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Alcohol-Mediated Renal Denervation Using the Peregrine System Infusion Catheter for Treatment of Hypertension

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ABSTRACT

OBJECTIVES The aim of this multicenter, open-label trial was to evaluate the safety and efficacy of alcohol-mediated renal denervation using a novel catheter system (the Peregrine System Infusion Catheter) for the infusion of dehydrated alcohol as a neurolytic agent into the renal periarterial space.

BACKGROUND The number of hypertensive patients with uncontrolled blood pressure (BP) remains unacceptably low. The renal sympathetic nervous system has been identified as an attractive therapeutic target.

METHODS Forty-five patients with uncontrolled hypertension on ≥3 antihypertensive medications underwent bilateral renal denervation using the Peregrine Catheter with 0.6 ml alcohol infused per renal artery.

RESULTS All patients were treated as intended. Mean 24-h ambulatory BP reduction at 6 months versus baseline was −11 mm Hg (95% confidence interval [CI]: −15 to −7 mm Hg) for systolic BP and −7 mm Hg (95% CI: −9 to −4 mm Hg) for diastolic BP ($p < 0.001$ for both). Office systolic BP was reduced by −18/−10 mm Hg (95% CI: −25 to −12/−13 to −6 mm Hg) at 6 months. Antihypertensive medications were reduced in 23% and increased in 5% of patients at 6 months. Adherence to the antihypertensive regimen remained stable over time. The primary safety endpoint, defined as the absence of periprocedural major vascular complications, major bleeding, acute kidney injury, or death within 1 month, was met in 96% of patients (95% CI: 85% to 99%). Two patients had major adverse events of periprocedural access-site pseudoaneurysms, with major bleeding in one. There were no deaths or instances of myocardial infarction, stroke, transient ischemic attack, or renal artery stenosis. Transient microleaks were noted in 42% and 49% of the left and right main renal arteries, respectively. There were 2 cases of minor vessel dissection that resolved without treatment.

CONCLUSIONS Primary results from this trial suggest that alcohol-mediated renal denervation using the Peregrine Catheter safely reduces blood pressure and as such may represent a novel approach for the treatment of hypertension. (J Am Coll Cardiol Intv 2020;13:471-84) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ABPM = ambulatory blood pressure monitoring

AE = adverse event

BP = blood pressure

CI = confidence interval

CTA = computed tomographic angiography

eGFR = estimated glomerular filtration rate

RDN = renal denervation

RDUS = renal duplex ultrasound

TML = transient microleak

Hypertension remains the most common preventable risk factor for premature death and disability worldwide (1). However, the number of patients with blood pressure (BP) controlled to guideline-recommended target values remains low (2). The renal sympathetic nerves are involved in the development and maintenance of hypertension (3,4). Catheter-based renal denervation (RDN) is under investigation for the treatment of uncontrolled hypertension, with variable success (5). The first systems for RDN used radiofrequency energy (6–8) but systems using ultrasound (9) and alcohol injection have also been developed. The Peregrine Catheter delivers microdoses of dehydrated alcohol, a potent neurolytic agent, locally into the periadventitial space (10) of the renal artery to perform perivascular ablation of the afferent and efferent sympathetic nerve bundles (11,12). The exact length of the curved needles is approximately 3.5 mm, which is one-third of the cross-sectional area of a 0.014-inch coronary guidewire. Preclinical studies have shown that the Peregrine Catheter (Ablative Solutions, San Jose, California) is safe and effective at delivering dehydrated alcohol at all evaluated doses (0.15 to 0.6 ml/artery) (12). A first-in-human clinical trial was conducted using 0.3 ml of alcohol per renal artery for RDN in hypertensive patients (10). The current feasibility trial was planned to provide clinical data on the safety and efficacy of the infusion of a higher dose of dehydrated alcohol (i.e., 0.6 ml) in patients with uncontrolled hypertension taking 3 or more antihypertensive medications (at least 1 diuretic agent) using contemporary, state-of-the-art methodology of device-based hypertension trials.

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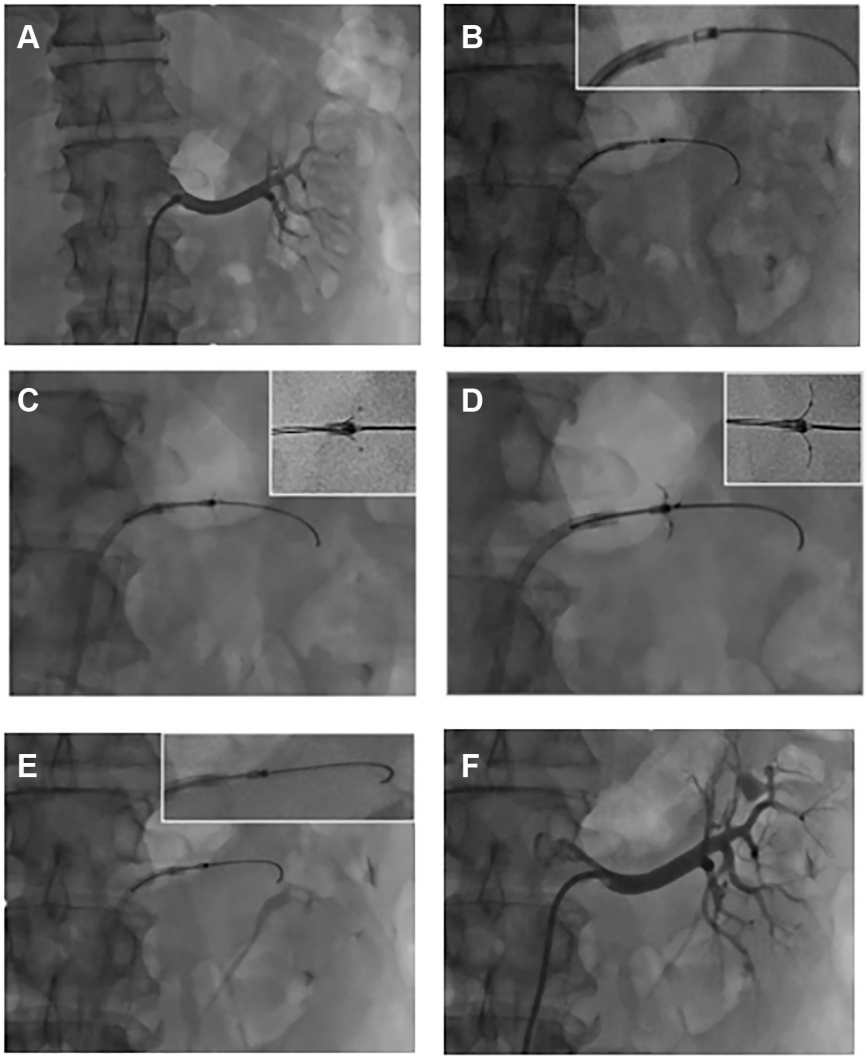
METHODS

This was a prospective, single-arm, open-label, multicenter trial intended to collect safety and efficacy data on the 3-needle-based delivery device, the Peregrine Catheter, to perform bilateral alcohol-mediated RDN in patients with hypertension with the use of a single 0.6-ml dose of alcohol per artery as the neurolytic agent. The trial was conducted at 9 research centers in Europe. Details of inclusion and exclusion criteria for this trial are provided in the Online Appendix (Online Table S1). All patients had uncontrolled hypertension, defined as mean office BP of ≥150/≥85 mm Hg, with a 24-h mean ambulatory systolic BP of ≥135 mm Hg while receiving a stable medication regimen of at least 3 antihypertensive medications of different classes (including a diuretic agent) for at least 4 consecutive weeks. Patients were included only if the renal artery diameter was ≥4 and ≤7 mm, with a renal artery length ≥5 mm. Accessory renal arteries with similar anatomy were also eligible. This trial is registered with ClinicalTrials.gov (NCT02570113).

ETHICAL STANDARDS. The trial was reviewed by the ethics committees of the participating centers and, if applicable, by the relevant competent authorities. This trial was conducted in conformity with the ethical principles stated in the Declaration of Helsinki, and all patients provided written informed consent. Safety was monitored by a data and safety monitoring board. Primary safety endpoints, including major adverse events (AEs) and serious AEs, were reviewed and adjudicated by an independent clinical events committee composed minimally of 2 independent physicians experienced with clinical trials in RDN.

CLINICAL AND LABORATORY ASSESSMENTS PERFORMED. Baseline assessments included collection of medical history, antihypertensive medication use, physical examination, electrocardiographic results, blood and urine tests, office BP, and 24-h ambulatory BP monitoring (ABPM). Clinical and laboratory follow-up data were obtained from patients in the hospital, at 7 days, and at 1, 3, and 6 months after bilateral RDN. Additional follow-up is ongoing to collect data at 12-month follow-up, prior to patients' end-of-trial participation. Laboratory measurements included routine blood chemistry, serum albumin, creatinine, estimated glomerular filtration rate (eGFR) calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula, liver function tests, cystatin C, and urine analysis. Office systolic and diastolic BPs at each visit were reported as the mean of 3 consecutive BP readings, taken seated and 1 to 3 min apart, and performed by a registered nurse or physician using an Omron BP monitor (Omron 705IT with printer, Omron, Kyoto, Japan). The ABPM devices (Spacelabs Healthcare Monitor, Spacelabs Healthcare, Snoqualmie, Washington) recorded BP every 30 min for 24 h, and a core laboratory (ERT, St. Louis, Missouri) collected, validated, and calculated the 24-h mean ambulatory systolic and diastolic BPs. On the basis of patients' recorded sleep and waking times, mean daytime and nighttime ambulatory systolic and diastolic BPs were calculated by the core laboratory. Antihypertensive medication use and doses were recorded at baseline and at 1, 3, and 6 months post-procedure. Urine samples from baseline (pre-procedure) and follow-up were tested at a

FIGURE 1 Angiographic Images Showing RDN With the Peregrine Catheter



(A) Pre-procedural angiogram. **(B)** Peregrine Catheter inserted in the renal artery. **(C)** Guide tube deployed. **(D)** Microneedles deployed. **(E)** Microneedles and guide tubes retracted. **(F)** Post-procedural angiogram.

specialized central core laboratory (SYNLAB, Lucerne, Switzerland) to monitor adherence to the antihypertensive medication regimen by assessment of antihypertensive drugs or their metabolites. Samples were assessed using high-performance liquid chromatography/mass spectrometry.

IMAGING. Renal duplex ultrasound (RDUS) was performed on all patients at baseline and 6 months to determine the presence of potential flow-limiting stenosis (VasCore, Boston, Massachusetts). Imaging by magnetic resonance angiography or computed tomography angiography (CTA) was performed for baseline assessment of existing anatomic abnormalities of the renal arteries. At 6-month follow-up, the vascular safety of the first 20 patients was assessed using renal magnetic resonance angiography or CTA and compared with baseline images. No safety concerns were identified, and therefore subsequent patients were assessed using RDUS to reduce the amount of exposure to contrast. Images were assessed by an independent core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University, Stanford, California).

PROCEDURE. A 7-F guiding catheter was first introduced into both renal arteries via the femoral artery using fluoroscopic guidance. The procedure was performed without the administration of general anesthesia and with minimal conscious sedation. **Figure 1** shows angiographic images capturing various stages of the RDN procedure using the Peregrine Catheter. Needle penetration occurred ≥4 mm distal from the renal artery ostium and >1 mm away from any branches of the vessel. Interventionists were advised to treat the mid segment of the main renal artery. The neurolytic agent (0.6 ml of undiluted alcohol) was infused over 2 to 3 min through the central lumen of the catheter to reduce pain during the infusion and to enhance diffuse spread of the alcohol. After treatment of 1 renal artery, the device was removed, inspected for patency, and flushed with heparinized saline. The contralateral renal artery was then engaged, and the same procedure was performed. The patients were queried about pain level and/or discomfort experienced immediately before and during each alcohol infusion. Pain was scored on a visual scale from 0 (no pain) to 10 (worst pain). If patients reported procedure-related pain of >5 in severity, the assessment was repeated 2 min post-infusion, and pain medications were given as needed. Angiographic images were obtained post-infusion to identify any vascular events related to the device or the intervention (i.e., spasm, dissection, or perforation).

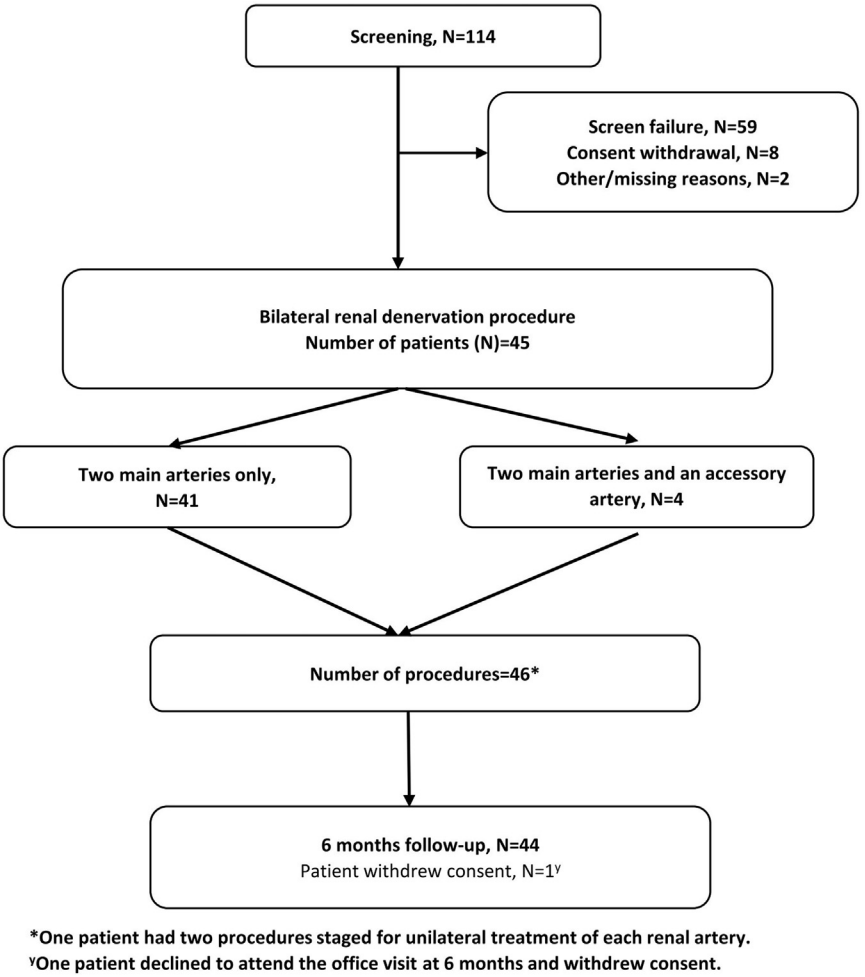
ENDPOINTS. Primary safety endpoints included the absence of any peri-procedural major vascular complications, major bleeding as defined by the TIMI (Thrombolysis In Myocardial Infarction) bleeding classification, acute kidney injury (per the modified risk, injury, failure, loss of kidney function, and end-stage kidney disease criteria) (13), or death within 1 month of the procedure. The primary efficacy endpoint was defined as reduction of 24-h mean ambulatory systolic BP at 6 months versus baseline. Secondary safety endpoints included stroke, myocardial infarction, or transient ischemic attack within 1 month of procedure and any renal artery stenosis (>60%), deterioration in renal function (>25% decline in eGFR, change in serum creatinine levels), and major AEs within 6 months of procedure, including death, end-stage renal failure, embolic events, adverse vascular events, or cardiovascular complications. Secondary efficacy endpoints included office BP, 24-h mean ambulatory diastolic BP, daytime and nighttime ambulatory BPs, changes in antihypertensive medications, and renal function laboratory parameters (eGFR, albuminuria, serum creatinine, and cystatin C), evaluated at 1, 3, and 6 months compared with baseline.

STATISTICAL ANALYSIS. Data were summarized using descriptive statistics. Continuous variables are expressed as mean ± SD and categorical variables as percentages by categories. If the distribution of a continuous variable was suspected to be skewed, the median and interquartile range are presented. When applicable, the baseline value was defined as the last value collected prior to the procedure. The trial was not powered for formal hypothesis testing. The number of patients needed to establish trial device feasibility was informed by the sample sizes in similar feasibility studies assessing continuous endpoints (14). Forty-five patients was considered an appropriate sample size for this feasibility trial and in accordance with available recommendations (15). P values and 95% confidence intervals (CIs), when presented, are intended to be descriptive in nature and informative only. For binary variables, CIs were calculated using exact binomial methods. For continuous variables, the CI of the mean was constructed using the normal approximation. For normally distributed continuous data, the p value for change from baseline was calculated using a paired Student's *t*-test. Predictors of response were explored using logistic regression, and the associated p values are presented. In post hoc sensitivity analyses, changes in BP were also explored relative to medication adherence using generalized linear models. A p value of <0.05 was considered to indicate statistical significance, without adjustment for multiplicity. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENT AND PROCEDURAL CHARACTERISTICS. A flow diagram for the trial is presented in **Figure 2**, and patient demographic data and medical histories are summarized in **Table 1**. A total of 114 patients were enrolled, and 45 patients were treated after undergoing a minimum 4-week screening period with no changes in antihypertensive medications. Among treated patients, 62% were men, with a mean age of 55 ± 10 years, a mean body mass index of 30.7 ± 5.8 kg/m^2, and a mean eGFR of 85 ± 16 ml/min/1.73 m^2. Baseline office BP was 169/99 ± 15/13 mm Hg, with a 24-h mean ambulatory BP of 151/89 ± 14/12 mm Hg. Patients were treated with an average of 5.1 ± 1.5 antihypertensive drugs at baseline. All patients, except 1, underwent bilateral RDN performed in a single procedure. One patient underwent 2 procedures for unilateral

FIGURE 2 Schematic of the Flow of Patient Enrollment and Follow-Up



Flow diagram showing the flow of patients in the clinical trial through the selection process, treatment procedure, and follow-up.

treatment of each main renal artery (because of difficulties in accessing the contralateral renal artery and to avoid extended exposure of the patient to contrast and radiation), and 4 patients had 1 accessory artery treated in addition to the 2 main renal arteries. A total of 94 renal arteries in 45 patients were therefore treated in 46 procedures. All 45 patients in this trial were successfully treated with the Peregrine Catheter (100% [45 of 45 patients]); all 46 procedures were completed (100% [46 of 46 procedures]) with a mean treatment time (infusion catheter insertion to time of retraction) of 7 ± 3 min/artery (**Table 2**). Details on procedural and device success are provided in the Online Appendix (Online Table S2). Total procedure time (from femoral artery access to sheath removal) was 49 ± 21 min (range 22 to 135 min). Pain during alcohol infusion was assessed as "mild" or "no pain" (pain score 0 to 5) in 57% of the arteries for which pain assessment was recorded and as "moderate" to "severe" (pain score >5) in 43%. Approximately 36% of patients received pain medication or sedation for 26% of the arteries treated. In all cases, pain had spontaneously diminished after 2 min. Immediately after retraction of the microneedles and guide tubes, minimal leaks from the needle puncture site were monitored on post-infusion angiography. Resolution of the leaks was confirmed by additional angiography performed at least 2 min after initial angiography. Procedural angiographic images were reviewed and analyzed by the core laboratory, and transient microleaks (TMLs) (notable extravasation of contrast medium at needle puncture sites that disappeared within

TABLE 1 Patient Demographics and Medical and Surgical History (N = 45)

Age, yrs	55.2 ± 9.7
Male	62
BMI, kg/m^2	30.7 ± 5.8
eGFR (CKD-EPI formula), ml/min/1.73 m^2	85 ± 16
Chronic kidney disease (eGFR <60 ml/min/1.73 m^2)	2
Type 2 diabetes	33
Hyperlipidemia	49
Coronary artery disease	9
Peripheral vascular occlusive disease	7
Heart failure	4
Prior myocardial infarction	4
Cerebrovascular accident/transient ischemic attack	7
Office systolic/diastolic BP, mm Hg	169/99 ± 15/13
Ambulatory systolic/diastolic BP, mm Hg	151/89 ± 14/12
Mean number of antihypertensive medications	5.1 ± 1.5
Medication class	
ACE inhibitor	29
Angiotensin 2 receptor blocker	73
Calcium channel blocker	82
Diuretic agent	98
Spironolactone	42
Beta-blocker	76
Centrally acting alpha agonist	44
Direct acting vasodilator	29
Renin inhibitor	4
Other	9

Values are mean ± SD or %.

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate.

2 min) were documented in 42% of the left renal arteries and in 49% of the right renal arteries. Resolution of TMLs was confirmed within 5 to 10 min in 26 of 40 renal arteries. Reassessment angiography to identify resolution of TML was not performed in 14 of 40 renal arteries, as the interventionist judged the changes as minimal. There were no vessel perforations or tears requiring intervention or persistent spasms observed in any of the vessels treated. Three device-related AEs were reported by the site investigators: 1 case of procedural pain that resolved with medication and 2 cases of minor vessel dissection that resolved without treatment. One renal artery dissection was secondary to a user error (classified as a device deficiency) and was assessed as resolved without sequelae at 6 months, as confirmed by CTA. The second renal artery dissection was reported by the site after core laboratory review of the procedural angiographic images; it resolved immediately without treatment and was assessed as not clinically significant. There were 5 device deficiencies reported; 1 device deficiency identified as operator error (removal of the device with the needles deployed) led to 1 of the AEs of minor vessel dissection. The other 4 deficiencies occurred with the devices outside the body and did not affect patients' safety. None of these device deficiencies required catheter design change but rather an update to the instructions for use and training materials.

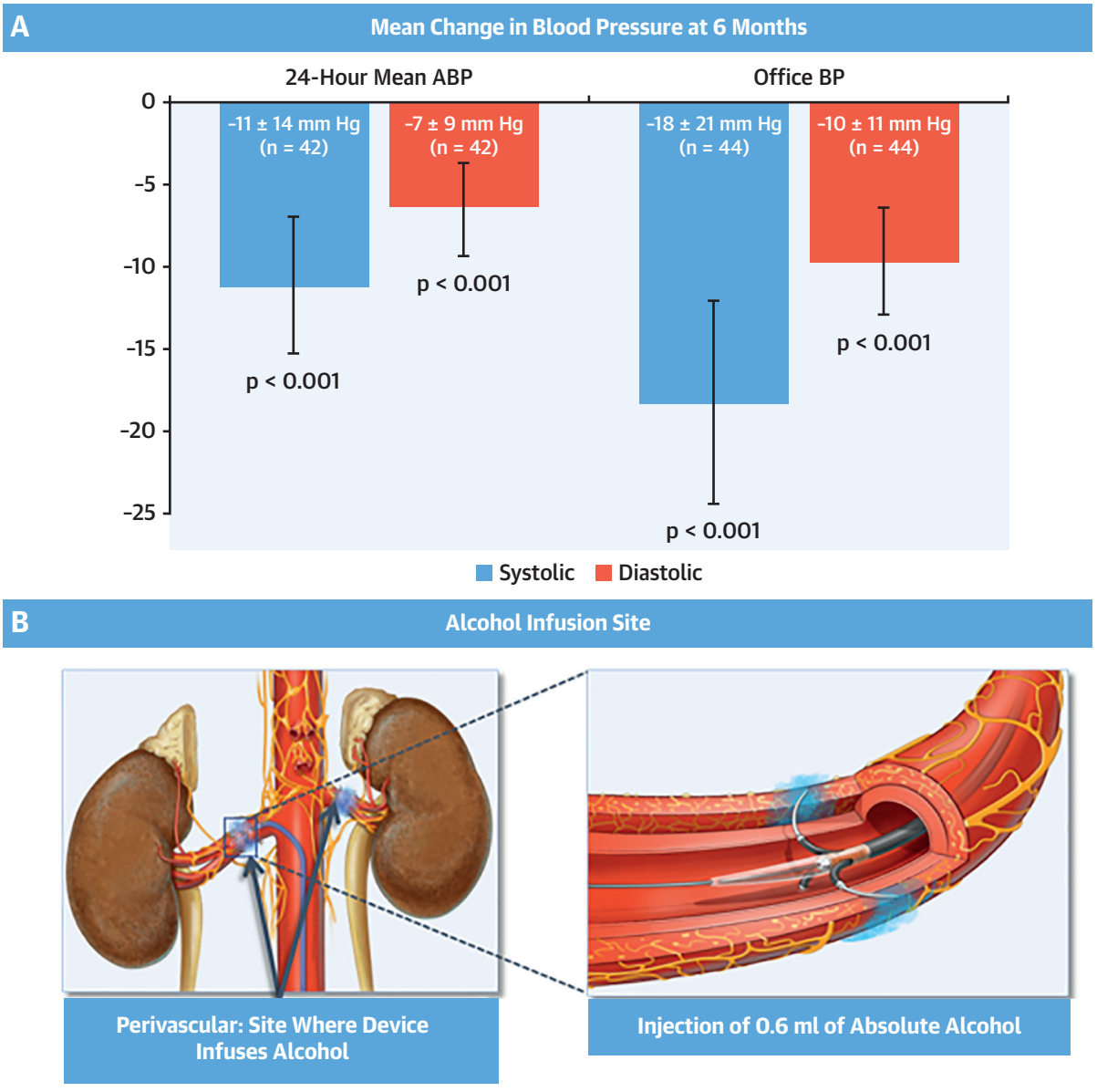
TABLE 2 Procedural Details (N = 46)

Device time per artery (infusion catheter insertion to time of retraction), min	7 ± 3
Procedure time (skin to skin) from femoral artery access to sheath removal, min	49 ± 21
Volume of alcohol infused, per artery, ml	0.6 ± 0.0
Volume contrast used, per procedure, ml	92 ± 46
Fluoroscopy time, per procedure, min	10.8 ± 10.8
Vessel closure	
Closure device	67
Complication during vessel closure	0
Length of hospital stay, days	1 (1-2)

Values are mean ± SD, %, or median (interquartile range). N = 45 patients, including 46 procedures and 94 arteries.

EFFICACY ASSESSMENTS. The mean 24-h ambulatory BP was significantly reduced by −11/−7 mm Hg (95% CI: −15 to −7/−9 to −4 mm Hg) at 6 months compared with baseline ($p < 0.001$) (**Central Illustration, Table 3**). At 1 and 3 months, 24-h ambulatory BP was reduced by −9/−6 mm Hg (95% CI: −12 to −5/−8 to −3 mm Hg) and by −10/−6 mm Hg (95% CI: −14 to −6/−9 to −4 mm Hg) ($p < 0.001$ for all 3 time points). Decreases of ≥5 and ≥10 mm Hg in 24-h mean ambulatory systolic BP at 6 months were recorded in 71% (30 of 42) and 52% (22 of 42) of patients, respectively. Mean daytime systolic and diastolic ambulatory BPs showed larger reductions (−12/−7 mm Hg; 95% CI: −16 to −7/−10 to −4 mm Hg) than mean nighttime ambulatory BP (−9/−5 mm Hg; 95% CI: −14 to −5/−8 to −2 mm Hg) at 6 months (Online Table S3). Mean systolic and diastolic office BPs were reduced by −18/−9 mm Hg (95% CI: −24 to −12/−12 to −6) at 1 month, by −18/−8 mm Hg (95% CI: −24 to −11/−12 to −5 mm Hg) at 3 months, and by −18/−10 mm Hg (95% CI: −25 to −12/−13 to −6 mm Hg) at 6-month follow-up, respectively ($p < 0.001$ for all 3 time points). Decreases of ≥5 and ≥10 mm Hg in office systolic BP at 6 months were recorded in 70% (31 of 44) and 61% (27 of 44) of patients, respectively (**Figure 3**). At 6 months, 21% (9 of 42) and 30% (13 of 44) of patients were controlled to <130/80 mm Hg for 24-h mean ambulatory BP and <140/90 mm Hg for office BP, respectively. Individual patient changes in 24-h mean ambulatory and office systolic BP at 6 months are presented in **Figure 4**.

CENTRAL ILLUSTRATION **Alcohol-Mediated Renal Denervation in Hypertension**



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(A) 6-month follow-up of change in 24-h ambulatory and office blood pressure. Data are mean ± SD with 95% confidence intervals. **(B)** Site of infusion of 0.6 ml of alcohol in the perivascular space of the renal arteries using the Peregrine Catheter. ABP = ambulatory blood pressure; BP = blood pressure; CI = confidence interval.

Patient-reported antihypertensive medications were reduced in 13% (6 of 45), 14% (6 of 44), and 23% (10 of 44) of patients at 1, 3, and 6 months, respectively. Antihypertensive medications were increased at 1, 3, and 6 months in 2% (1 of 45), 2% (1 of 44), and 5% (2 of 44) of patients, respectively. There were no notable changes in the types of antihypertensive medications taken at 6 months. Urine toxicological analyses revealed that adherence to the antihypertensive regimen remained relatively consistent over time: 74.6% (n = 42), 81.9% (n = 43), and 77.9% (n = 41) after 1, 3, and 6 months of follow-up, respectively. This was also reflected in the proportion of patients who were fully adherent (100%) with

TABLE 3 Efficacy Assessment: Ambulatory and Office Blood Pressure

	Systolic			Diastolic		
	1 Month	3 Months	6 Months	1 Month	3 Months	6 Months
Ambulatory blood pressure, 24-h mean						
n	42	36	42	42	36	42
Matched baseline, mm Hg	150 ± 13	150 ± 13	151 ± 14	88 ± 11	88 ± 11	89 ± 12
Blood pressure, mm Hg	141 ± 15	140 ± 15	140 ± 16	82 ± 11	81 ± 10	83 ± 12
Change from baseline, mm Hg	−9 ± 13 (−12 to −5)	−10 ± 12 (−14 to −6)	−11 ± 14 (−15 to −7)	−6 ± 7 (−8 to −3)	−6 ± 8 (−9 to −4)	−7 ± 9 (−9 to −4)
p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
≥5 mm Hg, %	64	67	71	52	56	69
≥10 mm Hg, %	45	42	52	21	25	24
Office blood pressure						
n	45	43	44	45	43	44
Matched baseline, mm Hg	169 ± 15	169 ± 15	169 ± 15	99 ± 13	99 ± 13	99 ± 13
Blood pressure, mm Hg	151 ± 19	152 ± 20	151 ± 21	90 ± 14	91 ± 14	90 ± 14
Change from baseline, mm Hg	−18 ± 21 (−24 to −12)	−18 ± 22 (−24 to −11)	−18 ± 21 (−25 to −12)	−9 ± 10 (−12 to −6)	−8 ± 12 (−12 to −5)	−10 ± 11 (−13 to −6)
p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
≥5 mm Hg, %	78	67	70	73	63	70
≥10 mm Hg, %	69	58	61	47	40	48

Values are n, mean ± SD, or mean ± SD (95% confidence interval), unless otherwise indicated.

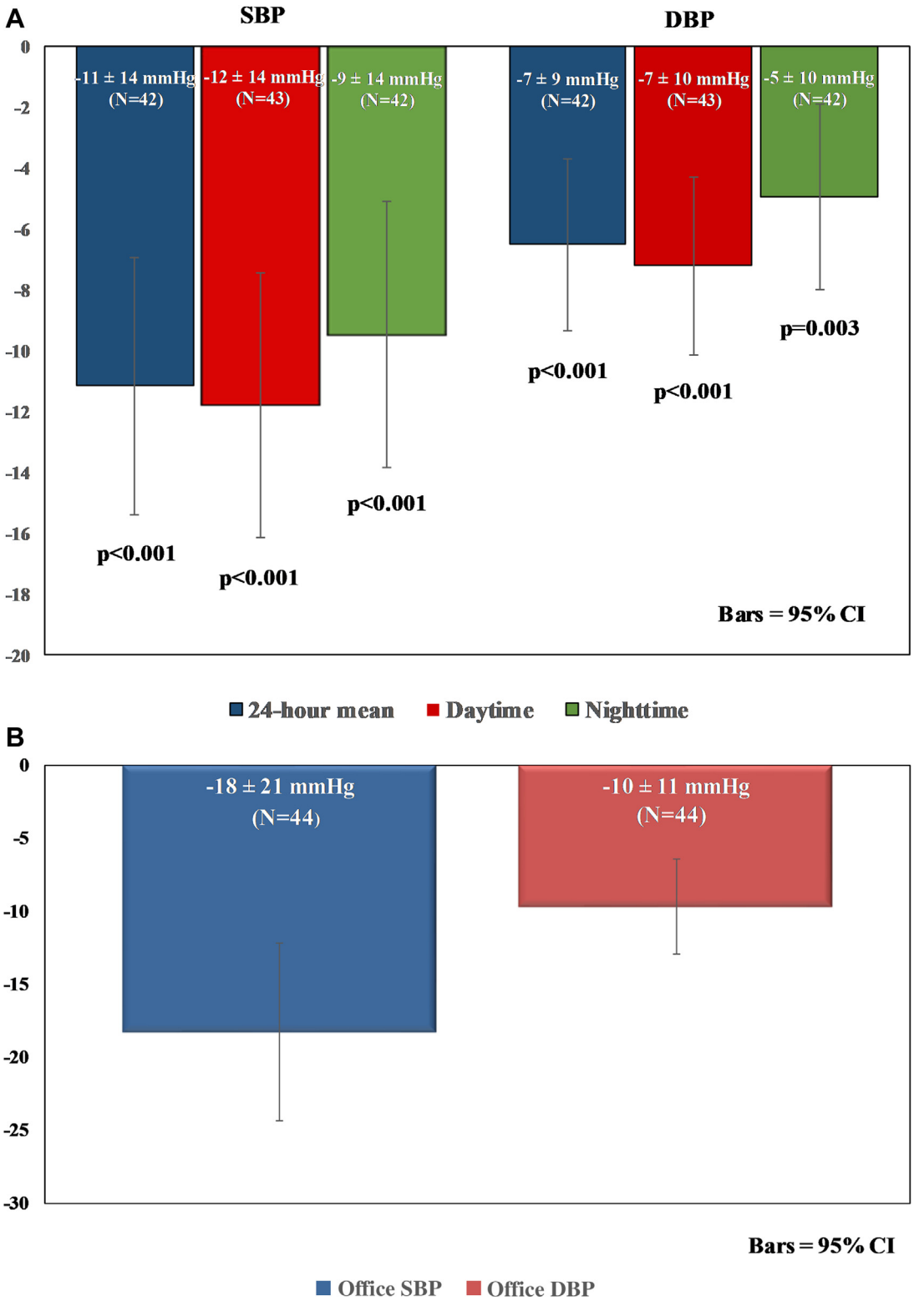
their antihypertensive regimens, with 52.4%, 60.5%, and 58.5% of patients at 1, 3, and 6 months of follow-up, respectively.

In an analysis to identify predictors of 24-h mean ambulatory systolic BP response (decreases of 5 and 10 mm Hg at 6-month follow-up, n = 42), we were unable to identify strong predictors of response. Both lower baseline serum creatinine (odds ratio: 0.005 [95% CI: <0.001 to 0.536; p = 0.026] and odds ratio: 0.017 [95% CI: <0.001 to 0.958]; p = 0.048] for decreases of 5 and 10 mm Hg, respectively) and lower mean body mass index (odds ratio: 0.875 [95% CI: 0.767 to 0.998; p = 0.047] and odds ratio: 0.852 [95% CI: 0.738 to 0.983; p = 0.028] for decreases of 5 and 10 mm Hg, respectively) were related to response, but power was too limited to draw any conclusions.

RENAL FUNCTION ASSESSMENTS. Serum creatinine levels remained stable from baseline to 6 months (0.92 ± 0.19 mg/dl [n = 45] to 0.94 ± 0.17 mg/dl [n = 44]; p = 0.55), with no patient showing a clinically significant change. eGFR decreased slightly (−2.7 ± 12.1 ml/min/1.73 m^2) from baseline to 6 months (from 85 ± 16 to 81 ± 17 ml/min/1.73 m^2; p = 0.15). In addition, cystatin C remained unchanged through follow-up (0.98 ± 0.19 to 1.04 ± 0.52 mg/l; p = 0.39). No patient had a reduction in eGFR after baseline that was considered clinically significant by the investigator or clinical events committee at any visit through 6 months. Transient drops of >25% in eGFR were noted in 2 patients during the 6-month follow-up visit (Table 4). In 1 of these patients, eGFR was within the normal range at 7 days, 1 month, and 3 months, and the decrease in eGFR had improved at a subsequent visit. For the other patient, eGFR was within the normal range at 7 days, 1 month, and 3 months, and the decrease of >25% at 6 months was considered secondary to dehydration. The subsequent eGFR had improved slightly. Mean spot urine albumin levels remained stable from baseline to 6 months (20 ± 75 to 20 ± 58 mg/dl).

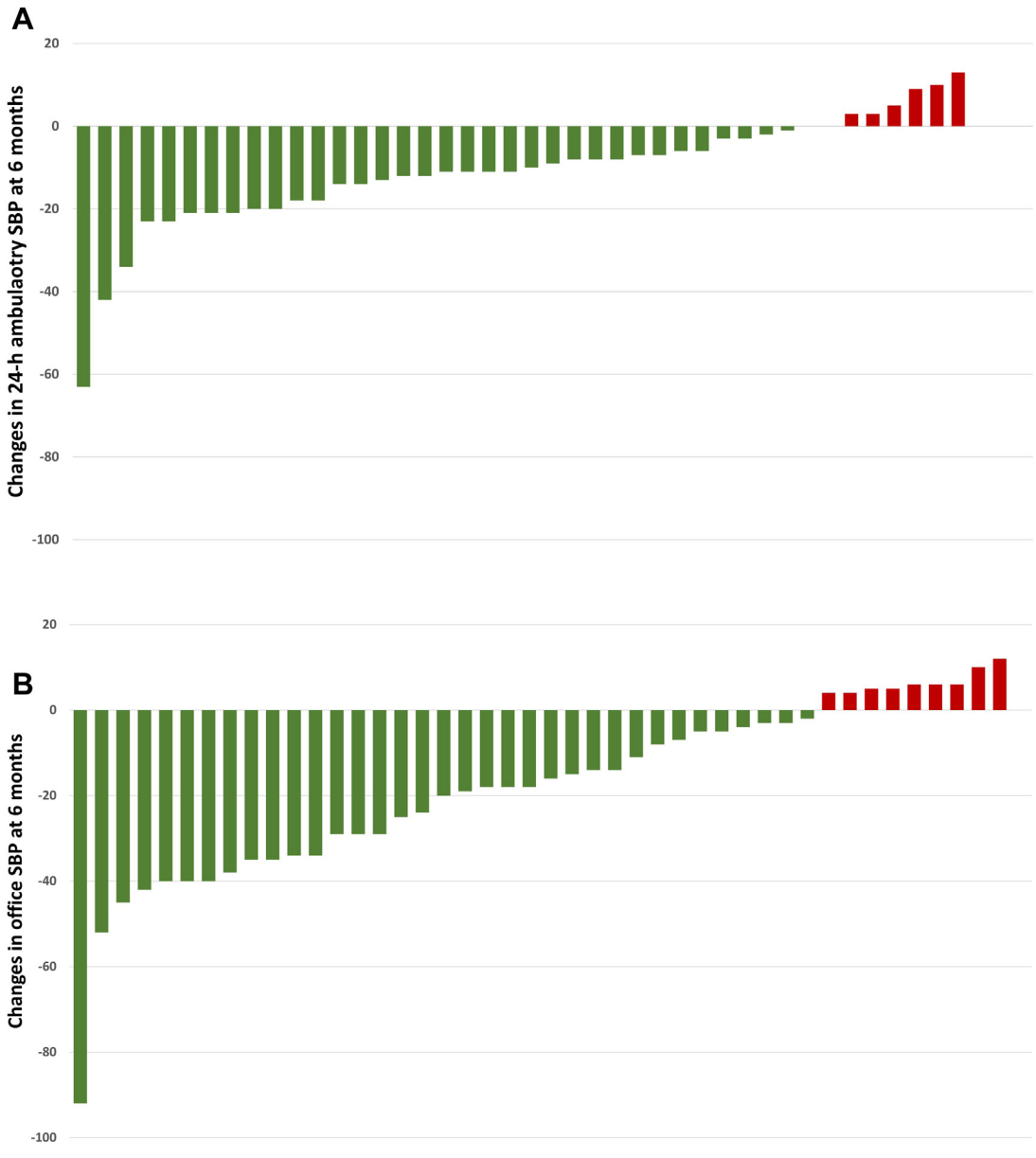
SAFETY ASSESSMENTS. The primary safety endpoint, defined as the absence of any periprocedural major vascular complications or major bleeding, acute kidney injury, or death within 1 month of the procedure, was met in 43 of 45 patients (96%; 95% CI: 85% to 99%) (Table 4). The remaining 2 patients had post-procedural AEs that were not related to the Peregrine Catheter as assessed by the investigator and the clinical events committee. One patient had a nonserious AE of vascular pseudoaneurysm at day 0 at the access site, which was due to a user error, and the patient who underwent 2 procedures had an AE of access-site pseudoaneurysm and major bleeding requiring transfusion at day 8 (day 1 after the second contralateral procedure). No cases of acute kidney injury or death were reported within 1 month of the procedure. There were no cases of stroke, myocardial infarction, or transient ischemic attack within 1 month of the procedure (Table 4). Three major AEs occurred within 6 months of the procedure due to vascular access-site complications and included the 2 periprocedural vascular complications described earlier and 1 case of hypotension observed in 1 patient

FIGURE 3 Six-Month Follow-Up of Ambulatory and Office Blood Pressure Results



Mean decreases in 24-h mean, daytime, and nighttime ambulatory **(A)** and office **(B)** systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 6 months.

FIGURE 4 Individual Patient Blood Pressure Changes at 6 Months



(A) 24-h mean ambulatory systolic blood pressure (SBP). **(B)** Office SBP.

due to a vasovagal event, related to pain during the infusion. No evidence of new renal artery stenosis of >60% was identified at 6 months post-procedure by magnetic resonance angiography, CTA, or RDUS in 43 patients with available data.

DISCUSSION

In patients with uncontrolled hypertension on multiple medications, bilateral infusion of 0.6 ml of alcohol in the perivascular space of the renal arteries using the Peregrine Catheter was associated with reductions in ambulatory and office BP of clinically relevant magnitude. The procedural duration was relatively short and showed a favorable safety profile.

The renal sympathetic nerves, which are located in the adventitia of the renal arteries, can be affected by different means. The first systems for RDN used radiofrequency energy in a manner analogous to ablation for cardiac conditions (16–18). Related to the

nerve distribution along the renal artery and the penetration depth of commercially available radiofrequency systems, a revised approach of treating the main and branch renal arteries has been proposed to increase treatment effects and subsequently investigated in clinical studies (19–21). The randomized, sham-controlled SPYRAL HTN-OFF (6) and SPYRAL HTN-ON (7) trials recently confirmed the BP-lowering efficacy of this revised approach in patients with and without concomitant antihypertensive medications. An alternative technology delivers ultrasound energy to thermally ablate the renal sympathetic nerves (22). This endovascular, balloon-based approach of circumferential nerve ablation recently achieved in the RADIANCE-HTN SOLO (9) trial a greater reduction in daytime ambulatory systolic BP at 2 months compared with a sham procedure. Of note, the 3-arm, randomized, controlled RADIOSOUND-HTN trial compared treatment with: 1) radiofrequency RDN of the main renal arteries; 2) radiofrequency RDN of the main renal arteries plus side branches; and 3) an endovascular ultrasound-based RDN of the main renal artery in patients with resistant hypertension (23). Endovascular ultrasound-based RDN of the main renal artery was associated with larger decreases in BP compared with radiofrequency RDN of the main renal arteries and comparable with radiofrequency RDN of the main renal arteries plus side branches.

The Peregrine Catheter represents a novel technology (i.e., alcohol-mediated RDN). The catheter is used under fluoroscopic guidance to ensure correct placement of guide tubes and 3 microneedles in the main renal artery to infuse alcohol directly into the perivascular space. Preclinical studies have demonstrated the feasibility of this chemical approach using doses of 0.15 to 0.6 ml, and all doses have been shown to cause RDN by neurolysis (12). Histopathology has verified circumferential alcohol treatment zones and neurolysis at depths of up to 16 mm from the intima, depending on the microanatomy. No histological or angiographic evidence of dissection, perforation, necrosis, or fibrosis of the renal artery was noted in this series of evaluations. The volume of 0.6 ml (per renal artery), however, demonstrated the highest effectiveness, equal in magnitude to test arms using surgical denervation, while maintaining a good safety profile, which provided the translational rationale for investigating this dose in the present clinical trial. Possible reinnervation associated with alcohol-mediated RDN is difficult to assess. Recent preclinical evidence suggests sustained decrease in BP and reduced anatomic and functional reinnervation of renal nerves in hypertensive sheep at long-term follow-up 30 months after catheter-based radiofrequency RDN (24). In addition, the consistency of the systolic ABPM decrease from 3 to 6 months and to 1 year does not suggest a loss of effect related to reinnervation. In a long-term study of RDN with radiofrequency, similarly, there were no signs from 1 to 3 years of a degradation of the BP-lowering effect to suggest, clinically, that there is reinnervation (25).

The present trial used contemporary, state-of-the art methodology of device-based hypertension trials, including adherence measurements by urine toxicological analyses and ABPM as the primary efficacy endpoint. At 6 months, ambulatory BP was reduced by −11/−7 mm Hg (95% CI: −15 to −7/−9 to −4 mm Hg) and office BP by −18/−10 mm Hg (95% CI: −25 to −12/−13 to −6 mm Hg). The proportions of patients with clinically meaningful changes in BP (≥10 mm Hg in office systolic BP or ≥5 mm Hg in ambulatory systolic BP) were 61% and 71%, respectively, comparable with previously published evidence (26). However, procedural performance of the evaluated device appears to be significantly different. Although radiofrequency and ultrasound RDN require a generator to be connected to the device, alcohol-mediated RDN can be obtained without the use of active components. This

TABLE 4 Primary and Secondary Safety Endpoints (N = 45)

Primary safety endpoints	
Primary safety endpoint reached*	96 (43/45)
Primary safety endpoint events within 1 month of the procedure	4 (2/45)‡
Periprocedural major vascular complication	4 (2/45)§
Major bleeding (TIMI classification)	2 (1/45)
Acute kidney injury	0
Periprocedural death	0
Secondary safety endpoints	
Stroke or TIA within 1 month of the procedure	0
MI within 1 month of the procedure	0
MAEs through 6 months post-procedure	7 (3/44)
All-cause death	0
End-stage renal failure	0
Significant embolic event resulting in end-organ damage or requiring intervention to prevent it	0
Major vascular complications	5 (2/44)
Significant new renal artery stenosis (>60% diameter stenosis)	0
Hypertensive crisis	0
Severe hypotension or syncope	2 (1/44)
Clinically significant serum creatinine levels change at 6 months from baseline†	0 (0/44)
eGFR >25% decrease at 6 months from baseline	5 (2/44)

Values are % (n/N) or %. *The primary safety endpoint was defined as the absence of the following: periprocedural major vascular complications, major bleeding as defined by the TIMI bleeding classification, acute kidney injury, and periprocedural death within 1 month of the procedure. †Clinically significant when investigator judges the levels to be a safety concern. ‡One patient had a major vascular complication event and a major bleeding event. §The 2 major vascular complications were pseudoaneurysms.

eGFR = estimated glomerular filtration rate; MAE = major adverse event; MI = myocardial infarction; TIA = transient ischemic attack, TIMI = Thrombolysis In Myocardial Infarction.

significantly reduces the complexity of the setup and potential costs associated with the procedure. The single injection of 0.6 ml of alcohol in the main renal artery shortens procedure time, reduces radiation exposure, and allows minimal injection of contrast and hence reduces risk for contrast-induced nephropathy, which is particularly important in patients with renal insufficiency. The mean volume of contrast medium used during this trial (92 ± 46 ml) was lower than that reported in any other trial published so far (RADIANCE-HTN SOLO, 141 ± 69 ml; SPYRAL HTN-ON MED, 270.8 ± 101.6 ml; SPYRAL HTN-OFF MED, 251 ± 99.4 ml) (6,7,9). One may speculate that shortly after injection, alcohol anesthetizes the afferent, sensory nerves, which may explain the observed effect of almost no pain during the procedure, which is a distinct feature of the RDN approach. In some patients, TMLs were documented directly after needle removal, which typically disappeared within 2 min. Although short- and mid-term vascular safety was reasonable in this trial, the long-term clinical consequences of this phenomenon need to be investigated.

Nonadherence to prescribed antihypertensive medication represents a major challenge in the treatment of hypertension. Recent analysis documented that up to 50% of all patients become nonadherent over time (27). Toxicological testing has been recommended as an integral component of device-based hypertension trials (28,29). Sensitivity analyses indicate that the observed BP changes were not related to improvements in adherence to antihypertensive medication, which has also been documented in other studies (30).

The primary safety endpoint, defined as the absence of any periprocedural major vascular complications or major bleeding, acute kidney injury, or death within 1 month of the procedure, was met in 96% of all patients. Two patients had post-procedural AEs that were not related to the Peregrine Catheter (2 vascular pseudoaneurysms with major bleeding requiring transfusion in 1 patient). There were no cases of acute kidney injury, and renal function remained stable over time. CTA or RDUS indicated no evidence of new renal artery stenosis of >60% at 6 months. There were no vessel perforations or tears requiring intervention or persistent spasms observed in any of the vessels treated and 2 cases of minor renal artery dissection that resolved without treatment.

STUDY LIMITATIONS. Limitations include the open-label design of the trial and the lack of a sham control, making it vulnerable to the Hawthorne effect and other patient- and physician-related biases (31). However, we used contemporary, state-of-the art methodology, such as toxicological analyses for adherence measurement and ABPM to control for confounding factors. Furthermore, the trial included patients on more than 5 antihypertensive medications, and evidence suggests that a larger number of prescribed drugs is associated with a high rate of nonadherence (30). Patients with known or suspected secondary hypertension were not included. However, secondary causes of hypertension were not excluded systematically as part of the study protocol. All patients were treated with 0.6 ml of alcohol. Whether one dose fits all or an increased dose results in larger treatment effect or reduced variability remains to be shown. Longer follow-up of this trial and greater numbers of patients undergoing alcohol-mediated RDN will be necessary to provide greater assurance of vascular and overall safety and to exclude rare AEs. In addition, we do not have confirmatory evidence in this patient population that either afferent or efferent renal nerves have been denervated.

CONCLUSIONS

Alcohol-mediated RDN using the Peregrine Catheter significantly lowered ambulatory and office BPs in patients with severe uncontrolled hypertension. The safety profile of the procedure was acceptable. The ongoing, sham-controlled, randomized, blinded TARGET BP OFF-MED (NCT03503773) and TARGET BP I (NCT02910414) clinical trials will provide further important information.

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PERSPECTIVES

WHAT IS KNOWN? Hypertension is the most common preventable risk factor for premature death and disability worldwide, but the number of patients with BP controlled to guideline-recommended target values remains unacceptably low. The renal sympathetic nervous system has been identified as a major contributor to the pathophysiology of hypertension, and catheter-based denervation of the kidneys using different modalities is under clinical investigation.

WHAT IS NEW? A novel endovascular approach to perform catheter-based chemical RDN using dehydrated alcohol as the neurolytic agent has been developed. The procedure significantly lowered ambulatory and office BPs in patients with severe uncontrolled hypertension. The safety profile of the procedure was acceptable.

WHAT IS NEXT? The ongoing, sham-controlled, randomized, blinded TARGET BP OFF MED and TARGET BP I clinical trials will provide further data with regard to safety and efficacy.

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KEY WORDS alcohol, catheter, hypertension, neurolysis, renal denervation

APPENDIX For study collaborators as well as supplemental tables, please see the online version of this paper.