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Renal Denervation for Treatment of Hypertension: a Second Start and New Challenges

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Abstract Following the publication of the randomized controlled but open-label trial Symplicity HTN-2, catheter-based renal sympathetic denervation was proposed as a novel treatment for drug-resistant hypertension. Thousands of procedures were routinely performed in Europe, Australia and Asia, and many observational studies were published. A sudden shift from overoptimistic views to radical scepticism occurred later, when the large US randomized sham-controlled trial Symplicity HTN-3 failed to meet its primary blood pressure lowering efficacy endpoint. Experts are divided on the reasons accounting for the large discrepancy between the results of initial studies and those of Symplicity HTN-3. Indeed, the blood pressure lowering effect associated with renal denervation was overestimated in initial trials due to various patient and physician-related biases, whereas it could have been underestimated in Symplicity HTN-3, which was well designed but not rigorously executed. Still, there is a large consensus on the need to further study catheter-based renal denervation in more controlled conditions, with particular emphasis on identification of predictors of blood pressure response. US and European experts have recently issued very similar recommendations on design of upcoming trials, procedural aspects, drug treatment, patient population and inclusion–exclusion criteria. Application of these new standards may represent a second chance for renal denervation to demonstrate—or not—its efficacy and safety in various patient populations. With its highly standardized treatment regimen, the French trial DENERHTN paved the way for this new approach and may inspire upcoming studies testing novel renal denervation systems in different populations.

Keywords Renal denervation · Renal sympathetic denervation · Sympathetic nervous system · Resistant hypertension · Mild hypertension · Ambulatory blood pressure · Renal nerve stimulation

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Introduction

As of now, renal denervation (RDN) has been studied in 7 randomized controlled trials [1, 2••, 3, 4••, 5–7] including over 980 patients with resistant hypertension. Only two studies were blinded using a sham design [2••, 6]. In all studies, RDN was performed using the single electrode Symplicity

radiofrequency catheter. In a recent meta-analysis published by the European Network Coordinating Research On Renal Denervation (ENCOReD) [8••], after subtracting the placebo effects observed in control arms, the net benefit of RDN on the short term (6 months) was limited to a non-significant −4.9/−3.5 mmHg for office blood pressure and −2.8/−1.5 mmHg for 24-h ambulatory blood pressure (Fig. 1), but there was significant heterogeneity between the trials. While the incidence of adverse events was similar ($p = 0.24$) in RDN (9.9 %) and control (74 %) arms, these results confirm that RDN is not yet ready for wide dissemination in clinical practice.

However, this does not imply that research on new RDN devices should be stopped. First, RDN is supported by a strong rationale [9, 10]. Second, the heterogeneity of trials designs (sham-controlled or not), comparators (stable vs. intensified drug treatment) and primary endpoints (office versus ambulatory blood pressure) in current randomized controlled trials makes it difficult to draw firm conclusions on overall efficacy of RDN (Table 1). Third, the Symplicity HTN-3 study [2••] contributed for more than 50 % of patients included in the meta-analysis [8••]. Fourth, current randomized controlled studies all used the Symplicity™ unipolar radiofrequency RDN catheter, and the results cannot be readily extrapolated to other catheters (multiple electrodes, balloon-based….) and/or renal ablation systems (highly focused ultrasound, ethanol injection, cooling, etc.). Fifth, the external validity of the meta-analysis [8••] is restricted to patients with resistant hypertension, glomerular filtration rate >45 ml/min/m^2 and specific renal anatomy. Sixth, the meta-analysis [8••] cannot rule out a major blood pressure response to RDN in a minority of cases, as witnessed by most investigators. Finally, there is still an unmet medical need to treat patients with resistant hypertension and high risk or cardiovascular, cerebrovascular or renal morbid events with alternative non-pharmacological treatments since (i) all method developed up to now to improve the long-term adherence to complex regimens of antihypertensive medications have failed and (ii) no new drugs targeting new pathways are clearly on the horizon [11, 12].

The Renal Denervation Story: a Three-Step Process

The deployment of RDN as a novel treatment of resistant hypertension has followed a three-step course influenced by scientific evidence, but also economic interests, excessive enthusiasm and unjustified pessimism.

Step 1. In 2009–2010, publication of an observational first-in-man study, Symplicity HTN-1 [13], quickly followed by the randomized controlled trial Symplicity HTN-2 [1] in The Lancet demonstrated the feasibility and short-term safety of renal sympathetic denervation, with an impressive blood pressure lowering of 25–30 mmHg 6 months after the procedure (Table 1). Similar results were obtained in several uncontrolled observational studies, generating an unprecedented "hype" for RDN [14]. Whereas RDN was performed by hundreds of centres in Europe, mostly outside the context of a research protocol, in the USA, the Food and Drug Administration requested demonstration of efficacy and safety of the technique in a trial with blind endpoint evaluation before deployment of the technique. The large multicentre Symplicity HTN-3 trial was designed to meet these requirements [15] and was expected by many to confirm RDN as an established technique for the management of resistant hypertension. Of note, the pre-set superiority margin in terms of office blood pressure between the RDN and the sham group was only 5 mmHg, even though Simplicity HTN-2 reported a 30-mmHg difference in office blood pressure between the treated groups.

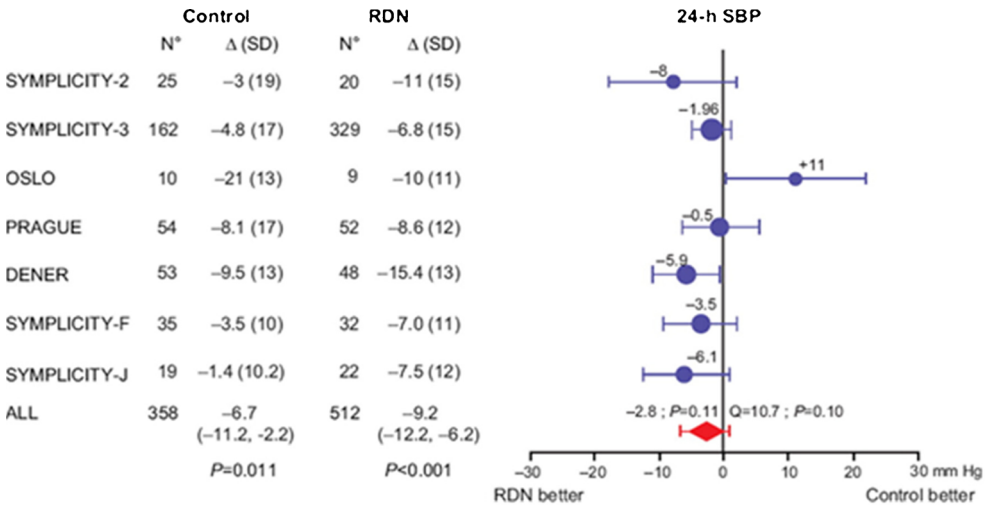

Fig. 1 Meta-analysis of randomized controlled trials of renal denervation in treatment-resistant hypertension [8]. Six-month response of 24 h systolic blood pressure (SBP) to renal denervation (RDN) or to follow-up in the control group. *Solid points* represent the effect size in individual studies and have a size proportional to the inverse of the variance. The *diamond* represents the pooled estimate. *Horizontal lines and diamonds* denote the 95 % confidence intervals (CIs)

Table 1 Overview of randomized controlled studies comparing renal denervation with drug treatment alone in patients with resistant hypertension

Study	Intervention in the control arm	Intervention in the RDN arm	Pro	Contra	Mean Δ office SBP (RDN-control)	Mean Δ 24-h ambulatory SBP (RDN-control)
Simplicity HTN-2 ($n = 106$)	-	-		No exclusion of secondary and white coat resistant HTN; 24-h ambulatory BP available only in 45 patients	−33	−8 (NS)
Simplicity HTN-3 ($n = 535$)	–	–	Sham	Suboptimal renal nerve ablation ; non standardized drug treatment changes after randomization in 40 % of patients	−2.4 (NS)	−1.96 (NS)
Symplicity HTN Japan ($n = 41$)	–	–			−8.7 (NS)	−6.1 (NS)
Symplicity-Flex ($n = 71$)	–	–	Sham ; Symplicity-Flex catheter		NR	−3.5 (NS)
Oslo-RDN ($n = 20$)	Adjustment according to hemodynamic condition	–	Drug adherence demonstrated by witnessed drug intake		+20	+11
PRAGUE-15 ($n = 106$)	Intensified drug treatment + spironolactone	–	Drug adherence demonstrated by drug dosages in plasma	Spironolactone stopped before 6 months in 21/41 patients from the control group	+1.9 (NS)	−0.5 (NS)
DENERHTN ($n = 106$)	Standardized drug treatment adjustment	Standardized drug treatment adjustment	Standardized drug treatment adjustment in both arms		−5.6 (NS)	−5.9

Blood pressure values are in mmHg

BP blood pressure, *HTN* hypertension, *RDN* renal denervation, *SBP* systolic blood pressure

Step 2. In 2014, the publication of Simplicity HTN-3 results [2••] tempered the initial enthusiasm. A mean decrease in office systolic blood pressure of 14.1 ± 23.9 mmHg was reported in the RDN group at 6 months, as compared with 11.7 ± 25.9 mmHg decrease in the sham group, leading to a modest 2.4 mmHg difference (95 % CI: −6.9 to 2.1), lower than the pre-set superiority margin of 5 mmHg, with patients being treated with 5.0 ± 1.4 and 5.2 ± 1.6 antihypertensive drugs, respectively [2••]. Similarly, the 24-h ambulatory blood pressure decrease was modest and of the same order of magnitude in both groups (−6.8 and −4.8 mmHg, respectively; $P < 0.001$ for both) [2••] (Table 1). In a fortnight, excessive optimism was replaced by radical pessimism [16]. It turned out that part of the large blood pressure decrease observed after RDN in previous open-label randomized trials or observational studies was not due to RDN, but rather reflected Hawthorne, placebo and white coat effects and regression to the mean [17–19]. Within the following months, several companies abandoned the development of their own RDN systems or stopped ongoing or planned trials, insurances companies cancelled reimbursement of RDN [20] and many physicians stopped referring patients for RDN, which in its turn made recruitment of still ongoing trials even more difficult. Later, claims that the disappointing results of Symplicity HTN-3 [2••] were likely due to insufficient renal ablation, uncontrolled drug changes in ≈40 % of patients after randomisation or high proportion of African-Americans [21, 22] were not sufficient to reverse the negative opinion. Overall, the results of Symplicity HTN-3 [2] are in agreement with those of the recently published sham-controlled trial by Desch et al. using the Symplicity-Flex catheter [6], as well as with Symplicity HTN-Japan [7], both of which failed to show a clear advantage of RDN over medical treatment alone (Table 1). However, the trial sponsored by Medtronic [7] was stopped after the results of Symplicity HTN-3 [2••] and was thus underpowered. In the German, institutionally sponsored, sham-controlled, randomized trial [6], the primary outcome, 24-h ambulatory systolic BP at 6 months, was not significantly reduced versus the control group with maintained antihypertensive treatment in the intention-to-treat analysis ($p = 0.15$). Still, the difference of 5–6 mmHg between the two groups was significant in terms of 24 h ($p = 0.04$) and daytime systolic BP ($p = 0.012$) in the per-protocol analysis. These results may be explained by the fact that the Desch trial [6] was slightly underpowered and should thus be interpreted with caution.

Along the same lines, in the PRAGUE-15 trial [5], RDN was not superior to drug treatment intensification including spironolactone, but spironolactone use led to an expected increase of adverse effects (hyperkalemia,

11 %; antiandrogen effect of spironolactone, 13 %). The average number of antihypertensive drugs used after 6 months was significantly higher in the pharmacological group (+0.3 drugs; $P < 0.001$). A significant increase in serum creatinine and a parallel decrease of creatinine clearance were also observed in the control group [5]. In the Oslo-RDN study [3], RDN proved to be much less efficient than drug treatment adjustment guided by non-invasive hemodynamic measurements, but the number of patients included in the study was limited. While the two last studies [3, 5] addressed slightly different questions than the Symplicity trials [1, 2••], in whom RDN on top of "maintained" drug treatment was compared to "maintained" drug treatment alone without further intensification, they confirm that RDN with the Simplicity™ catheter is not a panacea and should not replace skilful drug treatment adjustment [18]. Notably, these two studies [3, 5] were characterized by a particularly rigorous screening to exclude spurious causes of resistant hypertension, including assessment of drug adherence by witnessed drug intake [3] or plasma drug dosage [5].

Step 3. In this context, the publication of the multicentre, open-label controlled French trial DENERHTN sponsored by the French Ministry of Health in The Lancet [4••], showing a significant −5.9 mmHg additional decrease in daytime ambulatory blood pressure in the Simplicity™ catheter-based RDN arm vs. control arm ($p = 0.03$), with similar trends for office and home blood pressure, led to a slow but steady trend towards a more balanced evaluation of RDN. This difference in blood pressure is clinically meaningful and might contribute to a reduction in cardiovascular morbidity if maintained in the long term after RDN [23]. Though smaller than Symplicity HTN-3 [2••] and not sham-controlled, DENERHTN [4••] has several major assets: by contrast with the US trial [2••], RDN was performed by a limited number of well-trained investigators, the population of patients with resistant hypertension was well selected in European Society of Hypertension excellence centres excluding secondary hypertension, BP measurements were highly standardized, the primary endpoint was based on blinded assessment of ambulatory blood pressure measurement and, most importantly, optimum and stepped-care standardized antihypertensive treatment was applied in both arms based on home rather than office blood pressure measurements, both before and after randomisation.

Still, the modest but significant net effect of RDN in the DENERHTN trial [4••] should not conceal the huge variability of blood pressure responses observed in individual patients [4••, 24, 25]. In line with a patient-level meta-analysis from the ENCOReD network [24], the overall benefit of RDN may be strongly influenced by a low proportion of extreme-responders [25], thus putting to the forefront the need to identify reliable and easily accessible predictors of response [8••, 26••, 27••]. While in DENERHTN [4••], adherence assessed by the Morisky questionnaire [28] did not differ significantly between the RDN and control groups, either at baseline or 6 months after randomisation, an influence of differential changes in drug adherence on the results of the trial is not excluded. However, this question will be addressed more directly, as toxicological analysis of drugs in the urine was performed.

Renal Denervation After DENERHTN: Back to Basics

The rise and fall of RDN, followed by new, more reasonable expectations generated, between others, by DENERHTN [4••] has convinced the medical community [8••, 26••, 27••], and device companies that widespread dissemination of RDN had been premature. Before new renal nerve ablation systems are launched on the market, their efficacy and safety has to be demonstrated in carefully designed and executed studies. During the last months, several European and American networks [8••, 26••, 27••] discussed in depth research needs to move the field forward and proposed a stepwise approach for the development of new RDN systems, including animal studies, target populations, inclusion and exclusion criteria, safety, procedural and design aspects. A lot of emphasis was put on the need to identify simple, reproducible and easily accessible predictors of procedural success and clinical response. While experts from the US and Europe disagree on the need and importance of a sham-controlled arm [26••, 27••, 29] (see below), they agree on almost every other aspects. The main directions proposed are discussed below.

Animal Studies

Even though surgical RDN was able to prevent or delay the development of hypertension in various experimental models [9], until recently, published studies documenting the efficacy and safety of endovascular renal denervation in the animal were scarce. Indeed, Rippy et al. [30] published results obtained in 7 swine after publication of Symplicity HTN-2 [1] and after the catheter had obtained the CE label[1] in Europe. Six months after the procedure with the Simplicity catheter, the

[1] CE stands for Conformité Européenne, meaning European Conformity. The CE label ascertains that a product conforms with all applicable EC directives. Medical devices must not only be safe, but also function in a medical-technical way as described in the manufacturer's intended purpose.

renal arteries showed fibrosis from 10 to 25 % of the total media and the underlying adventitia, with mild disruption of the external elastic lamina, but the intima was healed and no thrombosis was seen. Renal nerve injury involved nerve fibrosis, replacement of nerve fascicles with fibrous connective tissue and thickening of the epineurium and perineurium [30].

After the failure of Symplicity HTN-3 [2••], more attention was directed to the identification of the biophysical factors involved in radiofrequency lesion formation [31], as well as the potential impact of anatomical variations of perivascular nerves and ganglia on the efficacy of RDN [32]. In particular, the density of peri-arterial renal sympathetic nerve fibers was shown to be lower in distal segments and dorsal locations of the human renal arteries, although with increasing distance from the aorta, nerve, and ganglia they are localized closer to the lumen [33]. Accordingly, it was shown that radiofrequency-based RDN lowers renal noradrenaline more significantly when performed in distal segments of the main renal arteries and in renal artery branches compared to more limited/proximal denervation [34, 35]. Understanding these anatomic patterns is thus important for optimizing RDN procedures. Finally, renal nerve ablation with a radiofrequency catheter was shown to lower blood pressure, as well in the Spontaneously Hypertensive Rat [36] as in obese, hypertensive dogs, an experimental model that closely mimics cardiorenal and metabolic changes in obese hypertensive humans [37, 38].

However, it was not until 2015 that in-depth analysis of the time course of nerve and vascular damage following RDN with the Symplicity system was published [39]. A total of 49 arteries from 28 swine were analysed at 4 different time points (7, 30, 60 and 180 days). Notably, while renal arterial injury progressively decreased, suggesting complete healing of the arterial wall at 180 days, focal nerve regeneration was observed at the sites of radiofrequency delivery, both at 60 and 180 days. These data are consistent with earlier findings of re-innervation after surgical RDN in the Spontaneously Hypertensive Rat [9], as well as the recent demonstration of functional re-innervation 11 months after RDN with the Symplicity Flex catheter in normotensive sheep [40], as shown by restored responses to electric nerve stimulation and normal anatomic distribution of at least the renal efferent nerves. Whether these different findings can be extrapolated to other RDN catheters or systems remains to be established [22]. It remains also unclear whether functional re-innervation occurs in human and may lead to long-term blood pressure increase in a proportion of patients who initially responded to RDN.

Both European and US experts [26••, 27••] have emphasized the need for preclinical studies in the animal, for testing various methodologies to produce RDN lesions, evaluating safety and efficacy of novel RDN systems, developing various biomarkers and assessing potential non-blood pressure related benefits. Prerequisites to propose new RDN systems include histological documentation of effective renal nerve ablation, decreased renal noradrenaline (though there is no evidence that this will automatically translate into a blood pressure decrease) in normotensive, healthy animals and, if possible, decreased systemic blood pressure in suitable animal models of hypertension.

Safety

In theory, the vascular thermal lesions provoked by radiofrequency may induce renal artery stenosis, as reported for pulmonary veins after radiofrequency ablation for atrial fibrillation [41]. Optical coherence tomography (OCT) performed in a prospective series of 16 patients with resistant hypertension disclosed renal artery constriction and local tissue damage with oedema and thrombus formation at the ablation sites after RDN using the Symplicity or the EnligHTN multi-electrode RDN catheters [42]. While the clinical relevance and prognostic value of such lesions are still unclear [43], a systematic review disclosed 24 cases of de novo renal artery stenosis or stenosis progression occurring after RDN performed using four different renal ablation systems [44, 45].

Few cohorts have assessed the prevalence of renal artery stenosis after RDN using state-of-the art methods [46–48]. In the largest ($n = 76$) [49], MRI disclosed only 2 cases of new non-significant stenosis (50 to 69 % lumen diameter reduction) 6 months after RDN using the Symplicity™ system. However, long-term incidence of renal artery stenosis after RDN remains a legitimate concern [26••, 44], even though its incidence is probably low (<5 %) and less than that reported after renal artery angioplasty in patients with atherosclerotic renal artery stenosis. Many factors including the design of the catheter, the use of a balloon, the presence or absence of a cooling/irrigation system, the depth profile of the temperature increase during ablation, the type of energy and the procedure itself depending on the precise localization of the ablation points (distal vs. proximal and renal artery branches *vs*. main renal artery) may influence the risk of vascular damage after RDN [44]. Variable degrees of vascular injury were observed after RDN with different balloon-based and non-balloon-based catheters. A significant reduction in renal artery lumen size was observed in non-balloon denervation but not in balloon denervation. In contrast, the risk of dissection detected with OCT was higher in balloon-based denervation catheters [50]. In addition, in a porcine model, catheter-based ultrasound delivered within a cooling balloon was effective at targeting the renal nerves circumferentially without damaging the arterial wall [51]. Hence, safety data obtained for the Symplicity™ unipolar system cannot be readily extrapolated to other renal ablations systems. Whether the risk associated with the use of different catheters is different in humans is not known. Assessment of the risk of occurrence of de novo renal artery stenosis by CT or MRI should be incorporated in the

design of phase II trials evaluating new RDN systems on the mid- and long-term, and at least short-term safety (6 months) should be demonstrated before further deployment. Furthermore, all cases of renal artery stenosis or stenosis progression should be collected in an independent registry [44].

Predictors of Blood Pressure Response to RDN

Most experts agree on the fact that the overall modest mean effects of RDN on blood pressure may be strongly influenced by a small proportion of responders. Hence, identification of reliable and easily accessible predictor(s) of the blood pressure response, the design of new catheters allowing a safe, complete and reproducible renal nerve ablation and the measurement of the extent of RDN during the procedure by a simple, accurate, sensitive and reproducible method are top research priorities and *sine qua non* conditions before RDN can make it to clinical practice [8••, 25, 26••, 27••].

In earlier, mostly observational or unblinded studies, identification of confounders has been made difficult by dilution of the true effect of RDN by non-specific responses related to white-coat effect, Hawthorne effect and regression to the mean, and also by the heterogeneity of the "resistant hypertension" phenotype. Besides baseline blood pressure [1, 4••, 13, 52], younger age, higher glomerular filtration [24, 25] and adherence to antihypertensive treatment [4••] were identified as predictors of a more pronounced blood pressure response. These results are consistent with post hoc analysis of the Symplicity HTN-3 trial suggesting a significantly better office [2••]—but not ambulatory [53]—blood pressure response to RDN in patients aged less than 65 year old or with estimated glomerular filtration rate >60 ml/min/1.73 m^2. By contrast, in elderly patients, patients with isolated systolic hypertension [54] and/or altered renal function, irreversible vascular damage and increased arterial stiffness may limit the potential benefits of RDN [18, 24, 26••, 27••].

Screening of registries, cohorts and randomized controlled studies led to the identification other potential predictors, including slower heart rate [1], use of central sympatholytic agents [55] or aldosterone antagonists [52] and non-use of vasodilators agents [52], high circulating levels of soluble fms-like tyrosine kinase-1 and endothelial adhesion molecules [56] and even low levels of vitamin D [57]. However, most of them are not supported by a strong rationale, were never confirmed in independent randomised controlled studies and, as such, have at most a hypothesis-generating value.

The level of brain-derived neurotrophic factor (BDNF), an important modulator of synaptic plasticity and activity of the sympathetic nervous system, was suggested to be a reliable indicator of effective renal nerve ablation, and may thus predict blood pressure responses [27••]. Indeed, a pilot study involving 100 patients with resistant hypertension showed a correlation between the decrease in BNDF plasma levels 2 h after RDN and systolic blood pressure reduction at 6-month follow-up ($p < 0.001$) [58]. However, since BDNF has a circadian rhythm [59, 60], the absence of a control group in this study does not allow firm conclusions.

Along the same lines, in normotensive dogs, high frequency electric stimulation was associated with increased serum adrenaline and noradrenaline and higher heart rate variability and blood pressure [61]. This blood pressure rise and the associated sympathetic reaction were selectively abolished or substantially decreased after unilateral RDN [61]. Gal. et al. subsequently confirmed the feasibility and safety of renal nerve stimulation (RNS) as a marker of effective renal denervation in anesthetized hypertensive patients undergoing RDN [62•]. In the future, RNS may help to guide renal nerve ablation, but the optimal RNS procedure in humans remains to be determined. Besides completeness of renal nerve ablation, the decrease in RNS-induced blood pressure rise after RDN may also predict blood pressure response at 6 months. However, this hypothesis remains to be validated.

Patient Population

Firm evidence of sympathetic overactivity in patients with resistant hypertension is lacking, although it may be implicated in more severe forms of so-called refractory hypertension [63]. The blood pressure response to different antihypertensive treatment strategies in patients with resistant hypertension may unravel the underlying pathophysiological pathways. Mineralocorticoid receptor blockers [64, 65], endothelin antagonists [66, 67] and sequential nephron blockade but not sequential renin angiotensin system blockade [68, 69] have been shown to lower blood pressure in patients with resistant hypertension. Moreover, the results of the PATHWAY-2 study [70] which included patients with resistant hypertension on a triple combination therapy showed that spironolactone was the most effective add-on drug as compared with drugs interfering with the peripheral sympathetic nervous system (bisoprolol and doxazosin), at least for the short term (12 weeks). Altogether, these data emphasize the role of sodium overload, mineralocorticoid and endothelin receptors and possibly sympathetic overactivity in the pathophysiology of resistant hypertension.

Apparently resistant hypertension is a heterogeneous group including patients with white coat and secondary resistant hypertension, suboptimal treatment regimen or poor treatment adherence. Furthermore, due to irreversible arterial damage, many of these patients may be less responsive to an intervention targeting the sympathetic nervous system. The main reason for selecting resistant hypertension as the target population for RDN was that a technique with unknown side

effects was ethically acceptable only in high cardiovascular risk patients with no or little other treatment alternative [26••]. Now that the safety of RDN on both the short and mid-term is reasonably established, there is a growing consensus to test RDN in either never treated or less resistant patients with mild or moderate hypertension [8••, 26••, 27••]. Younger patients are characterized by high sympathetic nervous activity [71, 72], did not yet develop advanced vascular damage and may thus respond better to RDN. Furthermore, inclusion of untreated or less treated patients with mild-to-moderate hypertension would limit the confounding effect of variable drug adherence [73–75]. Besides these new potential indications, RDN still deserves to be studied in patients with truly resistant hypertension, but treatment optimization and assessment of the blood pressure response by 24-h ambulatory blood pressure monitoring should be prerequisites. While the level of standardization obtained by the DENERHTN investigators [4••] may not be achieved in all cases, a minimal consensus is that treatment at baseline should at least include a long-acting and potent thiazide diuretic, a renin-angiotensin system blocker and a calcium channel blocker, all at maximally tolerated dosage [26••, 27••, 76]. Whether spironolactone 25 to 50 mg/day should be part of this initial drug regimen should be now discussed after the publication of the PATHWAY-2 results [70]. However, in PATHWAY-2, sodium depletion was not optimized and primary aldosteronism was not systematically excluded before randomisation, even though its prevalence is very high in patients with resistant hypertension [77], possibly leading to an overestimation of the blood pressure response to spironolactone. Moreover, the use of spironolactone is associated with adverse effects which may lead to long-term treatment withdrawal in a substantial proportion of patients. Furthermore, direct assessment of drug adherence by witnessed drug intake, although not easy to perform [3] or drug detection in plasma or urine using sensitive liquid chromatography–mass spectrometry methods, although exposed to white coat adherence [5], should become an integral part of upcoming protocols in this population. Finally, for all aforementioned reasons, there is general agreement that patients with stage 4 chronic kidney disease, isolated systolic hypertension [54] or other known causes of increased arterial stiffness should not be offered RDN [26••, 27••, 76].

Design

The use of 24-h ambulatory rather than office blood pressure measurement is recommended, as well for patients inclusion and evaluation of efficacy (primary endpoint), as to exclude patients with white-coat resistant hypertension from upcoming trials [26••, 27••, 29]. Indeed, compared with office measurement, ambulatory blood pressure measurement (ABPM) removes observer bias and measurement error, minimizes the white-coat effect and has greater reproducibility, and therefore provides a better estimate of a patient's usual blood pressure and cardiovascular prognosis [78–80]. ABPM is a better predictor of cardiovascular events than office blood pressure [78, 79], particularly in patients with resistant hypertension [81]. Patients with white-coat resistant hypertension—up to 40 % of patients with apparently resistant hypertension [82]—do not have the same increased cardiovascular risk as truly resistant hypertensive patients [83] and will probably not have any benefits from RDN in terms of ambulatory blood pressure decrease [84].

US experts recommend the use of a sham procedure in order to ensure blinding in both RDN and placebo arms [27••], whereas most European investigators [26••, 29] consider that this procedure has little added value, provided that the primary endpoint is based on blind assessment of 24-h ambulatory blood pressure (not mandatory for US experts) [27••] and drug adherence is assessed, both at baseline and throughout the trial [29]. Having this in mind, a sham control may appear too invasive and potentially harmful, and thus questionable from an ethical standpoint, especially in patients with mild-to-moderate hypertension [26••]. However, new FDA-approved trials have adopted this design.

Other controversies focus on the duration of stable antihypertensive medication before randomization. Besides unscheduled changes after randomization [52], carry-over effects of drugs occurring beyond the 2 weeks of requested stable treatment [2••] may have contributed to dilute the potential benefits of RDN in Symplicity HTN-3 [85]. In upcoming trials, there is general agreement that patients should be on stable treatment for at least 6 to 8 weeks before randomization [27••].

Procedural Aspects

In the first RDN studies, emphasis was put on ablating nerves located at the ostium of renal arteries, where the density of sympathetic nerve traffic is thought to be the highest. This was also the case in the Symplicity HTN-3 study [2••]. However, renal nerves are closer to the artery wall at the distal part [86], and thus, ablation performed at the distal part of vessels is more likely to be effective. Also, in the Symplicity HTN-3 trial [2••], 74 % of patients failed to have at least one circumferential ablation [52], and the office—but not ambulatory—blood pressure decrease after RDN was correlated with the number of ablation points [52]. Notably, however, in a recent study performed in pigs, the number of radiofrequency ablation points was not associated with the extent of nerve lesions assessed by noradrenaline tissue content and renal cortical axon density [35].

Whatever the impact of insufficient renal nerve ablation on the blood pressure outcome of Symplicity HTN-3 [2••], completeness of renal nerve ablation is a justified concern. Renal

nerve ablation should be circumferential, the number of ablation points should be as high as possible and specific targeting of the distal part of the arteries should be a priority [22, 26••]. Admittedly, these recommendations have been mostly developed for the unipolar Symplicity RDN system, and new RDN systems may achieve more effective, reproducible and less operator-dependent renal nerve ablation. Still, as for every new procedure, high-quality proctoring should be provided to study sites [27••].

Another debated issue is whether patients with multiple renal arteries (A2-A3 according to the Okada classification) or early bifurcation (B1) [87] should be offered RDN [26••]. The issue is by no way trivial, as such anatomical variants are found on at least one side in >50 % of cases [87]. In initial RDN trials [1, 13], patients with multiple or accessory arteries were excluded, which may have contributed to the apparently larger benefits of RDN. Whether accessory branches (A2) or bifurcations accessible to RDN (>3 mm) should be denervated remains a controversial issue. On one side, non-denervated accessory arteries or branches may be an unaddressed source of sympathetic overactivity [88], with subsequent decreased blood pressure benefit [89]. On the other side, denervation of small renal arteries may increase the risk of overheating, especially when using non-cooling catheters and that of de novo renal artery stenosis or other complications [26••]. Novel renal nerve ablation systems allowing successful and safe denervation of small renal arteries are necessary [26••].

Conclusion

While the uncontrolled deployment of catheter-based RDN has led to successive waves of enthusiasm and disenchantment, as well as burning controversies between experts with various backgrounds [17, 18, 22, 90], there is now a large consensus on the need for further studies testing novel catheter-based or external RDN systems in different populations, and general agreement on the way in which these studies should be conducted [26••, 27••, 29]. Expert recommendations include (1) extension of the target population to patients with milder forms of hypertension, either untreated or treated with less complex treatment regimens, (2) standardization of renal nerve ablation and antihypertensive treatment, (3) assessment of drug adherence and (4) use of 24-h ambulatory blood pressure measurement, both for patient selection and evaluation of efficacy. Identification of procedural endpoints and predictors of blood pressure response to RDN are a top research priority. While the major breakthrough of RDN was based on inconsistent evidence [14], RDN is offered a second chance to prove—or disprove—its benefits in various populations using a cautious, step-by-step, truly evidence-based approach.

Compliance with Ethical Standards

Conflict of Interest Dr. Azizi reports grants from French Minisitry of Health, Vessix, Boston Scientific Corporation, Medtronic and Servier, and personal fees from Vessix, Boston Scientific Corporation, Medtronic, and Servier. Dr. Kjeldsen reports honoraria from Bayer, MSD, and Takeda. Drs. Persu and Staessen report no conflicst of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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