“We have hit a nerve, Updates in Renal Denervation”

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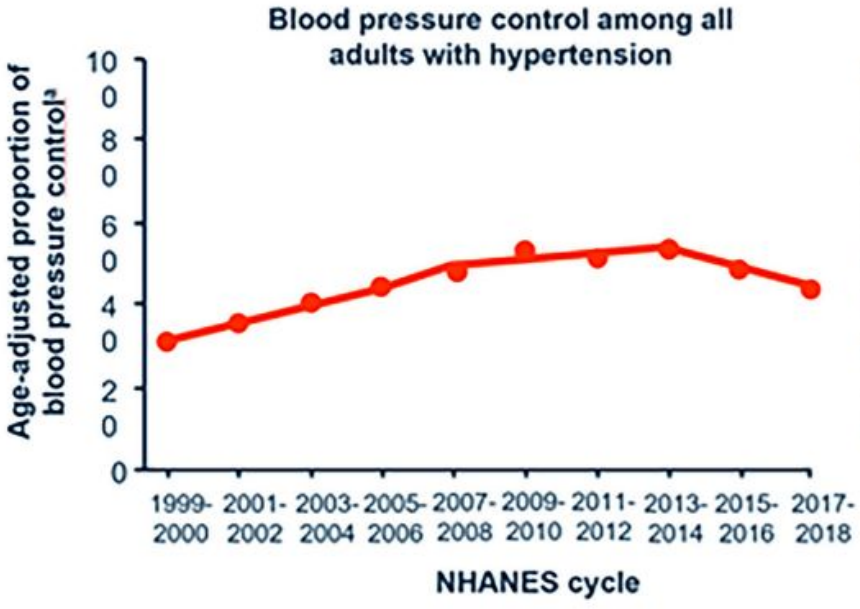
Disclosures

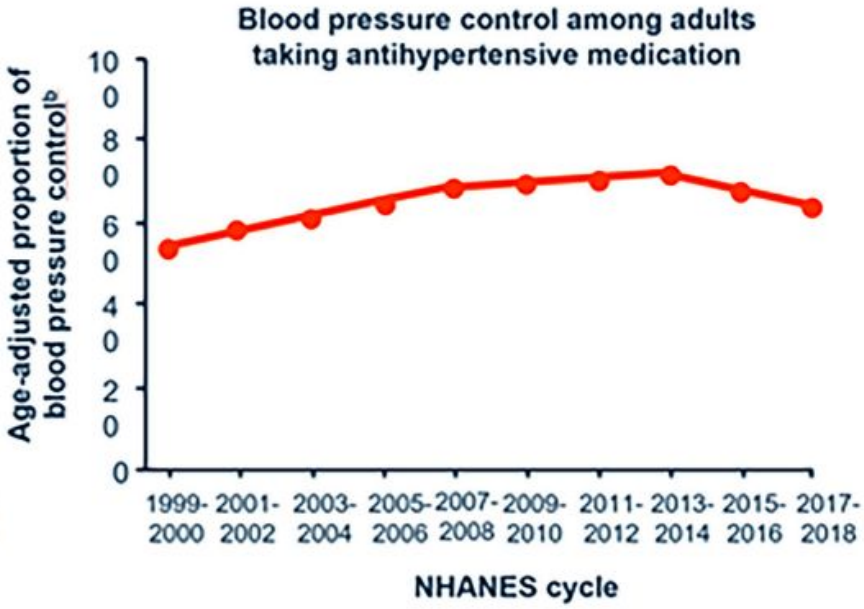
None

Objectives

- Pathophysiology of renal denervation
- Review original trials on renal denervation
- Review more recent trials on renal denervation

Trends in Blood Pressure control

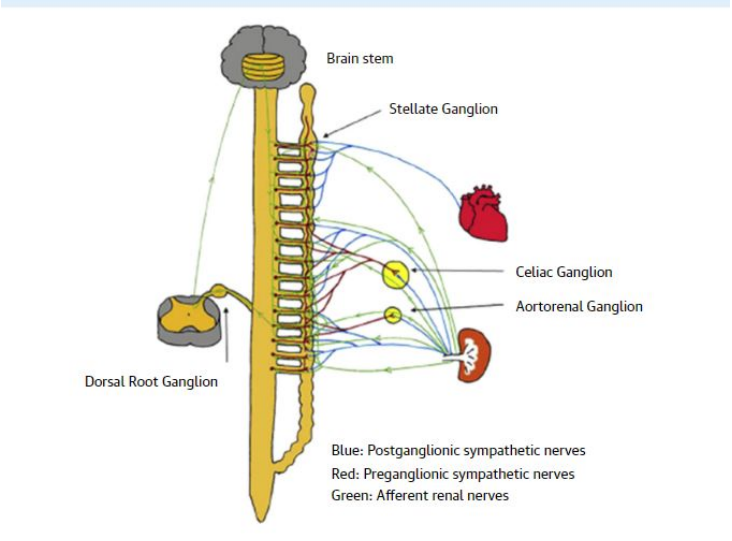




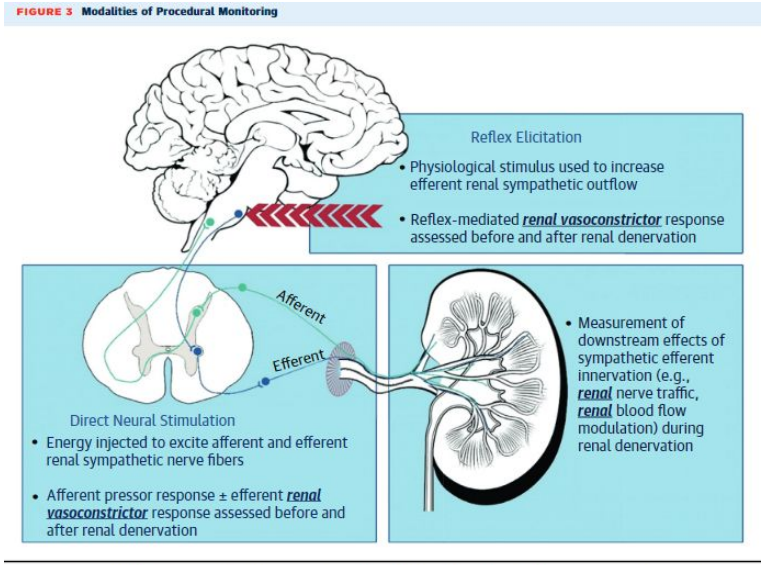
[a] Among all adults with hypertension.
[b] Among adults who self-reported taking antihypertensive medication.

Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, Colantonio LD. Trends in Blood Pressure Control Among US Adults With Hypertension, 1999-2000 to 2017-2018. JAMA. 2020 Sep 22;324(12):1190-1200. doi: 10.1001/jama.2020.14545. PMID: 32902588; PMCID: PMC7489367.

Pathways of Renal Denervation



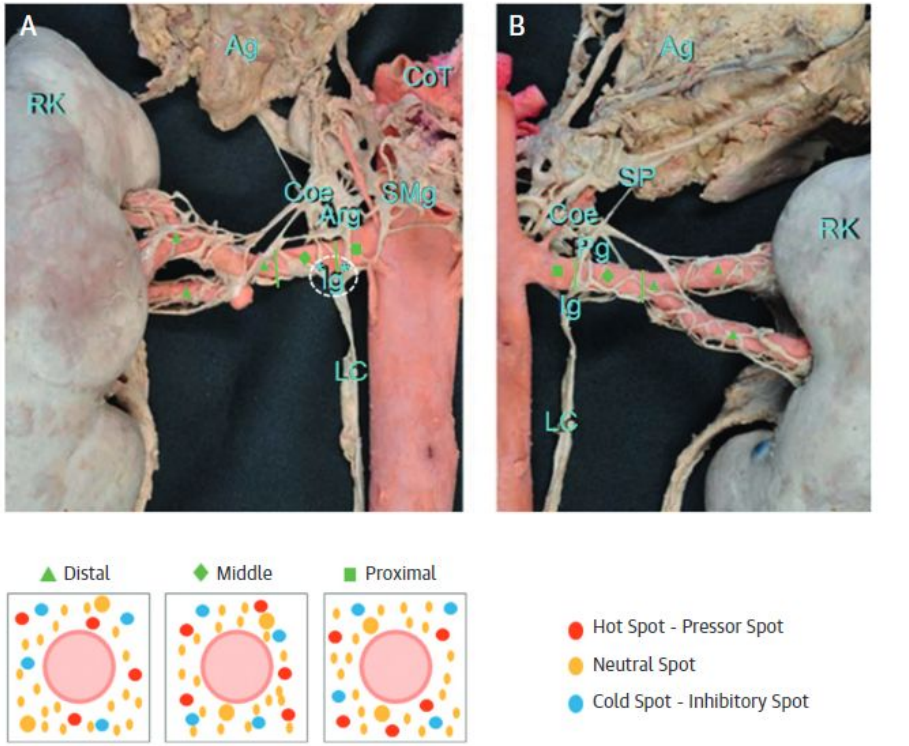
There are multiple pathways through which renal denervation can directly and indirectly result in brain stem and stellate ganglion remodeling and reduced nerve activity. These include inhibition of afferent nerve signaling **(green lines)** and retrograde trans-synaptic degeneration **(blue lines)** (28).



The promising 3 modalities of procedural monitoring (direct neural stimulation, reflex elicitation, and passive monitoring) evaluated by new technologies, providing intraprocedural validation of renal denervation.

Kiuchi M, Esler M, Fink G, et al. Renal Denervation Update From the International Sympathetic Nervous System Summit. *J Am Coll Cardiol.* 2019 Jun, 73 (23) 3006–3017.
https://doi.org/10.1016/j.jacc.2019.04.015

FIGURE 4 Theoretical Framework for Selective Versus Nonselective Renal Denervation



(Top) The right renal artery sympathetic innervation in **(A)** anterior and **(B)** posterior views divided in 3 segments: proximal **(green squares)**, middle **(green diamonds)**, and distal **(green triangles)**. **(Bottom)** A schematic concept for selective versus global renal denervation: **red dots** represent "hot spots"—pressor spots. These are nerves that when stimulated increase BP. They are the ideal target for renal denervation. **Blue dots** represent "cold spots"—inhibitory spots, which lower BP when stimulated. The **yellow dots** represent the majority of nerve fibers, which are neutral in their contribution to BP control and do not show hemodynamic effects when stimulated. *Connection between ganglia.

Kiuchi M, Esler M, Fink G, et al. Renal Denervation Update From the International Sympathetic Nervous System Summit. *J Am Coll Cardiol.* 2019 Jun, 73 (23) 3006–3017.
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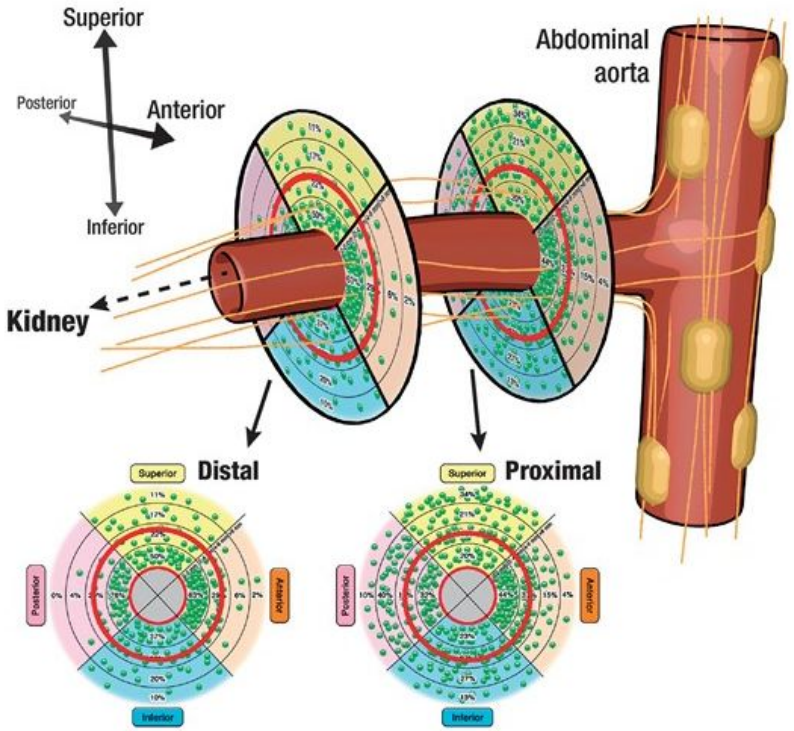


Schematic illustration of the renal artery with its surrounding nerves. The sympathetic nerve fibres originate from the abdominal ganglia and run conically to the distal part of the vessel. The lower circles show the nerve distribution stratified according to the total number (each green dot represents 10 nerves) and relative number (as percent per segment) of nerves. Adapted with permission from[91].

Techniques of Renal Denervation

Technology	System/Catheter	Design	Evidence available
RF	Symplicity Flex	Single electrode, unipolar, 6fr	Symplicity HTN-1, 2, 3, DENERHTN [7,35,63,69]
	EnligHTN	Multielectrode, basket, unipolar, 8fr	EnligHTN I, II [38,39]
	Symplicity Spyral	Multielectrode, over wire, unipolar, 6fr	Spyral feasibility study, Spyral HTN-Off MED/On MED [40,74,75]
	Iberis	Single electrode, radial or ulnar approach, unipolar, 4 fr	Case reports only [44]
	One-Shot	Balloon based, Irrigated, over the wire, unipolar, 6fr	In-man, RAPID [46]
	Vessix V2	Balloon based, over the wire, bipolar, 8fr	In-man, REDUCE-HTN [43]
US	Paradise	Active cooling balloon, 6fr	Porcine model studies In-man, REDUCE, RADIANCE HTN SOLO [49–51]
	Surround Sound System	Non-invasive	Feasibility study in canine, In-man 'WAVE I-IV' [47,48,52]
Chemical	Vincristine, Modified angioplasty catheter	Angioplasty balloon catheter Over the wire, 8fr	Swine model study, In-man single case report [53,55]
	Alcohol, Peregrine system	Three-needle catheter, 7fr	Proof of concept in swine, Randomised comparison with RF in swine, First-in-man feasibility study [54,57,58]
Microwave	In-house built catheter	Irrigated catheter, 8.5fr	Proof of concept study in sheep [60]

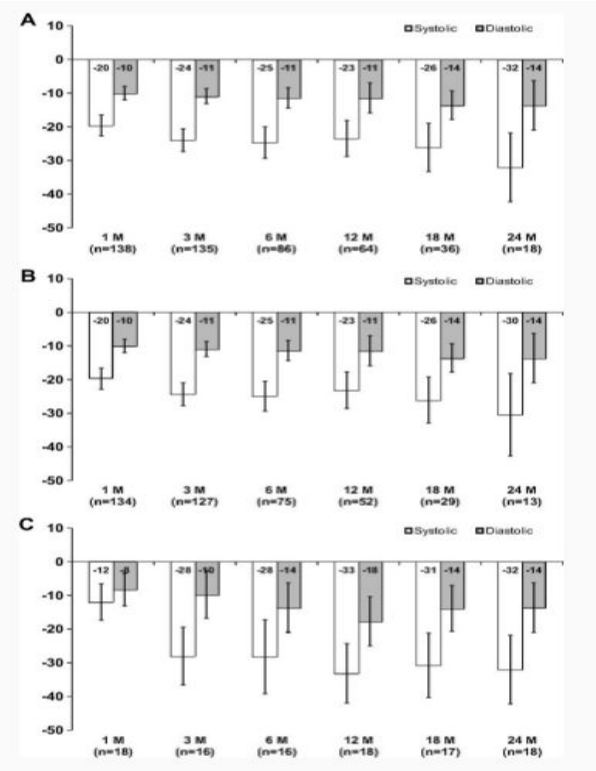
Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, Colantonio LD. Trends in Blood Pressure Control Among US Adults With Hypertension, 1999-2000 to 2017-2018. JAMA. 2020 Sep 22;324(12):1190-1200. doi: 10.1001/jama.2020.14545. PMID: 32902588; PMCID: PMC7489367.

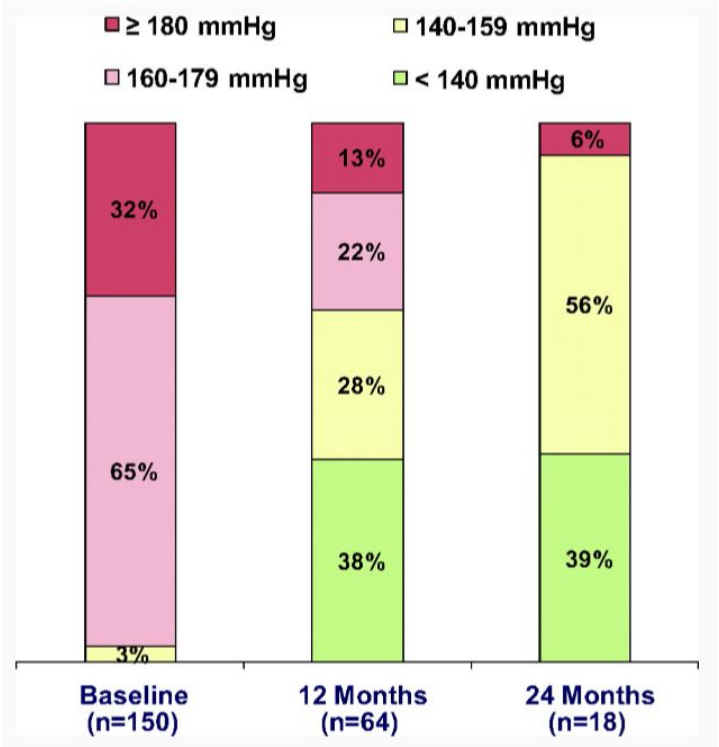
Review of Initial trials of renal denervation

Symplicity HTN-1

Symplicity HTN-2

Symplicity HTN-1



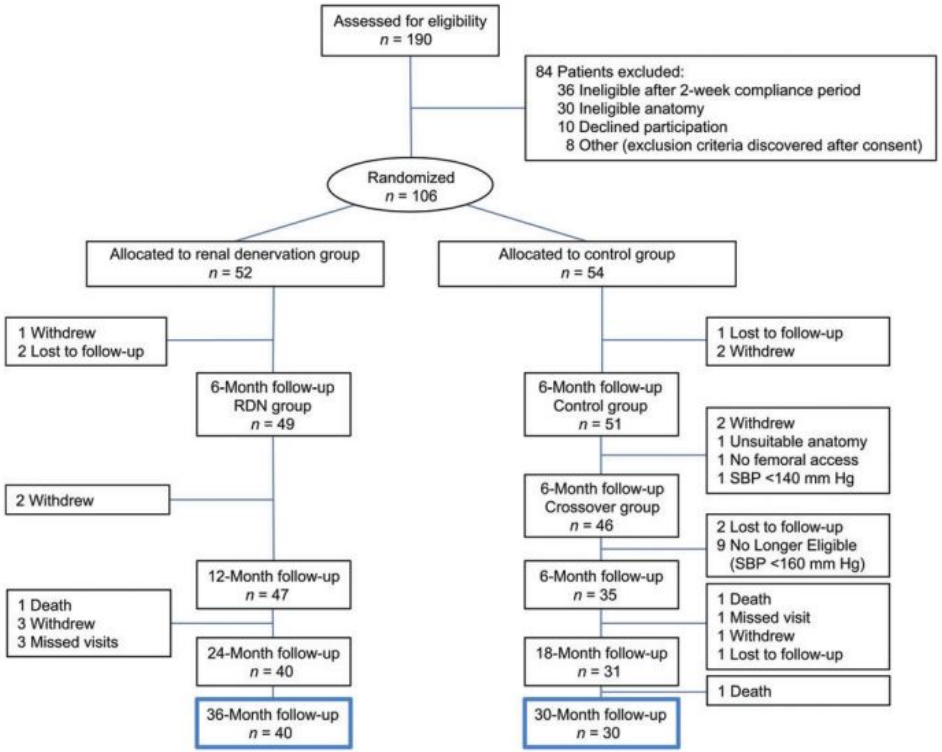


O'Brien E. Renal denervation for resistant hypertension--the Symplicity HTN-1 study. Lancet. 2014 May 31;383(9932):1884. doi: 10.1016/S0140-6736(14)60910-7. PMID: 24881985.

Symplicity HTN-2

Symplicity HTN-2 was a prospective, multi-centre, unblinded study that randomised 106 patients to either RAD (n = 52) or control arm [34]. Similarly, the RAD arm had a significant reduction in office BP at 6 months (-32/-12 mmHg) with 84% responders. In follow-up studies, office BP reduction was persistent at 1 (-28/-9.7 mmHg, n = 49) and 3 years (-33/-14 mmHg, n = 40

Symplicity HTN-2



Esler MD, Böhm M, Sievert H, Rump CL, Schmieder RE, Krum H, Mahfoud F, Schlaich MP. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. Eur Heart J. 2014 Jul;35(26):1752-9. doi: 10.1093/eurheartj/ehu209. Epub 2014 Jun 4. PMID: 24898552; PMCID: PMC5994826.

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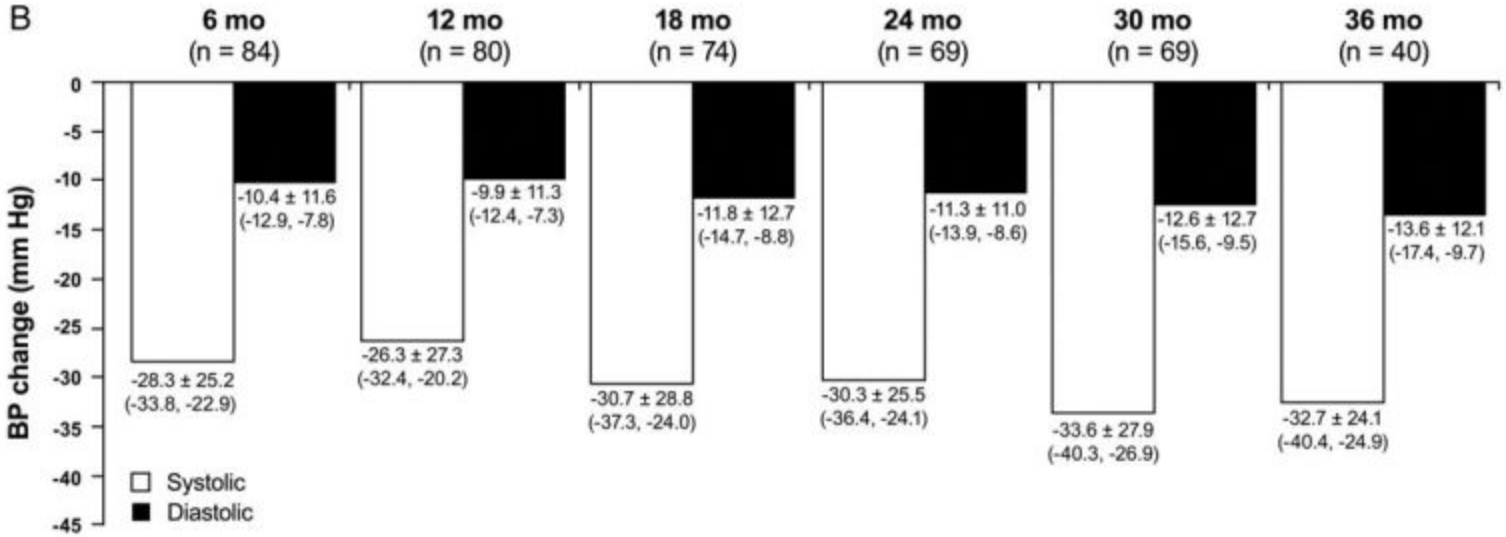

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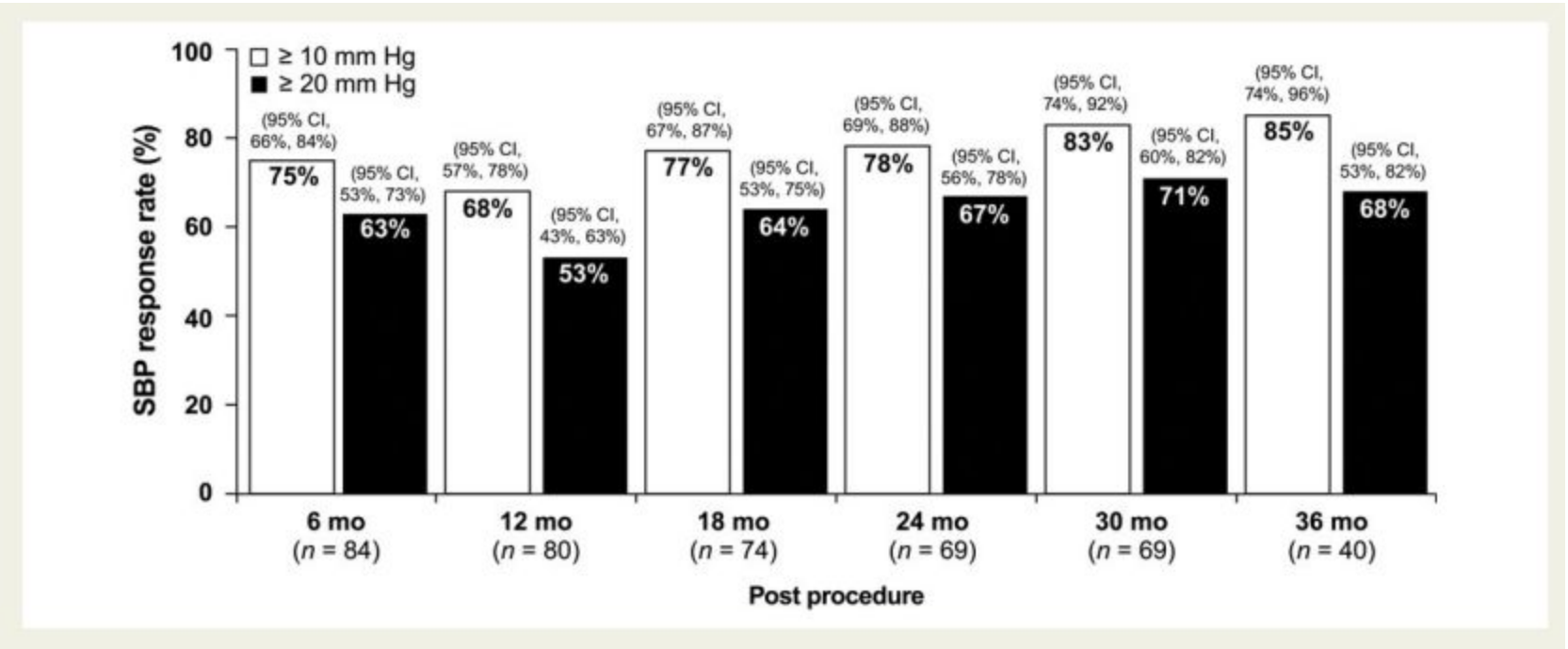

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Second General trials of Renal Denervation

Symplicity HTN-3

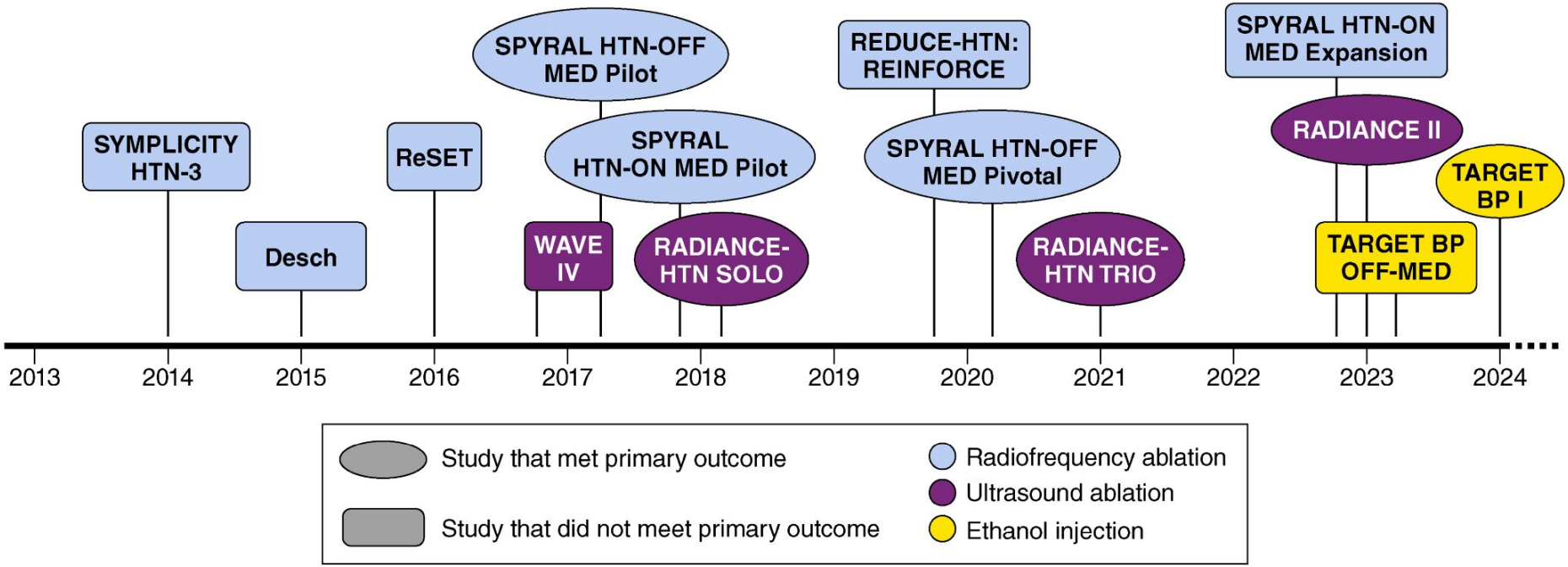
SPYRAL HTN OFF-MED

SPYRAL HTN ON-MED

RADIANCE SOLO-HTN

TARGET BP OFF-MED

TARGET BP I


SYMPLICITY HTN-3
Desch
ReSET
SPYRAL HTN-OFF MED Pilot
SPYRAL HTN-ON MED Pilot
WAVE IV
RADIANCE-HTN SOLO
REDUCE-HTN: REINFORCE
SPYRAL HTN-OFF MED Pivotal
RADIANCE-HTN TRIO
SPYRAL HTN-ON MED Expansion
RADIANCE II
TARGET BP I
TARGET BP OFF-MED
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
Study that met primary outcome
Study that did not meet primary outcome
Radiofrequency ablation
Ultrasound ablation
Ethanol injection

Symplicity HTN-3

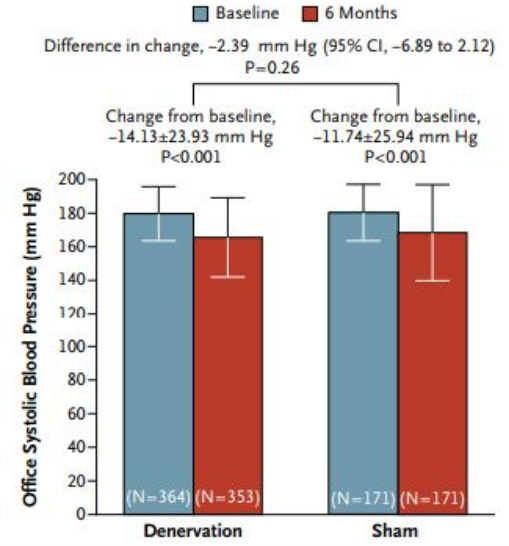


Figure 1. Primary Efficacy End Point.

A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mm Hg. The I bars indicate standard deviations.

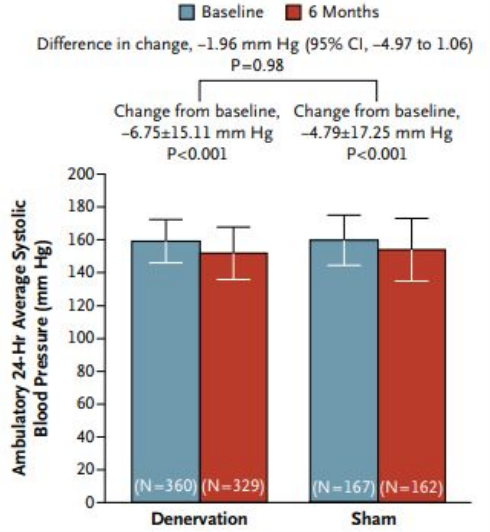


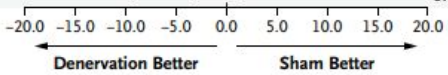
Figure 2. Secondary Efficacy End Point.

A significant change from baseline to 6 months in ambulatory 24-hour average systolic blood pressure was observed in both groups. The between-group difference (the secondary efficacy end point for which the study was powered) did not meet a test of superiority with a margin of 2 mm Hg. The I bars indicate standard deviations.

Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014 Apr 10;370(15):1393-401. doi: 10.1056/NEJMoa1402670. Epub 2014 Mar 29. PMID: 24678939.

Symplicity HTN-3

Subgroup	Denervation	Sham	Between-Group Difference in Change in Office Systolic Blood Pressure (95% CI)	P Value	P Value for Interaction
	no. of patients		*mm Hg*		
All patients	353	171	−2.39 (−6.89 to 2.12)	0.26	
Diabetes mellitus					0.82
Yes	169	68	−4.53 (−11.51 to 2.46)	0.20	
No	181	101	−3.46 (−9.55 to 2.62)	0.26	
Sex					0.37
Male	208	108	−2.30 (−7.63 to 3.03)	0.40	
Female	142	61	−6.64 (−14.94 to 1.65)	0.12	
Black race					0.09
Yes	85	49	2.25 (−7.27 to 11.78)	0.64	
No	264	120	−6.63 (−11.81 to −1.44)	0.01	
Body-mass index					0.77
<30	91	42	−2.77 (−11.47 to 5.93)	0.53	
≥30	259	126	−4.36 (−9.76 to 1.03)	0.11	
Receiving aldosterone antagonist at baseline					0.36
Yes	76	47	−8.05 (−17.63 to 1.52)	0.10	
No	274	122	−3.24 (−8.42 to 1.93)	0.22	
Estimated GFR					0.31
<60 ml/min/1.73 m^2	68	38	0.54 (−8.29 to 9.37)	0.90	
≥60 ml/min/1.73 m^2	282	131	−5.22 (−10.51 to 0.06)	0.05	
Age					0.27
<65 yr	246	128	−5.73 (−11.06 to −0.40)	0.04	
≥65 yr	104	41	0.09 (−8.80 to 8.99)	0.99	
Any medication change					0.68
Yes	132	70	−5.41 (−13.49 to 2.67)	0.19	
No	218	99	−3.44 (−8.83 to 1.96)	0.21	



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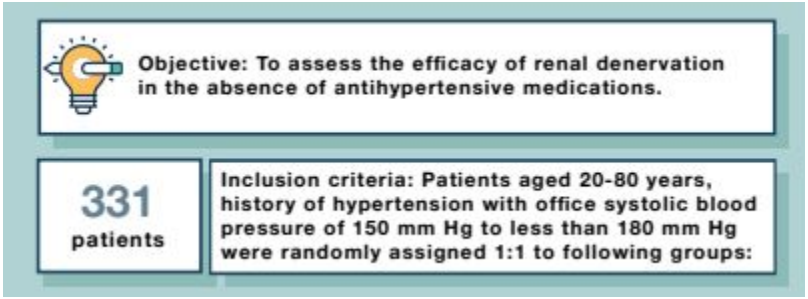
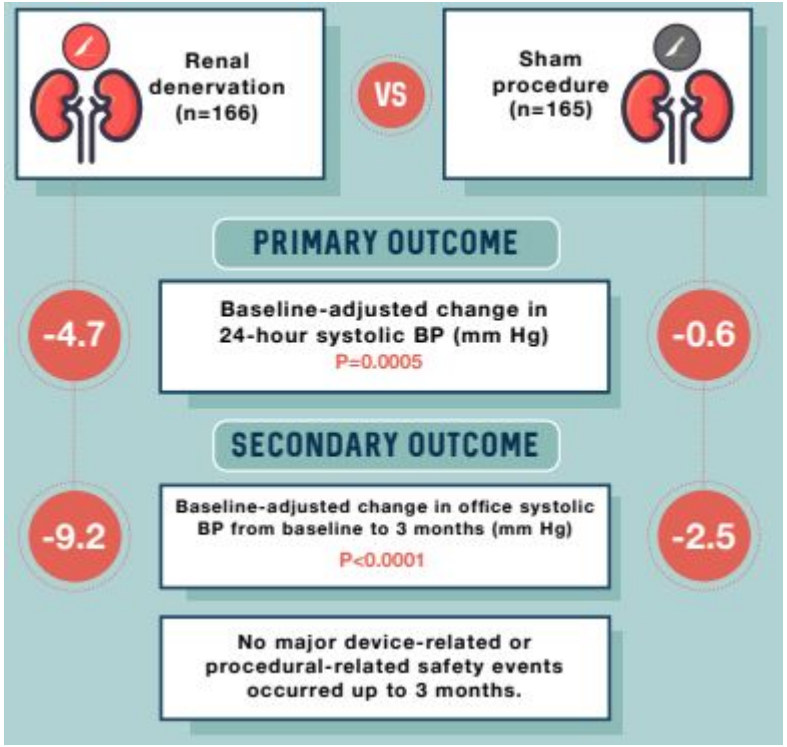
SPYRAL HTN-OFF MED

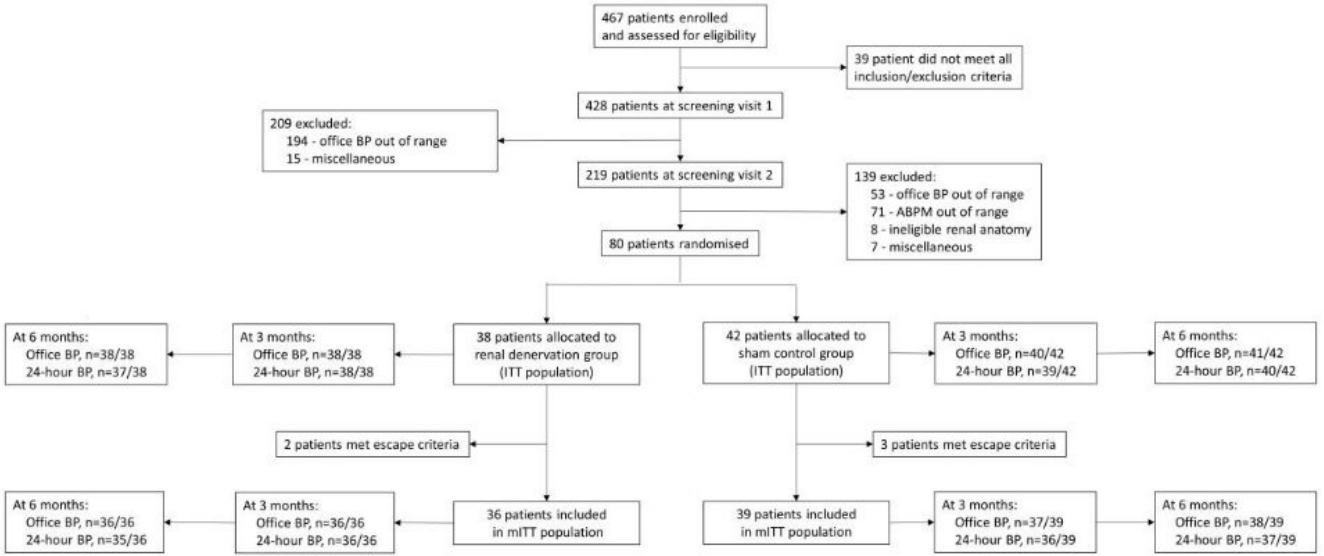




Conclusion: SPYRAL Pivotal showed the superiority of catheter-based renal denervation compared with a sham procedure to safely lower blood pressure in the absence of antihypertensive medications alone.

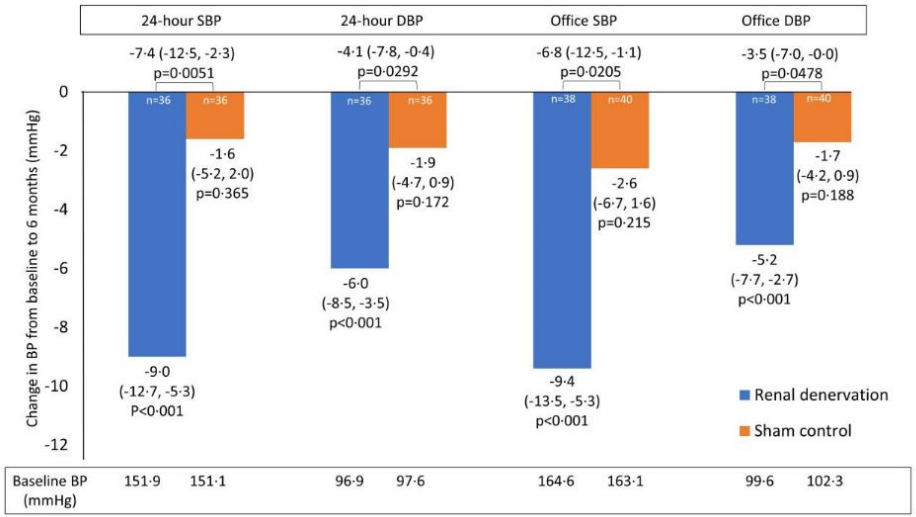
Böhm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE, Tsioufis K, Pocock S, Konstantinidis D, Choi JW, East C, Lee DP, Ma A, Ewen S, Cohen DL, Wilensky R, Devireddy CM, Lea J, Schmid A, Weil J, Agdirlioglu T, Reedus D, Jefferson BK, Reyes D, D'Souza R, Sharp ASP, Sharif F, Fahy M, DeBruin V, Cohen SA, Brar S, Townsend RR; SPYRAL HTN-OFF MED Pivotal Investigators. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. Lancet. 2020 May 2;395(10234):1444-1451. doi: 10.1016/S0140-6736(20)30554-7. Epub 2020 Mar 29. PMID: 32234534.

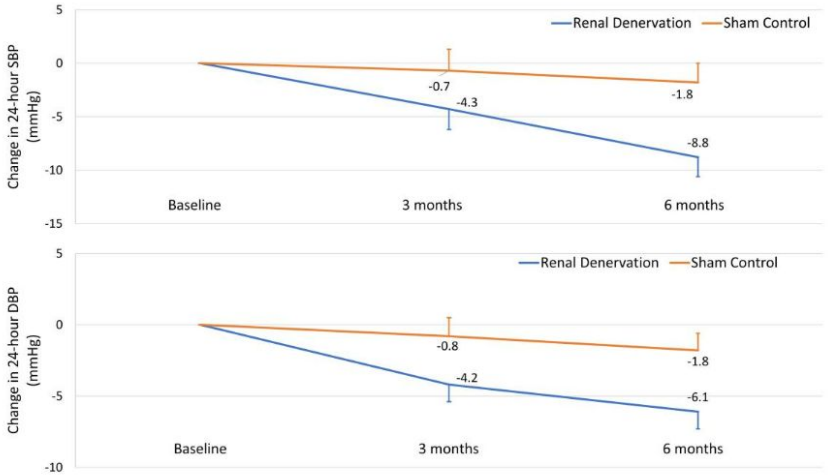
SPYRAL HTN-ON MED



Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, Tsioufis K, Tousoulis D, Choi JW, East C, Brar S, Cohen SA, Fahy M, Pilcher G, Kario K; SPYRAL HTN-ON MED Trial Investigators. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet. 2018 Jun 9;391(10137):2346-2355. doi: 10.1016/S0140-6736(18)30951-6. Epub 2018 May 23. PMID: 29803589.

SPYRAL HTN-ON MED





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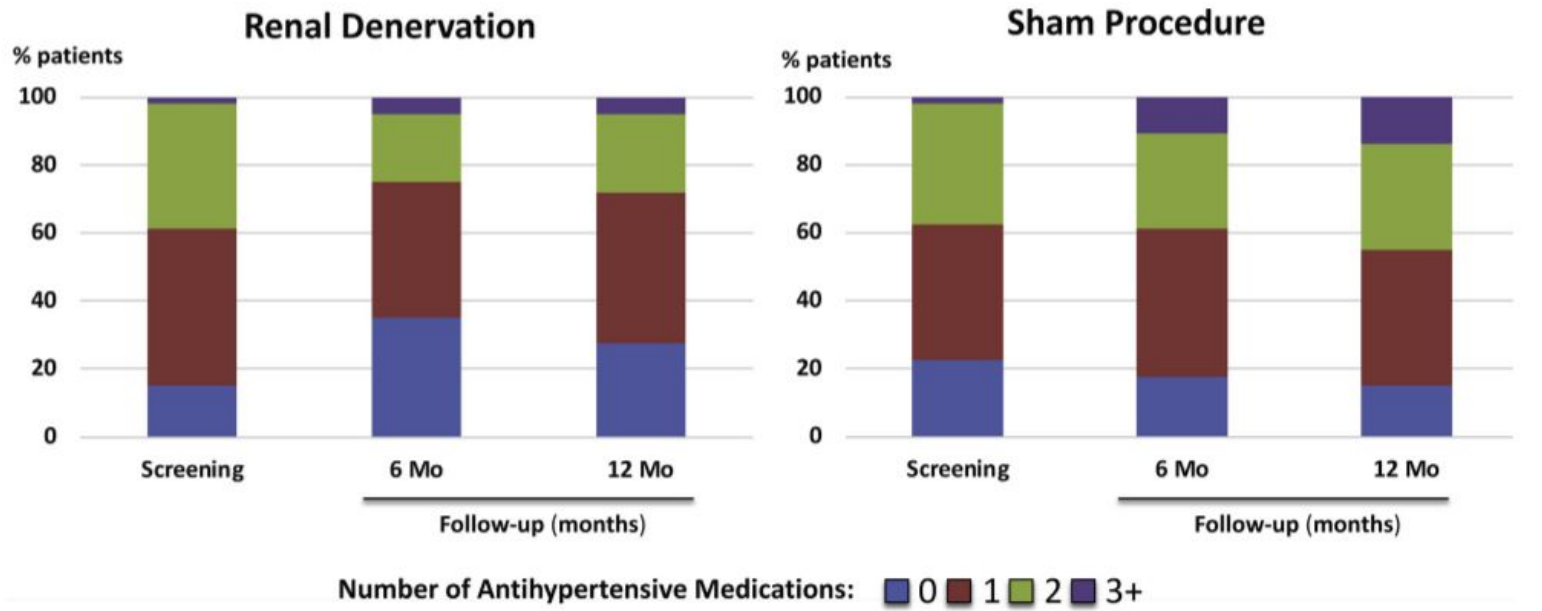
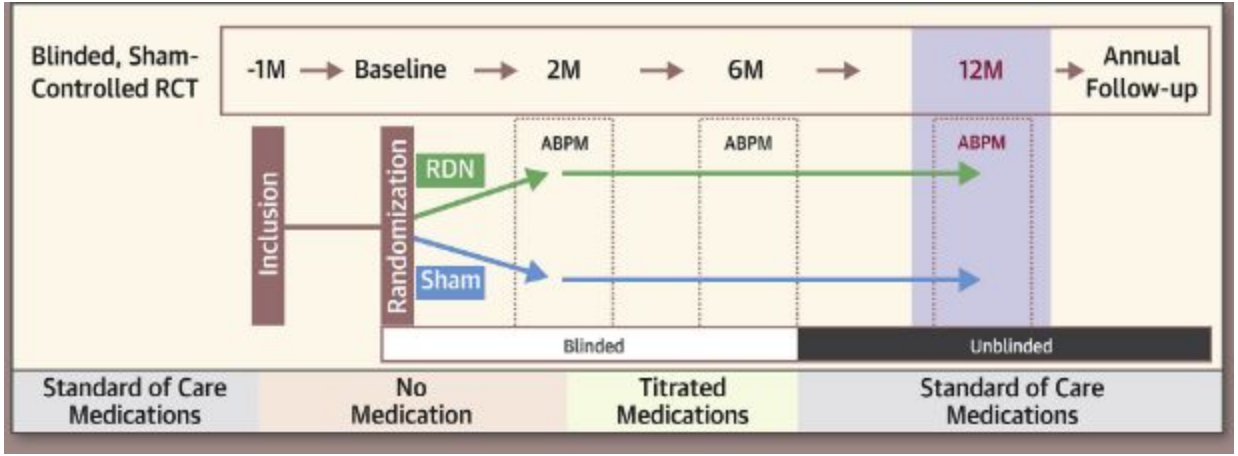
RADIANCE HTN-SOLO

FIGURE 1 Proportion of Patients on 0, 1, 2, and 3 Antihypertensive Medications in the Renal Denervation Group and the Sham Group From Screening to 6 and 12 Months



Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, Basile J, Kirtane AJ, Wang Y, Lobo MD, Saxena M, Feyz L, Rader F, Lurz P, Sayer J, Sapoval M, Levy T, Sanghvi K, Abraham J, Sharp ASP, Fisher NDL, Bloch MJ, Reeve-Stoffer H, Coleman L, Mullin C, Mauri L; RADIANCE-HTN Investigators. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet. 2018 Jun 9;391(10137):2335-2345. doi: 10.1016/S0140-6736(18)31082-1. Epub 2018 May 23. Erratum in: Lancet. 2018 Sep 8;392(10150):820. PMID: 29803590.

RADIANCE HTN-SOLO



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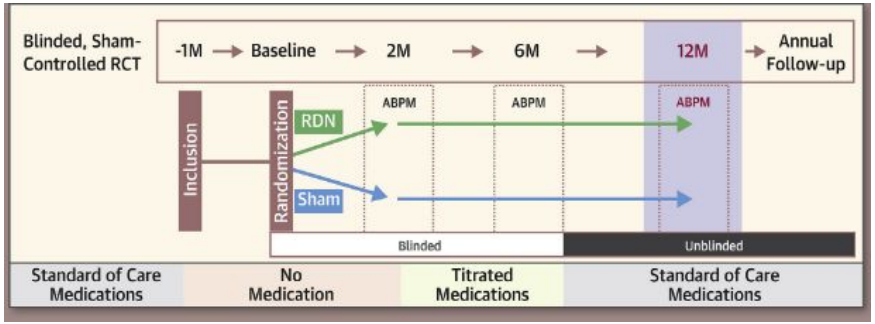
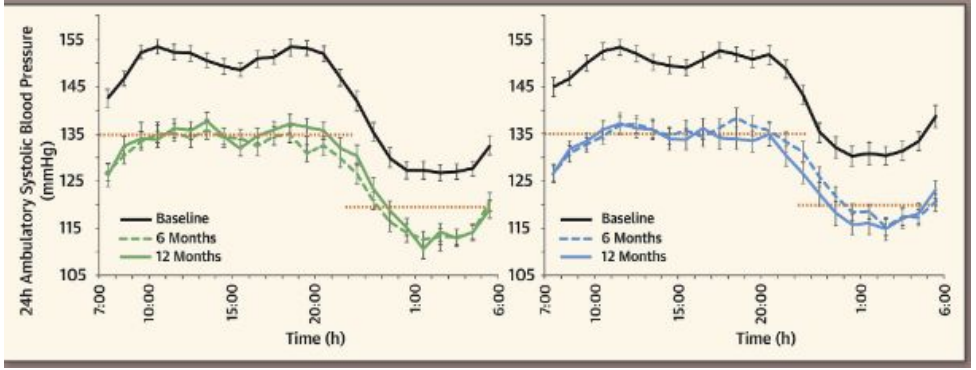
RADIANCE HTN-SOLO



Medication Burden	Renal Denervation			12M Between-group p Value	Sham		
	Randomization	6M	12M		Randomization	6M	12M
Number of Antihypertensive Medications (mean)	0.0	0.9	1.0	0.015	0.0	1.3	1.4
Defined Daily Dose (mean)	0.0	1.4	1.4	0.007	0.0	2.1	2.2



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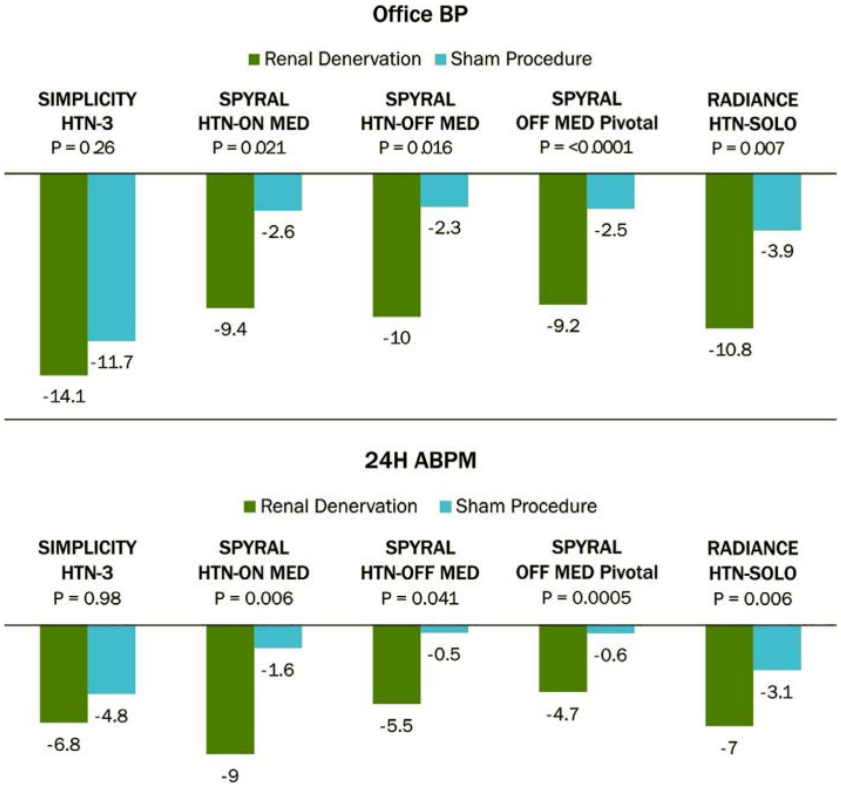
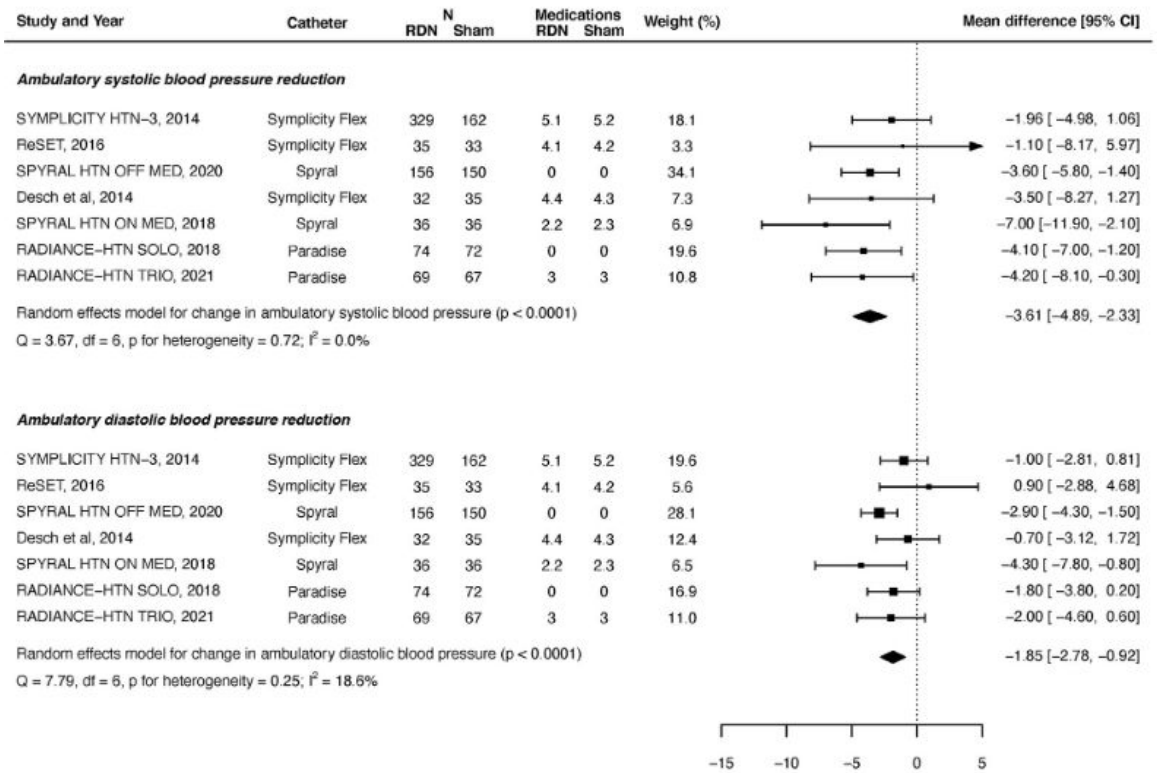
Review and Comparison of Newer RDN Trials



Kiuchi MG, Esler MD, Fink GD, et al. Renal Denervation Update From the International Sympathetic Nervous System Summit: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;73(23):3006-3017. doi:10.1016/j.jacc.2019.04.015

Review and Comparison of Newer RDN Trials



Ahmad Y, Francis DP, Bhatt DL, Howard JP. Renal Denervation for Hypertension: A Systematic Review and Meta-Analysis of Randomized, Blinded, Placebo-Controlled Trials. JACC Cardiovasc Interv. 2021 Dec 13;14(23):2614-2624. doi: 10.1016/j.jcin.2021.09.020. Epub 2021 Nov 4. PMID: 34743900.

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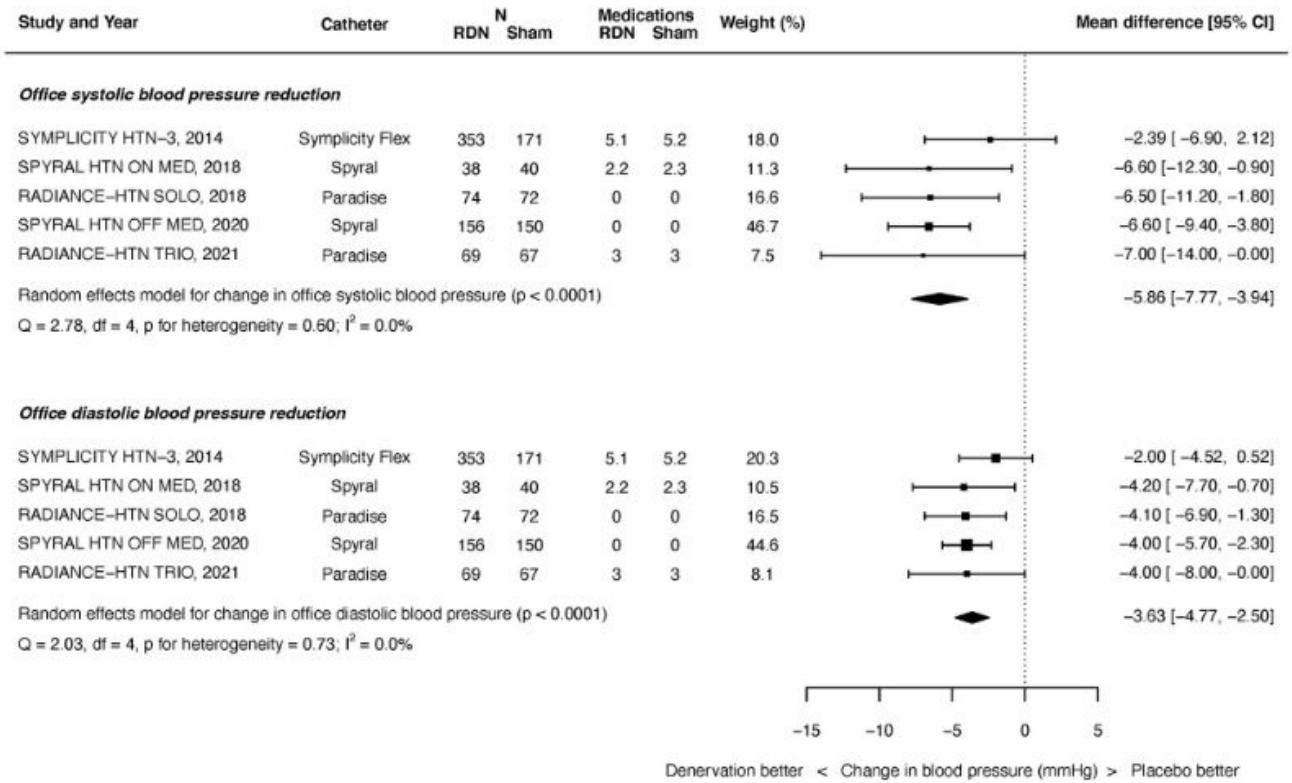

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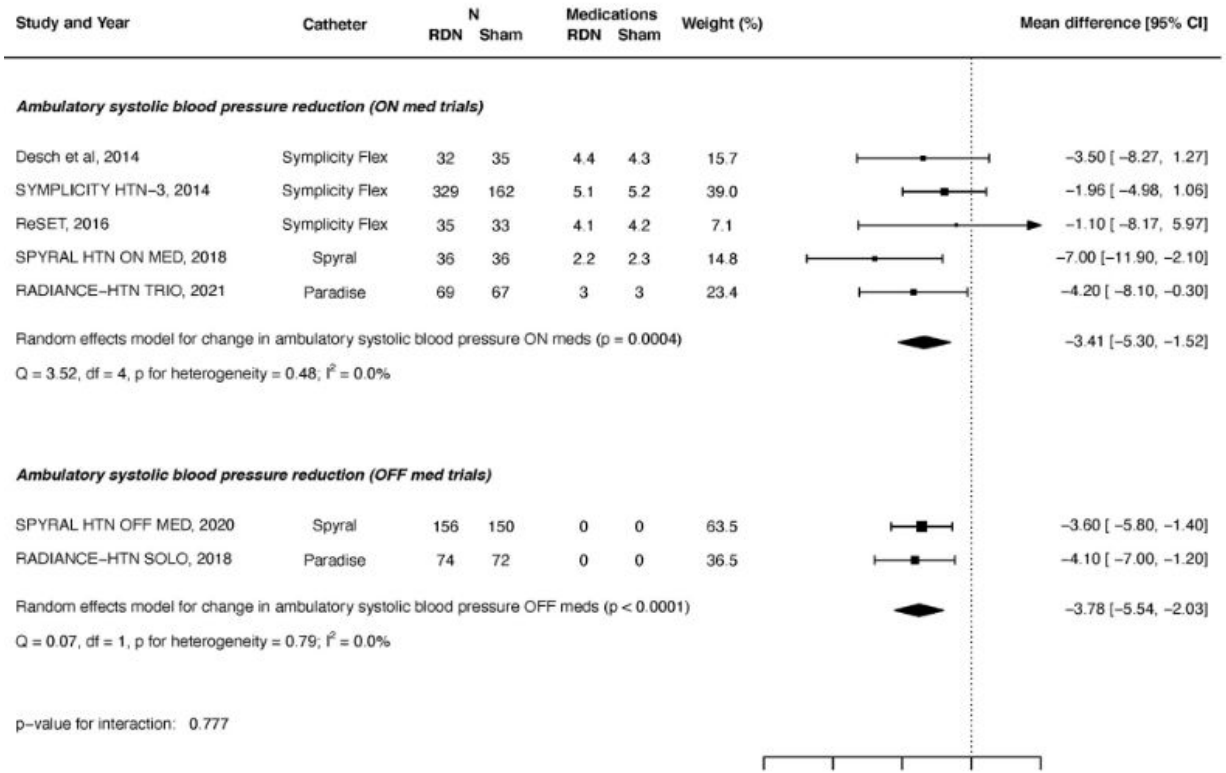

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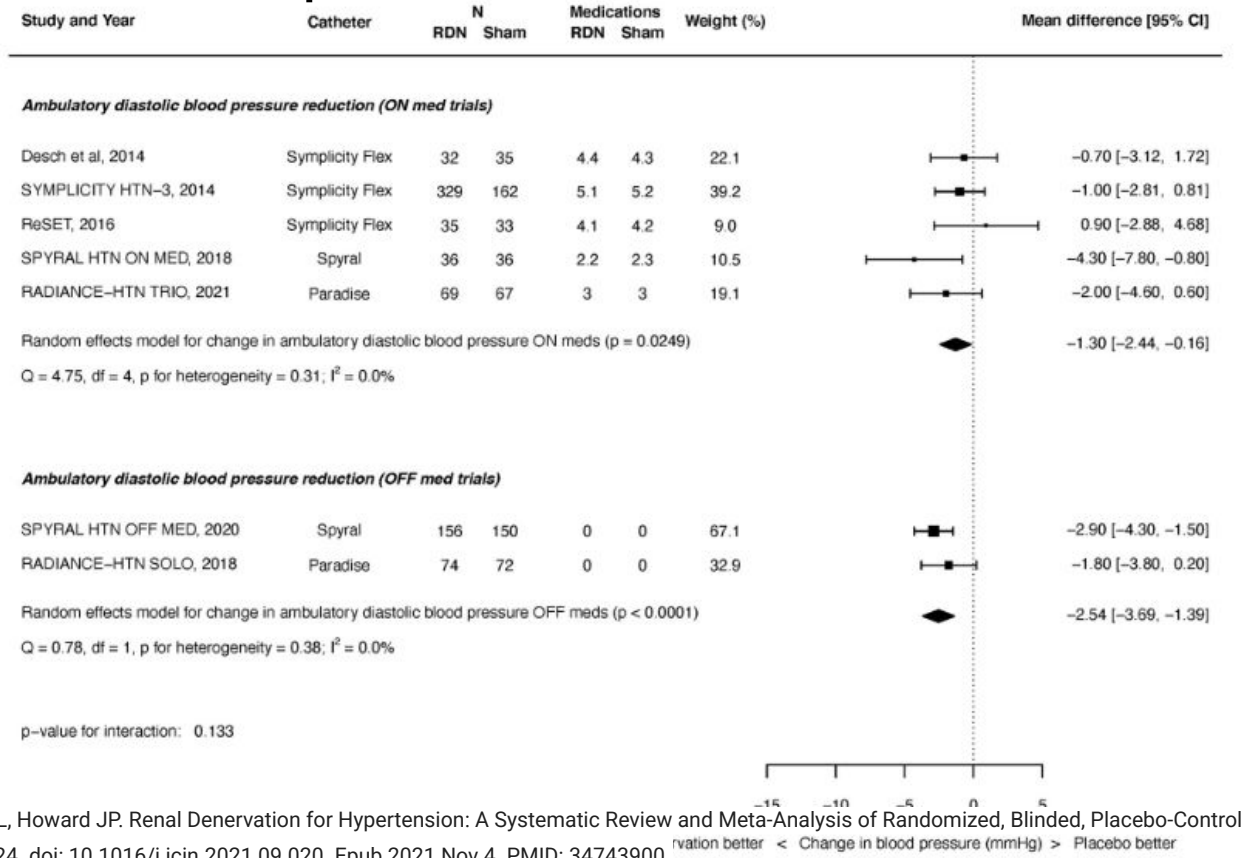

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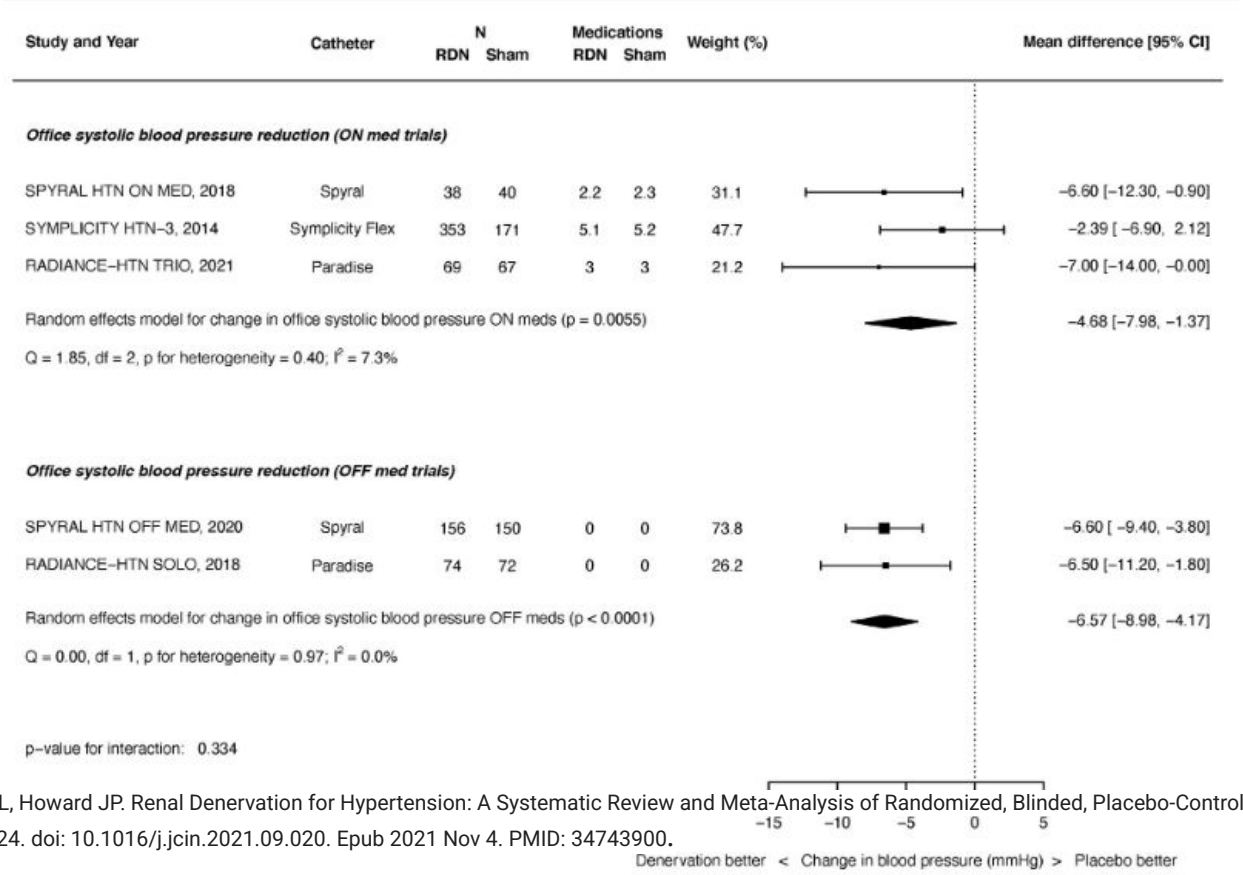

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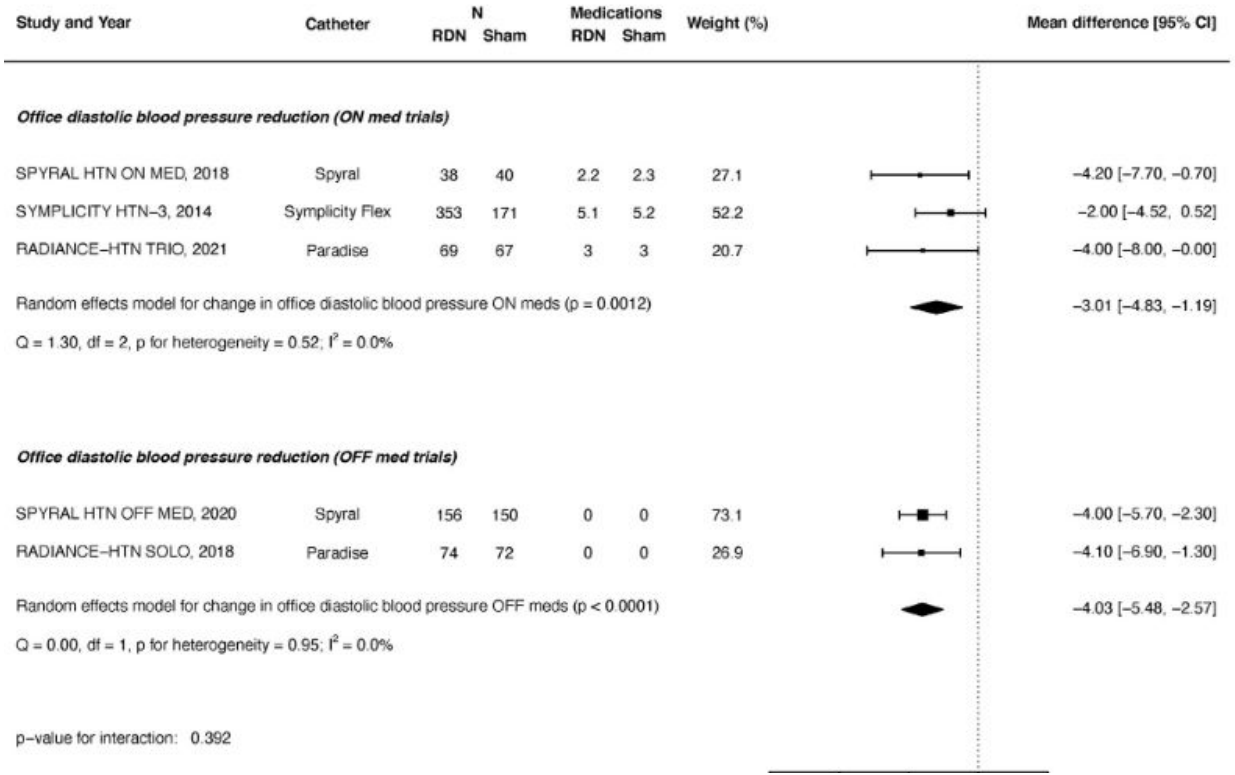

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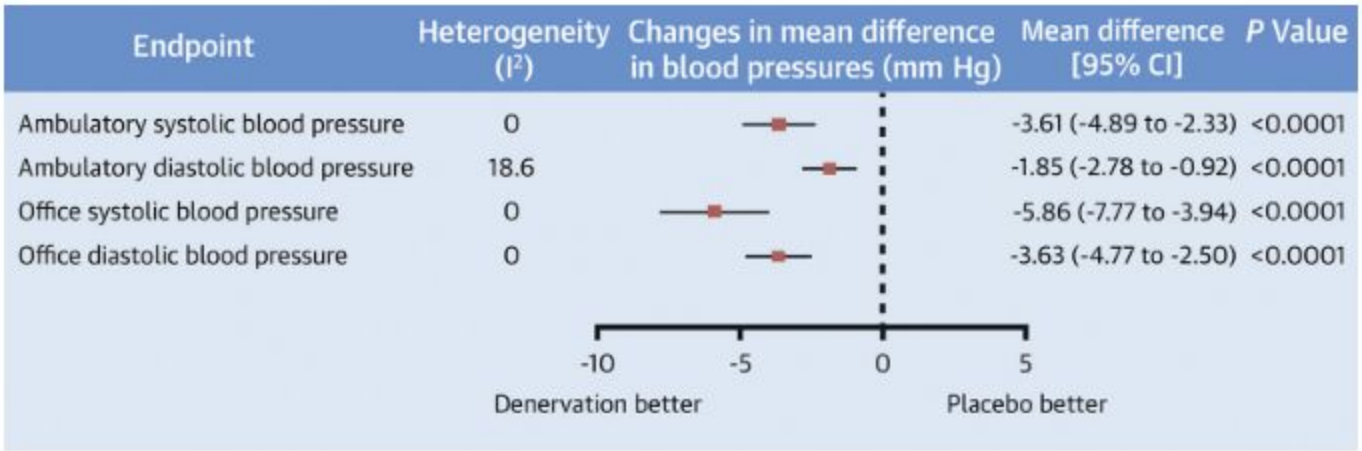
CENTRAL ILLUSTRATION **Renal Denervation Versus Placebo Meta-Analysis (N = 1,368)**



Ahmad, Y. et al. J Am Coll Cardiol Intv. 2021;14(23):2614-2624.

A summary of the effect of renal denervation on ambulatory systolic, ambulatory diastolic, office systolic, and office diastolic blood pressure. Mean difference in blood pressure in millimeters of mercury with 95% CIs, *P* values, and heterogeneity as assessed using the I^2 statistic. All meta-analyses were random effects and by the intention-to-treat principle.

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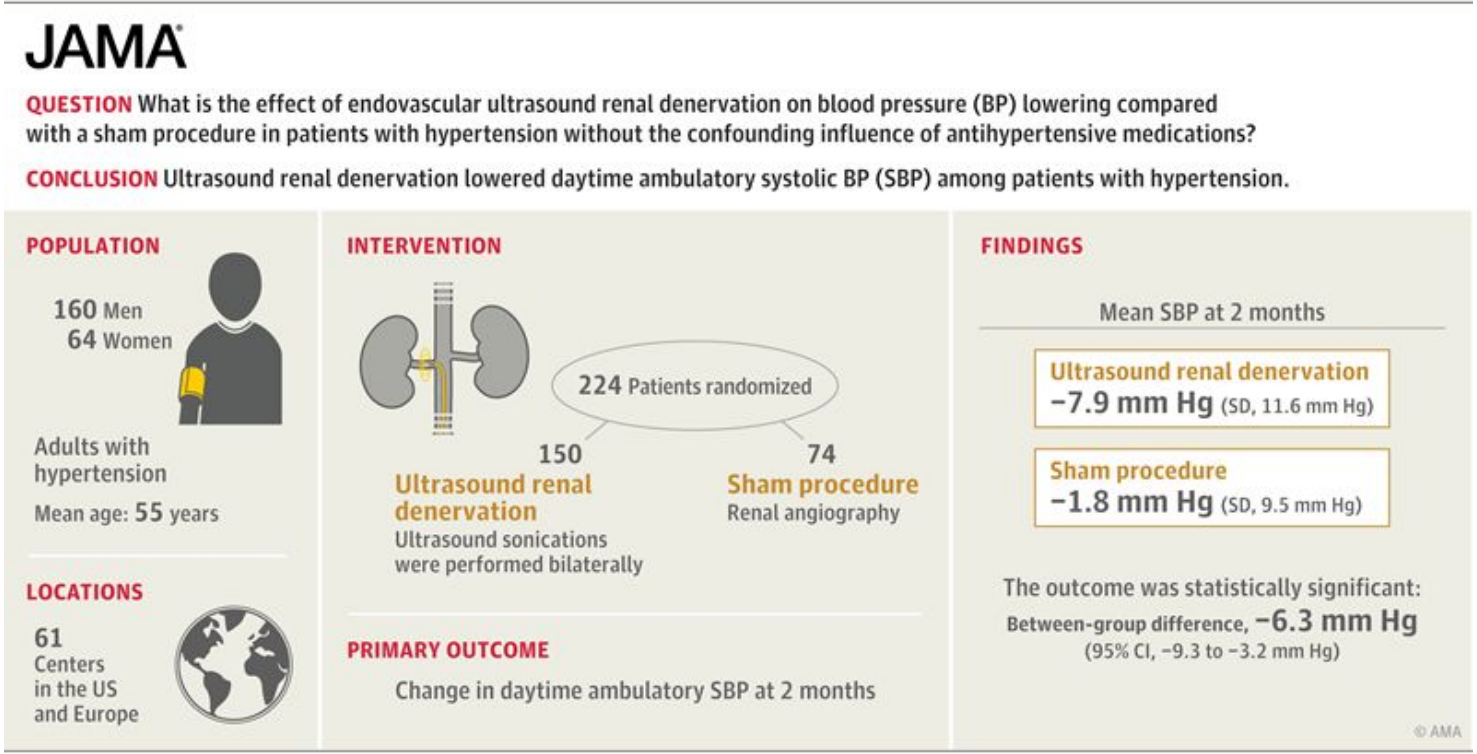
RADIANCE II



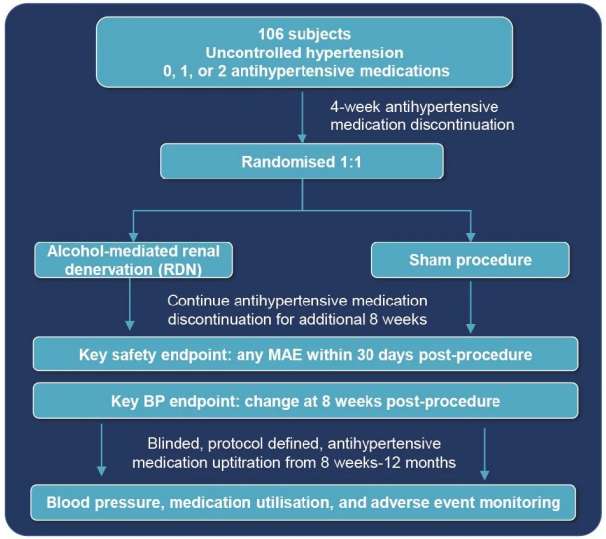
Azizi M, Saxena M, Wang Y, et al; RADIANCE II Investigators and Collaborators. Endovascular ultrasound renal denervation to treat hypertension: the RADIANCE II randomized clinical trial. *JAMA*. Published February 28, 2023. doi:10.1001/jama.2023.0713

Ongoing Trials (since 2022)

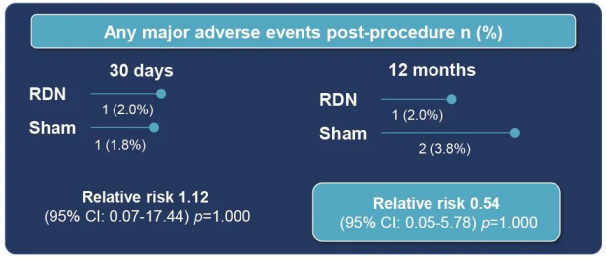
Trial, NCT*	Catheter system	Design, (randomisation ratio)	Sample size	Inclusion criteria	Primary efficacy outcome
SPYRAL HTN-ON MED Expansion, NCT02439775	Symplicity Spyral (multi-electrode RF)	Bayesian adaptive design, RDN vs sham (1:1)	340	Uncontrolled office and 24-hour BP on 1-3 antihypertensive drugs	Change in 24-hour SBP at 6 months
RADIANCE II, NCT03614260	Paradise (US)	RDN vs sham (1:1)	225	Uncontrolled stage II hypertension (office and daytime ambulatory BP) in absence of antihypertensive drugs	Change in daytime ambulatory SBP at 2 months
TARGET BP OFF-MED, NCT03503773	Peregrine (ethanol injection via microneedles)	RDN vs sham (1:1)	90	Uncontrolled office and 24-hour BP in absence of antihypertensive drugs	Change in 24-hour ambulatory SBP at 2 months
TARGET BP I, NCT02910414	Peregrine (ethanol injection via microneedles)	RDN vs sham (1:1)	300	Uncontrolled office and 24-hour BP on 2-5 antihypertensive drugs	Change in ambulatory 24-hour SBP at 3 months

TARGET BP OFF MED Trial

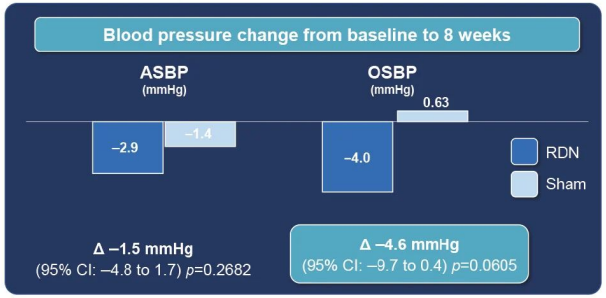
Study design



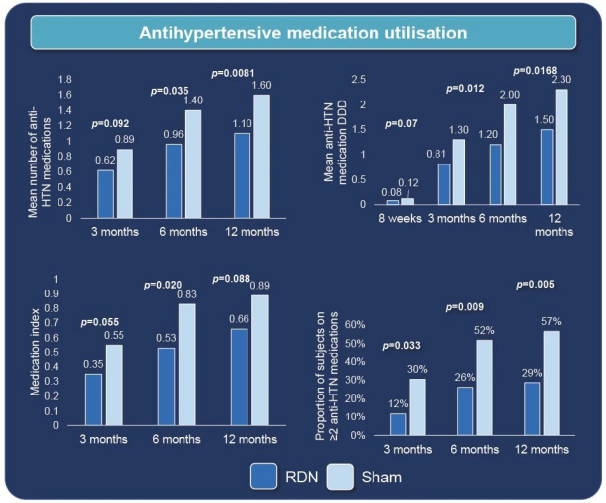
Primary safety findings



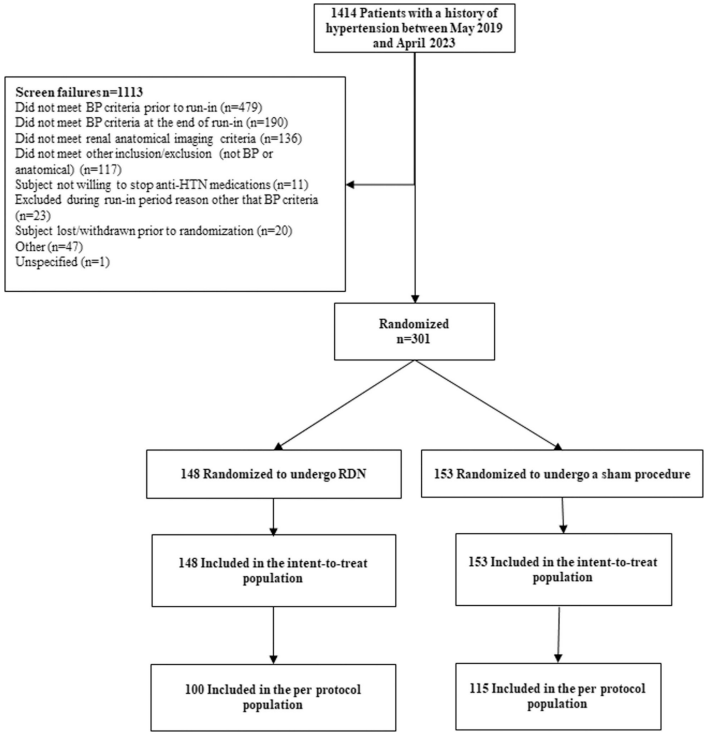
Primary blood pressure findings



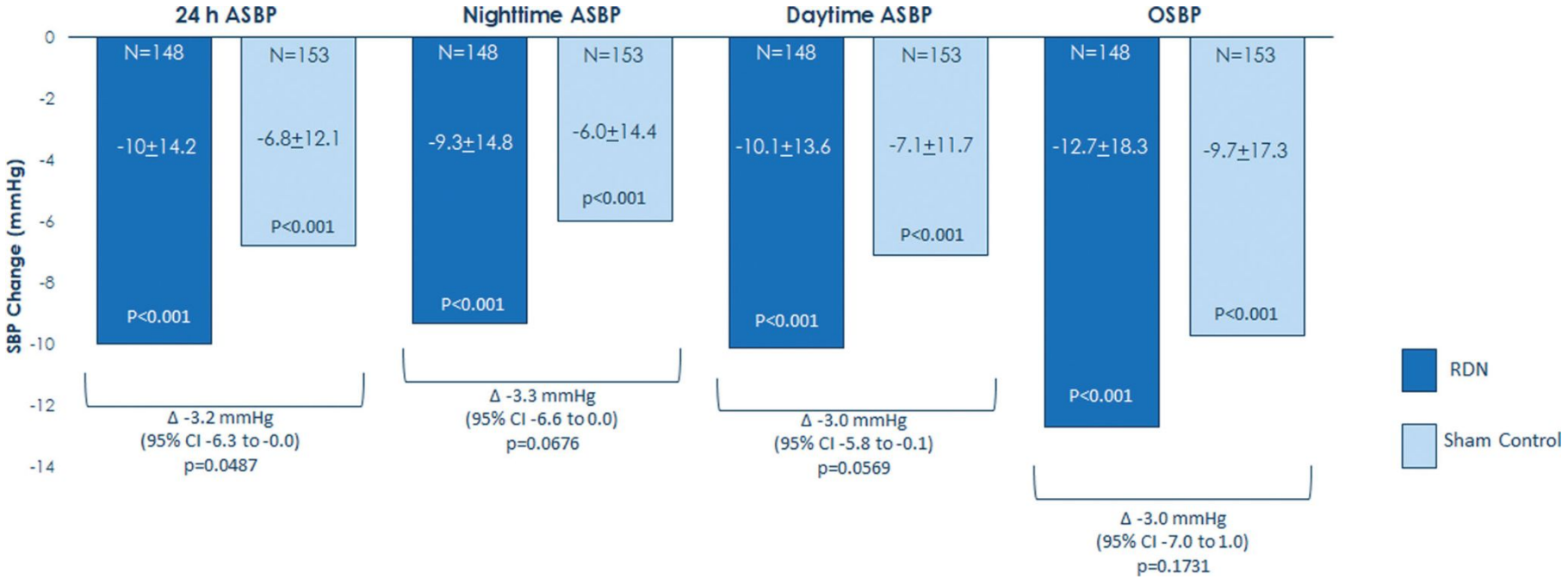
Key secondary findings



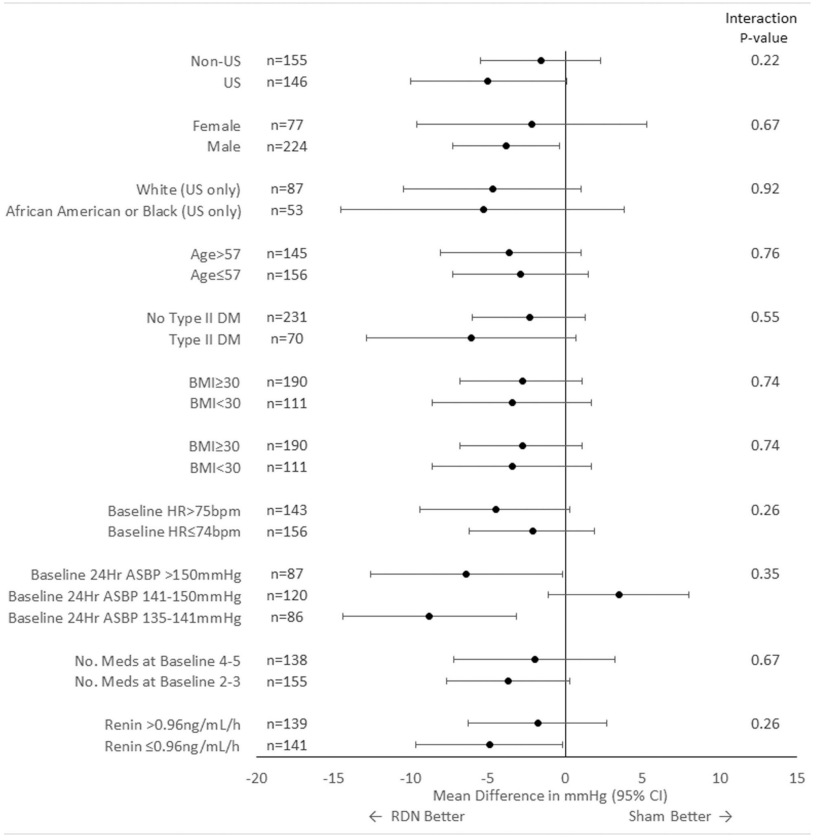
TARGET BP I Trial



TARGET BP I Trial



TARGET BP I Trial

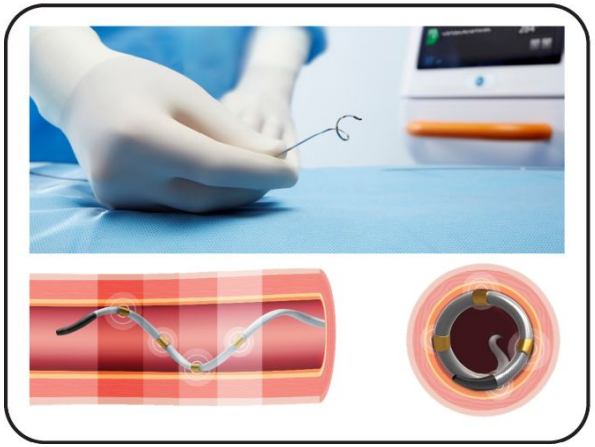


Considerations

- exclude secondary causes of HTN before RDN is considered
- RDN may be possible for patients unable to tolerate antihypertensive drugs in the long term or patient preference in a tailored, shared decision making process
- do not perform RDN in kidney transplant patients, FMD patients, untreated secondary htn, or patients with a single kidney

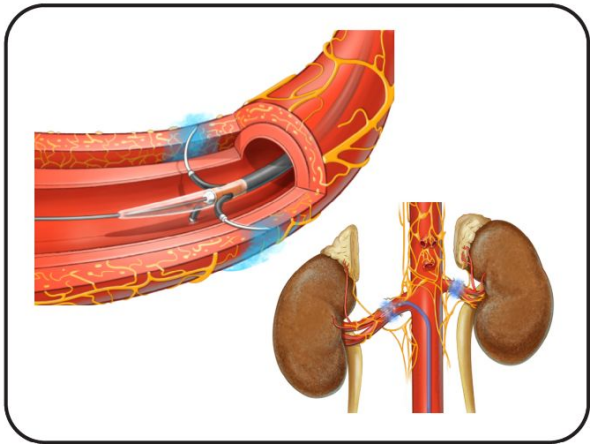
Renal Denervation Devices

Spyral® System



Paradise® System

Peregrine® System

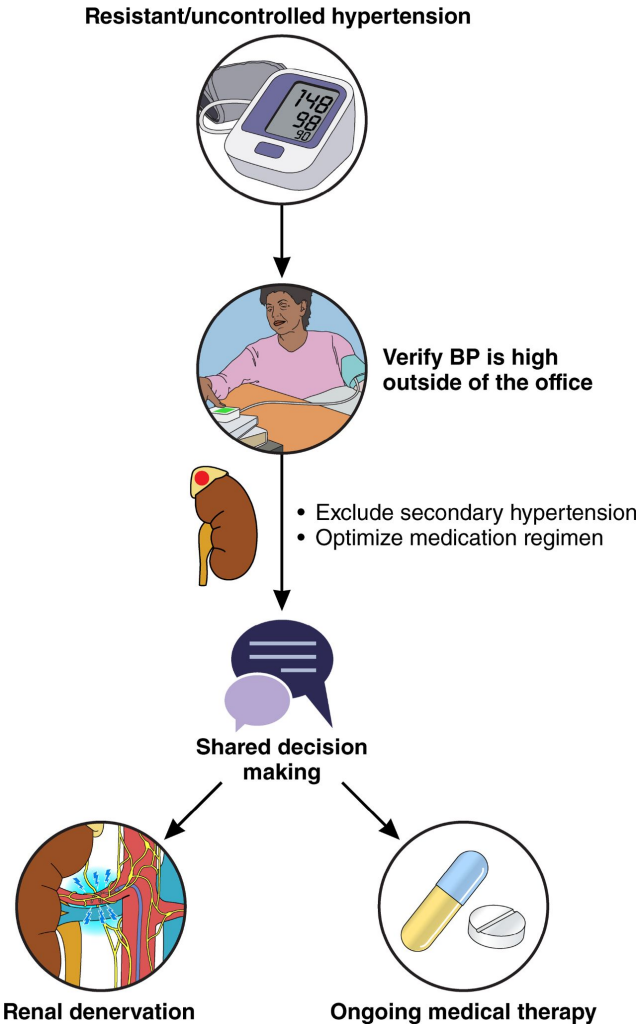


	Symplicity Spyral RF catheter system	Paradise US catheter system
Anatomical eligibility criteria	Treatment of all accessible arteries with a diameter of 3-8 mm	Treatment of accessible main renal arteries with a diameter of 3-8 mm
Access	Femoral access (6 Fr)	Femoral access (7 Fr)
Wiring	Consider use of extra-support wires or buddy wires in tortuous anatomy	Consider use of extra-support wires or buddy wires in tortuous anatomy
Ablation sites	Main renal artery and branches	Main renal artery, 2-3 ablations per artery. The selection of catheter size and ablation site required preprocedural planning with CT/MRA in trials. Final sizing can be done during the renal angiogram before the procedure
Arterial wall contact	Ensure appropriate contact of the RF electrodes and the vessel wall Ensure energy delivery (for at least 45 sec, ideally 60 sec)	Ensure complete occlusion of the renal artery after balloon inflation
Duration	Simultaneous ablation at 4 points (for at least 45 sec, ideally 60 sec)	7 seconds per ablation

CT: computed tomography; MRA: magnetic resonance angiography; RF: radiofrequency; US: ultrasound

Possible Procedural Complications and preventative measures

Complications	Preventive measures/management strategies
Access-site vascular complication, i.e., haematoma, pseudoaneurysm, fistula, bleeding, etc.	US-guided puncture, vascular closure device, blood pressure control
Contrast-induced acute kidney injury	Adequate (preprocedural) hydration, minimal contrast volume (or diluted contrast)
Vascular complications, i.e., renal artery spasm, dissections, distal perforation, intracapsular renal haematoma, renal artery stenosis/dissections, aortic dissection, embolisation	Non-selective abdominal aorta angiogram, no-touch technique to selectively engage the renal artery, avoidance of hydrophilic guidewires, proper RDN technique, intra-arterial injection of a vasodilator, availability of adequately sized stents on site in case of acute renal artery complication which cannot be reversed by prolonged renal artery ballooning


Resistant/uncontrolled hypertension
148
98
90
Verify BP is high outside of the office
• Exclude secondary hypertension
• Optimize medication regimen
Shared decision making
Renal denervation
Ongoing medical therapy

Conclusions

1. RDN for treatment of uncontrolled hypertension has been consistently demonstrated in randomized trials both in the presence and absence of medications.

2. RDN suggests a constant reduction in BP over day and night that is distinct from pharmacokinetic profiles and dosing regimens with medications and patient nonadherence.

3. RDN has a good safety profile. Renal denervation did not result in any significant long-term increase in renal artery stenosis or worsening of renal function.

4. The BP-lowering effect of renal denervation was sustained for up to 3 years. Benefit is like a single medication, roughly 5-10 mm Hg, with some variation.

5. Centers offering renal denervation should include a multidisciplinary team of hypertension specialists and expert interventionalists who are trained specifically for renal denervation and whose outcomes are closely monitored.

6. Predictors of RDN responsiveness need to be identified.

7. Longer term surveillance of existing trials and additional studies may inform durability and clinical impact

Questions?

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