Introducing the SHINE Trial
An Overview

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Administrative PI

Disclosure of Financial Relationships

- **Research Grants/Contracts:**
- **NIH-NINDS U01 NS069498**

- **Financial Conflict**
- **Dr. Rattan Juneja – Endocrinologist**
  - **Royalties from sale of GlucoStabilizer**

The Problem

- Over 750,000 strokes/ year (~80% ischemic)
- ~30-50% hyperglycemic on admission

- Hyperglycemia associated with worse clin outcome
- Hypoglycemia bad for ischemic brain

- Unknown if Rx of hyperglycemia improves outcome
- Unknown if risks of aggressive Rx outweigh benefit

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The Problem

- Stroke community deals with hyperglycemic acute stroke patients every day without evidence on what is best

Agenda

- Brief Background of Middle Phase Trials
- Overview of SHINE Design

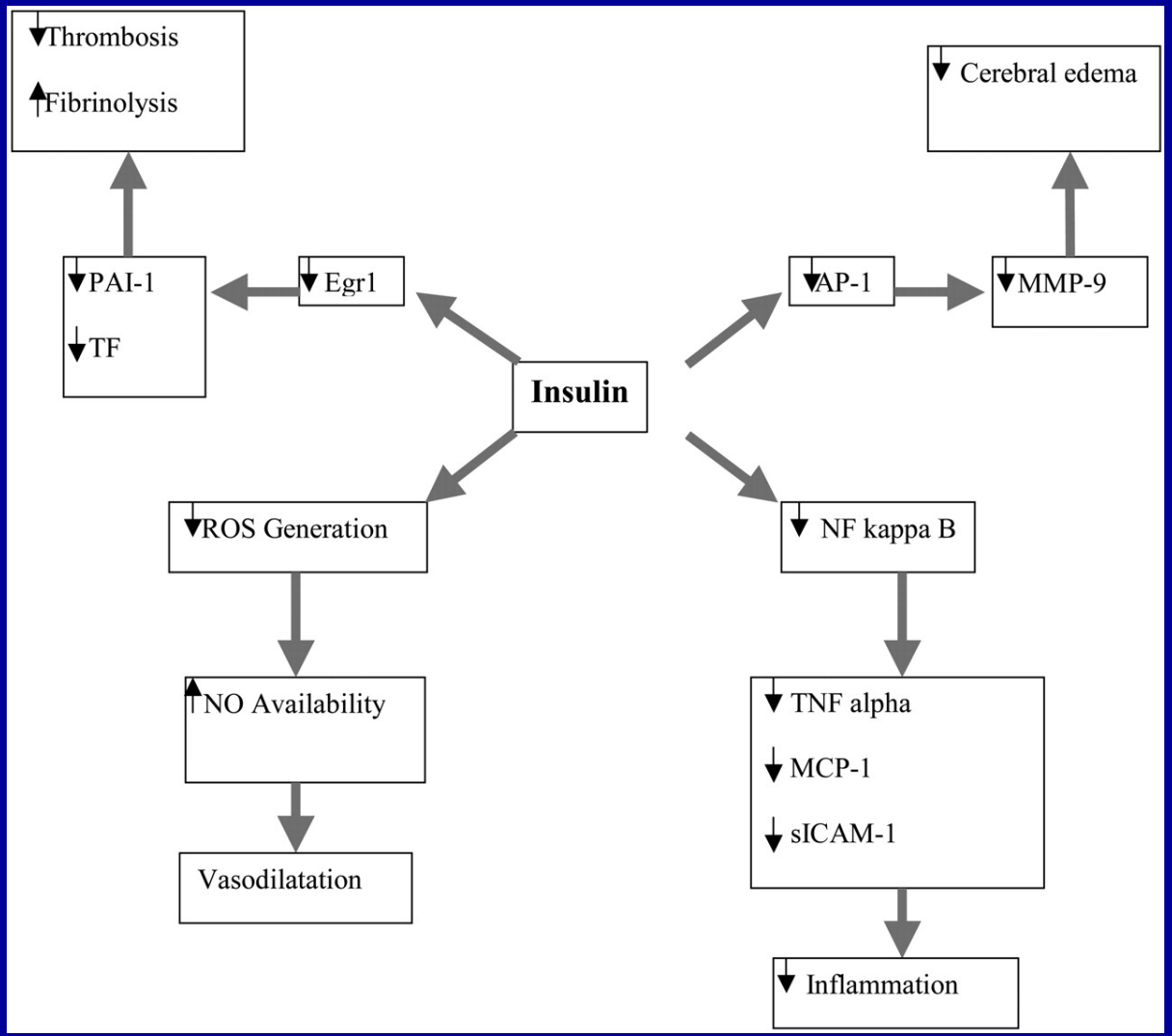
Potential Mechanisms

- **Enhanced Acidosis**
  - Anaerobic metabolism – intracellular acidosis
  - Hypometabolism
  - Mitochondrial dysfunction
- **Stress response**
  - Activation of hypothalamo-hypophyseal-adrenal axis increase cortisol and catecholamines
- **Extension of infarct**
  - NO mediated reduced blood flow
  - Increased penumbral depolarizations
- **Excitotoxicity**
  - NMDA mediated calcium influx
- **Proinflammatory** and/or **procoagulant** effects

Anti-inflammatory, anticoagulant, and vasodilatory effect of insulin

Reduce coagulability

Reduce oxidative stress



Reduce edema

Reduce inflammation

Stroke

Garg, R. et al. Stroke 2006;37:267-273

American Stroke Association®
A Division of American Heart Association

Preclinical Data

- Hamilton, et al – Neurosurg 1995

- Transient (2 hour) focal ischemia rat model
- 3 groups - Pretreatment with
  - control
  - insulin
  - insulin/glucose

- Is the benefit due to the insulin or the glucose concentration?

Summary of Hamilton Data

- Acute focal ischemia animal model
  - Pretreatment with insulin therapy is beneficial
  - It is the glucose concentration and not the presence of insulin that is beneficial

Aggressive Glucose Regulation In Stroke Populations

- Glucose Insulin in Stroke Trial (GIST-UK)
  - Definitive efficacy trial (intent)
- Treatment of Hyperglycemia In Stroke (THIS)
  - Middle phase (pilot) trial
- Glucose Regulation in Acute Stroke Patients (GRASP)
  - Middle phase trial

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GIST Trial (Glucose Insulin Stroke Trial)

- Intended as definitive efficacy
- Multicenter, randomized, controlled – many UK sites
- BG 108-306, 24 hr window, GIK vs saline (24 hr Rx)
- Target 72-126 mg/dL (saline group – Rx at 306 mg/dL)
- Excluded insulin treated DM
- Outcome – death at 3 months

- Trial terminated early after steering committee determined recruitment not feasible with current funds
- 933 enrolled/ 2355 planned – 40% enrollment

Gray, Lancet Neurology 2007

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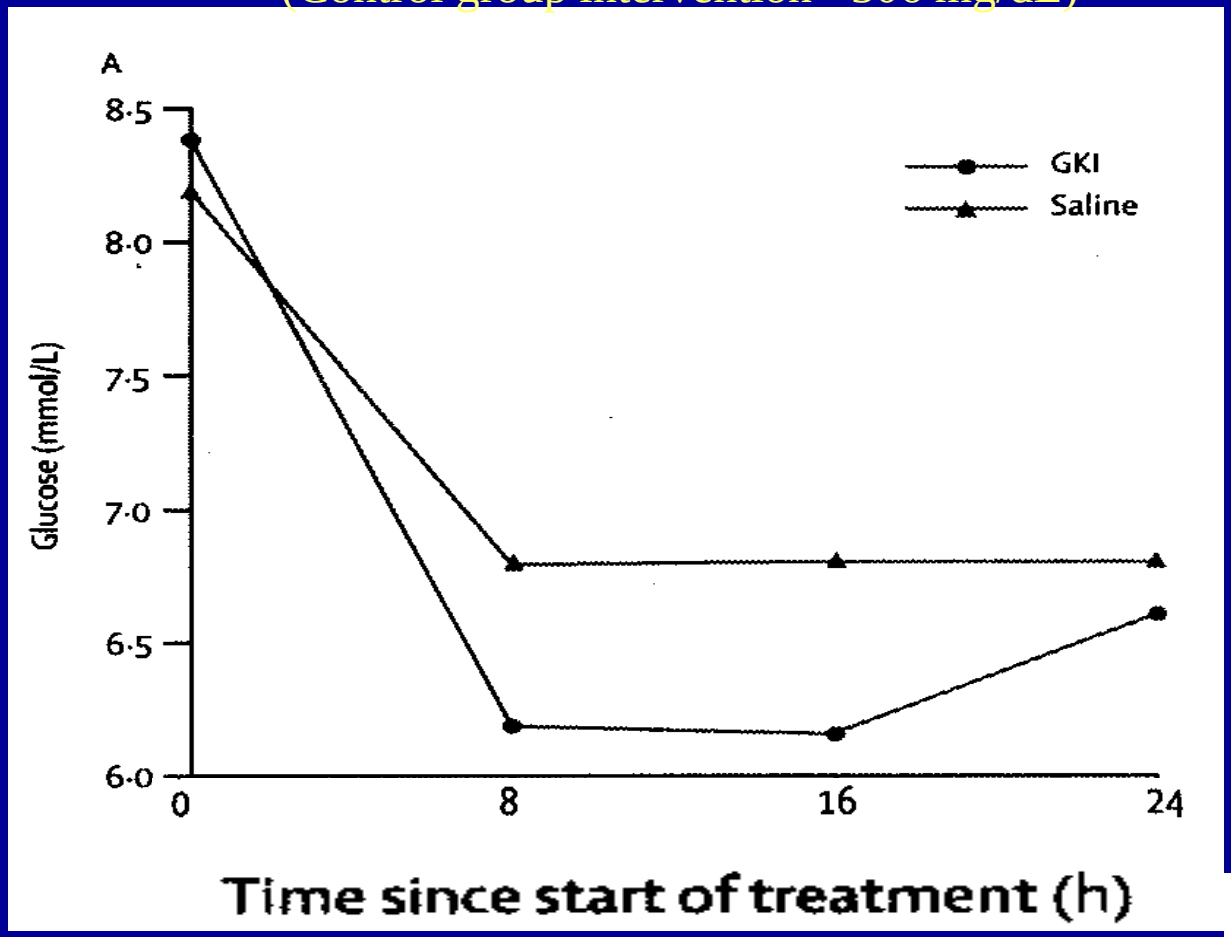
GIST Glucose Concentrations

(Target intervention 72-126 mg/dL)

(Control group intervention >306 mg/dL)

153 mg/dL

BG ~147 – 151 mg/dL



~ 122 mg/dL

~ 118 mg/dL

108 mg/dL

6.1 mmol/L ~ 110 mg/dL

Gray, Lancet Neurology 2007

GIST Primary Outcome - Survival

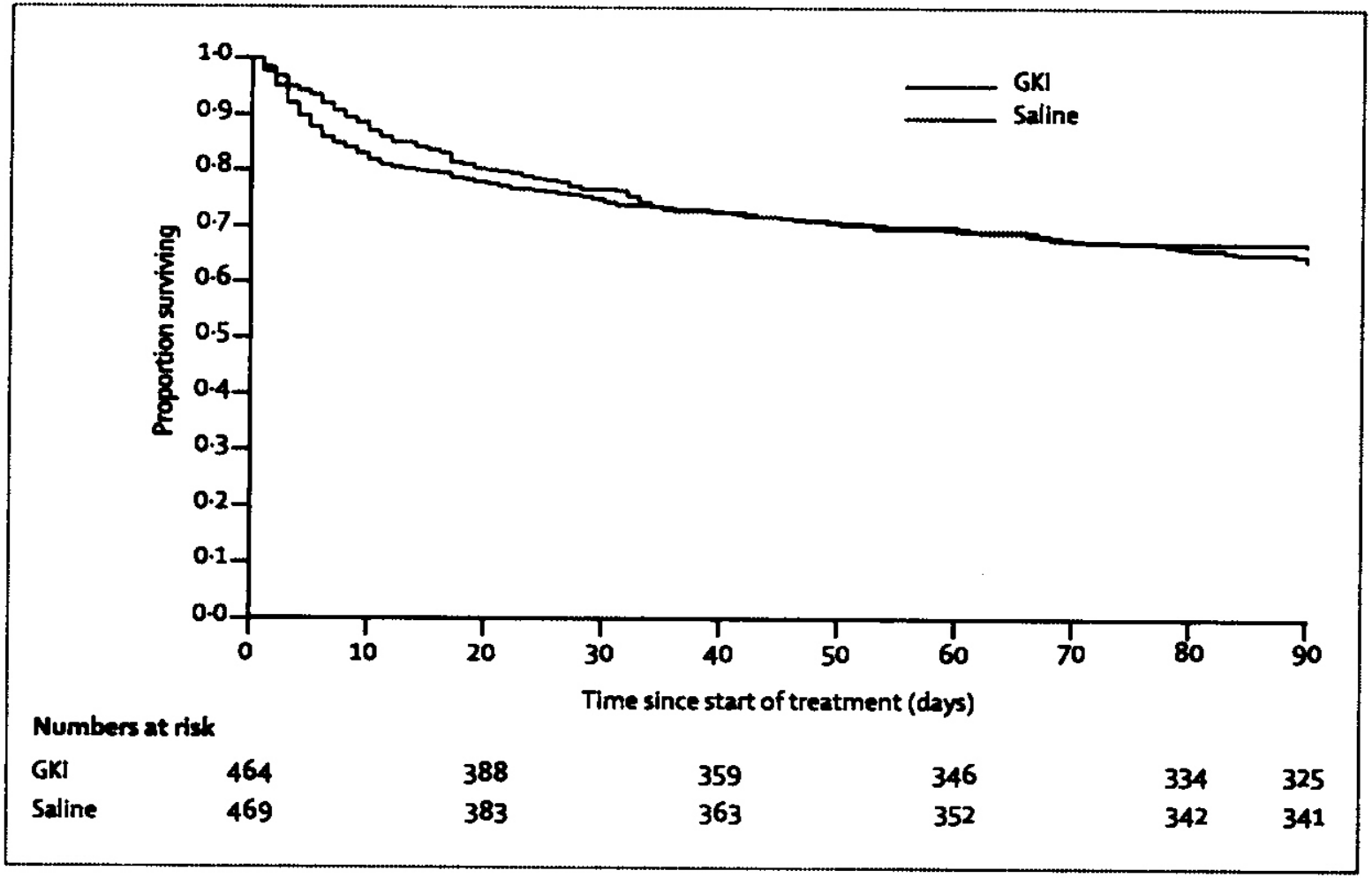


Figure 6: **Kaplan-Meier survival curves to 90 days for glucose-potassium-insulin (GKI) and saline treatment groups**
GKI=glucose-potassium-insulin.

Gray, Lancet Neurology 2007

GIST Trial Summary

- Large randomized controlled trial but did not answer clinical question:

- Terminated early w/ 40% enrollment so concern re Type II error
- Enrolled 83% non diabetics and 17% NIDDM
- Both treatment groups got “intervention target” (no comparison)

Gray, Lancet Neurology 2007

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THIS Trial

Treatment of Hyperglycemia in Ischemic Stroke

- Randomized (2:1), controlled, blinded (single–Rx, double-outcome)
- 5 sites
- Diabetic ischemic stroke – 12 hour window
- NIHSS = 3-22
- Glucose level >150 mg/dL
- Insulin infusion vs sq insulin (ss) for 3 days

- Target for insulin infusion – 70-130 mg/dL
- Outcomes - Hypoglycemia <60 mg/dL, mRankin 0-2

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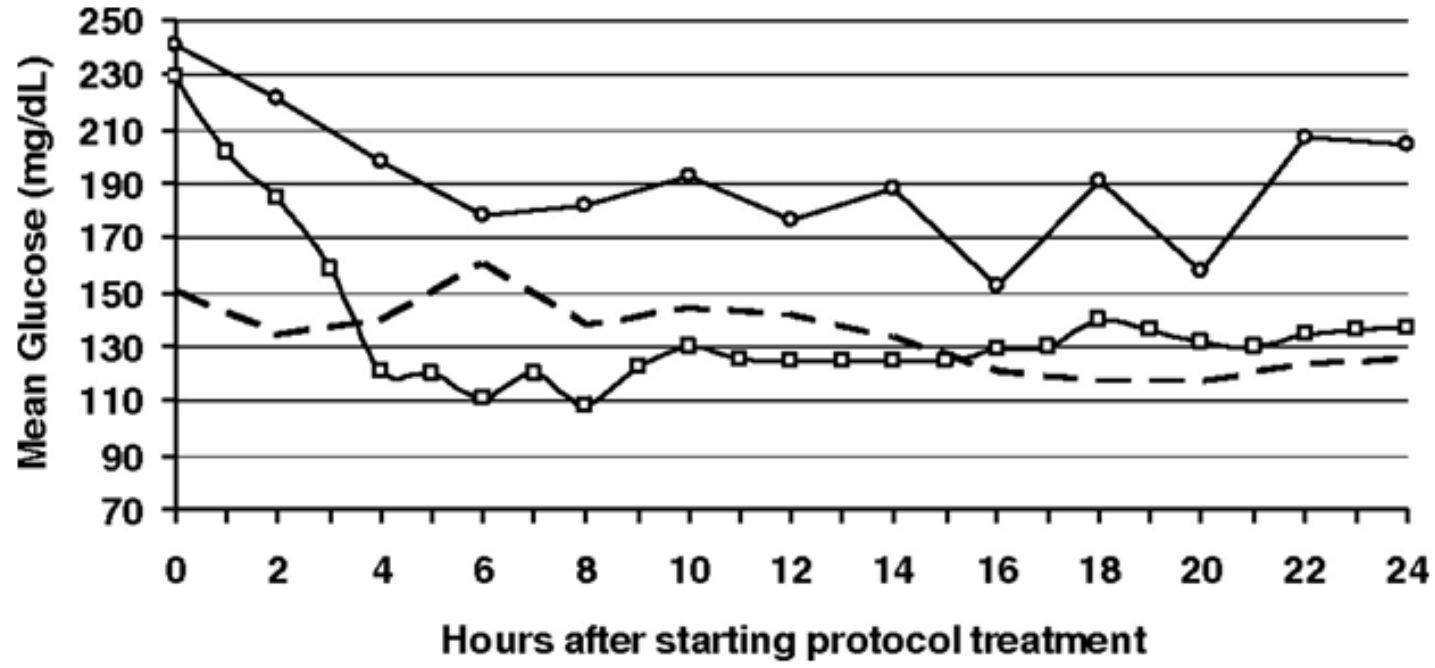
THIS Trial Glucose Concentrations

N=46 subjects

Target 70-130mg/dL

Figure. Mean glucose levels during the first 24 hours of protocol treatment before patients resumed eating. ○, Usual-care group (n=15); □, aggressive-treatment group (n=31); interrupted line, the 4 patients without diabetes randomized to usual care.



Usual Care

~200 mg/dL

Aggressive

~135mg/dL

Non DM – usual care

~120 mg/dL

Bruno, *Stroke* 2008

GRASP Trial

Glucose Regulation in Acute Stroke Patients

- Middle phase feasibility, safety, dose finding
- Multicenter, controlled, blinded outcome

- Feasibility, safety and dose finding study
- 24 hour window – Rx -5 days

- 3 treatment groups:
  1. Usual care (community control) – target 70-300 mg/dL
  2. Loose control - target 70 – 200 mg/dL – insulin infusion
  3. Tight control – target 70 – 110 mg/dL – insulin infusion

Johnston KC, et al. Stroke, 2009

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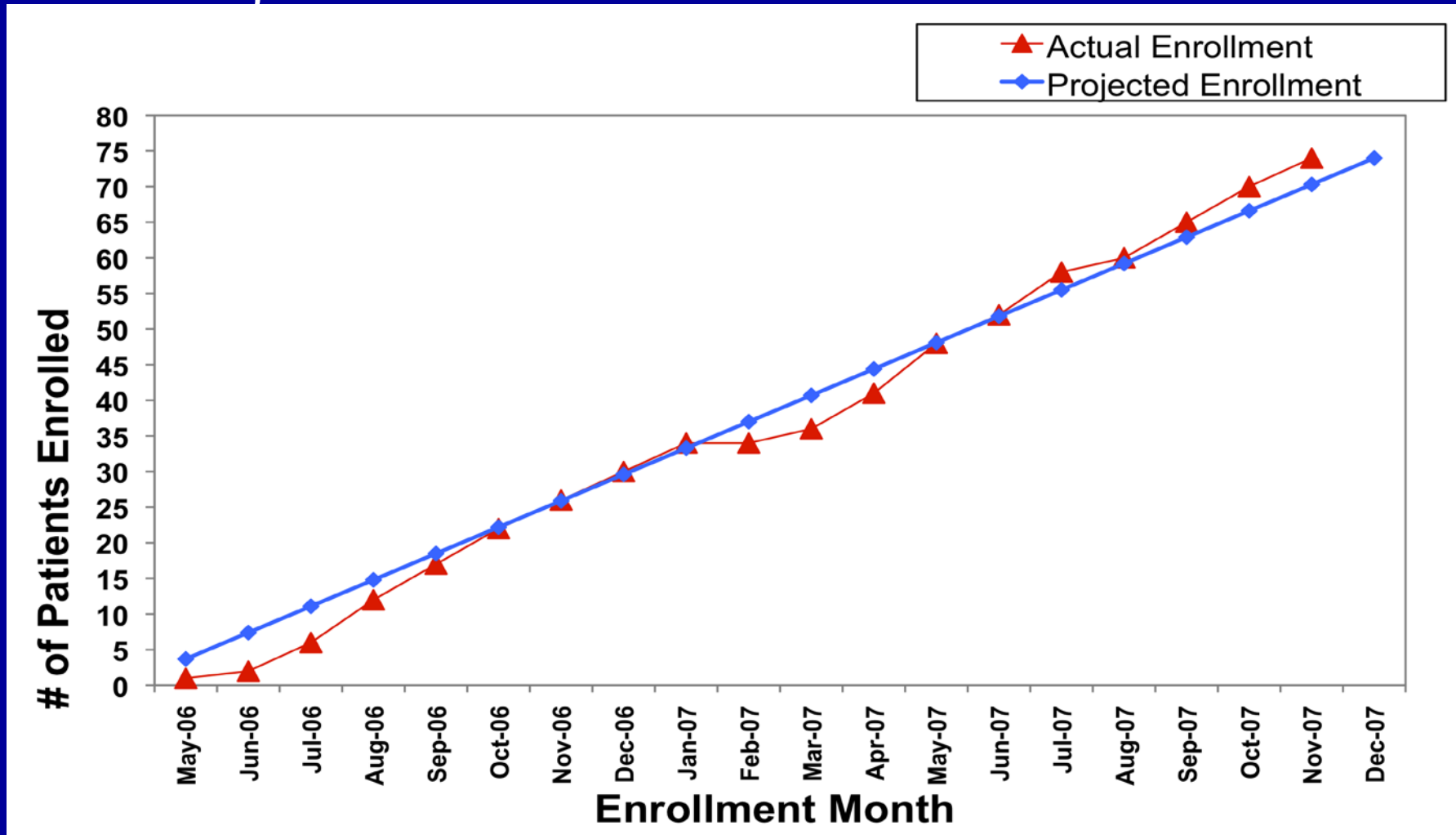
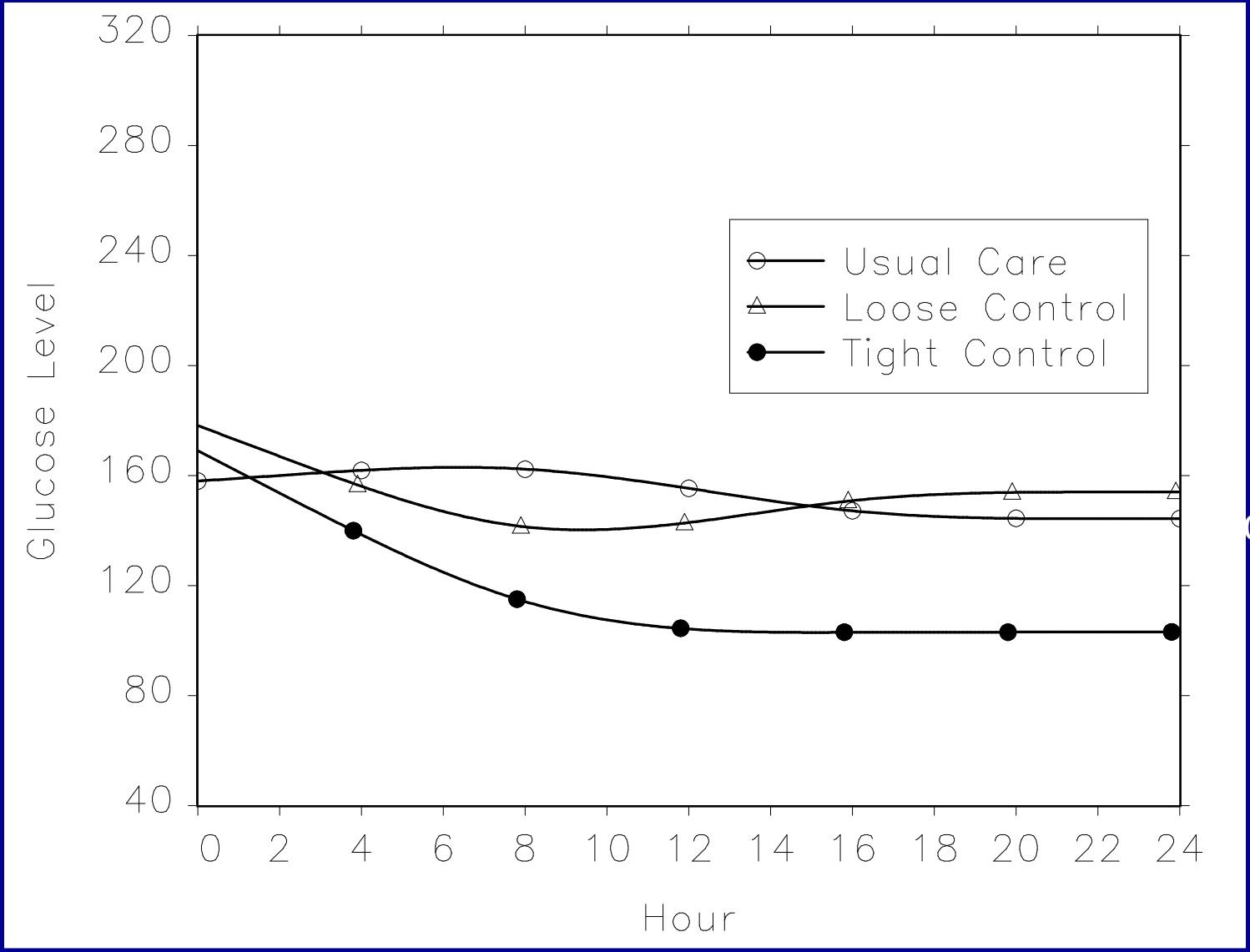
GRASP Trial Enrollment Success

- Enrollment – May 2006 – November 2007
- 74 subjects enrolled



Glucose Concentration Curves

N=74



Medians

Loose -151mg/dL

Control – 151 mg/dL

Tight – 111 mg/dL

Johnston KC, et al. Stroke, 2009

Overall Summary of Background

- Feasible
- Safe
- Clinically relevant
- Non diabetics glucose comes down on own
- Phase III trial is warranted

Introducing The SHINE Trial

(Stroke Hyperglycemia Insulin Network Effort)

NIH-NINDS U01 NSO69498

SHINE Trial

NIH-NINDS U01 NSO69498

- Stroke Hyperglycemia Insulin Network Effort
- Definitive Phase III efficacy trial
- Combined Effort of the GRASP and THIS investigators
  - 2 NIH- NINDS middle phase trials
- Funded by the NIH- NINDS
- Conducted in conjunction with the Neurological Emergency Treatment Trials (NETT) network (NINDS)

Phase III SHINE Trial

NIH-NINDS U01 NSO69498

Specific Aim 1

- To determine the efficacy of tight glucose control to a target range of 80-130 mg/dL with IV insulin infusion in hyperglycemic acute ischemic stroke patients within 12 hours of symptom onset as measured by mRS at 90 days after stroke.

Specific Aim 2

- To determine the safety of tight glucose control with IV insulin infusion in hyperglycemic acute ischemic stroke patients treated for up to 72 hrs.

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Phase III SHINE Trial Sites

NIH-NINDS U01 NSO69498

- NETT Hubs and Spokes (17 hubs, ~50 total)
- Non NETT sites (~10 total)
- Site PIs include
  - Emerg med
  - Neuro crit care
  - Vascular Neuro

Trial Leadership Organization

NIH-NINDS U01 NSO69498

- Multiple PIs
  - Chris Hall (UTSW)– Recruitment PI (all sites)
  - Askiel Bruno (GHSU) – Protocol PI (all insulin protocols)
  - Karen Johnston (UVA)– Administrative PI (oversight of all)
- Project Director (UVA) – Amy Fansler
- CCC – Bill Barsan – (Michigan)
  - NETT CCC will monitor all sites
- SDMC – Valerie Durkalski – (MUSC)
  - WebDCU will capture and manage all data
- Study Endocrinologist – Rattan Juneja (Indiana)
- Study Independent Safety Monitor – Tom Bleck (Rush)
- GlucoStabilizer lead – Denise Zito (MAS)

Phase III SHINE Trial

NIH-NINDS U01 NSO69498

- Hyperglycemic acute ischemic stroke patients (~1400)
- Single blind Rx; double blind outcomes
- 12 hr window from symptom onset (3 hrs door to Rx)
- Treatment Groups
  - Insulin drip – target 80-130 mg/dL
  - Control -SQ insulin <180 mg/dL
- Up to 72 hrs treatment
- 90 day outcomes – mRS (sliding dichotomy)

- 80% power to detect 7% absolute improvement in favorable outcome (mRS)

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Phase III SHINE Trial

Design Innovations

NIH-NINDS U01 NSO69498

- Response Adaptive Randomization (RAR)
- GlucoStabilizer – electronic decision support tool
- Responder Analysis (sliding dichotomy)
  - successful outcome based on enrollment stroke severity
  - allows consideration of expected outcome to be considered in determination of favorable outcome

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