

Renal denervation for resistant hypertension: a glimpse of hope on the horizon?

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ABSTRACT

Renal denervation by a minimally-invasive catheter-based procedure has been extensively studied over the last decade as a powerful tool for treating resistant hypertension, a high-risk condition the clinical management of which remains a major challenge. Initial promising results from uncontrolled pilot studies set the stage for a plethora of larger randomized, sham-controlled trials which, however, had unexpectedly negative findings. Despite this transient setback, positive although weak results from the latest Symplicity Spyral studies and a series of new procedural approaches beyond radiofrequency have rekindled enthusiasm for this procedure. New studies are warranted to fully elucidate, once and for all, the limits and potential of and indications for renal denervation in the treatment of resistant hypertension.

Keywords: renal denervation, resistant hypertension, nerve ablation.

INTRODUCTION

Hypertension remains a major public health problem and one of the most relevant causes of mortality, morbidity and hospitalizations worldwide. In the general populations, the overall prevalence of this condition peaked at 26% in 2000 and it is forecast that more than 1.56 billion patients will be hypertensive by 2025¹. Roughly 3 to 6 % of the whole hypertensive population is considered as “resistant”². Individuals with resistant hypertension, by definition, show an office blood pressure $\geq 140/90$ mmHg despite taking three different classes of anti-hypertensives (including a diuretic) at maximally tolerated doses or using ≥ 4 medications irrespective of blood pressure³. Resistant hypertension ranks among the most important prognostic risk factors for adverse cardiovascular and renal outcomes⁴. Unfortunately, various dietary, lifestyle or behavioral

programs, alone or in addition to stepped therapeutic algorithms, have failed to significantly improve this condition. The search for effective treatments to properly manage resistant hypertension has been acknowledged by the scientific community as a true research priority. In recent years, improved understanding of the role of the sympathetic nervous system and the enormous advancement in health technology have laid the groundwork for several minimally invasive, device-based approaches targeting nervous reflexes that might contribute to a unstable blood pressure control. Among these, renal denervation remains the procedure that has accumulated the most relevant amount of pre-clinical and randomized experience, with over 4000 indexed publications in scientific literature and a wealth of promising, ongoing studies, the results of which are expected to be available within the next few years.

■ A RATIONALE FOR RENAL DENERVATION IN RESISTANT HYPERTENSION

The pathophysiological rationale for renal denervation as a measure for improving blood pressure control relies on the sophisticated bidirectional interaction between the kidney and the sympathetic nervous system. Efferent nervous fibers, the stimulation of which elicits renal vasoconstriction, renin release, retention of water and sodium and blood flow reduction, originate in the brain and terminate in the juxtaglomerular apparatus in the renal cortex after traveling through the spinal cord. On the contrary, afferent fibers arise in the renal pelvis, conveying sympatho-excitatory stimuli to the autonomic regulatory *nucleus tractus solitarius* in the midbrain⁵. Sympathetic over-reactivity of the renal nervous autonomic plexus plays a key role in the pathophysiology of arterial hypertension, a concept that was already known in the pre-pharmacological era of hypertension management in which the most severe forms were clumsily treated by extensive splanchnicectomy⁶. However, although effective, this unselective, highly destructive surgical approach was unsuitable to be routinely performed, taking into consideration the high peri-operative risk and the several major neurological sequelae that impacted patients' conditions more significantly than resistant hypertension itself.

In recent years, the smart idea to destruct renal nerves in a minimally invasive way, by means of energy delivered from the lumen of the arterial vascular branches, has injected fresh excitement into the possibility of successfully challenging resistant hypertension using a non-pharmacological approach.

As a result, myriad highly specialized, catheter-based devices have been conceived, leading to a wealth of pre-clinical and clinical experience with contradictory findings that, unfortunately, still prevents the drawing of any final conclusions on the potential use of this procedure in routine practice.

■ RENAL DENERVATION BY RADIOFREQUENCY: A "MATTER OF SIMPLICITY"

Energy delivered by radiofrequency was the first and is the most studied technique to obtain renal nerve ablation and the Symplicity System (Medtronic, US) is the pioneering, catheter-based device which has led

the majority of scientific studies conducted so far on renal denervation.

The first generation of this device consisted of a radiofrequency, generator-coupled arched catheter with a max 8W energy delivery to target tissue temperature of 40-75°C. A second spiral version (Symplicity Spyral) was subsequently conceived to overcome the problem of concentrating focal energy into a single artery segment. Other radiofrequency catheters exist, including the OneShot (Medtronic, US; formerly Covidien), the Vessix System (Boston Scientific, US), the EnligHTN (Abbott, US; formerly St. Jude), the PRDS-001 System (Otsuka, Japan), the SyMapCath (Terumo Corporation, Japan), the Synaptic device (Synaptic Medical Limited, China) the Golden Leaf catheter (Shanghai Golden Leaf MedTec Co., China), the saline-irrigated, radiofrequency catheter Thermacool (Biosense-Webster, California, US) and the Iberis System (Terumo Corporation, Japan). Findings on these devices has rapidly accumulated but remains mostly limited to small proof-of-principle, uncontrolled studies⁷⁻⁹.

The SYMPLICITY HTN-1, a large pilot, uncontrolled prospective study, was the first trial demonstrating the Symplicity radiofrequency catheter's capacity to reduce blood pressure by renal denervation in individuals with resistant hypertension and to maintain this benefit long-term¹⁰. The SYMPLICITY HTN-2¹¹, a multicenter, prospective, open-label, controlled trial, followed soon after. This study randomized 106 resistant hypertensive patients to renal denervation or standard therapy, demonstrating, after 6 months, a reduction in office systolic/diastolic blood pressure in the renal denervation group by 32/12 mmHg ($p<0.0001$) with no changes in the control group and a between-group difference of 33/11 mmHg ($p<0.0001$).

The following SYMPLICITY HTN-3¹² was the first multicenter, randomized, pivotal trial employing a controlled group receiving a sham-procedure. The study recruited 535 participants with resistant hypertension worldwide. Despite high hopes, the study failed to prove the superiority of renal denervation over sham to improve office blood pressure. Unexpectedly, the mean systolic blood pressure decreased at 6 months in both the experimental and control group (-14.13 ± 23.93 and -11.74 ± 25.94 mmHg, respectively; $p<0.001$ for both comparisons of the change from baseline) with a non-significant between-group difference ($p=0.26$), an observation confirmed also when looking at the pattern of 24h ambulatory systolic blood pressure¹³. Two other independent randomized studies (14,

15) implementing a sham-control arm echoed such negative findings. Failure of the SYMPLICITY HTN-3 also led to premature stopping of another sponsored randomized, (non-sham) controlled trial, the SYMPLICITY HTN-JAPAN¹⁶, which results were eventually inconclusive due to underpowering.

Despite this setback apparently crushing spirits and dreams, results from two recent multicenter trials specifically designed to overcome potential limits of the SYMPLICITY HTN-3 have sparked new enthusiasm about the potential of this procedure.

The SPYRAL HTN-OFF and ON MED trials (17, 18) were two randomized, sham-controlled, proof-of-principle studies implementing the last-generation Symplicity Spyral in the absence (SPYRAL HTN-OFF MED) and presence (SPYRAL HTN-ON MED) of background antihypertensive therapy. In a 3-month analysis of the SPYRAL HTN-OFF MED¹⁷, the renal denervation group (n=38) experienced a statistically significant decrease in blood pressure compared with the sham-controlled group (n=42) although change differences were as little as 5 and 4.4 mmHg for 24-h systolic and diastolic ambulatory measurement and 7.7 and 4.9 mmHg for office blood pressure, respectively. The first recently published 6-month interim report of the SPYRAL HTN-ON MED showed similar, clinically limited, benefits¹⁸ with systolic and diastolic drop differences between the renal denervation and the sham-control group of 7.4 and 4.1

mmHg for 24h-ABPM and 6.8 and 3.5 mmHg for office blood pressure measurements, respectively.

Three more randomized, open-label, controlled trials adopting the first generation Symplicity catheter deserve mentioning. The PRAGUE-15 trial¹⁹, allocated 106 individuals with resistant hypertension to renal denervation or an intensified drug treatment. Again, a significant reduction in 24-h and office systolic blood pressure was observed in both groups with no significant between-group difference after 6-months. The OSLO RDN study²⁰, randomized 19 patients with uncontrolled hypertension to renal denervation (n=9) or clinically adjusted drug treatment (n=10). The study was interrupted prematurely due to futility of results on the main blood pressure endpoints.

Finally, the DENERHTN²¹ compared the efficacy of renal denervation on daytime ambulatory blood pressure control in addition to a structured, stepped-care antihypertensive treatment versus the same treatment alone. Interestingly, this study was apparently the only one reporting convincing results in favor of renal denervation with a mean change in systolic ABPM at 6 months of -15.8 mmHg (95% CI -19.7 to -11.9) versus -9.9 mmHg (95% CI -13.6 to -6.2) in the control group, with a significant baseline-adjusted, between-group difference of -5.9 mmHg (95% CI -11.3 to -0.5; p=0.03). An overview of the most important randomized controlled trials of renal denervation is provided in Table 1.

Table 1

Main randomized controlled trials on renal denervation

Study ID	Design	Population characteristics	Intervention	Comparator	Results
Symplicity HTN-2 ¹¹	Multicenter, randomized, open-label	Individuals with uncontrolled hypertension aged 18-85, systolic BP \geq 160 (\geq 150 in diabetes) and \geq 3 anti-hypertensive drugs	Renal denervation (n=53) by the Symplicity radiofrequency catheter plus standard treatment	Standard treatment alone (n=54)	Blood pressure in the renal denervation group reduced by 32/12 mm Hg (SD 23/11, baseline of 178/96 mm Hg, p<0.0001) but did not differ from baseline in the control group. Between-group differences in blood pressure at 6 months were 33/11 mm Hg (p<0.0001).
Symplicity HTN-3 ^{12,13}	Multicenter, randomized, patients and outcome assessors-blinded	Individuals with uncontrolled hypertension aged 18-80, systolic BP \geq 160 and \geq 3 anti-hypertensive drugs including diuretic	Renal denervation (n=364) by the Symplicity radiofrequency catheter plus standard treatment	Sham procedure plus standard treatment (n=171)	– Mean (+/-SD) change in systolic blood pressure at 6 months was -14.13+/-23.93 in the denervation group vs. -11.74+/-25.94 mmHg in the sham-procedure group (P<0.001 for both comparisons of the change from baseline; P=0.26 between-group difference). – Change in 24h ABMP systolic blood pressure was -6.75+/-15.11 in the denervation group vs. -4.79+/-17.25 mmHg in the sham-procedure group (P=0.98 between-group difference).
Symplicity-FLEX ¹⁴	Single-center, randomized, single-blinded	Individuals with uncontrolled hypertension aged 18-75 and \geq 3 anti-hypertensive drugs including diuretic	Renal denervation (n=35) by the Symplicity radiofrequency catheter plus drug treatment	Sham procedure (n=36) plus drug treatment	Mean change in 24h systolic ABPM in the intention to treat cohort at 6 months was -7.0 mm Hg (95% CI -10.8 to -3.2) for patients undergoing denervation and -3.5 mm Hg (95% CI -6.7 to -0.2) in the sham group (P=0.15)

Study ID	Design	Population characteristics	Intervention	Comparator	Results
RESET ¹⁵	Single-center, randomized, single-blinded	Individuals with uncontrolled hypertension and daytime systolic ABPM \geq 45 mmHg following 1 month of stable medication	Renal denervation (n=36) by the Symplicity radiofrequency catheter	Sham procedure (n=33)	Similar reductions in daytime systolic ABPM compared with baseline at 3 months [-6.2 +/- 18.8 mmHg (RDN) vs. -6.0 +/- 13.5 mmHg (SHAM)] and at 6 months [-6.1 +/- 18.9 mmHg (RDN) vs. -4.3 +/- 15.1 mmHg (SHAM)].
Symplicity HTN-Japan ¹⁶	Multicenter, randomized, open-label	Individuals with uncontrolled hypertension aged 20-79, BP \geq 160 and \geq 3 anti-hypertensive drugs including diuretic	Renal denervation (n=22) by the Symplicity radiofrequency catheter plus standard treatment	Standard treatment alone (n=19)	<ul style="list-style-type: none"> - 6-month office SBP change was -16.6+/-18.5 mmHg after RDN (P<0.001) and -7.9+/-21.0 mmHg in controls (P=0.117); the difference between the 6-month change in RDN and control s was -8.64 (95% CI: -21.12 to 3.84, P=0.169). - The study enrollment has been prematurely stopped by the sponsor due to the negative findings of the Symplicity HTN-3 trial, resulting in an underpowered cohort
SPYRAL HTN-OFF MED ¹⁷	Multicenter, randomized, patients and outcome assessors-blinded	Individuals with mild uncontrolled hypertension aged 20-80, office systolic BP=150-180 and diastolic \geq 90 and 24h-systolic ABPM=140-170	Renal denervation (n=38) by the Symplicity Spyral radiofrequency catheter	Sham procedure (n=42)	Change in blood pressure was significantly greater at 6 months in the renal denervation group than the sham-control group for office systolic blood pressure (difference -7.7 mmHg; p=0.0205), 24h systolic ABPM (difference -5.0 mmHg; p=0.0051), office diastolic blood pressure (difference -4.9 mmHg; p=0.0478), and 24h diastolic ABPM (difference -4.4 mmHg; p=0.0292)
SPYRAL HTN-ON MED (18)	Multicenter, randomized, patients and outcome assessors-blinded	Individuals with mild uncontrolled hypertension aged 20-80, office systolic BP=150-180 and diastolic \geq 90 and 24h-systolic ABPM=140-170	Renal denervation (n=38) by the Symplicity Spyral radiofrequency catheter	Sham procedure (n=42)	Change in blood pressure was significantly greater at 6 months in the renal denervation group than the sham-control group for office systolic blood pressure (difference -6.8 mmHg; p=0.0205), 24h systolic ABPM (difference -7.4 mmHg; p=0.0051), office diastolic blood pressure (difference -3.5 mmHg; p=0.0478), and 24h diastolic ABPM (difference -4.1 mmHg; p=0.0292)
PRAGUE-15 (19)	Multicenter, randomized, open-label	Individuals with uncontrolled hypertension aged \geq 18, systolic BP>140 and \geq 3 anti-hypertensive drugs including diuretic	Renal denervation (n=52) by the Symplicity radiofrequency catheter	Intensified treatment including spironolactone (n=54)	<ul style="list-style-type: none"> - Decrease of 8.6 [95% CI -11.8, -5.3] mmHg; p<0.001 in renal denervation versus -8.1 [95% CI -12.7, -3.4] mmHg; p=0.001 in control group - Decrease of -12.4 [95% CI: -17.0, -7.8] mmHg; p<0.001 in renal denervation versus -14.3 [95% CI: -19.7, -8.9] mmHg; p<0.001 in control group - No significant differences between groups
OSLO RDN (20)	Single-center, randomized, open-label	Individuals with uncontrolled hypertension aged 18-80, systolic BP>140 and \geq 3 anti-hypertensive drugs including diuretic	Renal denervation (n=9) by the Symplicity radiofrequency catheter	Adjusted drug treatment (n=10)	Systolic and diastolic BP changed from 160 \pm 14/88 \pm 13 to 132 \pm 10/77 \pm 8 mmHg at 6 months (p<0.0005 and p=0.02 respectively) in the control group with no significant change in the active group. Study was prematurely stopped for futility
DENERHTN (21)	Multicenter, randomized, open-label	Individuals with uncontrolled hypertension aged 18-75, BP \geq 140/90 and \geq 3 anti-hypertensive drugs including diuretic	Renal denervation (n=53) by the Symplicity radiofrequency catheter plus a standardized stepped-care antihypertensive treatment	Standardized stepped-care antihypertensive treatment alone (n=53)	Decrease of -15.8 mm Hg (95% CI -19.7 to -11.9) in the renal denervation group versus -9.9 mmHg (95% CI -13.6 to -6.2) in the control group, with a baseline-adjusted difference of -5.9 mmHg (95% CI -11.3 to -0.5; p=0.03)

RENAL DENERVATION BEYOND RADIOFREQUENCY: ALTERNATIVE METHODS

Alternative techniques to radiofrequency have been studied for improving renal nerve ablation success and minimize safety risks. The Paradise system (ReCor

Medical, US), the TIVUS (Cardiosonic, Israel), the Kona (Kona Medical, US) and the Sound 360 system (Sound Interventions, US) are device-based catheters designed to ablate renal nerves via ultrasound-derived energy generated by a piezoelectric micro-transducer usually placed inside a low-pressure balloon. Efficacy and safety of these devices is object of several ongoing investigations (Table 2).

Table 2

Main ongoing randomized, sham-controlled trials on renal denervation

Study ID	NCT	Country	n.	Device (manufacturer)	RDN Method
SYNAPTIC	NCT03511313	China	264	Synaptic device (Synaptic Medical Limited, China)	Radiofrequency
Golden Leaf	NCT03261375	China	110	Golden leaf catheter (Golden Leaf MedTec Co., China)	Radiofrequency
REDUCE HTN:REINFORCE	NCT02392351	US	51	Vessix system (Boston Scientific, Massachusetts, US)	Radiofrequency
IBERIS-HTN	NCT02901704	China	216	Iberis System (Terumo Corp. Japan)	Radiofrequency
SMART	NCT02761811	China	212	SyMapCath (Terumo Corporation, Japan)	Radiofrequency
RADIANCE HTN	NCT02649426	US, EU	146	Paradise System (ReCor Medical, California, US)	Ultrasounds
REQUIRE	NCT02918305	JAP	140	PRDS-001 System (Otsuka, Japan)	Ultrasounds
RADIANCE II	NCT03614260	US, EU	225	Paradise System (ReCor Medical, California, US)	Ultrasounds
TARGET BP OFF-MED	NCT03503773	Global	400	Peregrine catheter (Ablative Solutions, Michigan, US)	Ethanol
TARGET BP I	NCT02910414	Global	100	Peregrine catheter (Ablative Solutions, Michigan, US)	Ethanol

The Peregrine catheter (Ablative Solutions, US) is coupled with a triple micro-needle system to inject ethanol into the perivascular space. Alcohol is endowed with strong neurolytic effects, leading to fast nerve disruption²². Efficacy and safety of this approach is presently being tested by two global, randomized, double-blind, multicenter, sham-controlled trials^{23,24}. Alternative to ethanol, other neurotoxic agents such as vincristine and the pro-apoptotic neurotrophic agent NW2013 have shown promising findings in small uncontrolled studies²⁵.

Further, innovative procedures to achieve renal nerve ablation include vascular brachytherapy with renal sympathetic nerve destruction via β -radiation exposure²⁶ and cryotherapy²⁷.

This latter procedure was successfully conducted in two case series^{27,28} of individuals who were refractory to standard renal denervation by radiofrequency, through a standard electrophysiology cardiac cryoablation catheter (Freezor(R)Xtra, Medtronic, US) targeting a tissue temperature of -75°C for 4 mins in each renal artery. Positive results with no major damages to kidney and vasculature have laid the groundwork for a larger, non-randomized, controlled study that is currently ongoing²⁹.

DISCUSSION

Failure of the SYMPPLICITY HTN-3 and the other sham-controlled RCTs have brought renal denervation to a screeching halt, which was duly justified by negative findings from pooled efficacy meta-analyses^{30,31}. Nevertheless, recent bittersweet results in clinical benefits from the SPYRAL HTN-OFF/ON MED studies and the large bunch of ongoing studies at the horizon are suggesting that the momentum for renal denervation may continue.

Some key issues which emerged from the SYMPPLICITY HTN-3 and the other large sham-controlled trials were not or only marginally addressed by the following SPYRAL evidence. Overcoming these limitations represents a plausible basis for intelligent and unbiased investigations designed to clarify the true usefulness of this procedure in the real world.

One main problem, for instance, is the importance of the study population selection. As a successful blood pressure decrease is usually manifested one month after the procedure, early prediction of responding individuals becomes rather challenging. Renal nerve ablation by radiofrequency or ultrasound energy is mediated by inflammatory or degenerative processes

that require some days before leading to a concrete functional damage. This paradigm justifies the search for alternative strategies to speed up or make more efficient the ablation process. As briefly alluded to, various innovative approaches (e.g. brachytherapy, cryotherapy or ethanol injection) for achieving renal nerve ablation are currently the object of multiple investigations.

At present, no concrete, reproducible surrogates of successful denervation exist. Yet, various observations indicate that “one size cannot fit all”, suggesting that future trials should target selected sub-groups of patients rather than the whole resistant hypertensive population. For example, specific analyses of the Global SYMPPLICITY Registry³², a prospective, multicenter international database collecting information from over 3000 patients who underwent renal denervation, advised excluding persons with large pulse pressure or isolated systolic hypertension as less likely to benefit from this procedure, probably due to pervasive arterial stiffness. Another stratified analysis by racial origin in the SYMPPLICITY HTN-3 trial pointed out Caucasian patients in the intervention group as being more prone to experience improvements in systolic BP³³. Conversely, although initially hypothesized, no impact of BMI on successful renal ablation has been clearly established³⁴.

Another important lesson from the SYMPPLICITY HTN-3 was the high frequency of medication changes. Roughly 40% of subjects underwent known modifications in their therapeutic regimen during the trial and further data published during and after the study suggested an additional high rate of drug non-adherence that would not otherwise have been known to the investigators³⁵. Although the design of subsequent trials of renal denervation began to incorporate serum and urine medication adherence testing, therapeutic compliance remains a significant factor in studies which evaluate this procedure.

The fact that the renal nerves have a specific anatomy in the renal arteries is another key problem. In fact, the distance to the lumen increases as renal nerves track back in the direction of the vessel origin. Therefore, performing the procedure in the lumen of more distal renal vessels may improve success, but may significantly increase the risk of damaging the ureter or the renal veins⁵. Inadequate renal denervation may also depend on the operator's skills and practice and on inter-operator variability. And, very disappointingly, the majority of specialists performing renal denervation

in the SYMPPLICITY HTN-3 study were relatively unfamiliar with this technique and performed no more than two procedures during the trial¹².

CONCLUSIONS

In the wasteland of clinical research into improving blood pressure control and key outcomes in individuals with resistant hypertension, renal denervation remains a very promising technique that, however, deserves additional research efforts to fully elucidate its limits, potential and suitability.

Lessons from past mistakes underline the need to identify early markers of procedural response, defining subpopulations that are more likely to be responsive and optimizing ablation success, perhaps by innovative and more efficacious techniques that are an alternative to radiofrequency. Upcoming research is warranted in the near future, intended to revolutionize the intricate clinical management of such a complex disease condition.

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References

- Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365(9455):217-23.
- Weitzman D, Chodick G, Shalev V, Grossman C, Grossman E. Prevalence and factors associated with resistant hypertension in a large health maintenance organization in Israel. *Hypertension*. 2014;64(3):501-7.
- Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension*. 2008;51(6):1403-19.
- De Nicola L, Gabbai FB, Agarwal R, Chiodini P, Borrelli S, Bellizzi V, et al. Prevalence and prognostic role of resistant hypertension in chronic kidney disease patients. *J Am Coll Cardiol*. 2013;61(24):2461-7.
- Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol*. 2014;64(7):635-43.
- Larsen R, Thorp A, Schlaich M. Regulation of the sympathetic nervous system by the kidney. *Curr Opin Nephrol Hypertens*. 2014;23(1):61-8.
- Tsioufis CP, Papademetriou V, Dimitriadis KS, Kasiakogias D, Tsiachris D, Worthley MI, et al. Catheter-based renal denervation for resistant hypertension: Twenty-four month results of the EnligHTN I first-in-human study using a multi-electrode ablation system. *Int J Cardiol*. 2015;201:345-50.
- Verheye S, Ormiston J, Bergmann MW, Sievert H, Schwindt A, Werner N, et al. Twelve-month results of the rapid renal sympathetic denervation for resistant hypertension using the OneShot™ ablation system (RAPID) study. *EuroIntervention*. 2015;10(10):1221-9.
- Sievert H, Schofer J, Ormiston J, Hoppe UC, Meredith IT, Walters DL, et al. Bipolar radiofrequency renal denervation with the Vessix catheter in patients with resistant hypertension: 2-year results from the REDUCE-HTN trial. *J Hum Hypertens*. 2017;31(5):366-8.
- Krum H, Schlaich MP, Sobotka PA, Bohm M, Mahfoud F, Rocha-Singh K, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet*. 2014;383(9917):622-9.
- Symplicity HTN1, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet*. 2010;376(9756):1903-9.
- Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370(15):1393-401.
- Bakris GL, Townsend RR, Liu M, Cohen SA, D'Agostino R, Flack JM, et al. Impact of renal denervation on 24-hour ambulatory blood pressure: results from SYMPPLICITY HTN-3. *J Am Coll Cardiol*. 2014;64(11):1071-8.

14. Desch S, Okon T, Heinemann D, Kulle K, Rohnert K, Sonabend M, et al. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. *Hypertension*. 2015;65(6):1202-8.
15. Mathiassen ON, Vase H, Bech JN, Christensen KL, Buus NH, Schroeder AP, et al. Renal denervation in treatment-resistant essential hypertension. A randomized, SHAM-controlled, double-blinded 24-h blood pressure-based trial. *J Hypertens*. 2016;34(8):1639-47.
16. Kario K, Ogawa H, Okumura K, Okura T, Saito S, Ueno T, et al. SYMPLICITY HTN-Japan – First randomized controlled trial of catheter-based renal denervation in Asian patients. *Circ J*. 2015;79(6):1222-9.
17. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet*. 2017;390(10108):2160-70.
18. Kandzari DE, Bohm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, et al. 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;391(10137):2346-55.
19. Rosa J, Widimsky P, Tousek P, Petrak O, Curila K, Waldauf P, et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension*. 2015;65(2):407-13.
20. Fadl Elmula FE, Hoffmann P, Larstorp AC, Fossum E, Brekke M, Kjeldsen SE, et al. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension*. 2014;63(5):991-9.
21. Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet*. 2015;385(9981):1957-65.
22. Fischell TA, Ebner A, Gallo S, Ikeno F, Minarsch L, Vega F, et al. Transcatheter alcohol-mediated perivascular renal denervation with the peregrine system: first-in-human experience. *JACC Cardiovasc Interv*. 2016;9(6):589-98.
23. TARGET BP I Clinical Trial (TARGET BP I) 2018 [Available from: <https://clinicaltrials.gov/ct2/show/NCT02910414>].
24. The TARGET BP OFF-MED Trial 2018 [Available from: <https://clinicaltrials.gov/ct2/show/NCT03503773>].
25. Kipshidze N, Sievert H, Wholey MH, Kipiani K, Kipiani V, Mukhuradze T, et al. First clinical experience with targeted renal nerve femodulation (TREND-1) using a neurotropic agent for the treatment of sympathetic hypertension. *J Invasive Cardiol*. 2017;29(3):97-103.
26. Waksman R, Barbash IM, Chan R, Randolph P, Makuria AT, Virmani R. Beta radiation for renal nerve denervation: initial feasibility and safety. *EuroIntervention*. 2013;9(6):738-44.
27. Prochnau D, Figulla HR, Surber R. Cryoenergy is effective in the treatment of resistant hypertension in non-responders to radiofrequency renal denervation. *Int J Cardiol*. 2013;167(2):588-90.
28. Prochnau D, Heymel S, Otto S, Figulla HR, Surber R. Renal denervation with cryoenergy as second-line option is effective in the treatment of resistant hypertension in non-responders to radiofrequency ablation. *EuroIntervention*. 2014;10(5):640-5.
29. Pilot Study of Renal Arterial Sympathetic Denervation by Cryotherapy (PRASDEN) 2018 [Available from: <https://clinicaltrials.gov/ct2/show/NCT02345603>].
30. Pappaccogli M, Covella M, Berra E, Fulcheri C, Di Monaco S, Perlo E, et al. Effectiveness of renal denervation in resistant hypertension: a meta-analysis of 11 controlled studies. *High Blood Press Cardiovasc Prev*. 2018;25:167.
31. Coppolino G, Pisano A, Rivoli L, Bolignano D. Renal denervation for resistant hypertension. *Cochrane Database Syst Rev*. 2017;2:CD011499.
32. Mahfoud F, Bakris G, Bhatt DL, Esler M, Ewen S, Fahy M, et al. Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: data from SYMPLICITY HTN-3 and the Global SYMPLICITY Registry. *Eur Heart J*. 2017;38(2):93-100.
33. Kotsis V, Stabouli S. Renal denervation for resistant hypertension. *N Engl J Med*. 2014;371(2):183.
34. Bhatt DL, Bakris GL. Renal denervation for resistant hypertension. *N Engl J Med*. 2014;371(2):184.
35. Patel P, Gupta PK, White CM, Stanley AG, Williams B, Tomaszewski M. Screening for non-adherence to antihypertensive treatment as a part of the diagnostic pathway to renal denervation. *J Hum Hypertens*. 2016;30(6):368-73.

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