






ORIGINAL RESEARCH

Comparison of Long-Term Outcomes for Responders Versus Non-Responders Following Renal Denervation in Resistant Hypertension

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BACKGROUND: Recent trial results support the efficacy of renal sympathetic denervation in lowering blood pressure (BP). While BP reduction in general is associated with a clinically meaningful reduction in cardiovascular events and mortality, such a relationship has not been described for patients undergoing renal sympathetic denervation.

METHODS AND RESULTS: Clinical events were assessed in patients who underwent renal sympathetic denervation at our center using telephone- and clinical follow-up, interviews with general practitioners, as well as review of hospital databases. Event rates were compared between BP responders (≥ 5 mm Hg 24-hour ambulatory BP reduction) and non-responders; 296 patients were included. Compared with baseline, 24-hour systolic ambulatory BP was reduced by 8.3 ± 12.2 mm Hg and diastolic BP by 4.8 ± 7.0 mm Hg ($P < 0.001$ for both) after 3 months. One hundred eighty patients were classified as BP responders and 116 as non-responders. During a median follow-up time of 48 months, significantly less major adverse cardiovascular events (cardiovascular death, stroke, myocardial infarction, critical limb ischemia, renal failure) occurred in responders than in non-responders (22 versus 23 events, hazard ratio [HR], 0.53 [95% CI, 0.28 to 0.97], $P = 0.041$). This was consistent after adjustment for potential confounders as well as confirmed by propensity-score matching. A proportional relationship was found between BP reduction after 3 months and frequency of major adverse cardiovascular events (HR, 0.75 [95% CI, 0.58 to 0.97] per 10 mm Hg 24-hour systolic ambulatory BP reduction).

CONCLUSIONS: Based on these observational data, blood pressure response to renal sympathetic denervation is associated with improved long-term clinical outcome.

Key Words: arterial hypertension ■ clinical outcome ■ renal denervation

High blood pressure (BP) is one of the most dominant predictors for cardiovascular outcome and mortality among patients worldwide. Current guidelines uniformly recommend BP treatment in patients with diagnosed hypertension and elevated BP to prevent long-term sequelae,^{1,2} as there is clear evidence for a drug- or lifestyle-induced BP reduction to lower cardiovascular event rates in these patients.^{3,4}

In contrast, there is a gap of knowledge for such relationships in patients undergoing renal sympathetic denervation (RDN); recent RDN research focused on short- and long-term efficacy of BP reduction as well as long-term safety,^{5–10} meanwhile an effect of this BP reduction on long-term clinical outcome has not been described yet. This is of clinical importance, as the effects caused by RDN are independent from

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CLINICAL PERSPECTIVE

What Is New?

- This study shows the interplay of renal sympathetic denervation and blood pressure reduction on long-term outcome in patients with therapy resistant hypertension.

What Are the Clinical Implications?

- Blood pressure reduction after renal sympathetic denervation is associated with improved clinical outcome.

Nonstandard Abbreviations and Acronyms

ABPM	ambulatory blood pressure measurement
MACE	major adverse cardiovascular event
RDN	renal denervation

drug adherence and thus might reduce cardiovascular events even more than drug-based antihypertensive treatment.

Consequently, we aimed to close this gap by investigating the effect of BP reduction after RDN on long-term cardiovascular outcome in a single-center cohort of patients with therapy resistant hypertension.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patients

We conducted a retrospective single-center study. To investigate clinical outcome in patients with therapy resistant hypertension after RDN, events were assessed in patients from previous RDN trials and clinical routine at our center.^{11–16}

All enclosed studies were approved by the local ethics committee and were performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Patients with therapy resistant hypertension (following the definition of the European Society of Cardiology¹⁷—elevated systolic office BP and systolic daytime BP average >135 mm Hg in ambulatory blood pressure measurement (ABPM) despite ≥3 antihypertensive drugs including at least 1 diuretic, unless intolerant to diuretics) and stable medication for at least

4 weeks underwent RDN within previously published trials^{11–16} and in clinical routine. Patients were included into the analysis if baseline and 3 months ABPM results were available.

Blood Pressure Measurement

Office BP was measured with automated BP monitors. ABPM was acquired with a cuff-based oscillometric device (Spacelabs model 90207, Spacelabs Healthcare, Snoqualmie, USA) at baseline and follow-up after 3, 6, and 12 months. BP recordings were taken every 15 minutes at daytime (7:00 am–10:00 pm) and every 30 minutes during nighttime (10:00 pm–7:00 am). In some rare cases, where ABPM was unavailable after 6 or 12 months, measurements were provided by the patient's treating physicians if possible.

RDN Procedure

RDN was performed according to standardized protocols as described previously.^{11,12,18,19} In brief, repeated ablation runs were delivered to each renal artery. The ablation regions were placed circumferentially to the renal artery wall from distal to proximal. All patients received intravenous remifentanyl to control visceral pain. A total of 117 of the patients included in the final analysis underwent unipolar radiofrequency ablation of the main renal artery with a Symplicity Flex catheter, 49 patients received treatment of the main renal artery with the multielectrode radiofrequency Spyral catheters and 38 patients received combined treatment of the main renal artery and an additional ablation of the side branches using the Spyral catheter¹⁸ (both devices Medtronic, Minnesota, MN, USA). Ninety-two underwent ablation with a balloon-irrigated ultrasound-based denervation system (Paradise, ReCor Medical, Palo Alto, CA, USA).¹² A transfemoral access route was used in all patients.

Follow-Up

Patients were contacted via telephone between January and April 2020. Clinical outcome was assessed by a standardized questionnaire by a single investigator (P.R.), who was masked to blood pressure outcome. If contacting the patients was unsuccessful, or if necessary to complete clinical event assessment, patient's last treating general practitioners were contacted. In addition, hospital database was searched for clinical events for every individual patient. In all patients, antihypertensive drug treatment was kept stable until the 6 months follow-up was reached unless indicated otherwise (e.g., for symptomatic hypertensive crisis or hypotension).

Definitions

BP response was defined as reduction of ≥ 5 mm Hg in 24-hour average systolic BP on ABPM between baseline and 3 months.²⁰

Outcome

Major adverse cardiovascular event (MACE) was defined as a composite of cardiovascular death, ischemic stroke or intracranial bleeding, acute myocardial infarction, critical limb ischemia as well as acute renal failure.

The ischemic events end point was defined as a composite of ischemic stroke, acute myocardial infarction, peripheral artery disease requiring intervention and critical limb ischemia.

To assess the effect of BP reduction, clinical events were compared between BP responders and non-responders. In a second step, a postulated proportional relationship between BP reduction and clinical events was tested by Cox regression analysis.

Statistical Analysis

Continuous variables are presented as mean and SD, dichotomous variables as number and percentage unless indicated otherwise. Normal distribution was tested using Kolmogorov–Smirnov test. Student *t*-tests or Mann–Whitney *U* tests were used to compare continuous variables. Time-to-event analyses were conducted using log-rank tests for unadjusted comparisons and Cox regression with stepwise-forward selection ($P < 0.05$) for adjusted comparisons. Results are presented as hazard ratios (HR) with corresponding 95% CI.

In addition, a propensity-score matching was used to compare BP responders and BP non-responders. Patients were matched for age, sex, and baseline 24-hour systolic and diastolic ABPM values before RDN in a 1:1 ratio.

The underlying assumptions of the statistical tests were evaluated. Statistical significance was inferred when $P < 0.05$.

Statistical analyses were performed with SPSS 24.0.0.0 (IBM, NY, USA) and MedCalc 16.4.3 (MedCalc Software, Ostend, Belgium).

RESULTS

Between June 2011 and May 2019, 311 patients underwent RDN. Of these, 14 (4.5%) were lost to follow-up or had missing 3 months BP values and 1 patient (0.3%) died before reaching the 3 months follow-up. In total, 296 patients (95.2%) with a median follow-up time of 48 months were available for analysis.

Baseline Characteristics and Blood Pressure Outcome

Clinical baseline characteristics, BP, and medication for the full cohort as well as responders and non-responders are shown in Tables 1 and 2. At baseline, responders had higher systolic and diastolic ABPM values as well as a lower rate of isolated systolic hypertension (Table 1). Baseline medication and number of antihypertensive drug classes were balanced between responders and non-responders (Table 2). At 3 months, systolic 24-hour ABPM was reduced by

Table 1. Clinical Baseline Characteristics

	All (n=296)		Responders (n=180)		Non-responders (n=116)		P value
Age, y	63.1	±9.7	62.7	±9.6	63.6	±9.8	0.36
Body mass index [kg/m ²]	32.2	±6.4	31.8	±4.8	32.2	±8.5	0.51
Women, n (%)	88	(30)	53	(29)	35	(30)	0.88
Serum creatinine [μmol/L]	88.5	±26.8	88.6	±27.5	88.4	±25.8	0.88
eGFR [mL/min]	78.4	±19.7	78.3	±19.3	78.6	±20.3	0.90
Smoker, n (%)	145	(49)	87	(48)	58	(50)	0.76
Diabetes, n (%)	139	(47)	85	(47)	54	(47)	0.93
Peripheral artery disease, n (%)	32	(11)	19	(11)	13	(11)	0.85
Coronary artery disease, n (%)	113	(38)	69	(38)	44	(38)	0.96
Previous stroke, n (%)	20	(7)	8	(4)	12	(10)	0.05
Previous myocardial infarction, n (%)	40	(14)	28	(16)	12	(10)	0.20
Atrial fibrillation, n (%)	41	(14)	26	(14)	15	(13)	0.72
Dyslipidemia, n (%)	211	(71)	128	(71)	83	(72)	0.90
24-h systolic blood pressure [mm Hg]	152.3	±12.9	154.0	±13.5	149.7	±11.5	0.01
24-h diastolic blood pressure [mm Hg]	83.7	±11.8	85.1	±11.7	81.5	±11.5	0.002
Isolated systolic hypertension, n (%)	127	(43)	66	(37)	61	(53)	0.007

eGFR indicates estimated glomerular filtration rate.

Table 2. Baseline Medication

	All (n=296)		Responders (n=180)		Non-responders (n=116)		P value
No. of antihypertensive drug classes	5.2	1.4	5.2	±1.4	5.2	±1.4	0.74
Five or more drug classes, n (%)	197	(67)	116	(64)	81	(70)	0.32
Angiotensin-converting enzyme inhibitors, n (%)	114	(39)	66	(37)	48	(41)	0.40
Angiotensin receptor antagonists, n (%)	196	(66)	119	(66)	77	(66)	0.93
Renin antagonists, n (%)	26	(9)	19	(11)	7	(6)	0.18
Beta-blockers, n (%)	262	(89)	159	(88)	103	(89)	0.84
Calcium channel blockers, n (%)	214	(72)	130	(72)	84	(72)	0.94
Diuretics, n (%)	281	(95)	173	(96)	108	(93)	0.27
Second diuretic, n (%)	65	(22)	43	(24)	22	(19)	0.32
Aldosterone antagonists, n (%)	35	(12)	21	(12)	14	(12)	0.91
Vasodilators, n (%)	41	(14)	25	(14)	16	(14)	0.99
Alpha blockers, n (%)	102	(34)	62	(34)	40	(34)	0.99
Centrally acting sympatholytics, n (%)	169	(57)	100	(56)	69	(59)	0.48

8.3±12.2 mm Hg and diastolic 24-hour ambulatory BP was reduced by 4.8±7.0 mm Hg ($P<0.001$ for both). One hundred eighty patients (61%) were classified as BP responders and 116 (39%) as non-responders.

After 6 and 12 months, systolic and diastolic ABPM (available for 253 and 183 patients) remained reduced by 8.0/5.1±12.4/7.1 and 8.7/5.4±14.1/7.8 mm Hg ($P<0.001$ for all versus baseline) as compared with baseline. Systolic BP at 6 and 12 months remained significantly more reduced in 3-month responders than in 3-month non-responders (12.1±2.8 versus 2.8±13.8 and 11.7±12.0 versus 2.0±10.7 mm Hg, $P<0.001$ for both, compared with baseline BP values).

Outcome Relevant Events During Follow-Up

MACE and ischemic events occurred more frequently in non-responders than in responders (23 versus 22 and 19 versus 15 events; HR, 0.53 [95% CI, 0.28 to 0.97] and 0.44 [95% CI, 0.22 to 0.89], $P=0.041$ and 0.022, respectively, Figure 1). All clinical events for responders, non-responders and the entire cohort are shown in Table 3.

After adjustment for age, sex, baseline systolic and baseline diastolic ABPM before RDN as well as presence of isolated systolic hypertension and a history of stroke using Cox regression analysis and a stepwise forward approach, besides baseline systolic BP, isolated systolic hypertension, and previous stroke-only responder status reached significance level ($P=0.041$, Figure 2A). Baseline diastolic BP, age, and sex did not reach statistical significance for inclusion into the model. In an additional Cox regression analysis including BP reduction in 10 mm Hg steps instead of responder status, a proportional relationship between reduction of 24-hour ABPM at 3 months and a reduced risk for MACE was found (HR, 0.75 [CI, 0.58–0.97] per 10 mm Hg, $P=0.031$). Baseline blood

pressure corrected event rates by blood pressure reduction quartiles (quartile 1: <1 mm Hg, quartile 2: 1 to 7 mm Hg, quartile 3: 7 to 15 mm Hg and quartile 4: >15 mm Hg 24-hour ABPM reduction after 3 months) using Cox regression also suggested a proportional relation of blood pressure reduction but did not reach significance level between the different quartiles (Figure 2B).

Propensity Score Matching

Propensity score matching was used to adjust for baseline differences between the 2 groups. One-hundred-ninety-six patients were matched (98 responders and 98 non-responders). In the propensity score matched cohort, baseline BP values did not differ between the groups (Table 4). MACE were significantly less frequent in responders than in non-responders ($P=0.043$ by log-rank, Figure 2C, Table 5).

DISCUSSION

This study shows a strong protective association between RDN related BP change and long-term clinical outcome, with the main findings being that: (1) responders to RDN, despite having higher baseline BP, had a reduced estimated long-term rate of MACE, (2) this held true after adjustment for relevant covariates and a propensity matched analysis, and (3) further BP reduction was associated with reduced MACE rates in a proportional fashion implying an at least partial causality of BP reduction and MACE, irrespectively of baseline confounders.

In line with previous publications from the Global Symplicity Registry in >1000 patients,^{5,6} the BP change we observed after RDN was long lasting, consistent at follow-up measurements and of comparable extent. With such continuity in results at different timepoints

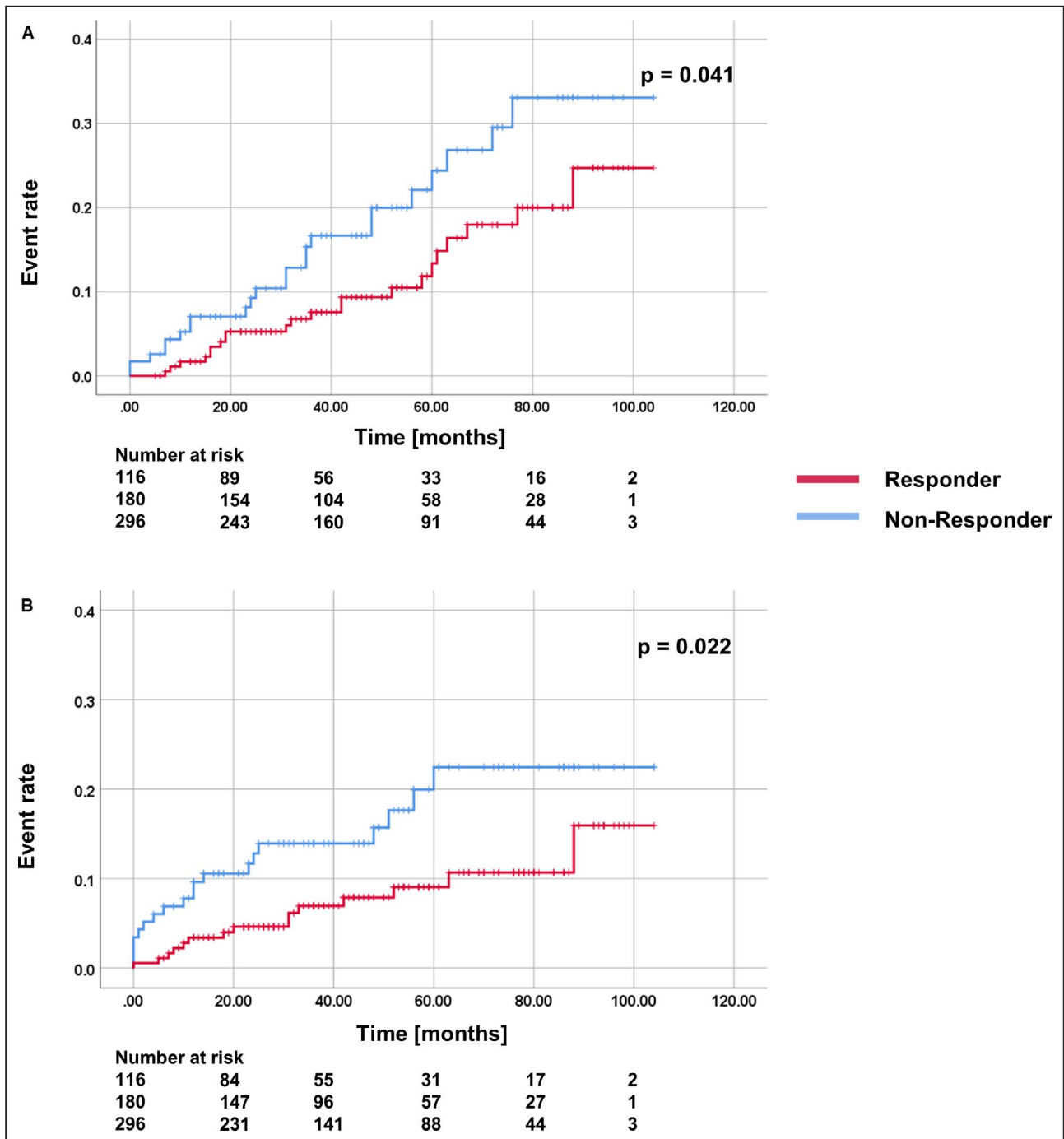


Figure 1. Kaplan–Meier curves in responders and non-responders after renal denervation for major adverse cardiovascular events (A) and ischemic events (B).

during follow-up, a true RDN related effect is probable. In contrast, a transient increase in medication adherence after enrollment or a result of regression to mean are unlikely as this would typically result in varying BP values at different follow-up measurements. Again, this is supported by the Global Symplicity Registry data, where the average number of antihypertensive drug classes was slightly reduced during follow-up despite a persistent

BP reduction.⁵ While medication adherence in general shows strong fluctuations^{21,22} and is especially poor in patients with resistant hypertension,²³ the BP lowering effects of RDN are likely independent from the patient’s cooperation and adherence. Moreover, RDN has shown positive BP-independent effects on cardiac remodeling.^{24,25} Together, this bears the hope to amplify a hypothetical protective effects of RDN-induced BP reduction

Table 3. Clinical Events During Follow-Up

	All (n=296)		Responders (n=180)		Non-responders (n=116)		Hazard ratio	95% CI	P value (log-rank)
Death, n (%)	29	(10)	19	(11)	10	(9)	1.22	0.58–2.57	0.69
Cardiovascular death, n (%)	16	(5)	9	(5)	7	(6)	0.82	0.30–2.23	0.69
Stroke, n (%)	9	(3)	3	(2)	6	(5)	0.31	0.08–1.17	0.08
Intracranial hemorrhage, n (%)	4	(1)	3	(2)	1	(1)	1.82	0.24–13.54	0.55
NSTE-ACS, n (%)	12	(6)	6	(3)	6	(5)	0.62	0.19–1.99	0.43
STEMI, n (%)	2	(1)	1	(1)	1	(1)	0.62	0.04–10.64	0.74
PAD requiring intervention, n (%)	13	(4)	6	(3)	7	(6)	0.53	0.17–1.61	0.26
Critical limb ischemia, n (%)	3	(1)	1	(1)	2	(2)	0.33	0.03–3.29	0.34
Acute renal failure, n (%)	11	(3)	4	(2)	7	(6)	0.36	0.11–1.21	0.10
Heart failure hospitalization, n (%)	20	(7)	13	(7)	7	(6)	1.27	0.52–3.11	0.59
MACE (cardiovascular death, stroke/intracranial bleeding, AMI, acute renal failure), n (%)	45	(15)	22	(12)	23	(20)	0.53	0.28–0.97	0.041
Ischemic events (stroke, AMI, PAD requiring intervention, critical limb ischemia), n (%)	34	(11)	15	(8)	19	(16)	0.44	0.22–0.89	0.026

AMI indicates acute myocardial infarction; MACE, major adverse cardiovascular events; NSTE-ACS, non-ST-segment-elevation acute coronary syndrome; PAD, peripheral artery disease; and STEMI, ST-segment-elevation myocardial infarction.

in comparison to the effects which have been observed for drug-based antihypertensive treatment. Ideally, this should be tested in randomized controlled trials with predefined clinical end points and extended long-term follow-up over several years. However, given the complexity of such a trial and the large number of patients needed to enroll, results are unlikely to be available in the near future. In the meantime, our approach to simplify comparison by using the BP responder-non-responder classification might give an impression of the BP-related effects caused by RDN instead.

While we did observe the presumed positive relationship between BP reduction and clinical events, several baseline imbalances were found between the 2 groups. In previous studies, a BP non-response after RDN was associated with lower baseline BP, age, and advanced arterial stiffness,^{14,26,27} which are partly independent predictors for cardiovascular events.²⁸ Importantly, the effects observed here are independent of these baseline imbalances including isolated systolic hypertension as a relatively broad marker of vascular stiffness: The RDN-related reduction of clinical events was confirmed after Cox regression analysis in the full cohort and also in a propensity-matched cohort. Moreover, beyond the binary response-non-response pattern we were able to show a partly proportional relationship between a BP reduction and a reduced risk for MACE, which suggest a strong and sustained BP-related risk-reduction – even after a long period of time with a median follow-up of 4 years and up to 8.7 years. This is encouraging, as patients with treatment resistant hypertension have a poor prognosis,²⁹ and RDN might be the long-desired game-changer in these patients if applied in an early stage of the disease before irreversible end-organ damage occurs. As this

proportional relationship was not found statistically significant when using blood pressure reduction quartiles instead of the binary BP responder/non-responder pattern, a chance finding remains possible, which is why our data should be interpreted with caution.

The exact mechanism of a possible clinical event reduction after RDN is unclear. A reduced progression of atherosclerosis is a less likely mechanism for the reduced event rates with the intermediate follow-up duration given. It has been described previously that increased BP morning surge and BP variability are both linked to an elevated sympathetic activity.^{30,31} Both state independent predictors for cardiovascular events and mortality^{32–36} and are reduced following RDN.^{37,38} Hypothetically, attenuation of extreme BP values after RDN prevents from these clinical events, which would explain the high efficacy within a relatively short period of time. Beyond this, long-term protective effects on the vasculature and progression of arteriosclerotic, cardiac, and renal diseases seem conceivable and could contribute to further risk reduction, especially in longer-term follow-up.

Limitations

Several limitations need to be mentioned: First, this is a retrospective single-center registry from a highly specialized center with its inherent limitations like selection bias, which hinders generalization of its results. Second, we cannot provide drug adherence testing for the patients enrolled. Thus, part of the observed effects might also be attributed to alterations in antihypertensive drug intake during follow-up, even though this is unlikely as discussed above. Third, because of the study design and the lack of a control group, it is impossible to

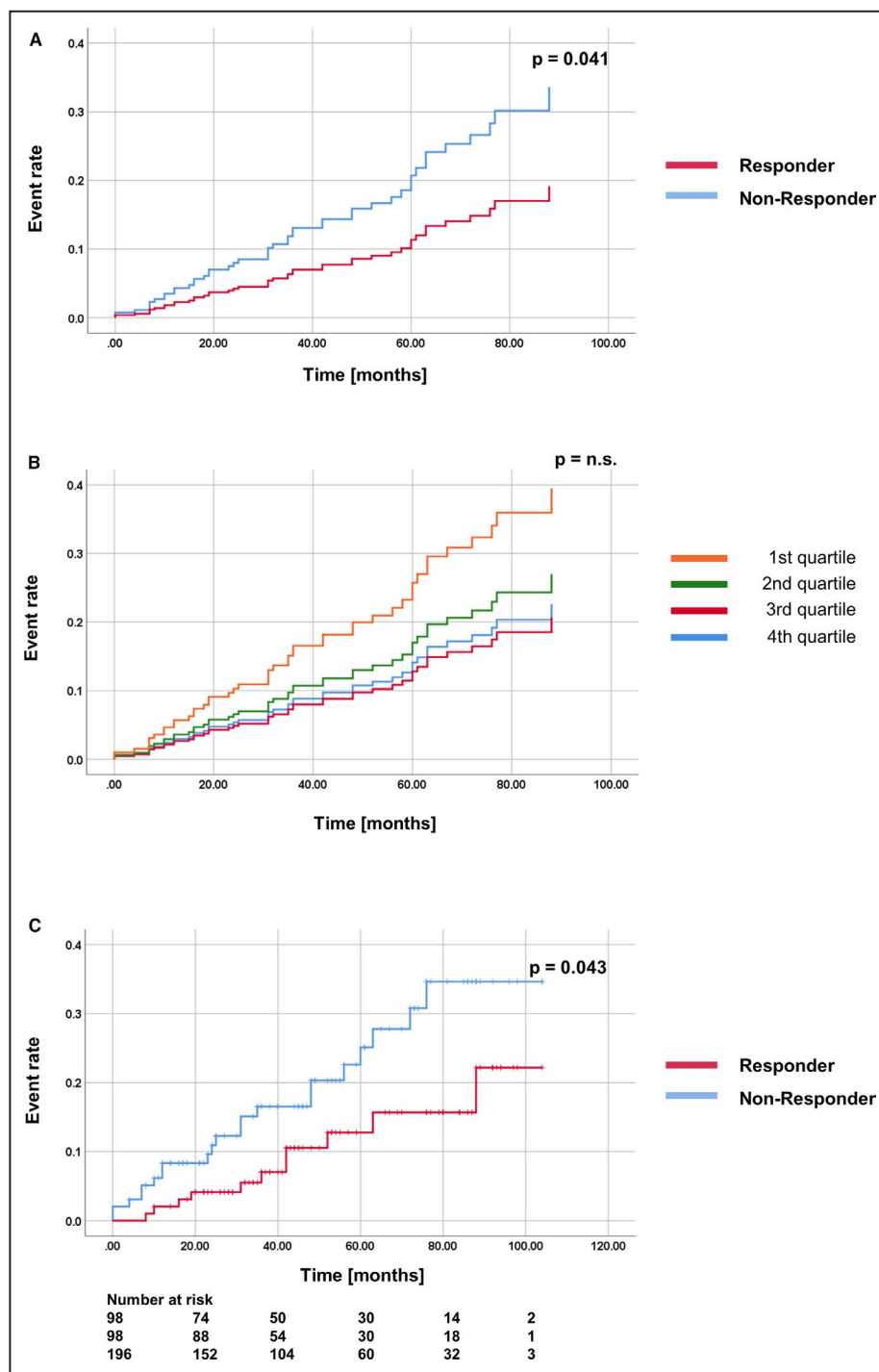


Figure 2. Time-to-event curves for major adverse cardiovascular events in responders and non-responders after adjustment for age, sex, isolated systolic hypertension, history of stroke, systolic and diastolic blood pressure (Cox regression, **A**).

Baseline blood pressure corrected time-to-event curves per quartiles of blood pressure reduction (quartile 1, <1 mm Hg; quartile, 2: 1–7 mm Hg; quartile, 3: 7–15 mm Hg; and quartile 4, >15 mm Hg 24-hour ambulatory blood pressure measurement reduction after 3 months, Cox regression, **B**). Kaplan–Meier curves for major adverse cardiovascular events in the propensity-score matched cohort (**C**). ABPM indicates ambulatory blood pressure measurement.

separately analyze effects of RDN from effects by BP reduction in general, but the proportional association of BP reduction within the immediate timeframe of RDN

on long-term outcomes suggest an at least partial effect. This needs to be verified in future multicenter trials with an adequate control group. Fourth, even though

Table 4. Baseline Characteristics in the Propensity-Score Matched Cohort

	All (n=196)		Responders (n=98)		Non-responders (n=98)		P value
Age, y	63.7	±10.0	63.4	±9.9	63.9	±10.1	0.56
Body mass index, kg/m ²	31.7	±7.0	31.3	±4.3	32.2	±9.0	0.81
Women, n (%)	61	(31)	30	(31)	31	(31)	0.88
Serum creatinine, μmol/L	88.8	±27.9	88.7	±28.8	88.9	±27.0	0.93
eGFR, mL/min	78.2	±20.1	78.1	±19.1	78.3	±21.1	0.95
Smoker, n (%)	96	(49)	49	(50)	47	(48)	0.77
Diabetes, n (%)	91	(46)	48	(49)	41	(42)	0.47
Peripheral artery disease, n (%)	18	(9)	6	(6)	12	(12)	0.14
Coronary artery disease, n (%)	75	(38)	36	(37)	39	(40)	0.66
Previous stroke, n (%)	15	(8)	4	(4)	11	(11)	0.06
Previous myocardial infarction, n (%)	22	(11)	12	(12)	10	(10)	0.65
Atrial fibrillation, n (%)	26	(13)	14	(14)	12	(12)	0.67
Dyslipidemia, n (%)	139	(71)	71	(72)	68	(69)	0.63
24-h systolic blood pressure [mm Hg]	149.6	±10.6	149.5	±11.0	149.8	±10.3	0.66
24-h diastolic blood pressure [mm Hg]	81.9	±10.4	82.5	±10.4	81.3	±10.5	0.20
Isolated systolic hypertension, n (%)	92	(47)	41	(42)	51	(52)	0.15

eGFR indicates estimated glomerular filtration rate.

we acquired follow-up data from almost all patients, an underreporting of clinical events is possible, which might have influenced the results, yet we report only a low rate of patients lost to follow-up especially given the long time since the index procedure. Nevertheless, as the overall rate of events is relatively small, outcome of patients lost to follow-up might have altered our results if available. Fifth, the composite end point (MACE) herein differs from other, larger-scaled cardiovascular outcome trials as it is a concession to the smaller sample size available. Effects of RDN on hard clinical end points should be tested in larger-scaled analyses in the future.

Lastly, the relatively small number of events and patients included give this study only a hypothesis generating character and all findings warrant confirmation in larger, prospectively designed trials.

Perspectives

This study is the first to show possible beneficial long-term effects of RDN on adverse clinical events in patients with therapy resistant hypertension. This effect seems to depend on the extent of BP reduction following RDN.

Table 5. Clinical Events in the Propensity-Score Matched Cohort

	All (n=196)		Responders (n=98)		Non-responders (n=98)		Hazard ratio	95% CI	P value (log-rank)
Death, n (%)	15	(8)	6	(6)	9	(9)	0.71	0.26–1.95	0.48
Cardiovascular death, n (%)	10	(5)	4	(4)	6	(6)	0.71	0.21–2.45	0.59
Stroke, n (%)	8	(4)	2	(2)	6	(6)	0.38	0.09–1.50	0.16
Intracranial hemorrhage, n (%)	2	(1)	1	(1)	1	(1)	1.03	0.06–16.50	0.99
NSTE-ACS, n (%)	10	(5)	4	(4)	6	(6)	0.67	0.19–2.32	0.51
STEMI, n (%)	2	(1)	1	(1)	1	(1)	1.02	0.06–16.41	0.99
PAD requiring intervention, n (%)	10	(5)	3	(3)	7	(7)	0.55	0.17–1.80	0.19
Critical limb ischemia, n (%)	2	(1)	0	(0)	2	(2)	0.16
Acute renal failure, n (%)	7	(4)	1	(1)	6	(6)	0.25	0.06–1.12	0.07
Heart failure hospitalization, n (%)	12	(6)	6	(6)	6	(6)	1.18	0.38–3.67	0.81
MACE (cardiovascular death, stroke/intracranial bleeding, AMI, critical limb ischemia, acute renal failure), n (%)	32	(16)	11	(11)	21	(21)	0.49	0.24–0.98	0.043
Ischemic events (stroke, AMI, PAD requiring intervention, critical limb ischemia), n (%)	30	(15)	11	(11)	19	(19)	0.53	0.26–1.08	0.08

AMI indicates acute myocardial infarction; MACE, major adverse cardiovascular events; NSTE-ACS, non-ST-segment-elevation acute coronary syndrome; PAD, peripheral artery disease; and STEMI, ST-segment-elevation myocardial infarction.

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