Original Article

Impact of Medication Adherence on the Effect of Renal Denervation

The SYMPATHY Trial

Rosa L. de Jager, Esther de Beus, Martine M.A. Beeftink, Margreet F. Sanders, Evert-Jan Vonken, Michiel Voskuil, Erik M. van Maarseveen, Michiel L. Bots, Peter J. Blankestijn; on behalf of the SYMPATHY Investigators

See Editorial Commentary, pp 582–583

Abstract—Randomized trials of catheter-based renal denervation (RDN) as therapy for resistant hypertension showed conflicting results in blood pressure (BP) lowering effect. Adherence to medication is modest in this patient group and may importantly drive these conflicting results. SYMPATHY is a prospective open label multicenter trial in Dutch patients with resistant hypertension. Primary outcome was change in daytime systolic ambulatory BP at 6 months. Patients were randomly assigned to RDN on top of usual care. Adherence to BP lowering drugs was assessed at baseline and follow-up, using blood samples drawn synchronously with BP measurements. Patients and physicians were unaware of the adherence assessment. Primary analyses showed a mean difference between RDN (n=95) and control (n=44) in changes in daytime systolic ambulatory BP after 6 months of 2.0 mm Hg (95% confidence interval, −6.1 to 10.2 mm Hg) in favor of control. In 80% of patients, fewer medications were detected than prescribed and adherence changed during follow-up in 31%. In those with stable adherence during follow-up, mean difference between RDN and control for daytime systolic ambulatory BP was −3.3 mm Hg (−13.7 to 7.2 mm Hg) in favor of RDN. RDN as therapy for resistant hypertension was not superior to usual care. Objective assessment of medication use shows that medication adherence is extremely poor, when patients are unaware of monitoring. Changes over time in adherence are common and affect treatment estimates considerably. Objective measurement of medication adherence during follow-up is strongly recommended in randomized trials.

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Key Words: blood pressure ■ meta-analysis ■ randomized controlled trial ■ renal denervation ■ sympathetic nervous system

The effects of percutaneous catheter-based renal denervation (RDN) as new therapy for resistant hypertension have been evaluated several times in the past years.[1–8] First studies suggested large effects on blood pressure (BP). However, in the first sham-controlled randomized trial, no difference in treated versus controlled participants was found.[2] Subgroup analyses of RDN studies have identified different factors of relevance in determining the overall effect of the intervention on BP.[9–11] Of particular interest is medication adherence. To quantify the effect of the addition of RDN to medical treatment, it is imperative that antihypertensive medical treatment remains unchanged. Recent small studies, using urine or blood samples to detect medication, suggested that adherence is particularly poor in presumed resistant hypertensive participants.[12–14]

The present randomized controlled trial (RCT) was designed to assess the efficacy of RDN in resistant hypertension participants, the primary end point being daytime systolic ambulatory BP (ABPM) at 6 months after RDN. In addition, we explored the effect of adherence on the study outcomes.

Methods

Study Design and Population

The rationale and design of SYMPATHY have been described previously.[15] Briefly, SYMPATHY is a multicenter RCT in 14 centers in the Netherlands. For this trial, a system of conditional reimbursement was available for 4 years (2013–2016), indicating that the intervention was covered by the healthcare insurance, only when patients participated in SYMPATHY. The consequence was that SYMPATHY findings were used by National Health Care Institute to advise the

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From the Department of Nephrology and Hypertension (R.L.d.J., E.d.B., M.F.S., P.J.B.), Department of Cardiology (M.M.A.B., M.V.), Department of Radiology (E.-J.V.), Department of Clinical Pharmacy (E.M.v.M.), and Julius Center for Health Sciences and Primary Care (M.L.B.), University Medical Center Utrecht, The Netherlands.

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Correspondence to Peter J. Blankestijn, Department of Nephrology and Hypertension, University Medical Center Utrecht, HP F03.223, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. E-mail p.j.blankestijn@umcutrecht.nl

government at the end of 2016 whether RDN should be part of the standard reimbursement package of the Dutch healthcare insurances (https://english.zorginstituutnederland.nl/publications/reports/2012/04/06/conditional-reimbursement-of-health-care). Because we had to deliver the report on the SYMPATHY findings to the National Health Care Institute no later than August 1, 2016, participants had to be included before January 1, 2016.

In SYMPATHY adults were included with resistant hypertension, defined as an average daytime systolic ABPM measurement ≥135 mm Hg, despite use ≥3 BP lowering agents or with documented intolerance for ≥2 BP lowering agents. Participating physicians were advised to exclude white coat hypertension, secondary causes of hypertension, and anatomic abnormalities that would make RDN nonfeasible, using a standardized protocol.[16] Randomization was performed in a 2:1 ratio to receive either RDN on top of usual care or usual care alone using a web-based computerized approach, with stratification by hospital and estimated glomerular filtration rate (20–60 and >60 mL min^{-1} 1.73 m^{-2}).[15]

Ethics approval was obtained at the University Medical Center Utrecht (No. 12/540). All subjects gave informed consent. The trial was performed in accordance with the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

Outcome Assessment

The primary outcome was change in daytime systolic ABPM 6 months after RDN or inclusion into the study (control group). Secondary outcomes were change in office systolic BP (SBP), prescribed BP lowering drugs, and change in kidney function. Other outcomes were periprocedural complications. ABPM monitoring was performed noninvasively, with readings every 30 minutes during daytime and every 60 minutes during nighttime and was considered valid when ≥70% of the recordings were successful. Office BP was taken using an automatic device, in sitting position after 10 minutes of rest, twice at both arms using an appropriate cuff size. The mean was used as office BP. Both ABPM and office BP were measured with recommended devices according to the European Society Hypertension/European Society of Cardiology guidelines.[17] Blood was sampled on the same day as BP was assessed. At study visits, the use of all medication was queried. BP lowering agents were classified according to the Anatomical Therapeutic Chemical classification system of the World Health Organization Collaborating Centre for Drug Statistics. We calculated the defined daily dose of BP lowering agents per participant per visit. The intention was to unchange baseline BP lowering medication till the 6-month visit (primary end point). In case adjustments in medication were necessary, these were made according to a predefined protocol (online-only Data Supplement).[15]

Important Adjustments During the Course of the Trial

In January 2014, we added participants with documented intolerance to ≥2 BP lowering agents. These participants represent a sizable group of difficult to treat hypertensive patients, for whom RDN could be beneficial as well. Second, from October 2014, National Health Care Institute allowed conditional reimbursement when participants were treated with the EnligHTN Ablation catheter (St Jude Medical, St Paul, MN).[15,18] Choice of catheter was made by the interventionist.

During the course of the trial, it became increasingly clear that the objective assessment of medication adherence is of utmost importance based on reports suggesting poor adherence in this class of participants.[12–14] We decided to use stored samples for drug level measurements. Of relevance, participants and attending physicians were unaware of the adherence assessments.

The original sample size estimation was set at 300 randomized participants. However, after SYMPLICITY-HTN-3, inclusion slowed dramatically. DENERHTN provided data to assume that a study size of 100 to 150 participants could be sufficient.[1] We estimated that such a number could be feasible by January 1, 2016. We expected a difference of 5 mm Hg in SBP (with SD of 10 mm Hg) between the RDN and control group. Our power would be between 80% and 90% with a 2-side α of 0.05. After consultation with the data safety monitoring board, we decided to continue the study. All described adjustments were approved by the Ethical Committee of University Medical Center Utrecht.

Adherence Measurements

Liquid chromatography combined with tandem mass spectrometry was used to screen BP lowering drugs. This technique has proved to be reliable, accurate, and precise.[19] The acquired mass spectra were compared with an in-house library (compound library and tandem mass spectrometry mass spectral library) built with automated screening software (TOD ID, Thermo Fisher Scientific) which contained the mass/charge of the precursor ion, retention time, product ions, and the entire tandem mass spectrometry spectra of 40 compounds, including metabolites covering over 95% of all BP lowering drugs registered in The Netherlands. Identification was achieved by comparing full tandem mass spectrometry spectra and mass/charge of precursor ion with the confirmation by the second selected reaction monitoring transitions. Using the developed method, the identification results from spiked serum samples within therapeutic concentration ranges indicated 95% sensitivity and 91% specificity.

Participants were categorized into adherent (81%–100% match prescribed versus measured), poorly adherent (1%–80% match prescribed versus measured), and completely nonadherent (0% match prescribed versus measured).[20]

Intervention

Usual care was based on the guidelines of the European Society Hypertension/European Society of Cardiology.[17] The RDN procedure was performed by an interventional radiologist or cardiologist.

Data Analyses

Primary efficacy analysis was based on the (modified) intention-to-treat population, including all participants randomized with available BP data ≥1 follow-up visit. The primary analysis, that is, mean of change in daytime systolic ABPM between treatment arms was based on *t* test. All other analyses were performed using either *t* tests (continuous variables [mean of change]) or χ^2 test for dichotomous variables. Linear regression models were used to study whether treatment effects differed across predefined subgroups, using multiplicative interaction terms (treatment group×subgroup). Linear regression models with adjustments for lifestyle changes and for changes in prescribed and detected medication were run to study the effects of these factors on the observed change in the daytime ABPM and in office systolic pressure. A 2-sided 0.05 level of significance is used. Statistical analyses were done using SPSS version 22 (IBM Corp, Armonk, NY).

Meta-Analysis

To place the SYMPATHY results in perspective of other RDN RCT results, we performed a systematic meta-analysis (online-only Data Supplement).

Results

From May 23, 2013 until January 1, 2016, 139 participants were randomized, 95 to RDN and 44 to usual care. After randomization, 4 participants declined RDN. One participant, randomized to the usual care group, received RDN within the first 6 months. Before the first 6-month visit, 8 participants (5 RDN) withdrew their participation for follow-up measurements (Figure 1). Baseline characteristics are shown in Table 1. Mean daytime systolic ABPM was 160 mm Hg (SD 17 mm Hg), and daytime diastolic ABPM was 93 mm Hg (15 mm Hg). Mean office BP was 169 (25)/96 (16) mm Hg. In 60 participants, the Symplicity catheter was used and in 31

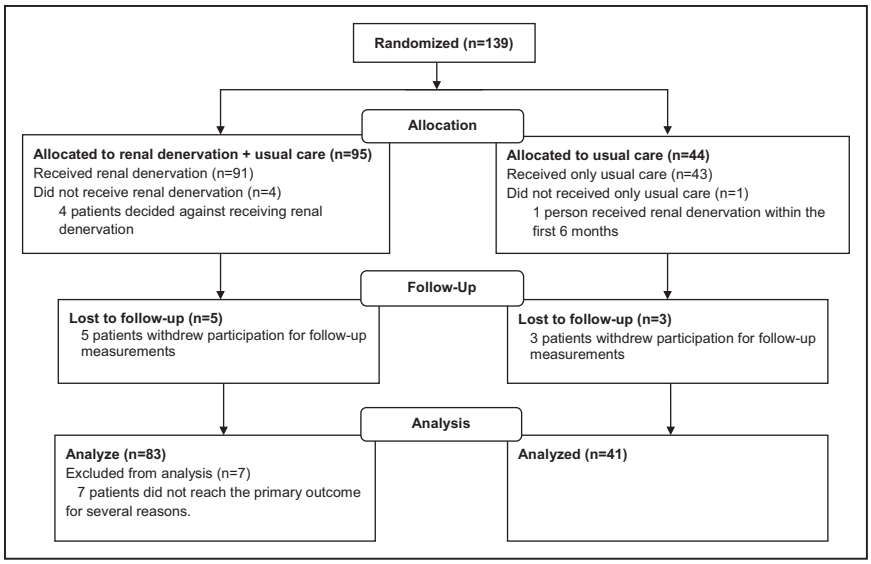

Figure 1. Flow-diagram of SYMPATHY trial.

the EnligHTN Ablation catheter. Mean number of ablations was 15 (7).

Effect of RDN on BP

Six-month data on daytime ABPM were available for 124 participants (Figure 1). Overall, BP levels declined significantly (Table 2). Mean differences between groups in changes in daytime systolic ABPM after 6 months were 2.0 mm Hg (−6.1 to 10.2 mm Hg), in 24-hour systolic ABPM 1.0 mm Hg (−7.1 to 9.1 mm Hg), and in office SBP −8.2 mm Hg (−17.1 to 0.7 mm Hg). The findings were the same when using a complete case analysis approach (Table S1 in the online-only Data Supplement) or sensitivity analysis for patients with true resistant hypertension, defined as the use ≥3 classes of BP lowering drugs (data not shown). Our meta-analysis (including 984 subjects from 7 studies) showed no significant benefit of RDN compared with usual care alone for daytime systolic ABPM (−1.60 mm Hg [−4.32 to 1.11 mm Hg]).

Adverse Events

We observed 17 periprocedural complications, including 4 vascular, 8 bleeding, and 5 other (mild) complications (Table S2). All participants recovered without sequelae. Kidney function declined by 1.5 (−3.1 to 0.1) mL min^{-1} 1.73 m^{-2} at 6 months, with no difference between groups. During 6-month follow-up, 36 self-reported, unadjudicated serious adverse events were registered: 24 (26%) in the intervention group and 12 (27%) in the usual care group (Table S3).

Subgroup Analyses

Predefined subgroup analysis showed no statistically significant interaction between kidney function or baseline BP and RDN effects on BP. None of several post hoc subgroup analyses (sex, body mass index, previous cardiovascular history, smoking, urinary sodium excretion, size of the hospital (large centers/small centers), baseline use of spironolactone, and catheter type) reached statistical significance.

Medication Adherence at Baseline and Follow-Up

Prescribed medication did not differ significantly between treatment groups at 6 months and increased in both groups over time (Table 3; Table S4). Information on adherence was available for 98 and 83 participants at baseline and at follow-up, respectively (78 pairs). At both study time points, adherence was poor: 80% were either poorly adherent or completely nonadherent. In 54 (29 in RDN group) participants, adherence remained stable. The adherence category changed (eg, from poorly adherent to completely nonadherent) in 31% of the participants (n=24). There was no significant difference in change in adherence between treatment arms (Table 3).

Medication Adherence and BP

Baseline and 6-month daytime systolic ABPM were the highest in participants completely nonadherent in an analysis restricted to the 78 participants with adherence measurements at baseline and at follow-up (Table S5). When medication adherence was the same at baseline and follow-up, daytime systolic ABPM was 3.3 mm Hg (−13.7 to 7.2 mm Hg) lower in favor of the RDN group (Figure 2). The same trend was seen for 24-hour systolic ABPM (−4.7 mm Hg [−15.3 to 5.8 mm Hg]) and office SBP (−14.0 mm Hg [−25.7 to −2.4 mm Hg]; P=0.422 for the interaction term). Baseline characteristics did not differ significantly between the intervention and control group in this selected population (Table S6). In particular, no difference was found in factors that potentially drive a larger RDN effect.

Discussion

This is the second largest RCT studying the effect of RDN on BP in participants defined as treatment-resistant hypertensives. Six months after RDN, no significant reduction in daytime or 24-hour systolic ABPM was observed compared with usual care alone.

Effect of RDN on office SBP was of borderline significance. Results are in line with most of the other trials.[1–3,5,6,8] Our systematic review showed that the pooled effect of RDN on BP is most pronounced for office SBP (−5.4 mm Hg; Figure S2), yet, not statistically significant (P=0.27).

Table 1. Baseline Characteristics of the Intention-to-Treat Population

Characteristics	Renal Denervation Group (n=95)	Control Group (n=44)
Age, y	62 (12)	60 (10)
Male*	40 (42.1)	13 (29.5)
White*	92 (96.8)	42 (95.5)
History of cardiovascular disease*	41 (43.2)	19 (43.2)
Current smoking*	22 (23.2)	10 (22.7)
Diabetes mellitus*	26 (27.4)	14 (31.8)
BMI, kg/m^2	28.6 (4.8)	29.4 (4.6)
Plasma creatinine, μmol/L	87 (36)	88 (27)
eGFR estimated with CKD-epi (mL min^{-1} 1.73 m^{-2})	77 (19)	80 (21)
LDL, mmol/L	3.1 (1.1)	2.8 (1.0)
Office SBP, mm Hg	170.3 (25.9)	164.7 (22.0)
Office DBP, mm Hg	96.1 (17.7)	94.4 (12.5)
24-h systolic ABPM, mm Hg	157.3 (15.6)	155.8 (17.4)
24-h diastolic ABPM, mm Hg	90.1 (14.3)	91.4 (12.6)
Daytime systolic ABPM, mm Hg	160.8 (16.0)	159.5 (18.2)
Daytime diastolic ABPM, mm Hg	92.4 (15.0)	94.5 (13.5)
Nighttime systolic ABPM, mm Hg	146.0 (16.7)	144.8 (16.7)
Nighttime diastolic ABPM, mm Hg	81.7 (12.5)	82.7 (12.1)
No. of BP lowering drugs	3.7 (1.5)	3.4 (1.5)
No. BP lowering classes	3.5 (1.3)	3.2 (1.3)
Daily dose used of BP lowering drugs	5.5 (4.0)	5.3 (3.4)
Diuretics*†	69 (72.6)	26 (59.1)
β-Blocker*	60 (63.2)	26 (59.1)
ACE inhibitor*	25 (26.3)	15 (34.1)
Angiotensin receptor blocker*	57 (60)	26 (59.1)
Renin inhibitor*	3 (3.2)	0 (0)
Calcium antagonist*	60 (63.2)	27 (61.4)
Spironolactone*	23 (24.2)	10 (22.7)
Aldosterone antagonist*	5 (5.3)	3 (6.8)
α-Blocker*	30 (31.6)	11 (25.0)
Centrally acting antihypertensive drug*	9 (9.5)	3 (6.8)
Other*	4 (4.2)	0 (0)

Data are expressed as mean±SD unless stated otherwise. ABPM indicates ambulatory blood pressure measurement; ACE, angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; CKD-epi, chronic kidney disease epidemiology collaboration equation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL, low density lipoprotein; and SBP, systolic blood pressure.

*Data are expressed as n (%).

†Diuretics without spironolactone or other aldosterone antagonists.

The possible reasons of the variability in the effects on BP between participants and between studies have been extensively discussed over recent years.[9,11,21] Relevant factors could be related to the device, the procedure itself, and participant characteristics. In this respect, medication adherence is of particular relevance because recent studies suggested poor adherence in this type of participants.[12–14,22–24] To our knowledge, we are the first trial on RDN to objectively assess medication adherence changes during the study. Strong features of our study are that blood samples were taken on the day of the ABPM and the fact that both participants and treating physicians were unaware of the assessments, resulting in an accurate representation of the every-day reality. Questionnaires used in trials on RDN are likely to overestimate adherence.[1,2,4,6] With a direct adherence assessment, we confirm that BP medication adherence is very low at baseline and at follow-up. This finding is in line with the single direct adherence measurements in the PRAGUE trial (at screening) and DENERHTN trial (at 6-month follow-up).[7,22] In addition, BP was higher in participants with poor adherence (Table S5). Therefore, our data support the notion that poor medication adherence contributes to the condition of apparent resistant hypertension.

A second important aspect is that in about one third of the participants adherence to BP lowering drugs either increased or decreased during follow-up. There was a trend toward more detected BP lowering pills at follow-up, more pronounced in the control group than in the RDN group. This may be because of the more intensive follow-up during the trial and the absence of blinding for the intervention (no sham procedure). The large percentage of change, with either decrease or increase in medication use, makes it virtually impossible to quantify the effect of the addition of RDN to medical treatment. This is especially the case when, as in our study, changes occur without the treating physicians knowing it. In those patients with the same number of medication at baseline and at follow-up, all BP measurements suggested a greater, albeit not statistically significant, decrease in the RDN arm. Figure 2 clearly suggests that the overall direction of the effect on BP considerably changed when taking medication adherence into account. In none of the previous RCTs in the RDN field, was adherence quantified in both arms at both baseline and follow-up. It could be that in the other trials, adherence was better than in this study, but it seems appropriate to conclude that poor adherence and changes in adherence were probably major factors of concern.

Our results may have considerable societal impact. These patients use healthcare facilities by (frequently) visiting physicians, by collecting medication from the pharmacy, without using it, meanwhile staying at increased cardiovascular risk. Although the relation between hypertension and increased cardiovascular risk is well established, some participants feel great resistance for prolonged pharmacological therapy. The reasons are likely complex and include the fact that hypertension is usually free of symptoms and that participants experience side effects of medication. This triggers 2 lines of thinking. First, there is great need to more extensively focus on interventions that potentially improve medication adherence. Indeed, in DENERHTN, in which specific efforts were undertaken to improve medication use, full adherence was found in half of the study population,[22] which is much better than the 20% found in this study, but still far from perfect. Alternatively, society could accept that a certain percentage of hypertensive

Table 2. BP Levels at Baseline, Follow-Up, and the Mean Difference in the SYMPATHY Trial of All Participants

	Renal Denervation Group			Control Group			Mean Difference Between Groups (95% CI)	*P* Value
	Baseline	6 mo	Mean Difference (95% CI)	Baseline	6 mo	Mean Difference (95% CI)		
ABPM	n=95	n=83		n=44	n=41			
Daytime systolic ABPM	160.8±16.0	155.2±23.9	−6.0 (−10.7 to −1.2)	159.5±18.2	152.4±20.1	−7.9 (−14.7 to −1.3)	2.0 (−6.1 to 10.2)	0.625
Daytime diastolic ABPM	92.4±15.0	90.3±16.2	−3.5 (−6.4 to −0.7)	94.5±13.5	89.4±13.3	−4.7 (−8.3 to −1.1)	1.2 (−3.5 to 5.9)	0.615
Night systolic ABPM	146.0±16.7	141.9±21.5	−3.8 (−8.7 to 1.1)	144.8±16.7	139.4±23.3	−7.9 (−15.0 to −0.8)	4.1 (−4.4 to 12.6)	0.340
Night diastolic ABPM	81.7±12.5	80.2±13.3	−2.6 (−5.6 to 0.4)	82.7±12.1	80.6±13.9	−3.3 (−7.8 to 1.2)	0.7 (−4.5 to 5.9)	0.780
24-h systolic ABPM	157.3±15.6	152.0±23.5	−5.6 (−10.2 to −0.9)	155.8±17.4	150.2±22.2	−6.6 (−13.3 to −0.2)	1.0 (−7.1 to 9.1)	0.805
24-h diastolic ABPM	90.0±14.2	87.8±15.4	−3.5 (−6.3 to −0.8)	91.4±12.6	87.2±12.8	−3.9 (−7.7 to −0.1)	0.4 (−4.3 to 5.1)	0.871
Office BP	n=95	n=94		n=44	n=44			
Office SBP	170.3±25.9	162.7±26.7	−7.5 (−12.5 to −2.5)	164.7±22.0	165.4±25.4	0.7 (−6.9 to 8.3)	−8.2 (−17.1 to 0.7)	0.069
Office DBP	96.1±17.7	91.6±18.4	−4.4 (−7.4 to −1.4)	94.4±12.5	95.4±16.6	0.9 (−3.7 to 5.6)	−5.3 (−10.7 to 0.1)	0.053

Data are expressed as mean±SD unless stated otherwise. *P* value presented for the mean difference in effect between the intervention group and control group. ABPM indicates ambulatory blood pressure measurement; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

participants are not able or willing to use medical treatment for whatever (set of) reason(s). For such participants, alternative approaches, including device-related treatment strategies, could be considered as options worth exploration.

An important limitation of our trial is probably that participants were not blinded to the intervention (no sham procedure). We tried to offset this by blinded assessment of the primary outcome, assessment of lifestyle changes that may affect BP for adjustment (salt intake and weight change), and objective measurements of (change in) medication adherence for use in the statistical analyses of the results. Second, although we had a mix of patients (resistant and intolerant), it is unlikely that this affects our findings because our sensitivity analysis revealed no difference in effect when taken the resistant group separately. Another potential limitation might be the use of 2 different devices. This is only an issue when the 2 devices differ in their BP lowering effect, of which no evidence is available, yet. Further, not all patients were on diuretics, which is presently (more or less) accepted as mandatory to meet the definition resistant hypertension. At the time, we designed our study that was not yet so clearly the case. Indeed, it is possible that the lack of diuretic use has influenced our results. Finally, the drug level measurements provided qualitative results: the drug is either detectable or not detectable. Therefore, we might have underestimated the number of changes because dosage and class changes were not detected.

Perspectives

This study shows in primary analysis that RDN is not superior to usual care in reducing BP in participants with resistant hypertension. Medication adherence seems to be very low when participants are unaware of monitoring. Our data suggest that poor adherence (partially) explains the condition of resistant hypertension. Second, and importantly, our data suggest that the direction and the magnitude of the treatment effect considerably change when medication adherence is taken into account. This factor could also have been of relevance in earlier RDN studies. It can only be overcome in future trials by studying unmedicated participants or by detailed monitoring of prescribed and actually used medication.

Table 3. Prescribed Versus Measured BP Lowering Drugs and Change in Adherence (n=78)

Determinants of BP Lowering Drugs	Renal Denervation Group			Control Group			Mean Difference Between Groups†
	Baseline (n=63)	6 mo (n=51)	Mean Change*	Baseline (n=35)	6 mo (n=32)	Mean Change*	
No. of BP lowering drugs prescribed	3.7±1.5	4.0±1.7	0.3±0.1	3.4±1.5	3.9±1.2	0.4±0.2	−0.1 (−0.4 to 0.1)
No. of BP lowering drugs detected	1.8±1.4	2.0±1.5	0.2±0.2	1.7±1.3	2.0±1.0	0.4±0.2	−0.2 (−0.7 to 0.4)
Mean difference between prescribed and measured	1.8 (1.3 to 2.2)	1.9 (1.5 to 2.4)	0.1±0.2	1.8 (1.3 to 2.4)	1.8 (1.3 to 2.3)	−0.1±0.2	0.2 (−0.4 to 0.8)
P value	<0.001	<0.001	0.705	<0.001	<0.001	0.474	

Data are expressed as mean±SD, unless stated otherwise. *P* value presented for the mean difference between number of prescribed BP lowering drugs and number of measured BP lowering drugs in blood. BP indicates blood pressure.

*Mean change expressed as mean (±SE).

†Mean difference between renal denervation and control group for changes 6 mo after renal denervation.

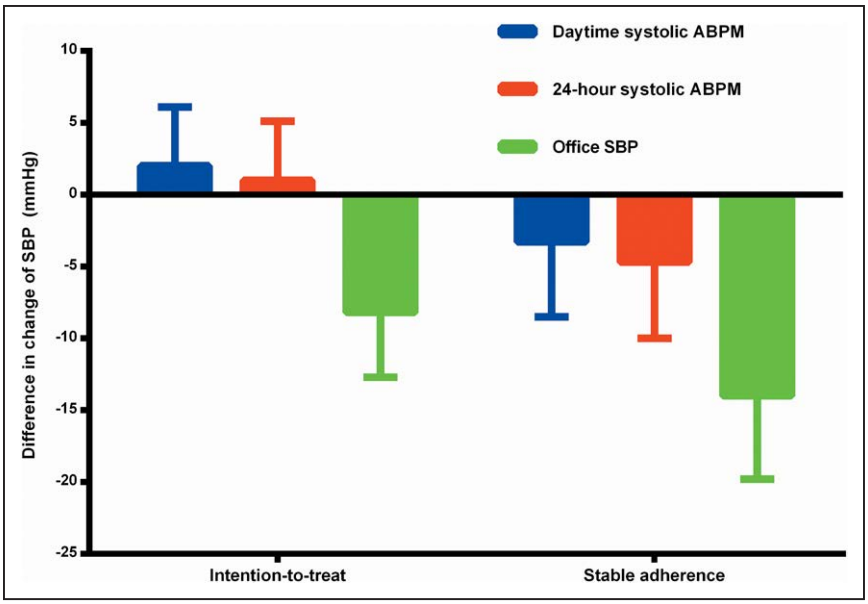

Figure 2. Mean difference (±SE) between control group and renal denervation for change in systolic blood pressure (SBP) after 6 mo, presented for intention-to-treat population (n=139) and population with stable medication adherence (n=54). ABPM indicates ambulatory blood pressure measurement.

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Disclosures

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Novelty and Significance

What Is New?

- This is the first randomized controlled trial on the effect of renal denervation on blood pressure that included a baseline and end-of-study objective measurement of adherence to antihypertensive medication.

What Is Relevant?

- In primary analysis renal denervation was not superior to usual care alone in patients with resistant hypertension.
- Medication adherence was very low in resistant hypertensive patients participating in a trial.
- In patients with proven stable adherence during the study, the direction and magnitude of the effect on blood pressure differed from the primary analysis.

Summary

Medication adherence is very low in resistant hypertension patients and changes over time, which has considerable effect on the overall interpretation of the results. Objective assessment of medication adherence is mandatory in future trials in (resistant) hypertensive patients.

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Impact of Medication Adherence on the Effect of Renal Denervation: The SYMPATHY Trial

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Supplementary material

THE IMPACT OF MEDICATION ADHERENCE ON THE EFFECT OF RENAL DENERVATION. THE SYMPATHY TRIAL.

Rosa L de Jager, MD[a], Esther de Beus, MD[a], Martine MA Beeftink, MD[b], Margreet F Sanders, MD[a], Evert-Jan Vonken, MD[c], Michiel Voskuil, MD[b], Erik M van Maarseveen, PharmD[d], Michiel L Bots, MD[e], Peter J Blankestijn, MD[a]*, on behalf of the SYMPATHY investigators.

[a] Department of Nephrology & Hypertension,

[b] Department of Cardiology,

[c] Department of Radiology,

[d] Department of Clinical Pharmacy,

[e] Julius Center for Health Sciences and Primary Care,

From the University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands.

[*]Corresponding author:

Peter J. Blankestijn, MD, PhD

Department of Nephrology & Hypertension, HP F03.223

Heidelberglaan 100, 3584 CX Utrecht, the Netherlands

Telephone number: +31 88 755 7329 / Fax number: +31 88 755 6283

Email: p.j.blankestijn@umcutrecht.nl

Trial Registration clinicaltrials.gov Identifier: NCT01850901

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SYMPATHY investigators and committees

Albert Schweitzer Hospital Dordrecht (5 inclusions), O Elgersma, AJJ IJsselmuiden, PHM van der Valk, P Smak Gregoor, S Roodenburg.
Amphia Hospital, **Breda (1) ,** M Meuwissen, W Dewilde, I Hunze, J den Hollander.
Antonius Hospital, Nieuwegein (6), HH Vincent, B Rensing, WJ Bos, I. van Weverwijk.
Catharina Hospital, Eindhoven (8), PAL Tonino, BRG Brueren, CJAM Konings, H Hendrix-van Gompel.
Isala Clinics, Zwolle (19), JE Heeg, J Lambert, JJ Smit, A Elvan, A Berends, B de Jager.
Hospital group Twente, Almelo (2), G Laverman, PAM de Vries, A van Balen, M Stoel.
Martini Hospital, Groningen (29), R Steggerda, L Niamut, W Bossen, J Biermann, I Knot.
Medical Center Alkmaar, Alkmaar (5), JOJ Peels, JB de Swart, G Kimman, W Bax, Y van der Meij, J Reekers.
Medical Center Haaglanden, The Hague (1), AJ Wardeh, JHM Groeneveld, C Dille.
Medical Center Leeuwarden, Leeuwarden (18), MH Hemmelder, R Folkeringa, M Sietzema, C Wassenaar.
Rijnstate Hospital, Arnhem (4), K Parlevliet, W Aengevaeren, M Tjon, M Hovens, A van den Berg, H Monajemi.
Scheper Hospital, Emmen (1), FGH van der Kleij, A Schramm, A Wiersum.
University Hospital Maastricht, Maastricht (2), B Kroon, M de Haan, M Das, H Jongen, E Herben, R Rennenberg.
University Medical Center Utrecht, Utrecht (34), PJ Blankestijn, ML Bots, MM Beeftink, E de Beus, B Dijker, GWJ Frederix, RL de Jager, E van Maarseveen, MF Sanders, W Spiering, IS Velikopolskaia, L Vendrig, WL Verloop, EE Vink, EPA Vonken, M Voskuil, GA de Wit.
All centers were located in The Netherlands.

Executive committee: PJ Blankestijn, ML Bots, E de Beus, RL de Jager, L Vendrig.
Steering committee: PJ Blankestijn (chair), ML Bots (vice-chair), RL de Jager, L Vendrig, E de Beus, B Dijker, JE Heeg, J Vincent, CB Roes, J Deinum.
Data Safety Monitoring Board: AJ Rabelink (chair), J Lenders, René Eijkemans.
Monitoring: Julius Clinical.

Meta-analysis

Methods

PubMed, Embase and Cochrane databases were searched. We chose “resistant hypertension” and “renal denervation” and their synonyms (table S7) as search terms for titles and abstracts. Eligible for inclusion were reports of RCTs comparing RDN with care as usual in resistant hypertension. SBP had to be measured by ABPM monitoring at baseline and at six months. We used the GRADE-approach (Grading of Recommendations, Assessment, Development and Evaluations) to critically assess study design, generalizability and quality of the study of the remaining RCTs and to give a final score for the available evidence in a summary of findings table (http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665072.html). We extracted the change in daytime systolic ABPM between baseline and six-month follow-up for both RDN and control groups. The pooled effect size and its confidence interval were estimated using Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). As we assumed that the true effect size differed among studies, we used a random-effects model.

Results

Our systematic review included seventeen relevant studies (figure S1). One study was excluded, as treatment in the control group could not be considered care as usual. Eight other excluded studies did not provide data on six months. Finally, we included eight studies.[1-8] Three studies were sham controlled, including the largest trial, HTN-3 (tables S8, S9). In our meta-analysis, including the SYMPATHY results, pooled effect on daytime systolic ABPM and office BP showed no significant decline in favour of RDN (P=0.25 and P=0.27, respectively). The decline in systolic ABPM was significant in favor of the denervated population, with a mean difference of -2.8 (-5.4 to -0.1) mmHg (table S10, figure S2).

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Tables

Table S1. Blood pressure levels at baseline, follow-up and the mean difference in the SYMPATHY trial
Only in participants with blood pressure data on both baseline and 6 months follow-up

	Renal denervation group			Control group		
Blood pressure	**Baseline**	**6 months**	**Mean difference**	**Baseline**	**6 months**	**Mean difference**
ABPM	N=83	N=83	**(95%CI)**	N=41	N=41	**(95%CI)**
Daytime systolic ABPM	161.2 ±16.1	155.2 ±23.9	-6.0 (-10.7 to -1.2)	160.4 ±18.5	152.4 ±20.8	-8.0 (-14.6 to -1.3)
Daytime diastolic ABPM	93.9 ±14.6	90.3 ±16.2	-3.5 (-6.4 to -0.7)	94.2 ±13.9	89.4 ±13.3	-4.7 (-8.3 to -1.1)
Night systolic ABPM	145.2±16.5	141.5 ±21.3	-3.8 (-8.7 to 1.1)	146.3 ±16.8	138.4 ±22.8	-7.9 (-15.0 to -0.8)
Night diastolic ABPM	82.5 ±12.1	80.0 ±13.3	-2.6 (-5.6 to 0.4)	83.4 ±11.4	80.1 ±13.7	-3.3 (-7.8 to 1.2)
24-h systolic ABPM	157.5 ±16.1	151.3 ±22.0	-6.2 (-10.7 to -1.7)	156.7 ±17.5	150.1 ±22.2	-6.6 (-13.3 to 0.2)
24-h diastolic ABPM	91.5 ±14.0	87.4 ±15.2	-4.1 (-6.8 to -1.4)	91.1 ±12.9	87.2 ±12.8	-3.9 (-7.7 to -0.1)
Office BP	N=79	N=79		N=40	N=40	
Office SBP	170.7±25.0	162.0 ±28.1	-8.7 (-14.0 to -3.2)	165.5 ±22.3	165.4 ±25.4	-1.3 (-8.1 to 5.6)
Office DBP	97.7 ±17.3	92.7 ±18.3	-5.0 (-8.4 to -1.6)	94.0 ±12.7	93.1 ±14.3	-0.8 (-4.9 to 3.4)

Data analysed with paired samples T-test.
Data are expressed as mean ±SD unless stated otherwise.
ABPM: ambulatory blood pressure measurements; 24-h: 24-hour; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table S2. Peri-procedural complications in renal denervation group

Complications	No. of participants (%)
Vascular complications	4 (4.4)
Aneurysm spurium	2
Arrhythmia	1
Other	1
Bleeding complications	8 (8.8)
Hematoma	6
Other	2
Total no. of complications	12 (13.2)
Other complaints	5 (5.5)
Back pain	3
Groin pain	1
Hypotension	1
Prolonged admission	4 (4.4)

Data are expressed as number (percentage of denervated participants, n=91))
No.: number.

Definitions
Vascular complications: pseudo aneurysm, perforation or obstruction of the femoral artery, arterio-venous-fistula, haematoma, infection, anaphylaxis, mild allergic reaction, cardiac arrhythmias, death,
Kidney failure: decline of 30% of eGFR compared to baseline value.

Table S3. Serious adverse events.

Serious adverse events	Renal denervation group (n=91)	Control group (n=44)
Ablation retinae	1	
Arrhythmia	4	1
Carcinoma	1	
Cerebra Vascular Accident	2	
Collapse		1
Collapse and weight loss		2
Decompensation cordis	1	
Diarrhea	1	
Dyspnea with fever	1	
Elective coronary angiography		1
Elective Coronary Artery Bypass Grafting		1
Elective hospitalization to adjust antihypertensive medication	2	1
Elective surgery	4	4
Epileptic insult	2	
Intoxication	1	
Microcytic anemia		1
Pericarditis	1	
Readmission due slow bleeding complication leg	1	
Recanalization occluded stent	2	
Trauma	1	
Total number serious adverse events	24	12

Serious adverse events were self-reported and not adjudicated.

Table S4. Mean change in prescribed medication between baseline and 6 months

Determinants of prescribed BP lowering drugs	Renal denervation group (n=95)	Control group (n=44)	Mean difference (95%CI)	P-value
No. of classes of BP lowering drugs	0.2 ±0.1	0.3 ±0.1	-0.1 (-0.3 to 0.1)	0.433
Number of BP lowering drugs	0.3 ±0.1	0.4 ±0.2	-0.1 (-0.4 to 0.1)	0.331
Daily defined use of BP lowering drugs	-0.1 ±0.1	0.1 ±0.3	-0.1 (-0.6 to 0.4)	0.680

Data presented as mean change ±SE, unless stated otherwise.
No.: number; BP: blood pressure.

Table S5. Daytime systolic ambulatory blood pressure at baseline and 6 months by adherence category

Daytime systolic ABPM	Non-adherent (n=18)	Poorly-adherent (n=56)	Adherent (n=24)
Baseline	166.3 (16.9)	157.8 (15.5)	161.9 (19.8)
	Non-adherent (n=10)	Poorly-adherent (n=60)	Adherent (n=13)
6 months	173.2 (23.5)	148.6 (17.1)	147.6 (28.0)

Data are expressed as mean ±SD, unless stated otherwise.

Table S6. Baseline characteristics of study population with a stable medication adherence.

Characteristics	Renal denervation group (n=29)	Control group (n=25)
Age (years)	63 (10)	62 (10)
Male *	14 (48.3)	8 (32.0)
Caucasian *	28 (96.6)	23 (92.0)
History of cardiovascular disease *	15 (51.7)	11 (44.0)
Current smoking *	6 (20.7)	6 (24.0)
Diabetes mellitus *	7 (24.1)	8 (32.0)
BMI (kg/m^2)	28.6 (4.7)	29.5 (4.9)
Plasma creatinine (µmol/l)	86 (22)	94 (26)
eGFR estimated with CKD-epi ($ml/min*1.73m^2$)	75 (18)	73 (19)
LDL (mmol/l)	3.5 (1.2)	2.9 (1.1)
Office SBP (mmHg)	163.1 (18.2)	160.3 (23.3)
Office DBP (mmHg)	91.1 (12.6)	89.6 (11.5)
24-h systolic ABPM (mmHg)	155.3 (12.4)	154.0 (19.3)
24-h diastolic ABPM (mmHg)	89.4 (13.3)	89.0 (15.2)
Daytime systolic ABPM (mmHg)	158.7 (12.5)	157.6 (19.8)
Daytime diastolic ABPM (mmHg)	90.9 (13.7)	91.8 (15.9)
Nighttime systolic ABPM (mmHg)	144.2 (16.4)	142.4 (16.6)
Nighttime diastolic ABPM (mmHg)	81.9 (13.8)	79.9 (13.6)

Data are expressed as mean±SD unless stated otherwise. * Data are expressed as n(%).

BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; LDL: Low Density Lipoprotein.

SBP: systolic blood pressure; DBP: diastolic blood pressure; 24-h: 24-hour; ABPM: ambulatory blood pressure measurements.

Table S7. Search strategy

Search items	Pubmed	Embase	Cochrane
Domain	(((((((high BP*[Title/Abstract]) OR elevated BP*[Title/Abstract]) OR hypertens*[Title/Abstract]) OR raised BP*[Title/Abstract]) OR hypertension [MeSH Terms])) AND (((resistant[Title/Abstract]) OR uncontrolled[Title/Abstract]) OR refractory[Title/Abstract])))	hypertens*:ab,ti OR 'high BP':ab,ti OR 'elevated BP':ab,ti OR 'raised BP':ab,ti AND (resistant:ab,ti OR uncontrolled:ab,ti OR refractory:ab,ti) OR 'resistant hypertension'/exp	((hypertens*:ti,ab OR "high BP":ti,ab OR "elevated BP":ti,ab OR "raised BP":ti,ab OR hypertension [MeSH]) AND (resistant:ti,ab OR uncontrolled:ti,ab OR refractory:ti,ab))
AND			
Determinant	((((((renal[Title/Abstract]) OR kidney[Title/Abstract]) OR kidney [MeSH Terms]) OR renal artery[MeSH Terms])) AND (((((denervation[Title/Abstract]) OR sympathectomy[Title/Abstract]) OR radio frequency ablation[Title/Abstract]) OR sympathectomy[MeSH Terms]) OR denervation[MeSH Terms]))	renal:ab,ti OR kidney:ab,ti OR 'kidney'/exp AND (denervation:ab,ti OR sympathectomy:ab,ti OR 'radio frequency ablation':ab,ti) OR 'kidney denervation'/exp	((renal:ti,ab OR kidney:ti,ab OR kidney [MeSH] OR “renal artery” [MeSH]) AND denervation:ti,ab OR sympathectomy:ti,ab OR "radio frequency ablation":ti,ab OR denervation [MeSH] OR sympathectomy [MeSH]))
Outcome	x	x	x
Results	852 hits	1888 hits	161 hits

Table S8. Study characteristics[1-8]

Characteristics	HTN-2 2010	HTN-3 2014	Oslo 2014	PRAGUE 2015	DENERHTN 2015	Symplicity-F 2015	Symplicity-J 2015	ReSET 2016
Location	Europe, Australia, New Zealand	USA	Norway	Czech Republic	France	Germany	Japan	Denmark
Center	Multiple	Multiple	Single	Multiple	Multiple	Single	Multiple	Single
Primary BP endpoint	Office systolic	Office systolic	Office systolic	24 hour systolic	Daytime systolic	24 hour systolic	Office systolic	Daytime systolic
ABPM entry criteria (mmHg)	-	24 hour ≥160/-	Daytime >135/-	24 hour >130/-	Daytime ≥135/≥85	Daytime 135-149/90-94	24 hour ≥135/-	Daytime ≥145/-
eGFR criteria (ml/min/1.73m2)	≥45	≥45	≥45	-	≥40	≥45	≥45	>30
No. of participants randomised (No. RDN/CON)	106 (52/54)	535 (364/171)	20 (10/10)	106 (52/54)	106 (53/53)	71 (35/36)	41 (22/19)	99 (36/33)
Treatment in control group	Drug treatment	Sham plus maintained drug treatment	Drugs adjusted to hemodynamic condition	Intensified drug treatment plus spironolactone	Standardized drug treatment guided by home BP	Sham plus maintained drug treatment	Drug treatment	Sham plus maintained drug treatment
Women %RDN/%CON	35/50	36/41	0/22	23/37	40/36	31/23	32/16	25/27
Mean age (years)	58/58	58/56	57/63	56/59	55/55	65/57	60/56	54/57
White ethnicity %RDN/%CON	98/96	73/70	100/100	100/100	79/77	100/100	0/0	97/97
No. of BP lowering drugs	5.2/5.3	5.1/5.2	5.1/5.0	5.4/5.4	3.0/3.0	4.4/4.3	4.9/4.9	4.1/4.2
Drug adherence assessment	Diary	Diary	Witnessed intake	Plasma drug concentrations at baseline	Diary	Interview	Diary	-

BP: blood pressure; ABPM: ambulatory blood pressure measurement; eGFR: estimated glomerular filtration rate; RDN: renal denervation; CON: control.

Table S9. Quality assessment table for GRADE approach per study

Study	HTN-2	HTN-3	OSLO	PRAGUE	DENERHTN	Symplicity-J	Symplicity-F	ReSET	SYMPATHY
	2010	2014	2014	2015	2015	2015	2015	2016	2016
General									
Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Sample size	106	535	20	106	106	41	71	68	139
Generalizability									
Population of interest (a)	+	+	+	+	+	+	+	+	+
Intervention (b)	+	+	+	+	+	+	+	+	+
Control (c)	+	+	+	+	+	+	+	+	+
Outcome (d)	+	+	+	+	+	+	+	+	+
Daytime systolic ABPM	3	2	2	2	1	3	2	1	1
24-hour systolic ABPM	2	2	2	1	2	2	1	2	2
Office SBP	1	1	1	2	2	1	3	2	2
Quality									
no selective inclusion of participants (e)	+	+	+	+	+	+	+	+	+
Random sequence generation (f)	+/-	+	+	-	+	+	+	+	+
Concealment of allocation (g)	-	+	+	-	+	-	+	+	+
Blinding Participant (h)	-	+	-	-	-	-	+	+	-
Outcome	-	+	-	-	+	-	+	+	+
Trial ended as scheduled (i)	+	+	-	-	+	+	+	+	+
Loss to follow-up (j)	+	+	+	+	+	+	+	+	+
Intention-to-treat analysis (k)	+	+	+	+	-	+	-	+	+
no selective outcome reporting (l)	+	+	+	+	+	+	+	+	+
no suspected conflict of interest o	-*	+	+	+	+	+	+	+	+

(a) participants with uncontrolled hypertension

(b) renal denervation

(c) usual care

(d)1: primary outcome 2: secondary outcome

3: not available

(e) +: no selective inclusion, -: selective inclusion

(f) +: random sequence generation, +/-: predetermined sequence / small blocks, -: no random sequence generation reported

(g) +:concealed allocation, -: -no concealed allocation or unclear method reported

(h)+: sham-procedure, -: open label

(i) +: ended as scheduled, -: trial ended preliminary

(j) + ≤ 20% loss to follow-up, non-selective; -: ≥ 20% loss to follow-up, non-selective

(k) +: intention to treat analysis, -: modified intention to treat analysis or per-protocol analysis

(l) +: non-selective outcome reporting, -: selective outcome reporting

* The sponsor designed the study in collaboration with the study investigators and was responsible for data collection and analysis

Table S10. Summary of findings table (meta-analysis).

Renal sympathetic denervation as a new treatment for therapy resistant hypertension
Study population: resistant hypertension
Setting: secondary / third line centers
Intervention: renal denervation
Comparison: usual care

Outcomes	Mean difference (95% CI) mmHg	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Daytime systolic ABPM (follow-up 6 months)	-1.60 (-4.32 to 1.11)	984 (7)	Moderate	High score on: RCT's, generalizable to our population. Low score on: (sham and open label studies), inconsistent results.
24-hour systolic ABPM (follow-up 6 months)	-2.76 (-5.43 to -0.10)	1110 (9)	Moderate	High score on: RCT's, generalizable to our population, large number of studies Low score on: sham and open label studies, inconsistent results,
Office SBP (follow-up 6 months)	-5.44 (-15.09 to 4.22)	1030 (7)	Moderate	High score on: RCT's, generalizable to our population, Low score on: sham and open label studies, inconsistent results, concealment of allocation in some studies unclear,

GRADE: Grading of Recommendations, Assessment, Development and Evaluations, score based on BMJ Clinical Evidence[1]; No.: numbers; RCTs: Randomised Controlled Trials; ABPM ambulatory blood pressure measurement; SBP: systolic blood pressure.

Figures

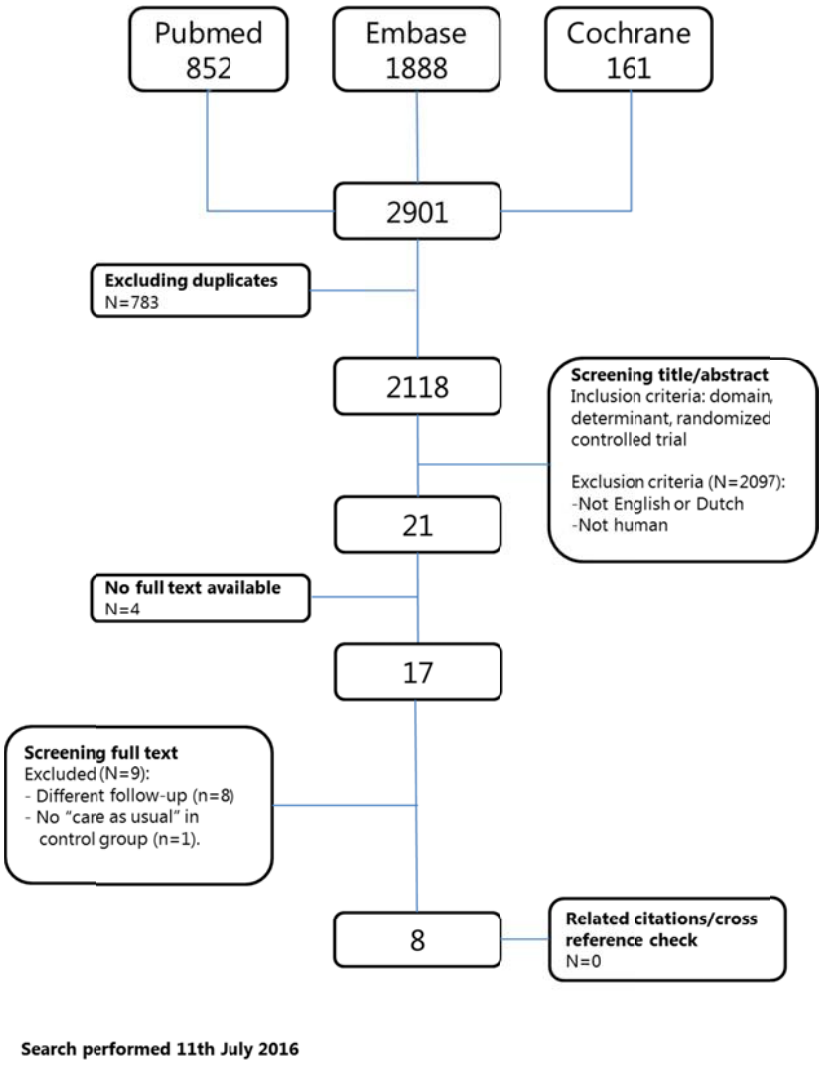
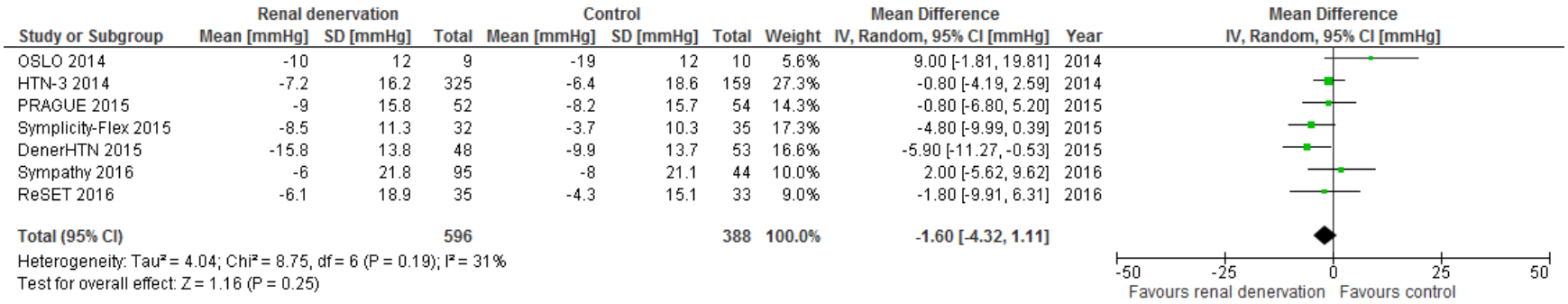
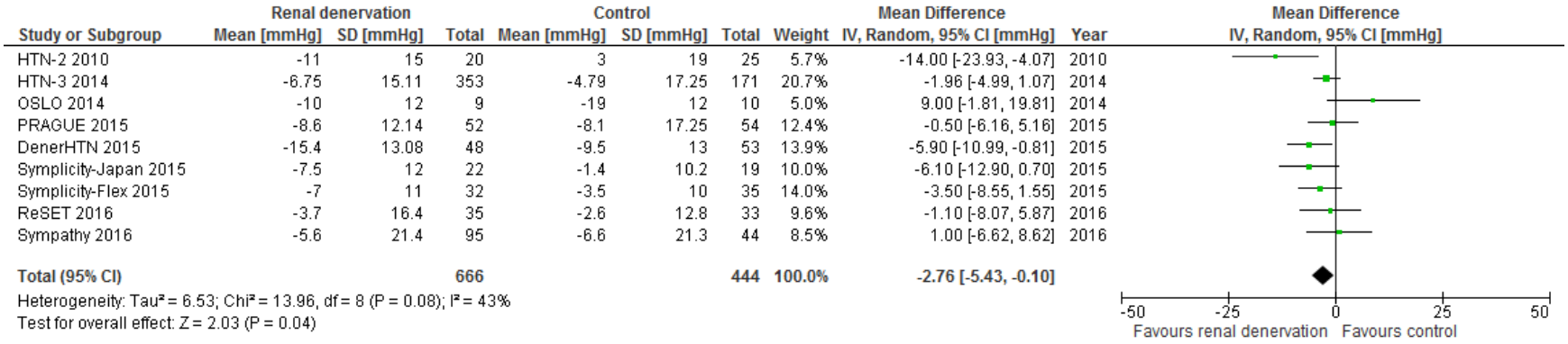


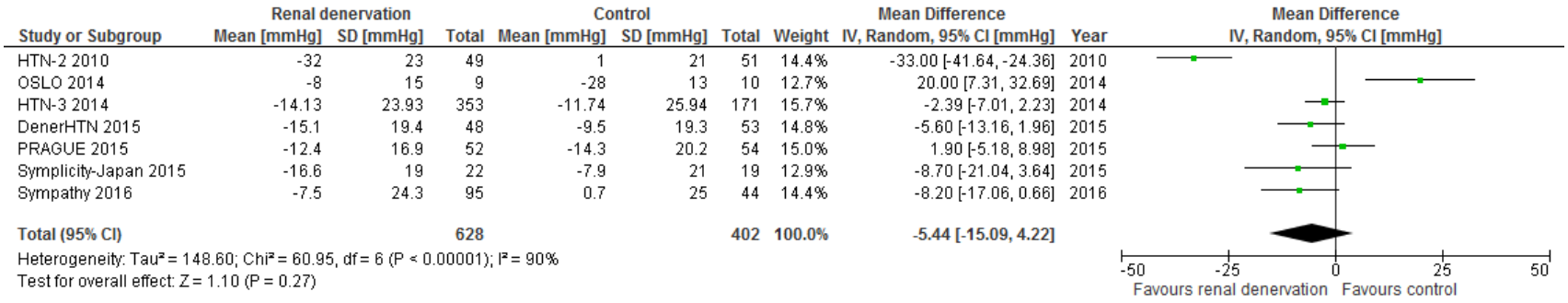
Figure S1. Systematic search of the literature.


Renal denervation
Control
Mean Difference
Mean Difference
Study or Subgroup Mean [mmHg] SD [mmHg] Total Mean [mmHg] SD [mmHg] Total Weight IV, Random, 95% CI [mmHg] Year
IV, Random, 95% CI [mmHg]
OSLO 2014 -10 12 9 -19 12 10 5.6% 9.00 [-1.81, 19.81] 2014
HTN-3 2014 -7.2 16.2 325 -6.4 18.6 159 27.3% -0.80 [-4.19, 2.59] 2014
PRAGUE 2015 -9 15.8 52 -8.2 15.7 54 14.3% -0.80 [-6.80, 5.20] 2015
Symplicity-Flex 2015 -8.5 11.3 32 -3.7 10.3 35 17.3% -4.80 [-9.99, 0.39] 2015
DenerHTN 2015 -15.8 13.8 48 -9.9 13.7 53 16.6% -5.90 [-11.27, -0.53] 2015
Sympathy 2016 -6 21.8 95 -8 21.1 44 10.0% 2.00 [-5.62, 9.62] 2016
ReSET 2016 -6.1 18.9 35 -4.3 15.1 33 9.0% -1.80 [-9.91, 6.31] 2016
Total (95% CI) 596 388 100.0% -1.60 [-4.32, 1.11]
Heterogeneity: Tau² = 4.04; Chi² = 8.75, df = 6 (P = 0.19); I² = 31%
Test for overall effect: Z = 1.16 (P = 0.25)
-50 -25 0 25 50
Favours renal denervation Favours control

A.


Renal denervation
Control
Mean Difference
Mean Difference
Study or Subgroup Mean [mmHg] SD [mmHg] Total Mean [mmHg] SD [mmHg] Total Weight IV, Random, 95% CI [mmHg] Year
IV, Random, 95% CI [mmHg]
HTN-2 2010 -11 15 20 3 19 25 5.7% -14.00 [-23.93, -4.07] 2010
HTN-3 2014 -6.75 15.11 353 -4.79 17.25 171 20.7% -1.96 [-4.99, 1.07] 2014
OSLO 2014 -10 12 9 -19 12 10 5.0% 9.00 [-1.81, 19.81] 2014
PRAGUE 2015 -8.6 12.14 52 -8.1 17.25 54 12.4% -0.50 [-6.16, 5.16] 2015
DenerHTN 2015 -15.4 13.08 48 -9.5 13 53 13.9% -5.90 [-10.99, -0.81] 2015
Symplicity-Japan 2015 -7.5 12 22 -1.4 10.2 19 10.0% -6.10 [-12.90, 0.70] 2015
Symplicity-Flex 2015 -7 11 32 -3.5 10 35 14.0% -3.50 [-8.55, 1.55] 2015
ReSET 2016 -3.7 16.4 35 -2.6 12.8 33 9.6% -1.10 [-8.07, 5.87] 2016
Sympathy 2016 -5.6 21.4 95 -6.6 21.3 44 8.5% 1.00 [-6.62, 8.62] 2016
Total (95% CI) 666 444 100.0% -2.76 [-5.43, -0.10]
Heterogeneity: Tau² = 6.53; Chi² = 13.96, df = 8 (P = 0.08); I² = 43%
Test for overall effect: Z = 2.03 (P = 0.04)
-50 -25 0 25 50
Favours renal denervation Favours control

B.



C.

Figure S2. Forest plots of comparison renal denervation vs. control for change in daytime systolic ambulatory blood pressure (A), 24-hour systolic ambulatory blood pressure (B) and office systolic blood pressure (C) 6 months after inclusion.[1-8]