



Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study

Henry Krum, Markus P Schlaich, Paul A Sobotka, Michael Böhm, Felix Mahfoud, Krishna Rocha-Singh, Richard Katholi, Murray D Esler

Summary

Background Renal denervation (RDN) with radiofrequency ablation substantially reduces blood pressure in patients with treatment-resistant hypertension. We assessed the long-term antihypertensive effects and safety.

Methods Symplicity HTN-1 is an open-label study that enrolled 153 patients, of whom 111 consented to follow-up for 36 months. Eligible patients had a systolic blood pressure of at least 160 mm Hg and were taking at least three antihypertensive drugs, including a diuretic, at the optimum doses. Changes in office systolic blood pressure and safety were assessed every 6 months and reported every 12 months. This study is registered with ClinicalTrials.gov, numbers NCT00483808, NCT00664638, and NCT00753285.

Findings 88 patients had complete data at 36 months. At baseline the mean age was 57 (SD 11) years, 37 (42%) patients were women, 25 (28%) had type 2 diabetes mellitus, the mean estimated glomerular filtration rate was 85 (SD 19) mL/min per 1.73 m², and mean blood pressure was 175/98 (SD 16/14) mm Hg. At 36 months significant changes were seen in systolic (−32.0 mm Hg, 95% CI −35.7 to −28.2) and diastolic blood pressure (−14.4 mm Hg, −16.9 to −11.9). Drops of 10 mm Hg or more in systolic blood pressure were seen in 69% of patients at 1 month, 81% at 6 months, 85% at 12 months, 83% at 24 months, and 93% at 36 months. One new renal artery stenosis requiring stenting and three deaths unrelated to RDN occurred during follow-up.

Interpretation Changes in blood pressure after RDN persist long term in patients with treatment-resistant hypertension, with good safety.

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Introduction

Systemic hypertension is the single largest contributor to death worldwide.¹ One in three adults (around 1 billion people) worldwide are affected and the number is expected to increase to 1.6 billion by 2025.^{2,3} Hypertension strikingly increases the risk of stroke, myocardial infarction, heart failure, and kidney disease.^{3,4}

Despite the use of multiple antihypertensive drugs, including diuretics, at recommended or target doses, hypertension remains uncontrolled in a substantial proportion of patients.^{5,6} Multiple factors can contribute to poor control of blood pressure: suboptimum pharmaceutical care and patients deciding not to commit to lifelong polypharmacy. Furthermore, drugs are associated with adverse clinical events and patients frequently do not adhere to therapy because of side-effects, financial concerns, or a lack of hypertensive symptoms.⁷ Finally, antihypertensive medications do not lower blood pressure in some patients despite full adherence and attentive health care.

Strategies that target the contribution of overactivity of the sympathetic nervous system have proven clinically important in several disorders.⁸ Patients with hypertension might benefit from agents that inhibit central release of catecholamines, or from use of β and α blockers, which inhibit catecholamine receptors. Early

research into the role of adrenergic overdrive in hypertension described increased norepinephrine concentrations in plasma that arose from renal and systemic spillover into the circulation.^{9,10}

Renal denervation (RDN) by radiofrequency ablation has been associated with reductions in blood pressure.^{11–13} A patient with treatment-resistant hypertension who presented with notable norepinephrine spillover had substantially reduced whole-body norepinephrine concentrations and reduced blood pressure after RDN.¹⁴ A substantial reduction in central sympathetic outflow has also been reported.¹⁵ RDN, therefore, offers a therapeutic option for the management of treatment-resistant hypertension for patients who cannot attain targeted blood pressures with medications alone.¹⁶

In a proof-of-concept study of RDN (Symplicity HTN-1¹⁷), we found significant substantial reductions in blood pressure by 1 month after treatment that continued to the 12 month endpoint. The longer-term durability of the treatment response has been questioned because, theoretically, the treated renal nerves could regrow and regain function or a counter-regulatory response might develop.^{18–20} For this reason, we extended follow-up to 36 months specifically to assess the durability of blood-pressure-lowering effects and investigate any late adverse vascular or renal effects.

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Monash Centre of

Cardiovascular Research and

Education in Therapeutics,

School of Public Health and

Preventive Medicine, Monash

University, Alfred Hospital,

Melbourne, VIC, Australia

(Prof H Krum PhD);

Neurovascular Hypertension

and Kidney Disease Laboratory,

Baker IDI Heart and Diabetes

Institute and Heart Centre,

Alfred Hospital, Melbourne,

VIC, Australia

(Prof M P Schlaich MD); Davis

Heart and Lung Research

Institute, Ohio State

University, Columbus, OH, USA

(Prof P A Sobotka MD);

Kardiologie, Angiologie und

Internistische Intensivmedizin,

Universitätsklinikum des

Saarlandes, Homburg,

Germany (M Böhm MD,

F Mahfoud MD); Prairie Heart

Institute at St John's Hospital,

Springfield, IL, USA

(K Rocha-Singh MD,

R Katholi MD); and Baker IDI

Heart and Diabetes Institute,

Melbourne, VIC, Australia

(Prof M D Esler MBBS)

Correspondence to:

Prof Henry Krum, Centre of

Cardiovascular Research and

Education in Therapeutics,

Department of Epidemiology

and Preventive Medicine, School

of Public Health and Preventive

Medicine, Monash University/

Alfred Hospital, Melbourne,

VIC 3004, Australia

henry.krum@monash.edu

Methods

Patients

Symplicity HTN-1[†] is an open-label cohort study that enrolled 153 patients into four protocols at 19 centres in Australia, Europe, and the USA. Detailed study methods have been reported previously.¹⁷ Briefly, patients were required to have an office systolic blood pressure of 160 mm Hg or higher despite treatment with at least three antihypertensive drugs, including one diuretic, or confirmed intolerance to medications. Estimated glomerular filtration rate (eGFR), based on creatinine concentrations in serum, was required to be at least 45 mL/min per 1.73 m². We took care not to enrol patients with renovascular abnormalities, including renal-artery stenosis, previous renal stent or angioplasty, dual renal arteries, or polar arteries. In the first 12 months after RDN investigators were encouraged not to change background antihypertensive medicine unless clinically indicated. After 12 months, patients chose whether to give consent to be followed up for 24 or 36 months, dependent on the protocol to which they were assigned (figure 1). During extended follow-up medications could be changed as required. 111 patients gave consent to be followed up for 36 months.

Study procedure

The percutaneous RDN procedure has been described previously.¹⁷ Briefly, a Symplicity renal denervation catheter (Medtronic, Santa Rosa, CA, USA) was introduced into each renal artery via the femoral artery. Multiple radiofrequency ablations of 8 W or less for up to

2 min each were applied. After each delivery the catheter was drawn back by at least 5 mm and circumferentially rotated to ensure disruption of the sympathetic plexus surrounding the renal artery.

Blood pressure was measured during follow-up office visits. Adverse events, blood chemistry (including renal function), and vital signs were assessed per protocol at each visit. Patients underwent renal angiography before RDN, and renal imaging (duplex scan or angiography) was done at 6 months and at various timepoints after the procedure to assess the renal arteries for pathological changes. From 12 months onwards we assessed changes in sitting office systolic and diastolic blood pressures every 12 months.

Statistical analysis

Mean (95% CI) changes from baseline in blood pressure and eGFR at 1, 3, 6, 12, 24, and 36 months were calculated. Changes in office blood pressure from baseline to each follow up timepoint were assessed by the paired *t* test. We deemed *p* values of 0.05 or lower to be significant. All statistical analyses were done with SAS (version 9.2). We set 10 mm Hg as the threshold for clinically relevant response because the time to response is of interest. We

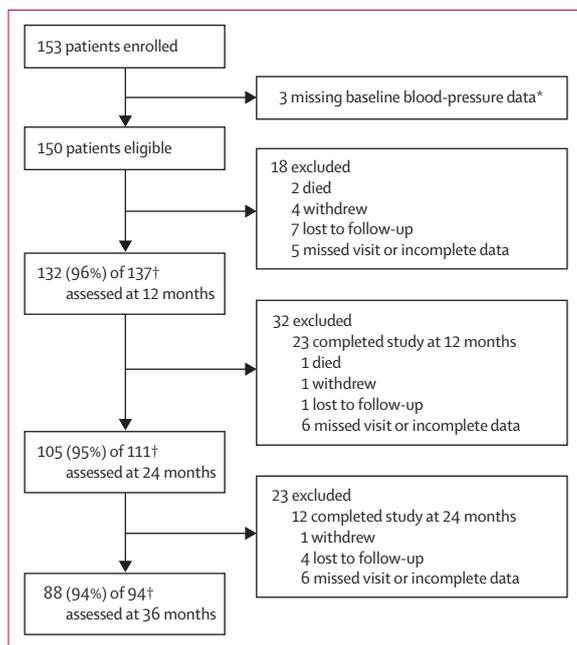


Figure 1: Trial profile

*Included in safety analysis. †Numerators include patients who consented to be followed and who completed follow-up to the timepoint stated.

	Enrolled patients (n=150)*	Patients followed up to 36 months (n=88)
Demographics		
Age (years)	57.1 (11.1)	57.0 (11.4)
Female sex (%)	56 (38%)	37 (42%)
Non-white ethnic origin (%)	7 (5%)	4 (5%)
Comorbidities		
Type 2 diabetes mellitus (%)	47 (31%)	25 (28%)
Coronary artery disease (%)	33 (22%)	20 (23%)
Hyperlipidaemia (%)	92 (61%)	62 (71%)
Estimated GFR (mL/min per 1.73m ²)	83.4 (19.7)	84.6 (18.9)
Blood pressure		
Baseline systolic (mm Hg)	175.1 (15.9)	174.6 (12.5)
Number of antihypertensive medications	5.0 (1.7)	5.2 (1.7)
Diuretic (%)	138 (92%)	82 (93%)
Aldosterone antagonist (%)	41 (27%)	25 (28%)
Angiotensin-receptor blocker (%)	102 (68%)	61 (69%)
ACE inhibitor (%)	80 (53%)	45 (51%)
Direct renin inhibitor (%)	25 (17%)	16 (18%)
β blocker (%)	126 (84%)	76 (86%)
Calcium-channel blocker (%)	120 (80%)	70 (80%)
Centrally acting sympatholytic (%)	54 (36%)	33 (38%)
Vasodilator (%)	32 (21%)	16 (18%)
α-1 adrenergic blocker (%)	32 (21%)	19 (22%)
Data are mean (SD) or number (%). GFR=glomerular filtration rate. ACE=angiotensin-converting enzyme. *Baseline blood pressure values missing for three patients.		

Table 1: Characteristics of patients at baseline and 36 months

	Systolic blood pressure		Diastolic blood pressure	
	Mean (SD) pressure (mm Hg)	Mean (SD) change from baseline (95% CI)	Mean (SD) pressure (mm Hg)	Mean (SD) change from baseline (95% CI)
Baseline (n=150)	175.1 (15.9)	..	97.7 (14.3)	..
1 month (n=141)	156.1 (20.9)	-18.9 (19.2) (-22.1 to -15.7)	88.2 (13.7)	-9.4 (12.1) (-11.4 to -7.4)
6 months (n=144)	152.7 (21.1)	-22.0 (21.9) (-25.7 to -18.4)	87.3 (13.2)	-10.2 (13.6) (-12.4 to -7.9)
12 months (n=132)	149.1 (22.6)	-26.5 (21.5) (-30.2 to -22.8)	84.3 (13.5)	-13.5 (14.1) (-15.9 to -11.1)
24 months (n=105)	145.4 (21.7)	-28.9 (23.5) (-33.5 to -24.4)	82.9 (13.0)	-14.0 (15.2) (-16.9 to -11.1)
36 months (n=88)	142.6 (17.7)	-32.0 (17.6) (-35.7 to -28.2)	82.0 (11.0)	-14.4 (11.8) (-16.9 to -11.9)

Table 2: Changes in blood pressure from baseline at follow-up visits

used reductions of 20 mm Hg or more as a more rigorous measure. We also compared response to RDN in subgroups of patient, by age (older than 65 years vs 65 years and younger), renal function (eGFR higher than 60 vs 45–60 mL/min per 1.73 m²), and diabetes status (type 2 diabetes vs no diabetes).

Role of funding source

The sponsor designed the study in collaboration with the study investigators and was responsible for data collection and data analysis. The authors are responsible for data interpretation and writing of the report. The corresponding author had full access to all the study data and had final responsibility for the decision to submit.

Results

153 patients with treatment-resistant hypertension were enrolled in the Symplicity HTN-1 study, of whom 88 had complete data at 36 months (figure 1). Patients did not differ significantly at baseline and at 36 months for demographic characteristics, comorbidities, blood pressure, number of antihypertensive medications, and use of antihypertensive drugs (table 1).

Patients received an average of 4.0 ablations per artery (range 1.0–6.0). Intravenous narcotics and sedatives were used to manage pain during the delivery of radiofrequency energy. The mean total procedure time from initial femoral access to withdrawal of the catheter was 66.1 (SD 23.0) min.

There were no catheter or generator malfunctions and no major clinical complications associated with RDN. Complications were reported in four (2.6%) of 153 patients: one renal-artery dissection occurred during catheter delivery before the application of radiofrequency energy, and three patients had access-related complications in the groin. All events were treated without further sequelae. Eight (5.2%) patients had episodes of bradycardia associated with the ablation procedure, but

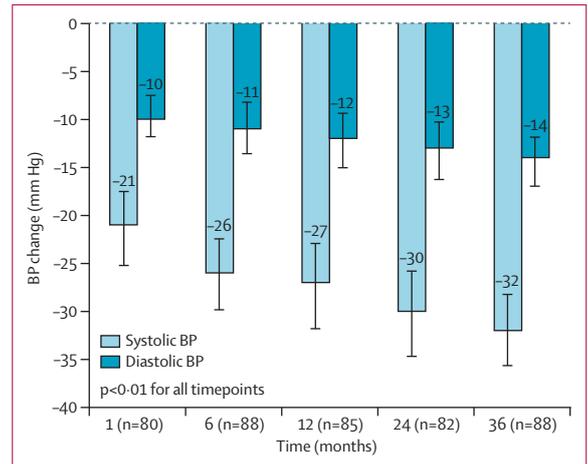


Figure 2: Change from baseline in office blood pressure in patients who completed 36 months of follow-up. Data are mean (error bars show 95% CI). BP=blood pressure.

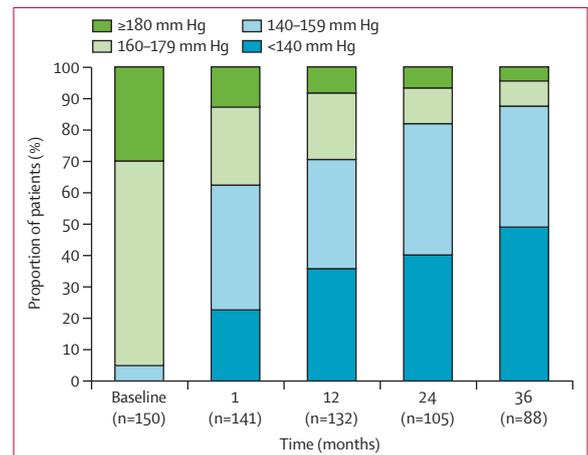


Figure 3: Distribution of changes in systolic blood pressure for all treated patients

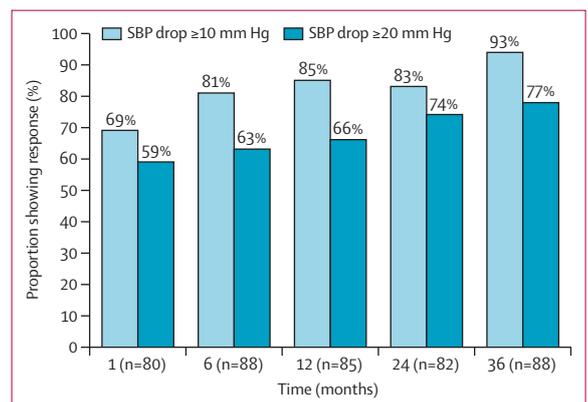


Figure 4: Proportions of patients assessed to 36 months who showed treatment responses at different timepoints in the study. Treatment response was defined as reductions of 10 mm Hg or more in systolic blood pressure, and reductions of 20 mm Hg or more were used as a more rigorous measure of response.

no episodes occurred after catheter removal, and no episodes of vasovagal syncope were reported. No patient experienced orthostatic hypotension after RDN.

Possible renal-artery stenosis was investigated in four (2.6%) patients. Two have been previously reported and included one progression of a pre-existing stenosis to 50% unrelated to RDN that was stented without further sequelae, and one was a moderate stenosis that was not haemodynamically relevant and did not require treatment. One patient had a new 70–80% stenosis of the left renal artery seen on duplex ultrasonography at 18 months, but it was found to be only 20–30% on follow-up angiography. The fourth case occurred in a patient with a history of peripheral artery disease, coronary artery disease, lymphoma, hypercholesterolaemia, and renal insufficiency who had presented with recurrent high blood pressure and developed an angiographically confirmed new 80% stenosis of the right renal artery 24 months after RDN. The stenosis was successfully stented.

Three patients died during follow-up, but all deaths were unrelated to the device or treatment: one myocardial infarction on day 3, one sudden cardiac death after the 6-month visit, and one cardiac and respiratory arrest after the 18-month visit. At 18 months one patient had a hypotensive event with acute renal failure related to severe left-leg cellulitis that required admission to hospital for antibiotics and intravenous fluids. The episode resolved and was deemed unrelated to RDN. Another patient was admitted to hospital with a hypotensive event associated with severe diarrhoea and dehydration. The episode resolved after treatment, with no sequelae and was also not attributed to RDN. One patient experienced orthostatic hypotension on two occasions (31 and 32 months after RDN) that were managed by discontinuation of an antihypertensive drug. 13 patients were admitted to hospital for hypertensive episodes, but all were treated and discharged without complications.

One patient presented at 24 months with acute renal failure and dehydration secondary to vomiting and diarrhoea after undergoing surgery for breast reconstruction. She was diagnosed as having acute tubular necrosis that was attributed to multiple antihypertensive agents, including hydrochlorothiazide, spironolactone, and aliskiren. Although she temporarily required haemodialysis at the time of the event, renal function recovered to normal (creatinine concentration in serum 71 $\mu\text{mol/L}$ and blood urea nitrogen 6.1 mmol/L).

Reductions in systolic and diastolic blood pressure that were seen by 12 months persisted to 36 months (table 2, figure 2). Heart rate did not change significantly from baseline to 36 months. The proportions of patients with systolic blood pressure of 180 mm Hg or higher decreased over the duration of the study, from 30% at baseline to 5% at 36 months. The proportion who achieved target systolic blood pressure values of less than 140 mm Hg increased significantly at all timepoints (figure 3). At 1 month after

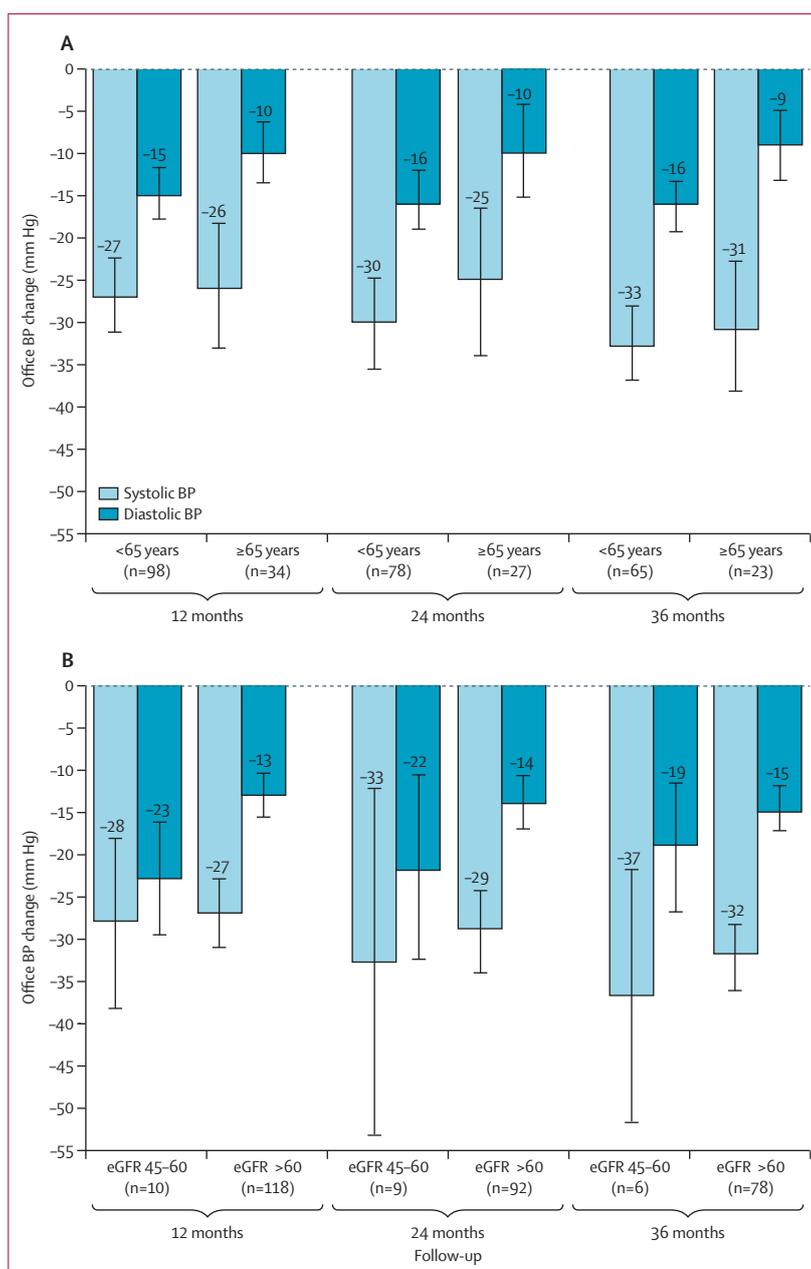


Figure 5: Change in office blood pressure by subgroup

(A) Age and (B) renal function, expressed as eGFR (mL/min per 1.73 m²). Data are mean (95% CI). BP=blood pressure. eGFR=estimated glomerular filtration rate.

RDN, 55 (69%) of 80 patients had reductions in systolic blood pressure of at least 10 mm Hg, which rose progressively to 82 (93%) of 88 at 36 months. Reductions of 20 mm Hg or more were seen in 68 (77%) of these 88 patients (figure 4).

Blood pressure responses at 12, 24, and 36 months did not differ significantly between age groups or by renal function (figure 5). Similarly, changes in blood pressure from baseline for patients with and without type 2 diabetes were similar (data not shown).

	Baseline (n=88)	6 months (n=86)	12 months (n=85)	24 months (n=80)	36 months (n=88)
Diuretic	82 (93%)	81 (94%)	80 (94%)	75 (94%)	84 (95%)
Aldosterone antagonist	25 (28%)	26 (30%)	26 (31%)	26 (33%)	29 (33%)
Angiotensin-receptor blocker	51 (69%)	59 (69%)	60 (71%)	58 (73%)	63 (72%)
ACE inhibitor	45 (51%)	46 (53%)	45 (53%)	43 (54%)	49 (56%)
Direct renin inhibitor	16 (18%)	15 (17%)	15 (18%)	14 (18%)	17 (19%)
β blocker	76 (86%)	74 (86%)	75 (88%)	72 (90%)	80 (91%)
Calcium-channel blocker	70 (80%)	71 (83%)	69 (81%)	65 (81%)	74 (84%)
Centrally acting sympatholytic	33 (38%)	33 (38%)	33 (39%)	32 (40%)	35 (40%)
Vasodilator	16 (18%)	16 (19%)	16 (19%)	15 (19%)	17 (19%)
α -1 adrenergic blocker	19 (22%)	18 (21%)	19 (22%)	19 (24%)	21 (24%)

ACE=angiotensin-converting enzyme.

Table 3: Medication use, by class, during the study

The average number of antihypertensive medications used at baseline was 5.1 (SD 1.7) for the overall population and 5.2 (1.7) for the patients assessed at 36 months. At 6 months after RDN the mean number of medications taken was 5.1 (1.6), at 24 months was 5.4 (1.7), and at 36 months was 5.6 (1.6). The proportions of medication use, by class, at 36 months were similar to those at baseline (table 3).

Concentrations of sodium, potassium, chloride, and glucose in serum were within normal limits at baseline and remained essentially unchanged throughout follow-up. Mean creatinine concentrations in serum increased progressively from 83.8 (SD 20.1) $\mu\text{mol/L}$ to 92.0 (32.5) $\mu\text{mol/L}$ over the 36 months ($p=0.05$). This change was associated with a corresponding decrease in mean eGFR, from 83.6 (SD 19.7) to 74.3 (28.0) mL/min per 1.73 m² ($p=0.05$). 28 patients experienced a fall in eGFR of more than 25% at one or more timepoints after RDN. These decreases were transient in 16 (57%) patients, with renal function having improved at the next follow-up visit. Of the 12 (43%) patients with decreased eGFR on more than one occasion, baseline eGFR values were higher than 100 mL/min per 1.73 m² in five, and in four of these five eGFR values never fell below 60 mL/min per 1.73 m² (eGFR was 57 mL/min per 1.73 m² at one visit for the fifth patient). Three patients had eGFR lower than 45 mL/min per 1.73 m².

Discussion

Percutaneous RDN with radiofrequency ablation is safe, effective, and leads to persistent reductions in blood pressure in patients with severe treatment-resistant hypertension. In most (93%) patients assessed at 36 months, initial blood-pressure responses were maintained, although the potential role of modifications to antihypertensive drug therapy is unclear. Advanced age, renal impairment, and diabetes status had no substantial effects on treatment response or time to treatment effect. We saw no evidence of major vascular or renal adverse events.

These long-term findings are of mechanistic interest and are clinically important. First, they indicate no functional re-innervation or any counter-regulatory mechanisms develop over time that could lessen the efficacy of the procedure. Additionally, although blood pressure did not drop immediately after RDN in all patients, the response rate rose with follow-up longer than 12 months. The response definition we selected for reduction in blood pressure (10 mm Hg or more systolic) is somewhat arbitrary, but we believe it represents a clinically relevant drop in blood pressure in patients with treatment-resistant hypertension. The potential benefit of RDN is further indicated by our finding that 68 (77%) of 88 patients had reductions of at least 20 mm Hg in systolic blood pressure at 36 months. A meta-analysis by Lewington and colleagues²¹ showed a doubling of cardiovascular mortality risk for each 20/10 mm Hg increase in blood pressure, which suggests that the reductions in our study would confer a meaningful benefit in patients whose blood pressures remain above the target range despite already having been substantially lowered. Furthermore, half of patients assessed at 36 months had blood pressures lower than 140 mm Hg. The reasons for delayed blood-pressure responses in some patients after RDN are unclear. We speculate that the timecourse of vascular remodelling, delay in resetting of the baroreflex, or changes in renin-angiotensin-system activity might contribute. Further research will be needed to address this question.

Whether or not specific subgroups of patients are particularly responsive to RDN is an important consideration. The numbers in this study alone are too small to undertake a meaningful analysis of potential predictors. In another study, however, of ambulatory and office blood pressures after RDN in patients with treatment-resistant hypertension, office systolic blood pressure at baseline was the only independent correlate of response.²² We assessed the effects of age, renal function, and diabetes status because some mechanistic differences between subgroups could plausibly affect blood pressure. We noted no significant differences between any subgroups and,

therefore, RDN might be beneficial in patients with treatment-resistant hypertension irrespective of these features. Nevertheless, efficacy will need to be confirmed in these and other subgroups in larger studies or through assessment of data collected in planned registry activities.

Concerns have been expressed about potential late vascular complications and biochemical disruption after RDN. The only vascular events were expected periprocedural local events related to femoral-artery haemostasis. These were all managed according to current medical practice without complications. Importantly, the rate of stenosis in late follow-up was very low. The incidence was consistent with rates in severely hypertensive populations and, although not thought to be related to RDN, cannot be entirely dissociated from the procedure.²³ We found no evidence of other vascular pathologies, which is consistent with animal studies in which minimum endothelial disruption, rapid re-endothelialisation in the renal artery, and no evidence of late stenosis were seen after RDN.²⁴

Although eGFR was well preserved overall, renal function worsened in some patients, possibly because of progression before hypertensive kidney disease, continued renal injury due to hypertension, or changes in diuretic use.²⁵ An analysis of 88 patients showed that percutaneous RDN did not negatively affect renal function, as measured by cystatin C eGFR.²⁶ RDN has been suggested as a useful approach to manage high-risk patients with hypertension and kidney disease.²⁷ The feasibility of using RDN in patients with chronic kidney disease and treatment-resistant hypertension was tested in 15 patients, in whom blood pressure was significantly reduced with no decline in eGFR over 12 months.²⁸ This is an active area of research and clearly requires longer follow-up of larger numbers of patients.

Our study has several limitations. The first is that only a subset of the original 153 patients consented to 36 months of follow-up and of these not all had full data available at the final follow-up visit. Nevertheless, although small, our analysis is among the largest and the only one so far to report follow-up to 36 months. Selection bias cannot be excluded, but long-term safety and durability of blood-pressure reduction at 36 months was seen in most patients.

We did not include a control group in this proof-of-concept trial and, therefore, issues of regression to the mean, placebo, and Hawthorne effects might affect the findings even late after the procedure. For example, blood pressure might drop simply because patients have improved adherence to lifestyle changes or medication regimens while being observed in a study. The long-term blood-pressure effects, however, differ from the expected disease course in patients with treatment-resistant hypertension, which is progressive worsening of blood-pressure control.^{6,29}

All patients might not have been receiving optimum medical treatment before RDN. Specifically, only 28% of

Panel: Research in context

Systematic review

Overactivity of the sympathetic nervous system plays an important part in the development of hypertension. Studies in normotensive individuals and hypertensive patients have shown increased rates of norepinephrine spillover from renal sympathetic nerves to plasma and increased rates of sympathetic nerve firing in hypertensive patients compared with normotensive individuals.³⁴ Since 1948, surgical sympathectomy, such as thoracolumbar sympathectomy, splanchnicectomy, and coeliac ganglionectomy, has led to substantial reductions in blood pressure, which provides clear evidence that the sympathetic nervous system is an important contributor to the pathogenesis of high blood pressure.^{35,36} Adverse effects, however, ultimately led to treatment with pharmacological options. Blood-pressure reductions have been reported after bilateral nephrectomy in patients with end-stage renal disease and in animal studies of renal sympathectomy.^{37,38} Radiofrequency ablation was developed to provide a minimally invasive, safe, and effective alternative treatment for severely hypertensive patients who are unresponsive to traditional pharmacological therapies. We searched PubMed for studies published between January, 2009, and January, 2013, on the use of this procedure with the terms “percutaneous renal denervation”, “sympathetic”, “clinical trial”, and “resistant hypertension”. We identified 14 clinical trials and one randomised trial of radiofrequency RDN for resistant hypertension^{12,13,17,22,26,28,39–46} that consistently show blood-pressure-lowering effects after this procedure in patients with resistant hypertension, but mostly up to 12 months. Longer-term follow-up has been limited to the previous Symplicity HTN-1 report in 18 patients at 24 months.¹² No notable safety concerns were raised in these trials, and in a trial done to assess renal haemodynamics and renal function after catheter-based RDN showed no adverse effects on glomerular filtration rate or renal artery structure in 88 patients after 6 months.²⁶

Interpretation

After follow-up of 36 months in patients with resistant hypertension who had previously not responded to multiple (mean five) antihypertensive medications, RDN was associated with a significant and sustained reduction in blood pressure without serious adverse effects. RDN seems to offer a novel and complementary approach for patients in whom pharmacological options seem exhausted. Adequately powered clinical trials with long-term follow-up are warranted to confirm these results in larger numbers of patients.

patients were receiving an aldosterone-receptor antagonist at baseline. These drugs are thought to be useful as add-on therapy in patients with treatment-resistant hypertension and their use should be considered before RDN.^{17,30,31} Caution should, however, be applied. In position papers from the European Society of Cardiology and the European Society of Hypertension, concerns have been raised about the long-term safety of aldosterone-receptor antagonists, especially in patients with reduced renal function and existing blockade of the renin-angiotensin system.^{20,32}

Another limitation is the lack of data to assess the effects of medication dose or drug changes within a medication class. These data were not collected beyond 12 months and, therefore, are not reported. Thus, we draw no conclusions about the potential effects of antihypertensive medication changes on outcomes or whether the procedure alters the ongoing need for certain antihypertensive medication. The role of antihypertensive medications or other interventions in the

lowering of blood pressure cannot be ruled out in these patients. Ambulatory monitoring of blood pressure was not included in the follow-up period.

Finally, these results were obtained in a select group of patients who met the study inclusion and exclusion criteria and were willing to participate in a research study and thus may not be broadly applicable to real-world hypertensive patients. The Global SYMPLICITY registry aims to accrue up to 5000 hypertensive patients from practice to better assess this issue.³³

Overactivity of the sympathetic nervous system plays an important role in the development of hypertension. RDN is a straightforward, minimally invasive percutaneous method of denervation (panel). We found that this procedure was associated with substantial lowering of blood pressure in patients with treatment-resistant hypertension, could be performed without any major safety issues, and that the effects persisted up to 36 months. The blood-pressure-lowering effects were not altered by age, baseline renal function, or diabetes status. We suggest that durable responses after RDN will eventually be possible in most if not all patients with treatment-resistant hypertension.

Contributors

HK was the principal investigator and wrote the paper. All authors participated in data collection and interpretation. MPS, MB, FM, KR-S, RK, and MDE provided critical revisions of the drafts. PAS contributed to the original hypothesis, trial execution, data analysis and interpretation, and manuscript writing and review.

Conflicts of interest

All authors received a research grant from Medtronic to undertake the Symplicity HTN-1 clinical trial. HK, MPS, and MDE have received honoraria and travel support from Medtronic. MPS and MDE are supported by an NHMRC Senior Research Fellowship. PAS receives royalties related to sales of the Medtronic renal denervation catheter, is a consultant for Medtronic, Abbott Ventures, and Rox Medical, and is an employee of Cibiem. MB and FM are supported by the Deutsche Forschungsgemeinschaft (KFO 196) and received speaker honoraria from Medtronic, St Jude Medical, and Cordis, and scientific support from Medtronic, St Jude Medical, Vessix, and Recor. FM is supported by Deutsche Hochdruckliga and Deutsche Gesellschaft für Kardiologie. KR-S is a consultant for Medtronic, BSC, CardioSonic, and Cibiem.

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