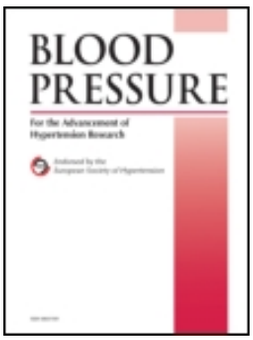

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Meta-analysis of randomized controlled trials of renal denervation in treatment-resistant hypertension

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META-ANALYSIS

Meta-analysis of randomized controlled trials of renal denervation in treatment-resistant hypertension

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Abstract

Objective. The blood pressure (BP)-lowering effect of renal sympathetic nervous denervation (RDN) in resistant hypertension (rHT) shows large variation among studies. *Methods.* We meta-analyzed summary statistics of randomized clinical trials on RDN in rHT. For continuous outcomes, we assessed heterogeneity by Cochran's *Q* test and used random-effect models weighted for the inverse of the variance. We assessed safety by assessing the risk of major adverse events from stratified contingency tables. *Results.* Of 5652 patients screened in seven trials, 985 (17.4%) qualified and were randomized to control ($n = 397$) or RDN with SYMPLICITY™ catheters ($n = 588$). Follow-up was 6 months. In both control and RDN patients, antihypertensive treatment was continued or optimized. At enrolment, age averaged 58.1 years, systolic/diastolic office and 24 h BP 168.5/93.3 mmHg and 151.8/86.1 mmHg, respectively, and estimated glomerular filtration rate (eGFR) 79.3 ml/min/1.73 m². For BP outcomes, there was heterogeneity among trials. Pooled effects (control minus RDN) were −4.9/−3.5 mmHg (95% confidence interval, −20.9 to 11.1/−8.9 to 1.9) for office BP, −2.8/−1.5 mmHg (−6.5 to 0.8/−3.3 to 0.4) for 24 h BP and 0.81 ml/min/1.73 m² (−1.69 to 3.30) for eGFR. Removing one trial at a time produced confirmatory results. Adverse events occurred in 7.4% and 9.9% of control and RDN patients, respectively ($p = 0.24$). *Conclusion.* In selected rHT patients maintained on antihypertensive drugs, RDN with the SYMPLICITY systems does not significantly decrease BP but is safe. Future trials with next-generation catheters should aim at identifying responders in patients with evidence of sympathetic nervous overactivity.

Key Words: *Blood pressure-lowering treatment, meta-analysis, randomized clinical trial, renal sympathetic nervous denervation, resistant hypertension*

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Introduction

Resistant hypertension is an office blood pressure (BP) of at least 140 mmHg systolic or 90 mmHg diastolic on treatment with three antihypertensive drug classes at maximal doses, including a diuretic (1,2). In 2009, Krum and colleagues (3) reported a non-randomized proof-of-concept study (SYMPLICITY HTN-1), showing that percutaneous radiofrequency (RF) catheter-based renal sympathetic nervous denervation (RDN) was feasible, effective and safe in patients with treatment-resistant hypertension (1,2). Subsequently, the SYMPLICITY HTN-2 study (4), an open-label randomized clinical trial, reported an impressive BP reduction 6 months after RDN using the SYMPLICITY™ RF catheter in polymedicated hypertensive patients unresponsive to treatment.

In spite of the limitations of SYMPLICITY HTN-2 (4), reviewed elsewhere (5), CE label certification (Conformité Européenne) (Data Supplement, p. 10) led to the fast deployment of RDN systems as a treatment modality for treatment-resistant hypertension in Europe and Asia, but not in the USA. In addition, numerous uncontrolled studies, using different denervation catheters, claimed benefit of RDN in a wide variety of clinical conditions, including obstructive sleep apnoea, insulin resistance, heart failure, left ventricular hypertrophy combined with diastolic dysfunction, and polycystic ovary syndrome (5). However, in 2014, the properly powered SYMPLICITY HTN-3 trial (6), which had a randomized design with a sham arm, as requested by the Food and Drug Administration, failed to reach its efficacy endpoint, a reduction in office systolic BP 6 months after RDN with the single-electrode SYMPLICITY™ RF catheter. This trial annihilated the seemingly unlimited prospects of a large market, thereby stalling research on RDN. In the wake of SYMPLICITY HTN-3 (6), other randomized controlled trials with different designs, but using catheters from the same manufacturer, reported conflicting results (7–11). We therefore conducted a systematic literature review based on published summary statistics in an attempt to sum up the randomized evidence on the efficacy and safety of RDN as treatment modality in treatment-resistant hypertensive patients.

Materials and methods

Literature search

We identified original research papers, reviews and editorial comments by systematically searching the table of contents of general-interest and speciality journals that publish research on RDN, since 1 January 2009, the year in which the first proof-of-concept study was published (3). In addition, we searched the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (http://www.elsevier.com/online-tools/embase) databases for publications in English on RDN as a treatment modality of hypertension. We chose as search terms for titles and abstracts: "renal denervation" AND "blood pressure" AND "hypertension". Finally, we examined the www.clinicaltrials.gov website for published and ongoing randomized trials of RDN in hypertensive patients.

Selection criteria

Articles eligible for inclusion in our quantitative review were reports of randomized clinical trials comparing RDN with no intervention in resistant hypertensive patients all maintained on unchanged or optimized antihypertensive drug treatment. Trials qualified for inclusion if the reports included sufficient information on key points required for their interpretation. These criteria were: (i) a detailed study protocol; (ii) inclusion and exclusion criteria; (iii) the number of screened and randomized patients; (iv) the characteristics of the overall study population and relevant subgroups; (v) the central tendency (mean) and spread (SD) of the office and ambulatory BP at randomization and follow-up; (vi) the incidence of adverse effects; and (vii) medical treatment at enrolment and during follow-up. Patients enrolled in eligible trials, while on treatment with three or more drug classes, had to have a systolic BP of at least 140 mmHg, 135 mmHg or 130 mmHg on office, daytime or 24 h ambulatory measurement, respectively. Eligible trials also had to comply with the Consolidated Standards of Reporting Trials (CONSORT) quality criteria (12).

Data extraction

In a first step, titles and abstracts of retrieved publications were reviewed. The articles were ordered by the last name of the first author and year of publication, given a unique identification number, and entered into a dedicated literature database, using Reference Manager, version 12.0.3 (Thomson Reuters: http://www.refman.com). Next, one investigator (FEMFE) read all papers that passed the first stage of selection, assessed eligibility, extracted and computerized the relevant information, and provided copies of eligible papers to the senior coauthors (YJ, SEK, JAS), who checked the data extraction and summary statistics. The reference lists of eligible manuscripts were also inspected to retrieve possibly missing information and to identify duplicate publication of the same data. In addition to the analysis of summary statistics, we carefully reviewed the trial protocols (Data Supplement, pp. 3–9), because differences in design might explain divergent results.

Statistical analysis

We used SAS software version 9.3 (SAS Institute, Cary, NC, USA) to enter the extracted data into a

dedicated database for subsequent statistical analysis. We expressed the central tendency and spread of continuous variables as mean and SD, respectively.

We calculated the within-study effect size by subtracting the treatment effect in the control group from that in the RDN group. Efficacy was assessed by the BP changes from baseline to 6 months. Changes in the estimated glomerular filtration rate (eGFR) from baseline to 6 months were evaluated as a measure of safety. We assumed that the true effect sizes differed among studies. Therefore, we estimated the pooled effect size and its confidence interval (CI) from random-effects models as implemented in the PROC MIXED procedure of the SAS package. Each study was weighted by the inverse of the within- and between-study variances. The latter were estimated using an iterative maximum likelihood method. We checked the null hypothesis of homogeneity across individual studies by the Cochran's Q and the I^2 tests (12). For Cochran's Q test, the p value indicating significance was set at less than 0.10. For I^2, values less than 25%, from 25% to 50%, and more than 50% indicated modest, moderate and substantial heterogeneity, respectively. We performed sensitivity analyses by assessing the effect on the pooled estimates after removal of one study at a time. Finally, we computed pooled odds ratios for the risk of a major adverse event from stratified 2×2 contingency tables.

Results

Excluded and included studies

We identified eight published randomized controlled trials (Figure 1). We excluded one study because of serious concerns regarding changes in design, primary endpoint, sample size, and inclusion and exclusion criteria in successive protocols posted at http://www.clinicaltrials.gov and the finally published report (13), and because, as reviewed elsewhere (14), it did therefore not meet the CONSORT standards (15). Thus, the current meta-analysis includes seven randomized controlled trials (Figure 1).

Characteristics of trials

Table I summarizes the design of the seven studies included in our meta-analyses and the Data Supplement (pp. 3–9) describes each of the trials in detail. All trials (4,6–11) recruited patients with resistant hypertension, aged 18 years (4,6–10) or 20 years (11) or older without upper age limit (8) or with an upper age limit ranging from 75 years (9) to 85 years (4). Resistant hypertension was maintaining an office systolic BP equal to or exceeding a range from 140 mmHg (7–9) to 160 mmHg (4,6,11), while on treatment with three antihypertensive drug classes including a diuretic in six studies (6–11). In the same six trials (6–11), resistant hypertension required confirmation by reaching or exceeding a systolic BP of 135 mmHg on daytime ambulatory monitoring (7,9–11) or a 24 h systolic BP level reaching (6) or exceeding (6,8) 130 mmHg (8) or 135 mmHg (6). DENERHTN (9) and SYMPLICITY-FLEX (10) were the only trials that applied a diastolic level of 90 mmHg on office (9) or of 85 mmHg (9) or 90 mmHg (10) on daytime ambulatory monitoring as an alternative to the corresponding systolic BP thresholds. A particular design aspect of SYMPLICITY-FLEX was that office BP was not considered in selecting patients (10). Patients with severe renal

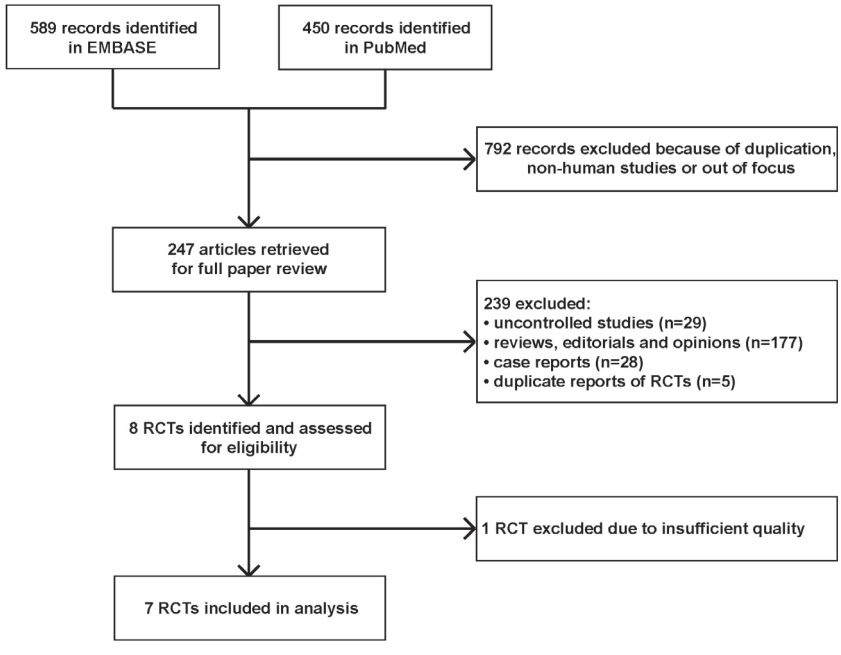

Figure 1. Selection of randomized controlled trials (RCTs) for inclusion in the meta-analysis.

Table I. Design features of randomized trials of renal denervation in patients with treatment-resistant hypertension.

NCT no.	NCT00888433	NCT01418261	NCT01673516	NCT01560312	NCT01570777	NCT01656096	NCT01644604
Acronym	SYMPLICITY HTN-2	SYMPLICITY HTN-3	OSLO RDN	PRAGUE-15	DENERHTN	SYMPLICITY-FLEX	SYMPLICITY HTN-Japan
Year of report (reference)	2010 (4)	2014 (6)	2014 (7)	2014 (8)	2015 (9)	2015 (10)	2015 (11)
Location	Europe, Australia, New Zealand	USA	Norway	Czech Republic	France	Germany	Japan
Center	Multiple	Multiple	Single	Multiple	Multiple	Single	Multiple
Age range (years)	18–85	18–80	18–80	≥18	18–75	18–75	20–79
BP entry criteria							
Office systolic/diastolic BP (mmHg)	≥160/– (≥150/– in t2DM)	≥160/–	>140/–	>140/–	≥140/≥90	–/–	≥160/–
Ambulatory BP							
Period of day	–	24 h	Daytime	24 h	Daytime	Daytime	24 h
Systolic/diastolic BP (mmHg)	–	≥135/–	>135/–	>130/–	≥135/≥85	135–149/90–94	≥135/–
Antihypertensive drug classes (*n*)	≥3	≥3 including diuretic	≥3 including diuretic	≥3 including diuretic	≥3 including diuretic	≥3 including diuretic	≥3 including diuretic
eGFR (ml/min/1.73 m²)	≥45	≥45	≥45	–	≥40	≥45	≥45
Serum creatinine (μmol/l)	–	–	–	≤200	–	–	–
Patients screened (*n*)	190	1441	65	~1450	1416	1006	84
Patients randomized [*n* (%)]	106 (55.8)	535 (37.1)	20 (30.8)	106 (7.3)	106 (7.5)	71 (7.1)	41 (48.8)
Proportion control vs intervention	1:1	1:2	1:1	1:1	1:1	1:1	1:1
Treatment in control group	Drug treatment	Sham plus drug treatment	Drugs adjusted to hemodynamic condition	Intensified drug treatment plus spironolactone	Standardized drug treatment guided by home BP	Sham plus drug treatment	Drug treatment
Primary BP endpoint	Office systolic	Office systolic	Office systolic	24 h systolic	Daytime systolic	24 h systolic	Office systolic
Drug adherence assessment	Diary	Diary	Witnessed intake	Plasma drug concentrations	Morisky score plus drug concentration	Interview	Diary
Imaging	Renal duplex, aCT, aMR or RAA	RAA	aCT or aMR	aCT or aMR	aCT	NR	RAA

In all trials, the intervention consisted of intra-arterial renal sympathetic nervous denervation by means of the ARDIAN™ or SYMPLICITY™ device and the primary endpoint refers to the baseline-corrected between-group difference in systolic blood pressure 6 months after the intervention. For the PRAGUE-15 trial, the number of screened patients was extrapolated from the first year of recruitment (15 patients randomized for 206 screened).

BP, blood pressure; eGFR, glomerular filtration rate estimated from the serum creatinine concentration; t2DM, type 2 diabetes mellitus; aCT, computerized tomographic angiography; aMR, magnetic resonance angiography; RAA, renal arterial angiography; NR, not reported; – criterion was not applicable.

dysfunction, defined as an eGFR below 40 ml/min/1.73 m² (9) or 45 ml/min/1.73 m² (4,6,7,10,11) or a serum creatinine concentration of more than 200 μmol/l (2.26 mg/dl) (8), were not eligible for enrolment in all studies.

Sample size ranged from 20 (7) to 535 (6) patients randomized to RDN or control in a 1:1 (4,7–11) or 2:1 (6) proportion. As summarized in Table I, SYMPLICITY HTN-3 (6) and SYMPLICITY-FLEX (10) were trials with a sham design, while the five other trials had an open design (6–9,11), but with blinded assessment of the primary endpoint in DENERHTN (9). The baseline-corrected between-group difference in the achieved systolic BP as assessed at 6 months after randomization was the primary endpoint in all studies (4,6–11), but only in PRAGUE-15 (8), DENERHTN (9) and SYMPLICITY-FLEX (10) was it assessed by 24 h (8,10) or daytime (9) ambulatory monitoring, respectively, instead of office measurement. The daytime (7) or 24 h (6,8,11) ambulatory BP was a predefined secondary endpoint in four other trials, but not in SYMPLICITY HTN-2 (4). The success rate of screening ranged from approximately 7% (8–10) to 56% (4), and the number of randomized patients from 20 (7) to 535 (6). For PRAGUE-15, we extrapolated the screening success rate from recruitment during the first year (15 patients randomized of 206 screened (16) (Table I). Remarkably, the number of randomized patients was 106 in three studies (4,8,9).

In all trials (Table I) (4,6–11), RDN was carried out by means of a single-electrode RF SYMPLICITY™ catheter (Medtronic, Minneapolis, MN, USA) with largely similar anatomical constraints, including pre-existing renal artery lesions, prior interventions on the renal artery, a renal artery of less than 4 mm in diameter or a treatable segment of less than 20 mm in length. For the selection and follow-up of patients, renal imaging was not standardized in SYMPLICITY HTN-2 (4), where ultrasound was an acceptable approach, but in other studies (6-9, 11) only relied on predefined state-of-the-art approaches. The SYMPLICITY-FLEX report did not state the imaging method applied for the diagnostic work-up of patients during recruitment (10). The control intervention was a sham procedure in the SYMPLICITY HTN-3 (6) and SYMPLICITY-FLEX (10) trials. In the other trials, it consisted of maintaining antihypertensive drug treatment unchanged as far as it was clinically justifiable (4,11), or optimizing drug treatment based on non-invasive hemodynamic measurement in the OSLO trial (7), by adding spironolactone in PRAGUE-15 (8), or in DENERHTN by applying a highly standardized step-up BP-lowering treatment regimen with spironolactone as the first step and sympatholytic agents in the next three steps (9). In DENERHTN, the same highly standardized step-up BP-lowering treatment regimen was also administered to the RDN group (9).

Characteristics of patients

Across the seven trials (4,6–11), a total of 985 patients with resistant hypertension were randomized, 397 to control and 588 to RDN (Table II). In general, baseline characteristics, such as ethnicity, gender, age, body mass index, systolic and diastolic BPs on office and 24 h ambulatory measurement and eGFR were not significantly different between the groups randomized in each study. Only in SYMPLICITY-FLEX was age substantially lower in the sham than in the intervention group (57.4 vs 64.5 years; $p< 0.001$) (10). With the exception of SYMPLICITY-Japan (11), patients were predominantly overweight or obese, with mean body mass index in the other trials ranging from 29.5 kg/m² in OSLO RDN (7) to 34.0 kg/m² in SYMPLICITY HTN-3 (6). The total number of women and non-Caucasians enrolled across all trials (4,6–11) amounted to 358 (36.3%) and 217 (22.0%), respectively. In all trials, women were underrepresented, with proportions ranging from 10.0% (7) to 42.5% (4). The same also applied to the enrolment of non-whites, except in SYMPLICITY HTN Japan (11), with the proportions of non-whites in the other trials ranging from 0% (7) to 28.0% (6). SYMPLICITY HTN-3 enrolled 140 (26.2%) African-Americans (6). Type 1 diabetes mellitus was an exclusion criterion in all trials (4,6–11). The overall number of patients randomized with type 2 diabetes mellitus was 378 (38.4%), with proportions ranging from 19.8% (8) to 48.8% (11) in individual trials.

At randomization, mean values across all trials weighted for study size were 58.1 years for age, 168.5 mmHg systolic and 93.3 mmHg diastolic for office BP, 151.8 mmHg systolic and 86.1 mmHg diastolic for the 24 h ambulatory BP, and 79.3 ml/min/1.72 m² for the eGFR. In individual trials (Table II), mean values at entry ranged from 55.2 years (9) to 61.0 years (10) for age, from 157.0 mmHg (8) to 179.6 mmHg (6) systolic and from 88.0 mmHg (7) to 97.5 mmHg (4) diastolic for office BP, from 140.0 mmHg (11) to 159.2 mmHg (6) systolic and from to 85.0 mmHg (8) to 89.5 mmHg (6,9) diastolic for the 24 h BP, and from 73.3 ml/min/1.73 m² (6) to 89.0 ml/min/1.73 m² (9) for the eGFR. The aforementioned estimates do not include SYMPLICITY-FLEX (10) for office BP and SYMPLICITY HTN-2 (4) for the 24 h BP. SYMPLICITY-FLEX (10) did not report any data on office BP. Baseline levels of the ambulatory BP were unavailable in the SYMPLICITY HTN-2 report (4) and could not be obtained by the authors from the sponsor (Murray Esler, personal communication). Baseline office BP was on average over 20 mmHg systolic and over 5 mmHg diastolic higher in the three SYMPLICITY studies (4,6,11) compared with the other trials (7–9,11). At randomization, patients were on average taking five or more antihypertensive drug classes (4,6–8,10,11), except in

Table II. Patient characteristics at baseline and follow-up.

Characteristic	SYMPLICITY HTN-2 CON/RDN	SYMPLICITY HTN-3 CON/RDN	OSLO RDN CON/RDN	PRAGUE-15 CON/RDN	DENERHTN CON/RDN	SYMPLICITY-FLEX CON/RDN	SYMPLICITY HTN-Japan CON/RDN
No. of randomized patients	54/52	171/364	10/10	54/52	53/53	36/35	19/22
No. of analysed patients	51/49	171/353	10/9	54/52	53/48	35/32	19/22
Women (%)	50/35	36/41	0/22	37/23	40/36	31/23	16/32
Type 2 diabetes mellitus (%)	28/40	41/47	33/20	17/23	26/17	36/54	63/36
White ethnicity (%)	96/98	70/73	100/100	100/100	77/79	–/–	0/0
Mean age (years)	58/58	56/58	63/57	59/56	55/55	57/65	56/60
Mean body mass index (kg/m²)	31/31	34/34	30/29	33/31	30/31	31/32	28/27
No. of drugs							
Baseline	5.3/5.2	5.2/5.1	5.0/5.1	5.4/5.1	3.0/3.0	4.3/4.4	4.9/4.9
At 6 months	–/–	5.2/5.0	5.2/4.9	5.6/5.0	5.4/5.3	–/–	4.9/4.9
Systolic BP (mmHg)							
Office, baseline	178/178	180/180	160/156	155/159	156/160	–/–	179/181
Office, change at 6 months	+ 1/−32	−11.7/−14.1	−28/−8	−14.3/−12.4	−9.5/−15.1	–/–	−7.9/−16.6
24 h, baseline	–/–	160/159	149/151	147/149	147/152	140/140	163/165
24 h, change at 6 months	−3/−11	−4.8/−6.7	−21/−10	−8.1/−8.6	−9.5/−15.4	−3.5/−7.0	−1.4/−7.5
Diastolic BP (mmHg)							
Office, baseline	98/97	99/97	88/91	89/92	91/93	–/–	93.7/92.4
Office, change at 6 months	0/–12	−4.6/−6.6	−11/−2	−7/−7	−6.0/−9.1	–/–	−1.0/−5.9
24 h, baseline	–/–	91/88	85/89	84/86	89/90	81/78	–/–
24 h, change at 6 months	−1/−7	−3.1/−4.1	−11/−7	−5/−6	−6.6/−9.7	−2.1/−2.8	−0.4/−4.2
eGFR (ml/min/1.73 m²)							
Baseline	86/77	74/73	77/78	80/84	90/88	84/79	70/70
Change at 6 months	+ 0.9/+ 0.2	−1.7/−2.1	−4.7/+ 1.8	−3.1/+ 1.5	−5.8/−4.6	−0.01/−2.8	−3.8/−1.86

In SYMPLICITY HTN-2, the ambulatory blood pressure at baseline was not reported and results rest on a subgroup of 45 (42.4%) of 106 randomized patients.
CON, control group; RDN, renal denervation group; BP, blood pressure; eGFR, glomerular filtration rate estimated from serum creatinine; –, information was unavailable.

DENERHTN (9), where by design all patients were switched for 4 weeks to a standardized three-class drug regimen before randomization.

Blood pressure

Table II provides information on the number of patients retained in the 6 month intention-to-treat analyses. Of 985 randomized patients, 958 (97.3%) were analysed, 393 allocated to control and 565 to RDN. The proportion of patients not analysed was slightly greater in the RDN than in the control group (3.9% vs 1.0%). The median number of antihypertensive drugs taken at the end of the 6 month follow-up was around five in the intervention and control groups of all trials with this information reported (4,6–9).

For office systolic BP ($Q = 60.5$, $p < 0.001$, $I^2 = 91.7\%$) but not for 24 h systolic BP ($Q = 10.7$, $p = 0.10$, $I^2 = 43.7\%$), there was heterogeneity among the reviewed trials (4,6–11). For office systolic BP (Figure 2), the pooled effect size of RDN versus control, computed by subtracting the treatment effect over 6 months in the RDN group from that in the control group, was −4.89 mmHg (95% CI −20.9 to 11.1 mmHg; $p = 0.47$). For the 24 h systolic BP (Figure 3), the corresponding estimate amounted to −2.81 mmHg (95% CI −6.46 to 0.83 mmHg; $p = 0.11$). Sensitivity analyses from which we excluded one trial at a time were confirmatory (Supplementary Tables I and II to be found online at http://informahealthcare.com/doi/abs/10.3109/08037051.2015.1058595). All pooled estimates in the sensitivity analysis were within the 95% CI for all available studies. Thus, no study had an excessive influence on the estimate based on all seven studies (4,6–11) combined.

Results for diastolic BP appear in Supplementary Table III to be found online at http://informahealthcare.com/doi/abs/10.3109/08037051.2015.1058595. There was significant heterogeneity among the five studies for office BP ($Q = 26.1$; $p < 0.001$; $I^2 = 80.8\%$), but not for 24 h BP ($Q = 8.23$; $p = 0.22$; $I^2 = 27.1\%$). The pooled estimates were −3.5 mmHg (−8.9 to 1.9 mmHg; $p = 0.32$) for office diastolic pressure and −1.5 mmHg (−3.3 to 0.4 mmHg; $p = 0.10$) for 24 h diastolic pressure.

Safety

Figure 4 shows that in none of the seven trials (4,6–11) did significant between-group differences occur in baseline-corrected changes in the eGFR. Consequently, there was no heterogeneity among trials ($Q = 8.6$; $p = 0.20$; $I^2 = 30.4\%$). The pooled estimate, computed by subtracting the treatment effect over 6 months in the RDN group from that in the control group, was not significant (+0.81 ml/min/1.73 m²; 95% CI, −1.69 to 3.30 ml/min/1.73 m²; $p = 0.46$). The sensitivity analysis, excluding one trial at a time, was confirmatory (Supplementary Table IV to be found online at http://informahealthcare.com/doi/abs/10.3109/08037051.2015.1058595).

Across the seven trials, the number of patients with major adverse effects (Table III) was 29 (7.4%) and 56 (9.9%) among those randomized to control and RDN, respectively ($p = 0.20$).

Discussion

The key finding of our meta-analysis was that the BP-lowering effect of RDN with the SYMPLIC-

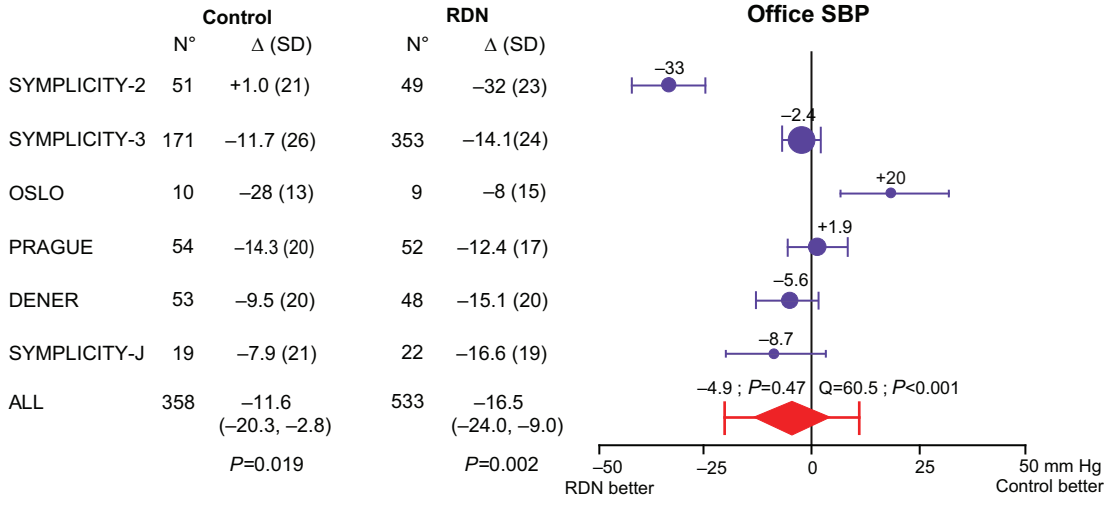

Figure 2. Six-month response of office systolic blood pressure (SBP) to renal denervation (RDN) or to follow-up in the control group. Solid points represent the effect size in individual studies and have a size proportional to the inverse of the variance. The diamond represents the pooled estimate. Horizontal lines and diamonds denote the 95% confidence intervals (CIs). For all trials combined, the pooled within-group change is given with 95% CI. P-values refer to the significance of the pooled between-group estimate and Cochran's Q test for heterogeneity.

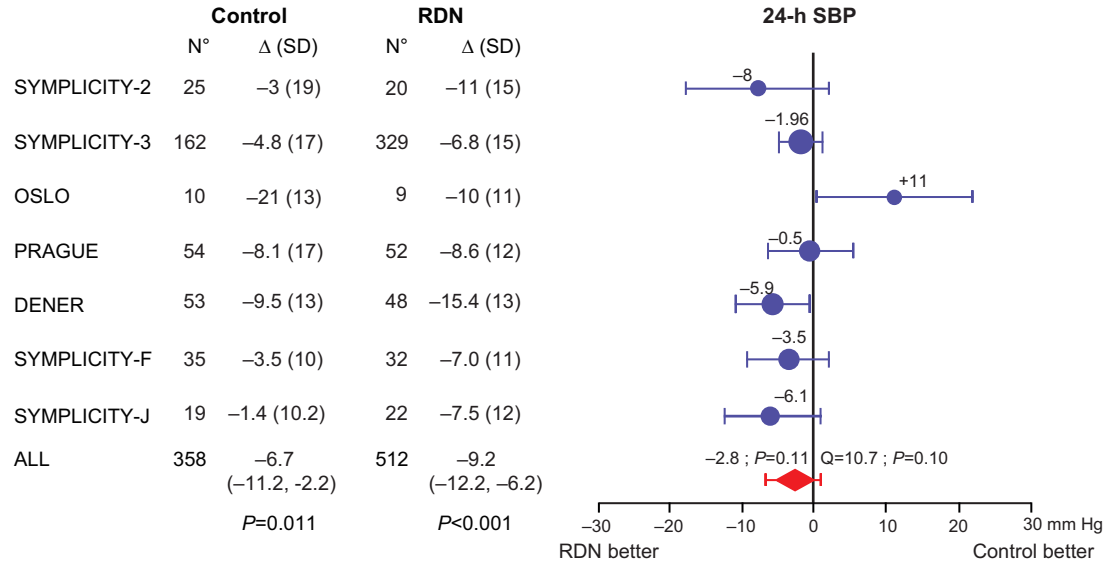

Figure 3. Six-month response of 24 h systolic blood pressure (SBP) to renal denervation (RDN) or to follow-up in the control group. Solid points represent the effect size in individual studies and have a size proportional to the inverse of the variance. The diamond represents the pooled estimate. Horizontal lines and diamonds denote the 95% confidence intervals (CIs). For all trials combined, the pooled within-group change is given with 95% CI. P-values refer to the significance of the pooled between-group estimate and Cochran's *Q* test for heterogeneity.

ITY™ catheter system on top of continued or optimized antihypertensive drug treatment is modest, averaging 4.9 mmHg systolic and 3.5 mmHg diastolic on office measurement, and 2.8 mmHg systolic and 1.5 mmHg diastolic on 24 h ambulatory monitoring. RDN by the SYMPLICITY systems is probably safe, as evidenced by the unchanged glomerular filtration rate and the similar risks of major adverse events in the control and RDN groups, averaging 7.4% and 9.9%, respectively. The risk of publication bias is small, because RDN has a high profile in hypertension research today and because we carefully checked the clinicaltrials.gov website for unpublished data (Table S5).

Compared to previous quantitative reviews published on RDN, the current results move the field forward. First, pooled estimates in previous publications (17–19) combined non-randomized and randomized studies and were therefore confounded by the weaknesses of uncontrolled studies, in particular placebo and nocebo (20) (Data Supplement, p. 10) effects, and inaccuracies in data extraction and

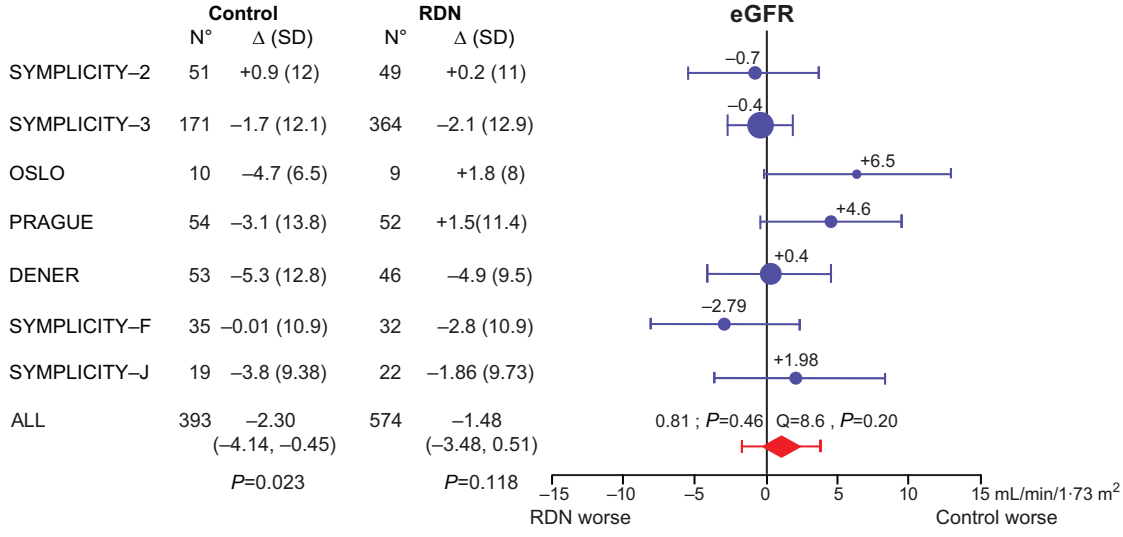

Figure 4. Six-month response of the estimated glomerular filtration rate (eGFR) to renal denervation (RDN) or to follow-up in the control group, respectively. Solid points represent the effect size in individual studies and have a size proportional to the inverse of the variance. The diamond represents the pooled estimate. Horizontal lines and diamonds denote the 95% confidence intervals (CIs). For all trials combined, the pooled within-group change is given with 95% CI. P-values refer to the significance of the pooled between-group estimate and Cochran's *Q* test for heterogeneity.

Table III. Major adverse events.

Characteristic	SYMPLICITY HTN-2 CON/RDN	SYMPLICITY HTN-3 CON/RDN	OSLO RDN CON/RDN	PRAGUE-15 CON/RDN	DENERHTN CON/RDN	SYMPLICITY-FLEX CON/RDN	SYMPLICITY HTN-Japan CON/RDN
No. of randomized patients	54/52	171/364	10/10	54/52	53/53	36/35	19/22
No. of analysed patients	51/49	171/353	10/9	54/52	53/48	35/32	19/22
No. with major adverse event	5/7	19/38	0/1	1/3	4/5	0/1	0/1
Per cent with major adverse event	9.8/14.3	11.1/10.8	0/11.1	1.9/5.8	8.3/9.4	0/0	0/4.5
No. of deaths	0/0	1/2	0/0	0/0	0/0	0/0	0/0
No. of vascular complications							
Acute coronary event	1/1	3/6	0/1	1/1	1/1	0/0	0/0
Cerebrovascular event	5/1	2/4	0/0	0/1	0/1	0/0	0/0
Renal artery complications	0/1	0/2	0/0	0/1	0/0	0/1	0/0
No. of renal complications							
Doubling of serum creatinine	0/0	1/5	0/0	0/0	0/0	0/0	0/1
End-stage renal disease	0/0	0/0	0/0	0/0	0/0	0/0	0/0
No. of events requiring hospitalization							
Atrial fibrillation	0/0	0/1	0/0	0/0	0/0	0/0	0/0
Hypertensive crisis	2/4	9/9	0/0	0/0	3/3	0/0	0/0
Heart failure	0/0	3/9	0/0	0/0	0/0	0/0	0/0

CON, control group; RDN, renal denervation group.

reporting (21). Secondly, the earlier reviews (17–19) included the trial conducted by Pokushalov and colleagues (13) which, for reasons explained elsewhere (14), did not meet the CONSORT criteria (12) and was therefore excluded from the current review. Finally, the previous meta-analyses included only two (17) or three (18,19) randomized trials, thereby justifying the present update (22) that accounts for all published randomized clinical trials (4,6–11).

SYMPLICITY HTN-2, the first randomized clinical trial of RDN, reported impressive BP reductions adjusted for baseline and control, amounting to 33 mmHg systolic and 12 mmHg diastolic on office measurement (4). OSLO RDN represents the other end of the spectrum, with BP decreases after RDN averaging 20 mmHg systolic and 8 mmHg diastolic less in the RDN than in the control group (7). The reasons accounting for the diversity in BP responses among the seven trials probably include differences in the selection of patients, choice of the primary endpoint, technique of BP measurement, interventions in the control group, blinding and adherence of patients to medication. The Data Supplement includes an in-depth discussion of these design aspects (pp. 9–12).

Changes in background medical treatment may have played a major role in the observed BP outcomes after RDN. Although nearly all SYMPLICITY HTN-3 patients were on maximal medical therapy for at least 6 weeks before entry, 39% underwent medication changes between randomization and the 6 month endpoint (6). The same occurred in the RDN arms of most other trials (4,7–9). OSLO RDN (7) and PRAGUE-15 (8) had a peculiar design in this respect, because in the control arm antihypertensive treatment was optimized under guidance of the patients' haemodynamic condition as assessed by impedance cardiography (7) or by adding spironolactone (8). In DENERHTN, antihypertensive treatment was highly standardized and stepwise optimized in both treatment arms (9). Over follow-up, the median number of drugs increased from three to five and the proportion of patients with a high adherence rate (Morisky score 8/8) (23) increased from 63% to 73%. In OSLO RDN (7), among 65 referred patients, witnessed drug intake identified non-adherence in 20, either by normalization of the daytime ambulatory BP ($n = 19$) or by severe hypotension ($n = 1$) (7). In PRAGUE-15 (8,16), only patients with confirmed drug adherence assessed by quantitative measurement of plasma drug levels were eligible.

SYMPLICITY HTN-1 was the only study in which the completeness of RDN was assessed, albeit in an incomplete and non-randomized fashion (3).

The mean reduction in renal noradrenaline spillover was 47% (95% CI 28% to 65%) in 10 of 45 denervated patients. In SYMPLICITY HTN-3, office and ambulatory BP decreased more with a higher number of ablations and energy delivery in a four-quadrant pattern (24). SYMPLICITY HTN-3 involved 88 centres and 111 interventionists (6). Hands-on training in RDN was not permissible in the USA. Esler proposed that the typically less than complete denervation in the hands of experienced interventionists, as evident in 10 SYMPLICITY HTN-1 patients (3), was further compromised in SYMPLICITY HTN-3 by operator inexperience and lack of training and skill (32). Moreover, the renal sympathetic nerves run closer to the distal than the proximal renal arteries (25). Based on insights available at the time of the design of SYMPLICITY HTN-3, energy delivery in this trial was preferentially directed to the proximal renal artery (6).

The physiological insights underpinning ablation of the efferent and afferent renal sympathetic nerves as a treatment modality for severe hypertension developed over more than half a century (26–30). Surgical sympathectomy, applied as a treatment for severe hypertension in the 1950s, lowered BP and was life saving, but came at a cost of severe adverse events (31). SYMPLICITY HTN-1 (3) and HTN-2 (4) revived these concepts and raised high hopes, which were not confirmed by subsequent studies (6–9). They nevertheless initiated extensive research, which has changed the field of RDN as a treatment modality for hypertension. First, in all trials (4,6–11), RDN was performed with the single-electrode SYMPLICITY RF catheter (Medtronic, Mountain View, CA, USA), a device that is too imprecise and operator dependent to meet the objective of effective renal sympathetic nervous denervation. Improved multielectrode catheter designs, stabilized by an inflatable balloon or expandable basket, are currently available. In contrast to the RF approach, circumferential delivery of ultrasound energy at an adjustable depth in the renal arterial adventitia leaves the endothelium undamaged. Secondly, in all reviewed trials, patients remained on multiple drug treatment with or without RDN. Up to now, the current indication of RDN has been mainly driven by the uncertainty of the safety of the procedure at the time of SYMPLICITY HTN-1 (3) and SYMPLICITY HTN-2 (4), thus limiting the target population to patients with severe hypertension, resistant to multiple drug treatment and with no other treatment options. This meta-analysis provides evidence of the safety of the procedure and suggests the existence of a BP-lowering effect. In line with the pathophysiological evidence (32), sympathetic overactivity in hypertension, preferably in untreated patients, might become the prime indication for RDN. Furthermore, renal nerve stimulation is a way to ascertain the completeness of denervation (33) and may allow identification of the anatomical sites where lesions have to be made, thereby addressing the huge variability in the course of the renal sympathetic nerves along the renal arteries (33). Accessory renal arteries, which cannot be engaged for denervation, represent an additional anatomical constraint, so far unaccounted for in most trials (33). Short-term 6 month BP results or incomplete follow-up (34) cannot be extrapolated into durability of the BP response or the prevention of cardiovascular complications. This is particularly the case in view of a recent report describing renal reinnervation within 60 days after renal nerve ablation in an experimental model (35). The DENERHTN investigators will soon report whether or not the need to continue or intensify antihypertensive drug treatment after RDN limits the cost-effectiveness of the procedure (9). In addition, the DENERHTN results of serial computerized renal angiography at baseline and at 12 months after RDN will be important to confirm the safety of intravascular RDN.

In conclusion, all experts leading the denervation trials agree that a minority of highly selected patients experience a spectacular BP response to RDN (36,37). The future of RDN will be determined by clinical trials showing long-lasting benefit in terms of BP lowering in never-treated patients with stage I–II hypertension (2), low risk factor profile and evidence of sympathetic overactivity. Targeting these patients would exclude comorbidities and irreversible target organ damage, including stiffening of the conduit arteries and remodelling of the microcirculation. Since guidelines propose lifestyle measures in such patients for several weeks to months (2), they can be kept off medications, avoiding confounding by non-adherence and changes in drug treatment. The ethics of such trials could be further motivated by the safety of the procedure. Trials designed along these lines, perhaps stratified according to the RDN system or place of energy delivery, could definitely establish or annihilate RDN as a treatment modality in hypertension. In the meantime, RDN should only be offered to patients within a context of clinical research in highly skilled tertiary referral centres that share data with registries independent of the manufacturers (5).

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Supplementary material available online

Supplementary Tables I–V showing to be found online at http://informahealthcare.com/doi/abs/10.3109/08037051.2015.1058595.