Primary Prevention of Brain Edema after CNS Injury

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Disclosures

- National Institutes of Health
  - UO1NS106513
  - R01NS110721
  - RO1NR018335
  - U24NS107215
  - U24NS107136
- American Heart Association 17CSA33550004
- Biogen, Novartis, Bard, Hyperfine, Astrocyte, Alva Health

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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

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Left MCA Infarction with NIHSS 24

Primary Injury

- Maximal tissue protection
- Minutes to hours

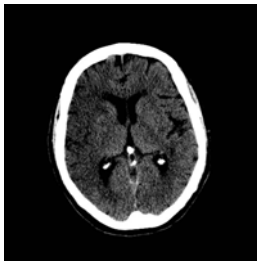
Secondary Injury

- Tissue protection
- Hours to days

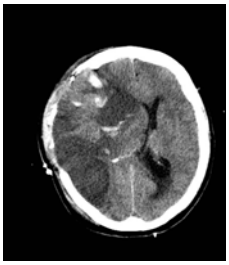
3

Historical Patient

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



Day 1



Day 3

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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

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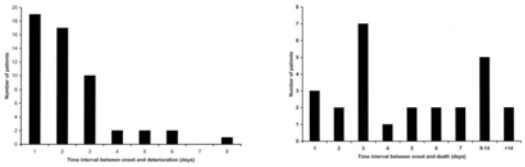
Timing of deterioration



- 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

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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

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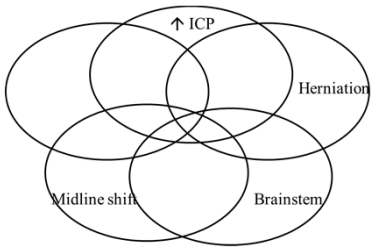
Differential Diagnosis



Level of arousal is the common finding!

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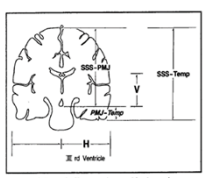

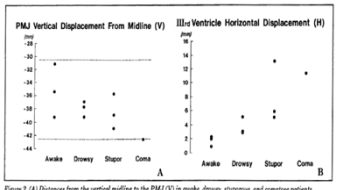

Figure 1. Schematic diagram of coronal brain section showing the main measurements in the study. H = horizontal distance from the midline (one-half of side-to-side distance) to the center of the 3rd ventricle; V = vertical distance from the midline (one-half of SSS-Temp) to the PMJ.

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

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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

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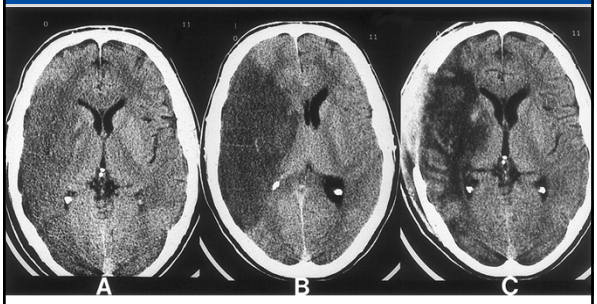
Decompressive Craniectomy



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

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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.

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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

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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

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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

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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

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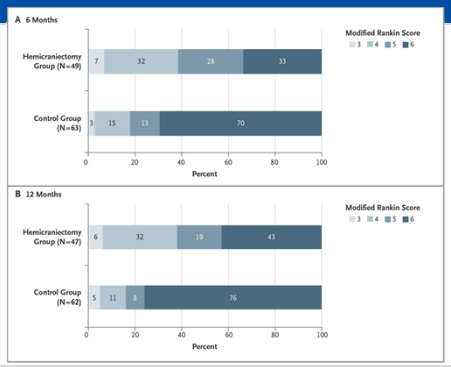
Results



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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**)

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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)**

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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

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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

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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

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Brain edema: an old problem

1967 Cytotoxic and Vasogenic edema

JOURNAL OF NEUROPATHOLOGY & EXPERIMENTAL NEUROLOGY
VOLUME 26 January 1967 NUMBER 1

PRESIDENTIAL ADDRESS*

NEUROPATHOLOGICAL ASPECTS OF BRAIN EDEMA†

IGOR KLATZO, M.D.
(*Bethesda, Maryland*)

The importance of brain edema (BE) can be hardly overemphasized. In this regard it is sufficient to realize the frequency of this potentially disastrous complication in brain tumors, head injuries, cerebrovascular accidents, and inflammatory lesions. BE is also observed in a considerable number of exoge-

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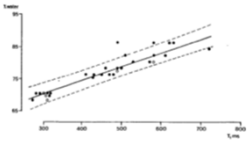
Brain edema: new insights

Measuring water content in human brain:
Magnetic Resonance Imaging

T1 relaxation time
T2 relaxation time
Proton density



Bell, BA et al. Lancet (1987) 329:66-69.

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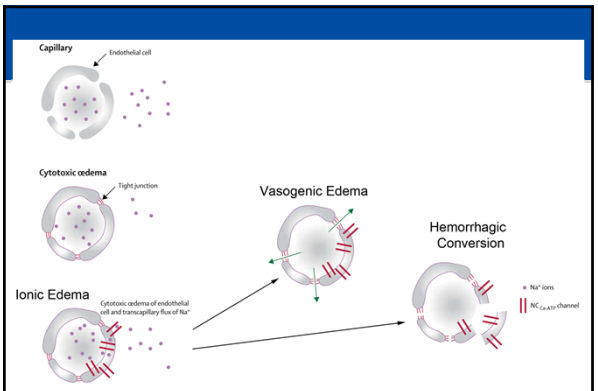

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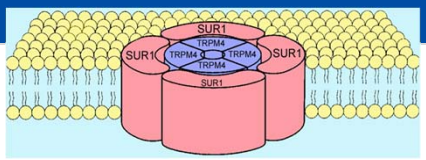

- TRPM4 allows sodium into the cell and is implicated in formation of cerebral edema formation
- Channel is normally not expressed but upregulated in the hours following ischemia

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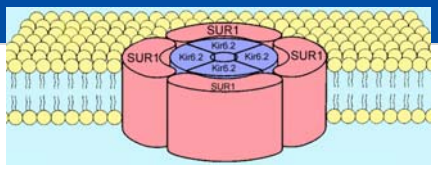

- Pore forming Kir allows potassium channels to open when ATP drops.
- With abundant ATP, channel is closed and insulin is released

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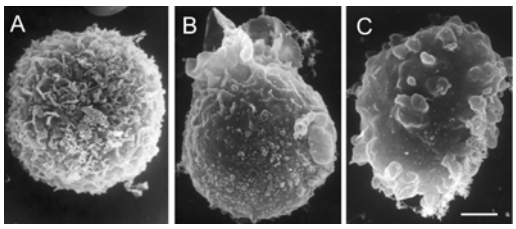
Channel Opening Causes Cytotoxic Edema



Control | ATP depletion 5 min | ATP depletion 25 min

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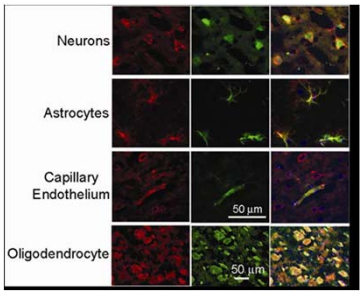
Multiple Cell Targets



Simard JM, Nature Medicine, 2006

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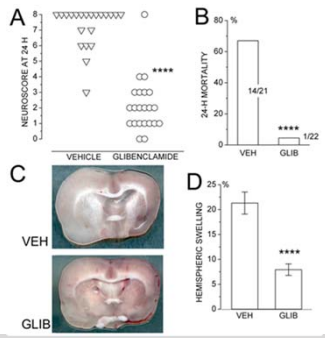
Glyburide Reduces Mortality and Swelling in Malignant Cerebral Edema Model



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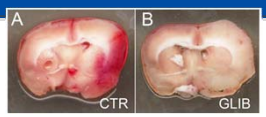
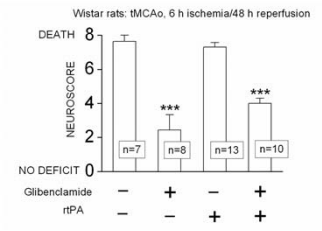
Glyburide Improves Outcome with rtPA





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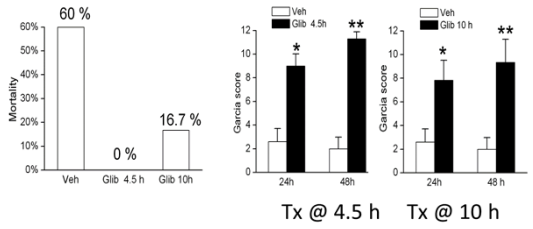
Rodent model of GAMES protocol

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



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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

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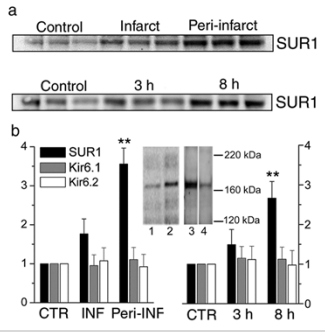
Delayed SUR1 Expression



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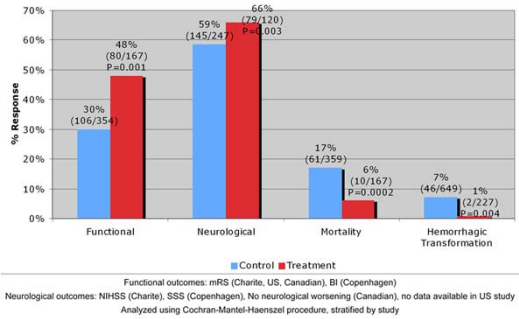
Meta-analysis of 4 Retrospective Human Studies with Sulfonylureas



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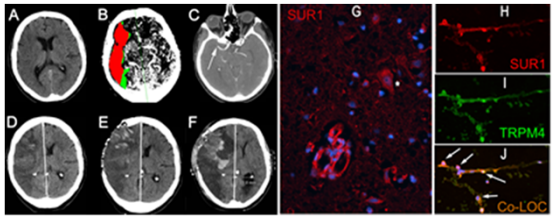
Historical Patient



Human tissue shows SUR1 and TRM4 in neurons and vessels

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What is unique about this strategy?

- Concept of neuro-vascular unit. Glyburide will act as an anti-ischemia and anti-edema agent.
- Molecular process takes hours to evolve and this is different than the short time course classically used
- Multiple pre-clinical models of ischemia, with and without tpa, all with physiological monitoring, histological and behavioral endpoints
- Independent laboratory confirmation of results
- Novel channel and strategy targeted with drug with which we have decades of experience!

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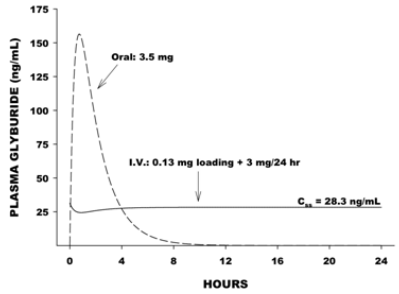
Oral vs IV Formulation



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Academic Industry Partnership

- Remedy Pharmaceuticals developed and IV formulation of glyburide RP-1127
- Phase I study completed at multiple doses in healthy volunteers
- Maximal tolerated dose (MTD) of 3 mg resulted in serum levels that were higher than most effective levels in preclinical models

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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

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	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.

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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

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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

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Patient Selection and Enrollment

EXCLUSION

- Commitment to DC prior to study entry
- Patients who underwent endovascular therapy
- Clinical evidence of herniation
- Prior sulfonylurea treatment

CLINICAL STANDARDIZATION

- Clinical guideline adherence including surgical decompression trigger, osmotic therapy, sodium and glycemia management

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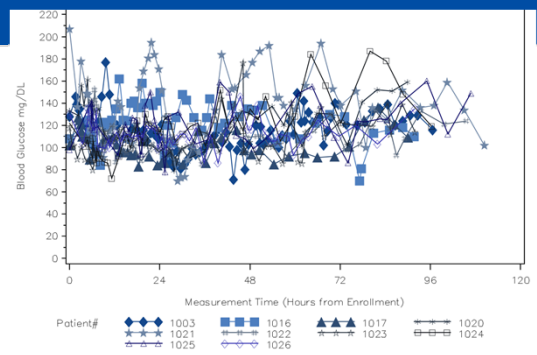

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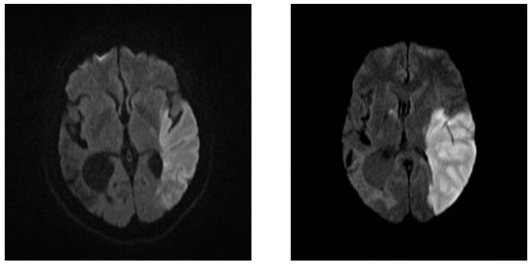
Patient 1

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



Baseline 72 hours

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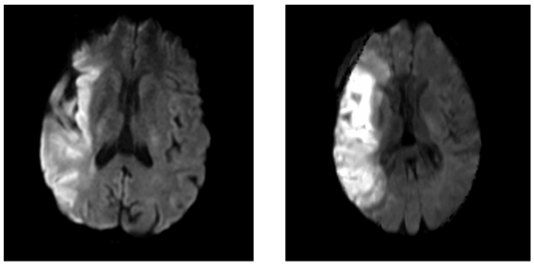
Patient 2

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



Baseline 72 hours

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Preliminary Impressions

- Imaging evidence that beats historical data
  - Decreased DWI volume growth
  - Diminished mass effect by midline shift, etc and possibly hemispheric volume
  - Preservation of sulci
- Clinical evidence that beats historical data
  - 10% mortality rate
  - Decreased critical care interventions
- 100% enrollment rate
- Change from deteriorating, vicious cycle to a stable, positive cycle

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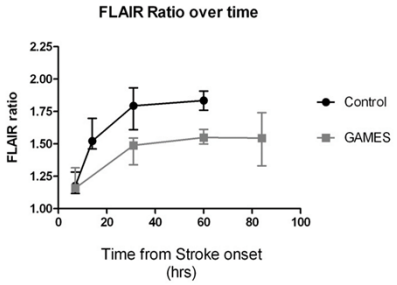
Day 2 FLAIR Ratio



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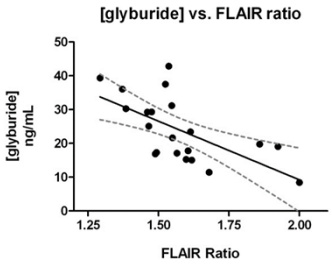
Day 2 FLAIR Ratio



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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

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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

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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

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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

Yale SCHOOL OF MEDICINE SLIDE 54

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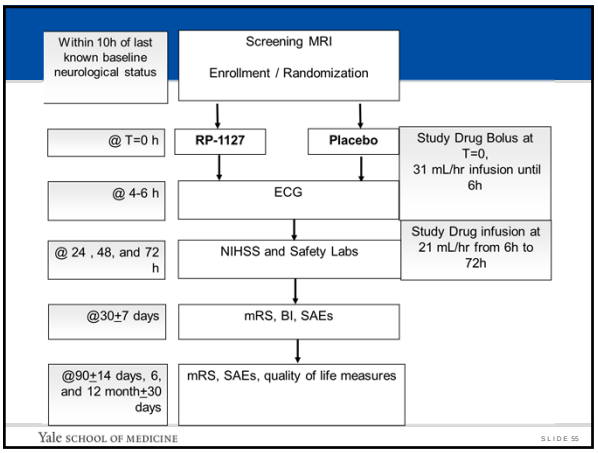

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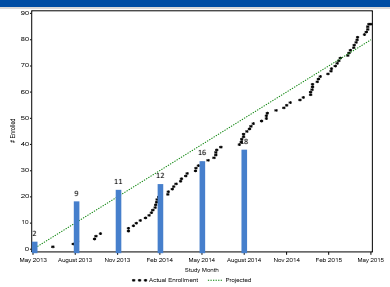
Enrollment



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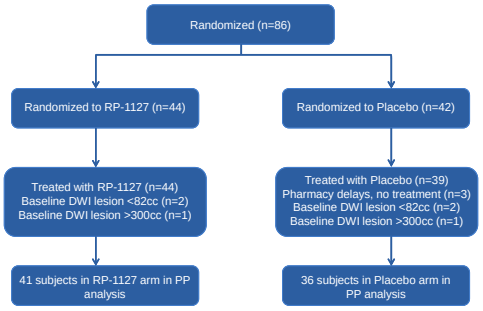
Randomization & Follow Up



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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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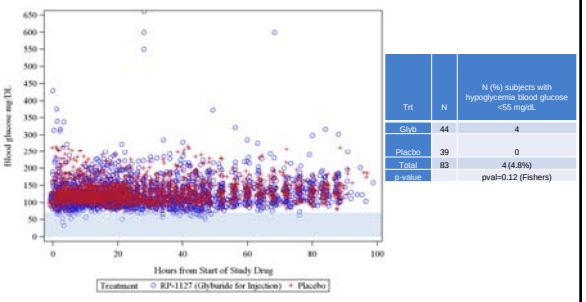
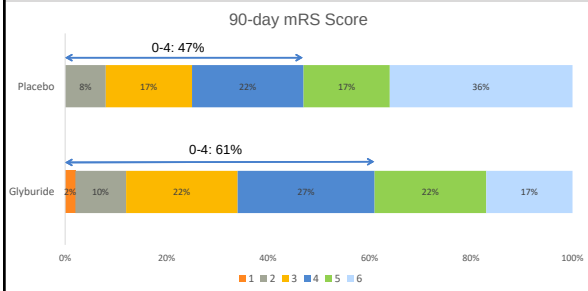
Blood Glucose & Hypoglycemia



Trt	N	N (%) subjects with hypoglycemia blood glucose <55 mg/dL
Glyb	44	4
Placbo	39	0
Total	83	4 (4.8%)
p-value		pval=0.12 (Fishers)

60

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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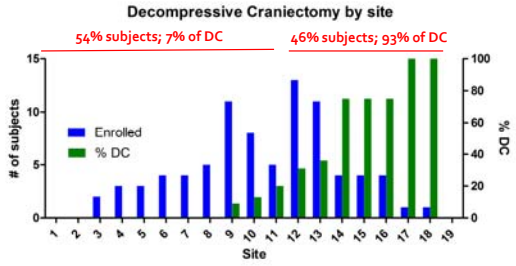
Secondary and Tertiary Endpoints



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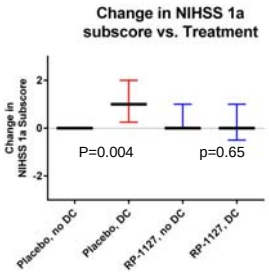
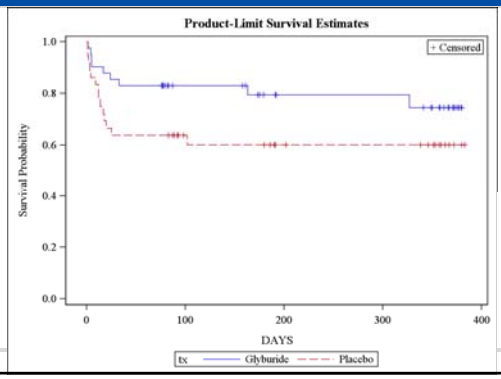
DC and Decreased Level of Arousal



63

Secondary and Tertiary Endpoints



P=0.06

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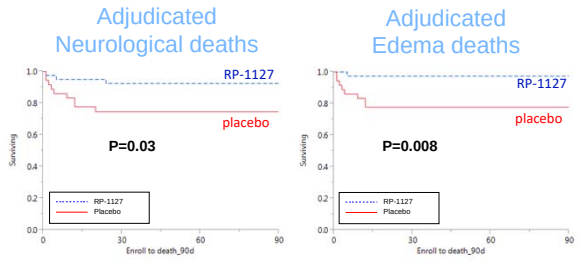
Other Clinical Endpoints



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

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

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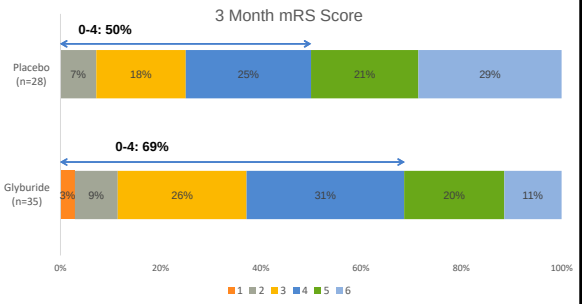
Exploratory Analysis Under Age 70



SHIFT Analysis (p-value=0.048)

66

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**

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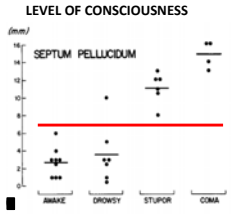
Midline Shift



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

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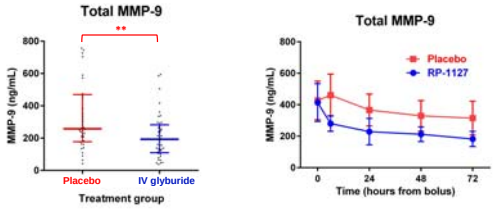
Total MMP-9



**, *P*=0.006

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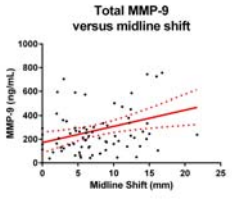
Total MMP-9 and Edema



P=0.024

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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

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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)

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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

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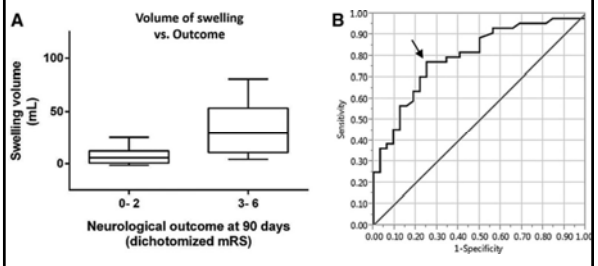
Greater swelling is associated with poor neurological outcome



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

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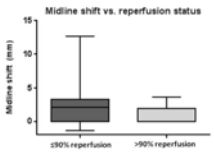
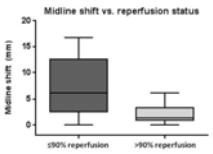
Thrombectomy and Edema

EPITHET: IV tPA trial



P < 0.001

MR RESCUE: 1st Gen EVT trial



P < 0.001

→ Reperfusion definition based on serial PWI

Irvine et al 2017

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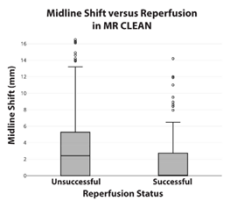
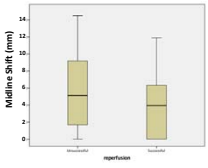
Thrombectomy and Edema

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, unpub

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New Directions

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Net Water Uptake

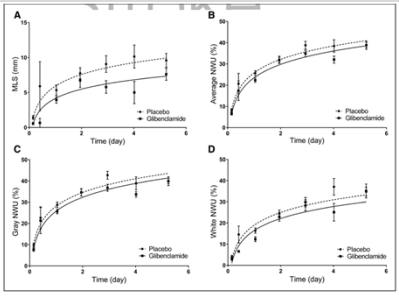

Figure 3. Intravenous (IV) glibenclamide reduces net water uptake (NWU) and midline shift (MLS) over time. **A**, Treatment with IV glibenclamide reduced the amount of MLS over time, reflected by the downward shift in the curve (P=0.016). **B**, IV glibenclamide also reduced average NWU (P=0.016), (**C**) gray matter NWU (P=0.003), and (**D**) white matter NWU, P=0.006.

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Low Field MRI for Acute & Serial Imaging

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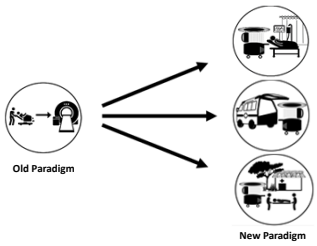

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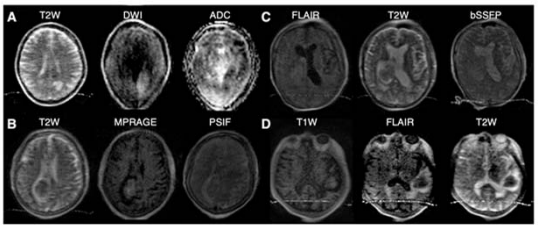

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In Our Own Words

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

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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."

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