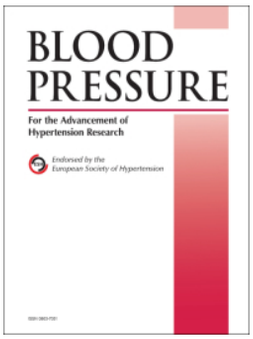

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NEWS

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Long-term efficacy and safety of renal denervation: an update from registries and randomised trials

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KEY POINTS

- Hypertension remains the leading treatable global cause of mortality due to high incidence and poor control rates despite of safe and effective drug therapy.
- Animal studies do not support functional nerve regrowth after RF-RDN and accordingly clinical evidence verify that RDN leads to durable BP reduction.
- Renal denervation is safe, as up to 36 months after the procedure, there are no statistically significant difference in procedure-related adverse events, deterioration of renal function and adverse cardiovascular outcome
- Renal denervation is efficient in reducing BP in patients with no drug therapy, independently of the number of antihypertensive drugs and phenotype of patient. This sustained and safe reduction in BP observed up to 36 months after RDN could be associated with lower rates of renal and cardiovascular events.

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Hypertension remains the leading treatable global cause of mortality due to high incidence and poor control rates despite of safe and effective drug therapy [1]. The safety and efficacy of radiofrequency (RF) and ultrasound (US) catheter-based renal denervation (RDN) for blood pressure (BP) reduction has recently been demonstrated in several randomised, sham-controlled trials both in the absence and presence of antihypertensive drug therapy [1]. However, information about long-term effects are sparse. This newsletter aims to summarise the important preclinical and clinical data on intermediate- and long-term durability of BP reducing effects of RDN.

Pathophysiological processes associated with the durability of nerve destruction in preclinical trials

As recently shown in a normotensive swine model, RF-RDN caused persistent reductions in renal norepinephrine, cortical axon density and downstream axonal loss. Axonal destruction persists through 180 days post-procedure [2]. These results suggest that functional nerve regrowth after RF-RDN is unlikely supporting published clinical evidence that the procedure results in durable BP reduction [2]. In another study, pre-bifurcation RDN was performed with a multi-electrode catheter in one renal artery of 12 healthy pigs, with the contralateral artery and kidney being used as controls. Histology taken 1-month post-procedure revealed a statistically significant accumulation of collagen as sign of intramural fibrosis and a near absence of tyrosine hydroxylase labelling in the denervated artery, suggesting a clear reduction in nervous terminals [3]. In another study reinnervation of renal nerves were analysed in hypertensive sheeps with hypertensive chronic kidney disease 30 months after catheter-based RDN. There was no complete lack of reinnervation in this model, since a reduced vasoconstriction to nerve stimulation together with reduced nerve regrowth was observed [4]. The authors concluded that anatomic and functional regrowth of renal nerves occurs but is not complete and does not adversely impact on the BP-lowering [4].

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Long-term BP reducing effects of RDN in registries and single centre series

The long-term safety and efficacy after RDN in real-world patients with uncontrolled hypertension, was demonstrated in the Global SYMPLICITY Registry. Out of 2237 patients treated with the SYMPLICITY Flex catheter, 78% ($N=1742$) were eligible for follow-up at 36-months. After 3 years office and 24-h ambulatory systolic BP were sustainedly decreased to −16.5 ± 28.6 mmHg ($p<0.001$) and −8.0 ± 20.0 mmHg ($p<0.001$), respectively [5]. No long-term safety concerns were observed following the RDN procedure. However potential limitations are that there may be errors or inaccuracies in the data, especially if it is entered manually, and data were not audited. Most important, we do not have clinical data of those patients who have not been followed for 3 years.

Long-term safety and efficacy data beyond 3 years are scarce. Sesa-Ashton and co-workers report on outcomes 9 years after RDN in a cohort of patients with resistant hypertension. As compared with baseline ambulatory systolic BP was reduced by −12.1 ± 21.6 (from 145.2 to 133.1) mmHg ($p<0.0001$) and diastolic BP by −8.8 ± 12.8 (from 81.2 to 72.7) mmHg ($p<0.0001$) [6] .At follow-up, participants were on one less antihypertensive medication compared with baseline ($p=0.0052$). There were no safety concerns. There are also recent data, regarding 36-month, long term safety and efficacy outcomes of RDN in patients with atrial fibrillation. In the AFFORD study [7], mean 24-h ambulatory systolic BP decreased by −2.2 mmHg/year, while daily doses of both antihypertensive and antiarrhythmic drugs did remain unchanged in the follow-up period of 36 months. No device-related adverse events were reported. The smaller decreases in BP reported in AFFORD study are in disagreement with the rest data from the literature; *the small size, the lack of sham-arm and blindness and the presence of atrial fibrillation are possible reasons accounting for this discrepancy.* In a single-arm, single-centre study, that enrolled 107 patients with resistant hypertension, undergone RDN from August 2010 to October 2012 and 39 of them were followed-up for 10 years, one of the longest follow-up period in RDN trials [8]. Regarding efficacy, 24-h SBP and DBP decreased by −16.2 mmHg ($p<0.001$) and −5.5 mmHg ($p<0.027$), respectively, while mean number of antihypertensive drugs remained stable (4.9 ± 1.4 at baseline vs 4.5 ± 1.2 at 10 years; $p=0.087$).

Long-term BP reducing effects and safety of RDN in randomised controlled trials

In SPYRAL HTN-ON MED at 36 months, ambulatory systolic BP reduction was −18.7 mmHg (SD 12.4) for the RDN group ($n=30$) and −8.6 mmHg (SD 14.6) for the sham control group ($n=32$; adjusted treatment difference −10.0 mmHg, 95% CI −16.6 to −3.3; $p=0.0039$) [6]. Treatment differences were −5.9 mmHg (95% CI −10.1 to −1.8; $p=0.0055$) for mean ambulatory diastolic BP, −11.0 mmHg (−19.8 to −2.1; $p=0.016$) for morning systolic BP and −11.8 mmHg (−19.0 to −4.7; $p=0.0017$) for night-time systolic BP. Safety events were rare and did not differ between groups [9]. At 36 months, the number of prescribed antihypertensive medications in the RDN group was not different from the sham control group (3.03 vs 3.05, $p=0.76$) [9]. In RADIANCE-HTN SOLO 74 patients were randomised to US-RDN, of which 69% ($N=51$) completed the 3 years follow-up. In summary, office BP decreased by 18/11 ± 15/9 mmHg and BP control (office BP <140/90 mmHg) improved significantly from 29.4% at screening to 45.1% at 3 years ($p=0.059$). There was no difference in the overall antihypertensive medication between baseline and follow-up [10]. *(All long-term follow-up data presented in* Table 1).

Critical appraisal and relevance for clinical practice

The long-term results of the SPYRAL HTN-ON MED trial and the RADIANCE-HTN SOLO trial demonstrated the durable efficacy and safety of RF- and US-RDN in patients who are already on one to three antihypertensive drugs. RDN significantly reduced 24-h systolic and diastolic BP at 36 months without any safety concerns and without a significant increase in medication [9, 10] (Figure 1). The sustained reductions in BP observed up to 36 months after RDN in this study showed no significant functional reinnervation in this cohort of patients with hypertension. Notably, the sustained and significantly reduced lower BP levels throughout the 24-h achieved by RDN treatment are clinically meaningful and could be associated with lower rates of cardiovascular events [1].

While implementing the abovementioned long-term studies' results into daily practice, it is noteworthy to keep in mind that the results are specific to RF- and US-RDN procedures and might not be generalisable to other RDN modalities. Further, the current studies did not evaluate clinical data regarding patients' exercise, diet, or smoking habits, which could have influenced BP measurements. Last but not least, the percentage of women enrolled in the studies was relatively low.

Table 1. Long-term BP reducing effects of RDN in registries, single centre series and RCTs.

Study	Device	Design	Follow-up Size (at 36 months)	Efficacy	Safety
Global SYMPLICITY Registry[5]	Symplicity (RF)	Registry	1732	Baseline systolic OBP were 166 ± 25 mmHg Baseline systolic ABPM was 154 ± 18 mmHg SBP reduction after RDN was sustained over 3 years, including decreases: • in systolic OBP (-16.5 ± 28.6 mmHg, p < 0.001) and • in systolic ABPM (-8.0 ± 20.0 mmHg; p < 0.001)	eGFR declined: • by 7.1 in patients without CKD • by 3.7 in patients with CKD No long-term safety concerns were observed following the RDN procedure.
Sesa-Ashton et al[6]	RF	Cohort	66 (at 8.8 ± 1.2 years post-procedure)	Systolic ABPM reduced by −12.1 ± 21.6 (from 145.2 to 133.1) mmHg (p < 0.0001)Diastolic ABPM reduce by −8.8 ± 12.8 (from 81.2 to 72.7) mmHg (p < 0.0001)Mean HR unchangedAt follow-up, participants were on one less AHM compared with baseline (P = 0.0052).	No short-term or long-term AEs associated with RDN
AFFORD[7]	St. JudeEnligHTN™ system (RF)	Single-arm Pilot study (RDN in AF)	20	At baseline, mean ABPM was 129.5/77.3 ± 15.5/9.3 mmHgMean systolic ABPM decreased with − 2.2 (95% CI − 3.9, − 0.6; p = 0.01) mmHg/yearNumber of AHM remained stable over time Baseline daily AF burden was 1.4 [0.0-10.9] minutes/day and throughout a 3-year follow-up period, no significant change was observed	No short-term or long-term AEs associated with RDN
Al Ghorani et al[8]	RDN (RF)	Single-armSingle-centre study	39 (10 years follow-up)	Systolic ABPM decreased by −16.2 mmHg (p< 0.001)Diastolic ABPM decreased by - −5.5 mmHg (p < 0.027) Mean number of AHM remained stable	No short-term or long-term AEs associated with RDN
SPYRAL HTN-ON MED[9]	Symplicity Spyral (RF)	RCTRDN vs sham (1:1)	62RDN 30 sham 32	Systolic ABPM reduction was −18.7 mm Hg (SD 12.4) for the RDN group (n = 30) vs −8.6 mm Hg (14.6) for the sham control group (n = 32) Treatment differences between the RDN and sham were: • −5·9 mm Hg (95% CI −10·1 to −1·8; p = 0·0055) for mean diastolic ABPM • −11·0 mm Hg (-19·8 to −2·1; p = 0·016) for morning systolic ABPM • −11·8 mm Hg (-19·0 to −4·7; p = 0·0017) for night-time systolic ABPM	No short-term or long-term AEs associated with RDN
RADIANCE-HTN SOLO[10]	Paradise(US)	RCTRDN vs sham (1:1)	RDN 51 (out of 74 originally assigned)	OBP decreased by 18/11 ± 15/9 mmHgBP control improved significantly from 29.4% at screening to 45.1% (p = 0.059)No difference in the overall AHM between baseline and follow-up	No short-term or long-term AEs associated with RDN

ABPM: Ambulatory blood pressure monitoring, AF: Atrial fibrillation, AHM: Antihypertensive medication,CKD: Chronic kidney disease (defined as eGFR < 60 mL/min/1.73 m^2) , eGFR: estimated glomerural filtration rate l OBP: Office blood pressure, HR: Heart rate, RDN: Renal denervation, RCT: Randomised controlled trial, RF: Radiofrequency, US: Ultrasound.

Although the aforementioned registries and trials on renal denervation demonstrated promising long-term results in patients with hypertension, there are still some limitations and uncertainties that need to be considered. Firstly, the studies were conducted on a relatively small sample size, which may limit the generalisability of the results, especially regarding safety, *although future larger trials can prove that this very low AEs' rate and the safety-friendly profile of the procedure will remain steady*. Secondly, the study did not evaluate the impact of renal denervation on other important clinical outcomes such as cardiovascular events or mortality. Finally, while the studies showed no significant safety concerns, the long-term effects of renal denervation on renal function and other organs remains unclear. Therefore, further research is needed to confirm the long-term safety and efficacy of renal denervation in patients with hypertension.

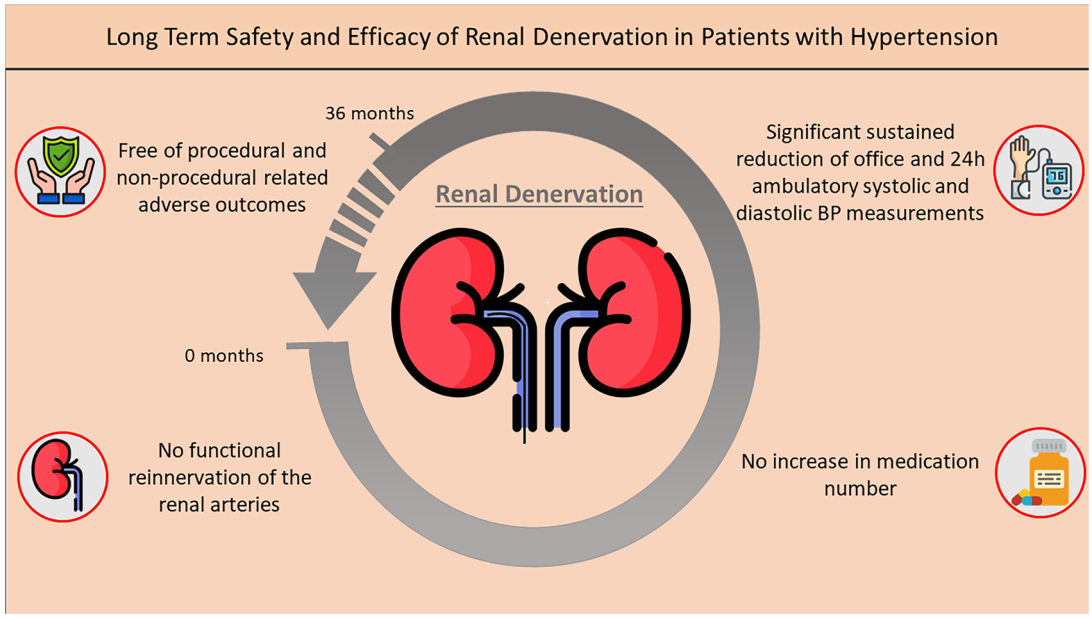

Figure 1. Long-term safety and efficacy of renal denervation.

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