A Three-Arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients with Resistant Hypertension (RADIOSOUND-HTN)

Running Title: Fengler et al.; Comparison of Renal Denervation Devices and Techniques

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Abstract

**Background:** Both, radiofrequency and ultrasound endovascular renal sympathetic denervation (RDN) have proven clinical efficacy for the treatment of hypertension. We performed a head-to-head comparison of these technologies.

**Methods:** Patients with resistant hypertension were randomized in a 1:1:1 manner to receive either treatment with 1) radiofrequency RDN of the main renal arteries, 2) radiofrequency RDN of the main renal arteries, side-branches and accessories, or 3) an endovascular ultrasound-based RDN of the main renal artery. The primary endpoint was change in systolic daytime ambulatory blood pressure (ABPM) at 3 months.

**Results:** Between June 2015 and June 2018, 120 patients were enrolled (mean age 64±9 years, mean daytime blood pressure 153/86±12/13 mmHg). Of these, 39 were randomized to radiofrequency main renal artery ablation, 39 to combined radiofrequency ablation of the main artery and branches and 42 to ultrasound-based treatment. Baseline daytime blood pressure, clinical characteristics and treatment were well-balanced between the groups. At three months, systolic daytime ABPM decreased by 9.5±12.3 mmHg (p<0.001) in the whole cohort. While blood pressure was significantly more reduced in the ultrasound ablation group than in the radiofrequency ablation group of the main renal artery (-13.2±13.7 vs. -6.5±10.3 mmHg, mean difference -6.7 mmHg, global p=0.038 by ANOVA, adjusted p=0.043), no significant difference was found between the radiofrequency ablation groups (-8.3±11.7 mmHg for additional side branch ablation, mean difference -1.8 mmHg, adjusted p>0.99). Similarly, the blood pressure reduction was not found to be significantly different between the ultrasound and the side branch ablation groups. Frequencies of blood pressure response ≥5 mmHg were not significantly different (global p=0.77).

**Conclusions:** In patients with resistant hypertension, endovascular ultrasound based RDN was found to be superior to radiofrequency ablation of the main renal arteries only, whereas a combined approach of radiofrequency ablation of the main arteries, accessories and side branches was not.

**Clinical Trial Registration:** URL: https://clinicaltrials.gov Unique Identifier: NCT02920034)

**Key Words:** hypertension; hypertension, kidney; renal nerves; sympathetic nervous system; renal denervation.
Clinical Perspective

What is new?
• This is the first trial to compare three different techniques and technologies for catheter based renal denervation.
• Ultrasound-based ablation of the main renal arteries seems to be superior to multipolar radiofrequency ablation of the main renal arteries
• The benefit from additional radiofrequency-based ablation of the renal artery’s side branches over ablation of the main renal artery remains undetermined.

What are the clinical implications?
• Efficacy of catheter based renal sympathetic denervation depends on the used devices and techniques
• Further research focusing on identification of patients with an optimal probability of lowering blood pressure by renal denervation is required.
Introduction

Effective treatment of hypertension remains one of the most important tasks for health care systems worldwide. While control of blood pressure (BP) can be achieved in many patients by lifestyle modification and medical treatment, in other cases this treatment is unsuccessful, resulting in resistant hypertension. In these patients, interventional treatment approaches such as catheter based renal sympathetic denervation (RDN) have emerged as potential alternative in the past decade. Following the neutral results of the first sham-controlled RDN study, the SYMPLICITY-HTN3 trial, the benefit of this technique has been doubted, until subsequently three proof-of-principle studies confirmed overall efficacy of RDN.

All these RDN studies revealed substantial variability of the BP lowering effects, an aspect of growing interest in the past years, resulting in research on patient specific characteristics, effects of co-medication and adherence as well as technical aspects of the RDN procedure itself. Analyses raised some uncertainties about the completeness of denervation within the SYMPLICITY-HTN3 trial along with the finding that especially in larger renal arteries sympathetic nerves might be too distant from the lumen of the main renal artery but closer to the lumen within the branch renal arteries and therefore more amenable to RDN. Consequently, the procedural specifics applied in the SPYRAL HTN-OFF MED and ON-MED trials included the use of a spiral catheter ensuring circumferential ablations as well as ablation in the main and branch renal arteries. An alternative RDN technology was assessed within the RADIANCE SOLO trial, using ultrasound energy for full circumferential thermal ablation of the renal sympathetic nerve with a penetration depth of 6-7 mm, which is the expected location of sympathetic nerves in the adventitia of the main renal artery, thereby eliminating the necessity of branch renal artery denervation.
Previous smaller studies suggested that ultrasound energy seems to be effective in patients in whom radiofrequency RDN was unsuccessful. Also, radiofrequency ablation of the renal artery’s side branches and accessories seems to be superior over isolated ablation of the main renal arteries.

Both approaches seem reasonable for achieving a more complete denervation and thereby increasing the magnitude of the BP lowering effect. However, a head-to-head comparison of these different ablation techniques has never been performed. Therefore, our aim was to investigate the effects of ultrasound-based or additional side-branch ablation in patients with large renal arteries and compare them to radiofrequency ablation of the main renal artery as a reference standard in a prospective randomized clinical trial.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure upon reasonable request to the corresponding author.

Trial design

We conducted a single-blind, single-center three-arm randomized clinical trial to compare three different techniques of RDN in patients with resistant hypertension: Radiofrequency ablation of the main renal artery (RFM-RDN), radiofrequency ablation of the main renal artery, branches and accessories (RFB-RDN) and ultrasound-based ablation of the main renal artery (USM-RDN). Patients were randomized in a 1:1:1 ratio using a time-based non-restricted computer algorithm. Patients were blinded to the assigned treatment.
The study was approved by local ethics committee and was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. The trial was registered at clinicaltrials.gov (identifier NCT02920034).

**Study participants**

Patients were screened if diagnosed with resistant hypertension (office BP >160 mmHg systolic or >90 mmHg diastolic, despite treatment with three or more different classes of antihypertensive drugs on at least 50% of maximum dosage for hypertension including at least one diuretic unless intolerant to diuretics). Antihypertensive medication had to be stable for at least 4 weeks.

Patients then underwent ambulatory blood pressure measurement (ABPM) to exclude white-coat hypertension. Inclusion criteria were resistant hypertension with systolic daytime BP >135 mmHg on ABPM and renal artery diameter of at least one main renal artery ≥5.5 mm. Exclusion criteria were age <18 or >75 years, pregnancy, life-expectancy <6 months, evidence for secondary hypertension, participation in any other randomized clinical trial, known renal artery stenosis or anatomy unsuitable for interventional RDN and any main renal artery diameter <4.0 mm.

To provide optimal adherence, the patient’s general practitioners were contacted and asked if participation was possible and if the patient was considered adherent to medication. Patients without sufficient medication adherence according to treating physician’s view were excluded.

**Blood Pressure Measurement**

Screening office BP was measured with automated BP monitors (Omron M300, Omron Healthcare, Kyoto, Japan and Boso medicus uno, Boso, Jungingen, Germany) from a single measurement in sitting position after 5 min. of rest (attended BP measurement). ABPM was
acquired with a cuff-based oscillometric device (Spacelabs model 90207, Spacelabs Healthcare GmbH, Feucht, Germany), adapted to patient’s arm circumference. BP recordings were registered every 15 minutes during daytime (7:00 AM - 10:00 PM) and every 30 minutes during nighttime (10:00 PM - 7:00 AM).  

**Anatomic assessment and exclusion of secondary hypertension**  
Patients underwent magnetic resonance imaging (MRI) for assessment of the renal artery anatomy. If MRI was not feasible, duplex ultrasound was performed to exclude renal artery stenosis. In these cases, as well as in case of inconclusive MRI results, final anatomic assessment was achieved using conventional cinefluoroscopic angiography. To guarantee full comparability, renal artery diameters were acquired from cinefluoroscopic images prior to the procedure.

All patients were screened for hyperaldosteronism prior to study procedure by lab testing for aldosterone-to-renin ratio. In case of pathological values (>19 [ng/l]/[ng/l]), lab testing was repeated after medication adjustment and further evaluation by endocrinologists was arranged if necessary. Screening for obstructive sleep apnea was prompted if patient’s history was suspicious for sleep apnea (extensive tiredness during the daytime, snoring or observed apnea by partners) or if ABPM showed inverse dipping pattern. Other secondary causes of arterial hypertension were excluded as appropriate.

**Procedures**  
Two different devices were used for RDN. For radiofrequency ablation the multipolar Symplicity Spyral™ catheter was used (Medtronic, Minneapolis, MN, USA). This catheter type administers up to four ablations simultaneously in a spiral pattern by creating heat using high-frequency electric energy. Ultrasound RDN was performed using the Paradise™ catheter (ReCor Medical, Palo Alto, CA, USA), a balloon-cooled device that creates a fully circumferential
thermal ablation pattern using acoustic energy. In the RFM-RDN group, multiple ablation runs of 1 minute were delivered to the main renal artery from distal to proximal. In case of early renal artery bifurcations, the larger renal branch was considered as main artery and treated to the first bifurcation. In the RFB-RDN group the main renal arteries, any side branch >3.0 mm as well as all accessory renal arteries >3.0 mm were treated, with lesion distribution from distal to proximal. Lesions were placed strictly outside renal contours on cinefluoroscopy as described previously. USM-RDN was conducted in the main renal artery only, as described for the RFM-RDN group. Details of the procedure have been published previously. In brief, a size adapted balloon was inserted to the renal artery and inflated under cinefluoroscopic control to ascertain full contact to the renal artery wall. Ultrasound energy was delivered for 7 seconds at each treatment site, after which the balloon was deflated. Lesions were placed from distal to proximal. All procedures were performed by experienced interventional cardiologists with experience in RDN using all three treatment strategies. Intravenous remifentanil was used to control visceral pain during the procedure. A transfemoral access route was used in all patients.

**Follow-up**

Patients were contacted via telephone after 1 month to assess reported BP, early complications and vital status. At 3 months, ABPM was repeated to assess the primary and key secondary endpoints. MRI was repeated after three months to detect possible renal vascular complications. In patients, where MRI was not feasible at baseline, duplex sonography was repeated at 3 months follow-up. Medication changes and adherence were assessed at 1 and 3 months by structured patient interviews.
Outcomes

The primary endpoint was change in systolic daytime BP on ABPM at 3 months. Key secondary endpoints were rate of responders, change in 24 h systolic ABPM as well as diastolic BP changes.

Definitions

BP response was defined as reduction of ≥5 mmHg in systolic daytime BP on ABPM at 3 months. Profound BP response was defined as reduction of ≥20 mmHg in systolic daytime BP on ABPM at 3 months. Isolated systolic hypertension was defined as daytime BP >135 mmHg systolic and <85 mmHg diastolic.

Sample size

The trial was designed to compare the primary outcome between the three groups after a follow-up period of three months. We assumed a change of 12 mmHg in systolic daytime BP on ABPM after three months in the USM-RDN and RFB-RDN groups and 6 mmHg in the RFM-RDN group, as well as a standard deviation of 11 mmHg. To achieve a power of 80% at a two-sided alpha level of 0.05, a sample size of 114 patients was required. To compensate for a potential loss to follow-up, enrollment of 120 patients was planned for the entire cohort.

Statistical Analysis

Continuous variables are presented as mean and standard deviation, dichotomous variables as number and percentage unless indicated otherwise. Normal distribution was tested using Kolmogorov-Smirnov Test, paired t-tests were used for within group comparisons. Homogeneity of variance was tested using Levene’s test. ANOVA or Kruskal-Wallis-Test were used to compare continuous variables, Pearson’s Chi-Square-Test was used to compare categorical variables. For pairwise testing, multiple Student’s t-tests or Mann-Whitney-U-tests were used, p-
values were adjusted for multiple comparisons using the Bonferroni method. As secondary analysis, BP results for the primary endpoint were adjusted for baseline systolic daytime values by ANCOVA. Any p-value <0.05 was considered significant.

G-Power 3.1.9.2 was used for power calculation (University of Düsseldorf, Germany)\textsuperscript{23}. All other statistical analyses were calculated with SPSS 24.0.0.0 (IBM, NY, USA).

**Results**

Between June 2015 and June 2018, a total of 120 patients were enrolled (Figure 1). Of these, 39 were randomized to RFM-RDN, 39 to RFB-RDN and 42 to USM-RDN. All patients were treated as randomized. One patient in the RFM-RDN and two patients in the RFB-RDN group did not attend follow-up. In total, 117 patients were available for analysis.

**Baseline characteristics**

Clinical baseline characteristics and medication were well balanced between the groups, except for a numerically different prescription rate of alpha blockers and centrally acting sympathicolytics that did not reach statistical significance (Table 1 and 2).

**Procedural characteristics**

The number of treated arteries and ablation points was significantly higher in the RFB-RDN group than in the other two groups (global p<0.001 by Kruskal-Wallis and adjusted p<0.001 for both, Table 3). The number of ablation sites was also higher in the RFM-RDN group than in the USM-RDN group (adjusted p<0.001), while the number of ablated arteries did not differ significantly (adjusted p>0.99). Cinefluoroscopy times and administered contrast agent volume did not differ between the RFM-RDN and USM-RDN groups but were significantly higher in the
RFB-RDN group (global \( p < 0.001 \) by ANOVA, adjusted \( p < 0.005 \) for both vs. RFM-RDN and USM-RDN, Table 3).

**Blood pressure**

Baseline BP values for 24 h and daytime ABPM were balanced between groups (Table 4). At three months, daytime systolic and diastolic BP decreased significantly in the overall cohort by 9.5/6.3±12.3/7.8 mmHg \(( p < 0.001 \) for both) and also within each treatment group \(( p < 0.001 \) for all). The primary endpoint, change in systolic daytime APBM, differed significantly between the groups \(( p=0.038 \) by ANOVA). While BP was significantly more reduced in the ultrasound ablation group than in the radiofrequency ablation group of the main renal artery \((-13.2±13.7 \text{ vs. } -6.5±10.3 \text{ mmHg, mean difference } -6.7 \text{ [98.3% confidence interval } -13.2 \text{ to } -0.2], \text{ adjusted } p=0.043)\), no significant difference was found between the radiofrequency ablation groups \((-8.3±11.7 \text{ mmHg for additional side branch ablation, mean difference } -1.8 \text{ mmHg [98.3% confidence interval } -8.5 \text{ to } 4.9], \text{ adjusted } p>0.99)\). Also, no significant difference was found between the ultrasound and the side branch ablation groups \((\text{mean difference } -4.9 \text{ mmHg [98.3% confidence interval } -11.5 \text{ to } 1.7], \text{ adjusted } p=0.22, \text{ Figure 2 and 3})\). The results for systolic daytime BP were comparable after adjustment for baseline BP values \(( p=0.048 \) by ANCOVA). Daytime diastolic as well as systolic and diastolic 24h BP changes also differed significantly between USM-RDN and RFM-RDN but not between the RFM-RDN and RFB-RDN groups \((\text{global } p\text{-values by ANOVA and adjusted } p\text{-values } <0.05 \text{ for all, Figure 2})\).

Systolic BP response of greater or equal than 5 mmHg was observed in 66% of the patients treated with RFM-RDN vs. 73% in the RFB-RDN and 67% in the USM-RDN groups \(( p=0.77)\). Profound BP response was found in 8%, 14% and 29% of patients \(( p=0.039)\).
Systolic nighttime blood pressure was lower in the RFM-RDN group than in the USM-RDN group (p=0.043 by ANOVA, adjusted p=0.040), but was not different from the RFB-RDN Group (adjusted p>0.99). At three months, systolic nighttime BP decreased by 6.1 ±14.2 mmHg in the overall cohort (p<0.001), 10.2 ±13.9 mmHg in the USM-RDN group (p<0.001) and by 5.1 ±16.0 mmHg in the RFB-RDN group (p=0.041) but was unchanged in the RFM-RDN group (-2.1 ±13.3 mmHg, p=0.34). Unadjusted comparison of these changes was also significantly different between the groups (global p=0.043 by ANOVA) but did not reach statistical significance after adjustment for systolic nighttime BP at baseline (global p=0.32 by ANCOVA).

**Procedural safety**

Transient renal artery spasm was observed in one patient in the USM-RDN group. Transient non-invasive ventilation was necessary in one patient in the USM-RDN group after conscious sedation. One symptomatic groin hematoma was observed in a patient in the RFB-RDN group without the need for further medical interventions. One patient in the USM-RDN group developed a pseudoaneurysm that could be treated successfully with ultrasound directed compression therapy. A post-procedural intracapsular and retroperitoneal hematoma was observed in one patient in the RFM-RDN group, which resolved spontaneously. All events resolved without sequelae.

**Adverse events at follow-up**

Symptomatic hypotension was observed in two patients in the RFB-RDN group. Symptomatic hypertension requiring medical treatment occurred in one patient in the RFM-RDN and two patients in the RFB-RDN group. One patient in the RFB-RDN group was hospitalized for acute decompensated heart failure during follow-up. One patient in the RFM-RDN group died from acute aortic dissection two months after the study procedure, for whom retrospective review of
the final procedural angiogram revealed no signs of dissection. No renal vascular complications or stenosis were detected at follow-up in any patient.

**Medication adherence**

Medication was changed in 11 (9%) patients, 3 in the RFM-RDN group (increased medication doses or number of drugs in all patients), 7 in the RFB-RDN group (2 decreased, 5 increased) and in one patient in the USM-RDN group (decreased number of drugs, global p=0.039 by ANOVA). When analyzing patients on stable medication only, results for between-group comparison of systolic and diastolic 24h and daytime ABPM were consistent with those for the entire cohort (global p<0.05 by ANOVA for all between-group comparisons, adjusted p<0.05 for pairwise comparison of RFM-RDN vs. USM-RDN).

**Discussion**

We present the results from a randomized prospective trial comparing three different techniques of RDN for the treatment of resistant hypertension: RFM-RDN as the reference standard, RFB-RDN and USM-RDN. Our results show 1) effective BP reduction using RDN in all groups and 2) superiority of USM-RDN over RFM-RDN, while RFB-RDN was not superior to RFM-RDN. RDN is thought to affect BP by destruction of the sympathetic fibers adjacent to the renal arteries. These fibers control sodium and water retention, activate the renin-angiotensin-aldosterone system and also interact with the central nervous system, leading to an increased BP. In patients with hypertension, sympathetic activation plays a key role, making it a promising target for BP control. As radiofrequency energy delivered by most catheters reaches only about 3 mm into the perivascular tissue, destruction of renal nerves might be incomplete.
when applied in the main renal artery, where sympathetic fibers can be found in up to 10 mm
distance from the lumen. Improving this technique should result in better efficacy of RDN.

In general, two different approaches seem reasonable to achieve a more thorough
destruction of the perivascular sympathetic nerves: Additional ablation of the renal side branches
and accessory arteries or a more complete ablation of the main renal artery by improved tissue
penetration.

As renal nerves are located closer to the intima layer in the distal part of the renal arteries
and the side-branches, placing the treatment lesions in these areas might improve RDN. A
non-randomized comparison of RFM-RDN and RFB-RDN and one randomized trial using a
unipolar ablation system suggested beneficial effects at the cost of increased contrast volume
required and cinefluoroscopy times. However, the first trial was small and non-randomized.

In the second trial, very large BP lowering effects in both treatment groups were observed,
raising questions if these findings could be generalized. In our trial, we could not demonstrate a
significantly greater BP lowering effect with RFB-RDN as compared with RFM-RDN. A
number of issues have to be considered when interpreting these findings. On the one hand, the
proportion of patients with isolated systolic hypertension, a known predictor for poor response to
RDN, is relatively high in this trial, even if some of these patients might still show a good
response to RDN. This might have reduced the between group differences, leading to the
neutral results in the RFB-RDN group. Also, the number of ablations in the RFB-RDN group is
slightly lower than in the landmark SPYRAL-HTN studies, which again could have
contributed to the non-significant results in this group. Altogether, no definite conclusion on the
value of an additional side branch ablation can be drawn and warrants further research.
The use of a balloon-cooled ultrasound catheter has been shown to lead to improved tissue penetration of 6-7 mm from the lumen, affecting up to 90% of sympathetic nerve fibers in contrast to the 3-4 mm that can be achieved by radiofrequency catheters. In addition, the device and technology ensure full circumferential ablations. It was effective in lowering BP as compared with a sham procedure in drug naïve patients within a multicenter randomized trial. This approach led to an improved BP reduction in our study as compared with the RFM-RDN group at comparable levels of cinefluoroscopy times and contrast agent volume. These results are in line with previous, non-randomized research from our group, including a significant treatment effect in non-responders to RFM-RDN. Although not directly assessed in our study, it seems reasonable that the observed stronger BP reduction could be attributed to an improved treatment depth and/or full circumferential ablation.

Overall responder rates are in line with previous publications. Interestingly, responder rates did not differ between the treatment groups despite the difference in BP changes. The magnitude of treatment effect might not necessarily go along with improved frequency of BP response. This should be considered when analyzing and interpreting effects of RDN in future trials. In principal, non-response to RDN should be attributable to either anatomic specifics which reduce the completeness of denervation or – and probably more important – to a procedure performed in patients without a substrate for the intervention, namely the absence of elevated sympathetic nervous activity as the main contributor to their hypertension. In fact, elevated sympathetic activity as relevant contributor to hypertension is only present in 45-60% of patients with essential hypertension. Even if these numbers might be higher in patients with resistant hypertension, increasing success rates for RDN far beyond these dimensions does not seem realistic. Instead, future trials should focus on identifying these patients to avoid futile
RDN procedures but also on defining specific anatomic predictors associated with a more
effective RDN procedure.

It is encouraging, that RDN seems to effectively reduce not only daytime but also
nighttime BP values, as elevated nocturnal BP is an established cardiovascular risk factor.\(^{28}\)
Even though the pronounced effect on nocturnal BP in the USM-RDN group did not persist after
adjustment for baseline values, it is possible that the improved effect on daytime BP will be
similar for nighttime BP, as our study was neither designed nor sufficiently powered to compare
nocturnal BP between the groups. Supporting this hypothesis remains a task for future trials.

**Limitations**

Our study is the first randomized head-to-head comparisons of different RDN treatment
strategies and techniques. Within the field of RDN the sample size is comparably large; however,
the total number of patients is limited, especially considering a three-arm approach, and our
results warrant confirmation in a larger, multicenter trial. Nevertheless, according to power
analysis and observed outcomes, the study was adequately powered to assess the primary
endpoint. An important limitation is the single center design, although observed treatment effects
were in the range of recently published trials. Further, the primary endpoint of our trial was
assessed at 3 months only, while data from the SPYRAL-HTN-ON-MED but also the
SYMPLECTICITY-HTN-2 trials suggest a more pronounced effect after 6 months.\(^{7,29}\) While it is
encouraging that an effective BP reduction was present already after three months in all
treatment groups, the early assessment might have precluded definitive comparisons between the
RFM-RDN and RFB-RDN groups. Furthermore, our results do not allow any comparison of
long-term effects on the renal arteries between the groups, which must be considered before
recommending a specific treatment form. The drug classes used for medical treatment were not
prespecified, and mineralocorticoid receptor antagonists are underused in this cohort. Also, we cannot provide medication adherence laboratory testing for our patients. However, even though medical adherence is generally poor in patients with arterial hypertension, we believe our results represent everyday clinical practice experience. Lastly, the present study included patients with larger renal arteries only, based on the assumption that sympathetic fibers are in greater distance from the lumen than in smaller arteries and therefore RFB-RDN or higher penetration depth would be more relevant. Therefore, results might have differed in a cohort of patients with smaller renal artery diameters.

**Conclusion**

In this trial in patients with resistant hypertension, RDN effectively lowered BP. Endovascular ultrasound based RDN was found to be superior to radiofrequency ablation of the main renal arteries whereas a combined approach of radiofrequency ablation of the main arteries, accessories and side branches was not. However, responder rates to RDN were comparable between groups.

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Disclosures

PL received speaker fees and works as a consultant to ReCor Medical and Medtronic. The other authors declare that they have no competing interests.

References


Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All (n = 120)</th>
<th>RF main only (n = 39)</th>
<th>RF branches (n = 39)</th>
<th>US (n = 42)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age</td>
<td>63.5 ± 9.4</td>
<td>63.8 ± 9.9</td>
<td>62.1 ± 10.2</td>
<td>64.6 ± 8.0</td>
<td>0.48*</td>
</tr>
<tr>
<td>Body mass index [kg/m²]</td>
<td>31.6 ± 5.6</td>
<td>30.6 ± 5.4</td>
<td>31.6 ± 5.9</td>
<td>32.6 ± 5.4</td>
<td>0.27*</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>37 (31)</td>
<td>13 (33)</td>
<td>15 (38)</td>
<td>10 (24)</td>
<td>0.36†</td>
</tr>
<tr>
<td>Serum creatinine [mg/dl]</td>
<td>0.98 ± 0.24</td>
<td>0.94 ± 0.17</td>
<td>0.98 ± 0.25</td>
<td>1.01 ± 0.27</td>
<td>0.30*</td>
</tr>
<tr>
<td>eGFR [ml/min/1.73m²]</td>
<td>77.4 ± 17.9</td>
<td>79.3 ± 15.2</td>
<td>76.9 ± 18.0</td>
<td>76.2 ± 20.3</td>
<td>0.72*</td>
</tr>
<tr>
<td>Right renal artery diameter [mm]</td>
<td>5.8 ± 0.7</td>
<td>5.7 ± 0.8</td>
<td>5.9 ± 0.7</td>
<td>5.9 ± 0.6</td>
<td>0.41*</td>
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<tr>
<td>Left renal artery diameter [mm]</td>
<td>6.0 ± 0.8</td>
<td>6.1 ± 0.8</td>
<td>5.9 ± 0.9</td>
<td>6.0 ± 0.7</td>
<td>0.53*</td>
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<td>Smoker, n (%)</td>
<td>55 (46)</td>
<td>17 (44)</td>
<td>20 (51)</td>
<td>18 (43)</td>
<td>0.75†</td>
</tr>
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<td>Diabetes, n (%)</td>
<td>55 (46)</td>
<td>15 (38)</td>
<td>18 (46)</td>
<td>22 (52)</td>
<td>0.59†</td>
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<tr>
<td>Peripheral arterial disease, n (%)</td>
<td>11 (9)</td>
<td>3 (8)</td>
<td>4 (10)</td>
<td>4 (10)</td>
<td>0.92†</td>
</tr>
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<td>Coronary artery disease, n (%)</td>
<td>43 (36)</td>
<td>9 (23)</td>
<td>15 (38)</td>
<td>19 (45)</td>
<td>0.11†</td>
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<td>Previous stroke, n (%)</td>
<td>6 (5)</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>0.99†</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>18 (15)</td>
<td>3 (8)</td>
<td>7 (18)</td>
<td>8 (19)</td>
<td>0.30†</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>21 (18)</td>
<td>7 (18)</td>
<td>6 (15)</td>
<td>8 (19)</td>
<td>0.91†</td>
</tr>
<tr>
<td>Oral anticoagulation, n (%)</td>
<td>25 (21)</td>
<td>8 (21)</td>
<td>8 (21)</td>
<td>9 (21)</td>
<td>0.99†</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>101 (84)</td>
<td>35 (90)</td>
<td>33 (85)</td>
<td>33 (79)</td>
<td>0.39†</td>
</tr>
</tbody>
</table>

eGFR = estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula), RF = radiofrequency ablation, US = ultrasound ablation.

* p-value by ANOVA, † p-value by Pearson’s Chi Square test
Table 2. Baseline medication

<table>
<thead>
<tr>
<th></th>
<th>All (n = 120)</th>
<th>RF main only (n = 39)</th>
<th>RF branches (n = 39)</th>
<th>US (n = 42)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of antihypertensive drug classes</td>
<td>5.0 ±1.4</td>
<td>4.7 ±1.4</td>
<td>5.3 ±1.4</td>
<td>5.0 ±1.5</td>
<td>0.22*</td>
</tr>
<tr>
<td>Five or more drug classes, n (%)</td>
<td>69 (58)</td>
<td>20 (51)</td>
<td>26 (67)</td>
<td>23 (55)</td>
<td>0.27†</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors, n (%)</td>
<td>38 (32)</td>
<td>12 (31)</td>
<td>13 (33)</td>
<td>13 (31)</td>
<td>0.96†</td>
</tr>
<tr>
<td>Angiotensin receptor blockers, n (%)</td>
<td>85 (71)</td>
<td>30 (77)</td>
<td>25 (64)</td>
<td>30 (71)</td>
<td>0.46†</td>
</tr>
<tr>
<td>Renin antagonists, n (%)</td>
<td>4 (3)</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>0.75†</td>
</tr>
<tr>
<td>Beta blockers, n (%)</td>
<td>104 (87)</td>
<td>34 (87)</td>
<td>32 (82)</td>
<td>38 (90)</td>
<td>0.53†</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>91 (76)</td>
<td>29 (74)</td>
<td>31 (79)</td>
<td>31 (74)</td>
<td>0.72†</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>117 (98)</td>
<td>38 (97)</td>
<td>37 (95)</td>
<td>42 (100)</td>
<td>0.34†</td>
</tr>
<tr>
<td>Second diuretic, n (%)</td>
<td>24 (20)</td>
<td>4 (10)</td>
<td>10 (26)</td>
<td>10 (24)</td>
<td>0.18†</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists, n (%)</td>
<td>28 (23)</td>
<td>6 (15)</td>
<td>12 (31)</td>
<td>10 (24)</td>
<td>0.27†</td>
</tr>
<tr>
<td>Vasodilators, n (%)</td>
<td>13 (11)</td>
<td>2 (5)</td>
<td>6 (15)</td>
<td>5 (12)</td>
<td>0.33†</td>
</tr>
<tr>
<td>Alpha blockers, n (%)</td>
<td>38 (32)</td>
<td>9 (23)</td>
<td>17 (44)</td>
<td>12 (29)</td>
<td>0.13†</td>
</tr>
<tr>
<td>Centrally acting sympathicolytics, n (%)</td>
<td>57 (48)</td>
<td>20 (51)</td>
<td>22 (56)</td>
<td>15 (36)</td>
<td>0.15†</td>
</tr>
</tbody>
</table>

* p-value by ANOVA, † p-value by Pearson’s Chi Square test
RF = radiofrequency ablation, US = ultrasound ablation.
Table 3. Procedural characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (n = 120)</th>
<th>RF main only (n = 39)</th>
<th>RF branches (n = 39)</th>
<th>US (n = 42)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation points right renal artery</td>
<td>10.0 ±7.4</td>
<td>9.1 ±3.0</td>
<td>18.3 ±6.1</td>
<td>3.2 ±0.8</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Ablation points left renal artery</td>
<td>9.2 ±6.7</td>
<td>8.1 ±2.2</td>
<td>16.8 ±6.0</td>
<td>3.2 ±0.9</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Right renal arteries treated</td>
<td>1.8 ±1.2</td>
<td>1.1 ±0.4</td>
<td>3.3 ±0.9</td>
<td>1.0 ±0.0</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Left renal arteries treated</td>
<td>1.7 ±1.2</td>
<td>1.1 ±0.2</td>
<td>3.2 ±1.0</td>
<td>1.0 ±0.2</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Contrast agent used [ml]</td>
<td>110.6 ±62.2</td>
<td>90.8 ±54.8</td>
<td>143.1 ±66.6</td>
<td>98.7 ±52.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Cincefluoroscopy time [min]</td>
<td>11.2 ±7.8</td>
<td>8.9 ±5.6</td>
<td>16.8 ±8.0</td>
<td>8.1 ±6.5</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

* p-value by ANOVA, † p-value by Kruskal-Wallis

RF = radiofrequency ablation, US = ultrasound ablation.
Table 4. Baseline ambulatory blood pressure.

<table>
<thead>
<tr>
<th></th>
<th>All (n = 120)</th>
<th>RF main only (n = 39)</th>
<th>RF branches (n = 39)</th>
<th>US (n = 42)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h average [mmHg]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>149.8 ±11.9</td>
<td>147.4 ±10.9</td>
<td>150.6 ±11.4</td>
<td>151.3 ±13.0</td>
<td>0.31*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83.6 ±12.5</td>
<td>83.6 ±10.4</td>
<td>83.5 ±14.5</td>
<td>83.6 ±12.5</td>
<td>0.99*</td>
</tr>
<tr>
<td>Daytime [mmHg]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>153.1 ±12.4</td>
<td>151.3 ±12.3</td>
<td>154.2 ±11.4</td>
<td>153.9 ±13.6</td>
<td>0.53*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>86.3 ±13.2</td>
<td>86.7 ±11.0</td>
<td>86.3 ±15.3</td>
<td>86.0 ±13.3</td>
<td>0.98*</td>
</tr>
<tr>
<td>Nighttime [mmHg]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>139.9 ±15.6</td>
<td>135.3 ±13.9</td>
<td>140.3 ±15.9</td>
<td>143.9 ±15.9</td>
<td>0.043*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75.3 ±13.1</td>
<td>73.9 ±11.7</td>
<td>75.1 ±15.2</td>
<td>76.7 ±12.3</td>
<td>0.62*</td>
</tr>
<tr>
<td>Isolated systolic hypertension (%)</td>
<td>62 (52)</td>
<td>20 (51)</td>
<td>22 (56)</td>
<td>20 (48)</td>
<td>0.73†</td>
</tr>
</tbody>
</table>

* p-value by ANOVA, † p-value by Pearson’s Chi Square test
RF = radiofrequency ablation, US = ultrasound ablation.
**Figure Legends**

**Figure 1.** Study Flow. ABPM = ambulatory blood pressure measurement, PAD = peripheral arterial disease.

**Figure 2.** Change in systolic and diastolic ambulatory blood pressure from baseline to 3 months. (A) change in daytime ambulatory blood pressure (global p=0.038 and 0.025 respectively by ANOVA). (B) change in 24h ambulatory blood pressure (global p=0.027 and 0.018 respectively by ANOVA). Data are presented as means and 95% confidence intervals, p-values presented in the figure are from pairwise testing and are adjusted using Bonferroni correction. n.s. = p-value not significant.

**Figure 3.** Individual patient systolic daytime ambulatory blood pressure changes between baseline and at 3 months and responder rates per group.
1884 patients with elevated office blood pressure screened for eligibility

1695 excluded
- 555 patient or general practitioner denied participation or patients were considered non-adherent to medication
- 1140 had normotensive ABPM

189 patients assessed for final eligibility

69 excluded
- 35 were considered non-adherent to medication
- 14 had renal artery stenosis
- 13 had renal artery diameter outside inclusion criteria
- 6 were enrolled in concurrent trial
- 1 had no femoral access (severe PAD)

120 patients met final inclusion criteria

120 patients met final inclusion criteria

39 underwent radiofrequency main renal artery ablation
- 1 lost to follow up
- 1 died from acute aortic dissection after 2 months
- 38 available for primary analysis

39 underwent radiofrequency combined main renal artery and branch ablation
- 2 lost to follow up
- 1 unable to attend follow up
- 1 withdrew consent
- 37 available for primary analysis

42 underwent ultrasound main renal artery ablation
- 0 lost to follow up
- 42 available for primary analysis
A

Change in daytime ambulatory blood pressure (mmHg)

Systolic

-5

-10

-15

-20

n.s.

n.s.

n.s.

p = 0.043

p = 0.025

Diastolic

Radiofrequency ablation main artery

Radiofrequency ablation main artery and branches

Ultrasound ablation main artery

B

Change in 24th ambulatory blood pressure (mmHg)

Systolic

0

-5

-10

-15

-20

n.s.

n.s.

n.s.

p = 0.029

Diastolic

Radiofrequency ablation main artery

Radiofrequency ablation main artery and branches

Ultrasound ablation main artery

p = 0.015
Radiofrequency ablation main artery

66% responder

Radiofrequency ablation main artery and branches

73% responder

Ultrasound ablation main artery

67% responder