

# Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle clinical study



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## Summary

**Background** Carotid baroreflex activation lowers blood pressure and might have potential application for the treatment of resistant hypertension. We did a proof-of-principle trial with a novel endovascular baroreceptor amplification device, MobiusHD (Vascular Dynamics, Mountain View, CA, USA), in patients with resistant hypertension.

**Methods** CALM-FIM\_EUR was a prospective, first-in-human, open-label study done at six European centres. Eligible patients were adults with resistant hypertension (office systolic blood pressure  $\geq 160$  mm Hg despite taking at least three antihypertensive agents, including a diuretic). MobiusHD devices were implanted unilaterally in the internal carotid artery. The primary endpoint was the incidence of serious adverse events at 6 months. Secondary endpoints included changes in office and 24 h ambulatory blood pressure. This trial is registered with ClinicalTrials.gov, number NCT01911897.

**Findings** Between December, 2013, and February, 2016, 30 patients were enrolled and underwent successful implantation. Mean age was 52 years (SD 12), 15 patients (50%) were men, and mean antihypertensive use was 4.4 drugs (1.4). Mean office blood pressure was 184/109 mm Hg (18/14) at baseline and was reduced by 24/12 mm Hg (13–34/6–18) at 6 months ( $p=0.0003$  for systolic and  $p=0.0001$  diastolic blood pressure). Mean baseline 24 h ambulatory blood pressure was 166/100 mm Hg (17/14) at baseline and was reduced by 21/12 mm Hg (14–29/7–16) at 6 months ( $p<0.0001$  for systolic and diastolic blood pressure). Five serious adverse events had occurred in four patients (13%) at 6 months: hypotension ( $n=2$ ), worsening hypertension ( $n=1$ ), intermittent claudication ( $n=1$ ) and wound infection ( $n=1$ ).

**Interpretation** In patients with resistant hypertension, endovascular baroreceptor amplification with the MobiusHD device substantially lowered blood pressure with an acceptable safety profile. Randomised, double-blind, sham-controlled trials are warranted to investigate the use of this treatment further.

**Funding** Vascular Dynamics.

## Introduction

Approximately 10% of all treated hypertensive patients have resistant hypertension, defined as uncontrolled blood pressure despite treatment with three or more drugs, including a diuretic. Patients with resistant hypertension have increased risks of cardiovascular and renal complications and all-cause mortality compared with patients who have controlled hypertension.<sup>1,2</sup> Although additional drug therapies are effective,<sup>3</sup> not all patients can tolerate these medications long term. Several devices have thus been developed for the treatment of resistant hypertension, but none has so far been adopted for routine care because safety or efficacy data from testing in sham-controlled trials are needed.<sup>4</sup>

Stimulation of the carotid baroreflex pathway offers the potential to treat resistant hypertension effectively. Amplifying the signal sensed by the carotid baroreceptors results in inhibition of sympathetic outflow, which results in a decrease in blood pressure.<sup>5</sup> An implantable pulse generator that directly stimulates the carotid baroreceptors lowered blood pressure in a randomised clinical trial,<sup>6</sup> but implants required an invasive surgical procedure, were associated with side-effects, and battery

replacement was needed every few years.<sup>7</sup> An alternative, less invasive approach to achieve baroreceptor amplification has been developed. The MobiusHD (Vascular Dynamics, Mountain View, CA, USA) is an endovascular implant that reshapes the carotid sinus (figure 1). Increased wall strain in the carotid sinus is sensed by the baroreceptors as increased pressure, and they respond by inhibiting sympathetic outflow, thereby reducing blood pressure.<sup>8</sup>

The concept of endovascular baroreceptor activation is built on coupling known stress-strain relations with the fundamental principles of pulsatile stretch-induced carotid baroreceptor activation. Simulation of fluid-structure interaction in different carotid artery models indicated that the MobiusHD would induce a maximum increase of 7.5% in both circumferential and longitudinal wall stretch, and a maximum increase of 54.0% in von Mises arterial stress at the level of the carotid sinus, which suggested baroreceptors would be activated.<sup>9</sup> In an acute study in dogs, the device induced a more pronounced increase in carotid sinus nerve activity than a standard carotid stent. Blood pressure was reduced by around 50/30 mm Hg, which was sustained for 6 h after

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### Research in context

#### Evidence before this study

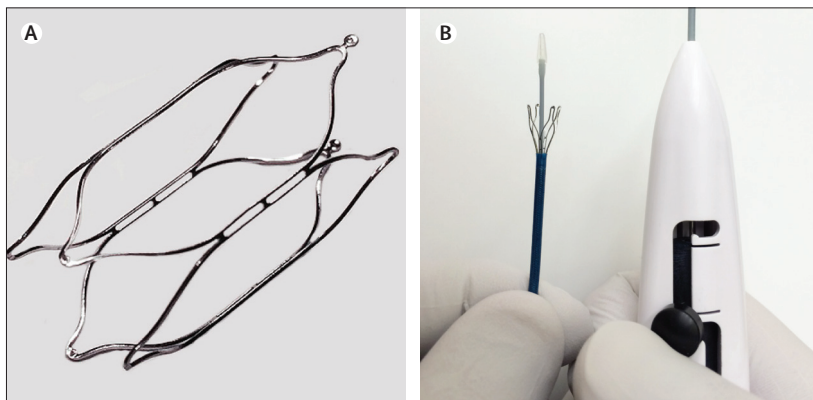
Endovascular baroreflex amplification is a novel technique for lowering blood pressure. We searched PubMed for case reports, clinical trials, observational studies, and randomised controlled trials published up to May 1, 2017, in English, with the search terms “baroreflex”, “baroreceptor”, “activation”, “stimulation”, “amplification”, “hypertension”, and “blood pressure”. An implantable pulse generator that directly stimulates the carotid baroreceptors was associated with lowering of blood pressure in a randomised clinical trial, but implantation required an invasive surgical procedure and the treatment was associated with side-effects and required battery replacement every few years. Less invasive interventions to stimulate the carotid baroreceptors to lower blood pressure were not described.

#### Added value of this study

We showed that in patients with resistant hypertension, endovascular passive baroreflex amplification with MobiusHD (Vascular Dynamics, Mountain View, CA, USA) resulted in substantial lowering of blood pressure and reduced use of antihypertensive medication with an acceptable safety profile.

#### Implications of all the available evidence

Therapeutic activation of the baroreflex, whether via an implantable pulse generator or by an endovascular passive device, can substantially lower blood pressure in patients with resistant hypertension. Randomised, double-blind, sham-controlled clinical trials are warranted to definitively prove the safety and efficacy of the MobiusHD device.



**Figure 1: MobiusHD device and delivery catheter**

(A) The MobiusHD is a passive baroreflex amplification device, available in 5.00–7.00 mm, 6.25–9.00 mm, and 8.00–11.75 mm sizes, which is implanted in the internal carotid artery. (B) The delivery catheter is introduced over a guidewire inserted via the femoral artery. Images reproduced by permission of Vascular Dynamics, Mountain View, CA, USA.

implantation without resetting or extinguishing of the haemodynamic effects (appendix). Long-term efficacy, however, was not possible because the canine carotid sinus is typically less than 1 mm in diameter, which leads to difficulty in maintaining device patency for extended periods of time. We therefore did a first-in-human study to assess the safety and efficacy of the device in patients with resistant hypertension.

## Methods

### Study design and participants

The Controlling And Lowering blood pressure with the MobiusHD, First In Man, in EUROpe study (CALM-FIM\_EUR) was a prospective open-label study investigating the safety and efficacy of this endovascular passive baroreflex amplification device in patients with resistant hypertension. The study recruited adults from six European centres, five in the Netherlands and one in Germany. Eligible patients were aged 18–80 years and

had resistant hypertension that had been stable for at least 30 days with the maximally tolerated doses of at least three antihypertensive drugs, including a diuretic. Inclusion criteria were at least 80% adherence to antihypertensive medication, as self-reported daily in diaries for at least 30 days before enrolment, mean office systolic blood pressure 160 mm Hg or greater, mean 24 h ambulatory systolic blood pressure 130 mm Hg or greater, and mean 24 h ambulatory diastolic blood pressure 80 mm Hg or greater. Principal exclusion criteria included hypertension secondary to an identifiable and treatable cause other than sleep apnoea; any plaque or ulceration in the carotid artery or aortic arch; internal carotid artery lumen diameter smaller than 5.00 mm or larger than 11.75 mm at the planned implantation location; body-mass index 40 kg/m<sup>2</sup> or greater; chronic atrial fibrillation; any contraindication for dual antiplatelet therapy; use of chronic oral anticoagulation therapy; myocardial infarction or unstable angina in the past 3 months; cerebrovascular accident in the past year; estimated glomerular filtration rate 45 mL/min per 1.73 m<sup>2</sup> or less (based on the Chronic Kidney Disease Epidemiology Collaboration equation<sup>10</sup>); previous surgery, radiation, or endovascular stent placement in either carotid region; cardiac valvular disease; decompensated heart failure, left-ventricular ejection fraction 30% or less, or both; use of an imidazoline-receptor agonist, other centrally acting antihypertensive drugs, or both; and deep venous thrombosis within the past year or documented recurrent deep venous thrombosis. Full inclusion and exclusion criteria are provided in the appendix.

The study was approved by the local research ethics committee at each participating site. All patients provided written informed consent. Data were monitored by an independent data safety monitoring board (DSMB), with prespecified assessments done after device implantation in one, five, and ten patients.

See Online for appendix

## Procedures

Before implantation, the carotid anatomy of potential recipients was assessed by duplex ultrasonography and CT angiography or magnetic resonance angiography to ensure that the carotid arteries were suitable for implantation (lumen diameters of the carotid sinuses between 5.00 and 11.75 mm without atherosclerosis). The MobiusHD device was implanted by interventionalists who had previously done at least 100 carotid stent placements. Each operator received training before the first implantation from a representative of the sponsor, including in-vivo implantations in sheep. All implantations were done in the presence of two sponsor representatives who monitored the procedure. Dual antiplatelet therapy with 80–325 mg aspirin and a P2Y<sub>12</sub>-receptor inhibitor (75 mg clopidogrel or equivalent substitute) was administered from 3 days before to 3 months after implantation. Aspirin was continued indefinitely.

A 6 Fr guide sheath or 8 Fr guiding catheter was inserted via the femoral artery over a 0.035 inch (0.09 mm) guidewire and advanced to the carotid artery. Angiographic measurements were undertaken to confirm the diameter of the carotid sinus and to select an appropriate implant size. The implants are available in three sizes: 5.00–7.00 mm, 6.25–9.00 mm, and 8.00–11.75 mm. A 0.014 inch (0.04 mm) guidewire was navigated into the distal internal carotid artery, and the delivery catheter was introduced over the guidewire and the implant was deployed at the target site. Devices were implanted unilaterally with no predefined preference for the right or left internal carotid artery. Intravenous heparin was given during the implantation procedure according to local hospital carotid stent protocols.

Baseline assessments included office and 24 h ambulatory blood pressure measurements, physical examination, National Institutes of Health Stroke Scale (NIHSS) scores, review of medications, basic blood chemistry and haematology, and duplex imaging of the carotid artery. Follow-up assessments were done on the day of discharge, 7 days and 1, 3, and 6 months after discharge, and every 6 months thereafter until 3 years after implantation. At the time of reporting, all patients had completed 6 months of follow-up.

Office blood pressure was measured at each follow-up visit, after 5 min rest while the patient was seated. Measurements were taken with an automated oscillometric device (Omron M10-IT, OMRON Healthcare, Hoofddorp, Netherlands) with selected appropriate cuff size in the non-dominant arm. Two readings were recorded for every assessment, 1 min apart, and the results were averaged. If the difference in systolic blood pressure between the two measurements was more than 5 mm Hg, a third measurement was taken and the latter two values were used to obtain the average. 24 h ambulatory blood pressure monitoring was done at baseline and at 3 and 6 months after implantation with an oscillometric device (Spacelabs 90217, Spacelabs Healthcare, Issaquah, WA,

USA) applied to the non-dominant arm. Blood pressure was recorded every 30 min during the day and every 60 min during the night. The 24 h recordings were deemed acceptable if at least 70% of the readings over the 24 h period were successfully recorded and at least 14 of them were recorded in the daytime and at least seven at night.

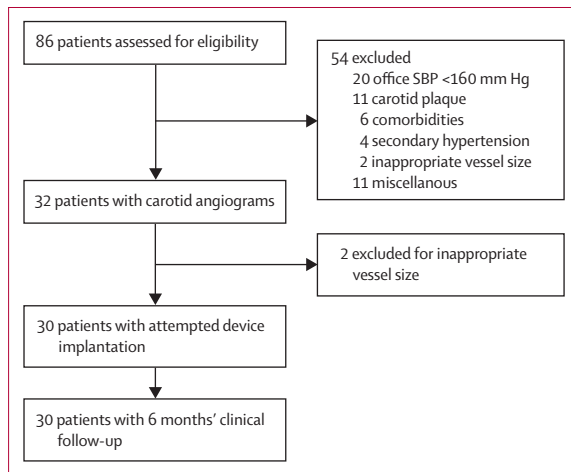
Laboratory chemistry and haematology measurements were analysed at local hospital laboratories. At each visit, adverse events were recorded. Investigators were told not to change patients' medications except when medically required for hypotension or worsening hypertension. Patients were asked to adhere to their prescribed antihypertensive drugs and to record use per day in a diary.

## Outcomes

The primary endpoint was the incidence of serious adverse events, including unanticipated adverse device effects, at 6 months. All adverse events were reviewed and adjudicated by the DSMB. Secondary endpoints included changes from baseline in office and 24 h ambulatory blood pressures and use of antihypertensive medication at any time during the 6-month follow-up period. To assess the intensity of antihypertensive medication use over time, doses were converted to total daily defined doses (DDD) by use of conversion factors provided by WHO's Collaborating Centre for Drug Statistics Methodology.<sup>11</sup> Reductions in mean office systolic blood pressure of 10 mm Hg or more, in mean 24 h ambulatory systolic blood pressure of 5 mm Hg or more, or use of antihypertensive medication at 6 months were taken to be clinically important responses. All data were centrally collected via an electronic case report form and monitored by the study sponsor.

## Statistical analysis

The number of patients needed to establish study device feasibility was informed by the sample sizes in similar feasibility studies assessing continuous endpoints.<sup>12</sup> The enrolment of 30 patients also met the minimum sample size for a feasibility study suggested by Browne.<sup>13</sup> In concert with regulatory bodies, it was therefore decided that a sample of 30 patients would be appropriate to establish signals related to safety and efficacy, since substantial improvement in blood pressure would be needed to justify the risk of a carotid implant. We calculated mean (SD) office and 24 h ambulatory blood pressures. Changes from baseline in blood pressure and medication use over the 6 months of follow-up were analysed by one-way ANOVA with pairwise comparisons of significant values and Bonferroni correction for multiple comparisons. A multivariate linear regression model was applied to explore which baseline and procedural characteristics were related to the change in 24 h mean ambulatory systolic blood pressure at 6 months, and used the Mann-Whitney *U* test for dichotomous comparisons in subgroups. Wilcoxon's signed rank test was used to compare changes in the number of antihypertensive medications used and DDD from baseline to 6 months. Two-tailed *p* values less



**Figure 2: Trial profile**  
SBP=systolic blood pressure.

	Patients undergoing implantation (n=30)
Age (years)	52 (12)
Women	15 (50%)
Non-white ethnic origin	3 (10%)
Cardiovascular disease	
Coronary artery disease	5 (17%)
Cerebrovascular disease	4 (13%)
Peripheral artery disease	2 (7%)
Current smoker	7 (23%)
Type 2 diabetes mellitus	6 (20%)
Failed renal denervation therapy	8 (27%)
Body-mass index (kg/m <sup>2</sup> )	28.0 (5.2)
eGFR (mL/min per 1.73 m <sup>2</sup> )	83 (17)
Office blood pressure (mm Hg)	184/109 (18/14)
Office heart rate (beats per min)	76 (11)
24 h ambulatory blood pressure (mm Hg)	166/100 (17/14)
Number of antihypertensive drugs	4.4 (1.4)
Daily defined dose	6.8 (4.8)
ACEI, ARB, or renin inhibitor	30 (100%)
Calcium-channel blocker	27 (90%)
Diuretic	30 (100%)
β blocker	14 (47%)
α blocker	11 (37%)
Mineralocorticoid antagonist	17 (57%)
Direct vasodilator	2 (7%)
Taking A/C/D regimen	25 (83%)

Data are mean (SD) or number (%). eGFR=estimated glomerular filtration rate. ACEI=angiotensin-converting-enzyme inhibitor. ARB=angiotensin-II-receptor blocker. A/C/D=renin-angiotensin-system blocker, calcium-channel blocker, and diuretic.

**Table 1: Baseline characteristics**

than 0.05 were taken to be significant. All analyses were done with SPSS version 24. This trial is registered with ClinicalTrials.gov, number NCT01911897.

**Role of the funding source**

The funder of the study had a role in the study design, data analysis, and had the right to a non-binding review of the final report. The funder had no role in the data analysis, data interpretation, or writing of the report. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

86 patients were screened between December, 2013, and February, 2016, among whom 32 (37%) underwent carotid angiography (figure 2). Two patients had inappropriate vessel diameters for device implantation and were excluded. The remaining 30 patients were included and underwent implantation (figure 2, table 1).

MobiusHD was successfully implanted in all patients, in the right internal carotid artery in 19 and in the left internal carotid artery in 11. Eight patients received implants of 5.00–7.00 mm, 20 of 6.25–9.00 mm, and two of 8.00–11.75 mm.

As adjudicated by the DSMB, five serious adverse events occurred in four patients that were deemed to be possibly related to the procedure or device (table 2), but none were classified as unanticipated adverse device effects. One patient was admitted to hospital 6 days after implantation with worsening of hypertension because of self-initiated discontinuation of medications. Antihypertensive medications were reintroduced, but resulted in hypotension, leading to dose adjustment that stabilised blood pressure. One patient developed hypotension 2 days after implantation and needed to be admitted to hospital for rehydration and medication reduction, to which the patient responded. One patient was admitted with worsening hypertension 33 days after implantation that was treatable with increased antihypertensive medication. In one patient, intermittent claudication developed due to a dislodged femoral closure device, which was treated with surgical thromboendarterectomy. The wound later became infected and needed drainage and antibiotic treatment. Ipsilateral focal neurological events immediately after implantation were reported in two patients treated at one study centre, which were initially interpreted as minor strokes. One patient had received an implant in the right carotid sinus during a procedure without complications and noticed reduced strength and numbness of her left arm and leg 5 min after implantation (NIHSS score 6). CT angiography showed no abnormalities. The symptoms were almost recovered at discharge 1 day later (NIHSS score 0), although the patient reported difficulty with walking due to “delay” of her left foot. The other patient had received a left-sided implant during a procedure without complications. Directly after implantation the patient complained of numbness and reduced strength of the right arm and leg (NIHSS score 2). CT angiography showed no abnormalities. Most of the symptoms had



resolved 1 day later (NIHSS score 0). At 3 weeks after implantation, the patient complained of pain, tiredness, and cramps in the right arm and leg. These two patients had not taken their antihypertensive medication before the implantation and both had systolic blood pressure greater than 200 mm Hg during the procedure. The DSMB did not feel the residual symptoms in these two patients were neurological and, because the NIHSS scores were 0 in both patients 1 day after implantation, these events were judged not to be strokes but, rather, transient ischaemic attacks.

No device migrations and no significant changes in plaque formations in the carotid arteries were seen. Of 42 adverse events, the most frequently reported were dizziness (n=9, 21%), musculoskeletal pain (n=7, 17%), and hypotension (n=5, 12%).

During the first 24 h after implantation, office blood pressure decreased by a mean of 38/23 mm Hg (95% CI 29–46/16–29). During follow-up, the mean reductions from baseline in office blood pressure were 27/14 mm Hg (18–37/8–21) at 1 week, 22/10 mm Hg (12–31/3–16) at 1 month, 24/11 mm Hg (12–35/4–18) at 3 months, and 24/12 mm Hg (13–34/6–18) at 6 months (figure 3). At all timepoints after implantation, mean office systolic and diastolic blood pressures were significantly lower than at baseline (all  $p < 0.02$  in the overall ANOVA and reaching  $p = 0.0003$  for systolic and  $p = 0.0001$  for diastolic blood pressure at 6 months in the pairwise analysis, figure 3). Reductions in 24 h mean ambulatory blood pressures were 15/8 mm Hg (95% CI 7–23/3–13) at 3 months and 21/12 mm Hg (14–29/7–16) at 6 months (all  $p < 0.002$  in the overall ANOVA, and reaching  $p < 0.0001$  for systolic and diastolic blood pressure at 6 months, figure 4).

In 22 (73%) patients, blood-pressure reductions met predefined criteria for clinically important response (reduction in office systolic blood pressure of  $\geq 10$  mm Hg and in 24 h mean ambulatory systolic blood pressure of  $\geq 5$  mm Hg or using less antihypertensive medication at 6 months). In 25 (83%) patients, a mean reduction in 24 h ambulatory systolic blood pressure of 5 mm Hg or more or reduced use of antihypertensive medication was seen at 6 months. We found no significant associations between change in 24 h mean ambulatory systolic blood pressure at 6 months and any of the following variables: age, sex, baseline body-mass index, baseline 24 h mean ambulatory systolic blood pressure, baseline office heart rate, baseline estimated glomerular filtration rate, previous renal denervation therapy, and side of implanted device (appendix). Dichotomous subgroup analyses of these variables also indicated no differences in change of mean 24 h ambulatory systolic blood pressure at 6 months, except in the comparison of mean baseline values greater than 168 mm Hg versus less than 168 mm Hg, where the changes were  $-29$  mm Hg (IQR  $-44$  to  $-14$ ) versus  $-9$  mm Hg ( $-19$  to  $-3$ ,  $p = 0.0080$ ; appendix).

Mean heart rates during follow-up were 74 (SD 14), 76 (14), 76 (15), and 78 (15) beats per min at 1 week, and 1,

	Number of patients (%)	Intervention	Outcome
<b>Serious adverse events</b>			
Hypotension*	2 (7%)	Reduction in antihypertensive dose	Resolved without sequelae
Worsening of hypertension*	2 (7%)	Increase in antihypertensive dose	Resolved without sequelae
Claudication left leg	1 (3%)	Thromboendarterectomy	Resolved without sequelae
Wound infection	1 (3%)	Wound irrigation and antibiotic	Resolved without sequelae
<b>Other adverse events</b>			
Dizziness	9 (30%)	Reduction in antihypertensive dose	Resolved without sequelae
Musculoskeletal pain	7 (23%)	Pain medication	Resolved without sequelae
Hypotension	5 (17%)	Reduction in antihypertensive dose	Resolved without sequelae
Groin haematoma	3 (10%)	No treatment required	Resolved without sequelae
Fatigue	2 (7%)	No treatment required	Resolved without sequelae
Headache	2 (7%)	Pain medication	Resolved without sequelae
Pseudoaneurysm	2 (7%)	Thrombin injection	Resolved without sequelae
Transient ischaemic attack	2 (7%)	No treatment required	Resolved without sequelae
Acute back pain	1 (3%)	Pain medication	Resolved without sequelae
Anxiety	1 (3%)	Benzodiazepine	Treatment ongoing
Groin puncture bleeding	1 (3%)	No treatment required	Resolved without sequelae
Facial loss of sensibility, left side	1 (3%)	No treatment required	Resolved without sequelae
Muscle pain right side of neck	1 (3%)	No treatment required	Resolved without sequelae
Nausea	1 (3%)	No treatment required	Resolved without sequelae
Numbness of left hand and upper lip	1 (3%)	No treatment required	Resolved without sequelae
Short-term memory loss	1 (3%)	No treatment required	Stable without impairment
Tickling, right side of neck	1 (3%)	No treatment required	Resolved without sequelae
Tinnitus	1 (3%)	Monitoring by physician	Ongoing

\*One case of worsening of hypertension and one of hypotension occurred in the same patient and were coded as a single event.

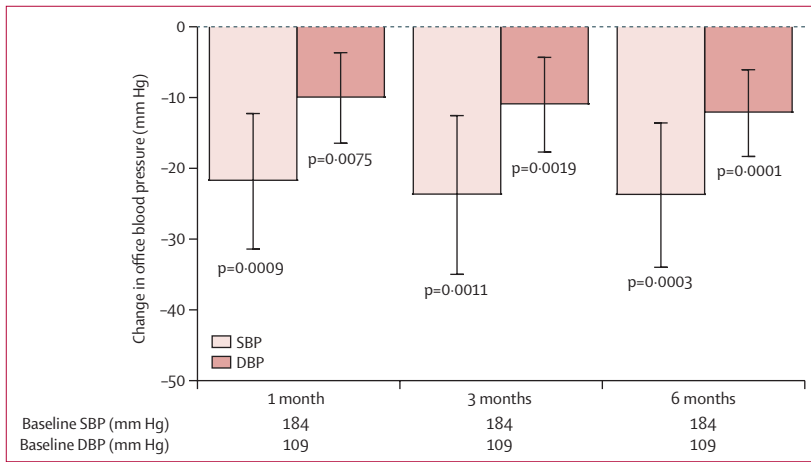
**Table 2: Adverse events related or possibly related to the procedure or device**

3, and 6 months, respectively. None differed significantly from baseline.

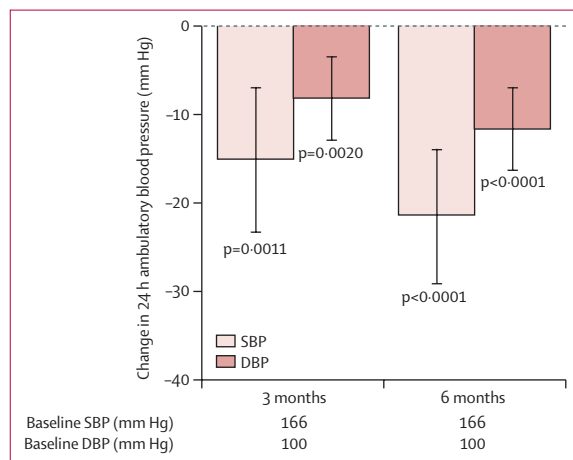
Self-reported adherence to prescribed medications was greater than 80% in all patients during follow-up. The median number of antihypertensive medications was reduced by 0.50 (IQR 1.25–0,  $p = 0.0020$ ) and the median DDD was reduced by 0.42 units (2.13–0.09,  $p = 0.010$ ) at 6 months.

## Discussion

This first-in-human study of a novel endovascular baroreflex amplification device, the MobiusHD, showed acceptable safety and resulted in clinically important reductions in office and 24 h ambulatory blood pressure in patients with resistant hypertension. Additionally, need for medication was lessened in most patients during 6 months of follow-up. The favourable effect on blood pressure occurred irrespective of patients' baseline characteristics, blood pressure, or medication use. Moreover, implantation of the MobiusHD was straightforward for interventionists



**Figure 3: Change from baseline in office blood pressure at 1, 3, and 6 months**  
Data are mean and error bars show 95% CIs. All 30 patients were assessed at all timepoints. SBP=systolic blood pressure. DBP=diastolic blood pressure.



**Figure 4: Change from baseline in 24 h mean ambulatory blood pressure at 3 and 6 months**  
Data are mean and error bars show 95% CIs. All 30 patients were assessed at all timepoints. SBP=systolic blood pressure. DBP=diastolic blood pressure.

experienced in carotid stent placement, who achieved 100% procedural success.

Reductions in blood pressure were substantial in most patients and resulted in symptomatic hypotension in 17% of patients. Most of these episodes were successfully managed by reductions in antihypertensive medications. However, as cerebral autoregulation might be impaired in patients with long-standing hypertension, a more controlled reduction in blood pressure is preferable. This effect might be achieved by routine periprocedural saline infusion. Also, despite the absence of atherosclerotic plaques in the treated vessels, ipsilateral focal neurological events were noted immediately after device implantation in two patients treated in one study centre. Both patients had stopped taking antihypertensive medication before implantation and, consequently, had very high blood pressures at the start of and during the procedures. Of

note, an autoinjector for contrast was used in these cases, but not at other sites, and we cannot exclude that this was the explanation for these two events. CT angiography in these two cases did not reveal any abnormalities, but might have been less sensitive than diffusion-weighted magnetic resonance angiography, which was not done. Given the ipsilateral nature of these two neurological events, platelet thromboemboli, contrast encephalopathy due to severe hypertension during the multiple angiograms, air emboli, device-related particulates, or focal hypoperfusion of a vulnerable area of the brain due to hypotension cannot be excluded.

We saw substantial decreases in blood pressure in the first 24 h after implantation of the MobiusHD, which is consistent with the proposed mechanism of action of the device. Previous studies have shown that stimulation of the carotid baroreceptors results in immediate inhibition of sympathetic outflow and reduction in blood pressure.<sup>5</sup> In this study, reductions in blood pressure persisted at 6 months, with the mean difference from baseline in office blood pressure being -24/-12 mm Hg despite less use of antihypertensive therapy than at baseline. Similar and sustained effects were noted on 24 h ambulatory blood pressure at 6 months (mean change -21/-12 mm Hg). Subgroup analyses indicated that only a higher 24 h ambulatory systolic blood pressure at baseline was significantly associated with the change in 24 h ambulatory systolic blood pressure at 6 months. Studies in baroreflex activation therapy show that right-sided stimulation has a more profound effect on blood pressure than left-sided stimulation.<sup>14</sup> We found no difference in effects between patients who had endovascular baroreflex amplification implants in the right or the left internal carotid artery, but the study was not powered to assess this difference, which might explain the discrepancy. We saw no tachyphylaxis or carotid-sinus resetting after blood pressure response, meaning that the effect of device implantation on blood pressure did not seem to diminish over time for up to 6 months.

Our study has several limitations. As a first-in-human study, the CALM-FIM\_EUR study was small, non-controlled, and unblinded. Although two focal ipsilateral neurological events were seen, major strokes did not occur, nor were there any unanticipated device-related safety issues up to 6 months. Larger studies with more patients and longer follow-up are needed to further assess the safety profile of this intervention and to determine whether device fracture, migration, thrombosis, intimal proliferation at the implantation site, or other complications occur. Our study was also not large enough to establish whether differential blood pressure responses would occur in specific subgroups of patients. Second, we cannot rule out the role of placebo and Hawthorne effects contributing to the magnitude of reductions in blood pressure owing to the unblinded and uncontrolled study design. In this regard, promising results were seen with renal denervation in the proof-of-principle Symplicity HTN-1 study,<sup>15</sup> and

even in the randomised, but unblinded, Symplicity HTN-2 trial.<sup>16</sup> The findings, however, were not replicated in the randomised, double-blind, sham-controlled Symplicity HTN-3 trial.<sup>17</sup> Third, although self-reported adherence to prescribed antihypertensive medications was good (>80%), we did not directly measure metabolites in blood or urine to confirm use. Adherence to antihypertensive medication might be an important confounder in characterising the true effects of novel therapies on lowering blood pressure in patients with resistant hypertension.<sup>18,19</sup> Finally, follow-up was not long enough to assess whether the haemodynamic responses are sustained over time.

Implantation of the passive endovascular baroreflex amplification device MobiusHD in patients with resistant hypertension was feasible and was associated with acceptable safety when done in carefully selected patients by an operator experienced in endovascular carotid artery intervention. Device placement resulted in immediate and substantial reductions in blood pressure that were sustained for at least 6 months. Based on these findings, two randomised, double-blind, sham-controlled trials of safety and efficacy with the MobiusHD in patients with resistant hypertension are planned—the CALM-START (off medication) and the CALM-II (treated resistant hypertension).

#### Contributors

JVdH was the principal investigator. JV collected the data WS analysed the data and prepared the final manuscript. BW, JV, GWS, and MB wrote the report. JVDH, MvK, RL, AM, AK, HR, and GA reviewed the final paper.

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#### Declaration of interests

WS has received a consulting fee and travel expenses and his institution has received a research grant from Vascular Dynamics. BW, JVdH, and AK have received consulting fees and travel expenses from Vascular Dynamics. MvK is paid from a research grant from Vascular Dynamics. GA is a consultant for Daiichi Sankyo and Vascular Dynamics. GWS is a consultant for Ablative Solutions, BackBeat Medical, Claret, Matrizyme, Medical Development Technologies, Miracor, Neovasc, Reva, Sirtex, St Jude, TherOx, Toray, V-wave, Valfix, and Vascular Dynamics, and has

equity or options in Aria, Biostar family of funds, Cagent, Caliber, Guided Delivery Systems, MedFocus family of funds, Micardia, and Qool Therapeutics. MB is a consultant for CeloNovaBioSciences, Nexeon MedSystems, Pulsus Medical, Touchstone Alpha, Vascular Dynamics, and W L Gore. The other authors declare no competing interests.

#### References

- 1 Irvin MR, Booth JN, Shimbo D, et al. Apparent treatment-resistant hypertension and risk for stroke, coronary heart disease, and all-cause mortality. *J Am Soc Hypertens* 2014; **8**: 405–13.
- 2 Muntner P, Davis BR, Cushman WC, et al. Treatment-resistant hypertension and the incidence of cardiovascular disease and end-stage renal disease: results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension* 2014; **64**: 1012–21.
- 3 Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015; **386**: 2059–68.
- 4 Yoruk A, Tankut SS, Gassler JP, Bisognano JD. Present and future of interventional treatment of resistant hypertension. *Curr Hypertens Rep* 2017; **19**: 4.
- 5 Heusser K, Tank J, Engeli S, et al. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. *Hypertension* 2010; **55**: 619–26.
- 6 Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. *J Am Coll Cardiol* 2011; **58**: 765–73.
- 7 Heusser K, Tank J, Brinkmann J, et al. Acute response to unilateral unipolar electrical carotid sinus stimulation in patients with resistant arterial hypertension. *Hypertension* 2016; **67**: 585–91.
- 8 Freeman R. Clinical practice. Neurogenic orthostatic hypotension. *N Engl J Med* 2008; **358**: 615–24.
- 9 Peter DA, Alemu Y, Xenos M, et al. Fluid structure interaction with contact surface methodology for evaluation of endovascular carotid implants for drug-resistant hypertension treatment. *J Biomech Eng* 2012; **134**: 41001.
- 10 Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–12.
- 11 WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health. Guidelines for ATC classification and DDD assignment. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2016.
- 12 Billingham SAM, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC Med Res Methodol* 2013; **13**: 104.
- 13 Browne RH. On the use of a pilot sample for sample size determination. *Stat Med* 1995; **14**: 1933–40.
- 14 de Leeuw PW, Alnima T, Lovett E, et al. Bilateral or unilateral stimulation for baroreflex activation therapy. *Hypertension* 2015; **65**: 187–92.
- 15 Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; **373**: 1275–81.
- 16 Symplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; **376**: 1903–09.
- 17 Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; **370**: 1393–401.
- 18 Tomaszewski M, White C, Patel P, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart* 2014; **100**: 855–61.
- 19 de Jager RL, de Beus E, Beeftink MMA, et al. Impact of medication adherence on the effect of renal denervation: the SYMPATHY trial. *Hypertension* 2017; **69**: 678–84.