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CKJ REVIEW

Late outcomes of renal denervation are more favourable than early ones: facts or fancies?

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ABSTRACT

Following second-generation randomized trials, there is evidence that renal denervation (RDN) decreases blood pressure (BP), although to a lesser extent than suggested in the initial controlled and observational studies. The recent publication of the 36-month follow-up of the Symplicity HTN-3 trial has raised expectations, suggesting increasing, late benefits of the procedure, despite initially negative results. These findings come after those obtained at 36 months in the sham-controlled trial SPYRAL HTN-ON MED and in the Global Symplicity Registry. However, they are susceptible to biases inherent in observational studies (after unblinding for sham-control) and non-random, substantial attrition of treatment groups at 36 months, and used interpolation of missing BPs. More importantly, in SPYRAL HTN-ON MED and Symplicity HTN-3, long-term BP changes in patients from the initial RDN group were compared with those in a heterogeneous control group, including both control patients who did not benefit from RDN and patients who eventually crossed over to RDN. In crossover patients, the last BP before RDN was imputed to subsequent follow-up. In Symplicity HTN-3, this particular approach led to the claim of increasing long-term benefits of RDN. However, comparison of BP changes in patients from the RDN group and control patients who did not undergo RDN, without imputation of BPs from crossover patients, does not support this view. The good news is that despite the suggestion of sympathetic nerve regrowth after RDN in some animal models, there is no strong signal in favour of a decreasing effect of RDN over time, up to 24 or even 36 months. Still, current data do not support a long-term increase in the effect of RDN and the durability of RDN-related BP reduction remains to be formally demonstrated.

Keywords: Global Symplicity Registry, long-term benefits, renal denervation, SPYRAL HTN-ON MED, Symplicity HTN-3

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THE STORY OF RENAL DENERVATION

Renal denervation (RDN) as a novel approach of hypertension management was first acclaimed without reservation based on the results of a single, never-replicated randomized clinical trial, Symplicity HTN-2 [1] and a number of observational studies. After the failure of the sham-controlled trial Symplicity HTN-3 [2] to demonstrate the efficacy of RDN over and above medical treatment, it entered into a purgatory that may have led to abandonment of the technique.

Fortunately, a number of investigators and companies remained and launched a second generation of trials that avoided the potential drawbacks of previous studies. They used not only a sham-controlled design, as was the case with Symplicity HTN-3 [2], but also more exhaustive and reproducible ablation techniques, ambulatory blood pressure (BP) measurement as a primary endpoint, standardization of antihypertensive treatment and direct evaluation of drug adherence by liquid chromatography–dual mass spectrometry (LC-MS/MS) [3].

RDN IS BECOMING AN ACCEPTED TREATMENT OF HYPERTENSION

The results obtained in second-generation studies mostly using radiofrequency or ultrasound-based renal nerve ablation have provided evidence that RDN is a safe and effective way to lower BP. As such, there is now increasing agreement that RDN is ready for clinical use in special indications, including treatment-resistant hypertension, patients with multiple side effects of drugs and/or patients unwilling to take lifelong medications. While the mean overall effect of RDN may be considered as modest, in the range of 4-6 mmHg for systolic BP (SBP), roughly corresponding to the effect of a single antihypertensive drug, this additional benefit may be particularly welcome in patients with a maximal, maximally tolerated or complex treatment regimen. Furthermore, it has been estimated that about one-third of patients have a much larger benefit from this approach, and intense research is dedicated to the identification of these 'extreme responders' [4]. Predicting which patients will better respond to RDN is further compounded by the fact that RDN is a blind technique. Whether RDN was successful or not cannot be ascertained at the time of the procedure. This contrasts with stenting of a coronary artery, where the evidence of success is immediately apparent. However, with respect to RDN, one must wait weeks or months to see the effect on BP.

Finally, other RDN techniques, such as ablation of renal nerves using local alcohol injection, have shown promising results in observational studies [5, 6] and results of sham-controlled studies using this approach are awaited soon.

While BP decreases observed in the days following RDN are probably due to the effect of anaesthetics, direct observed drug therapy in the hospital and/or abrupt improvement in drug adherence, it is widely admitted that it may take several weeks or even months to determine RDN-related BP benefits. In the initial studies, the primary efficacy endpoint was usually assessed at 6 months. Later, it was suggested that most of the benefit is captured 2 or 3 months after the procedure [7–10].

Duration of effect of RDN: animal data on renal nerve regrowth

On the other side of the spectrum, the question has been raised about the long-term duration of the effect of RDN. This question has been fuelled by observations of reinnervation after renal nerve ablation. Reinnervation after RDN has been suggested in rats (as early as 1980), swine and dogs, however, the functionality of these new renal nerves was unclear [11]. More recently, this question was addressed by Booth *et al.* [12] in sheep. While electric stimulation of renal nerves elicited an increase in BP and a decrease in heart rate (afferent response) and caused renal vasoconstriction and reduced renal blood flow (efferent response) before RDN, these responses were abolished after radiofrequency RDN using the Symplicity Flex catheter. These changes paralleled a substantial decrease in renal noradrenaline content and tissue expression of both tyrosine hydroxylase and calcitonin gene-related peptide, demonstrating successful renal nerve ablation. However, 11 months after the procedure, both responses to electric stimulation of renal nerves and markers of sympathetic nerves had returned to normal levels, suggesting functional reinnervation. Subsequently, similar analysis performed in chronic kidney disease (CKD) hypertensive and normotensive sheep again provided evidence of nerve regrowth at 30 months, although without *restauratio ad integrum* (noradrenaline content 49%, tyrosine hydroxylase 67% and calcitonin gene-related peptide 49% in CKD hypertensive sheep), consistent with maintenance of a BP-lowering effect [13]. Finally, in a study performed in swine, axon density and cortical noradrenaline levels were significantly reduced 7 days after RDN by radiofrequency (Spyral catheter) and remained suppressed at 180 days [14]. Both the extent and the very existence of functional renal nerve regrowth may therefore vary across different animal models. Whether this phenomenon occurs in humans after RDN and to what extent, whether it depends on the method of renal nerve ablation and whether, in the longer term, other phenomena take over to maintain lowered BP after RDN is unknown. Whatever the underlying mechanisms, the question of long-term maintenance of the BP-lowering effects of RDN is relevant.

Besides small size, purely observational studies, the effect of RDN has been assessed only up to 36 months. In this review, we focus on the results of the Global Symplicity Registry (GSR), the largest observational RDN study so far [15, 16] and long-term results of two randomized studies, i.e. the already mentioned Symplicity HTN-3 [17] and the second-generation SPYRAL HTN-ON MED trial [18].

Long-term effects of RDN on BP: the GSR

The GSR is a prospective, open-label registry currently involving 196 sites worldwide, established to evaluate the safety and effectiveness of RDN with the Symplicity Flex system and later the Spyral catheter [19]. Among 2237 patients (mean age 61 years, 58% male) with a high rate of comorbidities (cardiac disease 48%, type 2 diabetes 38%, CKD 21%) treated with the Symplicity Flex catheter, 1742 were eligible for a 3-year follow-up. Systolic office and 24-hour ambulatory BP were decreased by a mean of 16.5 and 8.0 mmHg at 36 months, respectively ($P < .001$ for both). Closer analysis of the results suggests a slightly but progressively increasing mean office BP drop until the last follow-up (11.7, 12.3, 14.7 and 16.5 mmHg at 6 months and 1, 2 and 3 years, respectively) [15].

However, these results should be interpreted with caution. First, the trend is much less impressive for 24-hour ambulatory SBP measurement (6.6, 7.2, 8.2 and 8 mmHg, respectively). Second, they were obtained in a decreasing number of patients over time, with a proportion of lost to follow-up of 36% (472/1321) for office SBP and 53% (397/750) for ambulatory SBP from 6 to 36 months. The mention 'All patients eligible for a 3-year follow-up' should therefore not be misunderstood or

taken for 'All patients followed up to 3 years'. A cohort analysis limited to patients actually followed until 36 months would have been of interest. However, these patients might also be the most adherent to lifestyle and drug treatments, followed by the most motivated healthcare professionals, thereby limiting the external validity of the conclusions.

A newer analysis [16] suggests a continuous decrease in both office and 24-hour SBP from 3 to 36 months, paralleled by an increase in time in therapeutic range (TTR) from 28.2 to 34.9% during the same period (TTR 28.2, 30.6, 32.8, 33.9 and 34.9% at 3, 6, 12, 24 and 36 months respectively). Although direct evidence is lacking for the long term, increasing TTR may be relevant for patient prognosis: a 10% increase in TTR after RDN through 6 months was associated with significant risk reductions from 6 to 36 months of 15% for major adverse cardiovascular events ($P < .001$), 11% for cardiovascular death ($P = .010$), 15% for myocardial infarction ($P = .023$) and 23% for stroke ($P < .001$).

TTR represents the percentage of all BP measurements recorded during the follow-up period that fall within a certain BP interval (e.g. SBP 120–140 mmHg) considered as the therapeutic target. It is a newly proposed index developed by analogy with indexes developed in other fields of medicine, such as anticoagulation with vitamin K antagonists. Provided the number of BP measurements available is large enough and homogeneously distributed across follow-up, TTR may be a reasonable estimate for the time in therapeutic range that would be obtained by daily BP measurements during the study period, thus approximating the real BP load over time. Accordingly, a higher TTR has been associated with a decreased incidence of all-cause mortality in a large cohort of veterans [20], a lower risk of all cardiovascular outcomes in a population-based cohort of subjects with newly identified high BP [21] and finally a decreased risk of a first major cardiovascular event in the SPRINT study [22]. However, the number and distribution of BP measurements required to achieve a reliable approximation of the true percentage of BP values in the therapeutic range and the impact of interpolation of missing BP values on the reliability of this approximation remain to be determined.

The use of TTR in the current analysis of GSR [16] has a number of particularities that require the reader's attention.

First, TTR was defined as a BP $\leq$140 mmHg for office SBP and $\leq$130 mmHg for 24-hour ambulatory SBP. The authors state that, 'To determine the TTR for each interval, the maximum TTR value using office SBP vs. ambulatory SBP was selected for each patient and then was averaged across patients in the GSR'. While the exact procedure is unclear, it appears that TTR was calculated using a mix of office and ambulatory SBP values. Why this was done and to what extent using only office or ambulatory BP values to compute TTR would have substantially modified the outcome is unknown.

Second, for patients with missing follow-up BP measures at a specific interval, TTR was calculated using their BP from the last observation carried forward (LOCF) and imputed to that interval. We could not find the proportion of interpolated values and therefore do not know whether an analysis without imputation would have given similar results.

Finally, in the absence of a control group, all analysis from the GSR are purely observational and therefore leave the door wide open to the Hawthorne effect and other patient- and physician-related unspecific effects. Further, the registry includes patients denervated for indications other than hypertension, little control on the quality of BP measurements is available, detailed data on the evolution of antihypertensive treatment over time, including not only drug class but the nature of the drugs and dosage are unavailable, and no data are available on drug adherence at baseline or during follow-up.

What can be said is that there is no signal in favour of a decreasing effect of RDN up to 36 months or, in the words of the authors, that the effect of RDN on BP is maintained at 3 years. However, this is also a questionable statement, as we all know patients with severe hypertension despite a maximal antihypertensive treatment whose BP improved over long-term follow-up in the absence of RDN, arguably due to progressive regression of vascular hypertrophy, improvement of drug adherence or a combination of both. This is also consistent with the substantial SBP decrease observed in control patients from Symplicity HTN-3 [17] who did not cross over to RDN (>20 mmHg at 3 years; see below). Therefore, it may well be that patients included in an observational registry such as the GSR show progressive BP improvement even if the effect of RDN partially subsides over time, be it due to sympathetic nerve regrowth or other unknown mechanisms.

Long-term effects of renal denervation on BP: SPYRAL HTN-ON MED

The SPYRAL HTN-ON MED enrolled patients with uncontrolled BP despite prescription of one to three antihypertensive medications [23]. Eighty patients (mean age ≈53 years, 84% male) with a low prevalence of comorbidities (type 2 diabetes 16%, coronary artery disease 2.5%) were randomised to RDN using the Symplicity Spyral catheter ($n = 38$) or a sham control procedure ($n = 42$). There was no difference in the number of prescribed antihypertensive drug classes between groups (mean 2.2 versus 2.3, $P = .70$) and adherence between groups was similar both at baseline (65.8 versus 59.5%, $P = .65$) and at 6 months (60.5% versus 64.3%, $P = .82$). At 6 months, the mean baseline-adjusted treatment differences were −7.0 mmHg for 24-hour SBP ($P = .0059$) and −6.6 mmHg for office SBP ($P = .0250$) in favour of the RDN group [23].

At 36 months, office BP could still be obtained in 67 (33 RDN/34 sham) of the initial 80 patients and ambulatory BP in 62 patients (30 RDN/32 sham). Both the number of prescribed drug classes (2.13 versus 2.55, $P = .26$) and level of drug adherence (77% versus 93%) tended to be lower in the RDN group, although the difference was far from statistical significance. The mean baseline-adjusted difference was borderline for office SBP (−8.2 mmHg, $P = .073$) but remained clearly significant in favour of RDN for 24-hour SBP (−10 mmHg, $P = .0039$) [18].

Notably however, the control group included both patients from the sham group who did not cross over to RDN and patients who crossed over between 24 and 36 months. In the latter group, the last BP measurements before crossover to RDN were assessed to impute their subsequent values (Fig. 1). Interestingly, in controls who were eventually treated by RDN, the last available mean office SBP before crossover was 20 mmHg higher than the corresponding BP value in non-crossover patients (165.7 versus 145.3 mmHg, $P < .001$) (Supplementary Table S1 of the original article) [18]. Possibly this was because patients who eventually crossed over had BP that was more difficult to control or did not improve their drug adherence because they were waiting for the procedure (Fig. 2).

The differences in BP changes between the initial RDN group and the control group (non-crossover + crossover patients with imputation from BP values before RDN) at 36 months are similar to those obtained in the same group at 24 months, i.e. before patients from the control group were able to cross over to

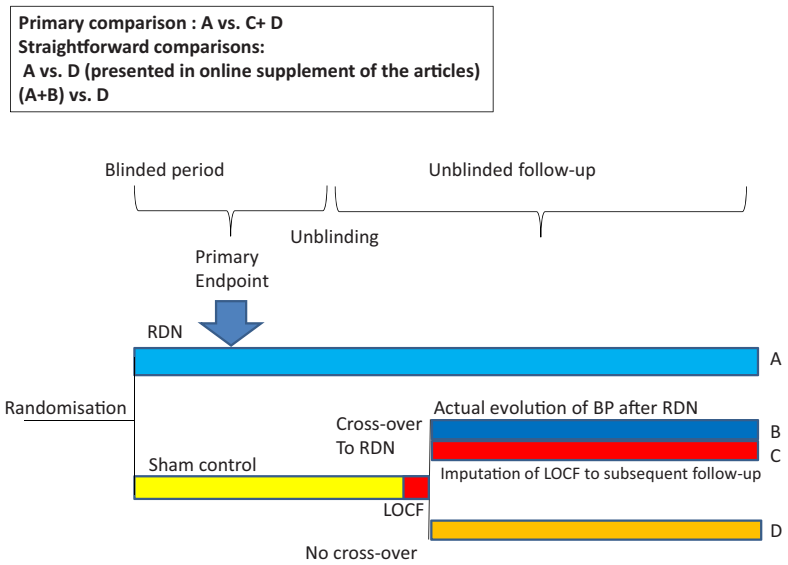

Figure 1: SPYRAL HTN-ON MED and Symplicity HTN-3 trials. Graphical representation of the comparison of long-term BP changes in patients from the RDN and control groups, including imputation of BP values from control subjects who crossed over to RDN (A versus C + D) versus comparisons without imputation (A versus D, A + B versus D).

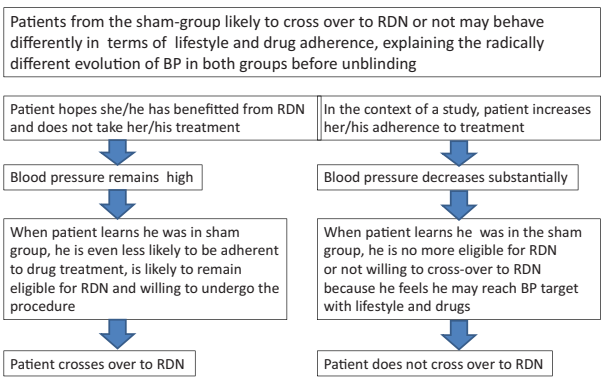

Figure 2: SPYRAL HTN-ON MED and Symplicity HTN-3 trials. Hypothetical explanation of the distinct evolution of BP before crossover in control subjects who later crossed over to renal denervation versus control subjects who did not benefit from RDN.

RDN (mean baseline adjusted differences at 24 months: −11.2 ($P = .0031$) and −11.1 ($P = .041$) for 24-hour ambulatory and office SBP, respectively). However, this difference shrinks to nothing at 36 months when patients from the initial RDN group ($n = 33$) are compared with those patients from the control group who did not cross over ($n = 21$) [office SBP change −20.9 versus −21.2 mmHg ($P = .92$) and 24-hour SBP change −18.7 versus −12.4 mmHg ($P = .11$)], without imputation of BP values from crossover patients ($n = 13$) [18] (Fig. 3). Whether the lack of significant BP difference at 36 months in the absence of imputation from the crossover group reflects a lack of statistical power due the small number of patients still in follow-up cannot be determined. Imputation does not replace an adequate follow-up. Overall, the data presented are consistent with maintenance of an RDN-related BP decrease at 24 months, with all aforementioned reservations during observational follow-up after unblinding, but no firm conclusion can be drawn at 36 months.

Long-term effects of RDN on BP: Symplicity HTN-3

While the methodology used to document maintenance of BP benefits using imputation of the LOCF in the crossover group does not change dramatically, the appreciation of a positive trial such as SPYRAL HTN-ON MED [18], its application to long-term follow-up of a negative trial such as Symplicity HTN-3 [2, 17], turning an initial failure into a final success [24], is even more questionable.

Readers may remember the earthquake generated by publication of this large sham-controlled trial that was expected to provide definitive evidence of the efficacy of RDN. The Symplicity HTN-3 trial [2] enrolled patients with treatment-resistant hypertension despite prescription of three or more drugs, including a diuretic. A total of 535 patients (mean age ≈57 years, 61% male, cardiac disease 35%, type 2 diabetes 45%, CKD 10%) were randomised 2:1 to RDN using the single-electrode Symplicity Flex catheter ($n = 364$) or a sham control procedure ($n = 171$).

The mean change in office SBP at 6 months was −14.13 mmHg in the RDN group as compared with −11.74 mmHg in the sham-procedure group ($P < .001$ for both comparisons of the change from baseline), but the difference in office SBP between both groups (−2.39 mm Hg) did not reach statistical significance ($P = .26$). These changes were paralleled by a change in 24-hour ambulatory SBP of 6.75 mmHg in the RDN group and 4.79 mmHg in the sham-procedure group, again corresponding to a non-significant ($P = .98$) difference of 1.96 mmHg. The reasons for the failure of Symplicity HTN-3 to meet its primary efficacy endpoint, including incomplete renal nerve ablation and lack of standardization of BP treatment, have been extensively discussed [25] and are beyond the scope of this short review.

At 12 months, the office SBP decrease from baseline was 18.9 in the RDN group ($n = 319$) versus 21.4 mmHg in the control group ($n = 48$ of 70 non-crossover patients) with a corresponding ambulatory BP decrease of 7.6 ($n = 247$) versus 6.1 mmHg ($n = 20$) [26]. Even in the absence of a formal statistical comparison and despite the small number of patients with ambulatory BP

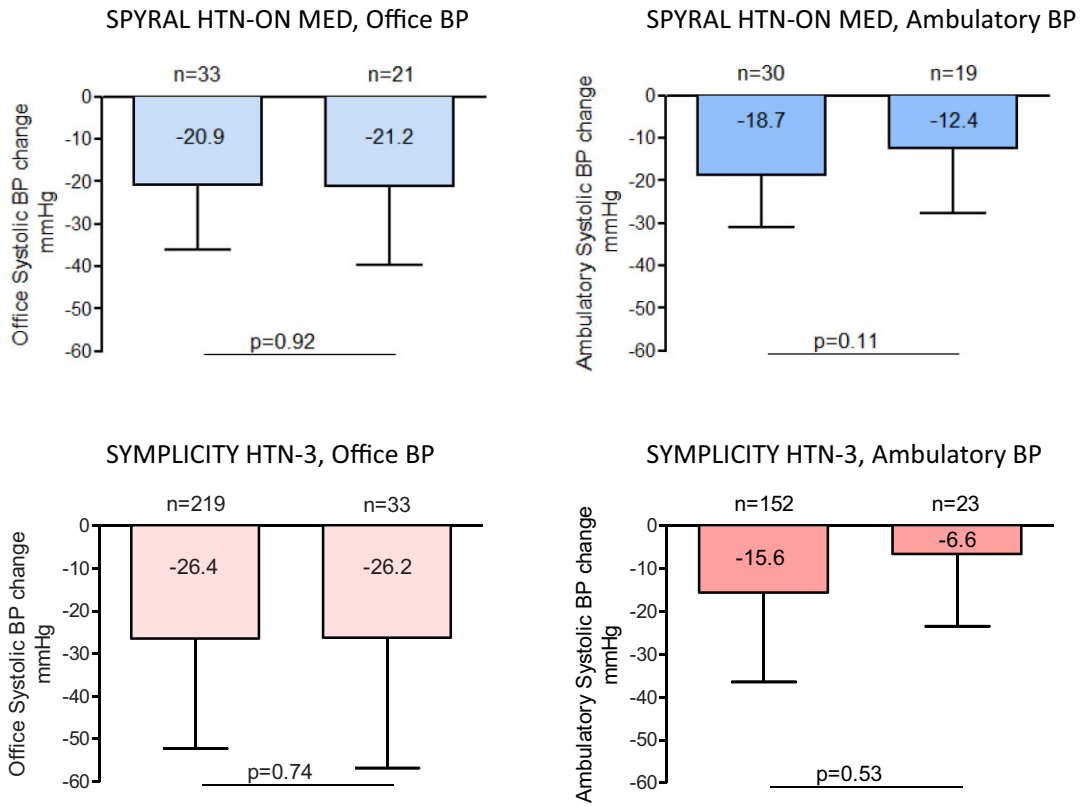

Figure 3: SPYRAL HTN-ON MED and Symplicity HTN-3 trials. Bar graph shows mean office and ambulatory SBP decrease at 36 months in patients from the initial RDN group versus control patients who did not benefit from RDN, in the absence of imputation from crossover patients. The reader may notice the small number of control subjects still on follow-up at 36 months, the large standard deviations and the lack of a significant BP difference between both groups.

measurements, it is obvious that there was no signal in favour of late benefits of RDN at 1 year.

The investigators of Symplicity HTN-3 therefore deserve praise for their efforts and persistence to report 3-year outcomes of denervated patients enrolled in an otherwise negative trial. A first look at the results of this final follow-up of Symplicity HTN-3 suggests that these efforts were rewarded, with final 22.1 and 16.5 mmHg mean adjusted differences in office and ambulatory SBP decreases in patients treated by RDN ($n = 219$) and controls ($n = 96$) ($P \leq .0001$ for both) [17], a surprisingly large benefit, of the same order of magnitude as that reported in the Symplicity HTN-1 [27] and HTN-2 [1] trials. The unfortunate exception of Symplicity HTN-3 [2] would therefore be almost obliterated, the story of RDN being one of unambiguous and cloudless success.

However, as in SPYRAL HTN-ON MED [18], the control group did not include only control subjects who did not cross over to RDN (only 33 of whom were still in follow-up), but also subjects who crossed over to RDN ($n = 63$). In the latter, the most recent BP values and medication burden before RDN were imputed to subsequent follow-up data, again following the principle of LOCF [28, 29] (Fig. 1).

In contrast, when comparing patients from the initial RDN group ($n = 219$) with control patients who did not cross over to RDN ($n = 33$), the mean BP decrease was not significantly different, neither for office [26.4 ± 25.9 versus 26.2 ± 30.6 mmHg ($P = .74$)] nor for 24-hour ambulatory [15.6 ± 20.8 versus 6.6 ± 16.8 mmHg ($P = .53$)] SBP, as was already the case at 12 and 24 months (Supplementary Table 4 of the original article) [17] (Fig. 3).

Furthermore, in agreement with previous observations in SPYRAL HTN-ON MED [18], while non-crossover control patients experienced a substantial BP decrease during the blinded period, partly maintained up to 36 months, patients who crossed over to RDN had maintained or slightly increasing BP during the same period (Supplementary Fig. 5 of the original article) [17]. Therefore, extrapolation of BP values from this period to subsequent follow-up and pooling with controls who did not cross over leads to dilution of the expected SBP decrease in the control group to a surprisingly small decrease of 5.7 mmHg, versus 26.2 mmHg when taking into account only controls who did not cross over to RDN [17] (Fig. 3).

The authors also state that the patients from the initial group spent a significantly longer time in the therapeutic BP range than patients in the sham control group (18% versus 8%, $P \leq .0001$) despite a similar medication burden. This difference was reportedly similar when comparing patients initially assigned to RDN with controls subjects who did not cross over to RDN, without imputation of BP values from the crossover group (18% versus 9%, $P \leq .0001$) [17]. However, all reservations already formulated for TTR analysis in GSR [16], including interpolation of missing BP values, potential patient and physician-related biases and non-random attrition of initial groups during unblinded follow-up, likely apply.

Therefore, these results should be taken *cum grano salis* and do not suffice to reverse our overall interpretation of the Symplicity HTN-3 trial [2, 17]. Negative it was at 6 and 12 months, and negative it remains at 36 months. Consequently, any discussion of mechanisms underlying late benefits of RDN in initial

Table 1: Summary of the results of the GSR and the SPYRAL HTN-ON MED and Symplicity HTN-3 studies at 6 months and 3 years.

Characteristics	GSR	SPYRAL HTN-ON MED[b]	Symplicity HTN-3[b]
Patients, *n*	2237	38 RDN/42 sham	364 RDN/171 sham
Age (years), mean ± SD	61 ± 12	53.9 ± 8.7	57.9 ± 10.4
Male, %	58	87	59
Office SBP at baseline (mmHg), mean ± SD	166 ± 25	164.6 ± 7.1	179.7 ± 16.1
SBP decrease[a] at 6 months (mmHg), mean ± SD			
Office BP	−12.8 ± 26.2 ($P < .0001$)	−6.6 (−12.4, −0.9) ($P = .0250$)	−2.39 (−6.89, 2.12) (NS)
Ambulatory BP	−7.2 ± 17.8 ($P < .0001$)	−7.0 (−12.0, −2.1) ($P = .0059$)	−1.96 (−4.97, 1.06) (NS)
SBP decrease[a] at 3 years (mmHg), mean ± SD			
Office BP without imputation from the crossover group	−16.5 ± 28.6 ($P < .001$)	0.5 (−8.8, 9.7) (NS)	−0.2 (−11.54, 11.14) (NS)
Office BP with imputation from the crossover group	–	−8.2 (−17.1, 0.8) ($P = .073$)	−22.1 (−27.2, −17.0) ($P < .0001$)
Ambulatory BP without imputation from the crossover group	−8.0 ± 20.0 ($P < .001$)	−6.1 (−13.6, 1.4) (NS)	−9.0 (−16.91, −1.1) (NS)
Ambulatory BP with imputation from the crossover group	–	−10.0 (−16.6, −3.3) ($P = .0039$)	−16.5 (−20.5, −12.5) ($P < .0001$)

NS: not significant.

[a]Global Symplicity HTN registry: BP decrease from baseline after RDN; SPYRAL HTN-ON MED and Symplicity HTN-3: difference in BP decrease between RDN and sham groups.

[b]All baseline values are provided for the RDN group.

Table 2: Potential biases influencing the conclusions of 36-month follow-up of patients included in the GSR, the SPYRAL HTN-ON MED and Symplicity HTN-3 sham-controlled studies.

GSR
- Inclusion of patients denervated for other indications than hypertension
- No or little control on the quality of BP measurements

GSR and sham-controlled studies
- Hawthorne effect and other patient- and physician-related biases (for sham-controlled studies, after unblinding)
- Unknown proportion of interpolated BP values used for the calculation of TTR (GSR and Symplicity HTN-3)
- Lack of detailed data on evolution of antihypertensive treatment over time (including not only drug classes, but exact nature of drugs and dosage—especially true for GSR)
- No data available on drug adherence (sham-controlled studies: long-term follow-up)
- Substantial/non-random attrition of groups during long-term follow-up (patients who remain on long-term follow-up are more likely to be adherent to drug treatment and lifestyle measures)

Sham-controlled studies
- Imputation of last available BP values before crossover to subsequent follow-up of control patients who cross over to RDN and pooling with BP values of control patients who did not cross over

non-responders or increasing benefits of RDN after 6 or 12 months would be purely speculative.

CONCLUSION

Our information on BP evolution up to 36 months after RDN mostly rests on observational data, coming from the GSR [15, 16] and other smaller observational studies, and from observational follow-up of patients included in the randomized sham-controlled trials SPYRAL HTN-ON MED [18] and Symplicity HTN-3 [17] (Table 1). Such data are subject to the Hawthorne effect, selective attrition biases and other patient- and physician-related unspecific effects (Table 2).

Besides these almost unavoidable biases, as blinded follow-up beyond 6 months would be both unpractical and unethical, our ability to conclude on long-term efficacy of RDN is further jeopardized by: (i) interpolation of missing BP values using the principle of LOCF, which is particularly questionable in patients with difficult-to-control, resistant hypertension, a condition associated with increased BP variability, further compounded by unpredictable changes in drug adherence [30]; (ii) more importantly, imputation of last BP values before RDN to subsequent follow-up in control patients who crossed over to RDN and pooling with actually measured BP values of non-crossover control patients, despite a radically different BP evolution in these two subsets already during the blinded phase, generating questionable BP differences with the initial RDN group (Figs. 1–3); and (iii) ad hoc use of TTR, a promising but newly developed index of treatment efficacy in association with the aforementioned statistical approaches to support long-term additional effects of RDN, even when more standard approaches fail to confirm this supposed benefit (Table 2).

In conclusion, as always, the devil is in the details, and accurate evaluation of evidence, especially when industry meets academia, bringing its specific competence, but also its own agenda and links of interest, requires careful analysis of apparently unattractive sections of articles such as methods, statistics and supplemental files. At the end of this exercise, we conclude that while there is no strong signal in favour of a loss of efficacy of RDN up to 24 or even 36 months, the concept of increasing long-term benefits of RDN is not supported by evidence thus far.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

A.P. has received honoraria for consultancy, grant support and travel grants from Ablative Solutions, Quantum Genomics, Servier and Recor Medical. R.K. reports honoraria for consultancy, lectures and support for research from Bayer Pharma, Berlin-Chemie Menarini, Daiichi Sankyo, Ferrer, Sanofi and Servier. G.M. reports honoraria from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Menarini, Merck, Novartis, Recordati, Sandoz, Sanofi and Servier. S.E.K. has received lecture honoraria from Getz Pharma, Vector-Intas, Merck Healthcare and Zydus Healthcare. The other authors report no conflicts related to this article.

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