Review paper

Renal denervation – can we press the "ON" button again?

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Abstract

Nearly ten years ago percutaneous renal denervation (RDN) was introduced in clinical trials as a possible method of interventional treatment of resistant hypertension. The promising results of the first clinical trials initiated the intensive development of this method. However, the role of percutaneous renal denervation in the treatment of patients with resistant hypertension has been questioned since the results of the Symplicity HTN-3 trial have been published. It also resulted in downgrading the indications for RDN in the European Society of Cardiology/European Society of Hypertension Guidelines 2018. The authors discuss potential shortcomings of that trial, describe new generation devices and present the results of recently published trials: SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED, RADIANCE-HTN SOLO and RADIOSOUND-HTN. The results of studies in patients with obstructive sleep apnea are also summarized and discussed. The upcoming large trials (SPYRAL PIVOTAL, RADIANCE II) are outlined – the results of those trials are expected to be published in the next 2–3 years. Until then, according to the European guidelines, the use of device-based therapies is not recommended for the treatment of hypertension, unless in the context of clinical studies and randomized controlled trials.

Key words: renal denervation, resistant hypertension, review.

Introduction

Nearly ten years ago percutaneous renal denervation (RDN) was introduced in clinical trials as a possible method of interventional treatment of resistant hypertension. The promising results of the first clinical trials initiated the intensive development of this method. The Symplicity HTN-1 trial was the first in-human study confirming the safety of the procedure in 45 patients, being then extended to a single-arm trial involving 138 patients. Symplicity HTN-2 was the first randomized controlled trial (RCT). In both trials, significant and sustained blood pressure (BP) reductions achieved after renal denervation (approximately 25 mm Hg) and favorable procedural safety brought hope for a long-term benefit from the treatment in terms of cardiovascular risk reduction [1–3].

Symplicity-HTN 3 trial – why did it fail?

Symplicity HTN-3 was the first study with sham treatment implementation. In brief, 535 patients with resistant hypertension were randomly assigned in a 2 : 1 ratio to undergo renal artery denervation or a sham procedure [4]. After 6 months, the differences in office BP and ambulatory blood pressure monitoring (ABPM) reductions between RDN and sham were not significant (14.1 vs. 11.7 mm Hg; 7.75 vs. 4.79 mm Hg respectively). The disappointing results of the trial raised some concerns for the efficacy of the procedure and initiated a discussion about potential reasons for this failure [5–7].

First of all, the inclusion criterion of resistant hypertension was based only on systolic office and ambulatory BP measurements. As a result, almost 1/3 of the patients were included in the study on the basis of isolated systolic hypertension, independently of their diastolic blood pressure. Additional analysis of these patients, characterized by increased arterial stiffness and diminished sympathetic nervous system activity, revealed that the effect of RDN was less pronounced as compared to the subjects with systolic-diastolic resistant hypertension.

Secondly, despite the protocol requirements, the antihypertensive drug regimen was changed during the follow-up period in 40% of patients. In might have had an impact on the results obtained after the treatment.

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Moreover, the experience of 112 operators performing the study procedures in 88 American sites was rather modest. It is of note that more than half of them carried out only 1 or 2 procedures in this trial, being just at the beginning of their learning process. On can speculate that if the reductions of the blood pressure had been similar to those obtained in previous studies (with more experienced operators), the difference would have been statistically significant and the HTN-3 study would have been successfully completed.

In summary, several factors had a substantial impact on the results of the HTN-3 trial. Therefore, the protocols of the next studies had to be modified taking into account the conclusions from the HTN-3 analyses and new modern devices enabling complete damage of the sympathetic nerve fibers were required.

New devices

During the last years, two companies introduced into clinical studies new RDN devices.

The Symplicity Spyral multi-electrode renal denervation catheter (Medtronic US), is a 4 Fr over-the-wire, helical-shaped catheter, whose distal tip is deployed by retracting the guide wire into the catheter lumen (Figure 1). Its multi-electrode and helical design enables delivery of radiofrequency energy from the generator to each quadrant of the vessel (simultaneously with all four electrodes), thus maximizing damage to the sympathetic nerves around the renal vessel in a consistent four-quadrant ablation pattern. This device conforms to a wide range of artery shapes and sizes (3 mm to 8 mm in diameter), eliminating the need for multiple catheters per procedure. The Symplicity G3 generator independently controls the temperature and impedance during 60-second treatments.

The Paradise system (ReCor Medical, US) consists of a 6 Fr over-the-wire, multi-lumen catheter shaft with a cylindrical piezoelectric ceramic transducer placed inside an inflatable balloon at the distal end of the catheter combined with a portable generator (Figure 2). The cylindrical transducer converts the electrical energy delivered from the generator to ultrasound energy, which is then radiated into the renal artery tissue. Due to the physics of sound propagation, direct tissue contact with the ultrasound source is not required for energy transmission. Each energy application lasts only 7 s. The generator is designed to control energy delivery and fluid management inside the balloon. The balloon-based fluid transfer

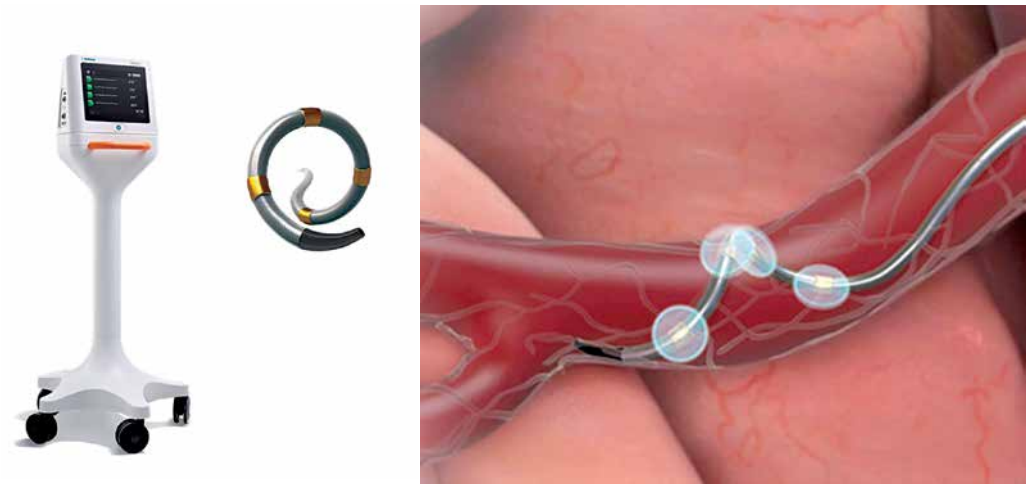

Figure 1. Spyral RDN system: the generator, the Spyral catheter, the catheter deployed in the renal artery

Figure 2. Paradise System: the generator, the Paradise catheter, the mechanism of action

mechanism is implemented for cooling the endothelial and medial layers of the arterial wall to preserve the integrity of the vessel wall during the energy delivery. This endovascular catheter achieves a circumferential ring of ablation at a depth of 1–6 mm from the vessel lumen, which is the expected location of the efferent and afferent renal nerves in the adventitia [8–10]. The different balloon sizes enable arteries from 3.5 mm up to 8 mm in diameter to be treated.

Second-generation sham-controlled trials

Taking into account the conclusions of the Symplicity HTN-3 study analysis, need for significant modification of the next generation sham-controlled randomized controlled trials' protocols was widely postulated. After the second European Clinical Consensus Conference for device-based therapies for hypertension, new recommendations for the next generation of sham-controlled RCT were published. The main principles assume at first the mandatory use of new devices and dedicated treatment recommendations. If monopolar radiofrequency renal denervation is used, four-quadrant ablation at each renal side is recommended. Furthermore, only experienced interventionalists from experienced centers should carry out the procedure, preferably in the absence of any medication, to assess the 'true' BP reduction of RDN. Witnessed intake of medication and/or medication adherence in each patient should be introduced in the study. The BP lowering efficacy of RDN should be assessed with 24-hour ambulatory blood pressure monitoring (ABPM) [11].

In the last 18 months the results of new RCTs using new radiofrequency or ultrasound based RDN catheters and including different populations of patients have been reported.

SPYRAL HTN trials

SPYRAL-HTN is a multicenter project launched by Medtronic using the abovementioned new generation multi-electrode SPYRAL catheter. Two preliminary randomized trials – SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED – were designed, with modified inclusion and exclusion criteria [12]. The SPYRAL study included patients with office systolic BP in the range of 150–180 mm Hg, diastolic BP above 90 mm Hg (patients with isolated systolic hypertension were excluded) and 24-hour systolic BP in the range of 140–170 mm Hg during the use of one to three antihypertensive drugs used for a period of at least 6 weeks (ON-MED study) or after the gradual withdrawal of antihypertensive drugs (OFF-MED study). In both studies, the concentration of antihypertensive drug metabolites in urine was assessed, either to confirm patients' adherence to antihypertensive therapy (ON-MED study) or to confirm not taking antihypertensive drugs (OFF-MED study). In the actively treated study group 'total' RDN (the largest possible number of energy applications in the main renal arteries within their trunk and their distal branches, as well as in additional renal arteries with a diameter of at least 3 mm) and in the control group sham treatment were performed. The results of the SPYRAL HTN-OFF MED study were presented at the ESC Congress in Barcelona, and then published in Lancet in August 2017 [13]. Townsend et al. presented an analysis of 80 patients remaining off antihypertensive medications throughout a 3-month follow-up. Thirty-eight patients had been previously randomly assigned to the RDN group and in 42 patients a sham procedure had been performed. At the 3-month follow-up, in the RDN group a significant reduction in office systolic and diastolic BP values was observed (–10 mm Hg and –5.3 mm Hg respectively). Also in ABPM, both systolic and diastolic BP decreased significantly (–5.5 mm Hg and –4.8 mm Hg, respectively). The sham treatment was not associated with a significant change in BP levels during the follow-up. The observed decrease in systolic BP was not as high as in the first-generation RCT. It should be noted however that in the SPYRAL HTN-OFF MED study patients with baseline systolic BP > 180 mm Hg were not included, which should be taken into consideration as high baseline systolic BP is one of the strongest predictors of BP response to RDN. The results of the SPYRAL HTN-OFF MED study confirmed the validity of further research on RDN, including the continuation of the SPYRAL HTN-ON MED trial. Four hundred sixty-seven patients were screened and 80 fulfilled the inclusion/exclusion criteria of this study. The results were presented in May 2018 at the European Congress of Interventional Cardiologists Euro-PCR and subsequently published in Lancet [14]. Thirty-eight patients with poorly controlled hypertension on one to three antihypertensive drugs in stable doses for at least 6 weeks were randomly assigned to the RDN group (with the same technique as in the OFF MED study) and in 44 patients a sham procedure was performed. Office and 24-hour ambulatory BP decreased significantly from baseline to 6 months in the RDN group (–9.4/–5.3 mm Hg and –9.0/–6.0 mm Hg, respectively). Similarly to the SPYRAL HTN-OFF MED study, in the HTN-ON MED study, the sham procedure was not associated with a significant change in BP at 6 months. Interestingly, despite the fact that the patients were informed about the measurements of drug concentrations, about half of the patients did not comply with the medical recommendations regarding the use of antihypertensive drugs.

In both SPYRAL HTN studies there were no significant procedure-associated adverse events, which confirms the safety of RDN using a new generation multi-electrode catheter.

RADIANCE-HTN SOLO study

The results of the RADIANCE-HTN SOLO study in which the new ultrasound catheter Paradise was implemented were presented in May 2018 in *Lancet* [15].

RADIANCE-HTN SOLO was a multicenter, international, single-blind, randomized, sham-controlled trial including patients with combined systolic–diastolic hypertension after a 4-week discontinuation of up to two antihypertensive medications and suitable renal artery anatomy. One hundred and forty-six patients meeting the inclusion/exclusion criteria were randomized to undergo RDN (n = 74) or a sham procedure (n = 72).

After 2 months the reduction in daytime ambulatory systolic BP was greater with RDN than with the sham procedure (–8.5 vs. –2.2 mm Hg, respectively). The primary end-point – baseline-adjusted difference between groups (–6.3 mm Hg, 95% CI: –9.4 to –3.1, p = 0.0001) – was met. No major adverse events were reported in either group. In summary, in the RADIANCE-HTN SOLO study the efficacy and short-time safety of endovascular ultrasound RDN was confirmed at 2 months in patients with combined systolic–diastolic hypertension in the absence of medications.

Comparison of available technologies

Recently, Fengler *et al.* presented the results of the first trial comparing three different techniques and technologies for catheter-based RDN. One hundred and twenty patients with resistant hypertension were randomized in a 1 : 1 : 1 manner to receive either treatment with 1) radiofrequency RDN of the main renal arteries (39 patients), 2) radiofrequency RDN of the main renal arteries, side-branches and accessories (39 patients), or 3) an endovascular ultrasound-based RDN of the main renal artery (42 patients). At 3 months, daytime systolic and diastolic BP decreased significantly in the overall cohort and also within each treatment group (p < 0.001). However, the systolic daytime blood pressure was significantly more reduced in the ultrasound ablation group than in the radiofrequency ablation group of the main renal artery (–13.2 ±13.7 vs. –6.5 ±10.3 mm Hg). No significant difference was found between the ultrasound RDN and the side branch ablation groups, nor between two strategies of radiofrequency RDN. The authors conclude that endovascular ultrasound based RDN seems to be superior to radiofrequency ablation of the main renal arteries only, whereas a combined approach of radiofrequency ablation of the main arteries, accessories and side branches was not [16].

European Society of Hypertension Position Paper on renal denervation 2018

The promising results of the second-generation RCTs confirming safety and short-time efficacy of RDN in new groups of patients and using new technologies prompted European Society for Hypertension (ESH) experts to develop an up-to-date position paper on RDN [17]. In all three studies, in patients who underwent RDN a similar, significant decrease in BP during the follow-up period was observed (Table I). ESH experts emphasize, however, that some questions about RDN remain unanswered. The heterogeneity of the blood pressure-lowering response point to the clinical need to identify predictors for efficacy, and questions on long-term safety could not be answered due to the short duration of the sham-controlled RCTs.

Table I. Comparison of the Symplicity HTN-3 and second-generation sham-controlled trials

Study		SYMPLICITY HTN-3	SPYRAL HTN-OFF MED [13]	SPYRAL HTN-ON MED [14]	RADIANCE-HTN SOLO [15]
Device used		Uni-electrode radiofrequency catheter	Multi-electrode radiofrequency catheter	Multi-electrode radiofrequency catheter	Ultrasound-based catheter
Main inclusion criteria of BP		Office SBP ≥ 160 mm Hg and 24 h ambulatory SBP ≥ 135 mm Hg on 3 ≥ anti-hypertensive medications at maximally tolerated dosage, including a diuretic	Office SBP 150–179 mm Hg and DBP ≥ 90 mm Hg and 24-hour ambulatory SBP 140–169 mm Hg off antihypertensive drugs	Office SBP 150–179 mm Hg and DBP ≥ 90 mm Hg and 24-hour ambulatory SBP 140–169 mm Hg on 1–3 antihypertensive drugs including diuretic	Ambulatory 24-hour SBP 135–169 mm Hg and 24-hour DBP 85–104 mm Hg, off antihypertensive drugs
No. of patients/controls included		364/171	38/42	38/42	74/72
Sham treatment?		No	Yes	Yes	Yes
Follow-up period [months]		6	3	6	2
BP lowering effect [mm Hg]	**Office SBP/DBP**	–14.1/–6.6	–10.0/–5.3	–9.4/–5.2	–10.8/–5.5
	24-hour ambulatory SBP/DBP	–6.75/–4.1	–5.5/–4.8	–9.0/–6.0	–7.0/–4.4
	Daytime ambulatory SBP/DBP	NA	NA	–8.8/–6.3	–8.5/–5.1

BP – blood pressure, SBP – systolic blood pressure, DPB – diastolic blood pressure, NA – not available.

It should also be noted that as afferent and efferent renal nerves also play a crucial role in cardiovascular, metabolic and renal diseases other than hypertension, RDN may offer a new interventional treatment option for various conditions (obstructive sleep apnea (OSA), congestive heart failure, atrial fibrillation, chronic renal failure, diabetes).

Renal denervation and obstructive sleep apnea

Considering RDN as a potential treatment option of various conditions other than hypertension, interesting data on the use of RDN in patients with OSA coexisting with resistant hypertension have been reported recently. In a proof-of-concept, observational study Witkowski *et al.* evaluated the effects of this procedure on BP and sleep apnea severity in patients with resistant hypertension and sleep apnea. Ten patients with refractory hypertension and sleep apnea (7 men and 3 women; median age: 49.5 years) underwent RDN and completed 3-month and 6-month follow-up evaluations, including polysomnography, selected blood chemistries, and BP measurements. Antihypertensive regimens were not changed during the 6 months of follow-up. Three and 6 months after RDN, decreases in office systolic and diastolic BPs (median: –34/–13 mm Hg for systolic and diastolic BPs at 6 months; both $p < 0.05$) as well as a decrease in apnea-hypopnea index (AHI) at 6 months after RDN (median: 16.3 vs. 4.5 events per hour; $p = 0.059$) were observed [18]. In their conclusions Witkowski *et al.* postulated that RDN may be a potentially useful option for selected patients with true resistant hypertension and moderate-to-severe OSA. The same group of authors designed a randomized controlled clinical trial based on a larger group of patients to confirm initial proof-of-concept data [19]. Sixty patients with true resistant hypertension coexisting with moderate-to-severe OSA (AHI ≥ 15) were randomly allocated to the RDN group (30 patients) and

Table II. Summary of renal denervation trials in patients with concomitant obstructive sleep apnea

Study		Witkowski *et al.* [18]	SYMPLICITY HTN-3 [5]	GLOBAL SYMPLICITY REGISTRY [21]	Daniels *et al.* [22]	Warchol-Celinska *et al.* [19]
Type of study		Proof-of-concept study	Post-hoc analysis of randomized, sham-controlled study	Post-hoc analysis of registry data	Single-arm prospective study	Randomized, controlled prospective study
Year of publication		2011	2016	2017	2017	2018
Device used		Uni-electrode radio-frequency catheter	Uni-electrode radio-frequency catheter	Uni-electrode radio-frequency catheter	Uni-electrode or multielectrode radiofrequency catheter	Uni-electrode radio-frequency catheter
Main inclusion criteria of uncontrolled or resistant hypertension		Office SBP ≥ 160 mm Hg despite at least 3 antihypertensive medications at maximally tolerated dosage, including a diuretic	Office SBP ≥ 160 mm Hg and 24 h ambulatory SBP ≥ 135 mm Hg despite at least 3 antihypertensive medications at maximally tolerated dosage, including a diuretic	All real-world patients with office SBP > 140 mm Hg	Office SBP ≥ 160 mm Hg despite at least 3 antihypertensive medications at maximally tolerated dosage, including a diuretic	Office SBP ≥ 140 mm Hg and 24 h ambulatory SBP ≥ 135 mm Hg despite at least 3 antihypertensive medications at maximally tolerated dosage, including a diuretic
Method of OSA confirmation		AHI ≥ 5 events/h in polysomnography	Self-reported	Self-reported	AHI ≥ 15 events/h in polysomnography	AHI > 15 events/h in polysomnography
No. of patients/ controls included		10/–	94/54	205/–	20/–	30/30
Follow-up [months]		6	6	6	6	3
BP lowering effect [mm Hg]	**Office SBP/DBP**	–34/–13	–17.0/–6.7	–14/NA	–6.6/–6.5	–22/–8
	24-hour ambulatory SBP/DBP	–6.0/NA	–5.0/–3.7	–4.9/NA	–8.3/–6.2	–12/–7
	Daytime ambulatory SBP/DBP	–7.0/NA	–5.2/NA	NA	NA	–14/–9
AHI change		–11.8 events/h	Not measured	Not measured	–0.9 events/h	–8.2 events/h

BP – blood pressure, SBP – systolic blood pressure, DPB – diastolic blood pressure, OSA – obstructive sleep apnea, AHI – apnea-hypopnea index, NA – not available.

to the control group (30 patients). The primary end point was reduction in office systolic BP at 3 months. Secondary end points included reduction in diastolic office and ambulatory BP, change in apnea/hypopnea index and biochemical measurements at 3 months, and change in echocardiographic measurements at 6 months. At 3 months in the RDN group, both office and ambulatory BP were significantly reduced, and a significant decrease in OSA severity (AHI, 39.4 vs. 31.2 events per hour; p = 0.015) was observed. The between-group difference in apnea/hypopnea index change was significant at 0.05. At 6 months in the RDN group, reductions in office and ambulatory BP were sustained and were accompanied by significant improvement in echocardiographic measures of global longitudinal strain. There were no differences in metabolic variables in the follow-up between the groups. Ewa Warchol-Celinska *et al.* concluded that for the first time in an RCT, RDN lowered both office and ambulatory BP in patients with resistant hypertension coexisting with OSA, which was accompanied by improvement of the clinical severity of OSA. The obtained data were in concordance with the post hoc analyses from Symplicity-HTN-3 [20] and Global Symplicity Registry studies [21], suggesting that patients with OSA may be particularly responsive to RDN therapy. In another prospective study including twenty resistant hypertensive patients with OSA, moderate blood pressure reduction was achieved after renal denervation with no significant changes in sleep apnea severity [22]. A summary of these trials is presented in Table II. Further studies are undoubtedly warranted to assess the impact of RDN on sleep apnea and its relation to BP decline and cardiovascular risk.

Conclusions

Over the last months, the results of important RCTs using sham treatment have been published, confirming the efficacy and safety of RDN in previously uninvestigated groups of patients – patients with hypertension after drug withdrawal, patients with poorly controlled hypertension despite 1–3 antihypertensive drugs, as well as in patients with resistant hypertension co-existing with obstructive sleep apnea. Despite these promising new results that again widely open up the field of RDN, ESH experts in the current position underline that in accordance with the current recommendations of the European Guidelines 2018 "device based therapies are not recommended in general for the treatment of HTN at least at the current moment" [23]. However, they also recommend conducting RDN in the framework of "clinical studies and sham-controlled RCT (to) further provide safety and efficacy in a larger set of patients". So far the number of patients included in the trials is small, the follow-up duration short and several important questions remain unanswered. The upcoming trials, including pivotal studies, presented in Table III [24–26], should provide

Table III. Ongoing and upcoming trials on renal denervation

Study	RADIANCE-HTN TRIO [24]	REQUIRE [24]	RADIANCE II (Pivotal study) [25]	SPYRAL PIVOTAL [26]
Type of study	Multicenter, blinded, randomized (1 : 1)	Multicenter (Japan, Korea), blinded, randomized (1 : 1)	Multicenter (Europe, US), blinded, randomized (2 : 1)	Multicenter (Europe, US, Japan), blinded, randomized (1 : 1)
Device used	Ultrasound-based catheter	Ultrasound-based catheter	Ultrasound-based catheter	Multi-electrode radio-frequency catheter
Sham controlled?	Yes	Yes	Yes	Yes
Number of participants planned	229	140	225	433
Main inclusion criteria of BP	Office BP ≥ 140/90 mm Hg and ambulatory 24-hour SBP 135–169 mm Hg and 24-hour DBP 85–104 mm Hg on at least 3 antihypertensive drugs including diuretic (single-pill)	Office BP ≥ 150/90 and ambulatory 24-hours SBP ≥ 140 on at least 3 antihypertensive drugs, including diuretic	Ambulatory daytime BP 135–169/85–104 mm Hg off antihypertensive agents	Ambulatory 24-hour SBP 135–170 mm Hg and 24-hour DBP 85–105 mm Hg off antihypertensive drugs
Primary end-point	Daytime ambulatory SBP change at 2 months	24-hour SBP change at 3 months	1 – incidence of major adverse events 2 – daytime ambulatory SBP change at 2 months	Office SBP 150–179 mm Hg and DBP ≥ 90 mm Hg and 24-hour ambulatory SBP 140–169 mm Hg off antihypertensive drugs
End of enrollment expected [year]	End of 2019	End of 2019	End of 2020	End of 2020
Results expected [year]	2020	2020	2021	2021

US – United States, BP – blood pressure, SBP – systolic blood pressure, DPB – diastolic blood pressure.

answers to many questions regarding RDN. It is also of note that RDN may offer a new interventional treatment option for various conditions other than hypertension, especially obstructive sleep apnea.

Conflict of interest

JK received nonfinancial support from Medtronic outside the submitted work, EWC received nonfinancial support from Servier, Krka, and Medtronic outside the submitted work, AP received personal fees and nonfinancial support from Medtronic outside the submitted work, AW received speaker's fees form Medtronic, AJ – none, KT – none.

References

1. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009; 373: 1275-81.
2. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension 2011; 57: 911-7.
3. Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 2010; 376: 1903-9.
4. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014; 370: 1393-401.
5. Mahfoud F, Bakris G, Bhatt DL, 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: 93-100.
6. Kandzari DE, Bhatt DL, Brar S, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. Eur Heart J 2015; 36: 219-27.
7. Flack JM, Bhatt DL, Kandzari DE, et al. An analysis of the blood pressure and safety outcomes to renal denervation in African Americans and non-African Americans in the SYMPLICITY HTN-3 trial. J Am Soc Hypertens 2015; 9: 769-79.
8. Sakakura K, Roth A, Ladich E, et al. Controlled circumferential renal sympathetic denervation with preservation of the renal arterial wall using intraluminal ultrasound: a next-generation approach for treating sympathetic overactivity. EuroIntervention 2015; 10: 1230-8.
9. Pathak A, Coleman L, Roth A, et al. Renal sympathetic nerve denervation using intraluminal ultrasound within a cooling balloon preserves the arterial wall and reduces sympathetic nerve activity. EuroIntervention 2015; 11: 477-884.
10. Sakakura K, Ladich E, Cheng Q, et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. J Am Coll Cardiol 2014; 64: 635-43.
11. Mahfoud F, Bohm M, Azizi M, et al. Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design. Eur Heart J 2015; 36: 2219-27.
12. Kandzari DE, Kario K, Mahfoud F, et al. The Spyral HTN global clinical trial program: rationale and design for studies of renal denervation in the absence (Spyral HTN OFF-MED) and presence (Spyral HTN ON-MED) of antihypertensive medications. Am Heart J 2016; 171: 82-91.
13. Townsend RR, Mahfoud F, Kandzari DE, 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: 2160-70.
14. Kandzari DE, Bohm M, Mahfoud F, 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: 2346-55.
15. Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (Radiance-HTN solo): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet 2018; 391: 2335-45.
16. Fengler K, Rommel KP, Blazek S, et al. A three-arm randomized trial of different renal denervation devices and techniques in patients with resistant hypertension (RADIOSOUND-HTN). Circulation 2018 Epub ahead of print, 10.1161/CIRCULATIONAHA.118.037654.
17. Schmieder RE, Redon J, Grassi G, et al. ESH position paper: renal denervation – an interventional therapy of resistant hypertension. J Hypertens 2012; 30: 837-41.
18. Witkowski A, Prejbisz A, Florczak E, et al. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. Hypertension 2011; 58: 559-65.
19. Warchol-Celinska E, Prejbisz A, Kadziela J, et al. Renal denervation in resistant hypertension and obstructive sleep apnea: randomized proof-of-concept phase ii trial. Hypertension 2018; 72: 381-90.
20. Kario K, Bhatt DL, Kandzari DE, et al. Impact of renal denervation on patients with obstructive sleep apnea and resistant hypertension- insights from the symplicity HTN-3 trial. Circ J 2016; 80: 1404-12.
21. Linz D, Mancia G, Mahfoud F, et al. Renal artery denervation for treatment of patients with self-reported obstructive sleep apnea and resistant hypertension: results from the global symplicity registry. J Hypertens 2017; 35: 148-53.
22. Daniels F, De Freitas S, Smyth A, et al. Effects of renal sympathetic denervation on blood pressure, sleep apnoea severity and metabolic indices: a prospective cohort study. Sleep Med 2017; 30: 180-4.
23. Williams B, Mancia G, Spiering W, et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens 2018; 36: 2284-309.
24. Mauri L, Kario K, Basile J, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: the RADIANCE-HTN and REQUIRE clinical study designs. Am Heart J 2018; 195: 115-29.
25. https://www.clinicaltrials.gov/ct2/show/NCT03614260
26. https://www.clinicaltrials.gov/ct2/show/study/NCT02439749