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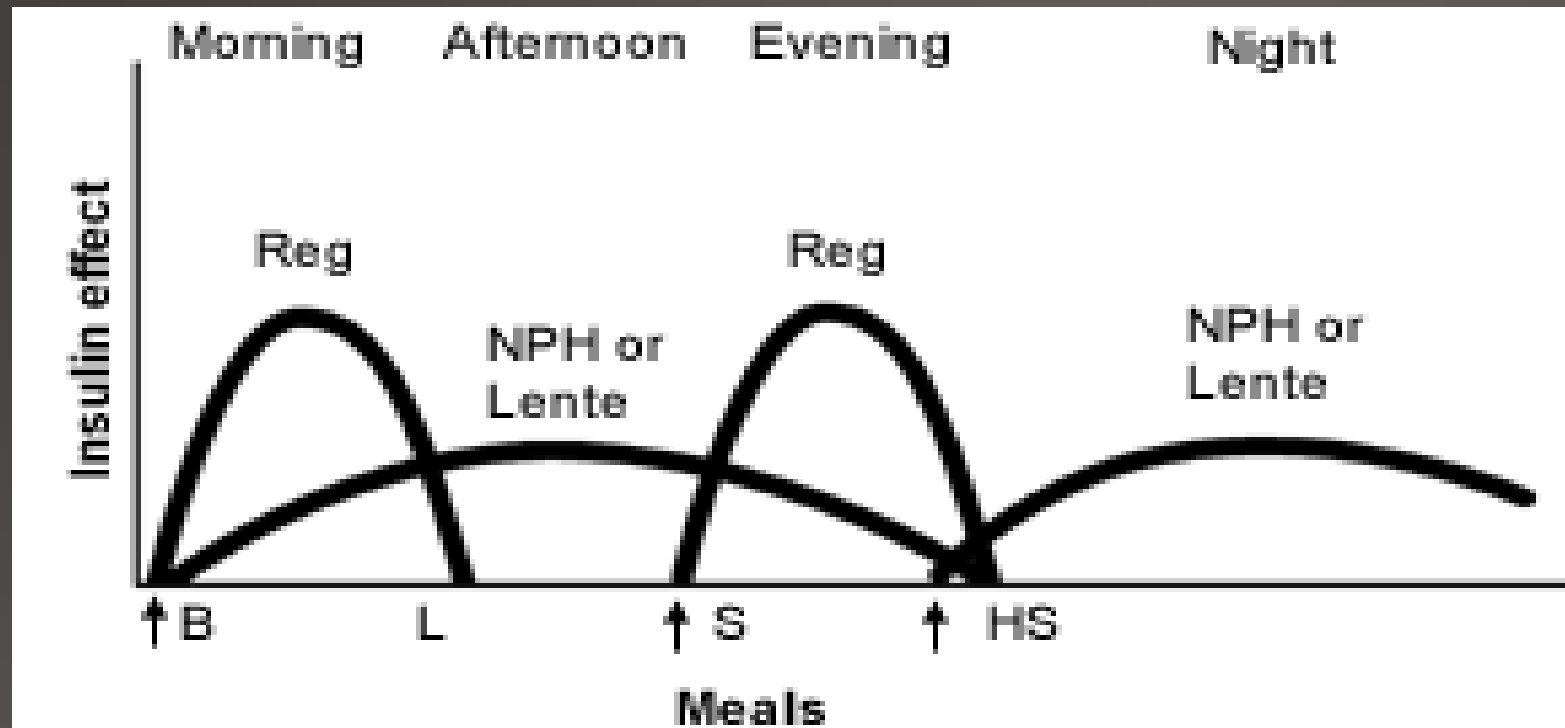
Naomi Berrie Diabetes Center, New York City

# Insulins, Pumps, and Glucose Sensors

# Insulin

- 1922 insulin is isolated and used in humans
- 1980s “Human” insulin is produced – synthetic and no longer derived from animals
- Mid 1990s rapid acting insulin is developed (Lispro/Humalog): PRANDIAL INSULIN
- Glargine (Lantus) available in 2000: BASAL INSULIN
- **Benefit of prandial and basal insulins: most physiologic treatment with the least risk of hypoglycemia**

## 2 injections per day: NPH and Regular



**MUST "FEED THE INSULIN" AT THE SAME  
TIME EVERY DAY AND EAT FIXED  
CARBOHYDRATE AMOUNTS**

# “Split-Mix” Insulin Therapy

## Advantages

- Relatively easy to use, only given at breakfast and dinner
- Covers insulin requirements through most of day
- Lower cost with NPH and Regular insulin

## Disadvantages

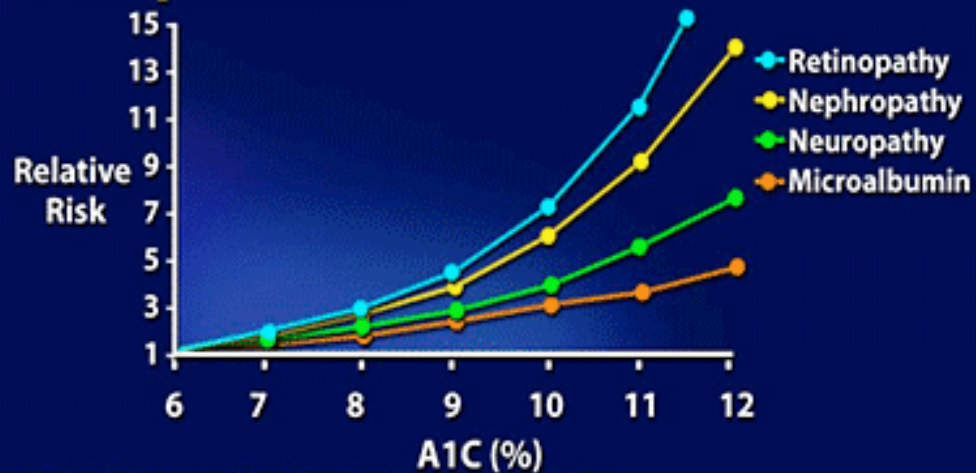
- Not very physiological
- Greater likelihood of nocturnal hypoglycemia
- Greater chance of fasting hyperglycemia
- Have to eat certain amounts at certain times “fixed meals”
- Difficult to achieve a goal A1c

# DCCT/EDIC

- Why intensive treatment?
- Landmark studies in type 1 diabetes
- Set the standard for diabetes care
- Reduces the risks of complications
- Critical for QOL

# Diabetes Control and Complications Trial: DCCT, NEJM, 1995

## DCCT: A1C and Microvascular Complications



Skyler JS. *Endocrinol Metab Clin North Am.* 1996;25:243-254.

Multiple daily injections (4 or more) versus conventional therapy (2 injections per day). MDI had a significant impact on A1c control and complications.

# Current Management – Best Practice

- Basal/bolus with a long acting 1 time per day insulin and rapid acting pre meals is the most modern, best method if possible
- The most freedom and spontaneity
- Can eat what you want when you want it
- No set carbohydrate amounts, can adjust for exercise
- Less risk of severe hypo/hyperglycemia

**BUT....**

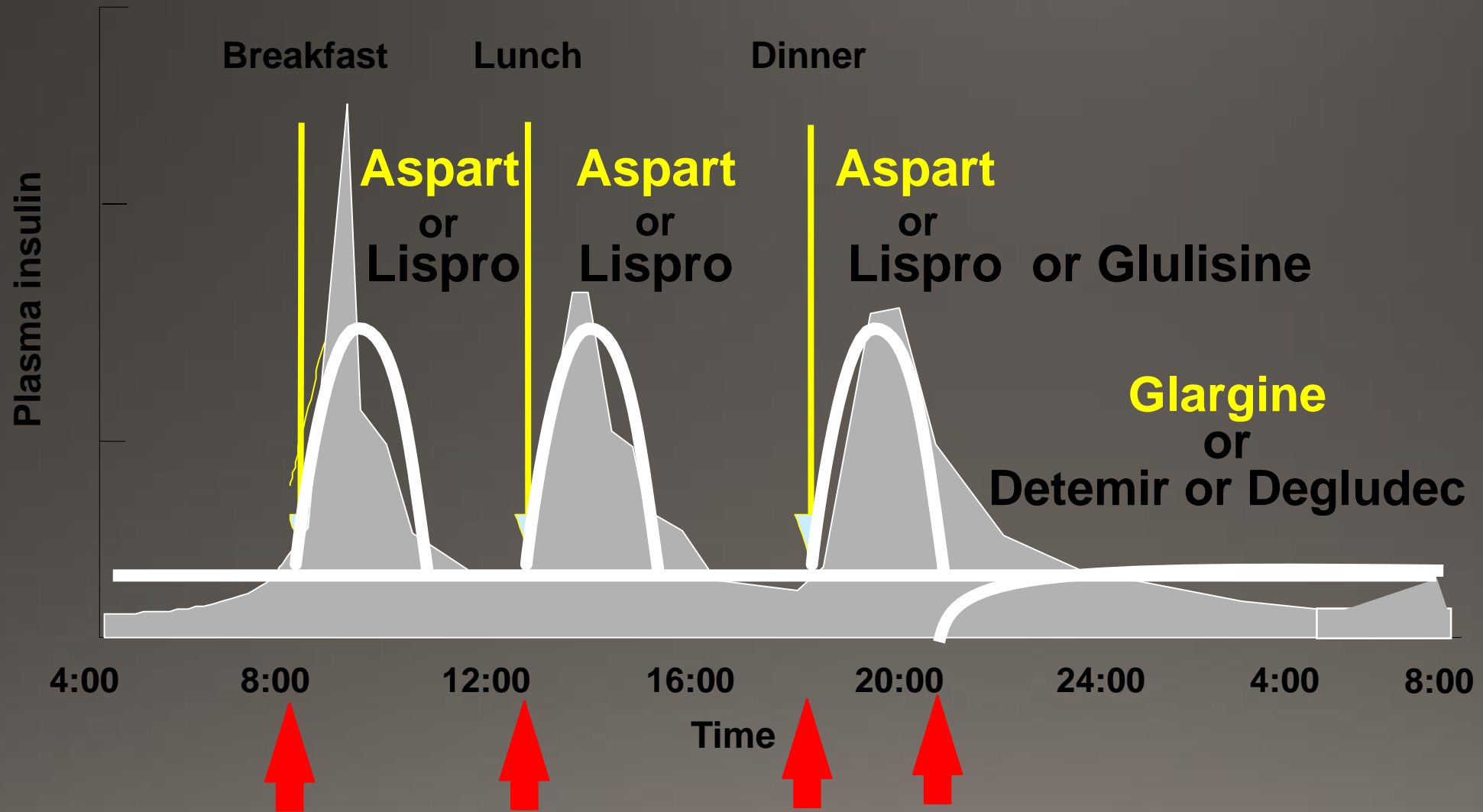
- Most intensive
- Requires frequent blood sugar checks and many injections
- Expensive

# The Basal/Bolus Insulin Concept

- **Basal insulin** (single injection of long-acting insulin or 2 injections of intermediate acting insulin)
  - Suppresses glucose production between meals and overnight
  - Usually 40% to 50% of daily needs
- **Bolus insulin** (mealtime rapidly-acting insulin)
  - Ideally given before eating, up to 15 minutes
    - Limits hyperglycemia after meals
    - Immediate rise and sharp peak at 1 hour
    - Usually 10% to 20% of total daily insulin requirement for each meal

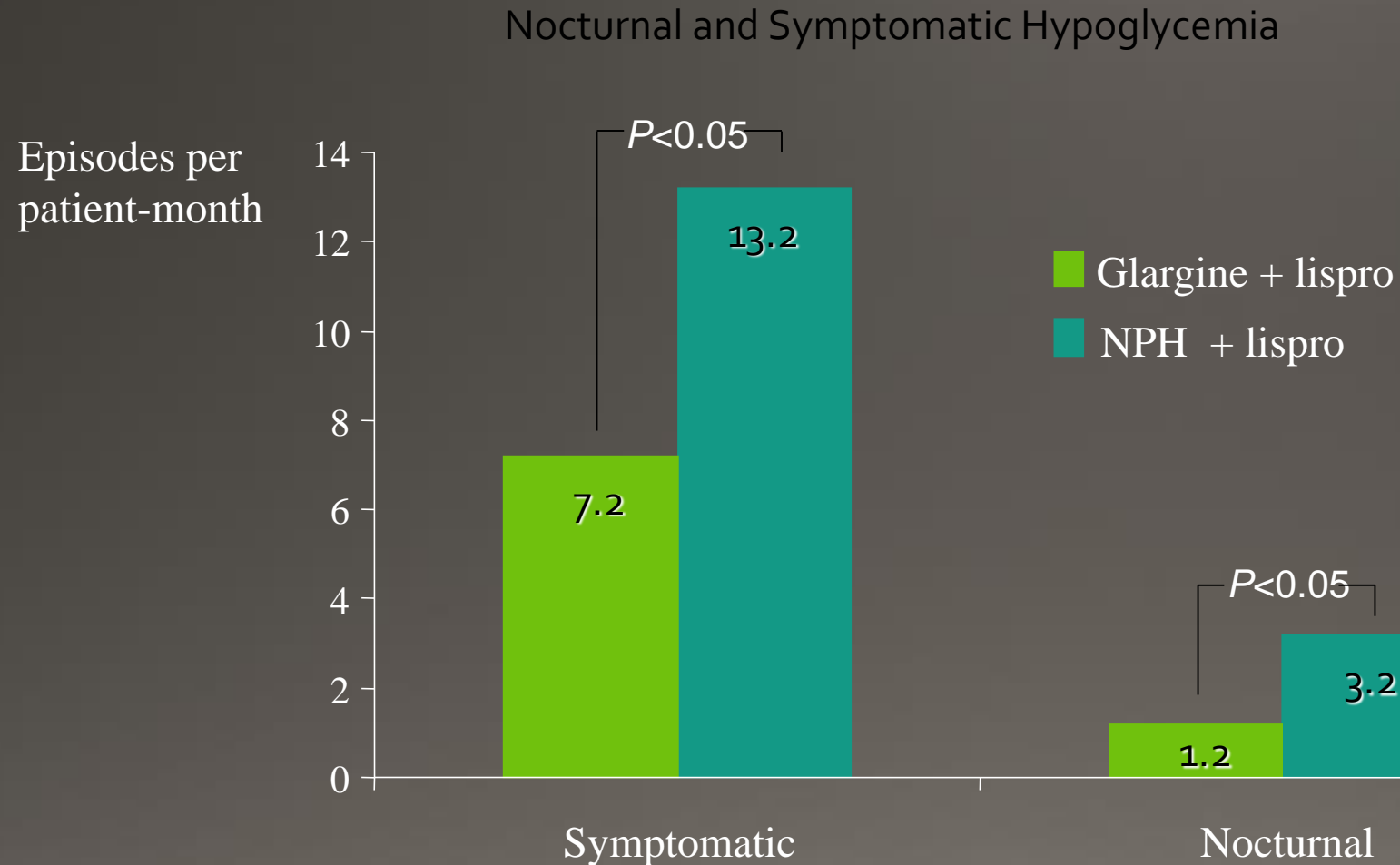


# Basal/Bolus Treatment Program with Rapid-acting and Long-acting Analogs

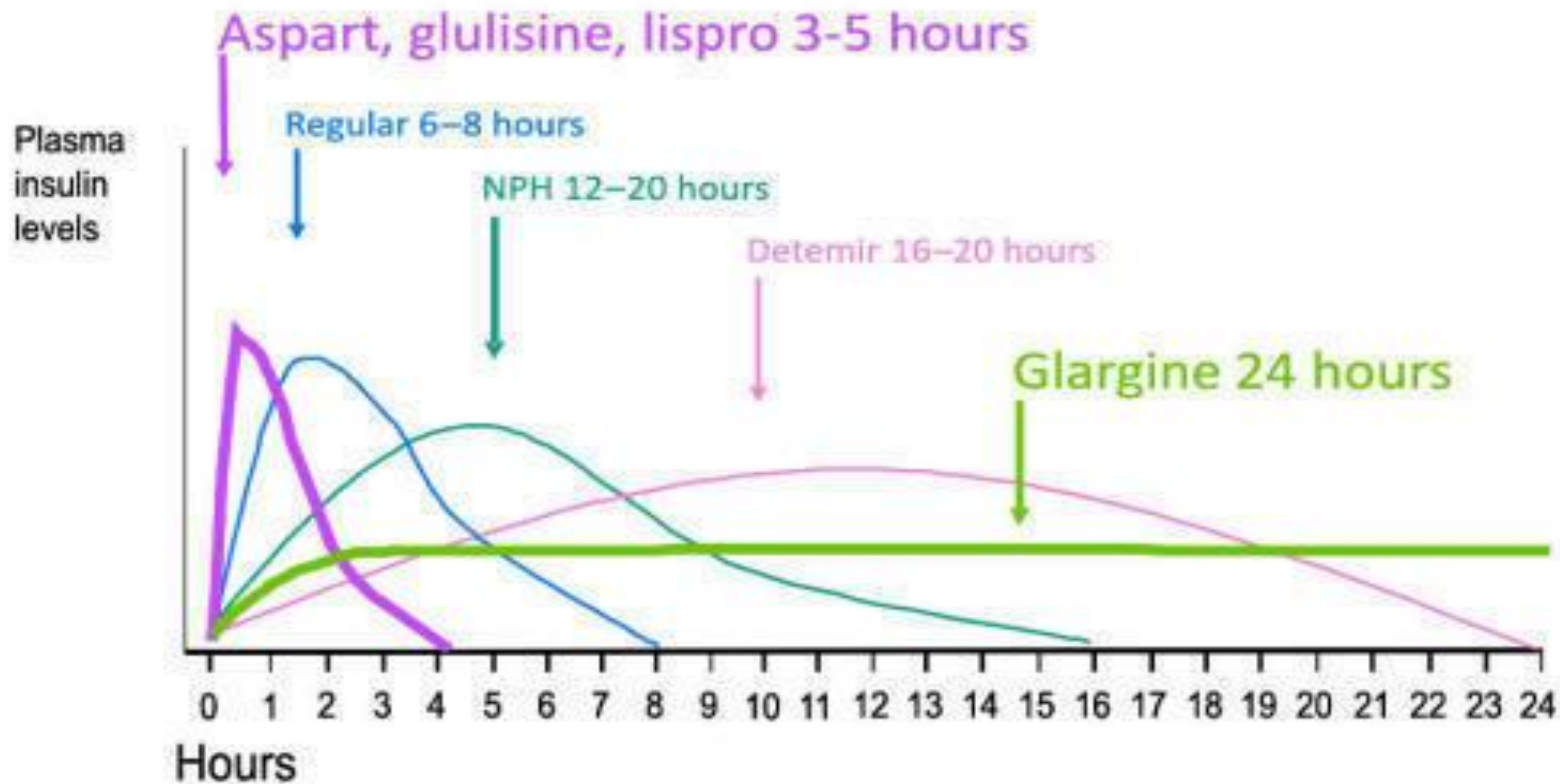


# Basal Insulin and Hypoglycemia

## Glargine vs NPH Insulin



# Insulin type and duration of action



# Insulin type and cost

- **Most popular combination is a long acting like glargine and a short acting like lispro**
- Cost is ~ \$900 per month
- Older insulins like NPH and Regular have fallen out of favor but do play a role in certain situations
- Cost is ~ \$300 per month
- Test strips ~ \$300-400 per month

# Summary: Basal Insulins (Subcutaneous Injections)

	Onset of Action	Peak Action	Duration of Action
Intermediate Acting:			
NPH, NPL, NPA	1 - 4 hours	4 – 10 hours	14 – 24 hours
Detemir	3 - 4 hours	4 – 8 hours	6 – 24 hours
Long Acting:			
Glargine	2 – 3 hours	none	22 – 30 hours
Ultra Long-Acting:			
Degludec	Steady start after 2-3 days	None (half-life ~ 25 hours)	Up to 42 hours +

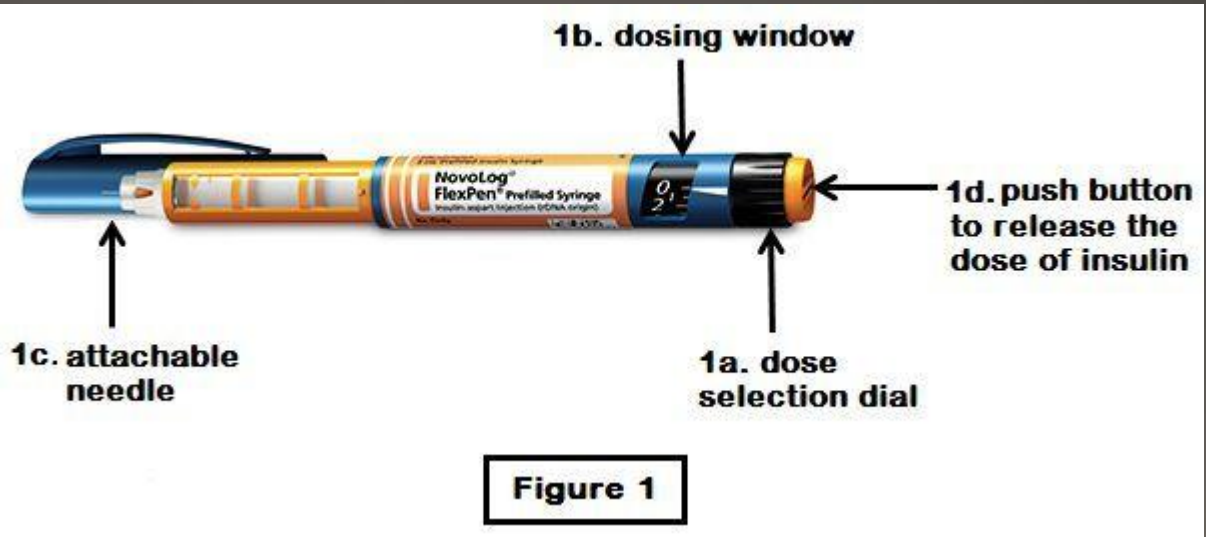
# Summary: Bolus Insulins

	Onset of Action	Peak Action	Duration of Action
<b>Rapid-Acting (U100): Subcutaneous injection</b>  Lispro, Aspart, Glulisine	5 - 30 min	0.5 – 3 hours	3 – 5 hours
<b>Short-Acting: Subcutaneous injection</b>  Regular (U-100)	30 - 60 min	1 – 5 hours	6 – 8 hours

# Premixed Insulins

Insulin	Components	Onset	Peak	Duration
Human 70/30	70% NPH 30% Regular	30 min	2-4 hrs	8-12 hrs
NovoLog Mix 70/30	70% aspart protamine 30% aspart	15 min	1-4 hrs (Mean 60 min)	8-12 hrs
Humalog Mix 75/25	75% lispro protamine 25% lispro	15 min	1-4 hrs (Mean 60 min)	8-12 hrs
Human 50/50	50% Regular 50% NPH	30 min	2-4 hrs	8-12 hrs
Humalog Mix 50/50	50% lispro 50% lispro protamine	15 min	1-4 hrs	8-12 hrs

# Insulin Delivery: Injections





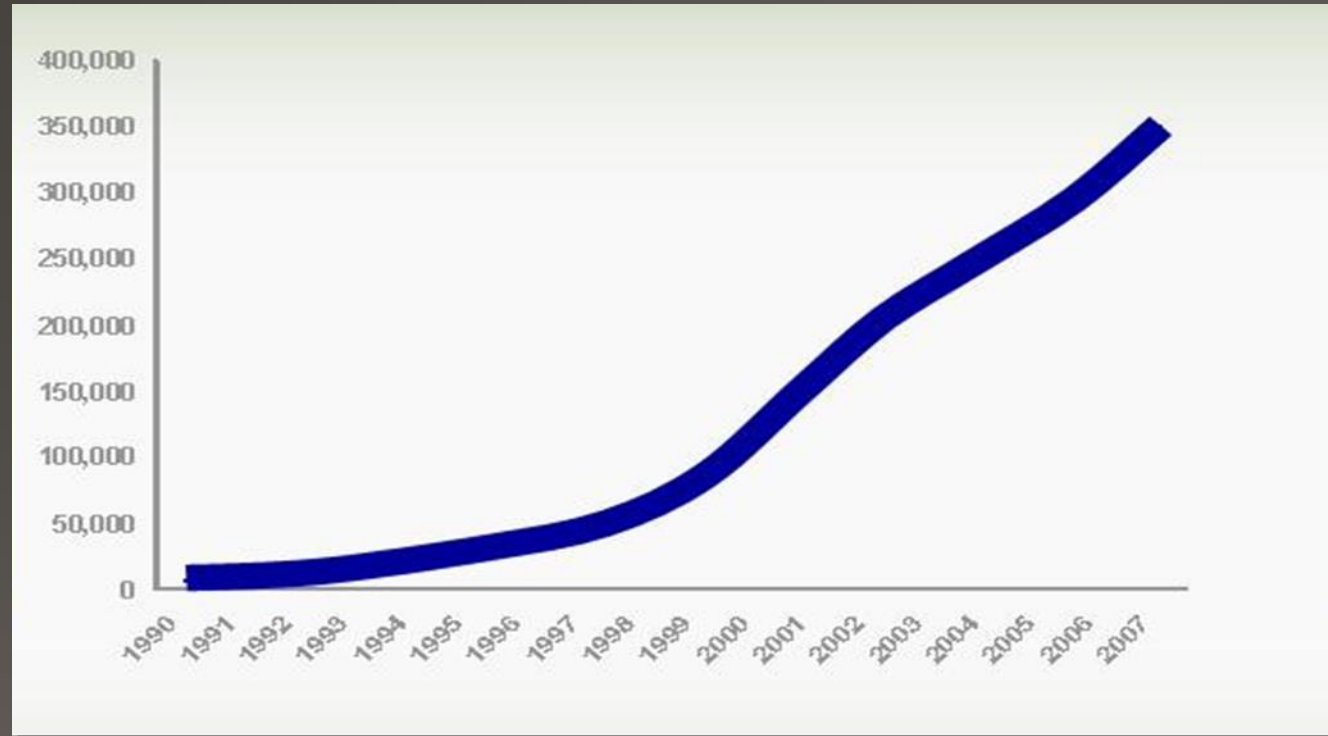
# Pumping Insulin

- Revolutionized diabetes management
- Precise and personalized
- Micro doses (0.025 units)
- **Greater lifestyle flexibility/spontaneity**
- Less pain

# Pumps have come a long way



# Number of People Using Insulin Pumps in U.S.



# Insulin Pumps (Continuous Subcutaneous Insulin Injection)

- External insulin pump connected to an indwelling subcutaneous catheter; infuses rapid-acting insulin
  - Can program variable basal profiles and temporary basal rates
  - Bolus doses for meals and correction
- Dose bolus calculator function
- Bolus history; Alarms/reminders
- Can download data to computer/smartphone
- Some pumps can integrate with CGM  $\pm$  low glucose threshold suspend feature

# Insulin Pumps

- Pumps do NOT check blood sugars
- Pumps do NOT count carbs
- Pumps DO the carb and correction calculations
- Pump DO account for insulin on board
- Pumps are worn during the day and night
- Can disconnect pump for exercise, shower and swimming – less than 2 hours (does not apply to tubeless pump)

# Pump Brands



# Pump Components

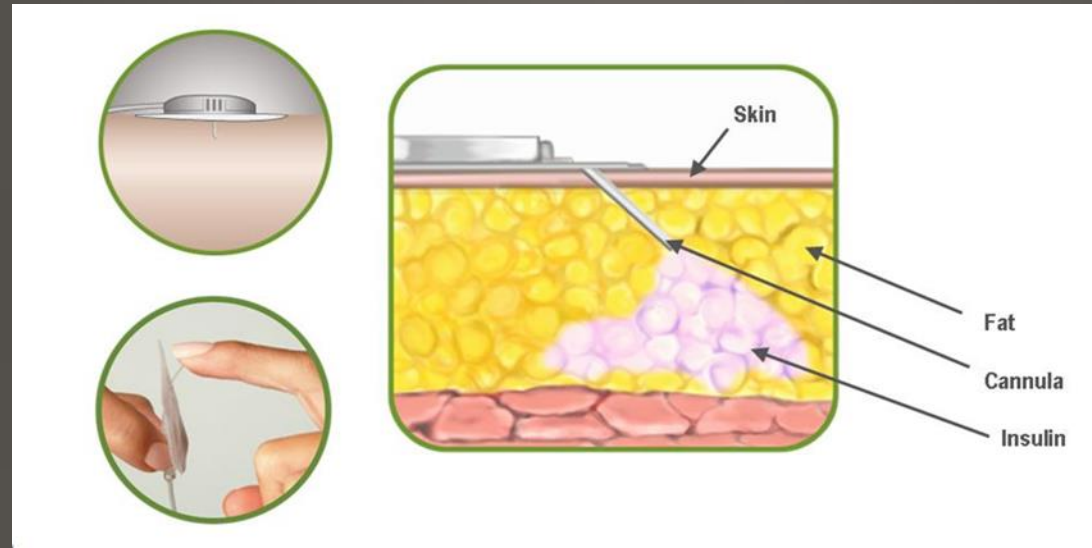


= Pump Therapy



- Cannula – The small plastic tube
- Pump Sites are inserted either manually or by an inserter
- Pump sites must be changed and rotated every 2-3 days to prevent infection, hypertrophy, or scar tissue

# Infusion Sites



Cannula slanted (45 Degrees )  
Or straight (90 Degrees)

Sites are the same body areas  
where you inject insulin

Infusion site failures cause  
unexplainable high sugars –  
high risk of DKA



# Pump Settings

- Basal rates
- Bolus dose
  - carbohydrate ratio
  - correction factor
- Target glucose level
- Active insulin time

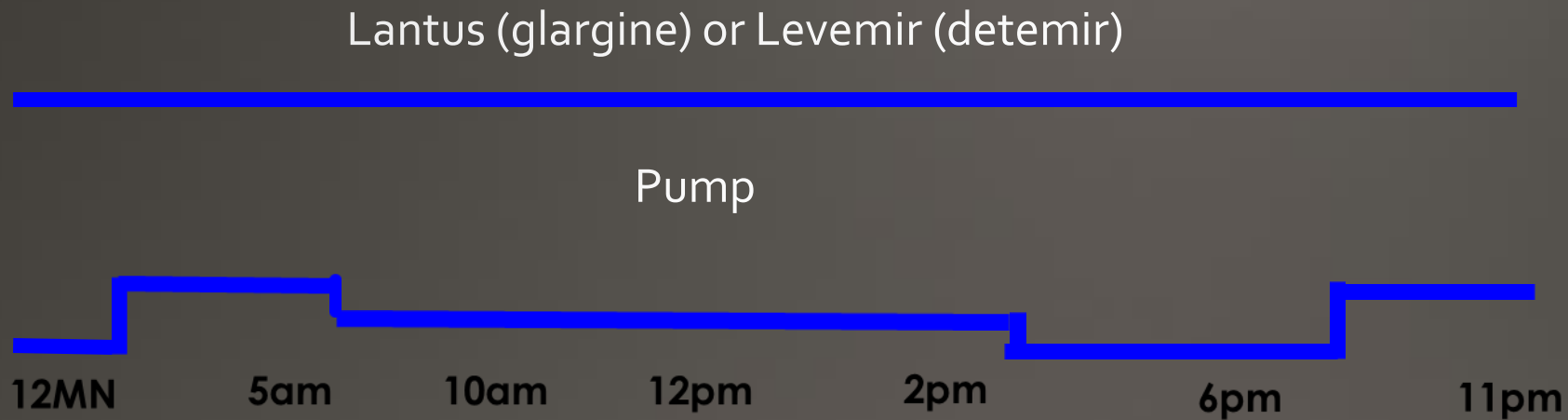
# Basal Insulin

- Replaces Lantus/Levemir insulin (basal insulin)
- Delivers small doses of insulin in Units per Hour (u/hr); doses determined by the physician
- Mimics physiologic insulin release
- Delivers insulin automatically and continuously throughout the day and night
- It is not meant to bring down/correct high blood sugars or cover food
- It is usual for people to need different basal rates for various times of day

# Basal Insulin

- Rates can be adjusted temporarily using a temporary basal rate
- Adjust the basal up by 10, 20, 30% etc to account for increased insulin needs (i.e., illness)
- Adjust the basal down to account for lower insulin requirements (i.e., activity)

# Basal Options: Multiple daily injections vs Insulin Pump



**Example Basal Pattern: 12MN 0.3 units/hr**

**2am 0.55**

**6am 0.4**

**3pm 0.3**

**9pm 0.55**

**Total basal 9.85 units**

A pump offers more reliable insulin delivery that matches need plus convenience

# Bolus Dose

- A bolus of insulin is given for meals and to correct hyperglycemia
- The pump will calculate the bolus based on the carbohydrate ratio, correction factor or both
- User enters the number of carbohydrates to be eaten and a blood sugar
- Can program multiple different ratios throughout the day
- A target blood sugar is set, for example 120 mg/dl during the day and 150 mg/dl overnight, to minimize the risk of hypoglycemia

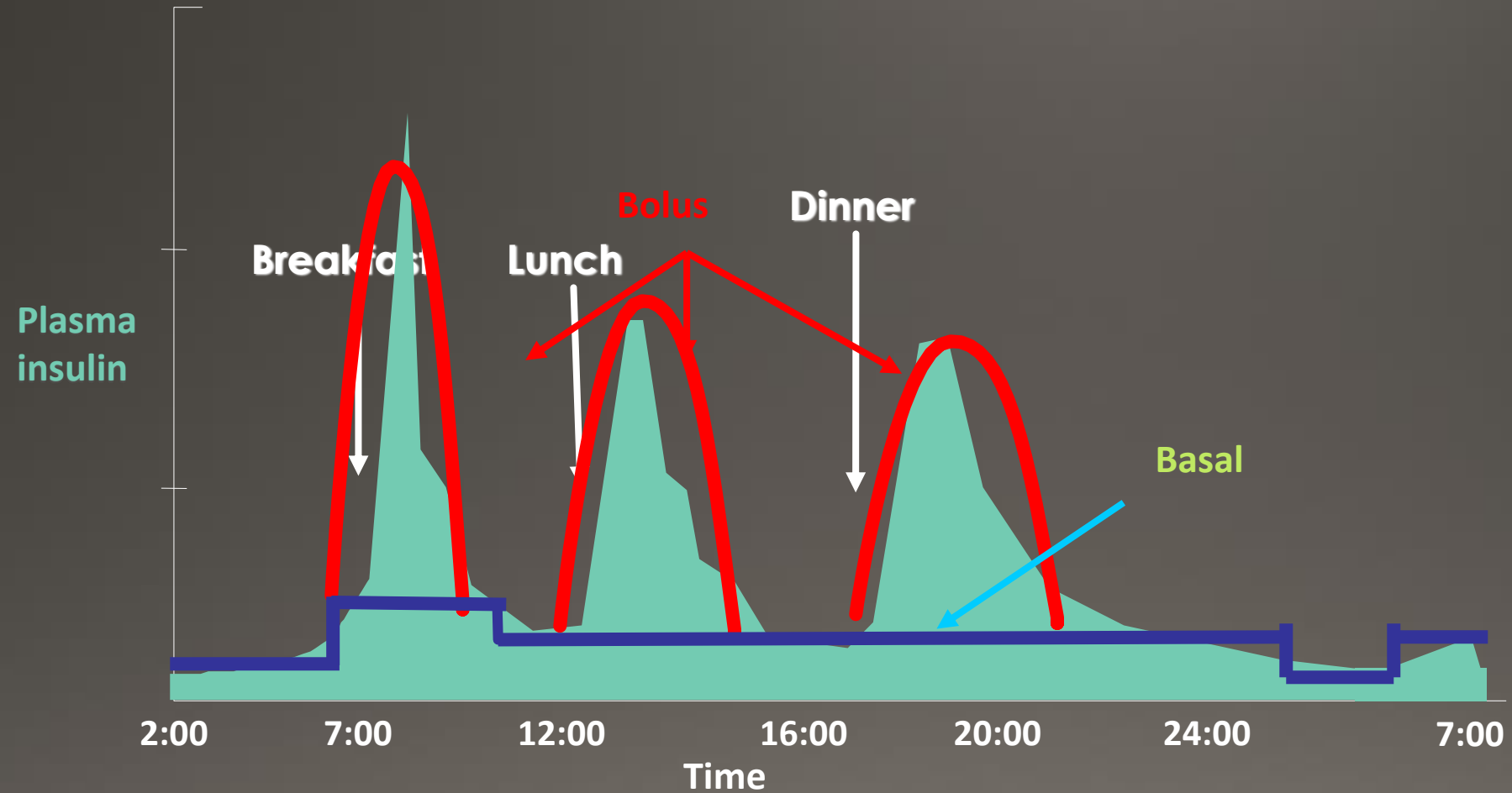
# Bolus Dose

- Carb Ratios (ICR):
  - ☐ Dose to cover grams of carbs
  - ☐ IC 1:10
  - ☐ A meal of 56g of carbs will be covered with 5.6 units
- Correction Ratio (Sensitivity):
  - ☐ Dose to bring down a high glucose value over the target
  - ☐ ISF 1: 50
  - ☐ Target 100
  - ☐ A high BG of 238 will be corrected with 2.76 units

# Bolus Dose

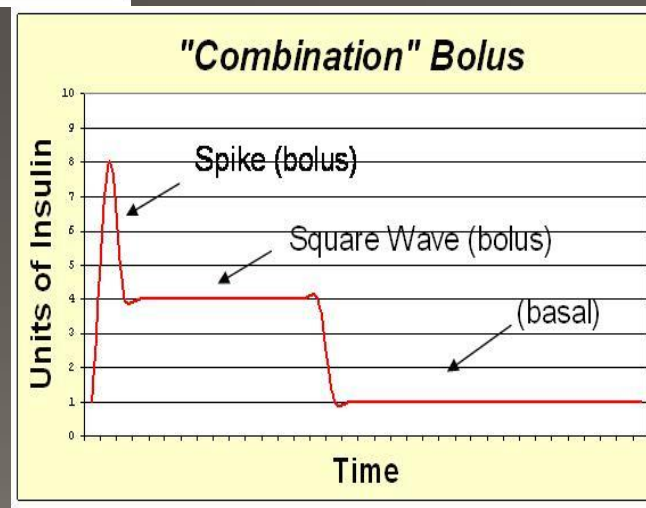
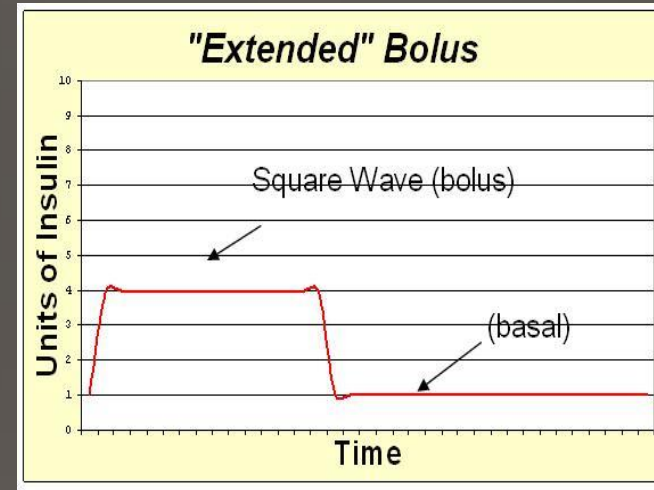
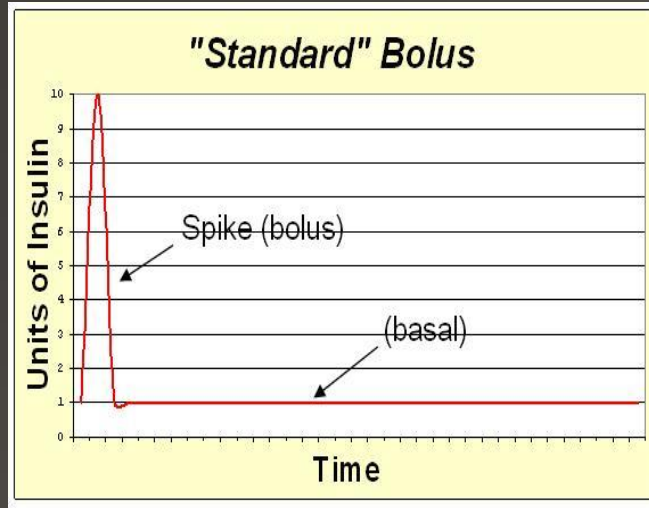
- Active Insulin Time: defines how soon the user can take another insulin bolus
- Logarithmic formula used by the pump to ensure that the user does not “stack” excessive insulin doses risking hypoglycemia
- Will account for “insulin on board” in determining the dose
- Usually set for 2.5-4 hours
- Any dose can be overridden by the user

# Pump Terms: Basals And Boluses





# Different Boluses



# Pump Candidates

- Adequate maturity and family support
- Acceptance of diabetes and pump
- Monitor blood sugar at least 4 times a day
- Count carbohydrates
- Extensive diabetes education
- Good problem-solving and diabetes management skills
- Improves glycemic control and quality of life if used correctly
- Will reduce severe glycemic excursions

# Pump Candidates

- Very useful in toddlers who are “picky” eaters
- Athletes
- Puberty
- Grazing

# Possible Disadvantages

- High degree of technical aptitude
- High level of engagement
- Skin reactions
- Risk of DKA from site malfunctions
- Body image
- Cost

# Checking blood sugars



# Continuous Glucose Monitor (CGM)

- Measures the interstitial glucose every 5 minutes
- Shows blood glucose trends/arrows
- Alert for low and high BS (ie 70mg/dl and 250mg/dl)
- Helps to reduce number of blood sugar checks per day
- Must test blood sugar to calibrate
- Sensor site changed every 6-7 (14) days
- Not as accurate at extreme high and low blood sugars
- Lags behind actual blood glucose levels



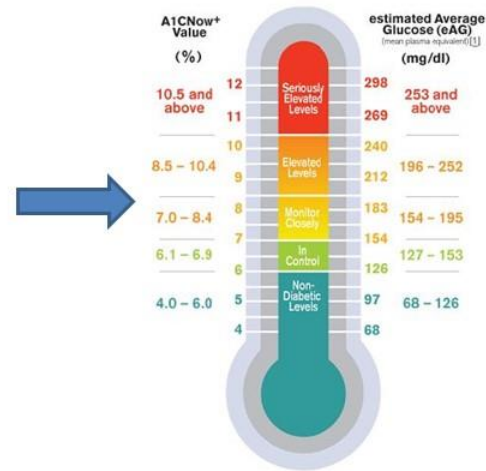
# ADA Guidelines 2017

Patients on multiple-dose insulin (MDI) or insulin pump therapy should do SMBG prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving.

# Knowledge is Power

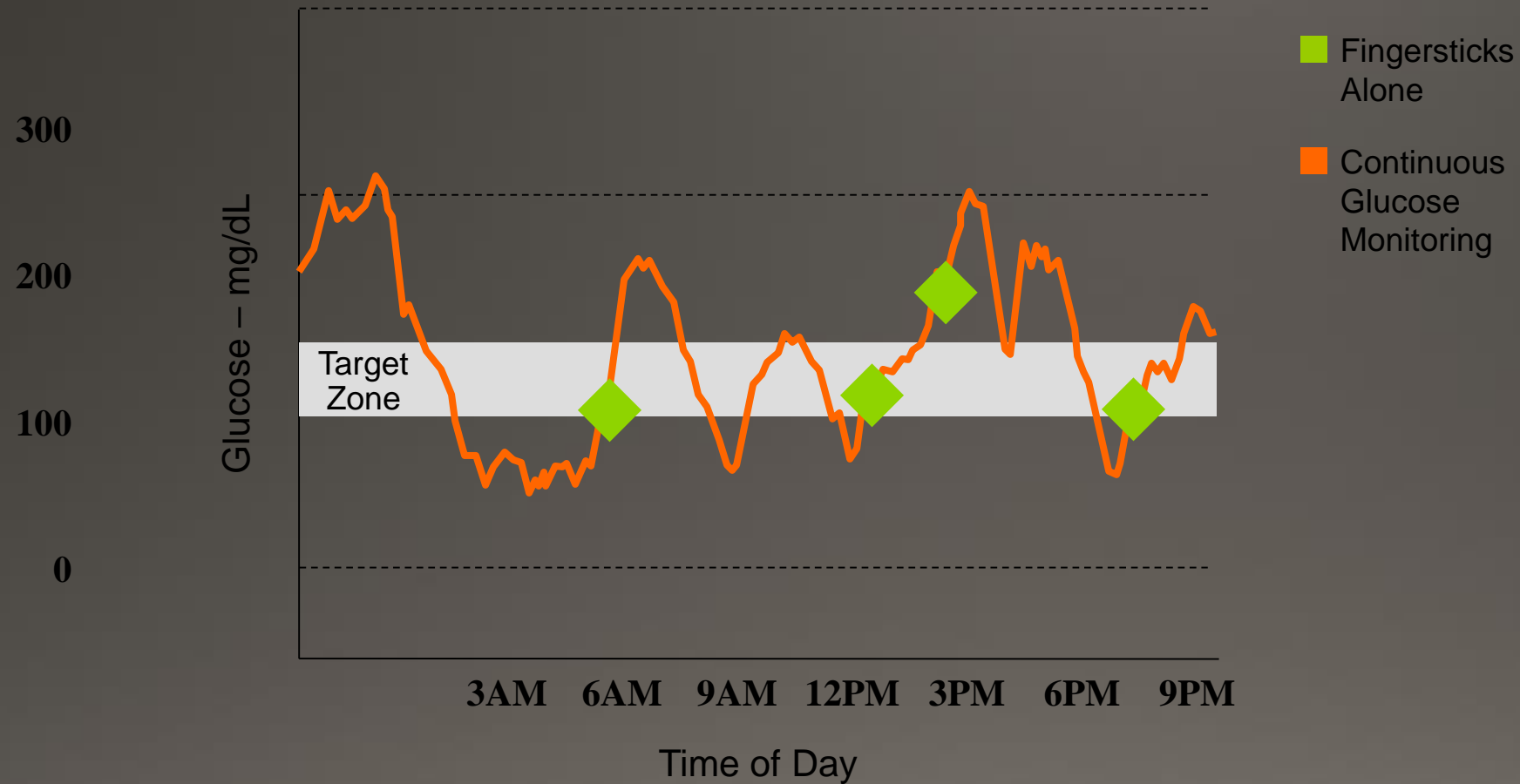
KNOW YOUR NUMBER!

INCREASED FINGERSTICK GLUCOSE TESTING  
CORRELATES WITH LOWER HBA1C





# Fingersticks don't tell the whole story: the value of CGM

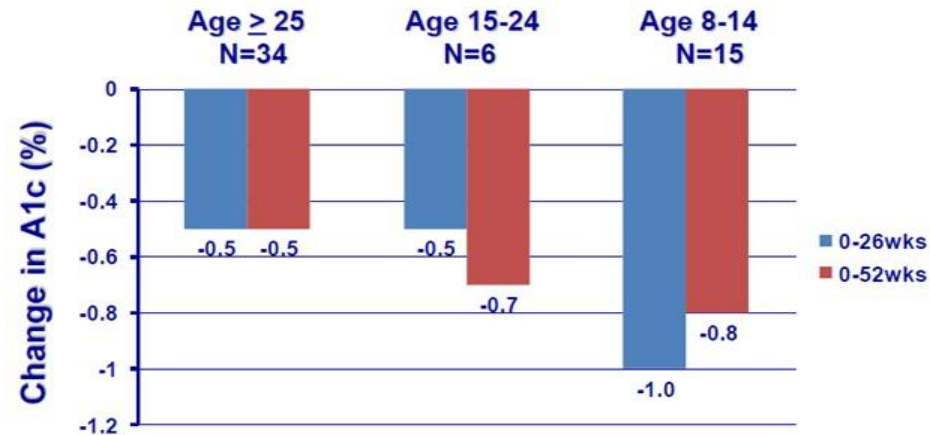


# ADA Guidelines 2017

- When used properly, continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens is a useful tool to lower A<sub>1</sub>C in selected adults (aged ≥25 years) with type 1 diabetes.
- Although the evidence for A<sub>1</sub>C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device.
- CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes.

# Benefits of CGM

Pediatrics, Adolescents and Adults with  $\geq 7\%$  A1c Showed Reduction of A1c with Frequency of CGM Use ( $\geq 6$  day/week) at 12 Months



*Diabetes Care.* 2009; 32:1947-1953.

*Diabetes Technology and Therapeutics.* 2010; 12(7):507-515.

# Benefits of CGM

- Reduction in A1c levels *without* increased hypoglycemia<sup>1,2,5,6</sup>
- Significant decrease in A1c in patients who wear it<sup>2,6,7</sup>
- More benefit with more frequent use<sup>2,6,7</sup>
- Reduced glucose variability<sup>3-4</sup>
- Increased time in target range<sup>1,2,4</sup>
- Reduced hypo-<sup>2-4,7</sup> and hyperglycemic excursions<sup>2,3,4</sup>
- Consistent accuracy over 7 days of use (G4Platinum)<sup>1,5</sup>
- A1c reduction with BOTH MDI and CSII patients<sup>1,2,5,6</sup>
- CGM helps improve A1c and glycemic control from both high and low A1c patients<sup>1,2,6,7</sup>

1. Garg S, et al. *Diabetes Care*. 2006;29(12):2644-2649.

2. JDRF Continuous Glucose Monitoring Study Group.  
*N Engl J Med*. 2008;359(14):1464-1476.

3. Garg S, et al. *Diabetes Care*. 2006;29(1):44-50.

4..Garg S, et al. *Diabetes Care*. 2007;30(12):3023-3025.

5. Bailey TS, et al. *Diabetes Technol Ther*. 2007;9(3):203-210.

6. Deiss D, et al. *Diabetes Care*. 2006;29(12):2730-2732.

7. Hirsch IB, et al. *Diabetes Technol Ther*. 2008;10(5):377-383.

# Two CGMs available...

## Dexcom

- G5 (Software 505) MARD 9.3%  
ability to connect via Bluetooth up to 5 apple mobile devices
- Can be used without pump
- Change site every 7 (14) days
- Software compatible with Mac and PC



\*Mean Absolute Relative Difference (MARD)\* the difference between the blood sugar and the sensor reading, lower MARD = increased accuracy

# Two CGMs available...

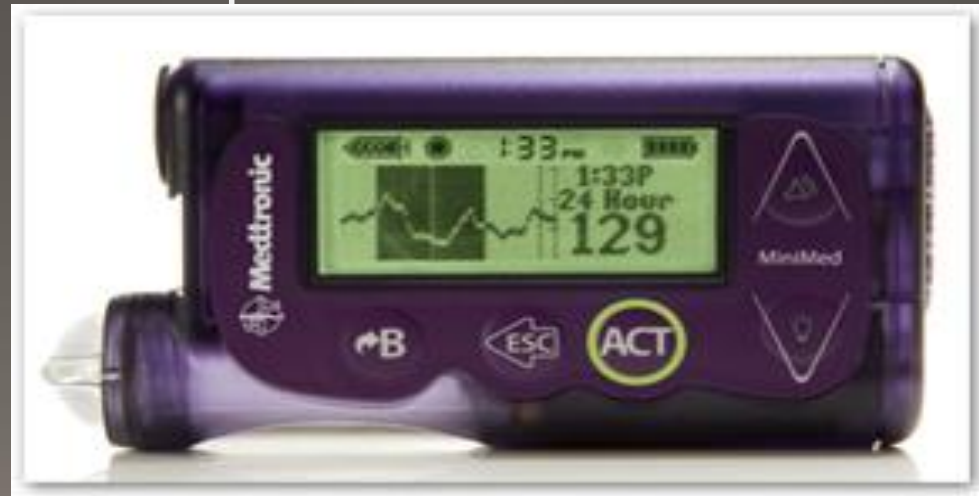


## Enlite

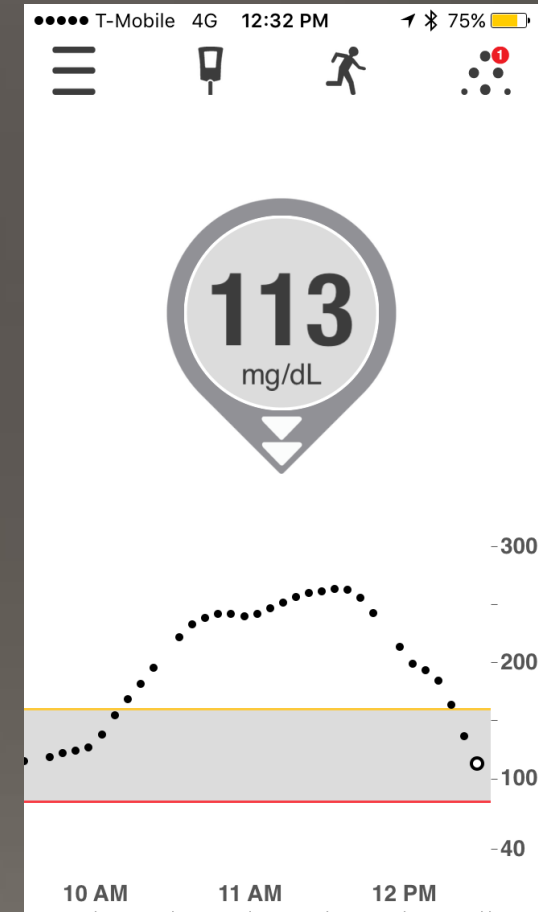
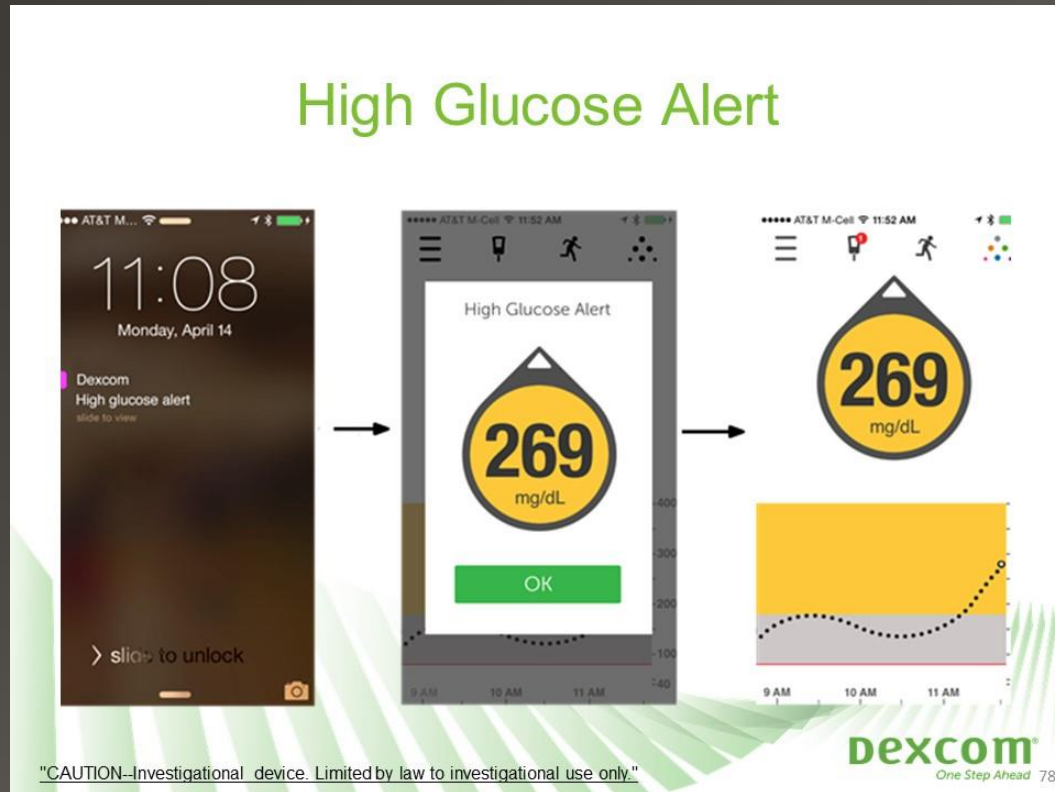
- Compatible with Medtronic pump
- Cannot be used without pump
- Change site every 6 days
- Compatible with Mac and PC



Product images for illustration purposes only



# CGM links to iPhone



# Real world....

- May lower A<sub>1c</sub>
- Security and **SLEEP** for parents/partners
- Trend arrows are very helpful for those afraid of lows
- Makes people aware of what food does to blood sugars
- Alarms can be very bothersome
- Not as reliable at extremes of blood sugars
- Many issues with the adhesives/2 sites can be a challenge



# Real World

- Unless you have the full picture of exercise/food can be very difficult to interpret CGM records
- Patients have to be committed to interpreting the moment to moment data themselves
- Distracting to micromanage each blood sugar
- Reacting to sugars can become a full time job and lead to excessive anxiety
- Not automatically covered by insurance in the US

# The Future....

# The Artificial Pancreas

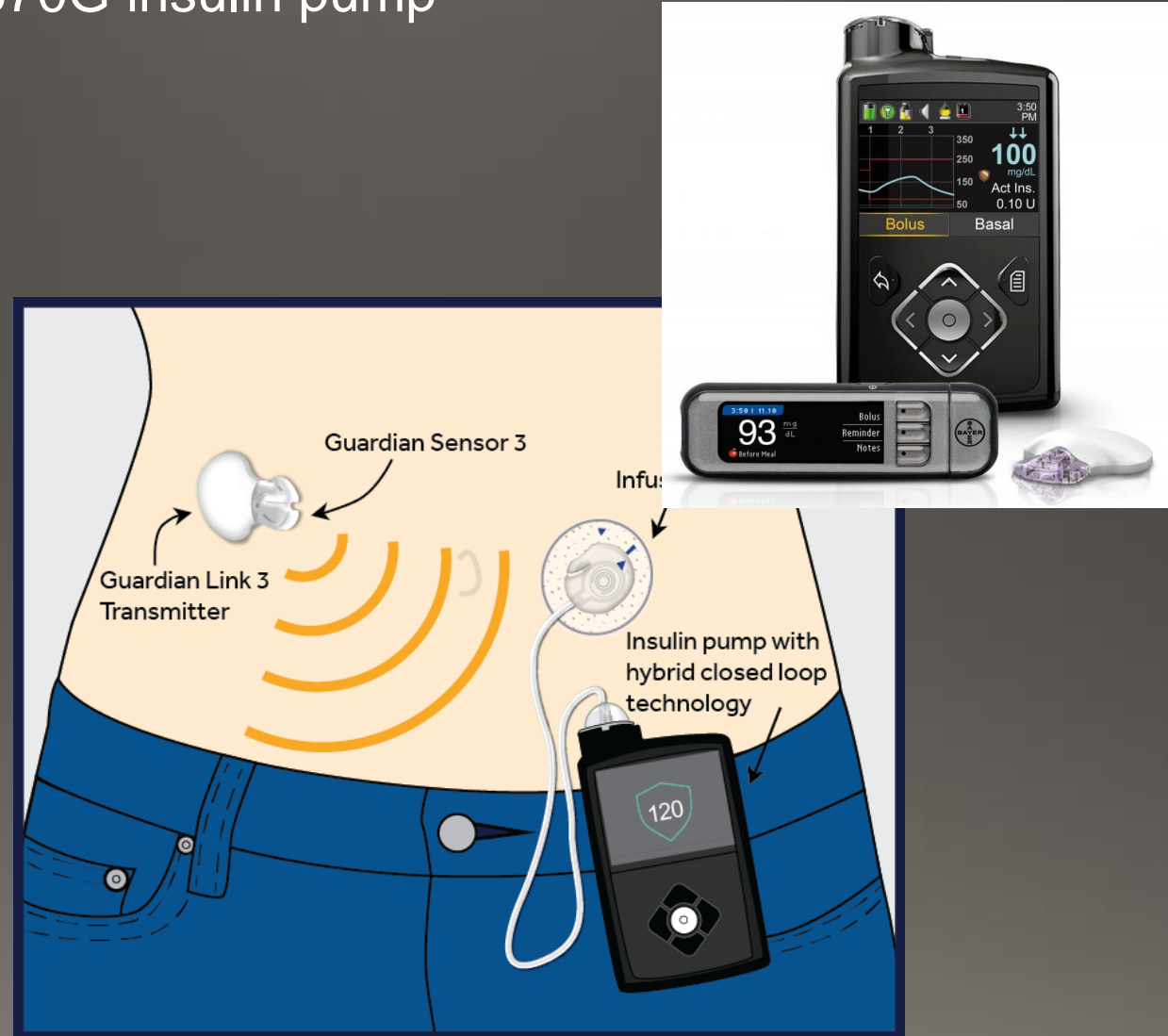
- Closed loop system
- Combines glucose sensor with insulin pump
- A control algorithm directs insulin delivery to increase or decrease depending on the blood sugar
- Suspends insulin delivery when a low threshold is reached
- Ideally would deliver glucagon if needed
- Minimize hypo and hyperglycemic excursions

# Medtronic 670G (Spring 2017)

## Hybrid Closed Loop Insulin Pump

Must wear Guardian Sensor 3 (MARD 10.3% with 2 calibrations/day, 9.64% with 3-4 calibrations/day) + 670G insulin pump

- **Pump:** automatically increase/decrease basal insulin to BG target of 120 mg/dL. Exercise BG target 160 mg/dL. Threshold suspend feature – stops insulin delivery at a set low blood sugar (ie 60mg/dL)
- **Patient:** must input mealtime carbohydrates, accept bolus recommendations, notify system of exercise
- If meal bolus is missed, basal increases up to a certain point to lower BG
- Pump does not automatically administer correction bolus based on CGM readings
- Requires a minimum of 8 units per day to operate safely



# iLet – Boston University, clinical trials

