

A trail of dark blue footprints starts from the bottom left and moves diagonally towards the top right, following the curve of the slide's background.

# A Stepped Approach to Prescribing for Type 2 Diabetes Glycemic Control

# FACULTY

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# FACULTY DECLARATIONS

Dr. Lorenzo declares that in the past 12 months she has nothing to disclose.



# Learning Objectives

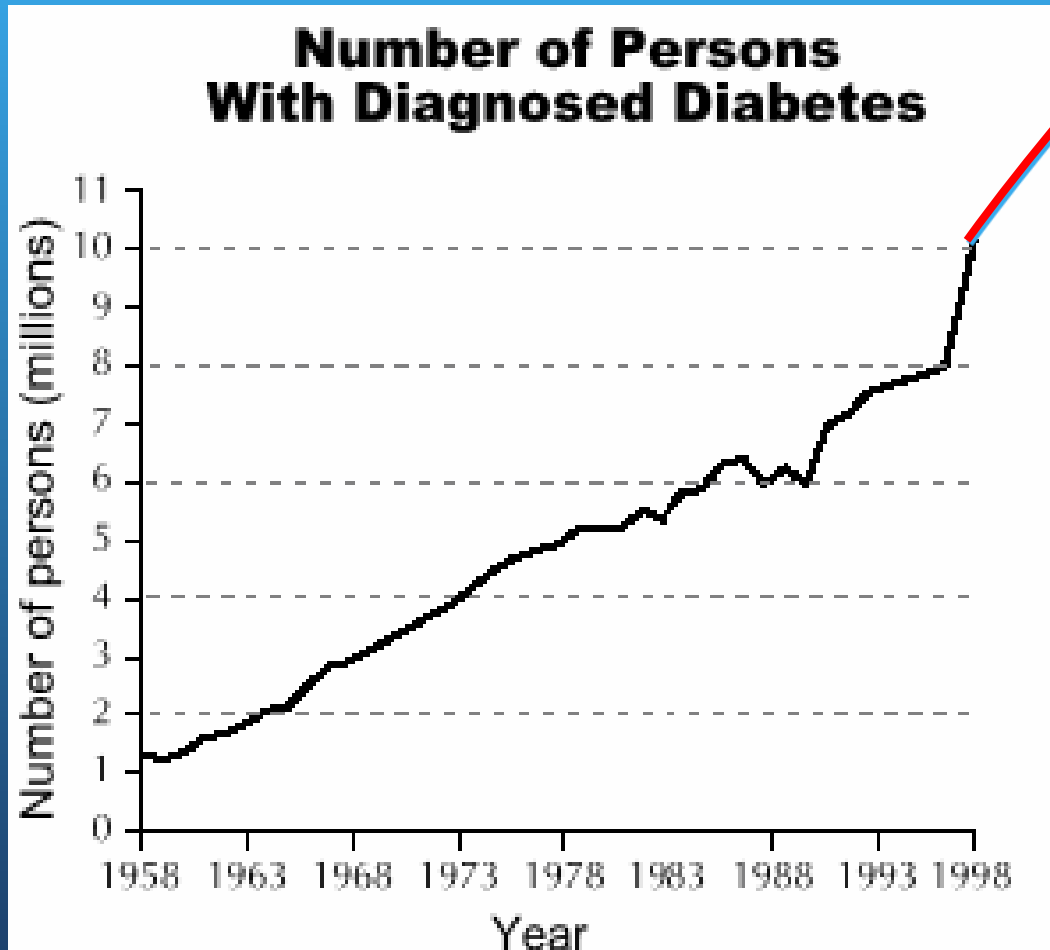
- ▶ Discuss relevant principles of physiology, pharmacokinetics and pharmacodynamics for Type 2 Diabetes (T2DM) glycemic control.
- ▶ Give rationale for selecting drugs of choice for T2 DM glycemic control, including evidence based guidelines.
- ▶ Identify the goals of therapy for T2DM glycemic control, desired effects and evaluation of patient response, including management of adverse reactions.

By 2020, 1 of every 2 Americans  
could have Diabetes or Prediabetes



United Health Center for Health Reform & Modernization. (2010). *The United States of diabetes*. Retrieved from [http://www.unitedhealthgroup.com/hrm/unh\\_workingpaper5.pdf](http://www.unitedhealthgroup.com/hrm/unh_workingpaper5.pdf)

# We Have an Epidemic of Diabetes !!



Source: National Institutes of Health and Centers for Disease Control and Prevention

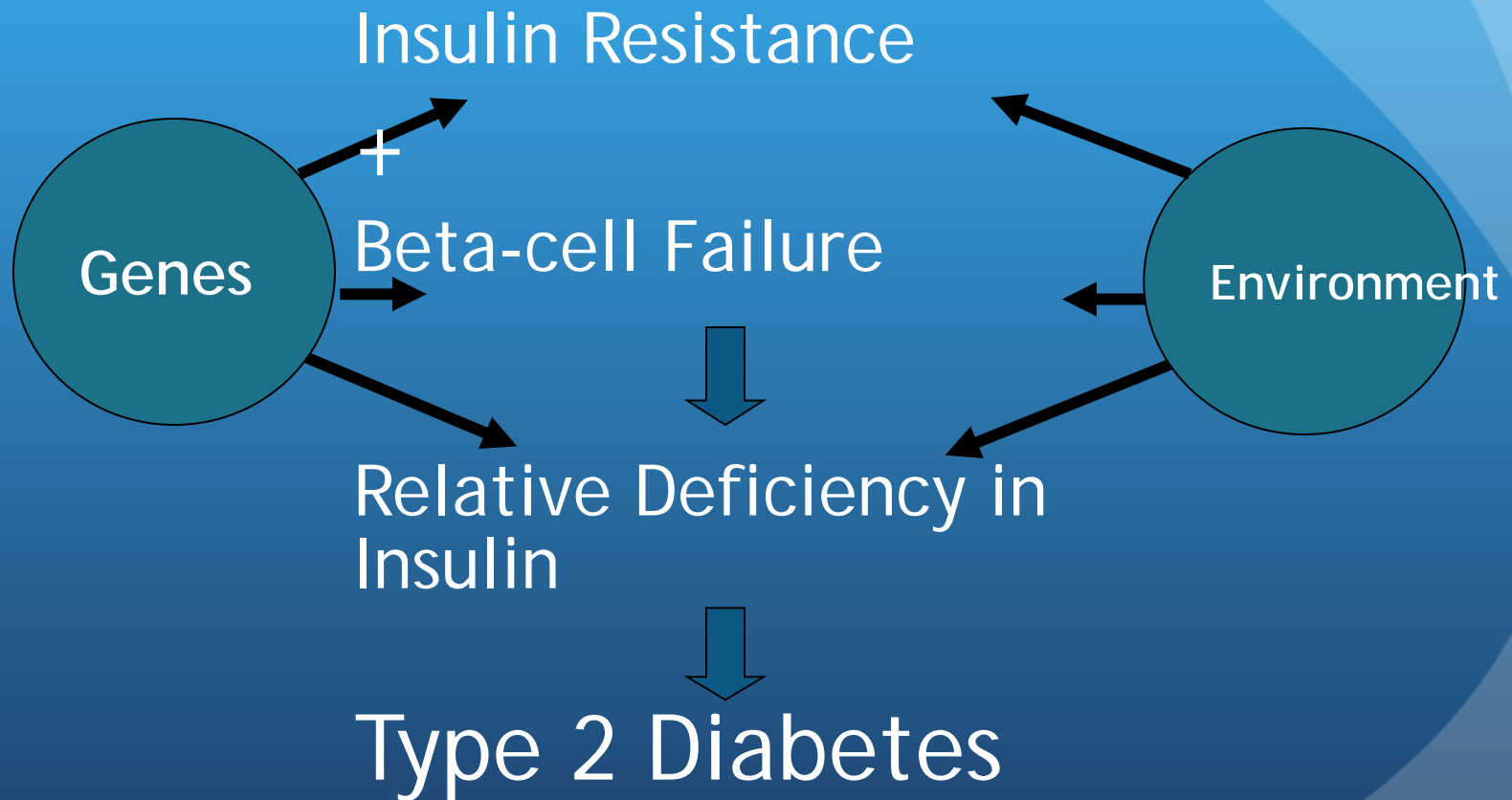


NATIONAL  
DIABETES  
EDUCATION  
PROGRAM



# Pathogenesis of Type 2 Diabetes

## Beta Cell Failure and Insulin Resistance



# Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

## Obesity



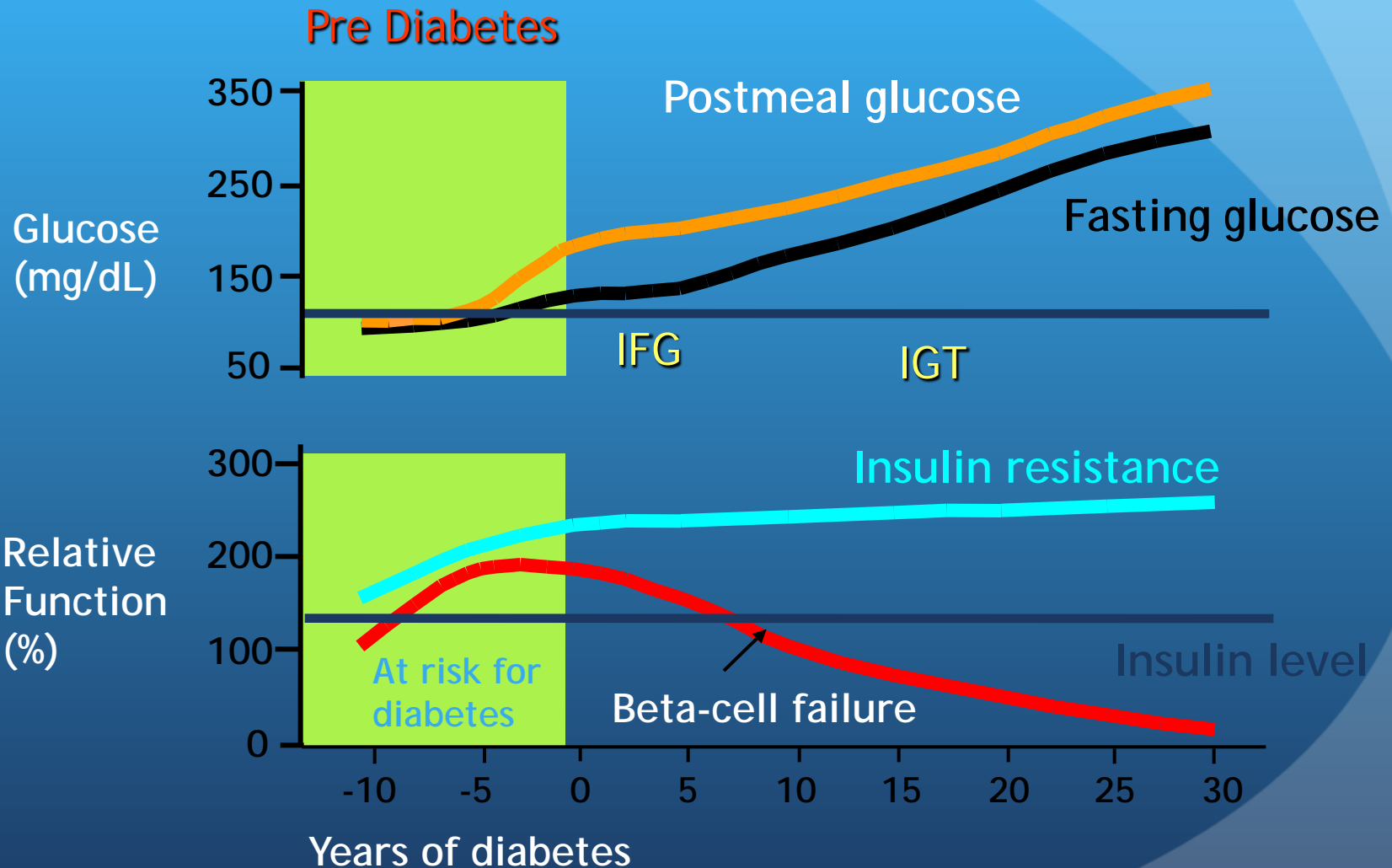
## Diabetes



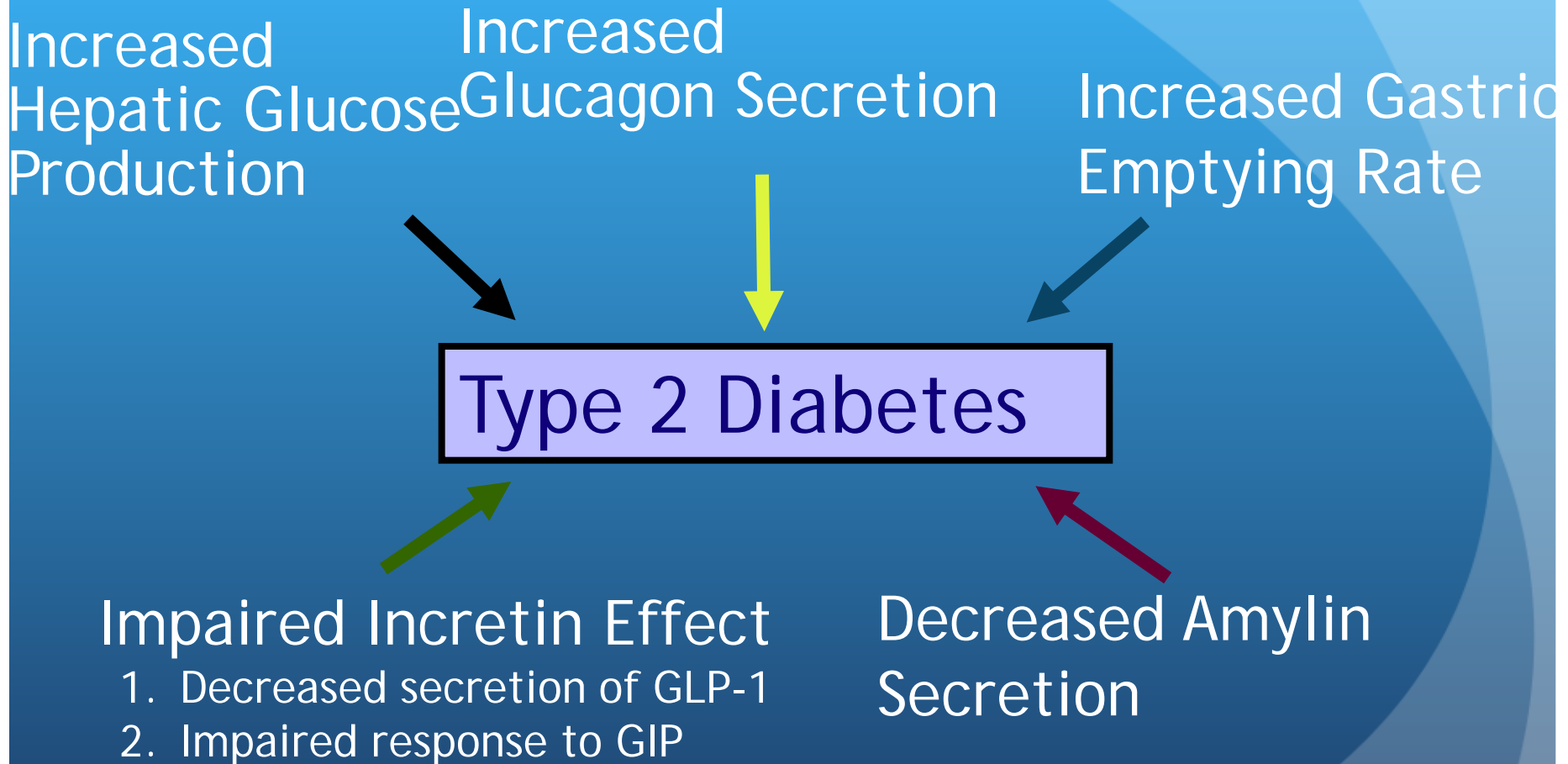


# Natural History of Type 2 Diabetes

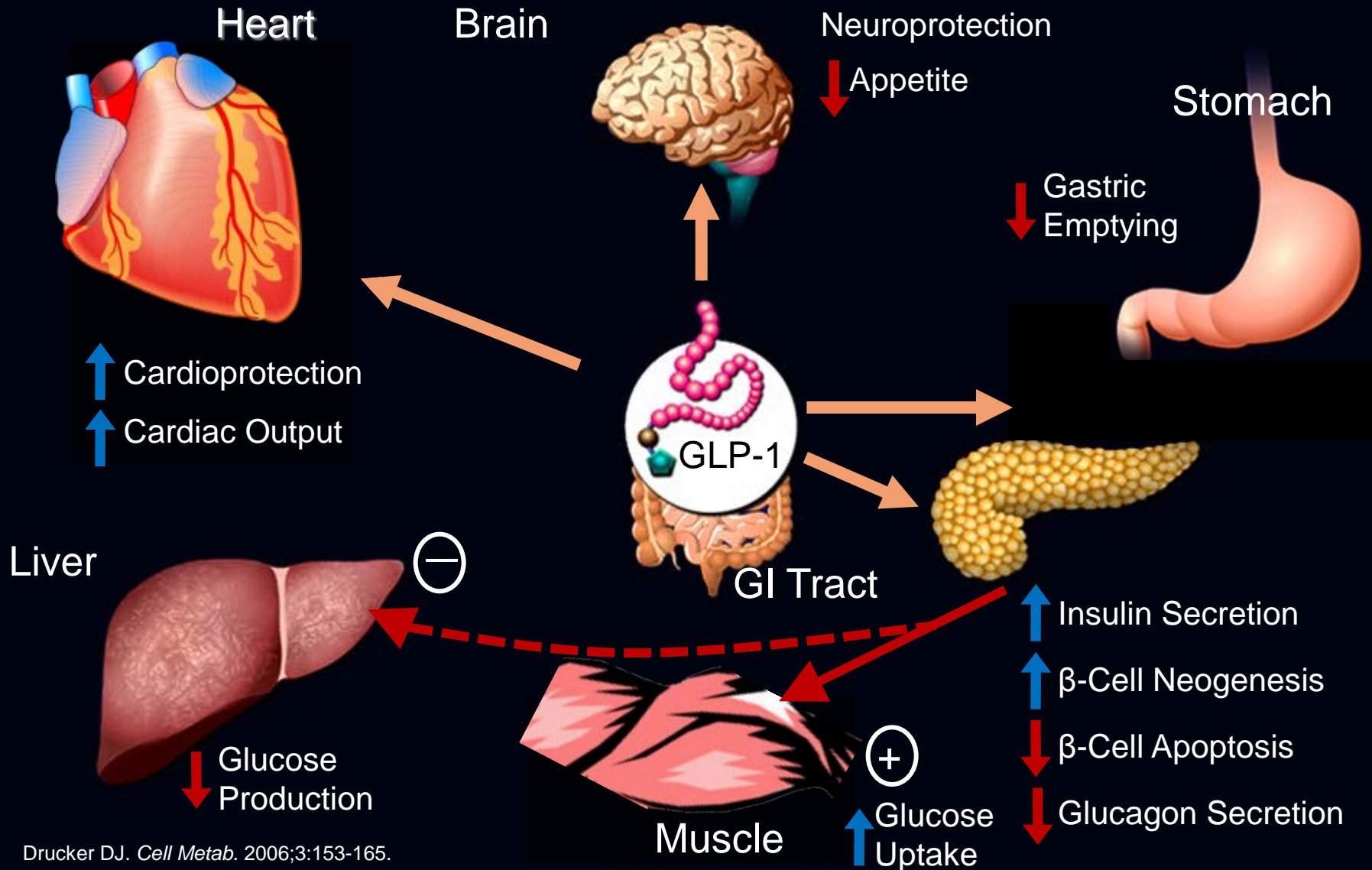
## Progression: Beta Cell Failure and Insulin Resistance



# Other Aspects of Type 2 Diabetes Pathophysiology



# Pleiotropic Actions of GLP-1



# Cardiovascular disease and diabetes

**~65% of deaths are due to CV disease**

No A1C threshold is apparent

Finnish study by Kuusisto et al;  
UKPDS epidemiologic analysis;  
EPIC-Norfolk Study

**Coronary heart disease deaths**  
↑2- to 4-fold

**Cardiovascular complications of T2DM**

**Stroke risk**  
↑2- to 4-fold

**Heart failure**  
↑2- to 5-fold

Impaired glucose tolerance (IGT) and postprandial hyperglycemia are CV risk factors

Funagata Diabetes Study;  
Honolulu Heart Program;  
DECODE Study;

Rancho Bernardo Study

**T2DM = type 2 diabetes**

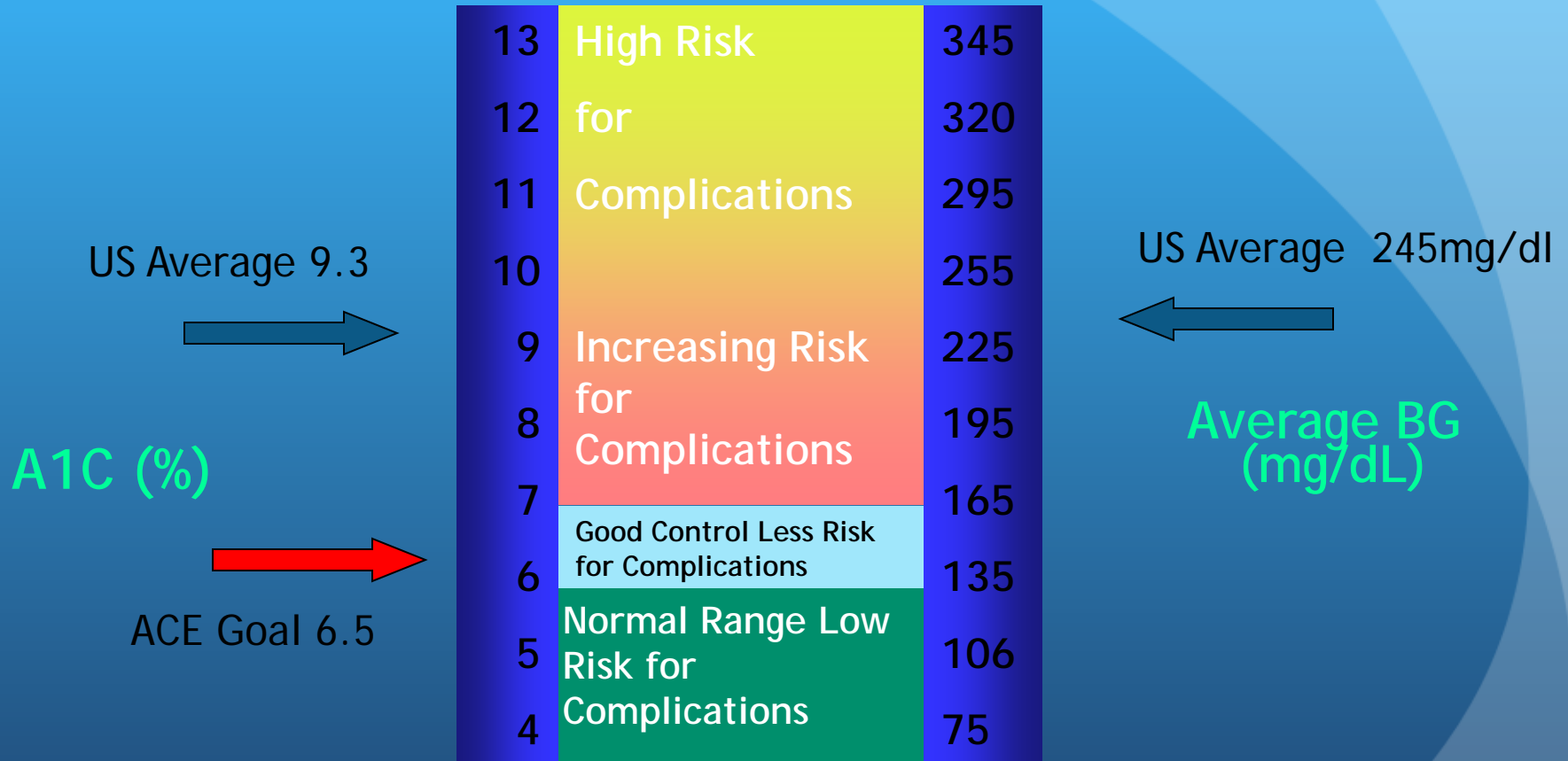
Bell DSH. *Diabetes Care*. 2003;26:2433-41.  
Centers for Disease Control (CDC).

# ABC Goals

	ADA	AACE/ACE	IDF
A = A1C	<7%	<6.5	
B = BP (mmHg)	<130/80	<130/80	<130/80
C = Cholesterol			
LDL ( mg/dL)	< 100 or <70	< 100 or < 70	< 95
HDL ( mg/dL)	> 40 (M) or >50 (F)	> 40 (M) or >50 (F)	> 39
TG ( mg/dL)	< 150	< 150	< 200
E= Eyes annual retinal exam			
F= FOOT EXAM			

# QUALITY OF PATIENT CARE

Data from Diabetes Control and Complications Trial (DCCT).



## Relationship Between A1C and Average Blood Glucose



# Glycemic Goals for all Patients

	Euglycemic	ADA	AACE/ACE
A1C	4.4-5.9%	< 7%	<= 6.5%
FBG (mg/dl)	<100	70 - 130	< 110
1-2hppBG (mg/dl)	<140	< 180 (bedtime: < 140)	<140

Establish A1c goals



Nonpharmacologic  
Therapy = TLC



**Recommended Monotherapy**

- Biguanides
- Sulfonylureas
- Insulin



**Recommended Combinations**

- Biguanides + sulfonylureas
- Biguanides + insulin
- Sulfonylureas + insulin

**Severe hyperglycemia, Type 2 DM**



**A1c >2% above target**



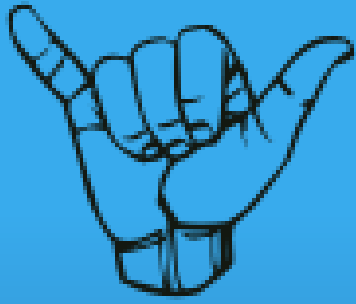
**Insulin**

**Glycemic goals not achieved**



# Pharmacologic Therapy

- **First line agents**
  - Metformin
  - Sulfonylureas
  - Insulin
- **Alternative agents**
  - Thiazolidinediones
- **Newer agents**
  - GLP-1 agonists
  - DPP-4 inhibitors
  - Amylin analog



# DIABETES CARE STEPPED METHOD



1



Oral medication



Therapeutic Life Style

2



Daily Insulin

Basal Insulin



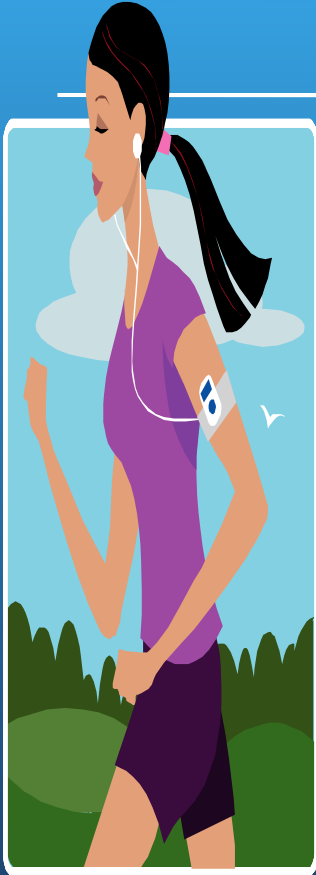
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Daily + Mealtime Insulin

Basal + Bolus Insulin

# Step # 1

# TLC + Oral Medications



# Pharmacologic Therapy

- **First line agents**
  - Metformin
  - Sulfonylureas
  - Insulin
- **Alternative agents**
  - Thiazolidinediones
- **Newer agents**
  - GLP-1 agonists
  - DPP-4 inhibitors
  - Amylin analog



# Biguanides - Metformin<sup>3,4</sup>

- First line therapy
- Now recommended at baseline diagnosis
- MOA
  - Decrease hepatic glucose output
  - Increase peripheral insulin sensitivity
  - Decrease intestinal absorption of glucose
- Decrease A1c ~1-2%
- Maximum clinical effective dose 2g/day

# Metformin

- **Monitor:**
  - Renal function, Caution with pts >80 y/o
  - May restore ovulation in women previously anovulatory due to insulin resistance
  - May be associated with vitamin B12 reduction
- **Counseling points:**
  - Take with food & titrate slow to avoid GI side effects
  - Hold metformin the day of iodine contrast media use and restart 2 days after when renal function returns

# Metformin<sup>4</sup>

## Benefits

- Reduction in microvascular complications
- Lack of associated hypoglycemia
- Weight neutral
  - possible weight loss (2-5kg)
- May reduce TG by 16%, LDL by 8%, CHOL by 5%
- May increase HDL by 2%
- Generic available

## Limitations

- Gastrointestinal intolerance
- Precautions
  1. Age >80
  2. Liver dysfunction
  3. Excessive alcohol intake
  4. Hypoxemia
- Contraindication
  - Serum creatinine (SCr )
    - ≥ 1.5 in males
    - ≥ 1.4 in female
- Precautions
  - History of lactic acidosis, liver disease, alcohol abuse

# Metformin: Clinical Pearls

- Drug of choice for initial therapy
- Majority of dose can be given at bedtime if FBS still above goal
- No hypoglycemia with metformin monotherapy
- XR formulation- better GI tolerability
- Liquid formulation- 500mg/5ml (Riomet)

# Sulfonylureas/Meglitinides

- **Mechanism of Action**

- Increases insulin release from pancreatic beta cells (primary mechanism)
- Decreases hepatic glucose production (sulfonylureas)
- Increases insulin sensitivity at peripheral sites (sulfonylureas)

# Sulfonylureas

## First Generation Agents

- Acetohexamide
- Chlorpropamide
- Tolazamide
- Tolbutamide

## Second Generation Agents

- Glipizide
- Glyburide
- Glimepiride



# Sulfonylureas

- **Glyburide**

- Metabolites can accumulate in patients with CKD -> hypoglycemia
- Dose: 2.5-20 mg daily
- Metabolism: hepatic (but renally eliminated)
- Not recommended with CrCl <50ml/min

- **Glipizide**

- Dose: 2.5-40 mg daily
- Not renally eliminated -> Less risk for hypoglycemia
- Doses >20mg/day have shown little increased benefit
- Dose conversion -1: 2
  - 5mg glyburide-> 10mg glipizide

# Sulfonylureas

- **Benefits**

- A1c lowering ~1-2%

- **Adverse drug reactions**

- Hypoglycemia

- Incidence: glipizide < glimiperide < glyburide

- Weight Gain of ~ 2kg

- Hypersensitivity (sulfa allergy - risk of cross reactivity exists)

- Hyponatremia with fluid retention

- Abnormal hepatic tests

- Increased sensitivity to sun light

# Sulfonylureas: Clinical Pearls

- Not first line therapy anymore
- May be more effective in lower doses as an add on medication

# Meglitinides

- Repaglinide (Prandin<sup>®</sup>)
  - 0.5-4mg 2-4x/day  
(max 16mg/day)
- CrCl 20-40mg/ml  
Starting dose 0.5mg  
TID and titrate up
- Nateglidine (Starlix<sup>®</sup>)
  - 120mg TID 30 minutes prior to meal
- No adjustments for renal or hepatic

# Meglitinide: Clinical Pearls

- **Benefits:** 0.5-1.5% A1c lowering
- **Adverse drug reactions:** bloating, abdominal cramps, diarrhea, gas
- **Clinical pearl:** weight neutral, repaglinide more effective for lowering A1c than nateglinide, not recommended as monotherapy, shorter T1/2 than SFU

# Thiazolidinediones

- AKA glitazones or TZDs

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- Mechanism of Action
  - Reduces insulin resistance in peripheral tissues and liver
- Benefit: A1c lowering 0.5 -1.4%

## Pioglitazone

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- Dose: 15 -45 mg daily
- Linked to increased risk of new or worsening heart failure (HF) exacerbation
- Non-formulary but VA preferred TZD given no contraindications



# TZDs

## Adverse reactions

- Black box warning -new onset or worsening of existing heart failure
  - Contraindicated in patients with Class III/IV heart failure
  - Edema and/or weight gain
  - Myocardial infarction
  - Liver toxicity -LFTs > 2.5X ULN
    - Troglitazone withdrawn from market for this reason
  - Bone loss

# TZDs Clinical Pearls

- No hypoglycemia
- Raises HDL levels, converts small dense to large LDL particle size (less atherogenic)
- After initiating or dose adjustment of TZD, 8-12 weeks of therapy are required to see full benefit.

# REMS-rosiglitazone

- Risk Evaluation and Mitigation Strategy (REMS)
- Due to increased risk of MI
- Enrollment required with Manufacturer
  - Providers
  - Patients
- Effective November 18, 2011

# Alpha-glucosidase inhibitors

- Mechanism of action: inhibits intestinal digestion of starches and all sugars composed of more than 1 simple sugar
- Benefit: 0.5-0.8% A1c lowering
- Adverse drug reactions: gas, bloating, diarrhea

# Alpha Glucosidase Inhibitors

## Acarbose (Precose) Miglitol (Glyset<sup>®</sup>)

- 25-100mg TID with meals
- Not on VA formulary

## Miglitol (Glyset<sup>®</sup>)

- 25-100mg TID with meals
- On VA Formulary

## Clinical pearls:

Effective for lowering post-prandial BG, titrate slowly to minimize GI upset, weight neutral, use as 3<sup>rd</sup> line agent, use fast absorbing simple sugars to treat hypoglycemia while on this therapy

# NEWER AGENTS

Incretin Mimetics

DPP-4 inhibitors

Amylin Analog

Peptide Agents

# Incretins

- Gut hormones - produced by GI tract
- Stimulate insulin release in response to food intake

GLP-1: glucagon like polypeptide

βcell response

- GIP: gastric inhibitory peptide  
glu-dependent insulinotropic peptide

βcell is resistant to GIP

DPP4

Sitagliptin  
(Januvia)

Saxagliptin  
(Onglyza)

Linagliptin  
(Tradjenta)

Vildagliptin  
(Galvus)



GLP-1

Stimulates  
Insulin

↓ Glucagon  
Secretions

↑ 1<sup>st</sup> Phase  
Insulin

↓  
Gluconeogenes  
is

↓ Gastric  
Motility

↓ Appetite



# GLP-1

- Mechanism of action:
  - Stimulates insulin and lowers glucagon secretion
  - Improves first phase insulin release
  - Reduces hepatic glucose production
  - Decreases appetite ( weight)
  - Decrease gastric motility



# Exenatide (Byetta®)

- 10 mcg subcutaneously bid ( 5 mcg 1<sup>st</sup> month)
- First GLP-1 agonist approved May 2005
- Increased resistance to DPP-4, extended t  $\frac{1}{2}$
- Benefits: 0.5-1% reduction in A1c
- Adverse Drug Reaction: HA, nausea, diarrhea, pancreatitis
- May be associated with renal insufficiency

# Liraglutide (Victoza®)

Liraglutide (Victoza®) -0.6-1.8 mg/day

approved January 2010

Benefit: 1.0-1.5% A1c lowering

Adverse drug reaction: HA, nausea, diarrhea, pancreatitis

Medullary thyroid cancer in rats

mild elevation in calcitonin in humans

limited cases of PTC in humans

# Future GLP-1 Agonist/Antagonist

- **Exenatide -LAR Bydureon®**

FDA approval delayed

concerns for clearance in CKD

effects on QT interval, HR at high dose

- **Taspoglutide:** 20-40 mg weekly

suspended phase III -N/V, heart sx

- **Alboglutide:** 9-32 mg weekly

# GLP-1

- Place in Therapy: type 2 diabetics not achieving glucose control on metformin, SU, and/or TZD

## Clinical pearls:

- Not effective in type 1 diabetes
- Effective in lowering post-prandial glucose
- Concurrent use with prandial insulin has not been studied and can not be recommended

# DPP-4 Inhibitors

- **Mechanism of Action**

provide competitive inhibition of the enzyme (DPP-4) responsible for GLP-1 inactivation, thus it prolongs effects of endogenous GLP-1

mimic effect of incretin

- **Benefits:** 0.5%-0.8% A1c reduction
- **Adverse Drug Reactions:** URI, HA, diarrhea, UTI, abdominal pain, \*acute pancreatitis with sitagliptin
- **Clinical Pearls:**
  - Low risk for hypoglycemia
  - Weight neutral

# DPP-4 Inhibitors

- **Sitagliptin (Januvia®)** approved 2008  
50 -100 mg/day
- **Saxagliptin (Onglyza ®)** approved 2009  
2.5-5 mg/day, reduce in renal failure
- **Linagliptin (Tradjenta ®)** approved 2011  
5mg/day
- **Vildagliptin (Galvus)** not available in US
- Not on usually formulary

# Amylin

- Amylin - $\beta$ cell peptide co-secreted with insulin
- **Mechanism of Action:**
  - delay gastric emptying
  - suppress appetite
  - inhibit glucagon secretion, reduces glucose production by liver



# Amylin Analog

- **Pramlintide (Symlin®)** -synthetic analog FDA approved 2007 for use with insulin
- Subcutaneous injection TID
- Type 1: 30 - 60 mcg; start at 15 mcg
- Type 2: 60-120 mcg; start at

No renal dose adjustment required

# Amylin

- **Benefit:** 0.5-1.% A1c lowering
- **Adverse drug reactions:** nausea (48%), anorexia, vomiting, fatigue, headache
- **Clinical Pearls:**
  - Must be taken with meals containing  $\geq 250$  calories or  $\geq 30$  gms CHO
  - Weight loss
  - Manufacturer recommends decreasing dose of bolus insulin by 50% when starting pramlintide

# Step # 2

TLC + Oral +  
Meds

## Daily Insulin



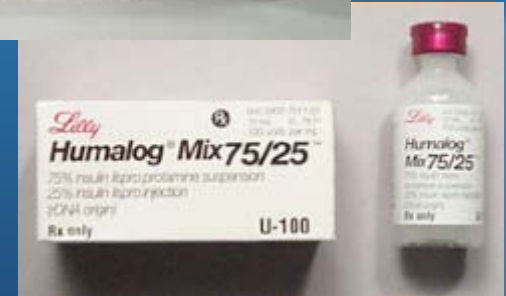
## Slow & Safe

- Replacement of Insulin Hormone
- Not Painful
- Safe, Quick and Easy
- Best way to Lower Blood Sugar Levels

Name	Generic	Brand
Action 2-4 hrs.	Intermediate acting	
Last 10 + hours	NPH	Humulin Novolin
	Long acting	
Last 20 + hours	Glargine Detemir	Lantus Levemir

# Insulin Therapies Available:

- Rapid Acting
  - Humalog (lispro), Novolog (aspart), & Aprida (glulisine)
- Regular (Short acting)
  - Humulin R & Novolin R
- NPH (Intermediate acting)
  - Humulin N & Novolin N
- Long Acting
  - Lantus (glargine) & Levemir (detemir)
- Mixes (NPH/Regular)
  - 70/30; 50/50; & others



# Benefits of Insulin Dosing Regimens

## One Injection

- ▶ Intermediate-Acting or Long-Acting Insulin Analog at Bedtime
- ▶ Premixed Insulin Before Dinner



## Two Injections

- ▶ Breakfast and Dinner Injections of Premixed Insulin
- ▶ Breakfast and Dinner: Short-Acting or Rapid-Acting Plus NPH or Long-Acting Insulin Analog

Chan JL, Abrahamson MJ. Pharmacological management of type 2 diabetes mellitus: rationals for rational use of insulin. *Mayo Clin Proc.* 2003;78:459-467 and Owens DR, Zinman B, Bolli GB. Insulins today and beyond. *Lancet.* 2001;358:739-746

# Treat to Target

Self-monitored FPG (mg/dL) From Preceding  
2 Days With no Episodes of Severe  
Hypoglycemia or  $PG \leq 72$  mg/dL (IU/d)

100-120 mg/dL

120-140 mg/dL

140-180 mg/dL

$\geq 180$  mg/dL

*FPG = fasting plasma glucose; PG = prandial  
glucose*

**Titration:  
Increase in  
Insulin Dose**

2

4

6

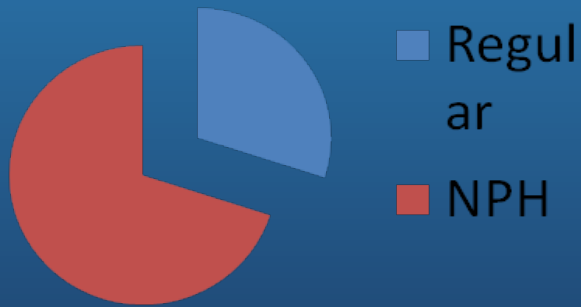
8

Riddle M, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26:3080-3086

# Step # 3: TLC + Daily & Mealtime Premixed

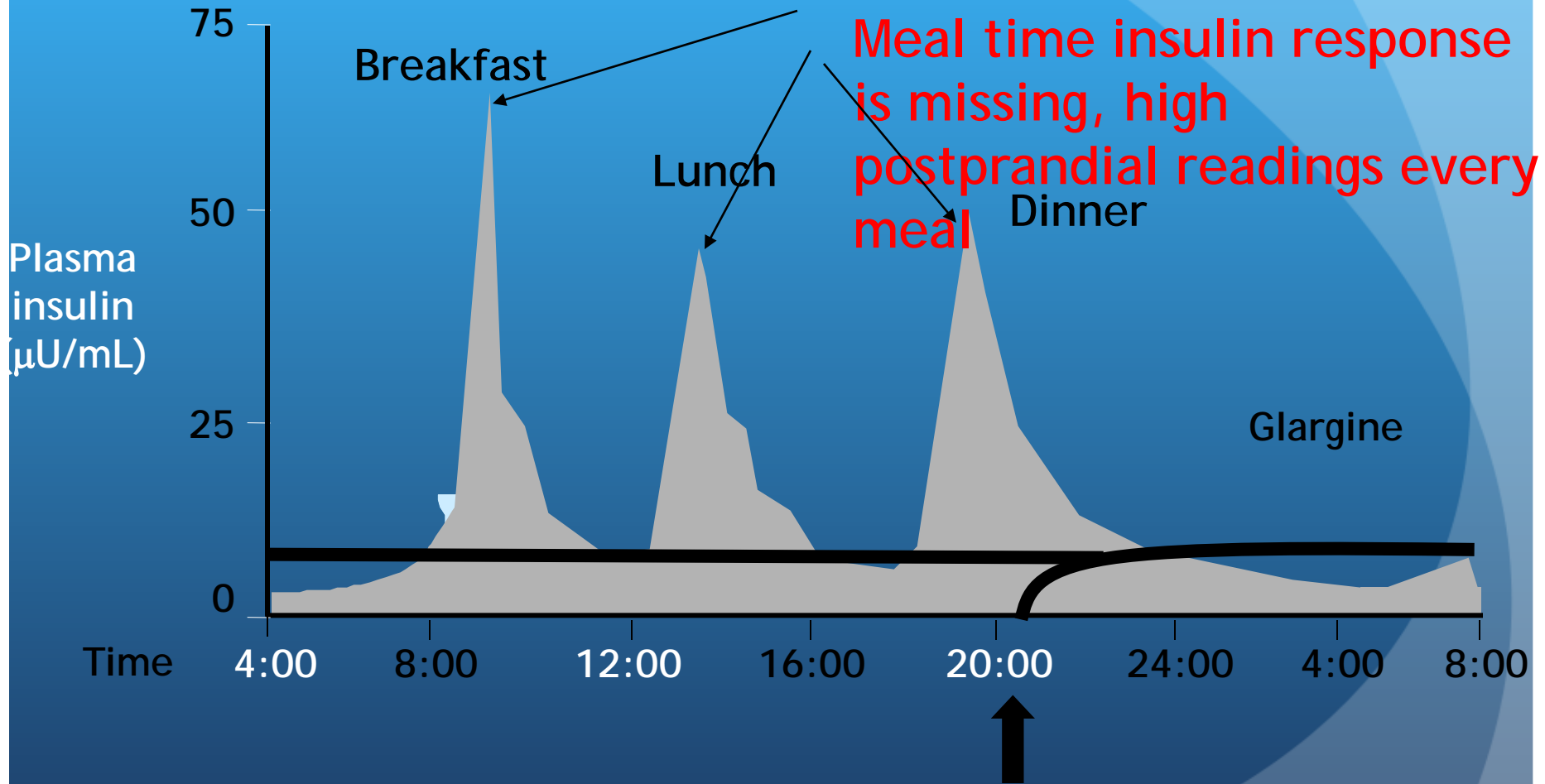
Insulin that covers both all through the day and meal times

**premix**



Name	Generic	Brand
Action 30- 60 min Lasts 10-16 hrs	<b>Premix NPH + Regular</b>	
Fast + Slow Mixture	NPH /Regular 70/30  NPH + Regular 50/50	Humulin 70/30 Novolin 70/30 Humulin 50/50
15-60 min Lasts 10-16 hrs	<b>Newer Premix (Analog)</b>	
Rapid + Slow Mixture	Aspart 70/30 Lispro 75/25 Lispro 50/50	Novolog 70/30 Humalog 75/25 Humalog 50/50

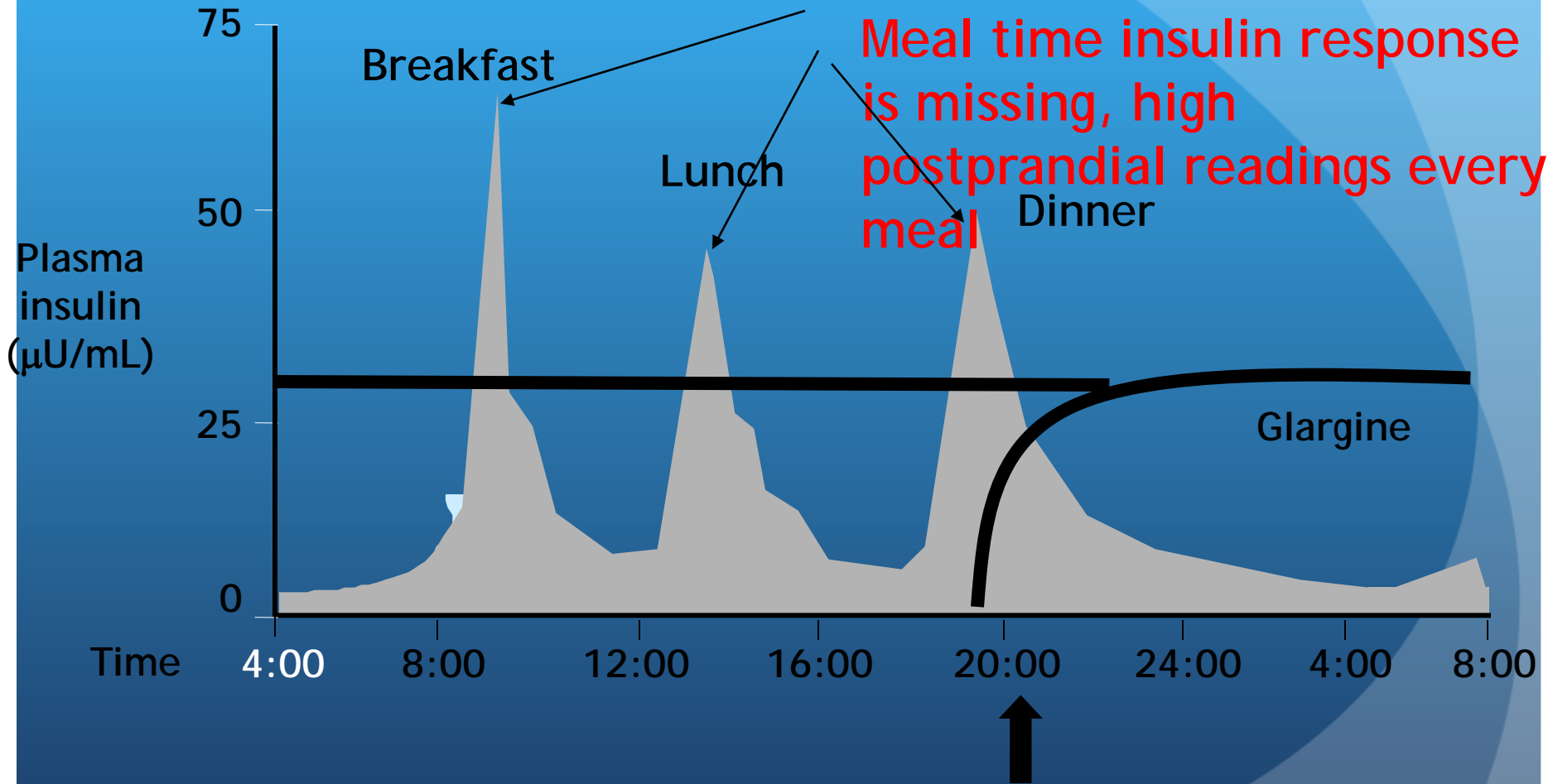
# Typical Starting Point Basal Treatment Program with Peakless Long-Acting Analogs Alone



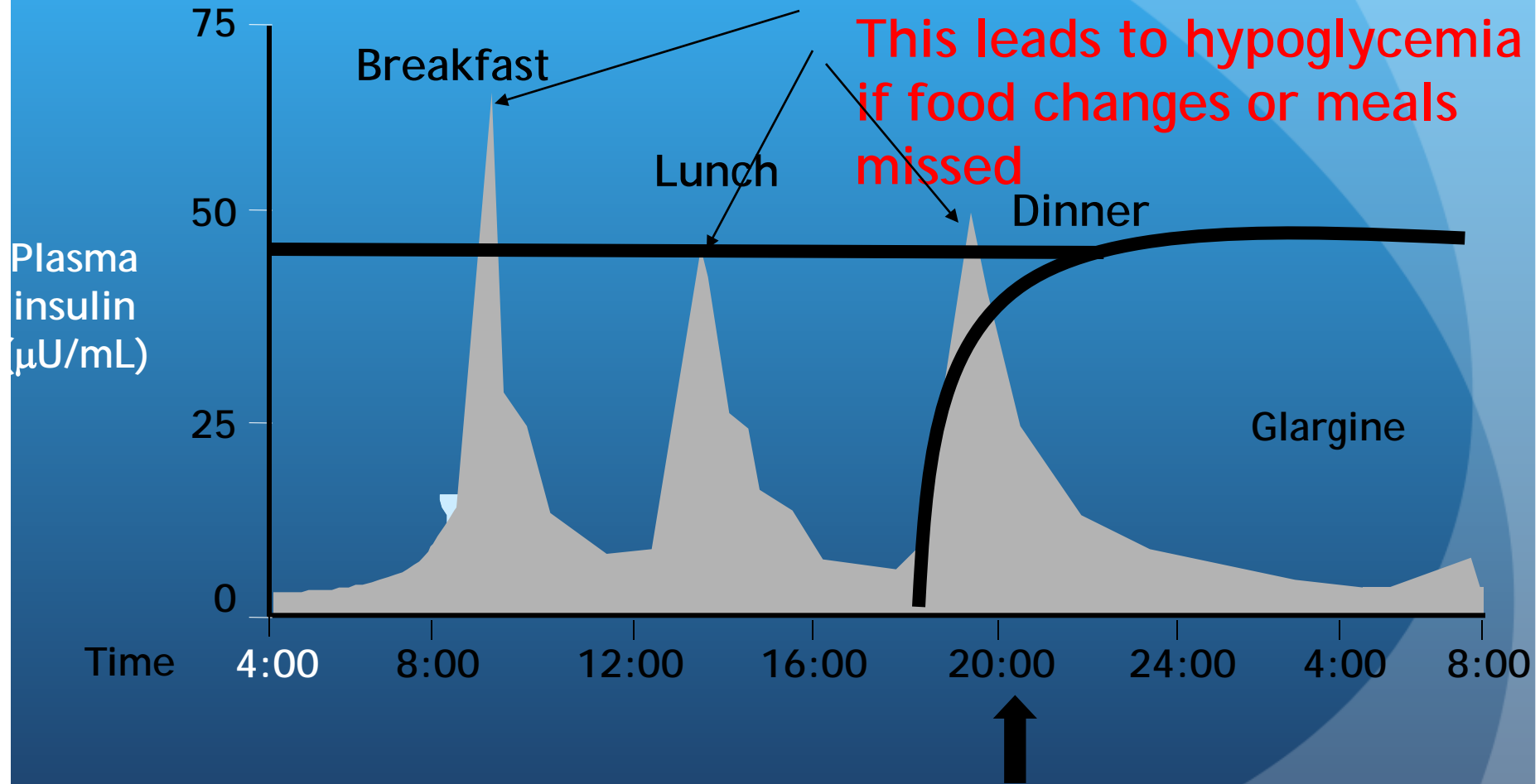
Verbal communication from Bode, BW. Atlanta, Ga; Feb. 2003.



# Clinicians often increase long acting insulin to address meal related glucose



# Clinicians continue increase long acting insulin to address meal related glucose



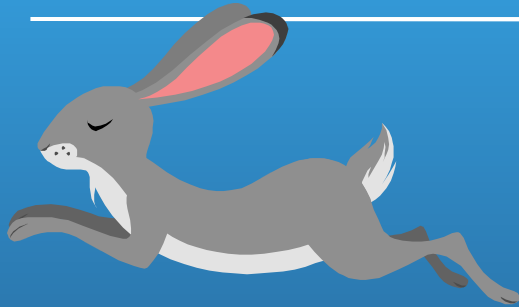
# Step # 3

## TLC

# Daily + Mealtime Insulin



Basal + Bolus

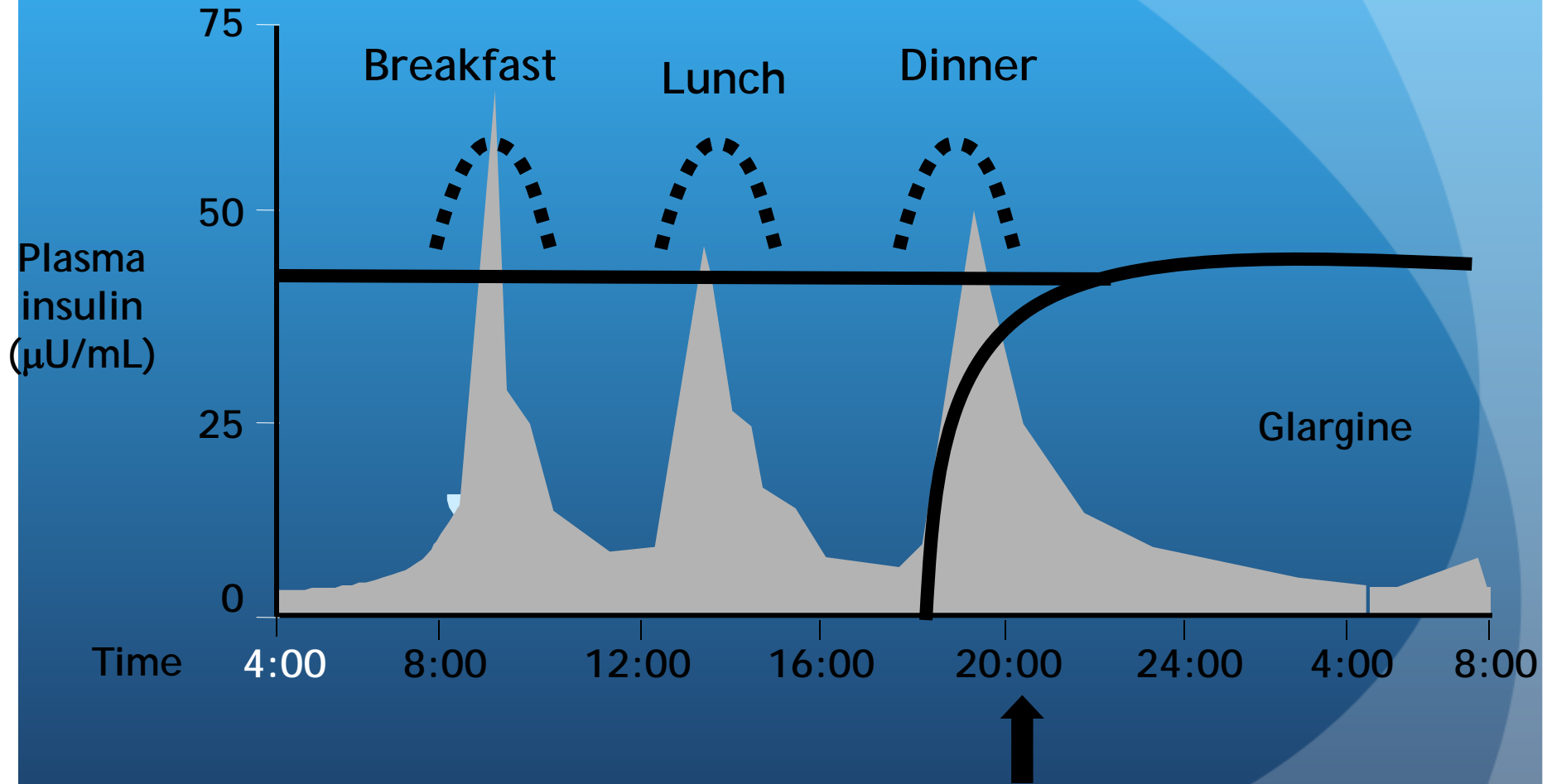


## Fast & Short



Name	Generic	Brand
Action	<b>Fast</b>	30 - 60 minutes
Lasts 3-6 hrs	Regular	Humulin R Novolin R
	<b>Rapid</b>	5 minutes
Lasts 2-4 hrs	Aspart Glulisine Lispro	Novolog Apidra Humalog

Clinicians then finally add prandial insulin to address meal related glucose



# Insulin: Effect on Glucose

Insulin	Onset	Peak (hours)	Duration (hours)
Rapid Acting	5-15 min	0.5-1.5	<5
Regular	30-60 min	2-3	5-8
NPH	2-4 hours	5-10	10-16
Long Acting	2-8 hours	No peak	~1 day

- Different insulins have a varied effect on glucose
- If someone is experiencing hypoglycemia due to an excessive amount of insulin, they need to be assessed and treated throughout the course of the insulin in the body.

# Starting MDI

- Starting insulin dose is based on weight  
 $0.2 \times \text{wgt. in lbs.}$  or  $0.45 \times \text{wgt. in kg}$
- Bolus dose (aspart/lispro) = 20% of starting dose at each meal
- Basal dose (glargine/NPH) = 40% of starting dose at bedtime

# Starting MDI in 180 lb person

- Starting dose =  $0.2 \times \text{wgt. in lbs.}$

$$0.2 \times 180 \text{ lbs.} = 36 \text{ units}$$

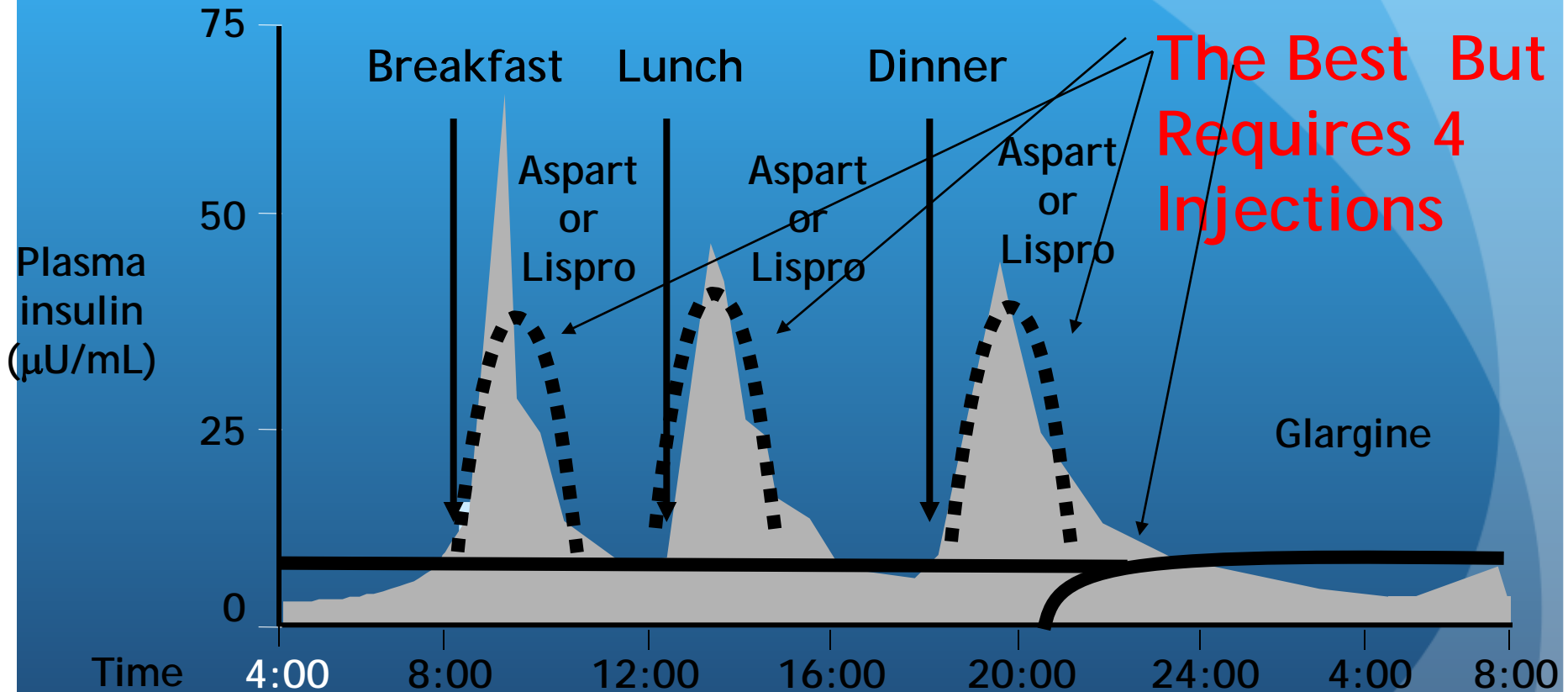
- Bolus dose = 20% of starting dose at each meal

$$20\% \text{ of } 36 \text{ units} = 7 \text{ units ac (tid)}$$

- Basal dose = 40% of starting dose at bedtime

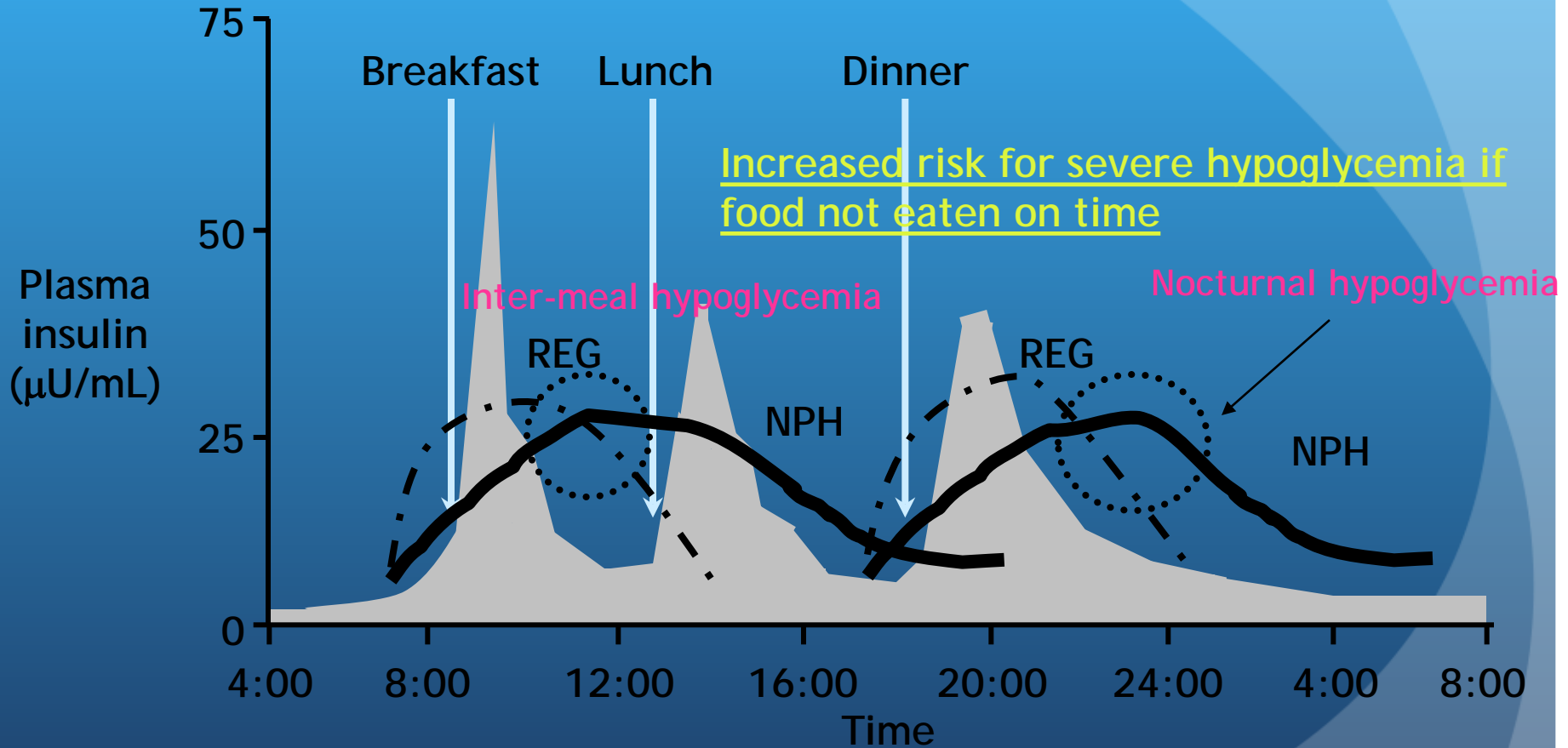
$$40\% \text{ of } 36 \text{ units} = 14 \text{ units at HS}$$

# Basal/Bolus Treatment Program with Rapid-Acting and Peakless Analogs

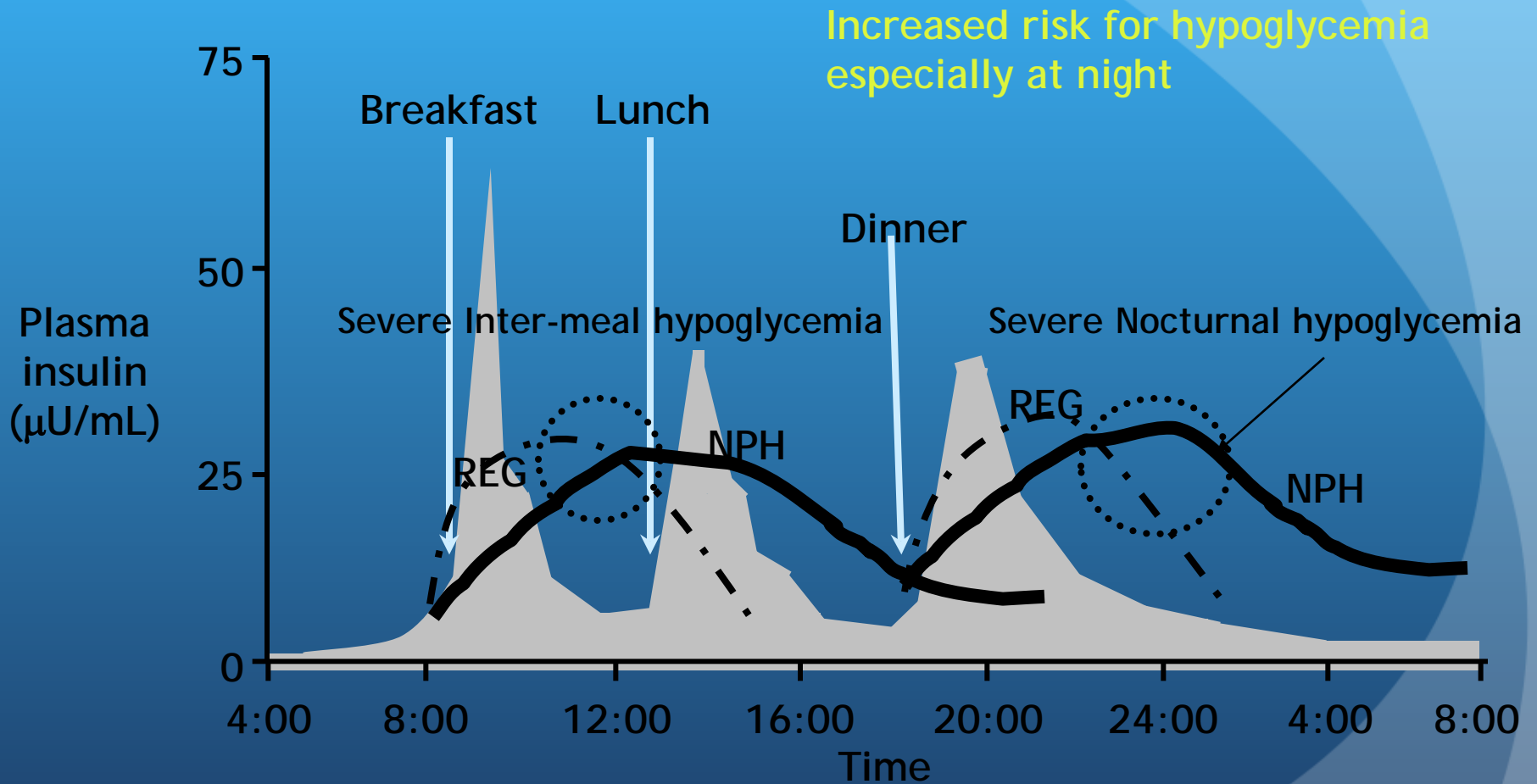




# Basal/Bolus Affect of Insulin Absorption with Regular and NPH Insulin Preparations injecting 45 minutes before a meal

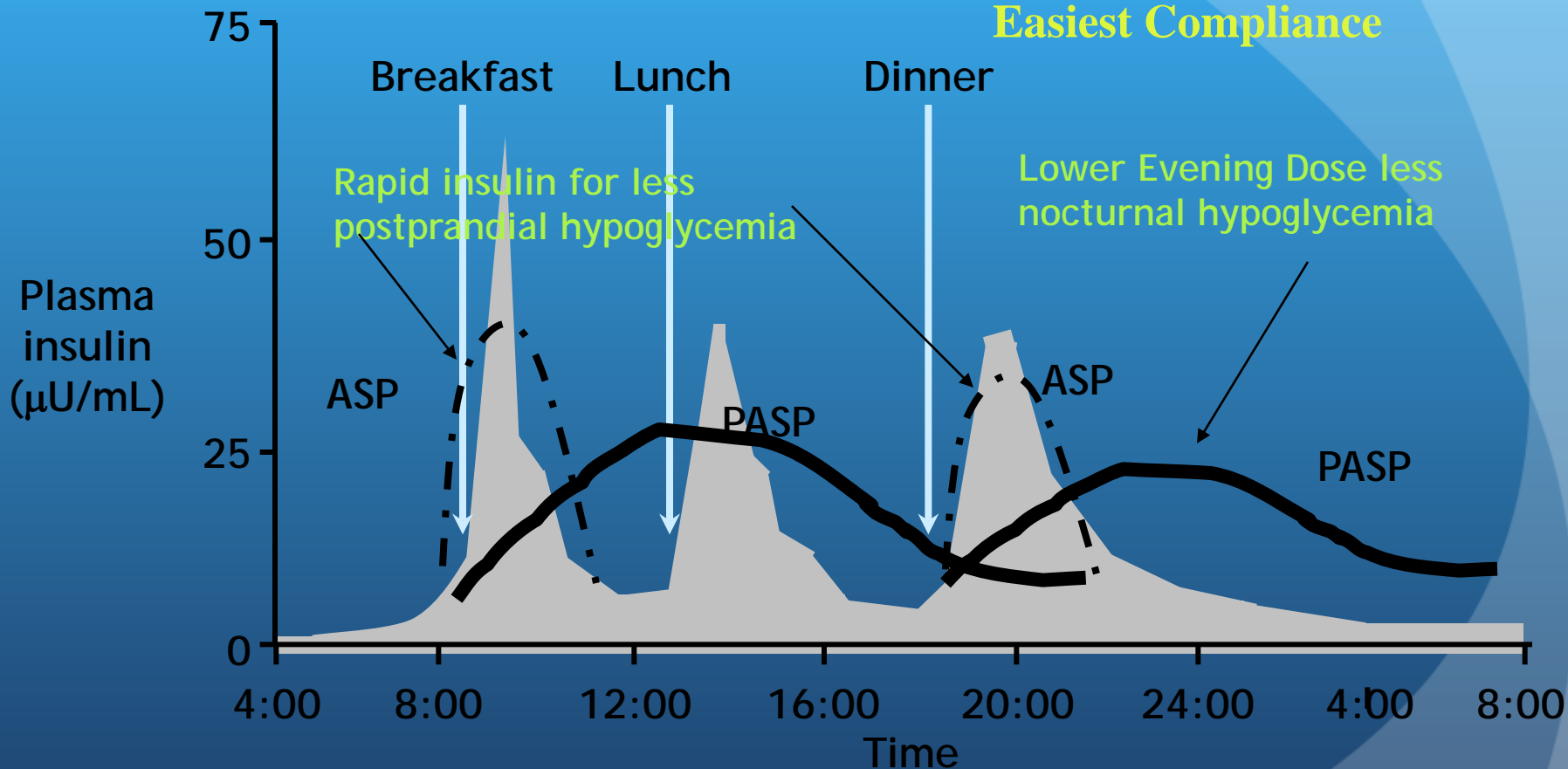


# Basal/Bolus Affect of Insulin Absorption with Regular and NPH Insulin Preparations Injecting with a Meal.



# Basal/Bolus Affect of Insulin Absorption with Aspart and Protamated Aspart Mixed Insulin Preparations Injecting with a Meal.

**The Best Method With The Easiest Compliance**



# Sliding Scale Insulin

## Types of Sliding Scales

- Pre Set Dose

- **Pros:**

- Easy to use
- No patient calculations necessary
- Increased patient compliance

- **Cons**

- No correlation with current glucose readings
- Decreases importance of SMBG
- Does not account for meal consumption
- Very high likelihood of hypoglycemia

<u>Meal or Time</u>	<u>Dose</u>
Breakfast	7units
Lunch	5 units
Dinner	6 units
Bedtime	2 units

# Correction Bolus Scale

- Must determine how much glucose is lowered by 1 unit of short- or rapid-acting insulin
- This number is known as the correction factor (CF)
- Use the 1700 rule to estimate the CF
- $CF = 1700$  divided by the total daily dose (TDD)

ex: if TDD = 36 units, then  $CF = 1700/36 = \sim 50$

meaning 1 unit will lower the BG  $\sim 50$  mg/dl

# Sliding Scale Insulin

## Sliding Scales

- Based on Pre-Meal Readings

- **Pros:**

- Easy to use
- No patient calculations necessary
- Increased patient compliance
- Increased reason for SMBG

- **Cons**

- Chasing high readings
- Does not account for meal consumption
- Higher likelihood of hypoglycemia

<u>Reading</u>		<u>Dose</u>
150mg/dl		1unit
200mg/dl		2 units
250		units
300		4 units
400		6 units

# Barriers to Starting Insulin Therapy



- Patient fear and resistance
- Clinician resistance
- Association of needles with pain
- Fear of complications (eg, amputations)
- Time commitment required
- Inconvenience



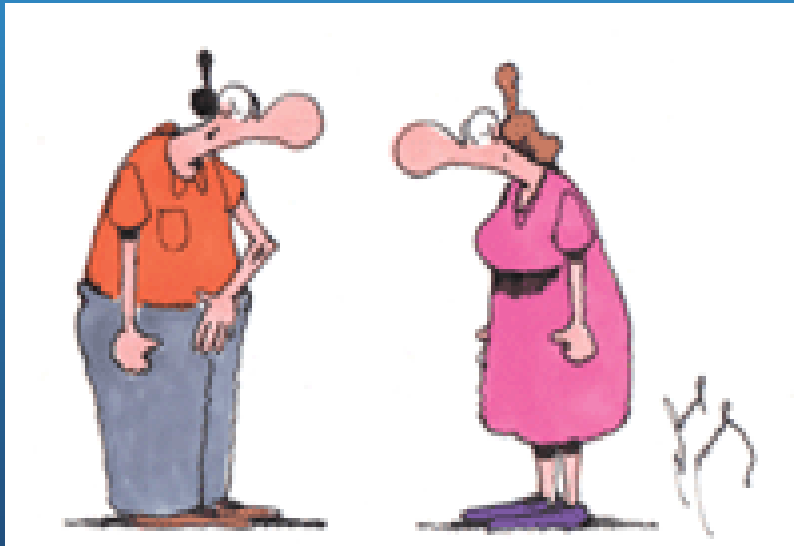
Weight gain

- Lack of education
- Cost



# Dispelling Fears

- Team's positive attitude toward insulin
- **Not Painful!**
- Devices are User Friendly



"It's not a tattoo. I mistook a Bic for an Insulin Pen"  
*2004 Diabetes Health*



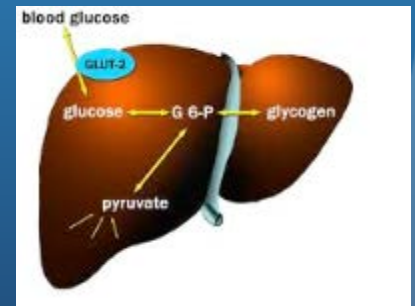
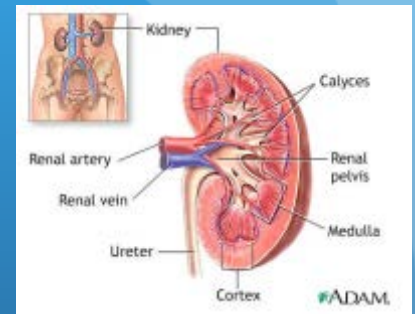


# Hypoglycemia: Recognition

- Sometimes difficult to diagnose based on symptoms
  - Whipple's Triad
    - Symptoms consistent with hypoglycemia
    - Low glucose reading
    - Reversal or improvement of symptoms after treatment
- There are a variety of symptoms associated with hypoglycemia
  - Adrenergic
  - Glucagon mediated
  - Neuroglycopenic

# Hypoglycemia: Pathophysiology

- The brain is the first organ effected by low blood glucose
- The body responds hypoglycemia by:
  - Glycogenolysis
    - Glycogen stores (~75g) in liver can be broken down into glucose monomers
    - Can keep the body out of coma for a short period of time
  - Gluconeogenesis
    - Production of glucose from non-carbohydrate sources such as lactate, glycerol, & glucogenic amino acids
    - Takes place in the liver & to lesser extent in the cortex of the kidney



# Hypoglycemia: Signs & Symptoms

Adrenergic:	Glucagon Mediated:	Neuroglycopenic:
<ul style="list-style-type: none"><li>• Shakiness &amp; Anxiety</li><li>• Sweating</li><li>• Pallor; feeling cold &amp; clammy</li><li>• Palpitations</li><li>• Tachycardia</li><li>• Mydriasis (dilation)</li><li>• Paresthesias</li></ul>	<ul style="list-style-type: none"><li>• Hunger</li><li>• Nausea &amp; Vomiting</li><li>• Abdominal Pain</li><li>• Headache</li><li>• Borborygmus</li></ul>	<ul style="list-style-type: none"><li>• Mental status changes</li><li>• Impaired judgment</li><li>• Dysphoria &amp; mood changes</li><li>• Fatigue/Weakness</li><li>• Confusion &amp; Amnesia</li><li>• Double/blurred vision</li><li>• Difficulty speaking</li><li>• Ataxia/motor deficit</li><li>• Coma</li><li>• Generalized or focal seizures</li></ul>

# Hypoglycemia: Treatment

- Mild to Moderate
  - <70mg/dl but patient is able to self treat
  - Usually characterized by sweating, trembling, difficulty concentrating, lightheadedness, & lack of coordination
  - Rule of 15
    - Consume 15 grams of glucose or a quick acting carbohydrate
    - Recheck glucose after 15 minutes to determine need to retreat
    - If continued hypoglycemia; repeat treatment



# Hypoglycemia: The Causes

- Can be induced by certain medications:
  - Salicylates
    - Generally only at high doses
  - Bactrim/Septra
  - Beta blockers
    - Decreased glycogenolysis & warning signs
  - Quinine
  - Pentamidine
    - Toxic to beta cells in pancreas
  - ACE inhibitors
  - Insulin or secretagogues



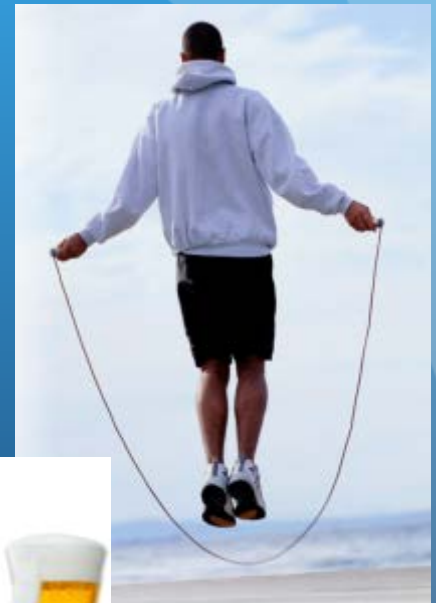
# Hypoglycemia: The Values

- Hypoglycemia is defined as a blood sugar of <70 mg/dl
- Depending on the person, different lab values will have differing implications and symptoms, so it is important to treat the patient regardless of labs appearing “low”

Glucose Lab Value	Signs/Symptoms
<65 mg/dl	Begin to see mental deficiencies
<40 mg/dl	Impaired action & judgment; seizure threshold is lowered
<10 mg/dl	Neurons essentially become electrically silent

# Hypoglycemia: The Causes

- Severe illness
  - Including sepsis
- Prolonged fasting
  - Including diarrheal/gastrointestinal illness
- Exercise
- Alcohol
  - Decreases liver gluconeogenesis
- Growth hormone deficiency
- Hypopituitarism
- Addison's disease
- Adrenal insufficiency
- Other metabolic disorders
- Organ failure



# Hypoglycemia: Treatment

- Quick-acting carbohydrate sources:
  - Glucose tablets/gels
    - Brand dependent, but ~5g/tablet & ~15g/gel dose
  - Hard candies: ~10g/piece
  - Raisins: 2 TBSP
  - Soda (NON-diet): 4-6 oz
  - Fruit Juice: 4-6 oz
  - Milk (NO or LOW fat only): 8 oz
- **FAT DELAYS ABSORPTION OF CARBS – HIGH FAT FOODS ARE POOR CHOICES WHEN TREATING HYPOGLYCEMIA**
  - For example - ice-cream, doughnuts, candy bars, cheese, chips, milkshakes, etc...





# Hypoglycemia: Treatment

- SEVERE
  - Usually characterized by the inability to self-treat due to mental status changes, lethargy, & unconsciousness
  - If patient is able to swallow:
    - Glucose gel
    - Honey
    - Juice
  - Unable to swallow:
    - Glucagon injection
    - Could potentially use IV dextrose in severe & prolonged cases OR if the patient does not respond to glucagon therapy



# Glucagon Injection:



- Used in severe hypoglycemia only
- Is in an emergency kit
  - Includes syringe, cap, & vial for reconstitution
  - SC/IM injection usually into top of the thigh
    - After injection patient needs to be turned on side to prevent choking
    - If patient does not wake up after 15 minutes give another shot of glucagon
    - When patient wakes up they need immediate oral fast acting carbs followed by a longer acting source of sugar to replenish carb sources in the body

# INSULIN

Type	Onset	Peak	Duration
Rapid– Apart, Lispro, Glulisine	<15 min	60-120 minutes	4-5 hours
Regular	30-45 min	2-4 hours	6-8 hours
NPH	1-2 hr	6-8 hours	18-26 hrs
Detimir	1-2 hr	Nearly none	18-26 hrs (dose related)
Glargine	1-2 hr	Nearly None	22-26 hours

# Mixed Insulins

Type	Long Acting	Short Acting	Devices
Humalog 75/25	75% Protamated Lispro	25% Lispro	KwikPen, Vial, Turbopen
Novolog 70/30	75% Protamated Aspart	25% Aspart	FlexPen, Vial
Humalog 50/50	50% Protamated Lispro	50% Lispro	KwikPen, Vial, Turbopen
Novolin 70/30	70% NPH	30% Regular	Innolet, Vial
Humulin 70/30	70% NPH	30% Regular	Turbopen, Vial

# Insulin Storage

- Vials:
  - Refrigerated (36-46°F):
    - Unopened: expiration date
    - Opened: 28 days
  - Room temperature (59-86°F):
    - Unopened: 28 days
    - Opened: 28 days



# Insulin Storage

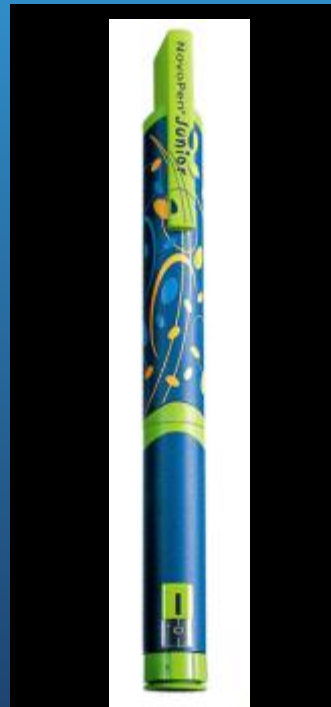
- Pens
  - Refrigerated (36-46°F):
    - Expiration date
    - In use
      - Lantus, Apidra solostar: 28 days
      - Levemir: 42 days
      - Novolog: 28 days
      - Novolog Mix 70/30: 14 days
  - Room temperature (59-86°F):
    - Humalog<sup>®</sup> Mix 75/25, 50/50: 10 days
    - 70/30: 10 days
    - NPH: 14 days
    - Lispro: 28 days
- Pens in use should not be refrigerated

# Lilly Insulin Pens



# Novo Nordisk devices in diabetes care

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



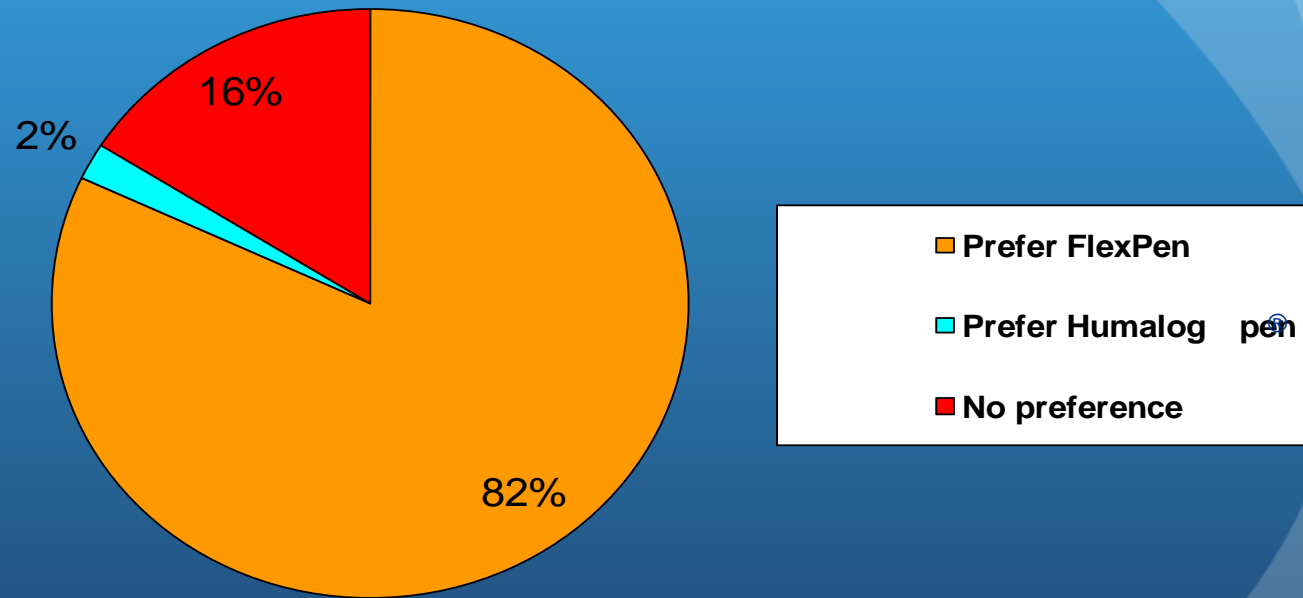


# Prefilled Syringe with Flexible Dosing



# NovoLog<sup>®</sup> FlexPen<sup>®</sup>

82% of DNEs Preferred FlexPen<sup>®</sup>



Source: Diabetes Nurse Educators In-Depth Study—Reactions to FlexPen.