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ORIGINAL ARTICLE

Long-Term Results up to 12 Months After Catheter-Based Alcohol-Mediated Renal Denervation for Treatment of Resistant Hypertension

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BACKGROUND: Primary results of this prospective, open-label, multicenter trial suggested that alcohol-mediated renal denervation with perivascular injection of dehydrated alcohol using the Peregrine System Infusion Catheter safely reduces blood pressure (BP) in patients with resistant hypertension. To date, maintenance of the BP-lowering effect beyond 6 months using this novel technology has not been reported. This article describes the final, 12-month follow-up data on the safety and efficacy of alcohol-mediated renal denervation in these patients.

METHODS: Forty-five patients with resistant hypertension on a stable regimen of on average 5.1±1.5 antihypertensive medications underwent successful bilateral renal denervation using the Peregrine Catheter with alcohol as the neurolytic agent (0.6 mL per renal artery). Apart from 2 vascular access pseudoaneurysms (both without sequelae), no major procedural complications occurred.

RESULTS: At 12 months post-procedure, mean 24-hour ambulatory systolic and diastolic BP were reduced by 10 mm Hg (95% CI, −16 to −5) and 7 mm Hg (−10 to −3), respectively (P<0.001). Office systolic/diastolic BP was reduced by 20/10 mm Hg (−27, −13/−14, −6; <0.001). Compared with baseline, the number of antihypertensive medications was reduced in 21% of patients, while it was increased in 19%. From baseline to 12 months, serum creatinine, urea, cystatin C, and spot urine albumin levels remained unchanged. The change in estimated glomerular filtration rates (−3.9±10.3 mL/minute per 1.73 m^2 [95% CI, −7.1 to −0.75]; P=0.02) was within the expected range. There were no cases of renal artery stenosis up to 12-month follow-up.

CONCLUSIONS: Catheter-based chemical renal denervation with dehydrated alcohol using the Peregrine Catheter seems to safely reduce BP at follow-up of up to 12 months. Further randomized and sham controlled studies are underway to further validate these findings.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02570113.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: alcohol ■ denervation ■ hypertension ■ renal artery

See Editorial by Flood and Aronow

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For Sources of Funding and Disclosures, see page 926.

WHAT IS KNOWN

- Modulating renal sympathetic nerve activity through catheter-based renal denervation is under investigation as a potential therapeutic approach for the treatment of resistant hypertension.
- Injection of dehydrated alcohol around the kidney artery using the Peregrine Catheter represents a novel approach for renal nerve ablation.

WHAT THE STUDY ADDS

- This is the first prospective trial evaluating the maintenance of safety and blood pressure-lowering effect up to 12 months after using chemical renal denervation with the Peregrine Catheter in patients with resistant hypertension.
- Findings from this trial highlight that catheter-based alcohol-mediated renal denervation appears to cause a significant blood pressure reduction that was maintained at 12 months.
- There were no renal artery stenoses or other major safety concerns throughout this 12-month period.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
eGFR	estimated glomerular filtration rate
RDN	renal denervation
RDUS	renal duplex ultrasound

Renal sympathetic nerves play a crucial role in blood pressure (BP) regulation. Increased sympathetic activity is an important contributor to elevated BP in many patients.[1] Accordingly, modulating sympathetic nerve activity at the level of the kidneys is under investigation as a therapeutic approach for the treatment of hypertension.[2,3] Catheter-based renal denervation (RDN) may represent a potential therapeutic approach, alone or as an adjunctive intervention, combined with lifestyle modification and appropriate medical therapy, to treat resistant hypertension.[4] Different approaches, using various catheters, have been developed such as thermal ablation using radiofrequency[5,6] and ultrasound.[7] An alternative approach is to perform alcohol-mediated RDN using the 3 needle-based delivery device (Peregrine Catheter, Ablative Solutions, Inc, San Jose, CA).[8] Alcohol delivered through the Peregrine Catheter had been evaluated in preclinical models, showing a radial diffusion of alcohol into the treatment zones and neurolysis at depths of ≈8 mm from the intimal surface, depending on the local anatomy.[9,10]

This international, multicenter, feasibility trial was designed to provide clinical data to evaluate the safety and efficacy of chemical RDN using the Peregrine Catheter. The primary 6-month results of this trial demonstrated both reductions in 24-hour ambulatory, and office-measured BP, with an acceptable safety profile.[11] The longer-term safety and BP-lowering effect of alcohol-mediated RDN has not been previously reported. Accordingly, the objective of the present final analysis was to examine the 12-month safety and BP-lowering efficacy of chemical RDN with the injection of 0.6 mL of alcohol per renal artery in patients with resistant hypertension.

METHODS

The data of this study are available from the corresponding author on reasonable request. The prospective, single-arm, open-label trial design and methodology, including the clinical and laboratory assessments and imaging performed and the RDN procedure, have been described previously.[11] The trial was approved by the ethics committees of all 9 participating centers in Europe (located in Poland, Czech Republic, Belgium, and Germany), and, if applicable, by the relevant Competent Authorities and conducted in accordance with the Declaration of Helsinki. Between January 28, 2016 and March 26, 2018, 45 patients were treated with the RDN procedure with consecutive 12 months follow-up. All patients provided written informed consent to complete up to 12 months follow-up.

Study Population and Procedures

To be eligible, patients were required to have a mean office-based BP of at least 150/85 mm Hg, with an accompanying 24-hour ambulatory systolic BP of 135 mm Hg or higher, despite treatment with at least 3 antihypertensive drug classes including a diuretic, thereby meeting the criteria for resistant hypertension.[12] Inclusion also required patients to have a renal artery diameter of ≥4 and ≤7 mm, a main renal artery length of ≥5 mm, and to be >18 years of age. Patients were not eligible if they had type 1 diabetes, severe untreated obstructive sleep apnea, nephrotic syndrome, an estimated glomerular filtration rate (eGFR) of ≤20 mL/minute per 1.73 m^2, or a history of cardiovascular or cerebrovascular events. Patients with renal artery stenosis, or one or more accessory arteries that were too small to be treated, as assessed by magnetic resonance angiography (N=26), computed tomographic angiography (N=18) and (quantitative) renal angiography (N=1), were excluded.

After a stable antihypertensive medication regimen of at least 4 weeks, 45 eligible patients with mean office BP of 169/99±15/13 mm Hg, corresponding 24-hour mean ambulatory BP of 151/89±14/12 mm Hg, and with suitable renal arterial anatomy evaluated with a preprocedural renal duplex ultrasound (RDUS) and computed tomographic angiography/magnetic resonance angiography, underwent bilateral RDN (of each of the 2 renal arteries). Four patients each had 1 accessory renal artery treated in addition to the 2 main renal arteries, and one patient had 2 procedures staged for

unilateral treatment of each renal artery. Therefore, a total of 94 renal arteries were treated using the Peregrine Catheter with 0.6 mL of alcohol infused per renal artery and with a mean (SD) distance from the ostium to the infusion site of 20.2 (6.6) mm. All 46 procedures were technically successful without device deficiencies, with a mean treatment time of 7±3 minute/artery (Table I in the Data Supplement). No general anesthesia and minimal conscious sedation was given. Mild or no pain was reported during alcohol infusion in 50/87 (57%) renal arteries for which periprocedural pain data were obtained. There were 2 vascular access pseudoaneurysms, both without longer-term sequelae. The patients were seen at scheduled visits at 7 days, 1 month, and 3, 6, and 12 months. At the 12-month visit, patients came to the study center to undergo seated office BP measurements (triplicate readings), RDUS, a physical exam and laboratory assessments, and to record adverse events and antihypertensive medications. Seated office BP was measured with the same validated device (Omron 705IT with printer, Omron, Kyoto, Japan) in all patients, as described previously.[11] Sequential 24-hour ambulatory BP measurements were recorded to assess eligibility at baseline, after the 4-week stable regimen of antihypertensive medications and at 1, 3, 6 and 12 months post-procedure (Spacelabs Healthcare Monitor, Spacelabs Healthcare, Snoqualmie, Washington), as described previously.[11] All 24-hour ambulatory BP readings were sent to a core laboratory (ERT, St. Louis, MO). Renal artery imaging by RDUS, computed tomographic angiography or magnetic resonance angiography was performed at baseline, and at 6 and 12 months to detect renal artery stenosis; images were assessed by a core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University, Stanford, California), as described previously.[11] The trial is registered at www.ClinicalTrials.gov, NCT02570113.

End Points

Primary end points previously reported were the absence of any periprocedural major vascular complications, major bleeding as defined by the Thrombolysis in Myocardial Infarction bleeding classification, acute kidney injury, or death within 1 month of the procedure, and reduction of 24-hour ambulatory systolic BP at 6 months versus baseline.[11] Final follow-up occurred at 12 months. Secondary efficacy end points were changes in office BP, ambulatory BP monitoring results (daytime and nighttime), antihypertensive medications, and renal function as evaluated using laboratory parameters (eGFR, serum creatinine, cystatin C, albuminuria, and albuminuria categorization).

In addition, major and serious adverse events reported by the study centers up to 12 months post-procedure were sent for review and adjudication by an independent clinical events committee.[11]

Statistical Analysis

This trial was not powered for formal hypothesis testing. Data were summarized using descriptive statistics.[11] To describe continuous variables, the mean±SD were used (or medians and percentiles of the interquartile range when non-normally distributed), and for categorical variables, frequencies, and percentages. The last value collected before the procedure represented the baseline value. For binary and continuous variables, CIs were estimated using exact binomial methods and the normal approximation, respectively. Univariate logistic regression analysis of key demographic, medical history and renal artery characteristics with 24-hour ambulatory systolic BP response was performed. *P* of ≤0.05 were considered statistically significant without adjustment for multiplicity. All analyses were

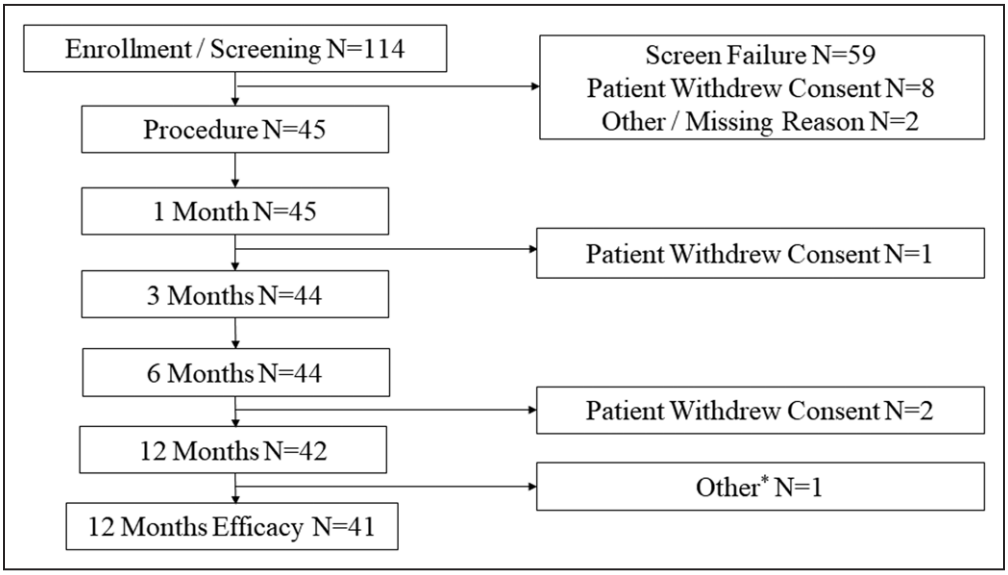

Figure 1. Schematic of the flow of patient enrollment and follow-up.
Flow diagram showing the flow of patients in the clinical trial through the selection process, treatment, and follow-up. *One patient returned for the 12-mo visit but was unable to complete efficacy assessments due to an adverse event (cerebrovascular accident). Note that the number of patients with valid ambulatory blood pressure measurement (ABPM) data at 12 mo is N=38 for 24-h and nighttime ABPM and N=39 for daytime ABPM.

performed using statistical analysis system (SAS) software, Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

After undergoing a 4-week run-in period not allowing changes in antihypertensive medications, 45 patients were treated. At the 12-month timepoint, 41 patients completed the trial. Three patients withdrew consent, and 1 patient was unable to complete efficacy assessments at the 12-month visit due to a stroke (Figure 1).

Baseline characteristics including demographics, medical history, and antihypertensive medications are listed in Table 1, as reported previously.[11] At the time of enrollment, patients took on average 5.1±1.5 antihypertensive medications, with the majority of patients taking diuretics (44/45, 98%), calcium channel blockers (38/45, 84%), beta blockers (34/45, 76%), and angiotensin receptor blockers (33/45, 73%). A total of 47% (21/45) of patients took a mineralocorticoid receptor antagonist.

Overall, 26 patients underwent magnetic resonance angiography and 18 patients underwent computed tomographic angiography at baseline. Forty-three out of 45 patients underwent RDUS at baseline.

Table 1. Patient Demographics and Medical and Surgical History

Characteristics	All patients N=45
Age, y	55.2±9.7
Male sex	62%
BMI, kg/m^2	30.7±5.8
eGFR (CKD-EPI formula), mL/min per 1.73 m^2	85±16
Chronic kidney disease (eGFR <60 mL/min per 1.73 m^2)	2%
Type 2 diabetes	33%
Hyperlipidemia	49%
Coronary artery disease	9%
Peripheral artery disease	7%
Smoking (ever)	42%
Isolated systolic hypertension*	4%
Heart failure	4%
Prior myocardial infarction	4%
Cerebrovascular accident/transient ischemic attack	7%
Office systolic/diastolic BP, mm Hg	169/99±15/13
24-h 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	84%
Diuretics	98%
Spironolactone	47%
β-blocker	76%
Centrally acting alpha agonist	44%
Direct acting vasodilator	29%
Renin inhibitor	4%
Other	9%

Data are percentages or mean±SD. ACE indicates angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; and eGFR, estimated glomerular filtration rate.

*Defined as office systolic BP >130 mm Hg and office diastolic BP <80 mm Hg.

Efficacy

The significant reduction in 24-hour ambulatory systolic and diastolic BP that was seen 1, 3, and 6 months after the procedure persisted at 12 months (Table 2, Figure 2). At all timepoints after the procedure including 12-month follow-up, both 24-hour ambulatory and office systolic and diastolic BP were significantly lower than baseline BP (P<0.001). The proportion of patients with a decrease in 24-hour ambulatory systolic BP from baseline to 12 months of at least 5 or 10 mm Hg was 61% (23/38) and 47% (18/38), respectively. At 12 months post-procedure, mean daytime ambulatory systolic and diastolic BP (95% CI) showed larger reductions (−12/−8 mm Hg [−17, −6/−12, −4]) than mean nighttime ambulatory systolic and diastolic BP (−8/−5 mm Hg [−15, −2/−9, −2]) (Figure 3). At 12 months post-procedure, decreases of at least 5 and 10 mm Hg in office systolic BP were recorded in 76% (31/41) and 71% (29/41) of patients, respectively (Table 2). A total of 13 out of 41 patients (32%) had controlled BP at 12 months (defined as office BP <140/90 mm Hg). Hourly ambulatory systolic and diastolic BP are presented at baseline and at 6, and 12 months in Figure 4. These ambulatory readings indicate continued BP reduction at all timepoints throughout the 24-hour period, a phenomenon that has been previously described as always on.[13]

The number of antihypertensive medications at 12 months of follow-up was unchanged as compared with baseline (−0.1±1.4 [95% CI, −0.5 to 0.4]). In addition, types of antihypertensive medications being taken at 12 months of follow-up were similar to baseline. Nine patients (21%) were on a reduced number of medications at 12 months compared with baseline; 8 (19%) were on an increased number of medications.

Univariate analysis of key preprocedure characteristics identified no strong independent predictor of treatment effect at 12 months (see Data Supplement).

Renal Function

Paired baseline and 12-month follow-up renal function parameter data were available for 41 patients. Serum creatinine and urea levels remained stable (0.92±0.19 [N=45] to 0.96±0.19 mg/dL [N=41], P=0.06; and

Table 2. Efficacy Assessment–Ambulatory and Office Blood Pressure

	Mean 24-h ambulatory blood pressure							
	Systolic				Diastolic			
	1 mo N=42	3 mo N=36	6 mo N=42	12 mo N=38	1 mo N=42	3 mo N=36	6 mo N=42	12 mo N=38
Matched baseline, mm Hg, mean±SD	150±13	150±13	151±14	149±12	88±11	88±11	89±12	88±11
Blood pressure, mm Hg, mean±SD	141±15	140±15	140±16	139±17	82±11	81±10	83±12	81±11
Change from baseline, mm Hg, mean±SD (95% CI)	−9±13 (−12 to −5)	−10±12 (−14 to −6)	−11±14 (−15 to −7)	−10±17 (−16 to −5)	−6±7 (−8 to −3)	−6±8 (−9 to −4)	−7±9 (−9 to −4)	−7±11 (−10 to −3)
P Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
≥5 mm Hg, %	64%	67%	71%	61%	52%	56%	69%	47%
≥10 mm Hg, %	45%	42%	52%	47%	21%	25%	24%	32%
	Office blood pressure							
	Systolic				Diastolic			
	1 mo N=45	3 mo N=43	6 mo N=44	12 mo N=41	1 mo N=45	3 mo N=43	6 mo N=44	12 mo N=41
Matched baseline, mm Hg, mean±SD	169±15	169±15	169±15	169±15	99±13	99±13	99±13	99±13
Blood pressure, mm Hg, mean±SD	151±19	152±20	151±21	149±23	90±14	91±14	90±14	89±14
Change from baseline, mm Hg, mean±SD (95% CI)	−18±21 (−24 to −12)	−18±22 (−24 to −11)	−18±21 (−25 to −12)	−20±23 (−27 to −13)	−9±10 (−12 to −6)	−8±12 (−12 to −5)	−10±11 (−13 to −6)	−10±12 (−14 to −6)
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
≥5 mm Hg, %	78%	67%	70%	76%	73%	63%	70%	66%
≥10 mm Hg, %	69%	58%	61%	71%	47%	40%	48%	49%

33.84±10.33 to 36.71±14.44 mg/dL, *P*=0.34). Cystatin C levels remained unchanged through 12-month follow-up (0.98±0.19 to 0.98±0.21 mg/L, *P*=0.67). Estimated GFR levels decreased from baseline to 12 months (85±16 to 80±17 mL/minute per 1.73 m^2, *P*=0.02) and were within the expected range in patients with resistant hypertension. No patient showed a clinically significant reduction in eGFR (as assessed by the investigator) after baseline through 12 months. Two patients had a reduction in eGFR of >25% between baseline and the 12-month follow-up visit. The first patient had normal eGFR values at 7 days, 1 month, and 3 months but a >25% drop at 6 months, as previously reported,[11] which improved but did not return to baseline values at the 12-month visit. For the other patient, the eGFR values decreased gradually throughout the trial (69.3–50.7 mL/minute per 1.73 m^2 from baseline to 12 months). Spot urine albumin levels remained stable up to 6 months[11] and even decreased at the 12-month visit (20±75 to 12±32 mg/dL, *P*=0.25). Albuminuria categorization remained normal to mild (albumin to creatinine ratio <30) in all patients at 12 months follow-up.

Vascular and Overall Safety

At 6 months, no renal artery stenoses were identified.[11] Long-term follow-up imaging by RDUS 12 months post-procedure showed no evidence of new renal artery stenosis or other anatomic abnormalities. Up to 12-months, 2 patients had events adjudicated as major vascular complications, both occurring peri-interventional (vascular access site/femoral artery pseudoaneurysm), and 1 patient had hypotension due to vasovagal stimulation related to pain during the infusion, as described previously.[11]

DISCUSSION

Final data from this feasibility trial have shown that the initially reported ambulatory and office BP reductions at 6 months after chemical RDN using the Peregrine Catheter are maintained at 12 months post-procedure. The persistent BP reduction at a clinically relevant magnitude occurred in patients who suffered from resistant hypertension while on multiple medications. Reductions of at least 5 mm Hg in office systolic BP were recorded in 76% of patients at 12 months. Moreover, in patients treated with alcohol-mediated RDN followed for 12 months, the procedure was safe and well tolerated with no significant late adverse events.

The office BP lowering associated with RDN at 12 months was 20/10 mm Hg. Although only a minority of patients were controlled to the 2017 American College of Cardiology and American Heart Association recommended targets of <130/80 mm Hg,[14] it is reasonable to suggest that RDN may beneficially impact cardiovascular

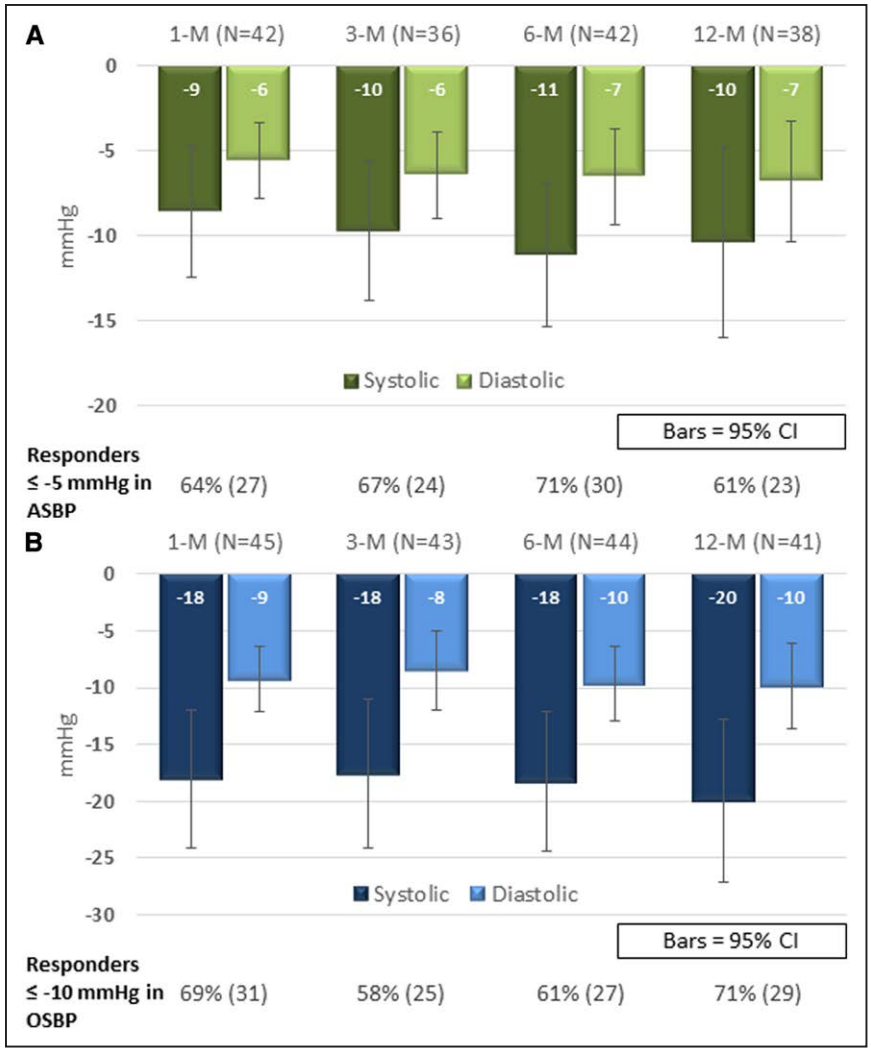

Figure 2. Ambulatory and office blood pressure results at 1-, 3-, 6-, and 12-mo follow-up.
Mean reductions in (**A**) 24-h ambulatory systolic blood pressure (ASBP) and diastolic blood pressure over time and (**B**) office systolic blood pressure (OSBP) and diastolic blood pressure over time. Note: all differences from baseline were statistically significant at $P<0.05$.

outcomes in this challenging patient population. Based on trial data with antihypertensive drugs, an effect size of 20 mm Hg on office systolic BP should confer 54% relative risk reduction in stroke, 56% in heart failure, and 26% in all-cause mortality.[15]

The extent of BP lowering at 12 months post-procedure is very similar to that observed at 6 months: −10/−7 mm Hg (−16, −5/−10, −3) versus −11/−7 mm Hg (−15, −7/−9, −4), respectively, for ambulatory BP and −20/−10 mm Hg (−27, −13/−14, −6) versus −18/−10 mm Hg (−25, −12/−13, −6) for office BP. Similar to radiofrequency-based RDN,[16,17] these results suggest that the BP-lowering effects of RDN are persistent, at least to 12 months, and that functional reinnervation may not occur post-procedure during this time interval. The longer-term effects, beyond 12 months, requires further evaluation in the ongoing randomized trials.[18] Furthermore, hourly ambulatory BP measurements demonstrate that the BP-lowering effect is maintained at all times over the circadian cycle (always on). This effect is maintained throughout 12 months of follow-up (Figure 4).

Resistant hypertension is an important contributor to the deterioration in renal function and lowering the BP could have renal protective effects. Overall, renal function laboratory parameters remained stable throughout the trial showing no substantial decline of renal function. Although no meaningful conclusions can be drawn from the slight decrease in eGFR at 12 months, the reductions in eGFR are within the expected range for hypertensive patients.[8,16,19] None of the individual changes were judged to be clinically meaningful by the investigator. It is also accepted that kidney function decreases in hypertensive patients with advancing patient age.[20] In addition, the reported P of 0.02 should be interpreted with caution due to the lack of Type I error control. Therefore, CIs were reported to provide an assessment of the strength of the estimated effect (−7.1 to −0.75). In the RADIANCE SOLO trial, a small increase in eGFR was observed in the RDN group (N=69) at 6 months (84.2±15.7 to 86.9±16.7 mL/minute per 1.73 m^2).[7] Comparable results were seen in the first small trials assessing chemical RDN with the Peregrine catheter and alcohol: 66±16 to 75±13 mL/minute per 1.73 m^2

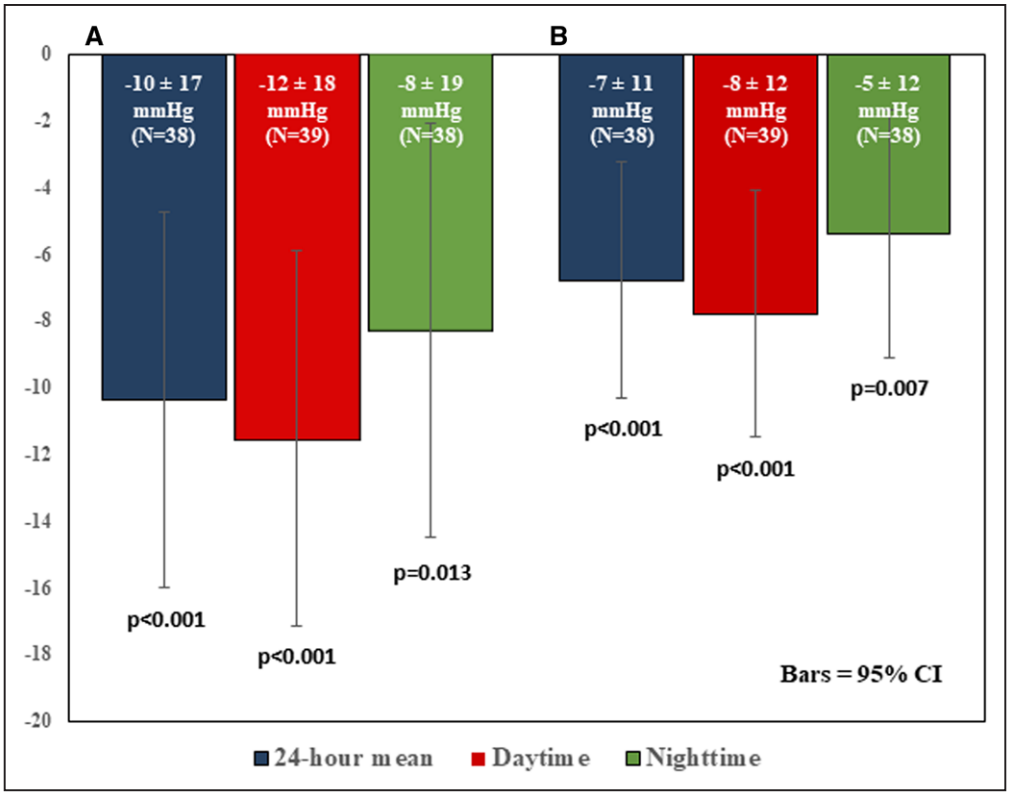

Figure 3. Twelve-month follow-up of ambulatory blood pressure.
Mean decrease in 24-h mean, daytime, and nighttime ambulatory systolic blood pressure (**A**) and ambulatory diastolic blood pressure at 12 mo (**B**). Note: all differences from baseline were statistically significant at *P*<0.05. Note: the number of patients with valid ambulatory blood pressure data at 12 mo is N=38 for 24-h and nighttime results and N=39 for daytime results.

(N=16) at 6 months[8] and 78±21 to 80±20, 77±20 and 85±14 mL/minute per 1.73 m^2 at 6 months (N=10), 12 months (N=10), and 24 months (N=8), respectively.[19]

Another important observation from this extended follow-up of alcohol-mediated RDN was the sustained safety. After this longer period of post-procedure follow-up, there were no safety signals. In particular, renal artery imaging at 12 months showed no new renal artery stenosis.

Limitations

Because of the limited power of the present trial and the small patient population, univariate analysis was performed to determine independent predictors of future BP reduction. In line with other studies,[18] no robust predictor has been identified.

This was an open-label study without a sham control. Therefore, the Hawthorne effect and other patient- and physician-related biases should be considered when interpreting these exploratory results.[21] This limitation will be addressed in 2 ongoing, sham-controlled, randomized, blinded clinical trials also using alcohol-mediated RDN (TARGET BP OFF-MED [NCT03503773] and TARGET BP I [NCT02910414]) in which similar patients are recruited and randomly assigned to RDN or a sham procedure.[22] Additionally, the longer-term follow-up of BP response and safety and larger sample size in these 2 sham-controlled trials will provide more confident information on vascular and overall safety and allow excluding rare adverse events.

Perspectives

The BP-lowering effect of chemical RDN with dehydrated alcohol using the Peregrine Catheter was maintained through 12 months. Throughout this follow-up period, no major safety signals with regards to renal function or renal vascular safety emerged. If efficacy and safety is sustained in the larger, ongoing, randomized, sham-controlled studies, alcohol-mediated RDN could prove to be a promising treatment for patients with resistant hypertension.

ARTICLE INFORMATION

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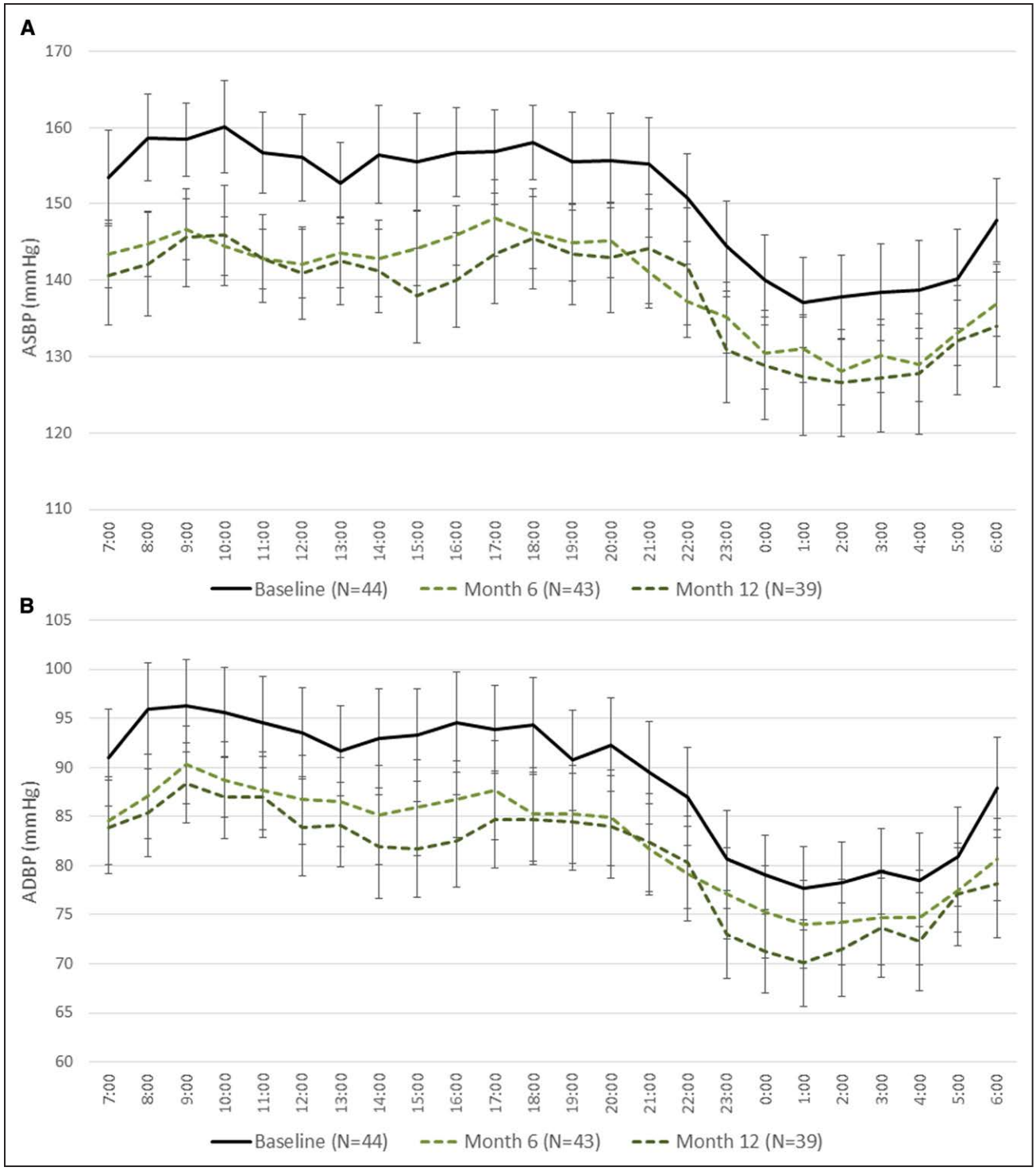

Figure 4. Hourly ambulatory blood pressure at baseline and 6 and 12 mo.
A, Hourly ambulatory systolic blood pressure (ASBP); (**B**) hourly ambulatory diastolic blood pressure (ADBP). Note: the number of patients with valid ambulatory blood pressure data at 12 mo is N=38 for 24-h and nighttime results and N=39 for daytime results.

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Supplemental Materials

Online Table I
Online Data: Predictors of Response

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