Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Symplicity HTN-2 Investigators

Summary

Background Activation of renal sympathetic nerves is key to pathogenesis of essential hypertension. We aimed to assess effectiveness and safety of catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension.

Methods In this multicentre, prospective, randomised trial, patients who had a baseline systolic blood pressure of 160 mm Hg or more (±150 mm Hg for patients with type 2 diabetes), despite taking three or more antihypertensive drugs, were randomly allocated in a one-to-one ratio to undergo renal denervation with previous treatment or to maintain previous treatment alone (control group) at 24 participating centres. Randomisation was done with sealed envelopes. Data analysers were not masked to treatment assignment. The primary effectiveness endpoint was change in seated office-based measurement of systolic blood pressure at 6 months. Primary analysis included all patients remaining in follow-up at 6 months. This trial is registered with ClinicalTrials.gov number NCT00888433.

Findings 106 (56%) of 190 patients screened for eligibility were randomly allocated to renal denervation (n=52) or control (n=54) groups between June 9, 2009, and Jan 15, 2010. 49 (94%) of 52 patients who underwent renal denervation and 51 (94%) of 54 controls were assessed for the primary endpoint at 6 months. Office-based blood pressure measurements in the renal denervation group reduced by 32/12 mm Hg (SD 23/11, baseline of 178/96 mm Hg, p<0.0001), whereas they did not differ from baseline in the control group (change of 1/0 mm Hg [21/10], baseline of 178/97 mm Hg, p=0.77 systolic and p=0.83 diastolic). Between-group differences in blood pressure at 6 months were 33/12 mm Hg (p<0.0001). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 18 (35%) of 51 controls (p<0.0001). We noted no serious procedure-related or device-related complications and occurrence of adverse events did not differ between groups; one patient who had renal denervation had possible progression of an underlying atherosclerotic lesion, but required no treatment.

Interpretation Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients.

Funding Ardian.
Symplicity HTN-2 was an international, multicentre, randomised study of the safety and effectiveness of renal denervation in patients with treatment-resistant hypertension. Patients aged 18–85 years with a systolic blood pressure of 160 mm Hg or more (≥150 mm Hg in patients with type 2 diabetes), despite compliance with three or more antihypertensive drugs, were eligible for inclusion. Exclusion criteria included an estimated glomerular filtration rate (eGFR; based on the Modification of Diet in Renal Disease criteria\(^1\)) of less than 45 mL/min per 1.73 m\(^2\), type 1 diabetes, contraindications to MRI, substantial stenotic valvular heart disease, pregnancy or planned pregnancy during the study, and a history of myocardial infarction, unstable angina, or cerebrovascular accident in the previous 6 months. Full details of inclusion and exclusion criteria are detailed in the online protocol.

Screening was done at 24 centres in Europe, Australia, and New Zealand; 16 (67%) were hypertension centres of excellence as designated by the European Society of Hypertension or by one of the European national hypertension societies. As part of the screening process, patients were required to record twice daily automated home blood pressure measurements and to document drug compliance for 2 weeks. Patients whose blood pressure was below the enrolment criteria when they returned to the clinic for blood-pressure measurement were excluded. Before randomisation, patients underwent renal artery anatomical screening with renal duplex, computed tomography, MRI, or renal angiography to confirm anatomical eligibility. Patients with haemodynamically significant renal artery stenosis, previous renal artery intervention, or renal artery anatomy that precluded treatment (defined as <4 mm diameter, <20 mm length, or more than one main renal arteries) were excluded. We recorded baseline serum creatinine, cystatin C, spot urine albumin-to-creatinine ratio, and 24-h ambulatory blood pressure before randomisation. The study was approved by the ethics committees at every participating site, and all patients provided written informed consent.

**Methods**

**Study design and patients**

Symplicity HTN-2 protocol see http://www.ardian.com/symplicityHTN2.pdf
Office-based blood pressure measurements were taken with an automatic oscillometric Omron HEM-705 monitor (Omron Healthcare, Vernon Hills, IL, USA) with a printer for documentation. Blood pressure was measured according to protocol-specified guidelines based on Standard Joint National Committee VII, European Society of Cardiology, and European Society of Hypertension recommendations. We used averages of triplicate measurements in our analysis.

For assessments of blood pressure at home, we provided patients with an automatic Omron HEM-705 monitor to record 2 weeks of daily seated blood pressure, three times in the morning and three times in the evening. We used averages of the home measurements at baseline and 6-month visits for analysis.

We measured 24-h ambulatory blood pressure with an oscillometric Spacelabs 90207 monitor (Spacelabs Healthcare, Issaquwa, WA, USA) with readings taken every 15 mins in daytime and every 30 mins at night-time, and calculated overall 24-h averages for every patient. Only ambulatory blood-pressure assessments that met European Society of Cardiology and European Society of Hypertension guidelines (with more than 70% of daytime and night-time readings) were regarded as technically sufficient for inclusion in the analysis.

Endpoints

The primary effectiveness endpoint was between-group change in average office-based measurements of systolic blood pressure from baseline to 6 months after randomisation. Secondary endpoints were acute procedural safety, chronic procedural safety (reduction of randomisation. Secondary endpoints were acute blood pressure from baseline to 6 months after change in average office-based measurements of systolic blood pressure, and change in home-based blood-pressure measurements. The principal investigator (MDE) measured overall 24-h averages for every patient. Only ambulatory blood-pressure assessments that met European Society of Cardiology and European Society of Hypertension guidelines (with more than 70% of daytime and night-time readings) were regarded as technically sufficient for inclusion in the analysis.

Statistical analysis

With a sample of 50 patients per group, we calculated that the study would have at least 80% power to show benefit of renal denervation over control intervention, with respect to the primary endpoint, assuming at least a 12 mm Hg difference between groups and a 21 mm Hg standard deviation of the change in systolic blood pressure from baseline to 6 months. All analyses were done with data for all patients at randomisation minus those lost to follow-up. We assessed continuous variables between groups, including the primary endpoint, with Student’s two-sample t test unless otherwise specified. We compared categorical variables with Fisher’s exact test. For within-group paired data, a paired t test was used unless otherwise specified. A two-sided alpha level of 0.05 was used for all superiority testing. All statistical analyses were done with SAS version 9.2.

This trial is registered with ClinicalTrials.gov, number NCT00888433.

Role of the funding source

The study was designed by MDE and advisers, including local investigators, and the sponsor (Ardian). Data were
Figure 2: Paired changes in office-based measurements of systolic and diastolic blood pressures at 1 month, 3 months, and 6 months for renal denervation and control groups

Error bars are 95% CI. Multivariable stepwise regression analysis of baseline characteristics, drugs, and treatment assignment was examined for predictors of increased 6-month systolic blood-pressure response; only variables with *p<0·05 remaining in the final model. Multivariable analysis of baseline characteristics showed that assignment to the renal denervation group (p<0·0001), higher baseline systolic blood pressure (p<0·0001), and slower heart rate (p<0·004) predicted increased 6-month blood-pressure reduction. SBP=systolic blood pressure. DBP=diastolic blood pressure.

*p=0·002. †p=0·005.

Figure 3: Proportion of patients in the renal denervation and control groups that at 6 months had no decrease in systolic blood pressure, a 10 mm Hg or greater decrease in SBP, or achieved a SBP of less than 140 mm Hg

SBP=systolic blood pressure.

Results

From June 9, 2009, to Jan 15, 2010, 106 (56%) of 190 patients screened were eligible for study inclusion and were randomly allocated to renal denervation or control groups (figure 1). Patients in the two study groups did not differ by age, sex, baseline systolic or diastolic blood pressure, race, most comorbidities, and reported duration spent on antihypertensive therapy (table 1). Patients in the renal denervation group had a lower baseline renal function than did the control group, as assessed by eGFR (77 mL/min per 1·73 m² vs 86 mL/min per 1·73 m²; p=0·013), but baseline cystatin C concentrations did not differ between groups. Patients in both groups were taking much the same numbers and types of antihypertensive drugs (table 1). Diuretics, including aldosterone antagonists, were used in more than 89% of patients.

Of 106 patients who were randomly allocated to intervention or control groups, we analysed the primary endpoint for 49 patients who underwent renal denervation and 51 controls. Three patients in each group were lost to follow-up because of withdrawal of consent or missed visits (figure 1). 6 months after randomisation, office-based measurements of blood pressure in the renal denervation group were reduced by 32/12 mm Hg (SD 23/11) from 178/96 mm Hg (18/16) at baseline (p=0·0001 for systolic and diastolic blood pressure). By contrast, office-based measurements of blood pressure in the control group changed by 1/0 mm Hg (SD 21/10) from 178/97 mm Hg (17/16) at baseline (p=0·77 for systolic blood pressure, p=0·83 for diastolic blood pressure; figure 2). Therefore, a 33/11 mm Hg reduction in blood pressure was noted in the renal denervation group compared with the control group (p<0·0001 for systolic and diastolic blood pressure) during 6-month follow-up.

We noted much the same changes in home-based blood pressure measurements. Blood pressure fell by 20/12 mm Hg (SD 17/11) in 32 patients in the renal denervation group, compared with a rise of 2/0 mm Hg (13/7) in 40 controls. The absolute difference between groups was 22/12 mm Hg (p=0·0001 for systolic and diastolic blood pressure).

Average blood pressure at 6 months derived from 24-h ambulatory blood-pressure monitoring changed in parallel with office-based and home-based systolic blood-pressure measurements. 24-h ambulatory blood-pressure recordings were available for 20 patients in the renal denervation group, showing a mean decrease of 11/7 mm Hg (SD 15/11; p=0·006 for systolic blood pressure change, p=0·014 for diastolic blood pressure change) from baseline to 6 months, whereas averages did not change for 25 patients in the control group (–3/–1 mm Hg [19/12]; p=0·51 for systolic, p=0·75 for diastolic).

Figure 3 shows the proportions of patients achieving defined thresholds of systolic blood pressure reduction at 6 months. More patients who underwent renal denervation had reductions in systolic blood pressure than did controls, with reductions of 10 mm Hg or greater more common, as was achievement of a target of less than 140 mm Hg (all p<0·0001; figure 3).

Ten (20%) of 49 patients who underwent renal denervation had drug reductions prior to the 6-month follow-up, compared with three (6%) of 51 controls monitored, collected, and managed by the sponsor. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Four (8%) of 49 patients who underwent renal denervation had drug increases prior to the 6-month follow-up, as did six (12%) of 51 controls (p=0.74).

In a subanalysis that censored all data after drug increases, we noted blood pressure reduction after 6 months of 31/12 mm Hg (SD 22/11) in patients who underwent renal denervation (<0·0001 for systolic and diastolic blood pressures) and a change of 0/–1 (20/10) in controls (p=0·90 for systolic blood pressure, p=0·61 for diastolic blood pressure). The absolute difference between groups was 31/11 mm Hg (p<0·0001 for systolic and diastolic blood pressures) for patients who had no drug increases.

There were no serious complications related to the device or procedure. Minor periprocedural events requiring treatment and possibly related to the procedure consisted of one femoral artery pseudoaneurysm that was treated with manual compression, one post-procedural drop in blood pressure resulting in a reduction in antihypertensive drugs, one urinary tract infection, one extended hospital admission for assessment of paraplegia, and one case of back pain that was treated with analgesics and resolved after 1 month. Seven (13%) of 52 patients who underwent renal denervation had transient intraprocedural bradycardia requiring atropine; none had any sequelae.

Renal function, as assessed by serum creatinine, eGFR, and cystatin C concentrations were unchanged from baseline in both groups at 6 months (table 2). During 6-month follow-up, no patient had a decrease of more than 50% in eGFR, although two patients who underwent renal denervation and three controls had a more than 25% decrease in eGFR.

We calculated a paired baseline and 6-month urine albumin-to-creatinine ratio for 38 patients who underwent renal denervation and 37 controls. The median changes in urine albumin-to-creatinine ratio at 6 months was −3 mg/g (range −1089 to 76) for patients who underwent renal denervation and 1 mg/g (range −538 to 227) for controls (p for significance=0·26; Wilcoxon test).

Of 49 patients who underwent renal denervation and were assessed at 6 months, 43 had renal imaging at 6 months (37 renal duplex imaging, five MRI, and five CT angiography). One patient had a possible progression of an underlying atherosclerotic lesion, but intervention was not needed. The stenosis was not at a location where radiofrequency energy was delivered during the procedure.

For the composite cardiovascular endpoint that was assessed at 6 months, we identified five hospital admissions for hypertensive emergency that were unrelated to non-adherence or non-persistence with drugs (three patients who had renal denervation and two controls); no other composite cardiovascular events occurred.

Additional serious adverse events in patients who had renal denervation requiring hospital admission were one patient with nausea and oedema possibly related to underlying hypertension, one patient with hypertension crisis after abrupt stopping of clonidine, one transient ischaemic attack, one hypotensive episode resulting in a reduction of antihypertensive drugs, and one patient received a coronary stent for angina. Two controls had transient ischaemic attacks, and one received a coronary stent for angina.

Discussion
Our study supports previous uncontrolled investigations that showed a significant reduction in blood pressure can be achieved with catheter-based renal denervation in patients whose essential hypertension was uncontrolled despite treatment with three or more antihypertensive drugs (panel). This benefit was evident by the concordance of measurements of office blood pressure, home blood pressure, and 24-h ambulatory blood-pressure monitoring. Measurements made in parallel in the comparator group of patients randomly assigned to continue antihypertensive drug only, without renal denervation, showed no fall in blood pressure over the 6-month follow-up.

In our study, renal denervation led to a reduction in blood pressure of 10 mm Hg or more in 84% of treated patients. Furthermore, the renal denervation procedure was done without any major adverse effects. Imaging of renal arteries for damage showed no evidence of renal artery stenosis or aneurysmal dilatation during the 6-month follow-up. In one patient, possible progression of an underlying atherosclerotic lesion was identified, but required no further intervention.

We showed no changes in measured renal function with denervation, suggesting that the procedure itself and associated haemodynamic changes have no adverse...
effects on the kidneys. Importantly, in renal denervation patients with eGFR of 45–60 mL/min per m², there was no evidence of worsening function, suggesting that this procedure is safe even in those with mild-to-moderately impaired renal function. The reduction of blood pressure alone would be expected to beneficially affect renal impairment. Analysis of large populations, followed up for more than 6 months might show renal preservation as a result of enhanced blood pressure control and probably reduced sympathetic outflow to the kidney.

Controls showed no Hawthorne effect after random allocation. Systolic blood pressures of 36 patients reduced to lower than 160 mm Hg during the 2-week screening period (before qualification blood pressure was measured), which was possibly because of a change to their clinical behaviours after enrolment in the trial. Exclusion of these patients from the study led to a control population whose blood pressure, on average, did not change for the 6-month follow-up.

Testing of this novel treatment technique has its theoretical basis in the previous demonstration of blood-pressure reduction with surgical renal denervation in laboratory models of hypertension, and the finding that the sympathetic outflow to the kidneys is commonly activated in patients with essential hypertension.

Catheter-based renal denervation selectively reduces renal sympathetic efferent activity, which is shown by reduction in renal noradrenaline spillover measurements and is accompanied by an increase in renal blood flow and reduction in plasma renin activity. Reduction of the kidney’s contribution to central sympathetic outflow is probably also important. Renal afferent nerve projections to the hypothalamus can stimulate sympathetic outflow, and hence cause rises of blood pressure and systemic vascular resistance. This CNS input from renal afferent fibres is crucial for production of the sympathetic activation and hypertension found in patients with end-stage renal disease, and is reduced after therapeutic nephrectomy. Renal denervation reduces whole-body noradrenaline spillover and reduces sympathetic nerve traffic to the skeletal muscle vasculature, as measured by muscle sympathetic nerve activity after renal sympathetic denervation. Thus, ablation of afferent and efferent renal nerves in patients with treatment-resistant hypertension probably contributes materially to the recorded reductions in blood pressure.

One problem is that sympathetic nerve regrowth might mitigate the treatment effect. Although nerve fibres might grow to transplanted organs, recovery of renal sympathetic function in man has not been shown.

Furthermore, afferent somatic fibres might never re-establish function as suggested by the absence of angina following cardiac transplantation. In pilot studies, no loss of antihypertensive response was evident with follow up of 2 years.

We anticipate that future trials will address the effectiveness of renal denervation in mild forms of essential hypertension, and in other diseases in which the renal sympathetic outflow was activated, such as cardiac failure, chronic kidney disease, and cirrhosis with ascites.

Catheter-based renal denervation, done in a multicentre, randomised trial in patients with treatment-resistant essential hypertension, resulted in significant reductions in blood pressure. The magnitude of blood-pressure reduction can be predicted to affect the development of hypertension-related diseases and mortality. The technique was applied without major complications. This therapeutic innovation, based on the described neural pathophysiology of essential hypertension, affirms the crucial relevance of renal nerves in the maintenance of raised blood pressure in patients with hypertension. Catheter-based renal denervation is very beneficial for patients with treatment-resistant essential hypertension.

**Panel: Research in context**

**Systematic review**
Catheter-based renal denervation for treatment of hypertension is a new technique for which we identified one observational multicentre safety and proof-of-principle study and one case report in a search of the PubMed database.

**Interpretation**
Our randomised, controlled trial confirms the role of renal sympathetic nerves in essential hypertension and validates a new therapy for treatment-resistant hypertension. The magnitude of blood-pressure reduction can be predicted to have a meaningful effect on cardiovascular mortality and numerous known sequelae of hypertension.
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