

What We Have Learned from IMS III

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- IMS III – P.I., co-investigator MR Rescue
- Receive drugs from Genentech for two ongoing NINDS studies and from Schoering-Plough/Merck for one NINDS study
- DSMB Chair for NEST III Study

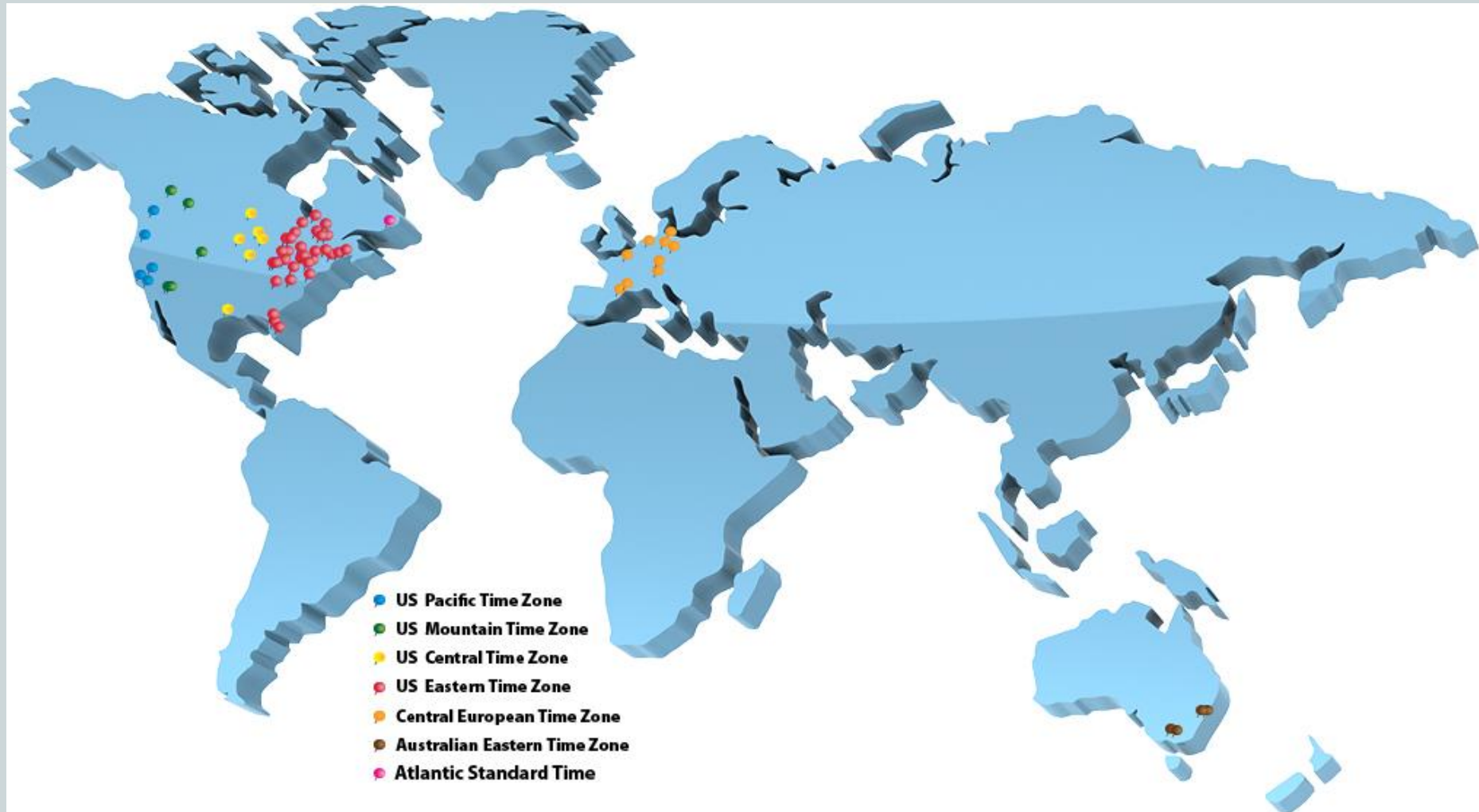
High-Quality Phase III Trials Comparing Endovascular Therapy with Best Medical Therapy Are Doable

- 656 subjects randomized into IMS III from August 25, 2006 to April 17, 2012 in the United States (41 sites), Canada (7), Australia (4), and Europe (6).

High-Quality Phase III Trials Comparing Endovascular Therapy with Best Medical Therapy Are Challenging

- Several sites in IMS I and II wouldn't randomize in IMS III because of “ equipoise ” and standard of care driven in part by reimbursement of devices.
- Several sites failed to randomize and left study because of equipoise regarding randomization.
- Recruitment rate per site in Europe > Australia > Canada > U.S.

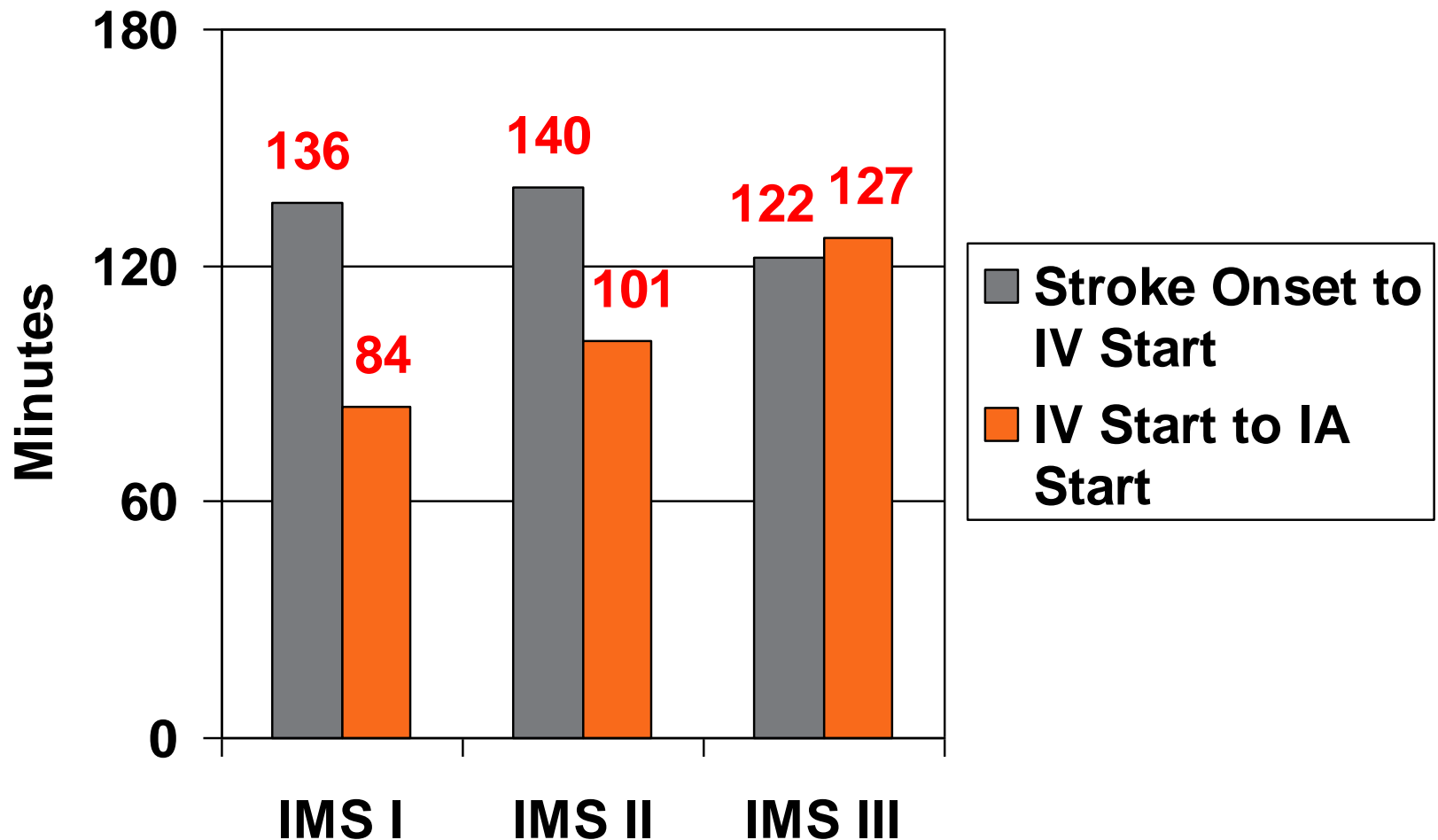
International Trials Are Needed for Phase III Trials Unless Commitment to Randomization Increases in U.S. (Voluntary or Forced)



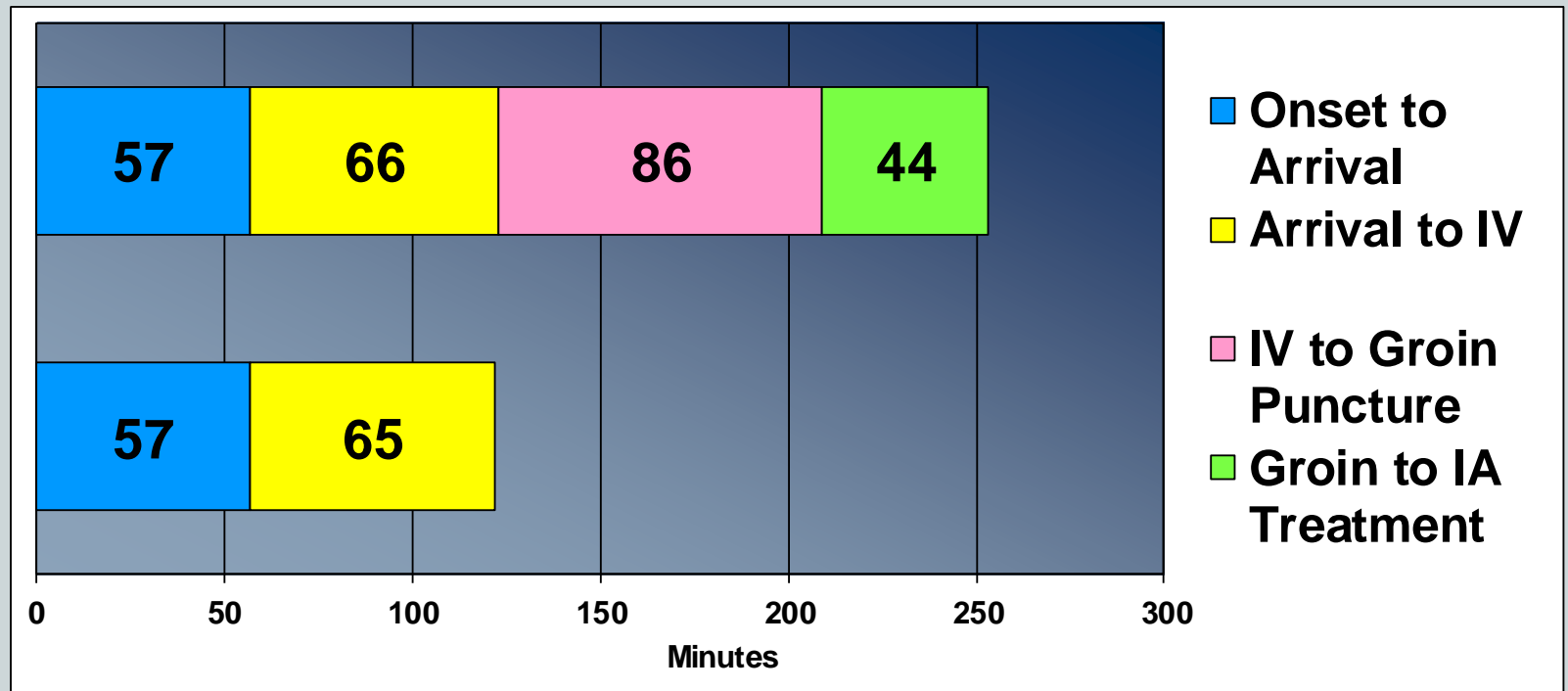
Many Stroke Patients Who Are Treated with IV t-PA Aren't Eligible for Trials of Endovascular Therapy

REASON	N (Percent)
NIHSS less than 10 when t-PA started	1385 (26.6)
Less than age 18 and greater than age 82	1360 (26.1)
Informed consent could not be obtained	315 (6.1)
Unable to be treated with IV t-PA within 3 hours	302 (5.8)
Unable to be randomized within 40 min. after start of IV t-PA	281 (5.4)
Refused consent (did not want to participate in research)	128 (2.5)
Competing trial	94 (1.8)
Any condition investigator judged would place patient at risk	93 (1.8)
Other reasons	427 (8.2)
Reason not categorized	812 (15.6)
Total	5197

Starting t-PA Prior to Randomization Substantially Decreases Time to t-PA



Time to Endovascular Therapy at Even Our Best Sites is Too Long



Time from Onset to IA Therapy: 249 minutes

IMS III Did Not Show Overall Clinical Benefit for Endovascular Therapy Following t-PA as Tested in Trial

	NIHSS 8-19		NIHSS ≥20		All	
	Endovascular	IV t-PA only	Endovascular	IV t-PA only	Endovascular	IV t-PA only
MRS ≤2 (%)	146 (48.3)	74 (49.3)	31 (23.5)	12 (16.7)	177 (40.8)	86 (38.7)
Risk Difference	-0.01 (-0.11, 0.09)		0.07 (-0.04, 0.18)		0.02 (-0.06, 0.09)	
CMH p-value 0.70						
Breslow Day p-value 0.27						

90-Day Modified Rankin Scale Score Distribution All Subjects

	0	1	2	3	4	5	6
Endovascular N=415	12.8	16.6	13.3	17.1	15.4	4.8	20
IV tPA Alone N=214	8.9	18.2	13.1	16.4	14.0	7	22.4

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

Patients with Moderately Severe
Deficits Had No Evidence of Benefit

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

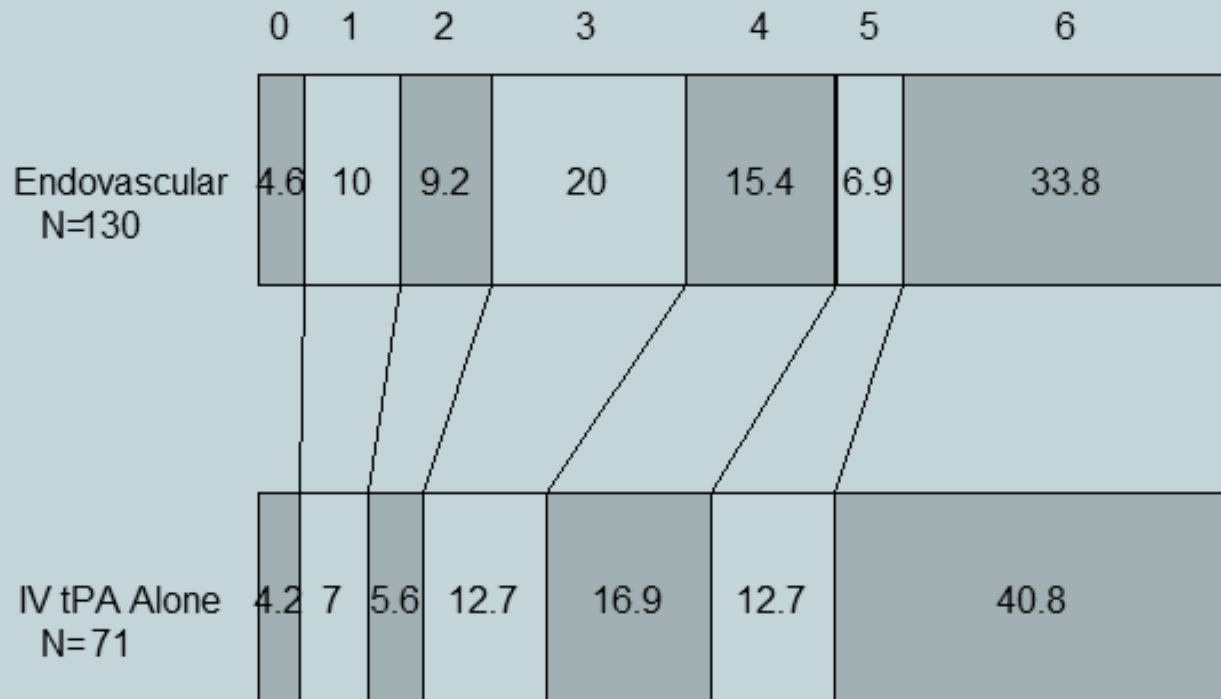
	0	1	2	3	4	5	6
Endovascular N=285	16.5	19.6	15.1	15.8	15.4	3.9	13.7
IV tPA Alone N=143	11.2	23.8	16.8	18.2	12.6	4.2	13.3

Differences between the two treatment groups across the entire distribution for the ≤ 19 NIHSS stratum

($p = 0.83$)

Most Signal for Benefit is in Those
with Very Severe Baseline Deficit,
Although Subgroup Not Statistically
Significant

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



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

Time to Start of Endovascular
Therapy is Important in The
Demonstration of Efficacy as
Compared to Best Medical Therapy

Time to IV t-PA and Time from t-PA to Groin Puncture

IV tPA to Puncture

Onset to IV

<=90 Minutes (N= 242):

All IV t-PA Treated(N=222)



1.15 [0.88 , 1.50]

>90 Minutes (N= 177):

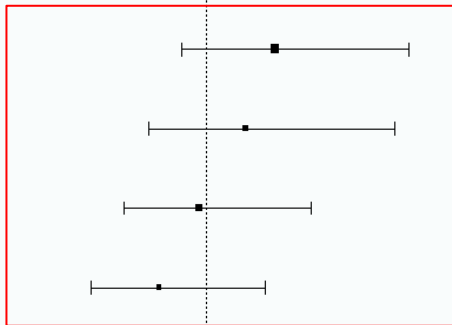
All IV t-PA Treated(N=222)



0.98 [0.72 , 1.32]

<=90 Minutes (N= 131):

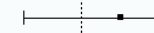
<=120 Minutes (N= 119)



1.29 [0.90 , 1.86]

>90 Minutes (N= 90):

<=120 Minutes (N= 119)



1.17 [0.76 , 1.80]

<=90 Minutes (N= 111):

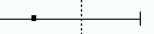
>120 Minutes (N= 103)



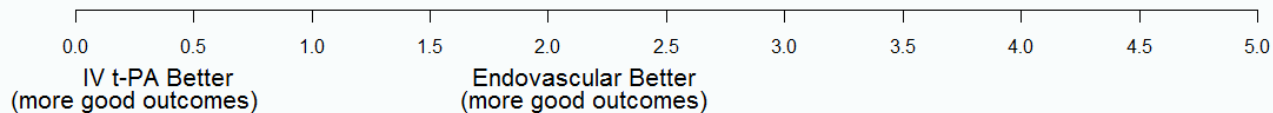
0.97 [0.66 , 1.44]

>90 Minutes (N= 87):

>120 Minutes (N= 103)

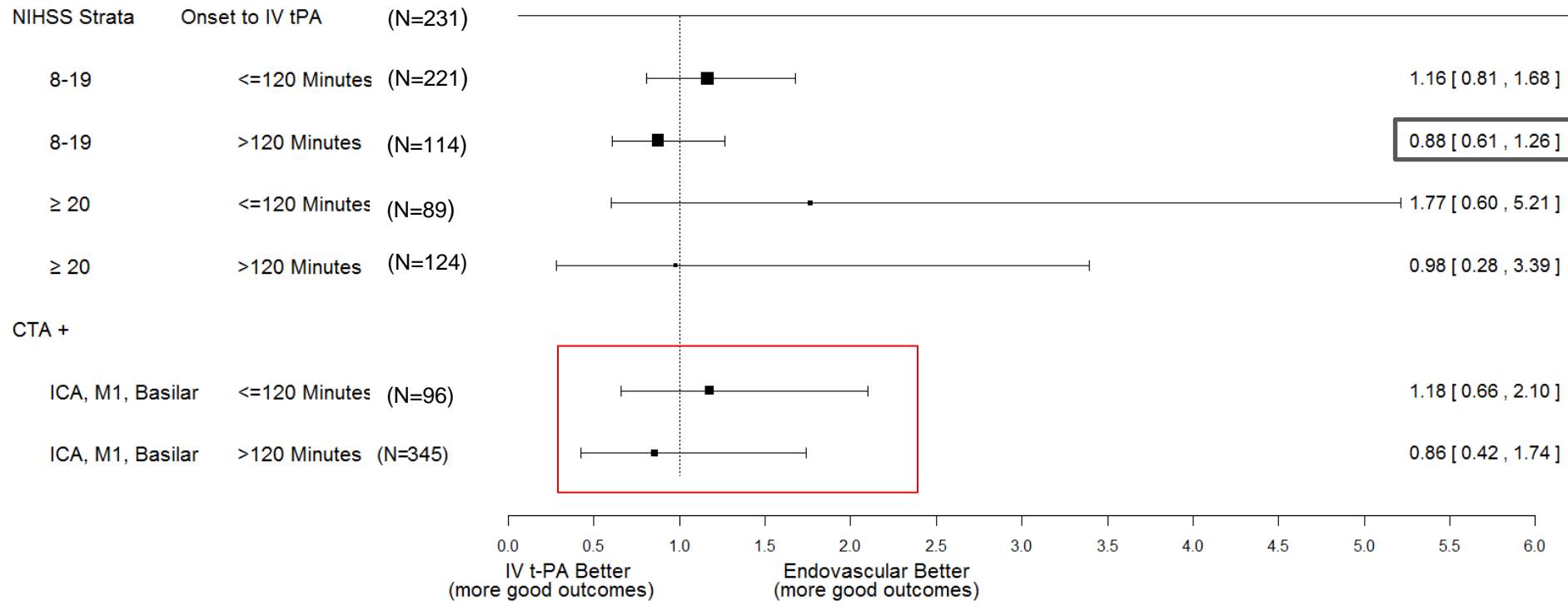


0.80 [0.52 , 1.25]



Overall, Patients with ICA, M1, or
Basilar Occlusion on Baseline CTA had
No Benefit from Endovascular
Therapy

NIHSS Strata and CTA+ by Time to IV t-PA

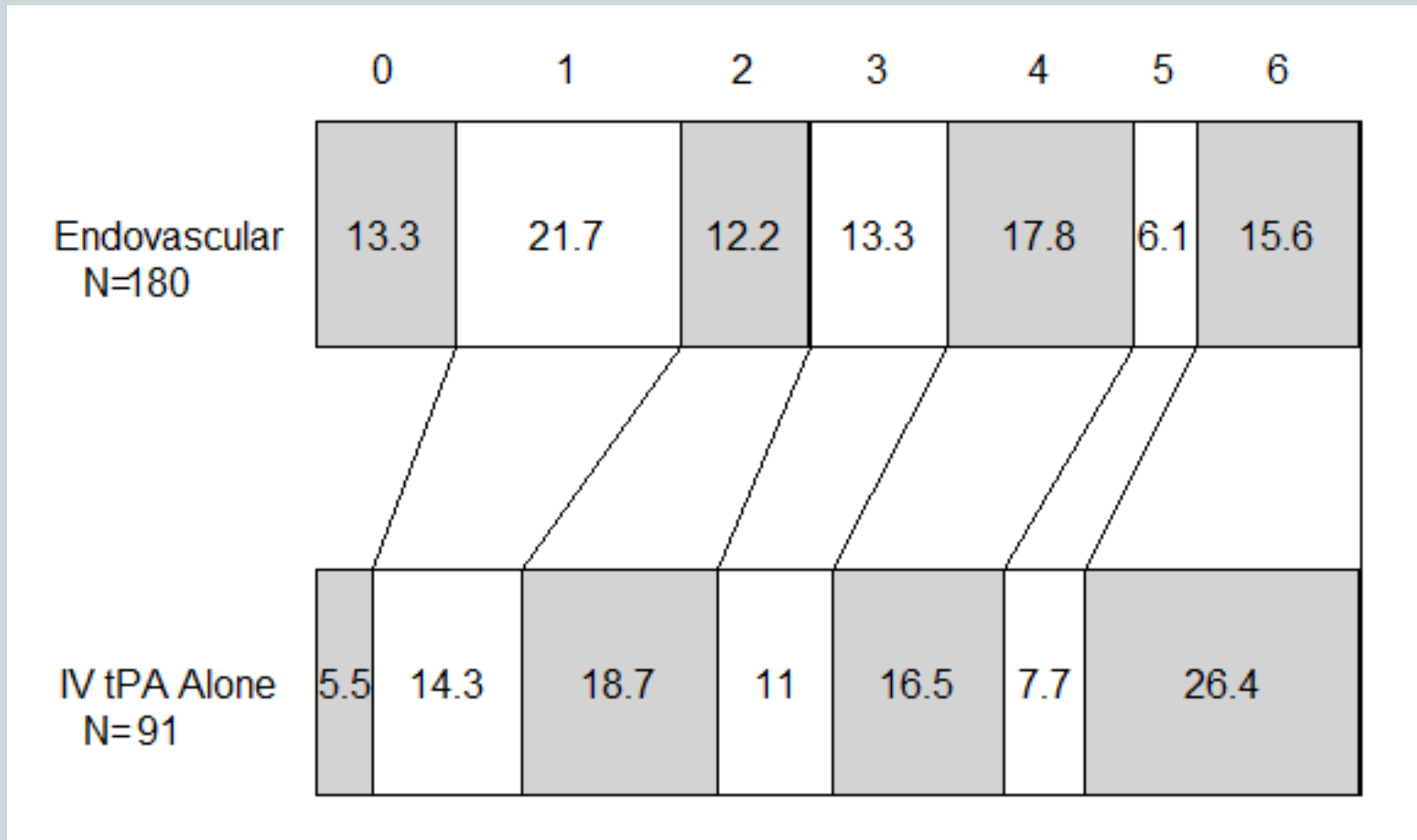


Endovascular Therapy's Potential
Benefit Varies By Location of Pre-
treatment Occlusion...

But Not Necessarily What We Thought

And IV t-PA Opens Up Major Artery
Occlusions Better than Expected,
Except for Terminal ICA

90-Day mRS Distribution, Baseline CTA Occlusion Present



van Elteren test p-value 0.0114

Post-hoc analysis

CTA Recanalization by Treatment Arm

Baseline Primary Occlusion Vessel Category	Endovascular			IV tPA Only		
	Subjects with Baseline CTA	Subjects with 24 hour* CTA	Percent Recanalized** of Subjects with 24 hour* CTA	Subjects with Baseline CTA	Subjects with 24 hour* CTA	Percent Recanalized** of Subjects with 24 hour* CTA
All	190	147	85.71%	92	69	60.87%
ICA-T/L	39	23	82.61%	19	14	28.57%
Other Intracranial ICA	5	3	66.67%	3	3	66.67%
M1	102	85	85.88%	47	34	67.65%
M2	34	26	88.46%	17	13	76.92%
Basilar only	1	1	100.0%	0	0	.
Vertebral & Basilar	3	3	66.67%	1	1	0.00%

Chi-square p value 0.001

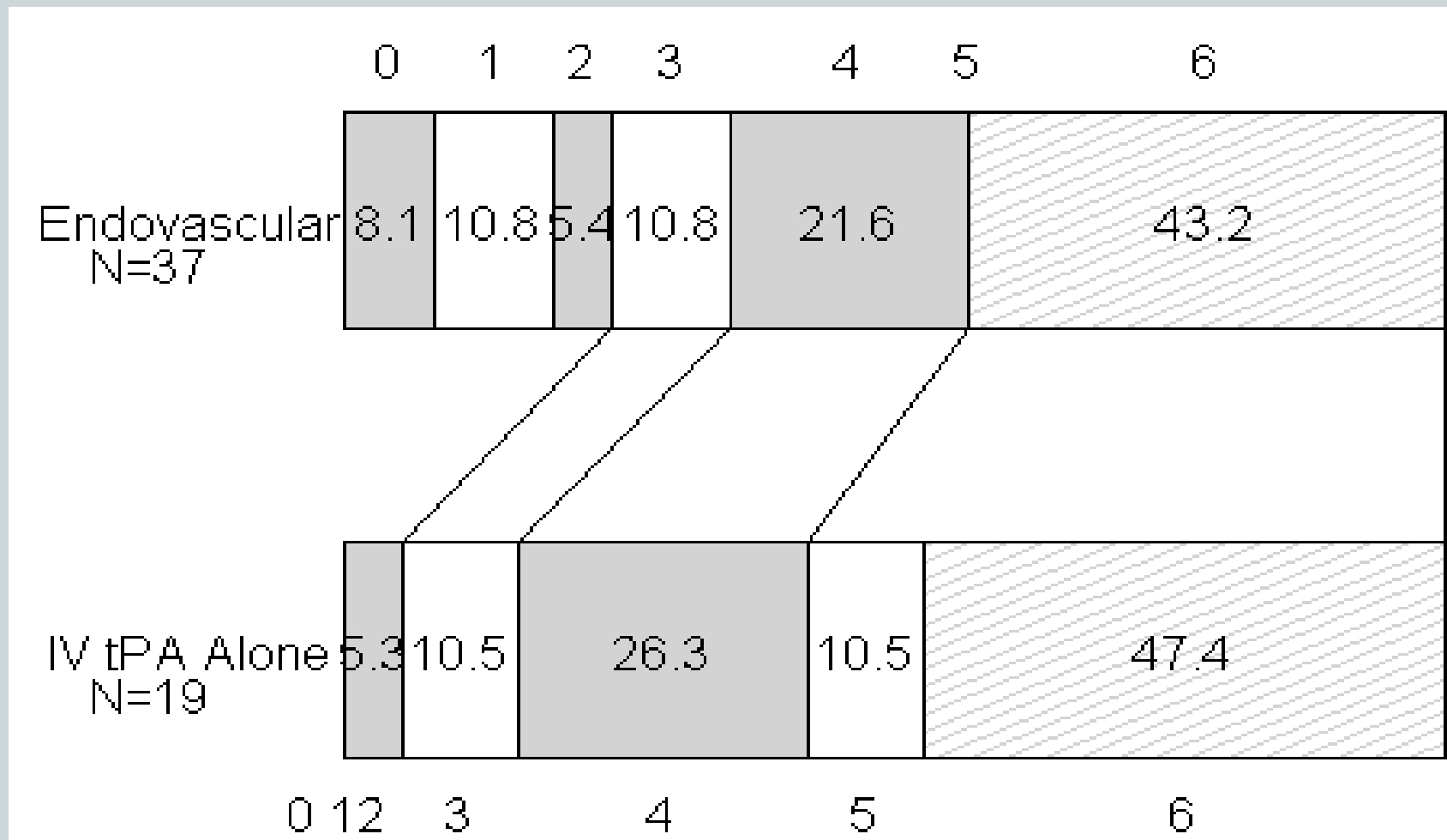
Post-hoc analysis: Carotid T/L or Tandem ICA+M1

Baseline Primary Occlusion Vessel Category	Endovascular				IV tPA Only			
	Subjects with Baseline CTA	mRS 0-2	Subjects with 24 hour* CTA	Percent Recanalized** of Subjects with 24 hour* CTA	Subjects with Baseline CTA	mRS 0-2	Subjects with 24 hour* CTA	Percent Recanalized** of Subjects with 24 hour* CTA
All	189	44.44%	146	86.30%	91	38.46%	68	64.71%
ICA-T/L	39	23.08%	23	82.61%	19	5.26%	14	28.57%
Tandem M1 with ICAo	7	42.86%	7	85.71%	4	0.00%	4	25.00%
Combined	46	26.09%*	30	83.33%**	23	4.35%*	18	27.78%**

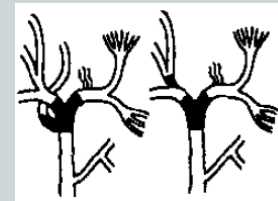
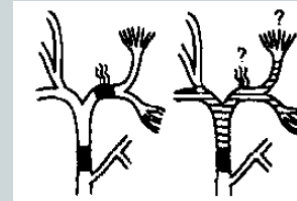
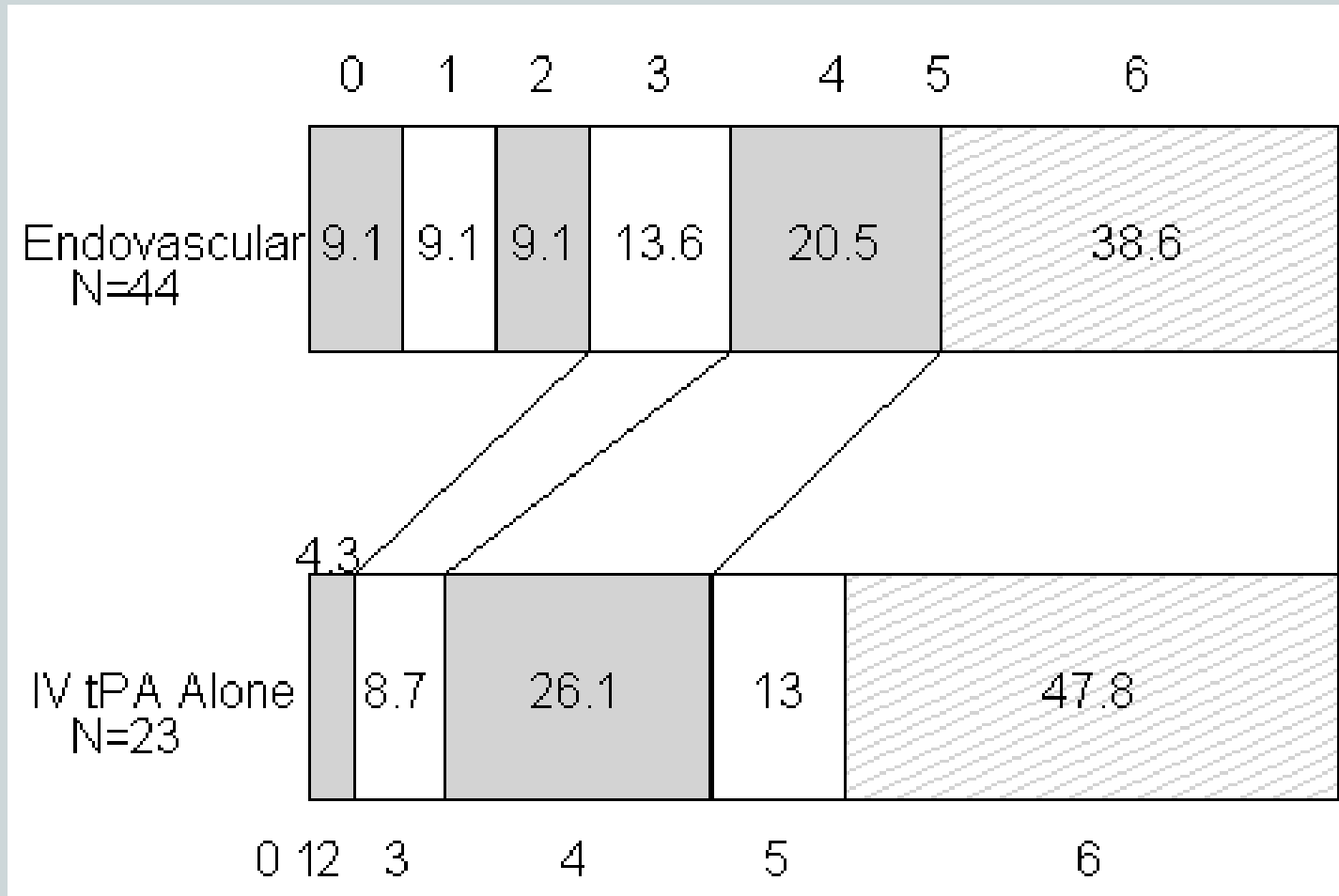
***Fisher p value 0.0471 (% mRS)**

****Chi-square p-value 0.0001 (% recanalized)**

90-Day mRS, Baseline CTA ICA-T/L Occlusions

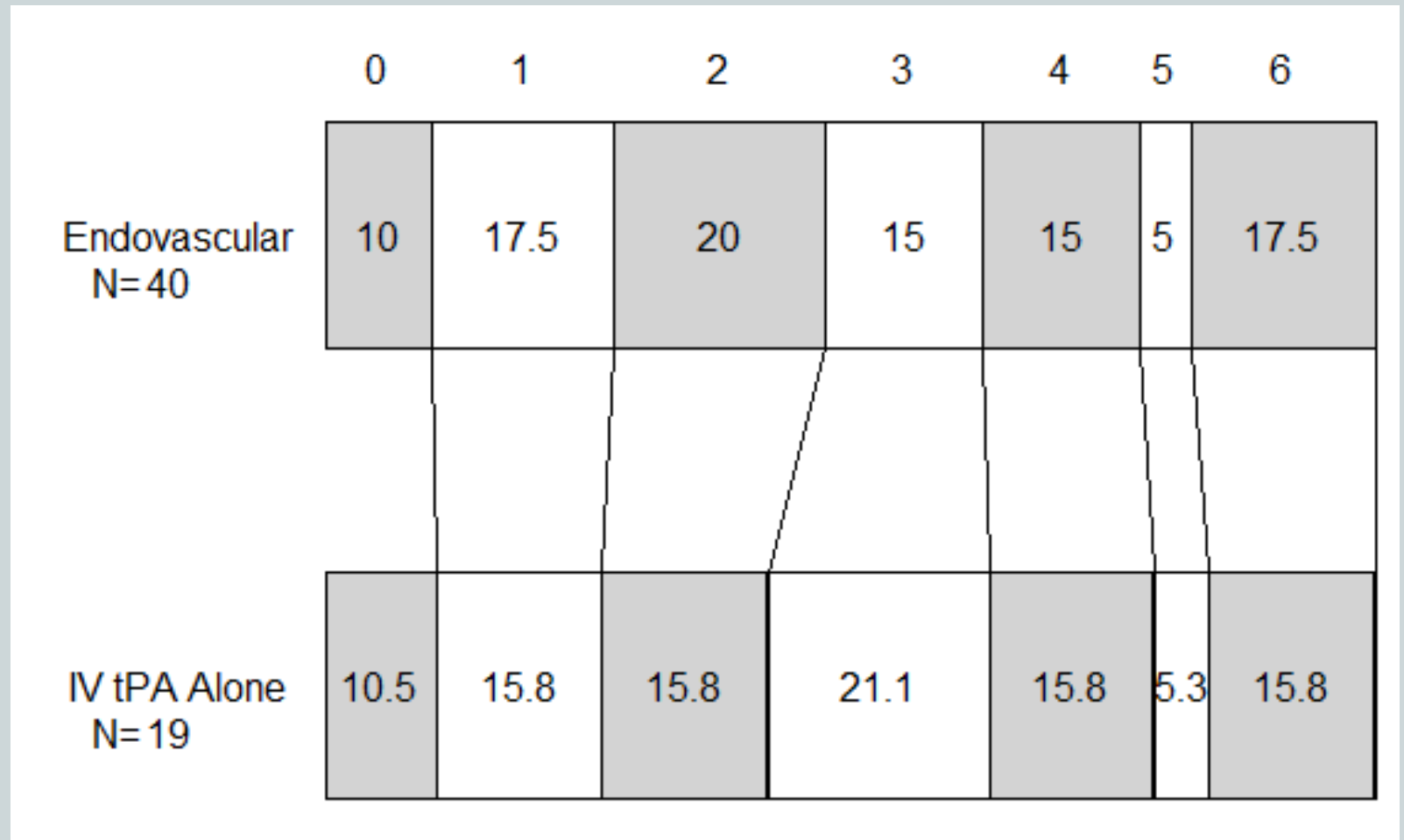


90-Day mRS Distribution, Baseline CTA: Carotid T/L or Tandem ICA+M1

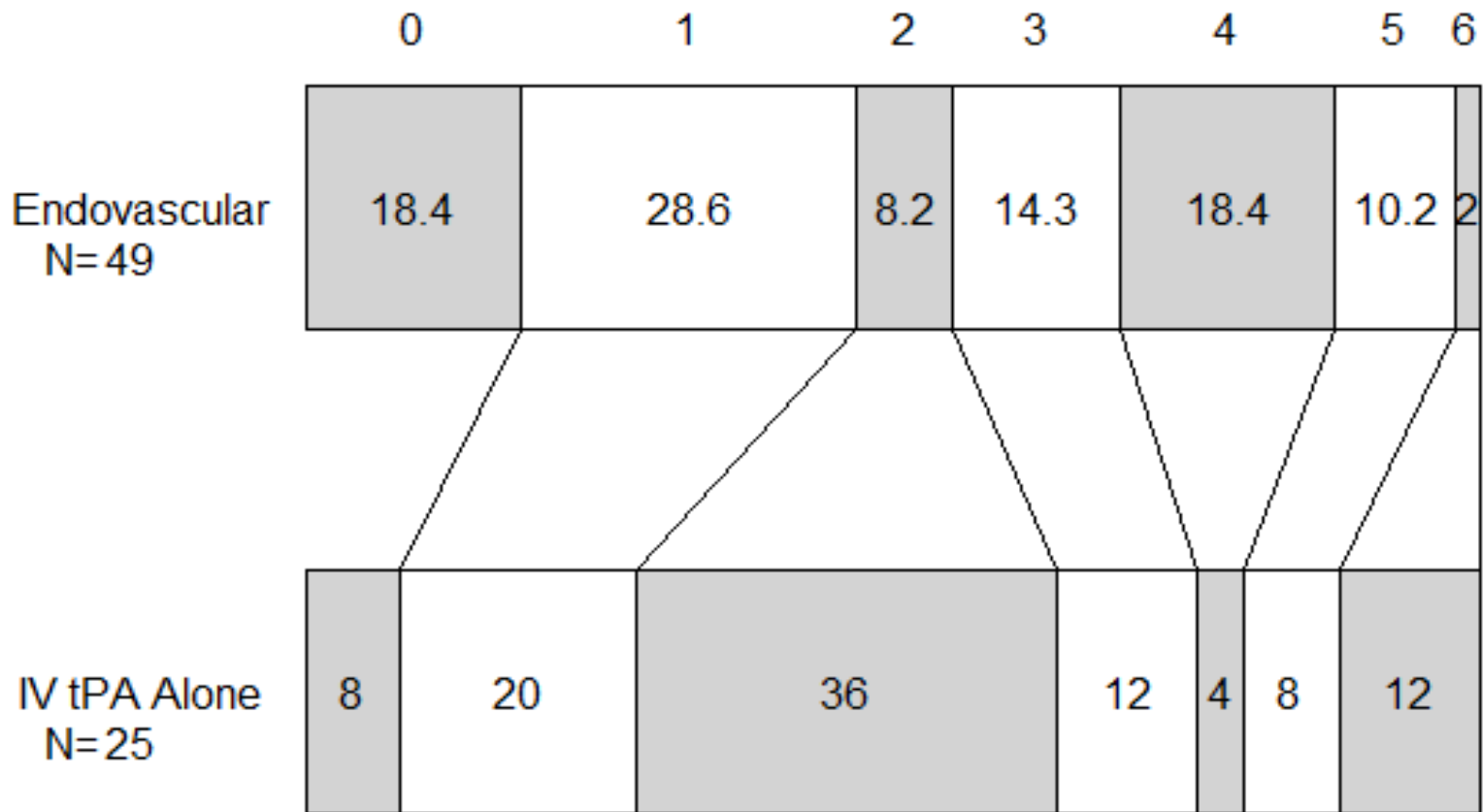


Ann Neurol 1992;32:78-86

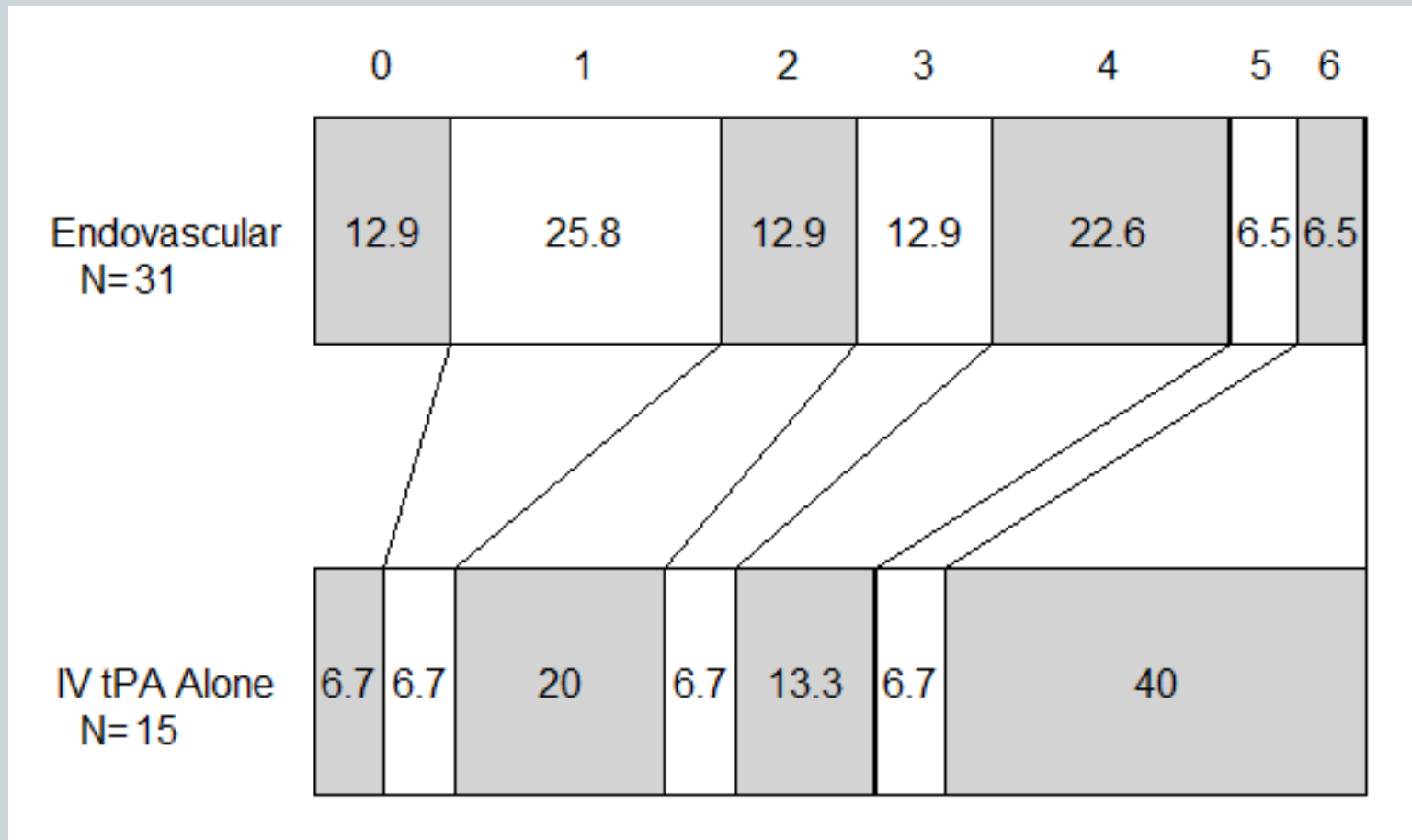
90-Day mRS Distribution, Baseline CTA Proximal M1, no ICAo Occlusion Present



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



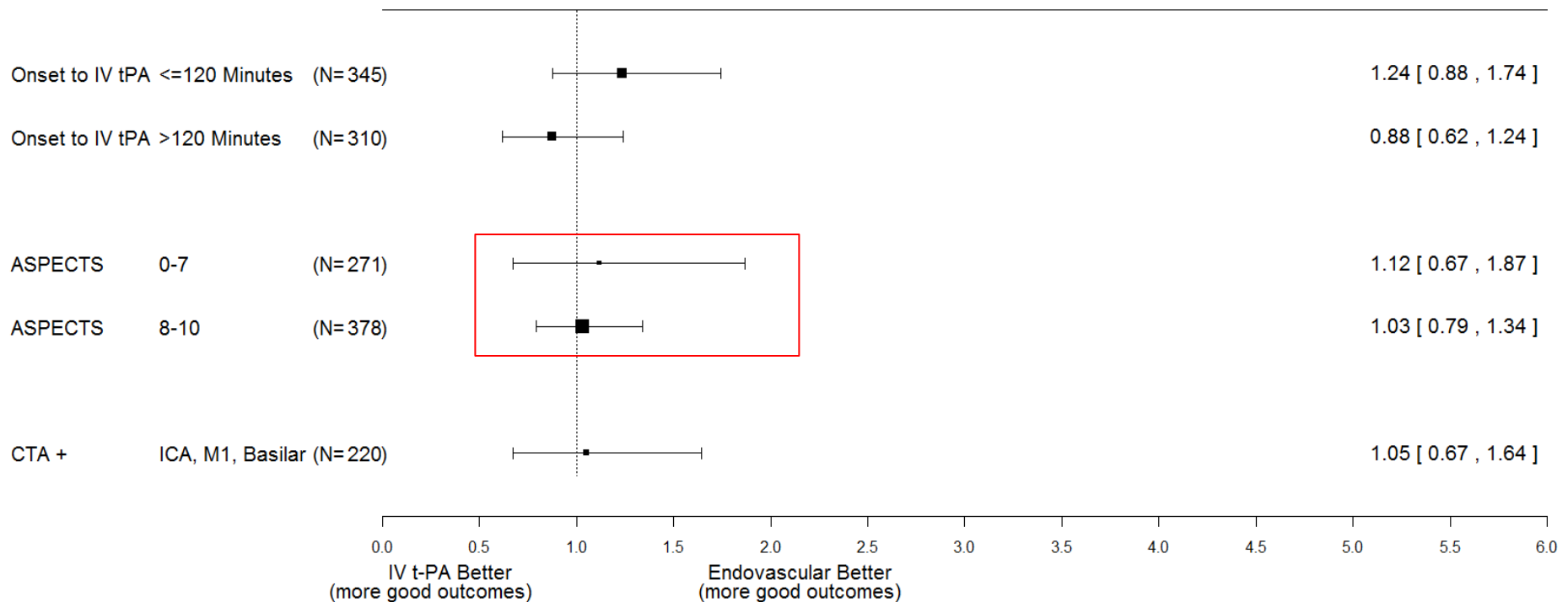
90-Day mRS Distribution, Baseline CTA M2, no ICAo Occlusion Present



van Elteren test p-value 0.0369

Baseline ASPECTS Score is Excellent
Predictor of Outcome but Poor
Predictor of Response to Therapy

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



Endovascular Therapy as Tested in
IMS III is Safe as Compared to IV t-
PA Alone As Measured by Death
and Symptomatic ICH

Safety Outcomes

	Endovascular	IV t-PA alone	CMH p-value
Death within 7 days (%)	52 (12)	24 (10.8)	0.57
Death within 90 days (%)	83 (19.1)	48 (21.6)	0.52
Symptomatic ICH within 30 hours of IV t-PA initiation (%)	27 (6.2)	13 (5.9)	0.83
Asymptomatic ICH within 30 hours of IV t-PA initiation (%)	119 (27.4)	42 (18.9)	0.01
PH2 ICH identified within 31 hours (%)	25 (6.0)	13 (6.3)	0.90

Safety Outcomes

	Endovascular	IV t-PA alone	CMH p-value
PH1 ICH identified within 31 hours (%)	15 (3.6)	3 (1.4)	0.12
Subarachnoid Hemorrhage	48 (11.5)	12 (5.8)	0.02
Intraventricular Hemorrhage	27 (6.5)	10 (4.8)	0.40
Major non-IC bleeding complications within 5 days (%)	13 (3)	5 (2.3)	0.55
Recurrent stroke within 90 days (%)	22 (5.1)	14 (6.3)	0.54
Device/procedural complications *	70 (16.1)		

*Complications included groin hematoma, vessel dissection, vessel perforation, emboli in previously uninvolved territory, as identified by either the site investigator or the central reader.

However, Endovascular Therapy Has Associated Complications That Likely Negatively Impact Patient Outcome (e.g. Merci and Protocol Violators)

Safety

ICH – Endovascular Group

All Occlusions (Cont'd)

	Standard Microcatheter		Ekos		Merci		Penumbra		Solitaire		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	t-PA	No t-PA
	n= 132	n= 3	n= 22	n= 0	n= 57	n= 37	n= 38	n= 15	n= 2	n= 3	n= 8	n= 7
PH-2	4.5%	0.0%	4.5%	NA	14.0%	5.4%	2.6%	6.7%	0.0%	0.0%	0.0%	0.0%
PH-1	3.8%	0.0%	4.5%	NA	1.8%	8.1%	2.6%	13.3%	0.0%	0.0%	12.5%	0.0%
PH-1 or PH-2	8.1%		9.1%		14.9%		9.4%		0.0%		6.7%	
HI-2	14.4%	0.0%	40.9%	NA	21.1%	21.6%	18.4%	13.3%	50.0%	0.0%	25.0%	0.0%
SAH	6.8%	33.3%	9.1%	NA	29.8%	8.1%	7.9%	20.0%	50.0%	0.0%	12.5%	28.6%

Adverse Events

Endovascular Group

All Occlusions

	Standard Microcatheter		Ekos		Merci		Penumbra		Solitaire		Other	
	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	t-PA	No t-PA
	n= 138	n= 4	n= 22	n= 0	n= 57	n= 38	n= 38	n= 16	n= 2	n= 3	n= 9	n= 7
New Emboli (Core Lab)	4.3%	0.0%	4.5%	NA	21.1%	23.7%	0.0%	12.5%	50.0%	33.3%	11.1%	42.9%
Perforation (Core Lab)	0.0%	0.0%	0.0%	NA	0.0%	5.3%	0.0%	6.3%	50.0%	0.0%	0.0%	0.0%
Dissection (Operator)	0.7%	0.0%	0.0%	NA	1.8%	2.6%	2.6%	12.5%	0.0%	0.0%	0.0%	14.3%
Death 90 days	17.4%	50.0%	18.2%	NA	26.3%	34.2%	10.5%	25.0%	50.0%	0.0%	33.3%	42.9%

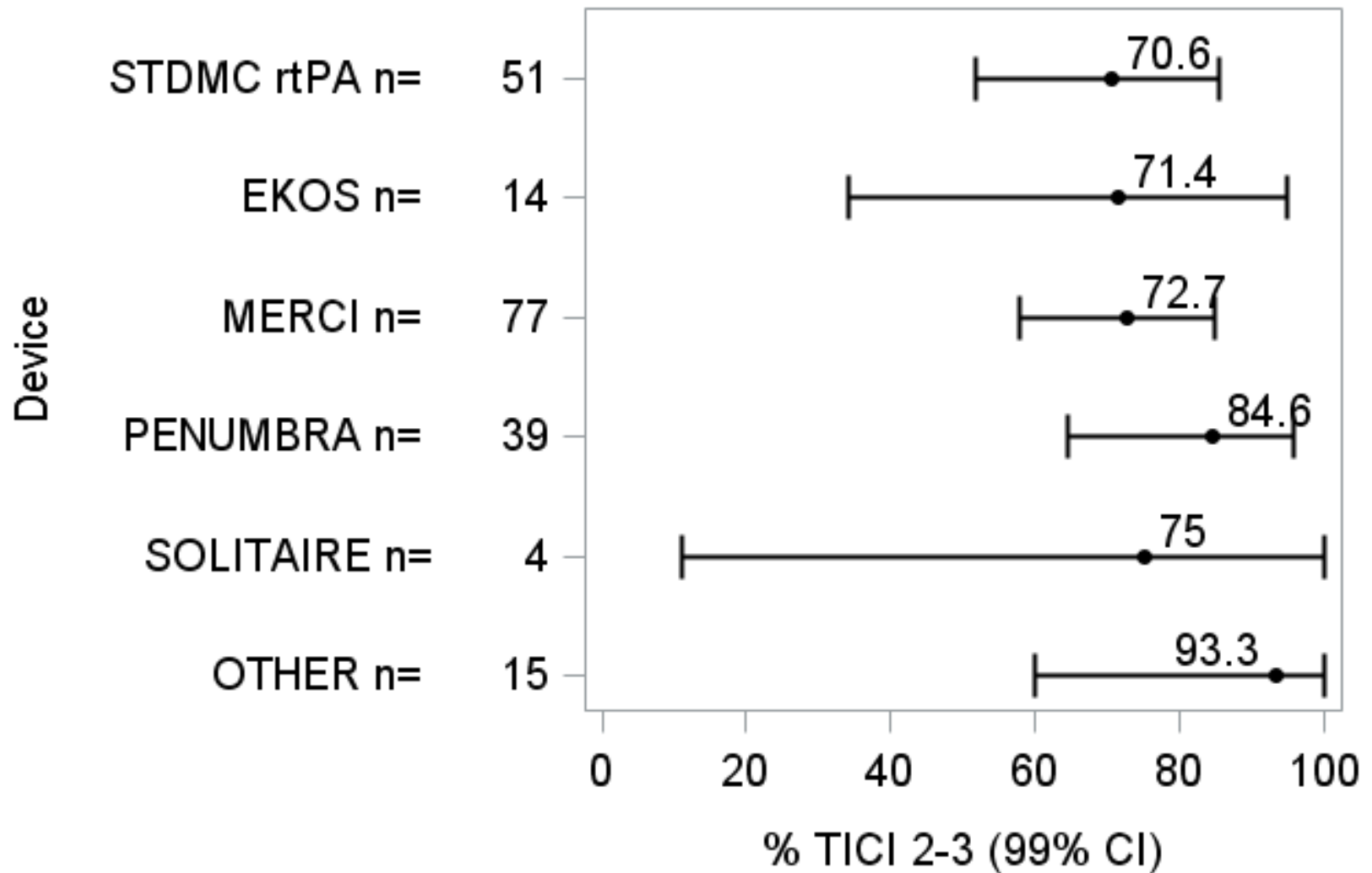
Significance of New Emboli?

90-day mRS Outcome by Presence of New Emboli
(ICA, M1 Occlusion)

New Emboli (Core Lab)	N	mRS ≤ 2	
		N	(%)
No	172	52	30.23%
Yes	28	5	17.86%

New Technology is Better Than Old Technology in Opening Intracranial Occlusions

% TICl 2-3 (99% CI) by Device for Subjects with ICA and M1 occlusions



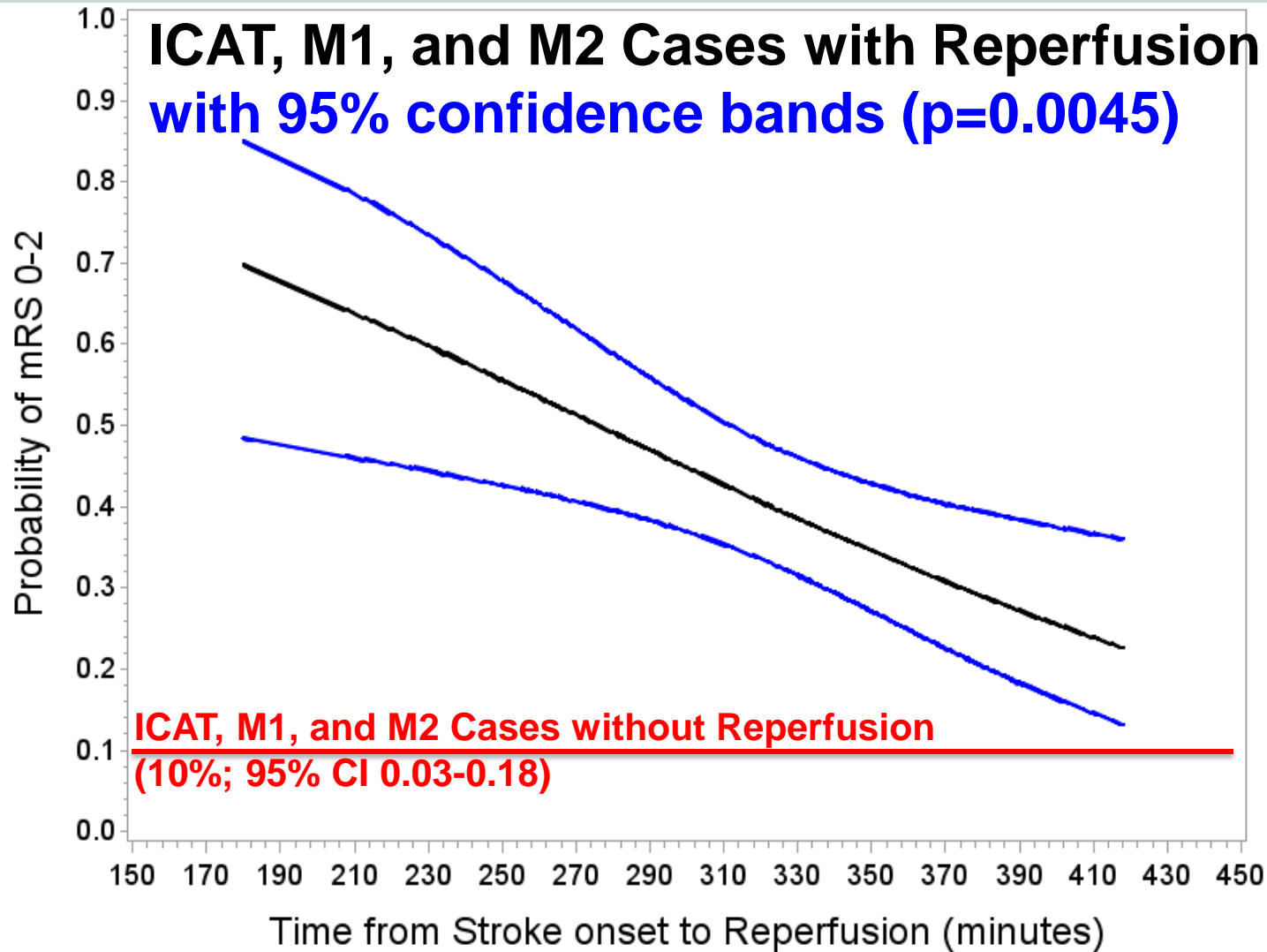
Reperfusion is Good But Time to
Reperfusion is More Important with
Regards to Clinical Outcome

Revascularization Predicts Good Outcome For ICA, M1 Occlusion

	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%	
	6.3%		35.5%			p < .0001
	13.9%			48.2%		p < .0001

Additional Considerations

Point of No Clinical Return?



Reperfusion vs No Reperfusion

Mean age
66.2 vs 65.6

Median NIHSS
18 vs 17

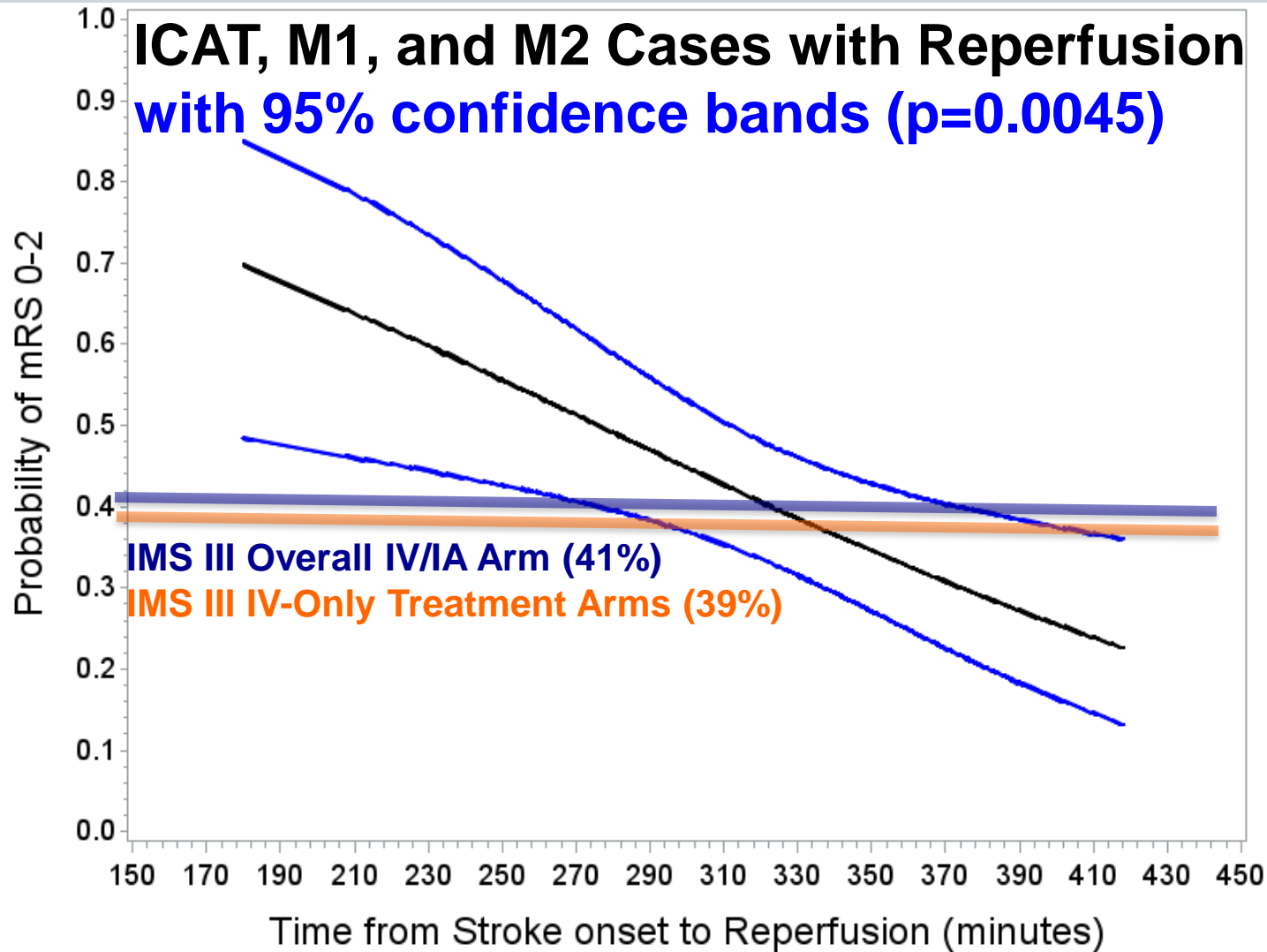
ASPECTS >4
85.5% vs 84.2%

mRS 2
40.1% vs 10.3%

Further analysis
pending

Additional Considerations

IMS III Result?



Would
faster transition
from IV start to
IA start
or
faster IA
procedure
times
have led to
better outcome
rates in
the IV/IA arm of
the IMS III?

Summary

- A great deal learned about endovascular therapy for acute stroke (more to come)
- Great equipoise about endovascular therapy as compared to IV t-PA alone in setting of M1 and M2 occlusions
- New randomized trials are needed to address this question as well as others and must focus on decreasing time to treatment and reperfusion