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Hypertension

Effect of Radiofrequency-Based Renal Denervation: The Impact of Unplanned Medication Change from a Systematic Review and Meta-Analysis

Lawrence Yu-Min Liu,[1,2] Po-Lin Lin,[1] Feng-Ching Liao,[3] Shu-I Lin,[3] Wei-Ru Chiou,[4] Yih-Jer Wu[3,5] and Ying-Hsiang Lee[3,5]

Background: Catheter-based renal denervation (RDN) has emerged as a promising treatment option for hypertension. However, randomized controlled trials (RCTs) have reported conflicting results on blood pressure (BP) reduction. Patient- and procedure-related confounders have been implied as the potential sources of inconsistent BP responses. We aimed to investigated whether unplanned and frequent medication changes in RDN studies affected the BP response to RDN by conducting sensitivity and subgroup analyses, according to antihypertensive medication change rates in a meta-analysis of RCTs.

Methods: We searched the PUBMED, EMBASE, and COCHRANE databases up to May 2018. RCTs that studied the effects of RDN on hypertensive patients were included. A meta-analysis was carried out using RevMan 5.3.

Results: A total of 12 studies were included, of which four fulfilled the inclusion criteria of < 10% medication change rate in our review. Subgroup meta-analyses of the four RCTs with < 10% medication change rates showed statistically significant reductions of 6.07 mmHg and 7.12 mmHg in 24-hour and office systolic BP, respectively. The 24-hour and office diastolic BP were also reduced (mean difference = -3.89 mmHg and -4.27 mmHg, respectively). These subgroup analyses had no heterogeneity (I^2 = 0%). In contrast, the pooled analysis of the 12 studies and the subgroup analysis of eight studies with > 10% medication change rates both had a high level of heterogeneity and no significant BP reduction.

Conclusions: The effectiveness of RDN was demonstrated across a broad range of antihypertensive medications used at baseline after removing the confounder of unplanned medication changes.

Key Words: Catheter ablation • Hypertension • Renal artery

INTRODUCTION

The strategy to treat hypertension has changed in recent years,[1-3] and catheter-based renal denervation (RDN) has emerged as an innovative and promising therapeutic intervention for patients with hypertension. The first randomized controlled trial (RCT), SYMPLICITY HTN-2, demonstrated a significant reduction in office-based blood pressure (BP) in the RDN group of patients with resistant hypertension which created much enthusiasm for and expectation in the procedure.[4] However, subsequent randomized controlled RDN studies have revealed

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[1]Division of Cardiology, Department of Internal Medicine, Hsinchu MacKay Memorial Hospital; [2]Department of Medical Science & Institute of Bioinformatics and Structural Biology, National Tsing Hua University, Hsinchu; [3]Cardiovascular Center, MacKay Memorial Hospital, Taipei; [4]Division of Cardiology, Taitung MacKay Memorial Hospital, Taitung; [5]Department of Medicine, Mackay Medical College, New Taipei City, Taiwan.
Corresponding author: Dr. Ying-Hsiang Lee, Cardiovascular Center, MacKay Memorial Hospital, No. 92, Section 2, Zhongshan North Road, Taipei, Taiwan. Tel: 886-2-2543-3535; E-mail: speakerlee@gmail.com

conflicting and less favorable results. One of the more recent and larger randomized trials showed that reductions in both office and 24-hour ambulatory systolic BP at 6 months were not statistically superior in the RDN group compared to the sham-procedure group.[5] Systematic reviews of 10 RCTs also suggested that RDN had no significant effects on BP.[6]

In more recent trials involving patients with mild to moderate hypertension, RDN again demonstrated an effective reduction in systemic and diastolic BP at 3 to 6 months compared to sham-control groups.[7,8] Many patient- and procedure-related factors, such as medication adherence, presence of a sham procedure, and number of ablation treatments have been suggested to account for these study discrepancies, which seems to be supported by high heterogeneity among these trials in meta-analyses.[9] One of the most important variables that has been shown to influence these RCTs is frequent and unplanned medication adjustments during study periods. Thus, the aim of this study was to provide an updated systematic review of RCTs, with an emphasis on meta-analysis of trials with a stable medication regimen. We believe that these trials reflect the true effects of catheter-based RDN in reducing blood pressure.

METHODS

Search strategy

We conducted a comprehensive search of PUBMED, COCHRANE, and EMBASE databases from inception to May 2018, with no language restrictions (Figure 1). Controlled vocabularies supplemented with free keywords were used to search for articles on RDN. We also manually searched relevant references in articles that were identified in the screening process. The review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10]

Study selection

We included all RCTs that studied the effects of catheter-based RDN on BP in adult hypertensive patients after a follow-up of at least 1 month at the title or abstract level. We excluded RDN studies using endovascular ultrasound to focus on radiofrequency-based RDN and to maintain the homogeneity of the analysis. Articles that were published in only abstract form or that were not published in a peer-reviewed journal were excluded after a full-text assessment. There were no restrictions on the presence of a sham procedure or concurrent antihypertensive treatment. We performed subgroup analysis by dividing trials with patients who were maintained on a stable antihypertensive treatment regimen (high medication change rate vs. low medication change rate). A stable antihypertensive regimen was defined as a medication change rate < 10% or the presence of a detailed prespecified antihypertensive treatment algorithm that was provided and rigorously followed in the trial. Trials with frequent medication changes or unequal changes in numbers of drugs between two arms during follow-up and trials that did not provide the rate of medication change were excluded.

Data extraction and quality assessment

Two reviewers (PLL and LYL) extracted and collected the data independently. Disagreements or uncertainties were resolved after discussion. We recorded the following data: the trial acronym, publication year, country, control treatment, number of participants, drug adherence assessment, number of drugs at baseline and at

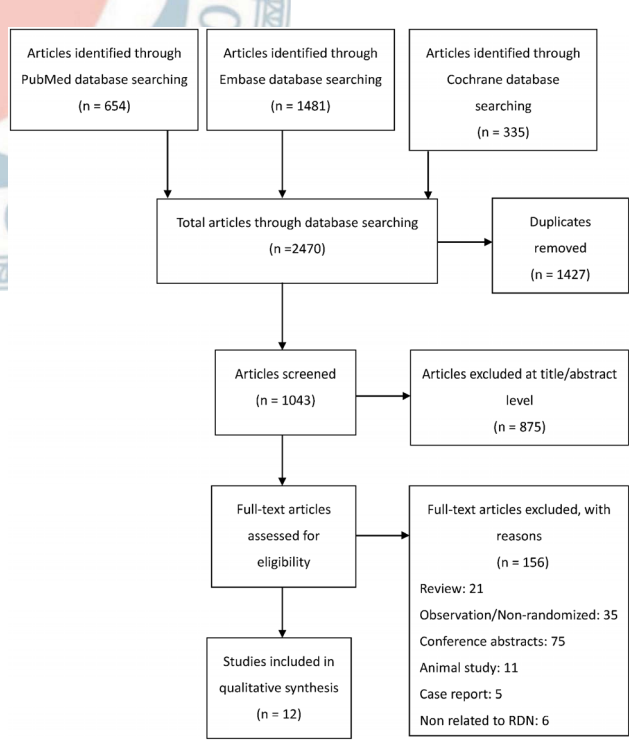

Figure 1. *Flow diagram for the study selection.*

follow-up, drug change rates, Jadad score, baseline office systolic and diastolic BP, 24-hour systolic and diastolic BP, changes in office/24-hour systolic and diastolic BP. The quality of the RCTs was assessed using the Jadad Scale.[11] The Jadad Scale is an assessment score based on the degree of participant randomization, application of the blinding method, and report of study withdrawals and dropouts. A threshold of ≥ 4 points was defined as being a high-quality study.

Statistical analysis

We conducted a meta-analysis of the included articles using Review Manager, version 5.3. We used the random effects model to pool results from the articles, accounting for variance among studies. Changes in BP were assessed by a pooled mean difference with 95% confidence interval (CI), which was estimated using the mean and standard deviation (SD). The significance of the mean difference was determined using a Z test, and a p value < 0.05 was considered to be statistically significant. We evaluated heterogeneity using a chi-square-based Q-test and the I^2 test.[12] A P_Q value < 0.05 and I^2 > 50% indicated the possibility of significant heterogeneity.[13] To address heterogeneity, we performed sensitivity analysis, in which we omitted one study at a time to evaluate the robustness of the results. We assessed potential publication bias via a funnel plot.

RESULTS

We identified 12 RCTs on RDN for our meta-analysis (Table 1 and 2). Four of the 12 RCTs met our predefined inclusion criteria for low medication change rates. Three trials had very low medication change rates (< 10%),[7,8,14] while one trial rigorously followed a clearly specified algorithm of a stepped-care antihypertensive treatment regimen (SAHHT).[15] The design of the six other studies intended to not change the antihypertensive regimens during the trials; nonetheless, the medications were still adjusted considerably due to the physicians' decisions. Sensitivity analysis revealed that heterogeneity remained low when the SYMPLICITY-FLEX study was added to the subgroup of low medication change rate (Supplementary

Table 1. Study design and patient characteristics

Study, year	Country	Control	No of participants (R/C)	Drug adherence assessment	No of drugs at baseline (R/C)	No of drugs at follow-up (R/C)	Drug change rates (R/C)	Jadad score
SYMPLICITY HTN-2, 2010	Europe, Australia, NZ	Usual drugs	106 (52/54)	Diary	5.2/5/3	-/-	33 (28.6/17.6)	3
SYMPLICITY HTN-3, 2014	USA	Sham + usual drugs	535 (364/171)	Diary	5/1/5/2	5.0/5.2	39 (38/40)	5
OSLO, 2014	Norway	Drugs	19 (9/10)	Witnessed intake	5/1/5/0	4.9/5.2	31.5 (11.1/50.0)	3
PRAGUE-15, 2015	Czech Republic	Drugs + spironolactone	106 (52/54)	Plasma drug conc.	5.1/5.4	5.0/5.6	- (-/-)	3
DENERHTN, 2015	France	SSAHT	101 (48/53)	Morisky score	3/3	5.3/5.4	- (-/-)	3
SYMPLICITY FLEX, 2015	Germany	Sham + usual drugs	71 (35/36)	Ineriew	4.4/4.3	-/-	21 (-/-)	5
SYMPLICITY HTN-JAPAN, 2015	Japan	Usual drugs	41 (22/19)	Diary	4.9/4.9	4.9/4.9	7.3 (9.1/5.3)	3
RESET, 2016	Denmark	Sham + usual drugs	69 (36/33)	Diary	4.1/4.2	4.1/4.2	39 (46/33)	5
DENERVHTA, 2016	Spain	Usual drugs + spironolactone	24 (11/13)	Haynes-Sackett test	4.3/3.9	-/-	29 (27/30)	3
SYMPATHY, 2017	Netherlands	Usual drugs	139 (95/44)	Plasma drug conc.	3.7/3.4	4.0/3.9	- (-/-)	3
SPYRAL HTN-OFF MED, 2017	Multiple	Sham only	80 (38/42)	Plasma drug conc.	92.1/88.1 (off med %)	94.3/92.7 (off med %)	- (-/-)	5
SPYRAL HTN-ON MED, 2018	Multiple	Sham + usual drugs	80 (38/42)	Plasma drug conc.	2.2/2.3	-/-	0/0	5

SSAHT, standardized stepped-care antihypertensive treatment.

Table 2. Change in office and 24-hour BP (mmHg)

Study, year	Baseline office SBP (R/C)	Baseline office DBP (R/C)	Office SBP Change at follow-up (R/C)	Office DBP change at follow-up (R/C)	Baseline 24-h SBP (R/C)	Baseline 24-h DBP (R/C)	24-h SBP change at follow-up (R/C)	24-h DBP change at follow-up (R/C)
SYMPLICITY HTN-2, 2010	178/178	97/98	-32/-1	-12/0	-/-	-/-	-11/-3	-7/-1
SYMPLICITY HTN-3, 2014	179.7/180.2	96.5/98.9	-14.3/-11.74	-6.6/-4.6	159.1/159.5	88.0/90.9	-6.75/-4.79	-4.1/-3.1
OSLO, 2014	156/160	91/88	-8/-28	-2.8/-10.8	152/152	93/88	-10/-19	-7/-11
PRAGUE-15, 2015	159/155	92/89	-12.4/-14.3	-7.4/-7.3	149/147	86/84	-3.7/-2.6	-5.7/-4.5
DENERHTN, 2015	159.3/155.9	93.9/91.4	-15.1/-9.5	-9.1/-6.0	151.6/146.8	90.2/88.8	-15.4/-9.5	-9.7/-6.6
SYMPLICITY FLEX, 2015	-/-	-/-	-/-	-/-	140.2/140.4	78.2/80.6	-7.0/-3.5	-2.8/-2.1
SYMPLICITY HTN-JAPAN, 2015	181.0/178.7	-/-	-16.6/-7.9	-5.9/1.0	164.7/163.3	-/-	-7.5/-1.3	-4.2/-0.4
RESET, 2016	160/166	95/90	-/-	-/-	152/153	91/89	-3.7/-2.6	-1.7/-2.6
HENERVHTN, 2016	168/171.2	89.6/90.2	-17.5/-29.4	-7.5/-12.7	149.2/155.4	81.3/80.9	-5.7/-23.6	-3.7/-10.2
SYMPATHY, 2017	170.3/164.7	96.1/94.4	-7.5/0.7	-4.4/0.9	157.3/155.8	90/91.4	-5.6/-6.6	-3.5/-3.9
SPYRAL HTN-OFF MED, 2017	162/161.4	99.9/101.5	-10/-2.3	-5.3/-0.3	153.4/151.6	99.1/98.7	-5.5/-0.5	-4.8/-0.4
SPYRAL HTN-ON MED, 2018	164.6/163.1	99.6/102.3	-9.4/-2.6	-5.2/-1.7	151.9/151.1	96.9/97.6	-9.0/-1.6	-6.0/-1.9

DBP, diastolic blood pressure; SBP, systolic blood pressure.

data). However, we did not consider increasing the cut-off level for low medication change rates because the authors reported that the changes in antihypertensive medication in the SYMPLICITY-FLEX study significantly changed the results.[16]

The meta-analysis of the four RCTs with low medication change rates showed that RDN resulted in a significant reduction in office systolic BP of 7.12 mmHg (95% CIs) -10.77 to -3.47 mmHg, p = 0.0001, n = 145 vs. 153 patients for RDN vs. control, respectively, Figure 2). A smaller but similarly significant reduction in 24-hour systolic BP was also observed (mean difference = -6.07 mmHg; 95% CI: -8.68–-3.46 mmHg; p < 0.00001, n = 141 vs. 144 patients for RDN vs. control, respectively, Figure 3). Both meta-analyses had an I^2 of 0%, indicating very low heterogeneity and a homogenous pool of patients in these selected trials. In contrast, the level of heterogeneity increased greatly and the reduction in systolic BP became insignificant when all of the RCTs or trials with high medication change rates were included.

For changes in diastolic BP, our meta-analysis showed a significant reduction in both 24-hour and office diastolic BP in the RDN group (MD = -3.89 mmHg; 95% CI: -5.56–-2.23 mmHg; p < 0.00001, and MD = -4.27 mmHg; 95% CI: -6.28–-2.27 mmHg; p < 0.0001, respectively, Figure 4 and 5), and there was also no heterogeneity in this

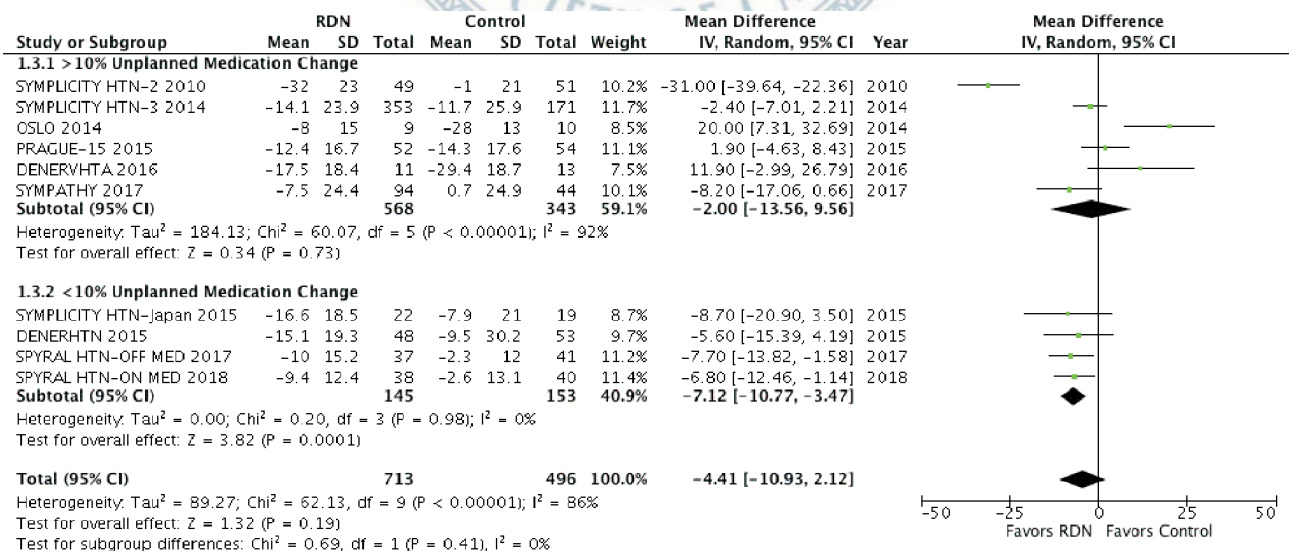

Figure 2. *Forest plot for mean difference in office SBP at 3-6 months follow-up. CI, confidence interval.*

pooled analysis (I^2 = 0%). When all of the RCTs were included, RDN had no effect on either the office or 24-hour diastolic BP.

We collected and pooled the BP changes at 6 months after randomization for our meta-analysis, except for the SPYRAL HTN-OFF study in which only BP changes at 3 months were available. Previous studies have shown that office and ambulatory 24-hour BP reduction in RDN tended to increase from baseline to 6 months. We performed sensitivity analysis by removing the SPYRAL HTN-OFF study, but this did not change the results of the meta-analysis. Thus, it was reasonable to combine BP changes at 3 or 6 months from these RDN trials for the purpose of determining its positive effect on BP pressure reduction.

DISCUSSION

The concept of reducing elevated sympathetic ner-

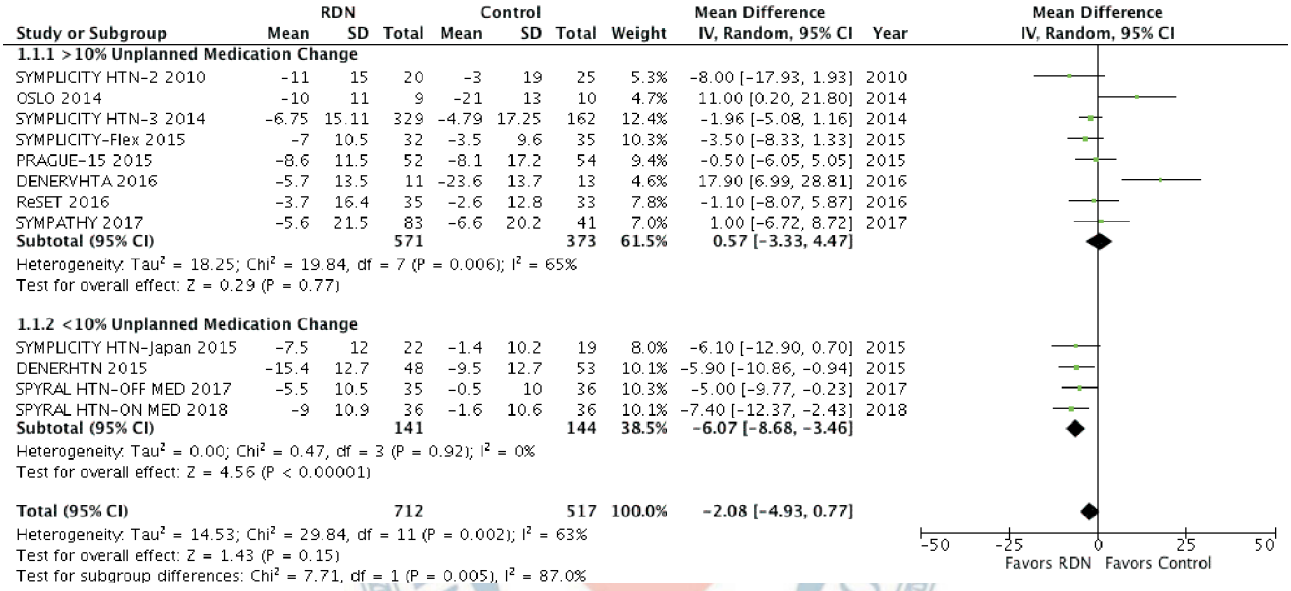

Figure 3. *Forest plot for mean difference in 24-hour SBP at 3-6 months follow-up. CI, confidence interval.*

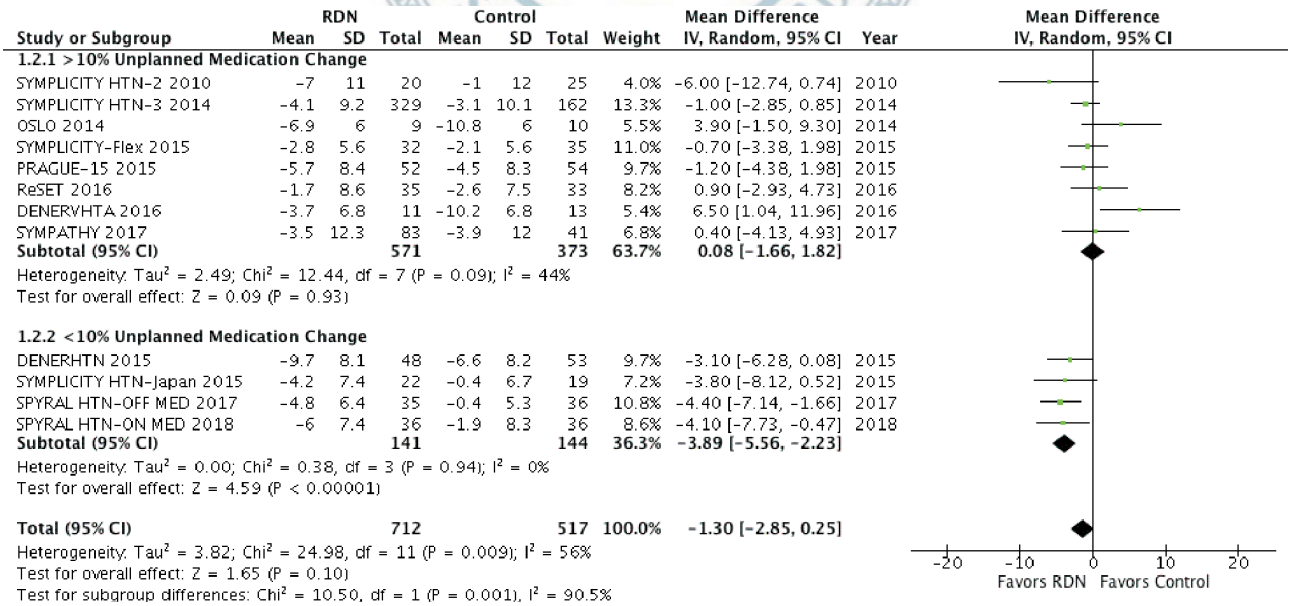

Figure 4. *Forest plot for mean difference in 24-hour DBP at 3-6 months follow-up.*

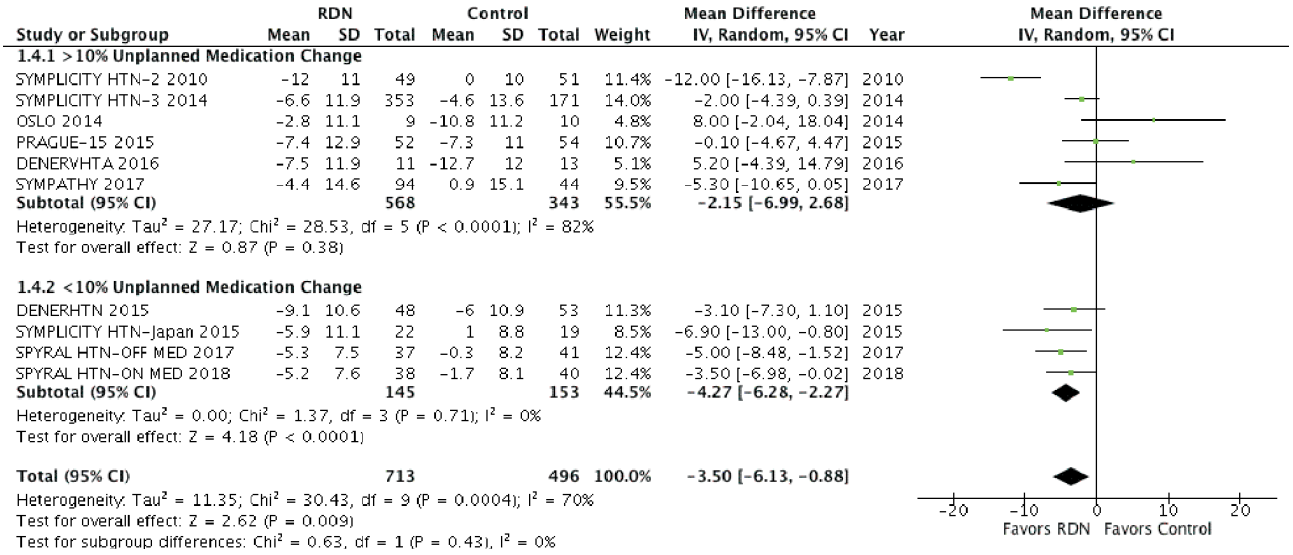

Figure 5. *Forest plot for mean difference in office DBP at 3-6 months follow-up.*

vous system activity to treat the increasing number of patients with hypertensive was suggested as early as the 1930s by performing surgical sympathectomy.[17] However, it only became a feasible and promising therapeutic option when catheter-based RDN offered a less invasive and safer route. By ablating the renal nerves that course through the renal artery adventitia using low-power radiofrequency energy, catheter-based RDN can lower BP by decreasing renal norepinephrine spillover, thereby increasing renal plasma flow and reducing elevated muscle sympathetic-nerve firing activities.[18] Early RDN clinical trials such as SYMPLICITY HTN-1 and SYMPLICITY HTN-2 showed robust BP reductions and the overall safety of this intervention.[4,19] However, enthusiasm for this procedure was quickly dampened when the SYMPLICITY HTN-3 trial did not demonstrate the effectiveness of RDN compared with a sham control.[5]

SYMPLICITY HTN-3 was the first large RCT to include a sham control, and a total of 535 patients were enrolled in 88 centers. The trial showed similar reductions in both the intervention group and the sham-controlled group. Subsequent smaller RCTs with and without sham control groups and several meta-analyses also did not support the potential benefits of this new technique in treating hypertension. Placebo effects of sham control, improved drug adherence in initially poorly adherent patients (Hawthorne effect), and technical variabilities in operators and devices have all been suggested to be potential confounding factors that may have led to the substantial differences in the trials.[6] With the complexity of hypertension management and involvement of this novel procedure, it is difficult to determine the true effect of RDN.

Drug adherence is one of the important factors that may have confounded the results of the previous RDN trials.[20] Eighty percent of the patients in the SYMPATHY trial were either poorly adherent or completely nonadherent, and the BP reduction effect was clearly greater when only patients with stable medication adherence were considered.[21] However, the DENERHTN trial found that the BP-lowering effects of RDN were not biased by a high rate (50%) of medication non-adherence.[15] The unpredictable effect of drug non-adherence on the trial results led to the suggestion that patients should be screened for non-adherence to antihypertensive treatment prior to consideration of RDN.

We believe that inappropriate and frequent medication changes can have a significant and often overlooked impact on an otherwise well-conducted randomized trial. Our meta-analysis is the latest study to evaluate the true efficacy of RDN by studying RCTs with few changes in medications or with strict adherence to trial protocols. SYMPLICITY-HTN Japan had very low medication change rates of 9.1% and 5.3% in the RDN and control groups, respectively. In SPYRAL HTN-OFF MED, 94.3% of the patients in the RDN group and 92.7% in the sham-control group had no antihypertensive medications detected at 3 months. In contrast, as many as 40% of pa-

tients in both arms of the SYMPLICITY-HTN 3 trial had medication changes at the end of the trial. In the other two RCTs with sham-control groups, both had medication change rates > 20%. The high rates of medication changes in the RCTs reflects the challenges clinicians face in treating patients with resistant hypertension. We also included the DENERHTN trial, even though the number of medications was significantly yet similarly increased during the trial. Prespecified types and doses of antihypertensive medications were added at fixed times if indicated and stated beforehand. As a result, our subgroup meta-analysis revealed a very homogenous population in these four trials. Our findings highlight the importance of a stable antihypertensive regimen in RDN trials, and future studies should aim to mitigate this effect.

Our study showed that 24-hour systolic and diastolic BP were substantially reduced in the RDN group when medication changes were considered. 24-hour ambulatory BP monitoring is considered to be a more effective and preferred method to reduce bias than the more invasive sham-control procedure.[6] Similar findings and greater BP reductions were again observed in office systolic and diastolic BP measurements. Removing one trial at a time did not change the positive results of our analyses (data not shown). Thus, RDN had a good efficacy in BP reduction in the patients with mild to moderate or resistant hypertension. This is in contrast to the findings reported in the SYMPLICITY-FLEX study in which RDN had no effect in patients with mildly resistant hypertension.[16] Interestingly, the SYMPLICITY-FLEX study did show a significant reduction in ambulatory systolic BP when the patients who actually had successful RDN were considered in the per-protocol analysis.

In the current study, we specifically examined the impact of inappropriate and frequent medication changes during the trials and attempted to reveal the true effect of RDN on BP by only including trials with adequate design and validity. Our pooled results yielded similar values of BP reduction as in the SPYRAL HTN-OFF MED trial in both office and 24-hour systolic and diastolic BP. These values reflected the true biological effect of RDN in the treatment of hypertension. However, our study has several limitations. The SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED trials used a multielectrode catheter and a significantly greater number of ablations were performed in each patient compared to the other trials. These differences in technical variabilities and study designs have been extensively discussed and are considered to account for the inconsistent results in RDN-related studies. Our meta-analysis had 0% heterogeneity, which implies that a high medication change rate was a major confounding factor. We pooled data at different follow-up times since only BP measurements at 3 months were available in the SPYRAL HTN-OFF MED trial due to ethical and safety reasons. The SYMPLICITY HTN-1 trial reported that a significant BP reduction was observed by 1 month and sustained for 3 years in patients with resistant hypertension. Several RCTs have also shown either a progressive decrease in BP from baseline to 6 months or similar BP reductions at 3 and 6 months in the RDN group.[4,15,22] Lastly, the four pooled studies were small and lacked longer outcomes.

CONCLUSIONS

Our meta-analysis supports the hypothesis that a significant reduction in office and 24-hour BP can be achieved 3 to 6 months after successful RDN in patients with hypertension. Removing the confounder of frequent and unplanned medication changes within RCTs, which compromised trial validity, the true effect of catheter-based RDN was revealed. Furthermore, the significant pooled effects from the four individual RCTs suggest that a wider range of patient subgroups may be eligible for RDN in the future.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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SUPPLEMENT

Supplementary data. Sensitivity analysis of heterogeneity on 24-h SBP

Studies included	Studies (N)	IV 95% CI	p	I^2
All studies	12	-2.08 (-4.93,0.77)	0.15	63
Studies with change rate < 35%*	8	-2.29 (-6.73, 2.15)	0.31	74
Studies with change rate < 30%[#]	6	-3.24 (-7.7, 1.22)	0.15	73
Studies with change rate < 25%[†]	5	-5.49 (-7.79, -3.2)	< 0.00001	0
Studies with change rate < 10%[‡]	4	-6.07 (-8.68, -3.46)	< 0.00001	0

* Included studies: SYMPLICITY HTN-2 [1], OSLO [19], DENERVHTA, SYMPLICITY FLEX [18], DENERHTN [12], SYMPLICITY HTN-JAPAN [11], SPYRAL HTN-OFF MED [4], SPYRAL HTN-ON MED [5]. [#] Included studies: DENERVHTA, SYMPLICITY FLEX [18], DENERHTN [12], SYMPLICITY HTN-JAPAN [11], SPYRAL HTN-OFF MED [4], SPYRAL HTN-ON MED [5]. [†] Included studies: SYMPLICITY FLEX [18], DENERHTN [12], SYMPLICITY HTN-JAPAN [11], SPYRAL HTN-OFF MED [4], SPYRAL HTN-ON MED [5]. [‡] Included studies: DENERHTN [12], SYMPLICITY HTN-JAPAN [11], SPYRAL HTN-OFF MED [4], SPYRAL HTN-ON MED [5].
N, number; IV 95% CI were calculated by RevMan 5.3