

1 **Renal denervation in the presence of antihypertensive medications: Blood pressure results through**
2 **six months follow-up from the randomised, blinded, sham-controlled SPYRAL HTN-ON MED trial**

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29 **SUMMARY**

30 **BACKGROUND:** Previous catheter-based renal denervation studies reported variable efficacy
31 results. Our study evaluated the effect of renal denervation on blood pressure (BP) in the
32 presence of specified anti-hypertensive medications and assessment of adherence.

33 **METHODS:** SPYRAL HTN-ON MED is a multicentre, international, blinded, randomised,
34 sham control, proof-of-concept trial (clinicaltrials.gov: NCT02439775). Patients were enrolled at
35 25 centres worldwide. Eligible patients were on one to three anti-hypertensive medications with
36 stable doses for at least six weeks. Patients with an office systolic BP (SBP) ≥ 150 mmHg and
37 < 180 mmHg, a diastolic BP (DBP) ≥ 90 mmHg and a 24-hour ambulatory SBP ≥ 140 mmHg and
38 < 170 mmHg at second screening underwent renal angiography and were randomised to renal
39 denervation with the Symplicity SpyralTM multielectrode catheter or sham control. Patients,
40 caregivers, and those assessing BP were blinded to randomisation assignments. The primary
41 endpoint, change in 24-hour blood pressure at six months, was compared between groups. Drug
42 surveillance was used to assess medication adherence. The primary analysis was done in the
43 intention-to-treat population. Safety events were assessed through six months.

44 **FINDINGS:** Eighty patients were randomised and followed through six months. Office and 24-
45 hour ambulatory BP decreased significantly from baseline to six months in the renal denervation
46 group (n=38). Mean baseline-adjusted treatment differences [95% confidence intervals] are: 24-
47 hour SBP (-7.0 mmHg [-12.0, -2.1], p=0.0059), 24-hour DBP (-4.3 mmHg [-7.8, -0.8],
48 p=0.0174), office SBP (-6.6 mmHg [-12.4, -0.9], p=0.0250), and office DBP (-4.2 mmHg [-7.7,
49 -0.7], p=0.0190). Evaluation of hourly changes in 24-hour SBP and DBP showed BP reduction
50 throughout 24 hours for the renal denervation group. Three-month BP reductions were not

51 significantly different between groups. Medication adherence was ~60% and varied for
52 individual patients throughout the study. There were no major adverse events.

53 **INTERPRETATION:** Renal denervation in the main renal arteries and branches significantly
54 reduced BP compared to sham control with no major safety events. Incomplete medication
55 adherence was common.

56 **FUNDING:** Medtronic.

57

58 **INTRODUCTION**

59 Against the background of preclinical and early human feasibility studies demonstrating
60 reductions in renal and systemic sympathetic tone with catheter-based renal denervation,^{1,2}
61 subsequent trials of variable size, design and method have demonstrated inconsistent blood
62 pressure results in the setting of treatment resistant hypertension.³⁻⁵ More recently, as an
63 exploratory trial intended to verify biologic proof-of-concept in the absence of antihypertensive
64 therapy, the blinded, sham-controlled SPYRAL HTN-OFF MED trial demonstrated statistically
65 significant and meaningful blood pressure reductions in a hypertension population utilizing a
66 revised procedural method.⁶

67 Despite these promising results, uncertainty regarding the efficacy of renal denervation in
68 the setting of concurrent antihypertensive medications persists. Previous study of renal
69 denervation amidst prescribed antihypertensive therapy has been challenged by variability in
70 medication classes, frequent medication and dose changes and unpredictable patient adherence.^{7,8}
71 although one of these trials, performed open label, did report a significant effect of renal
72 denervation compared with control in patients receiving antihypertensive medications.³
73 However, whether changes in blood pressure associated with this method of catheter-based
74 therapy are amplified or instead muted by pharmacotherapy is unstudied. Further, estimates
75 regarding the temporal pattern and magnitude of blood pressure change, and comparison of these
76 measures with those observed in the SPYRAL HTN-OFF MED trial population are only
77 speculative.

78 In parallel with the SPYRAL HTN-OFF MED study, a trial of similar design was
79 performed to evaluate the application of renal denervation in a setting more representative of

80 clinical practice for which integrating drug and procedural strategies may be anticipated. To this
81 purpose, the SPYRAL HTN-ON MED study⁹ was conducted to evaluate the safety and efficacy
82 of catheter-based renal denervation for treatment of moderate, uncontrolled hypertension despite
83 ongoing therapy with commonly prescribed antihypertensive medications.

84

85 **METHODS**

86 *Trial design and patients*

87 SPYRAL HTN-ON MED is a global, multicentre, blinded (patient and assessor), randomised,
88 sham-controlled, proof-of-concept trial. Details of the design have been reported (Appendix,
89 **Figure S1**).⁹ In brief, eligible patients were 20 to 80 years old with uncontrolled hypertension on
90 one, two, or three standard antihypertensive medications. Medications were required to be
91 prescribed at 50% or more of the maximum manufacturer's recommended dosage of a thiazide-
92 type diuretic, a dihydropyridine calcium channel blocker, an ACE-inhibitor/angiotensin receptor
93 blocker (ACE-I/ARB), or a beta blocker. In Japan, patients could be prescribed less than 50% of
94 maximum manufacturer's recommended dosage of a thiazide-type diuretic per standard of care.
95 Uncontrolled hypertension was defined as office systolic blood pressure (SBP) ≥ 150 and < 180
96 mmHg, office diastolic blood pressure (DBP) ≥ 90 mmHg, and a mean 24-hour ambulatory SBP
97 ≥ 140 and < 170 mmHg. Patients were enrolled at 25 centres in the USA, Germany, Japan, United
98 Kingdom, Australia, Austria, and Greece. The protocol was approved by all local ethics
99 committees and all patients provided written informed consent to participate in the trial. The trial
100 was designed in accordance with the Declaration of Helsinki and is registered at
101 www.clinicaltrials.gov as NCT02439775

102 *Screening and randomisation*

103 The first screening visit was conducted to confirm that patients had been prescribed
104 antihypertensive pharmacotherapy without change in dose for a minimum of 6 weeks and met
105 the office blood pressure criteria for inclusion. During screening visit 2 patients knowingly
106 underwent drug screening to assess antihypertensive medication adherence using tandem high
107 performance liquid chromatography and mass spectroscopy of urine and plasma by an
108 independent laboratory.¹⁰ If office blood pressure, measured using an automatic blood pressure
109 monitor (Omron, see appendix), remained within the required range (SBP \geq 150 mmHg and $<$ 180
110 mmHg and DBP \geq 90 mmHg) patients underwent 24-hour ambulatory blood pressure monitoring
111 (ABPM, Mobil-O-Graph; I.E.M GmbH, Stolberg, Germany). Before the ABPM was initiated,
112 study personnel documented pill identity and observed the patient swallowing their
113 antihypertensive medication(s) (directly observed therapy). Ambulatory blood pressure was
114 measured every 30 minutes. A minimum of 21 daytime (7:00 to 21:59) and 12 night-time (22:00
115 to 6:59) measurements were required for inclusion in the analysis. The ABPM could be repeated
116 once if the required number of readings was not reached or the average 24-hour SBP was
117 between 135-140 mmHg or between 170-175 mmHg. Patients who met all inclusion and
118 exclusion criteria at the second screening visit were scheduled for renal angiogram and, if
119 anatomical suitability was confirmed, proceeded to randomisation.

120 Patients were randomised 1:1 to renal denervation or sham procedure. Randomisation was
121 stratified by trial centre, using block randomisation with a block size of four. SAS-based
122 software was used to generate the lists of randomisation codes and participants were assigned to
123 an intervention by ICON plc via the website.

124

125 *Procedure*

126 Details of the renal denervation procedure were identical to those described in the SPYRAL
127 HTN-OFF MED trial.⁹ In brief, the Symplicity SpyralTM multielectrode renal denervation
128 catheter (Symplicity Spyral catheter, Medtronic, Galway, Ireland), and the Symplicity G3TM
129 renal denervation RF generator (Symplicity G3 generator) were used to provide circumferential
130 radiofrequency ablation treatments in a spiral pattern in the four quadrants of the renal artery and
131 branch vessels between three and eight mm in diameter. All cases were performed by
132 experienced proceduralists and proctored using detailed treatment plans.
133 The control group received a sham procedure consisting of only a renal angiogram and were
134 required to remain on the procedure table for at least 20 minutes with sensory masking post-
135 angiogram to help prevent possible unblinding of randomisation allocation.

136

137 *Maintenance of blinding*

138 Patients and selected trial staff were blinded to the randomisation allocation. During the
139 procedures (renal angiogram alone or followed by renal denervation) blinding was maintained by
140 the use of conscious sedation, blindfolding, music and patients' lack of familiarity with the
141 procedures. The blinded trial staff conducted all follow-up visits and the patient's
142 referring/managing physicians were unaware of a patient's treatment assignment. A blinding
143 assessment form was completed by patients and the blinded blood pressure assessors prior to
144 discharge and at three and six-month follow-up visits. In accordance with the study protocol,
145 blinding of patients and blood pressure assessors was maintained for up to 12 months after
146 randomisation.

147

148 *Follow-up*

149 Patients returned for office follow-up visits at one, three and six-months post procedure. All
150 patients underwent urine and blood analysis to assess adherence to their prescribed medications
151 and staff witnessed patients taking their medication prior to the 24-hour ABPM at three and six
152 months. Adherence was defined as detectable levels of all prescribed antihypertensive
153 medications at each follow-up visit and includes cases in which an extra antihypertensive
154 medication was also detected. No antihypertensive medication changes were allowed through six
155 months unless the escape criteria were met (office SBP exceeded 180 mmHg or was below 115
156 mmHg with symptoms of hypotension). Blood chemistries, including sodium, potassium,
157 glucose and serum creatinine, were obtained at each follow-up visit as well. Estimated
158 glomerular filtration rate (eGFR) was calculated using the four variable Modification of Diet in
159 Renal Disease (MDRD) Formula or the local Japanese criteria for patients enrolled in Japan.¹¹
160 Renal artery imaging using duplex ultrasound was performed at the six-month office visit. MRA,
161 CT or angiogram was suggested if the duplex ultrasound was deemed non-diagnostic.

162

163 *Efficacy endpoints*

164 The key efficacy endpoint was the blood pressure change from baseline (measured at screening
165 visit two) based on ABPM measurements assessed at six months. This endpoint was based on the
166 prespecified requirement for patients to be maintained on the same specified antihypertensive
167 medication regimen through six-months follow-up. Office and 24-hour SBP and DBP were
168 measured at three and six months post randomisation. The change in office and 24-hour blood
169 pressure measurements were then compared between the two treatment groups.

170 Office and 24-hour heart rate change from baseline was assessed at six months. The rate pressure
171 product (RPP) was then calculated using 24-hour heart rate and SBP measurements as follows:
172 heart rate x SBP = RPP.^{12,13}

173

174 *Safety endpoints*

175 Safety endpoints included all-cause mortality, end-stage renal disease, new renal artery stenosis
176 >70% (assessed at six months), any significant embolic event resulting in end-organ damage,
177 hospitalization for hypertensive crises not related to medication non-adherence, new myocardial
178 infarction, new stroke, renal artery re-intervention, major bleeding, major vascular
179 complications, dissections, perforations and increase in serum creatinine >50% from screening
180 assessment. End-stage renal disease is defined as two or more eGFR measurements <15
181 mL/min/1.73 m² at least 21 days apart and requiring dialysis.

182

183 *Statistical analysis*

184 Like the SPYRAL HTN-OFF MED trial, the current proof-of-concept trial was designed in
185 collaboration with and approved by the U.S. FDA with consideration of the recommendations in
186 the 2014 Scientific Statement by the American Society of Hypertension¹⁴ and by a consortium of
187 investigators¹⁵⁻¹⁷ that suggested a phase two-type trial in hypertensive patients. Given the
188 uncertainty regarding the future role of renal denervation for management of hypertension after
189 the results of SYMPPLICITY HTN-3 it was decided to proceed with two smaller proof-of-concept
190 trials that would minimize exposure of patients to an interventional procedure but have the
191 potential to establish sufficient evidence to justify moving to a larger, powered trial. The

192 SPYRAL HTN-OFF MED proof-of-concept trial has been published, and this report represents
193 the primary results of the SPYRAL HTN-ON MED trial. The protocol allowed up to 110
194 patients to be randomised with prospectively planned interim analyses after 40, 60, and 80
195 patients completed at three follow up, respectively. Because the current study prespecified that
196 patients should be maintained on the same medication regimen through six-months follow-up,
197 analysis of the 80-patient cohort was then performed to assess the pattern and progression of
198 blood pressure change over time. The purpose of each interim analysis was to confirm the safety
199 of the procedure and determine if the blood pressure lowering effect of renal denervation was
200 sufficient to support design of future trials.

201 There are no powered endpoints in the trial. Statistical analyses were performed based on the
202 intention-to-treat principle. For patients meeting escape criteria, the last observation was carried
203 forward for the six-month blood pressure assessment. A modified intention-to-treat cohort
204 excluded patients who met escape criteria (SBP \geq 180 mmHg or $<$ 115 mmHg with symptoms). A
205 per-protocol analysis was also performed which excluded patients meeting escape criteria, were
206 non-adherent with their baseline anti-hypertensive regimen and who had at least one non-
207 standardised blood pressure assessment. Analysis of Covariance (ANCOVA) was employed to
208 adjust for baseline blood pressure measurements. For specific daytime and night-time BP
209 measurements, daytime was defined as 7:00AM to 9:59 PM, and night-time defined as 10:00 PM
210 to 6:59 AM. Individual sleep/wake times were used to compare hourly BP measurements
211 between patients where time zero was specified as wake time for patients who self-reported wake
212 times. If a patient did not report a wake time, they were assigned a waking time of 7:00AM.
213 Continuous variables are presented as means and standard deviations. Between group differences
214 and blood pressure differences from baseline to the three- and six-month follow-up assessment

215 were tested using unpaired and paired t-tests, respectively. Counts and percentages are presented
216 per treatment group for categorical variables; values were tested using the exact test for binary
217 variables and the chi-square test for multilevel categorical variables.

218 A blinding index was calculated from the completed blinding assessment forms at hospital
219 discharge and at three and six months to verify the effectiveness of blinding.¹⁰

220 *Role of the funding source*

221 The SPYRAL HTN-ON MED trial was funded by Medtronic. The executive committee designed
222 the protocol and identified clinical sites in collaboration with the funder. The funder was
223 responsible for collection, monitoring and analysis of the data. The manuscript was written by
224 the lead author with contributions from the executive committee and co-authors. The funder
225 assisted in figure and table generation, copy editing and formatting. The authors had unrestricted
226 access to the data and were responsible for the decision to submit for publication.

227

228 **RESULTS**

229 Between July 2015 and September 2017, 467 patients were screened and enrolled. This analysis
230 presents results for the first 80 patients randomly assigned to renal denervation (n=38) and sham
231 control (n=42; **Figure 1**). Baseline clinical characteristics were similar between groups, except
232 there were more patients with obstructive sleep apnea in the sham control group (ten vs. two
233 patients, $p=0.0277$; **Table 1**). Mean baseline office and 24-hour SBP, DBP and heart rate were
234 similar between groups.

235

236 There was no difference in the number of prescribed anti-hypertensive medication classes at
237 baseline between groups (2.2 ± 0.9 for renal denervation and 2.3 ± 0.8 for sham control, $p=0.70$;
238 **Table 1**). The proportion of patients in each treatment group prescribed 3 classes of
239 antihypertensive medications was also similar (52.6% in the renal denervation group and 52.4%
240 in the sham control group; $p=1.00$). Calcium channel blockers were prescribed in 71.1% of the
241 renal denervation group and 73.8% of the sham control group ($p=0.81$), ACE-I/ARB for 81.6%
242 and 83.3% ($p=1.00$), and diuretics for 57.9% and 59.5% ($p=1.00$). Subject adherence to
243 prescribed medications was not consistent at different time points (**Appendix Figure S2**).

244

245

246 All patients underwent renal angiography and angiographic documentation of catheter position
247 for the renal denervation group was required. During the procedure, a mean of 270.8 ± 101.6 cc
248 of contrast was used in the renal denervation group compared with 86.0 ± 50.0 cc in the sham
249 control group. For the renal denervation group, proceduralists performed an average of $45.9 \pm$
250 13.7 total ablations and treated an average of 2.3 ± 0.5 main arteries (19.3 ± 8.9 ablations) and
251 5.8 ± 2.2 branch vessels (26.6 ± 11.7 ablations; Appendix, **Table S2**).

252

253 The blinding index was 0.78 (95% CI 0.70, 0.85) at discharge, 0.68 (0.57, 0.79) at 3 months and
254 0.64 (0.54, 0.74) at 6 months, indicative of effective blinding.¹⁸

255

256 Adherence was similar between groups (at baseline, 65.8% for renal denervation and 59.5% for
257 sham control, $p=0.65$; at three months, 52.6% vs. 57.1%, $p=0.82$; at six months, 60.5% vs.
258 64.3%, $p=0.82$; **Appendix Table S3**). Anti-hypertensive medications not prescribed by

259 physicians were detected in 10-15% of patients at each time point. There were no significant
260 differences in baseline laboratory values or in six-month change in values between renal
261 denervation and sham control groups (Appendix, **Table S4**).

262 Changes in SBP and DBP from baseline to six months for both 24-hour ambulatory and office
263 measurements in the renal denervation and sham control groups are displayed in **Figure 2 and**
264 **Table 2**. The change in blood pressure was significantly greater at six months for the renal
265 denervation group vs. sham control for office SBP (difference -6.8 mmHg [-12.5, -1.1],
266 $p=0.0205$), 24-hour SBP (difference -7.4 mmHg [-12.5, -2.3], $p=0.0051$), office DBP
267 (difference -3.5 mmHg [-7.0, -0.0], $p=0.0478$) and 24-hour DBP (difference -4.1 mmHg [-7.8, -
268 0.4] $p=0.0292$). Individual changes in 24-hour and office BP at six months are displayed in
269 Appendix **Figure S3**. Comparison of changes in 24-hour blood pressure measurements at three
270 and six months for renal denervation and sham control groups is shown in **Figure 3**, where blood
271 pressure reduction for the renal denervation group was greater at six months compared to three
272 months. Three-month changes in office and 24-hour ambulatory BP are listed in Appendix **Table**
273 **S5**, and BP measurements at baseline and three and six months for all available patients in
274 Appendix **Table S6**. Hourly changes in ambulatory SBP and DBP for renal denervation and
275 sham control groups at baseline and six months are presented in **Figure 4**.

276 Six-month changes in 24-hour and office SBP and DBP in the two treatment groups for the
277 adherent patients and those incompletely or not adherent are shown in Appendix **Figure S4**. All
278 patients receiving renal denervation had a significant drop from baseline at six months but
279 between group differences are not significant in the adherent patients. The sham control response
280 was minimal in the incomplete/nonadherent group and 24-hour SBP was significantly different
281 between renal denervation and sham in these patients.

282 Comparison of six-month changes, adjusted for baseline measures using ANCOVA, also showed
283 significant differences, with a 24-hour SBP between group difference of -7.0 mmHg [-12.0, -
284 2.1], $p=0.0059$ and 24-hour DBP between group difference of -4.3 mmHg [-7.8, -0.8],
285 $p=0.0174$. Office SBP difference was -6.6 [-12.4, -0.9], $p=0.0250$ and office DBP difference
286 was -4.2 mmHg [-7.7, -0.7], $p=0.0190$ (**Table 2**). Results for the modified ITT population
287 provided similar outcomes (**Appendix, Table S7**). The small number of patients in the per-
288 protocol population (15 renal denervation and 14 control patients) limits comparison of
289 outcomes.

290 There was no significant difference in office or 24-hour heart rate at six months (**Table 2**). To
291 further explore the effect of renal denervation on heart rate and blood pressure the RPP was
292 analysed (**appendix Figure S5**). The hourly 24-hour RPP change at six months was lower in the
293 renal denervation patients at all time points. This consistent change over time was not observed
294 in the sham control group.

295
296 Similar to reported results for SPYRAL HTN-OFF MED,⁶ there were no procedural or safety
297 events through six months follow up in SPYRAL HTN-ON MED (**Appendix, Table S8**).

298

299

300 **DISCUSSION**

301 In this trial designed to explore the safety and efficacy of catheter-based renal denervation in
302 moderate, uncontrolled hypertension despite specified antihypertensive therapy, the salient
303 findings of this study are: (1) in patients receiving medical therapy, renal denervation extending
304 into branch arteries was associated with statistically significant and clinically relevant reductions

305 in office and ambulatory measures compared with a sham procedure; (2) the extent of blood
306 pressure reduction with renal denervation increased over temporal follow-up through six months;
307 (3) no procedural- or intermediate-term adverse safety events associated with renal denervation
308 were observed; and (4) non-adherence to antihypertensive medications was common. These
309 promising results both encourage further study with this method of renal denervation for
310 persistent hypertension despite the prescription of medical therapy and inform the design and
311 conduct of subsequent trials.

312 Similar to the SPYRAL HTN OFF-MED study⁶ and unlike prior investigations of renal
313 denervation,³⁻⁵ the ON MED trial differs considerably regarding the patient population enrolled,
314 procedural method and restriction to selected antihypertensive medication classes. Regarding the
315 latter feature, antihypertensive therapy was limited to four pharmaceutical categories (ACE
316 inhibitors/ARBs, calcium channel blockers, beta blockers, and thiazide diuretics) routinely
317 prescribed in clinical practice in part to minimize potential confounding suggested in previous
318 studies.^{4,19} Further, enrolled patients had moderate, combined hypertension²⁰ (mean office SBP
319 164.6 ± 7.1 mm Hg and DBP 99.9 ± 6.9 mm Hg) requiring up to three antihypertensive agents
320 in comparison, for example, with the SYMPPLICITY HTN-3 study in which the mean office SBP
321 was 179.7 ± 16.1 mm Hg with no diastolic requirement in patients prescribed an average 5.1
322 medications. Also, like the SPYRAL HTN-OFF MED study, renal denervation using a multi-
323 electrode catheter that permitted simultaneous or sequential energy delivery to the main renal
324 arteries with extension into distal renal artery branches was performed to enable more complete,
325 circumferential ablative treatment based on an evolving understanding in renal nerve
326 anatomy^{1,21,22} and procedural technique.⁸

327 Investigation of renal denervation in the setting of concurrent medical therapy for
328 hypertension was necessary to better understand the role of device therapy in clinical indications
329 anticipated to be common in routine patient care. Specifically, in the treatment of difficult to
330 control hypertension, consideration of an interventional therapy may factor into the decision
331 process after patients have been prescribed guideline-recommended drug therapy^{11,23-25} that
332 commonly begins with one or two medications and may eventually include a third agent in more
333 difficult cases. By 24-hour ambulatory measurement at six months, average systolic and diastolic
334 blood pressure reductions were 9 and 6 mm Hg, respectively, with a corresponding similar
335 magnitude of decline in office systolic and diastolic measures. Importantly, the magnitude of
336 blood pressure decline is clinically significant, associated with lower rates of both cardiovascular
337 events and mortality in prior studies.²⁶⁻²⁸ Notably, the absolute reduction in 24-hour ABPM at
338 three months in this study was similar that observed in the SPYRAL HTN-OFF MED study,⁶
339 despite greater variance in the sham control cohorts. Yet a progressive trend for the fall in blood
340 pressure was observed across all blood pressure measures in the renal denervation cohort
341 between three and six months raising the possibility that further time may be required to fully
342 realize the benefit of renal denervation therapy associated with resetting of systemic sympathetic
343 tone.

344 In comparison with office measurement that has been associated with greater
345 variability,²⁹ 24-hour ABPM demonstrated directionally consistent findings at three and six
346 months with progressive blood pressure decrease in the treatment group and in parallel, relatively
347 modest change in the control group. Compared with traditional office measurement changes,
348 variance in 24-hour ambulatory blood pressure is less susceptible to measurement bias, placebo
349 effects, and day-to-day variability. This method provides more stable and reproducible blood

350 pressure values than office or random home measurements,³⁰ and the ability to provide frequent,
351 serial blood pressure readings permits dynamic assessment over a time course that yields
352 prognostic relevance associated with reduced nocturnal blood pressure fall,³¹ increased short-
353 term blood pressure variability³² and excessive morning blood pressure surge.³³ In addition,
354 ambulatory blood pressure is also more strongly correlated with cardiovascular risk than office
355 measures,^{34,35} and the extent of ambulatory blood pressure reduction in the present study is
356 consistent with that deemed clinically meaningful by expert consensus.^{15,16}

357 As another revision to trial conduct compared with most prior renal denervation studies,
358 inclusion of surveillance methods to objectively document protocol adherence was important to
359 interpreting results of an interventional therapy in the presence of prescribed pharmacologic
360 therapy. Monitoring is informative given that imbalances in drug adherence between treatment
361 groups may either over- or underestimate the treatment effect observed with the experimental
362 therapy. Indeed, in both previous pharmacologic and renal denervation studies for hypertension,
363 medical adherence despite protocol mandate is largely unpredictable as it was not objectively
364 measured. Among contemporary studies involving renal denervation, for example, the
365 prevalence of medical non-adherence commonly approaches 50%, with 5% to 30% of patients
366 demonstrating complete absence of prescribed medical therapy by biochemical assay.³⁶ For those
367 patients treated with a standardised antihypertensive regimen and randomised in open-label
368 fashion to renal denervation or control in the DENER HTN trial, only half of patients were fully
369 adherent to drug therapy by urine and blood analysis performed at six months.⁷ The present study
370 confirms observations regarding the frequency of medical non-adherence in hypertension trials
371 and also highlights the dynamic pattern and influences of patient behaviour in the context of
372 protocol mandate and pre-existing awareness of drug surveillance. Despite documentation of a

373 stable drug regimen for at least two months prior to randomisation and requirement of only 50%
374 maximal dose, adherence with prescribed medical therapy was approximately 60% with highly
375 variable individual patient adherence at all timepoints (**Appendix, Figure S2**). If the benefit of
376 renal denervation is proven consistent and durable in future study, a constant, ‘always on’
377 treatment effect distinguishes it from pharmaceutical therapy reliant upon patient daily action
378 and complicated by intolerances, dosing frequency or other common issues that challenge
379 adherence. Further, the more constant reduction in sympathetic tone with renal denervation may
380 reduce variation in blood pressure control associated with pharmaceutical trough levels,
381 especially at early morning and evening levels. Supporting this premise, ambulatory readings
382 demonstrate persistent blood pressure suppression at all time points during the 24-hour period for
383 patients treated with renal denervation. Combining blood pressure with heart rate, 24-hour
384 lowering of the RPP may also support a more consistent reduction in sympathetic activity.

385

386 Altogether, these results reaffirm the safety and efficacy of renal denervation observed in
387 previous trials but further extend our understanding in the context of medical therapy and with a
388 modified procedural technique. Nevertheless, limitations exist to the present study. As an
389 exploratory, proof-of-concept trial, the study did not prespecify a hypothesis for differences in
390 blood pressure measurements at any particular time interval. If the analyses were prespecified,
391 however, assuming a treatment difference of 7 ± 11 mm Hg between renal denervation and sham
392 control groups, and two-sided alpha level of 0.05, a sample size of 80 patients (40 per cohort)
393 would provide 80% statistical power to reject the null hypothesis of no treatment difference
394 between groups. Instead, the investigational plan included prospectively planned interim
395 analyses to ascertain whether an adequate treatment effect with acceptable reduction in blood

396 pressure variability in the control cohort could be achieved and therefore inform further study.
397 To this purpose, a particular limitation—and challenge for future investigation— relates to the
398 prevalence of medical non-adherence despite patient education and awareness of drug testing.
399 Although absence of detectable drug at a single timepoint implies more frequent non-adherence,
400 it is not predictable for a single patient at interval assessments, and increasing recognition of this
401 potential confounder as common among both pharmaceutical and device trials raises the question
402 whether such assays should be imposed as common practice in hypertension trials. In part related
403 to this issue, the present findings are suggestive of effect in both adherent and non-adherent
404 populations but cannot confirm the benefit of renal denervation among patients with higher drug
405 adherence given the small sample size. Nevertheless, the prevalence of both number of
406 medications and adherence were similar in both groups, and critically, as previously stated,
407 ambulatory blood pressure measurements were obtained only following witnessed pill ingestion
408 in all patients. For the same reasons related to size of the study population, the safety of renal
409 denervation involving main artery and branch treatment cannot be confirmed; however, the
410 absence of safety events through six months in the current study is consistent with none observed
411 at three months applying the same procedural method in the SPYRAL HTN-OFF MED trial.⁶
412 Also, as in prior studies of renal denervation, there is no measure of effective renal nerve
413 ablation; however, the number of ablations per patient and procedural technique were similar to
414 those observed in the SPYRAL HTN-OFF MED trial that demonstrated similar and significant
415 reductions in 24-hour blood pressure at three months using the same procedural method and
416 technology. In addition, the inclusion criteria in the protocol for number of required
417 antihypertensive medications was revised during enrollment to allow patients to be on up to three
418 medications, instead of exactly three, to facilitate enrollment. We did not assess sodium intake or

419 impose any restrictions on dietary or lifestyle habits (e.g., smoking), and these factors could have
420 influenced blood pressure measurements. Finally, the results observed with this therapy and in
421 this specific population may not be generalizable to more varied clinical populations and
422 alternative interventional therapies for hypertension or medication classes not represented in this
423 trial.

424 In conclusion, we found clinically and statistically significant greater reductions in blood
425 pressure six months post-renal denervation compared to the sham control group. Both main renal
426 arteries and branches were treated with no major safety events. Although patients were aware of
427 planned medication adherence assessments, roughly half the patients were not adherent to their
428 prescribed anti-hypertensive medication regimen.

429

430 **Contributors**

431 DK, MB, FM, RT, MW, SP, GP, SB, SC, and KK participated in the design of the study. DK,
432 KT, DT, JC and CE participated in patient data collection. All authors were involved in
433 interpretation of the data. MF was the study biostatistician responsible for the statistical analyses.
434 DK, MB, FM, RT, MW, SP, GP, SB, SC and MF participated in writing of the report. All
435 authors agreed on the content of the manuscript, reviewed drafts, and approved the final version.

436

437

438 **Declarations of Interest**

439 DK receives institutional support for conduct of clinical trials from Medtronic and research/grant
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493 Lexington, KY, USA.

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495

Research in Context

496 **Evidence before this study**

497 We searched PubMed using the search terms “renal denervation”, “hypertension” and clinical
498 trial for papers published from November 1, 2012, to February 1, 2018. 34 clinical trial reports of
499 renal denervation for treatment of hypertension were identified, as well as 46 systematic reviews,
500 consensus statements, or meta-analyses published from Jan 1, 2015, to February 1, 2018. In
501 addition, a search for “renal denervation,” “hypertension” and “medication adherence” identified
502 25 clinical trial reports of renal denervation in the presence of medication adherence assessment.

503

504 **Added value of this study**

505 This trial addresses the application of renal denervation in a setting representative of clinical
506 practice for which integrating drug and procedural strategies may be anticipated. Although not
507 powered for efficacy endpoints, renal denervation inpatients receiving medical therapy for moderate,
508 uncontrolled hypertension, was safe and associated with significant and clinically relevant reductions in
509 blood pressure measures compared with a sham procedure. The temporal pattern of blood pressure
510 reduction with renal denervation is characterized with progressive reduction through six-month follow-up.
511 Frequent non-adherence to medical therapy informs the design and conduct of future trials.

512

513 **Implications of all the available evidence**

514 The results of the proof of concept study reaffirm the safety and efficacy of renal denervation
515 observed in previous trials but further extend our understanding in the context of medical therapy
516 and with a modified procedural technique. The findings both encourage further study with this

517 method of renal denervation for persistent hypertension despite the prescription of medical therapy and
518 inform the design and conduct of subsequent trials.

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520

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641 **Table 1:** Patient characteristics, blood pressure measurements, and anti-hypertensive medications at
 642 baseline.

Characteristic Mean (SD) or N (%)	Renal Denervation Group (N=38)	Sham Procedure Group (N=42)
Age (years)	53.9 (8.7)	53.0 (10.7)
Male	33 (86.8)	34 (81.0)
BMI (kg/m ²)	31.4 (6.4)	32.5 (4.6)
Race		
White	13 (34.2)	15 (35.7)
Black/African American	4 (10.5)	5 (11.9)
Asian	0 (0.0)	1 (2.4)
Not reportable per local laws/regulations	18 (47.4)	20 (47.6)
Diabetes (all type 2)	5 (13.2)	8 (19.0)
Current smoker	8 (21.1)	11 (26.2)
Obstructive sleep apnea	2 (5.3)	10 (23.8)
Peripheral artery disease	0 (0.0)	0 (0.0)
Coronary artery disease†	1 (2.6)	1 (2.4)
Stroke and transient ischemic attack†	0 (0.0)	1 (2.4)
Myocardial infarction/Acute coronary syndrome	0 (0.0)	0 (0.0)
Office SBP (mm Hg)	164.6 (7.1)	163.5 (7.5)
Office DBP (mm Hg)	99.6 (6.9)	102.7 (8.0)
Mean 24-hour SBP (mm Hg)	152.1 (7.0)	151.3 (6.8)
Mean 24-hour DBP (mm Hg)	97.2 (6.9)	97.9 (8.4)
Office heart rate (bpm)	75.6 (11.8)	73.5 (10.4)
24-hour heart rate (bpm)	75.3 (11.3)	75.6 (10.7)
Number of anti-hypertensive medication classes		
Mean (SD)	2.2 (0.9)	2.3(0.8)
Median [1 st IQR, 3 rd IQR]	3.0 [1.0, 3.0]	3.0 [1.0, 3.0]
Prescribed medication classes:		
1	11 (28.9)	9 (21.4)
2	7 (18.4)	11 (26.2)
3	20 (52.6)	22 (52.4)
4	0 (0.0)	0 (0.0)
Medication class:		
Diuretic	22 (57.9)	25 (59.5)
Calcium channel blocker	27 (71.1)	31 (73.8)

ACE-I/ARB	31 (81.6)	35 (83.3)
Beta blocker	4 (10.5)	6 (14.3)

643 †These events occurred more than six months before randomisation.

644 Data are n (%), mean (SD) or median [1st IQR, 3rd IQR].

645 All comparisons of baseline medications between renal denervation and sham control groups were non-
646 significant.

647

648 BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; bpm: beats per
649 minute; SD: standard deviation; IQR: interquartile range

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656 **Table 2:** Baseline blood pressure and changes at six months in intent-to-treat (ITT) population. 95% confidence intervals and p-values are
 657 included for each comparison. Baseline BP and changes at six months presented as mean \pm SD, and mean differences expressed with [95%
 658 confidence intervals].

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660

	Renal Denervation Group			Sham Control Group			Mean Difference: Renal Denervation vs Sham Control	
	N	Baseline BP	Change at six months	N	Baseline BP	Change at six months	Unadjusted ¹	Baseline Adjusted ²
Office SBP	38	164.6 \pm 7.1	-9.4 \pm 12.5	40	163.1 \pm 7.2	-2.6 \pm 12.9	-6.8 [-12.5, -1.1] p=0.0205	-6.6 [-12.4, -0.9] p=0.0250
Office DBP	38	99.6 \pm 6.9	-5.2 \pm 7.6	40	102.3 \pm 8.0	-1.7 \pm 7.9	-3.5 [-7.0, -0.0] p=0.0478	-4.2 [-7.7, -0.7] p=0.0190
Office HR	38	75.6 \pm 11.8	-5.1 \pm 7.6	40	73.6 \pm 10.3	-3.2 \pm 7.9	-2.0 [-5.5, 1.5] p=0.2628	-1.4 [-4.7, 1.8] p=0.3863
24-Hour SBP	36	151.9 \pm 7.1	-9.0 \pm 11.0	36	151.1 \pm 6.8	-1.6 \pm 10.7	-7.4 [-12.5, -2.3] p=0.0051	-7.0 [-12.0, -2.1] p=0.0059
24-Hour DBP	36	96.9 \pm 6.9	-6.0 \pm 7.4	36	97.6 \pm 8.3	-1.9 \pm 8.2	-4.1 [-7.8, -0.4] p=0.0292	-4.3 [-7.8, -0.8] p=0.0174
24-Hour HR	36	75.5 \pm 11.4	-3.7 \pm 6.0	36	76.2 \pm 10.2	-1.5 \pm 6.6	-2.2 [-5.1, 0.8] p=0.1509	-2.3 [-5.1, 0.4] p=0.0944
Daytime SBP	36	156.4 \pm 8.1	-8.8 \pm 11.3	36	157.4 \pm 8.4	-3.2 \pm 11.4	-5.7 [-11.0, -0.3] p=0.0390	-6.1 [-11.2, -1.1] p=0.0181

Daytime DBP	36	101.0 ± 7.1	-6.3 ± 7.9	36	102.7 ± 9.3	-2.8 ± 8.3	-3.5 [-7.3, 0.3] p=0.0691	-4.1 [-7.7, -0.4] p=0.0297
Nighttime SBP	37	144.9 ± 11.0	-9.8 ± 13.9	38	141.0 ± 8.5	2.1 ± 13.5	-11.9 [-18.2, - 5.6] p=0.0003	-10.0 [-16.0, -3.9] p=0.0016
Nighttime DBP	37	90.5 ± 10.6	-5.9 ± 9.7	38	89.5 ± 8.9	-0.3 ± 10.2	-5.6 [-10.2, -1.1] p=0.0167	-5.1 [-9.1, -1.1] p=0.0134

661 BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation

662 ¹p-value from unpaired t-test

663 ²Treatment difference and p-value from ANCOVA model, adjusting for baseline BP

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666 **Figure legends**

667

668 **Figure 1:** Trial profile

669 ITT: Intention-to-treat; mITT: modified intention-to-treat; PPP: per-protocol population

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672 **Figure 2:** Change at 6 months in office and ambulatory SBP and DBP for treatment and sham control
673 patients. Results are expressed as mean (95% confidence intervals).

674

675 SBP: systolic blood pressure; DBP: diastolic blood pressure

676

677 **Figure 3:** Mean changes in ambulatory 24-hour blood pressure measurements at three and six months,
678 adjusted for baseline values.

679

680 **Figure 4:**

681 Hourly measurements, according to patient-recorded individual wake times; error bars represent the
682 standard error.

683 A) 24-hour ambulatory SBP at baseline and six months for renal denervation group. Wake time (W) was
684 reported by 25 patients at baseline and 34 patients at six months and was set to 7:00AM for those
685 patients not reporting.

686 B) 24-hour ambulatory SBP at baseline and six months for sham control group. Wake time (W) was
687 reported by 33 patients at baseline and 37 patients at six months and was set to 7:00AM for those
688 patients not reporting.

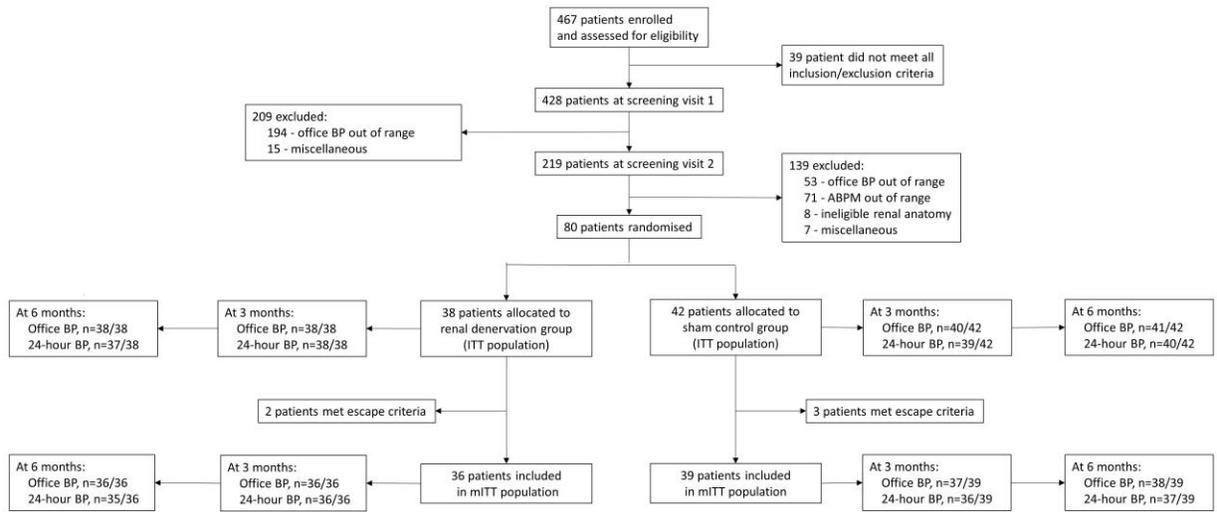
689 C) 24-hour ambulatory DBP at baseline and six months for renal denervation group. Wake time (W)
690 was reported by 25 patients at baseline and 34 patients at six months and was set to 7:00AM for
691 those patients not reporting.

692 D) 24-hour ambulatory DBP at baseline and six months for sham control group. Wake time (W) was
693 reported by 33 patients at baseline and 37 patients at six months and was set to 7:00AM for those
694 patients not reporting.

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697 **Figure 1:** Trial profile



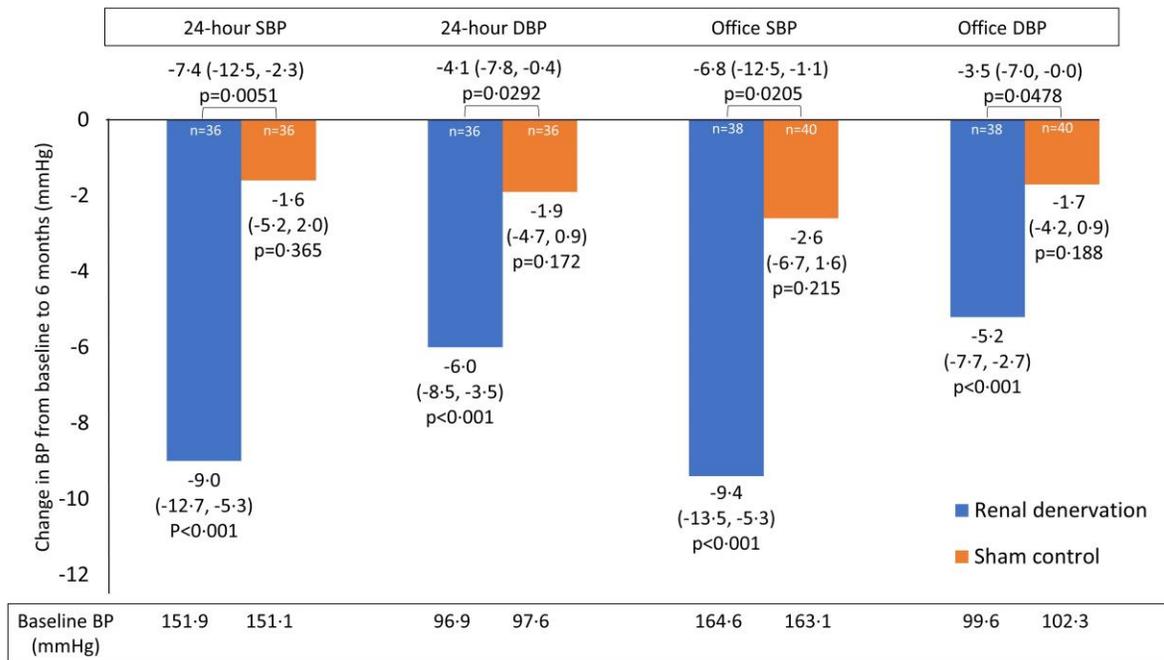
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702 **Figure 2:** Change at 6 months in office and ambulatory SBP and DBP for treatment and sham control
 703 patients. Results are expressed as mean (95% confidence intervals).



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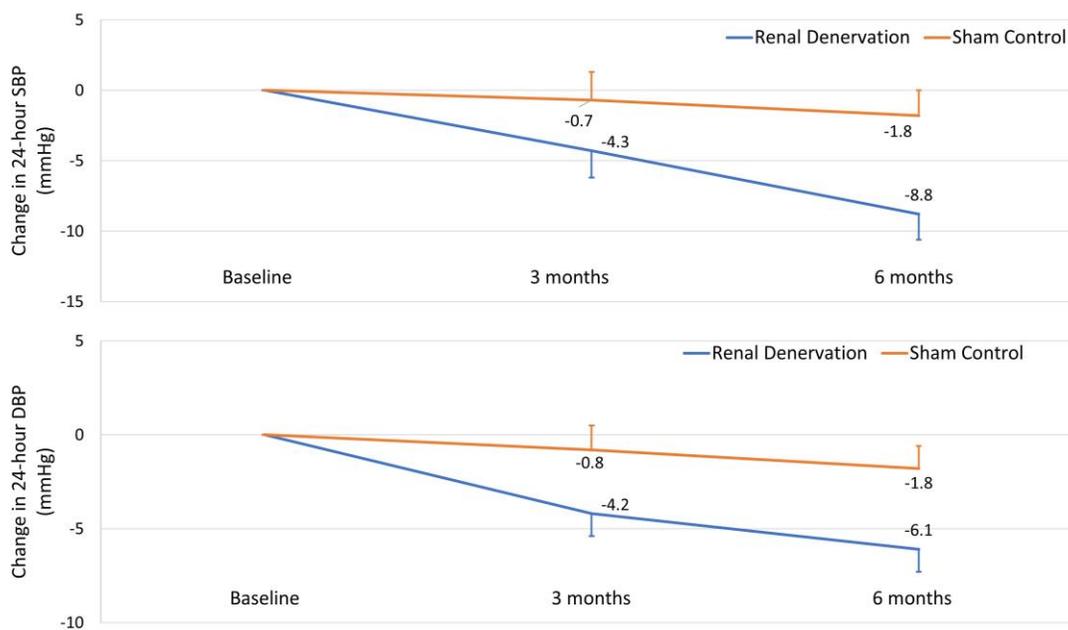
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709 **Figure 3:** Mean changes in ambulatory 24-hour blood pressure measurements at three and six months,
710 adjusted for baseline values.



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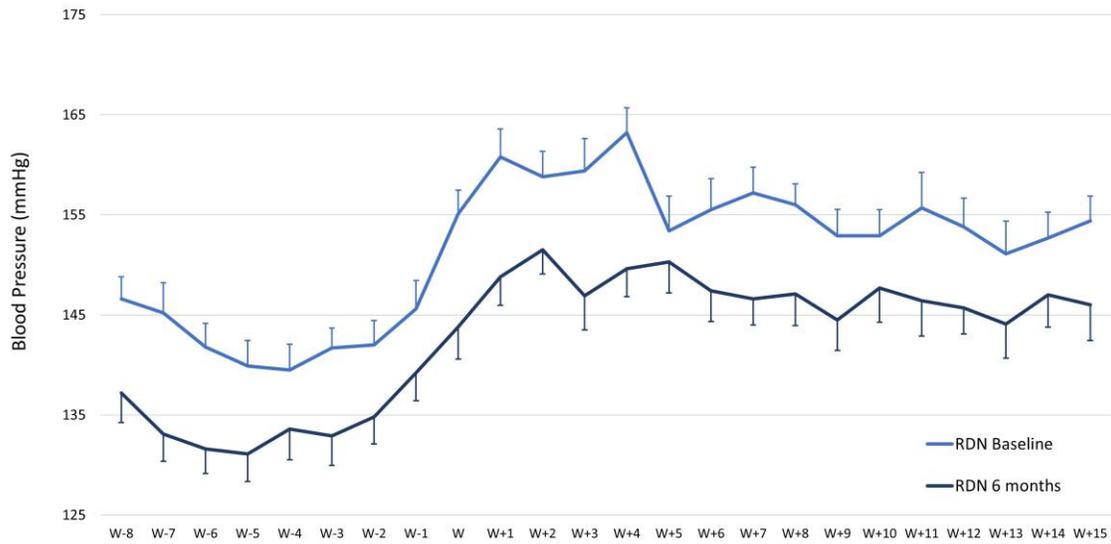
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714 **Figure 4:**

715 Hourly measurements, according to patient-recorded individual wake times; error bars represent the
716 standard error.

717 A) 24-hour ambulatory SBP at baseline and six months for renal denervation group.



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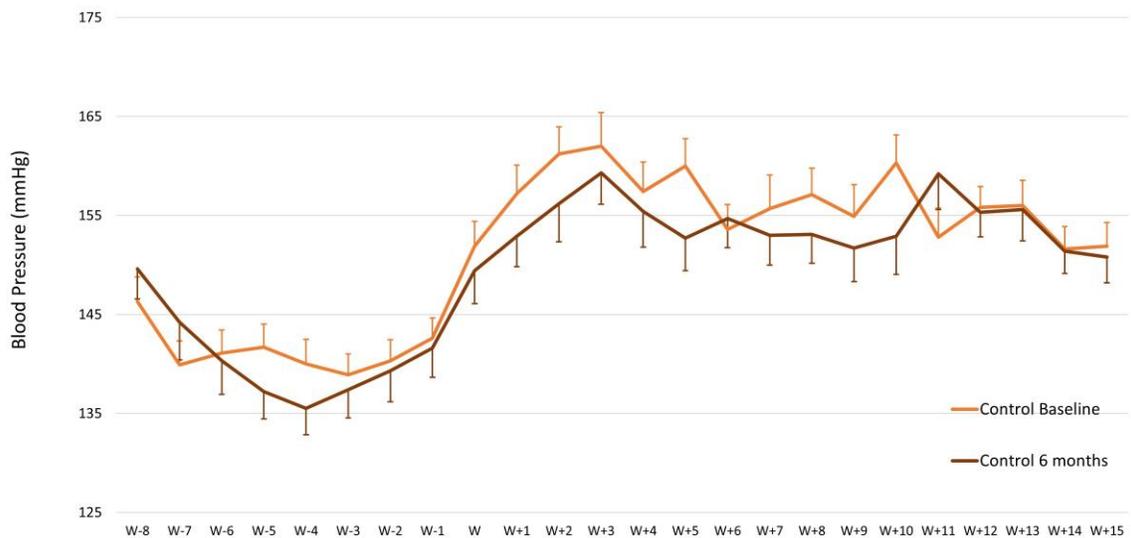
719 Wake time (W) was reported by 25 patients at baseline and 34 patients at six months and was set to
720 7:00AM for those patients not reporting.

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724 B) 24-hour ambulatory SBP at baseline and six months for sham control group.



725

726 Wake time (W) was reported by 33 patients at baseline and 37 patients at six months and was set to
727 7:00AM for those patients not reporting.

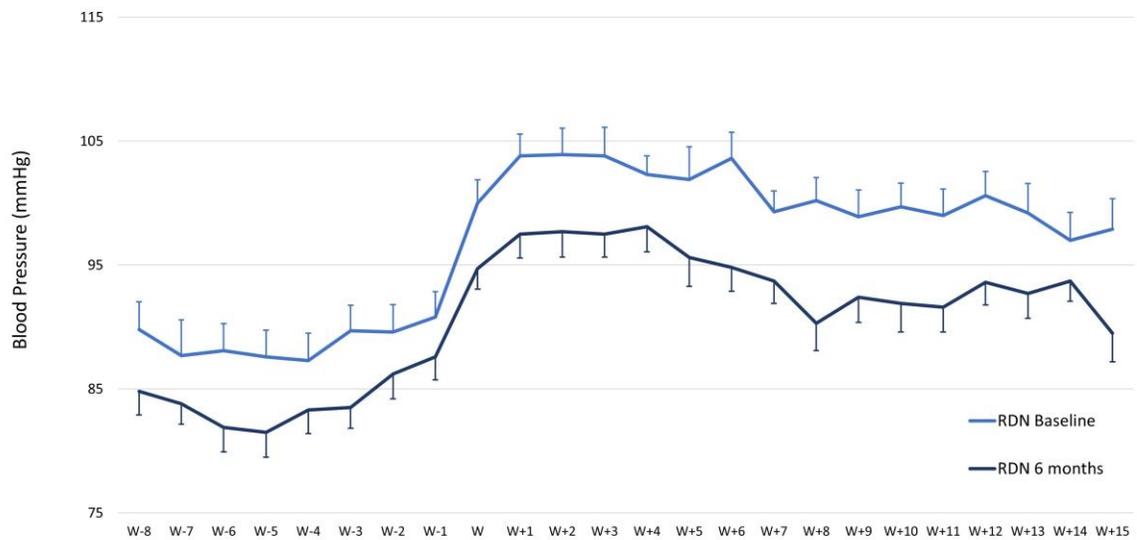
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731 C) 24-hour ambulatory DBP at baseline and six months for renal denervation group.

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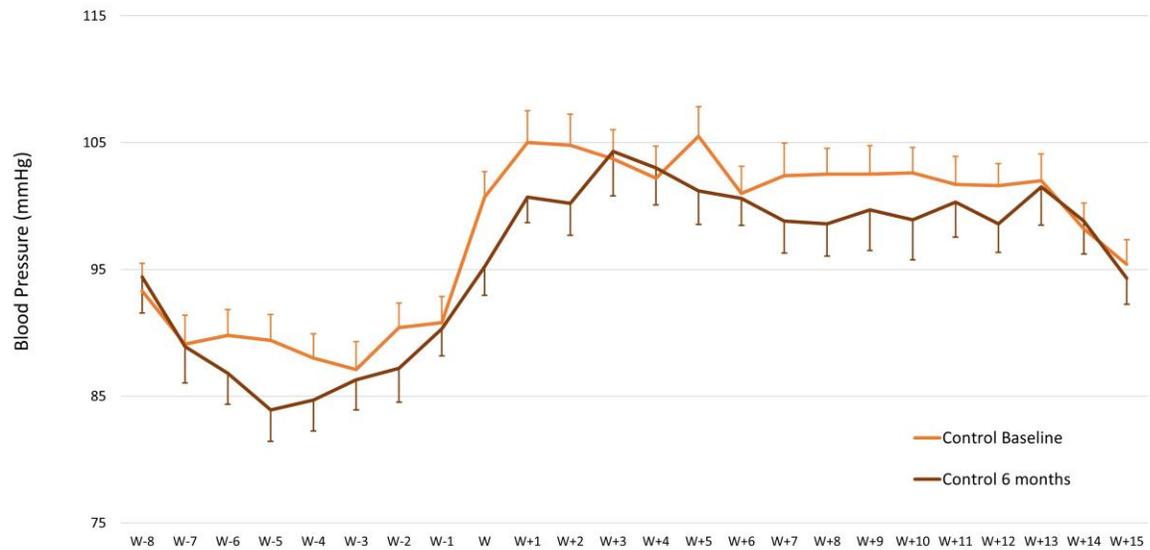
734 Wake time (W) was reported by 25 patients at baseline and 34 patients at six months and was set to
735 7:00AM for those patients not reporting.

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738 D) 24-hour ambulatory DBP at baseline and six months for sham control group.

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741 Wake time (W) was reported by 33 patients at baseline and 37 patients at six months and was set to
742 7:00AM for those patients not reporting.

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