



# **New Insulins and Insulin Delivery Systems**

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**Atlanta Diabetes Associates**  
**Atlanta, Georgia**

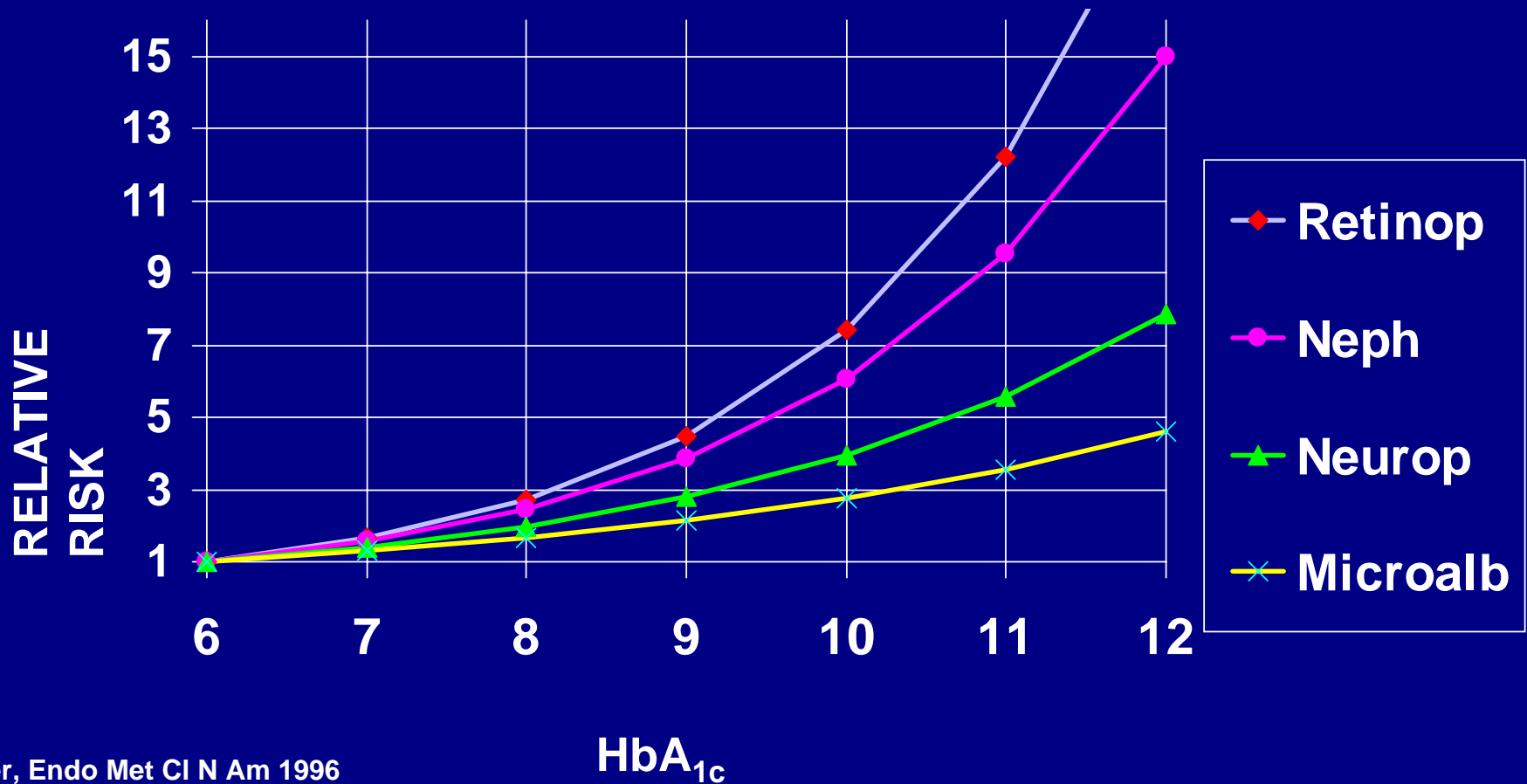
# Goals of Intensive Diabetes Management

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- 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

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- 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

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## The Importance of Controlling Postprandial Glucose

# ACE / AACE Targets for Glycemic Control

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**HbA<sub>1c</sub> < 6.5 %**

**Fasting/preprandial glucose < 110 mg/dL**

**Postprandial glucose < 140 mg/dL**

# Insulin

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**The most powerful agent we  
have  
to control glucose**



# The discovery of insulin (Toronto 1921)

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**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

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Patient J.L., December 15, 1922

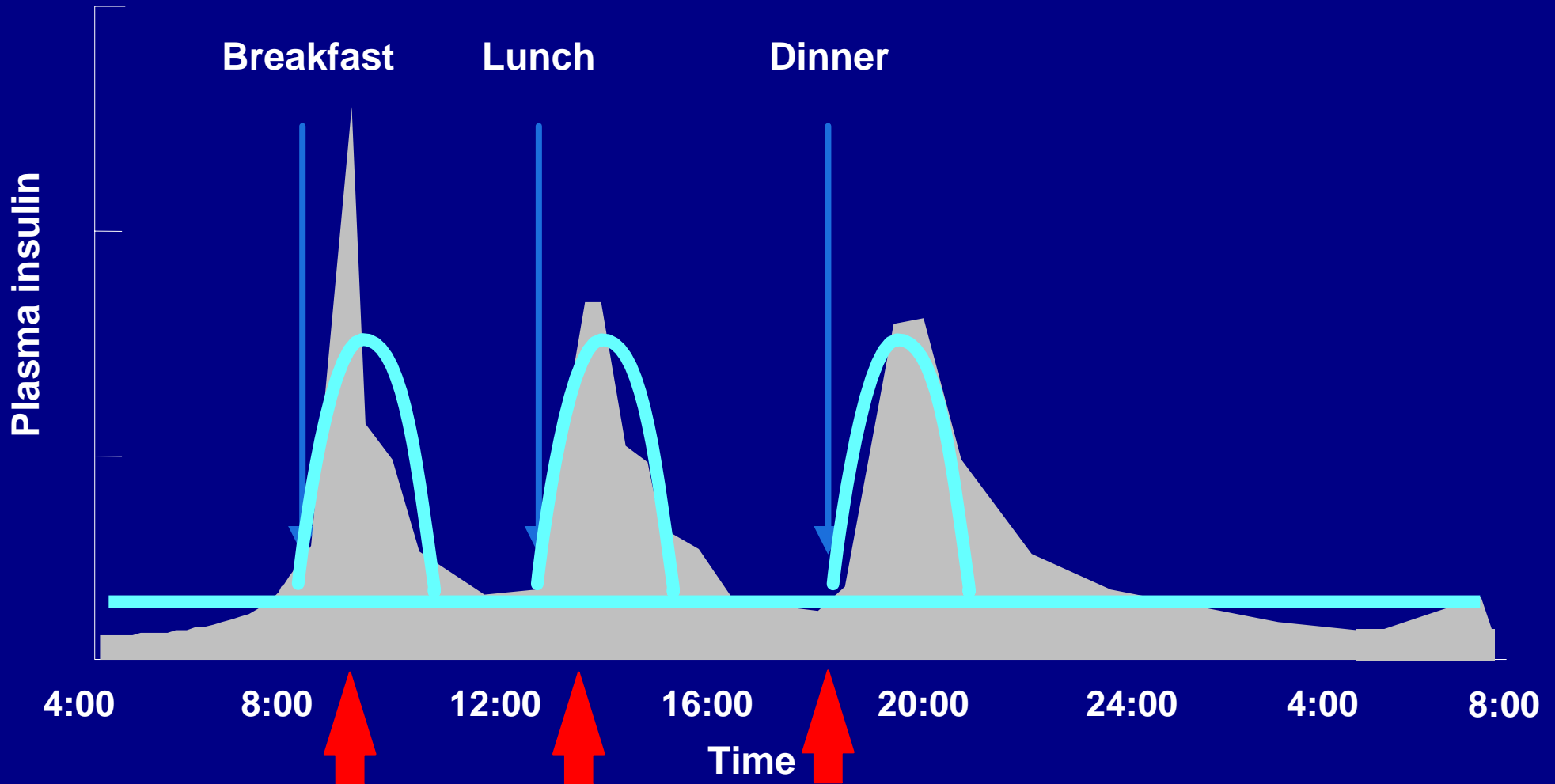


February 15, 1923

# 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

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

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

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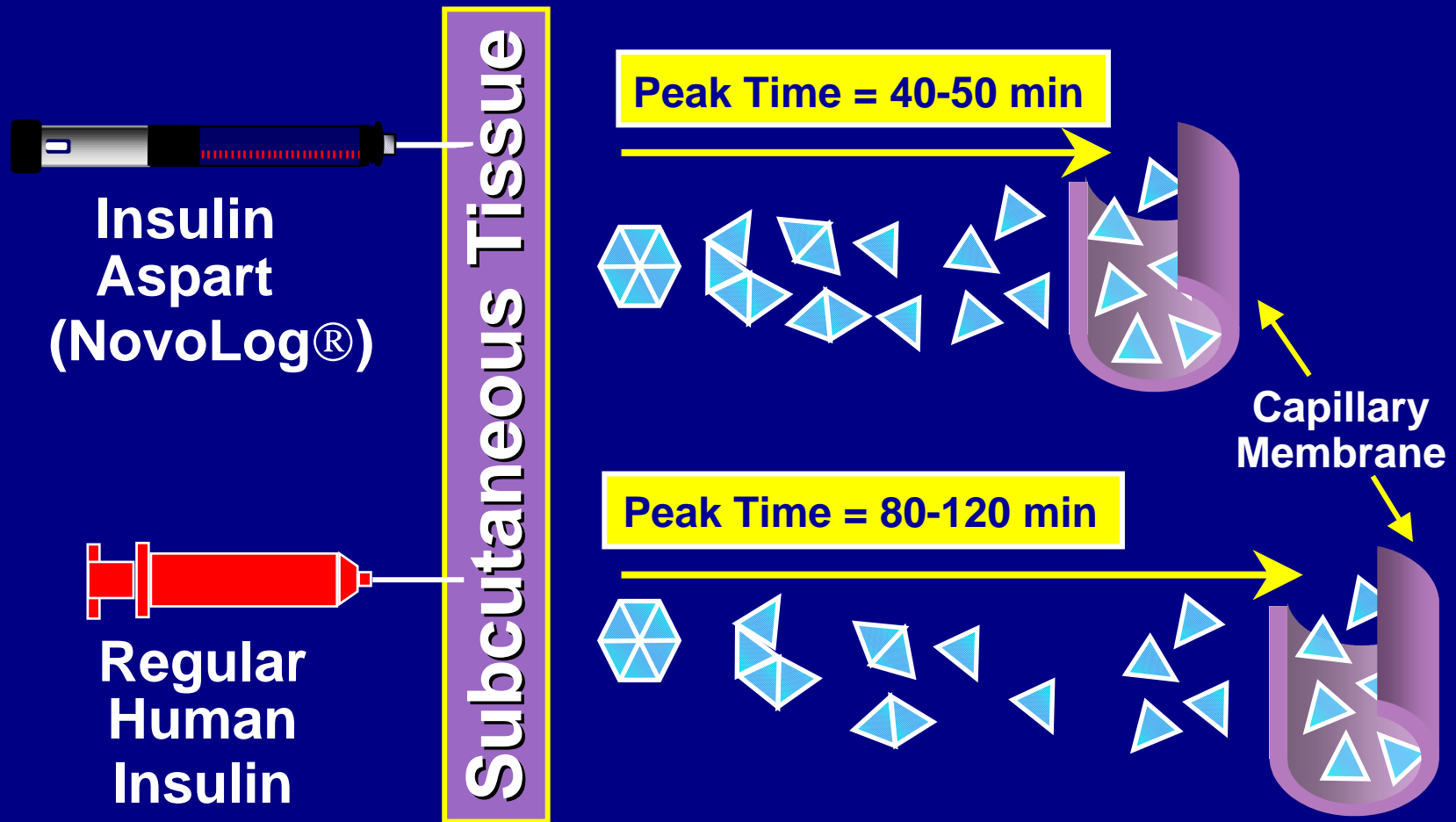


# Primary Structure of Asp(B28)-Insulin

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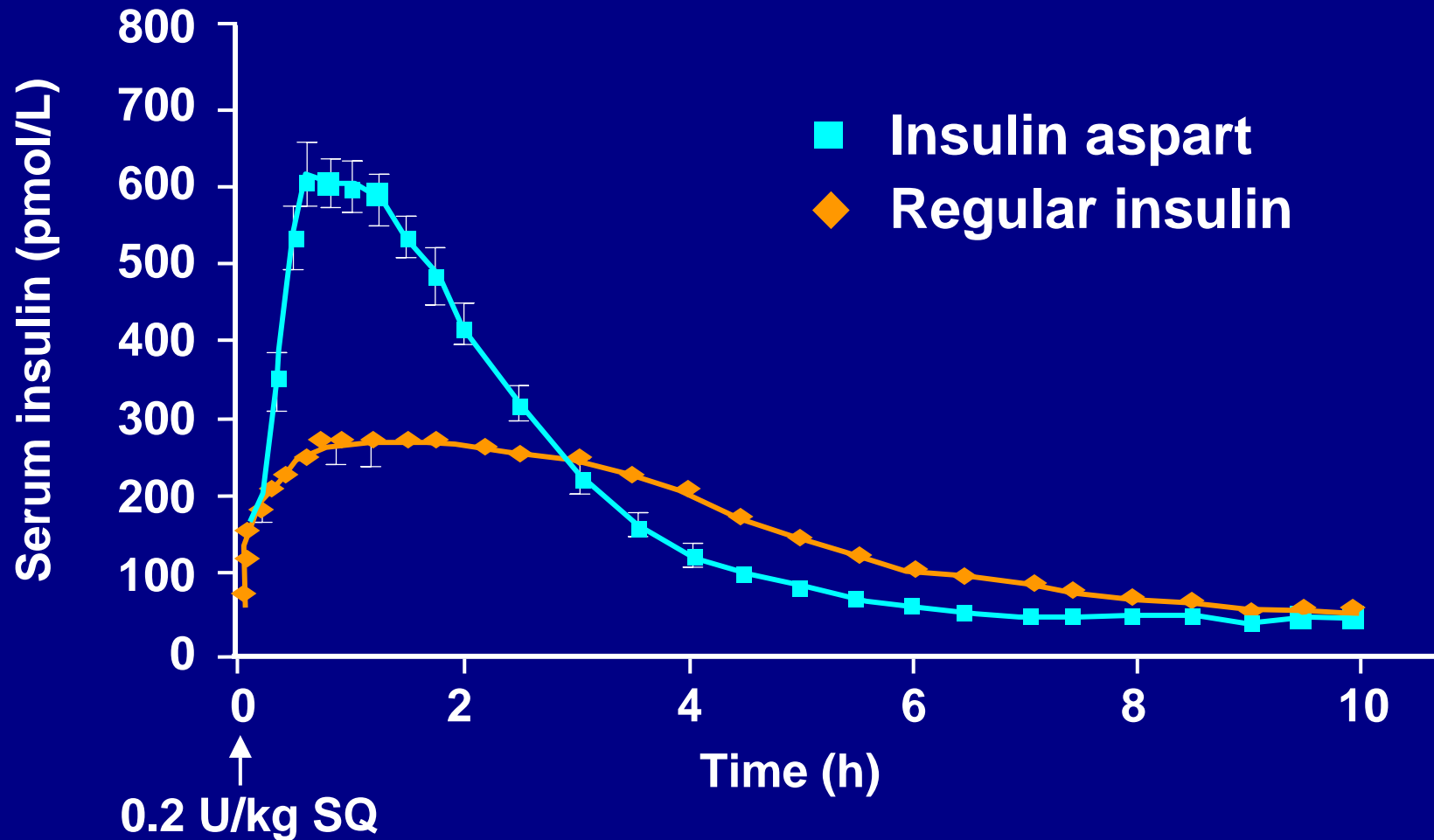


# Dissociation & Absorption of NovoLog<sup>®</sup>

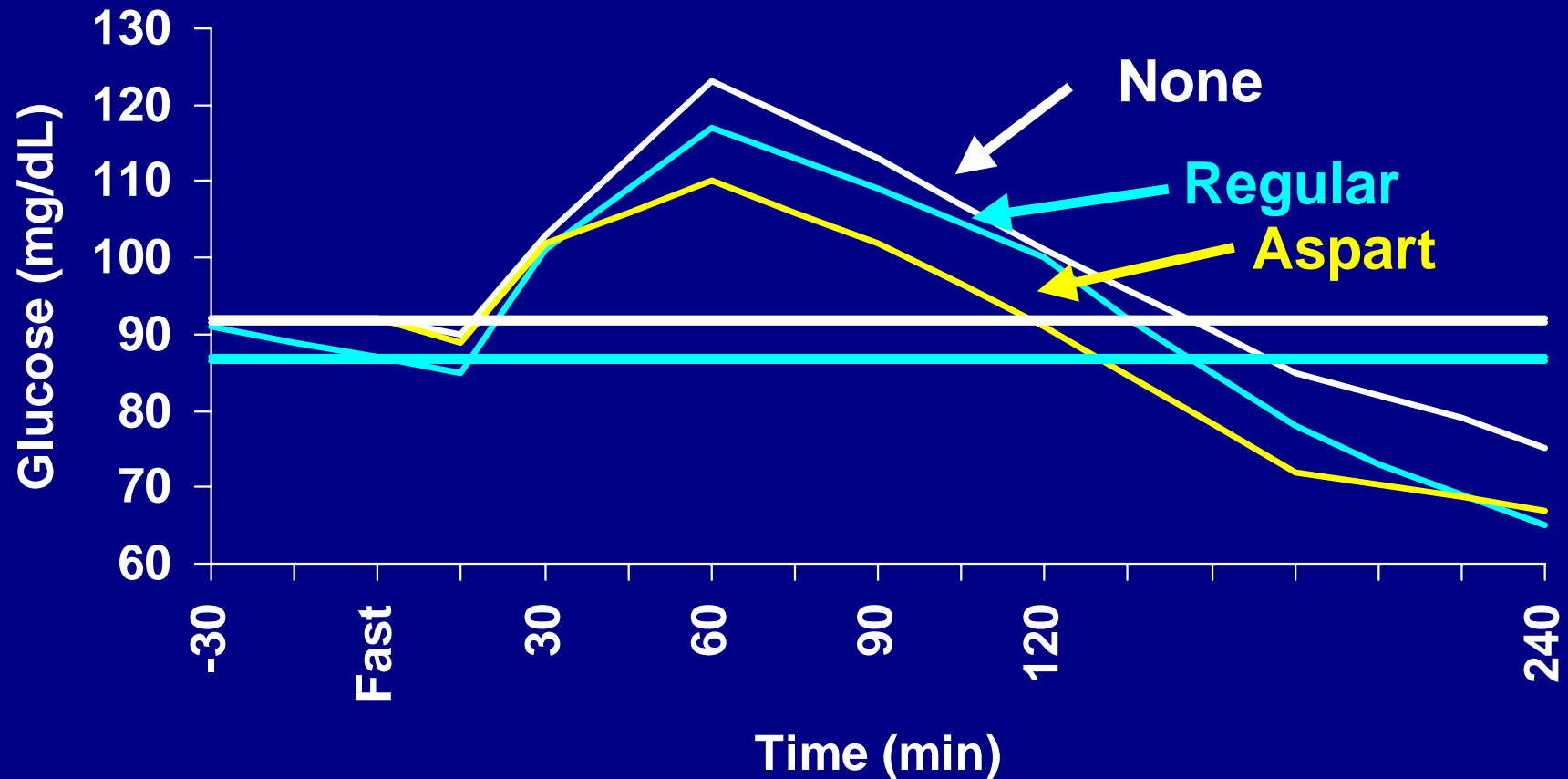




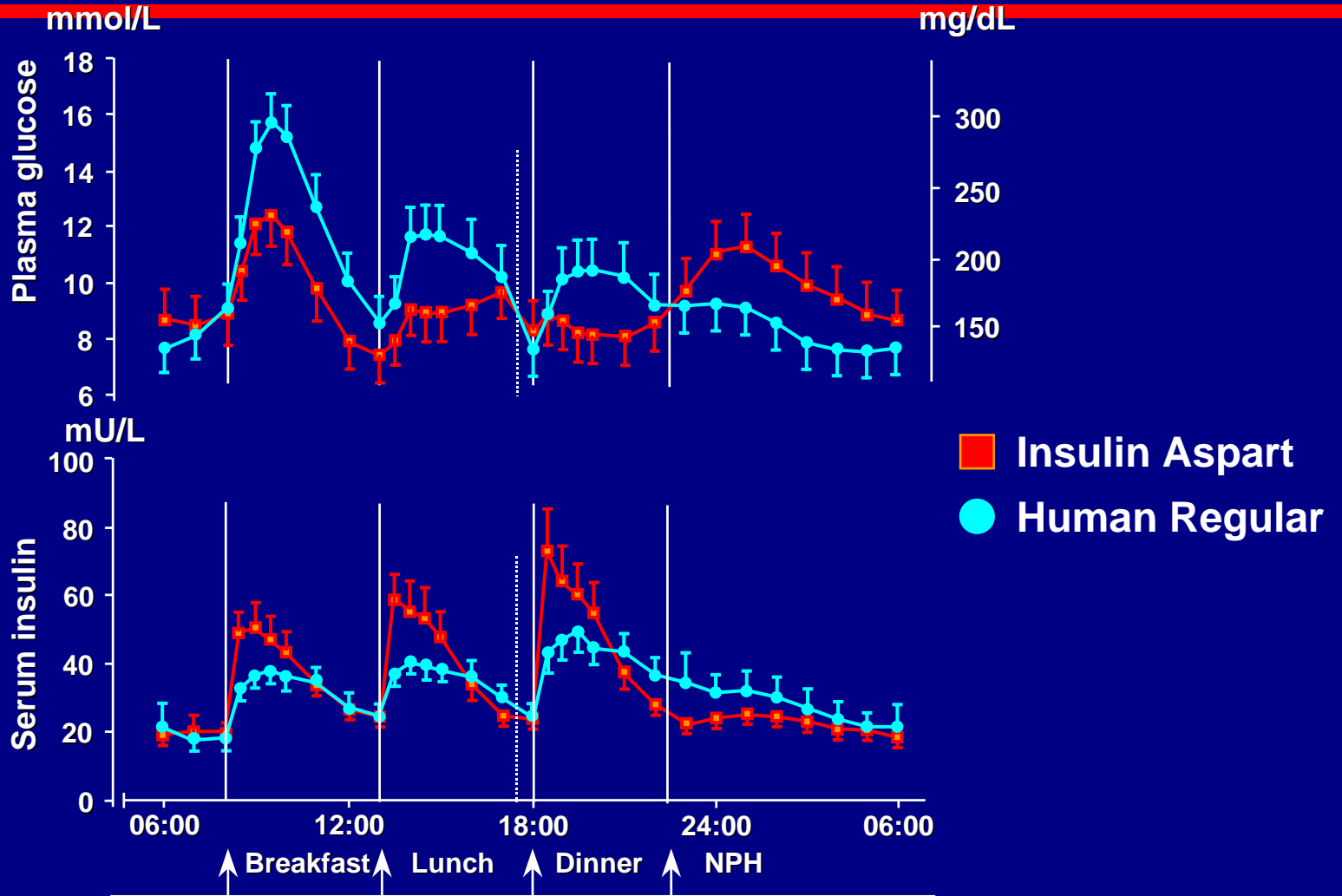
# Insulin Aspart: Mean Serum Insulin Profiles During Euglycemic Clamp in Healthy Volunteers



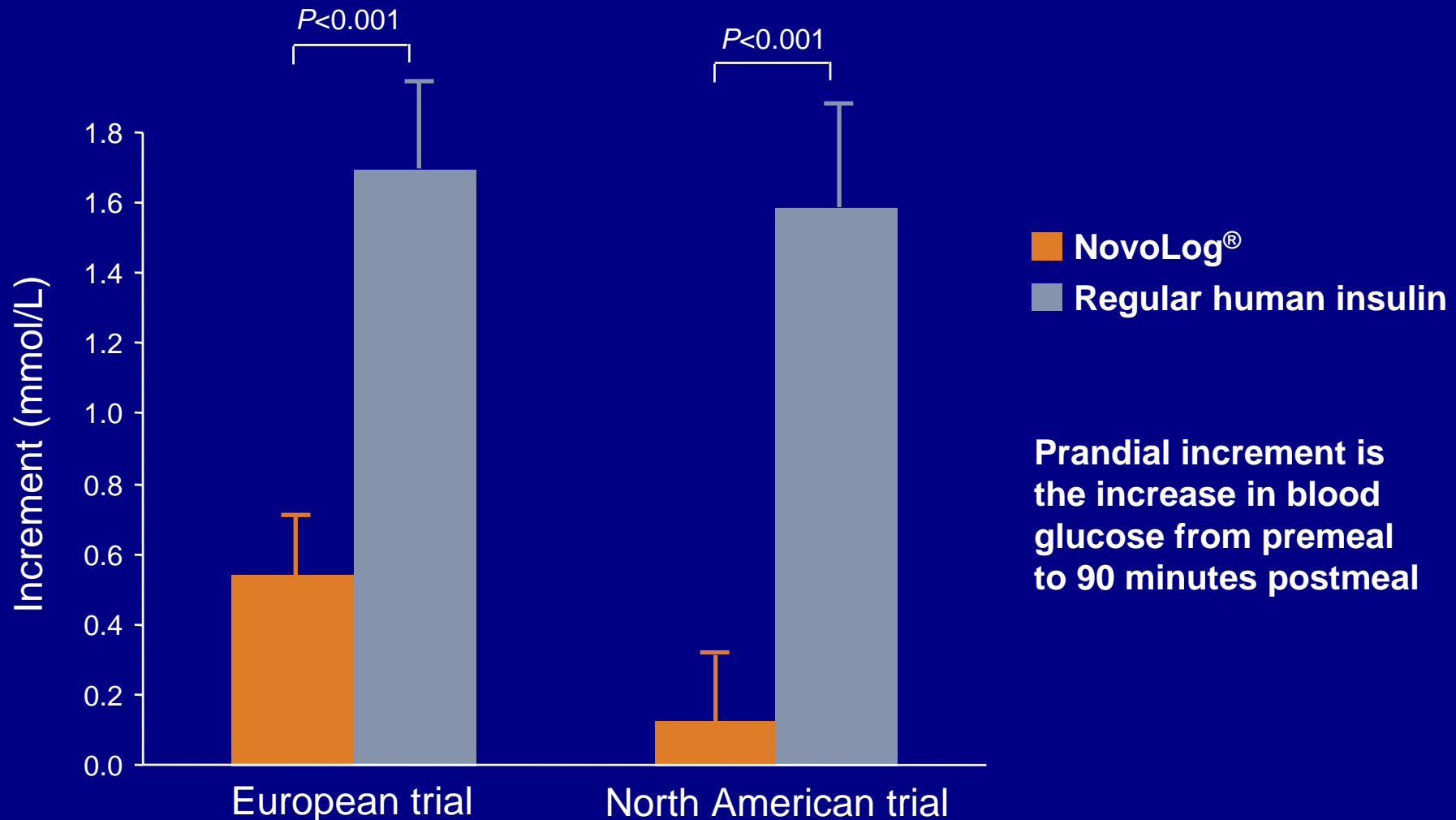
# Glucose Area Under the Curve



# Insulin Aspart vs Human Regular: Glycemic Control



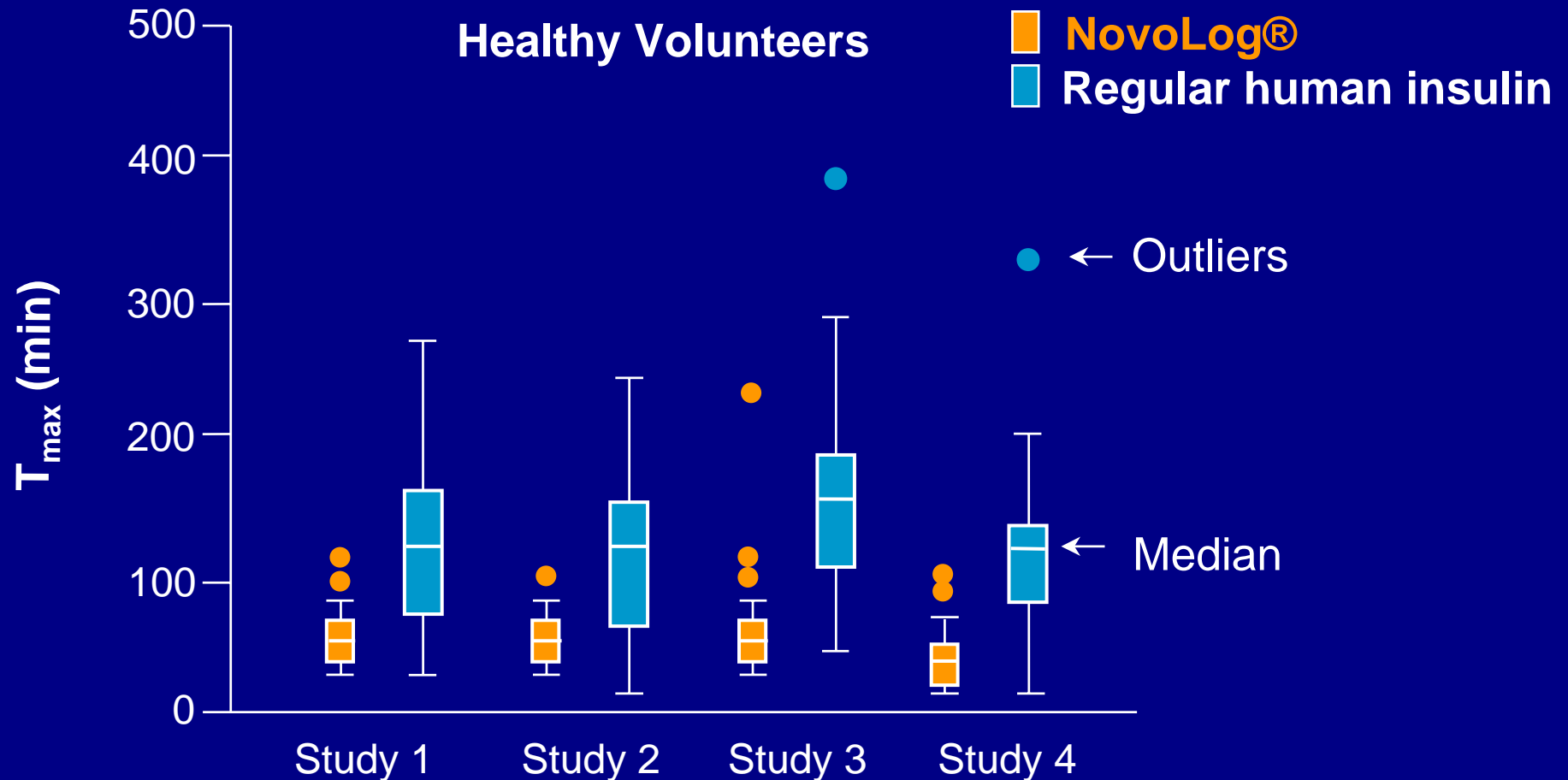
# Postprandial Blood Glucose Increment (Mean over the 3 Meals at 6 Months)



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

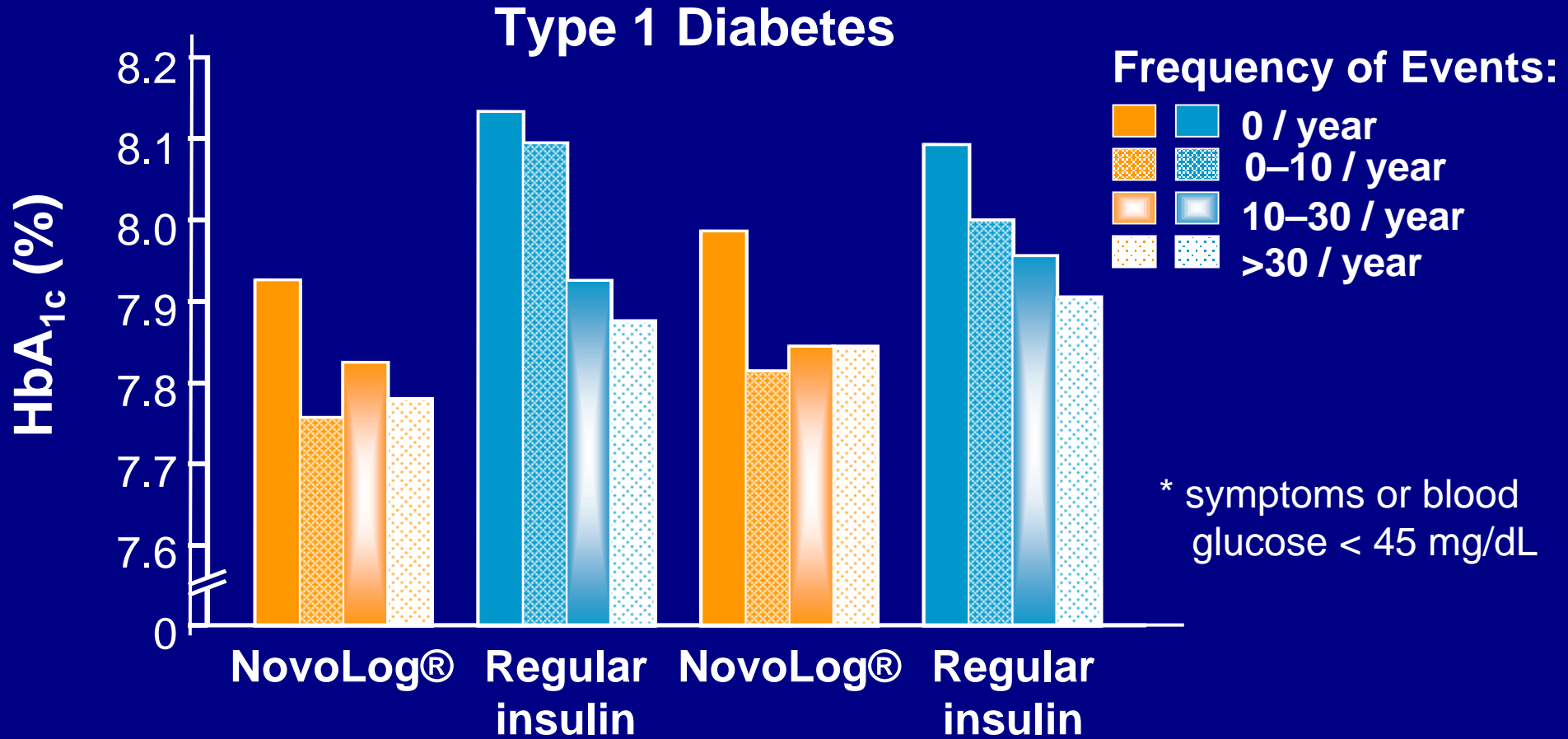
Home PD, et al. *Diabetic Medicine*. 2000;17:762.

# 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

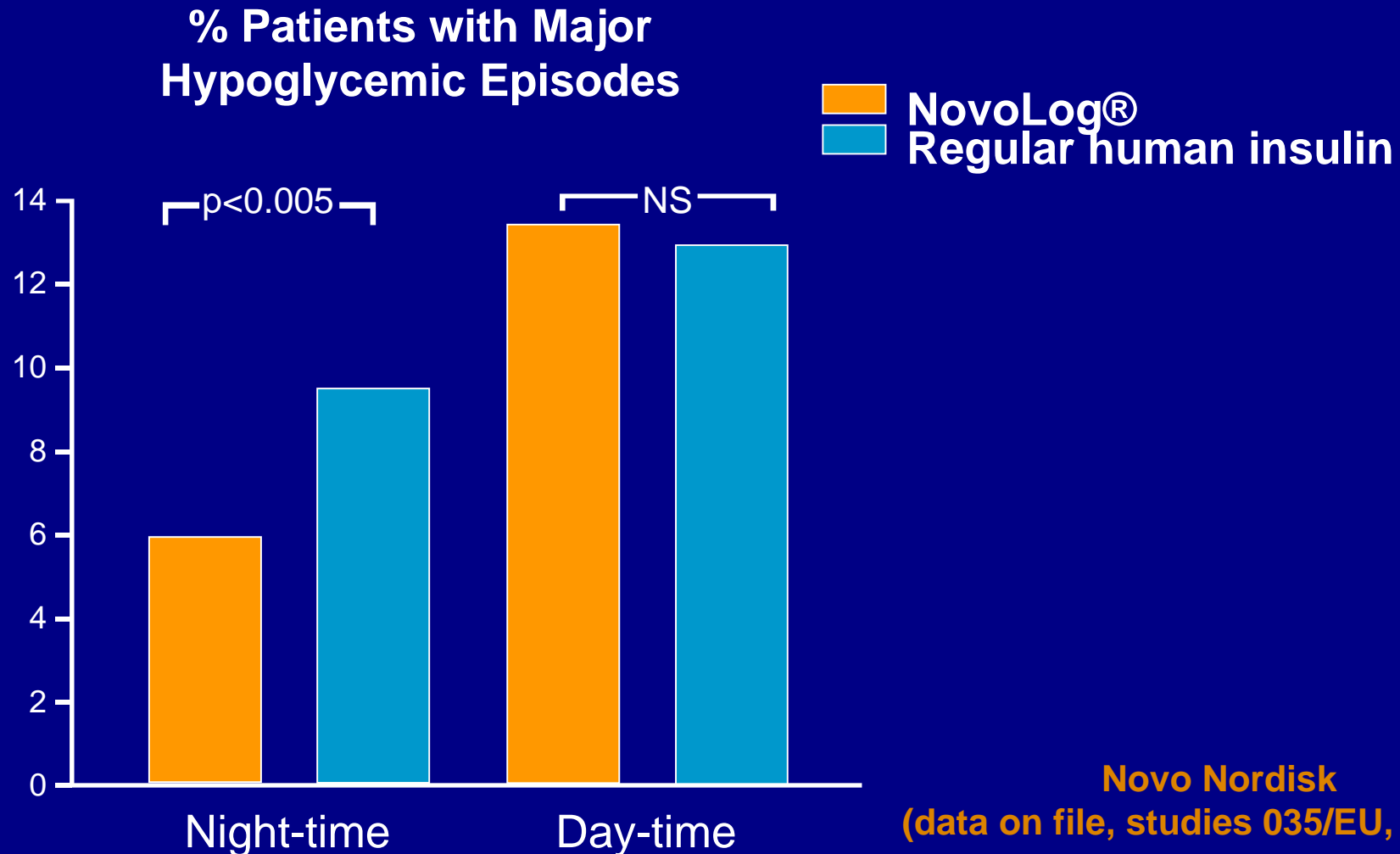


Study 035/EU

Study 036/US

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

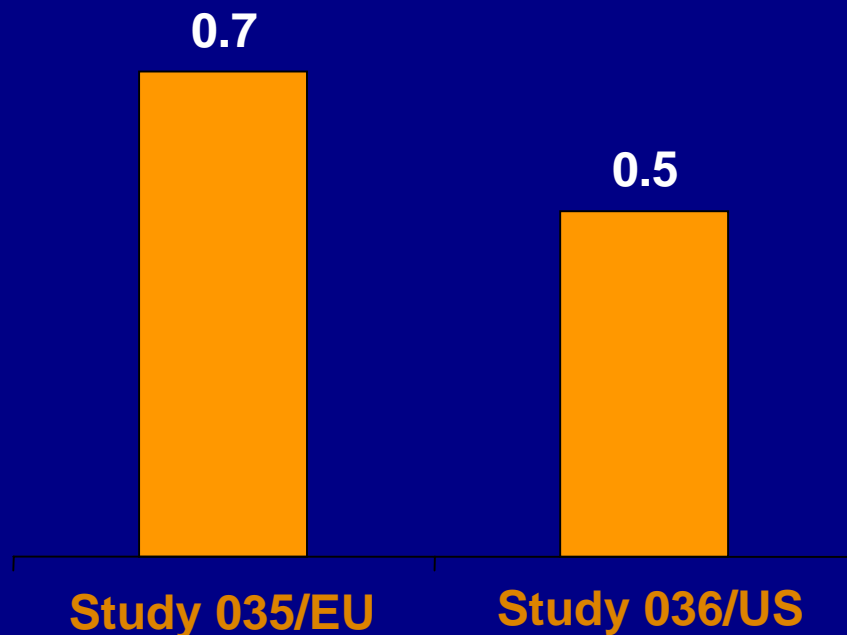
# Reduced Reporting of Major Nocturnal Hypoglycemia



# Reduced Risk of Major Nocturnal Hypoglycemia

## Relative Risk

NovoLog Compared to Regular Human Insulin (1.0 = equal)



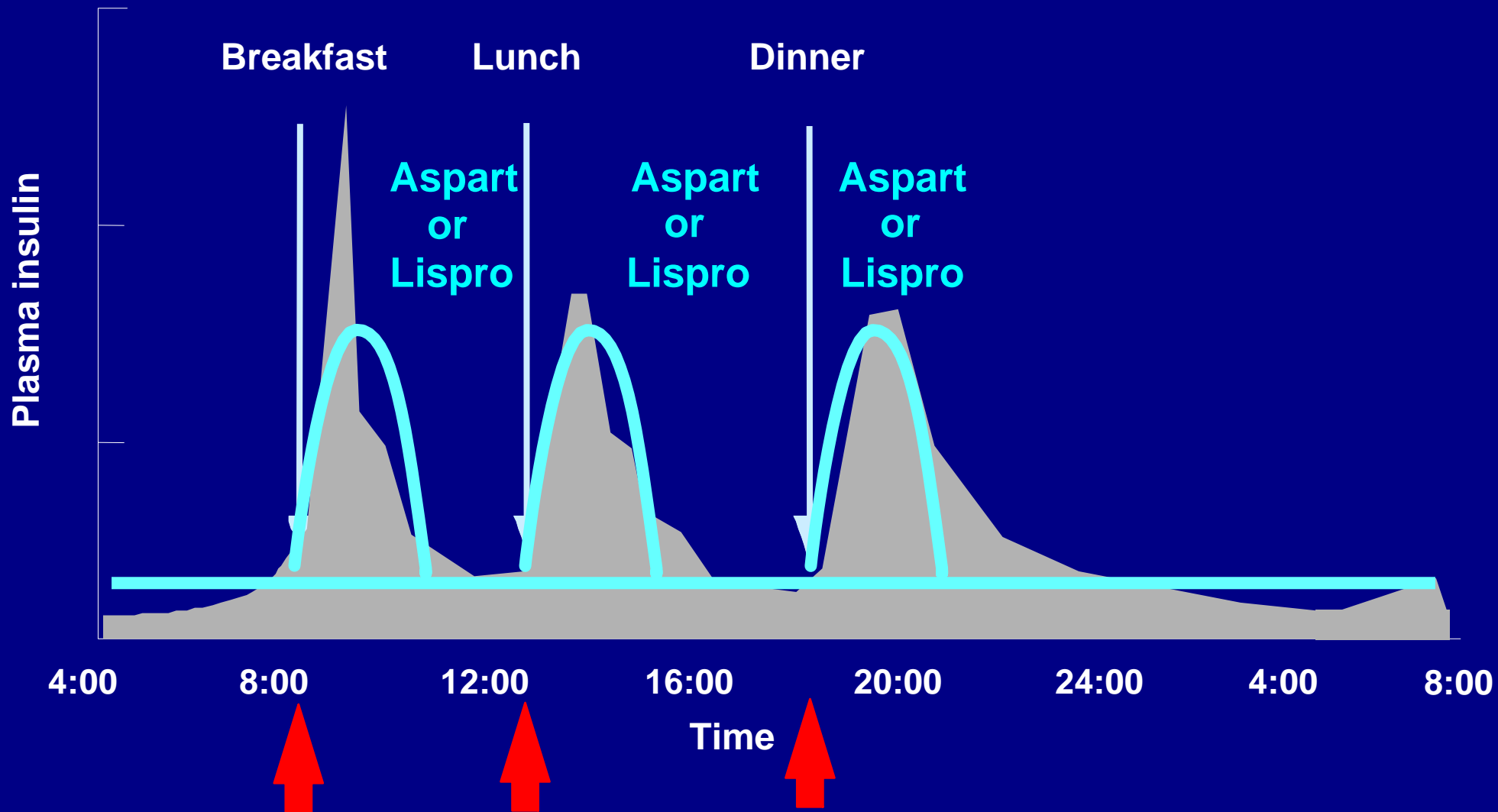
**NovoLog®**      **Human insulin**  
(N of patients with events)

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

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

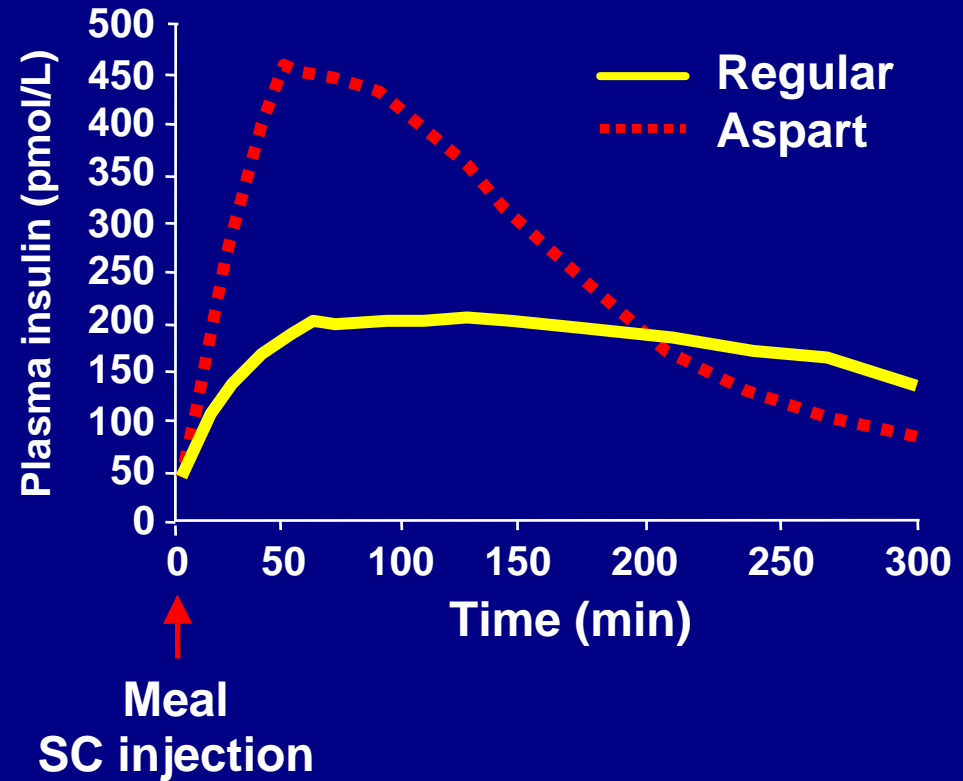
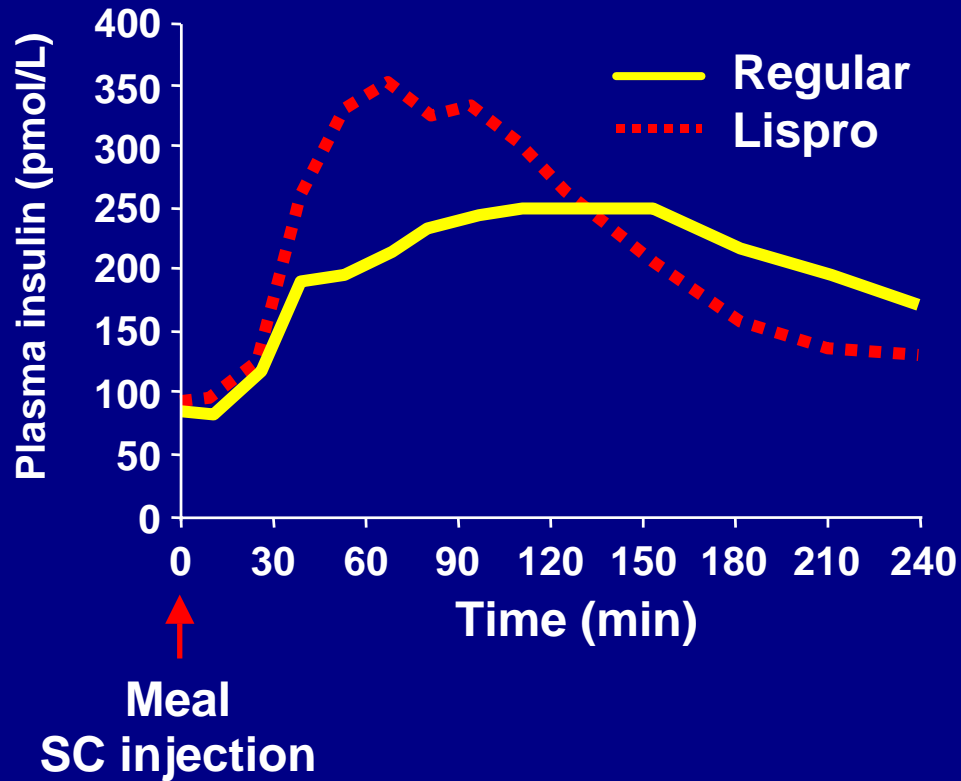


# Rapid-acting Insulin Analogues Provide Ideal Prandial Insulin Profile

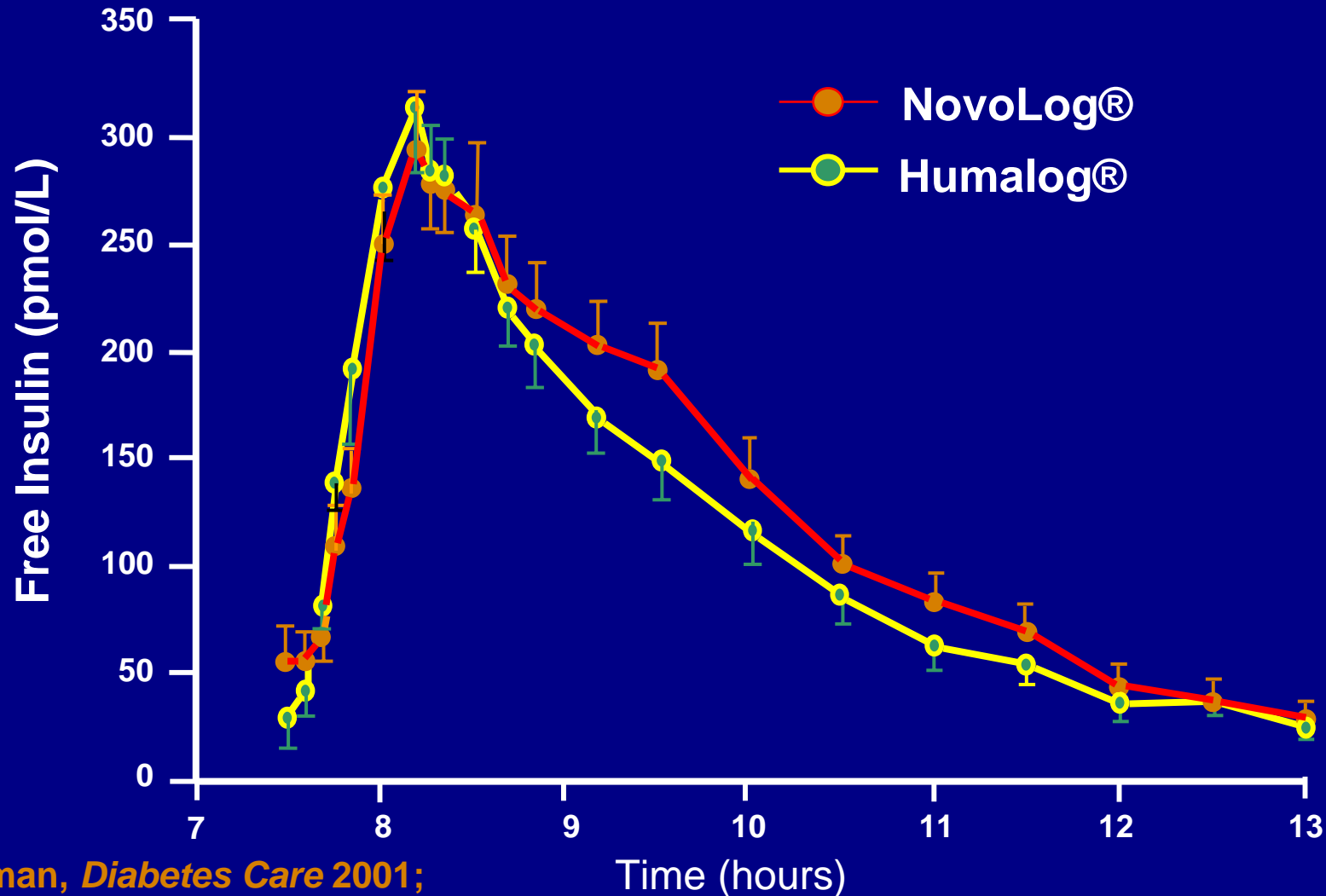


# Short-Acting Insulin Analogs

## Lispro and Aspart Plasma Insulin Profiles



# Pharmacokinetic Comparison NovoLog® vs Humalog®



# Long-acting Soluble Insulin Analogs: Medical Rationale

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

# Limitations of NPH, Lente, and Ultralente

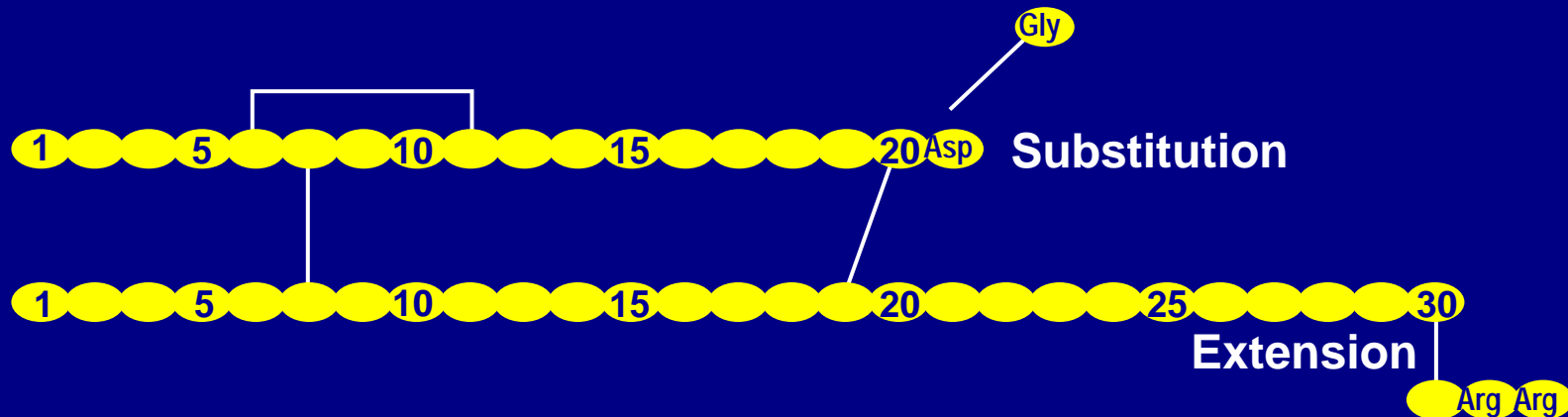
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- Do not mimic basal insulin profile
  - Variable absorption
  - Pronounced peaks
  - Less than 24-hour duration of action
- Cause unpredictable hypoglycemia
  - Major factor limiting insulin adjustments
  - More weight gain

# Insulin Glargine

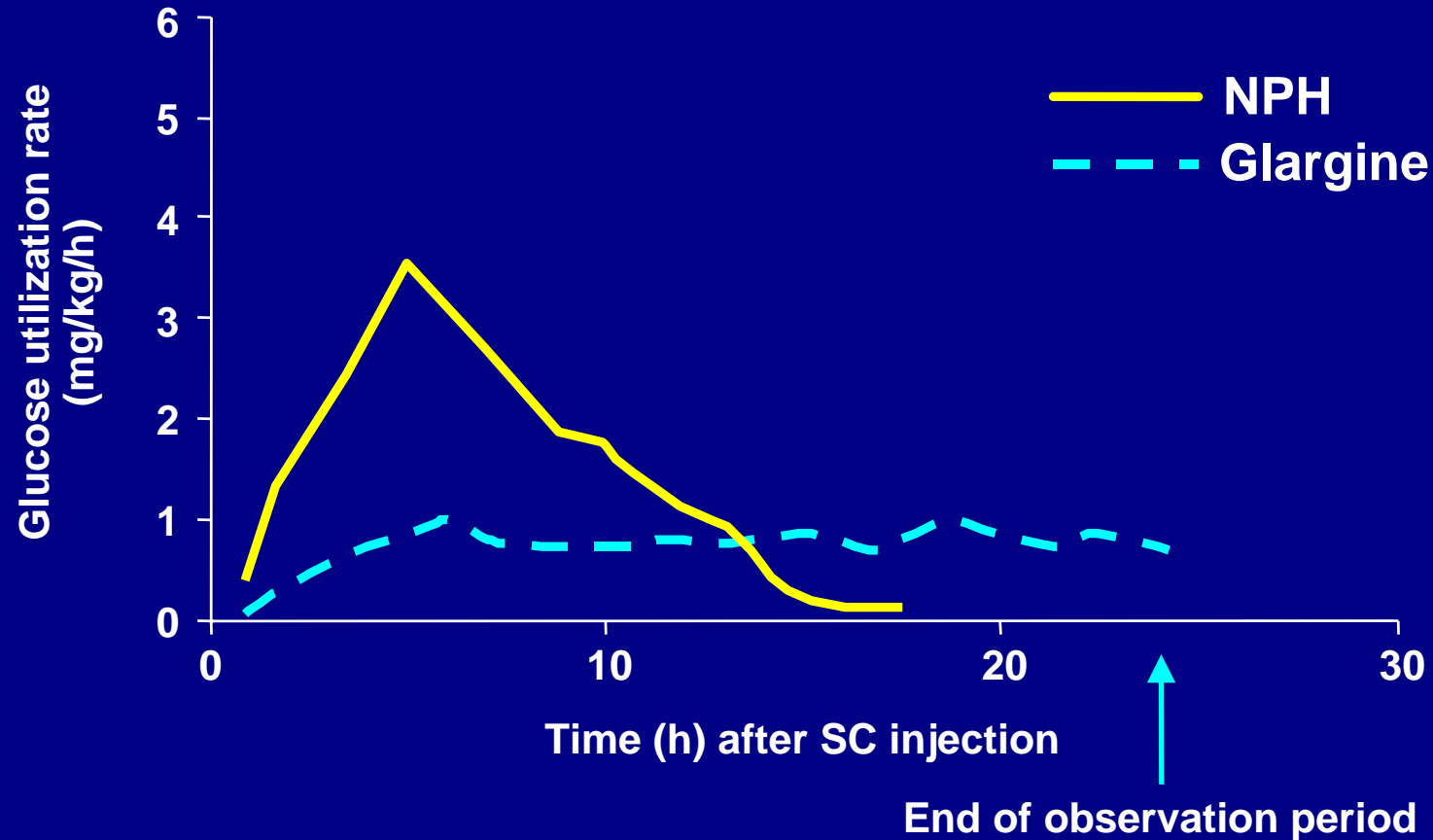
## A New Long-Acting Insulin Analog

- 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

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- **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**

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**Over time,  
most patients will need insulin  
to control glucose**

# Insulin Therapy in Type 2 Diabetes

## Indications

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- 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

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***Mimicking Nature***

***The Basal/Bolus Insulin  
Concept***

# The Basal/Bolus Insulin Concept

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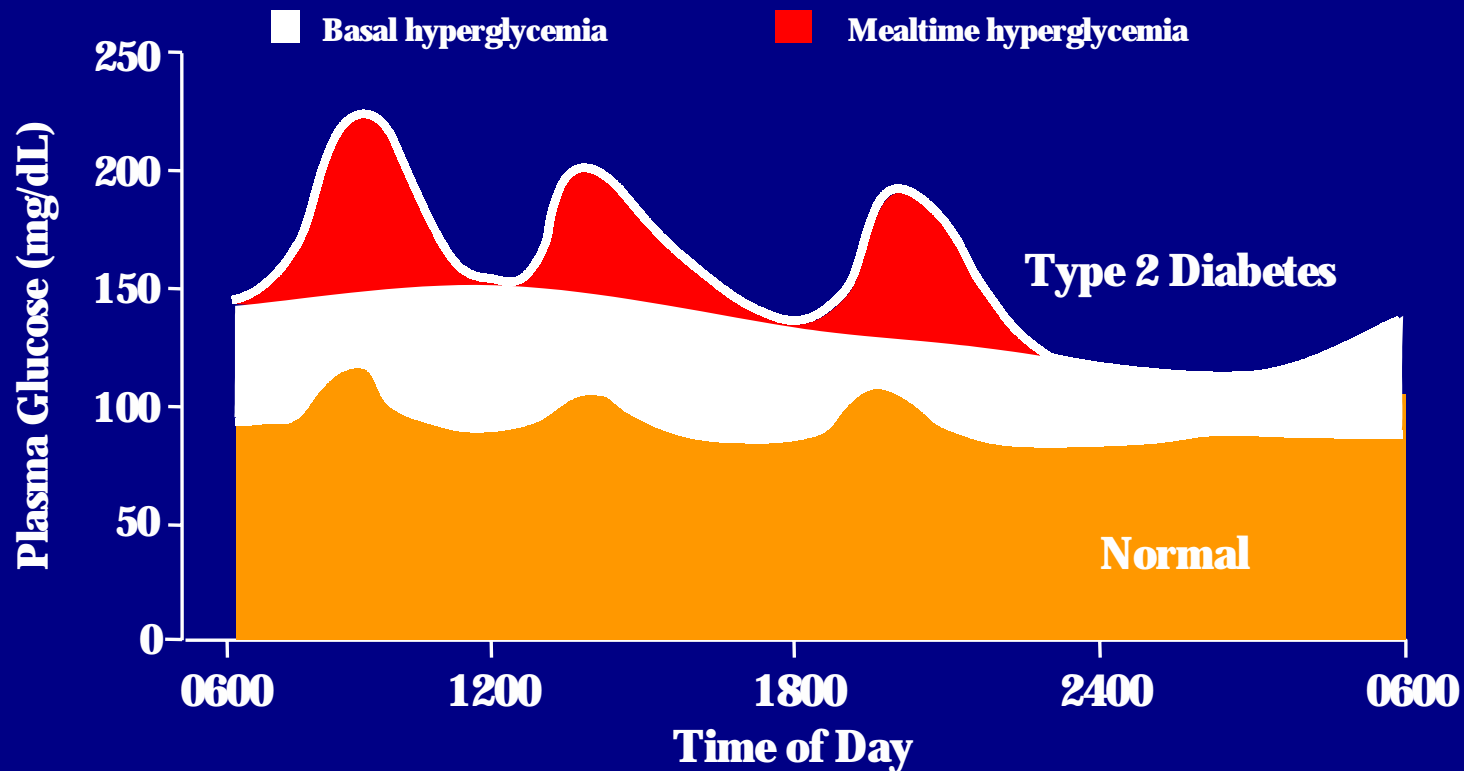
- **Basal insulin**

- 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

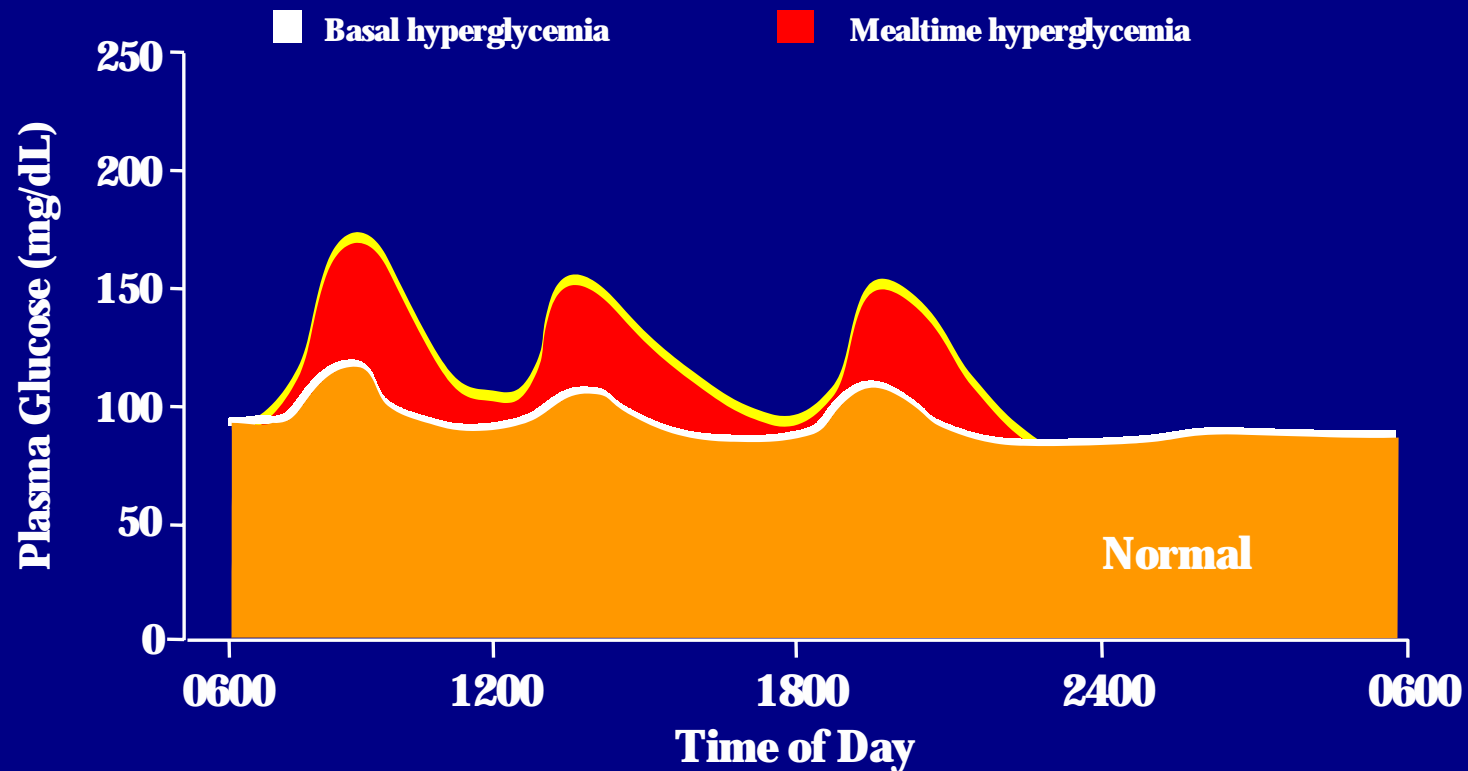
# Basal vs Mealtime Hyperglycemia in Diabetes



$\Delta$  AUC from normal basal >1875 mgm/dL·hr; Est HbA<sub>1c</sub> >8.7%

## Basal vs Mealtime Hyperglycemia in Diabetes

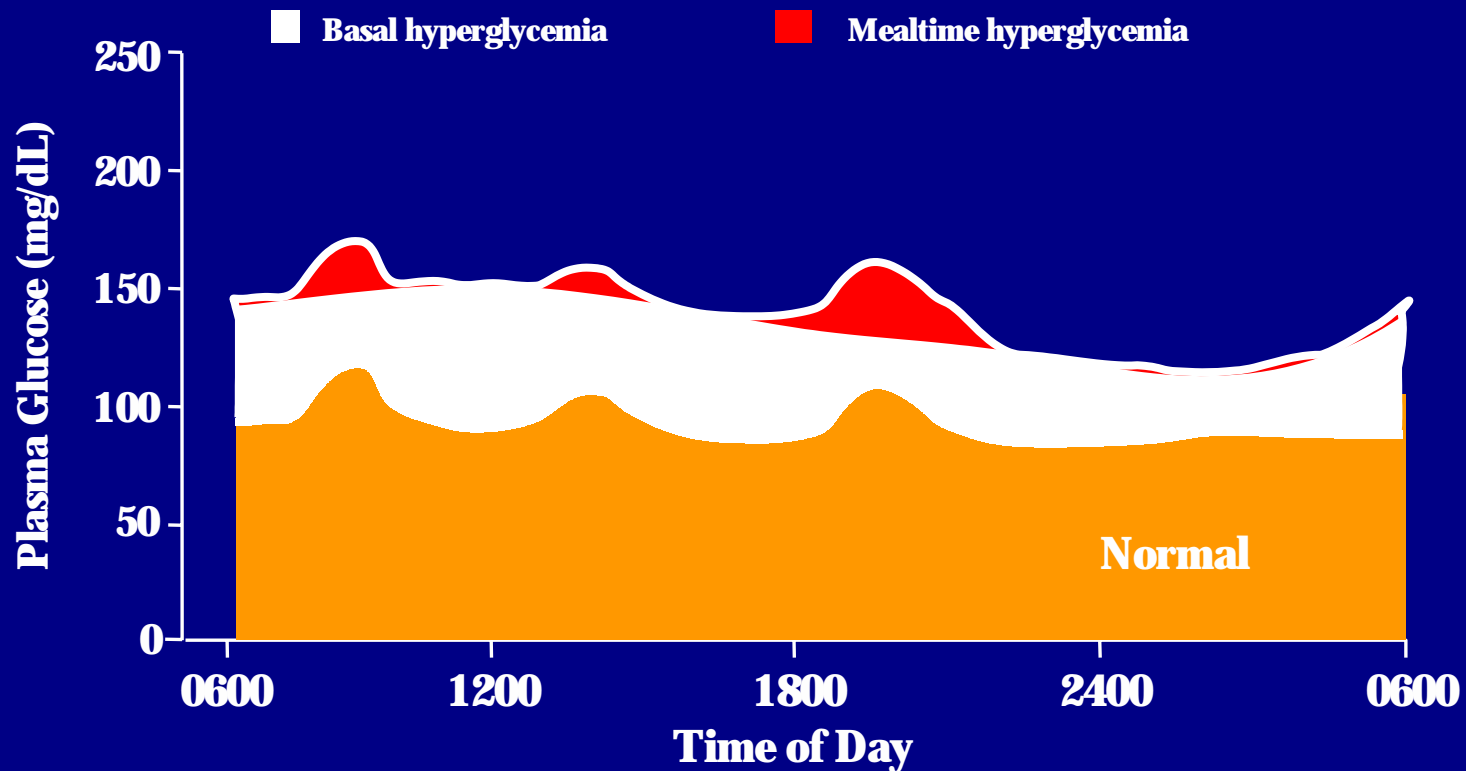
# When Basal Corrected



$\Delta$  AUC from normal basal 900 mgm/dL-hr; Est HbA<sub>1c</sub> 7.2%

## Basal vs Mealtime Hyperglycemia in Diabetes

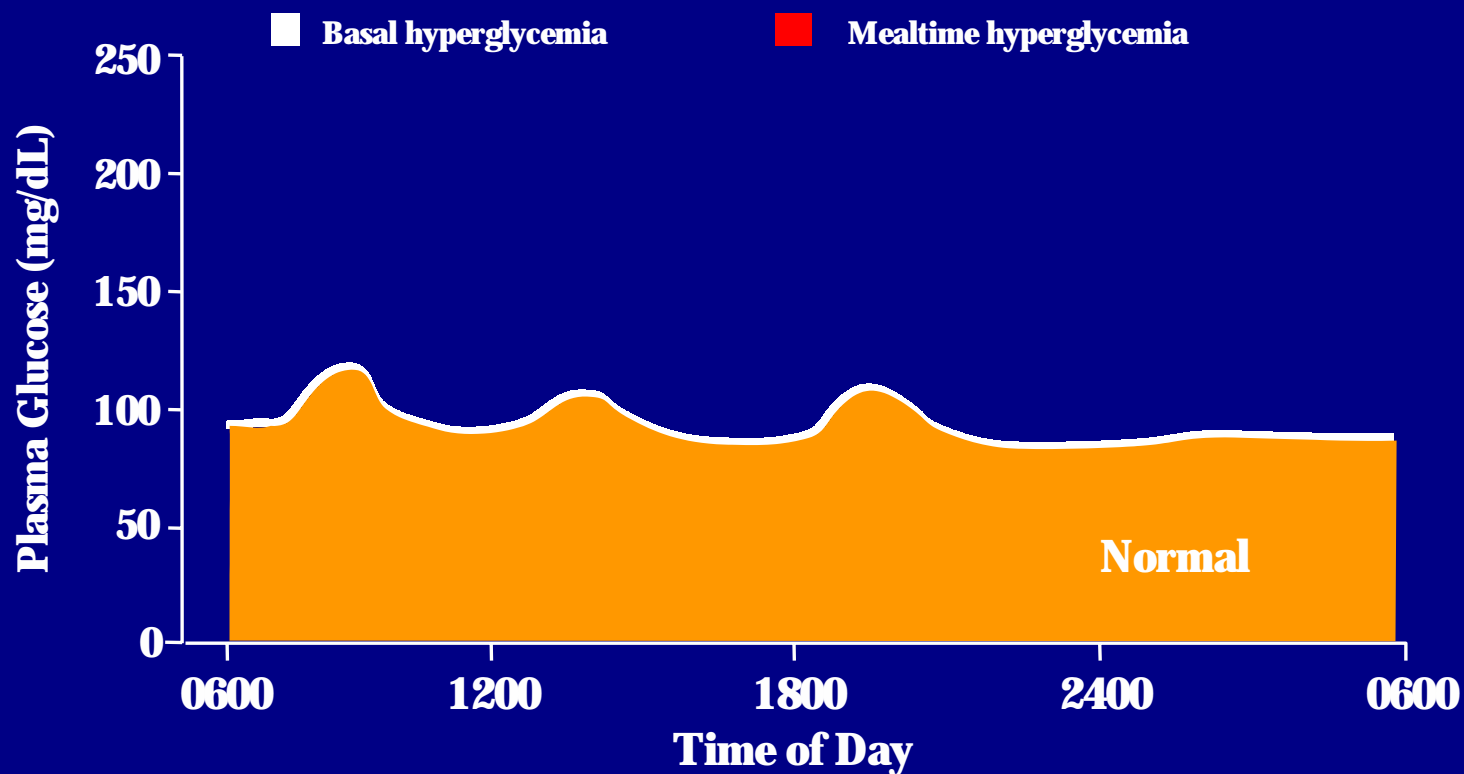
# When Mealtime Hyperglycemia Corrected



$\Delta$  AUC from normal basal 1425 mgm/dL·hr; Est HbA<sub>1c</sub> 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<sub>1c</sub> 6.4%



# MIMICKING NATURE WITH INSULIN THERAPY

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*Over time,*

*most patients will need*

*both basal and mealtime insulin*

*to control glucose*

# Starting With Basal Insulin

## Advantages

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- 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

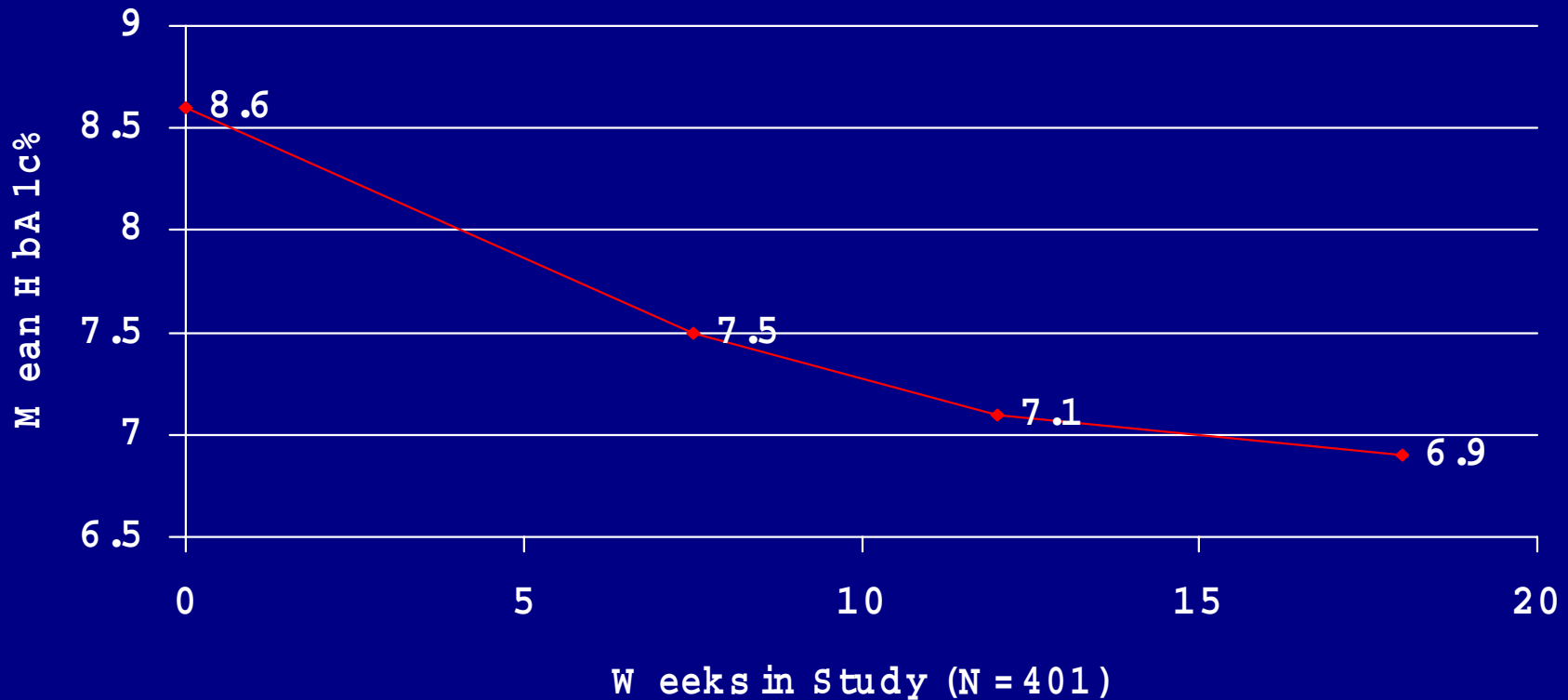
# Treatment to Target Study: NPH vs Glargine in DM2 patients on OHA

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- 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

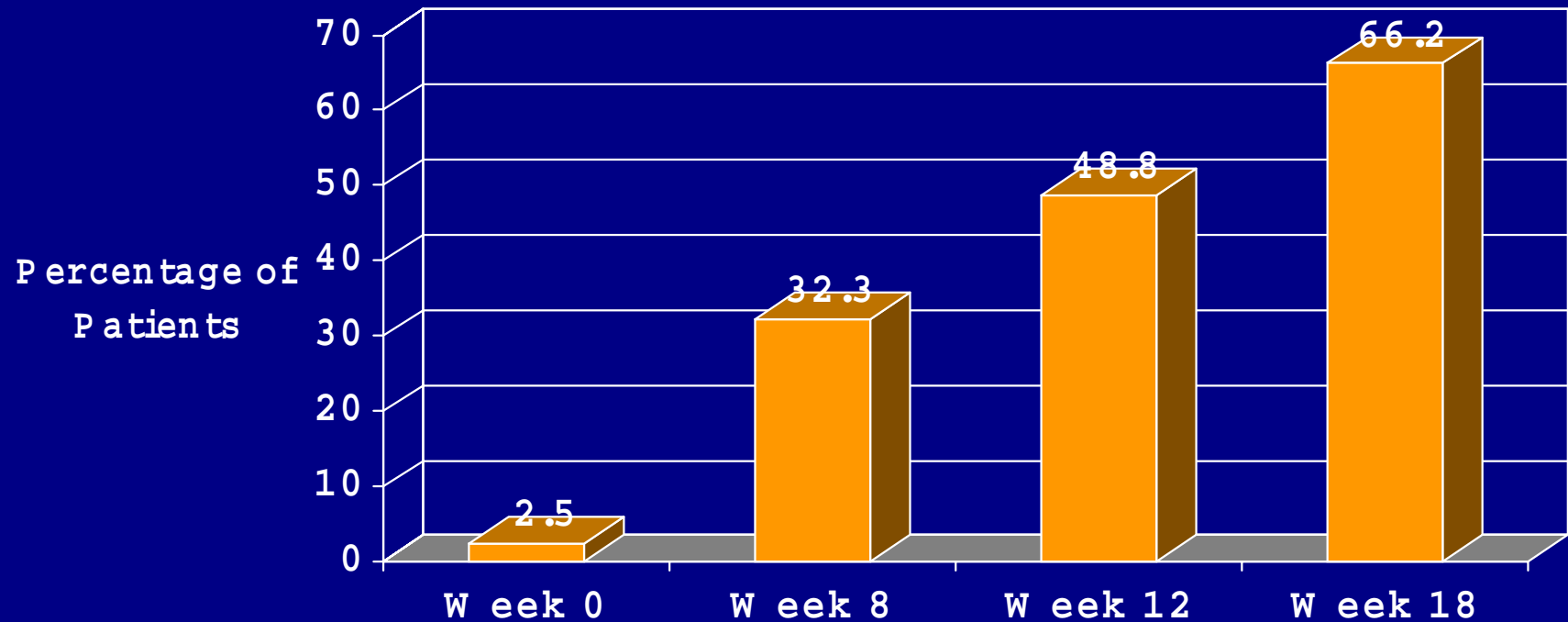
# Treatment to Target Study; A1C Decrease

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# Patients in Target (A1c < 7%)

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# Advancing Basal/Bolus Insulin

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- 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

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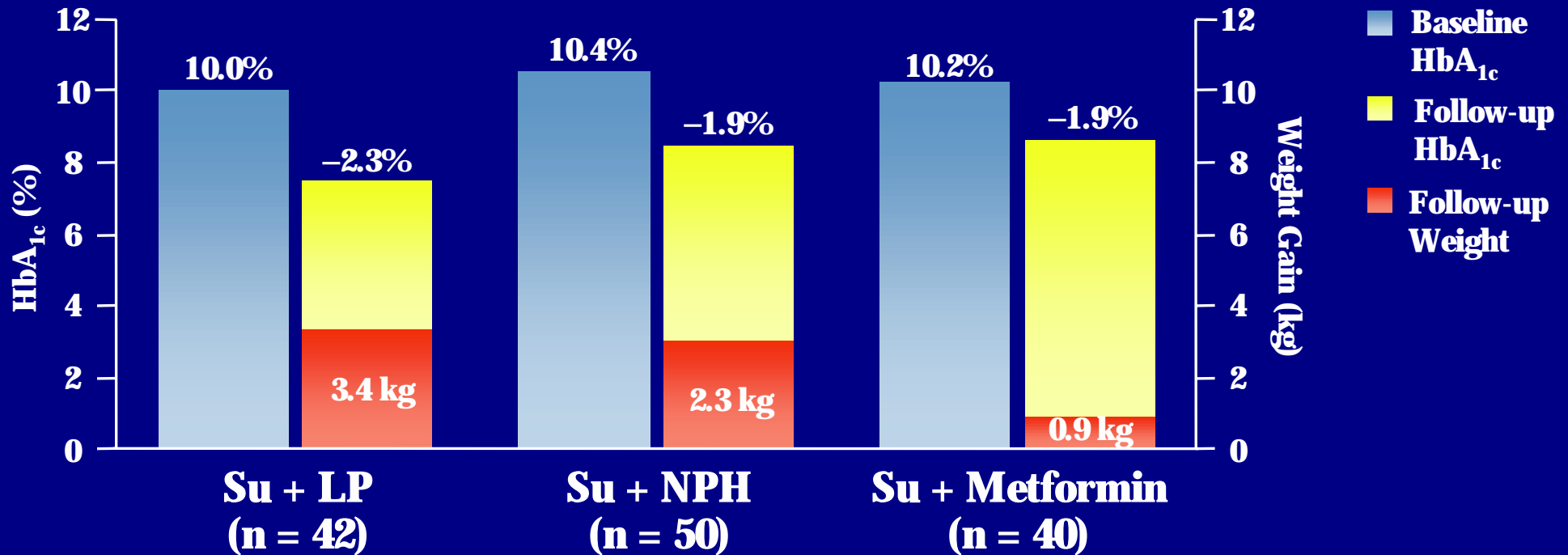
*Combination Oral Agents*

+

*Mealtime Insulin*

# Starting With Bolus Insulin

## Mealtime Lispro vs NPH or Metformin Added to Sulfonylurea





# Case #1: DM 2 on SU with infection

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- 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

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- 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

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

**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

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- 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

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- Monitor glycemic targets – Fasting and postprandial glucose, HbA<sub>1c</sub>
- 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

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- 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<sub>1c</sub>**
- **Basal / Bolus** insulin regimen

# Options in Insulin Therapy

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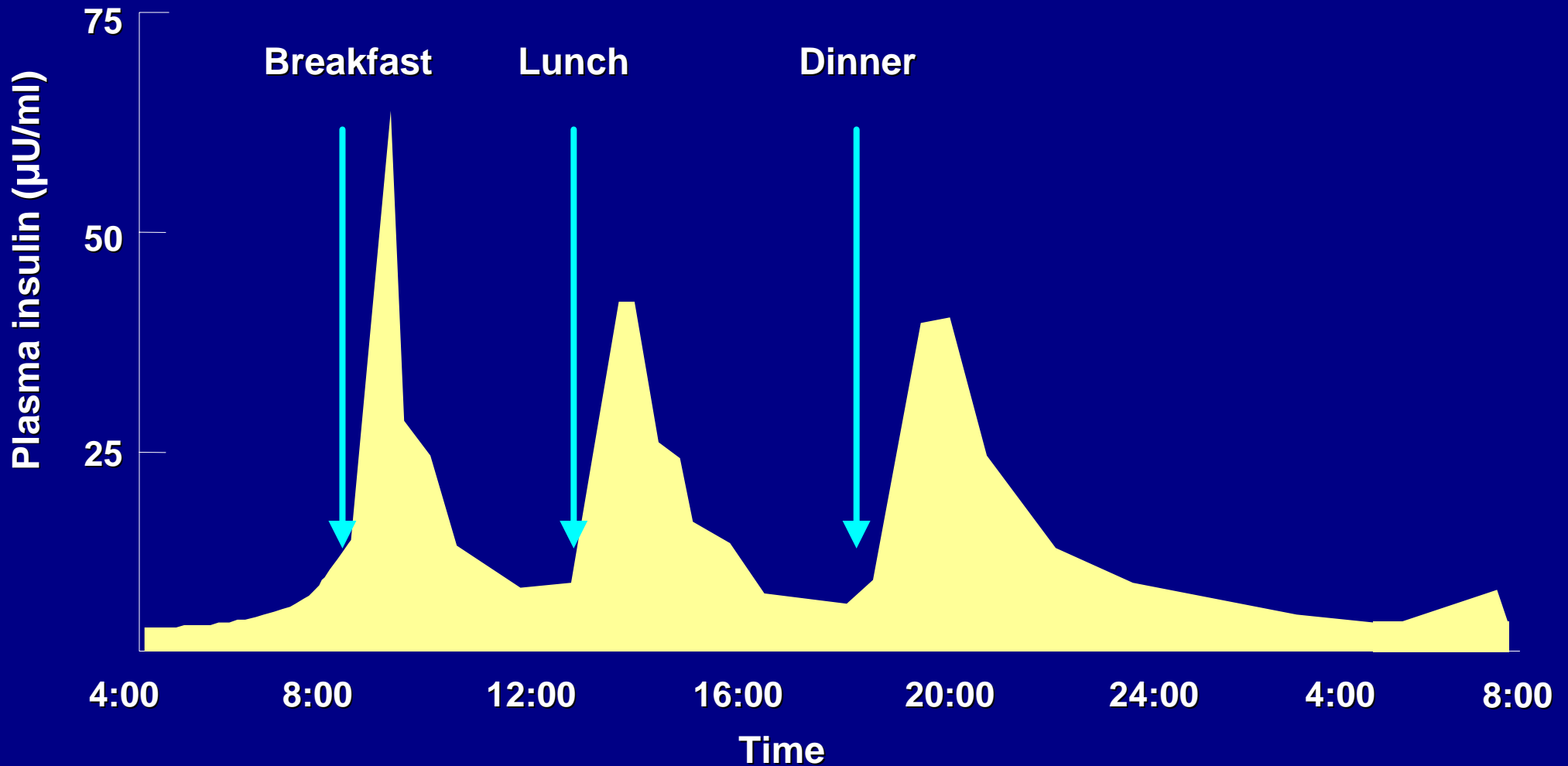
- **Current**

- Multiple injections
- Insulin pump (CSII)

- **Future**

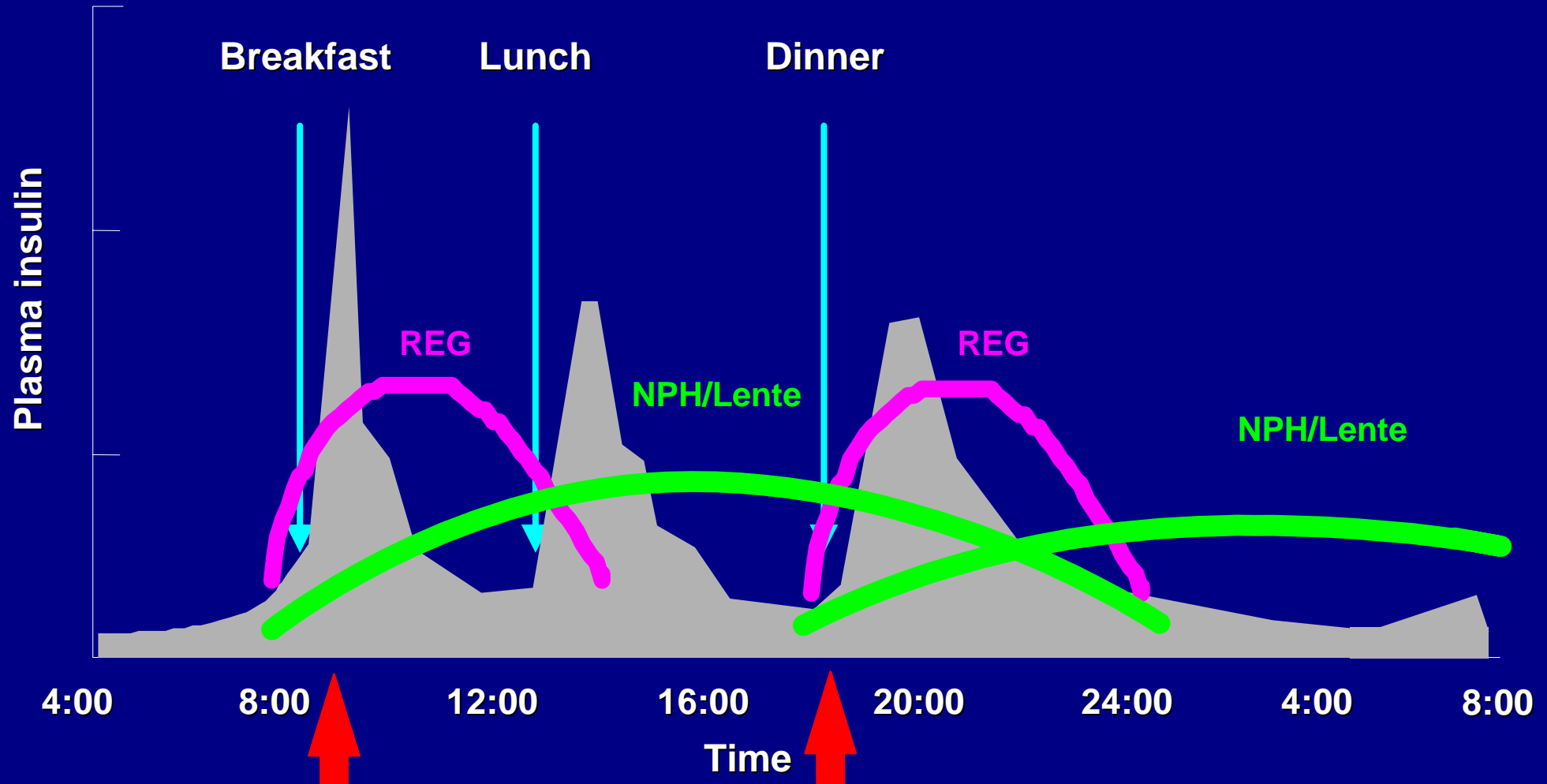
- Implant (artificial pancreas)
- Transplant (pancreas; islet cells)

# Physiological Serum Insulin Secretion Profile

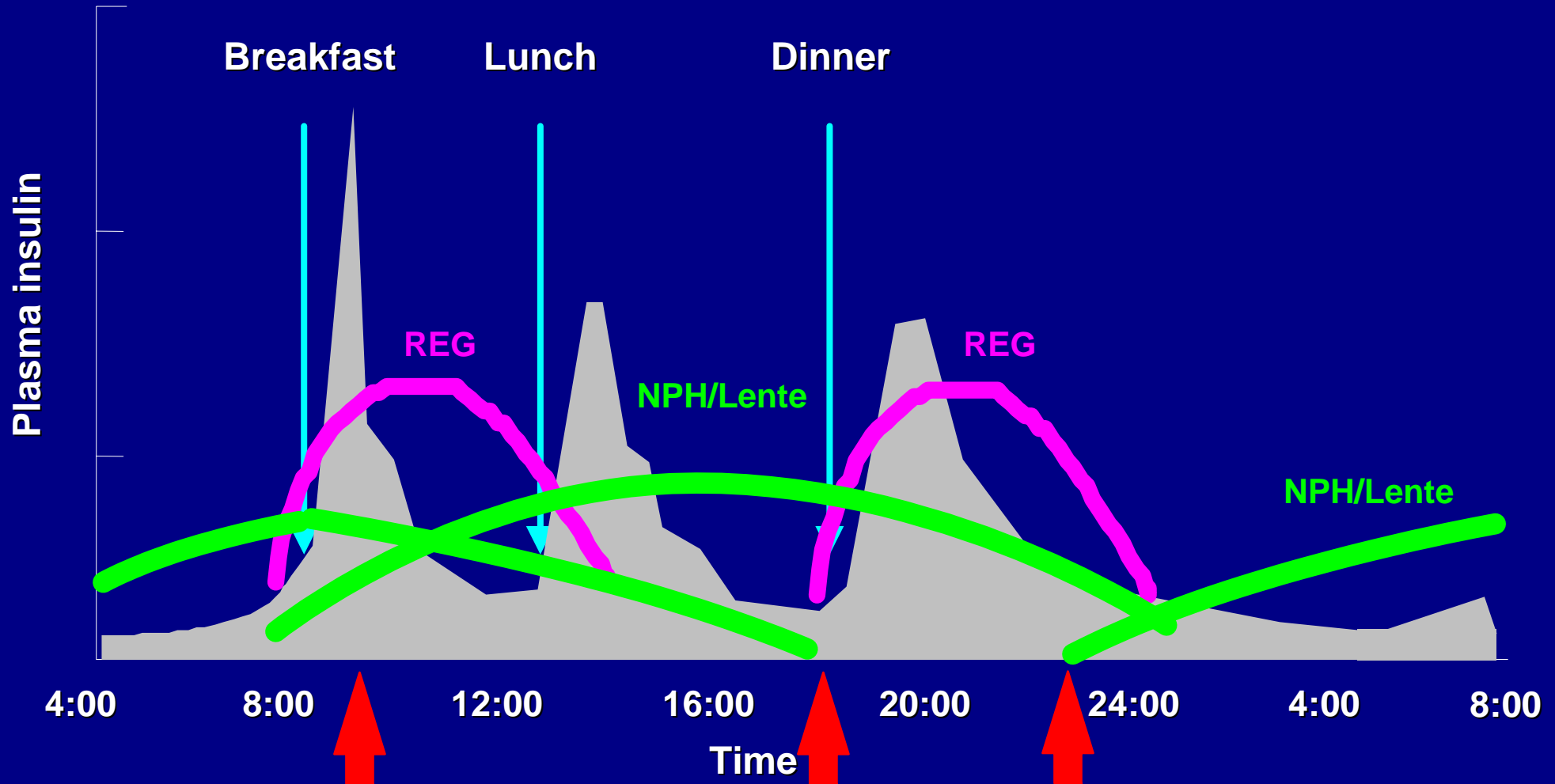




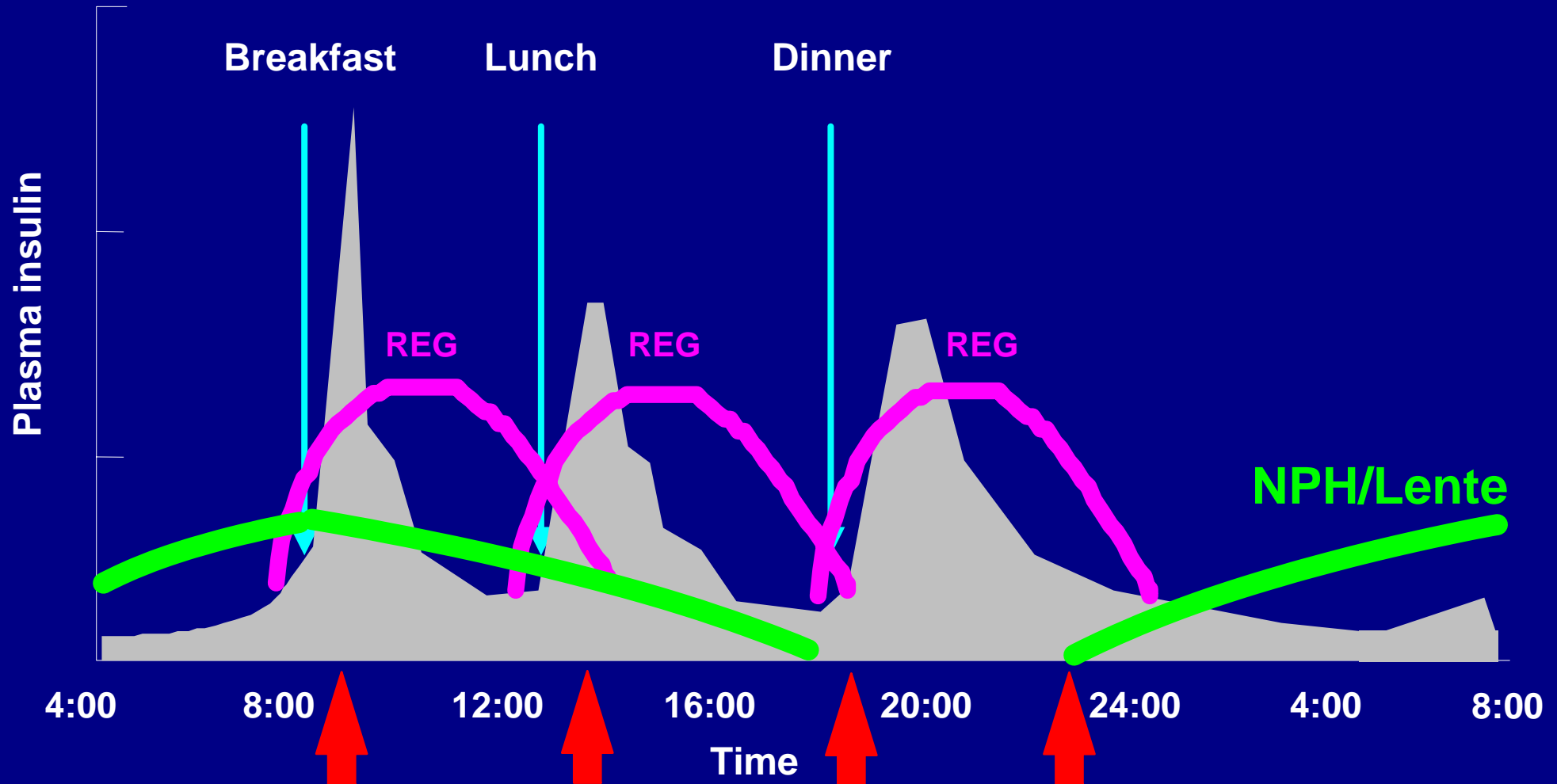
# Classical “Split-mixed” Treatment Program



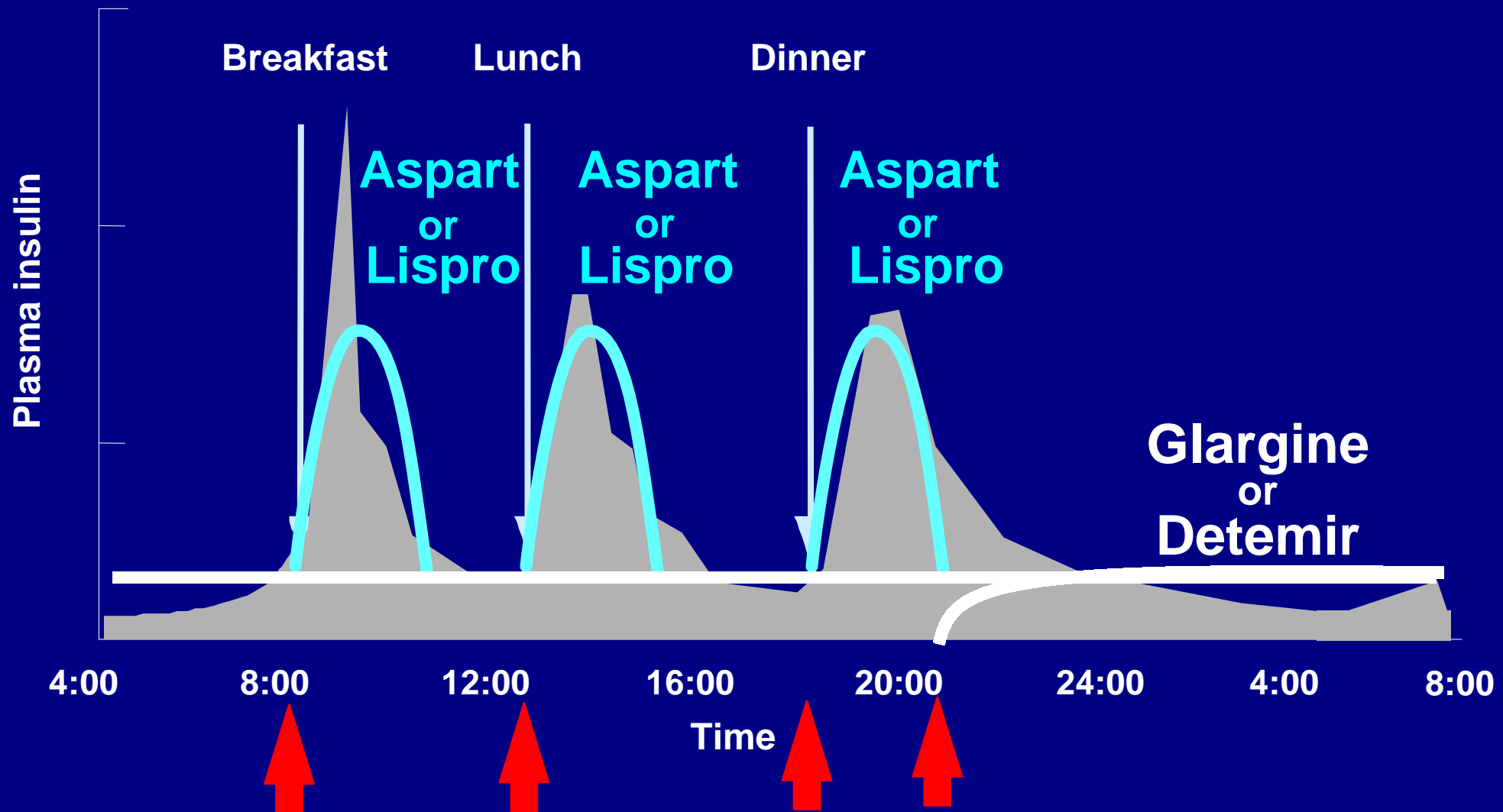
# “Split-mixed” Program with Bedtime Intermediate Insulin



# 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

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



# Lilly Insulin Pens

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# Introducing InDuo™

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- 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

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## Feature

- Compact, discreet design

## Benefit

- Allows discreet testing and injecting anywhere, anytime

# InDuo™ - Doser Remembers

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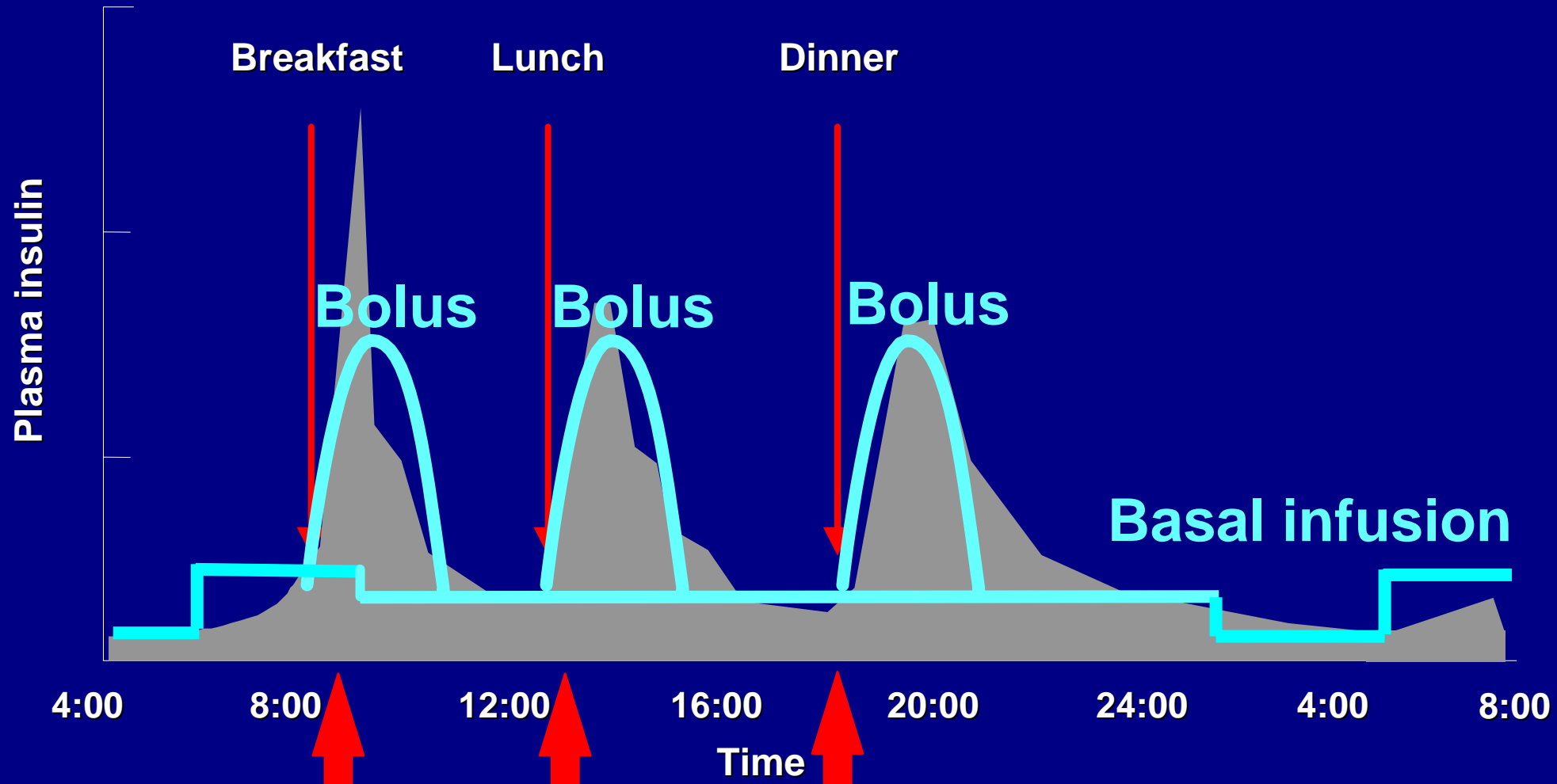
## Feature

- Remembers amount of insulin delivered and time since last dose

## Benefit

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

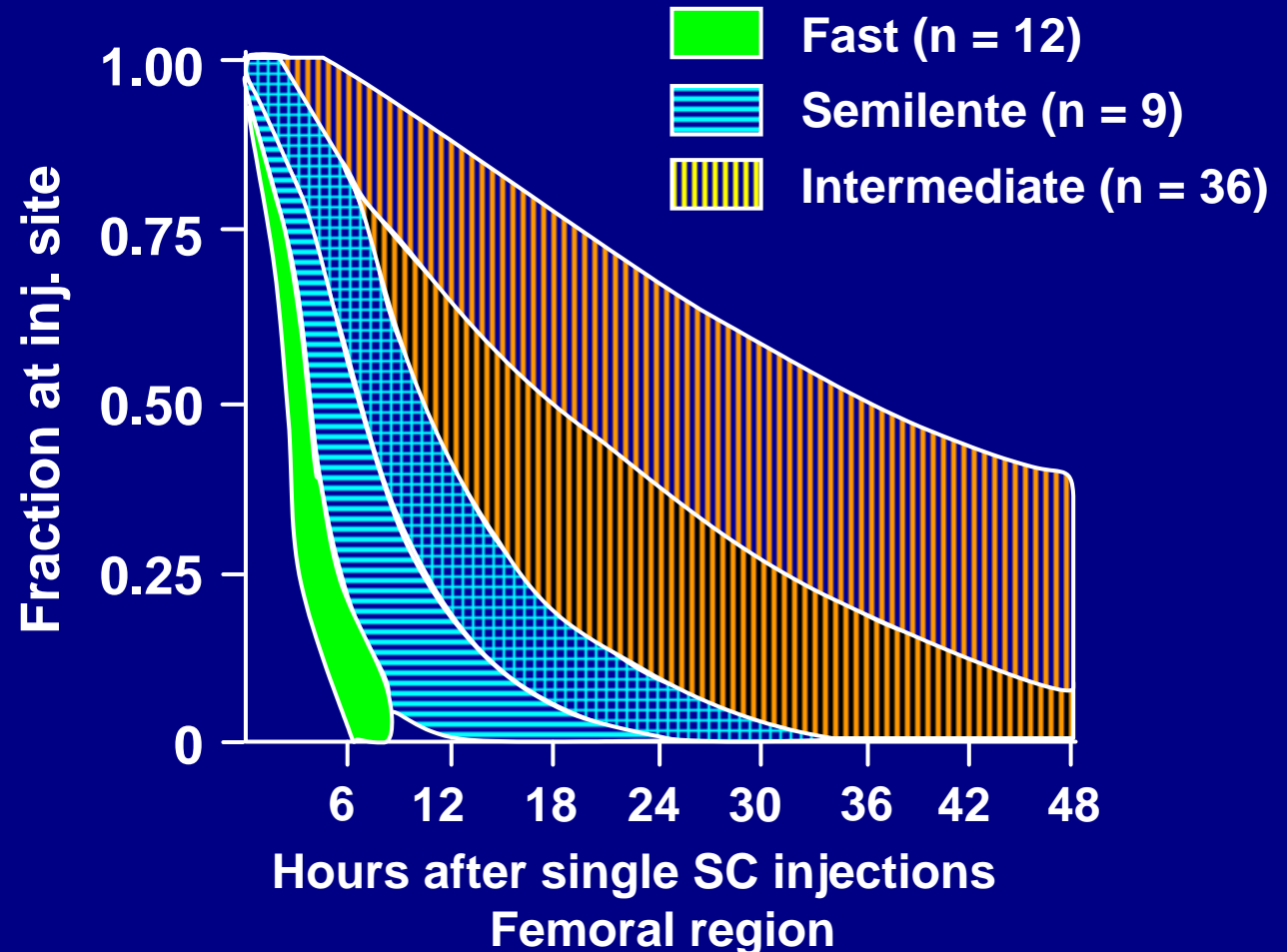
# Variable Basal Rate: CSII Program



# Variability of Insulin Absorption

CSII <2.8%

Subcutaneous  
Injectable  
10% to 52%



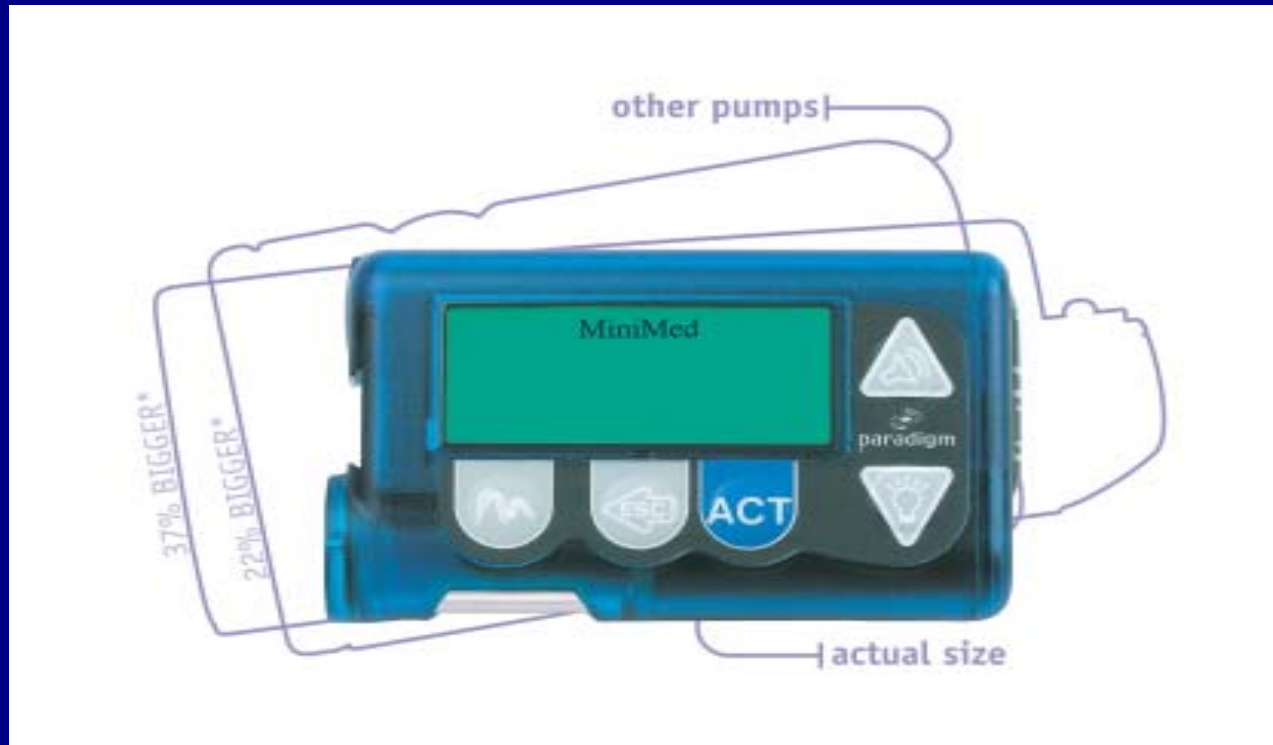
# History of Pumps





# PARADIGM PUMP

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Paradigm.  
Simple. Easy.

# Pump Infusion Sets

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**Softset QR**



**Silhouette**

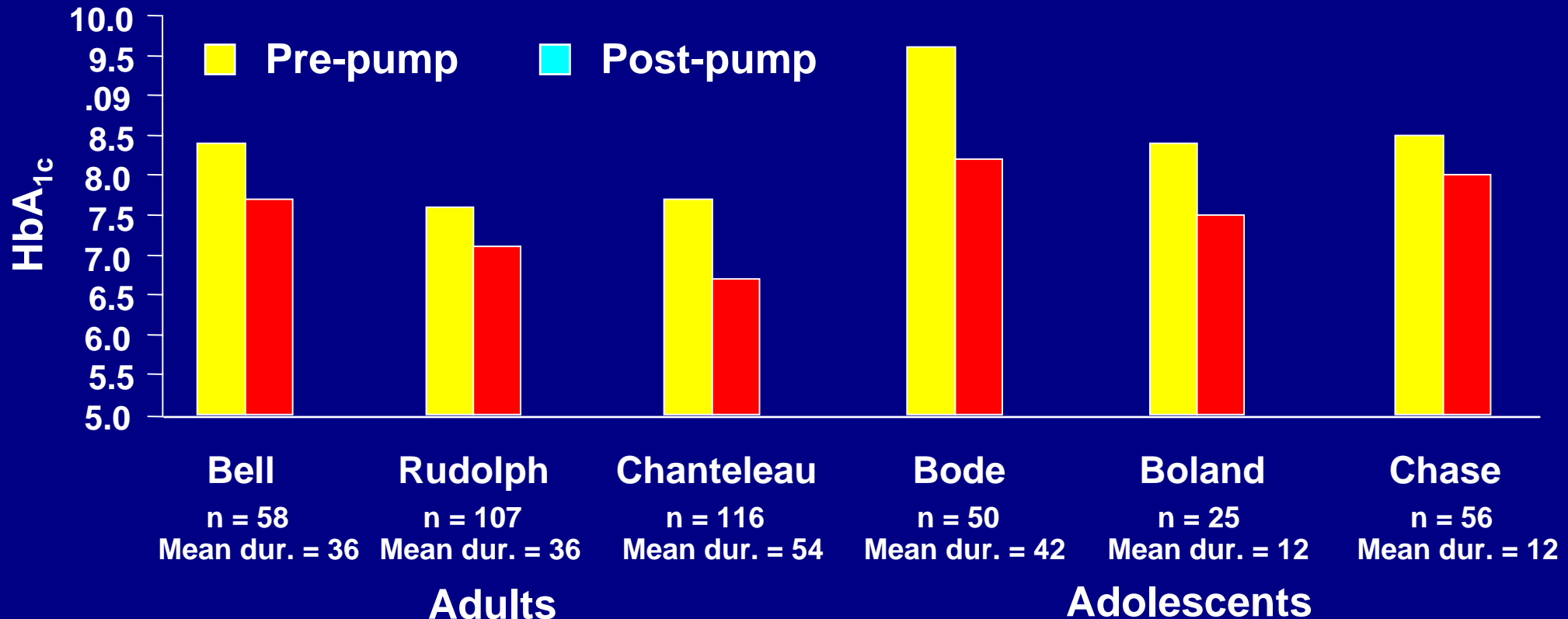


# Metabolic Advantages with CSII

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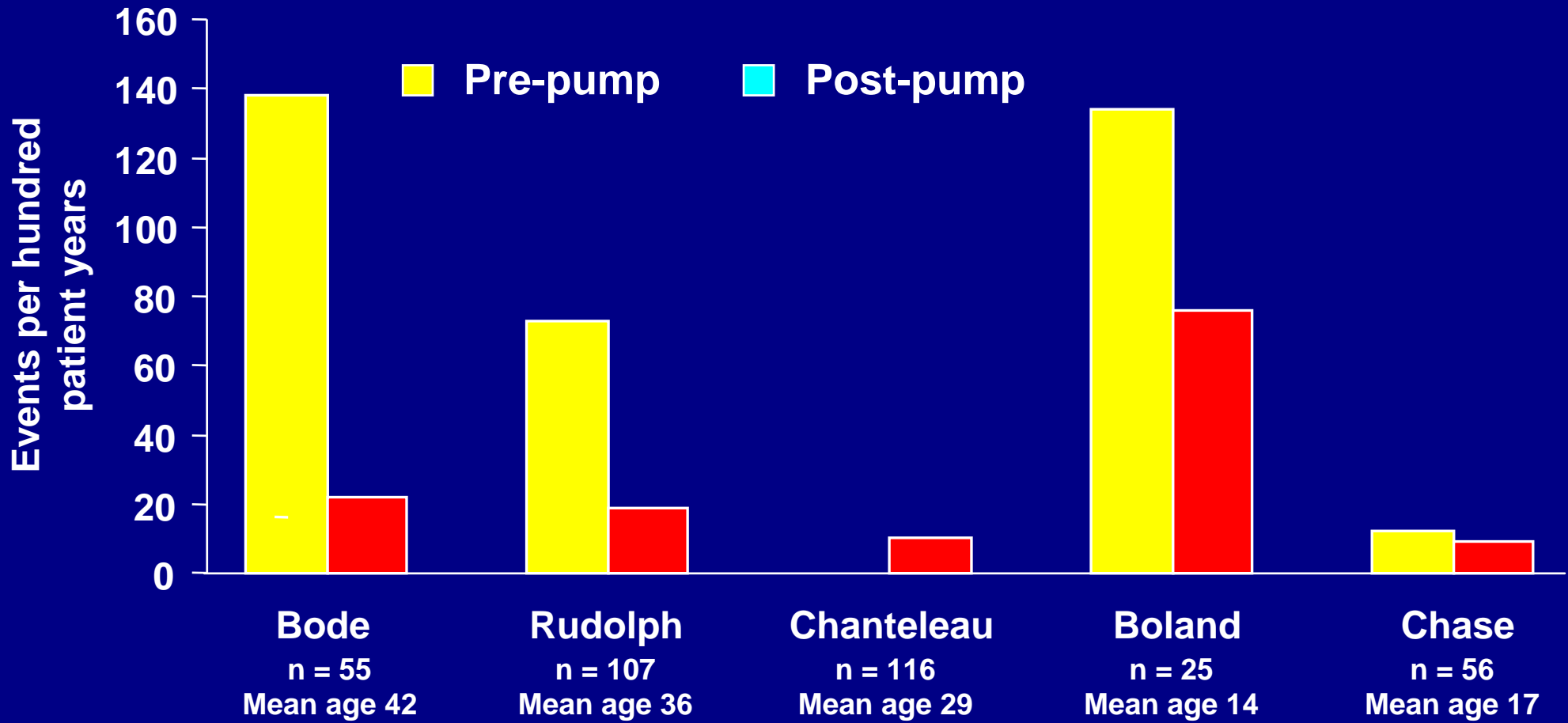
- Improved glycemic **control**
- Better pharmacokinetic **delivery** of insulin
  - Less hypoglycemia
  - Less insulin required
- Improved **quality** of life

# CSII Reduces HbA<sub>1c</sub>



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

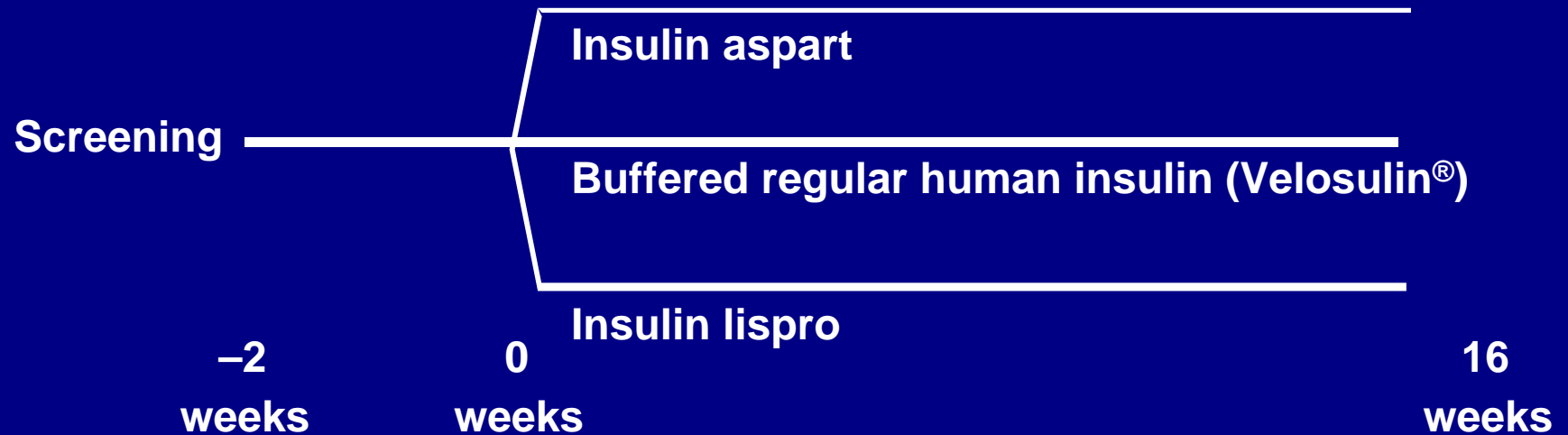
## Factors Affecting HbA<sub>1c</sub>

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- **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

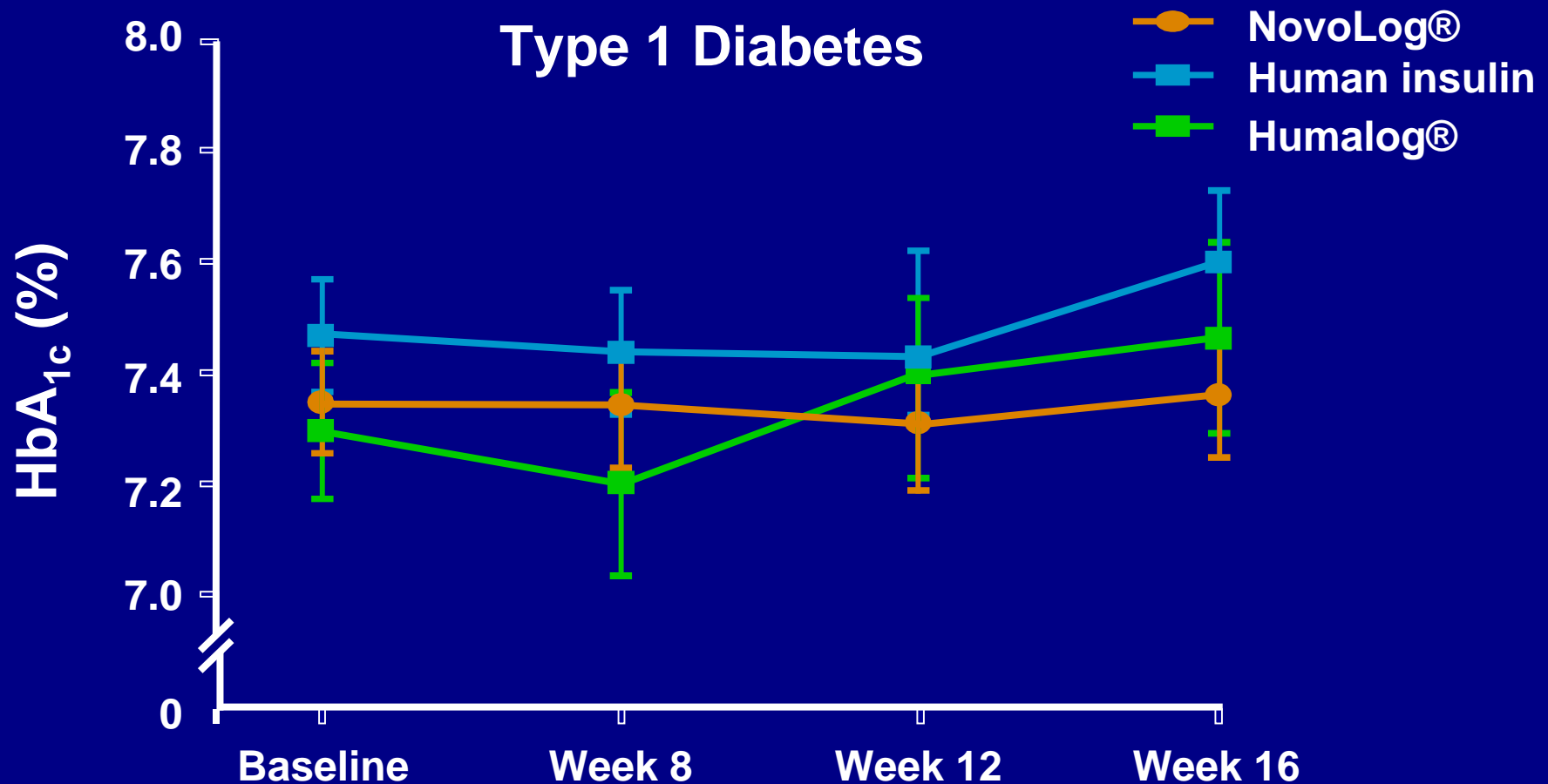
# Insulin aspart versus buffered R *versus* insulin lispro in CSII study:

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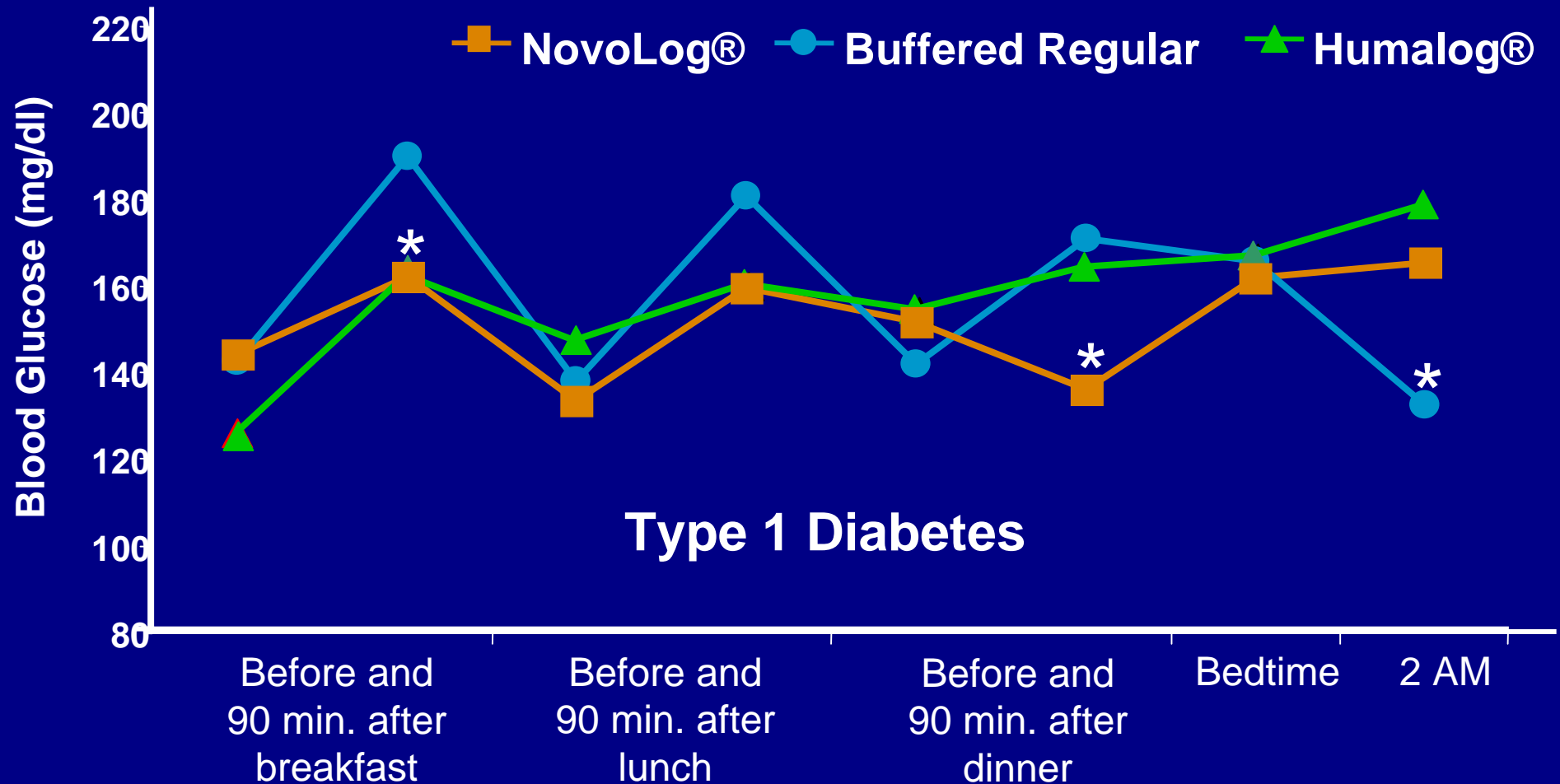


- 146 patients in the USA; 2–25 years with Type 1 diabetes;  $7\% \leq \text{HbA}_{1c} \leq 9\%$ ; previously treated with CSII for 3 months

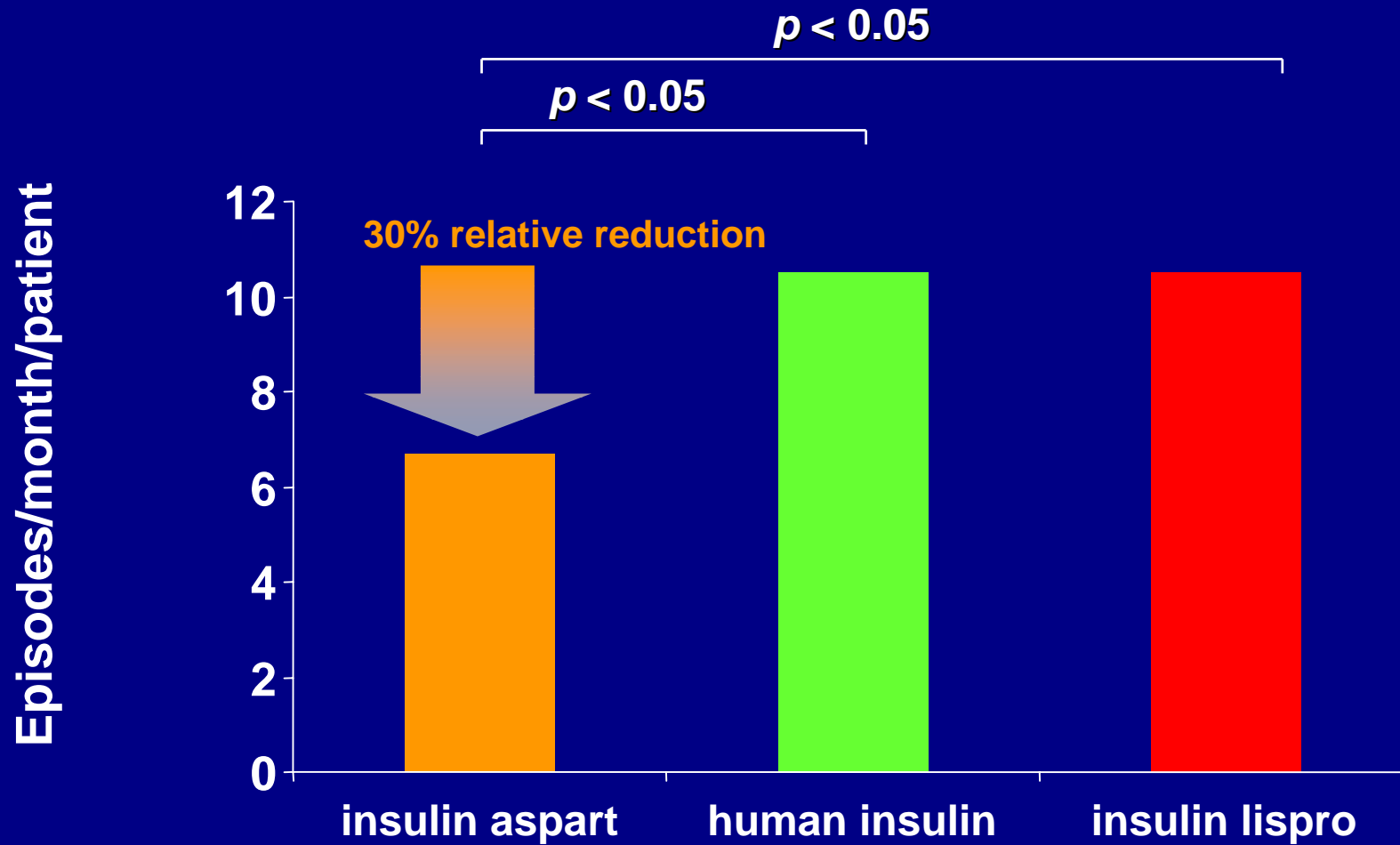
# Glycemic Control with CSII



# Self-Monitored Blood Glucose in CSII

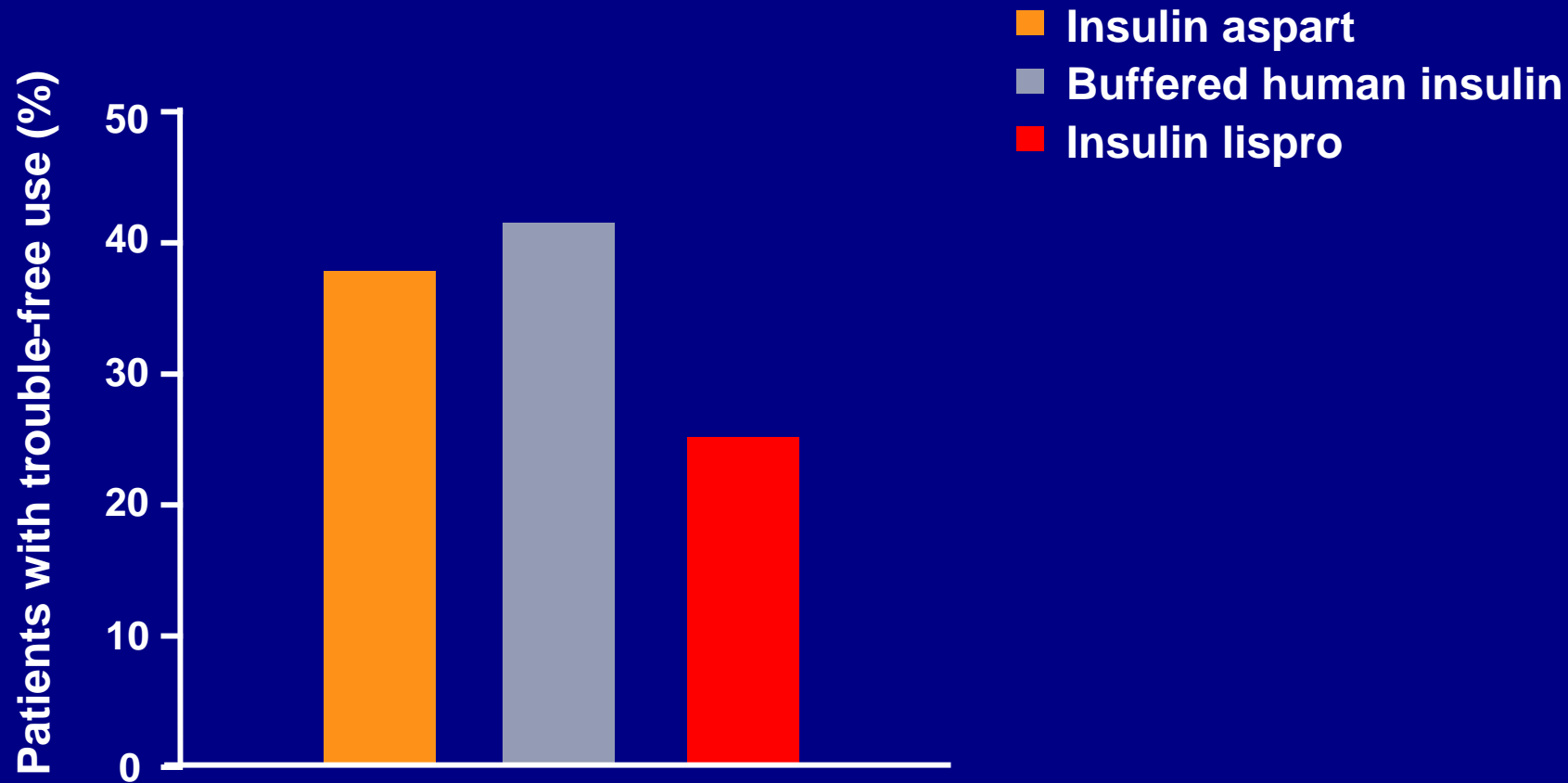


# Symptomatic or Confirmed Hypoglycaemia





# 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**

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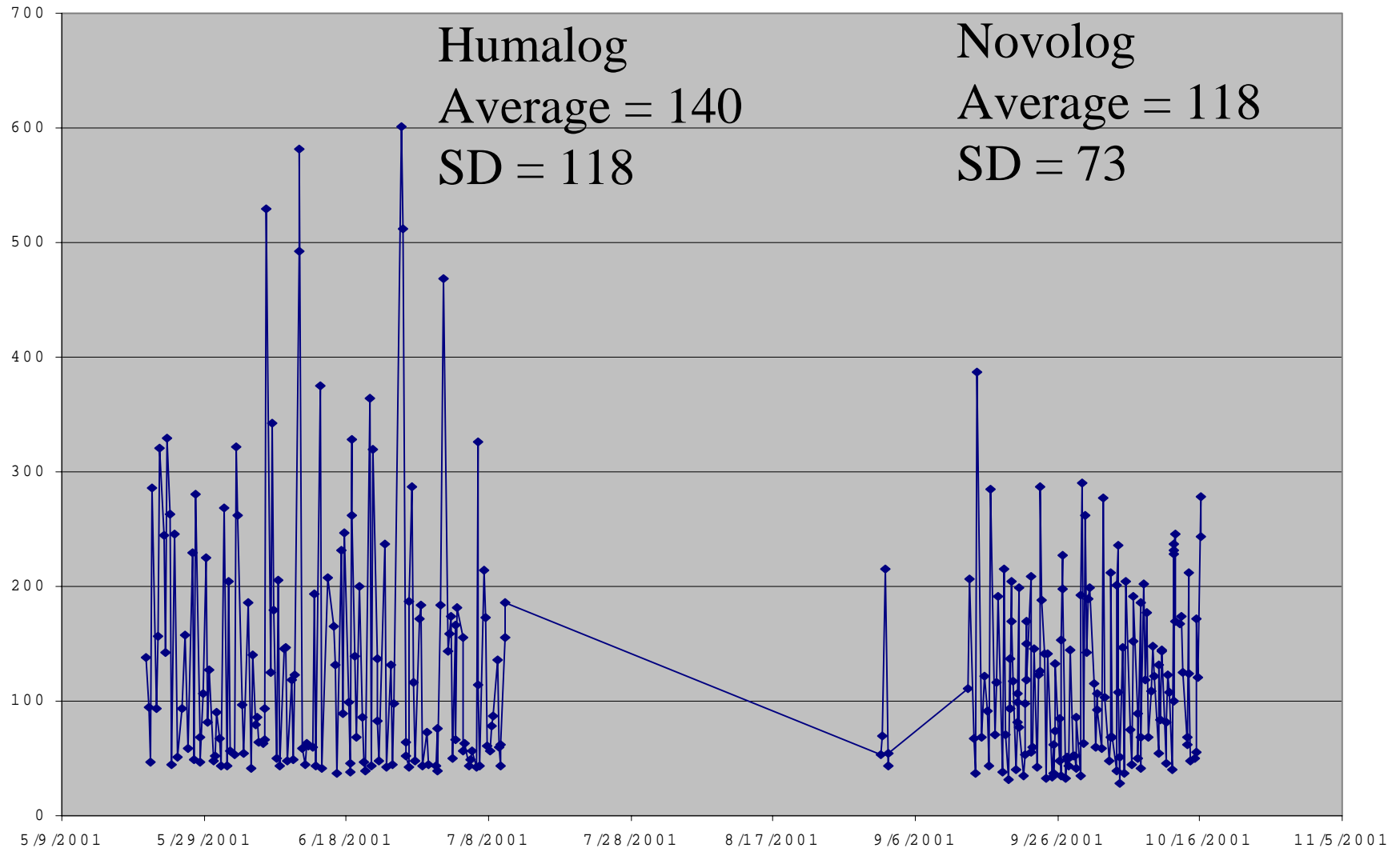
- **DM 1 onset age 21, 1968**
- **CSII 1998, A1C 7.8%**
- **Lipoatrophy with humalog 1999-2000**
- **Changed to Velosulin BR with still lipoatrophy**
- **Control suboptimal A1C 7.8%**

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

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- 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



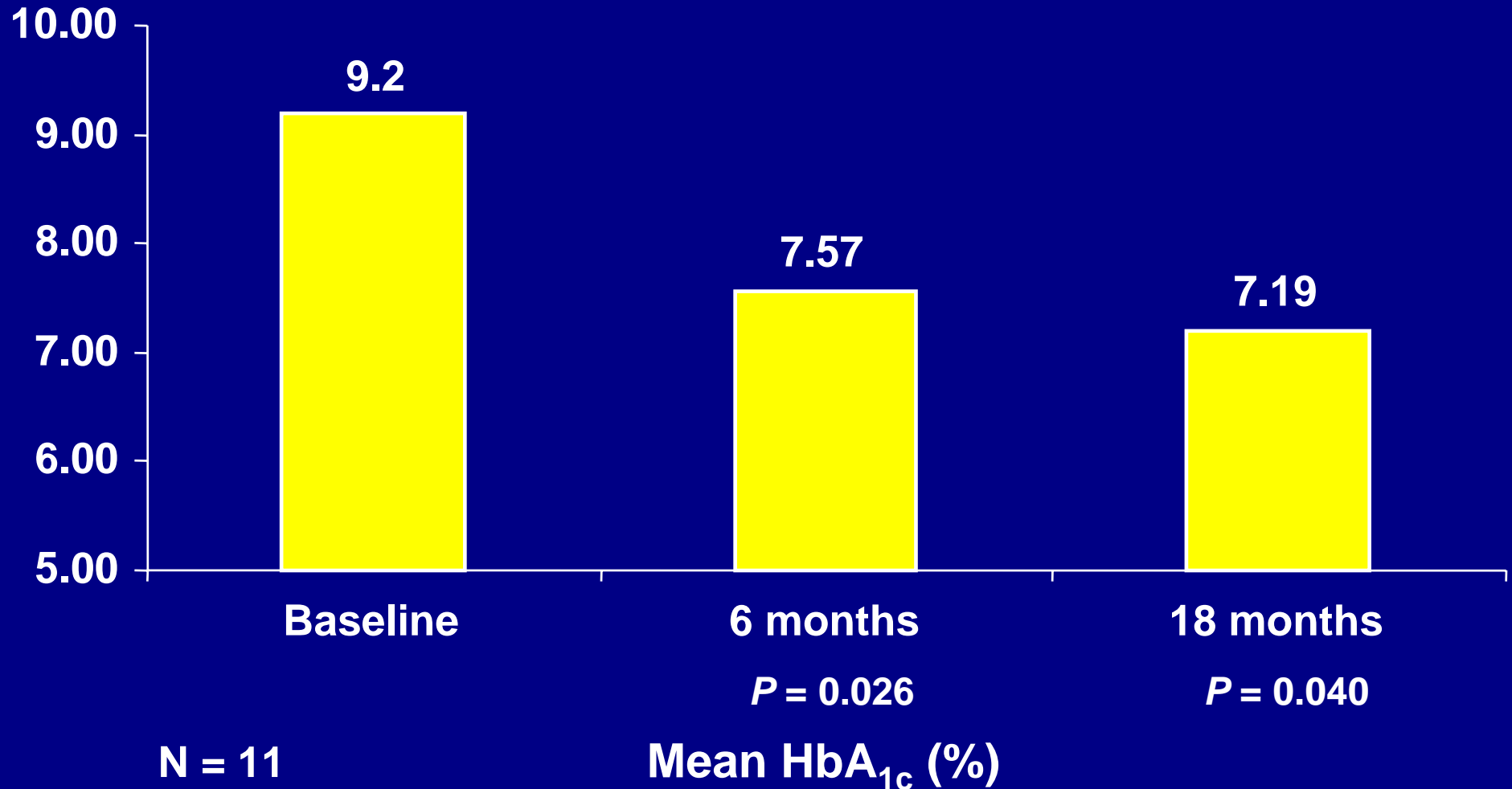
# **Case Study: 54 year old DM1 on CSII with Lipoatrophy and Insulin Antibodies**

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

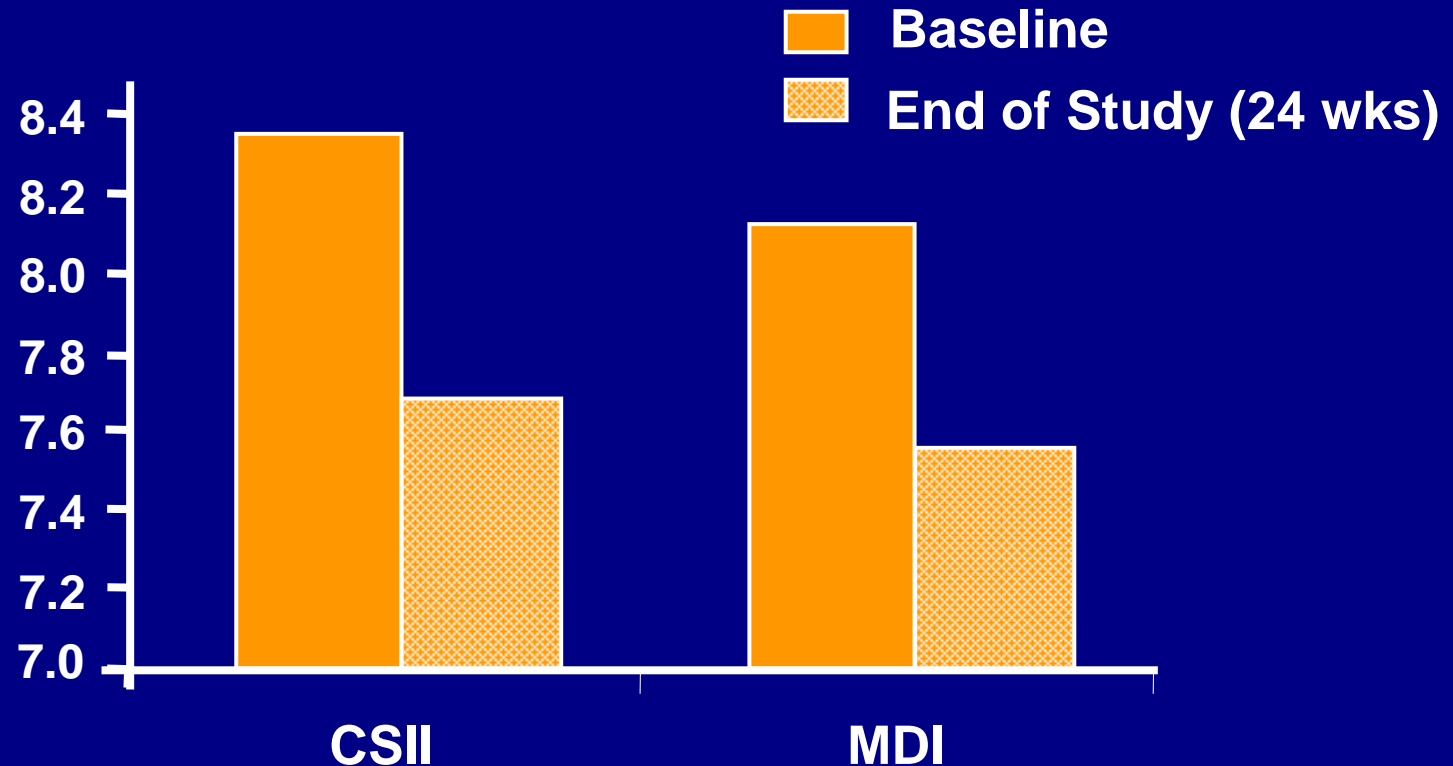
# CSII Usage in Type 2 Patients

## Atlanta Diabetes Experience



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

● A1C



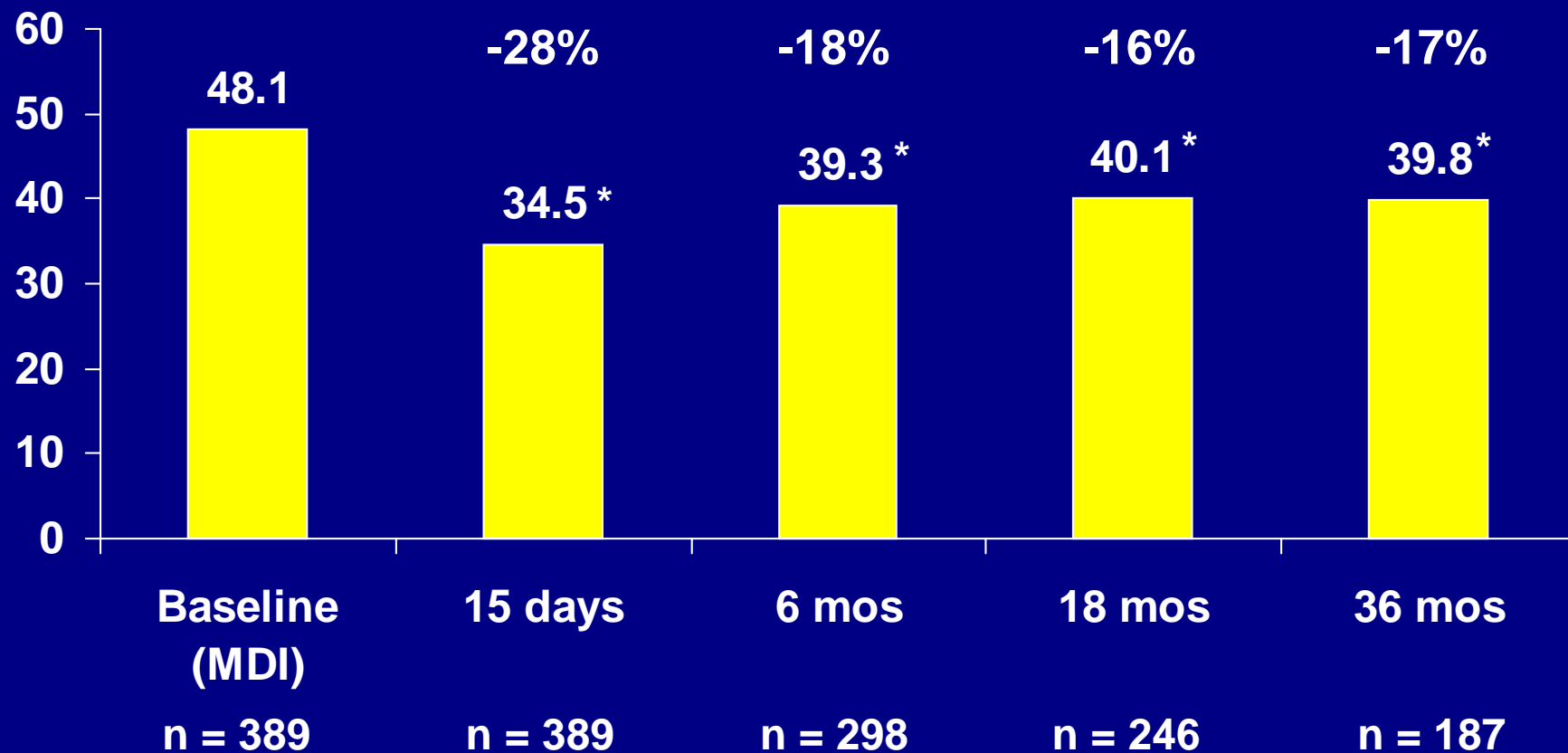
# DM 2 Study: CSII vs MDI

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- 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

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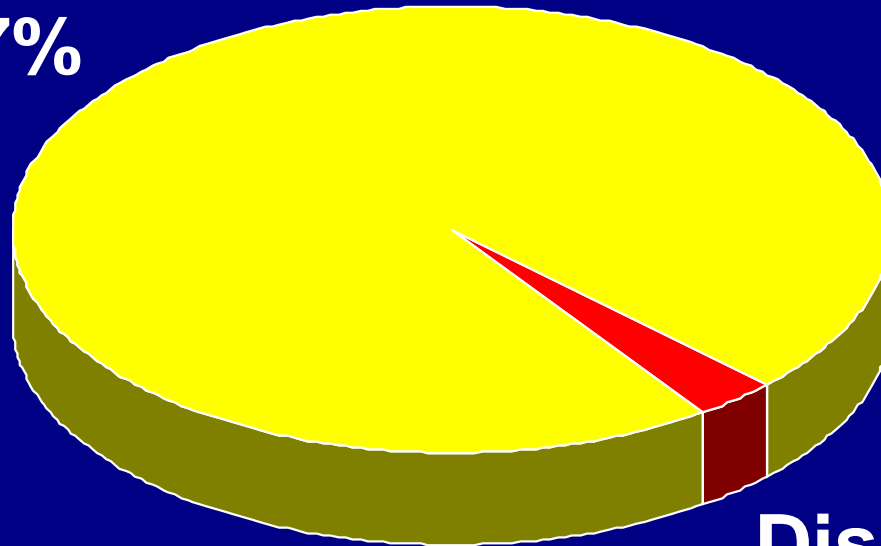
- Liberalization of diet — timing & amount
- Increased control with exercise
- Able to work shifts & through lunch
- Less hassle with travel — time zones
- Weight control
- Less anxiety in trying to keep on schedule

# Current Continuation Rate

## Continuous Subcutaneous Insulin Infusion (CSII)

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Continued 97%



Discontinued 3%

N = 165

Average Duration = 3.6 years

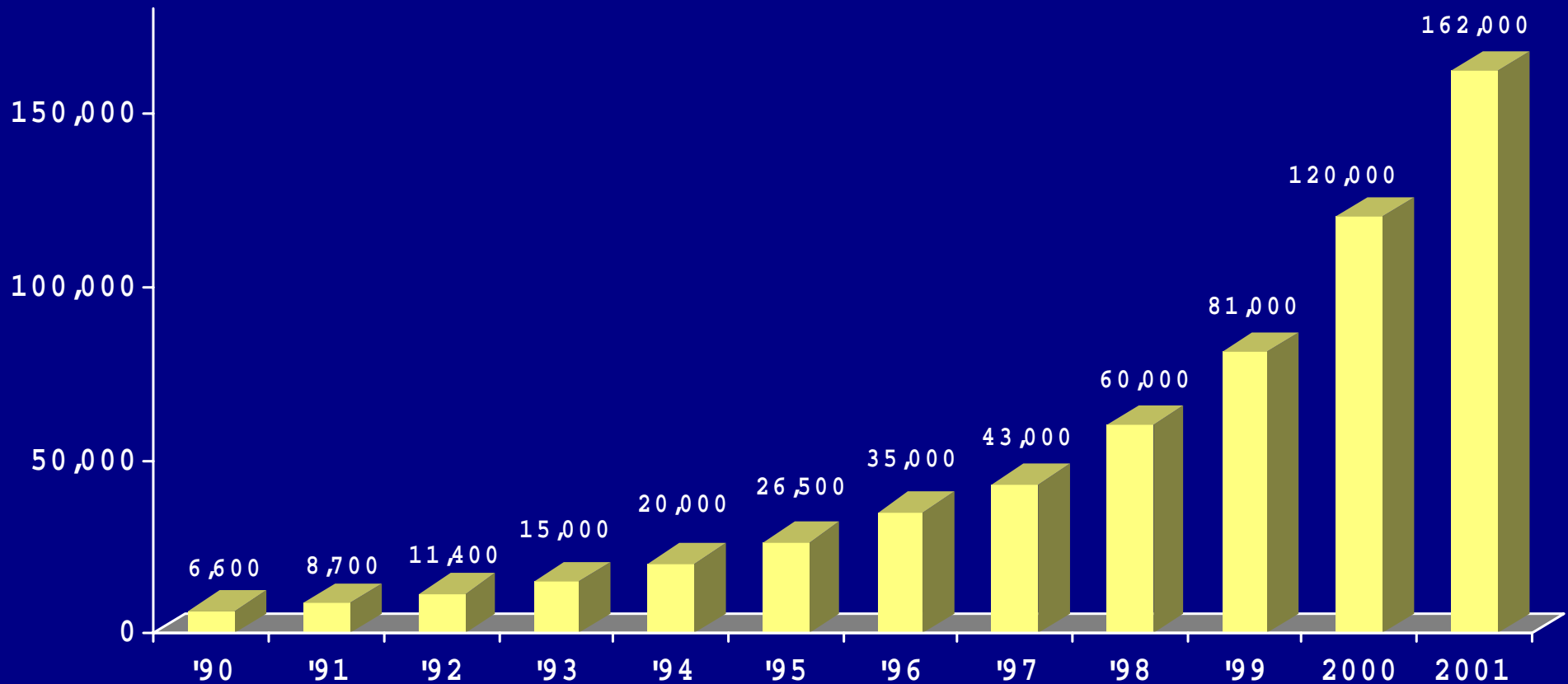
Average Discontinuation <1%/yr

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

# U.S. Pump Usage

## Total Patients Using Insulin Pumps

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# Pump Therapy Indications

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- HbA<sub>1c</sub> >7.0%
- Frequent hypoglycemia
- Dawn phenomenon
- Exercise
- Pediatrics
- Pregnancy
- Gastroparesis
- Hectic lifestyle
- Shift work
- Type 2



# Poor Candidates for CSII

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

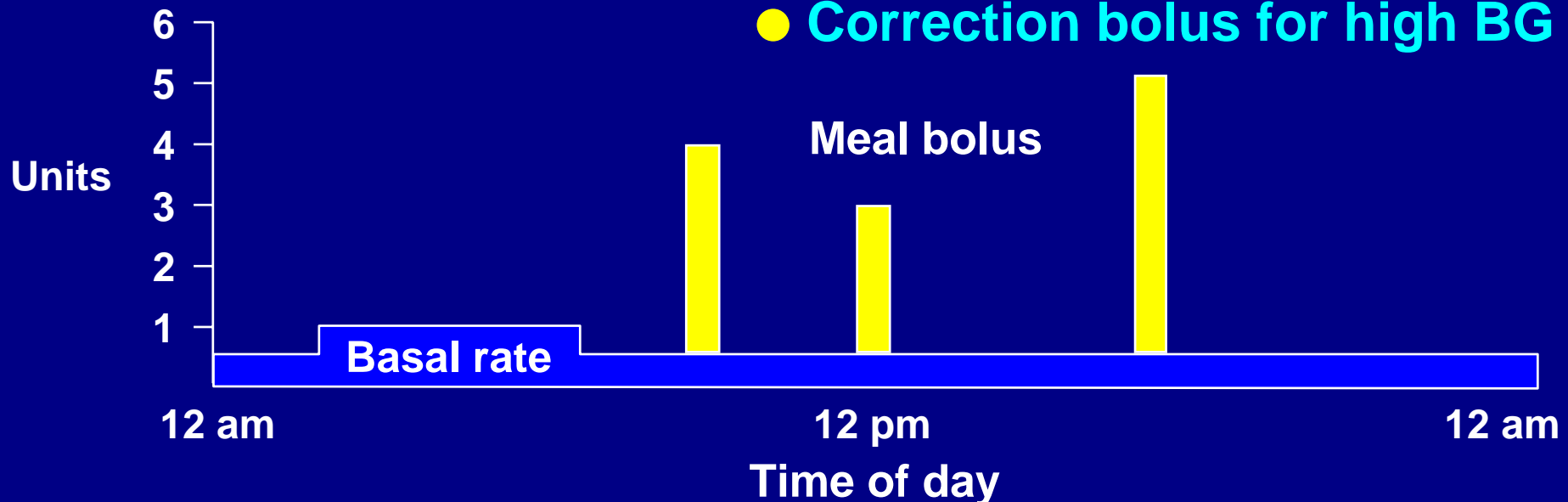
# Pump Therapy

## 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<sub>1c</sub> is Not to Goal

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## 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



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# **Future of Diabetes Management**

# Improvements in Insulin & Delivery

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- 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

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*subcutaneous  
glucose sensor*

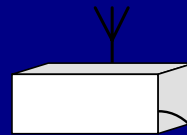
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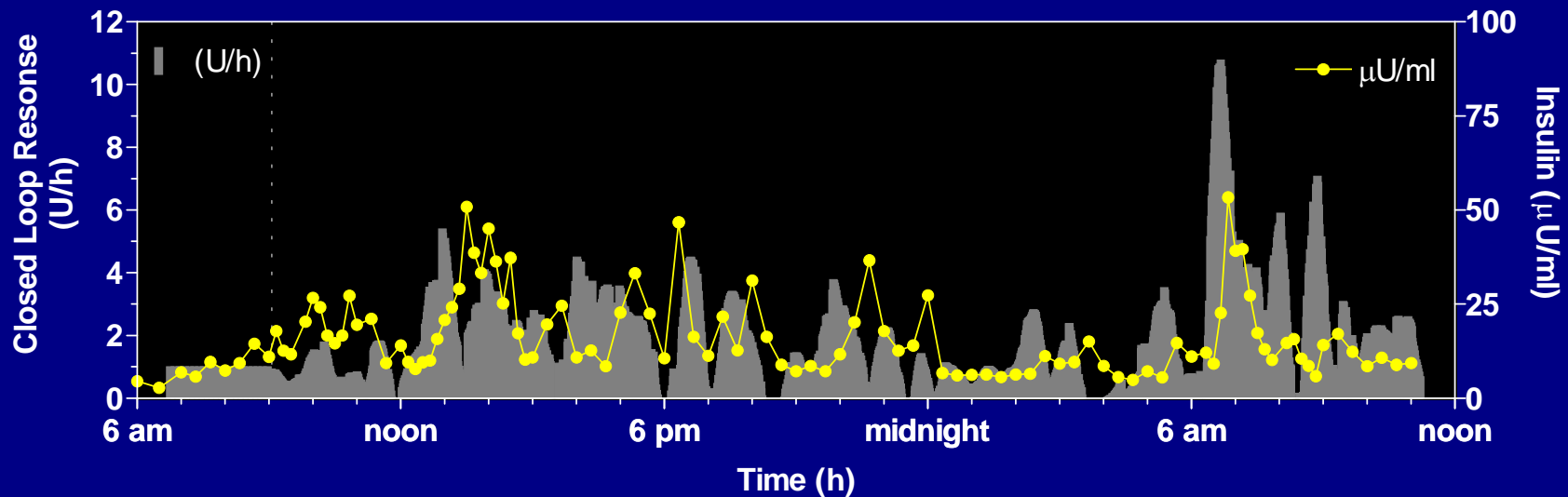
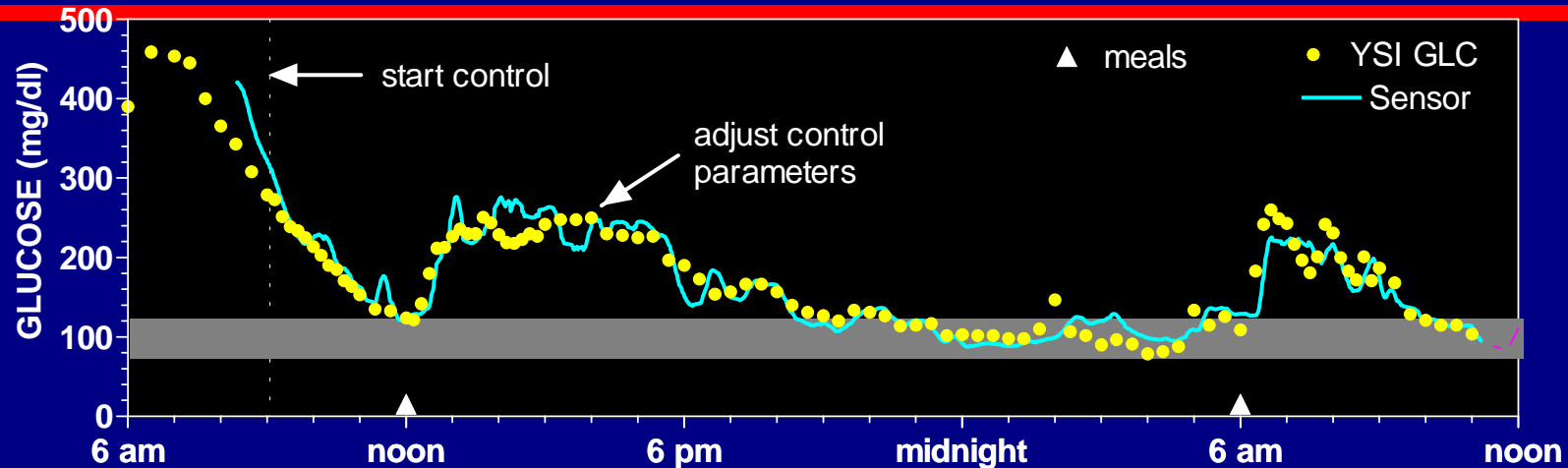
*Insulin infusion pump  
(currently MiniMed 508)*

# Closed-Loop Setup for Canine Studies

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# 24-h Closed-Loop Control (diabetic canine)



# Implantable Pump

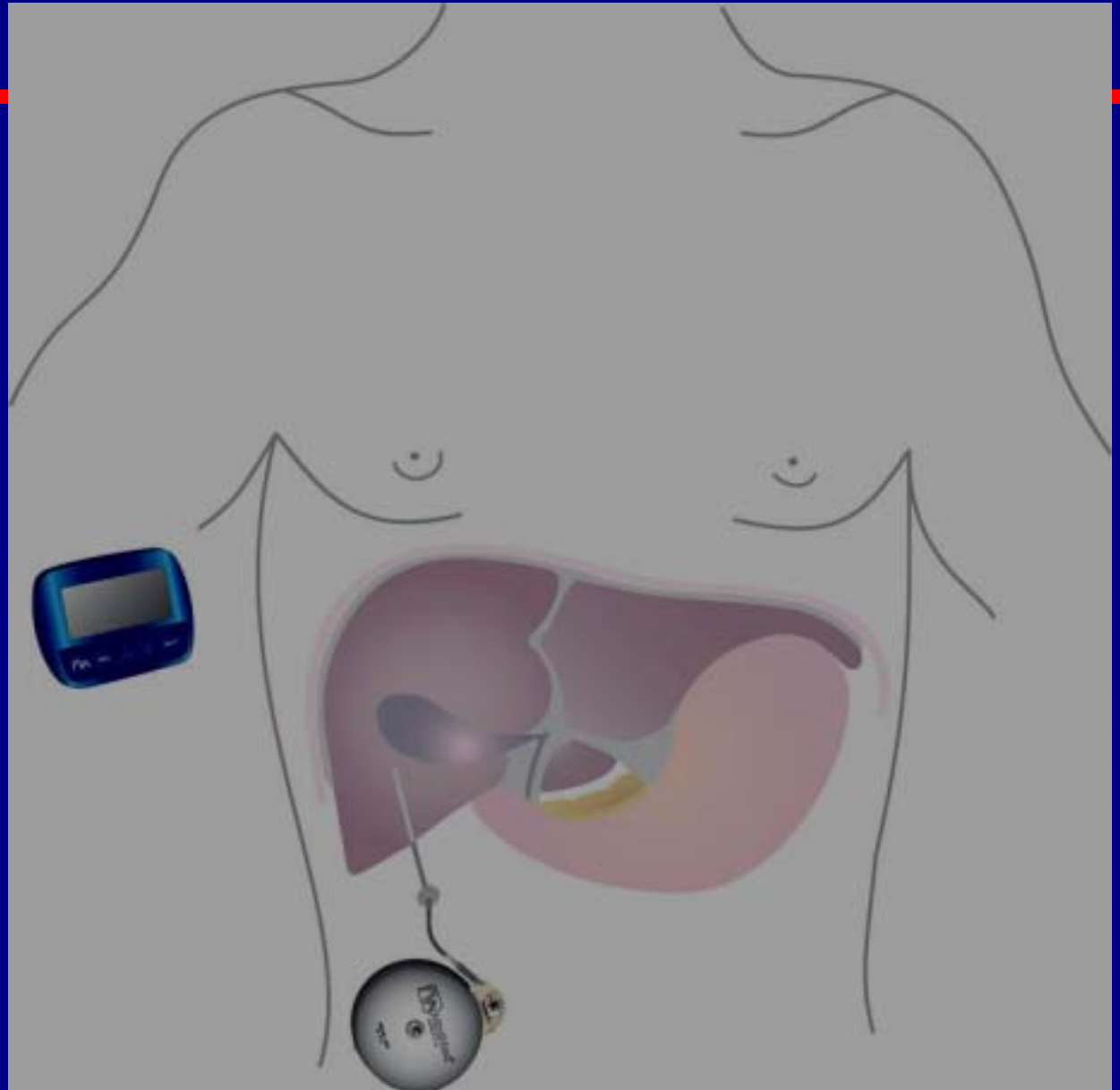
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- Average HbA<sub>1c</sub> 7.1%
- Hypoglycemic events reduce to 4 episodes per 100 pt-years

# MiniMed 2007 System

## Implantable Insulin Pump Placement



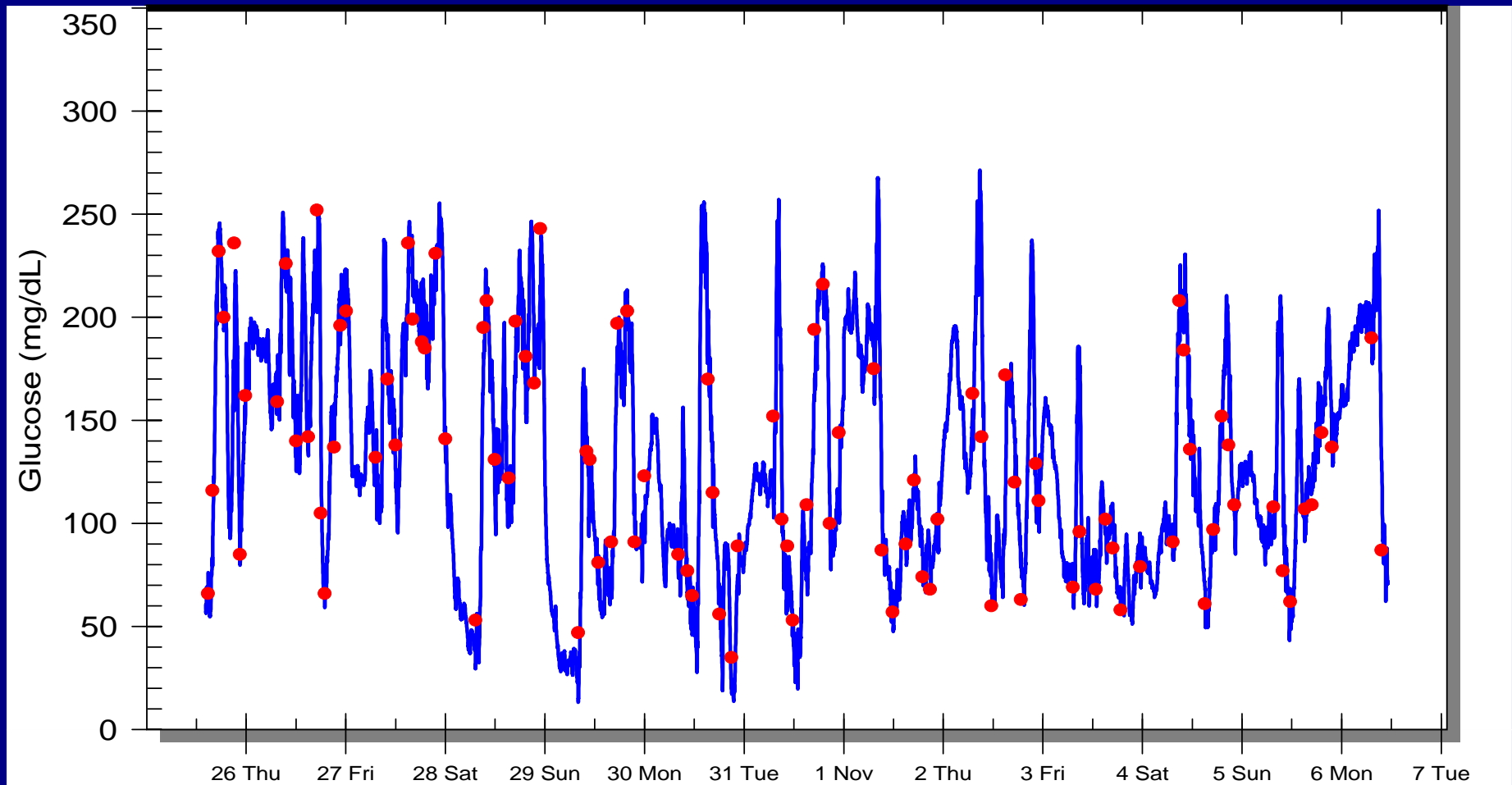


# Long-Term Glucose Sensor



# 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

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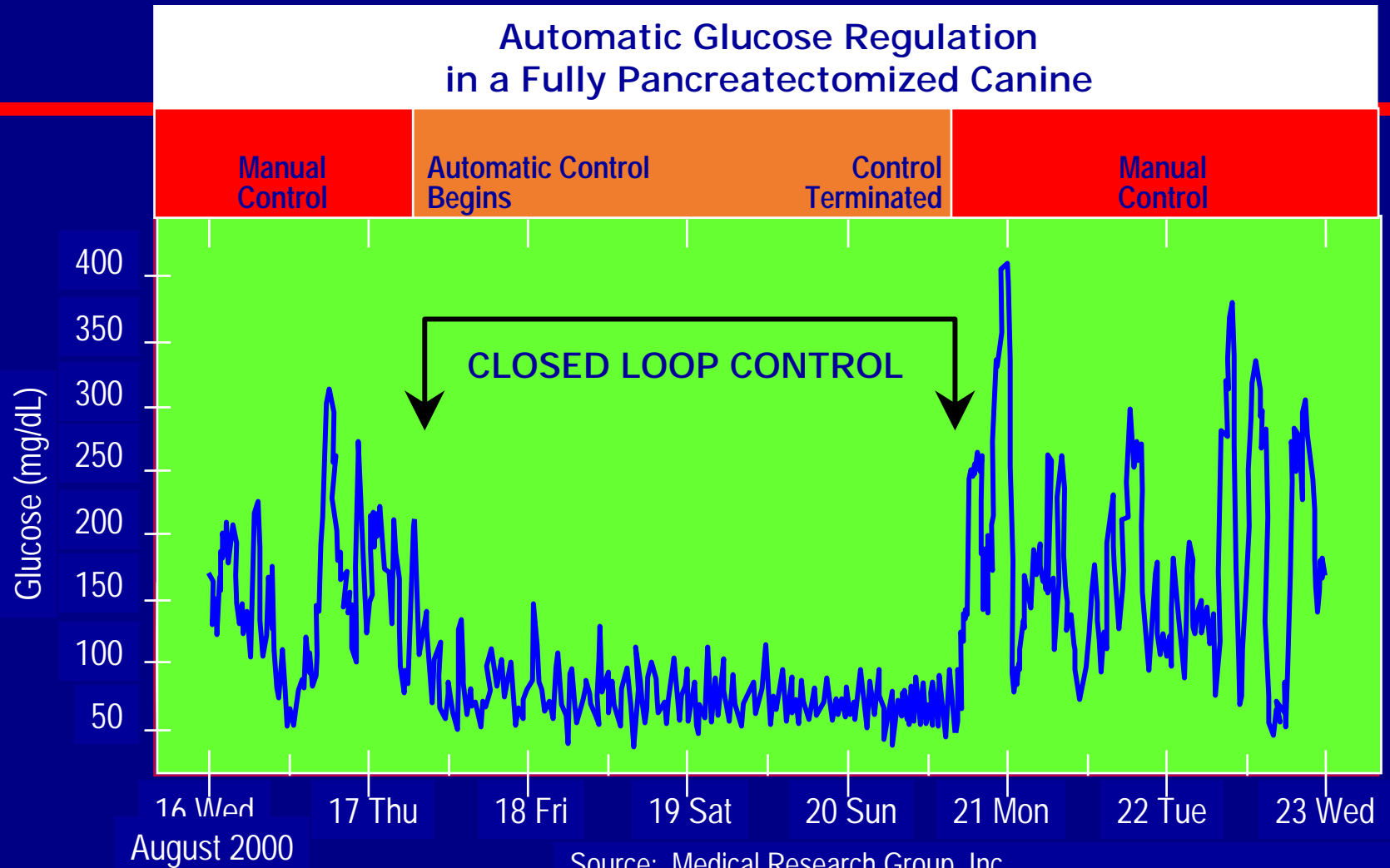
# Today's Reality

## Open-Loop Glucose Control

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# LONG TERM IMPLANTABLE SYSTEM



# Summary

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- **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

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**Intensive therapy is  
the best way to treat  
patients with diabetes**



# QUESTIONS

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- For a copy or viewing of these slides, contact

- [WWW.adaendo.com](http://WWW.adaendo.com)