From Bench to Brain

NEW ENGLAND CENTER FOR STROKE RESEARCH

Advancements in Thrombectomy for ELVO

UMASS

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AANS/CNS Joint Cerebrovascular Section Meeting

Disclosures

- Research Grants

(last 12 months):

  - NINDS, NIBIB, NIA, NCI
  - Philips Healthcare
  - Fraunhofer Institute
  - Stryker Neurovascular
  - Codman Neurovascular
  - eV3 Neurovascular / Covidien
  - InNeuroCo Inc
  - Blockade Medical
  - CereVasc LLC
  - Cook Medical
  - Neuronal Protection Systems
  - Spineology Inc
  - Silk Road
  - Wyss Institute
  - Microvention
  - Gentuity

- Consulting

(fee-per-hour, last 12 months):

  - Stryker Neurovascular

- Investment (Stocks)

  - Boston Scientific Inc
  - InNeuroCo Inc

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Disclosure Statement of Financial Interest

I, Matthew Gounis DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Acute Ischemic Stroke: Pre-Clinical Investigations for Devices – Does it Translate to Humans?

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Two Approved Treatments:
Both Target Vessel Revascularization

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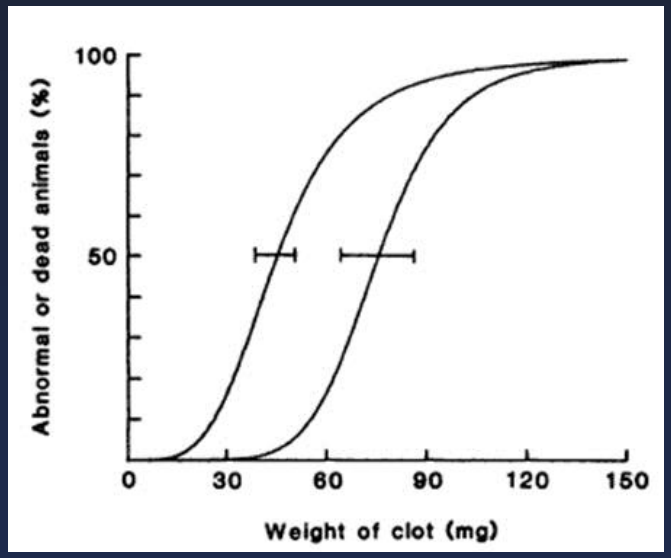
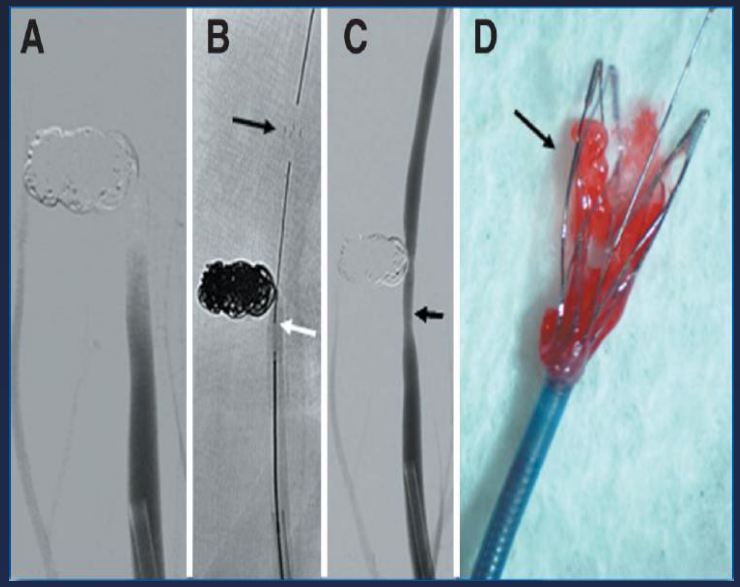
- Pre-Clinical Modeling has had an Impact:



With and without treatment with IV-tPA
Zivin, Fisher, DeGirolami. Science 1985; 230:1289-1292



(Wakhloo A.K. and Gounis M.J.,Neurosurgery 2008,62(5 Suppl 2): ONS390–ONS394.

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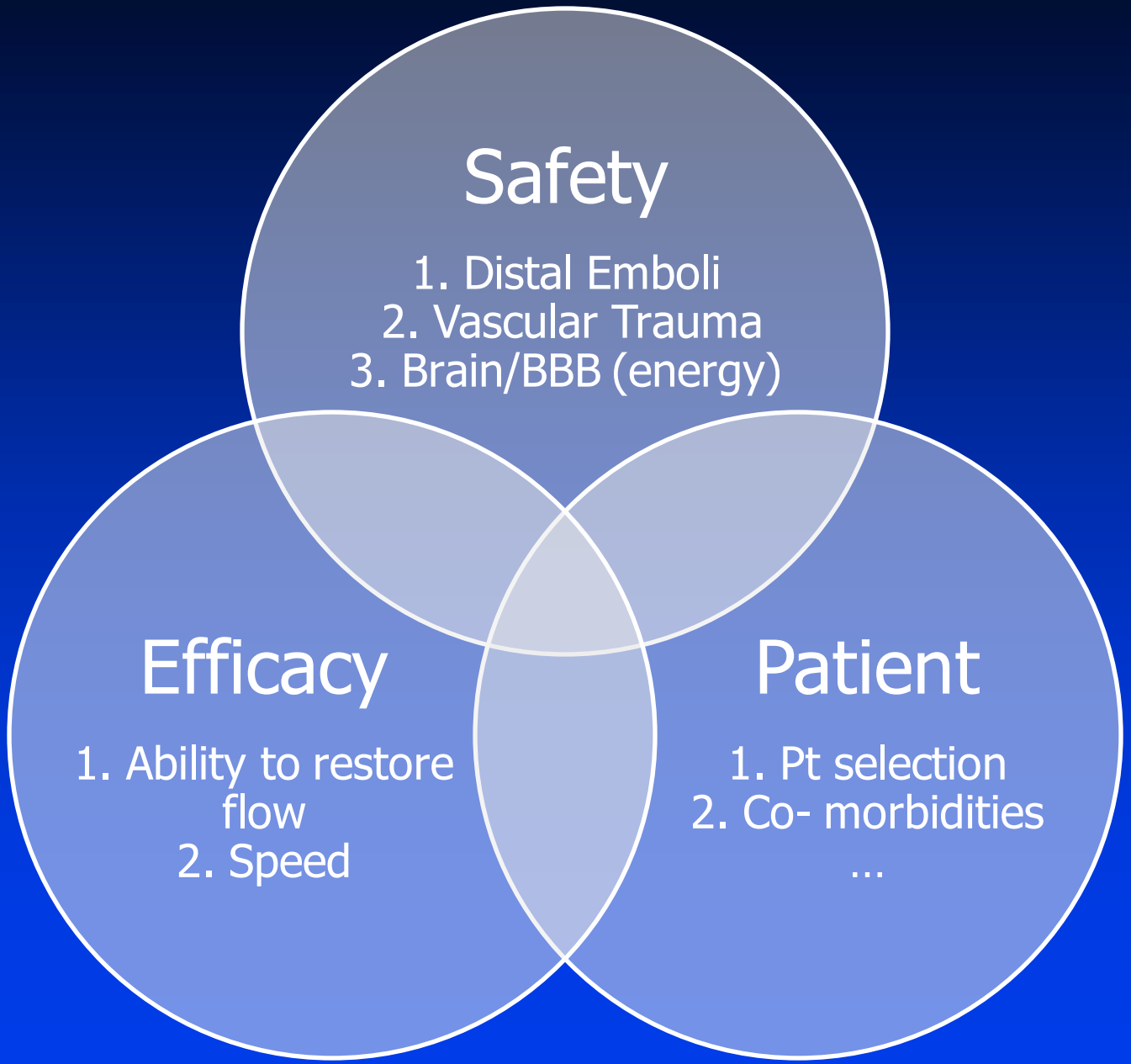
Considerations

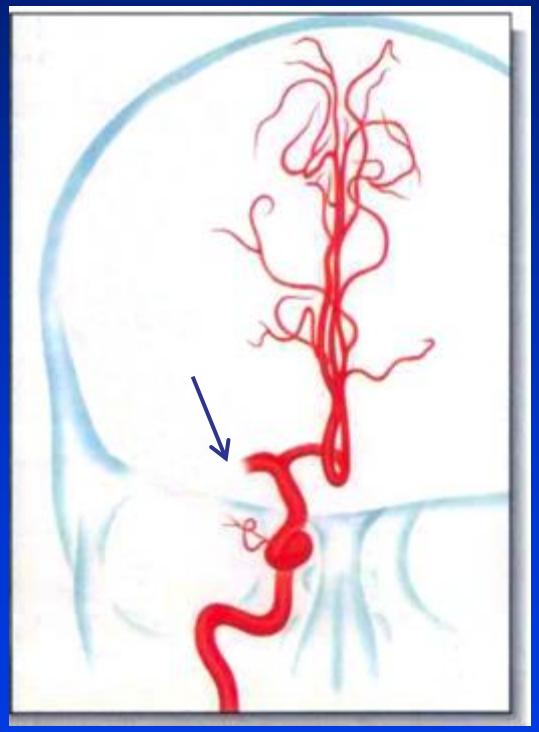


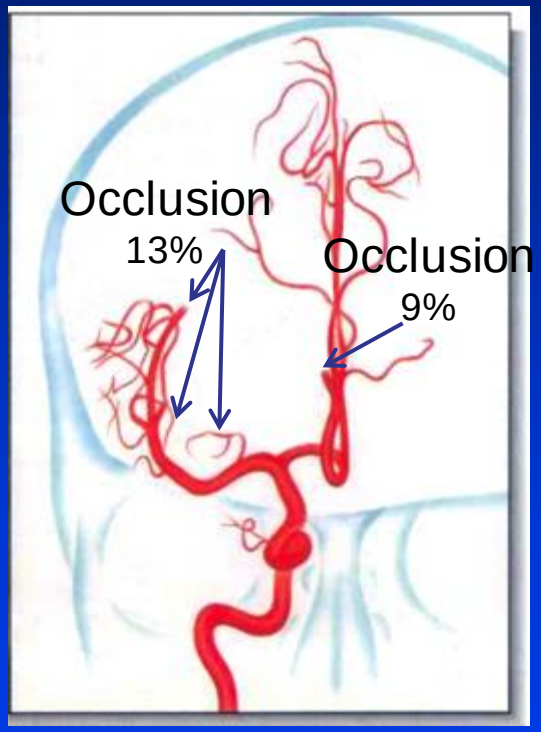
Distal Emboli

Thrombectomy <8hrs

Partial Recovery or Deterioration

Normal → Occlusive clot → Fragmentation*





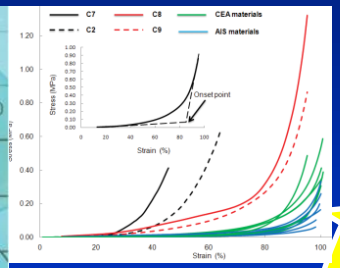
* Bonafe: ESMINT 2012

Distal Emboli

Address thrombus embolization with Stentrievers

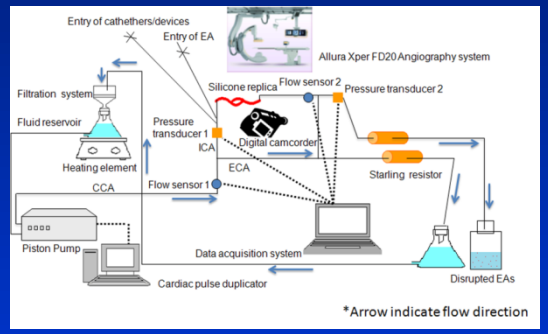
Trials	Embolization in New Vascular Territory	Clinical Signs of New Ischemic Stroke in Different Vascular Territory w/in 90 Days
EXTEND-IA	6%	---
MR CLEAN	8.6%	5.6%
REVASTAT	4.9%	---

In Vitro Assessment of Safety and Efficacy

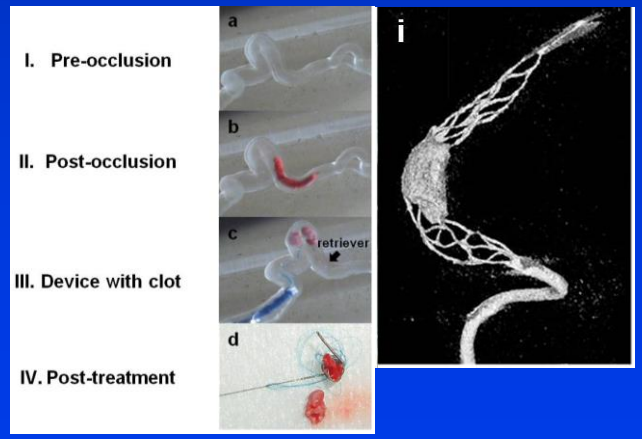


Clot Model

Circulation Loop



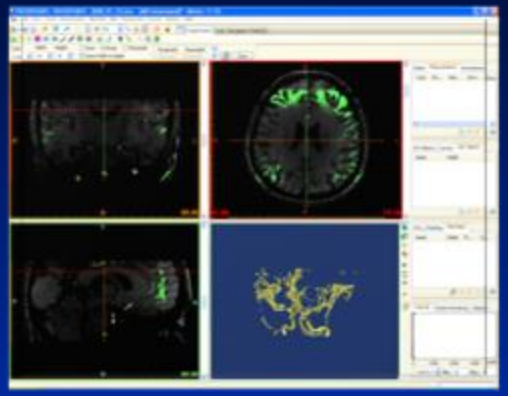
Imaging/ Medical Device



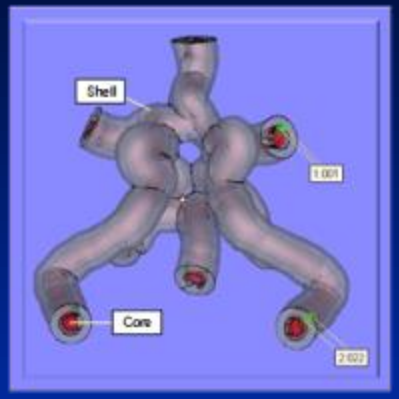
Bench-top Treatment Optimization

Vascular Model

Population Based Vascular Replica



MRA Dataset



Computer Core-Shell Model

Fused Deposit Manufacturing

Physical Core-Shell Model

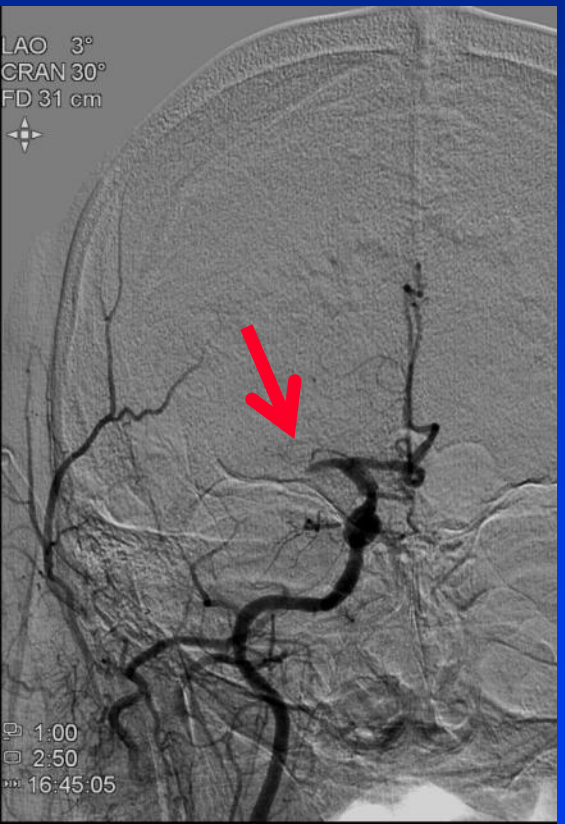
Silicone Replica

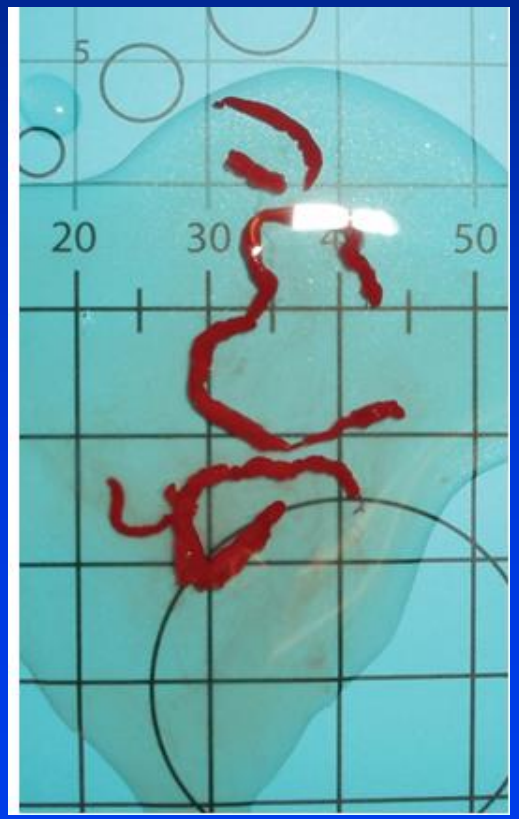
J Chueh, AK Wakhloo, and MJ Gounis. AJNR 2009

Mechanical Analysis of Clot Modeling

New England Center For Stroke Research

- 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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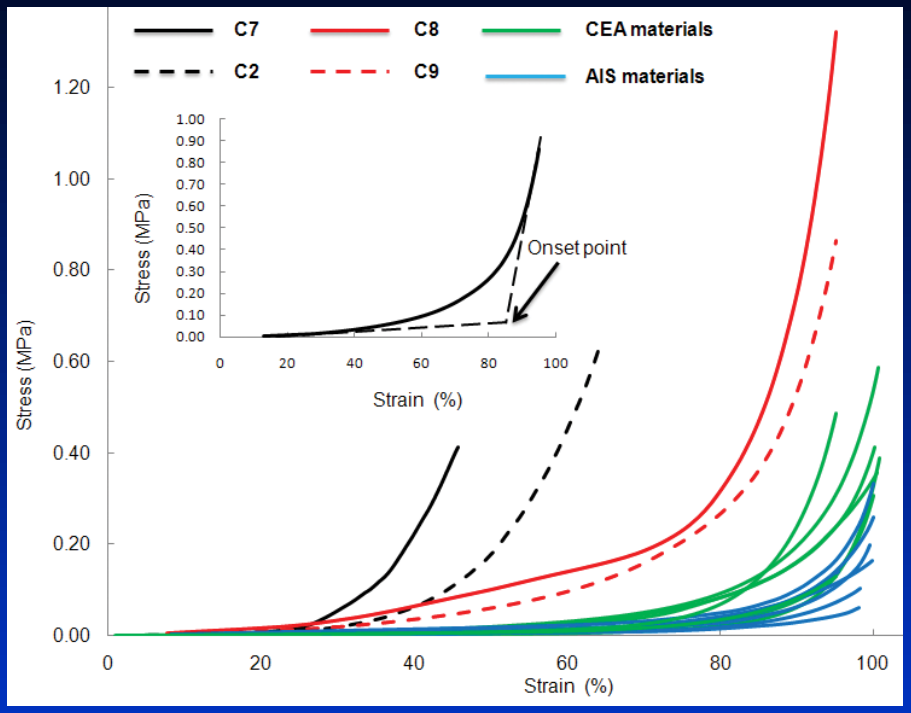
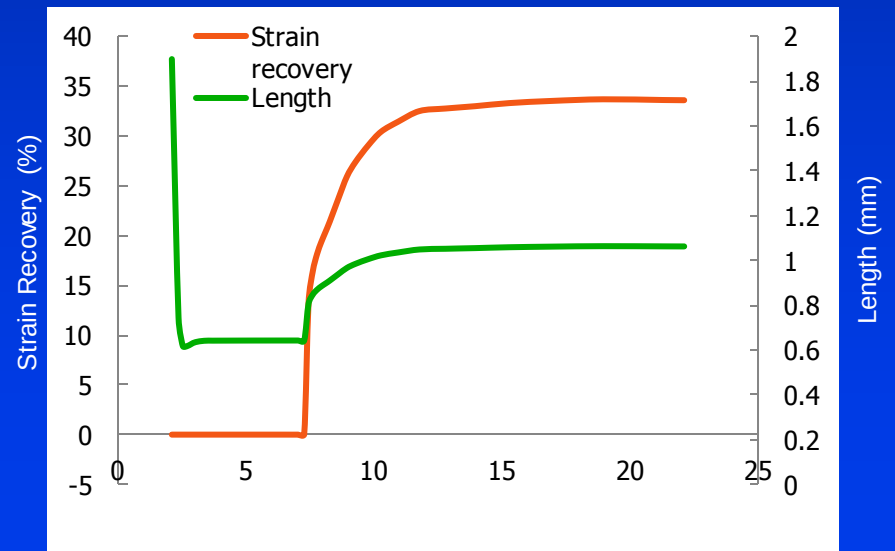
Mechanical Analysis of Clot



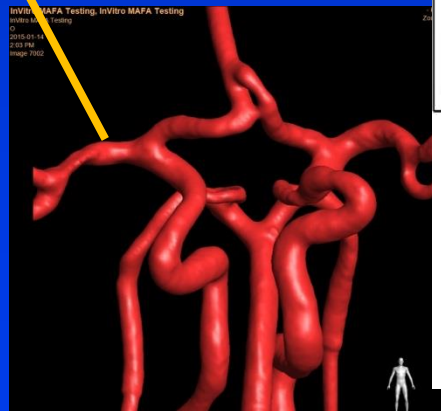


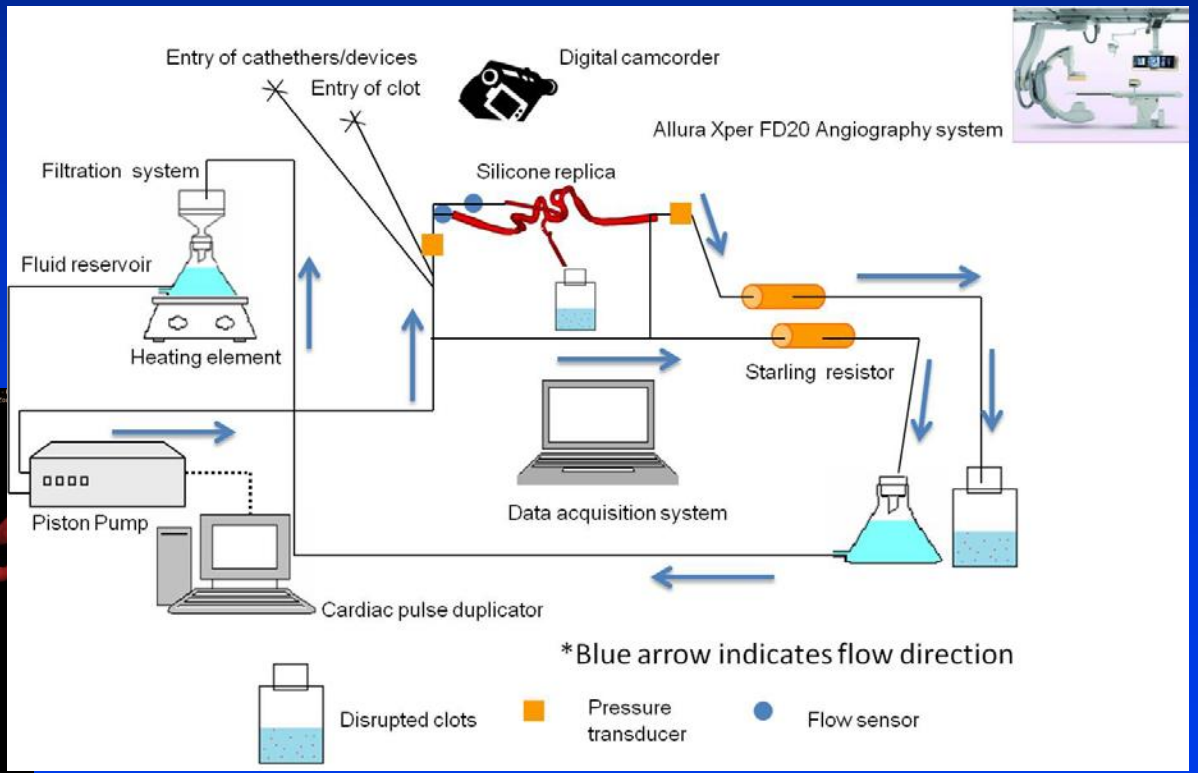
- Clot modeling – Need to know bulk mechanical properties
  - Stress-Strain: DMA compression test
  - Stress relaxation: Propensity for fragmentation

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

"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





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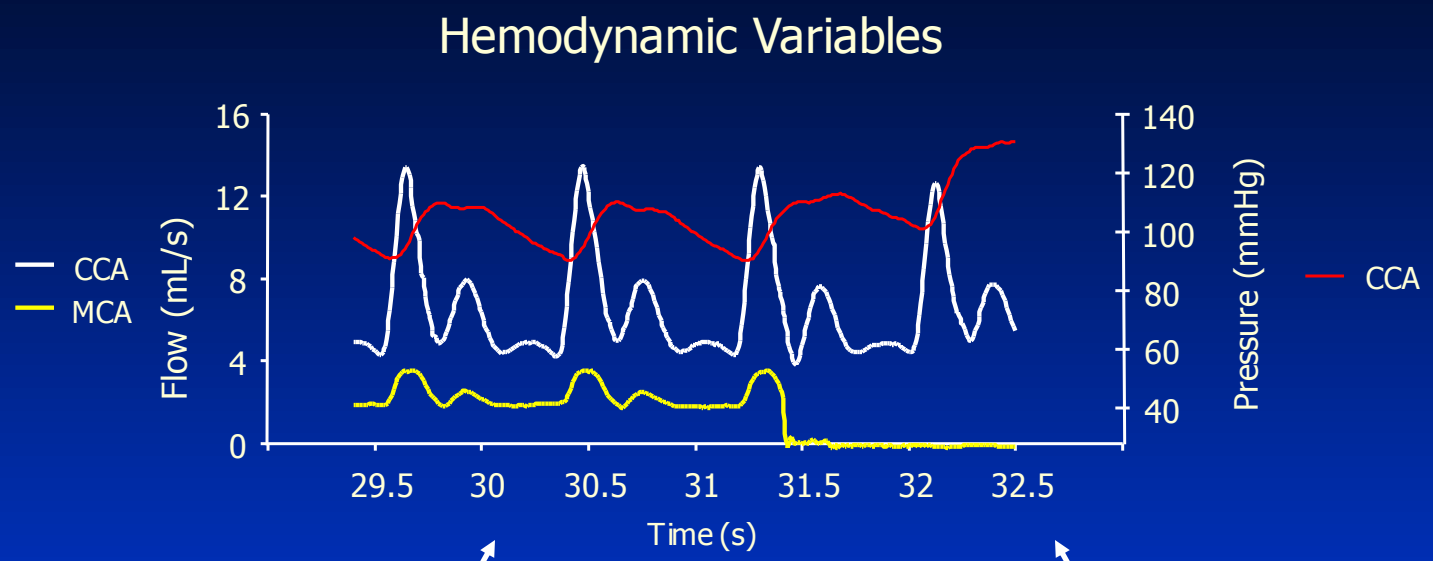
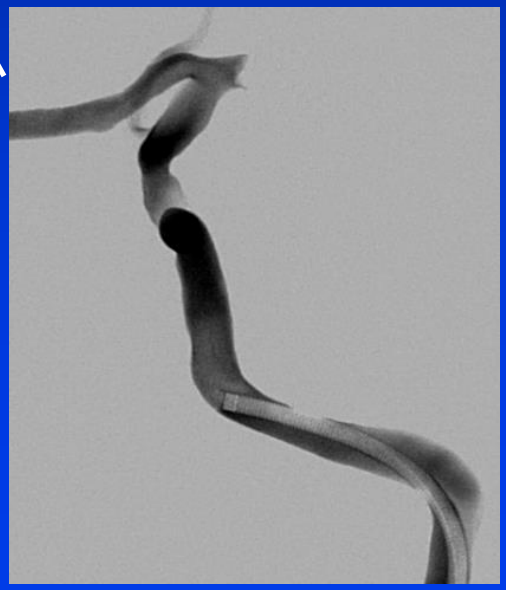
Vascular Occlusion





Translation?

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Experimental

Clinical

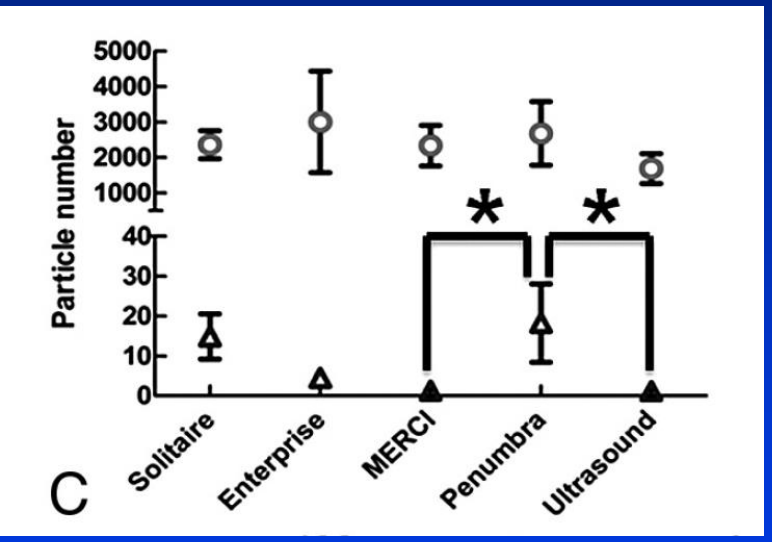

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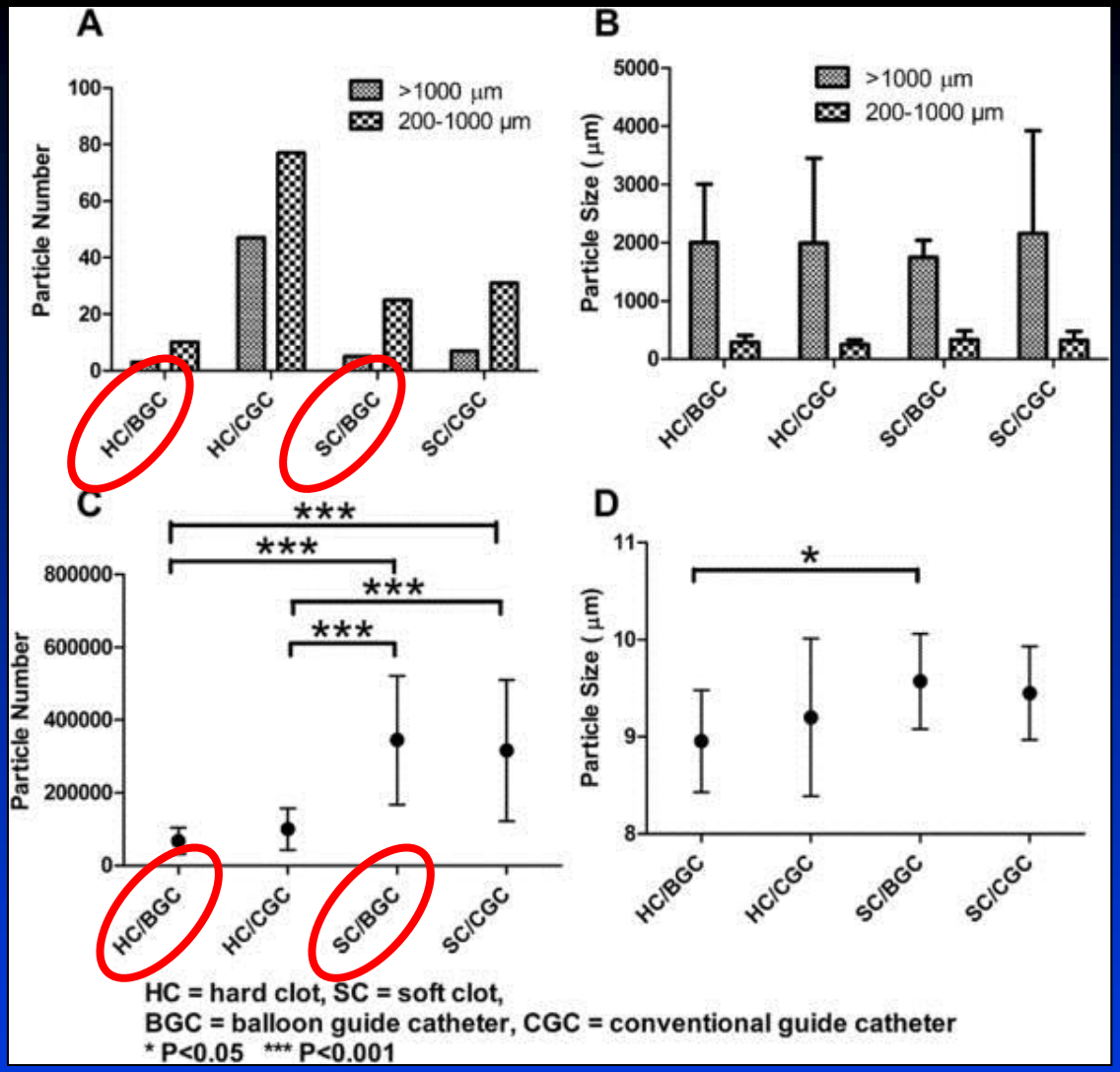
Table 2. Neurological and Functional Outcomes From Open versus Closed Vessels

Outcome	Percent With 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



Use of balloon guide catheter as compared to standard 6 Fr access reduces the number of distal emboli, depending on clot characteristics

Size and number of emboli produced in the stent-triever study. A, The total number of clot fragments with size >200 µm. B, The mean size of the large clot fragments. C, The average number of microemboli. D, The mean size of the microemboli.

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

Translation?

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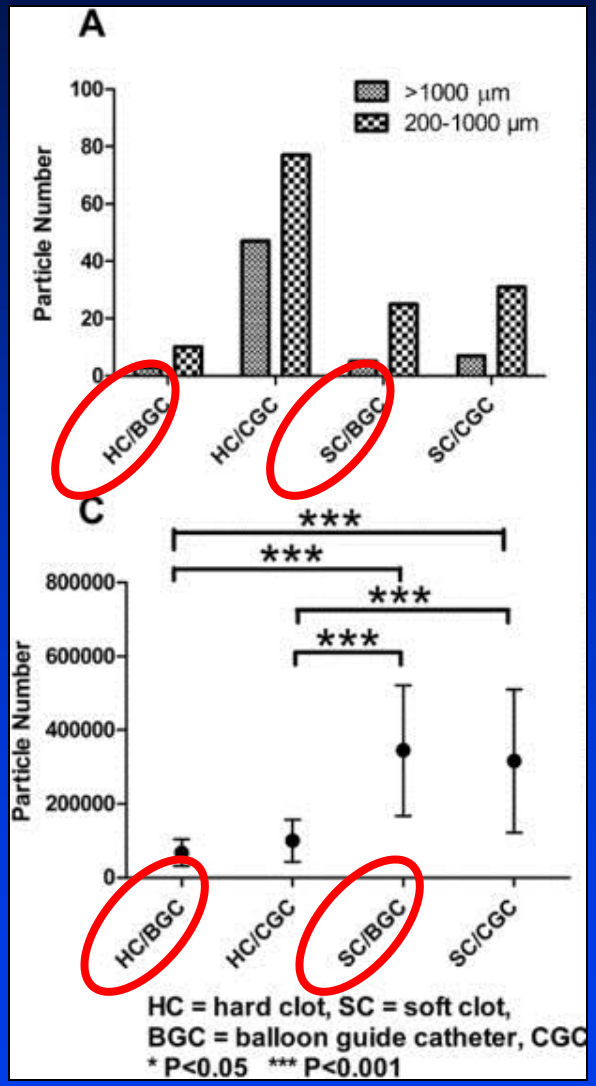
Experimental



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

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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.

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

New Devices for Reduction of Distal Emboli

The Cover

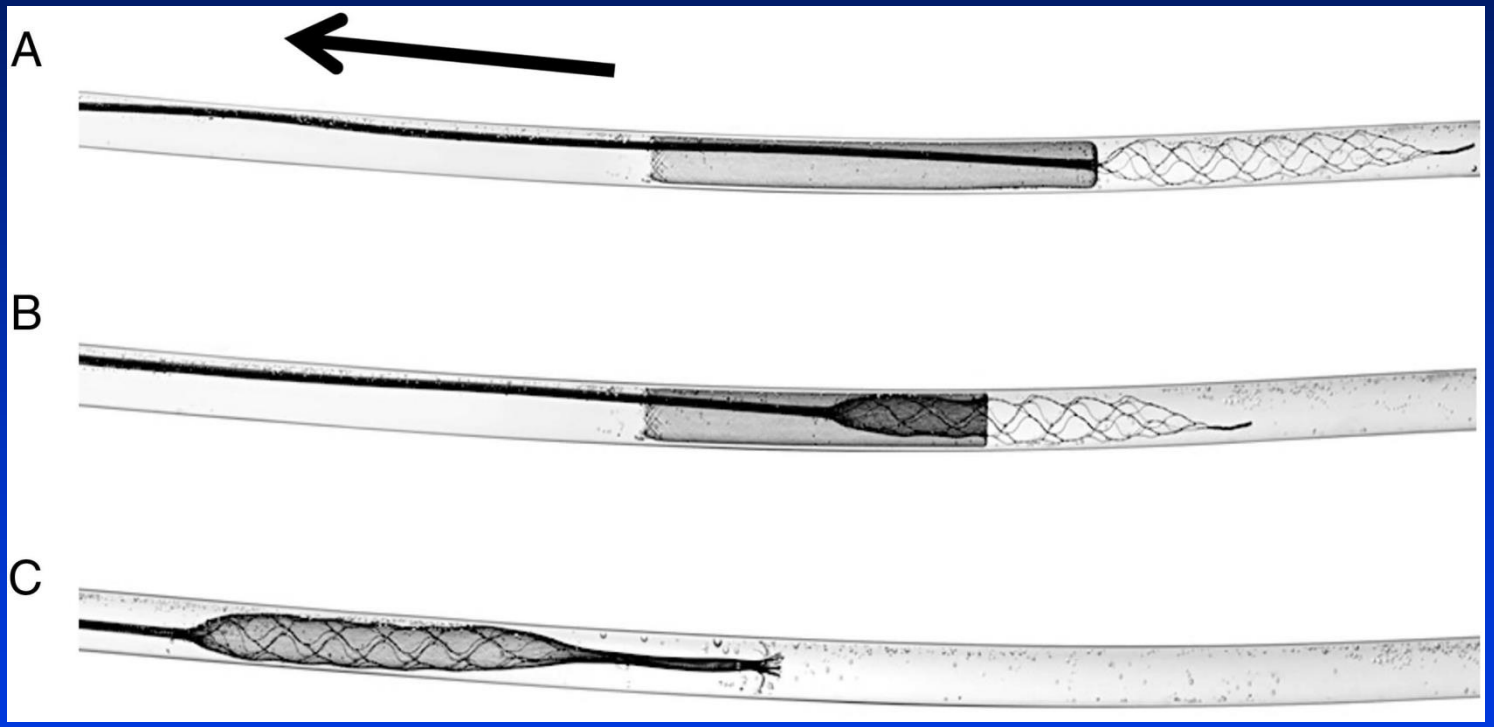
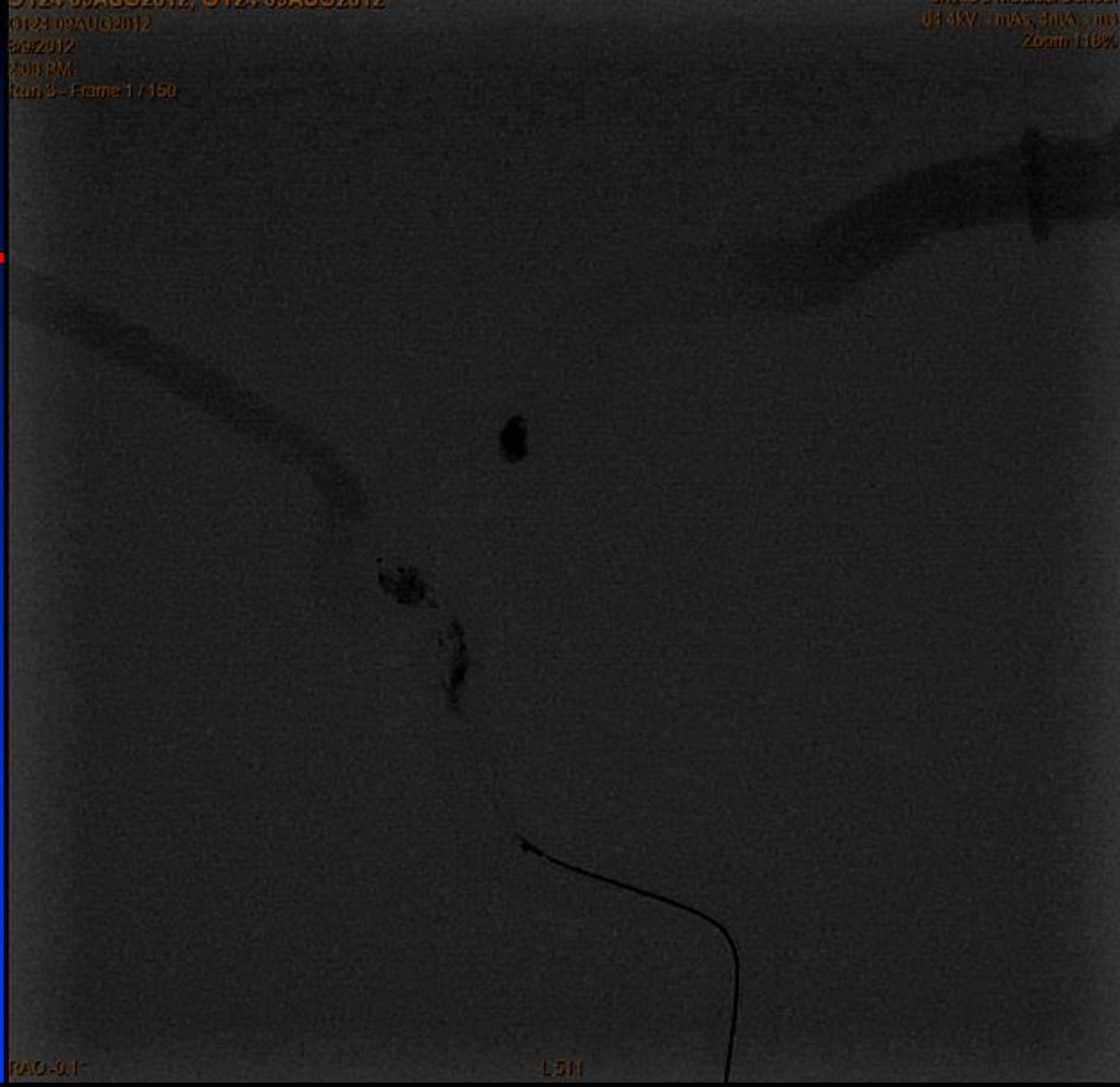


*Figure 1:
Mokin M, et al. J NeuroIntervent Surg 2015;0:1-5.doi:10.1135/neurointsurg-2014-011617

CE Mark. 510(k) pending. Not available for sale in the United States.

6 Fr Access, Solitaire

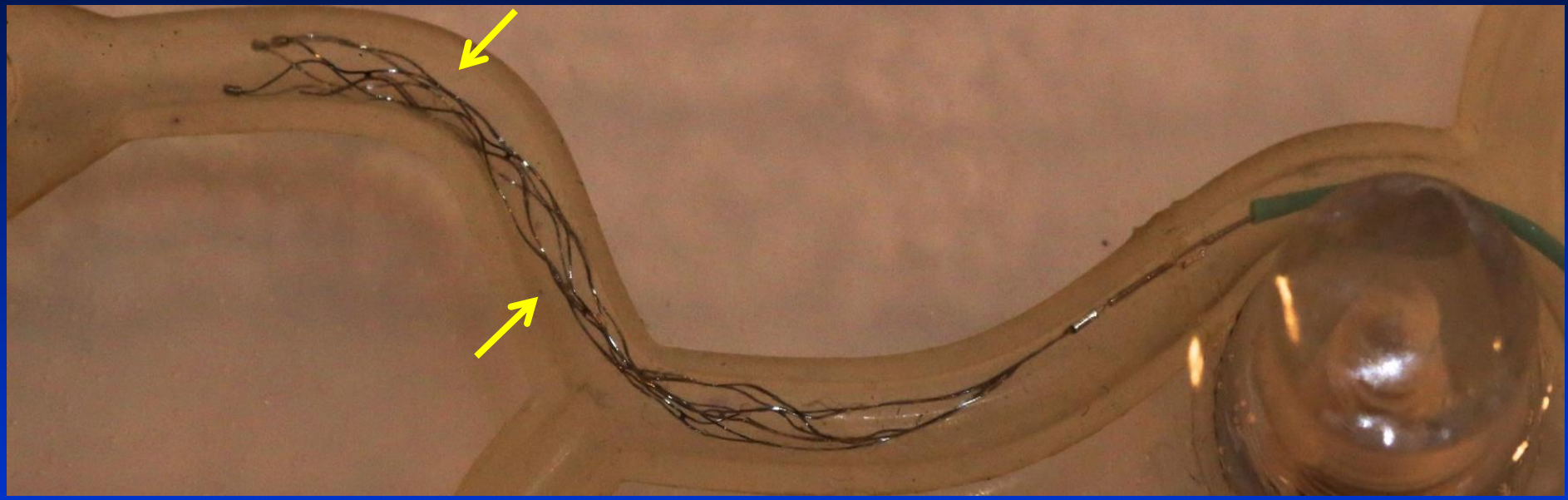


	8-200µm	200-1000µm	>1mm
Movie	121,450	4	18
Stroke, 2013 (n=16)	>100,000	5	3

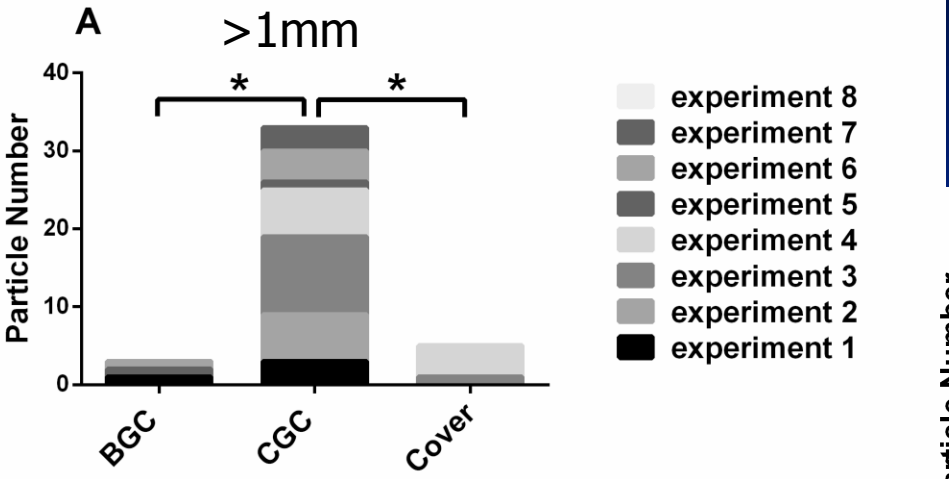
6 Fr Access, Solitaire + Cover

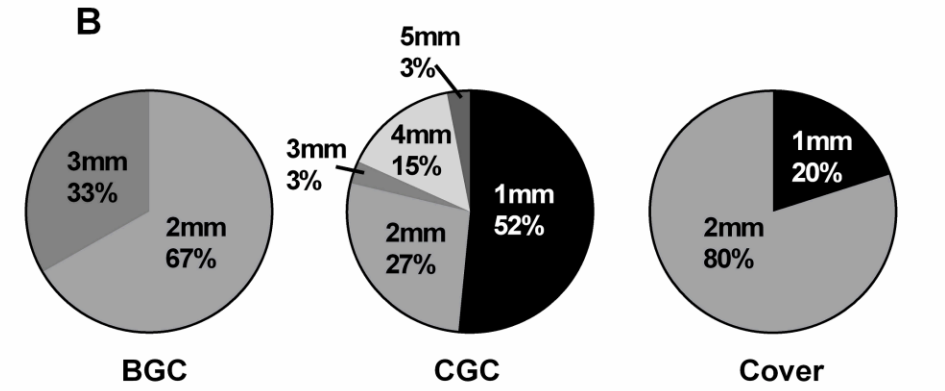
	8-200µm	200-1000µm	>1mm
Movie	18,731	0	0

The Toothpaste Effect

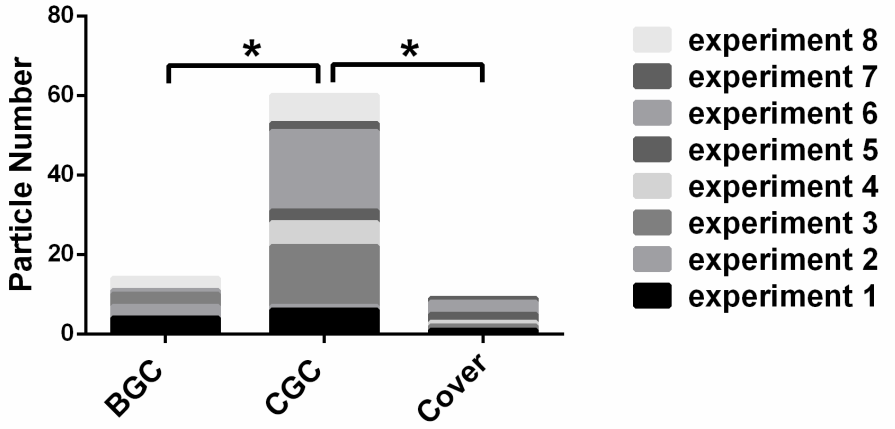


COMPARISON





0.2 – 1 mm



In Vivo Assessment of Safety

Safety Evaluation: Canine Vertebro-Basilar System


Merci V2.0 Firm


Enterprise VRD 4.5mm X22mm


Solitaire 4.0mm X20mm


Ultrasonic Waveguide

Angiographic Assessment

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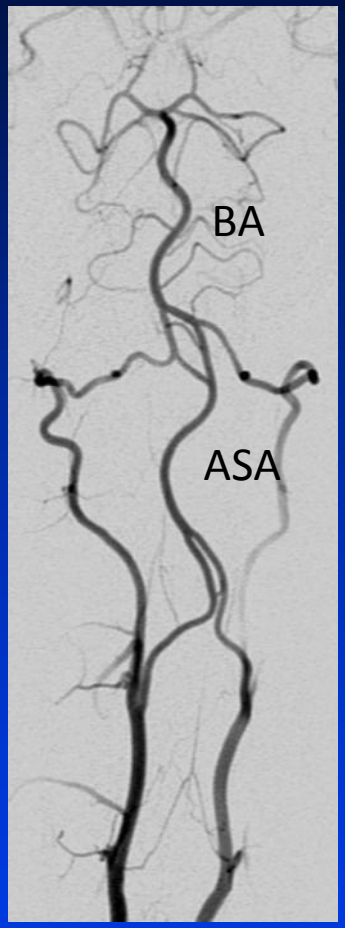
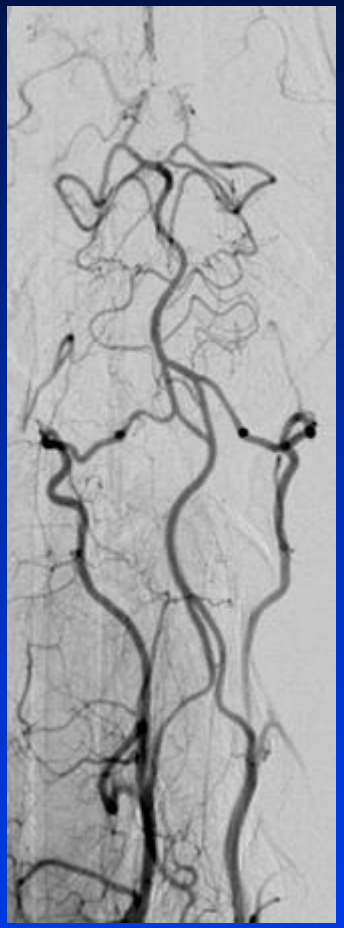
Stent-trievers

Merci V2-Firm



Pretreatment

First Pass
Grade 3



Fourth Pass
Grade 0

First Pass

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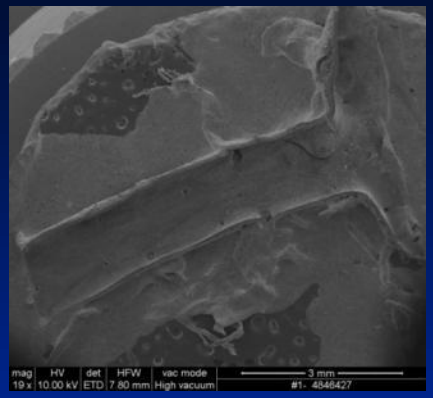
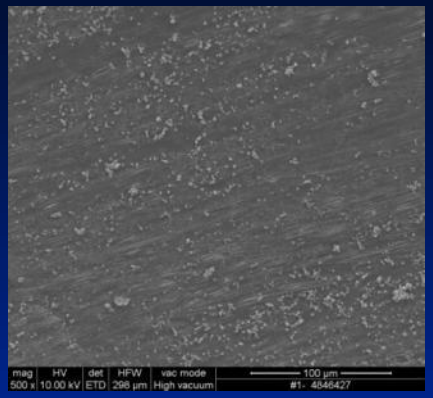
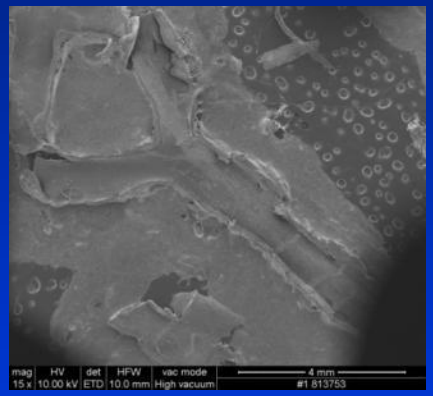
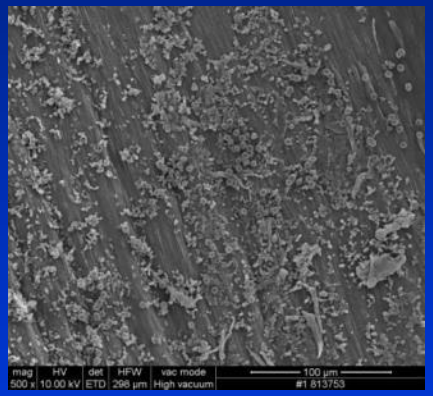
Histology Assessment

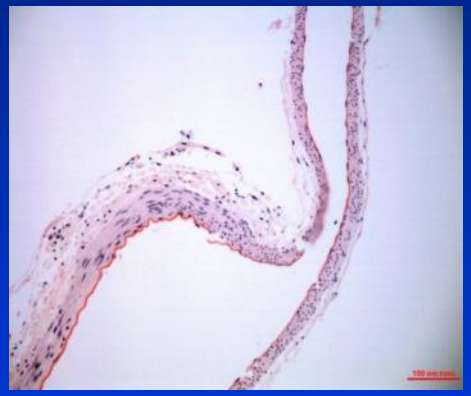




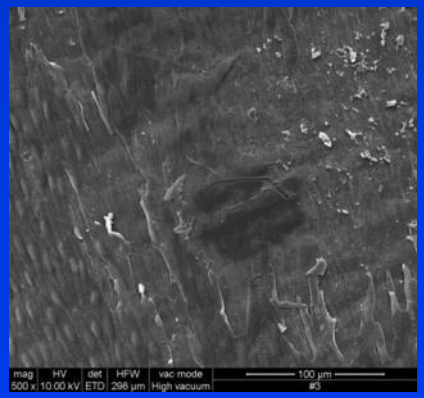
Stent-triever

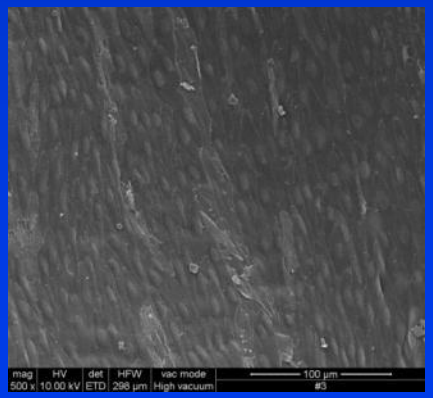






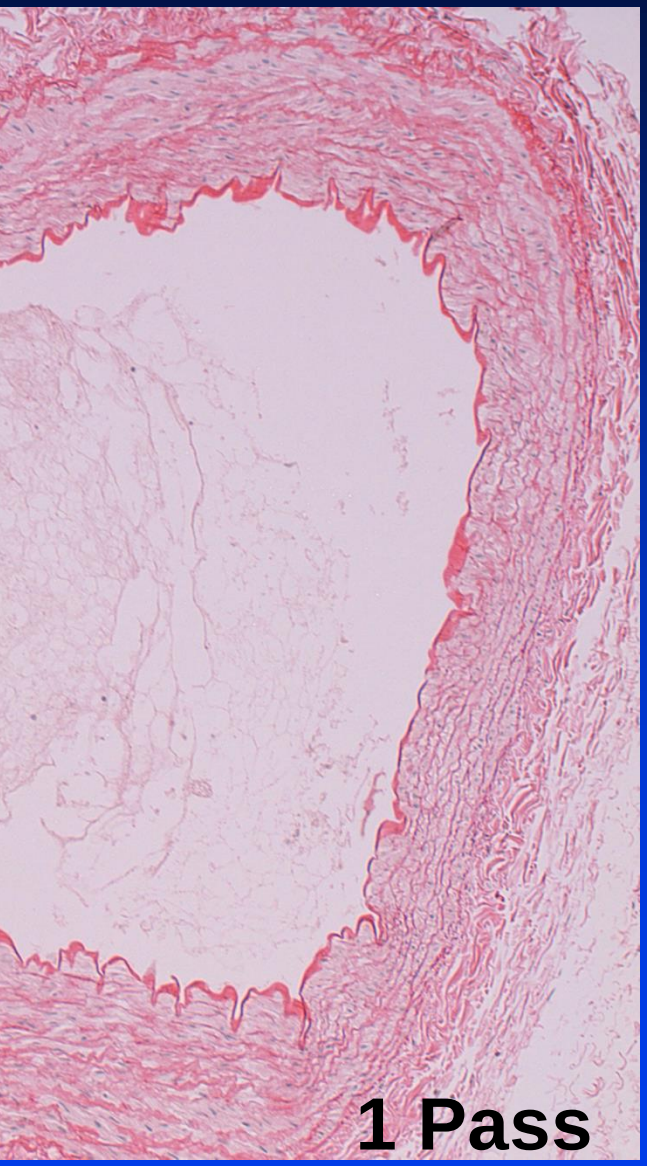
Merci V2



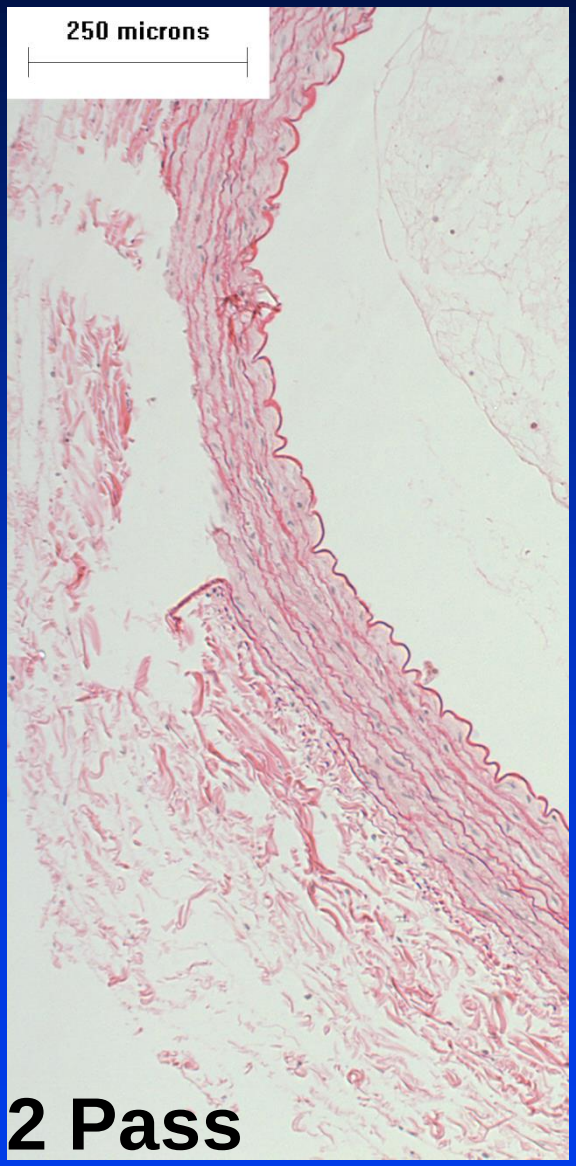


Control microcatheter

Stent-Thrombectomy



1 Pass

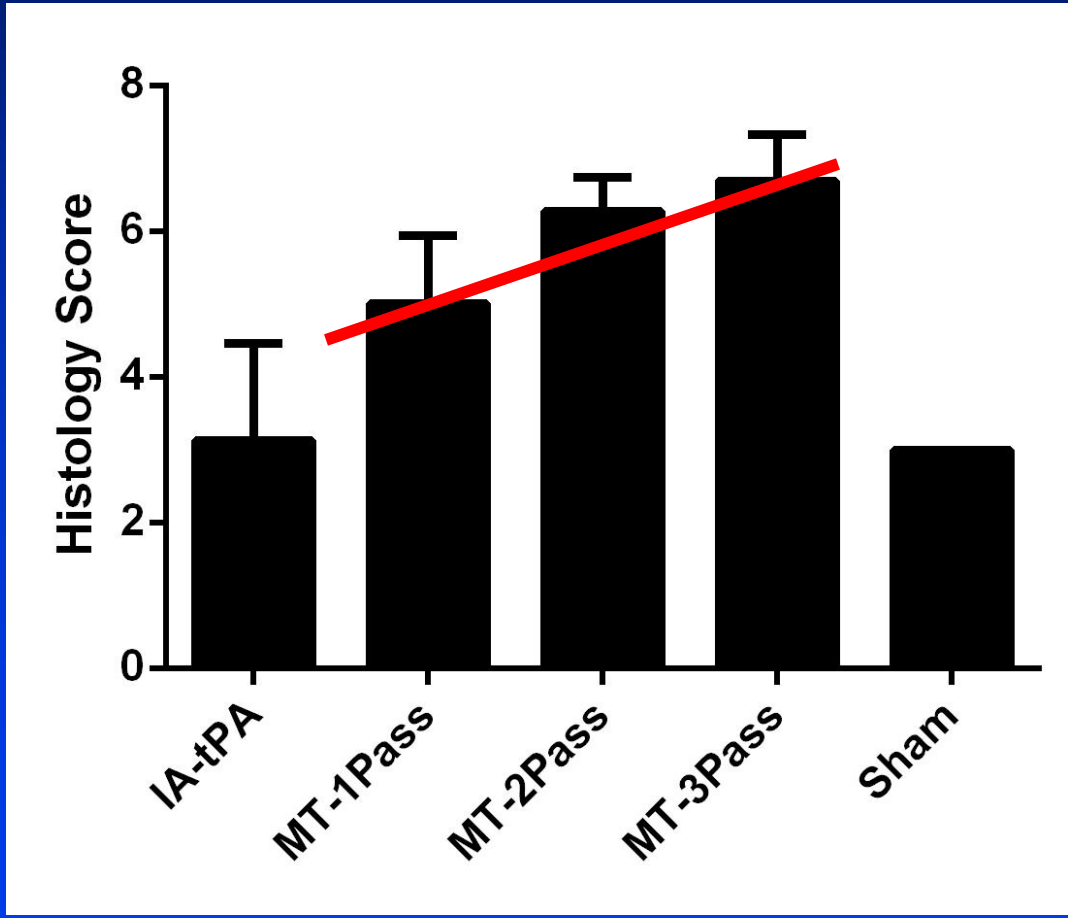


2 Pass

3 Pass

Stent-Thrombectomy

- Each pass causes more injury.



Mechano-Pharmacological Endovascular Treatment

Hypothesis

- Combination of a less traumatic endovascular approach, using temporary endovascular stent- bypass and targeted thrombolytic drug delivery can recanalize a large vessel occlusion
  - Primary efficacy endpoint: vessel recanalization
  - Primary safety endpoint: vascular pathology

Fabrication of Nano-particle Aggregates

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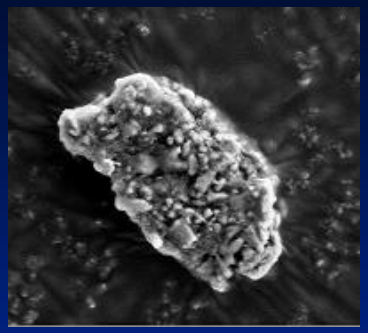
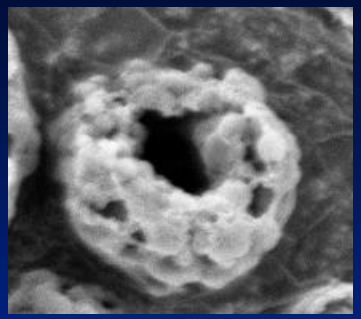
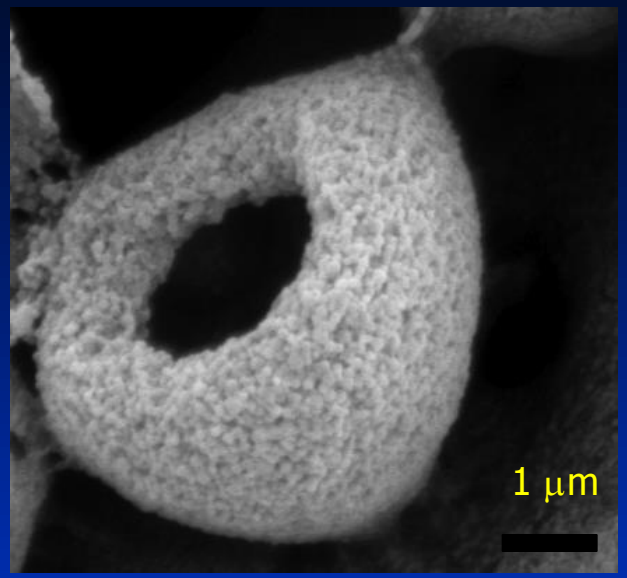


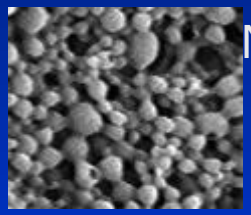
Spontaneous



Controlled

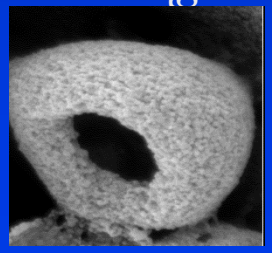


PLGA Nanoparticles (~ 200 nm))

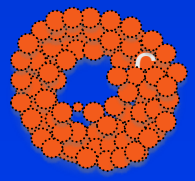


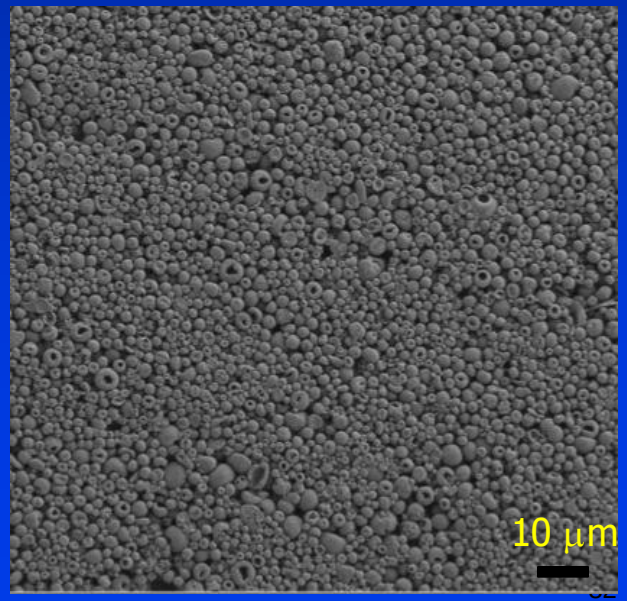
+ excipients

Spray drying



Nanoparticle Aggregates (~ 4.5 um)





Shear Induced Drug Delivery

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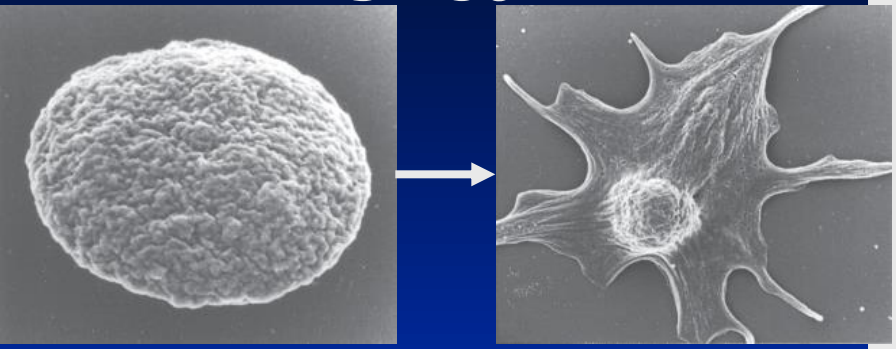
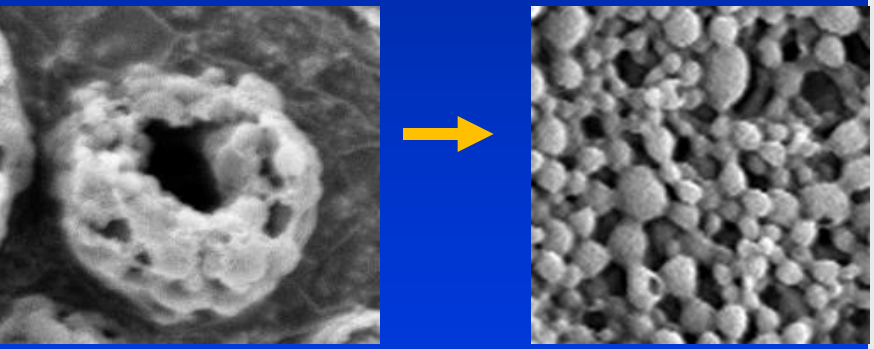
Shear

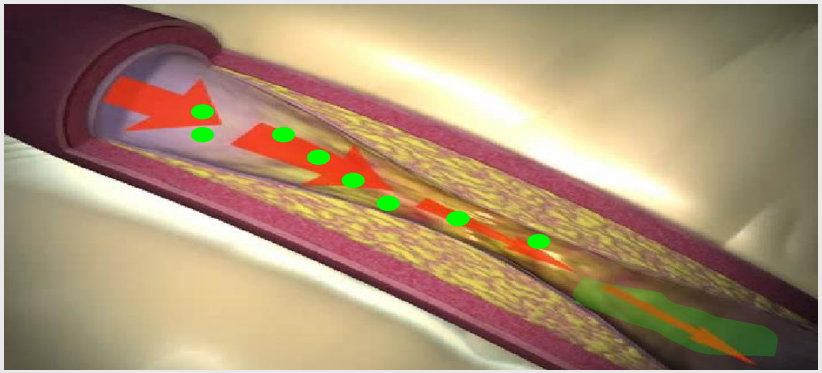


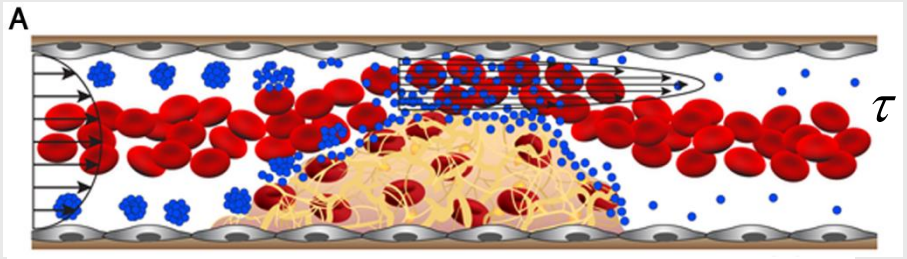
Shear induced platelet activation

Shear

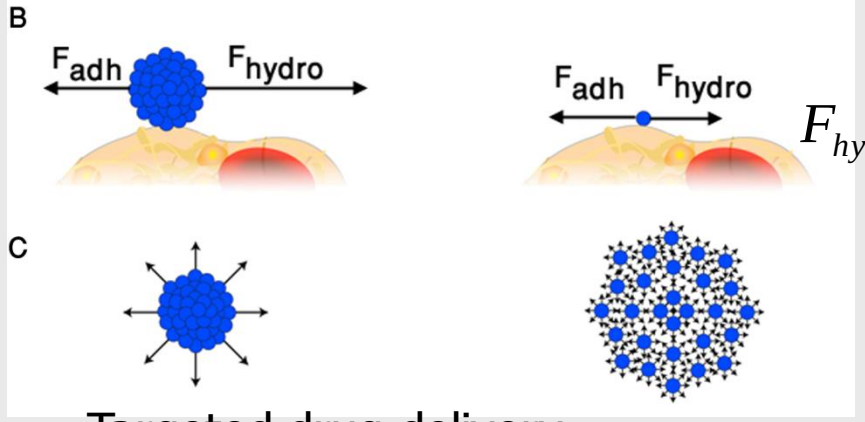


Shear induced particle activation





$$\tau \approx \frac{Q}{d^3}$$



$$F_{hydro} \approx r^2$$

Targeted drug delivery

Korin et al. ,Science, 2012

Technology

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N Korin et al. Science 2012 and JAMA Neurol 2014

Combined Therapy: Stent Bypass & Pharmacological Thrombolysis in a Large Vessel Occlusion Model

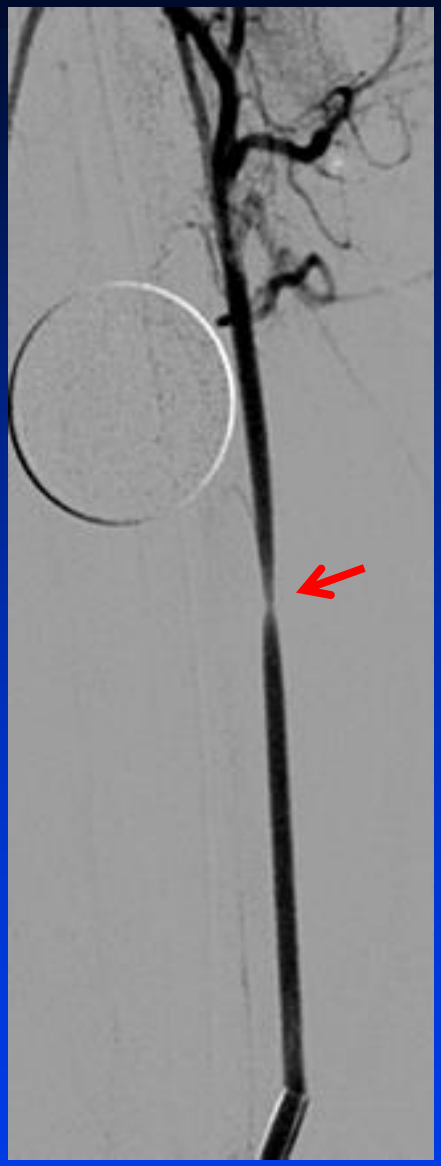
Rabbit CCA Thromboembolic Occlusion Model- Materials and Methods

- ✓ Coagulation profile and response to tPA closer to humans*.
- ✓ Controllable occlusion for a systematic analysis of the various treatment methodologies
- ✓ Diameter rabbit CCA ~ 2-2.5 mm comparable to the human MCA.
- ✓ Angiographic confirmation of the occlusion and revascularization
- ✓ Histological and SEM evaluation of vascular safety

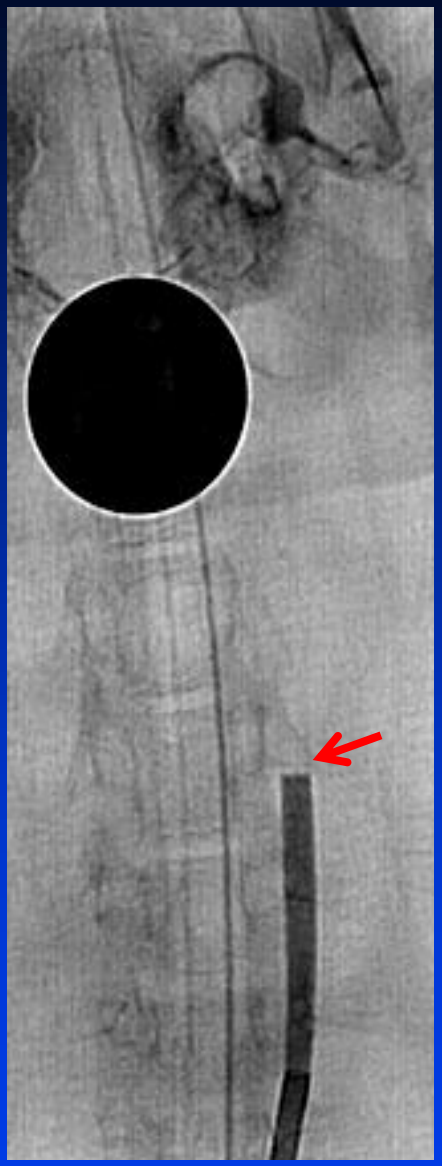
* SA Yakovlev, Thromb Res.1995;79:423

Materials and Methods

New England Center For Stroke Research



1. Create Stenosis

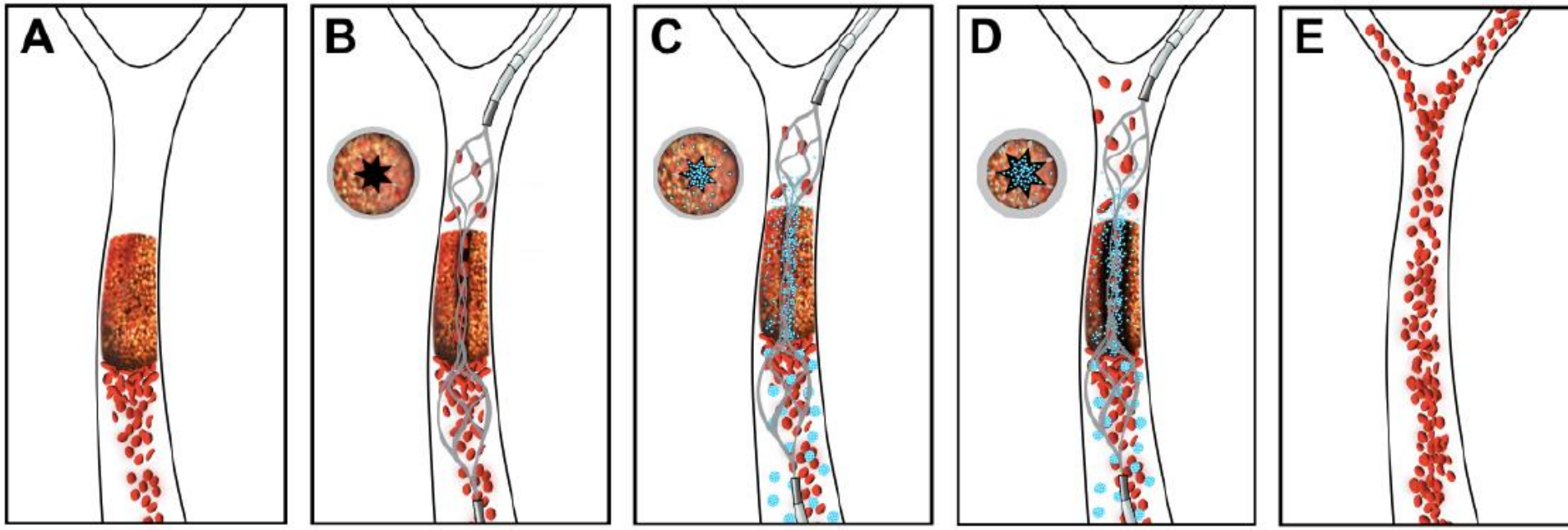


2. Inject allogenic clot (2.8x10 mm)

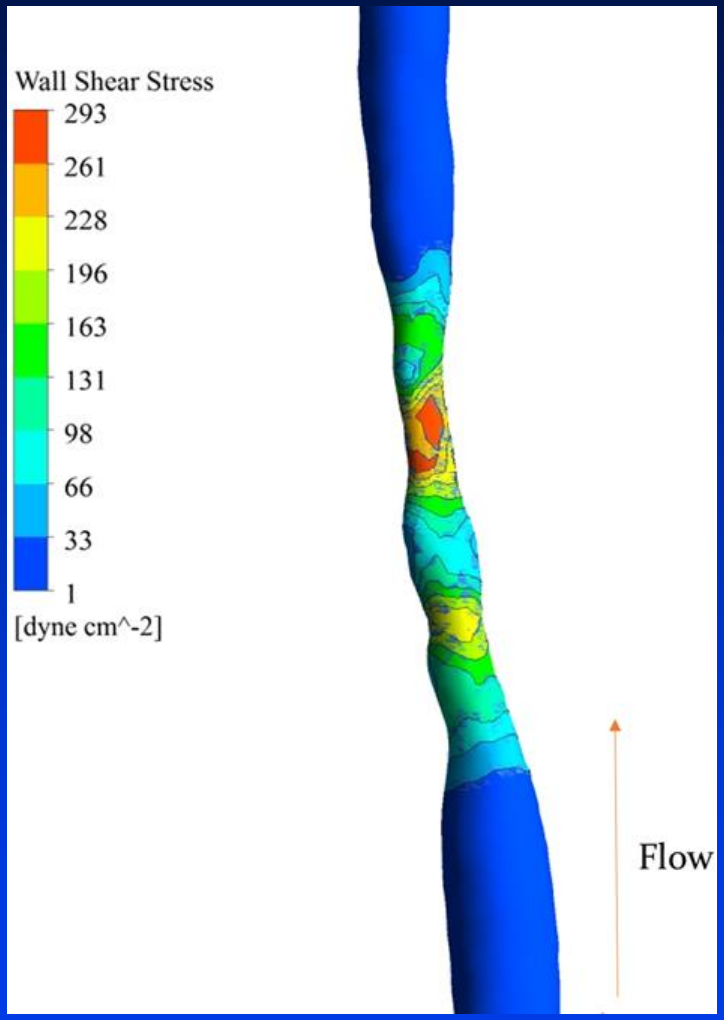
3. Remove Stenosis

Gounis, Nogueira, Mehra, Chueh, Wakhloo. JNIS 2013

Stent Bypass + SA-NP



WSS with Stent Bypass



Materials and Methods

- 7 --- 2 mg tPA
- 7 --- Stent only
- 7 --- Stent + 2 mg tPA
- 7 --- Stent + 20 mg tPA
- 7 --- Stent + NPA 2 mg tPA
- 7 --- Stent + NPA 20 mg tPA

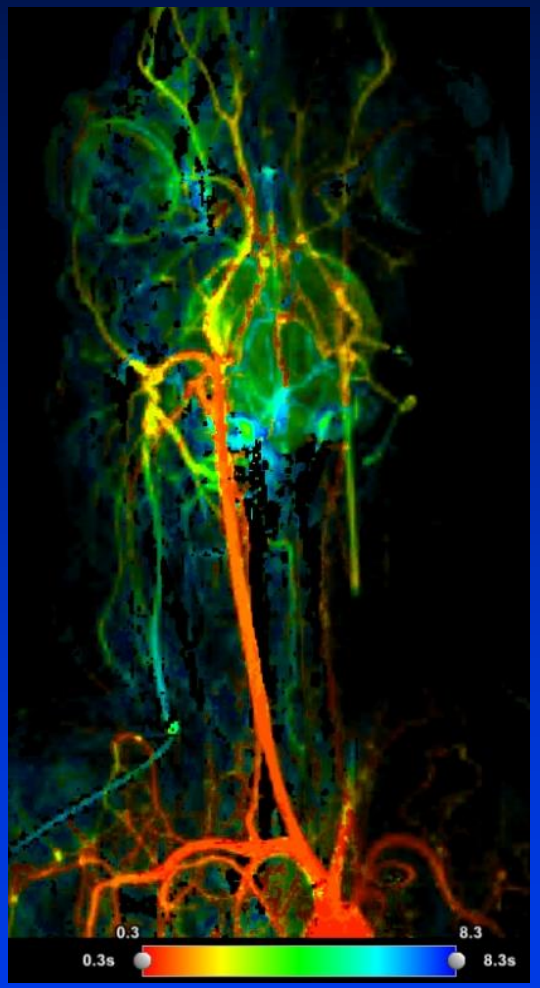
	N of distal vessels	***mTICI score***
0% reperfusion	0	0
Partial recan, but no distal perfusion	0	1
less than 50%	1-5	2A
more than 50%	6-10	2B
100% perfusion	11	3

100% reperfusion --- 11 point (max.)
missing vessel -1 pont


PRE
A2253 R14-457 A2253 R14-
A2253 R14-
UMASS Medical Sch
R201411250743
2D Perfus
Cerebral 2
S+20mg tPA

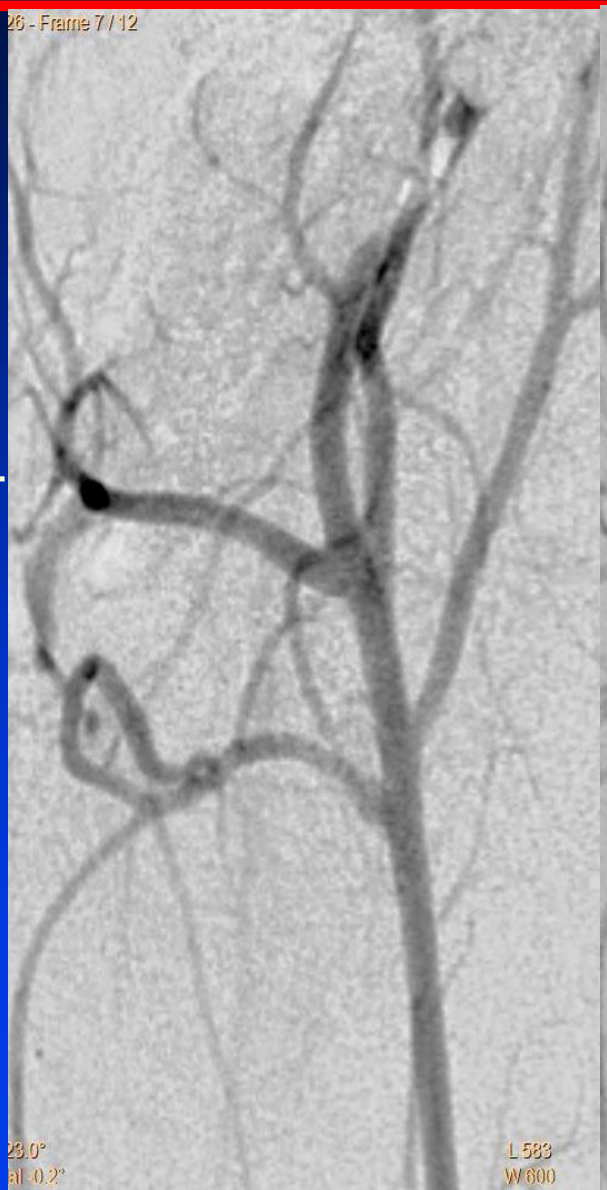

POST
A2253 R14-457 A2253
A2253
UMASS Medic
R20141125
2D
Cere
4 points – mTICI: 2A

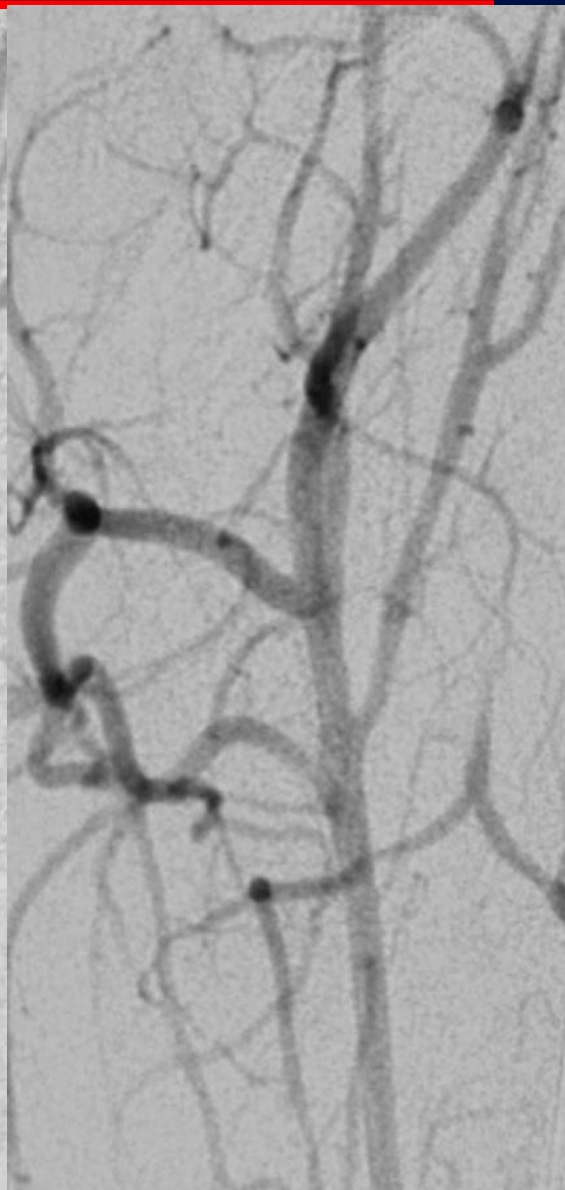
Results



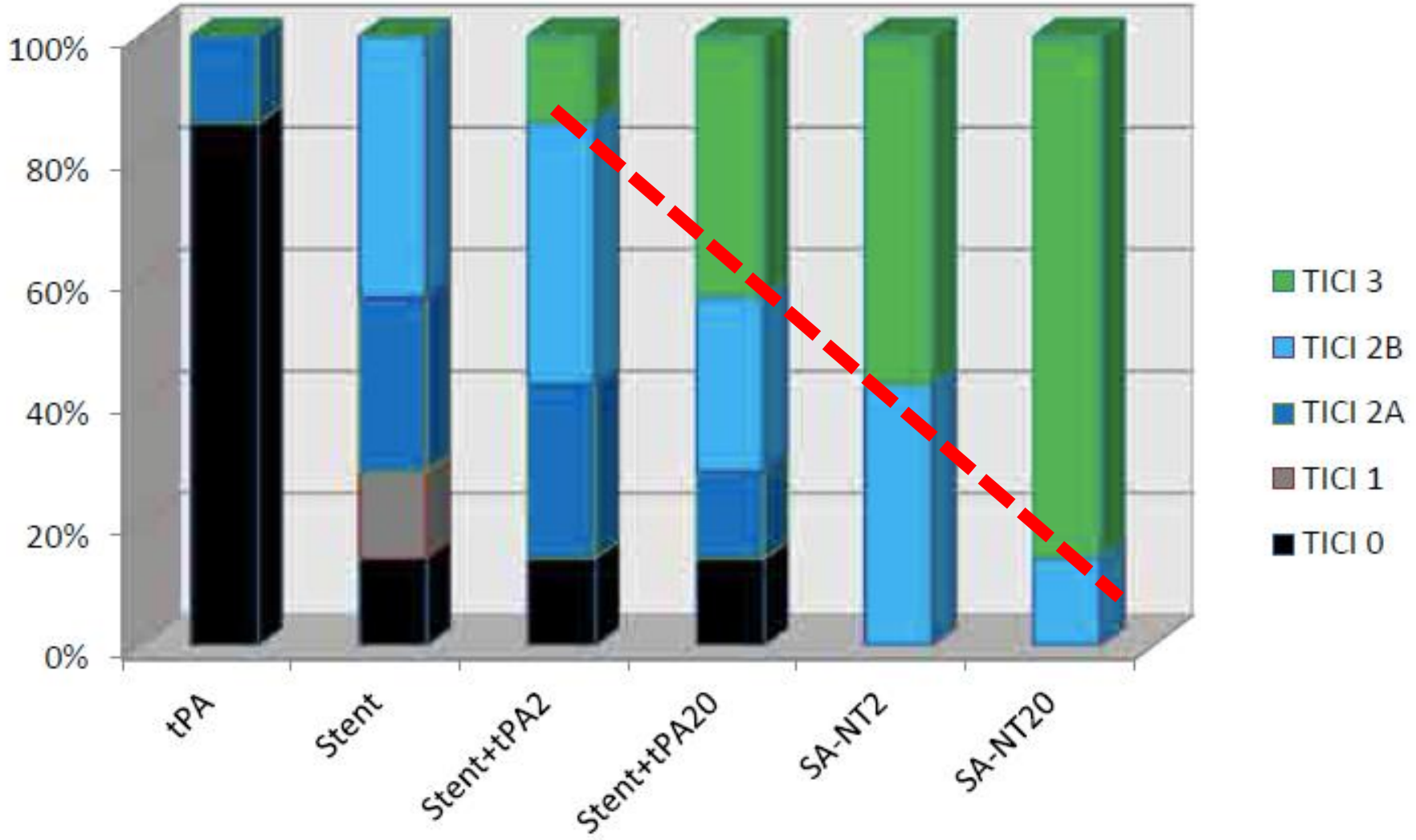
Continued Lysis

- SA-NT 2 mg: 29% had improvement of rmTICI after average of 36 min
- TEB-tPA 2 mg: 14% showed worsening after average of 36 min





Results


100%
80%
60%
40%
20%
0%
tPA
Stent
Stent+tPA2
Stent+tPA20
SA-NT2
SA-NT20
TICI 3
TICI 2B
TICI 2A
TICI 1
TICI 0

Results

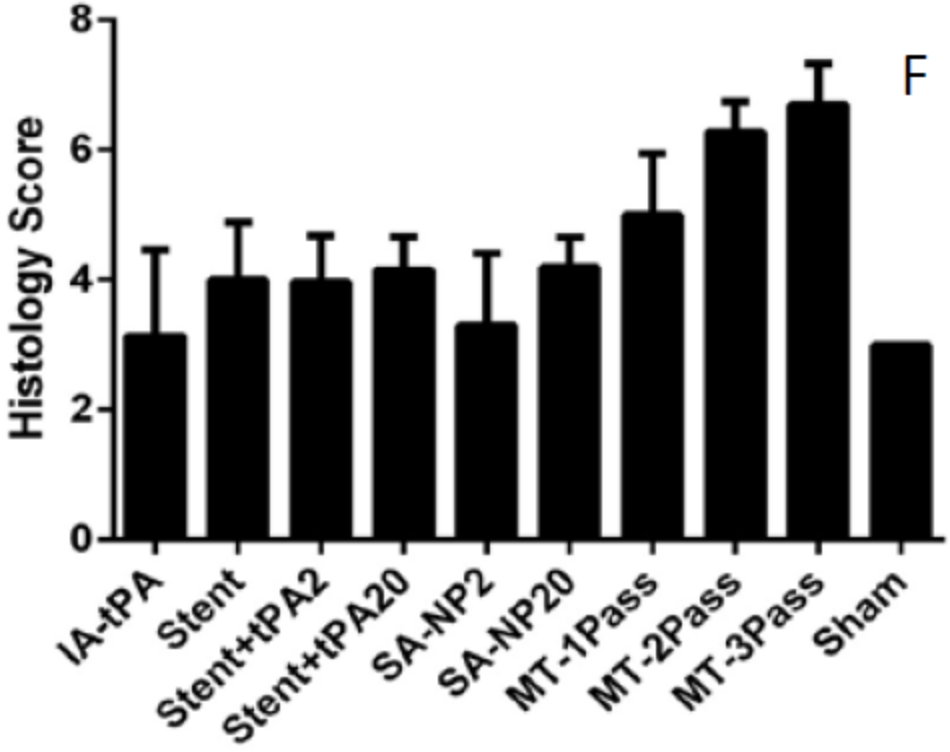
NEW ENGLAND CENTER FOR STROKE RESEARCH

- Shear-targeted delivery of r-tPA using the SA-NT resulted in the highest rate of complete recanalization when compared to controls (**p=0.0011**).
- SA-NT (20 mg) had a higher likelihood of obtaining complete recanalization (rmTICI:3) as compared to:
  - stent-bypass alone (OR: 65.019,95% CI:[1.77,>1000], **p=0.0231**),
  - intra-arterial r-tPA alone (OR: 65.019, 95% CI:[1.77,>1000], **p=0.0231**),
  - stent-bypass with soluble r-tPA (2 mg) (OR: 18.78, 95%CI: [1.28,275.05], **p=0.0322**).

UMASS

Vessel Wall Histology Results

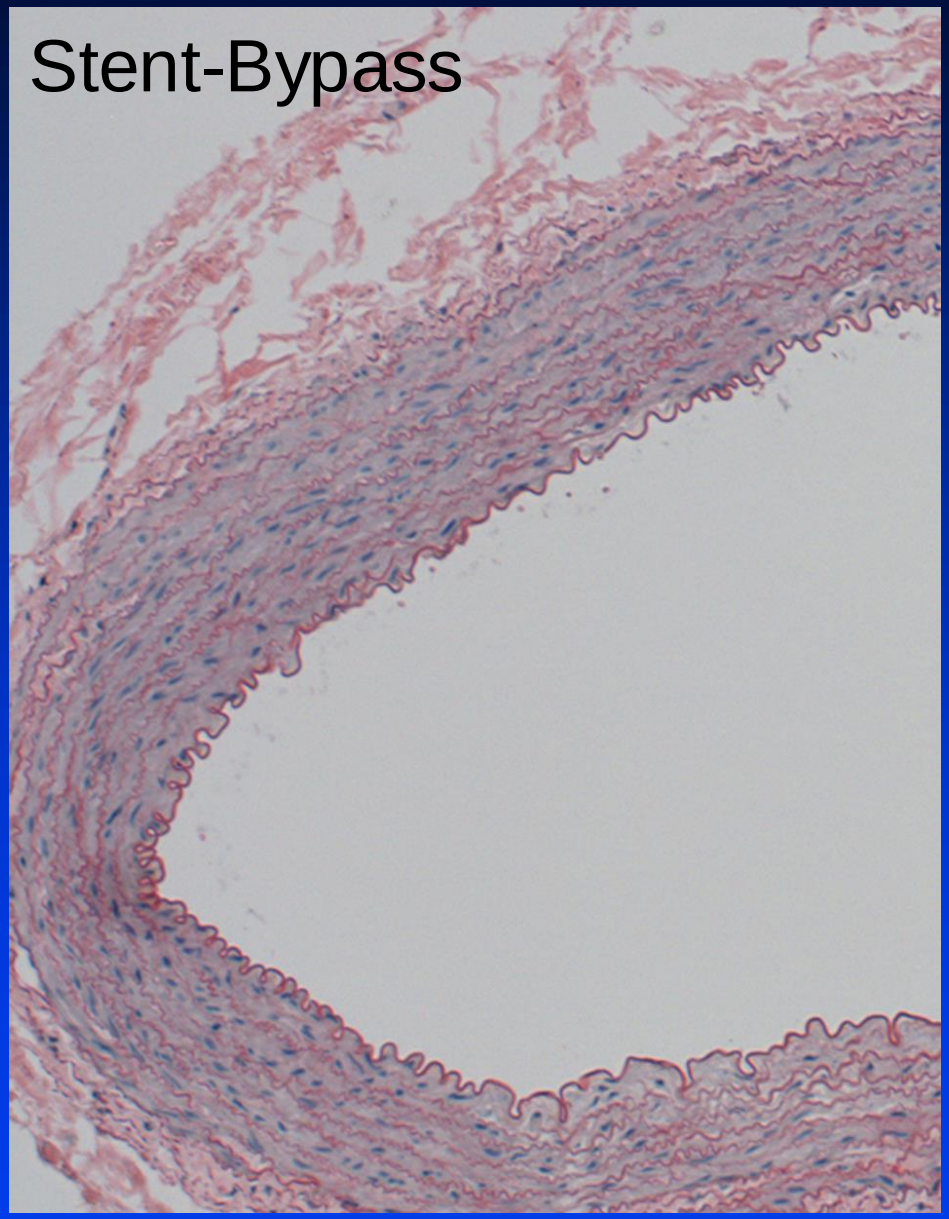
- Stent-bypass versus stent-retriever: Significantly less chance to have trauma score > 4
  - OR 27.36, 95% CI 9.286-80.64; p<0.0001)

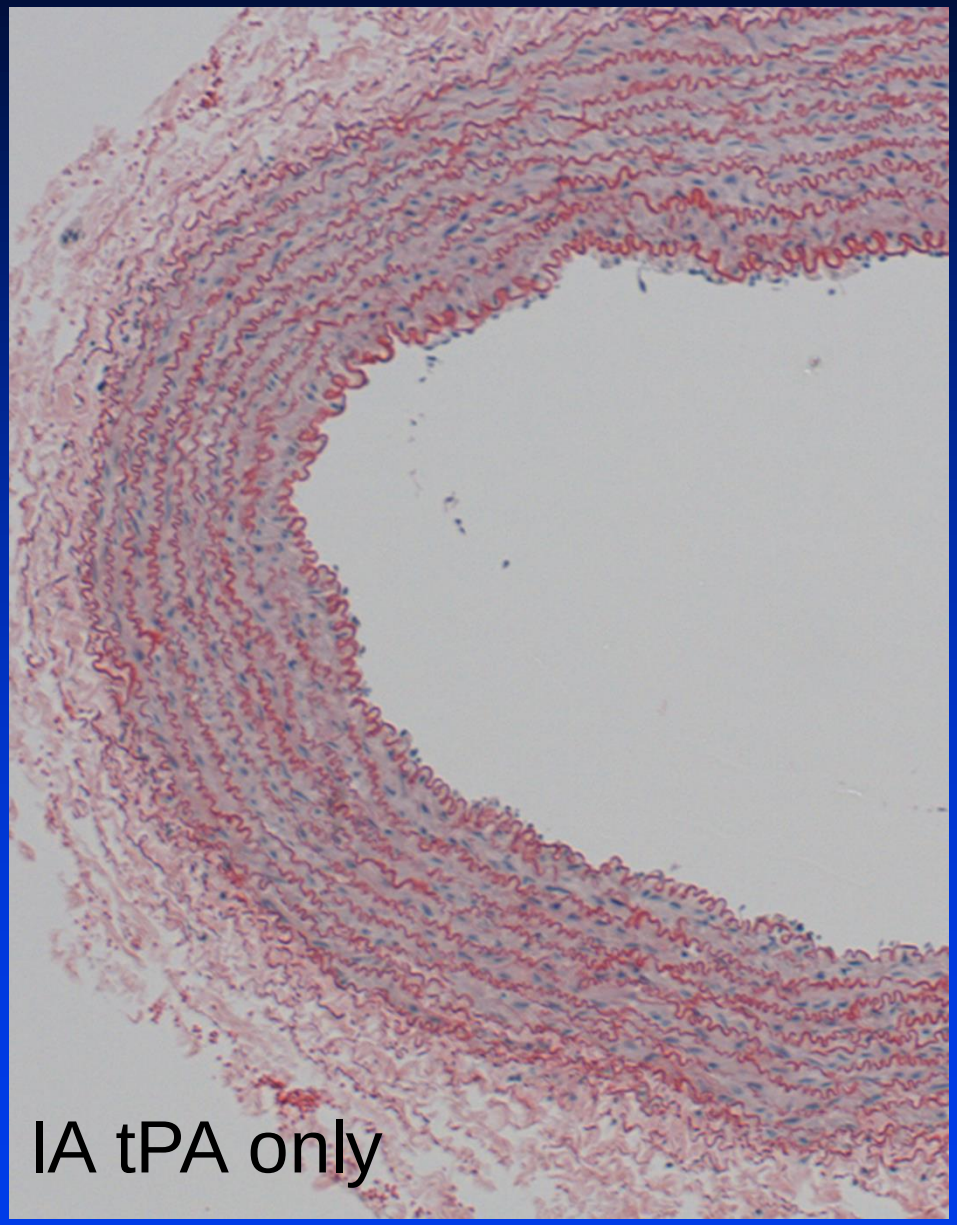


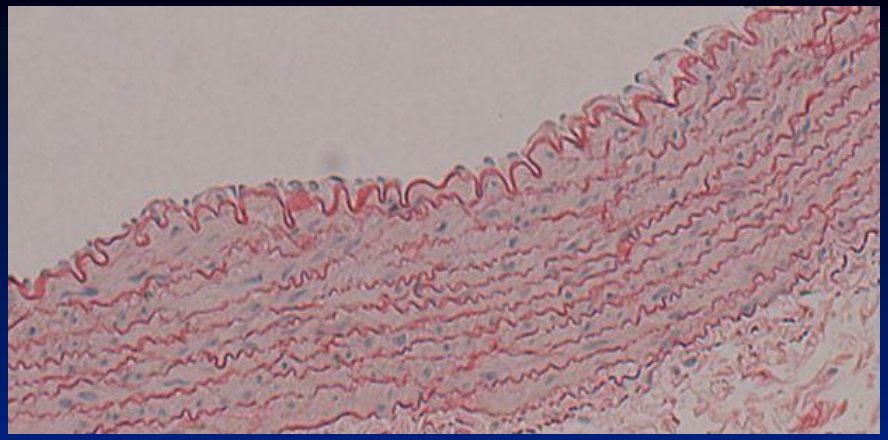
Histological Scoring Scale

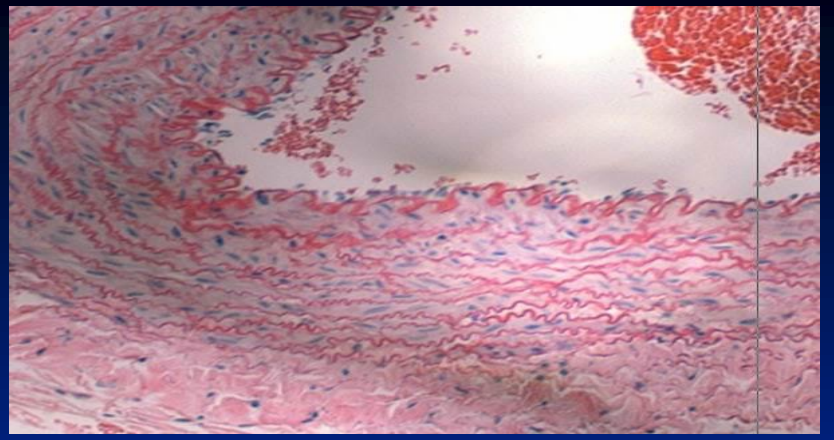
Score	0	1	2	3	4
Endothelial loss (% of the vessel circumference)	None	<25	25-50	51-75	>75
Disruption of the Internal Elastic Lamina (% of the vessel circumference)	None	<25	25-50	51-75	>75

Stent-Bypass Zone



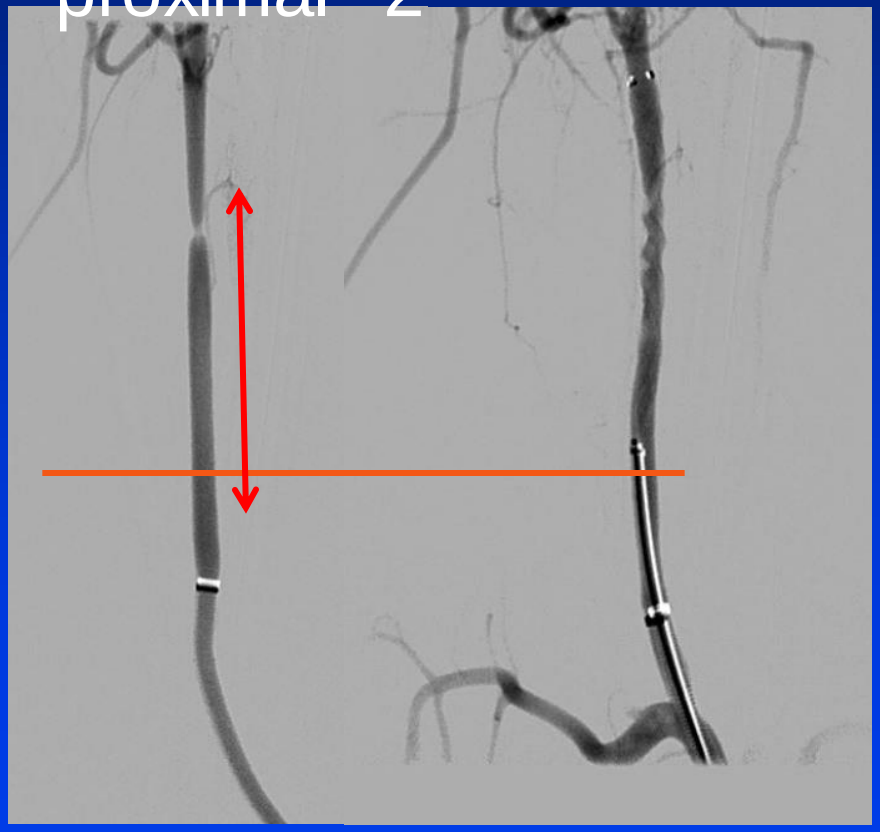






proximal -2

distal -3



Summary

- Complete recanalization is associated with better clinical outcomes
- SA-NT in the rabbit model of vascular occlusion with temporary stent bypass is associated with high rates of complete recanalization
- SA-NT + temporary stent bypass therapy has reduced vascular trauma

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NECStR

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