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Review Article

New data, new studies, new hopes for renal denervation in patients with uncontrolled hypertension

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ABSTRACT

Background: following the publication of SYMPLICITY HTN-3 the field of renal of denervation was put on hold. Although SYMPLICITY HTN-3 was well-designed and sham-controlled trial it failed to show any meaningful reduction in office or 24 h ambulatory blood pressure. The procedure was however safe and allowed research to continue. Although several pitfalls of the study have been pointed out, incomplete renal denervation was also implicated. Since then, a great deal of basic and clinical research took place and will be briefly commented on in this article.

Methods and results: Before and after SYMPLICITY-HTN-3, numerous uncontrolled, single or unblinded studies have shown substantial office BP reduction ranging from −7.7 to −32 mmHg and ambulatory BP ranging from −2.2 to 10.2 mmHg. Average weighted office systolic BP reduction was −20.8 mmHg and weighted average 24 h ambulatory BPM reduction was −7.8 mmHg. National and international registries have shown similar BP reductions, but results remained unconvincing due to lack of reliable sham controls. In recent years, 5 well-designed sham – controlled studies (beyond, SYMPLICITY-HTN-3) have been published. Of those studies two were single center and three were multicenter international studies. Four studies used single tip or multi-electrode, radio-frequency catheters and one used focused ultrasound. The three multicenter studies reported positive-placebo subtracted results and established BP reductions measured both in the office and by ambulatory monitoring. No serious adverse events were reported.

Conclusions: It can therefore be concluded that the latest sham controlled studies established efficacy and safety of renal denervation.

"Those who cannot remember the past are condemned to repeat it"

George Santayana (1863–1952)

1. Introduction

Following the publication of the first randomized sham-control renal denervation (RDN) trial (SYMPLICITY HTN-3) enthusiasm was dampened, funding was withdrawn, studies were discontinued or put on hold and the field fell into hibernation. SYMPLICITY HTN-3 was a well-designed sham-controlled trial of patients with drug-resistant hypertension [1]. Patients were randomized to active treatment (RDN) or sham-control, but the study, failed to show any statistically significant or clinically meaningful reduction in office blood pressure (BP) or 24 h ambulatory BP monitoring (BPM). Thankfully, the procedure seemed to be safe and no excess adverse events were reported in the RDN group and research continued. This study also wiped off the positive results of DENERHTN, which despite not being sham controlled showed a BP lowering effect in truly resistant hypertensive patient.

Although several pitfalls of the study have been pointed out (drug adherence, drug turbulence during follow-up, inhomogeneity of patient population, carry over diuretic effect, etc.), some authorities agree that

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incomplete denervation was probably the main culprit [2–6]. Catheter design, and operator inexperience were implicated (ie lack of appropriate circular ablation pattern, reduced number of ablation points). Since then, a great deal of basic and clinical research took place and findings are revealing. In this brief article therefore, we'll review relevant findings from basic research and clinical studies published before and after SYMPLICITY HTN-3 and speculate on the future.

2. Understanding renal denervation in the modern renal denervation era

It is well known that both efferent and afferent fibers coursing in the adventitia of the renal artery play an important role for development and maintenance of hypertension [7]. The efferent fibers can modulate renal function, sodium and fluid retention, norepinephrine production and plasma renin activity. Afferent fibers transmit signals to the brain, which are processed primarily in the nucleus tactus solidarius and can affect among others peripheral resistance and cardiac function. However, it is worth noting that despite the plethora of relevant publications, editorials and reviews, the precise mechanism by which the sympathetic nervous system increases BP or sympathetic denervation lowers BP remains elusive. A nice perspective on the subject matter is offered by Iliescu et al. [8]. The anatomic distribution of fibers is also important. Fibers course mostly 1–3 mm from the lumen but can be found as far as 12 mm from it. Fibers are more likely to be far from the lumen in the proximal segment of the renal artery and closer to the lumen in the distal segment and into the branches [9]. Experimental studies indicate that combination treatment with RF energy of the main artery plus branches produces the greatest change in renal NE and axon density with the least heterogeneity [10]. Thermal injury due to radiofrequency energy (RF) can penetrate up to 5 mm into the adventitia when no heat sink is noticed. Thus, not all fibers are reachable with RF energy through the transluminal technique particularly in the mid and proximal segment of the renal artery. Inflicting thermal injury in the distal segment and into the branches has better chances of destroying the sympathetic fibers. In experimental animal models, the gold standard of RDN is surgical resection of renal nerves bilaterally and painting with phenol for complete fiber destruction. The most reliable method for assessing sympathetic fiber injury is renal tissue nor-epinephrine decline following RDN (though assessing the content of fibers, synaptic cleft but also norepinephrine within the tissues, all regulated differently). Animal data indicate that surgical renal nerve resection leads to more than 90% decline of tissue nor-epinephrine, sodium and water excretion and BP reduction [11]. However, tissue nor-epinephrine cannot be measured in humans unless renal biopsies are performed after RDN. Data on surgical RDN in humans is scarce and results equivocal [12–16].

The technique of transluminal thermal delivery via RF ablation in humans has been adopted to include circumferential lesioning, so to affect all four quadrants and to burn at the distal segment of the renal artery and into the branches.

Lately other sources of energy have been used to achieve complete denervation. Those include focus ultrasound and alcohol injection into the adventitia around the renal artery. Ultrasound can damage sympathetic fibers up to 7 mm from the artery lumen (and is less influenced than RF by obstacle, or tissue composition/content), whereas alcohol infusion can essentially cause complete, circumferential neurolysis at depths of up to 7–14 mm from the intimal surface. These techniques have been implemented in some sham-control studies recently published and results will be discussed below.

Positive outcomes of these sham-controlled studies prompted the US Food and Drug Administration's Circulatory System Devices Panel to convene and make recommendations regarding issues relating to the emergence of medical devices intended to treat and control hypertension [17]. Furthermore, 10 additional randomized sham-controlled studies have been initiated (Table 1), while some others are about to be launched [18–27].

In general renal denervation has been safe. Besides some bruising and small hematomas due to femoral access no other major adverse events have been reported. One potential adverse event is renal artery stenosis due to endovascular injury. This has been reported as a rare complication in radiofrequency induced renal denervation in the early single arm studies, but none has been reported in the recent sham control trials. Vigilance is still prudent.

3. Uncontrolled, single arm or un-blinded studies

The early RDN studies, SYMPLICITY HTN-1 and -2 demonstrated impressive reductions of BP and stimulated a lot of interest across the research and medical communities [28,29]. Since then, several other studies with similar design have been completed and published. Most of these studies enrolled patients with uncontrolled and/or resistant hypertension taking 3 or more antihypertensive medications and monitored office BP and ambulatory BPM changes for at least 6 months or later [28–39]. Results are shown in Fig. 1. Systolic office BP was reduced in almost all studies but magnitude ranged from −7.5 to −32 mmHg. Similarly, reduction in systolic ambulatory BPM ranged from −2.2 to −10.2 mmHg except for the INSPiRED study [37], which demonstrated a −21 mmHg reduction in systolic ambulatory BPM. This study however had an unusual design and included only 6 patients in the ambulatory part of the study. The weighted average reduction of systolic office BP was −20.8 mmHg and that of systolic 24 h ambulatory BPM was −7.8 mmHg.

Several other studies randomized patients with drug resistant hypertension to either RDN or drug intensification. In a meta-analysis of pooled data from 9 randomized studies that included more than 1000 patients, with drug-resistant hypertension, the efficacy of RDN was compared to pharmacotherapy. Change in systolic office BP at 6 months was the primary outcome [40]. As compared to pharmacotherapy, RDN was associated with a significantly greater reduction in weighted mean systolic office BP by −12.8 mmHg [95% Confidence Intervals (CI): −22.8

Table 1
Ongoing randomized sham-controlled trials on renal denervation among patients with primary hypertension.

Clinical Trial	N	Condition	Renal denervation methodology	Completion day
Golden Leaf	110	CH; ≥ 2 drugs	Radiofrequency	August 2019
AUSHAM-RDN-01	105	Resistant hypertension	Radiofrequency	April 2020
SYNAPTIC	264	High systolic BP; ≥ 2 drugs	Radiofrequency	September 2020
REQUIRE	140	Resistant hypertension	Ultrasound	November 2020
RADIANCE II	225	CH; 0–2 drugs	Ultrasound	December 2020
RADIANCE-HTN	292	CH; 1–2 drugs in SOLO-arm; resistant hypertension in TRIO-arm	Ultrasound	August 2021
TARGET BP OFF-MED	400	CH; no drugs	Ethanol injection	September 2021
SPYRAL PIVOTAL HTN-OFF MED	433	CH; no drugs	Radiofrequency	December 2022
TARGET BP I	100	High systolic BP; 2–5 drugs	Ethanol injection	October 2023
SPYRAL HTN-ON MED	260	CH; 1–3 drugs	Radiofrequency	February 2024

Abbreviations: CH: combined systolic-diastolic hypertension; ISH: isolated systolic hypertension; BP: blood pressure.

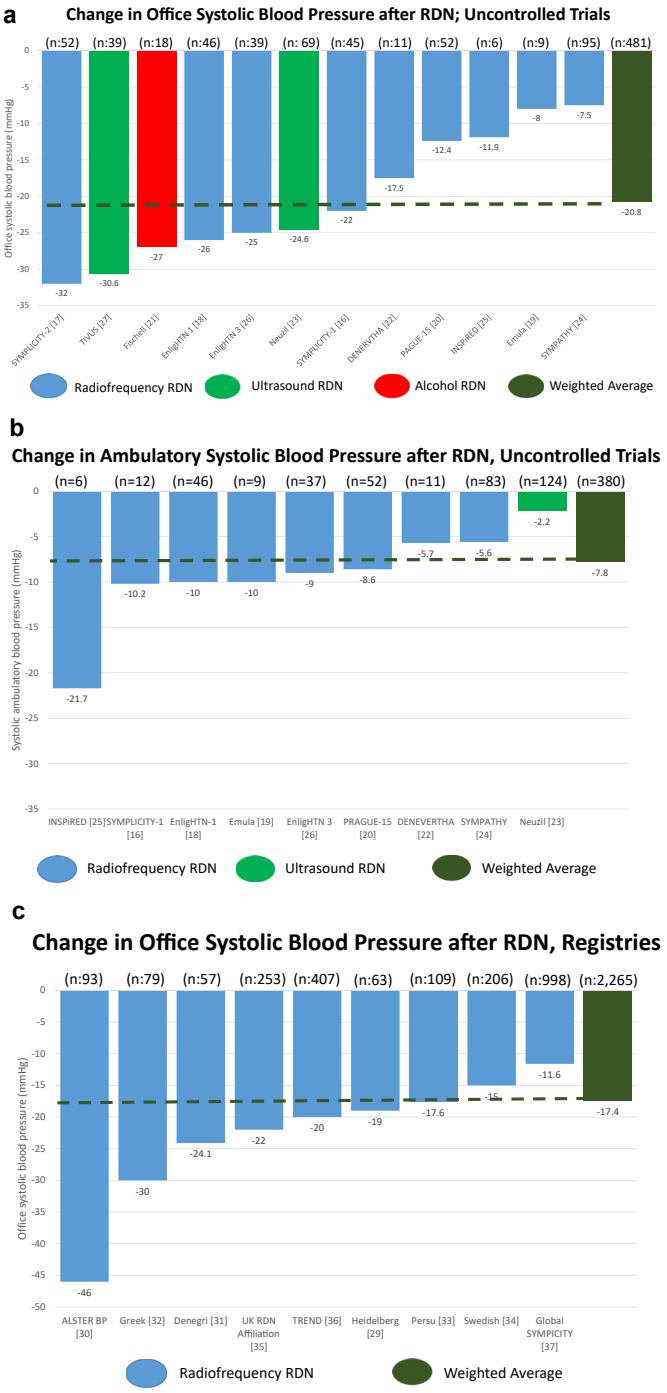

Fig. 1. **a** Average change in office systolic blood pressure at 6 months following renal denervation. Single arm, unblinded or, un-controlled clinical trials. **b.** Average change in 24 h ambulatory systolic blood pressure at 6 months after renal denervation. Single arm, unblinded or un-controlled clinical trials.**c**. Summary of registries assessing the impact of renal denervation on office systolic blood pressure among patients with difficult to control or drug-resistant hypertension Results at 6-months post-procedure.

to −2.9; I^2: 92%]. However, this effect seemed to have been driven by the outcomes of the non-randomized trials. RDN seemed to be safe in these studies and no signal of flow limiting renal artery stenosis or renal function deterioration was seen.

4. Single center quality programs, National and international registries

Positive data have also been reported in a number of "registries" and we'll briefly discuss them here.

Fig. 1c shows average office BP reduction from baseline in 9 registries, mostly in Europe but also from around the world [41–50]. These registries included in total 2265 patients with drug resistant hypertension. All patients had uncontrolled hypertension and most of them were treated with 3–5 antihypertensive medications. One of many available devices was used for renal denervation (EnligHTN, Symplicity Flex, Spyral, Paradise, Vessix or the OneShot). Office BP at baseline averaged from about 163/89 to 187/107 mmHg.

Across registries renal denervation resulted in substantial reduction of office BP ranging from −11.2 mmHg to as much as −46 mmHg. The weighted average office BP reduction was −17.4 mmHg. Serious adverse events were rare and only one case of significant renal artery stenosis was reported.

Impressive the registry results as they may be, are far from been reliable or definite. Results are variable and always subject to confounders; such as change in patient habits, change in medication compliance, weight gain or weight loss, salt consumption etc. In the luck of controls data cannot be taken at face value, but can be used as hypothesis generating for future studies to prove the point.

5. Sham-controlled studies

Following the publication of SYMPLICITY HTN-3, 5 other sham-controlled studies were completed and published.

Of those two were single center studies and used the single-tip Symplicity catheter, whereas the other three were multicenter, international studies. Of the last 3 studies, two used the multi-electrode Spyral catheter and the last one used the ReCor ultrasound catheter.

In the first study [51] 24 h ambulatory BPM was used to establish efficacy. Patients were included in the study if daytime systolic ambulatory BPM averaged at least 145 mmHg following 1 month on stable medication and patients demonstrated good compliance for two weeks. A total of 69 patients with drug-resistant hypertension were randomly assigned to RDN (n = 36) or sham-procedure (n = 33). Baseline demographics were similar between RDN and sham-control groups. The mean number of successful lesions was 10.9 for both renal arteries. The primary outcome of reduction in daytime systolic ambulatory BPM at 3 months was similar between the two groups (RDN: −6.2 vs −6 mmHg; p = 0.08). No significant adverse events were reported in ether group.

The second study [52], also a prospective, randomized, sham-controlled trial, evaluated potential benefits of RDN on patients with drug-resistant hypertension and mildly elevated BP based on 24 h ambulatory BPM (daytime systolic BP 135–149 and diastolic BP 90–94 mmHg). A total of 71 patients (73% males) were randomized to RDN (using the Symplicity Flex Catheter, n = 35) or sham-procedure (n = 36). Patients in the RDN group were 7.1-year older than those in the sham-group, but otherwise both groups had similar baseline demographics and comorbidities. Baseline BPs by ambulatory BPM were 140.2/78.2 and 140.4/80.6 mmHg (p = NS). On average 11.1 lesions were applied in both renal arteries. At 6-months, the mean change in 24 h systolic BP in the intention-to-treat cohort was −7.0 mmHg (95% CI: −10.8 to −3.2) for patients undergoing denervation and −3.5 mmHg (95% CI: −6.7 to −0.2) in the sham-group (between group difference, p = 0.15).

In the per protocol analysis, the change in 24 h systolic BP at 6 months was −8.3 mmHg for patients undergoing denervation and −3.5 mmHg in the sham-group (p = 0.042). In the per protocol analysis however 4 patients were problematic: two patients were excluded due to unsuccessful procedure (RDN group), 1 due to renal artery stenosis (RDN group), and

one did not undergo sham-procedure. When the analysis was restricted to patients without any change in antihypertensive medication (RDN, n = 22; sham-procedure, n = 29), RDN was associated with a greater reduction in systolic ambulatory BPM compared with sham-control by −6.3 mmHg (p = 0.007). No safety concerns were reported. Data on systolic office BP were not available in either study.

Both studies were well-designed but had shortcomings, were not conducted rigorously and have used the first generation RDN catheters which might have not been adequate to achieve complete 4 quadrant fiber interruption.

Likewise, in the Phase II randomized sham-controlled study of renal denervation for individuals with uncontrolled hypertension (WAVE IV) there was no proof of antihypertensive efficacy of externally delivered focused ultrasound [53]. Stabilization of BP at baseline was identified as an important determinant of BP changes that caused large variability of BP response.

The 3 positive, recently published sham controlled studies, utilized modern technologies and techniques to achieve optimal renal denervation.

The first SPYRAL HTN-OFF MED was a proof-of-concept RDN study, in patients with untreated hypertension [54]. The study was a multi-center, randomized, sham-controlled study of 80 patients with CH (71% males). not receiving antihypertensive medication (naïve or adequately discontinued). Patients were randomized to RDN of all accessible renal arterial vessels, including branches and accessory renal arteries with a diameter of 3–8 mm using the Symplicity Spyral multi-electrode catheter or the Symplicity G3 (n = 38), or a sham-procedure (n = 42). Baseline characteristics and demographics were similar between the RDN and sham-control groups. At 3-months, RDN resulted in a greater reduction in both the office and 24 h ambulatory BPM compared to sham-control group (−7.7/-4.9 (95% CI: −14/-8.5 to −1.5/-1.4) and −5.0/-4.4 (−9.9/-7.2 to −0.2/-1.6 mmHg, respectively). These outcomes remained essentially unchanged even after adjustment for baseline BP levels. It is worth noting that 21 of 35 patients in the RDN group experienced a reduction in systolic ambulatory BPM≥ 5 mmHg, while 10 patients experienced an increase. In the sham-control group about 50% of patients experienced decrease in BPs and about 50% increase. No patient reported any safety concerns.

The second study SPYRAL HTN-ON MED [55] was also a multi-center, single-blind, randomized, sham-controlled, proof-of-concept trial that evaluated the safety and efficacy of RDN using as the same ablation technique as described above. The study recruited patients with uncontrolled CH (systolic > 150 mmHg and diastolic > 90 mmHg) on 1–3 antihypertensive medication. In total, 80 patients (84% males) were randomly assigned to RDN (n = 38) or sham-procedure (n = 42). At baseline, both groups had similar characteristics and demographics and they were treated with a median of 3 antihypertensive medications. At 6-months after the procedure, RDN reduced both ambulatory and office BP better than sham-control (−7.4/-4.1 (95% CI: −12.5/-7.8 to −2.3/-0.4) and −6.8/-3.5 (95% CI: −12.5/-7 to −1.1/0; p = 0.048 mmHg). Blood pressure reduction remained significant even after adjustment for baseline BP levels. The between group difference in 24 h ambulatory BP was −5.0/-4.4 (p = 0.414, 0.0024, primary end point). RDN resulted in a gradual decrease in BP levels during the entire course of the study, while no significant change was observed in the interim-analysis at 3-months. Nine participants in the RDN group experienced increase in BP. It is worth noting than adherence to antihypertensive treatment was inadequate in both groups (about 65%). There was no significant change in renal function and no reports of renal artery stenosis in either group.

The third study, RADIANCE-HTN SOLO [56] was a multicenter, international, single-blind, randomized, sham-controlled trial done at 21 centers in the USA and 18 in Europe. The study designed to evaluate whether RDN, using endovascular ultrasound reduces ambulatory BP in patients with hypertension in the absence of antihypertensive medication. The study was pre-powered off the results of DENER-HTN and therefore, unlike SPYRAL ON and OFF, a pre-specified effect size could be achieved.

Patients with CH, aged 18–75 years were eligible for the study if they had ambulatory BPM≥ 135/85 mmHg and less than 170/105 mmHg after a 4-week discontinuation of up to two antihypertensive medications and had suitable renal artery anatomy. A total of 146 patients (58% males, 77% Caucasians) were randomly assigned to receive RDN (n = 74) or sham-treatment (n = 72). At 2-months, RDN achieved a greater reduction in office BP, ambulatory BPM, and home BP levels compared with sham-controls (−6.5/-4.1 (95% CI: −11.3/-7 to −1.8/-1.3), −4.1/-1.8 (−7.1/-3.7 to −1.2/0.2), and −7.1/-3.6 (95% CI: −10.4/-5.6 to −3.8/-1.5) mmHg after adjustment for baseline BP levels). The study design allowed administration of antihypertensive treatment in participants with office BP ≥ 180/110 mmHg or HBP≥ 170/105 mmHg. Herein, antihypertensive agents were initiated in 5, and 13 patients of RDN, and sham-control groups, respectively (p = 0.04). No major adverse events presented in either group.

6. Perspective

The last 3 sham-controlled studies presented above (SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED, and RADIANCE-HTN SOLO) (Fig. 2a,b), are the first to show in a convincing way that RDN lowers BP better than sham-control. The studies were rigorously designed and meticulously conducted. In fact, these are the first studies to have ever shown in a scientific way that RDN reduces BP in patients with hypertensive. The early reports of RDN that employed surgical renal nerve resection [12,13], showed very little effect on BP and surgical RDN gave way to the more radical surgical sympathectomy [14–16].

The early/modern transcatheter techniques that utilized RF energy, focus ultrasound, pure alcohol or other sources of energy were employed primarily in single-arm, uncontrolled studies or registries. Although these single-arm studies and registries (Fig. 1a–c) included several hundreds or thousands of patients and showed substantial reductions in both office BP and ambulatory BPM, results can be questioned. Having no controls and more precisely no sham-controls, makes it difficult to know how much of the effect is due to RDN, regression to the mean, Hawthorn effect or just noise. In particular, all studies that included patients with drug-resistant hypertension are subject to different kind of biases, due to protocol design such as “big day bias”, “check once more bias”, “unintentional baseline BP exaggeration bias” etc. [57].

Following the publication of the negative results of SIMPLICITY HTN-3 [2] the efficacy of RDN was put in question. The most plausible explanation given was that negative results seemed to be due to “incomplete denervation and luck of circumferential, four-quadrant sympathetic fiber interruption” [2,4]. The studies recently published took into consideration the pitfalls of SIMPLICITY HTN-3 and implemented a rigorous design and follow-up.

The reported studies—SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED, and RADIANCE-HTN SOLO— utilized different technologies, but similar protocol design and rigorously executed and monitored procedures [54–56]. All studies included patients with early but well-established CH and high likelihood of response, and excluded patients with end-stage renal disease, advanced hypertension or ISH. All three studies adopted procedures to help achieve maximal degree of RDN. All three studies provided reliable evidence that renal denervation works better than sham-control, in reducing BP in patients taking or not antihypertensive medication, using RF or ultrasound energy and the procedure was safe.

Yet the magnitude of BP reduction was smaller than initially anticipated [18–20]. Although the average sham-adjusted BP reductions were statistically significant and clinically meaningful, they were not better than changes expected from a single antihypertensive-pill added to patient's regimen [58,59]. Thus, at this point it is reasonable to suggest

that, RDN needs to be contrasted against drug therapy modification.

There was a great degree of variability in response. Although more patients demonstrated BP reduction with RDN than with the sham-procedure, many patients demonstrated increase in BP following RDN, suggesting that not all patients respond. Indeed, careful assessment of results indicates that the sham-corrected effect of RDN on BPs is lower in only a minority of patients. Some of these changes can be attributed to spontaneous visit-to-visit variability, regression to the mean or just noise for individual patients. Unfortunately it is difficult to characterize responders at this point. It is true that more patients in the RDN arm had lower BPs as compared to sham-control, but response was variable. Some patients had a reduction in systolic BP of as much as 40 mmHg, others only minimal reduction and some patients had increase in systolic BP following RDN. A change of 5–10 mmHg does not always identify true responders. Due to substantial visit-to-visit variability some patients could be responders in some visits and non-responders in others. Furthermore, results of current studies are only short-term and long-term efficacy is needed.

In an effort to recruit patients with the highest possibility of response patients with ISH were excluded. Only patients with CH were

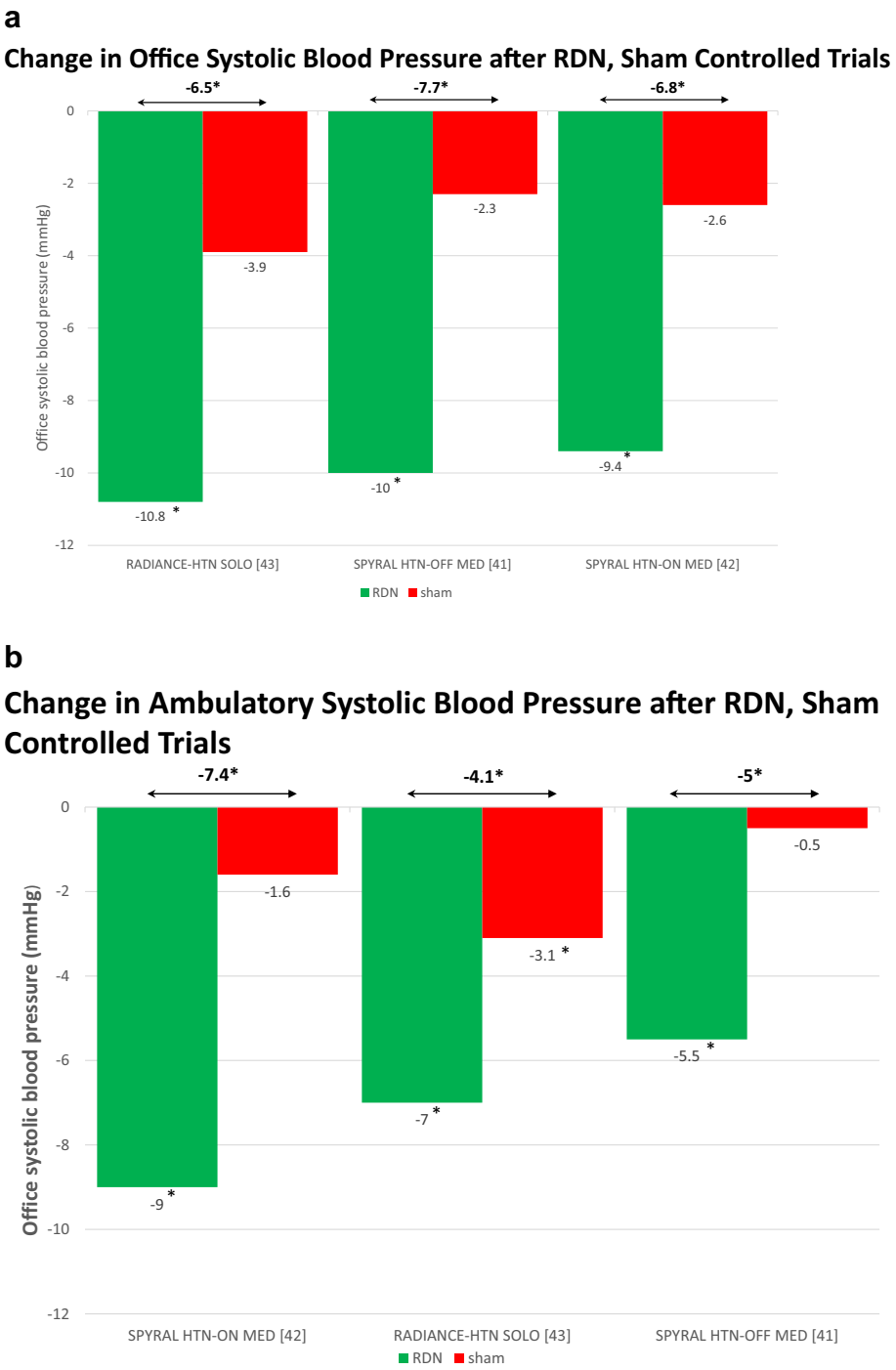

Fig. 2. **a** Summary of 3 sham-controlled randomized clinical trials assessing the impact of renal denervation on office systolic blood pressure. **b**. Summary of 3 sham-controlled randomized trials assessing the impact of renal denervation on 24- hour ambulatory systolic blood pressure levels. **Abbreviations:** RDN: renal denervation; *: $p < 0.05$.

allowed in the studies. Patients with ISH represent the majority of patient with hypertension especially among the elderly (>70%), and current data are not applicable to this important group. Patients with ISH benefit greatly from systolic BP reduction and RDN data are needed in this important group of patients. Whether different RDN devices and techniques provide different efficacy is not known. A recent study (RADIOSOUND-HTN) compared radiofrequency and ultrasound endovascular renal sympathetic denervation in three groups of patients with drug resistant hypertension [60]. Eligible patients were randomly assigned to receive either treatment with (1) radiofrequency RDN of the main renal arteries (N = 39); (2) radiofrequency RDN of the main renal arteries, side branches, and accessories (N = 39); or (3) an endovascular ultrasound–based RDN of the main renal artery (N = 42). The primary endpoint was change in systolic daytime ambulatory BP at 3 months. At 3 months systolic ambulatory BP was reduced by −13, 2 mmHg in the ultrasound RDN group, by −5.5 mmHg in the RF main renal artery group and by 8.3 mmHg in the RF main and side branches RDN group. These data indicate that the endovascular ultrasound–based RDN was 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. The study was well designed and results interesting. The ultrasound thermal energy delivery can reach a depth of 6–8 mm into the adventitia thus interrupting more than 90% of the sympathetic fibers with no need to address the branches.

Yet the numerical BP reduction in all three groups was small and the number of true responders limited.

A lot more work needs to be done, before RDN becomes prime-time. We still need data in patients with uncontrolled, resistant or difficult to control hypertension. We need data to assist in long-term management of patients and to better understand how RDN can fit in the total therapeutic scheme. Several questions still need answers:

Can RDN in some patients actually control hypertension? Can the number of medication be decreased or be discontinued? Can RDN cure hypertension in some patients? Does it work in patients with ISH?

Answers to these and other questions can only come from well-designed sham-controlled studies.

Furthermore, long-term safety needs to be established. Current data provide re-assurance than in the short-term there is no increase in the incidence of flow limiting renal artery lesions. But the currently employed method of assessment-renal ultrasound-has low sensitivity and can only detect severe or flow limiting lesions. Cannot exclude subclinical disease that may form after RDN and become a problem in the long run.

Our opinion on how to proceed into the future has been expressed elsewhere [61]; There is a space and a need, for future studies in the field of hypertension. Certainly, we need data using the new methods and techniques. We need well-designed studies to: a) prove that RDN can cure hypertension in some patients (borderline hypertension), b) reduce the need of antihypertensive medication or the number of medications, c) collect data in patients with ISH, and d) more carefully define characteristics of patients who are more likely to respond to RDN. Furthermore data are needed in the large group of patients with high –normal blood pressure to assess prevention of hypertension.

Until then we are glad that RDN is back on track and good research will continue. Patients who prefer procedure based therapies can be encouraged to participate in well-designed randomized and controlled trials, so answers can be provided soon.

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Conflicts of interest

None.

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