From Bench to Brain (and back)

New England Center for Stroke Research

Improving Mechanical Thrombectomy

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WLNC 2017, Los Angeles CA

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Disclosures

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- Research Grants (last 36 months):
  - NINDS, NIA, NCI
  - Philips Healthcare
  - BRACCO
  - Fraunhofer Institute
  - Stryker Neurovascular
  - Codman Neurovascular
  - Medtronic Neurovascular
  - InNeuroCo Inc
  - Blockade Medical
  - CereVasc LLC
  - Cook Medical
  - Medtronic
  - Microvention
  - NPS LLC
  - Neuravi
  - Rapid Medical
  - Wyss Institute
  - The Stroke Project

- Consulting (fee-per-hour, last 12 months):
  - Stryker Neurovascular
  - Harris Beach, Expert Witness
  - Codman Neurovascular
  - In Neuro Co
- Investment (Stocks)
  - Hologic (Spouse)
  - Boston Scientific Inc (Spouse)
  - InNeuroCo Inc
- Travel Support
  - Neuravi

Model development supported by the NIH NIBIB, device testing supported by Codman Neurovascular, Medtronic Neurovascular, Neuravi, and Stryker Neurovascular.

Support for imaging equipment generously provided by Philips Healthcare.

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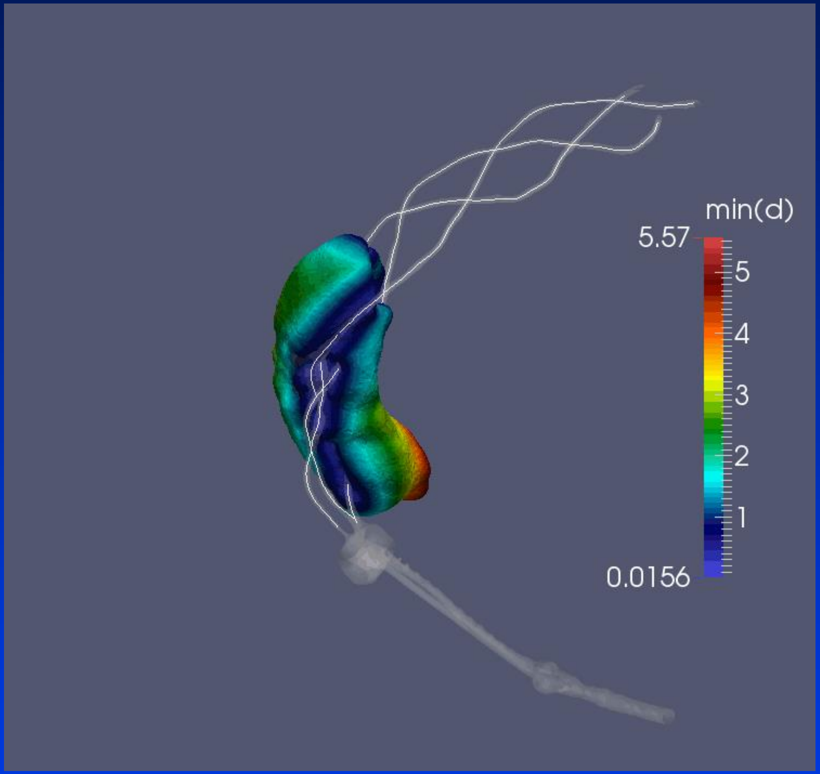
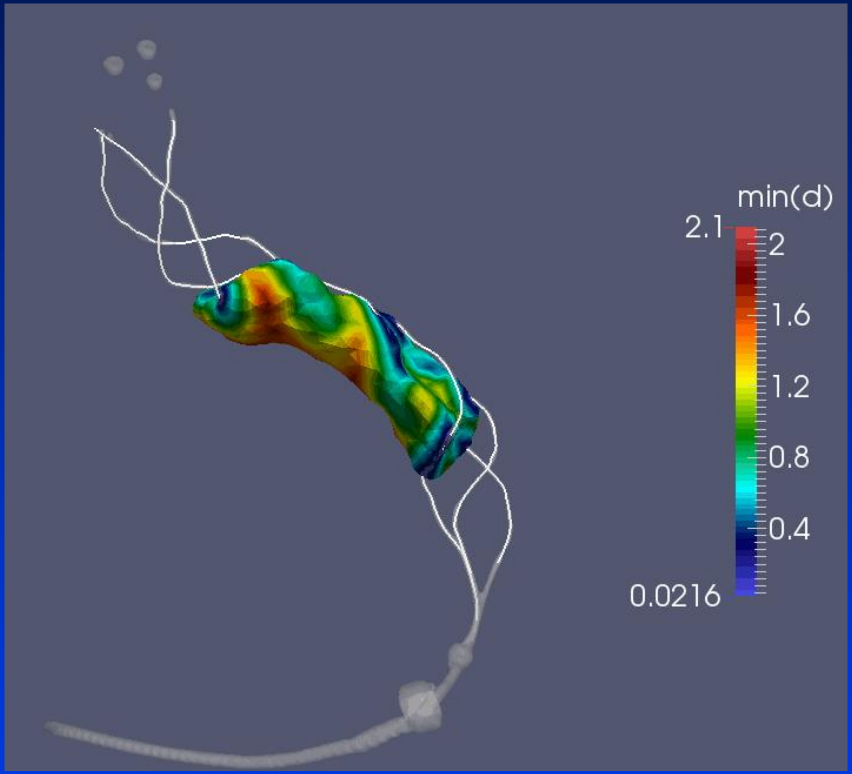
Clot Integration Factor

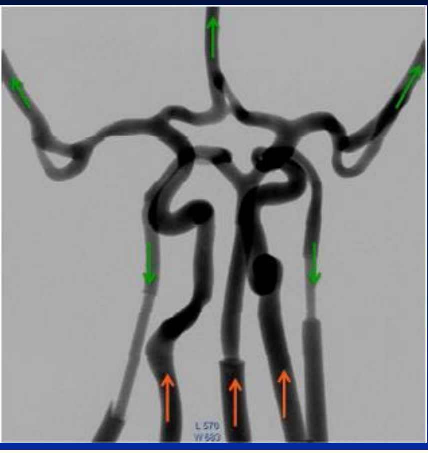


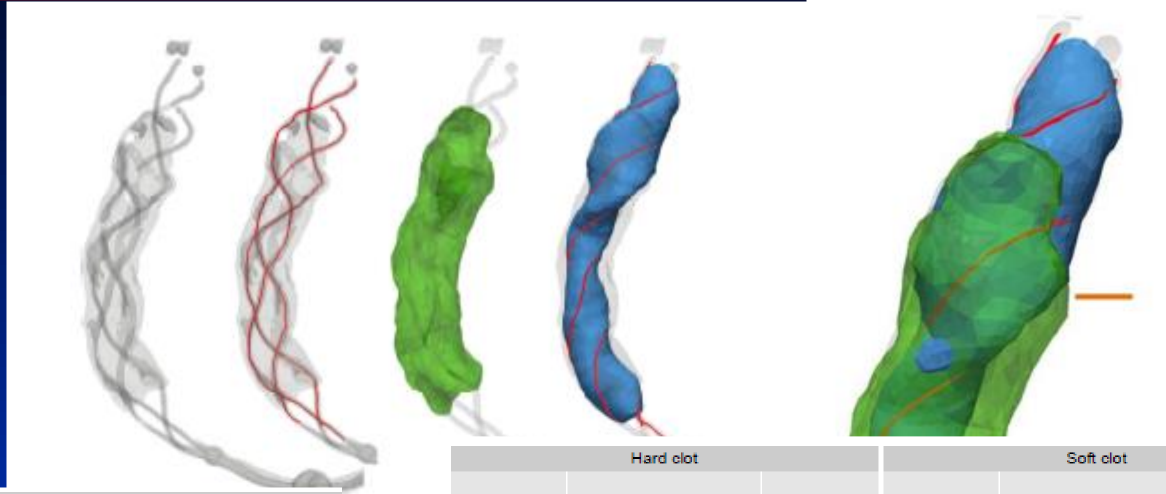


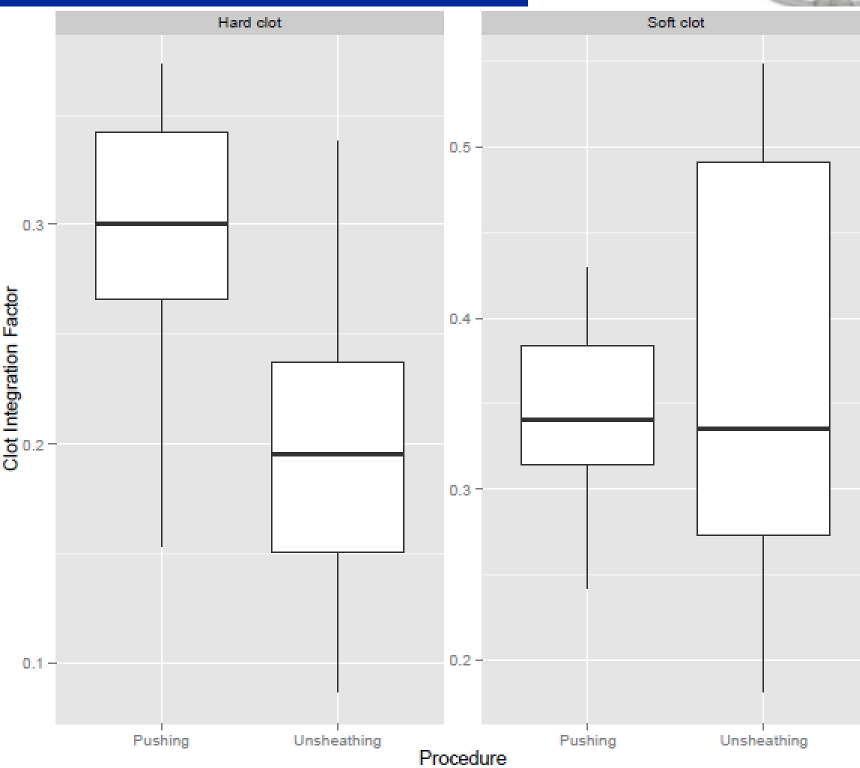
Unsheathing

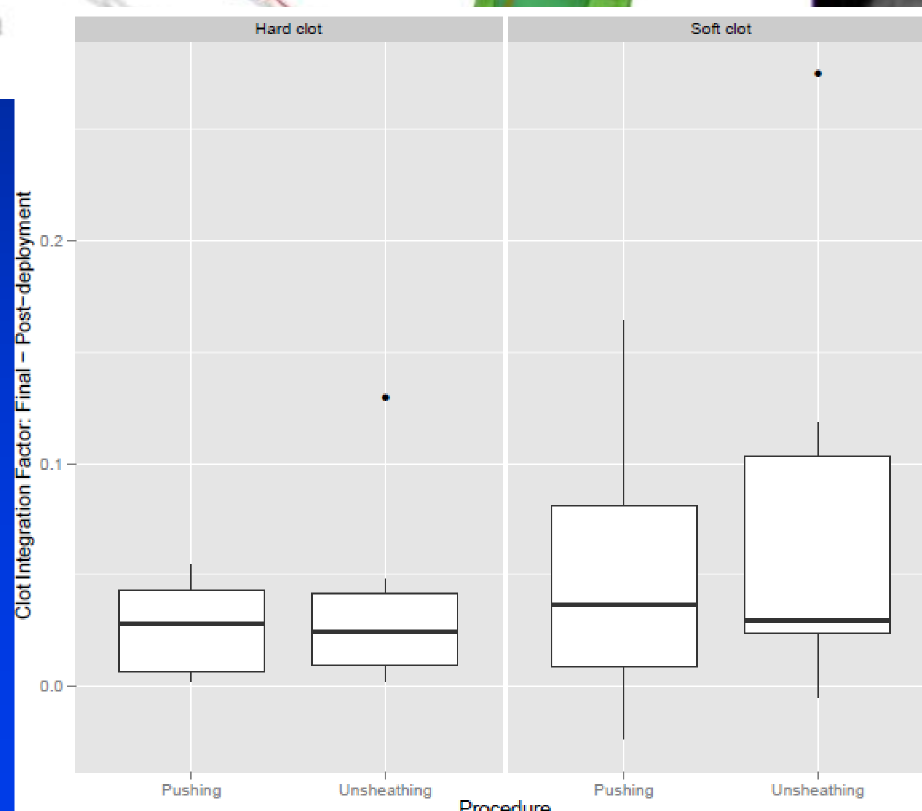
Unsheath-Push

Clot Integration Factor









Considerations

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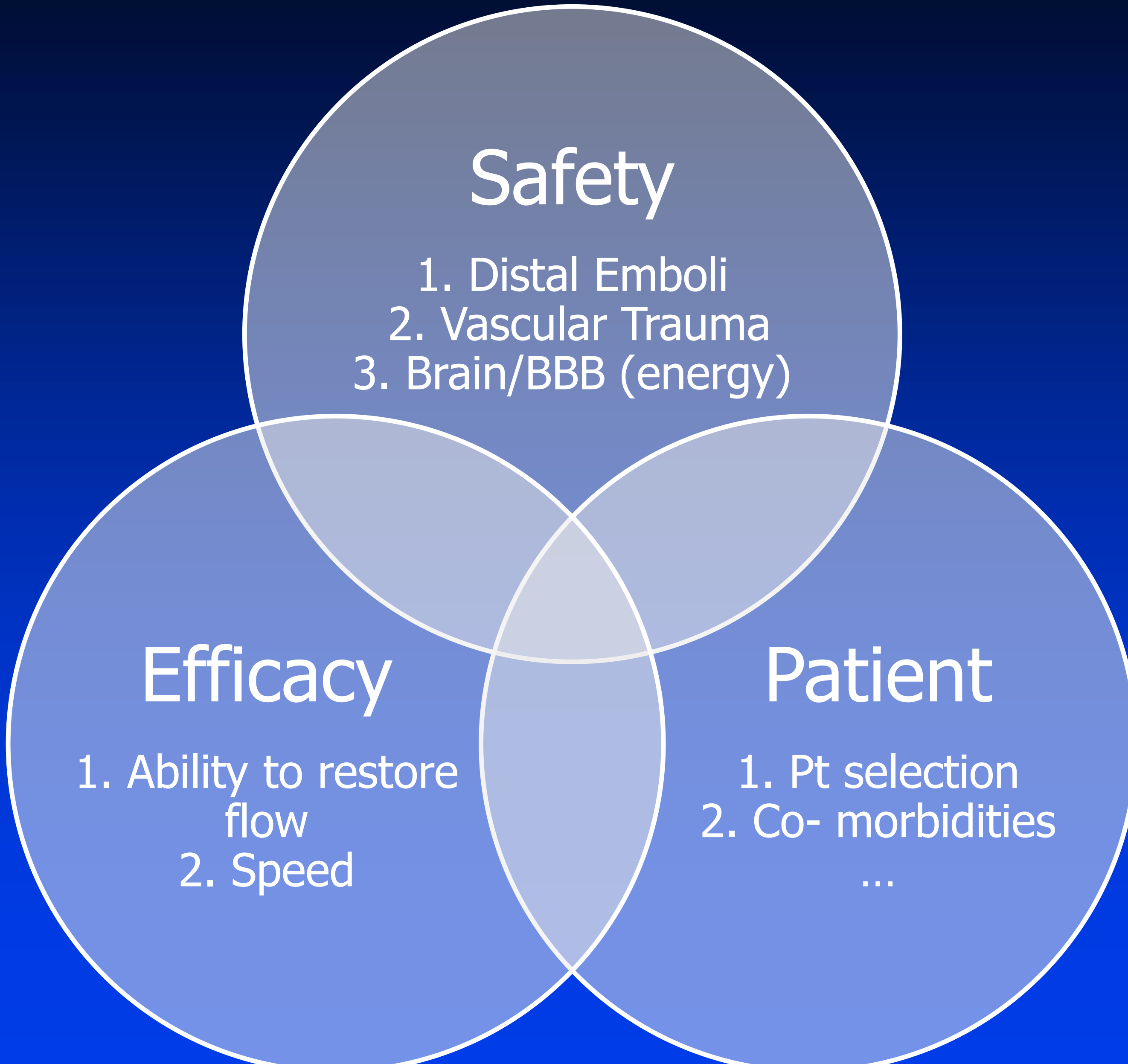

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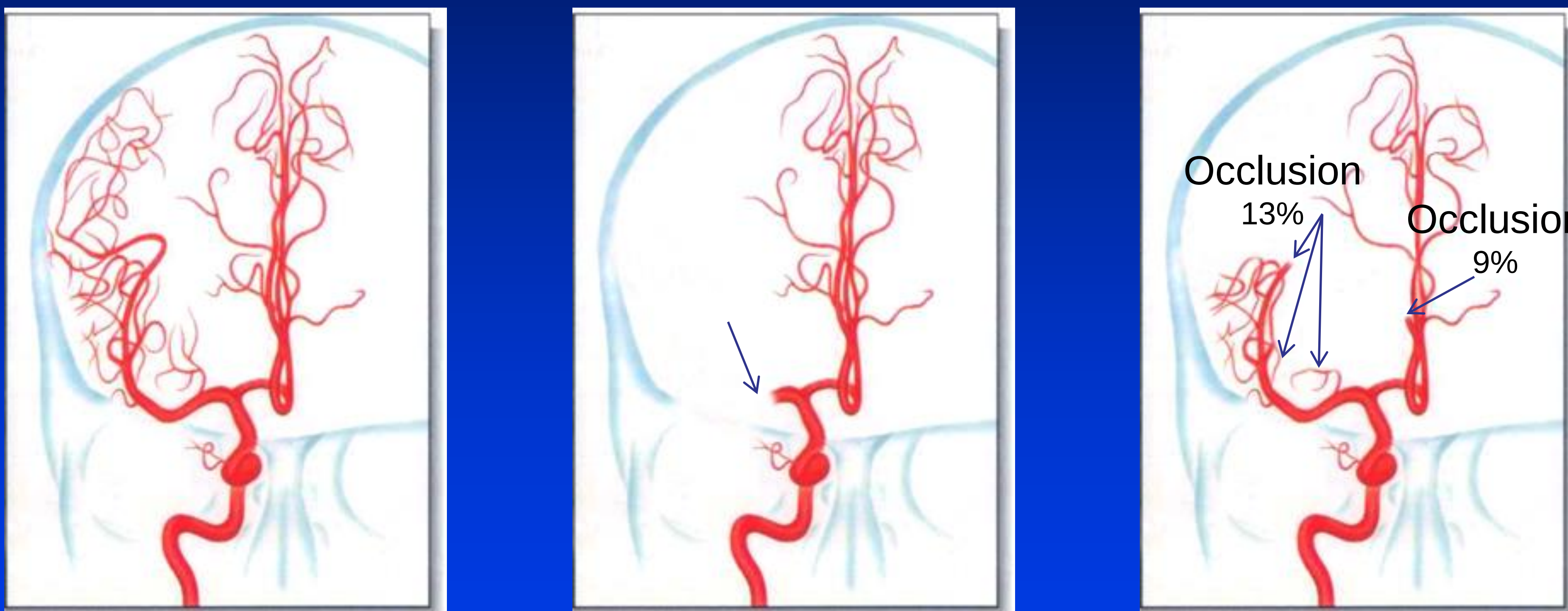
Distal Emboli: Reperfusion versus Recanalization

Thrombectomy <8hrs

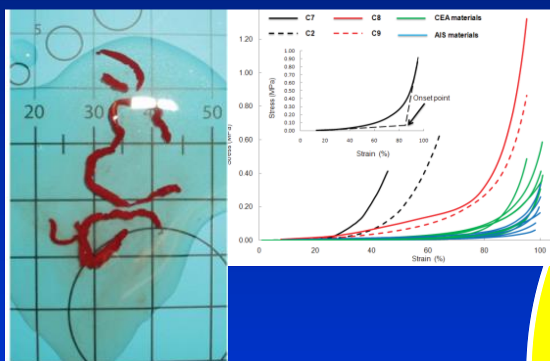
Partial Recovery or Deterioration

Normal → Occlusive clot → Fragmentation*



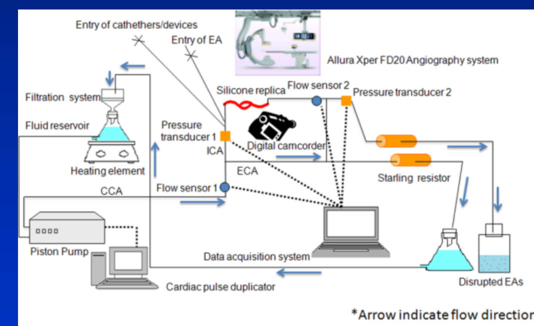
* Bonafe: ESMINT 2012

In Vitro Assessment of Safety and Efficacy



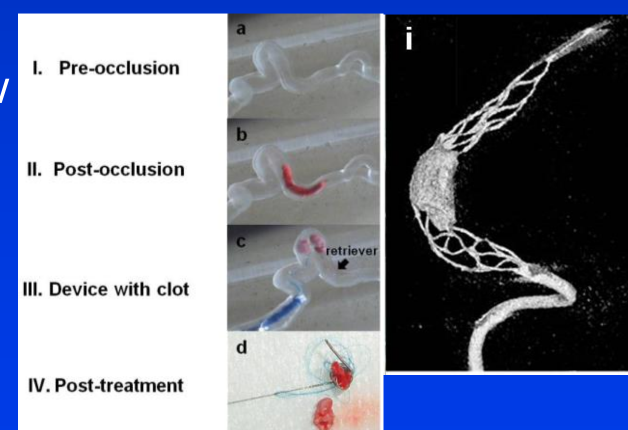
Clot Model

Circulation Loop



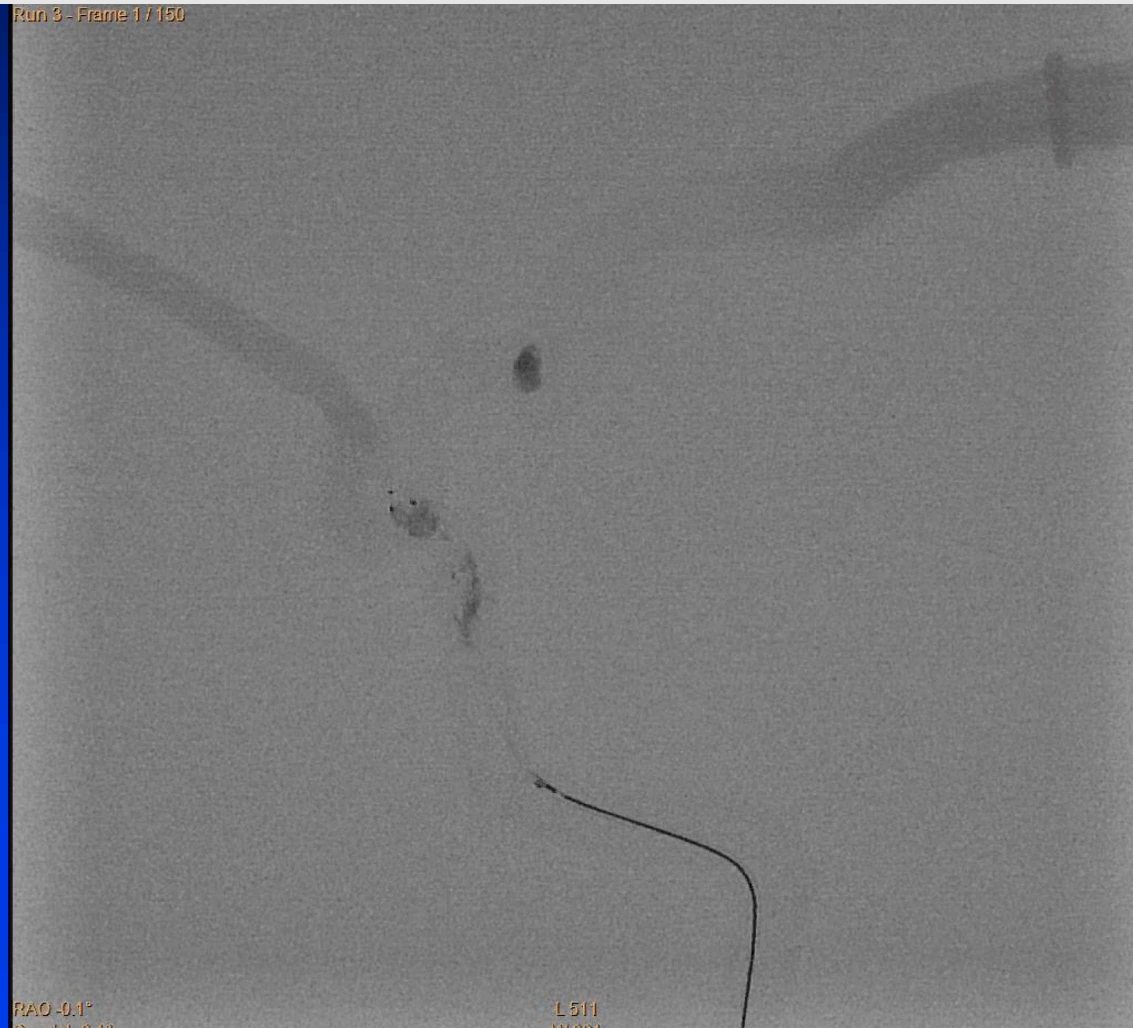
Vascular Model

Imaging/ Medical Device

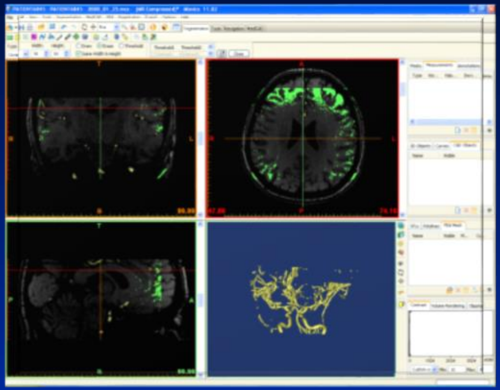


Bench-top Treatment Optimization

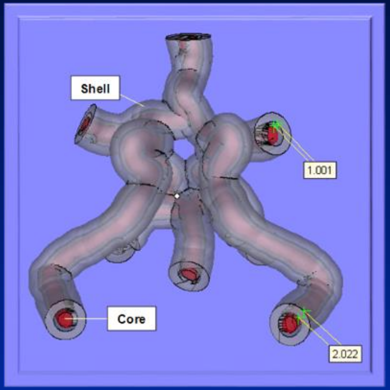
	8-200µm	200-1000µm	>1mm
Movie	121,450	4	18
Stroke, 2013 (n=16)	>100,000	5	3



Population Based Vascular Replica



MRA Dataset



Computer Core-Shell Model

Fused Deposit Manufacturing

Physical Core-Shell Model

Silicone Replica

J Chueh, AK Wakhloo, and MJ Gounis. AJNR 2009

Mechanical Analysis of Clot Modeling

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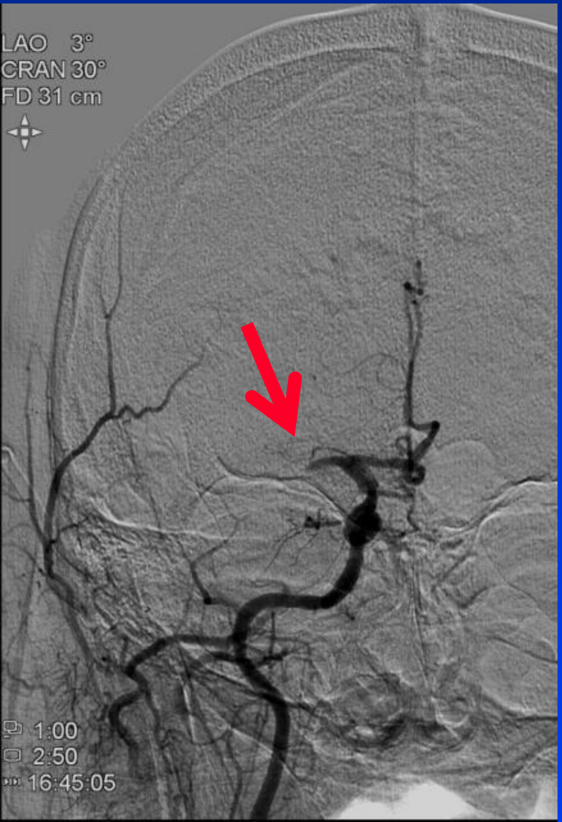
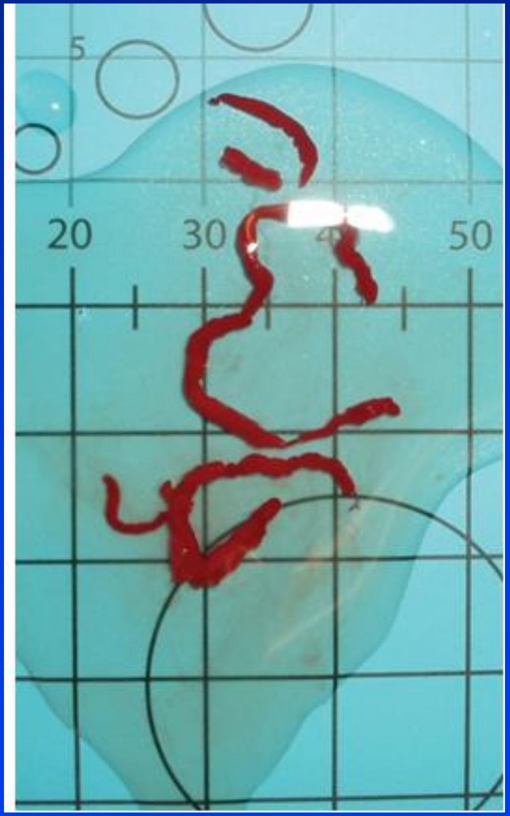
- 64 y-o M, Acute Ischemic Stroke
  - Entered ED >4.5hrs after symptom onset
  - CBV-MTT Mismatch
- Thrombus retrieved from R MCA with Penumbra Aspiration Device





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Mechanical Analysis of Clot

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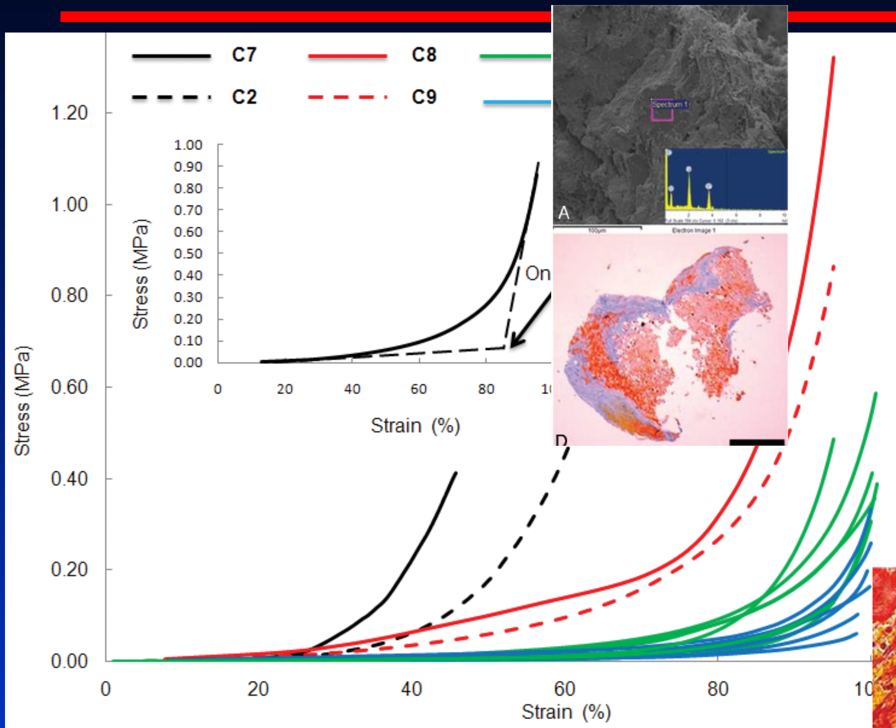
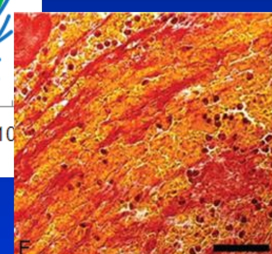
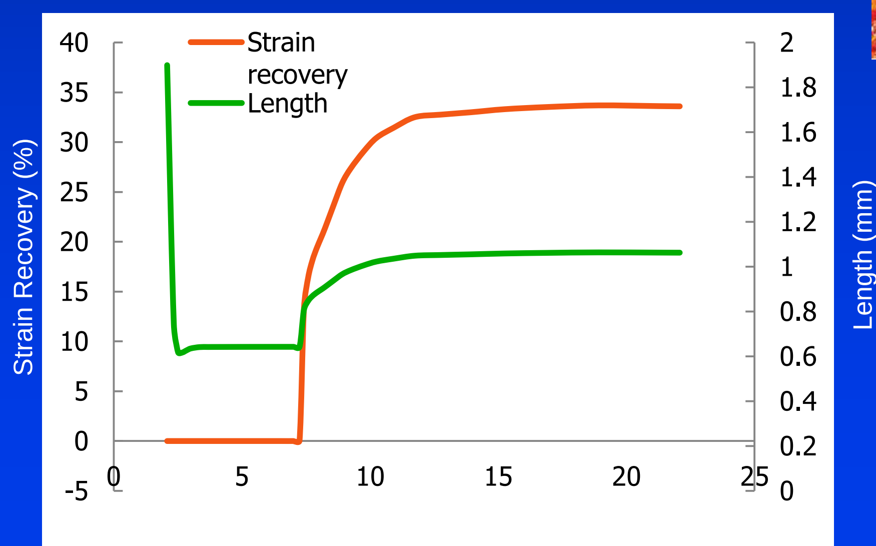


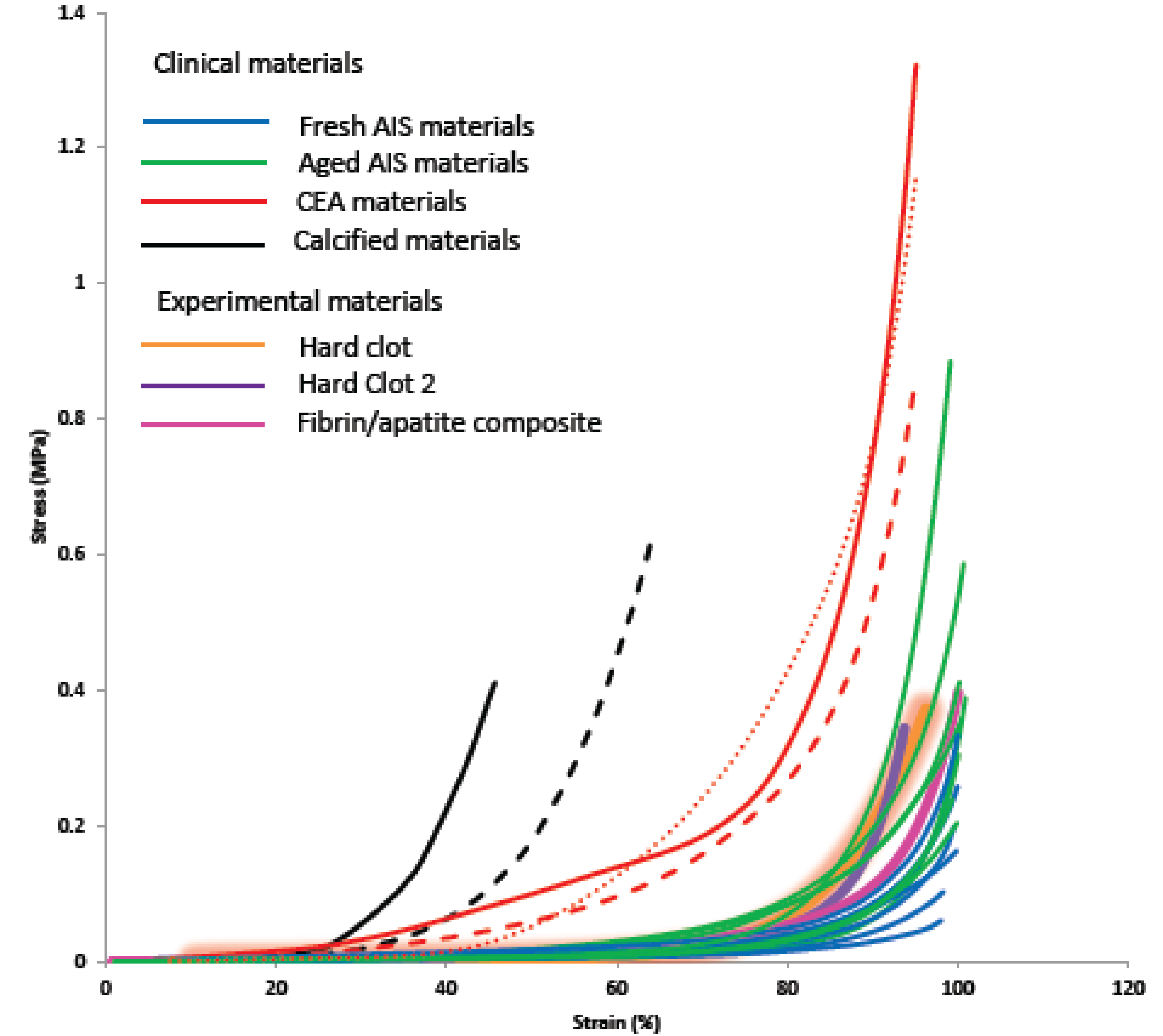
- Clot modeling – Need to know bulk mechanical properties



  - Stress-Strain: DMA compression test
  - Stress relaxation: Propensity for fragmentation



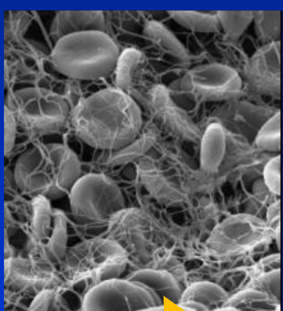
Chueh, Silva, Hendricks, Wakhloo, Gounis. AJNR 2011 32:1237

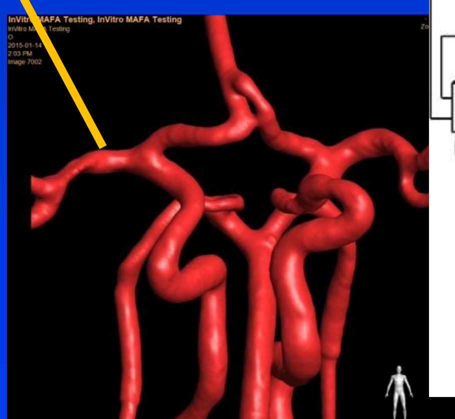


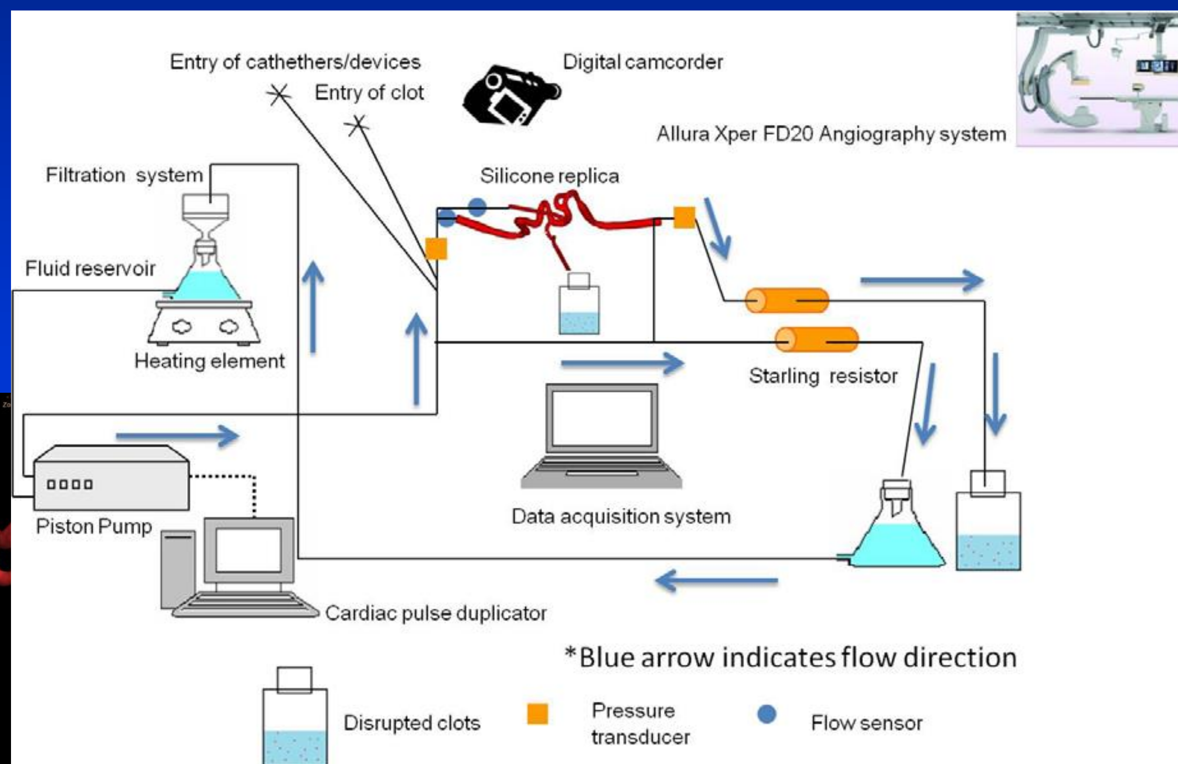
Clinical materials
Fresh AIS materials
Aged AIS materials
CEA materials
Calcified materials
Experimental materials
Hard clot
Hard Clot 2
Fibrin/apatite composite
Stress (MPa)
Strain (%)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
0
20
40
60
80
100
120

"Model System"

- Efficacy
  - Measures time and amount of flow restoration to thrombosed MCA in model
- Safety
  - Blood analog fluid is captured for particle/fragmentation analysis







Vascular Occlusion

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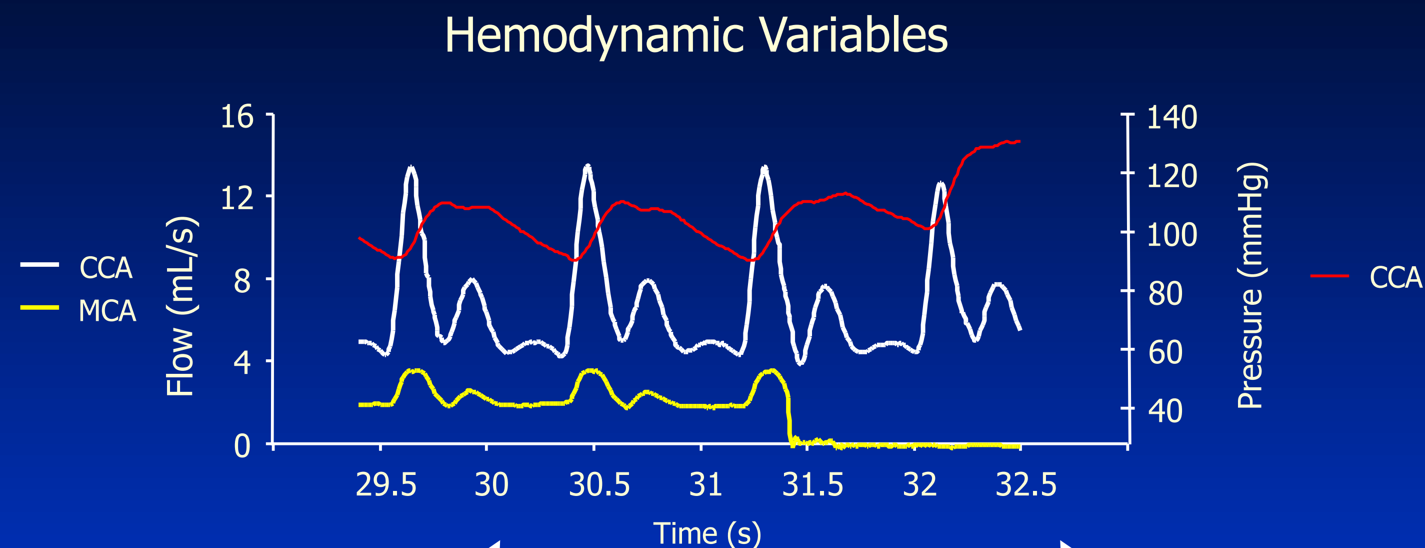

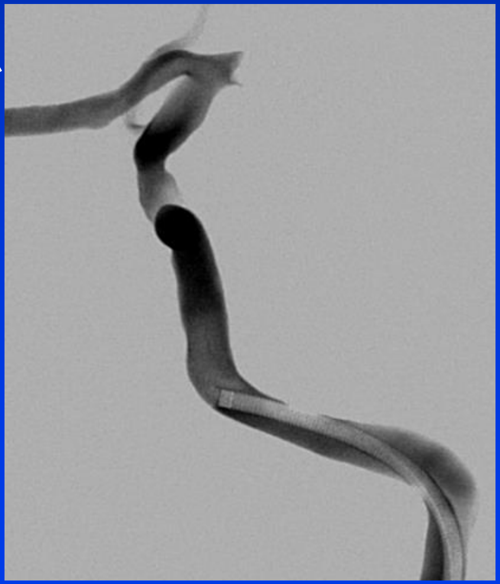

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Translation?

Experimental

Clinical

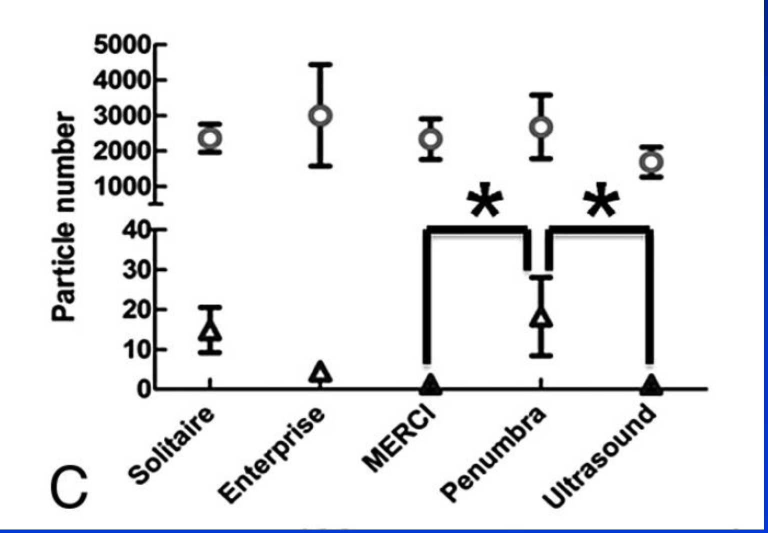

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Table 2. Neurological and Functional Outcomes From Open versus Closed Vessels

	Percent With Outcome			
Outcome	Overall (N=125)	TIMI 2–3 (N=102)	TIMI 0–1 (N=23)	*P**
Discharge NIHSS 0–1 or improved by ≥10	27	32	5	0.0127
Good clinical outcome at 30 days†	30	35	9	0.0199
mRS ≤2 at 90 days	25	29	9	0.0596
Death at 90 days	33	29	48	0.1384

Chueh J.Y. et al. *AJNR*. 2012; 33: 1998

Stroke 2009;40:2761

Translation?

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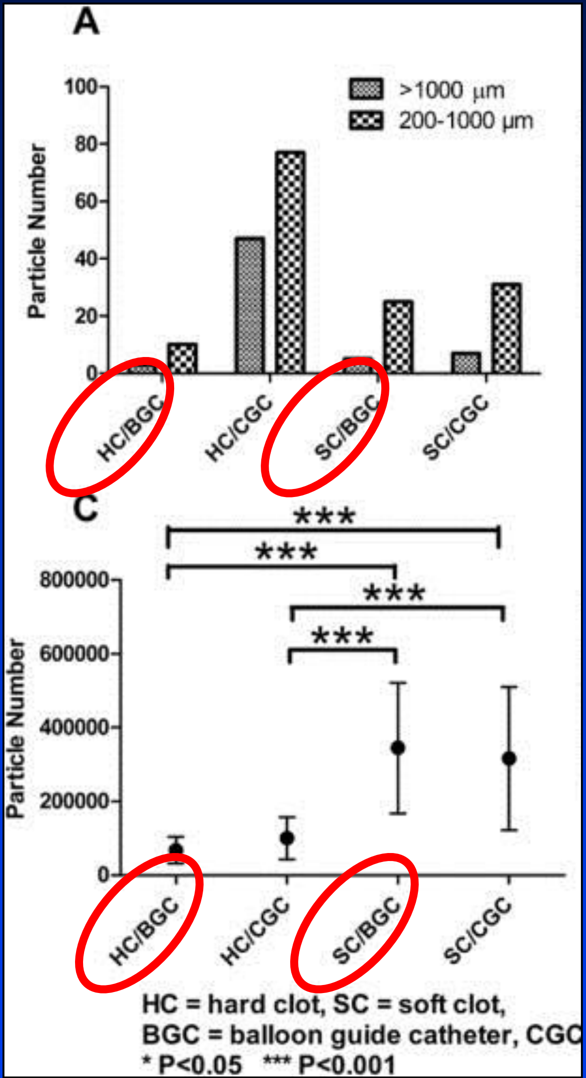
Experimental



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Clinical

Table 3. Independent Predictors of Clinical Outcome With Solitaire Treatment for Acute Ischemic Stroke

Variable	Nparm	DF	χ^2	*P* Value>χ^2
Age, y	2	1	94.54	<0.001*
Hypertension	2	1	3.93	0.0476
Atrial fibrillation	2	1	16.8	<0.0001*
Initial NIHSS score	2	2	9.47	0.0088*
Site	8	5	9.85	0.08
IV tPA	2	1	128.46	<0.0001*
TOG	2	1	0.58	0.45
TIMI success	2	2	2.75	0.25
BGC	2	1	66.66	<0.0001*
General anesthesia	2	2	5.56	0.026
Procedure time	2	2	5.56	0.06

BGC indicates balloon guide catheter; DF, degrees of freedom; IV tPA, intravenous tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; Nparm, number of parameters; TIMI, thrombolysis in myocardial infarction; and TOG, time of onset to groin puncture.

*Statistically significant.

Chueh J.Y. et al. *Stroke*. 2013; 44: 1396-1401

Nguyen T et al. Stroke 2014;45:141-5

Proximal Flow Control: Embolic Protection Evidence

Flow Restoration Procedure

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- **<u>Group 1:</u>**

Thrombectomy through an 8Fr balloon guide catheter (BGC) positioned at the cervical ICA

- **<u>Group 2:</u>**

Thromboaspiration via a 5Fr intracranial guide catheter (Solumbra) in the origin of the MCA

- **<u>Group 3:</u>**

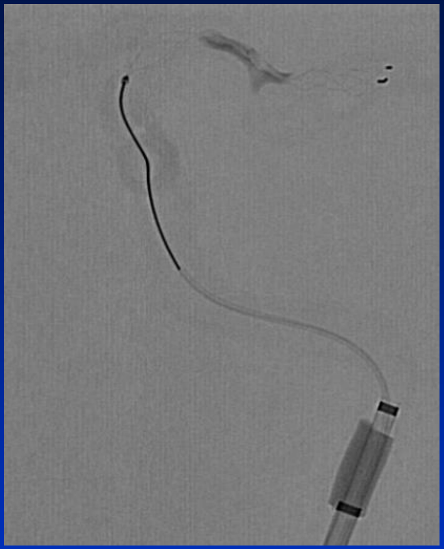
Thrombectomy through a 6Fr guide catheter (CGC) with the tip placed at the origin of the cervical ICA

- **<u>Group 4:</u>**

A Direct Aspiration first Pass

Technique (ADAPT). Aspiration through a 5MAX

<u>Group 1: BGC</u>



<u>Group 2: Solumbra</u>

<u>Group 3: CGC</u>

<u>Group 4: ADAPT</u>

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Total Number of Distal Emboli

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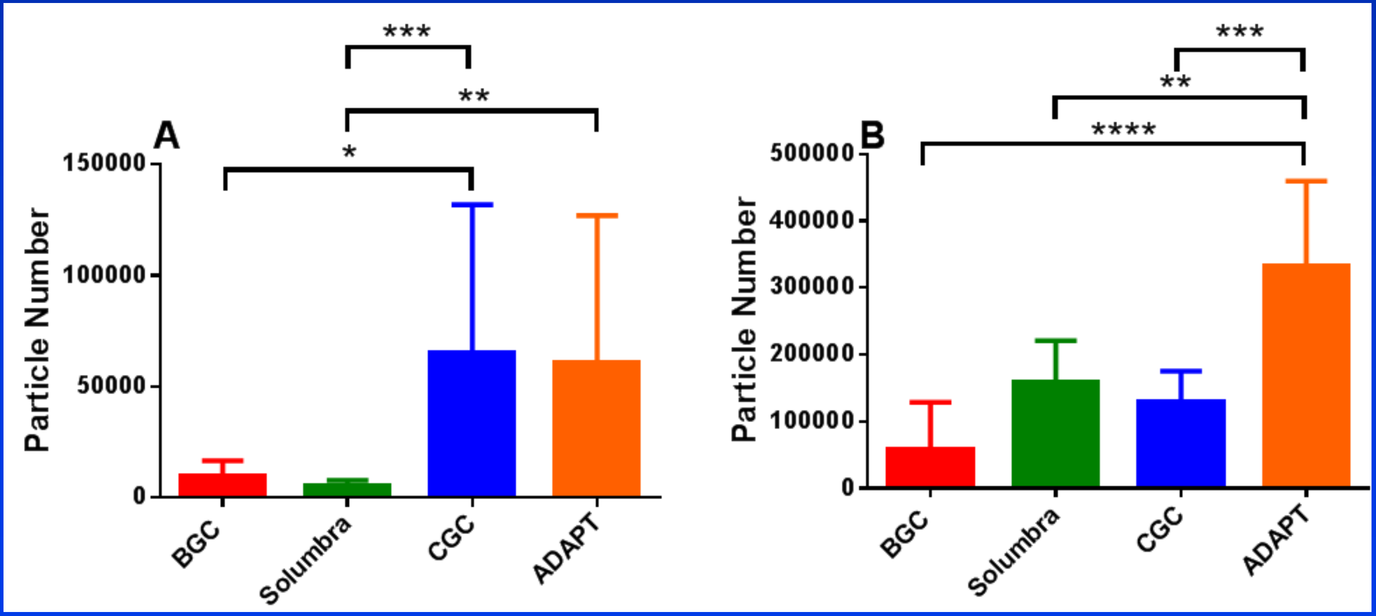
- Hard clot model: **Solumbra or BGC most effective in reducing the rate of forming clot fragments** compared to the CGC or the ADAPT technique.
- Soft clot model: **BGC technique** reduced **2-fold** total embolic particle creation **compared** to the other techniques.

Hard Clot



Soft Clot

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Conclusion

- Use of the BGC technique during a SR thrombectomy was associated with statistically lower rates of soft distal emboli across a broad range of embolic particle sizes.
- The Solumbra technique was shown to be numerically, although not statistically, superior in several hard clot subgroups.
- When encountering hard clot, use of the Solumbra or ADAPT techniques in addition to the BGC may provide an additional reduction in distal emboli and may be considered for comprehensive distal emboli reduction.

JY Chueh et al. Stroke. 2013; JY Chueh et al. JNIS 2016

Clinical Translation

ARTS Technique

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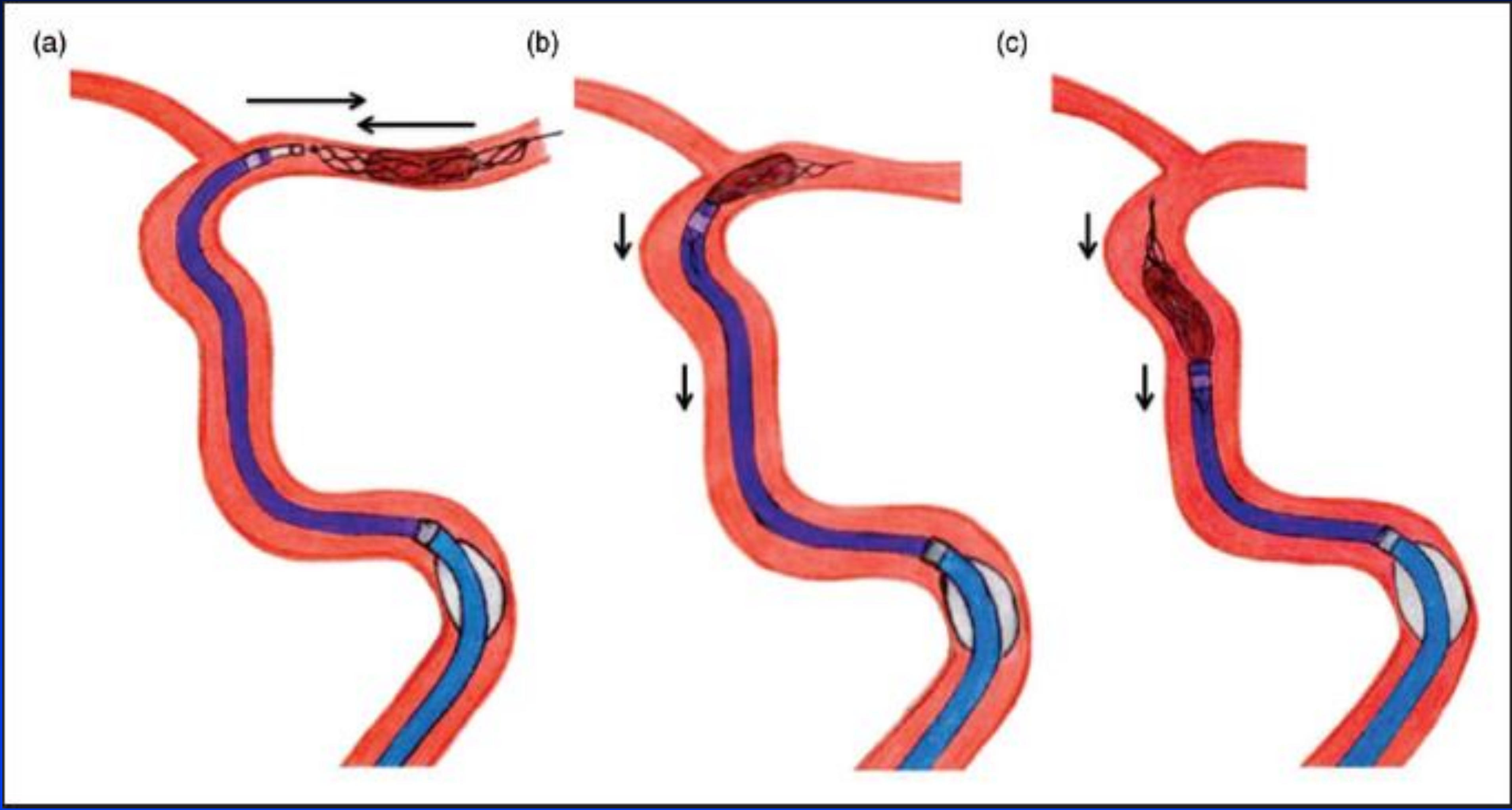

Massari, et al. Interv Neuroradiol 2016

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Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

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Balloon Guide Catheter Improves Revascularization and Clinical Outcomes With the Solitaire Device: Analysis of the North American Solitaire Acute Stroke Registry

Thanh N. Nguyen, Timothy Malisch, Alicia C. Castonguay, Rishi Gupta, Chung-Huan J. Sun, Coleman O. Martin, William E. Holloway, Nils Mueller-Kronast, Joey D. English, Italo Linfante, Guilherme Dabus, Franklin A. Marden, Hormozd Bozorgchami, Andrew Xavier, Ansaar T. Rai, Michael T. Froehler, Aamir Badruddin, Muhammad Taqi, Michael G. Abraham, Vallabh Janardhan, Hashem Shaltoni, Roberta Novakovic, Albert J. Yoo, Alex Abou-Chebl, Peng R. Chen, Gavin W. Britz, Ritesh Kaushal, Ashish Nanda, Mohammad A. Issa, Hesham Masoud, Raul G. Nogueira, Alexander M. Norbash and Osama O. Zaidat

Stroke. 2014;45:141-145; originally published online December
doi: 10.1161/STROKEAHA.113.002407

Radiology

Comparison of a Balloon Guide Catheter and a Non–Balloon Guide Catheter for Mechanical Thrombectomy[1]

Aglaé Velasco
Boris Buerke, MD
Christian P. Stracke, MD
Shoma Berkemeyer, PhD
Pascal J. Mosimann, MD
Wolfram Schwindt, MD
Pedro Alcázar, MD
Christian Cnyrim, MD
Thomas Niederstadt, MD
René Chapot, MD
Walter Heindel, MD

Purpose: To evaluate the effectiveness of mechanical thrombectomy with the use of a stent retriever in acute ischemic stroke, performed by using a balloon guide catheter or non–balloon guide catheter.

Materials and Methods: In accordance with the institutional review board approval obtained at the two participating institutions, retrospective analysis was performed in 183 consecutive patients treated between 2013 and 2014 for occlusions in the middle cerebral artery or carotid terminus by using a stent retriever with a balloon guide catheter (n = 102) at one center and a non–balloon guide catheter (n = 81) at

Analysis of Workflow and Time to Treatment on Thrombectomy Outcome in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) Randomized, Controlled Trial

Bijoy K. Menon, MD; Tolulope T. Sajobi, PhD; Yukun Zhang, MSc; Jeremy L. Rempel, MD; Ashfaq Shuaib, MD; John Thornton, MD; David Williams, MD; Daniel Roy, MD; Alexandre Y. Poppe, MD; Tudor G. Jovin, MD; Biggya Sapkota, MD; Blaise W. Baxter, MD; Timo Krings, MD; Frank L. Silver, MD; Donald F. Frei, MD; Christopher Fanale, MD; Donatella Tampieri, MD; Jeanne Teitelbaum, MD; Cheemun Lum, MD; Dar Dowlatshahi, MD; Muneer Eesa, MD; Mark W. Lowerison, PhD; Noreen R. Kamal, PhD; Andrew M. Demchuk, MD; Michael D. Hill, MD; Mayank Goyal, MD

Background—The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial used innovative imaging and aggressive target time metrics to demonstrate the benefit of endovascular treatment in patients with acute ischemic stroke. We analyze the impact of time on clinical outcome and the effect of patient, hospital, and health system characteristics on workflow within the trial.

Methods and Results—Relationship between outcome (modified Rankin Scale) and interval times was modeled by using logistic regression. Association between time intervals (stroke onset to arrival in endovascular-capable hospital, to qualifying computed tomography, to groin puncture, and to reperfusion) and patient, hospital, and health system characteristics were modeled by using negative binomial regression. Every 30-minute increase in computed tomography-to-reperfusion time reduced the probability of achieving a functionally independent outcome (90-day modified Rankin Scale 0–2) by 8.3% (P=0.006). Symptom onset-to-imaging time was not associated with outcome (P>0.05). Onset-to-endovascular hospital arrival time was 42% (34 minutes) longer among patients receiving intravenous alteplase at the referring hospital (drip and ship) versus direct transfer (mothership). Computed tomography-to-groin puncture time was 15% (8 minutes) shorter among patients presenting during work hours versus off hours, 41% (24 minutes) shorter in drip-ship patients versus mothership, and 43% (22 minutes) longer when general anesthesia was administered. The use of a balloon guide catheter during endovascular procedures shortened puncture-to-reperfusion time by 21% (8 minutes).

Conclusions—Imaging-to-reperfusion time is a significant predictor of outcome in the ESCAPE trial. Inefficiencies in triaging, off-hour presentation, intravenous alteplase administration, use of general anesthesia, and endovascular techniques offer major opportunities for improvement in workflow.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01778335. (***Circulation.* 2016;133:2279-2286. DOI: 10.1161/CIRCULATIONAHA.115.019983.**)

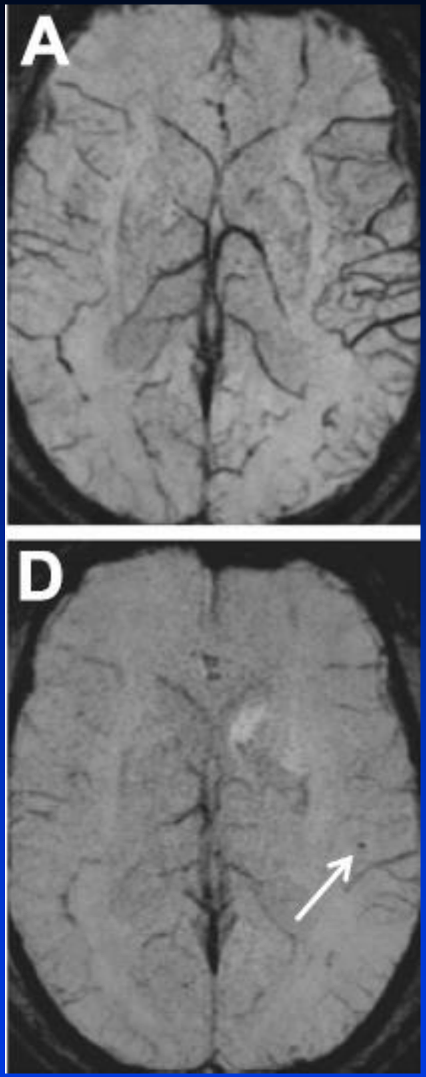
Key Words: cerebrovascular disorders ■ emergency treatment ■ endovascular procedures ■ stroke ■ thrombolytic therapy

Evidence: Proximal Flow Control

	NASA	ESCAPE	Velasco et al
Design	Multicenter Registry	RCT	2-center, retrospective case series
↓ Procedure Time	25% (40 min)	21% (8 min)	50% (21 min)
↑ Recanalization Rate	21% (TICI 3)	N/A	21.3% (TICI≥2b within 3 passes)
↑ mRS≤2 @90 days	30%	N/A	N/A
Ref	Stroke 2013	Circulation 2016	Radiology 2016

Table 3 Trials on endovascular treatment of anterior circulation stroke: clinical outcome in relation to baseline NIHSS score and endovascular techniques applied

Study designation	Number of patients undergoing endovascular treatment	Baseline NIHSS score, median	Favorable outcome (mRS score 0–2) at 3 months (%)	Endovascular techniques applied
PROACT II [18]	121	17	40	ia prourokinase
MELT [9]	57	14	49	ia urokinase
Mattle et al. [26]	55	17[a]	53	ia urokinase
Galimanis et al. [31]	623	15	49	ia urokinase, aspiration, stent retriever (Solitaire)
Multi MERCI trial [7]	164	19	36	Distal Thrombectomy (Merci)
Penumbra trial [6]	125	18[a]	25	Fragmentation/aspiration (Penumbra)
SWIFT [10]				
- Merci	58	18	28	Merci
- Solitaire	55	17	37	Solitaire (protection not mandatory)
TREVO 2 [5]				
- Merci	90	18	22	Merci
- TREVO	88	19	40	Stent retriever (Trevo, protection not mandatory)
MR CLEAN [1]	233	17	33	ia alteplase or urokinase, thrombus retraction, aspiration, wire disruption, stent retriever (protection not mandatory)
IMS III [15]	434	17	41	Merci, Penumbra, Solitaire (protection not mandatory), ia tPA
MR RESCUE [16]	64	16 (penumbral), 19 (non-penumbral	19	Merci, Penumbra, ia tPA
SYNTHESIS [17]	181	13	42	ia tPA, wire disruption, Merci, Penumbra, Trevo, Solitaire (protection not mandatory)
Dávalos et al. [2]	141	18	55	Solitaire (protection in 74 % of interventions)
STAR trial [3]	202	17	58	Solitaire (protection mandatory)
ESCAPE trial [11]	165	16	53	Stent retriever recommended (protection recommended)
EXTEND-IA trial [12]	35	17	71	Solitaire (protection mandatory)
REVASCAT [13]	103	17	44	Solitaire (protection not mandatory)
SWIFT prime [14]	98	17	60	Solitaire (protection mandatory)



Results from cases studies are not predictive of results in other cases. Results in other cases may vary.

Protected stent retriever thrombectomy prevents iatrogenic emboli in new vascular territories

Pascal P. Klinger-Gratz[1,2] · Gerhard Schroth[1] · Jan Gralla[1] · Simon Jung[1,3] · Christian Weisstanner[1] · Rajeev K. Verma[1] · Pasquale Mordasini[1] · Frauke Kellner-Weldon[1] · Kety Hsieh[1] · Mirjam R. Heldner[3] · Urs Fischer[3] · Marcel Arnold[3] · Heinrich P. Mattle[3] · Marwan El-Koussy[1]

Vascular Safety

A Brain Artery is NOT Just an Artery

- ✓ Well developed internal elastic lamina
- ✓ Higher percentage of smooth muscle cells and a paucity of elastic fibers in the media
- ✓ Absent external elastic lamina
- ✓ Less adventitia
- ✓ Float freely in the cerebrospinal fluid within the subarachnoid space unsupported by muscle, bone or deep fascia and experience significant vessel straightening during endovascular access

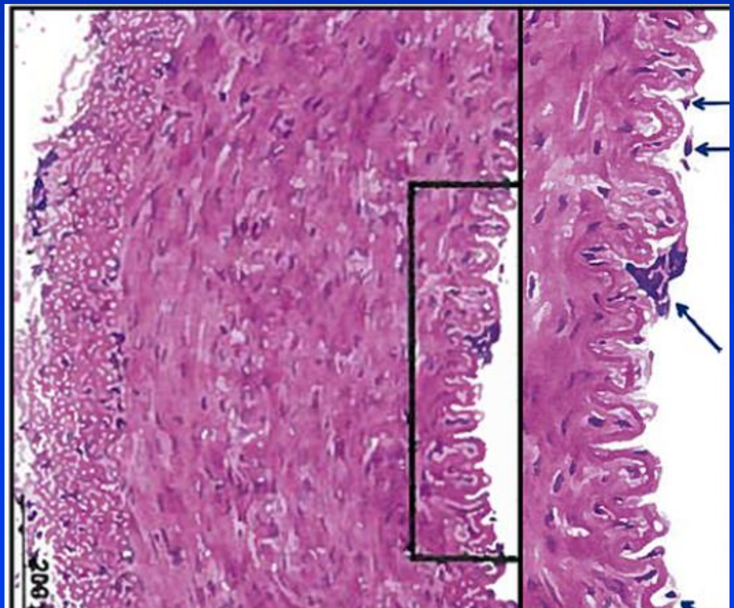
Color Atlas of Microscopic Anatomy. Urban & Schwarzenberg, Baltimore. pgs. 128-129.

Standard Approach

Baseline

TICI 0 Flow Injection of Clot

- Endpoints:
  - Acute vascular safety of a systemic artery
  - Angiographic recanalization



Nogueira, et al. JNIS 2011

Angiographic Assessment

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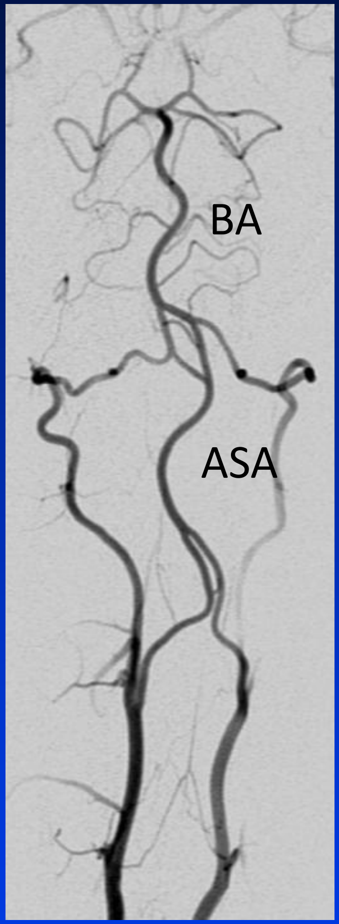
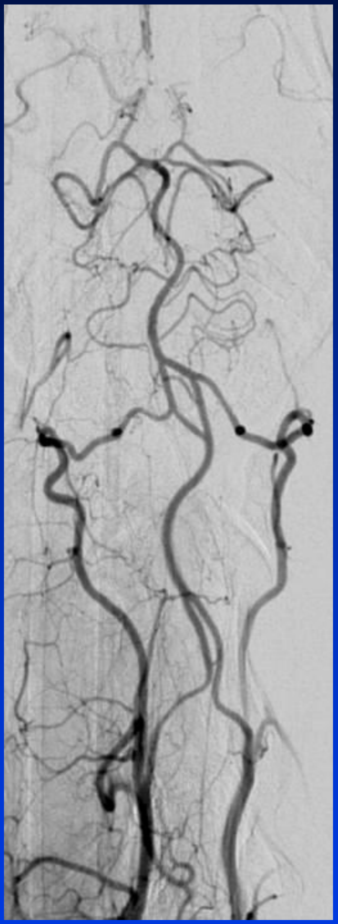
Stent-trievers

Merci V2-Firm



Pretreat-ment

First Pass Grade 3



Fourth Pass Grade 0

First Pass

Gounis, et al. Stroke 2013

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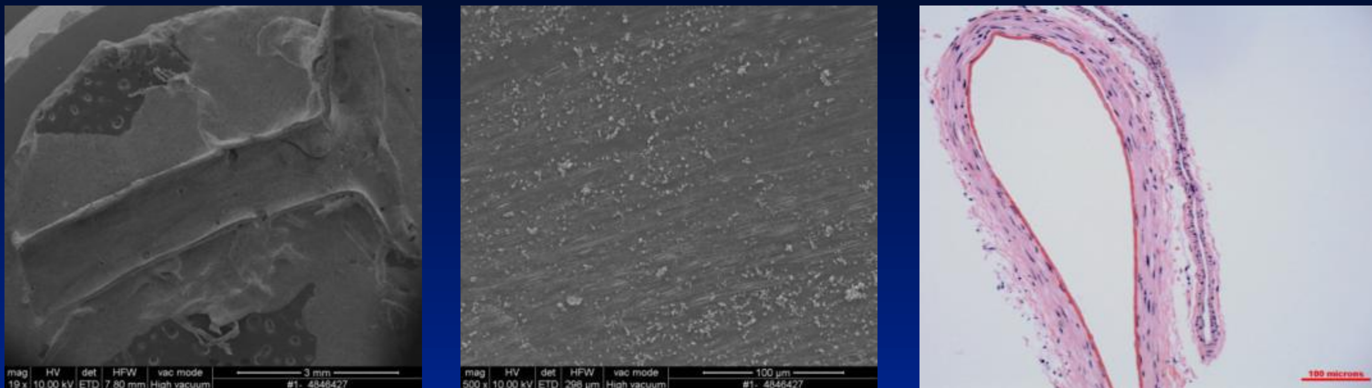
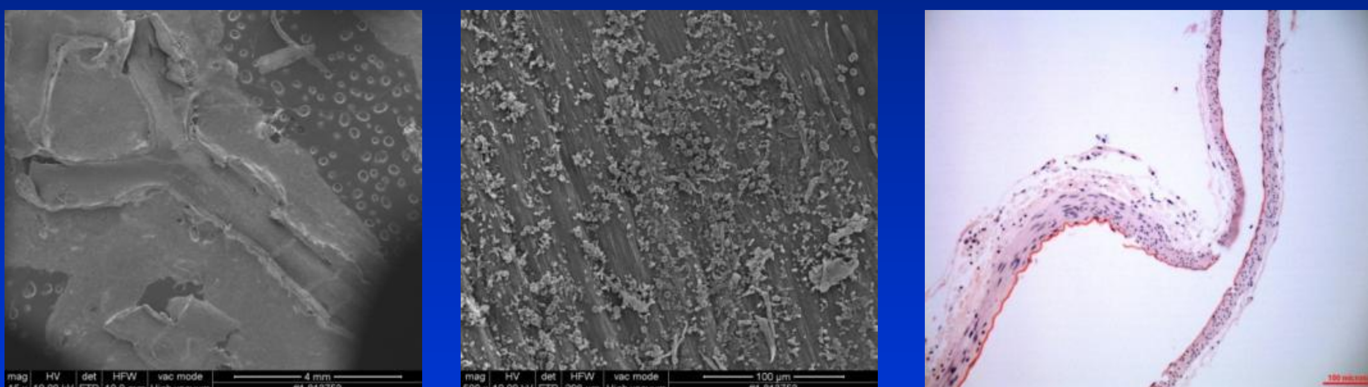
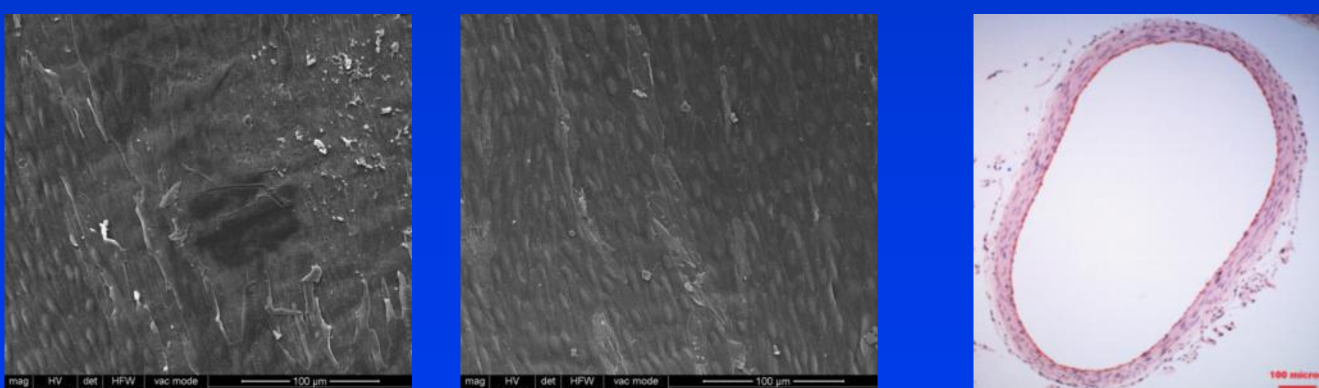
Histology Assessment



Stent-triever



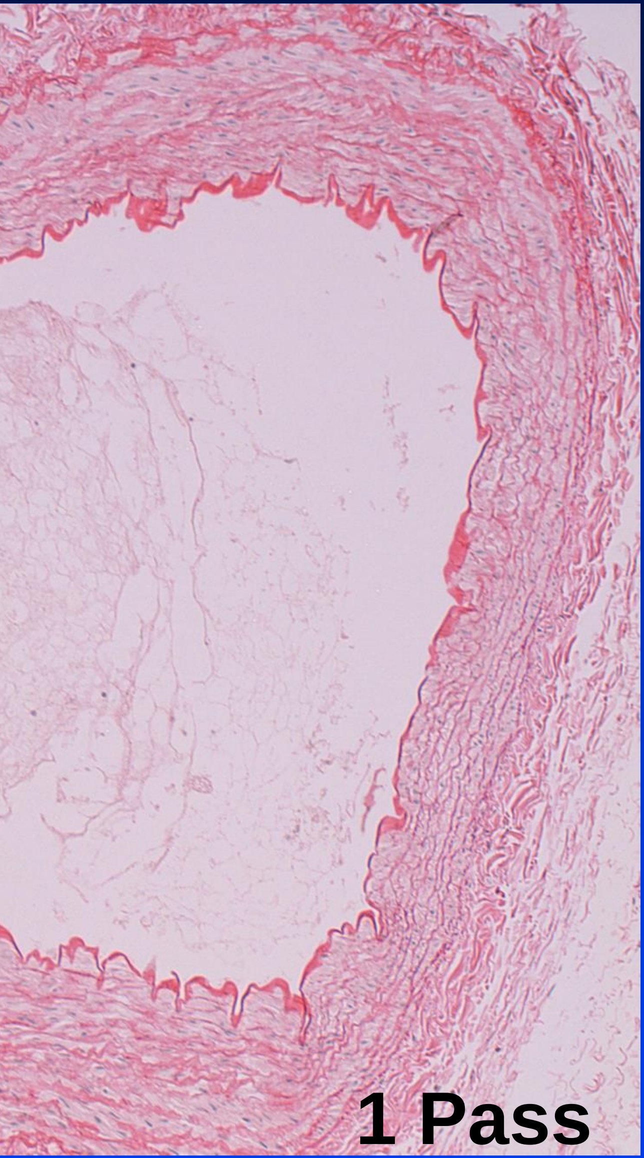
Merci V2

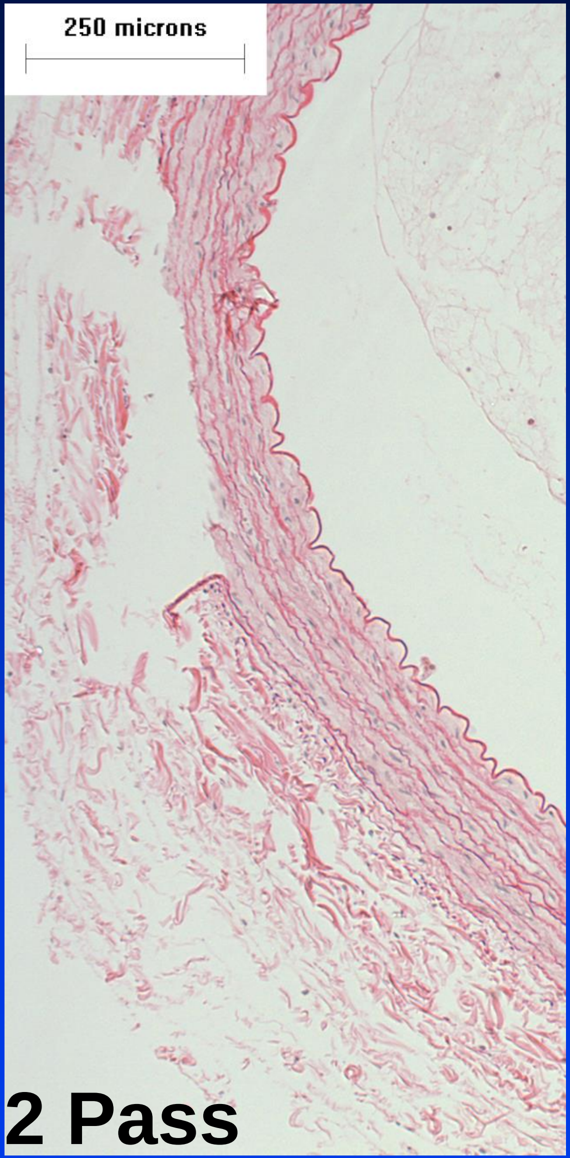


Control microcatheter

Stent-Thrombectomy (Rabbit CCA)

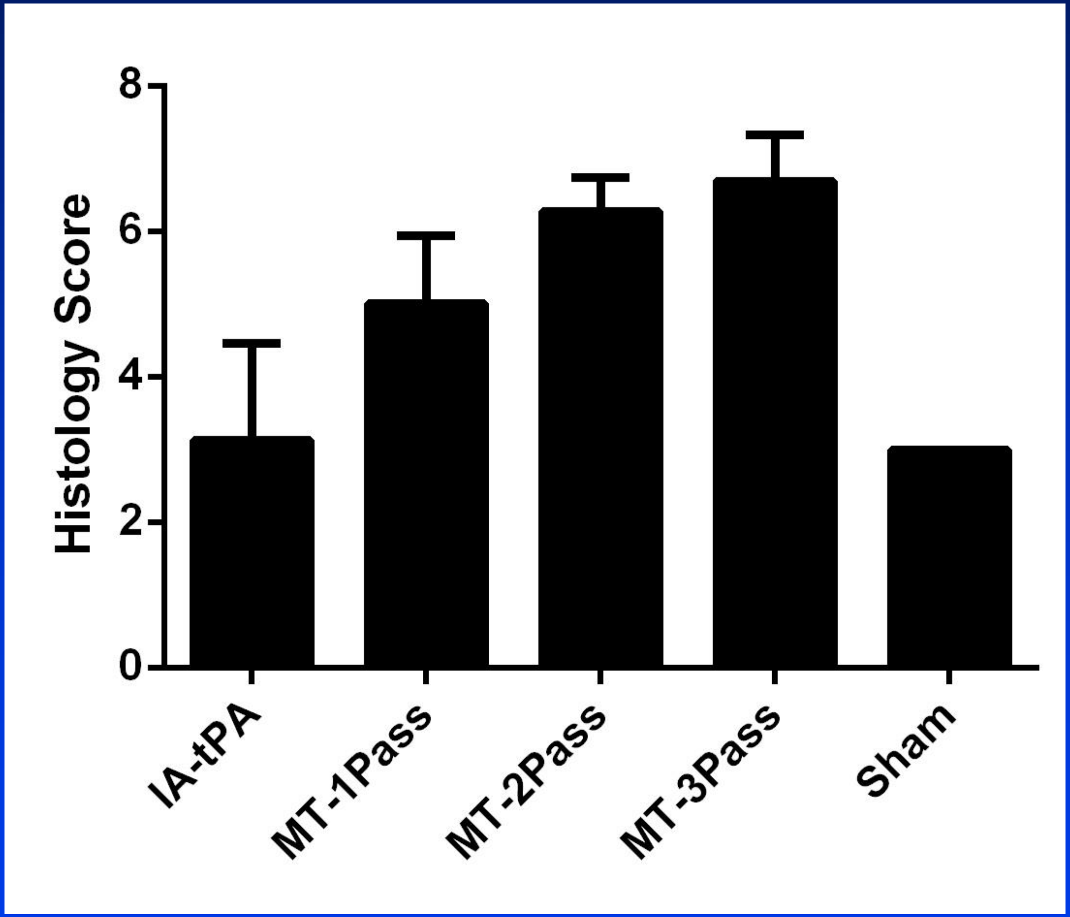
Marosfoi, et al. Stroke 2015





Stent-Thrombectomy

- Each pass causes more injury.



Marosfoi, et al. Stroke 2015

Future for Endovascular Therapy

NEW ENGLAND CENTER FOR STROKE RESEARCH

- Rapid diagnosis-Systems of Care
- Couple with Neuroprotection

- FASTER
  1. First-pASs
  2. TICI = 3
  3. Easy to use
  4. Reliable results (~95%)

UMASS

NECStR

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