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ORIGINAL RESEARCH

Impact of baseline systolic blood pressure on blood pressure changes following renal denervation

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ABSTRACT

BACKGROUND: Renal denervation (RDN) is a guideline-recommended treatment to reduce blood pressure (BP) in patients with uncontrolled hypertension. However, it is unclear if there are patient characteristics that are predictive of greater BP reduction. Baseline systolic blood pressure (SBP) has consistently been identified as an indicator of BP reduction after RDN.

AIMS: Our study aimed to quantify the expected SBP change after RDN based on baseline SBP.

METHODS: Patients undergoing radiofrequency RDN were pooled from multiple clinical studies, including SPYRAL First-In-Human (n=50), SYMPLICITY HTN-3 (n=364), SYMPLICITY HTN-Japan (n=22), SPYRAL HTN ON-MED (n=206), and the Global SYMPLICITY Registry DEFINE (n=2,735). Office and 24-hour ambulatory BP were measured at baseline and 6 months. Linear regression modelled patient-level 6-month SBP changes against baseline SBP.

RESULTS: The pooled cohort (N=3,377) had a mean age of 60±12 years, and 41% were female. Baseline office SBP (OSBP) and 24h ambulatory SBP (ASBP) were 171.8±20.5 mmHg and 155.9±17.3 mmHg, respectively. At 6 months, OSBP and 24h ASBP decreased by 16.3±24.0 and 7.5±16.7 mmHg, respectively. Patients were prescribed 4.4±1.5 antihypertensive drug classes at baseline and 4.3±1.5 at 6 months ($p<0.0001$). Higher baseline SBP correlated with greater SBP reductions ($p<0.0001$; $r^2=0.21$ for OSBP; $r^2=0.13$ for ASBP). Baseline OSBP of 150, 160, 170, and 180 mmHg were associated with 6-month reductions of 4.2, 9.8, 15.4, and 21.0 mmHg, respectively.

CONCLUSIONS: Baseline SBP was associated with 6-month SBP reductions after RDN in hypertensive patients. This relationship provides guidance for shared patient-clinician decision-making about what BP change to expect following radiofrequency RDN based on baseline SBP alone.

KEYWORDS: blood pressure reduction; renal denervation; uncontrolled hypertension

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Several position papers and guidelines recommend renal denervation (RDN) as an adjunctive treatment approach in patients with uncontrolled hypertension[1,2]. In November 2023, the Symplicity Spyral radiofrequency (RF) RDN system (Medtronic) received approval from the U.S. Food and Drug Administration (FDA) as an adjunctive blood pressure (BP)-lowering treatment for patients with hypertension whose BP remains above treatment goals despite lifestyle modifications and antihypertensive pharmacotherapy. BP reduction after RDN may be associated with a reduction in cardiovascular events[3,4], and model-based projections found significant reductions in major adverse cardiovascular events and low numbers needed to treat across 3 years of follow-up in a hypertensive population treated with RF RDN[5].

However, there is limited guidance on how clinicians can effectively assess individual response after RDN and in turn, inform shared decision-making with patients. Across multiple studies in different patient populations using different RDN techniques, the most consistent feature correlating with significant BP reductions was higher baseline BP[6-9]. However, the observed relationship between baseline BP and subsequent BP reduction has also been observed in pharmacological studies and is not limited to "blood pressure *per se*"[10,11]. This non-linear "law of initial value" was first described by Wilder[10] and should be considered in addition to regression to the mean[10,11] and visit-to-visit BP variability[12]. Wilder's law of initial value states that the response to a stimulus is related to the prestimulus level and is independent of both regression to the mean and BP variability[11]. Disentangling these potential effects remains a significant challenge to understanding the relationship between baseline BP and BP reduction after RF RDN, especially when pharmacotherapy alone has failed to adequately control hypertension.

In this *post hoc* analysis of pooled clinical trials of RF RDN, we attempted to exploit this biological phenomenon of baseline BP being indicative of subsequent BP change after a therapeutic intervention and to delineate the probabilities of expected BP change after RDN based on baseline BP alone.

Impact on daily practice

The findings from this pooled analysis of 3,377 patients indicate that higher baseline systolic blood pressure (SBP) is associated with greater SBP reduction at 6 months following radiofrequency renal denervation (RDN). This insight is important for interventionalists, as it provides a straightforward metric – baseline SBP – that can help estimate the potential benefits of RDN for patients. While the exact blood pressure (BP) response cannot be predicted, understanding the likelihood of significant BP reductions can enhance shared decision-making processes between clinicians and patients. This data-driven approach further supports the use of RDN for patients with uncontrolled hypertension.

Methods

Patients with baseline systolic blood pressure (SBP) ≥140 mmHg who underwent RF RDN and were prescribed antihypertensive medications at baseline were pooled from the following SYMPLICITY and SPYRAL global clinical trials (N=3,377), either from multiple randomised, sham-controlled trials such as SYMPLICITY HTN-3[13] (n=364; ≥3 prescribed antihypertensive [AH] medications); SPYRAL HTN-ON MED[14] (n=206; 1-3 AH medications); SYMPLICITY HTN-Japan[15], a randomised (but not sham-controlled) study (n=22; ≥3 AH drugs); SPYRAL First-In-Human[16] (FIH), a feasibility study (n=50; ≥3 prescribed AH drugs); and the Global SYMPLICITY Registry (GSR) DEFINE[17], an all-comers study reflecting a real-world population (as of March 2023, n=2,735; including patients with baseline SBP ≥140 mmHg who were prescribed any number of AH drugs). Patients with baseline SBP <140 mmHg were not included in this analysis as patients in this category would have been limited to a select few from the GSR DEFINE study, and could have potentially biased results[2]. Details of the included study designs have been published previously[13-17]. The SPYRAL HTN-OFF MED Pivotal Trial was not included because the study design required patients to discontinue AH medications before randomisation and permitted their reintroduction after 3 months, potentially confounding the 6-month results. At baseline, patient demographic and clinical characteristics were assessed, and office and 24-hour ambulatory SBP (ASBP) were measured according to guideline recommendations. Follow-up office and 24-hour ambulatory SBP were measured 6 months after RDN.

PROCEDURES

Procedural details have been published previously[14,18-20]. Briefly, RF RDN was performed using the Symplicity G3 RDN RF generator with either the Symplicity Flex catheter or the Symplicity Spyral RDN multielectrode catheter (all Medtronic), the latter allowing circumferential ablation treatments of all renal arteries and branch vessels between 3 and 8 mm in diameter. Cases were performed by experienced proceduralists and, in the case of randomised controlled trials, were proctored according to predetermined treatment plans. Angiography was performed throughout the procedure to verify anatomy and catheter placement.

STATISTICAL ANALYSIS

Statistical analyses were performed with SAS for Windows 9.4 (SAS Institute). Linear regression analyses were performed for office and 24-hour SBP to assess the correlation between baseline and 6-month change in SBP (SBP change=intercept+slope*baseline SBP). The resulting linear regression relationships were used to estimate (1) patient-level expected 6-month changes in SBP after RF

Abbreviations

AH	antihypertensive	**BP**	blood pressure	**RF**	radiofrequency
ASBP	ambulatory systolic blood pressure	**RDN**	renal denervation	**SBP**	systolic blood pressure

RDN based on baseline SBP (increments of 10 mmHg) with 50%, 75%, and 90% confidence intervals and (2) the probabilities of BP change in 20 mmHg increments based on baseline SBP. The probabilities were determined using the model-predicted BP changes and standard errors for different baseline BP values to calculate the area under the regression curve **(Central illustration)**. Categorical measures are expressed as percentages, and continuous measures are expressed as mean±standard deviation.

Results

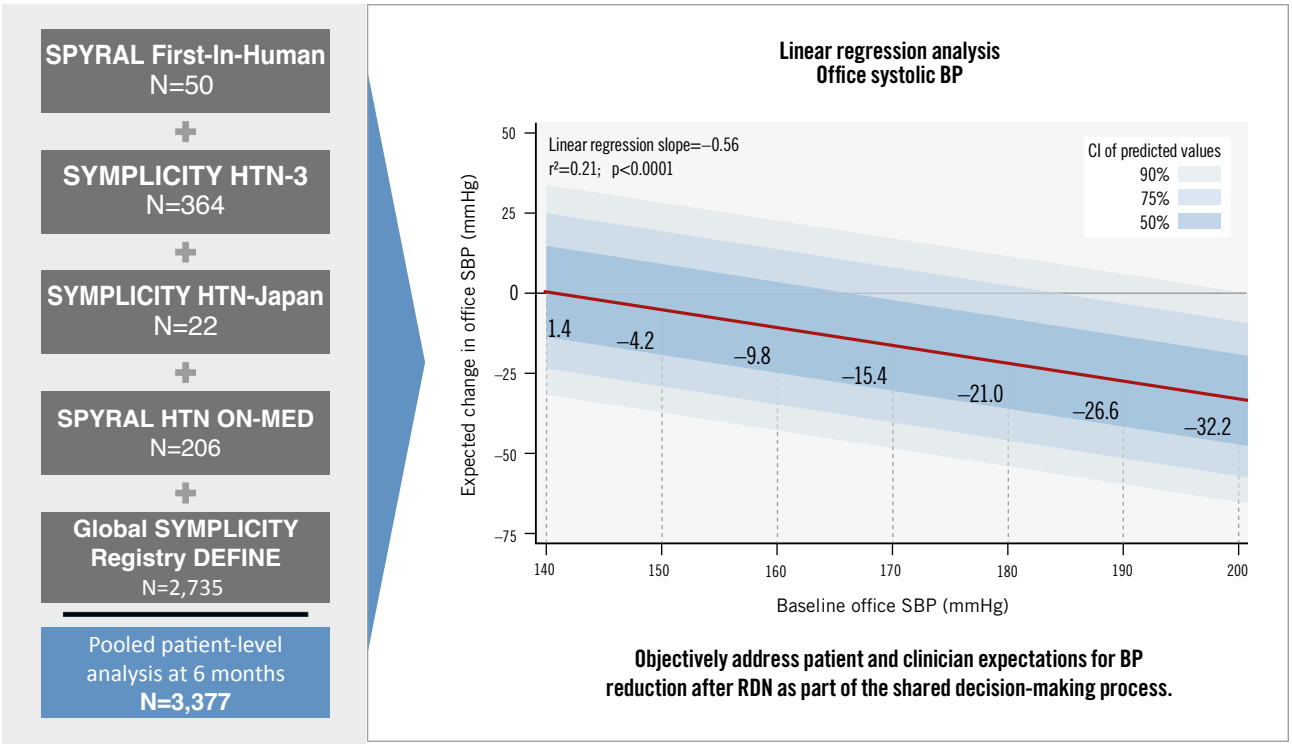
The baseline demographic and clinical characteristics of the pooled cohort are summarised in **Table 1**. Patients were 60±12 years old, 41.0% female, with a body mass index of 31.3±5.9 kg/m^2; 37.7% had type 2 diabetes mellitus, 8.4% had a history of myocardial infarction, and the estimated glomerular filtration rate was 76.5±24.1 mL/min/1.73 m^2. Baseline office SBP (OSBP) and 24-hour ASBP were 171.8±20.5 mmHg and 155.9±17.3 mmHg, respectively. Patients were prescribed 4.4±1.5 antihypertensive medications at baseline **(Table 1)**. Six months after RF RDN, OSBP and 24-hour ASBP decreased by 16.3±24.0 and 7.5±16.7 mmHg, respectively. At 6-month follow-up, patients were prescribed 4.3±1.5 antihypertensive medications (p<0.0001 compared to baseline).

Linear regression analysis of the relationship between baseline OSBP and 6-month change in OSBP showed that each 10 mmHg increase in baseline OSBP ≥140 mmHg was associated with a 5.6 mmHg (r^2=0.21; p<0.0001) reduction in OSBP. Similarly, each 10 mmHg increase in baseline ASBP ≥140 mmHg was associated with a 4.3 mmHg (r^2=0.13; p<0.0001) reduction in ASBP at 6 months. Baseline OSBP of 150, 160, 170, and 180 mmHg were associated with 6-month reductions of 4.2, 9.8, 15.4, and 21.0 mmHg, respectively.

The expected 6-month reductions in both office and 24-hour ambulatory SBP varied substantially from the baseline values of 140 mmHg to 180 mmHg **(Figure 1)**. The probabilities of expected SBP changes based on the separate linear regression models of baseline OSBP and ASBP were translated into a heat map, with higher probabilities in darker shades of green **(Figure 2)**. For example, a patient with a baseline OSBP of 170 mmHg has a 35% probability of an OSBP change between 0 and –20 mmHg, a 29% probability of a change between –20 and –40 mmHg, etc. **(Figure 2A)**. For baseline OSBP between 150 and 170 mmHg, the greatest probability of expected OSBP reduction is in the range of 0 to –20 mmHg (probabilities of 35% to 36%), and for baseline OSBP between 180 mmHg and 210 mmHg, the greatest probability of expected OSBP reduction is in the

EuroIntervention — Central **Illustration**

Blood pressure changes at 6 months following RF RDN based on baseline office SBP alone.



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BP: blood pressure; CI: confidence interval; RDN: renal denervation; RF: radiofrequency; SBP: systolic blood pressure

Table 1. Pooled cohort baseline characteristics.

Baseline characteristics	Pooled cohort (N=3,377)
Age, yrs	59.8±11.8 (3,377)
Male	59.0 (1,994/3,377)
Type 2 diabetes mellitus	37.7 (1,269/3,365)
Body mass index, kg/m^2	31.3±5.9 (3,353)
Estimated glomerular filtration rate, mL/min/1.73 m^2	76.5±24.1 (3,220)
Prior myocardial infarction	8.4 (255/3,036)
History of heart failure	10.7 (326/3,036)
History of sleep apnoea	21.3 (675/3,169)
History of atrial fibrillation	11.0 (371/3,360)
History of smoking	35.0 (1,180/3,374)
No. of antihypertensive drug classes prescribed	4.4±1.5 (3,113)
Number of ablations	20.8±17.7 (3,285)
Procedure duration, mins	83.9±43.8 (3,199)
Office SBP, mmHg	171.8±20.5 (3,377)
Office heart rate, bpm	70.9±13.2 (3,224)
Office pulse pressure, mmHg	78.4±19.4 (3,377)
24-hour ambulatory SBP, mmHg	155.9±17.3 (2,529)
24-hour heart rate, bpm	69.6±11.8 (2,194)
24-hour pulse pressure, mmHg	67.5±14.8 (2,529)

Data are mean±SD (N) or % (n/N). SBP: systolic blood pressure; SD: standard deviation

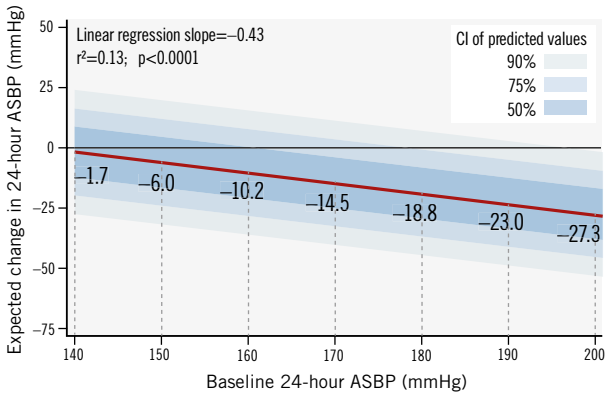

Figure 1. *Expected change in 24-hour ambulatory systolic BP at 6 months after radiofrequency RDN. The red line is the linear regression line. Different shades of blue around the linear regression line represent different confidence intervals. ASBP: ambulatory systolic blood pressure; BP: blood pressure; CI: confidence interval; RDN: renal denervation*

range of –20 mmHg to –40 mmHg (probabilities of 33% to 36%). A 12-month linear regression analysis revealed similar results to the 6-month analysis **(Supplementary Figure 1)**, and is consistent with a recently published linear mixed model investigating long-term reductions after RDN[21].

Discussion

The present analysis of a pooled database of 3,377 patients with uncontrolled office or 24-hour ambulatory SBP, despite treatment with antihypertensive medications, showed that higher baseline SBP was associated with greater SBP reduction at 6 months after RF RDN. However, it explained only 21% of the resulting BP reduction after RDN (r^2=0.21 for OSBP). Despite strong statistical significance, linear correlations were modest (r^2 values<0.5), suggesting that additional factors also influence SBP change after RDN. Another factor influencing correlations is likely visit-to-visit BP variability[22]. Therefore, accurate individual "prediction" of BP response appears to be impractical. However, the present analysis does facilitate estimation of the relative likelihood of different BP reductions. For example, a patient with a baseline office SBP of 170 mmHg has a 76.5% probability of experiencing a BP reduction within 6 months after RDN. Similarly, a patient with a baseline SBP of 190 mmHg has an 88.7% chance of experiencing a BP reduction and a 62.2% chance of experiencing a BP reduction greater than 20 mmHg. This data-driven relationship between baseline BP and BP change after RF RDN could help both clinicians and patients better understand the potential benefits on an individual basis, and thus could provide better guidance in the shared decision-making process currently recommended by hypertension guidelines and RDN position statements[1,2,23].

RDN in patients with uncontrolled hypertension is recommended by international guidelines for the treatment of arterial hypertension[1,2]. In clinical practice, there is a great need to better understand the expected BP change after an invasive therapy such as RDN, depending on the individual's clinical characteristics. Currently, there is no single characteristic that accurately predicts the best BP response to RDN in all patients and that has been prospectively validated. This may reflect the lack of a single, uniform, non-arbitrary definition of "response" to RDN[22]. Several associations have been proposed, such as renal artery anatomy; BP variability; clinical and demographic conditions such as sex, presence of diabetes or obesity; and pathophysiological factors such as skin sodium levels, plasma renin activity, and vascular stiffness (invasive pulse wave velocity and aortic distensibility). However, each of these associations do not have a high enough accuracy to be used as a guide to predict BP reduction after RDN in clinical practice. Similarly, the genetic profile of patients with resistant hypertension was not associated with 24-hour BP reduction, which does not support the use of a genetic score to identify potential responders to RDN[24].

However, several studies have consistently shown that pretreatment or baseline BP has the greatest impact on the magnitude of BP reduction after RDN[6-9]. Baseline BP is one of the easiest patient data points to collect in a real-world clinical setting. Our large, pooled database of RF RDN trials allowed us to show an expected range and mean BP change after RDN based on this single characteristic. A simple metric such as this may be useful as a guideline for primary care physicians and referring physicians, as it does not require complex and expensive investigations before referring patients to a specialist hypertension clinic for consideration of RDN. For patients at or near the threshold for guideline-recommended BP values for RDN treatment, a case-by-case

A Office SBP

Baseline OSBP, mmHg	140	150	160	170	180	190	200	210	220
BP CHANGE 40 to 20	15.7%	10.9%	7.1%	4.4%	2.5%	1.3%	0.7%	0.3%	0.1%
BP CHANGE 20 to 0	33.5%	29.4%	24.2%	18.7%	13.5%	9.1%	5.8%	3.5%	1.9%
BP CHANGE 0 to –20	31.6%	34.9%	36.1%	35.1%	31.9%	27.2%	21.8%	16.3%	11.5%
BP CHANGE –20 to –40	13.1%	18.2%	23.8%	29.0%	33.3%	35.7%	35.9%	33.9%	30.0%
BP CHANGE –40 to –60	2.4%	4.2%	6.9%	10.6%	15.3%	20.6%	26.1%	31.1%	34.6%
BP CHANGE –60 to –80	0.2%	0.4%	0.9%	1.7%	3.1%	5.2%	8.4%	12.5%	17.5%

B 24-hour ambulatory SBP

Baseline ASBP, mmHg	140	150	160	170	180	190	200	210	220
BP CHANGE 40 to 20	7.9%	4.7%	2.6%	1.4%	0.7%	0.3%	0.1%	0.1%	0%
BP CHANGE 20 to 0	37.3%	30.3%	23.0%	16.4%	10.9%	6.8%	4.0%	2.2%	1.1%
BP CHANGE 0 to –20	42.2%	46.2%	47.6%	45.9%	41.6%	35.3%	28.1%	20.9%	14.6%
BP CHANGE –20 to –40	11.5%	17.1%	23.8%	31.1%	38.0%	43.6%	47.0%	47.4%	44.9%
BP CHANGE –40 to –60	0.7%	1.5%	2.8%	5.0%	8.4%	13.0%	19.0%	26.0%	33.2%
BP CHANGE –60 to –80	0%	0%	0.1%	0.2%	0.4%	0.9%	1.8%	3.4%	5.9%

Figure 2. *Probability heat map of the expected 6-month SBP changes by baseline SBP after RF RDN. Values within squares represent the probabilities of BP change (%). Darker green shades represent higher probabilities, and lighter green shades represent lower probabilities of the expected BP change range. The red line in each table separates increase and decrease in SBP change from baseline. A) Office SBP; (B) 24-hour ambulatory SBP. ASBP: ambulatory systolic blood pressure; BP: blood pressure; OSBP: office systolic blood pressure; RF RDN: radiofrequency renal denervation; SBP: systolic blood pressure*

approach is recommended, including incorporating patient preference as part of the shared decision-making process. Ultimately, RDN should be considered for patients at higher cardiovascular risk, including those with higher BP in whom target BP values at or below 130/80 mmHg are recommended. Indeed, further investigation is needed to identify other specific patient characteristics, in addition to baseline BP, that contribute to better BP predictability after RDN.

Limitations

BP changes at 6 and 12 months were evaluated and any correlation beyond 12 months was not evaluated. Analysis of BP reduction up to 36 months showed sustained and even amplified BP reductions after RF RDN, suggesting that the estimated expected BP reductions underestimate the long-term BP reductions after RF RDN[5]. The SPYRAL HTN-OFF MED study was not pooled in this study because the antihypertensive drug protocol differed significantly from the other pooled studies, due to a permitted uptitration of medications between 3 and 6 months. Not all patients were on the same antihypertensive drug regimen, and medication adherence was not tested for a large proportion of patients included in this study. In addition, where medication testing was available, many patients did not adhere to their prescribed medications throughout the follow-up period[20], which may have influenced BP changes. This analysis pooled studies using different radiofrequency devices (first-generation Symplicity Flex and next-generation Symplicity Spyral catheters). Other variables not tested in this analysis may play an important role in SBP reduction after RF RDN.

Conclusions

In patients with uncontrolled hypertension, those with higher baseline office and 24-hour ambulatory SBP can expect greater SBP reductions after RF RDN at 6 months. Using baseline SBP as a guide for expected BP reduction after RDN may be useful in clinical practice and may serve as an aid in shared decision-making for RDN. Further research is needed to identify the best candidates for RDN.

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Conflict of interest statement

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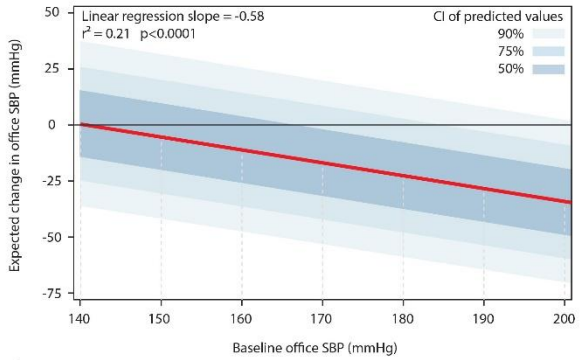
Supplementary data

Supplementary Figure 1. Expected systolic BP change and probability heat maps at 12 months after radiofrequency RDN.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-01131

Supplementary data

A



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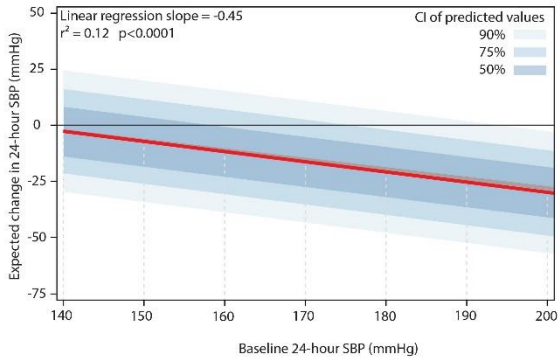

C

Baseline OSBP	140	150	160	170	180	190	200	210	220
BP CHANGE 40 to 20	15.0%	10.5%	6.8%	4.2%	2.4%	1.3%	0.7%	0.3%	0.1%
BP CHANGE 20 to 0	32.1%	27.9%	22.8%	17.4%	12.5%	8.4%	5.3%	3.2%	1.8%
BP CHANGE 0 to -20	31.6%	34.3%	35.0%	33.5%	30.0%	25.3%	20.0%	14.8%	10.3%
BP CHANGE -20 to -40	14.4%	19.5%	24.9%	29.7%	33.3%	35.0%	34.5%	31.9%	27.7%
BP CHANGE -40 to -60	3.0%	5.1%	8.2%	12.2%	17.0%	22.4%	27.5%	31.8%	34.4%
BP CHANGE -60 to -80	0.3%	0.6%	1.2%	2.3%	4.0%	6.6%	10.1%	14.6%	19.8%

D

Baseline ASBP	140	150	160	170	180	190	200	210	220
BP CHANGE 40 to 20	7.9%	4.7%	2.6%	1.3%	0.6%	0.3%	0.1%	0.0%	0.0%
BP CHANGE 20 to 0	35.2%	28.2%	21.0%	14.7%	9.5%	5.8%	3.3%	1.7%	0.9%
BP CHANGE 0 to -20	41.9%	45.2%	45.6%	42.9%	37.8%	31.0%	23.8%	17.1%	11.4%
BP CHANGE -20 to -40	13.4%	19.5%	26.5%	33.7%	39.9%	44.2%	45.8%	44.3%	40.1%
BP CHANGE -40 to -60	1.1%	2.2%	4.1%	7.0%	11.3%	16.9%	23.6%	30.8%	37.6%
BP CHANGE -60 to -80	0.0%	0.1%	0.2%	0.4%	0.8%	1.7%	3.2%	5.7%	9.4%

Supplementary Figure 1. Expected systolic BP change and probability heat maps at 12 months after radiofrequency RDN.

In A and B, the red line is the linear regression line. Different shades of grey around the linear regression line represent different confidence intervals. A) Office SBP, B) 24-h ambulatory SBP. In C and D, the darker green shades represent higher probabilities, and lighter green shades represent lower probabilities of the expected BP change range. The red line in each table separate increase and decrease in SBP change from baseline. C) Office SBP, D) 24-h ambulatory SBP. ASBP=ambulatory systolic blood pressure; OSBP=office systolic blood pressure; RF RDN= radiofrequency renal denervation; SBP=systolic blood pressure.