Cerebral Edema After Acute Brain Ischemia

Kevin N. Sheth, MD

Yale SCHOOL OF MEDICINE

Disclosures

- National Institutes of Health
- American Heart Association
- Biogen
- Hyperfine
- Bard
- Taylor Kimberly, MD, PhD

Objectives

- What is the clinical problem? Why is understanding edema after ischemia important?
- What are the fundamental scientific and clinical gaps in our current state of knowledge?
- An exciting basic science discovery and its (ongoing) translation to our patients
- New opportunities

Magnitude of the problem

- 70,000 US patients with malignant infarction every year
- Case fatality rates as high as 60-80%
- Revascularization therapies reach limited numbers of patients
- Only proven therapy is surgery which may not be available to elderly patients and can be quite morbid

Left MCA Infarction with NIHSS 24

<u>Primary Injury</u>

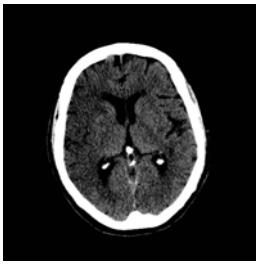
- Maximal tissue protection
- Minutes to hours

<u>Secondary Injury</u>

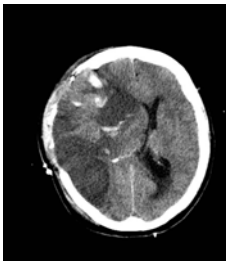
- Tissue protection
- Hours to days

Historical Patient

- 71 year old right MCA syndrome NIHSS 20 s/p IV TPA



Day 1



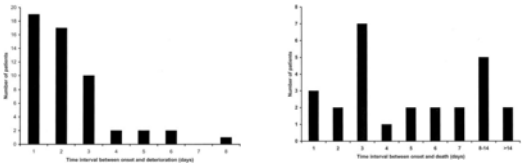
Day 3

Cerebral Edema – who is at risk?

- 201 patients with large MCA strokes. . .
- Multivariate analysis found predictors of fatal brain edema:
  - **h/o HTN** (OR 3.0)
  - **h/o CHF** (OR 2.1)
  - ↑**WBC** (OR 1.08 per 1000 WBC/mcl)
  - **>50% MCA hypodensity** (OR 6.3)
  - involvement of **additional vascular territories** (ACA, PCA, anterior choroidal; OR 3.3).
- Initial LOC, NIHSS, early nausea/vomiting, and serum glucose also associated

Kasner et al, Stroke 2001; 32(9): 2117-23

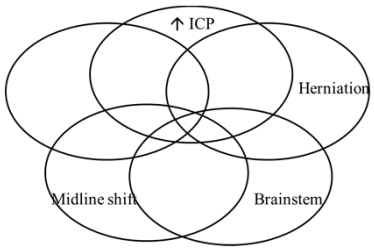
Timing of deterioration



- Quereshi et al performed a multicenter retrospective chart review of massive MCA infarctions, clinical deterioration at
  - 48 hours in 68%
  - 72 hours in 88%

Qureshi, Critical Care Medicine 2003: 31(1): 272-7

Differential Diagnosis



Level of arousal is the common finding!

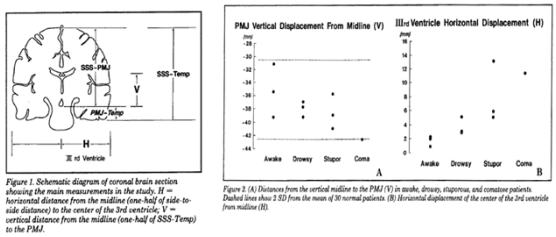


Figure 1. Schematic diagram of coronal brain section showing the main measurements in the study. H = horizontal distance from the midline (one-half of side-to-side distance) to the center of the 3rd ventricle; V = vertical distance from the midline (one-half of SSS-Temp) to the PMJ.

Figure 2. (A) Distances from the vertical midline to the PMJ (V) in awake, drowsy, stuporous, and comatose patients. Dashed lines show 2 SD from the mean of 30 normal patients. (B) Horizontal displacement of the center of the 3rd ventricle from midline (H).

Ropper AH. Lateral displacement of the brain and level of consciousness in patients with an acute hemispheral mass. *NEJM*. 1986

Table. Intracranial, arterial, and cerebral perfusion pressure in patients deteriorating from LHIE

Pt	Age (yr)	Timing of worsening (hr)	Intracranial pressure monitor	Initial intracranial pressure (mm Hg)	Initial mean arterial pressure (mm Hg)	Initial cerebral perfusion pressure (mm Hg)	Intracranial pressure for the first 12 hours of monitoring (mm Hg) Minimum	Maximum
1	67	64	Ipsilateral Camino	17	111	94	9	25
2	39	66	Contralateral ventric	30	103	67	30	121
3	72	6	Contralateral ventric	7	79	72	7	17
4	66	86	Contralateral ventric	15	83	68	14	22
5	27	33	Ipsilateral Camino	33	89	56	10	37
6	65	82	Ipsilateral Camino	15	100	85	10	15
7	61	48	Ipsilateral Camino	4	107	103	4	6
8	66	52	Ipsilateral Camino	6	65	59	2	10
9	77	120	Ipsilateral Camino	2	78	76	2	8
10	67	72	Ipsilateral epidural	10	97	87	3	10
11	65	40	Ipsilateral Camino	5	72	67	5	14
12	66	20	Ipsilateral Camino	8	98	90	7	11
13	64	52	Ipsilateral Camino	10	83	73	7	10
14	23	33	Ipsilateral epidural	38	80	42	10	40
15	61	55	Contralateral ventric	8	86	78	6	10
16	36	57	Contralateral ventric	20	108	88	10	20
17	53	166	Ipsilateral Camino	13	85	72	7	17
18	51	48	Ipsilateral Camino	10	89	79	8	15
19	71	64	Ipsilateral Camino	4	72	68	1	18

ventric Ventriculostomy.

Frank J. *Neurology* 1995

Recommendations

1. No prophylactic anti-edema therapy or elevation of sodium
2. Maintain eunatremia, eucarbia, and normothermia
3. Anti-edema therapy may be triggered with change in clinical not exam not only by radiological exam!
4. Anti-edema therapy may be instituted as a bridge but should not take the place of or delay surgery

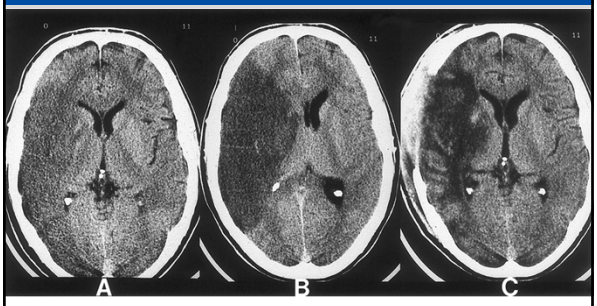
Recommendations for the Management of Cerebral and Cerebellar Infarction With Swelling

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.
Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons
Endorsed by the Neurocritical Care Society

Eelco F. M. Wijdicks, MD, PhD, FAHA, Chair; Kevin N. Sheth, MD, FAHA, Co-Chair; Bob S. Carter, MD, PhD; David M. Greer, MD, MA, FAHA; Scott E. Kasner, MD, FAHA; W. Taylor Kimberly, MD, PhD; Stefan Schwab, MD; Eric E. Smith, MD, MPH, FAHA; Rafael J. Tamargo, MD, FAANS; Max Wintermark, MD, MAS; on behalf of the American Heart Association Stroke Council

Decompressive Craniectomy



Schwab S et al. Early hemicraniectomy in patients with complete middle cerebral artery infarction. *Stroke*. 1998;29:1888-1893.

Decompressive Craniectomy

- HAMLET, DECIMAL and DESTINY pooled analysis of 93 patients
  - Favorable outcome 75% vs. 24% for mRS≤4 at 1 year (NNT=2)
  - 43% vs. 21% for mRS≤3 (NNT=4)
  - 78% vs. 29% for survival (NNT=2)

Vahedi K et al. *Lancet Neurol*. 2007;6:215-22.

What About the Impact of Age? DESTINY II

- Prospective, randomized, controlled, open, multicenter
- 13 German sites, 2009-2013
- Major Inclusion Criteria
  - Age 61 or greater
  - Symptoms less than 48 hours
  - NIHSS > 14 (Right), > 19 (Left)
  - 2/3 infarction of hemisphere and basal ganglia

Design

- Major Exclusion Criteria
  - Rankin more than 1
  - Brainstem signs of herniation
  - GCS< 3
  - Hemorrhagic transformation
- Standardized clinical protocol
- Large DC with 12 cm and duroplasty

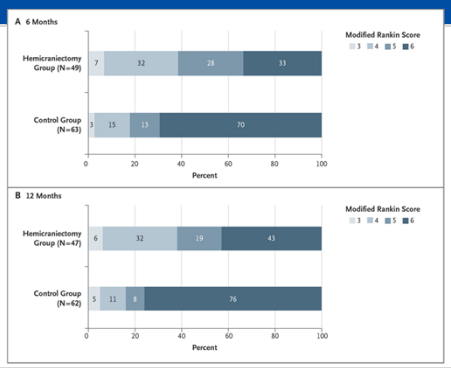
Endpoint

- Primary outcome: 0-4 Modified Rankin at 6 months
- Secondary outcome: All at 12 months, NIHSS, outcomes, quality of life
- Sequential interim analysis until harm, futility, or efficacy was shown; Odds ratio of 1.56

Endpoint

- DSMB stopped after 82 patients had been assessed
- ITT 38% (DC) vs 18% (Control) 95% CI – 1.06-7.49, p=.04
- 0-3 dichotomization did not confirm this result, there were no patients who went to a 2

Results



Neurosurgical Options

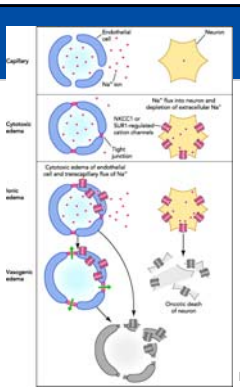
- In patients younger than 60 years of age who deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion is effective. (**Class I, Level of Evidence B**)
- Suboccipital craniectomy with dural expansion should be performed in patients with cerebellar infarctions who deteriorate neurologically despite maximal medical therapy. (**Class I, Level of Evidence B**)

Neurosurgical Options

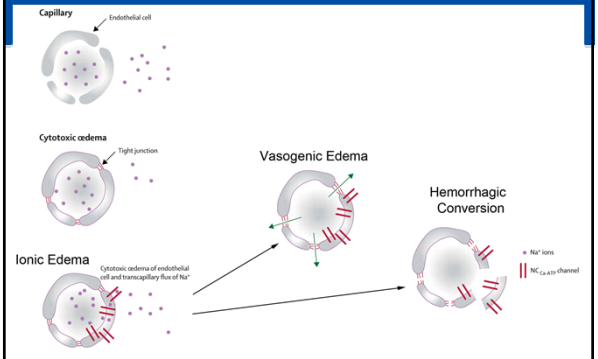
- While the optimal trigger for decompressive craniectomy is unknown, it is reasonable to use a decrease in level of consciousness and its attribution to brain swelling as selection criteria. **(Class IIa, Level of Evidence A)**
- The efficacy of decompressive craniectomy in patients older than 60 years of age and the optimal timing of surgery are uncertain. (**Class IIb, Level of Evidence C)**

Summary

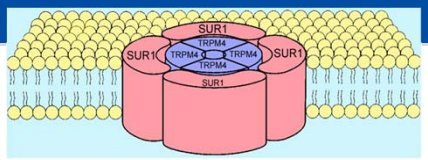
- Swelling after acute brain ischemia is common and deadly
- Level of arousal is the hallmark finding and tissue swelling is the culprit lesion
- Decompressive craniectomy, a potentially morbid procedure, is an accepted, available life-saving therapy
- Our current medical approach is largely supportive and reactive



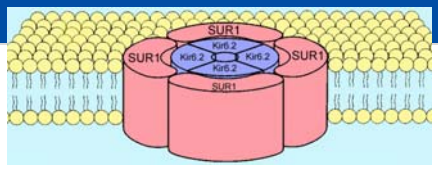
Kahle et al, Physiology, 2009, 24: 257-65



Simard et al, Lancet Neurology 2007, 6: 258-68

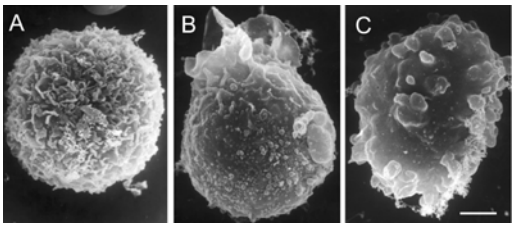


- TRPM4 allows sodium into the cell and is implicated in formation of cerebral edema formation
- Channel is normally not expressed but upregulated in the hours following ischemia



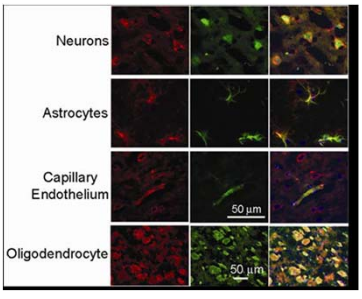
- Pore forming Kir allows potassium channels to open when ATP drops.
- With abundant ATP, channel is closed and insulin is released

Channel Opening Causes Cytotoxic Edema



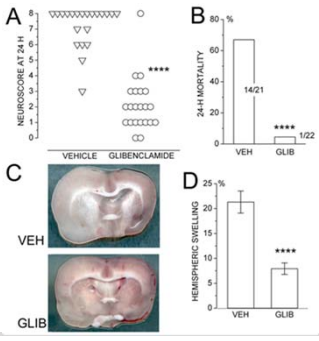
Control | ATP depletion 5 min | ATP depletion 25 min

Multiple Cell Targets

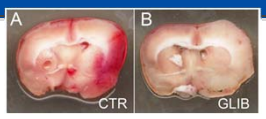


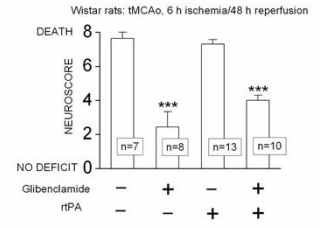
Simard JM, Nature Medicine, 2006

Glyburide Reduces Mortality and Swelling in Malignant Cerebral Edema Model



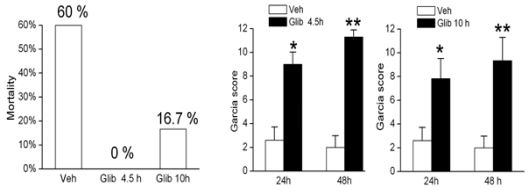
Glyburide Improves Outcome with rtPA





Rodent model of GAMES protocol

MCAo with thread occlusion
thread removal plus rtPA reperfusion at 4.5 hr (0.9 mg/kg)
vehicle vs. glyburide at 4.5 hours and at 10 hours

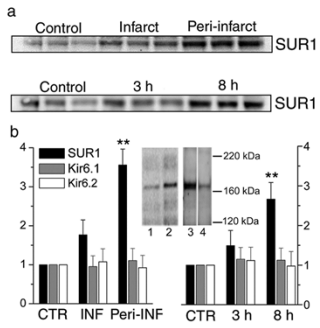


Tx @ 4.5 h Tx @ 10 h

What is the basis for the 10 hour window?

1. Endothelium dies more slowly than neurons
2. SUR1 expression is delayed
3. Sequential Transcriptional Gene Activation
   Hif1a → Sp1 → SUR1

Delayed SUR1 Expression



ORIGINAL ARTICLE

Prediction of Malignant Middle Cerebral Artery Infarction by Magnetic Resonance Imaging Within 6 Hours of Symptom Onset: A Prospective Multicenter Observational Study

Götz Thomalla, MD,[1] Frank Hartmann, PhD,[1] Eric Juettler, MD,[2,3] Oliver C. Singer, MD,[4] Fritz-Georg Lehnhardt, MD,[5] Martin Köhrmann, MD,[6] Jan F. Kersten, MSc,[7] Anna Krützelmann, MD,[1] Marek C. Humpich, MD,[8] Jan Sobesky, MD,[3] Christian Gerloff, MD,[1] Arno Villringer, MD, PhD,[3,9] Jens Fiehler, MD,[10] Tobias Neumann-Haefelin, MD,[4] Peter D. Schellinger, MD,[6] and Joachim Röther, MD[11] for the Clinical Trial Net of the German Competence Network Stroke

	Sensitivity	Specificity	NPV	PPV	Correct Classifications
Prespecified analysis					
DWI lesion >82 ml	0.52 (0.32-0.71)	0.98 (0.94-1.00)	0.90 (0.83-0.94)	0.88 (0.62-0.98)	125/140 (89.3%)
NIHSS score >18	0.63 (0.42-0.80)	0.71 (0.61-0.79)	0.89 (0.80-0.95)	0.34 (0.21-0.49)	97/140 (69.3%)
ICA + MCA occlusion	0.70 (0.50-0.86)	0.63 (0.53-0.72)	0.90 (0.81-0.96)	0.31 (0.20-0.44)	90/140 (64.3%)

95% confidence interval given in parentheses.
NPV = negative predictive value; PPV = positive predictive value; DWI = diffusion weighted imaging; NIHSS = National Institutes of Health Stroke Scale; ICA = internal carotid artery; MCA = middle cerebral artery.

GAMES Pilot Study

- Phase IIa open label of RP-1127 (glyburide for injection)
- 72 hours infusion for patients within 10 hours at 3 mg/day based on phase I study in healthy volunteers
- Primary objectives: safety (glucose) and feasibility of protocol
- Efficacy outcomes: Daily MRI for follow up over 72 hours with hemisphere and infarct volume measurements and 90 day mRS

Sheth et al. *Stroke*, 2014

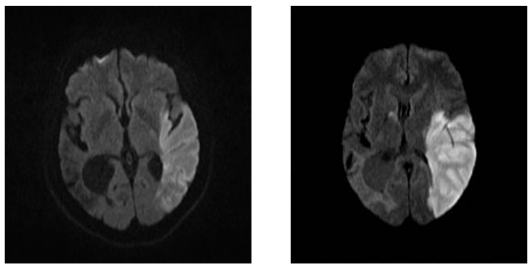
Patient Selection and Enrollment

INCLUSION

- Baseline DWI lesion 82-210 cm^3 (ABC/2)
- IV TPA permitted up to established criteria at 4.5 hours
- Start of drug infusion up to 10 hours from last seen well time
- Age 18-80 years

Patient 1

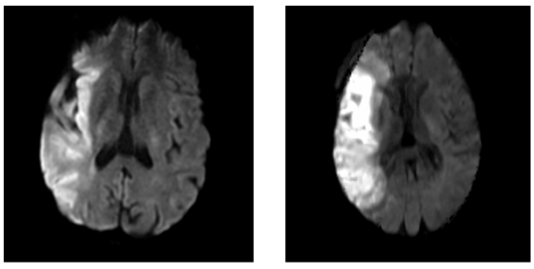
- 47 year old NIHSS 27 L MCA s/p TPA



Baseline 72 hours

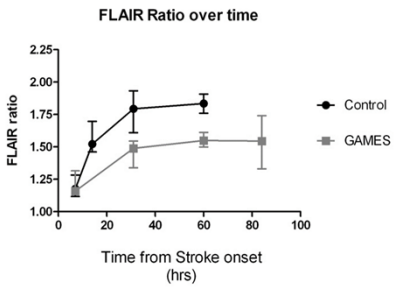
Patient 2

- 52 year old, NIHSS 23, R M1 occlusion s/p IV TPA

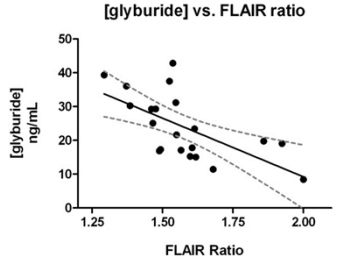


Baseline 72 hours

Day 2 FLAIR Ratio



Day 2 FLAIR Ratio



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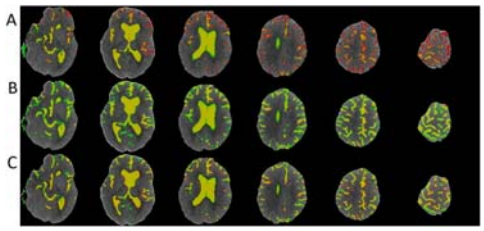


Chen Y, et al. Neuroimag Clin 2016

Can a medical therapy be used to PREVENT swelling before it occurs and improve outcome in patients with large infarction?

Sheth et al, Lancet Neurology, 2016

Objectives

- To assess the **safety** of RP-1127 compared to placebo with a focus on mortality, cardiac-related, and blood glucose related outcomes
- To assess the **efficacy** of RP-1127 compared to placebo in patients who are likely to develop malignant edema and to provide information for a phase III trial

Study Design

Design	U.S., multi-center, prospective, randomized double-blinded study
Population and Inclusion Criteria	- Age 18-80 - Large anterior circulation acute ischemic stroke - Able to undergo randomization within 10 hours - MRI DWI 82-300 cc - Patients exposed to IV tPA up to 4.5 hours, no TPA, endovascular patients excluded
Randomization	1:1 IV RP-1127 vs. Placebo
Sites	18 centers total
Sample Size	83 patients enrolled and treated
Follow Up	Follow-up: Day 30 and 90, 6 and 12 months

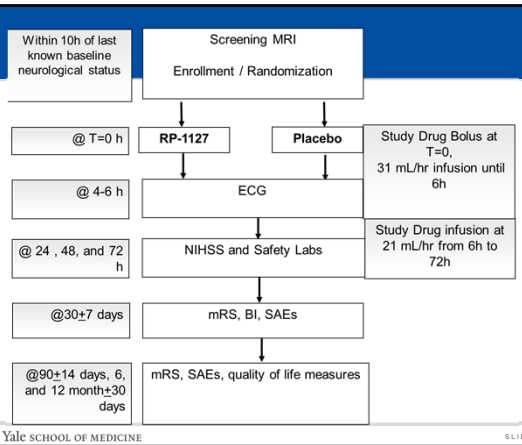
Analysis

Primary

- **Per protocol**
- Pre-specified lesion volume as determined by core imaging laboratory
- Subjects who received intervention within 11 hours

Secondary

- Modified intention to treat
- All randomized patients for whom study drug was initiated



Study Endpoints

Primary Safety	Frequency of (significant) adverse events All cause mortality
Primary Efficacy	Frequency of composite – Avoidance of decompressive craniectomy AND modified Rankin ≤ 4 at 90 days
Secondary Efficacy- Clinical	Subjects undergoing DC and death
Secondary Efficacy- Imaging	Change between baseline and 72-96 hour ipsilateral hemisphere volume by MRI Change between baseline and 72-96 hour swelling measurement by MRI
Other key a priori analyses	Midline shift between baseline and 72-96 hour imaging

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Baseline Characteristics

Characteristics	RP-1127 (N=41)	Placebo (N=36)	p-value
Gender (Male)	61% (25)	72% (26)	0.30
Age (Mean)	58	63	0.07
Race (White)	85% (35)	83% (30)	0.97
Glucose (mg/dL)	153	134	0.96
NIHSS	19	21	0.37
IV TPA	61% (25)	61% (22)	0.99
Left side infarct	49% (20)	56% (20)	0.55
Time to study drug (h)	8.8	9	0.55
Mean baseline DWI (cm^3)	**157**	**163**	**0.53**

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Primary Endpoint

	RP-1127	Placebo	p-value
EFFICACY			
Functional Outcome Composite: Avoidance of DC AND mRS 0-4	17 (42%)	14 (39%)	0.77
SAFETY			
Serious Adverse Events	30 (68%)	28 (72%)	0.72

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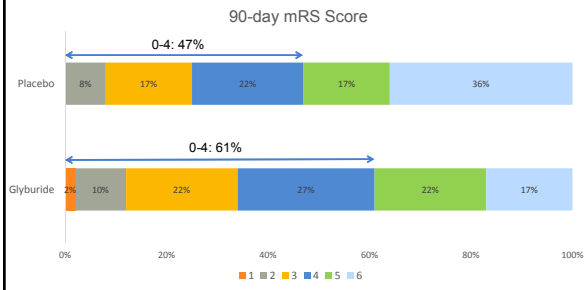
Secondary and Tertiary Endpoints



Odds Ratio 1.7 for mRS 0-4 (p-value=0.23)
SHIFT Analysis (p-value=0.12)

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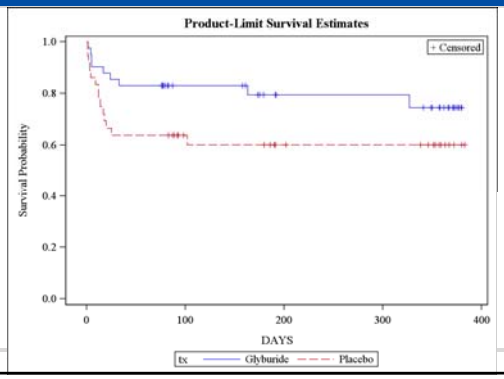
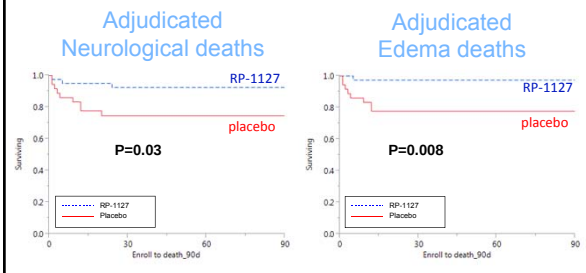
Secondary and Tertiary Endpoints



P=0.06

SLIDE 52

Other Clinical Endpoints



RP-1127 (7%) vs Placebo (25%)

RP-1127 (2%) vs Placebo (22%)

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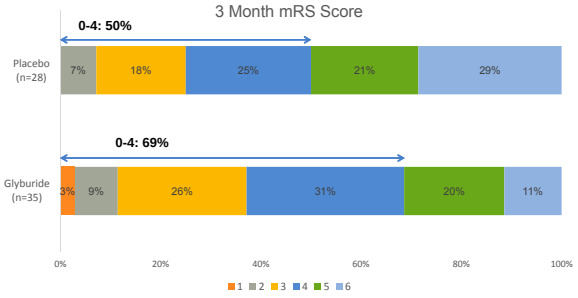
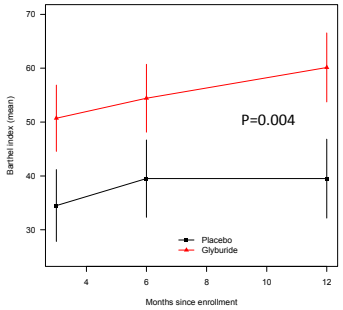
Exploratory Analysis Under Age 70

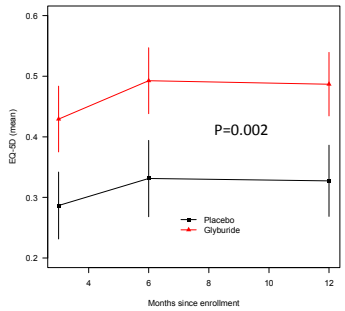


SHIFT Analysis (p-value=0.048)

Disability in Daily Activities – Barthel Index



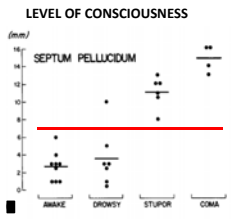
Health Related Quality of Life - EuroQol



Intermediate Endpoints

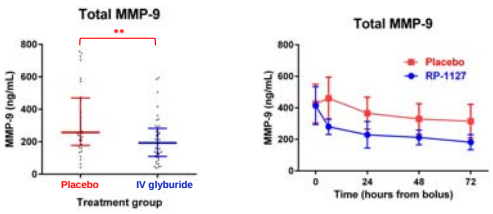
Characteristics	RP-1127 (N=41)	Placebo (N=36)	p-value
Time to BL MRI (hr)	6.0 ± 1.6	5.8 ± 1.6	0.50
Time to FU MRI (days)	3.4 ± 0.8	3.5 ± 0.6	0.48
Baseline DWI volume (mL)	157 ± 62	163 ± 64	0.59
Baseline MMP-9 (ng/mL)	413 ± 377	427 ± 357	0.88
Midline shift (mm)	**4.6 ± 3.6**	**8.4 ± 4.9**	**0.0006**
Average MMP-9 (ng/mL)	**211 ± 138**	**345 ± 251**	**0.006**

Midline Shift



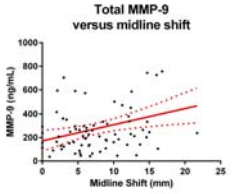
Ropper, AH. *N Engl J Med* 1987;314:953-8.

Total MMP-9



**, *P*=0.006

Total MMP-9 and Edema



P=0.024

Brain Edema Predicts Outcome After Nonlacunar Ischemic Stroke

Thomas W.K. Battey, BS; Mahima Karki, BA; Aneesh B. Singhal, MD; Ona Wu, PhD; Saloomeh Sadaghiani, BA; Bruce C.V. Campbell, MBBS, PhD; Stephen M. Davis, MD; Geoffrey A. Donnan, MD; Kevin N. Sheth, MD; W. Taylor Kimberly, MD, PhD

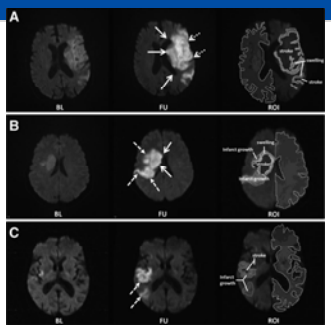
- Two stroke cohorts with serial MRI
- Wide range of NIHSS
- Wide range of initial infarct volumes

Stroke , 2014

Table 1. Clinical and Imaging Characteristics of the Patients

	NBO Cohort (n=19)	EPITHET Cohort (n=78)
Age, y, mean±SD	73±13	72±13
Sex, male, n (%)	15 (78)	42 (53)
Comorbidities, n (%)		
Diabetes mellitus	4 (21)	19 (24)
Hypertension	14 (74)	55 (71)
Hyperlipidemia	13 (63)	33 (42)
Atrial fibrillation	10 (53)	33 (42)
IV tPA, n (%)*	0 (0)	36 (46)
Admission NIHSS score, median (IQR)	14 (7–19)	13 (8–17)
Time from LSW to MRI, h, mean±SD*	7.0±3.0	4.1±0.9
Admission DWI volume, mL, median (IQR)†	33 (14–77)	21 (9–51)
Admission PWI volume, mL, median (IQR)	140 (85–189)	157 (95–239)
Admission FLAIR ratio, mean±SD	1.21±0.12	…
Admission ADC ratio, mean±SD	0.693±0.067	0.685±0.075
ΔDWI volume, mL, median (IQR)	25 (10–51)	14 (5–66)
Swelling, n (%)	13 (68)	53 (67)
Infarct growth, n (%)	7 (39)	34 (43)
Modified Rankin Scale score, median (IQR)	3 (2–6)	3 (1–4)

Examples of swelling, infarct growth, and both



Thomas W.K. Battey et al. Stroke. 2014;45:3643-3648

Table 3. Multivariable Modeling of the Volume of Swelling and Infarct Growth With Poor Outcome

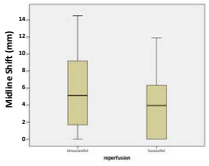
	mRS, 0–2			mRS, 0–2		
	Adjusted OR	95% CI	*P* Value	Adjusted OR	95% CI	*P* Value
Age	1.07	1.02–1.13	0.01	1.10	1.03–1.18	0.001
Admission glucose	4.47	0.57–49.4	0.18	6.58	0.64–103	0.12
Admission NIHSS score	1.13	0.99–1.30	0.07	1.18	1.02–1.39	0.03
Admission DWI volume	2.41	0.56–11.3	0.24	1.46	0.26–9.33	0.67
ΔDWI volume	4.29	2.00–11.5	<0.001	…	…	
Volume of swelling	…	…		1.09	1.03–1.17	0.003
Volume of infarct growth	…	…		1.08	0.68–1.78	0.74

Thrombectomy and Edema

MR CLEAN: 2nd Gen EVT trial

P < 0.001

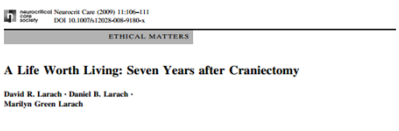
MR CLEAN: ASPECTS 0-5 subgroup



→ Successful reperfusion definition based on mTICI 2b/3

Kimberly et al, JAMA Neurology, 2018

In Our Own Words



ETHICAL MATTERS

A Life Worth Living: Seven Years after Craniectomy

David R. Larach · Daniel B. Larach · Marilyn Green Larach

- Age 49, IRB chairman, associate editor of *Anesthesiology*, chief of cardiac anesthesiology
- L MCA stroke, decompressive craniectomy, 31 day ICU stay, 8 months of intensive rehab at UT Galveston

Where there is life, there may be hope

" Instead of attending hospital meetings, I go to sessions at the local aphasia center. Following years of intensive physical therapy, I can now walk slowly with a cane. I also spend my premature retirement reading *The Washington Post* and *The Wall Street Journal*, watching movies, playing scrabble, and looking at family albums. I go on short walks and long wheelchair rides. I take personal pride in work ethic and refusal to capitulate. I also take pleasure in continually exceeding the expectations of my physicians and therapists. This is not the life I enjoyed prior to my stroke. Nor is it how I envisioned spending my fifties. However, it is still a life worth living. I only have it due to aggressive interventions I received after my stroke, and the therapy I continue to pursue."

Conclusions

- Glyburide does not result in edema attenuation secondary to glucose lowering. What other biomarkers are available?
- Glyburide is associated with a reduction in neurological death and markers of swelling such as midline shift and MMP-9
- Pharmacodynamics, pharmacogenetics, attenuation of inflammation
- Are there any edema and hemorrhage implications beyond ischemic stroke?
- Edema is important, there are likely many more targets, we have to go find them

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