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Plasma renin and aldosterone concentrations related to endovascular ultrasound renal denervation in the RADIANCE-HTN SOLO trial

Naomi D.L. Fisher, Ajay J. Kirtane, Joost Daemen, Florian Rader, Melvin D. Lobo, Manish Saxena, Josephine Abraham, Roland E. Schmieder, Andrew S.P. Sharp, Philippe Gosse, Lisa Claude, Yang Song, Michel Azizi, on behalf of the RADIANCE-HTN Investigators

Objective: The RADIANCE-HTN SOLO trial demonstrated a greater reduction in daytime ambulatory SBP at 2 months by endovascular ultrasound renal denervation than sham procedure. We hypothesized that plasma renin and aldosterone concentrations would be associated with the SBP response to renal denervation.

Methods: Hypertensive patients were randomized to renal denervation (n = 74) or sham (n = 72) after a 4-week washout of antihypertensive medications. In a 53-patient subset, 2-month and 6-month plasma renin and aldosterone concentration were measured. Dietary sodium was not controlled.

Results: Mean age of the 29 treatment and 24 sham patients was 54 years; 62% were men; 17% black. Daytime ambulatory SBP fell in the denervation but not the sham group at 2 months (−7.8 ± 10.7 vs. −0.1 ± 10.1 mmHg, P = 0.048). Baseline plasma renin and aldosterone concentrations were in the low-normal range, did not change significantly at 2 months in either group and did not predict response to renal denervation. At 6 months, after the addition of antihypertensive medications, there was a significant rise in renin in the sham but not the denervation group.

Conclusion: Although renal denervation but not sham resulted in a decrease in daytime ambulatory SBP at 2 months, renin and aldosterone concentrations did not predict the BP response to renal denervation; nor did they fall after denervation. A rise in renin at 6 months in the sham group likely represents confounding from antihypertensive medications. Whether the BP-lowering effect of renal denervation depends on reducing local intrarenal renin release requires further study.

Keywords: aldosterone, hypertension, renal denervation, renin

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CI, confidence intervals; eGFR, estimated glomerular filtration rate; PAC, plasma aldosterone concentration; PRC, plasma renin concentration; RAAS, renin–angiotensin–aldosterone system; RDN, renal denervation

INTRODUCTION

Endovascular catheter-based renal denervation (RDN), which targets the afferent and efferent renal sympathetic nerves, is a novel interventional approach being studied for hypertension control. Among patients with combined systolic–diastolic hypertension, the Paradise Ultrasound RDN System (ReCor Medical, Palo Alto, California, USA) achieved a greater reduction in daytime ambulatory SBP at 2 and 6 months than did a sham procedure [1,2]. Although the blood pressure (BP)-lowering effect of RDN in the RADIANCE-HTN SOLO trial was consistent across demographic groups and varying baseline BPs, a wide range of responsiveness was noted.

This prespecified analysis was undertaken to test the hypothesis that hormones relevant to its mechanism of action would predict greater BP responsiveness to RDN. Because of its well known interactions with the sympathetic nervous system, we hypothesized that an activated renin–angiotensin–aldosterone system (RAAS) would be associated with greater BP responsiveness to endovascular ultrasound RDN, and that denervation might result in decreased activity of the RAAS.

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METHODS

Study design and participants
The design of the RADIANCE-HTN SOLO trial was presented previously in detail [3]. Participants were recruited from 21 hospitals in the USA and 18 in Europe (France, Germany, the Netherlands, Belgium, and the United Kingdom). The study was approved by local ethics committees or institutional review boards and was done in accordance with the declaration of Helsinki. All participants provided written informed consent. The study is registered at www.clinicaltrials.gov (NCT02649426).

Briefly, eligible patients were men or women aged 18–75 years with combined systolic–diastolic hypertension that was either uncontrolled on zero to two antihypertensive medications (average seated office SBP and DBP ≥140/90 mmHg and <180/110 mmHg) or controlled on one to two antihypertensive medications (average seated office BP <140/90 mmHg). Patients also needed to have an estimated glomerular filtration rate (eGFR) ≥40 ml/min per 1.73 m² and no history of cardiovascular or cerebrovascular events. All antihypertensive medications were discontinued for 4 weeks before the ambulatory BP assessment to determine eligibility. Patients with subsequent daytime ambulatory SBP of at least 135 mmHg and DBP at least 85 mmHg and less than 170/105 mmHg underwent subsequent selective renal angiography via femoral arterial access to confirm anatomical eligibility. Patients with suitable renal artery anatomy were randomized in a 1:1 ratio to receive RDN (n = 74) or sham (n = 72). The randomization assignment was masked for 6 months for patients, outcome assessors, and clinicians involved in follow-up care. Sodium intake was unrestricted during the 6-month follow-up.

Procedures
After the postrandomization-qualifying renal angiogram, patients assigned to the RDN group underwent immediate endovascular ultrasound nerve ablation, whereas those randomized to the sham group had no further endovascular procedure.

Renal nerve ablation was performed with the Paradise Ultrasound RDN System; details are described previously [3].

Patients were evaluated at clinical visits at baseline and at 1 month and 2 months after randomization. All patients remained off antihypertensive medications until 2 months after randomization unless office BP reached levels requiring escape antihypertensive therapy sooner. Between 2 and 5 months, if monthly measured home BP was at least 135/85 mmHg, a standardized stepwise treatment protocol was recommended, consisting of the sequential addition of amlodipine 5 mg/day, a standard dose of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, hydrochlorothiazide 12.5 mg/day, followed by the sequential up-titration of hydrochlorothiazide (25 mg/day), and amlodipine (10 mg/day). The 24-h ambulatory BP measurements were performed at baseline, 2, and 6 months post randomization by use of an upper arm portable BP monitor (Microlife WatchBP, Taipei, Taiwan). All ambulatory BP recordings were sent to a core laboratory (dabl, Dublin, Ireland), with treatment assignments masked. The primary efficacy endpoint was the mean change in daytime ambulatory SBP from baseline to 2 months, adjusted for baseline SBP.

Population
Plasma hormone data was an optional assessment in the RADIANCE-HTN SOLO study. Fourteen sites (nine European and four American) collected plasma hormone data; 93% of patients within these 14 sites had plasma hormone data measured. This analysis includes all 55 patients (n = 29 RDN and n = 26 sham) who had plasma hormone data collected and who remained off antihypertensive medications prior to the 2-month visit. The primary objective of this analysis was to evaluate changes from baseline in seated plasma renin concentration (PRC) and plasma aldosterone concentration (PAC). Baseline hormones were measured after 4 weeks of medication washout and just prior to randomization. At the 2-month timepoint, PRC, PAC, and ambulatory blood pressure monitoring (ABPM) data were obtained in a subset of 50 patients, including 27 randomized to RDN and 23 randomized to sham (2M analysis population). At the 6-month timepoint, PRC, PAC, and ABPM data were obtained in a subset of 32 patients, including 16 randomized to RDN and 16 to sham (6M analysis population). One patient taking a mineralocorticoid receptor antagonist (spironolactone) at the 6-month visit was not included in the analysis. Some patients with data available at 6 months did not have data at 2 months. Dietary sodium was not controlled, and neither 24-h urinary sodium nor potassium was measured.

Laboratory
Blood was sampled after 30 min of rest in a semi-recumbent position after an overnight fast. Plasma samples were frozen at −20°C until assay. Care was taken to avoid cryoactivation of prorenin to renin during thawing. PRC was measured by a chemiluminescence assay (Liaison Analyzer, DiaSorin, Saluggia, Italy) with analytical sensitivity less than 0.53 mIU/l, as previously described (Gruson et al. [4] and Morganti [5]). This assay specifically determines the concentration of active renin by a sandwich method. Its working range extends from 0.53 to 500 mIU/l. Care was taken to avoid errors in renin measurement, including ensuring frozen samples did not thaw during storage and transport [6]. Frozen plasma samples were rapidly thawed before assay, and only once. PAC was measured by liquid chromatography with tandem mass spectrometry according to the Waters recommendations [7]. All hormones were measured by technicians blinded to the randomization sequence in a central laboratory.

Statistical analysis
Comparison of baseline demographics between RDN and sham was done using two-sample Student’s t test for continuous variables and Pearson chi-square test or Fisher’s exact test for categorical variables, as appropriate.

At 2 months, the treatment effect (change in daytime ambulatory SBP) between the RDN and the sham group was assessed using analysis of covariance, adjusting for baseline value. At 6 months, change in ambulatory SBP was assessed using analysis of covariance with RDN vs. sham as
the main effect, including the baseline value and also the number of medications at 6 months as covariates. For comparing plasma hormone values between groups, one-way analysis of variance was used. Within each treatment group, change in both BP and plasma hormone values between two timepoints was assessed using paired t tests. Because of right-skewed distributions, PRC and PAC were log-transformed for statistical analysis and geometric means with 95% confidence intervals (CI) were reported. All other continuous variables are presented as mean ± standard deviation, unless otherwise specified. Between-group differences are expressed as geometric mean and corresponding geometric two-sided 95% CI for plasma hormones and mean and corresponding two-sided 95% CI for BP.

Correlation analysis was utilized to assess the association between continuous variables; Pearson correlation coefficients and P values were reported. Correlation between log-transformed PAC and PRC were evaluated as well as their association with change in daytime ambulatory SBP at 2 months. In addition, correlation between baseline plasma potassium and aldosterone was assessed.

To assess further, the association between change in daytime ambulatory SBP at 2 months and plasma hormones (PRC, PAC), a responder analysis was performed. Patients with a fall in daytime ambulatory SBP of at least 5 mmHg at 2 months were defined as responders. Baseline and 2-month PRC and PAC values, and changes in PRC and PAC at 2 months were compared between responders and nonresponders using Wilcoxon rank-sum tests.

All analyses were performed using statistical analysis system (SAS) software version 9.4 (SAS Institute, Cary, North Carolina, USA). A P value less than 0.05 (two-sided) was considered significant.

RESULTS

Demographics of the cohort of 53 patients included in the analysis of plasma hormones (mean age of 53.8 ± 10.1 years, 62% men and 17% black) were similar to the overall RADIANCE-HTN SOLO population (mean age 54.1 ± 10.1 years, 58% men, and 17% black) (Supplemental Table 1, http://links.lww.com/HJH/B769). The RDN and sham groups did not differ in any characteristic (Table 1).

The daytime ambulatory SBP fell in the RDN but not the sham group at 2 months, and the difference was statistically significant (−7.8 ± 10.7 vs. −0.1 ± 10.1 mmHg; P = 0.048; Table 2). Following 2 months, patients with uncontrolled BP were managed with the treatment-blinded antihypertensive medication escalation protocol described above. At 6 months, daytime ambulatory SBP fell significantly more in the RDN than in the sham group (−18.8 ± 10.2 vs. −12.2 ± 8.3 mmHg; P = 0.010; Table 2).

At baseline, PAC on an unrestricted sodium diet was low in all patients (mean 13.8 mU/l, 95% CI 10.4–18.3) and not different between the groups. PAC was also low in both groups at baseline (mean 165.7 pmol/l, 95% CI 130.2–208.0), and did not differ between the groups (Table 1). Log-transformed PAC was significantly correlated to log-transformed PRC at baseline (r = 0.536, P = 0.009).

At 2 months, there was no significant change from baseline in PRC or PAC in either group, and the 2-month values were similar between groups (Fig. 1).

Neither baseline PRC nor baseline PAC predicted the BP response to RDN. There was no significant correlation between change in daytime ambulatory SBP at 2 months and log-transformed baseline PRC in either the RDN (r = −0.095, P = 0.636) or sham group (r = −0.062, P = 0.779). Likewise, there was no significant correlation between change in daytime ambulatory SBP at 2 months and log-transformed baseline PAC in either the RDN (r = −0.109, P = 0.588) or sham group (r = −0.334, P = 0.119). There was similarly no correlation between the change in daytime ambulatory SBP at 2 months and change in log-transformed PRC in the RDN (r = −0.054, P = 0.791) or sham group (r = −0.044, P = 0.842). The change in daytime ambulatory SBP at 2 months was also not correlated with change in log-transformed PAC in either the RDN (r = 0.100, P = 0.620) or sham group (r = 0.046, P = 0.834). Mean potassium values were similar in both

### TABLE 1. Baseline demographics

<table>
<thead>
<tr>
<th>Measure</th>
<th>Renal denervation (N = 29)</th>
<th>Sham (N = 24)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex [% (n)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62.1 (18)</td>
<td>62.5 (15)</td>
<td>0.974</td>
</tr>
<tr>
<td>Female</td>
<td>37.9 (11)</td>
<td>37.5 (9)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.6 ± 8.5</td>
<td>52.9 ± 11.8</td>
<td>0.553</td>
</tr>
<tr>
<td>Race [% (n)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>20.7 (6)</td>
<td>12.5 (3)</td>
<td>0.152</td>
</tr>
<tr>
<td>White</td>
<td>79.3 (23)</td>
<td>75.0 (18)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.0 (0)</td>
<td>12.5 (3)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.4 ± 7.4</td>
<td>29.4 ± 4.7</td>
<td>0.530</td>
</tr>
<tr>
<td>Baseline eGFR (ml/min per 1.73 m²)</td>
<td>87.5 ± 19.0</td>
<td>83.0 ± 14.4</td>
<td>0.341</td>
</tr>
<tr>
<td>Potassium, plasma (mmol/l)</td>
<td>4.1 ± 0.5</td>
<td>4.3 ± 0.7</td>
<td>0.423</td>
</tr>
<tr>
<td>Baseline pulse (bpm)</td>
<td>72.8 ± 11.8</td>
<td>72.9 ± 9.7</td>
<td>0.978</td>
</tr>
<tr>
<td>Baseline daytime ambulatory SBP (mmHg)</td>
<td>150.3 ± 7.1</td>
<td>147.6 ± 9.3</td>
<td>0.243</td>
</tr>
<tr>
<td>Baseline daytime ambulatory DBP (mmHg)</td>
<td>94.7 ± 4.4</td>
<td>93.1 ± 4.9</td>
<td>0.216</td>
</tr>
<tr>
<td>Baseline PRC (mU/l)</td>
<td>13.3 (8.4–21.0)</td>
<td>14.4 (10.3–20.1)</td>
<td>0.769</td>
</tr>
<tr>
<td>Baseline PAC (pmol/l)</td>
<td>155.8 (112.4–216.0)</td>
<td>178.6 (127.7–249.6)</td>
<td>0.554</td>
</tr>
</tbody>
</table>

Data presented as % (n), mean ± SD, or geometric mean (95% CI). eGFR, estimated glomerular filtration rate; PAC, plasma aldosterone concentration; PRC, plasma renin concentration.

*P value from student’s t test for continuous variables and chi-square test or Fisher’s exact test for categorical variables as appropriate comparing renal denervation arm to sham arm.
groups, and there was no significant correlation between baseline plasma potassium and log-transformed baseline PAC ($r = -0.143$, $P = 0.306$).

When patients were divided by the median PRC value of 14, those with higher values who received RDN showed a greater and statistically significant blood pressure fall compared with the sham group. Among those with PRC values lower than the median, the RDN group also had a greater fall in blood pressure than the sham patients, although this did not meet statistical significance (Fig. 2).

Among those patients who responded to active RDN treatment with a fall in daytime ambulatory SBP of at least 5 mmHg ($n = 17$), PRC did not change significantly: mean at baseline was 15.9 mIU/l compared with 19.2 mIU/l at 2 months. Among those who did not respond to RDN to this degree ($n = 10$), PRC fell from 50.8 to 22.4 mIU/l. Neither the change from baseline within each group nor the change from baseline between the two groups was statistically significant. PAC responses were similarly not significant either within each group from baseline to 2 months, or between groups. PAC fell by 67.4 pmol/l in those who responded with a fall in daytime ambulatory SBP of at least 5 mmHg, compared with a fall of 10.5 pmol/l in those who did not respond to this degree.

At 6 months, there was a significant increase from baseline in PRC in the sham group ($P = 0.0497$) but no change in the RDN group ($P = 0.201$). There was a trend to lower levels of PRC in the RDN group compared with sham; $P = 0.081$. In contrast, PAC did not change from baseline to 6 months in either group (Fig. 3).

Of note, 25% (4 of 16) in the RDN group and 37.5% (6 of 16) in the sham group were taking medications at 6 months that could raise PRC: thiazide, angiotensin II receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI). No patient was taking a beta blocker. PRC at 6 months increased significantly in both the RDN ($P = 0.018$) and sham groups ($P = 0.034$) in patient on thiazide, ARB or ACEI; in contrast there was no change in PRC values between baseline and 6 months in either group among patients not on one of these medications (Table 3).

**DISCUSSION**

Denervation of the renal nerves has shown to be effective in lowering BP in humans in multiple trials [1,2,8,9], yet the response to denervation is not universal. Two-thirds of patients in the parent RADIANCE-HTN SOLO trial had a

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**TABLE 2. Blood pressure change from baseline to 2 and 6 months**

<table>
<thead>
<tr>
<th></th>
<th>Renal denervation</th>
<th>Sham</th>
<th>Mean between-group difference adjusted for baseline SBP (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 2 months</td>
<td>Change</td>
<td>$P^a$</td>
</tr>
<tr>
<td>Daytime ambulatory SBP (mmHg)</td>
<td>$N = 27$</td>
<td>$N = 27$</td>
<td>$N = 27$</td>
</tr>
<tr>
<td></td>
<td>151.1 ± 6.6</td>
<td>143.4 ± 10.5</td>
<td>$-7.8 ± 10.7$</td>
</tr>
<tr>
<td>Daytime ambulatory SBP (mmHg)</td>
<td>$N = 16$</td>
<td>$N = 16$</td>
<td>$N = 16$</td>
</tr>
<tr>
<td></td>
<td>151.5 ± 8.3</td>
<td>132.8 ± 11.7</td>
<td>$-18.8 ± 10.2$</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD unless otherwise noted. CI, confidence interval.

$^aP$ value from paired $t$ test assessing the significance of the change from baseline to 2 or 6 months.

$^bP$ value from ANCOVA, adjusting for baseline value and number of medications at 2 or 6 months.
decrease of at least 5 mmHg in daytime ambulatory SBP and 20% achieved controlled BP (<135/85 mm Hg) in the absence of medications at 2 months, while a small proportion of patients in the intervention group had no BP-lowering [1]. Understanding its mechanisms of action and determining whether certain pathophysiologic features predict greater response to RDN would advance development of this therapy. This study was undertaken to test the hypothesis that patients with hypertension marked by a more activated RAAS would demonstrate greater BP fall following RDN, and that RDN would result in a decrease in RAAS activity as expected from experimental models [10–12].

Here, in conditions of unstimulated RAAS activity at baseline among hypertensive patients on an unrestricted sodium diet and off-antihypertensive medications, our results show that neither PRC nor PAC changed 2 months after RDN, and neither baseline PRC nor PAC predicted changes in daytime ambulatory SBP at 2 months in the RDN group. In contrast, while PRC remained stable from baseline to 6 months following RDN, it increased in the sham group, who showed a lesser decrease in daytime
ambulatory SBP. The rise in PRC in the sham group likely reflects the more frequent use of RAAS blockers and diuretics than in the RDN group. Whenever patients taking medications known to increase PRC were analyzed separately, although numbers were small, there was an increase in PRC at 6 months in both the sham and RDN groups. The significant effect of ACEIs, ARBs and diuretics in raising PRC makes off-drug hormonal assessments of much greater value, and emphasizes the need to consider this potential confounding. PAC remained stable through the 6-month follow-up.

The sympathetic nervous system plays a critical and complex role in control of BP. Efferent renal nerves modulate volume and sodium homeostasis, with stimulation resulting in volume and sodium retention, reduction in glomerular filtration, as well as renin release [13]. The contribution of renal sympathetic stimulation to renin release from the juxtaglomerular apparatus has been known for decades [14]; renin is released in response to stimulation of the beta-1 adrenergic receptor on the juxtaglomerular cells [15]. Its release is also dependent on other physiologic factors, including sodium depletion, decreased blood volume, decreased BP, which reduces perfusion pressure in the glomerular afferent arteriole, and the angiotensin II-renin negative feedback loop. Circulating renin concentration in our patients was low and remained low at 2 months. Twenty-four-hour urine collection for sodium was not obtained but the most likely explanation for suppressed PRC and PAC values in our patients is a high-sodium diet, as is usually observed in hypertensive patients in the countries where this trial was conducted.

Prior animal studies provided support for the theory that RDN would decrease BP preferentially when the RAAS is activated [10–12,16]; contrasting negative studies have also been reported [17,18]. Human studies measuring the hormonal effects of RDN are mixed; they follow an early report by Buhler demonstrating the antihypertensive effect of propranolol in 47 hypertensive patients correlated closely with both baseline levels of renin activity and with the degree of renin suppression produced, pointing to an associated neurogenic mechanism of action [19]. Results from uncontrolled studies of patients with hypertension have shown conflicting results in responses of renin and aldosterone following RDN [20–22]. Our results are consistent with findings from the proof-of-concept SPYRAL HTN-OFF MED study, in which plasma renin activity and PAC did not change 3 months after RDN in patients maintained off medications [23]. However, a follow-up publication from the SPYRAL HTN-OFF pivotal trial showed a small fall in PRA following RDN, and greater blood pressure responses in those patients with baseline PRA greater than 0.65 ng/ml per h, a prespecified cutoff based on older studies from Laragh’s therapeutic algorithm based on PRA above and below this cutoff [24]. Although our sample size is small, categorizing patients in a parallel way by median PRC did not predict blood pressure response to RDN. Methodologic and statistical differences may help explain their result. The assays differ but should not account for the discrepant results; PRA and PRC are normally highly correlated. PRC is determined by an immunoradiometric assay that measures the number of active renin molecules, whereas PRA is a bio-assay that measures the amount of angiotensin I generated per unit time during incubation of plasma samples in vitro. Under physiological conditions, PRA is proportional to the concentration of active renin, provided the concentration of renin substrate (angiotensinogen) is constant [25]. At this point, evidence does not appear sufficiently robust to allow measurements of renin, especially in nonstandardized conditions, to predict the blood pressure response to RDN in individual patients.

This analysis of PRC and PAC by definition measured activity of the systemic RAAS. However, a large body of evidence has demonstrated the critical role the intrarenal tissue RAAS plays in the pathophysiology of hypertension [26,27]. Any effects of RDN on a potentially hyperactive intrarenal RAAS would not be detectable by the measurements in this report.

### Limitations

As their assessment was optional in the protocol, plasma hormones were measured in only a 53-patient subset of the RADIANCE-HTN SOLO study. However, this subset is demographically representative of the overall SOLO population, and there were no differences in any baseline

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**TABLE 3. Plasma renin concentration and plasma aldosterone concentration for patients ON vs. OFF thiazide/angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor at 6-month visit**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients ON Thiazide/ARB/ACEI at 6 months</th>
<th>Patients OFF Thiazide/ARB/ACEI at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRC (mIU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Denervation</td>
<td>5.8 (1.0–34.5)</td>
<td>11.5 (5.7–22.9)</td>
</tr>
<tr>
<td>Sham</td>
<td>6</td>
<td>7.0 (1.1–35.6)</td>
</tr>
<tr>
<td>PRC (pmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Denervation</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Sham</td>
<td>99.4 (26.3–373.0)</td>
<td>134.2 (89.3–201.6)</td>
</tr>
</tbody>
</table>

Data presented as geometric mean (95% confidence interval). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; PAC, plasma aldosterone concentration; PRC, plasma renin concentration.

*One patient in renal denervation (RDN) and one patient in Sham group off ACEI/ARB/diuretic did not have PRC or PAC data at 2 months.
hemodynamic measure. Within the participating sites, which included both US and European centers, 93% of randomized patients had their plasma hormones measured. It was necessary to exclude patients who were started on antihypertensive medications for blood pressure control that were likely to influence plasma aldosterone and renin concentrations, rendering the group sizes in these post-treatment analyses smaller. Because of the limited sample size, the study may not have been adequately powered to detect a difference in plasma hormones.

Twenty-four-hour urinary sodium and potassium values, which optimize interpretation of PRC and PAC, were not collected. However, the very low values for both PRC and PAC are most likely secondary to a diet high in sodium. Several intermediate phenotypes of hypertension, including some that indicate an underlying activation of the intrarenal RAAS, are only appreciated after experimental activation with a restricted sodium intake. Nonmodulation is one example, a physiologic disturbance that describes a significant proportion of patients whose primary hypertension is marked by salt sensitivity and disordered regulation of the RAAS [28]. The complexity of the parent RADIANCE-HTN SOLO trial precluded additional periods of restricted dietary sodium intake to stimulate the RAAS. Controlling dietary sodium in physiologic research protocols is a time-consuming, effort-consuming and cost-consuming inclusion that would have necessitated, to achieve low salt balance, meticulously prepared meal consumption for about a week prior to each hormonal assessment. Including the stimulus of low-sodium intake may have uncovered between group differences in plasma aldosterone that were likely masked by a high sodium diet.

As with all human trials of RDN, the extent of denervation achieved could not be assessed during or after the procedure. The efficacy of the intervention is judged almost exclusively on BP reduction, which is an indirect and imprecise way of assessing the effectiveness of the procedure.

In conclusion, the hypotheses that an activated RAAS might be responsible for more robust BP lowering by RDN, and that denervation might result in decreased activity of the RAAS, were not borne out by this trial. Baseline renin and aldosterone concentrations did not predict the BP response to RDN. Although RDN resulted in a significant decrease in daytime ambulatory SBP at 2 months, there was no change in plasma renin or aldosterone concentrations observed at 2 months. A rise in renin at 6 months in the sham group likely represents confounding from antihypertensive medications.

The BP-lowering effect of RDN may depend on reducing local intrarenal renin release, a change not visible with standard plasma concentrations of renin and aldosterone. Future mechanistic studies of RDN will likely include investigation of renal hemodynamics as well as sodium handling, and will be most valuable if performed with controlled dietary sodium intake and without confounding from antihypertensive medications. Although necessarily preclinical in nature, or indirect if performed in humans, measurements of activity of the intrarenal RAAS before and after RDN have the potential to provide greater insight into the actions of RDN.

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Conflicts of interest

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