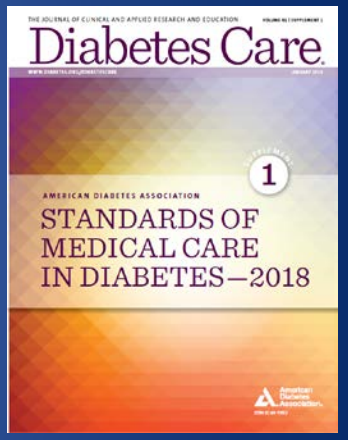
"New Medications and Prescribing Methods for Diabetic Patients"



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Disclosure

I have no relevant financial relationships or affiliations with commercial interests to disclose

Objectives

- Identify the sites of action of each of the diabetes treatments
- Identify contraindications and side effects of each diabetes treatment
- Differentiate the HbA1C reduction among each of the diabetes treatments
- Identify and differentiate between diabetes treatments that can cause weight gain or weight loss
- Identify preferred antihypertensive agents utilized in patients with diabetes
- Identify preferred lipid agents utilized in patients with diabetes

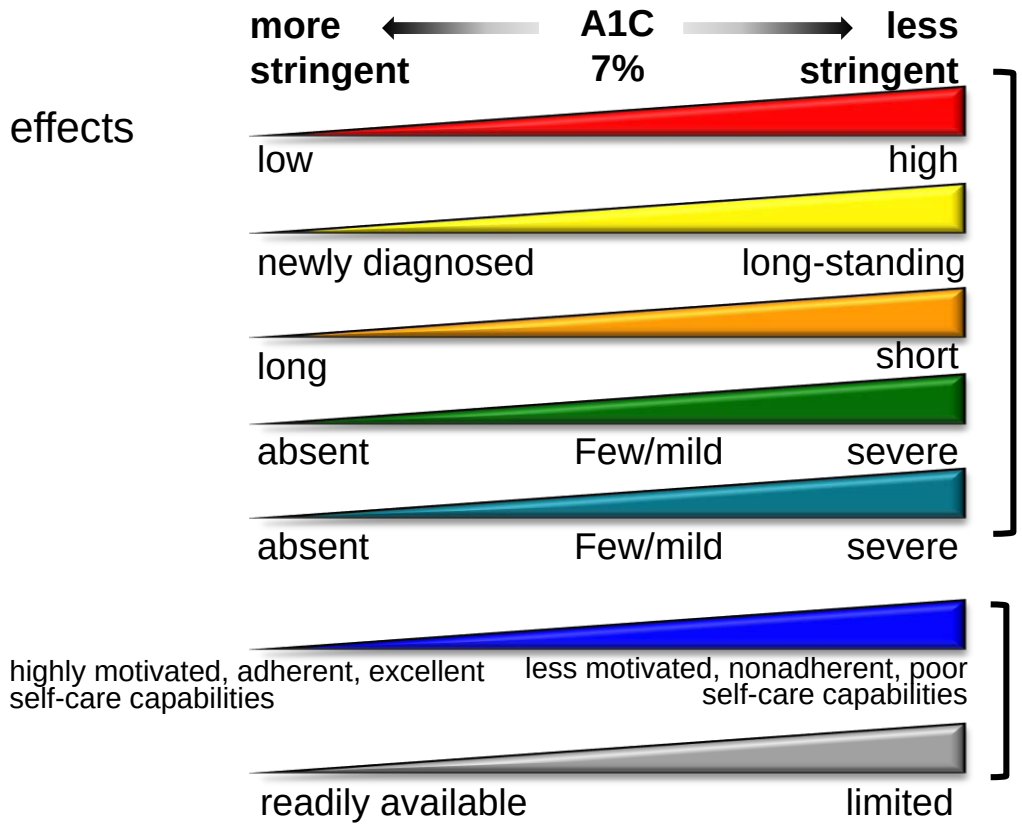
Guidelines-Goals

Variable	*ADA Recommendations*
Hb_{A1C}*	<7.0% (AACE ≤ 6.5%)
Preprandial	80-130mg/dL (AACE <110mg/dL)
Postprandial	<180mg/dL (AACE < 140mg/dL)
LDL*	<100mg/dL (<70mg/dL with CVD hx)
Triglycerides	<150mg/dL
HDL	>40mg/dL (women > 50mg/dL)
Non-HDL	<130mg/dL (If TG ≥ 200mg/dL)
Blood Pressure*	<140/90 mmHg (<130/80 in some)
Al/Cr	<30
Other	Aspirin, Pneumococcal and Influenza vaccines

Diabetes Care. 2018; 41.

Approach to the Management of Hyperglycemia

Patient/Disease Features



Glycemic Targets:
Standards of Medical Care in Diabetes - 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S55-S64

PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

TREAT ASCVD RISK FACTORS

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

- DYSLIPIDEMIA ROUTE
- HYPERTENSION ROUTE

WEIGHT LOSS THERAPIES

NORMAL GLYCEMIA

Progression

OVERT DIABETES

PROCEED TO HYPERGLYCEMIA ALGORITHM

TREAT HYPERGLYCEMIA
FPG > 100 | 2-hour PG > 140

1 PRE-DM CRITERION

Intensify Weight Loss Therapies

MULTIPLE PRE-DM CRITERIA

Low-risk Medications
- Metformin
- Acarbose

Consider with Caution
- TZD
- GLP-1 RA

If glycemia not normalized

LEGEND

Orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg, or bariatric surgery as indicated for obesity treatment

Diabetes Education

- Intensive Course for 2-4 weeks with certified diabetic educator
- Follow-up every 3 months, more frequent as needed

<u>Survival Skills</u>

- Insulin-preparation and injection
- Glucometer use and calibration, keeping logs
- Urine/serum ketone testing
- Glucagon emergency kit
- Nutrition

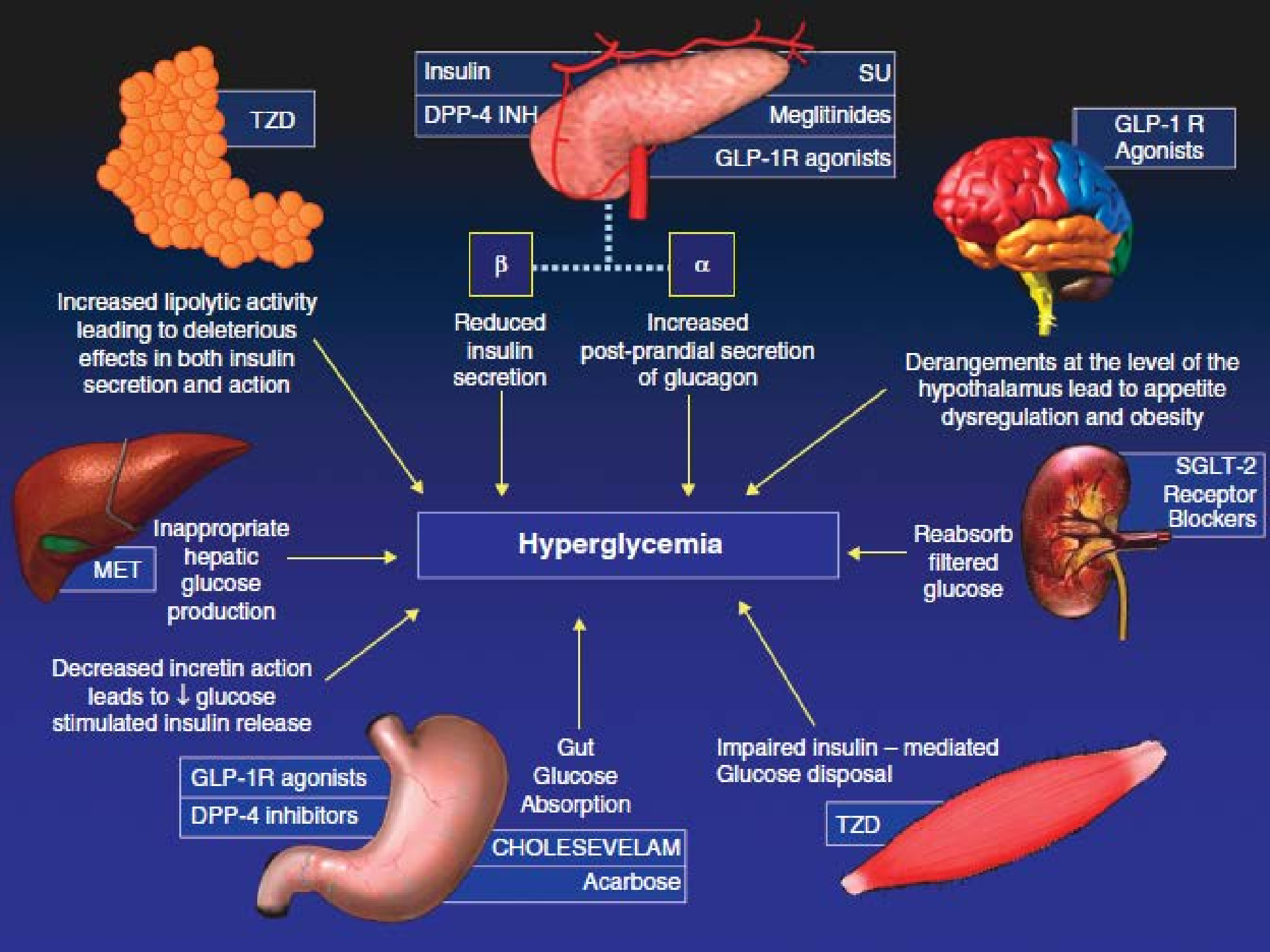
Lifestyle Management:
Standards of Medical Care in Diabetes - 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S38-S50

Lifestyle Intervention
(From the Diabetes Prevention Program)

An intensive program with the following specific goals:

- ≥ 7% loss of body weight and maintenance of weight loss
- Dietary fat goal: < 25% of calories from fat
- Calorie intake goal: 1200-1800 kcal/day
- ≥ 150 minutes per week of physical activity

The DPP Research Group, *NEJM 346*:393-403, 2002


TZD
Insulin
DPP-4 INH
SU
Meglitinides
GLP-1R agonists
β
α
GLP-1 R Agonists
Increased lipolytic activity leading to deleterious effects in both insulin secretion and action
Reduced insulin secretion
Increased post-prandial secretion of glucagon
Derangements at the level of the hypothalamus lead to appetite dysregulation and obesity
MET
Inappropriate hepatic glucose production
Hyperglycemia
Reabsorb filtered glucose
SGLT-2 Receptor Blockers
Decreased incretin action leads to ↓ glucose stimulated insulin release
GLP-1R agonists
DPP-4 inhibitors
Gut Glucose Absorption
CHOLESEVELAM
Acarbose
Impaired insulin – mediated Glucose disposal
TZD

Sulfonylureas

- Sulfonylureas increase endogenous insulin secretion
- Sulfonylureas stimulate insulin release by binding to a specific site on the β cell K_{ATP} channel complex (SUR) and inhibiting its activity. K_{ATP} channel inhibition causes cell membrane depolarization and the cascade of events leading to insulin secretion

- Efficacy
  - Decrease fasting plasma glucose 60-80 mg/dl
  - Reduce A1C by 1.5-2.0%

- Other Effects
  - Hypoglycemia
  - Weight gain*
  - No specific effect on plasma lipids or blood pressure
  - Generally the least expensive class of medication

- Medications in this Class:
  - First generation sulfonylureas:
    - chlorpropamide (Diabinese)
    - tolazamide
    - acetohexamide (Dymelor)
    - tolbutamide
  - Second generation sulfonylureas:
    - glyburide (Micronase, Glynase, and DiaBeta)
    - glimepiride (Amaryl)
    - glipizide (Glucotrol, Glucotrol XL)

Chan JL, Abrahamson MJ. Mayo Clin Proc 2003; 78: 459-67

Biguanides

- Biguanides decrease hepatic glucose production and increase insulin-mediated peripheral glucose uptake.
- Metformin has specific actions on mitochondrial respiration that reduce intracellular ATP and increase AMP.
- Efficacy
  - Decrease fasting plasma glucose 60-80 mg/dl
  - Reduce A1C 1.5-2.0%
- Other Effects
  - Diarrhea and abdominal discomfort
  - Lactic acidosis if improperly prescribed
  - Cause small decrease in LDL cholesterol level and triglycerides
  - No specific effect on blood pressure
  - No weight gain, with possible modest weight loss
  - B12 deficiency reported
  - Contraindicated in patients with an eGFR below 30 mL/minute/1.73 m^2.*
  - Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended.
- Medications in this Class:
  - metformin (Glucophage)
  - metformin hydrochloride extended release (Glucophage XR)

Chan JL, Abrahamson MJ. Mayo Clin Proc 2003; 78: 459-67

Thiazolidinediones

- Thiazolidinediones decrease insulin resistance by making muscle and adipose cells more sensitive to insulin. They also suppress hepatic glucose production.
- Thiazolidinediones are ligands for the PPARγ receptor, a nuclear hormone receptor that has two isoforms and is involved in the regulation of genes related to glucose and lipid metabolism.
- Efficacy
  - Decrease fasting plasma glucose ~50-80 mg/dl
  - Reduce A1C ~0.6-1.9%
  - 6 weeks for maximum effect
- Other Effects
  - Weight gain, edema
  - Contraindicated in patients with abnormal liver function or CHF (Class 3-4)
  - Improves HDL cholesterol and plasma triglycerides; usually LDL neutral
- Medications in this Class:
  - pioglitazone (Actos) – bladder cancer warning
  - rosiglitazone (Avandia) – cardiovascular disease warning
  - troglitazone (Rezulin) - taken off market due to liver toxicity

Chan JL, Abrahamson MJ. Mayo Clin Proc 2003; 78: 459-67

Meglitinides

- Meglitinides stimulate insulin secretion (rapidly and for a short duration) in the presence of glucose.
- Like sulfonylureas, stimulate insulin release by closing K_{ATP} channels in pancreatic β cells
- Efficacy
  - Decreases peak postprandial glucose
  - Decreases plasma glucose 60-70 mg/dl (3.3-3.9 mmol/L)
  - Reduce A1C 1.0-1.5%
- Other Effects
  - Hypoglycemia (although may be less than with sulfonylureas if patient has a variable eating schedule)
  - Weight gain
  - No significant effect on plasma lipid levels
  - Safe at higher levels of serum Cr than sulfonylureas
- Medications in this Class:
  - repaglinide (Prandin)
  - nateglinide (Starlix)

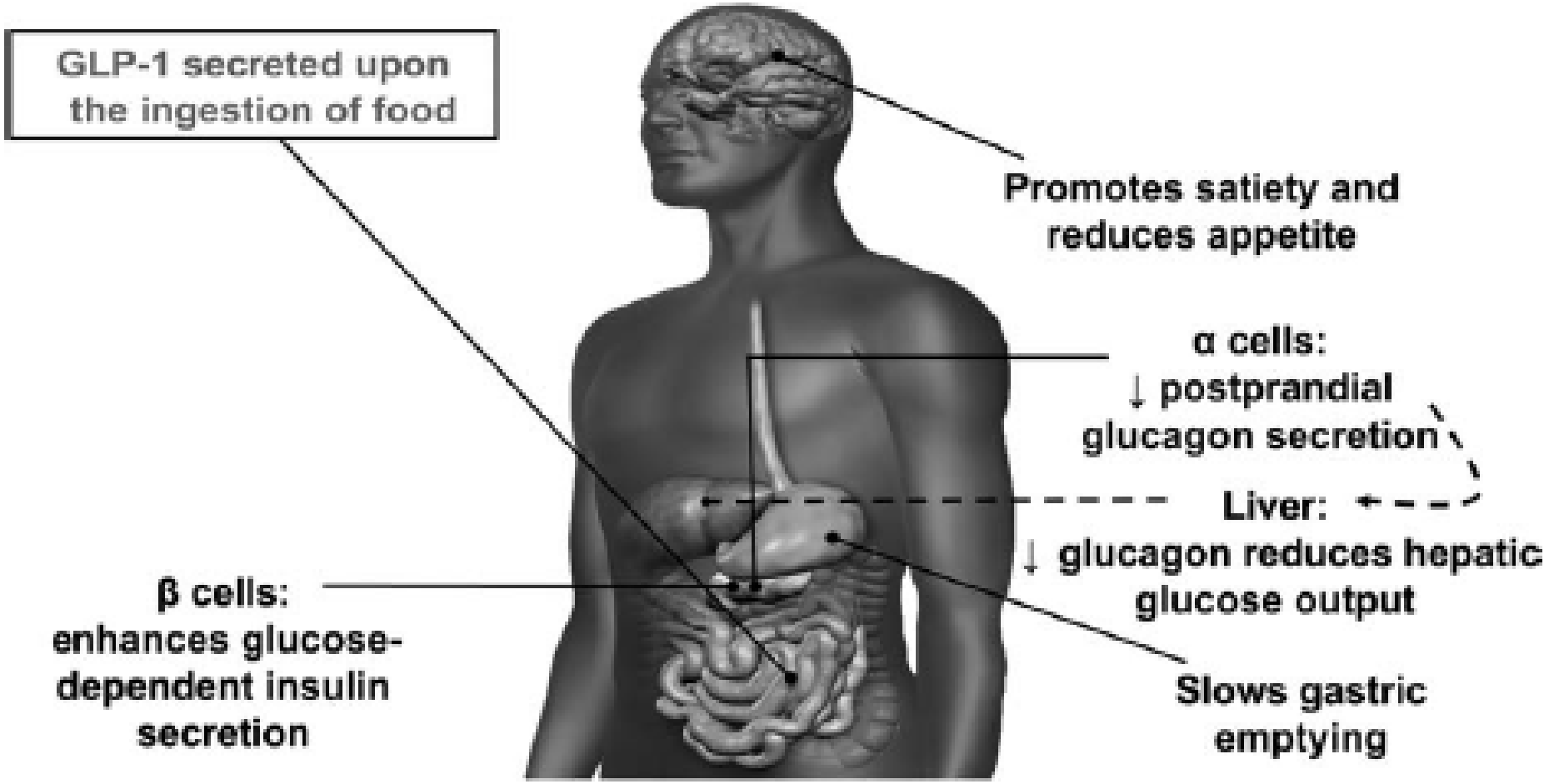
Chan JL, Abrahamson MJ. Mayo Clin Proc 2003; 78: 459-67

Alpha-glucosidase Inhibitors

- Alpha-glucosidase inhibitors block the enzymes that digest starches in the small intestine
- α-Glucosidase inhibitors reduce intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of α-glucosidase in the intestinal brush border
- Efficacy
  - Decrease peak postprandial glucose 40-50 mg/dl
  - Decrease fasting plasma glucose (no sig effect)
  - Decrease A1C 0.5-1.0%
- Other Effects
  - Flatulence or abdominal discomfort
  - No specific effect on lipids or blood pressure
  - No weight gain
  - Contraindicated in patients with inflammatory bowel disease or cirrhosis
- Medications in this Class:
  - acarbose (Precose)
  - miglitol (Glyset)

Chan JL, Abrahamson MJ. Mayo Clin Proc 2003; 78: 459-67

Effects of Glucagon-like peptide-1



Idris I and Donnelly R. Diabetes Obes Metab. 2007;9:153-65.

Incretin Mimetics

- Efficacy
  - Hemoglobin A1c lowering of 0.8%–1.9%
  - Primarily a postprandial glucose reduction with exenatide BID
  - Less postprandial and greater fasting glucose reduction with liraglutide and weekly products
- Dose
  - Exenatide (Byetta): 5 mcg subcutaneously 2 times/day (thigh, abdomen, or upper arm) 1–60 minutes before morning and evening meals, increase to 10 mcg 2 times/ day after 4 weeks if tolerated
  - Liraglutide (Victoza): 0.6 mg subcutaneously every day (independent of meals; inject into thigh, abdomen, or upper arm); increase by weekly intervals to 1.2 mg subcutaneously every day; then 1.8 mg subcutaneously every day if needed

Incretin Mimetics

- Dose
  - Exenatide LAR (Bydureon): 2 mg subcutaneously weekly (thigh, abdomen, or upper arm); two weeks before see effect (6-8 weeks full effect)
  - Albiglutide (Tanzeum): 30 mg subcutaneously weekly (independent of meals; inject into thigh, abdomen, or upper arm); can increase to 50 mg after 4 weeks if needed.
  - Dulaglutide (Trulicity): 0.75 mg subcutaneously weekly (independent of meals; inject into thigh, abdomen, or upper arm); can increase to 1.5 mg after 4 weeks if needed.

Incretin Mimetics

- Adverse Effects
  - GI: Nausea, Vomiting, Diarrhea
  - Headache
  - Rare: Pancreatitis/Renal dysfunction
- Contraindications
  - Gastroparesis
  - Creatinine clearance < 30 mL/minute: Exenatide and Exenatide LAR
  - Medullary thyroid carcinoma (MTC), personal or family history, or in patients with multiple endocrine neoplasia syndrome type 2 (MEN2): Liraglutide and Weekly products
  - Pancreatitis

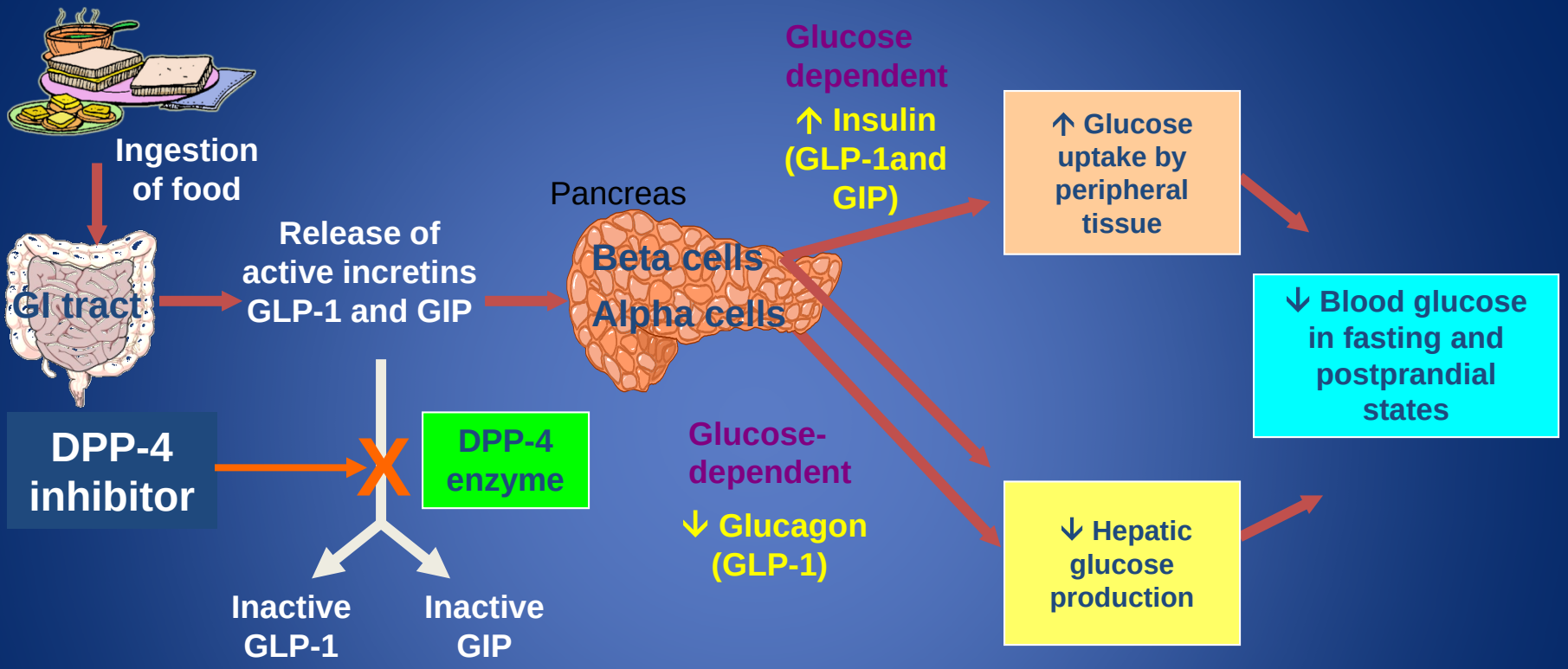
Incretin Mimetics

- Advantages
  - Use is associated with weight loss (2-3 kg)
  - Convenient dosing
  - B-cell sparing effect?
- Disadvantages
  - Parenteral administration
  - Gastrointestinal adverse effects
  - May reduce the rate and extent of absorption of drugs that require rapid absorption (pain relievers, antibiotics, and oral contraceptives); separate administration by at least 1 hour
  - Cost

GLP-1 Comparison Chart

Drug	Byetta	Bydureon	Tanzeum	Trulicity	Victoza
Generic	exenatide	exenatide	albiglutide	dulaglutide	liraglutide
Dosing Frequency	Twice daily	Weekly	Weekly	Weekly	Daily
Dosing	5 mcg 10 mcg	2 mg	30 mg 50 mg	0.75 mg 1.5 mg	0.6 mg 1.2 mg 1.8 mg
Mixing Required	No	Yes	Yes	No	No
Waiting Time post mixing	None	None	15 or 30 minutes	None	None
Needle Size	32 g; 4mm	23 g; 8 mm	29 g; 5 mm	29 g;built-in	32 g; 4 mm
Auto-injector	No	No	No	Yes	No
Use with basal insulin	Yes	No	Yes	No	Yes

Mechanism of Action of DPP-IV Inhibitors



- Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels ↑ in response to a meal.

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.

Pharmacology

	JANUVIA (SITAGLIPTIN)	ONGLYZA (SAXAGLIPTIN)	TRADJENTA (LINAGLIPTIN)	NESINA (ALOGLIPTIN)
Dosing Frequency	QD	QD	QD	QD
Dosage	25, 50, 100 mg	2.5 & 5 mg	5 mg	6.25, 12.5, 25 mg
Half-life (hours)	12.4	2.5 (active metabolite= 3.1)	> 100	21 (active metabolite)
Metabolism	Not extensively metabolized	CYP3A4/5	Not extensively metabolized	CYP2D6/3A4
Majority of Elimination	Renal	Renal	Bile	Renal
Dose Adjustment in CKD/ESRD	✓	✓	--	✓
Combination Products	✓	✓	✓	✓

DPP-IV Inhibitors
Good vs. Bad

Incretin Comparison

	GLP-1 Activation	DPP-IV Inhibition
↑ Insulin	+++	+++
↓ Glucagon	+++	++
↓ Gastric emptying	+++	--
Hypoglycemia	+/-	--
Nausea/Vomiting	+++	--
Weight	Loss	No Change
Route of admin	Injection	Oral

Other Available Agents

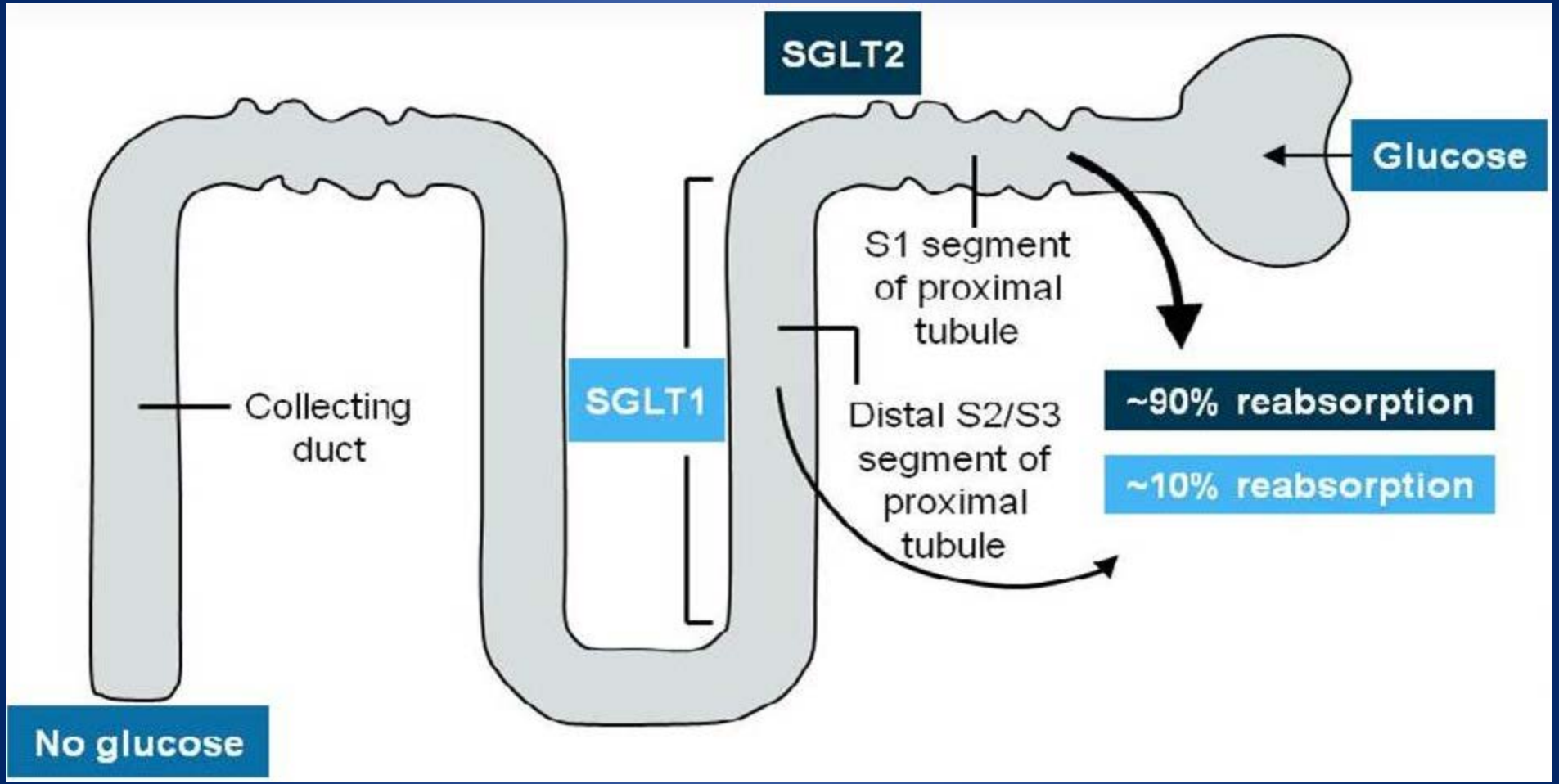
- Pramlintide (Symlin®)
  - Used in type 1 and type 2 diabetes
  - Amylin analog (hormone co-secreted with insulin)
  - Injectable three times daily
  - Weight loss
- Colesevelam (Welchol®)
  - Lipid agent
  - Used in type 2 diabetes
  - A1c reduction ~0.5%
- Bromocriptine (Cycloset®)
  - Dopamine receptor agonist
  - Used in type 2 diabetes
  - A1c reduction ~0.5%

Sodium- Glucose Cotransporters

	SGLT1	SGLT2
Site	Mostly intestine with some kidney	Almost exclusively kidney
Sugar Specificity	Glucose or galactose	Glucose
Affinity for glucose	High Km= 0.4 Mm	Low Km = 2 Mm
Capacity for glucose transport	Low	High
Role	Dietary glucose absorption Renal glucose reabsorption	Renal glucose reabsorption

Lee YJ, at al. *Kidney Int Suppl.* 2007;72:S27-S35.

Targeting the Kidney



Chao EC, et al. *Nat Rev Drug Discovery.* 2010;9:551-559.

Effects of SGLT2 Inhibitors

Inhibition of renal tubular Na^+- glucose cotransporter →

reversal of hyperglycemia → reversal of "glucotoxicity"

- ↑ Insulin sensitivity in muscle
  - ↑ GLUT4 translocation
  - ↑ Insulin signaling
- ↑ Insulin sensitivity in liver
  - ↓ Glucose-6-phosphatase
- ↓ Gluconeogenesis
  - ↓ Decreased Cori Cycle
  - ↓ PEP carboxykinase
- ↑ Improved beta cell function

DeFronzo RA, et al. *Diabetes Obes Metab*. 2012;14(1):5-14.

Sodium-Glucose co-Transporter 2 Inhibitors

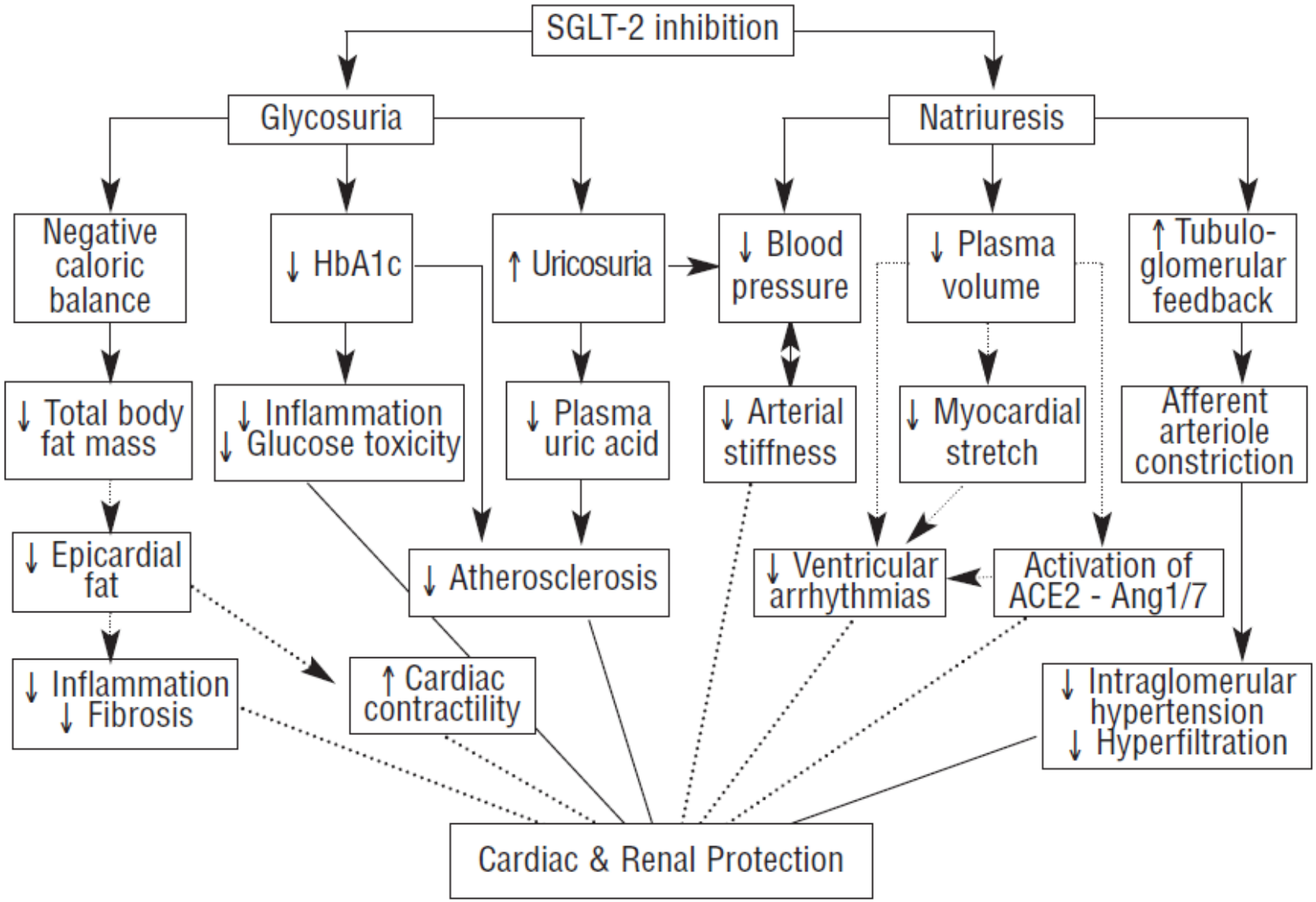
- Mechanism of Action
  - Blocks SGLT-2 receptors in the proximal tubule thus inhibiting renal reabsorption of glucose.
  - This results in glycosuria, as well as salt and water loss.
- Efficacy
  - Hemoglobin A1c lowering of 0.7%–1.1%.
  - Lowers fasting and postprandial glucose levels
  - Weight loss
  - BP reduction
- Dose
  - Canagliflozin (Invokana): 100 mg once daily; may increase to 300 mg
  - Dapagliflozin (Farxiga): 5 mg once daily; may increase to 10 mg
  - Empagliflozin (Jardiance): 10 mg daily once daily; may increase to 25 mg

Dose Adjustments for Renal Insufficiency

eGFR (mL/min/1.73m^{2})	Canagliflozin (Invokana)	Dapagliflozin (Farxiga)	Empagliflozin (Jardiance)
≥ 60	No dosage adjustment	No dosage adjustment	No dosage adjustment
45 – 60	100mg daily	Not recommended for eGFR <60	No dosage adjustment
< 45	Not recommended	Not recommended	Not recommended

INVOKANA™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013.
FARXIGA™ [prescribing information]. Bristol-Myers Squibb & AstraZeneca Pharmaceuticals, Inc.; 2014.
JARDIANCE™ [prescribing information]. Boehringer Ingelheim Pharmaceuticals, Inc. & Eli Lilly and Company; 2014.

Figure 5. SGLT-2 Inhibition:Mediators of CV and Renal Effects



SGLT-2 Inhibitors

Adverse Effects

- Genital mycotic infections
  - Women: **5.4-11.4% (SGLT2)** vs. **1.5-3.2% (placebo)**
  - Men (more common if uncircumcised): **1.6-4.2% (SGLT2)** vs. **0.3-0.6% (placebo)**
- Urinary tract infections
  - **4.3-9.3% (SGLT2)** vs. **3.7-7.6% (placebo)**
- Polyuria
- Risk of hypotension and hypovolemia due to osmotic diuresis
- Euglycemic ketoacidosis (EKA, euDKA)

Invokana PI; Farxiga PI; Jardiance PI

SGLT-2 Inhibitor Summary

Advantages

- Once daily oral administration
- Effect independent of insulin secretion or insulin resistance
- Low risk of hypoglycemia
- Decreases both FBG and PPG
- Weight Loss (2-3kg)
- Blood pressure lowering (~5 mmHG SBP)

Concerns

- Polyuria (additional 200-400 mL/day)
- Dehydration
- Hypotension
- Genital mycotic infection
- Urinary tract infection

The History of Insulins

- 1889: Pancreas & DM
- 1921: Extraction of insulin
- 1922: 1st successful use of insulin
- 1930's: Joslin advocates tight glycemic control
- 1936: PZI insulin
- 1946: NPH insulin
- 1951: Lente insulins
- 1970's: Single source insulins
- 1980's: Premixed insulin Human insulin
- 1990's: Insulin Analogs. (Quick-acting insulin) DCCT/UKPDS
- 2000: Basal Insulin DCCT/EDIC
- 2006: Inhaled Insulin

Insulin Therapy in Type 2 Diabetes

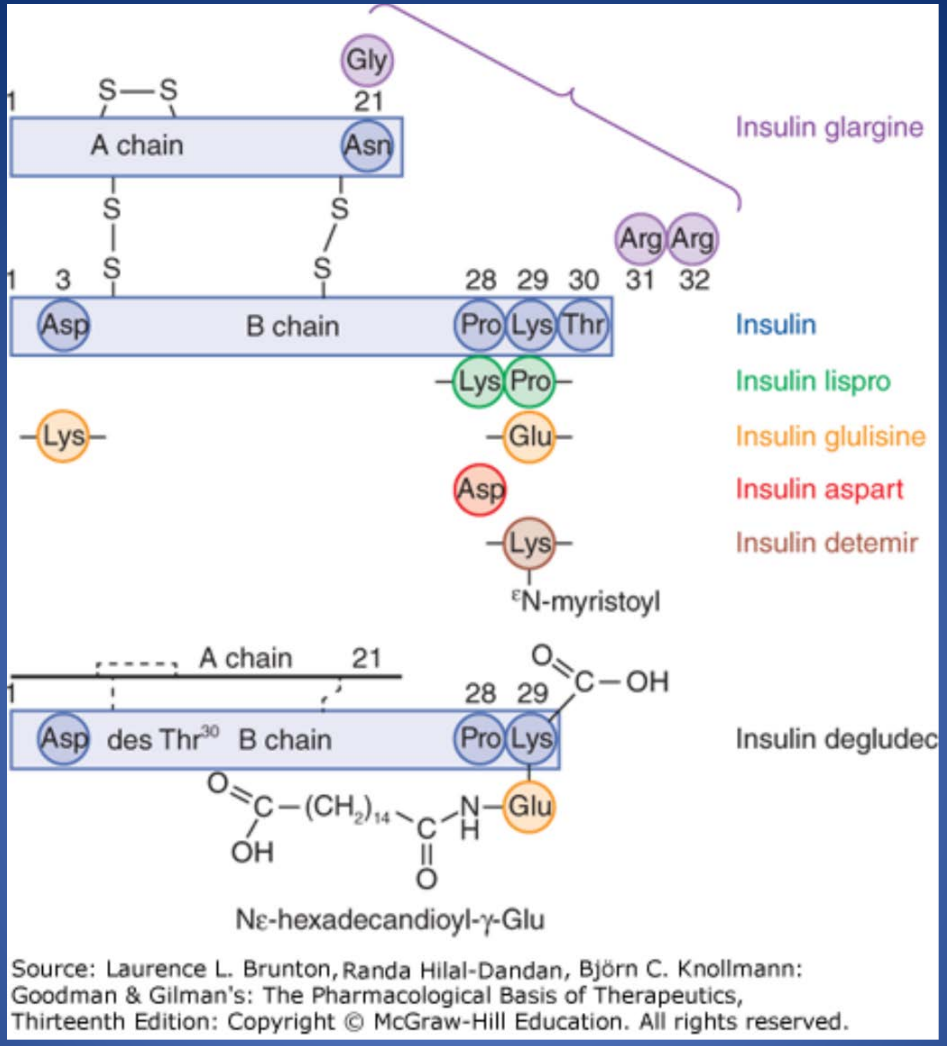
Arguments for Earlier Use

Pros

- No limit to potential glycemic lowering.
- Virtually 100% responder rate.
- Large doses can overcome insulin resistance.
- Addresses only one of the two underlying endocrinologic defects in those with Type 2 diabetes, but can overcome the other.

Cons

- Patients may be reluctant to initiate insulin earlier in the course of therapy due to their fear of injections and concerns about hypoglycemia and weight gain.
- Patients may view their transition to insulin as a signal that they have 'failed' and/or that their diabetes has worsened.
- Physicians and nurses need to spend considerable time teaching patients about the various types of insulin, how to mix and administer the agents, how to recognize and manage hypoglycemic events, as well as the intensive monitoring required to attain target goals.
- More difficult to understand and comply with an insulin regimen vs. oral medications.

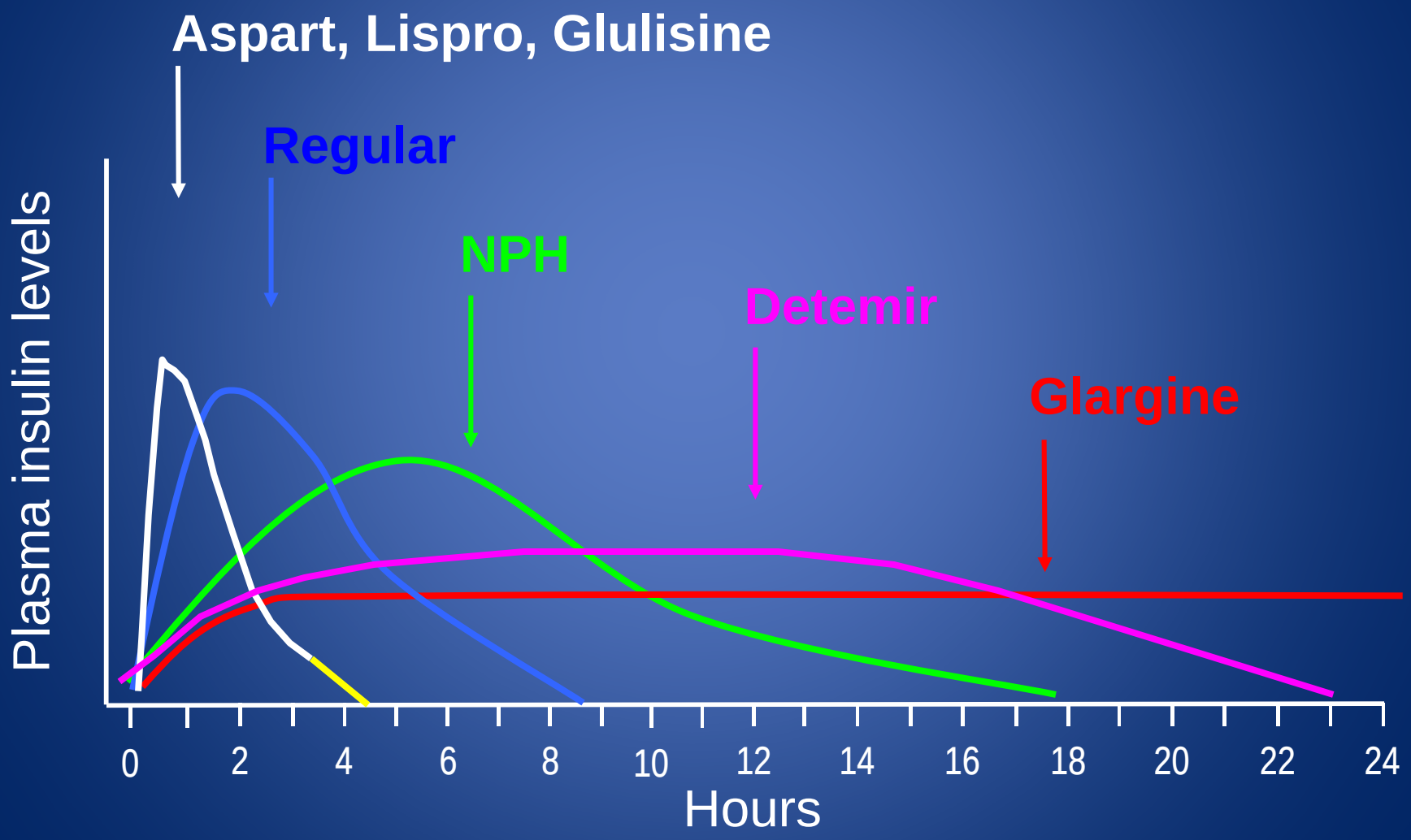


Insulin analogues. Modifications of native insulin can alter its pharmacokinetic profile. Reversing amino acids 28 and 29 in the B chain (lispro) or substituting Asp for Pro^{28B} (aspart) gives analogues with reduced tendencies for molecular self-association that are faster acting. Altering Asp^{3B} to Lys and Lys^{29B} to Glu produces an insulin (glulisine) with a more rapid onset and a shorter duration of action. Substituting Gly for Asn^{21A} and lengthening the B chain by adding Arg^{31} and Arg^{32} produces a derivative (glargine) with reduced solubility at pH 7.4 that is, consequently, absorbed more slowly and acts over a longer period of time. Deleting Thr^{30B} and adding a myristoyl group to the ε-amino group of Lys^{29B} (detemir) enhances reversible binding to albumin, thereby slowing transport across vascular endothelium to tissues and providing prolonged action. Insulin degludec is LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin. When degludec is injected subcutaneously, it forms multihexameric complexes that slow absorption; degludec also binds well to albumin; these two characteristics contribute to the prolonged effect of degludec (>24 h at steady state).

Comparison of Human Insulins

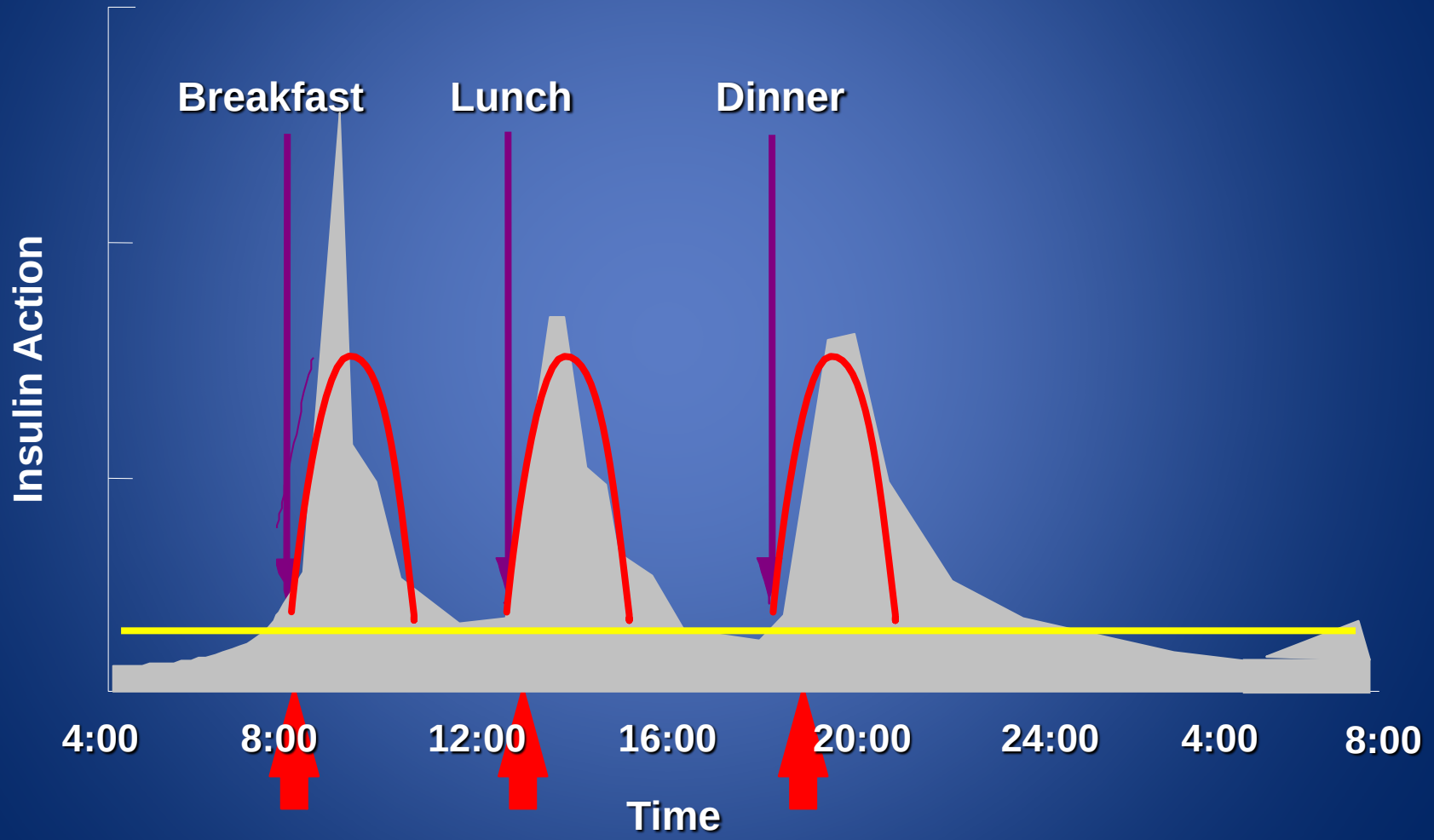
Insulin	Onset	Peak	Duration
Lispro, Aspart, Glulisine	5-15 mins	1-2 hrs	3-5 hrs
Inhaled Insulin	Minutes	12-15 min	2-3 hrs
Human Regular	30-60 mins	2-4 hrs	6-8 hrs
Human NPH	1-2 hrs	6-12 hrs	10-16 hrs
Insulin Detemir	3-4 hrs	Peakless	12-24 hrs
Insulin Glargine	4-6 hrs	Peakless	~24 hrs
Glargine U300	6 hrs	Peakless	~30-36 hrs
Insulin Degludec	6 hrs	Peakless	~42 hrs

Profiles Human Insulin and Analogs



Rosenstock J. *Clin Cornerstone.* 2001;4:50.

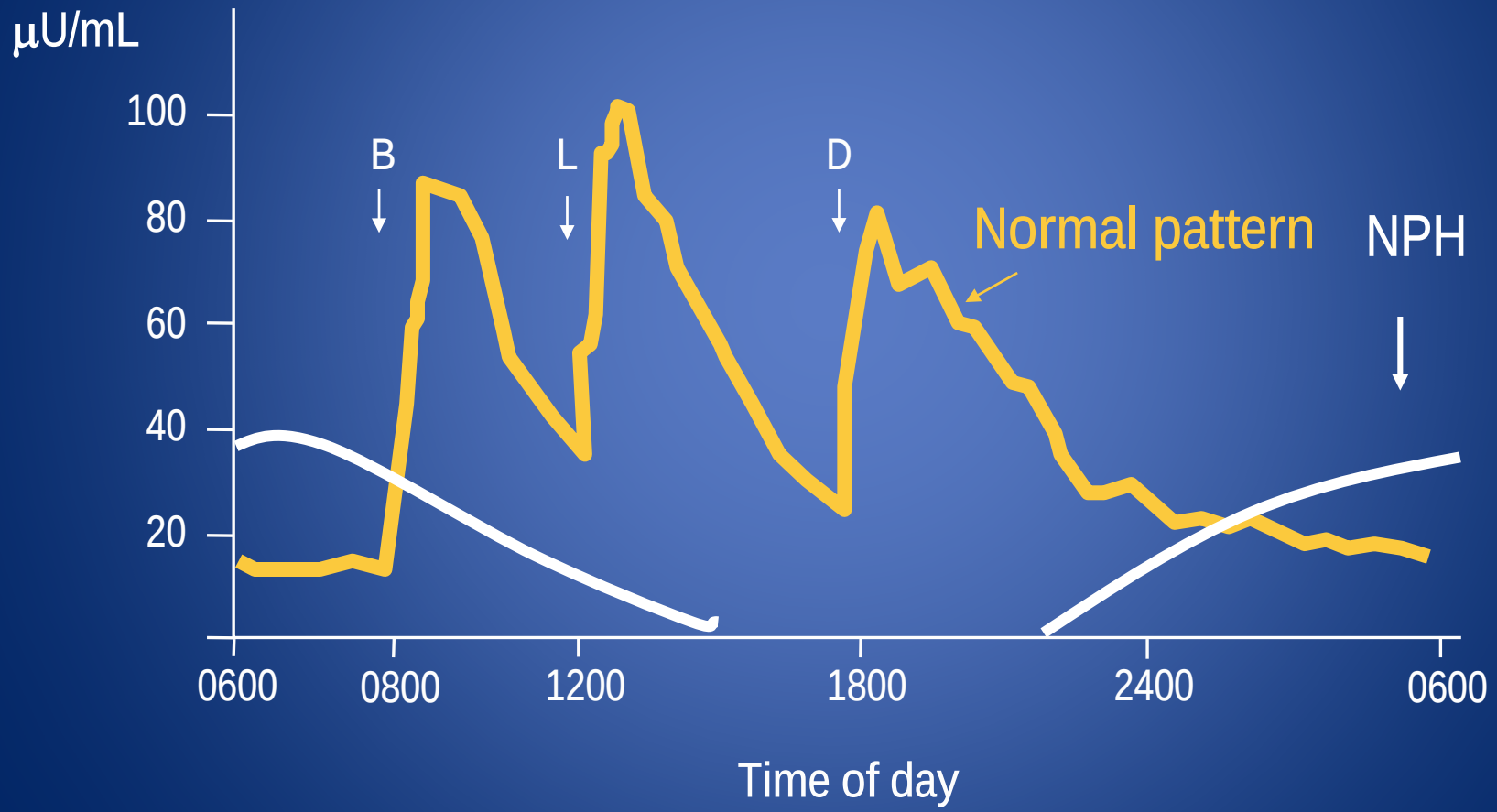
Mimicking Nature



Adapted with permission from Leahy J. In: Leahy J, Cefalu W, eds. *Insulin Therapy*. New York: Marcel Dekker; 2002:87; Nathan DM. *N Engl J Med.* 2002;347:1342

Evening Basal Insulin

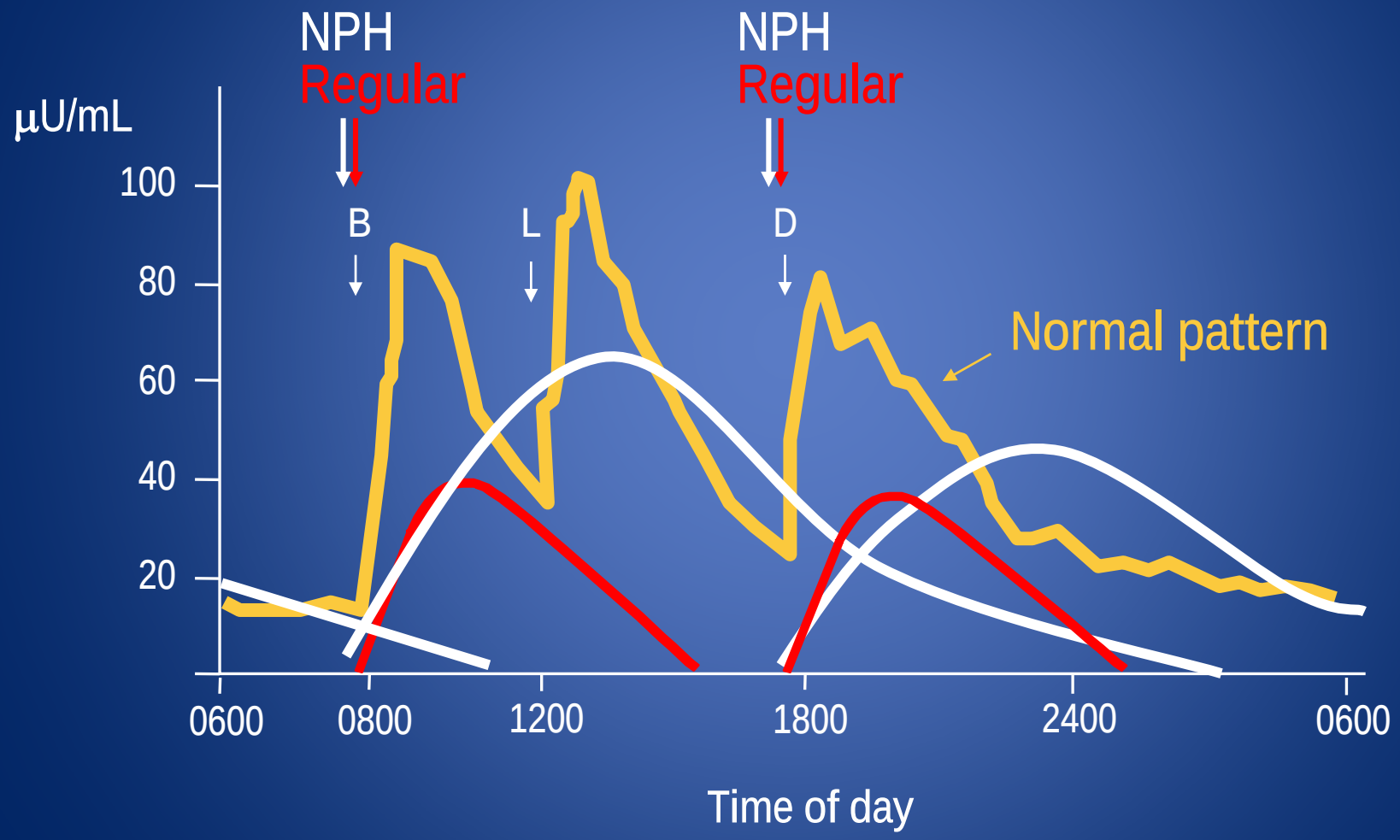
Bedtime NPH



B=breakfast; L=lunch; D=dinner

Split-Mixed Regimen

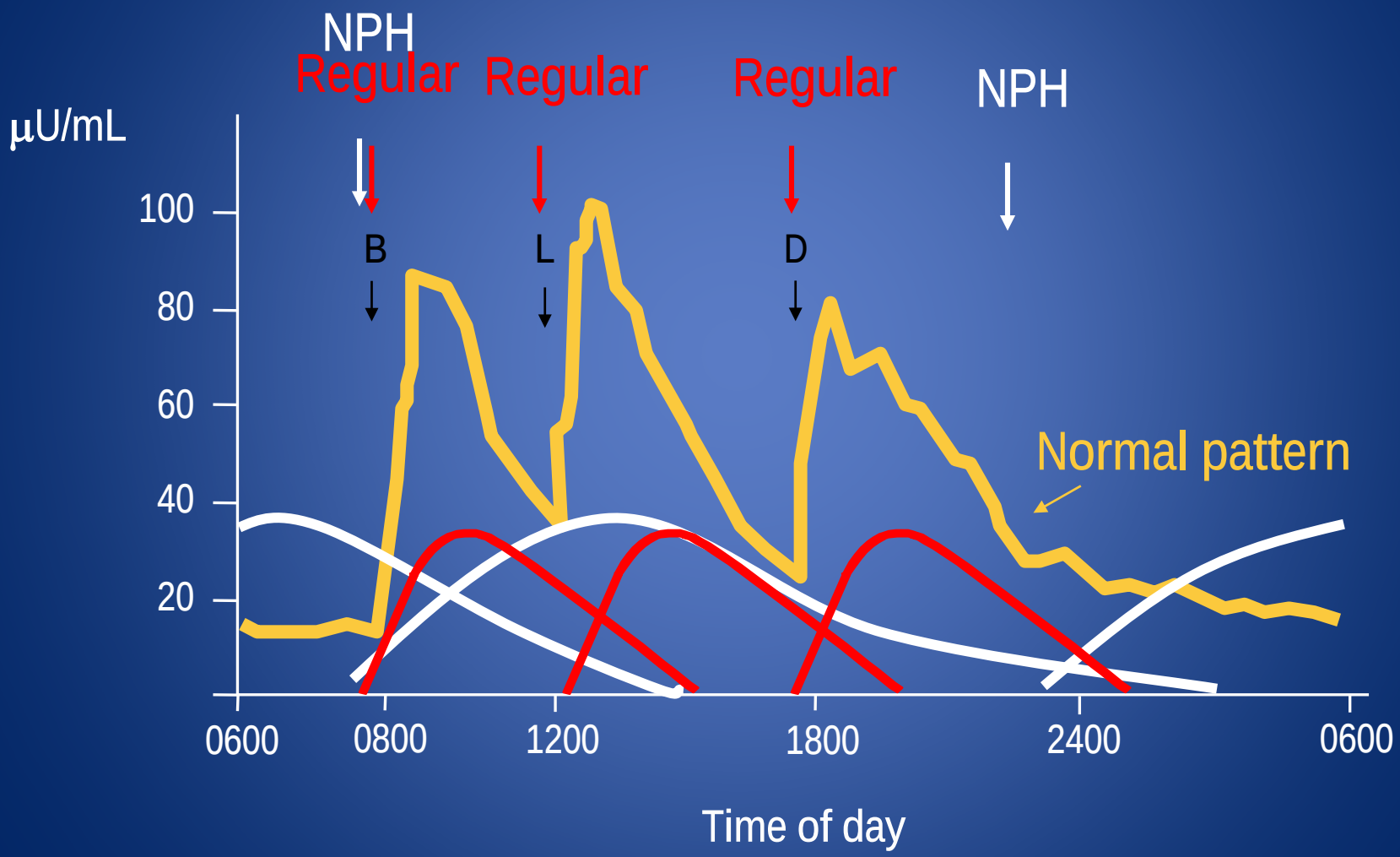
Human Insulins



B=breakfast; L=lunch; D=dinner

Multiple Daily Injections

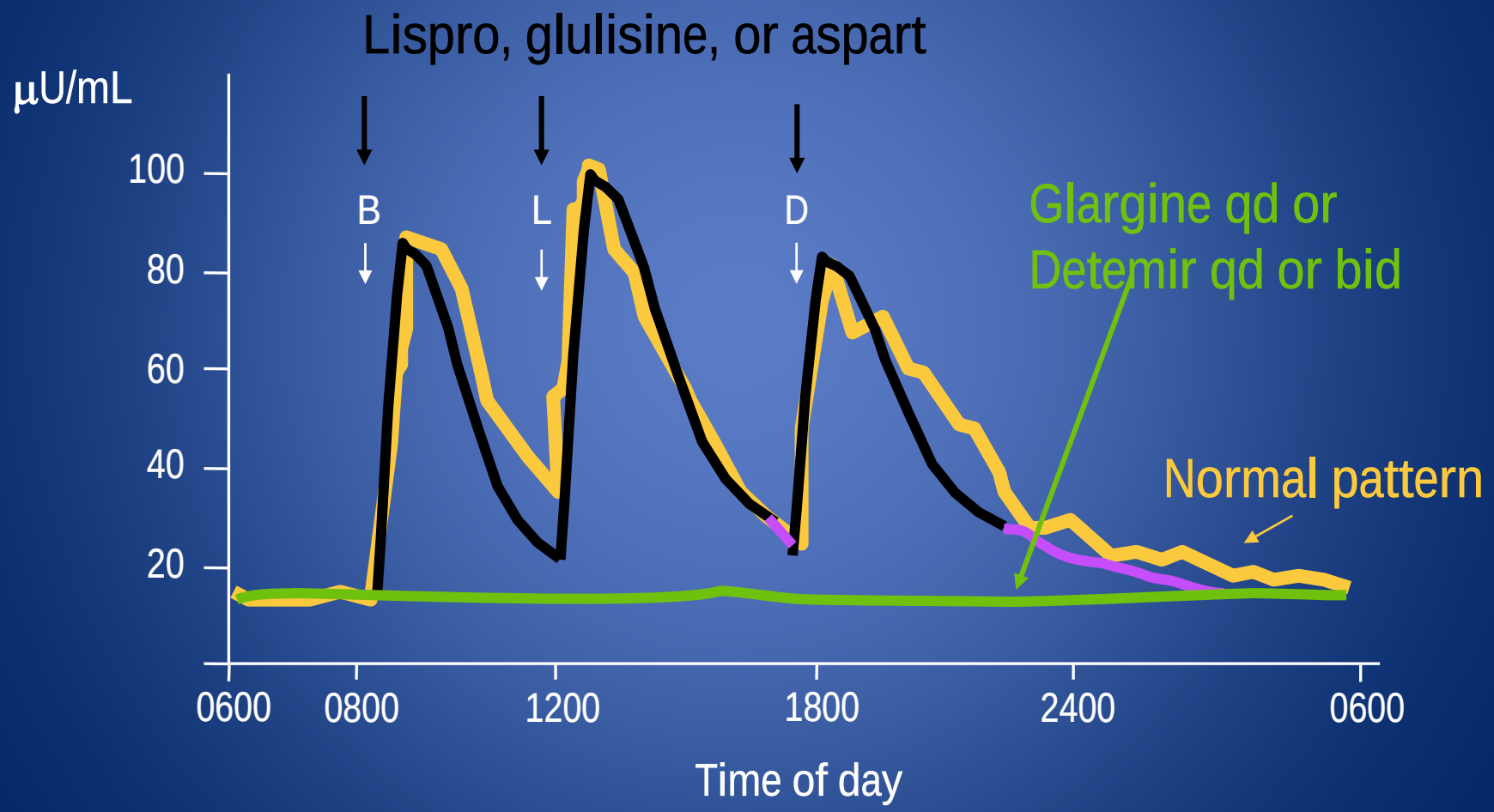
Human Insulins



B=breakfast; L=lunch; D=dinner

Basal-Bolus Insulin Treatment

With Insulin Analogues



B=breakfast; L=lunch; D=dinner

How To Initiate Insulin Therapy?

- Type 1 Patients
  - Utilize a Basal/Bolus Approach
    - Target Fasting & Postprandial Blood Sugars
- Type 2 Patients Failing Oral Therapy
  - 1st Target Fasting Blood Sugar
    - Forced Titration Schedule

Initiating Insulin Therapy

- Empiric Dosing (daily dose)
  - Insulin Analogues
    - Type 1: 0.5 units/kg/d
    - Type 2: 0.7-1.0 units/kg/d (obesity, activities)
- Give 50% as Basal Insulin
- Give 50% as Bolus Insulin
  - Split into three doses
  - Adjust accordingly:
    - Carbohydrate Counting

Initiating Basal Insulin Therapy

- Suppresses glucose production between meals and overnight
- Continue oral agent(s) at same dosage (may eventually reduce)
- Add single bedtime insulin dose (10–20 Units) [weight based at 0.2U/kg]
  - Glargine
  - Detemir
  - NPH
- Adjust dose according to Fasting Blood Sugars
- Adjust the insulin dose every 3-4 days as needed
  - Increase 2 U if FBG 100–120 mg/dL
  - Increase 4 U if FBG 121–140 mg/dL
  - Increase 6 U if FBG 141–180 mg/dL
  - Increase 8 U if FBG >180 mg/dL
- Treat to target (usually FPG 80–100 mg/dL)

Treat to Target

Table 1—*Forced weekly insulin titration schedule*

Start with 10 IU/day bedtime basal insulin and adjust weekly	
Mean of self-monitored FPG values from preceding 2 days	Increase of insulin dosage (IU/day)
≥180 mg/dl (10 mmol/l)	8
140–180 mg/dl (7.8–10.0 mmol/l)	6
120–140 mg/dl (6.7–7.8 mmol/l)	4
100–120 mg/dl (5.6–6.7 mmol/l)	2

Riddle MC et al. *Diabetes Care*. 2003;26:3080-3086
Rosenstock J et al. *Diabetologia.* 2008;51:408–416.

Prandial Insulin Dose Adjustments

- Prandial insulin limits hyperglycemia after meals
- Set dose with meals
  - Example dosing:
    - 2-5 units with each meal to start
- Carbohydrate counting
  - Typical start:
    - 1 unit for every 10-15g of carbohydrate
- Correction scales

Initiating Pre-Meal Dosing

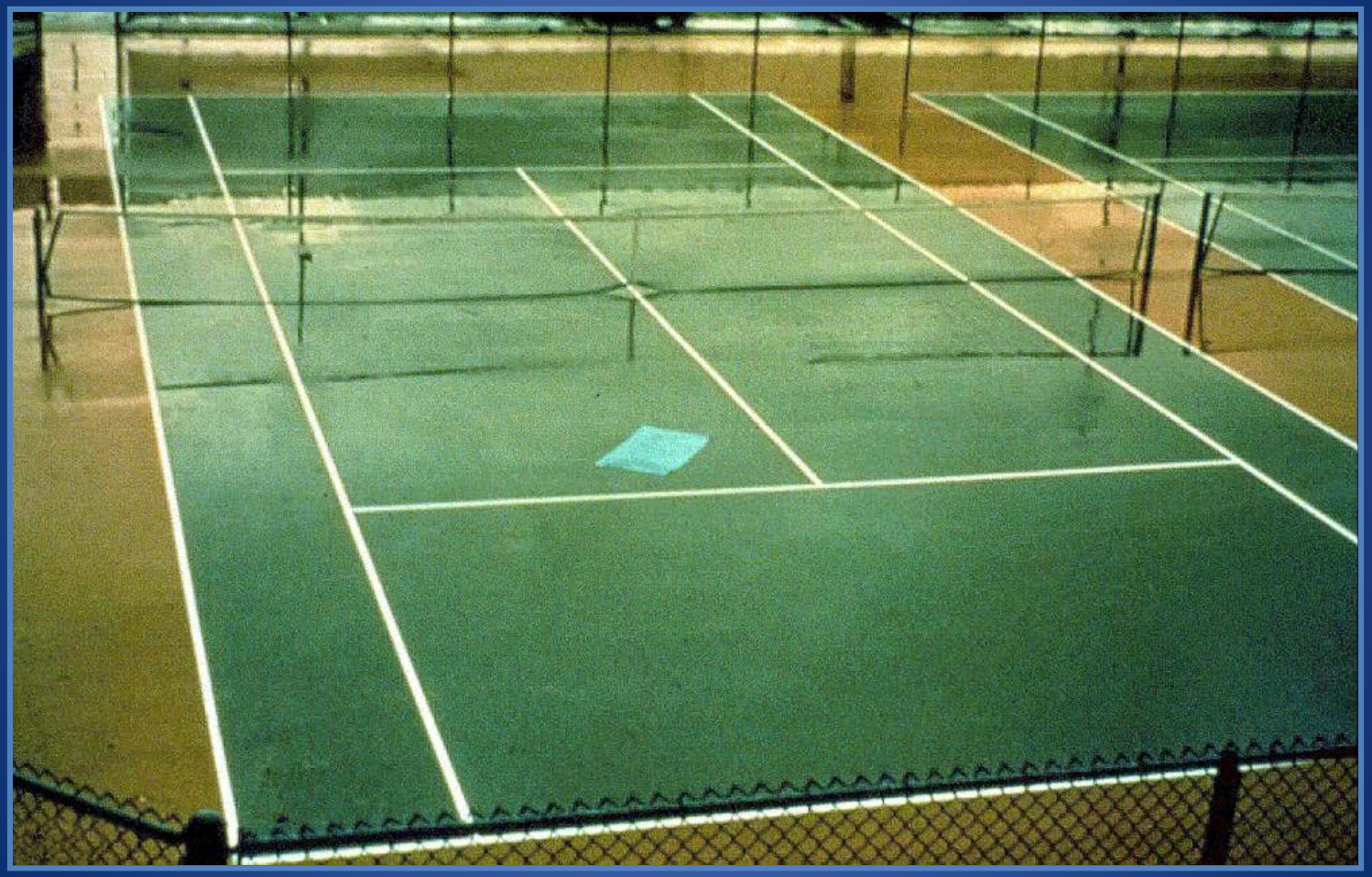
- Discontinue SFU or Meglitinide
- Initiate with the largest meal
- Once at goal, move to the next largest meal…

Diabetes Obes Metab. 2008; 10: 1178-1185.

Mixed Insulins

- Humulin 70/30
  - 70% NPH, 30% Regular
- Humulin 50/50
  - 50% NPH, 50% Regular
- Humalog Mix 75/25
  - 75% lispro protamine, 25% lispro
- Humalog Mix 50/50
  - 50% lispro protamine, 50% lispro
- Novolin 70/30
  - 70% NPH, 30% Regular
- Novolog Mix 70/30
  - 70% aspart protamine, 30% aspart

Respiratory Tract Surface Area



- **Total surface area of lungs = 140m^2**
- **Alveoli = regulation tennis court**
- **Bronchi= blue towel**

Insulin Human Inhalation Powder

- Inhaled, ultra-rapid-acting mealtime insulin
- Indicated for adults with T1DM or T2DM
- Administer at beginning of each meal
- 4 (blue), 8 (green), and 12 (yellow) unit packets
- Foil package; 2 blister cards, 15 cartridges each; strips of three; 2 inhalers.
- Dosing
  - Insulin-naive patients: 4 units before each meal
  - Prandial SC insulin users: convert 1:1 (round up to nearest 4 units)

Afrezza Prescribing Information. October 2014.

Table 4. Benefits and Limitations of Concentrated Insulins

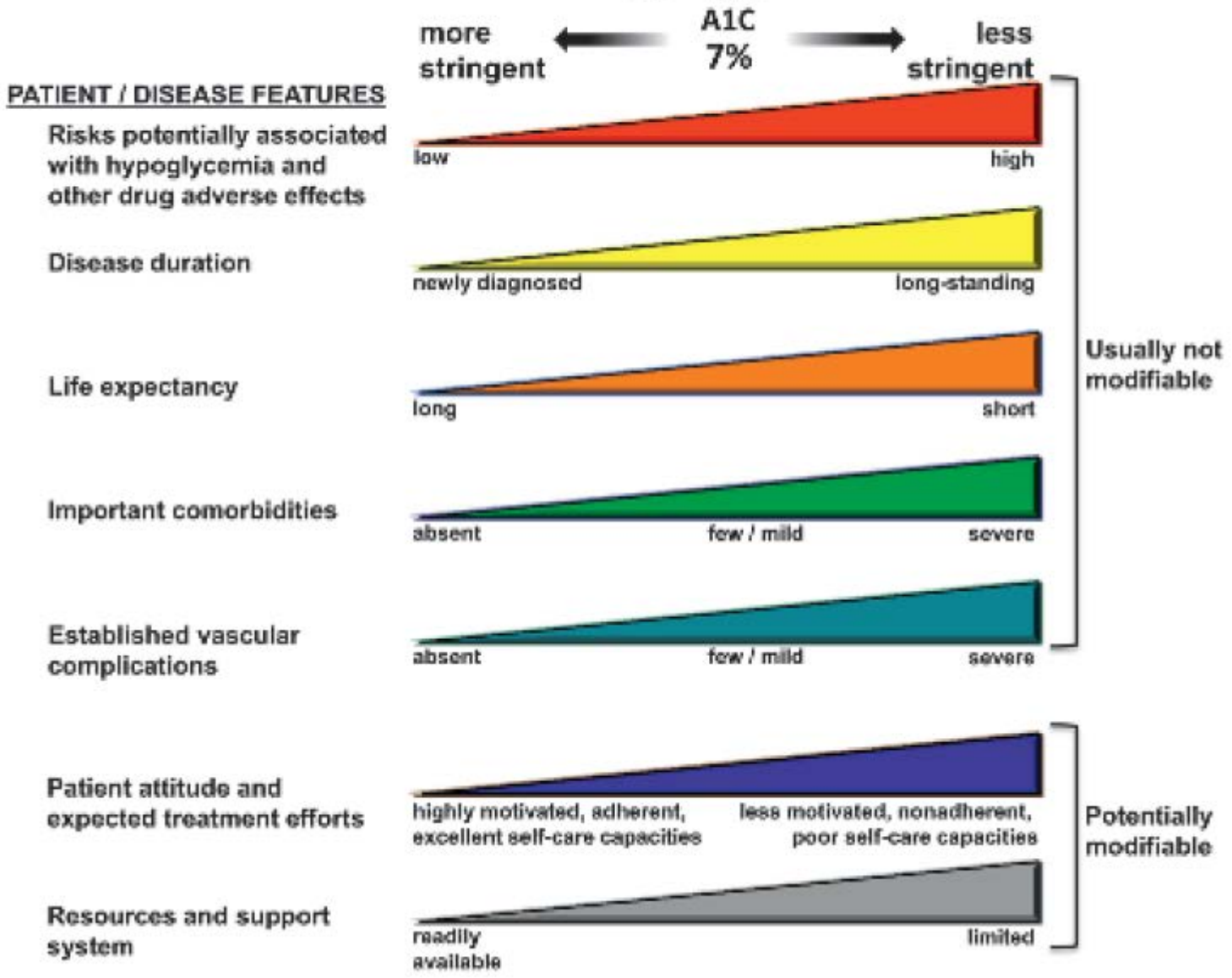
Insulin	*Onset Duration*	*Maximum Dose/ Injection (units)*	*Benefits*	*Limitations*
Regular U-500	30 min Up to 8 hr	100	■ Highly concentrated ■ Useful in pumps ■ Sustained glycemic control with minimal weight gain ■ Pen formulation resolves several medication safety issues	■ Long duration of action, potential stacking ■ Pumps are programmed for U-100 insulins ■ Bolus MUST be 30-60 minutes prior to meals ■ Onset too long to be useful as correction dose
Glargine U-300	1-6 hr 24-36 hr	80	■ Decreased hypoglycemia ■ Longer duration of action ■ Slightly more dosing flexibility (dosing window is q 24±3 hours	■ Decreased bioavailability (~10% increase in dose for conversion from U-100 to U-300) ■ Small pen size (1.5 ml) supplying 450 units total
Degludec U-200	1-9 hr > 42 hr	160	■ Longest duration of action ■ Large dose per injection ■ Bioequivalent to degludec U-100 (no dose titration between degludec formulations) ■ 3 ml pen size supplying 600 units total	■ Must down titrate dose (~10%) when converting from other basal insulins ■ 2 to 3 days to reach steady state ■ Formulary access/cost
Lispro U-200	10-30 min 3-5 hr	60	■ Useful when large prandial doses required (decreased volume of MDIs) ■ 3 ml pen size supplying 600 units total	■ Not yet FDA-approved for pump use

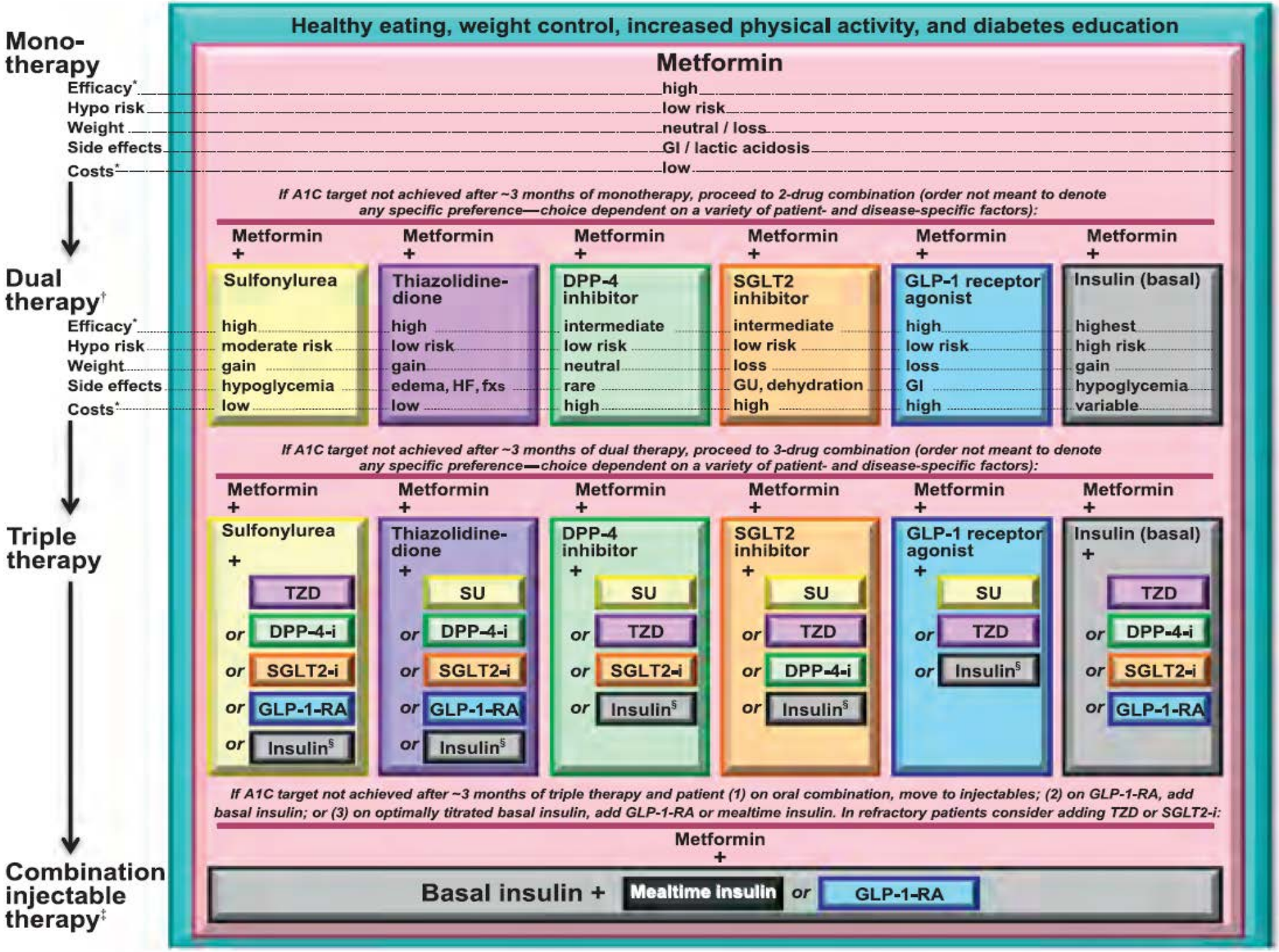
MDI=multiple daily injections.

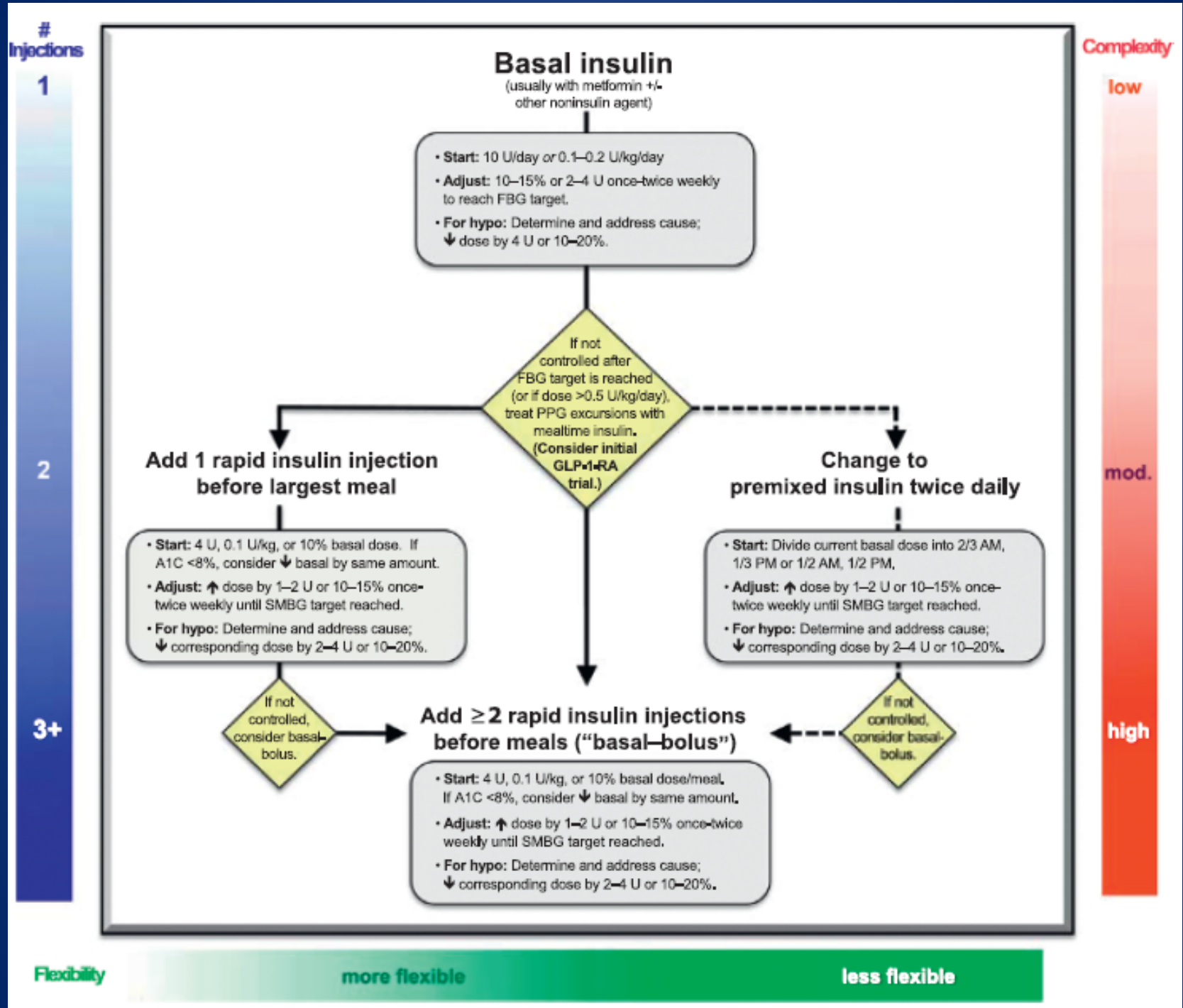
Treatment Guideline Algorithms

- American Diabetes Association
- American Association of Clinical Endocrinologists*

Approach to the management of hyperglycemia




Healthy eating, weight control, increased physical activity, and diabetes education
Metformin
Mono-therapy
Efficacy*
Hypo risk
Weight
Side effects
Costs*
high
low risk
neutral / loss
GI / lactic acidosis
low
If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Metformin + Sulfonylurea
high
moderate risk
gain
hypoglycemia
low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA


Injections
1
2
3+
Complexity
low
mod.
high
Basal insulin
(usually with metformin +/- other noninsulin agent)
• Start: 10 U/day or 0.1–0.2 U/kg/day
• Adjust: 10–15% or 2–4 U once-twice weekly to reach FBG target.
• For hypo: Determine and address cause; ↓ dose by 4 U or 10–20%.
If not controlled after FBG target is reached (or if dose >0.5 U/kg/day), treat PPG excursions with mealtime insulin. (Consider initial GLP-1-RA trial.)
Add 1 rapid insulin injection before largest meal
• Start: 4 U, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount.
• Adjust: ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
• For hypo: Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.
If not controlled, consider basal-bolus.
Change to premixed insulin twice daily
• Start: Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
• Adjust: ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
• For hypo: Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.
If not controlled, consider basal-bolus.
Add ≥2 rapid insulin injections before meals ("basal–bolus")
• Start: 4 U, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount.
• Adjust: ↑ dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
• For hypo: Determine and address cause; ↓ corresponding dose by 2–4 U or 10–20%.
Flexibility
more flexible
less flexible

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

A1C < 8%

TDD 0.1–0.2 U/kg

A1C > 8%

TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** > 180 mg/dL: add 20% of TDD
  - **FBG** 140–180 mg/dL: add 10% of TDD
  - **FBG** 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - **BG** < 70 mg/dL: 10% – 20%
  - **BG** < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

***Glycemic Goal:**

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)

Add GLP-1 RA

Or SGLT-2i
Or DPP-4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals

- Start: 10% of basal dose or 5 units

Basal Bolus

- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg

- Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

Which of the following drugs used in treatment of Type 2 DM is consistently associated with weight loss?

1. Sulfonylureas
2. Thiazolidinediones
3. Glucagon-like peptide 1 analogs
4. Insulin

Which of the following treatments for Type 2 DM is associated with the most profound reduction in HbA1c?

1. Metformin
2. Insulin
3. Sulfonylureas
4. Thiazolidinediones

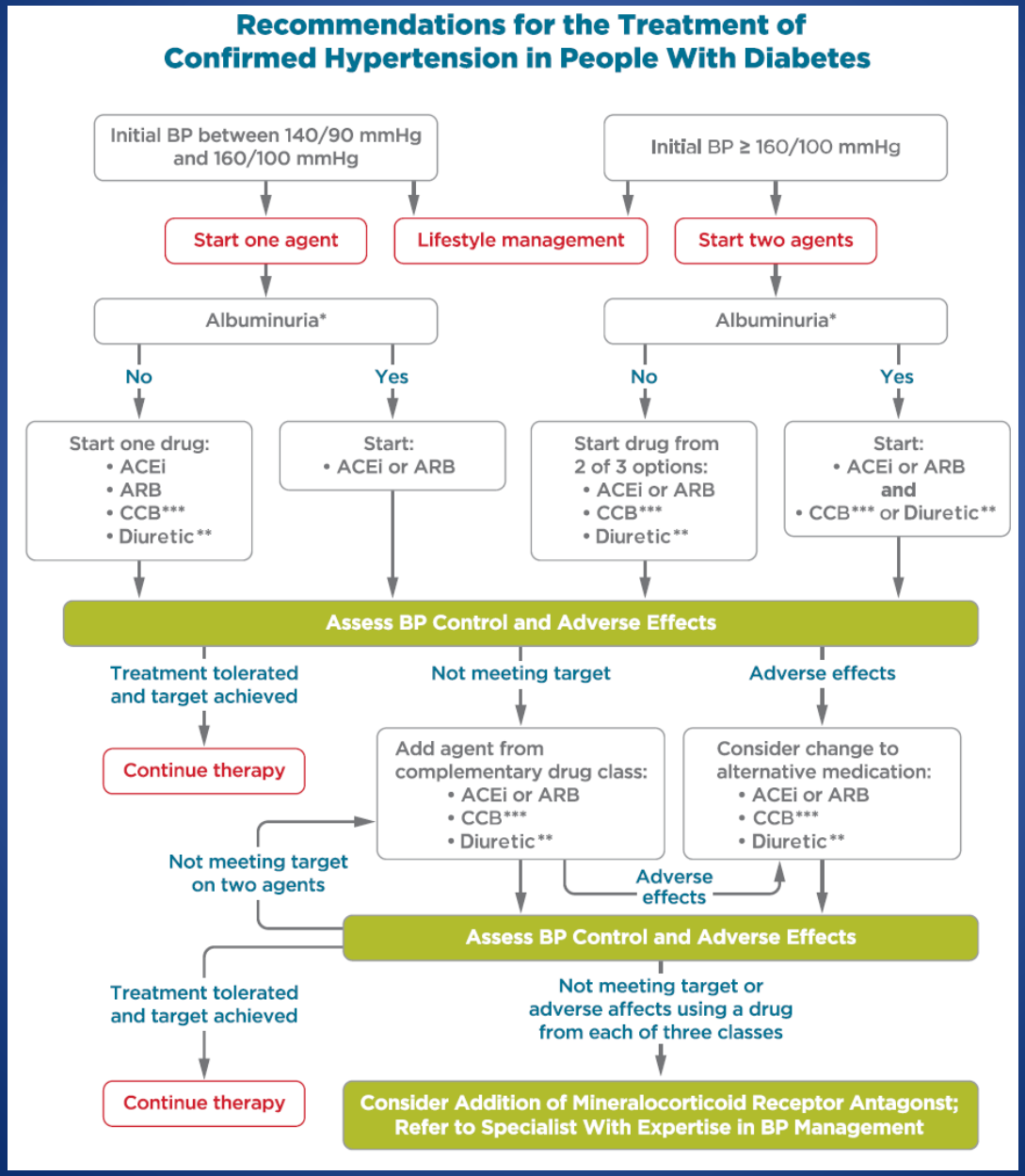
Which of the following agents is contraindicated with Class 3 or 4 Heart Failure?

1. Thiazolidinediones
2. Insulin
3. Sulfonylureas
4. Bromocriptine

Which of the following classes of diabetes medications works primarily at the level of the kidney?

1. DPP-IV inhibitors
2. Sulfonylureas
3. Insulin
4. SGLT-2 inhibitors

ADA Recommendations-HTN



ADA Recommendations-Statins

Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

*In addition to lifestyle therapy. ^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. †Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

High- and Moderate-Intensity Statin Therapy

Table 9.3—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30% to 50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2–4 mg

*Once-daily dosing. XL, extended release.

Cardiovascular Disease and Risk Management:
Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S86-S104

COMPLICATIONS-CENTRIC MODEL FOR CARE OF THE OVERWEIGHT/OBESE PATIENT

STEP 1 EVALUATION FOR COMPLICATIONS AND STAGING

CARDIOMETABOLIC DISEASE | BIOMECHANICAL COMPLICATIONS

NO COMPLICATIONS	COMPLICATIONS	
BMI ≥25	BMI 25–26.9	BMI ≥ 27: Stage Severity of Complications
	MILD TO MODERATE	SEVERE

STEP 2 SELECT: Therapeutic targets for improvement in complications + Treatment modality + Treatment intensity based on staging

Lifestyle Therapy:	Physician/RD counseling, web/remote program, structured multidisciplinary program
Medical Therapy (BMI ≥ 27):	Phentermine, orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg
Surgical Therapy (BMI ≥ 35):	Gastric banding, sleeve, or bypass

STEP 3 If therapeutic targets for complications not met, intensify lifestyle, medical, and/or surgical treatment modalities for greater weight loss.

Which of the following agents is preferred as an antihypertensive in patients with diabetes?

1. Beta blockers
2. ACE Inhibitors
3. Loop Diuretics
4. Hydralazine

QUESTIONS