Analogs as a Focus

Bruce W. Bode, MD, FACE

Atlanta Diabetes Associates

Atlanta, Georgia

Goals of Intensive Diabetes Management

- Near-normal glycemia
  - HbA_{1c} <6.5% to 7.0%
- Avoid short-term crisis
  - Hypoglycemia
  - Hyperglycemia
  - DKA
- Minimize long-term complications
- Improve QOL

ADA. *Clinical Practice Recommendations*. 2001.

ACE/AACE Targets for Glycemic Control

HbA_{1c}	<6.5%
Fasting/preprandial glucose	<110 mg/dL
Postprandial glucose	<140 mg/dL

ACE/AACE Consensus Conference. Washington, DC. August 2001.

Insulin

The Most Powerful Agent We Have to Control Glucose

The Discovery of Insulin (Toronto 1921)

Fred Banting (1891-1941)

Charles H. Best (1899-1978)

John J.R. McLeod (1876-1935)

James B. Collip
(1892-1965)

Marjorie (?-?)

The Miracle of Insulin

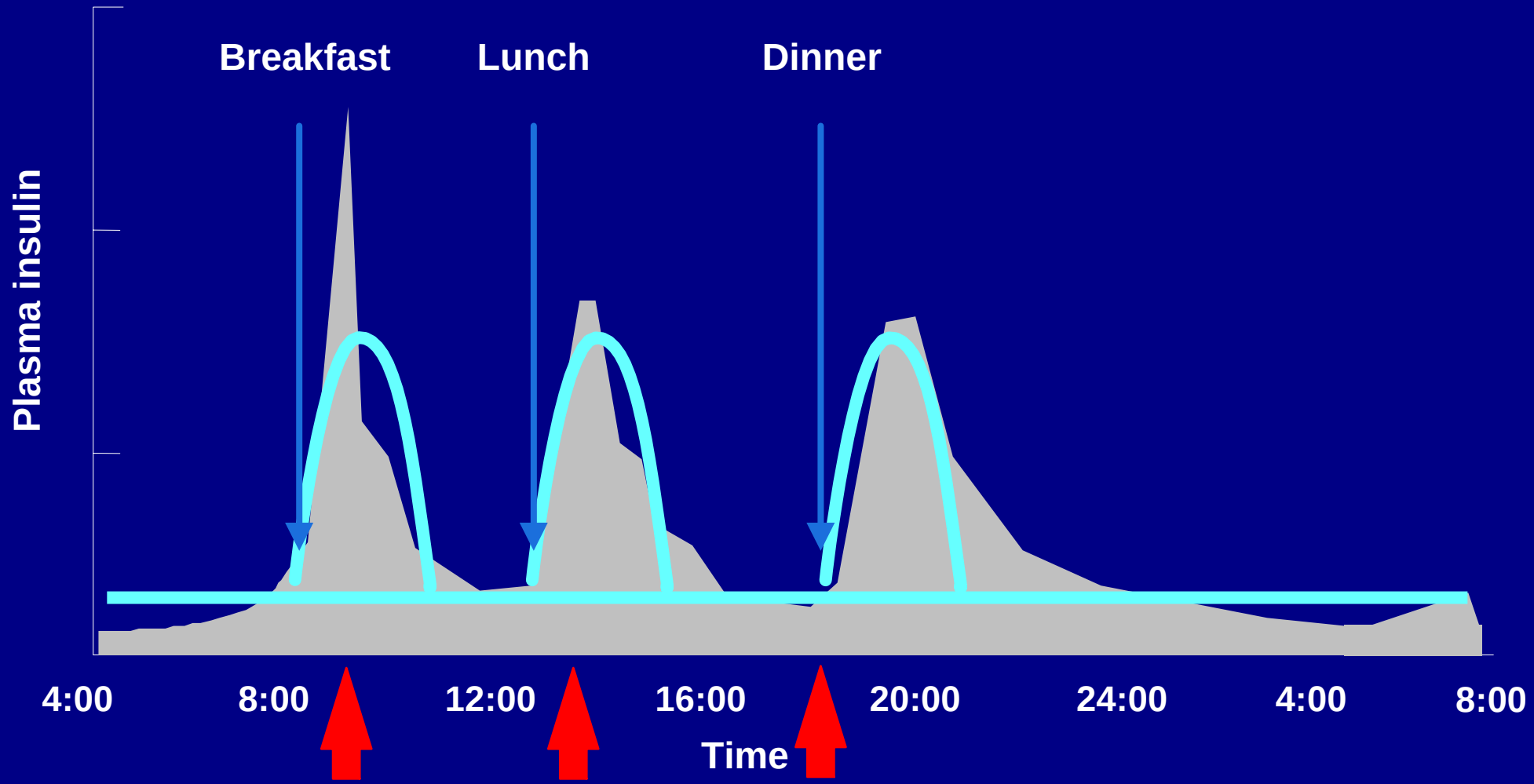
Patient J.L., December 15, 1922

February 15, 1923

Comparison of Human Insulins/Analogs

Insulin Preparations	Onset of Action	Peak	Duration of Action
Regular	30-60 min	2-4 h	6-10 h
NPH/lente	1-2 h	4-8 h	10-20 h
Ultralente	2-4 h	Unpredictable	16-20 h
Lispro/aspart	5-15 min	1-2 h	4-6 h
Glargine	1-2 h	Flat	~24 h

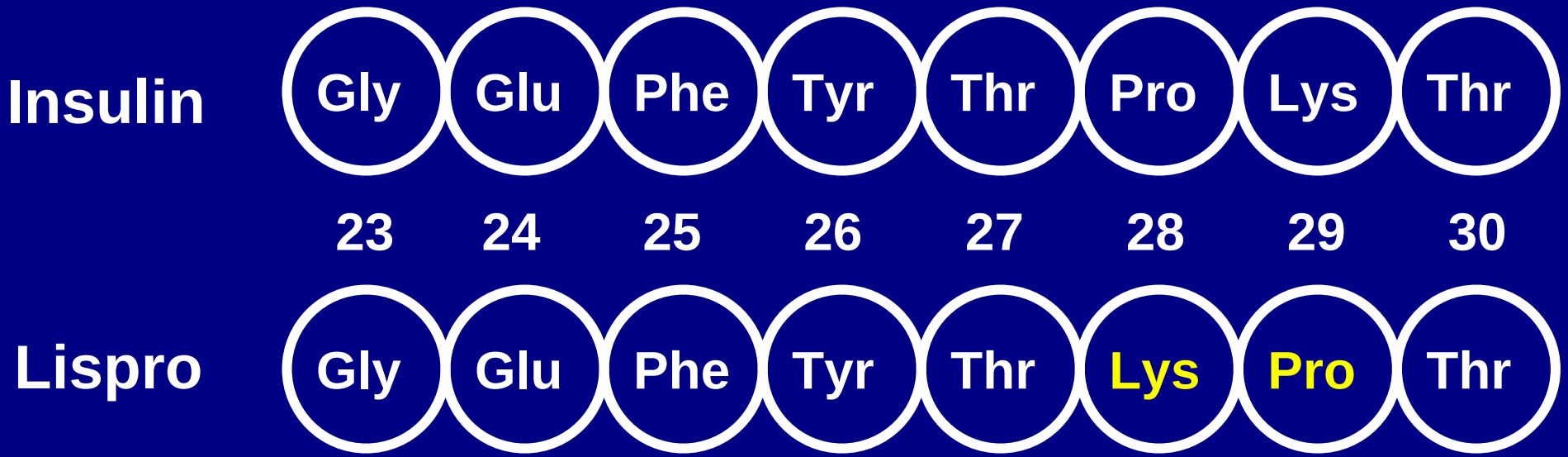
Ideal Basal/Bolus Insulin Absorption Pattern



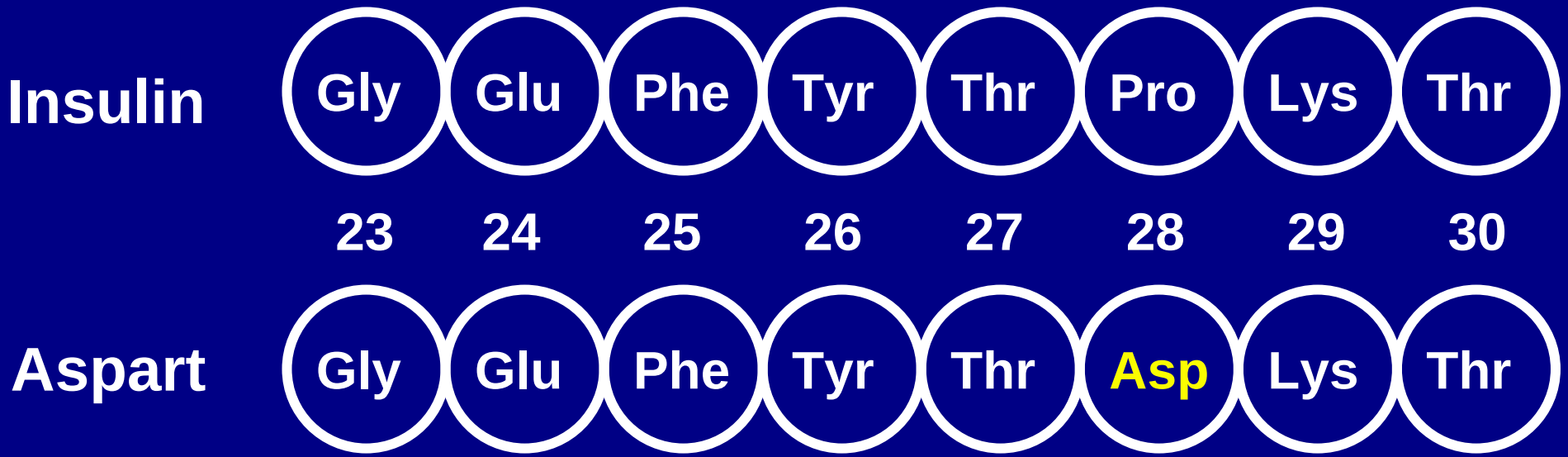
Rapid-acting Insulin Analogs: Medical Rationale

- Administration at mealtime
- Mimic physiologic insulin profile
- Improved postprandial glycemic control
- Lower risk of late hypoglycemia

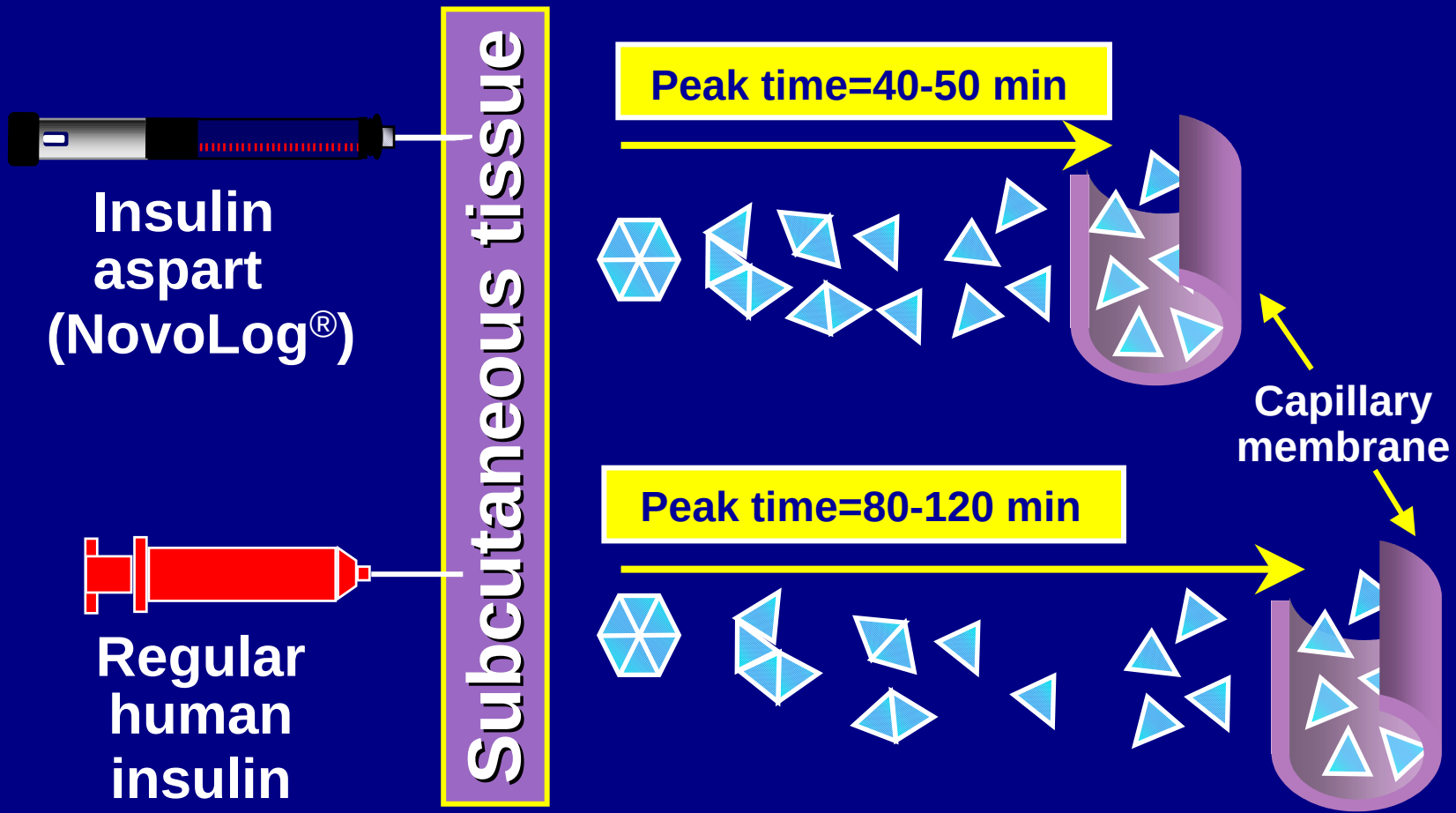
Primary Structure of Lys(B28), Pro(B29)–Insulin



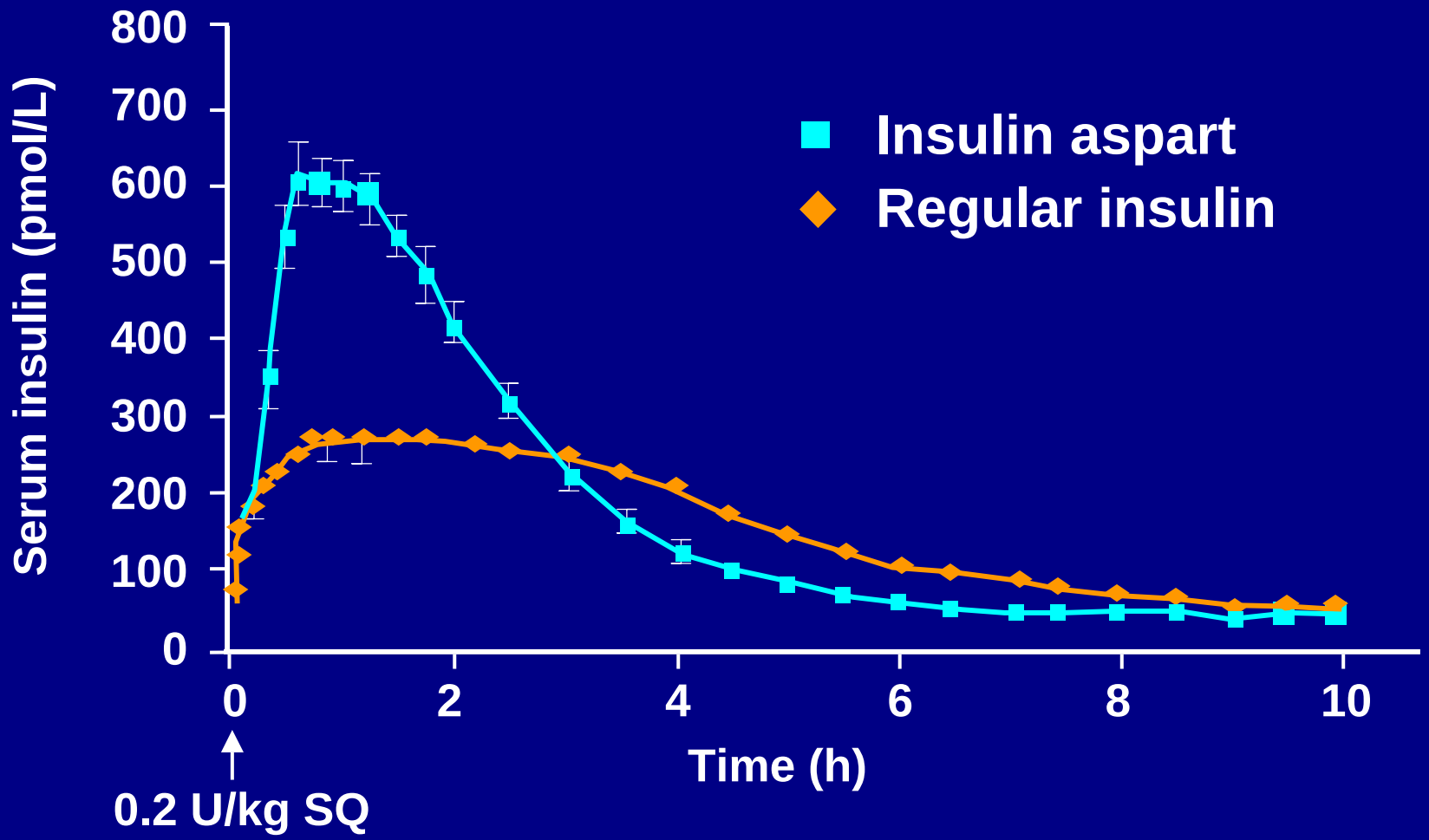
Primary Structure of Asp(B28)-Insulin



Dissociation and Absorption of NovoLog®

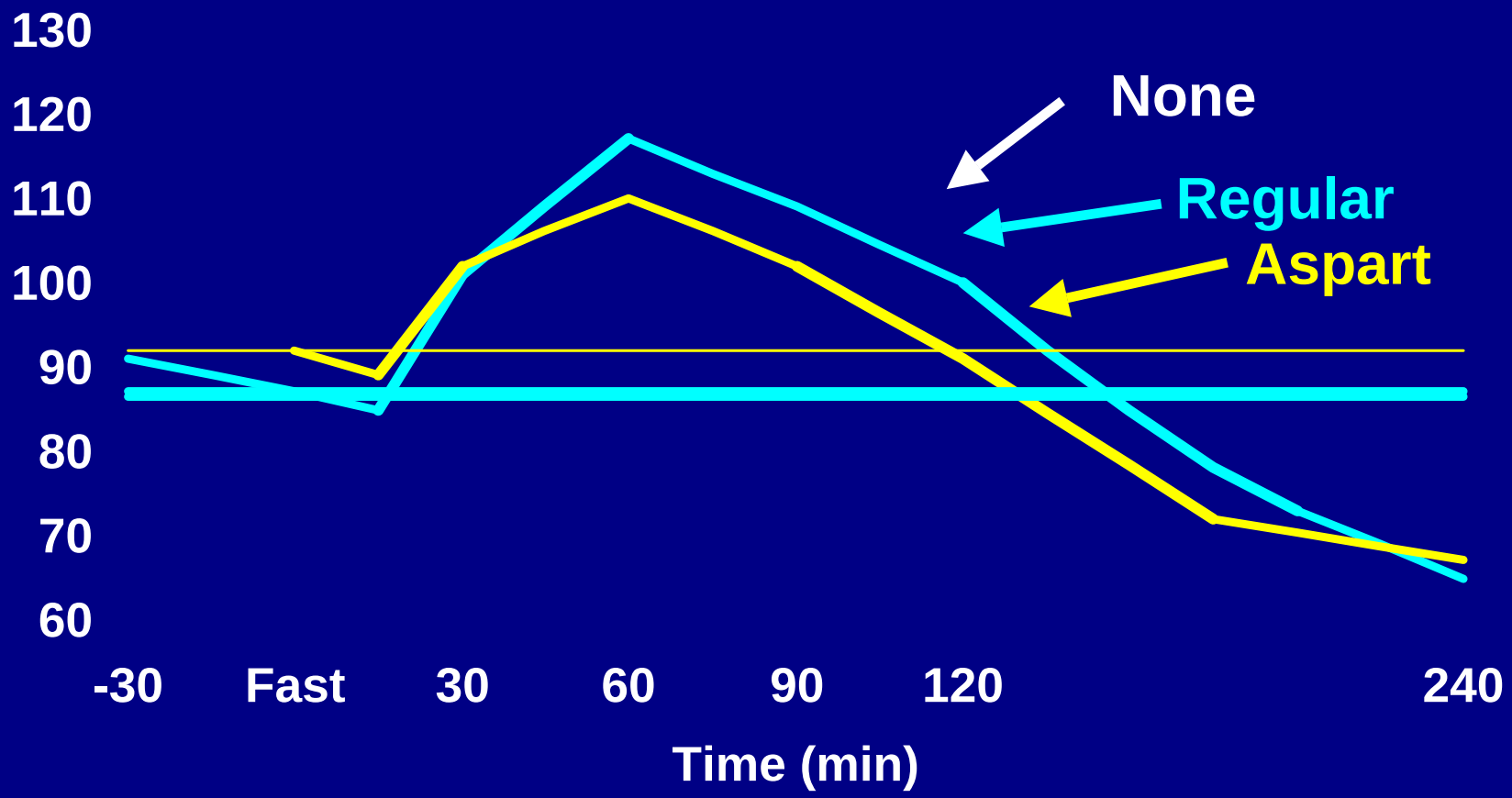


Insulin Aspart: Mean Serum Insulin Profiles During Euglycemic Clamp in Healthy Volunteers

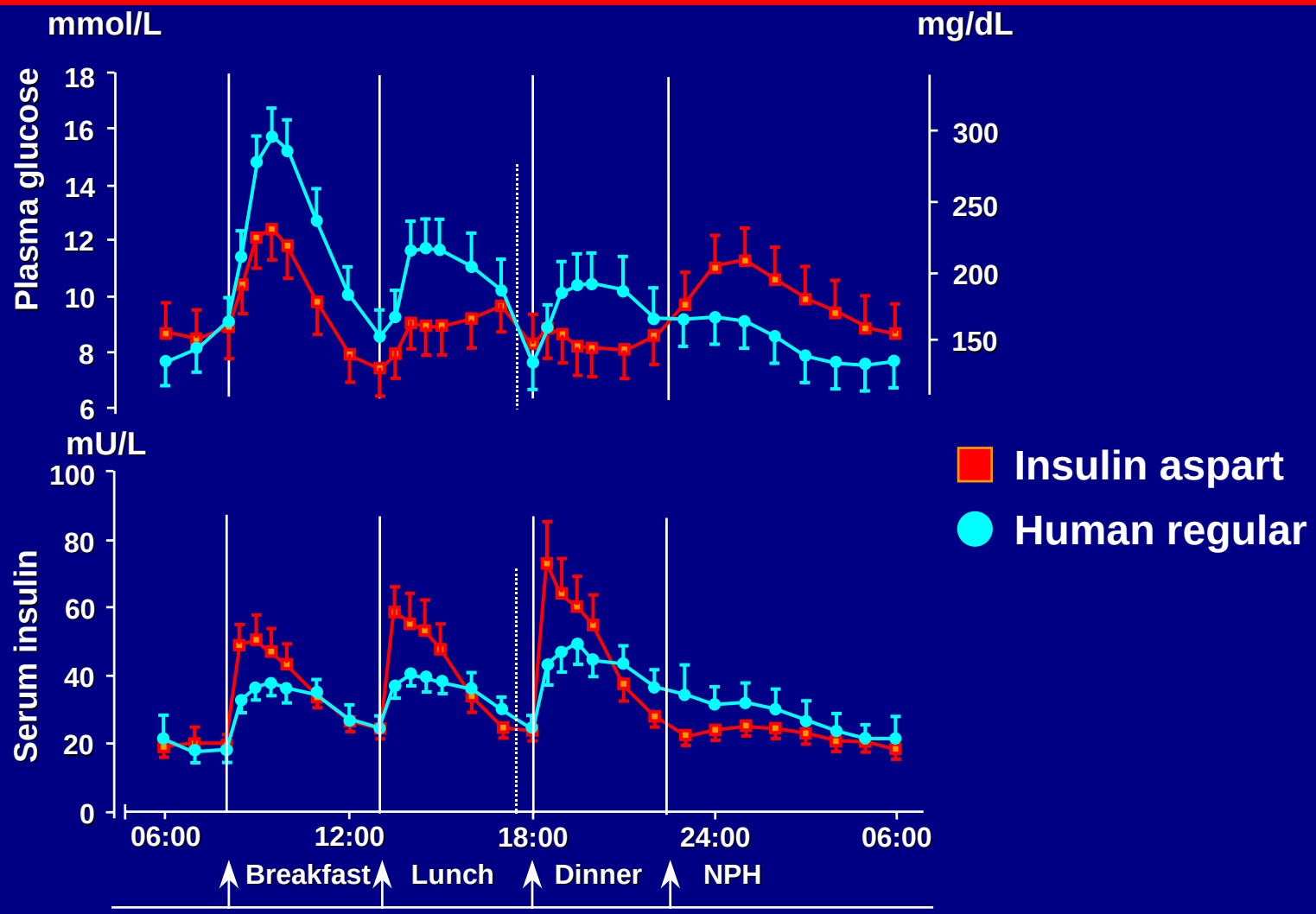


Heinemann L, et al. *Diabetes Care.* 1998;21:1910.

Glucose Area Under the Curve

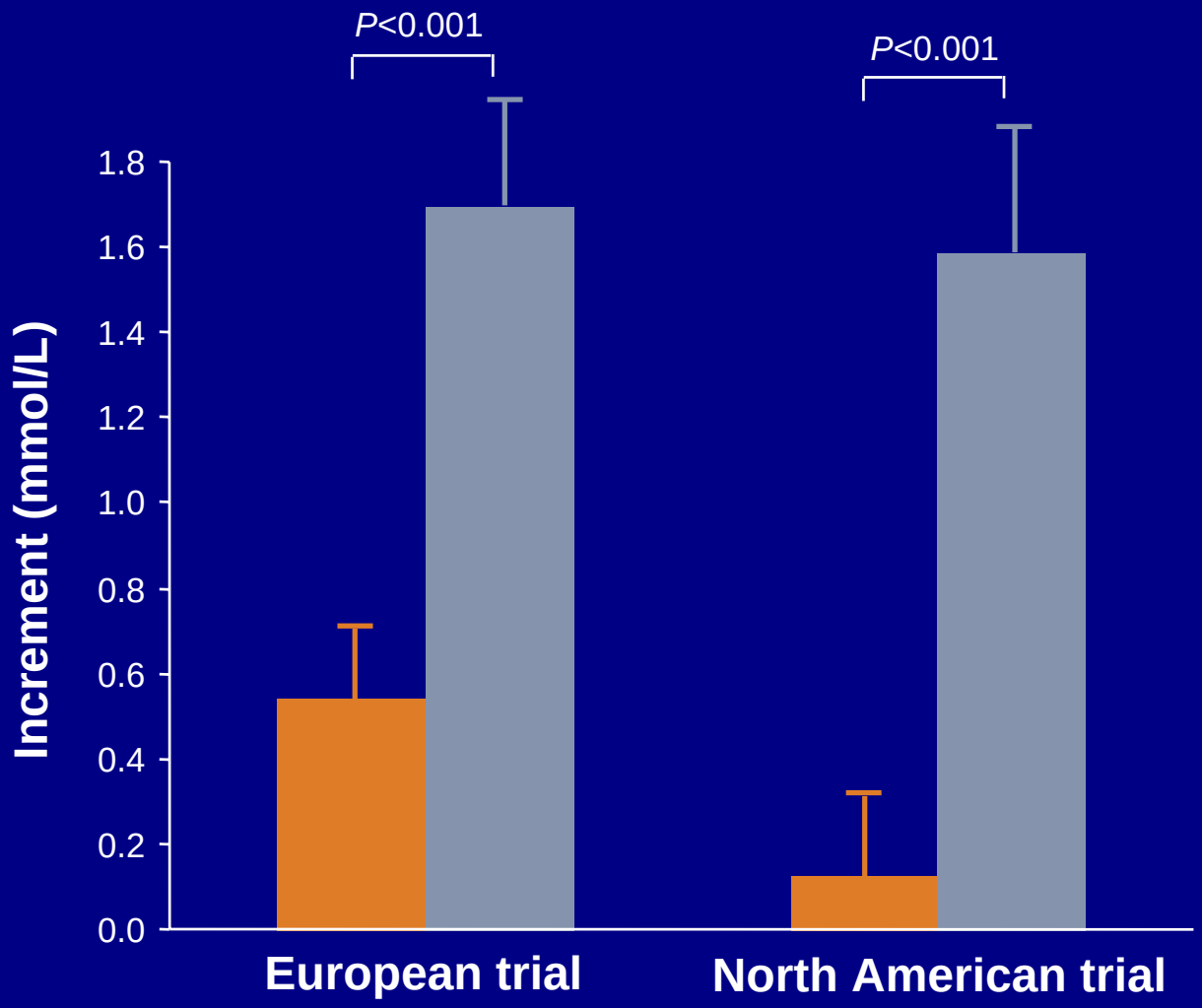


Insulin Aspart vs Human Regular: Glycemic Control



Home PD, et al. *Diabetes Care.* 1998;21:1904-1909.

Postprandial Blood Glucose Increment (Mean over the 3 Meals at 6 Months)



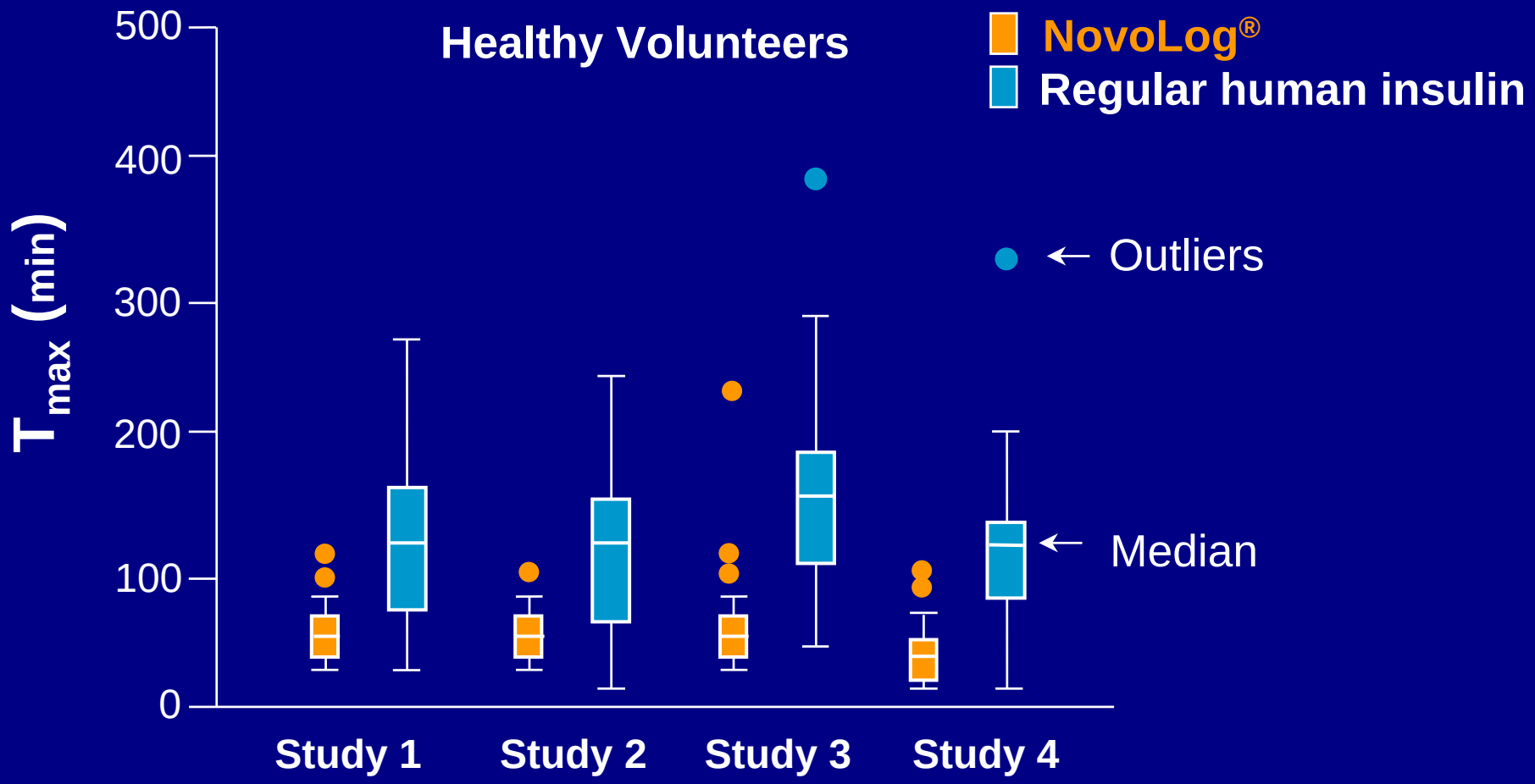
NovoLog®

Regular human insulin

Prandial increment is the increase in blood glucose from premeal to 90 minutes postmeal

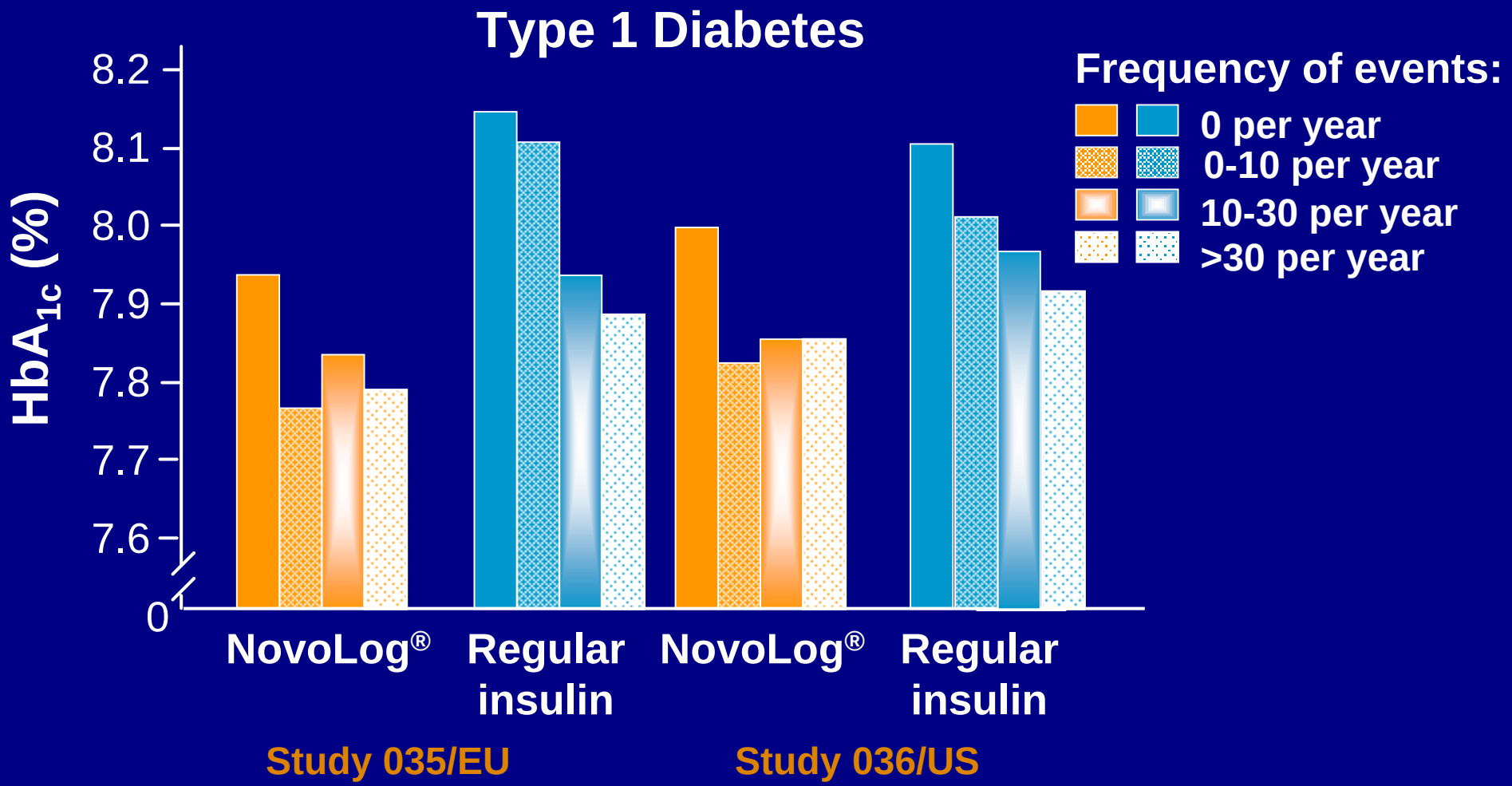
Raskin P, et al. *Diabetes Care. 2000*;23:583.
Home PD, et al. *Diabet Med*. 2000;17:762.

Decreased Interindividual Variability in NovoLog® Values for T_{max}



***Data from*:**
Home. *Eur J Clin Pharmacol.* 1999;55:199-203.
Heinemann. *Diabet Med.* 1996;13:683-684.
Mudaliar. *Diabetes Care.* 1999;22:1501-1506.
Heinemann. *Diabetes Care.* 1998;21:1910-1914.

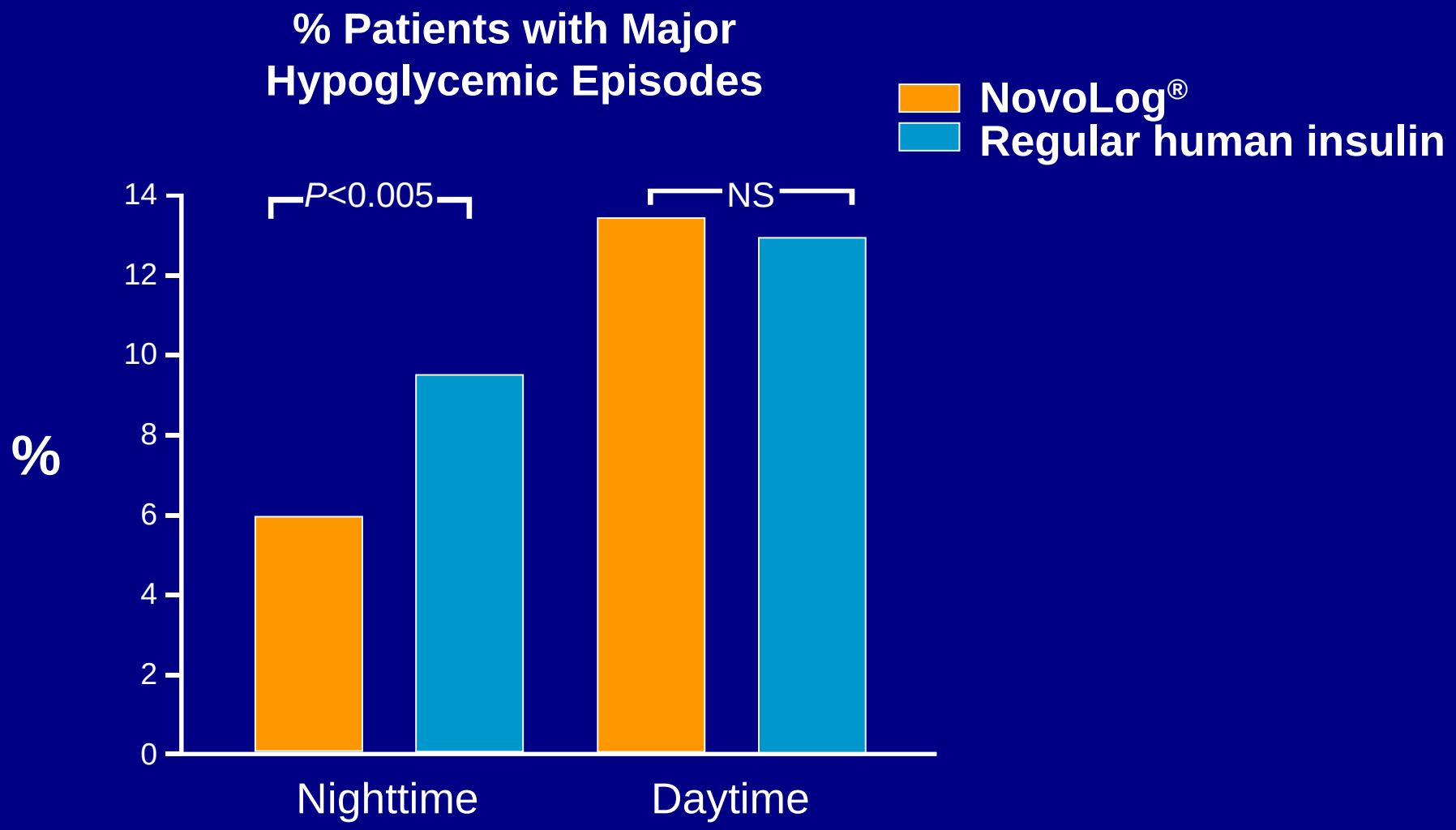
Frequency of Minor* Hypoglycemia Observed by Level of Glycemic Control



*Symptoms or blood glucose <45 mg/dL.

Data on file, Novo Nordisk. Studies 035/EU, 036/US.

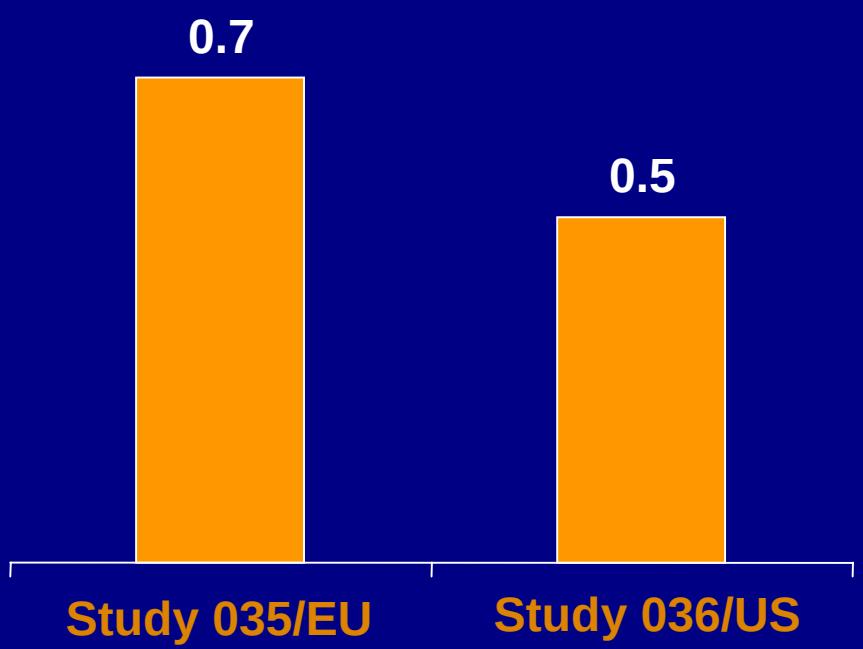
Reduced Reporting of Major Nocturnal Hypoglycemia



Data on file, Novo Nordisk. Studies 035/EU, 036/US.

Reduced Risk of Major Nocturnal Hypoglycemia

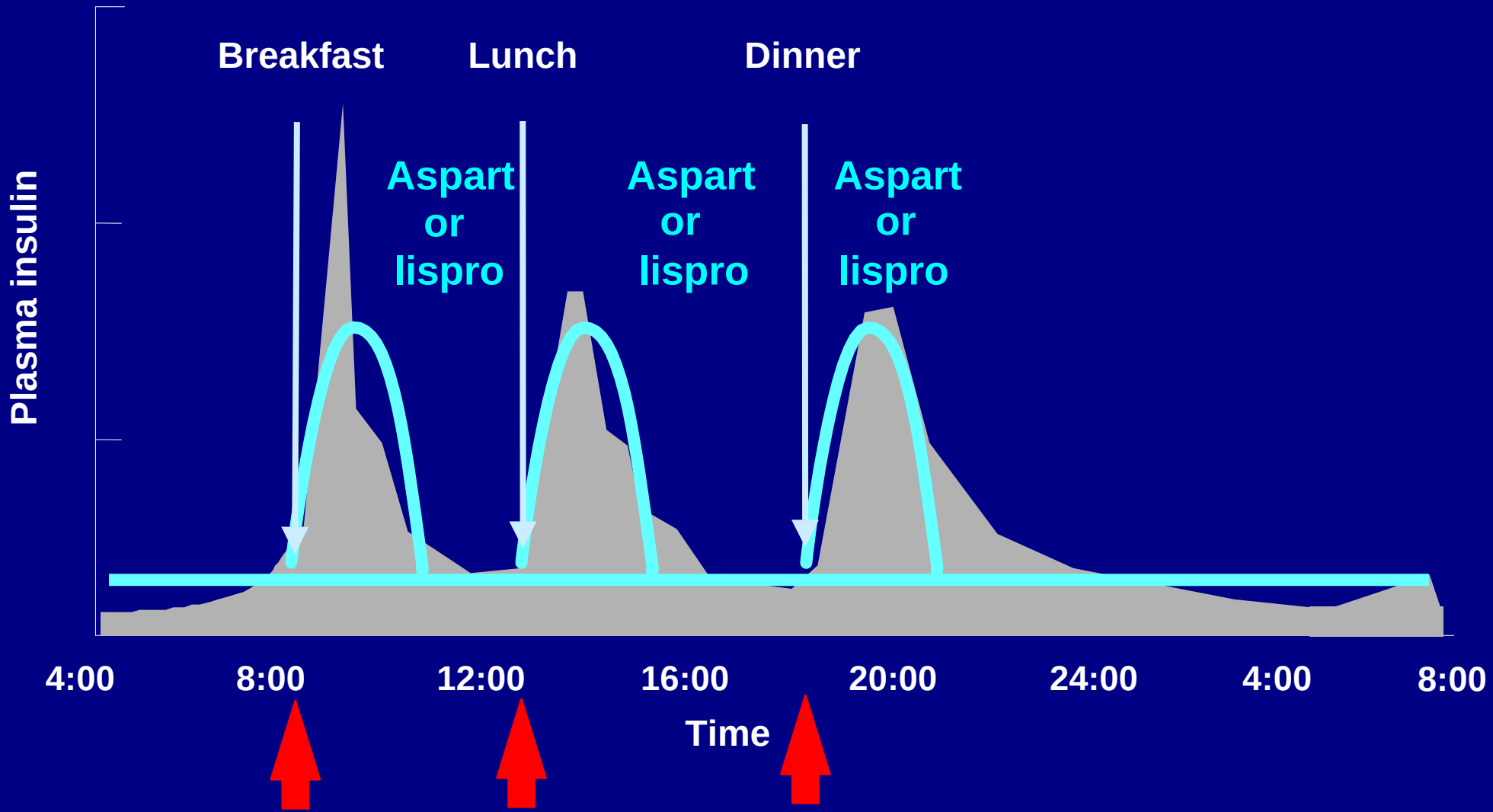
Relative Risk
NovoLog Compared with Regular Human Insulin



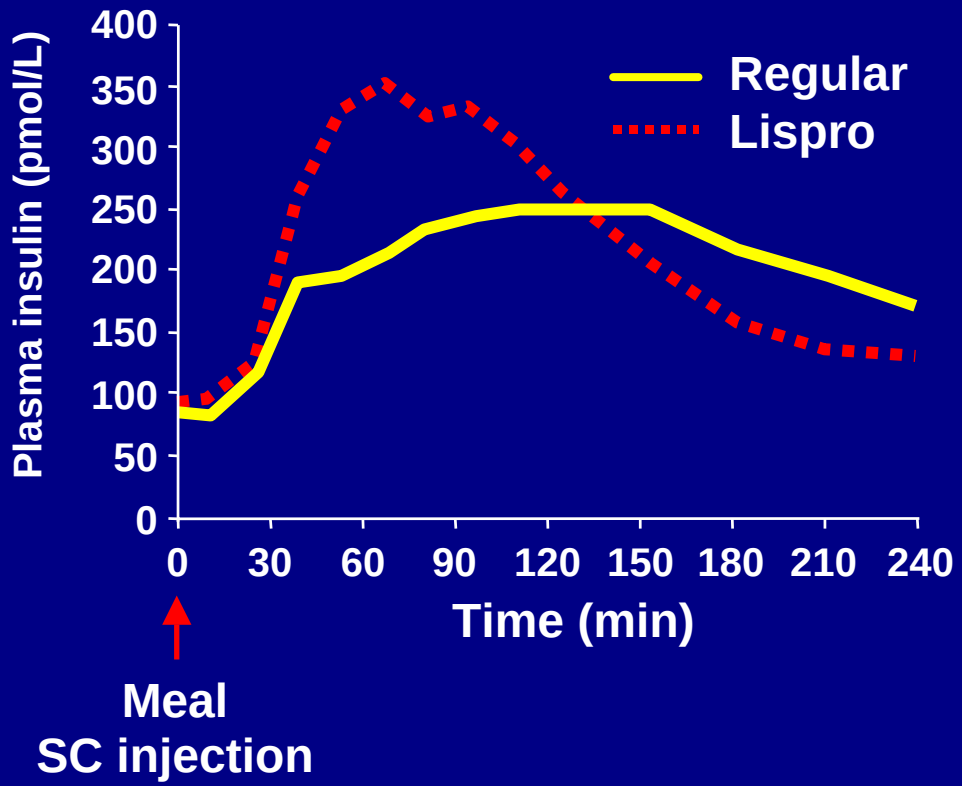
	NovoLog®	Human Insulin
	(No. of Patients with Events)	
Home	8% (54/707)	11% (39/358)
Raskin	4% (24/596)	8% (23/286)

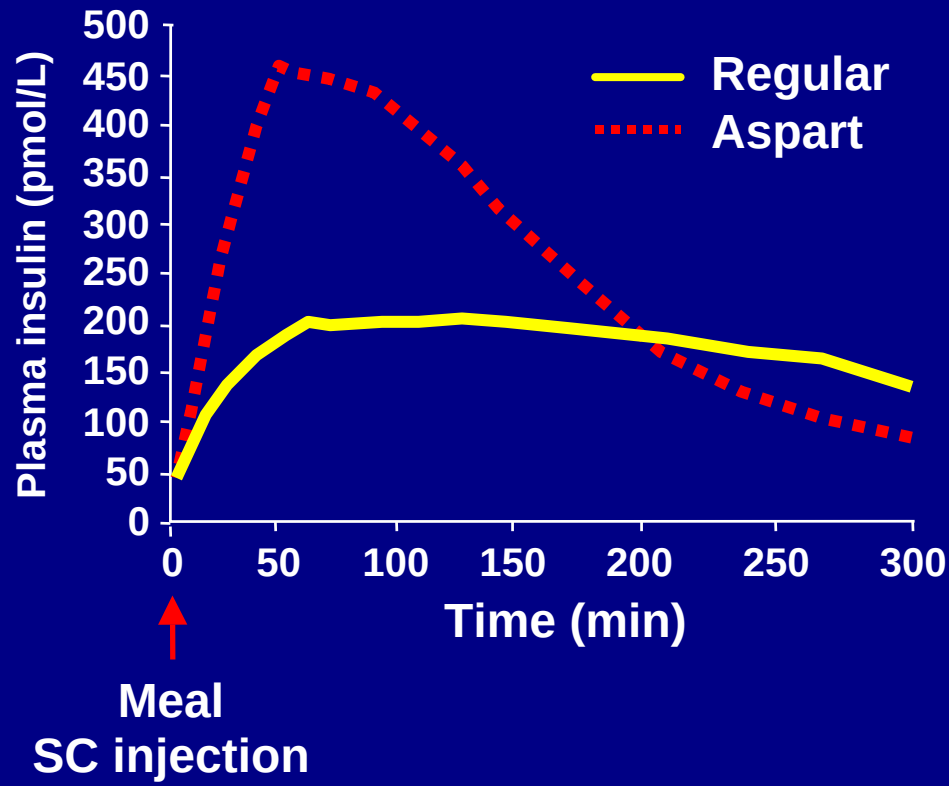
Data on file, Novo Nordisk. Studies 035/EU, 036/US.

Rapid-acting Insulin Analogs Provide Ideal Prandial Insulin Profile



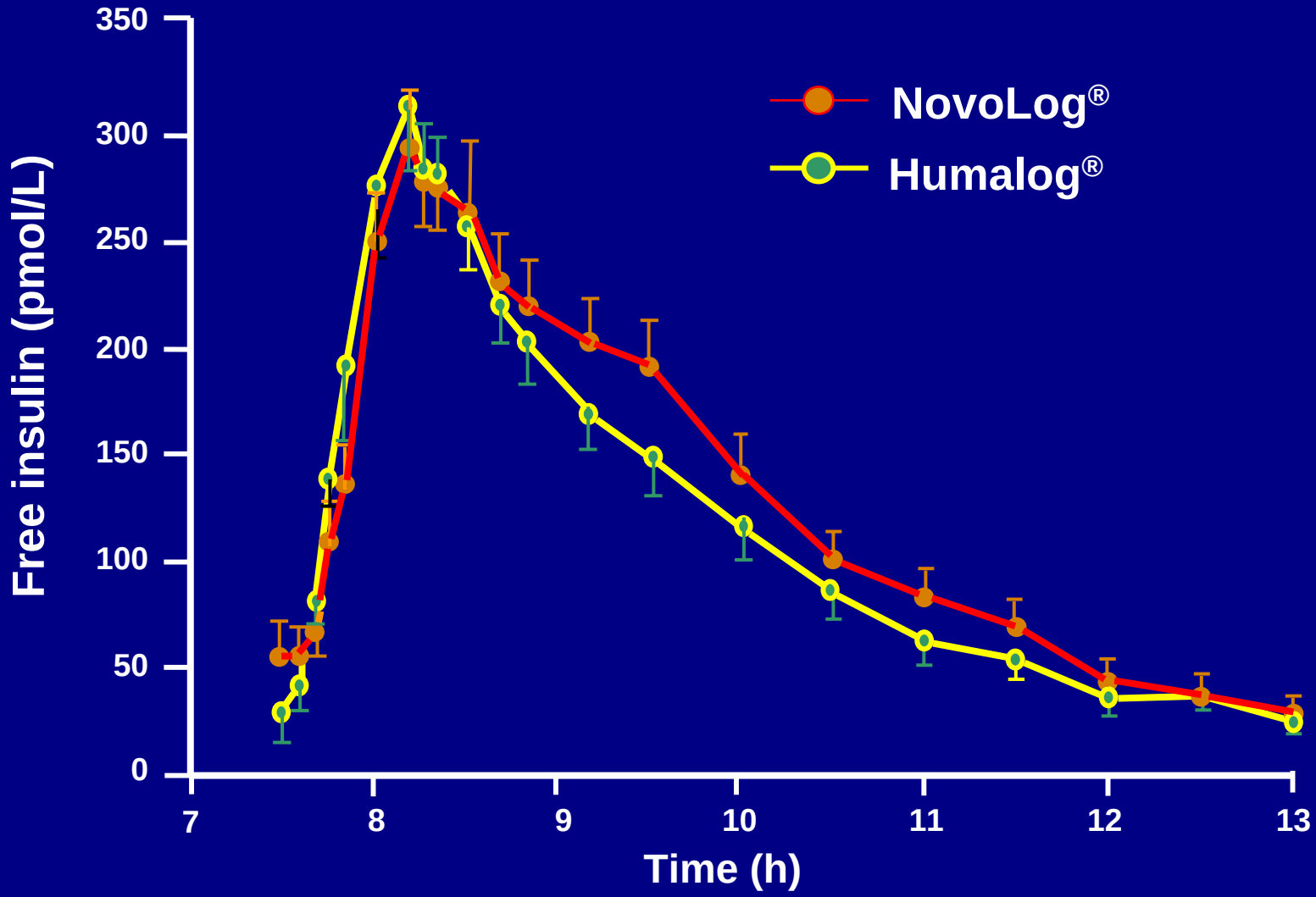
Short-acting Insulin Analogs: Lispro and Aspart Plasma Insulin Profiles





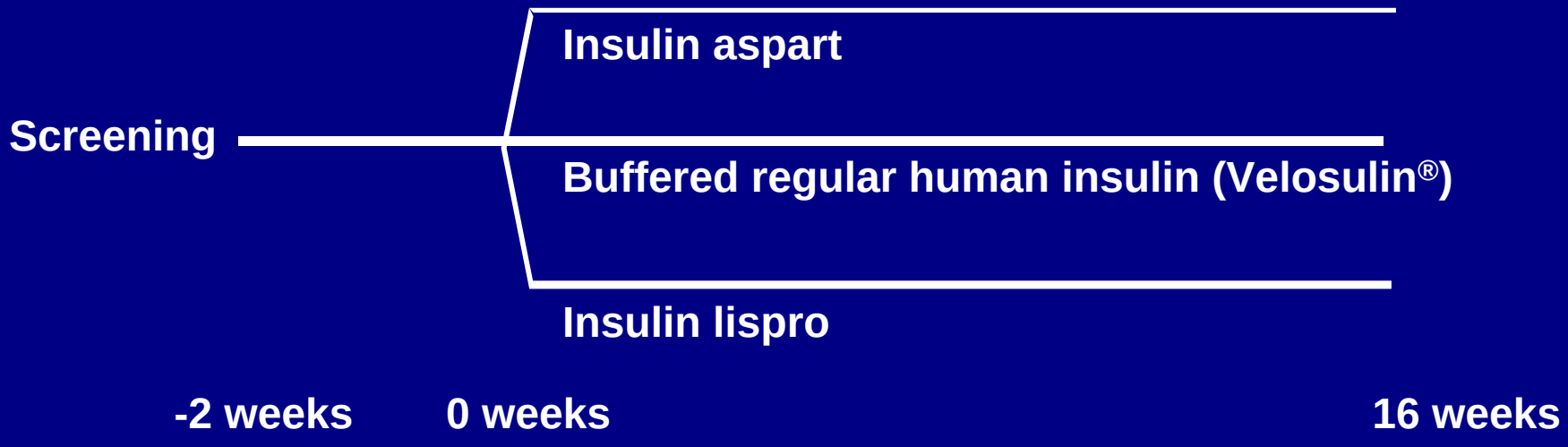
Heinemann, et al. *Diabet Med*. 1996;13:625-629.
Mudaliar SR, et al. *Diabetes Care*. 1999;22:1501-1506.

Pharmacokinetic Comparison: NovoLog® vs Humalog®



Hedman CA, et al. *Diabetes Care.* 2001;24:1120-1121.

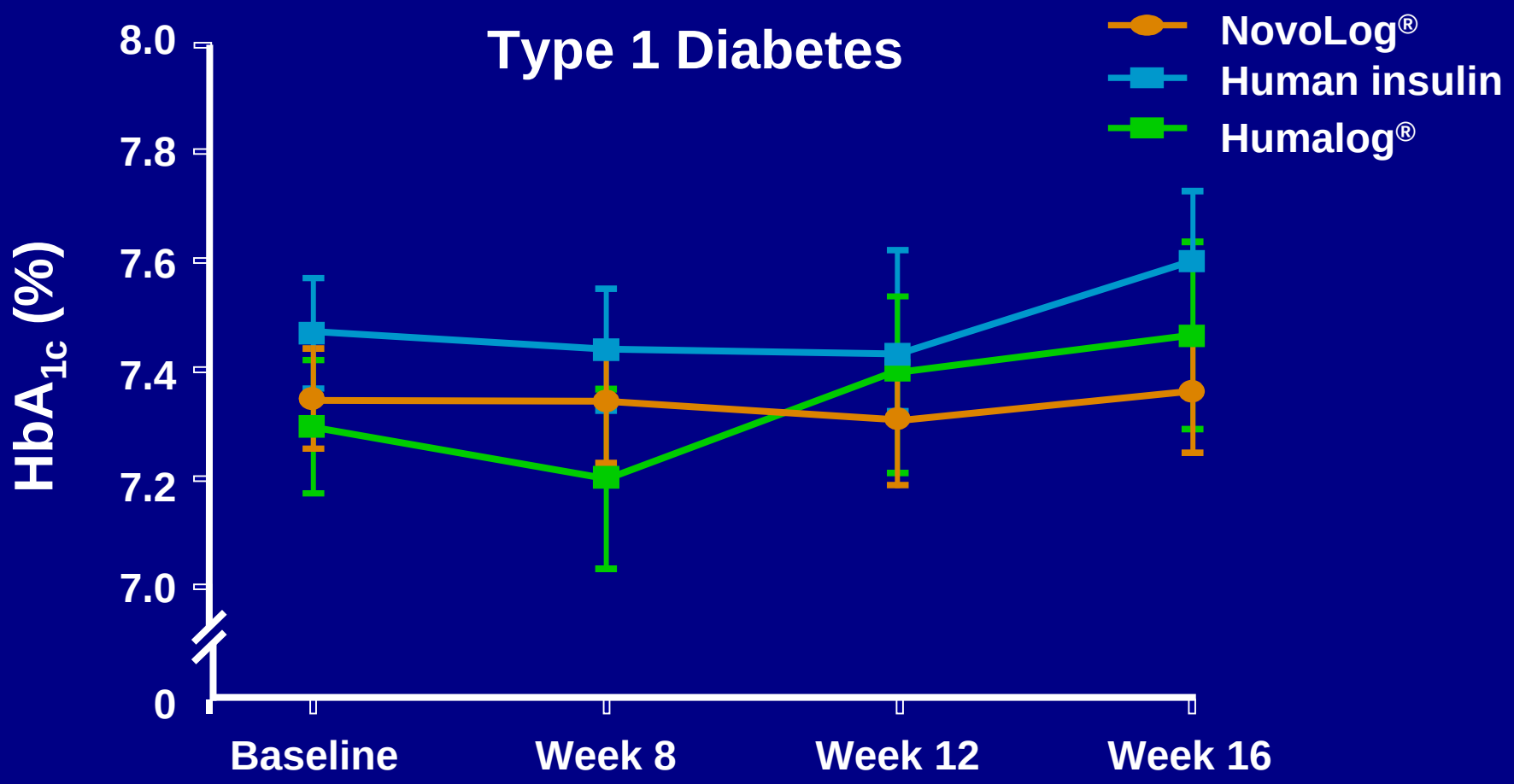
Insulin Aspart vs Buffered R vs Insulin Lispro in CSII Study



- 146 patients in the USA; 2-25 years with type 1 diabetes; $7\% \leq HbA_{1c} \leq 9\%$; previously treated with CSII for 3 months

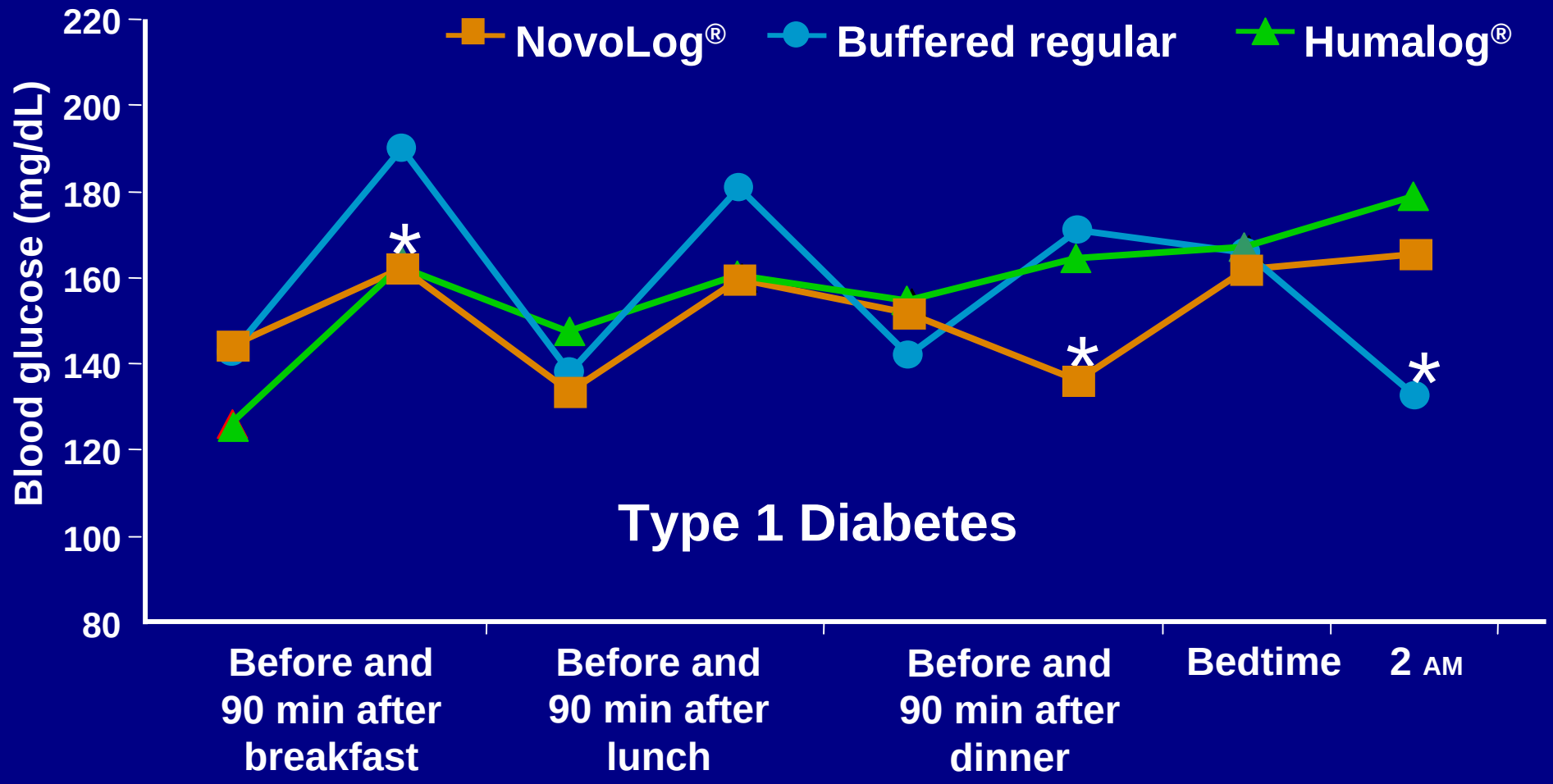
Bode B, et al. *Diabetes Care*. 2002;25:439-444.

Glycemic Control with CSII



Bode B. *Diabetes.* 2001;50(S2):A106.

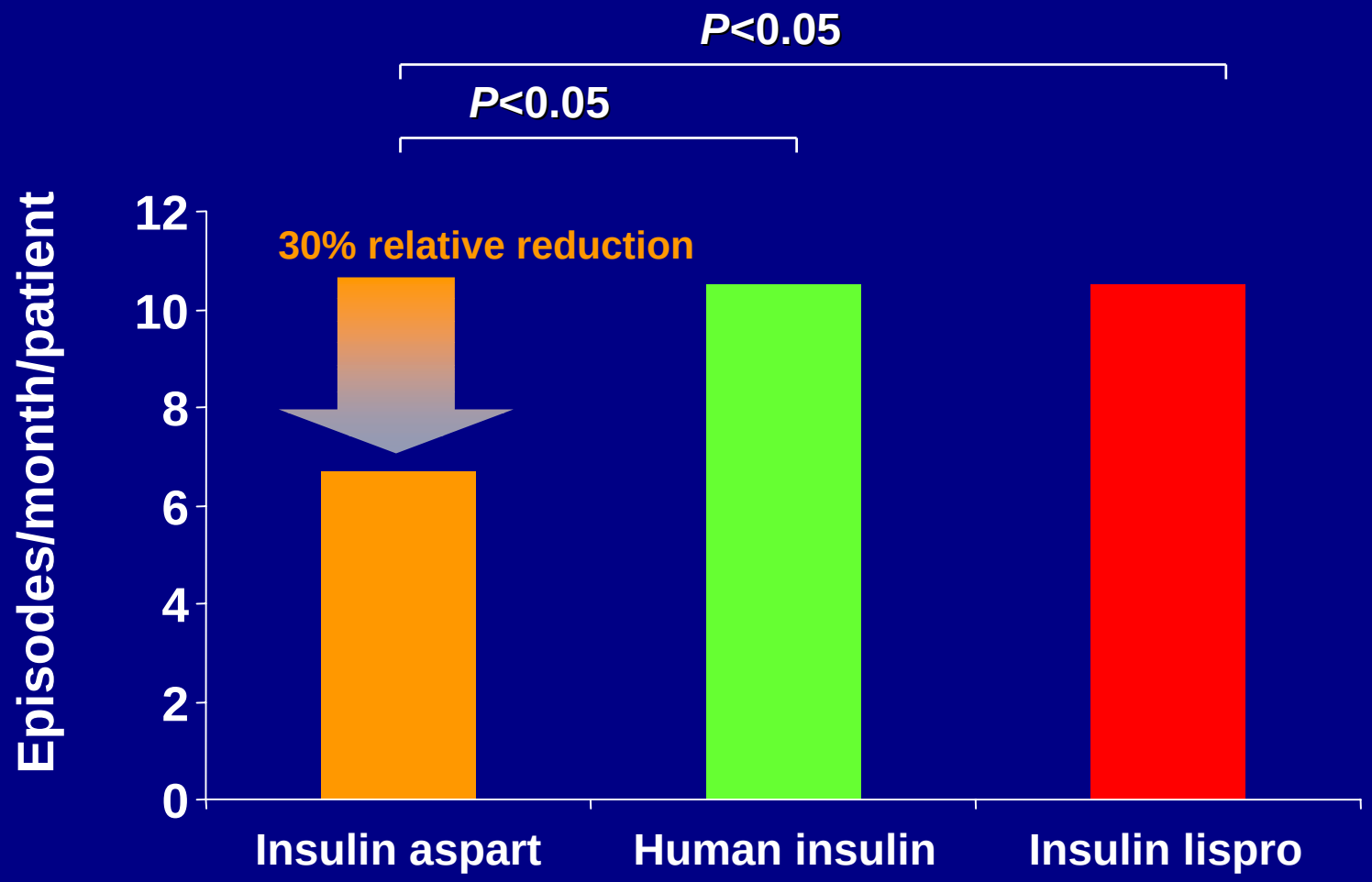
Self-monitored Blood Glucose in CSII



*P<0.01 vs buffered regular insulin.

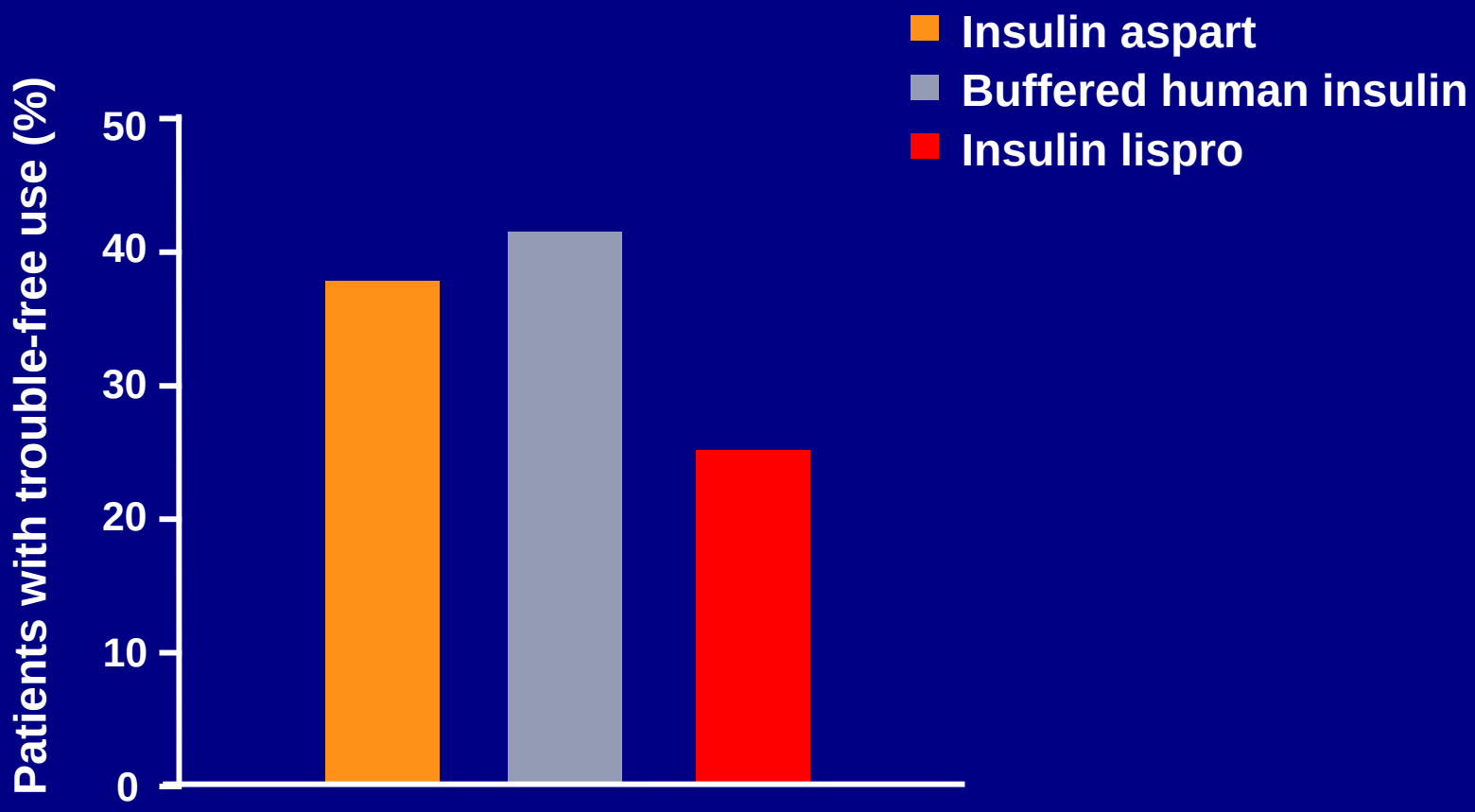
Bode B. *Diabetes.* 2001;50(S2):A106.

Symptomatic or Confirmed Hypoglycemia



Bode B, et al. *Diabetes Care*. 2002;25:439-444.

Insulin Aspart vs Buffered R vs Insulin Lispro in CSII Study: Pump Compatibility



Data on file, Novo Nordisk. Study ANA 2024.

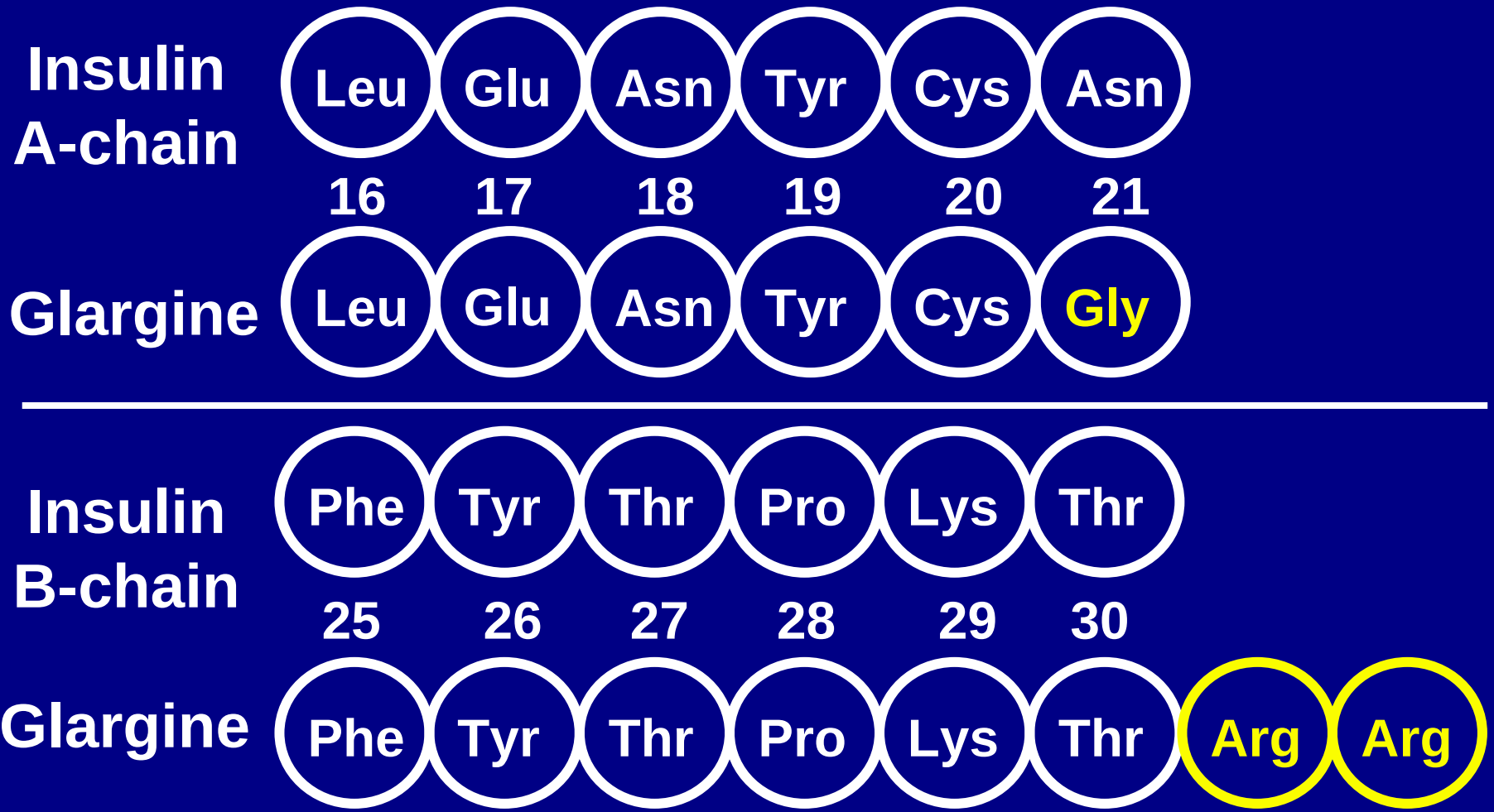
Long-acting Soluble Insulin Analogs: Medical Rationale

- Mimic basal physiological insulin profile
- Improved glycemic control
- More reproducible insulin delivery
- May be used in insulin pens

Limitations of NPH, Lente, and Ultralente

- Do not mimic basal insulin profile
  - Variable absorption
  - Pronounced peaks
  - Less than 24-hour duration of action
- Cause unpredictable hypoglycemia
  - Major factor limiting insulin adjustments

Primary Structure of Gly(A21), Arg(B31), Arg(B32)-Insulin

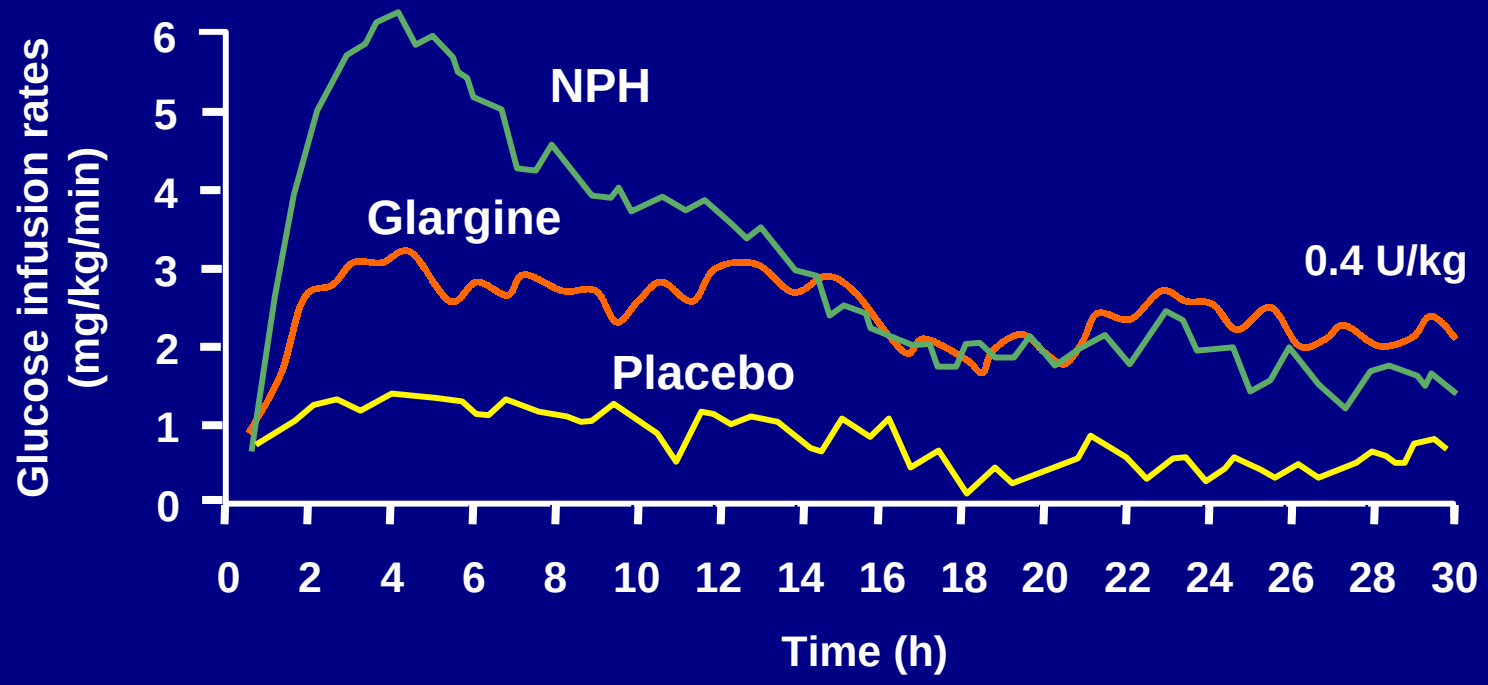


Primary Structure of Lys(B29)-N-ε-Tetradecanoyl, Des(B30)-Insulin

Basis of Effect of Insulin Glargine

- Isoelectric point change
- Precipitates at neutral tissue pH
  - Acid in solution; cannot be mixed with other insulins
- Retarded absorption rate
- Corresponding longer duration of action

Insulin Glargine in Nondiabetic Subjects: Pharmacokinetics by Glucose Clamp



Linkeschowa R, et al. *Diabetes*.1999;48(suppl 1):A97.

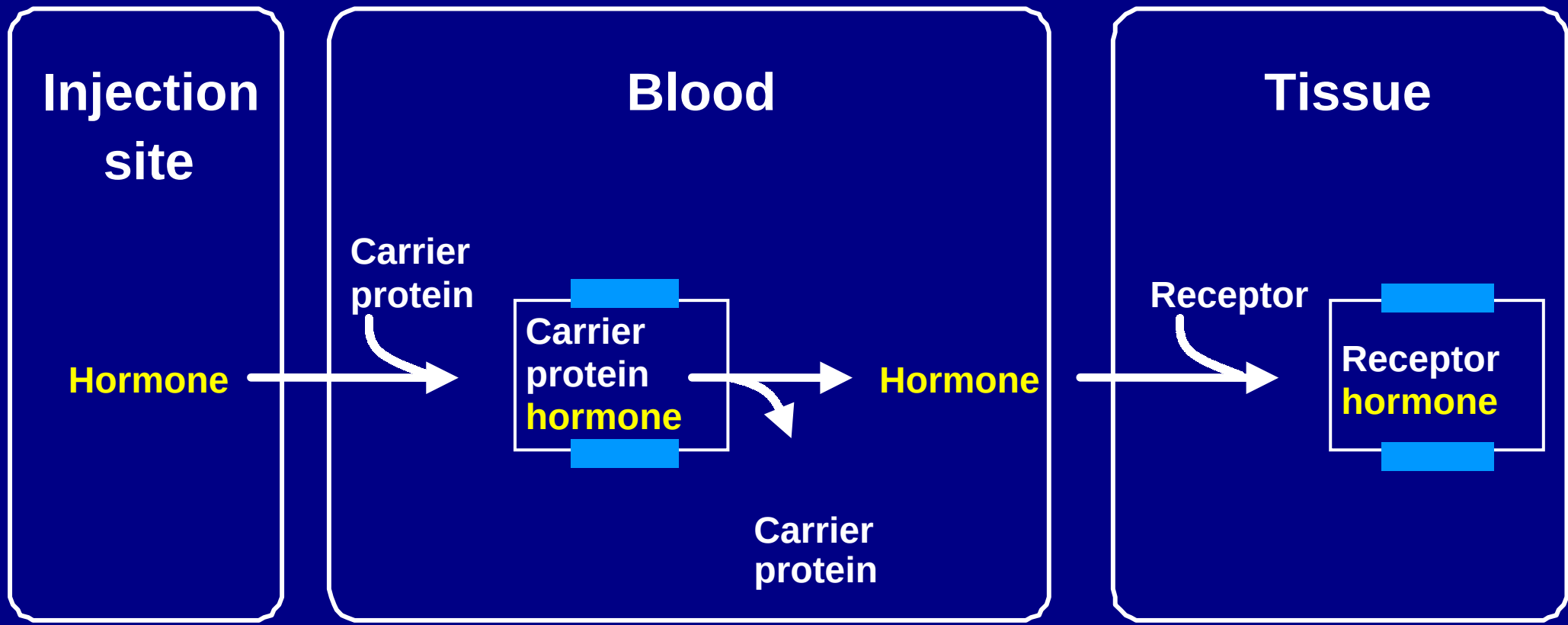
Overall Summary: Glargine

- Insulin glargine has the following clinical benefits:
  - Once-daily dosing because of its prolonged duration of action and smooth, peakless time-action profile
  - Comparable or better glycemic control (FBG)
  - Lower risk of nocturnal hypoglycemic events
  - Safety profile similar to that of human insulin

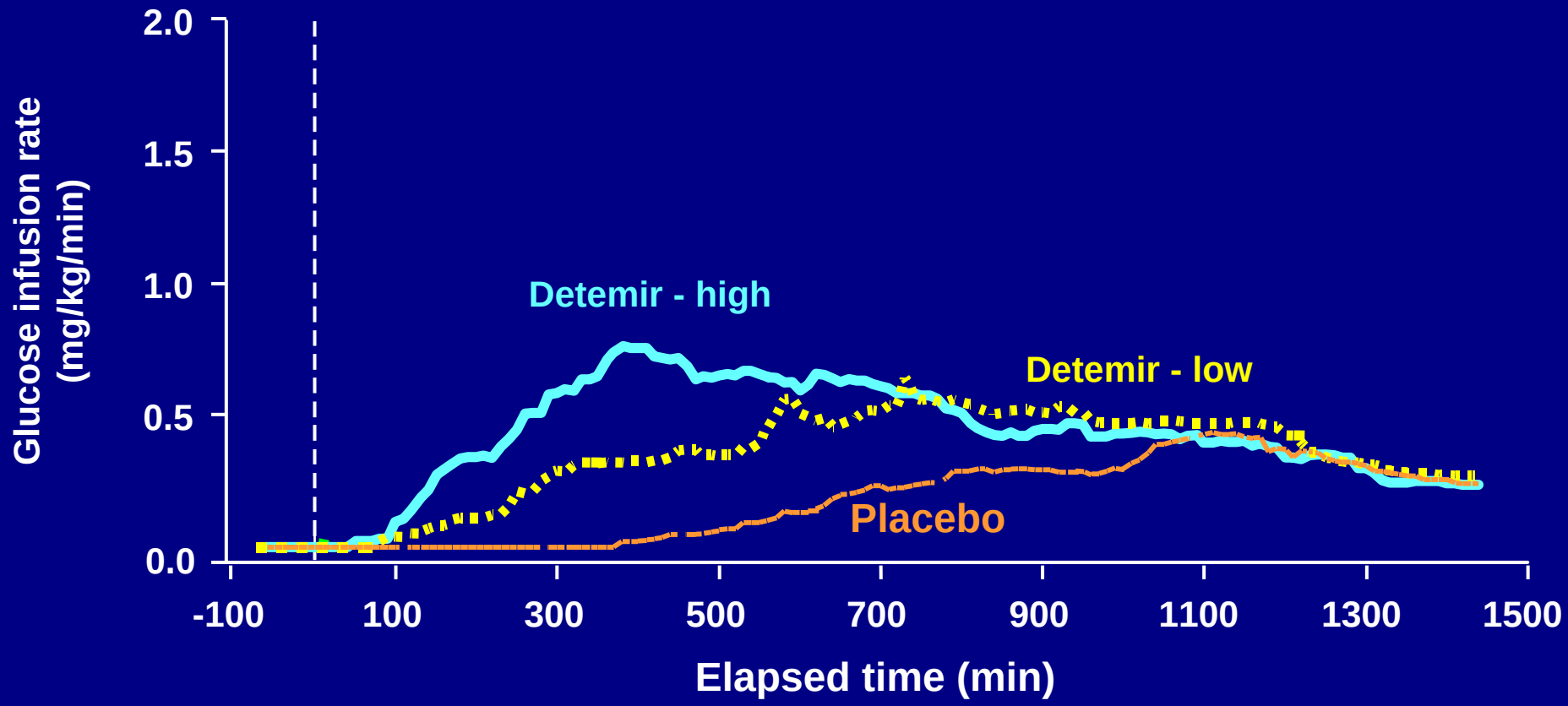
Basis of Effect of Acylated Insulin Analogs (Detemir)

- Bind to serum albumin
- Prolonged time in circulation
- Longer duration of action

Use of a Serum Carrier Protein (eg, Albumin) to Extend Time of Action

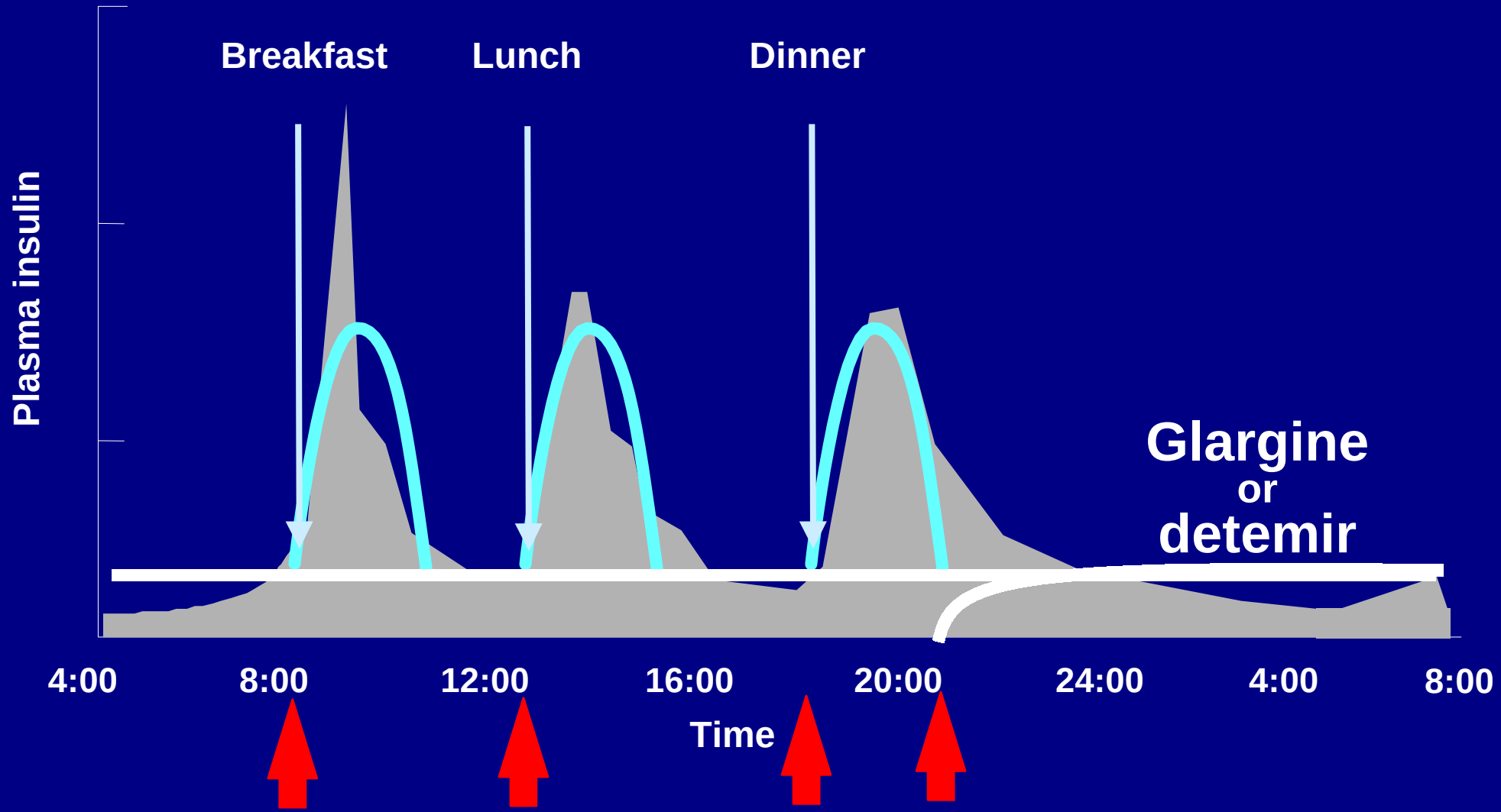


Insulin Detemir in Nondiabetic Subjects: Pharmacokinetics by Glucose Clamp

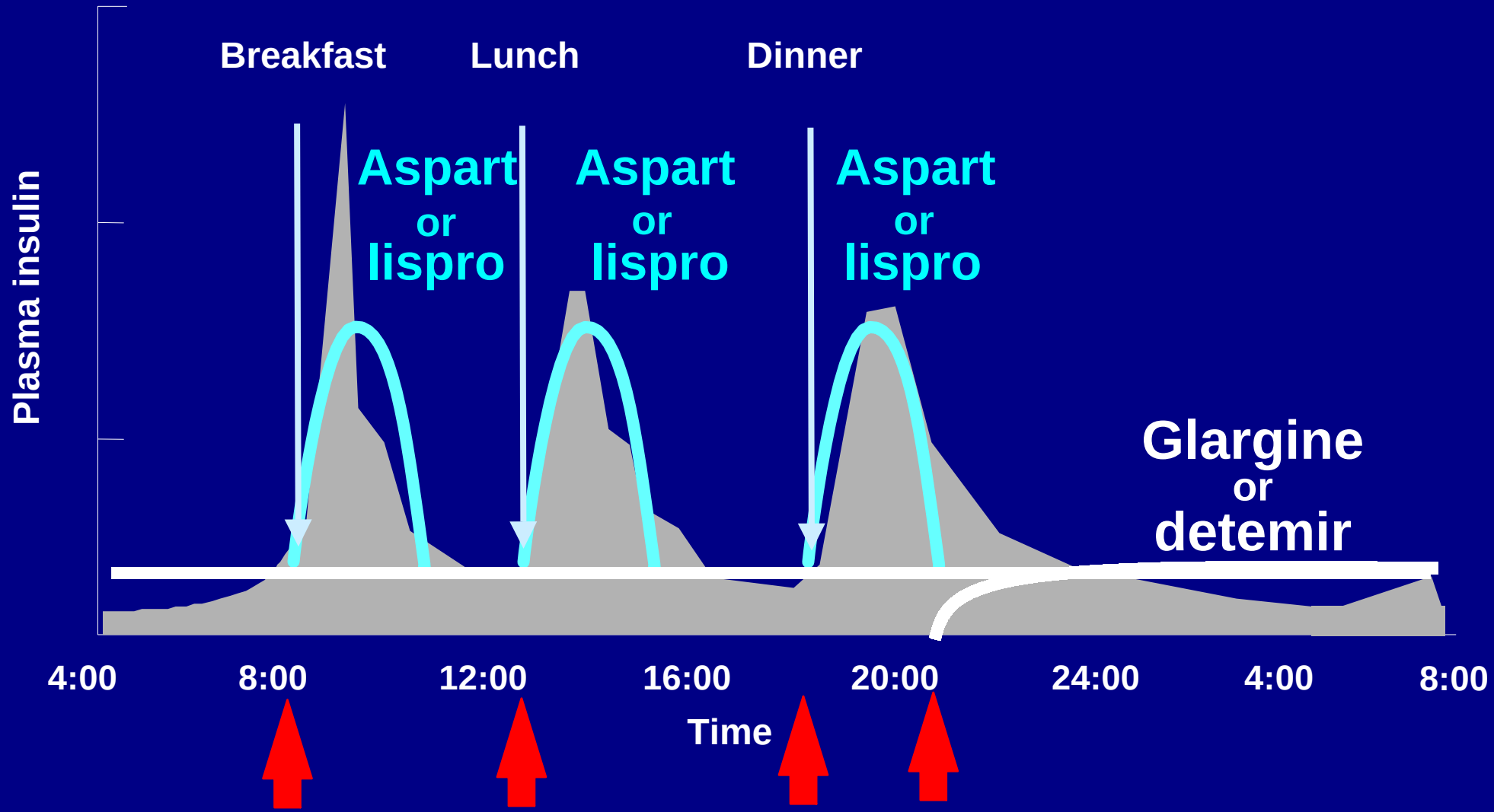


Brunner GA, et al. *Exp Clin Endocrinol Diabetes.* 2000;108:100-105.

Long-acting Insulin Analogs Provide Ideal Basal Insulin Profile



Basal/Bolus Treatment Program with Rapid-acting and Long-acting Analogs



Receptor Binding Affinities

	Insulin Receptor Affinity (%)		IGF-1 Receptor Affinity (%)	
	Cells	Solubilized Receptors	Cells	Solubilized Receptors
	Relative to human insulin		Relative to human insulin	
Human insulin	100	100	100	100
Insulin aspart	92	92	69	81
Insulin lispro	102	ND	142	156
Insulin glargine	ND	86	ND	641

ND = not determined.

Insulin Analogs

Fulfilling the Promise of Recombinant DNA Technology:

Better Basal
Better Bolus
Better Blood Glucose