Supplemental Material

The State of Renal Sympathetic Denervation for The Management of Patients with Hypertension: A Systematic Review & Meta-analysis

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Online Supplement

eTable-1. Checklist as per the Preferred Reporting System of Systematic Review and Meta-analysis (PRISMA) Guidelines	Page 3
eTable-2. Risk of bias assessments for included randomized clinical trials	Page 5
eFigure-1. Risk of bias summary in the included trials in the meta-analysis	Page 6
eTable-3. Baseline Characteristics of the studies included in the current meta-analysis	Page 7
eFigure-2. Forest plot with subgroup analysis of ON versus OFF groups for office systolic & diastolic blood pressure.	Page 8
eFigure-3. Forest plot reporting outcomes based on duration of follow-up for ambulatory systolic & diastolic blood pressure	Page 9
eFigure-4. Forest plot reporting outcomes based on duration of follow-up for office systolic & diastolic blood pressure	Page 10

eTable-1. Checklist as per the Preferred Reporting System of Systematic Review and Meta-analysis (PRISMA) Guidelines

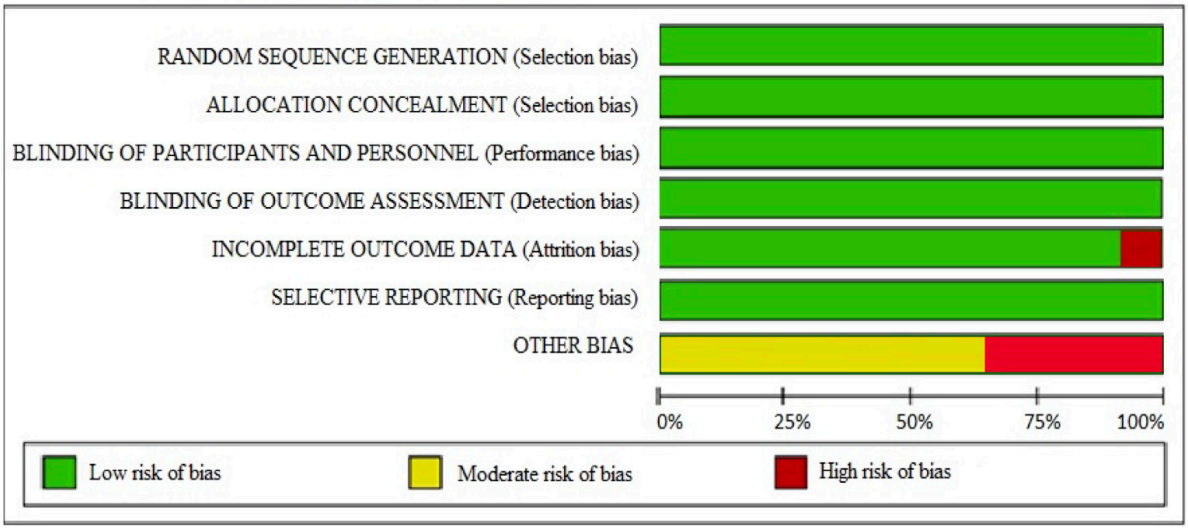
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
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.	4
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
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).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in 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.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

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).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
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.	6
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.	eTable-1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	eFigure-1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	All figures have outcomes as per individual studies
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	eFigure-1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-9
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).	9
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).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-10
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.	1

eTable-2. Risk of bias assessments for included randomized clinical trials

	Trial Name	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of Researchers	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
1.	Desch et al	Low	Low	Low	Low	Low	Low	Unclear
2.	SYMPLICITY HTN-3	Low	Low	Low	Low	Low	Low	Unclear
3.	ReSET	Low	Low	Low	Low	Low	Low	Unclear
4.	REINFORCE	Low	Low	Low	Low	High	Low	Unclear
5.	SPYRAL HTN-OFF MED Pivotal	Low	Low	Low	Low	Low	Low	High
6.	SPYRAL HTN-OFF MED	Low	Low	Low	Low	Low	Low	High
7.	RADIANCE-HTN SOLO	Low	Low	Low	Low	Low	Low	Unclear
8.	SPYRAL HTN-ON MED	Low	Low	Low	Low	Low	Low	High

eFigure-1. Risk of bias summary in the included trials in the meta-analysis

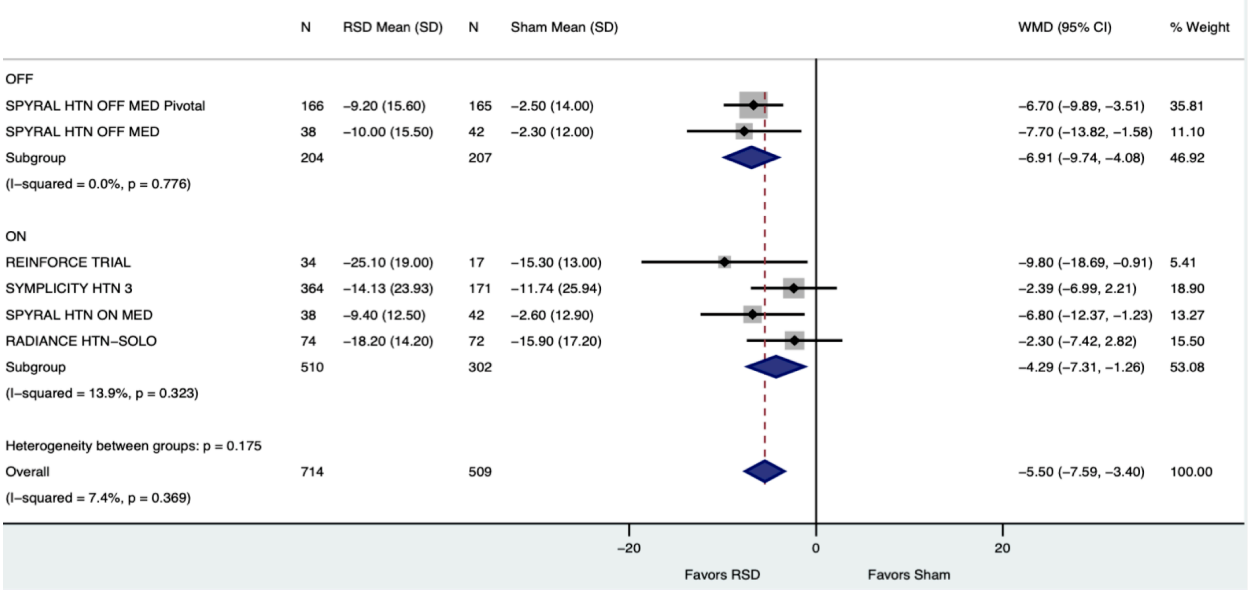


eTable-3. Baseline Characteristics of the studies included in the current meta-analysis

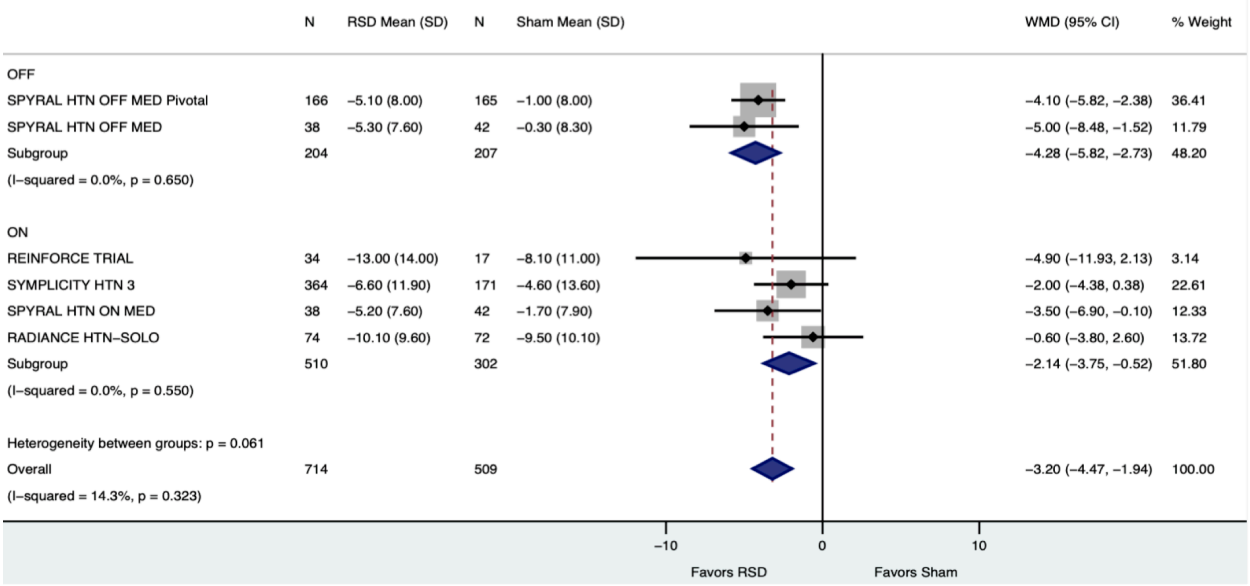
Study	Total Patients (RSD/Sham)	Follow-Up Duration (Months)	Denervation Method	Enrollment Period	Participating Centers
Desch et al	35/36	6	Radiofrequency ablation with Symplicity Flex Catheter (Medtronic, Santa Rosa, California)	July 2012 to January 2014	Single-center, Leipzig, Germany
SYMPLICITY HTN-3	364/171	6	Radiofrequency energy delivered by the Symplicity renal-denervation catheter (Medtronic)	October 2011 to May 2013	88 sites in the United States
ReSet	36/33	6	Radiofrequency ablation with unipolar Medtronic Flex catheter (Medtronic)	NR	Single-center, Skejby, Denmark
REINFORCE Trial	34/17	12	radiofrequency renal denervation with Vessix Renal Denervation	April 2015 to October 2017	Multiple centers I the usinted states
SPYRAL HTN-OFF MED Pivotal	166/165	3	Radiofrequency ablation with Symplicity Spyral multielectrode renal denervation catheter (Medtronic; Galway, Ireland) and the Symplicity G3 radiofrequency generator (Medtronic; Minneapolis, MN, USA)	June 25, 2015, to Oct 15, 2019	44 study sites in Australia, Austria, Canada, Germany, Greece, Ireland, Japan, the UK, and the USA
SPYRAL HTN- OFF MED	38/42	3	Radiofrequency ablation with Symplicity Spyral multielectrode catheter (Medtronic, Galway, Ireland) and the Symplicity G3 (Medtronic) generator	June 25, 2015 to January 30, 2017	21 centers in the United States, Europe, Japan, and Australia
RADIANCE-HTN SOLO	74/72	6	Endovascular ultrasound renal denervation with Paradise endovascular ultrasound renal denervation system ultrasound renal denervation system	March 28, 2016 to December 28, 2017	21 hospitals in the United States and 18 in Europe
SPYRAL HTN-ON MED	38/42	6	Radiofrequency ablation with Symplicity Spyral multielectrode catheter (Medtronic)	July 22, 2015 to June 14, 2017	25 centers in the United States, Germany, Japan, United Kingdom, Australia, Austria, and Greece

eFigure-2. Forest plot comparing the outcomes of Renal Sympathetic Denervation (RSD) versus sham. (A) Office systolic blood pressure outcomes with subgroups divided to ON medications versus OFF medications. (B) Office diastolic blood pressure outcomes with subgroups divided to ON medications versus OFF medications groups

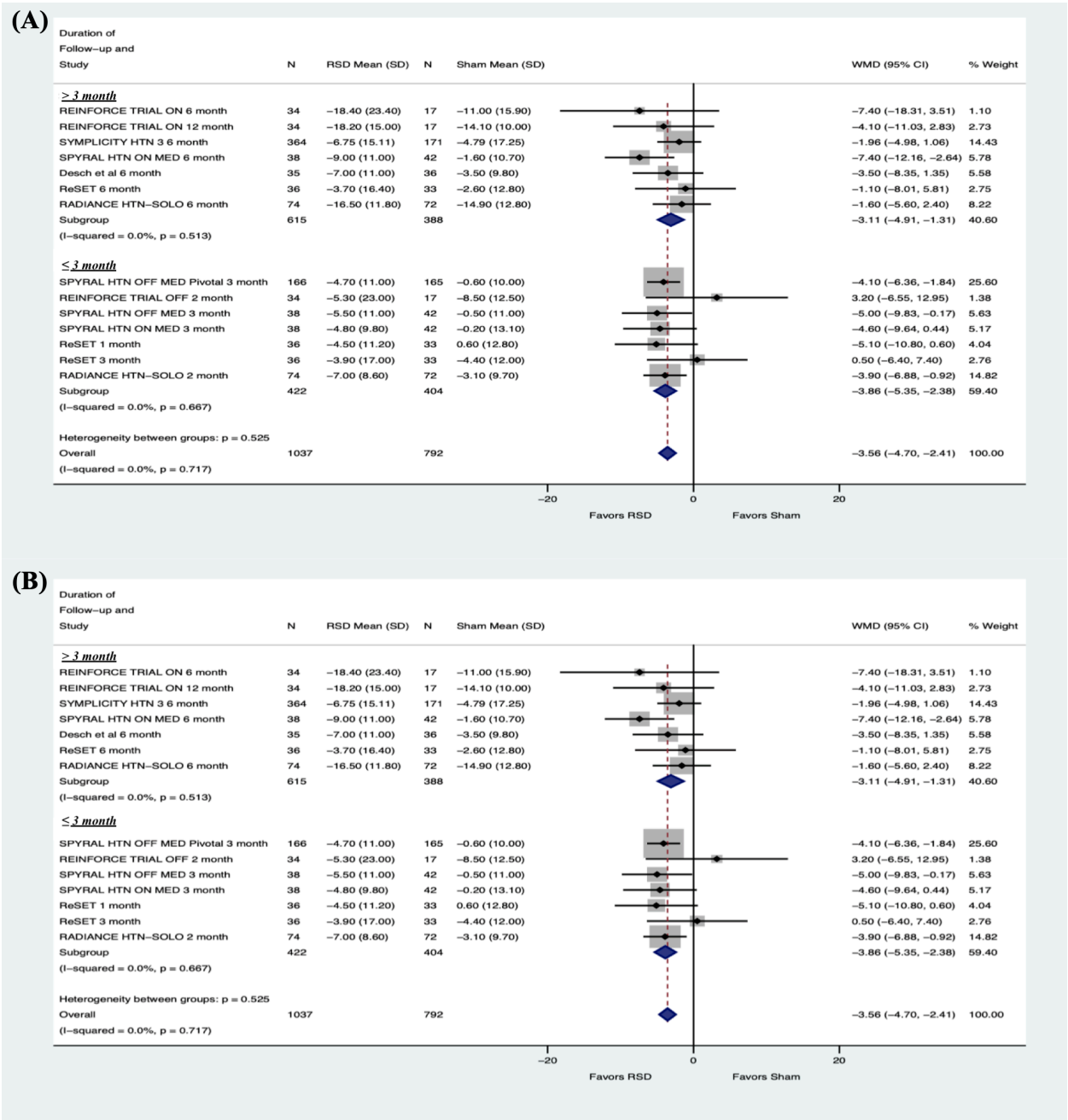
(A)



(B)

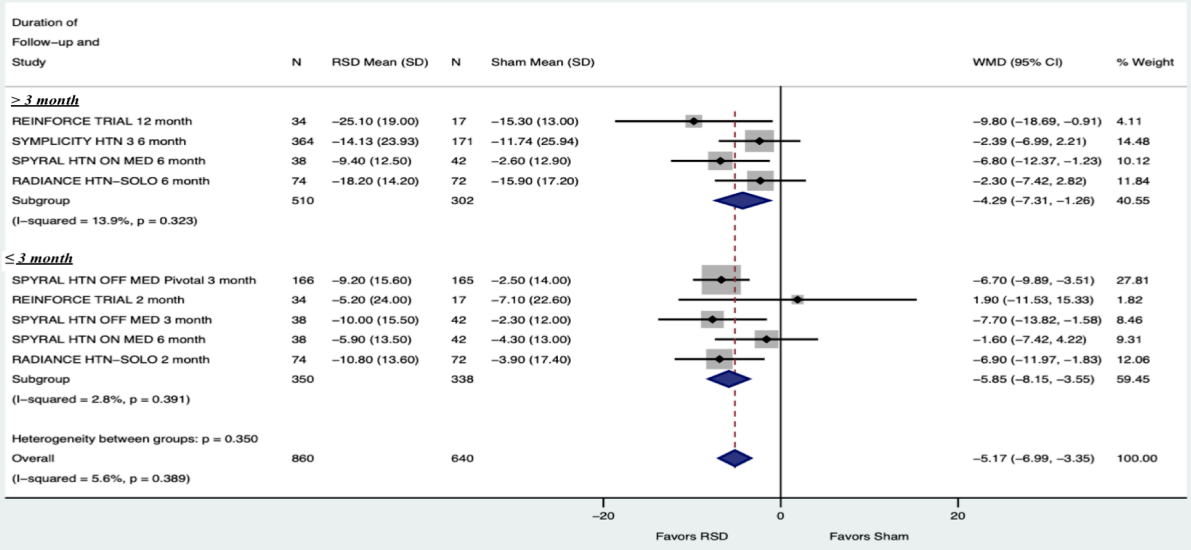


eFigure-3. Forest plot comparing the outcomes of Renal Sympathetic Denervation (RSD) versus sham. (A) Ambulatory systolic blood pressure in studies reporting outcomes at > 3 month of follow up and studies reporting ≤ 3month of follow-up. (B) Ambulatory diastolic blood pressure in studies reporting outcomes at > 3 month of follow up and studies reporting ≤ 3month of follow-up.



eFigure-4. Forest plot comparing the outcomes of Renal Sympathetic Denervation (RSD) versus sham. (A) Office systolic blood pressure in studies reporting outcomes at > 3 month of follow up and studies reporting ≤ 3month of follow-up. (B) Office diastolic blood pressure in studies reporting outcomes at > 3 month of follow up and studies reporting ≤ 3month of follow-up.

(A)



(B)