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H Sievert, J Schofer, J Ormiston, U C Hoppe, I T Meredith, D L Walters, M Azizi, J Diaz-Cartelle

### ► To cite this version:

H Sievert, J Schofer, J Ormiston, U C Hoppe, I T Meredith, et al.. Bipolar radiofrequency renal denervation with the Vessix catheter in patients with resistant hypertension: 2-year results from the REDUCE-HTN trial. *Journal of Human Hypertension*, 2017, 31 (5), pp.366-368. 10.1038/jhh.2016.82 . hal-04049276

**HAL Id: hal-04049276**

<https://hal.science/hal-04049276v1>

Submitted on 28 Apr 2023

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## RESEARCH LETTER

## Bipolar radiofrequency renal denervation with the Vessix catheter in patients with resistant hypertension: 2-year results from the REDUCE-HTN trial

*Journal of Human Hypertension* (2017) 31, 366–368; doi:10.1038/jhh.2016.82; published online 12 January 2017

**One hundred forty-six hypertensive patients were treated with bipolar radiofrequency balloon-based renal denervation. Significant office blood pressure (BP) reductions were sustained through 2 years of follow-up, with few patients experiencing related serious adverse events. Although confirmatory randomised controlled trials with designs to minimise confounding factors are needed, long-term follow-up after renal denervation continues to support procedure safety and suggests that it may have a lowering effect on BP.**

Between 5 and 30% of hypertensive adults have resistant hypertension, which confers a high cardiovascular risk.<sup>1,2</sup> Percutaneous catheter-based renal denervation has been proposed as an adjunctive therapy for blood pressure control in these patients. Several observational studies have shown favourable short-term (that is, 6 month) effects of radiofrequency renal denervation on office BP but results are more controversial in randomised controlled trials, especially when assessing the BP lowering effects with ambulatory BP monitoring.<sup>3</sup> The reasons for this controversy have been largely discussed.<sup>4</sup> Moreover, the long-term persistence of the BP lowering effect of renal denervation remains to be demonstrated, taking into account possible renal nerve regrowth which has been reported in animal models.<sup>5,6</sup> We report here the 2-year BP effects of renal denervation with the Vessix Renal Denervation System (Boston Scientific, Marlborough, MA, USA).

Patients in the REDUCE-HTN study ( $N = 146$ ) were followed for 2 years after receiving treatment with the Vessix Renal Denervation System. Methodological details of the REDUCE-HTN study have been described previously (clinicaltrials.gov identifier NCT01541865).<sup>7</sup> In brief, patients had seated office BP  $\geq 160/90$  mm Hg at baseline despite being on a stable regimen including at least 3 antihypertensive drugs at maximally tolerated doses for at least 2 weeks before enrolment. Renal artery anatomy requirements included length  $\geq 15$  mm and diameter of  $\geq 3.5$  mm and  $\leq 7.0$  mm for each kidney; patients with accessory renal arteries were allowed. All patients provided written informed consent. Eligible patients had radiofrequency energy ( $< 1$  W per electrode) delivered intra-arterially via balloon-based bipolar electrodes. Previously reported 6-month study results showed significant reductions in office-based and 24-h ambulatory BP values, stable mean estimated glomerular filtration rate (eGFR), and one patient with renal artery stenosis requiring an intervention.<sup>7</sup>

The 12- and 24-month follow-up visits were completed by 138 and 124 patients, respectively. At 24 months, 45.2% of patients continued to take the same number of antihypertensive medications as at baseline; 21.9% had reduced their regimen by one or more medications while 20.5% had added one, and 8.2% had added two antihypertensive medications.

Mean baseline office BP was  $182.4 \pm 18.4/100.2 \pm 14.0$  mm Hg. At 12 and 24 months, both office systolic and diastolic BP were significantly lower than baseline values at  $159.0 \pm 25.7/89.7 \pm$

$16.0$  mm Hg and  $154.2 \pm 23.4/88.8 \pm 17.1$  mm Hg, respectively (Figure 1). Office systolic BP was reduced by at least 5 mmHg, at least 10 mmHg and at least 15 mmHg for 85, 77 and 72% of patients at 24 months, respectively. Office systolic BP  $< 140$  mmHg was reached by 19% of patients at 12 months and 26% of patients at 24 months. Significant office BP reductions were also observed for the subgroup of 24 patients with treated accessory renal arteries. Their mean baseline BP of  $178.0 \pm 16.1/99.1 \pm 11.2$  mmHg was reduced to  $155.1 \pm 26.0/85.1 \pm 15.3$  mmHg at 12 months ( $n = 23$ ) and  $147.6 \pm 20.5/84.1 \pm 14.8$  mmHg at 24 months ( $n = 19$ ), for a final change of  $-28.7 \pm 21.0/-13.7 \pm 11.8$  mmHg ( $P < 0.0005$  for both systolic and diastolic values at each time point versus baseline).

Twenty-four hour ambulatory BP was also significantly reduced, from a mean of  $152.9 \pm 15.2/87.5 \pm 13.3$  mmHg at baseline to  $145.7 \pm 14.7/82.8 \pm 12.6$  mmHg at 12 months ( $n = 86$ ), for a reduction of  $8.5 \pm 13.1/5.4 \pm 7.8$  mmHg ( $n = 69$ ). Twenty-four hour ambulatory systolic BP  $< 130$  mmHg was reached by 9% of patients at 12 months (ambulatory BP monitoring was not conducted at 24 months).

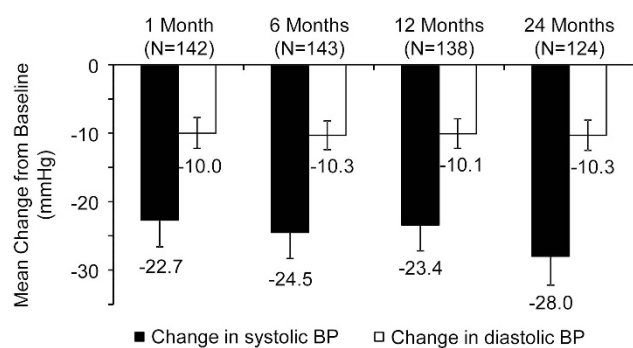
Safety measures included renal function and renal artery patency assessments and adverse event monitoring adjudicated by a Data Safety Monitoring Board.

At 24 months, 16 patients (13.2%) had a reduction in eGFR  $> 25\%$  from baseline. Only one of these 16 patients had a renal-related adverse event that was adjudicated as possibly related to the device; this non-serious occurrence of 'high urea and low eGFR' was conservatively adjudicated as possibly related to the device due to lack of recent renal artery imaging to rule out stenosis.

At baseline, mean eGFR was  $82.7 \pm 22.5$  ml min<sup>-1</sup> per 1.73 m<sup>2</sup> (range 36.0–175.9 ml min<sup>-1</sup> per 1.73 m<sup>2</sup>, median 80.5 ml min<sup>-1</sup> per 1.73 m<sup>2</sup>, interquartile range (IQR) 68.4–92.0 ml min<sup>-1</sup> per 1.73 m<sup>2</sup>); 28% of patients had type 2 diabetes. The mean change in eGFR overall was  $-8.1 \pm 18.6$  ml min<sup>-1</sup> per 1.73 m<sup>2</sup> at 24 months ( $N = 121$ ). The change was greatest among those with higher eGFR at baseline: patients with baseline eGFR  $\geq 90$  ml min<sup>-1</sup> had a mean percent change in eGFR of  $-8.2\%$  at 12 months and  $-18.2\%$  at 24 months compared with baseline, whereas those with eGFR  $< 90$  ml min<sup>-1</sup> at baseline had a change of  $+2.9\%$  at 12 months and  $-1.5\%$  at 24 months. Consistent with this observation, 14 of the 16 patients with a clinically significant decrease in eGFR at 24 months still had values  $\geq 50$  ml min<sup>-1</sup>.

The eGFR changes observed in the REDUCE-HTN study cannot be clearly explained because renal denervation affects sympathetic tone and BP, both of which may independently affect renal function.<sup>8</sup> An inverse correlation between sympathetic tone and eGFR has been reported previously.<sup>9</sup> Other factors such as comorbid disease and persistent hypertension despite a lowering of BP in individual patients also complicate the interpretation of these observations. More studies are needed to determine whether renal denervation, like sympatholytic drugs, may slow progression of renal disease.

Seven patients had renal artery stenosis detected during the study period, only one of whom required angioplasty and stenting.<sup>7</sup> Four of these seven patients had stenosis identified



**Figure 1.** Office BP reductions through 24 months. Error bars represent 95% confidence bounds.  $P < 0.0001$  for each time point vs baseline.

within 6 months of the procedure and were described previously.<sup>7</sup> Of the remaining 3 patients, one had stenosis identified via computed tomography angiography undertaken after the protocol-mandated duplex ultrasound at the 6-month visit was not interpretable, but the patient did not report any stenosis-related symptoms. The second had progression of a baseline stenosis (41% at baseline to 51% ~10 months post-procedure) and the third had a small dissection observed during angiography at ~11 months post-procedure; these factors could have increased their susceptibility to stenosis. None of these three patients required treatment for the observed stenosis during the study period.

Through adverse event monitoring and adjudication, a total of eight serious adverse events (in five patients) occurring between 6 and 24 months post-procedure were identified as possibly related to the renal denervation procedure and/or device. All of these events were hypertensive emergencies and the Data Safety Monitoring Board conservatively adjudicated each as possibly related because recent renal artery imaging was not available to rule out renal artery stenosis. In one case, a possible issue with antihypertensive medication compliance could not be ruled out.

Study limitations are similar to those of other initial studies of renal denervation<sup>10,11</sup> and include the non-blinded, single-arm design, required (but not strictly monitored) compliance with current antihypertensive medications throughout the study period, and reliance on office BP to determine patient eligibility and as the primary efficacy measure.

Previous studies of radiofrequency renal denervation that reported longer-term BP results described magnitudes of reduction at 24 months similar to those observed in the REDUCE-HTN study;<sup>10,12</sup> however, these studies share many of the major limitations noted above. These study design shortcomings prohibit a firm conclusion regarding the effect of the renal denervation procedure on BP. Subsequent discussion has identified trial designs for minimising the potential confounding effects associated with medication compliance, patient selection and other biases in future studies.<sup>4,13</sup> In addition, the more recent DENERHTN trial overcame some of these study design factors.<sup>14</sup> In this open randomised study with blinded endpoint evaluation, patients with confirmed resistant hypertension who received standardised stepped-care antihypertensive treatment in addition to single-electrode radiofrequency renal denervation had a significantly greater decrease in daytime ambulatory systolic BP at 6 months than patients who received the same standardised antihypertensive treatment alone. These encouraging short-term results provide additional justification for conducting additional trials with designs intended to manage many of the confounding factors associated with study of renal denervation for treating uncontrolled hypertension.

The REDUCE-HTN study suggests persistent BP reductions in patients with resistant hypertension who were treated with the Vessix Renal Denervation System. The acute<sup>7</sup> and long-term safety results suggest a low-risk safety profile for appropriately selected patients.

## CONFLICT OF INTEREST

HS has received study honoraria, travel expenses and consulting fees from Abbott, Acoredis, Atrium, Biosense Webster, Bioventrix, Boston Scientific, Carag, Cardiac Dimensions, CardioKinetix, Celonova, CGuard, Coherex, Comed BV, Contego, CSI, CVRx, ev3, FlowCardia, Gardia, Gore, GTIMD Medical, Guided Delivery Systems, Hemoteq, InspireMD, Kona Medical, Lumen Biomedical, Lifetech, Medtronic, Occlutech, pfm Medical, Recor, SenteHeart, Svelte Medical Systems, Terumo, Trivascular, Valtech, Vascular Dynamics, Venus Medical and Veryan; and has stock options with CardioKinetix, Access Closure, Coherex, SMT. JS received speakers' honoraria from Boston Scientific Corporation. UCH has received grant support and honoraria from Boston Scientific Corporation/Vessix Vascular, grant support and consultancy fees from Medtronic, Inc., and consultancy fees from St Jude Medical. IM received honoraria and consulting fees from Boston Scientific. MA has received honoraria for advisory board meetings from Vessix, Boston Scientific Corporation, and Cordis and speakers' honoraria from Cordis and CVRx. JD-C is an employee of Boston Scientific Corporation and holds stock in the company. The remaining authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

This study was supported by Vessix Vascular, Laguna Hills, CA, USA and Boston Scientific Corporation, Marlborough, MA, USA.

H Sievert<sup>1,2</sup>, J Schofer<sup>3</sup>, J Ormiston<sup>4</sup>, UC Hoppe<sup>5</sup>, IT Meredith<sup>6</sup>, DL Walters<sup>7</sup>, M Azizi<sup>8,9</sup> and J Diaz-Cartelle<sup>10</sup> on behalf of the REDUCE-HTN Investigators

<sup>1</sup>Cardiovascular Center Frankfurt CVC, Frankfurt, Germany;

<sup>2</sup>Neuroscience and Vascular Simulation Unit, Anglia Ruskin University, Chelmsford, UK;

<sup>3</sup>Department of Cardiology, Universitäres Herz- und Gefäßzentrum, Hamburg, Germany;

<sup>4</sup>Mercy Angiography, Auckland, New Zealand;

<sup>5</sup>Department of Internal Medicine II, Paracelsus Medical University, Salzburg, Austria;

<sup>6</sup>MonashHEART, Monash Health, Monash University, Melbourne, Australia;

<sup>7</sup>Department of Cardiology, The Prince Charles Hospital, Brisbane, Australia;

<sup>8</sup>APHP, Hôpital Européen Georges Pompidou, Hypertension Unit, Paris, France;

<sup>9</sup>Department of Vascular Medicine and Hypertension, Paris Descartes University, Paris, France and

<sup>10</sup>Peripheral Interventions, Boston Scientific Corporation, Marlborough, MA, USA

E-mail: horstsievertmd@aol.com

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