# Modern Era Clinical Trial Strategies for Cerebral Embolic Protection Devices

*Alexandra Lansky, MD*
*Professor of Medicine*
*Yale School of Medicine, New Haven, CT*

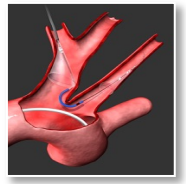
# Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had a financial relationship with a company producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

| Nature of Financial Relationship | Ineligible Company |
| --- | --- |
| Grant/Research Support | Abiomed, Abbott Vascular, Bard, Boston Scientific, Biocardia, Biotronik, Conformal, Emboline, Filterlex, Gore, Intact Vascular, Keystone Heart, Venus, Limflow, Microport, Myocardia, Reva, Sinomed, Shockwave, Surmodics, Veryan Medical |
| Consultant Fees/Honoraria | Boston Scientific |

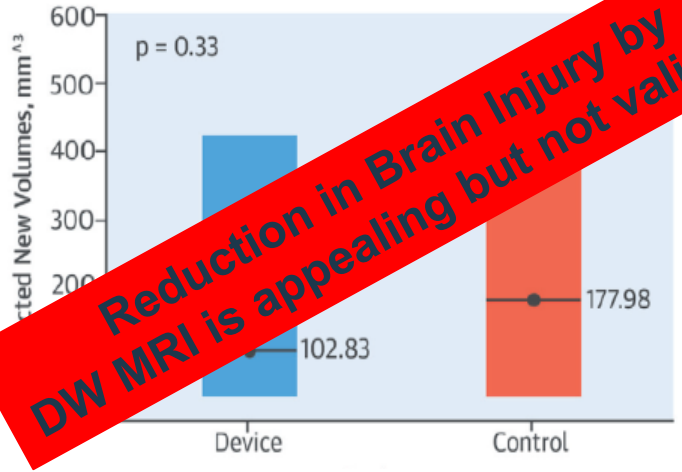
**All financial relationships have been mitigated.**
Faculty disclosure information can be found on the app

# Challenges for Future CEP Trial Design
# Predicate has modest Effectiveness



## SENTINEL IDE (N=435)

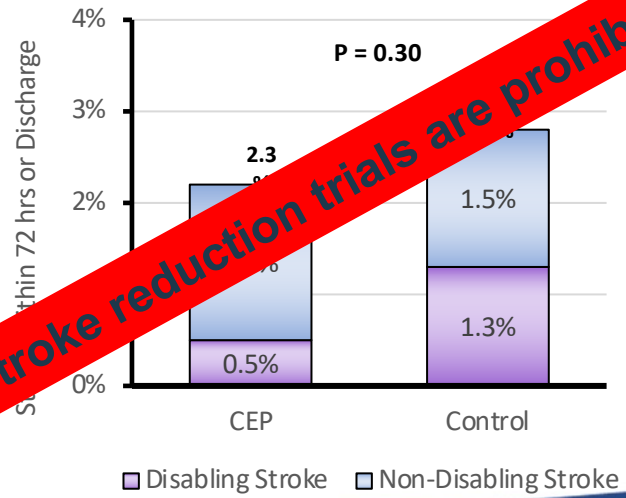
Primary Efficacy Endpoint: Mean lesion volume in protected brain by MRI at 2-7 days




Reduction in Brain Injury by DW MRI is appealing but not validated

## PROTECTED TAVR (N=3000)

Primary Efficacy Endpoint
All stroke at 72 hours




Stroke reduction trials are prohibitive



Kapadia et al. JACC 2017; 69: 367-77

# Predicate 510K vs Denovo 510K
# RCT vs CEP or no CEP or SC

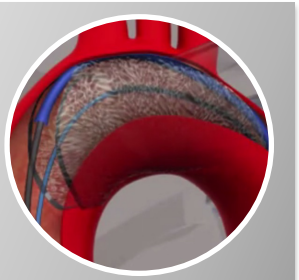
**Safety:** Non-Inferiority

- Combined Safety and Efficacy
  - MACE defined as Death, Stroke, AKI stage 2-3

**Efficacy:** Superiority vs Non-inferiority

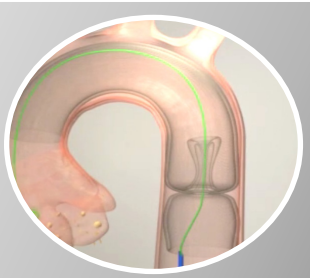
- Efficacy:
  - Stroke
  - All AKI
  - Systemic embolization
  - CNS Injury imaging (DW MRI surrogate?)

# Trial Design for CEP Capture Devices



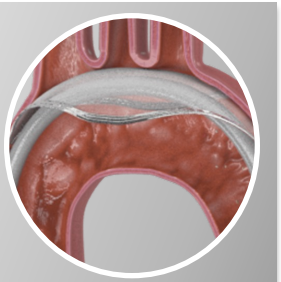
Emblok™
**Clinical studies**

- 100µm
- Femoral
- 11F
- 3 vessel capture
- Non-Inferiority



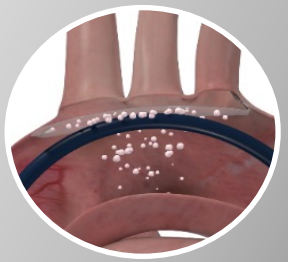
Emboliner™
**Clinical studies**

- 150µm
- Femoral
- 10F
- 3 vessel+ body capture
- Non-Inferiority



CAPTIS™
Preclinical

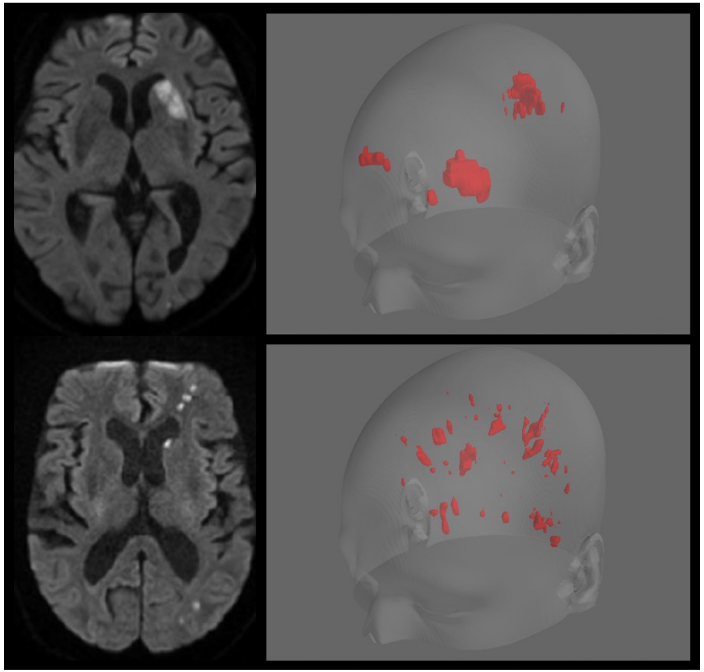
- 115x145µm
- Femoral
- 16F
- 3 vessel + body capture
- Superiority



ProtEmbo®
FIH completed

- 60µm pore
- L-radial
- 6F
- Covers all 3 vessels
- Superiority

# Can DW MRI discriminate stroke after TAVR? What DW MRI measure is most reliable?

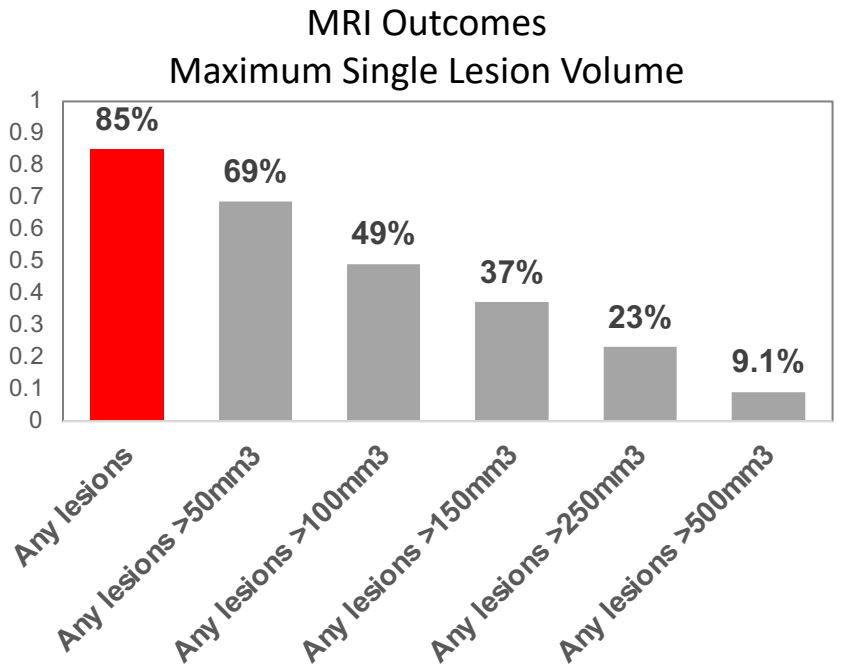


Count: 7 discrete lesions
ILV or Max ILV
TLV= 6558.6 $mm^3$
Acute stroke
Change in NIHSS: 11
Stroke Disability

Count: 51 discrete lesions
ILV or Max ILV
TLV= 5681 $mm^3$
Acute stroke
Change in NIHSS: 3
Stroke Recovery

# Patient Level Pooled analysis (N=479)
## Same Methods, DWI imaging, Core Lab, CEC, Neurologic evaluation

| Neurologic Outcomes | Total |
|---|---|
| | 479 |
| Fatal or Ischemic Stroke, no (%) | 36 (7.5) |
| Ischemic Stroke, no (%) | 33 (6.9) |
| Fatal or Disabling stroke, no (%) | 15 (3.1) |
| Fatal stroke | 0 (0.0) |
| Disabling stroke | 15 (3.1) |
| Non-disabling stroke | 17 (3.6) |
| Stroke recovery, No (%) | 26 (6.6) |
| Complete | 16 (4.1) |
| Incomplete | 10 (2.5) |
| TIA, no (%) | 4 (0.8) |
| Stroke or TIA, no (%) | 37 (7.7) |
| Delirium, no (%) | 4 (1.0) |
| Death (all-cause), no (%) | 4 (0.8) |




100% of patients with stroke, 84% of patients without stroke

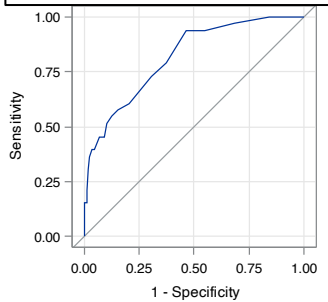
Lansky et al. JACC in press

# Ischemic Stroke at 30 days

## AUC-ROC of DW-MRI Lesions to predict Ischemic Stroke

Total Lesion Number (TLN)

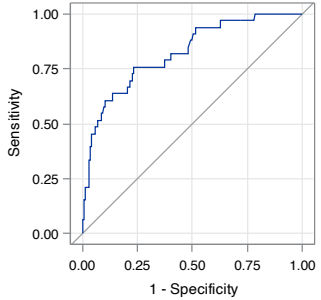
**C –statistic = 0.81**




| Criterion | Cutoff |
|---|---|
| Distance to 0,1 | 4 |
| Youden | 5 |

Maximum Individual Lesion Volume (ILV)

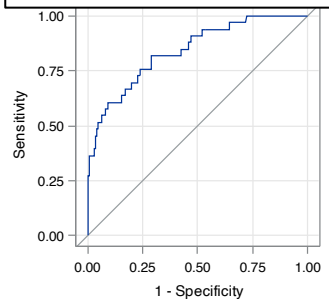
**C –statistic = 0.82**




| Criterion | Cutoff |
|---|---|
| Distance to 0,1 | 216 $mm^3$ |
| Youden | 216 $mm^3$ |

Total Lesion Volume (TLV)

**C –statistic = 0.84**



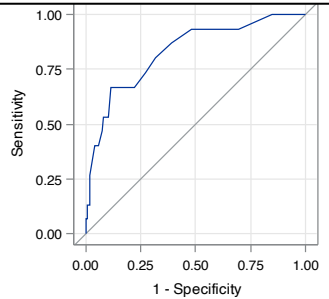

| Criterion | Cutoff |
|---|---|
| Distance to 0,1 | 547 $mm^3$ |
| Youden | 440 $mm^3$ |

# Disabling Stroke at 30 days

## AUC ROC of DW-MRI Lesions to Predict Ischemic Stroke

### Total Lesion Number (TLN)

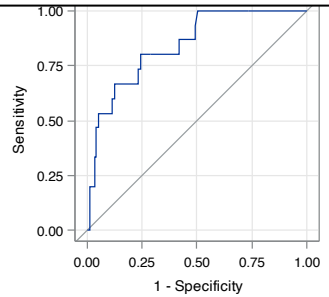
**C Statistic = 0.83**




| Criterion | Cutoff |
|---|---|
| Distance to 0,1 | 11 |
| Youden | 11 |

### Max Individual Lesion Volume (ILV)

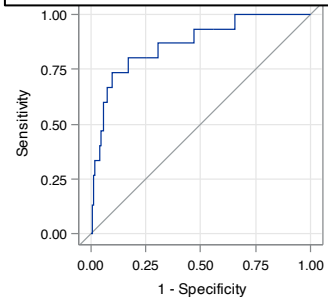
**C Statistic = 0.83**




| Criterion | Cutoff |
|---|---|
| Distance to 0,1 | 222 $mm^3$ |
| Youden | 222 $mm^3$ |

### Total Lesion Volume (TLV)

**C Statistic = 0.86**




| Criterion | Cutoff |
|---|---|
| Distance to 0,1 | 802.1 $mm^3$ |
| Youden | 1156 $mm^3$ |

# Outcomes based on TLV threshold

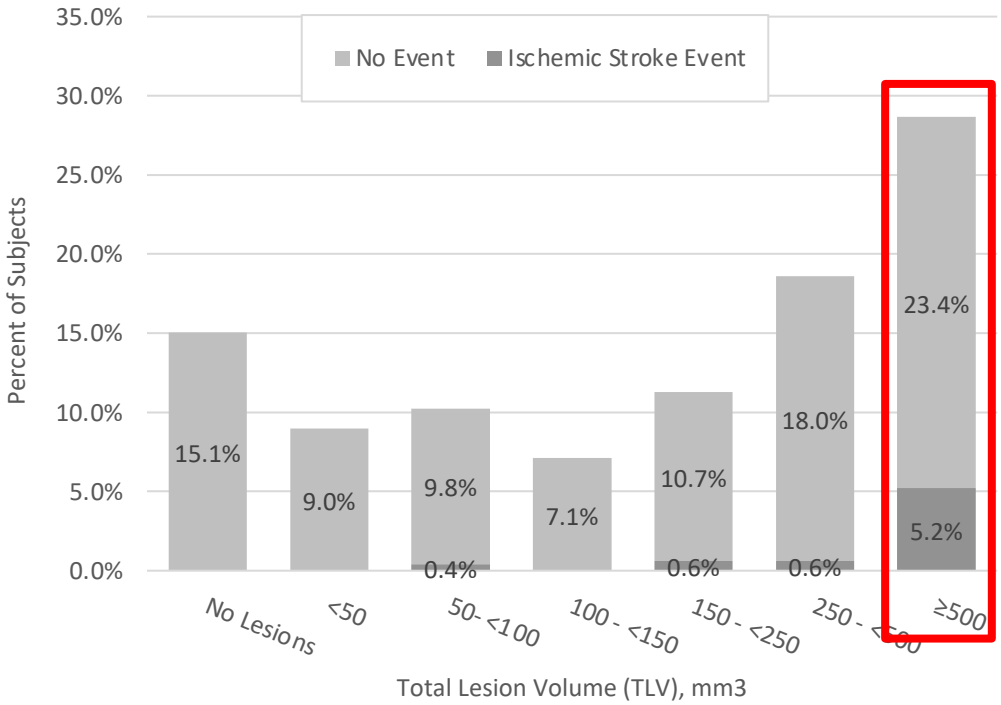
| | TLV>500 (N=137) | TLV<=500 (N=342) | P-value |
|---|---|---|---|
| Fatal or Ischemic Stroke, no (%) | 26 (19.0) | 10 (2.9) | <.0001 |
| **Stroke, no (%)** | 25 (18.2) | 8 (2.3) | <.0001 |
| Ischemic | 25 (18.2) | 8 (2.3) | <.0001 |
| Hemorrhagic | 0 (0.0) | 0 (0.0) | |
| Fatal or Disabling stroke, no (%) | 12 (8.8) | 3 (0.9) | <.0001 |
| Fatal stroke | 0 (0.0) | 0 (0.0) | |
| **Disabling stroke** | 12 (8.8) | 3 (0.9) | <.0001 |
| Non-disabling stroke | 12 (8.8) | 5 (1.5) | 0.0003 |
| **Stroke recovery, No (%)** | 19/25 (76) | 7/8 (87.5) | <.0001 |
| **Complete** | 11 (44) | 5 (62) | 0.0008 |
| Incomplete | 8 (32) | 2 (25) | 0.001 |
| Stroke or TIA, no (%) | 25 (18.2) | 12 (3.5) | <.0001 |
| Delirium, no (%) | 0 (0.0) | 4 (1.4) | 0.581 |
| Cardiovascular Death, no (%) | 2 (1.5) | 2 (0.6) | 0.3235 |
| Myocardial infarction, no (%) | 3 (2.2) | 5 (1.5) | 0.6946 |
| Any Acute Kidney Injury, no (%) | 6 (4.4) | 10 (2.9) | 0.4086 |
| Any Bleeding, no (%) | 38 (27.1) | 60 (17.4) | 0.0181 |
| VARC 2 early safety | 37 (26.6) | 32 (9.3) | <.0001 |

**TLV>500mm$^3$ is**

- Highly associate with ischemic stroke (76% of all strokes)
- Highly associated with disabling stroke (80% of disabling strokes)
- Less stroke recovery
- Less complete recovery

# TLV Thresholds and Ischemic Stroke Rates

TLV ≥500 is common (29% of patients)



# CEP trial strategies

- Currently many approaches for approval- no right or wrong
  - RCT designs
  - Controls can be Sentinel (NI) OR no CEP (Sup) or SOC (sup)
  - Until one device shows benefit over Sentinel

- Sentinel is the current predicate: easy to use and safe
  - Need to show benefit- if not in the IDE trial then in post market

- Brain imaging is a good surrogate to discriminate stroke
  - Best measure is TLV