EuroIntervention
2026;22:585-593
DOI: 10.4244/EIJ-D-26-00161

ORIGINAL RESEARCH

Long-term clinical benefit after radiofrequency renal denervation: pooled 36-month results from the SPYRAL Clinical Program

David E. Kandzari[1]*, MD; Michael Böhm[2], MD; Roland E. Schmieder[3], MD; Raymond R. Townsend[4], MD; Markus P. Schlaich[5], MD, PhD; Kazuomi Kario[6], MD, PhD; Robert Whitbourn[7], MD; Miranda Gilbertson[8], MS; Felix Mahfoud[9,10], MD

Corresponding author: Piedmont Heart Institute, Suite 2065, 95 Collier Road NW, Atlanta, GA, 30309, USA. E-mail: dkandzari@gmail.com

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-26-00161

ABSTRACT

BACKGROUND: Catheter-based renal denervation (RDN) is a guideline-recommended therapy for uncontrolled hypertension. Late-term follow-up among RDN trials is essential to characterise the durability of its efficacy, and further study is needed to ascertain the proportion of patients experiencing a clinical benefit.

AIMS: We aimed to evaluate 36-month blood pressure (BP) changes after radiofrequency (RF)-RDN across four clinical studies from the SPYRAL programme and to determine the proportion of patients who experienced a clinical benefit.

METHODS: Data were pooled from the Global SYMPLICITY Registry DEFINE, SPYRAL First-In-Human, and SPYRAL HTN-OFF MED and -ON MED trials. All patients were treated with RF-RDN (Symplicity Spyral). Medications, BP changes, and adverse events were evaluated through 36 months.

RESULTS: A total of 2,137 patients treated with RF-RDN using the Spyral device were included in the analysis. Baseline office systolic (OS)BP was 163±23 mmHg, baseline 24-hour ambulatory systolic (AS)BP was 152±17 mmHg, and the baseline number of antihypertensive medications was 3.8±2.1. At 36 months, the number of medications was 3.5±1.9, and reductions in OSBP and ASBP were significant (–18.1±23.4 mmHg and –13.3±17.6 mmHg, respectively; p<0.0001). Overall, adverse event rates were low. The proportion of patients who experienced a reduction in OSBP ≥10 mmHg, ASBP ≥5 mmHg, and/or ≥1 medication was 88% at 36 months.

CONCLUSIONS: In this large, pooled cohort of Spyral RF-RDN patients, there were significant BP reductions through 36 months with few adverse events. Additionally, nearly 9 out of 10 patients experienced a clinical benefit. These findings suggest the long-term efficacy and safety of RF-RDN across a broad spectrum of patients with uncontrolled hypertension.

KEYWORDS: blood pressure reduction; renal denervation; uncontrolled hypertension

SUBMITTED ON 02/02/2026 - REVISION RECEIVED ON 1st 23/02/2026 / 2nd 03/03/2026 - ACCEPTED ON 03/03/2026

Hypertension is the leading modifiable risk factor for cardiovascular disease and remains a major global health challenge, affecting more than 1 billion adults worldwide.[1-3] Despite the established efficacy of lifestyle interventions and antihypertensive (AH) medications, adherence remains poor, and a significant proportion of hypertensive patients have persistent uncontrolled blood pressure (BP), underscoring the need for alternative therapeutic options to achieve and maintain BP control.[4] Catheter-based renal denervation (RDN) is a minimally invasive, guideline-recommended procedure that targets sympathetic nerves in the renal arteries, offering a novel approach to treat hypertension.[5-8] Multiple randomised, sham-controlled trials and global registries have demonstrated the safety and efficacy of RDN, both in the presence and absence of AH medications.[9-14] Although the results of recent pooled studies and meta-analyses across numerous different populations and device types suggest a consistent, durable BP-lowering effect with RDN,[15-18] a systematic assessment of the long-term efficacy and safety of RDN using the latest-generation, U.S. Food and Drug Administration-approved, Symplicity Spyral multielectrode radiofrequency (RF) catheter (Medtronic) remains warranted. Moreover, while multiple studies have investigated which patients are most likely to experience a clinical benefit after the procedure, only higher preprocedure baseline BP has been consistently associated with future BP response.[15,16] However, a broader question remains unaddressed that is essential to informing practice: what proportion of patients experience a meaningful clinical benefit after RDN?

We leveraged comprehensive follow-up data from over 2,000 patients in the SPYRAL clinical trial programme, including the Global SYMPLICITY Registry (GSR) DEFINE, SPYRAL First-In-Human (FIH), and the SPYRAL HTN-OFF MED and -ON MED trials to evaluate long-term changes in BP, prescribed AH medications, and safety outcomes among RDN patients treated with the Spyral device through 3 years.[9,10,12,19] Additionally, we evaluated the proportion of hypertensive patients who experienced a clinical benefit after undergoing RDN with the Spyral device.

Impact on daily practice

Renal denervation (RDN) is a guideline-recommended therapy for uncontrolled hypertension. In this study, 3-year blood pressure (BP) changes and the proportion of patients who experienced a clinical benefit after RDN using the Symplicity Spyral device were evaluated. BP reductions after RDN were significant and were sustained over the long term, with nearly 9 out of 10 patients experiencing a clinical benefit.

Methods

STUDY DESIGNS AND PATIENT POPULATION

This *post hoc* analysis included patients from GSR DEFINE who were treated with the latest-generation Spyral catheter, those included in SPYRAL FIH, and those randomised to the RDN cohorts from the randomised controlled SPYRAL HTN-OFF MED and -ON MED trials.[9-12] Details of the study designs have been previously published.[12,20,21] Follow-up through 3 years was prespecified for all 4 studies. GSR DEFINE is an all-comers, real-world, international registry evaluating the safety and efficacy of RF-RDN. SPYRAL FIH was a feasibility study of the Symplicity Spyral RF-RDN catheter in patients with an office systolic BP ≥160 mmHg, or ≥150 mmHg for those with type 2 diabetes, despite prescription of ≥3 AH medication classes. The SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED studies were global, randomised, blinded, sham-controlled trials evaluating the safety and efficacy of RF-RDN using the Spyral device in the absence or presence of AH medications, respectively. Eligible patients had an office systolic BP ≥150 and <180 mmHg, an office diastolic BP ≥90 mmHg, and a 24 h ambulatory systolic BP ≥140 and <170 mmHg. In the OFF MED trial, enrolled patients remained off medications for the first 3 months, whereas in the ON MED trial, patients were prescribed a stable regimen of 1-3 AH medications through 6 months.

PROCEDURE

The procedure was performed using the Symplicity Spyral multielectrode RDN catheter and the Symplicity G3 RDN RF generator (Medtronic) to deliver circumferential RF ablation to the renal arteries and all accessible branch vessels with diameters of 3-8 mm.[12] All cases were performed by an experienced operator and, in the case of the OFF and ON MED trials, were also case-supported according to predetermined treatment plans.

FOLLOW-UP

Patients had planned follow-up at 3, 6, 12, 24, and 36 months. Office and 24 h ambulatory BP, medication information, and adverse events – including renal artery stenosis, stroke, death, cardiovascular death, myocardial infarction (MI), and hospitalisation for a hypertensive emergency or crisis – were recorded at each follow-up.

STATISTICAL ANALYSIS

Categorical variables are shown as percentages and counts (N), whereas continuous variables are reported as mean±standard deviation. Changes in continuous variables from baseline to follow-up were evaluated using paired t-tests. Patients with complete follow-up at 36 months versus those without were compared using Fisher's exact test for categorical variables and t-tests for continuous variables. The cumulative proportions of subjects who experienced adverse events across all studies were summarised based on

Abbreviations

AH	antihypertensive	**FIH**	first-in-human
BP	blood pressure	**RF-RDN**	radiofrequency renal denervation

available follow-up. Mixed models for repeated measures were fitted with office and ambulatory systolic BP as outcome variables. The models included the study, baseline BP, and the number of AH medications over time as fixed effects; subject was included as a random effect using a first-order autoregressive covariance structure. As a separate analysis, we calculated the proportion of patients that experienced either a ≥10 mmHg office systolic BP reduction, a ≥5 mmHg 24 h ambulatory systolic BP reduction, a reduction of ≥1 AH medication, or a combination thereof. For this analysis, we considered all Spyral-treated patients who completed 36-month follow-up and had uncontrolled BP (office systolic BP ≥140 mmHg) at baseline.

ROLE OF THE FUNDING SOURCE

All studies were funded by Medtronic. The executive committees, in collaboration with the funder, designed the protocols and identified suitable clinical sites for the studies. The funder was responsible for transparent data collection, monitoring, and analysis. The lead author wrote the manuscript with contributions from the co-authors and copyediting assistance from the funder. Medtronic aided in figure preparation, table generation, and manuscript formatting. All authors had full access to the data and were solely responsible for the submission for publication. The data are proprietary; however, they may be available upon reasonable request to the first author.

Results

PATIENT CHARACTERISTICS

As of September 2025, data were pooled from 2,137 patients treated with the Symplicity Spyral device across the 4 studies of the SPYRAL clinical programme **(Central illustration)**. Patient demographics at baseline are provided in **Table 1**. At baseline, patients were 58±13 years old, and 38.8% were female. Baseline office and 24 h ambulatory systolic BPs were 163±23 mmHg and 152±17 mmHg, respectively. The mean number of AH medications at baseline was 3.8±2.1. Among pooled patients, 3.6% had a history of MI, 29.9% had type 2 diabetes, 3.3% had prior stroke, 18.2% had sleep apnoea, 7.9% had atrial fibrillation, and 34.2% had a history of smoking. The mean estimated glomerular filtration rate (eGFR) was 78.1±25.4 mL/min/1.73 m^2, with 22.0% having chronic kidney disease (eGFR <60 mL/min/1.73 m^2). Procedural characteristics are provided in **Supplementary Table 1**.

BLOOD PRESSURE CHANGES AND MEDICATIONS THROUGH 36 MONTHS

In GSR, follow-up through 36 months is still ongoing for many patients, with 24% (401/1,699) and 12% (208/1,699) having completed 36-month office BP and 24 h ambulatory BP measures, respectively, as of March 2025. Importantly, it was not mandated that 24 h ambulatory BP measures be collected in GSR. In the SPYRAL First-In-Human, OFF MED, and ON MED studies, 82% (41/50), 85% (154/182), and 85% (175/206) of patients, respectively, completed their 36-month office BP measures, and 70% (35/50), 71% (129/182), and 75% (155/206), respectively, completed their 36-month 24 h ambulatory BP measures. At 36 months after RF-RDN, the pooled patient cohort had statistically significant reductions in office systolic BP (–18.1±23.4 mmHg), 24 h ambulatory systolic BP (–13.3±17.6 mmHg), office diastolic BP (–8.1±13.9 mmHg), and 24 h ambulatory diastolic BP (–8.7±10.6 mmHg; p<0.0001 for all) **(Central illustration, Supplementary Figure 1)**. Among a matched patient cohort with available follow-up through 36 months, BP reductions increased over time **(Supplementary Figure 2)**. A mixed model – accounting for missing data, baseline BP, differing studies, and changing medications throughout long-term follow-up – yielded similar results **(Supplementary Figure 3)**. The benefit of RDN was observed throughout the 24-hour period, with significant systolic and diastolic BP reductions at 36 months during both daytime and nighttime **(Figure 1)**. The pooled patient population had greatly improved BP control after RF-RDN through 36 months **(Figure 2)**. The number of AH medications among the pooled cohort from baseline to 36 months is plotted in **Figure 3**. At 36 months, the mean eGFR among pooled Spyral patients was 75.6±23.2 mL/min/1.73 m^2.

PROPORTION OF PATIENTS EXPERIENCING A CLINICAL BENEFIT AFTER RDN

Among the evaluable patients at 36 months (n=428) **(Supplementary Table 2)**, 87.6% experienced either a 10 mmHg or greater reduction in office systolic BP, a 5 mmHg or greater reduction in 24 h ambulatory systolic BP, and/or the reduction of at least 1 AH medication **(Figure 4)**. As a sensitivity analysis, we also calculated the proportion of patients who experienced a clinical benefit without any increase in either office or 24 h ambulatory BP **(Supplementary Figure 4)**. The proportion of patients experiencing a clinical benefit by study is provided in **Supplementary Table 3**. The mean office and 24 h ambulatory systolic BP changes at 36 months in this cohort were –22.6±18.1 mmHg and –16.3±16.0 mmHg, respectively. The number of medications in this subgroup was 2.3±2.2 at baseline and 2.9±1.8 at 36 months.

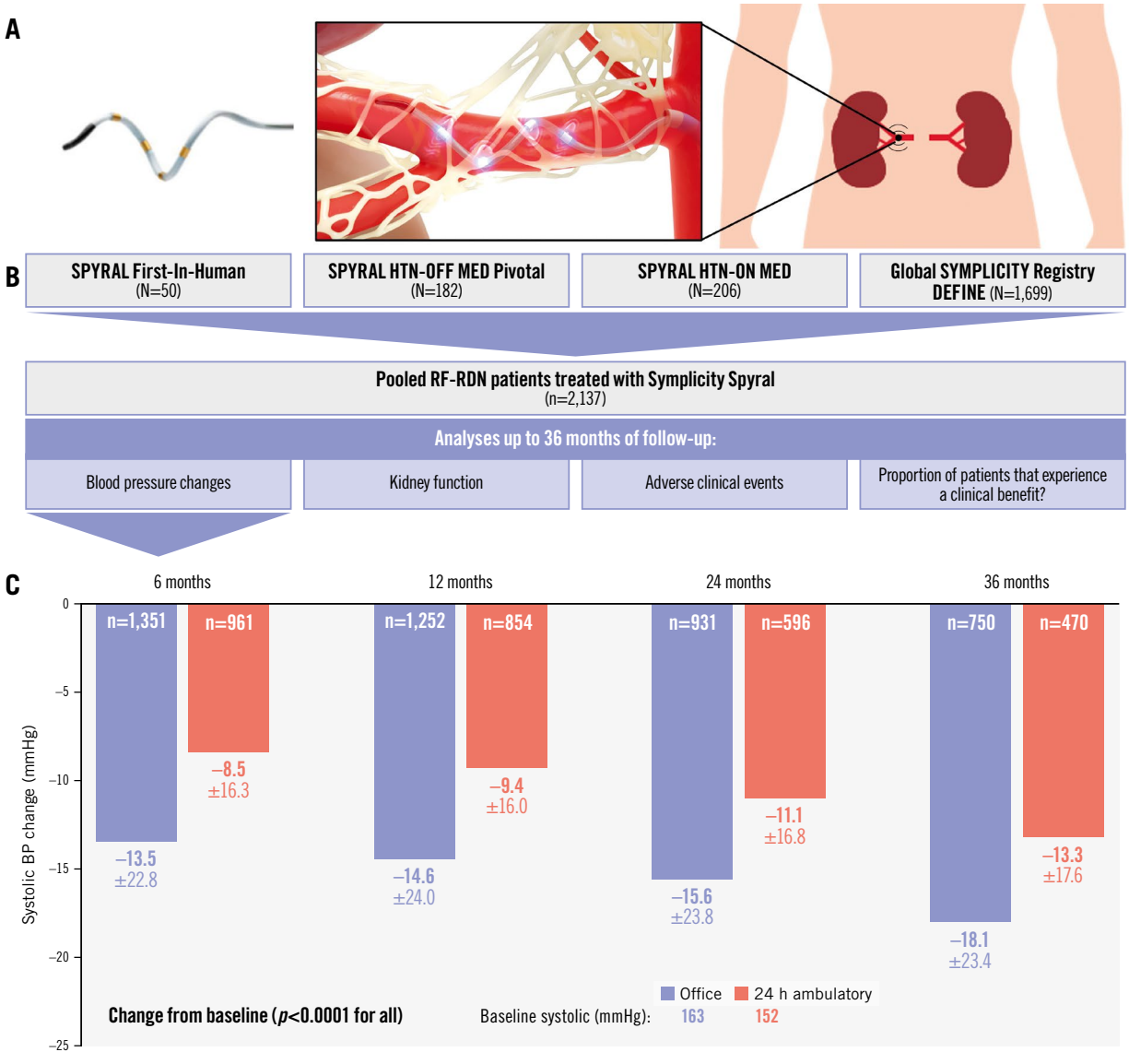
CLINICAL OUTCOMES THROUGH 36 MONTHS

Safety events were uncommon through 36 months after RF-RDN **(Supplementary Table 4)**. The rate of renal artery stenosis was 0.1% (1/1,000), with 1 patient identified as having renal artery stenosis greater than 70%. However, this patient declined confirmatory imaging of renal artery stenosis by angiography. No patient required renal artery reintervention or stent implantation through 36 months after treatment with the Spyral device. The rates of death, cardiovascular death, myocardial infarction, and stroke were 5.2%, 2.5%, 1.8%, and 4.5%, respectively. The rate of hospitalisation for hypertensive crisis was 2.2%. Among the patients who experienced a 10 mmHg or greater reduction in office systolic BP, a 5 mmHg or greater reduction in 24 h ambulatory systolic BP, or the reduction of at least 1 AH medication, the rates of death, cardiovascular death, myocardial infarction, stroke, and hospitalisation for hypertensive crisis were 0.0%, 0.0%, 1.1%, 1.1%, and 1.1%, respectively.

Discussion

This study pooled data from 2,137 patients treated with the Spyral device in the SPYRAL clinical programme. Through 36 months after RF-RDN, patients experienced

Flowchart and blood pressure changes among pooled patients treated with the Spyral radiofrequency RDN device.



David E. Kandzari *et al.* • *EuroIntervention* 2026;22:585-593 • DOI: 10.4244/EIJ-D-26-00161

Data from 2,137 patients treated with the Spyral radiofrequency renal denervation device (A) were pooled from 4 studies: SPYRAL First-In-Human, SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED, and the Global SYMPLICITY Registry DEFINE (B). Among pooled Spyral patients, the office (blue) and 24 h ambulatory (red) systolic BP changes from baseline to 36 months were statistically significant (C). BP: blood pressure; RF-RDN: radiofrequency renal denervation

statistically significant and clinically meaningful reductions in office and 24-hour ambulatory systolic and diastolic blood pressure. Overall, the rates of office and ambulatory BP control improved over time, highlighting the sustained efficacy of RDN. Adverse events were rare through long-term follow-up with few procedure-related complications.

Numerous single-arm and randomised controlled studies have demonstrated the sustained efficacy of RDN through 3 years of follow-up.[17,22] In the present study, the persistent BP reductions considerably exceeded the treatment effect of a single AH medication.[23] The observation of continual BP lowering through long-term follow-up and in the absence of escalating medications is a consistent finding following RF-RDN.[15] Although the biological mechanisms for this finding remain uncertain, attenuation of the neurohormonal system, vascular remodelling with reduced peripheral vascular

Table 1. Patient baseline characteristics.

	Pooled Spyral (n=2,137)
Office systolic BP, mmHg	163±23
Office diastolic BP, mmHg	93±16
24 h ambulatory systolic BP, mmHg	152±17
24 h ambulatory diastolic BP, mmHg	90±14
Age, years	58±13
Male	61.2 (1,308)
BMI, kg/m^2	30.6±6.4
eGFR, mL/min/1.73 m^2	78.1±25.4
CKD (eGFR <60 mL/min/1.73 m^2)	22.0 (454)
Previous myocardial infarction	3.6 (76)
Type 2 diabetes mellitus	29.9 (630)
Prior stroke	3.3 (68)
Heart failure	3.3 (70)
Sleep apnoea	18.2 (354)
Atrial fibrillation	7.9 (166)
Number of antihypertensive medications	3.8±2.1

Data are presented as mean±SD or % (n). BMI: body mass index; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SD: standard deviation

resistance, and resetting baroreflex physiology have been hypothesised.

Measurement of BP is an established surrogate endpoint, [24-27] with a 5 mmHg reduction in office systolic BP being associated with a 10% reduction in the risk of major adverse cardiovascular events.[23] Among patients with all evaluable measures through 36 months, nearly 9 out of 10 experienced a clinical benefit after RDN, indicated by an office systolic BP reduction of at least 10 mmHg, a 24 h ambulatory systolic BP reduction of at least 5 mmHg, a reduction of at least 1 AH medication, or a combination thereof. In real terms, these results provide practical guidance for treating clinicians to inform late-term expectations as part of clinical decision-making with patients. Two recent linear regression models investigating the BP response in patients from the SPYRAL clinical programme, both of which included a subcohort of Spyral-treated patients, found that baseline BP was the only consistent patient characteristic associated with expected BP changes after RDN.[15,16] Similarly, BP response to pharmacotherapy is also dependent on the baseline or starting blood pressure.[28,29] Even in the absence of other identified variables predictive of a BP-lowering effect after

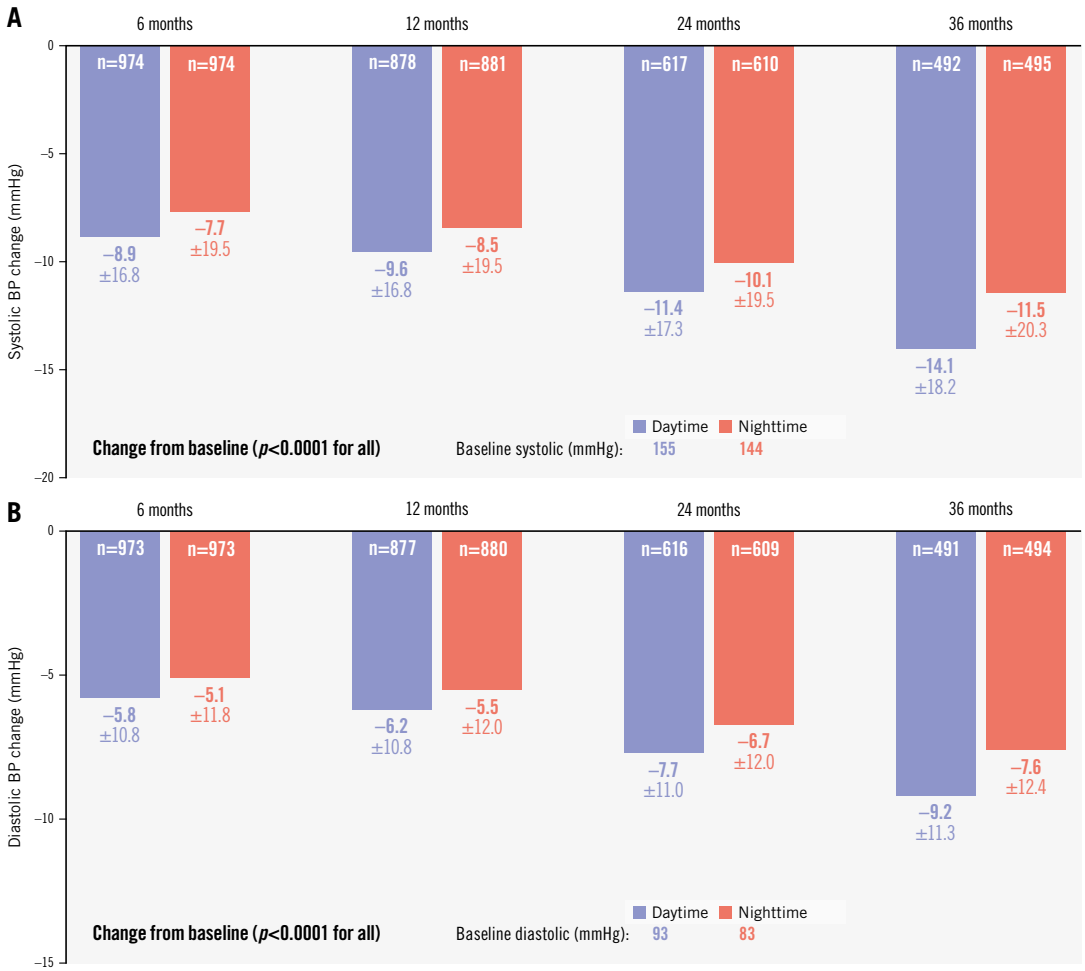


Figure 1. *Daytime and nighttime systolic and diastolic ambulatory BP changes through 36 months. The daytime (blue) and nighttime (red) systolic (A) and diastolic (B) BP changes of the pooled Spyral cohort from baseline through 36 months are plotted. BP: blood pressure*

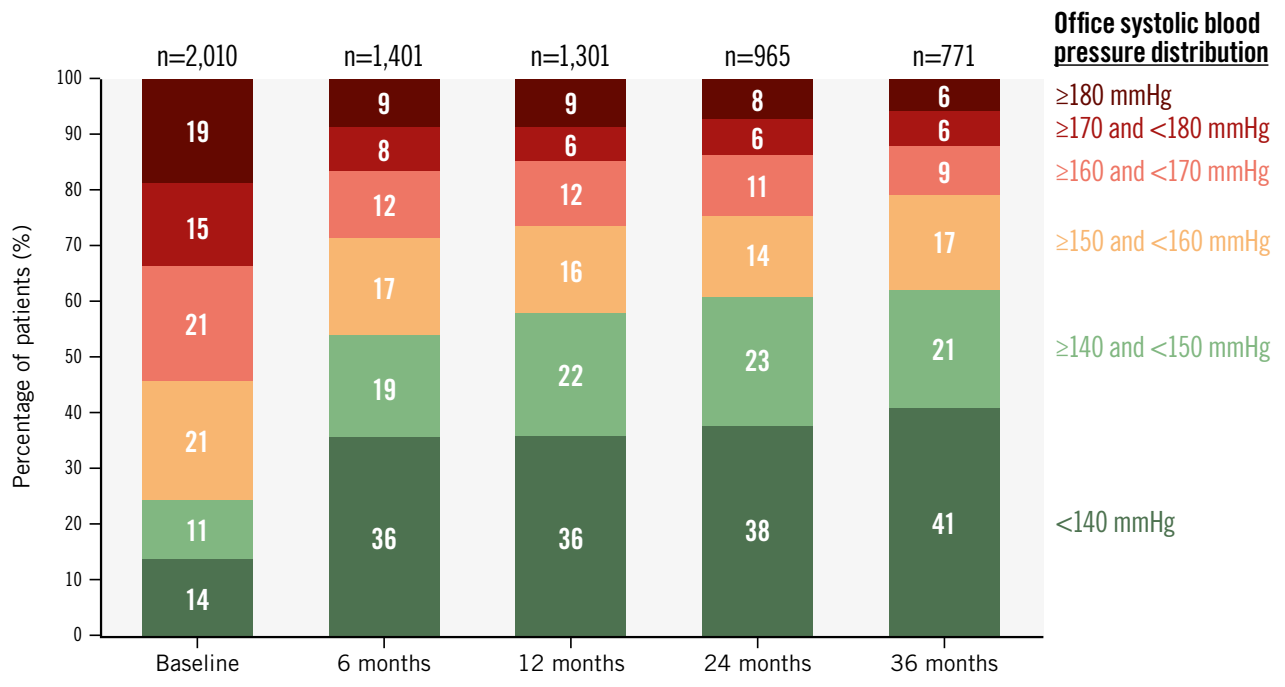


Figure 2. *Distribution of office systolic BP reductions after RDN at 36 months. The proportion of patients in the indicated office systolic BP ranges from baseline to 36 months are plotted. BP: blood pressure; RDN: renal denervation*

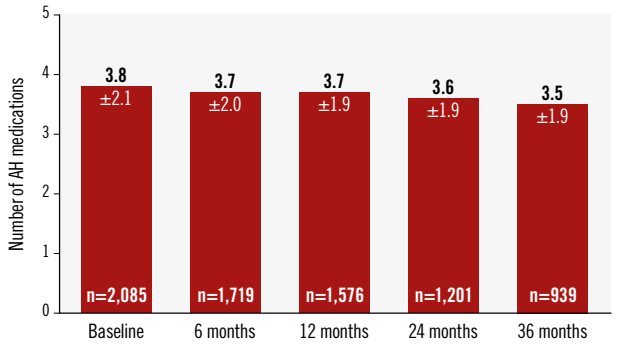


Figure 3. *Antihypertensive medications among pooled Spyral patients through 36 months. The number of prescribed antihypertensive (AH) medications from baseline up to 36 months are plotted.*

RDN, it is reassuring that nearly 90% of patients experience some meaningful benefit.

It remains to be seen whether other patient or procedural characteristics might also be associated with BP response. However, individuals who remain hypertensive despite adherence to lifestyle modifications and prescribed AH medications should be prioritised for consideration for RDN. This is consistent with multiple recent hypertension guidelines.[8,30,31] Patients that should be especially considered for RDN are those taking multiple AH medications and those who wish to reduce their medication burden. Polypharmacy risks increased incidence of side effects, non-adherence, and medication intolerance.[32,33] By reducing the number of prescribed AH medications, patients may also have considerable improvements in their quality of life.[34] The results herein, coupled with increased patient awareness of interventional treatment options, should serve to inform the shared decision-making process between physicians and their patients in shaping a personalised hypertension management plan.[35,36]

Limitations

This study has several limitations. Patients' data were pooled across 4 different studies with varying study designs, inclusion criteria (or lack thereof), and prescribed AH medication regimens (or lack of AH medications, in the instance of the OFF MED trial). Due to the heterogeneity of the pooled studies, results should be regarded as descriptive rather than confirmatory. In the two randomised controlled trials, after the primary endpoint was ascertained, treating clinicians were encouraged to lower patients' BP if it remained uncontrolled, which necessarily increased patients' medication burden. Due to the inclusion of patients from the GSR and FIH study, and because the majority of sham-control patients crossed over to undergo RDN after the primary endpoint, blood pressure reductions are not sham adjusted. Thus, the results presented for the long-term durability of the procedure do not include comparative data. Not all patients had continuous follow-up through 36 months, as some have not reached 36 months since the procedure. Patients from the GSR did not undergo systematic imaging of the renal arteries or adjudication at later timepoints. Therefore, late renal function complications may have been underreported.

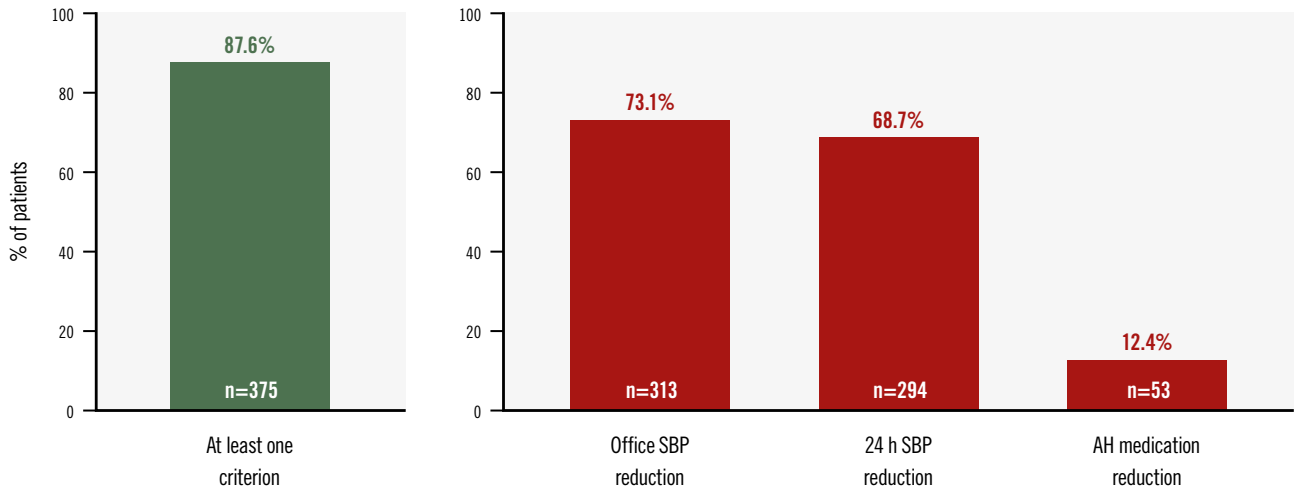


Figure 4. *The proportion of patients experiencing a clinical benefit 36 months after RDN. The proportion of patients experiencing a clinical benefit (green) is broken down into its non-mutually exclusive components (red). AH: antihypertensive; RDN: renal denervation; SBP: systolic blood pressure*

Conclusions

In this large, pooled dataset of patients treated with the Symplicity Spyral RF-RDN catheter, there were statistically significant and clinically meaningful BP reductions through 36 months with few adverse events. Sensitivity analyses including a matched analysis and mixed model showed similar efficacy results. Additionally, rates of systolic blood pressure control improved over time. Moreover, nearly 9 out of 10 patients experienced a clinical benefit. These findings are consistent with the durable efficacy and safety of RF-RDN in hypertensive patients with a wide range of demographics.

Authors' affiliations

1. Piedmont Heart Institute, Atlanta, GA, USA; 2. HOMICAREM (HOMburg Institute for CArdioREnalMetabolic Medicine), Medical Faculty, Campus Homburg, Saarland University, Homburg, Germany; 3. University Hospital Erlangen, Erlangen, Germany; 4. Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; 5. Dobney Hypertension Centre, University of Western Australia – Royal Perth Hospital Research Foundation, Perth, Australia; 6. Department of Cardiovascular Medicine, Jichi Medical University School of Medicine, Tochigi, Japan; 7. St Vincent's Heart Centre, Melbourne, Australia; 8. Medtronic, Minneapolis, MN, USA; 9. Department of Cardiology, University Heart Center, University Hospital Basel, Basel, Switzerland; 10. Cardiovascular Research Institute Basel (CRIB), University Heart Center, University Hospital Basel, Basel, Switzerland

Acknowledgements

Benjamin Woods, PhD, of Medtronic provided editorial support under the direction of the first author, including the preparation of figures and tables, and editing of text. The executive committee designed the protocol and identified suitable clinical sites to conduct the study in collaboration with Medtronic. Medtronic was responsible for data collection, monitoring, and analysis. The article was written by the lead author with contributions from the co-authors. All authors have access to all data and were responsible for the decision to submit the manuscript for publication.

Conflict of interest statement

D.E. Kandzari receives institutional research/grant support from Biotronik, Boston Scientific, OrbusNeich, Teleflex, Medtronic, and Abbott; he also receives personal consulting honoraria from Boston Scientific, Medtronic, HyperQure, Cordis Corporation, and Brattea Medical. M. Böhm is supported by the Deutsche Forschungsgemeinshaft (SFB TTR219); and receives personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Edwards Lifesciences, Medtronic, Novartis, Recor Medical, Servier, and Vifor. R.E. Schmieder has received speaker and consulting honoraria from Medtronic, Recor Medical, Boston Scientific, and Ablative Solutions; and research grants have been given to his institution from Medtronic, Recor Medical, SoniVie/Boston Scientific, and Ablative Solutions. M.P. Schlaich has received support from the National Health and Medical Research Council Senior Research Fellowship; and has received consulting fees or travel and research support from Medtronic, Abbott, Novartis, Servier, Pfizer, and Boehringer Ingelheim. R.R. Townsend is a consultant for Medtronic, Axio, Regeneron, Bard, OBIO, Corcept, and AstraZeneca; and receives royalties from UpToDate. K. Kario receives research grants from A&D Company and Omron Healthcare; and receives honoraria from Medtronic, Otsuka Pharmaceutical, and Omron Healthcare. M. Gilbertson is an employee of Medtronic. F. Mahfoud has been supported by Deutsche Forschungsgemeinschaft (SFB TRR219, Project-ID 322900939), and Deutsche Herzstiftung; Saarland University has received scientific support from Ablative Solutions, Medtronic, and Recor Medical; until May 2024, he received speaker honoraria/consulting fees from Ablative Solutions, AstraZeneca, Inari, Medtronic, Merck, Novartis, Philips, and Recor Medical, all outside the submitted work. R. Whitbourn has no conflicts of interest to declare.

References

1. Flint AC, Conell C, Ren X, et al. Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes. *N Engl J Med*. 2019;381:243-51.
2. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217-23.
3. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nat Rev Cardiol*. 2021;18:785-802.
4. Kario K, Okura A, Hoshide S, Mogi M. The WHO Global report 2023 on hypertension warning the emerging hypertension burden in globe and its treatment strategy. *Hypertens Res*. 2024;47:1099-102.
5. Mahfoud F, Schlaich MP, Lobo MD. Device Therapy of Hypertension. *Circ Res*. 2021;128:1080-99.
6. Cluett JL, Blazek O, Brown AL, et al. Renal Denervation for the Treatment of Hypertension: A Scientific Statement From the American Heart Association. *Hypertension*. 2024;81:e135-48.
7. Barbato E, Azizi M, Schmieder RE, et al. Renal denervation in the management of hypertension in adults. A clinical consensus statement of the ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2023;44:1313-30.
8. Jones DW, Ferdinand KC, Taler SJ, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2025;152:e114-218.
9. Böhm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet*. 2020;395:1444-51.
10. Kandzari DE, Townsend RR, Kario K, et al. Safety and Efficacy of Renal Denervation in Patients Taking Antihypertensive Medications. *J Am Coll Cardiol*. 2023;82:1809-23.
11. Mahfoud F, Mancia G, Schmieder RE, et al. Outcomes Following Radiofrequency Renal Denervation According to Antihypertensive Medications: Subgroup Analysis of the Global SYMPLICITY Registry DEFINE. *Hypertension*. 2023;80:1759-70.
12. Whitbourn R, Harding SA, Walton A. Symplicity multi-electrode radiofrequency renal denervation system feasibility study. *EuroIntervention*. 2015;11:104-9.
13. Azizi M, Sanghvi K, Saxena M, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. *Lancet*. 2021;397:2476-86.
14. Azizi M, Saxena M, Wang Y, et al. Endovascular Ultrasound Renal Denervation to Treat Hypertension: The RADIANCE II Randomized Clinical Trial. *JAMA*. 2023;329:651-61.
15. Mahfoud F, Townsend RR, Kandzari DE, et al. Long-Term, Patient-Level Analysis of Radiofrequency Renal Denervation in the SYMPLICITY Clinical Trial Program. *JACC Adv*. 2025;4:101606.
16. Schmieder RE, Mahfoud F, Mancia G, et al. Impact of baseline systolic blood pressure on blood pressure changes following renal denervation. *EuroIntervention*. 2025;21:e1281-7.
17. Mahfoud F, Kandzari DE, Schlaich MP, et al. Long-term outcomes following radiofrequency renal denervation: meta-analysis of 18 reports. *Eur J Prev Cardiol*. 2025 Jul 15. [Epub ahead of print].
18. Vukadinović D, Lauder L, Kandzari DE, et al. Effects of Catheter-Based Renal Denervation in Hypertension: A Systematic Review and Meta-Analysis. *Circulation*. 2024;150:1599-611.
19. Mahfoud F, Mancia G, Schmieder R, et al. Renal Denervation in High-Risk Patients With Hypertension. *J Am Coll Cardiol*. 2020;75:2879-88.
20. Böhm M, Mahfoud F, Ukena C, et al. Rationale and design of a large registry on renal denervation: the Global SYMPLICITY registry. *EuroIntervention*. 2013;9:484-92.
21. Böhm M, Townsend RR, Kario K, et al. Rationale and design of two randomized sham-controlled trials of catheter-based renal denervation in subjects with uncontrolled hypertension in the absence (SPYRAL HTN-OFF MED Pivotal) and presence (SPYRAL HTN-ON MED Expansion) of antihypertensive medications: a novel approach using Bayesian design. *Clin Res Cardiol*. 2020;109:289-302.
22. Sharp ASP, Sanderson A, Hansell N, et al. Renal denervation for uncontrolled hypertension: a systematic review and meta-analysis examining multiple subgroups. *J Hypertens*. 2024;42:1133-44.
23. Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet*. 2021;397:1625-36.
24. Jaeger BC, Bress AP, Bundy JD, et al. Longer-Term All-Cause and Cardiovascular Mortality With Intensive Blood Pressure Control: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol*. 2022;7:1138-46.
25. Lewis CE, Fine LJ, Beddhu S, et al. Final Report of a Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2021;384:1921-30.
26. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957-67.
27. Canoy D, Copland E, Nazarzadeh M, et al. Antihypertensive drug effects on long-term blood pressure: an individual-level data meta-analysis of randomised clinical trials. *Heart*. 2022;108:1281-9.
28. Levy PD, Willock RJ, Burla M, et al. Total antihypertensive therapeutic intensity score and its relationship to blood pressure reduction. *J Am Soc Hypertens*. 2016;10:906-16.
29. Zhou D, Xi B, Zhao M, Wang L, Veeranki SP. Uncontrolled hypertension increases risk of all-cause and cardiovascular disease mortality in US adults: the NHANES III Linked Mortality Study. *Sci Rep*. 2018;8:9418.
30. McEvoy JW, McCarthy CP, Bruno RM, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J*. 2024;45:3912-4018.
31. Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens*. 2023;41:1874-2071.
32. Gupta P, Patel P, Štrauch B, et al. Risk Factors for Nonadherence to Antihypertensive Treatment. *Hypertension*. 2017;69:1113-20.
33. Franchi C, Ardoino I, Ludergnani M, Cukay G, Merlino L, Nobili A. Medication adherence in community-dwelling older people exposed to chronic polypharmacy. *J Epidemiol Community Health*. 2021;75:854-9.
34. Karnes JH, Cooper-DeHoff RM. Antihypertensive medications: benefits of blood pressure lowering and hazards of metabolic effects. *Expert Rev Cardiovasc Ther*. 2009;7:689-702.
35. Kandzari DE, Weber MA, Poulos C, et al. Patient Preferences for Pharmaceutical and Device-Based Treatments for Uncontrolled Hypertension: Discrete Choice Experiment. *Circ Cardiovasc Qual Outcomes*. 2023;16:e008997.
36. Pathak A, Weber MA, Poulos C, Cohen SA, DeBruin V, Kandzari DE. Impact of expected blood pressure reduction on patient preferences for pharmaceutical and renal denervation treatment. *J Hypertens*. 2025;43:228-35.

Supplementary data

Supplementary Table 1. Procedural characteristics among pooled Spyral patients.

Supplementary Table 2. Baseline characteristics in patients with and without complete 36-month follow-up.
Supplementary Table 3. Proportion of patients experiencing a clinical benefit at 36 months by study.
Supplementary Table 4. Adverse events among pooled Spyral patients up to 36 months.
Supplementary Figure 1. Diastolic BP changes among pooled Spyral patients up to 36 months.
Supplementary Figure 2. Systolic BP changes in matched patients up to 36 months.
Supplementary Figure 3. Mixed model systolic BP changes during long-term follow-up.
Supplementary Figure 4. The proportion of patients experiencing a clinical benefit at 36 months after RDN, excluding those who had a BP increase after a medication decrease.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-26-00161

Supplementary data

Supplementary Table 1. Procedural characteristics among pooled Spyral patients.

Procedural characteristic	Mean ± SD (median)
Procedure duration (min)	84.8 ± 44.7 (75)
Catheter duration (min)	47.9 ± 25.7 (43)
Contrast volume (mL)	153.7 ± 88.4 (140)
Number of ablation attempts	34.6 ± 22.9 (30)

Supplementary Table 2. Baseline characteristics in patients with and without complete 36-month follow-up.

Mean±SD or % (n)	Complete (n=428)	Incomplete (n=1709)	P-value
Office systolic BP, mmHg	164 ± 12	162 ± 25	0.028
Office diastolic BP, mmHg	98 ± 11	91 ± 17	<0.0001
24-h ambulatory systolic BP, mmHg	151 ± 11	152 + 19	0.049
24-h ambulatory diastolic BP, mmHg	93 ± 11	89 ± 14	<0.0001
Age, y	56 ± 11	58 ± 13	0.0004
Male	69.4% (297)	59.2% (1011)	0.0001
BMI, kg/m^2	31.3 ± 5.8	30.5 ± 6.6	0.0099
eGFR, mL/min/1.73 m^2	80.9 ± 20.6	77.3 ± 26.4	0.0027
CKD; eGFR <60 mL/min/1.73 m^2	11.3% (48)	24.9% (406)	<0.0001
Previous myocardial infarction	3.0% (13)	3.8% (63)	0.56
Type 2 diabetes mellitus	19.2% (82)	32.6% (548)	<0.0001
Prior stroke	2.3% (10)	3.5% (58)	0.29
Heart failure	3.0% (13)	3.4% (57)	0.88
Sleep apnea	14.6% (62)	19.2% (292)	0.028
Atrial fibrillation	3.7% (16)	9.0% (150)	0.0002
Number of antihypertensive medications	2.3 ± 2.2	4.2 ± 1.9	<0.0001

BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease. Complete defined as having office, 24-h ambulatory blood pressure measures and medication information available at 36 months.

Supplementary Table 3. Proportion of patients experiencing a clinical benefit at 36 months by study.

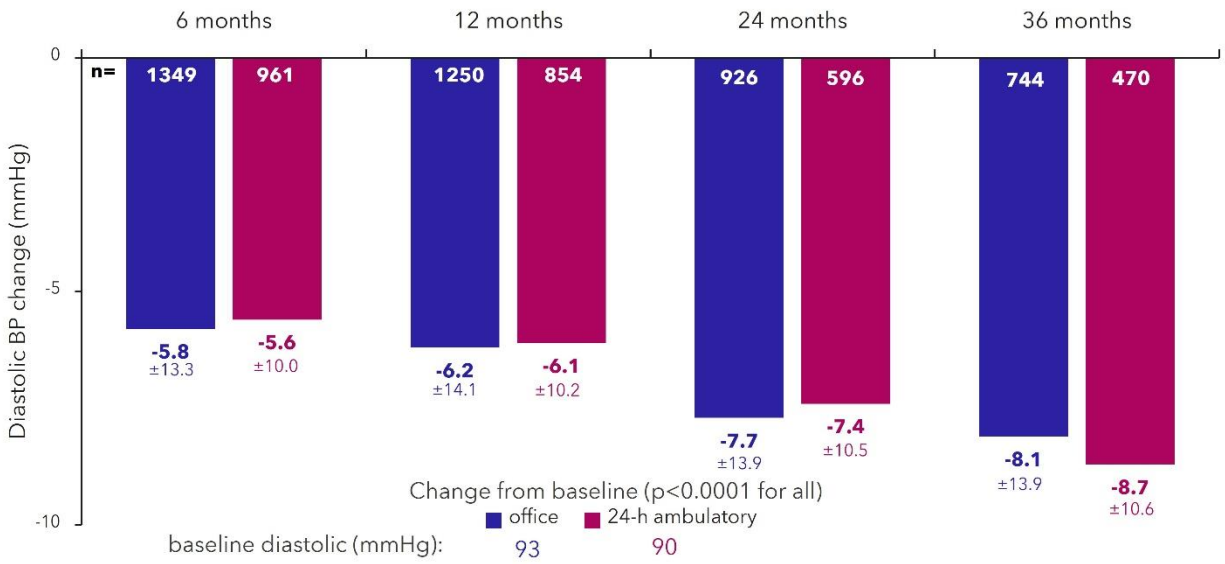
Pooled Spyral	Spyral FIH	GSR Spyral	HTN-OFF MED	HTN-ON MED
87.6%	88.2%	88.4%	88.2%	86.5%

FIH, First-in-Human; GSR, Global SYMPLICITY Registry. Those experiencing a clinical benefit includes an office systolic BP reduction ≥10 mmHg, a 24-h ambulatory systolic BP reduction ≥5 mmHg, or a reduction of ≥1 AH medication.

Supplementary Table 4. Adverse events among pooled Spyral patients up to 36 months.

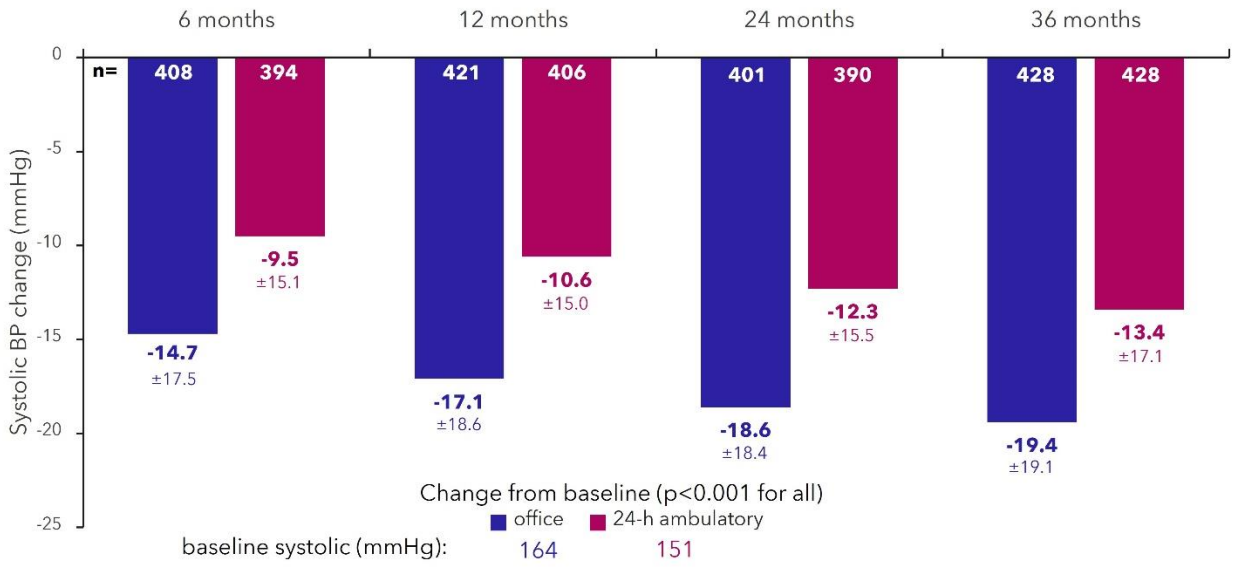
% (n)	Pooled Spyral patients (n=1046)	Clinical Benefit (n=369)
All cause death	5.2% (54)	0.0%
Cardiovascular death	2.5% (26)	0.0%
Myocardial infarction	1.8% (19)	1.1% (4)
Stroke	4.5% (47)	1.1% (4)
Renal artery stenosis	0.1% (1)	0.0%
Hospitalization for hypertensive crisis	2.2% (23)	1.1% (4)

Reported event rates are pooled across all four studies.



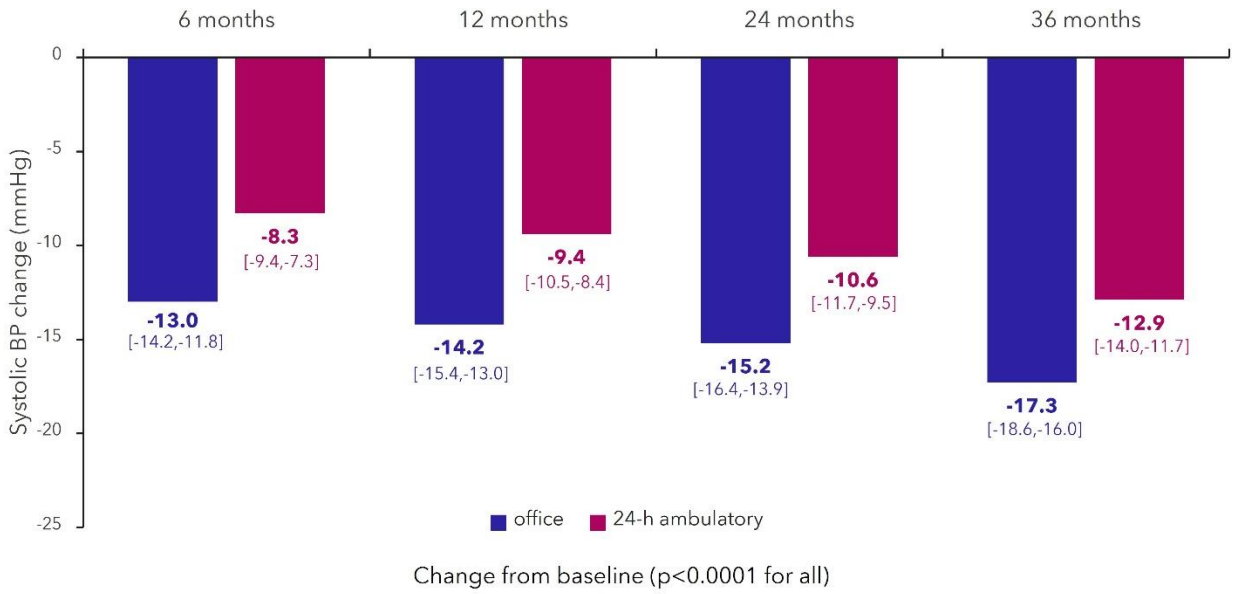
Supplementary Figure 1. Diastolic BP changes among pooled Spyral patients up to 36 months.

The office (blue) and 24-h ambulatory (magenta) diastolic BP changes of the pooled Spyral cohort from baseline through 36 months are plotted.



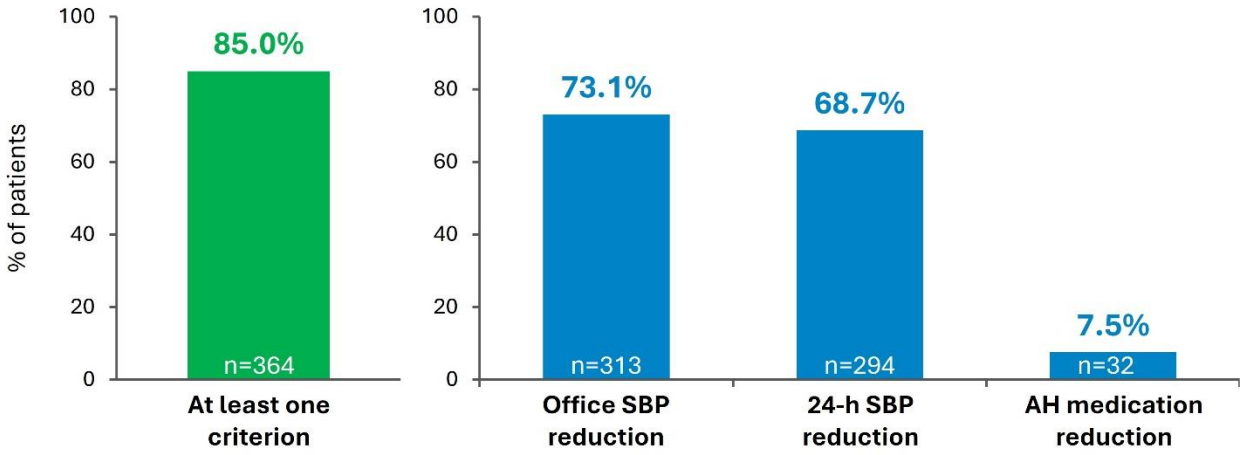
Supplementary Figure 2. Systolic BP changes in matched patients up to 36 months.

The office (blue) and 24-h ambulatory (magenta) systolic BP changes of matched patients are plotted from baseline through 36 months.



Supplementary Figure 3. Mixed model systolic BP changes during long-term follow-up.

Mixed model results adjusted for medications, baseline systolic BP, and study for office (blue) and 24-h ambulatory (magenta) systolic BP changes from baseline are plotted through 36 months. 95% confidence intervals are in brackets.



Supplementary Figure 4. The proportion of patients experiencing a clinical benefit at 36 months after RDN, excluding those who had a BP increase after a medication decrease.

The proportion of patients experiencing a clinical benefit (green) is broken down into its non-mutually exclusive components (blue).