Spironolactone versus sympathetic renal denervation to treat true resistant hypertension: results from the DENERVHTA study – a randomized controlled trial

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**Objective:** Both renal denervation (RDN) and spironolactone have been proposed for the treatment of resistant hypertension. However, they have not been compared in a randomized clinical trial. We aimed to compare the efficacy of spironolactone versus RDN in patients with resistant hypertension.

**Methods:** A total of 24 patients with office SBP at least 150 mmHg and 24-h SBP at least 140 mmHg despite receiving at least three full-dose antihypertensive drugs, one a diuretic, but without aldosterone antagonists, were randomized to receive RDN or spironolactone (50 mg) as add-on therapy. Primary endpoint was change in 24-h SBP at 6 months. Comparisons between treatment groups were performed using generalized linear models adjusted by age, sex, and baseline values.

**Results:** Spironolactone was more effective than RDN in reducing 24-h SBP and 24-h DBP: mean baseline-adjusted differences between the two groups were \(-17.9\) mmHg (95%CI \(-30.9\) to \(-4.9\); \(P = 0.010\) and \(-6.6\) mmHg (95%CI \(-12.9\) to \(-0.3\); \(P = 0.041\), for 24-h SBP and 24-h DBP, respectively. As regards changes in office blood pressure, mean baseline-adjusted differences between the two groups were \(-12.1\) mmHg (95%CI \(-29.1\) to 5.1); \(P = 0.158\) and of \(-5.3\) mmHg (95%CI \(-16.3\) to 5.8); \(P = 0.332\), for office SBP and office DBP, respectively. Otherwise, the decrease of estimated glomerular filtration rate was greater in the spironolactone group; mean baseline-adjusted difference between the two groups was \(-10.7\) ml/min per 1.73 m\(^2\) (95%CI \(-20.1\) to \(-1.4\); \(P = 0.027\).

**Conclusion:** We conclude that spironolactone is more effective than RDN to reduce 24-h SBP and 24-h DBP in patients with resistant hypertension. Therefore, spironolactone should be the fourth antihypertensive drug to prescribe if deemed well tolerated in all patients with resistant hypertension before considering RDN.

**Keywords:** ablation, hypertension, renal denervation, resistant hypertension, spironolactone

**Abbreviations:** ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DENERVHTA, DENERVación en HiperTensión Arterial; eGFR, estimated glomerular filtration rate; HR, heart rate; RDN, renal denervation
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both office SBP (14.6 mmHg) and 24-h SBP (10.6 mmHg), that were significantly higher than corresponding reductions in the respective control groups, in which baseline antihypertensive treatment was maintained. More newly, results from the PATHWAY-2 (Optimum Treatment for Drug-Resistant Hypertension) trial [12] have shown that spironolactone is superior to other drugs as add-on therapy in patients with resistant hypertension.

Therefore, we designed a randomized clinical trial to evaluate the efficacy of radiofrequency RDN in patients with resistant hypertension, as compared with the addition of spironolactone to the therapeutic regimen at baseline.

METHODS

Study design and patients

The DENERVHTA (DENERVación en HiperTensio Arterial) study is a prospective, multicentre, open-label, randomized, controlled trial, which enrolled patients from October 2012 to April 2015 at three tertiary care centres specialized for hypertension diagnosis and management, all in Catalonia, Spain. The trial was approved by the local institutional Ethics Committees in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants. Patients aged at least 18 years and 80 years or less with an office SBP at least 150 mmHg and a 24-h SBP at least 140 mmHg despite a prescribed therapeutic schedule with an appropriate combination of three or more full-dose antihypertensive drugs, including a diuretic, and maintained for the last 3 months, were eligible to participate in the trial. All patients underwent renal artery imaging, either a MRI or a computed tomography, to ensure anatomical eligibility. Recruited patients for this study required to have a suitable anatomy for RDN to ensure that it was affordable with satisfactory technical outcomes. Therefore, only patients with main renal arteries with a diameter wide enough (≥ 4 mm) to enable denervation were included. Branches were also denervated when technically possible according to this diameter. Exclusion criteria included inability to perform either imaging tests; secondary hypertension, with appropriate tests being performed according to investigator criteria (with special focus on primary aldosteronism, that was ruled out by both plasmatic aldosterone and renin activity determinations after stopping interfering medications as well as by computed tomography or MRI); estimated glomerular filtration rate (eGFR) less than 45 ml/min/1.73 m²; patients currently on treatment with an aldosterone receptor blocker or who had previously received one of such class of drugs and had been withdrawn because of lack of efficacy and/or adverse effects; patients unlikely compliant with treatment (assessed according to Haynes–Sackett test [13]). Other exclusion criteria comprised prerandomization serum potassium level at least 5.5 mmol/l, pregnant women, significant valvular heart disease, or the occurrence of a major vascular event (myocardial infarction, unstable angina, or stroke) within 6 months prior to study enrolment.

After eligibility confirmation, all patients were randomized (in a 1:1 ratio) to either receive sympathetic RDN plus baseline antihypertensive treatment or spironolactone plus baseline antihypertensive treatment. The randomization sequence was generated by computer and stratified by centres using randomized blocks of small size and permutation of treatments within each block. For patients allocated to the spironolactone arm, this drug was started in a morning daily dosage of 25 mg with forced titration to 50 mg after 1 month. Physicians were encouraged to maintain study participants of both treatment groups on the initial antihypertensive drug regimen throughout the study, although for safety reasons the protocol provided the possibility of modifications when strictly required. The open design of the study allowed us to realize that the decrease in BP could be higher in the spironolactone group. Therefore, we performed an interim analysis that confirmed this suspicion. Based on this analysis, the inclusion of patients was definitely discontinued before planned and the results of patients randomized until then were analysed, which are presented here.

Procedures

A 24-h ABPM registry and laboratory tests were obtained at prerandomization and at 6 months. Validated Spacelabs 90207, (Issaquah, Washington, USA) devices and suitable sized cuffs were used for 24-h ABPM. The monitoring started at around 8–10 a.m. of a working day, with ABP readings obtained at 20-min intervals throughout both awake and asleep periods. These periods were defined according to the sleep and wake-up times reported by the patients during the monitoring day. A good technical quality recording (minimum 80% of valid readings) was required for a 24-h ABPM registry to be evaluable. Moreover, office BP was measured during the outpatient visits at baseline and at 2 weeks, 1, 3, and 6 months after randomization. BP was assessed after 5 min of rest in the sitting position using appropriate sized cuffs, between 0800–1000 h before taking any antihypertensive drug, through validated oscillometric semiautomatic devices (Omron 705IT, Kyoto, Japan). Three measurements spaced by 1–2 min were averaged to determine the final office BP values. Self-reported adverse events were also recorded at each visit. As prespecified in the protocol, serum potassium levels were closely monitored in patients who received spironolactone, concretely in 2 weeks after having started or increased the dose of the drug. For safety reasons, there were extra BP measurements or laboratory tests throughout the study according to medical discretion. BP measurements were performed by trained nurses, and the investigator responsible of the inclusion of each patient attended the medical outpatient visits, recording any adverse event and making decisions as prespecified in the protocol in accordance with BP measurements and analyses results.

Sympathetic renal denervation

All RDN procedures were performed in one single intervention centre by one specifically trained interventionalist alone, who had previous experience with the system before the study started. The single electrode radiofrequency Symplicity catheter (Medtronic, Galway, Ireland) was used in all procedures, performed 2 ± 1 week after
randomization. As recommended [14], 4–6 applications of low-power (~8 W) radiofrequency energy were delivered to each renal artery, in a helical pattern from distal to proximal within the main renal artery, with a distance between ablation sites near 5 mm. Before and during the procedure, patients were administered analgo-sedation and intravenous heparin. Intraarterial nitroglycerine was administered through renal guide and heparinized saline was continuously flushed during the procedure.

Outcomes
The primary endpoint was the between-group comparison of mean changes in ambulatory 24-h SBP from baseline to 6 months. Secondary endpoints included mean changes in all other BP and heart rate parameters from baseline to 6 months as assessed by ambulatory and office measurements. Safety outcomes, that is, acute renal failure (doubling of serum creatinine or dialysis requirement), hyperkalaemia (serum potassium levels persistently higher than 5.8 mmol/l despite implementation of lowering potassium measures) as well as mean changes in eGFR (as measured by using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula) were evaluated. A decrease of at least 25% of the baseline eGFR was considered clinically relevant. Self-reported adverse events from baseline to 6 months were also recorded.

Statistical analyses
We did the statistical analyses on the ‘intention-to-treat’ population, using the last observation carried forward. Ordinary statistical methods were performed with statistical package SPSS for Windows version 21.0 (Cary, North Carolina, USA). Briefly, variables following normal distribution are summarized as mean ± SD or as median (interquartile range) if asymmetrically distributed, and categorical data are presented as frequencies and percentages. Comparisons of baseline characteristics of patients in one treatment strategy arm or another were carried out by unpaired t-tests in continuous normally distributed data, by nonparametric Mann–Whitney test in asymmetrically distributed data, or by χ²-test in categorical data. Between-group comparisons of changes in BP and heart rate measurements as well as laboratory parameters were performed by using generalized linear models adjusted by age, sex, and respective baseline values. A change was considered significant if the two-side α level was 0.05 or less.

RESULTS
Total 38 patients with suspected resistant hypertension on the basis of office BP were screened for eligibility. Eleven patients were not randomized because of 24-h SBP less than 140 mmHg (n = 7), unsuitable renal artery anatomy (n = 3) and consent withdrawal (n = 1). In all 27 patients fulfilled inclusion criteria and were randomized after confirming they had office SBP at least 150 mmHg and 24-h SBP at least 140 mmHg. Thirteen patients were allocated to the RDN group and 14 patients were allocated to the spironolactone group. In the RDN group, two patients did not undergo the procedure because of refusal. One patient in the spironolactone group was also excluded from this analysis because of no 24-h ABPM data (Fig. 1). In total, 24 patients were analysed. Mean age was 63.5 ± 7.5 years and 63% were men. Mean office SBP was 170.1 ± 20.4 mmHg and mean office DBP was 91.8 ± 12.0 mmHg. Mean 24-h ambulatory SBP and DBP were 152.5 ± 9.0 mmHg and 81.1 ± 9.1 mmHg, respectively. Main baseline clinical characteristics and BP values of patients are shown in Table 1. As regards these baseline characteristics, there were no statistically significant differences between groups (P = NS for all comparisons). The proportions of patients in each pharmacological drug class are shown in Table 2.

One patient in the spironolactone group was withdrawn 8 weeks after randomization because of hyperkalaemia, according to the prespecified safety procedures. This patient underwent a 24-h ABPM registry and laboratory analyses at the early final visit and was included in the ‘intention-to-treat’ analyses. Patients randomized to RDN group received a median (interquartile range) of 10 (10; 11) renal artery ablations. As abovementioned, the RDN consisted on four to six applications of low-power radiofrequency energy delivered to each renal artery (82% of the patients received 10–12 applications in total). These ablations successfully followed a circumferential pattern from distal to proximal within the main renal artery in all cases, with a distance between ablation sites near 5 mm, as recommended by the device company and according to consensus documents [14].

The 24-h ambulatory blood pressure
After 6 months, the mean reduction in 24-h SBP was significantly superior in the spironolactone group than in the RDN group. After adjusting by age, sex, and baseline 24-h SBP, a mean difference between the two groups of −17.9 mmHg (95% CI −30.9 to −4.9 mmHg); P = 0.01 (Table 3) was observed. Similarly, there was a statistically significant more substantial decrease in 24-h DBP in the spironolactone group, with a mean difference between the two groups of −6.6 mmHg (95% CI −12.9 to −0.3); P = 0.04. All changes in BP parameters and comparisons between groups are summarized in Table 3. Similar results were observed as for daytime SBP and DBP. As regards nighttime BP, changes in both SBP and DBP were not significantly different between groups, although there was a trend toward a higher decrease in night-time SBP in the spironolactone group (P = 0.06). Finally, mean baseline-adjusted pulse pressure significantly decreased in the spironolactone group as compared with the RDN group in 24 h, daytime and night-time periods.

Moreover, 24-h SBP control rate, that is, the percentage of patients with 24-h SBP less than 130 mmHg at 6 months, was 53.9% in the spironolactone group, but no patient in the RDN group achieved a 24-h SBP lower than 130 mmHg (P = 0.006).

Office blood pressure and heart rate
As regards office SBP and DBP and office and ambulatory heart rate, no statistically significant differences were observed in the between-group comparisons (Table 3). Moreover, patients with controlled office SBP
(<140 mmHg) were 36% (n = 4) in the RDN group and 62% (n = 8) in the spironolactone group, with no statistically significant differences between groups (P = 0.4).

Safety issues
Table 4 shows the main changes in potassium and renal laboratory parameters. Mean baseline-adjusted variation of eGFR at 6 months showed a decrease in the spironolactone group that was significantly more profound than changes in eGFR in the RDN group. Thus, the mean baseline-adjusted difference between the two groups (spironolactone versus RDN) in eGFR was -10.7 ml/min/1.73m² (95% CI -20.1 to -1.4), P = 0.03. On the other hand, baseline-adjusted serum potassium levels significantly increased in the spironolactone group in comparison to changes in RDN (P < 0.001 for the mean baseline-adjusted difference between groups) as expected. One patient in the spironolactone group withdrew the study because of hyperkalaemia, as prespecified in the protocol. Another patient could not reach the dose of 50mg of spironolactone because of high serum potassium levels. As regards changes in eGFR, the number of patients with at least a 25% decrease of baseline eGFR at 6 months was 0 and 5 (39%) in the RDN and spironolactone groups, respectively. Otherwise, no other serious adverse event was observed. Thus, acute renal failure did not develop in any patient.

As regards other adverse events, mild groin hematoma (n = 3) and transient symptomatic hypotension (n = 3) developed in five patients in the RDN group, and one patient in the spironolactone group reported hypotension, muscle cramps, and transient symptomatic hypotension. None patient withdrew the study because of these adverse events.
Overall there were no between-group statistically significant differences as regards changes in the number or dose of drugs ($P = 0.5$). Total 73% of patients in the RDN group ($n = 8$) and 64% ($n = 9$) of patients in the spironolactone group remained with the same baseline antihypertensive regimen at 6 months.

### DISCUSSION

The main finding of the DENERVHTA study is that in patients with true resistant hypertension, the addition of spironolactone to the baseline antihypertensive drug therapy reduced 24-h SBP at 6 months more than RDN. Correspondingly, the 6-month 24-h SBP control rate was significantly higher in the group with added spironolactone. The percentage of patients who needed to add or to withdraw antihypertensive drugs was similar in both groups, and there were no differences as for the occurrence of self-reported adverse events. As regards office BP, the decrease in both SBP and DBP from baseline to 6 months did not significantly differ between groups.
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### TABLE 3. Mean baseline-adjusted changes in office and ambulatory blood pressure variables at 6 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Renal denervation (n = 11)</th>
<th>Spironolactone (n = 13)</th>
<th>Mean baseline-adjusted difference (95% CI) between the two groups at 6 months (spironolactone versus RDN)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h SBP (mmHg)</td>
<td>−5.7 (−14.0 to 3.4)</td>
<td>−23.6 (−31.9 to −15.3)</td>
<td>−17.9 (−30.9 to −4.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>24-h DBP (mmHg)</td>
<td>−3.7 (−8.2 to 0.9)</td>
<td>−10.2 (−14.4 to −6.1)</td>
<td>−6.6 (−12.9 to −0.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>24-h PP (mmHg)</td>
<td>−1.7 (−7.2 to 3.9)</td>
<td>−13.9 (−19.0 to −8.8)</td>
<td>−12.3 (−20.1 to −4.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Day SBP (mmHg)</td>
<td>−5.7 (−14.8 to 3.4)</td>
<td>−23.6 (−31.9 to −15.3)</td>
<td>−17.9 (−30.8 to −4.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Day DBP (mmHg)</td>
<td>−3.0 (−7.4 to 1.5)</td>
<td>−9.8 (−13.9 to −5.8)</td>
<td>−6.9 (−13.0 to −0.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Day PP (mmHg)</td>
<td>−1.9 (−8.5 to 4.8)</td>
<td>−14.1 (−20.1 to −8.0)</td>
<td>−12.2 (−21.7 to −2.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Day HR (bpm)</td>
<td>0.4 (−3.4 to 4.1)</td>
<td>4.0 (0.6 to 7.4)</td>
<td>3.6 (−1.6 to 8.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Night SBP (mmHg)</td>
<td>−7.7 (−18.8 to 3.4)</td>
<td>−22.3 (−32.4 to −12.2)</td>
<td>−14.6 (−30.2 to 0.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Night DBP (mmHg)</td>
<td>−5.5 (−11.2 to 0.3)</td>
<td>−10.9 (−16.1 to −5.9)</td>
<td>−5.4 (−13.4 to 2.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Night PP (mmHg)</td>
<td>−2.5 (−8.2 to 3.3)</td>
<td>−11.5 (−16.7 to −6.2)</td>
<td>−9.0 (−17.0 to −1.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Night HR (bpm)</td>
<td>0.6 (−3.0 to 4.3)</td>
<td>3.3 (0.0–6.7)</td>
<td>2.7 (−2.5 to 7.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>−17.5 (−29.7 to −5.1)</td>
<td>−29.4 (−40.7 to −18.1)</td>
<td>−12.1 (−29.1 to 5.1)</td>
<td>0.2</td>
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<td>Office DBP (mmHg)</td>
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<td>−5.3 (−16.3 to 5.8)</td>
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<tr>
<td>Office PP (mmHg)</td>
<td>−10.4 (−19.6 to −1.2)</td>
<td>−18.5 (−26.9 to −10.1)</td>
<td>−8.1 (−20.8 to 4.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Office HR (bpm)</td>
<td>0.9 (−14.9 to 16.7)</td>
<td>11.7 (−1.9 to 25.3)</td>
<td>10.8 (−10.5 to 32.1)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

BP, blood pressure; bpm, beats per minute; CI, confidence interval; HR, heart rate.

Symplicity HTN-3 study [9] where patients were randomized to RDN or to ‘sham’ procedure, failed to demonstrate between-group statistically significant differences in SBP decrease, neither when assessed by office BP nor by 24-h ABP recording. Other studies have compared RDN and ‘sham’ procedure [17] to treat patients with resistant hypertension and some trials have compared RDN versus adjusted antihypertensive drug treatment [18–20]. Taking together, as shown in a recent meta-analysis [21], although these studies suggested that RDN is superior to an appropriate pharmacological strategy, it becomes necessary further confirmation because of the high heterogeneity among study populations. As regards the role of spironolactone in the treatment of patients with resistant hypertension, the very recently published results from the PATHWAY-2 trial [12] have shown that the addition of spironolactone 25–50 mg is by far more effective to reduce home SBP as the primary endpoint. The results clearly favoured the addition of spironolactone to the baseline antihypertensive treatment when facing the challenge of reducing high BP and of achieving BP control in patients with resistant hypertension. Several factors may justify the higher BP reduction in the spironolactone group. The main reason may be that in our study, the therapeutic algorithm for the antihypertensive schedule in the pharmacological group of treatment. However, none of them planned a head-to-head comparison of RDN versus spironolactone as exclusive add-on therapy. Therefore we designed the DENERVHTA study to determine between-group differences in changes in 24-h SBP in patients randomized to receive RDN or the addition of spironolactone to the antihypertensive drug treatment scheduled at that time. To our knowledge, this is the first randomized clinical trial that compares head-to-head two different concrete treatments added to the previous antihypertensive drug regimen, that is, the addition of a single drug, spironolactone, or the addition of a device-based treatment, RDN. Furthermore, 24-h BP is considered the most reliable way to measure BP [22], and therefore we planned to evaluate changes in 24-h SBP as the primary endpoint. The results clearly favoured the addition of spironolactone to the baseline antihypertensive treatment when facing the challenge of reducing high BP and of achieving BP control in patients with resistant hypertension. Several factors may justify the higher BP reduction in the spironolactone group. The main reason may be that in our study, the therapeutic algorithm for the antihypertensive schedule in the pharmacological group of treatment. However, none of them planned a head-to-head comparison of RDN versus spironolactone as exclusive add-on therapy. Therefore we designed the DENERVHTA study to determine between-group differences in changes in 24-h SBP in patients randomized to receive RDN or the addition of spironolactone to the antihypertensive drug treatment scheduled at that time. To our knowledge, this is the first randomized clinical trial that compares head-to-head two different concrete treatments added to the previous antihypertensive drug regimen, that is, the addition of a single drug, spironolactone, or the addition of a device-based treatment, RDN. Furthermore, 24-h BP is considered the most reliable way to measure BP [22], and therefore we planned to evaluate changes in 24-h SBP as the primary endpoint. The results clearly favoured the addition of spironolactone to the baseline antihypertensive treatment when facing the challenge of reducing high BP and of achieving BP control in patients with resistant hypertension. Several factors may justify the higher BP reduction in the spironolactone group. The main reason may be that in our study, the therapeutic algorithm for the antihypertensive schedule in the pharmacological group of treatment.

### TABLE 4. Mean baseline-adjusted changes in renal function parameters at 6 months

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</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>5.9 (−2.3 to 14.1)</td>
<td>14.9 (7.4–22.4)</td>
<td>9.0 (−2.5 to 20.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>eGFR (mL/min per 1.73 m²)</td>
<td>−3.0 (−9.8 to 3.9)</td>
<td>−13.7 (−20.0 to −7.4)</td>
<td>−10.7 (−20.1 to −1.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>−0.13 (−0.36 to 0.11)</td>
<td>0.81 (0.60–1.03)</td>
<td>0.94 (0.62–1.25)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence intervals; eGFR, estimated glomerular filtration rate; RDN, renal denervation.
Spironolactone versus renal denervation

The work was supported by the Spanish Health Authority: EC11–426. The funder had no role in study design;
REFERENCES


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collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication.

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Conflicts of interest

A.O. contributes to scientific advisory with Medtronic Ibérica, S.A since February 2015. All the remaining authors declare no conflicts of interest.

Clinical Trial Registration – URL: http://www.clinicaltrials.gov. Unique identifier: NCT02039492
Reviewer’s Summary Evaluation

Reviewer 1
The study is strengthened by its randomized, prospective design and lengthy follow-up. Study weaknesses include it being done as an unblinded study and its relatively small cohort size. The study is novel in directly comparing the antihypertensive efficacy of spironolactone versus renal nerve denervation (RND) and the findings are provocative in finding the former so much better. It does add to the literature in indicating the superiority of pharmacologic approaches and highlights the relatively modest effects of RND, at least in this cohort.

Referee 2
This small randomized, open label study suggests that in patients with resistant hypertension spironolactone (50 mg/day) is more effective in reducing ambulatory blood pressure at 6 months follow-up compared to renal denervation using a single electrode ablation catheter. These findings support the utility of aldosterone antagonists as a fourth line treatment for resistant hypertension but also highlight the need to closely monitor renal function. Whether sufficient renal denervation was actually achieved in the interventional group could not be determined. Ongoing sham-controlled studies with multi-electrode devices will clarify whether more complete denervation can match the blood pressure-lowering efficacy of spironolactone.