INTERVENTIONAL MANAGEMENT OF STROKE TRIAL III

Supported by: NIH/NINDS

PI: Joseph P. Broderick, MD
Co PI: Thomas Tomsick. MD
University of Cincinnati Clinical Coordinating and Angiographic Imaging Center
Grant Number: U01 – NS052220

PI: Yuko Palesch, PhD
Statistics & Data Coordinating Center
Medical University of South Carolina
Grant Number: U01 – NS054630

PI: Andrew Demchuk, MD
CT Image Analysis Center
University of Calgary

ClinicalTrials.gov Indentifier
NCT 00359424

IMS III: Final Results and Key Subgroup Analysis Lessons Learned for the future

Andrew M. Demchuk, MD FRCPC
Director, Calgary Stroke Program
Professor, Dept Clinical Neurosciences and Radiology
Heart and Stroke Foundation Chair in Stroke Research
University of Calgary

UNIVERSITY OF Cincinnati

UNIVERSITY OF CALGARY MEDICINE

MUSC MEDICAL UNIVERSITY of SOUTH CAROLINA

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

Disclosure Slide

- I have received honorarium from Covidien (supplier of SOLITAIRE FR stentriever).

- IMS-3- Exec committee, CT core lab PI
- ESCAPE- Neuro-PI
- REVASCAT- CT core lab co-PI
- CLOTBUST-ER – CTA substudy PI
- ARGIS-2 – CTA substudy core lab PI
- ENCHANTED – International Advisory Committee

- I have no stocks or direct investments with pharmaceutical or device companies involved in stroke

INTERVENTIONAL MANAGEMENT OF STROKE TRIAL III

Supported by: NIH/NINDS

PI: Joseph P. Broderick, MD
Co PI: Thomas Tomsick. MD
University of Cincinnati Clinical Coordinating and Angiographic Imaging Center
Grant Number: U01 – NS052220

PI: Yuko Palesch, PhD
Statistics & Data Coordinating Center
Medical University of South Carolina
Grant Number: U01 – NS054630

PI: Andrew Demchuk, MD
CT Image Analysis Center
University of Calgary

ClinicalTrials.gov Indentifier
NCT 00359424

IMS III Support

GRANT SUPPORT:

NIH/NINDS Grant Numbers:
UC U01NS052220
MUSC U01NS054630 and U01NS077304.

FDA IND: #5785

Study Drug: Genentech,Inc.
Microcatheters: EKOS Corp., Concentric Inc., Cordis Neurovascular, Inc.

UNIVERSITY OF Cincinnati

UNIVERSITY OF CALGARY MEDICINE

MUSC MEDICAL UNIVERSITY of SOUTH CAROLINA

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

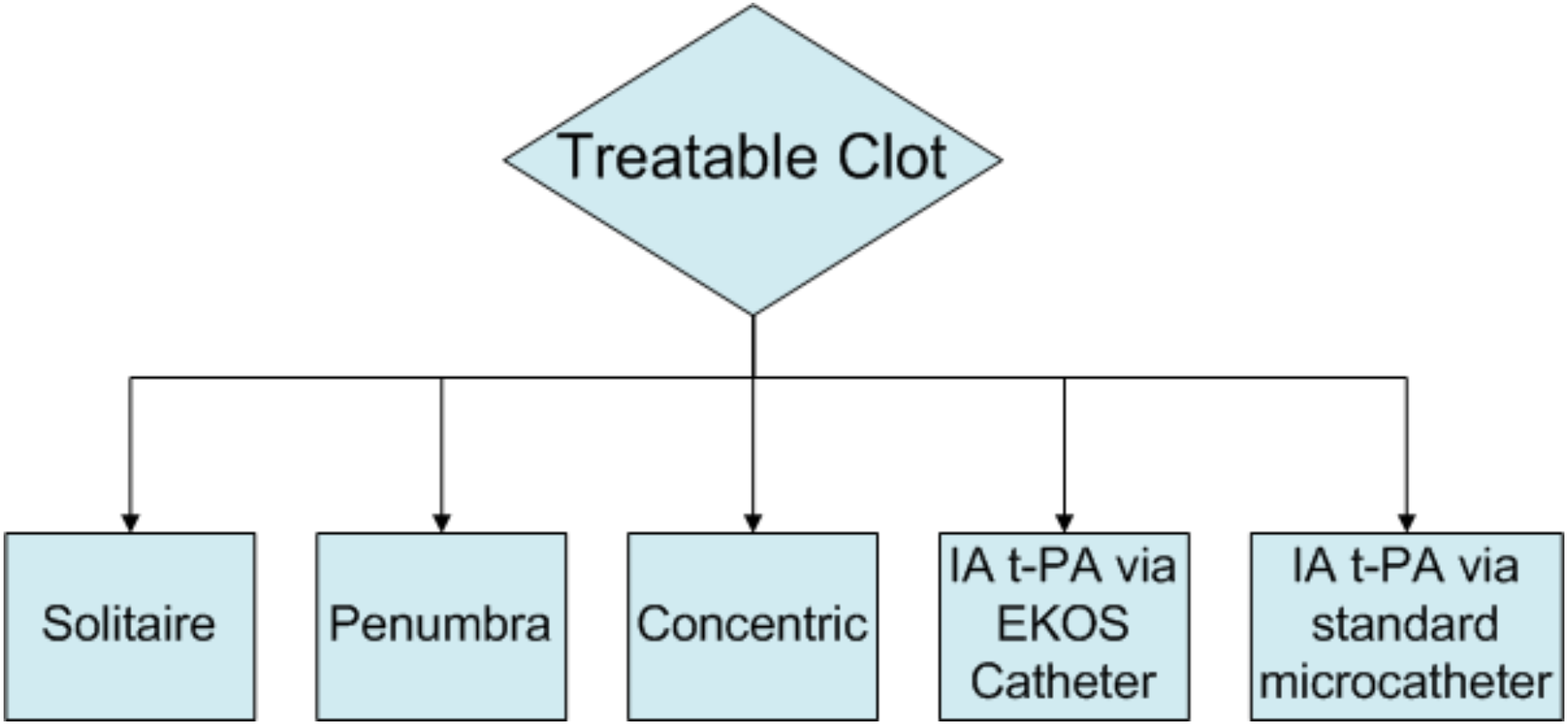
Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke

Joseph P. Broderick, M.D., Yuko Y. Palesch, Ph.D., Andrew M. Demchuk, M.D., Sharon D. Yeatts, Ph.D., Pooja Khatri, M.D., Michael D. Hill, M.D., Edward C. Jauch, M.D., Tudor G. Jovin, M.D., Bernard Yan, M.D., Frank L. Silver, M.D., Rüdiger von Kummer, M.D., Carlos A. Molina, M.D., Bart M. Demaerschalk, M.D., Ronald Budzik, M.D., Wayne M. Clark, M.D., Osama O. Zaidat, M.D., Tim W. Malisch, M.D., Mayank Goyal, M.D., Wouter J. Schonewille, M.D., Mikael Mazighi, M.D., Ph.D., Stefan T. Engelter, M.D., Craig Anderson, M.D., Ph.D., Judith Spilker, R.N., B.S.N., Janice Carrozzella, R.N., B.A., R.T.(R.), Karla J. Ryckborst, R.N., B.N., L. Scott Janis, Ph.D., Renée H. Martin, Ph.D., Lydia D. Foster, M.S., and Thomas A. Tomsick, M.D., for the Interventional Management of Stroke (IMS) III Investigators

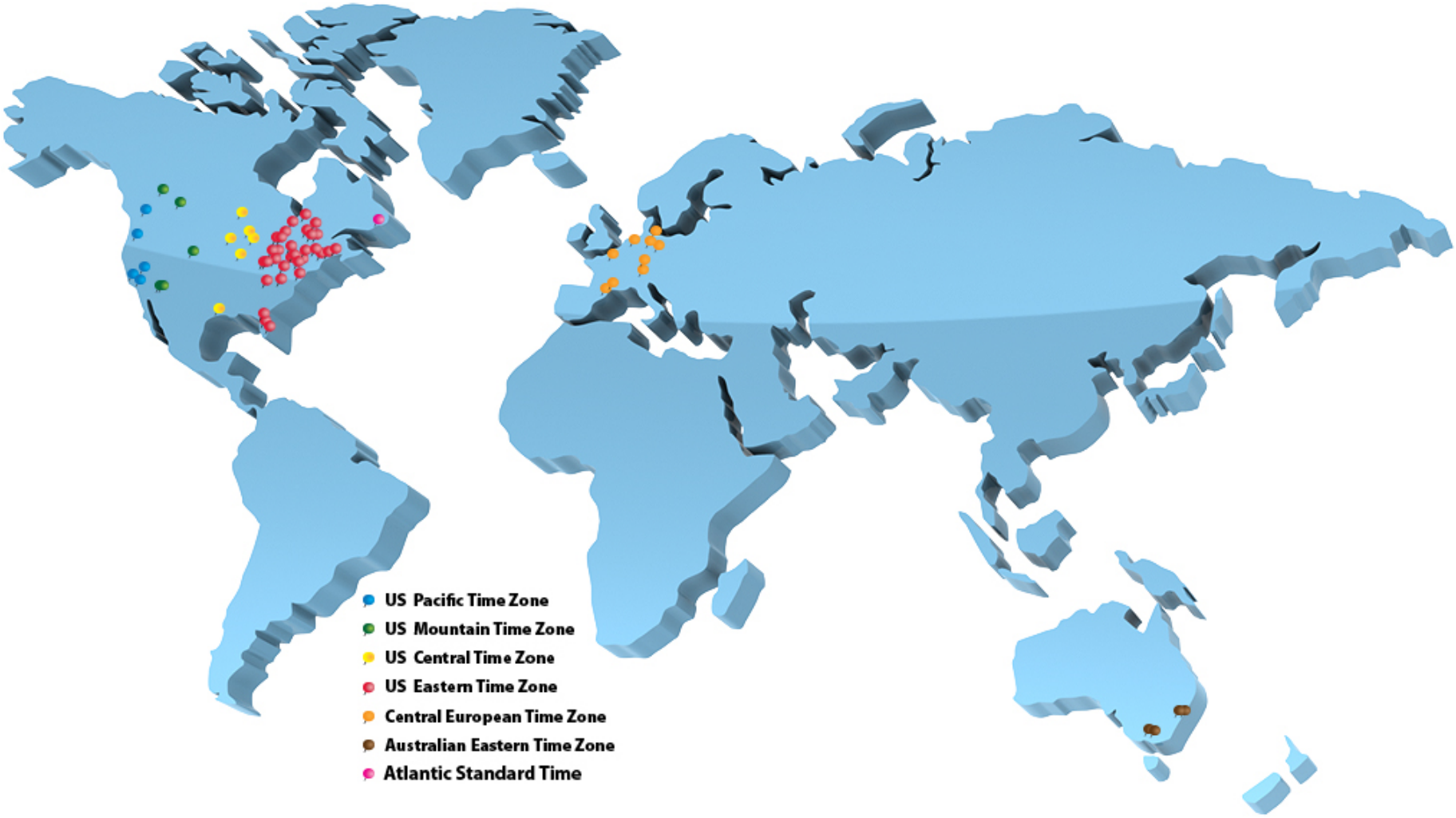
This article was published on February 8, 2013, at NEJM.org.

Key Design Features of IMS III

- Combined IV t-PA (0.6 mg/kg) + endo vs IV tPA (0.9 mg/kg)
- Planned **900** subjects
- **<3 hours** LSN time window
- **2 endo : 1 IV t-PA** ratio randomization
- Age **18-82** years
- **NIHSS >/= 10**, or NIHSS 8-9 with CTA evidence of ICA, M1 or basilar occlusion prior to initiation of IV t-PA
- Consent/randomization within first 40-minutes IV t-PA infusion



But *must* follow the instructions for use and could only choose one device. OK to also use endovascular t-PA via standard microcatheter if time remaining after use of device.



IMS III
INTERVENTIONAL
MANAGEMENT OF
STROKE

April 2012: Preplanned 2/3rd DSMB IMS III – Crossed Futility Boundary

- Upon recommendation of the DSMB, NINDS stopped enrollment because a predefined futility boundary was crossed, based upon the low conditional power, given an expected difference of 10% between the two groups and a sample size of 900. There were no significant safety concerns.

- 656 subjects had been enrolled.

No Significant Baseline Differences

Table 1. Characteristics of the Patients at Baseline.*

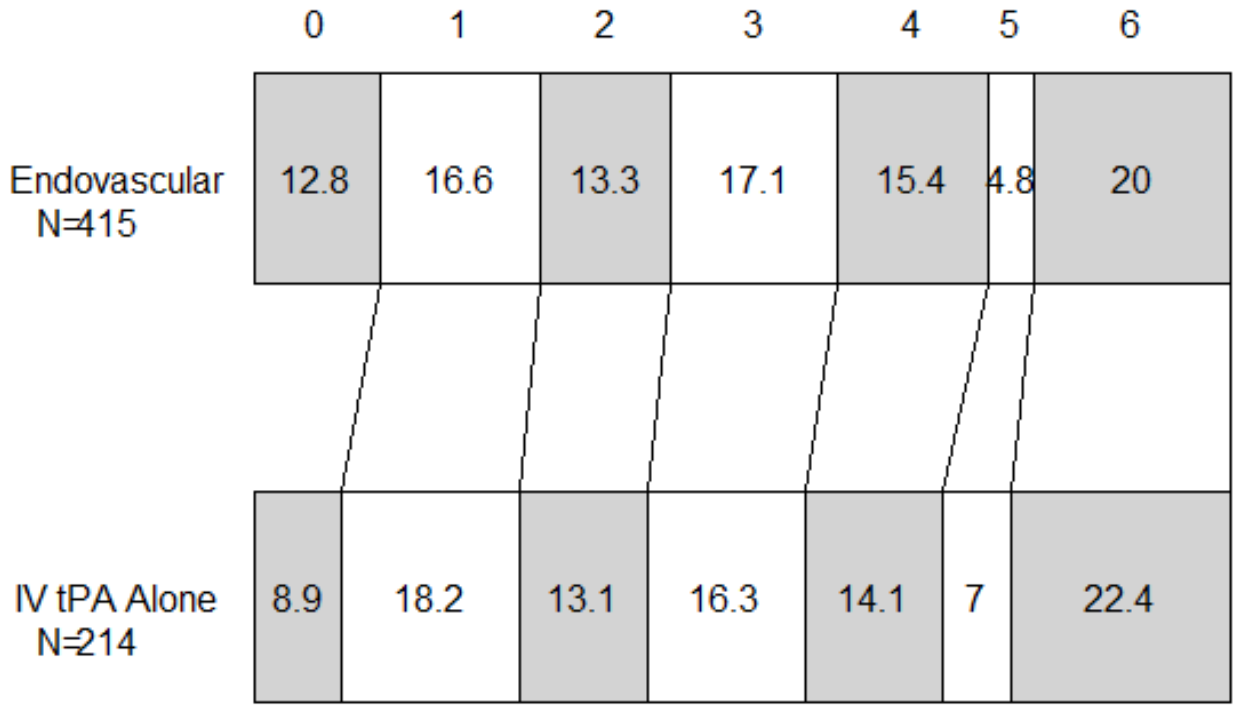
Characteristic	Endovascular Therapy (N = 434)	Intravenous t-PA Alone (N = 222)
Age — yr		
Median	69	68
Range	23–89	23–84
Male sex — no. (%)	218 (50.2)	122 (55.0)
Race or ethnic group — no. (%)†		
Black	51 (11.8)	19 (8.6)
Hispanic	11 (2.5)	12 (5.4)
NIHSS score‡		
Median	17	16
Range	7–40	8–30
ASPECTS of 8, 9, or 10 — no. (%)§	247 (56.9)	131 (59.0)
Presumptive location of stroke — no. (%)		
Left hemisphere	224 (51.6)	106 (47.7)
Right hemisphere	197 (45.4)	109 (49.1)
Brain stem or cerebellum	10 (2.3)	4 (1.8)
Unknown or multiple locations	3 (0.7)	3 (1.4)
Atrial fibrillation — no. (%)	153 (35.3)	70 (31.5)
History of hypertension — no. (%)	319 (73.5)	171 (77.0)
History of diabetes — no. (%)	94 (21.7)	54 (24.3)
History of congestive heart failure — no. (%)	50 (11.5)	31 (14.0)
History of coronary artery disease — no. (%)	102 (23.5)	72 (32.4)
History of hyperlipidemia — no. (%)	215 (49.5)	112 (50.5)
Serum glucose — mmol/liter	7.4±2.9	7.6±3.1
Time from stroke onset to initiation of intravenous t-PA — min	122.4±33.7	121.2±33.8

69 vs 68

17 vs 16

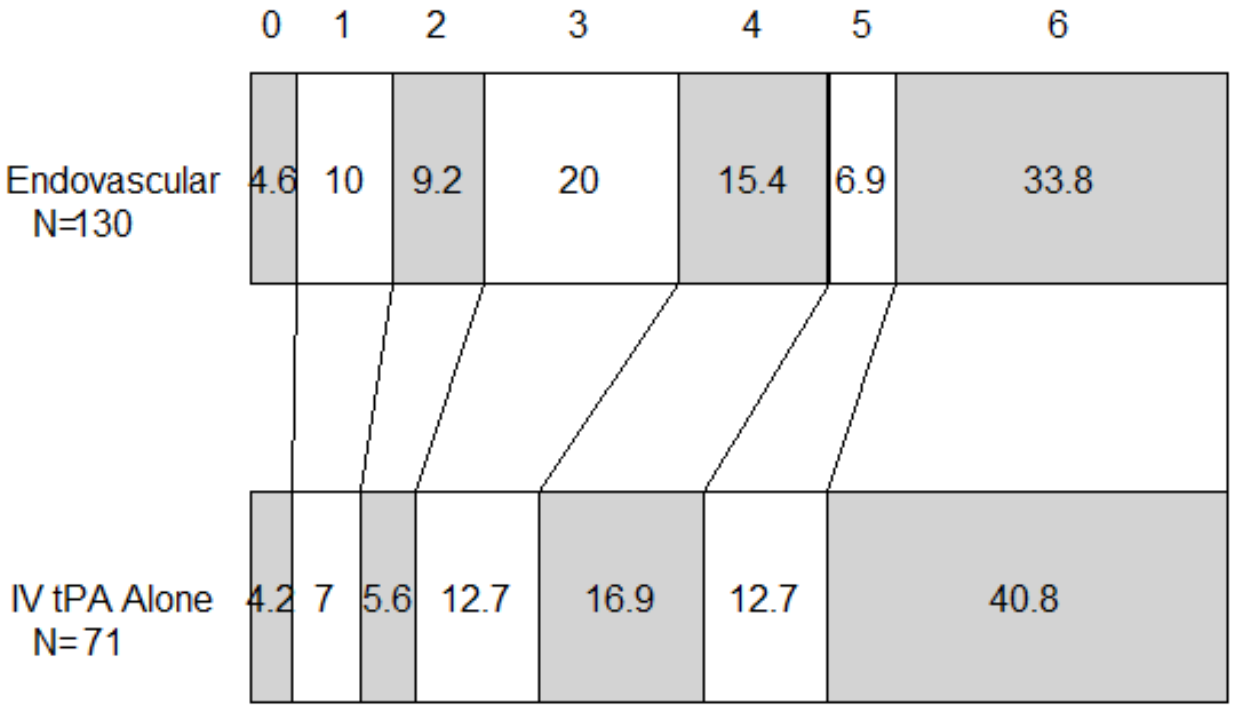
122 vs 121

90-Day Modified Rankin Scale Score Distribution All Subjects



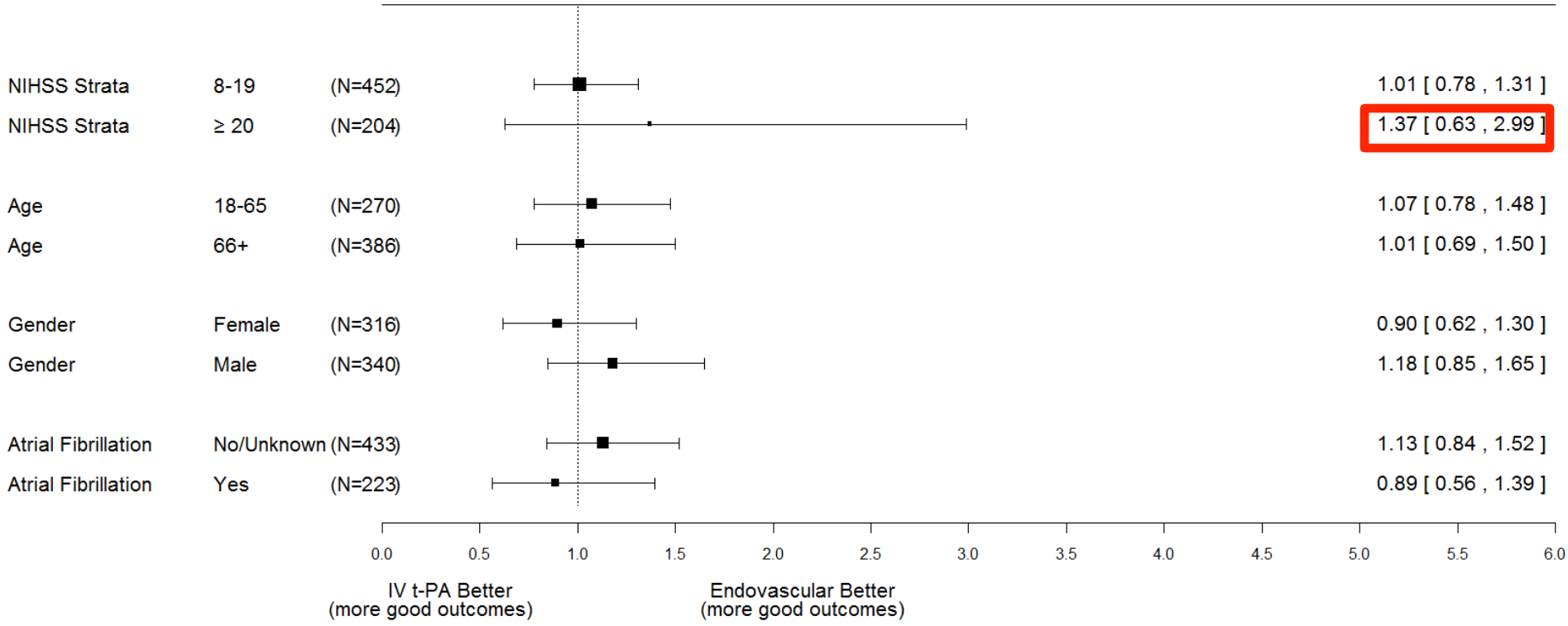
Differences between the two treatment groups across the entire distribution of the mRS ($p = 0.25$, van Elterin test)

90-Day Modified Rankin Scale Score Distribution by Treatment Group: Baseline NIHSS ≥ 20

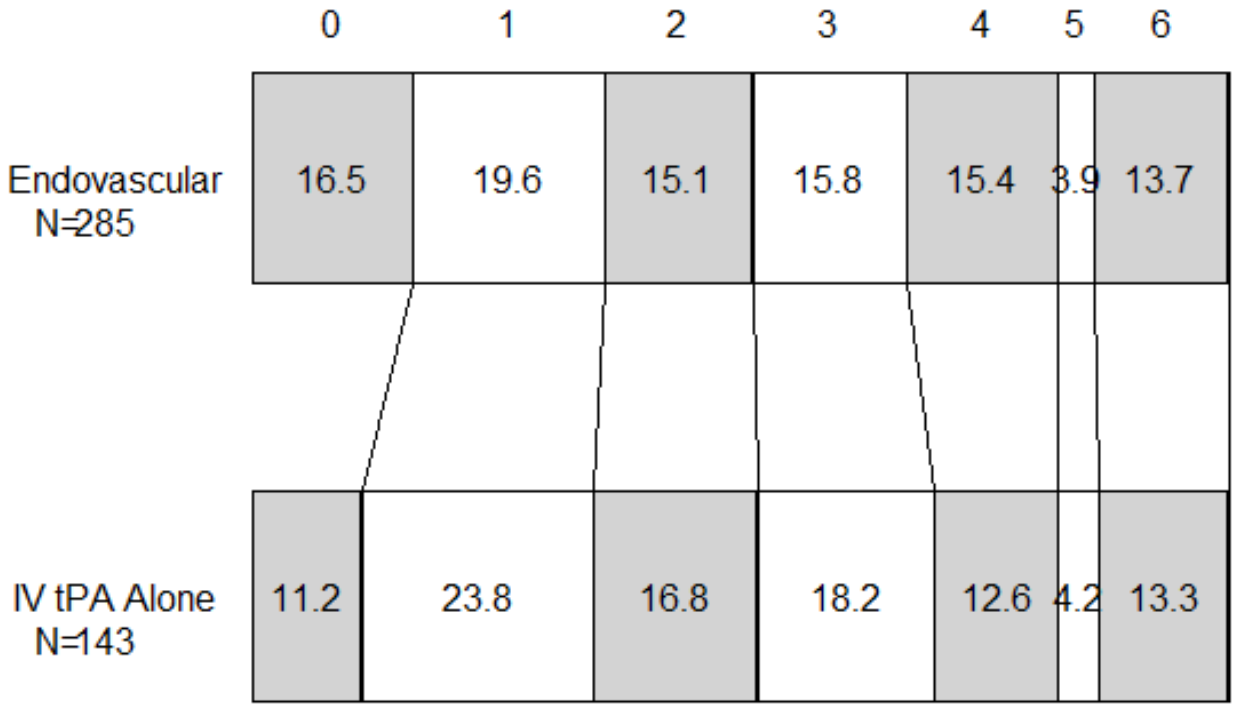


Differences between the two treatment groups across the entire distribution (p = 0.065)

NIHSS Strata, Age, Gender, and Atrial Fibrillation



90-Day Modified Rankin Scale Score Distribution by Treatment Group: Baseline NIHSS 8-19



Differences between the two treatment groups across the entire distribution for the ≤ 19 NIHSS stratum (p = 0.83)

INTERVENTIONAL MANAGEMENT OF STROKE TRIAL III

Supported by: NIH/NINDS

PI: Joseph P. Broderick, MD
Co PI: Thomas Tomsick. MD
University of Cincinnati Clinical Coordinating and Angiographic Imaging Center
Grant Number: U01 – NS052220

PI: Yuko Palesch, PhD
Statistics & Data Coordinating Center
Medical University of South Carolina
Grant Number: U01 – NS054630

PI: Andrew Demchuk, MD
CT Image Analysis Center
University of Calgary

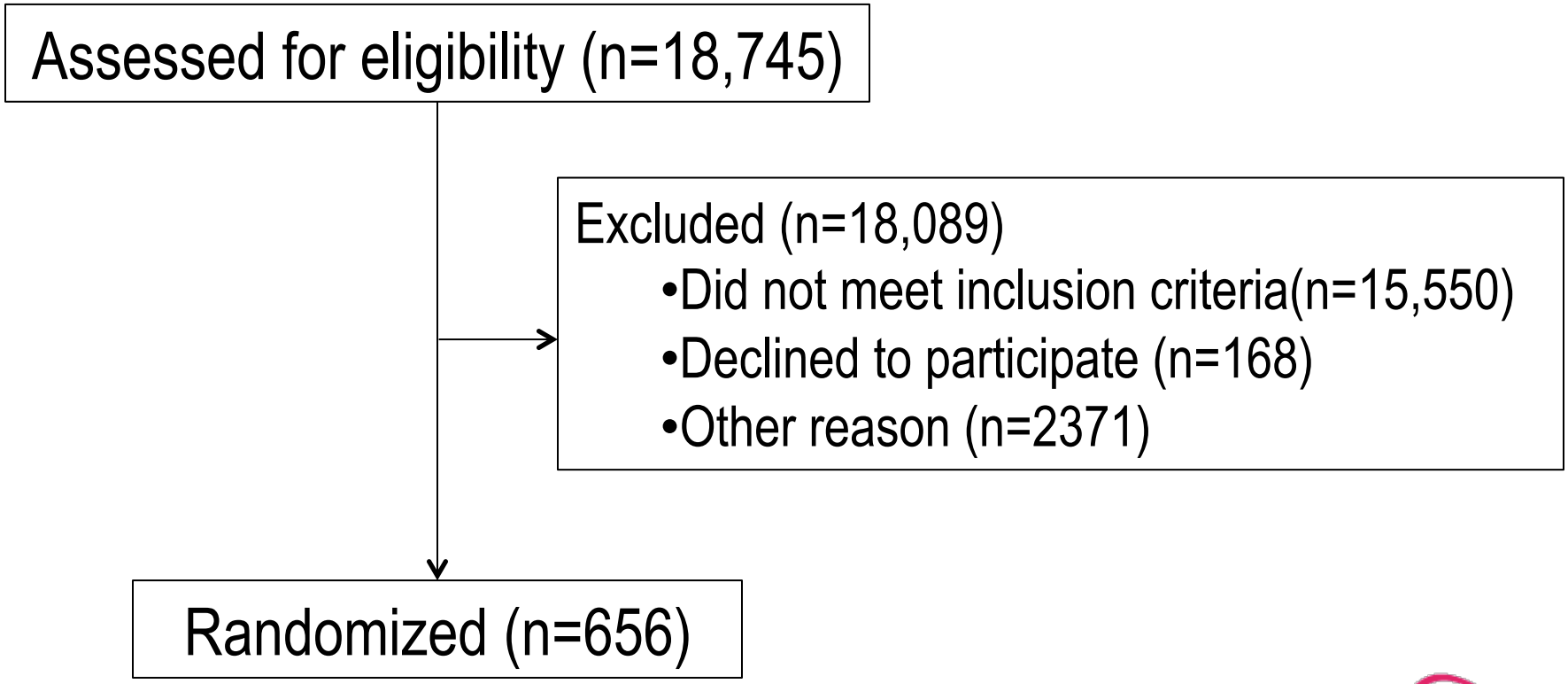
ClinicalTrials.gov Indentifier
NCT 00359424

A Perspective: What Lessons Should be Learned from IMS-III for the future

Study population enrolled

Pre-specified/post-hoc clinical/imaging analysis

Eligibility and Enrollment

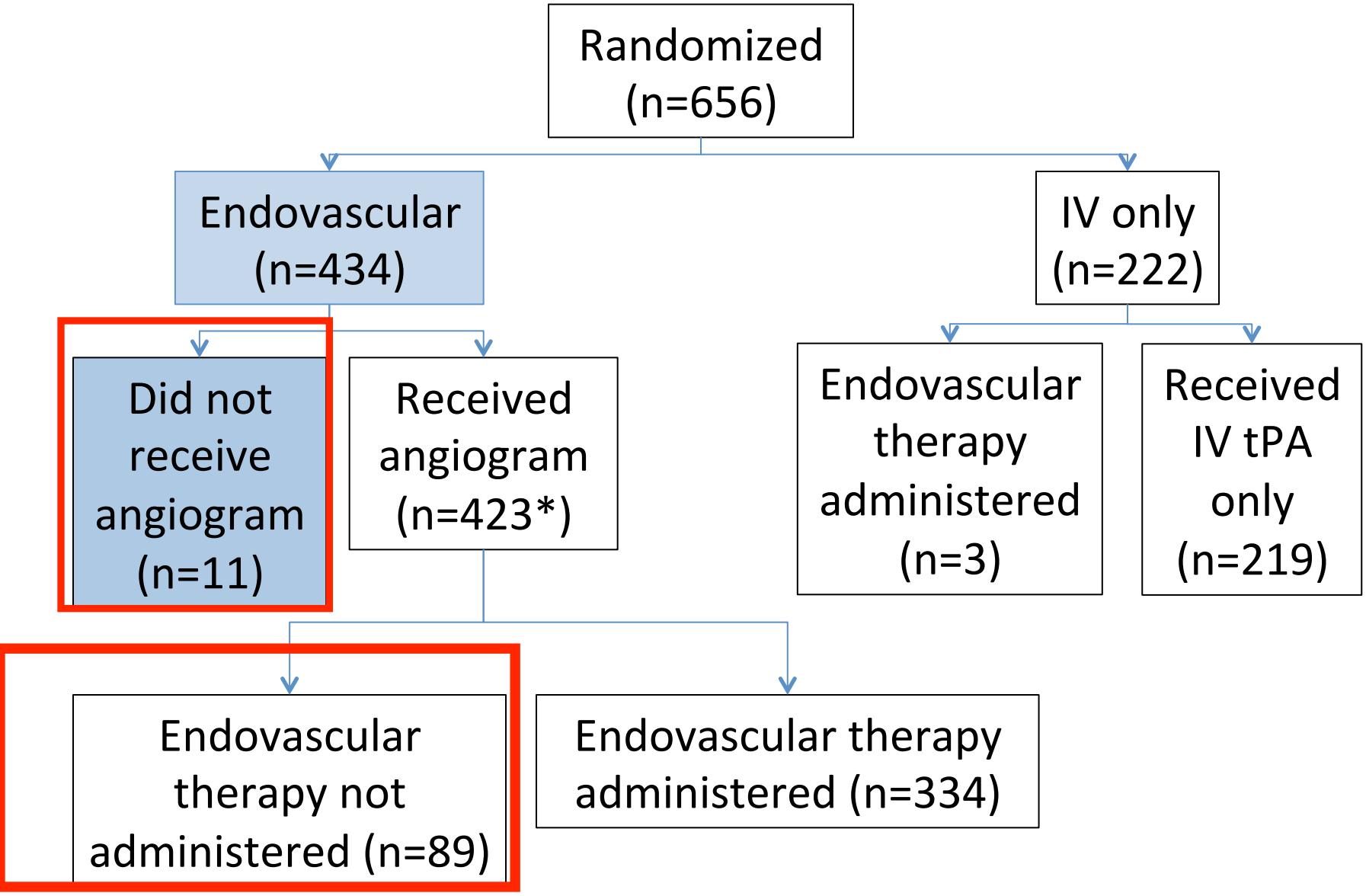


Lessons learned from IMS-3

All eligible patients weren't randomized at participating centres

- **No cherry-picking, enrol consecutive eligible patients**

Subject Accountability



* Includes 2 subjects treatment with IA therapy but with angiogram data not available

Lessons learned from IMS-3

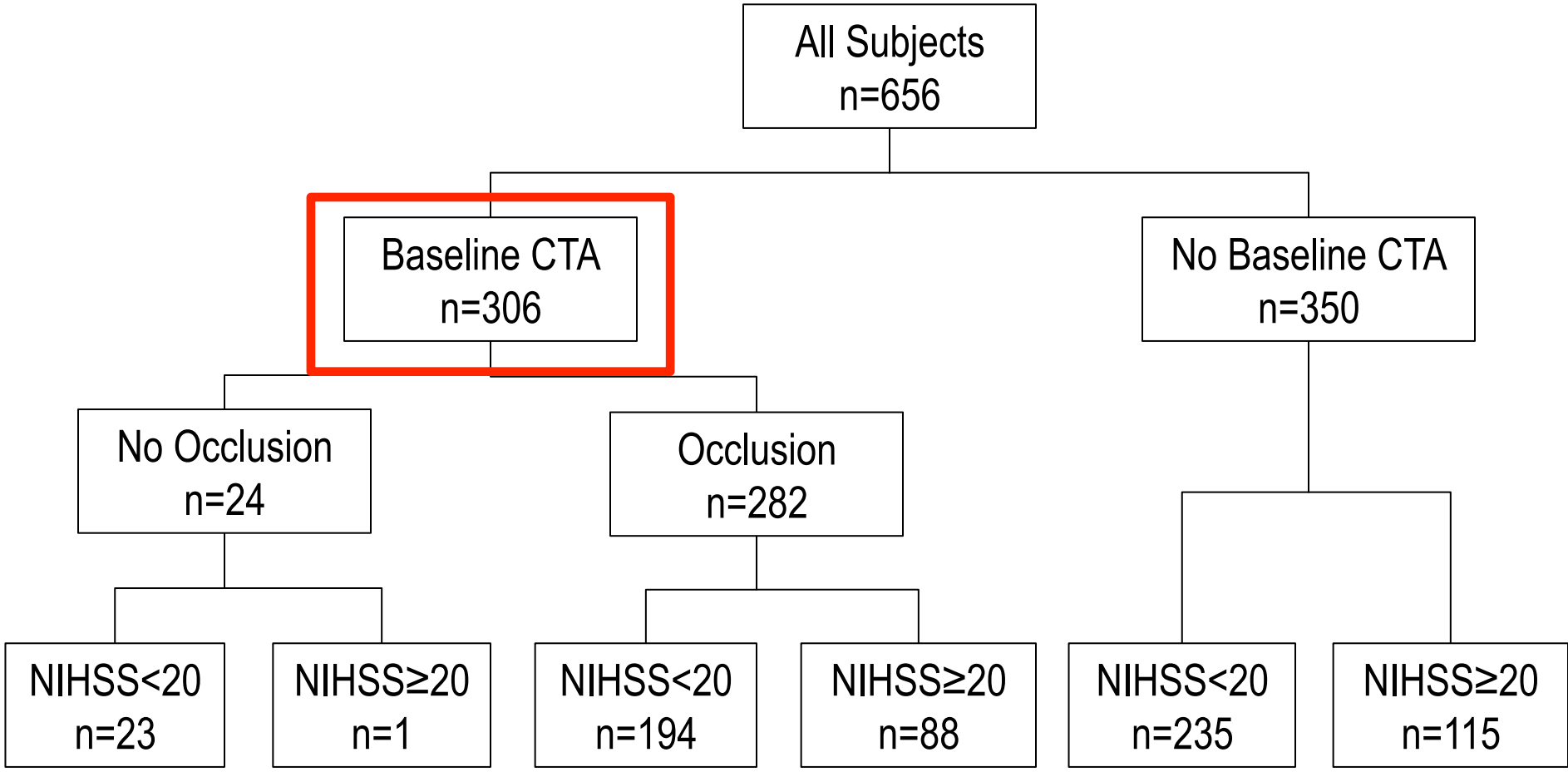
All eligible patients weren't randomized at participating centres

- No cherry-picking, enrol consecutive eligible patients

Patient selection did not confirm accessible/persistent occlusion

- **Baseline CTA or thrombus selection essential**

Enrollment by CTA and Treatment Group



24hr Recanalization by Occlusion Site

	Percent Recanalized of Subjects with 24 hour CTA (95% CI)		
Baseline Primary Occlusion Vessel Category	Endovascular	IV t-PA Only	Treatment Difference (95% CI)
All*	86.3% (79.6, 91.4)	64.7% (52.2, 75.9)	21.6% (8.9, 34.3)

INTERVENTIONAL MANAGEMENT OF STROKE TRIAL III

Supported by: NIH/NINDS

PI: Joseph P. Broderick, MD
Co PI: Thomas Tomsick. MD
University of Cincinnati Clinical Coordinating and Angiographic Imaging Center
Grant Number: U01 – NS052220

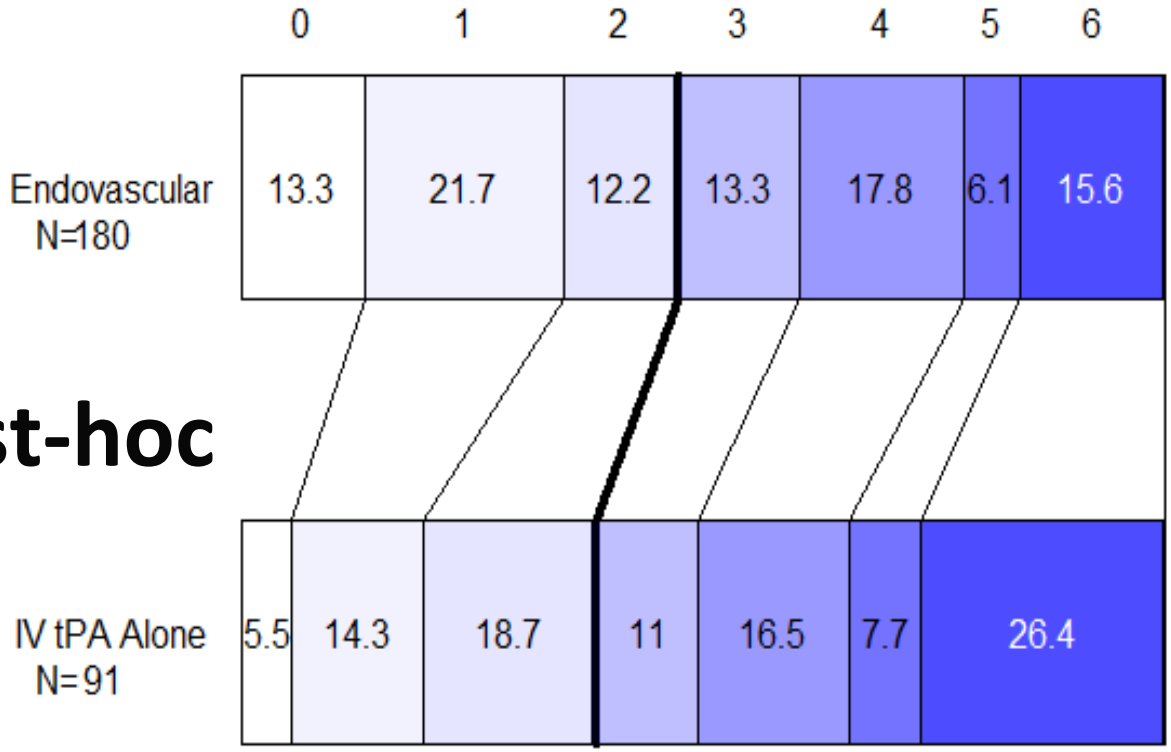
PI: Yuko Palesch, PhD
Statistics & Data Coordinating Center
Medical University of South Carolina
Grant Number: U01 – NS054630

PI: Andrew Demchuk, MD
CT Image Analysis Center
University of Calgary

ClinicalTrials.gov Indentifier
NCT 00359424

90-Day mRS Distribution bCTAoccl+

Post-hoc



Differences between the two treatment groups across the entire distribution of the mRS ($p = 0.0114$, van Elterin test)

UNIVERSITY OF Cincinnati

UNIVERSITY OF CALGARY MEDICINE

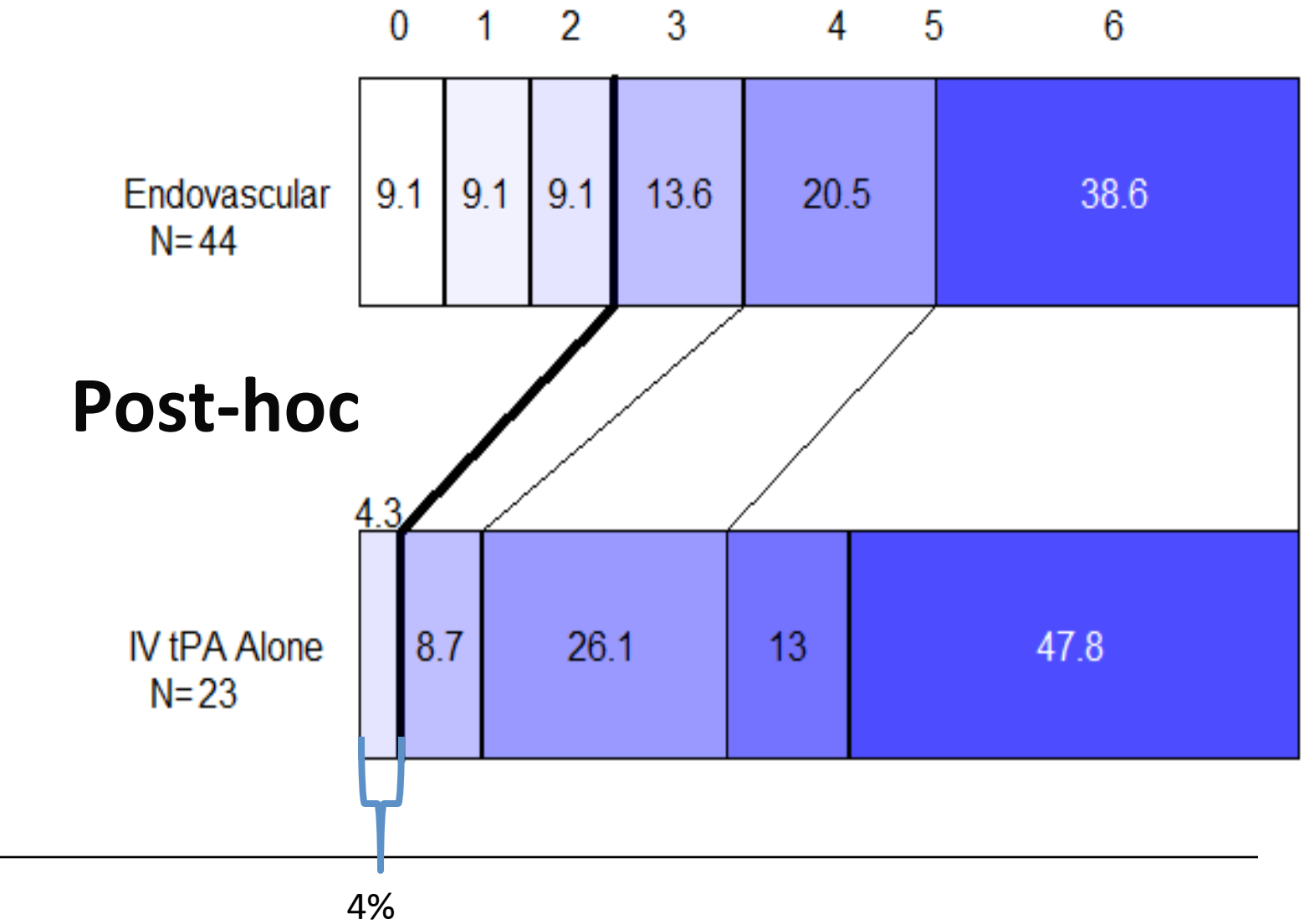
MUSC MEDICAL UNIVERSITY of SOUTH CAROLINA

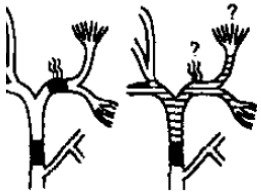
NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

24hr Recanalization by Occlusion Site

	Percent Recanalized of Subjects with 24 hour CTA (95% CI)		
Baseline Primary Occlusion Vessel Category	Endovascular	IV t-PA Only	Treatment Difference (95% CI)
All*	86.3% (79.6, 91.4)	64.7% (52.2, 75.9)	21.6% (8.9, 34.3)
Proximal: ICA, M1, BA	84.3% (76.4, 90.5)	55.8% (41.3, 69.5)	28.6% (13.5, 43.6)
ICA-T/L or Tandem ICA/M1	83.3% (65.3, 94.4)	27.8% (9.7, 53.5)	55.6% (30.9, 80.2)
Proximal M1, no ICAo	90.3% (74.3, 98.0)	80.0% (44.4, 97.5)	10.3% (-16.6, 37.2)
Distal M1, no ICAo	85.1% (71.7, 93.8)	85.7% (63.7, 97.0)	-0.6% (-18.7, 17.5)
M2 with or without ICAo	88.5% (69.9, 97.6)	78.6% (49.2, 95.3)	9.9% (-14.9, 34.6)
M3/M4 with or without ICAo	100.0% (NA)	100.0% (NA)	NA
BA; VA+BA; PCA	83.3% (35.9, 99.6)	33.3% (0.8, 90.6)	50.0% (-11.1, 100.0)

90-Day mRS Distribution, Baseline CTA: Carotid T/L or Tandem ICA+M1

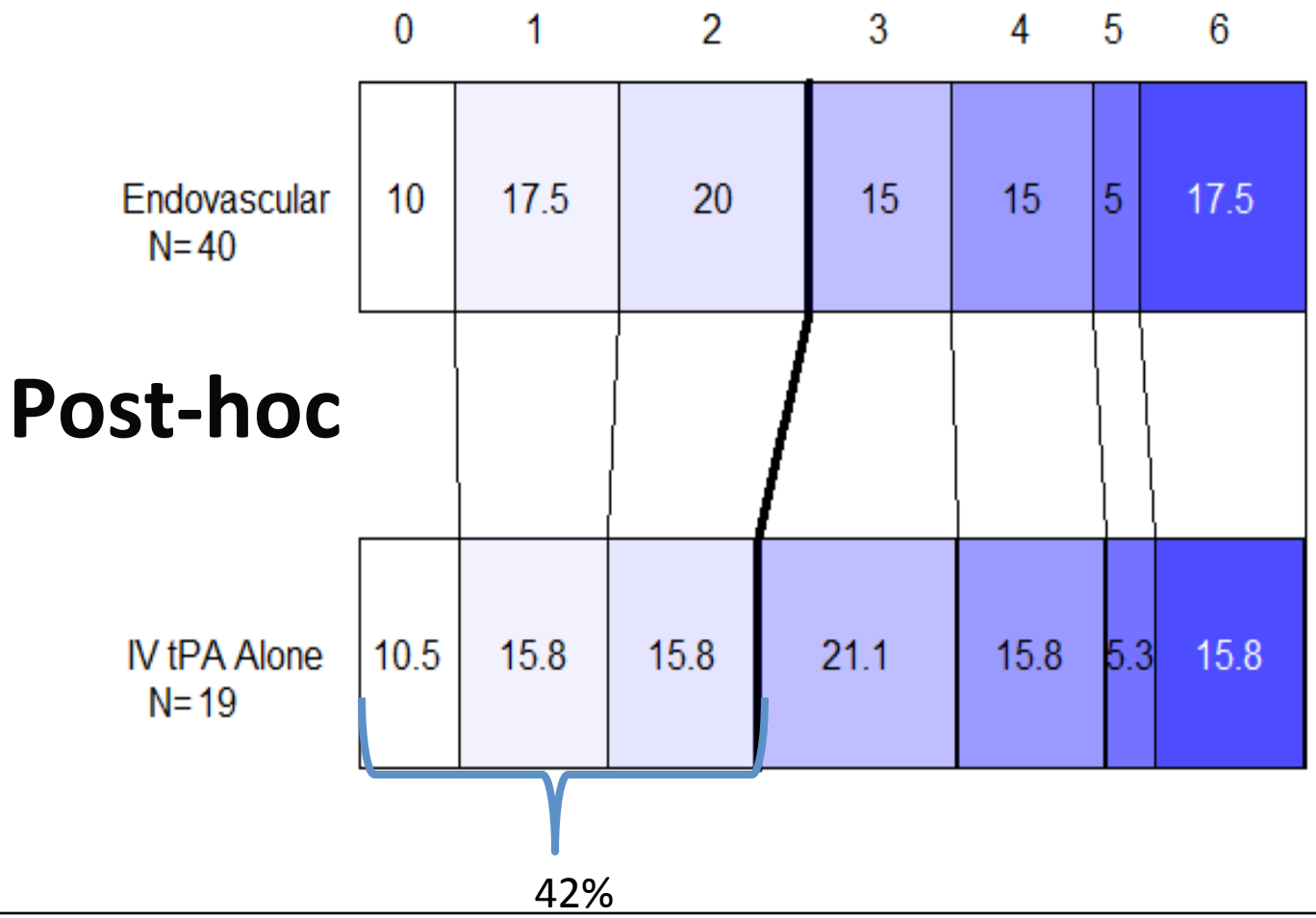




Ann Neurol 1992;32:78–86

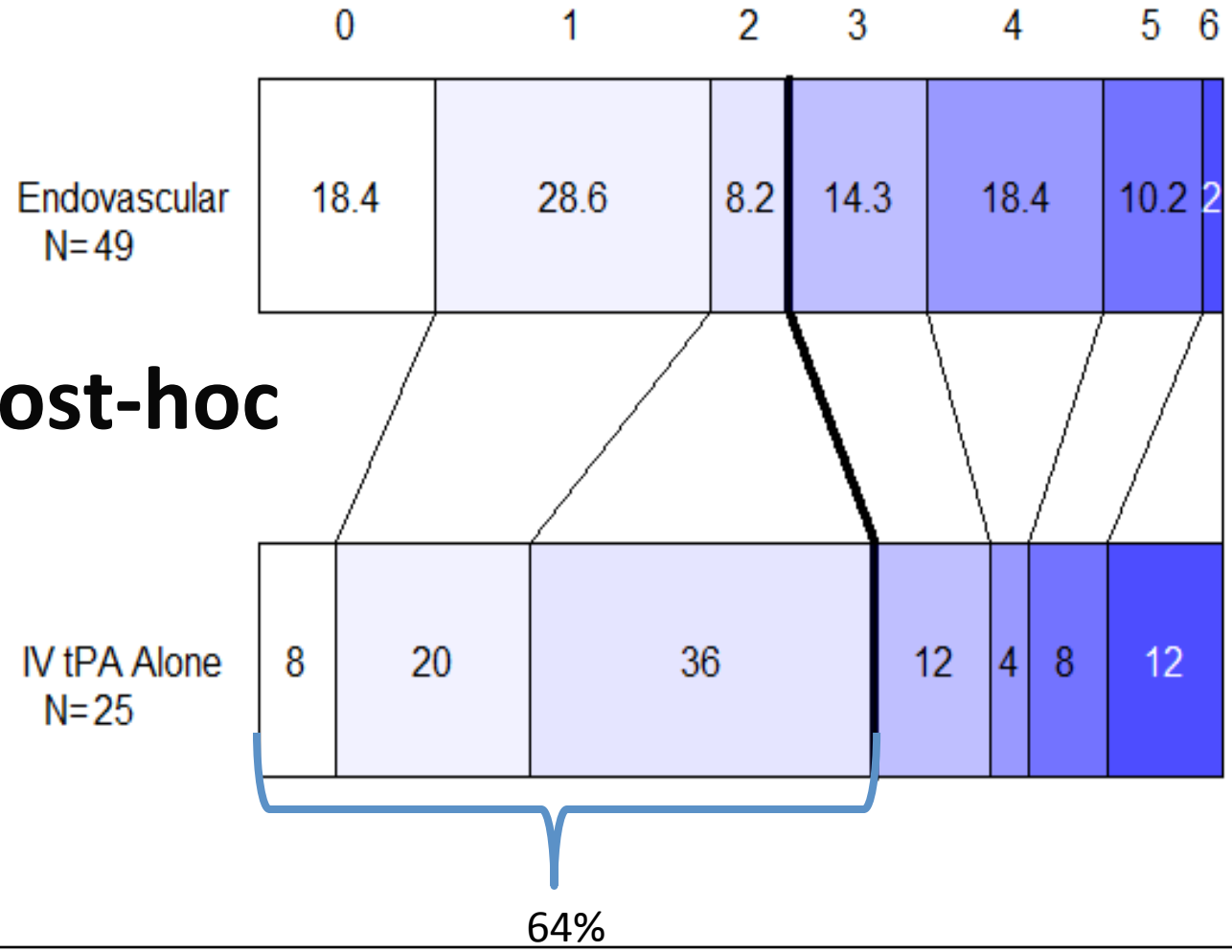
IMS III INTERVENTIONAL MANAGEMENT OF STROKE

90-Day mRS Distribution, Baseline CTA Proximal M1, no ICAo Occlusion Present



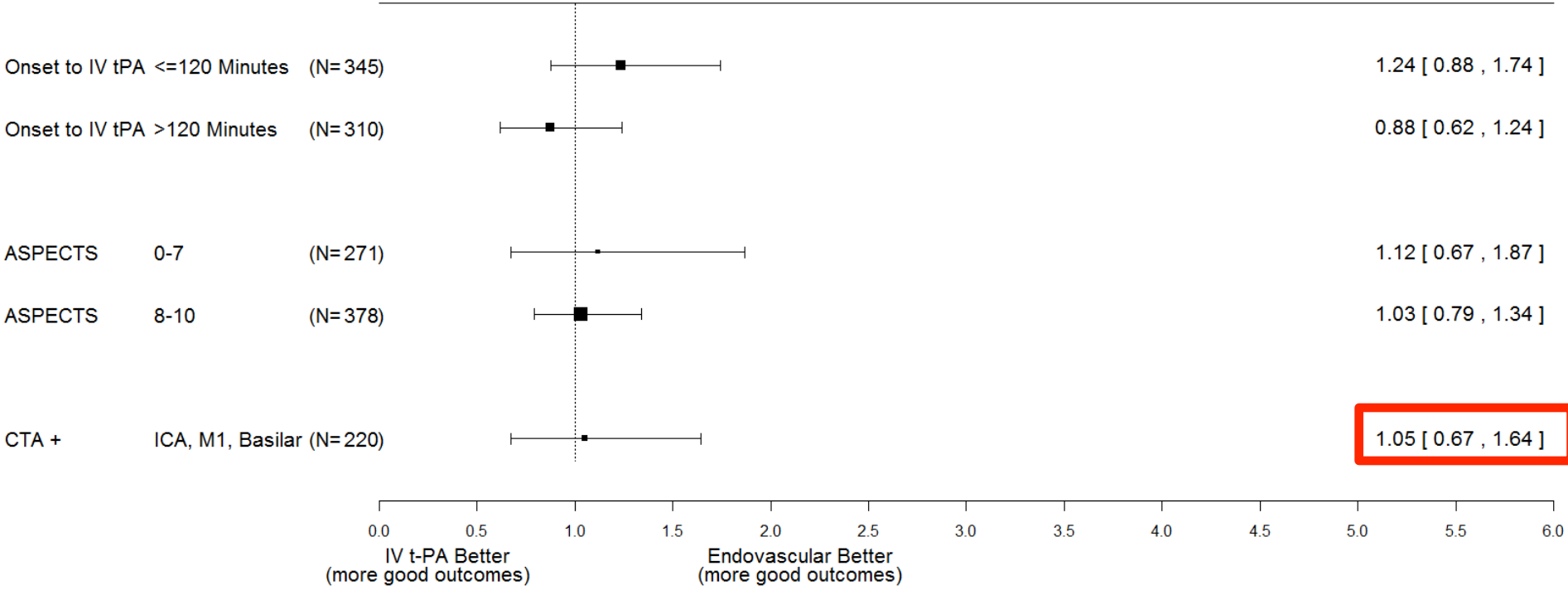
Post-hoc

90-Day mRS Distribution, Baseline CTA Distal M1, no ICAo Occlusion Present



Post-hoc

Onset to IV t-PA, ASPECTS Score, CTA +



Lessons learned from IMS-3

All eligible patients weren't randomized at participating centres

- No cherry-picking, enrol consecutive patients

Patient selection did not confirm accessible/persistent occlusion

- Baseline CTA or thrombus selection essential

Occlusion sites differ in IV t-PA response

- **Carotid T/L occl data very encouraging**
- **M1 MCA occlusion will need big trials if vs iv tPA**

INTERVENTIONAL MANAGEMENT OF STROKE TRIAL III

Supported by: NIH/NINDS

PI: Joseph P. Broderick, MD
Co PI: Thomas Tomsick. MD
University of Cincinnati Clinical Coordinating and Angiographic Imaging Center
Grant Number: U01 – NS052220

PI: Yuko Palesch, PhD
Statistics & Data Coordinating Center
Medical University of South Carolina
Grant Number: U01 – NS054630

PI: Andrew Demchuk, MD
CT Image Analysis Center
University of Calgary

ClinicalTrials.gov Indentifier
NCT 00359424

Table 2. Primary and Secondary Safety End Points.*

End Point	Endovascular Therapy (N=434)	Intravenous t-PA Alone (N=222)	P Value
Death — no. (%)			
Within 7 days	52 (12.0)	24 (10.8)	0.57
Within 90 days	83 (19.1)	48 (21.6)	0.52
Intracerebral hemorrhage within 30 hr — no. (%)			
Symptomatic	27 (6.2)	13 (5.9)	0.83
Asymptomatic	119 (27.4)	42 (18.9)	0.01
Parenchymal hematoma identified within 30 hr — no./total no. (%)†			
Type 2	25/417 (6.0)	13/207 (6.3)	0.90
Type 1	15/417 (3.6)	3/207 (1.4)	0.12
Hemorrhage — no./total no. (%)			
Subarachnoid	48/417 (11.5)	12/207 (5.8)	0.02
Intraventricular	27/417 (6.5)	10/207 (4.8)	0.40
Major complication due to nonintracerebral bleeding within 5 days — no. (%)‡	13 (3.0)	5 (2.3)	0.55
Recurrent stroke within 90 days — no. (%)	22 (5.1)	14 (6.3)	0.54
Device or procedural complication — no. (%)‡	70 (16.1)	—	

University of Cincinnati
University of Calgary Medicine
MUSC Medical University of South Carolina
National Institute of Neurological Disorders and Stroke

Safety:
ICH – Endovascular Group All Occlusions

	Standard Microcatheter		Ekos		Merci		Penumbra		Other (Protocol Violations)	
	t-PA	No t-PA	t-PA	No t-PA	t-PA	No t-PA	t-PA	No t-PA	t-PA	No t-PA
	n= 132	n= 3	n= 22	n= 0	n= 57	n= 37	n= 38	n= 15	n= 8	n= 7
PH-1 or PH-2	8.1%		9.1%		**14.9%**		9.4%		6.7%	
SAH	6.8%		9.1%	NA	**29.8%**	**8.1%**	7.9%	20.0%	**12.5%**	**28.6%**
New Emboli (Core Lab)	4.3%		4.5%	NA	**21.1%**	**23.7%**	0.0%	12.5%	11.1%	**42.9%**
Perforation (Core Lab)	0.0%		0.0%	NA	0.0%	**5.3%**	0.0%	**6.3%**	0.0%	0.0%
Dissection (Operator)	0.7%		0.0%	NA	1.8%	2.6%	2.6%	12.5%	0.0%	14.3%
Death 90 days	17.9%		18.2%	NA	26.3%	34.2%	10.5%	25.0%	33.3%	42.9%

Lessons learned from IMS-3

All eligible patients weren't randomized at participating centres

- No cherry-picking, enrol consecutive patients

Patient selection did not confirm accessible/persistent occlusion

- Baseline CTA or thrombus selection essential

Occlusion sites differ in IV t-PA response

- Carotid T/L occl data very encouraging; M1o will need big trials

Endovascular treatments weren't safe enough (SAH, 16% dev/proc SAE)

- **Newer technology and more operator experience**

TICI Reperfusion by Primary Target Occlusion

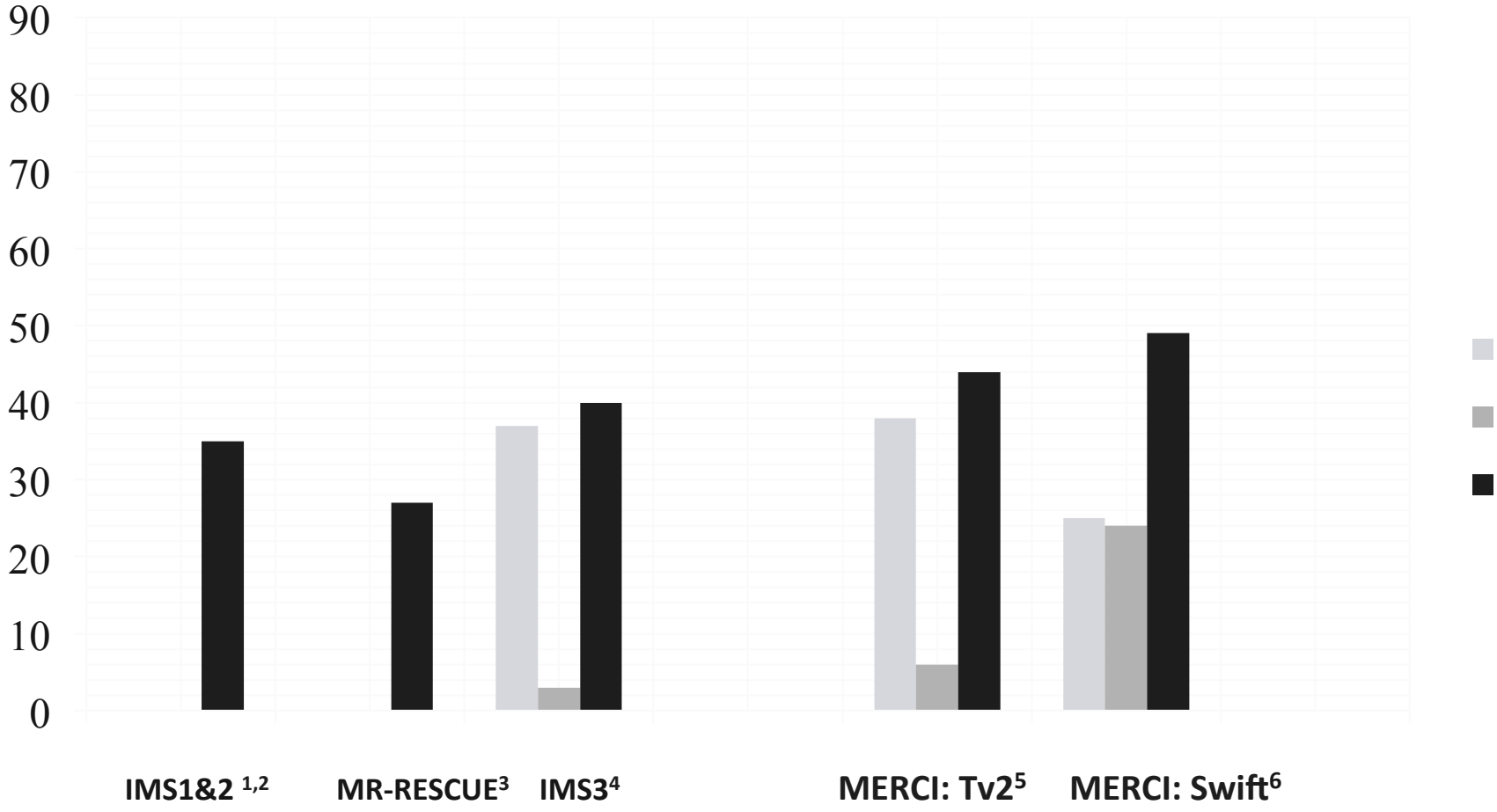
Primary Target Vessel	Frequency	Percent with TICI 2b-3 at completion of procedure
All	328	40%
ICA Intracranial	65	38%
M1	135	44%
Single M2	61	44%
Multiple M2 s	22	23%
M3	20	25%

More reperfusion is better

IMS-3: 40% substantial reperfusion rate

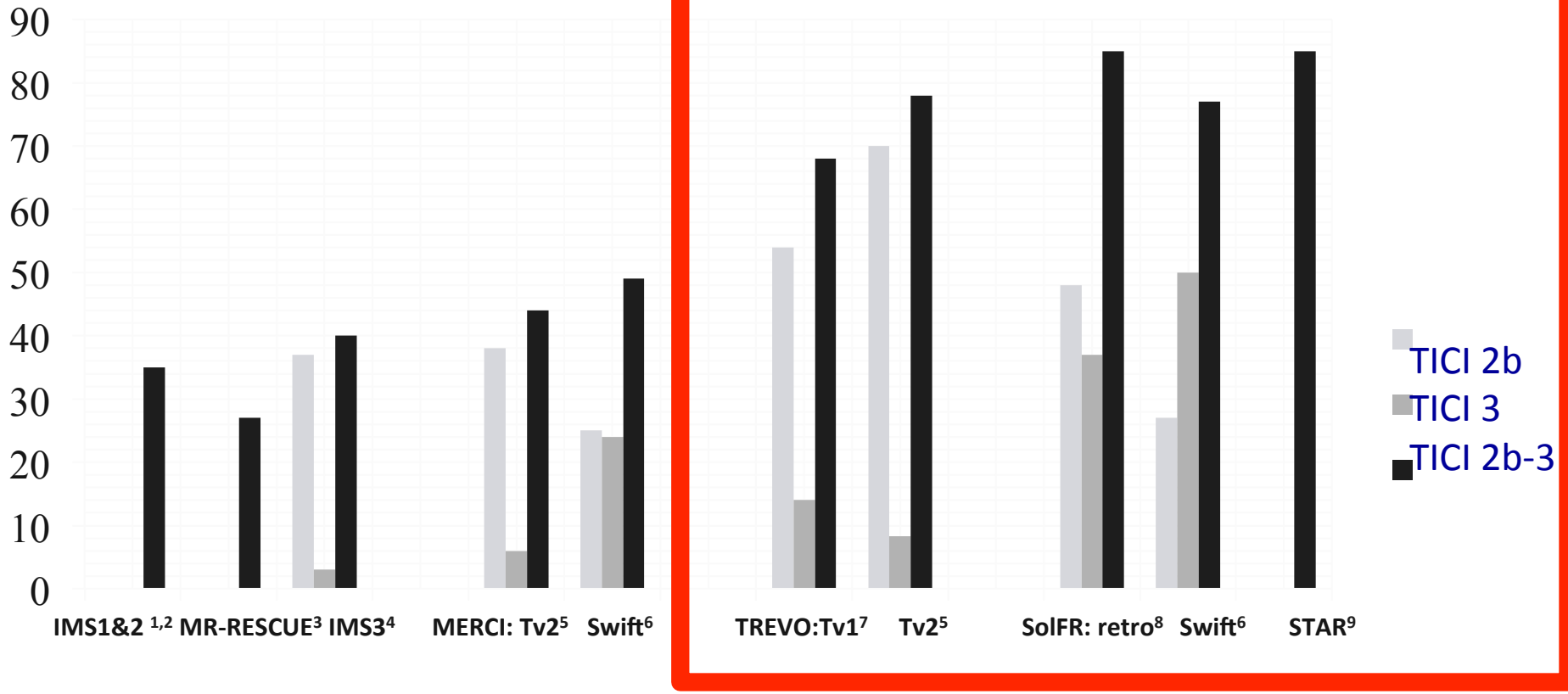
	TICI=0	TICI=1	TICI=2a	TICI=2b	TICI=3	
	n= 32	n= 16	n= 67	n= 80	n= 5	
% 90 Day mRS 0-2	3.1%	12.5%	19.4%	46.3%	80%	
	13.9%			48.2%		p < .0001

Central Core Lab Adjudicated TICI Scores



Stroke 2004 [1] ; Stroke 2007 [2]; NEJM 2013 [3,4]; Lancet 2012 [5]; Lancet 2012 [6]

Central Core Lab Adjudicated TICI Scores



Stroke 2004 [1] ; Stroke 2007 [2]; NEJM 2013 [3,4]; Lancet 2012 [5]; Lancet 2012[6] ; ISC 2012[7] ; Stroke 2012[8]; ISC 2013[9]

Lessons learned from IMS-3

All eligible patients weren't randomized at participating centres

- No cherry-picking, enrol consecutive patients

Patient selection did not confirm accessible/persistent occlusion

- Baseline CTA or thrombus selection essential

Occlusion sites differ in IV t-PA response

- Carotid T/L occl data very encouraging; M1o will need big trials

Endovascular treatments weren't safe enough(SAH, 16% dev/proc SAE)

- Newer technology and more operator experience

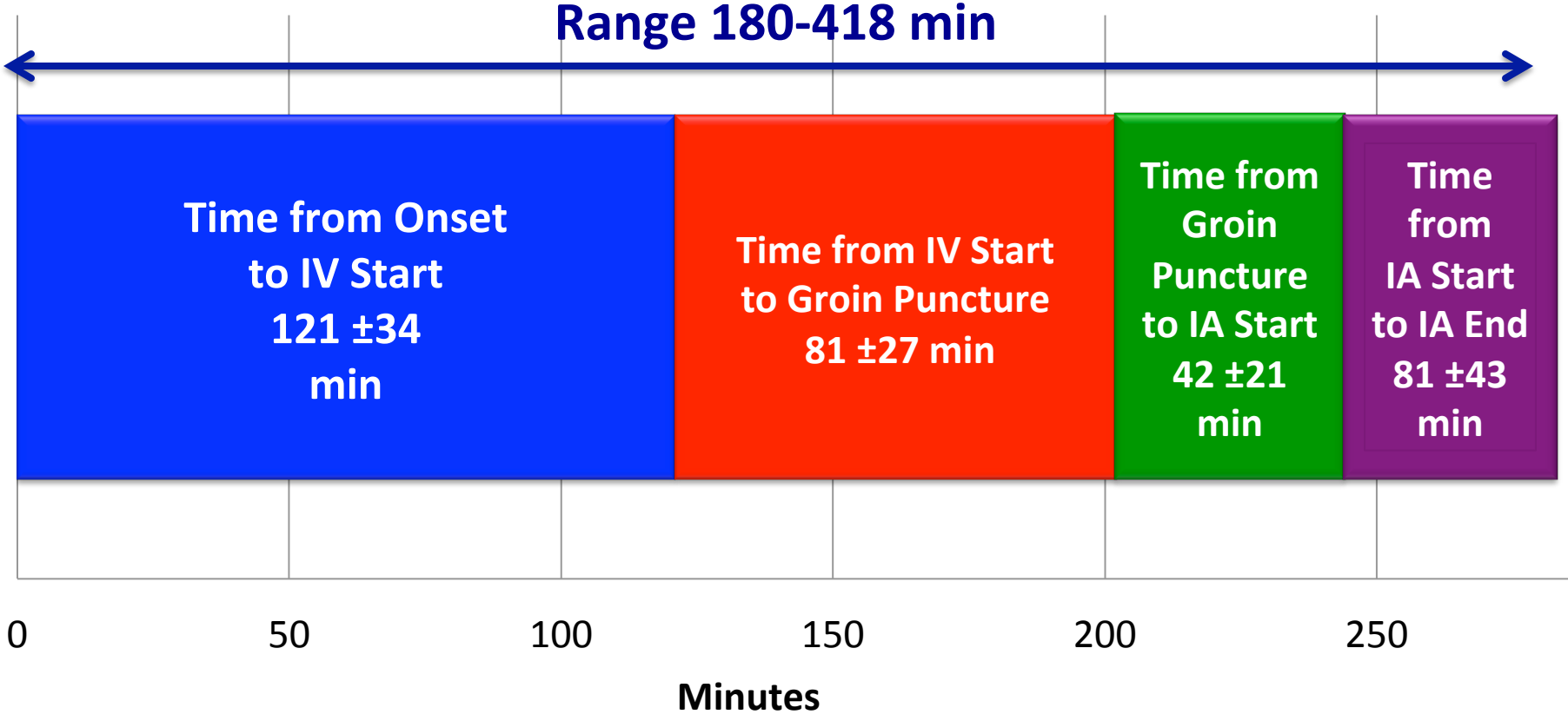
Endovascular treatment technology suboptimal (TICI 2b-3 ~40%)

- **Mechanical + aspiration thrombectomy + proximal flow arrest**

Descriptive Characteristics

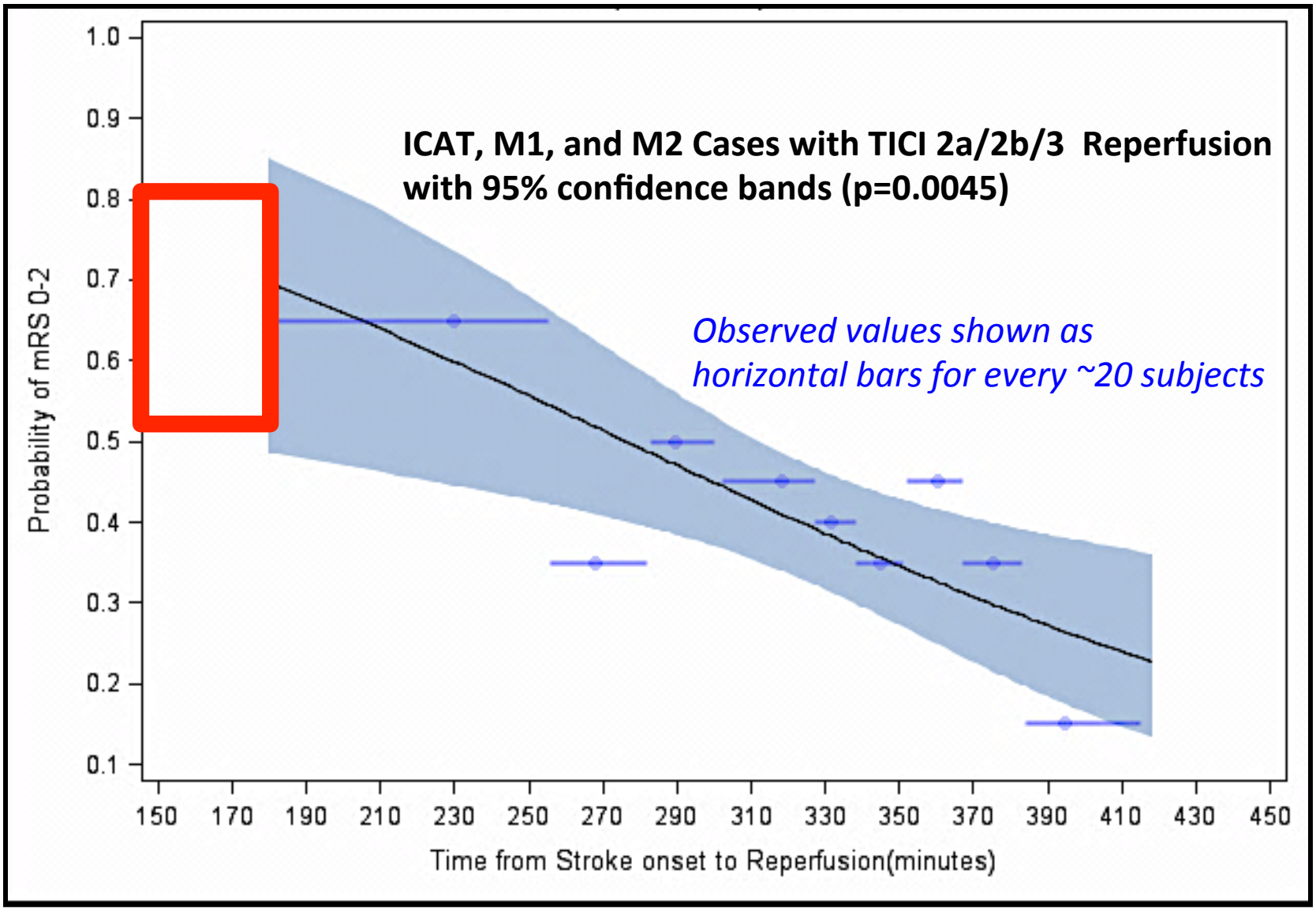
Time Parameters

Time from Symptom Onset to IA End/Reperfusion
Mean (SD) = 325 (±52) min
Range 180-418 min



Time to Reperfusion and Good Clinical Outcome

Observed Vs Predicted

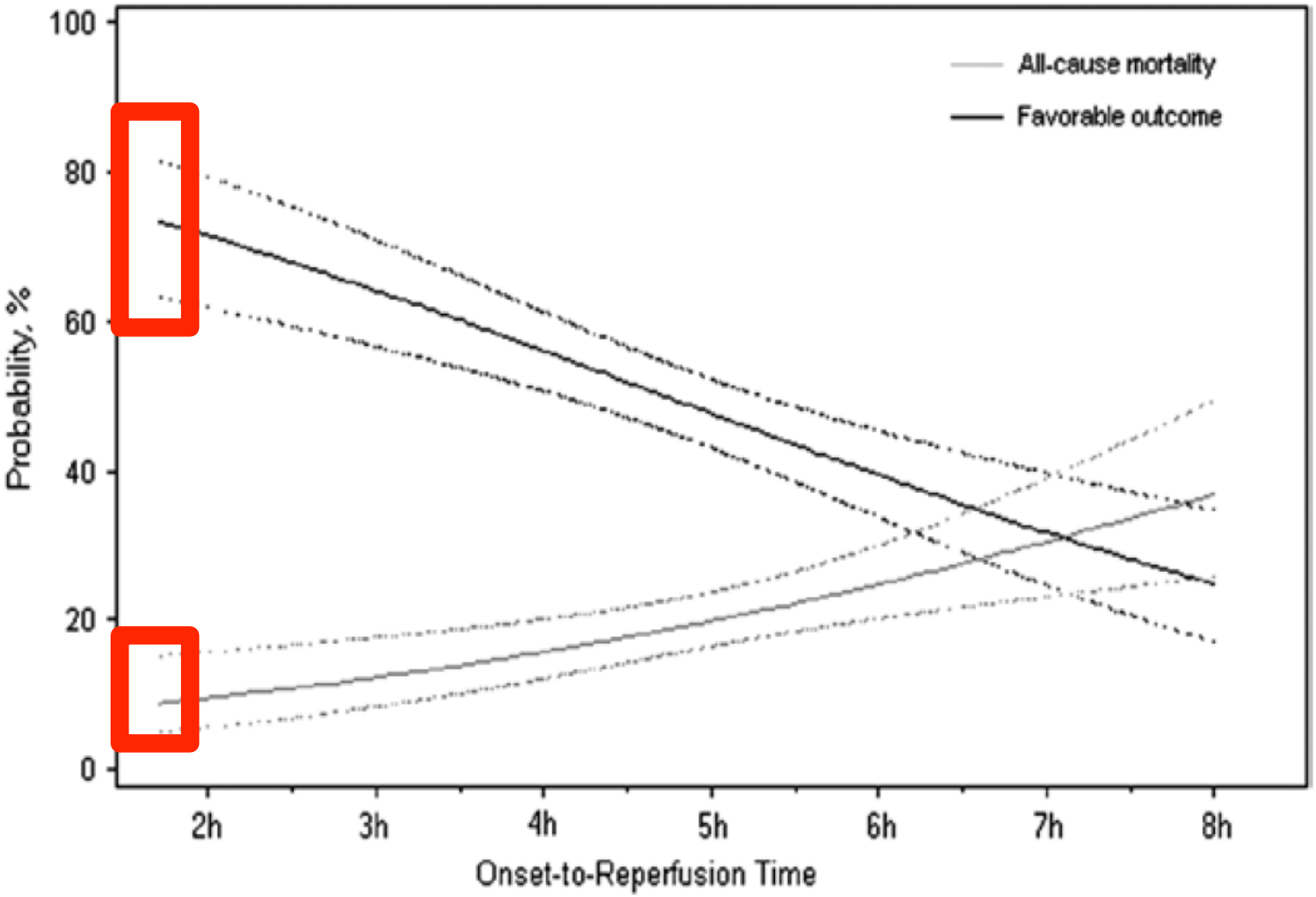


Impact of Onset-to-Reperfusion Time on Stroke Mortality

A Collaborative Pooled Analysis

(*Circulation*. 2013;127:1980-1985.)

Mikael Mazighi, MD, PhD; Saqib A. Chaudhry, MD; Marc Ribo, MD; Pooja Khatri, MD, MSc; David Skoloudik, MD; Maxim Mokin, MD; Julien Labreuche, BST; Elena Meseguer, MD;



Lessons learned from IMS-3

All eligible patients weren't randomized at participating centres

- No cherry-picking, enrol consecutive patients

Patient selection did not confirm accessible/persistent occlusion

- Baseline CTA or thrombus selection essential

Occlusion sites differ in IV t-PA response

- Carotid T/L occl data very encouraging; M1o will need big trials

Endovascular treatments weren't safe enough (SAH, 16% dev/proc SAE)

- Newer technology and more operator experience

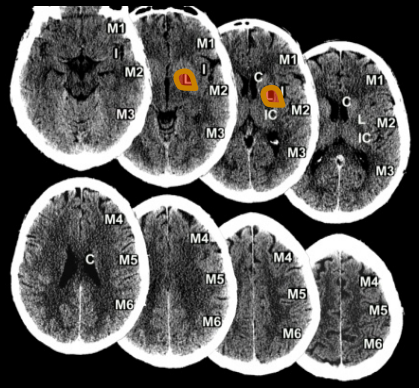
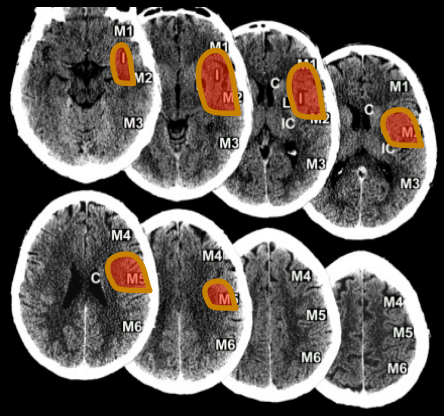
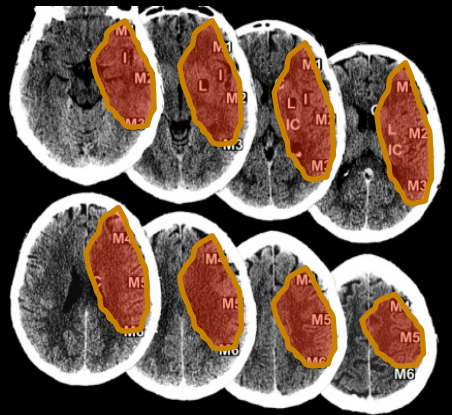
Endovascular treatment technology suboptimal (TICI 2b-3 ~40%)

- Mechanical+aspiration thrombectomy+proximal flow arrest

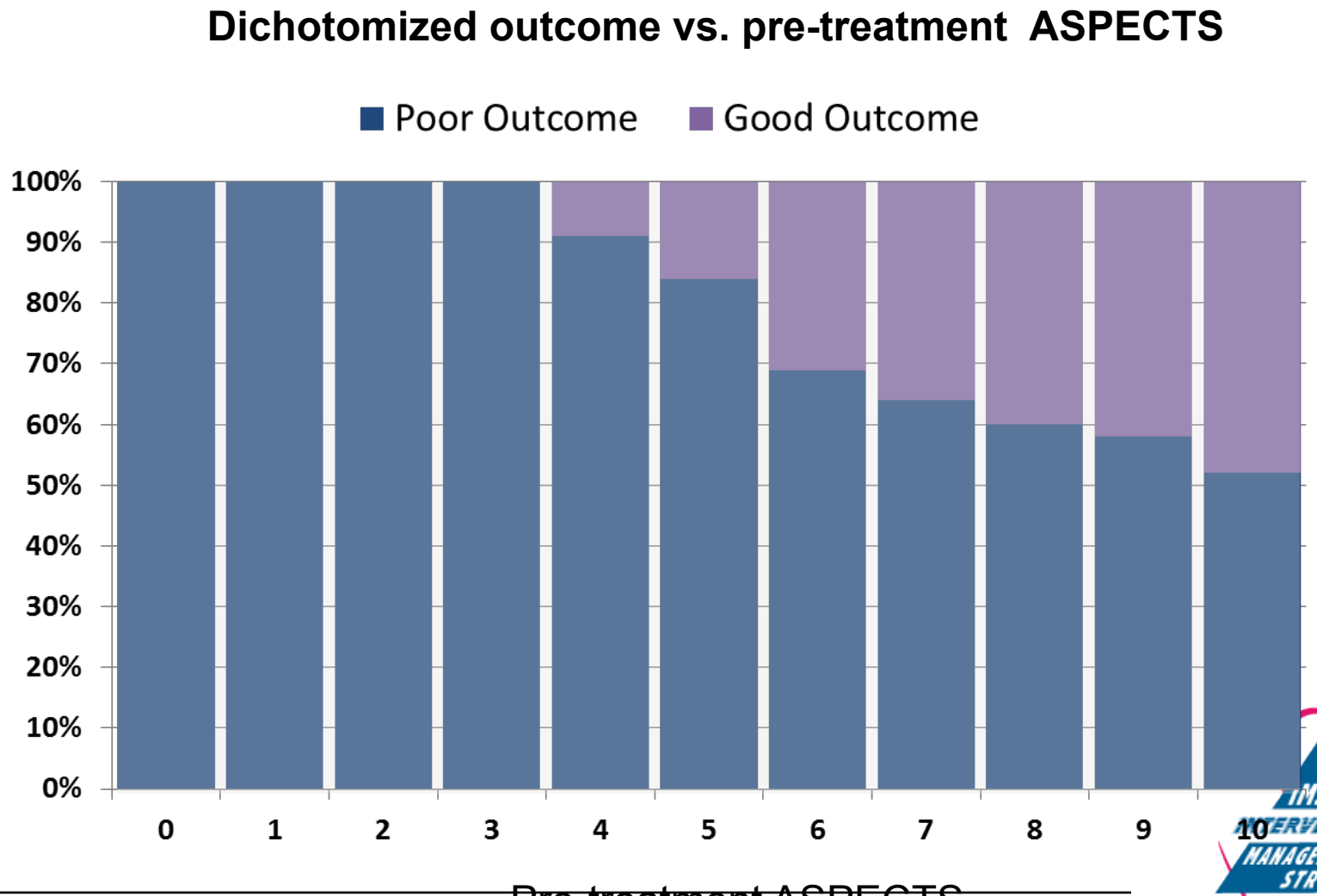
Time was not managed efficiently (iv tPA 121 min but recan ~325 min)

- **Onset to reperfusion <180 minutes (70-90% mRS 0-2!)**
- **EMS redirect to comprehensive stroke centre**

ASPECTS Trichotomy

	NCCT	ASPECTS score
Good scan		8-10
Fair scan		5-7
Poor scan		0-4

PENUMBRA trials: Reperfusion and ASPECTS



Yoo AJ, et al. ISC 2012

Graded Prognosis by ASPECTS

ITT population	ASPECTS 8-10 (Good scan)		ASPECTS 5-7 (Fair scan)		ASPECTS 0-4 (Poor scan)	
	IV-endo (n=247)	IV tPA (n=131)	IV-endo (n=130)	IV tPA (n=56)	IV-endo (n=57)	IV tPA (n=35)
mRS 0-2 at 90d	51%	47%	32%	29%	19%	23%
mRS 0-1 at 90d	36%	31%	22%	20%	9%	17%
NIHSS 0-1 at 90d	34%	29%	25%	16%	5%	9%

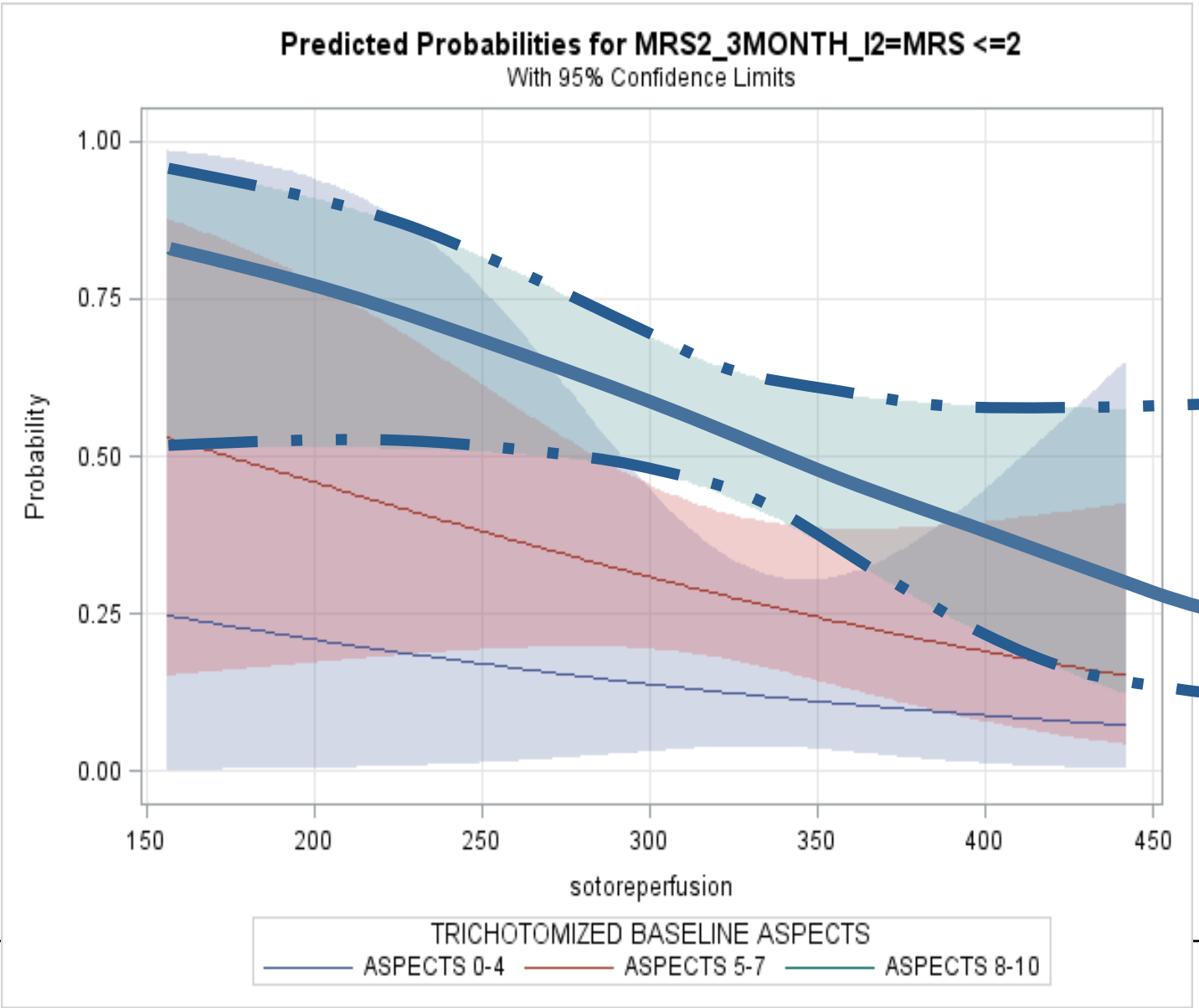
IMS III INTERVENTIONAL MANAGEMENT OF STROKE

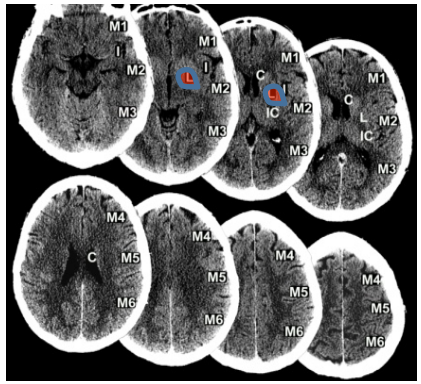
ASPECTS – CTA: ICA or MCA occlusions

ITT population	**ASPECTS 8-10** (Good scan)		**ASPECTS 5-7** (Fair scan)		**ASPECTS 0-4** (Poor scan)	
	IV-endo (n=92)	IV tPA (n=52)	IV-endo (n=66)	IV tPA (n=22)	IV-endo (n=25)	IV tPA (n=15)
mRS 0-2 at 90d	57%	50%	33%	32%	24%	13%
mRS 0-1 at 90d	46%	27%	21%	18%	8%	0%
NIHSS 0-1 at 90d	42%	25%	24%	18%	4%	0%

IMS III INTERVENTIONAL MANAGEMENT OF STROKE

ASPECTS Time Relationship

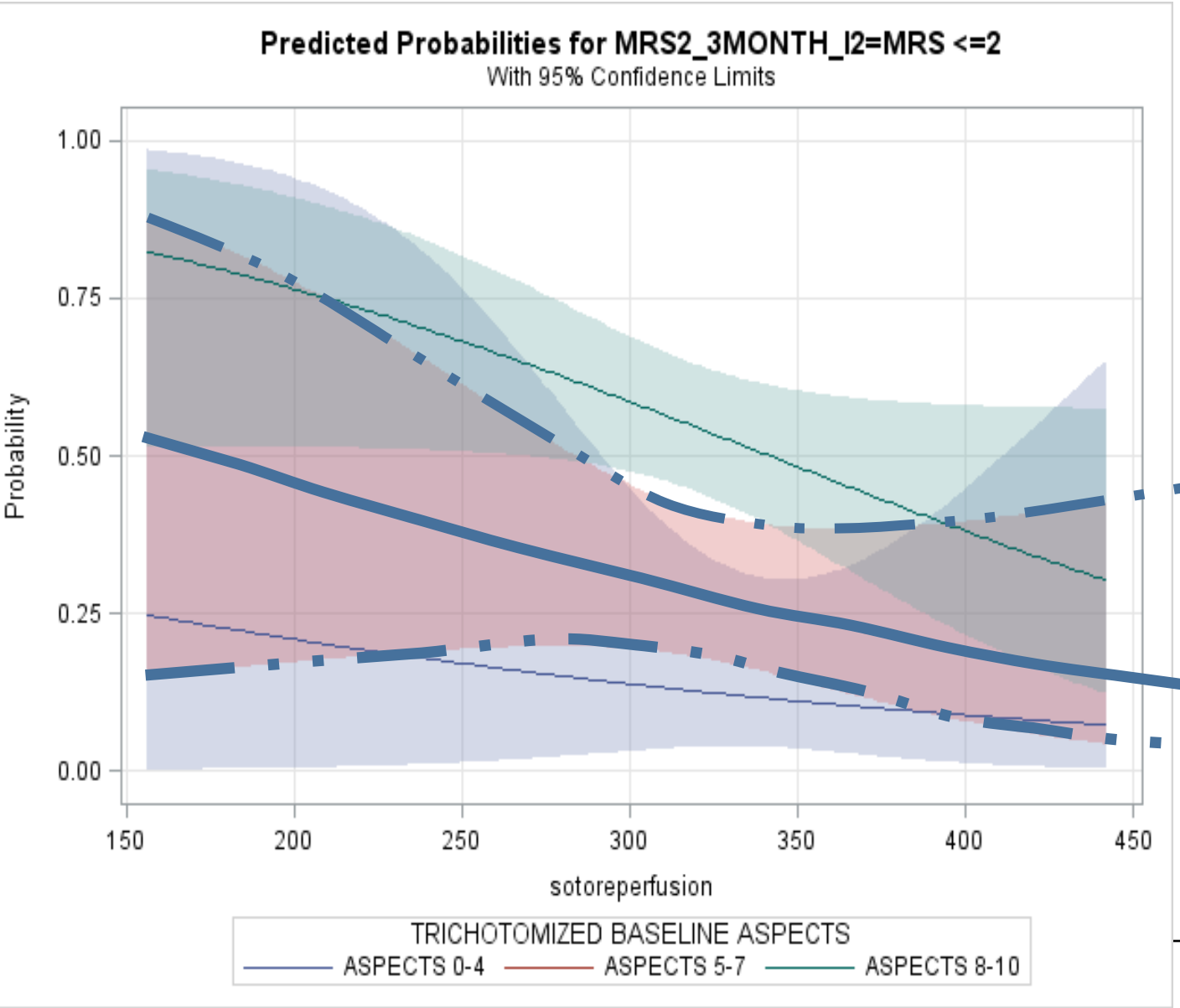


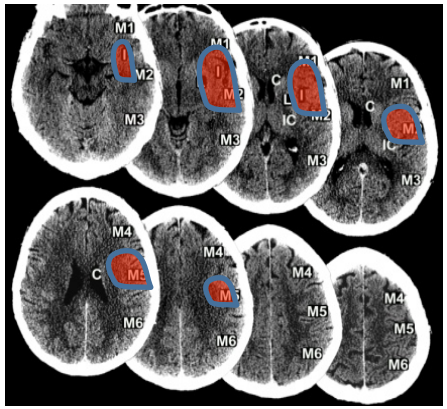


ASPECTS 8-10

IMS III INTERVENTIONAL MANAGEMENT OF STROKE

ASPECTS Time Relationship

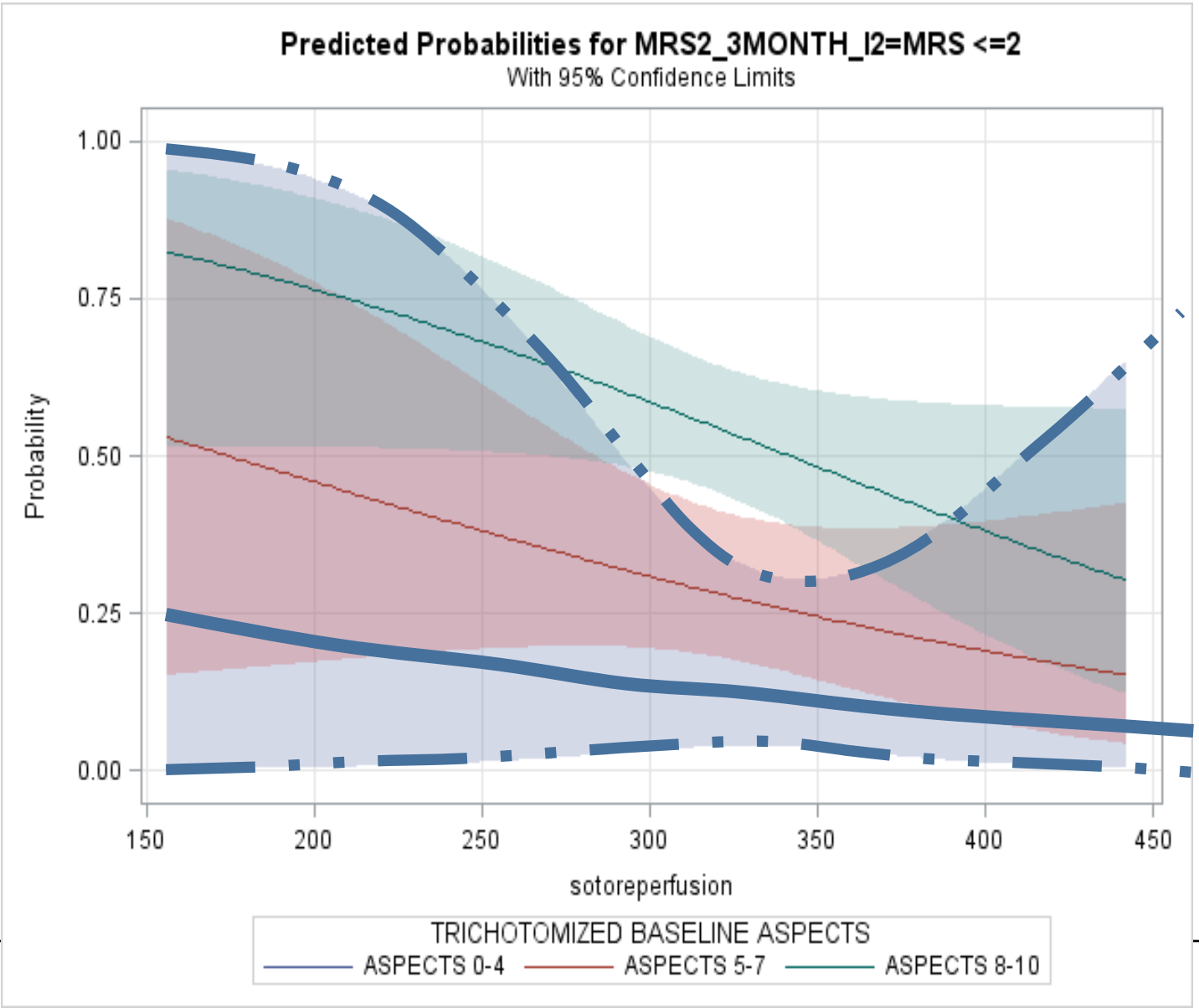


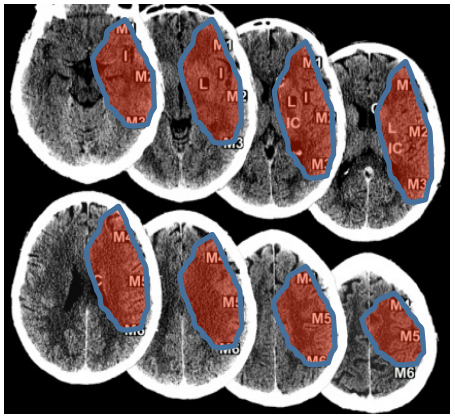


ASPECTS 5-7

IMS III INTERVENTIONAL MANAGEMENT OF STROKE

ASPECTS Time Relationship





ASPECTS 0-4

Lessons learned from IMS-3

All eligible patients weren't randomized at participating centres
- No cherry-picking, enrol consecutive patients

Patient selection did not confirm accessible/persistent occlusion
- Baseline CTA or thrombus selection essential

Occlusion sites differ in IV t-PA response
- Carotid T/L occl data very encouraging; M1o will need big trials

Endovascular treatments weren't safe enough (SAH, 16% dev/proc SAE)
- Newer technology and more operator experience

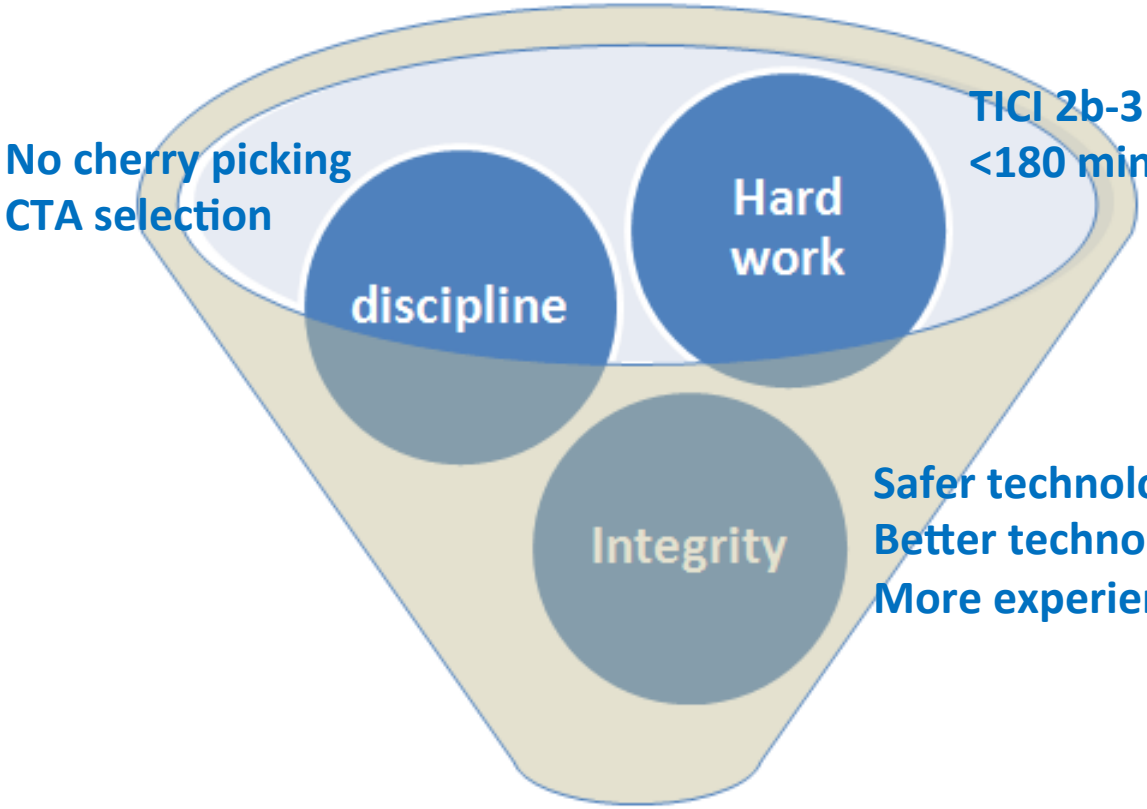
Endovascular treatment technology suboptimal (TICI 2b-3 ~40%)
- Mechanical + aspiration thrombectomy + proximal flow arrest

Time was not managed efficiently (iv tPA 121 min recan ~325 min)
- Onset to reperfusion <180 minutes; redirect to CSC

Imaging – Reperfusion timing may trump all else
- **ASPECTS – predicts outcome, but no tx interaction**
- **CTA collaterals – ISC 2014**
- **Hyperdense signs/ CTA clot characteristics – ESC 2014?**

Randomize to a new Endo Trial !

Recipe



Success

2009

CALGARY STROKE PROGRAM

Thank-you for your attention!

UNIVERSITY OF CALGARY

CALGARY STROKE PROGRAM

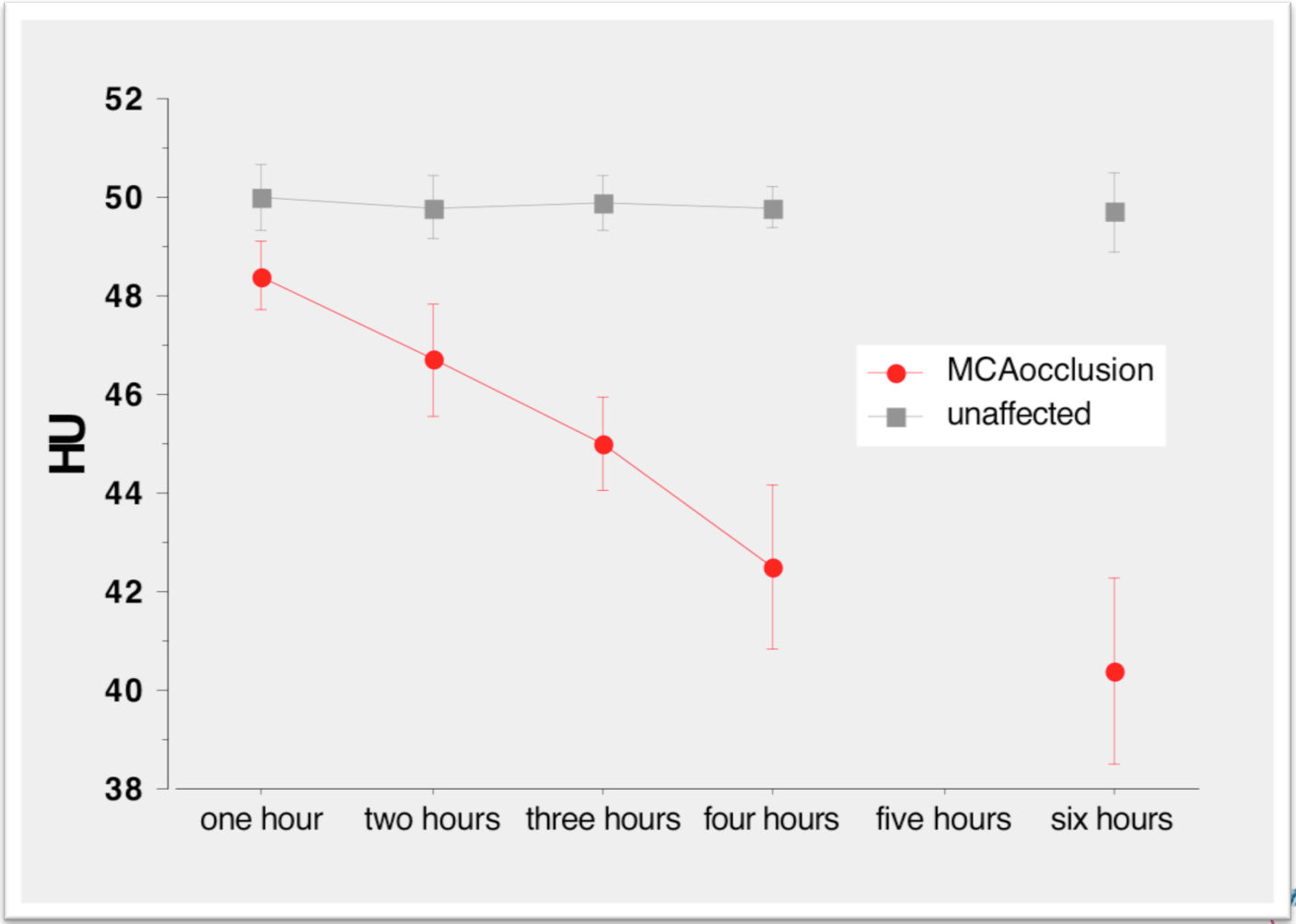
HOTCHKISS BRAIN INSTITUTE

ENROLLING CLINICAL CENTERS:

- **University of Cincinnati College of Medicine** (72 subjects) J. Broderick, T. Tomsick;
- **University of Pittsburgh Medical Center** (46) L Wechsler, T. Jovin;
- **Calgary Health Region/Foothills Medical Centre** (44) A. Demchuk, M. Goyal;
- **Toronto Western Hospital** (29) F. Silver, K. Murphy;
- **Hospital Vall d'Hebron** (28) C. Molina, M. Ribo;
- **Royal Melbourne Hospital** (27) B. Yan, P. Mitchell;
- **Mayo Clinic Arizona** (26) B. Demaerschalk, B. Chong;
- **Oregon Health Sciences University, Oregon Stroke Center** (24) W. Clark, S. Barnwell;
- **Riverside Methodist Hospital** (24) R. Budzik;
- **Alexian Brothers Hospital Network** (23) T. Malisch;
- **Froedtert Hospital/ Medical College of Wisconsin** (23) O.Zaidat;
- **Colorado Neurological Institute/Swedish Medical Center** (21) C. Fanale, D. Frei;
- **Allegheny General Hospital** (18) A. Tayal, A. Ku;
- **Dresden University of Technology** (17), U. Bodechtel, R. von Kummer;
- **Ruan Neurology /Mercy Medical Center**, (16) M Jacoby, W. Young;
- **Lehigh Valley Hospital** (15) Y. Isayev, D. Shaff;
- **UCLA Medical Center** (14) S. Starkman, F. Vinuela;
- **University of Louisville** (11) A. Abou-Chebl;
- **Martin Luther University** (10) K. Wartenberg, K. Stock;
- **Royal Prince Alfred Hospital** (10) C. Anderson, G. Parker;
- **Abington Memorial Hospital** (9) Q. Shah;
- **Vancouver General Hospital** (9) A. Woolfenden, G. Redekop;
- **Henry Ford Hospital** (8) C. Lewandowski, W. Sanders;
- **University of Virginia Health System** (8) E. Clarke Haley, A. Evans;
- **Washington University** (8) P. Panagos, C. Derdeyn;
- **Hoag Memorial Hospital Presbyterian** (7) D. Brown, M. Brandt-Zawadzki;
- **Morton Plant Mease Health Care** (7) A. Arora, E. Lopez De Valle;
- **PENN State M.S. Hershey Medical Center** (7) K. Cockroft;

- **University of Miami Miller School of Medicine/Jackson Memorial Hospital** (7) D. Yavagal;
- **Lahey Clinic Medical Center (6)** In Sup Choi;
- **Mission Hospitals/Mission Neurology Services (6)** A. Schneider, J. Short;
- **Monash Medical Centre (6)**T. Phan, W. Chong;
- **University of North Carolina (5) D.** Huang, S. Solander;
- **University of Texas Medical School at Houston (5),** J. Grotta, P. Chen;
- **Upstate Medical University (**5) Z. El Zammar, E. Deshaies;
- **Bichat Stroke Centre and Paris Diderot University** (4) P. Amarenco, M. Mazighi;,
- **Medical University of South Carolina** (4) E. Jauch, A.Turk;
- **Ottawa Hospital-Civic Campus** (4) G. Stotts, C. Lum;
- **Park Nicollet Institute** (4) S. Hanson, M. Madison;
- **Trillium Health Care** (4) D. Selchen, D. Rosso;
- **Chattanooga Ctr. for Neurological Res** (3) T. Delvin, B. Baxter;
- **Jewish Hospital Louisville** (3) J. Gebel, R. Paulson;
- **Nevada Neuroscience Institute Research Foundation** (3) S. Selco, L. Blake;
- **St. Antonius Hospital** (3) W. Schonewille, JA. Vos;
- **Stroke Center at Hartford** (3) L. Abbott, G. Spiegel;
- **University of Montreal Notre Dame Hospital** (3) A. Poppe, J. Raymond;
- **Barrow Neurology Clinics at St. Joseph's Hospital and Med. Ctr.** (2), J. Frey, F. Albuquerque;
- **Cleveland Clinic** (2) D. Krieger, T. Masaryk;
- **Michigan State University Sparrow Hospital** (2), S. Hussain;
- **Sunnybrook Health Sciences Centre** (2) R. Swartz, P. Howard;
- **University Hospitals Case Medical Center** (2) R. Tarr;
- **Rhode Island Hospitals** (1) P. Panagos, R. Haas;
- **Hospital Universitari Germans Trias i Pujol** (1) A. Davalos, P. Bermejo;
- **Johns Hopkins University** (1) V. Urrutia, M. Radvany;
- **Massachusetts General Hospital** (1) L. Schwamm, R. Nogueira;
- **St. Vincent's Hospital** (1) R. Markus, R. Parkinson;
- **University Medical Center at Brackenridge & Seton Medical Center** (1) J. Neal Rutledge;
- **William Beaumont Hospital** (1) C. Kazmierczak.

X-ray Hypoattenuation after Experimental Occlusion of MCA



von Kummer R, Weber J Neurology 1997;49(Suppl 4):S52-S55

IMS III INTERVENTIONAL MANAGEMENT OF STROKE

Time dependence of reliability of noncontrast computed tomography in comparison to computed tomography angiography source image in acute ischemic stroke

Simerpreet Bal[1,5], Rohit Bhatia[3], Bijoy K. Menon[1], Nandavar Shobha[1], Volker Puetz[4], Imanuel Dzialowski[4], Jayesh Modi[2], Mayank Goyal[2], Michael D. Hill[1], Eric E. Smith[1], and Andrew M. Demchuk[1,2]*

© 2012 The Authors.
International Journal of Stroke © 2012 World Stroke Organization

Really early NCCT scans hard to interpret for core

Table 1 Interobserver reliability of ASPECTS scoring on NCCT and CTASI in different time categories from stroke onset

	NCCT		CTASI	
Time	Intraclass correlation	95% CI (lower, upper)	Intraclass correlation	95% CI (lower, upper)
0–90	0·48*	0·28–0·71	0·96*	0·93–0·98
91–180	0·80	0·66–0·90	0·94	0·89–0·97
181–360	0·81	0·69–0·91	0·87	0·78–0·94
>360	0·89	0·81–0·95	0·89	0·80–0·95
Overall	0·78	0·69–0·84	0·93	0·90–0·95

*Comparison of the intraclass correlation at 0–90 mins vs. 90 mins or greater, $P = 0{\cdot}0001$ for NCCT and $P = 0{\cdot}178$ for CTASI.
ASPECTS, Alberta Stroke Program Early CT Score; NCCT, noncontrast computed tomography; CTASI, CT angiography source image; CI, confidence interval.

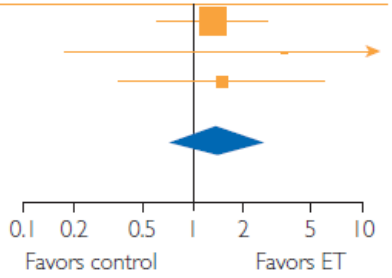
Balwinder Singh, MD; Ajay K. Parsaik, MD; Larry J. Prokop, MLS; and Manoj K. Mittal, MBBS

A

Excellent outcome (mRS ≤1)

Study or subgroup	ET Events	ET Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
Broderick et al,[6] 2013	19	130	8	71	73.1%	1.30 [0.60, 2.81]
Ciccone et al,[21] 2010	1	5	0	6	4.8%	3.50 [0.17, 70.94]
Ciccone et al,[7] 2013	4	28	3	31	22.1%	1.48 [0.36, 6.03]
Total (95% CI)		**163**		**108**	**100.0%**	**1.40 [0.72, 2.71]**
Total events	24		11			

Heterogeneity: Tau^2=0.00; χ^2=0.40, *df*=2 (*P*=.82); I^2=0%
Test for overall effect: *Z*=1.00 (*P*=.32)

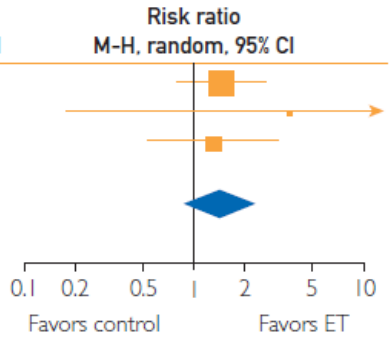


B

Good outcome (mRS ≤2)

Study or subgroup	ET Events	ET Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
Broderick et al,[6] 2013	31	130	12	71	66.3%	1.41 [0.77, 2.57]
Ciccone et al,[21] 2010	1	5	0	6	2.6%	3.50 [0.17, 70.94]
Ciccone et al,[7] 2013	8	28	7	31	31.1%	1.27 [0.53, 3.04]
Total (95% CI)		**163**		**108**	**100.0%**	**1.40 [0.86, 2.28]**
Total events	40		19			

Heterogeneity: Tau^2=0.00; χ^2=0.41, *df*=2 (*P*=.81); I^2=0%
Test for overall effect: *Z*=1.34 (*P*=.18)



C

Fair outcome (mRS ≤3)

Study or subgroup	ET Events	ET Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
Broderick et al,[6] 2013	57	130	21	71	70.1%	1.48 [0.99, 2.23]
Ciccone et al,[21] 2010	1	5	0	6	1.3%	3.50 [0.17, 70.94]
Ciccone et al,[7] 2013	12	28	11	31	28.6%	1.21 [0.64, 2.29]
Total (95% CI)		**163**		**108**	**100.0%**	**1.41 [1.00, 1.99]**
Total events	70		32			

Heterogeneity: Tau^2=0.00; χ^2=0.64, *df*=2 (*P*=.73); I^2=0%
Test for overall effect: *Z*=1.98 (*P*=.05)

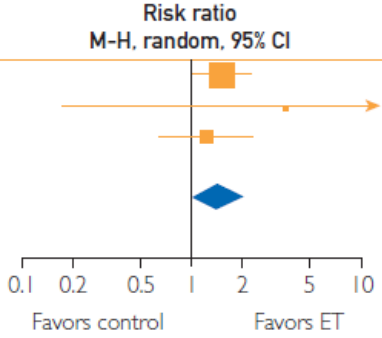


FIGURE 2. Outcomes in patients with severe stroke. A, Excellent outcome (mRS score ≤1). B, Good outcome (mRS score ≤2). C, Fair outcome (mRS score ≤3). ET = endovascular therapy; M-H = Mantel-Haenszel; mRS = modified Rankin Scale.

Who should get what?

	iv tPA+endo ideal "sweet spot"	iv tPA + endo modest net benefit	Avoid endo
Onset to reperfusion	<180 min	180-360 min	>360 min
Age	young		elderly?
NIHSS	>20	11-20	<10
Occlusion site	ICA T/L	tandem ICA/M1	M1o	distal occl?

RANDOMIZE TO AN ENDO TRIAL

AUTHORIZED NON ENROLLING SITES:

- **Intercoastal Medical Group/Sarasota Memorial Hospital-M**. Concha, N. Razack;
- **University of Rochester Medical Center**-C. Benesch, B. Jahromi;
- **St. Louis University**-R. Edgell, N. Vora;
- **Reading Hospital and Medical Center**-R. Chavali;
- **Methodist Research Institute/Clarian Health Partners**-J. Scott;
- **Central DuPage Hospital**-H. Shownkeen;
- **QEII Health Sciences Centre**, Dalhousie University-S. Phillips, E. Versnick;
- **Hospital of the University of Pennsylvania**- S. Kasner, R. Hurs;
- **University of Alberta Stroke Program**- A. Shuaib, D. Emery;
- **Sutter Medical Facility of Sacramento**-B. Varjavand, R. Atkinson;
- **St. John Providence Medical Center**-R. Fessler;
- **University of Freiburg**- W. Niesen, C. Hader,
- **Ernst Moritz; Arndt University**-A. Khaw, S. Langner;
- **University of Basel**- P.Lyrer, C. Stippich.

UNIVERSITY OF CINCINNATI CLINICAL COORDINATING AND ANGIOGRAM IMAGE ANALYSIS CENTER:

- J. Broderick, T. Tomsick, P. Khatri, D. Kanter, J. Spilker, J. Carrozzella, J. Frasure, R. Beckmann,
- D. Liebeskind (UCLA-contracted angio central reader),
- Neuroscience Trials Australia (Heidelberg, Victoria AU-contracted AU CRO-T. Soulis General Manager) and AU drug distribution Center at The Royal Melbourne Hospital Clinical Trials Pharmacy - G. Hong,
- Clinical Research Services (Kelkheim/Ts, DE-contracted EU CRO-Dr. med. D. Salein), K. MacDonald-Device Regulatory Consultant.

STATISTICAL AND DATA COORDINATION UNIT AT MEDICAL UNIVERSITY SOUTH CAROLINA:

- Y. Palesch, S. Yeatts, R. Martin, L. Foster, R. Leinster, K. Briggs, C. Dillon, P. Mauldin, K. Simpson, A. Simpson.

CT IMAGING ANALYSIS AND CANADIAN DRUG DISTRIBUTION AND COORDINATING CENTER:

- A.M. Demchuk, M. Goyal, J. Modi, E. Qazi, M.D. Hill, K. Ryckborst, M. Hudon, J. Kosior, C. O'Reilly, A. Mahajan, H. Brar, S. Idris, N. Idris, S.B. Coutts, M. Simpson, J.R. Mitchell, A. Martin.

INDEPENDENT MEDICAL AND NEUROINTERVATIONAL MONITORS:

- Internal: P. Khatri, D. Kanter, J. Spilker, J. Frasure, J. Carrozzella.
- External: S. Levine and P. Meyers.

SCIENTIFIC ADVISORY COMMITTEE:

- T. Brott, G. DelZoppo, H. Cloft, G. Howard.

DATA AND SAFETY MONITORING BOARD:

- P. Lyden, C. Coffey, M. Di Tullio, C. Jungreis, C. Wijman and from NINDS J. Cordell.

NINDS ADMINISTRATION:

- S. Janis, W. Galpern.

COORPORATE PARTNERS:

- Genentech, Inc.,
- Codman Neurovascular (a business unit of Codman & Surtleff, Inc.),
- EKOS Corporation,
- Concentric Medical Inc. (a wholly owned subsidiary of Stryker Neurovascular),
- Penumbra, Inc,
- ev3 Neurovascular (division of Tyco Healthcare Group d/ b/a/ Covidien).