The SHINE Trial

Intensive versus Standard Treatment of Hyperglycemia in Acute Ischemic Stroke

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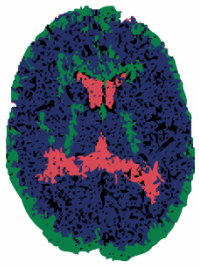


Neurological Emergencies Treatment Trials

NIH National Institute of Neurological Disorders and Stroke

SHINE

Stroke Hyperglycemia Insulin Network Effort

Financial Disclosures

- The study was funded by the National Institute of Neurological Disorders and Stroke (NINDS) of NIH.
- 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

National Institute of Neurological Disorders and Stroke

Background

- Hyperglycemia in acute ischemic stroke common
- Preclinical/clinical data show hyperglycemia during acute cerebral ischemia is associated with worse outcome
- Severe hypoglycemia increases injury to ischemic brain
- Unclear if glucose lowering improves outcome

Background

- GIST-UK Trial
  - 933 patients (40% of planned), AIS/ICH, 24hr window
  - Randomized to insulin or saline infusion
  - Target 72-126 mg/dL (4-7 mmol/L)
  - No difference in mortality

- 2 NIH-NINDS funded middle phase trials
  - THIS/GRASP – safety and feasibility
  - Phase III trial warranted
- Underpowered for efficacy
- Best glucose control approach remains unknown

Hypotheses

Efficacy

- Intensive glucose control to target range of 80-130 mg/dL with IV insulin infusion in hyperglycemic acute ischemic stroke patients within 12 hours of symptom onset will improve favorable outcome by absolute 7% as measured by mRS at 90 days after stroke.

Safety

- Intensive glucose control will be safe as measured by <4% increase in severe hypoglycemia (<40 mg/dL) compared to standard control in acute ischemic stroke patients treated up to 72 hours

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)

Design

- Prospective, multicenter, randomized, blinded
  - 70 US sites, maximum of 1400 patients
- Randomization balance for NIHSS & tPA
- Single blind treatment
- Double blind outcome assessment
- Treatment (up to 72 hours)
  - Intensive: Insulin drip – target 80-130 mg/dL
  - Standard: SQ insulin q6 hr – target <180 mg/dL
- 4 planned interim analyses (500, 700, 900, 1100)

Main Eligibility Criteria

SHINE

- Age 18 years or older
- Clinical diagnosis of ischemic stroke
- Randomization w/in 12 hours of LKW (last known well)
- Type 2 diabetes and glucose >110 mg/dL

  OR

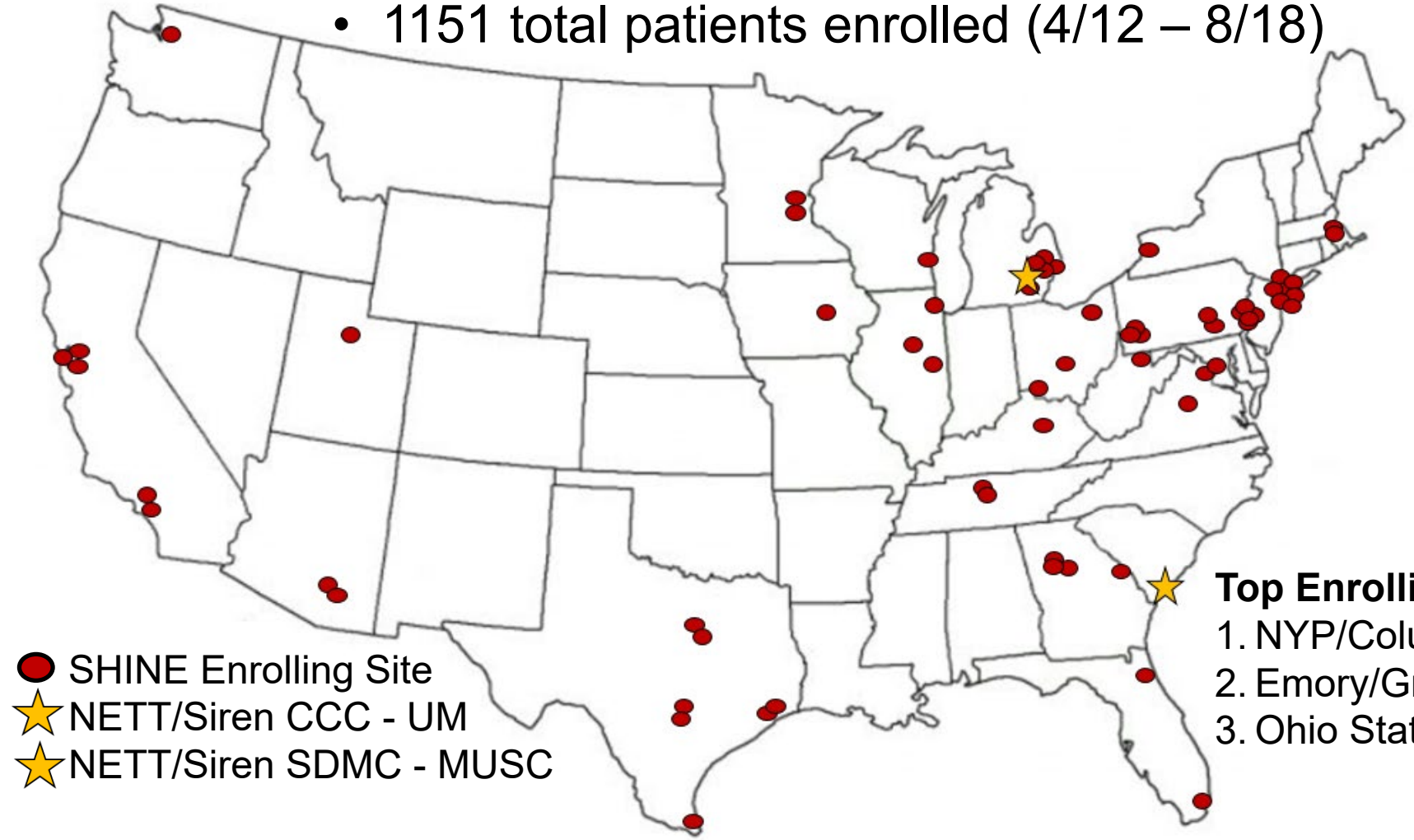
  No known diabetes and glucose ≥150 mg/dL
- Baseline NIHSS score 3-22

Main Exclusion Criteria

- Type I Diabetes
- Pre-existing confounding conditions
- Renal dialysis
- Inability to follow the protocol including:
  - Required insulin infusion
  - Unable to follow up

SHINE Trial Sites

- 70 participating sites
- 63 sites enrolled
- 1151 total patients enrolled (4/12 – 8/18)



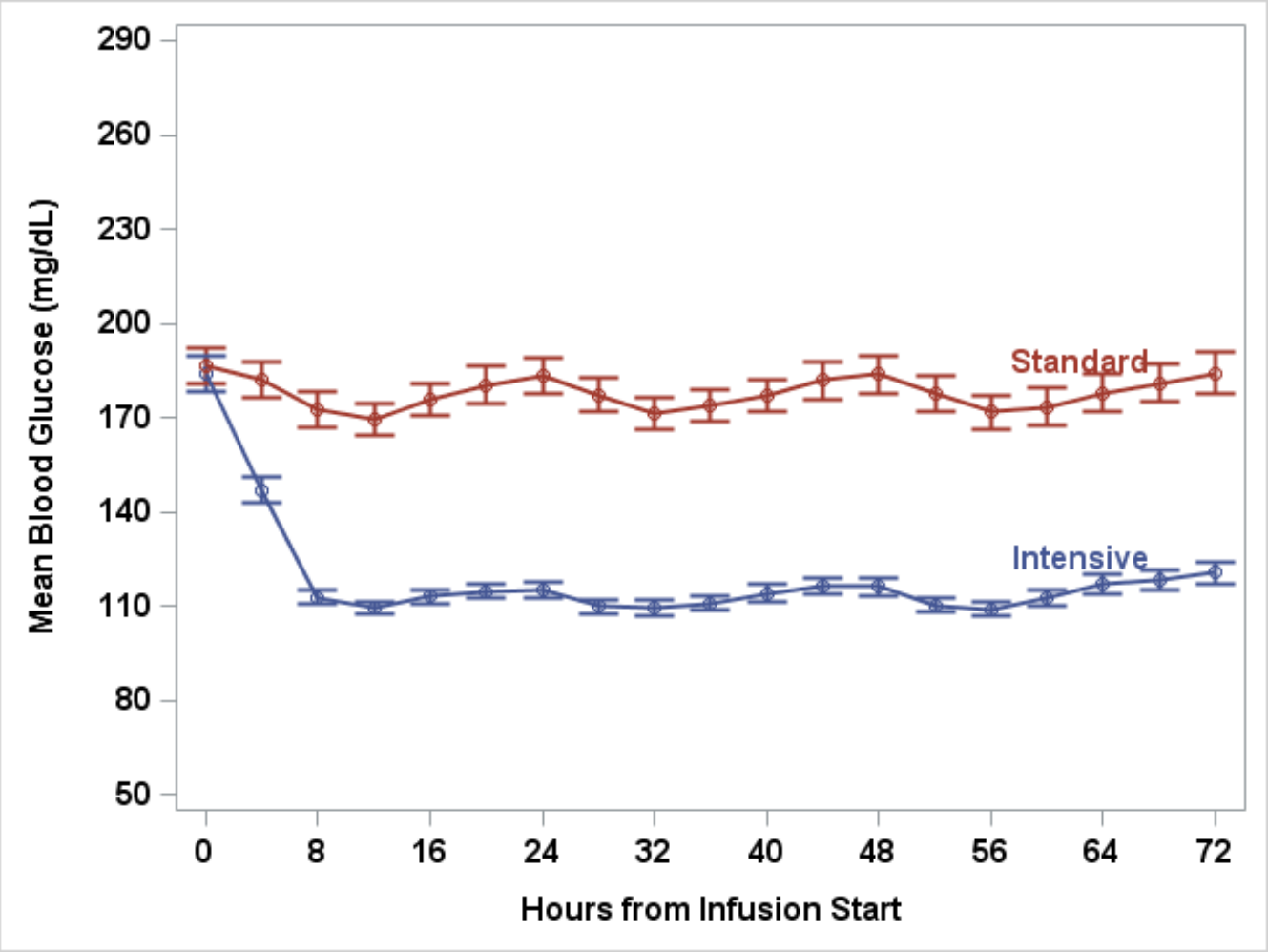
Baseline Characteristics

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)

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)

Blood Glucose Separation



Overall Mean

179 mg/dL

118 mg/dL

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

Primary Results

- Stopped for futility at 4th interim analysis
- 82% (1151/1400) of the planned maximum number of patients were enrolled
- No safety boundary was crossed

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)	

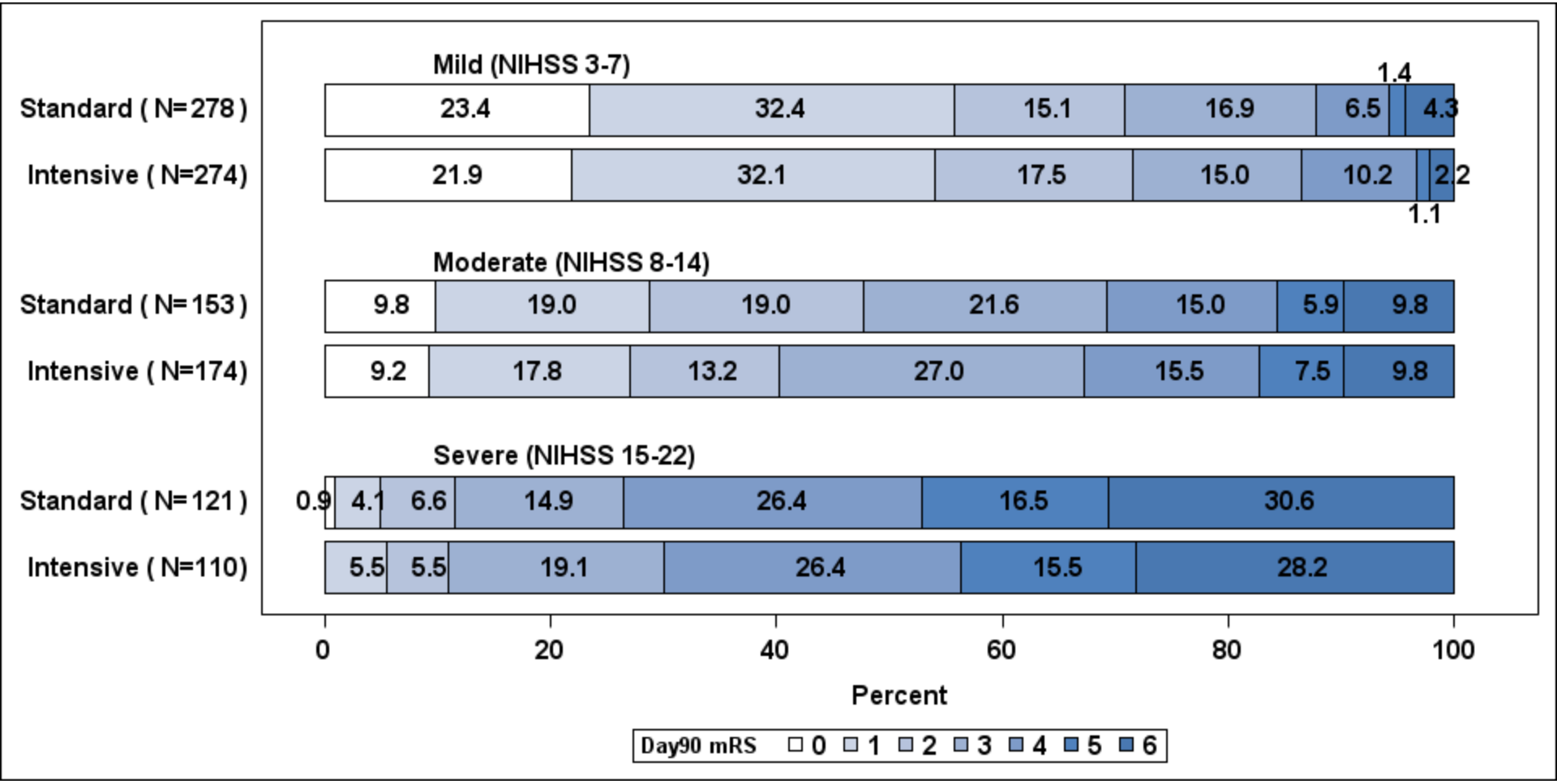
*adjusted for baseline stroke severity and thrombolysis use

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



Conclusions

- Successful & efficient completion of SHINE Trial
- Answered question of best glucose control for hyperglycemic AIS
- Intensive glucose control (80- 130 mg/dL) does not improve 90 day functional outcome and increases risk of severe hypoglycemia
- SQ insulin with target <180 mg/dL is preferred

On behalf of the SHINE Leadership Team

Thank You

Patients

Participating Site Teams

GlucoStabilizer®Team

SHINE DSMB

NIH-NINDS

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NCT01369069

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