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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, Georgia 30309, USA.
E-mail: dkandzari@gmail.com

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 characterize the durability of efficacy, and further study is needed to ascertain the proportion of patients experiencing a clinical benefit.

AIMS: We evaluated 36-month blood pressure (BP) changes after radiofrequency (RF)-RDN across four clinical studies from the Symplicity program and determined the proportion of patients who experience a clinical benefit.

METHODS: Data were pooled from the Global SYMPLICITY Registry (GSR) DEFINE, SPYRAL First-In-Human, SPYRAL HTN-OFF MED, and -ON MED trials. All patients were treated with RF-RDN (SpyralTM, Medtronic). 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-h ambulatory (A)SBP 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 either 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 nine in ten patients experienced a clinical benefit. These findings suggest a long-term efficacy and safety of RF-RDN across a broad spectrum of patients with uncontrolled hypertension.

KEYWORDS: renal denervation; uncontrolled hypertension; blood pressure reduction

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

[1] Piedmont Heart Institute, Atlanta, GA, United States

[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, United States

[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, United States

[9] Department of Cardiology, University Heart Center, University Hospital Basel, Switzerland

[10] Cardiovascular Research Institute Basel (CRIB), University Heart Center, University Hospital Basel, Switzerland

Running Title: Clinical Benefit of RDN through 3 Years

Corresponding author:

David E. Kandzari, MD

Piedmont Heart Institute

Suite 2065, 95 Collier Road NW

Atlanta, Georgia 30309, USA

E-mail: dkandzari@gmail.com

Conflicts of Interest

Dr. Kandzari receives institutional research/grant support from Biotronik, Boston Scientific, Orbus Neich, Teleflex, Medtronic, and Abbott Vascular; he also receives personal consulting honoraria from Boston Scientific, Medtronic, HyperQure, Cordis Corporation, and Brattea Medical.

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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 characterize the durability of efficacy, and further study is needed to ascertain the proportion of patients experiencing a clinical benefit.

Aims

We evaluated 36-month blood pressure (BP) changes after radiofrequency (RF)-RDN across four clinical studies from the Symplicity program and determined the proportion of patients who experience a clinical benefit.

Methods

Data were pooled from the Global SYMPLICITY Registry (GSR) DEFINE, SPYRAL First-In-Human, SPYRAL HTN-OFF MED, and -ON MED trials. All patients were treated with RF-RDN (Spyral™, Medtronic). 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-h ambulatory (A)SBP 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 either 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 nine in ten patients experienced a clinical benefit. These findings suggest a long-term efficacy and safety of RF-RDN across a broad spectrum of patients with uncontrolled hypertension.

Key words: renal denervation, uncontrolled hypertension, blood pressure reduction

Abbreviations: radiofrequency renal denervation (RF-RDN); Global SYMPLICITY Registry (GSR); First-In-Human (FIH); blood pressure (BP); antihypertensive (AH)

Introduction

Hypertension is the leading modifiable risk factor for cardiovascular disease and remains a major global health challenge, affecting more than one 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 randomized, 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, Spyral™ multi-electrode radiofrequency (RF) catheter (Medtronic Plc, Santa Rosa, California) remains warranted. Moreover, while multiple studies have investigated which patients are most likely to experience a clinical benefit after the procedure, only higher pre-procedure, 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 across the Symplicity Clinical Trial program, 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.

Methods

Study designs and patient population

This *post hoc* analysis included patients from the GSR DEFINE and treated with the latest generation, Spyral catheter, Spyral FIH, and those randomized to the RDN cohorts from the randomized control 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 pre-specified for all four 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 Spyral RF-RDN catheter, requiring patients to have 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, randomized, 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 required 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 multi-electrode RDN catheter (Medtronic, Santa Rosa, California) and Symplicity G3 RF generator (Medtronic) to provide circumferential RF ablations to the renal arteries and all accessible branch vessels 3-8 mm in diameter.[12] All cases were performed by an experienced proceduralist and, in the case of the OFF and ON MED trials, were also case-supported based on 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, and hospitalization for a hypertensive emergency or crisis were recorded at each follow-up.

Statistical analyses

Categorial variables are shown as percentages and counts (N), whereas continuous variables are reported as mean ± standard deviation (SD). 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 summarized based on available follow-up. Mixed models for repeated measures were fitted with office and ambulatory systolic BP as outcome variables. The models included the number of antihypertensive medications over time, study, and baseline BP as fixed effects and subject 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 with 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 to conduct 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 had copy-editing assistance from the funder. Medtronic aided in figure preparation, tables 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 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 Spyral device across the four studies of the Symplicity Clinical program (**Central Illustration**). Patient demographics at baseline are provided in **Table 1.** Patients at baseline were 58±13 yrs old, 38.8% of whom 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 apnea, 7.9% had atrial fibrillation, and 34.2% had a history of smoking. The mean estimated glomerular filtration rate was 78.1 ±2 5.4 mL/min/1.73m^2, with

22.0% (454) having chronic kidney disease (eGFR <60 mL/min/1.73m^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% (401/1699) and 12% (208/1699) 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 24-h ambulatory BP measures. After RF-RDN through 36 months, 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** and **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 through long-term follow-up yielded similar results (**Supplementary Figure 3**). The benefit of RDN was observed throughout the day, with significant systolic and diastolic BP reductions at 36 months during the day 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 through 36 months are plotted in **Figure 3**. At 36 months, the mean eGFR among pooled Spyral patients was 75.6 ± 23.2 mL/min/1.73m^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 reduction or greater in office systolic BP, a 5-mmHg reduction or greater in 24-h ambulatory systolic BP, and/or the reduction of at least one AH medication (**Figure 4**). As a sensitivity analysis, we also calculated the proportion of patients who experienced a clinical benefit without any increase in office and 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 one patient identified having renal artery stenosis greater than 70%. However, this patient declined confirmatory imaging of renal artery stenosis by angiography. No patient required renal artery re-intervention or stent implantation after treatment with the Spyral device through 36 months. The rate of death, cardiovascular death, myocardial infarction, and stroke were 5.2%, 2.5%, 1.8%, and 4.5% respectively. The rate of hospitalization for hypertensive crisis was 2.2%. Among the patients who experienced a 10-mmHg reduction or greater in office systolic BP, a 5-mmHg reduction or greater in 24-h ambulatory systolic BP, or the reduction of at least one AH medication the rate of death, cardiovascular death, myocardial infarction, stroke, and hospitalization for hypertensive crisis was 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 Symplicity Clinical program. Through 36 months after RF-RDN, patients experienced statistically significant and clinically meaningful reductions in office and 24-hour ambulatory systolic and diastolic blood pressure. Overall, 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 procedural-related complications.

Numerous single-arm and randomized controlled studies have demonstrated 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 over late 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 remodeling with reduced peripheral vascular resistance, and resetting baroreflex physiology has been hypothesized.

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 cardiovascular events.[23] Among patients with all evaluable measures through 36-months, nearly nine in ten 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, the reduction of at least one AH medication, or some 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. Recent linear regression models investigating the BP response in patients

from the Symplicity Clinical program, both of which included a sub-cohort 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 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 prioritized in 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 antihypertensive medications and/or 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 to shape a personalized hypertension management plan.[35,36]

This study has several limitations. Patients' data were pooled across four different studies with varying study designs, inclusion criteria (or lack thereof), and prescribed AH medication regimen (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 randomized controlled trials, after the primary endpoint was ascertained, treating clinicians were encouraged to lower patients' BP if still uncontrolled,

necessarily increasing patients' medication burden. Due to the inclusion of patients from the registry and First-in-Human 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, results presented of the long-term durability of the procedure do not include comparative data. Not all patients had continuous follow-up through 36 months, some of whom have not reached 36 months since the procedure. Patients from the registry did not undergo systematic imaging of the renal arteries or adjudication at later timepoints. Therefore, late renal function complications may have been underreported.

Conclusion

In this large, pooled dataset of patients treated with the 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 nine in ten 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.

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article was written by the lead author with contributions from the co-authors. All authors have access to all data and are responsible for the decision to submit the manuscript for publication.

Impact on Daily Practice

RDN is a guideline-recommended therapy for uncontrolled hypertension. In this study, 3-year BP changes and the proportion of patients who experienced a clinical benefit after RDN using the Spyral device were evaluated. Long-term BP reductions after RDN were significant and were sustained over time, with nearly nine in ten patients experiencing a clinical benefit.

References

1. Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, et al. Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes. *N Engl J Med* 2019;**381**:243–251.

2. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet Lond Engl* 2005;**365**:217–223.

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**:1099–1102.

5. Mahfoud F, Schlaich MP, Lobo MD. Device Therapy of Hypertension. *Circ Res* 2021;**128**:1080–1099.

6. Cluett JL, Blazek O, Brown AL, East C, Ferdinand KC, Fisher NDL, et al. Renal Denervation for the Treatment of Hypertension: A Scientific Statement From the American Heart Association. *Hypertension* 2024;**81**.

7. Barbato E, Azizi M, Schmieder RE, Lauder L, Böhm M, Brouwers S, 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**:1313–1330.

8. Jones DW, Ferdinand KC, Taler SJ, Johnson HM, Shimbo D, Abdalla M, 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:CIR.0000000000001356.

9. Böhm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE, 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. *The Lancet* 2020;**395**:1444–1451.

10. Kandzari DE, Townsend RR, Kario K, Mahfoud F, Weber MA, Schmieder RE, et al. Safety and Efficacy of Renal Denervation in Patients Taking Antihypertensive Medications. *J Am Coll Cardiol* 2023;**82**:1809–1823.

11. Mahfoud F, Mancia G, Schmieder RE, Ruilope L, Narkiewicz K, Schlaich M, et al. Outcomes Following Radiofrequency Renal Denervation According to Antihypertensive Medications: Subgroup Analysis of the Global SYMPLICITY Registry DEFINE. *Hypertens Dallas Tex 1979* 2023;**80**:1759–1770.

12. Whitbourn R, Harding SA, Walton A. Symplicity multi-electrode radiofrequency renal denervation system feasibility study. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol* 2015;**11**:104–109.

13. Azizi M, Sanghvi K, Saxena M, Gosse P, Reilly JP, Levy T, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. *The Lancet* 2021;**397**:2476–2486.

14. Azizi M, Saxena M, Wang Y, Jenkins JS, Devireddy C, Rader F, et al. Endovascular Ultrasound Renal Denervation to Treat Hypertension: The RADIANCE II Randomized Clinical Trial. *JAMA* 2023;**329**:651.

15. Mahfoud F, Townsend RR, Kandzari DE, Mancia G, Whitbourn R, Lauder L, 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, Townsend RR, Kandzari DE, Kario K, et al. Impact of baseline systolic blood pressure on blood pressure changes following renal denervation. *EuroIntervention* 2025;**21**:e1281–e1287.

17. Mahfoud F, Kandzari DE, Schlaich MP, Schmieder RE, Lauder L, Ruilope L, et al. Long-term outcomes following radiofrequency renal denervation: meta-analysis of 18 reports. *Eur J Prev Cardiol* 2025:zwaf368.

18. Vukadinović D, Lauder L, Kandzari DE, Bhatt DL, Kirtane AJ, Edelman ER, et al. Effects of Catheter-Based Renal Denervation in Hypertension: A Systematic Review and Meta-Analysis. *Circulation* 2024;**150**:1599–1611.

19. Mahfoud F, Mancia G, Schmieder R, Narkiewicz K, Ruilope L, Schlaich M, et al. Renal Denervation in High-Risk Patients With Hypertension. *J Am Coll Cardiol* 2020;**75**:2879–2888.

20. Böhm M, Mahfoud F, Ukena C, Bauer A, Fleck E, Hoppe UC, et al. Rationale and design of a large registry on renal denervation: the Global SYMPLICITY registry. *EuroIntervention* 2013;**9**:484–492.

21. Böhm M, Townsend RR, Kario K, Kandzari D, Mahfoud F, Weber MA, 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, Reddish K, Miller P, Moss J, et al. Renal denervation for uncontrolled hypertension: a systematic review and meta-analysis examining multiple subgroups. *J Hypertens* 2024;**42**:1133–1144.

23. Rahimi K, Bidel Z, Nazarzadeh M, Copland E, Canoy D, Ramakrishnan R, et al. 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. *The Lancet* 2021;**397**:1625–1636.

24. Jaeger BC, Bress AP, Bundy JD, Cheung AK, Cushman WC, Drawz PE, 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.

25. The SPRINT Research Group. Final Report of a Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2021;**384**:1921–1930.

26. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *The Lancet* 2016;**387**:957–967.

27. Canoy D, Copland E, Nazarzadeh M, Ramakrishnan R, Pinho-Gomes A-C, Salam A, et al. Antihypertensive drug effects on long-term blood pressure: an individual-level data meta-analysis of randomised clinical trials. *Heart* 2022;**108**:1281–1289.

28. Levy PD, Willock RJ, Burla M, Brody A, Mahn J, Marinica A, et al. Total antihypertensive therapeutic intensity score and its relationship to blood pressure reduction. *J Am Soc Hypertens JASH* 2016;**10**:906–916.

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, Brouwers S, Canavan MD, Ceconi C, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J* 2024:ehae178.

31. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, 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, Lai FY, Akbarov A, Marešová V, et al. Risk Factors for Nonadherence to Antihypertensive Treatment. *Hypertension* 2017;**69**:1113–1120.

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**:854–859.

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, Coulter J, Cohen SA, DeBruin V, et al. Patient Preferences for Pharmaceutical and Device-based Treatments for Uncontrolled Hypertension: Discrete Choice Experiment. *Circ Cardiovasc Qual Outcomes* 2022: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* 2024;**42**.

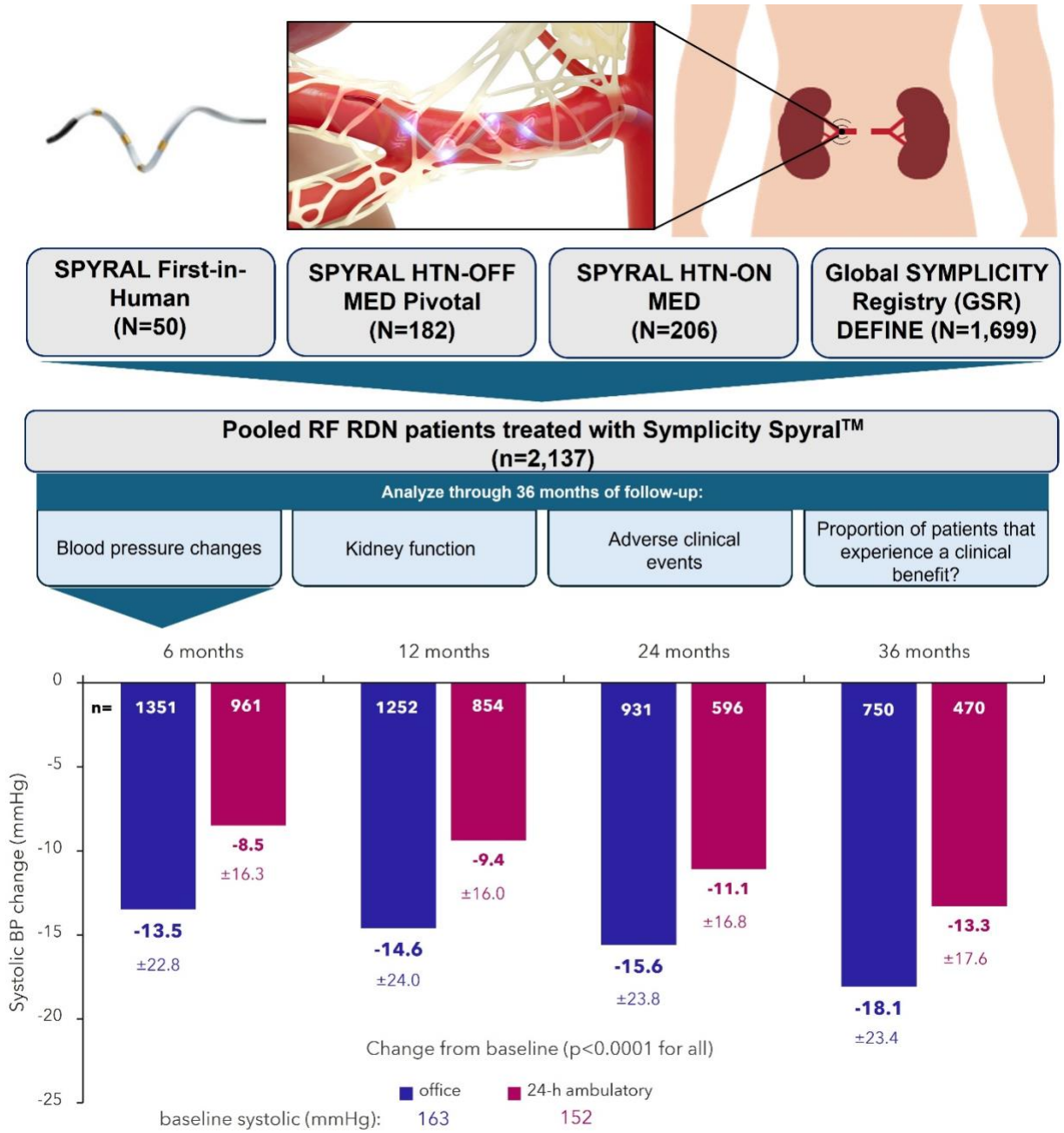
Tables and Figures

Table 1. Patient baseline characteristics

Mean±SD or % (n)	Pooled Spyral (n=2137)
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, y	58 ± 13
Male	61.2% (1308)
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 infraction	3.6% (76)
Type 2 diabetes mellitus	29.9% (630)
Prior stroke	3.3% (68)
Heart failure	3.3% (70)
Sleep apnea	18.2% (354)
Atrial fibrillation	7.9% (166)
Number of antihypertensive medications	3.8 ± 2.1

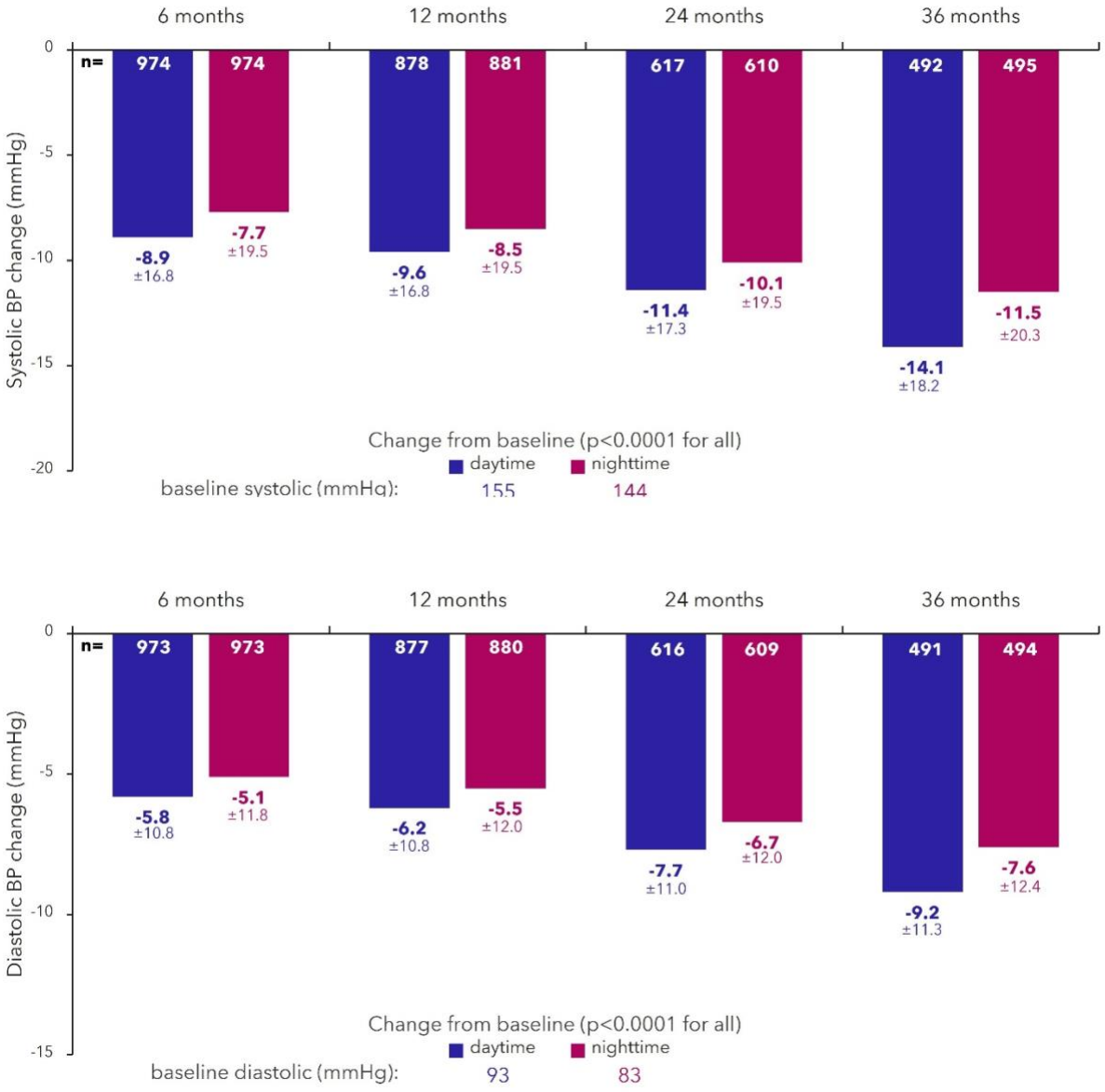
BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Central Illustration. Flow chart and blood pressure changes among pooled patients treated with the radiofrequency RDN Spyral device



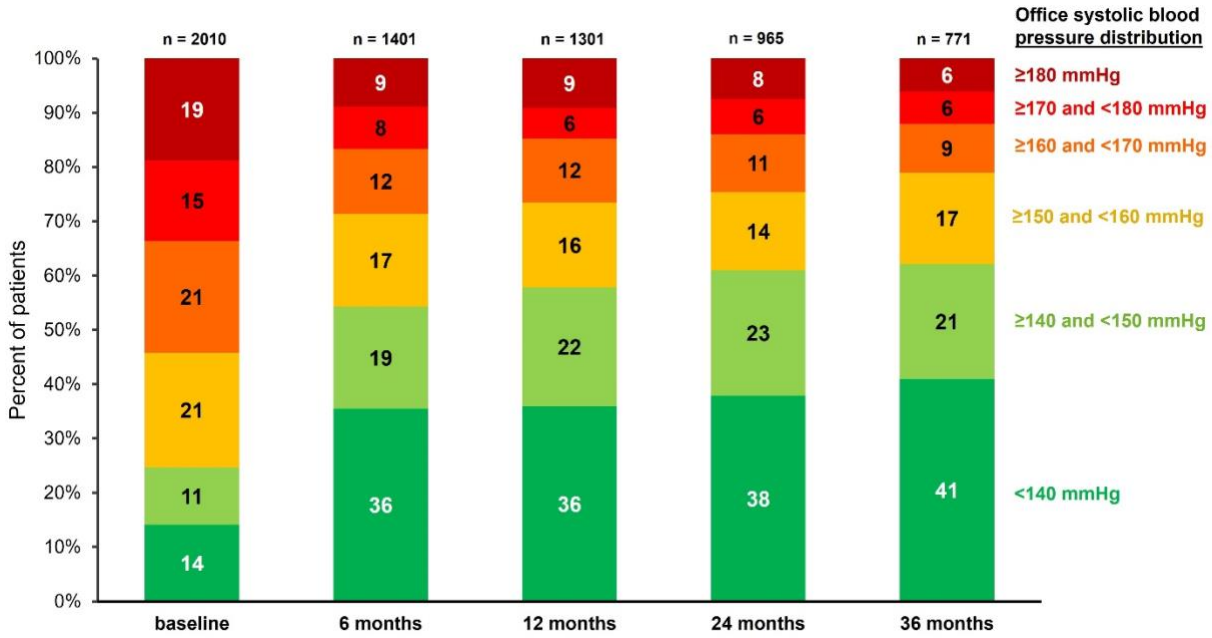
Data from 2,137 patients treated with the Spyral radiofrequency renal denervation device (top) were pooled from 4 studies: SPYRAL First-in-Human, SPYRAL HTN-OFF MED, HTN-ON MED, and the Global SYMPLICITY Registry DEFINE (middle). Among pooled Spyral patients, the office (blue) and 24-h ambulatory (magenta) systolic BP changes of from baseline through 36 months were statistically significant (bottom).

Figure 1. Day and nighttime systolic and diastolic ambulatory BP changes through 36 months



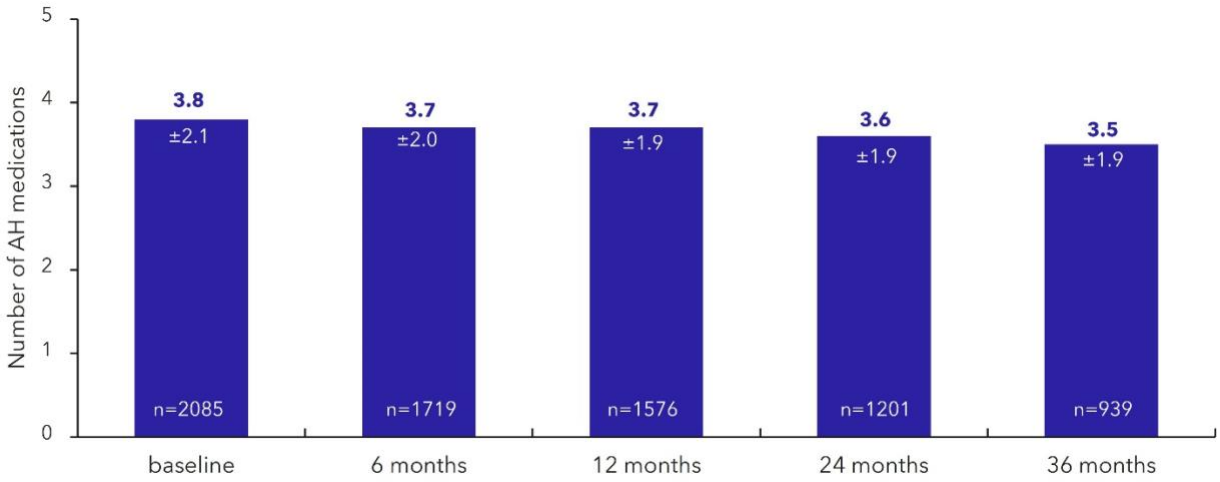
The daytime (blue) and nighttime (magenta) systolic (top) and diastolic (bottom) BP changes of the pooled Spyral cohort from baseline through 36 months are plotted.

Figure 2. Distribution of office systolic BP reductions after RDN at 36 months



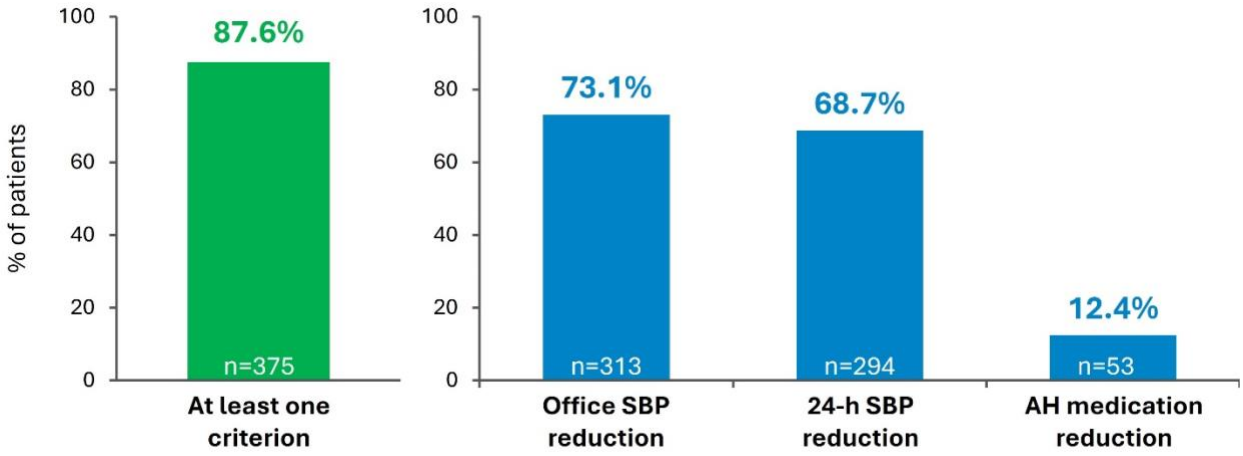
The proportion of patients in the indicated office systolic BP ranges at baseline through 36 months are plotted.

Figure 3. Antihypertensive medications among pooled Spyral patients through 36 months



The number of prescribed antihypertensive medications at baseline and through 36 months are plotted.

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 (blue).

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%

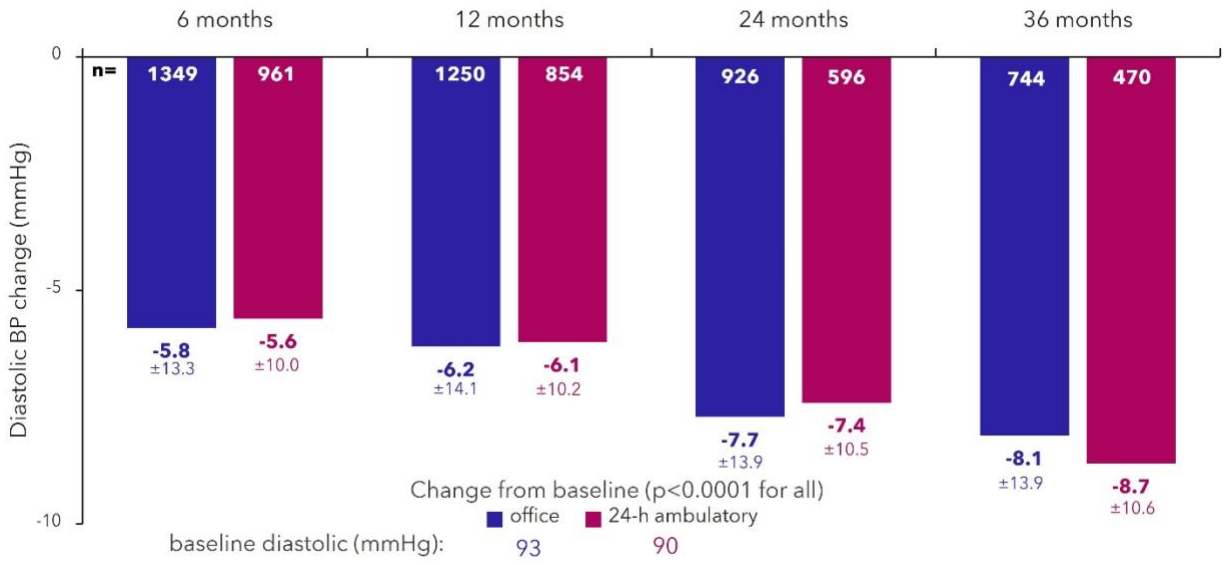
FIH, First-in-Human; GSR, Global SYMPLICITY Registry. Those experiencing a clinical benefit includes an office systolic BP reduction ≥10 mmHg, a 24-h ambulatory systolic BP reduction ≥5 mmHg, or a reduction of ≥1 AH medication.

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

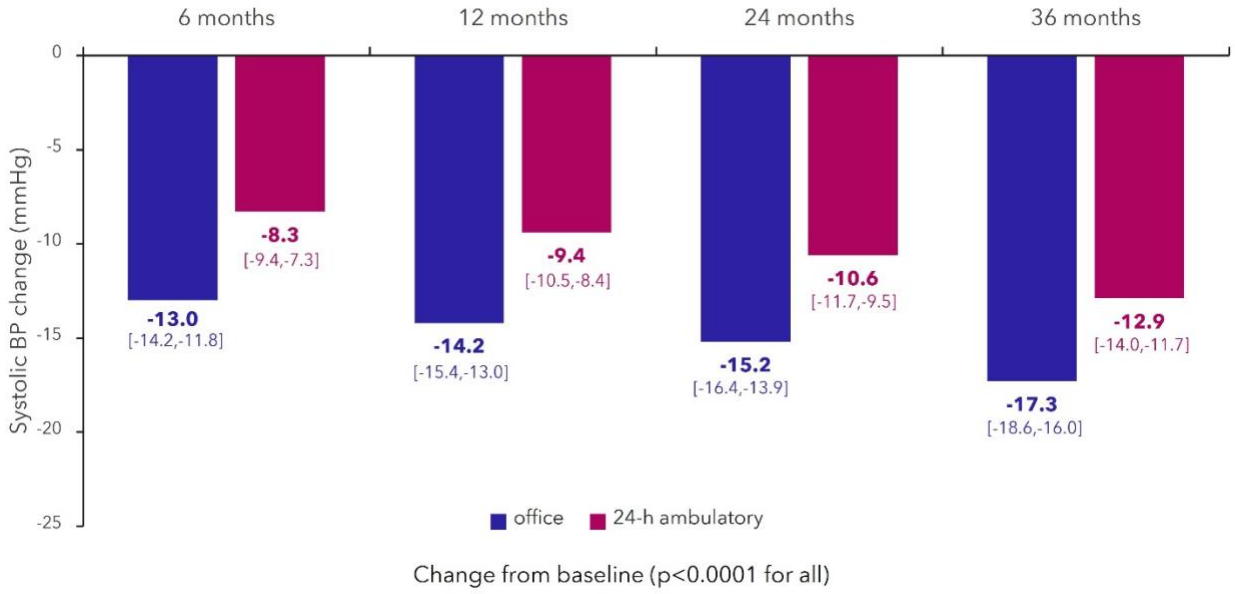


The office (blue) and 24-h ambulatory (magenta) diastolic BP changes of the pooled Spyral cohort from baseline through 36 months are plotted.

Supplementary Figure 2. Systolic BP changes and the number of medications in matched patients through 36 months

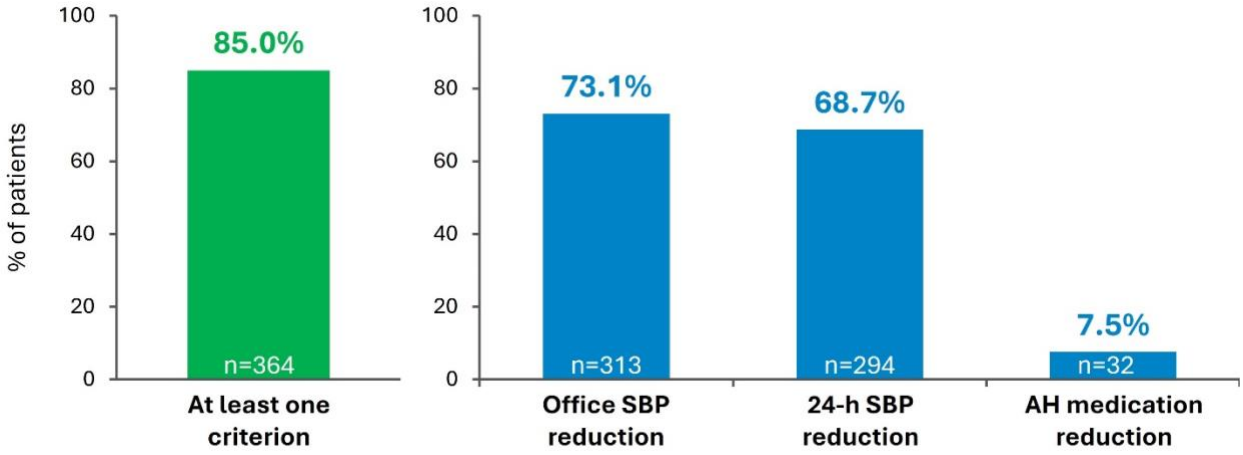
The office (blue) and 24-h ambulatory (magenta) systolic BP changes of matched patients are plotted from baseline through 36 months.

Supplementary Figure 3. Mixed model systolic BP changes through 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 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).