Clinical Kidney Journal, 2024, vol. 17, no. 1, 1–11

https://doi.org/10.1093/ckj/sfad237
Advance Access Publication Date: 17 November 2023
Original Article

ORIGINAL ARTICLE

Blood pressure reduction after renal denervation in patients with or without chronic kidney disease

Merve Günes-Altan[1], Axel Schmid[2], Christian Ott[1], Agnes Bosch[1], Robert Pietschner[1], Mario Schiffer[1], Michael Uder[2], Roland E. Schmieder[1] and Dennis Kannenkeril[1]

[1]Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg (FAU), Erlangen, Germany and [2]Institute of Radiology, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg (FAU), Erlangen, Germany

Correspondence to: Roland E. Schmieder; E-mail: roland.schmieder@uk-erlangen.de

ABSTRACT

Background. Renal denervation (RDN) has emerged as an adjacent option for the treatment of hypertension. This analysis of the Erlanger registry aimed to compare the blood pressure (BP)-lowering effects and safety of RDN in patients with and without chronic kidney disease (CKD).

Methods. In this single-center retrospective analysis, 47 patients with and 127 without CKD underwent radiofrequency-, ultrasound- or alcohol-infusion-based RDN. Office and 24-h ambulatory BP and estimated glomerular filtration rate (eGFR) were measured at baseline, and after 6 and 12 months.

Results. A total of 174 patients with a mean age of 59.0 ± 10 years were followed up for 12 months. At baseline, mean eGFR was 55.8 ± 21 mL/min/1.73 m^2 in patients with CKD and 87.3 ± 13 mL/min/1.73 m^2 in patients without CKD. There was no significant eGFR decline in either of the groups during 12 months of follow-up. In patients without CKD, office systolic and diastolic BP were reduced by –15.3 ± 17.5/–7.9 ± 10.8 mmHg 6 months after RDN and by –16.1 ± 18.2/–7.7 ± 9.6 mmHg 12 months after RDN. In patients with CKD, office systolic and diastolic BP were reduced by –10.7 ± 24.0/–5.8 ± 13.2 mmHg 6 months after RDN and by –15.1 ± 24.9/–5.9 ± 12.9 mmHg 12 months after RDN. Accordingly, in patients without CKD, 24-h ambulatory systolic and diastolic BP were reduced by –7.2 ± 15.8/–4.9 ± 8.8 mmHg 6 months after RDN and by –9.0 ± 17.0/–6.2 ± 9.8 mmHg 12 months after RDN. In patients with CKD, 24-h systolic and diastolic BP were reduced by –7.4 ± 12.9/–4.2 ± 9.9 mmHg 6 months after RDN and by –8.0 ± 14.0/–3.6 ± 9.6 mmHg 12 months after RDN. There was no difference in the reduction of office and 24-h ambulatory BP between the two groups at any time point (all $P > .2$). Similar results have been found for the 6 months data. With exception of rare local adverse events, we did not observe any safety signals.

Conclusion. According to our single-center experience, we observed a similar reduction in 24-h, day and night-time ambulatory BP as well as in-office BP in patients with and without CKD at any time point up to 12 months. We conclude that RDN is an effective and safe treatment option for patients with hypertension and CKD.

Keywords: blood pressure, chronic kidney disease, hypertension, post-hoc analysis, renal denervation

Received: 14.8.2023; Editorial decision: 12.9.2023

KEY LEARNING POINTS

What was known:

- Renal denervation (RDN) has been shown in randomized sham-controlled clinical trials to effectively reduce blood pressure in patients with uncontrolled hypertension.
- Limited data exist on the effects of RDN in patients with chronic kidney disease (CKD).

This study adds:

- Our Erlanger registry analysis provides evidence that RDN is similarly effective in patients with or without CKD.
- Our findings also show that RDN is a safe treatment option, particularly for patients with CKD.

Potential impact:

- According to our data RDN appears to be a safe and an effective treatment option for hypertensive patients with CKD.

INTRODUCTION

Chronic kidney disease (CKD) is a serious health condition and a major cardiovascular risk factor worldwide. The overall prevalence of CKD has increased over time and it is expected to increase in the future [1]. This can be attributed to improved survival of patients with risk of developing renal complications, including those with hypertension [2]. There are multifactorial mechanisms that can lead to elevated blood pressure (BP) in patients with CKD. It has been shown that intensive BP control in patients with CKD can reduce mortality [3], but patients with CKD nevertheless have a poor BP control, despite receiving a high number of antihypertensive medications [4]. The German Chronic Kidney Disease study showed that at any given level of antihypertensive medication the percentage of patients with controlled hypertension was only approximately 50% [5].

Elevated activity of the central sympathetic nervous system (SNS) has been repeatedly found to play a pivotal role in the development and severity of arterial hypertension [6, 7]. Several human studies have demonstrated that renal sympathetic denervation reduces sympathetic overactivity not only to the kidneys, but also in the whole body, and decreases BP while being safe [8, 9]. The most recent published results documented that renal denervation (RDN) leads to a durable BP reduction in patients with mild to moderate as well as severe hypertension [10, 11]. The presence or absence of antihypertensive medication seem not to make a difference in terms of BP response [9]. Therefore, the 2021 European Society of Hypertension and 2023 European Society of Cardiology consensus statements recommend RDN as an adjacent option to achieve BP control in patients with uncontrolled resistant hypertension as well as in patients unable to tolerate antihypertensive drugs with estimated glomerular filtration rate (eGFR) $\geq$40 mL/min/1.73 m^2 [8, 9].

Many studies in patients with primary hypertension have been done to prove the effectiveness of RDN in terms of BP reduction and safety, but the amount of data including hypertensive patients with CKD is limited as yet, even though patients with reduced renal function and hypertension may benefit most [12]. In patients with CKD, the activity of the SNS increases with decreasing eGFR [13]. Interruption of the pathogenetic pathway of the progressive decline of renal function may attenuate the progression of CKD [12, 13]. Pilot studies in hypertensive patients with CKD have shown that the progression of renal functional loss could be slowed down or even stopped after RDN [14–17]. On the other hand, influencing renal adaptive processes by RDN, in particular high renal sympathetic activity, may cause deterioration of the kidney function in the long term.

In this analysis of the Erlanger registry we included all hypertensive patients so far treated with RDN at our center and categorized them into two groups, those with and without CKD. We aimed at comparing the 12-month BP-lowering effects and safety of RDN between the two groups. We hypothesized that RDN is similarly safe and effective in terms of BP reduction in patients with and without CKD.

MATERIALS AND METHODS

Study design

The Erlanger registry is a single-center, retrospective analysis and includes 174 patients who underwent RDN from July 2009 to April 2022. One hundred and twenty patients participated in the "Renal Denervation in Treatment Resistant Hypertension" trial (NCT01687725), an investigator-initiated study program performed only in our Erlanger center. The remaining 54 patients participated in one of the following randomized or non-randomized, sham-controlled or non-sham controlled, device company sponsored trials (http://www.clinicaltrials.gov): "SPYRAL PIVOTAL—SPYRAL HTN-OFF MED Study" (NCT02439749), "A Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN SOLO)," (NCT02649426), "The Peregrine Post-Market Study for the Treatment of Hypertension" (NCT02570113), "A Study of the ReCor Medical Paradise System in Clinical Hypertension" (NCT02649426), (RADIANCE-HTN TRIO), "SPYRAL HTN-ON MED Study" (NCT02439775), "SPYRAL DYSTAL Renal Denervation Global Clinical Study" (NCT04311086), "The RADIANCE II Pivotal Study: A Study of the ReCor Medical Paradise System in Stage II Hypertension (RADIANCE-II)" (NCT03614260) and the "The TARGET BP-OFF-MED Trial" (NCT03503773).

The Clinical Research Center of the Department of Nephrology and Hypertension, University Hospital Erlangen-Nuremberg, Germany (www.crc-erlangen.de) was a site of the multicenter clinical trials. The respective study protocols were approved by the local Ethical Review Committee (ethics committee of the University of Erlangen-Nuremberg) and the studies were conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients and prior to study inclusion.

Study cohort

The study population consisted of adult patients with uncontrolled hypertension including patients with treatment resistant hypertension taking at least three antihypertensive drugs (including one diuretic) (N = 130), patients with one to three

antihypertensive drugs ($N = 28$) and patients without any antihypertensive medication ($N = 16$). The BP criteria differed slightly between the various studies but in all these patients the uncontrolled hypertension was confirmed by 24-h ambulatory BP monitoring thereby excluding white coat hypertension. All patients fulfilled the following exclusion criteria: no known secondary cause of arterial hypertension, no pregnancy, no type 1 diabetes, no significant renal artery pathologies, no prior RDN and no known contraindication for RDN procedure. In particular, in all patients, including those with treatment resistant hypertension, secondary causes of hypertension have been excluded as a part of standard of care. Of the study cohort 47 patients had CKD defined either by clinical diagnosis, eGFR 15–59 mL/min/1.73 m^2, repeatedly confirmed A2 albuminuria (≥30 mg/g creatinine in the spontaneous urine) or several of these criteria [18].

Assessments

Baseline assessments included physical examination, office and 24-h ambulatory BP measurements, collection of medical history and antihypertensive medication, as well as blood and urine tests. Laboratory measurements included routine blood chemistry and serum creatinine and eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the creatinine/cystatin C formula [19, 20]. Directly observed therapy (DOT) was done in all patients treated with a second-generation catheter system ($N = 54$) to ensure partial adherence. At baseline, 6 and 12 months office and 24-h ambulatory BP were measured with validated devices following the recommendations of the European Society of Hypertension/European Society of Cardiology [21, 22]. Each office measurement was taken after a rest of at least 5 min and repeated twice in a sitting position. The mean values for 24-h ambulatory, day-time and night-time BP were calculated according to the published recommendations [21].

RDN procedures

Four different denervation catheters were used for procedures: Radiofrequency-based Symplicity-Flex catheter (Symplicity by Ardian Inc., Palo Alto, CA, USA), Radiofrequency-based Symplicity-Spyral catheter (Symplicity by Medtronic, Santa Rosa, CA, USA), Ultrasound-based Paradise catheter (Paradise by ReCor Medical, Palo Alto, CA, USA) and Alcohol infusion-based Peregrine-system catheter (Peregrine System Infusion Catheter, Ablative Solutions, Inc., Kalamazoo, MI, USA). All procedures were performed via femoral access and renal arteries of both sides were treated in one session. A detailed description of the procedures can be found in the previously published studies [11, 23–27].

Statistical analysis

All statistical analyses were performed with SPSS Statistics 28.0 (IBM, Armonk, NY, USA) and normally distributed data are expressed as mean ± standard deviation (SD) in text and tables. The study cohort has been categorized into patients with CKD and patients without CKD. A two-sided P-value $<.05$ was considered statistically significant. Unpaired t-test was performed for the comparison of continuous variables and Chi-square test was performed to compare categorical variables between the two groups. Paired t-test was applied for the comparison of 6- and 12-month follow-up data versus baseline. We also prespecified a subgroup analysis in patients with type 2 diabetes (T2D) defined by history of clinical diagnosis, use of antidiabetic medication, HbA1c ≥6.5 or fasting blood glucose ≥126 mg/dL. Since patients with CKD and T2D have a fast decline of eGFR, we analyzed this subgroup separately. Predictors of BP change in 24-h ambulatory and office BP were assessed by comparing responders versus non-responders defined by the median reduction of 24-h systolic BP at 6 months. Multiple regression analysis was performed at 6 and 12 months after RDN using all parameters with $P < .10$ identified in the univariate analysis.

RESULTS

Baseline characteristics

The clinical characteristics of the entire population ($N = 174$) and of the two groups with ($N = 127$) and without ($N = 47$) CKD are shown in Table 1. The patients were aged 28–79 years with a mean age of 59.0 ± 10.4 years. In the CKD group, 38.3% of the patients had an eGFR <45 mL/min/1.73 m^2. Patients with or without CKD did not differ in terms of demographic data. Patients with CKD had more comorbidities, e.g. T2D ($P < .001$) and also a higher number of antihypertensive medications (3.8 ± 3.87 versus 6.21 ± 1.8; $P = .001$) compared with patients without CKD. Patients with CKD also had lower diastolic office BPs at baseline ($P < .001$) compared with patients without CKD, whereas there was no difference in office systolic BP at baseline between the two groups.

BP reduction

The 24-h ambulatory BP in our study cohort was on average 149/90 mmHg for patients without CKD and 156/85 mmHg for patients with CKD (Table 1). While 24-h systolic BP was higher in patients with CKD ($P = .008$), diastolic BP was lower ($P = .028$). Office and 24-h BP were reduced from baseline in patients with or without CKD at all time points after RDN (all $P < .001$, Table 2). There was no significant difference in the reduction of 24-h, day-time and night-time ambulatory BP between the two groups during 12 months of follow-up (shown in Fig. 1). Even after adjustment for age and baseline 24-h ambulatory and office BP, respectively (see Table 2), there was no significant difference in BP reduction (all adjusted $P > .10$).

Medication change (conducted according to the discretion of the primary care physician) did not differ between the two groups ($P = .434$): at 6 months, decrease in number of drugs took place (without CKD versus with CKD) in 16.5% versus 25.5% and reduction in dosage in 16.5% versus 29.8%, whereas increase in medication number occurred in 20.5% versus 21.3%. Thus, in patients with and without CKD medication burden was reduced and there was no difference between the two groups.

Renal function

At baseline mean eGFR was 55.8 ± 21 mL/min/1.73 m^2 in patients with CKD and 87.3 ± 13 mL/min/1.73 m^2 in patients without CKD according to the CKD-EPI formula. After 12 months there was no significant decline of eGFR compared with the baseline value according to CKD-EPI or creatinine/cystatin C formula in either of the two groups (all $P > .05$, Table 3).

Table 1: Patient characteristics at baseline.

	All (N = 174)	Without CKD (N = 127)	With CKD (N = 47)	P-value (with versus without CKD)
Demographic data				
Age (years)	59.0 ± 10.4	58.3 ± 10.1	61.2 ± 11.1	.107
Male/female (*n*/*n*)	131/43	94/33	37/10	.525
Body mass index (kg/m^2)	30.0 ± 4.8	29.8 ± 4.7	30.5 ± 4.9	.354
Weight (kg)	91.7 ± 17.3	91.2 ± 16.5	91.8 ± 18.4	.854
Comorbidities				
Diabetes mellitus, *n* (%)	55 (32)	29 (23)	26 (55)	<.001
Coronary artery disease, *n* (%)	39 (22)	16 (13)	23 (49)	<.001
Left ventricular hypertrophy, *n* (%)	27 (16)	11 (9)	16 (34)	<.001
Hyperlipidemia, *n* (%)	65 (37)	39 (31)	26 (55)	.003
Stroke, TIA, *n* (%)	19 (11)	8 (6)	11 (24)	.002
Smoking, *n* (%)	20 (12)	17 (13)	3 (6)	.159
Office BP				
Office systolic BP (mmHg)	157.5 ± 19.8	158.1 ± 18.7	155.7 ± 22.7	.468
Office diastolic BP (mmHg)	89.8 ± 13.9	91.9 ± 12.6	83.9 ± 15.7	<.001
Office HR (bpm)	69.6 ± 13.3	69.6 ± 12.4	69.8 ± 15.8	.906
24-h ambulatory blood pressure				
Ambulatory 24-h systolic BP (mmHg)	151.1 ± 15.4	149.2 ± 14.4	156.2 ± 16.8	.008
Ambulatory 24-h diastolic BP (mmHg)	88.7 ± 12.2	90.0 ± 10.7	85.4 ± 15.2	.028
Ambulatory 24-h HR (bpm)	68.4 ± 10.6	69.1 ± 10.5	66.7 ± 10.9	.200
Laboratory values				
HbA1c (%)	6.1 ± 1.0	5.9 ± 0.9	6.5 ± 1.0	.004
Creatinine (mg/dL)	1.0 ± 0.4	0.9 ± 0.2	1.4 ± 0.5	<.001
eGFR, CKD-EPI formula (mL/min/1.73 m²)	79.0 ± 21	87.3 ± 13	55.8 ± 21	<.001
Cystatin C (mg/dL)	1.2 ± 0.7	1.0 ± 0.73	1.4 ± 0.4	<.001
eGFR, creatinine/cystatin C formula (mL/min/1.73 m²)	75.0 ± 23.9	85.3 ± 17.3	54.1 ± 21.7	<.001
LDL-cholesterol (mg/dL)	140 ± 37	144 ± 35	132 ± 41	.069
Uric acid (mg/dL)	6.7 ± 1.7	6.3 ± 1.5	7.6 ± 1.7	<.001
Urea (mg/dL)	41.1 ± 18.3	35.2 ± 10.9	57.0 ± 23.9	<.001
Hemoglobin (g/dL)	14.2 ± 1.3	14.5 ± 1.2	13.6 ± 1.5	<.001
Hematocrit (%)	41.8 ± 3.9	42.5 ± 3.4	39.9 ± 4.6	<.001

Data are presented as mean ± SD or *n* (%).
TIA, transient ischemic attack; LDL, low-density lipoprotein; HbA1c, glycated hemoglobin.

Subgroup analysis—T2D

The study population included 55 patients (31.6%) with T2D. The prevalence of patients with T2D was higher in patients with CKD compared with patients without CKD (55.3% versus 22.8%; $P < .001$). In this subgroup there were 29 patients (out of 127) without and 26 patients (out of 47) with CKD. There was no significant decline in eGFR comparing baseline and 12 months values between the two groups (Table 3). The eGFR decline observed at 6-month follow-up was possibly related to intermittent acute eGFR decline due to comorbidities. This was not observed in eGFR measurements taken before the 6-month visit as well as at the 12-month visit. Similar to the results for the whole study population, there was no significant difference in office, 24-h, day-time and night-time BP reduction after 6 and 12 months comparing patients with and without CKD (all $P > .10$).

Predictors of BP response

To identify any potential predictors for BP reduction we split the study cohort according to the median systolic 24-h ambulatory BP reduction after 6 months into responders and non-responders (median ≤–9 mmHg versus >–9 mmHg, Table 4). Renal function (i.e. eGFR), age, sex, body mass index and number of antihypertensive medications were not identified as determinants of BP response. All parameters with $P < .10$ identified by the split-half analysis, as well as age and sex were included in multiple regression analyses. In addition to 24-h ambulatory baseline systolic BP (which is expected according to the biological law of initial value [28]) we identified several predictors at 6 and 12 months of follow-up (all $P < .05$, Table 5). Patients with a high baseline office heart rate (HR), without T2D, without diuretic medication and who were current smokers were more likely to be responders. In accordance, systolic BP response was related to baseline systolic BP and baseline HR (shown in Fig. 2). Diastolic BP response was also related to baseline diastolic BP (6 months after RDN: $P < .001$, $r = –0.660$; 12 months after RDN: $P < .001$, $r = –0.644$). We repeated the analysis for patients with and without CKD separately (Table 5). For patients without CKD we obtained similar results as for the whole study population, whereas in patients with CKD we could not identify any predictors of BP response with exception of baseline BP. When replacing office HR with 24-h ($P = .018$), day-time ($P = .011$) or night-time ($P = .018$) ambulatory HR predicted BP response after RDN at the 6-month follow-up visit in patients with CKD. This was not observed in hypertensive patients without CKD.

Safety

In our study no periprocedural complications of the renal artery or the kidneys (e.g. infarction due to embolism) occurred. In addition to that, in a sub-analysis 51 out of 174 patients received

Table 2: Changes in office and 24-h systolic and diastolic BP through 12 month.

	6 months					12 months				
BP change	All	Without CKD	With CKD	P-value (with versus without CKD)	P-value[a]	All	Without CKD	With CKD	P-value (with versus without CKD)	P-value[a]
Office systolic BP (mmHg)	−14.0 ± 19.5 (*n* = 154)	−15.3 ± 17.5 (*n* = 112)	−10.7 ± 24.0 (*n* = 42)	.201	.696	−15.8 ± 20.3 (*n* = 139)	−16.1 ± 18.2 (*n* = 98)	−15.1 ± 24.9 (*n* = 41)	.788	.749
Office diastolic BP (mmHg)	−7.3 ± 11.5 (*n* = 154)	−7.9 ± 10.8 (*n* = 112)	−5.8 ± 13.2 (*n* = 42)	.310	.092	−7.2 ± 10.7 (*n* = 139)	−7.7 ± 9.6 (*n* = 98)	−5.9 ± 12.9 (*n* = 41)	.369	.339
Office HR (bpm)	−1.7 ± 10.4 (*n* = 154)	−1.1 ± 10.0 (*n* = 112)	−3.3 ± 11.4 (*n* = 42)	.243	.172	−2.6 ± 11.1 (*n* = 139)	−2.3 ± 10.1 (= 98)	−3.4 ± 13.4 (*n* = 41)	.628	.329
Ambulatory 24-h systolic BP (mmHg)	−7.3 ± 15.0 (*n* = 145)	−7.2 ± 15.8 (*n* = 105)	−7.4 ± 12.9 (*n* = 40)	.946	.827	−8.7 ± 16.1 (*n* = 128)	−9.0 ± 17.0 (*n* = 89)	−8.0 ± 14.0 (*n* = 39)	.745	.457
Ambulatory day-time systolic BP (mmHg)	−7.5 ± 15.9 (*n* = 145)	−6.9 ± 16.4 (*n* = 105)	−9.3 ± 14.5 (*n* = 40)	.421	.428	−8.6 ± 17.8 (*n* = 128)	−8.3 ± 18.6 (*n* = 89)	−9.3 ± 15.9 (*n* = 39)	.761	.845
Ambulatory night-time systolic BP (mmHg)	−6.1 ± 19.4 (*n* = 146)	−5.5 ± 19.9 (*n* = 106)	−7.5 ± 18.4 (*n* = 40)	.592	.751	−7.8 ± 19.7 (*n* = 129)	−7.8 ± 19.1 (*n* = 90)	−7.8 ± 17.8 (*n* = 39)	.990	.255
Ambulatory 24-h diastolic BP (mmHg)	−4.7 ± 9.1 (*n* = 145)	−4.9 ± 8.8 (*n* = 105)	−4.2 ± 9.9 (*n* = 40)	.668	.194	−5.4 ± 9.8 (*n* = 128)	−6.2 ± 9.8 (*n* = 89)	−3.6 ± 9.6 (*n* = 39)	.160	.945
Ambulatory day-time diastolic BP (mmHg)	−4.8 ± 9.7 (*n* = 145)	−4.8 ± 9.2 (*n* = 105)	−4.8 ± 11.0 (*n* = 40)	.992	.032	−5.4 ± 10.4 (*n* = 128)	−5.9 ± 10.5 (*n* = 89)	−4.1 ± 10.2 (*n* = 39)	.348	.400
Ambulatory night-time diastolic BP (mmHg)	−3.3 ± 11.3 (*n* = 146)	−3.3 ± 11.8 (*n* = 106)	−3.2 ± 10.0 (*n* = 40)	.961	.606	−4.1 ± 11.8 (*n* = 129)	−4.7 ± 12.1 (*n* = 90)	−2.5 ± 11.2 (*n* = 39)	.329	.567

Data are presented as mean ± SD.

[a]Adjusted for age and baseline office and 24-h ambulatory BP.

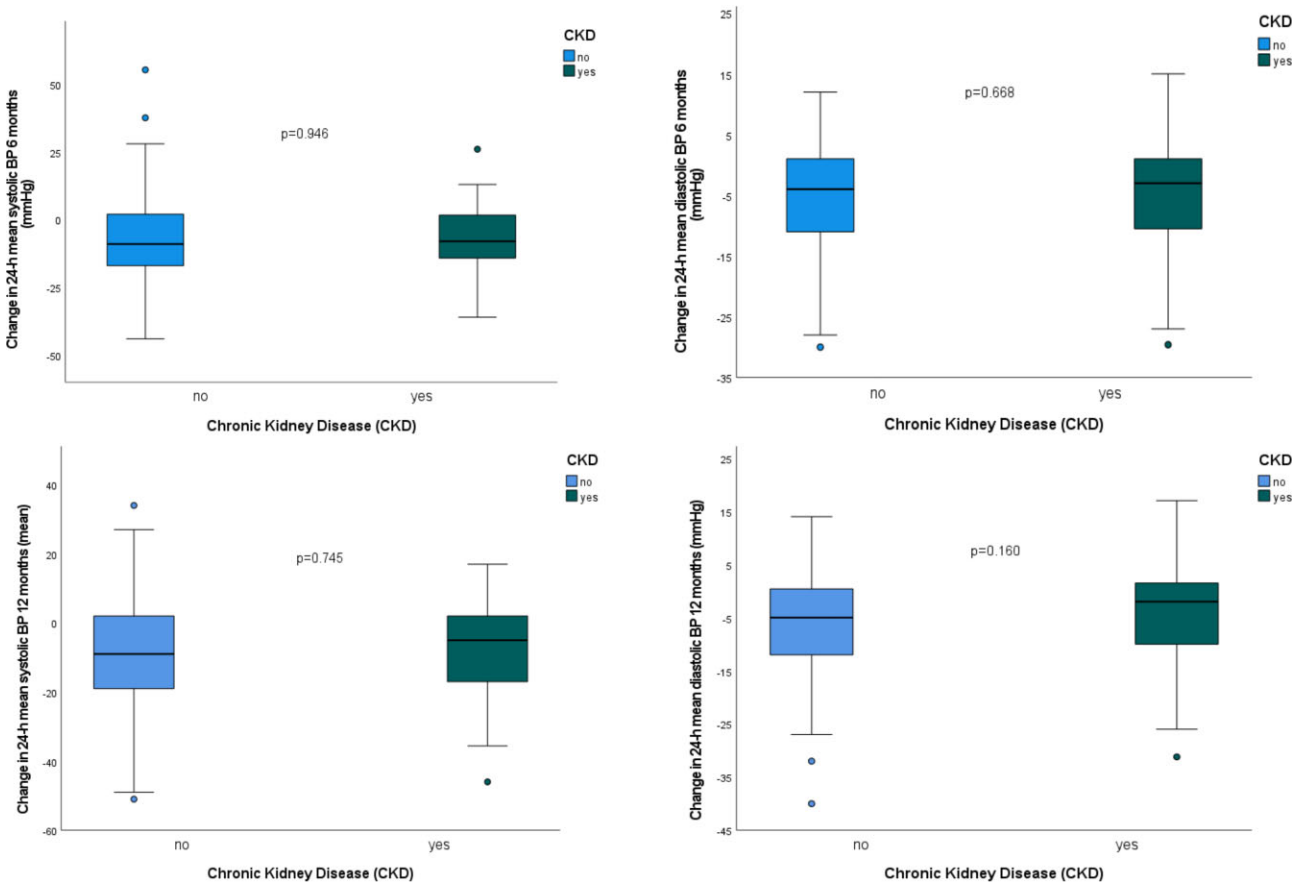

Figure 1: Comparison of the change of 24-h ambulatory systolic and diastolic BP 6 and 12 months after RDN between patients with or without CKD.

a follow-up magnetic resonance imaging (MRI) at a median of 11 months after RDN procedure [29]. Compared with the MRIs at baseline, no new renal artery stenosis or focal aneurysm was observed. Local complications related to puncture of femoral artery were rarely observed (e.g. hematoma) and were resolved within 28 days without sequelae. No periprocedural complications such as cardiovascular events or renal events (in particular acute renal failure) occurred in any of the patients after RDN.

DISCUSSION

In this study we performed a retrospective analysis of 127 patients without and 47 patients with CKD who underwent RDN for uncontrolled hypertension. Our main results are that RDN appears to be similarly effective and safe in patients without or with CKD. In our study we observed a reduction of office BP by 16.1/7.7 mmHg for patients without CKD and 15.1/5.9 mmHg for patients with CKD 12 months after RDN. Similarly, 24-h ambulatory BP reduced by 9.0/6.2 mmHg for patients without CKD and 8.0/3.6 mmHg for patients with CKD. Irrespective of whether we compared office or 24-h ambulatory BP, no difference in BP reduction was observed between patients with and without CKD. In both groups the number of antihypertensive medications was reduced without any difference between the two groups. There were no safety signals obtained.

First- and second-generation radiofrequency-, ultrasound- and alcohol-infusion-based endovascular intervention catheters were used. To date there is only one study comparing radiofrequency- and ultrasound-based catheters and they did not observe any significant difference regarding BP reduction after RDN [30]. In support of that, according to sham-controlled randomized controlled trials radiofrequency- and ultrasound-based catheters appeared to have similar BP-lowering effects, without any safety signals in either of the studies [8]. Results of the sham-controlled trials using the alcohol-infusion based Peregrine catheter have not yet been published.

In the worldwide Global SYMPLICITY Registry, ambulatory BP decreased by 8.1/4.4 mmHg at 12 months, 8.9/4.8 mmHg at 24 months and 8.5/4.6 mmHg at 36 months in patients without CKD. In patients with CKD the ambulatory BP decreased by 6.0/3.5 mmHg at 12 months, 7.2/4.0 mmHg at 24 months and 9.2/4.2 mmHg at 36 months without any significant difference from patients without CKD [16].

Many previous studies have excluded patients with eGFR <45 mL/min/1.73 m^2 and eGFR <40 mL/min/1.73 m^2, respectively, because of safety concerns. In our study, patients with eGFR ≥ 15 mL/min/1.73 m^2 were included and we did not observe any major adverse cardiovascular or renal event or sustained decline in eGFR after a follow-up of 12 months. Previous studies of patients with CKD undergoing RDN reported similar results regarding BP reduction and safety and are consistent with our results [14–17]. In contrast to previous reports, we used the CKD-EPI formula and creatinine/cystatin C formula to estimate eGFR. Consistently, we did not find any significant decline of eGFR after 12 months. Our results are similar to the results of the Global SYMPLICITY Registry which did not observe any difference in

Table 3: eGFR throughout 12 months in patients with or without CKD and patients with T2D according to CKD-EPI and creatinine/cystatin C formula.

	Baseline	6 months	P-value	Baseline	12 months	P-value
All patients						
With CKD						
eGFR CKD-EPI (mL/min/1.73 m^2)	54.4 ± 18.5 (n = 40)	51.7 ± 21.5 (n = 40)	.100	54.9 ± 17.8 (n = 40)	53.6 ± 22.7 (n = 40)	.499
eGFR creatinine/cystatin C (mL/min/1.73 m^2)	52.0 ± 19.8 (n = 39)	49.4 ± 22.4 (n = 39)	.086	52.7 ± 20.6 (n = 32)	52.2 ± 26.0 (n = 32)	.819
Without CKD						
eGFR CKD-EPI (mL/min/1.73 m^2)	86.7 ± 13.5 (n = 112)	86.8 ± 14.5 (n = 112)	.929	86.7 ± 13.4 (n = 97)	86.5 ± 14.5 (n = 97)	.799
eGFR creatinine/cystatin C (mL/min/1.73 m^2)	84.5 ± 16.9 (n = 82)	86.2 ± 18.0 (n = 82)	.140	84.0 ± 16.0 (n = 48)	83.3 ± 16.8 (n = 48)	.509
T2D						
With CKD						
eGFR CKD-EPI (mL/min/1.73 m^2)	54.6 ± 22.8 (n = 25)	49.4 ± 25.1 (n = 25)	.020	55.4 ± 21.8 (n = 25)	53.8 ± 25.8 (n = 25)	.635
eGFR creatinine/cystatin C (mL/min/1.73 m^2)	52.2 ± 23.1 (n = 25)	47.4 ± 24.4 (n = 25)	<.010	53.8 ± 24.2 (n = 20)	50.2 ± 27.3 (n = 20)	.073
Without CKD						
eGFR CKD-EPI (mL/min/1.73 m^2)	82.4 ± 14.8 (n = 33)	80.6 ± 16.8 (n = 33)	.392	82.9 ± 14.8 (n = 31)	80.3 ± 14.5 (n = 31)	.228
eGFR creatinine/cystatin C (mL/min/1.73 m^2)	77.8 ± 19.4 (n = 32)	78.9 ± 18.6 (n = 32)	.628	77.4 ± 16.2 (n = 25)	76.8 ± 15.5 (n = 25)	.735

Data are presented as mean ± SD.
First eGFR based on CKD-EPI formula, second eGFR based on creatinine/cystatin C formula.

Table 4: Analysis of responders versus non-responders at 6 months (only those variables with $P < .10$ are shown).

	Baseline		
	Median ≤–9.0 Responder (n = 74)	Median >–9.0 Non-responder (n = 71)	P-value
Change of 24-h systolic BP at 6 months	–18.4 ± 8.7	4.2 ± 11.0	<.001
Comorbidities			
Smoking, n (%)	14 (19)	5 (7)	**.042**
T2D, n (%)	23 (31)	32 (45)	.059
Office baseline BP			
Diastolic BP (mmHg)	92.6 ± 13.9	86.6 ± 13.3	**.009**
HR (bpm)	71.8 ± 12.8	65.9 ± 13.2	**.007**
Ambulatory baseline BP			
24-h systolic BP (mmHg)	154.2 ± 12.9	147.5 ± 14.8	**.004**
24-h diastolic BP (mmHg)	91.2 ± 11.4	85.7 ± 10.8	**.004**
24-h HR (bpm)	70.0 ± 10.0	65.8 ± 11.0	**.025**
Day-time systolic BP (mmHg)	158.1 ± 13.0	151.4 ± 14.8	**.005**
Day-time diastolic BP (mmHg)	94.4 ± 12.1	88.9 ± 11.6	**.006**
Day-time HR (bpm)	72.4 ± 10.5	67.8 ± 11.9	**.019**
Night-time systolic BP (mmHg)	145.5 ± 18.3	138.4 ± 21.2	**.031**
Night-time diastolic BP (mmHg)	83.4 ± 11.8	77.4 ± 12.4	**.004**
Night-time HR (bpm)	64.9 ± 9.4	60.5 ± 9.5	**.009**
Laboratory values			
Hemoglobin (g/dL)	14.5 ± 1.2	14.0 ± 1.4	**.042**
Hematocrit (%)	42.5 ± 3.2	41.0 ± 4.4	**.030**
Cholesterol (mg/dL)	221.3 ± 45.8	195.2 ± 43.1	**.001**
LDL-cholesterol (mg/dL)	149.9 ± 36.8	129.1 ± 33.5	**.001**
Uric acid (mg/dL)	6.5 ± 1.6	7.1 ± 1.6	.062
Antihypertensive medication			
Diuretics, n (%)	47 (64)	57 (80)	**.019**
Beta-blockers, n (%)	43 (58)	51 (72)	.060

Data are presented as mean ± SD or n (%).
LDL, low-density lipoprotein.
Bold values represent P-values ≤0.05.

Table 5: Multiple regression analysis at 6 and 12 months.

	Change in 24-h systolic ambulatory BP at 6 months		Change in 24-h systolic ambulatory BP at 12 months	
	Beta-value	P-value	Beta-value	P-value
All patients				
24-h systolic BP baseline	–0.361	**<.001**	**–0.555**	**<.001**
Office HR baseline	–0.148	.132	**–0.260**	**.007**
Sex	–0.080	.399	–0.080	.372
Age	0.068	.462	0.058	.516
Diuretics	0.247	**.035**	0.260	**.024**
T2D	0.090	.395	0.224	**.027**
Smoking	–0.061	.505	0.233	**.012**
LDL-cholesterol	–0.045	.630	0.074	.421
Uric acid	–0.041	.665	0.027	.762
Beta-blockers	–0.018	.875	–0.062	.585
Without CKD				
24-h systolic BP baseline	–0.276	**.017**	–0.478	**<.001**
Office HR baseline	–0.132	.280	–0.390	**.001**
Sex	–0.080	.503	–0.062	.567
Age	0.097	.400	0.032	.773
Diuretics	0.287	**.043**	0.305	**.025**
T2D	0.040	.764	0.303	**.019**
Smoking	–0.102	.372	0.258	**.024**
LDL-cholesterol	–0.070	.559	0.208	.064
Uric acid	–0.089	.429	0.016	.876
Beta-blockers	–0.036	.807	–0.110	.442
With CKD				
24-h systolic BP baseline	–0.683	**.001**	–0.674	**.002**
Office HR baseline	–0.247	.176	0.009	.963
Sex	–0.213	.215	–0.110	.549
Age	0.192	.270	0.171	.360
Diuretics	0.086	.677	–0.034	.877
T2D	0.333	.092	0.189	.372
Smoking	–0.024	.901	0.092	.664
LDL-cholesterol	–0.003	.984	–0.189	.289
Uric acid	0.320	.071	0.195	.299
Beta-blockers	–0.203	.366	–0.001	.997

LDL, low-density lipoprotein.
Bold values represent P-values ≤0.05.

eGFR decline between patients with and without CKD after 24 and 36 months [16]. This indicates that RDN in patients with CKD seems to be as effective and safe as RDN in patients without CKD.

We performed a subgroup analysis in T2D patients because these patients have a faster decline of renal function once CKD is diagnosed. We found no significant decline of eGFR after 12 months in this subgroup compared with the whole study cohort, and we observed similar reductions in office and 24-h ambulatory BP. A previous study has analyzed whether patients with T2D may more likely be non-responders to RDN due to the advanced arterial stiffness in T2D but did not find any difference in BP response compared with the whole study cohort [31]. In accordance, Kandzari *et al.* did not identify diagnosis of T2D as a confounder of BP response after RDN [32].

It is important to identify predictors for BP response to RDN as there is a large variability of BP response after RDN. In accordance with previous studies, we identified baseline 24-h ambulatory systolic BP as a predictor for BP response to RDN, i.e. patients with uncontrolled severe hypertension had the greatest BP reduction [11, 23, 24, 27, 28, 32–35]. However, this phenomenon that the pretreatment value determines post-treatment response is unspecific (i.e. not related to changes of BP only). It is found by any antihypertensive treatment and known as law of initial value (Wilder's principle) [28]. Nevertheless, in daily clinical practice pretreatment BP may serve as guidance of selecting patients for RDN.

In addition, we identified a high office baseline HR as a predictor for good BP response to RDN. The SPYRAL HTN-OFF MED pivotal trial has shown similar results, with a baseline ambulatory HR above median >73.5 bpm being a predictor of BP reduction after RDN [36]. In contrast to that, Esler *et al.* found no correlation between HR and renal sympathetic activation but only between HR and cardiac sympathetic activation [37]. Interestingly, in our study 24-h, day-time and night-time HR were of predictive value for the BP reduction 6 months after RDN only in patients with CKD. Increased HR might reflect increased activity of the SNS, commonly seen in patients with CKD [38].

In our multivariate regression analysis, besides BP and HR, diagnosis of T2D, diuretic medication and smoking status emerged as predictors in patients without CKD. Surprisingly, smokers responded better to RDN in patients without CKD. In another trial comparing 31 patients, smokers were also found to have a better BP reduction after RDN [39]. Smoking is associated with an increased activity of the SNS and may therefore explain the better BP response of smokers after RDN [40].

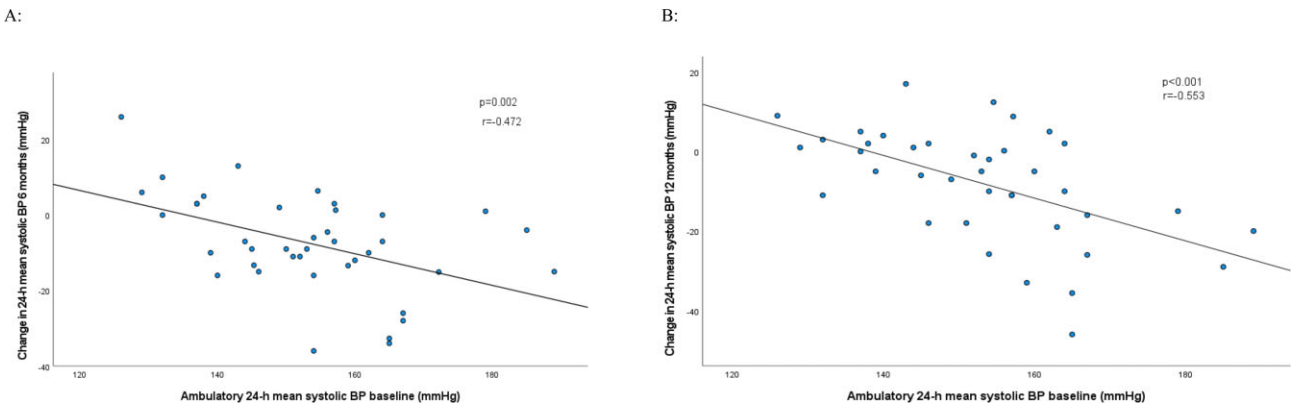

Figure 2: Correlation of baseline 24-h ambulatory BP and the change of 24-h ambulatory BP 6 or 12 months after RDN for patients with CKD. (**A**) Systolic BP after 6 months. (**B**) Systolic BP after 12 months.

Limitations

Our study has several limitations. It is a single-center, retrospective study and some patients were lost to follow-up. There is also a heterogeneous nature to the population and devices. Another limitation of our study is that we have no adherence data for antihypertensive medication. However, DOT was done in all patients treated with a second-generation catheter system. This process at least ensures partial adherence. Further prospective, double-blind and sham-controlled studies are needed to support our findings.

CONCLUSION

In conclusion, according to our data RDN appears to be a safe and an effective treatment option for hypertensive patients with and without CKD, but controlled studies are needed. No serious adverse events were noted in the whole study cohort, but importantly in patients with CKD.

ACKNOWLEDGEMENTS

We gratefully acknowledge the expert technical assistance of Dorothea Bader-Schmieder, Ingrid Fleischmann, Kerstin Fröhlich-Endreß, Ulrike Heinritz, Simone Pejkovic, Wiebke Maurer and Theresa Federlein.

FUNDING

No funding received.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed for this register are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST STATEMENT

M.G.-A., A.S., C.O., A.B., R.P., M.S., M.U. and D.K. declare that they have no conflict of interest with respect to this study. R.E.S. has conflict of interests: grants to the institution: Medtronic, Recor Medical, Ablative Solutions; speaker and adviser bureau: Medtronic, Recor Medical, Ablative Solutions.

REFERENCES

1. Burrows NR, Koyama A, Pavkov ME. Reported cases of end-stage kidney disease - United States, 2000-2019. *MMWR Morb Mortal Wkly Rep* 2022;**71**:412–5. https://doi.org/10.15585/mmwr.mm7111a3
2. Virani SS, Alonso A, Benjamin EJ *et al*. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation* 2020;**141**:e139–596. https://doi.org/10.1161/CIR.0000000000000757
3. Malhotra R, Nguyen HA, Benavente O *et al*. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: a systematic review and meta-analysis. *JAMA Intern Med* 2017;**177**:1498–505. https://doi.org/10.1001/jamainternmed.2017.4377
4. Ott C, Schmieder RE. Diagnosis and treatment of arterial hypertension 2021. *Kidney Int* 2022;**101**:36–46. https://doi.org/10.1016/j.kint.2021.09.026
5. Schneider MP, Hilgers KF, Schmid M *et al*. Blood pressure control in chronic kidney disease: a cross-sectional analysis from the German Chronic Kidney Disease (GCKD) study. *PLoS One* 2018;**13**:e0202604. https://doi.org/10.1371/journal.pone.0202604
6. Grassi G, Bertoli S, Seravalle G. Sympathetic nervous system: role in hypertension and in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2012;**21**:46–51. https://doi.org/10.1097/MNH.0b013e32834db45d
7. Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. *Eur Heart J* 2012;**33**:1058–66. https://doi.org/10.1093/eurheartj/ehs041
8. Barbato E, Azizi M, Schmieder RE *et al*. Renal denervation in the management of hypertension in adults. A clinical consensus statement of the ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2023;**44**:1313–30.
9. Schmieder RE, Mahfoud F, Mancia G *et al*. European Society of Hypertension position paper on renal denervation 2021. *J Hypertens* 2021;**39**:1733–41. https://doi.org/10.1097/HJH.0000000000002933
10. Bhatt DL, Vaduganathan M, Kandzari DE *et al*. Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 Trial. *Lancet* 2022;**400**:1405–16. https://doi.org/10.1016/S0140-6736(22)01787-1

11. Mahfoud F, Kandzari DE, Kario K *et al*. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. *Lancet* 2022;**399**:1401–10. https://doi.org/10.1016/S0140-6736(22)00455-X
12. Schmieder RE. Renal denervation in patients with chronic kidney disease: current evidence and future perspectives. *Nephrol Dial Transplant* 2023;**38**:1089–96.
13. Grassi G, Biffi A, Seravalle G *et al*. Sympathetic nerve traffic overactivity in chronic kidney disease: a systematic review and meta-analysis. *J Hypertens* 2021;**39**:408–16. https://doi.org/10.1097/HJH.0000000000002661
14. Hering D, Marusic P, Duval J *et al*. Effect of renal denervation on kidney function in patients with chronic kidney disease. *Int J Cardiol* 2017;**232**:93–7. https://doi.org/10.1016/j.ijcard.2017.01.047
15. Kiuchi MG, Graciano ML, Carreira MAMDQ *et al*. Long-term effects of renal sympathetic denervation on hypertensive patients with mild to moderate chronic kidney disease. *J Clin Hypertens (Greenwich)* 2016;**18**:190–6. https://doi.org/10.1111/jch.12724
16. Ott C, Mahfoud F, Mancia G *et al*. Renal denervation in patients with versus without chronic kidney disease: results from the Global SYMPLICITY Registry with follow-up data of 3 years. *Nephrol Dial Transplant* 2022;**37**:304–10. https://doi.org/10.1093/ndt/gfab154
17. Ott C, Mahfoud F, Schmid A *et al*. Renal denervation preserves renal function in patients with chronic kidney disease and resistant hypertension. *J Hypertens* 2015;**33**:1261–6. https://doi.org/10.1097/HJH.0000000000000556
18. Levey AS, De Jong PE, Coresh J *et al*. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2011;**80**:17–28. https://doi.org/10.1038/ki.2010.483
19. Inker LA, Schmid CH, Tighiouart H *et al*. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012;**367**:20–9. https://doi.org/10.1056/NEJMoa1114248
20. Levey AS, Stevens LA, Schmid CH *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
21. O'brien E, Parati G, Stergiou G *et al*. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013;**31**:1731–68. https://doi.org/10.1097/HJH.0b013e328363e964
22. Williams B, Mancia G, Spiering W *et al*. 2018 ESC/ESH Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018;**36**:1953–2041.
23. Azizi M, Sanghvi K, Saxena M *et al*. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. *Lancet* 2021;**397**:2476–86. https://doi.org/10.1016/S0140-6736(21)00788-1
24. Azizi M, Schmieder RE, Mahfoud F *et al*. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018;**391**:2335–45. https://doi.org/10.1016/S0140-6736(18)31082-1
25. Mahfoud F, Renkin J, Sievert H *et al*. Alcohol-mediated renal denervation using the Peregrine system infusion catheter for treatment of hypertension. *JACC Cardiovasc Interv* 2020;**13**:471–84. https://doi.org/10.1016/j.jcin.2019.10.048
26. Mahfoud F, Weber M, Schmieder RE *et al*. Catheter-based alcohol-mediated renal denervation for the treatment of uncontrolled hypertension: design of two sham-controlled, randomized, blinded trials in the absence (TARGET BP OFF-MED) and presence (TARGET BP I) of antihypertensive medications. *Am Heart J* 2021;**239**:90–9. https://doi.org/10.1016/j.ahj.2021.05.015
27. Townsend RR, Mahfoud F, Kandzari DE *et al*. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet* 2017;**390**:2160–70. https://doi.org/10.1016/S0140-6736(17)32281-X
28. Messerli FH, Bangalore S, Schmieder RE. Wilder's principle: pre-treatment value determines post-treatment response. *Eur Heart J* 2015;**36**:576–9. https://doi.org/10.1093/eurheartj/ehu467
29. Schmid A, Schmieder R, Lell M *et al*. Mid-term vascular safety of renal denervation assessed by follow-up MR imaging. *Cardiovasc Intervent Radiol* 2016;**39**:426–32. https://doi.org/10.1007/s00270-015-1192-2
30. Lurz P, Fengler K. Lessons learned from RADIOSOUND-HTN: different technologies and techniques for catheter-based renal denervation and their effect on blood pressure. *Interv Cardiol* 2019;**14**:102–6. https://doi.org/10.15420/icr.2019.03.R1
31. Reshetnik A, Gohlisch C, Scheurig-Münkler C *et al*. Predictors for success in renal denervation-a single centre retrospective analysis. *Sci Rep* 2018;**8**:15505. https://doi.org/10.1038/s41598-018-33783-3
32. Kandzari DE, Bhatt DL, Brar S *et al*. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J* 2015;**36**:219–27. https://doi.org/10.1093/eurheartj/ehu441
33. Böhm M, Kario K, Kandzari DE *et al*. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet* 2020;**395**:1444–51. https://doi.org/10.1016/S0140-6736(20)30554-7
34. Kandzari DE, Böhm M, Mahfoud F *et al*. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018;**391**:2346–55. https://doi.org/10.1016/S0140-6736(18)30951-6
35. Lauder L, Böhm M, Mahfoud F. The current status of renal denervation for the treatment of arterial hypertension. *Prog Cardiovasc Dis* 2021;**65**:76–83. https://doi.org/10.1016/j.pcad.2021.02.005
36. Böhm M, Tsioufis K, Kandzari DE *et al*. Effect of heart rate on the outcome of renal denervation in patients with uncontrolled hypertension. *J Am Coll Cardiol* 2021;**78**:1028–38. https://doi.org/10.1016/j.jacc.2021.06.044
37. Esler M, Lambert G, Esler D *et al*. Evaluation of elevated heart rate as a sympathetic nervous system biomarker in essential hypertension. *J Hypertens* 2020;**38**:1488–95. https://doi.org/10.1097/HJH.0000000000002407
38. Grassi G, Fowler B, Scali B *et al*. Sympathetic activation and heart rate thresholds for cardiovascular risk in chronic kidney disease. *J Hypertens* 2022;**40**:1530–6. https://doi.org/10.1097/HJH.0000000000003179

39. Bartus K, Litwinowicz R, Sadowski J *et al*. Clinical factors predicting blood pressure reduction after catheter-based renal denervation. *Postepy Kardiol Interwencyjnej* 2018;**14**: 270–5.

40. Shinozaki N, Yuasa T, Takata S. Cigarette smoking augments sympathetic nerve activity in patients with coronary heart disease. *Int Heart J* 2008;**49**:261–72. https://doi.org/10.1536/ihj.49.261

Received: 14.8.2023; Editorial decision: 12.9.2023