JACC: CARDIOVASCULAR INTERVENTIONS VOL. 15, NO. 3, 2022

PUBLISHED BY ELSEVIER

Treatment of Resistant Hypertension With Endovascular Baroreflex Amplification

3-Year Results From the CALM-FIM Study

Monique E.A.M. van Kleef, MD, PhD,[a] Chandan M. Devireddy, MD, MBA,[b] Jan van der Heyden, MD, PhD,[c] Mark C. Bates, MD, DSc,[d] George L. Bakris, MD,[e] Gregg W. Stone, MD,[f] Bryan Williams, MD,[g] Wilko Spiering, MD, PhD,[a] on behalf of the CALM-FIM Investigators

ABSTRACT

OBJECTIVES The aim of this study was to evaluate the long-term (3-year) safety and effectiveness of endovascular baroreflex amplification (EVBA) from both the European and American CALM-FIM cohorts.

BACKGROUND The CALM-FIM study demonstrated that EVBA in patients with resistant hypertension significantly lowered blood pressure (BP) with an acceptable safety profile during 6-month follow-up.

METHODS The CALM-FIM studies were prospective, nonrandomized, first-in-human studies that enrolled patients with resistant hypertension (office systolic BP ≥160 mm Hg and mean 24-hour ambulatory BP ≥130/80 mm Hg despite a stable regimen of ≥3 antihypertensive medications, including a diuretic agent). The incidence of (serious) adverse events and changes in BP, heart rate, and prescribed antihypertensive medication up to 3 years after implantation were determined.

RESULTS The Mobius device was implanted in 47 patients (30 in Europe, 17 in the United States; mean age 54 years, 23 women). Five serious adverse events (hypotension, n = 2; hypertension, n = 1; vascular access complications, n = 2) and 2 transient ischemic attacks occurred within 30 days postprocedure. Two strokes and 1 transient ischemic attack occurred more than 2 years postimplantation. Mean office BP at baseline was 181 ± 17/107 ± 16 mm Hg and decreased by 25/12 mm Hg (95% CI: 17-33/8-17 mm Hg) at 6 months and 30/12 mm Hg (95% CI: 21-38/8-17 mm Hg) at 3 years. Mean 24-hour ambulatory BP at baseline was 166 ± 16/98 ± 15 mm Hg and decreased by 20/11 mm Hg (95% CI: 14-25/8-15 mm Hg) at 6 months.

CONCLUSIONS EVBA with the MobiusHD was effective in reducing BP at 3-year follow-up and appears to have an acceptable safety profile in patients with uncomplicated implantation, although data from randomized sham-controlled trials are needed to further evaluate the risk-benefit profile. (Controlling and Lowering Blood Pressure With the MobiusHD™ [CALM-FIM_EUR], NCT01911897; Controlling and Lowering Blood Pressure With the MobiusHD™ [CALM-FIM_US], NCT01831895) (J Am Coll Cardiol Intv 2022;15:321-332) © 2022 by the American College of Cardiology Foundation.

From the [a]Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, the Netherlands; [b]Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia, USA; [c]Department of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands; [d]CAMC Institute of Academic Medicine and West Virginia University, Charleston, West Virginia, USA; [e]Department of Medicine, American Society of Hypertension Comprehensive Hypertension Center, University of Chicago Medicine, Chicago, Illinois, USA; [f]The Zena and Michael A. Wiener Cardiovascular Institute, The Icahn School of Medicine at Mount Sinai, New York, New York, USA; and the [g]University College London Institute of Cardiovascular Science and National Institute for Health Research UCL Hospitals Biomedical Research Centre, London, United Kingdom. Dr van der Heyden is currently working at the St. Jan Hospital, Bruges, Belgium.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 3, 2021; revised manuscript received November 23, 2021, accepted December 7, 2021.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2021.12.015

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 15, NO. 3, 2022
FEBRUARY 14, 2022:321–332

ABBREVIATIONS AND ACRONYMS

BAT = baroreflex activation therapy

BP = blood pressure

DDD = daily defined dose

EVBA = endovascular baroreflex amplification

TIA = transient ischemic attack

Despite the availability of effective pharmacologic treatments, at least one-half of patients with treated hypertension do not achieve blood pressure (BP) lowering to <140/90 mm Hg[1] and remain at increased risk for cardiovascular events, particularly stroke.[2,3] In the absence of novel potent pharmaceutical solutions, there is increasing interest in device-based alternatives for patients with resistant hypertension.

Most antihypertensive devices are designed to reduce sympathetic activity either by inactivating renal sympathetic nerves or through activation of the baroreflex.[4] Although the first randomized sham-controlled trial of renal denervation failed to show significant BP reduction,[5] 4 more recent sham-controlled trials have shown modest but significant decreases of 4 to 8 mm Hg in 24-hour ambulatory systolic BP after 2 to 6 months.[6-9] Activation of the baroreflex by an implantable electric stimulator effectively lowered BP[10,11] but with the disadvantages of an open surgical implantation[12]; associated side effects of jaw or neck pain, nerve injury, globus sensation, cough, and dysphonia; and the need for frequent battery replacement.[13] Given the efficacy of baroreflex stimulation in BP lowering, an alternative, less invasive therapy was developed: endovascular baroreflex amplification (EVBA) using the Mobius HD endoprosthesis (Vascular Dynamics)[14] (**Figure 1**).

SEE PAGE 333

The MobiusHD changes the carotid sinus geometry such that the increased relative radius within each of the 4 quadrant windows results in passively increased focal pulsatile wall strain. This stimulates baroreceptor firing with resultant sympathetic outflow inhibition and a decrease in BP.[15] The pulsatile geometric change of the carotid bulb caused by the MobiusHD is thought to enable sustained BP responses not seen with conventional carotid stents.

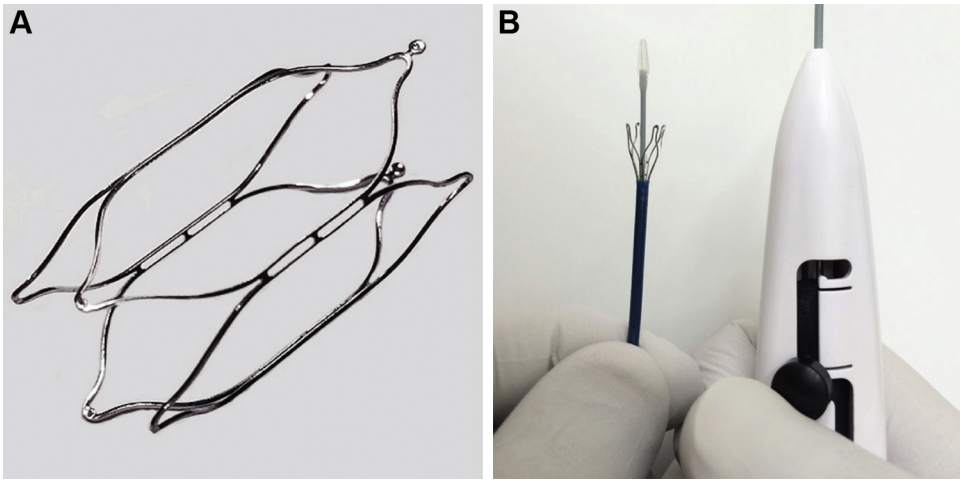
The European first-in-human study (CALM-FIM_EUR [Controlling and Lowering Blood Pressure With the MobiusHD - First in Man]) showed an acceptable safety profile and substantial BP response at 6 months postimplantation.[16] In the present report, the 3-year safety and effectiveness of EVBA in both the European and American first-in-human studies are presented.

METHODS

STUDY DESIGN AND PARTICIPANTS. CALM-FIM_EUR (NCT01911897) and CALM-FIM_US (NCT01831895) were 2 parallel, prospective, open-label studies conducted in Europe and the United States, respectively. The studies had mirrored protocols and were designed to determine the safety and effectiveness of EVBA in patients with resistant hypertension. CALM-FIM_EUR recruited adult patients from 6 centers in Europe (5 in the Netherlands and 1 in Germany), while CALM-FIM_US recruited adult patients from 7 centers in the United States. Patients were eligible if they were 18 to 80 years of age and diagnosed with resistant hypertension as defined by mean office systolic BP ≥160 mm Hg and mean 24-hour ambulatory BP ≥130/80 mm Hg on a stable regimen of at least 3 antihypertensive drugs (including a diuretic agent) for at least 30 days. Main exclusion criteria included hypertension secondary to an identifiable and treatable cause other than sleep apnea, vulnerable plaque, ulceration or stenosis in the carotid artery or the aortic arch, and carotid artery lumen diameter < 5.00 or >11.75 mm or excessive carotid bulb tapering at the planned implant location. Detailed exclusion criteria of the CALM-FIM studies are outlined in Supplemental Text 1. The studies were approved by the local ethics committees of participating centers (Germany and the United States) or nation (the Netherlands). All patients provided informed written consent. Safety was monitored by an independent data and safety monitoring board. All serious adverse events and adverse events reported as related or possibly related to the device or procedure or relatedness unknown were reviewed by an independent clinical endpoint committee.

PROCEDURES. To ensure that the carotid arteries could be accessed safely and that the target carotid bulb was free of atherosclerotic disease, all patients underwent carotid duplex and computed tomographic angiography or magnetic resonance angiography prior to implantation. To confirm eligibility, invasive carotid angiography was performed to assess if one of the carotid arteries was suitable for device implantation. A 6-F guide sheath or 8-F guiding catheter was advanced into the selected common carotid artery via the femoral artery over a 0.035-inch (0.9-mm) guidewire using standard carotid artery access techniques. The MobiusHD delivery system was advanced over a 0.014-inch (0.4-mm) guidewire into the carotid bulb, where the device was deployed without the use of a distal embolic protection device. The MobiusHD was implanted unilaterally on the anatomically best suited side with the device size selected on the basis of carotid bulb diameters: 5.00 to 7.00 mm (size A), 6.25 to 9.00 mm (size B), and 8.00 to 11.75 mm (size C). All patients received

FIGURE 1 **MobiusHD Device and Delivery Catheter**



(A) The MobiusHD is a self-expendable Nitinol device implanted in the carotid sinus. **(B)** The delivery catheter is introduced over a guidewire inserted via the femoral artery, delivering the MobiusHD device at the preferred location. Reproduced with permission from Vascular Dynamics.

dual-antiplatelet therapy with 80 to 320 mg aspirin and 75 mg clopidogrel or equivalent from 3 days before implantation to 3 months after implantation. Intravenous heparin was administered during the implantation procedure, and aspirin was continued indefinitely.

Baseline measurements included office and 24-hour ambulatory BP measurements, physical examination, National Institutes of Health Stroke Scale scores, blood chemistry and hematology, and electrocardiography. Follow-up visits were scheduled on the day of discharge, 7 days, 1 month, 3 months, and 6 months after implantation, and every 6 months thereafter until 3 years after implantation. At each follow-up visit office BP was measured after 5 minutes of rest with the patient seated. Office BP measurements were performed using an automated oscillometric device (Omron M10-IT, Omron Healthcare) on the nondominant arm. Two measurements were performed, 1 minute apart, using the average of both measurements. If the difference in systolic BP between the measurements was more than 5 mm Hg, a third measurement was performed, and the average of the last 2 measurements was taken. Twenty-four hour ambulatory BP was measured at baseline and at 3 and 6 months after implantation, also using an oscillometric device (SpaceLabs 90217 [n = 41], SunTech Medical Oscar 2 [n = 3], Schiller BR-102 Plus [n = 2], Microlife WatchBP O3 [n = 1]) on the nondominant arm. BP was recorded at least every 30 minutes during the day and every 60 minutes during the night. If <70% of BP readings were successful, the 24-hour measurement was repeated.

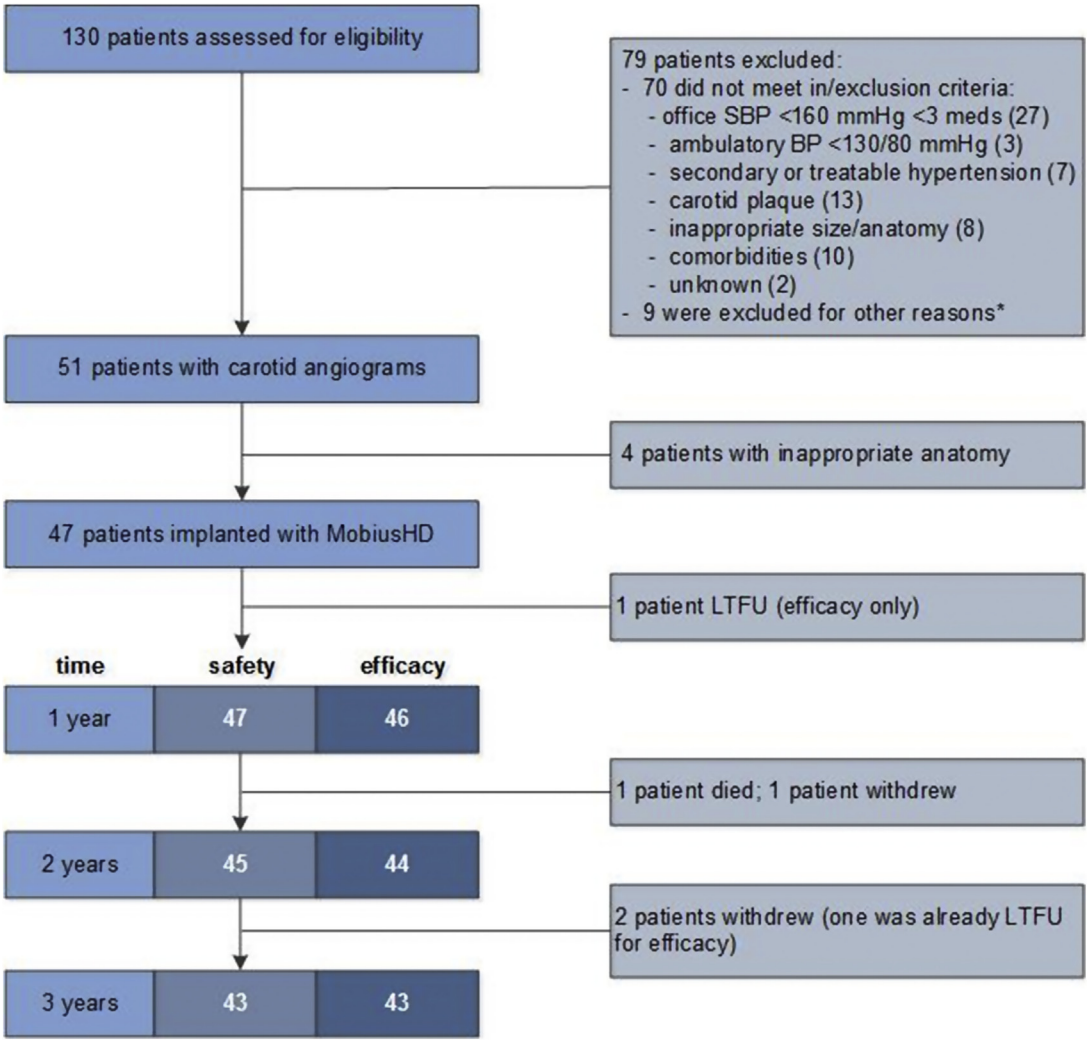
Investigators were asked not to change antihypertensive medications except when medically required to treat symptomatic hypotension or worsening of hypertension. Patients were instructed to adhere to prescribed medication regimens and record medications in a diary.

SAFETY OUTCOMES. Safety outcomes included the incidence of cerebrovascular events (stroke and transient ischemic attack [TIA]), (serious) adverse events reported as related or possibly related to the device or procedure or etiology unknown, and unanticipated adverse device effects. The timing of the events was categorized as short-term (≤30 days postprocedure) or long-term (>30 days postprocedure).

EFFECTIVENESS OUTCOMES. Effectiveness outcomes of the CALM-FIM study were change in seated office and 24-hour ambulatory BP, as well as change in antihypertensive medication: number of antihypertensive drugs and daily defined dose (DDD). The DDD is a standardized measure of a patient's total burden of medication.[17,18] A clinically relevant BP response was defined as a decrease of at least 10 mm Hg in mean office systolic BP or at least 1 DDD reduction in antihypertensive medication without an office systolic BP increase. For the 3- and 6-month

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 15, NO. 3, 2022
FEBRUARY 14, 2022:321–332

FIGURE 2 Flowchart Showing the Patients Assessed for Eligibility and Reasons for Exclusion



*Other reasons included voluntary withdrawal (8 patients) or exclusion in best interest of the patient as deemed by the local investigator (1 patient). BP = blood pressure; LTFU = lost to follow-up; SBP = systolic blood pressure.

endpoints, a reduction in 24-hour ambulatory systolic BP of at least 5 mm Hg was also considered clinically relevant or at least 1 DDD reduction in antihypertensive medication without 24-hour ambulatory systolic BP increase.

DATA ANALYSIS. Adverse events are reported as count (percentage). Mean change in office BP, ambulatory BP, heart rate and prescribed antihypertensive medication at each time point from baseline were estimated using a mixed-effects linear model for repeated measurements. For this analysis 24-hour, daytime, and nighttime ambulatory BP averages were documented as the device's reported averages. As device-reported averages may overestimate mean 24-hour BP,[19] additional area-under-the-curve analysis was performed. This method calculates an integrated mean BP using all available data (interpolating missing data points) for day and night separately. The integrated means were analyzed in a repeated-

TABLE 1 Baseline Characteristics of the Implanted Patients (n = 47)

Age, y	53.5 ± 11.6
Women	23 (49)
Caucasian	38 (81)
Current smoking	9 (19)
Cardiovascular disease	
Coronary artery disease	5 (11)
Cerebrovascular disease	6 (13)
Peripheral artery disease	0 (0)
Diabetes mellitus	10 (21)
Prior renal denervation	11 (23)
Body mass index, kg/m^2	29.2 ± 5.2
eGFR, mL/min/1.73 m^2[a]	84 ± 19
Office blood pressure, mm Hg	181 ± 17/107 ± 16
Office pulse pressure, mm Hg	74 ± 16
24-h ambulatory blood pressure, mm Hg	166 ± 16/98 ± 15
Heart rate, beats/min	74 ± 11
Number of antihypertensive medications	4 (3-5)
Daily defined dose	6 (4-8)
ARB, ACE inhibitor, or renin inhibitor	44 (94)
Calcium antagonist	37 (79)
Diuretic agent	39 (83)
Mineralocorticoid receptor antagonist	24 (51)
β-blocker	26 (55)
α-blocker	9 (19)
Direct vasodilator	9 (19)
A+C+D regimen	29 (62)
A+C+D+MRA regimen	14 (30)

Values are mean ± SD, n (%), or median (IQR). [a]eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula.

A = angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, or direct renin inhibitor; ARB = angiotensin receptor blocker; C = calcium antagonist; D = diuretic agent; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid receptor antagonist.

measures mixed-effects model, which allows for missing day or night averages and estimates the 24-hour BP as a weighted average of two-thirds of the daytime mean and one-third of the nighttime mean. A detailed description of the methodology is provided in Supplemental Text 2.

We also tested whether office BP response remained stable over time in a mixed-effects linear model with patient as random effect and time (at time points 3, 6, 12, 18, 24, 30, and 36 months) as fixed effects. Additionally, we explored the association between patient and procedure characteristics and office BP response in a mixed-effects linear model for repeated measurements with patient as random effect and time, DDD, and baseline characteristics of interest as fixed effects. For this exploratory analysis, 3 models were used: 1) univariate; 2) adjusted for age and sex; and 3) additionally adjusted for history of renal denervation, office systolic BP, office pulse pressure, heart rate, body mass index, estimated glomerular filtration rate, and side of implantation. A sensitivity analysis was performed by modeling ambulatory instead of office systolic BP response. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

PATIENT ELIGIBILITY AND BASELINE CHARACTERISTICS. In total, 130 patients were screened between December 2013 and June 2017. Seventy-nine patients were excluded before the procedure was planned: 70 patients did not meet the inclusion or exclusion criteria, of whom 13 were excluded because of plaque, calcification, or ulceration of the carotid artery (**Figure 2**). Nine patients were excluded for other reasons. Four patients underwent carotid angiography but were excluded because of incompatible vessel diameters. The remaining 47 patients (36%) (mean age 54 ± 12 years, 23 women [49%]) all underwent successful implantation of the MobiusHD device (**Table 1**), 33 (70%) in the right carotid artery and 14 (30%) in the left carotid artery. Thirteen patients (28%) received size A implants, 32 (68%) size B implants, and 2 (4%) size C implants.

Six-month data from the first 30 European patients were presented previously.[16] Six-month safety and efficacy results of the 17 U.S. patients are presented in Supplemental Table 1. Safety outcomes were available for 47 (100%), 45 (96%), and 43 (91%) patients at 1, 2, and 3 years, respectively. Effectiveness outcomes were available in 46 (98%), 44 (94%), and 43 (91%) patients at 1, 2, and 3 years (**Figure 2**). The median follow-up times for safety and effectiveness were 3.00 years (IQR: 2.98-3.02 years). One patient with persistent high BP (office BP 209/110 mm Hg and 24-hour ambulatory BP 190/95 mm Hg at 6-month follow-up) underwent Barostim neo (CVRx) implantation on the contralateral side of the MobiusHD implant, shortly after the 6-month endpoint. Although the Barostim neo did not reduce BP, a sensitivity analysis was conducted excluding this patient.

SAFETY OF EVBA. Adverse events during the first 3 years of follow-up are shown in **Tables 2A and 2B**, with more details of the events reported in the Supplemental Table 2. Five serious adverse events occurred within 30 days postprocedure, all of which were related to the device or procedure: 2 patients experienced severe hypotension requiring

TABLE 2A Incidence of Cerebrovascular Events and Serious and Nonserious Adverse Events That Occurred Within 30 Days Postprocedure

Cerebrovascular events and serious adverse events[a]	
Stroke	0 (0)
Transient ischemic attack	2 (4.3)
Hypotension requiring hospitalization	2 (4.3)
Hypertension requiring hospitalization	1 (2.1)
Vascular access complications[b]	2 (4.3)
Adverse events[c]	
Vascular access complications[d]	10 (23.4)
Hypotension	6 (12.8)
Dizziness	5 (10.6)
Musculoskeletal pain	5 (10.6)
Sensibility disorder	2 (4.3)
Headache	2 (4.3)
Visual problems	2 (4.3)
Fatigue	2 (4.3)
Gastrointestinal symptoms	2 (4.3)
Hypertension	1 (2.1)
Cognitive problems	1 (2.1)
Bradycardia	1 (2.1)
Infectious disease	1 (2.1)

Values are number of patients (% of implanted patients). [a]All cerebrovascular events (stroke and transient ischemic attack) and serious adverse events reported as related or possibly related to the device or procedure or relatedness unknown, during the first 30 days postprocedure. [b]Including one closure device failure and one large groin hematoma resulting in hypotension. [c]Adverse events reported as related or possibly related to the device or procedure or relatedness unknown, during the first 30 days postprocedure. [d]Including groin bleeding, hematoma, pseudoaneurysm, and pain at puncture site requiring analgesics.

(prolonged) hospitalization for intravenous treatment and reduction of antihypertensive medication; 1 patient had a hypertensive crisis requiring hospitalization; 1 patient developed symptoms of acute lower extremity ischemia due to a dislodged femoral closure device, which was treated surgically; and 1 patient had a large groin hematoma causing hypotension that required volume resuscitation. In addition, 2 TIAs with neurologic findings corresponding to the ipsilateral vascular territory of the implant (but without confirmed stroke) occurred and were also attributed to the device or procedure. Details of these 2 events were presented previously.[14] Additional common procedure- or device-related nonserious adverse events that occurred within 30 days included minor vascular access complications not requiring surgical intervention (n = 10) and hypotension (n = 6).

TABLE 2B Incidence of Cerebrovascular Events and Serious and Nonserious Adverse Events That Occurred More Than 30 Days Postimplantation

	Number of Patients (% of Implanted Patients)	Time From Procedure, mo
Cerebrovascular events and serious adverse events[a]		
Stroke	2 (4.3)	24-31
Transient ischemic attack	1 (2.1)	30
Hypotension requiring hospitalization	2 (4.3)	11-32
Hypertension requiring hospitalization	1 (2.1)	3
Adverse events[b]		
Hypotension	2 (4.3)	1-11
Musculoskeletal pain	2 (4.3)	1-2
Dizziness	1 (2.1)	1
Sensibility disorder	1 (2.1)	5
Cognitive problems	1 (2.1)	12

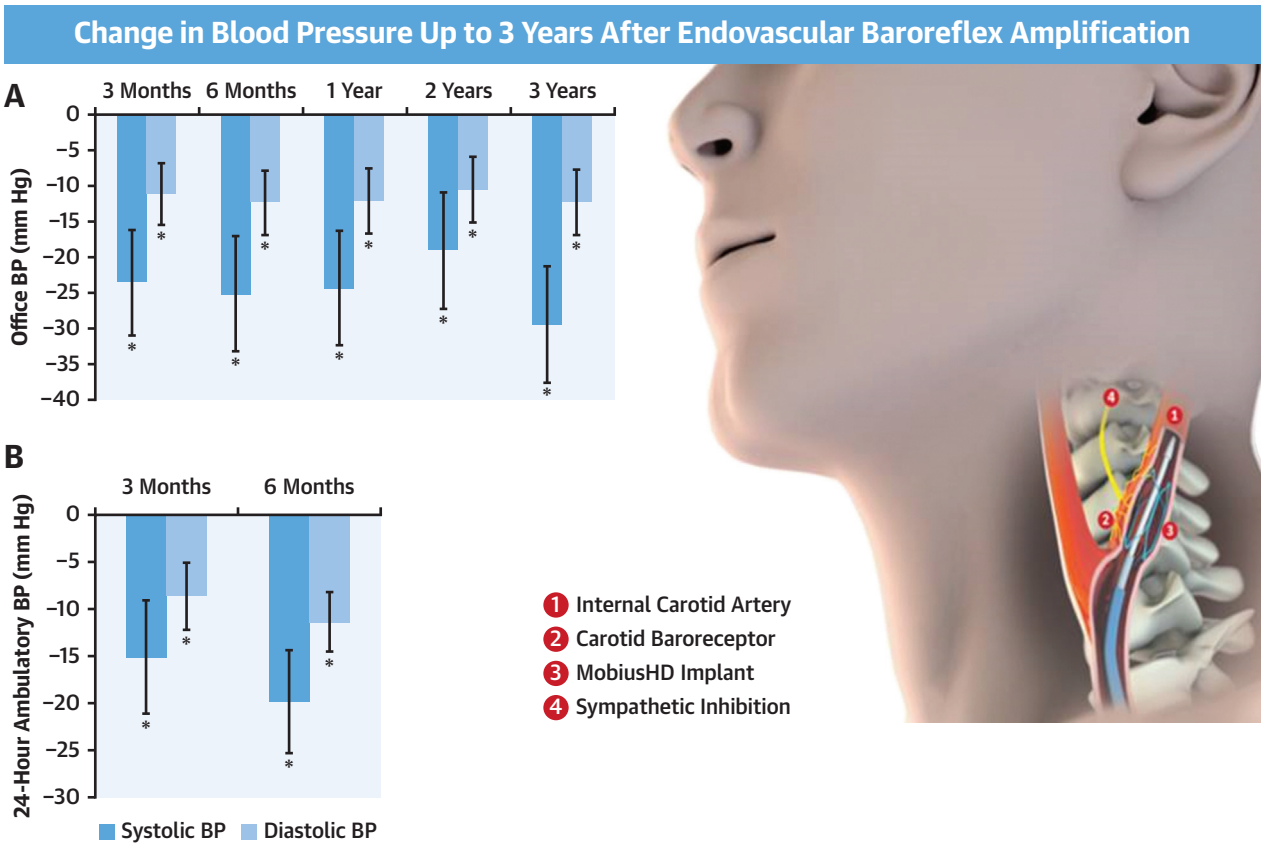
[a]All cerebrovascular events (stroke and transient ischemic attack) and serious adverse events reported as related or possibly related to the device or procedure or relatedness unknown, after 30 days. [b]Adverse events reported as related or possibly related to the device or procedure or relatedness unknown, after 30 days.

Six serious adverse or cerebrovascular events occurred more than 30 days postprocedure. Two patients had strokes at 24 and 31 months after implantation, the first on the contralateral side of the implant, the second ipsilateral. One patient experienced transient neurologic symptoms from the ipsilateral vascular territory of the device 30 months after MobiusHD implantation. Findings on diffusion-weighted magnetic resonance imaging were normal. Cerebral angiography showed a distal internal carotid artery stenosis, which was present before MobiusHD implantation. One patient required hospitalization for hypertension 3 months after treatment, and 2 patients experienced severe hypotension with syncope at 11 and 32 months postimplantation.

EFFECT OF EVBA ON OFFICE AND AMBULATORY BP.

Office BP decreased from baseline by 25/12 mm Hg (95% CI: 17 to 33/8 to 17 mm Hg) at 6 months, 24/12 mm Hg (95% CI: 16 to 32/8 to 17 mm Hg) at 1 year, 19/11 mm Hg (95% CI: 11 to 27/6 to 15 mm Hg) at 2 years, and 30/12 mm Hg (95% CI: 21 to 38/8 to 17 mm Hg) at 3 years (**Central Illustration**). Mean 24-hour ambulatory BP decreased by 20/11 mm Hg (95% CI: 14 to 25/8 to 15 mm Hg) at 6 months (**Central Illustration**). Analysis using the area-under-the-curve methodology confirmed these BP reductions (Supplemental Table 3). The BP reductions occurred despite a trend toward reduction in antihypertensive medication during follow-up: −1.1 DDD (95% CI: −2.1 to −0.2) at 6 months, −1.0 DDD (95% CI: −2.0 to 0.0) at 1 year, −0.5 DDD (95% CI: −1.6 to 0.6) at 2 years, and −0.5 DDD (95% CI: −1.6 to 0.7) at 3 years (**Table 3**). Heart rate did not change from baseline to 3 years (P = 0.32-0.91). Point estimates did not considerably change when observations from the single patient receiving the Barostim neo were excluded (Supplemental Table 4). The office systolic BP target of <140 mm Hg was reached in 33% of patients at 1 year (**Figure 3**), in 23% at 2 years, and in 37% at 3 years. A clinically relevant response (≥10 mm Hg decrease in office systolic BP or ≥1 DDD decrease in

CENTRAL ILLUSTRATION **Change in Office Blood Pressure and 24-Hour Ambulatory Blood Pressure During Follow-Up After Endovascular Baroreflex Amplification**



van Kleef, M.E.A.M. et al. J Am Coll Cardiol Intv. 2022;15(3):321–332.

(A) Change in office blood pressure up to 3 years after MobiusHD implantation. **(B)** Change in mean 24-hour ambulatory blood pressure at 3 and 6 months. **Bars** show means and **error bars** show 95% CIs estimated from mixed-effects linear model for repeated measurements. *$P < 0.0001$.

antihypertensive medication without an office systolic BP increase) was seen at 6 months in 73% of patients and remained stable at 1, 2, and 3 years (72%, 73%, and 77%). The proportion reaching a clinically relevant response at 6 months increased to 87% when the 24-hour ambulatory systolic BP requirement was added. Office systolic and diastolic BP remained stable over the 3-year follow-up period (P for time = 0.34 and 0.97, respectively).

ASSOCIATION BETWEEN BASELINE CHARACTERISTICS AND CHANGE IN OFFICE SYSTOLIC BP AFTER EVBA. By multivariable analysis, older age (per 10 years: −7.8 mm Hg; 95% CI: −14.6 to −1.1 mm Hg), higher baseline office systolic BP (per 10 mm Hg: −8.6 mm Hg; 95% CI: −13.4 to −3.9 mm Hg), and implantation of the MobiusHD on the left compared with the right (−22.6 mm Hg; 95% CI: −39.1 to −6.1 mm Hg) were associated with greater office systolic BP response (Table 4). Higher baseline office pulse pressure (per 10 mm Hg: 7.4 mm Hg; 95% CI: 2.1 to 12.7 mm Hg) was associated with less office systolic BP response. Sensitivity analysis for 24-hour ambulatory systolic BP response resulted in comparable estimates for baseline systolic BP, baseline pulse pressure, and side of implantation (Supplemental Table 5), although the latter two were not significant. The association between age and BP response was in the opposite direction compared with the main analysis but also not significant.

TABLE 3 Mean Baseline Blood Pressure, Heart Rate, Daily Defined Dose and Number of Drugs, and Changes Within 3 Years After MobiusHD Implantation

	Baseline		3 Months		6 Months		1 Year		2 Years		3 Years	
	Adjusted Mean	95% CI	Mean Change	95% CI	Mean Change	95% CI	Mean Change	95% CI	Mean Change	95% CI	Mean Change	95% CI
Office BP, mm Hg												
Systolic	181	(173 to 189)	−24	(−31 to −16)	−25	(−33 to −17)	−24	(−32 to −16)	−19	(−27 to −11)	−30	(−38 to −21)
Diastolic	107	(102 to 112)	−11	(−15 to −7)	−12	(−17 to −8)	−12	(−17 to −8)	−11	(−15 to −6)	−12	(−17 to −8)
24-h ambulatory BP, mm Hg												
Systolic	166	(161 to 170)	−15	(−21 to −9)	−20	(−25 to −14)	-	-	-	-	-	-
Diastolic	98	(94 to 103)	−9	(−12 to −5)	−11	(−15 to −8)	-	-	-	-	-	-
Daytime ambulatory BP, mm Hg												
Systolic	168	(164 to 173)	−15	(−21 to −9)	−20	(−25 to −14)	-	-	-	-	-	-
Diastolic	100	(96 to 105)	−8	(−11 to −4)	−11	(−14 to −8)	-	-	-	-	-	-
Nighttime ambulatory BP, mm Hg												
Systolic	157	(152 to 163)	−17	(−24 to −10)	−20	(−26 to −13)	-	-	-	-	-	-
Diastolic	92	(87 to 97)	−12	(−16 to −7)	−12	(−16 to −9)	-	-	-	-	-	-
Office heart rate, beats/min	74	(70 to 78)	−2	(−5 to 1)	−1	(−4 to 3)	0	(−4 to 3)	0	(−4 to 3)	0	(−3 to 4)
Daily defined dose	6.7	(5.3 to 8.2)	−1.3	(−2.1 to −0.5)	−1.1	(−2.1 to −0.2)	−1.0	(−2.0 to 0.0)	−0.5	(−1.6 to 0.6)	−0.5	(−1.6 to 0.7)
Number of drugs	4.2	(3.6 to 4.7)	−0.6	(−1.0 to −0.3)	−0.5	(−0.9 to −0.1)	−0.6	(−1.0 to −0.1)	−0.5	(−1.0 to −0.1)	−0.5	(−1.0 to −0.1)

Means are estimated from mixed-effects repeated measurements analysis.
BP = blood pressure.

DISCUSSION

Combined results from the 2 first-in-human studies of EVBA in patients with resistant hypertension demonstrated sustained, clinically meaningful BP reductions up to 3 years, despite trends toward a reduction in antihypertensive medication. The principal safety events concerned 2 TIAs in the early postprocedural period and 3 cerebrovascular events late during follow-up, some but not all of which were related to the device.

SAFETY. The most important concern of any permanent carotid implant is cerebrovascular safety. In the present study, 2 TIAs occurred within 30 days, directly after the procedure. Both patients had focal neurologic symptoms from the vascular territory ipsilateral to the implant, directly after device implantation, without confirmed stroke on cerebral computed tomography. Of note, these events occurred at 1 study center, at which (in contrast to all other sites) power injector-assisted carotid angiography was performed. Whether this contributed to these 2 events is unknown. Platelet thromboemboli, contrast encephalopathy due to severe hypertension during the multiple angiograms, air entrainment and emboli, device-related particulates, or focal hypoperfusion of a vulnerable area of the brain due to hypotension cannot be excluded.

In the absence of a control group, it is more challenging to adjudicate whether late events (>30 days) were related to the device or procedure versus whether they reflect the underlying natural history of a high-risk group of patients with resistant hypertension. In particular, 2 patients had late strokes: the stroke that occurred at 24 months on the contralateral side of the implant was not likely related to the device, whereas the stroke that occurred at 31 months on the ipsilateral of the implant may (or may not) have been related to the MobiusHD implant. The relatedness of the TIA occurring in 1 patient at 30 months (causing symptoms of ipsilateral amaurosis fugax and contralateral loss of sensibility in arm and leg) is also not unambiguous. Additional imaging with carotid duplex and carotid angiography showed plaque in the very distal part of the internal carotid artery, identical to baseline images. Given the generally low rate of stroke, a very large study would be required to determine whether the net effect of the MobiusHD on cerebrovascular events is harmful (because of the implant), beneficial (because of the substantial and sustained reduction in BP), or neutral.

The serious adverse events that occurred within 30 days postimplantation concerned hypotension requiring hospitalization (n = 2), hypertension requiring hospitalization (n = 1), and vascular access

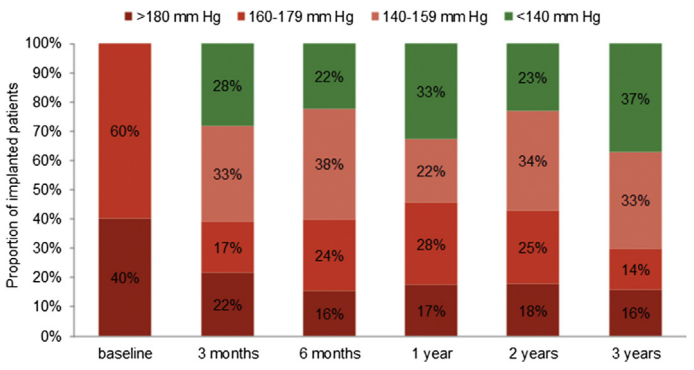
complications (n = 2), including 1 patient with closure device failure and 1 with a large groin hematoma that resulted in hypotension. All 5 events resolved without sequelae. The incidence of access-site complications could be reduced by introducing the device via the radial artery instead of the femoral artery,[20] but the current diameter of the delivery catheter precludes radial access.

EFFECTIVENESS. In patients with hypertension, the set point for baroreceptor firing is increased to adapt to the chronic high BP status,[21] resulting in increased sympathetic activity and persistence of hypertension. In animal experiments it has been demonstrated that endovascular modulation of the baroreflex increases baroreceptor firing,[16] which suppresses sympathetic nerve activity.[22] In the present study, EVBA by the implantable MobiusHD device substantially reduced BP in humans. The extent of office BP reduction observed in the present study was comparable with BP responses seen in observational studies evaluating baroreflex activation therapy (BAT).[11] The sustained BP reduction seen after MobiusHD implantation suggests that long-term resetting of the carotid baroreceptor response may be possible.

As EVBA is designed to inhibit the sympathetic nervous system by activating the baroreflex via alteration of carotid artery vessel wall geometry, patients with modulable baroreflexes, extreme sympathetic overactivity, and modifiable peripheral vasculature may benefit most. In the present study of patients with resistant hypertension across a wide range of ages (21-75 years) and cardiovascular risk, higher baseline systolic BP, older age, and implantation of the MobiusHD on the left were associated with greater systolic BP response. Baseline pulse pressure was associated with less systolic BP response. It is well recognized with all BP-lowering interventions that BP decreases more in patients with higher baseline BP than in those with lower baseline BP.[23,24] The observation that older age (after adjustment for baseline BP and pulse pressure) was associated with greater office BP response may be explained by increases in sympathetic activity with age,[25] although this was not confirmed in the sensitivity analysis of 6-month 24-hour ambulatory systolic BP. The observation that older age is favorable is important given the evidence that BP reduction is effective into old age (up to 85 years).[26] Patients with elevated pulse pressure (a measure of arterial stiffness) may respond less because of the structural changes of the vessel wall, which may render it less susceptible to modifications of autonomic activity.[27] Decreased BP response in patients with increased arterial stiffness has also been observed after treatment with BAT, in which patients with isolated systolic hypertension showed limited response.[11] Although patients with isolated systolic hypertension were not excluded in the present study, all enrolled patients had combined systolic-diastolic hypertension. These findings should be considered when evaluating patients for this treatment approach. The greater BP reduction in patients treated on the left compared with the right was unexpected. However, in a prior study stimulation of the left carotid baroreceptor (by positive neck pressure) caused greater muscle sympathetic nerve activity changes than stimulation of the right.[28] In the Rheos pivotal trial, stimulation of the right showed greater office systolic BP response than the left.[29] These discordances are not immediately explicable but may be due to differences in working mechanism: mechanically induced changes via EVBA versus direct stimulation of baroreflex afferents via BAT. As only 14 patients (30%) were treated on the left, the observed difference in the present study may also be due to chance.

It is important that identifiable and treatable causes of hypertension be excluded before patients are subjected to an invasive, potentially harmful, and costly treatment. A major factor contributing to resistant hypertension is medication nonadherence. Studies using direct screening methods to detect antihypertensive drugs in blood or urine have reported that 53% to 69% of patients with resistant hypertension are nonadherent, with one-third of nonadherent patients not taking any antihypertensive drugs at all.[30,31] Therefore, interventions aimed at increasing adherence (eg, confrontation of patients with negative medication screen results[32]) should be attempted before invasive antihypertensive

FIGURE 3 Proportions of Patients in 4 Office Systolic Blood Pressure Categories



Blood pressure categories at baseline and up to 3 years after MobiusHD implantation.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 15, NO. 3, 2022
FEBRUARY 14, 2022:321–332

TABLE 4 The Association Between Baseline Characteristics and Change in Office Systolic BP During Follow-Up

	Model 1			Model 2			Model 3		
		95% CI	*P* Value		95% CI	P Value		95% CI	*P* Value
Age (per 10 y)	−0.7	(−6.7 to 5.3)	0.810	−1.0	(−7.1 to 5.1)	0.740	−7.8	(−14.6 to −1.1)	0.024
Sex (female)	−4.7	(−18.6 to 9.2)	0.510	−5.0	(−19.2 to 9.2)	0.490	1.2	(−12.0 to 14.4)	0.860
History of renal denervation (yes)	−11.0	(−26.7 to 4.8)	0.170	−12.5	(−29.0 to 4.0)	0.140	−8.9	(−23.9 to 6.1)	0.250
Office systolic BP (per 10 mm Hg)	−5.2	(−8.8 to −1.6)	0.005	−5.6	(−9.3 to −1.9)	0.003	−8.6	(−13.4 to −3.9)	<0.001
Office pulse pressure (per 10 mm Hg)	−0.4	(4.7 to 4.0)	0.870	−0.3	(−5.1 to 4.4)	0.890	7.4	(2.1 to 12.7)	0.006
Heart rate (per 10 beats/min)	−2.5	(−8.7 to 3.7)	0.430	−2.5	(−9.1 to 4.1)	0.460	0.3	(−5.7 to 6.2)	0.930
Body mass index (per kg/m^2)	0.2	(−1.1 to 1.6)	0.720	0.2	(−1.2 to 1.6)	0.830	−0.3	(−1.6 to 1.0)	0.650
eGFR (per 10 mL/min/1.73 m^2)	2.1	(−1.6 to 5.8)	0.270	2.3	(−1.8 to 6.5)	0.270	1.0	(−2.5 to 4.5)	0.570
Side of implantation (right)	15.0	(0.5 to 29.4)	0.043	15.7	(0.0 to 31.4)	0.049	22.6	(6.1 to 39.1)	0.007

Results from mixed effects linear modeling: model 1 was adjusted for change in daily defined dose; model 2 was additionally adjusted for age and sex; model 3 was additionally adjusted for history of renal denervation, office systolic BP, office pulse pressure, heart rate, body mass index, eGFR (estimated using the Chronic Kidney Disease Epidemiology Collaboration formula), and side of implantation. Positive values indicate less blood pressure reduction, negative values indicate more blood pressure reduction (ie, the coefficient −7.8 for age means that for every 10 years older at baseline, BP decreases by 7.8 mmHg).

BP = blood pressure; eGFR = estimated glomerular filtration rate.

treatments are considered. As compliance with antihypertensive medications in the present study was assessed solely by self-reported adherence from the patient's diary, some patients treated with EVBA may have been nonadherent. Future studies with EVBA will perform direct screening for antihypertensive medication in blood or urine to identify nonadherent patients prior to randomization and during follow-up.

STUDY LIMITATIONS. The major limitation of the present study is that it is observational and uncontrolled, and thus, the observed effects can be attributed to extraneous factors including the Hawthorne effect, placebo effect, and regression to the mean. The lack of a control group also hinders the assessment of differences in adverse events. This is particularly important in trying to evaluate causal associations between device implantation and cerebrovascular events occurring remotely from the time of intervention in a population of patients at high risk for cardiovascular events. To overcome this limitation, randomized, sham-controlled, double-blind trials are being considered. These trials should provide more data on the unbiased safety and efficacy of MobiusHD implantation in patients with resistant hypertension. Until more evidence becomes available, EVBA should not be offered as a regular treatment for patients with hypertension. Whether EVBA may become an adjunct or alternative to evidence-based treatments such as renal denervation depends on the unbiased efficacy and cerebrovascular safety in future trials. Another limitation of the present study is that no direct adherence testing of drugs or metabolites in urine or blood was performed. Finally, we did not obtain 24-hour ambulatory BP data after 6 months. However, there was consistency between the office and 24-hour ambulatory BP response at earlier time points.

CONCLUSIONS

In the present open-label observational study, implantation of the passive endovascular MobiusHD device in patients with resistant hypertension substantially lowered BP with sustained effectiveness over the reported 3-year follow-up. Randomized, sham-controlled trials should further evaluate the risk-benefit profile of the MobiusHD device. Future studies are also warranted to identify the ideal patient profile for MobiusHD implantation and its appropriate use relative to other pharmacologic and device-based approaches to hypertension.

ACKNOWLEDGMENTS The authors thank all CALM-FIM investigators and the local study teams for the dedicated research support. Investigators are listed in the Supplemental Appendix.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by Vascular Dynamics, Inc. The study sponsor was involved in study design, data monitoring, and central storage of the data. Data analysis was performed by an external statistician who was hired by the study sponsor and performed the analysis according to the methods as requested by the authors. The authors determined the analytical methodology and data interpretation and prepared the manuscript. The sponsor had no role in data interpretation or manuscript preparation. The authors had final responsibility for the decision to submit the paper for publication. Dr van Kleef is paid through a research grant from Vascular Dynamics. Dr Devireddy is a consultant for Edwards Lifesciences, Medtronic, ReCor

Medical, and Shockwave Medical. Dr Van der Heyden is a paid proctor for Vascular Dynamics. Dr Bates is a consultant for CeloNova BioSciences, Vascular Dynamics, and W.L. Gore. Dr Bakris is a consultant for Merck, Janssen, Bayer, and Vascular Dynamics; and has received grant or clinical trials research support from Janssen, Bayer, Vascular Dynamics, Vifor, Novo Nordisk, Ionis, and Alnylam. Dr Stone has received speaker or other honoraria from Terumo and Cook; has served as a consultant to Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Abiomed, Ancora, Elucid Bio, Occlutech, CorFlow, Reva, Matrizyme, MAIA Pharmaceuticals, Vascular Dynamics, Shockwave, V-Wave, Cardiomech, and Gore; and has equity or options in Ancora, Cagent, Applied Therapeutics, the Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, the MedFocus family of funds. Dr Williams is a consultant for Vascular Dynamics. Dr Spiering is a consultant for Vascular Dynamics; and has received a research grant from Vascular Dynamics.

ADDRESS FOR CORRESPONDENCE: Dr Wilko Spiering, Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, P.O. Box 85500, 3508 GA Utrecht, the Netherlands. E-mail: w.spiering@umcutrecht.nl.

PERSPECTIVES

WHAT IS KNOWN? The CALM-FIM_EUR study demonstrated that EVBA in patients with resistant hypertension significantly lowered BP with an acceptable safety profile during 6-month follow-up.

WHAT IS NEW? The present study showed sustained, clinically meaningful BP reductions up to 3 years following MobiusHD implantation. EVBA appeared to have an acceptable safety profile in patients with uncomplicated implantation.

WHAT IS NEXT? Randomized, sham-controlled clinical trials should provide more information about the risk-benefit profile of MobiusHD implantation in patients with resistant hypertension. Future studies should also be performed to identify the ideal patient profile for MobiusHD implantation and its appropriate use relative to other pharmacologic and device-based approaches to hypertension.

REFERENCES

1. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation*. 2016;134(6):441–450.

2. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation*. 2012;125(13):1635–1642.

3. Salles GF, Cardoso CR, Muxfeldt ES. Prognostic influence of office and ambulatory blood pressures in resistant hypertension. *Arch Intern Med*. 2008;168(21):2340–2346.

4. Mahfoud F, Schlaich MP, Lobo MD. Device therapy of hypertension. *Circ Res*. 2021;128(7):1080–1099.

5. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370(15):1393–1401.

6. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet*. 2018;391(10137):2335–2345.

7. Kandzari DE, Bohm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet*. 2018;391(10137):2346–2355.

8. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet*. 2017;390(10108):2160–2170.

9. Azizi M, Sanghvi K, Saxena M, Gosse P, Reilly JP, Levy T, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. *Lancet*. 2021;397(10293):2476–2486.

10. Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J, 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(7):765–773.

11. de Leeuw PW, Bisognano JD, Bakris GL, Nadim MK, Haller H, Kroon AA, et al. Sustained reduction of blood pressure with baroreceptor activation therapy: results of the 6-year open follow-up. *Hypertension*. 2017;69(5):836–843.

12. Tordoir JH, Scheffers I, Schmidli J, Savolainen H, Liebeskind U, Hansky B, et al. An implantable carotid sinus baroreflex activating system: surgical technique and short-term outcome from a multi-center feasibility trial for the treatment of resistant hypertension. *Eur J Vasc Endovasc Surg*. 2007;33(4):414–421.

13. Heusser K, Tank J, Brinkmann J, Menne J, Kaufeld J, Linnenweber-Held S, et al. Acute response to unilateral unipolar electrical carotid sinus stimulation in patients with resistant arterial hypertension. *Hypertension*. 2016;67(3):585–591.

14. van Kleef M, Bates MC, Spiering W. Endovascular baroreflex amplification for resistant hypertension. *Curr Hypertens Rep*. 2018;20(5):46.

15. Mendelowitz D, Scher AM. Pulsatile sinus pressure changes evoke sustained baroreflex responses in awake dogs. *Am J Physiol*. 1988;255(3 Pt 2):H673–H678.

16. Spiering W, Williams B, Van der Heyden J, van Kleef M, Lo R, Versmissen J, et al. Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle clinical study. *Lancet*. 2017;390(10113):2655–2661.

17. Modolo R, de Faria AP, Ritter AMV, Coca A, Moreno H. Defined daily dose (DDD) and its potential use in clinical trials of resistant hypertension. *Int J Cardiol*. 2016;202:515–516.

18. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. Accessed December 20, 2021. https://www.whocc.no/filearchive/publications/1_2013guidelines.pdf

19. Frank M, Peyrard S, Bobrie G, Azizi M. Method of mean value calculation as an additional source of variability in ambulatory blood pressure measurement. *Am J Hypertens*. 2010;23(7):725–731.

20. Gragnano F, Branca M, Frigoli E, Leonardi S, Vranckx P, Di Maio D, et al. Access-site crossover in patients with acute coronary syndrome undergoing invasive management. *J Am Coll Cardiol Intv*. 2021;14(4):361–373.

21. Grassi G, Cattaneo BM, Seravalle G, Lanfranchi A, Mancia G. Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. *Hypertension*. 1998;31(1):68–72.

22. Lohmeier TE, Irwin ED, Rossing MA, Serdar DJ, Kieval RS. Prolonged activation of the baroreflex produces sustained hypotension. *Hypertension*. 2004;43(2):306–311.

23. Mokwe E, Ohmit SE, Nasser SA, Shafi T, Saunders E, Crook E, et al. Determinants of blood pressure response to quinapril in black and white hypertensive patients: the Quinapril Titration

Interval Management Evaluation trial. *Hypertension*. 2004;43(6):1202–1207.

24. Brunner M, Cooper-DeHoff RM, Gong Y, Karnes JH, Langaee TY, Pepine CJ, et al. Factors influencing blood pressure response to trandolapril add-on therapy in patients taking verapamil SR (from the International Verapamil SR/Trandolapril [INVEST] study). *Am J Cardiol*. 2007;99(11):1549–1554.

25. Sundlof G, Wallin BG. Human muscle nerve sympathetic activity at rest. Relationship to blood pressure and age. *J Physiol*. 1978;274:621–637.

26. Blood Pressure Lowering Treatment Trialists Collaboration. Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: an individual participant-level data meta-analysis. *Lancet*. 2021;398(10305):1053–1064.

27. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens*. 2002;15(5):426–444.

28. Williamson JW, Muzi M, Ebert TJ. Unilateral carotid sinus stimulation and muscle sympathetic nerve activity in man. *Med Sci Sports Exerc*. 1996;28(7):815–821.

29. de Leeuw PW, Alnima T, Lovett E, Sica D, Bisognano J, Haller H, et al. Bilateral or unilateral stimulation for baroreflex activation therapy. *Hypertension*. 2015;65(1):187–192.

30. de Jager RL, van Maarseveen EM, Bots ML, Blankestijn PJ, SYMPATHY Investigators. Medication adherence in patients with apparent resistant hypertension: findings from the SYMPATHY trial. *Br J Clin Pharmacol*. 2018;84(1):18–24.

31. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens*. 2013;31(4):766–774.

32. Gupta P, Patel P, Strauch B, Lai FY, Akbarov A, Gulsin GS, et al. Biochemical screening for nonadherence is associated with blood pressure reduction and improvement in adherence. *Hypertension*. 2017;70(5):1042–1048.

KEY WORDS antihypertension device, baroreceptor modulation, baroreflex, endovascular baroreflex amplification, hypertension

APPENDIX For a list of CALM-FIM investigators, a detailed description of the CALM-FIM study inclusion and exclusion criteria, a description of the area-under-the-curve methodology, and supplemental tables, please see the online version of this paper.