Initiating and Monitoring Insulin Therapy

Howard A. Wolpert, MD

Senior Physician

Joslin Diabetes Center

Boston, Massachusetts

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Historical Perspective on Intensive Diabetes Management

Insulin Delivery

8 H

Smart pump

1978 Insulin pump

CLOSED LOOP:
- Artificial beta cell
- Mechanical system
- Stem cell

Glucose Monitoring

1970 es meter ood test

Retrosp CGM

19 Bene Urine

Advances in Glucose Monitoring Have Driven Improvements in Insulin Therapy

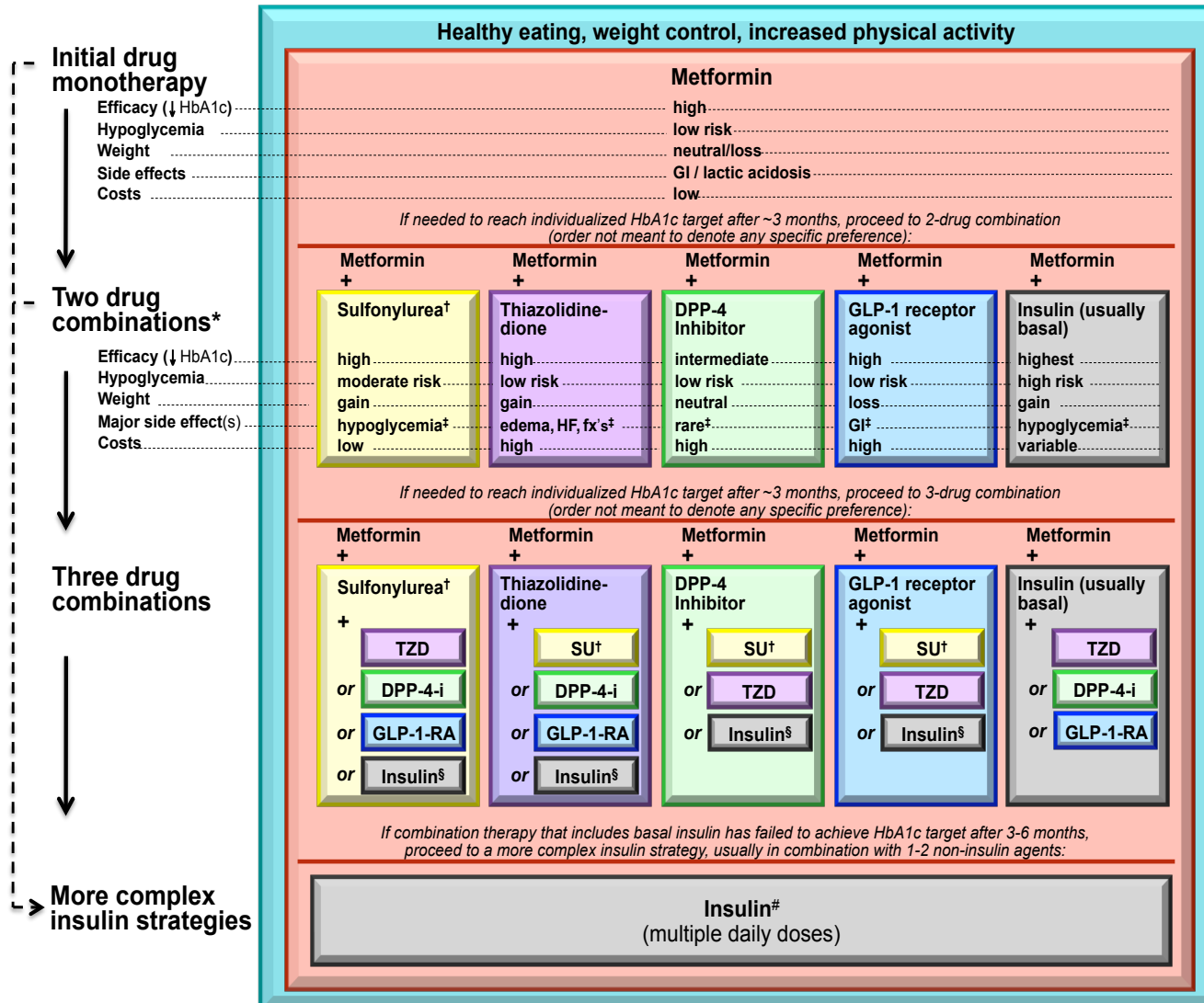| Technology		Therapeutic potential
Urine testing	→	Reduce severe hyperglycemia
Intermittent capillary blood monitoring	→	Intensive diabetes management
Continuous interstitial monitoring	→	Intensive diabetes management with less hypo- and hyper-glycemia

Presentation Outline

- Initiating Insulin Therapy:
  Physiologic and Practical Considerations

- Monitoring Insulin Therapy:
  Avoiding the extremes of Hyper- and Hypo-glyc[e]
    - New insights about the effect of dietary
      macronutrients on postprandial hyperglycemia
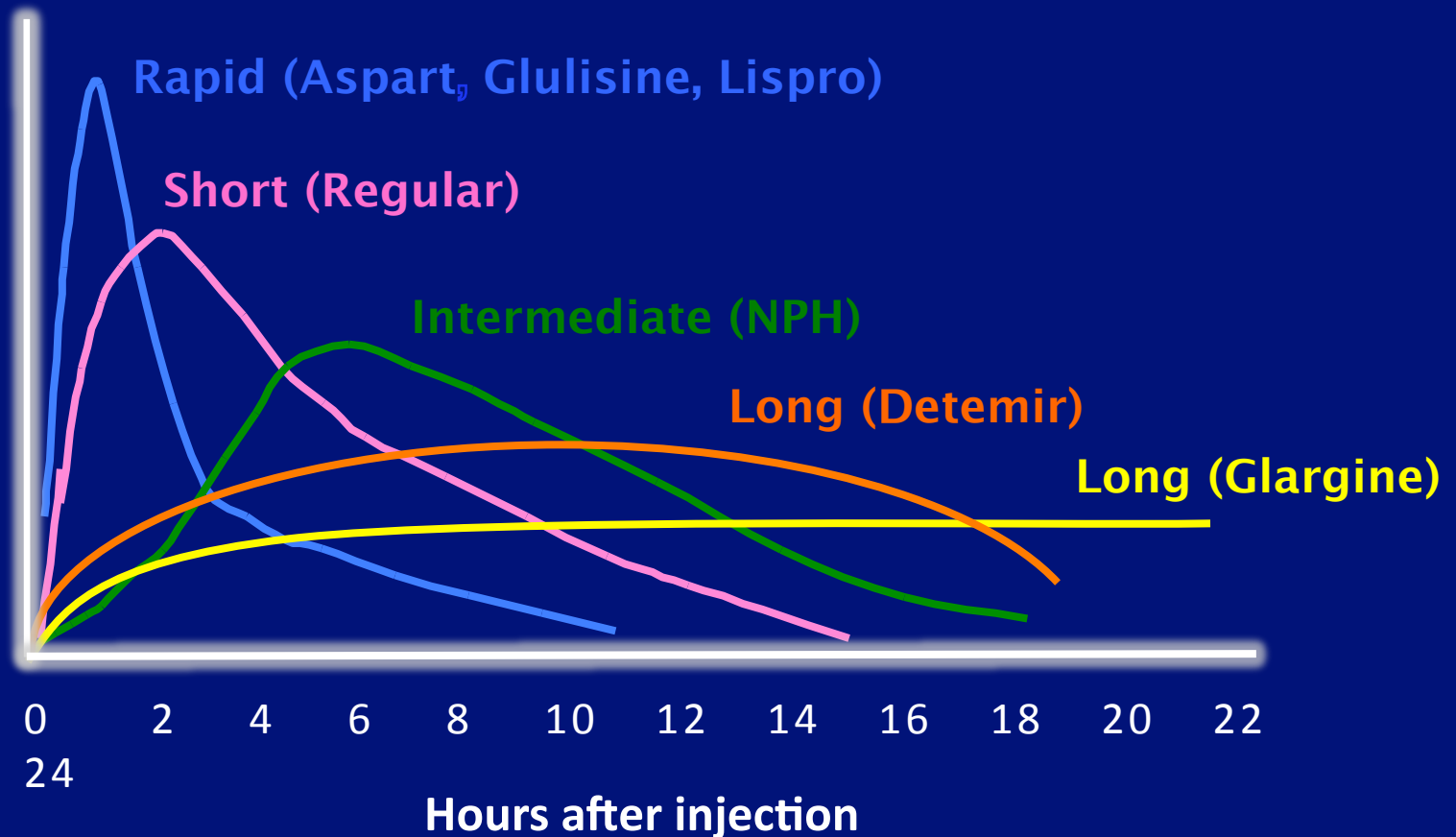   - New approaches to identify and minimize
      hypoglycemia risk

Management of Hyperglycemia in Type 2 Diabetes: A Patient–Centered Approach

Position Statement of the American Diabetes Association and and the European Association for the Study of Diabetes
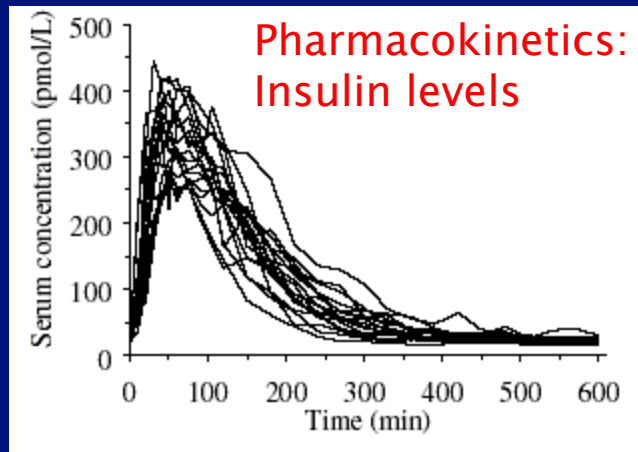

Initial drug monotherapy

- Efficacy (↓ HbA1c)
- Hypoglycemia
- Weight
- Side effects
- Costs

Two drug combinations*

- Efficacy (↓ HbA1c)
- Hypoglycemia
- Weight
- Major side effect(s)
- Costs

Three drug combinations

More complex insulin strategies

Healthy eating, weight control, increased physical activity

Metformin
- high
- low risk
- neutral/loss
- GI / lactic acidosis
- low

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

Metformin + Sulfonylurea†	Metformin + Thiazolidine-dione	Metformin + DPP-4 Inhibitor	Metformin + GLP-1 receptor agonist	Metformin + Insulin (usually basal)
high	high	intermediate	high	highest
moderate risk	low risk	low risk	low risk	high risk
gain	gain	neutral	loss	gain
hypoglycemia‡	edema, HF, fx's‡	rare‡	GI‡	hypoglycemia‡
low	high	high	high	variable

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

Metformin + Sulfonylurea† +	Metformin + Thiazolidine-dione +	Metformin + DPP-4 Inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + Insulin (usually basal) +
TZD	SU†	SU†	SU†	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or DPP-4-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§			

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

Insulin#
(multiple daily doses)

Pharmacokinetics and Pharmacodynamics of Aspart Insulin

Pharmacokinetics:
Insulin levels

Pharmacokinetic data (package inserts) is misleading about insulin action profile

Pharmacodynamics:
Insulin bioactivity
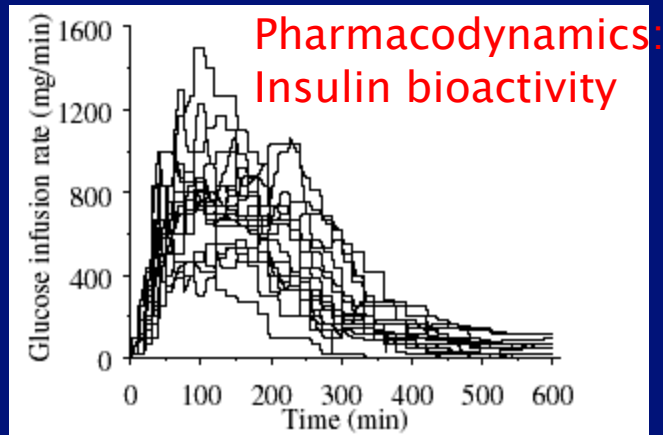
Marked inter- and intra-individual variab

Aspart (NovoLog) insulin

Pharmacokinetics and Pharmacodynamics of Human Regular Insulin

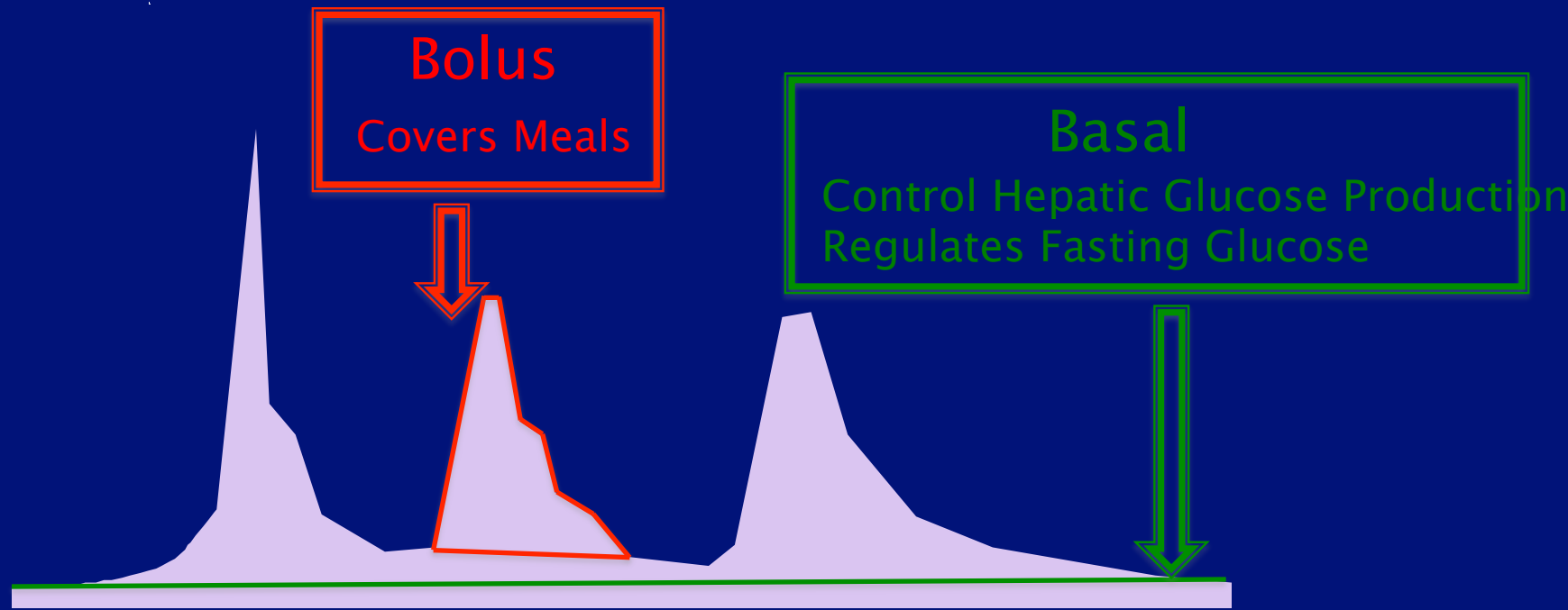Pharmacokinetics: Insulin levels

Pharmacodynamics: Insulin bioactivity
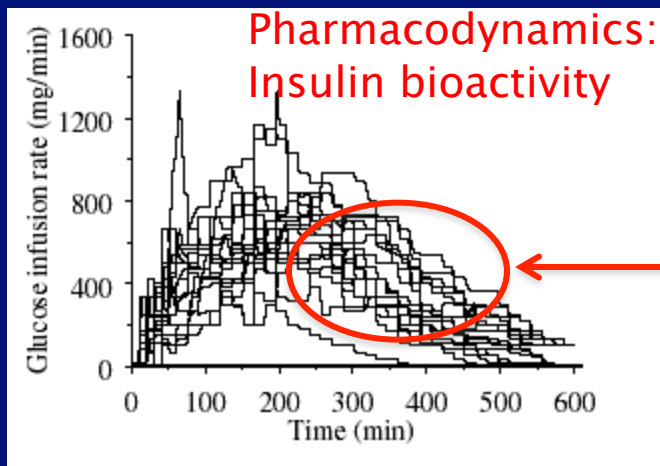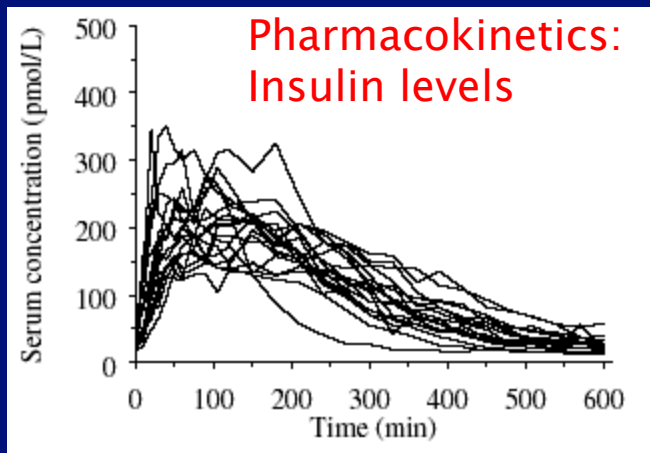
Insulin "tail": Risk for late post-prandial hypoglycemi

Human Regular insulin

Insulin Levels in Non-Diabetic Individual

Breakfast   Lunch   Dinner

4:00   8:00   12:00   16:00   20:00   24:00   4:00

Time
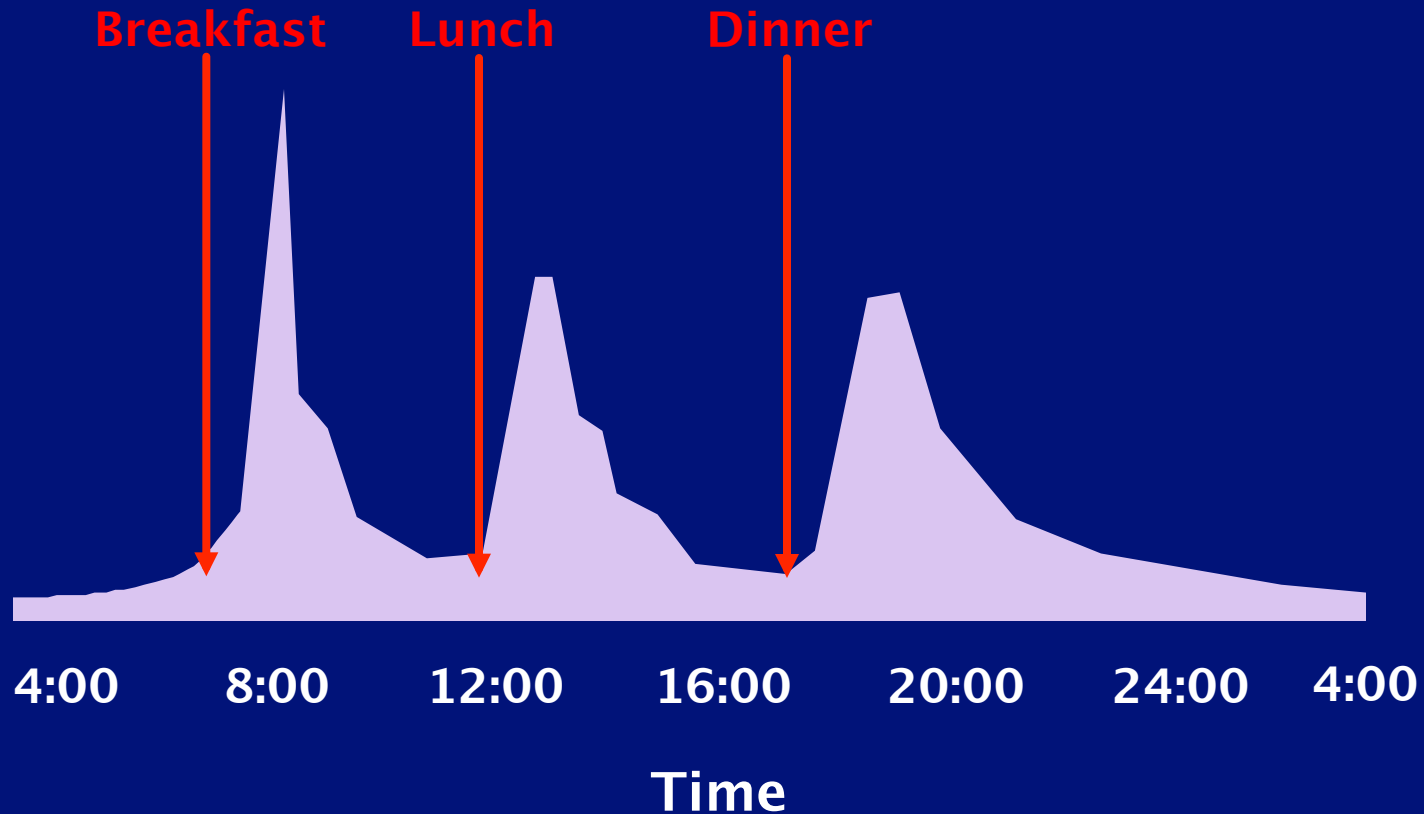
Insulin Replacement Therapy: Mimicking "Normal" Insulin Levels

Bolus
Covers Meals

Basal
Control Hepatic Glucose Production
Regulates Fasting Glucose

Basal insulin dose titrated to ensure that glucose is stable overnight and fasting glucose is in target range

Pre-Mixed Insulin Regimens with Regular
Humulin 70/30, Novolin70/30
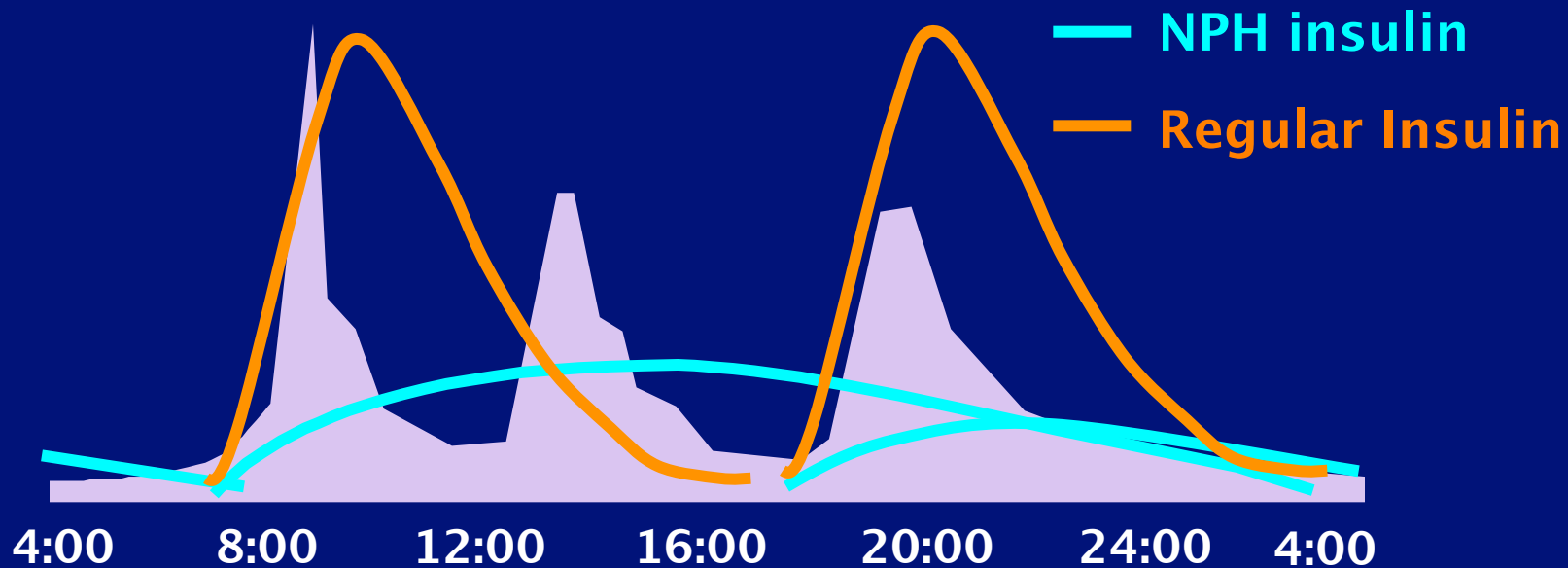
Benefits: Fewer injections, simpler (fixed doses)

Limitations: Need to eat on schedule around the insulin profiles:
missed meal/snack > hypoglycemia, excessive food intake > hyperglyc

Patients starting on pre-mixed insulin regimerence
Should be referred to RD for structured meal plan

Trade–off between Hyperglycemia and Hypoglycemia

DCCT Research Group, 1993
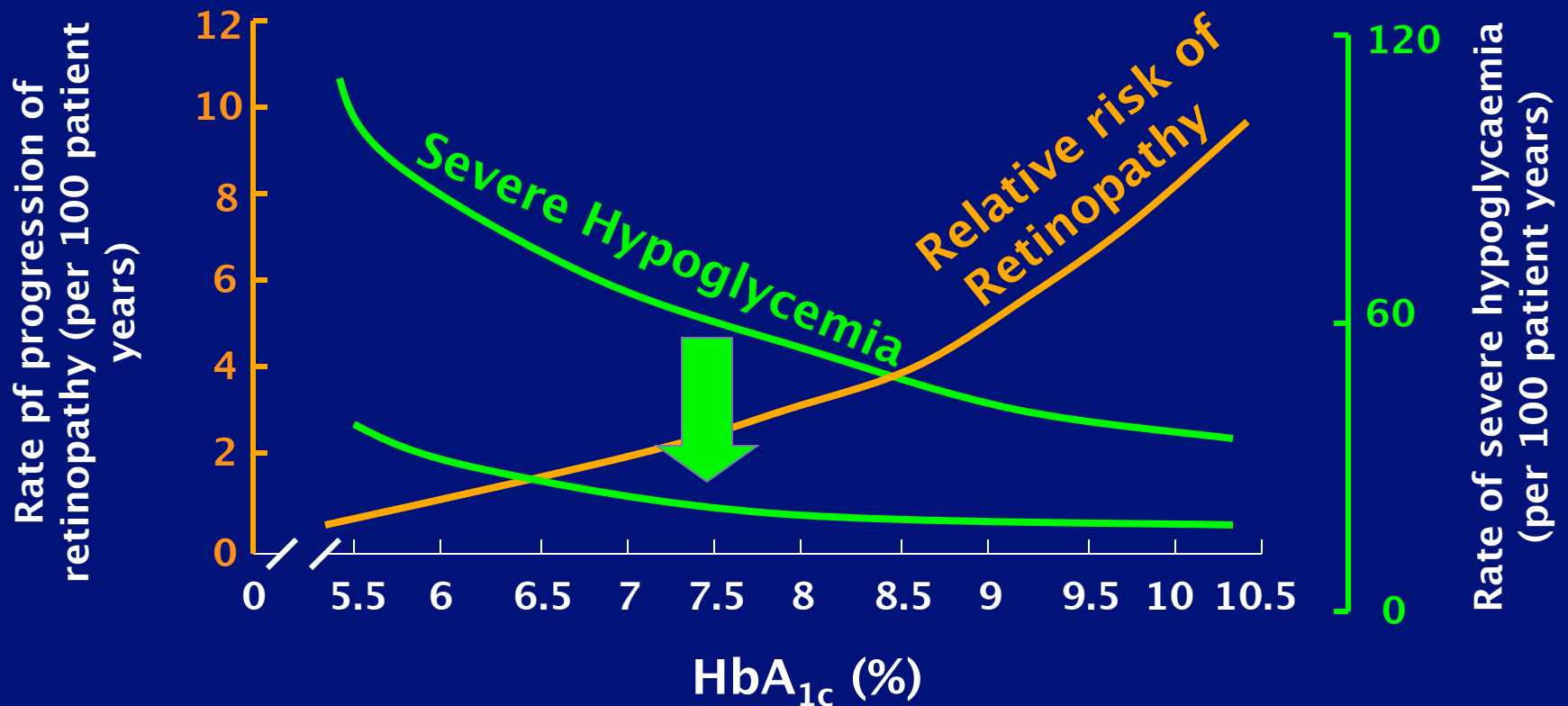
Pre-Mixed Insulin Regimens: Replacing Premeal Regular with Analog Insulin Humalog mix 75/25
Humalog mix 50/50, Novolog 70/30

Aspart, Lispro Insulin

Regular Insulin

4:00 8:00 12:00 16:00 20:00 24:00 4:00
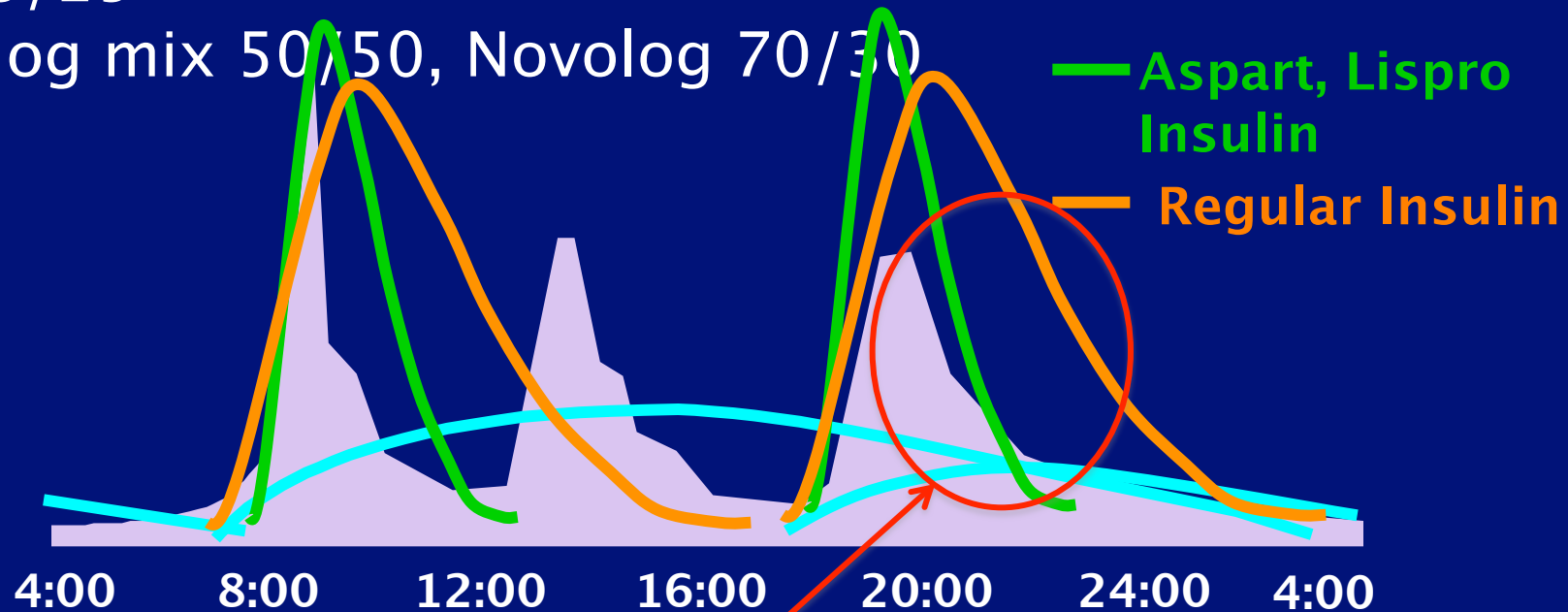
Pre-supper injection of analog insulin has shorter "tail" than regular insulin
> Less risk for early nocturnal hypoglycemia

Meta–analysis: Risk for Nocturnal Hypoglycemia with Premixed Aspart 30 vs Premixed Regular 30 in Type 2 Diabetes

Nine RCT
Parallel or cross–over
12–48 week duration
N = 1,67

Trial	Rate Ratio (95% CI)	P
	0.57 (0.20–1.58)	0.28
	0.89 (0.25–3.16)	0.86
	0.44 (0.22–0.89)	0.02
	1.03 (0.42–2.53)	0.95
	1.03 (0.38–2.76)	0.96
	0.33 (0.21–0.51)	0.01
	0.44 (0.11–1.47)	0.17
	1.05 (0.11–10.09)	0.97
	2.43 (0.31–18.90)	0.39
Overall*	0.50 (0.38–0.67)	<0.01

Test of Heterogeneity: I^2 = 32%

Favors BIAsp 30 — Favors BHI 30
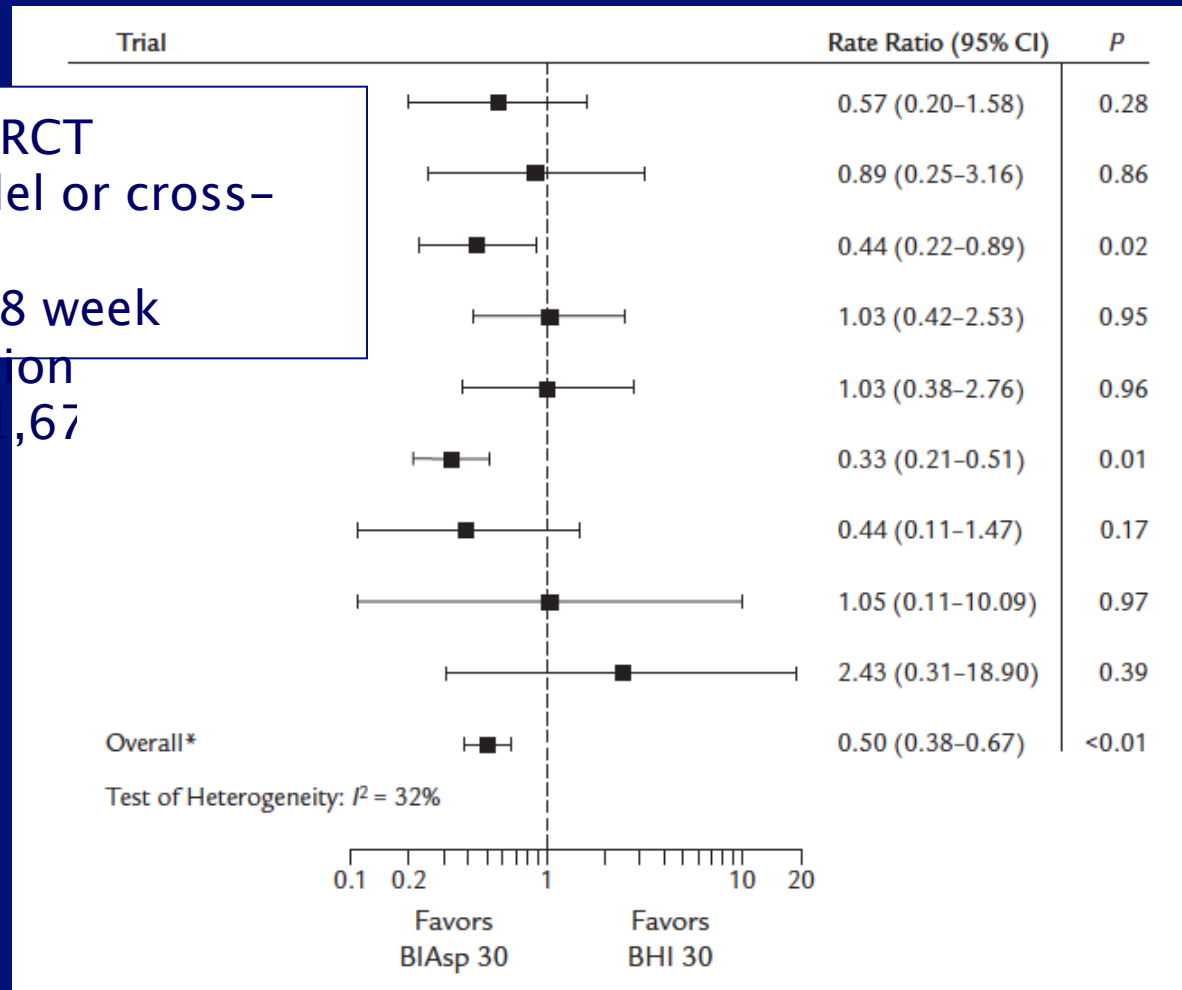
Pharmacodynamics of Basal Insulins

Increases risk for hypoglycemia due to day-to-day variability in insulin action

NPH insulin

Insulin glargine

Insulin detemir
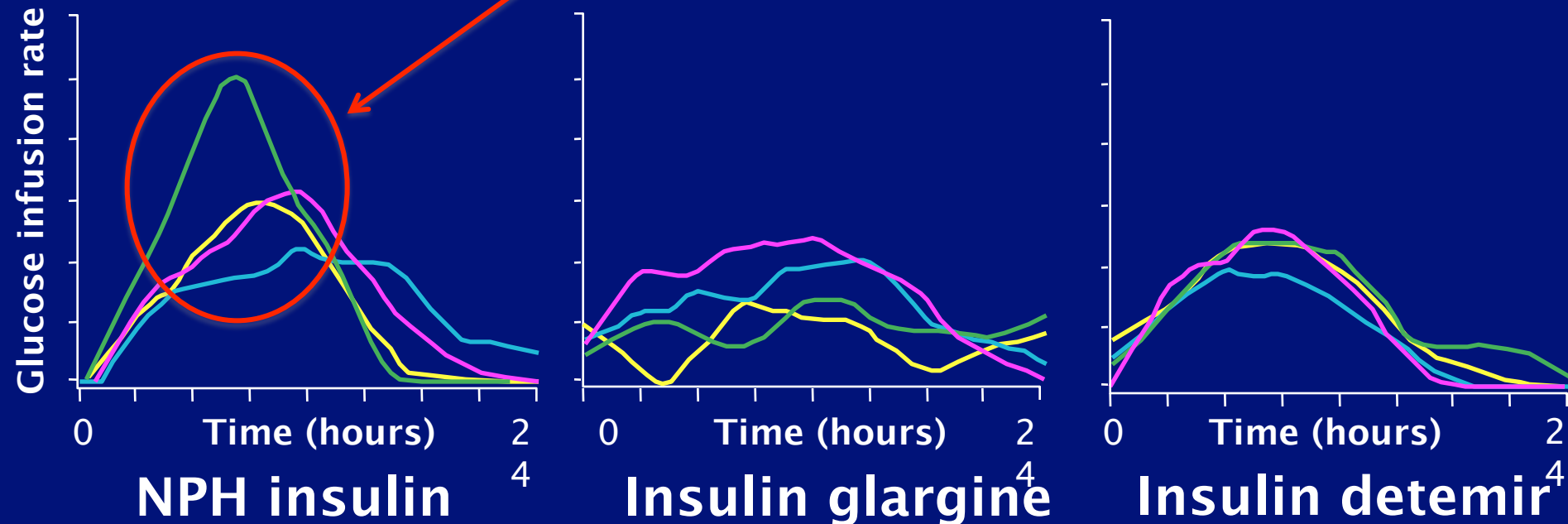
Glucose infusion rate profiles following four non-consecutive injections of identical doses (0.4U/kg, thigh) in the same patient

Heise et al, *Diabetes* 2004; 53:161

Basal with Prandial Bolus Insulin
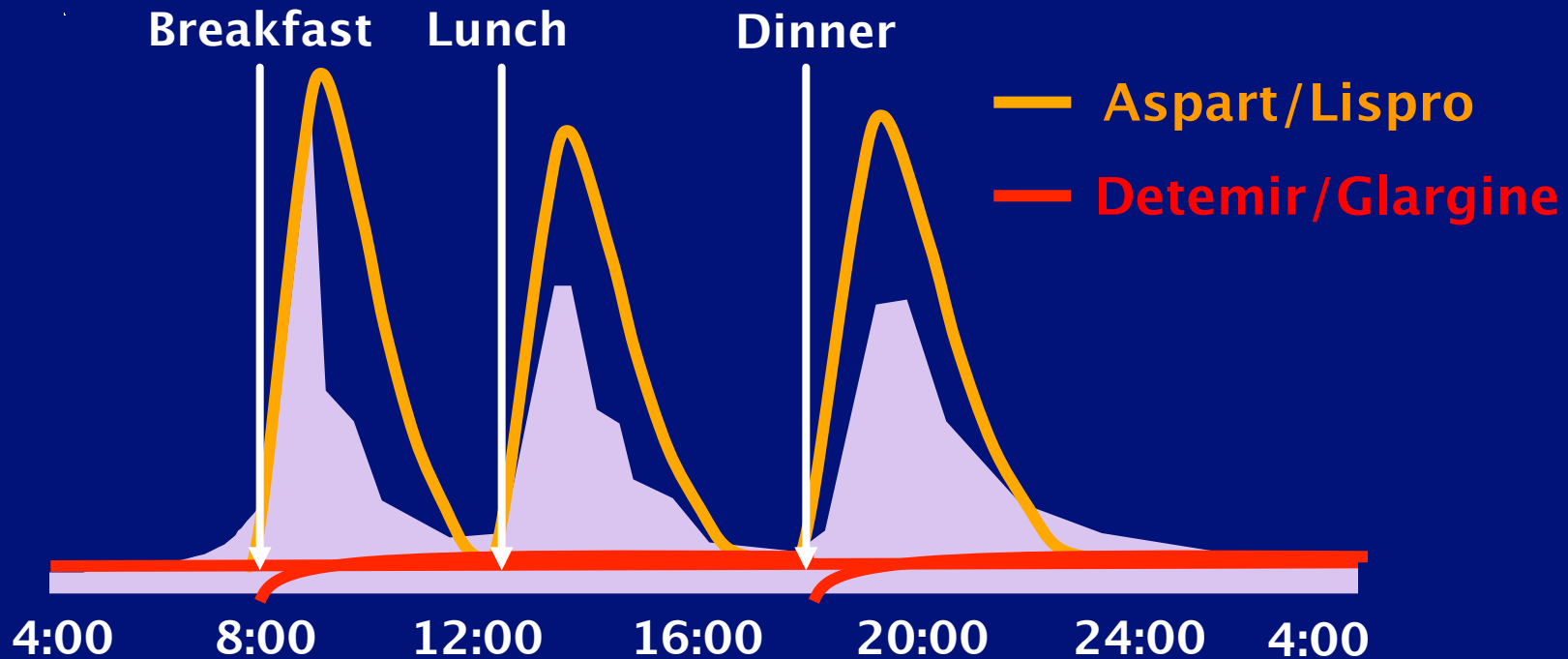
Benefits:
– More predictable insulin kinetics → less potential risk for hypoglycem
– No need for fixed meal plan → Increased lifestyle flexibility → often better adherence

Limitations: More injections/complexity

Presentation Outline

- Initiating Insulin Therapy:
  Physiologic and Practical Considerations

- Monitoring Insulin Therapy:
  Avoiding the extremes of Hyper- and Hypo-glyc

Continuous Glucose Monitoring: Device Features

The Transmitter

The Sensor/Probe

3:27 pm

152 mg/dl

EXIT   CLEAR   MENU

The Receiver

- Glucose alarms – threshold & predictive
- Glucose trend/rate of change
- More complete picture of glucose patterns than intermittent, capillary blood glucose monitoring

Fingerstick Blood Glucose Monitoring Provides a Limited Picture of Glucose Patterns
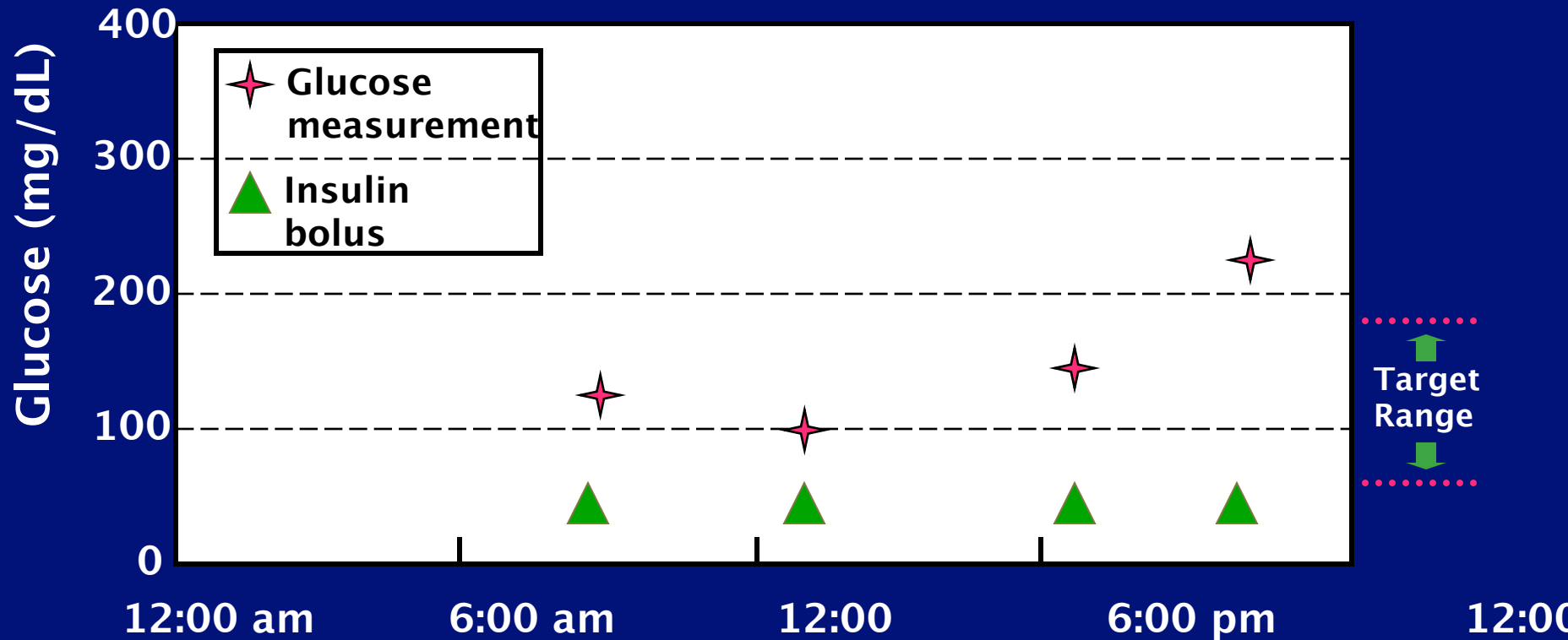
Continuous Glucose Monitoring uncovers Hyper- and Hypo-glycemic Excursions
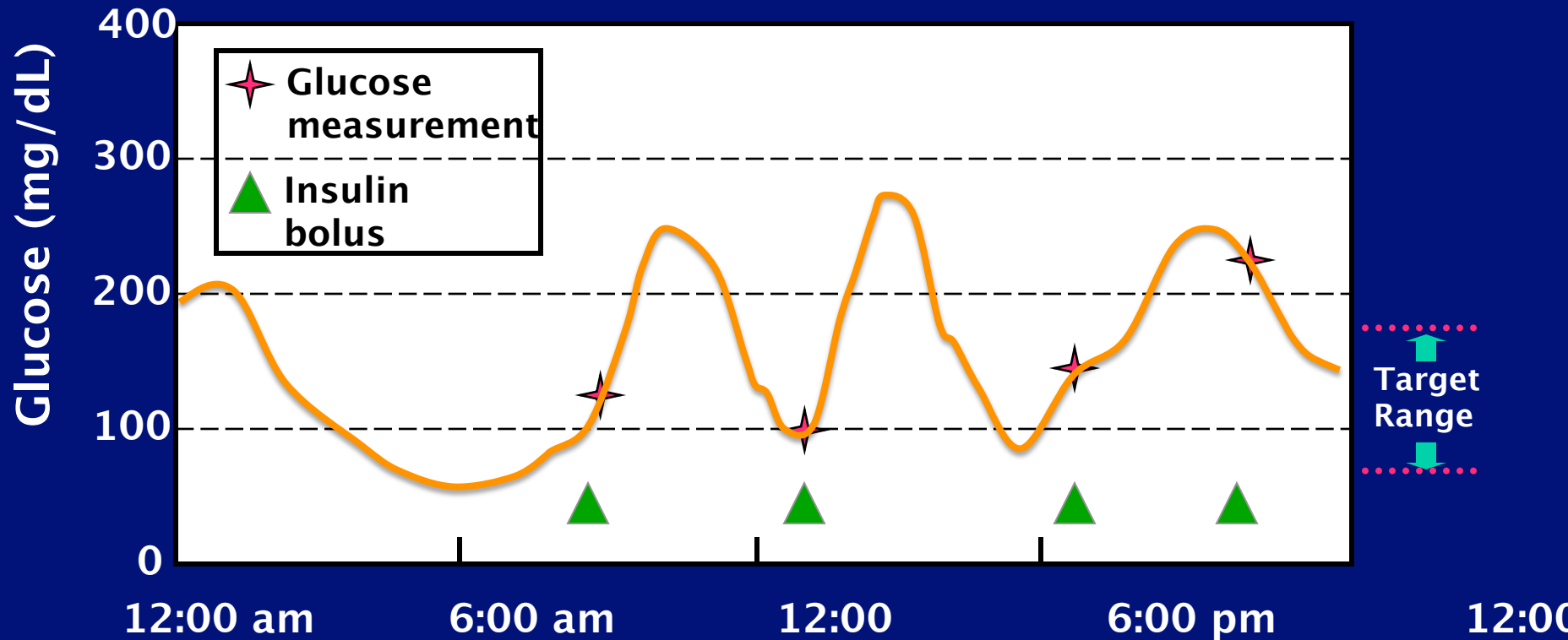
Glucose (mg/dL)

400
300
200
100
0

- ✦ Glucose measurement
- ▲ Insulin bolus

12:00 am   6:00 am   12:00   6:00 pm   12:00

Target Range

Presentation Outline

- Initiating Insulin Therapy:
  Physiologic and Practical Considerations

- Monitoring Insulin Therapy: Avoiding the
  Extremes of Hyper- and Hypo-glycemia
  - New insights about the contribution of dietar
  macronutrients on postprandial hyperglycemia

Insulin Pharmacodynamics

- ● **Aspart**
- ○ **Lispro**

Glucose - mg/dL

400

300

200

180

100

70

0

Cheerios Glycemic Index = 83

3:00 AM   6:00 AM   9:00 AM   12:00 PM   3:00 PM   6:00 PM   9:00 PM

Time Of Day
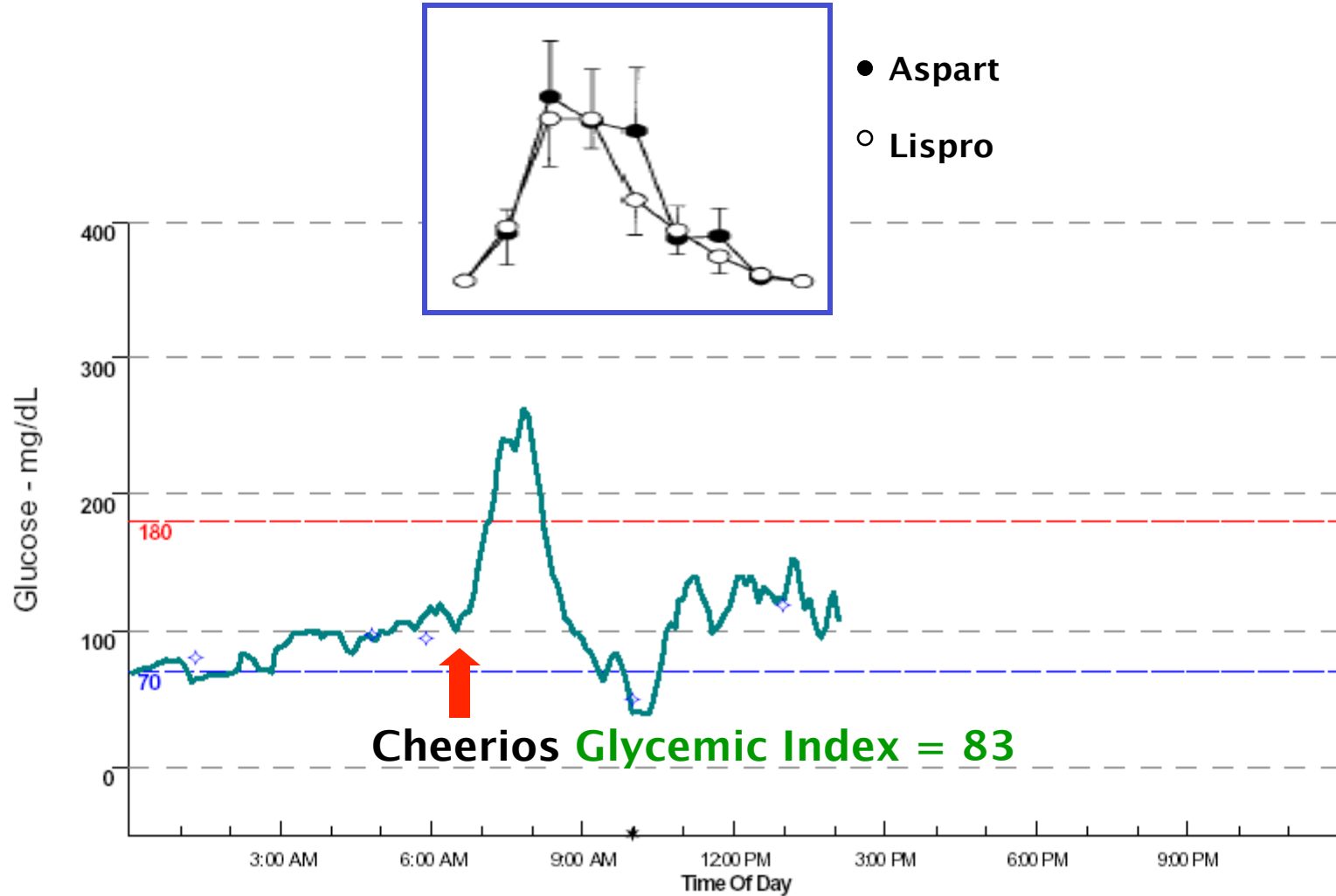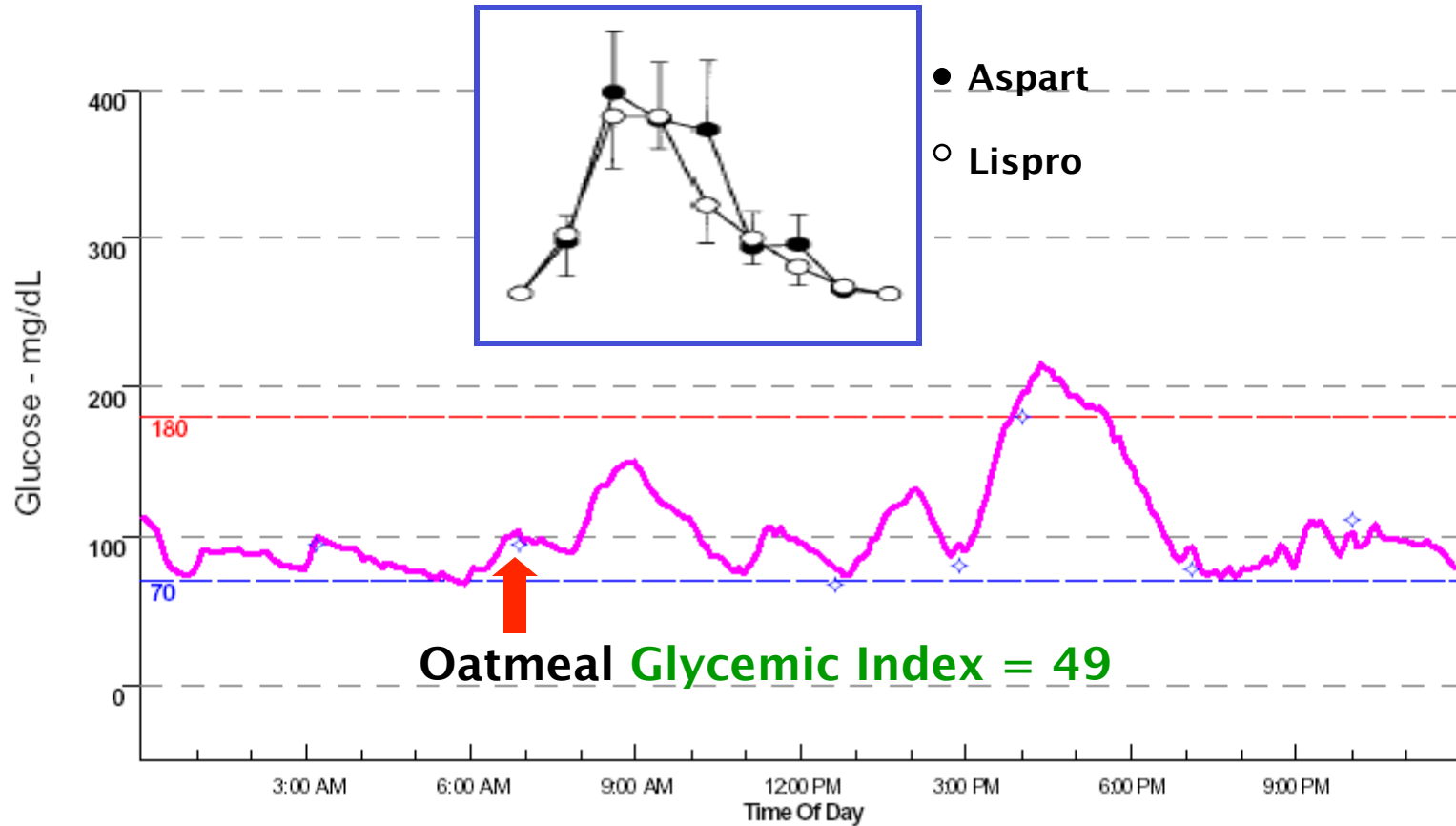
Practical Implication

Current focus:
Match insulin bolus with carbohydrate intake

CGM indicates that to optimize postprandial glucose control need to:
Match insulin action with carbohydrate absorption

Insulin Pharmacodynamics

- ● Aspart
- ○ Lispro

300

200

100

Steak & fries

0

3:00 PM   6:00 PM   9:00 PM
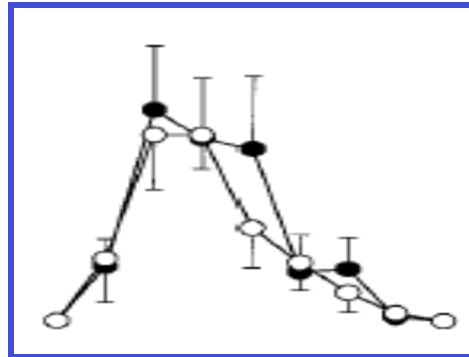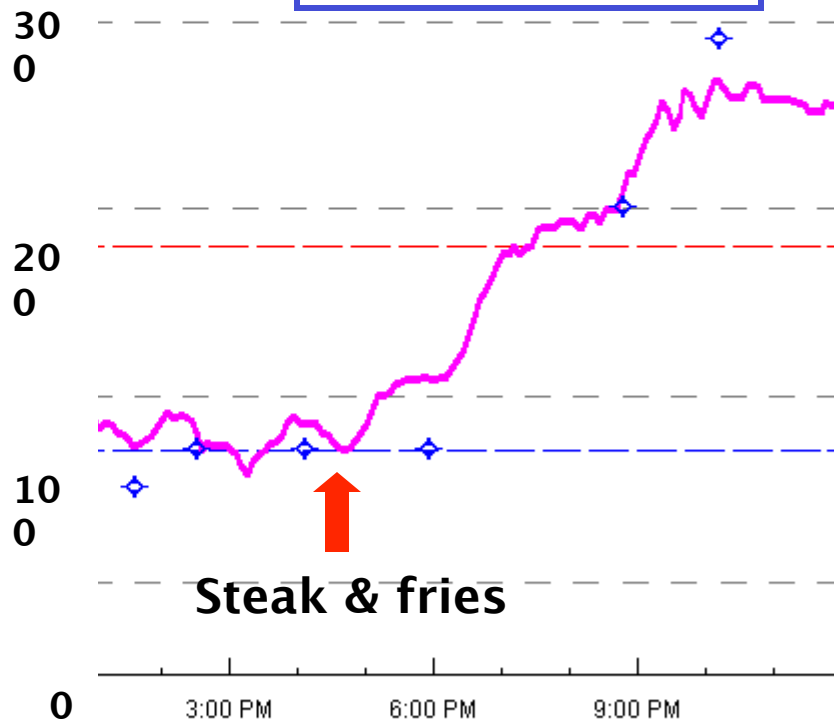
Free Fatty Acids Induce Insulin Resistance

Plasma FFA (mmol/L)
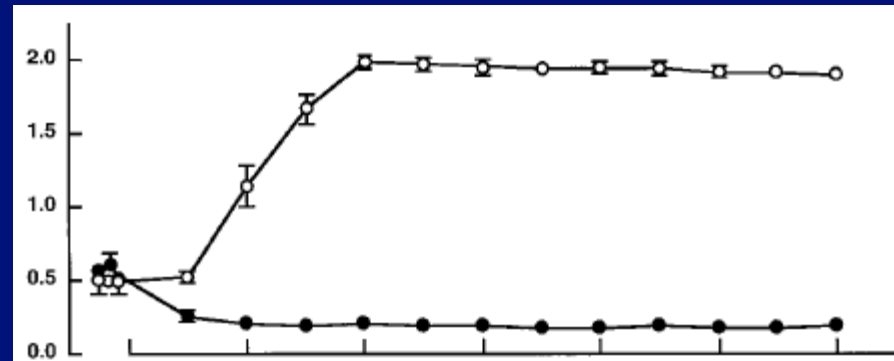
Glucose infusion rate (μmol/[kg·min])

Time (min)

+ p < 0.01
† p < 0.001

Roden et al, *J Clin Invest* 1996; 97:2859

Closed Loop Protocol in CRC

Day 1   Day 2   Day 3

Admit

↓ Open Loop

Closed Loop

Mild activity

12   6p   11p   8a   12   6p   11p   8a

↑ Lunch   ↑ Dinner

High Fat

or

Low Fat

Wolpert et al, *Diabetes Care* 2013; 36:810

Closed Loop Protocol in CRC

Wolpert et al, *Diabetes Care* 2013; 36:810
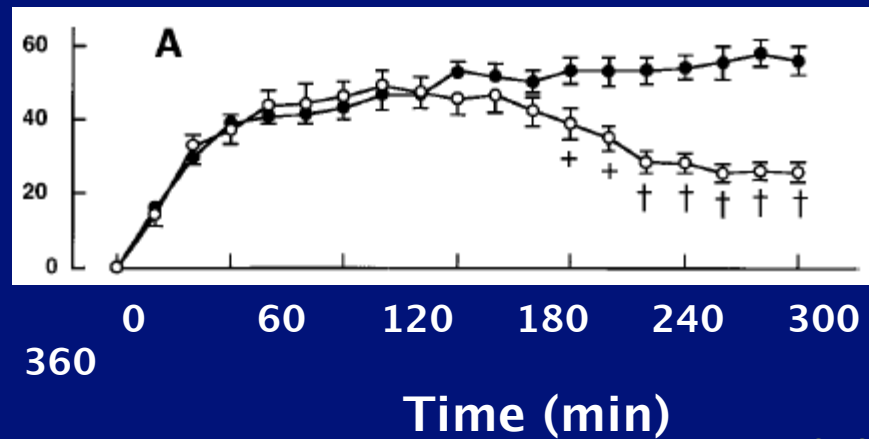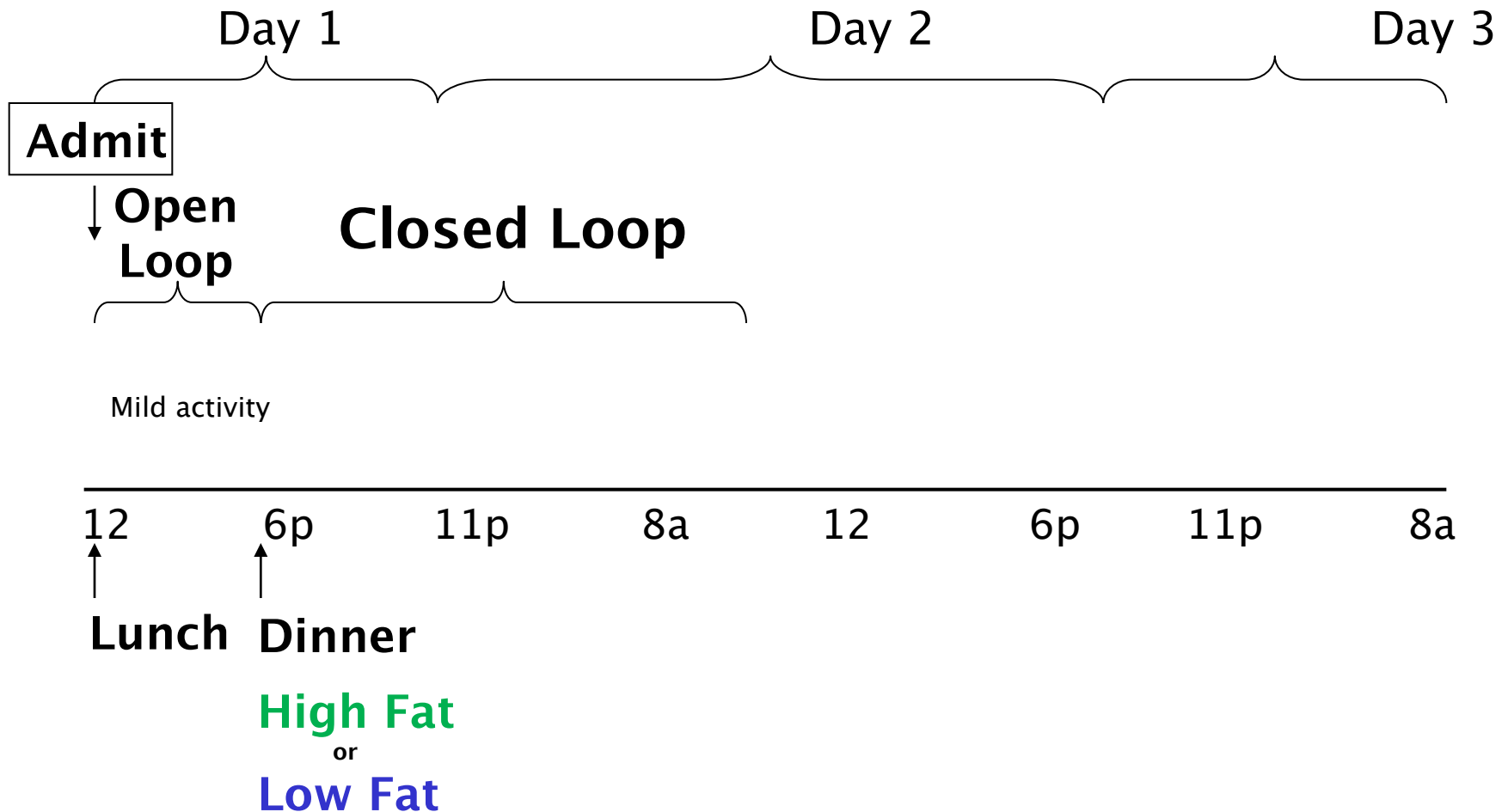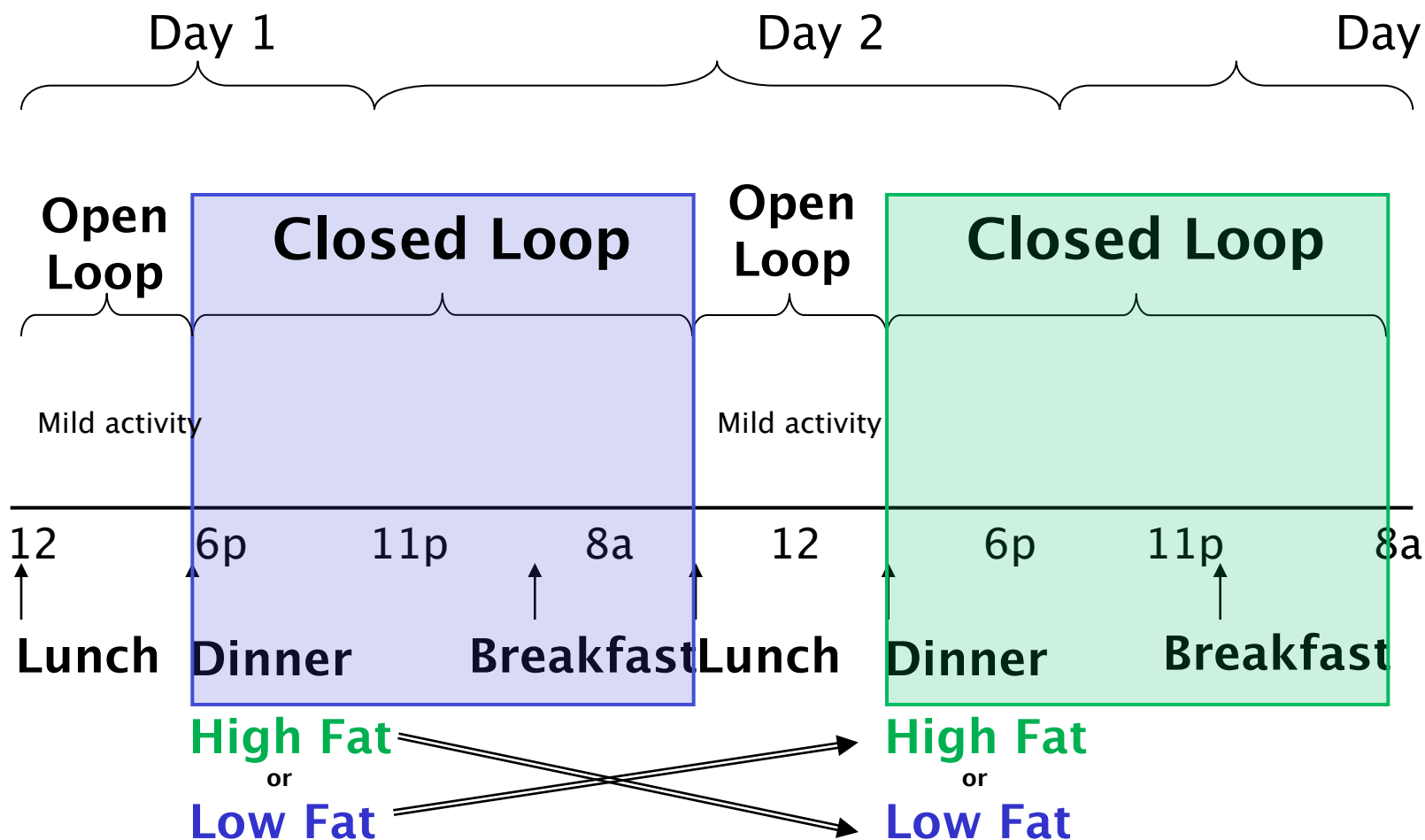
Dietary Fat Acutely Increases Glucose Concentrations and Insulin Requirements in Patients With Type 1 Diabetes

Implications for carbohydrate-based bolus dose calculation and intensive diabetes management

**** p < 0.0001

** p < 0.01

Wolpert et al, *Diabetes Care* 2013; 36:810
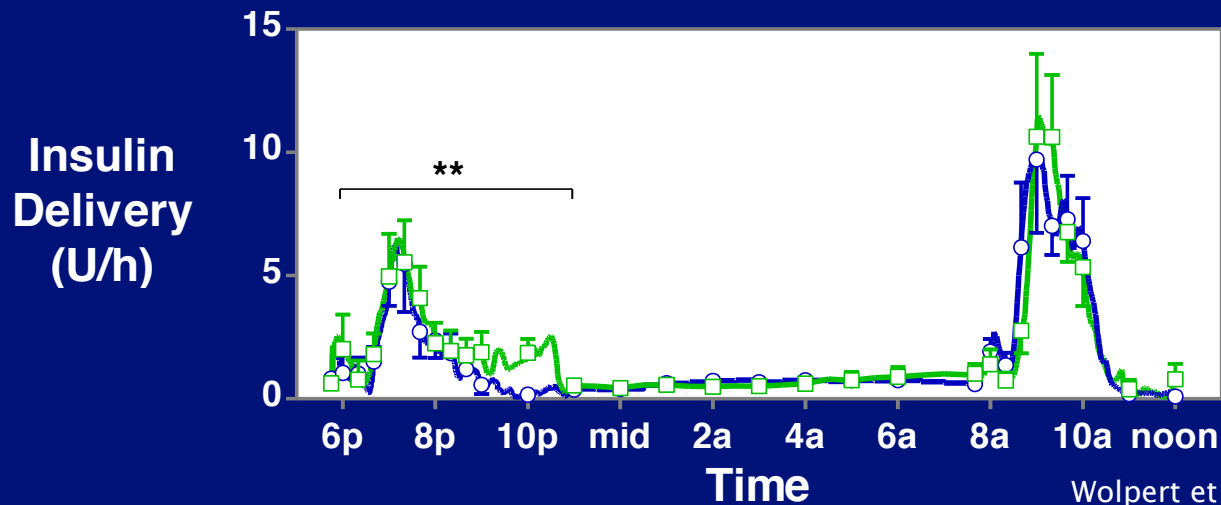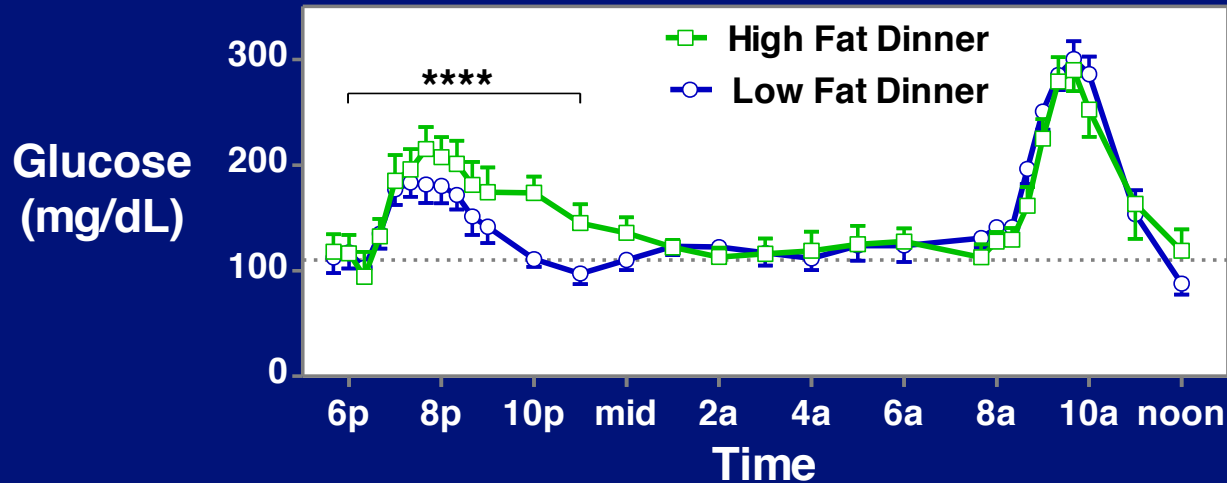
Practical Implications – Nutrition

Attention to dietary fat intake is an important nutritional consideration in individuals striving for tight glycemic control

Carbohydrate counting/meal exchanges are the foundation for calculating meal-time insulin doses. However, to achieve optimal glycemic control there needs to be:

1) Specific focus directed at identifying whether higher fat (or high glycemic index) meals are contributing to glycemic fluctuations, in conjunction with

2) Individualized guidance about changing to alternative meal/food choices with less glycemic impact

Practical Implications – Insulin dosing

These studies highlight the limitations of the carbohydrate counting-based method for calculating meal-time insulin dosage

Higher fat meals require alternative dosing algorithms with an altered insulin delivery pattern and dose

However:

Ø Marked inter-individual differences, so fixed dosing increase for higher fat meals will not be safe/effective

Ø Different fat types have different effect on insulin sensitivity: Saturated vs monounsaturated, palmito-oleic acid

Ø Dose response vs threshold effect ?

Consumption of Pizza

What We Eat in America, NHANES 2007-2010

Food Surveys Research Group
Dietary Data Brief No. 11
February 2014

Donna G. Rhodes, MS, RD; Meghan E. Adler, MS, RD; John C. Clemens, MS;
Randy P. LaComb, MS; and Alanna J. Moshfegh, MS, RD

On any given day, roughly 13 percent of the U.S. population, or more than 1 in 8 Americans, consumes pizza

In pizza-eaters:
– Pizza accounts for 25% (among kids) and 29% (among adults) of daily food energy intake
– Pizza accounts for 33% (among kids) and 39% (among adults) of daily saturated fat intake

Influence of Pure Protein on Postprandial Blood Glucose in Individuals with Type 1 Diabetes Mellitus

MEGAN A. PATERSON, CARMEL SMART, PATRICK MCELDUFF, PRUDENCE LOPEZ, CLAIRE MORBEY. JOHN ATTIA, BRUCE KING, Newcastle, Australia

T1DM, aged 7–40 years, fed several test meals:

- Varying amounts pure protein – 12.5g, 25g, 50g, 75g and 100g
- Two pure glucose powder test meals (10g and 20g) for comparison
- No insulin was given for test meals
- Postprandial glycemia assessed for 5 hours
- Protein amounts of O–50g > NO effect on glucose
- Protein amounts of 75 & 100 g > increase in glucose starting at 100 minutes, equaling rise with the 20g glucose test meal
- Equivalent to consuming an 8oz steak

Presentation Outline

- Initiating Insulin Therapy: Physiologic and Practical Considerations

- Monitoring Insulin Therapy: Avoiding the Extremes of Hyper- and Hypo-glycemia
  - New insights about the contribution of dietar macronutrients on postprandial hyperglycemia
  - Hypoglycemia: the downside of insulin therap New approaches to identify and minimize hypoglycemia risk

Glycemic Control in Accord Study

median A1c 7.5%

median A1c 6.4%
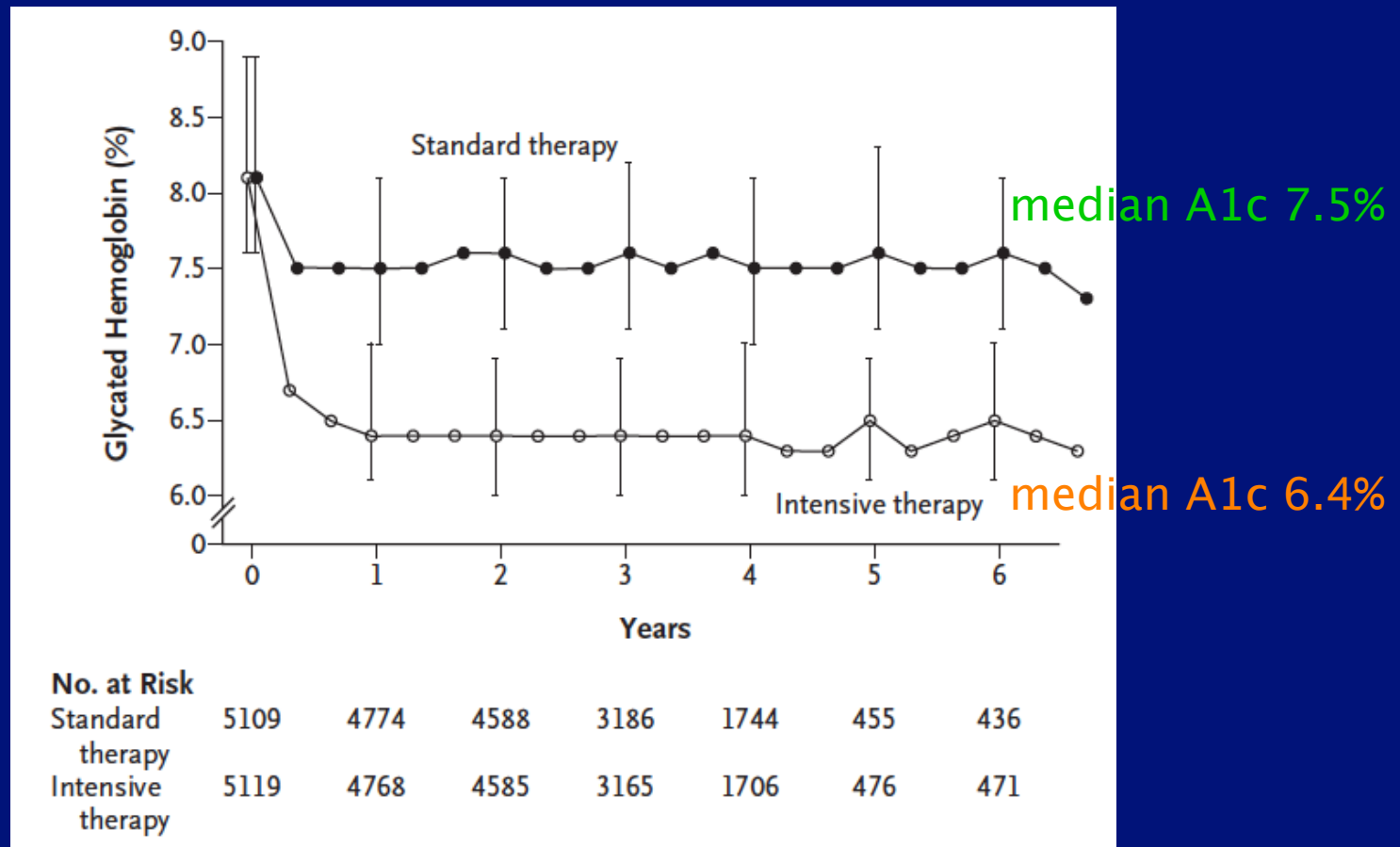
Accord Study
Increased all-cause and CV mortality

	Unadjusted HR intensive vs standard (CI)	P-value
All-cause mortality	1.19 (1.03–1.38)	0.02
Primary endpoint CV death, MI, stroke	0.091 (0.81–1.03)	0.12
CV death	1.29 (1.04–1.60)	0.02
Non-fatal MI	0.82 (0.70–0.96)	0.01
Non-fatal stroke	0.87 (0.65–1.17)	0.35

Why the Added Mortality with Intensive Therapy ?
Severe Hypoglycemia in Treatment Groups

Percentage of subjects with hypoglycemic events requiring assistance

Years of follow up

Accord Study Group. *BMJ* 2010;340:b5444
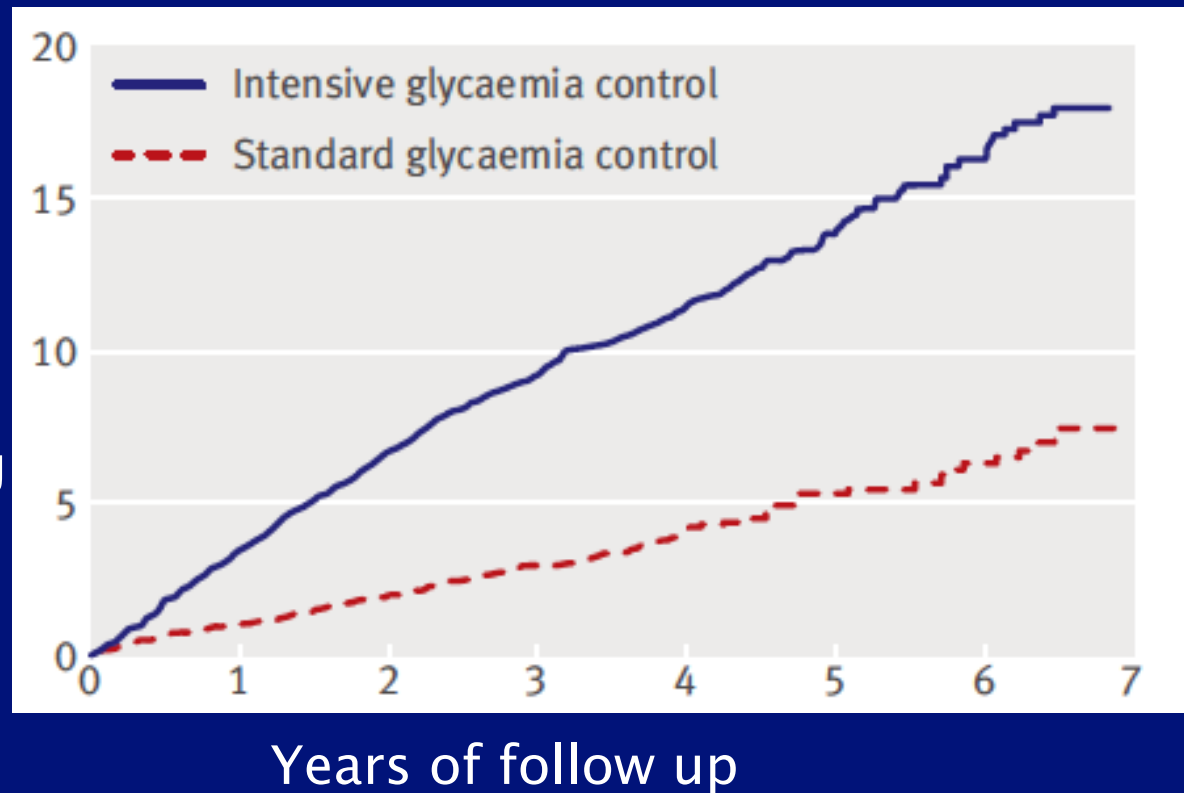
Hospital Admissions for Hyperglycemia and Hypoglycemia among Medicare Beneficiaries, 1999 – 2011

- Hypoglycemia rates 2–fold higher for older patients (≥75 years) compared to younger patients (65–74 years)
- Admission rates for both hyperglycemia and hypoglycemia were 4–fold higher for black patients compared to white patients

Total Charges for Severe Hypoglycemia Hospitalizations in the US

Type 2 Diabetes

Total hospitalizations = 248,422

Charges per hospitalization = $48,569

Total charges = $12.07 billion

Type 1 Diabetes

Total hospitalizations = 20,839

Charges per hospitalization = $46,039

Total charges = $0.96 billion

Average charge of US All–Cause Hospitalization = $33,232

Risk Factors for Severe Hypoglycemia

Risk for severe hypoglycemia is significantly increased in:

- Patients with **hypoglycemia unawareness** (inability to recognize when glucose is going low): up to **6 fold increase**

- **Previous severe hypoglycemic events** i.e. clusters in same individual

- Patients on intensive diabetes therapy

- Older patients

Henderson et al, *Diabet Med* 2003; 20:101
Cryer, *Diabetes* 2008; 57:3169

Apple iOS 8.1 Health Hub

●●●●● AT&T LTE 2:10 PM ⬈ 92% ▮

🔍 Search

- ☰ **All** ›
- 🧍 **Body Measurements** ›
- 🔥 **Fitness** ›
- 👤 **Me** ›
- 🥕 **Nutrition** ›
- ⚗️ **Results** ›
- 🌙 **Sleep** ›
- 🩺 **Vitals** ›

Dashboard | **Health Data** | Sources | Medical ID

●●●●● AT&T LTE 2:10 PM ⬈ 92% ▮

‹ Health Data **Results**

- Blood Alcohol Content ›
- **Blood Glucose** ›
- Electrodermal Activity ›
- Forced Expiratory Volume, 1… ›
- Forced Vital Capacity ›
- Inhaler Usage ›
- Number of Times Fallen ›
- Oxygen Saturation ›
- Peak Expiratory Flow Rate ›
- Peripheral Perfusion Index ›

Dashboard | **Health Data** | Sources | Medical ID

Glooko MeterSync device:
Uploads glucose data from meter to smartphone app via bluetooth

The app:
1) Identifies hypoglycemic measurements (BG $\leq$ 70 mg/dL),
2) Prompts the patient to record contextual information about the hypo event (treatment, cause, associated symptoms)

2 54 mg/dL　　　6:57 PM - 09/28/2014

Glucose Tablet

How many glucose tablets did…

Cancel　　　　Save

Gel

⊘

None

1	2 ABC	3 DEF
4 GHI	5 JKL	6 MNO
7 PQRS	8 TUV	9 WXYZ
	0	⌫

Tool to reinforce appropriate treatment of hypoglycemia:
In practice, over-treatment is a common cause of hyperglycemia following hypoglycemic events

On the treatment screen, there is also an option to record if assistance was needed for treatment (i.e. severe hypo event)

1 37 mg/dL   12:26 AM - 09/13/2014

Juice   Food   Glucose Tablet   Glucose Gel

None

Other   ›

Did you require assistance?

Glucagon Injection   EMT Assistance   Emergency Room

Anything else you want to add?

Care management system notified in near real–time about severe hypo, so that clinic follow–up can be scheduled soon after the event

Patient is prompted to record symptoms associated with hypoglycemia

Patient is prompted to record symptoms associated with hypoglycemia

Patient with normal hypoglycemic warning symptoms

Patient is prompted to record symptoms associated with hypoglycemia

Patient with hypoglycemic unawareness i.e. no autonomic warning symptoms
Neuroglycopenic symptoms are the first indicator of hypoglycemia

●●●●○ AT&T LTE   9:57 PM   ⌁ ⁂ 75% ▉

Quit   Next

1 37 mg/dL   12:26 AM - 09/13/2014

What symptoms did you feel?
[select all that apply]

Trembling   Nervous   Heart Pounding   Sweating

Fatigue   Unusual Hunger   Discomfort in Legs   Feeling Cold

Numb Lips   Depressed   Hard to Focus   Light Headed
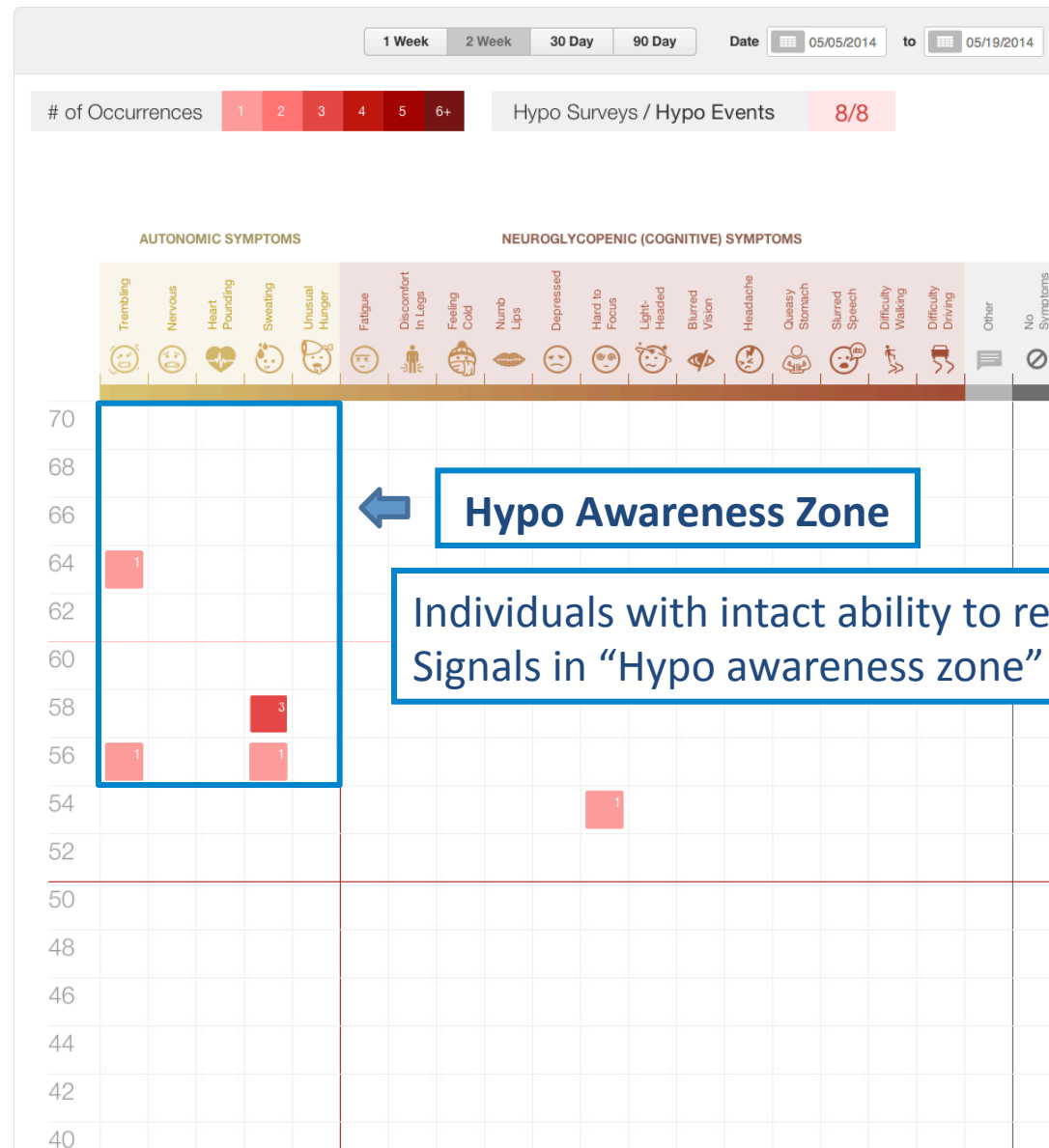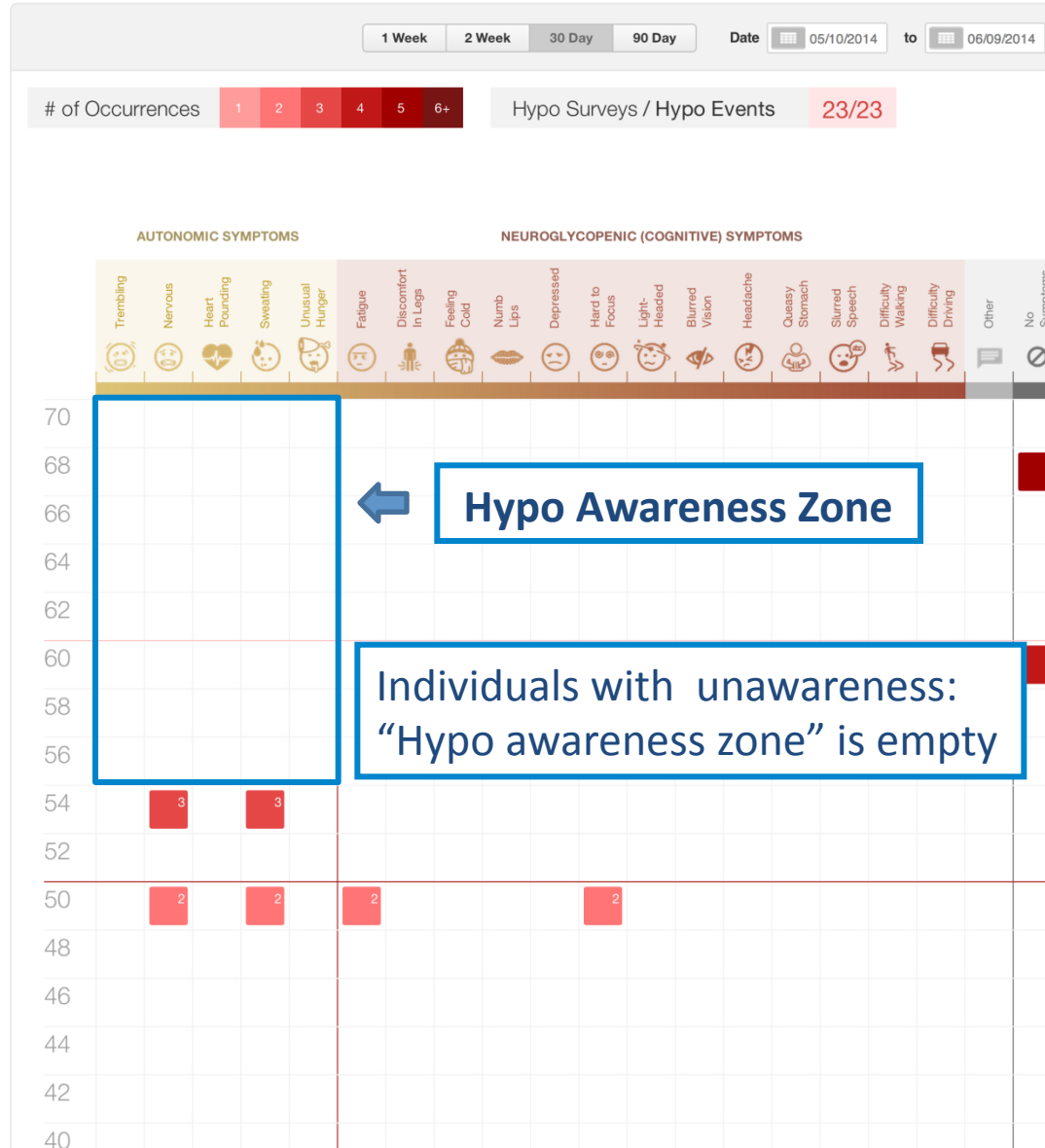
Blurred Vision   Headache   Queasy Stomach   Slurred Speech

Awareness | Patterns | Day

Joslin HypoMap

HypoAwareness

1 Week | 2 Week | **30 Day** | 90 Day   Date 05/10/2014 to 06/09/2014

# of Occurrences 1 2 3 4 5 6+   Hypo Surveys / Hypo Events **23/23**

AUTONOMIC SYMPTOMS   NEUROGLYCOPENIC (COGNITIVE) SYMPTOMS

Trembling | Nervous | Heart Pounding | Sweating | Unusual Hunger | Fatigue | Discomfort in Legs | Feeling Cold | Numb Lips | Depressed | Hard to Focus | Light-Headed | Blurred Vision | Headache | Queasy Stomach | Slurred Speech | Difficulty Walking | Difficulty Driving | Other | No Symptoms

Hypo Awareness Zone

Individuals with unawareness: "Hypo awareness zone" is empty

Awareness | Patterns | **Day**

Joslin HypoMap

HypoDay

| BG List | **Time of Day** | | 1 Week | 2 Week | **30 Day** | 90 Day | Date | 04/30/2014 | to | 05/30/2014 |

Displays collected contextual information from each hypo episode, and glucose data for 12 hours before and after the episode

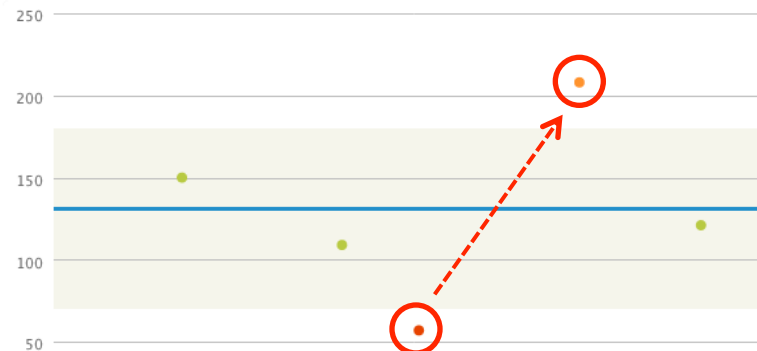PERCEIVED CAUSES | TREATMENT

12AM - 6AM

| TUE 20 MAY | 57 | ☾ 02:40 AM | Sweating | Exercise | Juice - 8 oz orange juice |

250

200

150

100

50

6:00 AM | 8:00 AM | 10:00 AM | 12:00 PM | 2:00 PM

Tuesday
05/20/14

- Provides **detailed information to enhance clinical decision-making**
- Turns hypo events into **'teachable moments' improving patient insights into how to prevent and treat hypos**
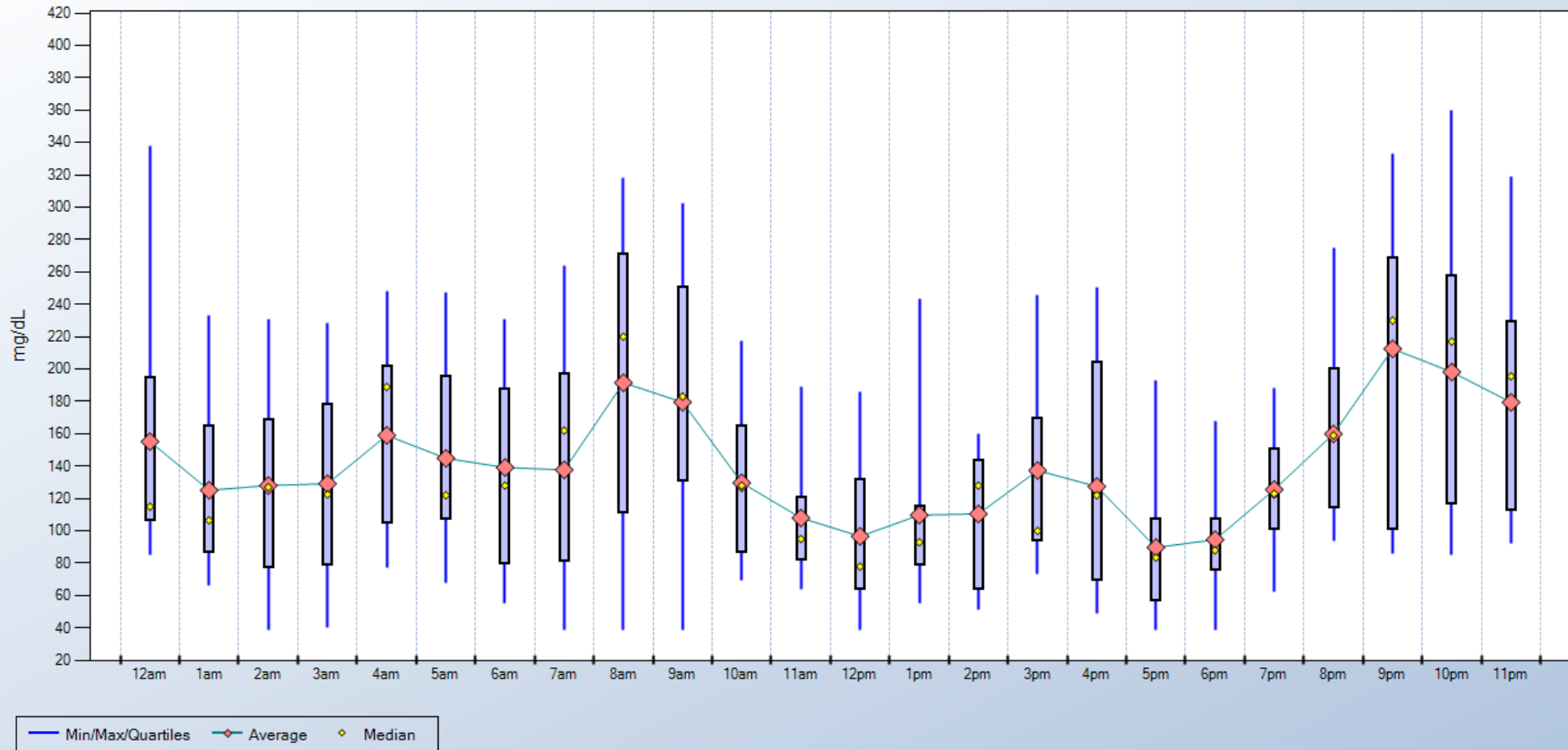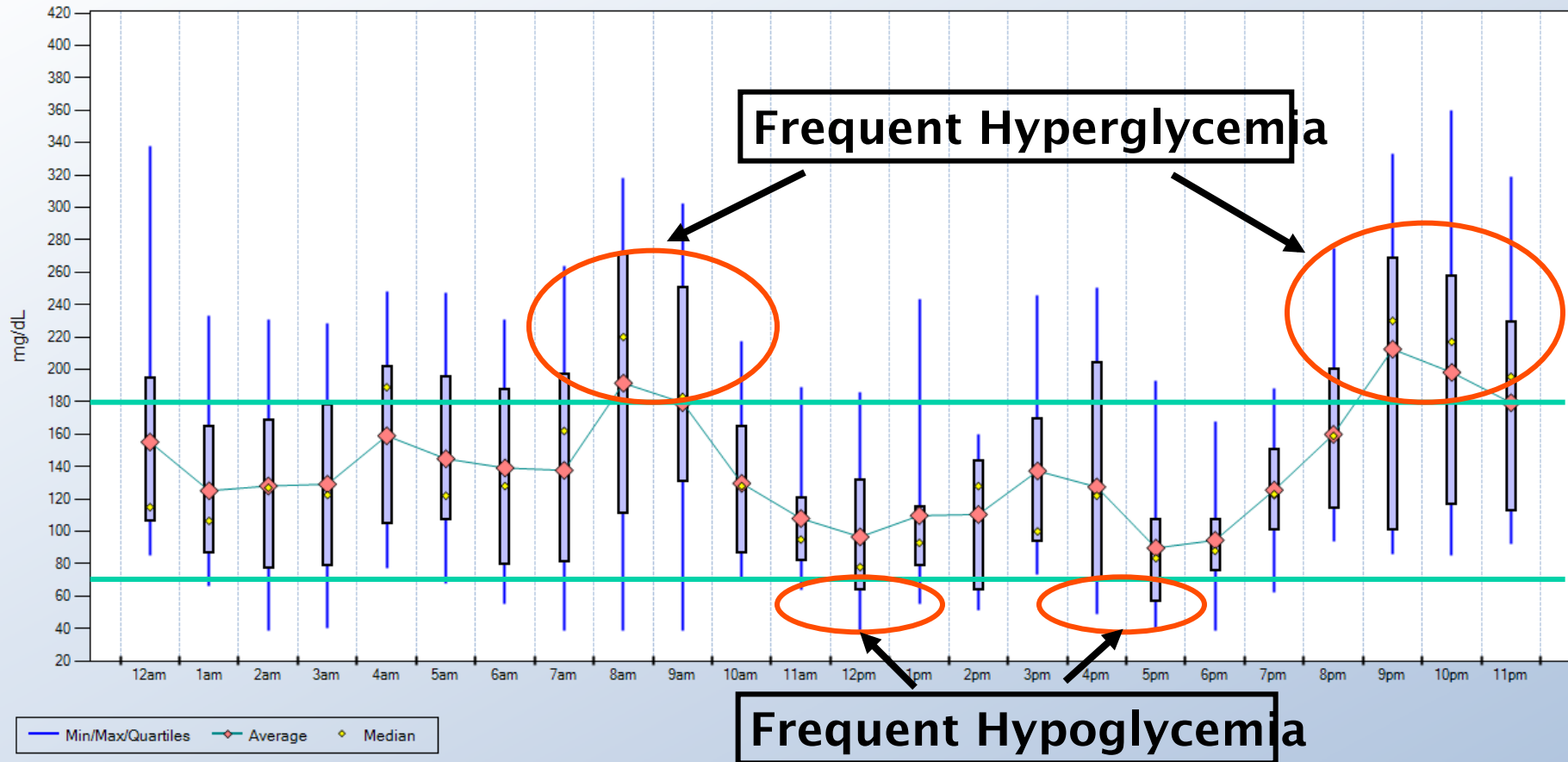
12PM - 6PM
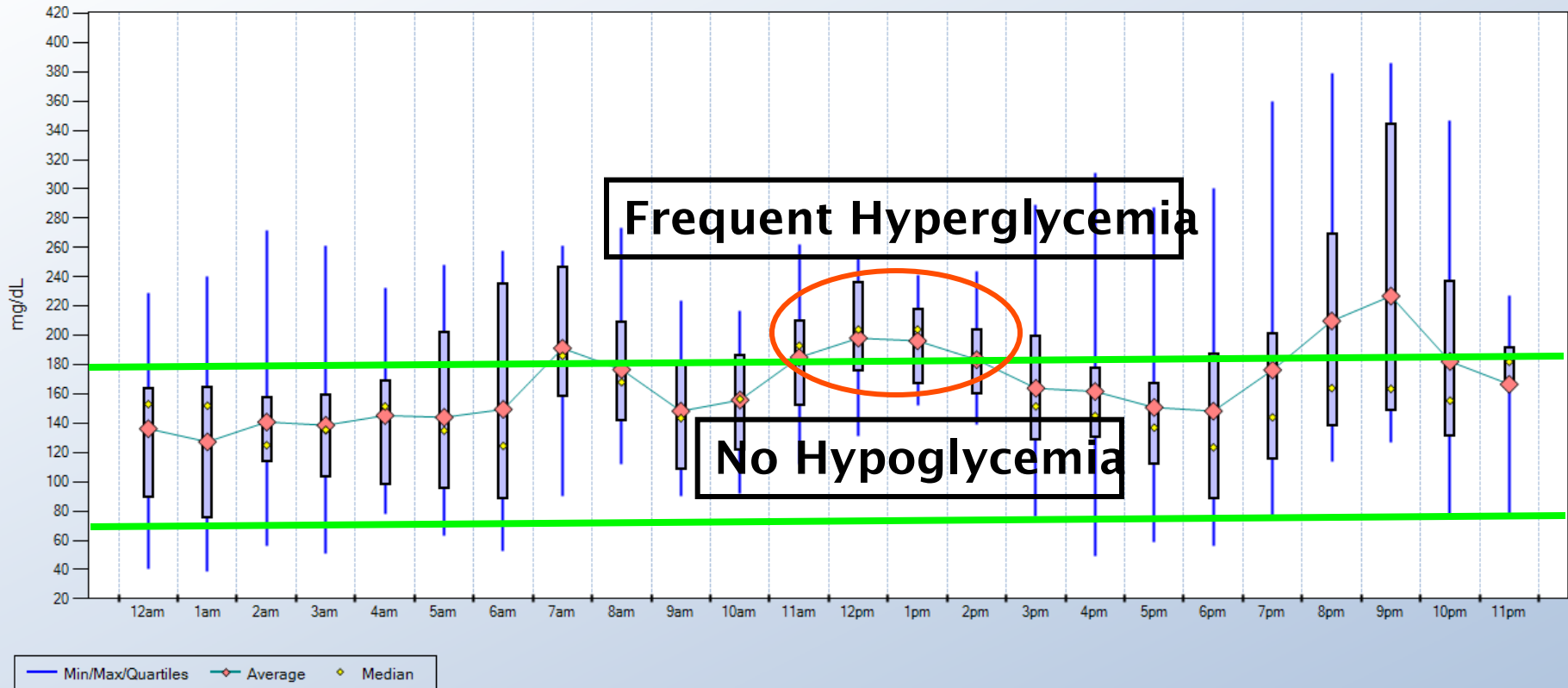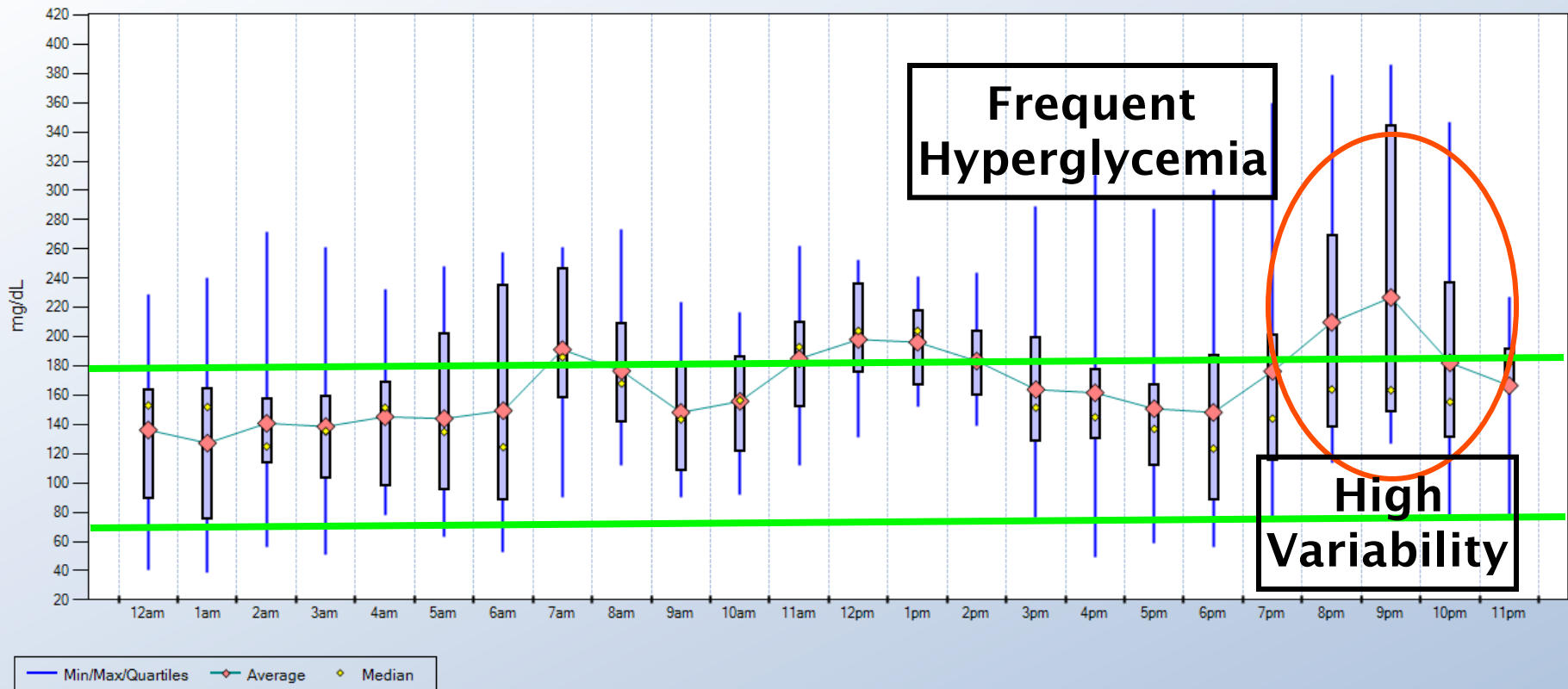
| MON 26 MAY | 60 | 04:15 PM |

Using Data Analytics to Identify Glycemic Trouble Spots

Using Data Analytics to Identify Glycemic Trouble Spots

Using Data Analytics to Identify Glycemic Trouble Spots

Using Data Analytics to Identify Glycemic Trouble Spots

Summary

Initiating Insulin Therapy:

- Importance of matching insulin action and food intake to

   avoid hyper- and hypo-glycemia
- More predictable kinetics of analog insulin with less risk for hypoglycemia

Monitoring Insulin Therapy:

- To avoid the extremes of hyper- and hypo-glycemia often need to do more than just adjust insulin doses
- Assess if dietary macronutrients (including fat) are impacting on postprandial glucose fluctuations