

# ACUTE STROKE THERAPY: CURRENT STATUS & FUTURE DIRECTIONS

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# Stroke Therapy Options

- Two primary therapeutic approaches to acute therapy exist
  - Reperfusion therapy
    - rt-PA approved in the US in 1996 for use <3 hours :11-13% increase in favorable outcome
    - ECASS III supports extending the window to 4.5h
    - Two devices, MERCI&PENUMBRA are cleared by the FDA for clot removal
  - Neuroprotection
    - No neuroprotective agent has demonstrated unequivocal efficacy in clinical trials

# Current Status of IV Thrombolysis

- I.V. rtPA 9mg/kg bw approved in US, Canada for 10 years in the 3 h time window
- Approval in Europe for 6 years
- Recently approved in almost all major Asian countries
- Substantially underused:
  - 4-5% in US, up to 10% in some European countries
  - Reasonable estimate of highest penetration: 15-20%
- Reason for reluctance
  - Doubt about efficacy still persists
  - Fear of hemorrhage

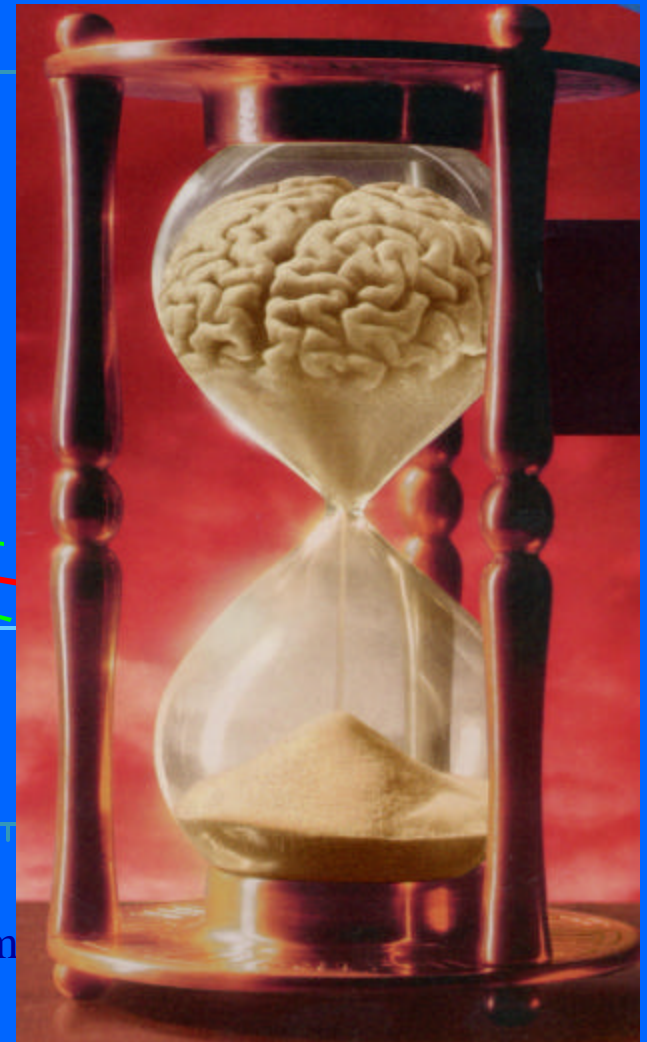
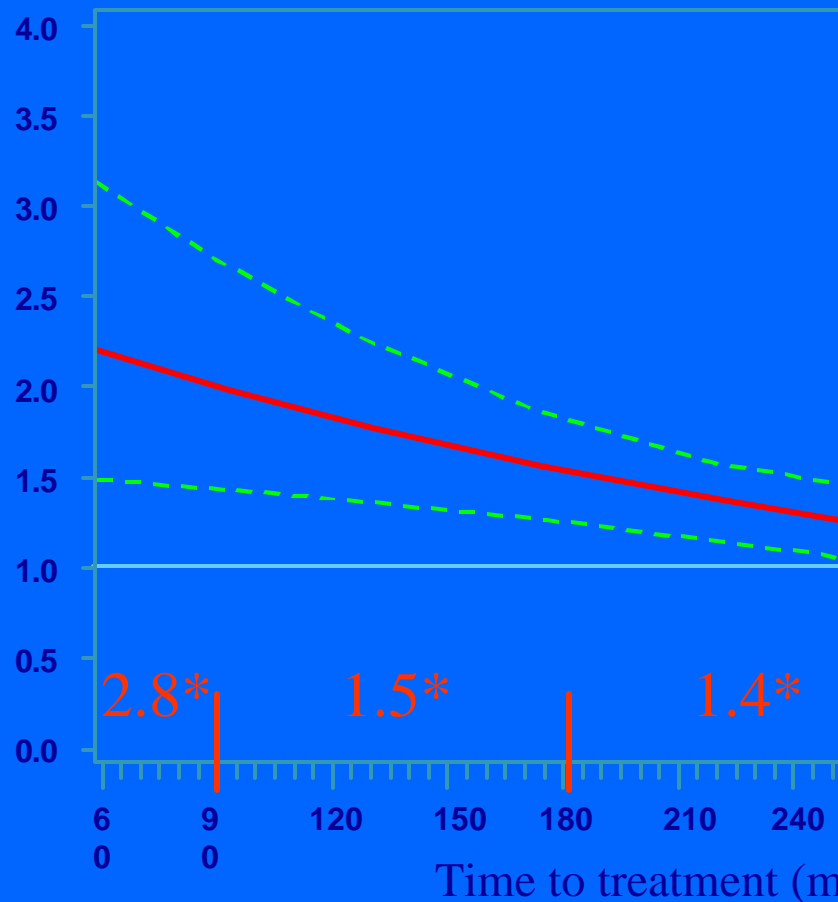
# NINDS, ECASS&ATLANTIS

Combined analysis of 2776 patients

mRS 0-1  
Day 90

Odds Ratio

95% CI



Lancet 2004

## Study Design

- Randomized, placebo-controlled, double-blind, clinical trial
- CT pre-randomization to exclude ICH or major ischaemic infarction
- 1:1 randomization by IVRS to i.v. alteplase (0.9 mg/kg bodyweight) or placebo
  - ❖ Alteplase administration: bolus (10% of total dose) in 1-2 min, remaining 90% infused i.v. over 60 min

## Efficacy Endpoints

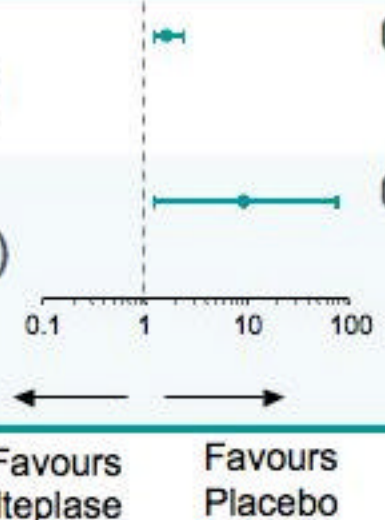
- Primary endpoint: Disability @ day 90
  - ❖ mRS dichotomized on a favourable (mRS 0–1) versus unfavourable outcome (mRS 2–6)
- Secondary endpoint
  - Global outcome analysis\* @ day 90, combining:
    - ❖ mRS score of 0–1
    - ❖ Barthel Index score  $\geq 95$
    - ❖ NIHSS score of 0–1 (including distal motor function)
    - ❖ Glasgow Outcome Scale score of 1

## Results: Key Demographic / Baseline Features

Variable	Treatment Group		p value
	Alteplase (N=418)	Placebo (N=403)	
Age Mean (yr)	64.9	65.6	0.36
Male sex (%)	63.2	57.3	0.10
<b>Baseline NIHSS</b>			
Mean (Median)	10.7 (9)	11.6 (10)	0.03
<b>Systolic blood pressure</b>			
Mean (mm Hg)	152.6	153.3	0.63
Diabetes (%)	14.8	16.6	0.47
Prior aspirin/AP use (%)	31.1	32.5	0.65
Hypertension (%)	62.4	62.8	0.88
Atrial flutter/fibrillation (%)	12.7	13.6	0.67
History of prior stroke (%)	7.7	14.1	0.03

# ICH and sICH

	Alteplase (N=418)	Placebo (N=403)	OR (95% CI)	<i>P</i>
Any ICH	113 (27.0%)	71 (17.6%)	1.73 (1.24–2.42)	0.001
sICH as per ECASS III	10 (2.4%)	1 (0.2%)	9.85 (1.26–77.32)	0.008

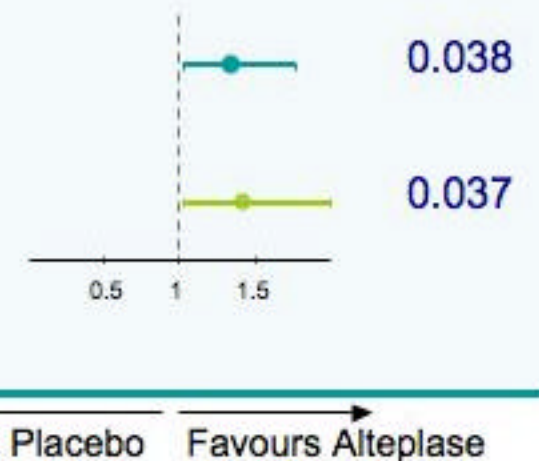


0.1    1    10    100  
 ←                      →  
 Favours              Favours  
 Alteplase            Placebo

## Primary endpoint (ITT)

Day 90: mRS 0,1 "Excellent recovery"

Analysis	Alteplase n/N (%)	Placebo n/N (%)	OR (95% CI)	<i>P</i>
Unadjusted	219/418 (52.4%)	182/403 (45.2%)	1.34 (1.02–1.76)	0.038
Adjusted*	–	–	1.42 (1.02–1.98)	0.037

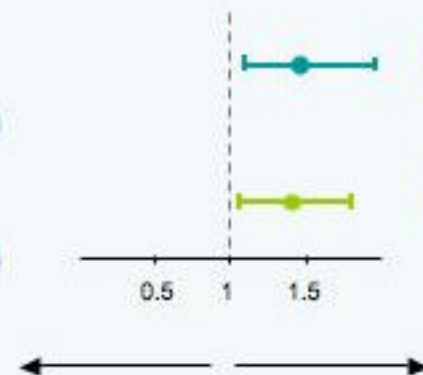


\*Adjusted for prognostic variables: treatment, baseline NIHSS, smoking history, stroke onset to treatment time, and prior hypertension

# PP Population: Primary & Secondary Endpoints

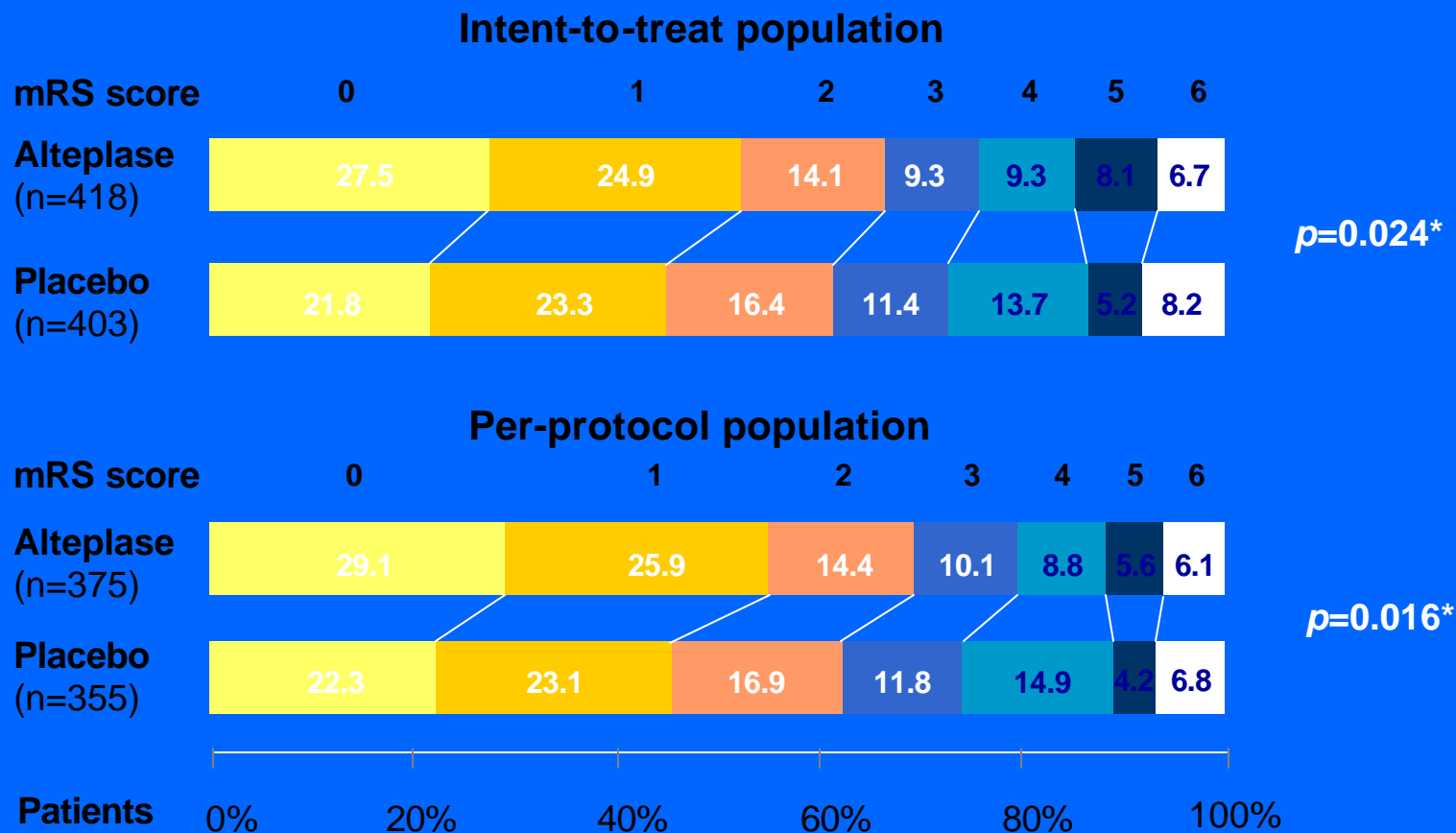
730 patients (out of 821 randomized)

Endpoint day 90	Alteplase (N=375)	Placebo (N=355)	OR (95% CI)	<i>P</i>
Primary (mRS 0,1)	206 (54.9%)	161 (45.4%)	1.47 (1.10–1.97)	0.010
Principal secondary (global statistic)	n/a	n/a	1.39 (1.07–1.80)	0.015



← Favours Placebo
Favours Alteplase →

# Distribution (Shift) Analysis# day 90



\*stratified on Cochran–Mantel–Haenszel test, adjusted for baseline NIHSS scores and time-to-treatment onset

# Method as per Lees et al. N Engl J Med 2006;354:588-600

# ECASS III SUBGROUP ANALYSES

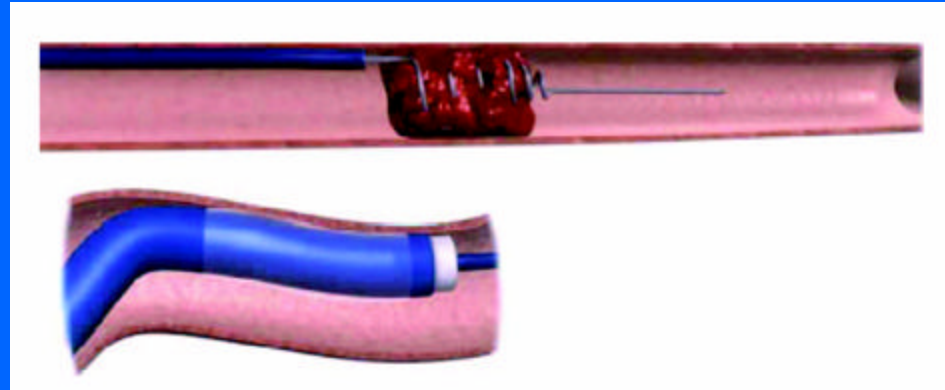
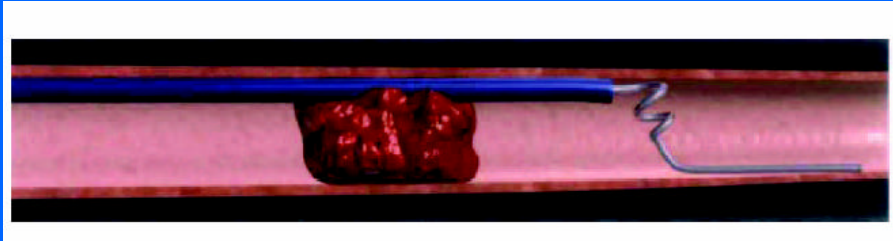
- mRS 0-1, <65 years old, 57% tPA and 45% placebo mRS 0-1, >65 49% and 45%
- Time to treat, 181- 210 min 58% v. 40%
  - 211-240 min 49% v. 47%
  - 241-270 min 56% v. 43%

History of DM 45% v. 49% (only 14% of total pts)

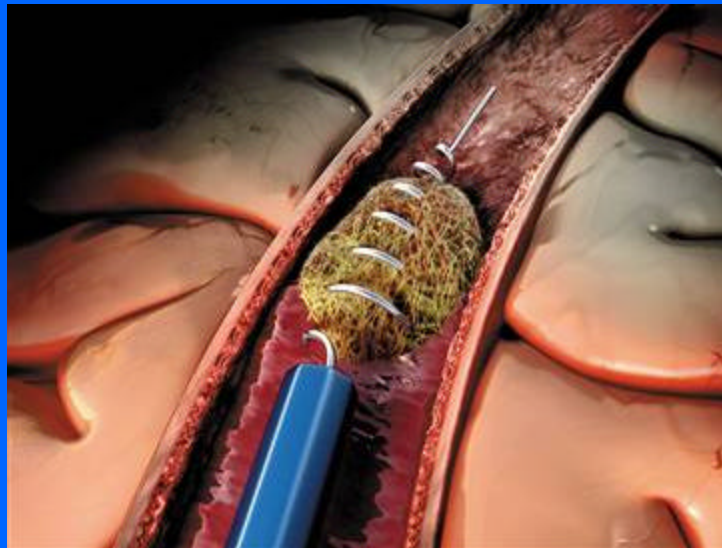
Safety Outcomes- Symptomatic ICH in 11% of tPA patients >65, only 2% of placebo (p<0.004). Also, in 11% of patients with NIH score of 10-19 and >20 versus 4% and 6% of placebo patients

# Problems to Consider with the ECASS III Results

- Exclusion Criteria-NIHSS>25, age over 80 and DM+prior stroke
- Imaging used was far from state of the art
- What do we do with patients who have no demonstrable vascular occlusion or imaging confirmed penumbra?
- How generalizable are the results?
- A study evaluating predictors of favorable and unfavorable outcome in the 3-4.5h window is needed



<http://stroke.ahajournals.org/cgi/reprint/35/12/2848>



[http://msnbcmedia.msn.com//msnbc/Components/Newsweek/Photos/mag/040308\\_Issue/040228\\_stroke\\_hu.hmedium.jpg](http://msnbcmedia.msn.com//msnbc/Components/Newsweek/Photos/mag/040308_Issue/040228_stroke_hu.hmedium.jpg)

# the MERCI Trial

**HYPOTHESIS: the retriever can access and revascularize occluded vessels in patients experiencing ischemic stroke while minimizing adverse events**

primary endpoint

**revascularization of treatable vessels  
(while limiting SAEs)**

**goal:** successful revascularization of  $\geq 30\%$   
of patients (statistical superiority to the  
18% benchmark derived from PROACT II  
control patients)

# MERCI vs. PROACT II

	MERCI (all patients) N=114 (129)	MERCI (MCA) N=72	PROACT II (r-proUK) N=121	PROACT II (placebo) N=59
median age	71		64	64
time to angio	6.1 hrs		4.5 hrs + 2	4.5 hrs + 2
median NIHSS	19	19	17	17
recanalization	53.5%	51%	66%	18%
mortality	38-40%	32%	25%	27%
symptomatic ICH	8%	6%	10%	2%
90 day mRS $\leq 2$	25%	30%	40%	25%

# MERCI vs. PROACT II

	MERCI recanalized (+)	MERCI recanalized (-)	PROACT II (r-proUK)	PROACT II (placebo)
mortality	25%	61%	25%	27%

recanalization rate = 53.5%

# MERCI SAEs

7% (8/114)

device related

2 strokes in previously uninvolved territory

2 vessel dissections/perforations

procedure related

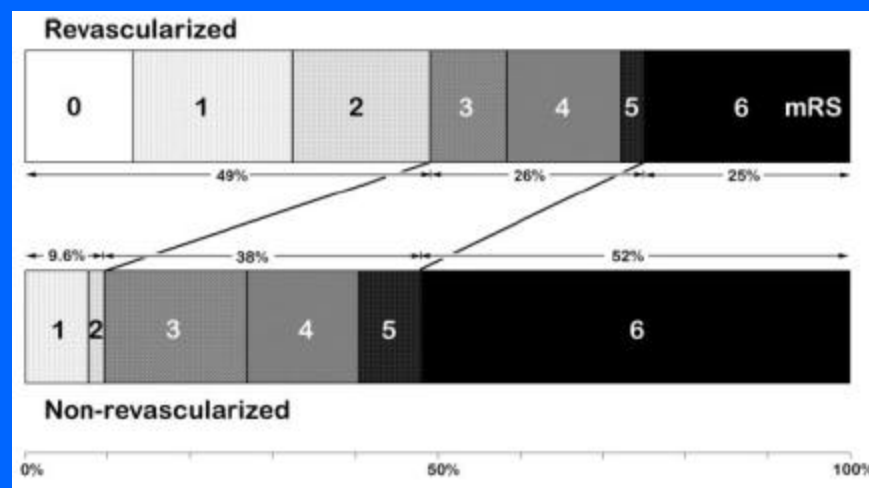
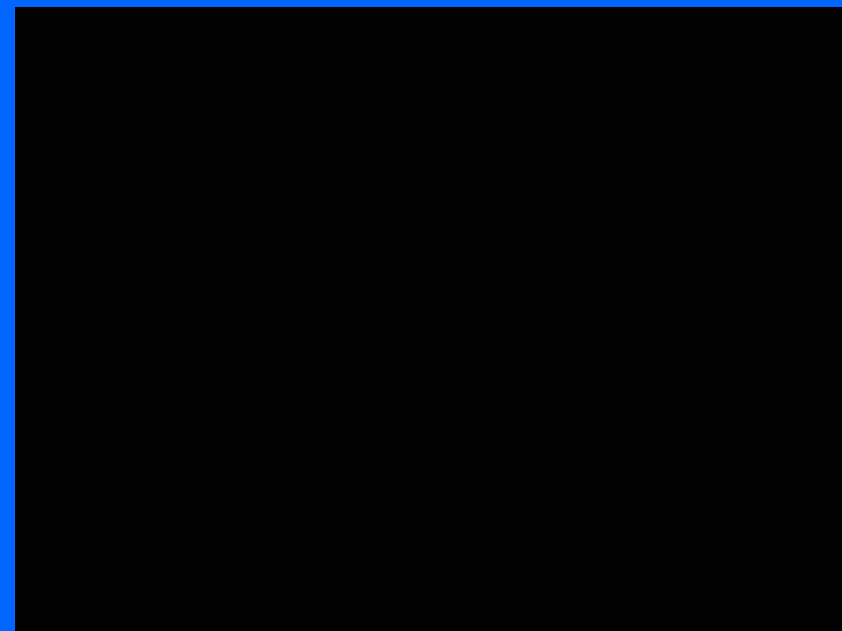
2 dissections in cervical ICA (due to balloon guide catheter placement)

2 perforations (due to guidewire placement)

**Also had 7.8% rate of sICH not included as an SAE**

# Medical Devices for Recanalization

- **MERCI Retriever**
  - Multi-MERCI trial: 17-center, non-controlled, technical efficacy study (n=177)
  - Recanalization in 55% of pts
  - Procedural complications in 9.8%
  - mRS = 2 at 90 days: 36%
    - 49% in pts with recanalization
    - 9.6% in pts without recanalization



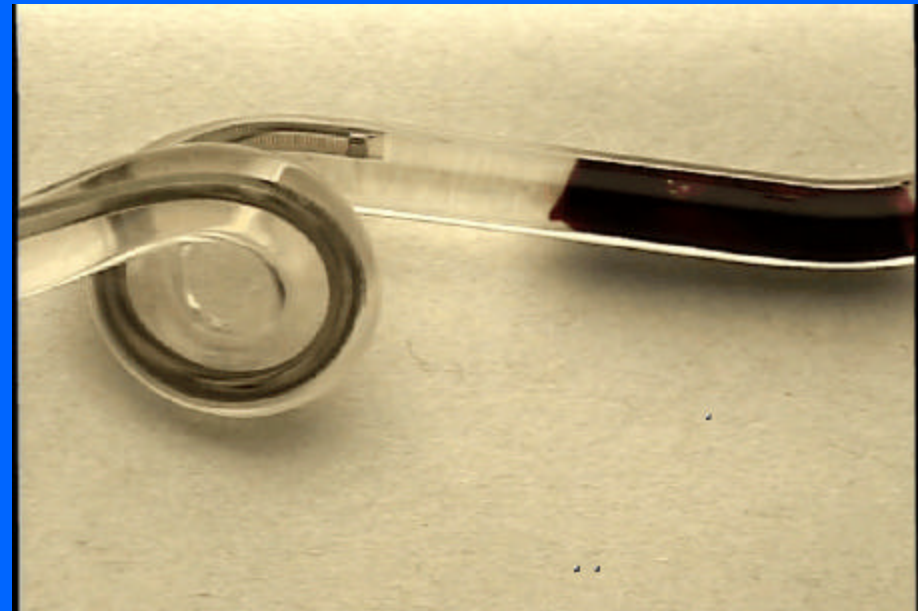
Smith WS, Sung G, Saver J, et al., for the MERCI Trial Investigators. *Stroke* 2008, 39: 1205

# Medical Devices for Recanalization

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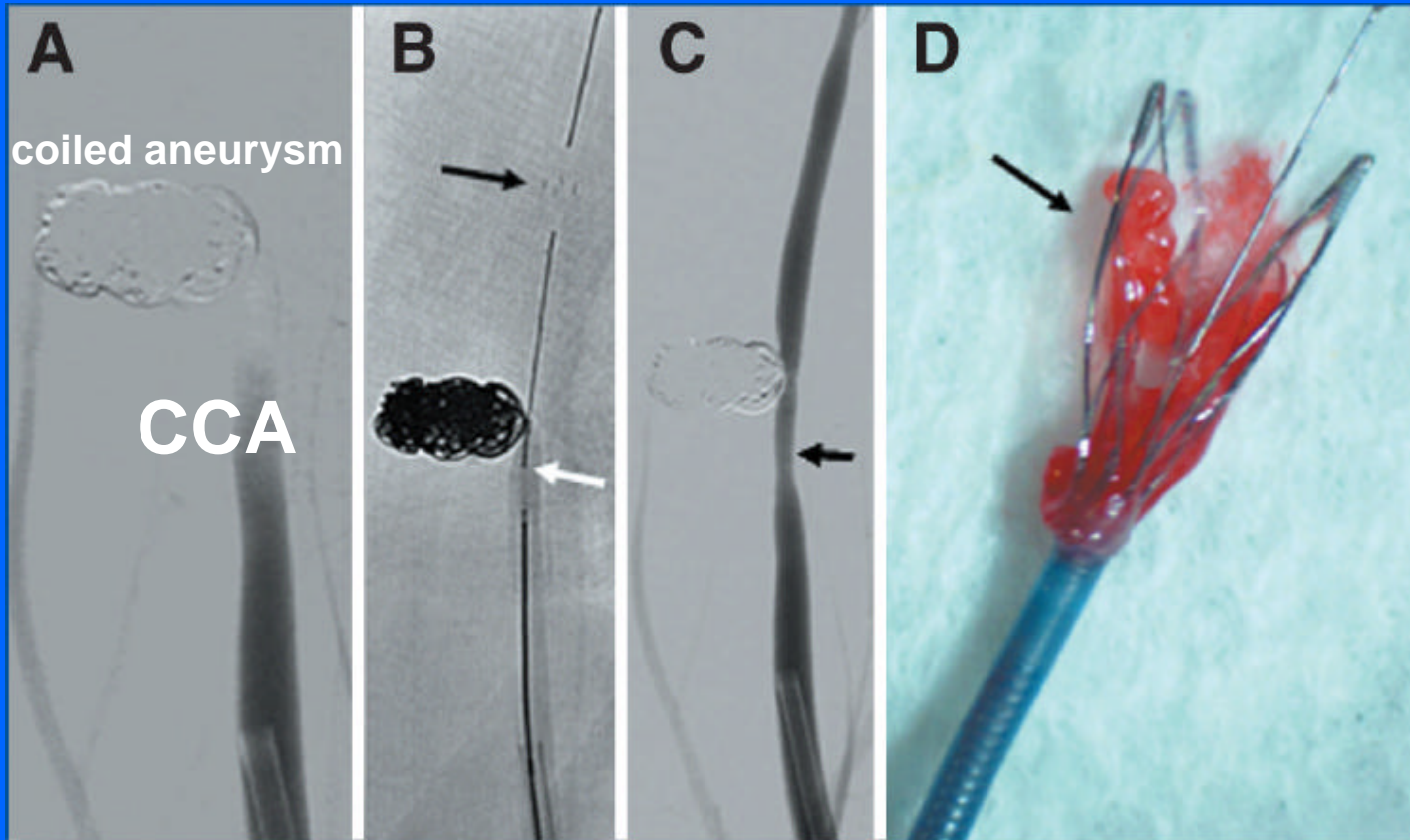
- **Penumbra System**

- Penumbra trial: 24-center, non-controlled, technical efficacy study (n=125)
- Recanalization in 82% of pts
- Procedural complications in 3.2%, 11.2% sICH
- mRS = 2 at 90 days: 25%
  - 29% in pts with recanalization
  - 9% in pts without recanalization



# Stent Based Thrombectomy

Enterprise  
stent



(Wakhloo A.K. and Gounis M.J., Neurosurgery 2008,62(5 Suppl 2):  
ONS390–ONS394. doi:10.1227/01.neu.0000326023.16596.88)

# Results of Stent Based Thrombectomy

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- Recanalization in 90% of patients

(thrombosis in cerebral ischemia grade 2b-3 classification was used instead of TIMI 2–3)

- No significant procedural events occurred
- mRS = 2 at 90 days: 45%



**A clot was retrieved by the Solitaire AB  
(ev3 Inc, Plymouth, MN)**

(Castaño C, Dorado L, Guerrero C, et al., Stroke 2010,41(8):1836)

# Future Beyond 3-4.5 Hour Trials

Patient selection is a key issue

- Penumbral imaging should be used
- Initial trials should exclude prior i.v. tpa use
- Exclude tpa because of ceiling effects on outcome measures and to avoid 4-arm studies