What You Need to Know to Help Your Patients with Diabetes

Part 2: focus on medications

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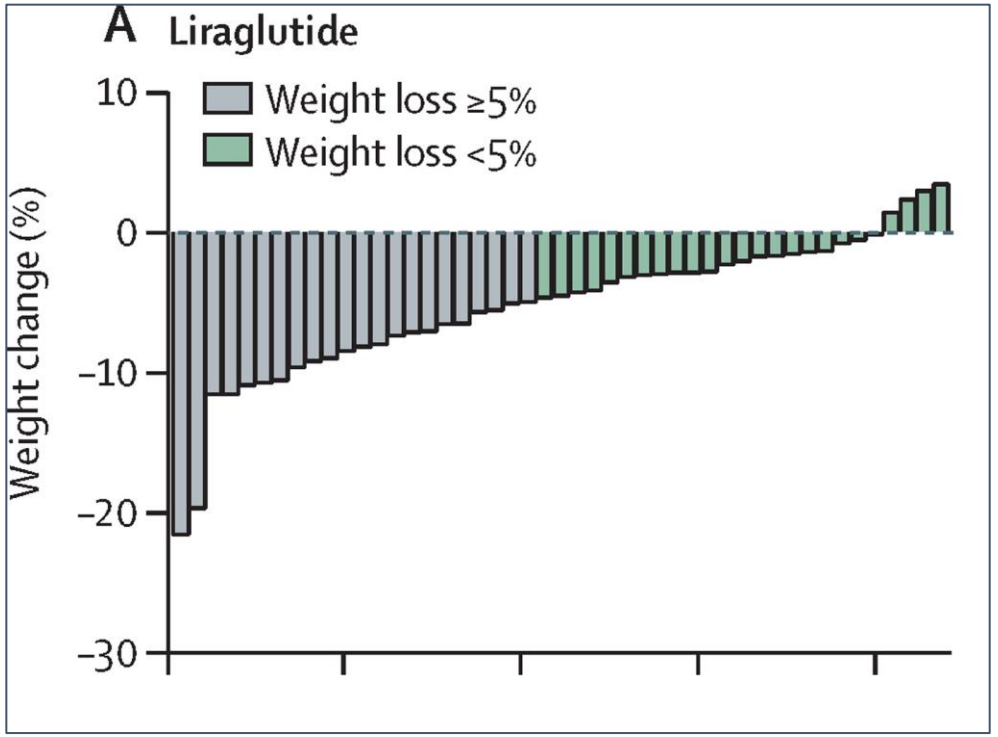
Diabetes Care is Preventive Care

- Primary Prevention – preventing diabetes
- **Secondary Prevention – preventing the complications of diabetes**
- **Tertiary Prevention – slowing the progression & preventing disability or harm from the complications**
  - **Incorporate "non-glycemic" benefits of medications**
    - **The higher the risk – the greater the benefits**

The goal of diabetes care is to help our patients with diabetes stay healthy – To prevent or delay complications, improve outcomes & optimize quality of life

Therapeutic Heterogeneity
(not everyone responds the same)

- Based on our individual make-up, some things work better or not as well for some of us- this includes:
  - Medications
    - for example, the research reports the average A1c lowering or weight loss with a medication but in the test group of patients, some had a greater than average response and some had less than average or worsening



Medications for Diabetes

Current algorithm based on desired effects/co-morbidities
not on specific pathophysiology (not yet available for most patients) –
But “it works” …

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit **EITHER/OR** SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

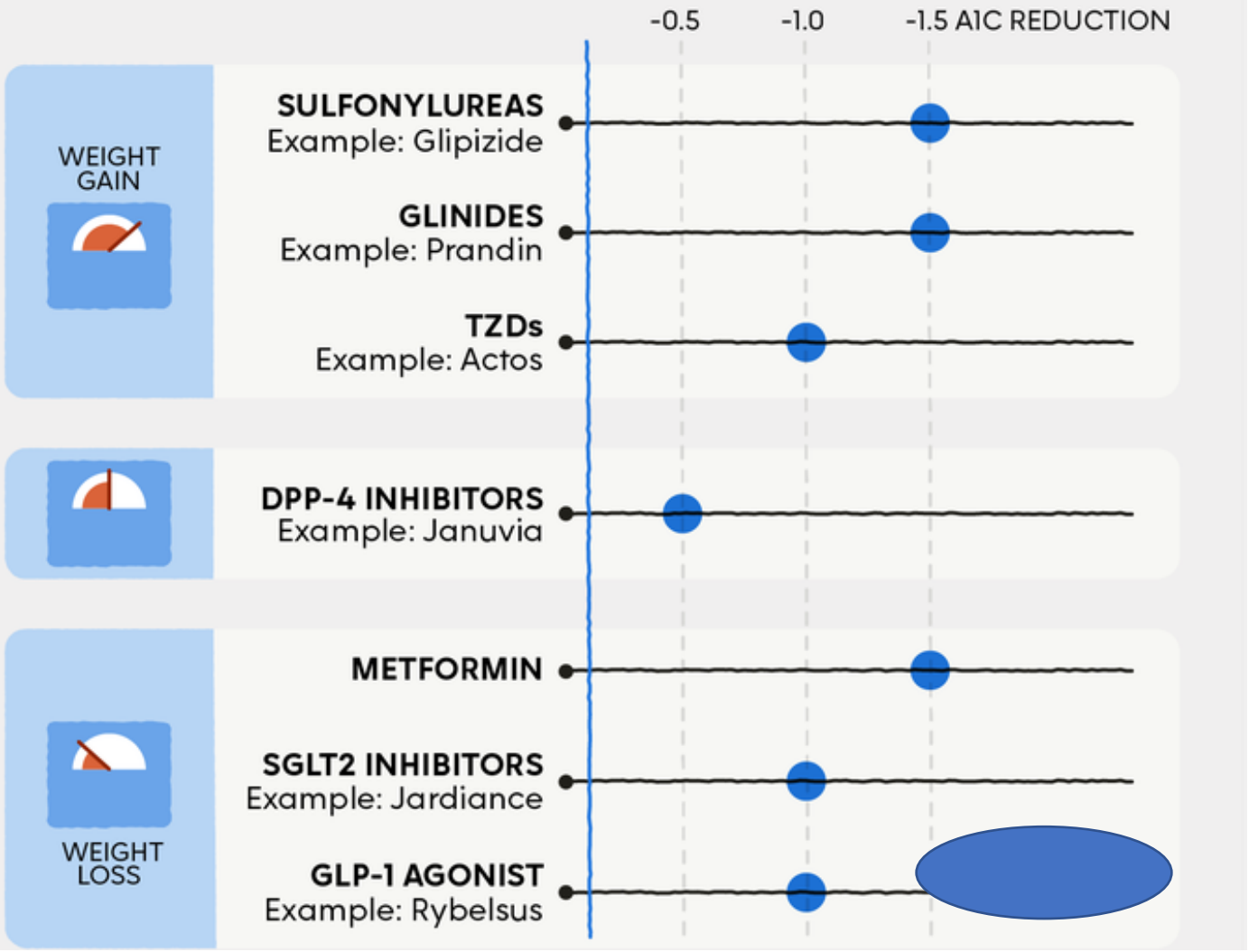
If A1C above target

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

How Diabetes Pills Affect Body Weight and A1C



"Non-glycemic Benefits"

Injectable GLP1 RA meds lower A1c more than the Current oral GLP1 RA

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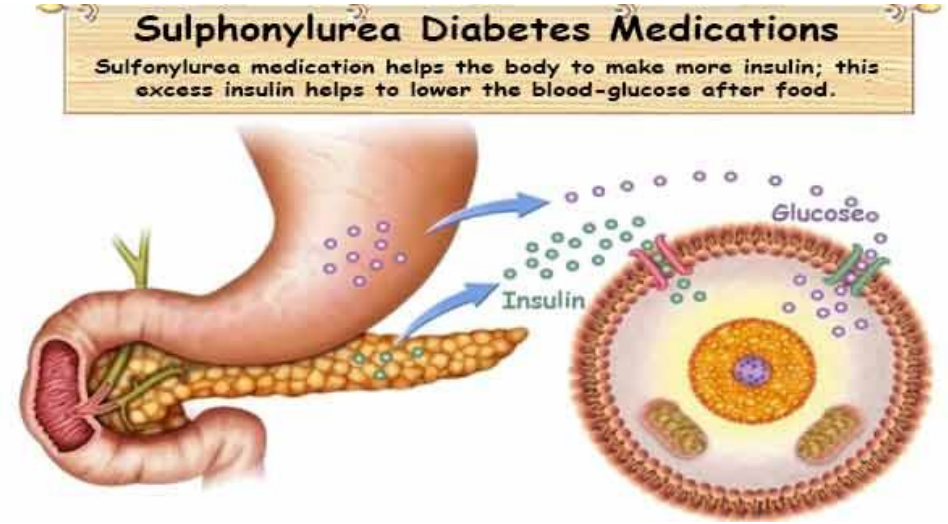
Sulfonylureas

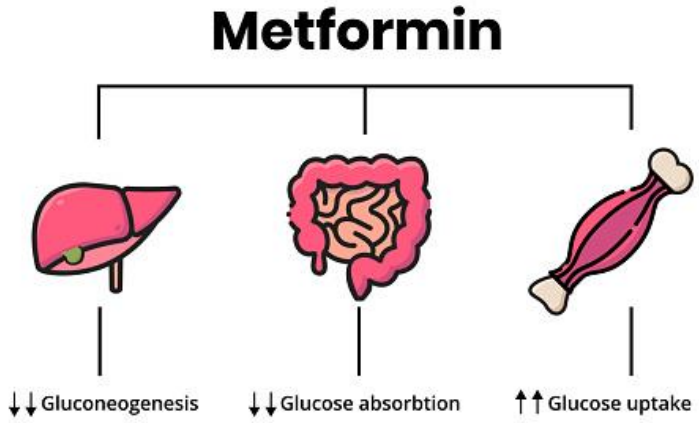
- Medications
  - Glipizide (Glucotrol XL)
  - Glimepiride (Amaryl)
  - Glyburide (DiaBeta, Glynase)
- Action
  - Trigger the release of insulin from the pancreas
- Advantages
  - Low cost
  - Effective in lowering blood sugar (~1.5% A1c drop)
- Possible side effects
  - Blood sugar levels drop too low (*hypoglycemia*)
    - Due to release of too much insulin
    - or needing less insulin (less carbs, more activity)
  - Weight gain
  - Skin rash
  - Renal adjustments
    - glyburide - avoid for eGFR <60
    - glimepiride
      - Reduce dose for eGFR <60
      - Avoid for eGFR <30
    - Glipizide – safe but increased hypoglycemia risk



Glinide meds (e.g., Prandin) also work to release extra insulin From the pancreas and can cause hypoglycemia

Metformin (biguanide)

- Medications
  - IR and ER forms
  - Glucophage, Glumetza, Glucophage XR, Fortamet, Riomet
- Actions
  - Anti-hyperglycemic agent
    - helps to restore the body's response (sensitivity) to insulin
    - decreases the amount of glucose that the liver produces (reduced gluconeogenesis – lower HGP)
    - reduces the amount of glucose that the intestines absorb
    - reduces appetite and caloric intake
- Advantages
  - Good glycemic lowering (up to 1.5% drop in A1c)
  - No weight gain/possible mild weight loss
  - No hypoglycemia
  - Survival benefit
- Possible side effects
  - GI – diarrhea, nausea, abdominal pain
    - Slow increase, caution with dairy intake
    - GI side effects are reduced with ER forms (10% of IR forms)
  - Up to 30% of people develop vitamin B12 deficiency with long-term use
  - Potential for high blood lactic acid level if used in overly large doses people with severe kidney problems (renal dose adjustments)

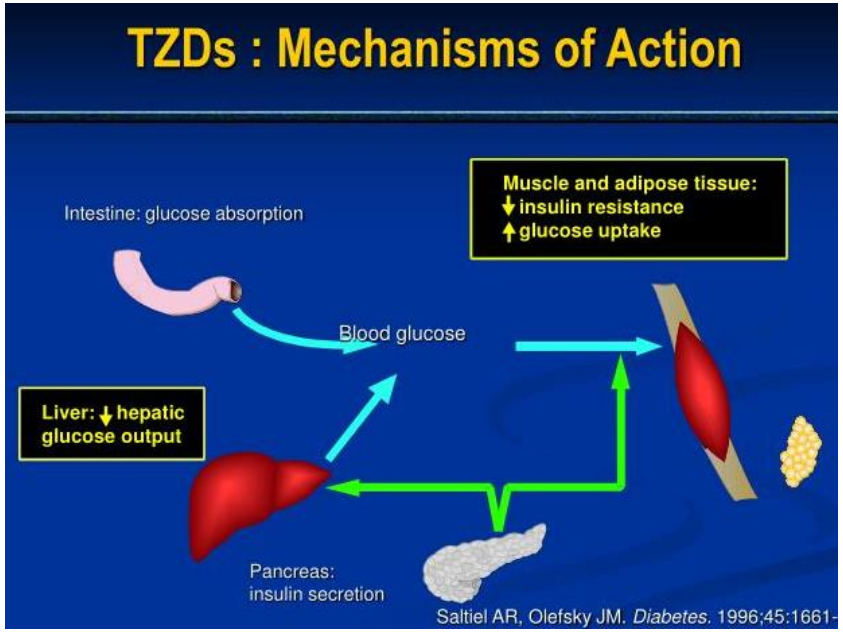


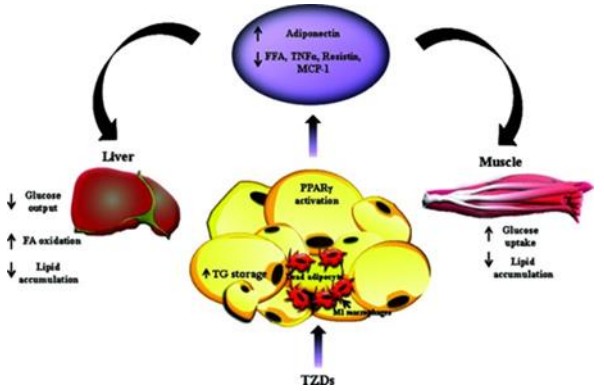
- The renal dosing recommendations from the FDA based on eGFR:
  - Patients with an **eGFR ≥60** require *no dose adjustments* and can safely use metformin with *annual* monitoring.
  - Patients with an **eGFR between 45 and 60** may continue treatment but require *more frequent renal function monitoring* every *3 to 6 months*.
  - Patients with *moderate chronic kidney disease* (**eGFR between 30 and 45**) aren't candidates for initiation of metformin, but patients currently maintained on the medication *may continue cautiously*.
    - The FDA suggests assessing the appropriateness of continuing metformin in this patient population and ***considering a 50% dose reduction*** with renal function monitoring every 3 months.
  - The FDA still recommends a **contraindication** in advanced kidney disease (eGFR <30 mL/min/1.73m^2).

Metformin *should be* ***temporarily discontinued*** *at the time of or before* ***iodinated contrast imaging procedures*** *in patients with* ***eGFR 30-60 mL****/min/1.73 m2*

Thiazolidinediones (TZDs or glitizones)

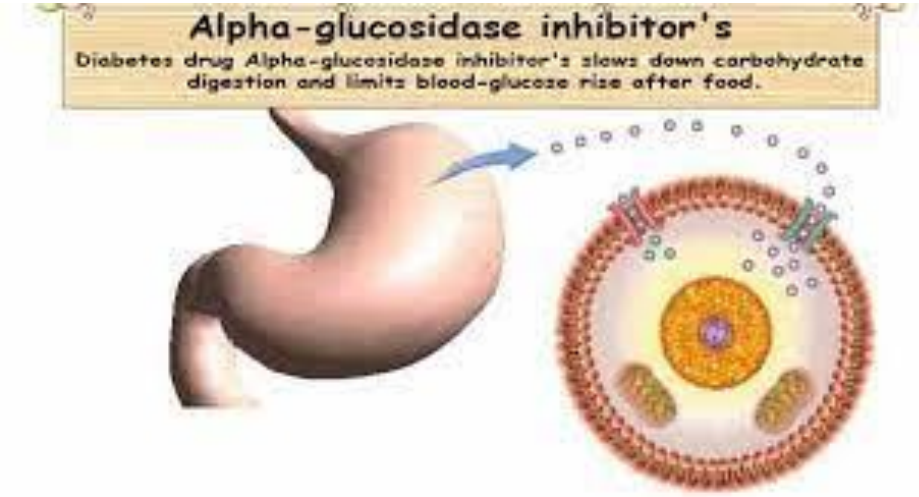
- Medications
  - Rosiglitazone (Avandia)
  - Pioglitazone (Actos)
- Action
  - Improve cells' sensitivity to insulin (reduce insulin resistance)
  - Limit the liver's ability to make & release sugar (reduce HGO)
- Advantages (~1.0% A1c drop)
  - May slightly increase high-density lipoprotein (HDL)
  - Decrease in inflammation
  - Improves Steatohepatitis (NAFLD)
  - No hypoglycemia
- Possible side effects
  - Weight gain
  - Fluid retention
    - People with a history of heart failure shouldn't take this kind of diabetes medicine.
  - Increased risk of fractures (osteoporosis)
  - Possible increased risk of bladder cancer with pioglitazone

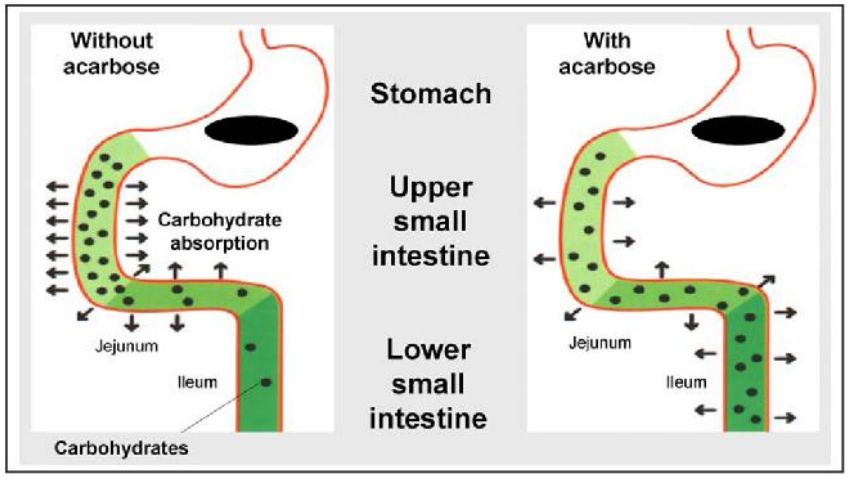




Alpha-glucosidase inhibitors

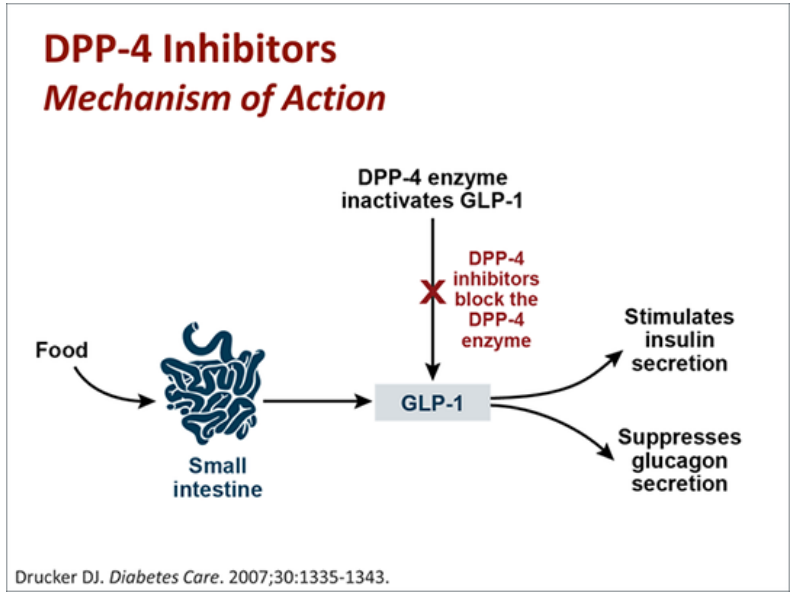
- Medications
  - acarbose (Precose)
  - miglitol (Glyset)
- Action
  - inhibit the absorption of carbohydrates from the small intestine
    - competitively inhibit enzymes that convert complex non-absorbable carbohydrates into simple absorbable carbohydrates.
- Advantages
  - Reduce glucose spikes after eating
  - No hypoglycemia
- Possible side effects
  - diarrhea, abdominal pain, flatulence





Dipeptidyl-peptidase 4 (DPP-4) inhibitors

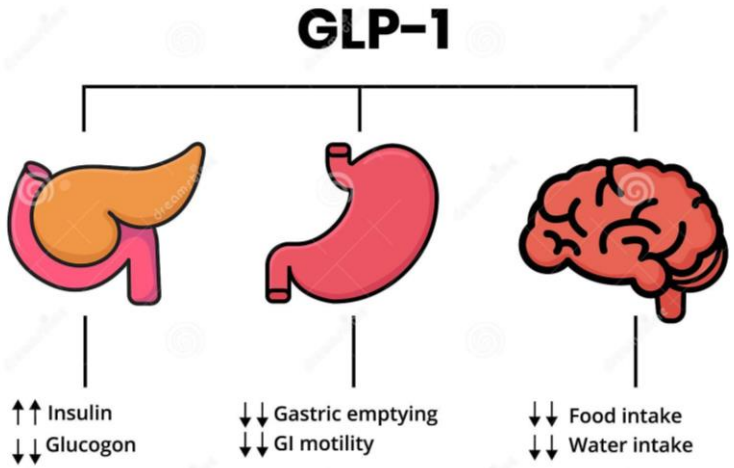
- Medications
  - Saxagliptin (Onglyza)
  - Sitagliptin (Januvia)
  - Linagliptin (Tradjenta)
  - Alogliptin (Nesina)
- Action
  - Increases GLP1 levels by blocking degradation (inhibiting DPP4 enzyme)
    - Cause the release of insulin when blood sugar is rising
- Advantages
  - Don't cause weight gain
  - No hypoglycemia
  - Only mild or minimal glucose lowering (~0.5 A1c drop)
    - Maybe more effective in some Asian populations & older patients
- Possible side effects
  - Upper respiratory tract infection /Sore throat / Headache
  - Heart failure worsening (Onglyza)
  - Acute pancreatitis
  - Stevens-Johnson syndrome
  - Joint pain



Studies show no advantage of combining DPP4i with GLP1 RA meds, only higher costs.

GLP-1 receptor agonists ("Incretin Mimetics")

- Medications
  - Dulaglutide (Trulicity)
  - Exenatide (Byetta, Bydureon Bcise)
  - Liraglutide (Saxenda, Victoza)
  - Lixisenatide (Adlyxin)
  - Semaglutide (Ozempic, Rybelsus, Wegovy)
- Action
  - Cause the release of insulin as blood sugar levels are rising
    - "glucose dependent" insulin release - **No hypoglycemia**
  - Increases satiety (weight loss)
  - Slows gastric emptying (lower glucose spikes after meals)
  - Good reduction in glucose levels (A1c reduced 1.0-2.0%)
- Advantages
  - May decrease hunger
  - May lead to weight loss
  - **Reduces ASCVD risk ("non-glycemic benefit")**
- Possible side effects
  - Nausea / Vomiting / Diarrhea / Abdominal pain
  - Increased gallbladder disease
  - ?Increased risk of pancreatitis – no increased risk pancreatic cancer

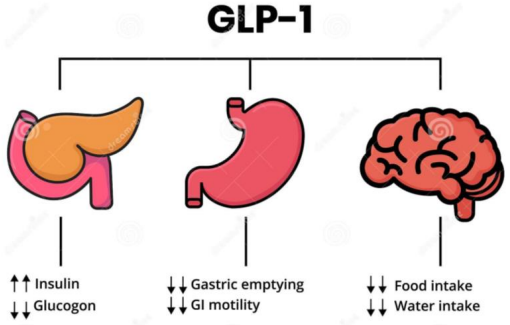


Build dose up slowly

GLP-1 receptor agonists ("Incretin Mimetics")

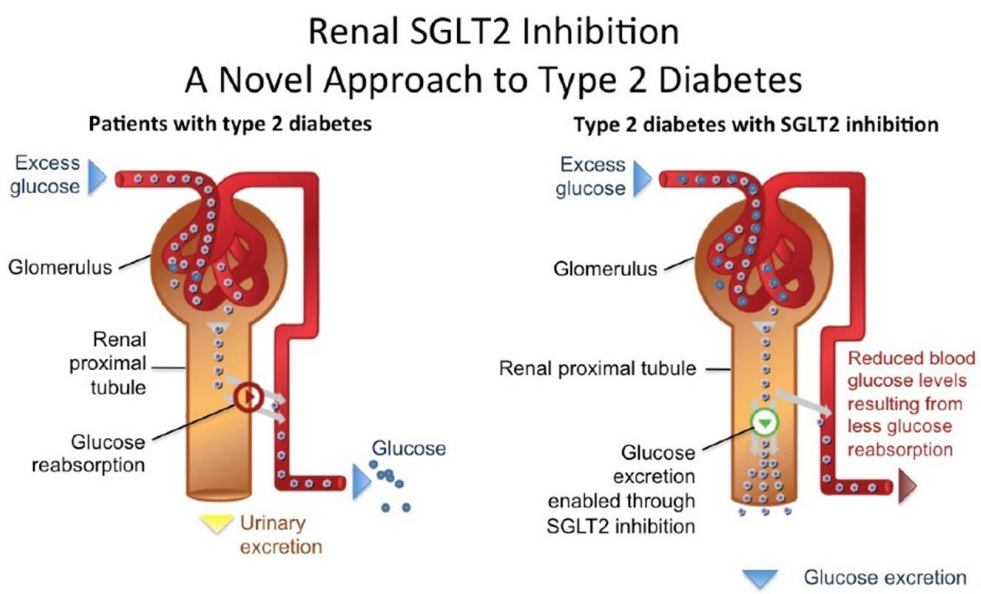
Counselling on nausea & diet (foods & volume)

- What some patients describe as nausea is more accurately described as a bloated feeling or a sense of gastric *fullness* after eating, most likely related to delayed gastric emptying.
  - Also just not feeling hungry (satiety or anorexia) can be confused with nausea
- There appears to be an association between nausea during GLP-1 RA therapy and both the ***fat*** content and ***size of meals***;
  - limiting or avoiding greasy, fatty or fried foods and eating smaller portions at mealtimes may help to prevent the feeling of nausea.
  - also limit soda (fizzy beverages) and foods such as onions, peppers (select more bland foods)
  - patients should be encouraged to eat slowly while undistracted and to pay careful attention to the amount and the pace at which that they eat.
    - Patients might be told **to eat less and to eat slower than they ever have before.**
    - **STOP EATING when feel full (satiety).**
- Patients may obtain some relief from nausea by consuming ginger (e.g., fresh ginger, ginger tea), soda crackers, or rice crackers. Slowly sipping hot water or sucking on sugar-free mints also may ease nausea.
  - Pharmacologic options are rarely needed.



Sodium-glucose transporter 2 (SGLT2) inhibitors

- Medications
  - Canagliflozin (Invokana)
  - Dapagliflozin (Farxiga)
  - Empagliflozin (Jardiance)
  - Ertugliflozin (Steglatro)
- Action
  - Limit the kidneys' ability to reabsorb sugar, which increases the amount of sugar that leaves the body in urine
- Advantages — No hypoglycemia
  - May lead to weight loss
  - May lower blood pressure
  - Reduces uric acid levels & gout
  - Protects kidneys
  - Reduces heart failure
  - Reduces ASCVD risk
- Possible side effects
  - Genital Mycotic (Yeast) infections
  - Diabetic Ketoacidosis
  - Rare Fournier's gangrene
  - ? Urinary tract infections
  - ? Increased risk of amputation



- Personal hygiene advice/education can reduce the infection risk in patients taking SGLT2 inhibitors
  - i.e., **rinse genital area with water after voiding and before bed**; wear cotton underwear
- When candidiasis occurs, it is often mild and responsive to treatment and often ***does not require discontinuation*** of the medication.
  - management strategies may include the use of
    - oral antifungals (i.e., single dose of oral fluconazole)
    - topical antifungal creams (i.e., miconazole or clotrimazole for 1-3 days)
    - over-the-counter topical antifungals in milder cases

SGLT2i effectiveness in people with CKD

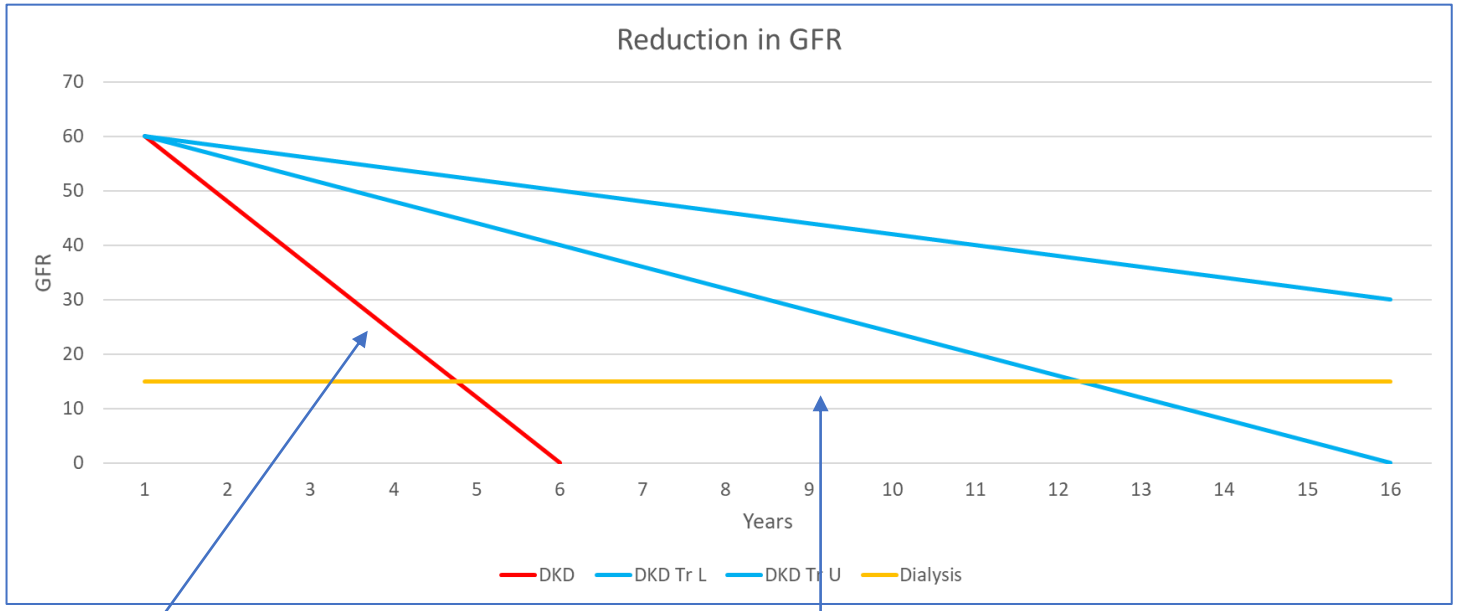
- ***Glycemic efficacy* of SGLT2 inhibitors is dependent on kidney function**.
  - The ***glucose-lowering efficacy*** of SGLT2i in the patients with an **eGFR <45 mL/min/1.73 m2 is *diminished*** because of their *reduced glucose filtration*
    - The glucose-lowering effect of SGLT2 inhibitors is attenuated in patients with eGFR <60 ml/min per 1.73 m2 and **minimal when eGFR is <30 ml/min** per 1.73 m2
    - Will need other agents for glycemic benefits (GLP1 RA preferred for safety & ASCVD risk)

- ***Non-glycemic benefits*** are **not diminished**
  - In patients with T2D and CKD with low eGFR, despite only modest reductions in A1c, SGLT2 inhibitors **reduce the risk of cardiovascular and renal outcomes**, without clear evidence of additional safety concerns

"SGLT2i should be given to all patients with stage 3 CKD or higher regardless of glycemic control, as they **slow CKD progression and reduce heart failure risk** independent of glycemic control" ADA Standards

SGLT2i therapy can be continued until the patient initiates dialysis therapy (currently not recommended to start at eGFR <20, but once started recommended to continue until renal replacement started) (for cardio-renal benefits)

Slowing Down the Loss of Kidney Function with Diabetes Kidney Disease



This is how quickly your kidneys will lose function without any treatment

The yellow line is the level where you need to start dialysis

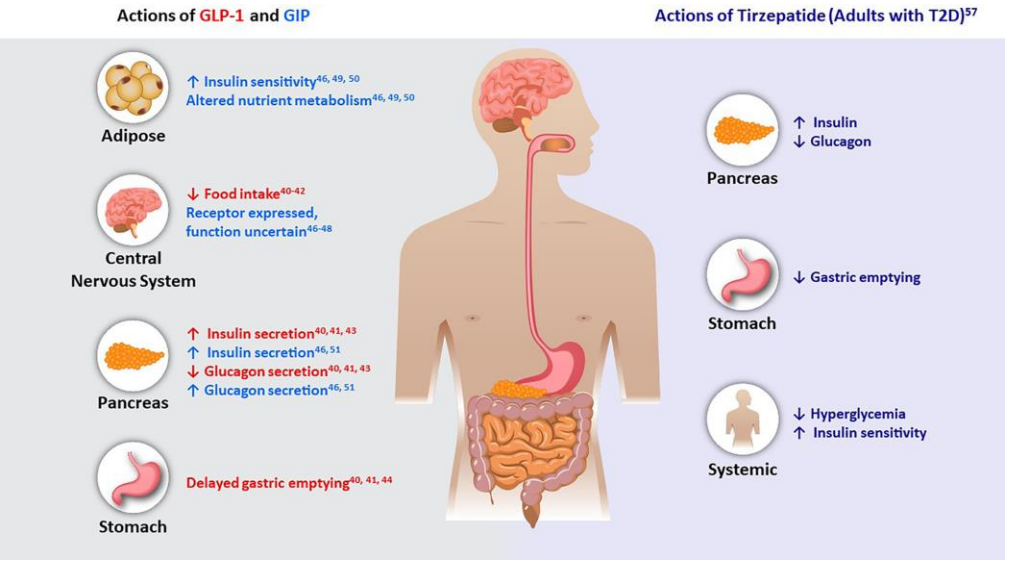
The aqua lines show how much treatment can reduce the rate at which your kidneys lose function

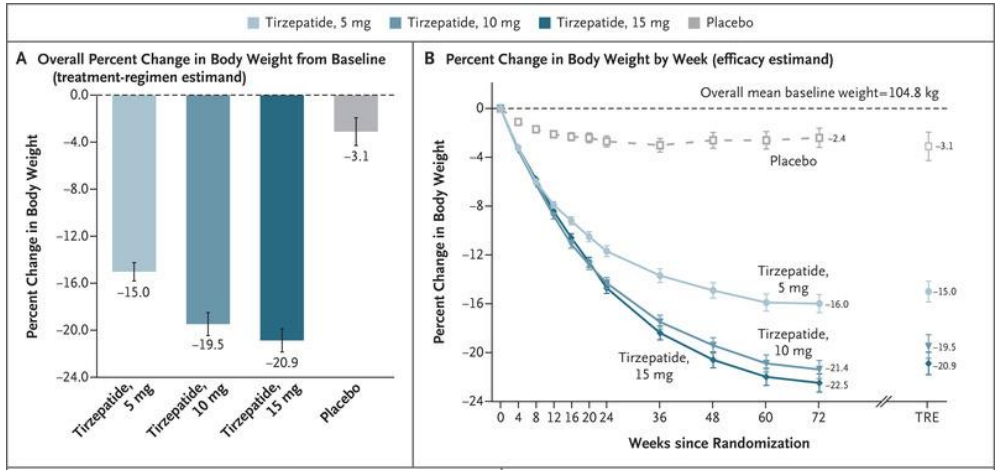
Treatment includes

- Optimal blood pressure, using an ACEI or ARB medication along with other meds if needed
- An SGLT2 inhibitor medication (and/or a GLP1 RA or MRA)
- Blood glucose levels in individualized safe range
- Avoiding drugs that hurt your kidneys such as NSAIDs (ibuprofen, Advil, Motrin, etc.)
- Keeping your muscles strong, avoiding being too sedentary
- Healthy food choices – especially, avoid excess animal protein & fats

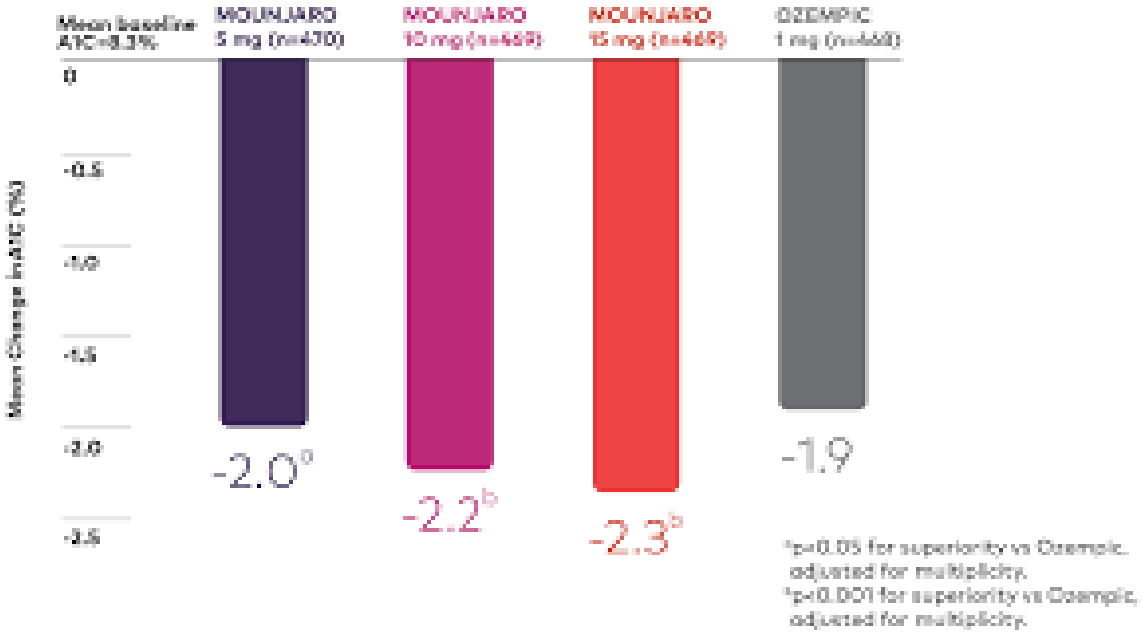
Dual GIP-GLP1 RA medications

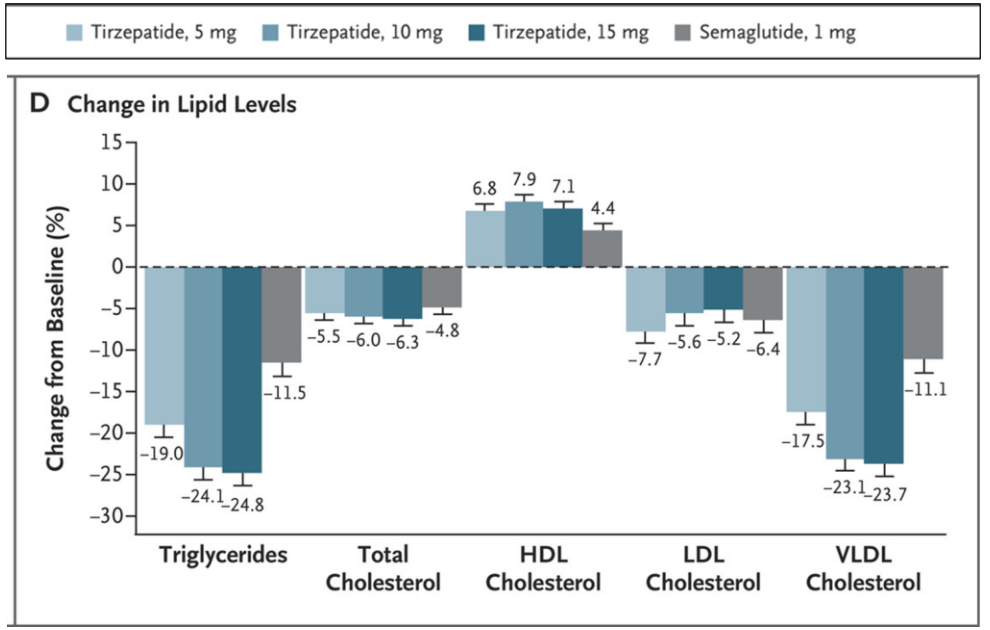
- Medications
  - Mounjaro (tirzepatide)
- Actions
  - GLP1 RA effects
  - GIP RA effects
    - enhanced appetite suppression and improved WAT health and storage capacity, reduced lipid 'spillover' ectopic fat accumulation
- Advantages
  - Significant weight loss (~20%)
  - Marked improved glycemia (>2% A1c drop)
  - Significant improvement lipids/sBP
  - Cardiorenal (CVOT) benefit studies underway
- Possible side effects
  - GI effects (N,V, D, abdominal pain)
  - GB, pancreatitis

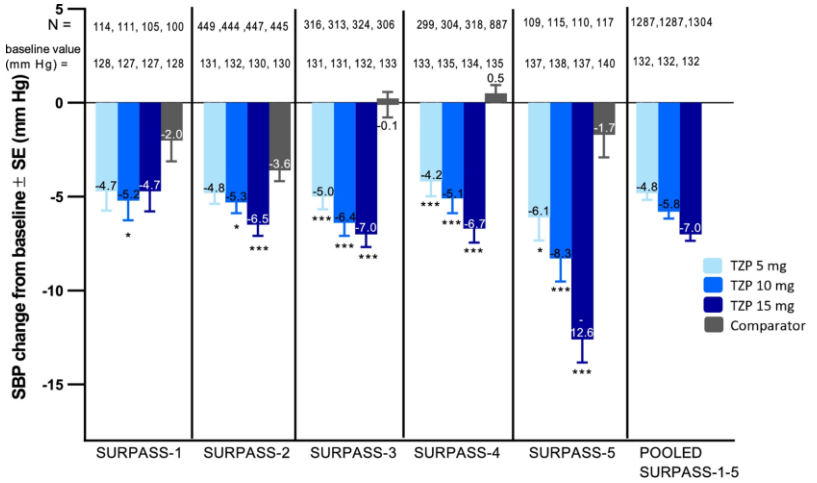




Tirzepatide effects

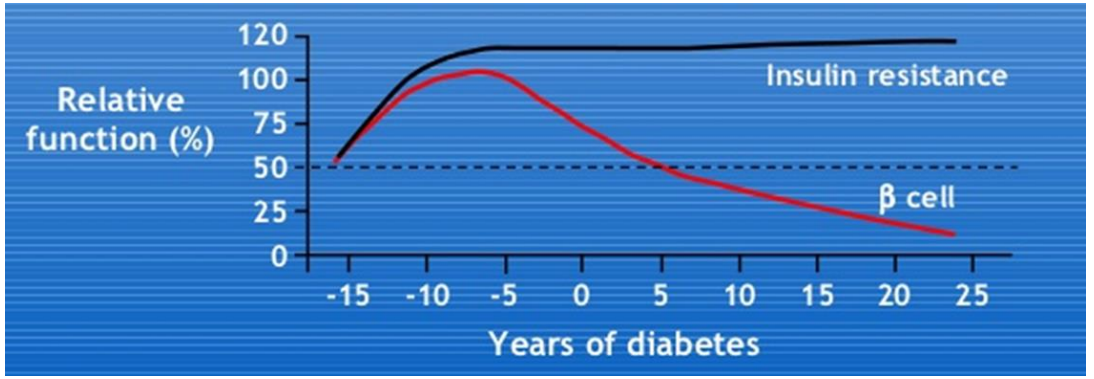






Many adults with type 2 diabetes eventually require and benefit from insulin therapy

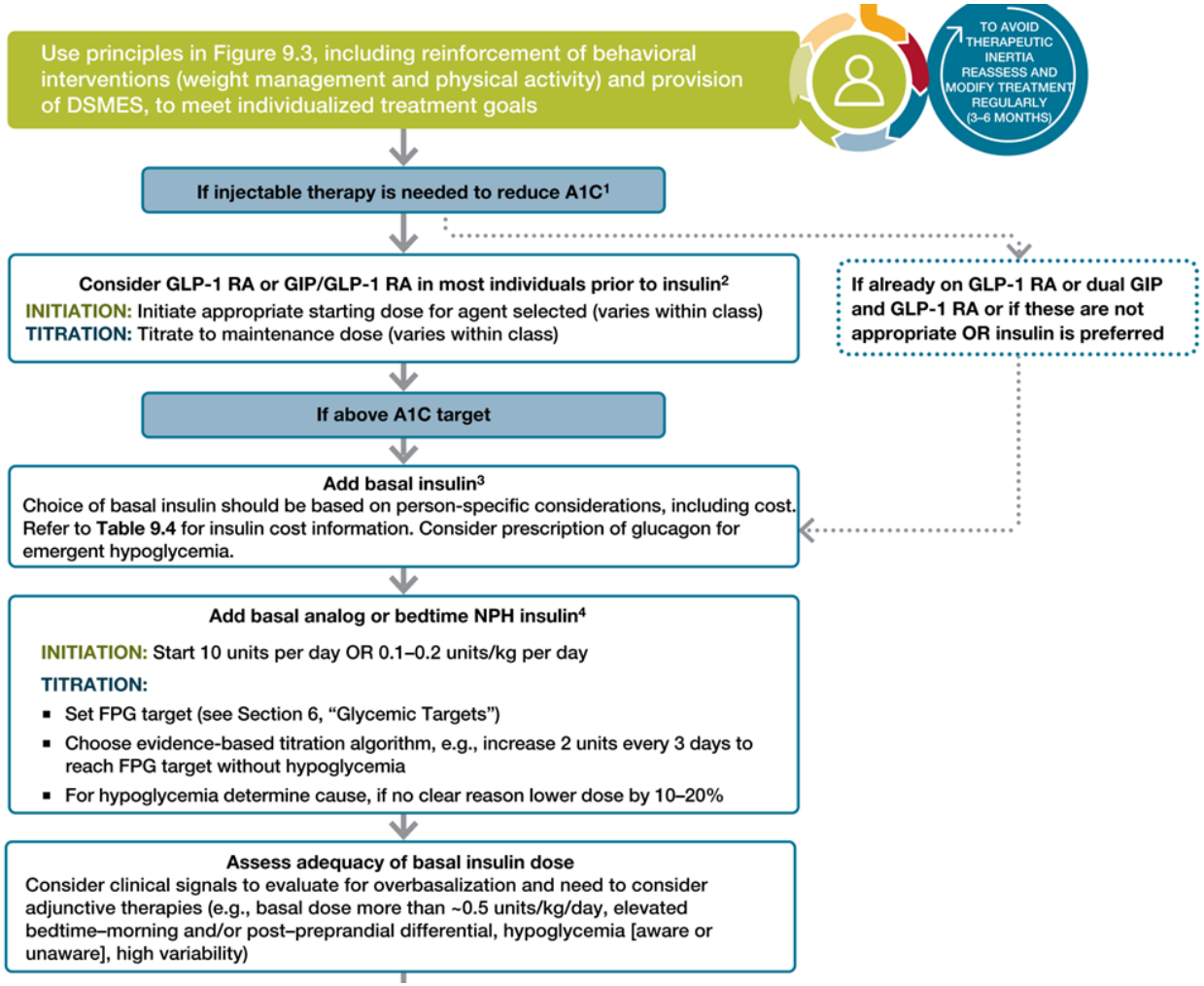
- The ***progressive nature of type 2 diabetes*** should be regularly and objectively explained to patients, and clinicians should ***avoid using insulin as a threat or describing it as a sign of personal failure or punishment.***
  - Rather, the utility and importance of insulin to maintain glycemic control once progression of the disease overcomes the effect of other agents should be emphasized.
- Educating and involving patients in insulin management is beneficial – including **education** regarding
  - correct injection technique
  - blood glucose monitoring
  - self-titration of insulin doses
  - nutrition
  - avoidance and appropriate treatment of ***hypoglycemia***



Explain that diabetes gets worse over time
It is not the patient's fault
It does not mean they "failed"

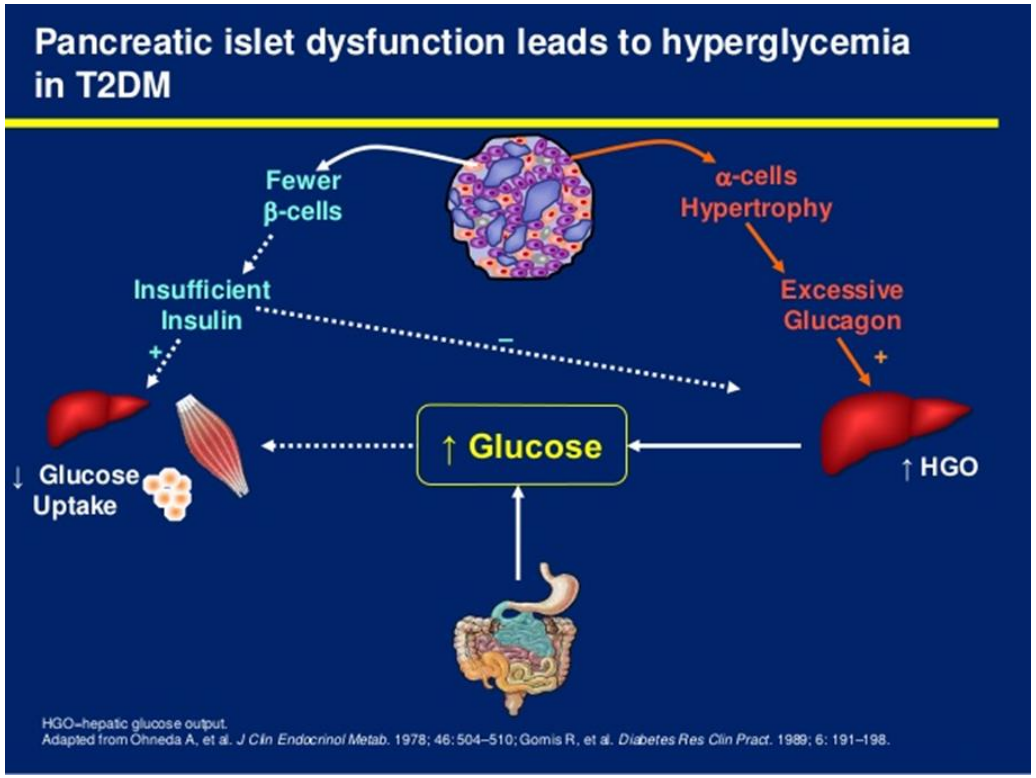
ADA 2023 Standards of Care

- 9.10 In adults with type 2 diabetes, a ***glucagon-like peptide 1 receptor agonist (GLP1 RA)*** is *preferred to insulin* when possible. A
- 9.11 *If insulin is used,* ***combination therapy with a GLP1 RA*** *is recommended* for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. A
  - If you need guidance on how to add in a GLP1 RA medication to someone already on Basal-Bolus Insulin – let me know and we can discuss



Basal (fasting) Hyperglycemia

- Predominate source of excess glucose in
  - Poorly controlled Type 2 diabetes or if A1c >8%
    - Typically, if A1c is >8% and/or if TIR is <66% - high BG is due to too much basal glycemia
  - Most new onset Type 2 diabetes
    - Impaired fasting glycemia (IFG)
    - Impaired glucose tolerance (IGT)
- Excess glucose from hepatic glucose output
  - Inadequate insulin
  - Excessive glucagon
  - Excessive free fatty acid (from adipose tissue & inadequate insulin)

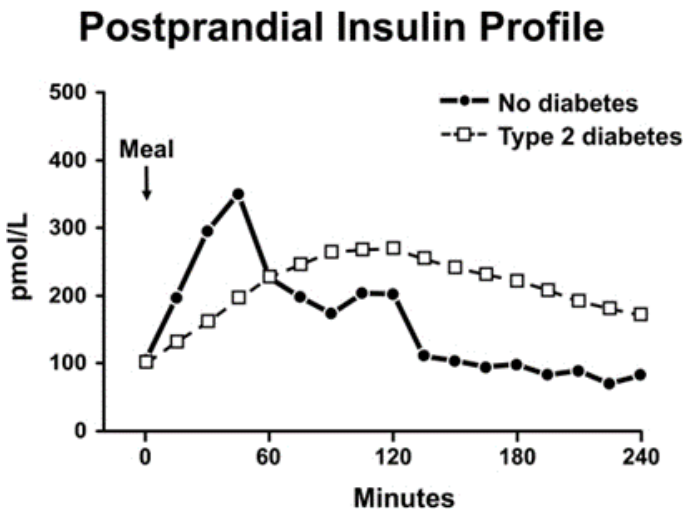


Basal (fasting) Hyperglycemia

- Most medications impact
  - **Metformin**
  - **Longer acting insulins** (Insulin direct effect on liver & on adipose tissue to reduce FFA = reduce hepatic glucose output)
  - **Sulfonyl-urea medications**
  - **TZDs**
  - **Long-acting GLP-1 Receptor agonists** (increase insulin (direct effect on liver/ reduce FFA from adipocytes) & reduce glucagon = reduced hepatic glucose output)
  - **DPP4-inhibitors**
  - **SGLT-2 inhibitors**

Postprandial Hyperglycemia

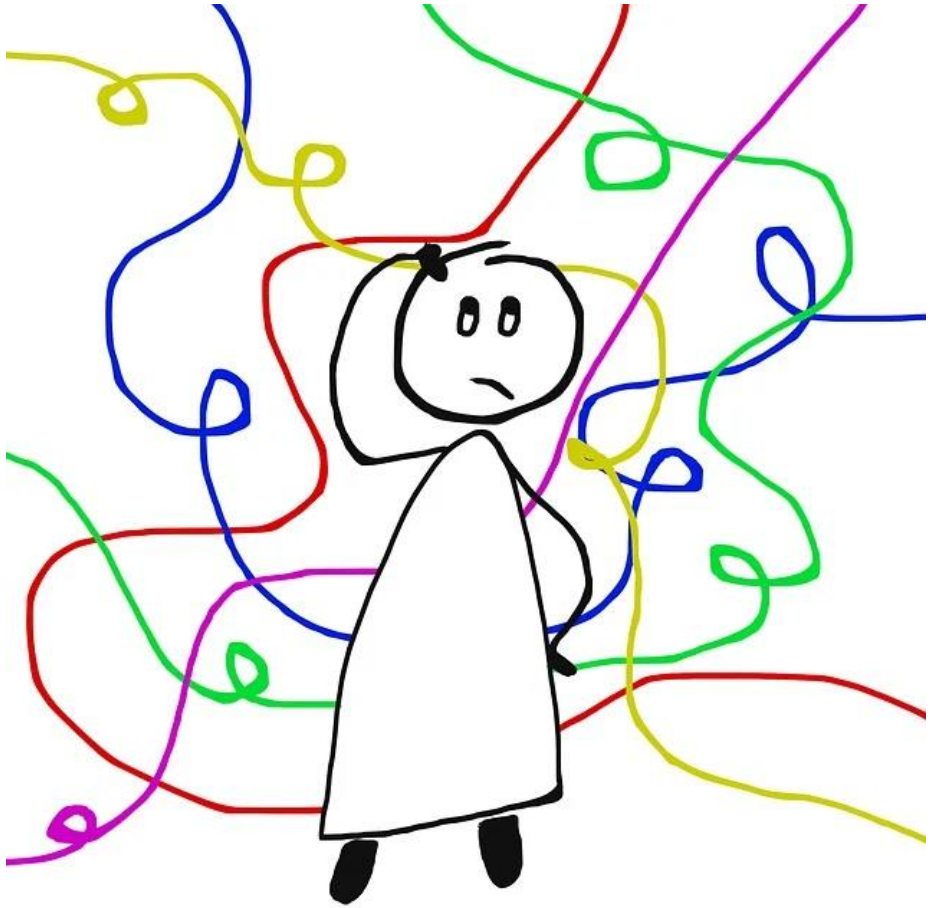
- Predominate source of excess glucose in
  - Better controlled Type 2 diabetes as A1c nears 7%
    - If A1c <8% and/or TIR >66% - target postprandial glucose
  - Longer duration of Type 2 diabetes (>10 years)
- More complex
  - Normal -rapid rise in Insulin & Amylin + gut hormones (GLP-1);
    - reduction in glucagon,
    - slowing of gastric emptying;
    - increase in satiety to reduce eating
  - Type 2 Diabetes:
    - Reduced & delayed rise and peak in insulin
    - Reduced & delayed rise and peak in amylin & gut hormones (GLP-1)
    - Gastric emptying not delayed (rapid absorption-spike)
    - Glucagon not reduced (high output of glucose from liver)
    - Satiety not enhanced (eating more)



Postprandial Hyperglycemia

- Fewer medications impact postprandial glycemia
  - Alpha- Glucosidase Inhibitors (Precose, Glyset)
  - Stepwise addition of **prandial insulin** (mealtime [bolus] insulin)
    - More rapidly absorbed prandial insulin
  - GLP-1 receptor agonists
    - GLP-1 receptor agonists provide improvements in ***both PPG and FPG levels*** because they
      - stimulate glucose-dependent insulin secretion
      - inhibit glucose-dependent glucagon secretion
      - slow gastric emptying
      - increase satiety
  - Amylin receptor agonist (Symlin (pramlintide))
  - SGLT2i helps reduce height of postprandial rise

Questions, Comments, Clarifications, etc.



USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit **EITHER/OR** SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If A1C above target

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.