Treatment of Hypertension (HTN) Today
Unmet clinical need -- Many Patients Uncontrolled Despite Treatment

<table>
<thead>
<tr>
<th>Per 2017 ACC/AHA Guidelines</th>
<th>United States Patients</th>
<th>% Medically Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with Hypertension</td>
<td>103.3M</td>
<td></td>
</tr>
<tr>
<td>Medically Treated</td>
<td>54.7M</td>
<td></td>
</tr>
<tr>
<td>1+ Medications &amp; BP above Goal</td>
<td>29.2M</td>
<td>53%</td>
</tr>
<tr>
<td>3+ Medications &amp; BP above Goal</td>
<td>7.6M</td>
<td>14%</td>
</tr>
</tbody>
</table>

-HTN uncontrolled in more than half of all patients receiving medical treatment

-~15% of patients uncontrolled despite receiving 3+ medications (drug resistant)

-HTN is associated with increased cardiovascular risk

-Aging population and increased overall prevalence of HTN means this is a growing problem

-Unmet clinical need has led to the development of new interventional device-based approaches

Hypertension-related lifetime risk

HTN significantly increases the risk of cardiovascular disease

Rapsomaniki, Lancet 2014
Blood pressure reduction reduces risk

Meta-analysis of 123 large-scale blood pressure lowering trials between Jan 1966 and July 2015

*Ettehad, Lancet 2016*

<table>
<thead>
<tr>
<th>Event</th>
<th>Studies</th>
<th>Intervention</th>
<th>Control</th>
<th>RR (95% CI) per 10 mmHg reduction in systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiovascular events</td>
<td>55</td>
<td>13209</td>
<td>14068</td>
<td>0.80 (0.77-0.83)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>56</td>
<td>4862</td>
<td>5201</td>
<td>0.83 (0.78-0.88)</td>
</tr>
<tr>
<td>Stroke</td>
<td>54</td>
<td>4635</td>
<td>5378</td>
<td>0.73 (0.68-0.77)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>43</td>
<td>3284</td>
<td>3760</td>
<td>0.72 (0.67-0.78)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>16</td>
<td>890</td>
<td>834</td>
<td>0.95 (0.84-1.07)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>57</td>
<td>9775</td>
<td>9998</td>
<td>0.87 (0.84-0.91)</td>
</tr>
</tbody>
</table>

**Reduction of SBP by 10 mmHg:**
- MACE -20%
- CHD -17%
- Stroke -27%
- Heart failure -28%
- Renal failure -5% (ns)
- All-cause mortality -13%
Baroreceptors and Baroreflex

- Baroreflex is an essential component of the body's natural regulation of BP
- Powerful centralized BP modulation
- Arterial baroreceptors are mechanoreceptors
  - Respond to stretch and wall tension
  - Important afferent input to central nervous system (CNS)
- Increased signaling from baroreceptors to CNS
  - Centralized correction of BP and lowering of heart rate
  - Sympathoinhibitory response to maintain homeostasis

Baroreceptor Neuromodulation or Amplification

- Based on long history of research on baroreceptors
- Increase baroreceptor signaling to CNS
- CNS modulates SNS to reduce BP

EndoVascular Baroreflex Amplification (EVBA)
MobiusHD® Implant Design

- Self-expanding nitinol implant
- Reshapes the carotid sinus
- Increases vessel radius without over-expansion
- Increases arterial stretch amplifying baroreceptor signals to CNS
**Controlling And Lowering Blood Pressure with the MobiusHD First-In-Man (CALM-FIM) Study**

- Multi-center, prospective, open-label feasibility study
- Subjects enrolled in centers in Europe (n=30) and USA (n=17)
- Resistant Hypertension
  - Mean Office Systolic BP ≥ 160 mmHg
  - Mean 24-hour Ambulatory Systolic BP ≥ 130 mmHg
  - Mean 24-hour Ambulatory Diastolic BP ≥ 80 mmHg
  - Stable ≥ 30 days on max tolerated doses of ≥ 3 antihypertensive drugs, including a diuretic
  - Adherence to antihypertensive medication, as self reported daily in diaries for at least 30 days

CALM-FIM Trial Design
Major Exclusion Criteria

- Identifiable secondary cause of Hypertension other than sleep apnea

- Anatomical criteria
  - Any plaque or ulceration in the carotid artery or aortic arch
  - Internal carotid artery lumen diameter <5.0 mm or >11.75 mm at intended implant location

- Use of Oral Anticoagulants or other contraindication to Dual Antiplatelet Therapy (DAPT)

- eGFR ≤ 45 mL/min per 1.73 m²

- MI in previous 3 months or CVA in previous year

CALM-FIM Trial Design
Procedural requirements

- Duplex ultrasonography and CT angiography or MRA of carotid arteries
- Interventionalists ≥ 100 carotid stent implants
- DAPT with 80–325 mg aspirin and a P2Y12 receptor inhibitor
  - 3 days pre to 3 months post implantation
  - Aspirin continued indefinitely.
- Angiographic confirmation of carotid anatomy and device sizing
- Over-the-wire implant deployment using 6Fr guide sheath or 8F guiding catheter
- Unilateral placement with no preference of either right or left ICA
- Anticoagulation according to local hospital carotid stent protocols

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

Willis Spiering, Bryan Williams, Jan Vander Heyden, Monique van Kleef, Rut Lie, Josie Versmissen, Adiasson Moreille, Abraham Koon, Hanneke Kruiter, Gary Arai, Gregg WShore, Malit Rates, forth CALM-FIM, EUL investigation

86 patients assessed for eligibility

54 excluded
- 20 office SBP <160 mm Hg
- 11 carotid plaque
- 6 comorbidities
- 4 secondary hypertension
- 2 inappropriate vessel size
- 11 miscellaneous

32 patients with carotid angiograms

2 excluded for inappropriate vessel size

30 patients with attempted device implantation

30 patients with 6 months' clinical follow-up

Figure 2: Trial profile
SBP=systolic blood pressure.


Rev. 21AUG18a
## CALM-FIM Europe Results

### Baseline Data

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>15 male: 15 female</td>
</tr>
<tr>
<td>Centers/Implants</td>
<td>30 implants at 6 centers</td>
</tr>
<tr>
<td>Mean age</td>
<td>52 years</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>28.0 kg/m2</td>
</tr>
<tr>
<td>Mean Office BP</td>
<td>184/108 mmHg (95% CI 178-190/102-144)</td>
</tr>
<tr>
<td>Mean 24-hr Ambulatory BP</td>
<td>166/100 mmHg (95% CI 160-174/95-105)</td>
</tr>
<tr>
<td>Mean antihypertensives</td>
<td>4.4</td>
</tr>
<tr>
<td>Spironolactone usage</td>
<td>17 patients</td>
</tr>
<tr>
<td>Mean Daily Defined Dose</td>
<td>6.8</td>
</tr>
<tr>
<td>Failed Renal Denervation Treatment</td>
<td>8/30 (27%)</td>
</tr>
</tbody>
</table>

CALM-FIM Europe Results

Safety

- Successful implant in all patients
  - 19 right ICA, 11 Left ICA

- No device embolization, migrations, or significant changes in plaque formation in carotid arteries

- Adverse events adjudicated by DSMB

- No Unanticipated Adverse Device Effects (UADEs)

- 5 Serious Adverse events in 4 patients deemed possibly related to device or procedure
  - All resolved without sequelae

CALM–FIM Europe Results
24-hour Ambulatory Blood Pressure Measurements

- Significant Office BP reductions at all time points through 6 months
- Significant Ambulatory BP reductions at 3 and 6 months
- Median number of antihypertensive medications reduced by 0.50 (IQR 1.25–0, p=.0020)
- Median DDD was reduced by 0.42 units (2.13–0.09, p=0.010)
- 80% self-reported medication adherence
- High rates of responders, and/or medication reductions

### CALM-FIM Combined Results (US and EUR)
#### Baseline Data and Procedure Overview

**Baseline Characteristics (n=42)**

**Patients with 6 month Results (5 patients with 6 month follow up pending)**

<table>
<thead>
<tr>
<th>Baseline Characteristic (Patients with 6 month results)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>21 male: 21 female</td>
</tr>
<tr>
<td>Mean age</td>
<td>54 years (21 to 76)</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>$29 \pm 5.2$ kg/m²</td>
</tr>
<tr>
<td>Mean Office BP</td>
<td>$182/108$ mmHg ($\pm 17/16$)</td>
</tr>
<tr>
<td>Mean 24-hr Ambulatory BP</td>
<td>$165/98$ mmHg ($\pm 16/15$)</td>
</tr>
<tr>
<td>Mean antihypertensives</td>
<td>$4.4 \pm 1.2$</td>
</tr>
<tr>
<td>Spironolactone usage</td>
<td>21 patients</td>
</tr>
<tr>
<td>Mean Daily Defined Dose</td>
<td>$7.0 \pm 4.4$</td>
</tr>
<tr>
<td>Failed Renal Denervation Treatment</td>
<td>$9/42$ (21%)</td>
</tr>
</tbody>
</table>

*Source: Bates, MC, TCT 2017*
## CALM-FIM Combined Results (US and EUR)
### Baseline Data and Procedure Overview

### EVBA Procedures (n=42)

**Successful Implants**

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers/Implants</td>
<td>42 implants at 13 centers (7 US and 6 EUR)</td>
</tr>
</tbody>
</table>
| Implant Site            | 29 right ICA  
                          | 13 left ICA |
| Implant Sizing          | 9 Size A (5.00 – 7.00 mm)  
                          | 31 Size B (6.25 – 9.00 mm)  
                          | 2 Size C (8.00 – 11.75) |

Source: Bates, MC, TCT 2017
CALM-FIM Combined Results (US and EUR)
Safety (n=42)

- Successful implant in all patients
- No device embolization, migrations, or significant changes in plaque formation in carotid arteries
- 42 patients through 6 month follow-up
- Adverse events adjudicated by DSMB
- No Unanticipated Adverse Device Effects (UADEs)
- 10 Serious Adverse events in 9 patients deemed possibly related to device or procedure
  - All resolved without sequelae

Source: Updated from Bates, MC, TCT 2017
CALM-FIM Updated Results
24-hour Ambulatory Blood Pressure Measurements

Mean 24h ABP (mmHg)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>90 Days</th>
<th>180 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>47</td>
<td>46</td>
<td>42</td>
</tr>
<tr>
<td>SBP</td>
<td>165</td>
<td>151</td>
<td>145</td>
</tr>
<tr>
<td>DBP</td>
<td>98</td>
<td>90</td>
<td>87</td>
</tr>
</tbody>
</table>

Δ’s for Paired Data
(Includes baseline and 90 day data for all treated subjects)

Source: Bates, MC, TCT 2017
The CALM-2 Pivotal FDA Approval Trial Design
Clinicaltrials.gov identifier NCT03179800

Principal Investigators:
Bryan Williams and Gregg W. Stone

Resistant Hypertension
n= up to 300
≥60 centers worldwide

Baseline DOT ABPM
Carotid Angiogram

1:1 Randomization

Intervention
MobiusHD Implant (DAPT)
Sham Procedure (placebo DAPT)

Primary Outcome
90D safety 180D Efficacy
90D safety 180D Efficacy

LT Follow-up
Through 5 Years
Through 5 Years

Key Baseline Assessments
- Urinalysis for antihypertensive medication compliance
- 8 weeks stable on up to 5 antihypertensive medications\(^1\) — A+C+D\(^2\)
- DOT-ABPM (24-hr ABPM after witnessed medication consumption)
- Seated automated office blood pressure
- Baseline carotid angiography

1 Stable* baseline ABPM24hr Screening and Baseline ABPM SBP > 145 mmHg
2 DOT = Direct Observational Therapy
3 DOT = Direct Observational Therapy
4 Rev. 21AUG18a

\(^1\) No change in medication or dos
\(^2\) A=ACE or ARB + C = CCB + D= Diuretic
The CALM-2 Pivotal FDA-Approval Trial Design
Clinicaltrials.gov identifier NCT03179800

Additional key study elements

• Follow-up: 7 Days, 30 Days, 90 Days, 180 Days, 365 Days, and every 6 months for 5 years
• Maintain medication regimen through 12 months (DOT, urinalysis)
• Independent hypertension eligibility committee reviews
• Primary Effectiveness: Change in Ambulatory Blood Pressure at 6 Months
• Safety: Composite of cardiovascular and neurovascular events at 3 Months
CALM-2 Enrollment Challenges

- Multiple medication compliance tests
- High baseline blood pressure requirements ($\geq 145$ mmHg)
  - Multiple blood pressure measurements prior to enrollment
    - Screening and Baseline ABPM Measurements
  - Within patient variability presents opportunities for screen failures
- Sham control arm
- Cross over requirements