

Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial

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

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53 <u>SUMMARY</u>

54 **BACKGROUND**

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

57 METHODS

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

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 daytime ambulatory systolic blood pressure more than the sham procedure (-8.0 mmHg vs. -3.0 73 mmHg; median between-group difference -4.5 mmHg, 95% CI (-8.5 to -0.3), adjusted P=0.022); the 74 75 median between-group difference was -5.8 mmHg, (-9.7 to -1.6 mmHg, adjusted P=0.0051) among subjects with complete ambulatory blood pressure data. There were no differences in safety between 76 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.

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82 Funding: ReCor Medical.

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RESEARCH IN CONTEXT:

85 Evidence before this study

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

100 Added value of this study

The RADIANCE-HTN TRIO trial was designed to overcome the methodological limitations of prior studies in patients with resistant hypertension The RADIANCE-HTN TRIO trial demonstrated a greater reduction in daytime, nighttime and 24-hour ambulatory systolic blood pressure in subjects with hypertension resistant to a guideline-approved single pill triple combination therapy with the second-generation endovascular ultrasound renal denervation as compared to a sham procedure. The difference between the renal denervation and the sham group was independent of the adherence of patients to the antihypertensive medications and its magnitude was consistent with the results of the above-mentioned meta-analyses ofsecond-generation sham-controlled trials.

110 Implications of all the available evidence

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

117

118 INTRODUCTION

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

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

141 METHODS

142 Study design and population

The international, multicentre, randomised, sham-controlled RADIANCE-HTN TRIO trial was
conducted in 28 tertiary centres in the United States and 25 in Europe (France, UK, Germany, Poland,
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 participants147 provided written informed consent.

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

161 Randomisation and Masking

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

168 Post-Procedural Follow-up

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

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

187 **Outcomes**

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

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

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

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

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

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

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

238 Role of the funding source

The study was funded by ReCor Medical, Inc. The executive committee designed the protocol with the sponsor, who was responsible for data collection, monitoring and analysis. The authors had unrestricted access to the data, and statistical analyses were independently validated (Baim Institute for Clinical Research, Boston, MA, USA). The manuscript was written by MA and AJK with contributions from co-authors. The authors had full responsibility for the decision to submit for 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

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 1). Importantly, once the single pill combination with valsartan or olmesartan was selected, it 254 remained the same throughout the trial. A total of 117/136 (86%) subjects received a single pill 255 combination containing amlodipine 10 mg for four weeks, the remaining being treated with a 256 combination containing amlodipine 5 mg (Table 1). The distribution of amlodipine 10 vs. 5 mg in the 257 258 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).

A total of 40 interventionalists at 35 study centres assigned patients to the renal denervation group. These 40 interventionalists performed an average of 2 renal denervation procedures (range 1–6). In the denervation arm, successful bilateral renal nerve ablations with 5·8±1·2 ultrasound emissions were performed in 67/69 (97%) subjects of whom 17/69 (25%) had accessory renal artery ablations (Table S2, Appendix). There was no difference between groups in post-procedure pain and blinding was maintained (Table S2 and S3, Appendix).

Between baseline and two months, 64/69 subjects (93%) in the renal denervation group and 57/67(85%) in the sham group had no change in their baseline antihypertensive treatment (P=0·15). Three patients in the renal denervation group and 8 in the sham group received additional antihypertensive medications (spironolactone for 2 and 7 patients, respectively; Table S4, Appendix). Four subjects in the renal denervation group and one subject in the sham group had a down-titration of the amlodipine dose from 10 to 5 mg in the single pill combination done by the treating physician. Full adherence to the combination medications remained high at two months in subjects with subjects with urine samples, with no difference between the renal denervation and sham groups (42/51 [82%] vs. 47/57 [82%]; respectively; P=0·99, Table S1). Four patients who were non-adherent at baseline became fully adherent at two months in the sham group vs. three patients in the renal denervation group. Three patients who were fully adherent at baseline became non-adherent at two months in the renal 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 pressure at two months with renal denervation compared with sham (median -8.0 mmHg; IQR, -16.4 283 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 284 285 -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 pressure (-4·2 mmHg vs. sham, 95% CI -8·3 to -0·3 mmHg, adjusted P=0·016, Figure S1, Appendix). 287 288 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).

Individual subject changes in daytime ambulatory systolic blood pressure are shown in Figure S2
(Appendix). In the intention-to-treat population, 24/69 (35%) subjects of the renal denervation group
attained controlled daytime ambulatory blood pressure vs. 14/67 (21%) in the sham group. The effect
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 non-ablated accessory renal arteries, and the number of renal denervation per interventionalist did not 305 influence the blood pressure response to renal denervation (not shown). Finally, the between group 306 307 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).

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

313 **DISCUSSION**

Among patients with hypertension confirmed to be resistant despite adherence to a 4-week 314 standardised, fixed-dose, single pill, triple combination of a thiazide, an angiotensin II receptor 315 316 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 effect of renal denervation was consistent for 24-hour ambulatory, nighttime ambulatory, office, and 318 home systolic blood pressures. The greater blood pressure lowering effect of renal denervation vs. 319 sham was achieved with patients of both groups remaining on the same standardised single-pill triple 320 combination (\pm beta-blocker in 10 patients) to which they were highly adherent and despite the more 321 frequent use of add-on new antihypertensive drugs, including spironolactone, in the sham group. The 322 effect of renal denervation was also consistent across various pre-specified subgroups, including sex, 323 324 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.

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

In the strictly controlled conditions of our trial, the renal denervation group experienced an 8.0 mmHg reduction in daytime ambulatory systolic blood pressure at two months that was 4.5 mmHg greater than with the sham procedure in the intention-to-treat population. This between-group difference was detected with patients maintained on the same standardised treatment than at baseline to which they 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}

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

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

380 The consistency of the primary endpoint results as shown by the similar magnitude in the decrease of ambulatory systolic blood pressure in patients either on- (TRIO) or off- (-8.5 mmHg in SOLO) 381 antihypertensive treatment at baseline reinforces the validity of the present results. Interestingly, 382 nighttime systolic blood pressure decreased more in the TRIO cohort (-8·1 mmHg) compared with the 383 SOLO cohort (-4.8 mmHg), though baseline nighttime blood pressure was 4.0 mmHg lower in SOLO.⁷ 384 385 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 the pathophysiology of resistant hypertension as compared with less severe hypertension.²³ Given the 387 strong association of nighttime blood pressure with cardiovascular disease risk,²⁴ these results may 388 have prognostic implication especially for patients with resistant hypertension at risk. Finally, in a 389 390 post-hoc analysis on the subgroup of patients with urine samples, renal denervation resulted in a greater decrease in blood pressure vs. sham regardless of adherence to treatment, i.e. in both adherent 391 392 patients with consequently true resistant hypertension and non-adherent patients with apparent resistant hypertension, consistent with the results of the DENERHTN trial.⁵ This result may have 393 important clinical implications but should be considered as hypothesis generating and thus be 394 395 confirmed in a larger study.

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

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

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

420 Our study has limitations. First, additional follow-up will be required to determine whether the blood pressure lowering effect of ultrasound renal denervation remains durable over time, especially when 421 patients receive additional antihypertensive medications, especially the aldosterone antagonist 422 spironolactone, to control their blood pressure in both blinded (two to six months) and unblinded 423 conditions after six months. ¹⁰ While adverse events were infrequent, longer follow-up of this trial and 424 additional numbers of treated subjects will be necessary to provide additional safety data. Finally, 425 similar to other trials of renal denervation, despite our efforts to reduce overall variability, there was 426 427 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

found none of the previously described patient- (including age, sex, ethnicity, obesity, and baseline 429 blood pressure levels) or procedure-related factors (including number of ablations or ablation of 430 accessory arteries) to explain such variability.³⁰ Between-patient variability might still be due to 431 variable renal nerve ablation despite the uniform use of circumferential ablations and treatment of 432 accessory renal arteries or may reflect differing contribution of renal nerve signalling to hypertension 433 434 perpetuation. At present, there is still no reliable peri-operative marker of successful renal denervation.³⁰ Also, we observed a very high adherence rate to antihypertensive medications, but the 435 true level of adherence to medications may have been lower, because patients were fully informed that 436 437 medication adherence was monitored throughout the trial, and this may have given rise to white coat adherence phenomenon. However, our assays enabled us to determine nonadherence to the 438 439 medications with high specificity, because non-detection of the medications in the urine samples collected at trough indicates that the non-detected drug(s) had not been ingested by the patient for a 440 duration that exceeded at least 5 plasma half-lives of that given drug. Despite this limitation, our 441 442 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 other clinical settings (including heart failure, sleep obstructive apnoea, or arrhythmias). 448

In conclusion, in this powered, sham-controlled randomised study of subjects with combined systolicdiastolic hypertension resistant to a fixed-dose, single pill, triple combination antihypertensive therapy as recommended by current guidelines,¹⁶ ultrasound renal denervation safely reduced ambulatory systolic blood pressure more than a sham procedure at two months. The six-month (blinded phase) and twelve-month (unblinded phase) follow-up of the RADIANCE-HTN TRIO study during which subjects of both groups receive spironolactone as fourth line therapy according to guidelines, will also 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 463 design of the study. MA, AJK, KS, MSax, PG, JPR, TL, LCR, AP, JB, MJB, JD, ML, FM, RES, 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 the report, agreed on the content of the manuscript, reviewed drafts, and approved the final version. 469

470

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476

477 Declaration of interests

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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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602

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



606

607

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



Renal Denervation (N=69)

Sham Procedure (N=67)

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

| | Renal Denervation | Sham Procedure |
|---|---------------------------|-----------------------------|
| Measure | (N=69) | (N=67) |
| Age (years) | 52.3 ± 7.5 | $52 \cdot 8 \pm 9 \cdot 1$ |
| 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 - $ml/min/1.73m^2$ | $86{\cdot}0\pm25{\cdot}2$ | $82 \cdot 2 \pm 19 \cdot 2$ |
| 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 | $4 \cdot 0 \pm 1 \cdot 0$ | 3.9 ± 1.1 |
| screening | | |

| | Renal Denervation | Sham Procedure |
|---|-------------------|----------------|
| Measure | (N=69) | (N=67) |
| 3 medications | 27/69 (39%) | 28/67 (42%) |
| 4 medications | 22/69 (32%) | 24/67 (36%) |
| \geq 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.



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
- for an 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 | Rosolino |
|---|----------------------------|-----------------------------|-----------------------|-----------------------------|----------------------------|----------------------|---|------------------------|
| | Randomisation | 2 Months | Difference | Randomisation | 2 Months | Difference | Group Difference (95% CI) * | Adjusted P- value † |
| Systolic Blood Pressure Parameters (mmHg) | | | | | | | | |
| Daytime Ambulatory ‡ | $150{\cdot}0\pm11{\cdot}9$ | 141.0 ± 16.1 | -8·0 (-16·4, 0·0) | $151{\cdot}1\pm12{\cdot}6$ | $146{\cdot}3\pm18{\cdot}8$ | -3·0 (-10·3, 1·8) | -4·5 (-8·5, -0·3) | 0.022 |
| 24 Hour Ambulatory | 143.9 ± 13.4 | $135{\cdot}2\pm16{\cdot}0$ | -8·5 (-15·1, 0·0) | $145{\cdot}4\pm14{\cdot}0$ | $140{\cdot}5\pm18{\cdot}7$ | -2·9 (-12·6, 2·5) | -4·2 (-8·3, -0·3) | 0.016 |
| Nighttime Ambulatory | $134{\cdot}4\pm18{\cdot}0$ | $126{\cdot}3\pm18{\cdot}4$ | -8·3 (-15·7, 0·0) | $136{\cdot}4\pm18{\cdot}6$ | 131.9 ± 20.9 | -1·8 (-16·2, 5·0) | -3.9 (-8.8, 1.0) | 0.044 |
| Office § | $155{\cdot}6\pm16{\cdot}7$ | 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) | $\begin{array}{c} -4.0 \\ (-8.0, 0.0) \end{array}$ | 0.052 |
| Diastolic Blood Pressure Parameters (mmHg) | | | | | | | | |
| Daytime Ambulatory | 93.8 ± 7.7 | $88{\cdot}5\pm11{\cdot}6$ | -4·9 (-10·4, 0·0) | $94 \cdot 6 \pm 9 \cdot 1$ | 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) | $\begin{array}{c} -2 \cdot 0 \\ (-4 \cdot 5, 0 \cdot 6) \end{array}$ | 0.12 |
| Nighttime Ambulatory | 81.3 ± 10.7 | $76 \cdot 2 \pm 12 \cdot 2$ | -5·1 (-12·7, 0·0) | $81 \cdot 3 \pm 12 \cdot 1$ | 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- | Baseline- |
|----------|----------------------------|-----------------------------|----------------------|---------------------------|-----------------|---------------------|--|------------------------|
| | Randomisation | 2 Months | Difference | Randomisation | 2 Months | Difference | Group Difference (95% CI) * | Adjusted P- value † |
| Office § | $101{\cdot}4\pm11{\cdot}6$ | $96 \cdot 6 \pm 13 \cdot 9$ | -5·0 (-13·5, 2·5) | $99{\cdot}4\pm10{\cdot}9$ | 98.7 ± 13.8 | -1·0 (-7·0, 6·0) | $\begin{array}{c} -4.0 \\ (-9.0, 0.0) \end{array}$ | 0.16 |
| Home | 96.5 ± 11.2 | $93 \cdot 2 \pm 14 \cdot 7$ | -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

- 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

| | Renal Denervation | Sham Procedure |
|---|--------------------------|-----------------|
| Safety Events | (n=69) | (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; | 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 $\ge 0.3 \text{ mg/dl}$ ($\ge 26.5 \mu \text{mol/l}$) 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.
- † 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.
- t 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
- 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