New Insulins and Insulin Delivery Systems

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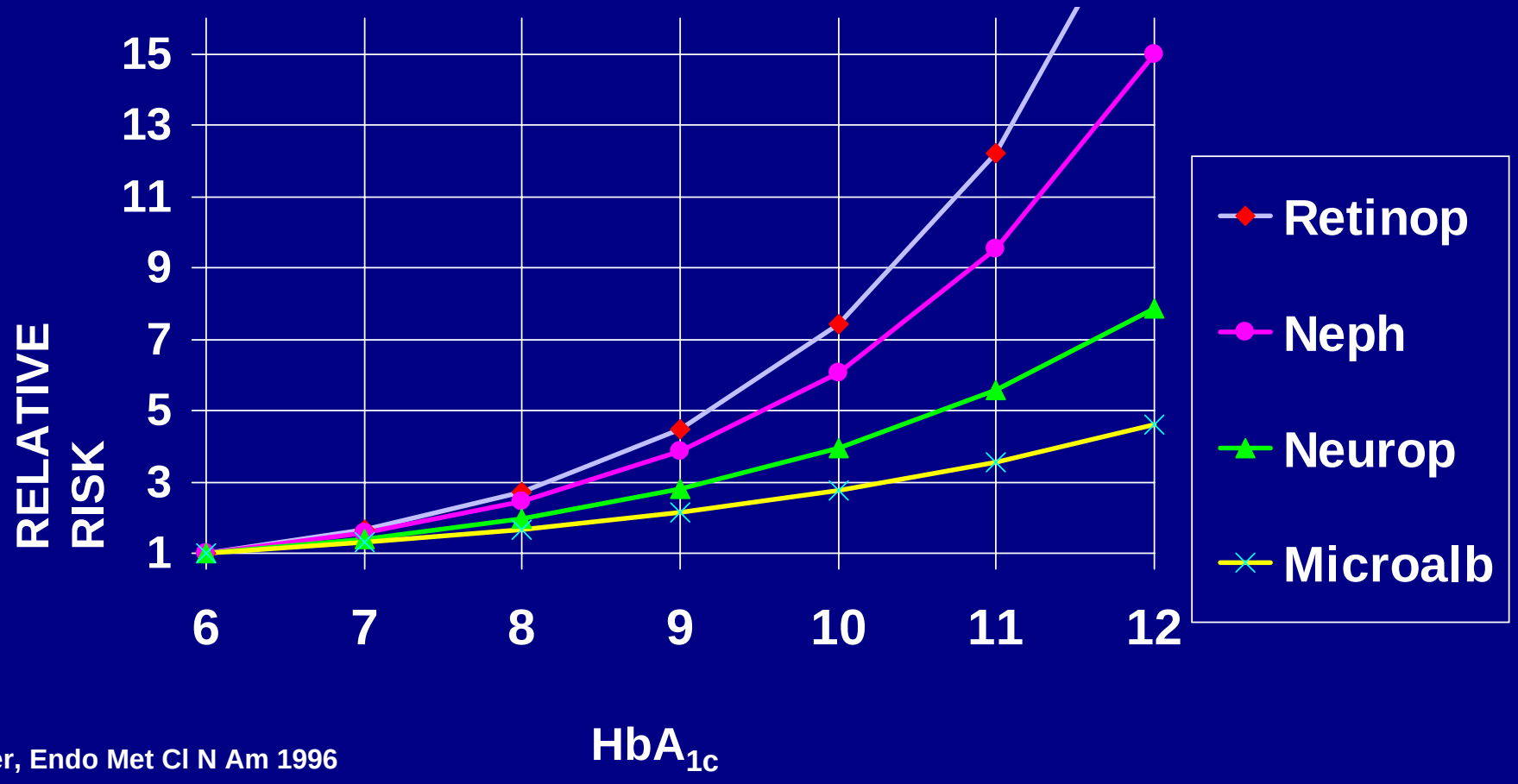
Goals of Intensive Diabetes Management

- 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

Comparison of Human Insulins / Analogues

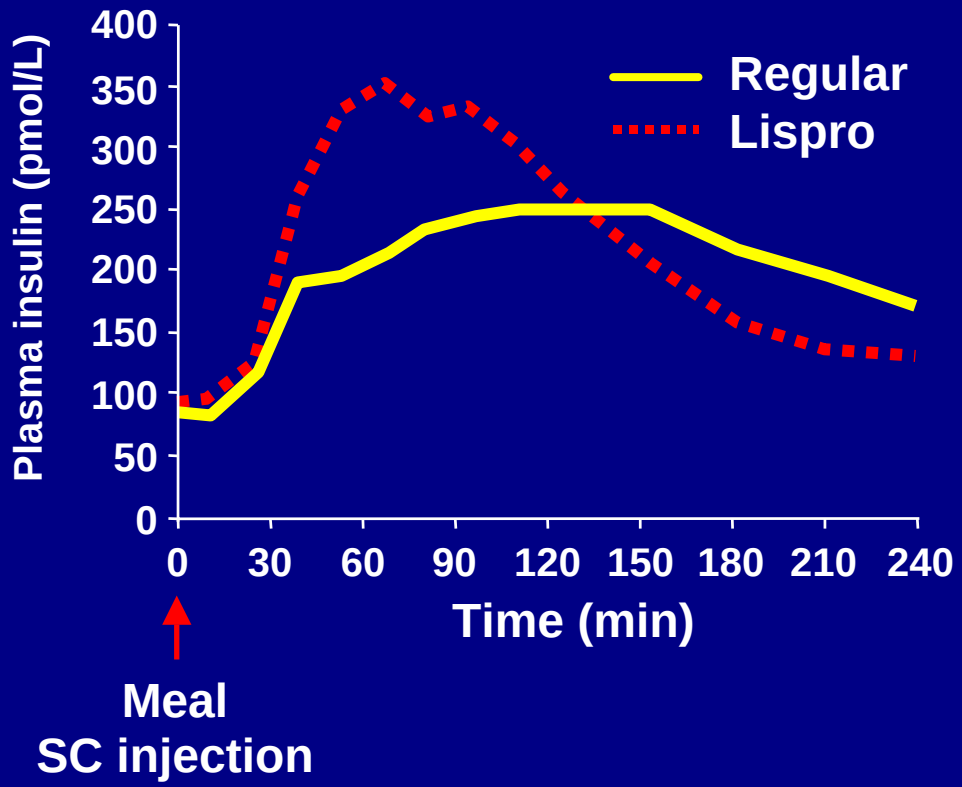
Insulin preparations	Onset of action	Peak	Duration of action
Regular	30–60 min	2–4 h	6–10 h
NPH/Lente	1–2 h	4–8 h	10–20 h
Ultralente	2–4 h	Unpredictable	16–20 h
Lispro/aspart	5–15 min	1–2 h	4–6 h
Glargine	1–2 h	Flat	~24 h

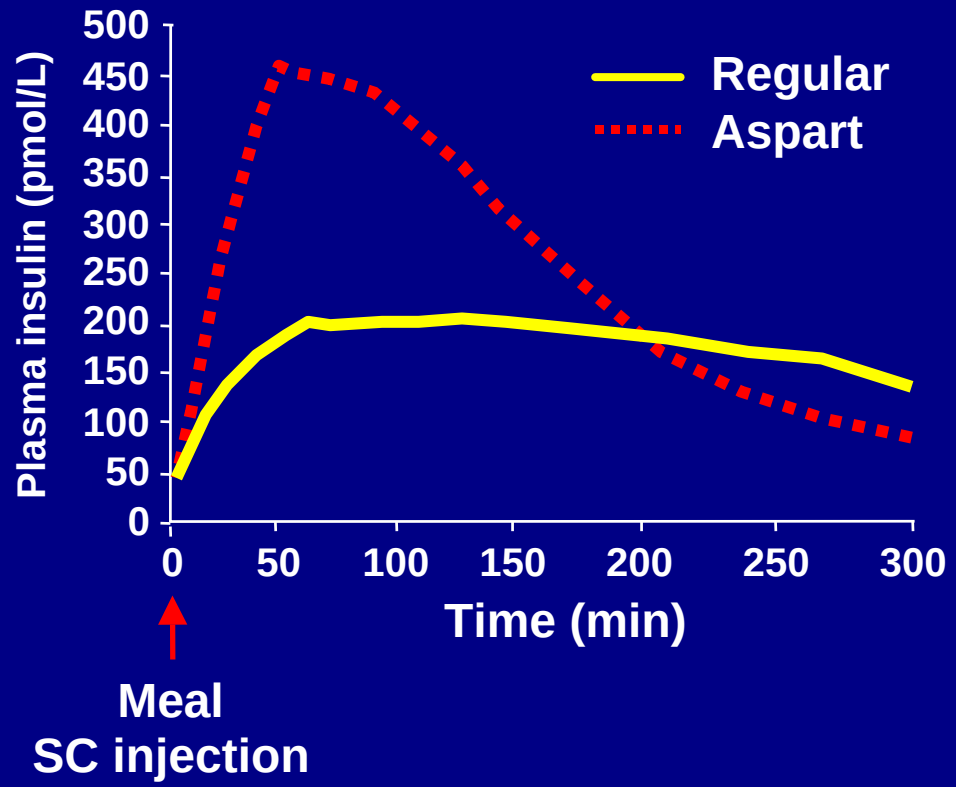
Short-Acting Analogs
Lispro and Aspart

- Convenient administration immediately prior to meals
- Faster onset of action
- Limit postprandial hyperglycemic peaks
- Shorter duration of activity
  - Reduce late postprandial *hypoglycemia*
  - Frequent late postprandial *hyperglycemia*
- Need for basal insulin replacement revealed

Short-Acting Insulin Analogs

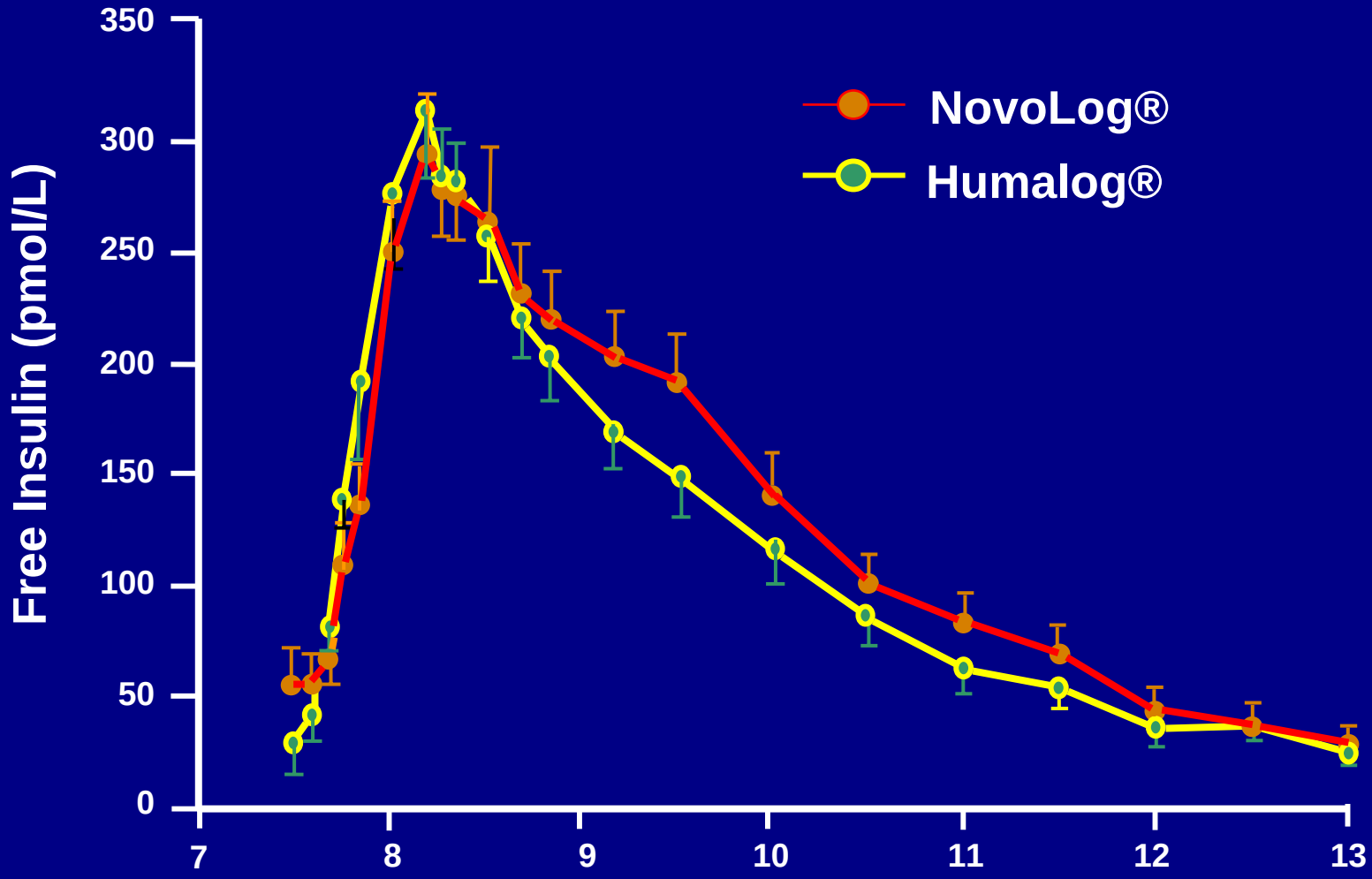
Lispro and Aspart Plasma Insulin Profiles





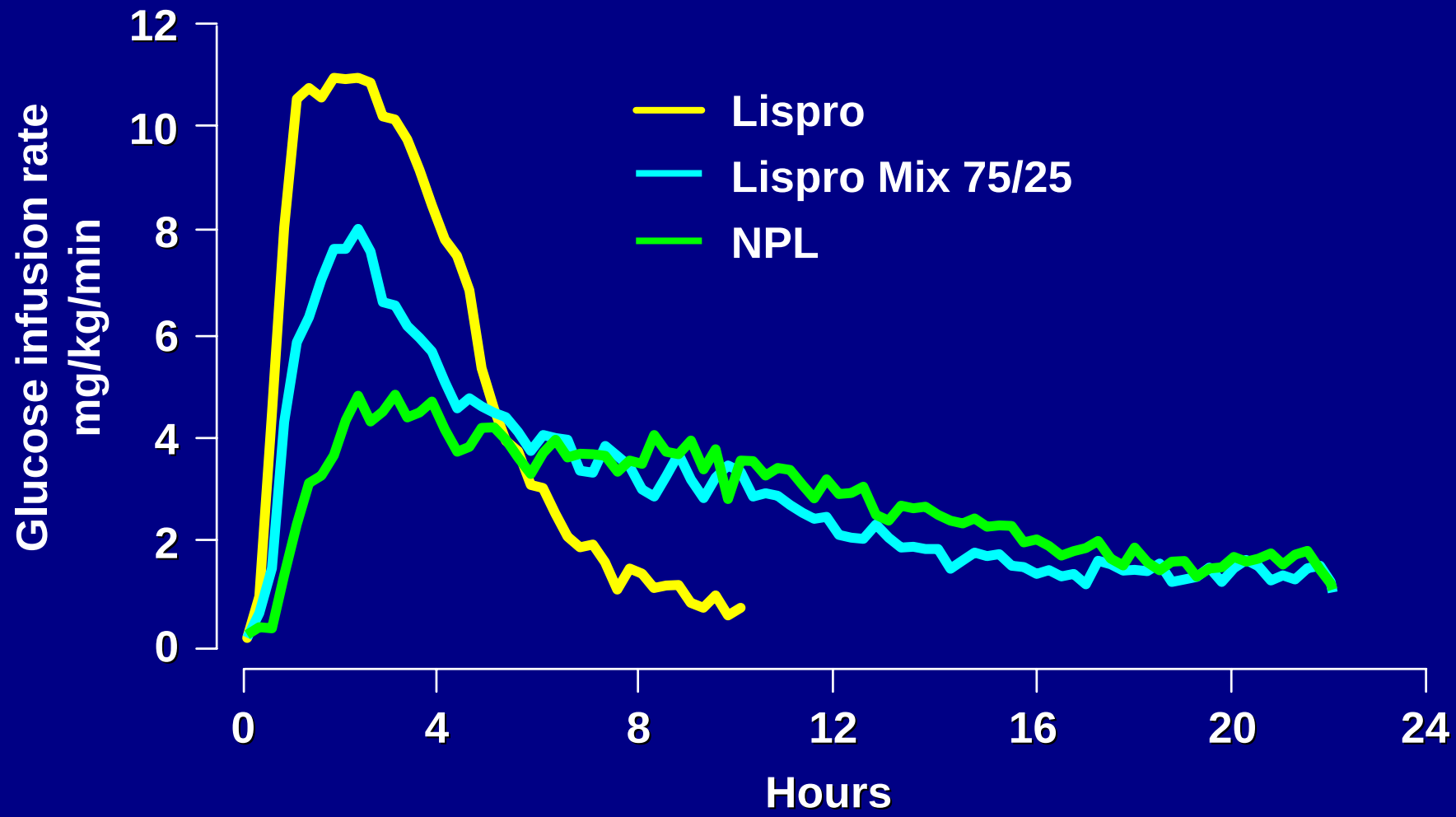
Heinemann, et al. *Diabet Med*. 1996;13:625–629; Mudaliar, et al. *Diabetes Care*. 1999;22:1501–1506.

Pharmacokinetic Comparison
NovoLog® *vs* Humalog®



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

Lispro Mix 75/25
Pharmacodynamics



Heise T, et al. *Diabetes Care*. 1998;21:800–803.

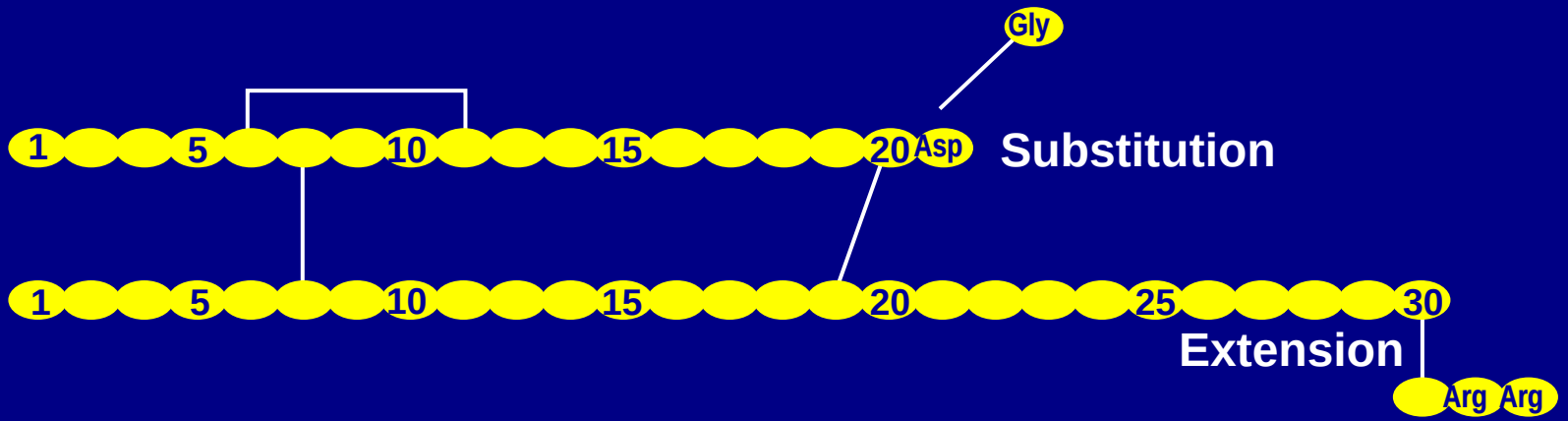
Limitations of NPH, Lente, and Ultralente

- 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

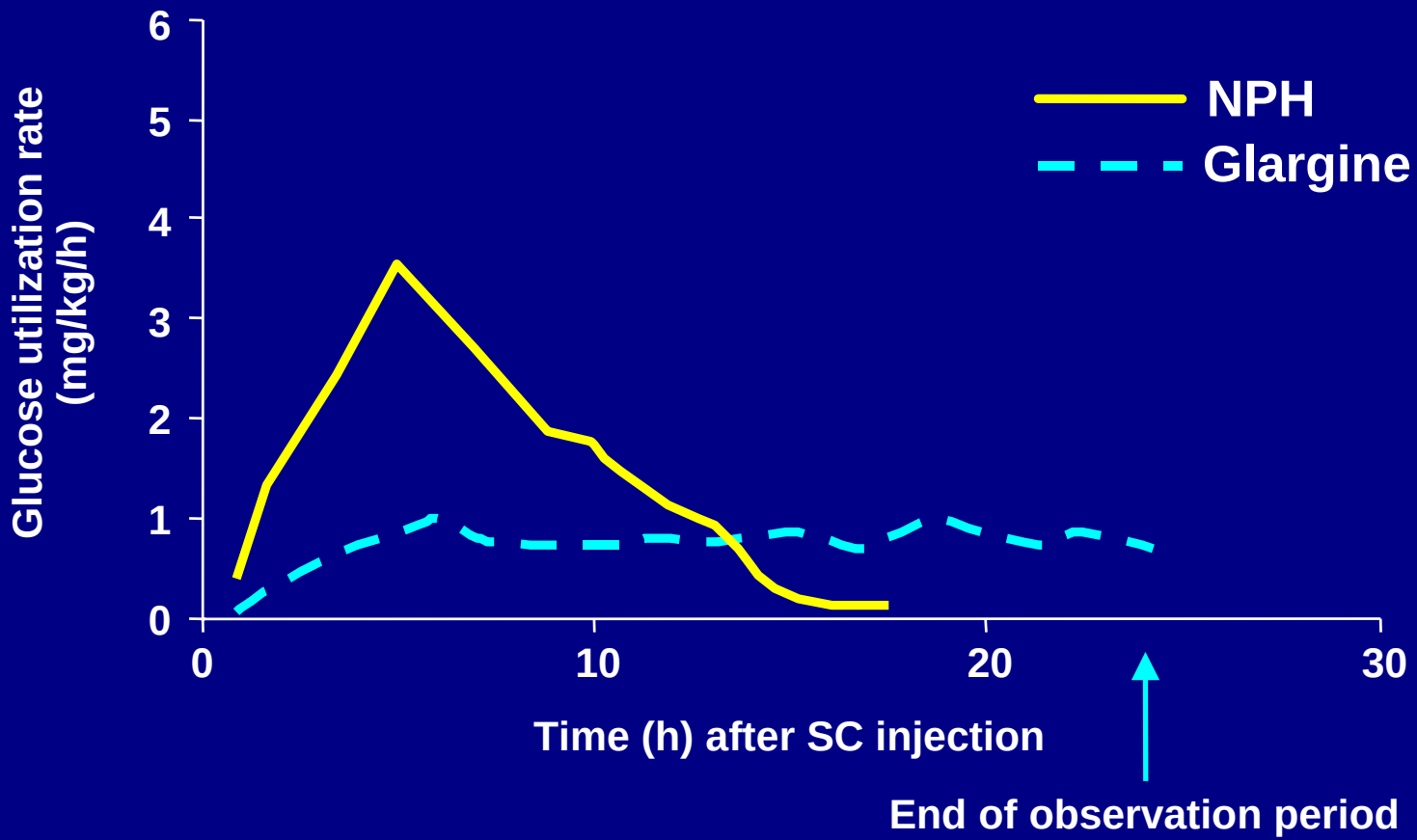
A New Long-Acting Insulin Analog

- 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



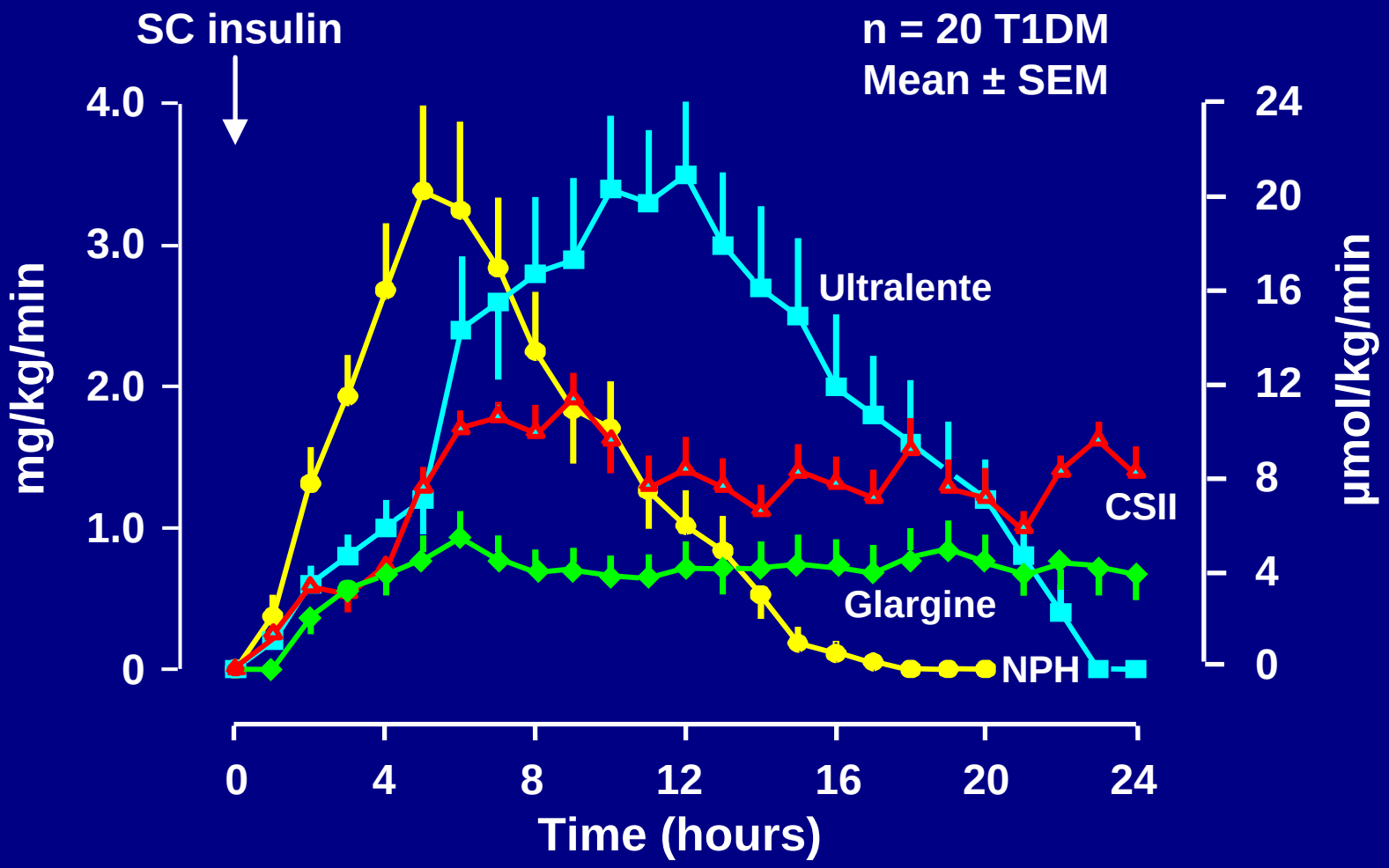
Glargine vs NPH Insulin in Type 1 Diabetes

Action Profiles by Glucose Clamp



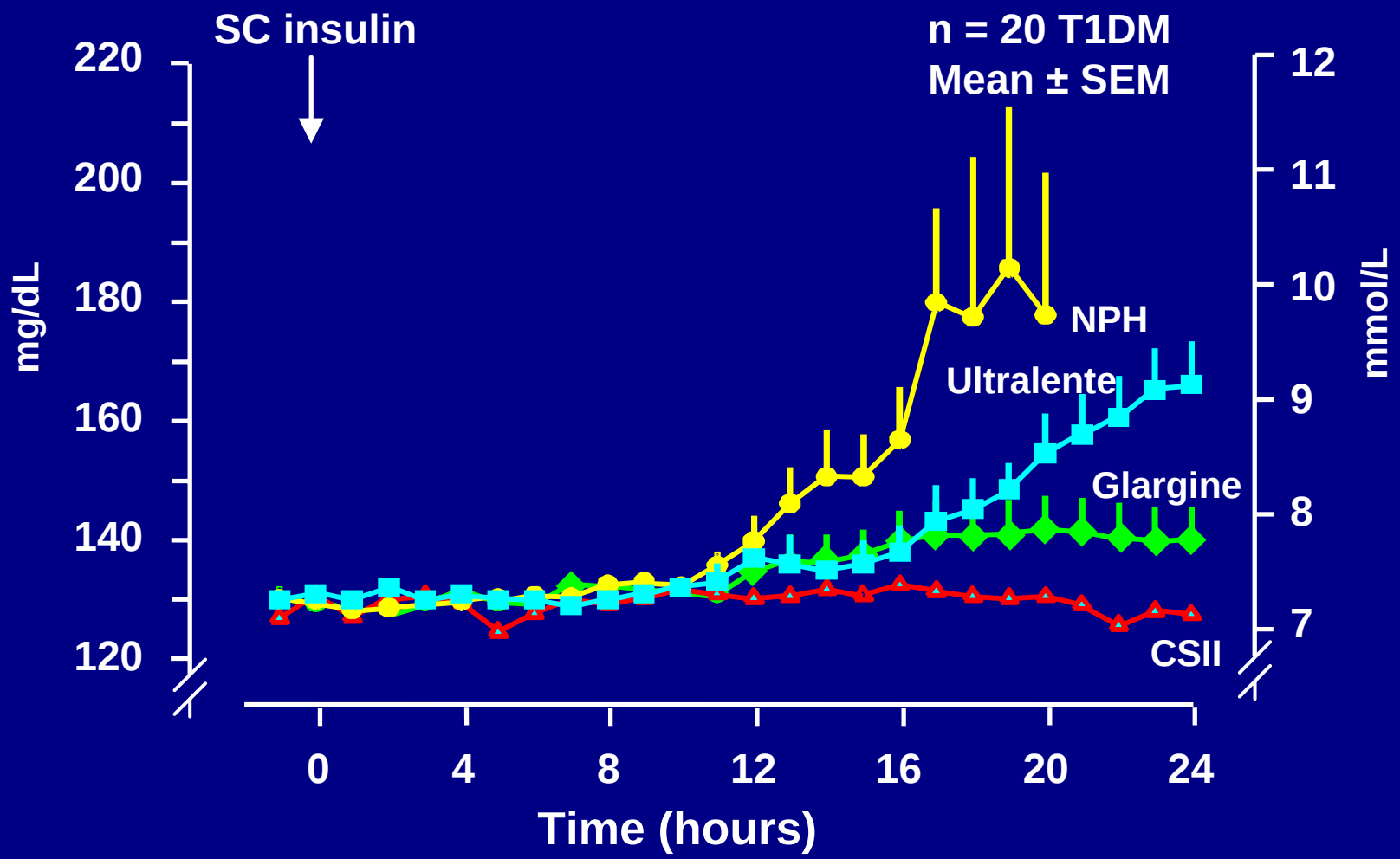
Lepore, et al. *Diabetes*. 1999;48(suppl 1):A97.

Glucose Infusion Rate



Lepore M, et al. *Diabetes*. 2000;49:2142–2148.

Plasma Glucose



Lepore M, et al. *Diabetes*. 2000;49:2142–2148.

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

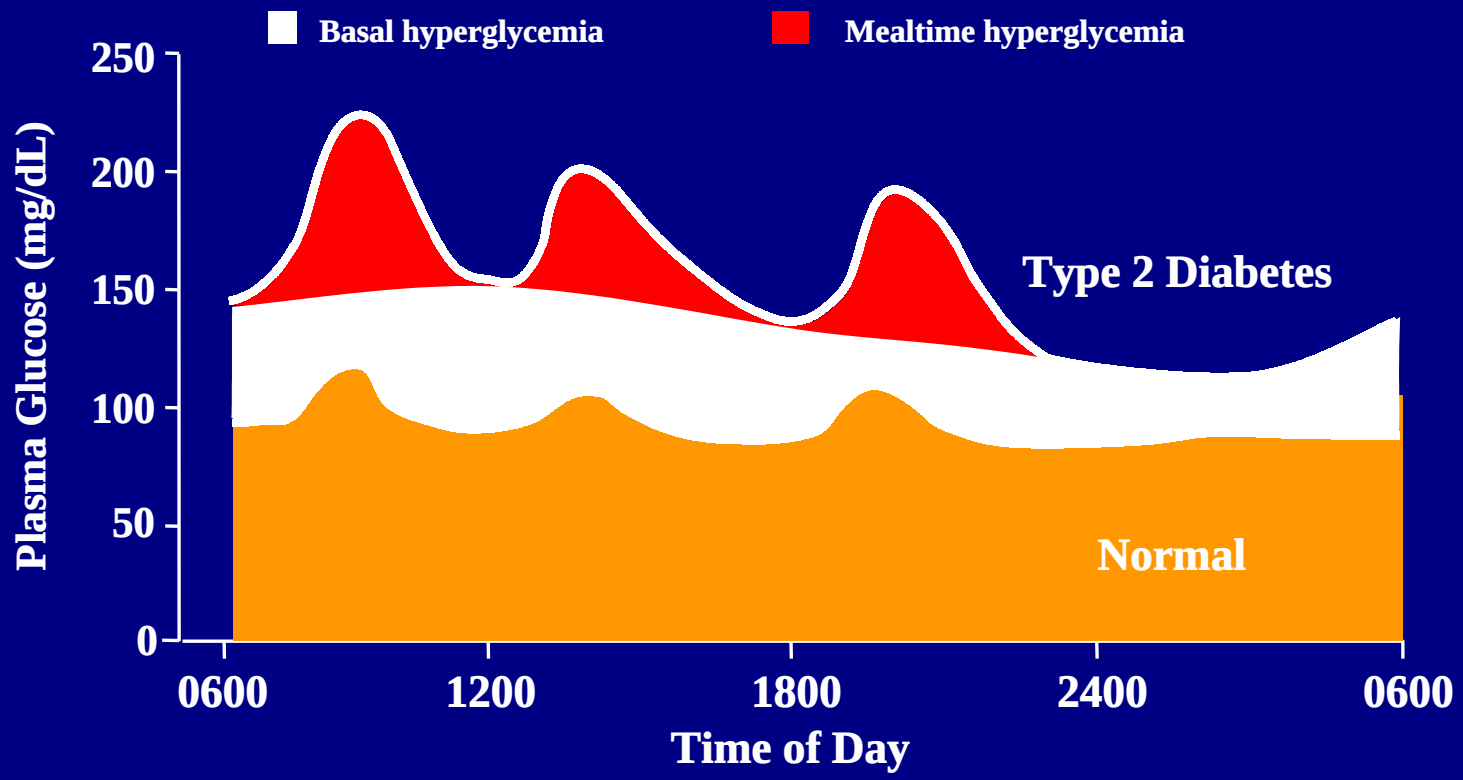
Mimicking Nature

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

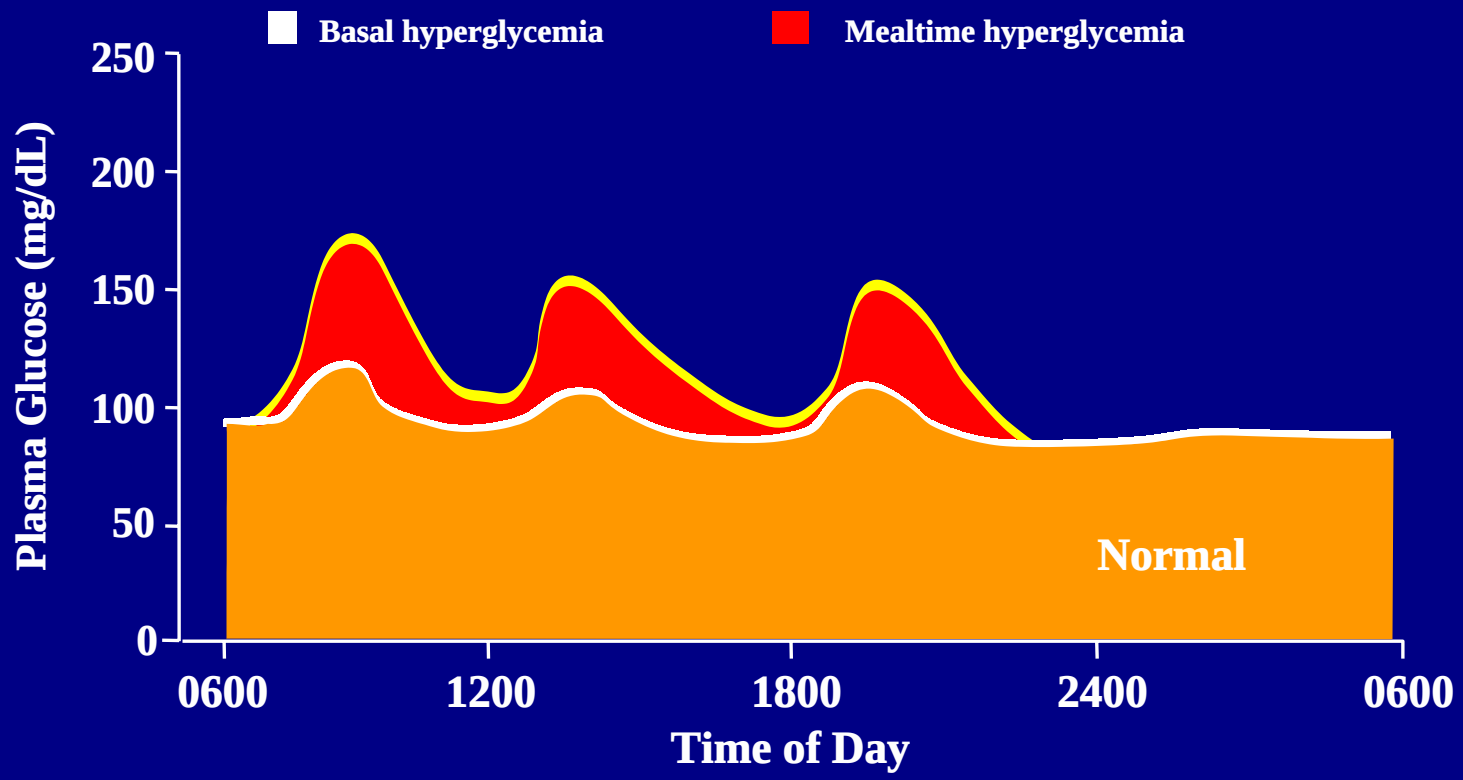
Basal vs Mealtime Hyperglycemia in Diabetes



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

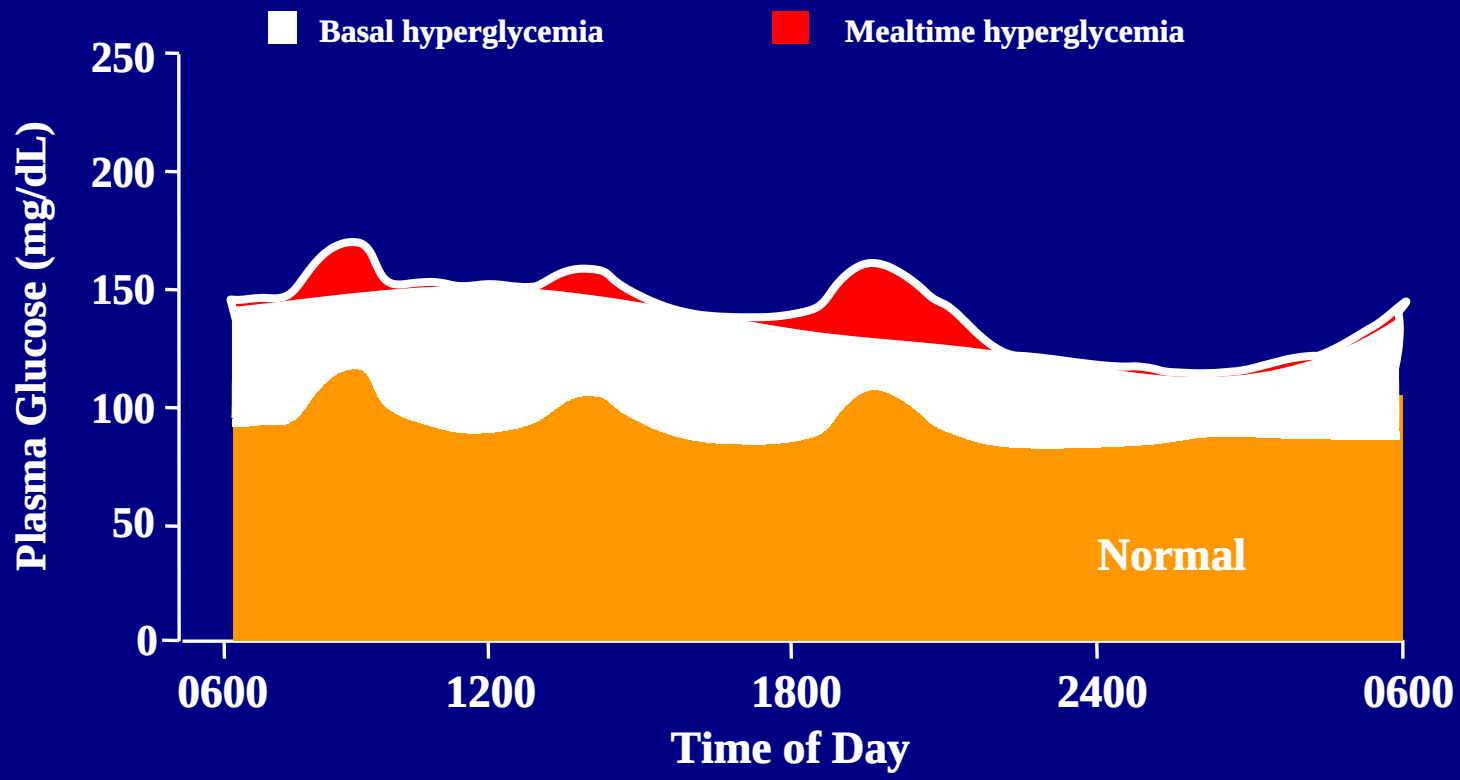
Riddle. *Diabetes Care.* 1990;13:676-686.

When Basal Corrected



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

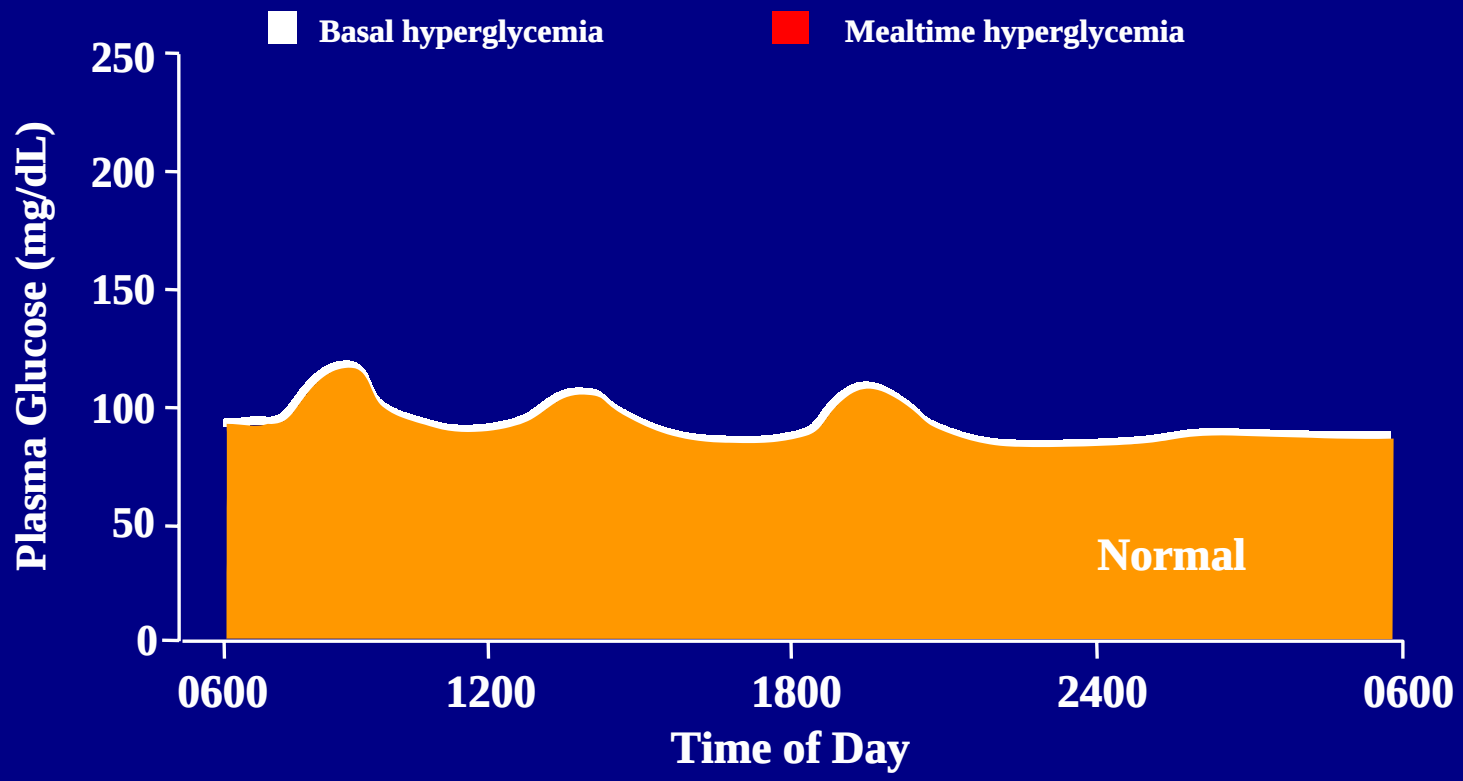
When Mealtime Hyperglycemia Corrected



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

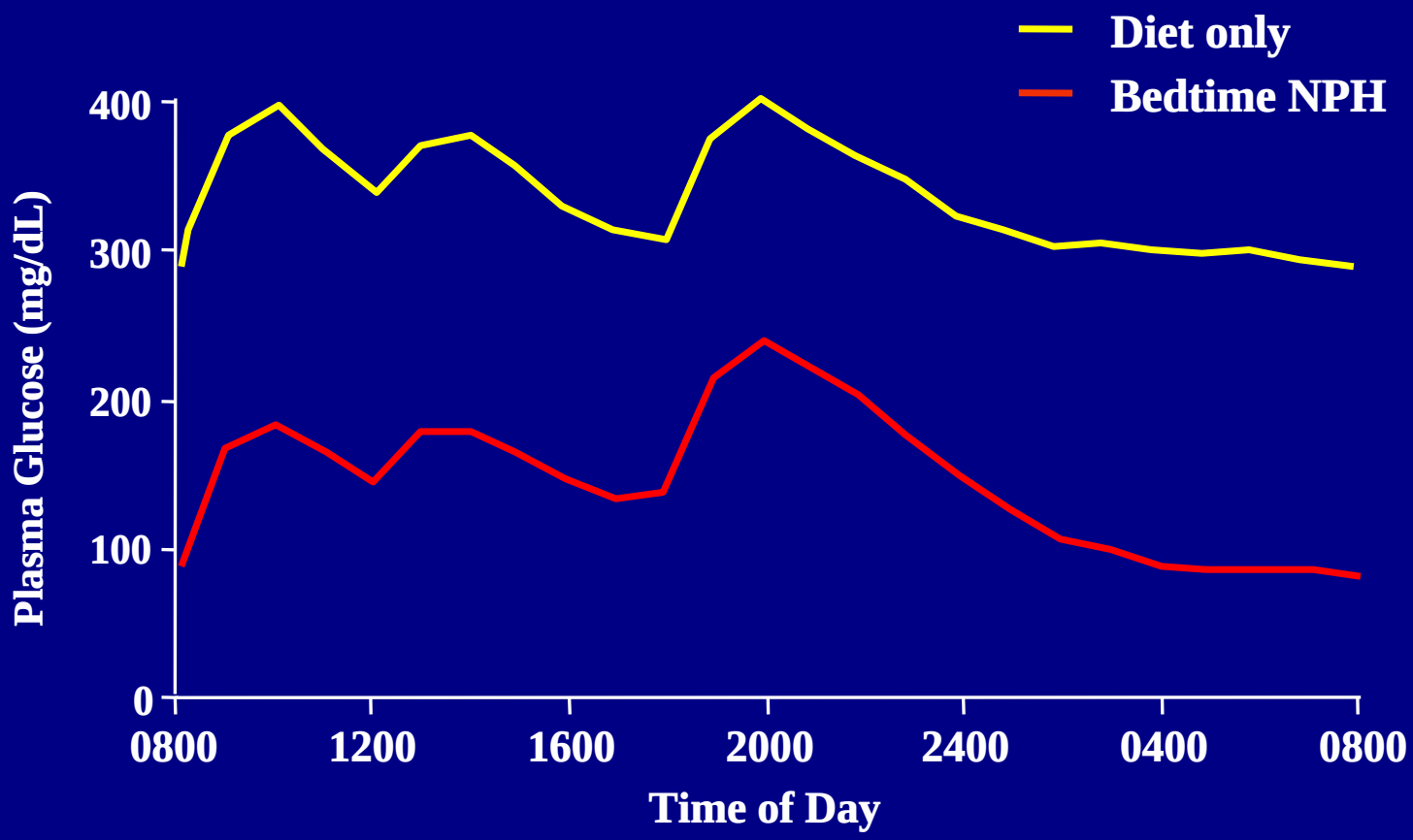
to control glucose

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

Starting With Basal Insulin

Bedtime NPH Added to Diet



Cusi & Cunningham. *Diabetes Care*. 1995;18:843-851.

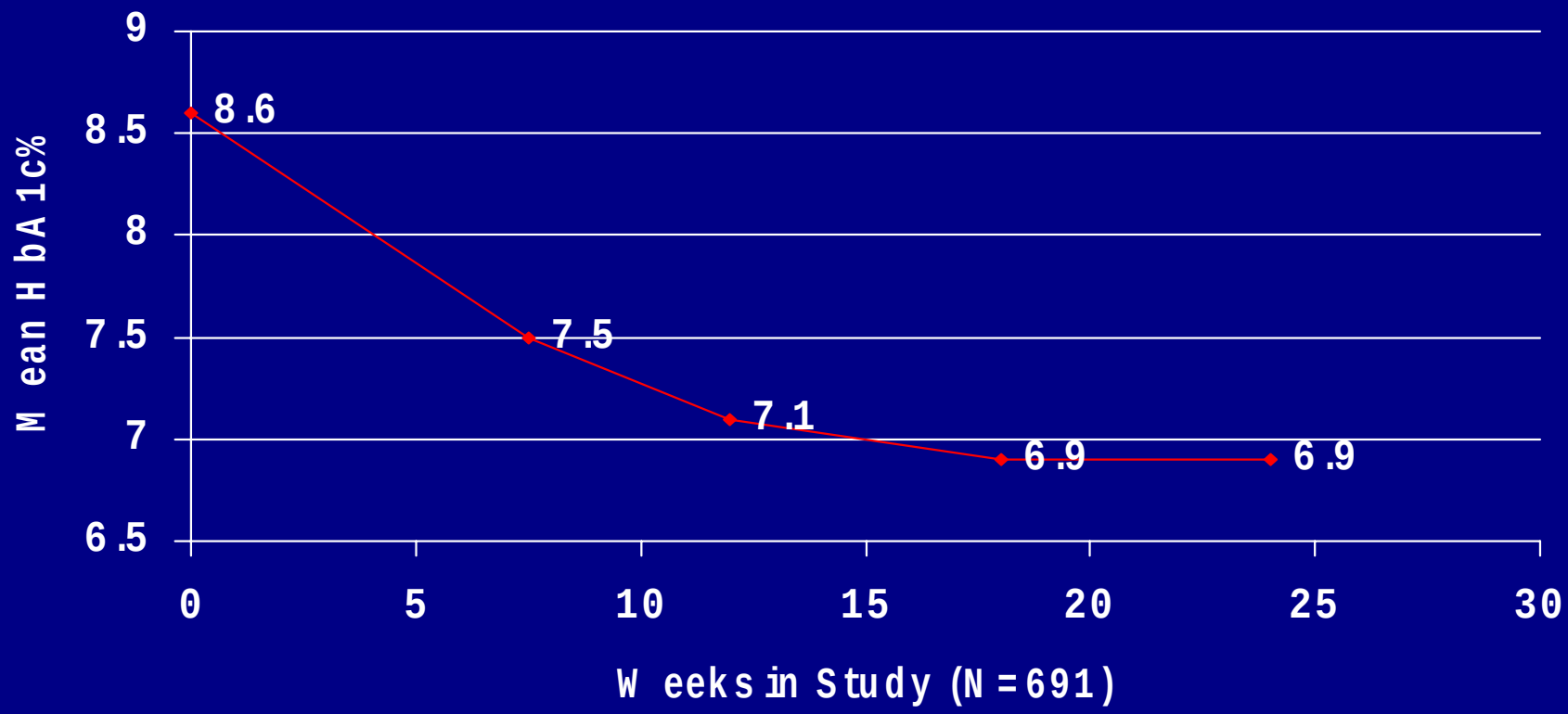
Treatment to Target Study: NPH vs Glargine in DM2 patients on OHA

- Type 2 DM on 1 or 2 oral agents (SU, MET, TZD)
- Age 30 to 70
- BMI 26 to 40
- A1C 7.5 to 10% and FPG > 140 mg/dL
- Anti GAD negative
- Willing to enter a 24 week randomized, open labeled study

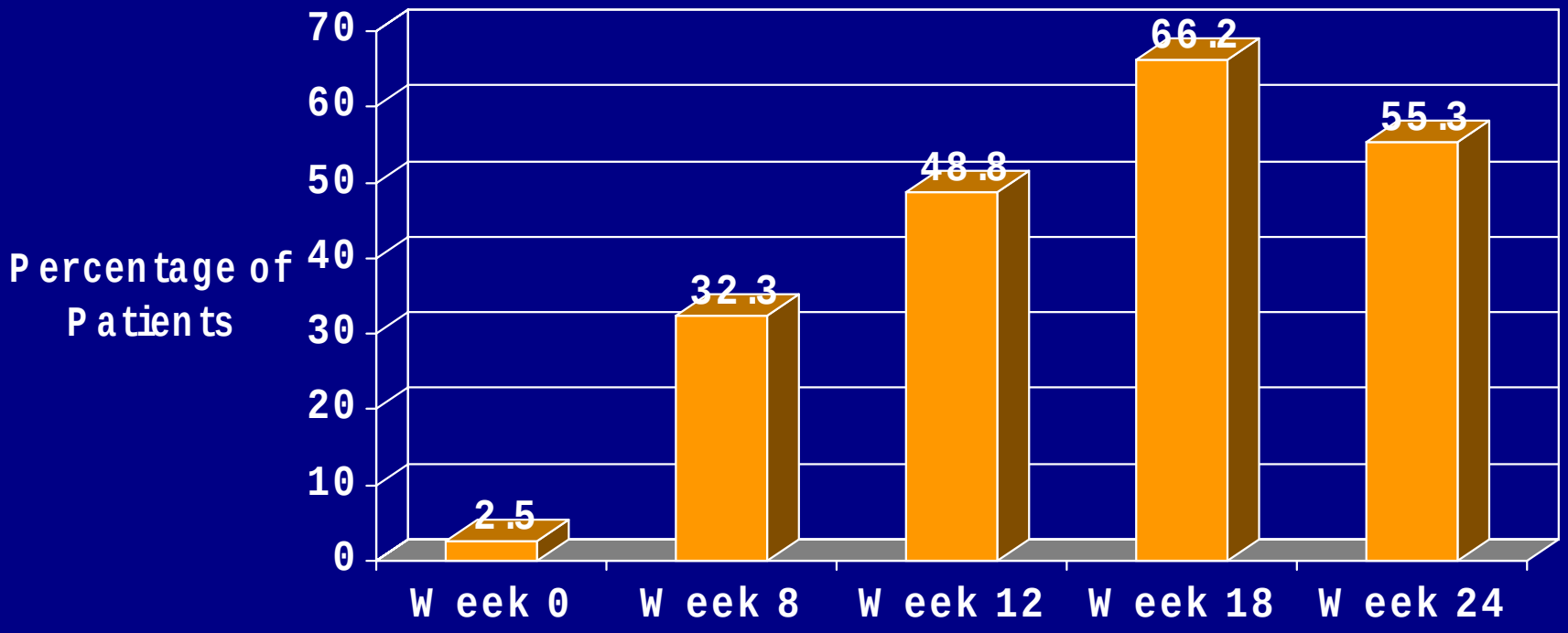
Treatment to Target Study: NPH vs Glargine in DM2 patients on OHA

- 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%)



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

- Nocturnal Hypoglycemia reduced by 40% in the Glargine group

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

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

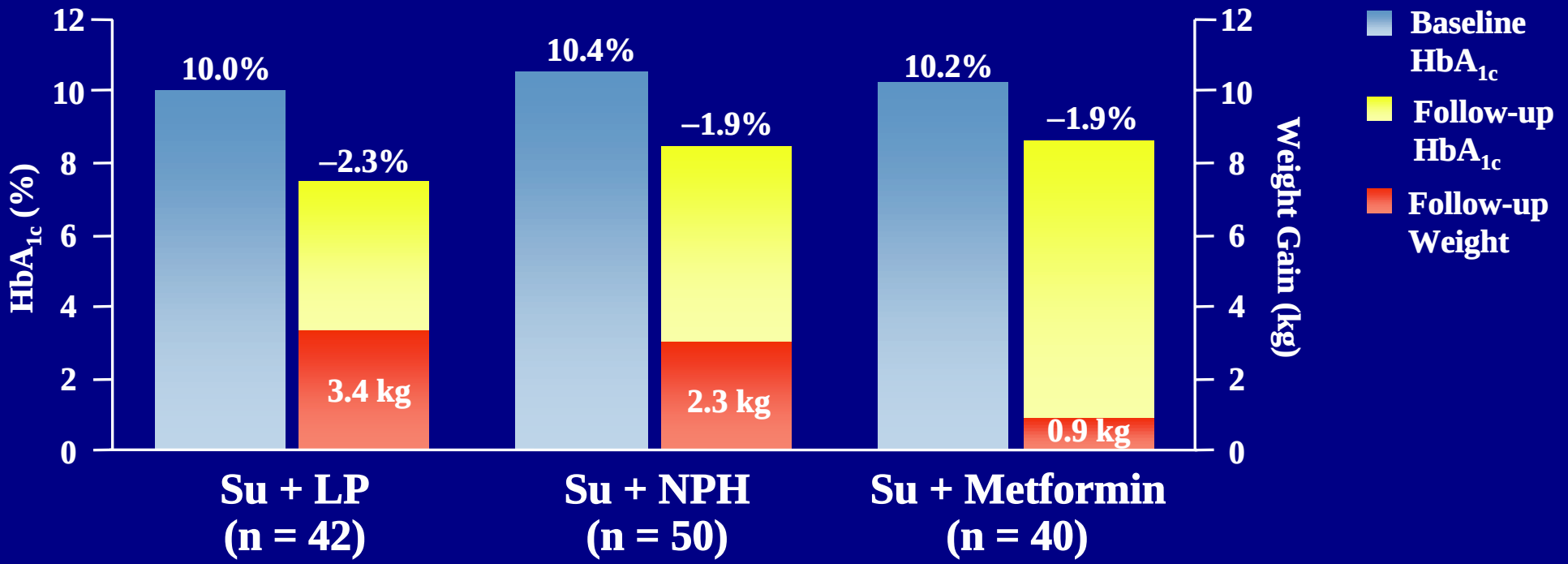
Combination Oral Agents

+

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

Initial Dosage Calculations

Correction Bolus

"1500 Rule"

- **insulin sensitivity factor**
- **determines the estimated BG drop per 1.0 unit of insulin**

Davidson PC, *The Insulin Pump Therapy Book: Insights from the Experts* 1995, 59-71.

Glucose Correction Factor

1500 Rule says:

John Smith is on:

- **36 units insulin/day**
- **1500/36= 40**
- **1 unit lowers BG 40 mg/dl**

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**

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

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

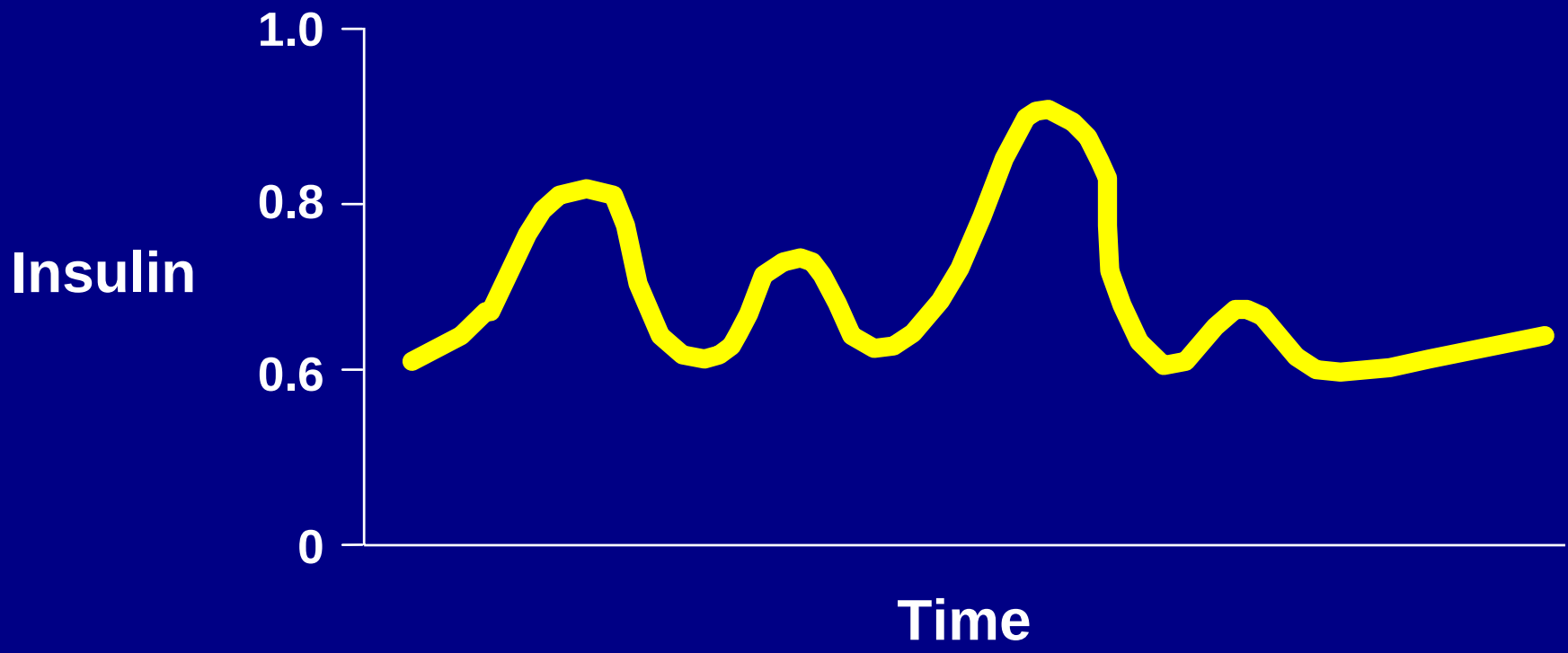
- Careful balance of food, activity, and insulin
- Daily self-monitoring BG
- Patient trained to vary insulin and food
- Define target BG levels (individualized)
- Frequent contact of patient and diabetes team
- Monitoring HbA_{1c}
- Basal / Bolus insulin regimen

Options in Insulin Therapy

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

Multiple Injection Therapy

Intermediate & Short-Acting Insulin Pre-Meal



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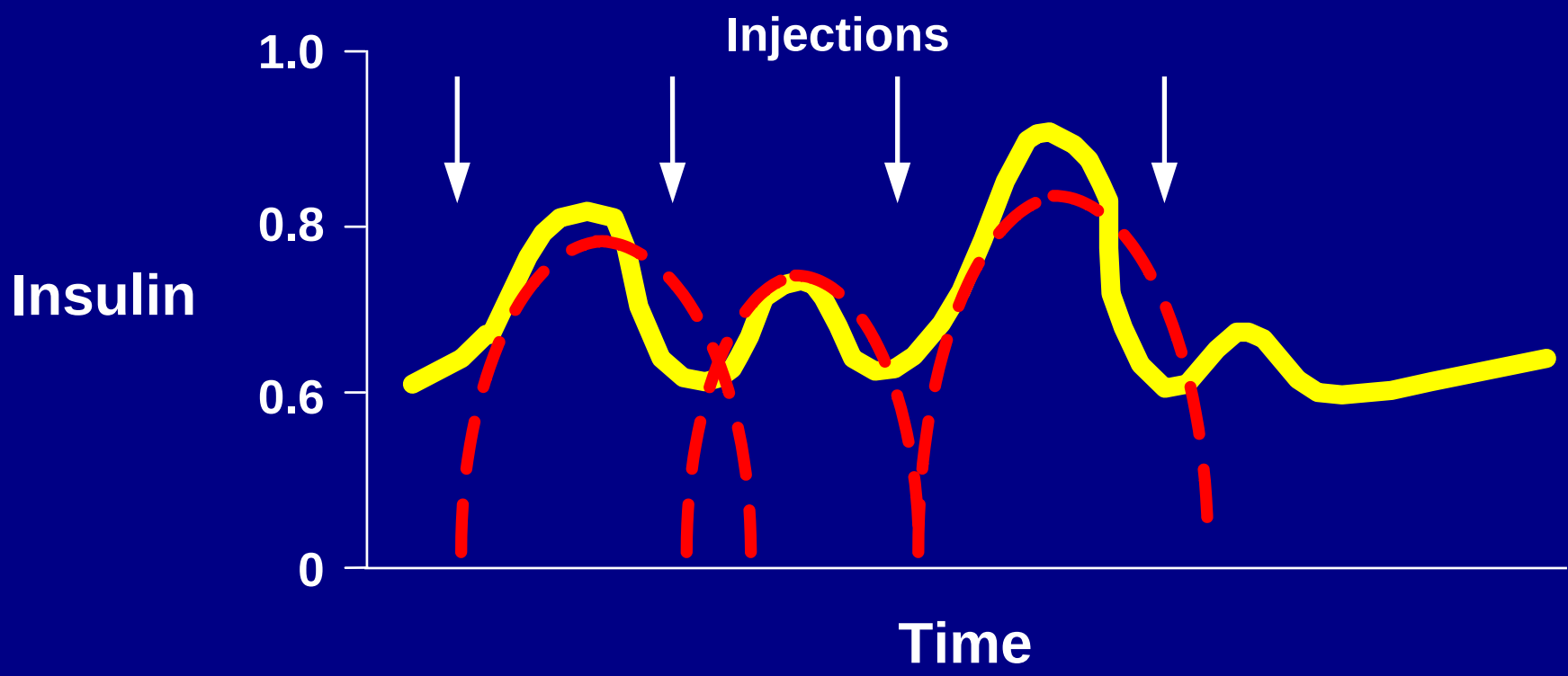

Multiple Injection Therapy

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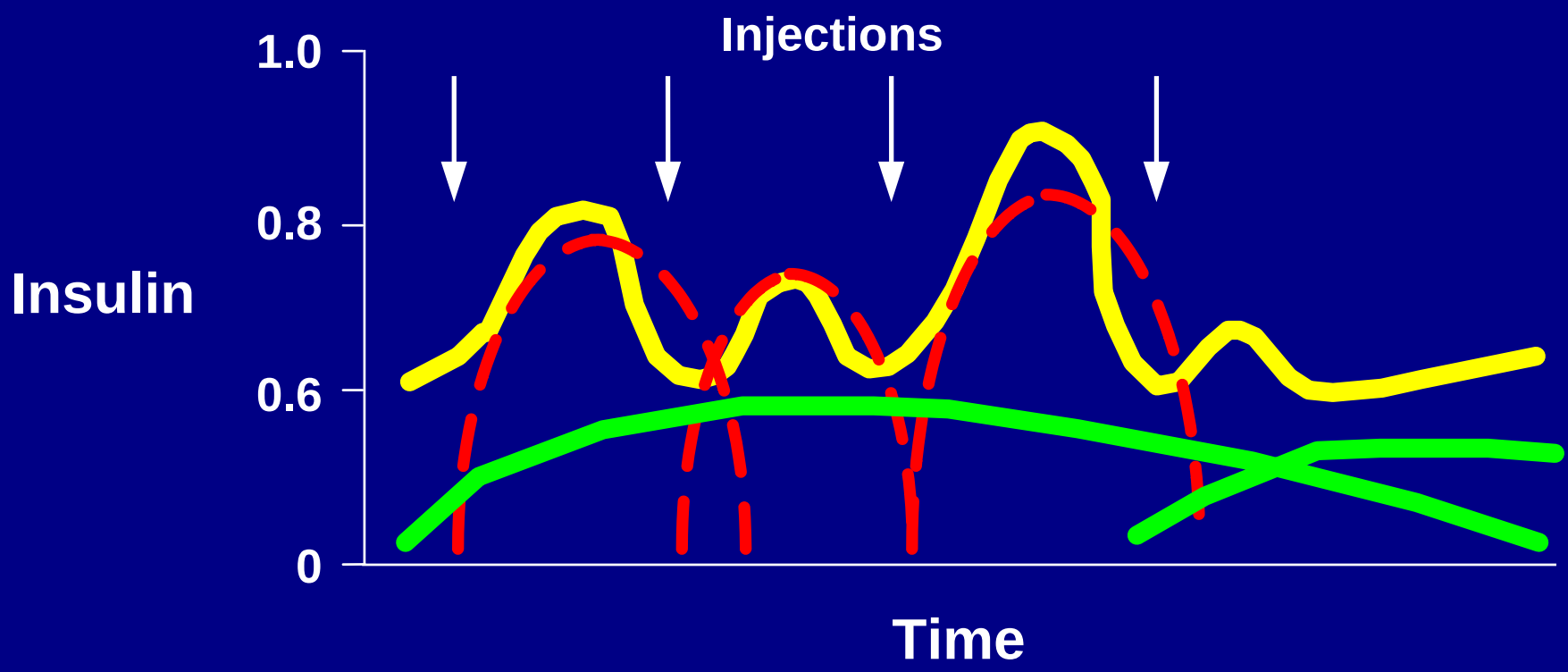


Case #2: DM 1 on MDI

- 46 year old white male power line supervisor
- DM 1 age 40
- On MDI: 10 u lispro pre-meal, 20 u NPH HS
- HbA1c 7.4%
- SMBG avg 124 mg/dL based on 1.9 tests/day (fasting 171 mg/dL, noon 105 mg/dL, pm 125 mg/dL, HS 75 mg/dL)

Case #2: DM 1 on MDI

- Lantus (glargine) 20 u HS added in place of NPH
- No change in behavior (diet, SMBG frequency)
- Seen three months later (8-16-01)
- HbA1c 6.3%
- SMBG average 104 mg/dL (fasting BG 91 mg/dL, noon 126 mg/dL, pm 116 mg/dL, HS 126 mg/dL
- NO HYPOGLYCEMIA
- HAPPY

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

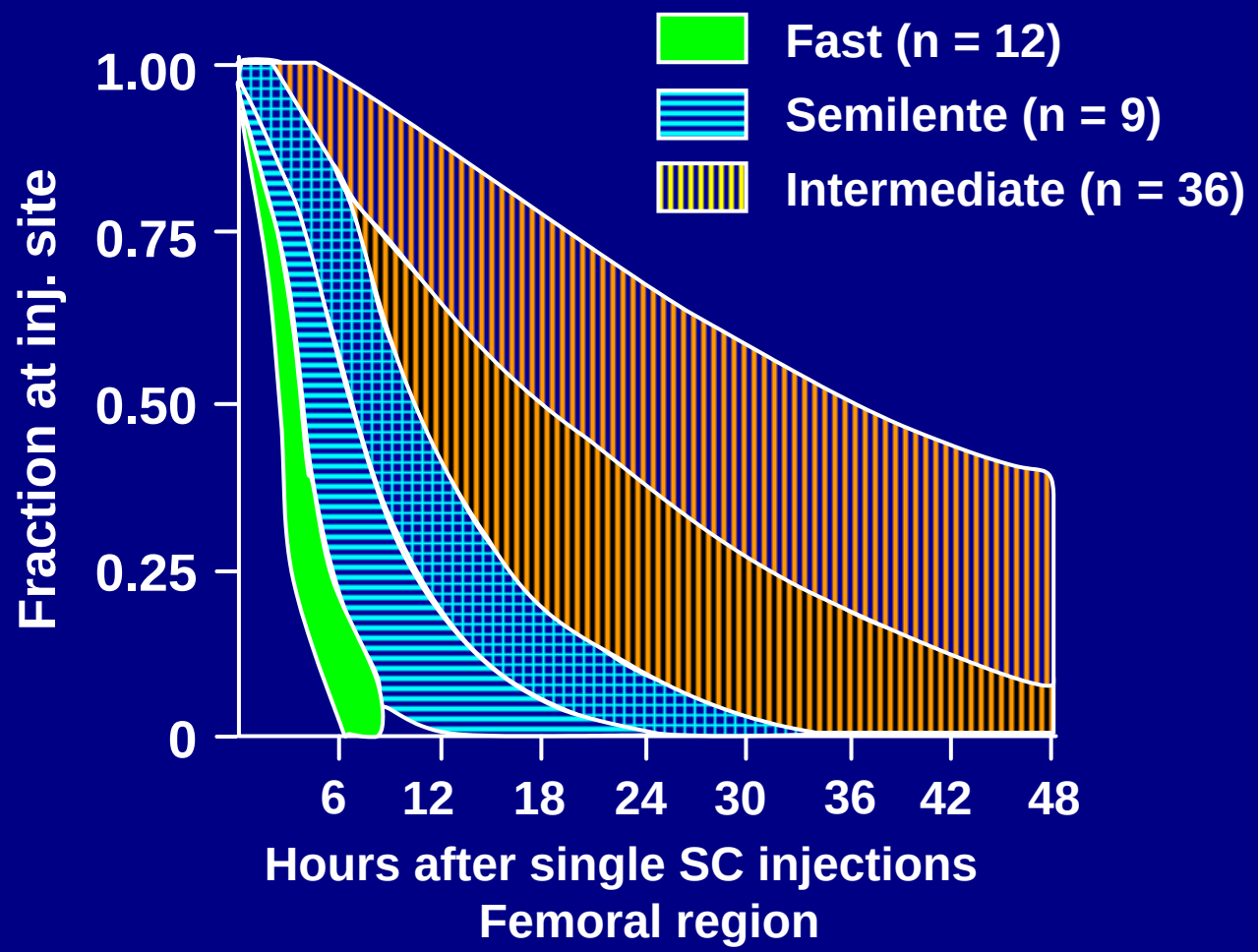
Benefit

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

Variability of Insulin Absorption

CSII <2.8%

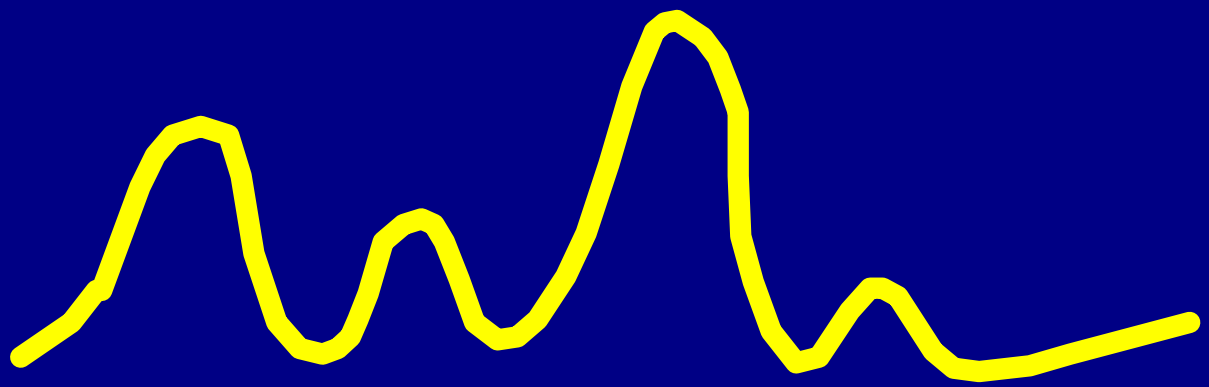
Subcutaneous Injectable 10% to 52%



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

Pump Therapy

Basal & Bolus Short-Acting Insulin



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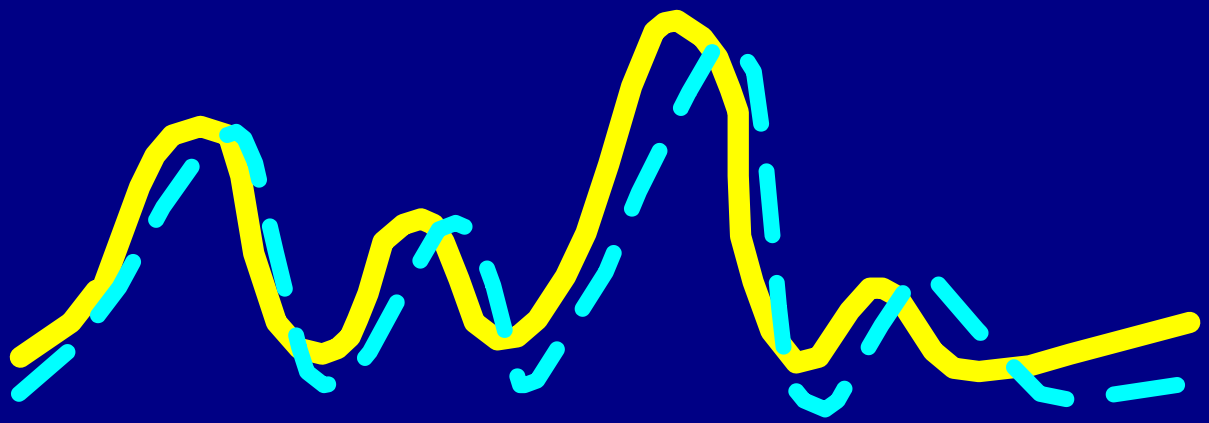

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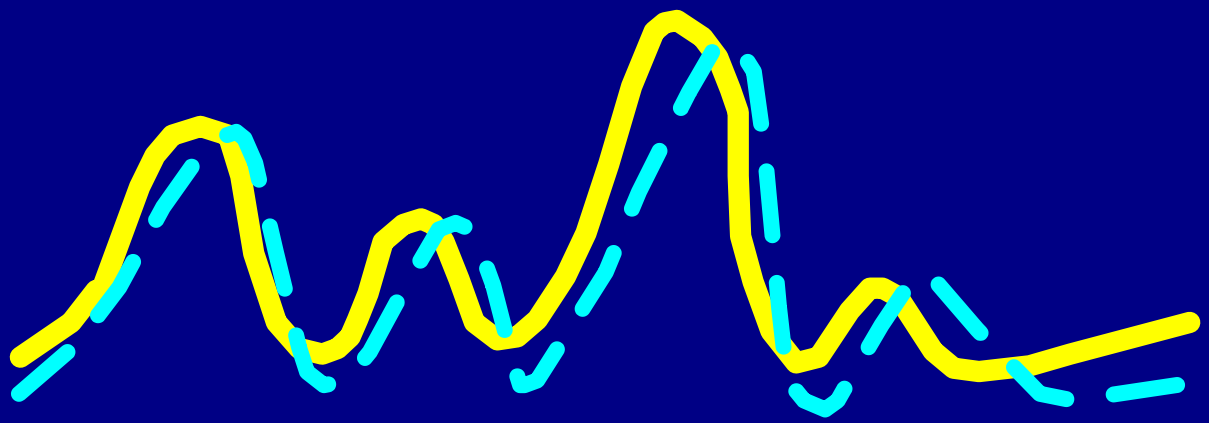


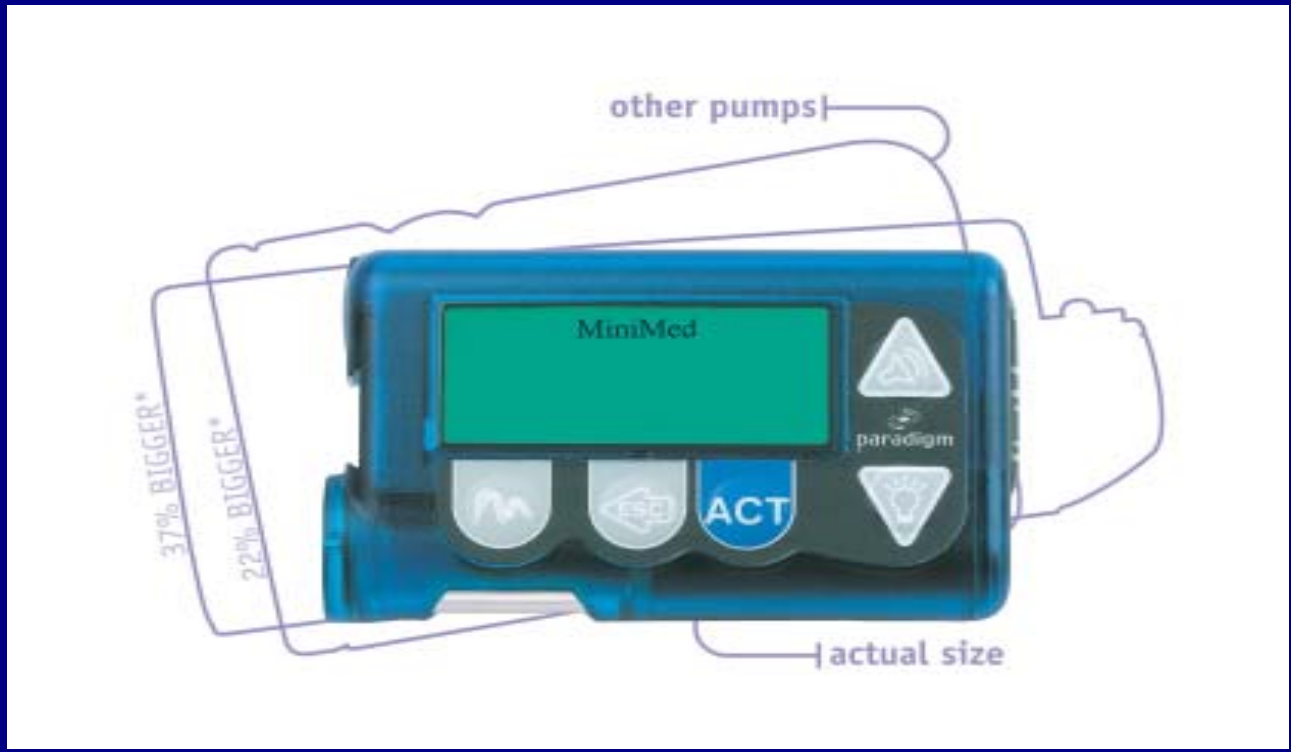
- Combined with SMBG, physiologic insulin requirements can be achieved more closely
- Flexibility in lifestyle

History of Pumps


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

Paradigm Pump

PARADIGM PUMP



Paradigm.
Simple. Easy.

Paradigm Pump: Advantages

- 29% smaller, water resistant
- Menu driven:

  bolus, suspend, basal, prime, utilities
- Reservoir based (easier to fill)
- Silent motor
- AAA batteries

Paradigm Pump: Advantages

- Various bolus options

  normal, square, dual, and “easy bolus”

- Enhanced memory
- Enhanced safety features

  (low reservoir alarm, auto off, etc.)

Pump Infusion Sets

Softset QR

Silhouette

Pharmacokinetic Advantages
CSII vs MDI

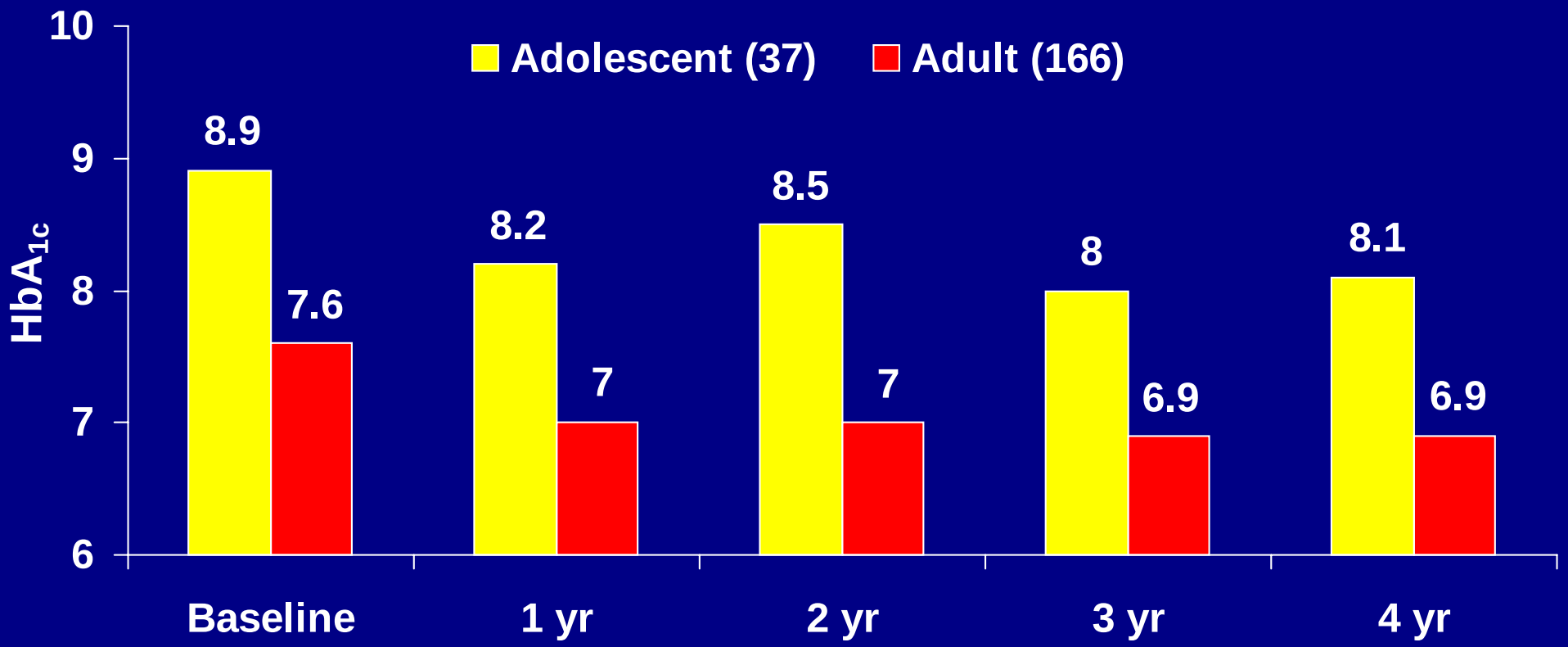
- Uses only regular or very rapid insulin
  - More predictable absorption than modified insulins (variation 3% vs 52%)
- Uses 1 injection site
  - Reduces variations in absorption due to site rotation
- Eliminates most of the subcutaneous insulin depot
- Programmable delivery simulates normal pancreatic function

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

Metabolic Advantages with CSII

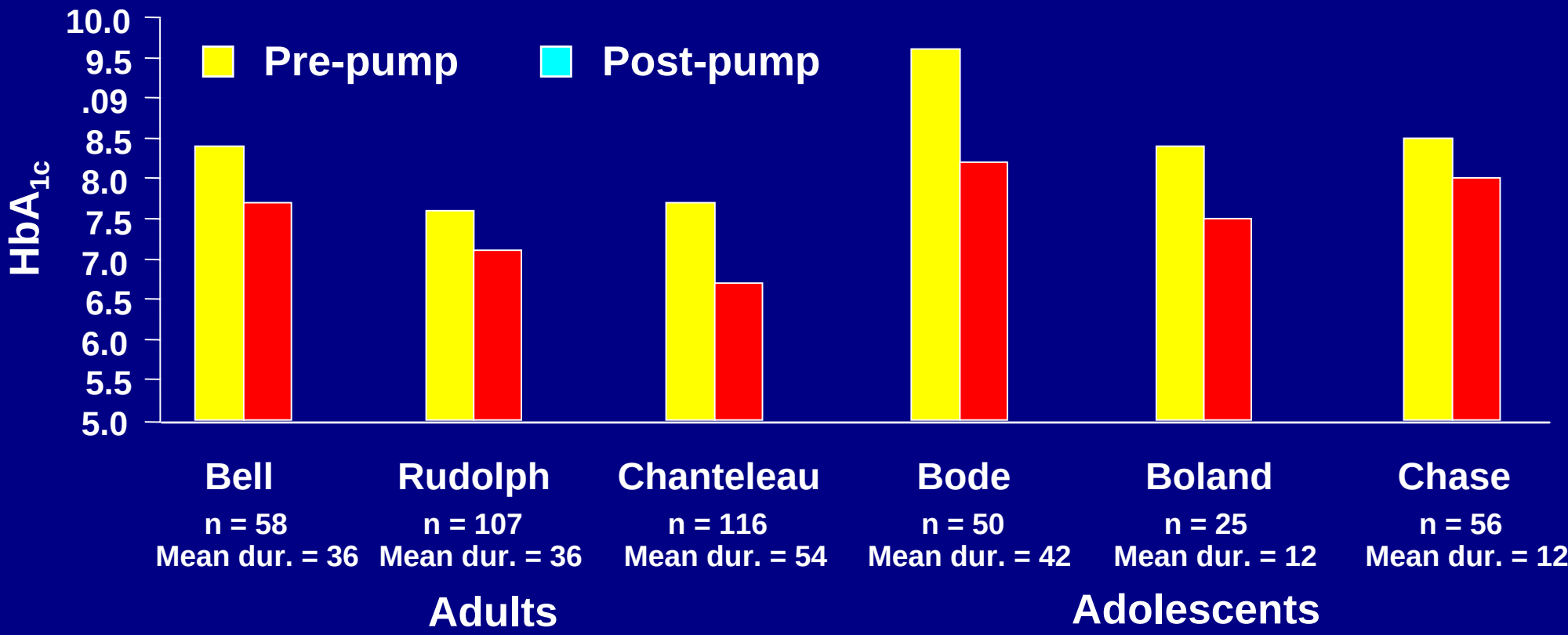
- Improved glycemic control
- Better pharmacokinetic delivery of insulin
  - Less hypoglycemia
  - Less insulin required
- Improved quality of life

Glycemic Control



Atlanta Diabetes Associates

CSII Reduces HbA_{1c}

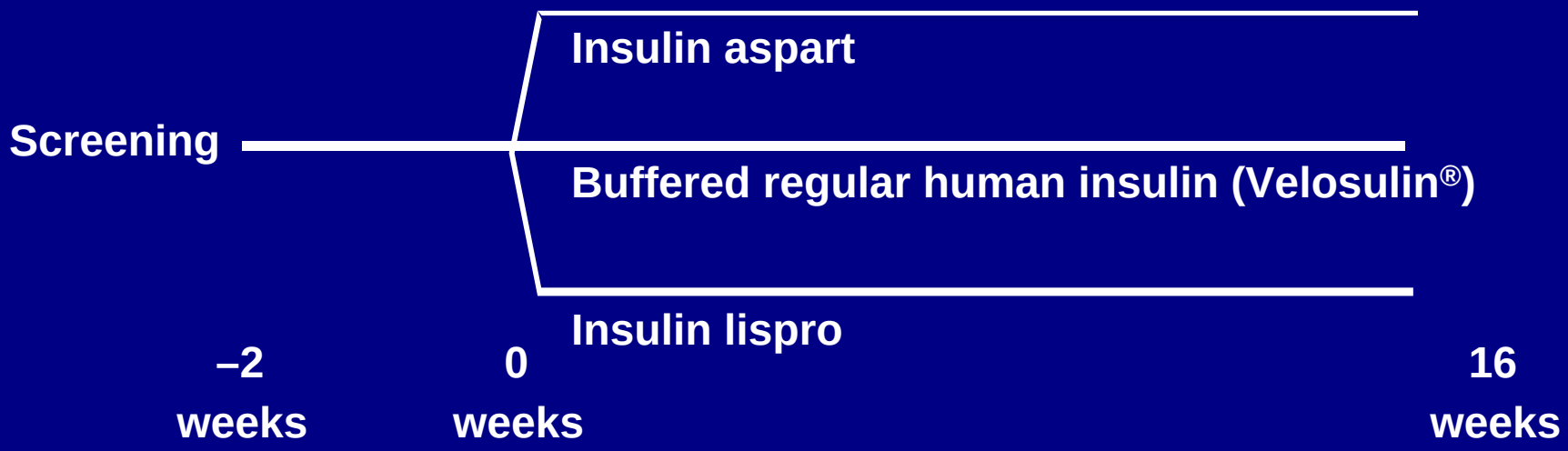


Chantelau E, et al. *Diabetologia*. 1989;32:421–426; Bode BW, et al. *Diabetes Care*. 1996;19:324–327; Boland EA, et al. *Diabetes Care*. 1999;22:1779–1784; Bell DSH, et al. *Endocrine Practice*. 2000;6:357–360; Chase HP, et al. *Pediatrics*. 2001;107:351–356.

CSII
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

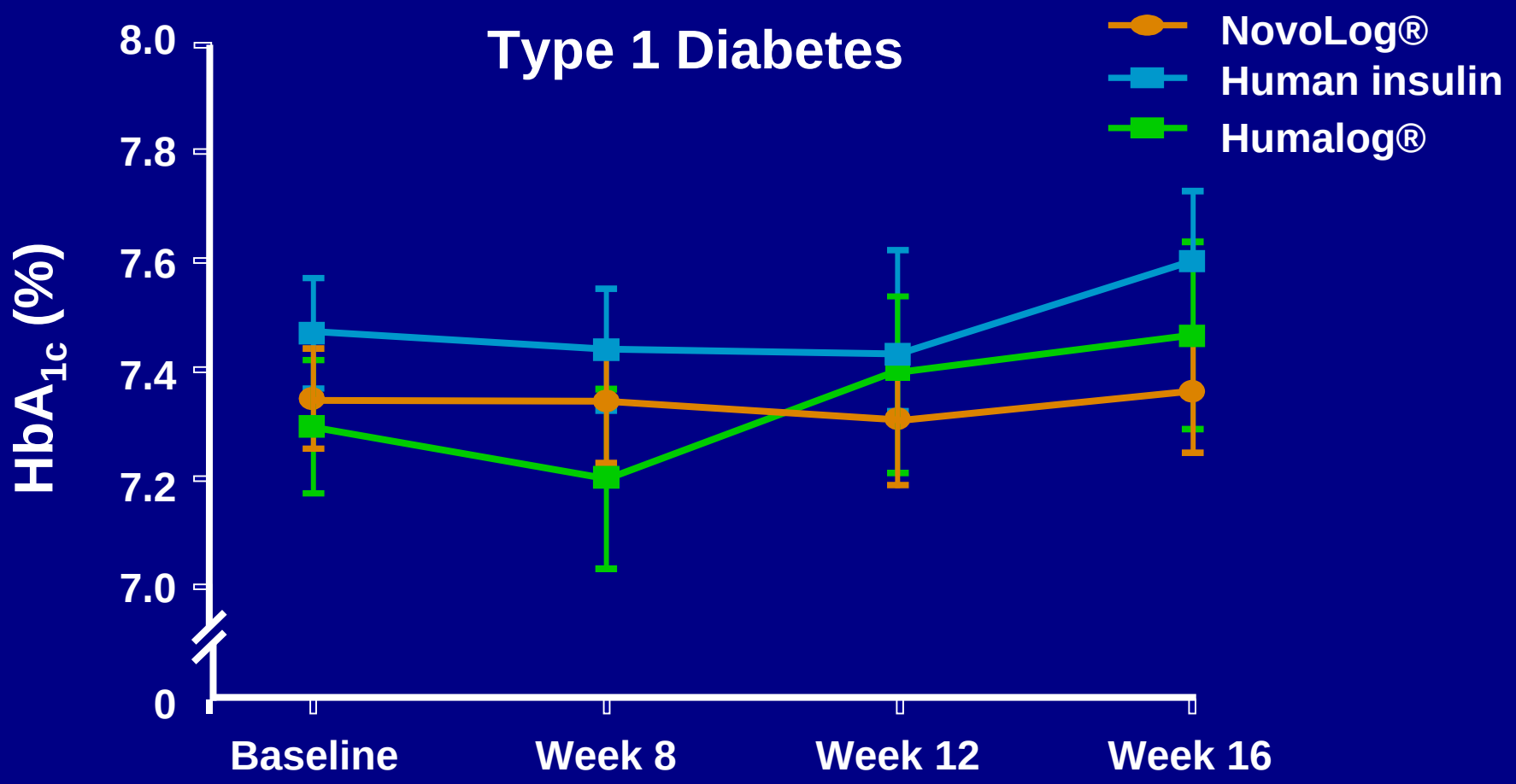
Insulin aspart versus buffered R *versus* insulin lispro in CSII study:



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

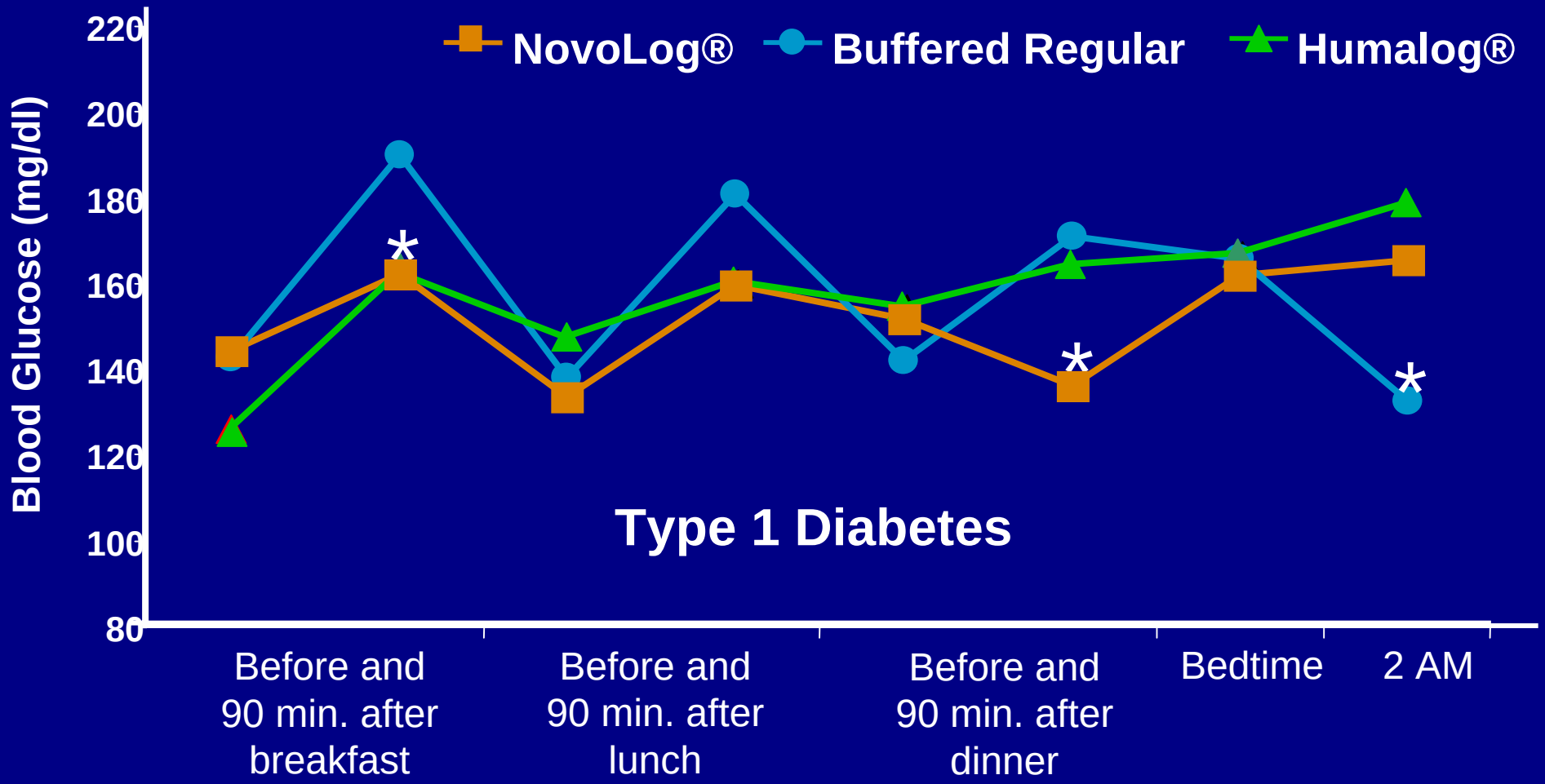
Bode et al: Diabetes Care, March 2002

Glycemic Control with CSII



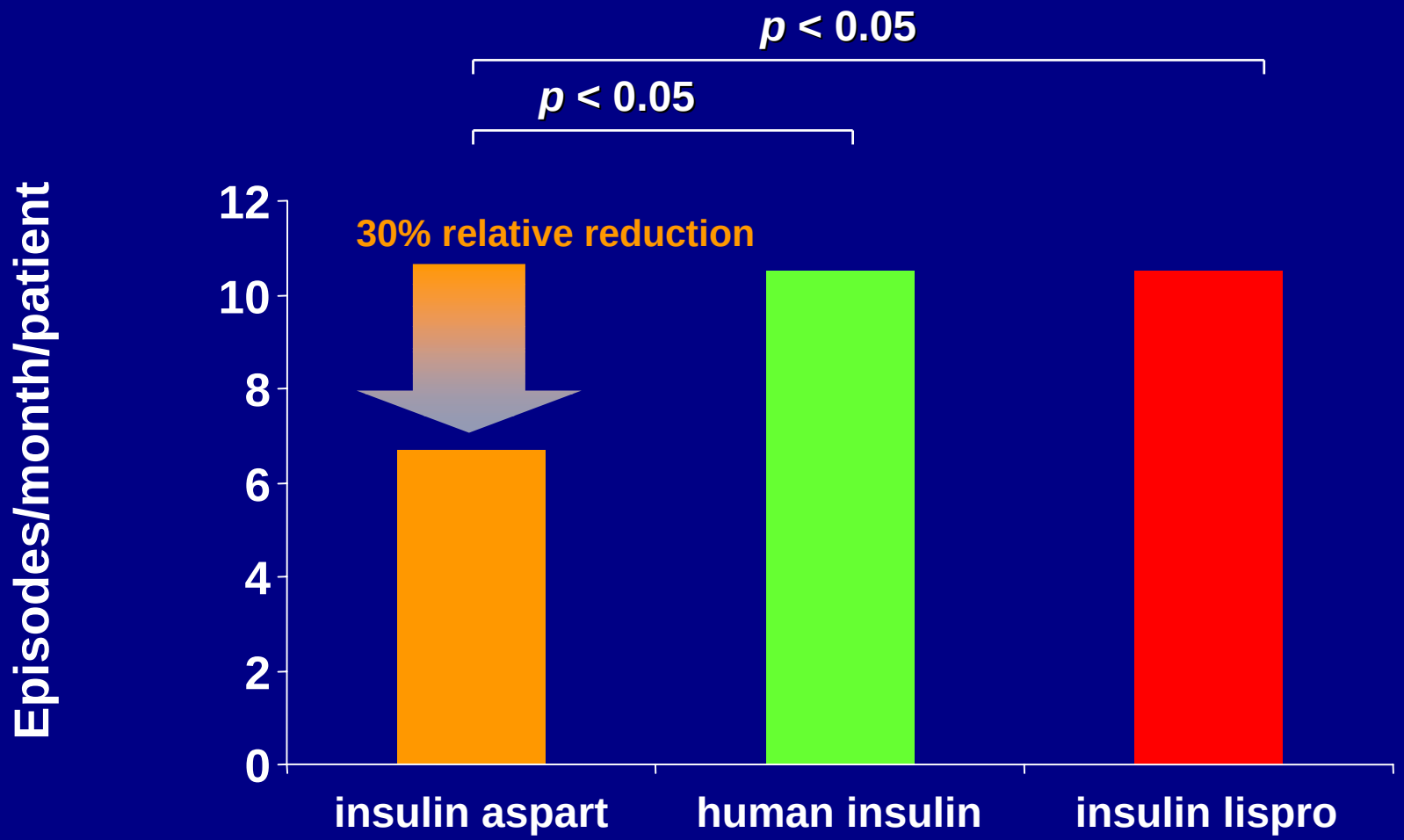
Bode, *Diabetes* 2001 ; 50(S2):A106

Self-Monitored Blood Glucose in CSII



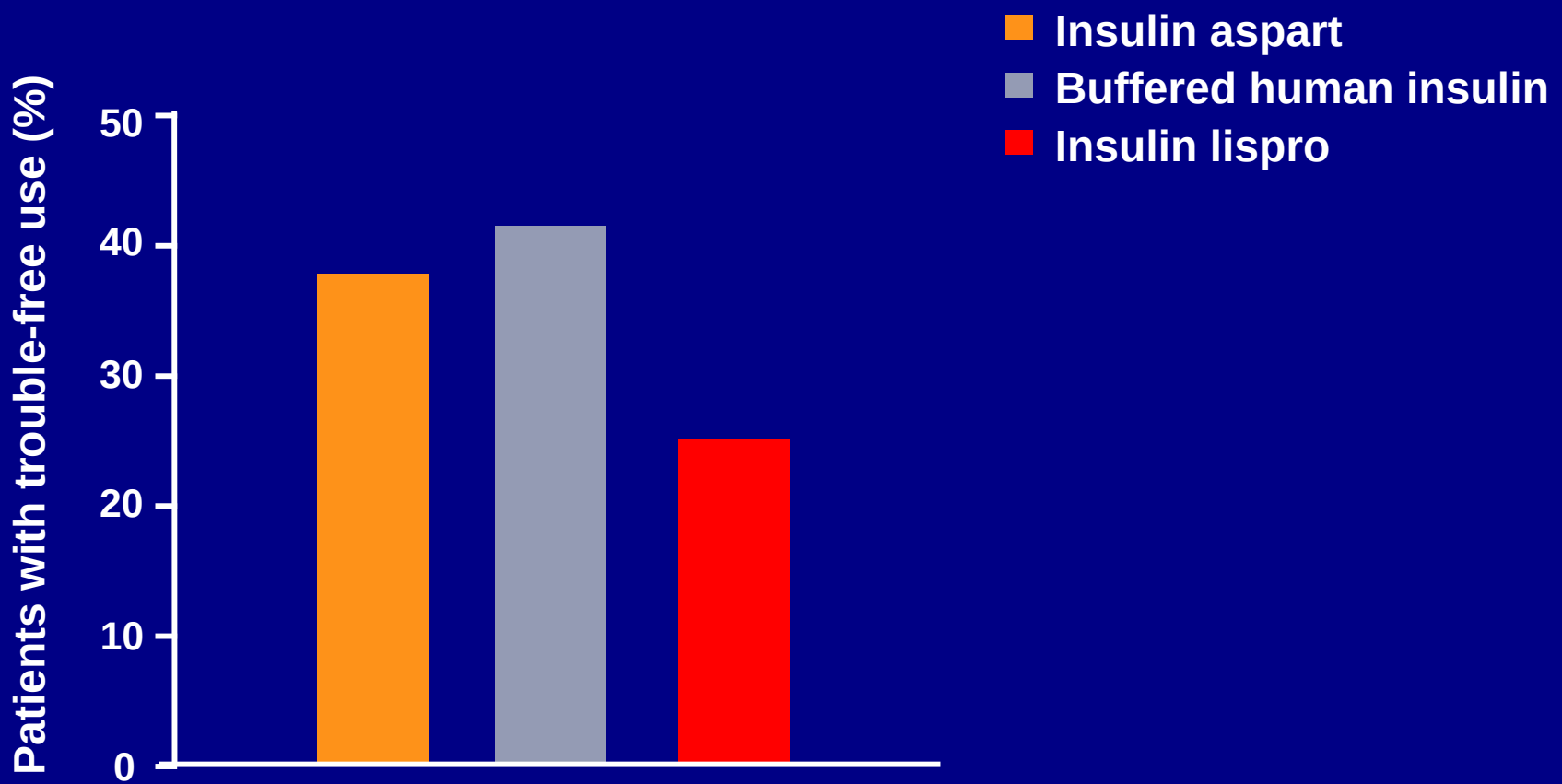
Bode, *Diabetes* 2001 ; 50(S2):A106

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)

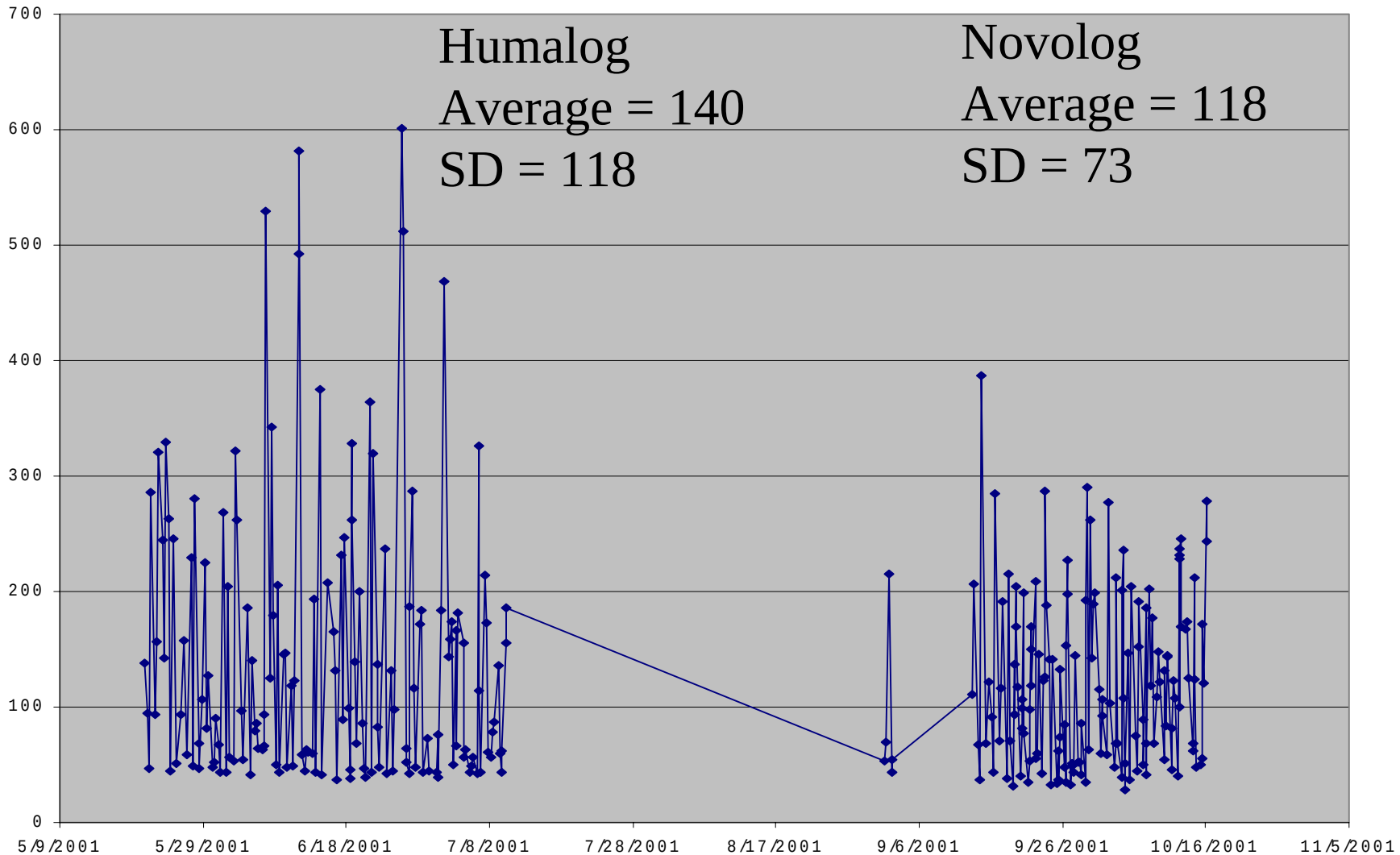
Case Study: 54 year old DM1 on CSII with Lipoatrophy and Insulin Antibodies

- 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

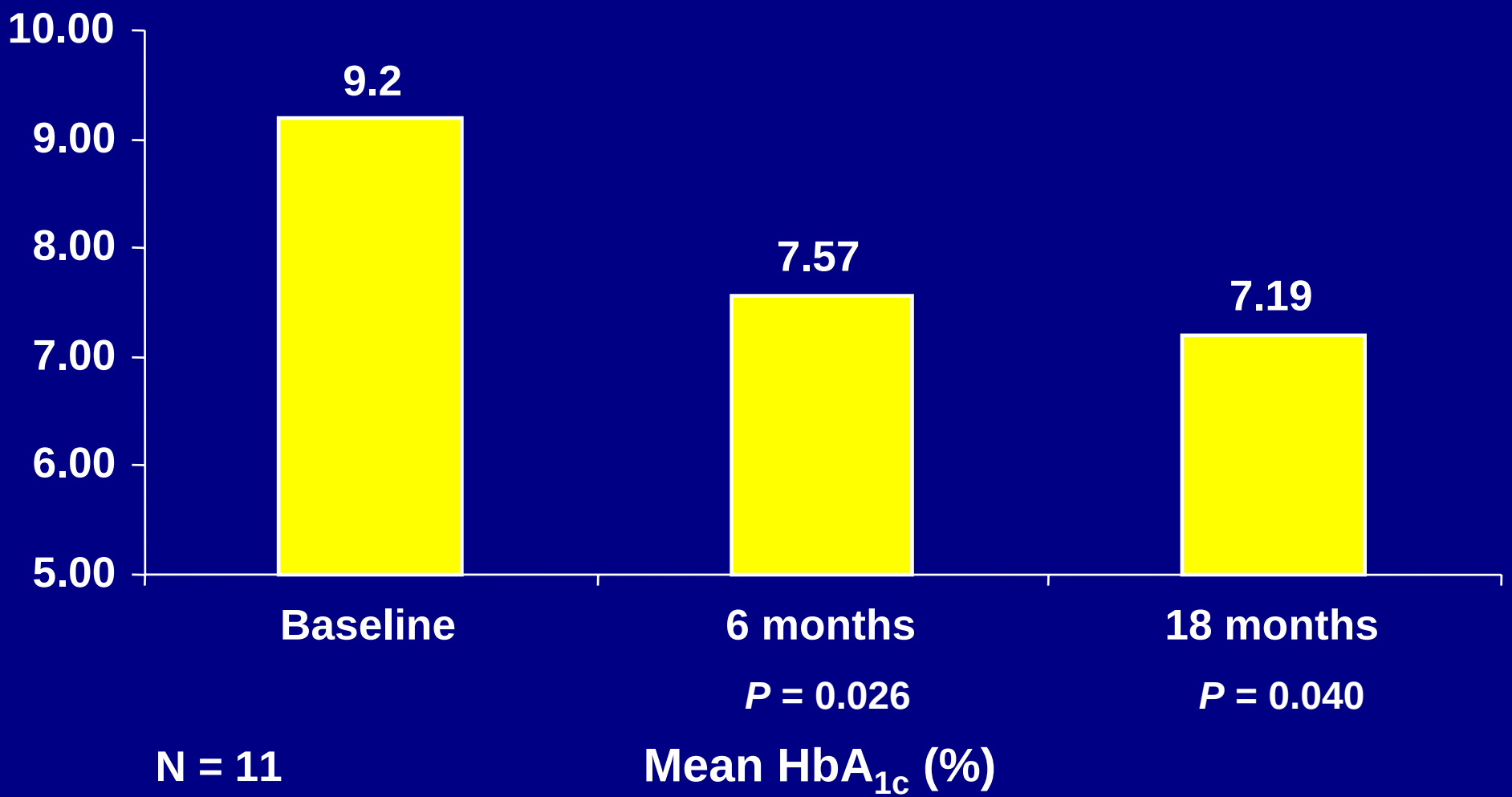


Case Study: 54 year old DM1 on CSII with Lipoatrophy and Insulin Antibodies

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

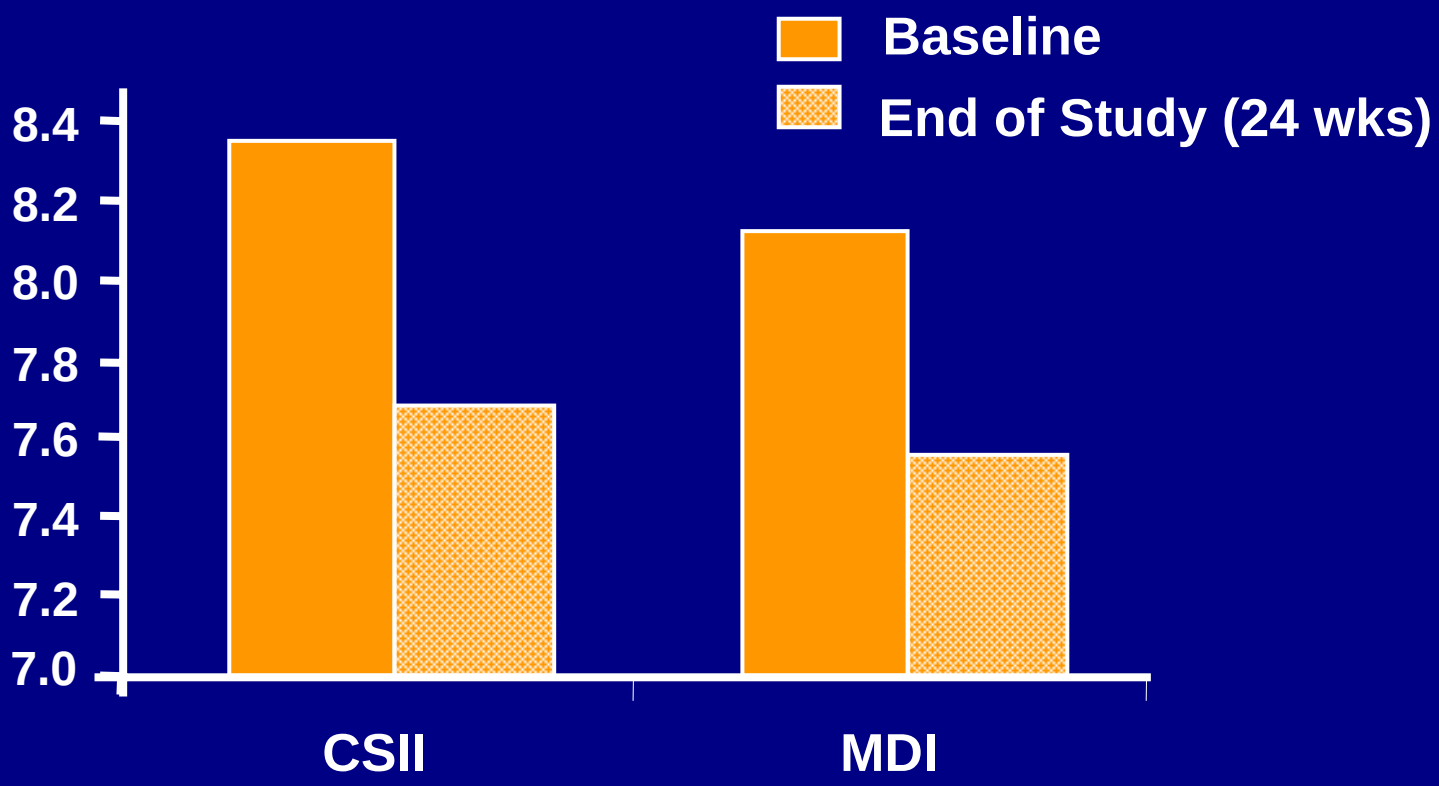
CSII Usage in Type 2 Patients

Atlanta Diabetes Experience



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

- A1C

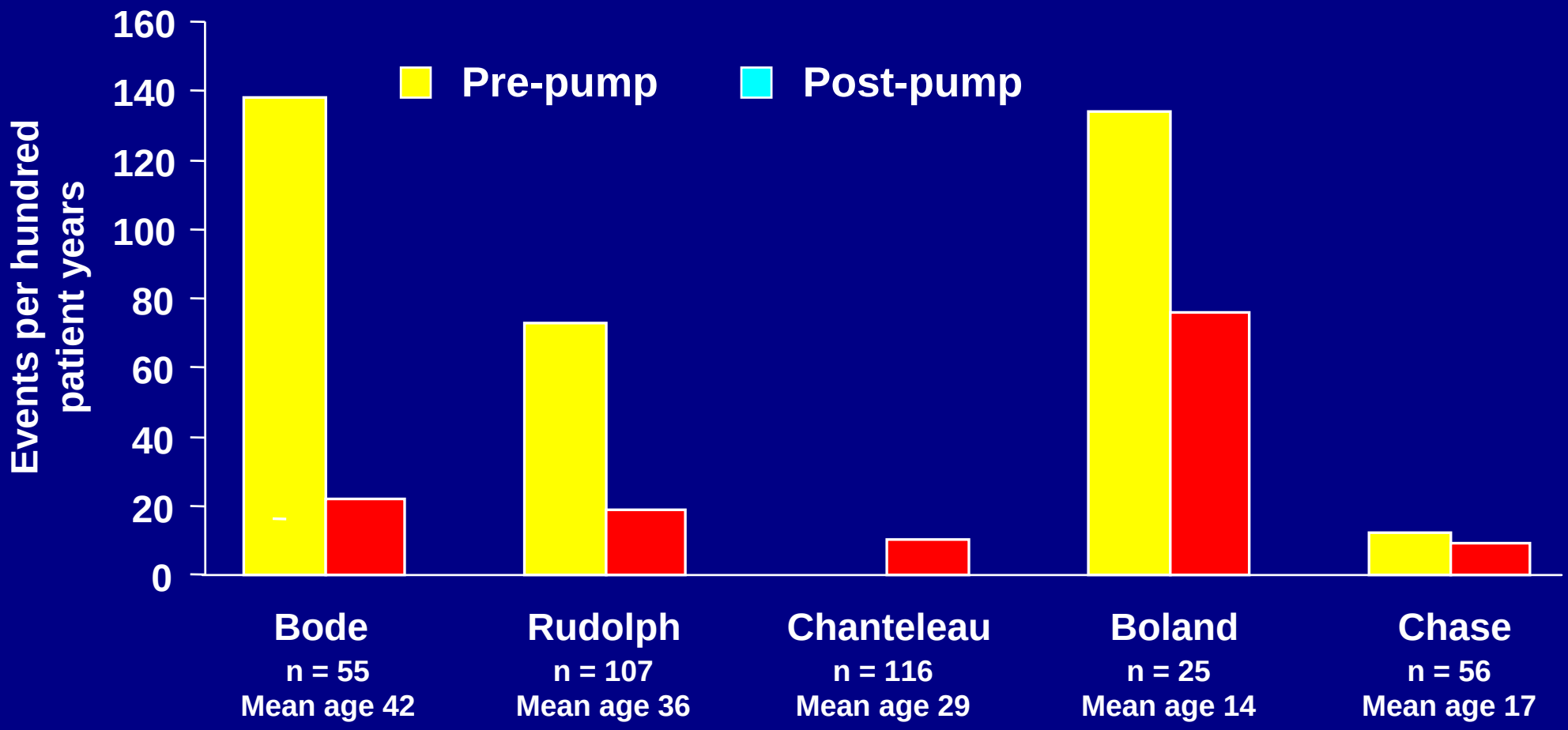


Raskin, *Diabetes* 2001; 50(S2):A106

DM 2 Study: CSII vs MDI

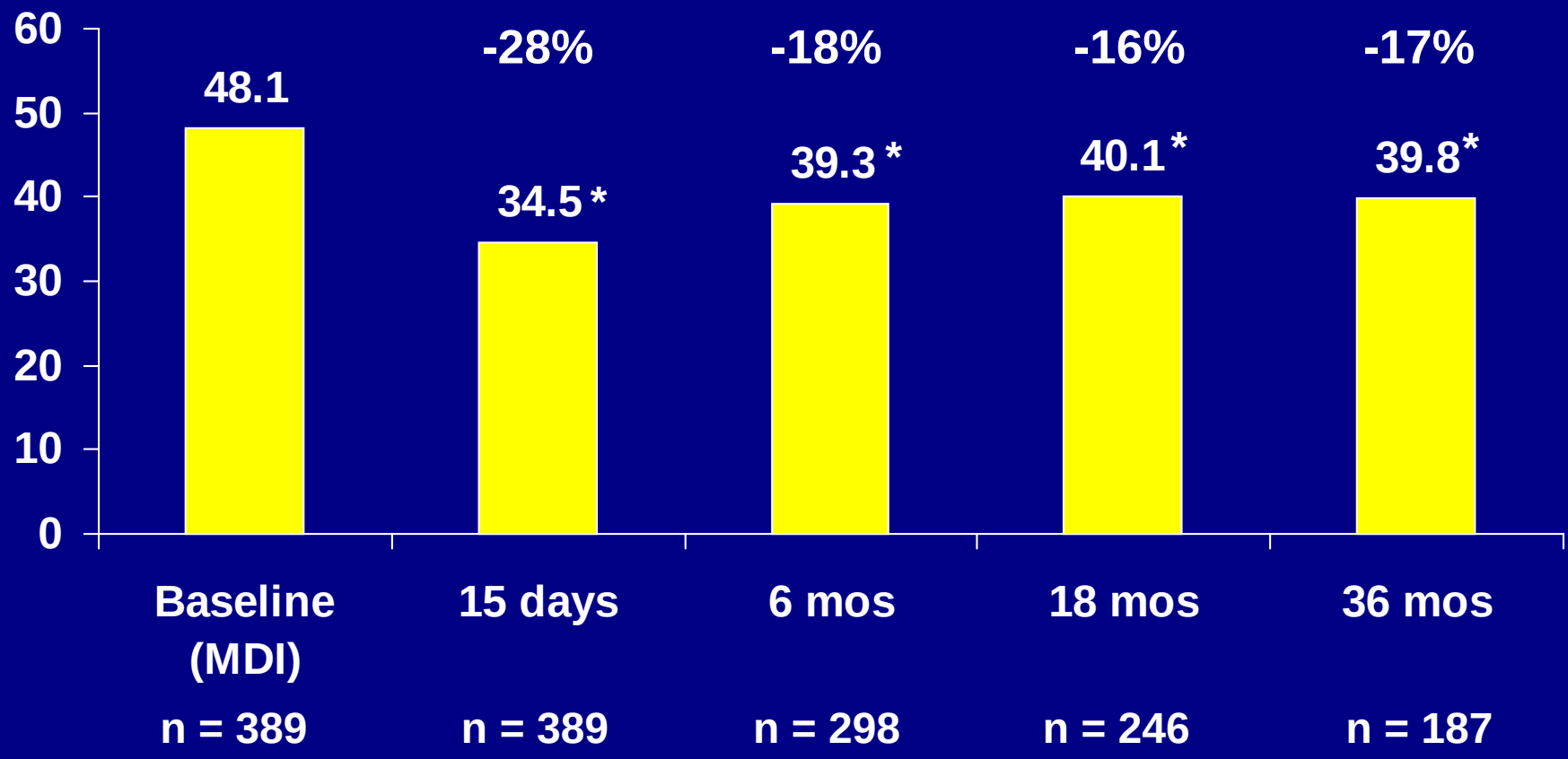
- Overall treatment satisfaction improved in the CSII group: 59% pre to 79% at 24 weeks
- 93% in the CSII group preferred the pump to their prior regiment (insulin +/- OHA)
- CSII group had less hyperglycemic episodes (3 subjects, 6 episodes vs. 11 subjects, 26 episodes in the MDI group)

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.

Insulin Reduction Following CSII



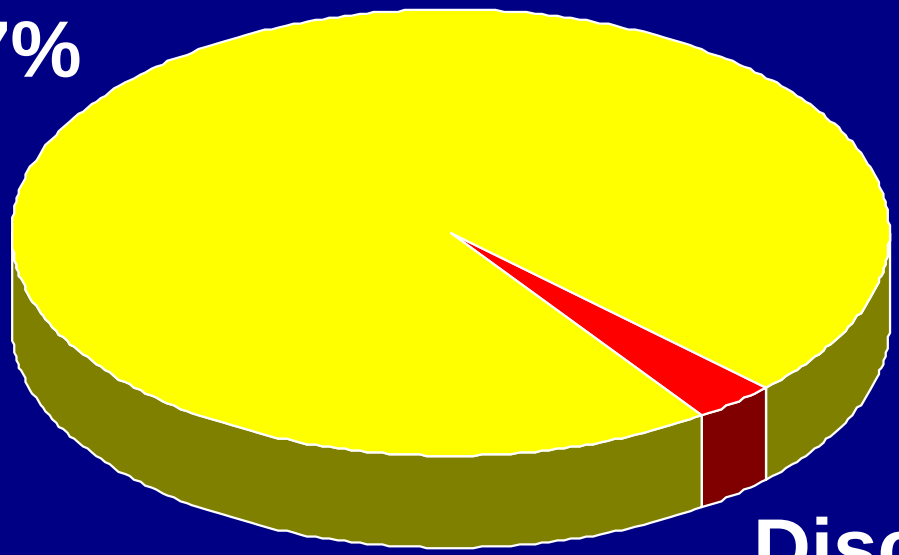
* *P* <0.001

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)

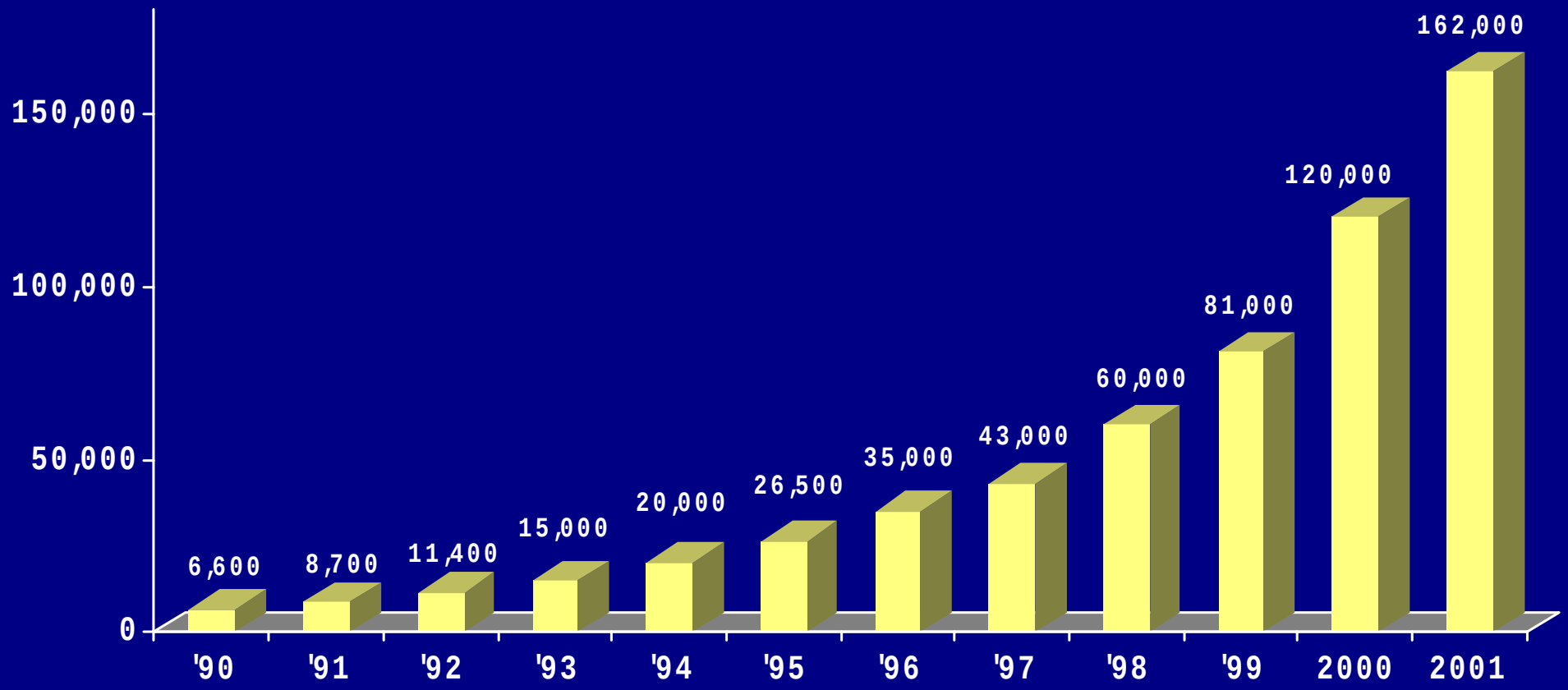


N = 165
Average Duration = 3.6 years
Average Discontinuation <1%/yr

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

Current Candidate Selection

Patient Requirements

- Willing to monitor and record BG
- Motivated to take insulin
- Willing to quantify food intake
- Willing to follow-up
- Interested in extending life

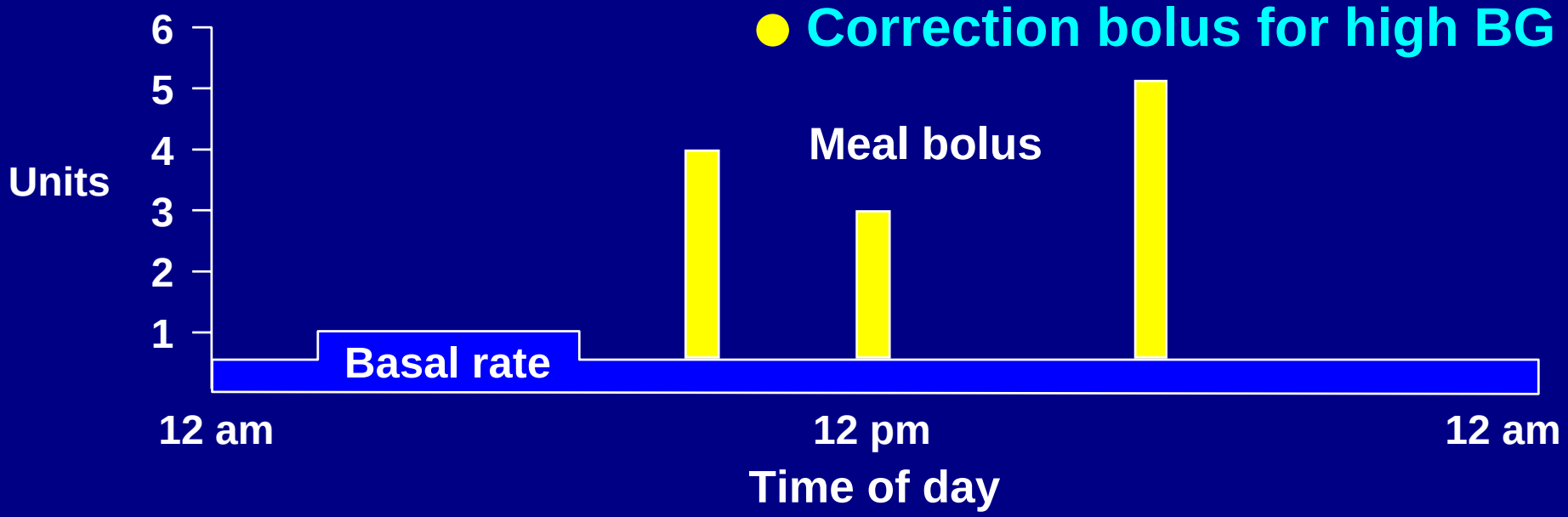
Pump Therapy

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



What Type of Bolus Should You Give?

- 9 DM 1 patients on CSII ate pizza and coke on four consecutive Saturdays
- Dual wave bolus (70% at meal, 30% as 2-h square):

  9 mg/dl glucose rise
- Single bolus: 33 mg/dl rise
- Double bolus at -10 and 90 min: 66 mg/dl rise
- Square wave bolus over 2 hours: 80 mg/dl rise

Chase et al, Diabetes June 2001 #365

Treatment of Hypoglycemia

- Education
  - Glucose tablets
  - Glucagon
- Call healthcare team
  - Any hypoglycemic events requiring assistance

Treatment of Hyperglycemia

- If blood glucose is above 250 mg/dl
  - Take a correction bolus by pump
  - Check BG again in 1 hr
- If still above 250 mg/dl
  - Take correction bolus by syringe
  - Change infusion set and reservoir
  - Check BG again in 1 hr
- If BG has not decreased
  - Increase correction bolus by syringe
  - CALL PHYSICIAN

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

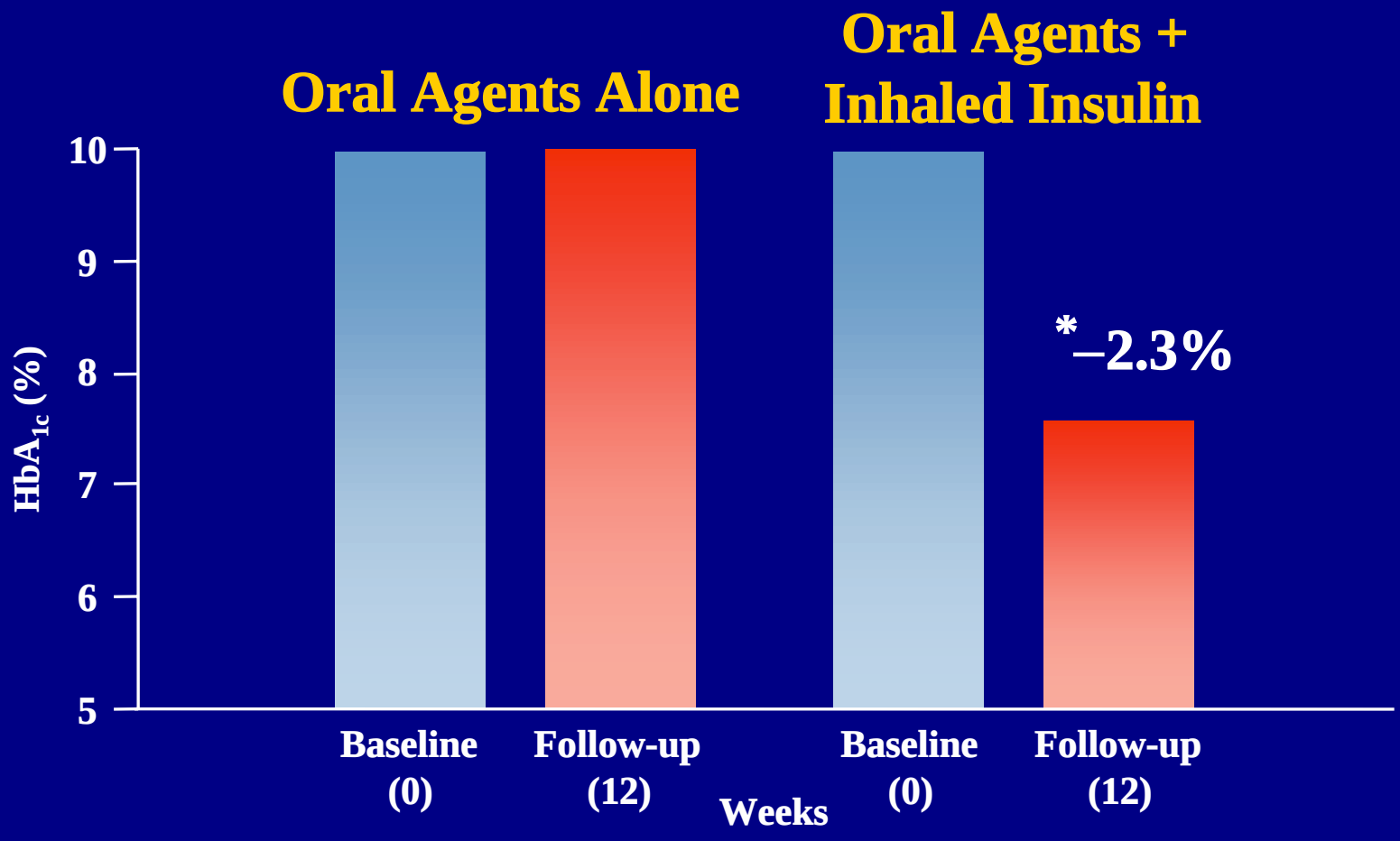
Future of Diabetes Management

Improvements in Insulin & Delivery

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

Pulmonary Insulin

Oral Agents + Mealtime Inhaled Insulin
Effect on HbA_{1c}



**P* < .001

Weiss, et al. *Diabetes*. 1999;48(suppl 1):A12.

Categories of Glucose Monitoring

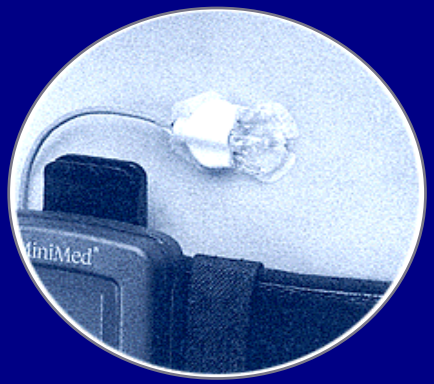
- Non-invasive
  - Near Infrared Spectroscopy (NIR)
- Minimally-invasive (ISF)
  - Micropore sampling
  - Iontophoresis
  - Subcutaneous sensors

Cygnus GlucoWatch

- Watch Component
- Electrode Component
- Initial calibration takes 3 hours
- Senses glucose and gives an average every 20 minutes up to 12 hours *(r = 0.80 home use)*
- Alarm for high, low and rapidly dropping blood sugars
- Indicated for 18 years and older

Cygnus GlucoWatch

GLUCOSE MONITORING SYSTEMS - EXTERNAL



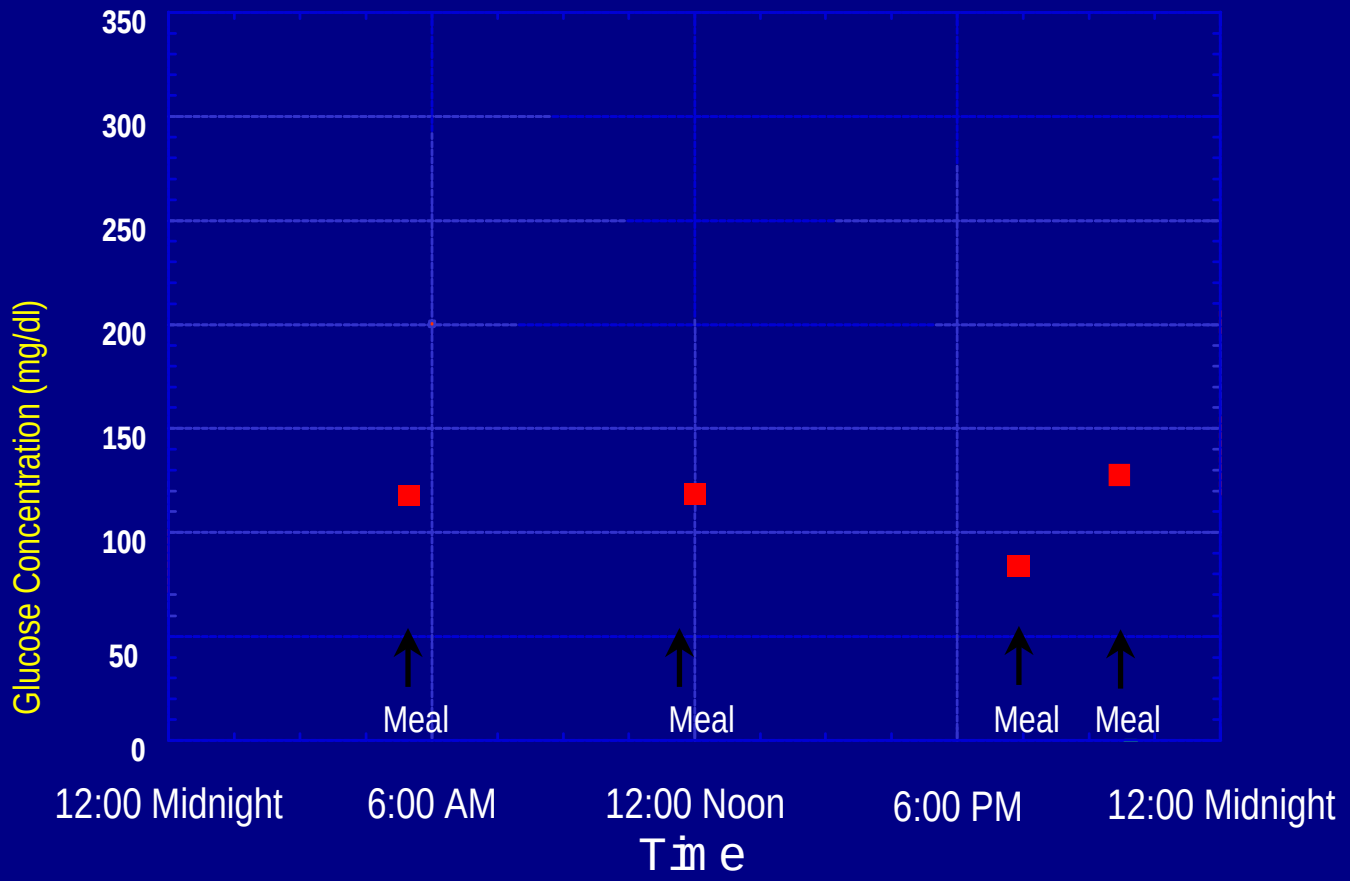
Physician Product

- Physician downloads data for retrospective analysis
- Com-Station and software packages combine data from:
  - Sensor
  - Models 508 and 507C insulin pumps
  - Traditional glucose meters

Glucose Profiles

Patient with Type 1 Diabetes

- **Practicing MDI**
- **HbA_{1C} of 8.5%**
- **Complications of High BG**
  - **Renal**
  - **Retinal**
  - **Neural**



Glucose Profiles

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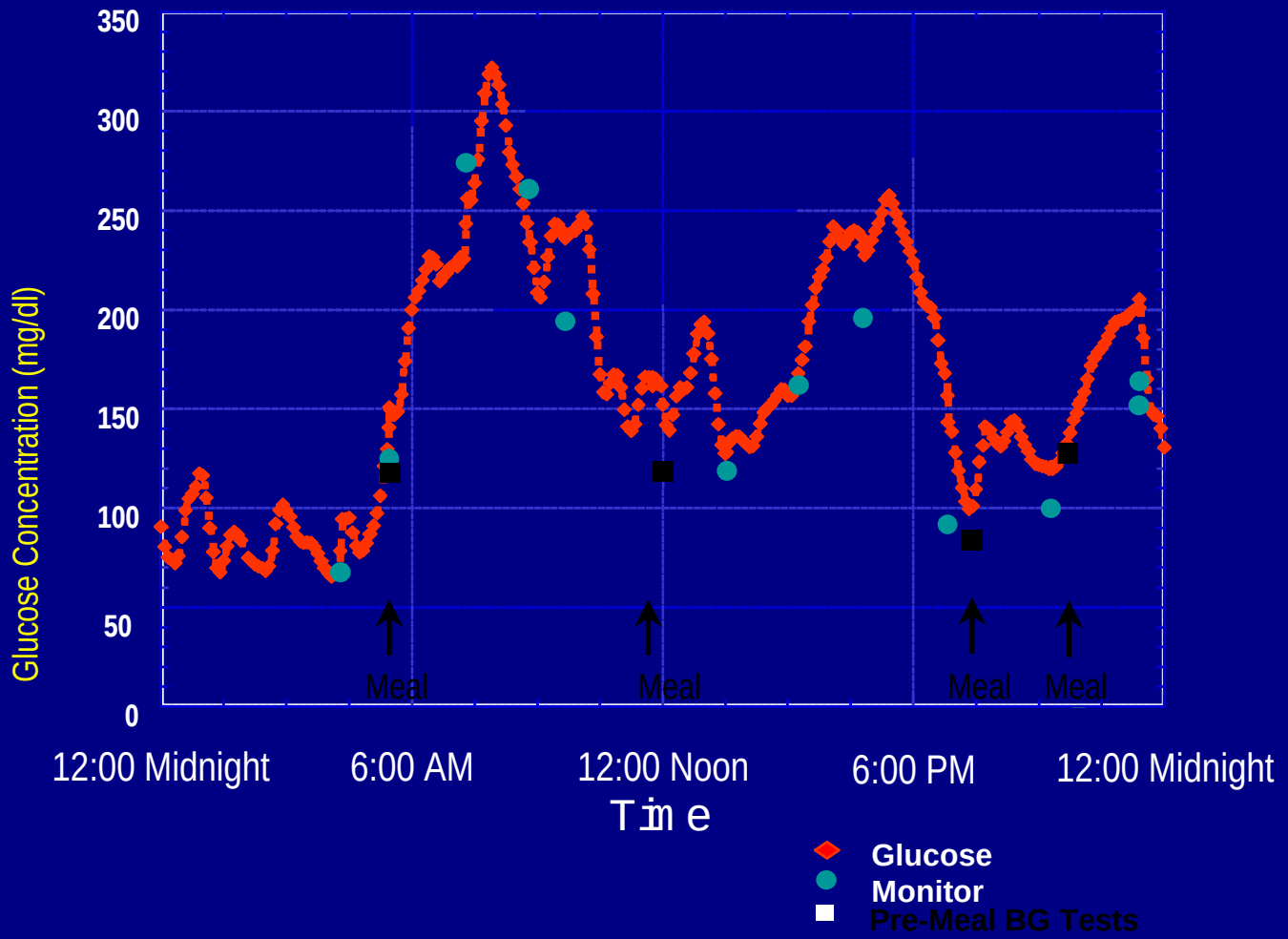


New CGMS Software 2-26-02

- Running 24 hour calibration: no 12 am shift
- Slope 2 to 12 ok: less disconnected graphs
- Improved algorithm: less noise
- Improved analysis and printouts: easier to interpret and provide feedback

Other CGMS Updates 2-27-02

- Improved quality of sensors (change in manufacturing ingredient)
- Increased reimbursement for Medicare CPT Code 95250: doubled from $52 to $109

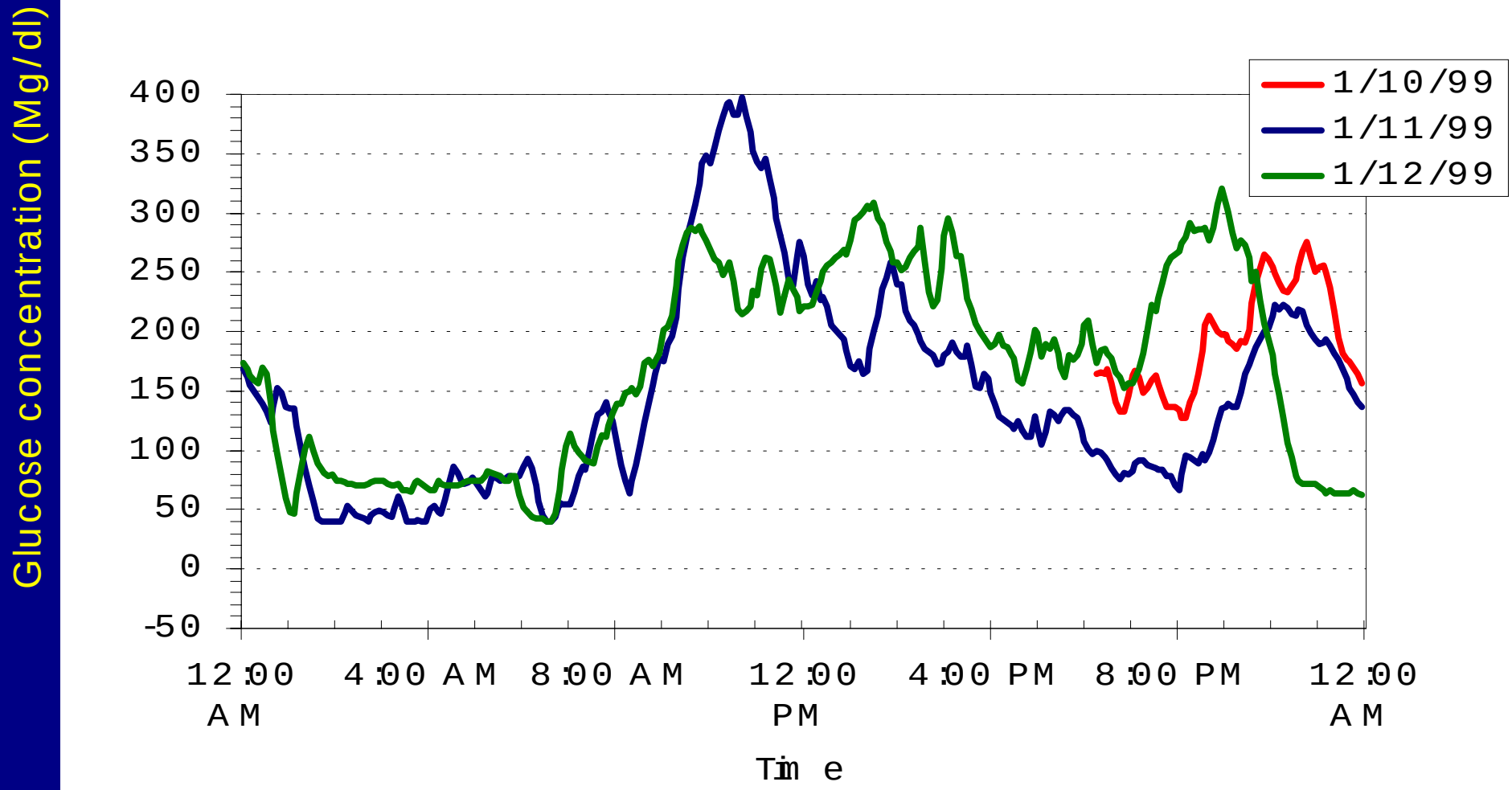
History

- 70 Year-old white male
- Type 2 DM, 15 years
- Current Treatment:
  - Glucophage 500mg AM, 1000mg PM
  - Glynase 6mg BID
  - Rezulin 400mg QD

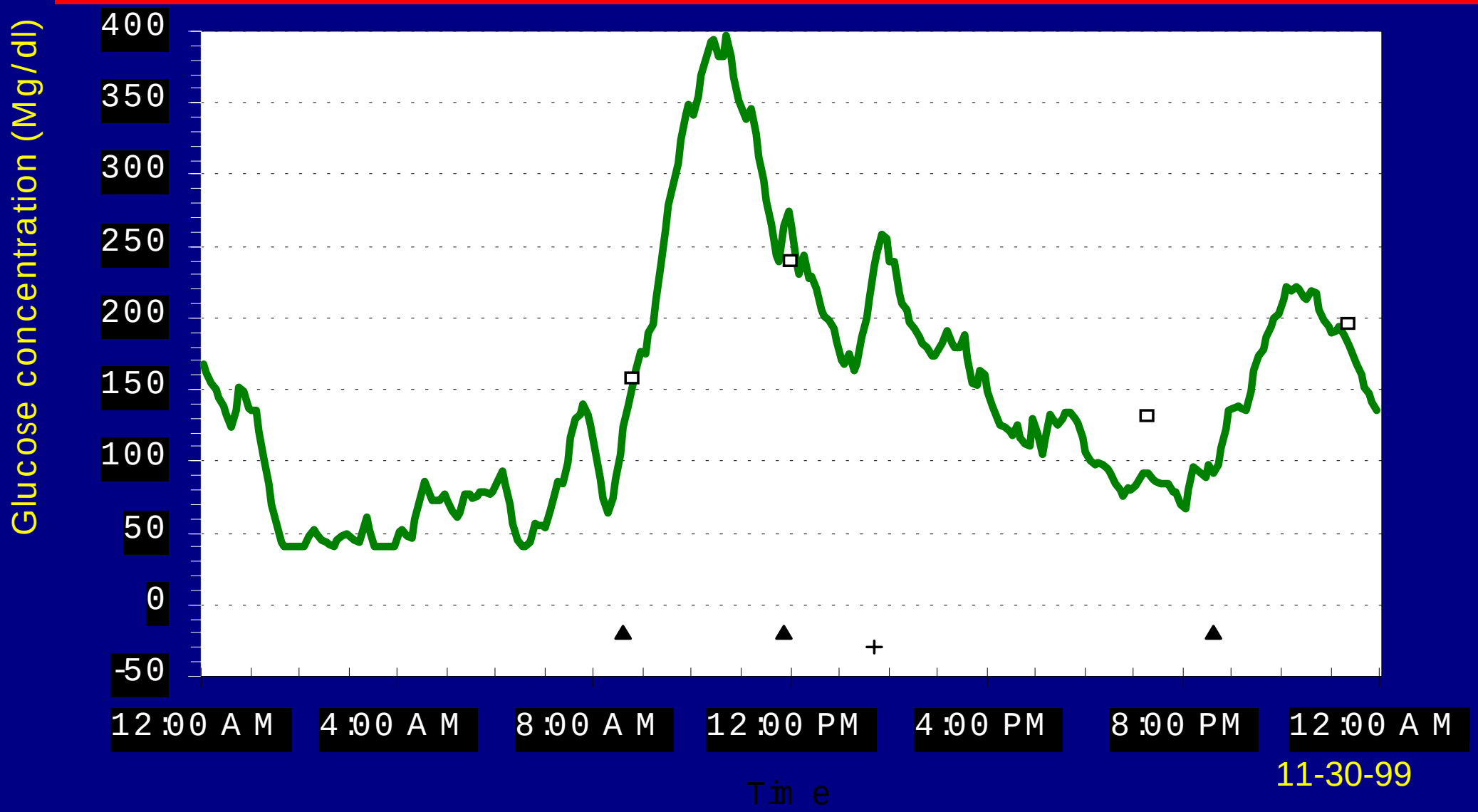
History

- HgA_{1c} increased to 8.0% from 6.5% 18 months earlier
- SMBG Average: 162 mg/dL
  - AM = 137
  - Noon = 199
  - PM = 151
  - HS = 188
- Ht= 73”; Wt= 180 lbs; BMI=23 kg/m2
- CGMS done to determine best course of treatment

Modal Day

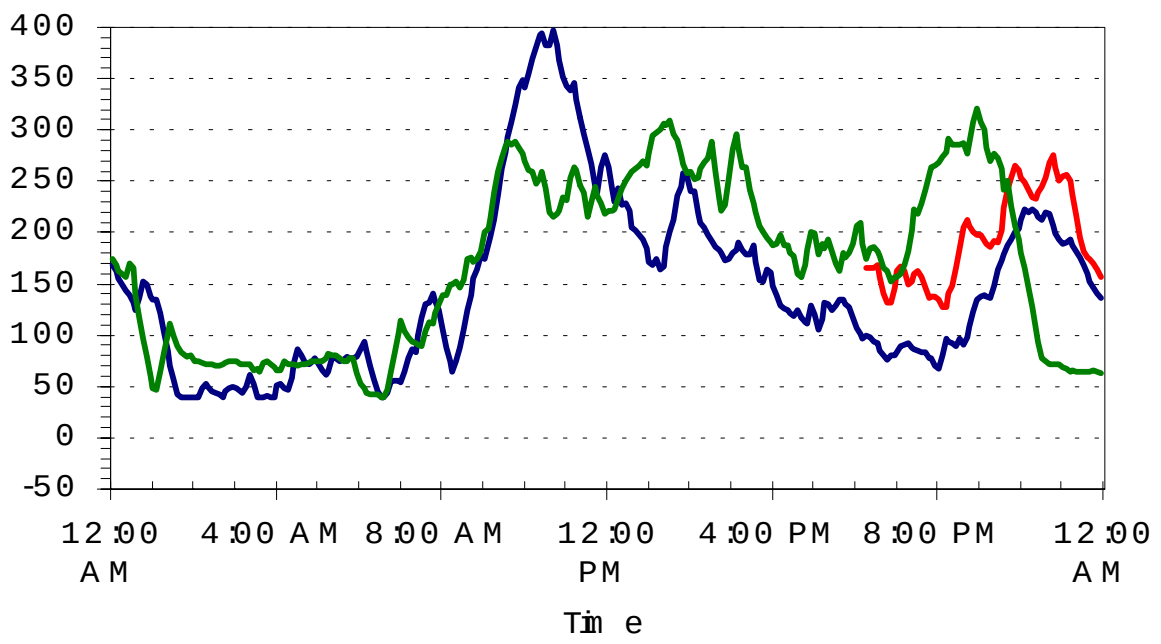

Glucose concentration (Mg/dl)
400
350
300
250
200
150
100
50
0
-50
12:00 AM
4:00 AM
8:00 AM
12:00 PM
4:00 PM
8:00 PM
12:00 AM
Time
1/10/99
1/11/99
1/12/99

Glucose Sensor Profile

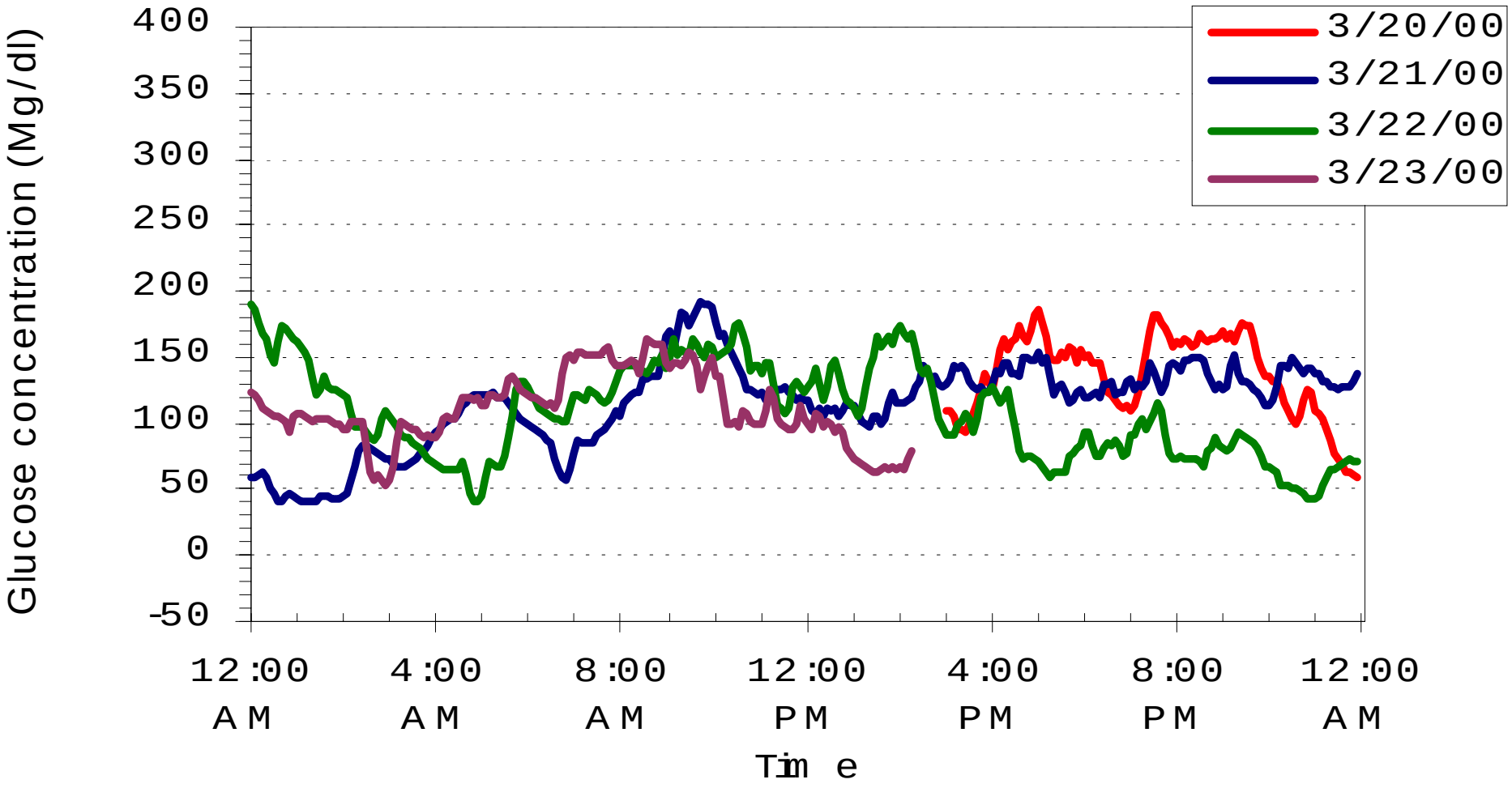


Changes to be made

- **Options discussed with patient:**
  1. **Add insulin pre-meal**
  2. **Change Glynase to Prandin**
- **CGMS re-done six weeks later**



Modal Day


Glucose concentration (Mg/dl)
400
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4:00 AM
8:00 AM
12:00 PM
4:00 PM
8:00 PM
12:00 AM
Time
3/20/00
3/21/00
3/22/00
3/23/00

Reasons to Use CGMS

- Improve glycemic control
- Reduce risk of hypoglycemic events
- Minimize risk of future hypoglycemia

GLUCOSE MONITORING SYSTEMS - Telemetry

Consumer Product

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

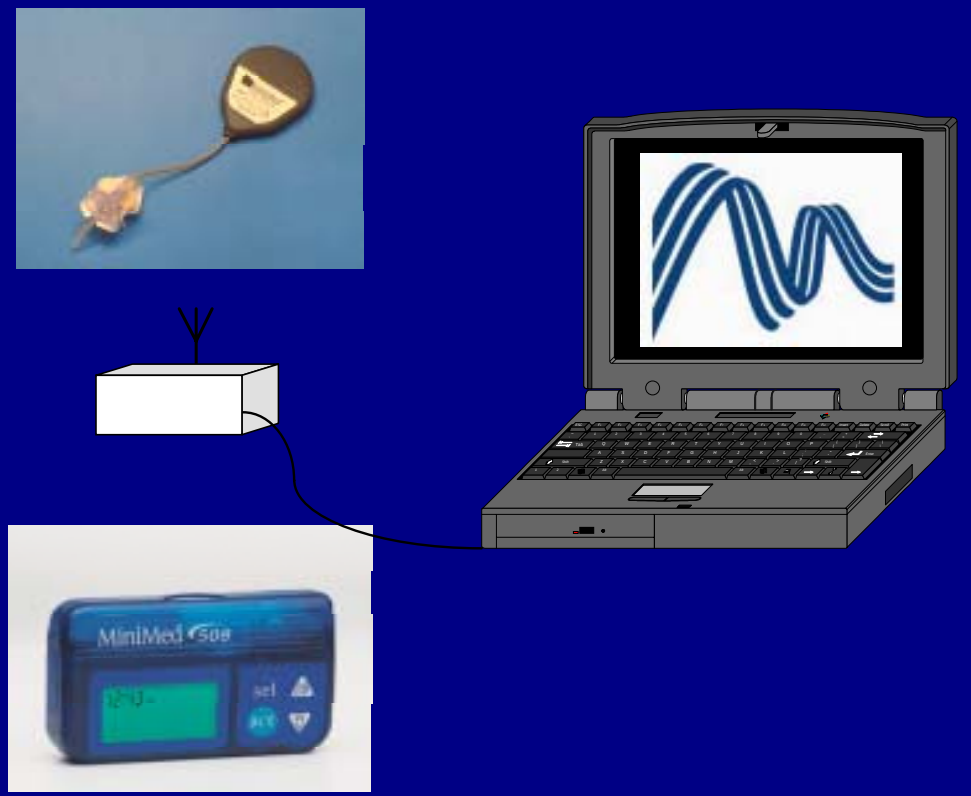
Closed-loop control using an external insulin pump and a subcutaneous glucose sensor

+

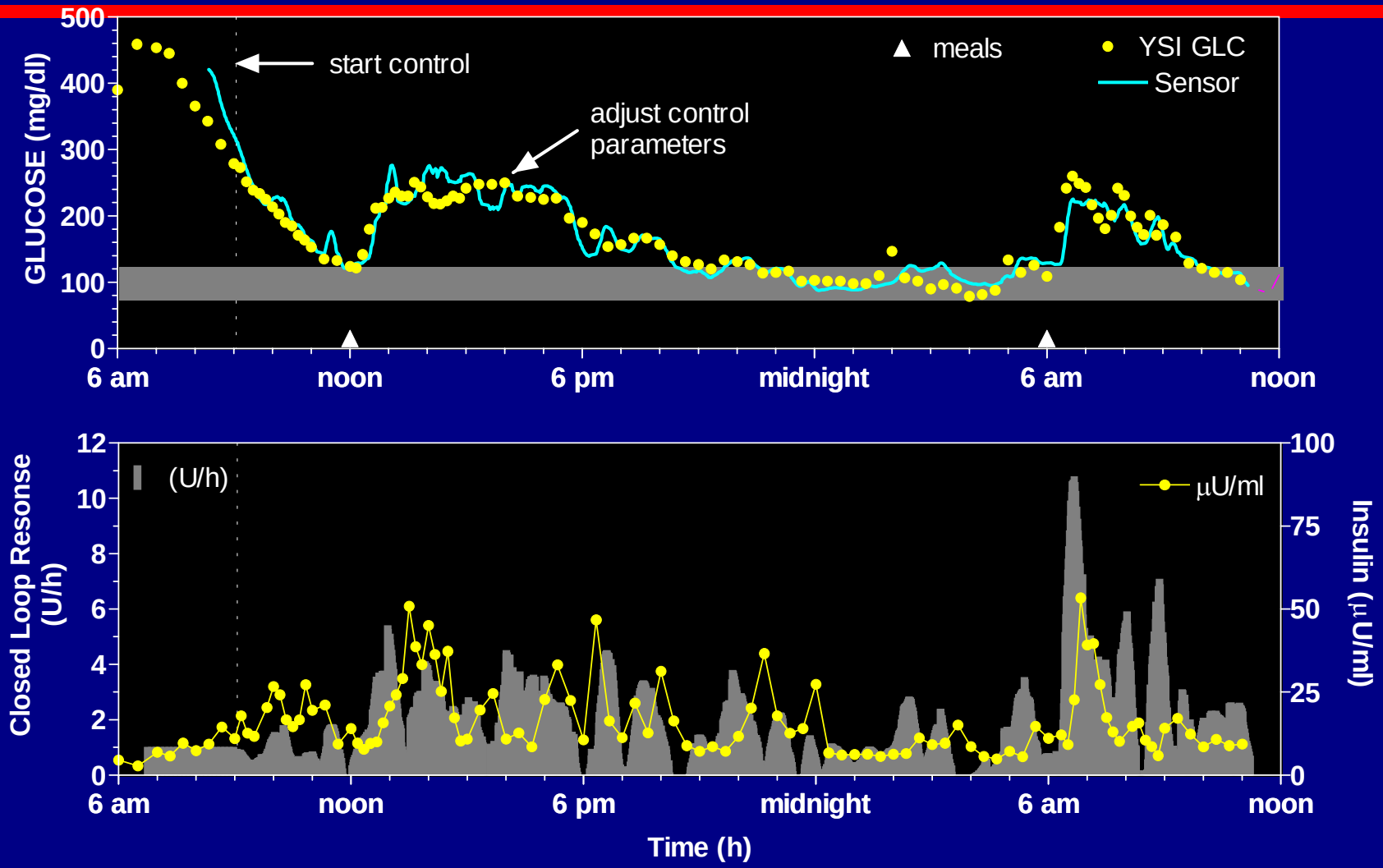
subcutaneous glucose sensor

Insulin infusion pump (currently MiniMed 508)

Closed-Loop Setup for Canine Studies



24-h Closed-Loop Control (diabetic canine)

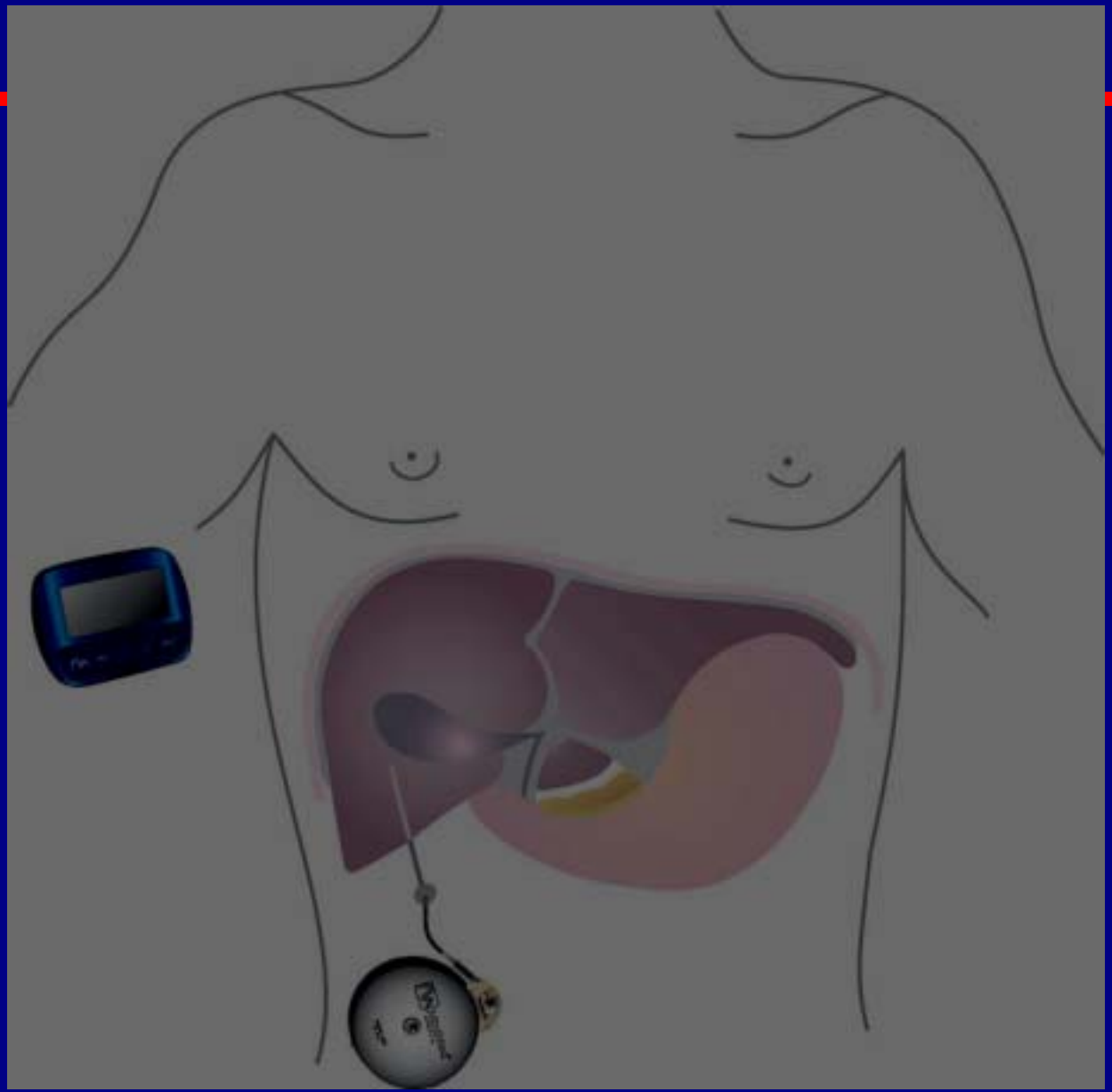


Implantable Pump

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

MiniMed 2007 System

Implantable Insulin Pump Placement



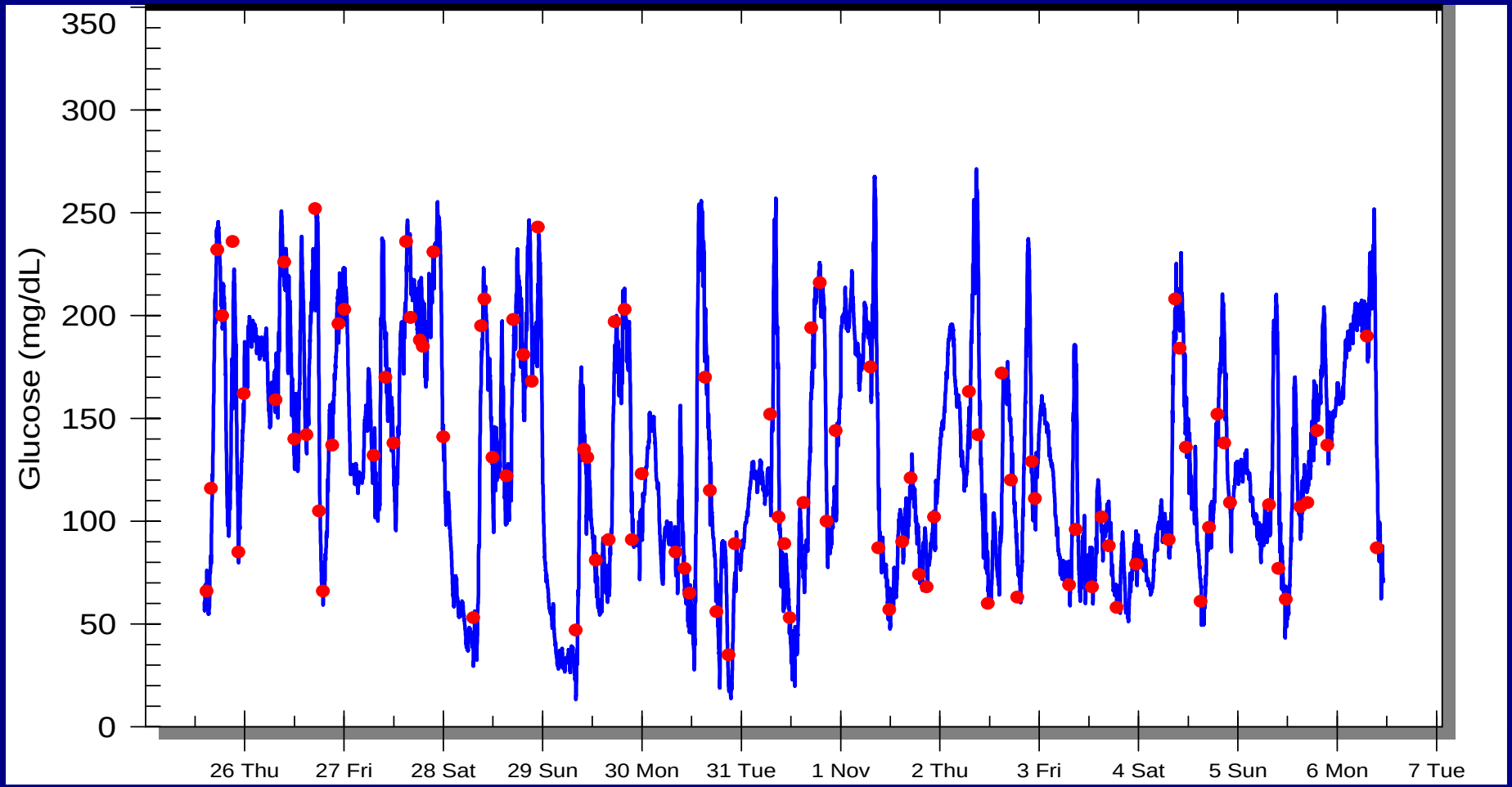
Implantable Insulin Pumps Indications for Use

- Diabetes out of control (frequent, rapid ρBG)
- Frequent hypoglycemic episodes
- Subcutaneous insulin absorption resistance
- Injection or infusion site reaction

Long-Term Glucose Sensor

LONG TERM IMPLANTABLE SYSTEM

Human Clinical Trial



Source: Medical Research Group, Inc.

Combine Pump and Sensor Technology

+

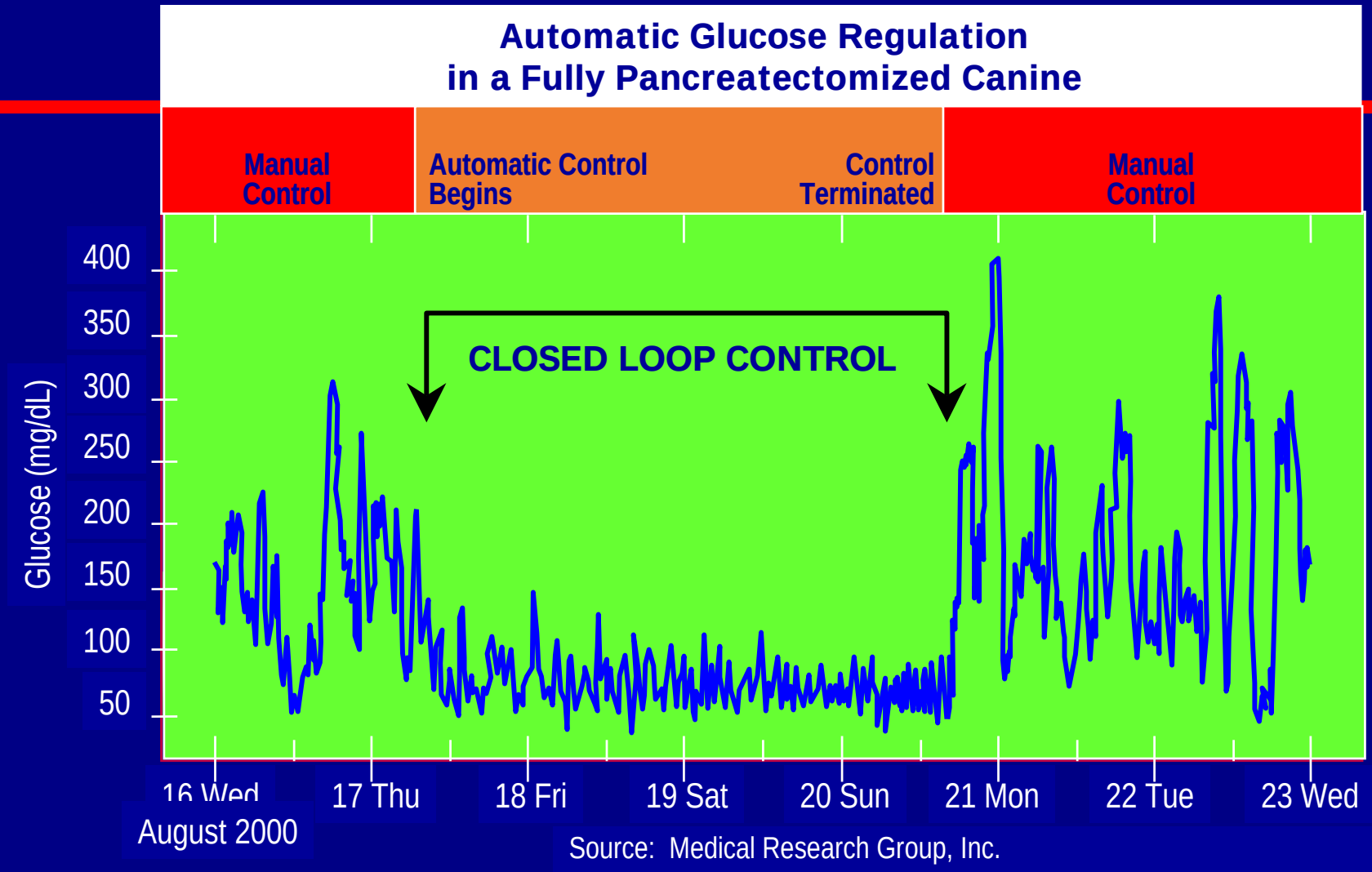
LTSS => Long Term Sensor System (“Open Loop Control”)

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

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- Email: Minimedtalk@adaendo.com