Intracranial Intervention and Acute Stroke Therapies

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Disclosure Statement of Financial Interest

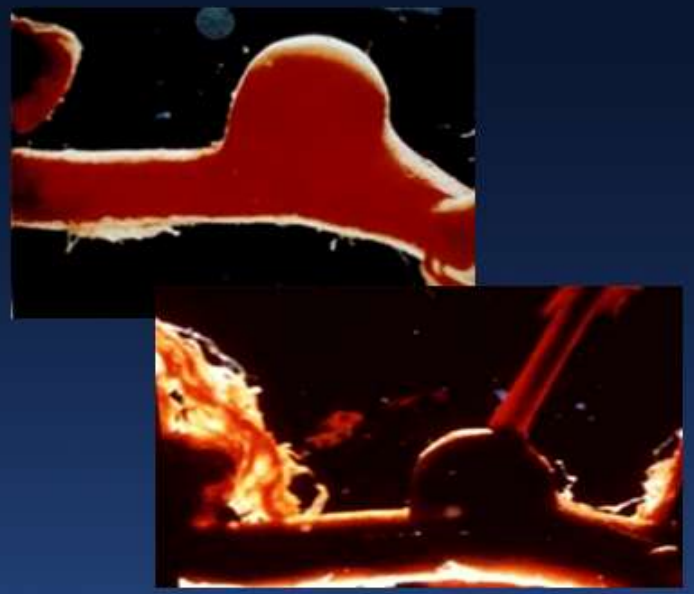
I, Philip Meyers, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Survey Topics

- Cerebral Aneurysms
- Brain Arteriovenous Malformation
- Acute Ischemic Stroke
- Intracranial Revascularization

Hemorrhagic Stroke Aneurysm

- 1/3 of strokes age < 65[1]
- 5-15% of stroke overall[2]
- 30-day mortality rate
  - 45% 1st rupture
  - 83% 2nd [4]
- 50% irreversible brain damage[3]
- Rupture risk is LOW: 0.05-1% for small aneurysms



[1]Johnston Neurology 52: 1799-1805, 1999

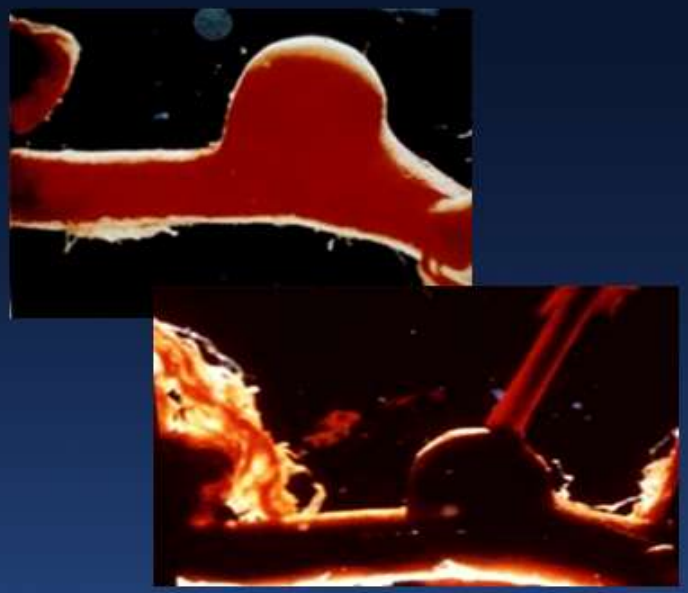
[2]Bederson Circulation 102: 2300-08, 2000

[3]Graves Vital Health Stat 13 113: 1-225, 1990

[4]ISUIA NEJM 339: 1725-33, 1998.

Hemorrhagic Stroke Aneurysm

- Surgical series
  - 0-6% mortality
  - 0-30% morbidity[2]
- NY discharge data
  - 1987-1993
  - 4.6-8.1% mortality[2]



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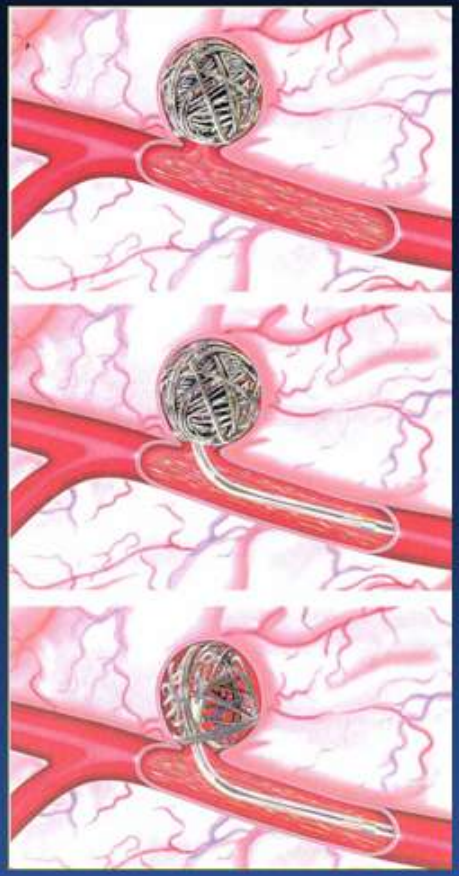
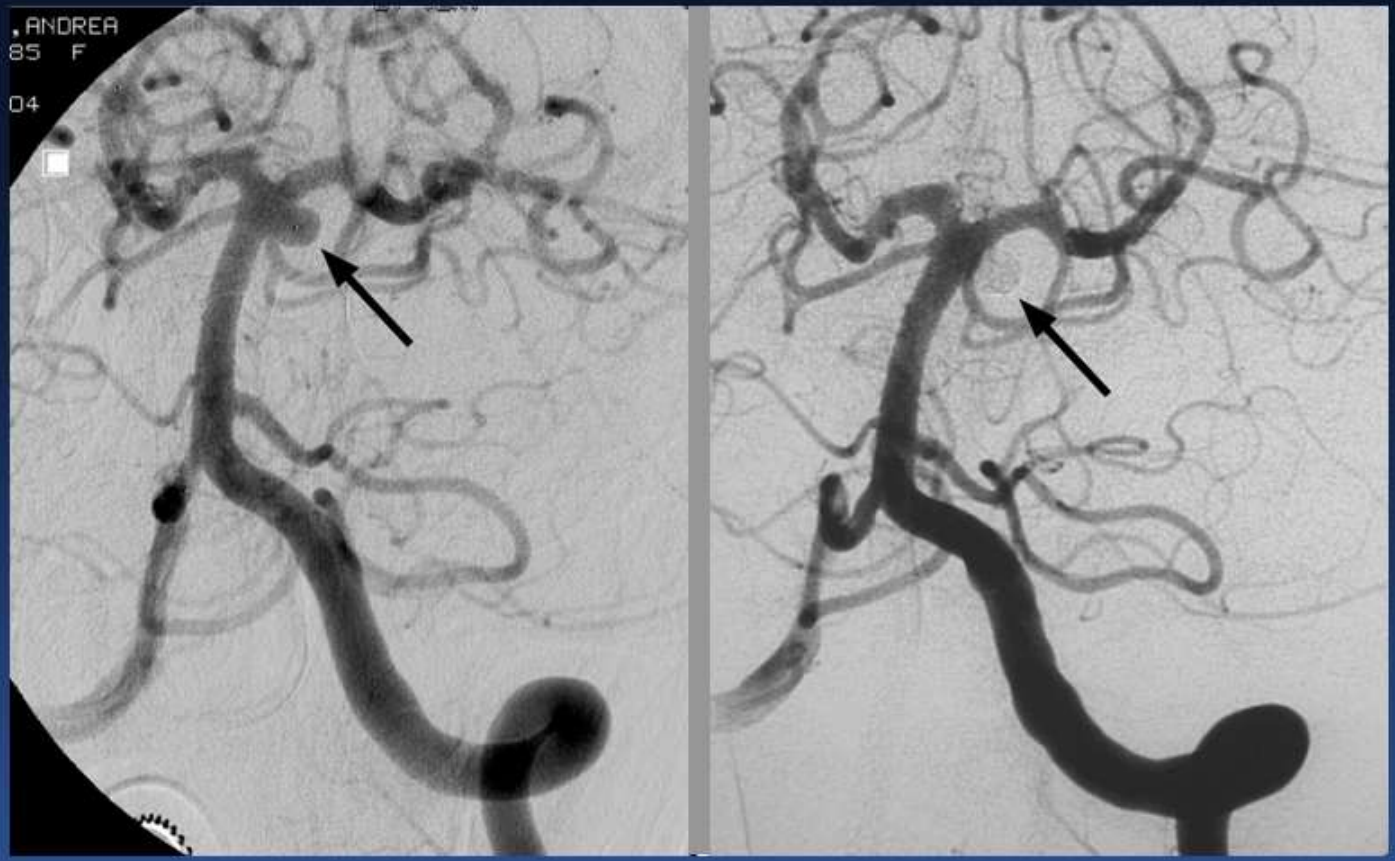
Endovascular Occlusion





International Subarachnoid Aneurysm Trial (ISAT)

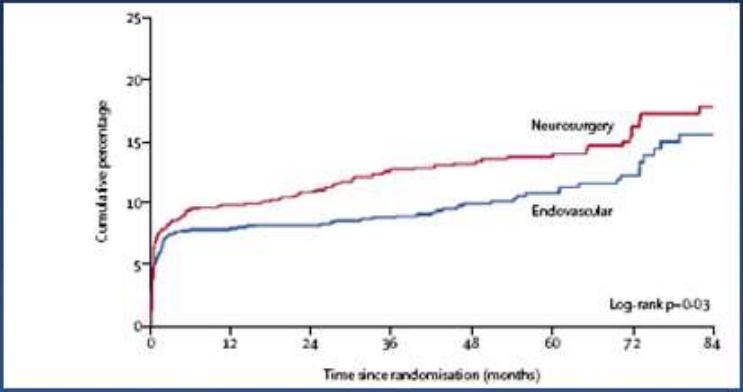
Risk Analysis Coil vs. Clip, N=2143

- **Relative reduction: 23.9%**
- **Absolute reduction: 7.4% p=0.00082**
- Point estimate: 0.76 (CI 0.64-.89)
- Equivalency: 76 pts/1000 treated
  Significant disparity at 1 yr

Lancet 360: 1267-1274, 2002

ISAT

	2002	2005	
• Relative risk reduction:	23.9%	26.8%	
• Absolute risk reduction:	7.4%	7.4%	
	Clip	**Coil**	
• Death or disability @ 1 yr:	32.1%	23.4%	
• Death or disability @ 1 yr:	30.9%	23.5%	up to 7 yrs



Lancet 266: 809-17, 2005

ISAT

- Follow up: 9 yrs, range 6-14 yrs
- 24 recurrent hemorrhage
  - Treated aneurysm: 13 patients (10 coil, 3 clip, p=0.06)
  - Pre-existing aneurysm: 4 patients
  - New aneurysm: 6 patients
- Risk of death remains lower in coil group, p=0.03

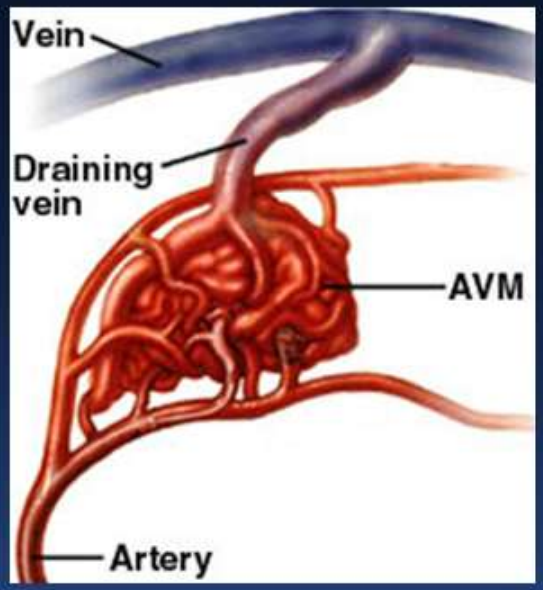
Size matters

All aneurysms, NY State, 1995-2000
By hospital volume

Outcome	Low	High	Improved
Adverse outcome	15%	6.6%	16%
In hospital death	3.3%	1.5%	11%

Stroke 34: 2200-7. 2003

Arteriovenous Malformation



Pial Arteriovenous Malformation

- Prevalence
  - 1.1-19/100000/yr
- Presentation: 33 yrs mean age
  64% by age 40
- Presentation
  - Hemorrhage: >50%
  - Seizures: 20-25%
  - Headache (15%)
  - focal deficit/tinnitus (<5%)

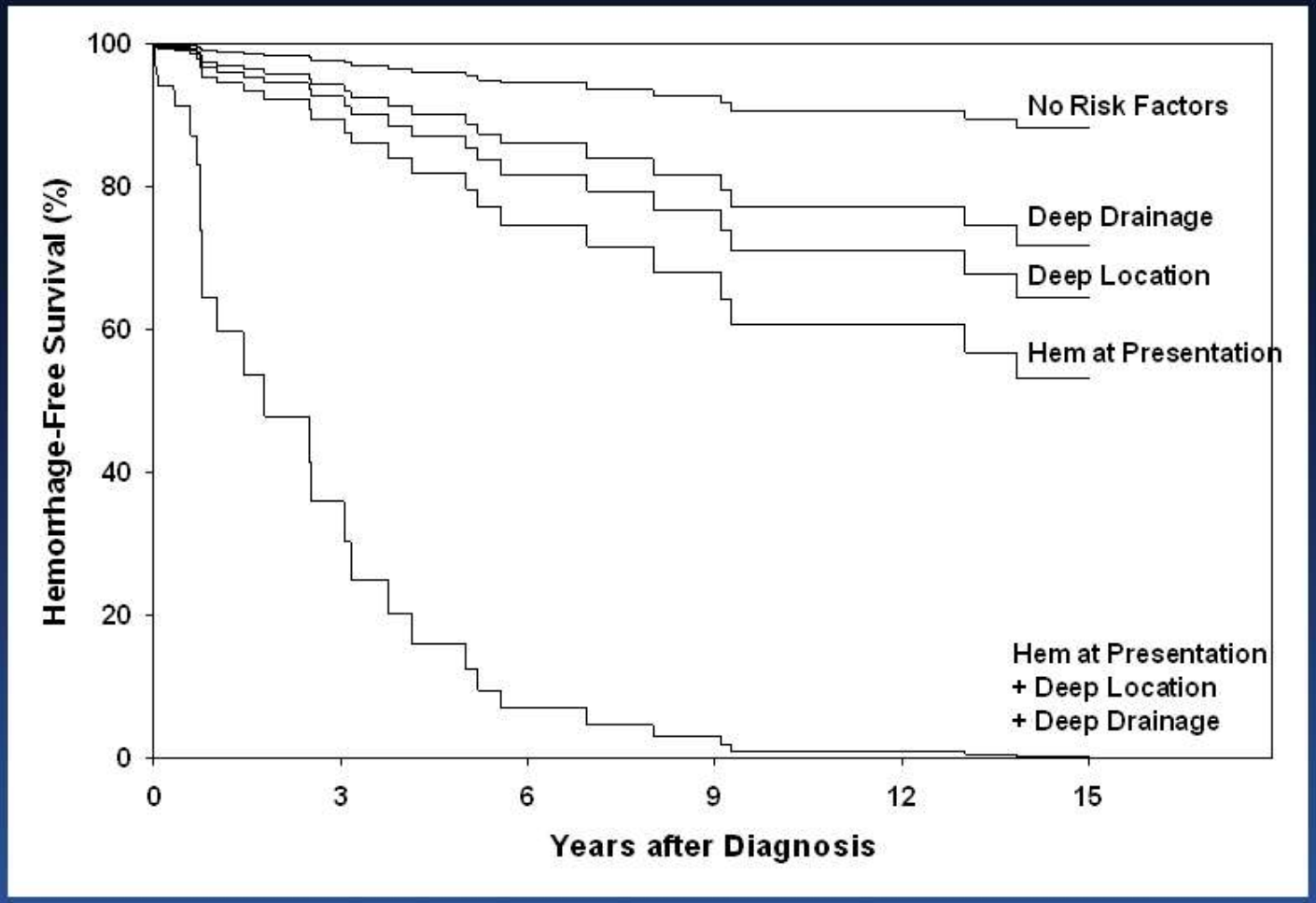
Brown Neurol 46: 949, 1996
Brown J Neurosurg 85: 29, 1996

AVM Hemorrhage

- M&M
  - 10% mortality
  - 30-50% morbidity
- Location
  - Parenchymal, 82%
  - Subarachnoid
  - Subdural
- Risk=105-(age in years)
- Treatment
  - Surgery
  - Embolization
  - Radiosurgery

Brown Neurosurg 46: 1024, 2000
Kondziolka Neurosurg 37: 851, 1995
Fults Neurosurg 15: 658, 1884
Forster J Neurosurg 37: 562, 1972

Effect of Clinical, and Morphological Variables on Follow-up AVM Hemorrhage (n=622)

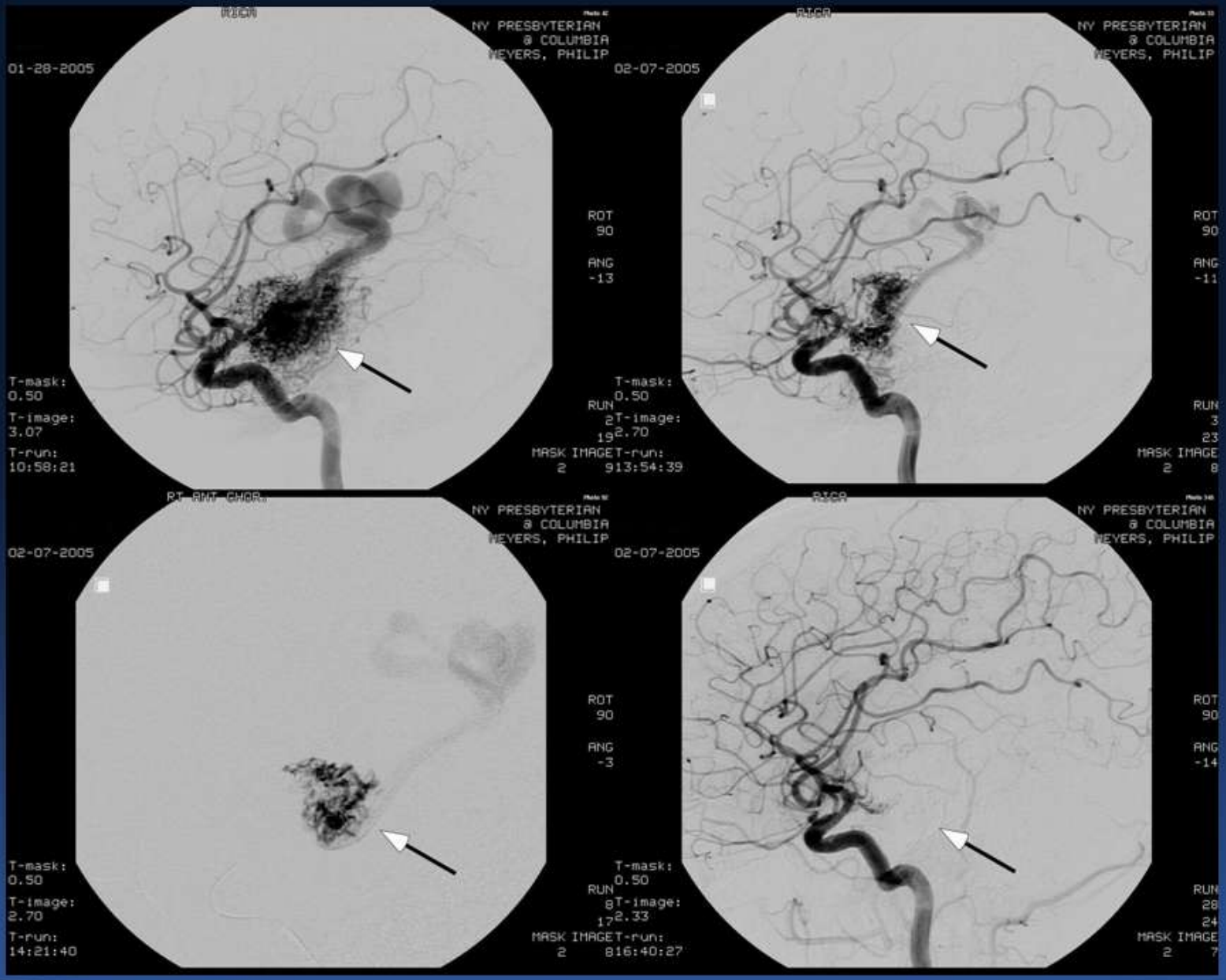


Lancet 1997; 350:1065 - 1068

Effect of Demographic, Clinical, and Morphological Variables on Follow-up AVM Hemorrhage (n=622)

Multivariate Cox proportional hazard model

	HR	Attributable Risk		P
Age (years)	*1.05*			*<0.0001*
Female gender	*0.64*			*0.21*
Hemorrhagic presentation	*5.38*	*47.4%*	*70.7%*	*<0.0001*
Deep brain location	*3.25*	*9.4%*		*0.01*
AVM size (mm)	*0.99*			*0.34*
Deep drainage only	*2.39*	*13.9%*		*0.04*
Associated aneurysms	*1.62*			*0.17*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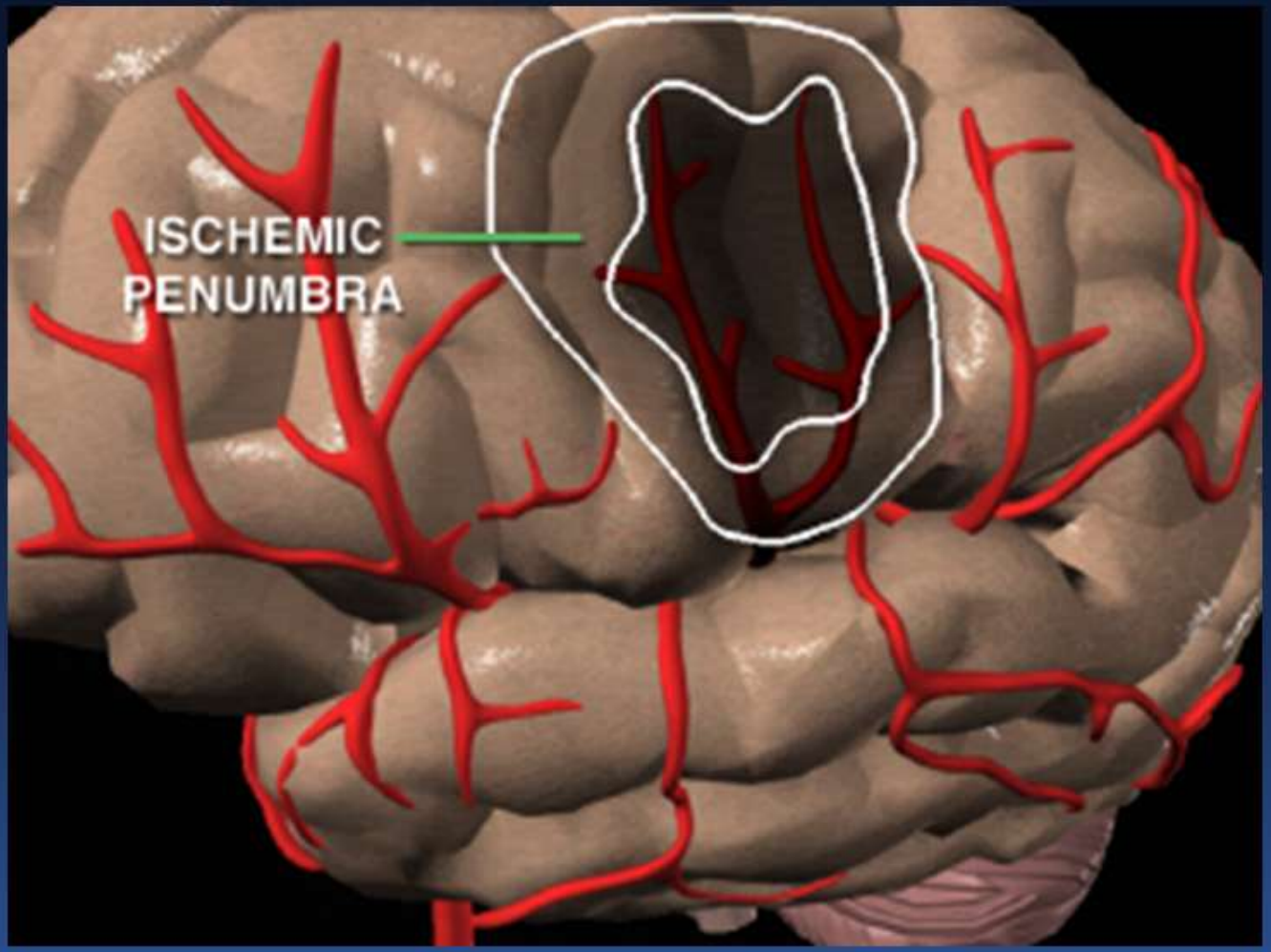
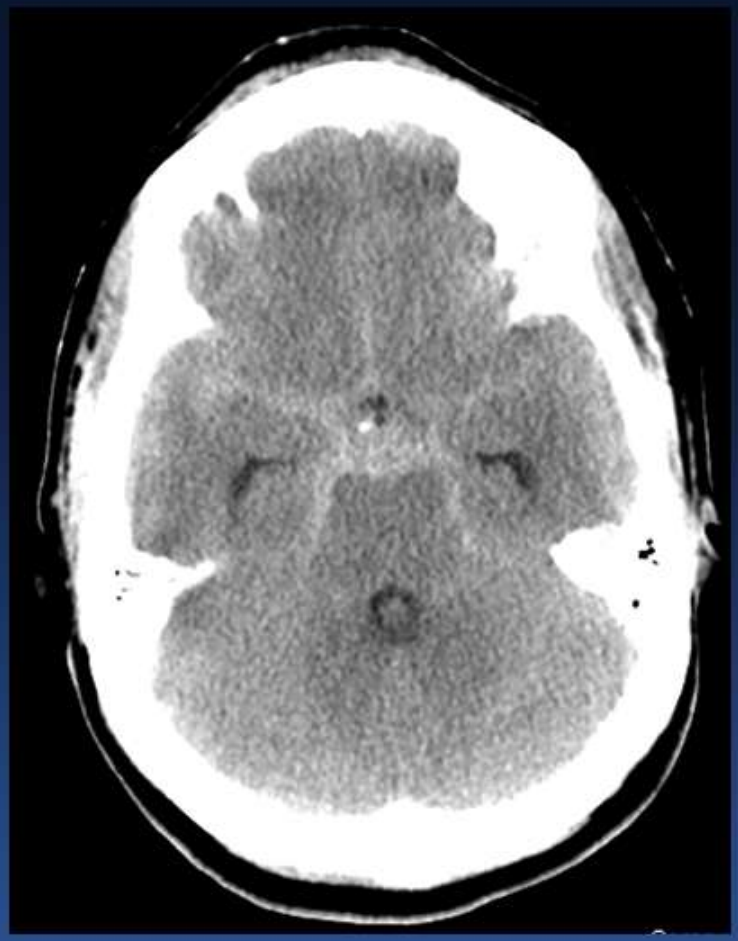
Acute Ischemic Stroke

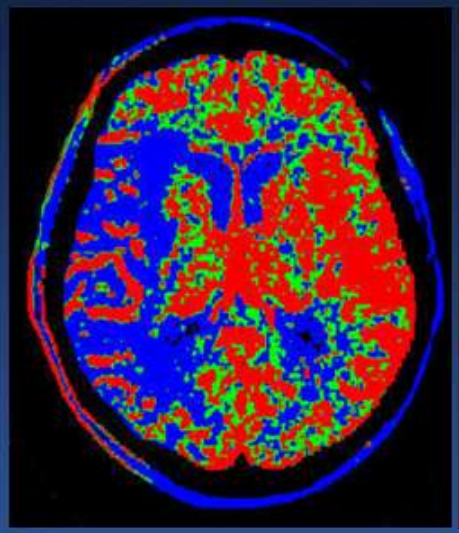


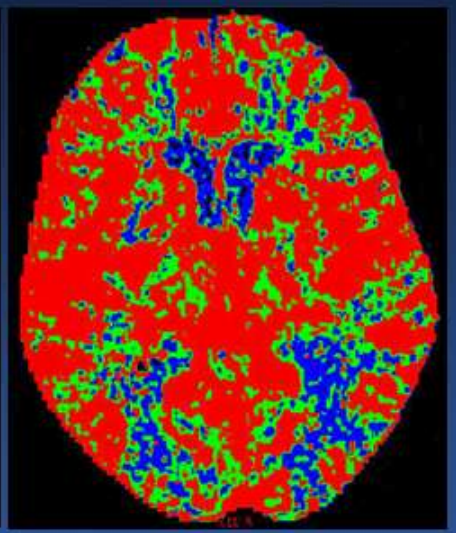
Pre-treatment Imaging Commonly still CT based



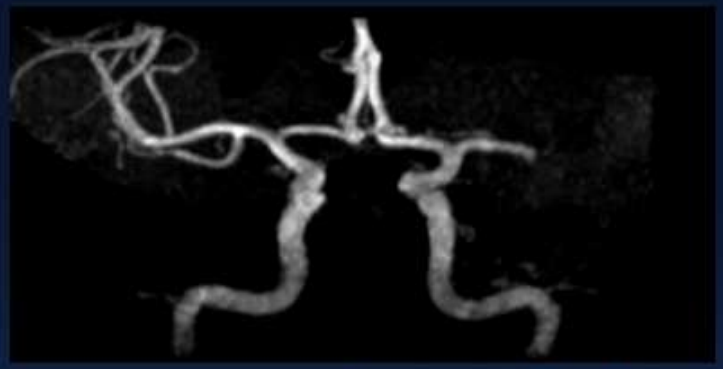
Viability Imaging – Role Undefined

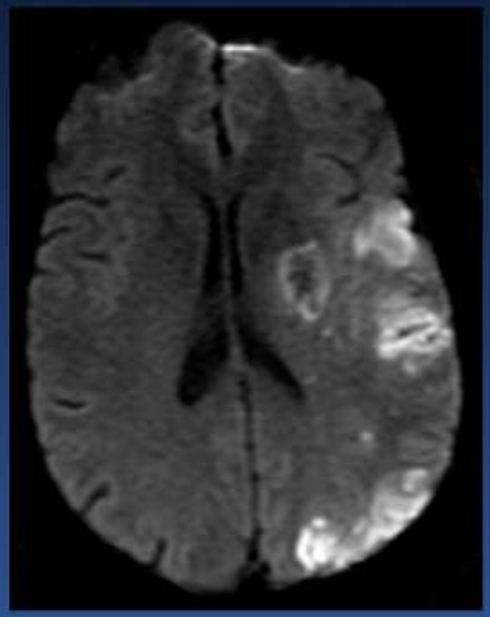
Computed Tomorgraphy

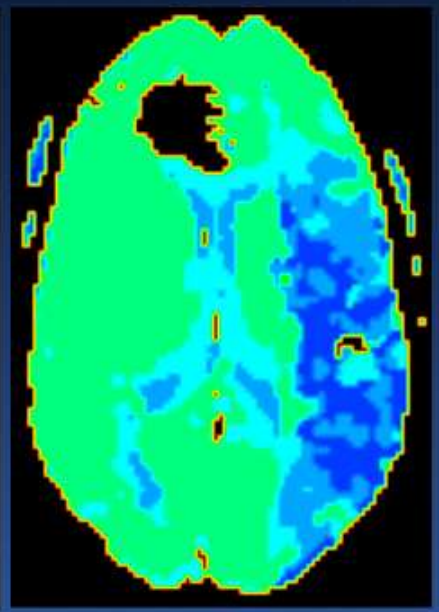




Magnetic Resonance







Intravenous Thrombolysis (t-PA)

- Treatment window 0-3 hours post ictus
- NINDS showed 30% increase of favorable outcome at 90 days versus placebo
- Limited efficacy:
  - IV t-PA opens 30 – 50% of major occluded intracranial vessels within 1 – 2 hours*
- The ONLY Class I Evidence for acute stroke treatment - FDA Approved

*Mori, 1992, Wolpert, 1993; von Kummer, 1993; Yamiguchi,1993.

Stroke rtPA Study. NEJM. 333:1581-7, 1995

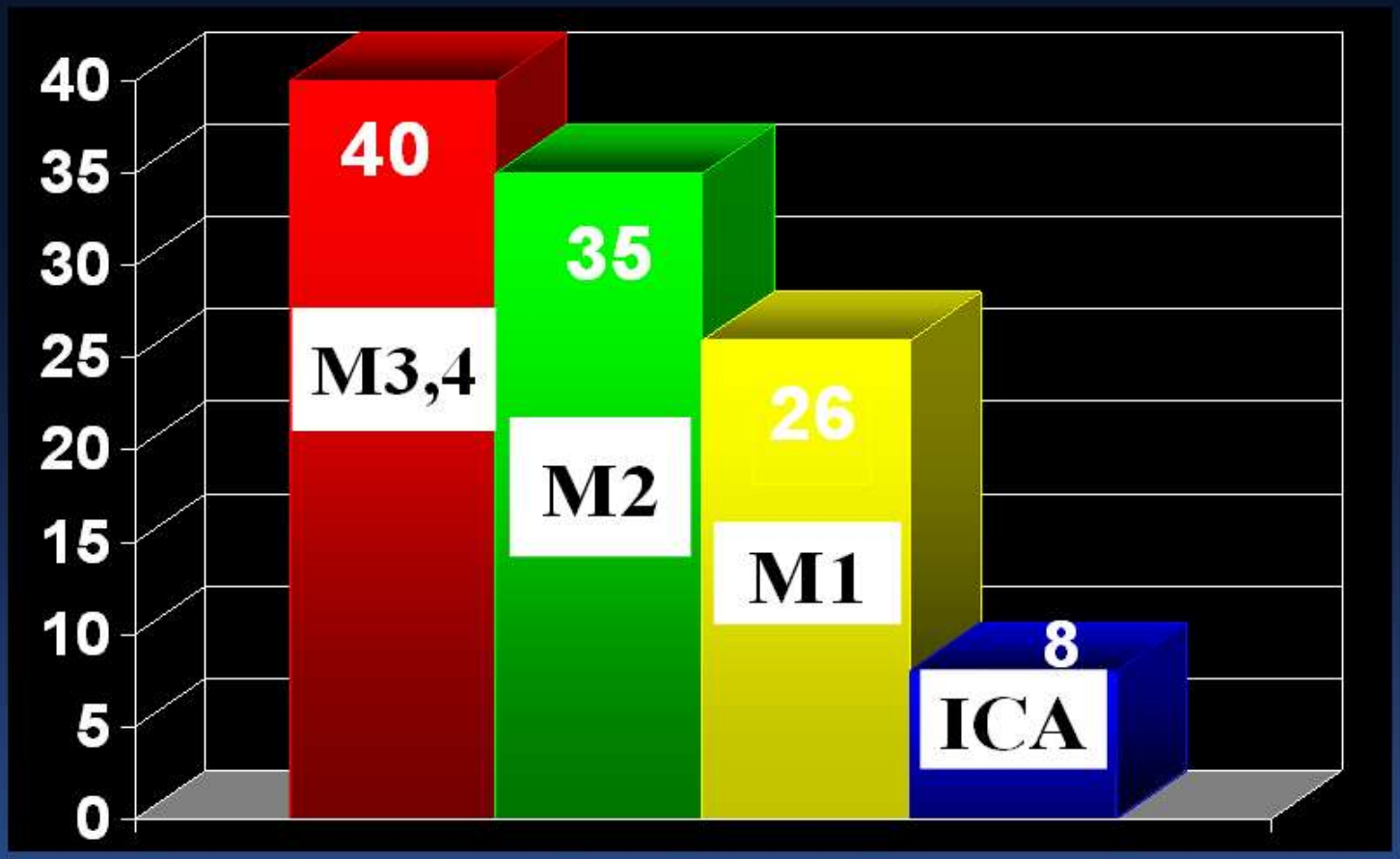
ECASS-III

European Cooperative Acute Stroke Study

- 821 patients
  - 418 rt-PA
  - 403 placebo
- Median time to treat: 3 hr 59 min
- Favorable outcome: 52% vs. 42%, P<.05
- Hemorrhage Rate: 27% vs. 18%, P=.001
- Mortality: 7.7 vs. 8.4%, P=0.68

Hacke W. NEJM 359:1317-29, 2008

Recanalization Rates: IV tPA ≤ 8 hrs



del Zoppo Ann Neurol 32: 78, 1992

ProACT II

Prolyse in Acute Cerebral Thromboembolism

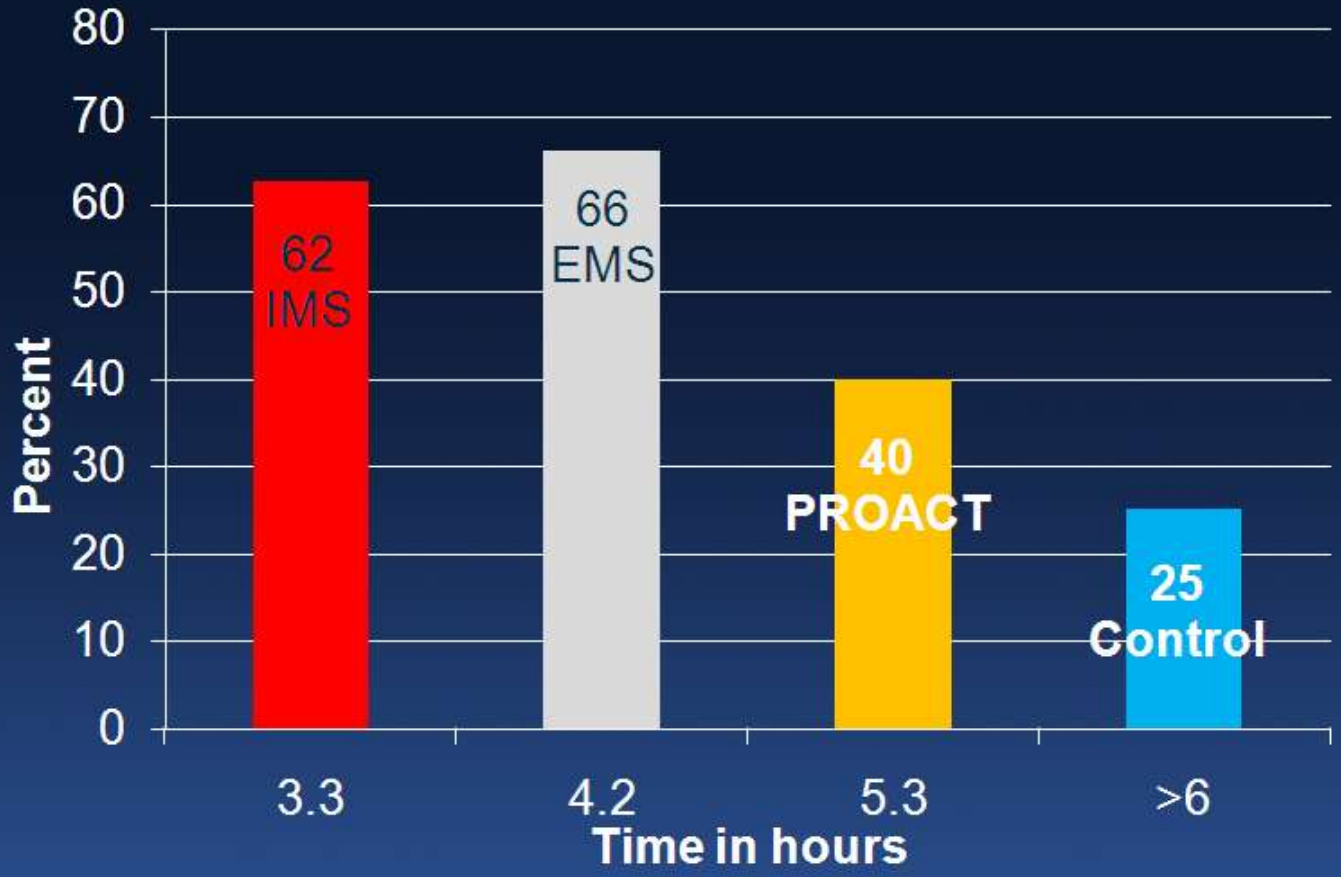
	rPro-UK	Control	*P*
90 Day Good/Excellent Outcome:	40%	25%	.04
Recanalization:	66%	18%	<.001
Mortality (90 day):	25%	27%	
Symptomatic Cerebral Hemorrhage <24 hrs:	10%	2%	.06

Furlan. JAMA 282: 2003-2011, 1999

PROACT II Summary

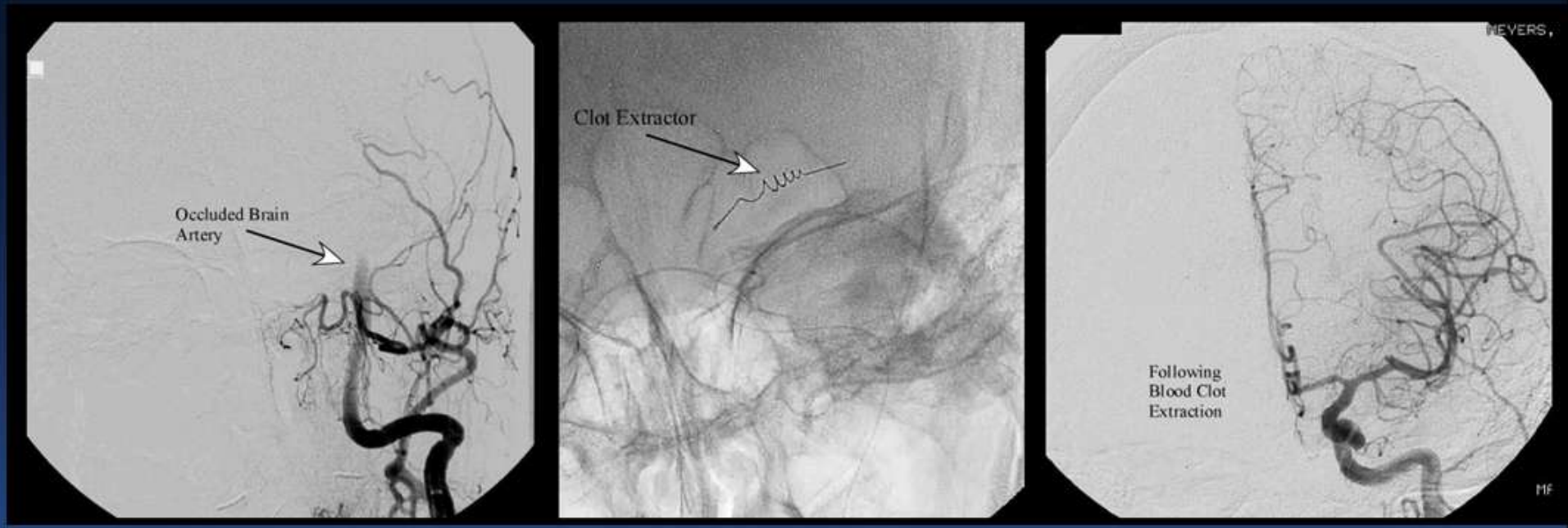
- Provides proof of principle in a worst-case scenario:
  - Late *time* to treatment (5.3 hours)
  - Limited manipulation, no mechanical maceration of clot
  - Patient selection, NIHSS=17
  - NOT Class I Evidence – NOT FDA approved.

Bridging Protocols: Outcome Percent mRS ≤ 2 vs. Time



Lewandowski *Stroke* 30: 2598, 1999
IMS Investigators. *Stroke*35: 904, 2004
Kathri P *Stroke* 39: 560, 2008

Concentric Merci Trial
Mechanical Thrombectomy



Concentric Merci Trial
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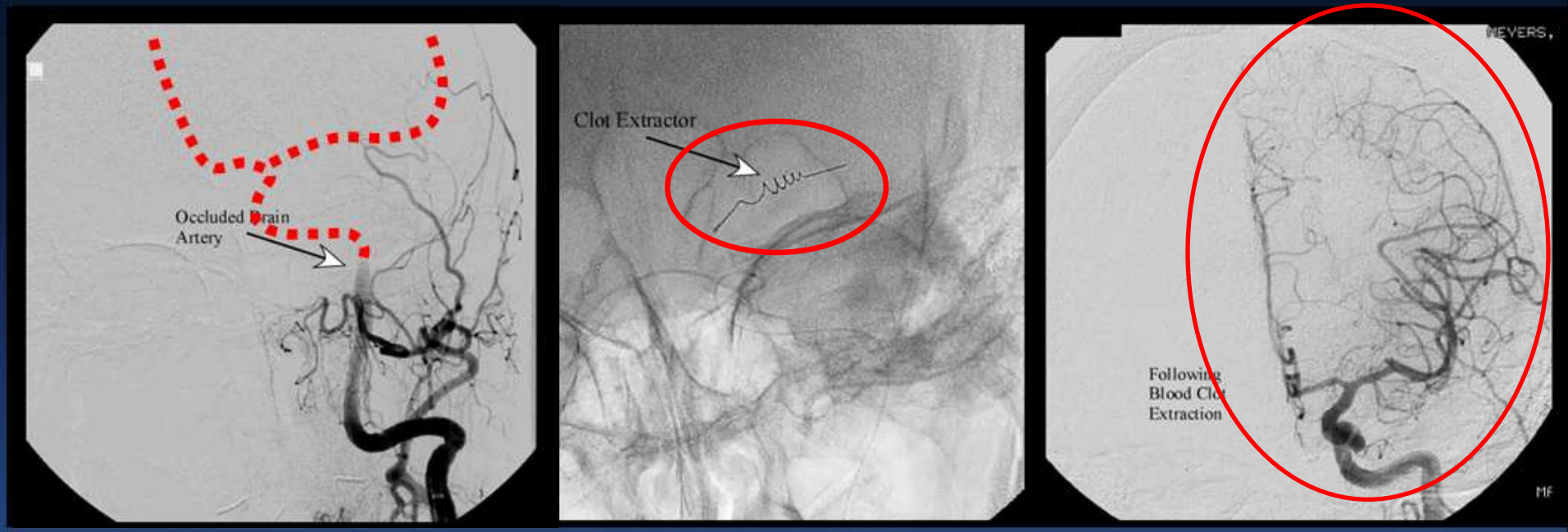

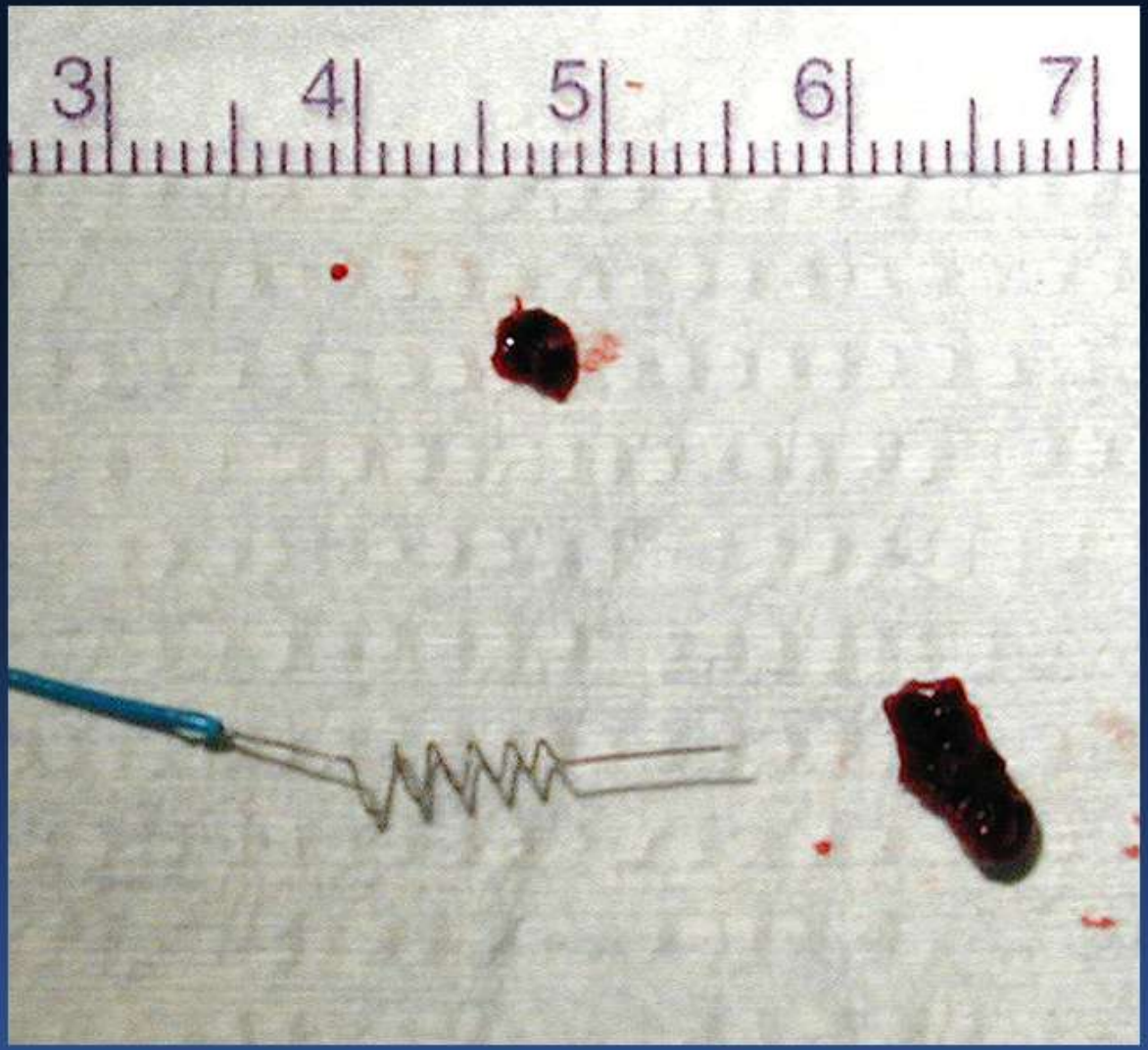
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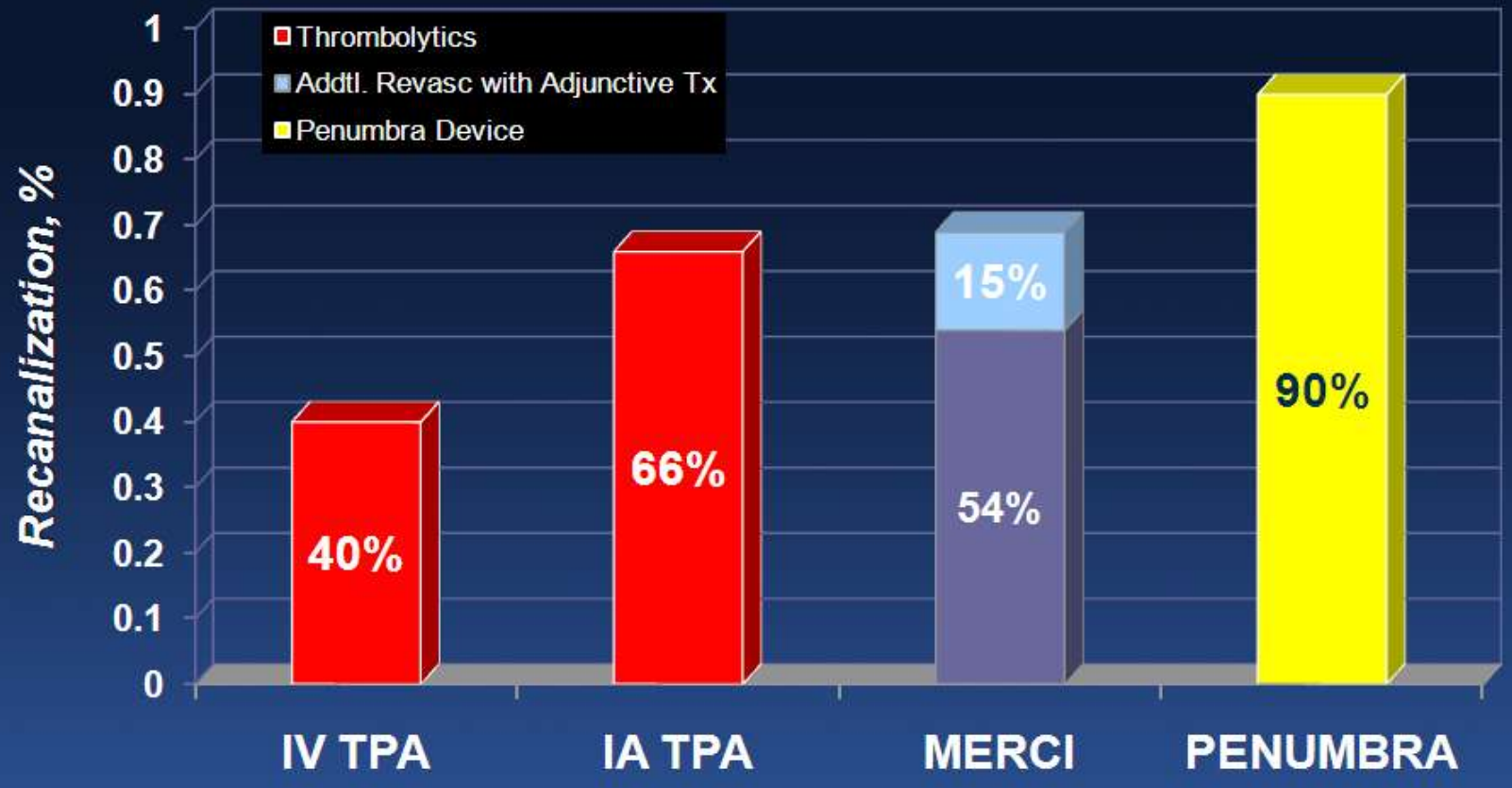
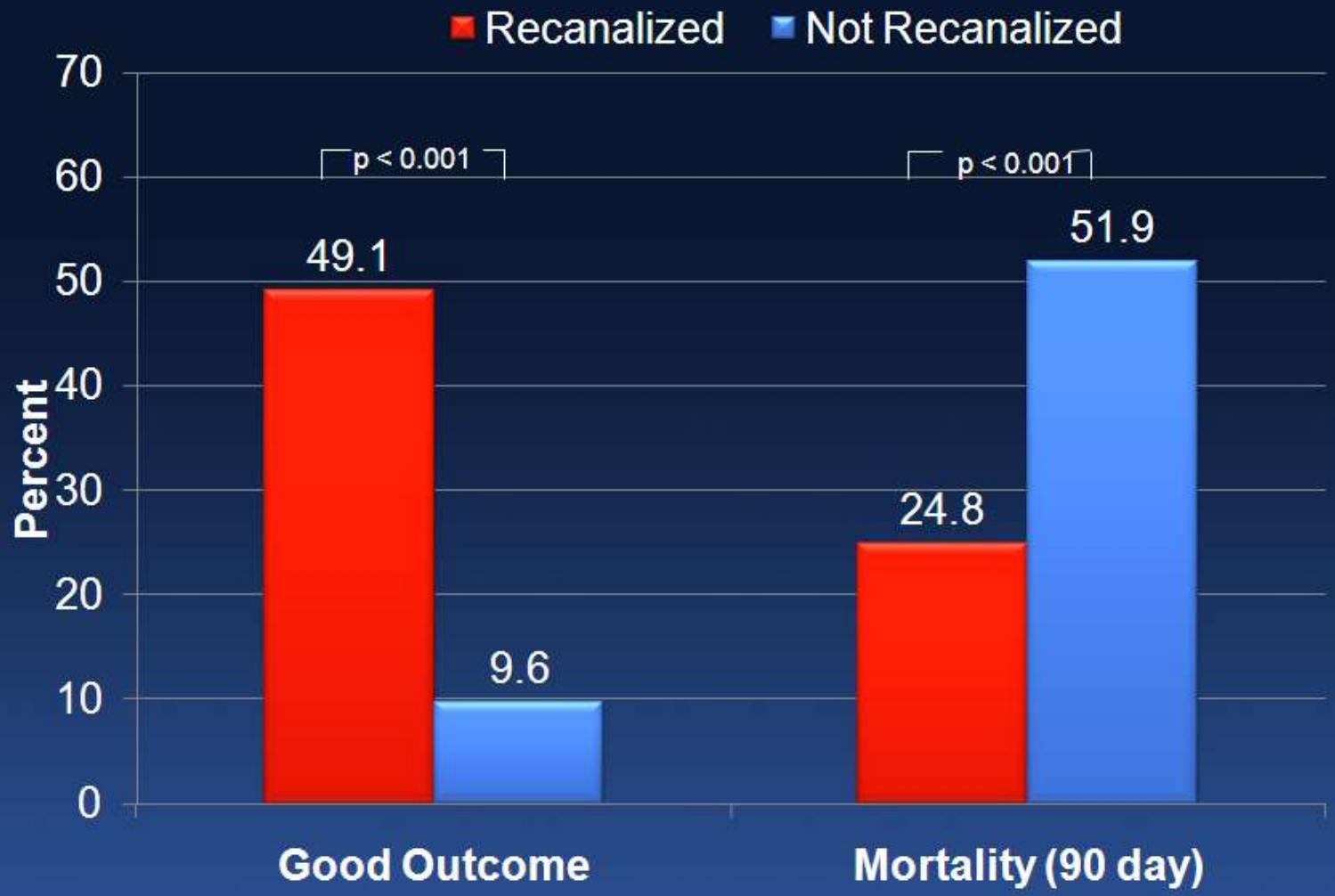
Recanalization
Comparison of Stroke Techniques

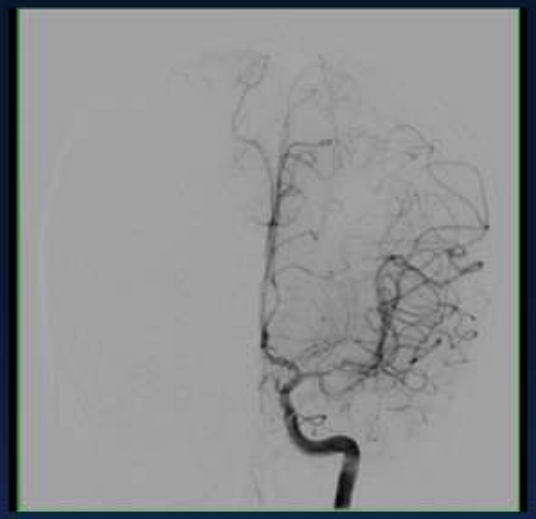
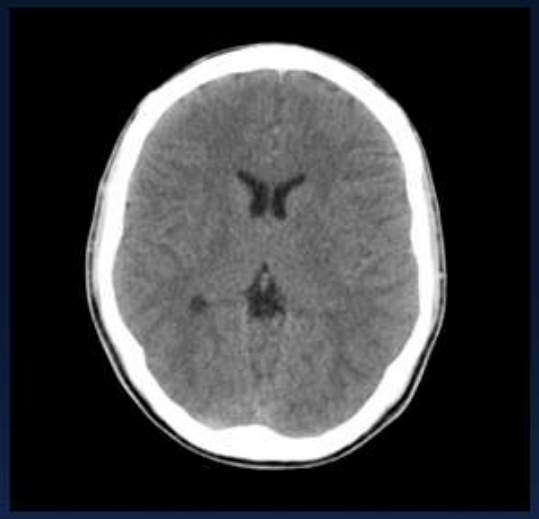


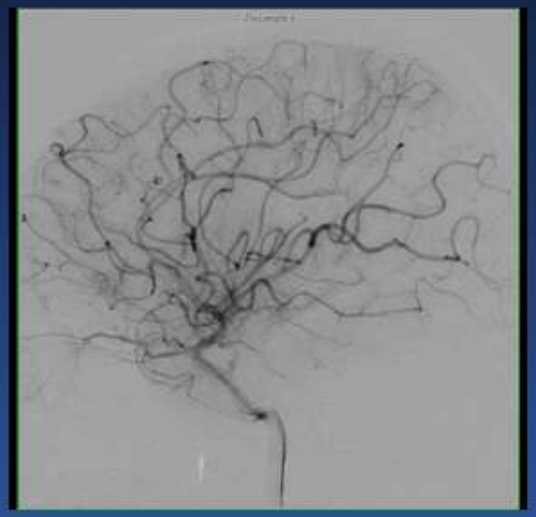
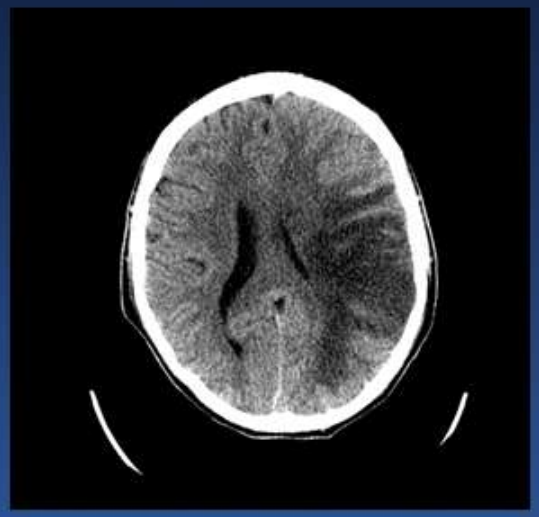
Multi MERCI Clinical Outcomes



Smith ISC 2007, San Francisco

13 year old boy s/p Fontan Procedure

Futile Revascularization

- Recanalization correlate with favorable neurological outcomes in several studies BUT
- Risk of death following stroke remains stable despite revascularization
- "Futile recanalization" – up to 36%!
- Patient selection remains limited

Hussein. AJNR 31: 454-58, 2010

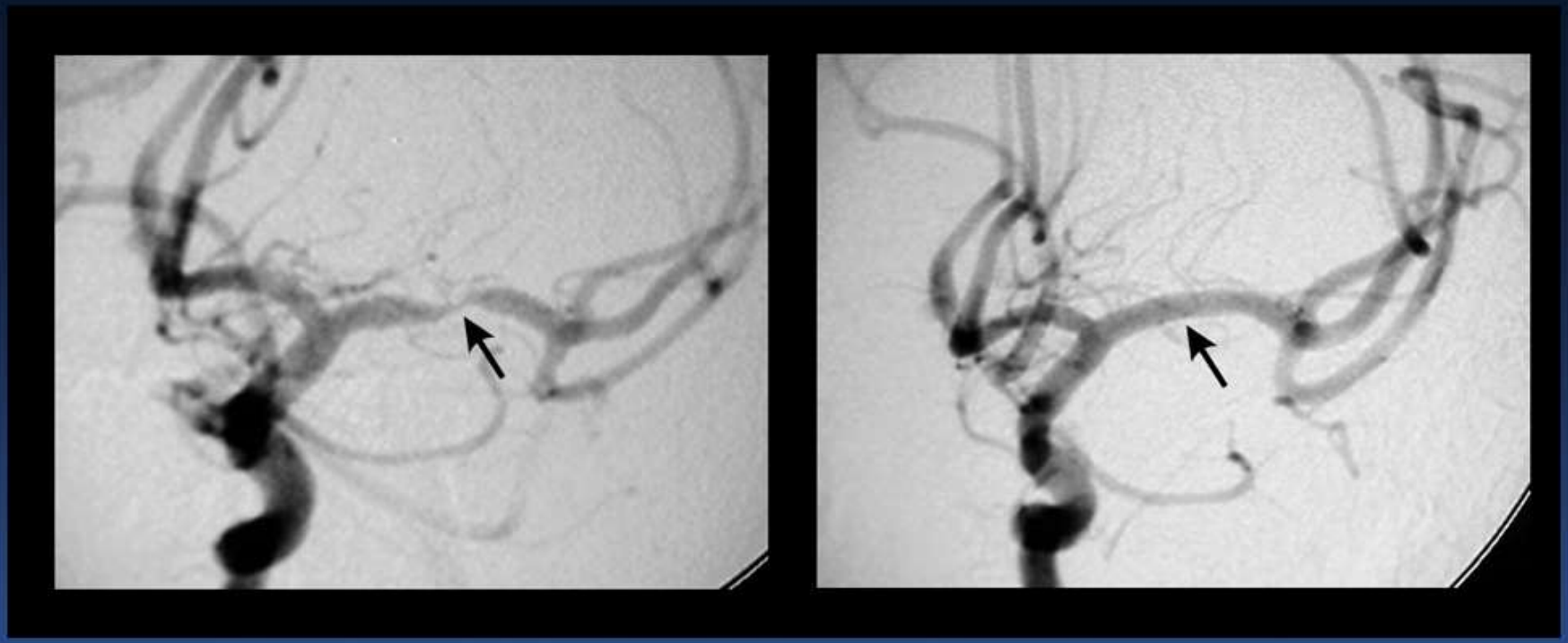
Outcome by NIHSS and TIMI

Study	NIHSS	% Recanalization, TIMI 2-3	% mRS 0-2 @ 90 days
PROACT I	17	58%	-
PROACT II	17	66	40
IMS I	18	56	43
IMS II	19	60	46
MERCI	22	46	28
Multi MERCI	19	68	36
Penumbra	18	82	25
PROACT II Control	17	18	25
NINDS IV rtPA	18	-	28
NINDS placebo	18	-	39

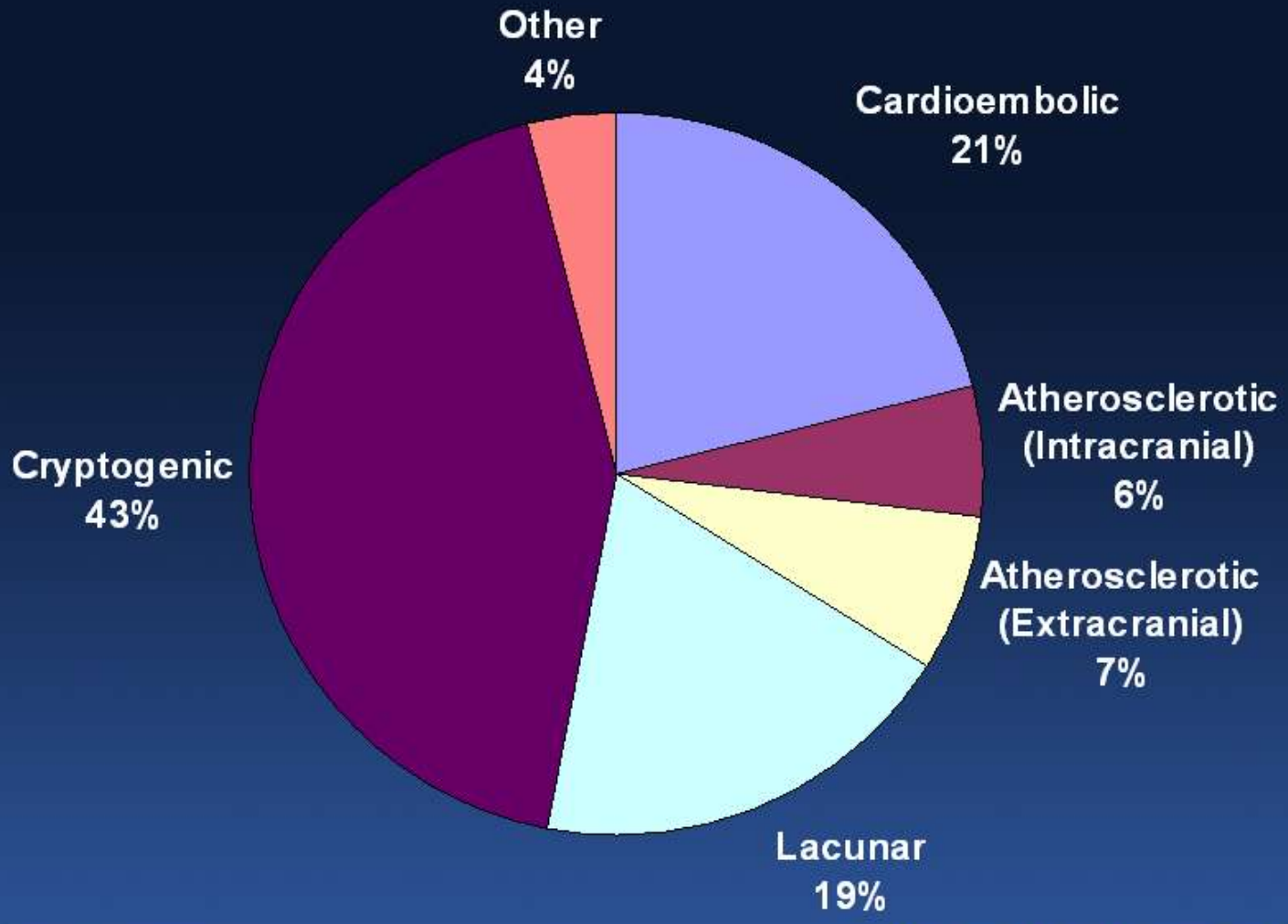
Mortality and ICH

Study	% Mortality @ 90 days	% Symptomatic ICH
PROACT I	27	15
PROACT II	25	10
IMS I	16	6
IMS II	16	10
MERCI	44	8
Multi MERCI	34	10
Penumbra	33	11
PROACT I	43	7
PROACT II Control	27	2
NINDS IV rtPA	24	1
NINDS placebo	21	7

Intracranial Atherosclerosis

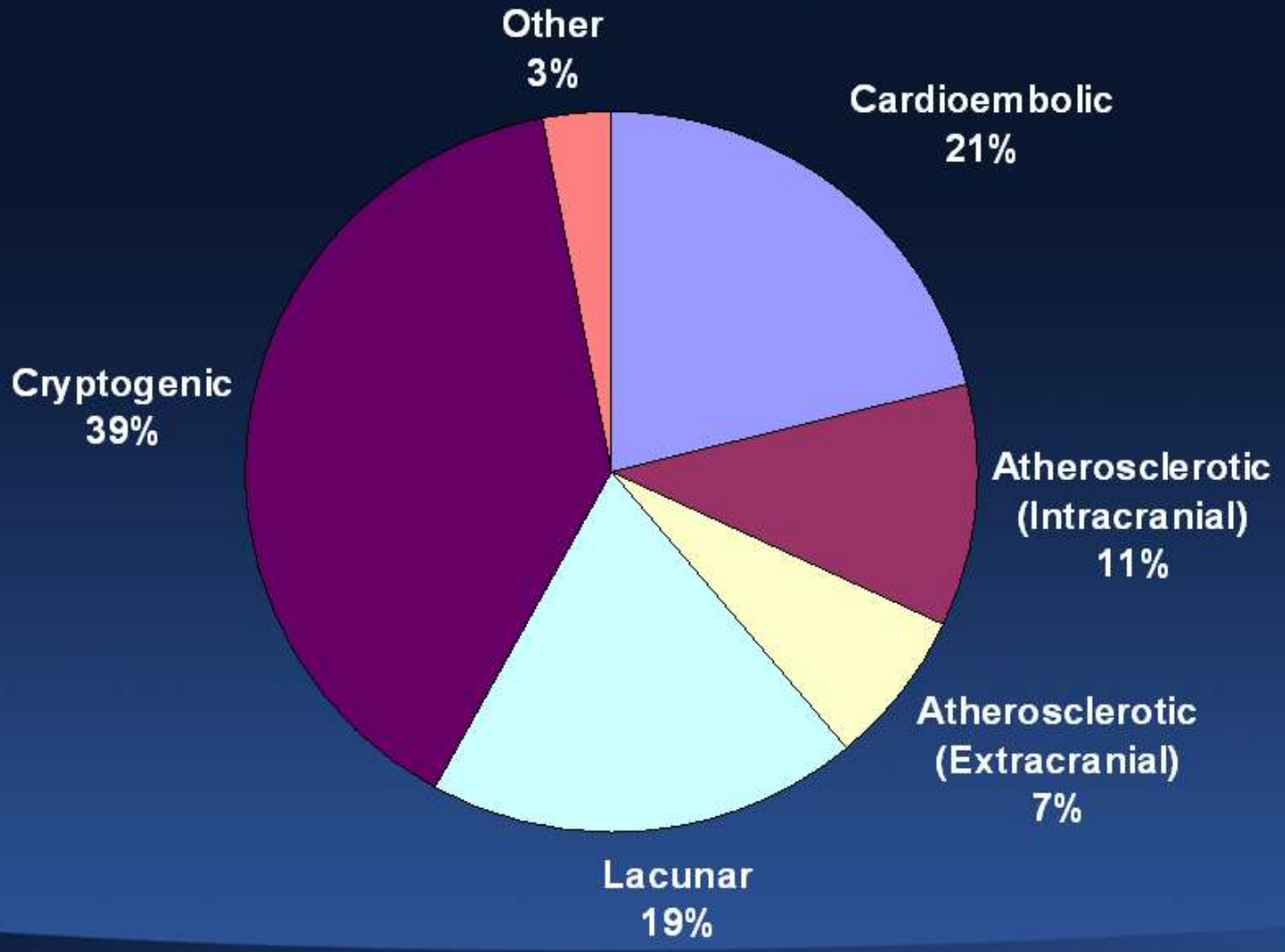


Ischemic Stroke Subtypes Northern Manhattan



Boden-Albala Neurology 1999;52:A557

Ischemic Stroke Subtypes Improved Imaging

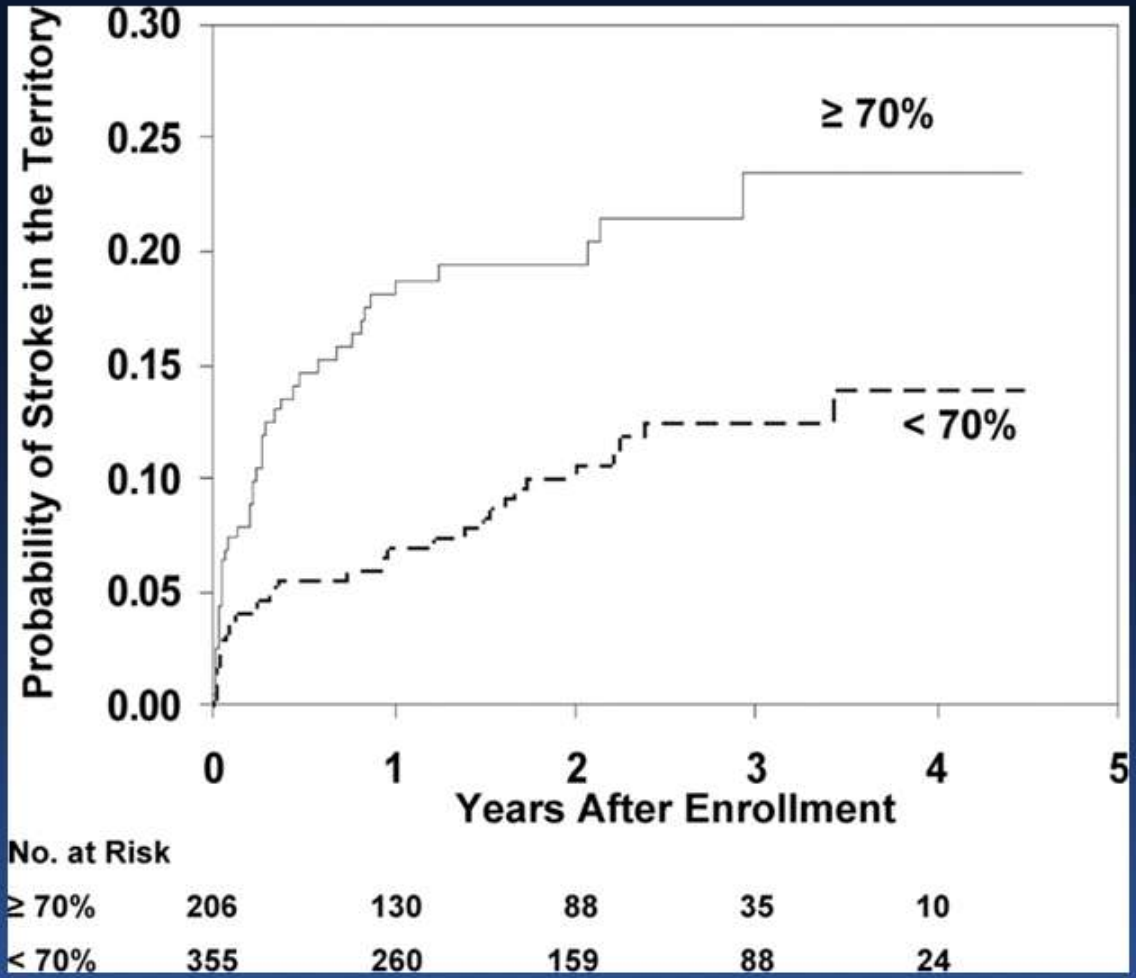


Risk Factors

- In general, IA is part of diffuse disease process
- Populations most at risk
  - Asian (Japanese, Chinese, Korean) [1]
  - African-American [2]
  - Hispanics [3]
- Other risk factors
  - Diabetes mellitus, hypercholesterolemia
  - Hypertension, smoking

[1] *Caplan Stroke 17: 648-655, 1986*
[2] *Wityk Stroke 27: 1974-1980, 1996*
[3] *Sacco Stroke 26:14-20, 1995*

Degree of Stenosis



Kasner. Circulation 2006;113:555-563

Intracranial Atherosclerosis: Therapeutic Options

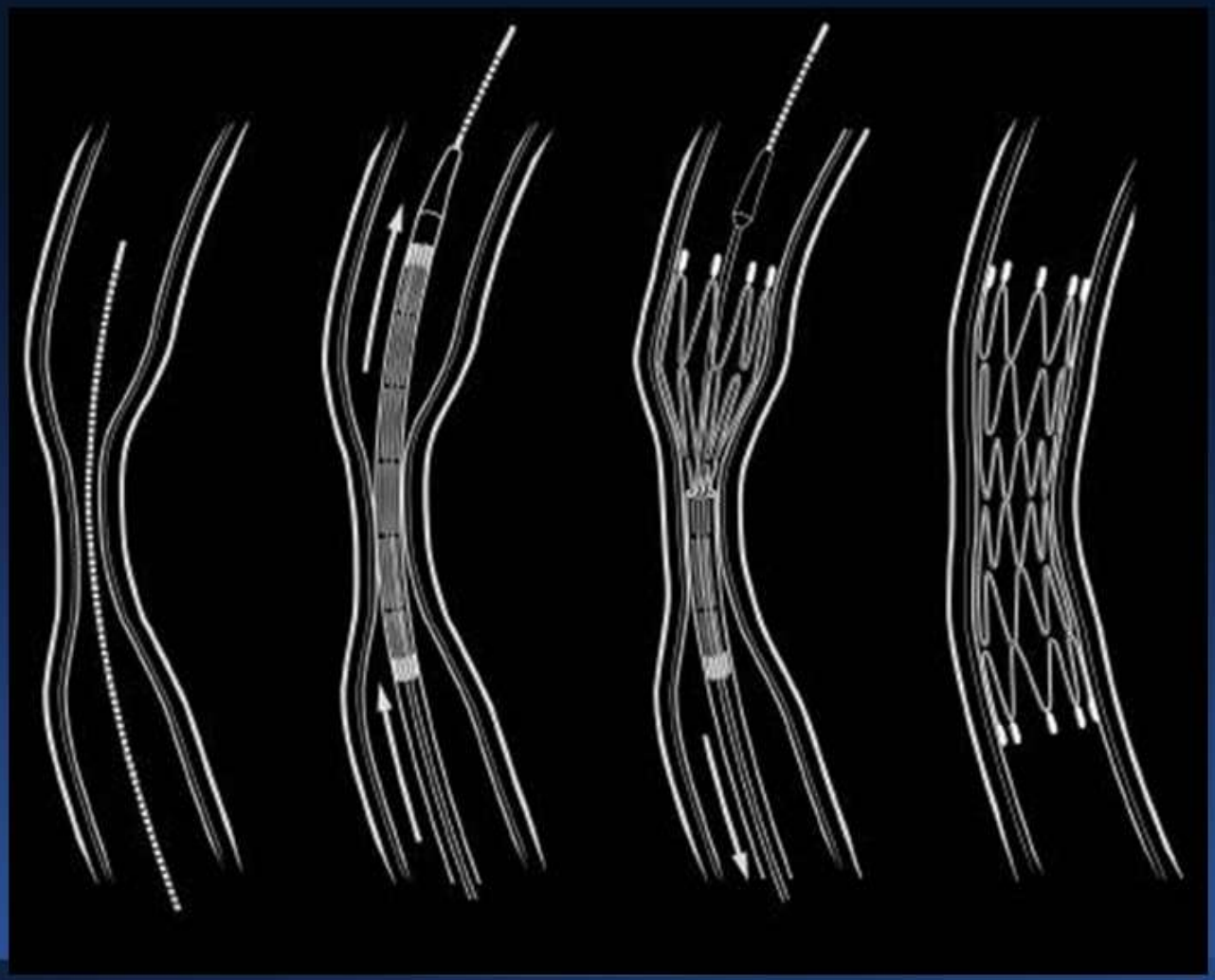
- **Medical Therapy**
  - Anti-platelet therapy > anti-coagulant therapy
  - Statins
  - ACE inhibitors
- **Bypass Surgery – largely discredited**
- **Endovascular Revascularization**
  - Angioplasty – effective but high recurrence
  - Stent Angioplasty – HDE devices but unreimbursed

NEJM 313: 1191-200, 1985
Neurology 70: 1518-24, 2008

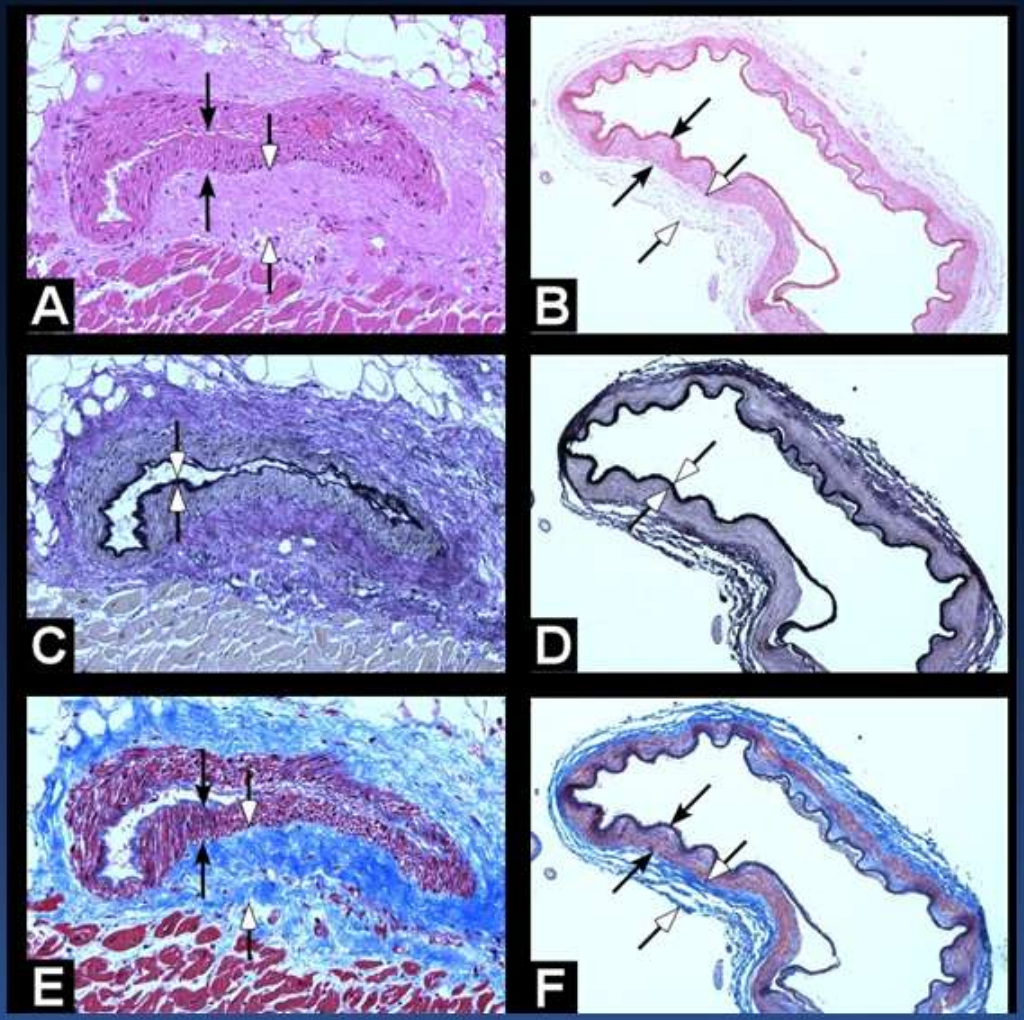
Identification of patients for stent-angioplasty

- Symptomatic disease
- Stroke syndrome must correlate with imaging
- Alternative diagnoses, e.g. inflammatory, neoplastic, metabolic diseases
- Perfusion failure vs. arterio-arterial embolization
- Large vessel disease vs. perforator ischemia

Mild Vessel Dilatation



Cerebral Artery Histology



Meyers PM ARM 58: 133, 2007

Wingspan Registry

- Periprocedural M&M: 12.8%
  - Major Stroke or Death: 6.4%
  - Minor complications: 6.4%
- 34.2% (13) had new DWI+ ischemic lesions
- 23% of new strokes were severe
- 30% restenosis at 6 mo. mean F/U
- 9.5% occlusion at 6 mo. mean F/U

Fiorella. Stroke 38: 881, 2007

SAMMPRIS

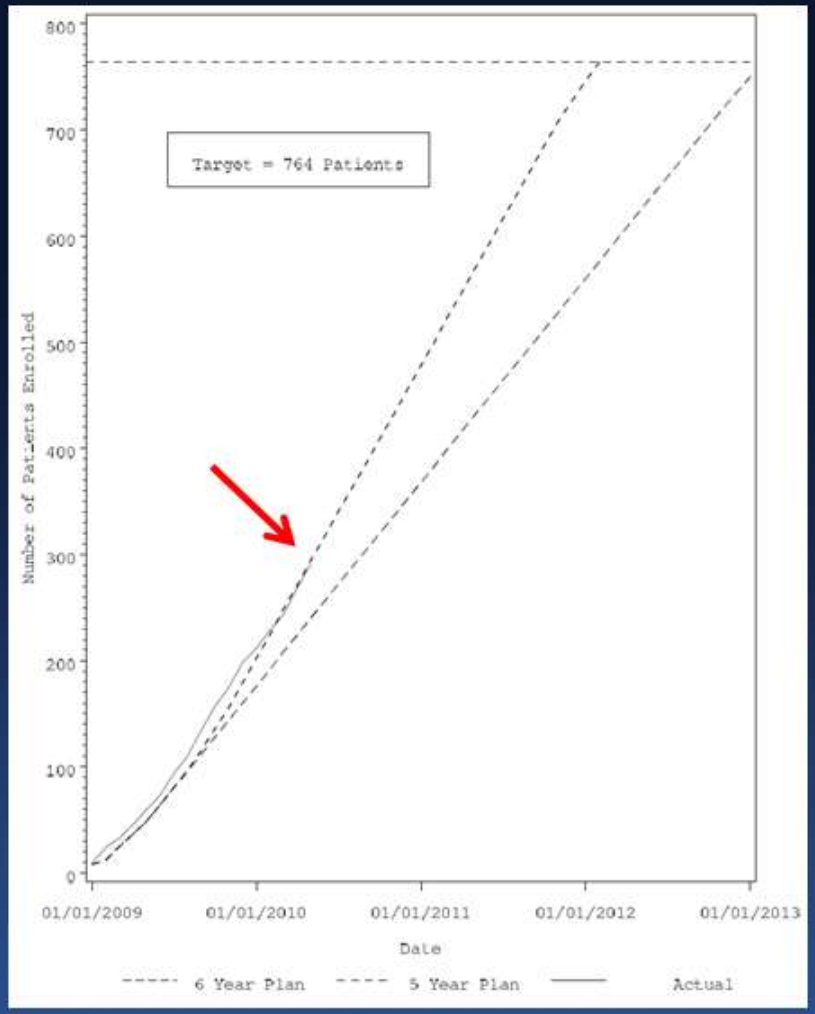
Stenting and Aggressive Medical Management for
Preventing Recurrent stroke in Intracranial Stenosis

- Stenting vs. intensive medical care
- 764 patients 1:1 random, 50 US Centers
- Intracranial stenosis 70-99%
- TIA or stroke within 30 days
- 2 yr average follow-up
- Primary hypothesis:
  35% stroke or death with stenting in 2 yrs

R01NS058728-01A1, NCT00576693

SAMMPRIS Enrollment

Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis



Courtesy of Colin Derdeyn, PI

Neurointervention

- Aneurysms – especially for SAH
- AVM – pre-operative adjunct
- Acute Ischemic Stroke – when IV thrombolysis is contra-indicated
- Intracranial atherosclerosis
  - HDE for symptomatic patients refractory to medical therapy
  - SAMMPRIS