

New Insulins and Insulin Delivery Systems

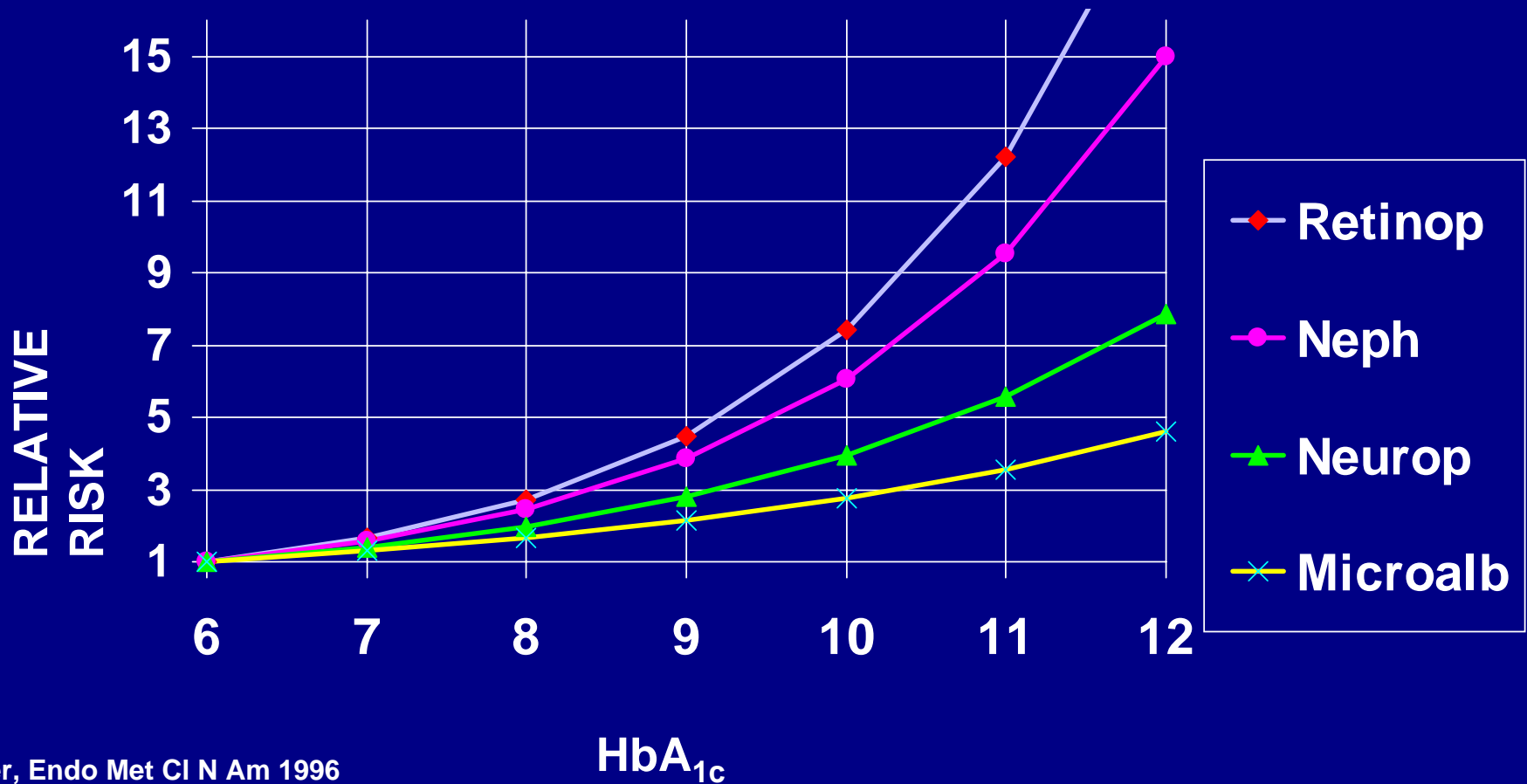
Bruce W. Bode, MD, FACE
Atlanta Diabetes Associates
Atlanta, Georgia

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

Relative Risk of Progression of Diabetic Complications by Mean HbA1C

Based on DCCT Data



HbA1c and Plasma Glucose

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

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

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

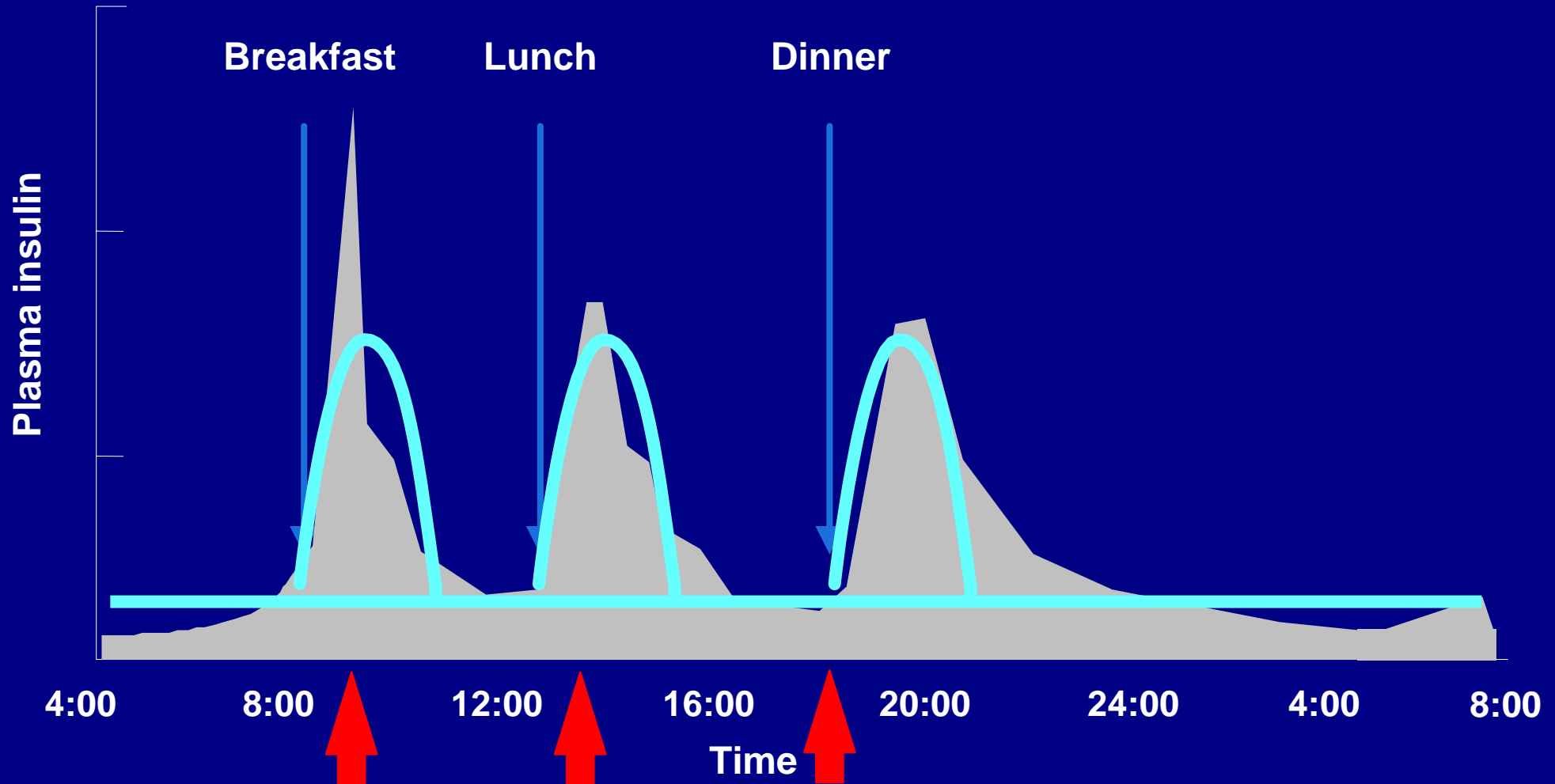


February 15, 1923

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

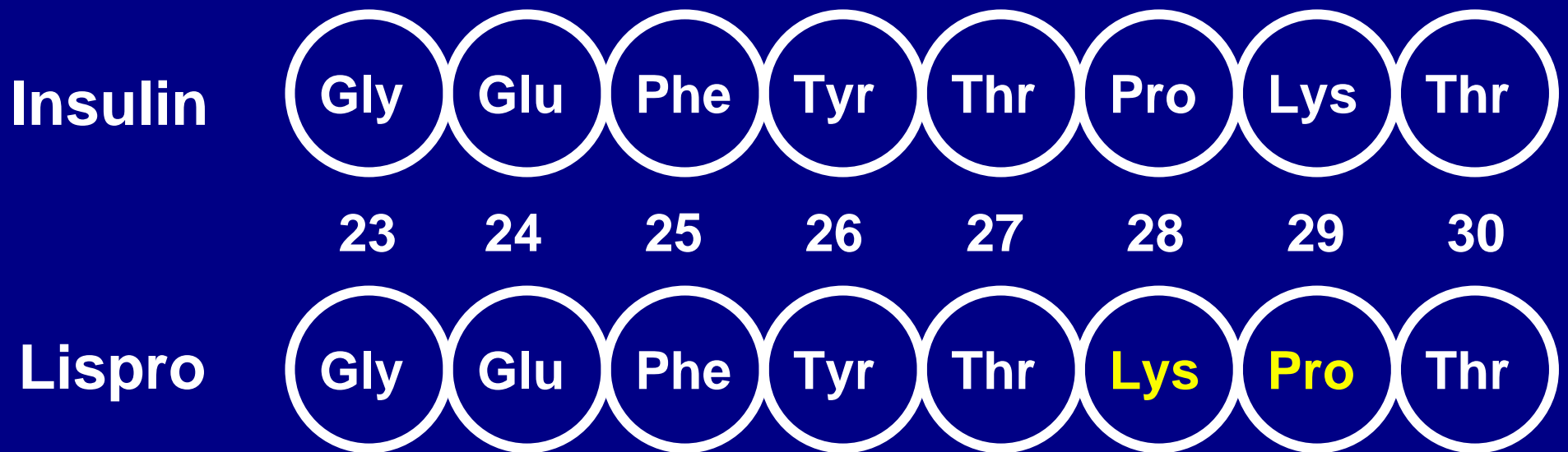
Ideal Basal/Bolus Insulin Absorption Pattern



Rapid-acting Insulin Analogs: Medical Rationale

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

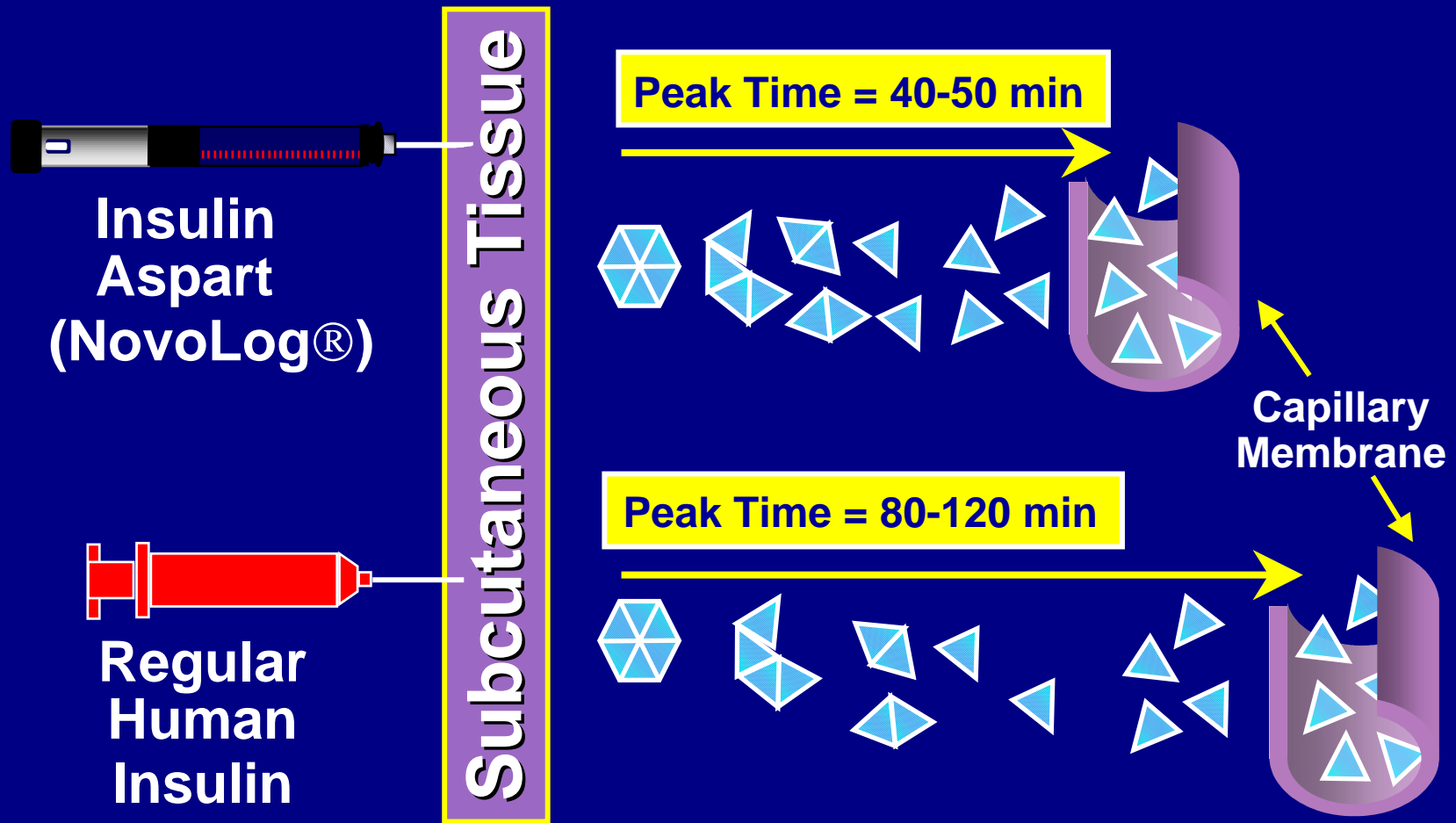
Primary Structure of Lys(B28), Pro(B29)-Insulin



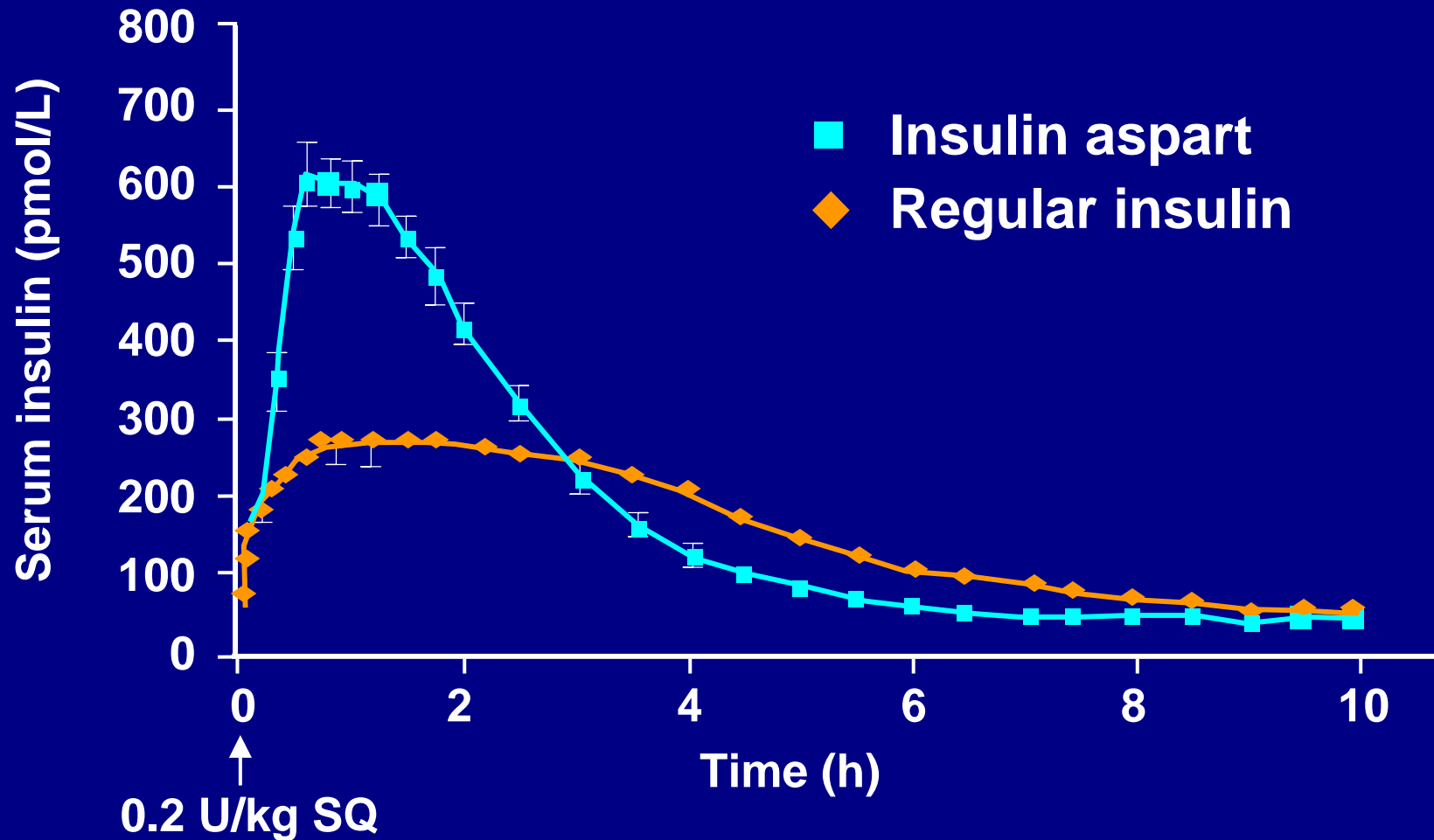
Primary Structure of Asp(B28)-Insulin



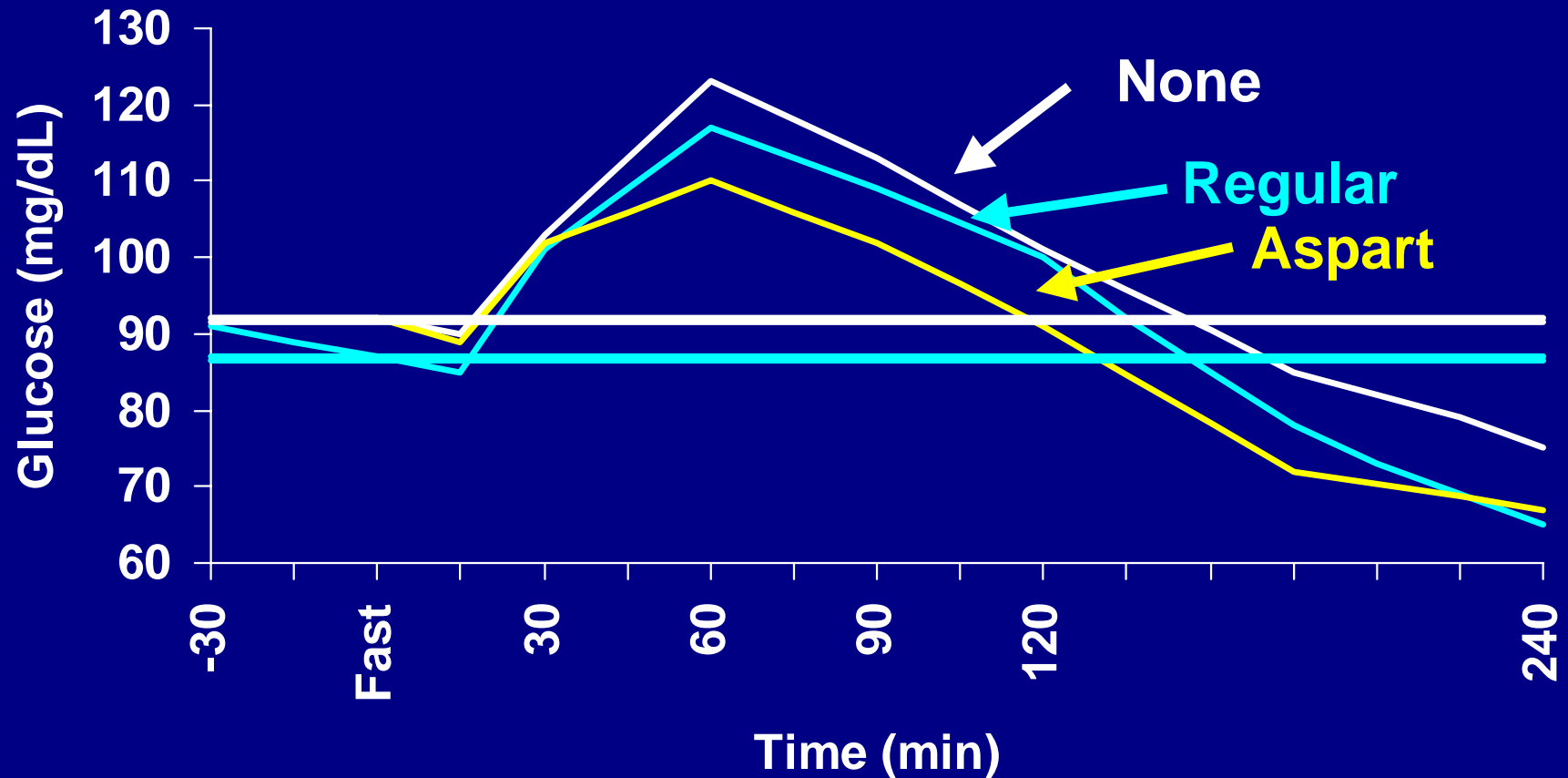
Dissociation & Absorption of NovoLog®



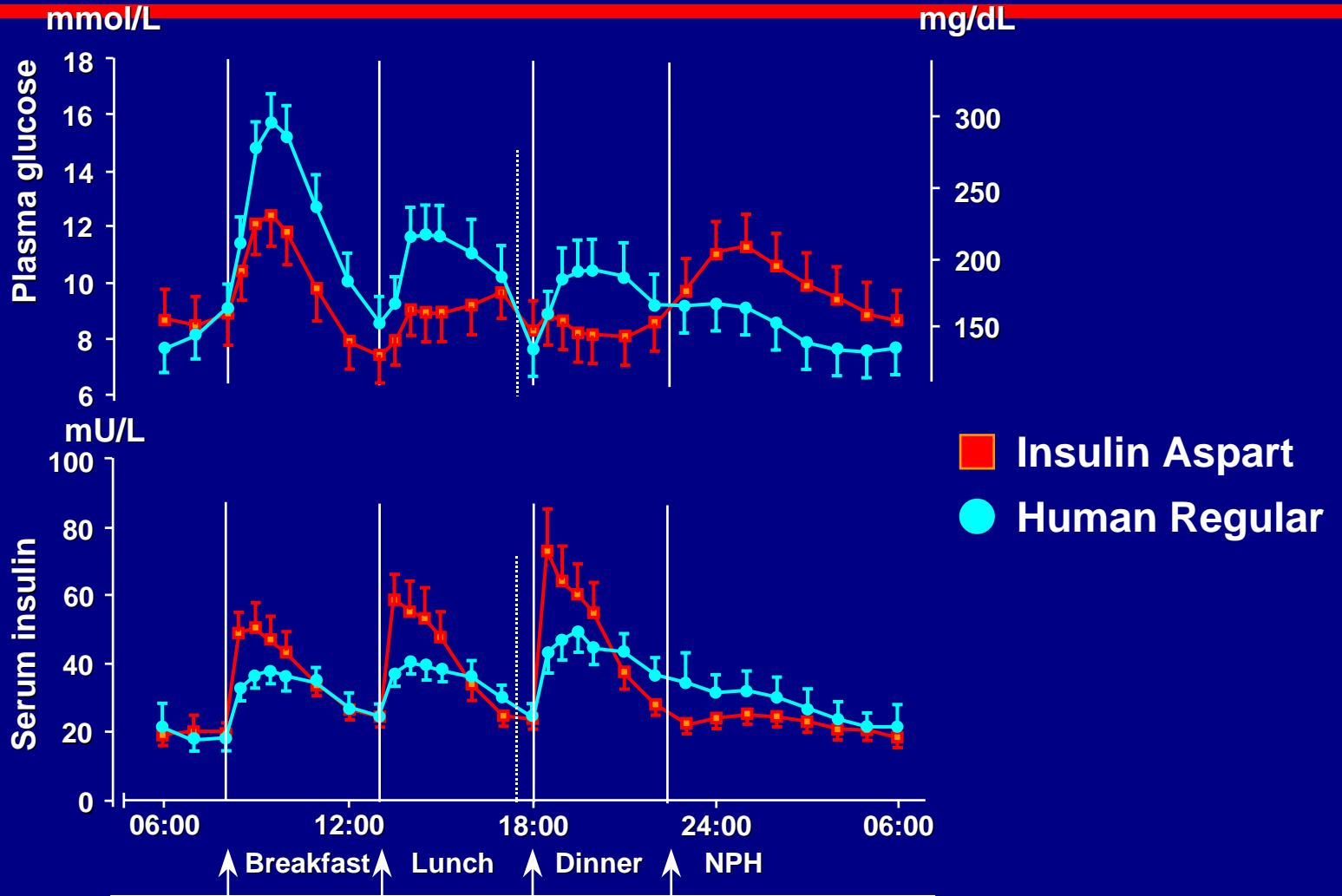
Insulin Aspart: Mean Serum Insulin Profiles During Euglycemic Clamp in Healthy Volunteers



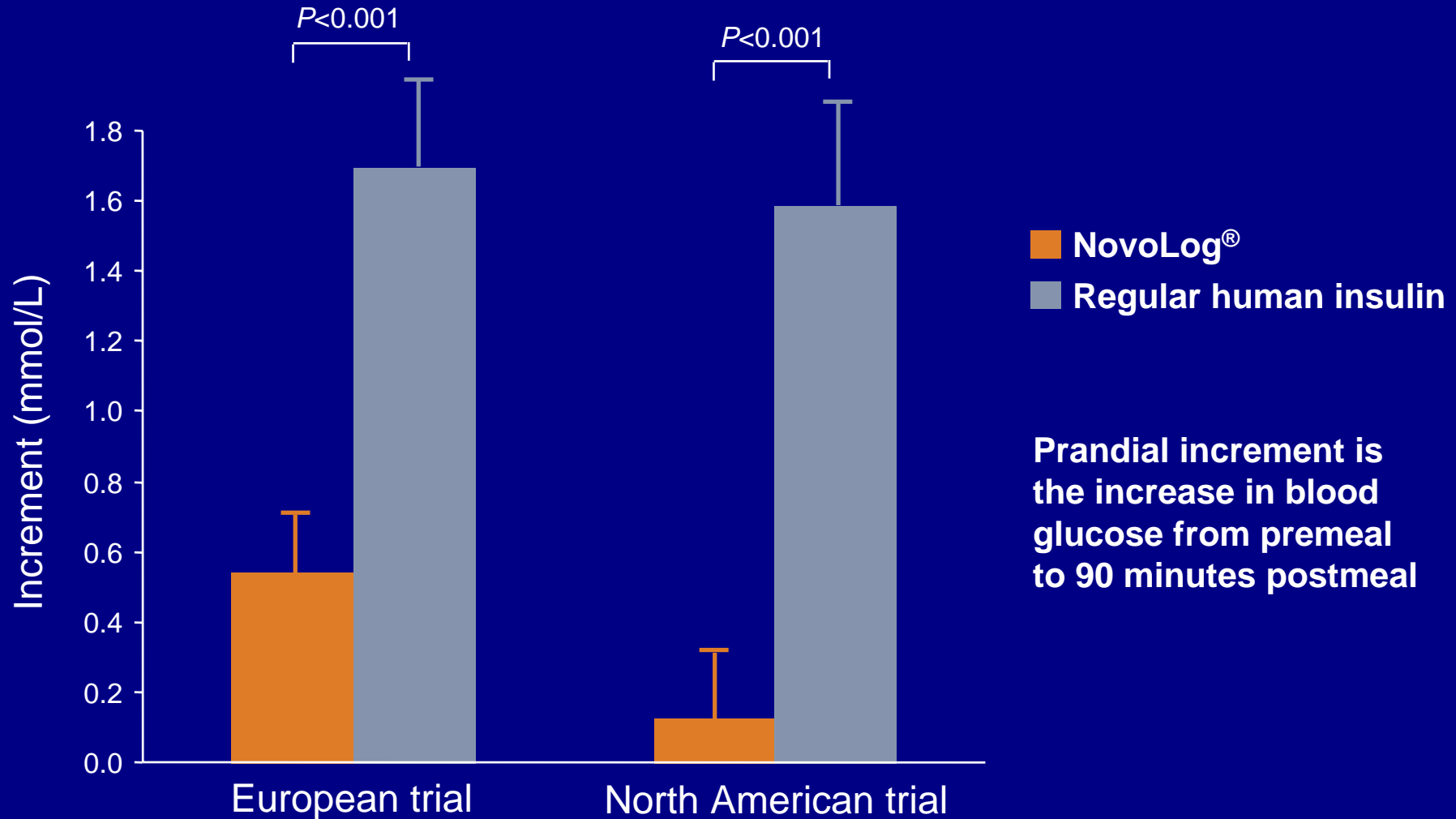
Glucose Area Under the Curve



Insulin Aspart vs Human Regular: Glycemic Control



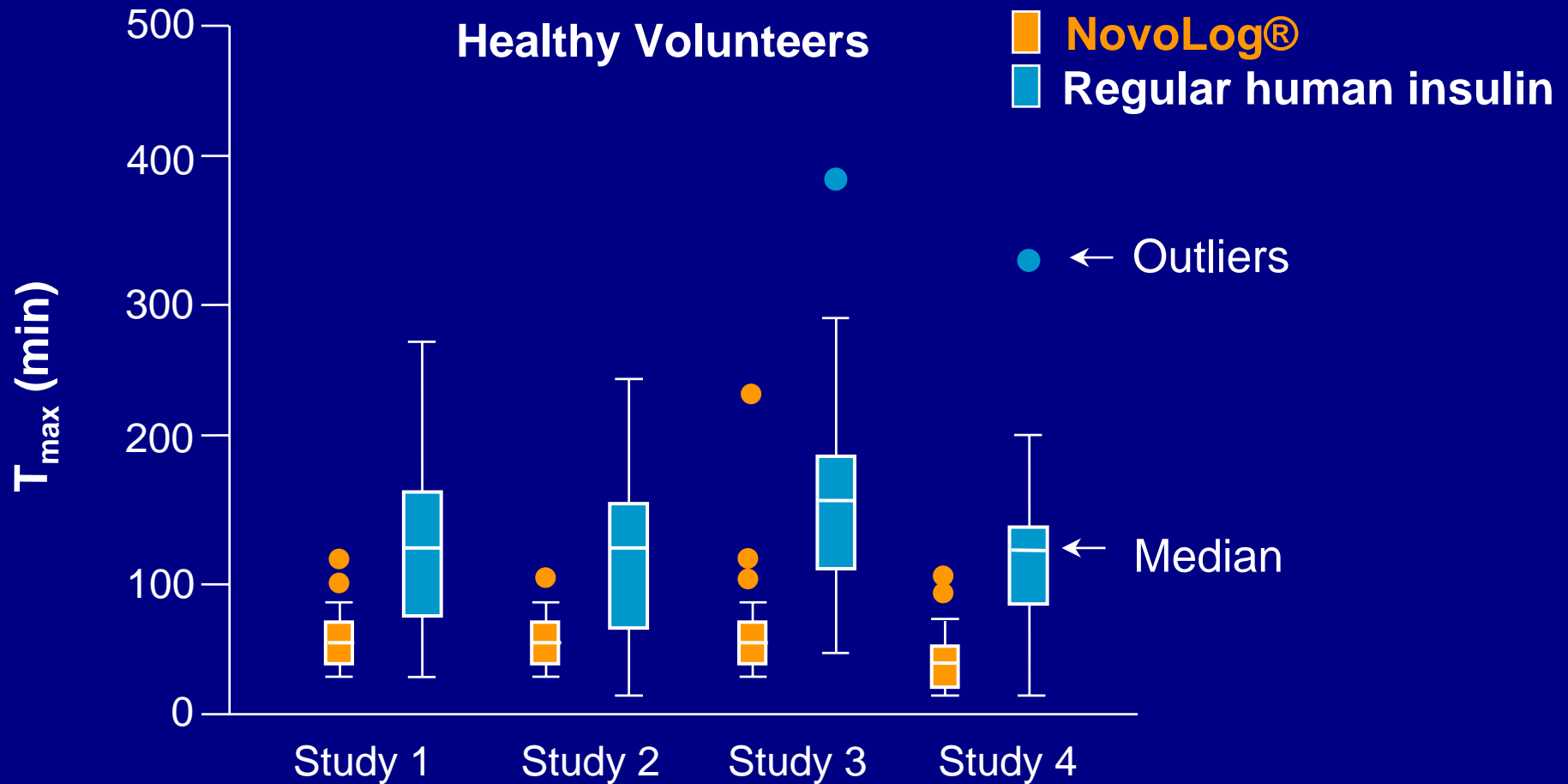
Postprandial Blood Glucose Increment (Mean over the 3 Meals at 6 Months)



Raskin P, et al. *Diabetes Care*. 2000;23:583.

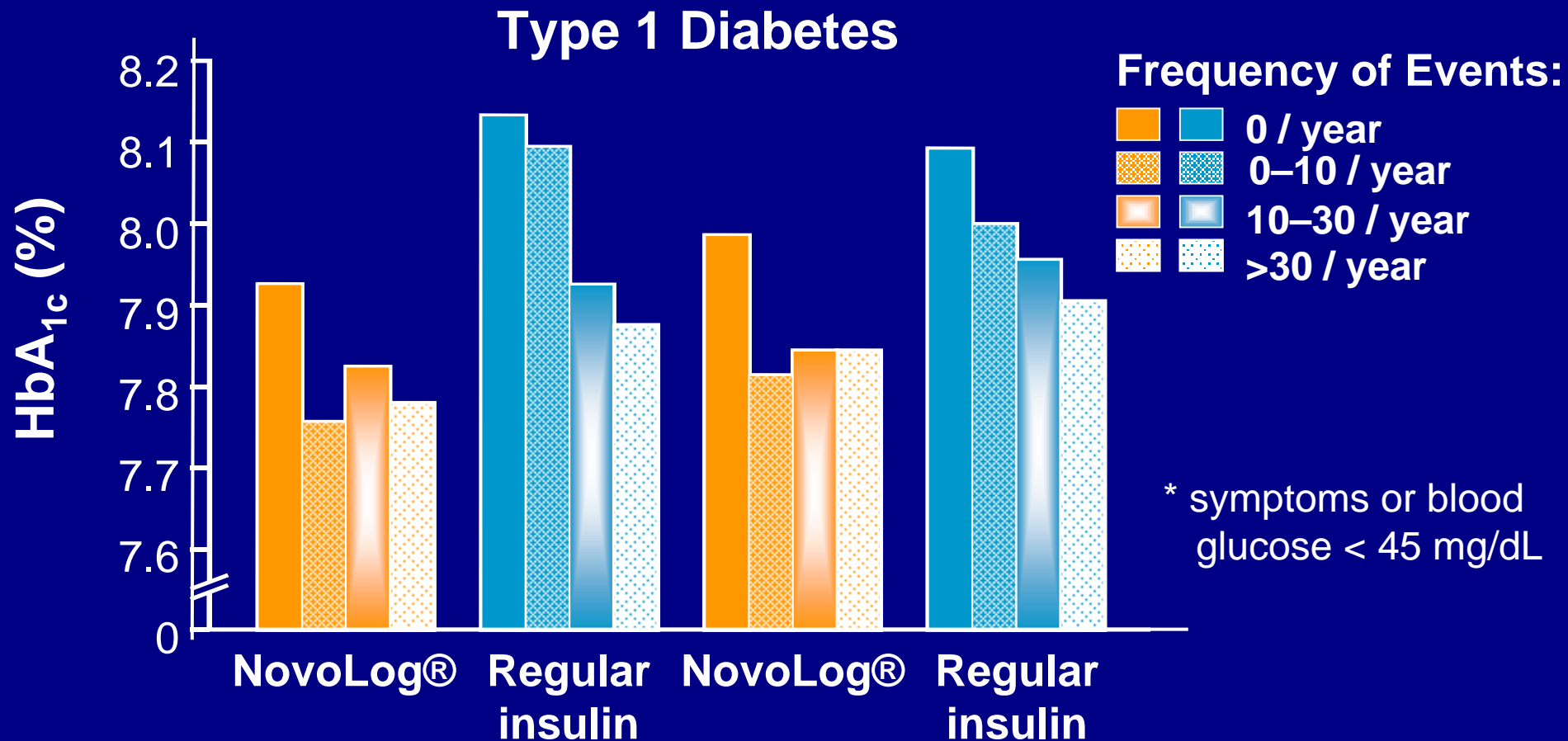
Home PD, et al. *Diabetic Medicine*. 2000;17:762.

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

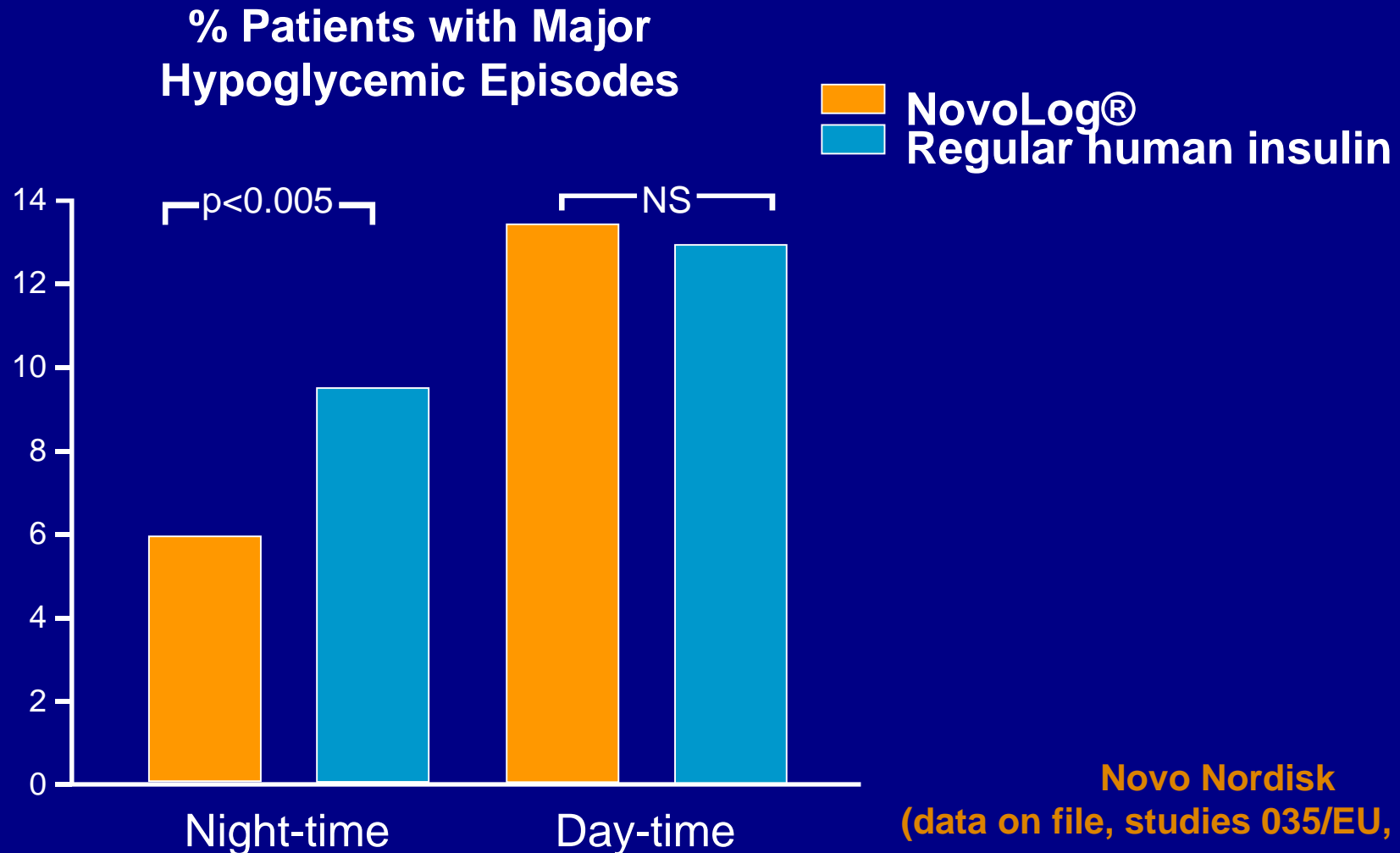


Study 035/EU

Study 036/US

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

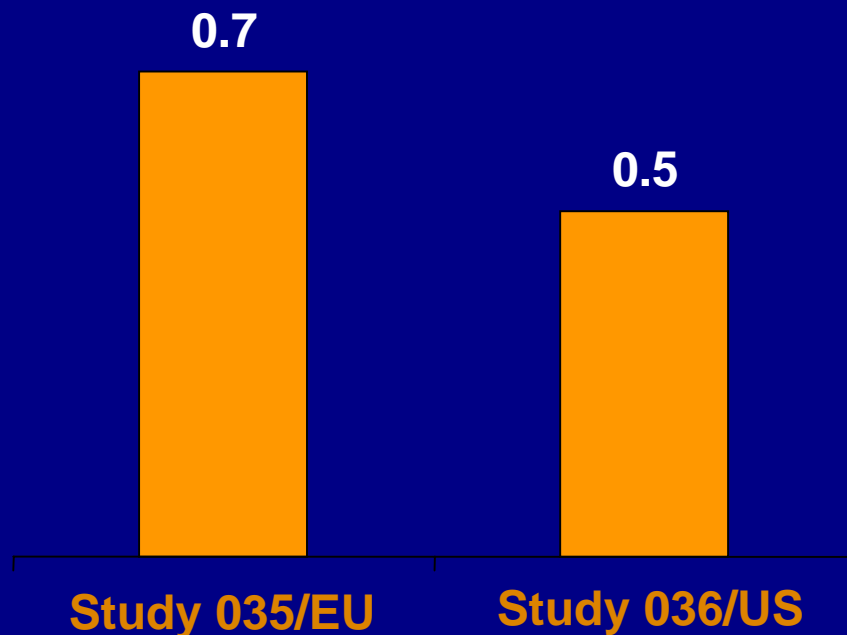
Reduced Reporting of Major Nocturnal Hypoglycemia



Reduced Risk of Major Nocturnal Hypoglycemia

Relative Risk

NovoLog Compared to Regular Human Insulin (1.0 = equal)

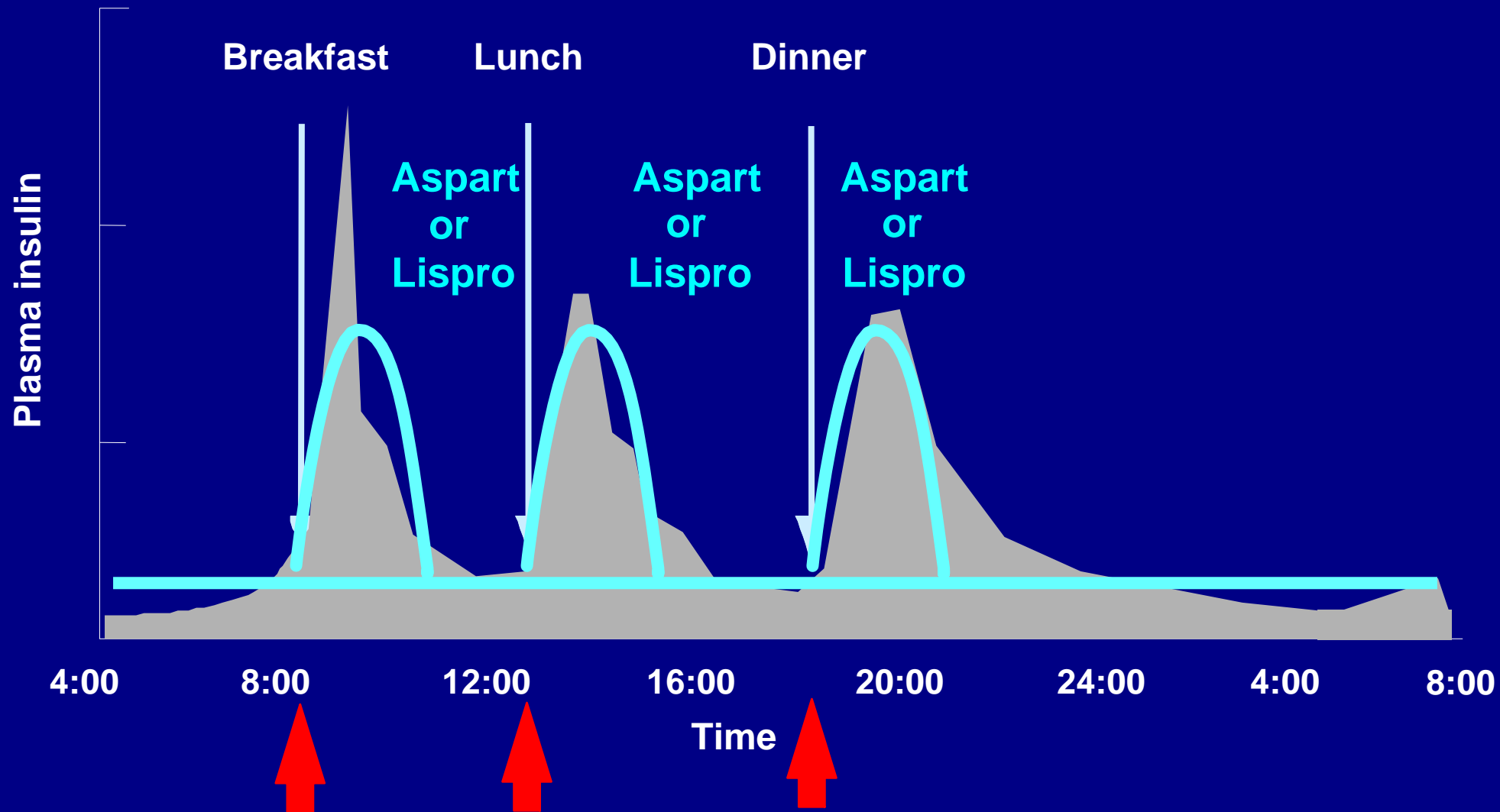


NovoLog® **Human insulin**
(N of patients with events)

Home	8% (54/707)	11% (39/358)
Raskin	4% (24/596)	8% (23/286)

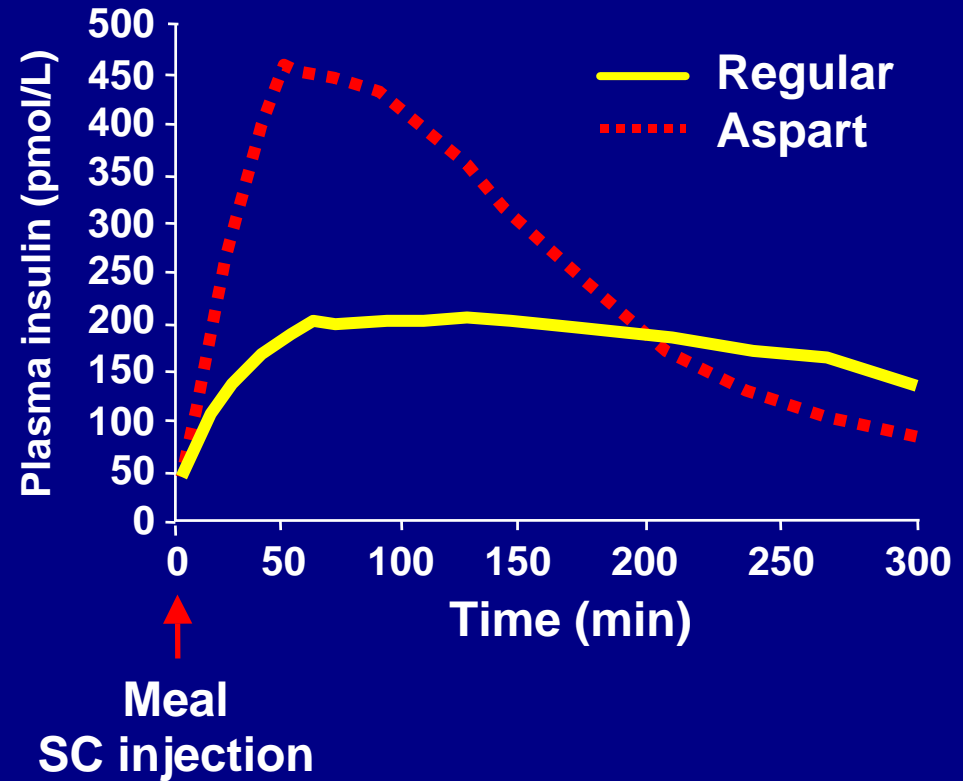
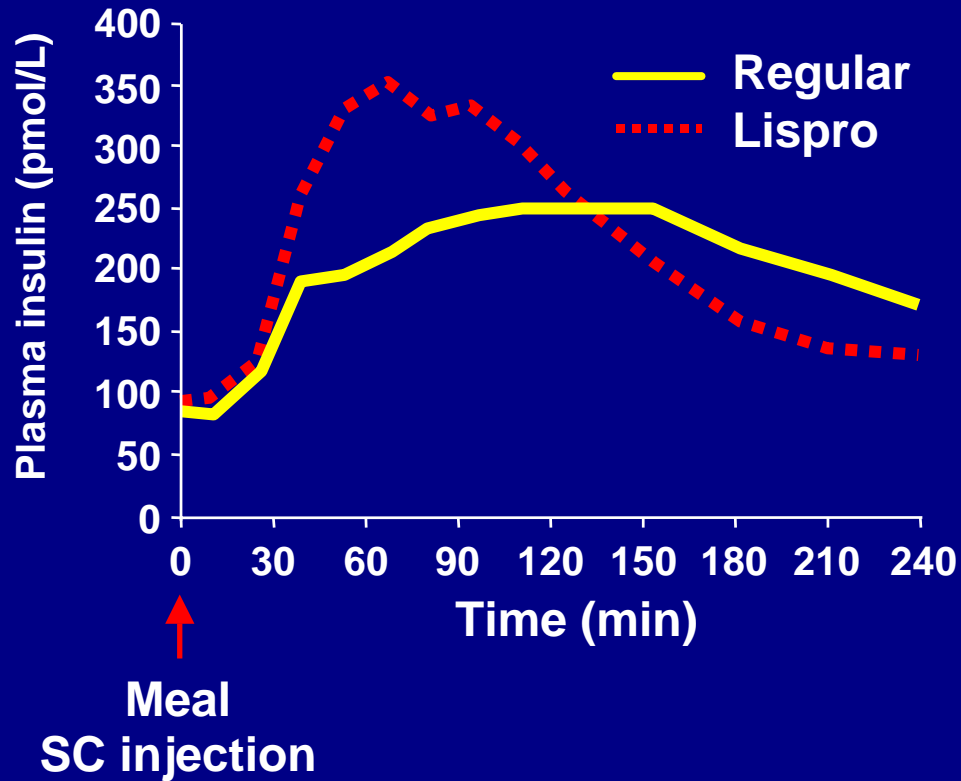
Novo Nordisk
(data on file, studies 035/EU, 036/US)

Rapid-acting Insulin Analogues Provide Ideal Prandial Insulin Profile

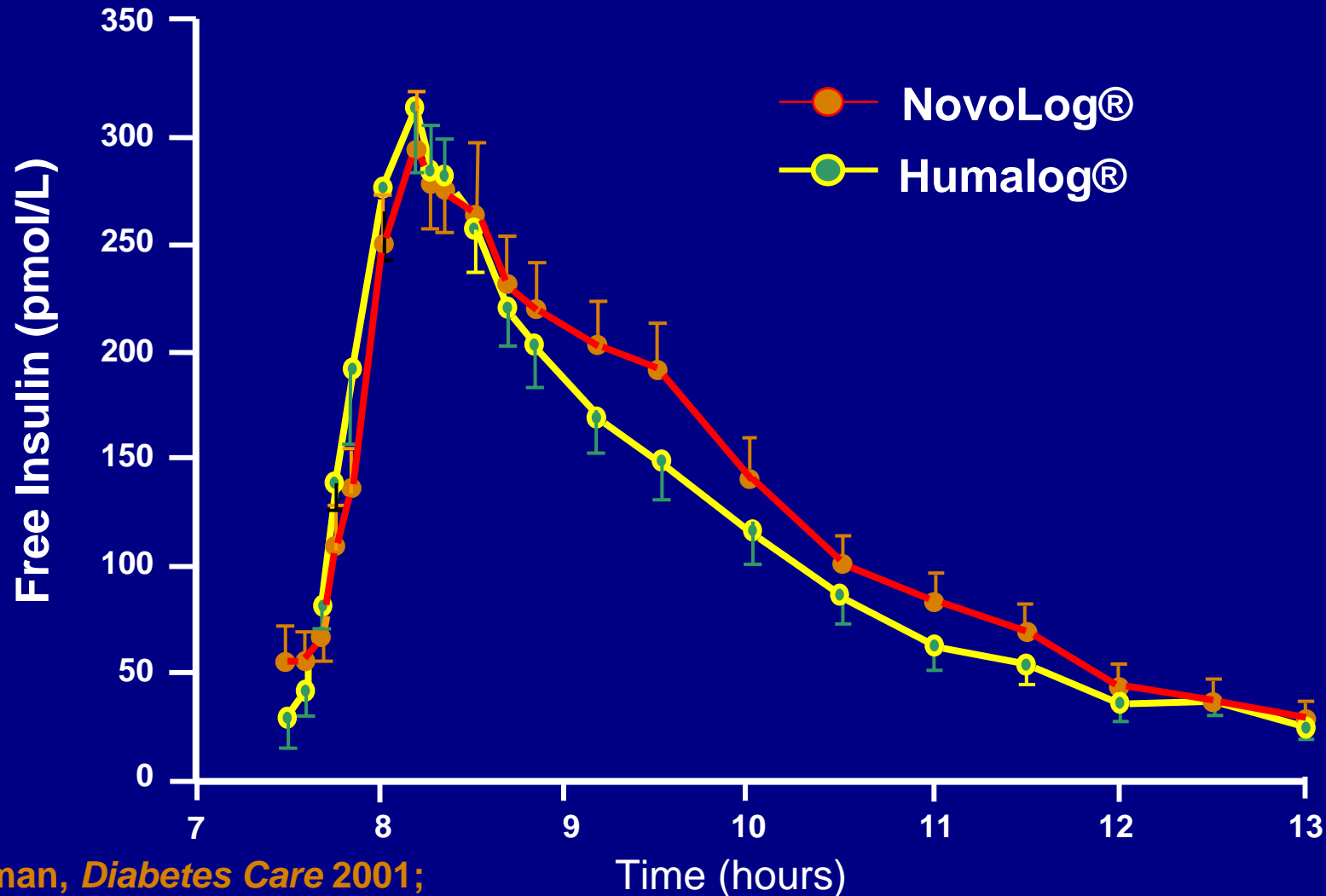


Short-Acting Insulin Analogs

Lispro and Aspart Plasma Insulin Profiles



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

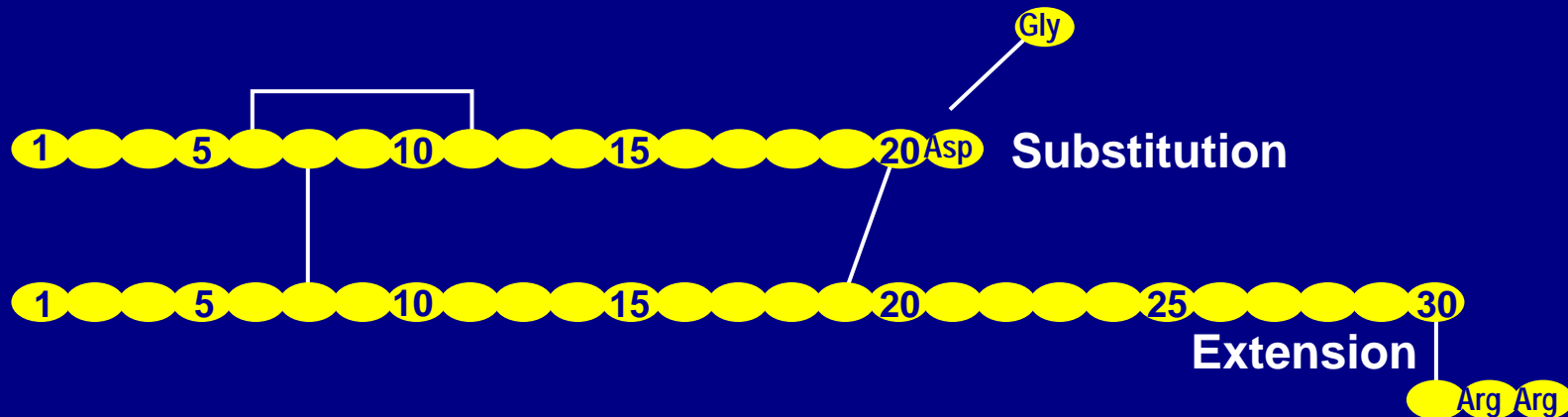
Limitations of NPH, Lente, and Ultralente

- 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

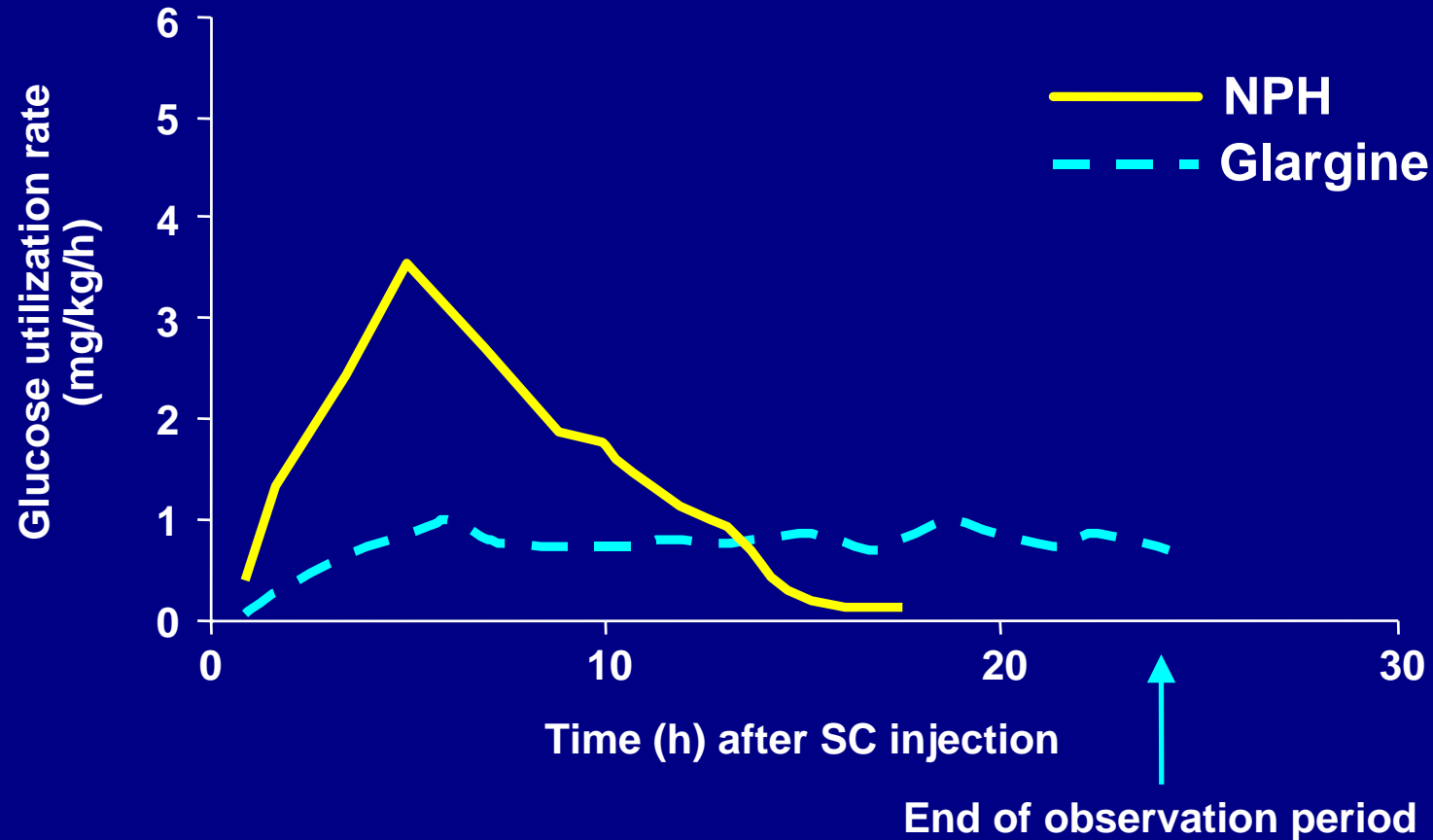
A New Long-Acting Insulin Analog

- 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



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

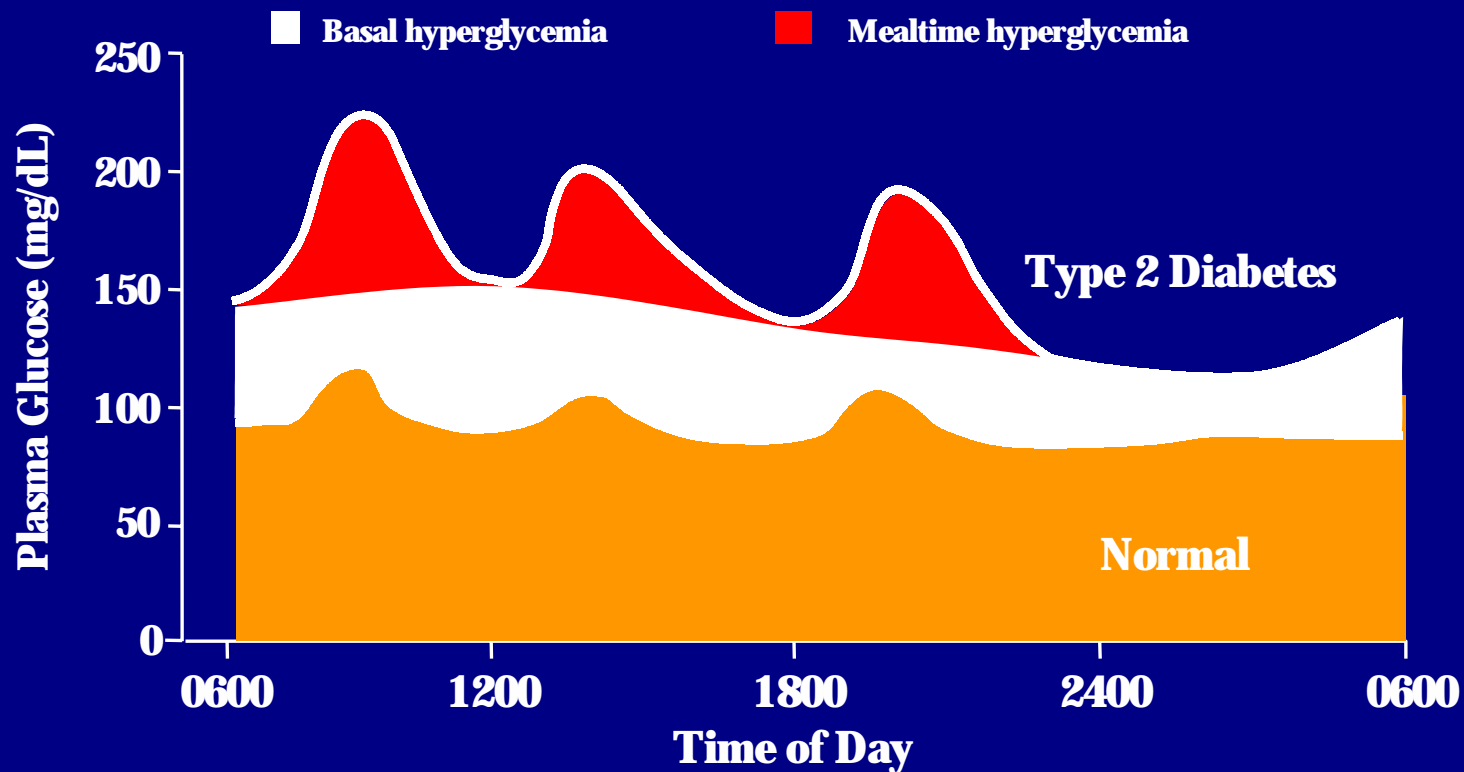
Mimicking Nature

***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

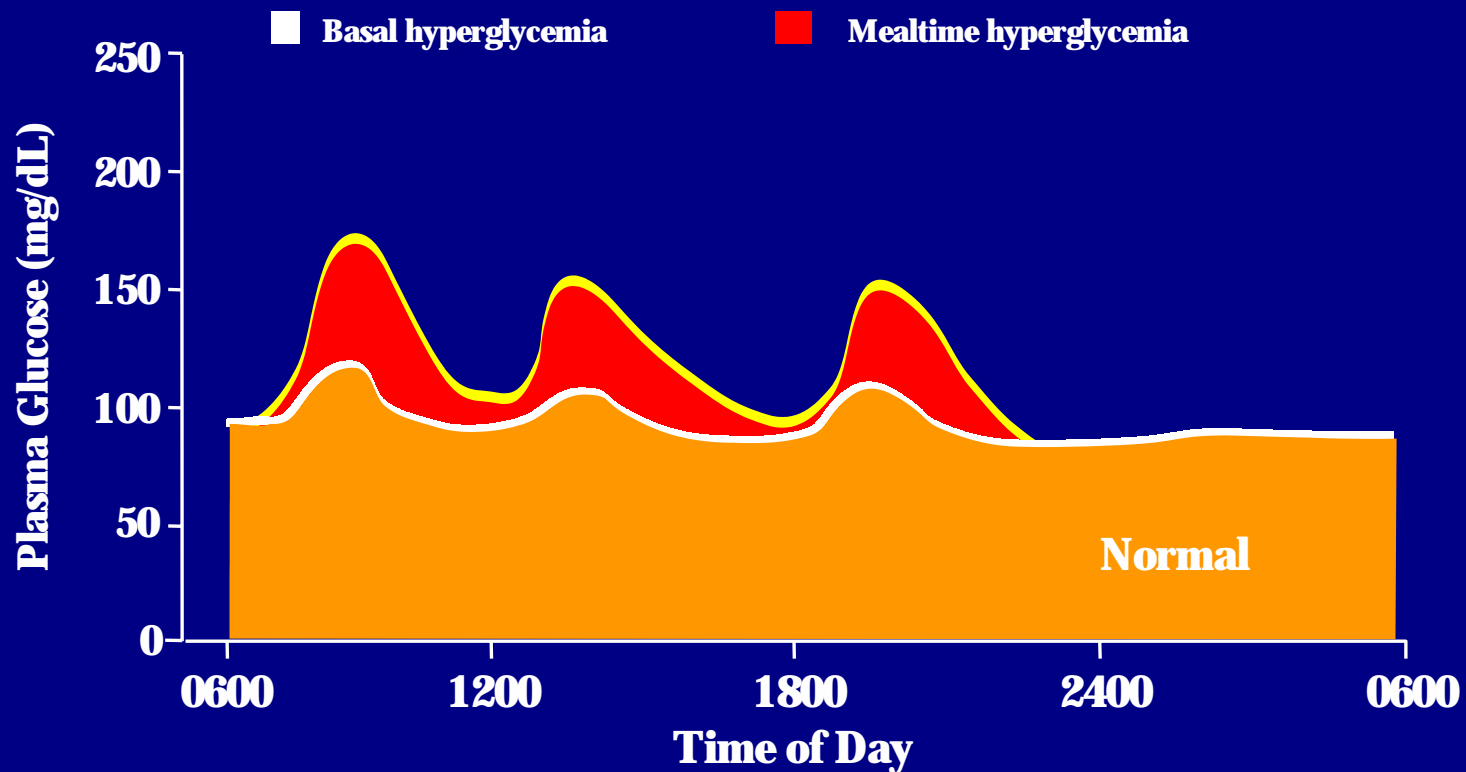
Basal vs Mealtime Hyperglycemia in Diabetes



Δ AUC from normal basal >1875 mgm/dL·hr; Est HbA_{1c} >8.7%

Basal vs Mealtime Hyperglycemia in Diabetes

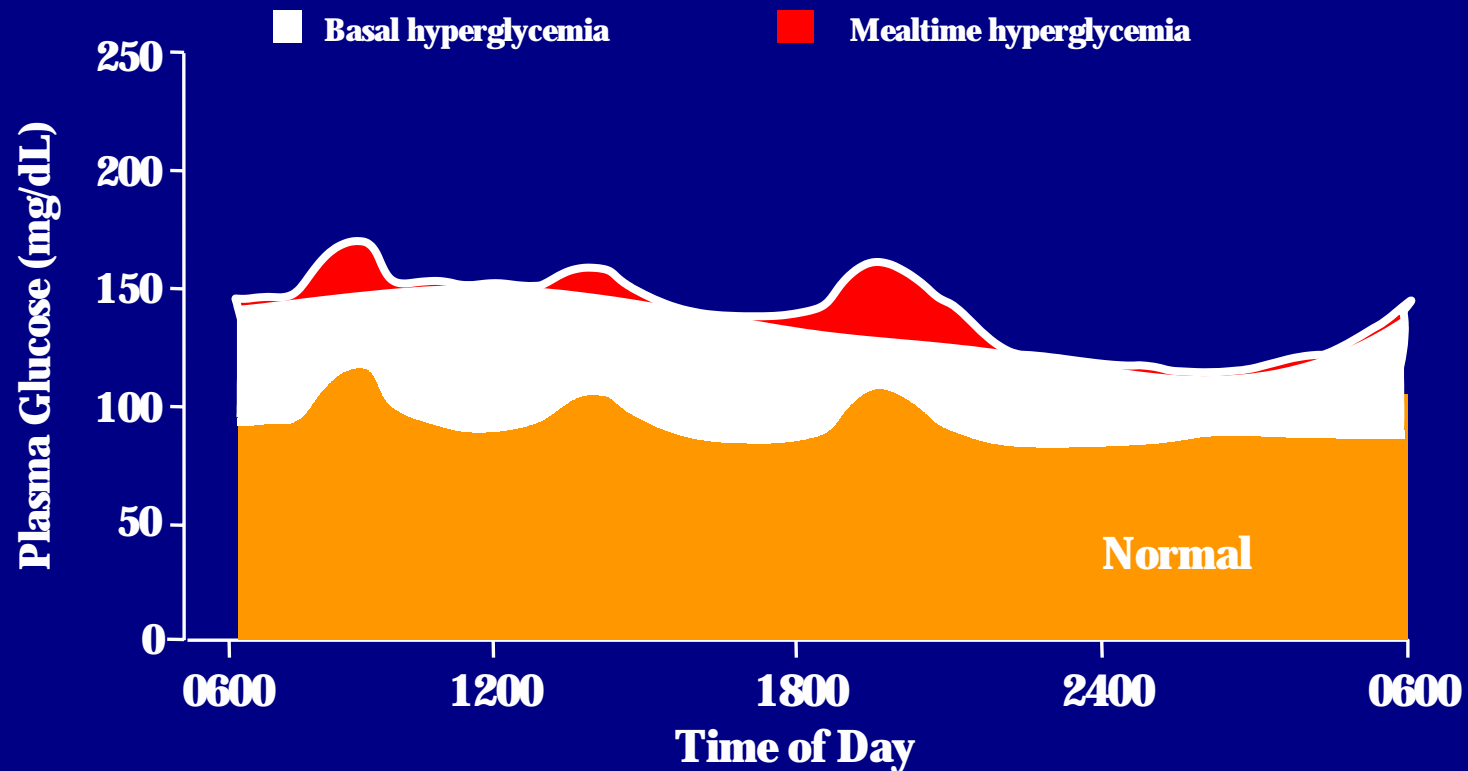
When Basal Corrected



Δ AUC from normal basal 900 mgm/dL·hr; Est HbA_{1c} 7.2%

Basal vs Mealtime Hyperglycemia in Diabetes

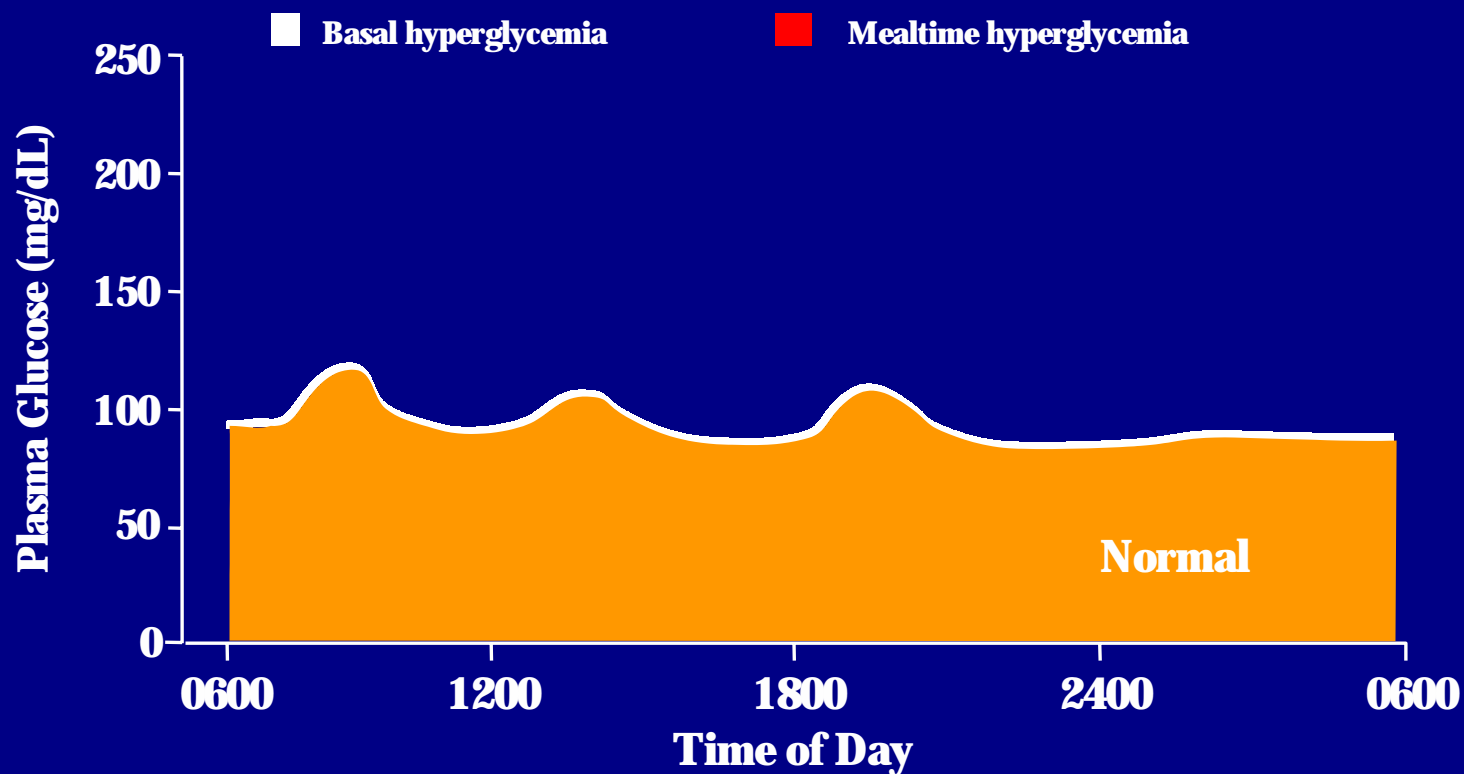
When Mealtime Hyperglycemia Corrected



Δ AUC from normal basal 1425 mgm/dL·hr; Est HbA_{1c} 7.9

Basal vs Mealtime Hyperglycemia in Diabetes

When Both Basal & Mealtime Hyperglycemia Corrected



Δ AUC from normal basal 225 mgm/dL·hr; Est HbA_{1c} 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

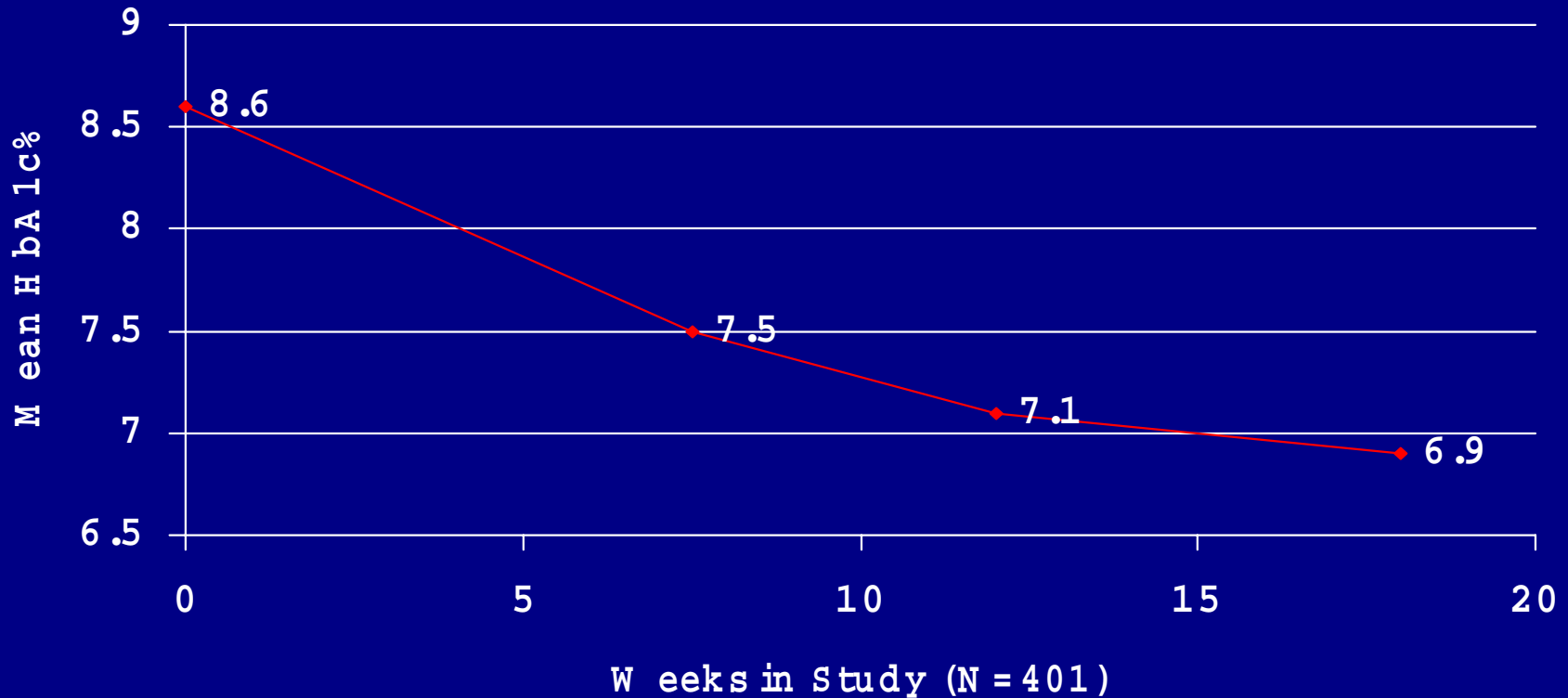
Advantages

- 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

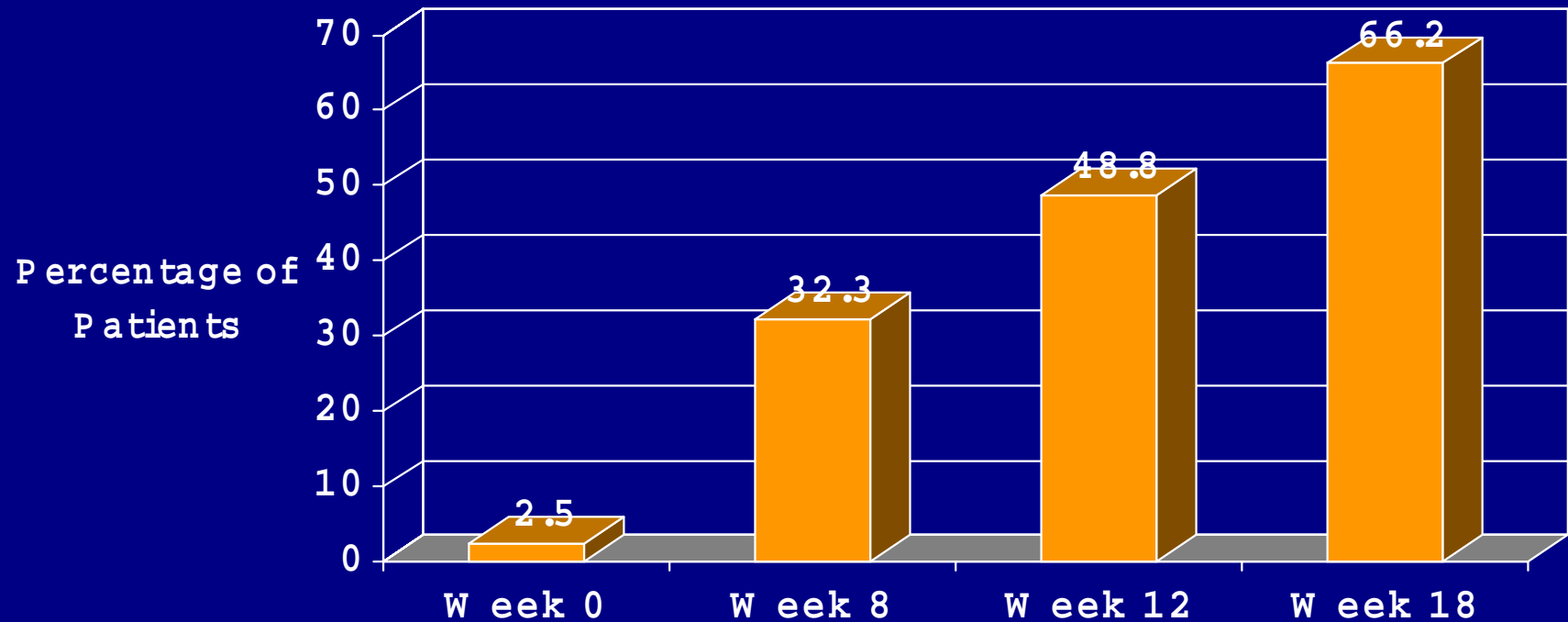
Treatment to Target Study: NPH vs Glargine in DM2 patients on OHA

- 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 supertime 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

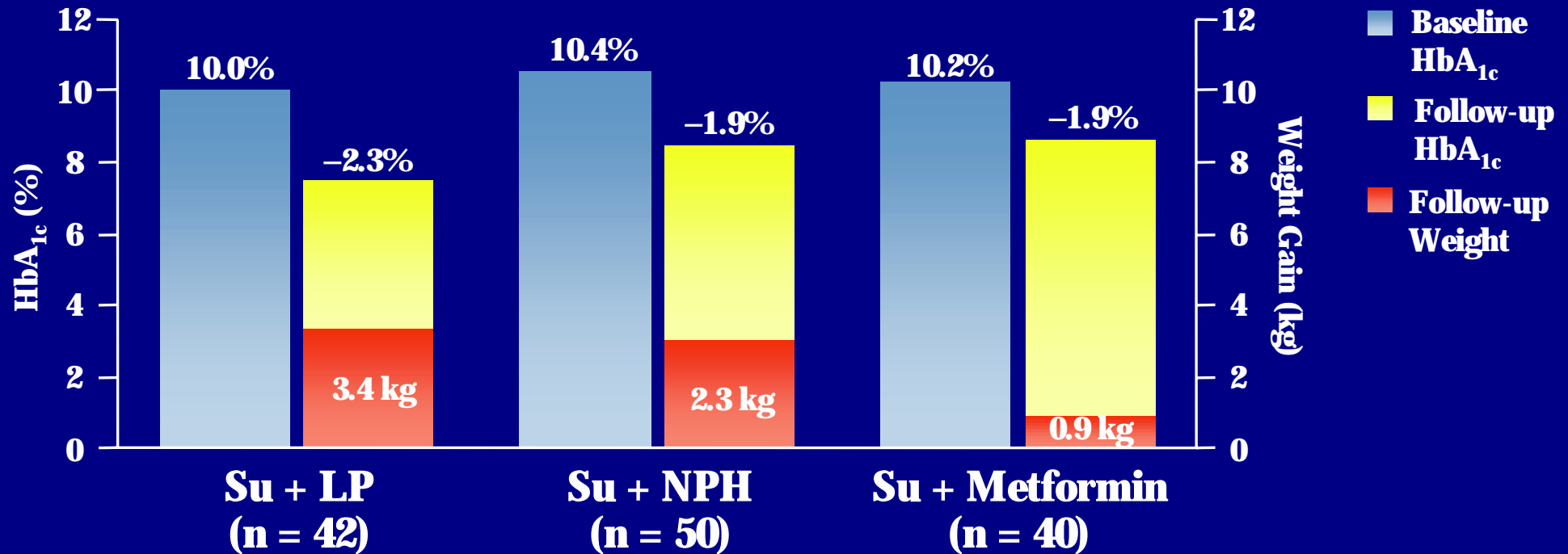
Combination Oral Agents

+

Mealtime Insulin

Starting With Bolus Insulin

Mealtime Lispro vs NPH or Metformin Added to Sulfonylurea



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 $SF = 1500 / \text{total daily dose}$; $SF = 40$

Correction Bolus Formula

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

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

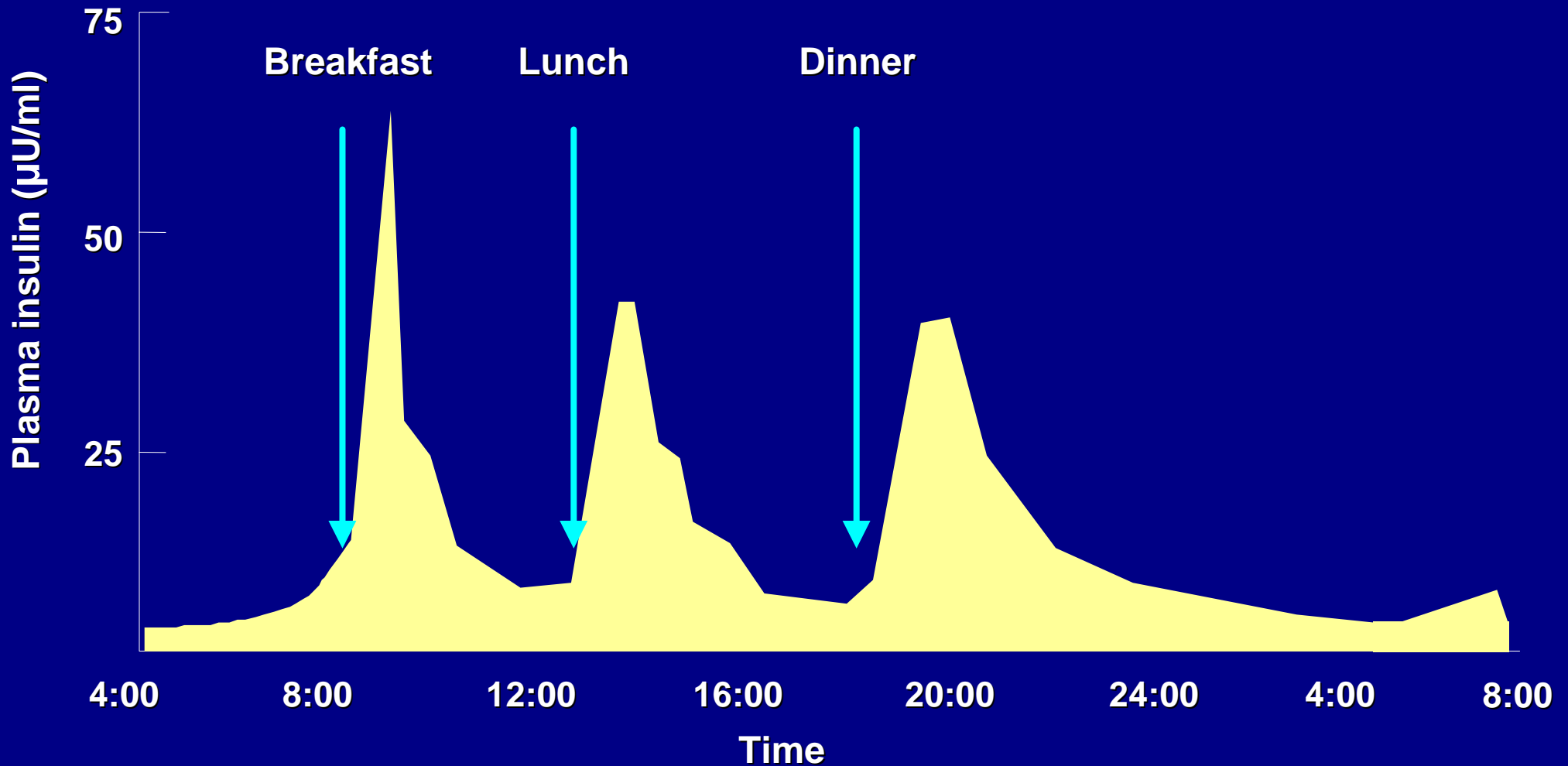
- **Current**

- Multiple injections
- Insulin pump (CSII)

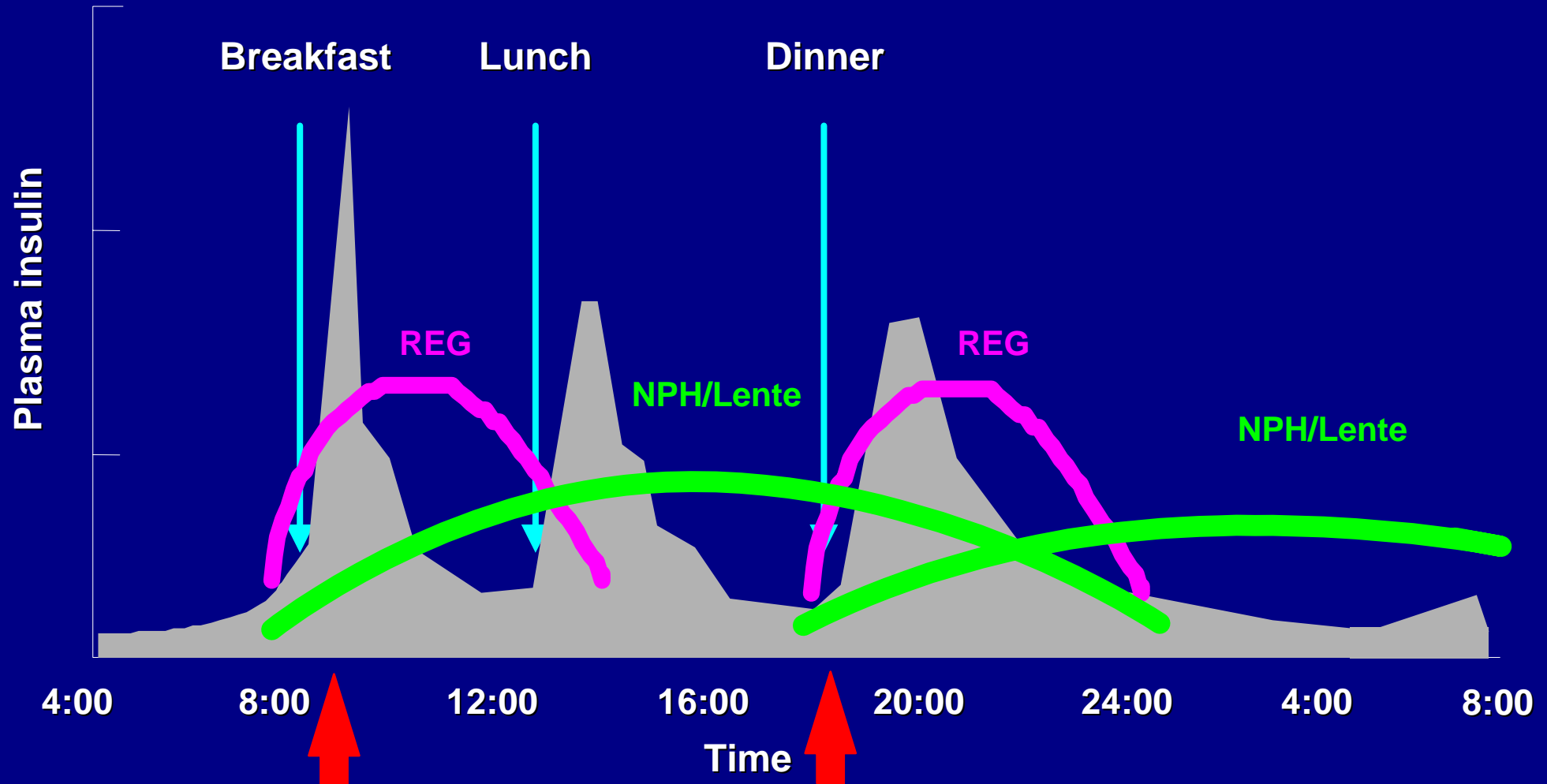
- **Future**

- Implant (artificial pancreas)
- Transplant (pancreas; islet cells)

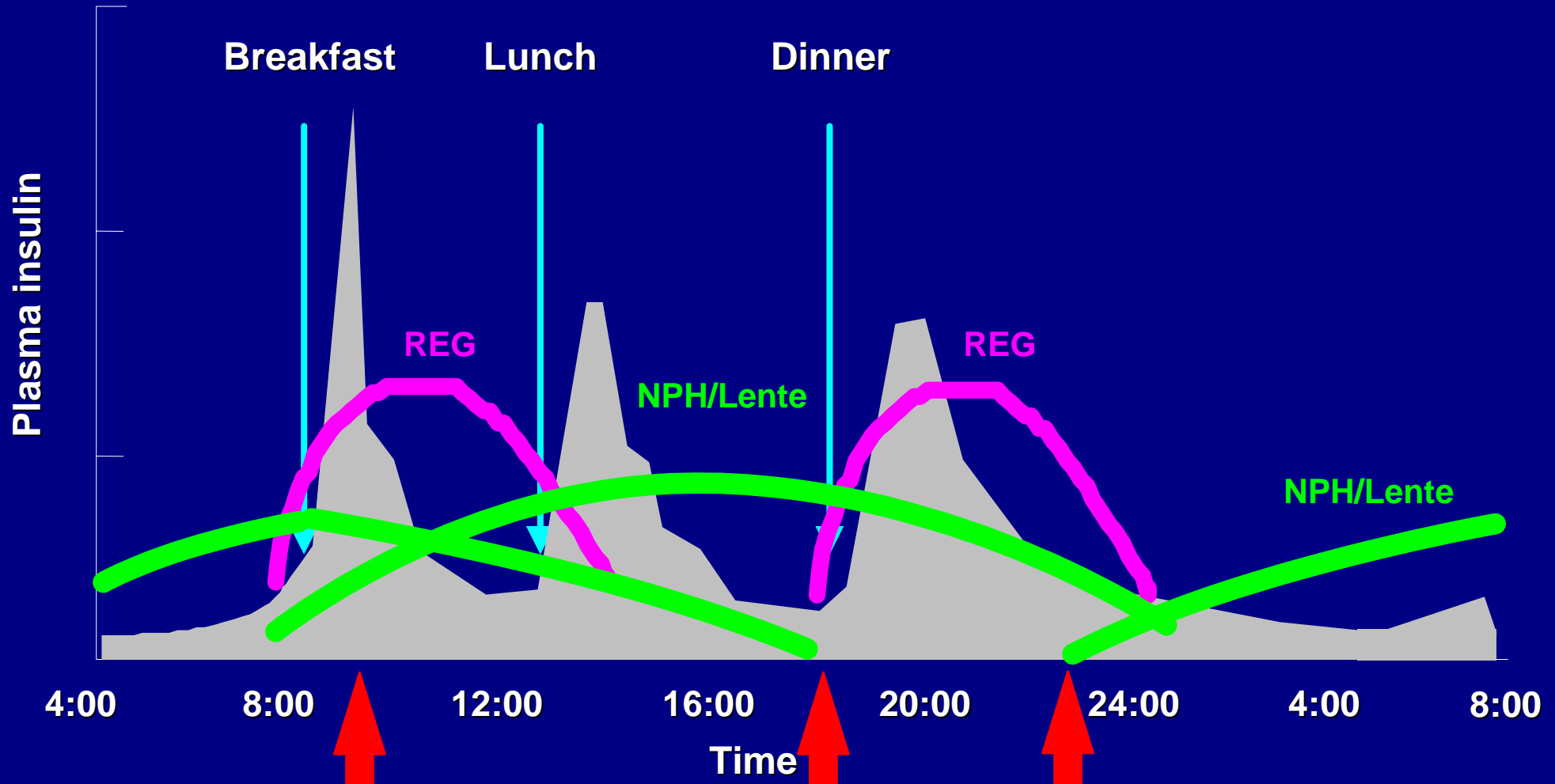
Physiological Serum Insulin Secretion Profile



Classical “Split-mixed” Treatment Program

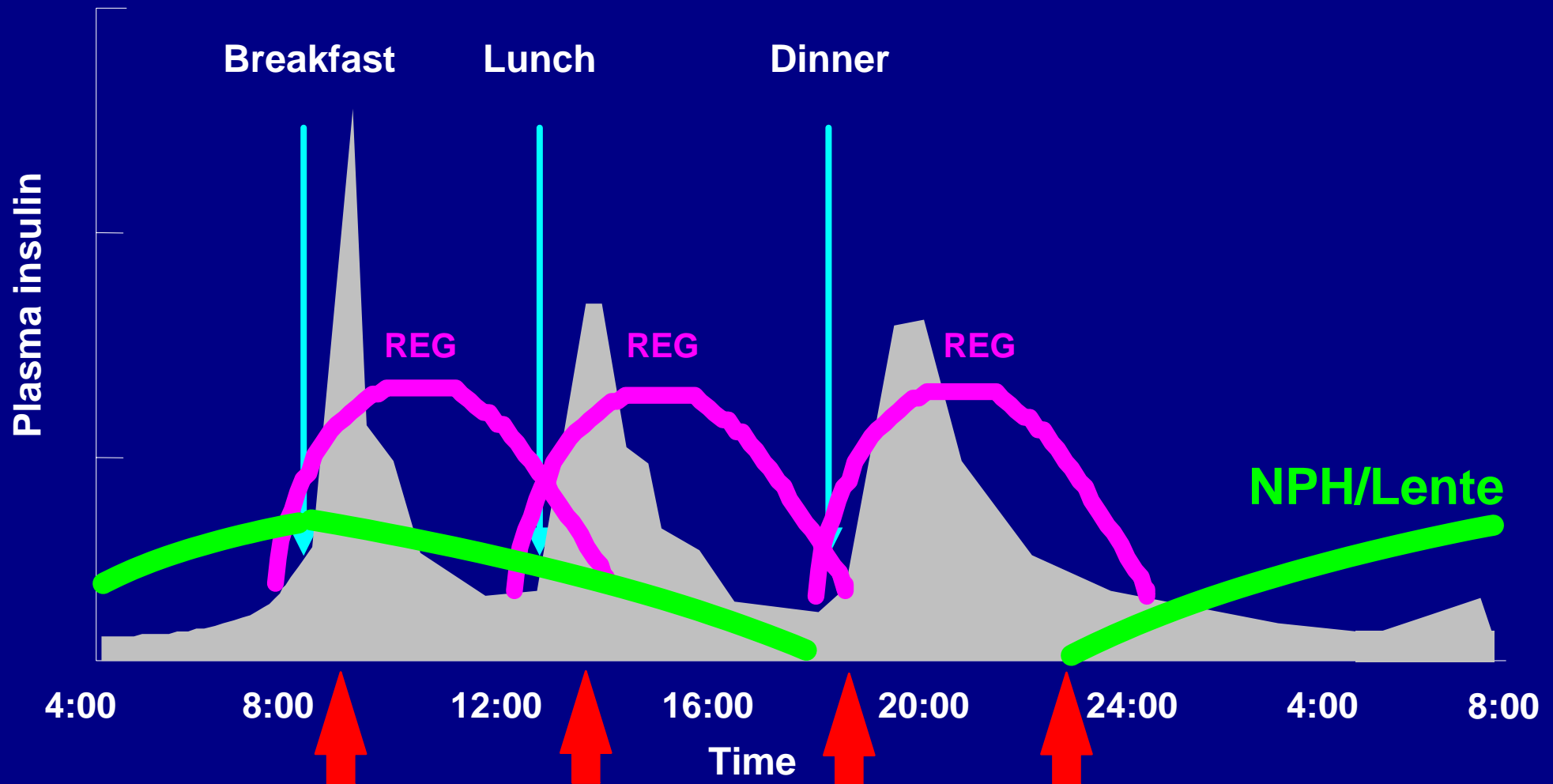


“Split-mixed” Program with Bedtime Intermediate Insulin

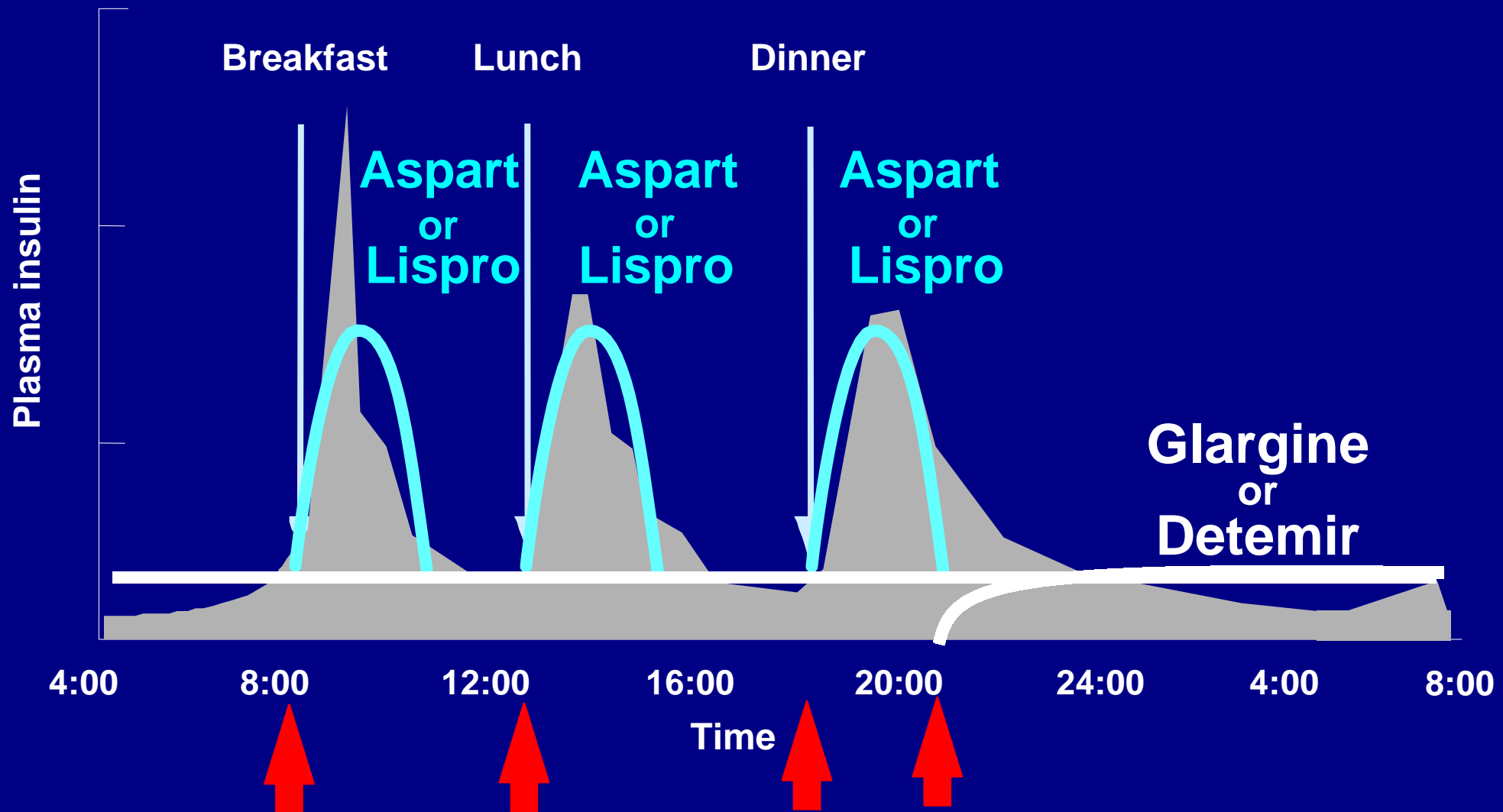


Basal/Bolus Insulin Absorption Pattern

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 breakthrough 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



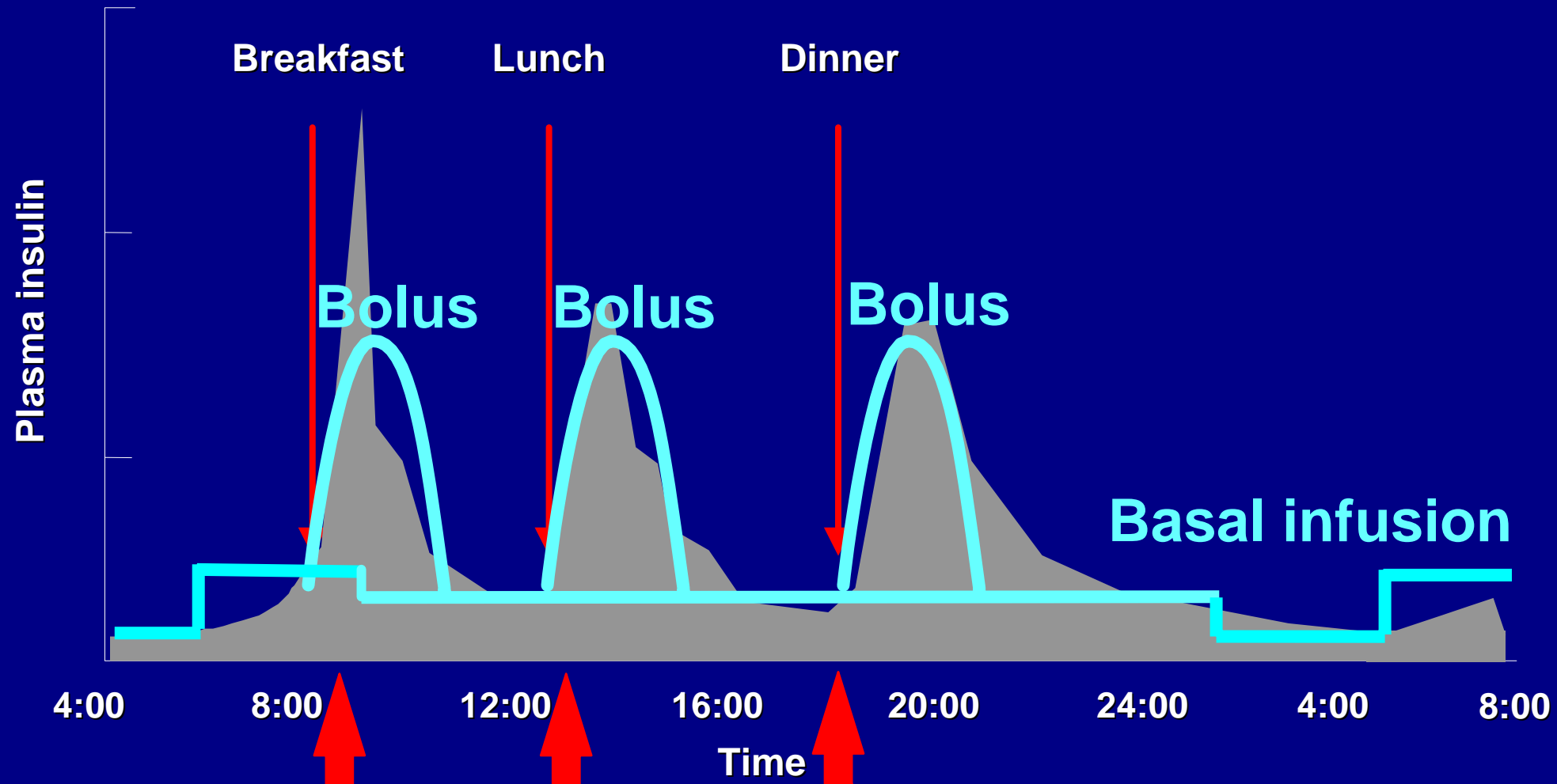
Feature

- Remembers amount of insulin delivered and time since last dose

Benefit

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

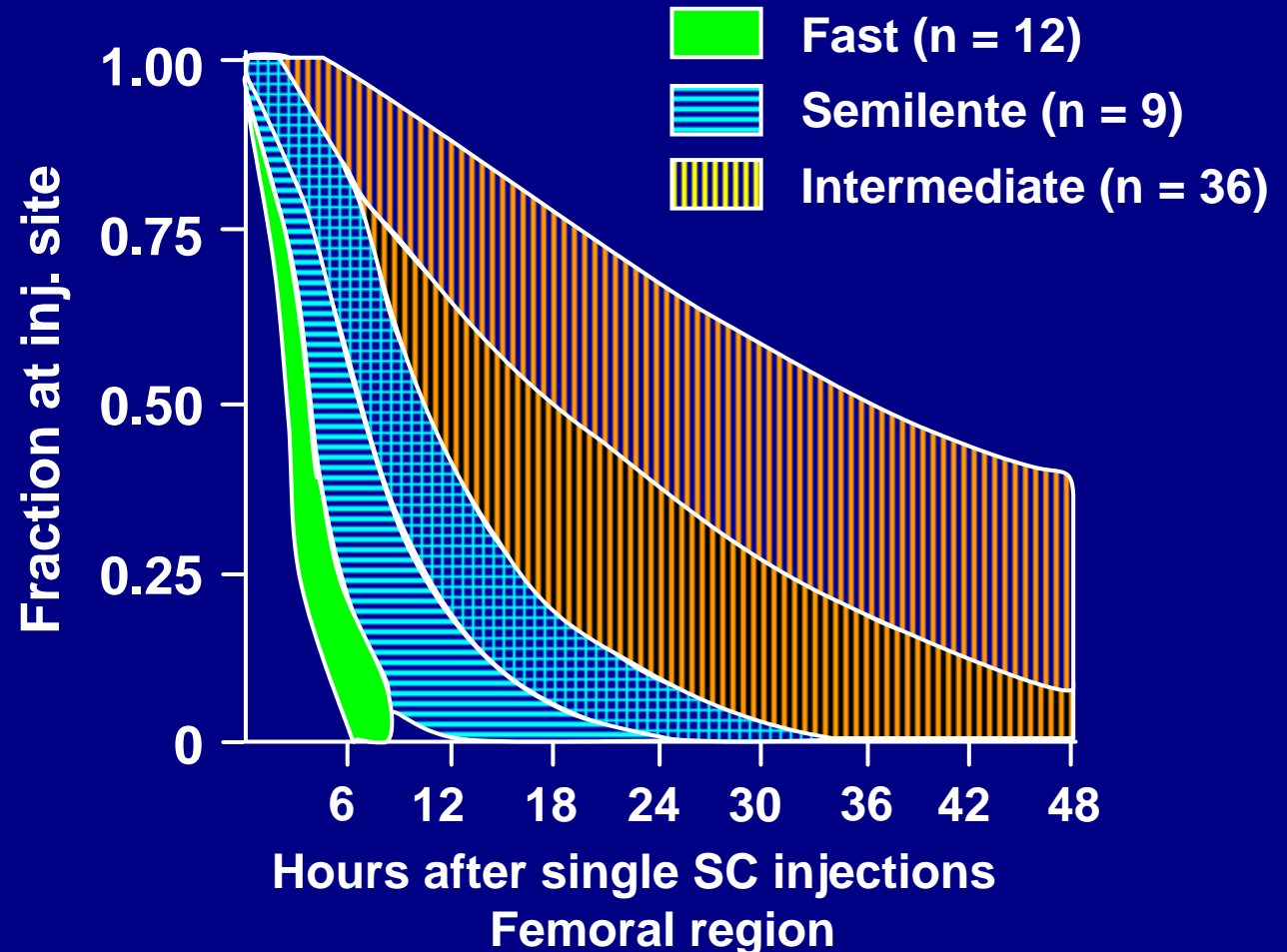
Variable Basal Rate: CSII Program



Variability of Insulin Absorption

CSII <2.8%

Subcutaneous
Injectable
10% to 52%

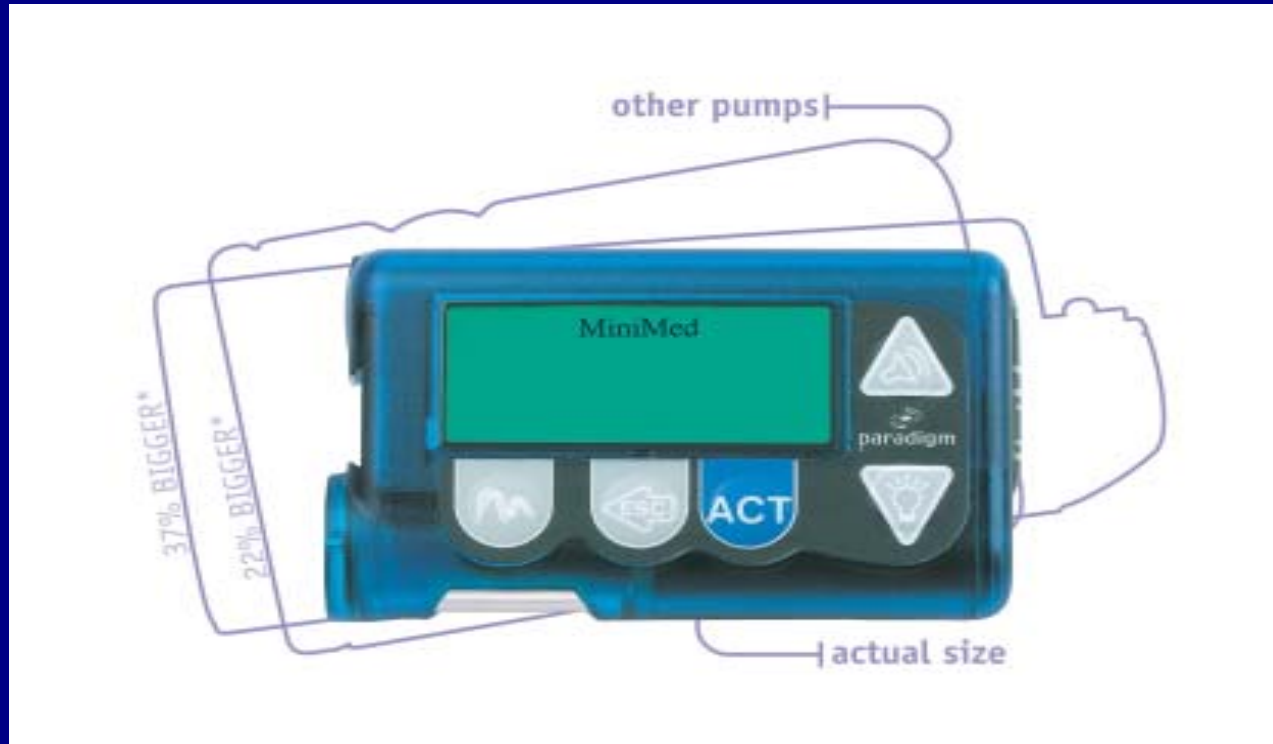


History of Pumps





PARADIGM PUMP



Paradigm.
Simple. Easy.

Pump Infusion Sets



Softset QR

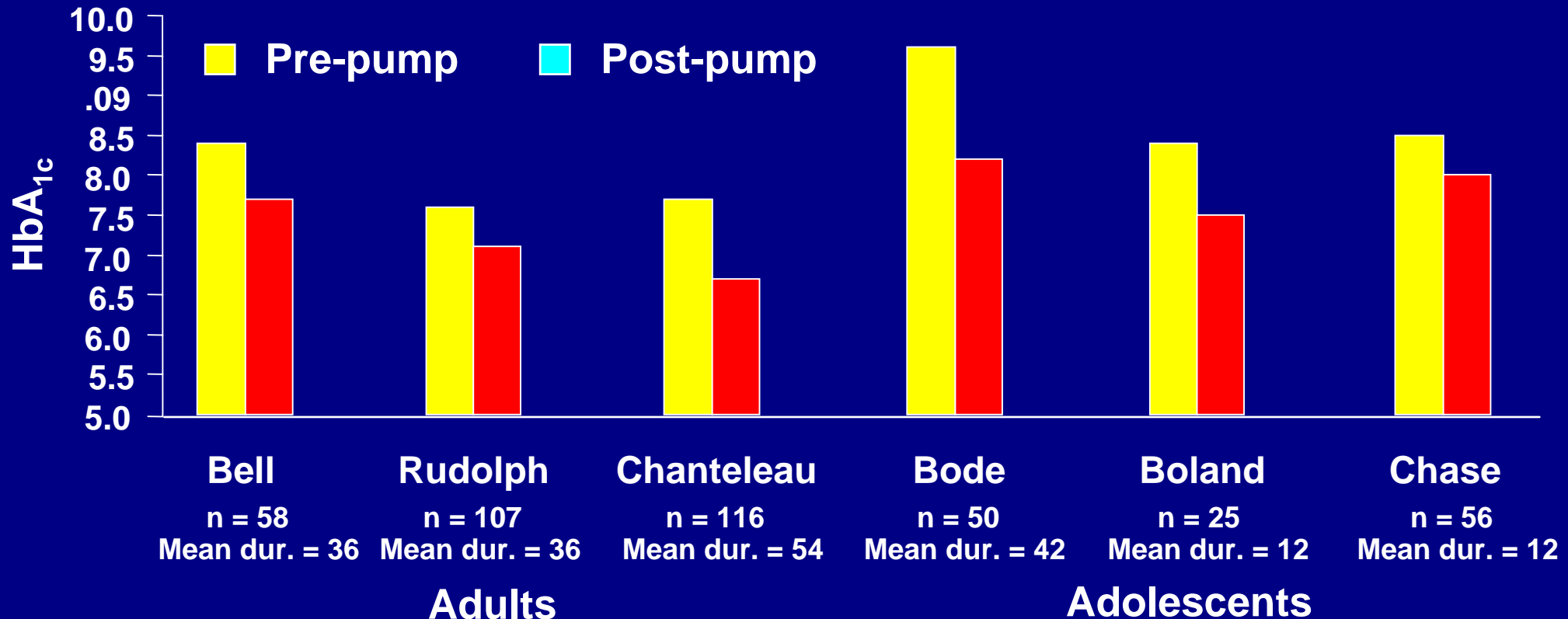


Silhouette

Metabolic Advantages with CSII

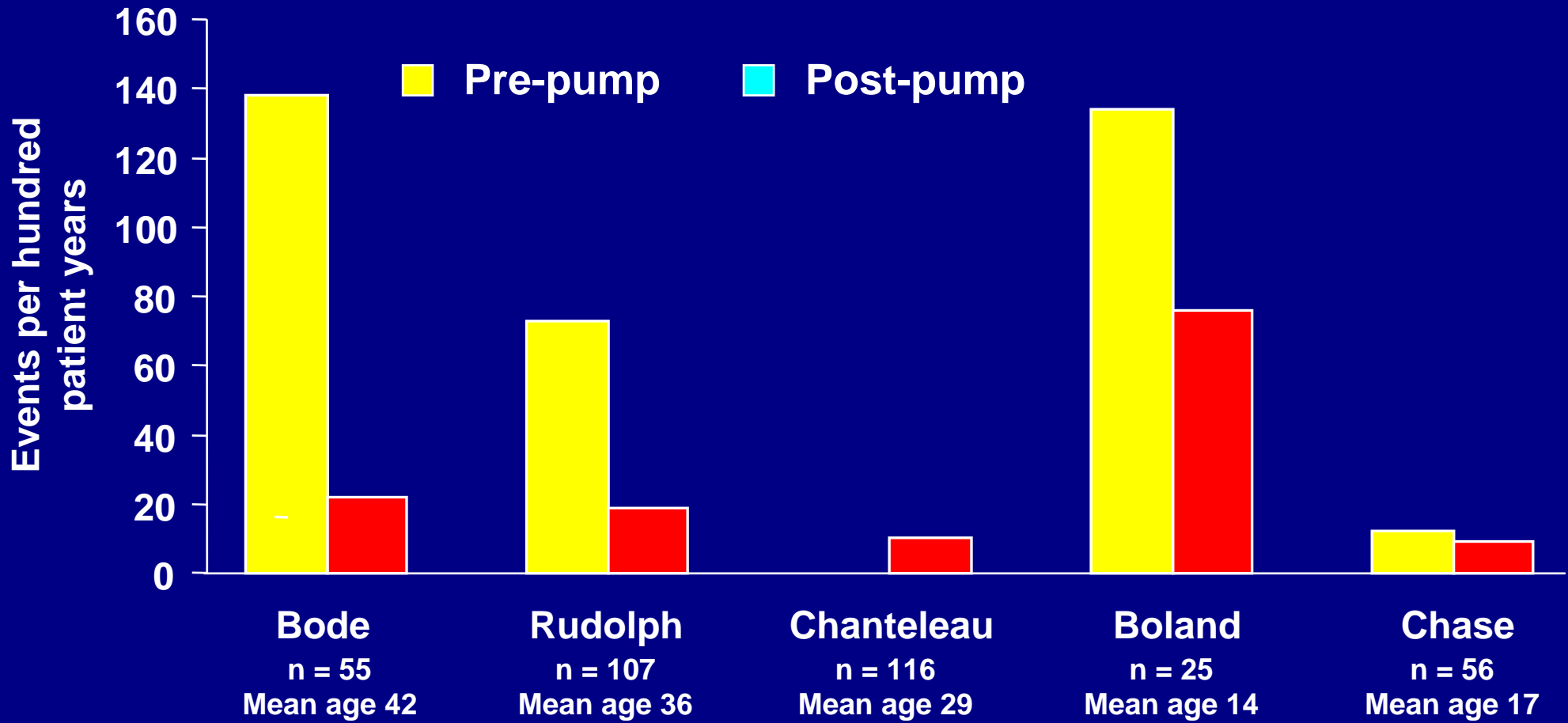
- Improved glycemic **control**
- Better pharmacokinetic **delivery** of insulin
 - **Less hypoglycemia**
 - **Less insulin required**
- Improved **quality** of life

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



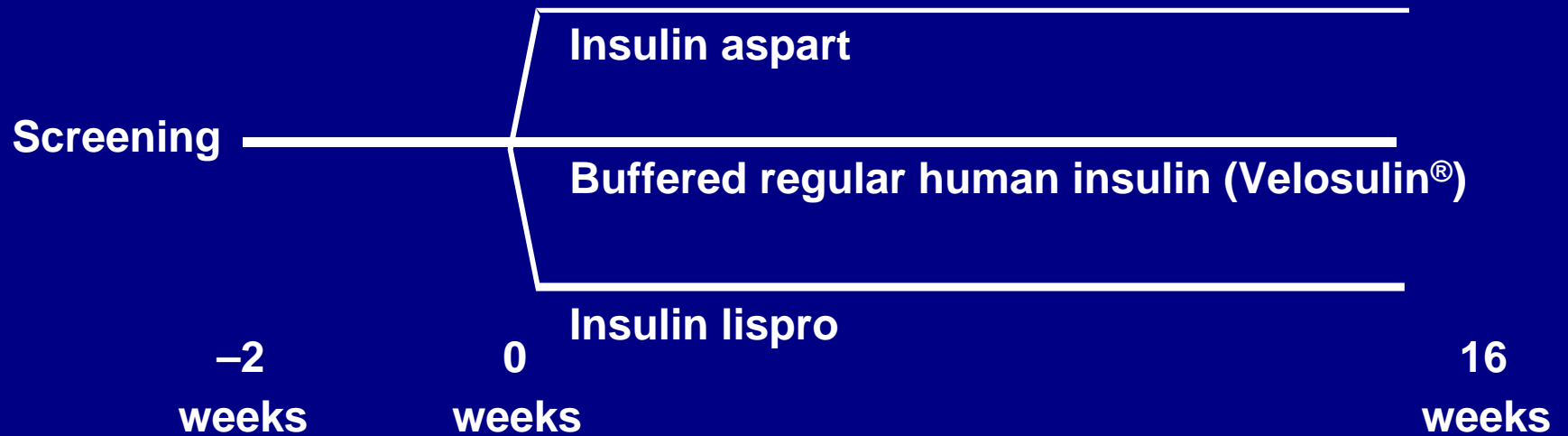
Chanteleau E, et al. *Diabetologia*. 1989;32:421-426; Bode BW, et al. *Diabetes Care*. 1996;19:324-327; Boland EA, et al. *Diabetes Care*. 1999;22:1779-1784; Chase HP, et al. *Pediatrics*. 2001;107:351-356.

CSII

Factors Affecting HbA_{1c}

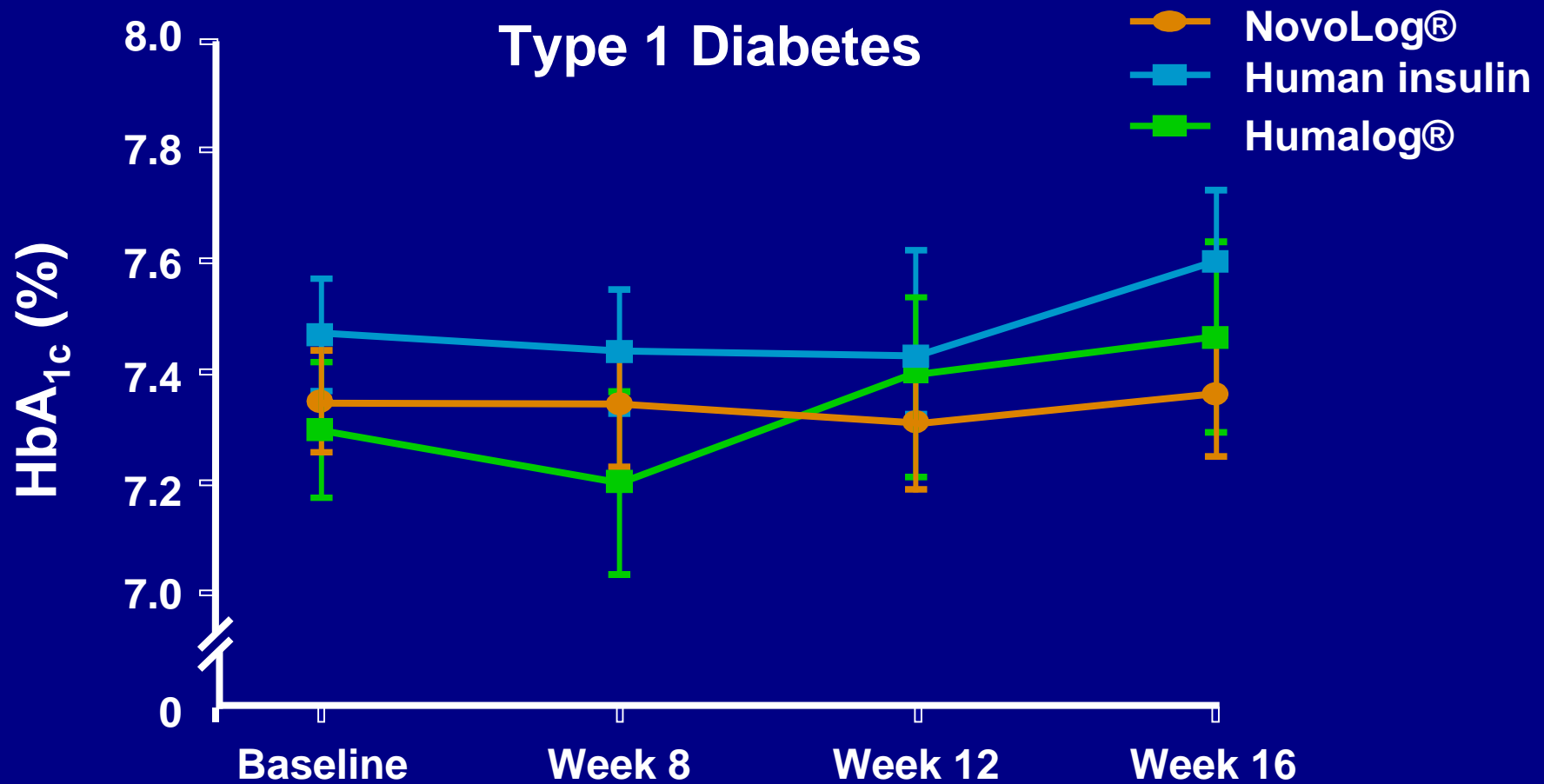
- **Monitoring**
 - $\text{HbA}_{1c} = 8.3 - (0.21 \times \text{BG per day})$
- **Recording** 7.4 vs 7.8
- **Diet practiced**
 - CHO: 7.2
 - Fixed: 7.5
 - Other: 8.0
- **Insulin type**
 - Lispro: 7.3
 - R: 7.7

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

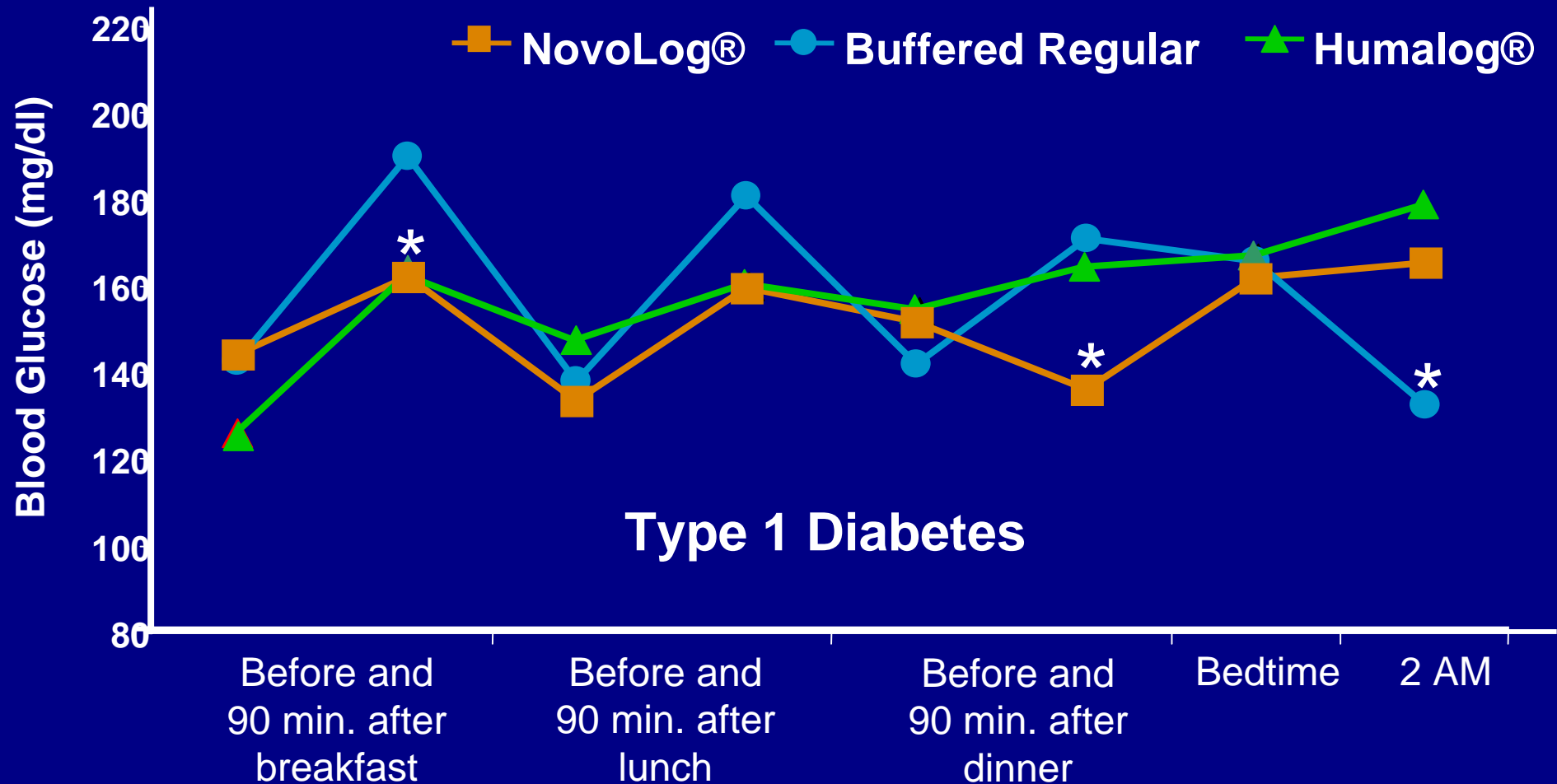


- 146 patients in the USA; 2–25 years with Type 1 diabetes; $7\% \leq \text{HbA}_{1c} \leq 9\%$; previously treated with CSII for 3 months

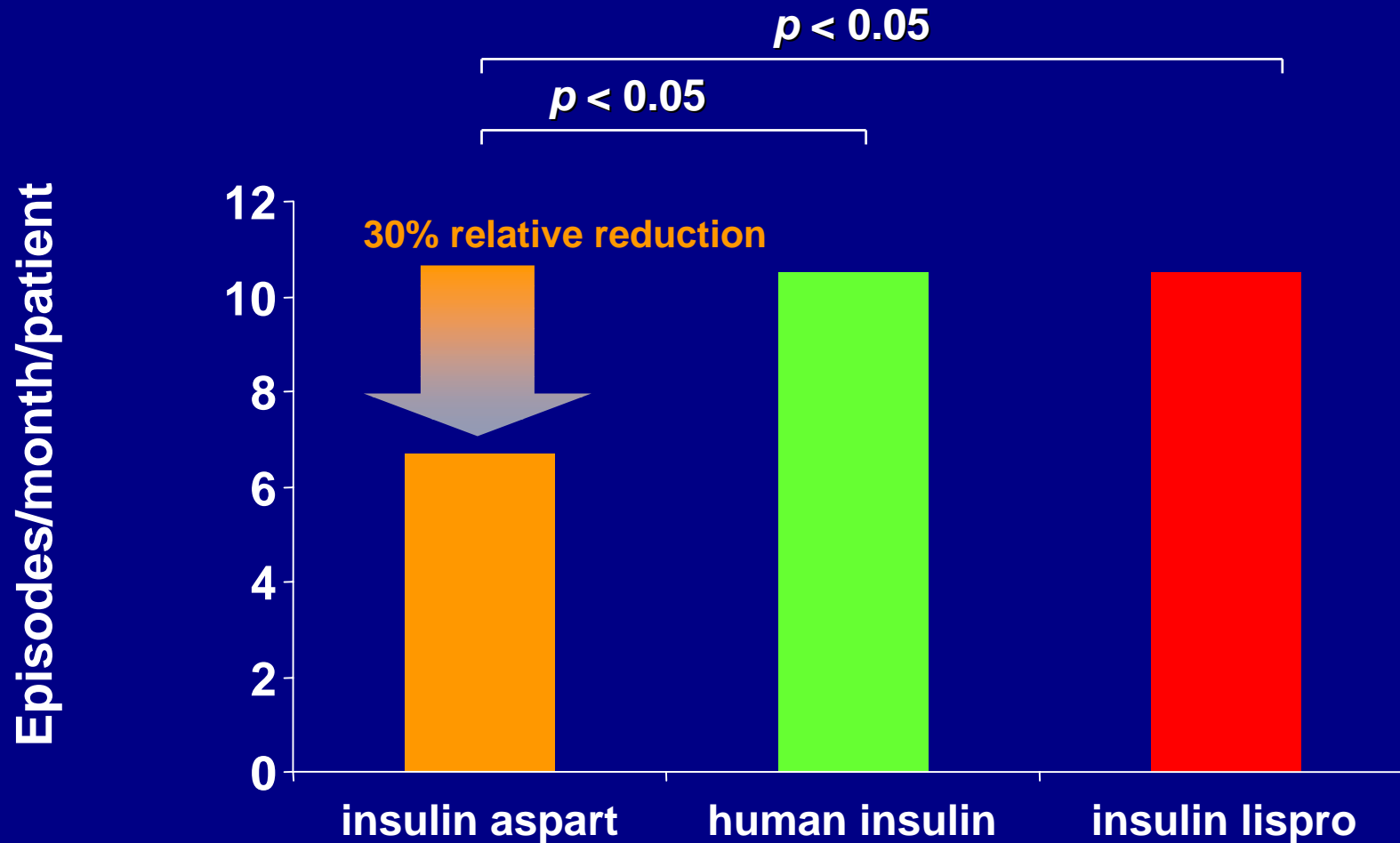
Glycemic Control with CSII



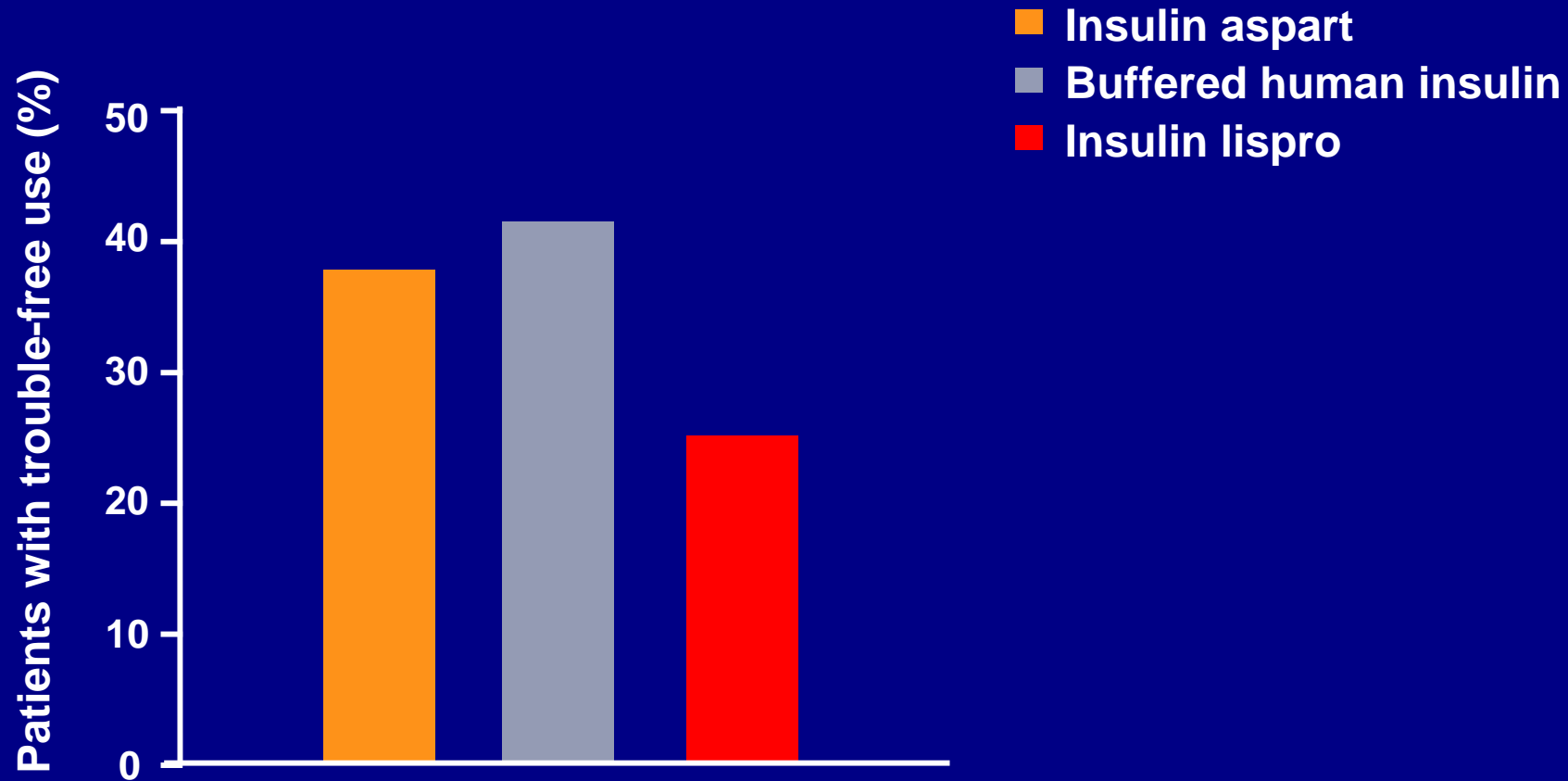
Self-Monitored Blood Glucose in CSII



Symptomatic or Confirmed Hypoglycaemia



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



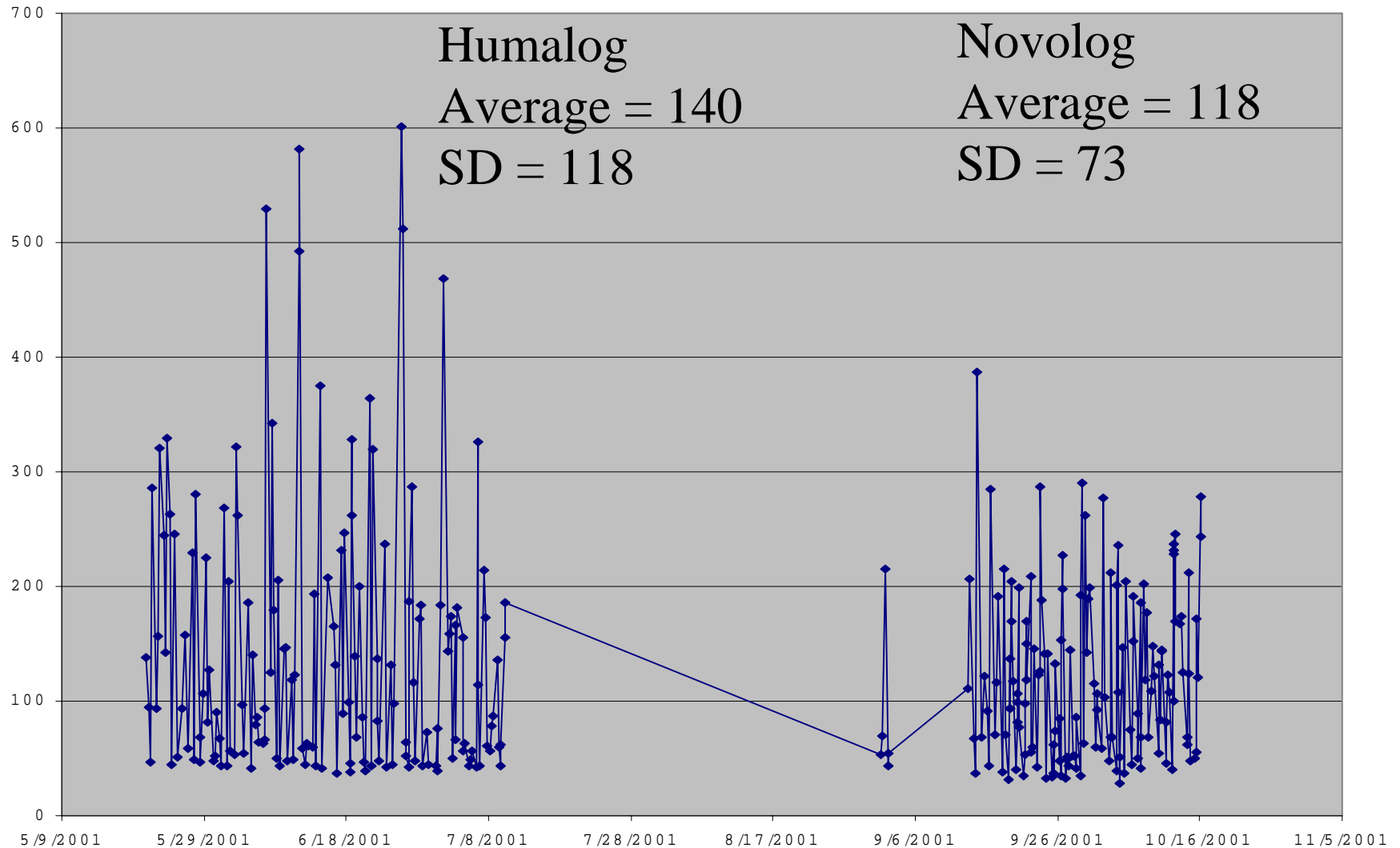
Case Study: 54 year old DM1 on CSII with Lipoatrophy and Insulin Antibodies

- **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

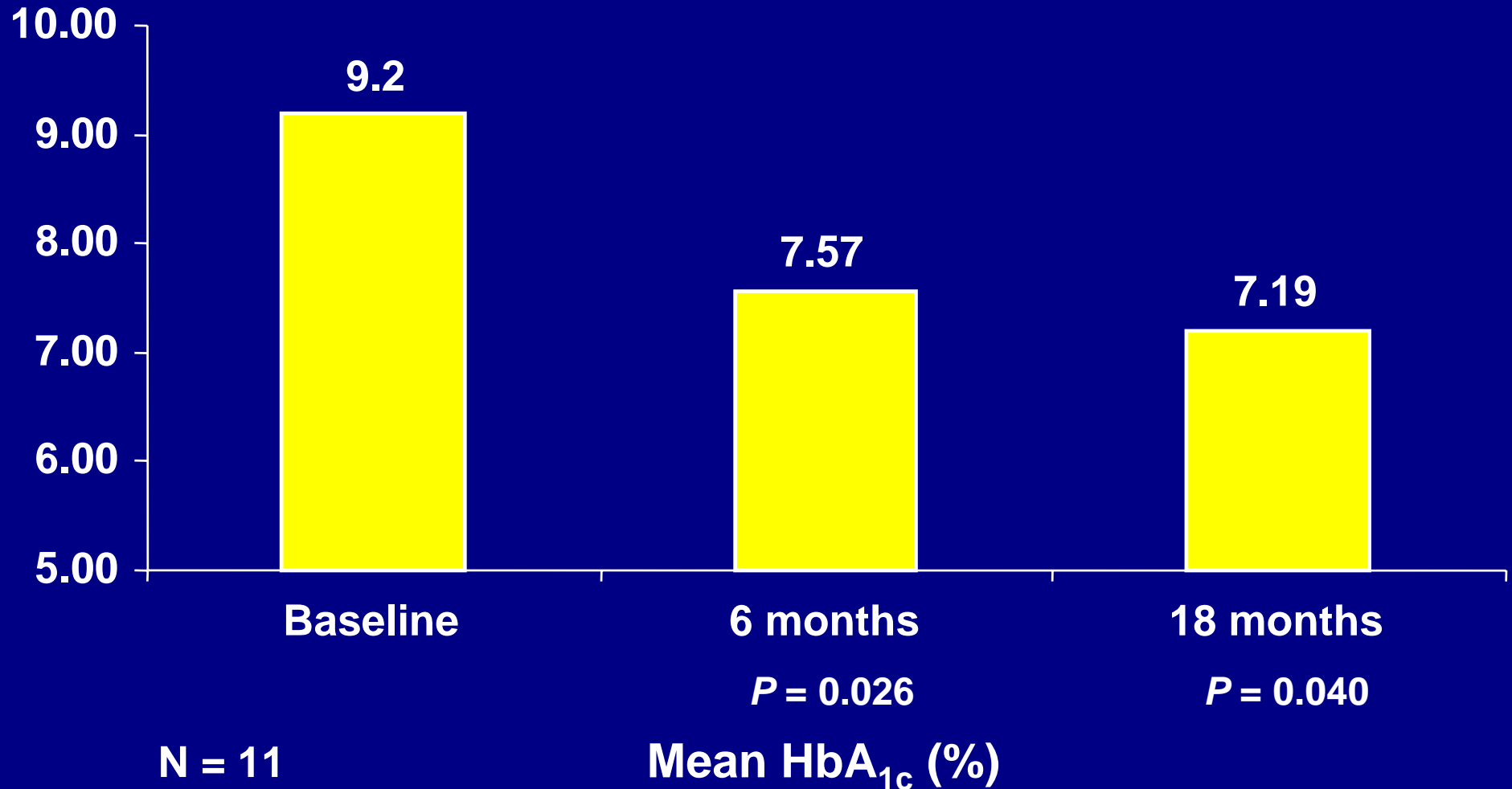


Case Study: 54 year old DM1 on CSII with Lipoatrophy and Insulin Antibodies

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

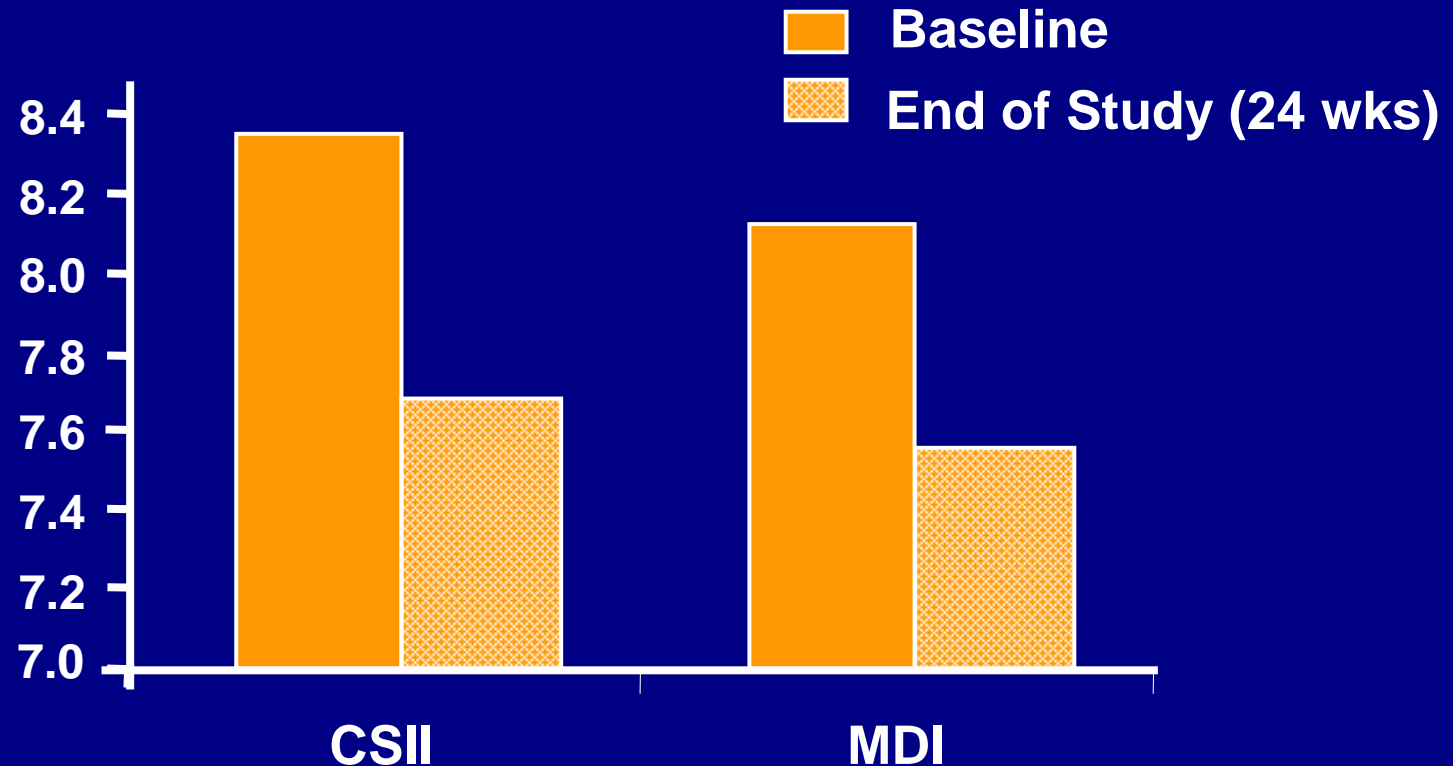
CSII Usage in Type 2 Patients

Atlanta Diabetes Experience



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

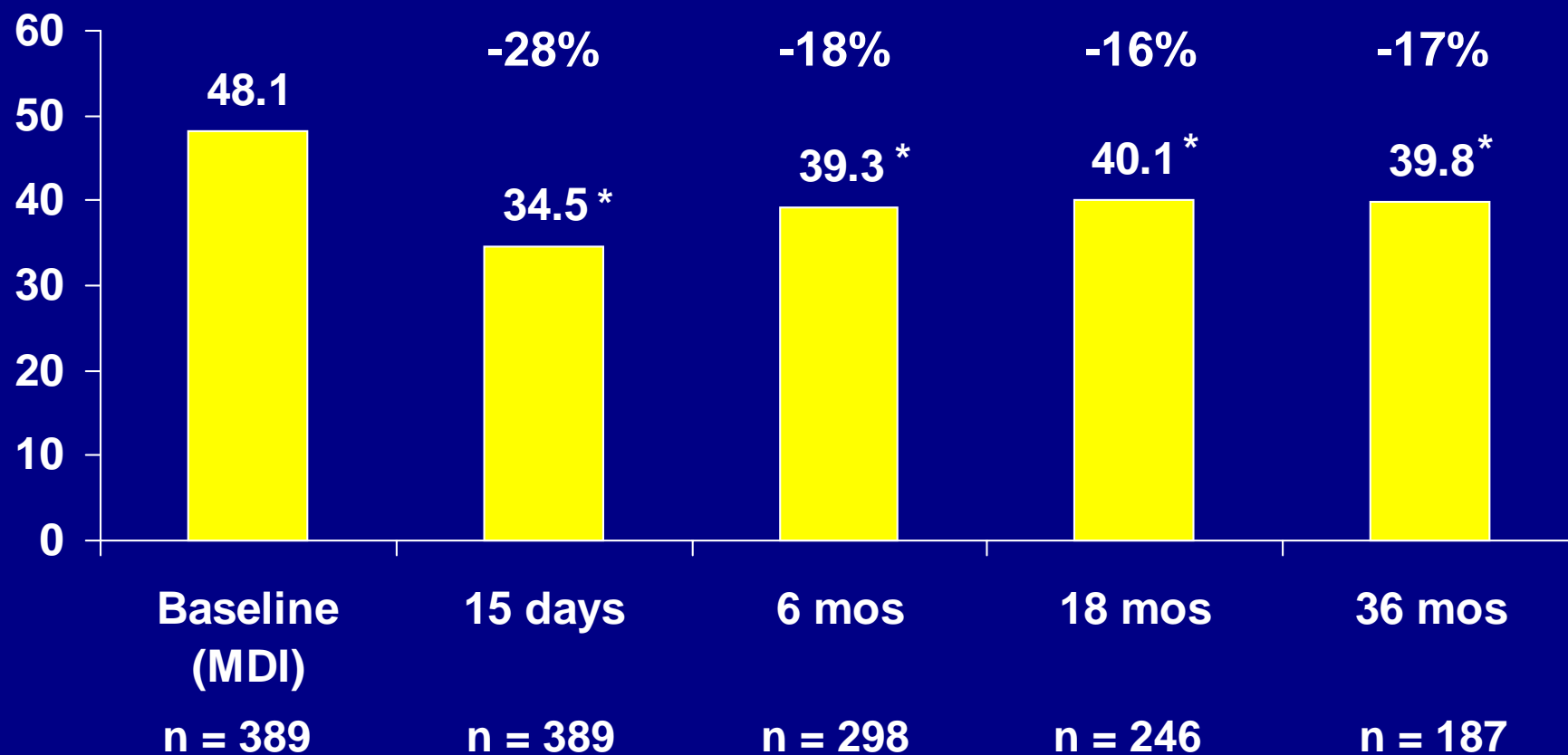
● A1C



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



* $P < 0.001$

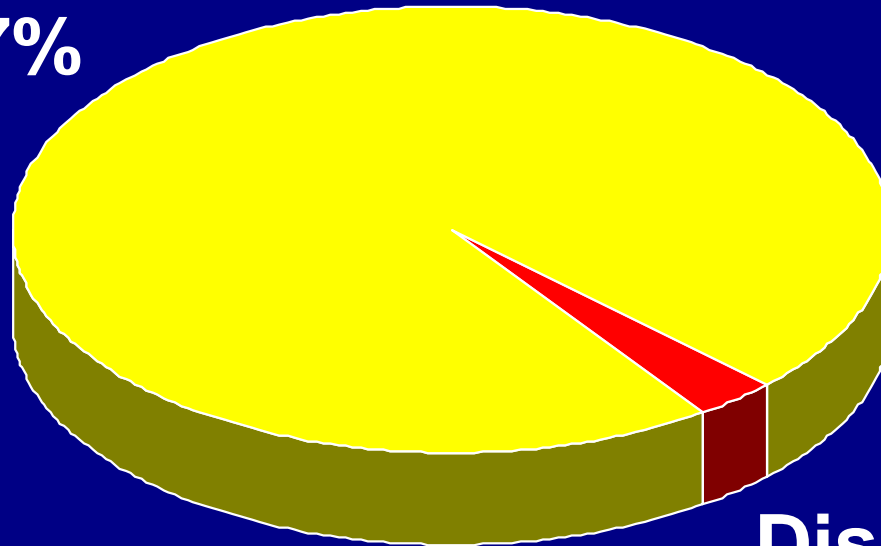
Normalization of Lifestyle

- 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)

Continued 97%



Discontinued 3%

N = 165

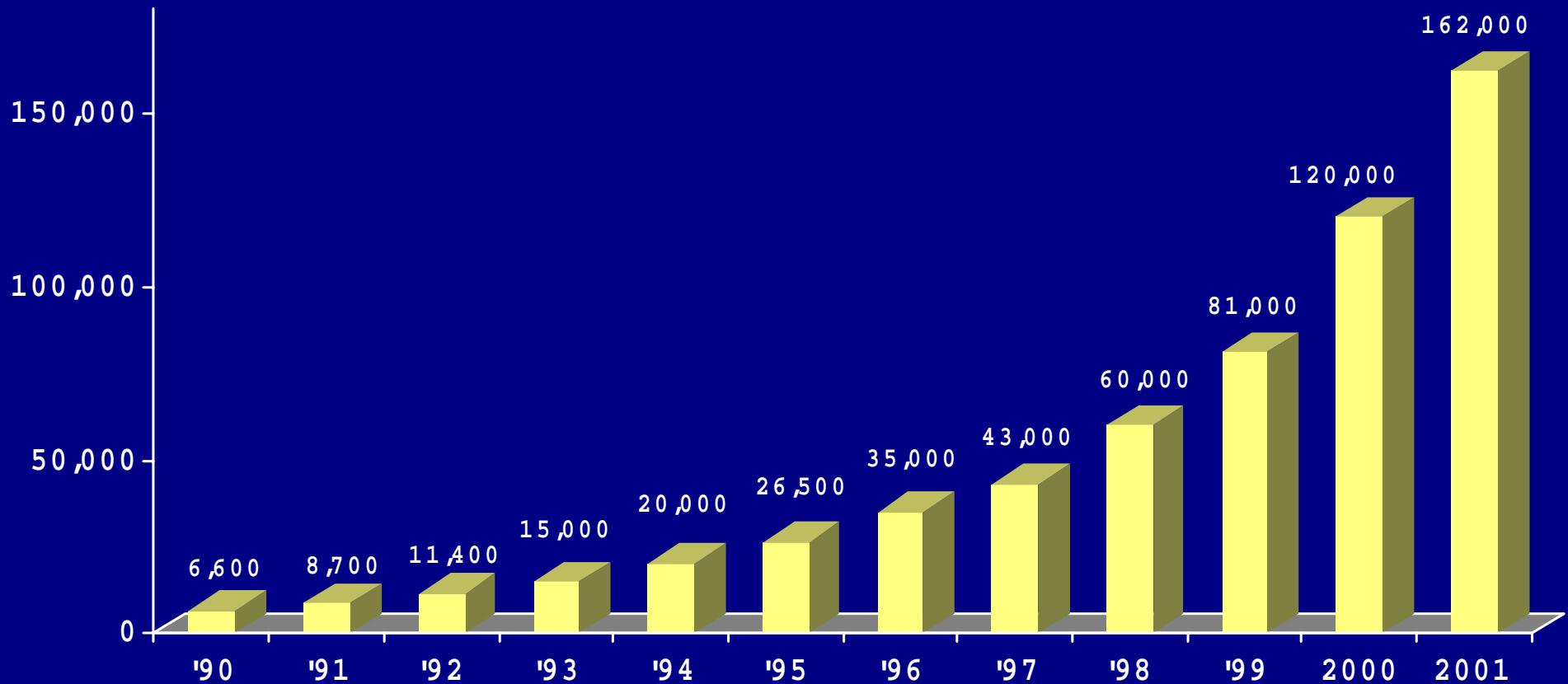
Average Duration = 3.6 years

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



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

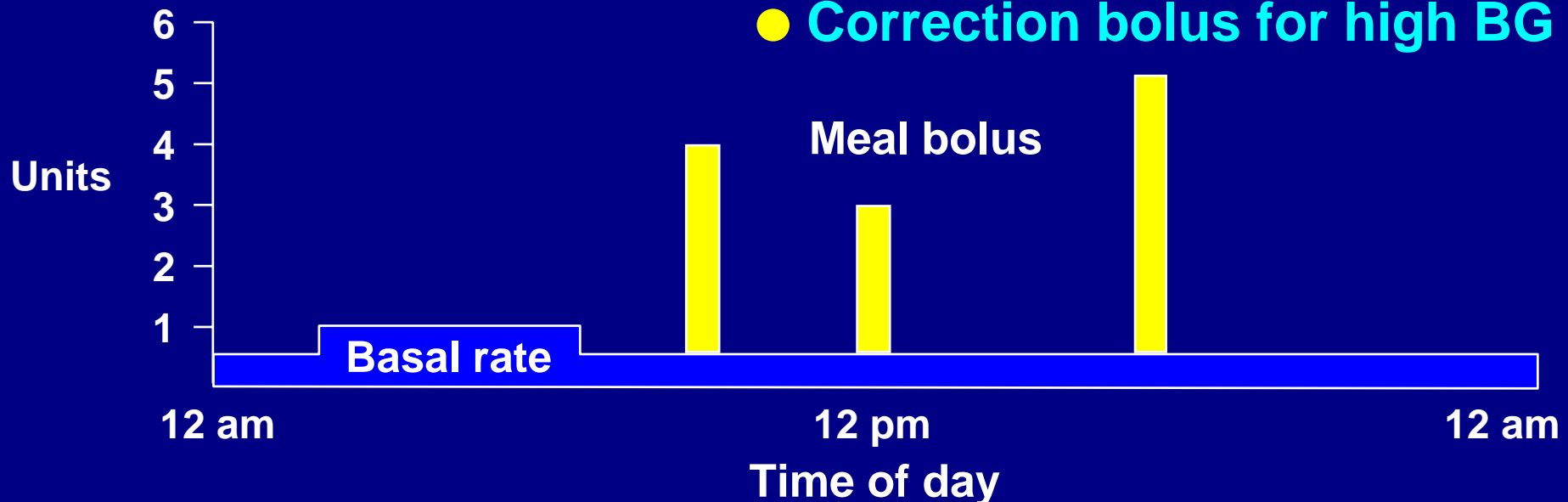
Pump Therapy

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



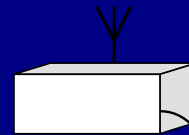
*subcutaneous
glucose sensor*

+

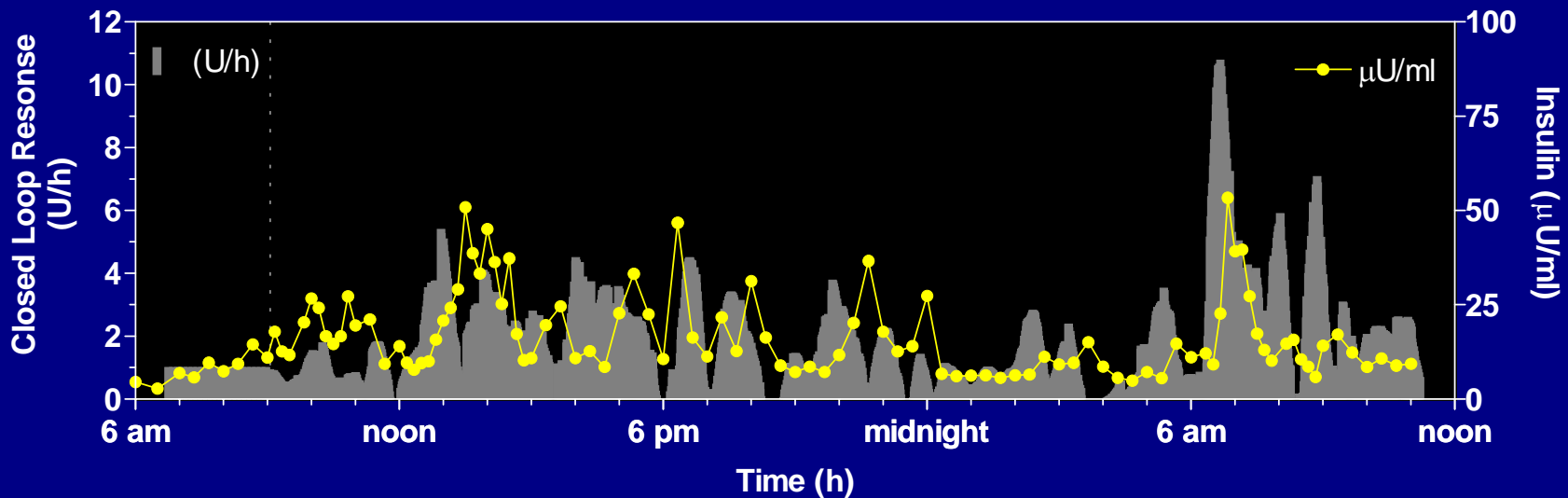
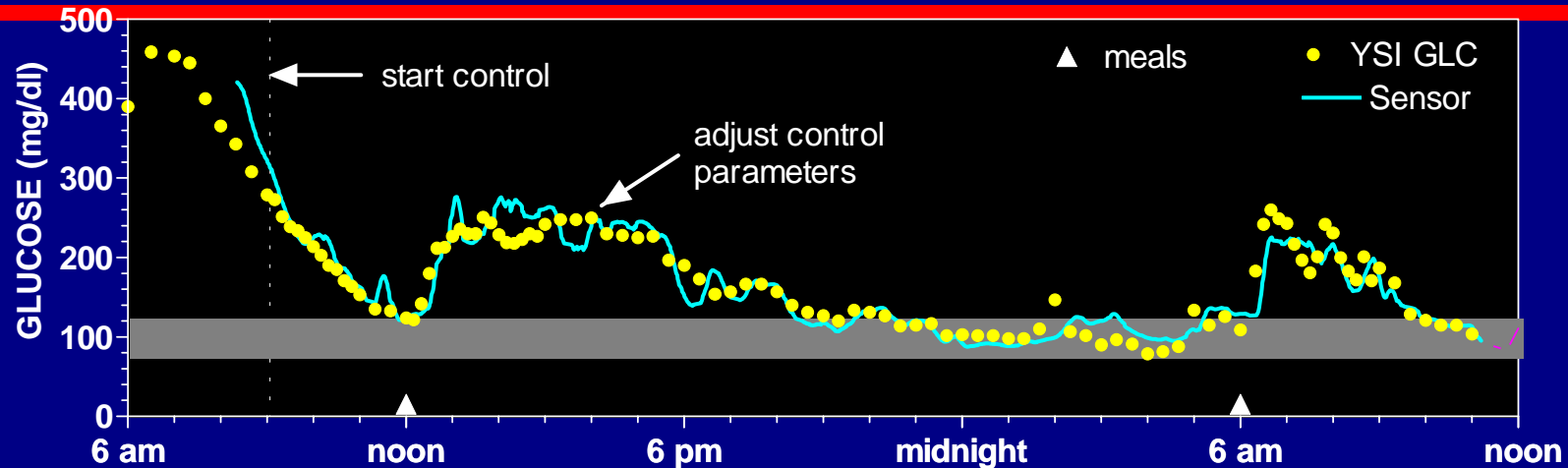


*Insulin infusion pump
(currently MiniMed 508)*

Closed-Loop Setup for Canine Studies



24-h Closed-Loop Control (diabetic canine)



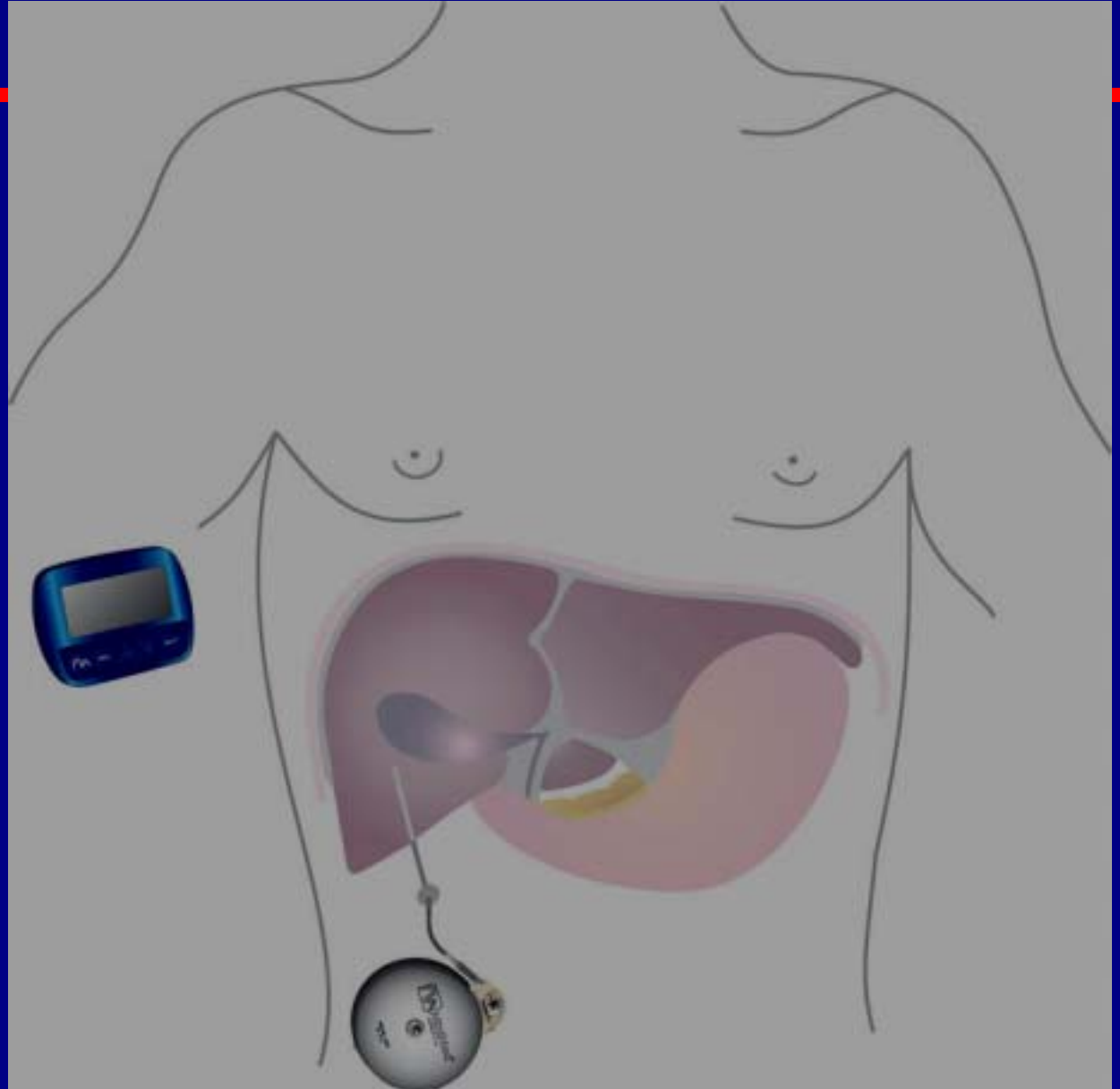
Implantable Pump



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

MiniMed 2007 System

Implantable Insulin Pump Placement

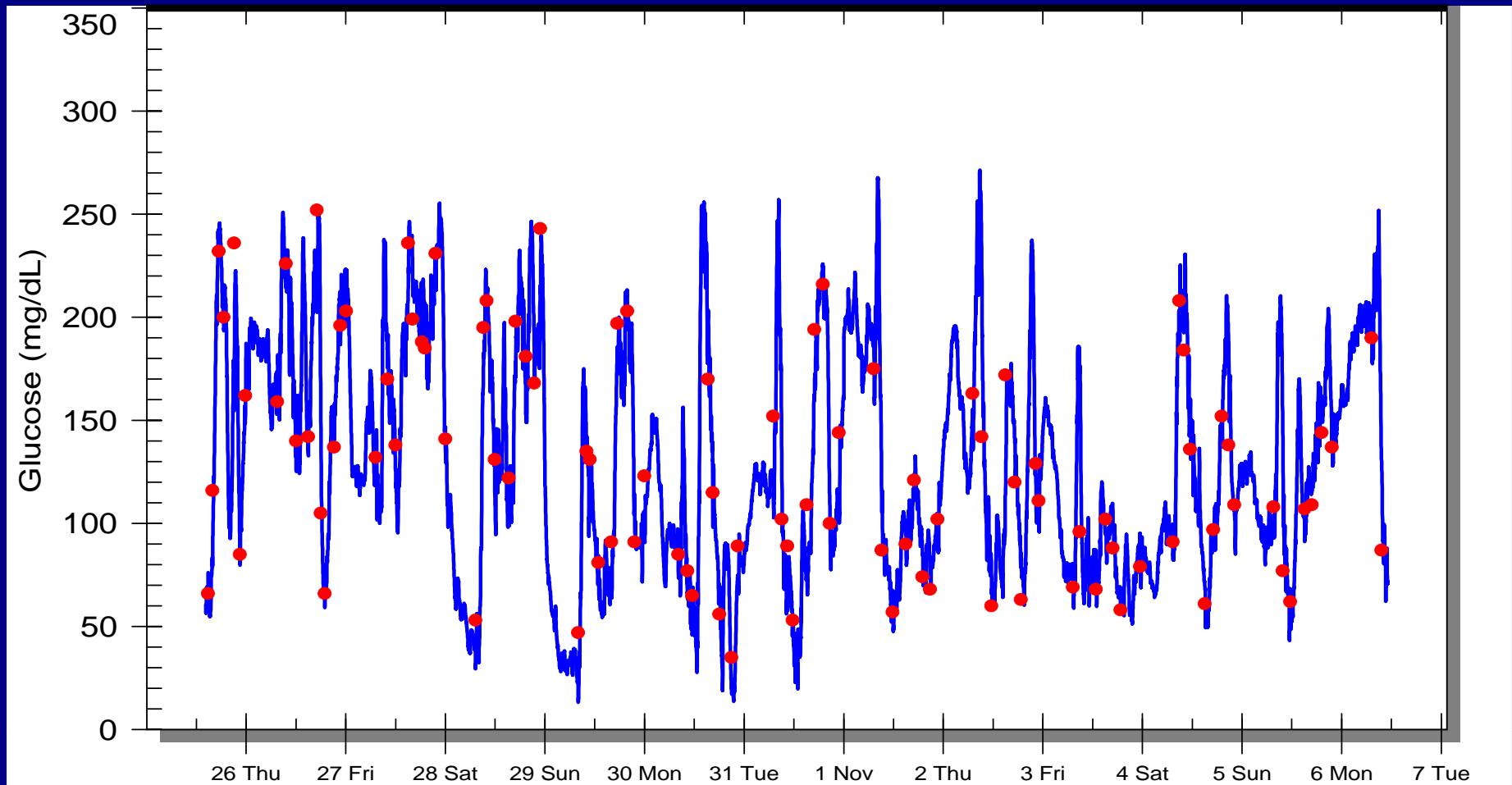


Long-Term Glucose Sensor



LONG TERM IMPLANTABLE SYSTEM

Human Clinical Trial



Source: Medical Research Group, Inc.

Combine Pump and Sensor Technology



+



**LTSS => Long Term Sensor
System (“Open Loop Control”)
Using an RF Telemetry Link.....**

Medtronic MiniMed's Implantable Biomechanical Beta Cell

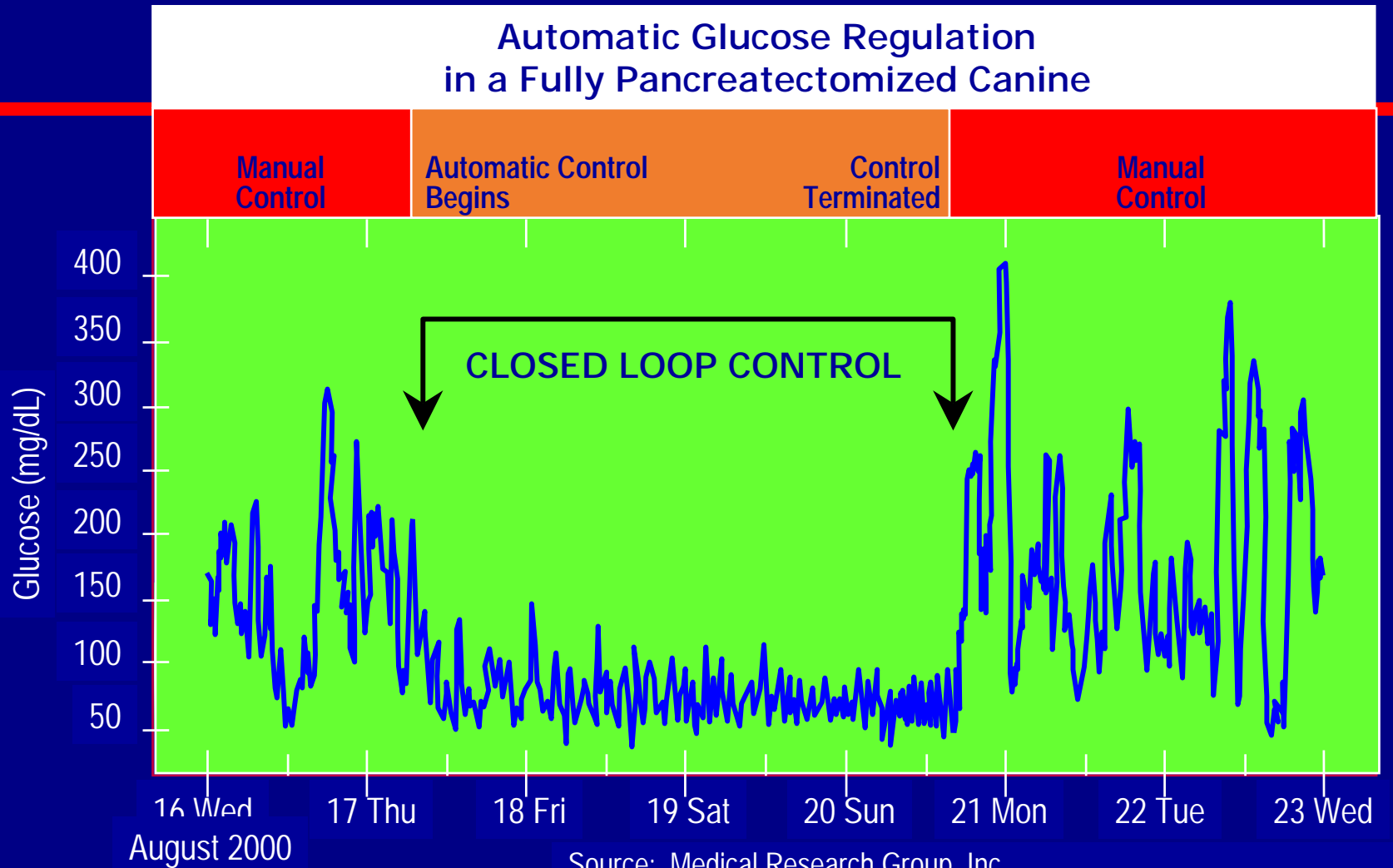


Today's Reality

Open-Loop Glucose Control



LONG TERM IMPLANTABLE SYSTEM



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