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Twelve-month Results from the Unblinded Phase of the RADIANCE-HTN SOLO Trial of Ultrasound Renal Denervation

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Tweet/handle: @ajaykirtane; In 12-mo unblinded FU of RADIANCE-SOLO in mod HTN, BP lowering by ultrasound-based RDN was maintained on less meds w/no renal artery stenosis observed

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ABSTRACT

Objectives: We report the 12-month results of the RADIANCE-HTN SOLO trial following unblinding of patients at 6 months.

Background: The blood pressure (BP) lowering efficacy and safety of endovascular ultrasound renal denervation (RDN) in the absence (2 months) and presence (6 months) of antihypertensive medications were previously reported.

Methods: Patients with daytime ambulatory BP $\geq 135/85$ mmHg after 4-week off medications were randomized to RDN (n=74) or sham (n=72) and maintained off-medication for 2 months. A standardized medication escalation protocol was instituted between 2-5 months (blinded phase). Between 6-12 months (unblinded phase), patients received antihypertensive medications at physicians' discretion. Outcomes at 12 months included: medication burden, change in daytime ambulatory systolic BP (dASBP) and office/home SBP, visit-to-visit variability (VVV) in SBP, and safety.

Results: 65/74 RDN and 67/72 sham patients had 12-month dASBP measurements. The proportion of patients on ≥ 2 medications, the number of medications and defined daily dose were less with RDN vs. sham (27.7% vs. 44.8%, $p=0.041$; 1.0 vs. 1.4, $p=0.015$; 1.4 vs. 2.2, $p=0.007$; respectively). The decrease in dASBP from baseline in the RDN group (-16.5 ± 12.9 mmHg) remained stable at 12 months. The RDN vs. sham adjusted difference at 12 months was -2.3mmHg (95%CI: -5.9, 1.3; $p=0.201$) for dASBP, -6.3mmHg (-11.1, -1.5; $p=0.010$) for office SBP and -3.4mmHg (-6.9, 0.1; $p=0.062$) for home SBP. VVV in SBP was smaller in the RDN group. No renal artery injury was detected on CT/MR-angiogram.

Conclusions: Despite unblinding, the BP lowering effect of RDN was maintained at 12 months with less prescribed medications vs. sham.

KEY WORDS hypertension, renal denervation, ultrasound, blood pressure, variability

CONDENSED ABSTRACT

We report the 12-month results following unblinding at 6 months of patients with hypertension randomized to endovascular ultrasound renal denervation (RDN) vs. sham in the RADIANCE-HTN SOLO trial. Despite unblinding, patients in the RDN group maintained their reductions in systolic blood pressure (SBP) on fewer medications than those initially allocated to the sham procedure. Baseline to 12 months visit-to-visit variability of SBP was also smaller in the RDN group. No significant renal artery stenoses were detected on CT/MR-angiogram at 12 months.

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CI = confidence interval

dASBP = daytime ambulatory systolic blood pressure

DBP = diastolic blood pressure

DDD = defined daily dose

eGFR = estimated glomerular filtration rate

HR = heart rate

RDN = renal denervation

SBP = systolic blood pressure

VVV = visit-to-visit variability

INTRODUCTION

Renal denervation has been demonstrated to lower blood pressure (BP) in several randomized sham-controlled clinical trials. Among these, the international, multicenter RADIANCE-HTN Trial was designed to compare the BP lowering efficacy and safety of an endovascular ultrasound renal denervation (RDN) system with a sham procedure in two separate cohorts: patients with mild-to-moderate hypertension, randomized while off antihypertensive medications (SOLO cohort), and patients with uncontrolled hypertension despite receiving three antihypertensive medications (TRIO cohort). Each cohort was independently powered to detect a difference between RDN and a sham procedure on the primary end point of change in daytime ambulatory systolic BP (SBP) at 2 months (1).

We previously reported the 2- and 6-month BP and safety results of the SOLO cohort. The trial met its primary endpoint, demonstrating a reduction in daytime ambulatory SBP of 6.3 mmHg with RDN relative to a sham procedure at 2 months with patients maintained off-medications (2). Patients of both groups were subsequently restarted in a blinded fashion on a protocol-defined standardized stepped-care antihypertensive treatment to lower BP to protocol recommended targets between 2 and 6 months, before unblinding took place (1). At 6 months, RDN with standardized stepped-care antihypertensive treatment had greater ambulatory BP-lowering efficacy than the sham procedure with standardized stepped-care antihypertensive treatment, with fewer medications administered in the RDN group (3). The RADIANCE-HTN SOLO trial, together with two other randomized sham-controlled trial using radiofrequency-based catheters, showed consistent reductions in ambulatory SBP in the absence or the presence of antihypertensive medications up to 6 months after the procedure (4).

Here, we report the BP response between 6 and 12 months, where the patient, investigator, and other treating physicians were unblinded to the original treatment assignment and treating physicians were allowed to adjust antihypertensive medications at their discretion, per standard of care. By the 12-month visit, subjects had also had multiple points of contact with the investigators and therefore visit-to-visit BP variability, an important prognostic marker in hypertension (5–8), could be calculated according to whether the patient had received RDN plus antihypertensive medications, or sham plus antihypertensive medications. Renal imaging results are also reported from baseline and 12-month computed tomography (CT) or magnetic resonance (MR) angiograms.

METHODS

Study design

The international, multicenter, randomized, sham controlled RADIANCE-HTN SOLO trial design has been described previously (1, 2). The study was approved by local ethics committees or institutional review boards and conducted in accordance with the declaration of Helsinki. All participants provided written informed consent to complete up to 3 years follow-up. The procedures followed were in accordance with institutional guidelines. The study is registered at <https://www.clinicaltrials.gov> (NCT02649426).

Study population

Briefly, eligible patients were aged 18–75 years with office systolic and diastolic BP $\geq 140/90$ mmHg but $< 180/110$ mmHg on 0-2 antihypertensive medications or with office BP $< 140/90$ mmHg on 1-2 antihypertensive medications, had no history of cardiovascular or

cerebrovascular events, and had an estimated glomerular filtration rate (eGFR) ≥ 40 mL/min/1.73m² (Modification of Diet in Renal Disease formula). After a four-week discontinuation of antihypertensive medications, a total of 146 patients with daytime ambulatory SBP ≥ 135 mmHg and diastolic BP (DBP) ≥ 85 mmHg but $< 170/105$ mmHg and with suitable renal artery anatomy on a pre-randomization renal CT- or MR-angiography were randomized (1:1) to endovascular ultrasound RDN (n=74) with the Paradise[®] RDN system (ReCor Medical, Inc., Palo Alto, CA, USA) or a sham procedure (restricted to the renal angiogram only, n=72) (2). The randomization assignment was masked for 6 months after randomization for patients and for clinical staff responsible for follow-up.

Procedures

Patients were to remain off antihypertensive medications throughout the initial 2 months of follow-up to assess the primary efficacy endpoint of changes from baseline in daytime ambulatory SBP, unless specified office or home BP criteria were exceeded (1, 2). Between 2 and 5 months, if monthly measured home BP was ≥ 135 mmHg, systolic, or ≥ 85 mmHg, diastolic, a standardized stepped-care antihypertensive treatment was recommended as previously described (1). After 6-month efficacy and safety endpoints were ascertained, patients and clinical staff were unblinded to group allocation (RDN or sham) and entered thus a second unblinded and open phase of the trial, as defined by the protocol (1, 2). From 6 to 12 months, patients were maintained in their initial assigned group with no crossover to RDN during the unblinded phase, and if needed, they were prescribed antihypertensive therapy at the treating

physician's discretion with medication initiation or titration and clinical visits per standard of care.

At 12 months, patients attended the study center at approximately 08:30 am (prior to ingestion of their morning antihypertensive treatment) for a mandatory visit to 1) undergo seated office BP, heart rate (HR), and laboratory assessments, 2) analyze their home BP results, and 3) record adverse events and concomitant medications. Seated office BP and home BP were measured with the same validated electronic device (Omron M10-IT, Kyoto, Japan) as previously described (2). Ambulatory BP measurement (Microlife WatchBP, Taipei, Taiwan) was performed following witnessed pill consumption at 12 months post-randomization and recordings were sent to a core laboratory (dabl, Dublin, Ireland), with treatment assignment masked, as previously described (2). Renal CT- or MR-angiogram was performed in patients randomized to RDN at 12 months to detect *de novo* renal artery stenosis (1).

Outcomes

The main efficacy endpoint was the baseline and covariate-adjusted change in daytime ambulatory SBP at 12 months taking into account medication burden. Medication burden was assessed by: 1) the total number of antihypertensive medications prescribed (disregarding the dose), 2) the sum of defined daily dose (DDD) of each individual antihypertensive medication (9), and 3) the antihypertensive load index (defined as

$$\sum_{\text{antihypertensive medications}} \frac{(\text{prescribed daily dosage})}{(\text{maximum daily dosage})} \text{ (10) as previously described (3).}$$

To take into account the changes in antihypertensive medications that may have occurred during the unblinded phase between 6 and 12 months, we also assessed the proportion of patients with controlled BP at 12 months defined as daytime ambulatory BP <135 and <85 mmHg in those treated with either the same or decreased DDD between 6 and 12 months. Other efficacy endpoints included baseline and covariate-adjusted changes at 12 months in all other ambulatory, home, and office BP measurements and in ambulatory HR, and change in eGFR at 12 months

Analyses of visit-to-visit variability (VTV) were performed in order to assess the consistency of BP measurements over the study timepoints. The endpoints used for the evaluation of VTV of daytime ambulatory SBP (including measurements at 2, 6, and 12 months) and home SBP and office SBP (including measurements at 2, 3, 4, 5, 6, and 12 months) after excluding the baseline SBP value included (i) the standard deviation of SBP measurements over 12 months, (ii) the coefficient of variation (mean SBP value / standard deviation ratio), (iii) the variability independent of the mean, (iv) the average real variability of SBP calculated by summation of the values obtained for the absolute difference between a SBP value and the immediately preceding SBP value, and (v) the maximum SBP difference between visits as previously described (5).

Safety assessments were performed as previously reported (1, 2). All prespecified potential serious adverse events up to the 12-month visit reported by study sites were sent for independent adjudication (1, 2). An independent data safety and monitoring board reviewed study data quarterly for all enrolled patients.

Statistical Analysis

The pre-specified 12-month endpoint analysis of this second open phase of the trial where patients and physicians were unblinded, was performed on all patients with complete baseline and 12-month ambulatory BP measurements assessed by a core lab with treatment assignments masked (65 and 67 patients in the RDN and sham groups, respectively, Supplementary Appendix, Figure S1). For these analyses, p-values are descriptive and have not been adjusted for multiple comparisons.

Treatment effects (change in BP parameters, HR or eGFR from baseline) were assessed using analysis of covariance with RDN vs. sham as the main effect, including the baseline value and also the number of antihypertensive medications at 12 months as covariates, as previously described (3). When the change in BP parameters, HR or eGFR from baseline was not normally distributed, an adjusted analysis of covariance based on ranks was also performed. Repeated measures analyses of the change in ambulatory and home BP from baseline to 12 months were also performed as supportive analyses using linear mixed models adjusting for baseline values and including the number of antihypertensive medications at each visit as covariate.

Additionally, the interaction between treatment arm and visit (categorical) were included as fixed effects and in these cases, p-values were adjusted for multiple comparisons using the Tukey-Kramer test. Finally, we assessed the net benefit of being included in the RDN- or the sham group by comparing the seated office SBP and medication burden at screening prior to the run-in/washout period of 1 month to those at 12-month post-randomization, using student's t-test or Wilcoxon two samples test, as appropriate.

The VVV of SBP parameters as described above was compared between the two groups using two sample t-test. We used multiple regression analysis to look at the main determinants of

VVV of daytime, home and office SBP, including treatment (RDN or sham), age, sex, BMI, baseline SBP and eGFR.

Comparisons between groups at baseline and 12 months were made using unpaired t-tests for continuous variables and Fisher's exact test or chi square, as appropriate, for categorical variables. Continuous variables are expressed as mean \pm standard deviation, unless otherwise specified and between-group differences are expressed as mean and corresponding two-sided 95% confidence intervals (CI). All analyses were performed using statistical analysis system (SAS) software version 9.4 (SAS Institute, Cary, NC, US). A p-value lower than 0.05 (two-sided) was considered significant.

RESULTS

Study population

Baseline characteristics of the analyzed population were similar across the RDN group (N=65) and the sham group (N=67; Supplementary Appendix, Table S1) and did not differ from those of the original intention-to-treat population previously reported (2).

Medication Burden

After unblinding at 6 months, medication burden at 12 months as assessed by the total number of antihypertensive medications prescribed, the DDD, and the antihypertensive load index remained lower in the RDN group than in the sham group (Table 1). The overall proportion of patients receiving any antihypertensive medications and those on two or more antihypertensive medications increased in both groups from 6 to 12 months but remained lower

in the RDN group than in the sham group at 12 months (proportion on any antihypertensive medication: 47/65 [72.3%] vs. 57/67 [85.1%], $p = 0.073$; proportion on two or more antihypertensive medications: 18/65 [27.7%] vs. 30/67 [44.8%], $p = 0.041$; Figure 1).

Conversely, the proportion of patients who were off-medications – even though decreasing from 6 to 12 months – remained higher in the RDN group than in the sham group at 12 months (Figure 1). Of note, the RDN group was on less medications and the sham group was on more medications compared with the initial status at trial screening before medication washout 13 months prior with regards to average number of medications, DDD, and antihypertensive load index (Supplementary appendix, Table S2).

Efficacy Endpoints

The change in daytime ambulatory SBP from baseline was stable between 6 and 12 months, reaching -16.5 ± 12.9 mmHg in the RDN group vs. -15.8 ± 13.1 mmHg in the sham group at 12 months (between-group difference adjusted for baseline value and number of medications at 12 months: -2.3 mmHg, 95%CI: -5.9 to 1.3 mmHg, $p=0.201$; Table 2 and Figure 2). The adjusted between-group differences in change in office and home SBP favored the RDN group (-6.3 mmHg, 95%CI: -11.1 to -1.5 mmHg, $p=0.010$ and -3.4 mmHg, 95%CI: -6.9 to 0.1 mmHg, $p=0.062$, respectively; Table 2 and Figure 3). In the linear mixed model, the overall between-group difference (RDN vs. sham) from baseline to 12 months was -4.8 mmHg for daytime ambulatory SBP (95%CI: -7.5 to -2.1 mmHg, $p<0.001$), -6.3 mmHg for office SBP (95%CI: -10.0 to -2.7 mmHg, $p<0.001$) and -6.1 mmHg for home SBP (95%CI: -8.8 to -3.3 mmHg, $p<0.001$). The adjusted between-group differences in changes of all other ambulatory, home, and office BP measurements at 12 months are shown in Table 2. The proportion of patients with

controlled daytime ABPM at 12 months (<135 and 85 mmHg) with either the same or decreased DDD between 6 and 12 months was higher in the RDN group compared with the sham group (25/65 [38.5%] vs. 17/67 [25.4%], $p=0.107$). There was no within-group or between-group difference in office or ambulatory HR (Supplementary Appendix, Table S3).

When compared to screening values 13 months earlier, office SBP decreased from 142.1 ± 15.0 mmHg to 136.2 ± 14.7 mmHg (mean difference from screening: -5.9 mmHg, 95% CI: -9.9 to -1.9 mmHg, $p=0.004$) in RDN patients despite being treated with less medications at 12 months than at screening. In contrast, office SBP decreased from 144.5 ± 16.3 mmHg to 140.2 ± 17.2 mmHg (mean difference from screening: -4.3 mmHg, 95% CI: -8.8 to 0.2 mmHg, $p=0.062$) in patients allocated to the sham procedure while being treated with more medications at 12 months. The between-group difference (RDN vs. sham) adjusted for screening BP value and number of medications was -4.8 mmHg (95%CI: -9.8 to 0.03 mmHg, $p=0.066$).

The VVV for daytime ambulatory home and office SBP demonstrated lesser variability of BP in the RDN group vs. the sham group (Table 3). Standard deviation, coefficient of variation, and variability independent of the mean were highly correlated with each other (Supplementary Appendix, Table S4). We also calculated VVV of home SBP after excluding the 2-month SBP value because of the large between-group differences in SBP. VVV of home SBP still remained lower in the RDN group vs. the sham group but was no longer statistically significant (Supplementary Appendix, Table S5). In the multiple regression analysis, the two primary correlates of the VVV parameters for daytime ambulatory and home SBP were RDN treatment and baseline SBP (Supplementary Appendix, Tables S6 and S7). For office SBP, only baseline SBP was a determinant for some of the VVV parameters (Supplementary Appendix, Table S8).

Safety Outcomes

One patient in the sham group died (suicide) and one suffered from a cerebrovascular event. There were no other major adverse events in either group at 12 months (Supplementary Appendix, Table S8). Twelve-month imaging was available in 63 RDN patients. As previously reported, one patient underwent renal artery stent placement at 6 months after mild progression in ostial renal artery plaque (3). No new renal artery stenosis greater than 70% was detected on CT- or MR-angiogram of the renal arteries at 12 months. Calculated eGFR remained stable from baseline to 12 months in the RDN group (Supplementary Appendix, Table S9).

DISCUSSION

The primary findings of the 12 month analysis of the RADIANCE-HTN SOLO results are: 1) the BP lowering effect of ultrasound RDN for primary hypertension appears durable at 12 months with patients in the RDN group maintaining reductions in BP at 12 months on fewer medications than those initially allocated to the sham procedure, 2) on the 12 month post-procedural renal artery CT/MR angiograms, there was no evidence of renal artery injury at the sites of denervation delivery, 3) patients in the RDN group had evidence of reduced VVV on all measures of BP.

From 6 to 12 months in the unblinded phase, less medications were administered among patients treated with RDN as compared to sham, but the average reductions observed in ambulatory, home, and office BP at 6 months after RDN were maintained at 12 months without evidence of a rebound phenomenon. However, the earlier differences in BP reduction between the RDN- and the sham group observed during the blinded phase were narrowed between 6-12

months of the unblinded phase. This occurred in conjunction with more intensified antihypertensive treatment particularly among sham patients with more medications at higher doses, which were prescribed at physician's discretion and no longer protocol-defined. While unblinded follow-up can better approximate "real world" conditions, it also may be characterized by potential performance bias due to differential behavior of patients, health professionals or both following knowledge of treatment assignment. Furthermore, with the accrual of additional time points of BP assessment afforded with 12-month follow-up, RDN patients had lower VVV of BP compared with sham.

Medication Burden and BP lowering efficacy outcome

Despite the initiation (for patients off-medication) or intensification (for patients already on-medications) of antihypertensive treatment between 6-12 months of the unblinded phase in both randomized groups, the number of antihypertensive medications, DDD, and antihypertensive load index remained lower in the RDN group than in the sham group at 12 months as observed at 6 months of the blinded phase (3). The difference in DDD and antihypertensive load index between the two groups at 12 months was larger than that at 6 months of the blinded phase (3) mainly due to further intensification of the antihypertensive treatment in the sham group after 6 months. Despite treatment with fewer and lower doses of antihypertensive medications throughout 12 months, patients who underwent RDN had greater overall mean BP reduction throughout follow-up compared with the sham group. In addition, the BP lowering efficacy of RDN was greater in the home and office BP measurements at 12 months. Further, the durability of the BP lowering effect of RDN was also confirmed by the

comparison of office SBP at enrolment in the trial to that achieved 12 months after randomization.

There was no increase of the antihypertensive effect of RDN over time between 6-12 months, even though some studies (3, 11) have reported this phenomenon during the first 6 months after RDN. However, the re-institution of medications or intensification of the ongoing treatment at treating physician's discretion makes it difficult to ascertain this lack of effect. Of note, trials evaluating the long-term BP lowering efficacy of an oral antihypertensive drug do not report further decreases in BP after the first few weeks of medication administration if no additional antihypertensive medication is prescribed (12). More specifically for RDN, the theoretical concern of renal sympathetic reinnervation cannot be excluded based upon preclinical observations, although these regrown nerves likely do not achieve normal levels of function (13).

Effect of RDN on Visit-to-visit Variability of SBP

We investigated for the first time the impact of RDN on VVV of SBP in a randomised sham-controlled trial. VVV of SBP is an independent risk factor for cardiovascular and cerebrovascular events and death beyond that afforded by mean SBP and other traditional risk factors (5–7). Here, we show that patients initially treated with RDN and subsequently with antihypertensive medications had consistently lower VVV of SBP over 12 months than those randomized to intensified medication therapy alone in the sham group. Indeed, the reduction in VVV of SBP with RDN over 12 months was consistent based upon each of 4 metrics used to assess BP variability (standard deviation, coefficient of variation, variability independent of the mean, and average real variability) (14) and for each method of SBP measurement (daytime

ambulatory, home, and office SBP). Intraindividual visit-to-visit standard deviation, coefficient of variation, and variability independent of the mean were tightly correlated as previously reported (15) and convey similar information on overall variability and dispersion of BP measurements, whereas average real variability is one of the metrics of the variability between consecutive visits (15, 16). We limited the impact of the number and timing of visits as well as the BP measurement device which influence VVV of SBP (15), by calculating VVV using the same number and timing of visits and the same devices in the RDN- and the sham group.

In the multiple regression analysis, treatment with RDN and baseline SBP were the only two significant determinants of VVV for daytime ambulatory and home SBP. The earlier BP decrease as well as the use of fewer (17) or the non-initiation of antihypertensive medications (18) may have contributed to the lower VVV of BP in the RDN group as suggested by the smaller difference in VVV of home SBP, still in favor of the RDN group, after excluding the 2-month values. Of note, despite the sham group receiving more frequently calcium channel blockers alone or in combination (not shown) which may have lowered VVV of BP (5, 19), VVV of BP remained lower in the RDN group. Finally, lower adherence to therapy has also been associated with higher VVV of SBP (20), but we did not measure adherence to medications. Further studies will be needed to confirm whether VVV of SBP will remain improved in the longer-term following RDN and, if confirmed, to analyze in depth the underlying mechanisms of such decrease in VVV of SBP.

Analysis of Safety

Importantly, the incidence of adverse events remained low among patients randomized to initial RDN as compared to those randomized to the sham procedure. We did not detect any significant *de novo* renal artery stenosis at the site of the ultrasound ablations on systematic CT- or MR-angiogram at 12 months. This is consistent with the results of a meta-analysis reporting a very low incidence of new significant renal artery stenosis (0.20%) after a median of 11 months post procedure (1 to 36 months) (21). Renal function, as measured by eGFR, remained stable following RDN. Of note, longer-term follow-up of the treatment effect and safety is planned to be extended from 3 to 5 years from this trial cohort.

Study Limitations

Analysis of the 12-month BP efficacy outcomes was more complex than at 6 months because of i) the confounding effect of a more intensified antihypertensive treatment in the sham group prescribed at discretion of the physicians following unblinding at 6 months, and 2) uncontrolled and unknown behavior of both patients and physicians after unblinding with variable physician-scheduled appointments and preference in drug prescription and variable decision of patients to seek care and possibly to take their medication. This potential performance bias illustrates the need for sham controlled blinded studies to evaluate the efficacy of RDN in initial pivotal trials (22). Another limitation includes the absence of objective assessments of medication adherence. Indeed, we cannot exclude differential adherence to the medications in the two randomized groups especially after unblinding of patients compared to the first 6 months where both patients and physicians were adequately blinded (2, 3). However, ambulatory BP measurements obtained after witnessed pill ingestion did not show major BP decreases in either group, suggesting that differential changes in adherence between the two

randomized groups, if any, had no major influence on the BP response. Moreover, the number of medications prescribed at 12 months remained small in the two groups (RDN: 1.0 (0.0; 3.0) vs. sham: 1.4 (0.0; 3.0), see Table 1). We estimate the risk of non-adherence to treatment and its consequences on the BP response in the RADIANCE-HTN SOLO trial to be small. Indeed, Gupta P et al. showed that the risk of nonadherence among patients who were prescribed only 1 antihypertensive was minimal in a UK and Czech cohort (23). Drug monitoring is currently performed in patients with resistant hypertension included in the RADIANCE-HTN TRIO trial (1). Though endovascular ultrasound RDN may be less operator dependent than single-point radiofrequency technologies, having an immediate and reliable marker of procedural success as with other RDN techniques, may help achieve greater levels of procedural consistency. Finally, there is also limited applicability of our results to other RDN techniques and technologies, that may achieve different degrees of renal nerve ablation (24).

CONCLUSION

In the less strictly controlled conditions of the open unblinded phase of RADIANCE-HTN SOLO trial of patients with combined systolic and diastolic hypertension, although the majority of patients needed the addition of antihypertensive medications in order to improve BP control, fewer medications were needed in the RDN group and the BP lowering effect of endovascular ultrasound RDN was maintained at 12 months. There were no adverse safety signals during 12-month follow-up. The decrease in BP with a treatment strategy including RDN followed by subsequent addition of antihypertensive medications was associated with a lower VVV of BP than a treatment strategy including stepped-care intensified antihypertensive treatment only.

PERSPECTIVES

WHAT IS KNOWN?

Endovascular ultrasound-based RDN reduced ambulatory SBP vs. Sham in the absence (2 months) or the presence of antihypertensive medications up to 6 months in the blinded conditions of the RADIANCE-HTN SOLO trial.

WHAT IS NEW?

We report the 12-month results after following unblinding of patients at 6 months. Our new results in “real life” unblinded conditions, showed that the BP lowering effect of RDN was maintained safely at 12 months with less prescribed medications vs. the control group. The decrease in BP with a treatment strategy including RDN was associated with a lower VVV.

WHAT IS NEXT?

Longer-term and larger studies will be needed to assess not only safety but also any potential impact on cardiovascular prognosis of the decrease in VVV with RDN.

REFERENCES

1. Mauri L, Kario K, Basile J, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs. *Am. Heart J.* 2018;195:115–129.
2. Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018;391:2335–2345.
3. Azizi M, Schmieder RE, Mahfoud F, et al. Six-Month Results of Treatment-Blinded Medication Titration for Hypertension Control After Randomization to Endovascular Ultrasound Renal Denervation or a Sham Procedure in the RADIANCE-HTN SOLO Trial. *Circulation* 2019;139:2542–2553.
4. Sardar P, Bhatt DL, Kirtane AJ, et al. Sham-Controlled Randomized Trials of Catheter-Based Renal Denervation in Patients With Hypertension. *J. Am. Coll. Cardiol.* 2019;73:1633–1642.
5. Hussein WF, Chang TI. Visit-to-Visit Variability of Systolic Blood Pressure and Cardiovascular Disease. *Curr. Hypertens. Rep.* 2015;17:8–13.
6. Wang J, Shi X, Ma C, et al. Visit-to-visit blood pressure variability is a risk factor for all-cause mortality and cardiovascular disease: a systematic review and meta-analysis. *J. Hypertens.* 2017;35:10–17.
7. Tully PJ, Yano Y, Launer LJ, et al. Association Between Blood Pressure Variability and Cerebral Small-Vessel Disease: A Systematic Review and Meta-Analysis. *J. Am. Heart Assoc.*

2020;9:e013841.

8. Messerli FH, Hofstetter L, Rimoldi SF, Rexhaj E, Bangalore S. Risk Factor Variability and Cardiovascular Outcome: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* 2019;73:2596–2603.

9. Anon. World Health Organization Collaborating Centre for Drug Statistics Methodology. ATC Classification Index with DDDs. Accessed [2019 february 25]; Available from: https://www.whocc.no/use_of_atc_ddd/.

10. Wan S-H, Hart M, Hajjar I. A Novel Measurement Index for Antihypertensive Medication Burden and Its Use. *Hypertension* 2009;54:e135–e136.

11. Kandzari DE, Böhm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018;391:2346–2355.

12. Schmieder RE, Philipp T, Guerediaga J, et al. Long-term antihypertensive efficacy and safety of the oral direct renin inhibitor aliskiren. A 12-month randomized, double-blind comparator trial with hydrochlorothiazide. *Circulation* 2009;119:417–425.

13. Singh RR, McArdle ZM, Iudica M, et al. Sustained Decrease in Blood Pressure and Reduced Anatomical and Functional Reinnervation of Renal Nerves in Hypertensive Sheep 30 Months After Catheter-Based Renal Denervation. *Hypertension* 2019;73:718–727.

14. Veloudi P, Sharman JE. Methodological factors affecting quantification of blood pressure variability: A scoping review. *J. Hypertens.* 2018;36:711–719.

15. Levitan EB, Kaciroti N, Oparil S, Julius S, Muntner P. Relationships between metrics of visit-to-visit variability of blood pressure. *J. Hum. Hypertens.* 2013;27:589–93.
16. Parati G, Stergiou GS, Dolan E, Bilo G. Blood pressure variability: clinical relevance and application. *J. Clin. Hypertens.* 2018;20:1133–1137.
17. Howard JP, Patel H, Shun-Shin MJ, et al. Impact of number of prescribed medications on visit-to-visit variability of blood pressure. *J. Hypertens.* 2015;33:2359–2367.
18. Levitan EB, Kaciroti N, Oparil S, Julius S, Muntner P. Blood Pressure Measurement Device, Number and Timing of Visits, and Intra-Individual Visit-to-Visit Variability of Blood Pressure. *J. Clin. Hypertens.* 2012;14:744–750.
19. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet* 2010;375:906–915.
20. Kronish IM, Lynch AI, Oparil S, et al. The Association Between Antihypertensive Medication Nonadherence and Visit-to-Visit Variability of Blood Pressure. *Hypertension* 2016;68:39–45.
21. Townsend RR, Walton A, Hettrick DA, et al. Review and meta-analysis of renal artery damage following percutaneous renal denervation with radiofrequency renal artery ablation. *EuroIntervention* 2020;16:89–96.
22. Mahfoud F, Azizi M, Ewen S, et al. Proceedings from the 3rd European Clinical Consensus Conference for clinical trials in device-based hypertension therapies. *Eur. Heart J.*

2020;41:1588–1599.

23. Gupta P, Patel P, Štrauch B, et al. Risk Factors for Nonadherence to Antihypertensive Treatment. *Hypertension* 2017;69:1113–1120.

24. Fengler K, Rommel K-P, Blazek S, et al. A Three-Arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients With Resistant Hypertension (RADIOSOUND-HTN). *Circulation* 2019;139:590–600.

FIGURE LEGENDS

Figure 1: Proportion of patients on 0, 1, 2 and 3 antihypertensive medications in the renal denervation group and the sham group from screening to 6 and 12 months.

Figure 2: Twenty-four-hour ambulatory profiles at baseline, six and twelve months in the renal denervation group (n=65, left panel) and the sham group (n=67, right panel) in the analysis population. Systolic blood pressure (SBP) is shown in the top panel and diastolic blood pressure (DBP) in the bottom panel; error bars represent standard error. Red dotted lines show the upper limit of normal daytime and nighttime systolic (135 and 120 mmHg, respectively; top panel) and diastolic blood pressure (85 and 70 mmHg, respectively; bottom panel).

Figure 3: Office systolic blood pressure (SBP) changes (top panel) and home systolic blood pressure changes (bottom panel) from baseline to 2, 3, 4, 5, 6 and 12 months in the renal denervation (RDN) group (green dots) and the sham group (blue dots) on evaluable patients. Error bars represent 95% CI.

Central Illustration: Top: RADIANCE-HTN SOLO study design. Bottom: Medication burden and 24h ambulatory systolic blood pressure profiles at baseline, 6 and 12 months in the endovascular ultrasound renal denervation group (RDN) and the sham group.

Table 1: Antihypertensive medications prescribed at physician's discretion at 12 months in the analysis population.

Characteristic	Renal Denervation (n=65)	Sham Procedure (n=67)	p Value
Total number of antihypertensive medications, mean (range)	1.0 (0.0; 3.0)	1.4 (0.0; 3.0)	0.015
Medication dose burden			
Defined Daily Dose, mean \pm SD	1.4 \pm 1.4	2.2 \pm 1.8	0.007
Antihypertensive medication load index, mean \pm SD	0.5 \pm 0.5	0.8 \pm 0.6	0.009
Number of antihypertensive medications, % (n/N)			
0	27.7% (18/65)	14.9% (10/67)	
1 medication	44.6% (29/65)	40.3% (27/67)	
2 medications in combination	23.1% (15/65)	31.3% (21/67)	
3 medications in combination	4.6% (3/65)	13.4% (9/67)	

BB: beta-blocker; CCB: calcium channel blocker; RASB: renin angiotensin system blocker; SD: standard deviation.

Medication dose burden at 6 months expressed as the sum of defined daily dose of each individual antihypertensive medication (9).

The antihypertensive medication load index calculated percentage of the maximum dose of each drug (

$$\sum_{\text{antihypertensive medications}} \frac{(\text{prescribed daily dosage})}{(\text{maximum daily dosage})} (10)$$

Table 2: Efficacy Endpoints: Change in Ambulatory, Office, and Home Blood Pressure at 12 Months after Renal Denervation or Sham Procedure following unblinding at 6 months (Analysis Population).

	Renal Denervation			Sham Procedure			Mean between- group difference adjusted for baseline value (95% CI)	p Value [*]	Mean between- group difference adjusted for baseline value and antihypertensive medications at 12M (95% CI)	p Value ^y
	Baseline	12 months	Difference	Baseline	12 months	Difference				
Daytime ABP (mm Hg)	(n=65)	(n=65)	(n=65)	(n=67)	(n=67)	(n=67)				
SBP	150.3±8.0	133.8±11.3	-16.5±12.9	150.0±10.0	134.2±11.4	-15.8±13.1	-0.4 (-4.3; 3.4)	0.836	-2.3 (-5.9; 1.3)	0.201
DBP	93.0±4.7	83.2±7.9	-9.8±8.3	93.3±5.5	83.7±8.2	-9.6±7.9	-0.4 (-3.0; 2.3)	0.770	-2.0 (-4.3; 0.4)	0.103

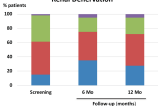
24-hour ABP (mm Hg)	(n=65)	(n=65)	(n=65)	(n=67)	(n=67)	(n=67)				
SBP	142.3±8.0	127.2±10.8	-15.1±12.4	143.7±10.6	128.5±11.3	-15.3±12.4	-0.8 (-4.5; 2.9)	0.656	-2.4 (-5.8; 0.9)	0.156
DBP	87.2±5.0	78.0±7.5	-9.2±7.8	88.4±5.7	78.9±8.0	-9.5±7.5	-0.2 (-2.7; 2.3)	0.875	-1.7 (-3.9; 0.6)	0.142
Nighttime ABP (mm Hg)^x	(n=65)	(n=65)	(n=65)	(n=66)	(n=66)	(n=66)				
SBP	129.4±11.3	116.6±12.5	-12.9±15.0	132.4±14.0	118.8±14.3	-13.6±14.5	-1.1 (-5.5; 3.2)	0.607	-2.6 (-6.7; 1.5)	0.217
DBP	77.8±8.2	69.8±8.7	-8.0±9.7	79.8±8.2	70.9±10.0	-8.9±9.7	-0.2 (-3.2; 2.8)	0.888 (0.645 ^z)	-1.5 (-4.4; 1.3)	0.290 (0.615 ^z)
Office BP (mm Hg)	(n=65)	(n=65)	(n=65)	(n=67)	(n=67)	(n=67)				
SBP	154.3±13.1	136.2±14.7	-18.1±14.9	153.8±16.0	140.2±17.2	-13.6±17.2	-4.3 (-9.2; 0.7)	0.091	-6.3 (-11.1; -1.5)	0.010
DBP	99.7±8.1	90.0±9.5	-9.7±9.8	99.3±9.3	90.9±11.0	-8.4±11.5	-1.1 (-4.4; 2.2)	0.527	-2.5 (-5.7; 0.7)	0.122

							2.2)			
Home BP (mm Hg)^{jj}	(n=61)	(n=61)	(n=61)	(n=58)	(n=58)	(n=58)				
SBP	147.6±9.1	132.9±8.4	-14.7±10.5	147.9±13.0	133.8±14.1	-14.1±13.6	-0.8 (-4.6; 3.0)	0.683 (0.558 ^z)	-3.4 (-6.9; 0.1)	0.058 (0.062 ^z)
DBP	94.5±7.1	85.7±7.1	-8.8±7.4	94.7±7.4	85.6±9.5	-9.1±8.3	0.2 (-2.4; 2.9)	0.858 (0.493 ^z)	-1.5 (-3.8; 0.8)	0.192 (0.486 ^z)

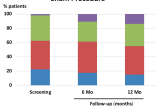
ABP: ambulatory blood pressure; BP: blood pressure; CI: Confidence interval; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Data displayed as mean ± standard deviation. ^{*}P value by analysis of covariance, adjusting for baseline value. ^yP value by analysis of covariance, adjusting for baseline value and number of antihypertensive medications at 6 months. ^zP value by adjusted analysis of covariance on the ranks. ^{*}1/67 patients in the sham group had a missing 12-month nighttime ABP measurement. ^{jj}4/65 patients in the renal denervation group and 9/67 patients in the sham group had missing 12-month home BP measurements.

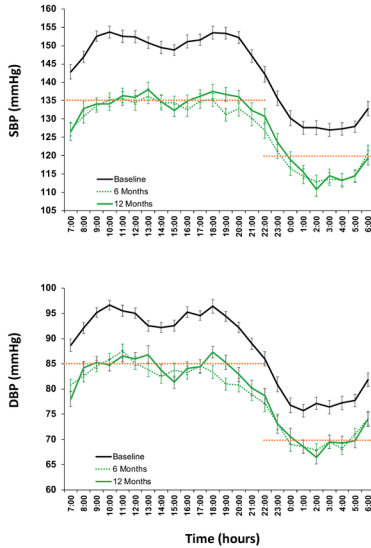
Renal Denervation



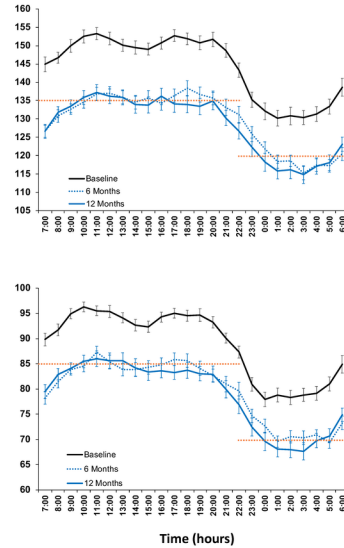
Sham Procedure



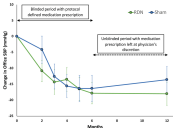
Number of Antihypertensive Medications: 0 1 2 3+



	Baseline	6M	12M
Number of Antihypertensive Medications (mean)	0.00	0.92	1.05
DDD (mean)	0.00	1.38	1.43



	Baseline	6M	12M
Number of Antihypertensive Medications (mean)	0.00	1.33	1.43
DDD (mean)	0.00	2.15	2.32

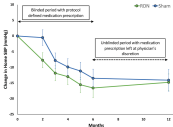


Number of anti-hypertensive medications (mean)

RDH	0.0	0.0	0.0	0.7	0.8	0.8	1.0
Sham	0.0	0.2	0.8	1.1	1.2	1.3	1.4

SD (mean)

RDH	0.0	0.1	0.8	1.0	1.2	1.4	1.4
Sham	0.0	0.4	1.2	1.6	1.9	2.2	2.3

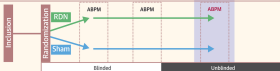


Number of anti-hypertensive medications (mean)							
RDN	8.0	0.0	8.5	0.7	0.8	8.8	1.8
Sham	8.0	0.2	8.8	1.3	1.2	9.8	1.4
SD (mean)							
RDN	8.0	0.1	8.6	1.3	1.2	9.3	1.4
Sham	8.0	0.4	1.2	1.8	1.9	2.3	2.3

RADIANCE-HTN SOLO

Blinded, Sham-Controlled RCT

-1M → Baseline → 2M → 6M → 12M → Annual Follow-up



Standard of Care Medications

No Medication

Titrated Medications

Standard of Care Medications

Medication Burden	Renal Denervation			12M Between-group p Value	Sham		
	Randomization	6M	12M		Randomization	6M	12M
Number of Antihypertensive Medications (mean)	0.00	0.92	1.05	0.005	0.00	1.33	1.43
Defined Daily Dose (mean)	0.00	1.38	1.43	0.007	0.00	2.15	2.32

