refractory Hypertension trial; RAPID = Rapid Renal Sympathetic Denervation for Resistant Hypertension trial; REDUCE-HTN = Treatment of Resistant Hypertension Using a Radiofrequency Percutaneous Transluminal Angioplasty Catheter; RELIEF = Renal Sympathetic Denervation for the Management of Chronic Hypertension trial; REALISE = Renal Denervation by Ultrasound Transcatheter Emission trial; RFA = radiofrequency ablation; RH = resistant hypertension; SAVE = Impact of Renal Sympathetic Denervation on Chronic Hypertension study; SWAN HT = Renal Sympathetic Modification in Patients With Essential Hypertension study; SYMPLICITY HTN-1 = SYMPLICITY I: One-Year Results Following Sympathetic Renal Denervation in Refractory Hypertension trial; SYMPLICITY HTN-2 = Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension trial; SYMPLICITY HTN-3 = Renal Denervation in Patients With Uncontrolled Hypertension trial; TIVUS = therapeutic intravascular ultrasound.

described in the SYMPLICITY trials. The EnligHTN RFA catheter system recently received CE Mark approval (May 2012) on the basis of preliminary results of St. Jude's ongoing ARSENAL (Safety and Efficacy Study of Renal Artery Ablation in Resistant Hypertension Patients) trial. This prospective, open-label, feasibility study began enrolling in October 2011 at centers in Greece and Australia. Study completion is anticipated in March 2013 after enrollment and 6-month follow-up of 47 participants. Primary outcome measures are all adverse events and office-based BP. Exclusion criteria are similar to that of the SYMPLICITY trials. Preliminary results presented at the 2012 European Association for Percutaneous Cardiovascular Interventions (EuroPCR) meeting included 1-month mean office BP change of −28/−10 mm Hg from baseline, with 78% of patients having systolic BP reduction of >10 mm Hg (22). No serious complications were reported. Minor complications that were reported included procedure-related access site hematomas (n = 4), vasovagal responses with sheath removal (n = 3), and post-procedural bradycardia (n = 2).

Vessix V2 renal denervation system. The Vessix V2 renal denervation system (Vessix Vascular Inc., Laguna Hills, California) offers a unique, over-the-wire low-pressure balloon equipped with bipolar RFA electrodes attached to the balloon surface that is claimed to offer treatment times of 30 s. The balloon catheter also accommodates smaller arterial diameters (3.0 mm). The Vessix V2 balloon catheter system is currently being studied in the REDUCE-HTN

Table 2. Summary of the SYMPLICITY HTN-1 and SYMPLICITY HTN-2 Trials

	SYMPLICITY HTN-1 (13)	SYMPLICITY HTN-2 (14)
Study characteristics		
Study design	• Nonrandomized, cohort, unblinded to treatment	• Randomized control, unblinded to treatment
Enrollment period	• June 2007 to November 2008	• June 2009 to January 2010
Patient population	• 45 subjects* • Mean age: 58 ± 9 yrs; 96% white, 44% women, 31% diabetic • Mean BP (mm Hg) at enrollment: 177/101 (SD 20/15)	• 106 subjects (52 treated, 54 control)* • Mean age: 58 ± 12 yrs; 97% white, 42% women, 67% diabetic • Mean BP (mm Hg) at enrollment: treatment group: 178/97 (SD 18/16); control group: 178/98 (SD 16/17)
Inclusion criteria	• Office-based SBP ≥160 mm Hg, on ≥3 antihypertensive medications, including a diuretic or drug intolerance	• Office-based SBP ≥ 160 mm Hg (or diabetics with SBP ≥150 mm Hg), on ≥3 antihypertensive medications, including a diuretic or drug intolerance
Exclusion criteria	• Known secondary cause of hypertension (except OSA or CKD) • Type I diabetes mellitus • Pregnancy • Significant valvular heart disease • Existing PPM or ICD • Use of clonidine, moxonidine, rilmenidine, or warfarin • Renovascular abnormalities† • CKD with eGFR <45 ml/min/1.73 m^2	• Type I diabetes mellitus • Pregnancy • Significant valvular heart disease • Existing PPM or ICD • Use of clonidine, moxonidine, rilmenidine, or warfarin • Renovascular abnormalities† • CKD with eGFR <45 ml/min/1.73 m^2 • Contraindications to MRI • History of recent MI, USA, or CVA within 6 months of enrollment
Outcomes		
Primary	• Acute procedural and long-term safety • Mean reduction in office-based SBP at 12 months	• Between-group difference in office-based mean SBP at 6 months
Results		
Primary efficacy outcomes	Follow-up period, month(s) / Subjects available for follow-up analysis, n (%), N = 45 / Mean change in office-based BP SBP/DBP (mm Hg) / 95% CI	Follow-up period, month(s) / Mean change in BP SBP/DBP (mm Hg) / Follow-up period, month(s) / Mean change in BP SBP/DBP (mm Hg)
	1 / 41 (91) / −14/−10 / 4/3	1 / −20/−7 / 1 / 0/0
	3 / 39 (87) / −21/−10 / 7/4	3 / −24/−8 / 3 / −4/−2
	6 / 26 (58) / −22/−11 / 10/5	6 / −32/−12 (SD 23/11) / 6 / 1/0 (SD 21/10)
	9 / 20 (44) / −24/−11 / 9/5	Denervation group (N = 49)‡ / Control group (N = 51)‡
	12 / 9 (20) / −27/−17 / 16/11	
Periprocedural safety outcomes	• Renal artery dissection (n = 1) • Pseudoaneurysm at femoral artery access site (n = 1) • No long-term vascular complications observed with post-procedure imaging studies (n = 18 had repeat renal angiograms <30 days after treatment; n = 14 had MRA, n = 17 had CTA within 6 months after treatment)	• 7 of 52 (13%) required atropine for intraprocedural bradycardia • Among treated subjects: TIA (n = 1), angina requiring coronary stent (n = 1), hypotension (n = 1), hypertensive crisis (n = 1), hospital admission for nausea and vomiting "possibly related to hypertension" (n = 1) • Among control subjects, TIA (n = 2), angina requiring coronary stent (n = 1)
Nonresponders	• 6 of 45 (13%) had SBP reductions <10 mm Hg	• 5 of 49 (10%) treated subjects and 24 of 51 (47%) control subjects had no decline in SBP • 4 of 49 (8%) treated subjects and 6 of 51 (12%) control subjects had drug increases before 6-month follow-up

*Number of subjects that received treatment and included in study analysis; all subjects ≥18 years and were referred to centers of hypertension specialty care. †Renovascular abnormalities included renal artery stenosis, prior renal artery angioplasty, or dual renal arterial supply per kidney. Renal artery must be at least 4 mm in diameter and have at least 20 mm of longitudinal renal arterial dimension accessible for ablation. ‡Three patients lost to follow-up at 6 months in each group.

BP = blood pressure; CI = confidence interval; CVA = cerebrovascular accident; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; MRI = magnetic resonance imaging; PPM = permanent pacemaker; SBP = systolic blood pressure; USA = unstable angina; other abbreviations as in Table 1.

(Treatment of Resistant Hypertension Using a Radiofrequency Percutaneous Transluminal Angioplasty Catheter) study. REDUCE-HTN is an ongoing prospective, open-label, feasibility study that began enrollment in February 2012 throughout centers in Europe and Australia. Enrollment is estimated at 64 participants with study completion anticipated in August 2014. The primary outcome is acute procedural safety. Secondary efficacy outcomes of 6-month office-based and 24-h ambulatory BP assessment will also be performed. Preliminary results of REDUCE-HTN were presented at EuroPCR 2012. In 10 patients, the mean office-based BP was −30/−11 mm Hg below baseline BP (23).

OneShot renal denervation system. The RAPID (Rapid Renal Sympathetic Denervation for Resistant Hypertension) trial is a prospective, open-label, feasibility study that began enrollment in May 2012 throughout Europe and New Zealand. The OneShot catheter (Maya Medical Inc., Campbell, California) was unveiled at EuroPCR 2012 and uses an irrigated balloon catheter with a helical electrode on its surface, allowing a single-treatment approach. Estimated enrollment for the RAPID trial is 40 patients with systolic

BP ≥160 mm Hg, although it requires a specific renal artery diameter of 4 to 7 mm and a segment amendable to ablate of >20 mm. The primary outcome is chronic procedural safety and office-based systolic BP reduction >10 mm Hg at 6 months compared with baseline. Study completion is anticipated December 2013. The OneShot technology received CE Mark approval in February 2012.

ThermoCool renal sympathetic denervation system. The Celsius ThermoCool RFA catheter system (Biosense Webster Inc., Diamond Bar, California) uses a saline-irrigated catheter to ablate the endoluminal surface of the renal artery. The SWAN HT (Renal Sympathetic Modification in Patients With Essential Hypertension) study is an ongoing, prospective, nonrandomized, open-label, safety and efficacy trial evaluating the ThermoCool catheter in patients with essential hypertension (≥140/90 mm Hg). The study began enrollment in August 2011, has an anticipated enrollment of 800 patients, and a study completion date of August 2016. Results of a small pilot study using the same catheter in 10 patients with uncontrolled hypertension was recently published, demonstrating improvement in blood pressure while reducing markers of sympathetic activity (24).

In a separate study, the Celsius ThermoCool RFA catheter and the Chilli II irrigated RFA catheter (Boston Scientific Inc., San Jose, California) are being evaluated in the long-term safety and efficacy SAVE (Impact of Renal Sympathetic Denervation on Chronic Hypertension) study. Enrollment began in May 2012. The study is planned to include 500 patients with BP ≥140/90 mm Hg with an anticipated study completion of December 2019. The primary outcome is change in ambulatory BP at 6 months, which is unique from many other renal denervation studies that use office-based measures. Secondary outcome measures are planned through 48 months and include office-based BP, renal artery blood flow and dimension, renal function, and difference in number of total antihypertensive medications.

Despite its limitations, RFA of the renal sympathetic nerves currently leads the available technologies for the endovascular treatment of RH. As alternatives to painful RFA, ultrasonic and tissue-directed pharmacological RSD have been introduced with early but intriguing BP-lowering results that deserve consideration.

Ultrasonic Ablation Technology

Ultrasound-based RFA may play a role in sympathetic denervation, offering a more targeted injury pattern to the renal sympathetic nerves contained within the adventitia of the renal artery. A number of companies are pursing ultrasound ablative technology with various invasive approaches as well as a unique noninvasive system.

PARADISE catheter system. The PARADISE (ReCor Percutaneous Renal Denervation System) catheter (ReCor Medical Inc., Ronkonkoma, New York) uses a 6-F ultrasonic balloon catheter and self-centering transducer that delivers a proprietary energy algorithm to circumferentially ablate the renal sympathetic nerves. The ultrasonic sound waves emitted from the central core of the balloon produce frictional heating of soft tissues outside of the artery while the fluid-filled balloon cools the endoluminal surface of the artery. The REALISE (Renal Denervation by Ultrasound Transcatheter Emission) study is a single-arm, open-label, first-in-man feasibility study of the PARADISE catheter in 20 RH patients with a primary outcome of acute procedural safety. Secondary outcomes include 12-month change ambulatory BP and 12-month change in baseline antihypertensive medication intake. Preliminary data from 15 patients was presented at EuroPCR 2012, demonstrating office-based BP was reduced by an average of −32/−16 mm Hg over a 3-month follow-up (25).

Therapeutic intravascular ultrasound catheter system. The therapeutic intravascular ultrasound (TIVUS) system was developed as a high-intensity, nonfocused catheter-based ablation system (Cardiosonic Ltd., Tel Aviv, Israel). The TIVUS catheter is delivered into the renal artery over a 0.014-inch guidewire via a 6-F flexible sheath. The RFA source does not contact the arterial wall, enabling remote thermal energy delivery to the adventitia while sparing the endoluminal surface. The technology offers self-regulating safety technology that monitors local tissue temperature that prevents overtreatment if blood temperature becomes elevated.

Ultrasound-based treatment for hypertension. Kona Medical Inc. (Bellevue, Washington) is developing a noninvasive technology using low-intensity focused ultrasound that avoids many of the challenges of invasive endovascular intervention. The system is integrated with an external imaging-modality that identifies and monitors the treatment areas while delivering low-intensity ultrasonic energy with an external ultrasound probe. This system is in the pre-clinical phase of development. Given a noninvasive approach, if the Kona system proves successful, it is sure to generate considerable medical interest.

Tissue-Directed Pharmacological Ablation Technology

An alternate approach to induce renal sympathetic nerve injury may be achieved through the delivery of neurotoxins. Vincristine is a vinca alkaloid antineoplastic drug mainly used to treat acute leukemia, lymphomas, and some sarcomas. Vincristine also exhibits neurotoxic properties that may make the drug suitable for RSD using microinfusion catheter technology (26). In a swine model, successful sympathetic renal denervation using vincristine and the Bullfrog

microcatheter was presented at the 2011 meeting of Transcatheter Therapeutics in San Francisco (27).

Bullfrog microinfusion catheters. The Bullfrog microinfusion catheter (Mercator MedSystems Inc., San Leandro, California) was designed to inject therapeutic agents directly through the arterial wall and into the perivascular tissues. For renal denervation, the sympatholytic neurotoxin guanethidine has been studied for injection in the renal arteries. The U.S. Food and Drug Administration approved guanethidine in 1960 for the treatment of moderate-to-severe hypertension. When taken orally, guanethidine accumulates in low concentrations in the sympathetic nerves and reversibly interferes with the transmission of neural hormones, thereby decreasing BP. Given locally, guanethidine induces an autonomic denervation directly and through an immune-mediated pathway (28).

The Bullfrog catheter is equipped with a 130-μm microneedle and protective balloon system. The balloon catheter is guided and inflated at low expansion pressures (approximately 2 atm) within the renal artery to deploy the neurotoxin. As the balloon is inflated, the needle becomes unsheathed from the balloon and penetrates the vessel wall, allowing for perivascular delivery of the therapeutic agent. The Bullfrog catheter has U.S. Food and Drug Administration 510(k) clearance for medication delivery to the vessel wall and perivascular area.

Other Nonendovascular Autonomic Modulation Therapies

Baroreceptor activation therapy, spinal cord stimulation, and vagal-nerve stimulation represent novel and nonendovascular treatments against RH (29–31) and other sympathetically driven conditions, such as chronic heart failure, among others. Though beyond of the scope of this review, these nonendovascular therapies may complement or supplant some of the RSD therapies described herein. Because these non-RSD treatments generally require more invasive, elaborate procedures, the aforementioned percutaneous options may have more long-term appeal.

Conclusions

The results of SYMPLICITY HTN-3, ARSENAL, and other pivotal trials are sure to expand the possibilities for endovascular treatment of RH. Whereas emerging evidence from these small trials are encouraging, results from larger randomized clinical trials are needed to confirm procedural safety and durability before more widespread clinical application occurs. Those at high risk for RH-related cardiovascular complications are likely to gain the most from RSD, particularly if a positive impact on important clinical outcomes can be demonstrated. With further confirmatory evidence of procedural safety, patient selection, and therapeutic durability, RSD is sure to strengthen the treatment options for poorly controlled hypertension.

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