Post Stroke Glucose Management Results from the SHINE trial

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Disclosure of Financial Relationships

Research Grants/Contracts:

- NIH-NINDS U01 NS069498 (SHINE)
- NIH-NINDS U01NS056975 (NETT CCC) – UM
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- NIH-NCATS UL1 TR003015 (CTSA)
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- Diffusion Pharm – 100-501 (PHAST TSC)
- NIH-NINDS R01 NS050192 (GRASP)

Honoraria:

- ANA
- AAN
- AUPN
- NINDS
- NHLBI

Consulting:

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FDA

University of Virginia Health System

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Financial Disclosures
SHINE Trial

- SHINE funded by the NIH-NINDS
- Medical Decision Network LLC (Charlottesville, VA) provided, the GlucoStabilizer®, a computer decision support tool, at no cost.
- Rattan Juneja has received royalties from GlucoStabilizer®
- No Unlabelled/Unapproved use

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Agenda

- Problem/Background
- Preclinical and middle phase data
- SHINE Trial
  - Design
  - Results
  - Implications

The Problem

- Almost 800,000 strokes/ year (~85% ischemic)
- ~30-50% hyperglycemic on admission

- Hyperglycemia associated w/ worse clinical outcome
- Hypoglycemia bad for ischemic brain

- Unknown if Rx of hyperglycemia improves outcome
- If improves outcome, unknown if benefit outweighs risk

The Urgency of the Problem

- Stroke providers deal w/ hyperglycemic acute stroke patients every day
- Variability across the country on glucose control approach
- Risk/benefit unclear due to lack of evidence
- SHINE trial designed to address this gap

Preclinical Data

- Hyperglycemic ischemic stroke rodent model
  - Hamilton, et al – 2 hour transient focal ischemia
- Is the benefit due to the insulin or the glucose concentration?

- 3 groups - Pretreatment with
  - Control (hyperglycemic)
  - Insulin (normal glucose)
  - Insulin/glucose (hyperglycemic)
- Insulin group did well, no benefit seen with glucose co-admin

Hamilton MG et al, *J Neurosurg* 1995

Middle Phase Data

- GIST – UK terminated early due to lack of funds
  - 933 enrolled (40%)
  - No difference in mortality - 1º outcome
  - Identified population

- NIH-NINDS funded middle phase trials

  THIS and GRASP:

  - Feasibility
  - Safety
  - Identified population
  - Utilization of decision support tool (GRASP)

Gray, *Lancet Neurology* 2007; Bruno, *Stroke* 2008;
Johnston, *Stroke* 2009

Phase III SHINE Trial

- Multicenter, controlled, 12 hour window
- PROBE design (clinical team unblinded during Rx)
- Phase III (definitive efficacy trial)
- Hyperglycemic acute ischemic stroke patients
- Comparison target 80-179 mg/dL to target 80-130 mg/dL

- Funded by NIH-NINDS
- Conducted in conjunction w/NIH-NINDS NETT
- Conducted in collaboration w/NIH-NINDS StrokeNet

SHINE Trial

NIH-NINDS U01 NS069498

Specific Aim 1

- To determine the **efficacy** of
  - Glucose control – target 80-130 mg/dL (IV insulin) vs
  - Glucose control – target 80-179 mg/dL (sliding scale)

Specific Aim 2

- To determine the **safety** of
  - Glucose control - target 80-130 mg/dL vs
  - Glucose control - target 80-179 mg/dL

SHINE Trial Design/Protocol

- Prospective, multicenter, randomized, blinded
  - 70 US sites, maximum of 1400 patients
- Randomization balance for NIHSS & tPA
- Treatment (up to 72 hours)
  - Intensive: Insulin drip – target 80-130 mg/dL
  - Standard: SQ insulin q6 hr – target <180 mg/dL
- Primary outcome – 90 day mRS
  - Based on enrollment stroke severity

SHINE Trial Outcomes

Primary Efficacy

- Severity adjusted favorable outcome (90 day mRS)

Baseline NIHSS	90-day mRS
3-7	0
8-14	0-1
15-22	0-2

Primary Safety

- Severe hypoglycemia <40mg/dL (2.22 mmol/L) (treatment period)

SHINE Trial Statistical Considerations

- 80% power to show 7% absolute benefit
- Pre-specified sample size recalculation
- Response adaptive randomization (RAR)
  - ↑ chance to whichever group doing better
- 4 planned interim analyses (500, 700, 900, 1100)
  - Early efficacy or futility

SHINE Eligibility Criteria

- Adult (>=18) with clinical diagnosis of ischemic stroke
- Randomization w/in 12 hrs of stroke symptom onset
- Known history of Type 2 DM and glucose >110 mg/dL **OR** admission blood glucose ≥150 mg/dL if no DM
- Baseline NIHSS 3-22 (3-7 mild, 8-14 mod, 15-22 severe)
- mRS of 0 if NIHSS 3-7; mRS of 0-1 if NIHSS of 8-22
  - 0 = no symptoms of stroke
  - 1 = symptoms from stroke, no disability (carry out usual activities)

SHINE Eligibility Criteria: Exclusion

- Known Type 1 diabetes mellitus
- Substantial preexisting confounding illness
- Receiving experimental therapy/ in trial
- Pregnancy
- Other serious conditions
  - Unlikely to live to f/u
  - Renal dialysis
  - Inability to follow protocol or return for 90 day f/u

Decision Support Tool - GlucoStabilizer®

- Designed at Indiana University/Clarian Health
- Licensed by Medical Decision Network LLC
- FDA cleared/ commercially available
- Considers individual patient response to insulin

- Severe hypoglycemia rate (<40 mg/dL) <2%
- Adherence to the recommendations – 99%
  - 91-98% in literature for decision support tools
  - 97% in GRASP

Tidswell, *Crit Care Med* 2008
Johnston, *Stroke* 2009

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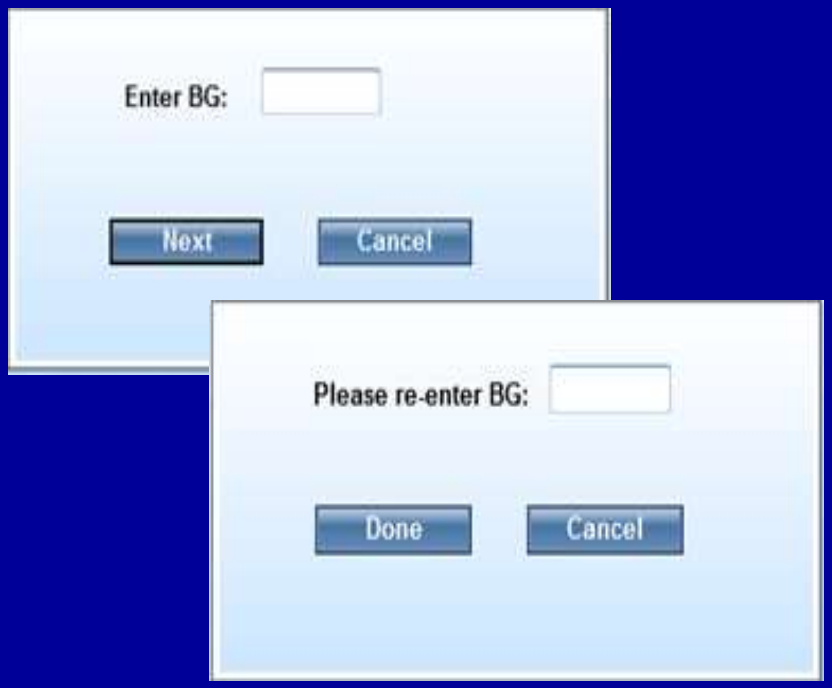
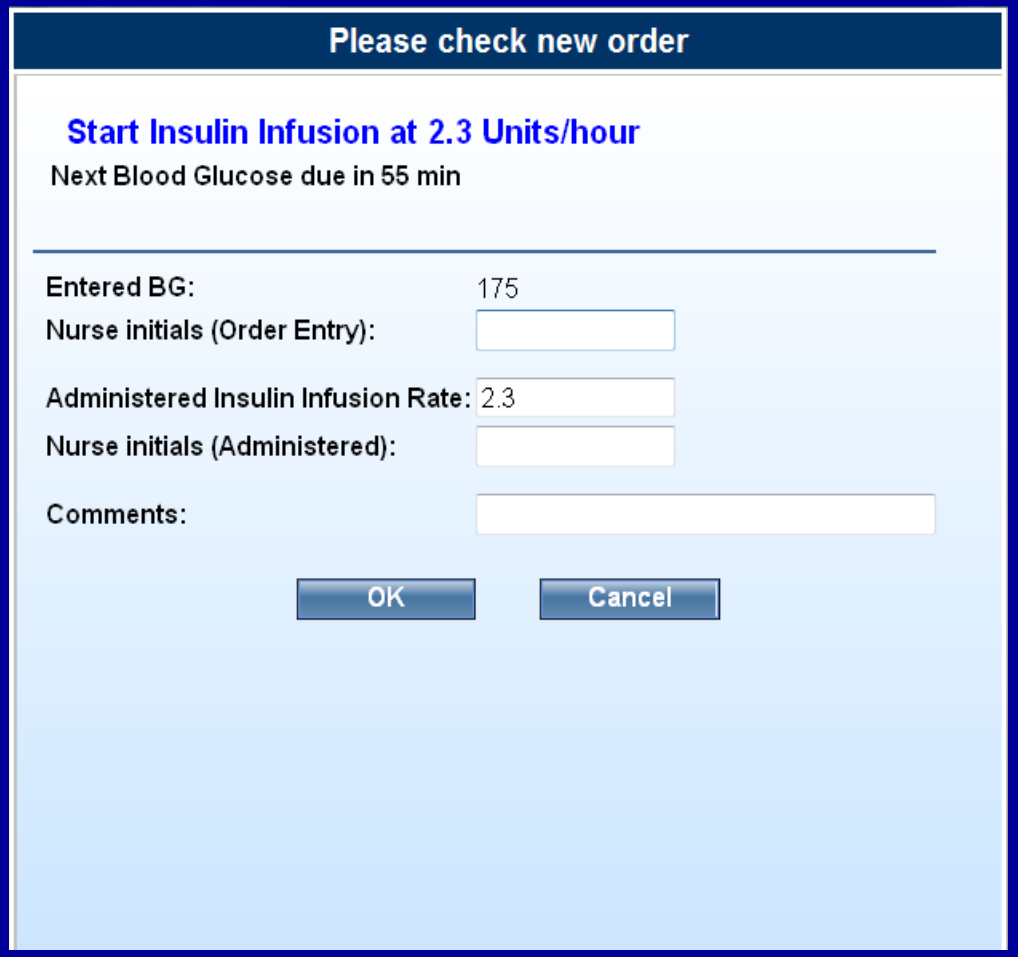
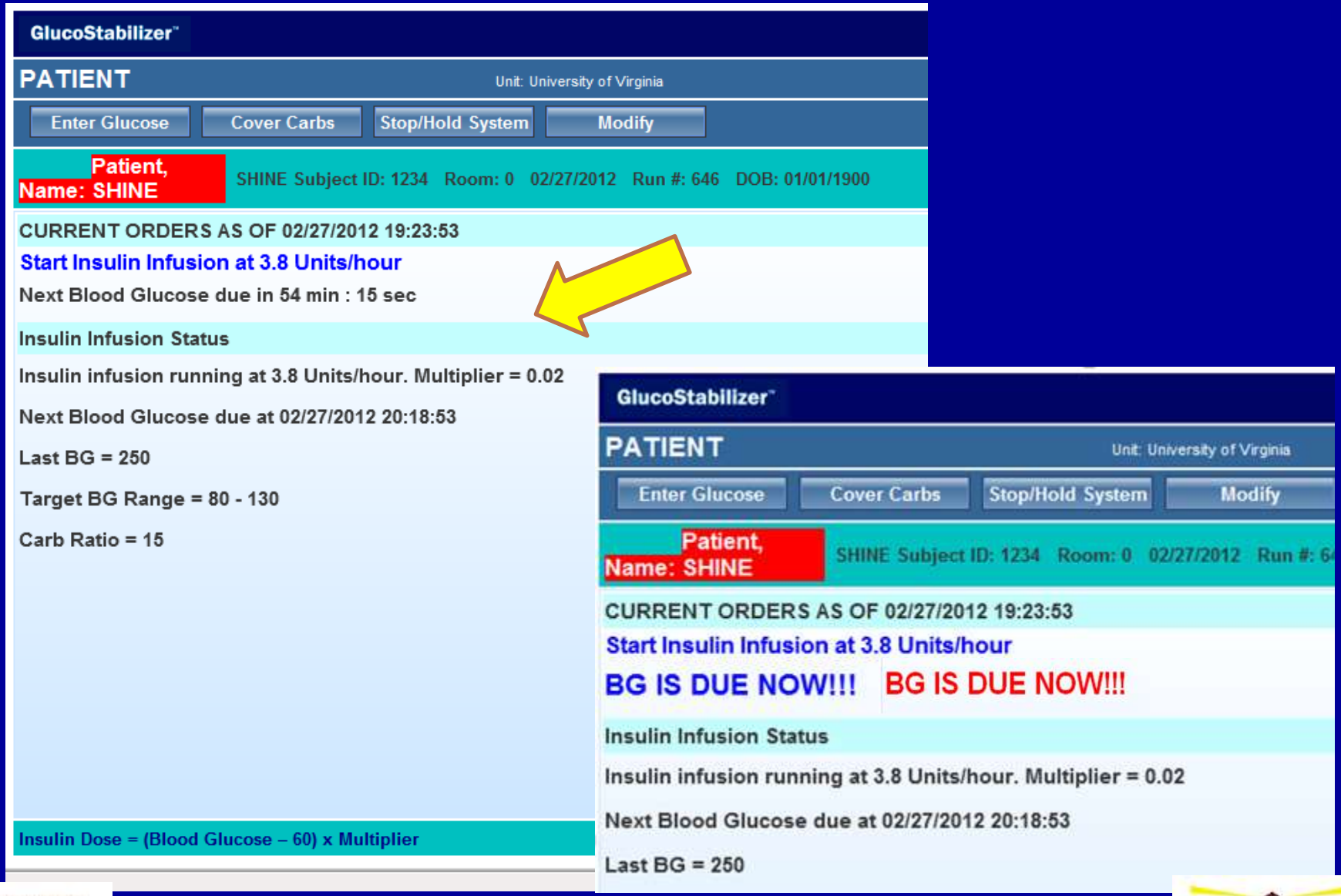
Intervention Group GlucoStabilizer®





Intervention Group Study Computer



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Control Group Sliding Scale

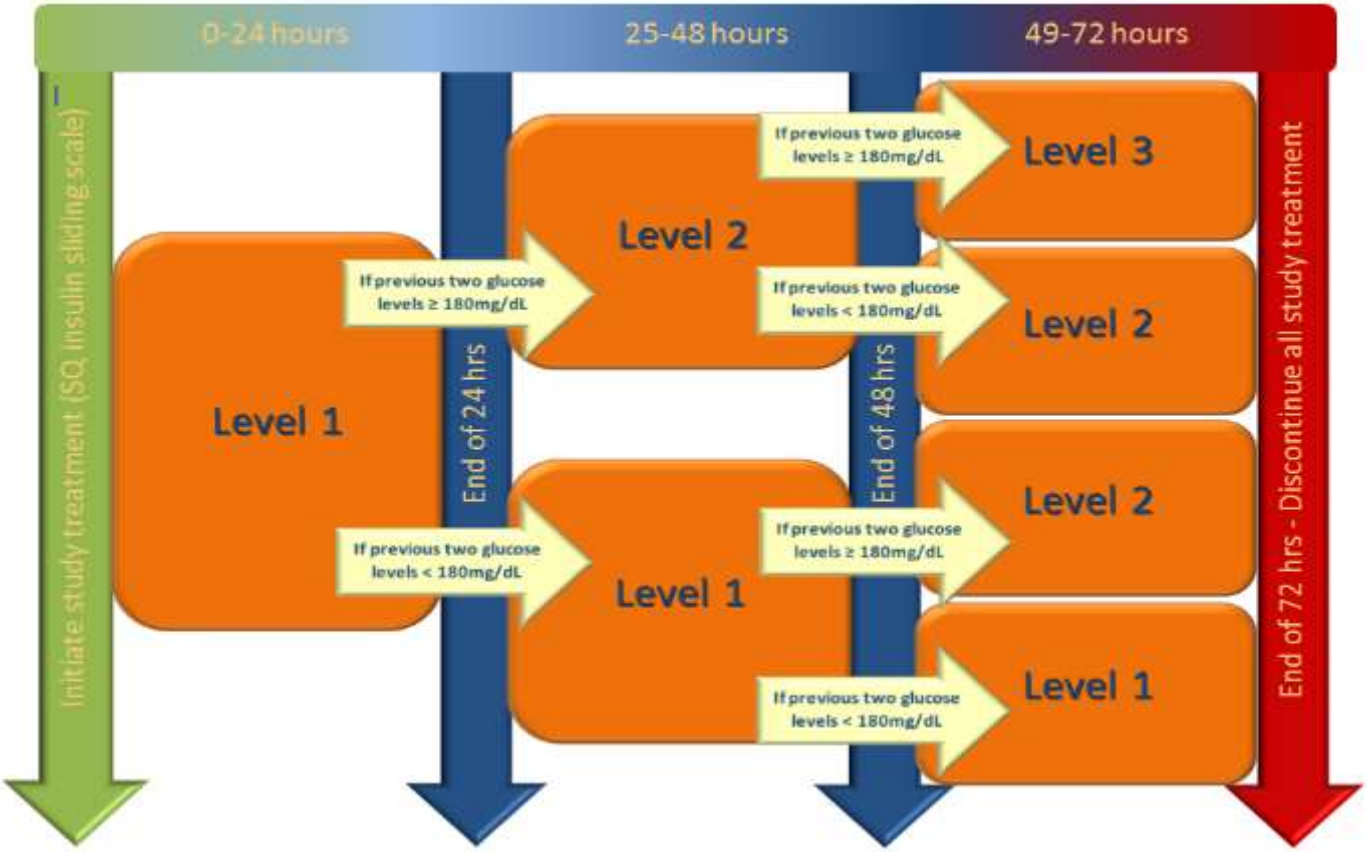
IV Saline	SQ ...n Regular Insulin (Humulin R or Novolin R) Sliding Scale			
Start at rate indicated below and adjust if indicated each time glucose is checked.	Start at Lev... at the end of the first 24 hours, ...evious two glucose levels remain ≥ 180mg/dL, advance to Level 2. If after 24 hours on Level 2, the previous two glucos... ...ls remain ≥ 180mg/dL, proceed ...vel 3. In Level 3, give a one-time subcutaneous basal insulin injection (Glargine) at a dose equal to 40% of p... ...s day's entire insulin dose and continue Level 2 insulin dose.			
mL/hr	Glucose (mg/dL)	Level 1 Insulin dose (units)	Level 2 Insulin dose (units)	Level 3 One time sq basal insulin (Glargine) and continue Level 2 Insulin dose (units)
5	>450	8	16	16
5	400-450	7	14	14
5	351-399	6	12	12
5	300-350	5	10	10
5	251-299	4	8	8
5	200-250	3	6	6
5	180-199	2	4	4
4	80-179	0	0	0
0	<80		See hypoglycemia protocol (Click Here)	

SHINE Subject ID: 1234 | New Event | Remove | Hide Protocol | Logged In: shine | Unit: University of Virginia | Tools | Lock Program | Log Out

Date/Time	Glucose (mg/dL)	Saline Drip (mL/hour)	SubQ Insulin If Applicable (Units)	Basal Insulin (Glargine) (Units)	D50 (mL)	Notes

- 3 levels of dosing
- Patients advance as necessary
- All patients start at Level 1

Control Group Level Changes



- At 24 and 48 hours, previous 2 glucose checks reviewed
  - If both ≥ 180 mg/dL, advance level
- Level 3 includes 1x dose of basal insulin; 40% previous 24 hr insulin

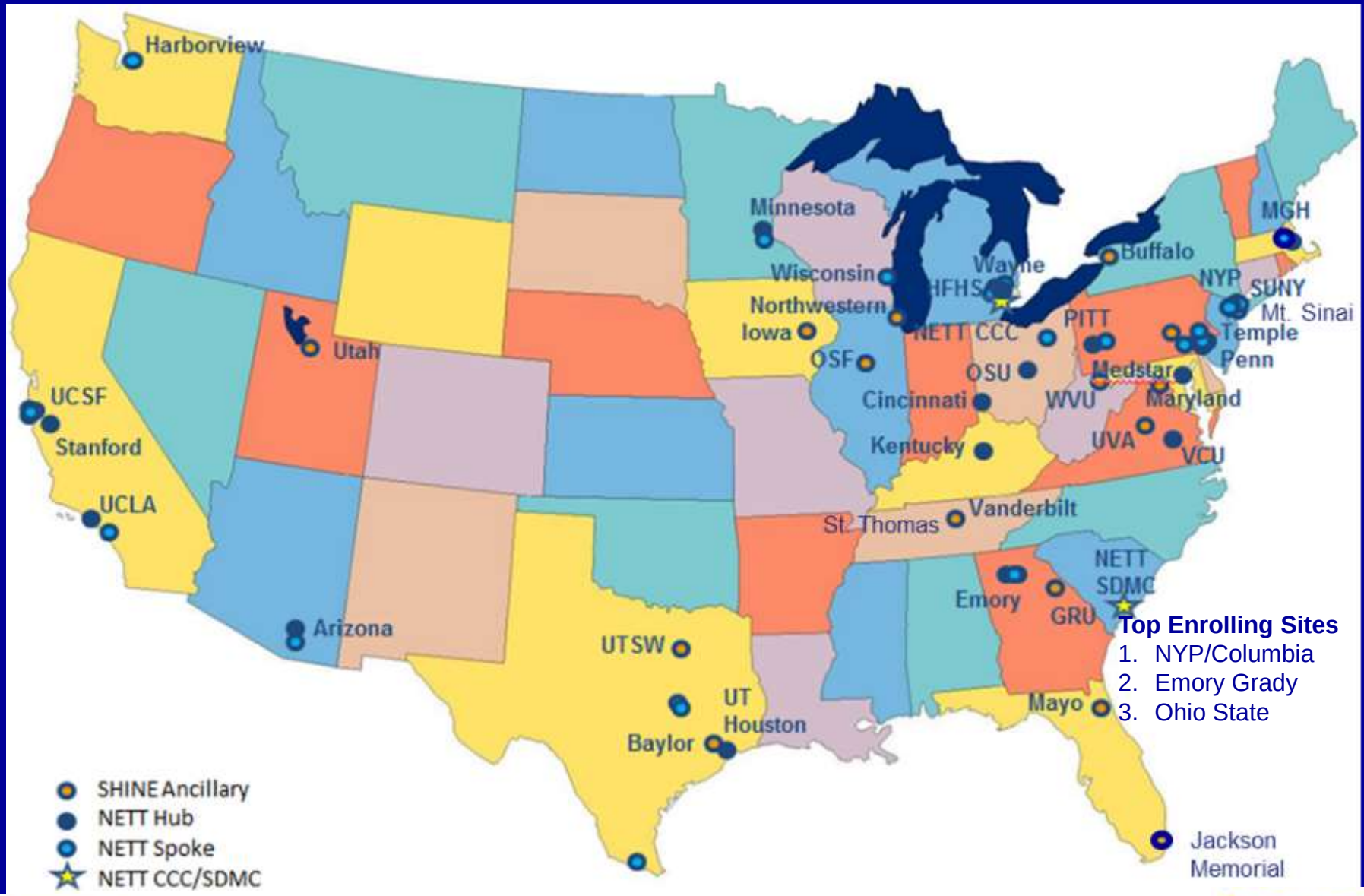
SHINE Trial Groups
General Concepts

- Two groups: both glucose control, both insulin
- All patients: IV drip & SQ injections
- Frequent glucose checks
- 60 gram carbohydrate diet
- All patients in unit that supports IV insulin
- 72 hr treatment period
- Daily neuro & AE assessments
- All sites provided with study laptops/Rx tools

SHINE Trial Timeline

- Trial start up 2011-2012
- First enrollment 2012
- 70 total sites activated
- 63 sites enrolled at least 1 patient
- Enrollment completed August, 2018
- Follow up completed November, 2018
- Results presented ISC 2019
- Results published JAMA 2019

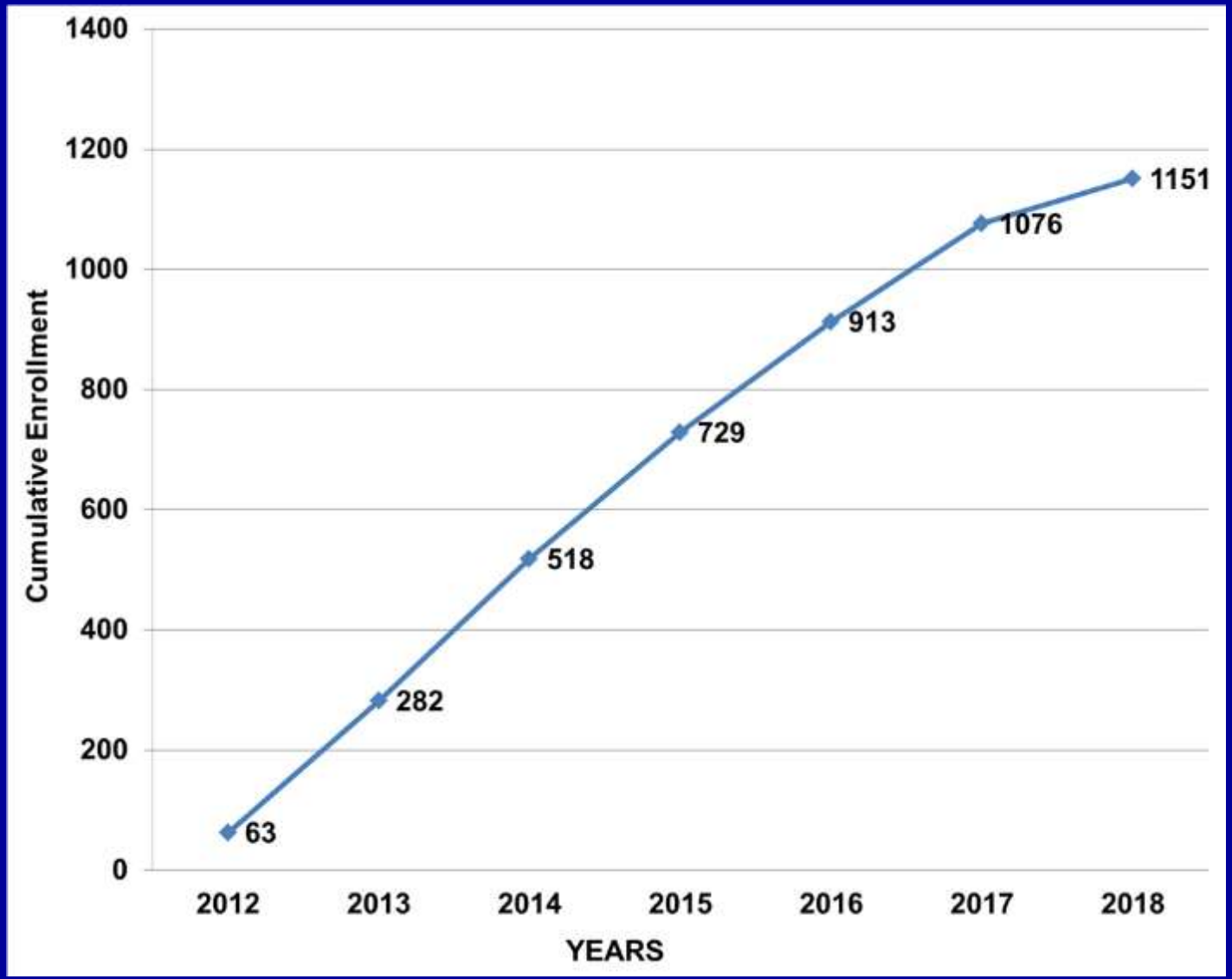
SHINE Sites



Top Enrolling Sites

1. NYP/Columbia
2. Emory Grady
3. Ohio State

SHINE Trial Recruitment



Research

JAMA | Original Investigation

Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients With Acute Ischemic Stroke
The SHINE Randomized Clinical Trial

Karen C. Johnston, MD; Askiel Bruno, MD; Qi Pauls, MS; Christiana E. Hall, MD; Kevin M. Barrett, MD; William Barsan, MD; Amy Fansler, MPH; Katrina Van de Bruinhorst, MA; Scott Janis, PhD; Valerie L. Durkalski-Mauldin, PhD; for the Neurological Emergencies Treatment Trials Network and the SHINE Trial Investigators

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Johnston, et al. JAMA, 2019

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SHINE Trial Primary Results

- Stopped for futility at 4th interim analysis
  - No difference
  - Probability of difference too low to continue

- 82% (1151/1400) of planned maximum number enrolled

- No safety boundary was crossed

SHINE Patient Population

Baseline Characteristics

SHINE

Characteristic	Intensive (N=581)	Standard (N=570)
Age (yr) - median (IQR)	66 (57-75)	66 (57-76)
Female sex – no. (%)	260 (44.8)	264 (46.3)
Race - no. (%)		
Black	180 (31.0)	154 (27.0)
White	366 (63.0)	369 (64.7)
Ethnicity - no. (%)		
Hispanic	87 (15.0)	91 (16.0)
Non Hispanic	460 (79.2)	449 (78.8)
Medical History - no. (%)		
Previous Ischemic stroke	104 (17.9)	99 (17.4)
Diabetes mellitus (Type II)	468 (80.6)	455 (79.8)
Hypertension	513 (88.3)	502 (88.1)
Median eligibility glucose (mg/dL)- (IQR)	188 (153-250)	187 (155-248)

SHINE Patient Population

Baseline Characteristics

Characteristic	Intensive (N=581)	Standard (N=570)
Final diagnosis - no. (%)		
Ischemic stroke	542 (93.3)	524 (91.9)
Transient ischemic attack	8 (1.4)	12 (2.1)
Baseline NIHSS - median (IQR)	7 (5-12)	7 (5-13)
Baseline NIHSS category - no. (%)		
Mild (NIHSS 3-7)	291 (50.1)	291 (51.1)
Moderate (NIHSS 8-14)	177 (30.5)	158 (27.7)
Severe (NIHSS 15-22)	113 (19.5)	121 (21.2)
Thrombolysis/thrombectomy - no. (%)		
Intravenous tPA	372 (64.0)	353 (61.9)
Intraarterial drug therapy	14 (2.4)	21 (3.7)
Mechanical thrombectomy	74 (12.7)	72 (12.6)
Median time to randomization (Hour) - (IQR)	7.1 (4.8,9.4)	7.1 (4.9,9.7)

Treatment Location

Day 1

Type of Unit	Intensive	Control	Total
ICU	66%	65%	66%
Step down	31%	30%	30%
Other	3%	4%	4%

Day 2

Type of Unit	Intensive	Control	Total
ICU	47%	50%	48%
Step down	40%	37%	39%
Other	3%	5%	4%

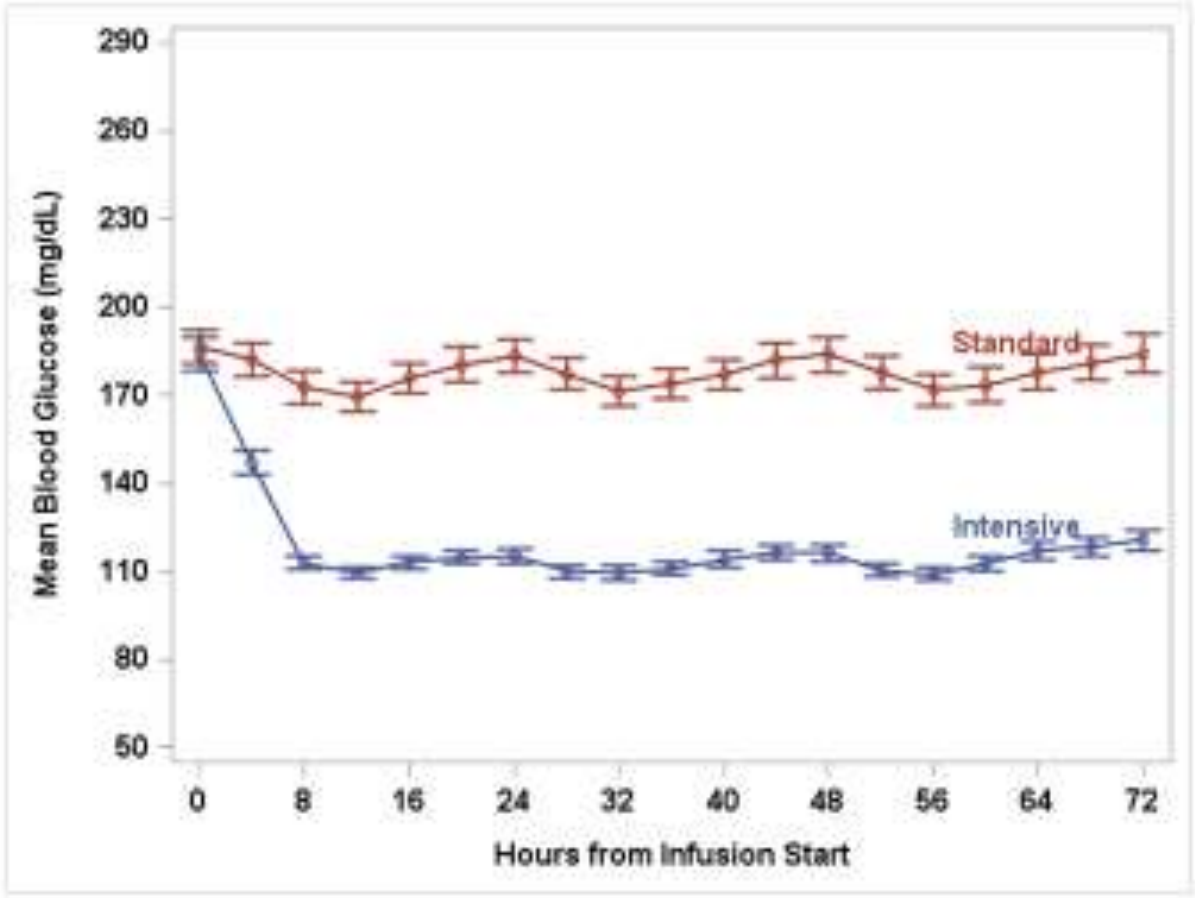
Day 3

Type of Unit	Intensive	Control	Total
ICU	32%	34%	33%
Step down	35%	38%	36%
Other	3%	6%	4%

Data reflect those still alive, in hospital, on protocol with dx of stroke

Glucose Concentration Curves

Blood Glucose Separation



Overall Mean

179 mg/dL

118 mg/dL

Intensive target: 80-130 mg/dL
Standard target: 80-179 mg/dL

SHINE Trial

Primary Results

	Intention-To-Treat N=1151	
	Intensive N=581	Standard N=570
Primary Efficacy Outcome- N (%)	119 (20.5)	123 (21.6)
Adjusted* Relative Risk 95% CI	0.97 (0.87, 1.08)	
P value for adjusted analysis	0.55	
Severe Hypoglycemia- N (%)	15 (2.6)	0
Risk Difference (%) (95% CI)	2.58 (1.29, 3.87)	

*adjusted for baseline stroke severity and thrombolysis use

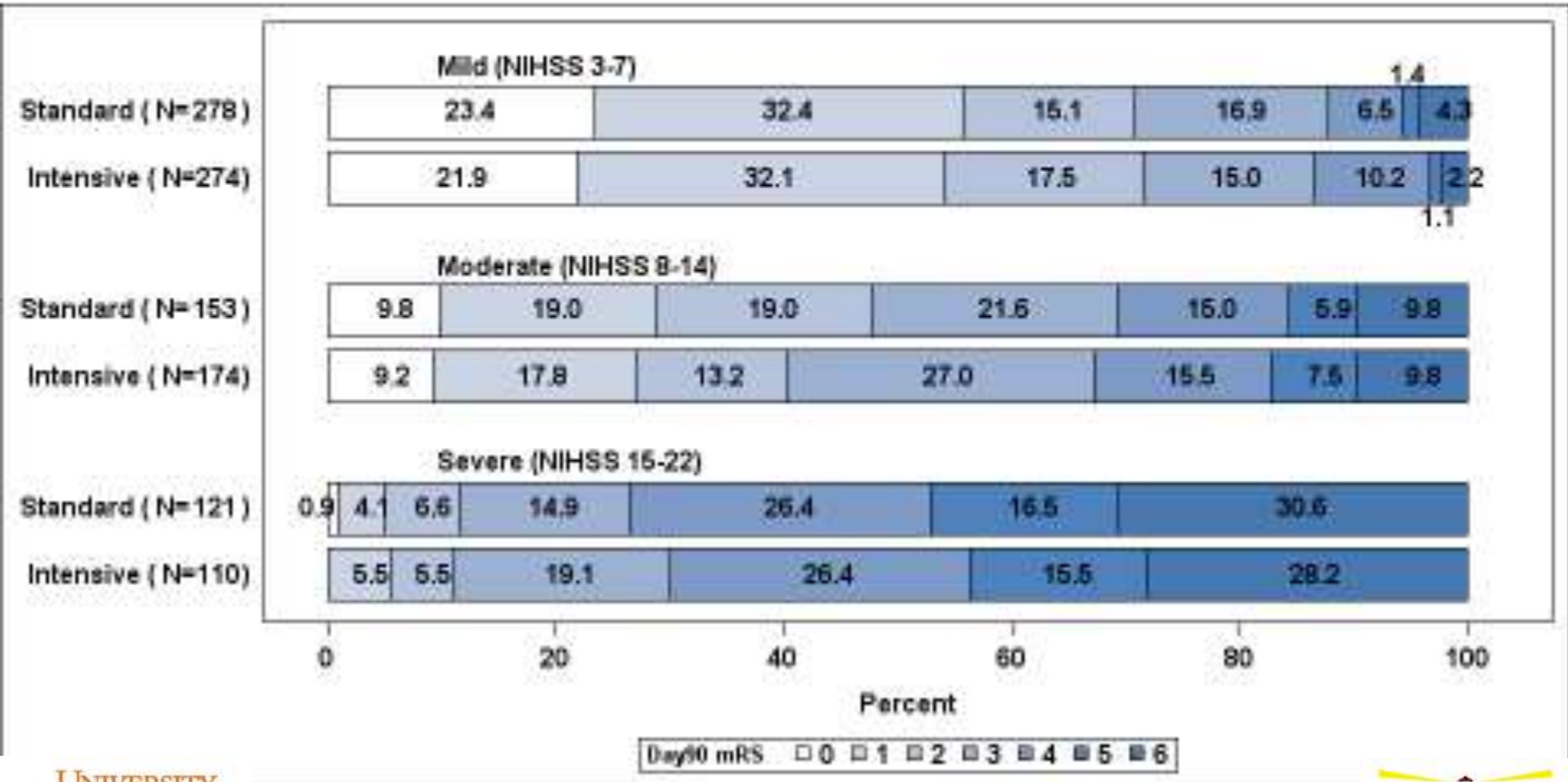
SHINE Trial

Additional Efficacy Outcomes

		Intensive	Standard
Favorable NIHSS (0 or 1)		43.7%	44.7%
Relative Risk (95% CI)		0.98 (0.83, 1.15)	
Favorable Barthel Index (95-100)		55.2%	54.7%
Relative Risk (95% CI)		1.01 (0.90, 1.13)	
SSQOL	Median (IQ)	3.8 (3.0, 4.4)	3.7 (3.0, 4.5)

Full Range mRS (90 days)

Stratified by stroke severity



SHINE Trial Conclusions

- Successfully (efficiently) completed SHINE Trial
- Answered the question of:

  "What is the best glucose control for hyperglycemic acute ischemic stroke patients?"

- Intensive glucose control (80 mg/dL – 130 mg/dL) does NOT improve 90 day functional outcome in hyperglycemic diabetic acute ischemic stroke patients
- Intensive control increases risk of severe hypoglycemia

SHINE Trial Implications

- Sliding scale protocols to keep glucose <180 in the post stroke period are preferred. Advance sliding scale as needed

- Almost 90% of SHINE patients were diabetic
- We know that the non diabetic patients come down on own
- Starting acute stroke patients on sliding scale quickly to keep them <180 mg/dL is appropriate

- Does not include needing insulin drip for other reasons
  - DKA, previous insulin drip, etc

Thank You

- Participating patients
- All Site teams
- National SHINE Leadership
  - Askiel Bruno, Kevin Barrett, Chris Hall/Katrina Van De Bruinhorst, Bill Barsan, Valerie Durkalski, Angela Pauls
  - Heather Haughey/Amy Fansler – Project Directors
  - Neurological Emergencies Treatment Trials (NETT) Clinical Coordinating Center (Univ of Michigan) and Data Mngmt Ctr (MUSC)
- SHINE DSMB
  - Michael Hill (Calgary)– Stroke - Chair
  - Bill Clarke (Iowa), Rema Ramam (UCSD) - Biostatisticians
  - Susan Braithewaite (UI Chicago)- Endo
  - Kama Guluma (UCSD)-Emerg Med
  - Jen Frontera (Clev Clin)-Neuro ICU
- Independent Safety Monitor
  - Tom Bleck (Rush)

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Thank You to NIH Funding Agency

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  - Walter Koroshetz – Director NIH-NINDS
  - Story Landis – Director NIH-NINDS (2011-14)

National Institute of Neurological Disorders and Stroke

Thank you
SHINE Investigators

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University of Virginia
SHINE Trial Administrative Core

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