ECHO Diabetes

Basal Insulin Therapy

Carol Greenlee MD

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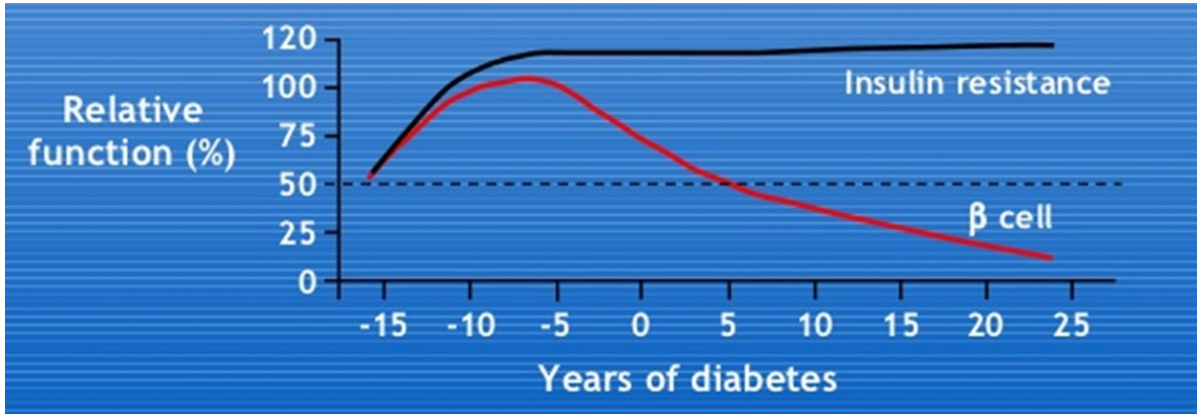
Pre-Question - which two options are correct?

- Basal Insulin therapy
  A. Should cover both fasting and mealtime insulin requirements
  B. Should not exceed a dosage of 0.2 units/kg
  C. Can be added to non-insulin diabetes medications
  D. Can be effectively titrated by patients using an algorithm to guide

  - A & B
  - A & C
  - A & D
  - B & C
  - B & D
  - C & D

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

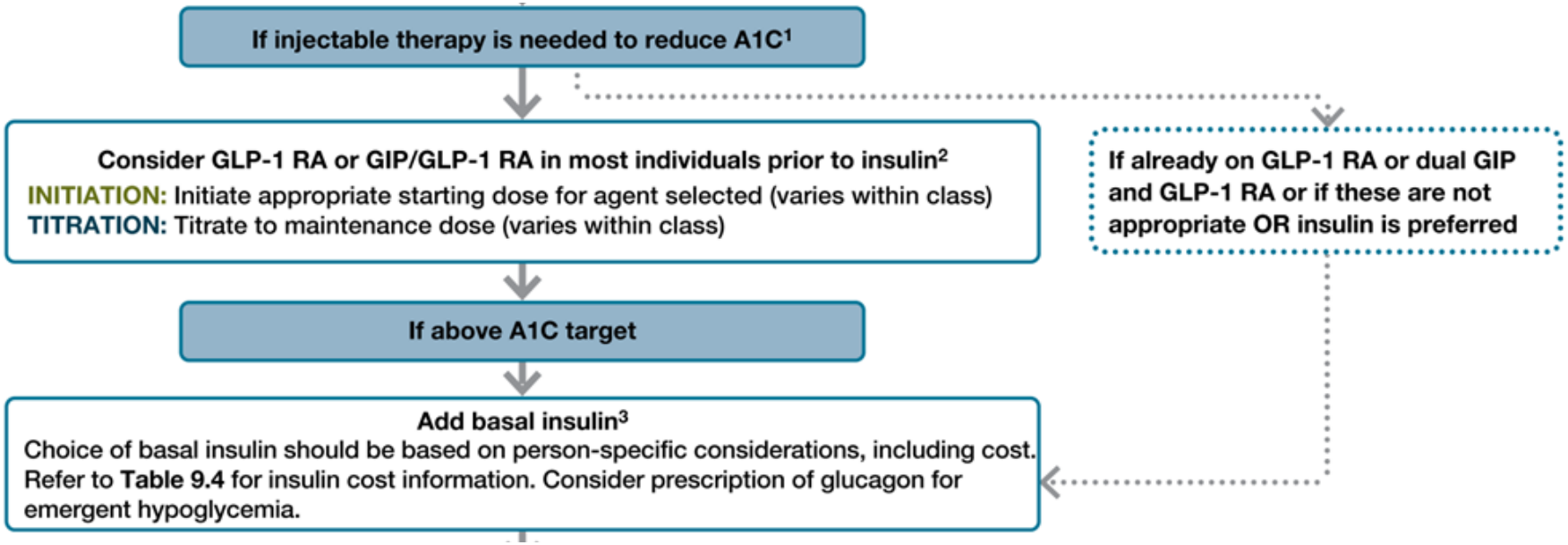
- The ***progressive nature of type 2 diabetes*** should be regularly and objectively explained to patients.
- Clinicians should ***avoid using insulin as a threat or describing it as a sign of personal failure or punishment.***
  - Rather, the utility and importance of insulin to maintain glycemic control once *progression of the disease* overcomes the effect of other agents should be emphasized. [Or if *intolerance of or cost* of other meds requires use of insulin]



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

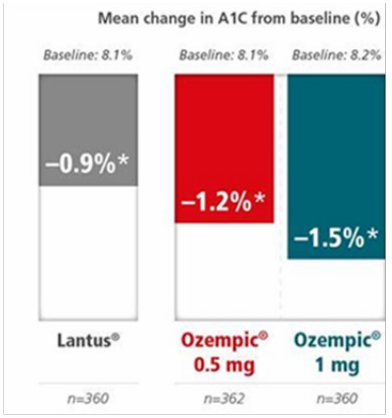
ADA 2023 Standards of Care
EASD & AACE/ACE

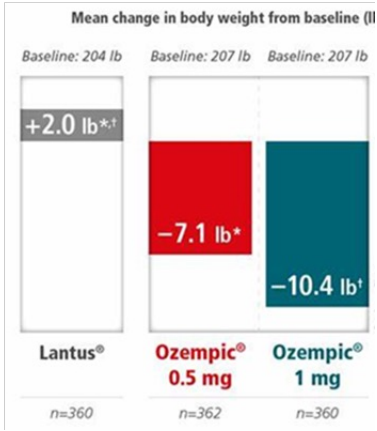
- 9.10 In adults with type 2 diabetes, a ***glucagon-like peptide 1 receptor agonist (GLP1 RA)*** is *preferred to insulin* when possible. A
- 9.11 *If insulin is used,* ***combination therapy with a GLP1 RA*** *is recommended* for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. A



Recommendation for Adding GLP1 RA

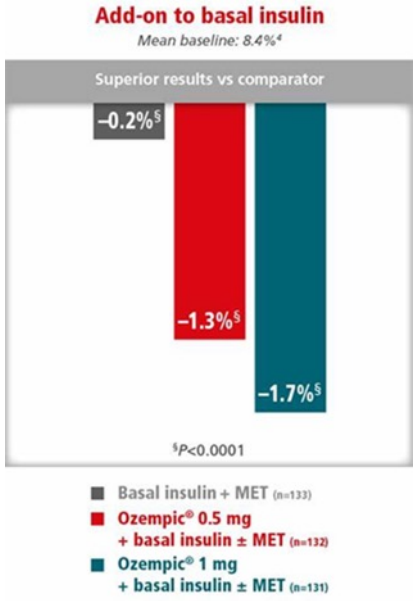
- A GLP-1 receptor agonist should be considered
  - *before basal insulin* therapy for most patients
  - as add-on therapy in patients needing treatment intensification *beyond basal insulin*.
    - Recommend reduce basal insulin dose by ~20% if A1c < 8.5%





Insulin titrated to target - limited by hypoglycemia

- This recommendation is based on evidence demonstrating
  - high efficacy [& less complexity]
  - lower risk of hypoglycemia
  - greater weight reduction
  - decrease in major adverse cardiovascular (CV) events and mortality



Insulin Therapy - Educating Patients

- *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 (see Nov 9,2023 ECHO)

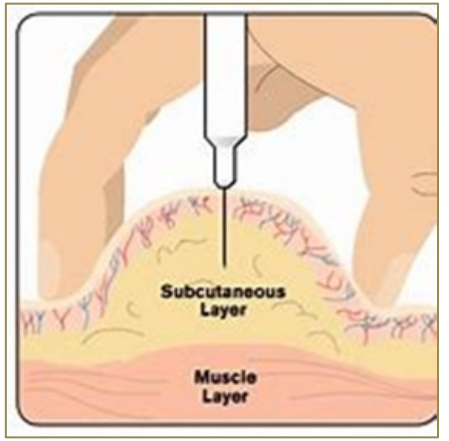
Insulin Injection Technique

- Ensuring that individuals &/or caregivers understand correct insulin injection technique is important to optimize glucose control and insulin use safety.
  - It is important that insulin be delivered into the proper tissue in the correct way (***"show me"*** – how & where - very valuable in ensuring proper technique)
    - **Many patients, even those who are confident in injecting, still do this incorrectly**

- Proper insulin injection technique includes
  - injecting into appropriate body areas ("sites")
  - injection *site rotation*
  - appropriate care of injection sites to avoid infection or other complications
    - Ongoing debate regarding use of alcohol swab – most say if site is clean, no need to use alcohol / can use alcohol or water or soap & water to clean if necessary
    - Clean hands with soap and water
  - avoidance of intramuscular (IM) insulin delivery

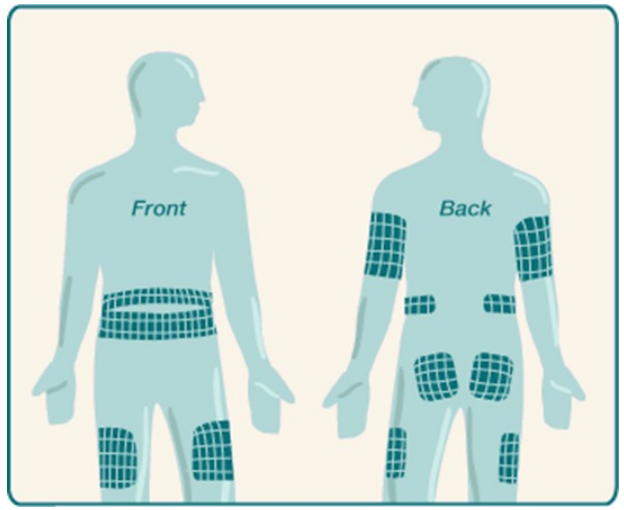
Insulin Injection Technique

- Exogenously delivered insulin should be injected into **subcutaneous tissue**, not intramuscularly.
  - Inadvertent IM injection can lead to *unpredictable insulin absorption* and variable effects on glucose and is associated with frequent and *unexplained hypoglycemia* (influenced by activity of the muscle)
  - Risk for IM insulin delivery is increased
    - in younger, **leaner individuals** when injecting into the limbs rather than truncal sites (abdomen and buttocks) [also some fat distribution patterns, forms of lipodystrophy]
    - when using **longer needles** (recent evidence supports the use of short needles [e.g., 4-mm pen needles] as effective and well tolerated when compared with longer needles, including a study performed in adults with obesity).
  - loosely pinch up skin & subcutaneous tissue
  - insert the needle
  - relax fingers as inject
    - If you have sample insulin needles, practice needle insertion on yourself

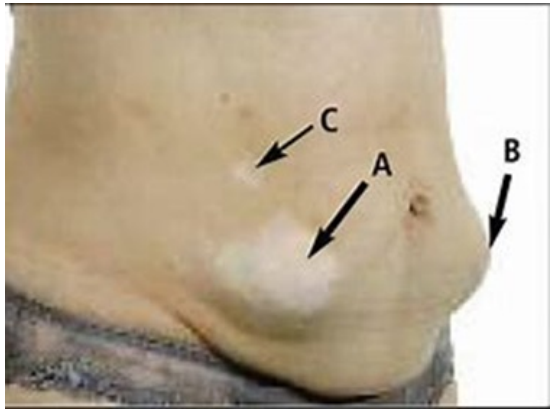


Insulin Injection Technique: sites & rotation

- Recommended sites for insulin injection include the
  - abdomen
  - thigh
  - buttock
  - upper arm



- Injection site rotation is necessary to avoid lipohypertrophy
  - an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections.
  - appears as soft, smooth raised areas
  - can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes.



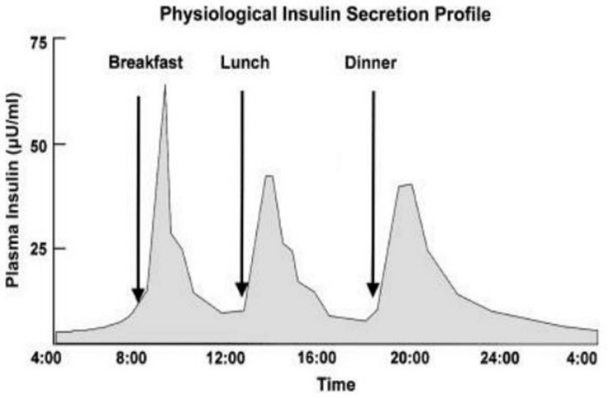
Insulins

- Dosing to try to replace /mimic the natural secretion of insulin
  - **Basal insulin** is designed to *suppress hepatic glucose production and improve basal (fasting) hyperglycemia*
  - **Bolus (mealtime, prandial) Insulin** –as rapid-acting insulin - limits hyperglycemia after *meals(covers food carbs)* – should hold(not give) if NPO or not eating
  - **Correction Insulin** – extra rapid-acting insulin given for *high blood glucose* to *decrease BG levels to target range* – based on patient's "sensitivity or correction factor" - can be used to:
    - Add more insulin to a mealtime bolus to correct for a high premeal blood glucose
    - Used alone *to correct a high blood glucose* outside of mealtime or if NPO or illness

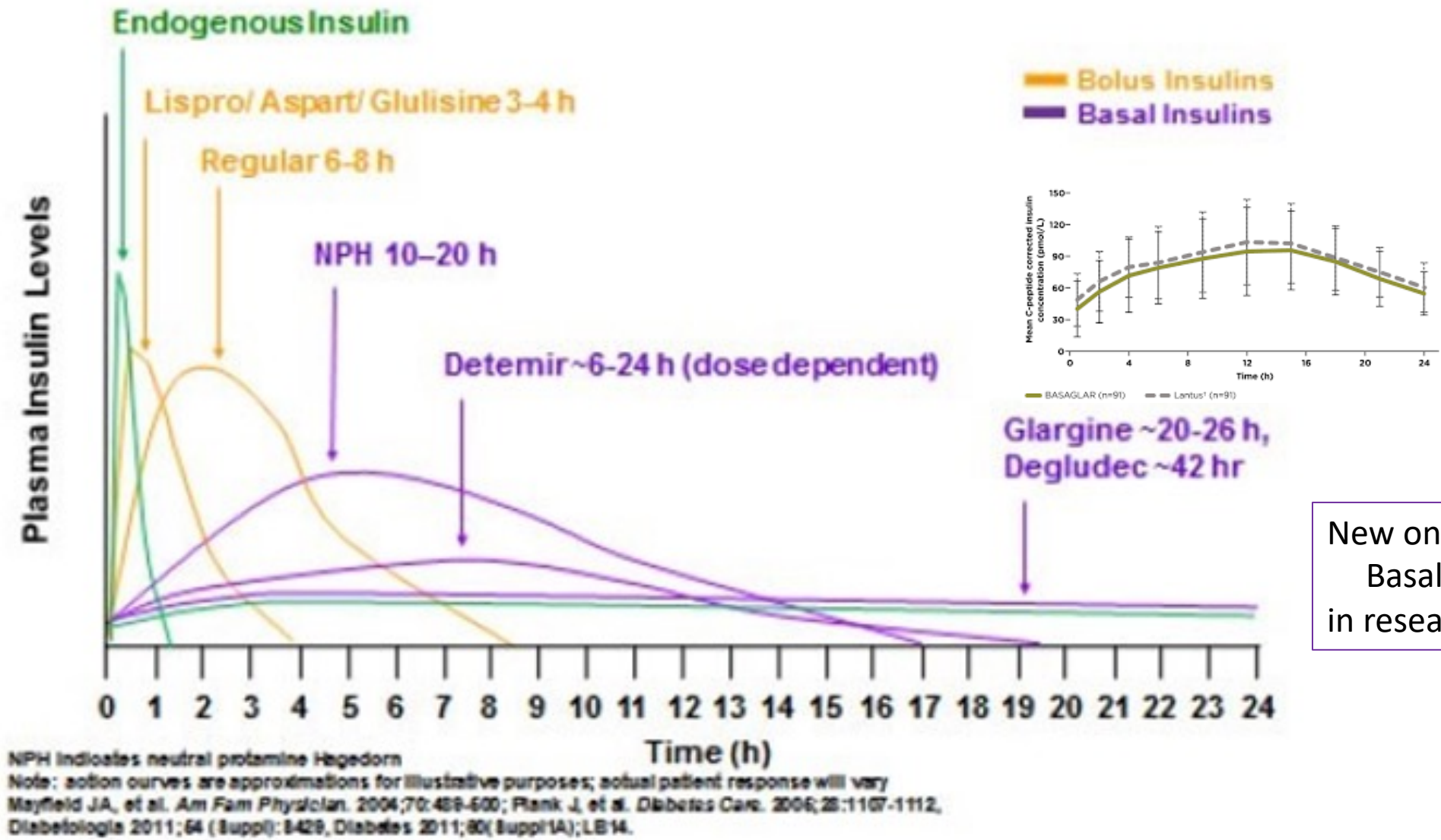
Definitions

1) **Basal Insulin:**
   - Prevents between meal and overnight hyperglycemia

2) **Bolus insulin:**
   - Limits hyperglycemia after meals



Action Profiles of Basal and Bolus Insulins



NPH indicates neutral protamine Hagedorn
Note: action curves are approximations for illustrative purposes; actual patient response will vary
Mayfield JA, et al. *Am Fam Physician*. 2004;70:489-500; Plank J, et al. *Diabetes Care*. 2006;29:1107-1112, Diabetologia 2011;54 (Suppl):S429, Diabetes 2011;60(Suppl1A);LB14.

New once-weekly
Basal insulins
in research phase

Levemir (Detemir Insulin) Discontinuation

- Novo Nordisk announced the following dates for the gradual discontinuation:
  - Mid-January 2024: Supply disruptions of Levemir FlexPen.
  - April 1, 2024: Discontinuation of Levemir FlexPen.
  - December 31, 2024: Full brand discontinuation, including Levemir vial.

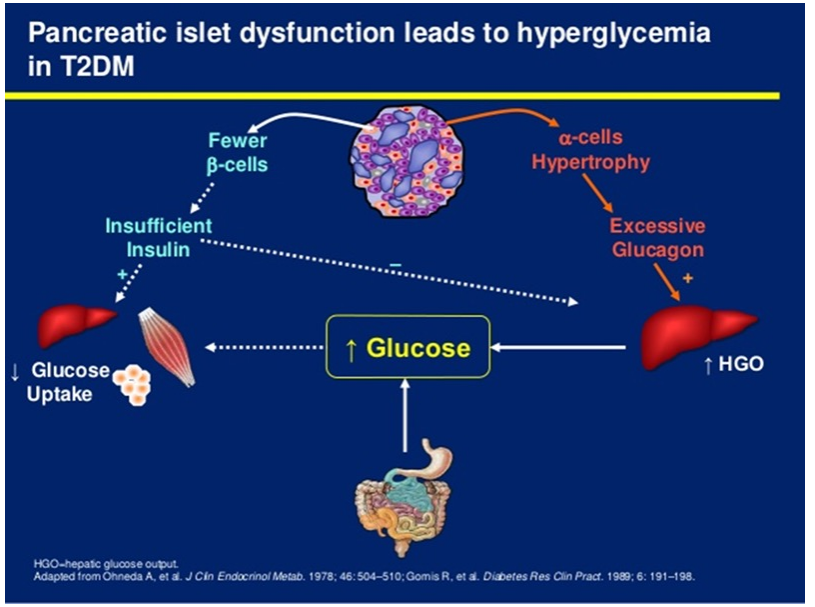
Nov 14, 2023:Novo Nordisk has announced that it is discontinuing Levemir, the company's basal insulin containing insulin detemir, which treats glycemic control in adults and children with diabetes mellitus. Novo Nordisk said it will continue providing Levemir vials and the Levemir FlexPen to wholesalers up until the discontinuation dates and *while supplies last*, but they do *anticipate supply disruptions* leading up the full product discontinuation at the end of 2024.

"Due to global manufacturing constraints, formulary losses impacting patient access, and the availability of alternative options, Novo Nordisk will be discontinuing Levemir in the US," the company announced in a statement.

[Novo Nordisk also makes Tresiba (degludec) Insulin]

Basal Insulin – Reduce Hepatic Glucose Output (HGO)

- Basal insulin alone is the **most convenient initial insulin** treatment (for T2D) and can be added to metformin and other noninsulin medications.
  - Can use human NPH insulin or a long-acting insulin analog to control fasting glucose
- The principal action of basal insulin is to ***restrain hepatic glucose production*** and *limit hyperglycemia overnight and between meals*.
  - Excess glucose from hepatic glucose output
    - Inadequate insulin
    - Excessive glucagon
    - Excessive free fatty acid (from adipose tissue & inadequate insulin)
  - 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 mainly due to too much basal glycemia



Basal Insulin – adding to other T2D meds

- ***Starting doses*** can be estimated based on
  - body weight (0.1–0.2 units/kg/day) & the degree of hyperglycemia (ADA/EASD)
    - another option is to start with 10 units
  - 0.1−0.2 units/kg/day for A1C <8.0%; 0.2−0.3 units/kg/day for A1C >8.0% (AACE/ACE)

- *Metformin* should be continued in combination with insulin therapy unless otherwise contraindicated
- *TZDs* (pioglitazone) combined with insulin increase weight gain & fluid retention – usually discontinued
- *Sulfonylureas* increase weight gain & hypoglycemia – can be gradually tapered & stopped (esp if mealtime insulin added) (may need to increase basal insulin dosage)
- *SGLT2 inhibitors*, when added to basal insulin, are associated with A1C and weight reduction, systolic blood pressure reduction, a lower incidence of hypoglycemia, less glucose variability and evidence of CV, renal & HHF benefit
- *DPP-4 inhibitors* – stop if/when add GLP1 RA

Basal Insulin – adding to other T2D meds

- Doses can be optimized with *individualized titration* over days as needed
  - Can teach patient/ care team members to adjust (titrate) dose to get BGs into the FBS target range (reduced therapeutic inertia) (*study – benefit of AI assistance*)
    - E.g., increase dose by 2 (2-4) units every 3 days until BGs are in the target range (longer duration for longer acting)
      - Titration is recommended every 2–3 days for insulin glargine 100 and detemir
        - » Even 1u /day for NPH, glargine 100 & detemir
      - Titration is recommended every 3-4 (4-7) days for insulin glargine 300 units/mL and insulin degludec 100 and 200 to minimize the risk of hypoglycemia resulting from their prolonged half-lives and a longer time to reach steady state
    - For Hypoglycemia (unexplained) reduce dose by 10-20%
  - Follow-up – phone call, patient portal, nursing visit, etc.

In two randomized, prospective studies, a simplified **patient-led insulin titration protocol** carried out every 3 days resulted in ***significantly greater A1C and FPG reductions compared to physician-led titration***, with no significant difference in the incidence of severe hypoglycemia between groups.

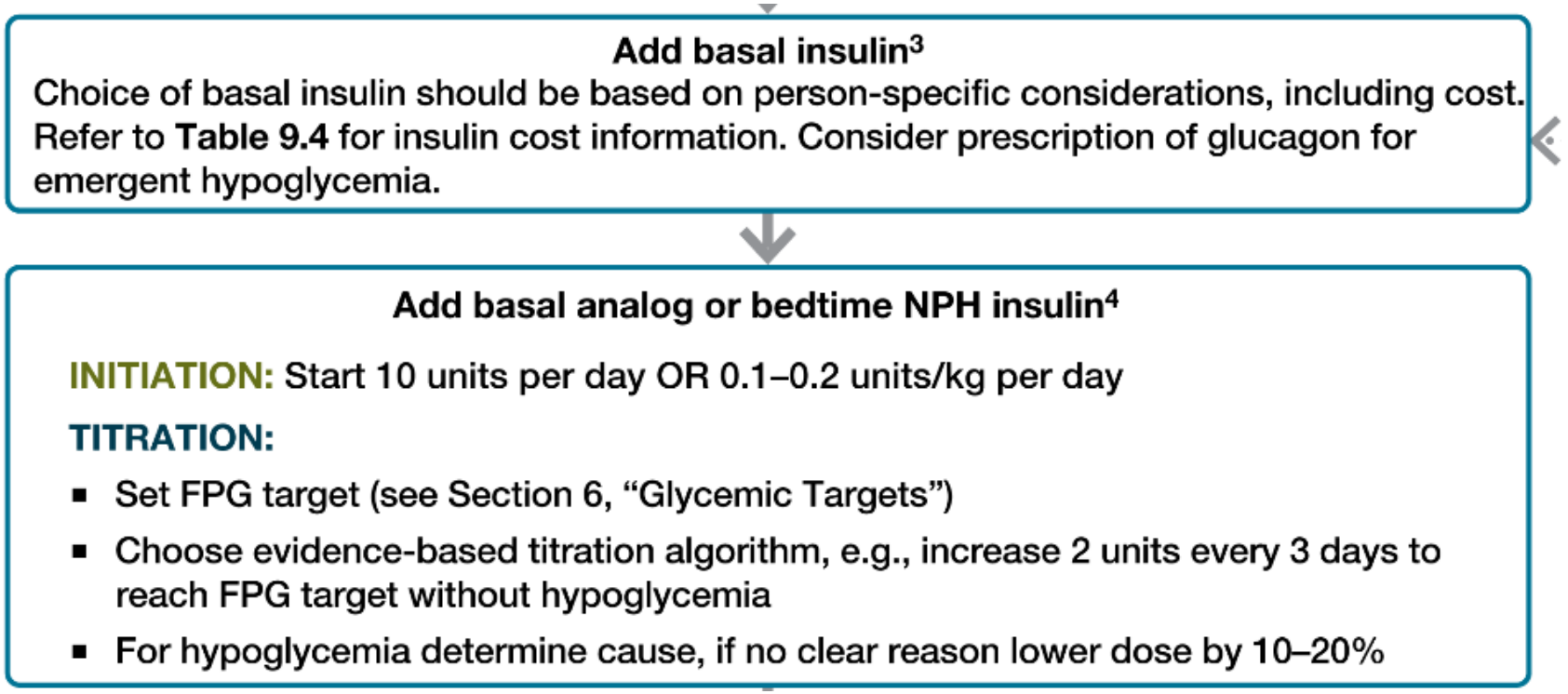
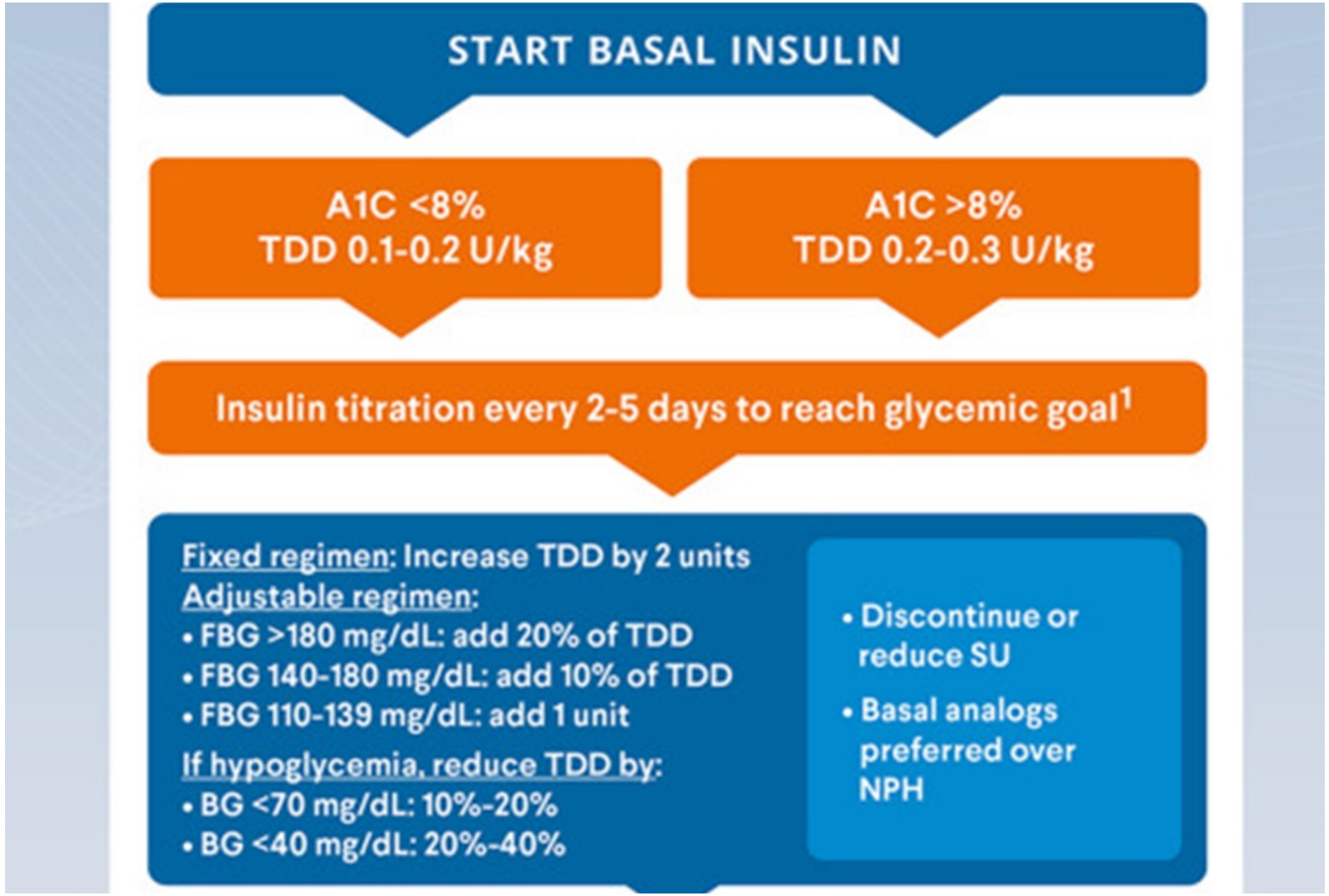


Figure Legend: Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (43).

AACE/ACE Basal Insulin Titration Algorithm



Basal Insulin – adding to other T2D meds – example

Case example
55-year-old man with A1c 8.2% despite maximum dose metformin, Semaglutide (Ozempic) & Empagliflozin (Jardiance)

- weight 240# /110 KG with FBS 140-210
- Target range for FBS 80-130
- Estimate 11 to 22 U glargine at HS (0.1-0.2u/kg)
  - opt to have him start with 16u
- The patient self-titrates dose up to 30u using algorithm
- Wakes up with BG of 66- Contacts care team
- Care team has him Reduce dose back to 27u (by 10%) & asks patient to call in BG results in 3 days (may need 28 u, etc. ….)

Research has shown that having patients follow algorithm to titrate the insulin dose reduces delay in getting BGs to target.

Recommend check-in with patient by phone, patient portal, etc. – response to initial dose, etc.

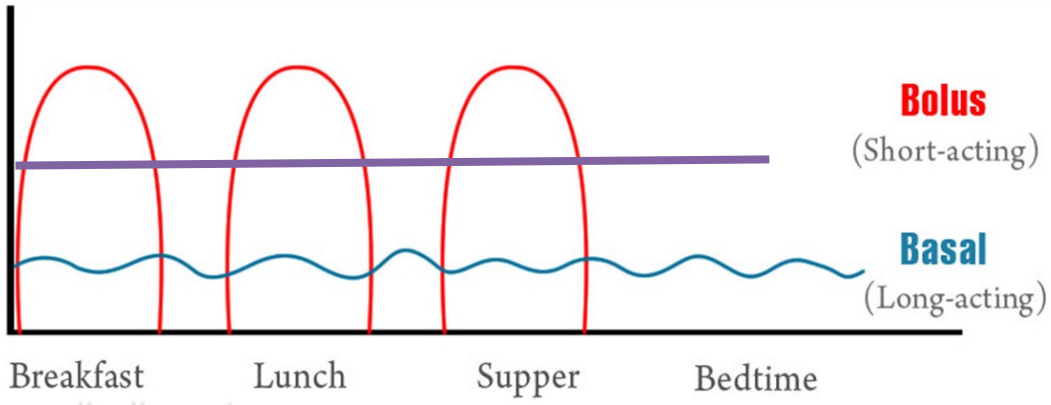
Check for explanations for Low BG (extra activity, Missed meal, etc.)

Pitfalls of Basal Insulin Therapy

- "Overbasalization" - the titration of basal insulin beyond an appropriate dose to achieve glycemic targets
  - "*Basal insulin dose is increased even further after fasting plasma glucose (FPG) targets have been achieved in an attempt to control postprandial glycemia during the day*".
  - This often leads to hypoglycemia, especially overnight.
  - Increasing doses of basal insulin are not very effective in controlling postprandial hyperglycemia, which requires *acute increases* in insulin (either endogenous or exogenous) that basal insulin cannot provide.
    - Overbasalization leads to hypoglycemia with persistent postprandial hyperglycemia in a basal-only insulin regimen

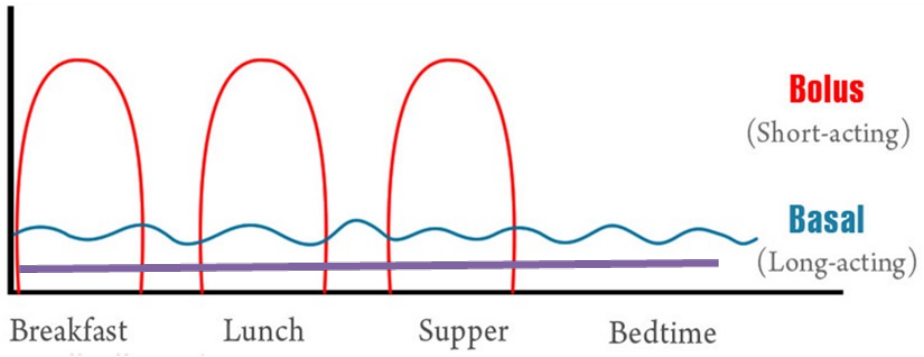
Overbasalization – ADA/EASD/AACE

- Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include:
  - basal dose greater than ~0.5 units/kg*
  - high bedtime–morning or post-preprandial glucose differential (e.g., bedtime–morning glucose differential ≥50 mg/dL)**
  - hypoglycemia (aware or unaware)
  - “feeding the insulin”
  - high variability



Pitfalls of Basal Insulin Therapy

- Not titrating Basal insulin dose high enough
  - Optimizing basal insulin can achieve glycemic targets in many patients
  - The appropriate dose is one that allows patients to reach FPG targets
    - Many people with type 2 diabetes will require basal insulin doses* >0.5 units/kg to achieve FPG targets – (often 0.5-1.0 units/kg)
      - *"Basal insulin dose should not be limited by an arbitrary maximum dose."*
  - The most important determinant of *postprandial* glucose concentrations is the *preprandial* value.
    - If patients do not receive appropriate amounts of basal insulin:
      - They will *unnecessarily* be prescribed preprandial insulin with its increased burden & complexity.
      - Preprandial insulin will have relatively little effect on meeting FPG targets. These patients will need higher preprandial insulin doses because of their fasting hyperglycemia.



**BeAM Differential (Bedtime BG – FBS)

- The BeAM differential is the difference between bedtime and pre-breakfast blood glucose values.
  - can be calculated by subtracting the morning blood glucose value from the previous night's bedtime blood glucose value.
  - The BeAM is clinically relevant, allowing clinicians to assess when it is appropriate to initiate prandial therapy (if due to high BG at bedtime vs low FBS)
    - E.g., Bedtime BG 260 – FBS 135 = 125 (needs prandial therapy vs more basal insulin) vs
    - Bedtime BG 130 – FBS 60 = 70 (overbasalization - needs less Basal Insulin)
- A BeAM value ≥50 mg/dL (high BG at Bedtime) in patients with type 2 diabetes using basal insulin can be indicative of need for attention to postprandial glycemia:
  - Meal CHO content &/or quantity
  - After meal walking or other activity
  - Pre-evening meal bolus insulin

Summary/Key Points

- If possible, add GLP1 RA medication before going to Basal Insulin
  - or add GLP1 RA med if already on Basal Insulin
  - increased efficacy with reduced weight gain, hypoglycemia, ASCVD risk
- Many patients with T2D will progress to requiring Insulin therapy –
  - avoid using insulin as a threat – explain natural progression of T2D
- Basal insulin can be added to non-insulin diabetes medications
  - consider discontinuation of TZD and/or Sulfonylurea meds to reduce side effects
- Patients need to understand proper insulin injection techniques
  - need subsequent follow-up on any issues with technique & routine injection site inspection.
- Starting with 10-unit dose is common –
  - can start with 0.1-0.3 units/kg dose based on glycemia
- It is important to optimize dose of basal insulin by titrating to FBS target
  - titration by patients using an algorithm can be as or more effective than clinician titration
- It is important to avoid excessive doses of basal insulin
  - watch for signals of overbasalization

Post-Question - which two options are correct?

- Basal Insulin therapy
  A. Should cover both fasting and mealtime insulin requirements
  B. Should not exceed a dosage of 0.2 units/kg
  C. Can be added to non-insulin diabetes medications
  D. Can effectively be titrated by patients using an algorithm to guide

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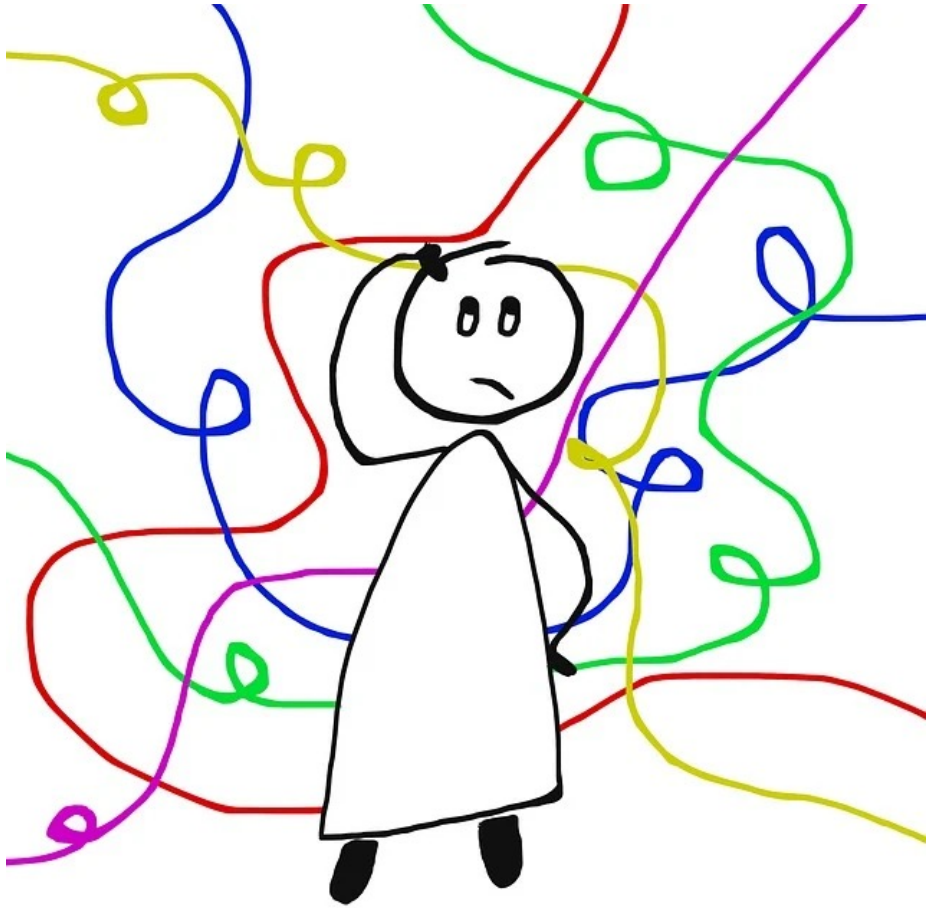
  - A & D
  - B & C
  - B & D
  - C & D

Questions, Comments, Clarifications, etc.



Once Weekly Basal Insulins (anticipate 2024-2025)

- Insulin icodec – Novo Nordisk – ONWARDS trials
  - T1/2 = 8 days
  - very concentrated 700u/ml so 350u/wk = same volume as 50u U100
  - Proposed dose titration app
  - Non-inferior to superior A1c reduction (vs daily glargine) for T2D
  - Slightly more frequent hypoglycemia for T2D
  - Good adherence and patient satisfaction scores
- Efsitora alfa insulin (Insulin BIF) – Lilly – QUINT trials
  - T1/2 = 17 days
  - Non-inferior for A1c reduction vs daily glargine for T2D
  - Same or slightly more hypoglycemia for T2D
- More research needed on exercise, NPO, illness, surgery/procedures
- Not as well suited for T1D

Some References

- Ann Med. 2021; 53(1): 998–1009. Practical guidance on the initiation, titration, and switching of basal insulins: a narrative review for primary care
  Roopa Mehta, Ronald Goldenberg, Daniel Katselnik, and Louis Kuritzky
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8231382/

- **https://diabetesjournals.org/clinical/article/37/4/368/32741/Practical-Guidance-on-Effective-Basal-Insulin**

- https://diabetesjournals.org/clinical/article/40/3/354/144838/Clinical-Overbasalization-Revisited

- https://diabetesjournals.org/clinical/article/39/4/411/137699/The-Clinical-Definition-of-Overbasalization

- **https://diabetesjournals.org/care/issue/46/Supplement_1**

- **https://www.endocrinepractice.org/article/S1530-891X(23)00034-4/fulltext**

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7185643/
- https://acpinternist.org/archives/2022/05/basal-insulin-for-beginners.htm

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**