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Efficacy of Renal Denervation With and Without Antihypertensives In Patients With Resistant Hypertension: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Resistant hypertension presents a clinical challenge. The efficacy of renal denervation (RDN) as a potential treatment has conflicting data. Multiple randomized controlled trials have been conducted to assess the impact of RDN.

Methods: We performed systematic search of the PubMed and EMBASE from inception to April 2024 to identify studies comparing various interventions for resistant hypertension. We employed a frequentist network meta-analysis model, utilizing the *net-meta* module and applying a random effects model in CRAN-R software.

Results: Data of 2553 patients from 20 RCTs was analyzed. Standard mean differences (SMDs) for diastolic blood pressure (DBP) and systolic blood pressure (SBP) were assessed at different time points, including daytime, nighttime, over 24 hours, and during office visits. Our results demonstrate an improvement in various BP parameters when comparing RDN with sham: daytime DBP (3.46, 95%CI: [1.89-5.02], P < 0.0001), nighttime SBP(2.87, 95%CI: [1.43-4.31], P < 0.0001), 24-hour SBP (2.82, 95%CI: [1.24-4.41], P = 0.001), and in-office DBP (2.70, 95%CI: [1.04-4.36], P = 0.002). However, no statistically significant difference was found in daytime SBP (3.60, 95% CI: [-0.67-7.87], P = 0.10), nighttime DBP (1.65, 95% CI: [-0.57-3.86], P = 0.15) and in-office SBP (3.89, 95% CI: [-10.07-17.86], P = 0.60) and in 24-hour DBP.

Conclusion: Our study supports the efficacy of RDN, when combined with antihypertensive treatment when compared to sham treatment, in the management of resistant hypertension.

Keywords: Renal Denervation; Resistant Hypertension; Meta-analysis; Intervention.

INTRODUCTION

Hypertension is a significant global risk factor for cardiovascular disease and mortality [1].While most patients can effectively manage their blood pressure through lifestyle adjustments and antihypertensive medications, there exists a subset of patients with resistant hypertension. Resistant hypertension is defined as uncontrolled blood pressure

despite the use of three or more antihypertensive drugs, including a diuretic [2]. In the US, this condition affects an estimated 12.8% of individuals and substantially increases the risk of target organ damage, cardiovascular events, and mortality [3]. Consequently, there is a pressing need for innovative therapeutic approaches. Catheter-based renal denervation (RDN) has emerged as a promising solution for resistant hypertension [4]. Renal sympathetic nerves contribute significantly to hypertension by influencing sodium retention, renin release, and renal blood flow [5]. Ablating these nerves via endovascular radiofrequency energy delivery offers a novel approach to reducing sympathetic nervous system over activity. Renal denervation has demonstrated to be an effective non-pharmacological treatment for resistant and uncontrolled hypertension in the presence or absence of concomitant antihypertensive therapy [6,8]. However, there have been conflicting results regarding the efficacy of renal denervation in resistant hypertension. Initial studies and registries have reported substantial reductions in in-office blood pressure, reductions typically averaging 25-30 mmHg [2]. Nevertheless, the Symplicity HTN-3 trial, a blinded sham-controlled study, did not demonstrate a significant advantage of RDN over placebo, possibly due to variations in denervation techniques and patient medication compliance [9].Recent sham-controlled trials have addressed the Symplicity HTN-3 trial limitations and demonstrated that RDN reduces 24-hour ambulatory systolic blood pressure by approximately 5-10 mmHg compared to a sham procedure, both with and without antihypertensive medications [10,11]. Therefore, RDN may complement medication therapy for resistant hypertension. Herein, we performed a comprehensive systematic review and updated network meta-analysis to compare the effectiveness of medical therapy, RDN, and their combination in managing resistant hypertension.

METHODS

The search strategy and methodology of our systematic review and network meta-analysis is consistent with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The checklist of these guidelines is shown in Supplemental S1. The methodological quality was assessed using the Assessing the methodological quality of systematic reviews-2 (AMSTAR-2) guidelines checklist. These are reported under Supplemental S2. This review was not registered.

Inclusion criteria for meta-analysis included papers in which patients between 18-80 years of age were diagnosed with resistant hypertension, with (1) In-office SBP from 140-180 mmHg despite a maximum tolerated dose of 3 or more different-class antihypertensive. (2) In-office DBP of at least 90 mmHg or higher. (3) 24-hour SBP 140-170 mmHg. (4) Mean daytime SBP 135-149 mmHg or DBP 90-94mmHg and (5) Stable renal artery anatomy on CT angiogram, magnetic resonance angiogram, or renal angiogram within the previous year. Exclusion criteria for meta-analysis included patients with: (1) Stable or unstable angina or myocardial infarction within the prior 3 months, history of heart failure, atrial fibrillation, transient ischemic attack, or cerebrovascular accident. (2) Renal artery anatomy ineligible for treatment. (3) Renal artery stenting within 3 months. (4) >50% stenosis in a treatable vessel. (5) Presence of fibromuscular dysplasia. (6) Previous renal denervation. (7) Secondary hypertension (Cushing disease, pheochromocytoma, hyperthyroidism, or aldosteronism, etc). (8) Severe renal artery stenosis (diameter less than 4mm). (9) Patients with eGFR<40 mL/min/1.73m2. (10) Pre-randomization serum potassium level at least- 5.5 mmol/l (11) Change in BP medication within 4 weeks from randomization. (12) pregnancy or (13) Comorbidities with limited life expectancy. Patients were required to discontinue prior use of antihypertensives for at least 4 weeks.

Additionally, we excluded case reports, case series, and review articles. A literature search was conducted using the MEDLINE Portal (PubMed and EMBASE utilizing a systematic

search strategy by PRISMA mentioned previously for randomized clinical trials and observational studies until April 2024. The search was performed using titles and keywords utilizing Boolean Operators "OR" and "AND" for terms including: "Renal Denervation", "Antihypertensives", or "Resistant Hypertension". The detailed strategy is given in Supplemental S3.

Study Selection:

Our study selection included randomized clinical trials, pilot trials, prospective and retrospective observational studies that met our inclusion criteria. Authors screened the articles and any potential full-text article that met the screening requirements, was reviewed again as part of the second phase of screening for evaluation of the outcome of interest. The data screening was then reviewed by another author.

Data Collection and Statistical Analysis:

The data and baseline characteristics were arranged in binary outcome format for discrete variables and continuous outcomes for continuous variables using Microsoft Excel software. Baseline characteristics and data included age, gender, race, BMI, smoking, diabetes mellitus, dyslipidemia, stroke/cardiovascular disease, obstructive sleep apnea, peripheral arterial disease, coronary artery disease, in-office systolic and diastolic blood pressure, 24-hour systolic and diastolic blood pressure, morning systolic and diastolic blood pressure, daytime systolic and diastolic blood pressure, nighttime systolic and diastolic blood pressure, in-office heart rate, 24-hour heart rate, duration of hypertension, use of antihypertensive medications (including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin blockers, beta-blockers, calcium channel blockers, diuretics, vasodilators, alpha 1 blockers, or centrally acting sympatholytic), serum creatinine, and estimated GFR. Data collection also included the type of blinding in the study design, country of study conduction, and duration of follow-up in study populations.

The outcomes studied were divided into primary and secondary outcomes. Primary outcomes included mean change in in-office blood pressure, along with, 24-hour, morning, daytime, and nighttime systolic and diastolic blood pressure at 3-6 months from baseline with RDN in comparison to either antihypertensives alone or sham. While secondary outcomes included mean change in in-office, 24-hour, morning, daytime, and nighttime systolic and diastolic blood pressure at 6-12 months from baseline with RDN compared to antihypertensives combined with either sham or RDN alone. Treatments were divided into the following categories:

1) Renal Denervation and Anti-hypertensive medication

2) Sham and Anti-hypertensive medication

3) Anti-hypertensive medication

4) Renal Denervation

25) Sham

We report the mean with standard deviations (SD) for baseline characteristics and study outcomes as extracted from the included clinical studies and randomized clinical trials. Statistical analysis was conducted by CRAN-R software (The R Foundation for Statistical Computing, Vienna, Austria). A *netmeta* module was used along with the random-effects model to pool the pre-calculated standard mean differences (SMD) along with standard errors (SE) with a probability value of $p < 0.05$ considered to be statistically significant. The overall net graph for this was also reported. Outcomes were reported as standard mean difference (SMD) with 95% confidence interval (CI). Since sham was used as a reference against which the efficacies of all other strategies were compared, it was given an RR (Risk Ratio) of 0.00. Treatments were ranked based on p values from a *netrank* module. We also did pairwise comparisons of treatment nodes using inverse variance and DerSimonian-Laird method to estimate between study variance [12]. Higgins I-squared (I^2) was determined

as a measure of statistical heterogeneity where values of ≤ 50% corresponded to low to moderate heterogeneity while values ≥75% indicated high heterogeneity. The potential inconsistencies between the direct and indirect evidence within the network were evaluated by using the design by treatment approach. Assessment of global inconsistencies was done using a generalized Cochran's Q statistic and local inconsistencies by using the "separate the indirect from direct design evidence' approach. [13] Publication bias was assessed by visually inspecting a funnel plot and mathematically using the Egger's test. The quality assessment for the included studies was performed using Cochrane Risk of Bias for the randomized clinical trials[14].

RESULTS:

Study Selection, trial characteristics, and quality assessment

An initial search of the PubMed/Medline and Embase databases yielded a total of 948 articles (PubMed: 191, Embase: 757). After exclusion based on the title, abstract and full text, a total of 20 randomized clinical trials (RCTs) were deemed eligible for inclusion in our meta-analysis. [6- 9, 15–30] (Figure 1). The studies varied in sample size, experimental design, patients' characteristics, and follow-up duration. (Reported in Table 1 and Supplementary 4) The follow-up duration in most of the included studies was 6 months while in other studies it ranged from 2 to 36 months. The net graph is shown in Figure 2 which is well connected. The results of this meta-analysis are presented as detailed forest plots (Figure 1-8 in Supplementary S4 3A and 3B) and funnel plots with Egger's p test values (Supplemental S5). Three of the studies were given a full text review but not included in the trial as two of them compared types of renal denervation with each other [31, 32] and one of them had no comparison group [33].

Daytime Systolic Blood Pressure: Our pooled analysis demonstrated that there was no statistically significant difference in SBP among group 1 patients undergoing RDN and antihypertensives (3.60, 95% CI: [-0.67-7.87], P = 0.10), in group 2 patients undergoing sham and antihypertensives (-2.93, 95%CI: [-7.72-1.86], P = 0.23) and group 3 patients with antihypertensives (-1.49, 95%CI: [-4.72-1.73], P = 0.37). There was significant reduction in daytime SBP in group 4 patients undergoing renal denervation alone (4.78, 95%CI: [3.10-6.47], P < 0.0001). There was a significantly high heterogeneity (I2 = 96.8%) across these studies.

Daytime Diastolic Blood pressure: Our analysis showed a substantial reduction in daytime DBP among group 1 patients (3.90, 95% CI: [0.58-7.22], P = 0.02), and group 4 patients (3.46, 95%CI: [1.89-5.02], P < 0.0001) compared to group 2 (1.41, 95%CI: [-2.30-5.13], P = 0.46),group 3 (0.42, 95%CI: [-2.16-2.99], P = 0.75), and group 5 patients (0.00) A significantly high heterogeneity (I2 = 95.4%) was found across these studies.

Nighttime Systolic Blood Pressure: Our analysis showed a statistically significant decrease in nighttime SBP among group 1 patients (5.31, 95% CI: [1.57-9.04], P = 0.005), and group 4 patients (2.87, 95%CI: [1.43-4.31], P < 0.0001), in comparison to group 2 (2.80, 95%CI: [-1.49-7.10], P = 0.20), group 3 (-0.30, 95%CI: [-3.15-2.55], P = 0.84), group 5 patients (0.00). We found a significantly high heterogeneity (I2 = 93.2%) across these studies.

Nighttime Diastolic Blood Pressure: Our analysis showed a statistically significant decrease in nighttime DBP among group 1 patients (4.78, 95% CI: [0.21-9.34], P = 0.04) compared to group 2 patients (2.74, 95%CI: [-2.42-7.90], P = 0.30), group 3 (-0.10, 95%CI: [-3.63-3.44], P = 0.96), group 4 (1.65, 95%CI: [-0.57-3.87], P = 0.20), and group 5

patients (0.00). There was a significantly high heterogeneity (I2 = 97.4%) across these studies.

24-hour Systolic Blood Pressure: Our analysis demonstrated a statistically significant reduction in 24-hour SBP among group 1 patients (5.67, 95% CI: [1.67-9.68], P = 0.006), and group 4 patients (2.82, 95%CI: [1.24-4.41], P = 0.001). However, no statistical difference in group 2 (-0.65, 95%CI: [-5.12-3.81], P = 0.78), group 3 (0.63, 95%CI: [-2.45-3.70], P = 0.69), and group 5 patients (0.00). There was a significantly high heterogeneity (I2 = 96.2%) across these studies.

24-hour Diastolic Blood Pressure: Our analysis demonstrated a statistically significant decrease in 24-hour DBP among group 1 (5.88, 95% CI: [3.02-8.74], P < 0.0001), group 2 (4.24, 95%CI: [0.97-7.51], P = 0.011), and group 3 patients (2.31, 95%CI: [0.10-4.52], P = 0.04). There was no statistically difference found in group 4 (0.68, 95%CI: [-0.41-1.78], P = 0.22), and group 5 patients (0.00). A significantly high heterogeneity (I2 = 97.1%) was found across these studies.

In-office Systolic Blood Pressure: Our analysis revealed no statistically significant change in in-office SBP among group 1 (3.89, 95% CI: [-10.07-17.86], P = 0.60), group 2 (-1.02, 95%CI: [-17.80-15.74], P = 0.91), group 3 (-2.99, 95%CI: [-13.97-8.00], P = 0.59), and group 5 patients (0.00). However, there is statistically significant reduction in in-office SBP in group 4 patients (6.09, 95%CI: [0.20-11.98], P = 0.04). There was significantly high heterogeneity (I2 = 99.7%) across these studies.

In-office Diastolic Blood Pressure: Our analysis also revealed a statistically significant decrease in in-office DBP among group 1 (4.95, 95% CI: [0.63-9.28], P = 0.03), and group 4 patients (2.70, 95%CI: [1.04-4.36], P = 0.002) compared to group 2 (1.54, 95%CI: [-

3.63-6.70], P = 0.56), group 3 (0.98, 95%CI: [-2.35-4.31], P = 0.56), and group 5 patients (0.00). There was significantly high heterogeneity (I2 = 98.3%) across these studies.

High heterogeneity was observed across all outcomes. This could be explained by the different types of renal denervation used, the difference in follow up duration and the difference in antihypertensive medication regimen and dose.

The risk of bias assessment for included trials is given in Supplemental S6. Furthermore, we included pairwise comparisons of treatment groups in Supplemental S7. The graphs of Figure 4 show outcomes of pairwise comparison of RDN with sham and of RDN and antihypertensives with sham and antihypertensives. In the comparison of renal denervation and antihypertensive versus sham and anti-hypertensive , the SMD was 1.53(95% CI: 0.63 to 2.42) for 24 hour DBP, 6.59 (95% CI: 2.61 to 10.6) for 24 hour SBP and 2.35 (95% CI: 1.01 to 3.70) for daytime DBP. However, in most of pairwise comparisons heterogeneity was high. The direct and indirect estimates of assessed outcomes are shown in Supplemental S8.

Moreover, the p- score ranking of treatment groups in all outcomes is depicted in bar charts in Supplemental S9. The treatment group of renal denervation and antihypertensive medication ranked highest in 24 hour DBP, 24 hour SBP, nighttime DBP, daytime DBP, office DBP and nighttime SBP. The results of Higgin's I squared for heterogeneity are given in Supplemental S10.

DISCUSSION

The management of resistant hypertension remains a challenge in clinical practice, and various therapeutic interventions have been explored to achieve better blood pressure control.[34] Among these interventions, RDN has emerged as a potential treatment option.[35]

This network meta-analysis aimed to systematically evaluate the efficacy of RDN, employed alone in conjunction with antihypertensive medications, in patients with resistant hypertension.

A previous meta-analysis compares RDN with anti-hypertensives and has concluded that RDN is a superior in blood pressure reduction. [36] Another recent meta-analysis has compared RDN with sham procedure and its finding revealed that RDN reduced ambulatory blood pressure and daytime systolic blood pressure significantly. [37] Although earlier meta-analyses have been published on this objective,[38] we utilized a *netmeta* module to provide more definitive results with more inclusive treatment categories. Our meta-analysis includes the comparison of RDN and antihypertensive combination compared to RDN or antihypertensives alone, upon which pooled effect from different trials has not been compared before.

Our findings revealed several significant findings in blood pressure measurements and outcomes with an RDN alone and with a combination of RDN and antihypertensive medications. These statistically significant reductions underscore the potential clinical significance of RDN as an adjunctive therapy for resistant hypertension.

A significant reduction in daytime DBP suggests that treatment with both RDN alone and as an adjunctive therapy to anti-hypertensives leads to better control of DBP during waking hours. However the daytime SBP was found to be significantly reduced with RDN alone. This improvement translates into a reduced risk of cardiovascular events and target organ damage associated with hypertension.[39] Additionally, nighttime hypertension is a known risk factor for adverse cardiovascular outcomes [40] and our analysis revealed a substantial reduction in nighttime SBP and DBP with the adjunctive treatment of RDN and

antihypertensive therapy. This finding is particularly noteworthy as it addresses the need for effective nighttime blood pressure management in patients with resistant hypertension. Furthermore, 24-hour systolic and diastolic blood pressure showed reductions with the adjunctive treatment of RDN and anti-hypertensives. These findings underscore the sustained efficacy of RDN and anti-hypertensives over a day, potentially mitigating the risks associated with fluctuations in blood pressure levels.[41] Additionally, RDN and anti-hypertensives demonstrated a substantial reduction in-office SBP and DBP. Our results suggest that RDN, in conjunction with antihypertensive therapy, can lead to improved blood pressure control during healthcare visits, which may enhance patient compliance and satisfaction. [42]

The findings of this network meta-analysis provide robust evidence supporting the efficacy of RDN in conjunction with antihypertensive treatment for the management of resistant hypertension. The significant reductions in blood pressure observed throughout the day, including daytime, nighttime, 24-hour monitoring, and in-office measurements, suggest that RDN when combined with antihypertensive medications, offers a promising approach to managing resistant hypertension. These results are consistent with a growing body of research that underscores the potential of RDN as a valuable adjunctive therapy in this challenging clinical scenario, especially for patients who struggle to achieve blood pressure control with conventional treatments. However, it is crucial to interpret these findings with a consideration of certain limitations.

Firstly, as this is a study-level meta-analysis, addressing individual confounding was difficult due to the lack of patient-specific data. Secondly, there was notable variance in the duration of the follow-up period across the included studies, which may have contributed to the observed heterogeneity in our analysis.

Furthermore, individual patient characteristics, diverse medication regimens, and long-term safety considerations necessitate further investigation. Variability in patient responses, potential adverse effects, and the durability of the observed blood pressure reductions should be carefully evaluated. The included trials have compared anti-hypertensives with RDN but the number, dosage and type of anti-hypertensive medication is not entirely same. A personalized approach considering these factors is essential when considering RDN as a therapeutic option for patients with resistant hypertension. Further research, including long-term follow-up and assessment of safety and adverse events, is warranted to establish the role of RDN definitively in the management of resistant hypertension, and clinical trials are needed to validate these findings and provide comprehensive guidance for clinicians managing patients with resistant hypertension.

In conclusion, Clinical trials demonstrating long-term effects in decreasing blood pressure in individuals with stage I–II hypertension who have never received treatment, a modest risk factor profile, and sympathetic over-activity will further determine the future of RDN.[43] By focusing on these individuals, comorbidities and irreversible target organ damage—such as conduit artery stiffness and microcirculation remodeling—would be eliminated. The patients can be maintained off pharmaceuticals, preventing ambiguity from non-adherence and changes in drug therapy, because current guidelines suggest lifestyle interventions for these patients for a few weeks to months[41]. The procedure's safety may provide another justification for the ethics of these experiments. Such trials, potentially stratified by the RDN system or energy delivery site, might establish or eliminate RDN as a method for treating resistant hypertension.

CONCLUSION

The results of our study revealed that RDN in combination with antihypertensive medications can be used in the management of resistant hypertension. Our network meta-analysis demonstrated substantial evidence supporting the efficacy of RDN, when combined with antihypertensive treatment, with significant reduction in both systolic and diastolic blood pressure measurements at different time points. These findings align with the recent research highlighting the role of RDN as a potential adjuvant therapy option in patients with resistant hypertension. Patients who have struggled to achieve adequate blood pressure control with conventional treatments may particularly benefit from this approach. However, individual patient characteristics, medication regimens, and long-term safety considerations warrant further investigation. Further research and clinical trials are needed to validate these findings.

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None

Conflict of interest

All authors have nothing to declare.

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Figure 1: PRISMA Flow Chart

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of number of systematic search results and process of screening and study selection

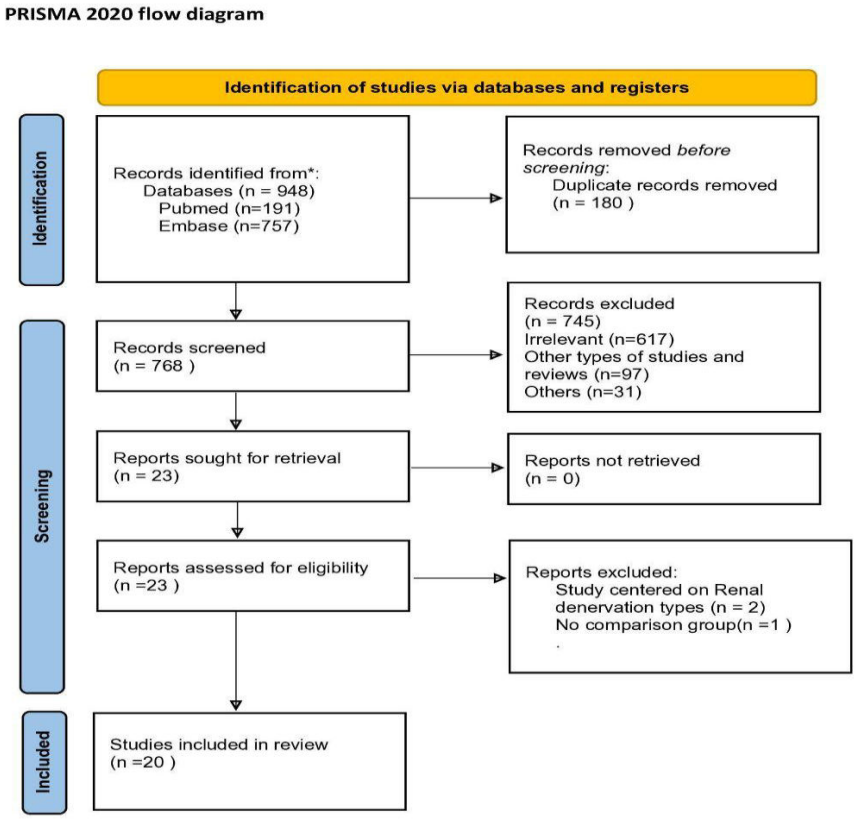


Figure 2: Net Diagram

Figure 2 shows a network diagram to show the connection and strength of direct evidence in our outcomes. The width of the edges correspond to the strength of the direct evidence (estimated by number of studies) between the treatment modalities which are represented by nodes.

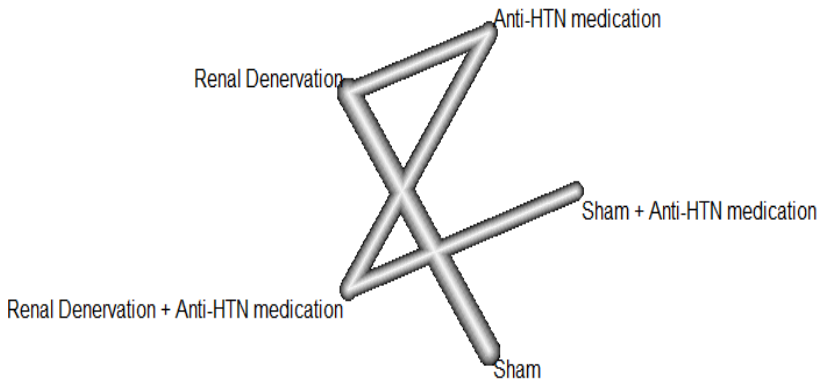


Figure 3: Outcomes of renal denervation and antihypertensives in patients with resistant hypertension

Fig 3A: Forest plots showing diastolic blood pressure outcomes (DBP= diastolic blood pressure, SMD=standardized mean difference, HTN= hypertension, CI=confidence interval)

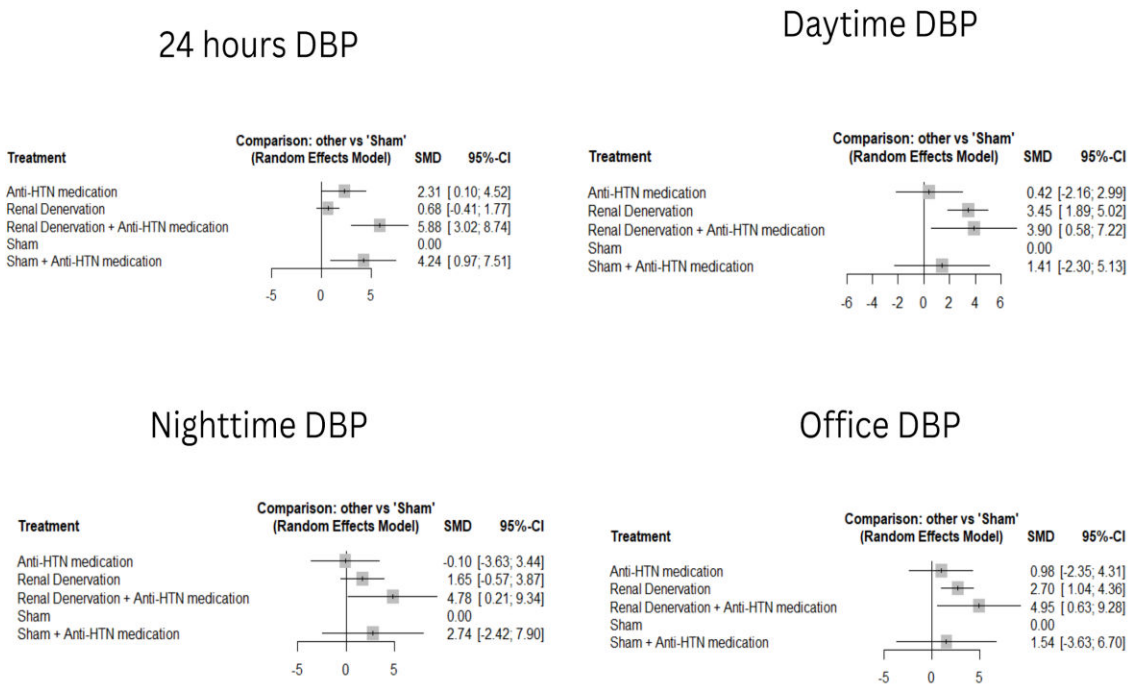


Figure 3b: Forest plots showing systolic blood pressure outcomes (SBP= systolic blood pressure, SMD=standardized mean difference, HTN= hypertension, CI=confidence interval)

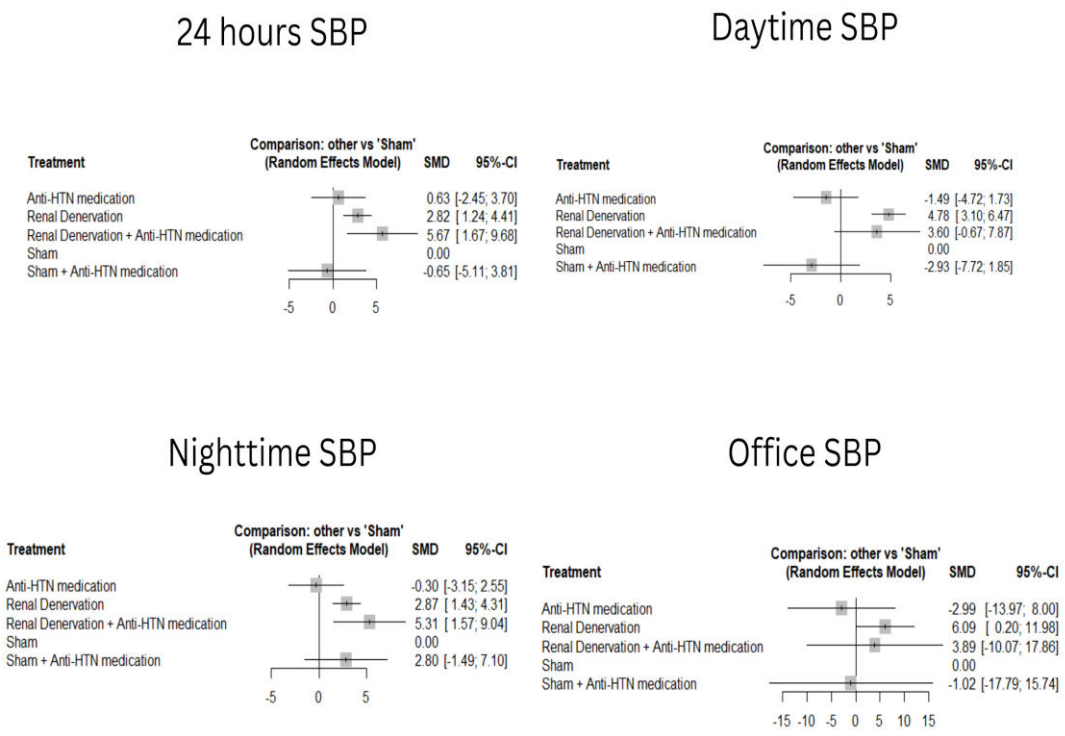
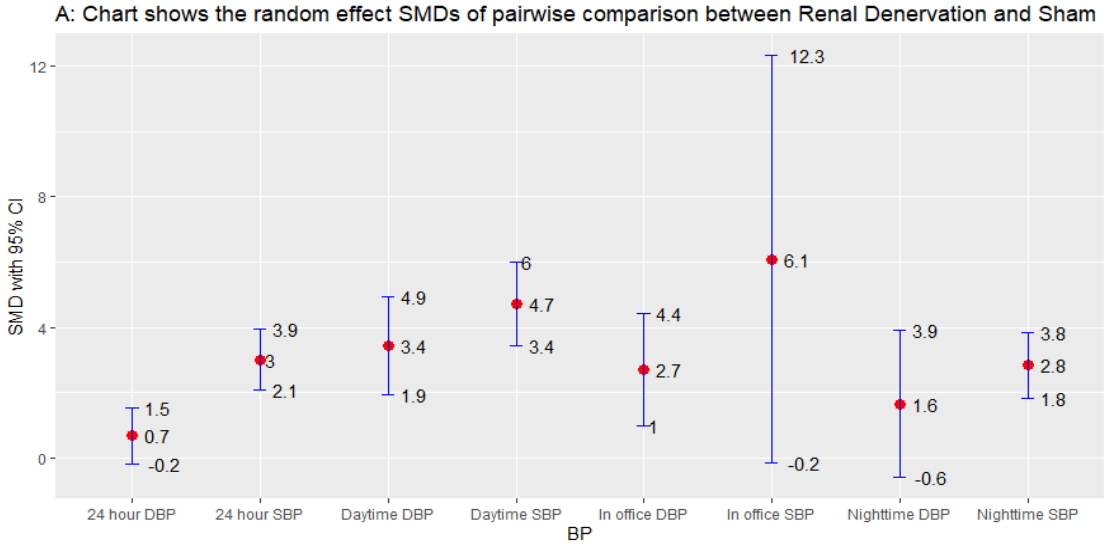


Figure 4: Figure 4 A and B show the random effects model standardized mean difference of pairwise comparison of interventions(SMD= standardized mean difference, CI= confidence interval, SBP= systolic blood pressure, DBP= diastolic blood pressure, AHT=anti-hypertensives, BP=blood pressure)



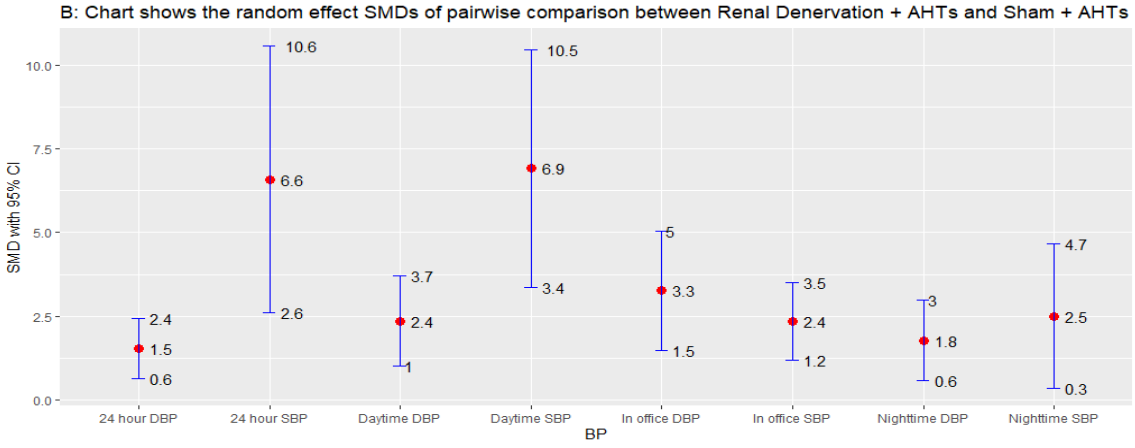


Table 1: Characteristics of Included Studies

Table 1 shows characteristics of included trials, the year of study conduction, the first author, the type of blinding, the intervention groups, the primary and secondary endpoints and duration of follow up

1. Blood pressure
2. Glomerular Filtration Rate

First Author	Year	Country	Blinding	Follow-up duration	Primary Endpoints	Secondary Endpoints	Renal Denervation (RD)	Treatment 2(T2)
D LBhatt	2014	International (Multi Center)	Single Blinded	6 months	change in office systolic blood pressure at 6 months;	a secondary efficacy endpoint change in mean 24-hour ambulatory systolic blood pressure.	Simplicity renal-denervation-tion catheter (Medtronic).	renal angiography
Michel Azizi	2021	International (Multi Center)	Single Blinded	2 months	change in mean 24-hour ambulatory systolic blood pressure.	24-ambulatory systolic and diastolic blood pressures, night-time ambulatory systolic and diastolic blood pressures, and daytime ambulatory diastolic blood pressure.	Ultrasonography renal denervation (Paradise System)	3 Anti HTN in 1 pill (amlodipine 10 mg (or 5 mg in the event of severe leg edema), valsartan 160 mg (or olmesartan 40 mg depending upon medication availability in each country),and hydrochlorothiazide 25 mg.)
Kazuomi Kario	2015	17 sites in Japan	Open label	6 Months	6-month change in office and 24-h ambulatory systolic BP [1] were compared	Hierarchical testing were change in average 24-h ambulatory BP	SymplicityTM Renal denervation system (Medtronic, Santa Rosa, CA, USA)	standard pharmacotherapy
Lotte Jacobs	2017	3 Belgian Center	Open label	6 month	Baseline-adjusted changes in systolic BP, diastolic BP(office,24hr, day and night time)		RDN by the EnligHTNTM multi-electrode system	Control group On 3 Hypertension meds
Ole N. Mathiassena	2016	Single center	Double blinded	6 months	Mean Change in 24 hr ambulatory BP at 1 and 3 Months	Systolic blood pressure, and average night-time ambulatory	Unipolar Medtronic Flex Catheter based renal denervation	Sham Control with 3/4 Antihypertensive including 1 diuretic

Rosa L. de Jager,	2017	multicenter RCT in 14 centers in Netherland	Open label	6 month	Change in daytime systolic ambulatory BP at 6 months.	Ambulatory diastolic blood pressure at 2 months, in this order.	Symplicity and EnligHTN catheter Ablation based Renal denervation	usual care with >3 Antihypertensive
Felix Mehfoud	2022	25 International Centers	Single Blinded	36 Months	Change in 24 hr ambulatory SBP at 24 months	outcomes were periprocedural complications.	Catheter based renal denervation	Sham Control
Steffen Desch	2015	Germany	Double blinded	6 months	change in 24-hour systolic BP at 6 months in intention to treat population.	change in diastolic BP, mean BP at 6 months, change in 24-hour mean systolic BP in the per-protocol population. and safety events.	renal sympathetic denervation with the Symplicity Flex Catheter (Medtronic)	invasive sham procedure (renal angiography and a simulated procedure with 4–6 sham runs for each renal artery guided by 2-minute acoustic signals)
Anna Oliveras	2016	Multicentered	Double blinded	6 months	change in 24-h SBP at 6 months		Renal Denervation	Spironolactone
Michel Azizi	2015	15 French tertiary care centers	Open label	6 months	change in daytime ambulatory systolic blood pressure at 6 months	Adverse events and eGFR^2 reduction at 6 months	radiofrequency-based renal denervation added to a standardized stepped-care antihypertensive treatment (SSAHT)	SSAHT alone (spironolactone 25 mg per day, bisoprolol 10 mg per day, prazosin 5 mg per day, and rilmenidine 1 mg per day)
Roland E. Schmiedera	2017	International	Double blinded	13 months	difference in office SBP, occurrence of adverse events during the first 6 weeks	change in 24-h ambulatory SBP between baseline and 24 weeks posttreatment	bilateral RDN using therapeutic levels of ultra-sound energy	bilateral sham treatment using diagnostic levels of ultrasound energy.
Kazuomi Kario 1	2021	Japan and South Korea	Single blinded	3 months	between-group difference in change in 24-hour ambulatory SBP from baseline at 3 months.	change in daytime and nighttime ambulatory SBP from baseline at 3 months, change in 24-hour, daytime and nighttime ambulatory diastolic BP (DBP) from baseline at 3 months, and change in seated office SBP and DBP from baseline at 3 months.	two 7-second ultrasound sonications delivered bilaterally to the main renal artery; ,6 French catheter	a renal angiogram without denervation
Rosa J. et al	2015	Multicenter	Open label	36 months	The differences in systolic and diastolic BP recorded between baseline and 6 months post-randomization	office and 24-hour BP differences between baseline and 1-, 2-, and 3-year post-randomization	Symplicity Renal Denervation System	Pharmacological treatment

Warchol-Celinska et al	2018	Poland	Open label	6 months	difference in mean change in office systolic BP from baseline to 3 months between the Renal Denervation group and the control group.	difference in mean change in office diastolic BP from baseline to 3 months and systolic and diastolic BP from baseline to 6 months, the difference in mean change in ambulatory systolic and diastolic BP	Renal denervation was performed using Symplicity Catheter System	Control
O. U. Bergland et al.	2020	Norway	Open label	84 months	The differences in systolic and diastolic BP recorded by 24-hour ABPM between baseline and 6 months post-randomization	change in diastolic BP, mean BP at 6 months, change in 24-hour mean systolic BP in the per-protocol population and safety events.	Renal denervation was performed using Symplicity Catheter System	Pharmacological Treatment
Michael A. Weber	2020	Multicentre	Single blinded	12 months	8 week change in 24 hour ambulatory systolic BP	6 month, 12 month change in 24:hour systolic BP	Bipolar radio frequency renal denervation	Sham procedure
Michel Azizi	2018	Multicenter	Single blinded	2 months	change in daytime ambulatory systolic blood pressure at 2 months	Change in average 24-h ambulatory systolic blood pressure, average 24-h ambulatory diastolic blood pressure, average night-time ambulatory systolic blood pressure, and average night-time ambu- latory diastolic blood pressure at 2 months,	Renal denervation with the Paradise system	Renal angiography only
Michael Bohm	2020	44 study cites internationally	Single Blinded	3 months	Baseline adjusted change in 24 hr SBP at 3 months	Baseline adjusted change in office SBP at 3 months	flex catheter	Sham
Atul Pathak	2023	25 centers in Europe and USA	Single blinded	12 month	Change in mean 24 hour ambulatory systolic blood pressure	Occurrence of major adverse effects	Alcohol based peregrine catheter	Sham
David E. Kandzari	2024	International	Double blinded	3 month	Mean 24 hour ambulatory systolic BP change	Change in office systolic BP in 3 months	Alcohol based peregrine catheter	Sham

Supplemental Files Index

1. Supplemental S1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist
2. Supplemental S2: AMSTAR-2 (Assessing the methodological quality of systematic reviews-2) Guidelines checklist
3. Supplemental S3: Research Question, PICO, MeSH, Keywords and Search Strategy
4. Supplemental S4: Patient Baseline Characteristics
5. Supplemental S5: Funnel Plots and Egger's p-test values
6. Supplemental S6: Cochrane Risk of Bias (ROB) tool assessment for included randomized controlled trials (RCTs)
7. Supplemental S7: Pairwise comparisons of intervention groups
8. Supplemental S8: Inconsistency
9. Supplemental S9: P-score graphs of treatment groups in all assessed outcomes
10. Supplemental S10: Heterogeneity

Supplemental S1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist

Section/Topic	Item #	Checklist Item	Reported on Page #

TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	*1*
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	*4*

Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	*5*
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection	10	Describe method of data extraction from reports (e.g., piloted	6,7

process		forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7,8
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	*8*
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	8
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to:	8

		• *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	*8*
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9

Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	*36*
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	*9*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	25-28
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Supplemental 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	*9-11*
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary	*11-12*

		measures were explored (such as treatment rankings), these should also be presented.	
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	*Supplemental 8*
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Supplemental 6
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	*Supplemental 7*
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	14

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

Supplemental S2: AMSTAR-2 (Assessing the methodological quality of systematic reviews-2) Guidelines checklist

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☑ Population
- ☑ Intervention
- ☑ Comparator group
- ☑ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☑ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☑ review question(s)
- ☑ a search strategy
- ☑ inclusion/exclusion criteria
- ☑ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☑ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☑ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

☑ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☑ searched at least 2 databases (relevant to research question)
- ☑ provided key word and/or search strategy
- ☑ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

☐ Yes
☑ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☑ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☑ Yes
☐ No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- ☒ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☒ Yes
☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- ☒ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- ☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☒ Partial Yes
☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:
- ☒ described population in detail
- ☒ described intervention in detail (including doses where relevant)
- ☒ described comparator in detail (including doses where relevant)
- ☒ described study's setting
- ☒ timeframe for follow-up

☒ Yes
☐ Partial Yes
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from
- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:
- ☒ allocation sequence that was not truly random, *and*
- ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome

☒ Yes
☐ Partial Yes
☐ No
☐ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:
- ☐ from confounding, *and*
- ☐ from selection bias

For Yes, must also have assessed RoB:
- ☐ methods used to ascertain exposures and outcomes, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☒ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes
- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☐ Yes
☒ No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs
For Yes:

- ☑ The authors justified combining the data in a meta-analysis
  - ☑ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☑ AND investigated the causes of any heterogeneity

☑ Yes
☐ No
☐ No meta-analysis conducted

For NRSI
For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ☐ included only low risk of bias RCTs
- ☑ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☑ Yes
☐ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ☐ included only low risk of bias RCTs
- ☑ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☑ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ☐ There was no significant heterogeneity in the results
- ☑ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☑ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☑ No
☐ No meta-analysis conducted

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes:	
☒ The authors reported no competing interests OR	☒ Yes
☐ The authors described their funding sources and how they managed potential conflicts of interest	☐ No

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Supplemental S3: Research Question, PICO, MeSH, Keywords, and Search Strategy

Research Question:

Efficacy of Renal Denervation and Antihypertensives in Patients with Resistant Hypertension: A Systematic Review and Network Meta-analysis

PICO:

Population: Patients with resistant hypertension

Intervention: Renal nerve denervation, antihypertensive medication, sham treatment

Comparison: of different treatment groups

Outcome:

1) Primary outcome *included mean change in in-office blood pressure, along with, 24-hour, morning, daytime, and nighttime systolic and diastolic blood pressure at 3-6 months from baseline*

2) Secondary outcomes *included mean change in in-office, 24-hour, morning, daytime, and nighttime systolic and diastolic blood pressure at 6-12 months from baseline*

Study type: Randomized controlled trials

Meta-analysis outcomes: Odds ratio to compare binary outcomes and standard mean difference to compare continuous outcomes meta-analyses.

MeSH Terms & Keywords:

Hypertension

Autonomic Denervation

Resistant Hypertension

Detailed search strategy for each of the included databases

Database	Search Strategy	Articles retrieved
Pubmed	(("Autonomic Denervation"[MeSH Terms] OR ("Autonomic Denervation"[MeSH Terms] OR ("autonomic"[All Fields] AND "denervation"[All Fields]) OR "Autonomic Denervation"[All Fields] OR ("autonomic"[All Fields] AND "denervations"[All Fields]) OR "autonomic denervations"[All Fields])) AND ("Hypertension"[MeSH Terms] OR ("Hypertension"[MeSH Terms] OR "Hypertension"[All Fields] OR ("high"[All Fields] AND "blood"[All Fields] AND "pressure"[All Fields]) OR "high blood pressure"[All Fields]) OR ("Hypertension"[MeSH Terms] OR "Hypertension"[All Fields] OR ("high"[All Fields] AND "blood"[All Fields] AND "pressures"[All Fields]) OR "high blood pressures"[All Fields]))) AND (clinicalstudy[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR multicenterstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])	191
Embase	('resistant hypertension'/exp OR 'drug resistant hypertension' OR 'medically refractory hypertension' OR 'refractory hypertension' OR 'resistant hypertension' OR 'therapeutically resistant hypertension' OR 'therapy resistant hypertension' OR 'treatment resistant hypertension') AND ('kidney denervation'/exp OR 'denervated kidney' OR	757

	'denervation, kidney' OR 'kidney denervation' OR 'renal denervation') AND (('clinical trial'/exp OR 'clinical drug trial' OR 'clinical trial' OR 'major clinical trial' OR 'trial, clinical') OR ('randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled'))	

Supplemental S4: Patient Baseline Characteristics

S4 shows the patient baseline characteristics, co morbidities and laboratory parameters of both treatment groups

1. Renal denervation
2. Standard deviation
3. Estimated glomerular filtration rate

First Author	Sample Size		Age				Sex Males %	BMI				Smoking		Diabetes		Stroke		Obstructive Sleep Apnea		eGFR[3]			
	RD[1]	T2	RD mean	RD SD[2]	T2 mean	T2 SD	RD %	RD mean	RD SD	T2 mean	T2 SD	RD %	T2 %	RD %	T2 %	RD %	T2 %	RD %	T2 %	RD mean	RD SD	T2 mean	T2 SD
DL Bhatt	364	171	57.9	10.4	56.2	11.2	59.1	34.2	6.5	33.9	6.4	9.9	12.3	47	40.9	8	11.1	25.8	31.6	72.78	15.67	74.03	18.74
Michel Azizi	69	67	52.3	7.1	52.8	9.1	81	32.8	5.7	32.6	5.4			30	25	12	13	28	16	86	25.2	82.2	19.2
Kazuomi Kario	22	19	59.5	11.9	56	13	15	27	5.5	28	3.9	7	6	8	12	3	4	2	2	4.5	1	15.8	3
Lotte Jacobs	6	9	48.4	10.8	47.9	8.8	50	29.3	4.5	31	4.9	66.7	11.1	0	33.3					93.5	12.4	80.1	23.9
Ole N. Mat	36	33	54.3	7.8	57.1	9.6	75	28.2	5	28.8	3.9	19	15	28	34	3	0	8	12	33.12	92	27.06	82

hiasena																						
Rosa L. de Jager,	95	44	62	12	60	10	42.1	28.6	4.8	29.4	4.6	23.2	22.7	27.4	31.8					77	19	80	21
Felix Mehfoud	38	42	53.9	8.7	53	10.7	87	31.4	6.4	32.5	4.6	21	26	13	19	0	2	5	24	81.9	15.3	82	20
Steffen Desch	35	36	64.5	7.6	57.4	8.6	77					17	11	54	36	6	8			79	20	84	20
Anna Oliveras	11	13	61.9	6.6	64.9	8.2	55	33.7	7.4	30.6	3.6	46	31	36	62	18	23			74.6		85	
Michel Azizi	53	53	55.2	10.8	55.2	10.8	64.2	30.7	4.8	29.7	4.5			17	26.4	13.2	7.5	30.2	24.5	88	24	90	24
Roland	42	39	60.3	11.2	62	11.1	81.4	29.9	4.5	29.8	4.2			27	26					81.8	20	76.3	16.8

E. Schmiedera																						
Kazuomi Kario1	69	67	50.7	11.4	55.6	12.1	69.6	29.5	5.5	28.4	4.5			26.1	29.9	0	7.5	15.9	11.9	74.2	16.2	69.6	17.1
Rosa J. et al	52	54	56	12	59	9	77	31.2	4.3	33.4	4.7	15	15										
Warchol-Celinska et al	30	30	55.9	9.4	54.5	9.2	80	34	6.2	34.7	4.5	53	33	47	30								
O. U. Bergland et al.	9	10	57	10.9	62.7	5.1	22	29	5.3	30	5.3			22	30	11	10			90.1	10	89.1	6.6
Michael AW	34	17	58.5	10.0	58.2	9.8	84					3	2	6	2	1	0	7	1	81.7	21	86.2	16.2

eber 2020																						
Michael Azizi 2018	74	72	54.4	10.2	53.8	10	62	29.9	5.9	29.0	5			3	7			8	11	84.7	16.2	83.2	16.1
Michael Bohm 2020	166	165	52.4	10.9	52.6	10.4	64	31.1	6	30.9	5.5			4	5	1	0	8	7				
Atul Pathak	50	56	53.8	11.0	54.4	11.5	80	28.1	4.2	28.9	4.4	16	5.4	4	8.9					85.8	14.0	85.9	13.0
David E. Kandzari	148	153	56.7	10.0	55.6	9.1	76.4	32.6	5.3	32.1	5.3	9.5	13.1	20.3	26.1								

Supplemental S5: Funnel Plots and Egger's p test values

Figure 1: Funnel plot showings diastolic blood pressure outcomes

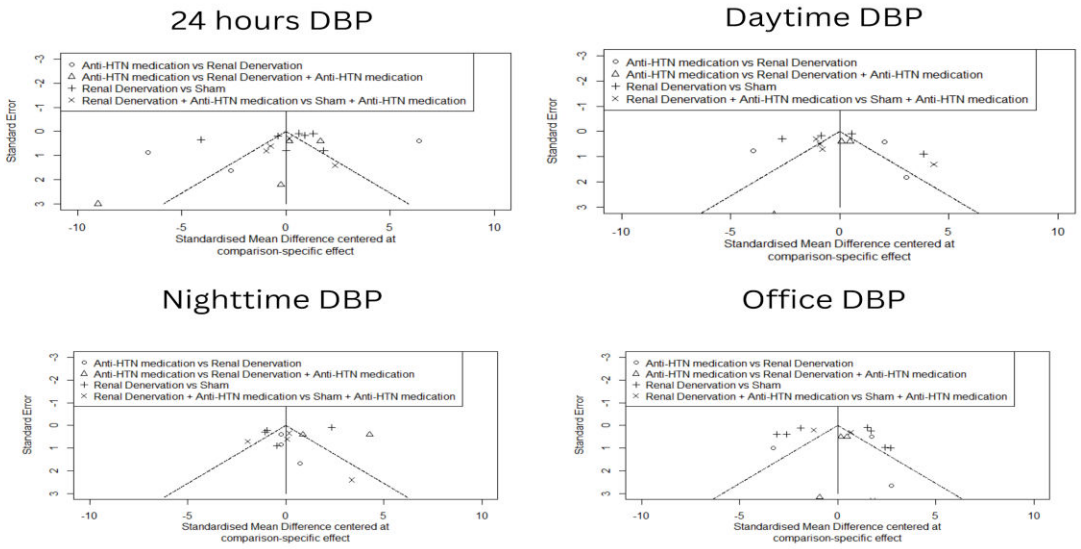
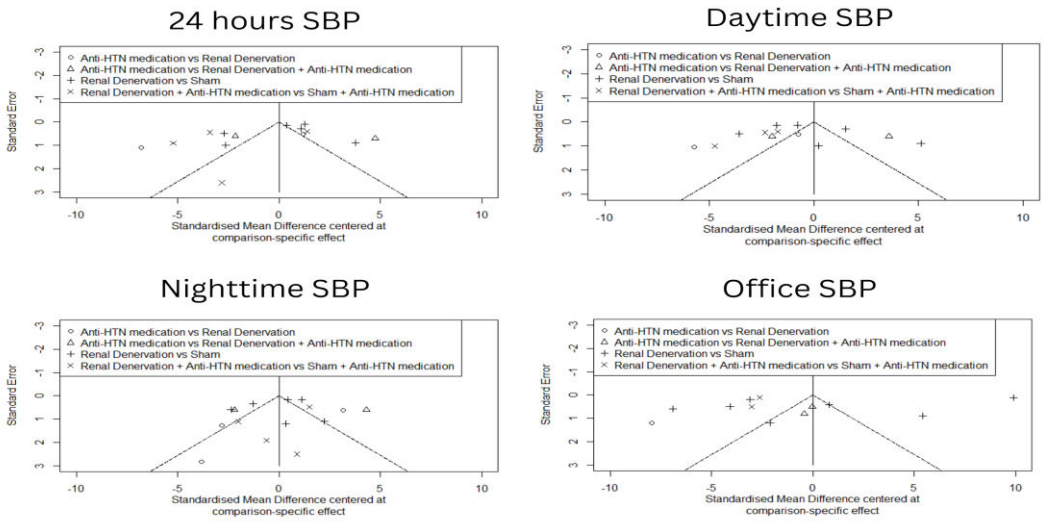


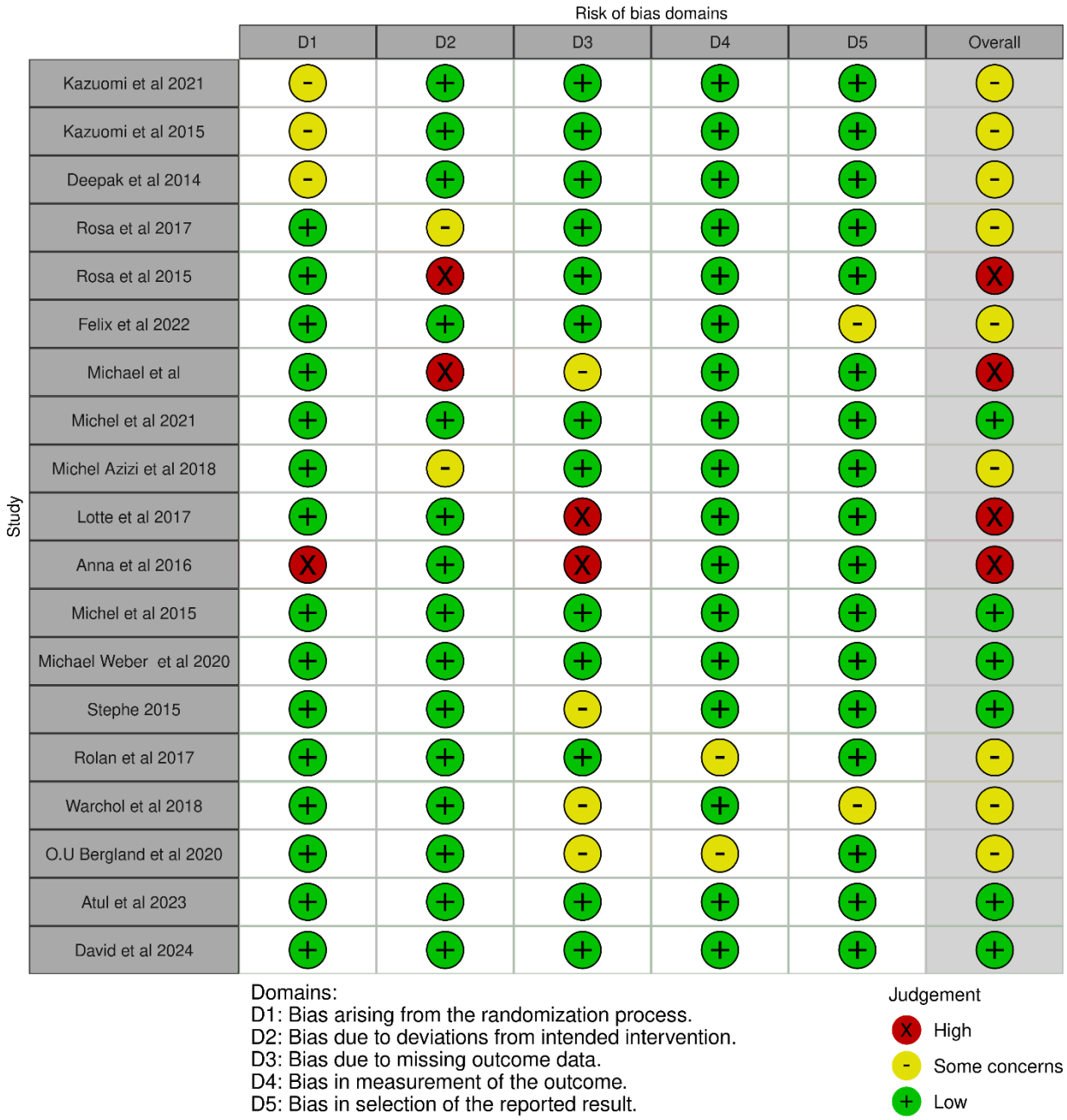
Figure 2: Funnel plot showing systolic blood pressure outside



Outcome Measured	Egger's p-value
24 hour DBP	0.32
24 hour SBP	0.29
Daytime DBP	0.69
Daytime SBP	0.48

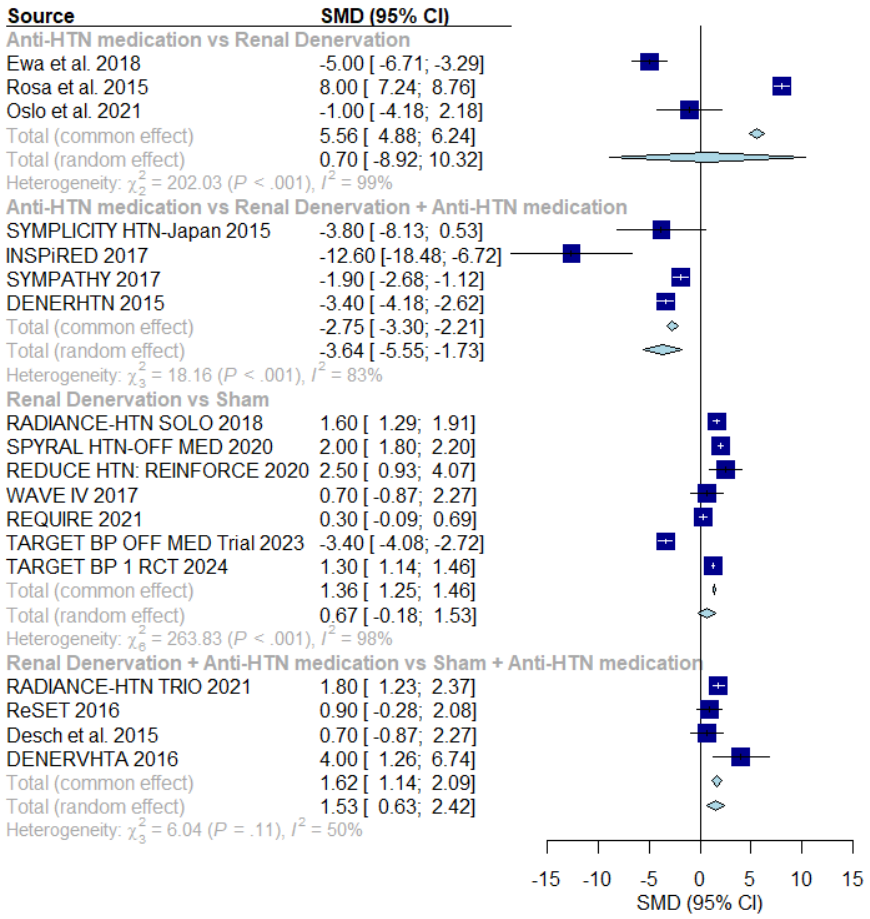
Nighttime DBP	0.25
Nighttime SBP	0.38
Office DBP	0.76
Office SBP	0.23

Supplemental S6: Cochrane Risk of Bias (ROB) tool assessment for included randomized controlled trials (RCTs)

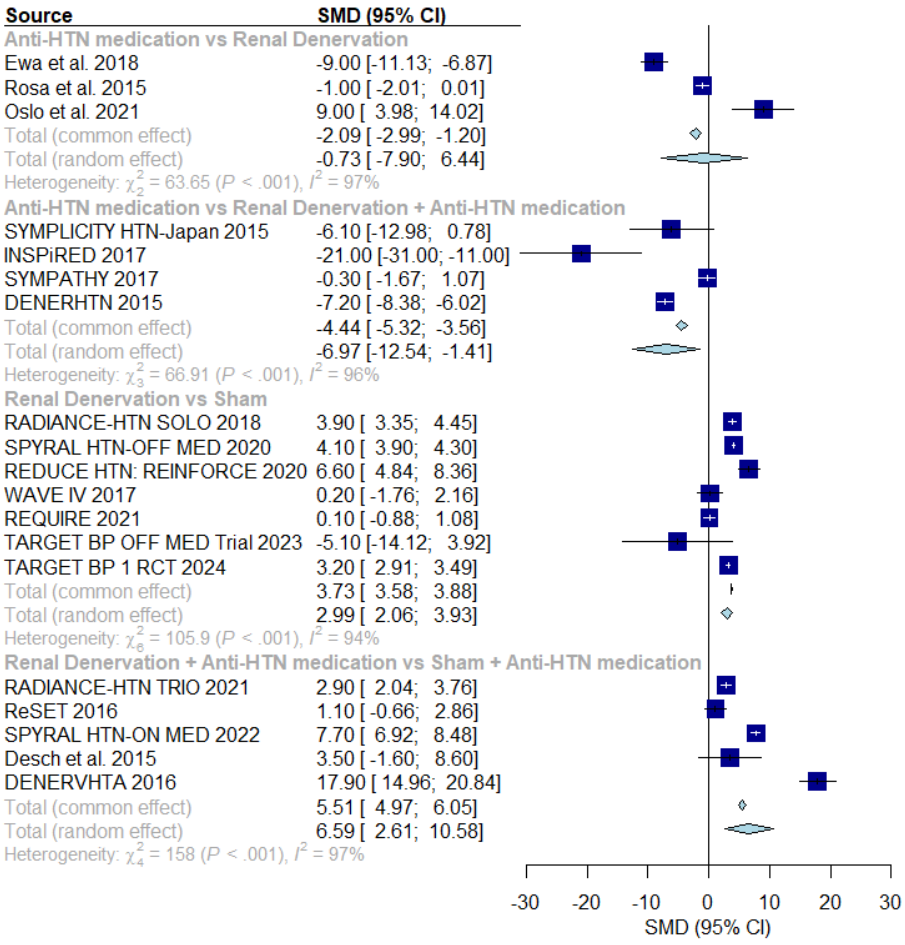


Supplemental S7: Pairwise Comparisons of Intervention Groups

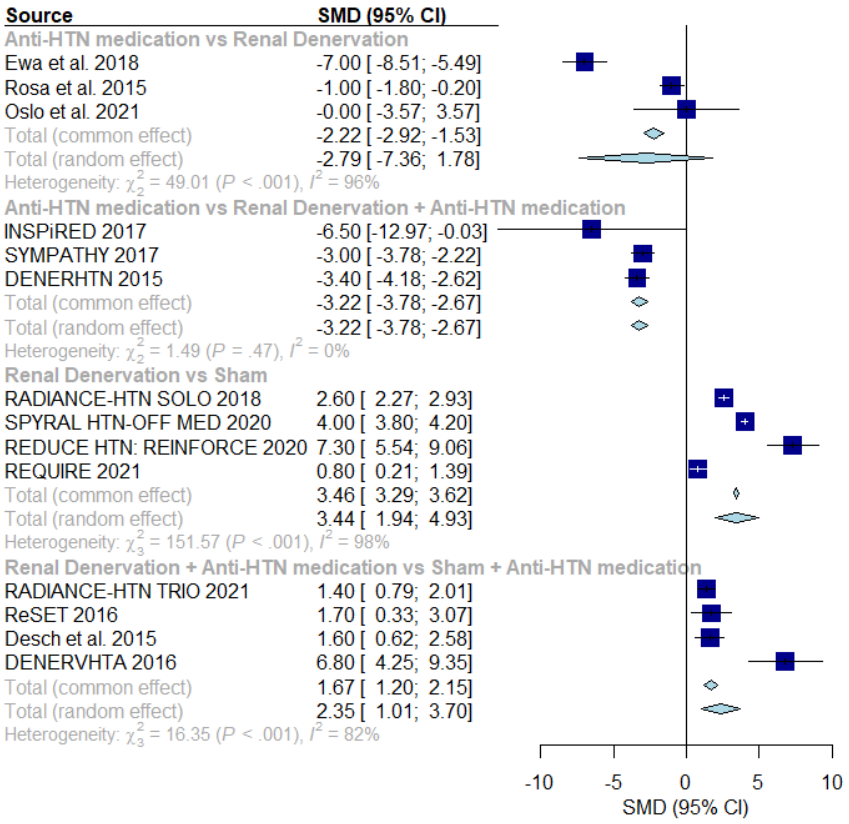
24 hour Diastolic Blood Pressure



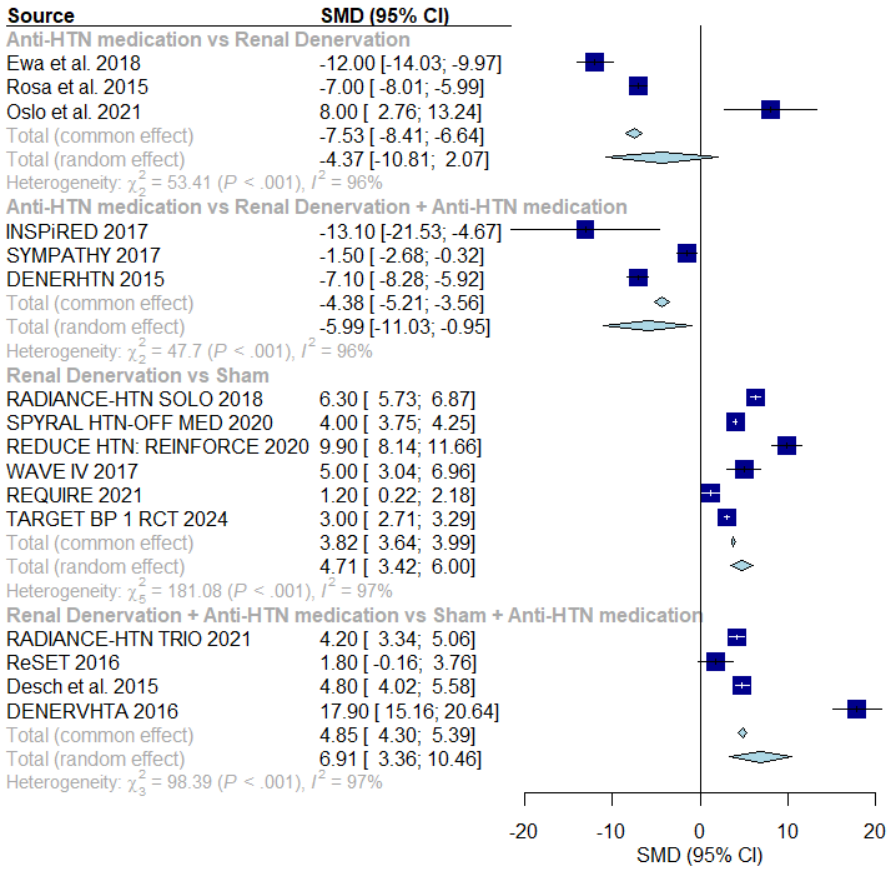
24 hour Systolic Blood Pressure



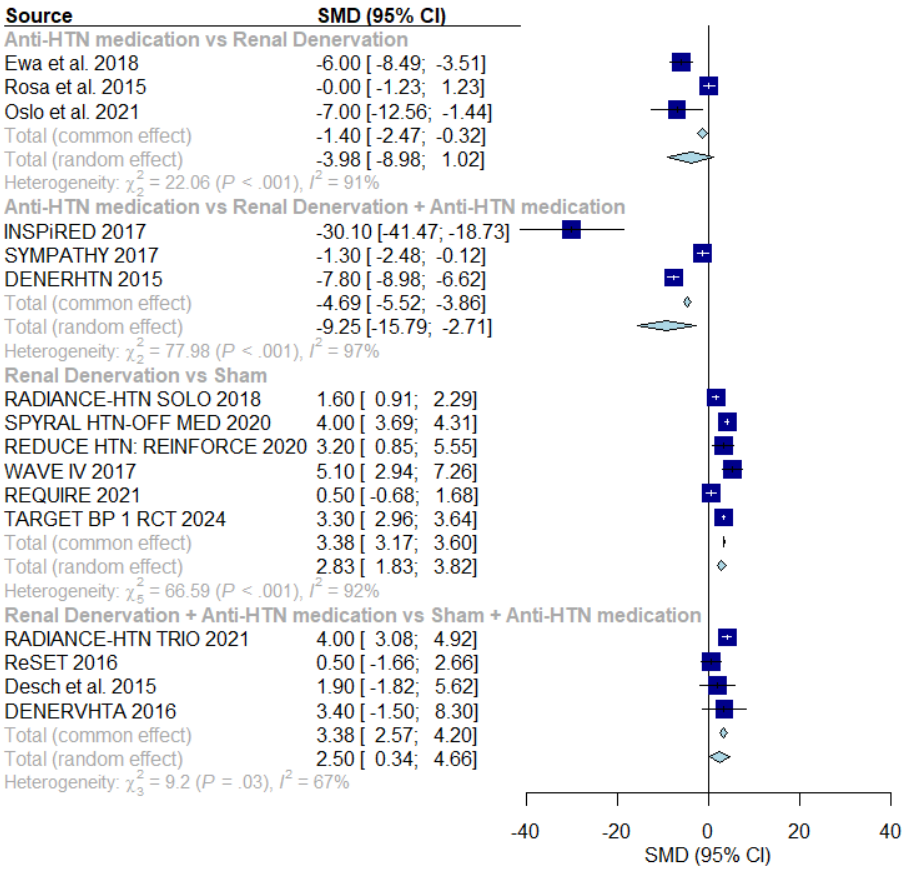
Daytime Diastolic Blood Pressure



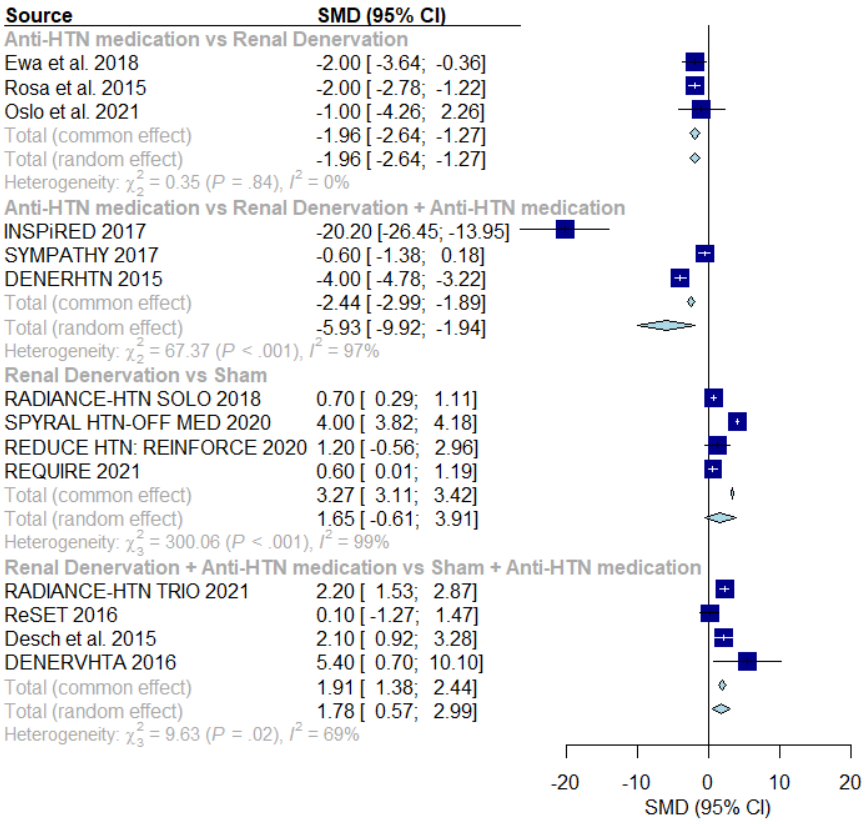
Daytime Systolic Blood Pressure



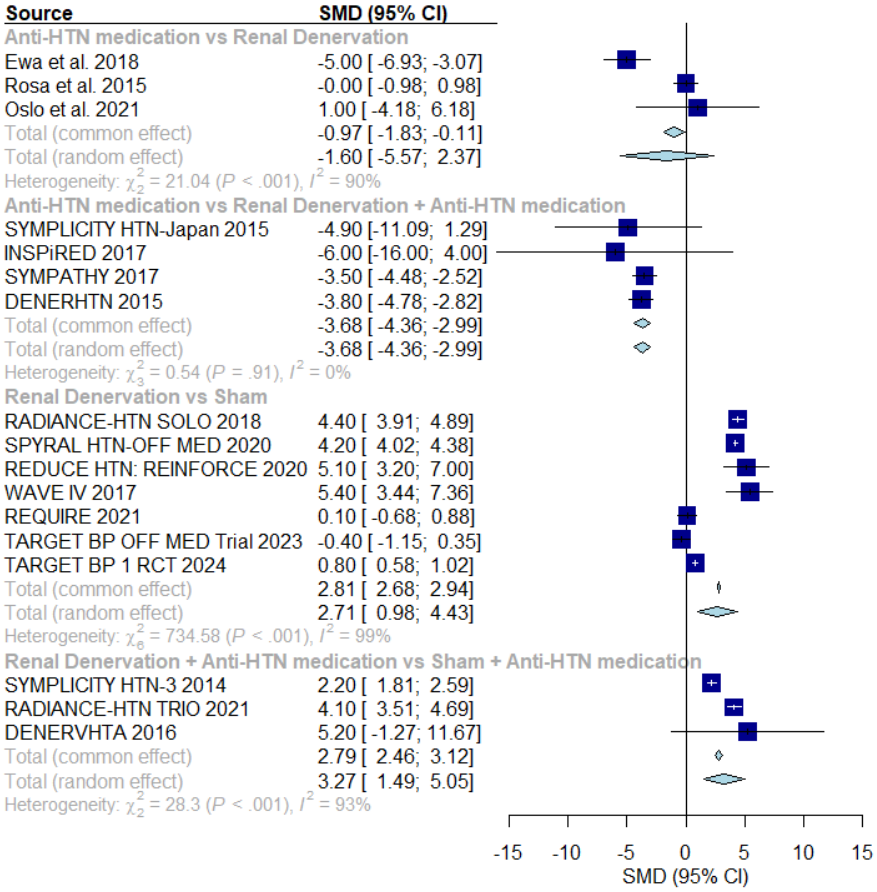
Nighttime Systolic Blood Pressure



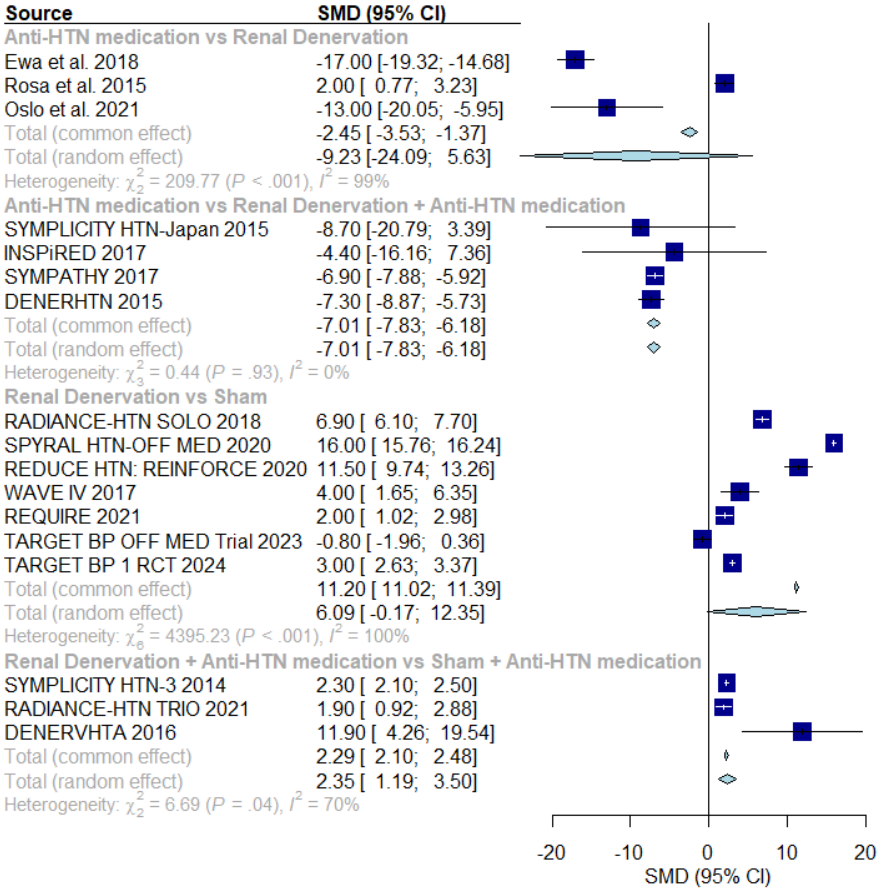
Nighttime Diastolic Blood Pressure



Office Diastolic Blood Pressure



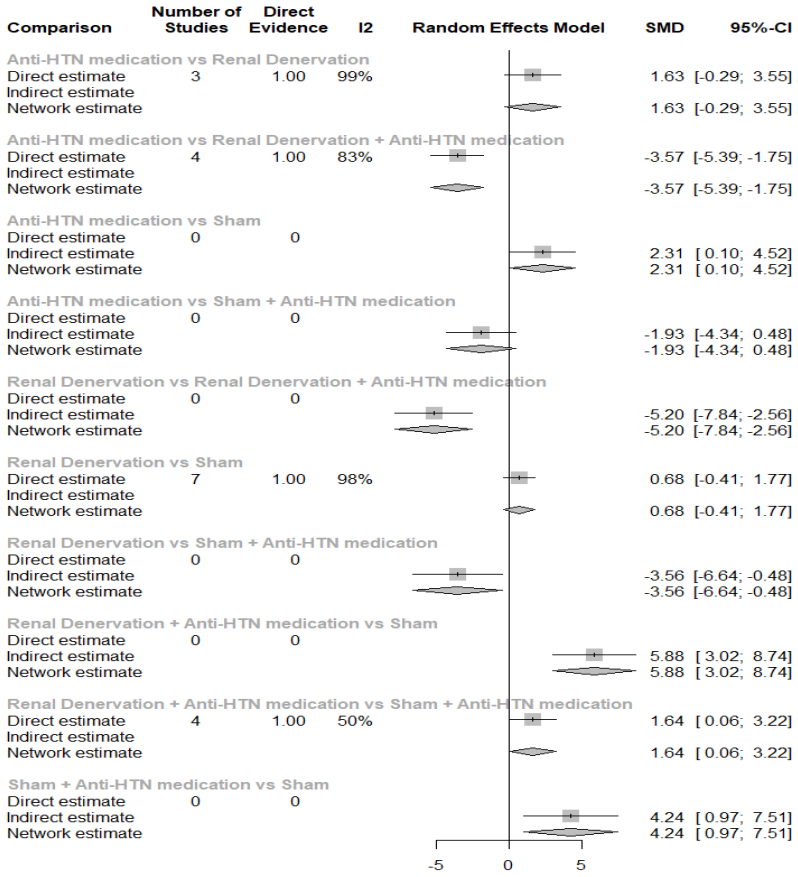
Office Systolic Blood Pressure


Source
SMD (95% CI)
Anti-HTN medication vs Renal Denervation
Ewa et al. 2018 -17.00 [-19.32; -14.68]
Rosa et al. 2015 2.00 [0.77; 3.23]
Oslo et al. 2021 -13.00 [-20.05; -5.95]
Total (common effect) -2.45 [-3.53; -1.37]
Total (random effect) -9.23 [-24.09; 5.63]
Heterogeneity: χ^2_2 = 209.77 (P < .001), I^2 = 99%
Anti-HTN medication vs Renal Denervation + Anti-HTN medication
SYMPLICITY HTN-Japan 2015 -8.70 [-20.79; 3.39]
INSPiRED 2017 -4.40 [-16.16; 7.36]
SYMPATHY 2017 -6.90 [-7.88; -5.92]
DENERHTN 2015 -7.30 [-8.87; -5.73]
Total (common effect) -7.01 [-7.83; -6.18]
Total (random effect) -7.01 [-7.83; -6.18]
Heterogeneity: χ^2_3 = 0.44 (P = .93), I^2 = 0%
Renal Denervation vs Sham
RADIANCE-HTN SOLO 2018 6.90 [6.10; 7.70]
SPYRAL HTN-OFF MED 2020 16.00 [15.76; 16.24]
REDUCE HTN: REINFORCE 2020 11.50 [9.74; 13.26]
WAVE IV 2017 4.00 [1.65; 6.35]
REQUIRE 2021 2.00 [1.02; 2.98]
TARGET BP OFF MED Trial 2023 -0.80 [-1.96; 0.36]
TARGET BP 1 RCT 2024 3.00 [2.63; 3.37]
Total (common effect) 11.20 [11.02; 11.39]
Total (random effect) 6.09 [-0.17; 12.35]
Heterogeneity: χ^2_6 = 4395.23 (P < .001), I^2 = 100%
Renal Denervation + Anti-HTN medication vs Sham + Anti-HTN medication
SYMPLICITY HTN-3 2014 2.30 [2.10; 2.50]
RADIANCE-HTN TRIO 2021 1.90 [0.92; 2.88]
DENERVHTA 2016 11.90 [4.26; 19.54]
Total (common effect) 2.29 [2.10; 2.48]
Total (random effect) 2.35 [1.19; 3.50]
Heterogeneity: χ^2_2 = 6.69 (P = .04), I^2 = 70%
-20
-10
0
10
20
SMD (95% CI)

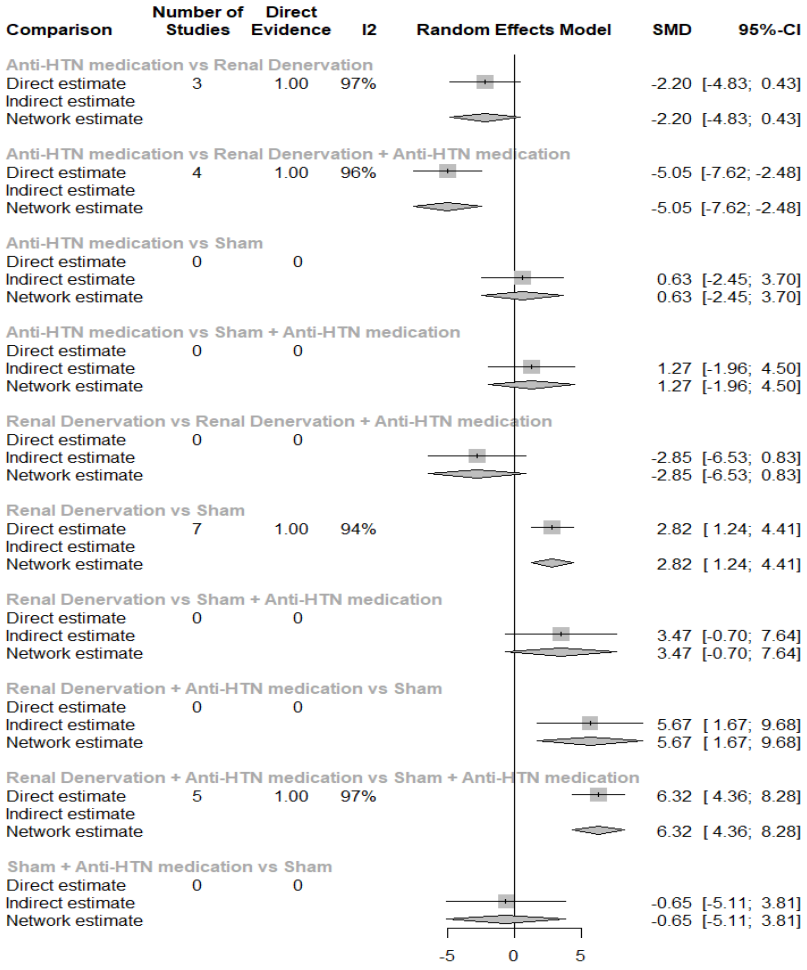
Supplemental S8: Inconsistency

Direct, Indirect and Network Estimate of Treatment Groups

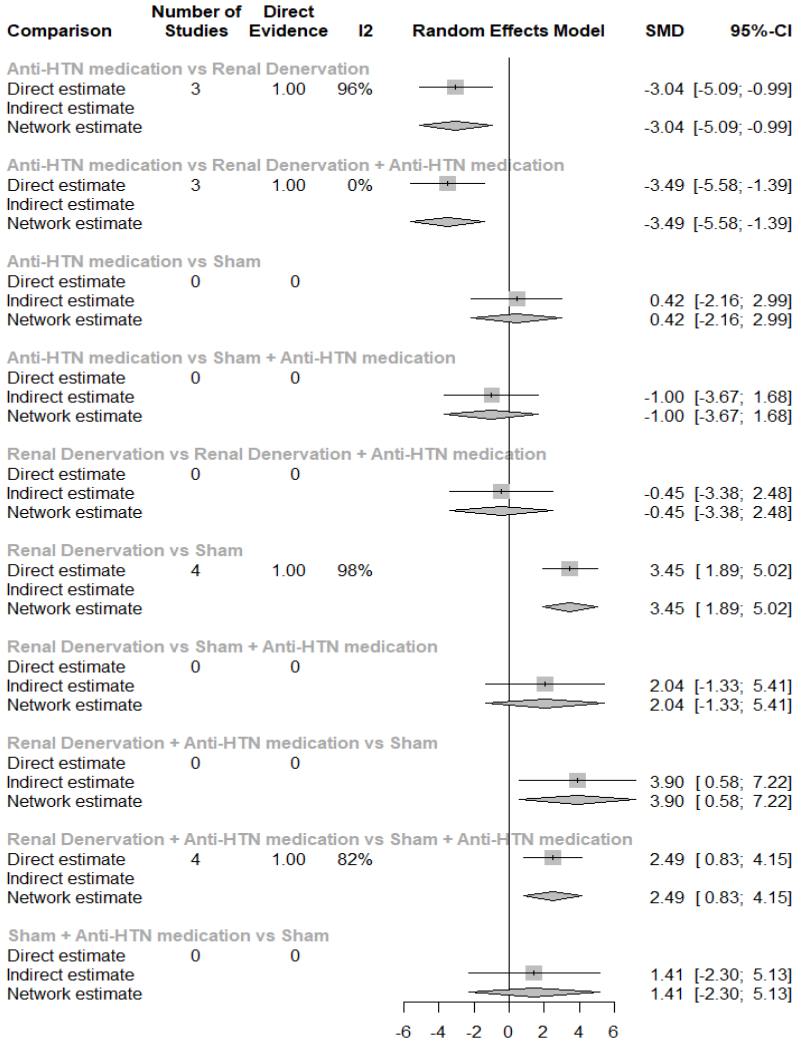
24 hour Diastolic Blood Pressure



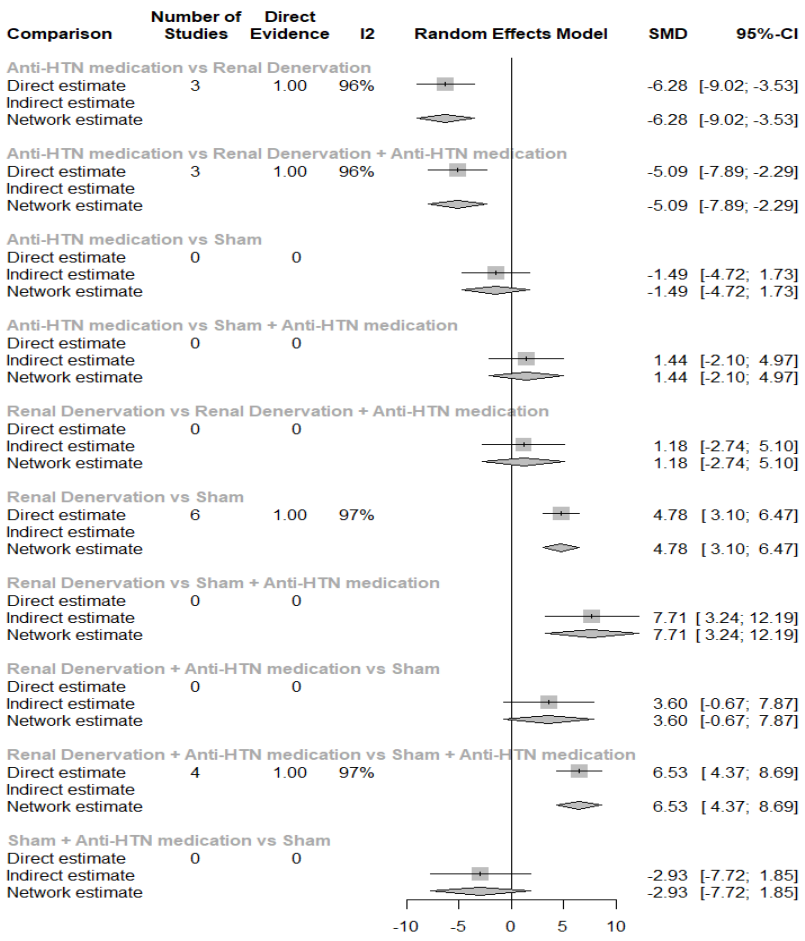
24 hour Systolic Blood Pressure



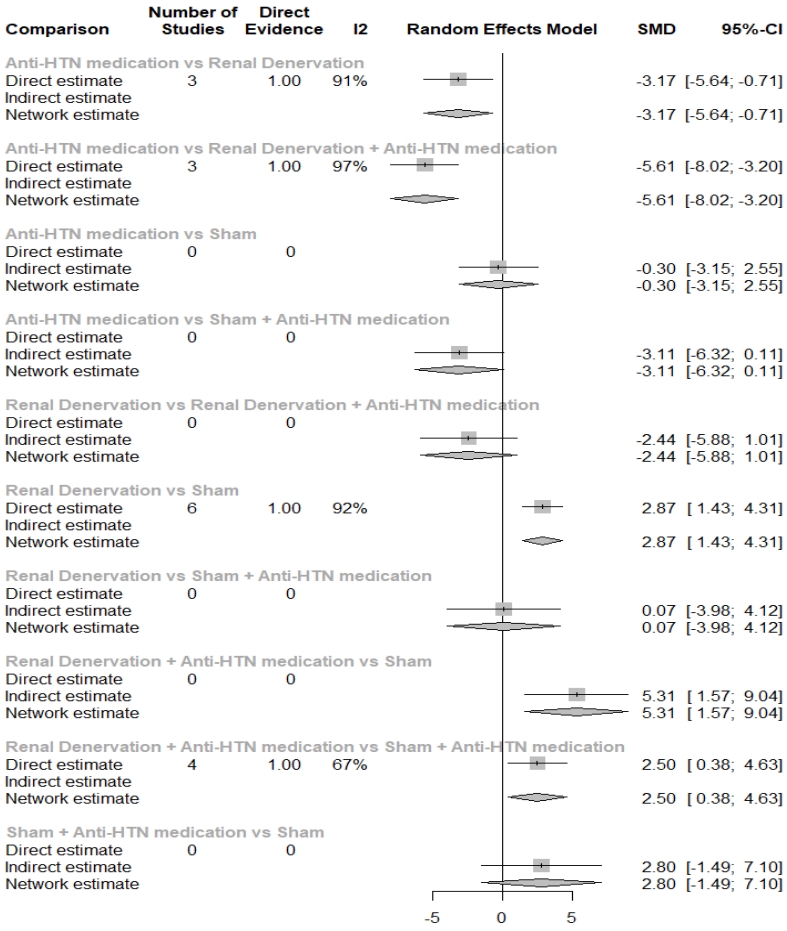
Daytime Diastolic Blood Pressure



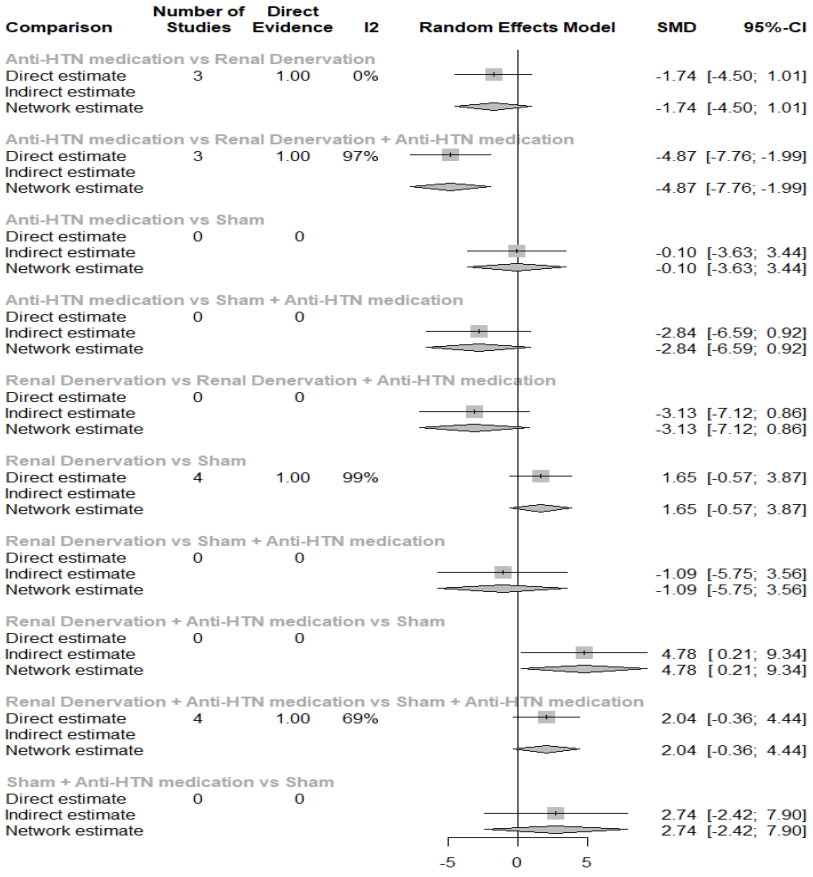
Daytime Systolic Blood Pressure



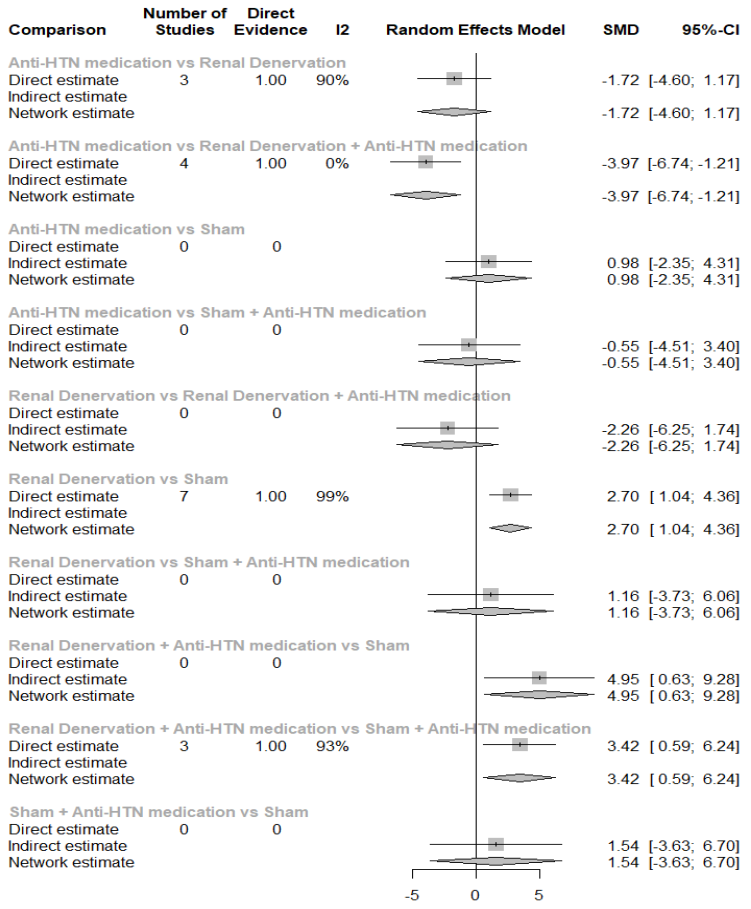
Nighttime Systolic Blood Pressure



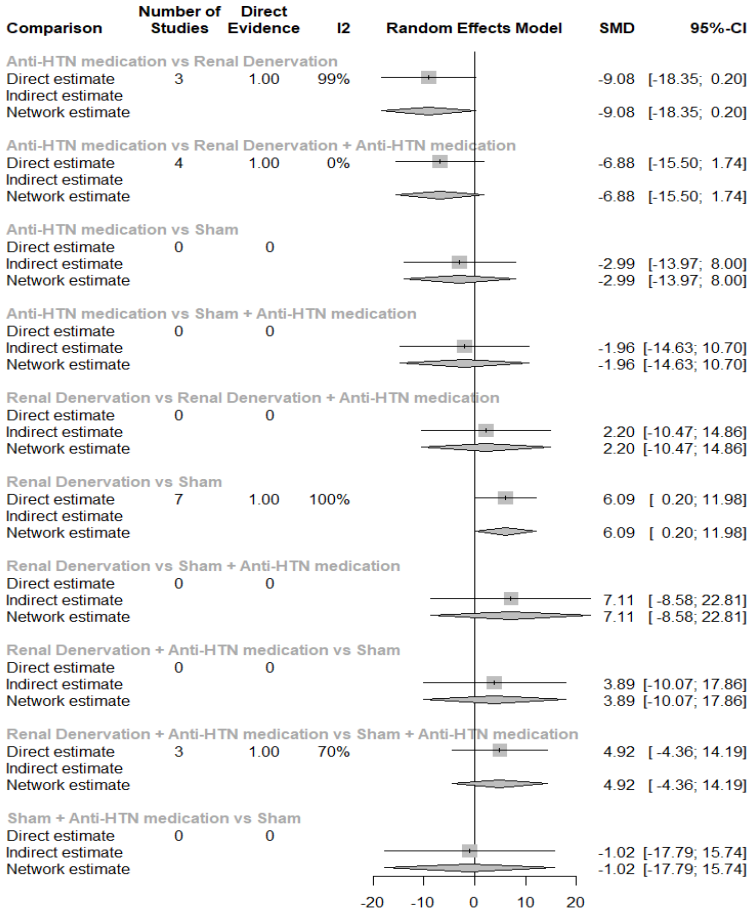
Nighttime Diastolic Blood Pressure



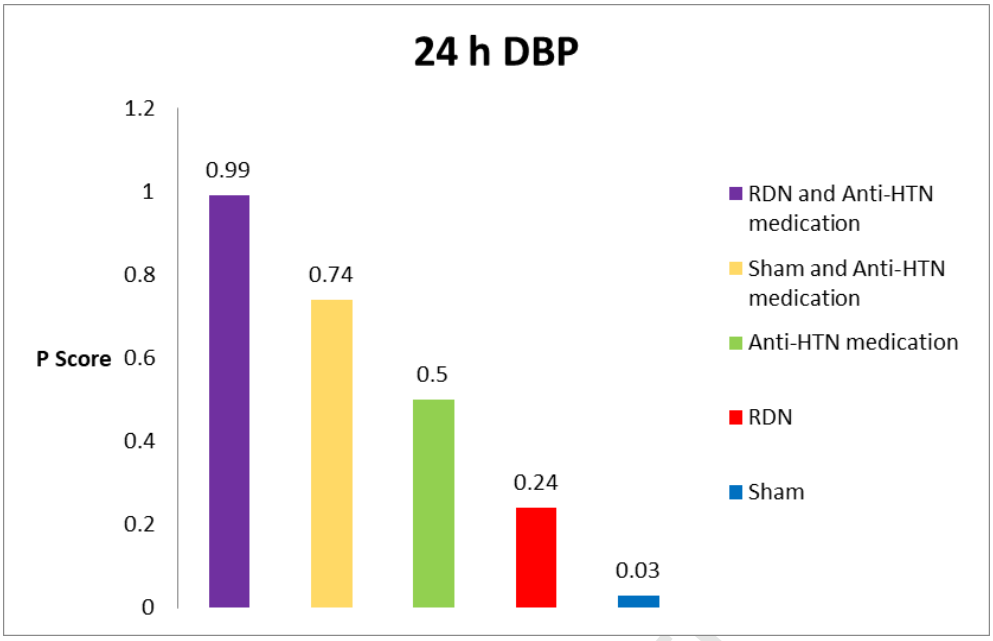
Office Diastolic Blood Pressure

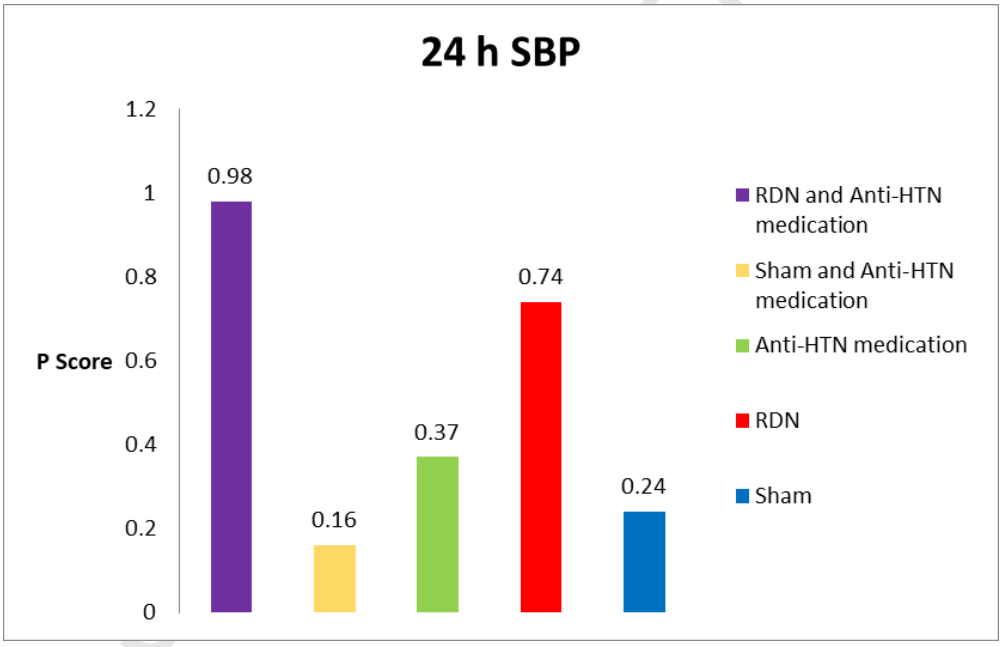


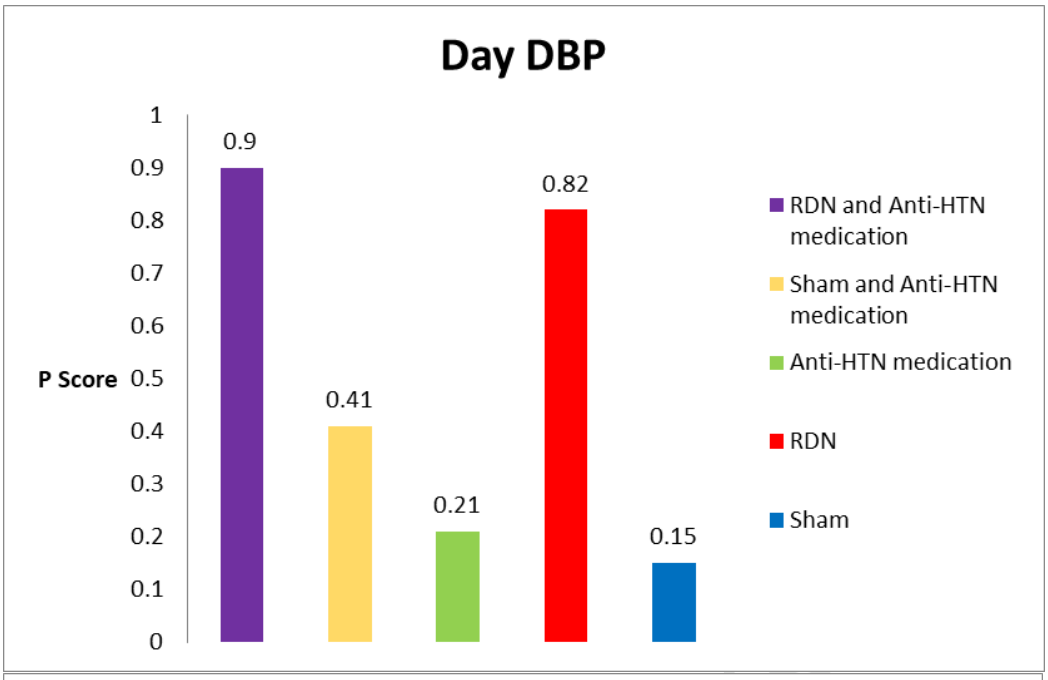
Office Systolic Blood Pressure

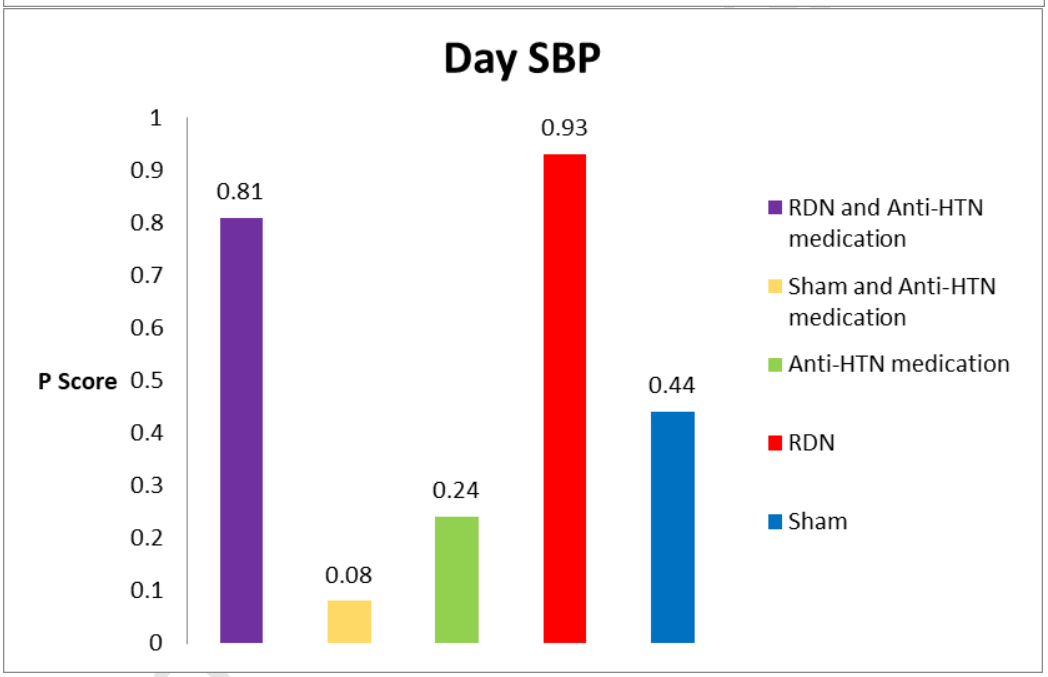


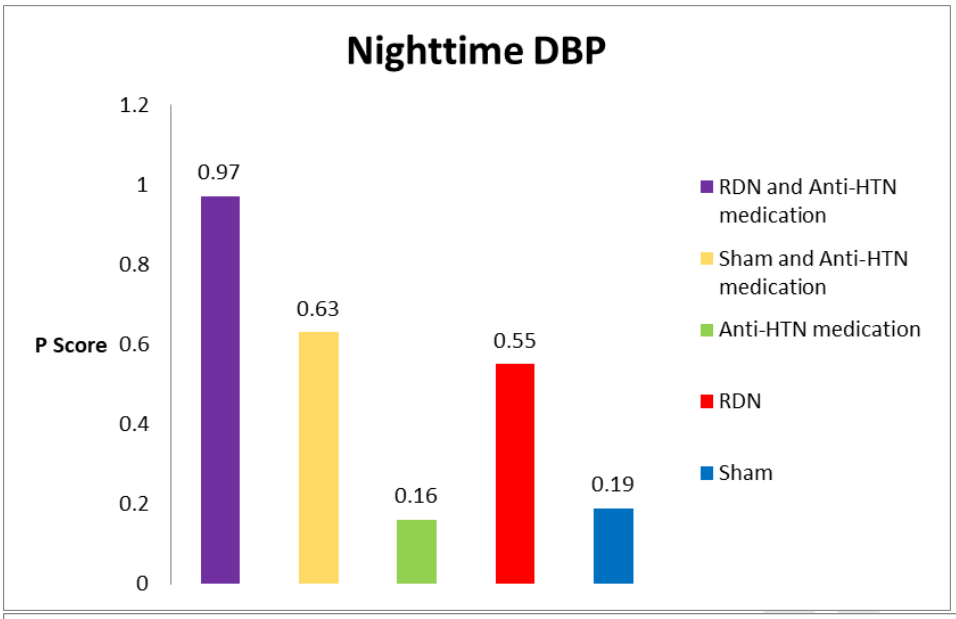
Supplemental S9: P-score graphs of treatment groups in all assessed outcomes

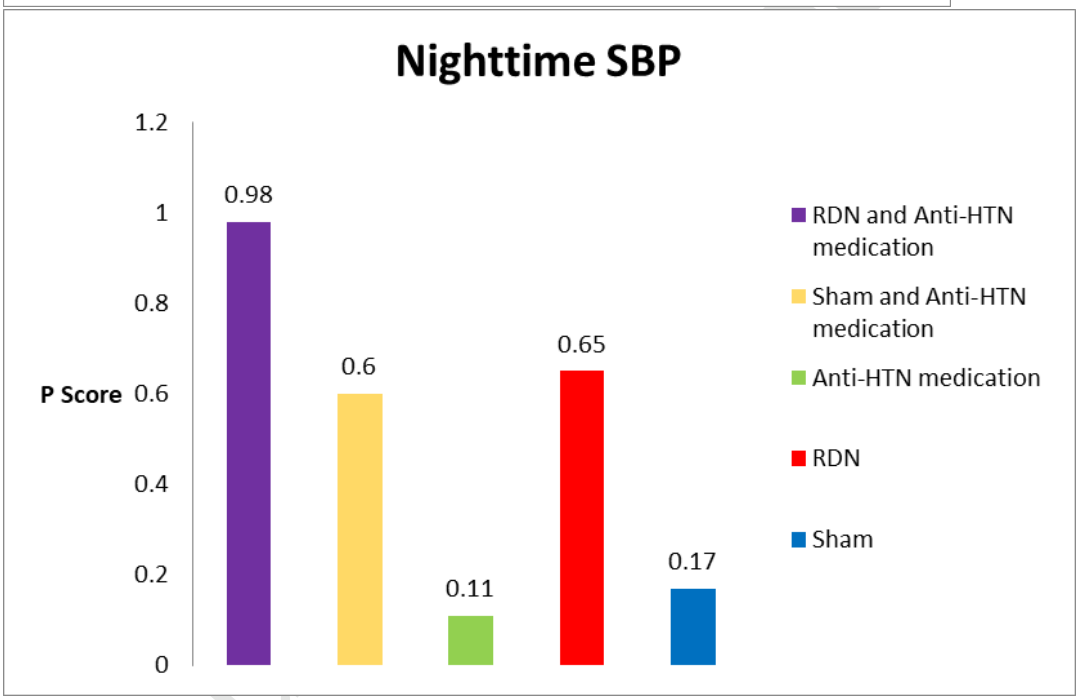


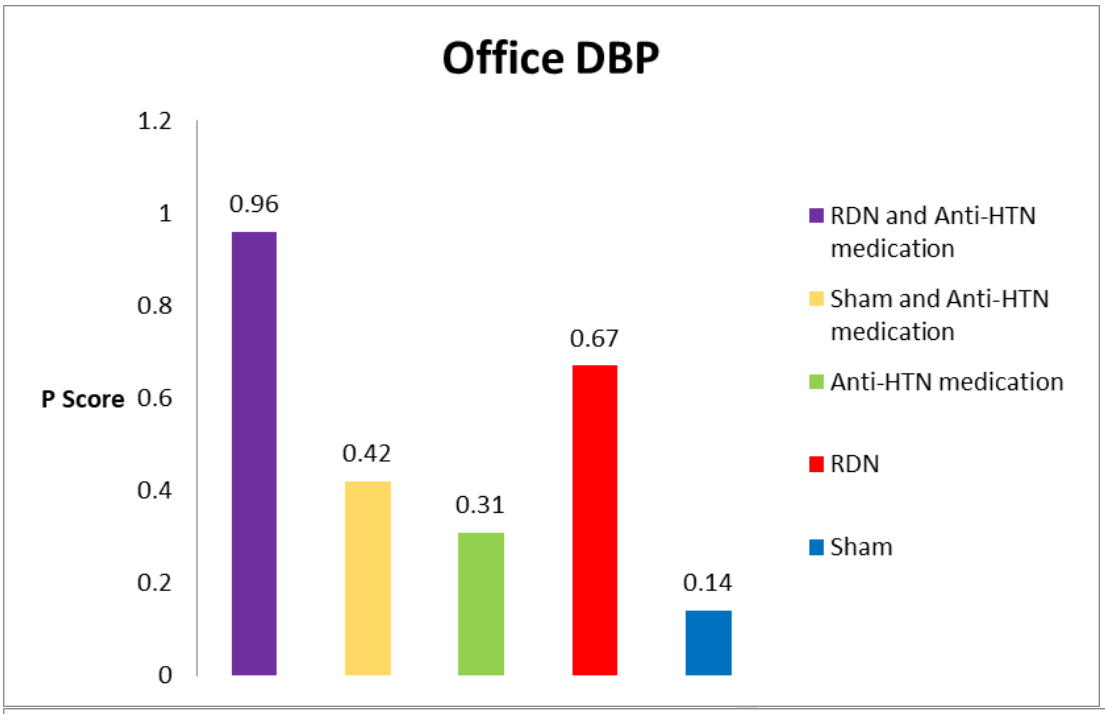


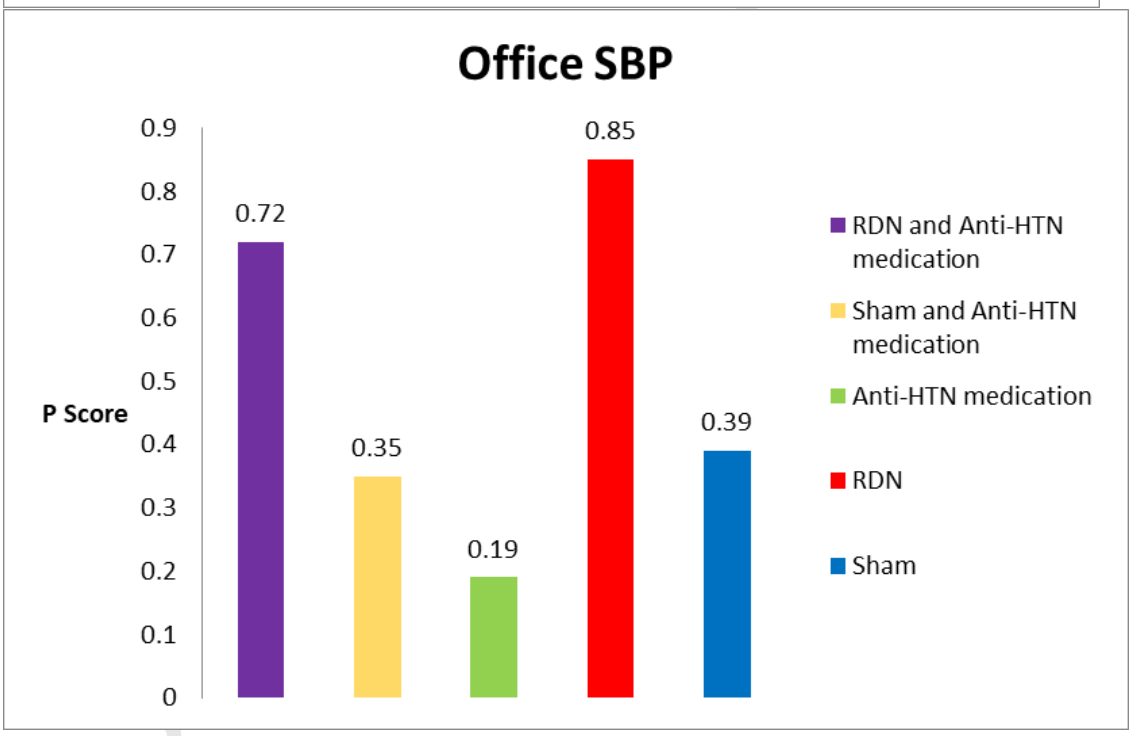

Day DBP
P Score
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.9
0.41
0.21
0.82
0.15
RDN and Anti-HTN medication
Sham and Anti-HTN medication
Anti-HTN medication
RDN
Sham


Day SBP
P Score
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.81
0.08
0.24
0.93
0.44
RDN and Anti-HTN medication
Sham and Anti-HTN medication
Anti-HTN medication
RDN
Sham


Nighttime DBP
1.2
1
0.8
P Score 0.6
0.4
0.2
0
0.97
0.63
0.16
0.55
0.19
RDN and Anti-HTN medication
Sham and Anti-HTN medication
Anti-HTN medication
RDN
Sham


Nighttime SBP
1.2
1
0.8
P Score 0.6
0.4
0.2
0
0.98
0.6
0.11
0.65
0.17
RDN and Anti-HTN medication
Sham and Anti-HTN medication
Anti-HTN medication
RDN
Sham





Supplemental S10: Heterogeneity

Outcome	Higgin's I squared value
24 hour DBP	97.1%
24 hour SBP	96.2%
Daytime DBP	95.4%
Daytime SBP	96.8%
Nighttime DBP	97.4%
Nighttime SBP	93.2%
Office DBP	98.3%
Office SBP	99.7%