THE ENDOCRINE PANCREAS & DIABETES MELLITUS: "Starvation in the midst of Plenty"

98% of the pancreas is exocrine; an **exocrine** gland secretes its product into a gland that then dumps its contents into another organ. The exocrine pancreas is the part that makes bicarbonate and digestive enzymes that squirt into a duct and into the duodenum.

2% is made of the "**Islets of Langerhans**" which are the endocrine part of the pancreas and essential for regulation of blood glucose levels. Remember an **endocrine** gland is one that secretes its **hormone**s into the bloodstream. That hormone then acts at **receptor**s in target organs.

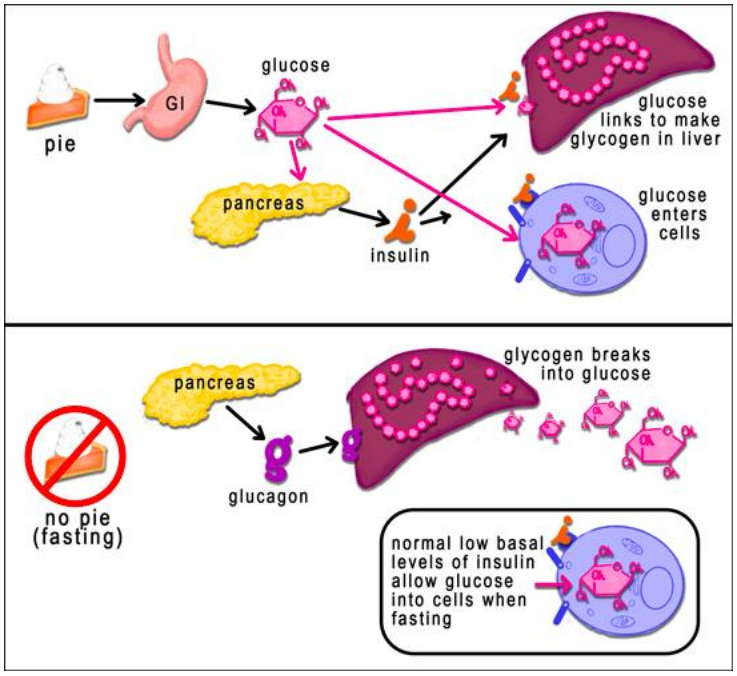
The islets of Langerhans produce:
1**. insulin**: hormone of energy storage
2. **glucagon**: hormone of energy release
3**.** somatostatin: inhibitory to the two above, released in nutrient overload. Also made in hypothalamus.
4. Pancreatic polypeptide & amylin
(these also regulate appetite and digestion)

Increases Blood Glucose:	Decreases Blood Glucose:
Glucagon Epinephrine Thyroxine (T3/T4) Cortisol Growth hormone (GH)	Insulin

Across a 24-hour period, even if you have a feast of candy bars and Pepsi, or eat nothing at all, your blood glucose level normally remains relatively *constant* between 80-100 mg/dl. This takes a tremendous amount of coordination between the many systems regulating blood sugar levels in your body. The main hormones that have some effect on your blood sugar include:

Only one hormone (insulin) reduces blood sugar because your brain and body must have glucose or you'll pass out (and be eaten by a lion). But *lots* of hormones work to increase blood sugar so you avoid being lion breakfast.

The way insulin and glucagons are regulated is fairly complex, but it is easiest to talk about them and their relationship with blood glucose levels.



When your blood sugar is LOW, **glucagon** promotes 1) the breakdown of fats, 2) the conversion of proteins into glucose (via gluconeogenesis) and 3) the breakdown of glycogen stored in the liver into glucose (glycogenolysis) to bring your blood sugar level back up.

When your blood sugar is HIGH, **insulin** is released and brings the level down by facilitating 1) sugar uptake by cells, 2) **storage** of sugar into glycogen **(glycogenesis),** and 3) **storage** of fat and protein. Thus, **insulin makes you gain weight.**

Now for the most important part: **Most tissues in the body cannot use glucose without the help of insulin.** Special insulin receptors in skeletal muscle, fat and the heart allow glucose entry into cells.

So, realize that you always have *some* low level of insulin secretion. Even when you are not eating, and glucagon is helping your body make sugar, you still need *some* insulin so that the glucose being made can get into your heart and muscle cells.

In fact, the ***ratio*** of Insulin to Glucagon is most important, not the individual amounts of each.

Diabetes Mellitus (DM). As of 2020, 36 million patients in the US have type 2 diabetes, and ~88million have "pre-diabetes" aka metabolic syndrome aka "it's really diabetes but it's still easily reversible". The words *diabetes mellitus* actually mean *"pees a lot sweetly"*. This is a symptom of the disease, caused by the loss of glucose into the urine and therefore "sweet-tasting" urine (oh you *know* someone just couldn't resist having a taste…)

There are four main types of DM:

1) Type 1 Diabetes (5-10%): Destruction or loss of the cells that make insulin. Usually starts before age 30. **Must treat with insulin.**

2) Type 2 Diabetes (90-95%): Usually related to obesity, the cells of the body have lost their responsiveness to insulin (fewer receptors), and there is a *relative* deficiency in insulin.

3) Gestational Diabetes (2-5% pregnant women): Any abnormality in glucose levels first diagnosed in 2nd or 3rd trimester. Usually goes away after pregnancy but increased risk of Type 2 DM later in life. Treatment is controversial: start with diet and weight control, then insulin, then oral drugs as a last resort (because they cross the placenta).

4) Other causes like:

Disease related: example: pancreatitis, cystic fibrosis

Drug-Induced: Increased glucose levels related to drugs such as prednisone, atypical antipsychotics, thiazides, some AIDS drugs.

Type 1 vs Type 2 Diabetes

Variable	Type 1 IDDM	Type 2 NIDDM
Also sometimes erroneously called	Juvenile Diabetes IDDM (Insulin Dependent DM)	Adult-Onset Diabetes NIDDM (Non-Insulin Dependent DM)
Age at Onset	usually <30 years	***usually* >30** (although more children now with obesity)
Insulin Production	**None**	Present, but drops over time.
Onset	Rapid	Slow, insidious
Symptoms	polydipsia/polyuria weight loss, blurred vision	often no symptoms otherwise similar symptoms
Weight	usually thin *(body can't use glucose, right?)*	usually obese *(constant eating means constant insulin production and down-regulation of receptors, right?)*
Ketoacidosis	common	rarely
Genetics	No overwhelming predisposition	**Strong predisposition**
Cause	Autoimmune process triggered by virus or other factor	**Obesity**
Meal planning and exercise	Imperative	Imperative
Medication	**Insulin. Always.**	Possibly none (diet, exercise, and weight loss). Next, oral or injectable meds other than insulin. Late in the disease process insulin may also be necessary

DIAGNOSIS OF DIABETES	Table from ADA 2020 Recommendations (https://doi.org/10.2337/cd20-as01)		
	Diabetes	"Prediabetes"	"Normal" Value
HbA1c	≥6.5%	5.7-6.4%	<5.7%
Fasting plasma glucose	≥126 mg/dL	100-125mg/dL	<100mg/dL
Oral glucose tolerance test	≥200 mg/dL	140-199 mg/dL	<140 mg/dL
Random plasma glucose	≥200 mg/dL	?	<200 mg/dL

Type 2 diabetes usually lasts for years before diagnosis, hidden by hyperinsulinemia.
This "prediabetes" is most easily reversible with exercise and weight loss.
It should make sense, therefore, that **long-term complications can sometimes soon follow diagnosis,** since the patient actually had diabetes a long time.

HbA1c: Glycosylated hemoglobin:with time, sugars get stuck to hemoglobin and the amount of sugar tells you how high the sugars have been over the preceding month or two
Every 1% drop in HbA1c in a patient = 35% drop in risk of blindness/kidney failure/amputation

A **calculator** for converting **HbA1c into estimated average daily glucose** is available on the ADA website at: **https://professional.diabetes.org/diapro/glucose_calc**

HOW YOU DIE FROM DIABETES MELLITUS:
The fast way: Diabetic ketoacidosis (DKA).

1. **No insulin means the cells can't get glucose.**
2. This triggers other hormones to increase Blood Glucose even more
3. **Glucose acts as osmotic diuretic** ("polyuria") and glucose is lost.
4. Patient drinks more water ("polydipsia") and urinates even more.
5. **Glucose-starved cells** in the body break down fat and protein to make glucose ; **form ketones which lower pH of blood: acidosis**
6. Ketones also act as osmotic diuretic
7. Patient gets even more dehydrated
8. Blood pH gets more acidic and electrolytes get more screwed up
9. Patient passes out (and dies if not treated in ICU)
10. **ICU admission with constant monitoring of pH and K^+**

Critical thinking question: Why K^+ and an expensive admission to the Intensive Care Unit (ICU)?
Answer: because insulin's other action is to move potassium (K^+) into cells. You can't just give a giant dose of insulin to fix the problem; it would cause all the K^+ to go into cells and out of the bloodstream, causing instant hypokalemia and heart dysrhythmia!

The **slow way:** chronic complications mostly due to **changes in small capillaries** in the eyes (**blindness**), kidneys (**kidney failure** and go on dialysis), peripheral nerves like in the toes and feet (leading to **amputations**), heart (leading to **MI**), skin (leading to **non-healing skin ulcers**), etc. The **decreased ability to heal** (due to poor vascularity) increases susceptibility to **infections**.

For **Type 1 Diabetics: you HAVE to give them insulin.** Also, **patients must stick to a constant schedule of eating and administration of insulin** in order to avoid ketosis or hypoglycemia.

For **Type 2 Diabetics**: diet, exercise, and try to keep glucose on a chosen target
1. Increase the secretion of insulin from residual islets (sulfonylureas and similar secretagogues)
2. Inhibit the absorption of glucose (alpha-glucosidase inhibitor)
3. Inhibit extra glucose production in the liver (biguanides)
4. Insulin-sensitizers (thiazolidinediones)
5. Inhibit the production of glucagon (DPP-IV and GLP-1)
6. And in advanced cases, give extra insulin to activate remaining insulin receptors

What target glucose/HbA1c to choose depends on the patient circumstances:

INSULIN

Insulin promotes glucose transport into tissues, potassium (K^+) uptake into muscles, incorporation of amino acids into proteins and suppresses the release of fatty acids from fat. Insulin is a protein, so it has to be injected either IV, IM, SQ or inhaled.
Why not PO?
The most common form of administration is subcutaneous (SQ). The different formulations vary the most by their duration of action.

Usually patients take some combination of a long-acting insulin and a short-acting form. The short-acting form takes care of the peaks in blood glucose after meals, and the long-acting form takes care of the baseline levels. This mimics what happens in your body naturally.

Patient survival and morbidity after hospitalization (and just generally in life) **appears to be directly related to tight glucose control**, so careful blood glucose monitoring and insulin dosing is becoming more and more important.

But tight control comes with risks, most importantly: **hypoglycemia**. That is why there is no universal "target" glucose or HbA1c. See table at right.

Glycated Hemoglobin Range

Most Intensive Level, Approximately 6.0%	Factors	Least Intensive Level, Approximately 8.0%
Highly motivated, adherent, knowledgeable, strong self-care capability	Psychosocial considerations	Less motivated, nonadherent, less knowledge, weak self-care capability
Adequate	Resources or support systems	Inadequate
Low	Risk of hypoglycemia	High
Short	Duration of type 2 diabetes	Long
Long	Life expectancy	Short
None	Microvascular disease	Advanced
None	Cardiovascular disease	Established
None	Coexisting conditions	Multiple, severe, or both

Figure 2. Suggested Goals for Glycemic Treatment in Patients with Type 2 Diabetes.

SIDE EFFECTS OF INSULIN:
1. **Hypoglycemia**: a blood glucose level that is dangerously low (<50-60mg/dl), from overdose of insulin or too little food intake. Symptoms: nausea, headache, hunger, sweats, tremor. Some diabetics have a blunted response to hypoglycemia and may just faint without warning. Beta-blockers, especially **propranolol**, will block the tremors especially and can be dangerous in this regard.

(Note, hypoglycemia can occur also with the oral drugs that stimulate insulin secretion, conveniently called secretagogues.)

Hypoglycemia can cause MI in susceptible patients, and a loss of consciousness can be complicated with injury or death.

Patients must be educated about what insulin does and how it is related to what the patient eats. When hypoglycemic they can take glucose tablets or sugar-containing foods or drinks to increase their blood sugar quickly. In emergency room they can have injection of **IV** or **IM glucagon** or **IV dextrose**. ("dextrose" is the same as D-glucose aka glucose).

Note: Type 2 patients on **α-glucosidase inhibitors** like acarbose can't easily break down carbohydrates like sucrose (table sugar), so if they are also on another drug that causes them to get hypoglycemic, they are best off eating/drinking something with free glucose like glucose tablets or anything with high-fructose corn syrup, which is ~50% free glucose *(there's always a silver lining!).*

2. **Lipodystrophy**: A loss of subcutaneous fat at the site where they inject their insulin (usually stomach, leg or arm. Teach patients to rotate the site where they inject.

3. **Hypokalemia**: Insulin also drives potassium into cells and out of the bloodstream. Usually this is a manageable problem, but in a very sick patient, insulin can drive their potassium over the edge and into dangerous levels.

4. **Weight gain:** Insulin drives sugar storage into glycogen and inhibits breakdown of fats and proteins into sugars, so it shouldn't be surprising that taking insulin makes it harder to lose weight.

What about **allergy**? All insulins in the US are available in recombinant human form so insulin allergy is uncommon these days (it used to come from pigs). The different preparations vary by only a few amino acids, and so allergy is usually due to some other molecule in the solution, like a preservative.

SOME COMMON INSULIN FORMULATIONS

The onset, peak and duration of action differs among insulin formulations. This is achieved by either putting the insulin into packed crystals that slowly dissolve over time (these crystals are seen most notably in **NPH insulin**), or by slight amino acid changes that cause polymerization of the insulin, causing a similar depot effect.

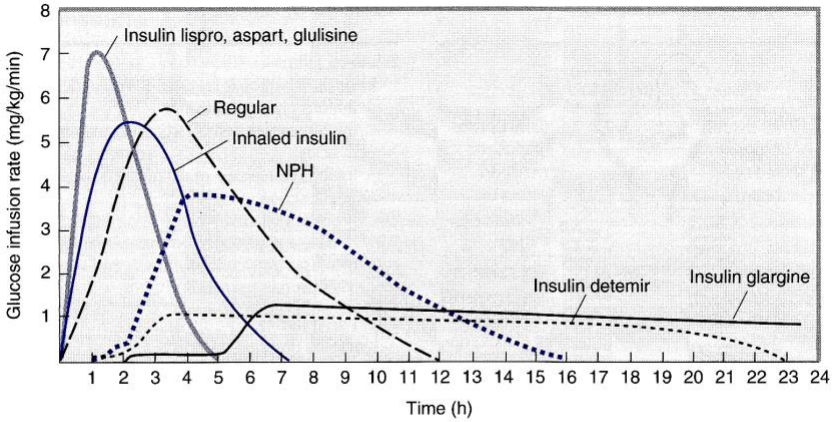
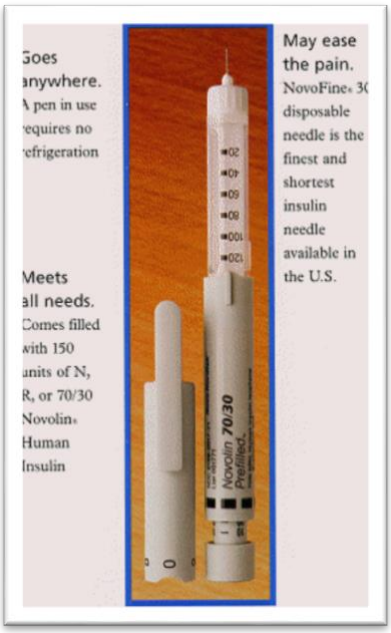


Figure 41–5. Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg; with the exception of insulin lispro, aspart, and glulisine, duration increases considerably when dosage is increased.

Speed of Action	Insulin Form	Peak effect	Looks	Notes
Rapid Acting (Short Duration)	Afrezza® insulin	1h	N/A	Inhaled (DPI) powder can aggravate COPD or asthma
	aspart lispro glulisine	1-3h	clear	SQ IV
Moderate	**regular**	1-5h	clear	IM IV SQ Mixes with other forms
Intermediate	**NPH**	6-14h	**cloudy**	SQ full of insoluble crystals so you **must not inject IV!**
Long-Acting gives relatively constant level lasting 24 hours	glargine (Lantus) detemir degludec	none	clear	SQ Cannot mix with other forms of insulin!

Dosing: Most insulins come as 100 units/cc: "U-100" with special syringes to make it easy for patients to determine how many units they are drawing up.

Cloudy NPH preparations are *gently* rolled before dispensing. *Why?*



70/30 Mixes (**70% NPH/30% regular**) makes dosing easier for patients, especially those with diabetic eye disease.

Insulin pens (shown at right) are prefilled, are easy to dose, and don't require refrigeration. (Nice not to have to store your insulin in the fridge with your co-workers' lunches, or be drawing up syringes in front of everyone. Good for privacy!)

Actual dose depends on patient, target glucoses, when and how much they eat. Starting doses are usually 0.5-1.0 unit/kg/day, and doses can be spread out over the day.

Most commonly administer subcutaneously via syringe, insulin pens or pumps. **Never inject over infection.**

Speed of absorption:
abdomen>arm>thigh>buttock

Patients monitor their own blood glucose levels several times a day. Insulin pumps monitor continuously.

Timing of doses:

To most closely mimic the normal functioning of insulin, use a long-acting insulin to mimic basal insulin secretion, and a short-acting agent to cover meals.

Insulin pumps generally pump a slow basal amount and then regular insulin in response to changes in blood glucose. There's an app for that. Seriously.

Injections are given **before** meals (Breakfast, Lunch, Supper, Bedtime Snack), the insulin type used depending on its peak of action.

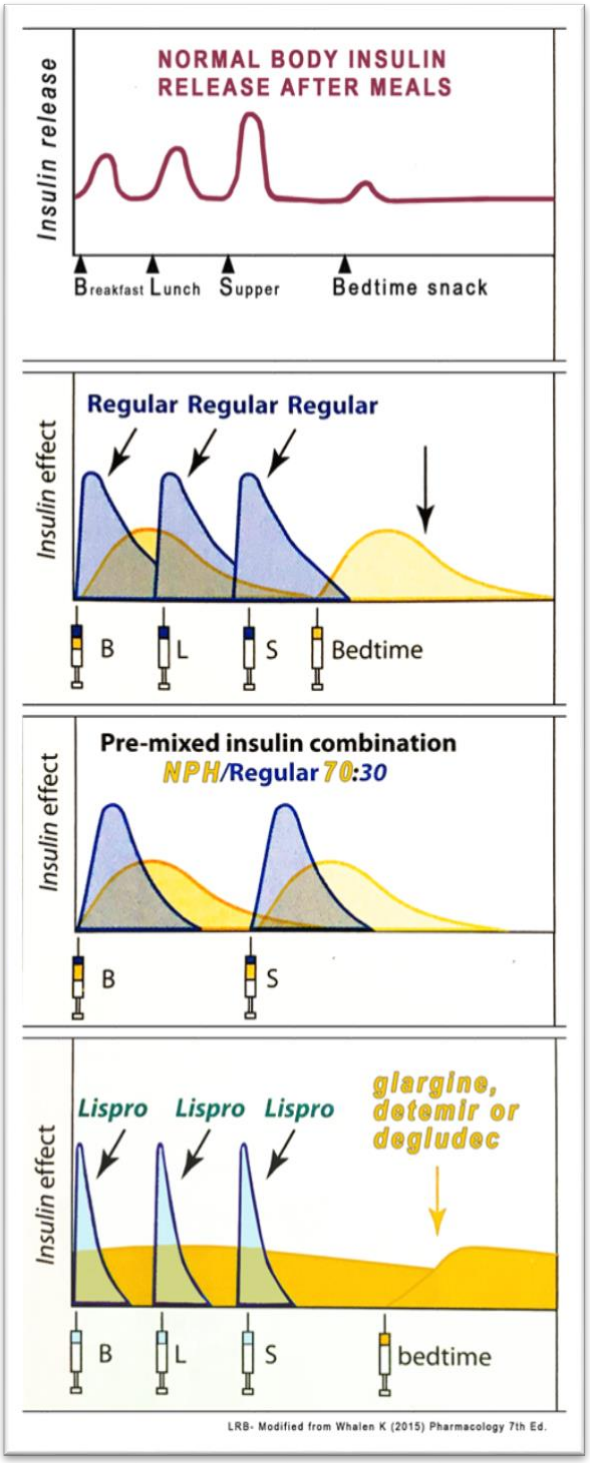
Very short acting insulins might be used in unexpected situations (i.e. birthday cake at the office)

Which dosing regimen to use completely depends on the patient's eating habits.

Two situations that can result in deceptively high glucose readings upon awakening:

1. **Somogyi Effect** (due to hypoglycemia in the middle of the night causing extra glucose release from the liver)

2. **Dawn Effect** (due to normal pre-dawn cortisol release): Can give deceptively high glucose readings first thing in the morning.



TYPE 2 DIABETES DRUGS

Note: **Oral drugs** work best for patients with **early Type 2 DM**; i.e., within 5 years of diagnosis

PO DRUGS

1. SECRETAGOGUES Secretagogues increase insulin production by the patient's pancreas.

They do not work for type 1 diabetics because those patients have no insulin to increase.

They make patients secrete insulin. Therefore they can cause **hypoglycemia. These are the only Type 2 drugs that commonly cause hypoglycemia.**

Have I mentioned? **The chances for a dangerous hypoglycemic episode are increased by beta-blockers** (and MAOIs, some antimicrobials, salicylates, and other type 2 diabetes drugs).

Secretagogues		
	2nd Generation Sulfonylurea **Secretagogues**	Nonsulfonylurea Secretagogues aka **meglitinides**
Example drugs	**glyburide** glipazide glimepiride	repa**glinide** (*Prandin*) nate**glinide** (*Starlix*)
PO Dosing Frequency	1-2/day	2-4/day
How they work	Binds K^+-channels on beta-cells to stimulate insulin release	Stimulates very early insulin release
Onset & Duration	Varies 1-4 h Lasts 12-24 h	Faster onset; use 10-20 min before meals
Other notes	Don't use Glyburide in kidney failure patients	
Side Effects	**Hypoglycemia**, weight gain	

2-4. OTHER COMMON ORAL DRUG CLASSES for TYPE 2 DIABETES

CLASS PO	**1. BIGUANIDES**	**2. ALPHA-GLUCOSIDASE INHIBITORS**	**3.THIAZOLINEDIONES (TZDs)**
Example	**Metformin** *(Glucophage)* **FIRST-LINE TREATMENT** (2020 guidelines)	**acarbose** *(Precose)* miglitol *(Glyset)*	piog**litazone** *(Actos)* rosig**litazone** *(Avandia)*
How they work	Inhibits glucose production by the liver and stimulates glucose uptake by tissues; increases insulin sensitivity	Inhibit glucosidase so slows carb. digestion, decreases blood glucose levels after eating; allows pancreas to "catch up"	Reduce glucose in liver, Increase insulin receptor sensitivity in fat and liver.
Side Effects	GI complaints: diarrhea, nausea, vomiting, B12 deficiency Rarely: lactic acidosis, especially in response to radiology contrast injections	Diarrhea, flatulence (drug is **metabolized by gut bacteria)** Acarbose can cause liver problems	Can precipitate CHF due to fluid retention in kidney Can affect liver function. Can interfere with birth control hormonal meds! Chance of bladder cancer
Notes	Avoid in kidney patients Drug not metabolized Often found in combo with other type 2 DM drugs	Good to use with other drugs, not great by itself	Takes a few months to reach maximal effect

NEWER drugs used for Type 2 Diabetes

1. drugs that mimic **amylin** and **incretins**.

These hormones reduce appetite, reduce glucagon secretion and delay gastric emptying and **cause you to "feel full"**.

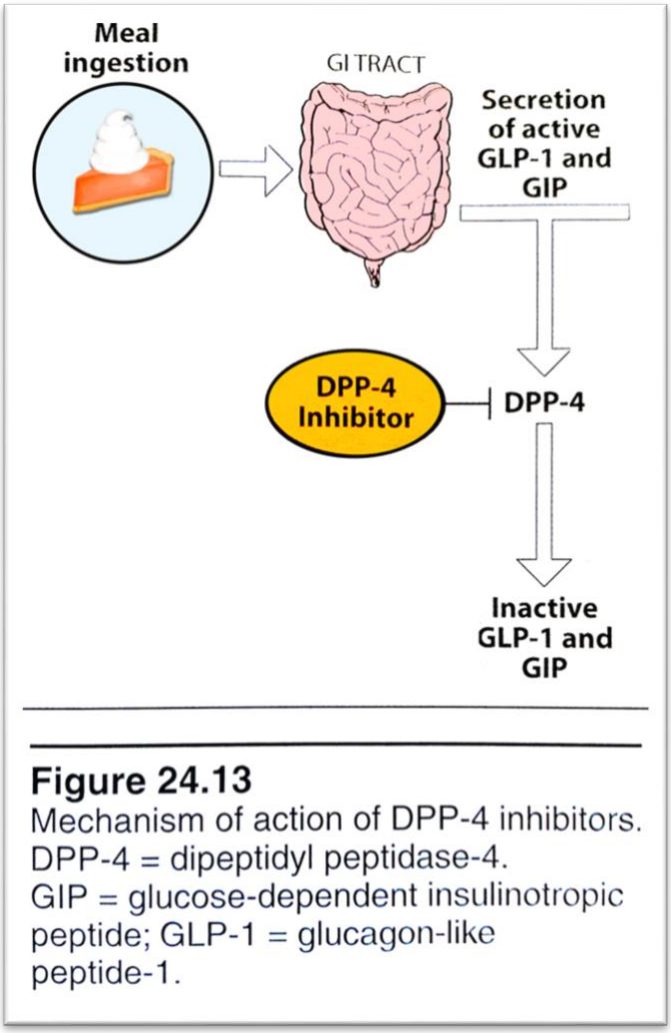


Figure 24.13
Mechanism of action of DPP-4 inhibitors. DPP-4 = dipeptidyl peptidase-4. GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1.

A. Amylinomimetics - injectibles
pramlintide (*Symlin*) amylin analog given SQ.
Cannot be mixed with insulin in same syringe
Can reduce insulin doses required

B. GLP-1 (Glucagon-Like Peptide-1) drugs:
Despite name, they work like **incretins**
Side effects include weight loss, reduced BP and cholesterol and can drop HbA1c by 1%

Ex: exenatide (*Byetta*), lira**glutide** (*Victoza*), sema**glutide** (*Ozempic*), dula**glutide** (*Trulicity*)

exenatide *(Byetta):* an **injection pen**;
doses given before meals
Fun fact: molecule in *Byetta* was originally isolated in lizard spit. Ha!
associated with pancreatitis
lira**glutide** *(Victoza):* longer-acting (once daily dosing)
an oral form of sema**glutide** was approved 2020

C. DPP-4 Inhibitors (Dipeptidyl Peptidase IV) drugs - PO
inhibitors of the enzyme that breaks down incretins (so increases incretins)
sitagliptin *(Januvia)*, lina**gliptin** *(Tradjenta),* saxa**gliptin** *(Onglyza),* alo**gliptitn** *(Nesina)*
side effects: terrible joint pain and pancreatitis
Various drugs in this class have widely different PK: some not metabolized, some excreted in gut

D. SGLT-2 Inhibitors : **Drugs that make you pee out even MORE glucose**
like **canagliflozin** (*Invokana*) – PO, empa**gliflozin** *(Jardiance),* dapa**gliflozin** *(Farxiga)*, ertu**gliflozin**
work by inhibiting a Sodium-GLucose Transporter in the kidney, thus causing **loss of more sugar into the urine** via **osmotic diuresis**
Causes higher urine concentration of sugar. Some reports of weight loss.
Risks: dehydration (*why*?), yeast infections *(why*?), hypotension *(why?),* and ketoacidosis in predisposed people *(why?)*
**Note: you are supposed to be able to figure out the above "why?s"*

Remember using any two drugs that affect the same body system can cause synergism. So drugs that might not cause hypoglycemia on their own might do so when combined with other drugs.

FDA-approved Jan2020: *Trijardy XR*: combination of empa**glilozin** (*Jardiance*), lina**gliptin** (*Tradjenta*) and extended-release **metformin**, *because why not combine drugs if you can, obtain a new patent, and then stuff all the money into your face? Yay! Okay, also it is more convenient. But worth the extra cost?*

OTHER DRUGS COMMONLY USED IN DIABETES:

ACE Inhibitors: have a protective effect for the kidneys
(Black patients of African or Caribbean descent: add a CCB or HCTZ to the ACEI)
bile acid sequestrants: reduce liver production of glucose and LDL

bromocriptine: that dopamine agonist! Can sometimes prevent insulin resistance

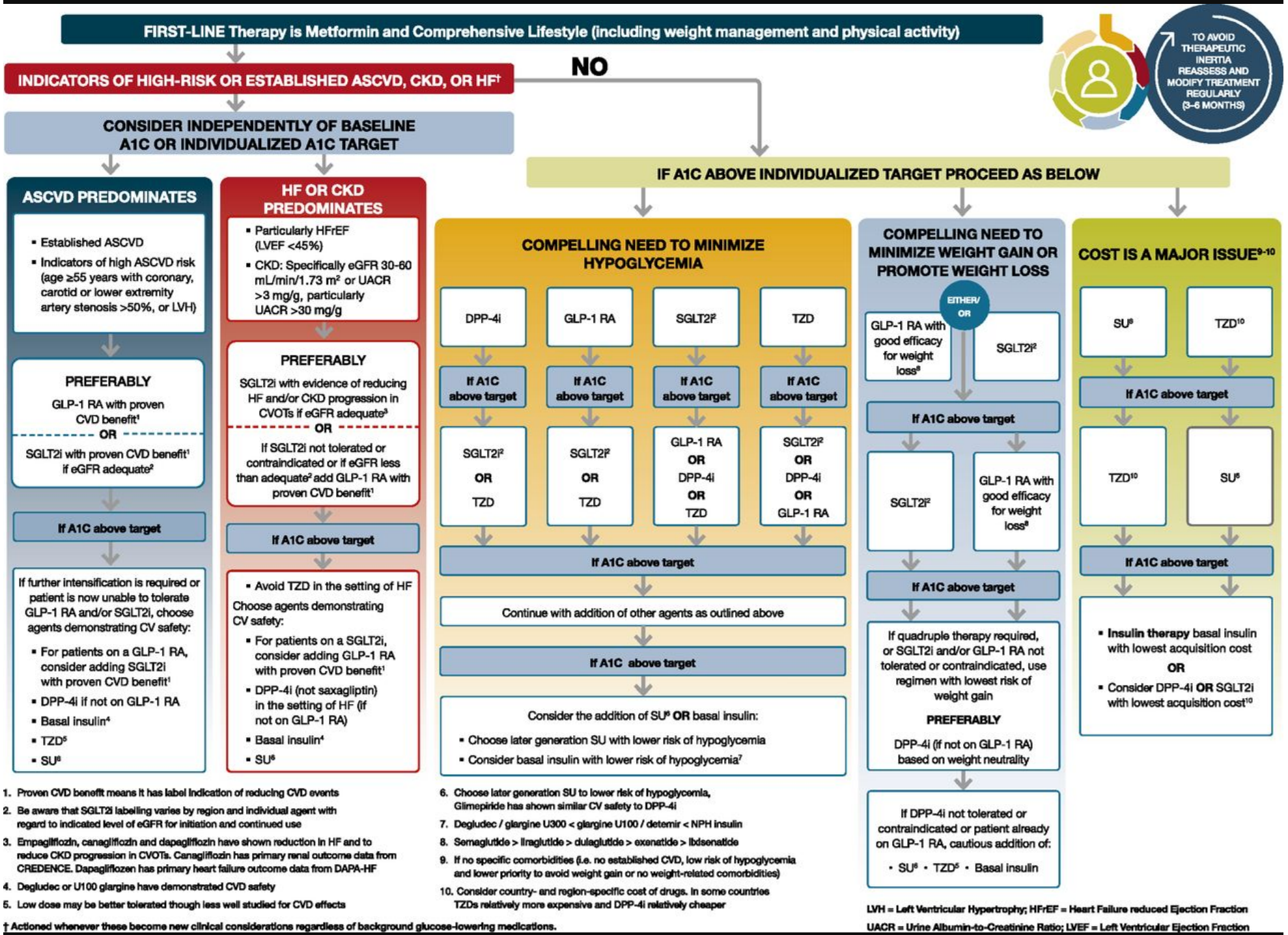
ALSO BE AWARE of drugs that should be **used with caution** in diabetics:

beta blockers (like propranolol) reduce the patient's ability to detect hypoglycemia
drugs that increase blood glucose levels: **thiazide diuretics**, **glucocorticoids**
niacin: increases insulin resistance
...have I mentioned that?

So, how do you decide what to do?

Luckily, the American Diabetes Association comes out with guidelines every few years to help you figure that out. I've attached one of the flow charts from the 2020 guidelines for you on the PDF version of this document to get a feel for how this sort of thing works. Please don't memorize it other than that usually **metformin** is the first drug tried in Type 2 DM.

Note the ASCVD risk factor mentioned on the flow chart refers to the same risk factor mentioned in the HEART handout. The link for that website calculation is:
http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > lraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction