New Clinical Trials For ICH: MISTIE III

Minimally invasive techniques for hemorrhagic stroke

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BIOS

MISTIE III

- Sponsored by NINDS, R01NS046309
- Donations
  - Genentech - North America
  - Boehringer Ingelheim - Europe
- IND #8523 (intracerebral use of rt-PA)

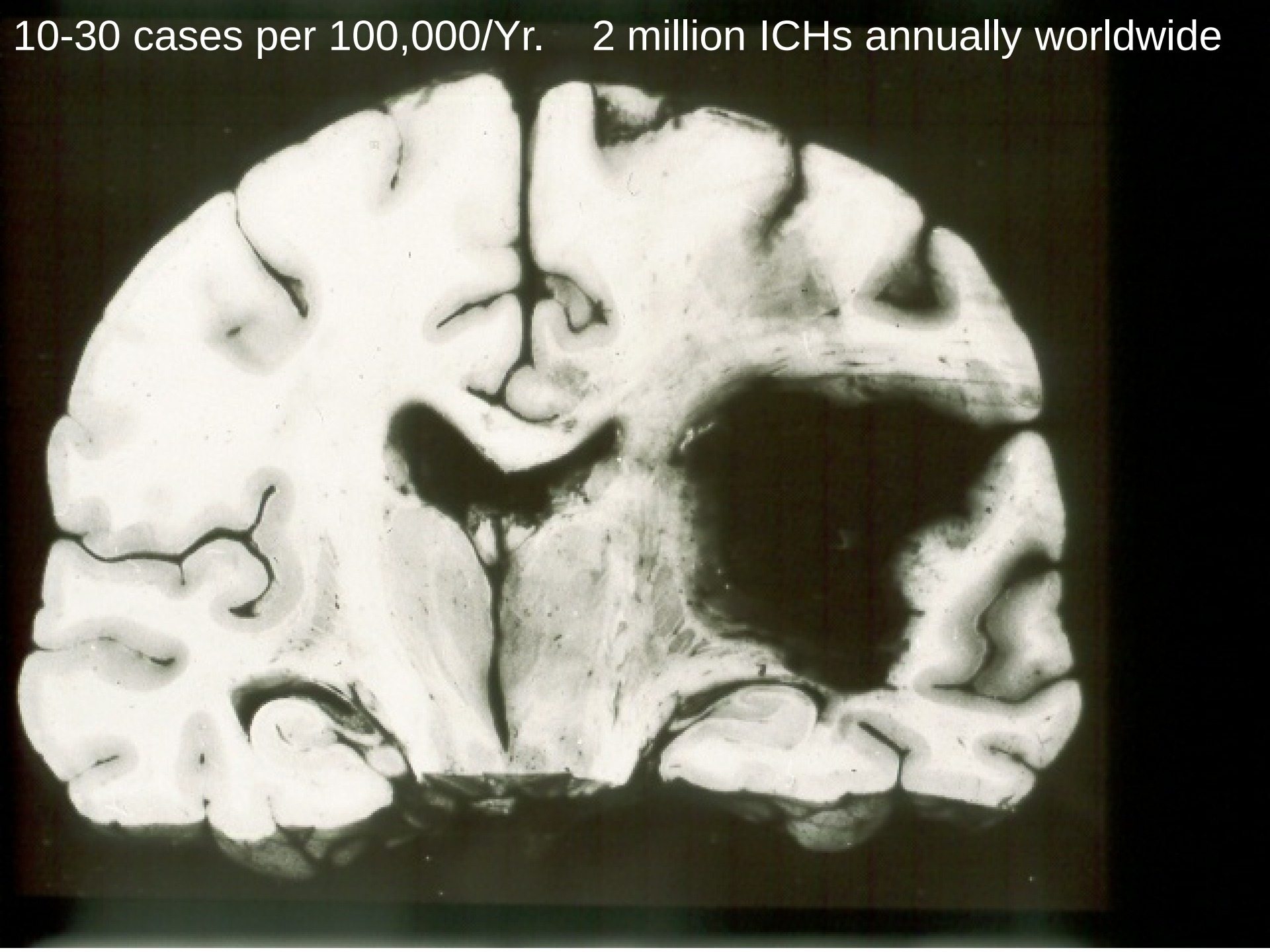
StrokeNet-MISTIE III Collaboration

- MISTIE III supports the StrokeNet Network
- MISTIE III is sharing its experience with StrokeNet
- 2/3 MISTIE III leadership are StrokeNet faculty / investigators

StrokeNet – MISTIE Collaboration

Percent	# Stroke Net Centers	Stroke Net Status
38%	16/42	ACTIVE SN primary centers or satellites
52%	28/54	PROJECTED August active
22%	4	8/37 SN ENROLLMENTS
	8	Nonparticipating SN sites: resources, conflicts, regulatory barriers

10-30 cases per 100,000/Yr. 2 million ICHs annually worldwide



Surgical Clot Removal Questions & Strategies

1. Does surgical intervention help?
2. When to operate?
3. What type of surgery?
   - Craniotomy
     - Pro: Direct visualization for removal & hemostasis
     - Con: Requires corticotomy and cautery
   - MIS
     - Pro: No cortex injury, no cautery
     - Con: No direct visualization
4. How much clot should be removed?
5. Which patients benefit from which intervention?

Meta-analysis: 15 ICH Surgical Trials*
(Death or Disability)

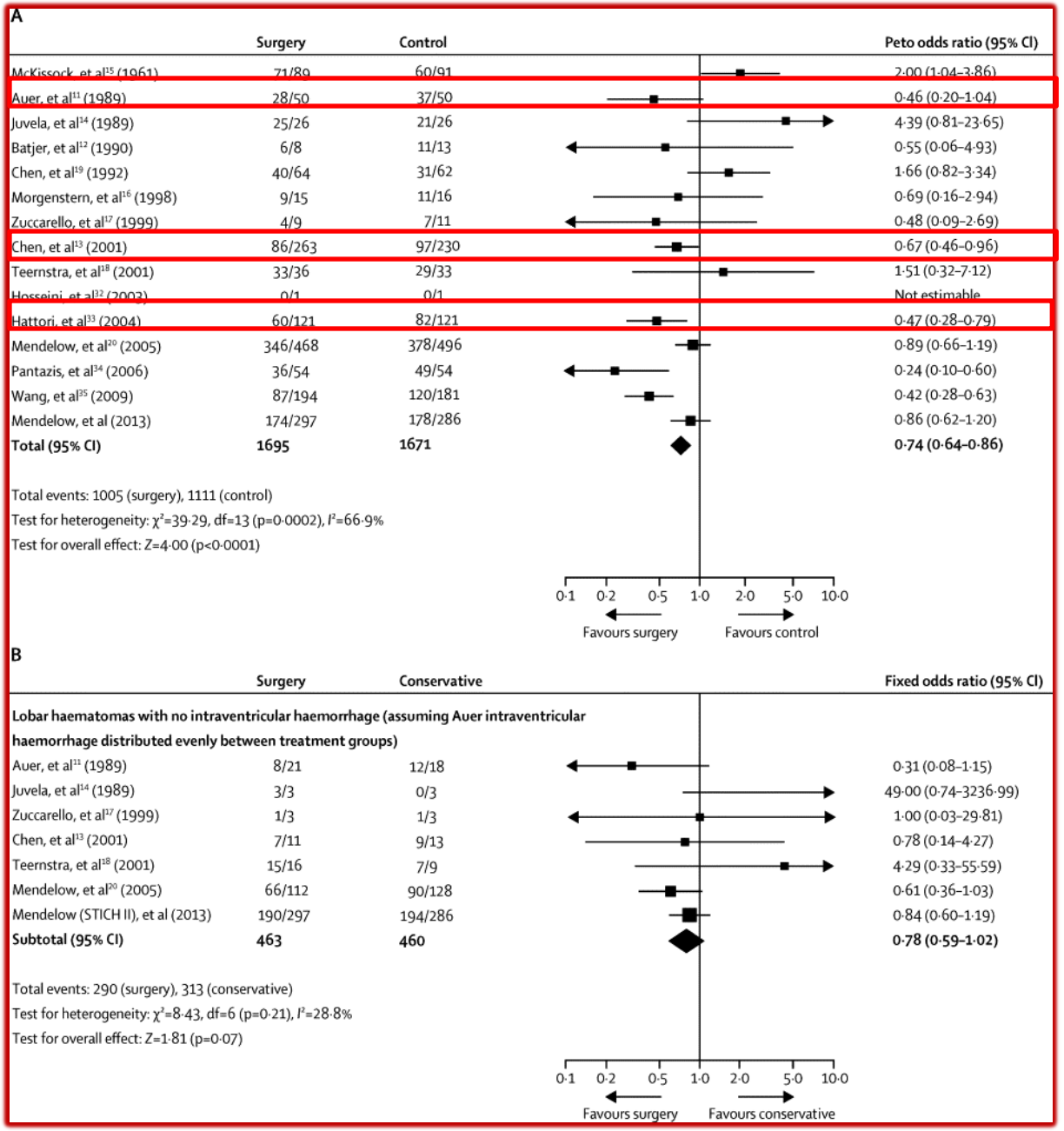
Significant advantage for surgery: OR=0.74

Significant heterogeneity by location, by surgery type

Lobar intracerebral hemorrhage and no IVH:

No heterogeneity

No benefit: p=0.07



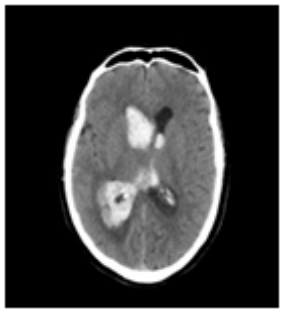
*Includes STICH I/II

Lancet. 2013 Aug 3;382(9890):397-408

Current BIOS Phase III Trials

MISTIE III

Minimally Invasive Surgery plus rt-PA for Intracerebral Hemorrhage Evacuation



CLEAR- III

Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage

Minimally Invasive Hemorrhage Evacuation

CONCEPT

- Minimally invasive access
- Single trajectory for tissue injury
- Precision-guided, aspiration/evacuation

APPROACHES:

- Mechanical clot disruption
- Endoscopic removal
- Ultrasound
- Injection of thrombolytic

365-Day Outcome & Cost Model

MISTIE II: A Phase II Proof-of-Concept Trial

UNIVERSITY OF Cincinnati

MISTIE Phase II – Overall Trial Goal

To fully test the novel idea that…

"Clot-*size* *reduction* decreases mortality and increases good outcomes"

Surgical Intervention

Post-Surgery

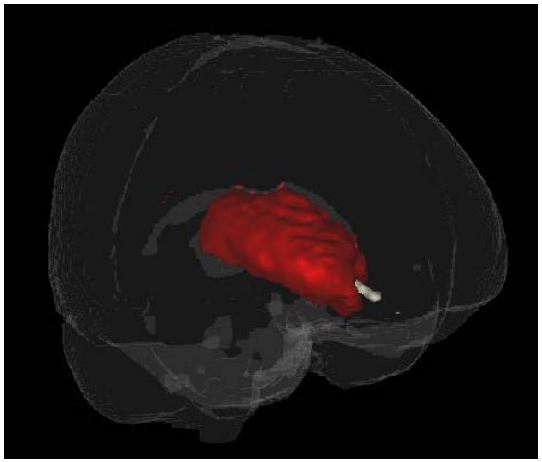
Pre-surgery

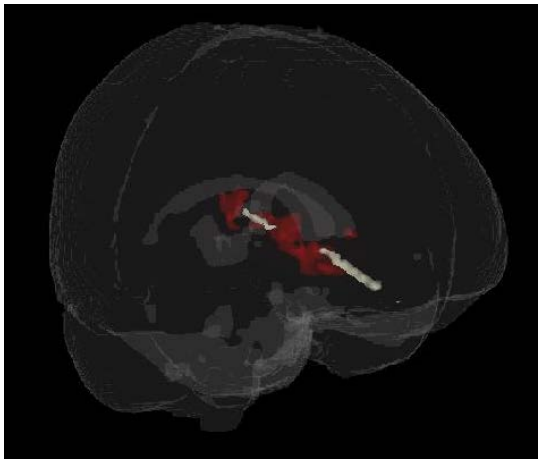
+20 Hr.

+42 Hr.

+52 Hrs.

3D post-op & post rt-PA

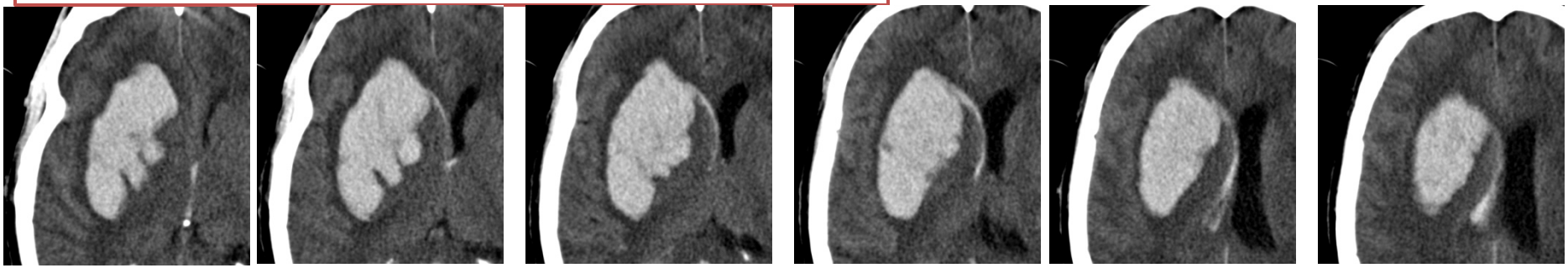




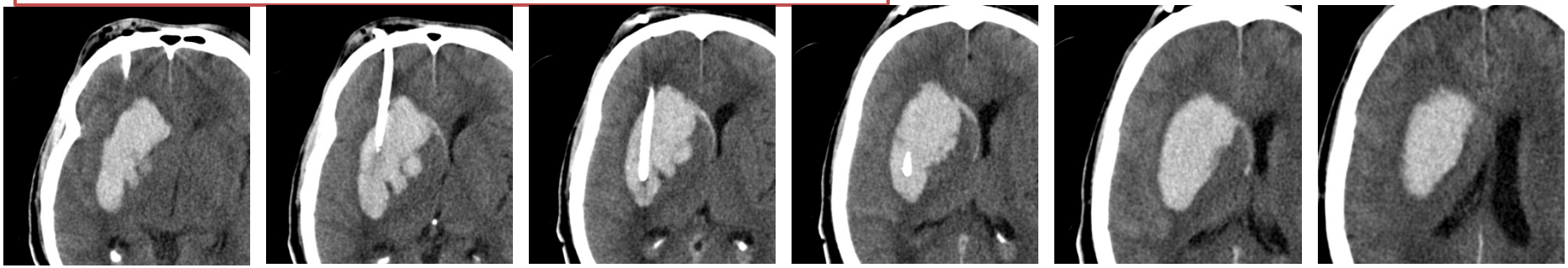
102-367

Stability Volume: 53.93
EOT Volume: 7.08
% Reduction: 86.87
Catheter Score: 116.5

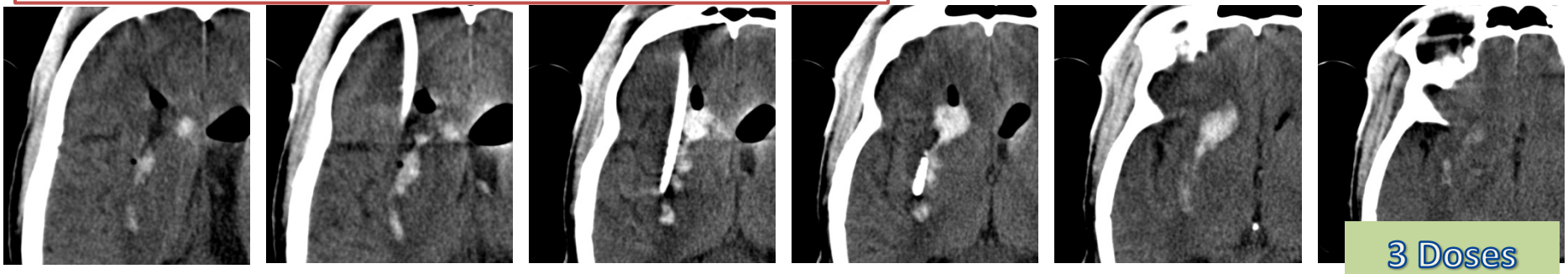
Stability CT Scan 04-Mar-10 8:41



Post-Surgery CT Scan 05-Mar-10 17:21

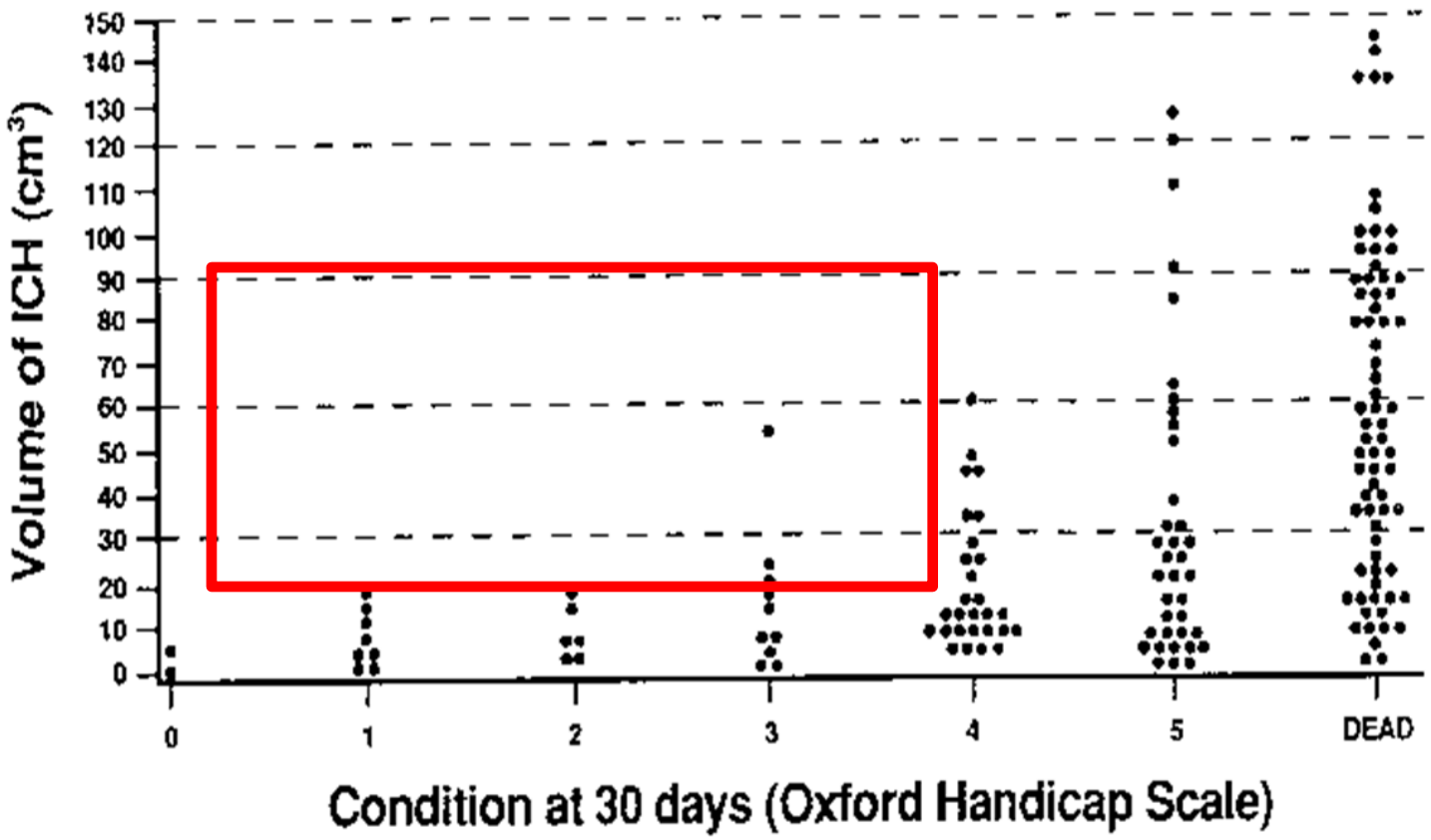


End of Treatment Scan 07-Mar-10 10:20



3 Doses

Effect of ICH Volume on Mortality



Broderick et. al *Stroke.* 1993;24:987-993

Key I/E Criteria

Exclusion

- Infratentorial ICH
- Vascular malformation or brain tumor
- Irreversibly impaired brainstem function

Inclusion

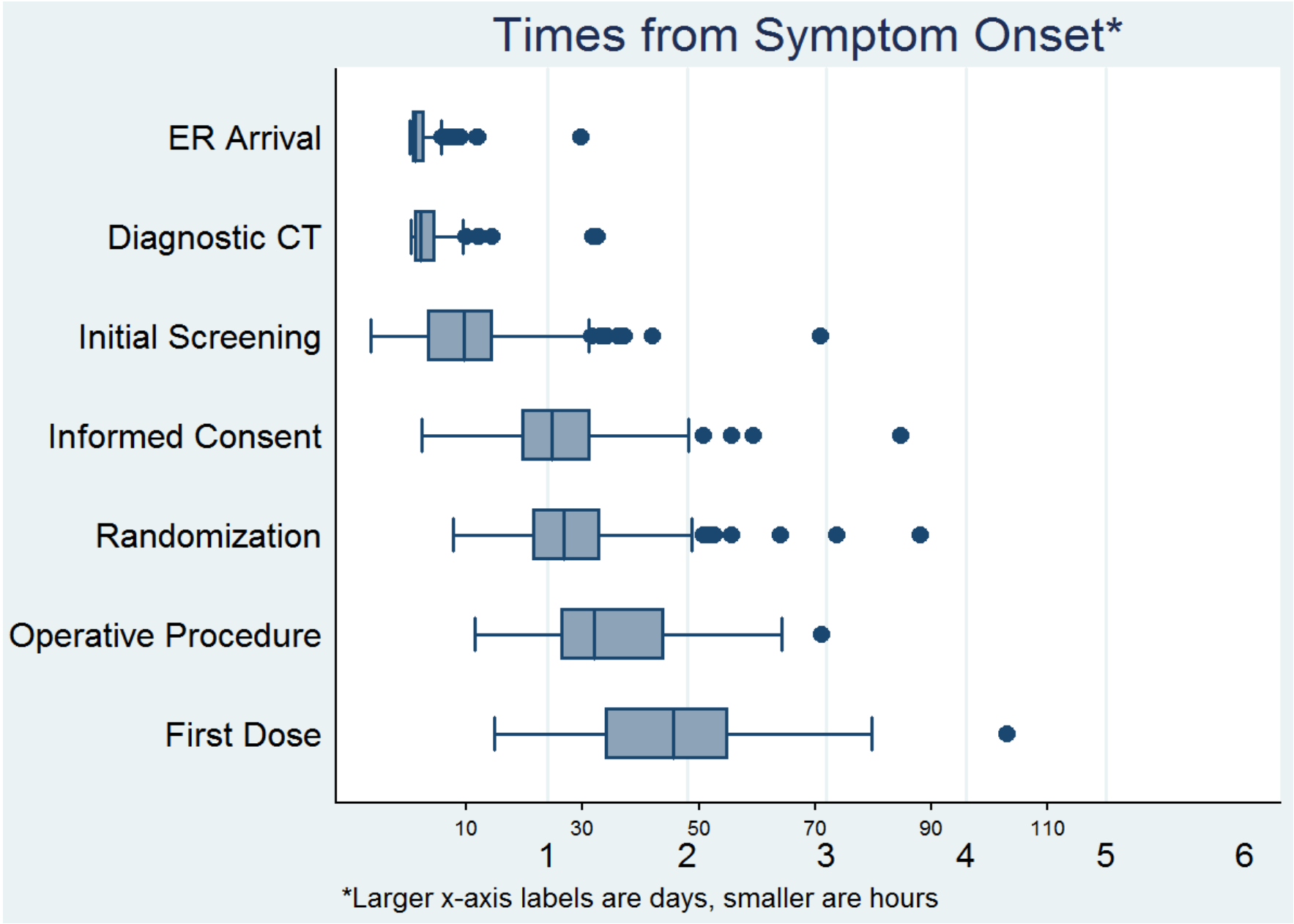
- Age 18-75
- GCS $\leq$ 13 or NIHSS $\geq$ 6
- Spontaneous supratentorial ICH $\geq$ 25cc
- Stable clot at second CT scan performed $\geq$ 6 hours after diagnosis

Baseline Demographics

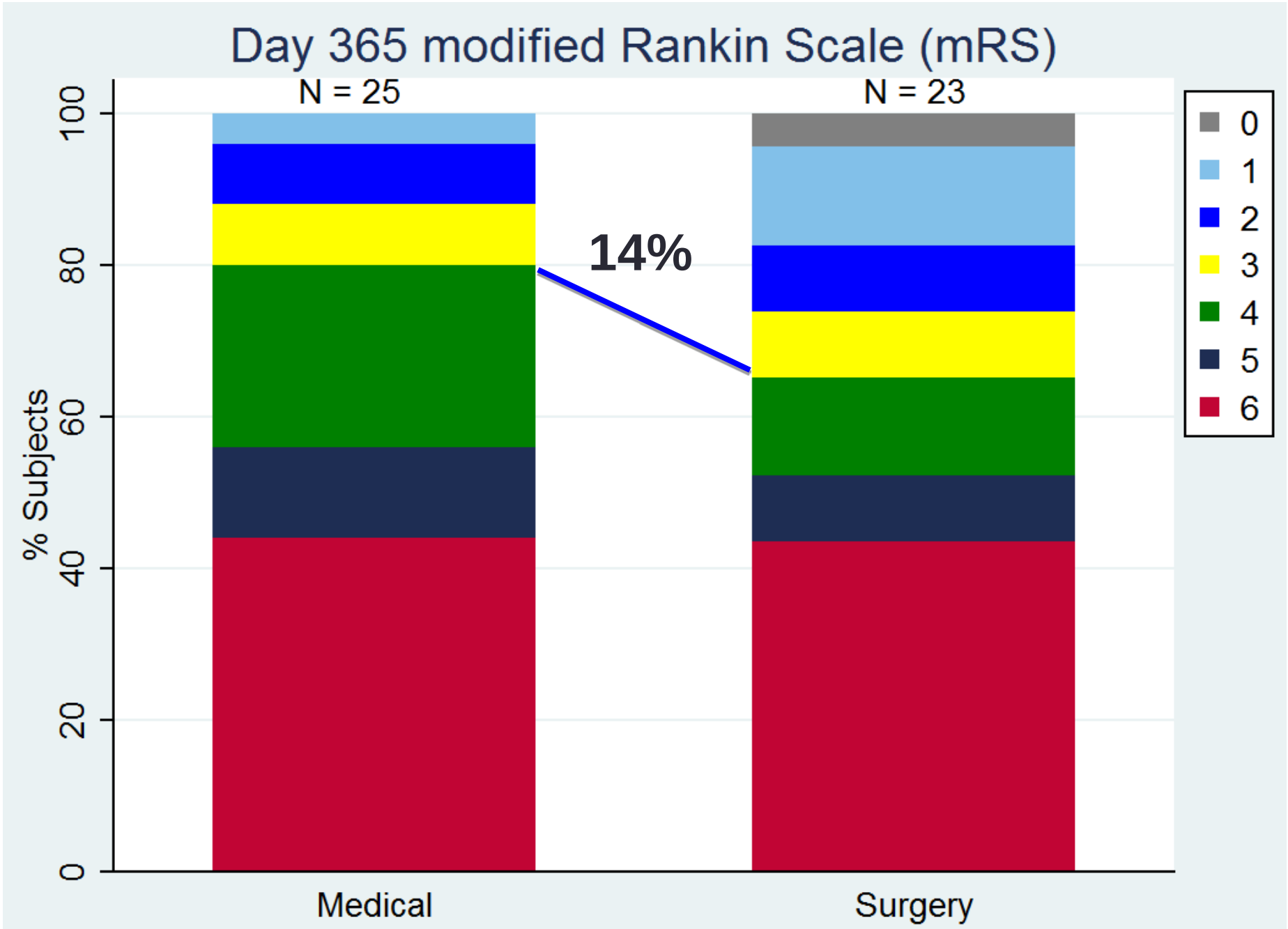
Characteristic	Medical N=42	Surgical N=54	Total N=96
Mean Age (SD)	61.1 (12.3)	60.7 (11.0)	60.9 (11.5)
Male	66.7%	64.8%	65.6%
Race			
Caucasian	54.8%	55.6%	55.2%
African American	26.2%	33.3%	30.2%
Asian or Pacific Islander	4.8%	3.7%	4.2%
Hispanic	11.9%	7.4%	9.4%
HX of HTN	81.0%	90.7%	86.5%
HX of Diabetes	26.8%	25.9%	26.3%
HX of Seizure	12.2%	14.8%	13.7%
HX of ETOH	17.5%	31.5%	25.5%
HX of Tobacco	7.1%	31.5%	20.8%
HX of Cocaine	7.1%	7.4%	7.3%

ER Presentation

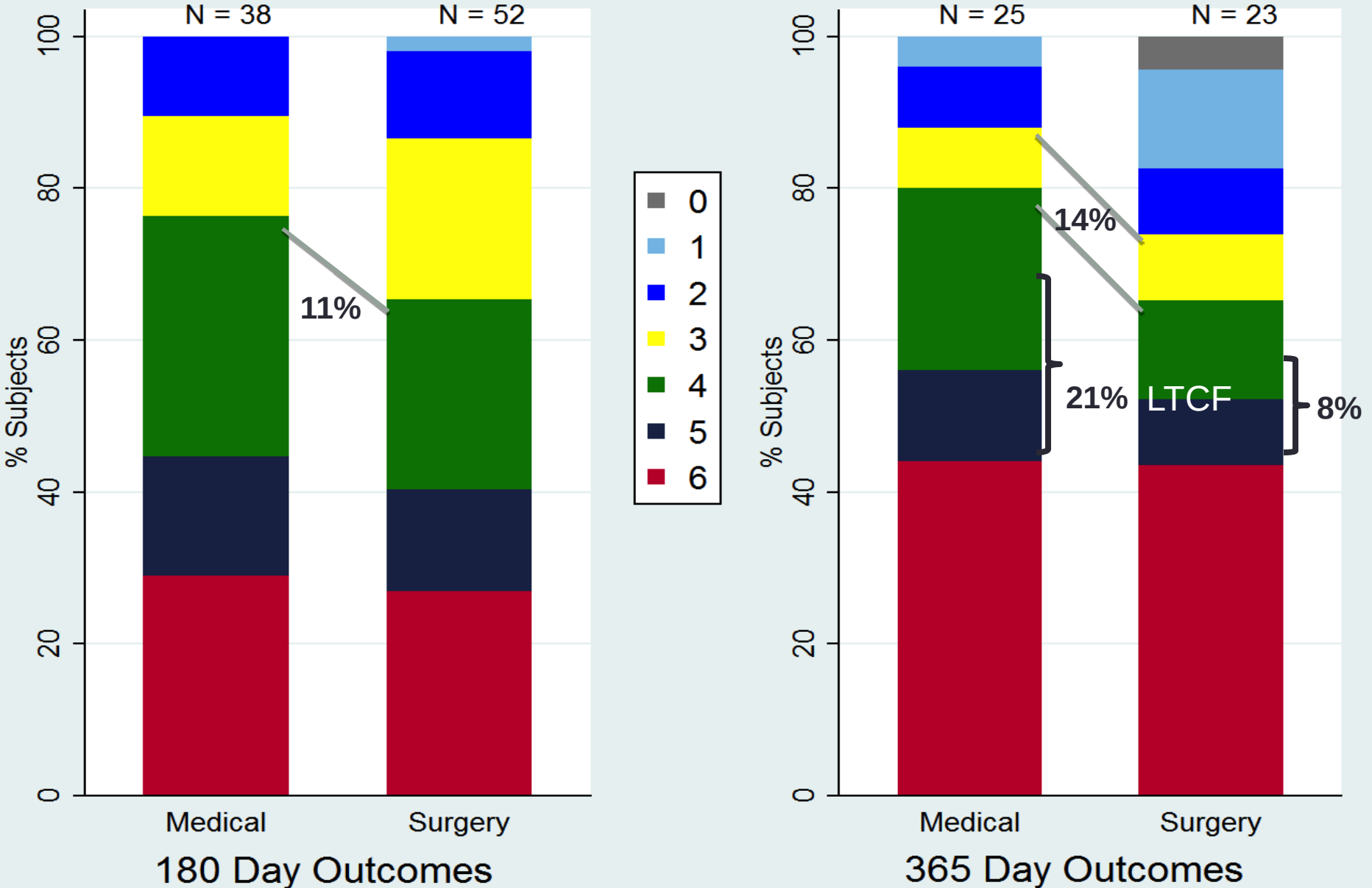
Presenting Parameter X (SD)		Medical N=42	Surgical N=54	Total N=96
ER Presentation SBP		186.7 (34.1)	186.4 (33.0)	186.5 (33.3)
ER Presentation DBP		101.9 (20.4)	106.8 (27.7)	104.6 (24.7)
ER Presentation MAP		130.2 (22.8)	133.2 (27.4)	131.9 (25.4)
ER Presentation GCS Total		11.6 (3.2)	11.4 (3.2)	11.5 (3.2)
Diagnostic ICH Volume		34.0 (15.8)	43.3 (22.5)	39.2 (20.3)
Diagnostic IVH Volume		1.6 (4.1)	4.3 (8.9)	3.2 (7.3)
Clot Location				
	Lobar	35.7%	33.3%	34.4%
	Deep	64.3 %	66.7 %	65.6%


Times from Symptom Onset*
ER Arrival
Diagnostic CT
Initial Screening
Informed Consent
Randomization
Operative Procedure
First Dose
10
30
50
70
90
110
1
2
3
4
5
6
*Larger x-axis labels are days, smaller are hours

What we learned about recovery

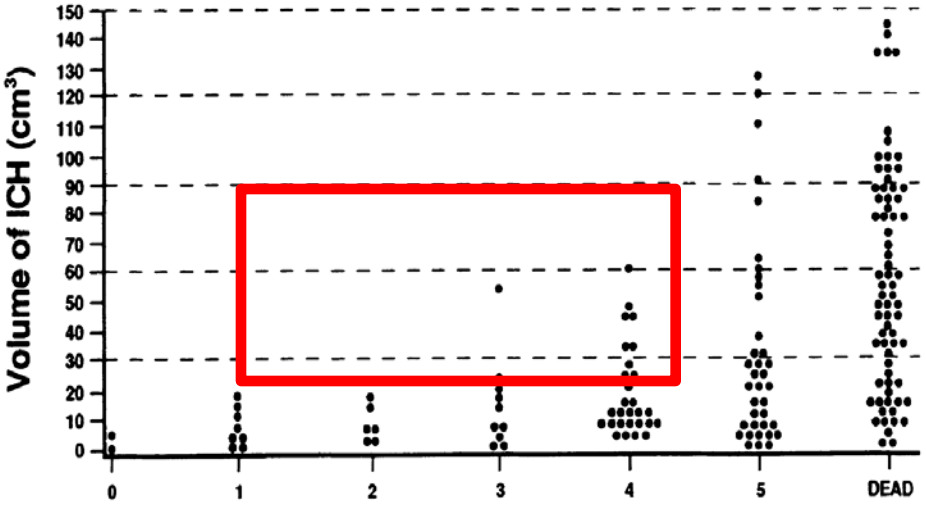

Day 365 modified Rankin Scale (mRS)
N = 25
N = 23
14%
% Subjects
0
20
40
60
80
100
Medical
Surgery
0
1
2
3
4
5
6

180 & 365-Day mRS



30-Day Outcomes Change With MIS+rt-PA

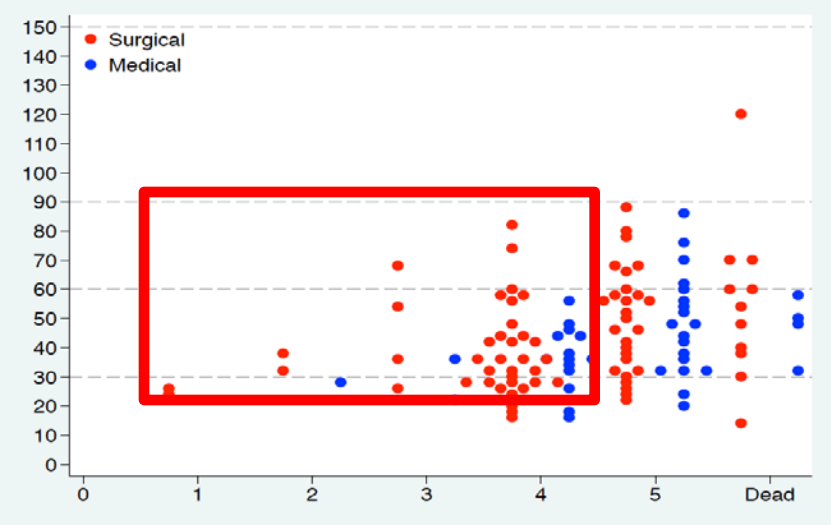
Cincinnati 1988



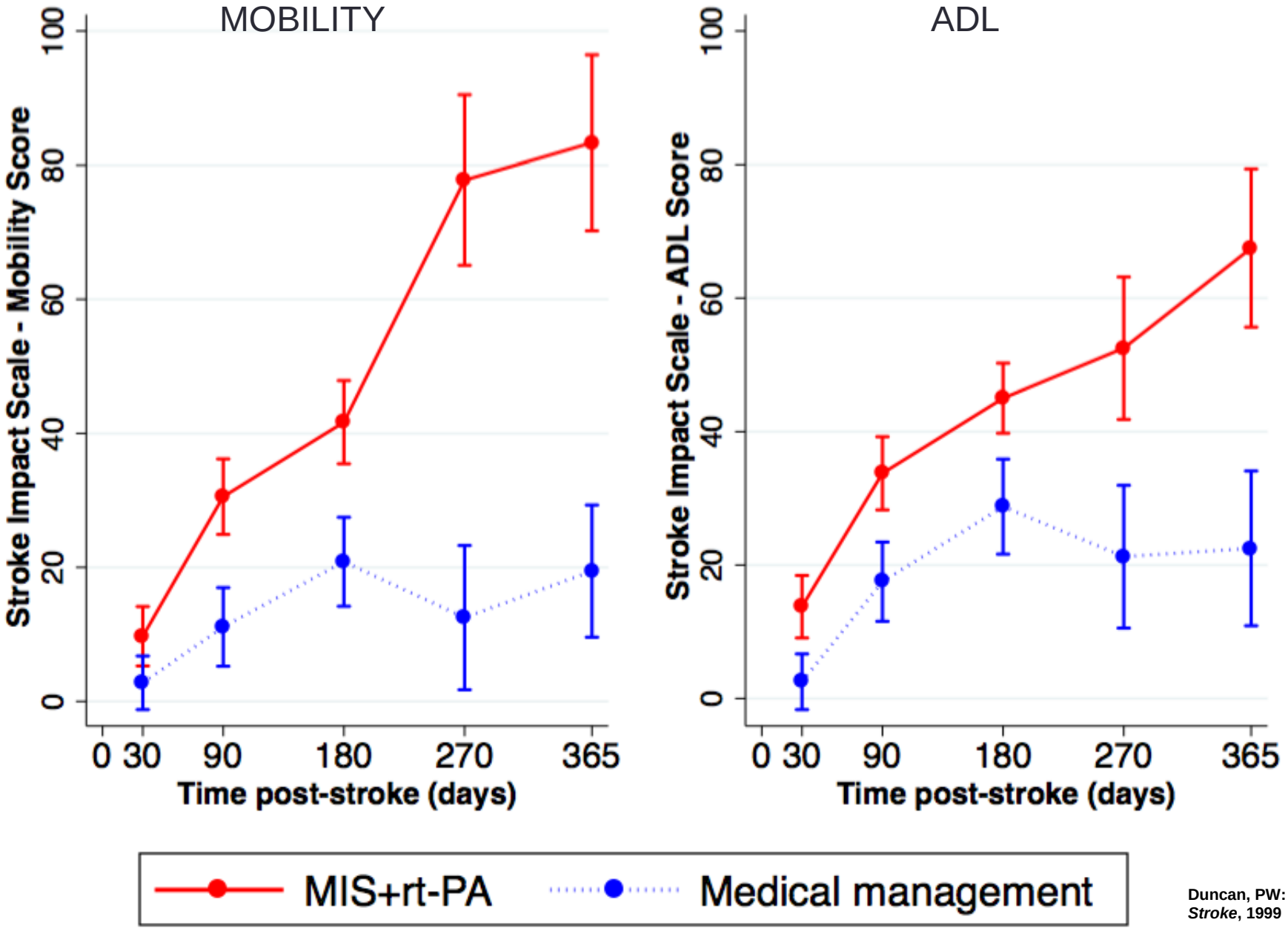
Oxford Handicap Scale

Broderick et. al *Stroke.* 1993;24:987-993

MISTIE II 2013

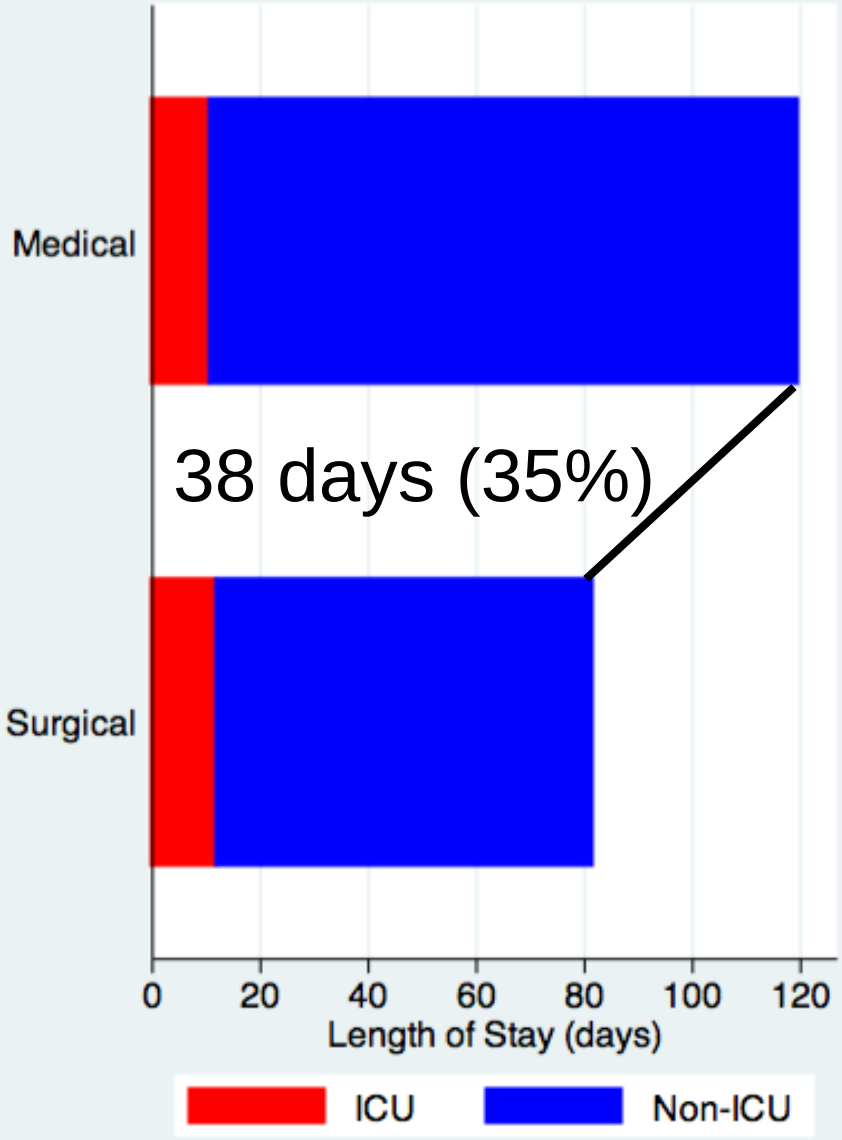


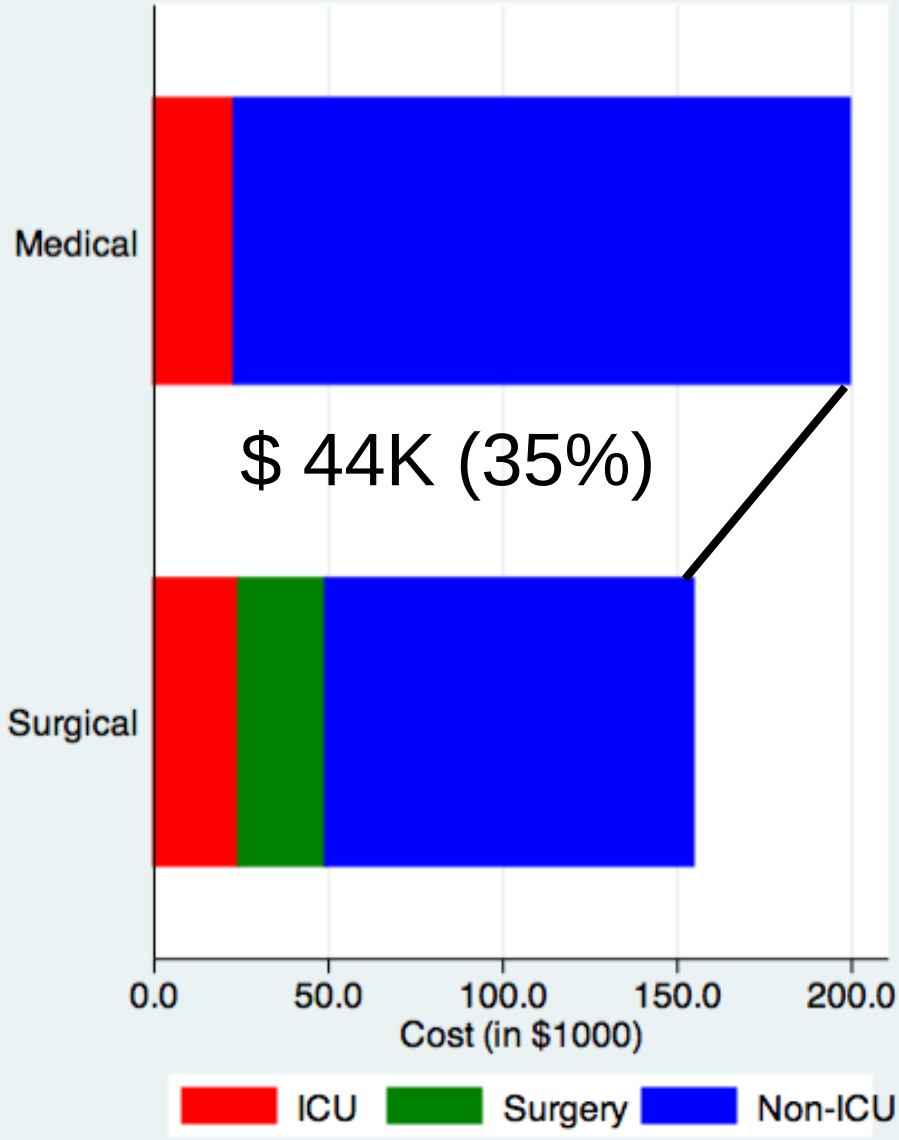
mRankin Scale



Duncan, PW: *Stroke*, 1999

Length of Stay and Cost by Treatment Arm



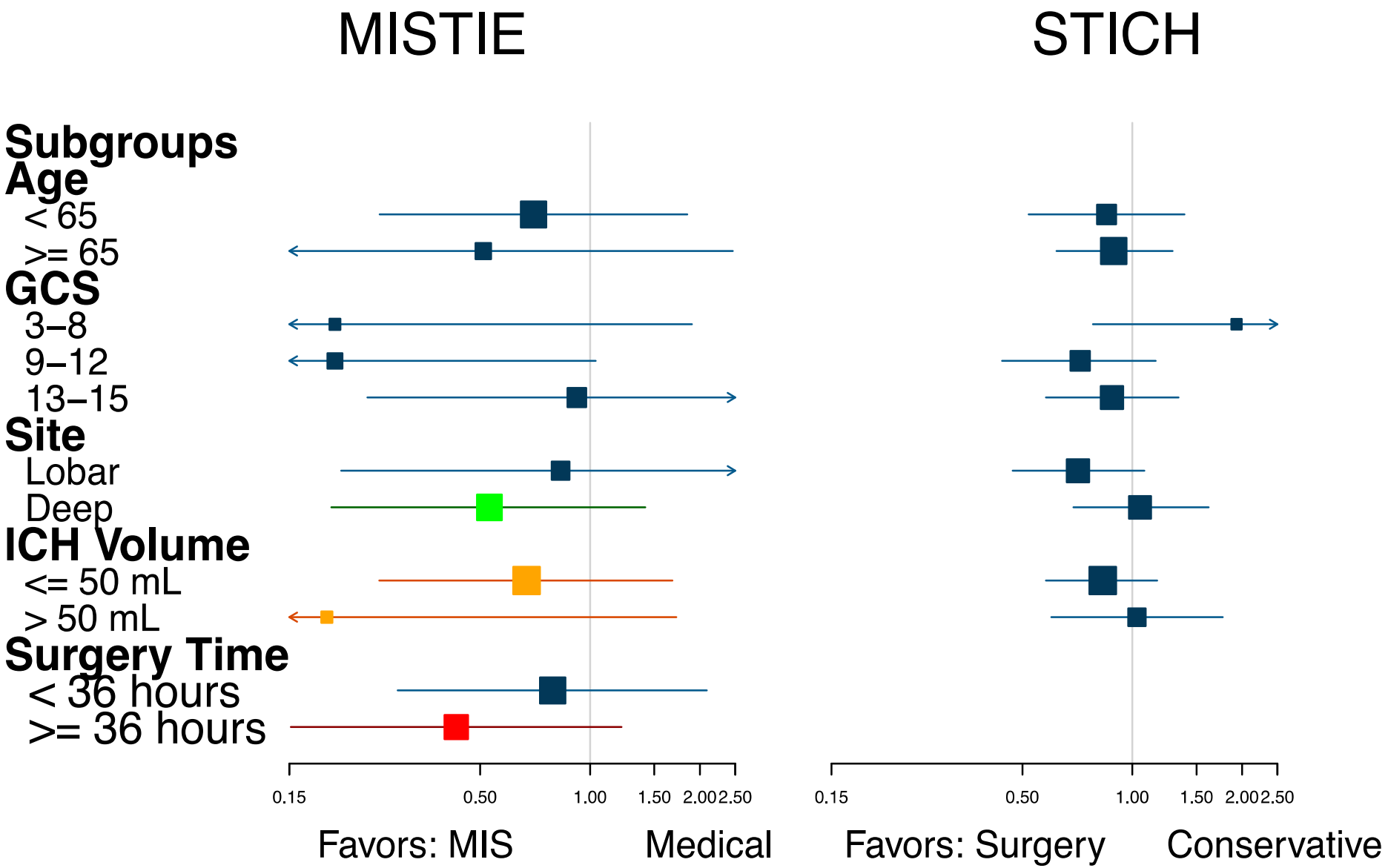


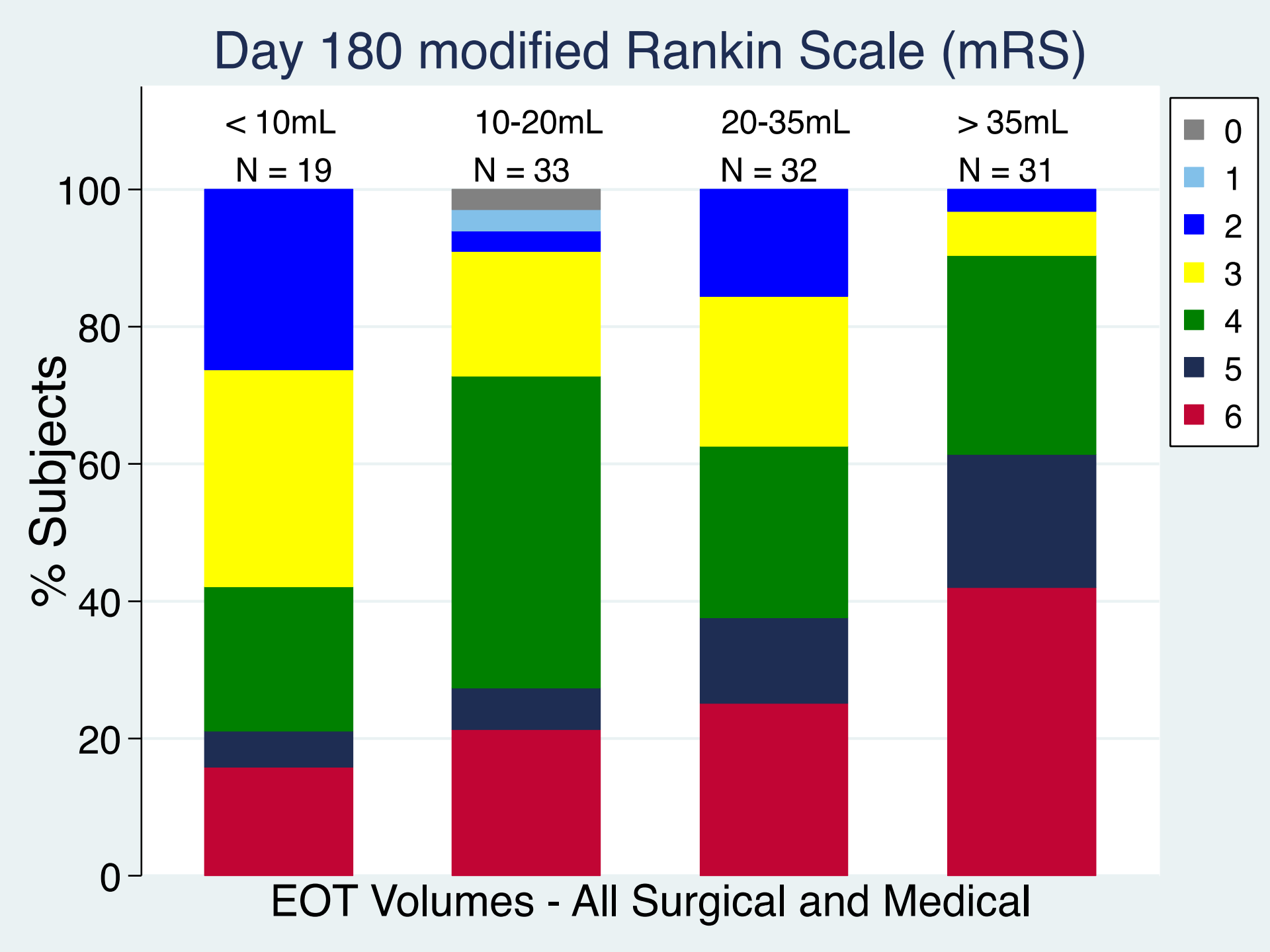
Factors Affecting Functional Outcome

ITT (n= 83)

	Univariate Analysis	Multivariate Models	
ICH Severity Parameters	**Odds Ratio of mRS>3 (p-value)**		
		Model 1	Model 2
Age per 1 year	1.05 (0.029)	1.08 (0.007)	1.09 (0.004)
Stability ICH per 10 cc	1.52 (0.009)	1.10 (0.581)	1.01 (0.971)
Enrollment Total GCS Score	0.63 (<0.001)	0.59 (<0.001)	0.57 (<0.001)
Surgical vs. Medical arm	0.67 (0.407)	NA	NA
End-of-treatment ≤ 15 ml ~ 3-day volume vs. >15 ml	0.33 (0.038)	NA	0.27 (0.062)

Subgroup treatment effect: odds mRS >3




Day 180 modified Rankin Scale (mRS)
< 10mL
N = 19
10-20mL
N = 33
20-35mL
N = 32
> 35mL
N = 31
0
1
2
3
4
5
6
100
80
60
40
20
0
% Subjects
EOT Volumes - All Surgical and Medical

What this means

The greater the reduction in clot size
the better the patient outcome.

Volume reduction matters!

MISTIE II – Benefits summary

Mechanism

- Reduction of clot burden
- “Saving tissue at risk”
- 2° injury occurs over days

Benefits

- Most likely MIS increases independence
- Appears to improve function & decrease cost

Upcoming MISTIE IM

On behalf of MISTIE III Trial, NIH/NINDS, and Genentech Inc., we would like to invite you to attend the

2014 MISTIE III Investigator-Coordinator Meeting

Who should attend?	**PIs, Neurosurgeons, & Coordinators**
When:	**August 22-24, 2014 (Friday 6:30 PM –Sunday 3 PM)**
Where:	**Westin BWI** **1110 Old Elkridge Landing Rd** **Linthicum Heights, MD 21090**

MISTIE III Coordinating Center

Daniel F. Hanley	Study Chairman & Principal Investigator
Wendy Ziai	Medical Monitor
Karen Lane	Project Director
Nichol McBee	Clinical Program Manager
Steve Mayo	Emissary International Monitoring
Janet Mighty	Pharmacy Manager
Andrew Mould	Reading Center Manager
Issam Awad	Co-PI, Chicago Surgical Center Director
Mario Zuccarello	Co-PI, Cincinnati Surgical Center Director
Kennedy Lees	University of Glasgow Outcomes Center
Claudia Moy	Program Official, NIH/NINDS
Scott Janis	Project Scientist, NIH/NINDS

MISTIE III Data Management Center

Richard Thompson	PI, Executive Director
Marie Diener-West	Senior Biostatistics Advisor
Michael Rosenblum	Biostatistician, Study Design
Elizabeth Sugar	Unblinded Biostatistician
Gayane Yenokyan	Biostatistician, Outcomes Research
Carol Thompson	Biostatistician
John Muschelli	Biostatistician/Analyst
Josh Betz	Biostatistician/Analyst
Andre Hackman	Director, Data Informatics Services Core
Rachel Dlugash	Senior Research Data Manager
Malathi Ram	Data Manager
Gwendolyn Clemens	Data Manager

Thank you