Treating No-Reflow in the Microcirculation after EVT

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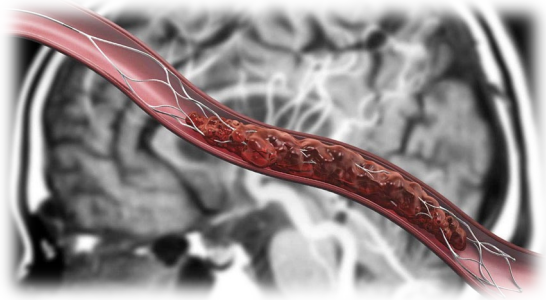
Disclosures

- NIH/NINDS – research and salary support (MOST Trial)
- Sense Diagnostics, Inc. – Founder and Equity Holder
- Clinical perspective
  - Not covering non-clinical investigations
- Likely missing something

Outline

- Background
- Translational Stroke Research: STAIR → SPAN → StrokeNet
- Approaches to microcirculatory thrombus dissolution

Background

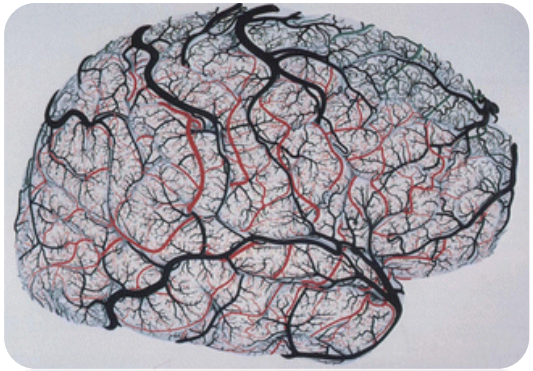


- Direct cost of stroke in 2020 was $34.5 billion
  - Projected to by $94.3 billion by 2035
- Death and disability disproportionately affects non-Hispanic, black populations
- Despite successful recanalization –
  - Only 27% of EVT patients are disability free at 90 days
  - Less than half achieve functional independence

Circulation. 2024;149(8).
Journal of Stroke and Cerebrovasc Diseases. 2022;31(10).
The Lancet. 2016;387(10029):1723-1731.

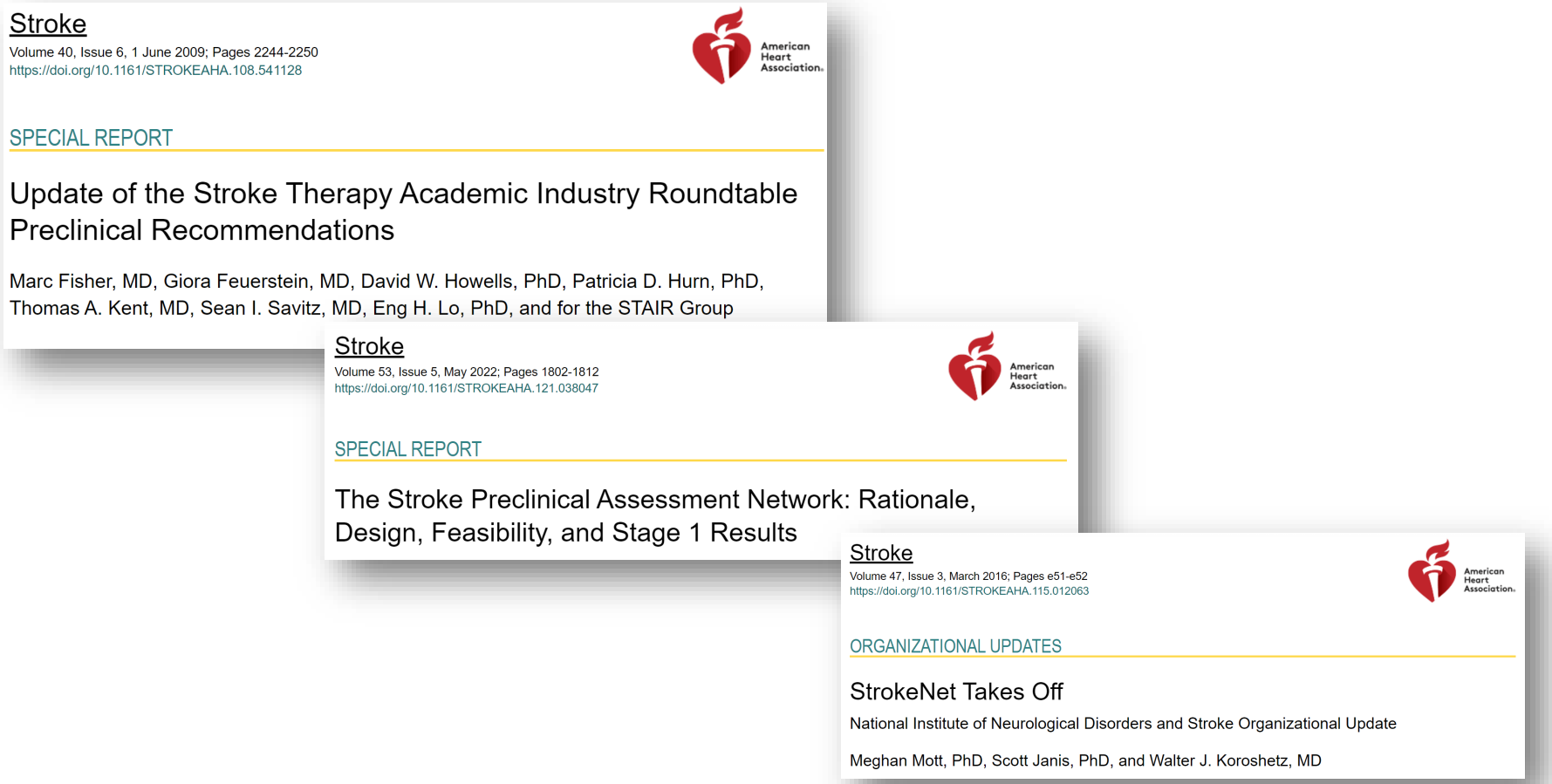
Background

- "No re-flow" - Recanalization of large arteries without effective tissue reperfusion
- Is incomplete microcirculatory reperfusion contributing to poor outcomes?



Stroke. 1991;22(10):1276-1283.
Journal of Cerebral Blood Flow and Metabolism. 2012;32(12):2091-2099.

Idealized Model of Translational Stroke Research



STAIR Criteria

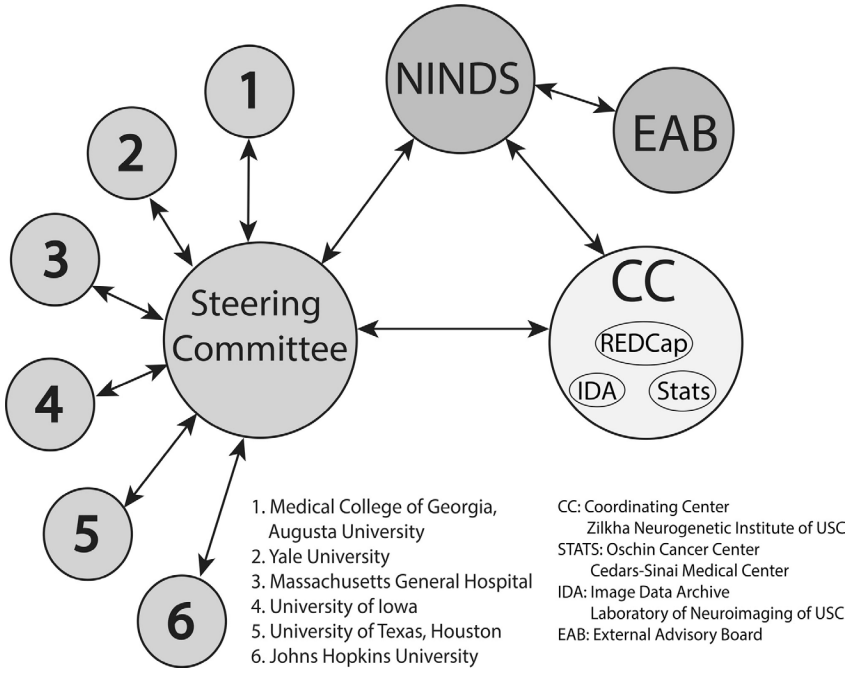
- Dose Response
- Therapeutic window
- Outcome measures
- Physiological monitoring
- Multiple species
- Reproducibility

- Sample size calculation
- Inclusion/exclusion criteria
- Randomization
- Allocation concealment
- Blinded outcome assessment
- Reporting potential conflicts

Stroke.1999;30:2752–2758
Stroke. 2009;40:2244-2250

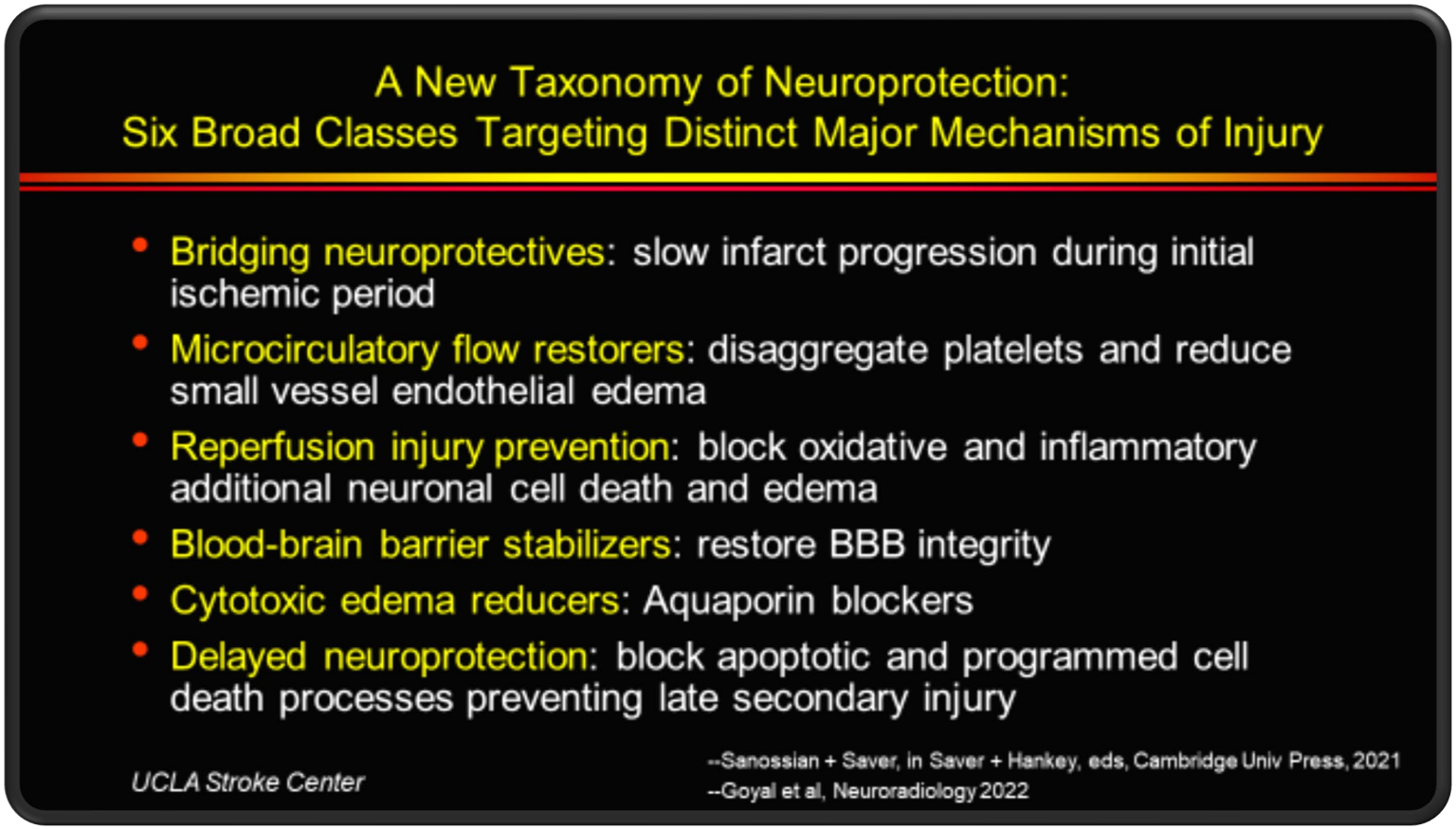
SPAN Design

- Improve rigor in preclinical assessment
- Randomized, placebo-controlled, blinded, multilaboratory trial
- Feasibility of treatment masking, randomization, prerandomization inclusion/exclusion criteria, and blinded assessment



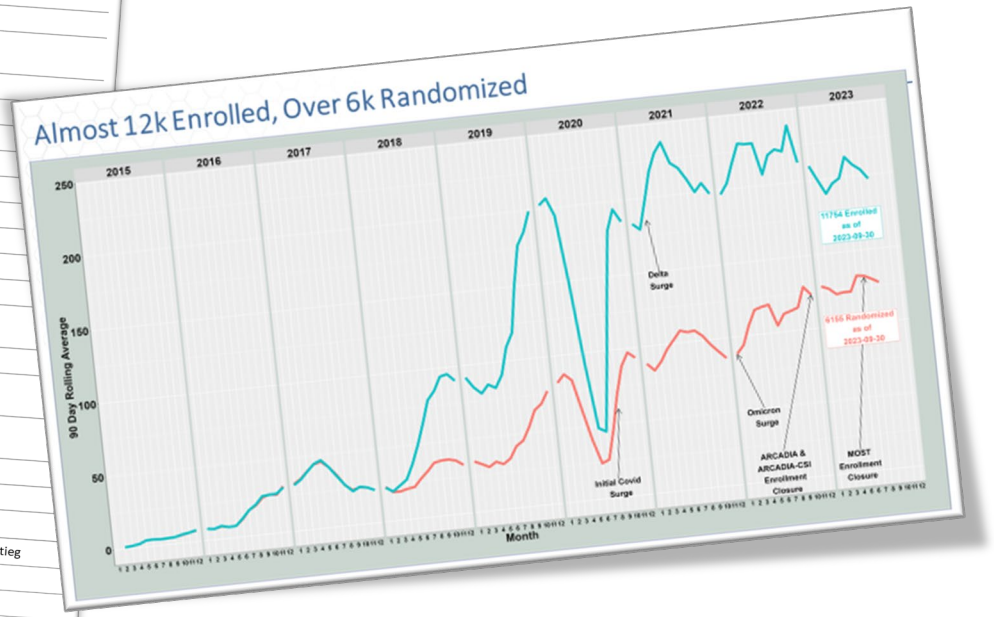
Stroke. 2022;53:1802–1812.

"Neuroprotection"



StrokeNet Infrastructure

Current RCCs (27)	
Case Western Reserve Regional Coordinating Center	Sophia Sundararajan, (Contact); Ken Uchino
Chicago Stroke Trials Consortium	Shyam Prabhakaran
(new) Duke-UNC Eastern North Carolina and Southern Virginia Regional Stroke Trial Consortium – ENVISION	Wayne Feng; David Hwang; Alexander Limkakeng
Georgia StrokeNet	Michael Frankel (Contact); Steven Wolf; David Wright
Gulf Regional Area Stroke Program and Oklahoma	Sean Savitz
Florida RCC for the NINDS Stroke Trials Network	Jose Romano
Los Angeles - Southern California (LASC)	Jeffrey Saver (Contact); Gene Sung
Mid-America RCC (MARCC)	Peter Panagos (Contact); Andria Ford
New England RCC (NERCC)	Aneesh Singhal
(new) New York City Collaborative RCC (NYCC-RCC)	J Mocco; Aaron Lord; Mark Mehler
NorCal RCC	Anthony Kim
Ohio Valley RCC	Eva Mistry (Contact); Stacie Demel
Philadelphia Regional Stroke Trials Network Coordinating Center (PRSTNCC)	Scott Kasner (Contact); Brett Cucchiara
San Diego StrokeNet+	Brett Meyer
Southeast Collaborative Alliance for Stroke Trials (SE-CoAST)	Tanya Turan (Contact); Christine Holmstedt
Southern New England Partnership In Stroke Research, Innovation and Treatment (SPIRIT)	Kevin Sheth (Contact); Mark Alberts; Karen Furie; Richard Temes
(new) Southwestern Stroke Alliance RCC	Michel Torbey
Stanford University RCC	Maarten Lansberg
Stroke Central Atlantic Network for Research (SCANR)	Peter Turkeltaub (Contact); Amie Hsia; Bradford Worrall
Stroke Trials Network of Columbia and Cornell	Randolph Marshall (Contact); E. Sander Connolly; Dana Leifer; Philip Stieg
StrokeBelt StrokeNet	Toby Gropen (Contact); Mark Harrigan; Ronald Lazar
StrokeNet University of Pittsburgh (STN-UP)	Marcelo Rocha (Contact); Raul Nogueira
University of Iowa Regional Stroke Research Network	Enrique Leira
University of Michigan RCC	Phillip Scott (Contact); Devin Brown
Upper Midwest StrokeNet	Christopher Streib (Contact); Kamakshi Lakshminarayan
University of Utah StrokeNet	Jennifer Majersik
Wake Forest StrokeNet	Cheryl Bushnell (Contact); Stacey Wolfe



Courtesy of Pooja Khatri, MD

Restoring Microcirculatory Flow

- Thrombus dissolution (platelet disaggregation is a component of thrombus dissolution)
  - Completed studies
  - Ongoing trials
  - Upcoming trials
- Reducing small vessel endothelial edema
- No reflow phenomenon – chicken or egg?
- Macrocirculatory dissolution – recanalization vs reperfusion

CHOICE

- Randomized LVO patients with successful EVT to IA-tPA or placebo
- Terminated early due to poor enrollment
- 59% (36/61) of IA-tPA subjects achieved mRS of 0 or 1 compared with 40% (21/52) placebo
  - Adjusted risk difference, 18.4%; 95%CI, 0.3%-36.4%
  - Small sample size resulted in wide CIs for treatment effect
  - *Non-significant effect in subjects receiving IV thrombolysis*

JAMA. 2022;327(9):826-835.

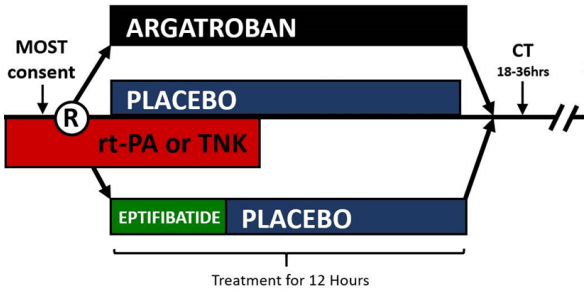
EPOCH/ANGEL-ACT

- EPOCH: single-arm, open-label of eptifibatide in EVT patients
  - IV/IA eptifibatide 135-180mcg/kg bolus, followed by 24-hour infusion
  - 115 subjects
  - sICH primary outcome – 4.4%
- ANGEL-ACT: prospective registry of patients treated with EVT
  - Propensity-matched analysis 162 subjects showed IA eptifibatide associated with higher rates of mRS 0-2 (53.1% vs 33.3%; P=0.016)
- Overall: lack of randomization, open label treatment, and lack of standardized dosing of eptifibatide

Stroke. 2022;53(5):1580-1588.

MOST

MOST
Multi-Arm Optimization of Stroke Thrombolysis



- Phase 3, single blind study with early treatment window and RAR
  - 514 subjects
  - IV argatroban, eptifibatide, placebo
- 44% received EVT
- No difference in sICH or functional outcome

International Journal of Stroke. 2021;16(7):873-880.

TIMELESS

Tenecteplase for Stroke at 4.5 to 24 Hours with Perfusion-Imaging Selection

G.W. Albers, M. Jumaa, B. Purdon, S.F. Zaidi, C. Streib, A. Shuaib, N. Sangha, M. Kim, M.T. Froehler, N.E. Schwartz, W.M. Clark, C.E. Kircher, M. Yang, L. Massaro, X.-Y. Lu, G.A. Rippon, J.P. Broderick, K. Butcher, M.G. Lansberg, D.S. Liebeskind, A. Nouh, L.H. Schwamm, and B.C.V. Campbell, for the TIMELESS Investigators*

- Patients with MCA/ICA occlusions randomized to IV-TNK or placebo
  - 458 patients
  - 0.25mg/kg TNK or placebo initiated 4.5 to 24 hours LKW, prior to thrombectomy
- Study drug to groin puncture time was 15 min
- No benefit or apparent harm
  - Primary outcome – ordinal mRS
  - Common odds ratio – 1.13 (95%CI 0.82 to 1.57; P=0.45)
  - sICH rate 3.2% vs 2.3%

NEJM. 2024;390(8):701-711.

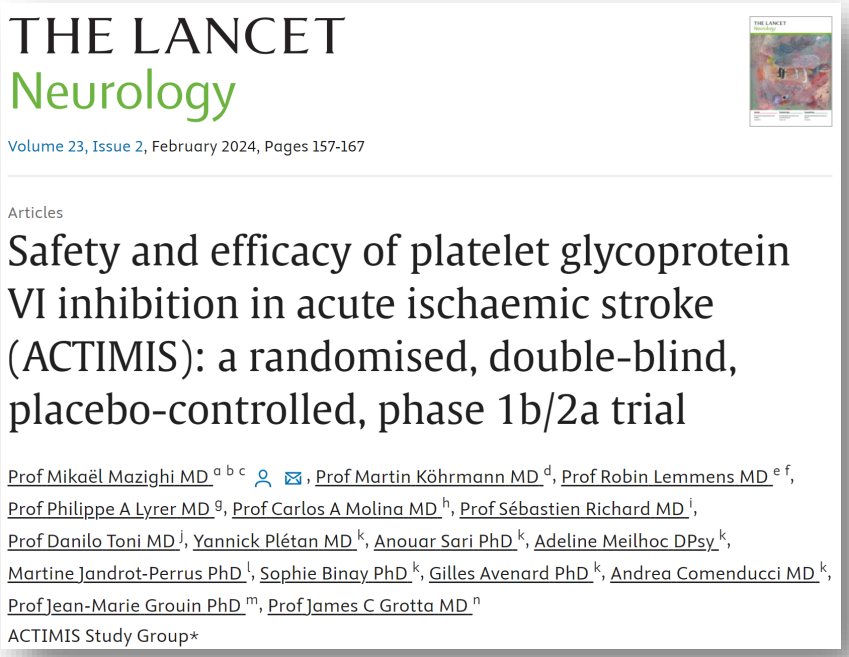
Stroke. 2021;52(4):1192-1202.
Journal of NeuroInterv Surg. 2024.

Meta-Analyses

- 4,581 EVT patients treated with IA thrombolysis or antiplatelet from 16 non-randomized, observational studies
  - Patients receiving IA medications more likely to achieve mRS 0-2
  - No difference in recanalization or sICH → potential benefit of IA medications may be in restoring microcirculatory perfusion

- 15,316 EVT patients in 41 randomized and non-randomized studies
  - Higher odds of functional independence in those receiving IA medications
  - No difference in recanalization or sICH
  - Favorable effect observed in patients receiving IA antiplatelet medication but not in those receiving IA thrombolysis

ACTISAVE



THE LANCET
Neurology

Volume 23, Issue 2, February 2024, Pages 157-167

Articles

Safety and efficacy of platelet glycoprotein VI inhibition in acute ischaemic stroke (ACTIMIS): a randomised, double-blind, placebo-controlled, phase 1b/2a trial

Prof Mikaël Mazighi MD [a b c], Prof Martin Köhrmann MD [d], Prof Robin Lemmens MD [e f], Prof Philippe A Lyrer MD [g], Prof Carlos A Molina MD [h], Prof Sébastien Richard MD [i], Prof Danilo Toni MD [j], Yannick Plétan MD [k], Anouar Sari PhD [k], Adeline Meilhoc DPsy [k], Martine Jandrot-Perrus PhD [l], Sophie Binay PhD [k], Gilles Avenard PhD [k], Andrea Comenducci MD [k], Prof Jean-Marie Grouin PhD [m], Prof James C Grotta MD [n]
ACTIMIS Study Group*

166 total subjects

- ACTISAVE: ACuTe Ischemic Stroke Study Evaluating Glenzocimab Used as Add-on Therapy Versus placEbo (ACTISAVE)

ClinicalTrials.gov Identifier: NCT05070260

Recruitment Status : Active, not recruiting
First Posted : October 7, 2021
Last Update Posted : December 6, 2023

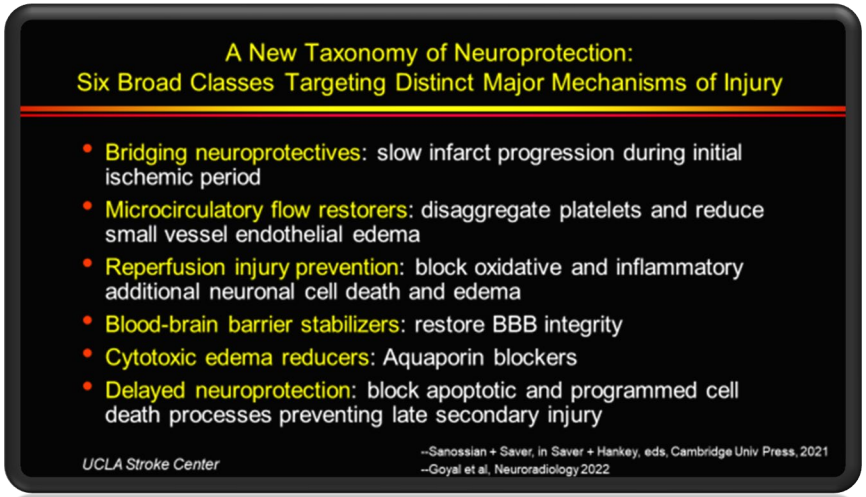
All subjects received SOC thrombolysis
Glenzocimab – GP VI Inhibitor

Prior studies – Summary

	CHOICE	EPOCH/ ANGEL-ACT	MOST	TIMELESS
Included LVO	Y	Y	Y (44%)	Y
Last Known Well	< 24 hrs	< 24 hrs	< 3 hrs	4.5-24 hrs
Standard of Care IV Thrombolysis	Y (60%)	N	Y (100%)	N
Investigational Product (IP)	Alteplase	Eptifibatide	Eptifibatide	Tenecteplase
Mode of Delivery	IA	IA	IV	IV
Timing of IP	After thrombectomy completed	After thrombectomy completed	Within 75 min of IV thrombolysis	Prior to thrombectomy attempt
Efficacy Outcomes	Suggests benefit	Suggests benefit	No benefit	No benefit
Safety Outcomes	No apparent harm	No apparent harm	No apparent harm*	No apparent harm

*There was no apparent harm in eptifibatide subjects. MOST argatroban subjects had increased mortality for unclear reasons.

Give up on antithrombotic approaches?



SISTER Trial – Ongoing

- Phase 2 randomized dose-ranging trial of monoclonal antibody (TS23)
- TS23 targets and inactivates alpha-2 antiplasmin, the dominant inhibitor of plasmin
  - Allows endogenous tPA to generate plasmin for (?) safer clot dissolution
- 4.5 – 24-hour window (i.e., no SOC thrombolysis)
  - NB: Excludes EVT patients

Other Emerging IV Therapies

- Dornase Alfa (DNase) – cleaves extracellular DNA in NETs
  - EXTEND-IA Dnase – ongoing Phase 2 trial
  - Dnase added to IV thrombolysis within 4.5 hours
- Cangrelor – platelet P2Y12 inhibitor
  - REPERFUSE trial – ongoing Phase 3 trial
  - IV cangrelor added to SOC within 24 hours in EVT patients
- BB-031 – vWF aptamer, inhibits platelet adhesion
  - RAISE trial – pending Phase 2 trial (non-thrombolysis patients)
- Prourokinase – mutant form targets partially degraded thrombi may be synergistic with alteplase (JAMA Neurol. 2023;80(7):714-722.)
  - Ongoing Chinese and European trials as alternative to alteplase

CHOICE Approach

- Intra-arterial thrombolysis
  - Multiple ongoing trials
- Could readily be applied to antiplatelets/other antithrombotics
  - Alone or in combination

JAMA | Preliminary Communication

Effect of Intra-arterial Alteplase vs Placebo Following Successful Thrombectomy on Functional Outcomes in Patients With Large Vessel Occlusion Acute Ischemic Stroke
The CHOICE Randomized Clinical Trial

Arturo Renú, MD; Mónica Millán, MD; Luis San Román, MD; Jordi Blasco, MD; Joan Martí-Fàbregas, MD; Mikel Terceño, MD; Sergio Amaro, MD; Joaquín Serena, MD; Xabier Urra, MD; Carlos Laredo, PhD; Roger Barranco, MD; Pol Camps-Renom, MD; Federico Zarco, MD; Laura Oleaga, MD; Pere Cardona, MD; Carlos Castaño, MD; Juan Macho, MD; Elisa Cuadrado-Godía, MD; Elio Vivas, MD; Antonio López-Rueda, MD; Leopoldo Guimaraens, MD; Anna Ramos-Pachón, MD; Jaume Roquer, MD; Marian Muchada, MD; Alejandro Tomasello, MD; Antonio Dávalos, MD; Ferran Torres, MD; Ángel Chamorro, MD; for the CHOICE Investigators

Proposed ERASE Trial

- Enhancing Reperfusion in Acute Stroke Thrombectomy
  - Proposed double blinded, three-arm, Phase 3 randomized trial
  - Using the StrokeNet Thrombectomy Endovascular Platform (STEP)

- Aim 1 - efficacy of IA tenecteplase or IA eptifibatide in AIS patients treated with EVT between 4.5 and 24 hours of symptom onset with post-EVT TICI 2b/3

- Aim 2 - safety of IA tenecteplase or IA eptifibatide in AIS
- patients treated with EVT between 4.5 and 24 hours of symptom onset with post-EVT TICI 2b/3

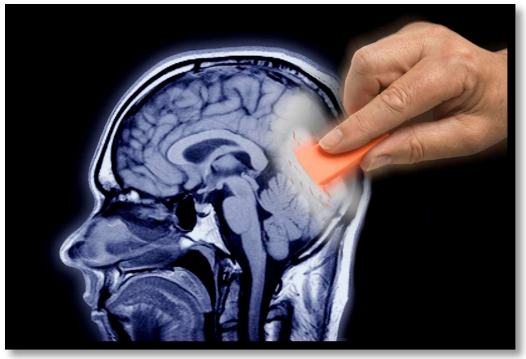
Rationale for ERASE

- Key gaps in knowledge include:
  - whether there is a difference in efficacy of IA thrombolysis and IA antiplatelet
  - whether there is a difference in safety of IA thrombolysis and IA antiplatelet after EVT in AIS
  - whether treatment effect of IA medication is modified by preceding intravenous thrombolysis

Proposed ERASE Trial

- Design
  - Initial 1:1:1 randomization
  - Then response adaptive randomization
  - Interim futility analyses
  - Ongoing safety analyses
- Efficacy endpoint – mRS 0-2 at 90 days
- Safety endpoint – sICH rates
- Sample size ~1,000

- Adjunct infused in 25mL over 5min
  - Arm #1 (Control) - Saline placebo
  - Arm #2 (Tenecteplase) - 0.0625mg/kg (max dose 6.25mg)
  - Arm #3 (Eptifibatide) - 135mcg/kg (max dose 13.5mg)



Prior studies compared to ERASE

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Summary

- A variety of approaches have been tested to dissolve thrombi in microvascular occlusion in stroke

- Ongoing trials are testing:
  - Alpha-2 antiplasmin inhibition
  - Intra-arterial thrombolysis
  - Dnase
  - Cangrelor – P2Y12 inhibition

  BB-031
  Prourokinase
  Among others

- ERASE plans to investigate IA TNK and IA antiplatelet in non-IV thrombolysis EVT patients

Thank you!

Questions?

Opeolu Adeoye, MD MS
BJC HealthCare Professor and Chair
Department of Emergency Medicine