For Dr. Gregg Stone

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tbody>
<tr>
<td>Consultant/Research Support</td>
<td>None</td>
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<tr>
<td>Consulting Fees/Phonovations</td>
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<tr>
<td>Major Stock Shareholder/Philly</td>
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<td>Royalties/Income</td>
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<td>Intellectual Property Rights</td>
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<td>Other Financial Benefits</td>
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Strain equation

- Strain = \( \frac{F - f_1}{f_2 - f_1} \)
- \( f_1 \) = wall strain
- \( f_2 \) = pressure inside artery
- \( f_3 \) = artery internal radius
- \( f_4 \) = artery wall thickness
- \( f_5 \) = Young’s Modulus
- \( f_6 \) = perimeter

Device Description
- 3 sizes for various carotid bulb diameters
- Recapture and reposition capability: balloon-on-wire system

Baseline patient data
- 40 patients (20 males, 20 females)
- Mean age 53 (21-76) years
- Mean BMI 28 ±5.2 kg/m²
- Mean office BP 182/108 (±17/16) mmHg
- Mean 24-hr BP 165/98 (±16/15) mmHg
- Mean 4.4±1.2 antihypertensives (DDD: 7.0±4.4 units)
- 21 patients used spironolactone
- 9 patients had failed on renal denervation

CALM FIM Study
- Endovascular baroex: a feasibility study for resistant hypertension; a safety and proof-of-principle clinical study
- Sponsor: Vascular Dynamics Inc.

Mechanism of Action
- Increase in strain/stretch within the device windows

- • 3 sizes for various carotid bulb diameters
- • Recapture and reposition capability: balloon-on-wire system

Endovascular baroex: a feasibility study for resistant hypertension; a safety and proof-of-principle clinical study

- • Prospective, open-label, multicenter, first-in-man, safety study
- • CALM-HIM-US (20 patients) and CALM-HIM-EUR (30 patients)
- • Severe resistant hypertension:
  - Office SBP 160+ mmHg
  - 23 antihypertensives, of which one is a diuretic
- • Primary outcomes: incidence of SAEs and unanticipated adverse device effects (UADE) at month 6
- • Secondary outcomes: changes in OBP and 24-hr ABP
- • Mean exclusion: obstructive cardiovascular disease
- • Follow-up: 3 years
- • Sponsor: Vascular Dynamics Inc.
**Implantations**

- All interventionalists had experience with >100 carotid stent placements
- Duplex and CTA/MRA prescreening of ICAs with central review
- Start DAPT 3 days before implantation
- So far, 40 implantations:
  - Regions
    - Netherlands: 28 implantations in 5 centers (14, 7, 4, 2, 1)
    - USA: 10 implantations in 5 centers (3, 3, 1, 1, 1)
    - Germany: 2 implantations in 1 center

**Safety**

- 37/40 patients have reached the 6 month safety endpoint
- 0 UADs and 9 SAEs adjudicated by the DSMB to date (possibly) related to procedure or device:
  - Bleeding (n=1):
    - Closure device failure (surgically repaired)
  - Symptomatic hypotension (n=6):
    - Large drop in BP and/or acute renal failure (hydration, meds reduction)
  - Symptomatic hypertension (n=2):
    - Hypertension with symptoms (hospitalization, meds increase)
- All SAEs have been adequately managed and/or resolved

**Introduction to the “Controlling and Lowering Blood Pressure With the MobiusHD™ (CALM-2)”**

**Study Chairs:**
- Bryan Williams, MD: University College London
- Gregg Stone, MD: CRF and Columbia University

**ClinicalTrials.gov**

NCT03179800

**What is Unique about CALM 2?**

- Strict Medication compliance adjudication
- Direct observed therapy
- Urine testing
- Permanent implant in the carotid
- Preprocedure anatomic risk assessment:
  - Stabilized DAPT is implantation can be extended to the carotid artery and beyond a disease
  - Permanent implantation to artery and landing zone on ultrasound (CTA or MRA)
    - Carotid disease >1.0 mm mild, <2.0 mm moderate, >2.0 mm severe
  - Postprocedure imaging of carotid bulb and implant

**24-hr ABP**

- Bl. n=40
- 90 d n=38
- 180 d n=37

**Primary Outcome**

- Primary outcome: DDC-ABPM
- 6% DDC-ABPM with central monitoring
- Baseline stable ARB -24 hr SBP >145 sys and within 20% between screening and randomization
- DAPT and/or implantation
- Stable baseline ABPM – 24 hr SBP >145 sys and within 20% between screening and randomization
- Primary Outcome
- 6% DDC-ABPM with central monitoring
- 6% change in medication or dose
- DOT = Direct Observational Therapy
- Significance of obstructive vascular of aortic arch and great vessels on ultrasound, CTA or MRA placement (CTA or MRA) or landing zone restrictions, i.e. inadequate vessel length or tapering, and/or curvature, precluding safe implant placement
Acknowledgements:

- Yossi Gross (Inventor and serial innovator)
- Wilko Spiering, MD who led the CALM FIM-EU and provided some of the slides used
- Bryan Williams, MD who’s work in this domain has significantly impacted the field and who kindly provided some of the slides presented
- Dr. Juri Siedentopf and Robert Shetty at Vascular Dynamics who have remained focused on patient safety and advancing strong clinical evidence for this technology
- Dr. Gregg Stone for his leadership and guidance on the clinical trials discussed.

Backup slides

- Secondary hypertension, except treated using active agents such as α-1 blockers, α-1 agonists
-近期使用β受体阻滞药

- Obstructive carotid disease, plaque, ulceration

- Significant obstruction vascular of aortic arch and great vessels on ultrasound, CTA or MRI

- ICA lesion diameter < 4.5 mm or > 12.5 mm within the planned location of the implant placement (CTA or MRI) or landing zone restrictions, i.e. inadequate vessel length or tapering, and/or anastomosis precluding safe implant placement

CALM-2 Study Typical Clinical Exclusion criteria

- Active infection within the last month requiring antibiotics
- Uncontrolled co-morbid medical or mental health conditions, that would adversely affect trial participation, or reduce life expectancy < 1 year
- Planned surgery or procedure within the next 6 months requiring cessation of antiplatelet medications
- Pregnancy or lactating females
- Chronic kidney disease (eGFR < 45 ml/min)

Efficacy End-points

Primary Outcome

- The difference in mean daytime and nighttime SBP from baseline to the 18C day and 365-day visits, comparing the MIRLIS FP implant arm versus the sham-controlled arm

Secondary Outcomes:

- Change in number and dosage of antihypertensive medications from baseline to 365 days
- Change in quality of life scores
- Change in healthcare utilization including number of hospitalizations and office visits due to hypertension
Safety End-points
• Composite Safety Outcome:
  • Includes: MI, Stroke, Death, device embolization, carotid occlusion, new ipsilateral carotid stenosis requiring surgical or percutaneous intervention, and bleeding during the 30-day followup.
  • Comprehensive Safety assessments:
    • Include: Adverse Events (AEs), Serious Adverse Events (SAEs), and unanticipated adverse device effects (UADDs) • From initial screening through the last visit (5 years).

Preclinical Highlights
Canine Studies
Hemodynamic Changes
Carotid sinus nerve firing

Carotid Sinus Physiologic Principles:
1. Only activated by stretch, NOT pressure
2. Sustained activation only with pulsatile stretch
3. “Resetting” occurs with HTN resulting in a blunted baroreceptor response

Adventitia is thick compared to the distal ICA increasing elasticity
Media has more collagen and less smooth muscle than the distal ICA increasing elasticity