



36-month durability of ultrasound renal denervation for hypertension resistant to combination therapy in RADIANCE-HTN TRIO

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Abstract

Endovascular ultrasound renal denervation (uRDN) reduced blood pressure (BP) compared to sham at 2 months in patients with resistant hypertension in the multicenter, blinded, randomized, sham-controlled RADIANCE-HTN TRIO trial. This analysis evaluates longer-term outcomes of patients randomized to uRDN. Patients with resistant hypertension to a 3-drug combination pill were randomized to uRDN ($n = 69$) or sham ($n = 67$). From 2–5 months, patients followed a standardized anti-hypertensive medication (AHM) titration protocol. At 6 months, patients were unblinded and received AHM per standard of care. In the uRDN group, 71% (49/69) completed 36-month follow-up. Screening office BP was 159/103 on 3.9 AHM. Baseline office BP on the single-pill combination was 153/99 mmHg. At 36 months, office BP changed by $-14.5 \pm 26.1/-9.0 \pm 14.8$ mmHg from screening ($p < 0.001$ for both) and $-8.0 \pm 24.5/-5.0 \pm 14.6$ mmHg from baseline ($p = 0.007$; $p = 0.022$) on 3.7 AHM. The efficacy of uRDN was durable to 36 months in patients with resistant hypertension with no safety concerns.

Keywords Hypertension · renal denervation · ultrasound · blood pressure

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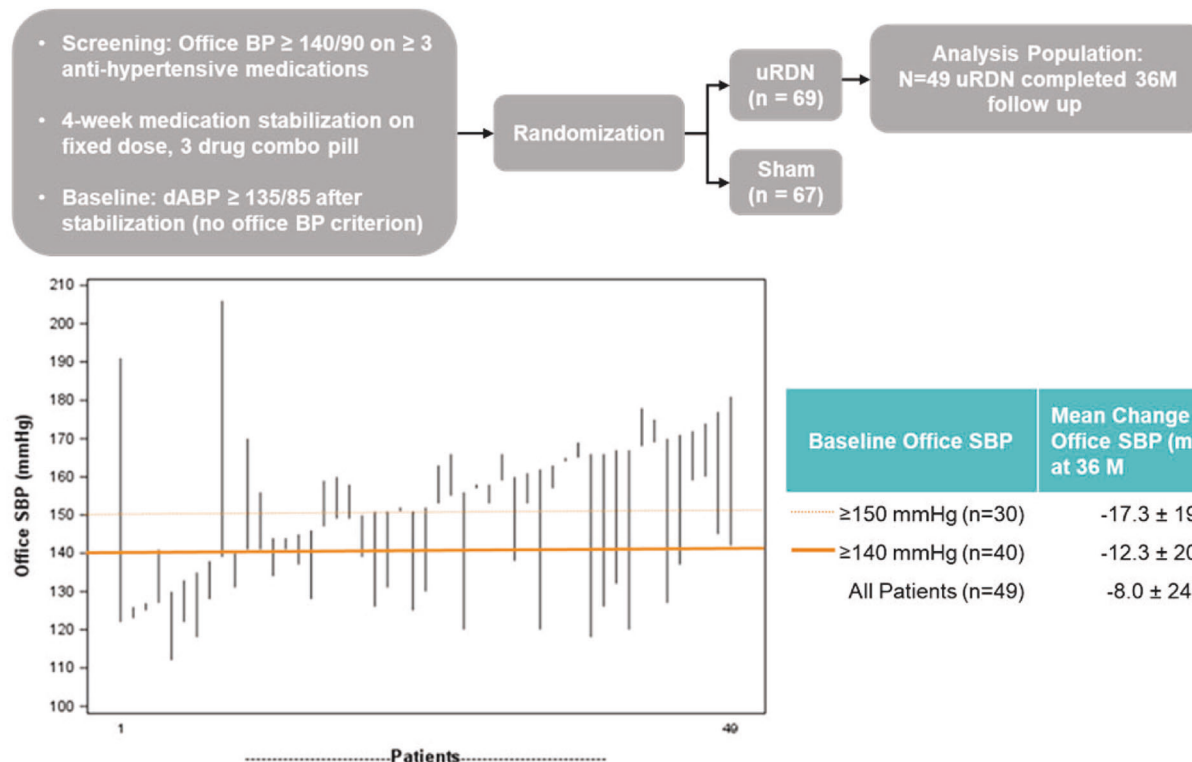
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Graphical Abstract

36 Month Results in Uncontrolled Hypertensive Patients following uRDN



Introduction

Endovascular ultrasound renal denervation (uRDN) effectively lowers daytime ambulatory systolic blood pressure in mild-to-moderate hypertension patients off anti-hypertensive medications (AHM) and those resistant to a single-pill fixed-dose of three AHMs [1]. While methodological and ethical considerations required the primary endpoint of uRDN studies to be at 2 months, the durability of the BP-lowering effect has been a topic of debate. This analysis evaluates the long-term efficacy and safety of uRDN over 36 months in resistant hypertensive patients under standard-of-care medications enrolled in the international, multicenter, randomized, sham-controlled RADIANCE-HTN TRIO trial, which was approved by local committees.

Methods

In RADIANCE-HTN TRIO, patients with office BP $\geq 140/90$ mmHg despite the use of ≥ 3 AHM at screening were switched to single-pill, fixed-dose combination of three medications (olmesartan/valsartan, amlodipine, hydrochlorothiazide) and

then randomized to uRDN or sham if their daytime ambulatory BP was $\geq 135/85$ mmHg, estimated glomerular filtration rate (eGFR) was ≥ 40 ml/min/1.73 m², and they had suitable renal anatomy [1]. From 2 to 5 months, if monthly home BP was $\geq 135/85$ mmHg, prespecified standardized stepped-care AHM was started under continuous blinding of patients and physicians [1]. After unblinding at 6-months, patients received AHM at the physician's discretion according to local standard of care [2]. After the primary endpoint was met, unblinded crossover for patients initially randomized to sham was permitted if specific criteria were met.

Results

In the uRDN group, 71% (49/69) completed their 36-month visit (mean age 53 years, 18% (9/49) female, 69% (34/49) White). Mean screening office BP was 159/103 mmHg on mean 3.9 AHM and mean baseline office BP was 153/99 mmHg on mean 3.1 AHM.

At 36 months, mean office BP in the uRDN group decreased by $-14.5 \pm 26.1/-9.0 \pm 14.8$ mmHg from screening ($p < 0.001$ for both) and $-8.0 \pm 24.5/-5.0 \pm 14.6$ mmHg

from baseline ($p = 0.007$; $p = 0.022$) on a mean of 3.7 AHM (Fig. 1). A total of 17/49 (35%) patients had their office BP controlled ($<140/90$ mmHg) at 36 months.

The decrease in office BP varied by patient and was greater in those with higher baseline office BP (Fig. 2). Patients with uncontrolled BP at baseline (office systolic BP ≥ 140 mmHg) had a change of -12.3 ± 20.0 mmHg in office systolic BP at 36 months and patients with baseline office systolic BP ≥ 150 mmHg had a change of -17.3 ± 19.2 mmHg at 36 months. Patients with baseline office systolic BP ≥ 140 mmHg and ≥ 150 mmHg were on similar number of AHMs (3.6 and 3.9, respectively).

There was a small increase in AHM compared with baseline ($+0.6 \pm 1.3$; $p = 0.004$), which may have

impacted the difference in BP at 36 months. However, importantly, there was no increase in medication as compared with the initial screening visit (-0.2 ± 1.3 ; $p = 0.130$) suggesting a medication independent BP lowering effect. The majority of uRDN patients remained on a renin-angiotensin system blocker (94%; 46/49), a calcium channel blocker (88%; 43/49), and a thiazide-type diuretic (86%; 42/49) at 36 months; 76%; 37/49 were taking all three of these drugs. Forty-one percent (20/49) were taking aldosterone antagonists. There were no new safety signals during the 36-month follow-up and no clinically significant ($>50\%$) site-reported renal artery stenosis. There was one early death previously reported and unrelated to the device or procedure [2].

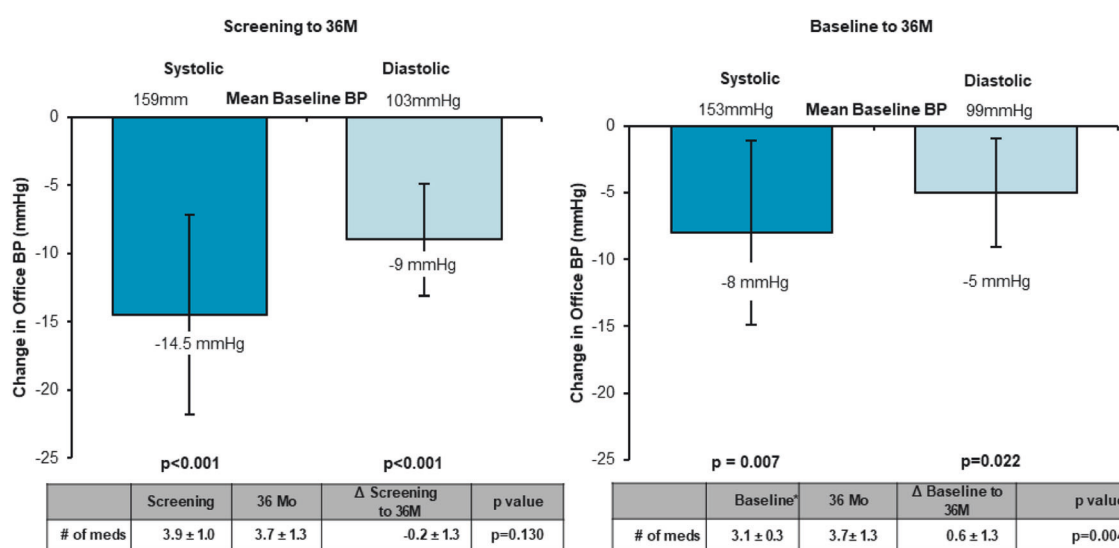


Fig. 1 Change in Office Blood Pressure from screening (prior to standardization on triple pill) (Left) and change from baseline (after standardization on triple pill) (Right)

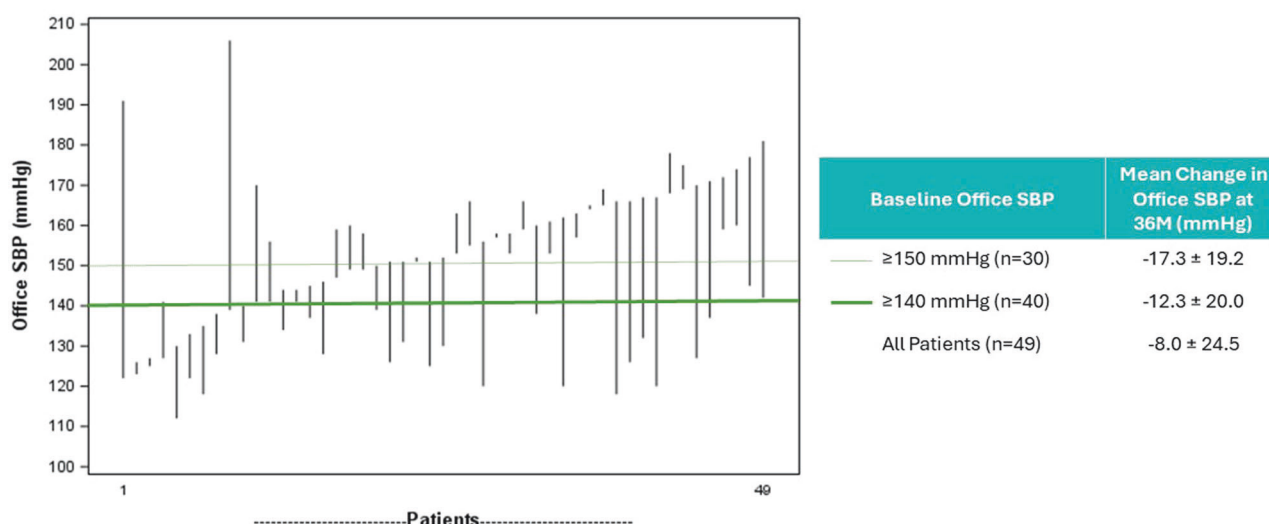


Fig. 2 Individual Changes From Baseline to 36 Months in Office Systolic Blood Pressure - TRIO 36M Follow-up

Discussion

These findings enhance understanding of uRDN's long-term effectiveness in real-world scenarios, where patients received standard of care anti-hypertensives prescribed by their doctors post-unblinding. The comparison to pre-randomization baseline is valuable, but represents unique study-specific conditions, with monitored adherence to a single pill fixed-dose combination, differing from typical clinical practice. In addition, several patients had a low baseline office BP, due to no office BP inclusion criteria at baseline. For these reasons, we feel that the comparison to screening is the best demonstration regarding the magnitude of the real-world efficacy of uRDN.

Although most patients (65%; 32/49) did not achieve office BP control due to probable clinical inertia and/or non-adherence to AHM, the clinical implications of this magnitude of office BP reduction are likely substantial. The change in office BP from baseline was ≥ 10 mmHg in 49% (24/49) and ≥ 5 mmHg in 59% (29/49) of patients. Studies have shown systolic office BP reductions of 5 and 10 mmHg are associated with reductions in cardiovascular events of 10% and 20%, respectively [3, 4].

This analysis had limitations. Only office BP measurements were available at the 36-month visit and follow-up rate was suboptimal. Unblinding to original treatment allocation after 6 months, unrestricted AHM prescription, and discontinuation of chemical adherence testing may have confounded results. Finally, there was no suitable sham group for comparison, due to crossover allowance post-primary endpoint. However, these factors may enhance the study's real-world relevance.

In conclusion, these data reinforce the safety and durable effectiveness of uRDN up to 36 months in patients with resistant hypertension who remain on standard of care background medication.

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Compliance with ethical standards

Conflict of interest MJB has received personal fees from Recor Medical and Medtronic. AJK reports institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Amgen, CSI, Philips, Recor Medical, Neurotron, Biotronik, Chiesi, Bolt Medical, Magenta Medical, Canon, SoniVie, and Merck. In addition to research grants, institutional funding includes fees paid to Columbia University and/or Cardiovascular Research Foundation for consulting and/or speaking engagements in which AJK controlled the content. Personal: Consulting from IMDS; Travel Expenses/Meals from Medtronic, Boston Scientific, Abbott Vascular, CSI, Siemens, Philips, Recor Medical, Chiesi, OpSens, Zoll, and Regeneron. MA has received research grants from the European Horizon 2020 programme; has received grant support and non-financial support from Recor Medical, Novartis, and Idorsia; and has received personal fees from Alnylam Pharmaceutical, Novartis, Medtronic, Astra Zeneca. FM is supported by Deutsche Gesellschaft für Kardiologie (DGK), Deutsche Forschungsgemeinschaft (SFB TRR219, Project-ID 322900939), and Deutsche Herzstiftung. He has received scientific support from Ablative Solutions, Medtronic and Recor Medical and speaker honoraria/consulting fees from Ablative Solutions, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Inari, Medtronic, Merck, Recor Medical, Servier, and Terumo. JB has reported receiving grants from Recor Medical and Ablative Solutions. JD has received institutional grant/research support from Abbott Vascular, Boston Scientific, ACIST Medical, Medtronic, Microport,

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