New Insulins and Insulin Delivery Systems

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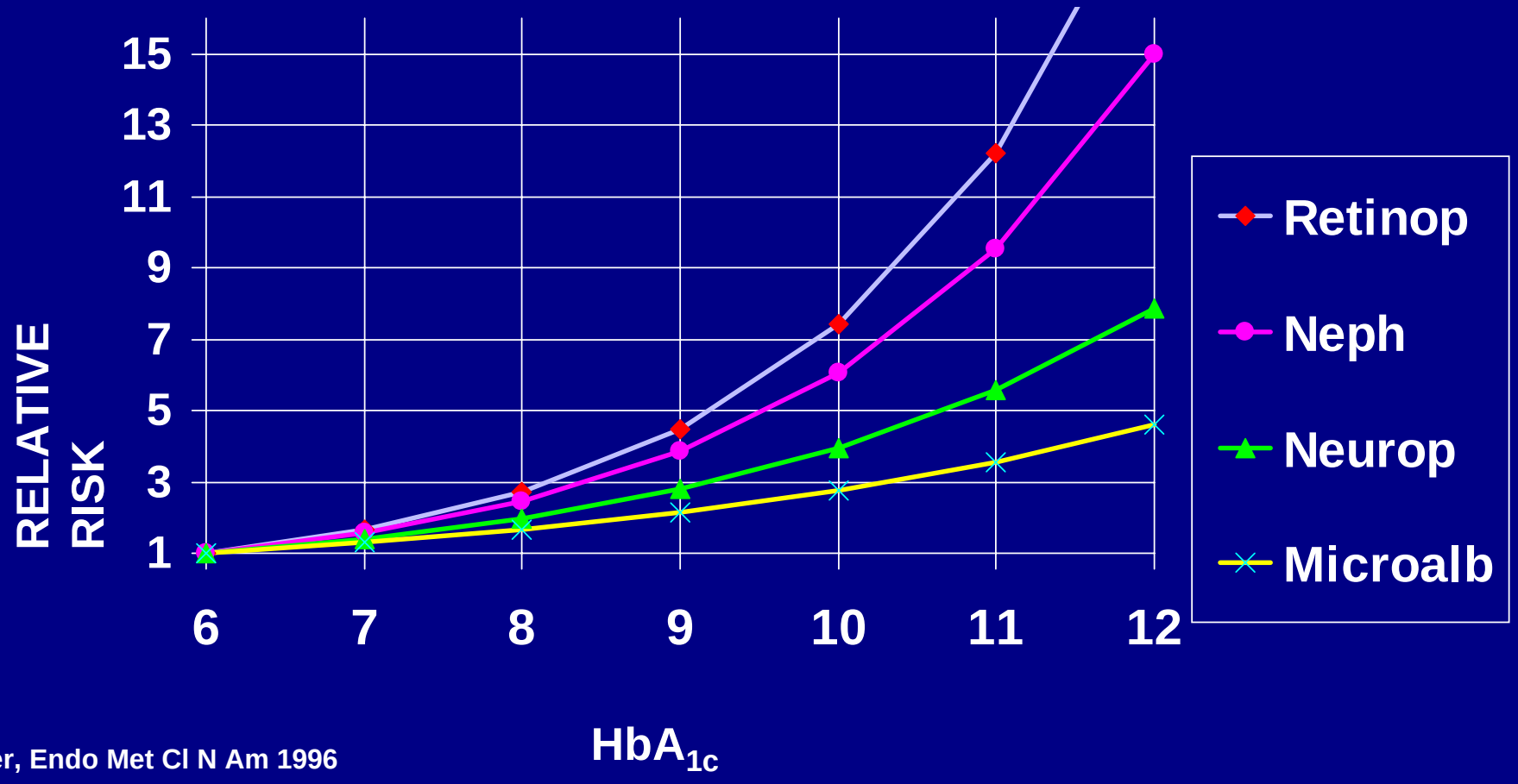
Goals of Intensive Diabetes Management

- Near-normal glycemia
  - HbA1c less than 6.5 to 7.0%
- Avoid short-term crisis
  - Hypoglycemia
  - Hyperglycemia
  - DKA
- Minimize long-term complications
- Improve QOL

ADA: *Clinical Practice Recommendations*. 2001.

Relative Risk of Progression of Diabetic Complications by Mean HbA1C

Based on DCCT Data



Skyler, Endo Met Cl N Am 1996

HbA1c and Plasma Glucose

- 26,056 data points (A1c and 7-point glucose profiles) from the DCCT
- Mean plasma glucose = (A1c x 35.6) – 77.3
- Post-lunch, pre-dinner, post-dinner, and bedtime correlated better with A1c than fasting, post-breakfast, or pre-lunch

Rohlfing et al, Diabetes Care 25 (2) Feb 2002

Emerging Concepts

The Importance of Controlling Postprandial Glucose

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)

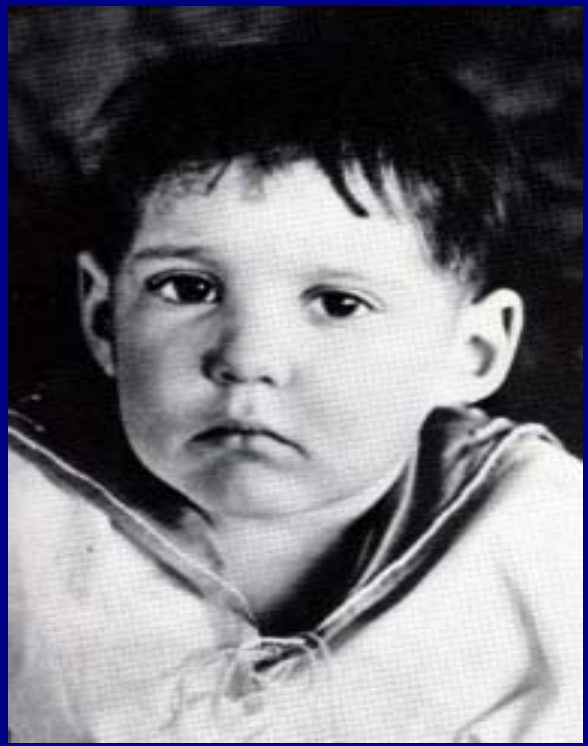
John J.R. McLeod (1876-1935)

James B. Collip
(1892-1965)

Marjorie (?-?)

The Miracle of Insulin

Patient J.L., December 15, 1922

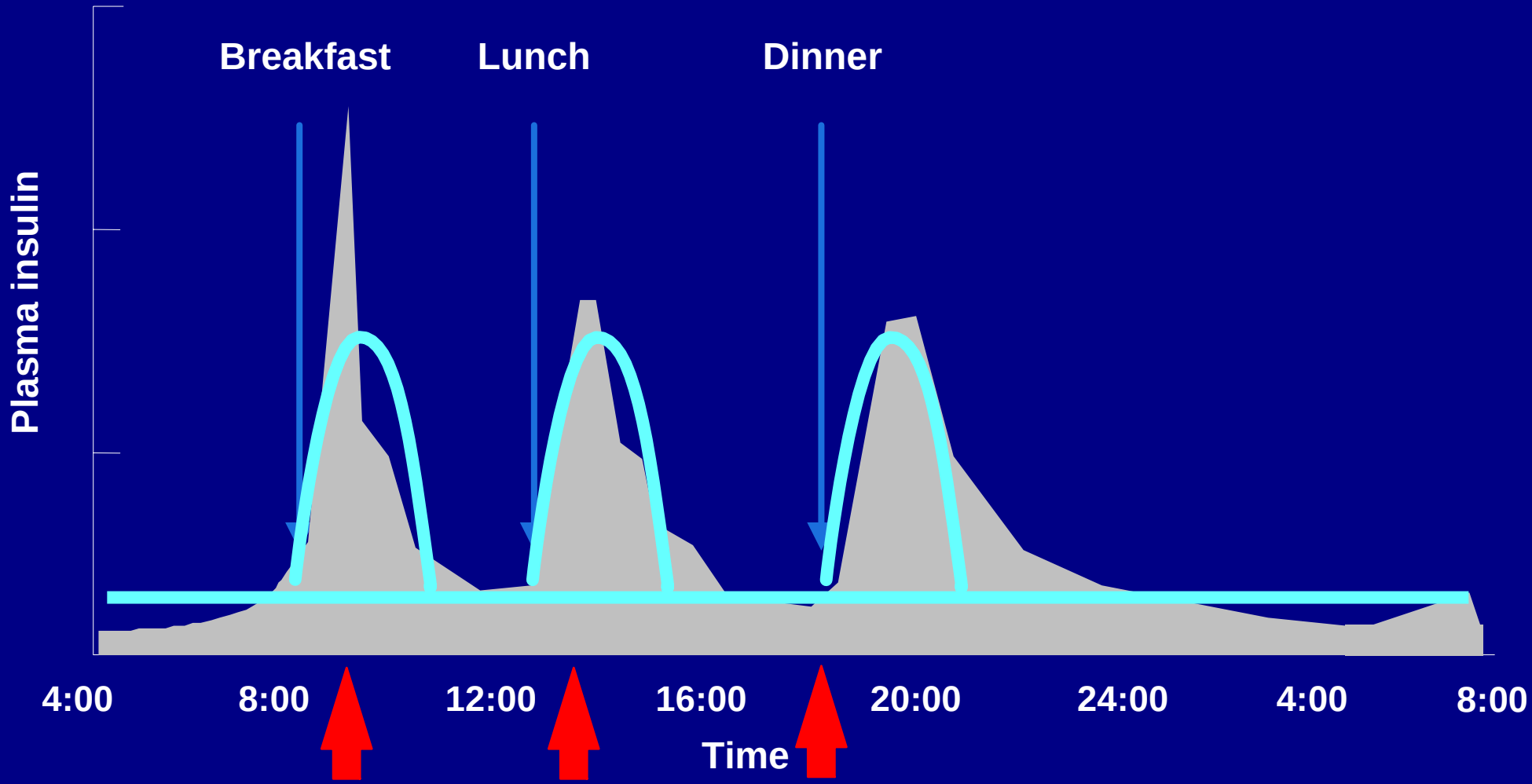


February 15, 1923

Comparison of Human Insulins / Analogues

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

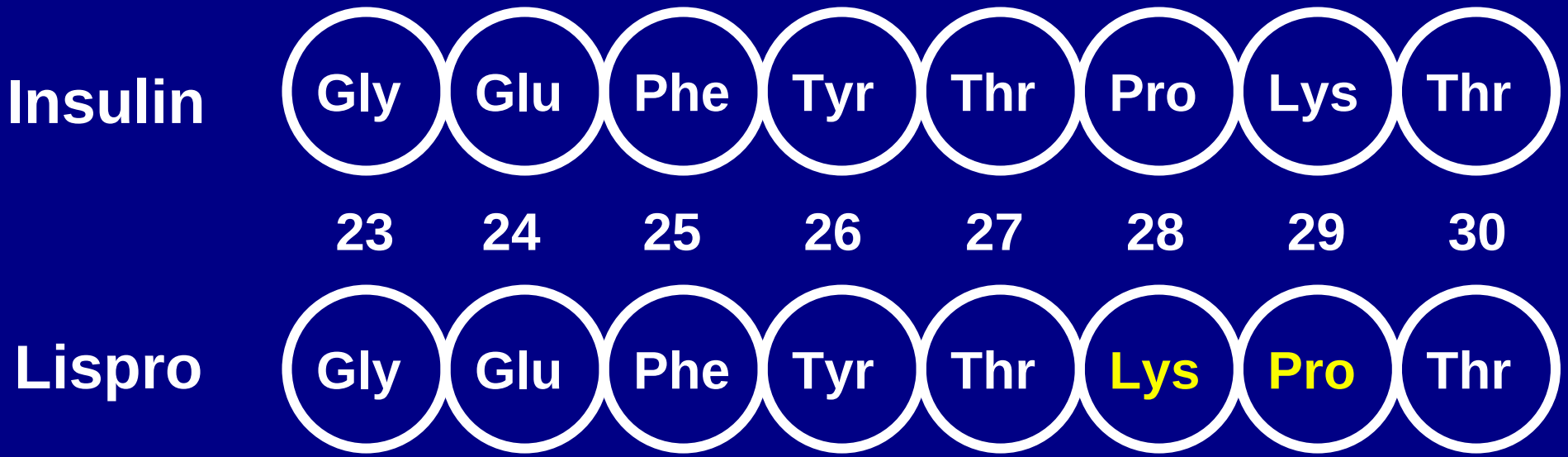
Ideal Basal/Bolus Insulin Absorption Pattern



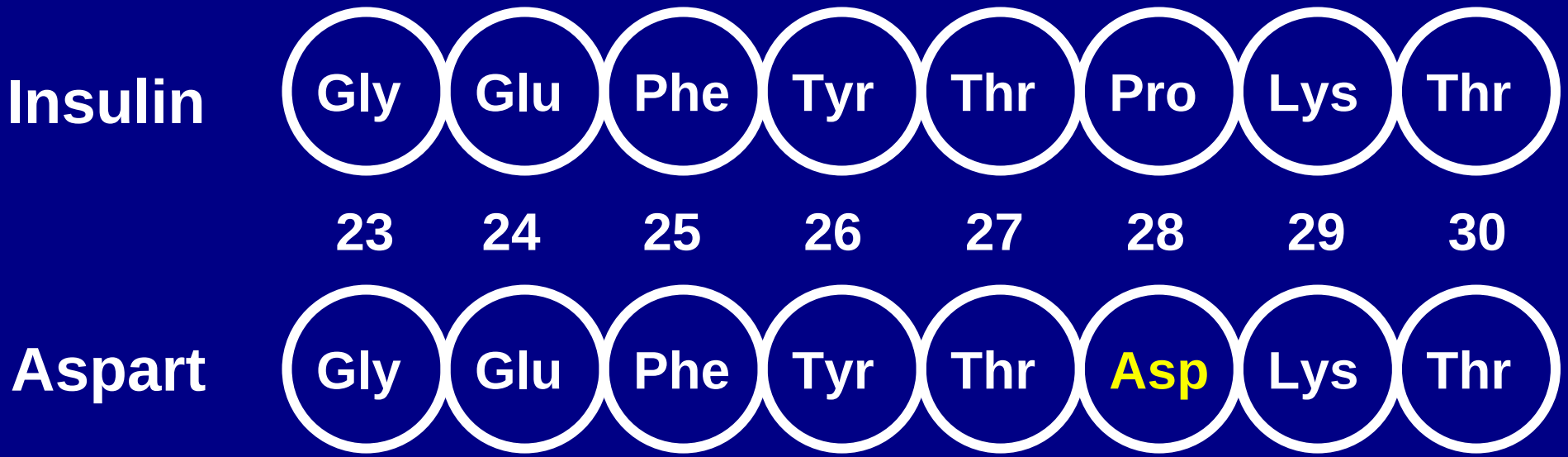
Rapid-acting Insulin Analogs: Medical Rationale

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

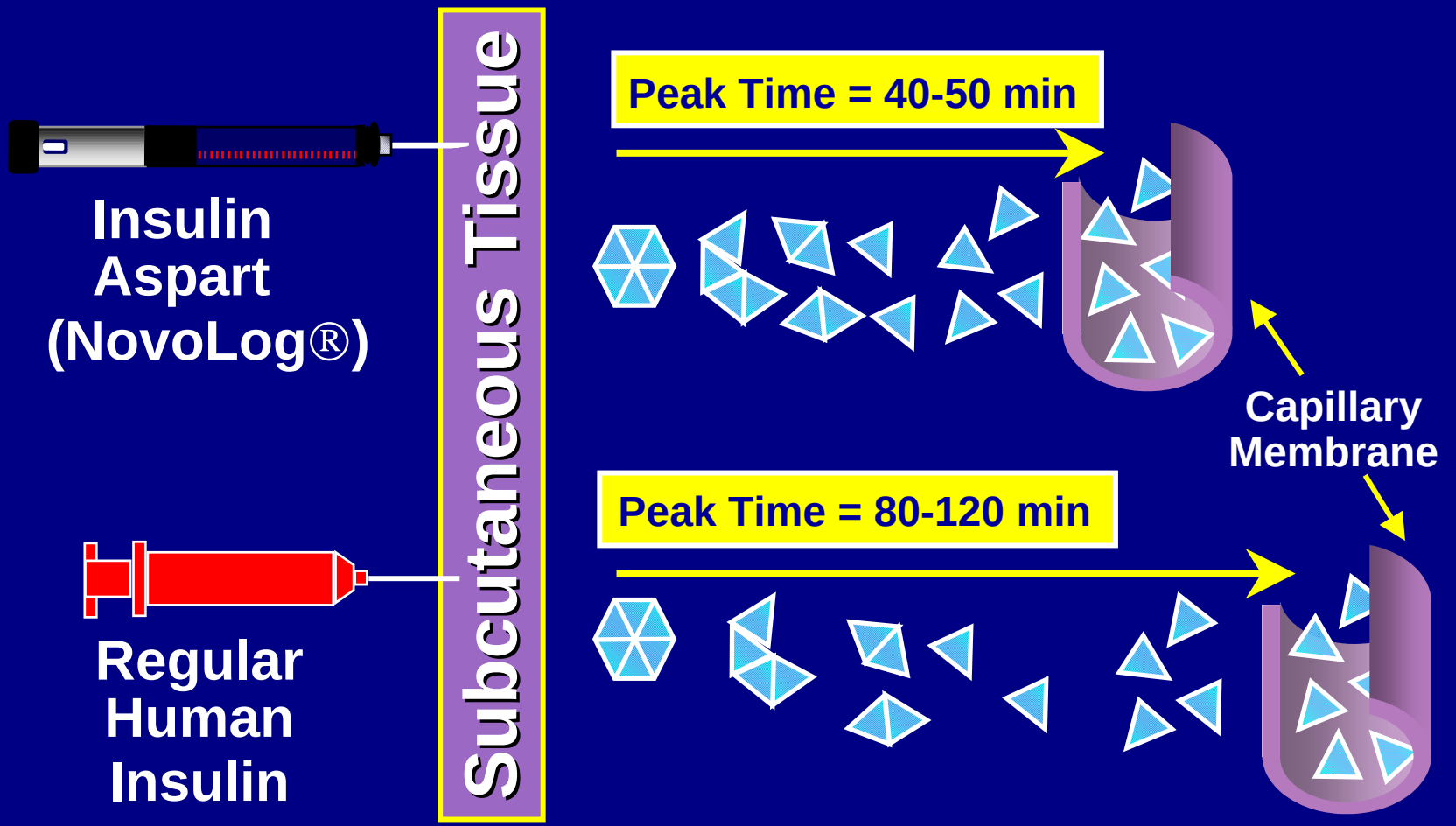
Primary Structure of Lys(B28), Pro(B29)-Insulin



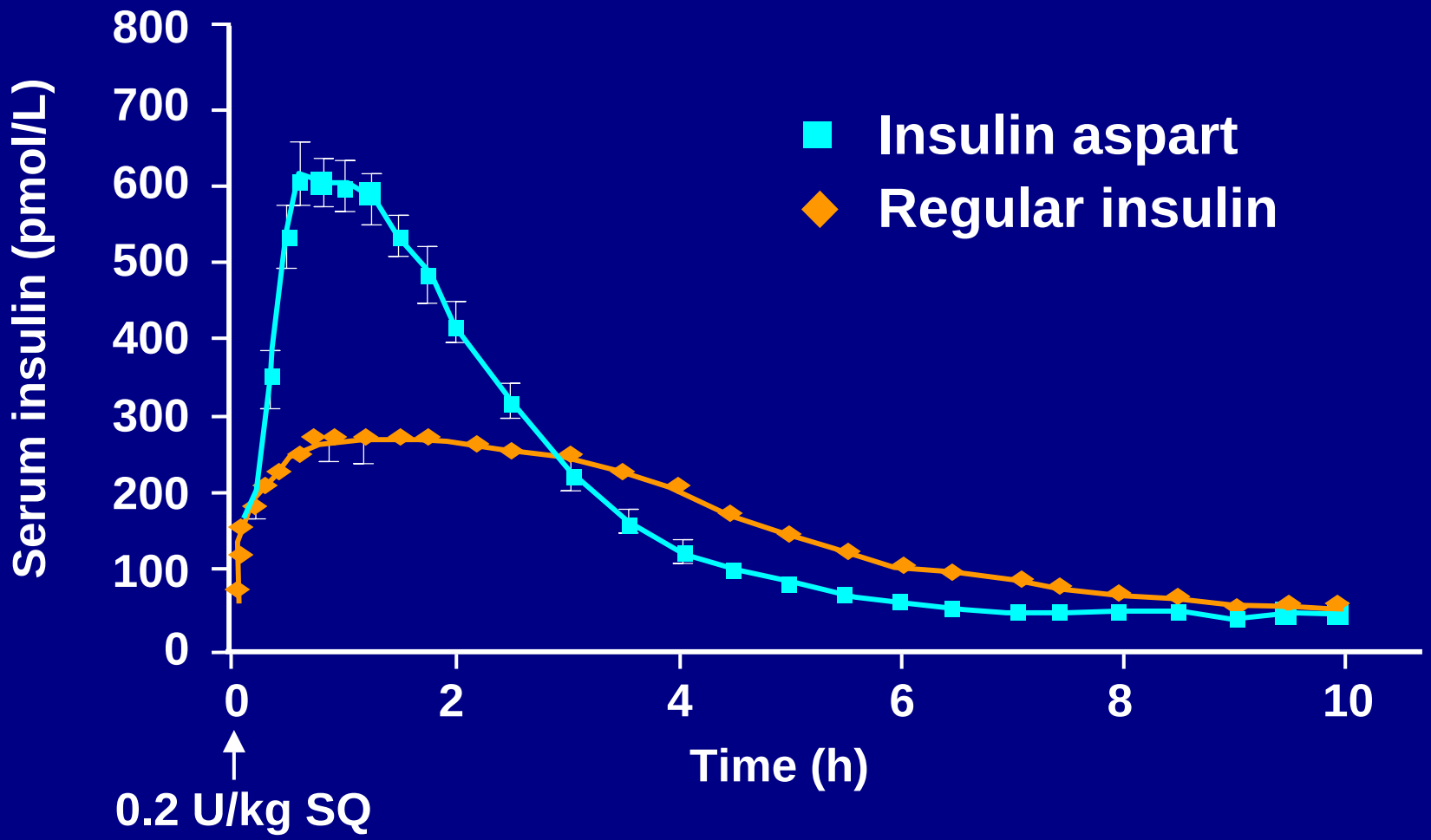
Primary Structure of Asp(B28)-Insulin



Dissociation & Absorption of NovoLog®

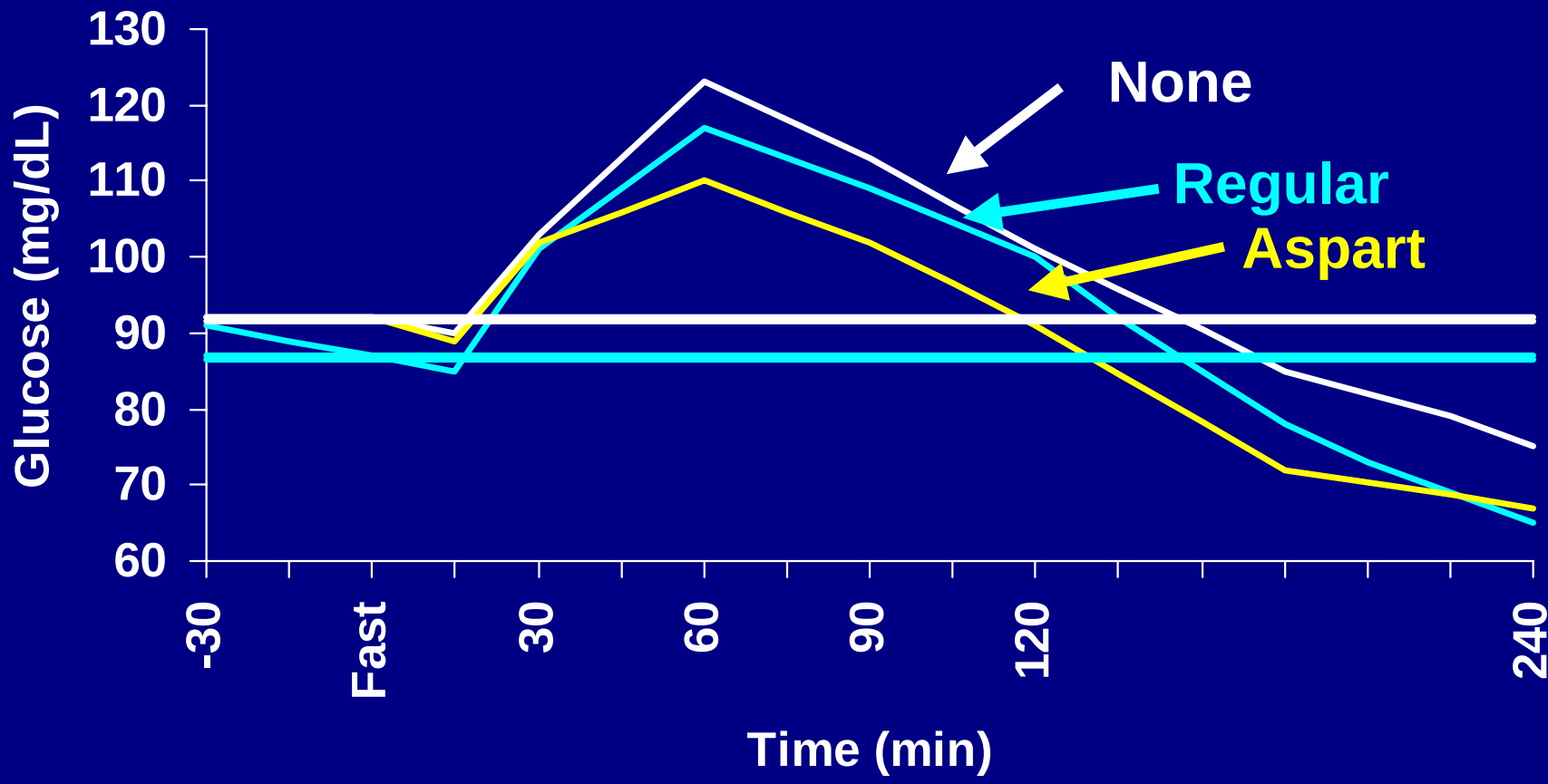


Insulin Aspart: Mean Serum Insulin Profiles During Euglycemic Clamp in Healthy Volunteers

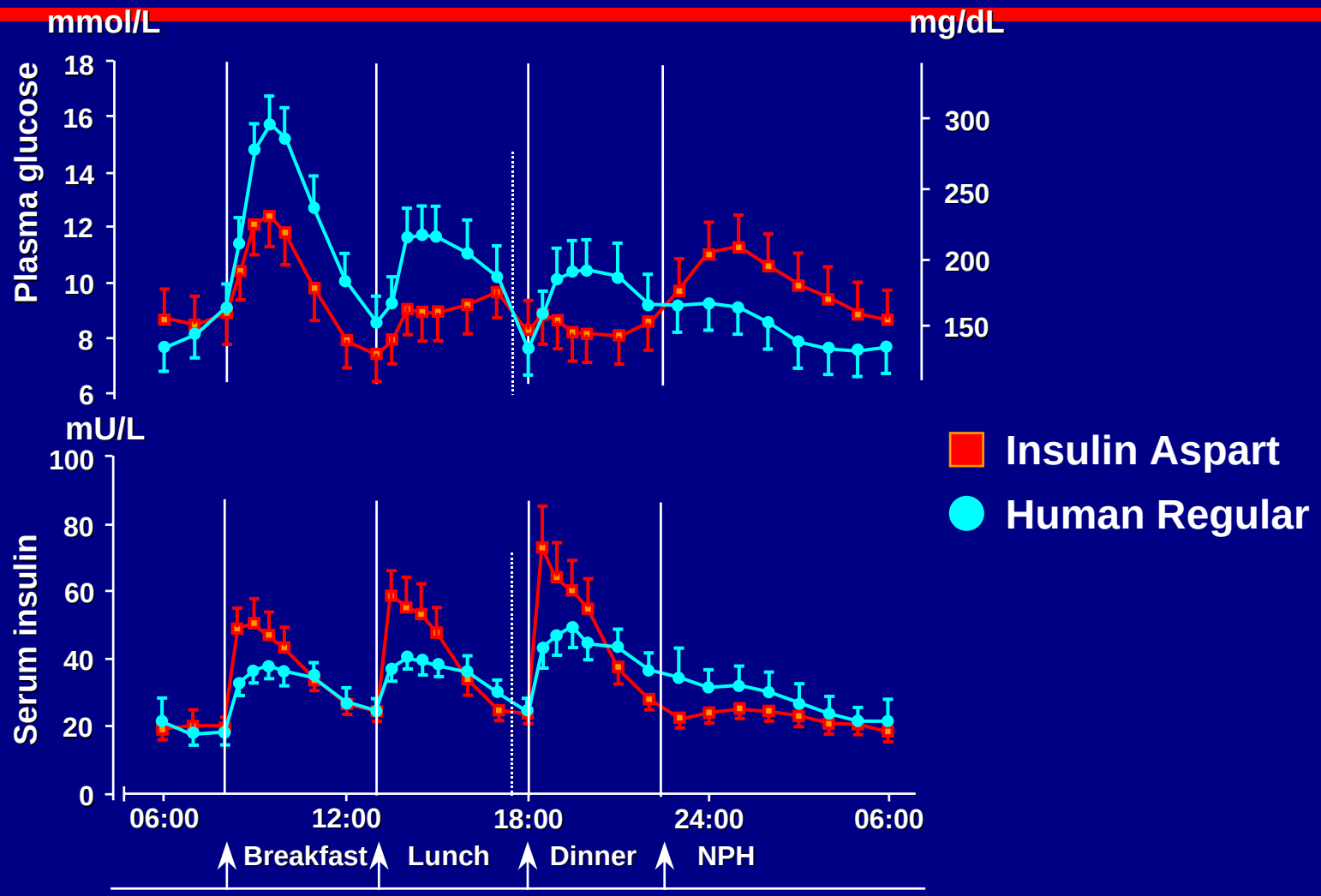


Heinemann L, et al. *Diabetes Care.* 1998;21:1910.

Glucose Area Under the Curve

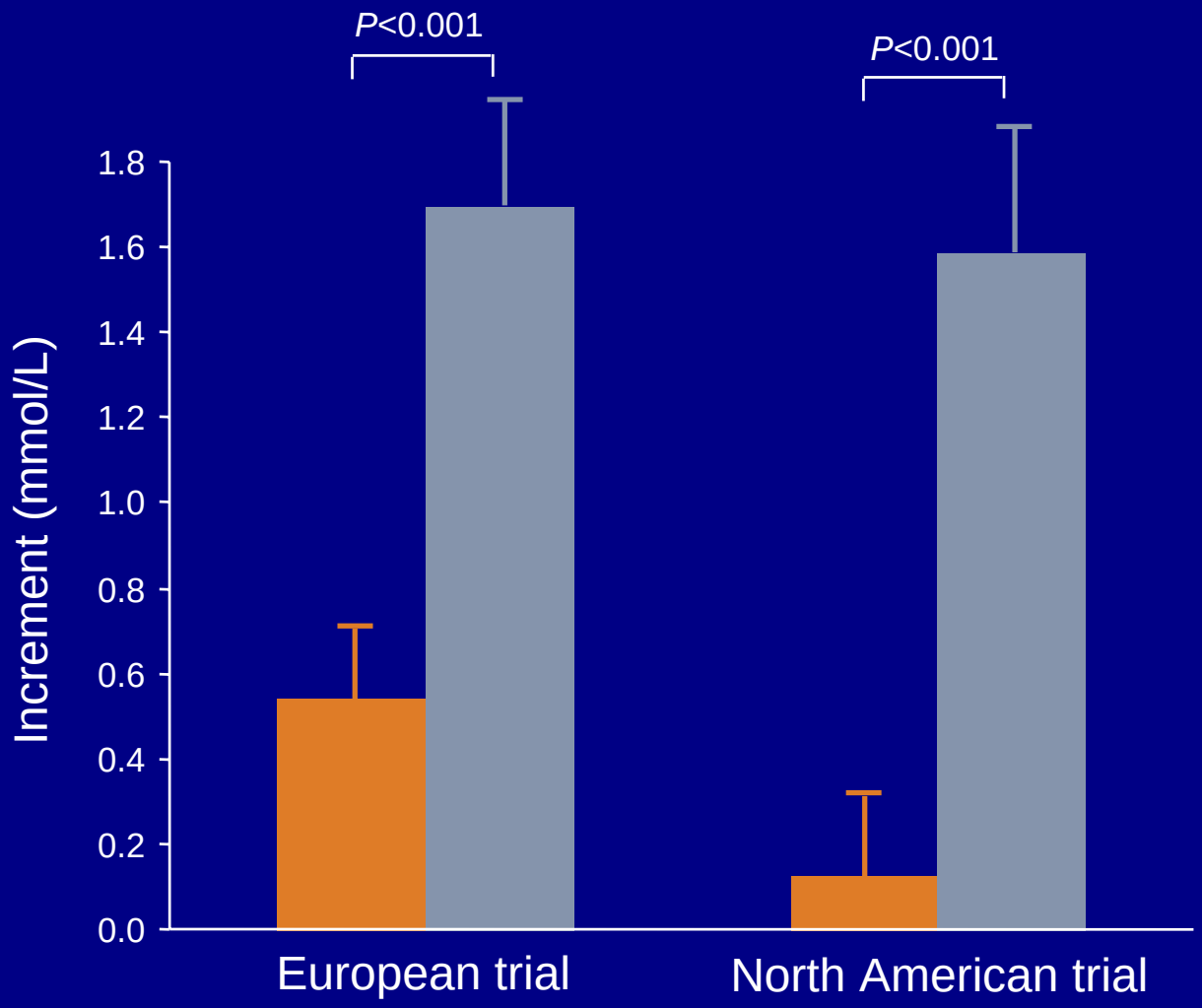


Insulin Aspart vs Human Regular: Glycemic Control



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

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



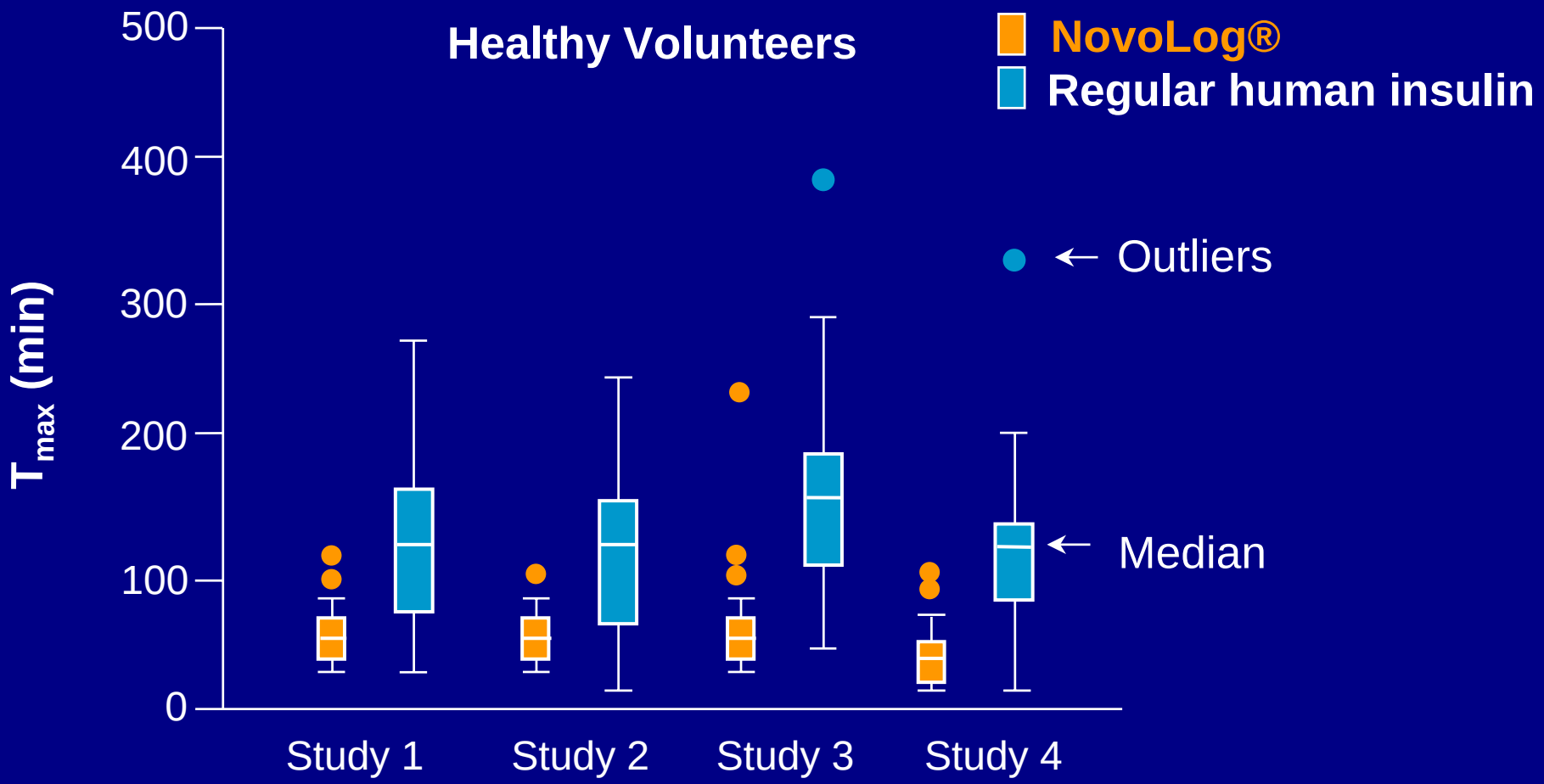
NovoLog®

Regular human insulin

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

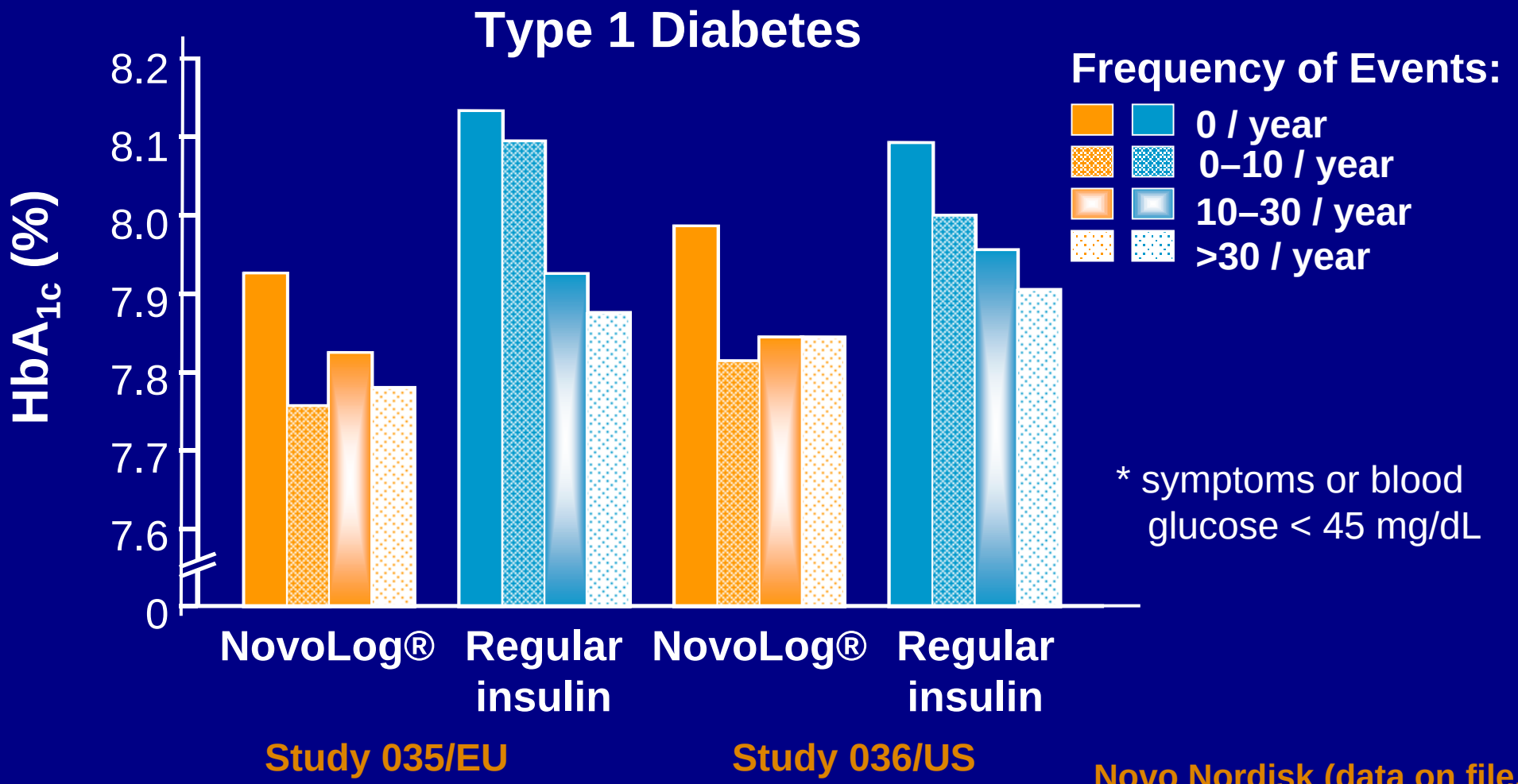
Raskin P, et al. *Diabetes Care. 2000*;23:583.
Home PD, et al. *Diabetic Medicine*. 2000;17:762.

Decreased Inter-individual Variability in NovoLog® Values for T_{max}



Data from: Home, *Eur J Clin Pharmacol* 1999; 55:199-203, Heinemann, *Diab Med* 1996; 13:683-4, Mudaliar, *Diabetes Care* 1999; 22:1501-6, Heinemann, *Diabetes Care* 1998; 21(11):1910-14.

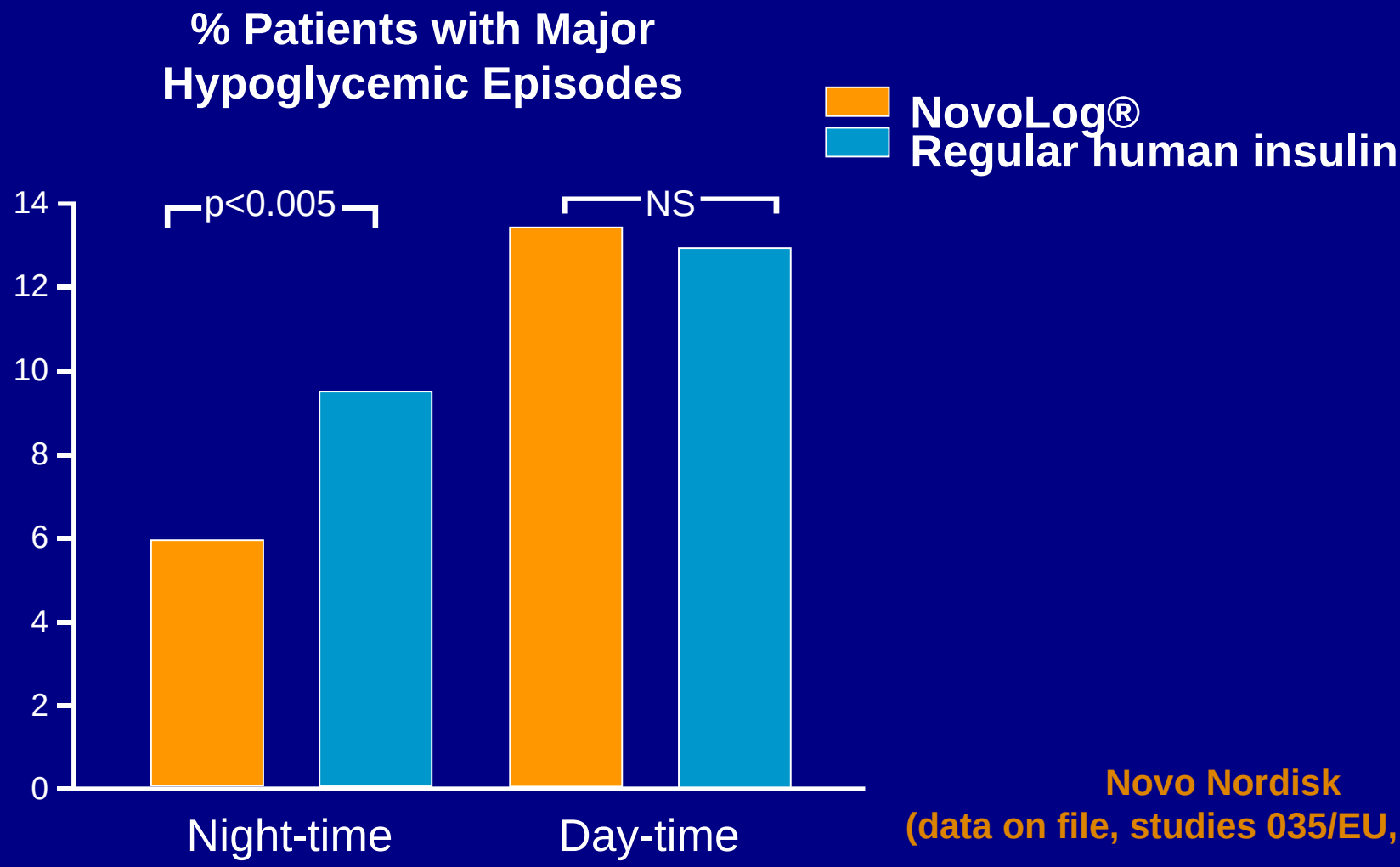
Frequency of Minor* Hypoglycemia Observed by Level of Glycemic Control



* symptoms or blood glucose < 45 mg/dL

Novo Nordisk (data on file, studies 035/EU, 036/US)

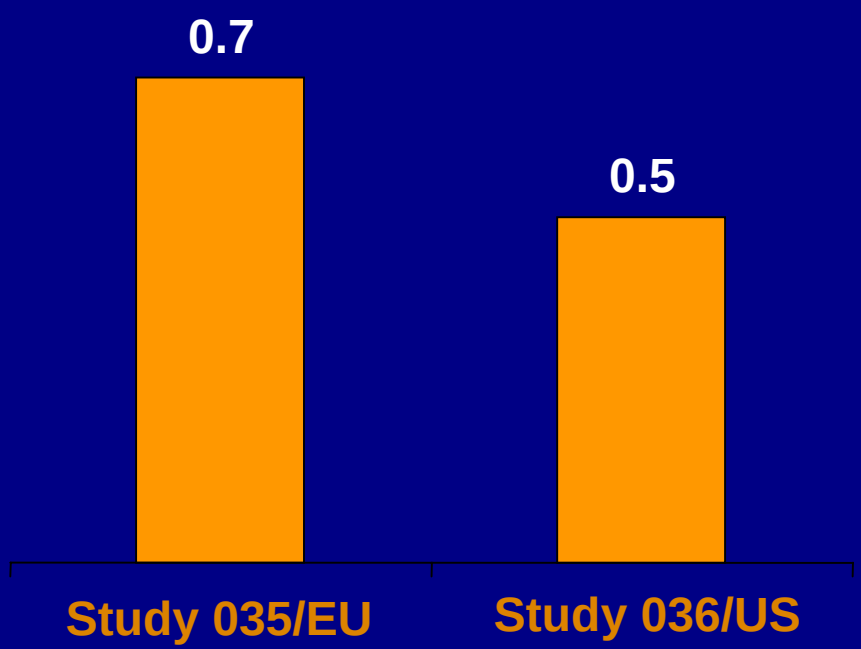
Reduced Reporting of Major Nocturnal Hypoglycemia



Novo Nordisk
(data on file, studies 035/EU, 036/US)

Reduced Risk of Major Nocturnal Hypoglycemia

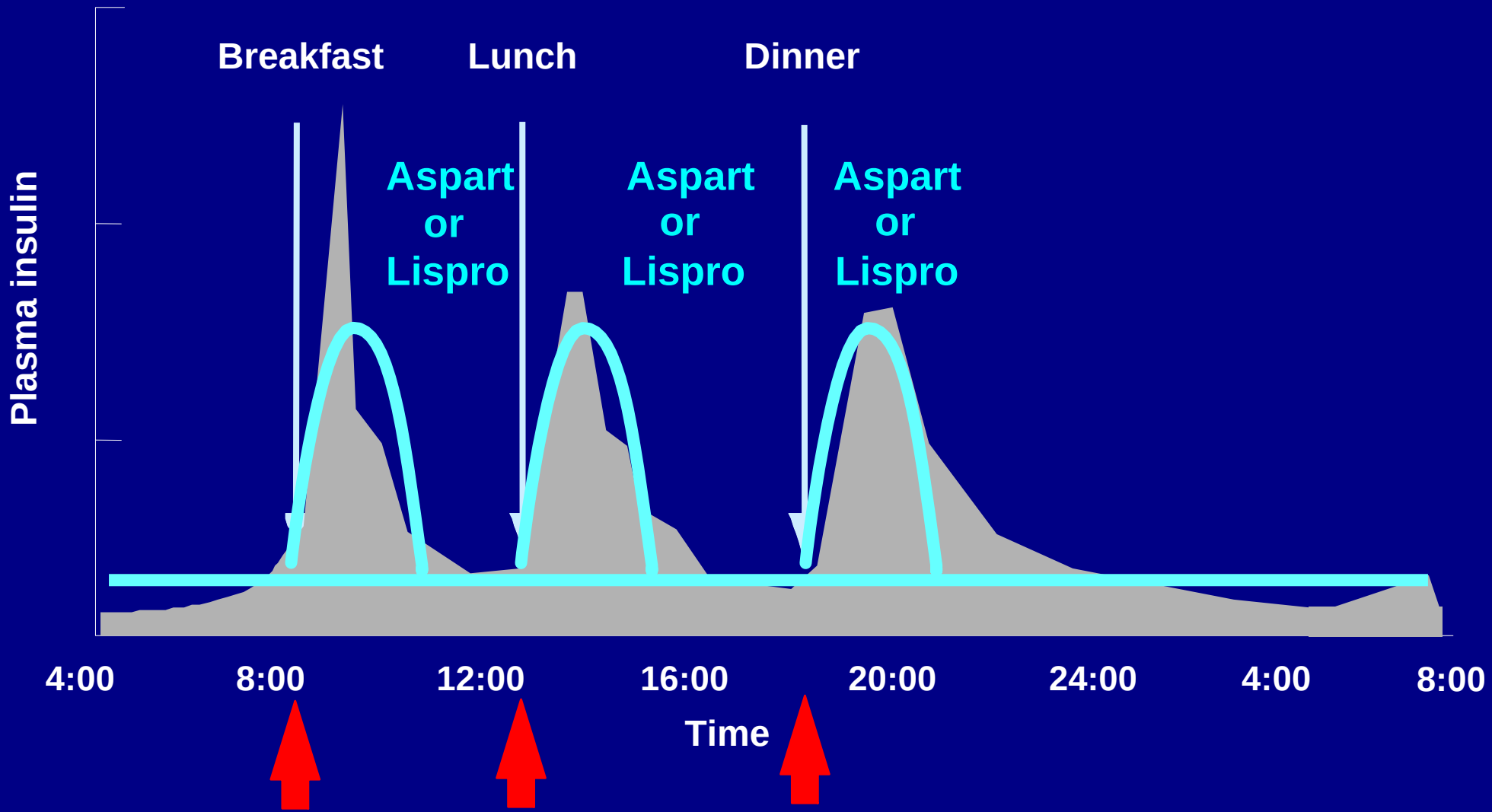
Relative Risk
NovoLog Compared to Regular Human Insulin (1.0 = equal)



	NovoLog®	Human insulin
	(N of patients with events)	
Home	8% (54/707)	11% (39/358)
Raskin	4% (24/596)	8% (23/286)

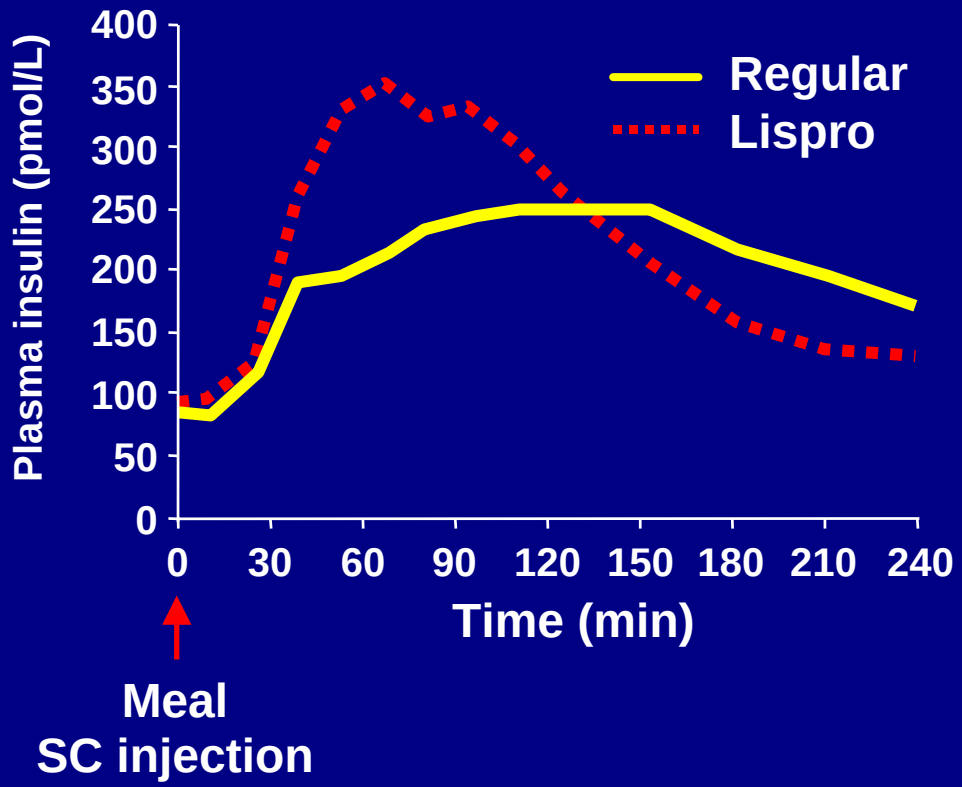
Novo Nordisk
(data on file, studies 035/EU, 036/US)

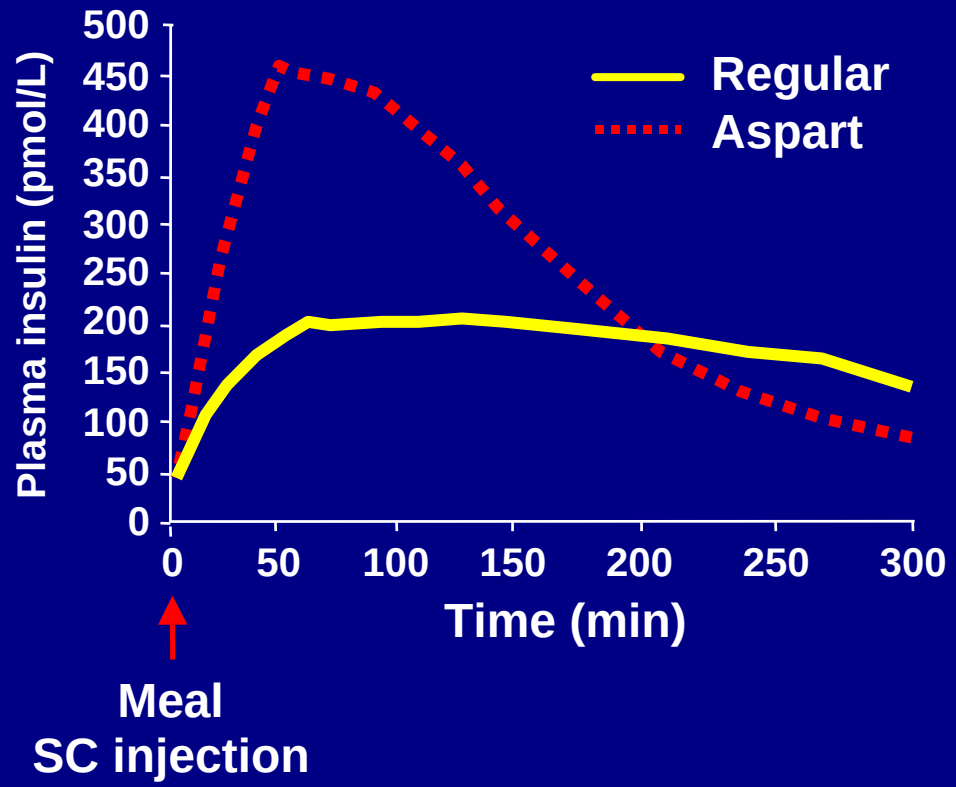
Rapid-acting Insulin Analogues Provide Ideal Prandial Insulin Profile



Short-Acting Insulin Analogs

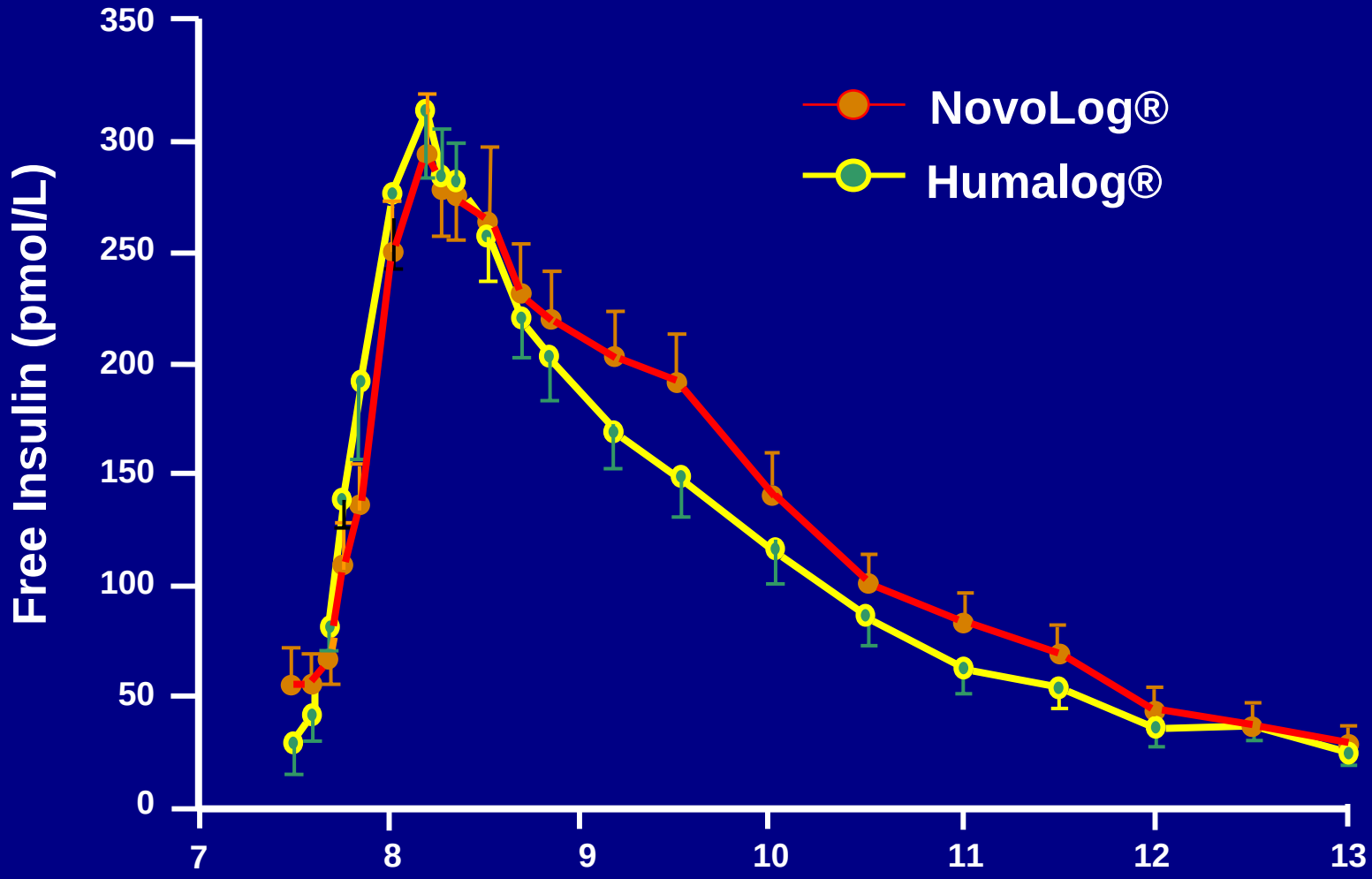
Lispro and Aspart Plasma Insulin Profiles





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

Pharmacokinetic Comparison
NovoLog® *vs* Humalog®



Hedman, *Diabetes Care* 2001; 24(6):1120-21

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

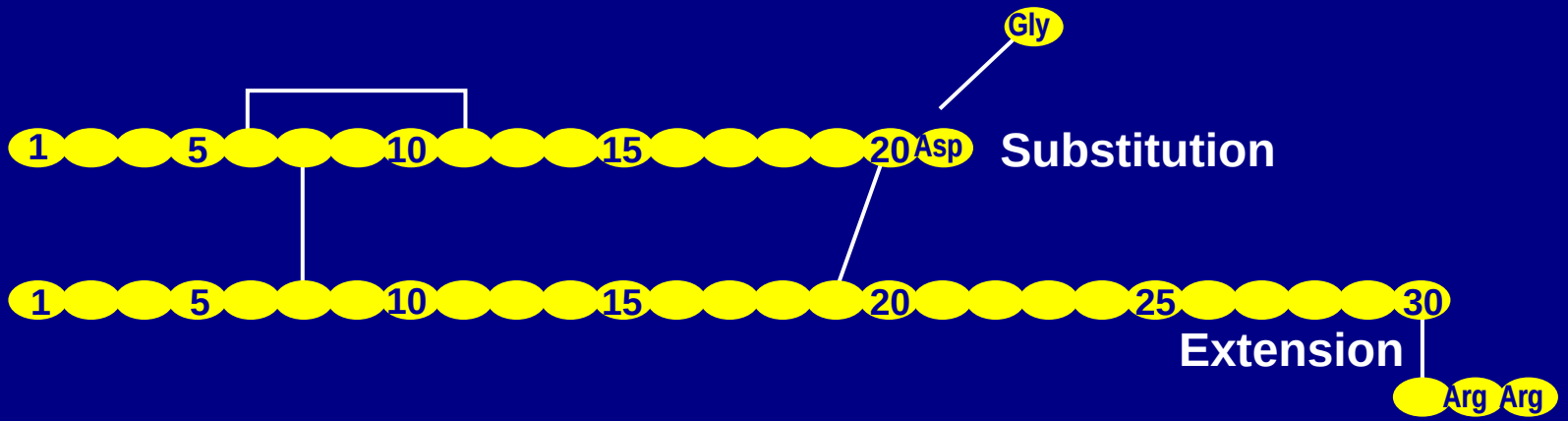
Limitations of NPH, Lente, and Ultralente

- 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
  - More weight gain

Insulin Glargine

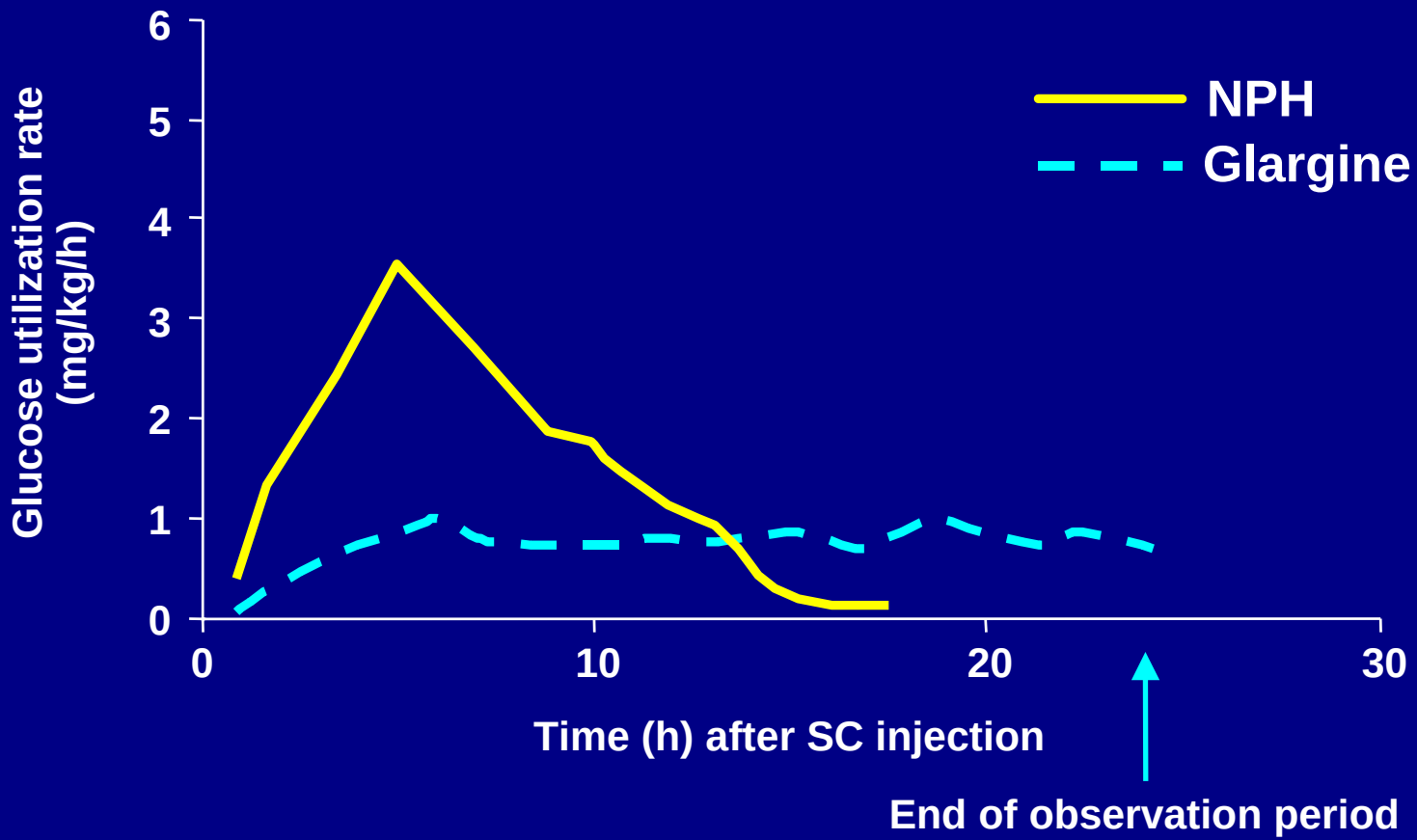
A New Long-Acting Insulin Analog

- Modifications to human insulin chain
  - Substitution of glycine at position A21
  - Addition of 2 arginines at position B30
- Gradual release from injection site
- Peakless, long-lasting insulin profile



Glargine vs NPH Insulin in Type 1 Diabetes

Action Profiles by Glucose Clamp



Lepore, 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

Type 2 Diabetes …
A Progressive Disease

Over time,
most patients will need insulin
to control glucose

Insulin Therapy in Type 2 Diabetes
Indications

- Significant hyperglycemia at presentation
- Hyperglycemia on maximal doses of oral agents
- Decompensation
  - Acute injury, stress, infection, myocardial ischemia
  - Severe hyperglycemia with ketonemia and/or ketonuria
  - Uncontrolled weight loss
  - Use of diabetogenic medications (eg, corticosteroids)
- Surgery
- Pregnancy
- Renal or hepatic disease

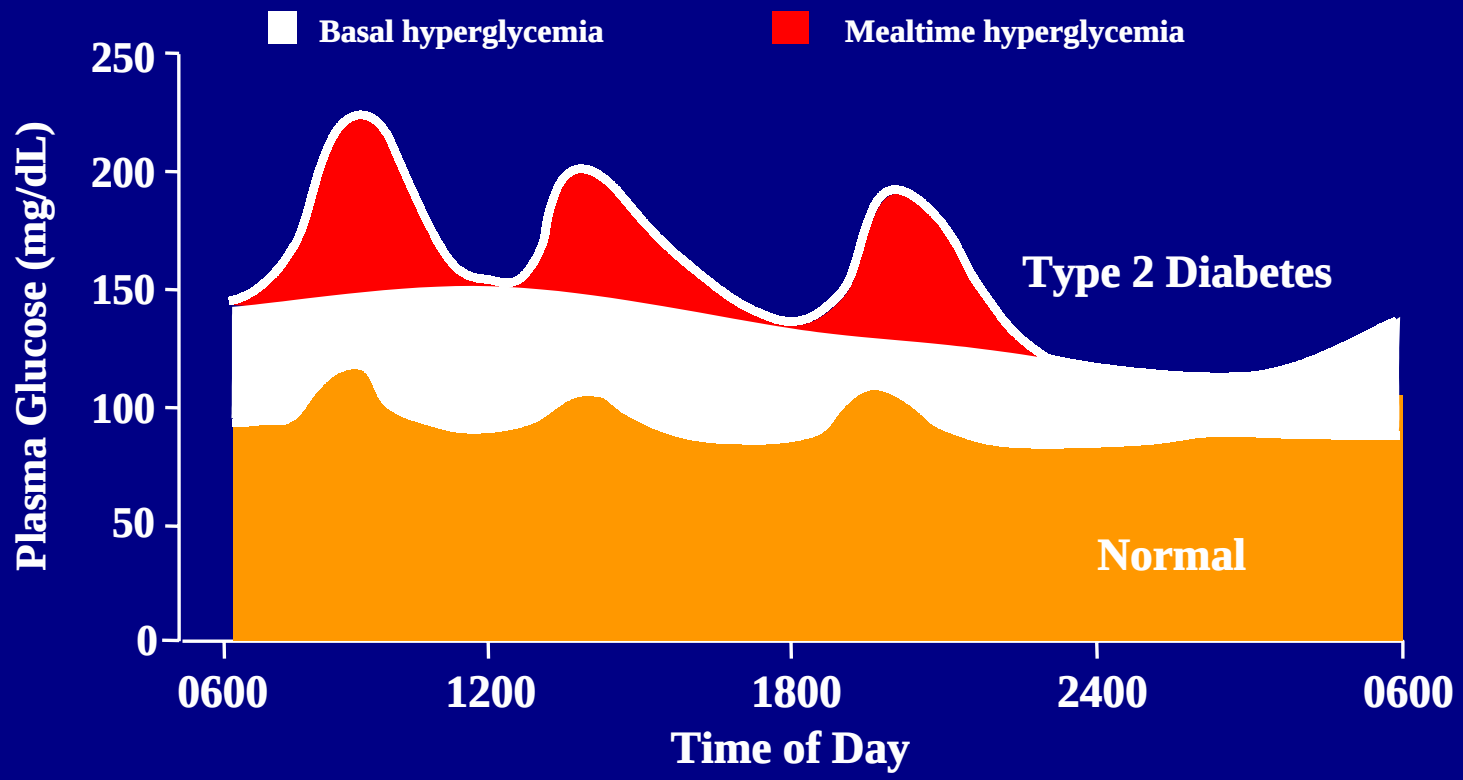
Mimicking Nature

The Basal/Bolus Insulin Concept

The Basal/Bolus Insulin Concept

- Basal insulin
  - Suppresses glucose production between meals and overnight
  - 40% to 50% of daily needs
- Bolus insulin (mealtime)
  - Limits hyperglycemia after meals
  - Immediate rise and sharp peak at 1 hour
  - 10% to 20% of total daily insulin requirement at each meal

Basal vs Mealtime Hyperglycemia in Diabetes

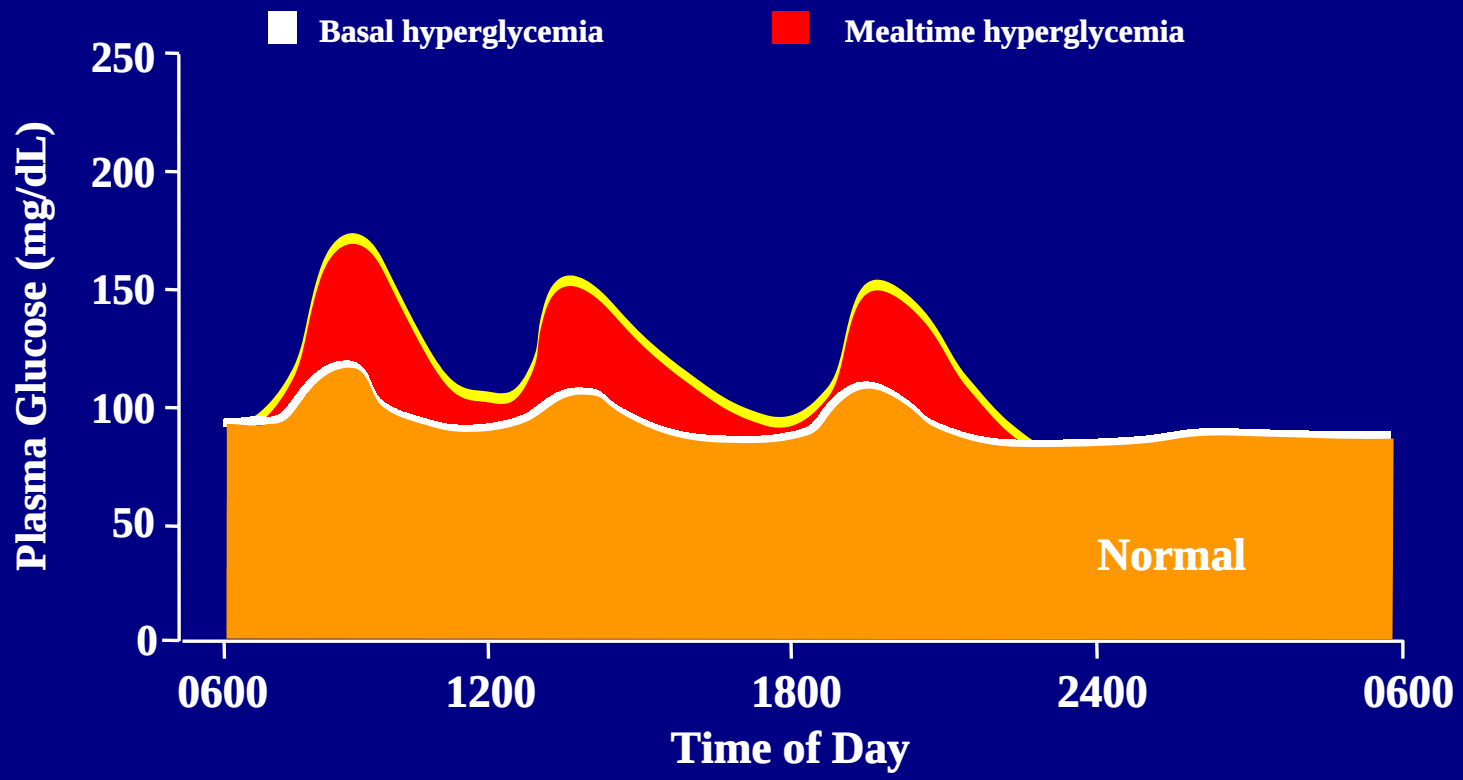


Δ AUC from normal basal >1875 mgm/dL·hr; Est $HbA1_c$ >8.7%

Riddle. *Diabetes Care.* 1990;13:676-686.

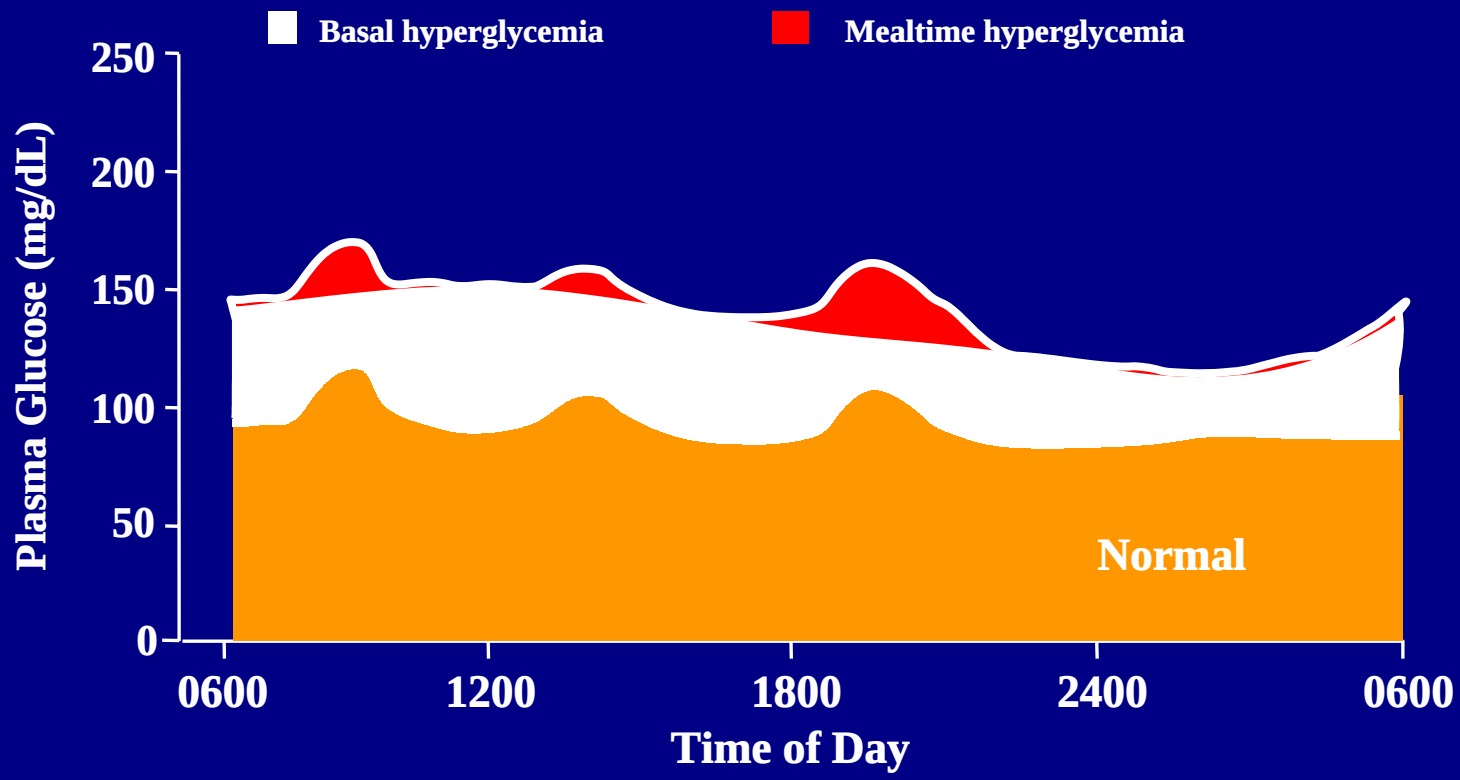
Basal vs Mealtime Hyperglycemia in Diabetes

When Basal Corrected



Δ AUC from normal basal 900 mgm/dL·hr; Est $HbA1_c$ 7.2%

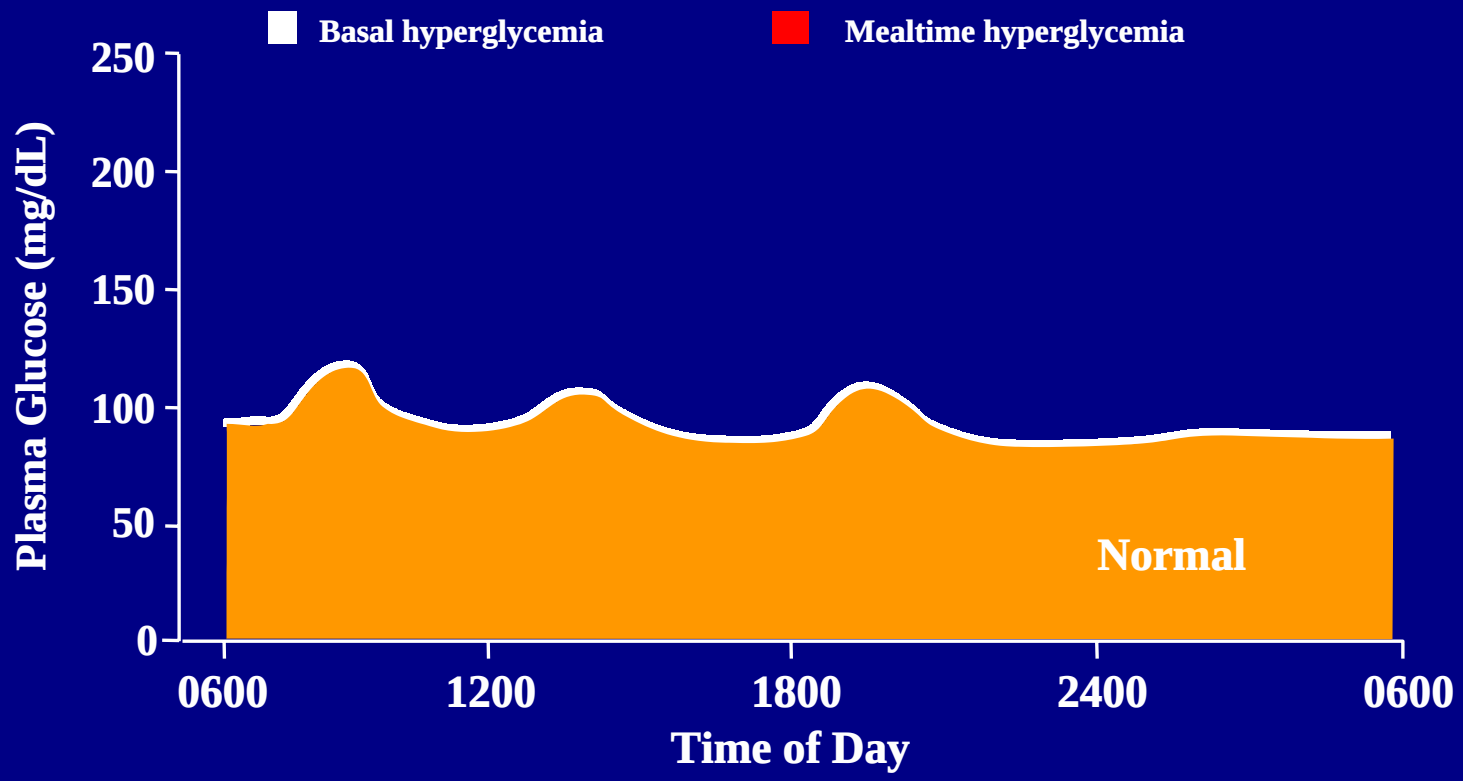
When Mealtime Hyperglycemia Corrected



Δ AUC from normal basal 1425 mgm/dL·hr; Est $HbA1_c$ 7.9

Basal vs Mealtime Hyperglycemia in Diabetes

When Both Basal & Mealtime Hyperglycemia Corrected



Δ AUC from normal basal 225 mgm/dL·hr; Est $HbA1_c$ 6.4%

MIMICKING NATURE WITH INSULIN THERAPY

Over time,

most patients will need

both basal and mealtime insulin

to control glucose

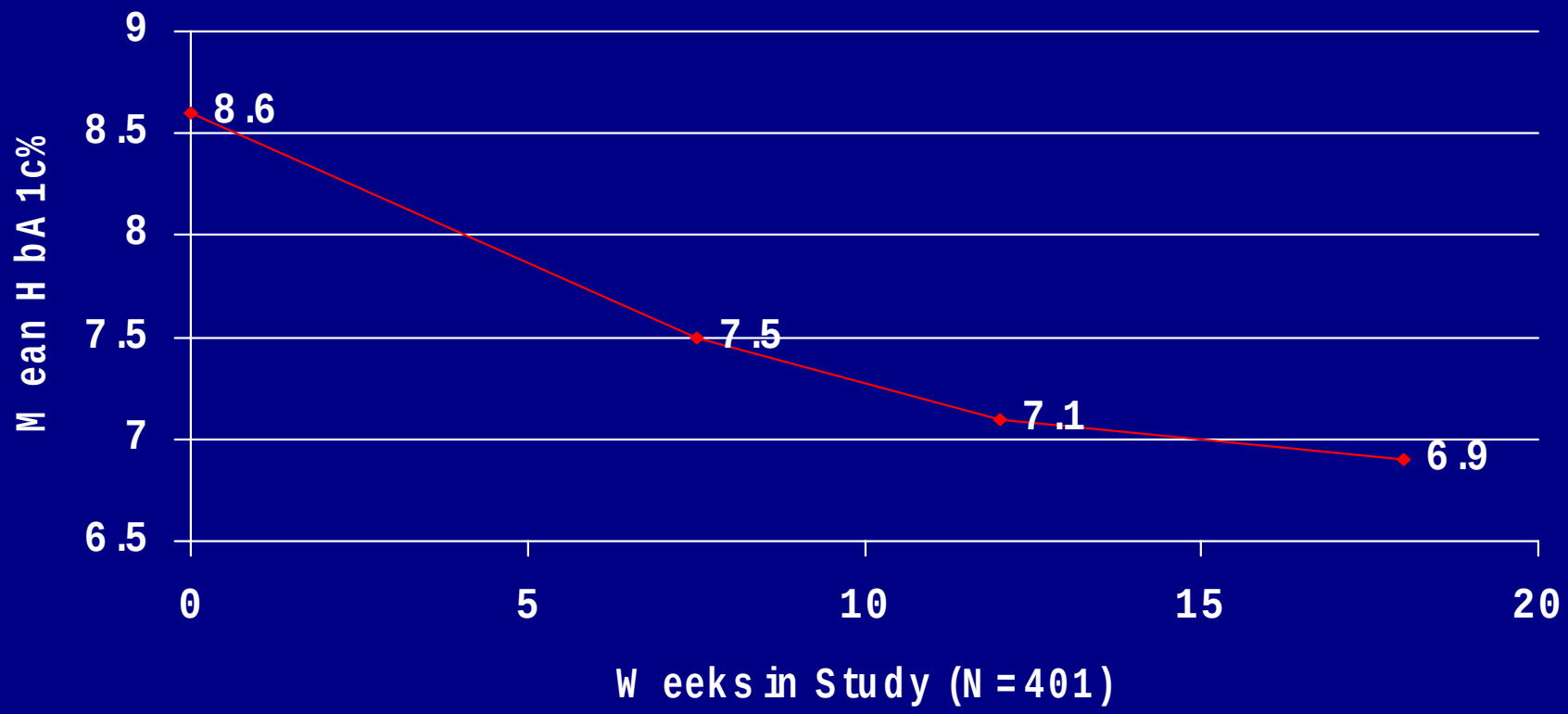
Starting With Basal Insulin
Advantages

- 1 injection with no mixing
- Insulin pens for increased acceptance
- Slow, safe, and simple titration
- Low dosage
- Effective improvement in glycemic control
- Limited weight gain

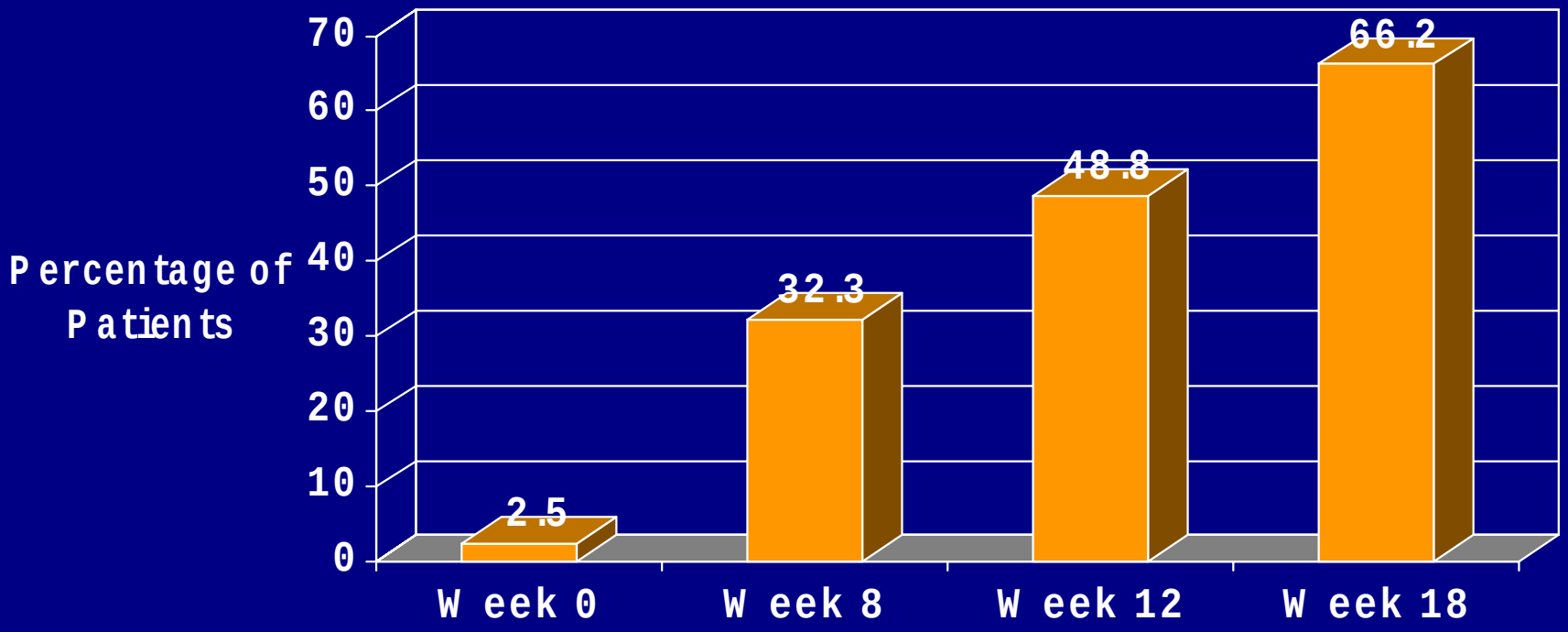
Treatment to Target Study: NPH vs Glargine in DM2 patients on OHA

- Add 10 units Basal insulin at bedtime (NPH or Glargine)
- Continue current oral agents
- Titrate insulin weekly to fasting BG < 100 mg/dL
  - if 100-120 mg/dL, increase 2 units
  - if 120-140 mg/dL, increase 4 units
  - if 140-160 mg/dL, increase 6 units
  - if 160-180 mg/dL, increase 8 units

Treatment to Target Study; A1C Decrease



Patients in Target (A1c < 7%)



Advancing Basal/Bolus Insulin

- Indicated when FBG acceptable but
  - HbA1c > 7% or > 6.5%
    and/or
  - SMBG before dinner > 140 mg/dL
- Insulin options
  - To glargine or NPH, add mealtime aspart / lispro
  - To suppertime 70/30, add morning 70/30
  - Consider insulin pump therapy
- Oral agent options
  - Usually stop sulfonylurea
  - Continue metformin for weight control
  - Continue glitazone for glycemic stability?

Starting With Bolus Insulin

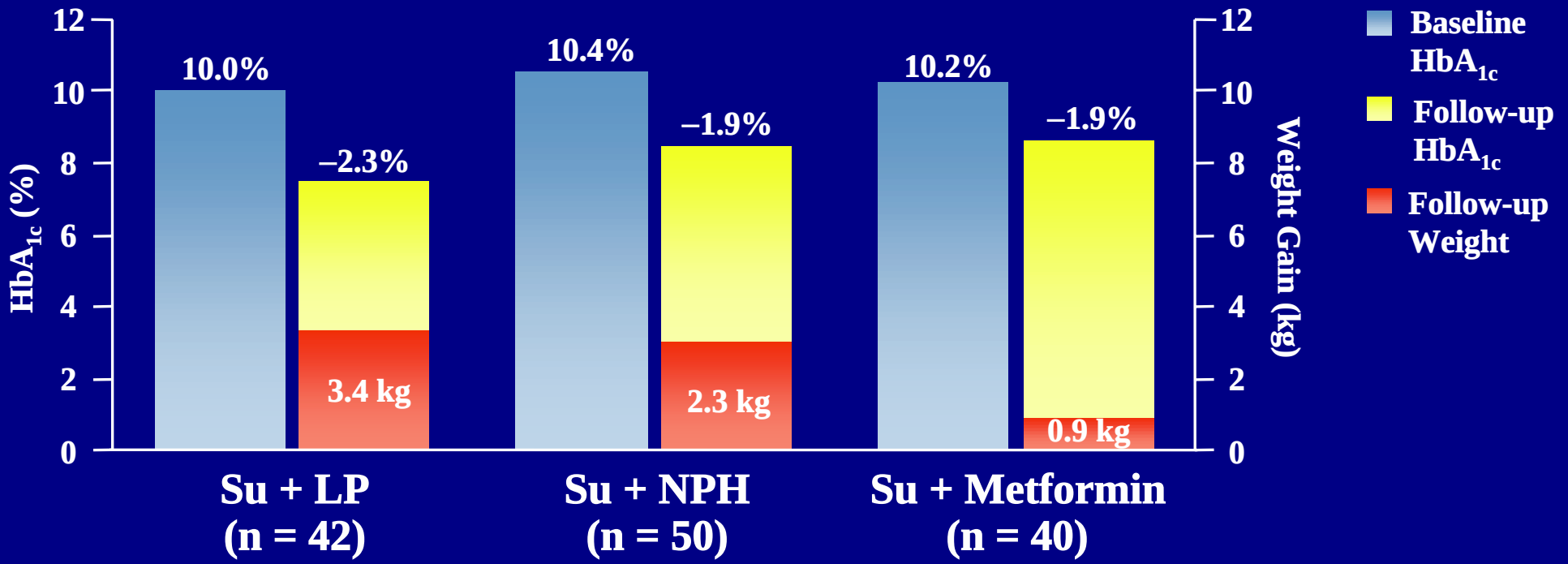
Combination Oral Agents

+

Mealtime Insulin

Starting With Bolus Insulin

Mealtime Lispro vs NPH or Metformin Added to Sulfonylurea



Browdos, et al. *Diabetes*. 1999;48(suppl 1):A104.

Case #1: DM 2 on SU with infection

- 49 year old white male
- DM 2 onset age 43, wt 173 lbs, Ht 70 inches
- On glimepiride (Amaryl) 4 mg/day , HbA1c 7.3% (intolerant to metformin)
- Infection in colostomy pouch (ulcerative colitis) glucose up to 300 mg/dL plus
- SBGM 3 times per day

Case #1: DM 2 on SU with infection

- Started on MDI; starting dose 0.2 x wgt. in lbs.
- Wgt. 180 lbs which = 36 units
- Bolus dose (lispro/aspart) = 20% of starting dose at each meal, which = 7 to 8 units ac (tid)
- Basal dose (glargine) = 40% of starting dose at HS, which = 14 units at HS
- Correction bolus = (BG - 100)/ SF, where SF = 1500/total daily dose; SF = 40

Correction Bolus Formula

$$\frac{\text{Current BG - Ideal BG}}{\text{Glucose Correction factor}}$$

Example:

- **Current BG: 220 mg/dl**
- **Ideal BG: 100 mg/dl**
- **Glucose Correction Factor: 40 mg/dl**

$$\frac{220 - 100}{40} = 3.0u$$

Case #1: DM 2 on SU with infection

- Started on MDI
- Did well, average BG 138 mg/dL at 1 month and 117 mg/dL at 2 months post episode with HbA1c 6.1%

Strategies to Improve Glycemic Control: Type 2 Diabetes

- Monitor glycemic targets – Fasting and postprandial glucose, HbA_{1c}
- Self-monitoring of blood glucose is essential
- Nutrition and activity are cornerstones of therapy
- Combinations of pharmacologic agents are often necessary to achieve glycemic targets

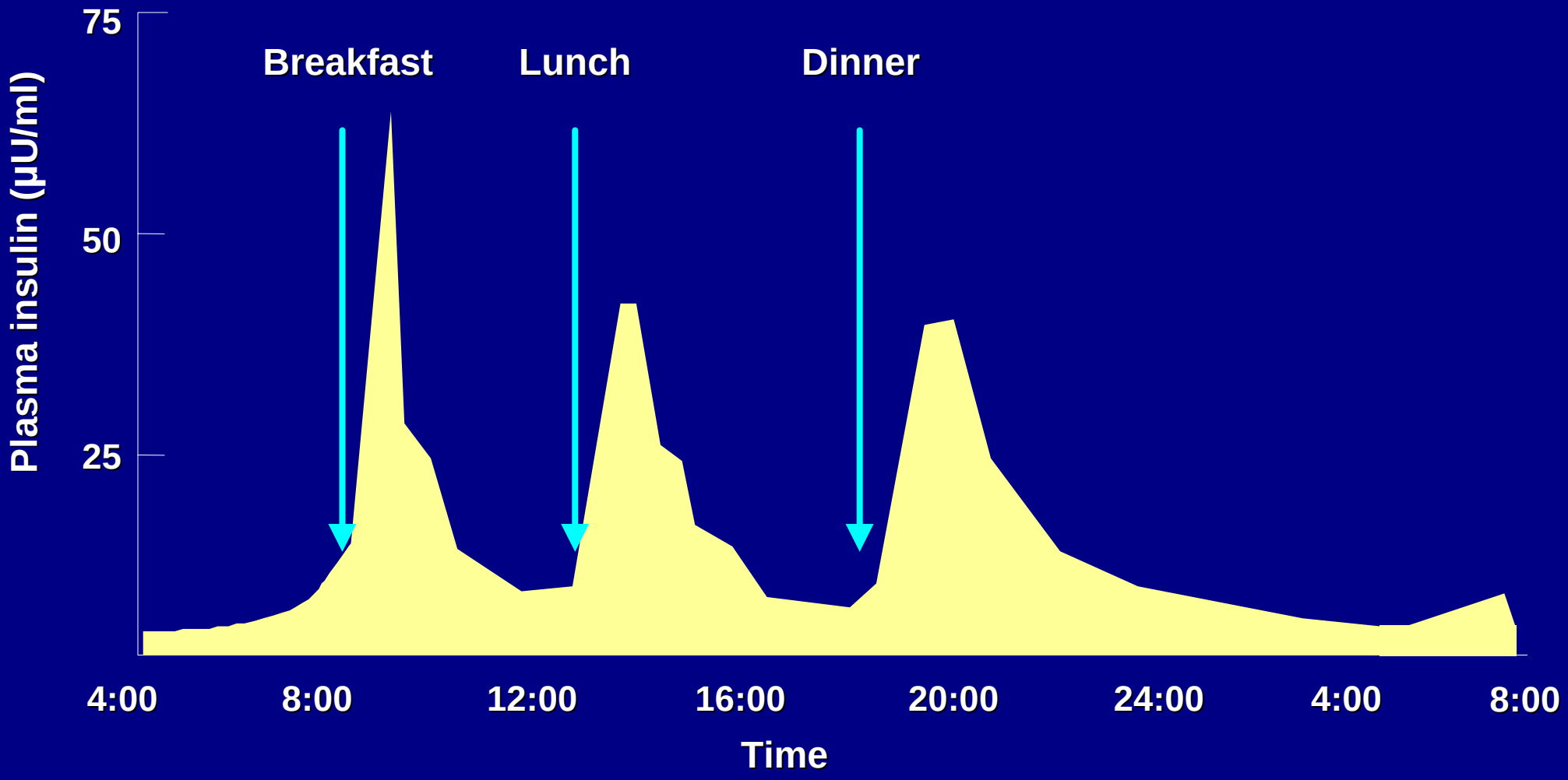
Intensive Therapy for Type 1 Diabetes

- Careful balance of food, activity, and insulin
- Daily self-monitoring BG
- Patient trained to vary insulin and food
- Define target BG levels (individualized)
- Frequent contact of patient and diabetes team
- Monitoring HbA_{1c}
- Basal / Bolus insulin regimen

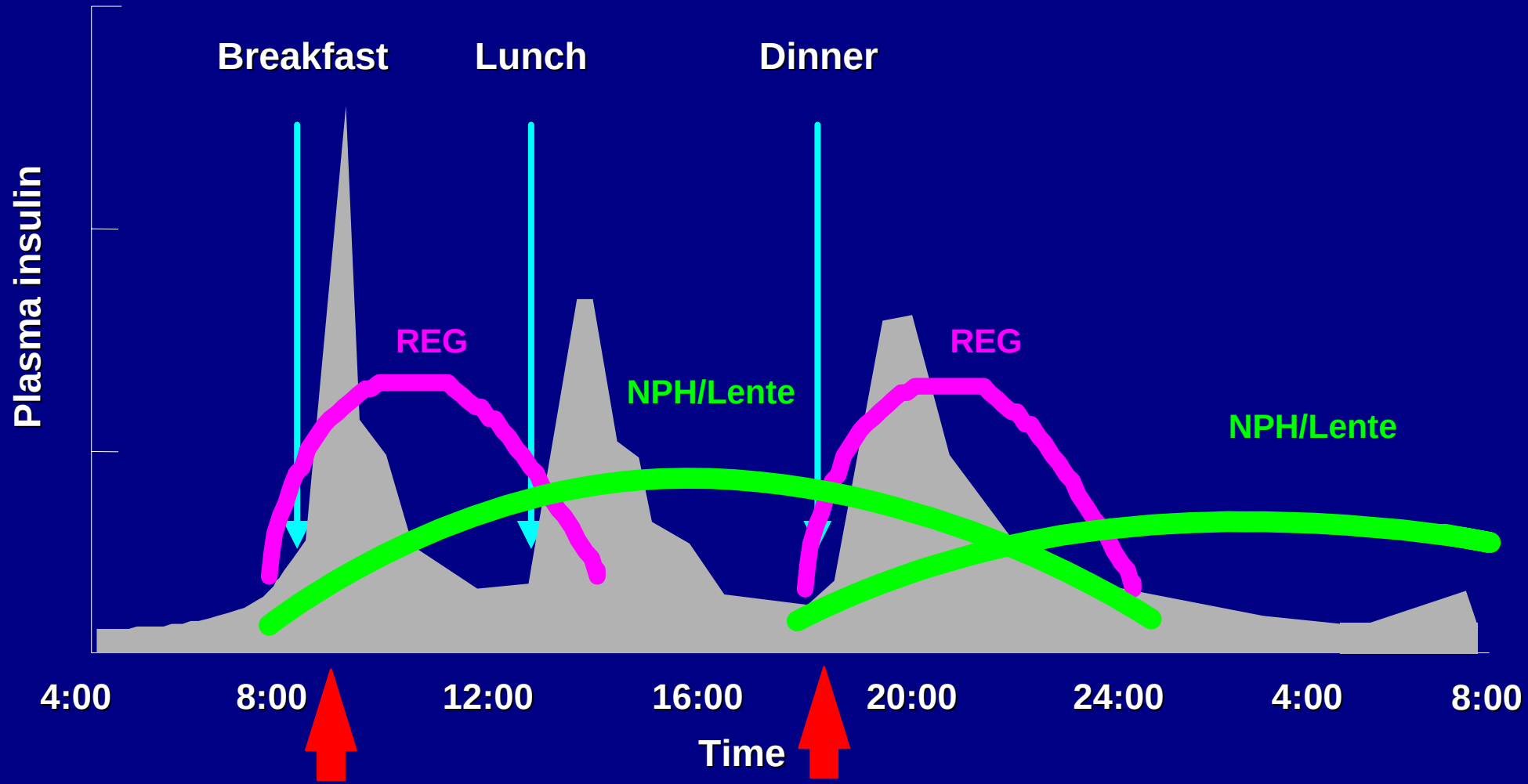
Options in Insulin Therapy

- Current
  - Multiple injections
  - Insulin pump (CSII)
- Future
  - Implant (artificial pancreas)
  - Transplant (pancreas; islet cells)

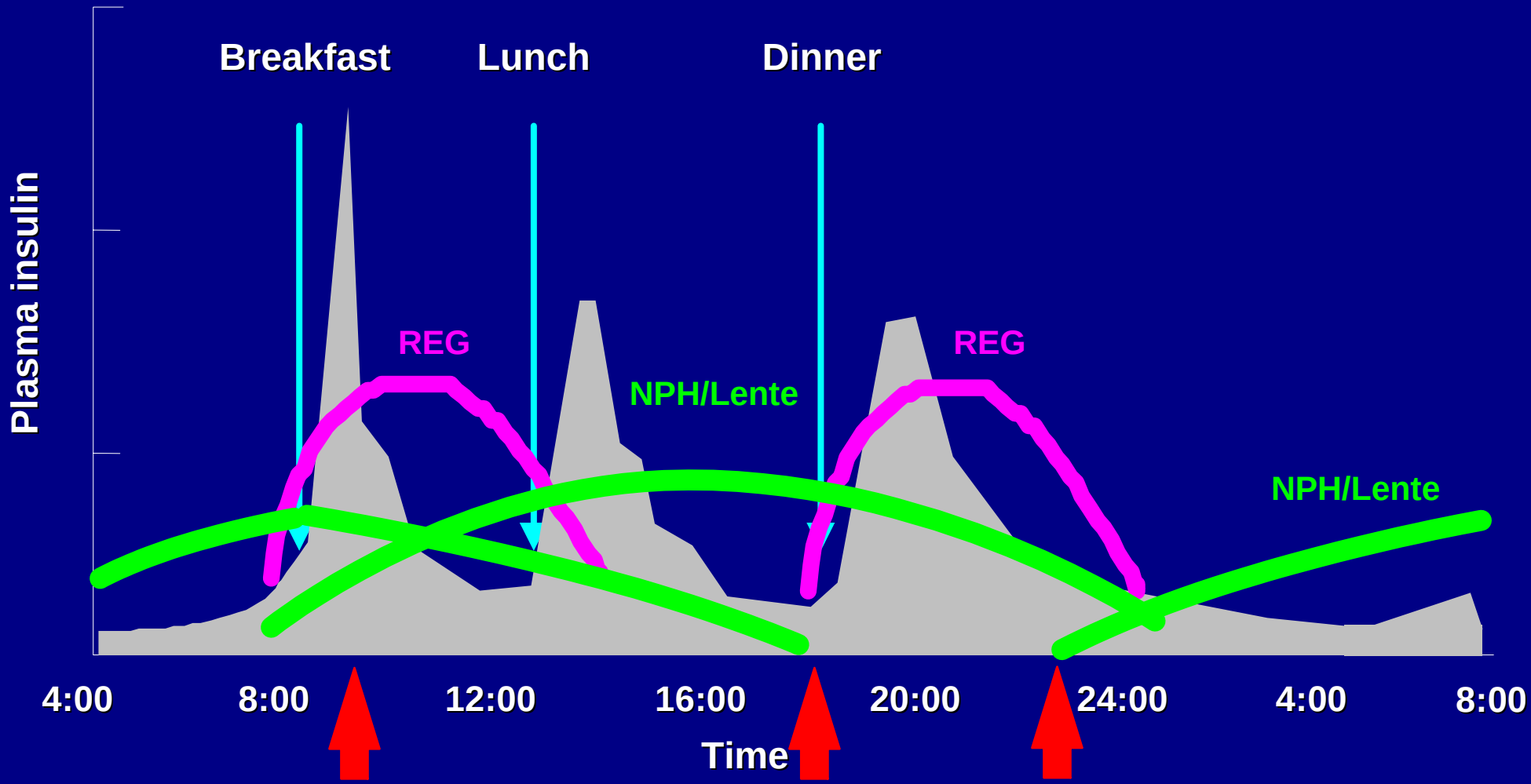
Physiological Serum Insulin Secretion Profile



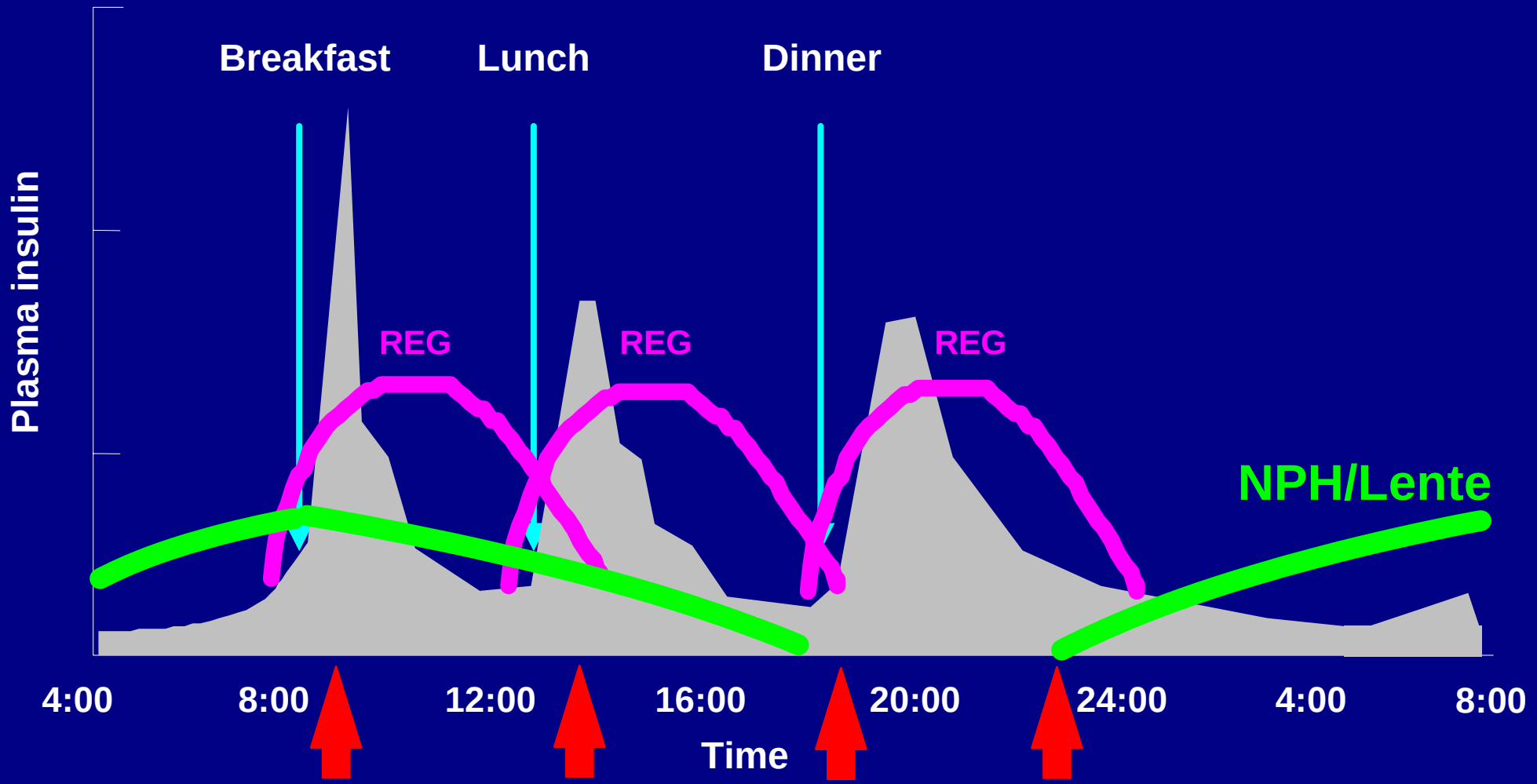
Classical “Split-mixed” Treatment Program



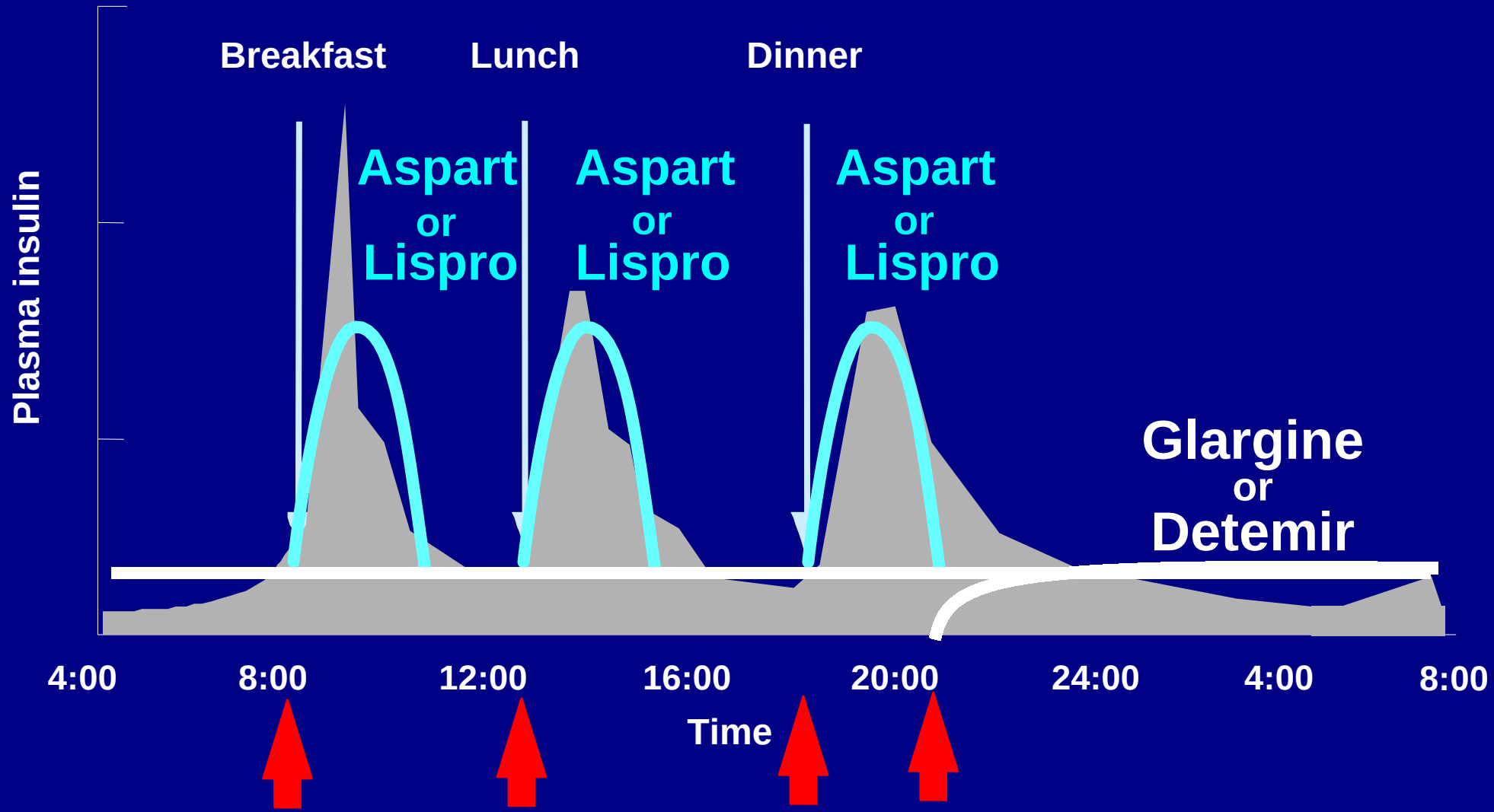
“Split-mixed” Program with Bedtime Intermediate Insulin



Basal/Bolus Insulin Absorption Pattern
Standard Insulin Preparations



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



Novo Nordisk devices in diabetes care

- First pen (NovoPen 1) launched in 1985
  - Committed to developing one new insulin administration system per year.

Lilly Insulin Pens

Introducing InDuo™

- The world's first combined insulin doser and blood glucose monitoring system
- A major break-through in Diabetes Care

InDuo™ - Integration

Feature

- Combined insulin doser and blood glucose monitor

InDuo™ - Compact Size

Feature

- Compact, discreet design

Benefit

- Allows discreet testing and injecting anywhere, anytime

InDuo™ - Doser Remembers

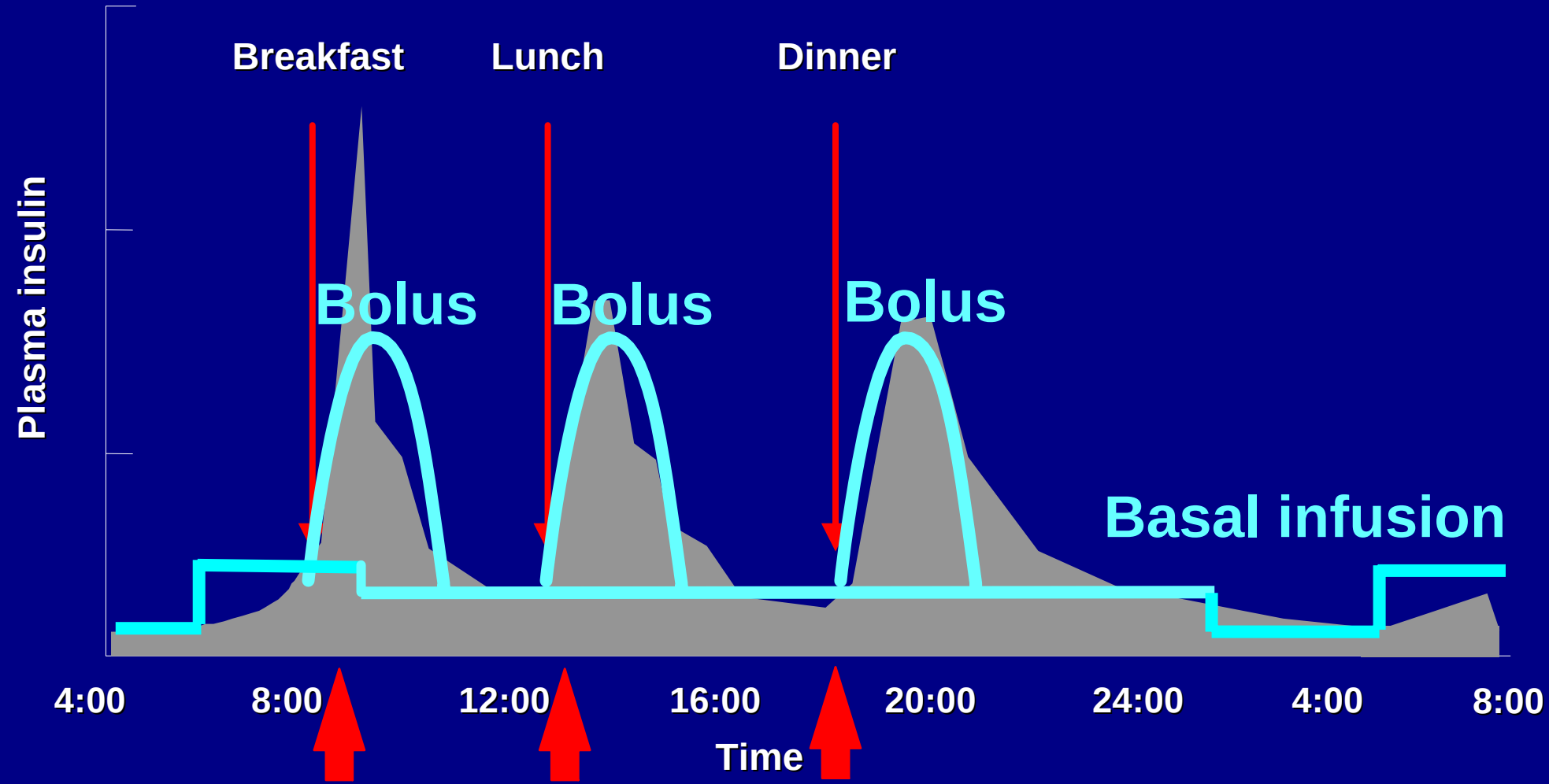
Feature

- Remembers amount of insulin delivered and time since last dose

Benefit

- Helps people inject the right amount of insulin at the right time

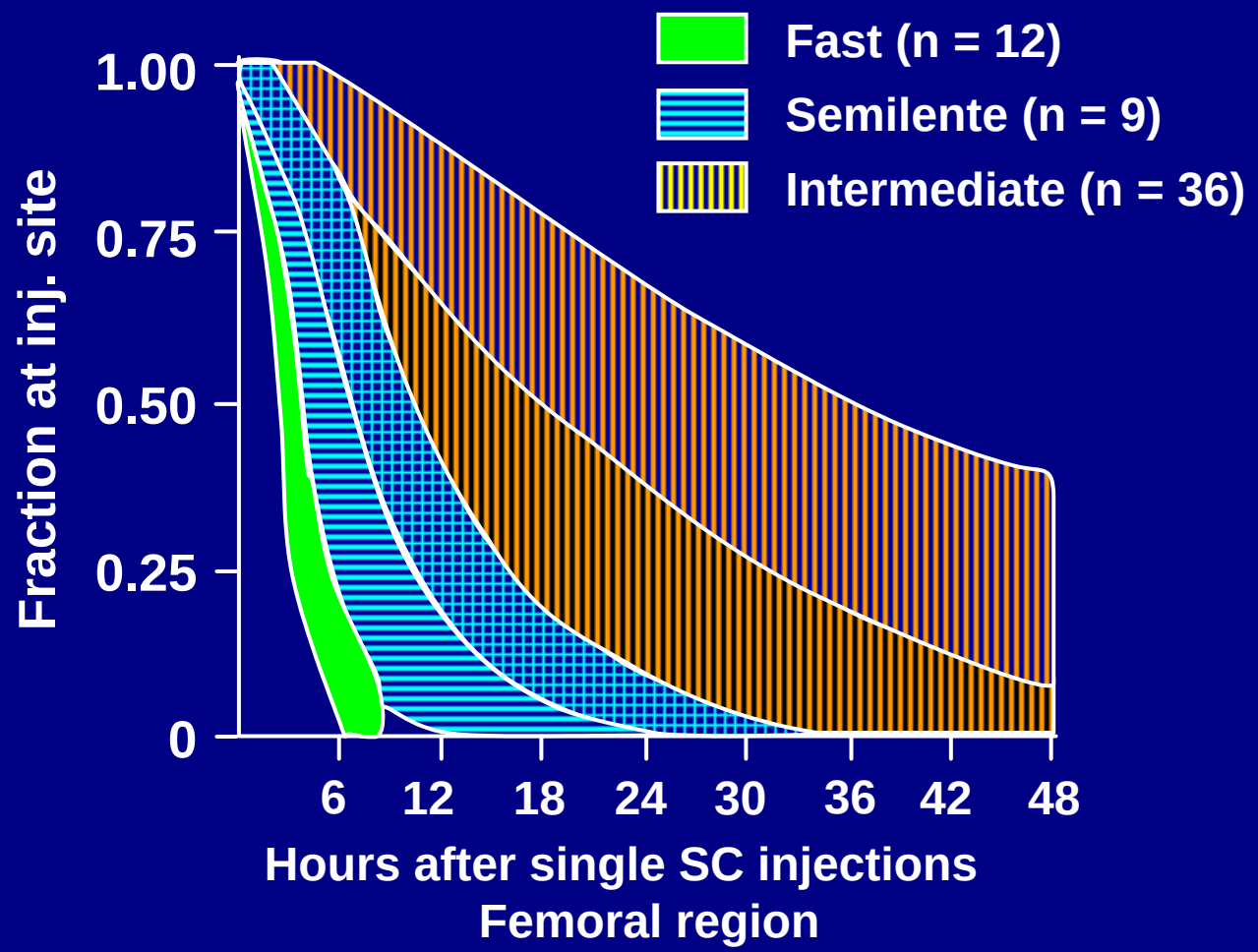
Variable Basal Rate: CSII Program



Variability of Insulin Absorption

CSII <2.8%

Subcutaneous Injectable 10% to 52%

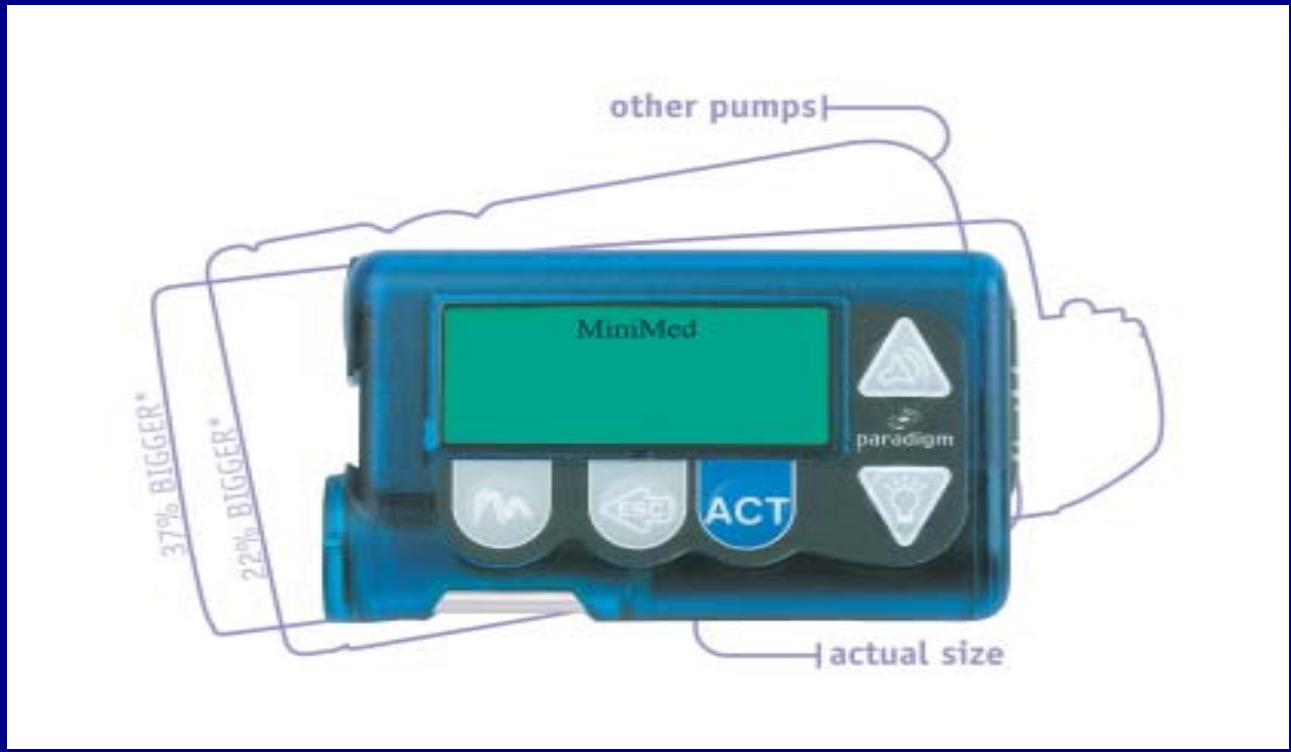


Lauritzen. *Diabetologia.* 1983;24:326–329.

History of Pumps


MiniMed 508
12:43 PM
sel
act
stop
bol
act
MiniMed

PARADIGM PUMP



Paradigm.
Simple. Easy.

Pump Infusion Sets

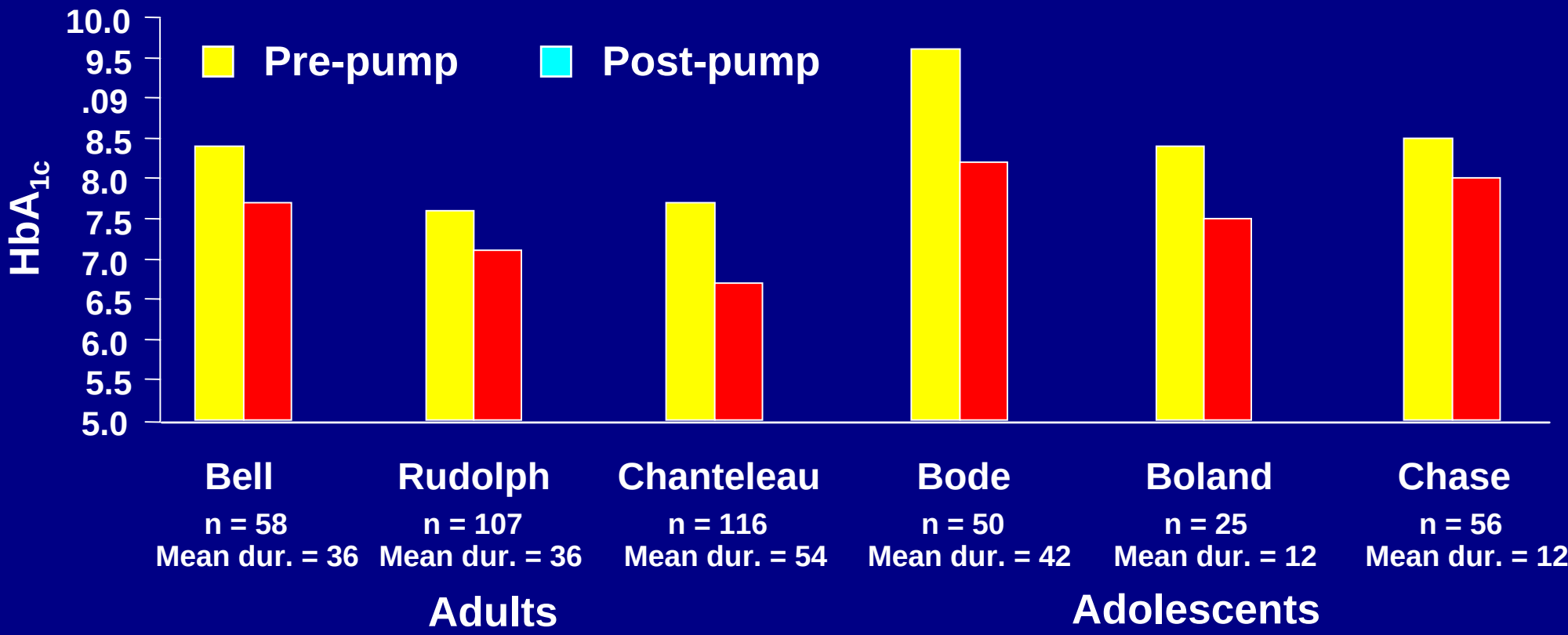
Softset QR

Silhouette

Metabolic Advantages with CSII

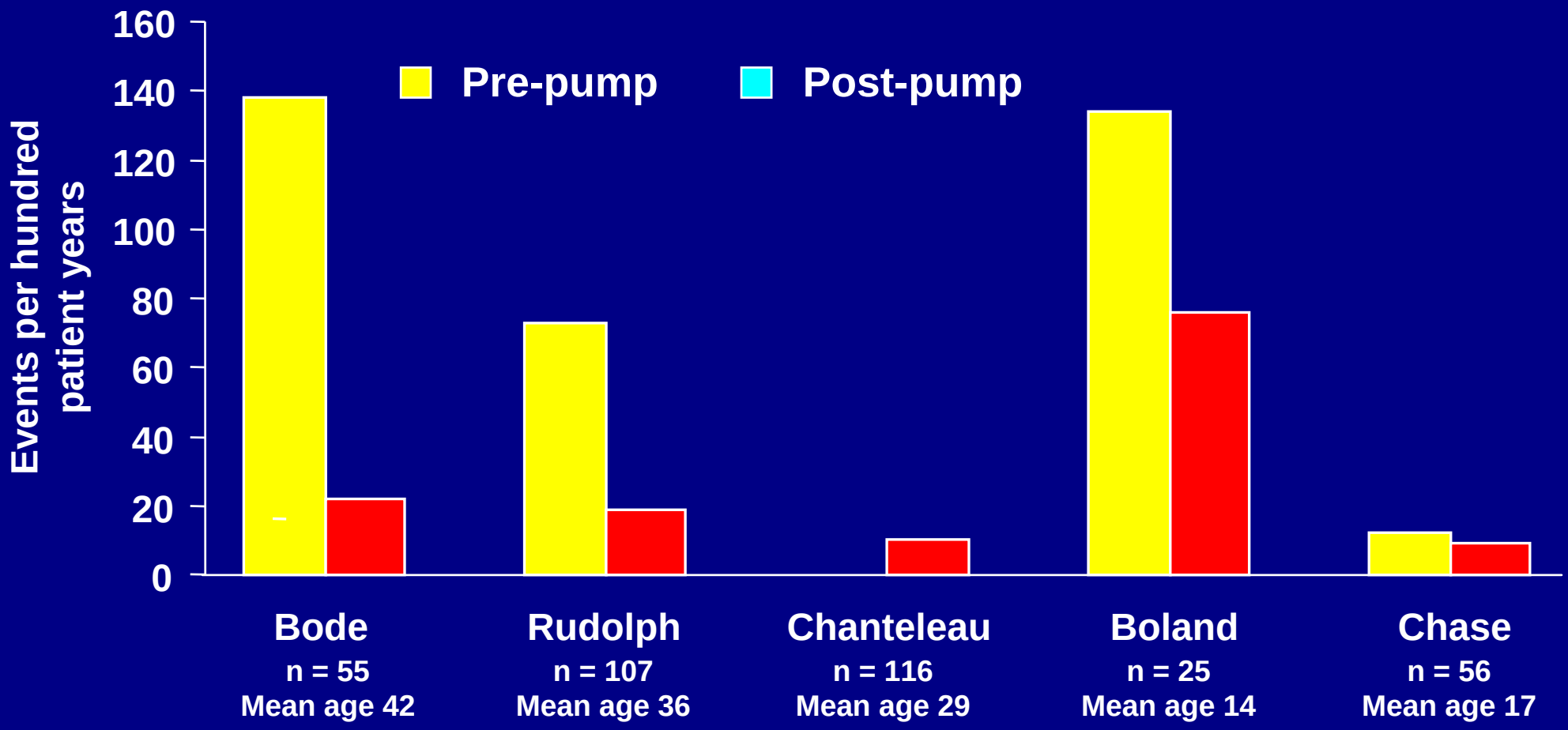
- Improved glycemic control
- Better pharmacokinetic delivery of insulin
  - Less hypoglycemia
  - Less insulin required
- Improved quality of life

CSII Reduces HbA_{1c}



Chantelau E, et al. *Diabetologia*. 1989;32:421–426; Bode BW, et al. *Diabetes Care*. 1996;19:324–327; Boland EA, et al. *Diabetes Care*. 1999;22:1779–1784; Bell DSH, et al. *Endocrine Practice*. 2000;6:357–360; Chase HP, et al. *Pediatrics*. 2001;107:351–356.

CSII Reduces Hypoglycemia

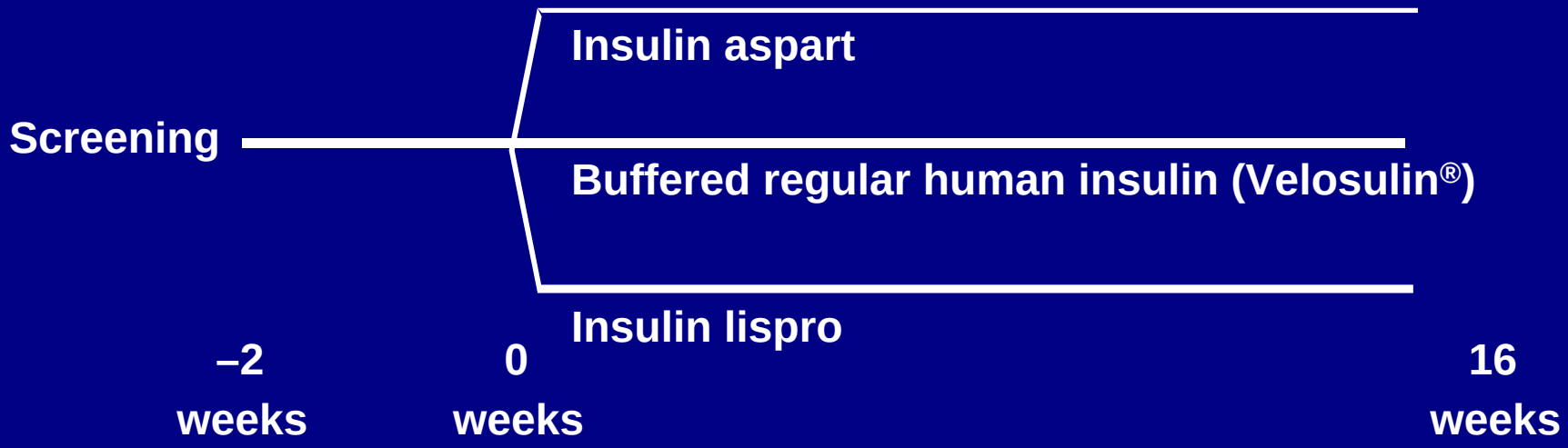


Chantelau E, et al. *Diabetologia*. 1989;32:421–426; Bode BW, et al. *Diabetes Care*. 1996;19:324–327; Boland EA, et al. *Diabetes Care*. 1999;22:1779–1784; Chase HP, et al. *Pediatrics*. 2001;107:351–356.

CSII
Factors Affecting HbA_{1c}

- Monitoring
  - HbA_{1c} = 8.3 - (0.21 x BG per day)
- Recording 7.4 vs 7.8
- Diet practiced
  - CHO: 7.2
  - Fixed: 7.5
  - Other: 8.0
- Insulin type
  - Lispro: 7.3
  - R: 7.7

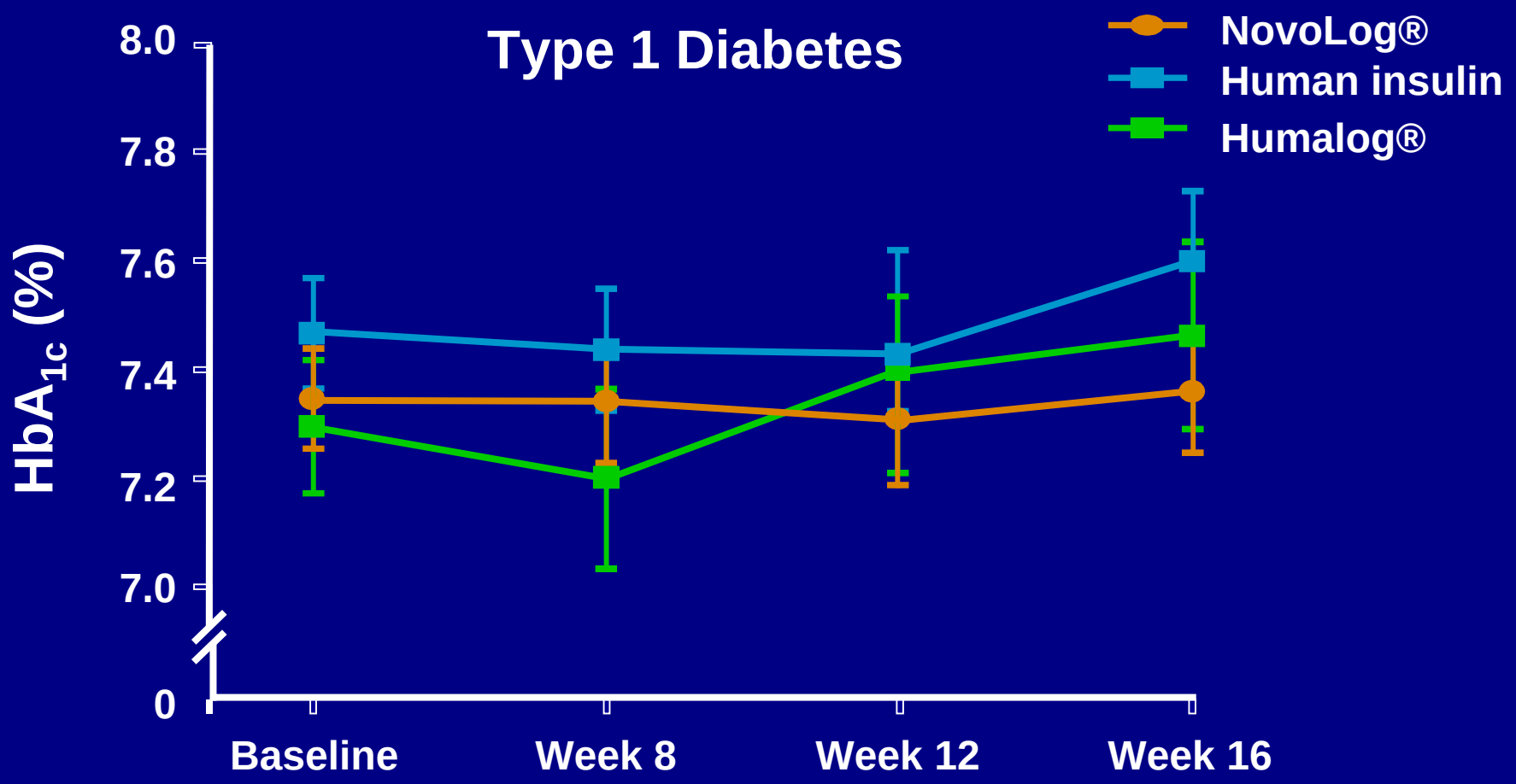
Insulin aspart versus buffered R *versus* insulin lispro in CSII study:



- 146 patients in the USA; 2–25 years with Type 1 diabetes; 7% ≤ HbA_{1c} ≤ 9%; previously treated with CSII for 3 months

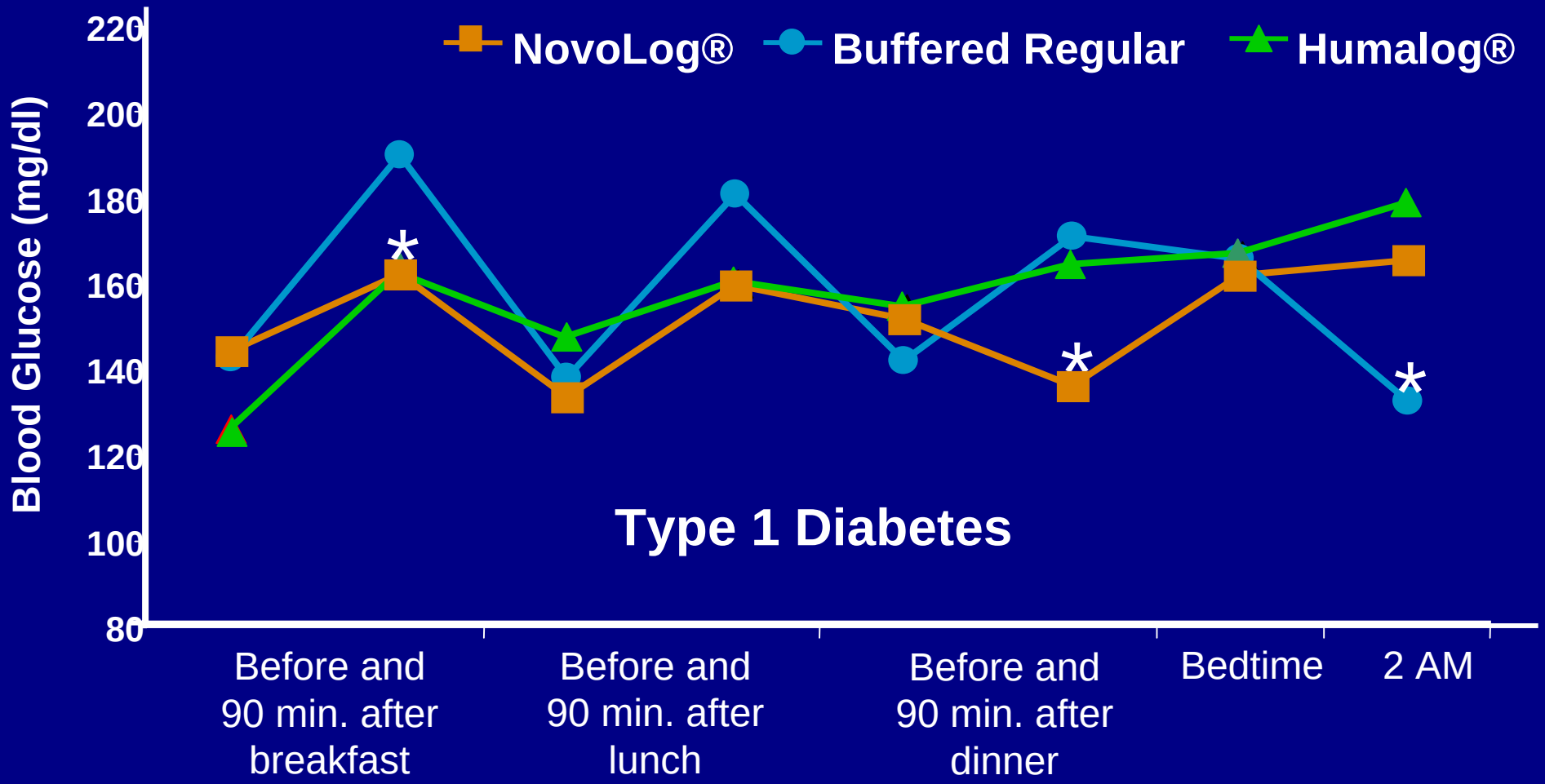
Bode et al: Diabetes Care, March 2002

Glycemic Control with CSII



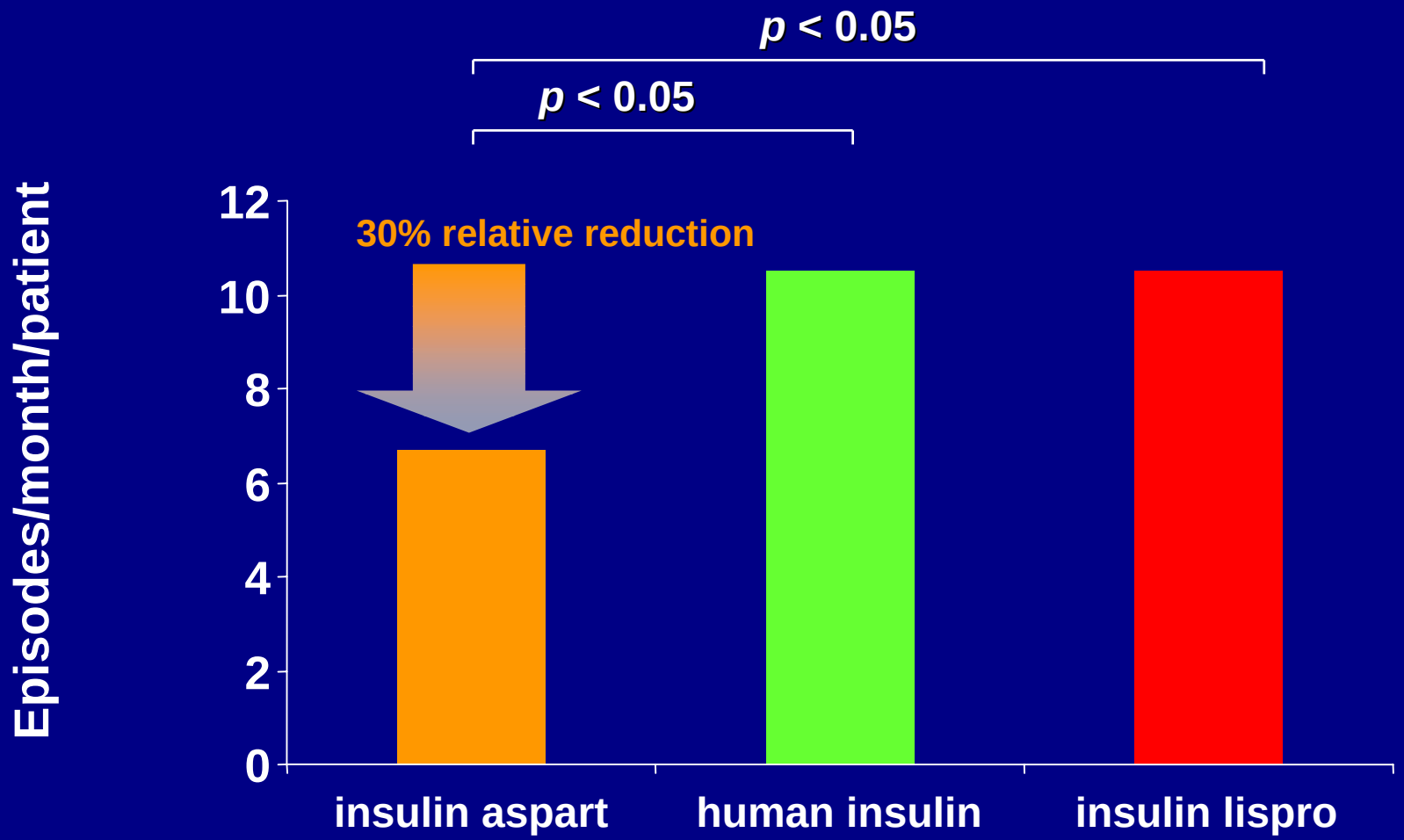
Bode, *Diabetes* 2001 ; 50(S2):A106

Self-Monitored Blood Glucose in CSII



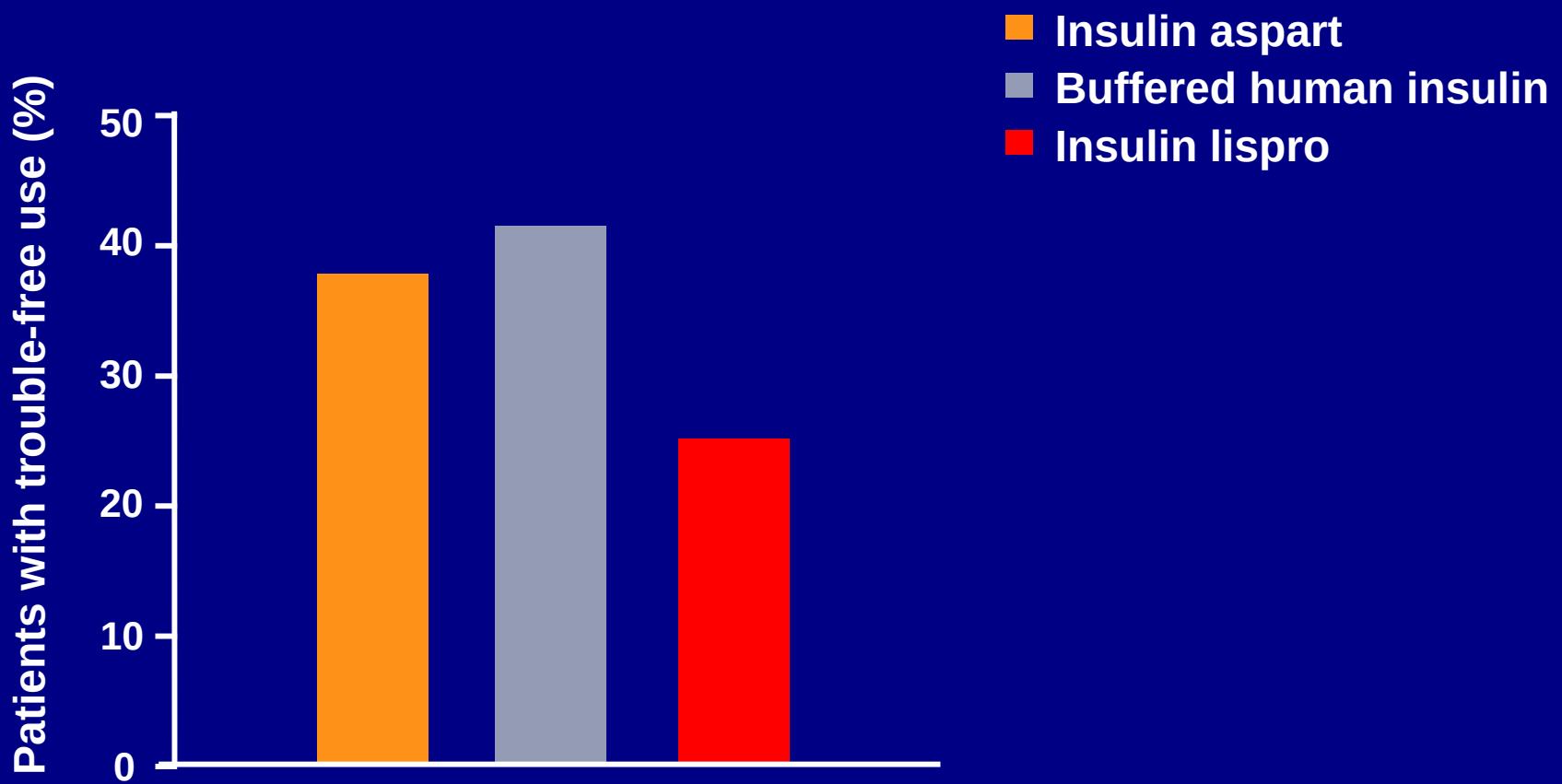
Bode, *Diabetes* 2001 ; 50(S2):A106

Symptomatic or Confirmed Hypoglycaemia



Bode et al: Diabetes Care, March 2002

Insulin aspart versus buffered R *versus* insulin lispro in CSII study: pump compatibility



Data on file (study ANA 2024)

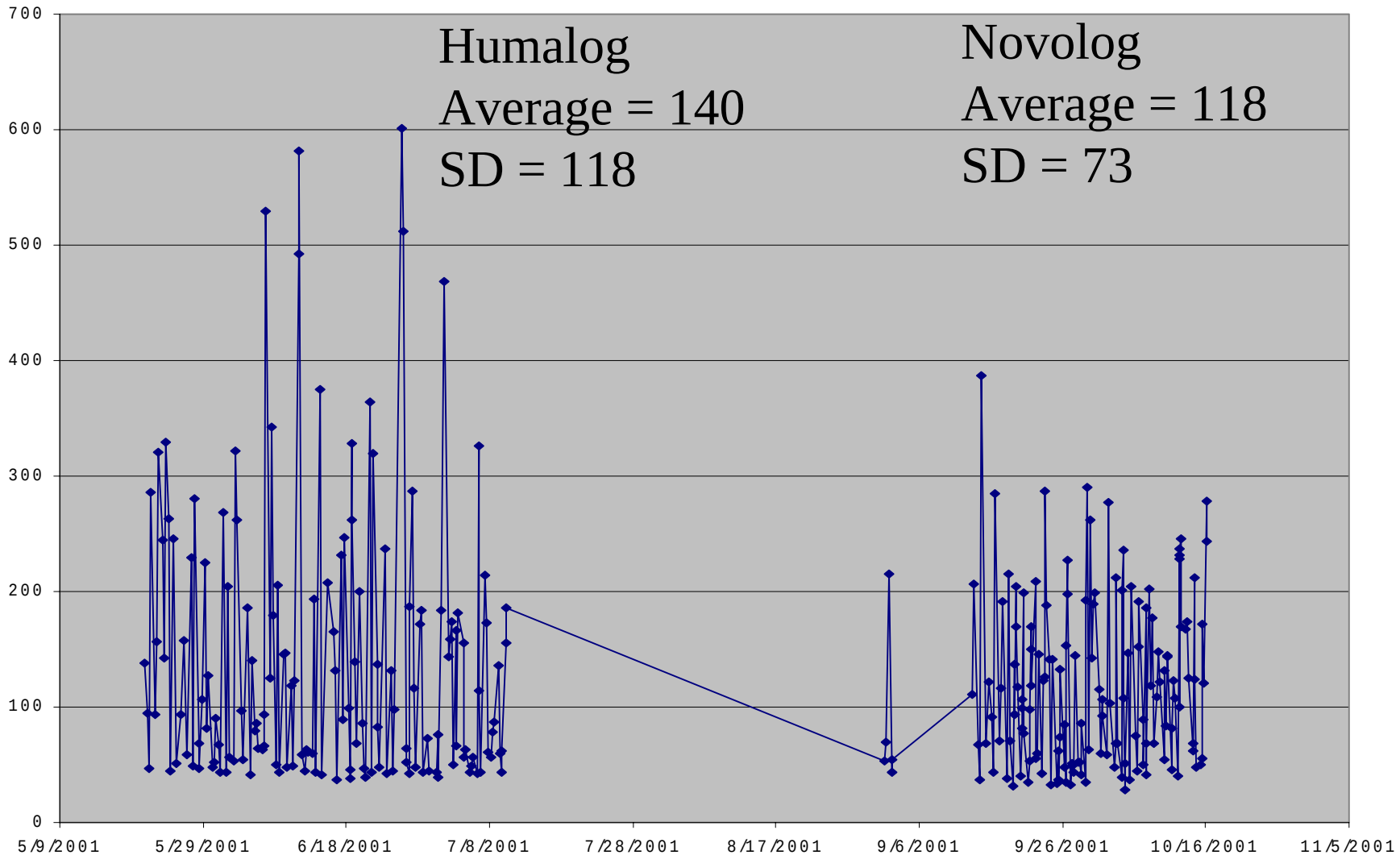
Case Study: 54 year old DM1 on CSII with Lipoatrophy and Insulin Antibodies

- DM 1 onset age 21, 1968
- CSII 1998, A1C 7.8%
- Lipoatrophy with humalog 1999-2000
- Changed to Velosulin BR with still lipoatrophy
- Control suboptimal A1C 7.8%

Case Study: 54 year old DM1 on CSII with Lipoatrophy and Insulin Antibodies

- 7-10-01 A1C 7.8% on 28.8 units per day
- SMBG Avg BG 140, SD 118 based on 2.9 tests/day
- Insulin antibodies positive 1:32
- Changed to Novolog 1 to 1 transfer
- 10-16-01 A1C 6.5% on 20.8 units per day
- SMBG Avg 118, SD 73 based on 3.0 tests per day

DM 1 CSII Patient: Humalog to Novolog

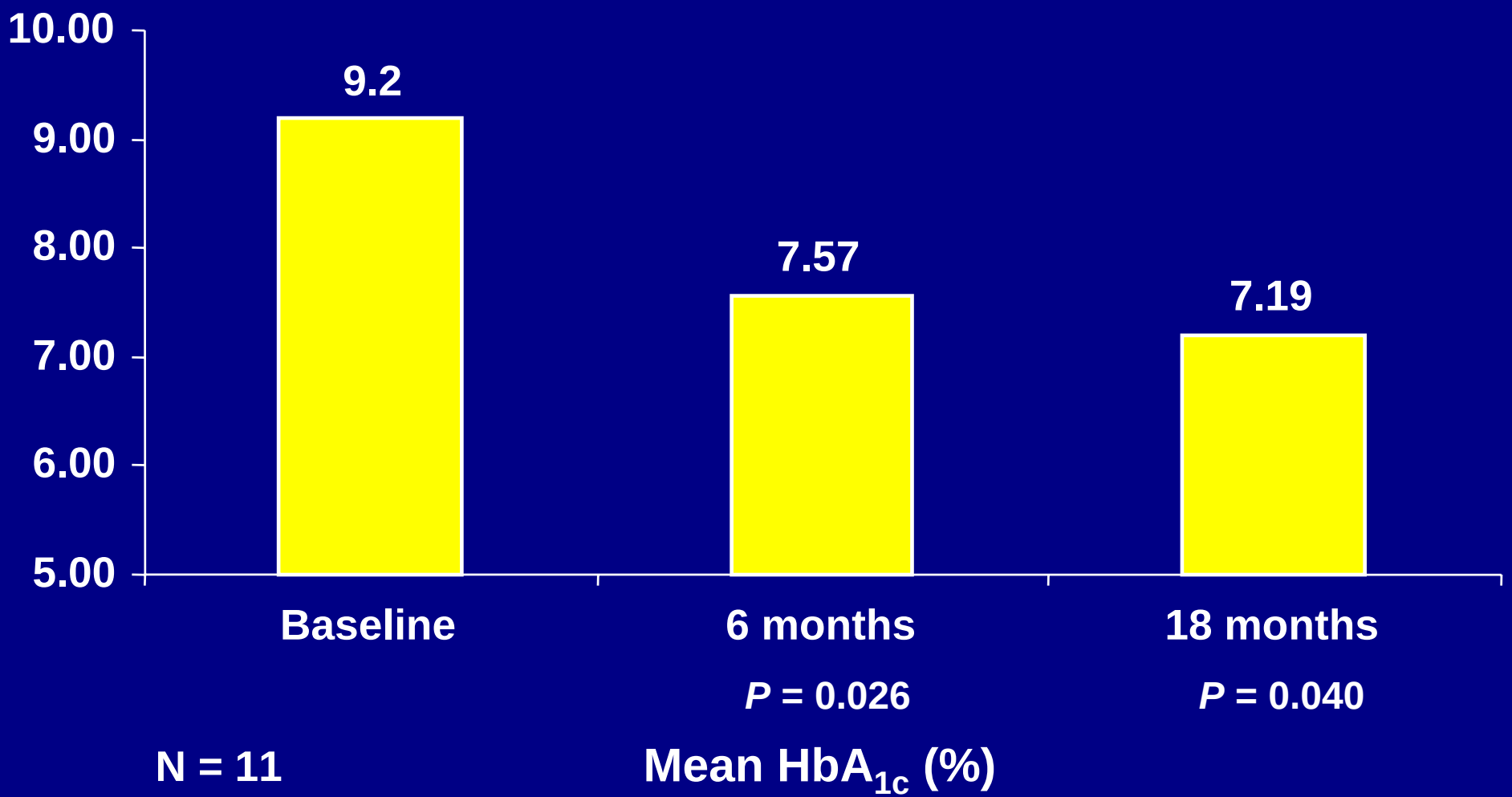


Case Study: 54 year old DM1 on CSII with Lipoatrophy and Insulin Antibodies

- 2-5-02 A1C 6.3% on 20 units per day
- SMBG Avg BG 104, SD 74 based on 3.1 tests/day

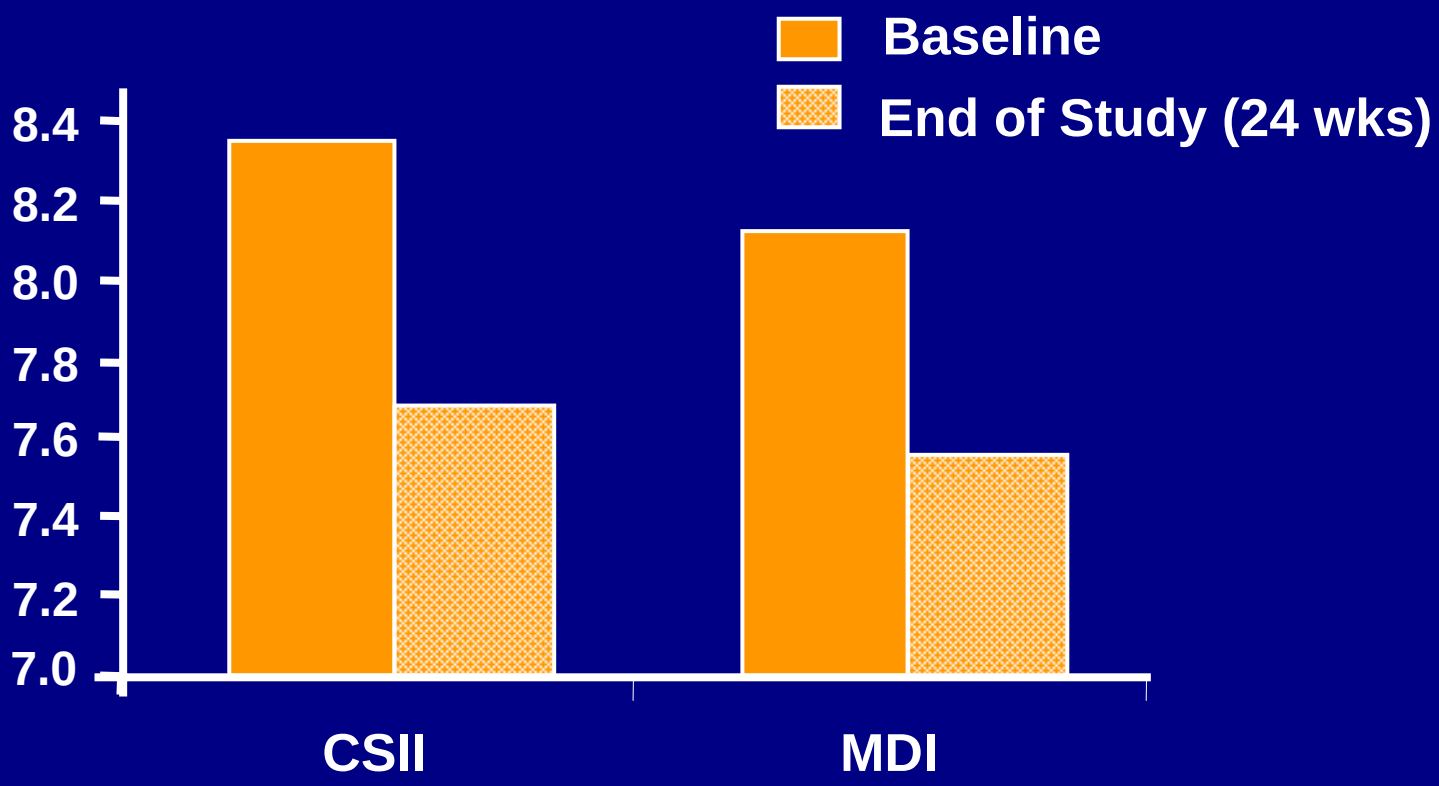
CSII Usage in Type 2 Patients

Atlanta Diabetes Experience



Glycemic Control in Type 2 DM: CSII *vs* MDI in 127 patients

- A1C

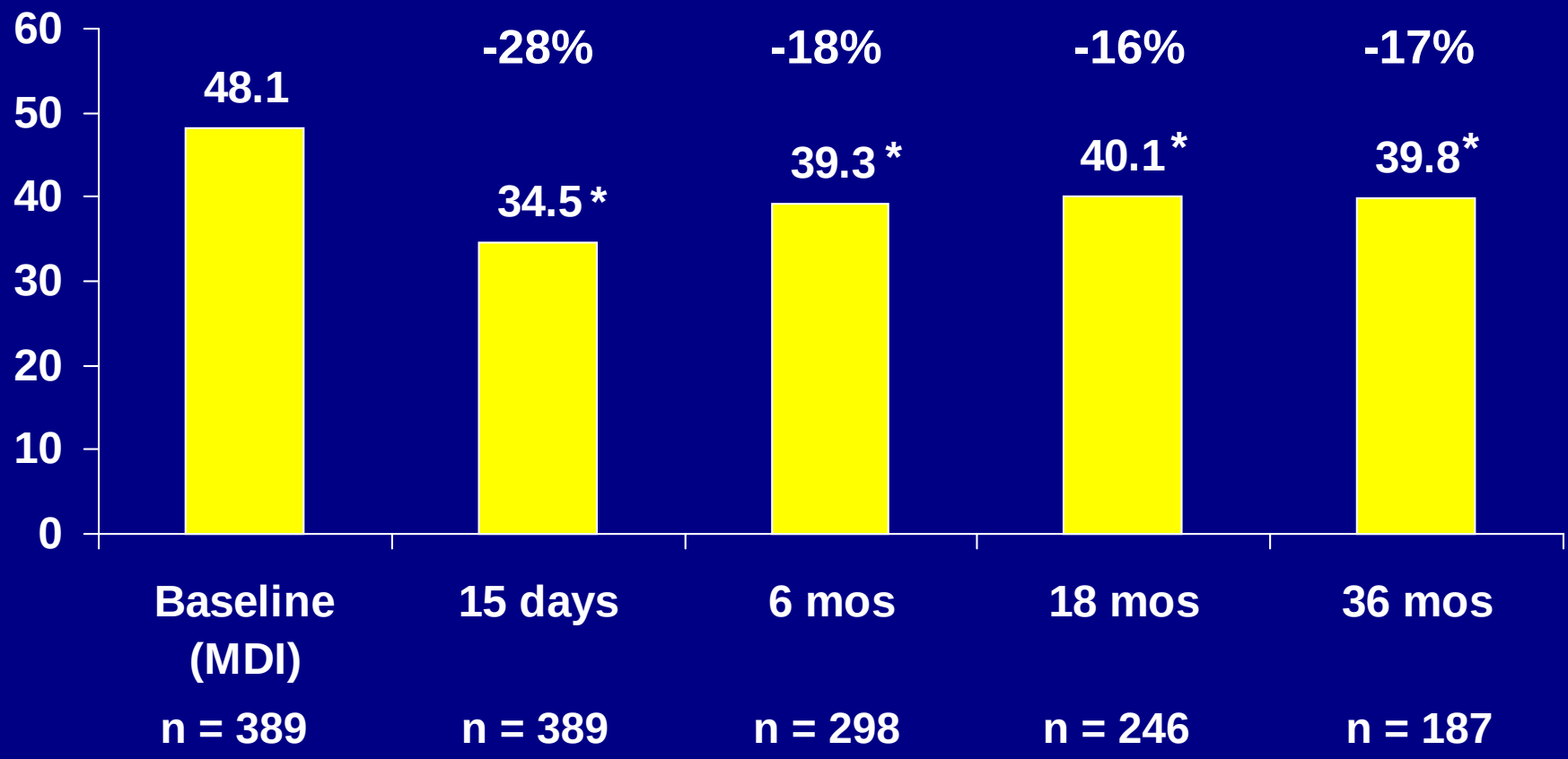


Raskin, *Diabetes* 2001; 50(S2):A106

DM 2 Study: CSII vs MDI

- Overall treatment satisfaction improved in the CSII group: 59% pre to 79% at 24 weeks
- 93% in the CSII group preferred the pump to their prior regiment (insulin +/- OHA)
- CSII group had less hyperglycemic episodes (3 subjects, 6 episodes vs. 11 subjects, 26 episodes in the MDI group)

Insulin Reduction Following CSII



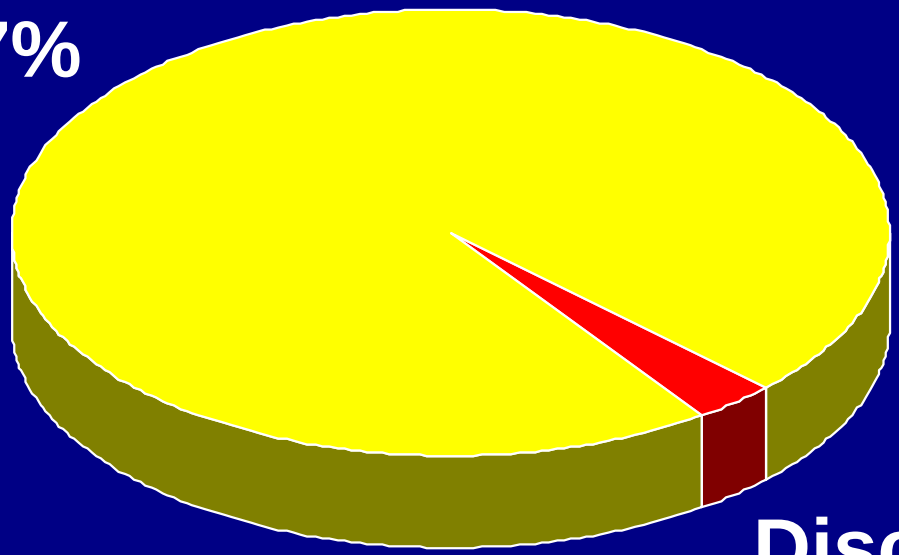
* *P* <0.001

Normalization of Lifestyle

- Liberalization of diet — timing & amount
- Increased control with exercise
- Able to work shifts & through lunch
- Less hassle with travel — time zones
- Weight control
- Less anxiety in trying to keep on schedule

Current Continuation Rate

Continuous Subcutaneous Insulin Infusion (CSII)

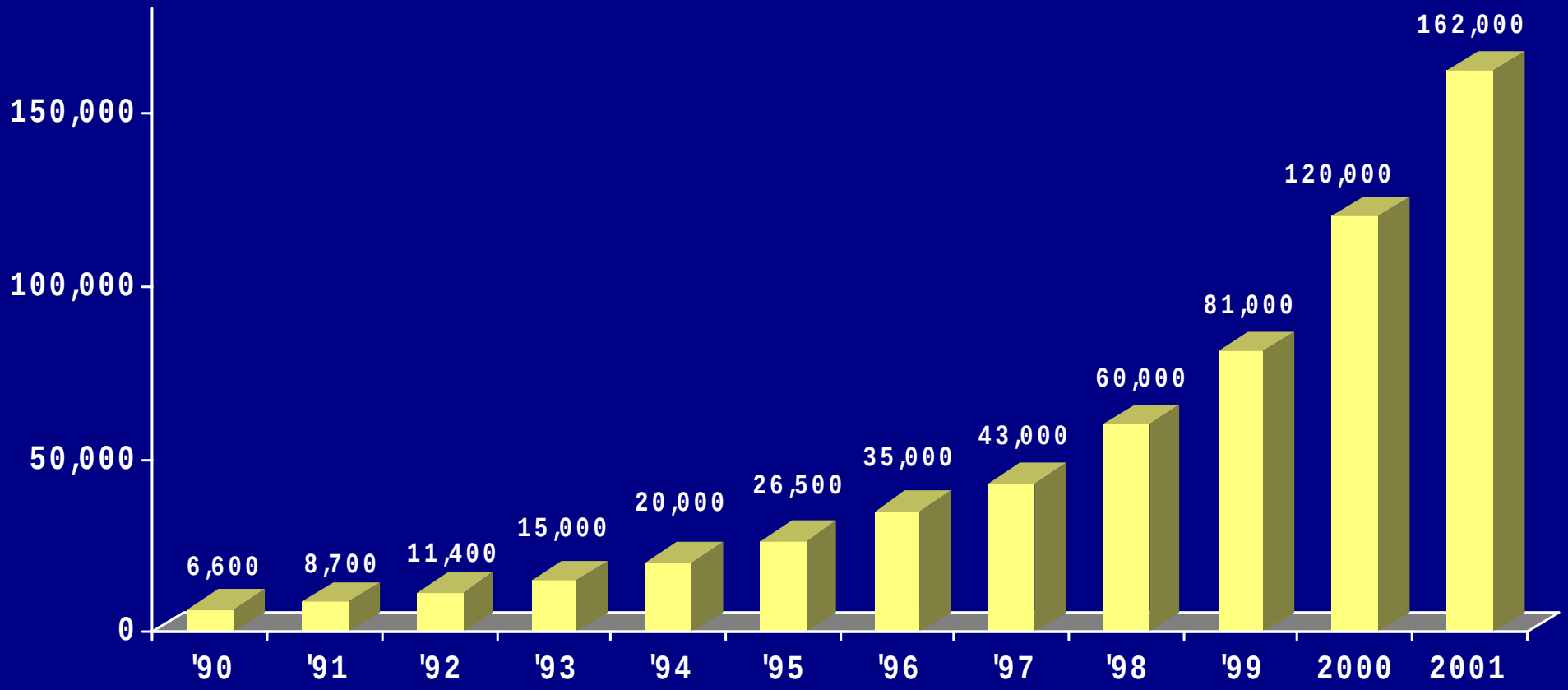


N = 165
Average Duration = 3.6 years
Average Discontinuation <1%/yr

Bode BW, et al. *Diabetes*. 1998;47(suppl 1):392.

U.S. Pump Usage

Total Patients Using Insulin Pumps



Pump Therapy Indications

- HbA_{1c} >7.0%
- Frequent hypoglycemia
- Dawn phenomenon
- Exercise
- Pediatrics
- Pregnancy
- Gastroparesis
- Hectic lifestyle
- Shift work
- Type 2

Marcus. *Postgrad Med*. 1995.

Poor Candidates for CSII

- Unwilling to comply with medical follow-up
- Unwilling to perform self blood glucose monitoring 4 times daily
- Unwilling to quantitate food intake

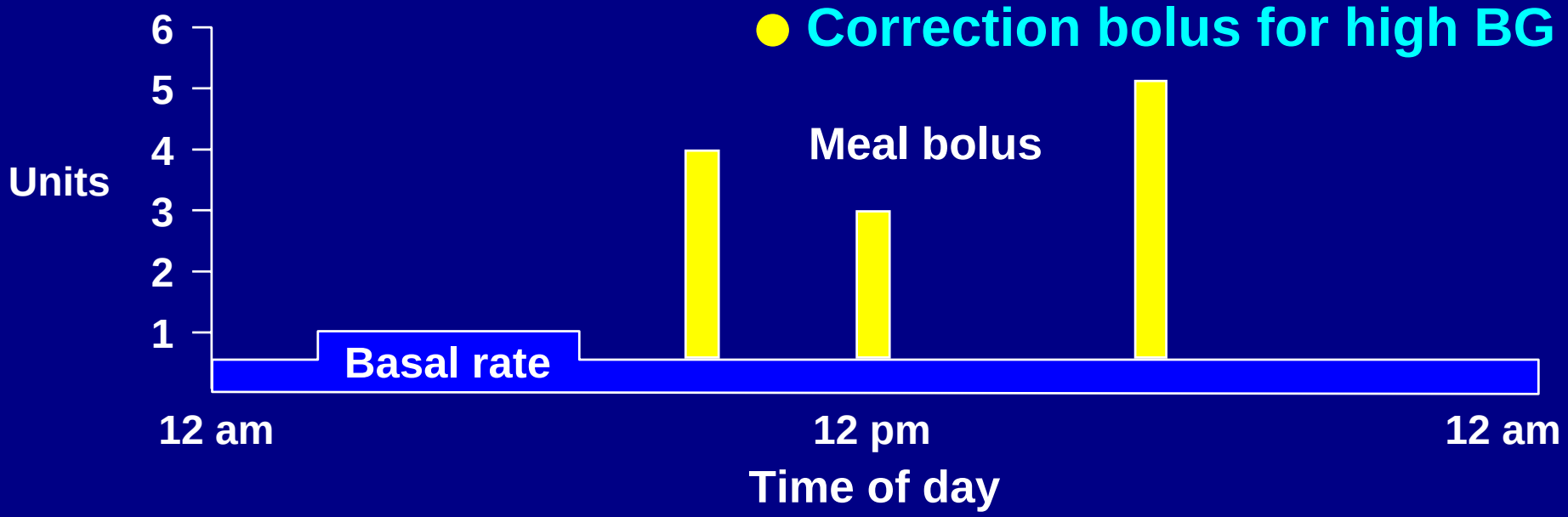
Pump Therapy

Basal rate

- Continuous flow of insulin
- Takes the place of NPH or ultralente insulin

Meal boluses

- Insulin needed pre-meal
  - Pre-meal BG
  - Carbohydrates in meal
  - Activity level
- Correction bolus for high BG



If HbA_{1c} is Not to Goal

Must look at:

- SMBG frequency and recording
- Diet practiced
  - Do they know what they are eating?
  - Do they bolus for all food and snacks?
- Infusion site areas
  - Are they in areas of lipohypertrophy?
- Other factors:
  - Fear of low BG
  - Overtreatment of low BG

Future of Diabetes Management

Improvements in Insulin & Delivery

- Insulin analogs and inhaled insulin
- External pumps
- Internal pumps
- Continuous glucose sensors
- Closed-loop systems

GLUCOSE MONITORING SYSTEMS - Telemetry

Consumer Product

- **“Real time” glucose readings**
- **Wireless communication from sensor to monitor**
- **High and low glucose alarms**
- **FDA panel pending**

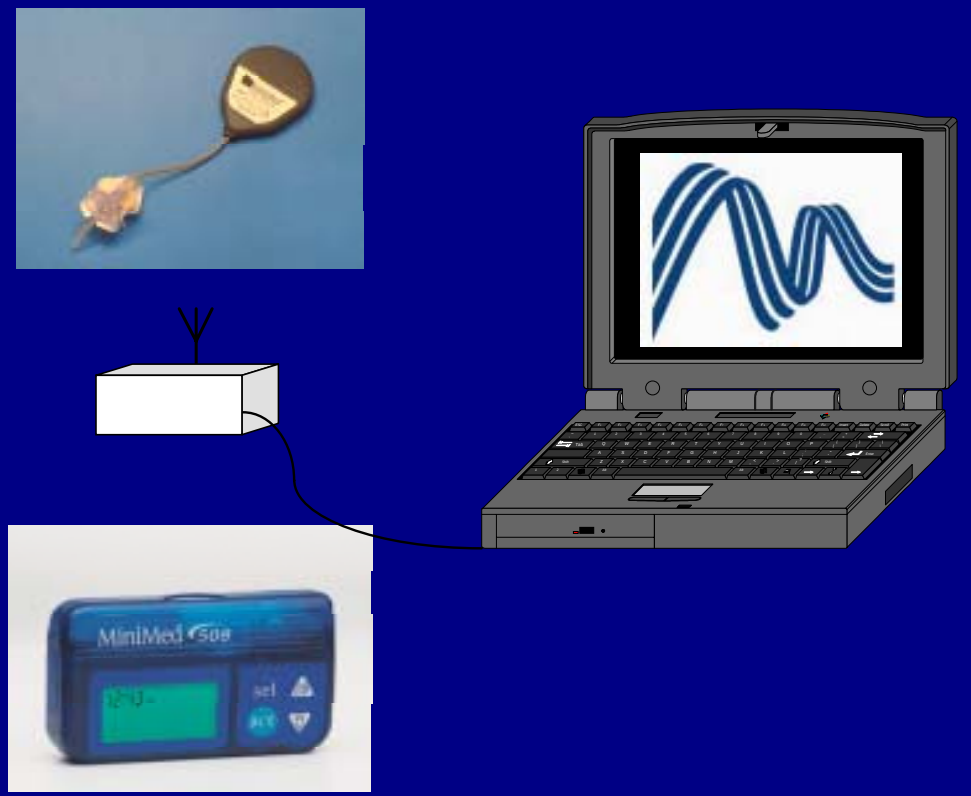
Closed-loop control using an external insulin pump and a subcutaneous glucose sensor

+

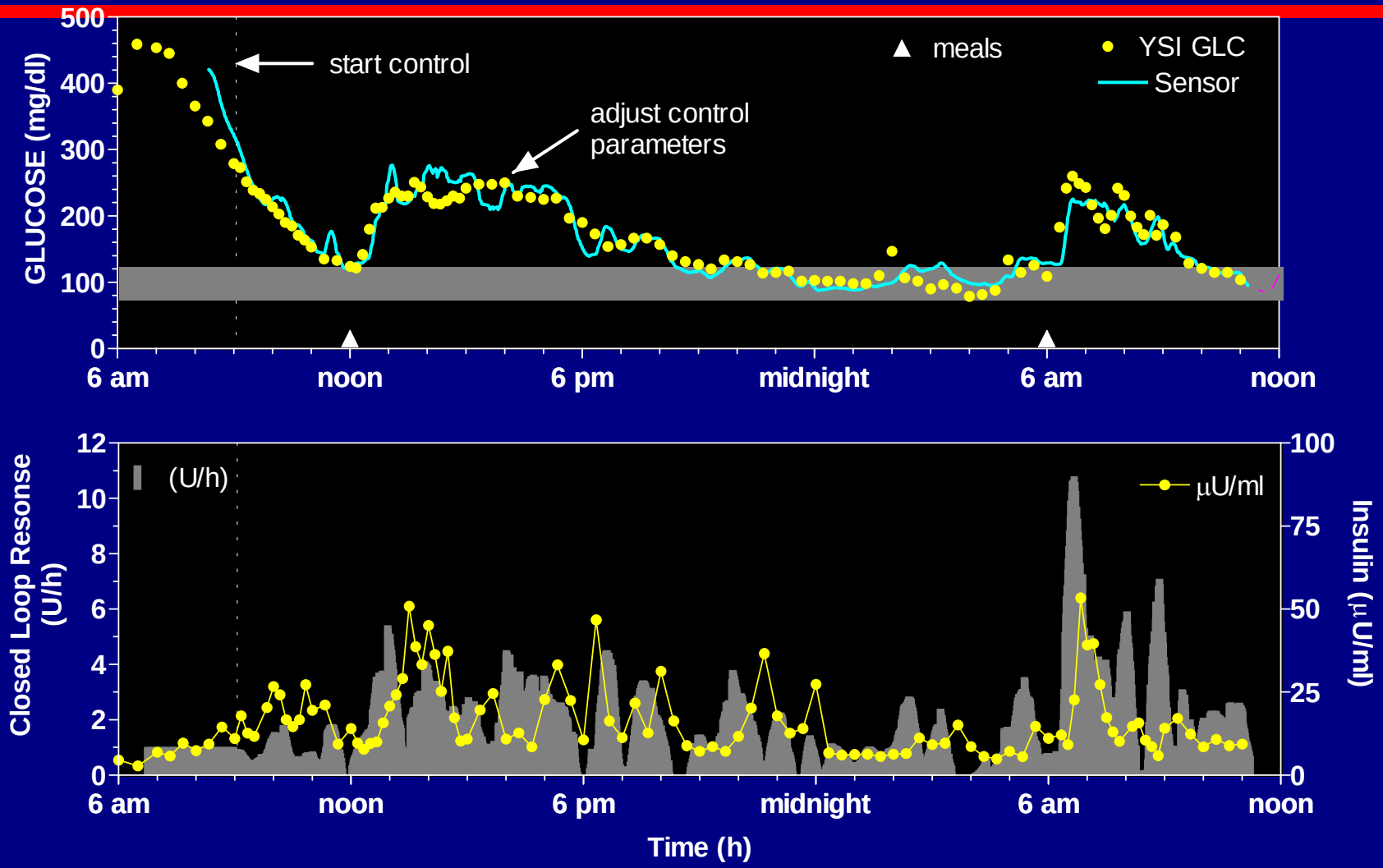
subcutaneous glucose sensor

Insulin infusion pump (currently MiniMed 508)

Closed-Loop Setup for Canine Studies



24-h Closed-Loop Control (diabetic canine)

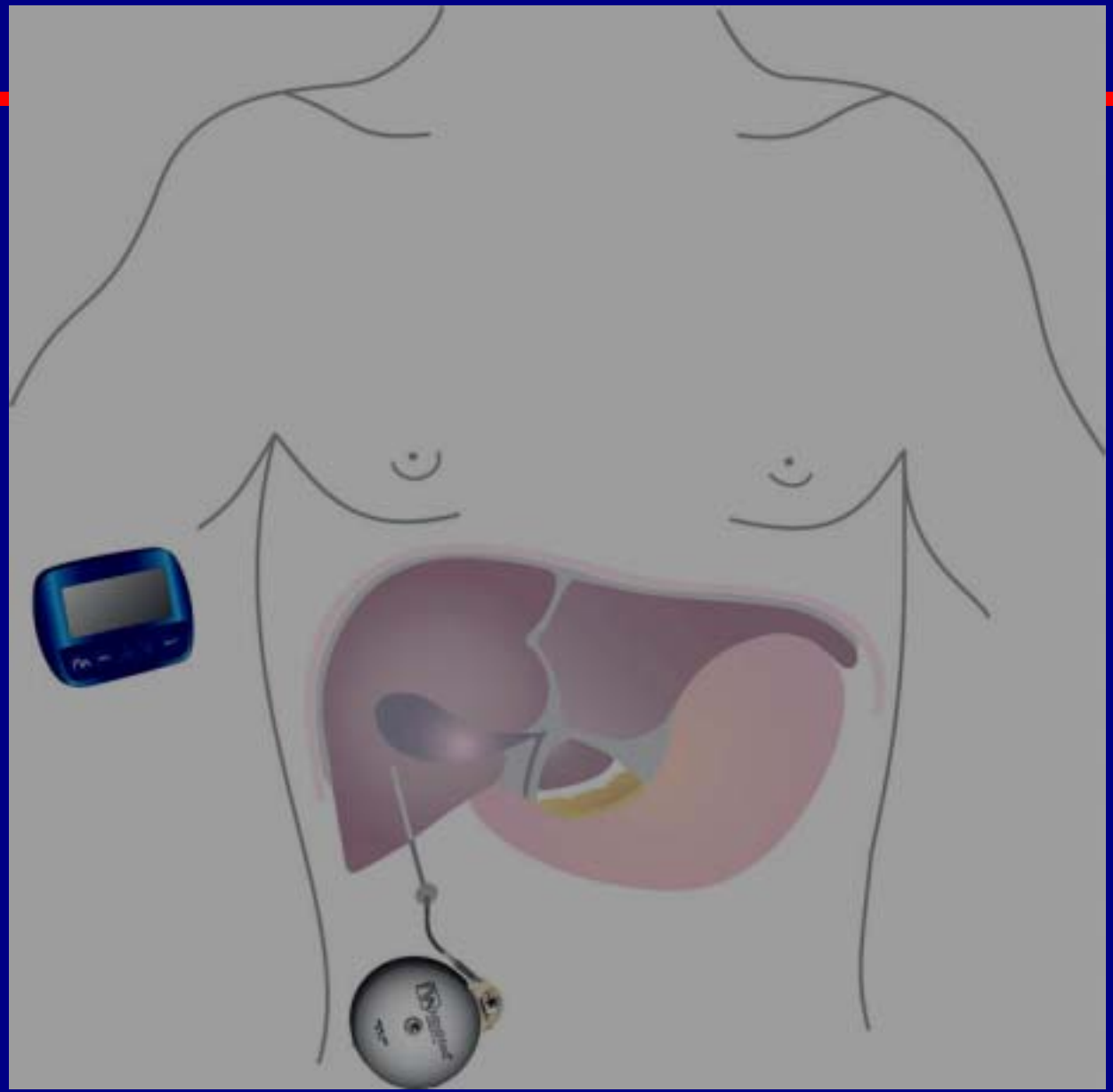


Implantable Pump

- Average HbA_{1c} 7.1%
- Hypoglycemic events reduce to 4 episodes per 100 pt-years

MiniMed 2007 System

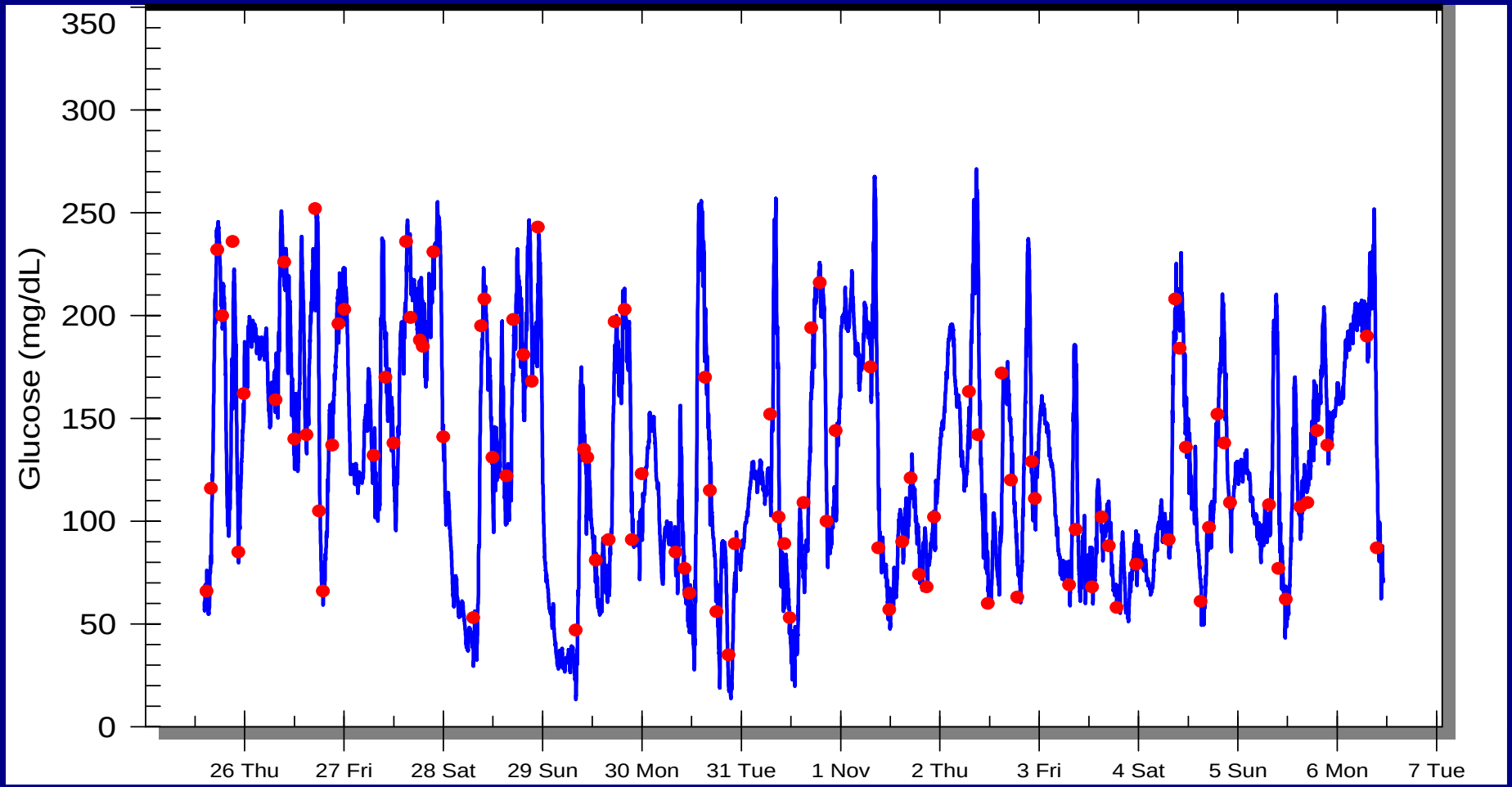
Implantable Insulin Pump Placement



Long-Term Glucose Sensor

LONG TERM IMPLANTABLE SYSTEM

Human Clinical Trial



Source: Medical Research Group, Inc.

Combine Pump and Sensor Technology

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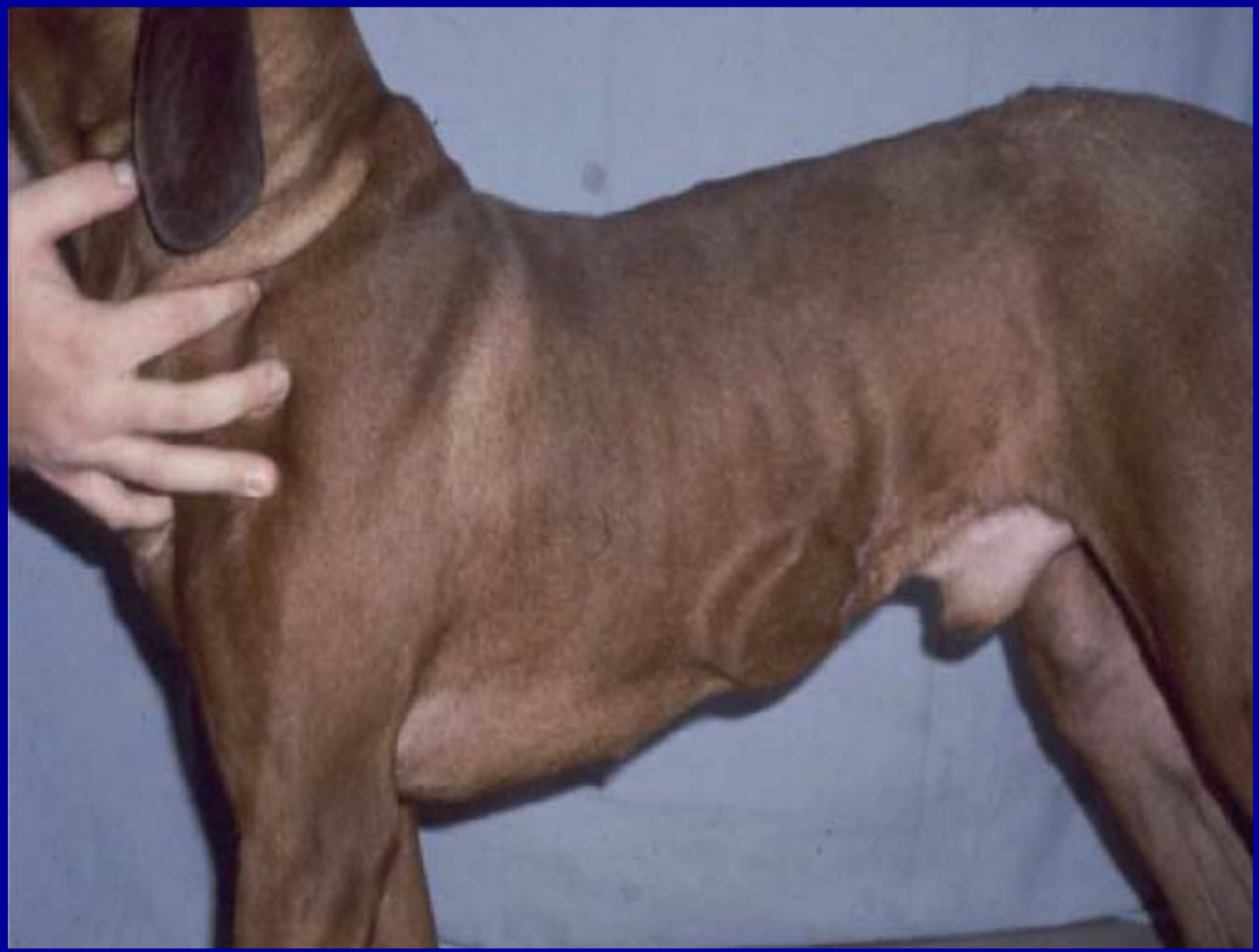
LTSS => Long Term Sensor System (“Open Loop Control”)

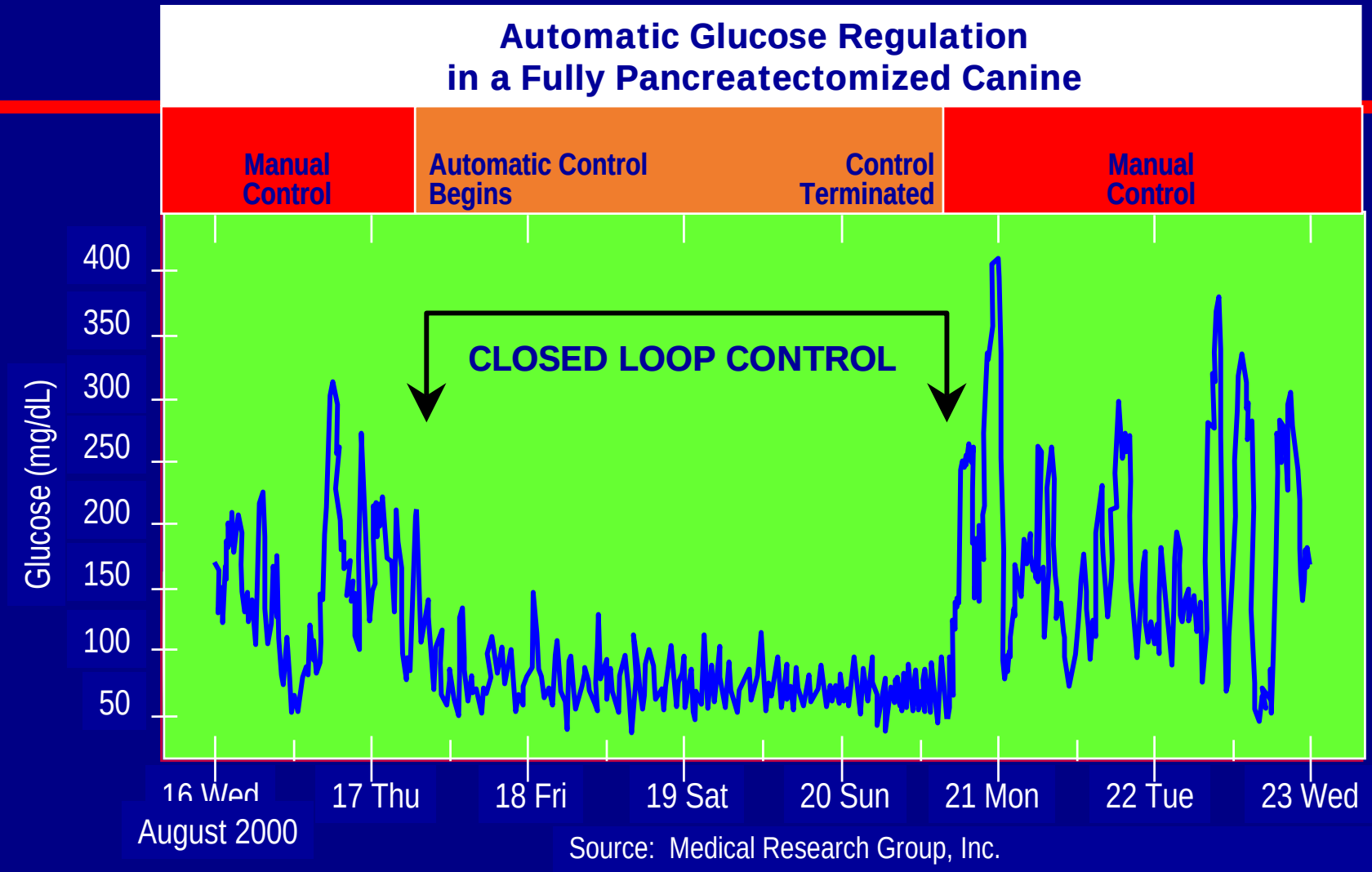
Using an RF Telemetry Link…...

Medtronic MiniMed's Implantable Biomechanical Beta Cell

Today's Reality
Open-Loop Glucose Control



LONG TERM IMPLANTABLE SYSTEM



Source: Medical Research Group, Inc.

Summary

- Insulin remains the most powerful agent we have to control diabetes
- When used appropriately in a basal/bolus format, near-normal glycemia can be achieved
- Newer insulins and insulin delivery devices along with glucose sensors will revolutionize our care of diabetes

Conclusion

Intensive therapy is the best way to treat patients with diabetes

QUESTIONS

- For a copy or viewing of these slides, contact

- WWW.adaendo.com