Use of NeuroFlo™ Catheter in Patients with Ischemic Stroke

FDA Neurological Devices Panel

CoAxia, Inc.

December 10, 2012

Sharon Kvistad

- Senior Regulatory Consultant – Anson Group
- Vice President, Regulatory Affairs – CoAxia, Inc. 2003 – 2012
- Financial Disclosure
  - Shareholder of CoAxia, Inc.
  - Paid consultant

Meeting Purpose

To solicit the Panel's input on:

"Current knowledge of the safety and effectiveness of the NeuroFlo Catheter for use in patients with acute ischemic stroke within 14 hours of symptom onset."

Introduction

- CoAxia seeks “ischemic stroke” labeling for use of the NeuroFlo catheter
- Basis for labeling:
  - Existing 510(k)
  - De Novo Classification
  - SENTIS clinical trial data
    - Device safety
    - Patient benefit
- Indicated patients: ischemic stroke
  - Large patient population in need
  - No effective treatment alternatives

Participants

Presenters

–Sharon Kvistad, Consultant, Anson Group

–Susan Alpert, PhD, MD, Consultant

–Louis Caplan, MD, Harvard/Beth Israel

–Jeffrey Saver, MD, UCLA

–Helmi Lutsep, MD, Oregon Health & Science University

–Raul Nogueira, MD, Emory University

Responders

–Chris Mullin, MS, Statistician, NAMSA Inc.

–Lisa Thackeray, MS, Statistician, NAMSA Inc.

–Rick Schallhorn, MS, CoAxia Inc.

–Kay Zander, MS, CoAxia Inc.

Presentation Schedule

• **Panel Discussion Context**	**Susan Alpert, PhD, MD**
• Device Description & History	Sharon Kvistad
• Stroke Treatment Perspectives	Louis Caplan, MD
• SENTIS Study and Interpretation	
– Study Design	Jeffrey Saver, MD
– Safety	Helmi Lutsep, MD
– Patient Benefit	Jeffrey Saver, MD
– Clinical Interpretation	Raul Nogueira, MD
• Conclusion	Susan Alpert, PhD, MD

Susan Alpert, PhD, MD

- Principal, SFA Consulting, LLC
- Former Senior Vice President, Global Regulatory Affairs, Medtronic Inc.
- Former Senior Vice President, Regulatory Sciences, C.R. Bard, Inc.
- Former Director, Office of Device Evaluation, CDRH, FDA
- Financial Disclosure
  - No financial interest in CoAxia
  - Paid Consultant to CoAxia

De Novo Classification

- Low to moderate risk devices
- Benefit commensurate with level of risk
- Benefit/risk evaluation in applicable patient group
- Requires medical judgment of clinical data
  - Consideration of alternative therapies available
- Subject to general and special controls

*De Novo Benefit / Risk Considerations**

- Magnitude and probability of device impact (safety and efficacy)
  - Impact on clinical management of patients
  - Improvements in quality of life
  - Reduction in the probability of death
  - Aiding in the improvement of patient function
- Patient population
  - Is there an unmet clinical need?
  - What alternative therapies are available?
  - Not all patients need to experience every benefit
- Clinical and non-clinical data

*** FDA Guidance Document: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications**

De Novo Guidance

"It is not unusual for novel devices that address an unmet medical need to have relatively small probable benefits, and FDA may determine the novel device to be reasonably safe and effective even though the applicant demonstrates a relatively small probable benefit.

"In addition, the development of innovative technology may provide additional future benefits to patients.

"With subsequent iterations of the device its benefit-risk profile may change (e.g., the benefits may increase or the risks may be reduced), the expected level of safety and effectiveness may change, and later versions may offer significant advantages over the initial device.

"In these circumstances, in order to facilitate patient access to new devices important for public health and to encourage innovation, we may tolerate greater uncertainty in an assessment of benefit or risk than for most established technologies, particularly when providers and patients have limited alternatives available."

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De Novo Controls

- General and special controls
- Labeling
  - Patient population
  - Risks
  - Procedure Instructions
- Training to ensure appropriate use
- Surveillance to further evaluate effects in subpopulations
- Guidance documents for testing requirements for new devices of this type

Conclusion

For NeuroFlo:

- Is there benefit for stroke patients who today have no alternatives?
- Is this benefit sufficient to support marketing considering the moderate risks of NeuroFlo use?
- Is NeuroFlo use reasonably safe in this population?

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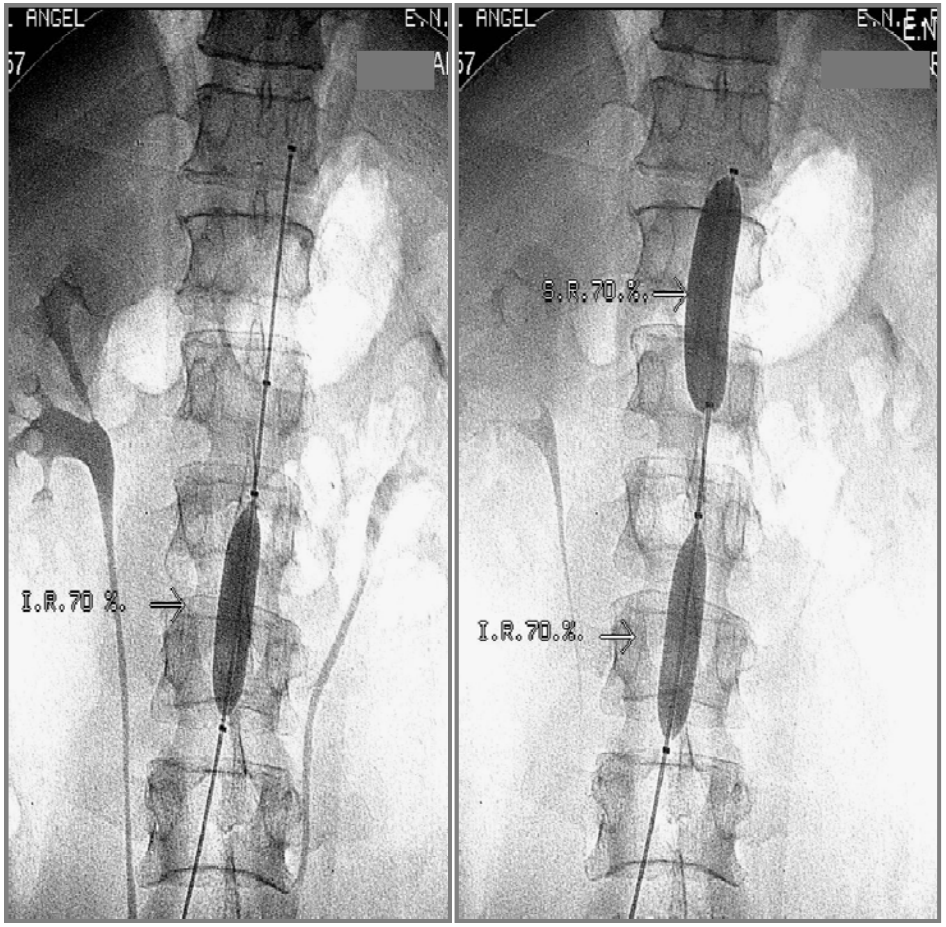
CoAxia NeuroFlo Catheter

- **FloControl** and **NeuroFlo** are the same device
- **Dual Balloon Catheter**
  - Manual, independent balloon inflation
  - Accommodates vessels 10mm-28mm in diameter
- **Procedure**
  - Placed in descending aorta via femoral access
  - 45 minutes of partial occlusion
  - Deflated and withdrawn

CoAxia NeuroFlo Catheter – Physiologic Effect



- Redirects blood flow
- Blood flow is decreased distal to the balloons and increased proximal to the balloons
- Use in abdominal aorta redirects blood flow to the cerebral vasculature

CoAxia Regulatory History

- FloControl 510(k) cleared 2003 & 2009
  - Indicated for “stopping/controlling blood flow in the descending aorta”
  - Redirection of cardiac output to the cardiac, spinal and cerebral vasculature described in the labeling
- NeuroFlo received Humanitarian Device Exemption approval for vasospasm-related cerebral ischemia after SAH - 2005
- NeuroFlo (FloControl) studied in specific ischemic stroke patient population – SENTIS
- Requested labeling for NeuroFlo to indicate use in ischemic stroke population via *de novo* petition

Clinical Discussion

- Stroke Treatment Perspectives (Louis Caplan, MD)
- SENTIS Study and Results
  - SENTIS Trial Design (Jeffrey Saver, MD)
  - SENTIS: Assessment of Safety results (Helmi Lutsep, MD)
  - SENTIS: Assessment of Benefit of NeuroFlo (Jeffrey Saver, MD)
- Importance in Patient Treatment (Raul Nogueira, MD)
  - Blood Flow Augmentation
  - Patient Selection
  - Clinical Need

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Louis Caplan, MD

- Professor of Neurology, Harvard Medical School, Beth Israel Deaconess Medical Center
- Founder, Harvard Stroke Registry
- Author/Editor of 41 books and over 600 articles
- Consulting Editor, The Stroke Journal
- Financial Disclosure
  - No financial interest in CoAxia
  - Not an investigator in SENTIS trial
  - Paid consultant for this Advisory Panel Meeting

Ischemic Stroke: No. 4 Killer in US

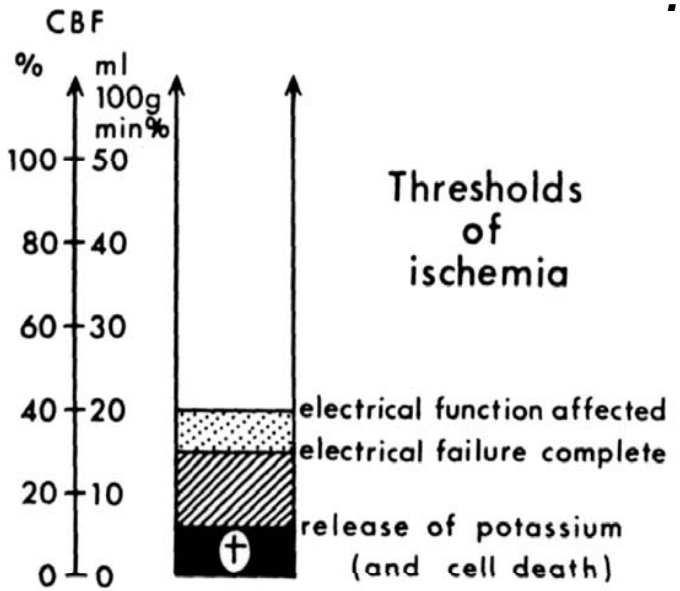
- 800,000 strokes annually in US of which 80% are ischemic
  - No. 1 cause of long term disability
  - $80B annual CMS long term care cost

- Less than 10% receive restorative acute treatment
  - Patients & families do not recognize stroke symptoms
  - Many cannot access stroke-center care
  - Many arrive too late for reperfusion therapies (thrombolysis and thrombectomy)
  - Blocked arteries often do not open, and even treated patients have strokes

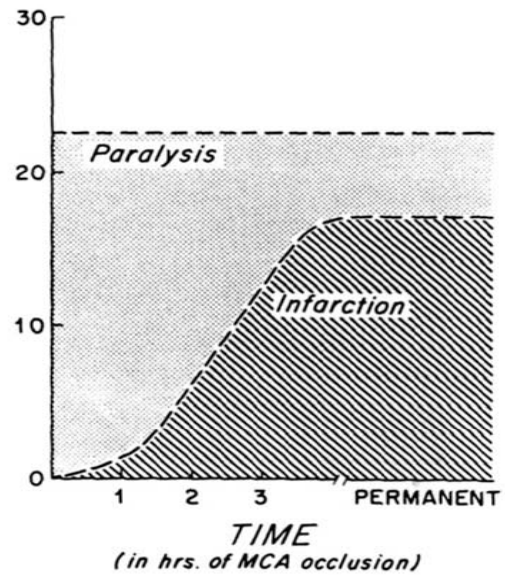
There is a Dramatic Need for New Acute Treatment Options for Patients with Ischemic Stroke

Stroke Pathophysiology

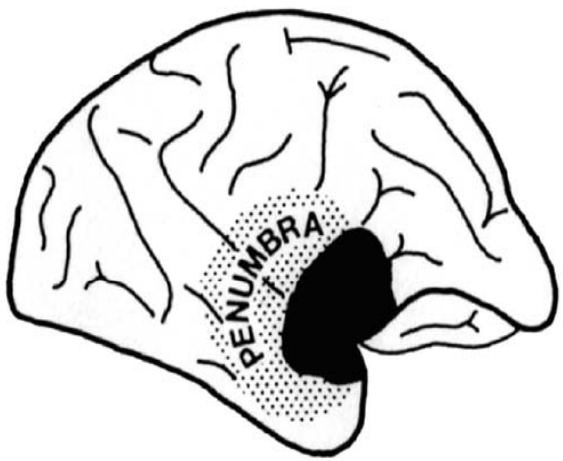
Occlusion Reduces Blood Flow Creating Ischemic Region . . .



. . . Which Over Time Creates Infarcted Tissue . . .



. . . Resulting in Dynamics Of Core Infarcted and Penumbral Regions



The Need for Reperfusion Has Been Known for Decades

Stroke Treatment Fundamentals

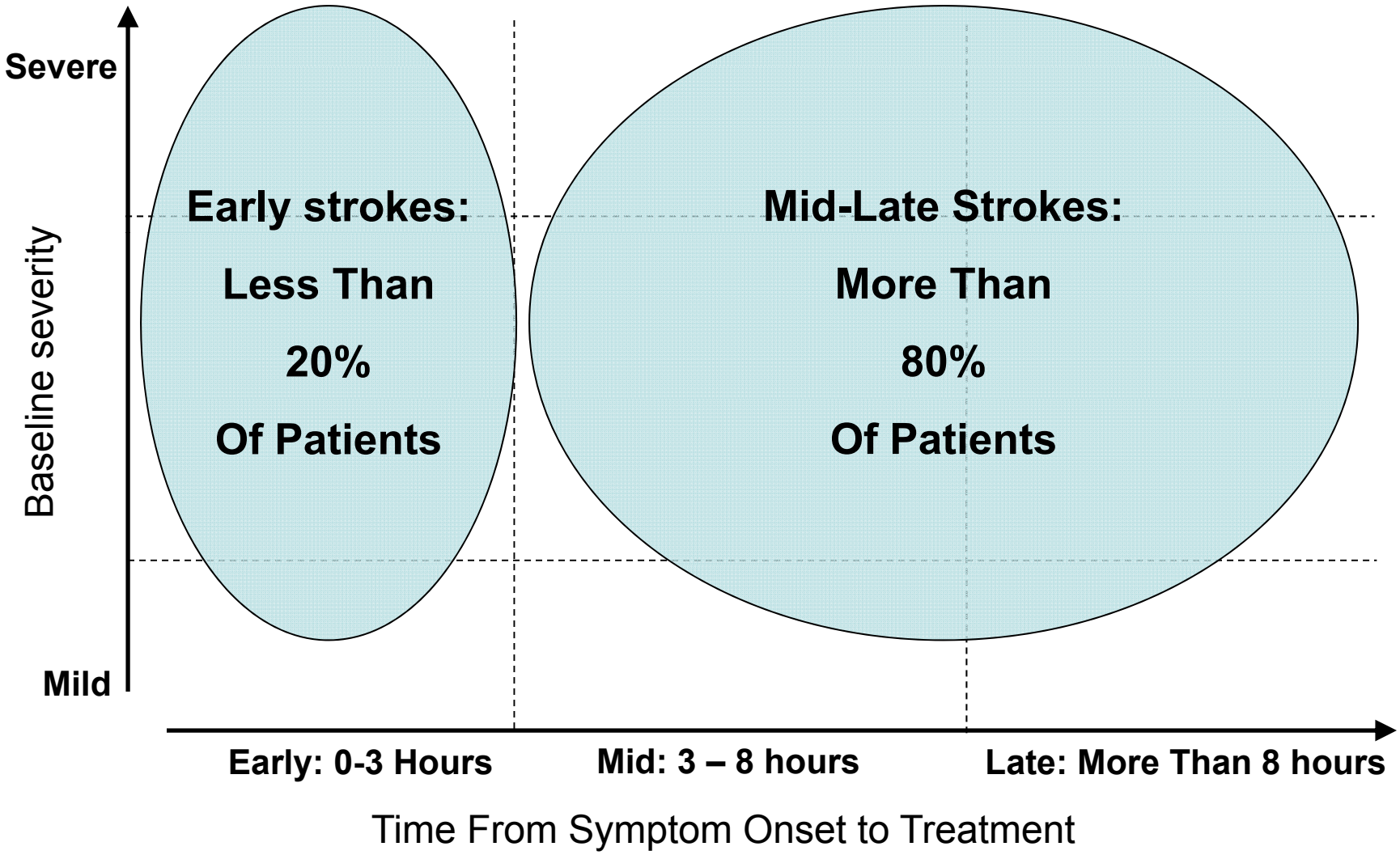
- Increase blood flow to the ischemic penumbra
- Improve tissue resistance to ischemic damage, i.e. neuroprotection

Increasing Blood Flow to the Ischemic Area

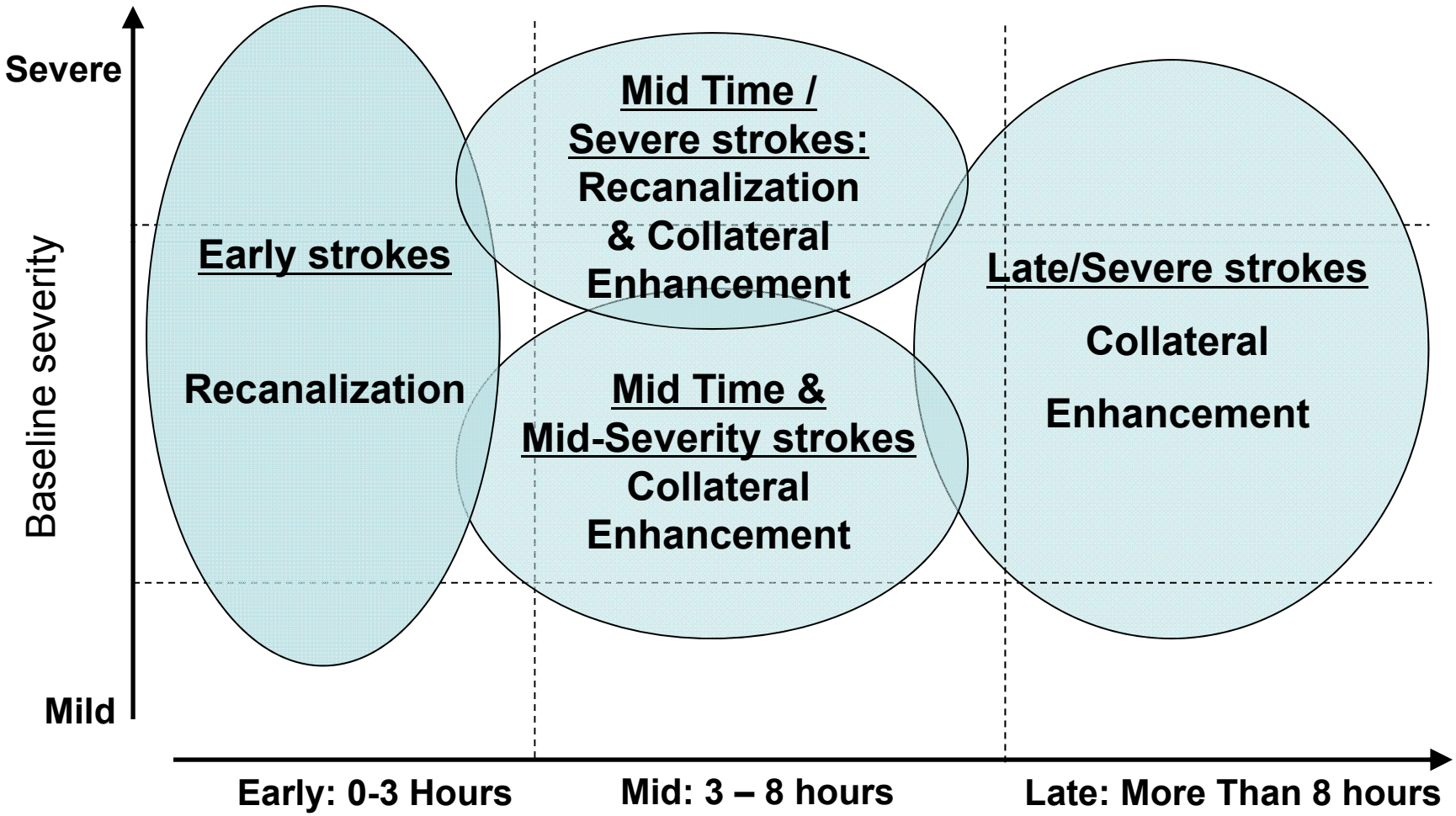
- **Open the blocked artery** ("on-label" and "off-label" techniques)
  - IV tPA (0 – 3 / 4.5 hours)
  - IA tPA and/or mechanical clot retrieval

- **Augment collateral flow**
  - Position in bed
  - Induced hypertension
    - Limited effect due to autoregulation
    - Risks include MI & CHF
  - Increase blood volume
    - Used in SAH-related vasoconstriction
    - Pulmonary congestion & hypoxemia decrease benefit
    - CHF & MI risks
  - NeuroFlo

Most Patients Ineligible for Current Acute Treatment Options

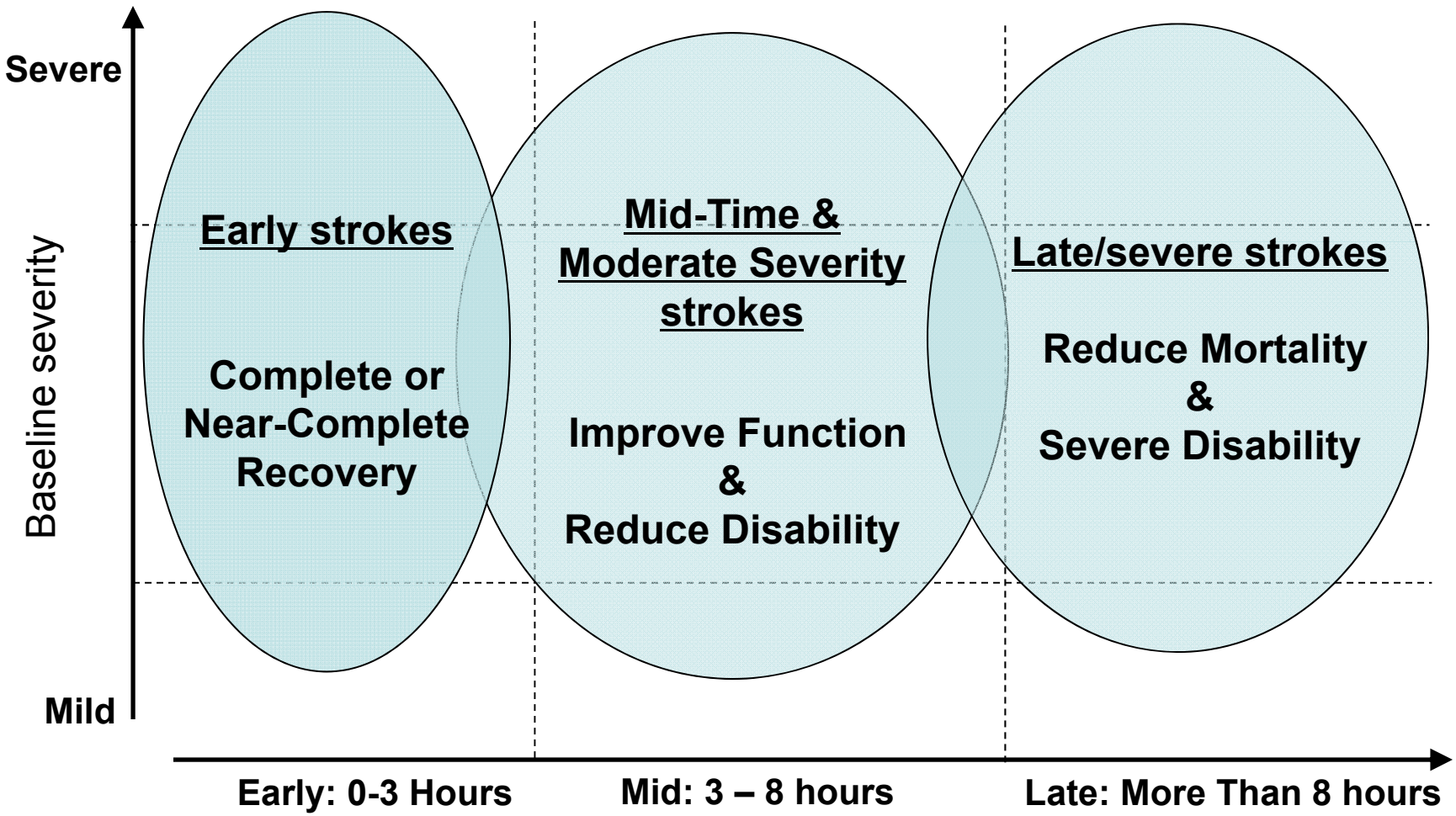


Treatment Modalities Vary By Patient



Time From Symptom Onset to Treatment

Treatment Objectives Vary By Patient



Time From Symptom Onset to Treatment

Ischemic Stroke Treatment Summary

- More than 80% of ischemic stroke patients arrive too late for, or are otherwise excluded from, recanalization treatments – and treated vessels often do not recanalize
- Collateral flow augmentation is the major reperfusion focus for excluded / mid / late patients
- Current collateral augmentation techniques have either not been effective or have important risks
- NeuroFlo augments collateral blood flow safely – even in excluded, mid-late arrival patients
- Any improvement in these patients to lower levels of disability is a very important benefit

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Jeffrey Saver M.D.

- Director, UCLA Stroke Center, Geffen School of Medicine
- Professor of Neurology, Geffen School of Medicine, UCLA

- Board Member, Society of Vascular and Interventional Neurology
- Former Chair, AHA Stroke Guidelines Committee
- Immediate Past Chair, AHA Stroke Leadership Council

- Financial Disclosure
  - No financial interest in CoAxia
  - Clinical Investigator and SENTIS Steering Committee member
  - Ongoing Advisor / Consultant
  - Paid Consultant for this Advisory Panel Meeting

SENTIS: Study Purpose

Evaluate safety and long term outcome of collateral augmentation via partial aortic occlusion in stroke patients ineligible for other interventions

Safety and
Efficacy of
NeuroFlo
Technology in
Ischemic
Stroke

SENTIS Trial Design

- Largest randomized study of an acute endovascular stroke device with a clinical endpoint (n=515 patients)
- Enrollment period: October 2005 thru January 2010
- Clinical outcome study
- Trial oversight by international Steering Committee
- Safety and data oversight by independent DSMB
  - All adverse events, SAEs, and deaths reviewed and adjudicated

SENTIS Trial Design

- Prospective, single-blind, randomized 1:1
- NeuroFlo treatment vs. standard medical management
- 90 Day follow-up
- Primary endpoints:
  - Effectiveness: Global Outcome Score at 90 days
  - Safety: All SAEs at 90 days
- Pre-specified, adjusted analyses for baseline covariates

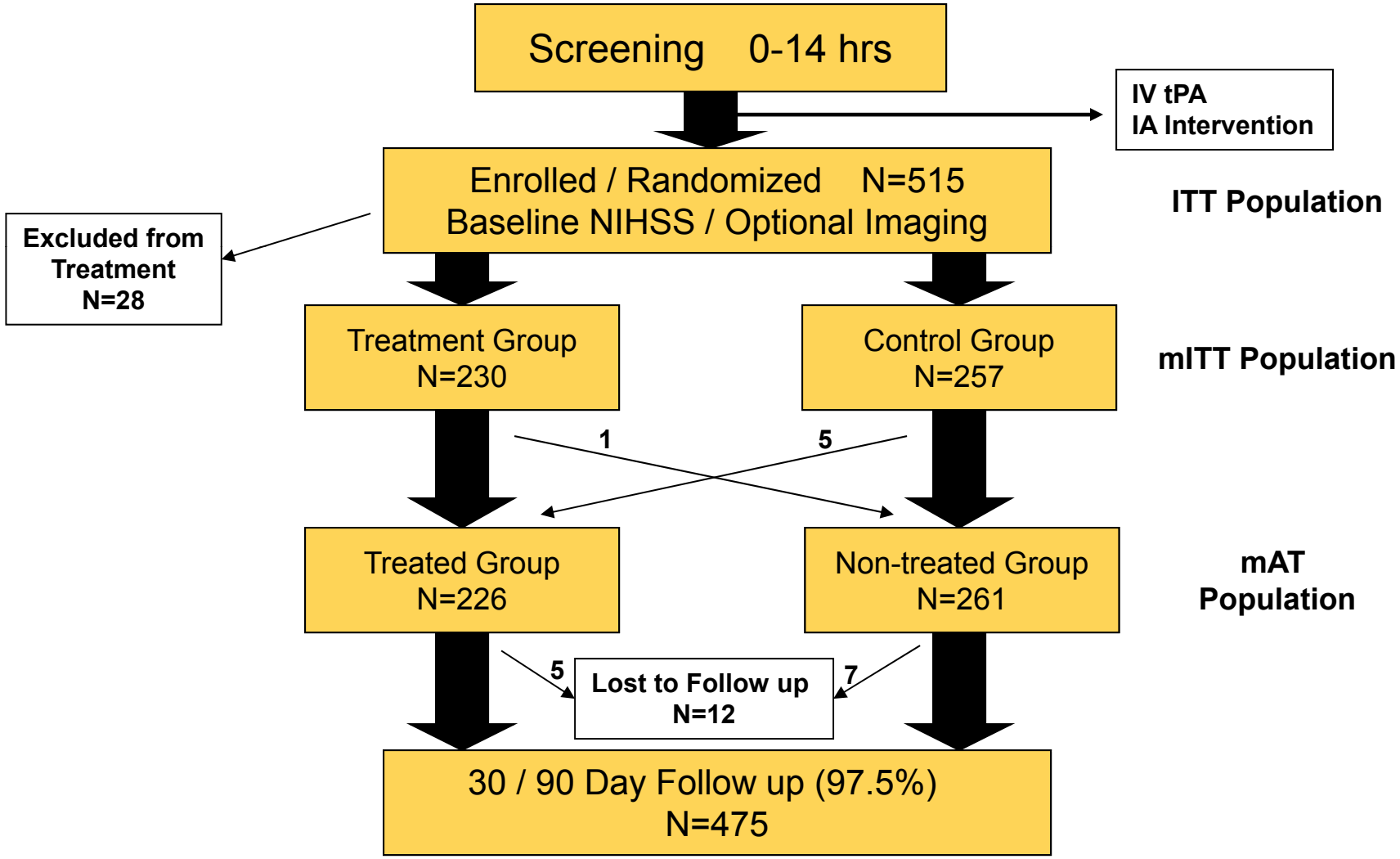
Rigorously managed trial at leading stroke centers

Patient Population

- Protocol Inclusion / Exclusion Criteria
  - Clinical diagnosis (cortical involvement)
  - No imaging entry criteria beyond ncCT (excl. if >1/3 MCA)
  - Baseline NIHSS 5-18; time from onset <14 hours
  - Key Exclusions: Cardiac or renal dysfunction, IV tPA, IA Intervention

- Population Enrolled
  - Mean time from onset to randomization: 8.1 hrs
  - Mean age: 67.5 yrs
  - Median NIHSS: 10
  - No demographic or medical hx differences between Tx & Control

SENTIS Subject Accounting



Baseline Characteristics

Characteristics		Treatment N=230	Control N=257	p-value
Demographics				
Age (years)	Mean ± SD	67.5 ± 14.1	68.3 ± 14.3	0.5209
Female	% (n/N)	44.8% (103 / 230)	49.4% (127 / 257)	0.3185
White	% (n/N)	84.8% (195 / 230)	83.7% (215 / 257)	0.8038
Presentation				
Time from symptom onset to Randomization (hours)	Mean ± SD	8.1 ± 2.9	8.1 ± 2.9	0.9607
Baseline NIHSS	Mean ± SD	10.9 ± 4.2	10.7 ± 4.4	0.4672
Medical History				
Diabetes Mellitus	% (n/N)	25.2% (58/230)	21.8% (56/257)	0.3924
Hypertension	% (n/N)	70.9% (163/230)	74.7% (192/257)	0.3593
Hyperlipidemia	% (n/N)	51.3% (118/230)	50.6% (130/257)	0.9277
Current Smoker	% (n/N)	25.2% (58/230)	24.9% (64/257)	1.0000
Cerebral Ischemic Infarct (stroke)	% (n/N)	12.2% (28/230)	17.5% (45/257)	0.1267
Atrial Fibrillation	% (n/N)	20.9% (48/230)	26.1% (67/257)	0.2000
Myocardial Infarction (MI)	% (n/N)	11.7% (27/230)	11.3% (29/257)	0.8878

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Helmi Lutsep, MD

- Professor and Vice Chair, Department of Neurology, Oregon Health & Science University, Portland, OR
- Associate Director, Oregon Stroke Center
- Fellow, AHA and American Stroke Association
- Fellow, American Academy of Neurology
- Financial Disclosure
  - No financial interest in CoAxia, Inc.
  - Paid Chair of SENTIS DSMB
  - Paid Consultant for this Advisory Panel Mtg.

DSMB Procedures

- Membership
- DSMB responsibilities
- Adjudication process
  - Relatedness
  - Ongoing reviews
  - Final review at close of trial

SENTIS Trial Results: Safety

Proportion of Subjects with SAEs

	NeuroFlo N=230		Control N=257		Adjusted p-value
	# Events	% of Subjects	# Events	% of Subjects	
Primary Safety: SAEs through 90 days	174	**43.9%**	177	**42.8%**	0.923
Index Stroke-Related SAEs	55	**20.9%**	70	**23.7%**	0.373*

*CMH calculation

Despite the addition of an interventional procedure, NeuroFlo did not increase SAEs

SENTIS Trial Results: 90-Day Hemorrhage

	NeuroFlo N=230		Control N=257	
	# Events	% [95% CI]	# Events	% [95% CI]
Hemorrhage AEs	41	**17.8%** [12.9, 22.8]	47	**17.1%** [12.5, 21.7]
Serious Hemorrhage	10	**4.3%** [1.7, 7.0]	14	**5.4%** [2.7, 8.2]
Fatal Hemorrhage	2*	**0.9%** [0.1, 3.1]	8*	**3.1%** [1.4, 6.0]
Symptomatic Hemorrhage**	3	**1.3%** [0.3, 3.8]	2	**0.8%** [0.1, 2.8]

* 2 NeuroFlo deaths at 24 hrs; 5 Control deaths at 24 hrs

** Per SITS-MOST trial definition utilizing 24 hour follow-up scan data

NeuroFlo use did not increase hemorrhage

SENTIS Adverse Events: DSMB Areas of Focus

- Neurologic events
  - Cerebral hemorrhage
  - Cerebral edema
  - Neurological deterioration
- Renal events
- Cardiac events

All events occurred well within expected rates

Serious Adverse Events

	NeuroFlo N=230			Control N=257		
	# Events	# Subjects	% of Subjects	# Events	# Subjects	% of Subjects
Any SAE	**174**	**101**	**43.9%**	**177**	**110**	**42.8%**
Cardiovascular	24	22	9.6%	19	18	7.0%
Renal	9	9	3.9%	5	4	1.6%
Neurological: Bleeding	10	10	4.3%	14	14	5.4%
Neurological: Other	52	47	20.4%	62	61	23.7%
Vascular	13	13	5.7%	9	9	3.5%
Pulmonary	32	27	11.7%	31	26	10.1%
Gastro-Intestinal	5	5	2.2%	6	5	1.9%
Laboratory	8	8	3.5%	10	10	3.9%
Other SAE	21	21	9.1%	21	19	7.4%

All subcategories also demonstrated no statistical difference: cardiac, renal, vascular, neurological, pulmonary, GI

SENTIS Adverse Events: Device- and Procedure-Related SAEs

Serious adverse events:

- Device only (n=0)
- Device and procedure (n=1)
- Procedure only (n=7)

The DSMB concluded no specific safety concerns relating to NeuroFlo treatment

SENTIS Trial Results: Mortality

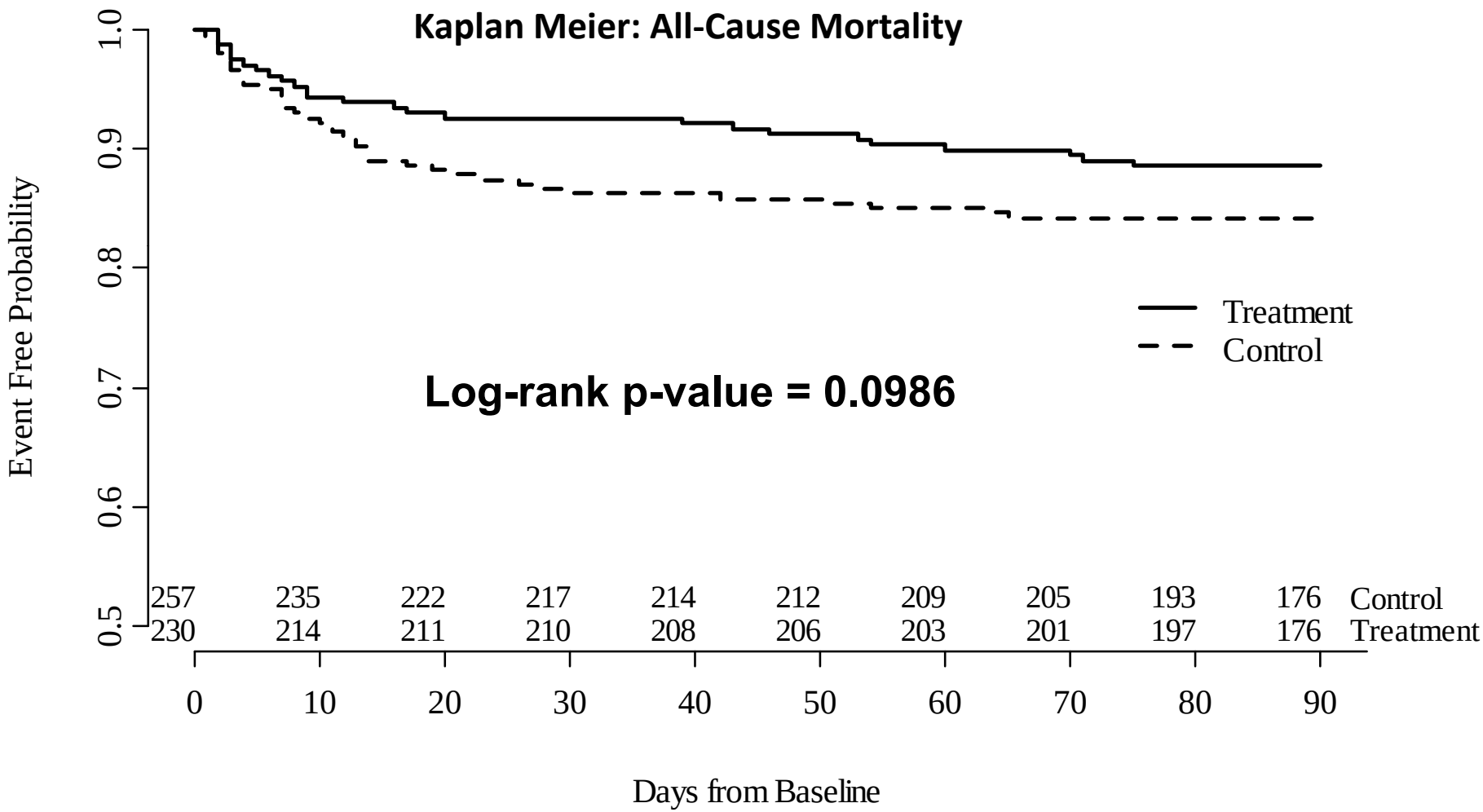
	NeuroFlo N=230		Control N=257		Adjusted p-value
	# Subjects	% [95% CI]	# Subjects	% [95% CI]	
All-Cause Mortality	26	**11.3%** [7.2, 15.4]	42	**16.3%** [11.8, 20.9]	0.0869
Stroke-Related Mortality	17	**7.4%** [4.0, 10.8]	37	**14.4%** [10.1, 18.7]	0.0111

NeuroFlo treated patients tended to have reduced mortality rates

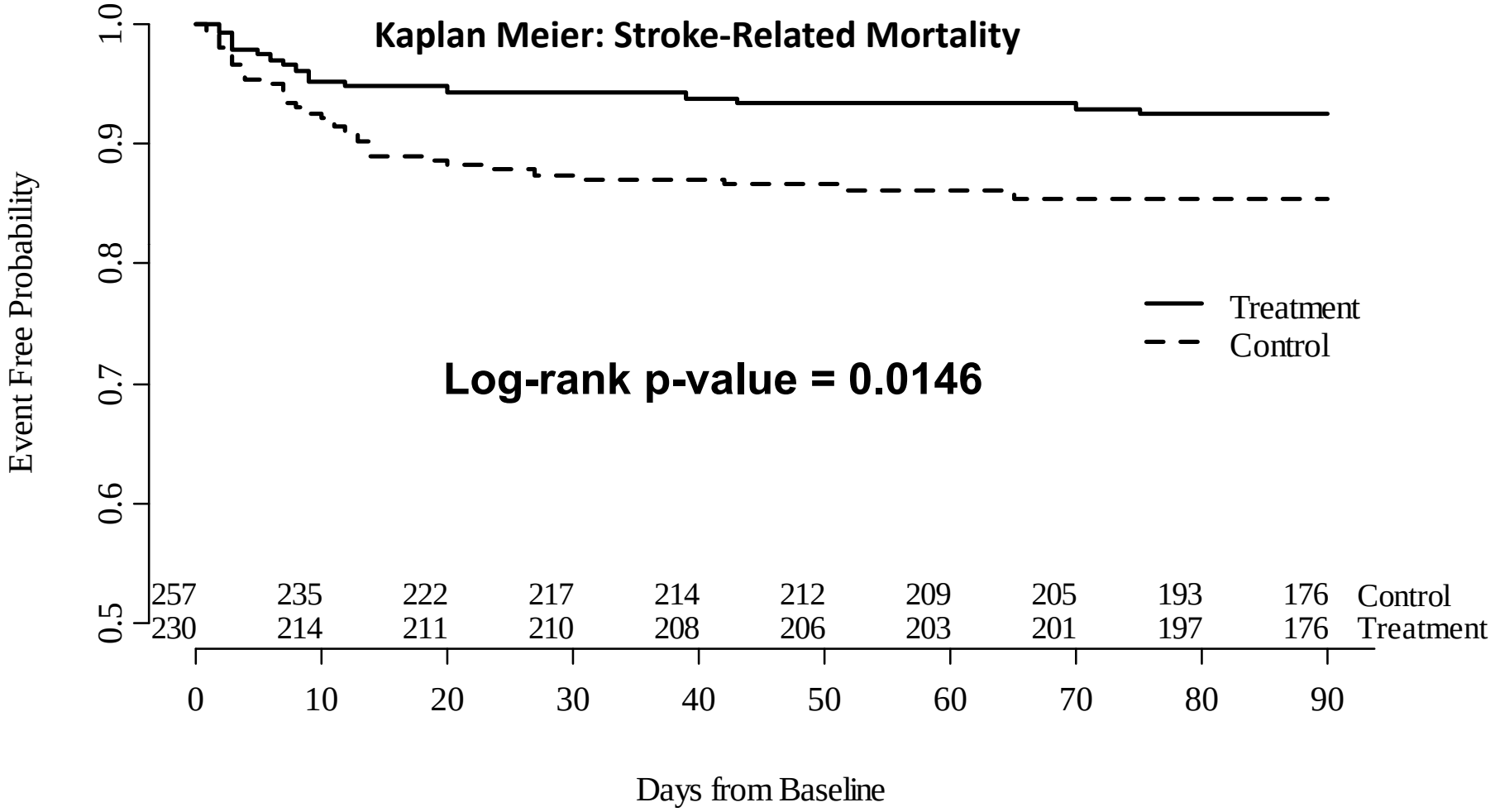
SENTIS Trial Results: Causes of Death and Adjudication

Primary Cause of Death		NeuroFlo N=230		Control N=257	
		# Subjects	% [95% CI]	# Subjects	% [95% CI]
Stroke-Related Deaths	Stroke	9	3.9% [1.4, 6.4]	18	7.0% [3.9, 10.1]
	Systemic Complications Associated with Stroke	8	3.5% [1.1, 5.8]	16	6.2% [3.3, 9.2]
	New Stroke	0	0.0% [0.0, 1.6]	3	1.2% [0.2, 3.4]
Non-Stroke-Related Deaths		9	3.9% [1.4, 6.4]	5	1.9% [0.3, 3.6]

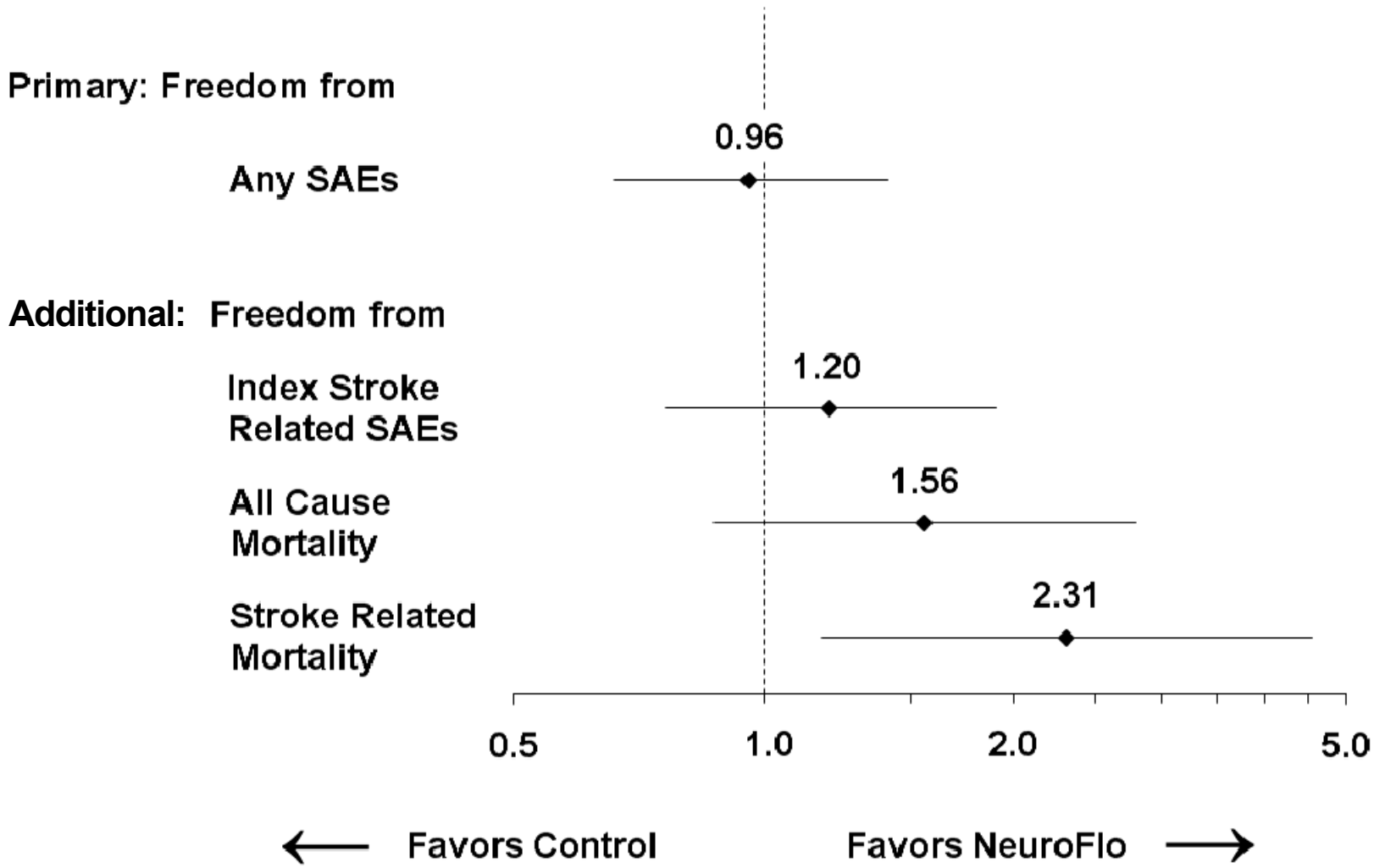
SENTIS Trial Results: All-Cause Mortality



SENTIS Trial Results: Stroke-Related Mortality



SENTIS Trial Results: Safety Summary



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Assessing the Benefit of NeuroFlo

- SENTIS outcomes
- Different measures in different stroke populations
- Interpreting SENTIS results

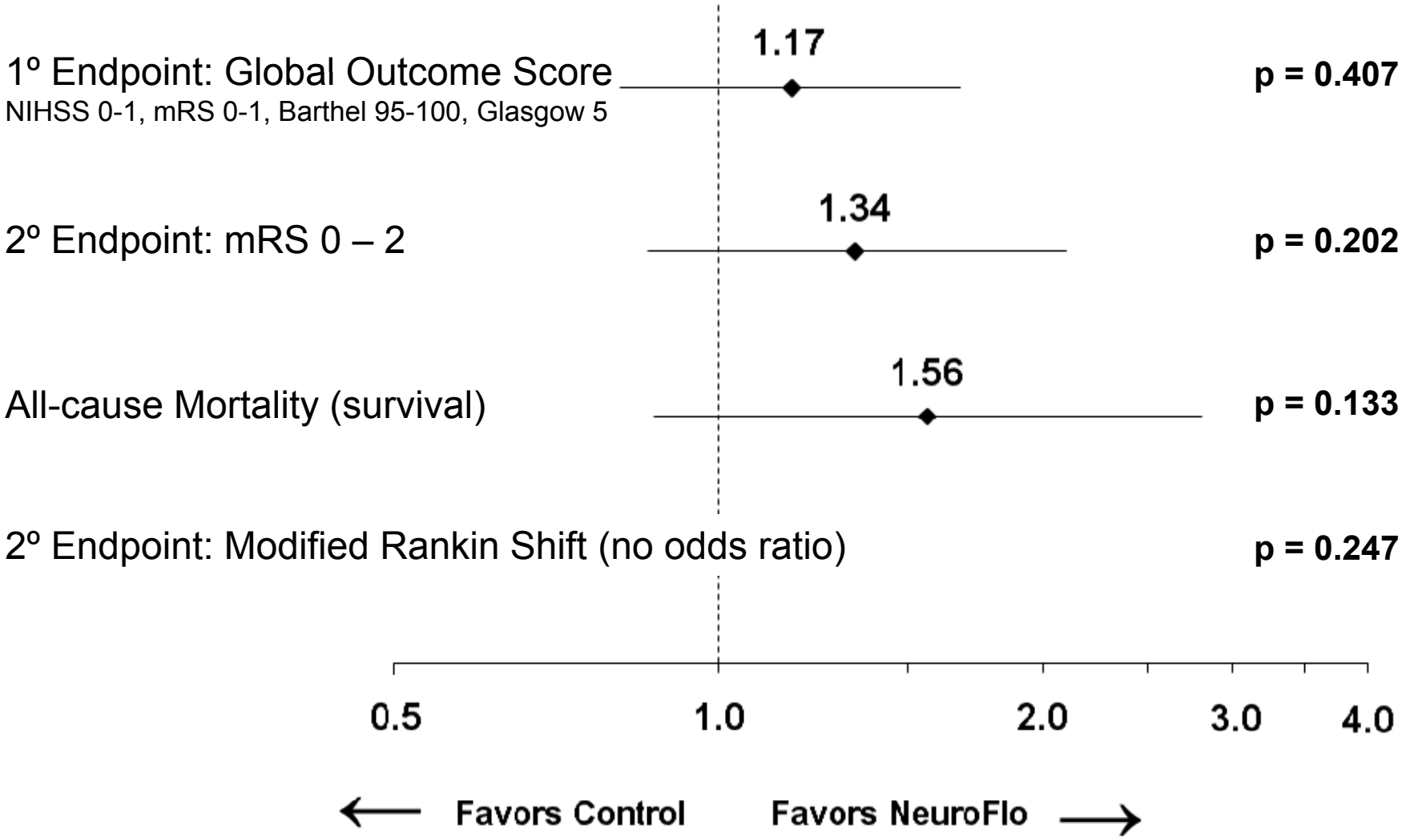
Effectiveness Outcome Measures

- SENTIS Primary Endpoint: Global Outcome Score
  - Excellent outcome on NIHSS, BI, mRS, GOS
  - Only powered endpoint
  - Discussed / selected in 2004
  - Best use: very acute and powerful interventions
- SENTIS Secondary Endpoints
  - Rankin Scale (mRS 0-2, mRS Shift – 6 level)
  - Additional clinical measures
- Additional Endpoint Developments
  - Recognition of endpoints informative for specific populations
  - New measures used today

Pre-Specified Endpoints

Endpoint	NeuroFlo (%)	Control (%)	Odds Ratio	P-value
Global Outcome	NA	NA	1.17	0.407
mRS 0-2	48.2%	44.2%	1.34	0.202
All-cause mortality	11.3%	16.3%	1.56	0.133

SENTIS Trial Results: Pre-Specified Endpoints



Informative Analyses

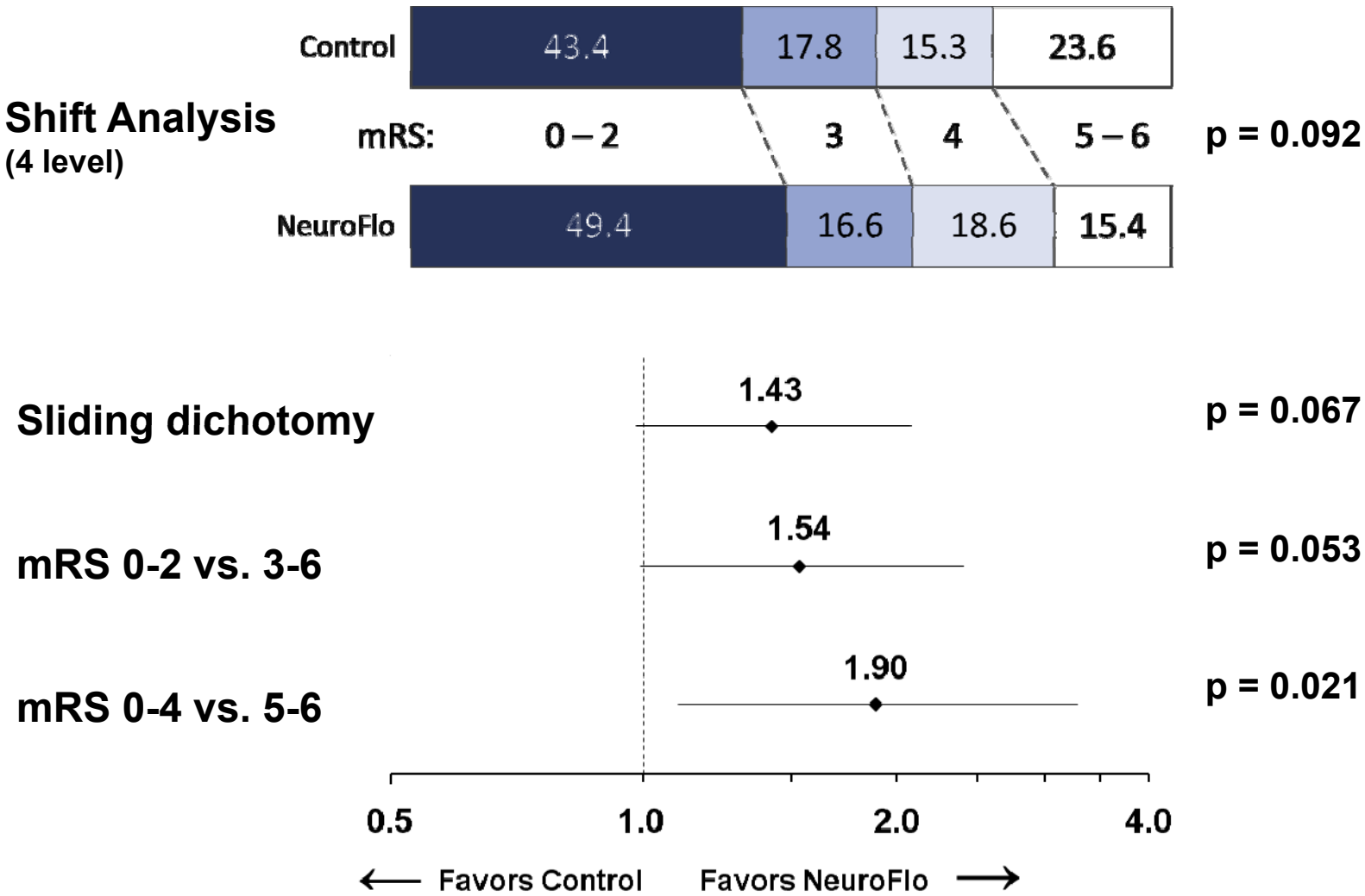
- Informative endpoints
  - Why the Global Score doesn't fit
    - Hyperacute vs subacute treatment window
    - Complete vs partial reperfusion
  - Stroke trial endpoints: current use
    - mRS 0-2
    - mRS 0-4
    - Rankin Shift (4 level)
  - New endpoint development & validation
    - Sliding Dichotomy

- Relevant patient populations
  - Remove stroke mimics

Informative Analyses
(ITT population without stroke mimics)

Endpoint	NeuroFlo (%)	Control (%)	Odds Ratio	P-value
Sliding Dichotomy	50.2%	43.0%	1.43	0.067
mRS 0-2 vs. 3-6	49.4%	43.4%	1.54	0.053
mRS 0-4 vs. 5-6	84.6%	76.4%	1.90	0.021

SENTIS Trial Results: Informative Analyses
(ITT population without stroke mimics)



Subgroup Analyses

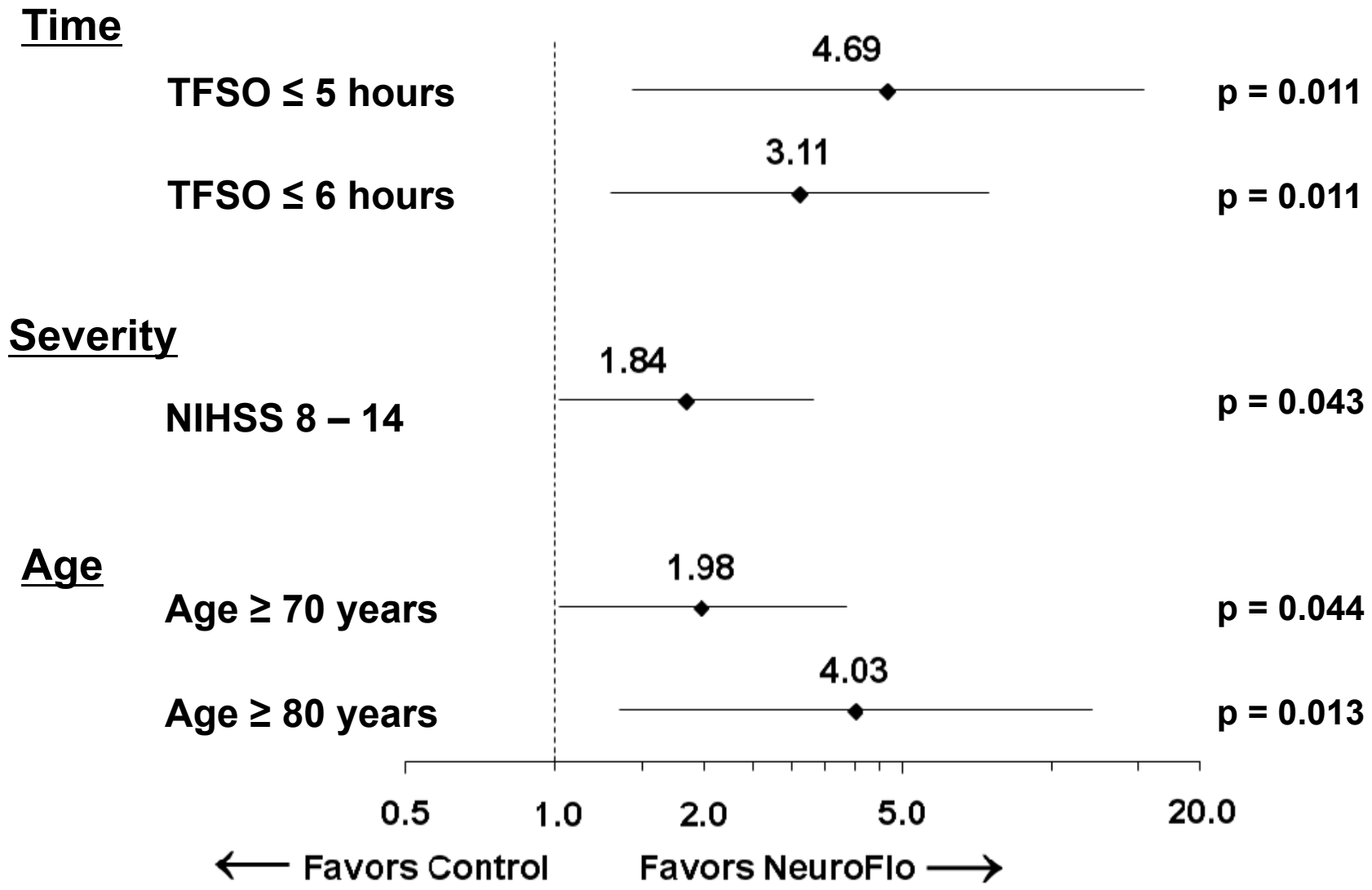
- Patients most likely to benefit from NeuroFlo
  - Active collateral routes supporting a penumbra
  - But those collaterals capable of supporting more flow

- Subgroups likely to meet those criteria:
  - Mid-severity strokes (indicative of penumbra supported by collaterals)
  - Elderly (more likely to have cardiovascular compromise resulting in suboptimal collateral filling)

Plus

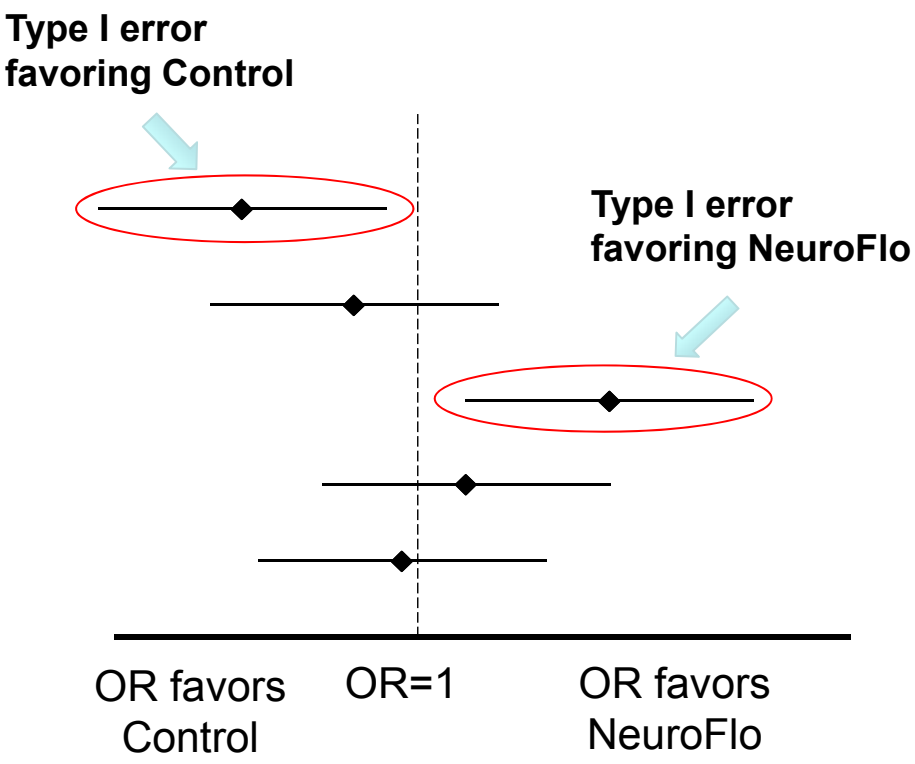
  - Early presenting patients (more responsive to all treatments)

SENTIS Subgroups: mRS 0 – 2
(mAT population)

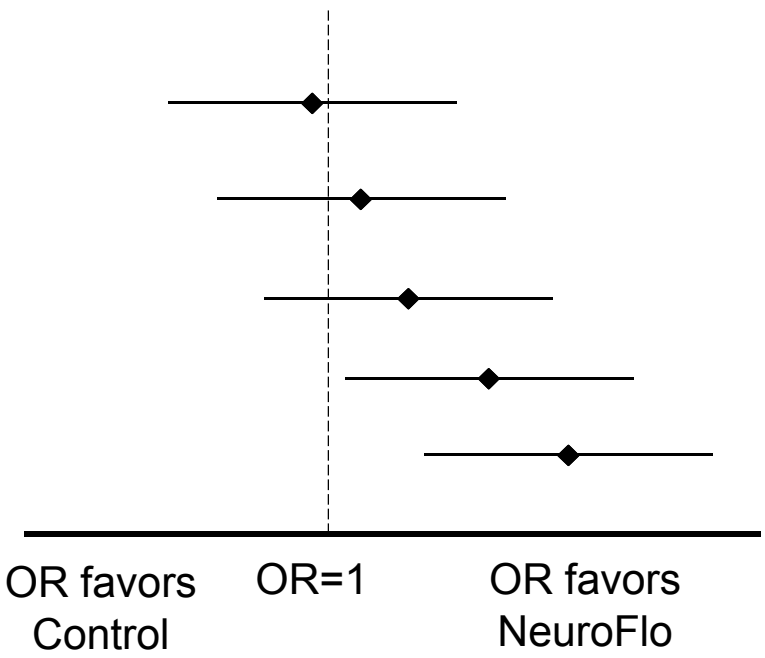


Type I Error Consideration

Hypothetical Type I Error Results



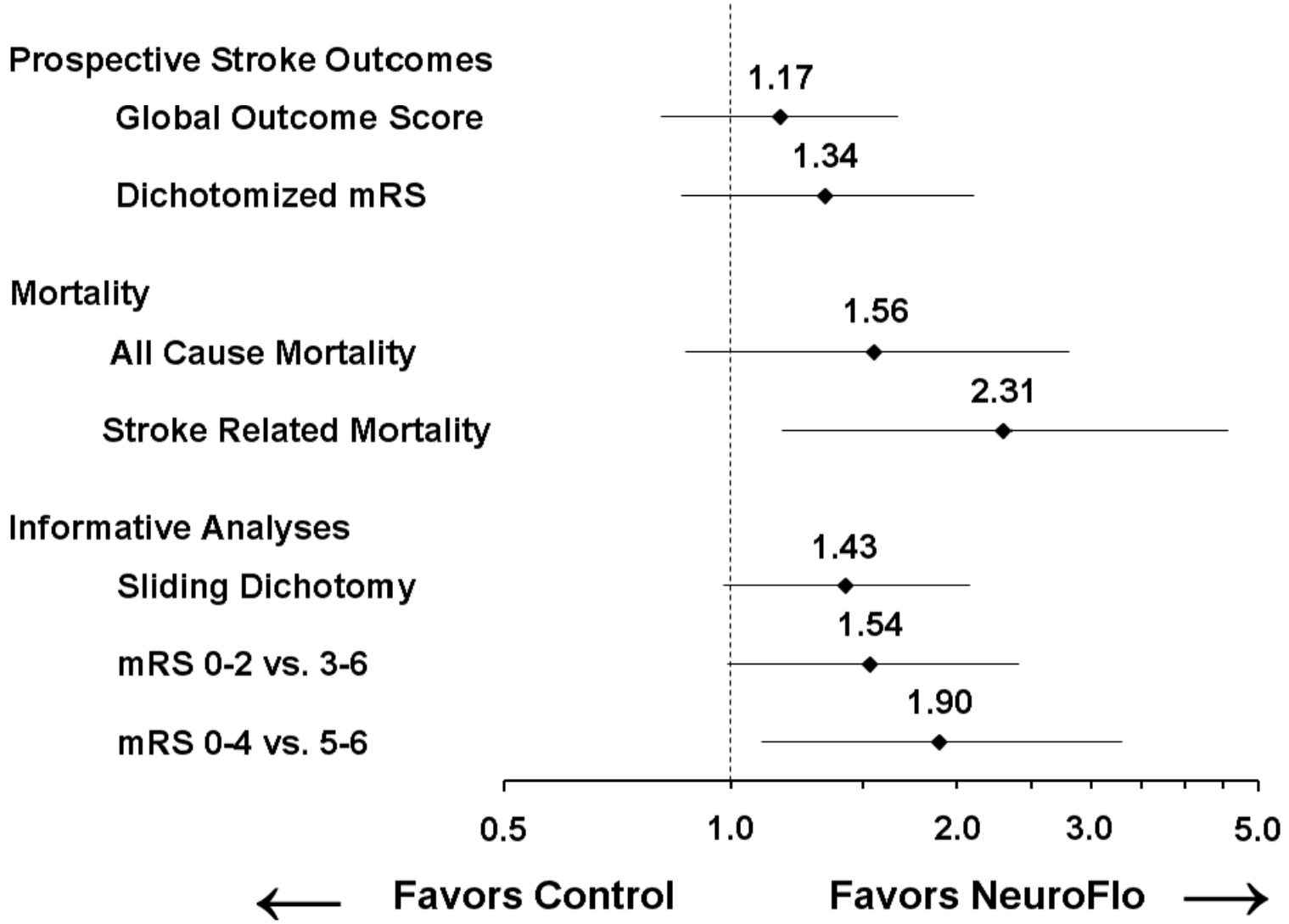
Hypothetical SENTIS Like Results
(modest treatment effect)



Type I Error Considerations

- Balance of results show benefit
  - Almost all odds ratios favor NeuroFlo
    - Among 1 primary, 11 secondary, 4 informative post-hoc analyses, 13/16 (81%) have point estimates favoring NeuroFlo
  - Multiple significant p-values favor NeuroFlo
  - No significant p-values favor control

SENTIS Outcome Summary



SENTIS Trial Summary

- No increase in SAEs vs. medical management
- No increase in cerebral hemorrhage
- Mortality reduced; stroke-related mortality significantly reduced
- Neutral on primary effectiveness endpoint
- Consistent trends to improved functional outcomes
  - Amplified using more sensitive endpoints
  - Amplified in key subgroups

SENTIS demonstrates safety and provides evidence of benefit

Presentation Schedule

- Panel Discussion Context — Susan Alpert, PhD, MD
- Device Description & History — Sharon Kvistad
- Stroke and Stroke Treatment — Lou Caplan, MD
- **SENTIS Study and Interpretation**
  - Study Design — Jeff Saver, MD
  - Safety — Helmi Lutsep, MD
  - Patient Benefit — Jeffrey Saver, MD
  - **Clinical Interpretation — Raul Nogueira, MD**
- Conclusion — Susan Alpert, PhD, MD

Raul Nogueira, M.D.

- Director, Neuroendovascular Service and Neurocritical Care Service, Marcus Stroke & Neuroscience Center, Grady Memorial Hospital
- Associate Professor of Neurology, Neurosurgery and Radiology; Emory University School of Medicine

- Founding Board Member, Society of Vascular and Interventional Neurology (SVIN)
- Board Member, Society of NeuroInterventional Surgery (SNIS)
- Member AHA Stroke Leadership Committee (American Heart Association)

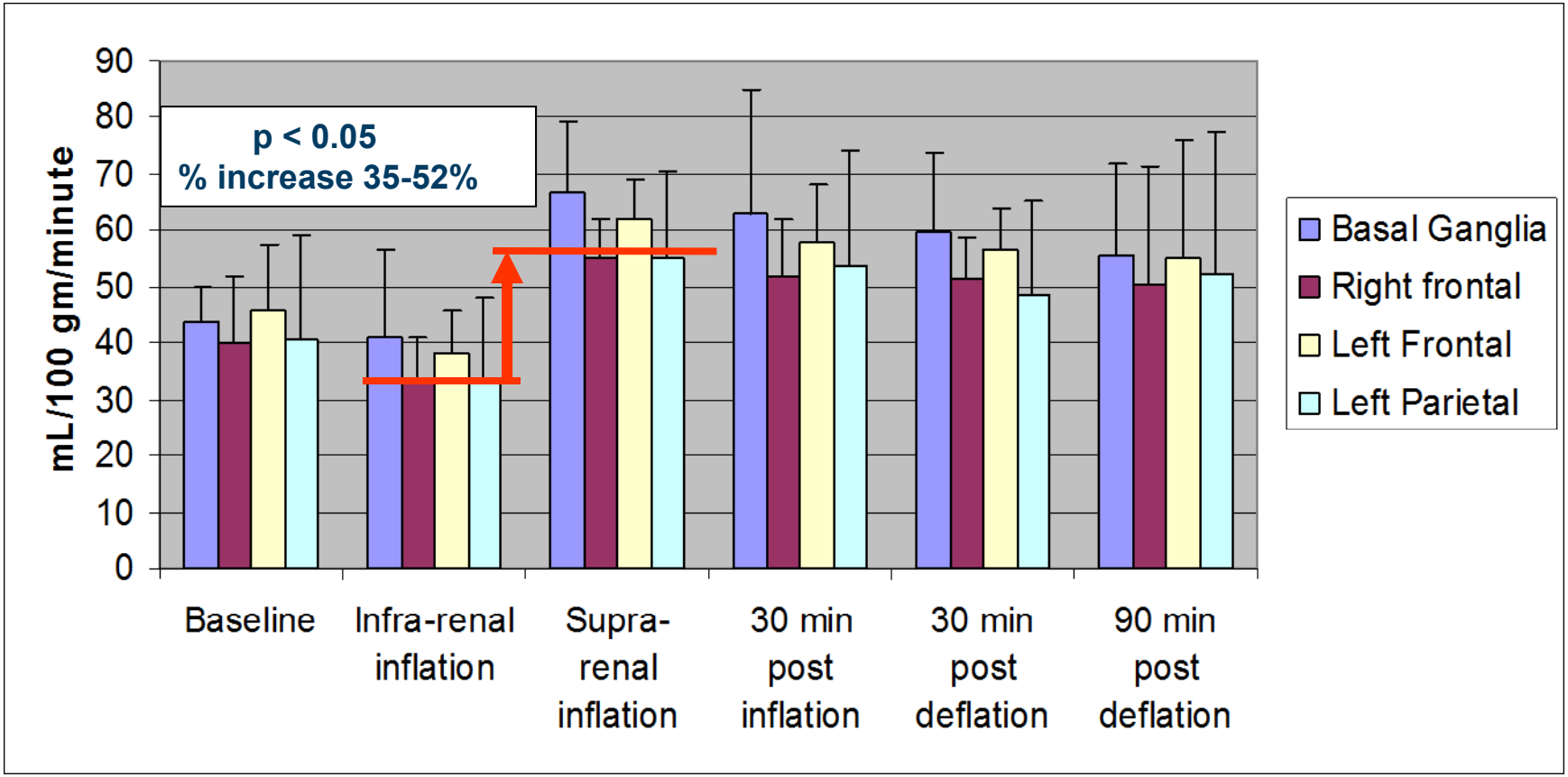
- Relationships with CoAxia
  - No financial interest in CoAxia
  - Paid Consultant for this Advisory Panel Meeting

A Neurointerventionalist Perspective

- NeuroFlo increases cerebral blood flow in animal models and stroke patients
- Why do I need NeuroFlo?
  - Limited treatment options for the vast majority of stroke patients
- How do I assess SENTIS results?
  - Need to adjust expected outcomes according to time to treatment and stroke severity

NeuroFlo Increases CBF in Animal Models: The Swine Model

"Gold-standard" microsphere measurement technique



Partial Occlusion of the Descending Aorta Increases Cerebral Blood Flow. *Maxim Hammer; Tudor Jovin; Joyce Wahr; Wolf-Dieter Heiss. Cerebrovascular Disease 2009; 28:406-410*

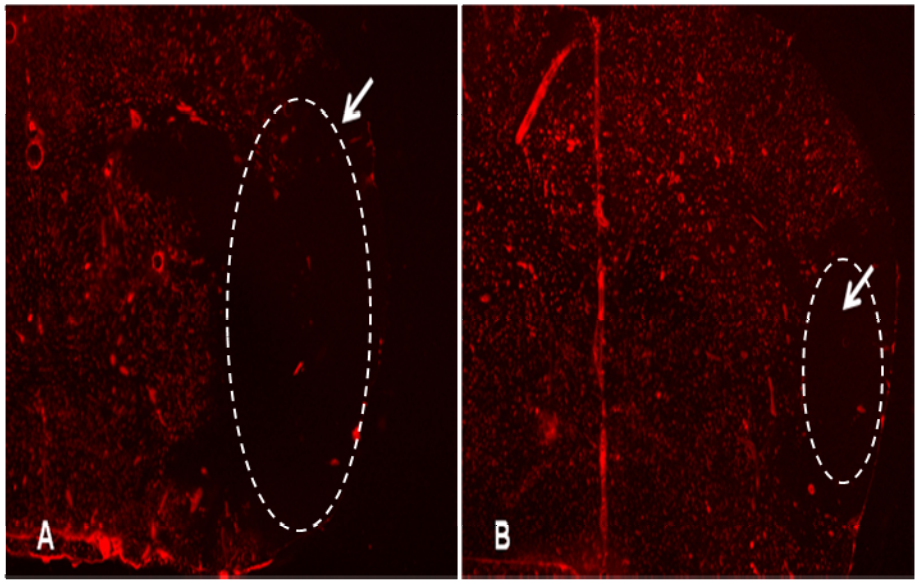
NeuroFlo Increases CBF in Animal Models: The Swine Model

Swine Cerebral Circulation

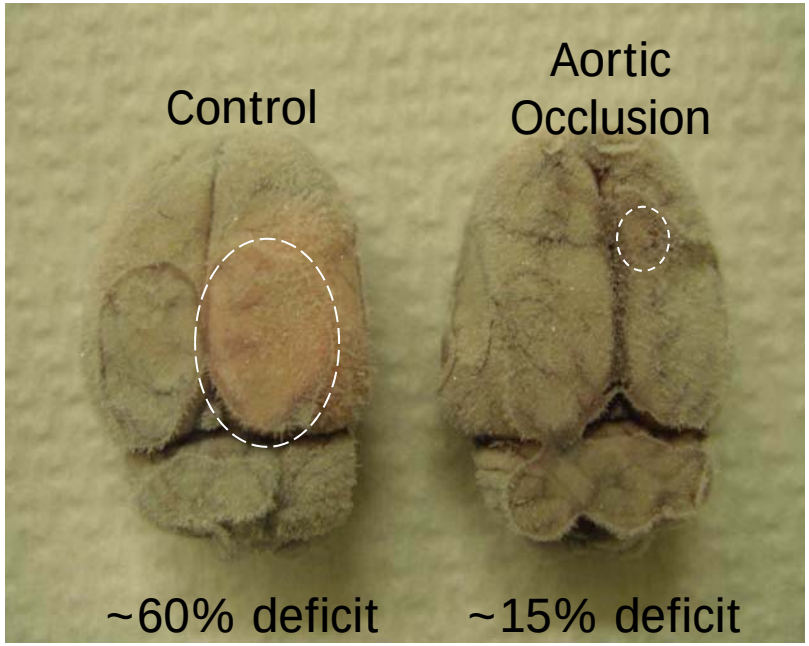
Human Cerebral Circulation

NeuroFlo Increases CBF in Animal Models: The Stroke Rat Model

Aortic Occlusion Resulted in Reduction in Perfusion Deficit and Stroke Volume



Control group (A), perfusion deficits 4.6 ± 0.6 mm^2 at 2 hours after embolization. Deficits significantly decreased (P=0.003) to 1.7 ± 0.6 mm^2 in the partial aortic occlusion group (B).

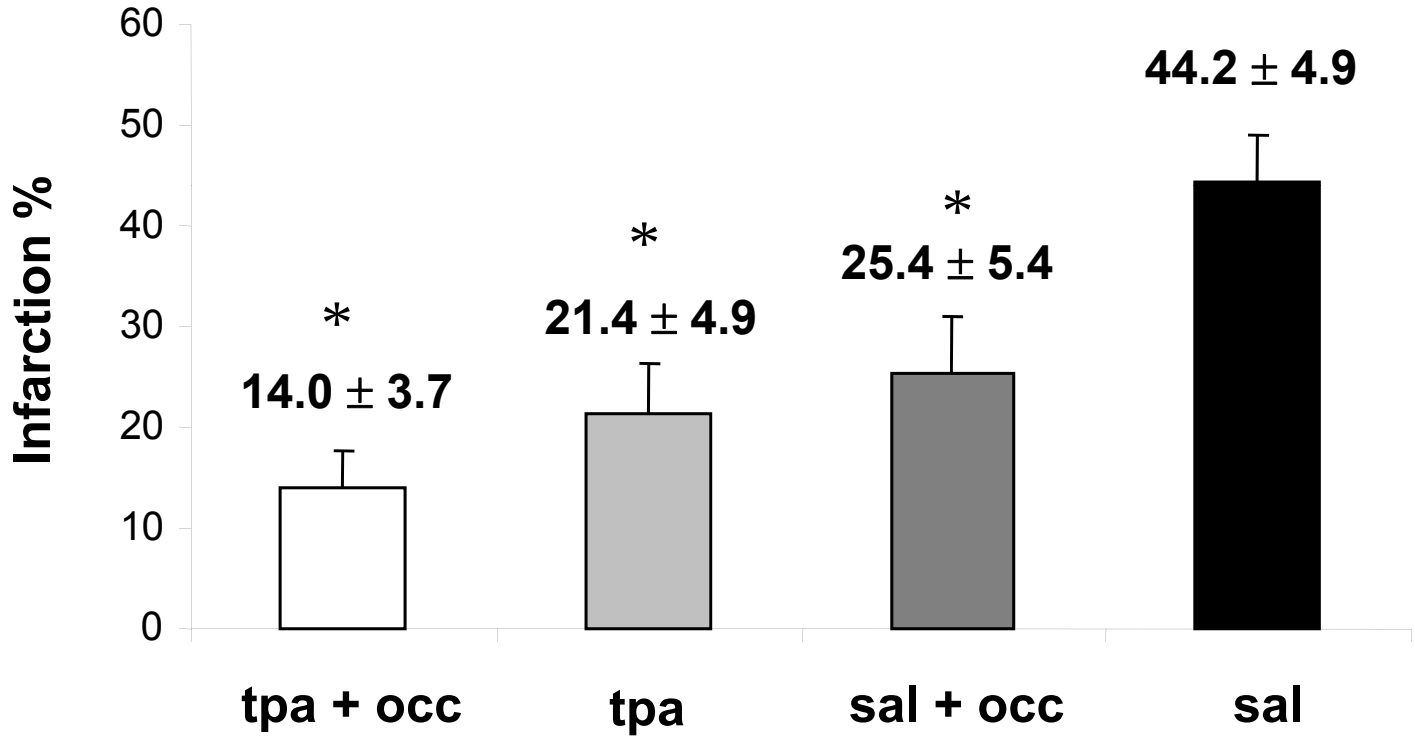


Sacrificed at two hours after ischemic injury; Absence of blue staining indicates perfusion deficit

Noor R et al. J Neuroimaging. 2010 Jul;20(3):272-6.

NeuroFlo Increases CBF in Animal Models: The Stroke Rat Model

Infarct Volume



Infarct Sizes significantly lower than saline alone group (P<0.05)

Noor R et al. J Neuroimaging. 2010 Jul;20(3):272-6.

Infarct Volume is the Strongest Predictor of Outcomes in Humans

Final Infarct Volume Is a Stronger Predictor of Outcome Than Recanalization in Patients With Proximal Middle Cerebral Artery Occlusion Treated With Endovascular Therapy

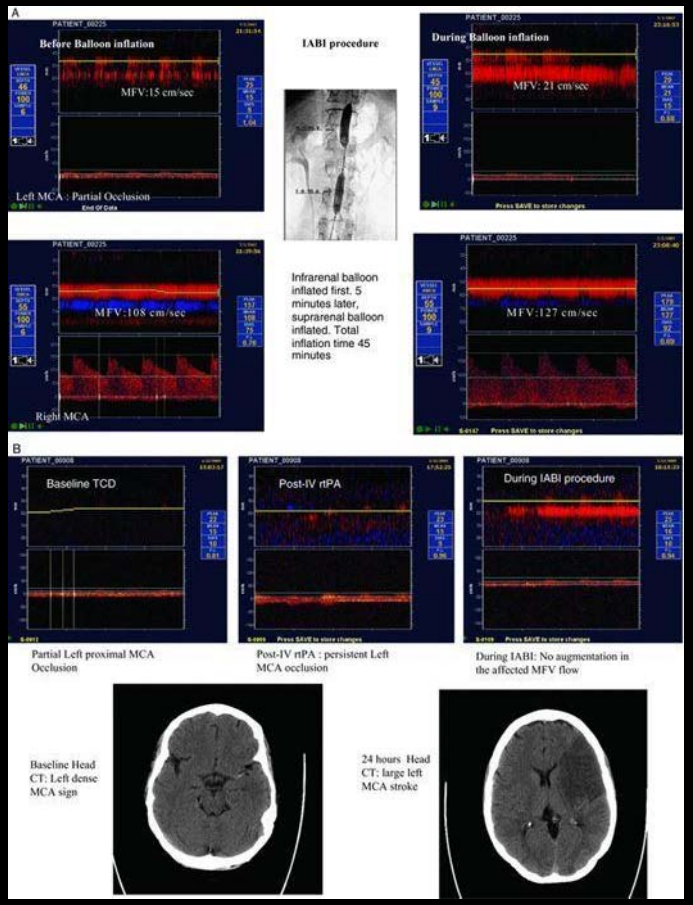
Syed F. Zaidi, MD; Amin Aghaebrahim, MD; Xabier Urra, MD; Mouhammad A. Jumaa, MD; Brian Jankowitz, MD; Maxim Hammer, MD; Raul Nogueira, MD; Michael Horowitz, MD; Vivek Reddy, MD; Tudor G. Jovin, MD

Conclusions—Successful recanalization leads to improved functional outcomes through a reduction in final infarct volumes. In our series, age and final infarct volume but not recanalization were found to be independent predictors of outcome, supporting the use of final infarct volume as surrogate marker of outcome in acute stroke trials. (*Stroke*. 2012;43:3238-3244.)

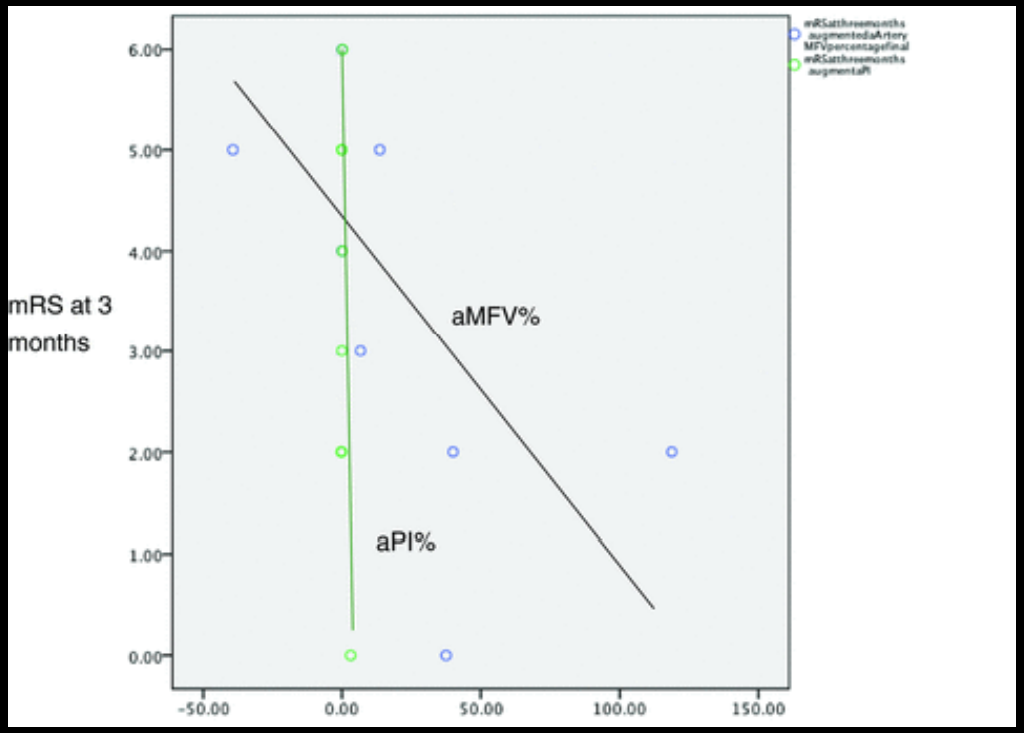
Does NeuroFlo Increase Cerebral Blood Flow in Stroke Patients?

- Transcranial Doppler
- CT Perfusion
- MRI Perfusion
- Digital Angiography
- PET

NeuroFlo Flow Velocity Improvement - TCD



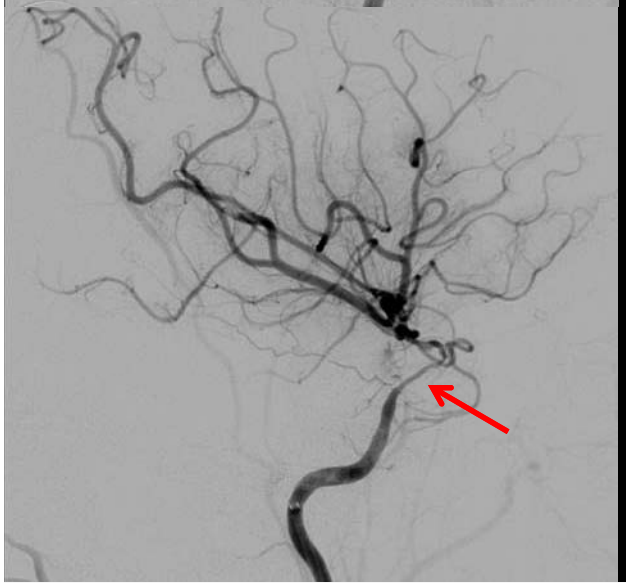
Proximal MCA or TICA occlusion (n=8)



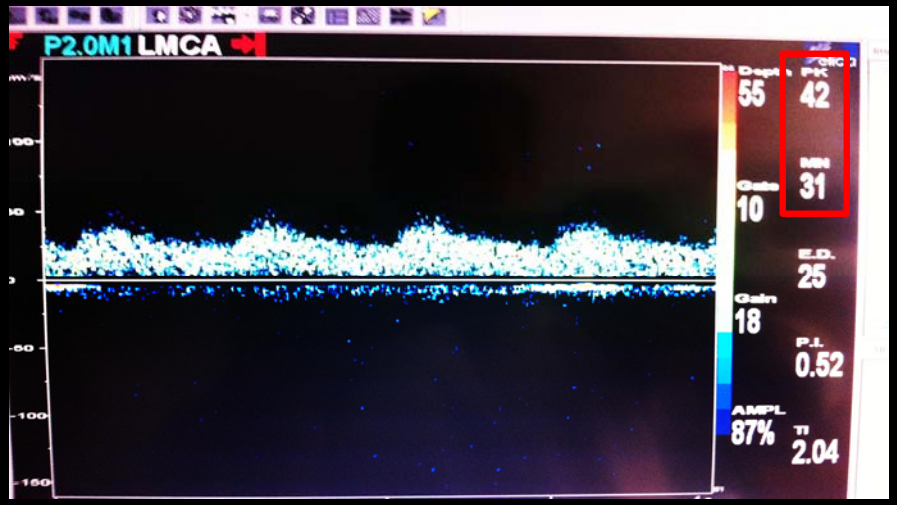
Higher the augmented blood flow, (MFV%) the better the long-term outcome.
MFV% in pts with good vs. poor outcome: 65.4 ± 46 and −3.7 ± 21 (*P* = .036).

Saquur M et al. J Neuroimaging. 2012. Jan 13.

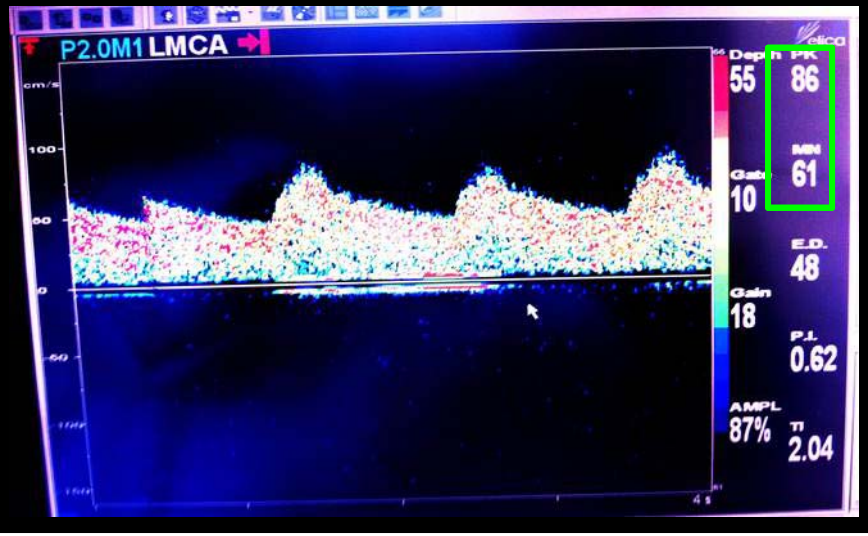
NeuroFlo Flow Velocity Improvement - TCD



Pre-balloon inflation



Post-balloon inflation

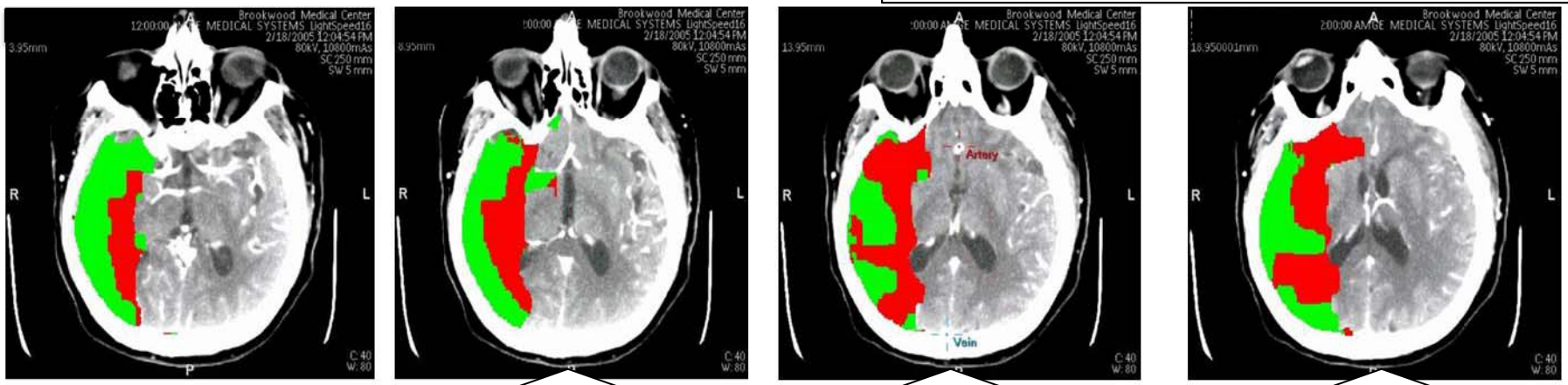


NeuroFlo Flow Augmentation CT Perfusion Scan

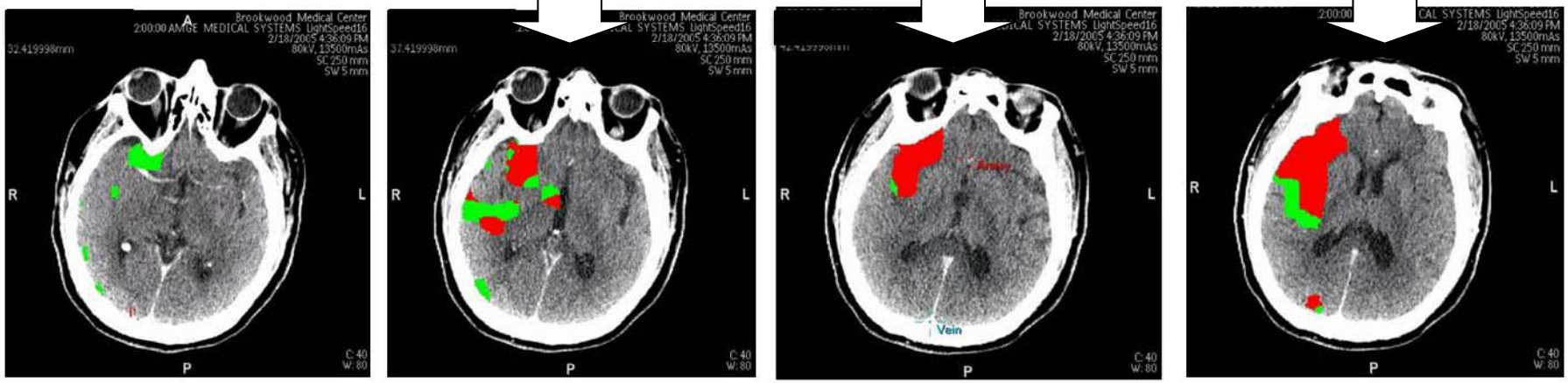
Feasibility Patient Example

% Change of summary maps (Pre vs Post-NeuroFlo)		
Total area	**"At risk"**	**"Infarct"**
- 54%	**- 78%**	**- 37%**

Pre-NeuroFlo Perfusion Maps

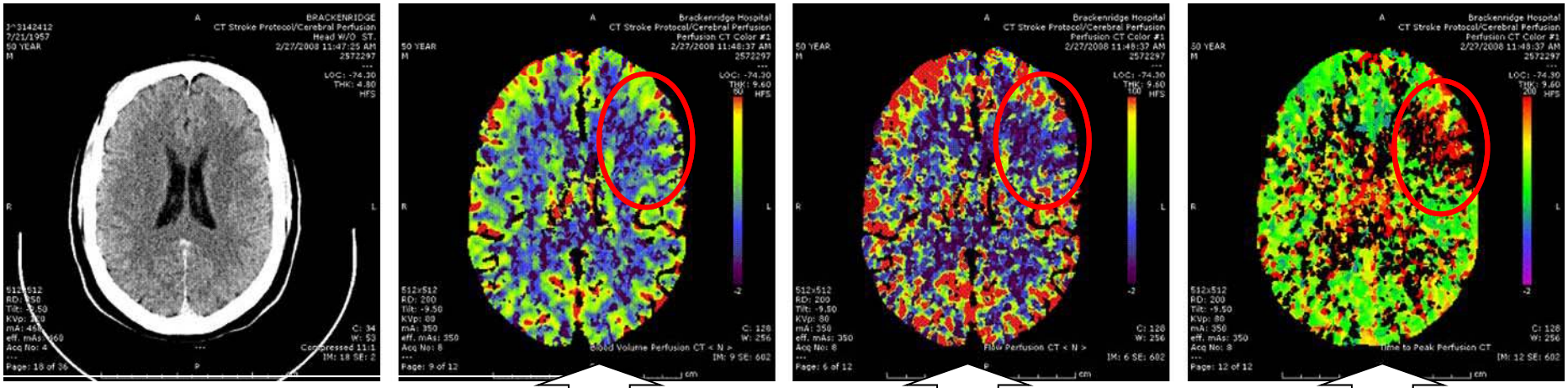


Post-NeuroFlo

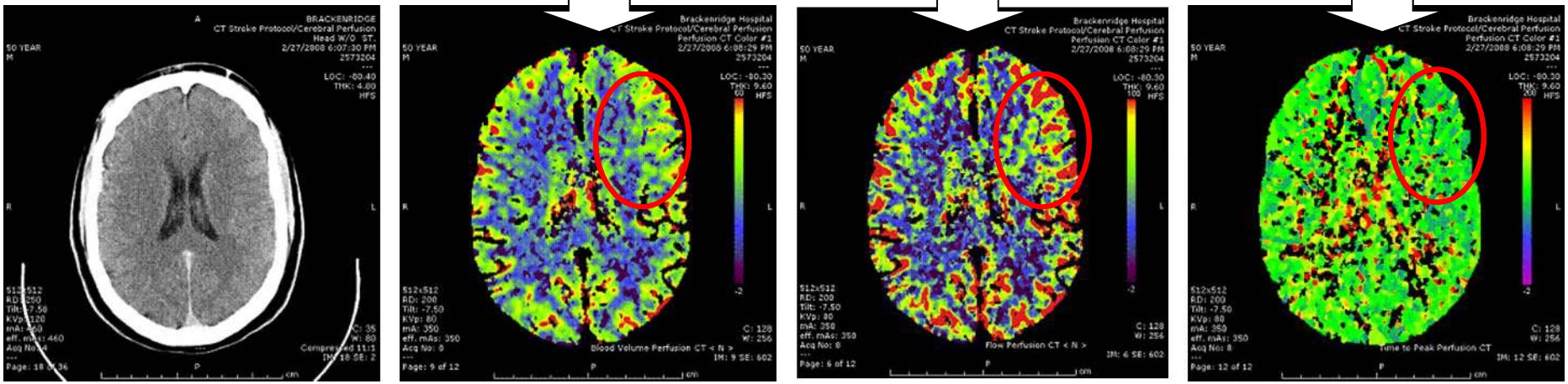


NeuroFlo Flow Augmentation CT Perfusion Scan

Baseline (10 hrs post onset)



Post Treatment (Baseline + 7 hrs)

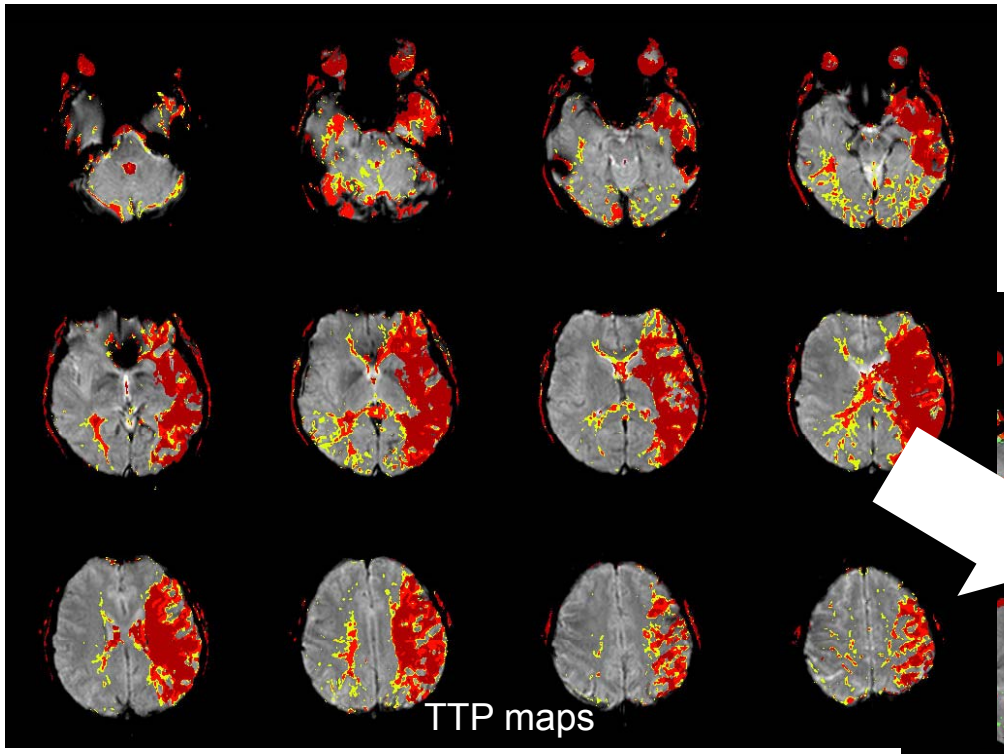


CT CBV CBF TTP

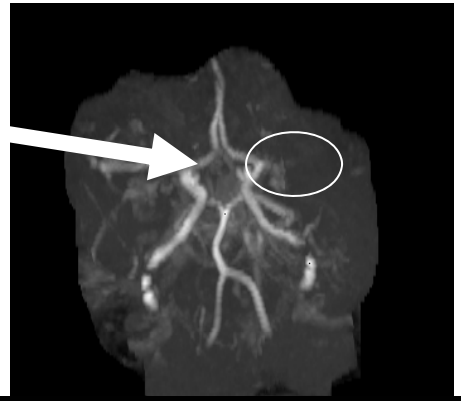
J Neal Rutledge, Seton Medical Center, Austin, TX

NeuroFlo Flow Augmentation MR Perfusion Scan

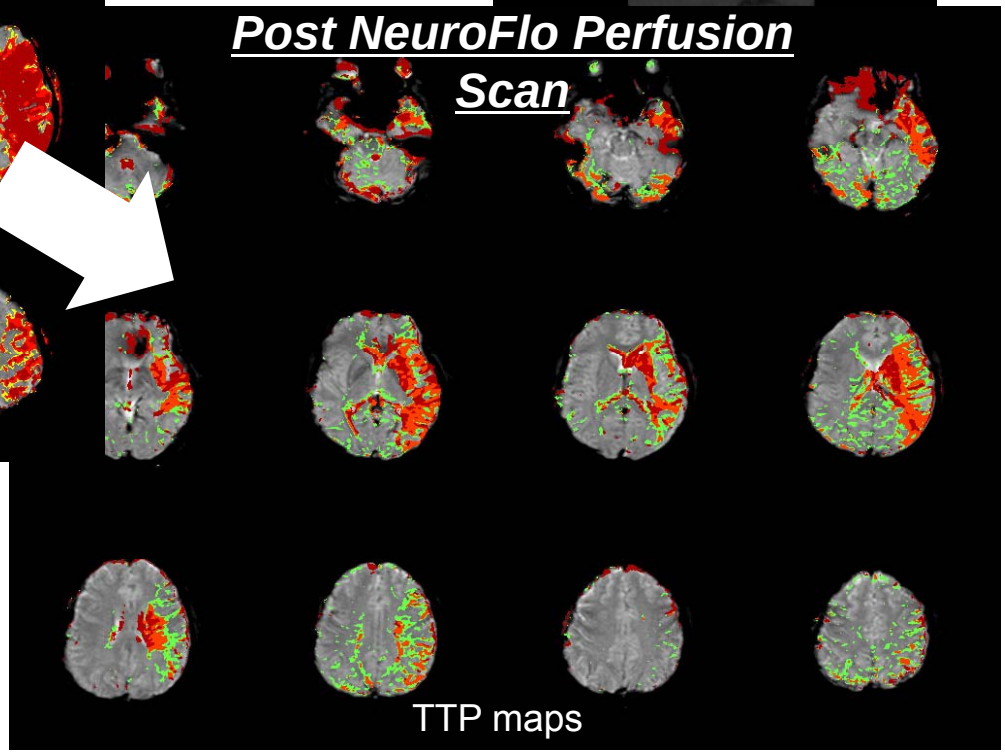
Post tPA/Pre NeuroFlo Perfusion Scan



Post tPA
Persistent Cerebral Artery Occlusion



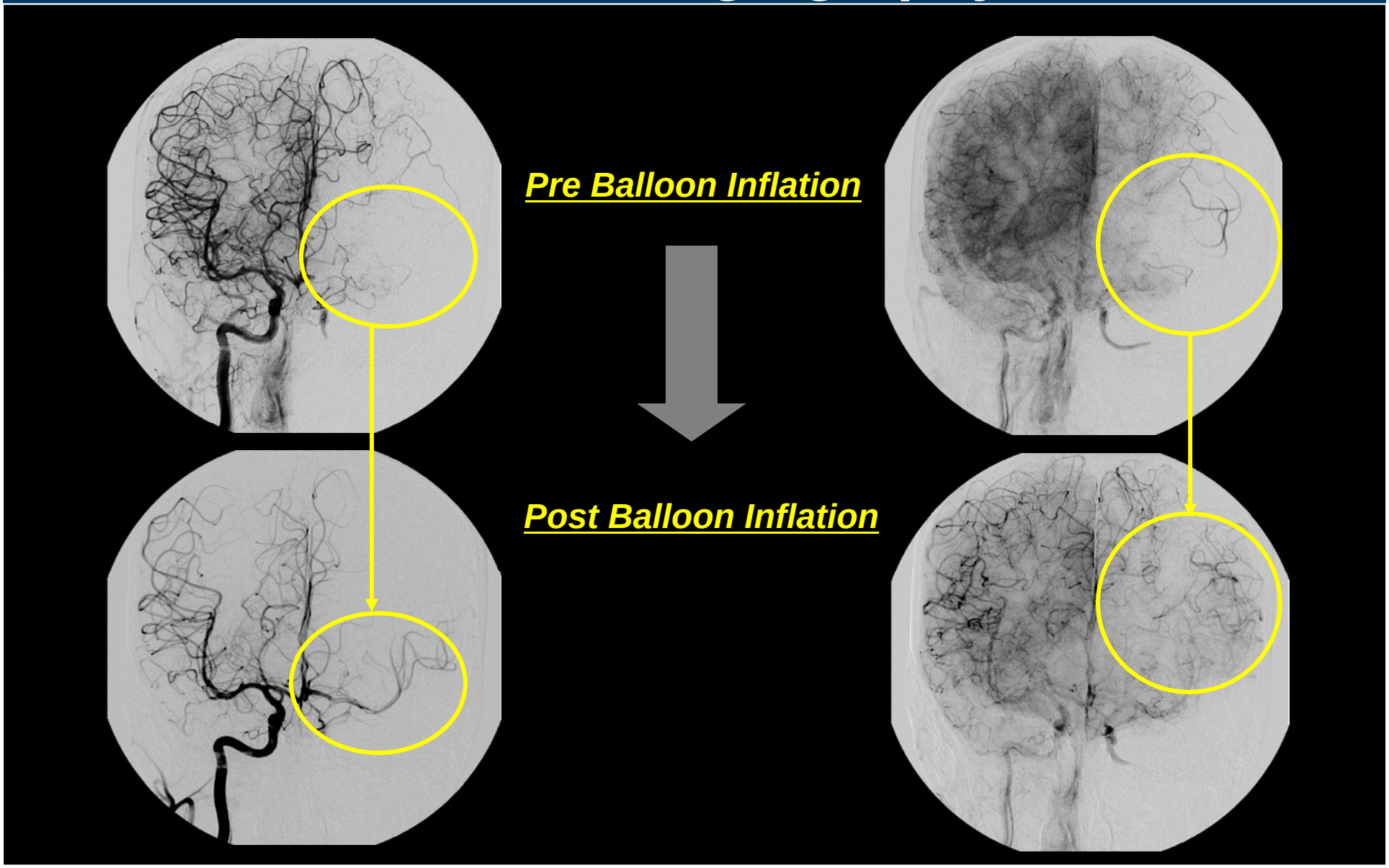
Post NeuroFlo Perfusion Scan



35 yo F – NIHSS 19. Failed tPA. NeuroFlo treatment. 30-day NIHSS 2

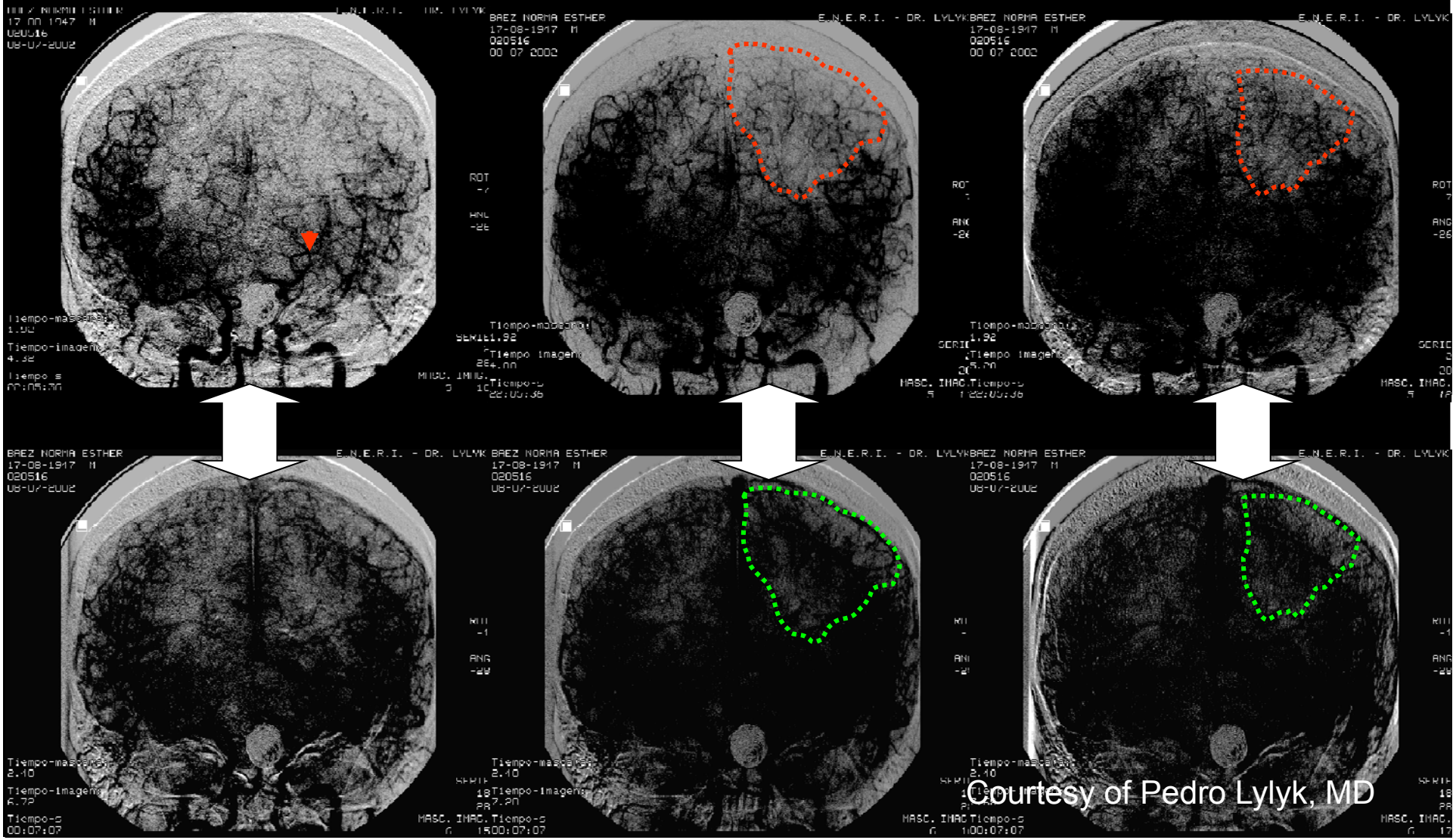
Ken Butcher MD; Ashfaq Shuaib MD

NeuroFlo Flow Augmentation Cerebral Angiography



NeuroFlo Flow Augmentation Cerebral Angiography

SAH Vasospasm

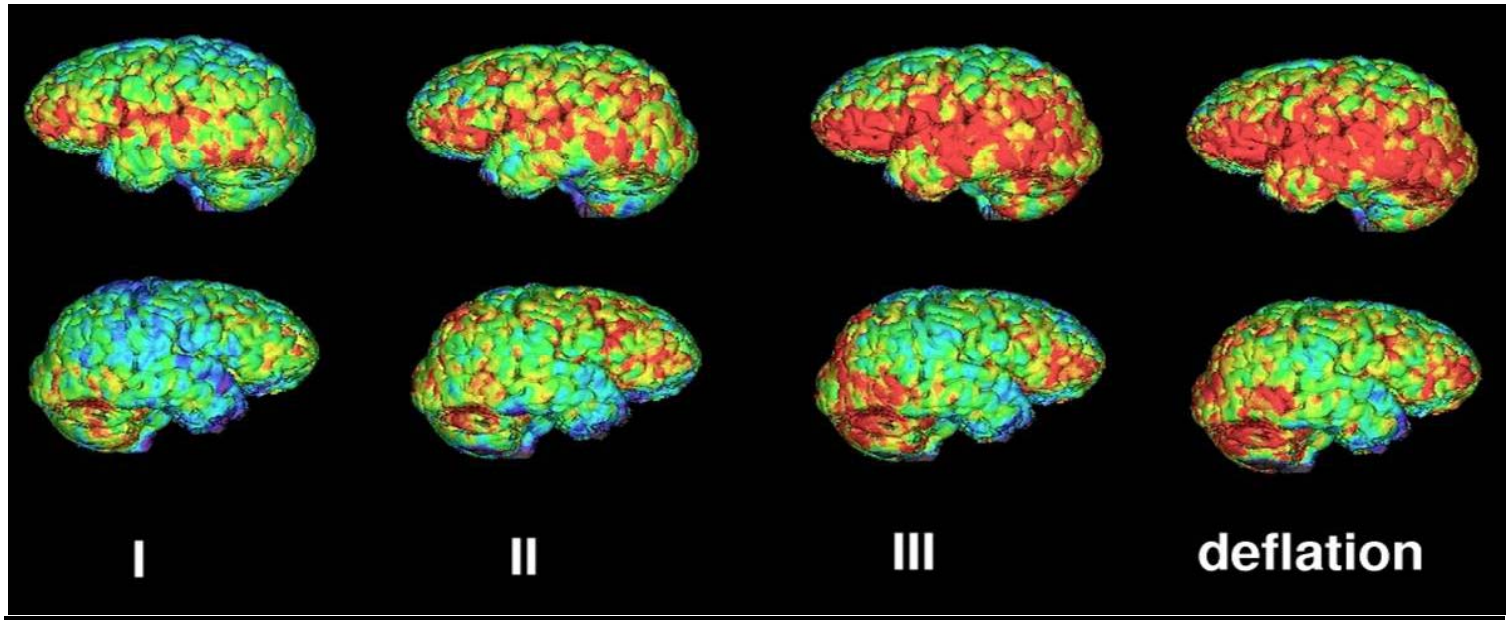


Courtesy of Pedro Lylyk, MD

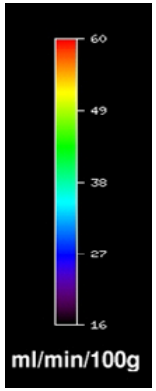
NeuroFlo Flow Augmentation Quantitative H_2O PET Imaging

Non-ischemic Hemisphere

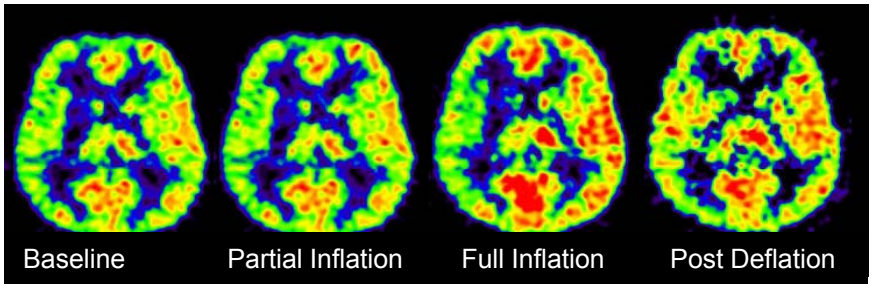
Ischemic Hemisphere

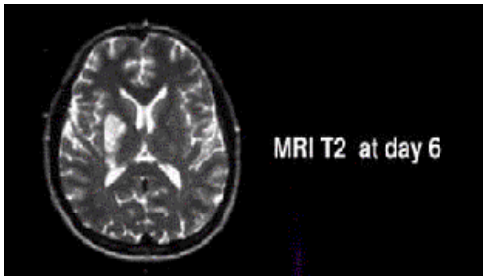


Baseline	Partial Inflation	Full Inflation	Post Deflation



Progressive Inflation ⟶





Prof. Wolf-Dieter Heiss
Max-Planck-Institute

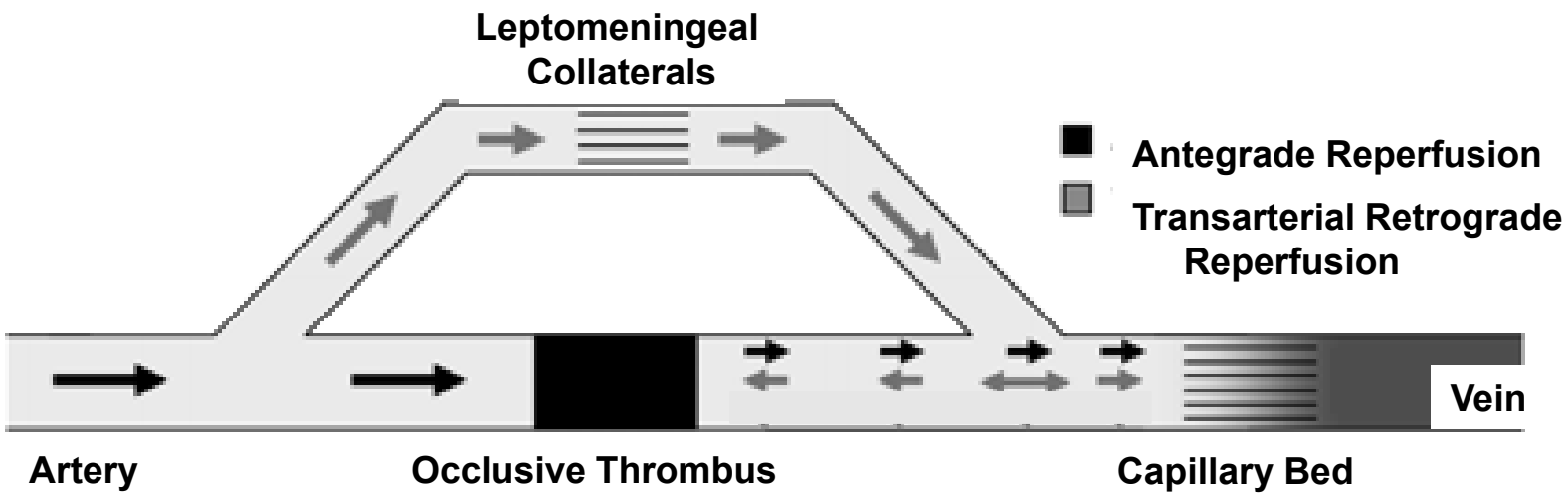
Ischemic Stroke Treatment: Whom and How to Treat?

- **Treatment Strategies**
  - Direct Recanalization (High Risk/ High Reward/ Small Target Population)
  - Flow Augmentation (Lower Risk/ More Modest Benefit/ Larger Target Population)

- **Risk/ Benefit Assessment**
  - Time to Presentation (Late vs. Early)
  - Stroke Severity (Mild/Mod vs. Severe)
  - Site of Occlusion (Proximal vs. Distal)
  - Patient/ Family Expectations

Two Fundamental Treatment Strategies:

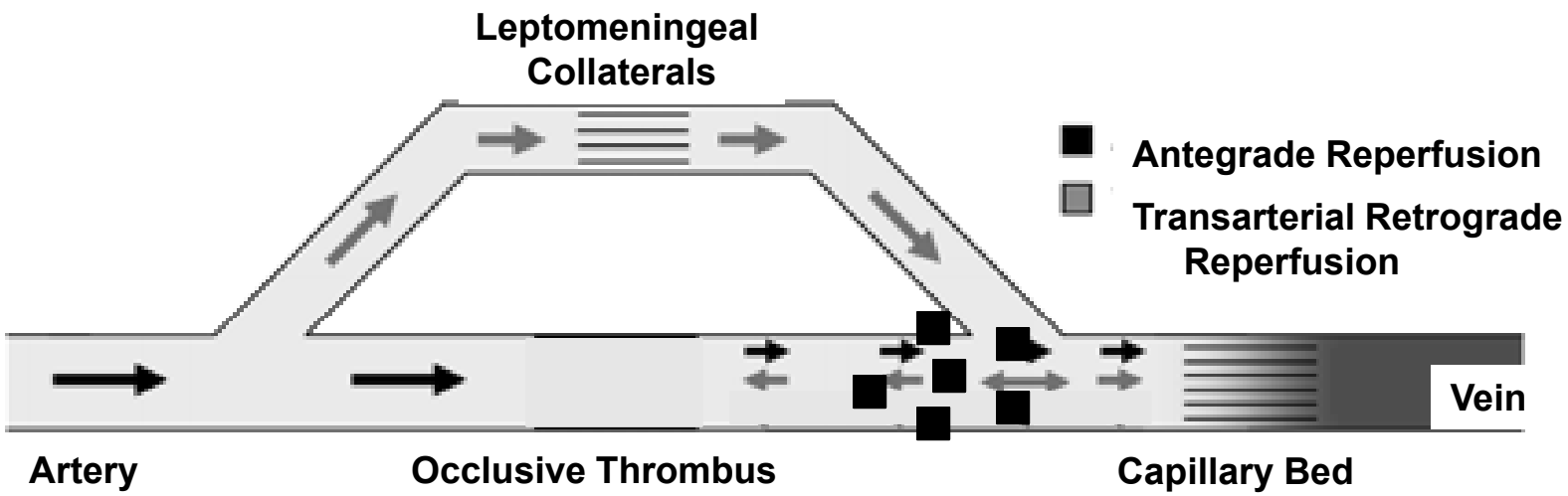
Direct Recanalization



Nogueira RG et al. AJNR. 2009 Apr;30(4):649-61

Two Fundamental Treatment Strategies:

Direct Recanalization



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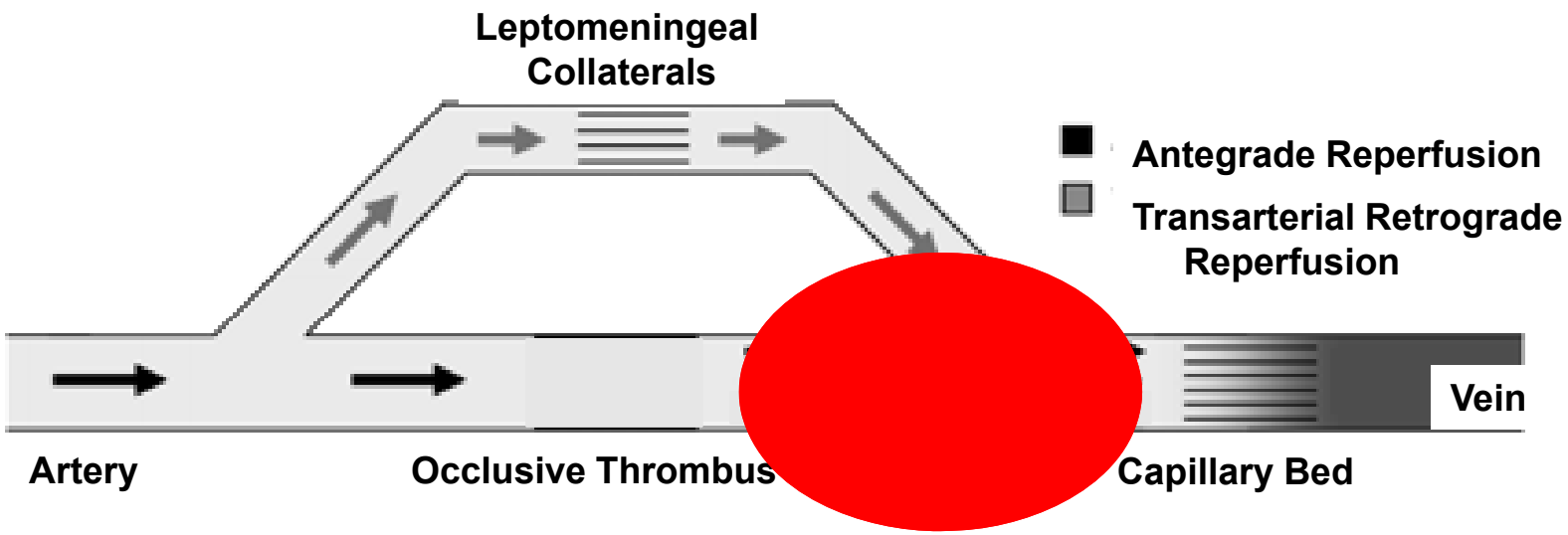
Two Fundamental Treatment Strategies:

Direct Recanalization



Nogueira RG et al. AJNR. 2009 Apr;30(4):649-61

Two Fundamental Treatment Strategies:

Direct Recanalization

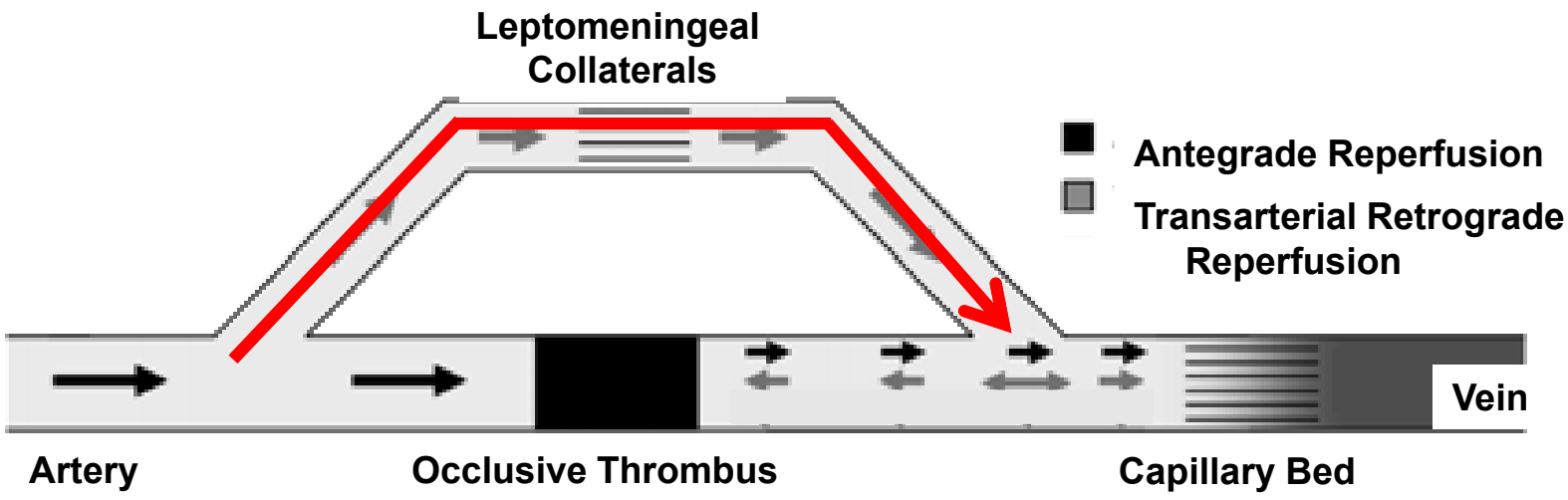
- IV tPA
  - Safe to 3-4.5 hours, potential to move beyond
  - Limited use – delays in presentation

- Thrombectomy
  - 4 cleared devices – no medical arm controls
  - Improving understanding of patient selection
  - Improving safety and success rates

- Overall, increasingly effective but still restricted patient selection
  - Proximal occlusion; limited core; relatively early presentation
  - Higher risk / Higher reward option

Two Fundamental Treatment Strategies:

Flow Augmentation



Nogueira RG et al. AJNR. 2009 Apr;30(4):649-61

Two Fundamental Treatment Strategies:

Flow Augmentation

- Increasing Blood Pressure (e.g. Pressors)
  - Limited effect due to autoregulation
  - Cardiopulmonary risks: CHF, MI, Pulmonary edema
- Increasing Volume
  - Used in vasospasm – controversial
  - Unproven in stroke
  - Cardiac risks: CHF, MI and much less reversible
- NeuroFlo – a unique alternative
  - No significant increase in BP or cardiac work

Treatment Objectives & Risk Tolerance

Symptoms/Occlusion	***Presentation Time***	
	Early	**Late**
Severe/ Proximal Occlusion	**Risk Tolerance: High** **-** **Treatment Goal:** **mRS 0-2**	**Risk Tolerance: Moderate** **-** **Treatment Goal:** **Survival, mRS 0-4**
Mild/Moderate Distal Occlusion	**Risk Tolerance: Moderate** **-** **Treatment Goal:** **mRS 0-1, 0-2**	**Risk Tolerance: Low** **-** **Treatment Goal:** **Minimize Disability** **mRS 0-3**

Ischemic Stroke Treatment Selection

Presentation Time

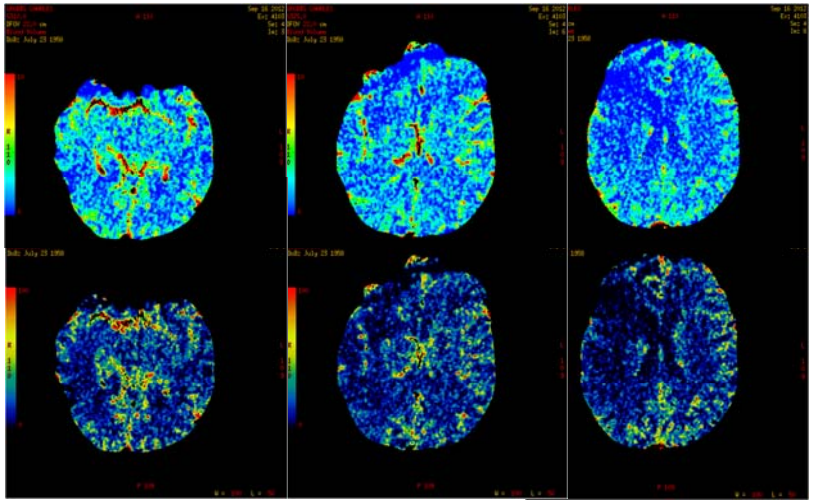
Symptoms/Occlusion	**Early**	**Late**
Severe/ Proximal Occlusion	**Direct Recanalization: IV tPA +/- Thrombectomy** **Flow Augmentation (contraindications only)**	**Select Thrombectomy** **Flow Augmentation**
Mild/Moderate Distal Occlusion	**Direct Recanalization: IV tPA** **Flow Augmentation (contraindications only)**	**Flow Augmentation**

Severe and Late Case Example

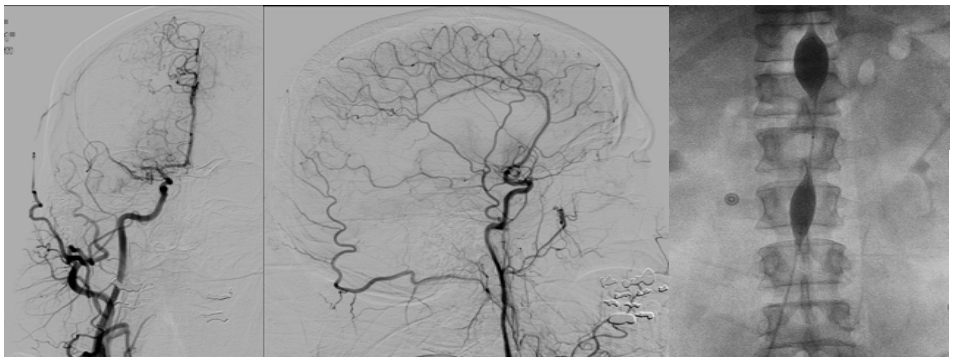
54yo M w/ acute onset L hemiplegia; NIHSS=15; 5hrs post onset

(1) NCCT: large R MCA infarct

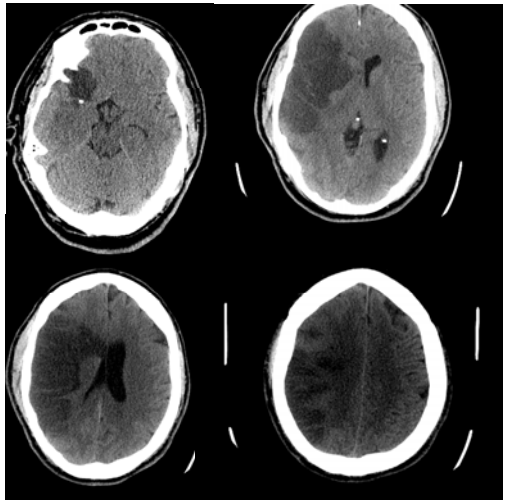
(2) CTP: large MCA infarct/some mismatch



(3) DSA: poor collateral flow.
NeuroFlo - reduce risk of hemicraniectomy/death (mRS 0-4)



(4) Five day CT
No hemicraniectomy



Stroke is Like a Fire in the Brain…

When a stroke strikes …

it spreads like a fire in the brain…

Stroke is Like a Fire in the Brain…

We would like to limit the damage to a minimum, and

… prevent complete devastation.

Clinical Conclusions

- **NeuroFlo can be an important complementary tool in the stroke armamentarium**
- **NeuroFlo is a safer approach that provides a benefit**
  - in reducing mortality and severe disability
  - in shifting outcomes

- **Risk-Benefit identifies an Untreated Target Population**
  - Late presentation (direct recanalization too risky for limited benefit)
  - Anatomic/medical exclusions for intracranial access or tPA
  - Others with marginal risk/benefit profile for direct recanalization (elderly, etc)

- **Overall clinical evidence provides ample support for the use of NeuroFlo in the treatment of ischemic stroke**

NeuroFlo should be made available for our clinical practice

Presentation Schedule

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• SENTIS Study and Interpretation	
– Study Design	Jeff Saver, MD
– Safety	Helmi Lutsep, MD
– Patient Benefit	Jeffrey Saver, MD
– Clinical Interpretation	Raul Nogueira, MD
• **Conclusion**	**Susan Alpert, PhD, MD**

Conclusion

- **NeuroFlo technology in clinical use today**
  - **Indicated for aortic partial occlusion**
  - **Label includes redirection of cardiac output to the cerebral vasculature**
- SENTIS patients represent >80% of presenting stroke patients - who have no alternative acute treatment options
- SENTIS study outcomes provide substantial – and sufficient – clinical data to support NeuroFlo use in stroke
  - Safety
  - Mortality reduction
  - Risk/benefit that favors treatment
- CoAxia seeks labeling to allow use in stroke patients via de novo petition
  - Safety is established
  - Clinical benefit achieved
  - General controls are well established
  - Sufficient “special controls” (labeling, training, surveillance) exist

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  - **Clinical benefit achieved**
  - **General controls are well established**
  - **Sufficient "special controls" (labeling, training, surveillance) exist**

*Revisiting FDA's De Novo Considerations**

- Magnitude and probability of device impact (safety and efficacy)
  - Impact on clinical management of patients
  - Improvements in quality of life
  - Reduction in the probability of death
  - Aiding in the improvement of patient function
- Patient population
  - Is there an unmet clinical need?
  - What alternative therapies are available?
  - Not all patients need to experience every benefit
- Clinical and non-clinical data

*** FDA Guidance Document: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications**

Conclusion

- Specific stroke labeling is required

  … so patients can receive the benefit of this treatment approach

  … so physicians can receive adequate training, instructions, and ongoing support for continued safe and effective use

  … so appropriate communication about this device can be developed and shared

Thank You