Subcutaneous exendin (9-39) effectively treats post-bariatric hypoglycemia

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Presenter Disclosure

Consultant:

Eiger BioPharmaceuticals

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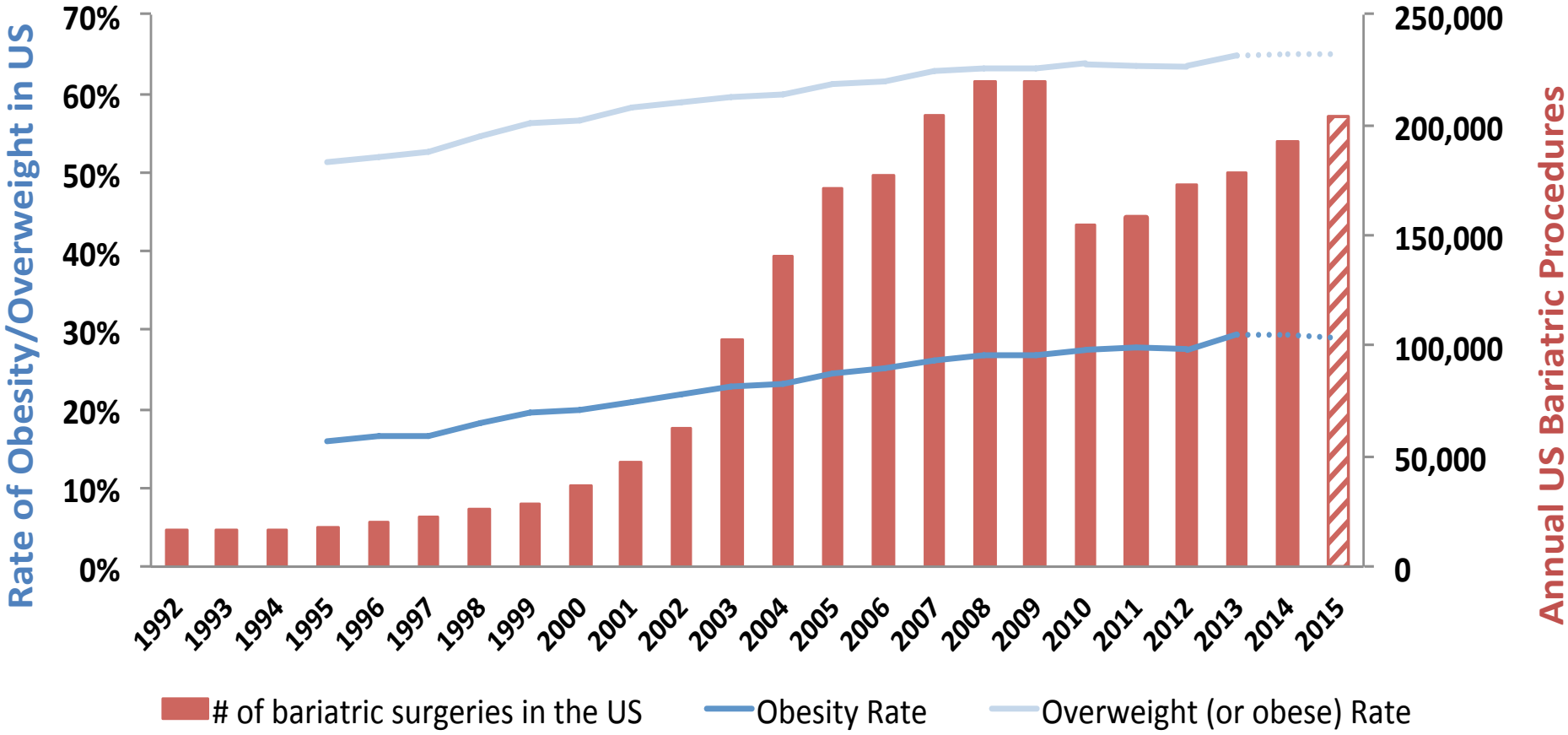
Rates of obesity and bariatric surgery increasing



Source: American Society for Metabolic & Bariatric Surgery; Behavioral Risk Factor Surveillance System (BRFSS)

Post Bariatric Hypoglycemia, a rare but disabling disease

Asymptomatic → **Symptomatic req. assistance**

Asymptomatic Patients with Lab Values	Patient Reported Symptoms	Partial Labs w/ Symptoms	Full Labs w/ Symptoms or Hospitalization
30% Goldfine 2007	**11.6%** Lee 2015	**6.2%** Nambron 2013	**0.2%** Marsk 2010
	0.1% Sarwar 2008		**0.36%** Kellogg 2008
			0.46% Nambron 2013
			6.6% Gribsholt 2016

Clinical Characteristics

Clinical Presentation

- 0.5-10 years post-GI surgery (RYGB)
- Postprandial hypoglycemia (1-3 hours)
- Symptoms of hypoglycemia
  - Autonomic
  - Neuroglycopenic
    - LOC or seizure
- Insulin inappropriately elevated (≥3uU/ml) at time of hypoglycemia

Therapeutic Approach

No pharmacotherapies approved

Dietary Changes:

- Frequent small meals/CHO restriction

Stepped Pharmacotherapy:

- Acarbose →Octreotide→Diazoxide
- Limited by efficacy/tolerability

Surgical Approaches:

- Gastrostomy tube/gastric band
- Partial pancreatectomy/RYGB reversal

Diagnosis

Whipple's Triad:

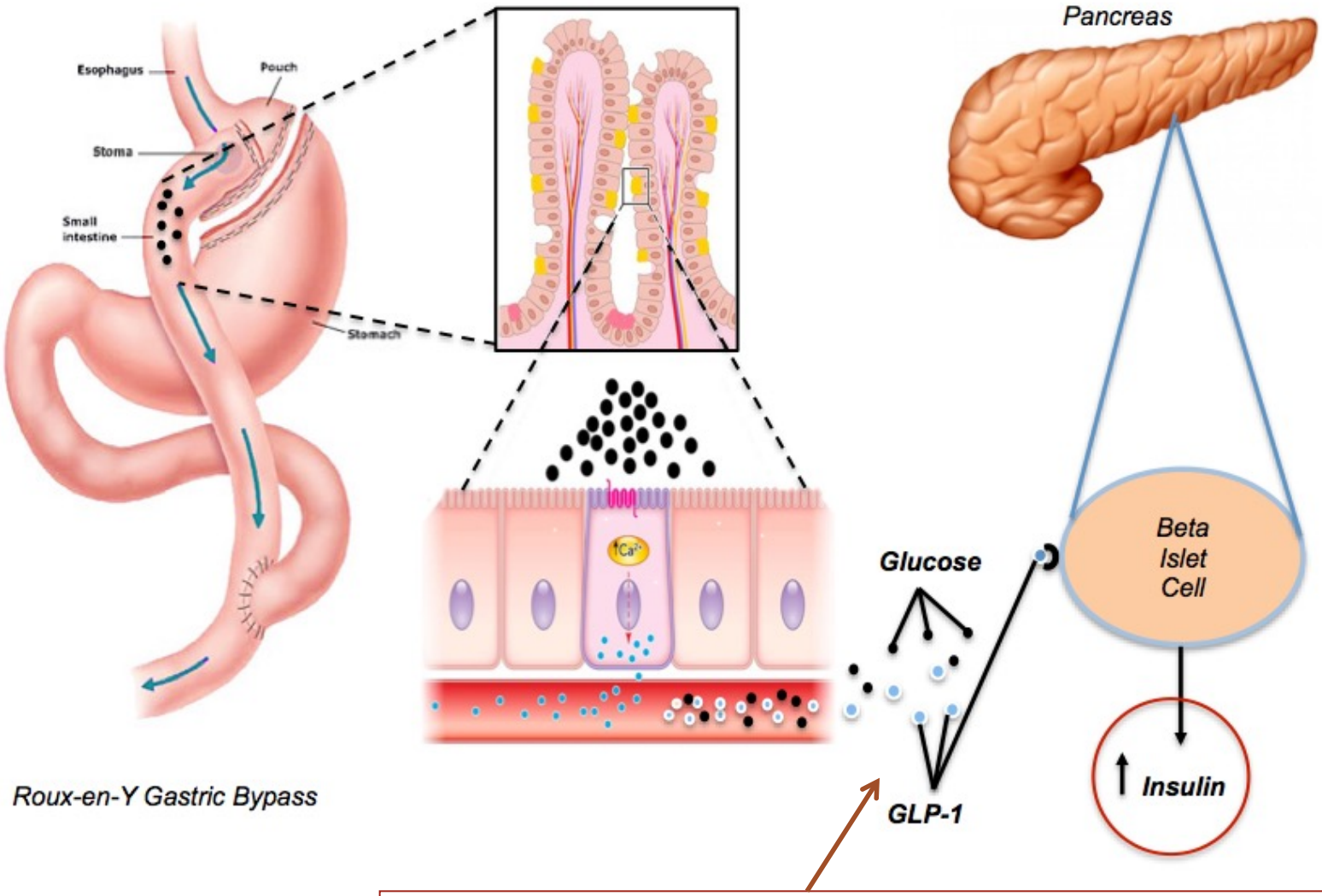
1. Symptoms and signs of hypoglycemia
2. Measured low plasma glucose
3. Resolution of symptoms when plasma glucose is normalized

Other etiologies ruled out

Proposed Etiologies

- β-cell hyperplasia and/or ↓apoptosis
- Enhanced β-cell sensitivity
- ↑insulin sensitivity /↓clearance
- Counter-regulatory failure
- Non-insulin mediated mechanisms
- Hypersecretion of incretin hormones

Early nutrient sensing by L cells → Hypersecretion of GLP-1

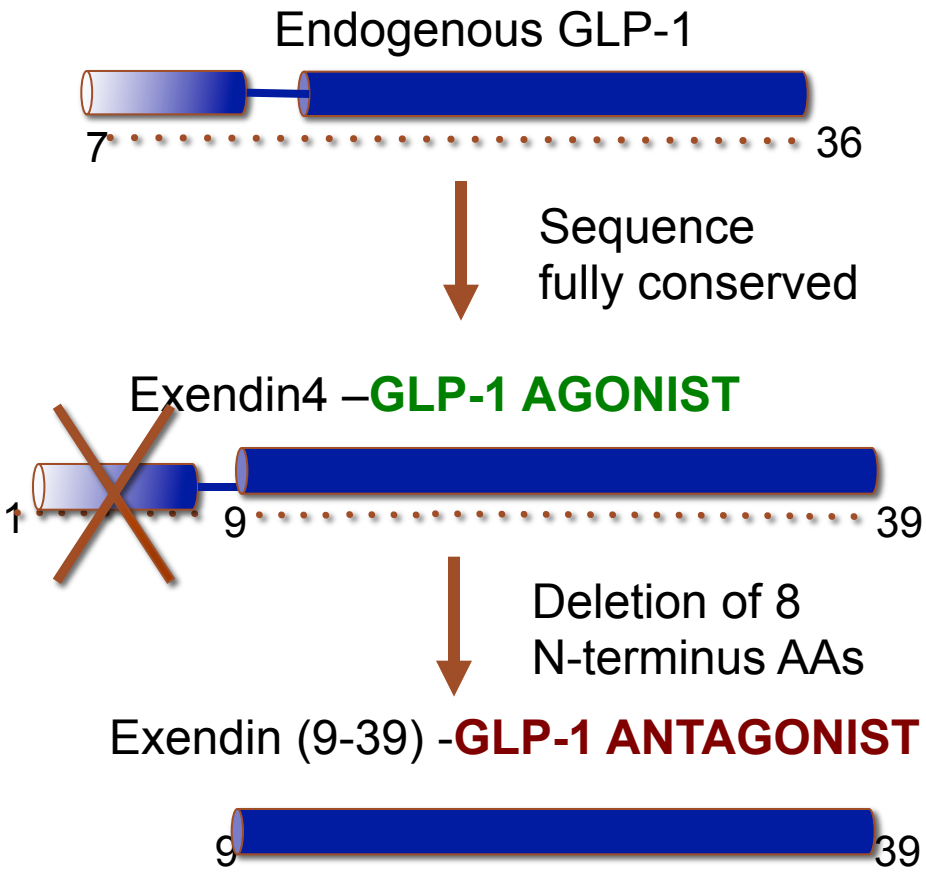


GLP-1 concentrations elevated >10-fold post-RYGB and are up to 50-fold higher in patients with PBH

Image adapted from Manning S. et al. Physiology 2015;30:50-62

Hypothesis

Antagonism of the GLP-1 receptor will result in a reversal of postprandial glucose lowering via inhibition of GLP-1 induced insulin secretion

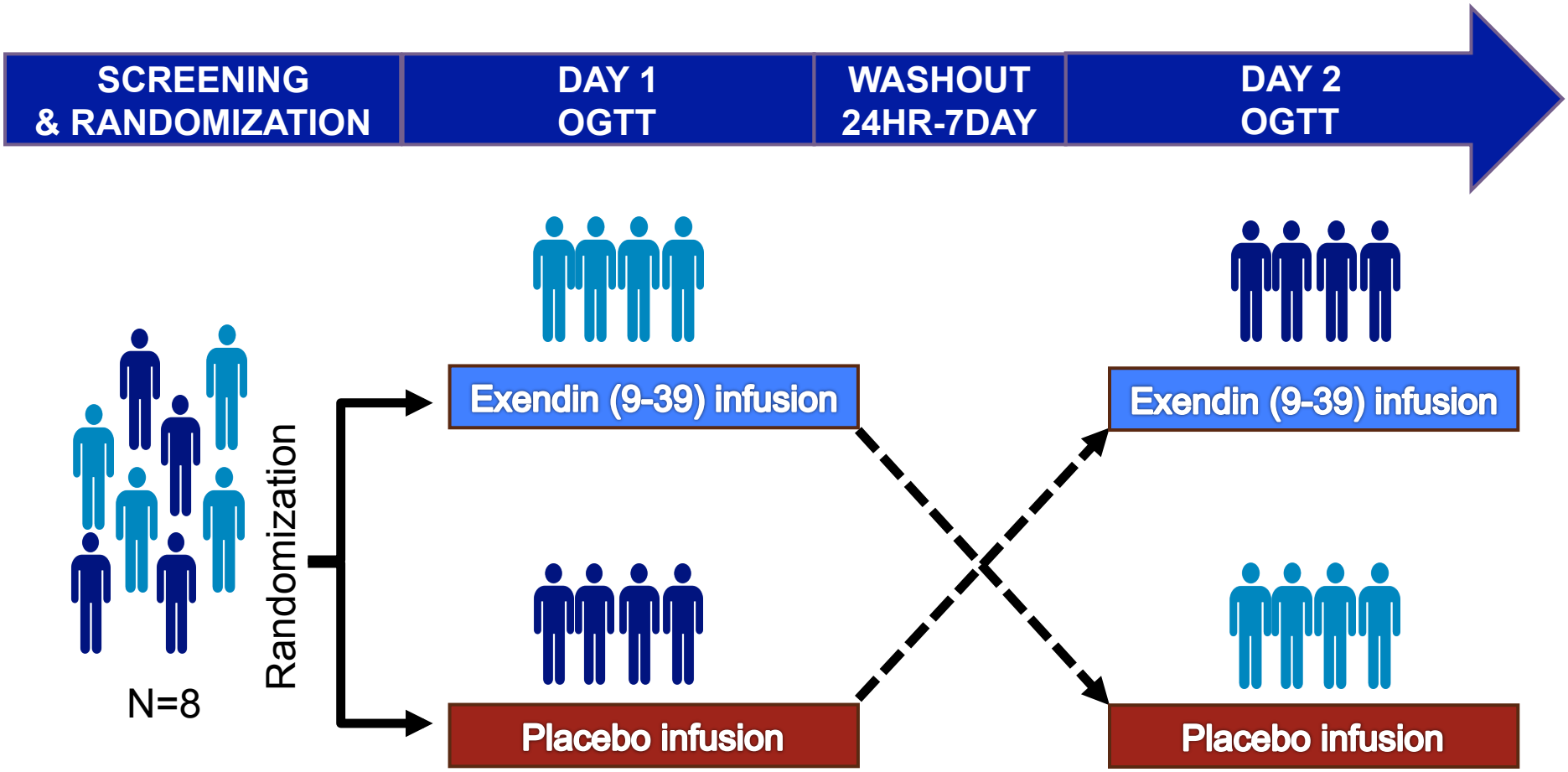


- Enhances secretion of insulin
- Inhibits secretion of glucagon
- Delays gastric emptying

- GLP-1 analogue (Gila monster)
- 53% homology to human GLP-1
- Agonist
- Synthetic Exendin4 = Exenatide

- 31 AA fragment of Exenatide
- Specific competitive antagonist

Phase 1 cross-over placebo-controlled trial: IV Exendin (9-39)



Inclusion Criteria:

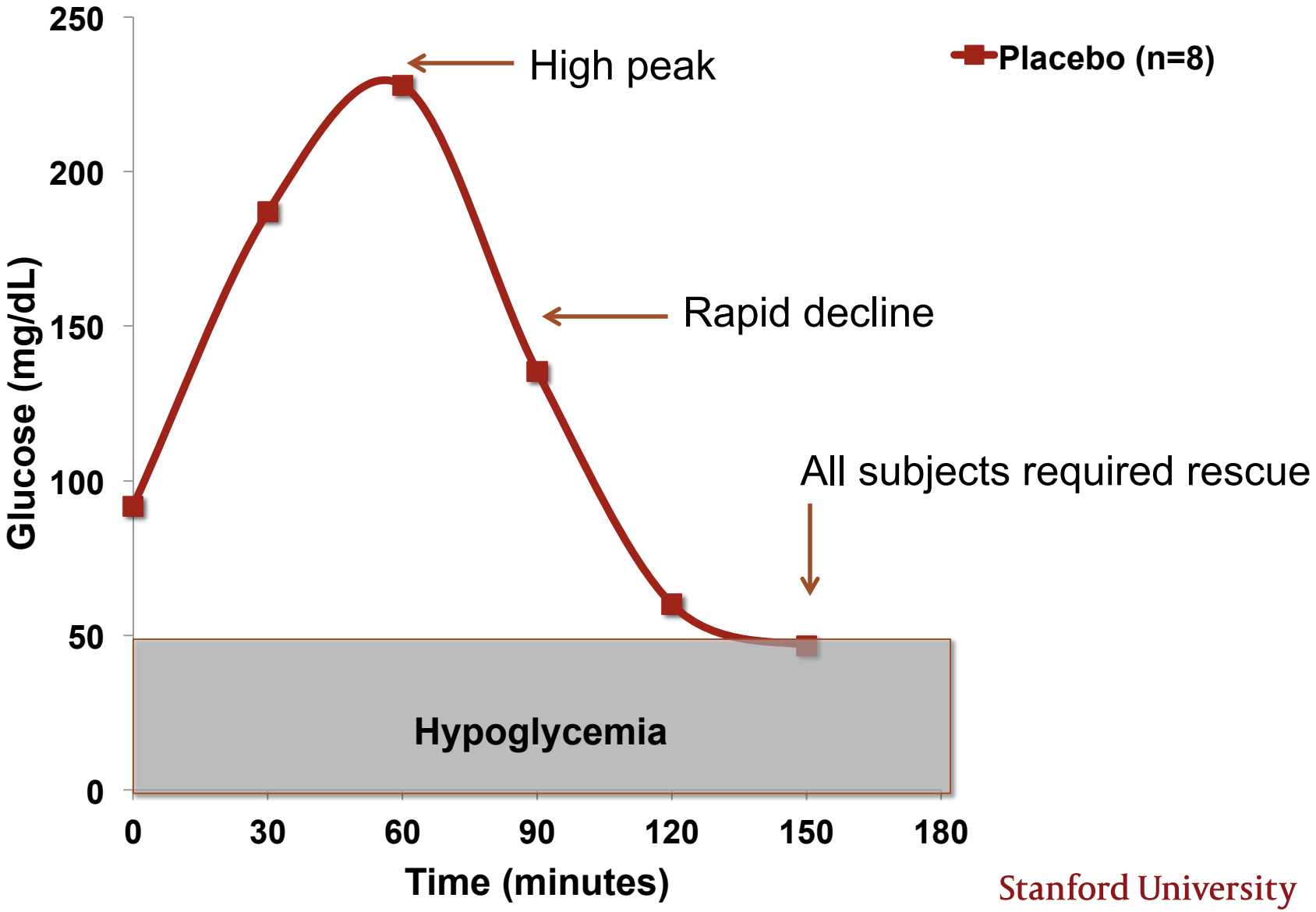
1) Whipple's triad
2) Hyperinsulinemia (>3uU/mL)

Endpoints:

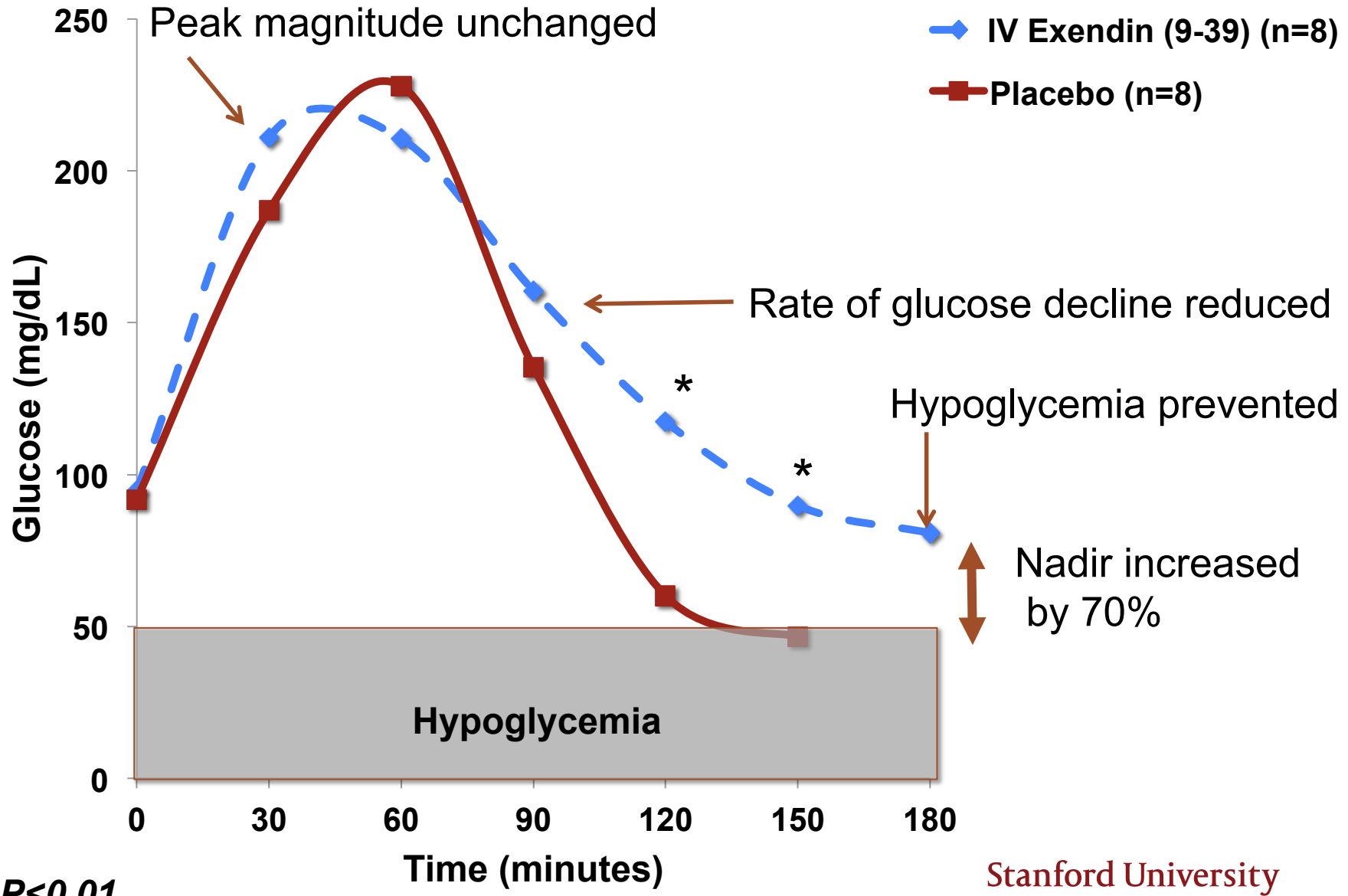
1°: Prevention of hypoglycemia (≤50mg/dL)

2°: Improvement in symptom score (Edinburgh Hypoglycemia Symptom Scale)

IV infusion placebo– All patients became hypoglycemic



IV infusion Exendin (9-39)– 100% reversal of hypoglyemia



*** P<0.01**

IV Exendin (9-39) – Improved symptoms of hypoglycemia

Subjects surveyed every 30 min for presence of:
- Autonomic
- Neuroglycopenic
- Malaise

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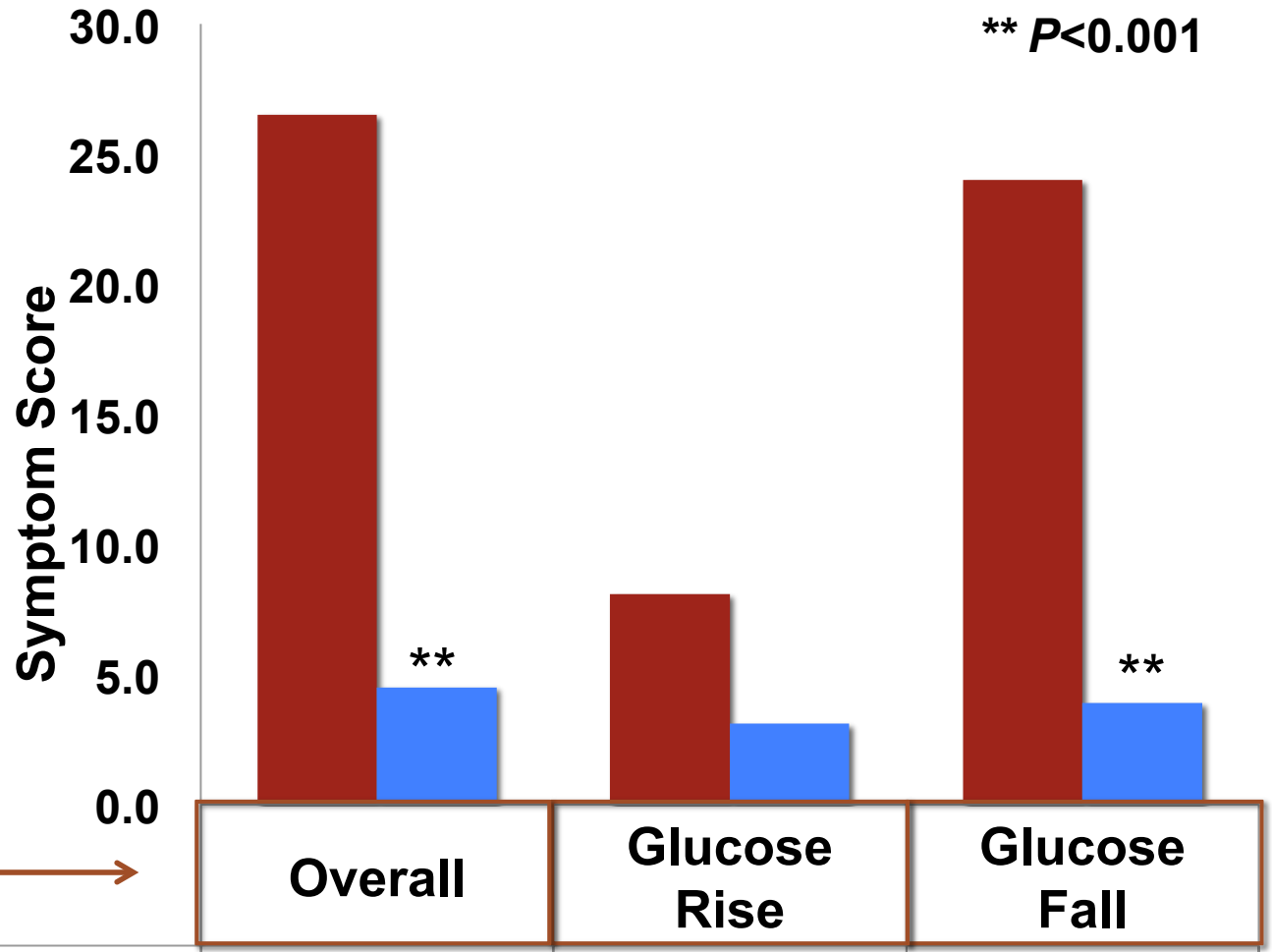
Severity ranked 5-point scale:
- 0=none
- 5=severe

↓

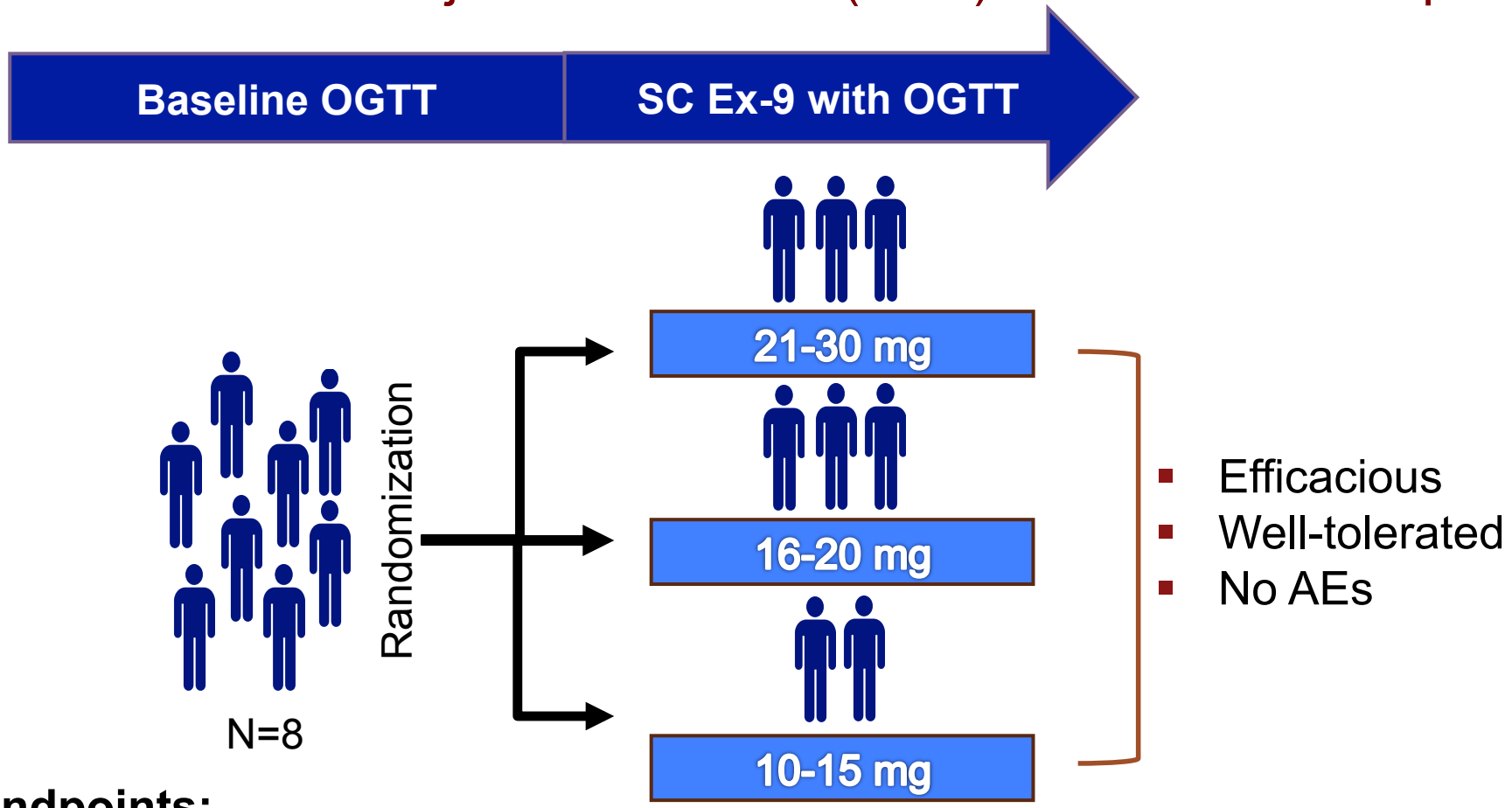
Composite Scores →



	Overall	Glucose Rise	Glucose Fall
Placebo	26.5	8.1	24.0
IV Exendin (9-39	4.5	3.1	3.9

Edinburgh Hypoglycemia Symptom Scale

Phase 1 SAD: SC injection Exendin (9-39) – All doses therapeutic



Endpoints:

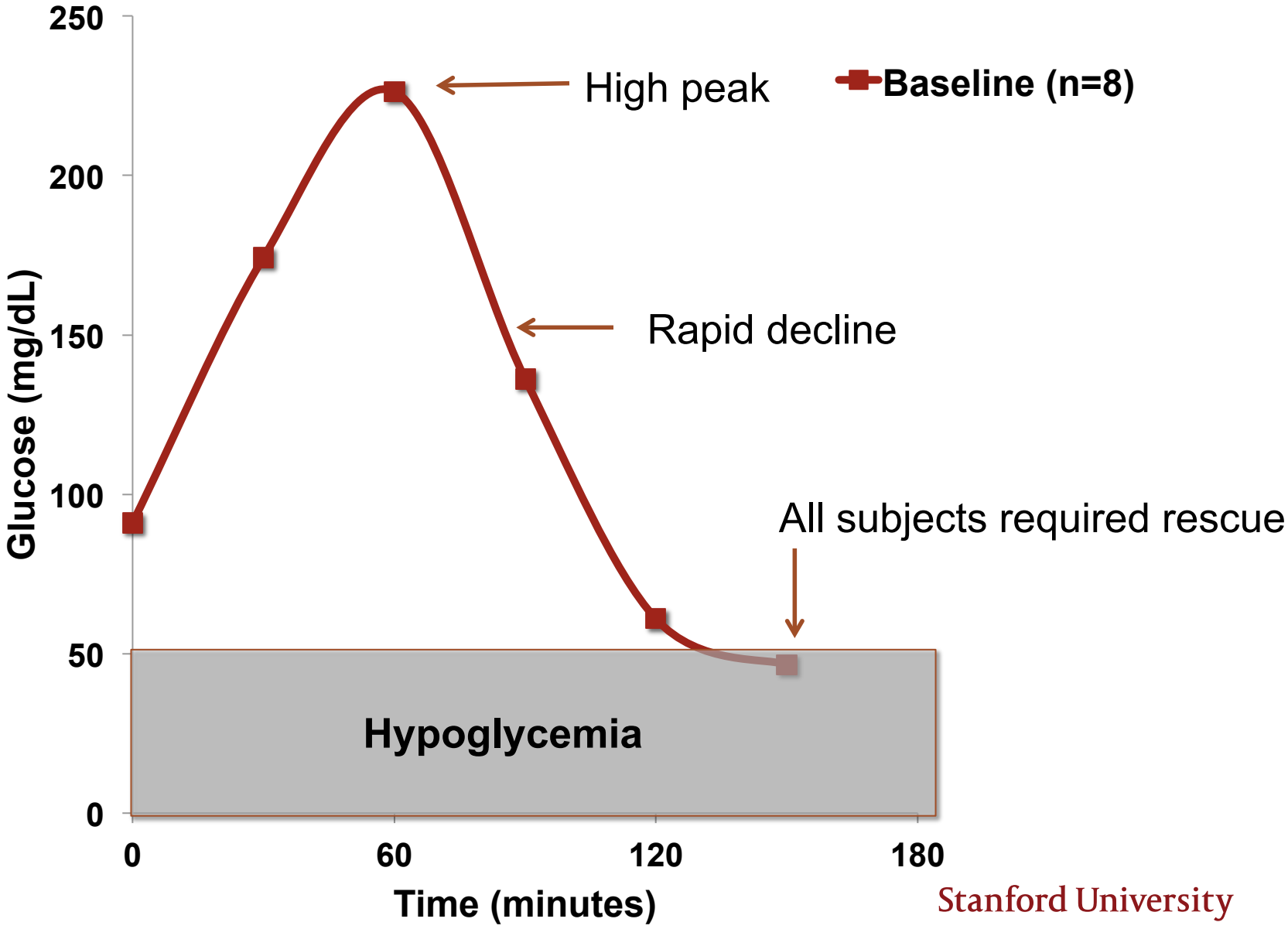
1°: Prevention of hypoglycemia (≤50mg/dL)

2°: Improvement in hypoglycemia symptom score

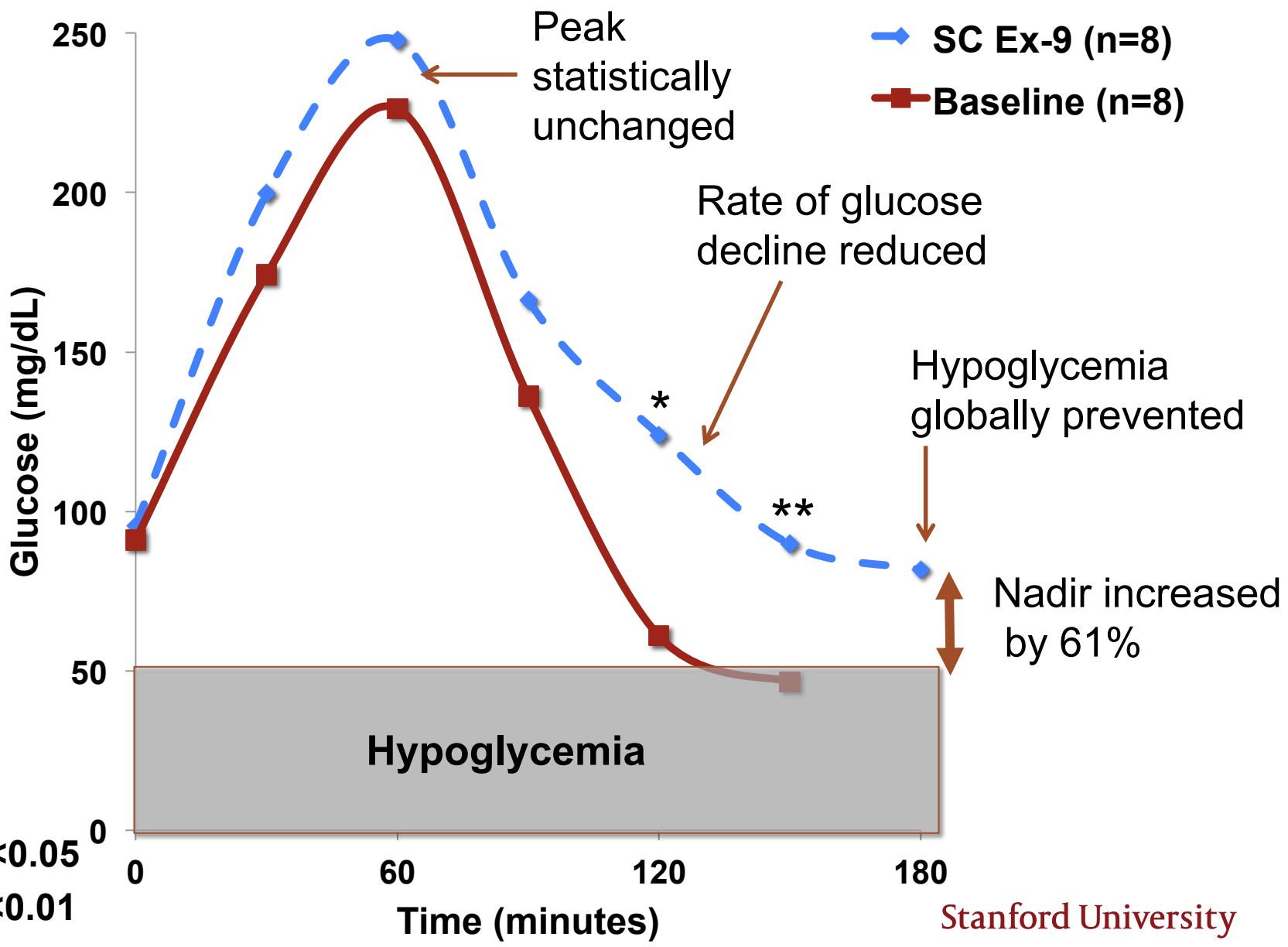
Pharmacokinetic profile

Safety & Tolerability

Baseline OGTT–All patients became hypoglycemic



SC Exendin (9-39)–Hypoglycemia prevented at all dose levels

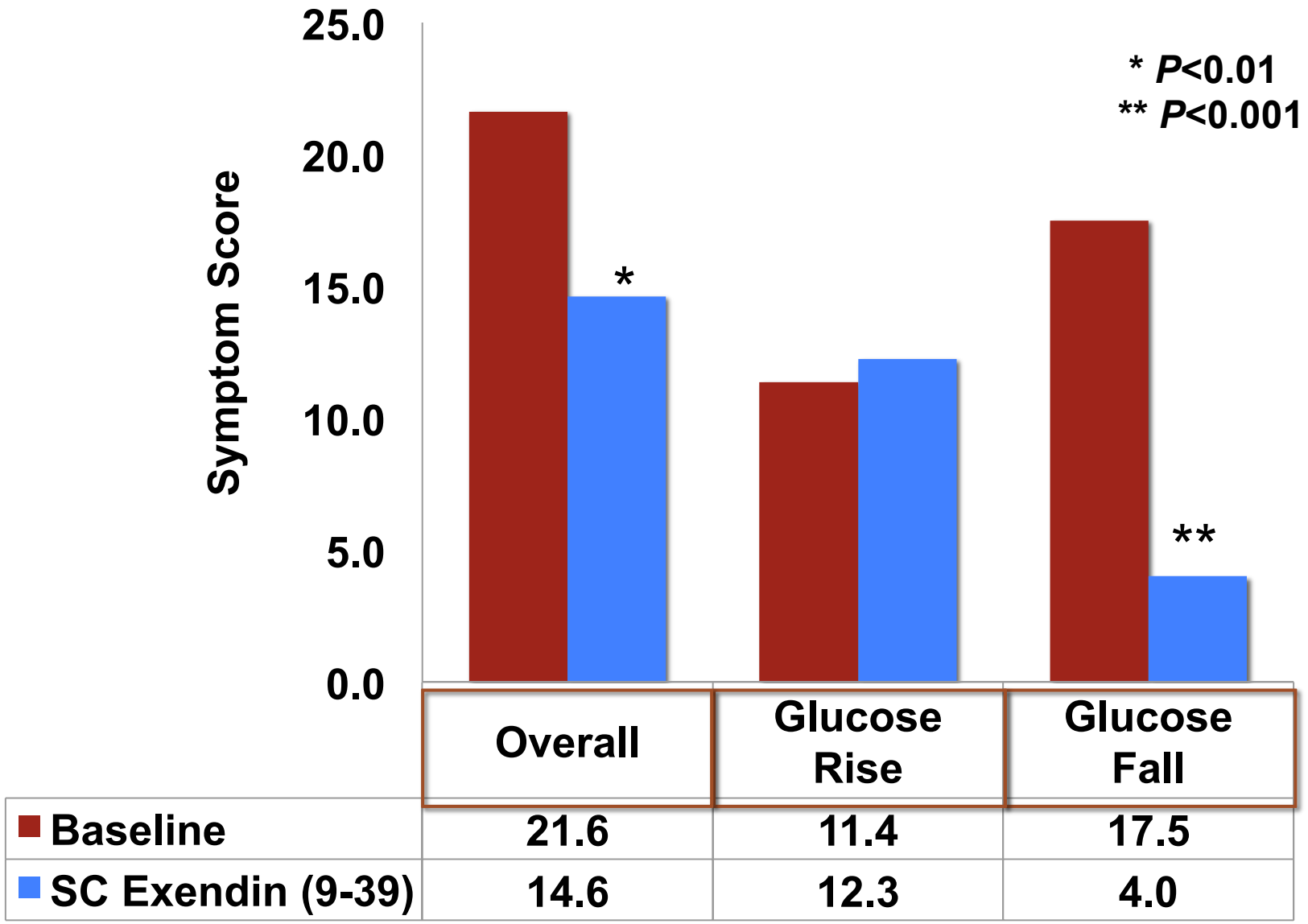


SC Exendin (9-39) significantly improved late glycemic responses

	Baseline	SC Ex(9-39)	P-value
Early Glycemic Responses	(n=8)	(n=8)	
Fasting plasma glucose (mg*dl-1)	91.6 ± 2	94.5 ± 2	0.125
Peak postprandial glucose (mg*dl-1)	229.3 ± 13.2	252.3 ± 24	0.258
Time to peak glucose (min)	54.5 ± 4	52.5 ± 5	0.351
AUC glucose (0,60)(mg*dl-1*min-1)	10171 ± 335	11135 ± 704	0.140
Late Glycemic Responses			
Nadir glucose (mg*dl-1)	47.7 ± 2	77.9 ± 4	<0.001
Time to nadir (min)	135.5 ± 5	180.0	<0.000
AUC glucose(0,180)(mg*dl-1*min-1)	21106 ± 1002	27471 ± 1963	0.007

RESULTS

SC Exendin (9-39) reduced symptoms of hypoglycemia



Edinburgh Hypoglycemia Symptom Scoring

Summary

- PBH is a rare, disabling disease for which no pharmacotherapy exists
- GLP-1 appears to play a critical role in the underlying pathophysiology
- Subcutaneous administration of a single dose of Exendin (9-39) at doses ranging from 10-30 mg safely, tolerably and effectively prevented hypoglycemia and improved symptoms in 8/8 subjects during an OGTT
- SC Exendin (9-39) represents a promising, targeted therapeutic

Future Directions

- Phase 2a Multi-Ascending Dose trial currently underway at Stanford
  - BID SC Ex-9 x 3 days (ClinicalTrials.gov: NCT02771574)

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