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1 **Ultrasound Renal Denervation for Hypertension Resistant to a Triple Medication Pill:**
2 **The Randomised, Sham-Controlled RADIANCE-HTN TRIO Trial**

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14
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52

53 **SUMMARY**

54 **BACKGROUND**

55 Endovascular renal denervation reduces blood pressure in patients with mild-to-moderate
56 hypertension, but its efficacy in patients with true resistant hypertension remains to be demonstrated.

57 **METHODS**

58 In a multicentre, single-blind, randomised, sham-controlled trial done at 28 tertiary centres in the USA
59 and 25 in Europe, we included subjects with office blood pressure of at least 140/90 mmHg despite
60 three or more antihypertensive medications including a diuretic. Eligible patients were switched to a
61 once daily, fixed-dose, single-pill combination of a calcium channel blocker, an angiotensin receptor
62 blocker and a thiazide diuretic. After 4 weeks of standardised therapy, patients with daytime
63 ambulatory blood pressure of at least 135/85 mmHg were randomised by computer (1:1, stratified by
64 centres) to undergo ultrasound renal denervation or a sham procedure. Subjects and outcome assessors
65 were blinded to randomisation. Addition of antihypertensive medications was allowed if specified
66 blood pressure thresholds were exceeded. The primary endpoint was the change in daytime
67 ambulatory systolic blood pressure at two months in the intention-to-treat population. This study is
68 registered with ClinicalTrials.gov, number NCT02649426.

69 **FINDINGS**

70 Between March 11, 2016 and March 13, 2020, 989 subjects were enrolled, and 136 were randomised
71 to undergo renal denervation (n=69) or a sham procedure (n=67). Medication adherence ascertained
72 by urine drug detection exceeded 80% in both groups at two months. Renal denervation reduced
73 daytime ambulatory systolic blood pressure more than the sham procedure (-8.0 mmHg vs. -3.0
74 mmHg; median between-group difference -4.5 mmHg, 95% CI (-8.5 to -0.3), adjusted P=0.022); the
75 median between-group difference was -5.8 mmHg, (-9.7 to -1.6 mmHg, adjusted P=0.0051) among
76 subjects with complete ambulatory blood pressure data. There were no differences in safety between
77 groups.

78 **INTERPRETATION**

79 Compared with a sham procedure, ultrasound renal denervation reduced blood pressure at two months
80 in subjects with hypertension resistant to a standardised triple combination pill.

81

82 Funding: ReCor Medical.

83

84 **RESEARCH IN CONTEXT:**

85 **Evidence before this study**

86 We searched PubMed from January 1, 2017 to March 7, 2021 with the terms “renal
87 denervation”, “hypertension”, “randomised”, “sham”, “hypertension”, and various
88 combinations of those words to identify systematic reviews and meta-analyses of blood
89 pressure-lowering efficacy of renal denervation that specifically included the second-
90 generation trials, without language restriction. We identified 6 among 11 meta-analyses that
91 included all sham-controlled randomised trials in patients with uncontrolled hypertension in
92 the absence or presence of antihypertensive medications. The 2021 meta-analysis by Ahmad
93 and coworkers that included six eligible sham-controlled studies using both first and second
94 generation devices (713 patients randomised to renal denervation and 519 to placebo)
95 demonstrated that renal denervation significantly reduced 24-h ambulatory systolic blood
96 pressure (-3.52 mmHg; 95% CI -4.94 to -2.09; $p < 0.0001$) The meta-analyses by Syed and
97 coworkers and Sardar and coworkers reported a more pronounced blood pressure lowering
98 effect with second generation devices, including the ultrasound Paradise™ and the
99 radiofrequency Spyral™ catheters, as compared with the earlier generation systems.

100 **Added value of this study**

101 The RADIANCE-HTN TRIO trial was designed to overcome the methodological limitations
102 of prior studies in patients with resistant hypertension The RADIANCE-HTN TRIO trial
103 demonstrated a greater reduction in daytime, nighttime and 24-hour ambulatory systolic blood
104 pressure in subjects with hypertension resistant to a guideline-approved single pill triple
105 combination therapy with the second-generation endovascular ultrasound renal denervation as
106 compared to a sham procedure. The difference between the renal denervation and the sham
107 group was independent of the adherence of patients to the antihypertensive medications and

108 its magnitude was consistent with the results of the above-mentioned meta-analyses of
109 second-generation sham-controlled trials.

110 **Implications of all the available evidence**

111 Overall, the RADIANCE-HTN TRIO study and the aforementioned trials and their meta-
112 analyses enrolled largely different patient populations, and yet yield consistent results,
113 demonstrating that catheter-based renal denervation, using ultrasound or radiofrequency,
114 lowers blood pressure across a spectrum of hypertension severity, from mild hypertension
115 among patients off antihypertensive medications to more severe hypertension among patients
116 resistant to multiple antihypertensive medications.

117

118 INTRODUCTION

119 Endovascular catheter-based denervation of the renal efferent and afferent nerves was initially
120 investigated as a novel blood pressure-lowering treatment for patients with resistant hypertension. The
121 first randomised open-label trial¹ using catheter-directed radiofrequency ablation as well as immediate
122 subsequent trials (reviewed in²) overestimated its office blood pressure lowering efficacy in this
123 clinical setting. Subsequently, a larger sham controlled trial, (SYMPPLICITY HTN-3) did not show
124 improvement in office or ambulatory blood pressure control³ whereas the renal DENERvation for
125 HyperTensioN (DENERHTN) open-label trial⁴ which included a strict and standardised drug
126 escalation protocol showed a plausible reduction of daytime ambulatory systolic blood pressure by ~6
127 mm Hg in favour of renal denervation, irrespective of adherence to antihypertensive medications.⁵

128 Recently, three sham-controlled trials with more optimised designs to reduce variability of adjunctive
129 medications, procedural performance, and endpoint ascertainment,² consistently confirmed the
130 ambulatory and office blood pressure lowering efficacy of both radiofrequency and ultrasound renal
131 denervation in the absence or the presence of medications in subjects with less severe hypertension.⁶⁻
132 ⁹Among these trials, the RADIANCE-HTN trial compared endovascular ultrasound renal denervation
133 with a sham procedure in two separate cohorts.¹⁰ Within the first (SOLO) cohort of subjects with
134 mild-to-moderate hypertension who were weaned off medications, a 6.3 mmHg greater reduction in
135 daytime ambulatory systolic blood pressure was demonstrated with renal denervation vs. a sham
136 procedure at two months.⁷ The blood pressure lowering effect of ultrasound renal denervation was
137 maintained at six- and twelve months even when subjects were restarted on antihypertensive
138 medications.^{11,12} We now report the primary efficacy and safety results of ultrasound renal denervation
139 in the TRIO cohort of subjects with more severe hypertension resistant to three or more
140 antihypertensive medications.¹⁰

141 METHODS

142 Study design and population

143 The international, multicentre, randomised, sham-controlled RADIANCE-HTN TRIO trial was
144 conducted in 28 tertiary centres in the United States and 25 in Europe (France, UK, Germany, Poland,
145 Belgium, Netherlands) has been described previously¹⁰ (full protocol in the Supplementary Appendix).

146 The study was approved by local ethics committees or institutional review boards. All participants
147 provided written informed consent.

148 Eligible subjects were men or women aged 18–75 years with (i) resistant hypertension defined as
149 seated office blood pressure of at least 140 mmHg systolic and 90 mmHg diastolic despite a stable
150 regimen of three or more antihypertensive medications including a diuretic, and (ii) an estimated
151 glomerular filtration rate (eGFR) of at least 40 mL/min/1.73m².¹⁰ At enrolment, subjects were
152 switched to a single-pill, fixed-dose, daily combination of amlodipine 10 mg (or 5 mg in the event of
153 severe leg oedema), valsartan 160 mg (or olmesartan 40 mg depending upon medication availability in
154 each country), and hydrochlorothiazide 25 mg. No other antihypertensive medications were allowed
155 except beta-blockers for chronic coronary syndrome or heart failure. After 4 weeks of standardised
156 therapy, subjects with daytime ambulatory blood pressure of at least 135 mmHg systolic and 85
157 mmHg diastolic and suitable renal artery anatomy on renal CT- or MR-angiography underwent renal
158 angiography to confirm anatomic eligibility. Eligible subjects were then randomised in a 1:1 ratio to
159 receive ultrasound renal denervation with the Paradise System (ReCor Medical, Inc., Palo Alto, CA,
160 USA) or a sham procedure (full procedural details in the Supplementary Appendix).

161 **Randomisation and Masking**

162 The randomisation sequence was generated by computer and stratified by centre using randomised
163 blocks of four or six and permutation of treatments within each block. To maintain blinding, subjects
164 were sedated and wore headphones and eye covers. Pain was assessed post-procedure using a visual
165 analogue scale. Subjects completed a blinding questionnaire at discharge and two-month follow-up.
166 Treatment assignment was blinded for subjects and clinicians involved in follow-up care for six
167 months following randomisation.

168 **Post-Procedural Follow-up**

169 Subjects were evaluated at monthly visits between 0800 and 1000, prior to ingestion of their
170 standardised antihypertensive treatment. Attended seated office blood pressure and heart rate (Omron

171 M10-IT, Kyoto, Japan), analysis of 7-day home blood pressure recordings (Omron M10-IT),
172 medication lists, and adverse events were recorded, and laboratory assessments as well as urine
173 samplings for chemical adherence testing were done at each visit, as previously described.^{7,10} All
174 subjects were to remain on the single-pill triple combination (\pm beta-blocker) until two-month post-
175 randomisation unless specified office or home BP criteria were exceeded (180/110 mm Hg or 170/105
176 mm Hg, respectively), in which case subjects received escape antihypertensive treatment. 24-h
177 ambulatory blood pressure measurements (Microlife WatchBP, Taipei, Taiwan) were performed at
178 baseline and at two-month post-randomisation, as previously described.^{7,10} All recordings were sent to
179 a core laboratory (dabl Ltd., Dublin, Ireland) blinded to treatment assignment. Urine samples were
180 sent to a core laboratory (Pharmacology Department of the Georges Pompidou hospital, Paris, France).
181 Adherence to antihypertensive medications was directly assessed using ultrahigh performance liquid
182 chromatography tandem mass spectrometry to detect drugs or their metabolites in urine at baseline
183 (n=117) and two months (n=108), by an independent pharmacologist (BK) blinded to the treatment
184 assignment, as previously described.^{5,13} Full adherence to medications was defined as the presence of
185 all prescribed drugs in the sample. Renal duplex ultrasound was performed at two months in
186 randomised subjects

187 **Outcomes**

188 The primary efficacy endpoint was the change in daytime ambulatory systolic blood pressure from
189 baseline to two months. Secondary efficacy endpoints specified for hierarchical testing included
190 change in 24-hour ambulatory systolic and diastolic blood pressures, night-time ambulatory systolic
191 and diastolic blood pressures, and daytime ambulatory diastolic blood pressure at two months. Other
192 observational assessments included change at two months in all other office and home blood pressure
193 and heart rate measurements; the proportion of subjects with at least 5, 10, and 15 mmHg decrease in
194 daytime ambulatory systolic blood pressure and with controlled daytime blood pressure at two months
195 (<135/85 mmHg); and change in eGFR at two months.

196 Prespecified major adverse events included all-cause mortality, renal failure, an embolic event, renal
197 artery or vascular complications requiring intervention, or hypertensive crisis within 30 days.^{7,10}
198 Additional prespecified safety endpoints are listed in the appendix. An independent data safety and
199 monitoring board reviewed study data quarterly for all enrolled subjects.

200 **Statistical Analysis**

201 At the time of the design of the study in 2015, the sample size calculations were based on the
202 DENERHTN study⁹, as well as the 2015 guidelines on renal denervation.² We thus calculated that a
203 sample size of 128 subjects would yield 80% power to detect a 6 mmHg difference in change in
204 daytime ambulatory systolic blood pressure at two months between the renal denervation and sham
205 groups (common standard deviation 12 mmHg, two-sided type I error rate of 5%). To account for up
206 to 10% missing observations, we initially planned to randomise 146 subjects. However, the decision
207 was made to stop enrolment on May 8, 2020 after randomisation of 134 patients with evaluable
208 follow-up at two months due to the COVID-19 pandemic constraining further recruitment. The
209 decision was consistent with FDA guidance.¹⁴

210 The primary endpoint was analysed by intention-to-treat. Subjects with missing two-month
211 ambulatory blood pressure or those who met protocol criteria for escape antihypertensive treatment for
212 elevated blood pressures had their baseline blood pressure imputed as their two-month ambulatory
213 blood pressure value (renal denervation group, n=6 vs. sham group, n=4). Further, a tipping point
214 analysis was performed on the primary endpoint to evaluate the effect of missing observations. For the
215 secondary endpoints specified for hierarchical analysis, tests were performed in order, until the first
216 non-significant test, such that subsequent secondary endpoints would not be used to make claims;
217 however, these results and corresponding significance tests are provided for descriptive purposes. The
218 per-protocol, modified intention-to-treat, and as treated populations, as well as a post-hoc analysis of
219 subjects with complete ABPM data used for supportive analyses are described in the appendix.

220 Treatment differences between groups from baseline to two months were assessed using analysis of
221 covariance, including the baseline value as a covariate. When the change of a parameter from baseline

222 was not normally distributed, a baseline-adjusted analysis of covariance based on the ranks was
223 performed.¹⁵

224 Analyses for pre-specified subgroups were performed as exploratory analyses using linear regression
225 analyses with change in daytime ambulatory systolic blood pressure at two months as the dependent
226 variable. Baseline daytime ambulatory systolic blood pressure, treatment group, subgroup, and
227 treatment group by subgroup interaction term were included as independent variables in the models.
228 Adjusted mean daytime ambulatory systolic blood pressure by subgroup and p-value for the treatment
229 by subgroup interaction term are presented.

230 Comparisons between groups were made using unpaired t-tests or Wilcoxon tests for continuous
231 variables and Fisher's exact test or chi-square for categorical variables, as appropriate. Continuous
232 variables are expressed as mean \pm standard deviation or median with interquartile range (IQR) if not
233 normally distributed. Between-group differences are expressed as means with their two-sided 95%
234 confidence intervals (CI) or medians with their 95% CIs estimated using the Hodges-Lehmann method
235 where appropriate. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, US). All
236 statistical analyses were pre-defined in the protocol unless specifically indicated as being post-hoc
237 analyses.

238 **Role of the funding source**

239 The study was funded by ReCor Medical, Inc. The executive committee designed the protocol with the
240 sponsor, who was responsible for data collection, monitoring and analysis. The authors had
241 unrestricted access to the data, and statistical analyses were independently validated (Baim Institute
242 for Clinical Research, Boston, MA, USA). The manuscript was written by MA and AJK with
243 contributions from co-authors. The authors had full responsibility for the decision to submit for
244 publication. The trial is registered with www.clinicaltrials.gov (NCT02649426).

245 **RESULTS**

246 Between March 11, 2016 and March 13, 2020, 989 subjects were enrolled, and 136 subjects met all
247 eligibility criteria for randomisation (renal denervation, n=69; sham procedure, n=67; Figure 1).

248 Baseline characteristics were similar across both study groups (Table 1). Office blood pressure was
249 161/100 mmHg despite 4.0 ± 1.0 antihypertensive drugs at screening. After switching subjects from
250 their non-standardised therapy to a single pill triple therapy, 99/136 (73%) patients received a single
251 pill combination containing valsartan 160 mg for four weeks until baseline, the remaining were treated
252 with a combination containing olmesartan 40 mg (Table 1). The distribution of valsartan vs.
253 olmesartan in the single pill combination was well balanced between the two groups at baseline (Table
254 1). Importantly, once the single pill combination with valsartan or olmesartan was selected, it
255 remained the same throughout the trial. A total of 117/136 (86%) subjects received a single pill
256 combination containing amlodipine 10 mg for four weeks, the remaining being treated with a
257 combination containing amlodipine 5 mg (Table 1). The distribution of amlodipine 10 vs. 5 mg in the
258 single pill combination was well balanced between the two groups at baseline (Table 1). After 4
259 weeks of standardised treatment with the single pill triple therapy (\pm beta-blocker, $n=10$; Table S1),
260 ambulatory blood pressure values confirmed treatment resistance (Table 2). Full adherence to the
261 standardised combination medication as measured by urine chromatography was high at baseline
262 among 117/136 subjects with urine samples ($n=93$, 79%; Table S1, Appendix).

263 A total of 40 interventionalists at 35 study centres assigned patients to the renal denervation group.
264 These 40 interventionalists performed an average of 2 renal denervation procedures (range 1–6). In the
265 denervation arm, successful bilateral renal nerve ablations with 5.8 ± 1.2 ultrasound emissions were
266 performed in 67/69 (97%) subjects of whom 17/69 (25%) had accessory renal artery ablations (Table
267 S2, Appendix). There was no difference between groups in post-procedure pain and blinding was
268 maintained (Table S2 and S3, Appendix).

269 Between baseline and two months, 64/69 subjects (93%) in the renal denervation group and 57/67
270 (85%) in the sham group had no change in their baseline antihypertensive treatment ($P=0.15$). Three
271 patients in the renal denervation group and 8 in the sham group received additional antihypertensive
272 medications (spironolactone for 2 and 7 patients, respectively; Table S4, Appendix). Four subjects in
273 the renal denervation group and one subject in the sham group had a down-titration of the amlodipine
274 dose from 10 to 5 mg in the single pill combination done by the treating physician. Full adherence to

275 the combination medications remained high at two months in subjects with subjects with urine
276 samples, with no difference between the renal denervation and sham groups (42/51 [82%] vs. 47/57
277 [82%]; respectively; $P=0.99$, Table S1). Four patients who were non-adherent at baseline became fully
278 adherent at two months in the sham group vs. three patients in the renal denervation group. Three
279 patients who were fully adherent at baseline became non-adherent at two months in the renal
280 denervation group vs. one patient in the sham group.

281 **Outcomes**

282 In the intention-to-treat population, there was a greater reduction in daytime ambulatory systolic blood
283 pressure at two months with renal denervation compared with sham (median -8.0 mmHg; IQR, -16.4
284 to 0.0 vs. -3.0 mmHg; IQR -10.3 to 1.8; median between-group difference -4.5 mmHg (95% CI, -8.5 to
285 -0.3 mmHg, baseline adjusted $P=0.022$; Table 2 and Figure S1, Appendix). Changes in all other
286 systolic blood pressure parameters also favoured renal denervation (Table 2), including 24-hour blood
287 pressure (-4.2 mmHg vs. sham, 95% CI -8.3 to -0.3 mmHg, adjusted $P=0.016$, Figure S1, Appendix).
288 The larger systolic blood pressure lowering effect over the 24-h circadian cycle with renal denervation
289 vs. sham is shown in Figure 2.

290 Changes in diastolic blood pressure parameters are shown in Table 2. There was no between-group
291 difference in heart rate at two months (Table S5, Appendix.). Analyses on additional study populations
292 were consistent with the intention-to-treat analysis (Table S6 to S8, Appendix). The median between-
293 group difference in the per-protocol population was -5.4 mmHg, (-9.5 to -1.3 mmHg, adjusted
294 $P=0.011$; Table S7, Appendix) and was -5.8 mmHg, (-9.7 to -1.6 mmHg, adjusted $P=0.0051$) among
295 subjects with complete ambulatory blood pressure data (Table S8, Appendix). Tipping point analysis
296 showed the results to be robust (Table S9, Appendix).

297 Individual subject changes in daytime ambulatory systolic blood pressure are shown in Figure S2
298 (Appendix). In the intention-to-treat population, 24/69 (35%) subjects of the renal denervation group
299 attained controlled daytime ambulatory blood pressure vs. 14/67 (21%) in the sham group. The effect
300 of renal denervation on the primary efficacy endpoint was consistent across sex, ethnicity, age,

301 abdominal circumference, and baseline blood pressures (Figure S3, Appendix). In a post-hoc analysis
302 using linear mixed models with the change in daytime systolic blood pressure as the dependent
303 variable, we found no significant interaction with the type of angiotensin II receptor blocker (valsartan
304 or olmesartan) or the dose of amlodipine used. The number of ultrasound emissions, the presence of
305 non-ablated accessory renal arteries, and the number of renal denervation per interventionalist did not
306 influence the blood pressure response to renal denervation (not shown). Finally, the between group
307 difference in daytime systolic blood pressure was in favour of renal denervation in both subjects fully
308 adherent and those non-adherent to medications in a post-hoc analysis (Table S10).

309 Three major adverse events occurred within 30 days after renal denervation of which only one (access
310 site pseudoaneurysm successfully treated) was adjudicated as being procedure-related (Table 3). eGFR
311 was similar in both groups at two months (Table S11, Appendix) and no new renal artery stenosis
312 greater than 50% was detected (Table 3).

313 **DISCUSSION**

314 Among patients with hypertension confirmed to be resistant despite adherence to a 4-week
315 standardised, fixed-dose, single pill, triple combination of a thiazide, an angiotensin II receptor
316 blocker and a dihydropyridine, ultrasound renal denervation achieved a greater reduction in daytime
317 ambulatory systolic blood pressure at two months compared with a sham procedure. The treatment
318 effect of renal denervation was consistent for 24-hour ambulatory, nighttime ambulatory, office, and
319 home systolic blood pressures. The greater blood pressure lowering effect of renal denervation vs.
320 sham was achieved with patients of both groups remaining on the same standardised single-pill triple
321 combination (\pm beta-blocker in 10 patients) to which they were highly adherent and despite the more
322 frequent use of add-on new antihypertensive drugs, including spironolactone, in the sham group. The
323 effect of renal denervation was also consistent across various pre-specified subgroups, including sex,
324 ethnicity, varying age, abdominal obesity and baseline blood pressures. There was only a single
325 reversible procedure-related adverse event at the vascular access site.

326 The design of the RADIANCE-HTN trial attempted to overcome potential limitations of previous
327 studies in resistant hypertension.^{2,3} We randomised patients with resistant hypertension confirmed by
328 ambulatory blood pressure after optimising their antihypertensive treatment with a single-pill, fixed-
329 dose, triple combination according to current guidelines.^{16,17} By reducing pill burden,¹⁸ a high
330 adherence to the standardised treatment was achieved at baseline, which was maintained through two
331 months in both groups. We also took care to reduce confounding factors¹⁹ by 1) planning optimised
332 circumferential renal denervation treatment based on the pre-procedural imaging,¹⁰ 2) ensuring
333 effective blinding of patients and clinical staff and, 3) strictly limiting any uncontrolled changes in the
334 antihypertensive medications during follow-up. Altogether, these various strengths in the design of our
335 study increased its internal validity but led to increase the number of study centres and increased the
336 duration the enrolment period to four years, with the last year being influenced by the COVID-19
337 pandemic. Finally, in accordance with international guidelines¹⁶ and with the approval of health
338 authorities and ethics committees, we assessed the primary endpoint at two months to prioritise safety
339 of our patients with resistant hypertension who were at higher risk than patients with mild-to-moderate
340 hypertension uncontrolled with less than three medications. Indeed, the SYMPPLICITY HTN-3 trial
341 reported 84 major cardiovascular and cerebrovascular events including 3 deaths among 535
342 randomised patients with resistant hypertension (16%) during a short follow-up of 6 months.³ This is
343 the main reason why (i) an escape antihypertensive treatment could be prescribed if blood pressure
344 exceeded a specified threshold through two months, and, (ii) a standardised drug titration protocol was
345 to be started in both groups while maintaining blinding, if blood pressure remained uncontrolled from
346 the second month onwards.¹⁰ The RADIANCE-HTN TRIO trial is ongoing 3-year follow-up to assess
347 longer-term safety and efficacy.

348 In the strictly controlled conditions of our trial, the renal denervation group experienced an 8·0 mmHg
349 reduction in daytime ambulatory systolic blood pressure at two months that was 4·5 mmHg greater
350 than with the sham procedure in the intention-to-treat population. This between-group difference was
351 detected with patients maintained on the same standardised treatment than at baseline to which they
352 were highly adherent. Of note, antihypertensive medications were more commonly added in the sham

353 group (n=8) than in the denervation group (n=3) during the two-month follow-up either according to
354 protocol defined safety criteria or to subject or physician preference. The systolic blood pressure
355 lowering effect of ultrasound renal denervation was consistent over the 24-h circadian cycle as shown
356 by the 8.1 mmHg decrease in nighttime ambulatory systolic blood pressure, as seen in the
357 RADIANCE-HTN SOLO⁷ and SPYRAL HTN trials.^{8,9}

358 The sham effect in the TRIO cohort, while patients were on standardized triple pill
359 combination treatment, was larger than that observed in the SOLO cohort while patients were
360 off-treatment (-3.0 mmHg vs. -2.2 mmHg in the intention-to-treat population, respectively;
361 and -3.3 vs. -0.1 mmHg in the per-protocol population when excluding patients who received
362 medications for any reason and had missing ambulatory blood pressure data, respectively).
363 The sham effect in the RADIANCE-HTN TRIO study may have been possibly amplified by
364 changes in adherence to medications from baseline to two months in some subjects. Indeed, 4
365 subjects who were non-adherent at baseline became fully adherent at two months in the sham
366 group and contributed to large individual decreases in daytime systolic blood pressures in the
367 sham group. Nevertheless, the overall sham effect in our trial was smaller than in the
368 Symplicity HTN-3 study²⁰ (-6.1 mmHg in daytime ambulatory systolic blood pressure) and
369 other studies²¹ and similar to the placebo effect reported in drug trials conducted in patients
370 with resistant hypertension.²² Indeed, the meta-analysis of Patel et al.²¹ on the placebo/sham
371 BP lowering effects in randomised controlled trials conducted in patients with resistant
372 hypertension, reported that invasive sham procedures showed a nonsignificant trend toward a
373 greater response on office systolic BP (no ambulatory blood pressure data available) than a
374 placebo pill in the treatment of resistant hypertension (-13.2±2.4 mm Hg versus -7.24±2.4
375 mmHg). The sham effect may have contributed to an underestimation of the blood pressure
376 lowering effect of renal denervation in the RADIANCE TRIO study. Moreover, the large
377 number of interventionalists may have increased the variability in the procedure performance.

378 However, the number of renal denervation procedures per interventionalist was not a predictor
379 of the blood pressure response.

380 The consistency of the primary endpoint results as shown by the similar magnitude in the decrease of
381 ambulatory systolic blood pressure in patients either on- (TRIO) or off- (-8.5 mmHg in SOLO)
382 antihypertensive treatment at baseline reinforces the validity of the present results. Interestingly,
383 nighttime systolic blood pressure decreased more in the TRIO cohort (-8.1 mmHg) compared with the
384 SOLO cohort (-4.8 mmHg), though baseline nighttime blood pressure was 4.0 mmHg lower in SOLO.⁷

385 Both the higher baseline nighttime blood pressure and the larger nighttime blood pressure response to
386 renal denervation may be consistent with the greater contribution of the sympathetic nervous system to
387 the pathophysiology of resistant hypertension as compared with less severe hypertension.²³ Given the
388 strong association of nighttime blood pressure with cardiovascular disease risk,²⁴ these results may
389 have prognostic implication especially for patients with resistant hypertension at risk. Finally, in a
390 post-hoc analysis on the subgroup of patients with urine samples, renal denervation resulted in a
391 greater decrease in blood pressure vs. sham regardless of adherence to treatment, i.e. in both adherent
392 patients with consequently true resistant hypertension and non-adherent patients with apparent
393 resistant hypertension, consistent with the results of the DENERHTN trial.⁵ This result may have
394 important clinical implications but should be considered as hypothesis generating and thus be
395 confirmed in a larger study.

396 Overall, the positive results of the RADIANCE-HTN TRIO trial in patients with resistant
397 hypertension expand the results of the pilot sham-controlled SPYRAL HTN-ON MED⁸ to a
398 larger population of patients with more severe and resistant hypertension to three and more
399 antihypertensive medications. SPYRAL HTN-ON MED trial enrolled 80 patients with
400 moderate hypertension requiring up to three antihypertensive agents in comparison, who
401 underwent multi-electrode radiofrequency-based renal denervation, and in whom the
402 difference with the sham group was significant at six months and not at three months while
403 patients were maintained on a stable free combination of antihypertensive treatments. While

404 both studies utilised a sham procedure for the control group, there were differences in study
405 populations, hypertension severity, standardised medication protocol, and conduct. The
406 method used for renal nerve ablation also differed, as endovascular ultrasound, and not
407 radiofrequency ablation of main, distal and accessory renal arteries was utilised. Finally, the
408 daytime ambulatory systolic blood pressure difference in favour of renal denervation vs. sham
409 is consistent with results of various meta-analyses on renal denervation with the second
410 generation of catheters.^{6,25,26}

411 Finally, if maintained in the long term as highlighted by the three-year report of the Global
412 SYMPPLICITY registry²⁷ as well as the 12-month results of the RADIANCE-HTN SOLO
413 study,¹² the average 9.0 mmHg reduction in office systolic blood pressure we observed after
414 renal denervation in patients with resistant hypertension who are at high risk of cardiovascular
415 event,²⁸ is of a magnitude previously associated with a reduction in stroke, coronary heart
416 disease, heart failure and all-cause mortality for antihypertensive drug therapy.²⁹ A reduction
417 in both cardiovascular and cerebrovascular events may also be expected if we confirm our
418 previous observation of a reduced visit-to-visit variability in blood pressure after renal
419 denervation in the RADIANCE-HTN SOLO trial.¹²

420 Our study has limitations. First, additional follow-up will be required to determine whether the blood
421 pressure lowering effect of ultrasound renal denervation remains durable over time, especially when
422 patients receive additional antihypertensive medications, especially the aldosterone antagonist
423 spironolactone, to control their blood pressure in both blinded (two to six months) and unblinded
424 conditions after six months.¹⁰ While adverse events were infrequent, longer follow-up of this trial and
425 additional numbers of treated subjects will be necessary to provide additional safety data. Finally,
426 similar to other trials of renal denervation, despite our efforts to reduce overall variability, there was
427 still between-patient variation in the response to renal denervation (as well as to the sham procedure;
428 see Table 2), some of which may be attributed to variable medication adherence or other factors. We

429 found none of the previously described patient- (including age, sex, ethnicity, obesity, and baseline
430 blood pressure levels) or procedure-related factors (including number of ablations or ablation of
431 accessory arteries) to explain such variability.³⁰ Between-patient variability might still be due to
432 variable renal nerve ablation despite the uniform use of circumferential ablations and treatment of
433 accessory renal arteries or may reflect differing contribution of renal nerve signalling to hypertension
434 perpetuation. At present, there is still no reliable peri-operative marker of successful renal
435 denervation.³⁰ Also, we observed a very high adherence rate to antihypertensive medications, but the
436 true level of adherence to medications may have been lower, because patients were fully informed that
437 medication adherence was monitored throughout the trial, and this may have given rise to white coat
438 adherence phenomenon. However, our assays enabled us to determine nonadherence to the
439 medications with high specificity, because non-detection of the medications in the urine samples
440 collected at trough indicates that the non-detected drug(s) had not been ingested by the patient for a
441 duration that exceeded at least 5 plasma half-lives of that given drug. Despite this limitation, our
442 analysis suggests that potential biases attributable to non-adherence to the treatment are likely to have
443 had minimal consequences for the results of the RADIANCE-HTN TRIO study, because the level of
444 exposure to the medications after 2 months follow-up was not different in the two groups. Finally, we
445 included patients with resistant hypertension and eGFR values above 40 ml/min of whom only 11%
446 had eGFR values below 60 ml/min, and thus, our results are not directly applicable to patients with
447 more severe renal insufficiency even though they have frequently resistant hypertension, as well as to
448 other clinical settings (including heart failure, sleep obstructive apnoea, or arrhythmias).

449 In conclusion, in this powered, sham-controlled randomised study of subjects with combined systolic–
450 diastolic hypertension resistant to a fixed-dose, single pill, triple combination antihypertensive therapy
451 as recommended by current guidelines,¹⁶ ultrasound renal denervation safely reduced ambulatory
452 systolic blood pressure more than a sham procedure at two months. The six-month (blinded phase) and
453 twelve-month (unblinded phase) follow-up of the RADIANCE-HTN TRIO study during which
454 subjects of both groups receive spironolactone as fourth line therapy according to guidelines, will also
455 determine whether renal denervation may be an alternative to the addition of further antihypertensive

456 medications to reduce the risk of drug-related side effects and non-adherence to medications.^{17,28}
457 Finally, ongoing follow-up of the present population for three years¹⁰ as well as additional studies will
458 be important to evaluate the durability, continued safety and long-term clinical impact of ultrasound
459 renal denervation in subjects with various forms of hypertension.

460

461 **Contributors**

462 MA, AJK, JB, MJB, JD, ML, FM, RES, ASPS, MAW, NCB, HR-S, LC, and CKM participated in the
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464 ASPS, MSap, PF, AP, PL, DH, SB, AW, JW, BK, NCB, HRS, LC, CKM participated in patient data
465 collection. All authors analysed and interpreted the data. CKM was the study biostatistician
466 responsible for the statistical analyses. Statistical analyses were validated independently by the Baim
467 Institute (Boston, MA, USA). MA and AJK wrote the first draft of the report. MA, AJK, NCB, HR-S,
468 LC, and CKM had access to and verified the underlying data. All authors participated in the writing of
469 the report, agreed on the content of the manuscript, reviewed drafts, and approved the final version.

470

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476

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514

515 **Data Sharing Statement**

516 Data will be shared with researchers who submit a research proposal approved by the study steering
517 committee. Individual patient data will be shared in data sets in a de-identified and anonymised
518 format. Data will be made available after research completion and approval of the product and product
519 use in the EU and the USA.

520

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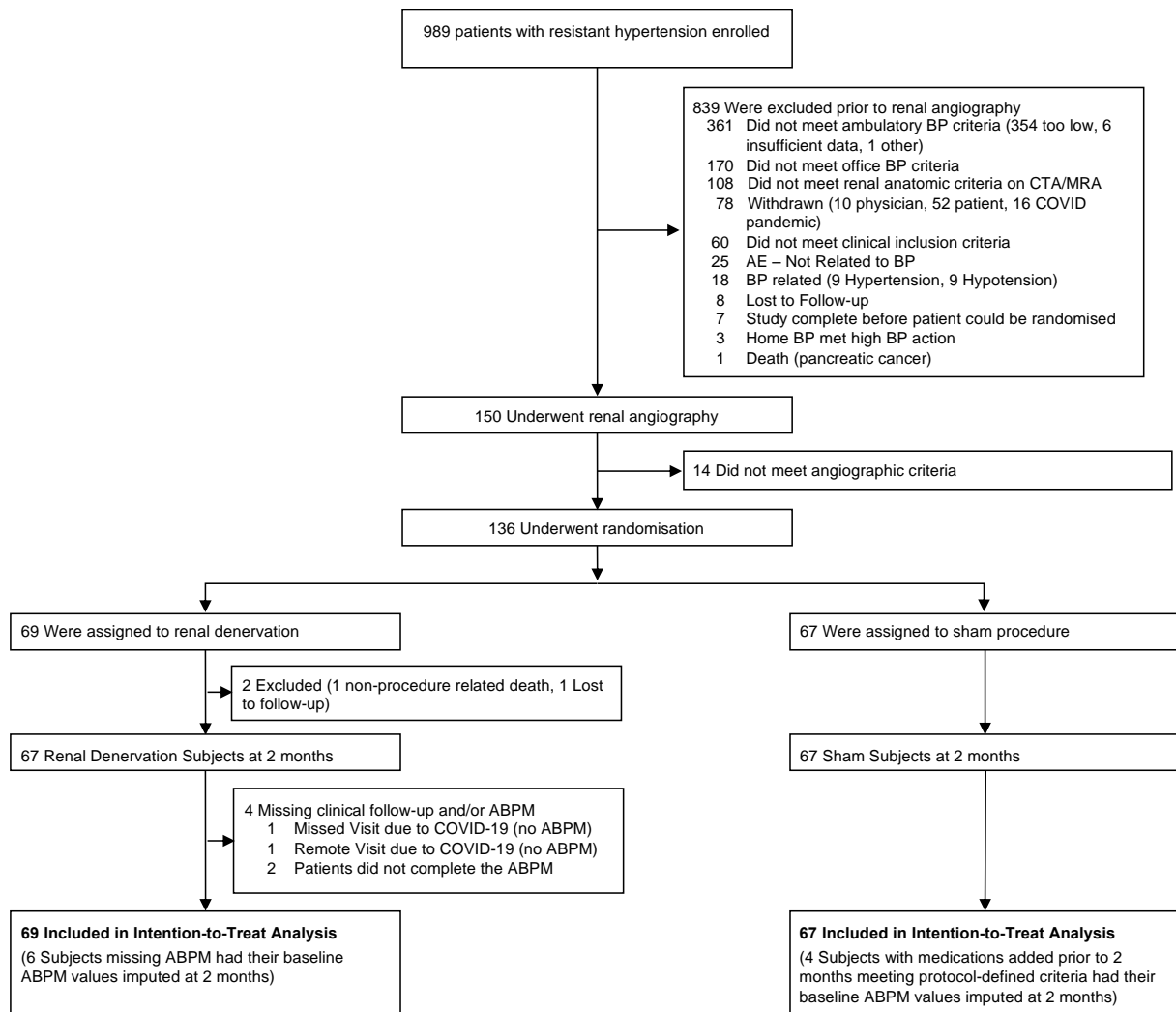
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602

603 **Figure 1. Subject Flow.** BP: blood pressure; CTA: CT-angiography; MRA: MR-angiography; AE: adverse
 604 event; ABPM: ambulatory BP monitoring.

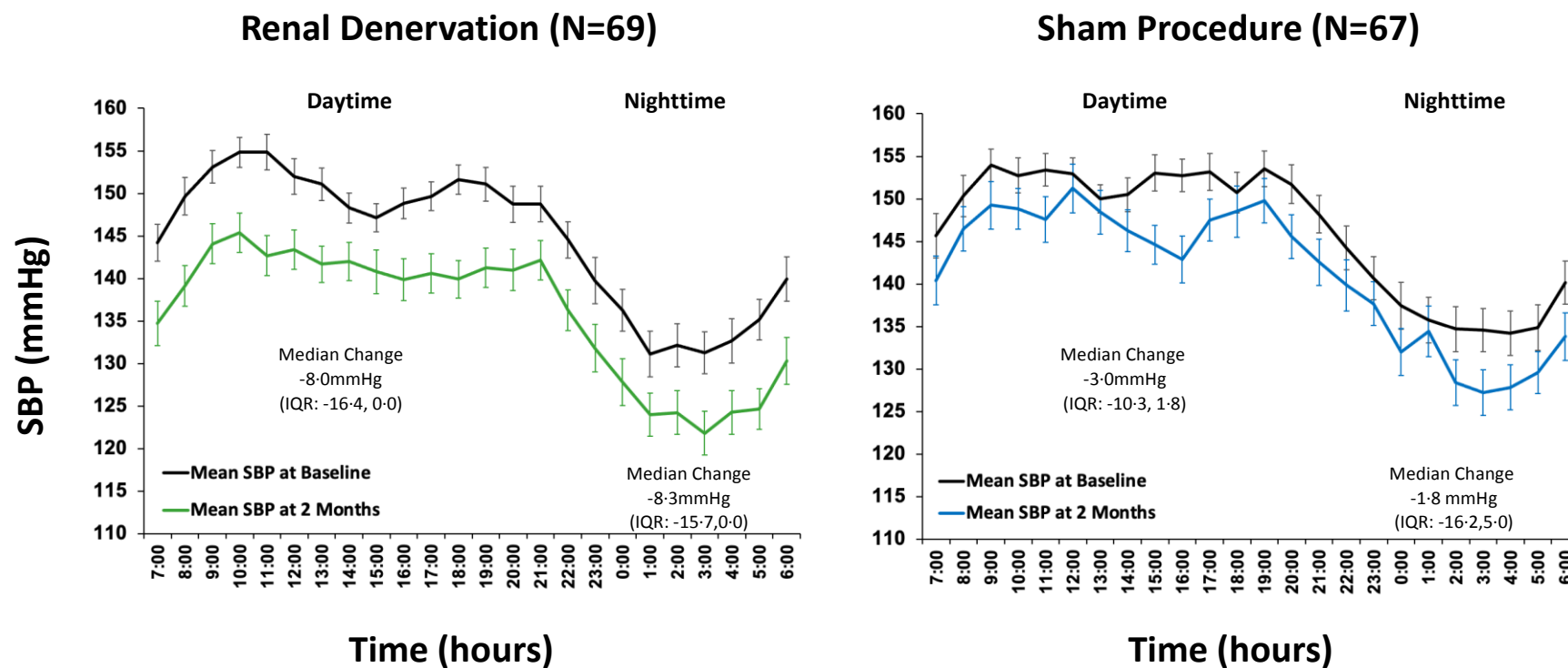


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608 **Figure 2. Twenty-four hour ambulatory profiles of systolic blood pressure (SBP) at baseline and two months in the renal denervation group (left) and**
 609 **the sham group (right) in the intention-to-treat population. Between baseline and two months, 64/69 patients (93%) in the renal denervation group**
 610 **and 57/67 (85%) in the sham group had no change in their baseline antihypertensive treatment. Error bars represent standard errors (SD/\sqrt{N}).**



611

612 **Table 1. Baseline demographics and clinical characteristics of the intention-to-treat population**

Measure	Renal Denervation (N=69)	Sham Procedure (N=67)
Age (years)	52.3 ± 7.5	52.8 ± 9.1
Female sex	13/69 (19%)	14/67 (21%)
Race		
White	44/69 (64%)	50/67 (75%)
Black	14/69 (20%)	13/67 (19%)
Other	11/69 (16%)	4/67 (6%)
Body mass index - kg/m ²	32.8 ± 5.7	32.6 ± 5.4
Abdominal obesity *	54/66 (82%)	55/67 (82%)
eGFR - ml/min/1.73m ²	86.0 ± 25.2	82.2 ± 19.2
eGFR <60 ml/min/1.73m ²	8/67 (12%)	7/65 (11%)
Type II Diabetes	21/69 (30%)	17/67 (25%)
Sleep apnea syndrome	19/69 (28%)	11/67 (16%)
Prior hospitalisation for hypertensive crisis	15/69 (22%)	11/67 (16%)
Prior cardiovascular / cerebrovascular event	8/69 (12%)	9/67 (13%)
History of heart failure	1/69 (1%)	3/67 (4%)
Office blood pressure and heart rate at screening		
Systolic blood pressure (mmHg)	161.0 (151.0, 171.0)	161.0 (151.0, 172.0)
Diastolic blood pressure (mmHg)	103.0 (96.0, 114.0)	99.0 (94.0, 110.0)
Heart rate (bpm)	77.0 (65.0, 82.0)	75.0 (69.0, 89.0)
Number of antihypertensive medications at screening	4.0 ± 1.0	3.9 ± 1.1

Measure	Renal Denervation (N=69)	Sham Procedure (N=67)
3 medications	27/69 (39%)	28/67 (42%)
4 medications	22/69 (32%)	24/67 (36%)
≥ 5 medications	20/69 (29%)	15/67 (22%)
Antihypertensive medications at screening		
Renin Angiotensin System blockers	67/69 (97%)	63/67 (94%)
Diuretics	63/69 (91%)	64/67 (96%)
Calcium channel blockers	61/69 (88%)	56/67 (84%)
Beta blockers	37/69 (54%)	29/67 (43%)
Aldosterone antagonists	25/69 (36%)	21/67 (31%)
Centrally acting drugs	9/69 (13%)	10/67 (15%)
Alpha-1 receptor blockers	6/69 (9%)	10/67 (15%)
Vasodilators	4/69 (6%)	4/67 (6%)
Antihypertensive medications at baseline prior to randomisation †		
Valsartan 160 mg	50/69 (72%)‡	49/67 (73%)
Olmesartan 40 mg	19/69 (28%)	18/67 (27%)
Amlodipine 10 mg	59/69 (86%)	58/67 (87%)
Amlodipine 5 mg	10/69 (14%)	9/67 (13%)
Hydrochlorothiazide 25 mg	69/69 (100%) §	67/67 (100%) §
Beta Blocker	7/69 (10%)	3/67 (4%)

613 Data are n (%), mean ± SD or median (IQR). eGFR=estimated glomerular filtration rate.

614 * Abdominal obesity was defined as a waist circumference greater than 102 cm for men and greater than

615 88 cm for women.

616 † At enrolment, subjects were switched to a single-pill, fixed-dose, daily combination of amlodipine 10
617 mg (or 5 mg in the event of severe leg oedema), valsartan 160 mg (or olmesartan 40 mg depending upon
618 medication availability in each country), and hydrochlorothiazide 25 mg prescribed for four weeks until
619 randomisation at baseline. No other antihypertensive medications were allowed except beta-blockers for
620 chronic coronary syndrome or heart failure.

621 ‡ 1 patient given Valsartan 320 mg in the renal denervation group.

622 § 1 patient given Hydrochlorothiazide 12.5 mg in both the renal denervation and sham group.

623

624 **Table 2. Primary and Secondary Efficacy Endpoints: Change in ambulatory, office, and home blood pressure at 2 months in patients with renal denervation (n=69)**
 625 **and sham (n=67) in the intention-to-treat population.**

	Renal Denervation			Sham Procedure			Unadjusted Median Between-Group Difference (95% CI) *	Baseline-Adjusted P-value †
	Randomisation	2 Months	Difference	Randomisation	2 Months	Difference		
Systolic Blood Pressure Parameters (mmHg)								
Daytime Ambulatory ‡	150.0 ± 11.9	141.0 ± 16.1	-8.0 (-16.4, 0.0)	151.1 ± 12.6	146.3 ± 18.8	-3.0 (-10.3, 1.8)	-4.5 (-8.5, -0.3)	0.022
24 Hour Ambulatory	143.9 ± 13.4	135.2 ± 16.0	-8.5 (-15.1, 0.0)	145.4 ± 14.0	140.5 ± 18.7	-2.9 (-12.6, 2.5)	-4.2 (-8.3, -0.3)	0.016
Nighttime Ambulatory	134.4 ± 18.0	126.3 ± 18.4	-8.3 (-15.7, 0.0)	136.4 ± 18.6	131.9 ± 20.9	-1.8 (-16.2, 5.0)	-3.9 (-8.8, 1.0)	0.044
Office §	155.6 ± 16.7	147.1 ± 20.3	-9.0 (-19.5, -1.5)	154.9 ± 16.8	152.1 ± 22.0	-4.0 (-12.0, 9.0)	-7.0 (-13.0, 0.0)	0.037
Home	152.0 ± 16.2	144.6 ± 18.2	-6.0 (-17.0, 1.5)	153.1 ± 17.0	149.9 ± 18.9	-2.0 (-9.5, 2.0)	-4.0 (-8.0, 0.0)	0.052
Diastolic Blood Pressure Parameters (mmHg)								
Daytime Ambulatory	93.8 ± 7.7	88.5 ± 11.6	-4.9 (-10.4, 0.0)	94.6 ± 9.1	90.7 ± 12.2	-2.0 (-7.8, 1.0)	-1.8 (-4.5, 0.8)	0.18
24 Hour Ambulatory	88.9 ± 8.2	83.6 ± 10.9	-5.4 (-10.4, 0.0)	89.5 ± 9.5	85.8 ± 12.0	-2.4 (-7.8, 0.5)	-2.0 (-4.5, 0.6)	0.12
Nighttime Ambulatory	81.3 ± 10.7	76.2 ± 12.2	-5.1 (-12.7, 0.0)	81.3 ± 12.1	78.4 ± 13.2	-2.0 (-9.5, 4.1)	-2.8 (-6.1, 0.2)	0.053

	Renal Denervation			Sham Procedure			Unadjusted Median Between-Group Difference (95% CI) *	Baseline-Adjusted P-value †
	Randomisation	2 Months	Difference	Randomisation	2 Months	Difference		
Office §	101.4 ± 11.6	96.6 ± 13.9	-5.0 (-13.5, 2.5)	99.4 ± 10.9	98.7 ± 13.8	-1.0 (-7.0, 6.0)	-4.0 (-9.0, 0.0)	0.16
Home	96.5 ± 11.2	93.2 ± 14.7	-4.0 (-9.0, 2.0)	96.7 ± 11.4	96.0 ± 12.8	-1.0 (-5.0, 4.0)	-3.0 (-6.0, 0.0)	0.053

626

627 Data displayed mean±SD and as median (IQR) unless otherwise noted.

628 DBP=diastolic blood pressure, SBP=systolic blood pressure* Hodges-Lehmann Estimate of Location Shift and 95% Asymptotic Confidence Intervals.

629 † Since change from baseline in either cohort was non-normal, the P-value from baseline adjusted ANCOVA on the ranks is provided for all parameters, except for home SBP

630 and DBP where the P-value value from baseline adjusted ANCOVA, is reported.

631 ‡ Primary efficacy endpoint.

632 § There were 64 patients in the renal denervation group and 66 patients in the sham group with office blood pressure measurements included in the intention-to-treat
633 population.634 || There were 60 patients in the renal denervation group and 64 patients in the sham group with home blood pressure measurements included in the intention-to-treat
635 population.

636 **Table 3. Incidence of safety events through 2 months**

Safety Events	Renal Denervation (n=69)	Sham Procedure (n=67)
Procedural safety events		
Death	0 (0%)	0 (0%)
Significant embolic events resulting in end organ damage	0 (0%)	0 (0%)
Any renal artery complication requiring intervention (e.g. dissection; perforation)	0 (0%)	0 (0%)
Acute renal injury *	0 (0%)	0 (0%)
Need for renal artery angioplasty or stenting	0 (0%)	0 (0%)
Major access site complications requiring intervention	1 (1%) §	0 (0%)
Procedure-related pain lasting for >2 days †	12 (17%)	10 (15%)
New onset renal artery stenosis of greater than 50% ‡	0 (0%)	0 (0%)
Other safety events through 2 months		
All-cause mortality	1 (1%)	0 (0%)
Hypertensive emergency resulting in hospitalisation	0 (0%)	0 (0%)
Hypotensive emergency resulting in hospitalisation	0 (0%)	0 (0%)
Hospitalisation for heart failure	0 (0%)	0 (0%)
Stroke, transient ischemic attack, cerebrovascular accident	0 (0%)	0 (0%)
Acute myocardial infarction (STEMI/non-STEMI)	1 (1%)	0 (0%)
Any coronary revascularisation	0 (0%)	1 (1%)
Doubling of plasma creatinine	1 (1%) ¶	0 (0%)
End stage renal disease, the need for permanent renal replacement therapy	0 (0%)	0 (0%)

637 Data displayed as: number of events (%).

638 * Acute renal injury defined as: increase in plasma/serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 μ mol/l) within 48hrs
639 of the procedure or, increase in serum/plasma creatinine to ≥ 1.5 times baseline known to have occurred during 7
640 days post-procedure or urine volume <0.5 ml/kg/h for 6 hours.

641 † In the renal denervation group there were 7 subjects with pain at the femoral access site, 4 back pain, and 1
642 extremity pain. For the sham group there were 8 subjects with pain at the femoral access site and 2 back pain.

643 ‡ Diagnosed by duplex ultrasound and confirmed by renal CT-/MR-angiography or as diagnosed/confirmed by
644 CT-/MR-angiography; Non-
645 invasive renal imaging was available in 61 renal denervation and 61 sham procedure subjects at 2 months.

646 In total, three events met the definition of a Major Adverse Event listed in temporal order: § One femoral access
647 site pseudoaneurysm post-procedure treated with thrombin injection. || One sudden death unrelated to device or
648 procedure 21 days post-procedure. ¶ One transient acute renal injury at 25 days post-procedure associated with
649 spironolactone use and