

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.

Summary of Topics

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

Hemorrhagic Stroke Aneurysm

- 5-15% of stroke overall
- ~1/3 of strokes age<65
- 30-day mortality rate: 50%
- 50% irreversible brain damage
- Surgical series: 0-6% mortality
0-30% morbidity
- NY discharge data
4.6-8.1% mortality



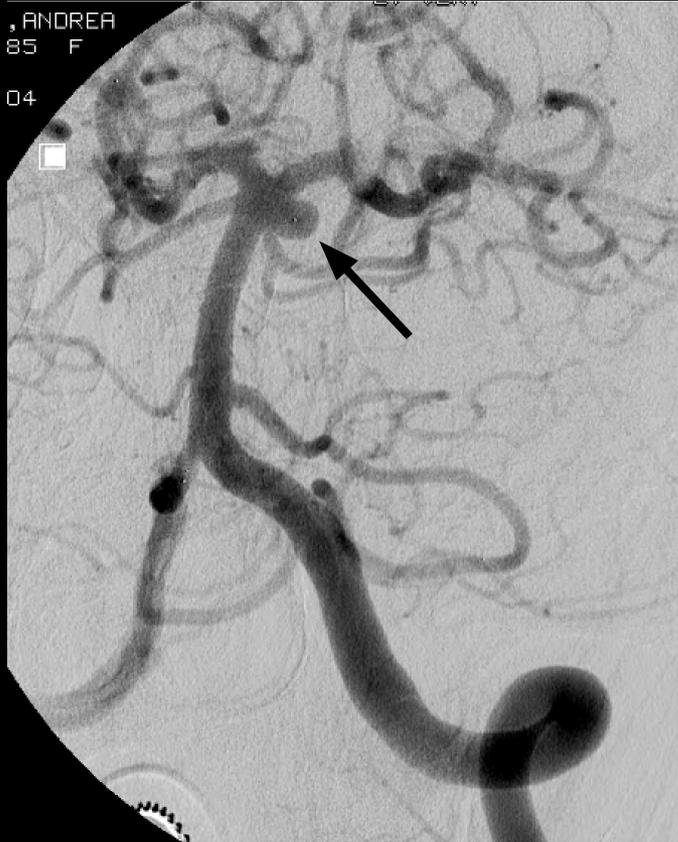
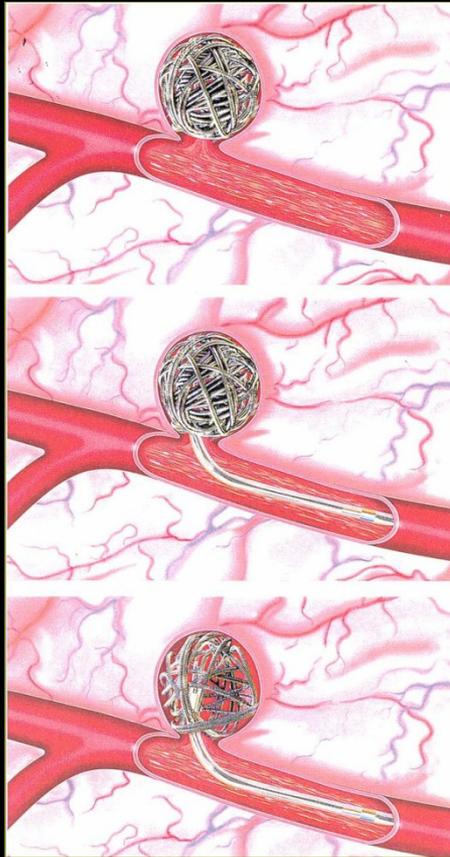
¹Johnston *Neurology* 52: 1799-1805, 1999

²Bederson *Circulation* 102: 2300-08, 2000

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

⁴ISUIA *NEJM* 339: 1725-33, 1998.

Endovascular Occlusion



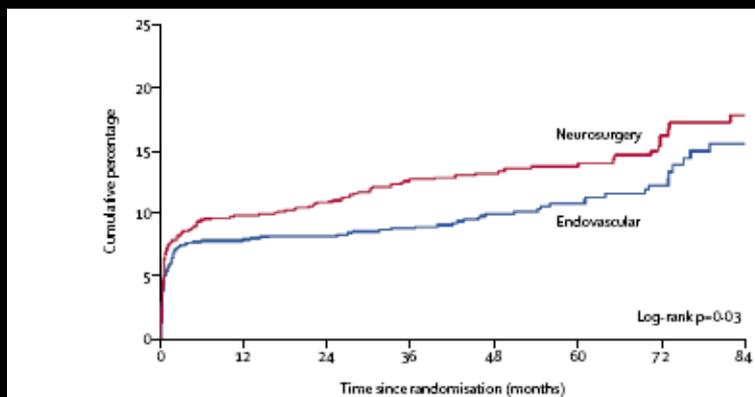
International Subarachnoid Aneurysm Trial (ISAT)

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

ISAT

- Relative risk reduction: 2002 22.6% **2005 26.8%**
- Absolute risk reduction: 6.9% **7.4%**
- Death or disability @ 1 yr: Clip 32.1% Coil 23.4%



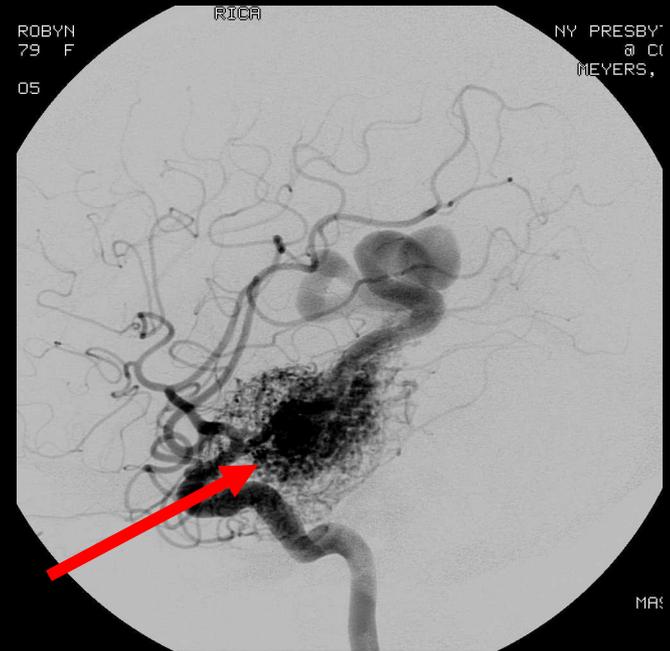
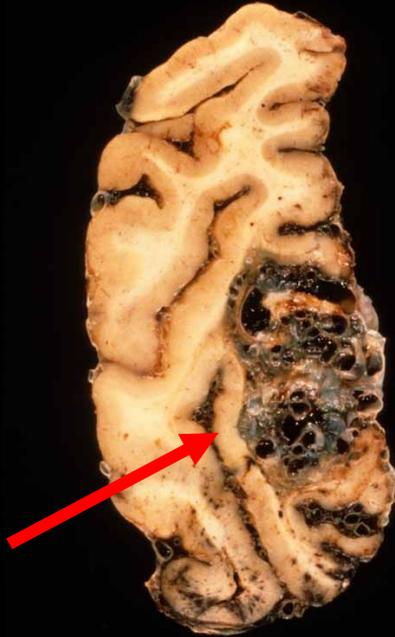
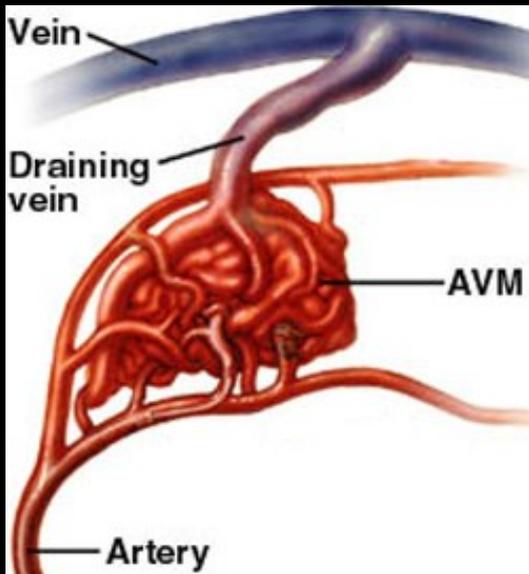
Size matters

All aneurysms, NY State, 1995-2000

By hospital volume

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

Arteriovenous Malformation



AVM Hemorrhage

- M&M
 - 10% mortality
 - 30-50% morbidity
- Location
 - Parenchymal, 82%
 - Subarachnoid
 - Subdural



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%	<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

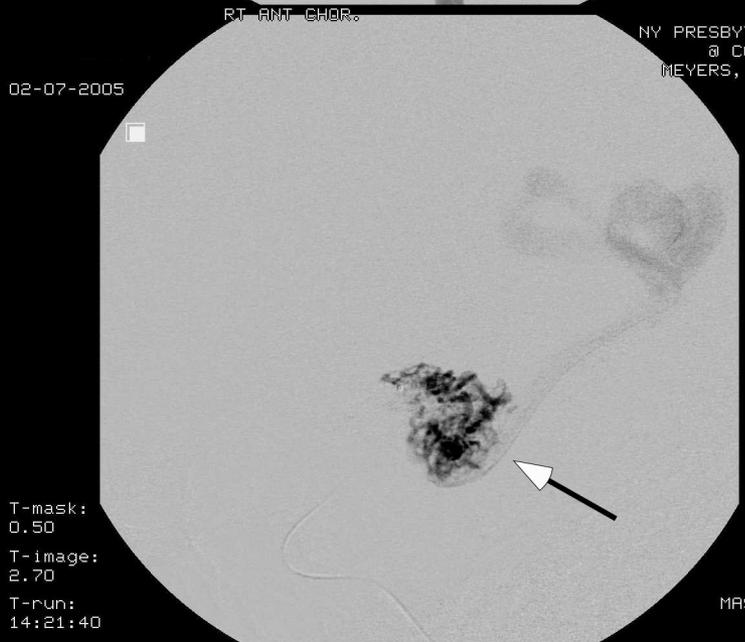
70.7%



02-07-2005

ROT
90
ANG
-13

T-mask:
0.50
RUN
2
T-image:
192.70
MASK IMAGET-run:
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02-07-2005

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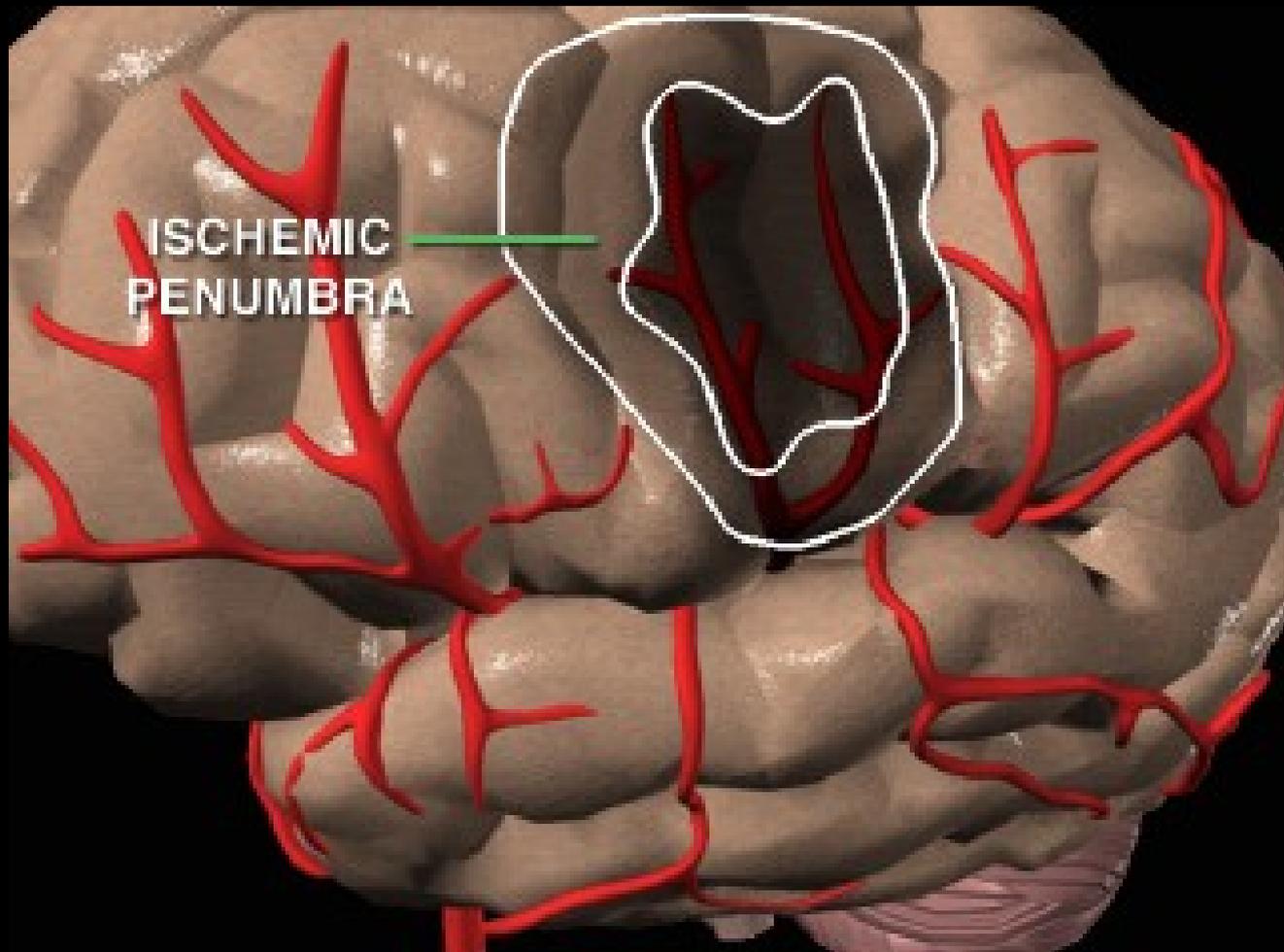


ARUBA

A Randomized trial of Unruptured Brain
Arteriovenous malformation

- NIH Funded
- International, Prospective, Internet-based
- Randomized (1:1 = 800 patients)
- Enrollment based on Ethical Equipoise

Acute Ischemic Stroke



Intravenous Thrombolysis (t-PA)

- FDA Approved
- 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*

Mori 1992, Wolpert 1993, von Kummer 1993, Yamiguchi 1993

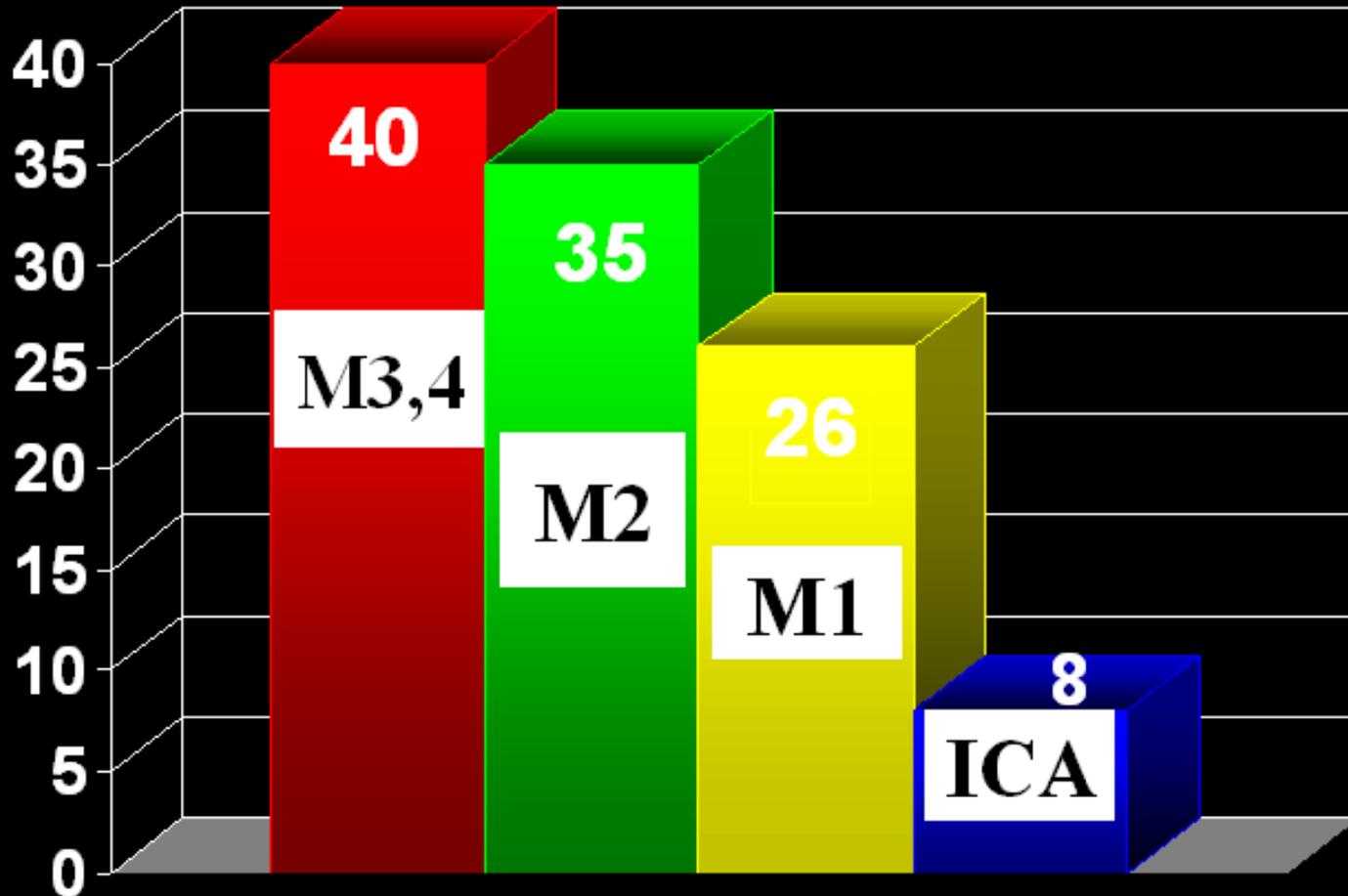
NINDS rtPA Stroke Group. NEJM 333: 1581-8, 1995

European Cooperative Acute Stroke Study (ECASS-III)

- 821 patients
- 1:1 randomization IV rtPA vs. placebo
- Median time to administration: 4 hours
- Favorable outcome: 52% vs. 45%
- Benefit despite increased hemorrhage
- Mortality rates did not differ
- Conclusion: IV rtPA significantly improves outcomes of stroke patients, 3-4.5 hours

Recanalization Rates: IV tPA \leq 8 hrs

(del Zoppo *Ann Neurol* 32: 78, 1992)



Intra-arterial Thrombolysis

PROACT II - Results

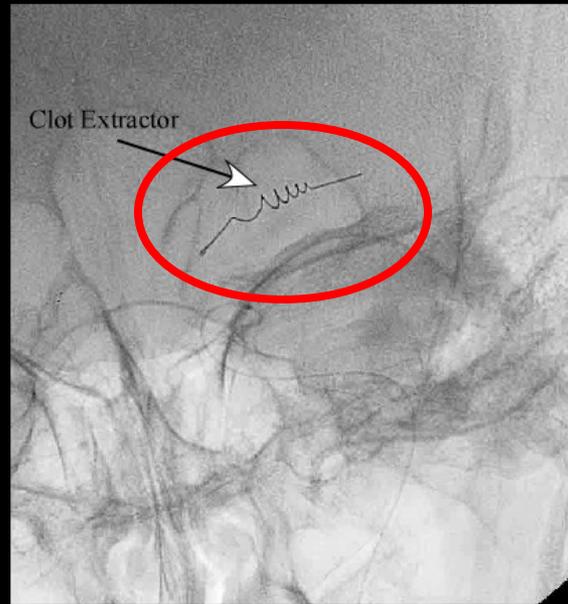
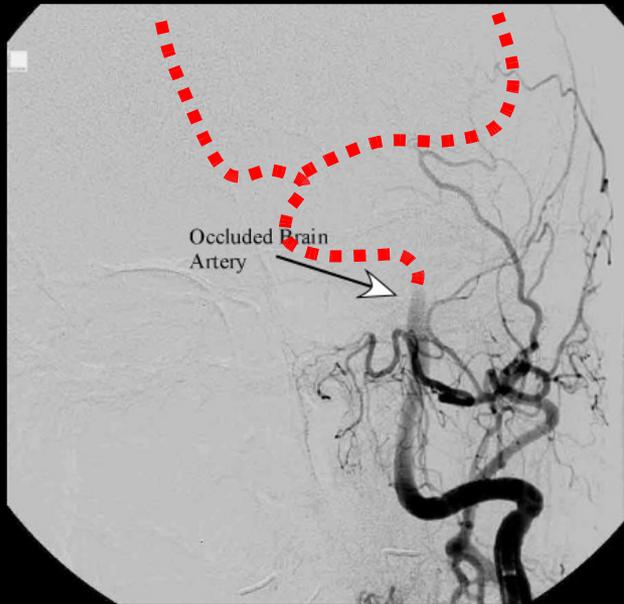
PROACT II Results

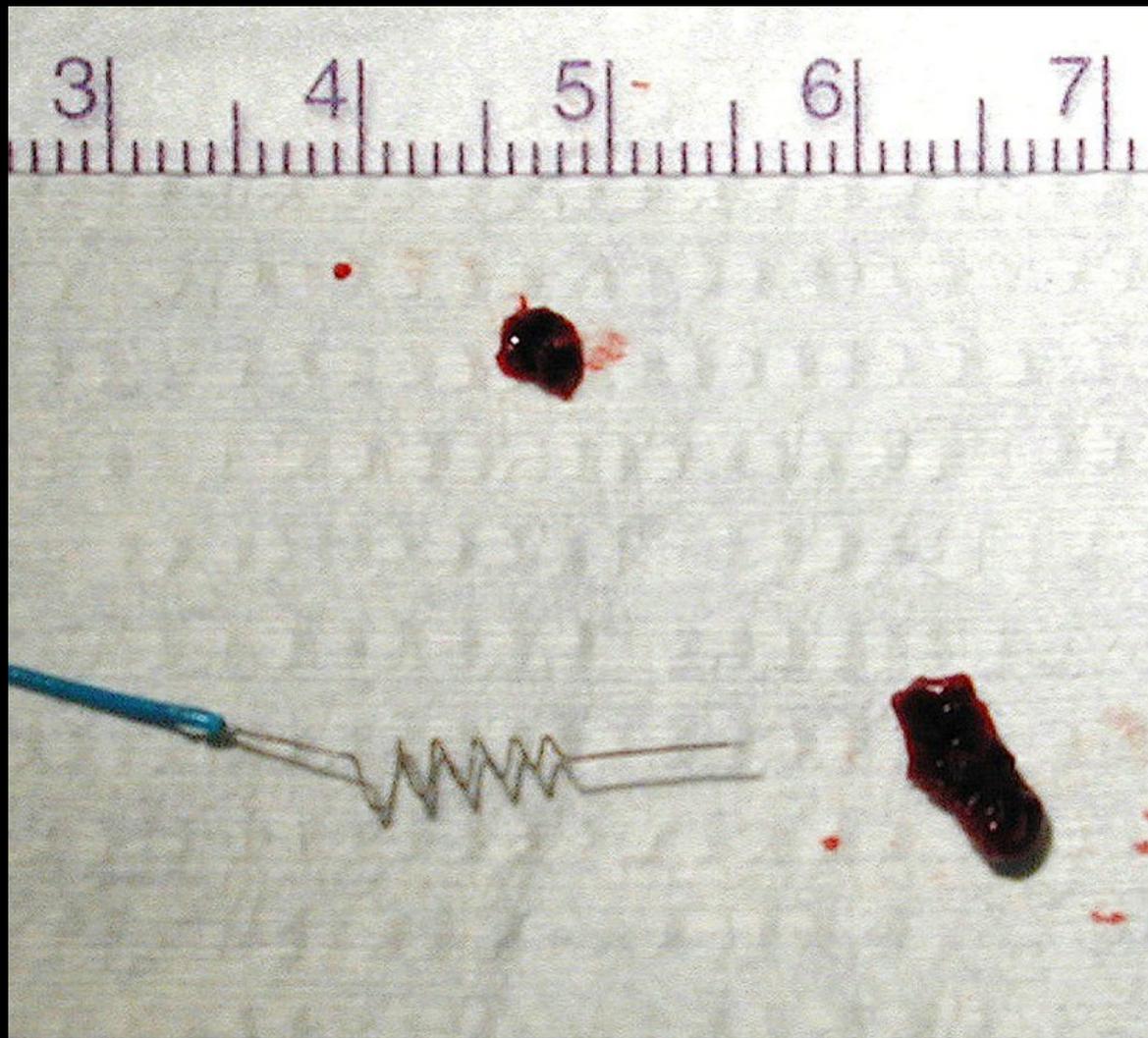
	IA pro-UK (n = 121)	Placebo (n = 59)
Mean time to treat: 5.3 hours		
Modified Rankin 0-2 at 3 months	40%	25%
TIMI 2 – 3	67%	2%
Intracerebral Hemorrhage	10%	2%

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

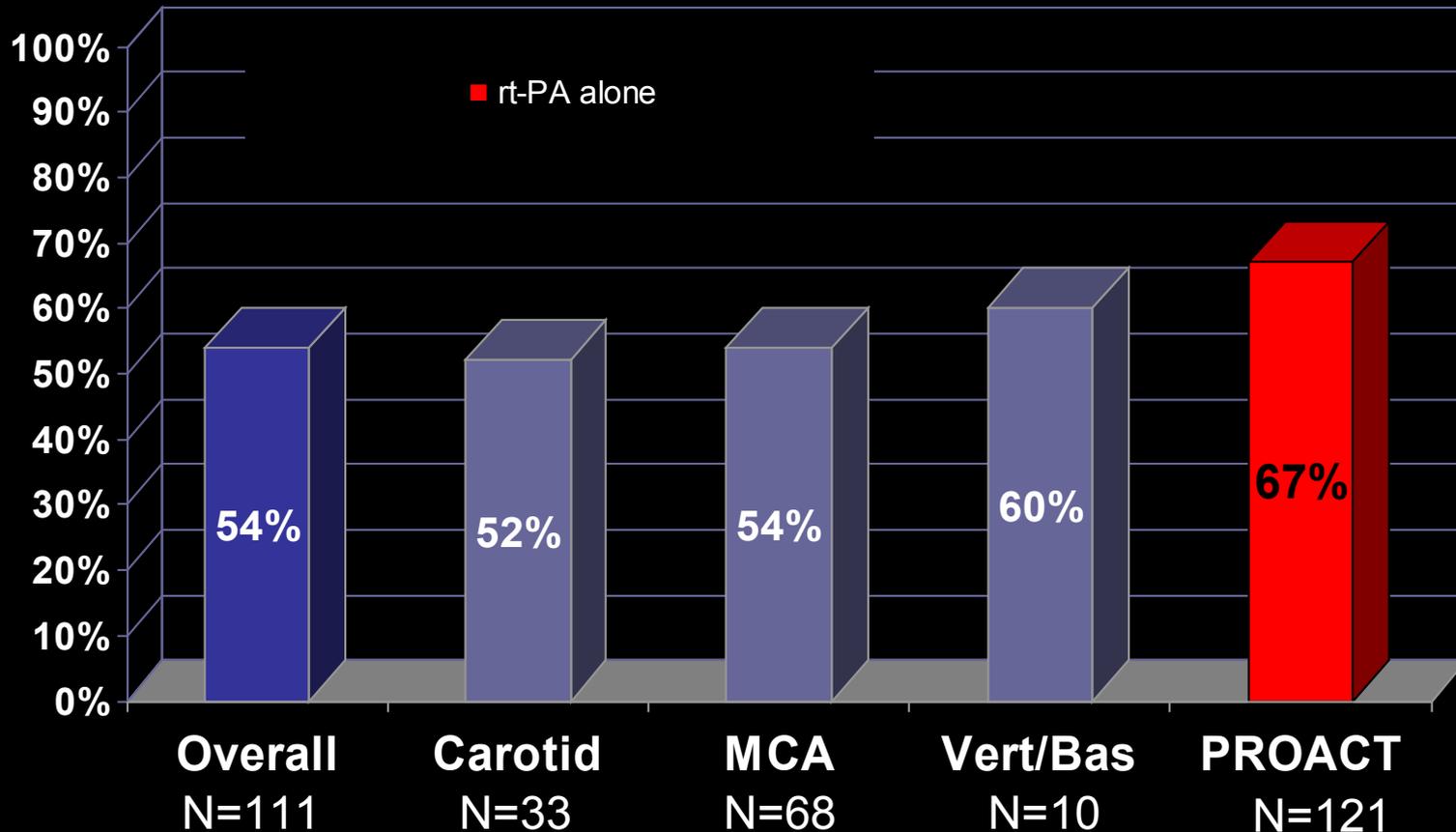
Concentric Merci Trial Mechanical Thrombectomy





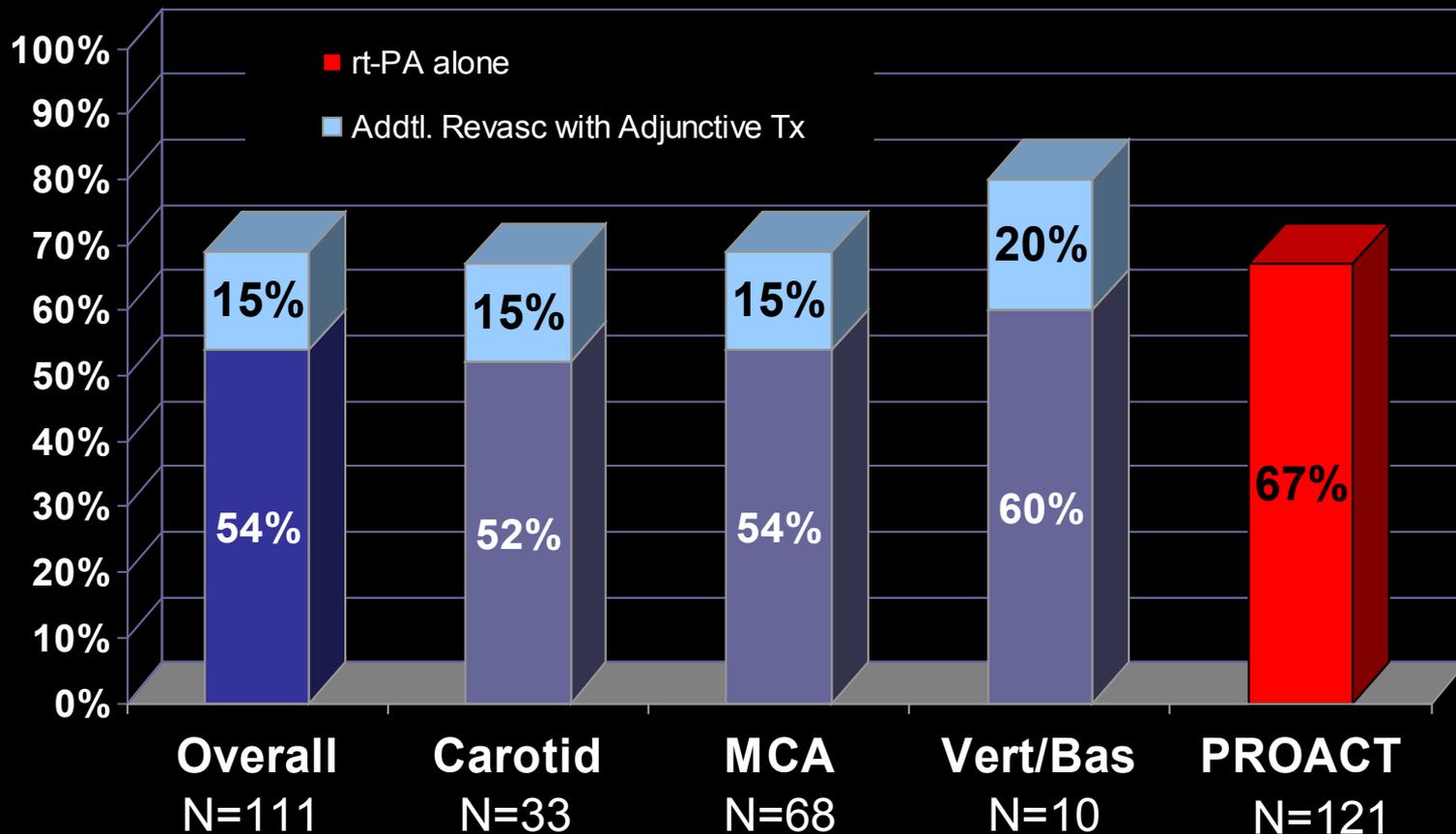
Multi MERCI (Part I) Revascularization by Vessel

Merci WITHOUT Adjunctive Therapy

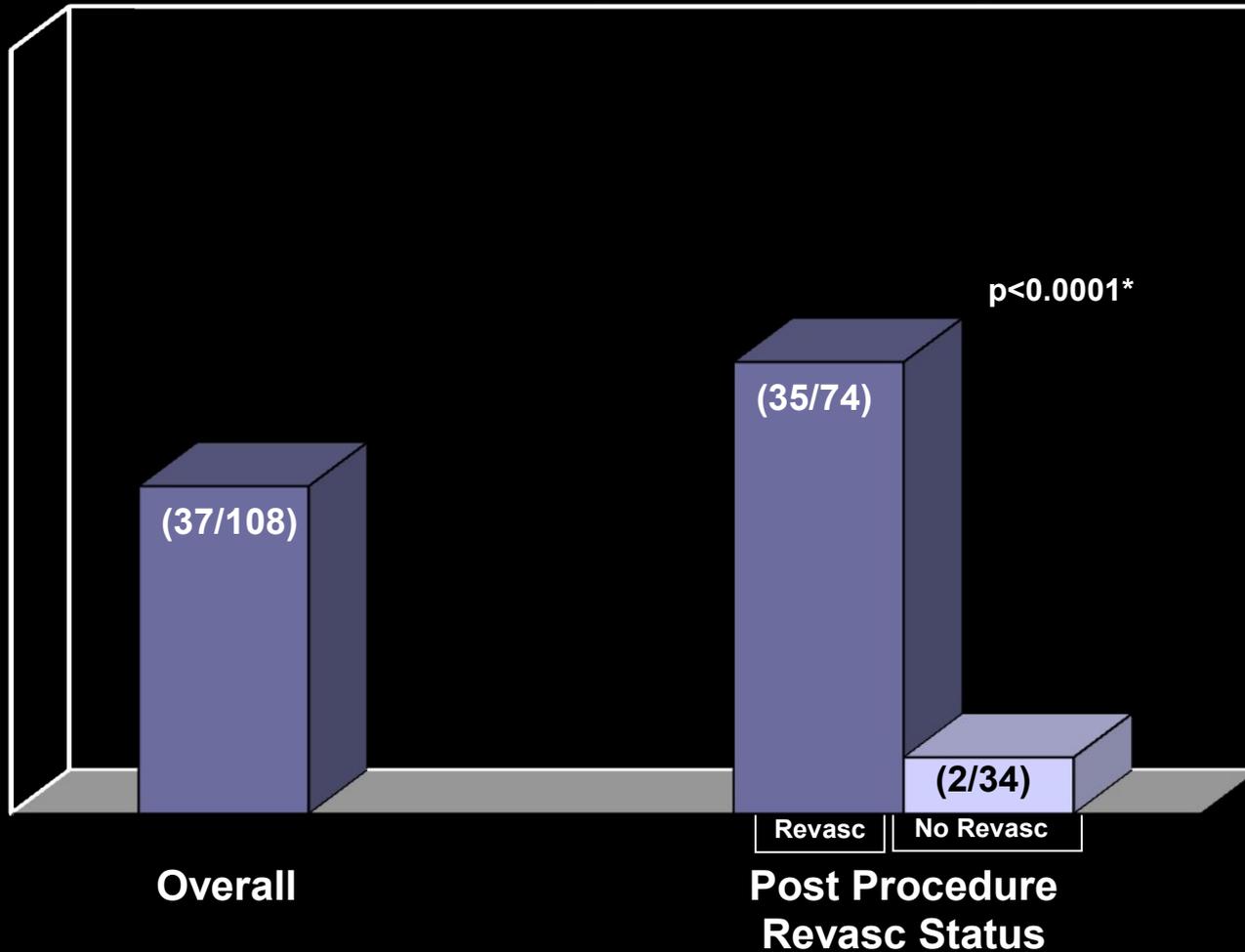


Multi MERCI (Part I) Revascularization by Vessel

Merci WITH Adjunctive Therapy



Good Outcome (mRS ≤ 2) at 90 Days



*p-values calculated with Fisher's exact test on post-hoc basis

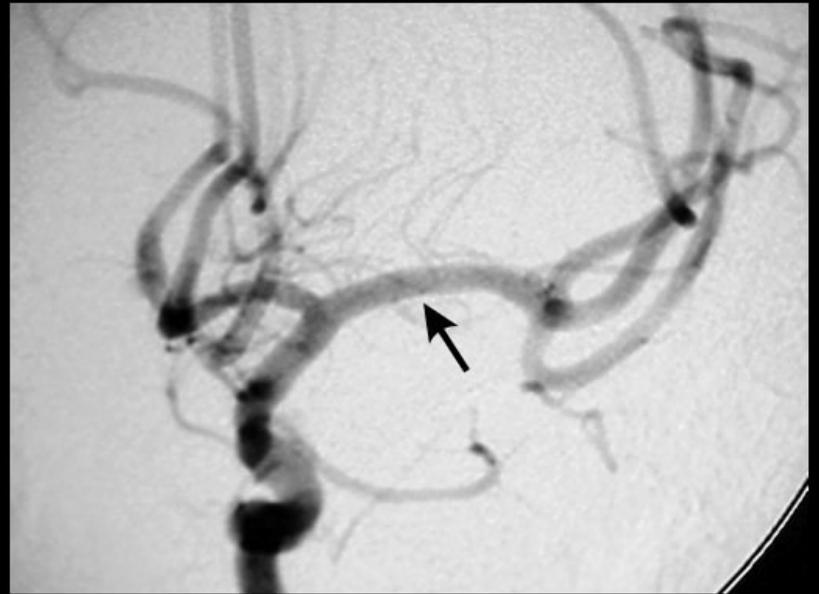
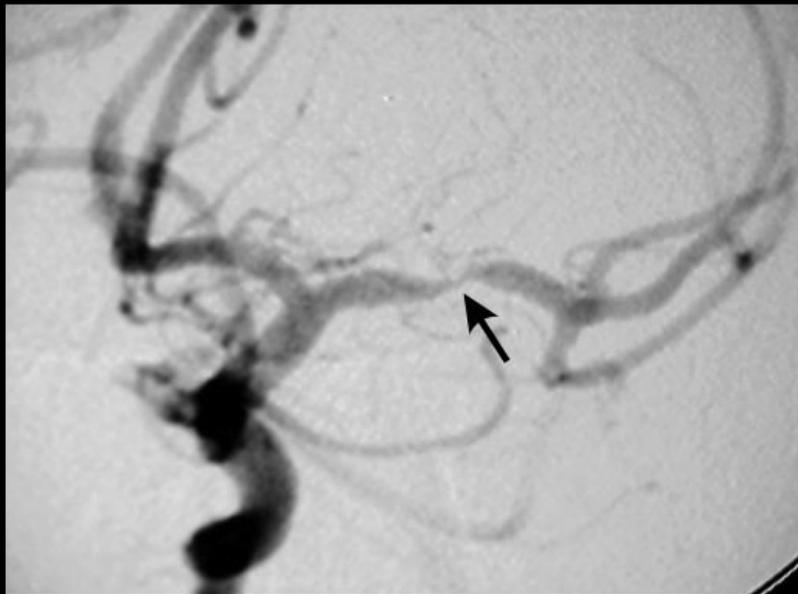
Safety in Multi-Merci

Result	Overall N=111	IV t-PA N=30
Procedure-related complication, % (N)	9.9 (11)	0 (0)
Dissection	2.7 (3)	0
Perforation	2.7 (3)	0
Embolization of an uninvolved vessel	0.9 (1)	0
Groin complications	0	0
Symptomatic ICH without perforation	2.7 (3)	0
Asymptomatic SAH leading to death	0.9 (1)	0
Significant procedure complication, % (N)	4.5 (5)	0 (0)

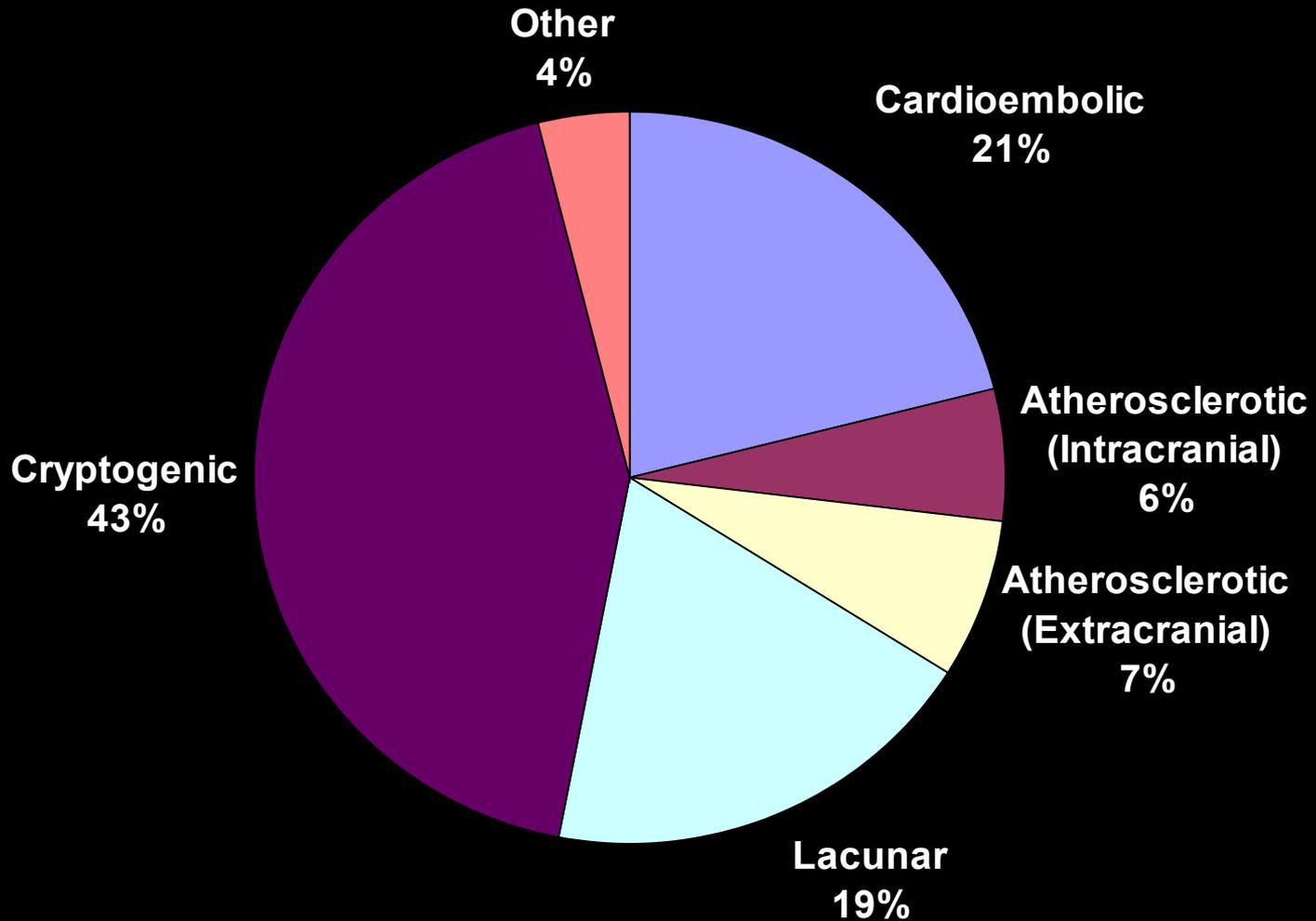
Intracranial Hemorrhage

Symptomatic ICH[†], % (N)	9.0 (10)	6.7 (2)
Asymptomatic ICH[‡], % (N)	29.7 (33)	40.0 (12)

Intracranial Atherosclerosis

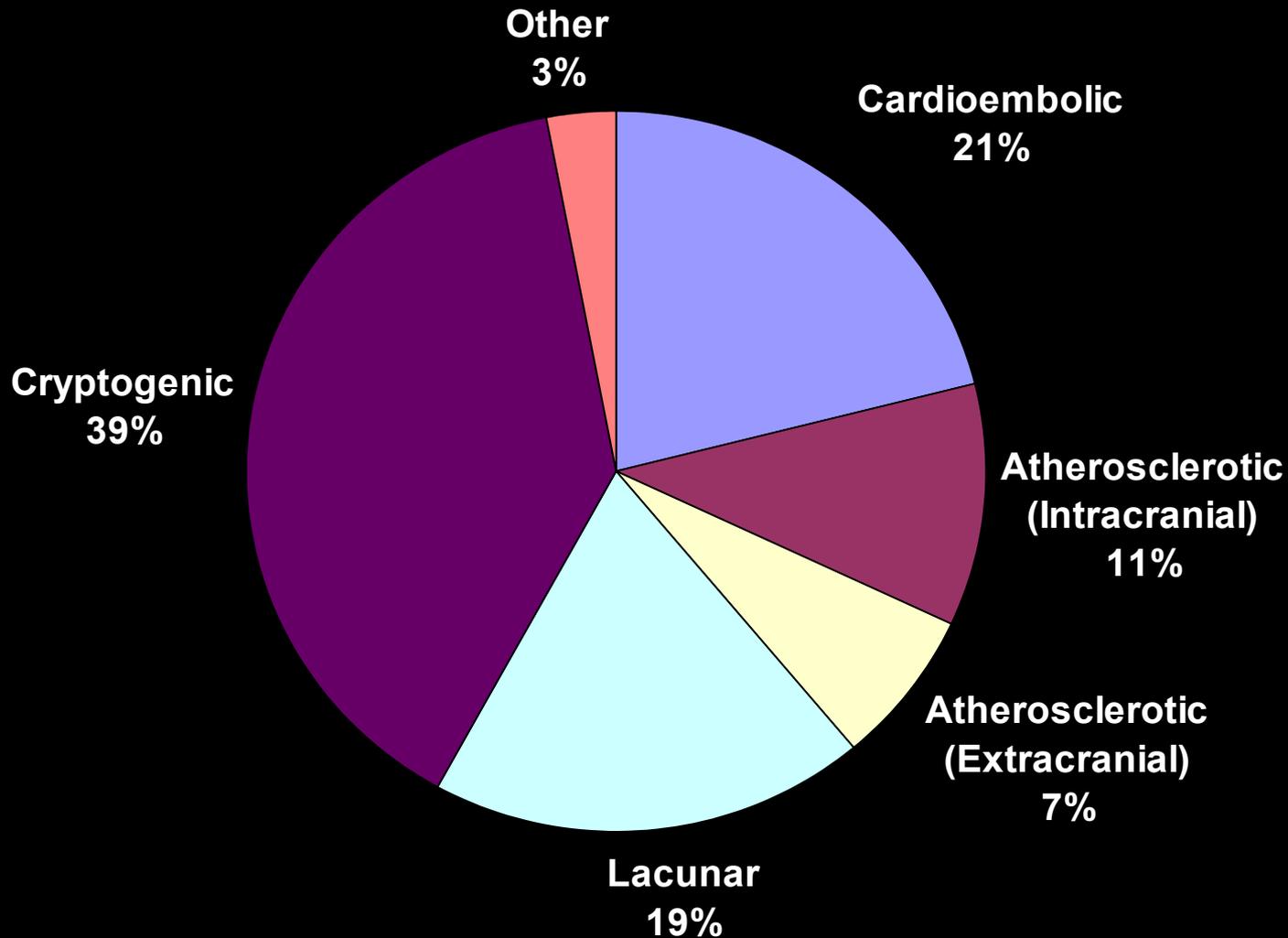


Ischemic Stroke Subtypes: N. Manhattan



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

WASID

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis

Conclusion

Warfarin was associated with significantly higher rates of adverse events and provided no benefit over aspirin in this trial. Aspirin should be used in preference to warfarin for patients with intracranial arterial stenosis.

NEJM, March 31, 2005

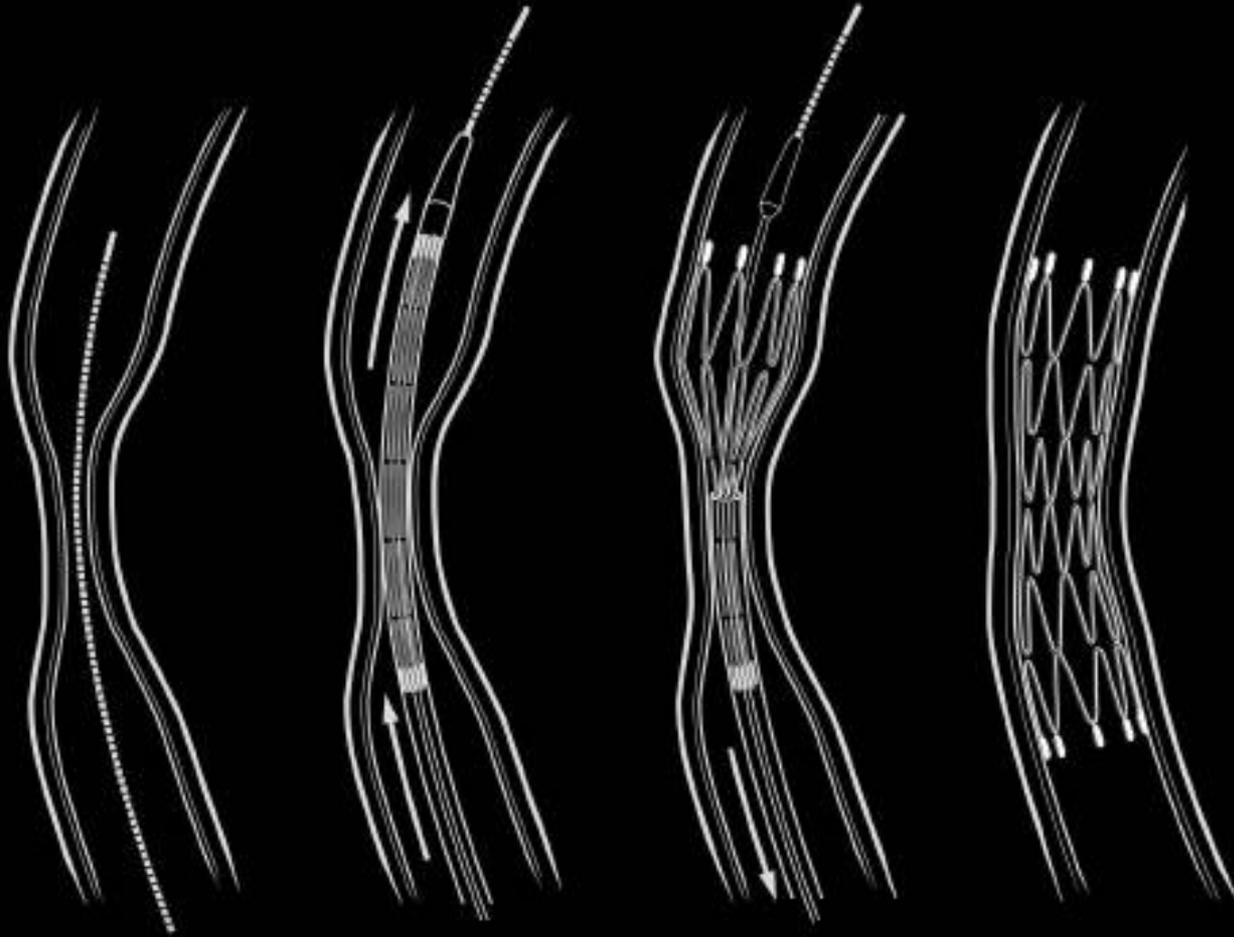
Intracranial Atherosclerosis: Therapeutic Options

- Medical Therapy:
 - Anti-platelet, Anticoagulation (ASA, Aggrenox, Plavix, Coumadin)
 - Statins, ACE inhibitors
- Bypass Surgery:
 - Bypass surgery (EC-IC); (CCA-VA); (OccA-PCA)...
- Endovascular Revascularization:
 - Intracranial angioplasty – effective but high recurrence
 - Intracranial Stent Angioplasty – now FDA approved device but unreimbursed

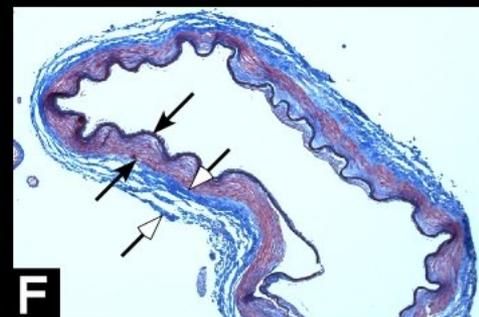
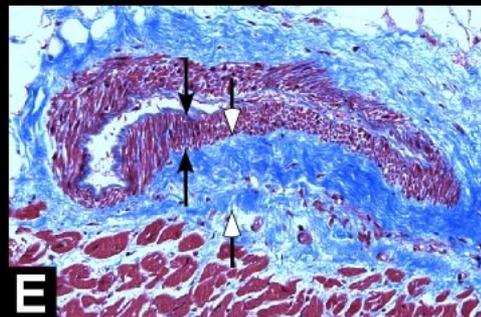
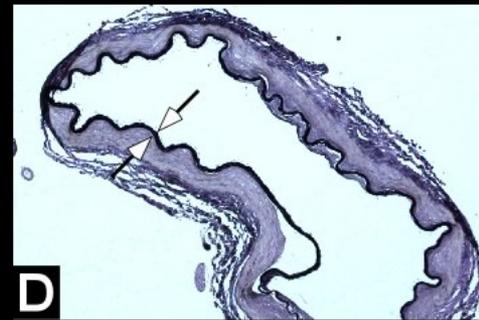
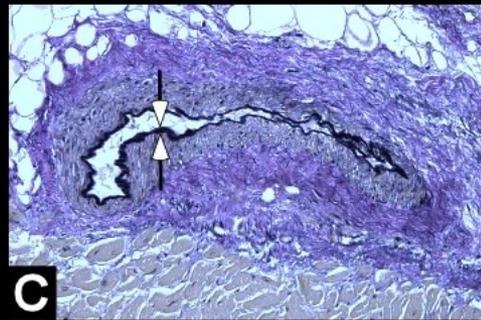
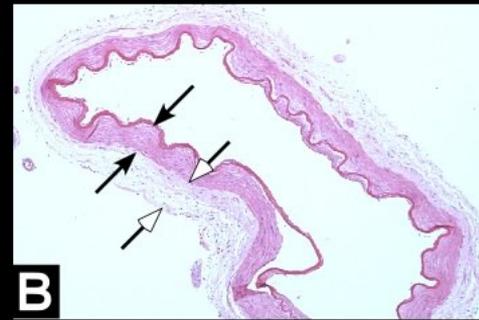
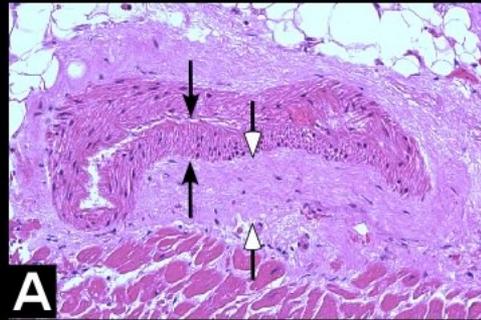
Identification of patients for stent-angioplasty

- 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



SSYLVIA vs. Wingspan

	SSYLVIA	WingSpan
N	61	45
Stent Success, %	95.1	100
Procedure Success, %	88.5	97.7
Adverse events, %	6.6	11.1
30-day stroke and death	6.6	4.4
6 mo. restenosis, >50%	32	7.5
Symptomatic restenosis, %	13.7	0
6 mo. All stroke and death	14	9.3
1 yr ipsilateral stroke, %	11.5	N/A

SSYLVIA *Stroke* 35: 1388, 2004

Henkes *Neuroradiology* 47: 222, 2005

SAMMPRIS

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

- Stenting vs. intensive medical care
- 764 patients (382 in each arm), 50 US Centers
- Intracranial stenosis 70-99%
- TIA or stroke within 30 days of enrollment
- 2 yr average follow-up
- Primary hypothesis: 35% stroke or death with stenting over 2 yrs.

Indications for Neurointerventional Procedures

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