ECHO Diabetes

Mealtime Insulin Therapy

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February 8, 2024

Question from January Tribal Diabetes ECHO

- Question: "*When is it okay to continue Sulfonylureas with insulin?*"
  - In general, some people will continue sulfonylurea meds when ***basal insulin*** added, and others will taper and stop when basal insulin added
    - For years BIDS (adding Bedtime [NPH] Insulin to Daytime Sulfonylureas) was a way to intensify treatment for people with T2D
      - Under-resourced communities still rely on SU meds and NPH insulin
    - Consider Benefit vs Risk (complexity, hypoglycemia, irregular/unpredictable meals or activity, etc.)
    - I also think with GLP1 RA (glucose-dependent insulin release), good to taper off SU
      - Risk of hypoglycemia
  - It is generally a universal recommendation to stop SU when start adding ***mealtime*** boluses.
  - From a practical standpoint, I think it is *easier* to taper off the SU meds while still only on basal insulin – this allows you to readjust the basal insulin dose as needed
    - some people will need a significant increase (e.g., increase of 20u of basal) whereas in others the SU was likely no longer doing much and not much more insulin will be needed
  - then add the mealtime insulin --- however,
    - You c*an* wait until you have added mealtime insulin to stop or taper off the SU
    - If a patient is still on SU meds while taking basal-bolus insulin, would taper off the SU
      - There is "therapeutic inertia" for *deprescribing* meds as well as for advancing meds

Indian J Endocrinol Metab. 2018 Jan-Feb; 22(1): 132–157.

Consensus Recommendations on Sulfonylurea and Sulfonylurea Combinations in the Management of Type 2 Diabetes Mellitus – International Task Force

- The current guidelines, developed by experts from **Africa, Asia, and the Middle East**, promote the safe and smart use of SUs in combination with other glucose-lowering drugs.
- SU and insulin combination:
  - C1. Modern SUs may be continued, with appropriate precaution, when basal insulin is initiated (Grade A; EL1)
  - C2. Modern SUs may be continued, in the antipodal meal, if premixed insulin is initiated once daily (Grade A; EL1)
  - C3. Short-acting SUs, or glinides, may be continued or added to the third meal, with appropriate glucose monitoring if premixed insulin is initiated twice daily (Grade B; EL 1).

Pre-Question - which two options are correct?

- Meal-time (Prandial) Insulin therapy
  A. Should always be divided equally between 3 meals per day
  B. Is a critical component of insulin treatment for type 1 diabetes
  C. For people with type 2 diabetes, can be added to cover one meal only
  D. Should *always* be administered 15-20 minutes before first bite of meal

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

ADA 2024 Standards of Care

Pharmacologic Therapy for Adults with *Type 1 Diabetes**

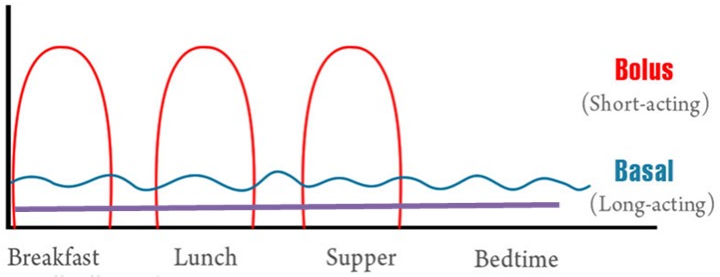
Recommendations

- 9.1 Treat most adults with type 1 diabetes with continuous subcutaneous insulin infusion or ***multiple daily doses of prandial (injected or inhaled) and basal insulin***. A
- 9.2 For most adults with type 1 diabetes, **insulin analogs** (or inhaled insulin) are preferred over injectable human insulins to minimize hypoglycemia risk. A
- 9.3 *Early use* of **continuous glucose monitoring** is recommended for adults with type 1 diabetes to improve glycemic outcomes and quality of life and minimize hypoglycemia. B
- 9.4 **Automated insulin delivery systems** should be considered for all adults with type 1 diabetes. A
- 9.5 To improve glycemic outcomes and quality of life and minimize hypoglycemia risk, most adults with type 1 diabetes should receive education on how to ***match mealtime insulin doses to carbohydrate intake*** and, additionally, to fat and protein intake.
  - They should also be ***taught how to modify the insulin dose*** (correction dose) based on concurrent glycemia, glycemic trends (if available), sick-day management, and anticipated physical activity. B

Can utilize the formulas for ICR & Correction factor that we will be discussing

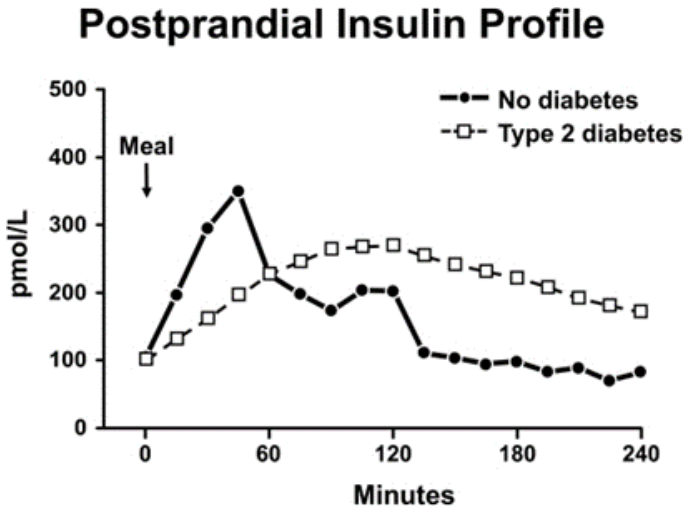
For People with Type 2 Diabetes

- *"The **first critical step is to optimize basal insulin** dosing to reach a fasting glucose of ~6.7 mmol/l (120mg/dl); this allows **~40%** of patients with baseline HbA1c >75 mmol/mol (9%) to be controlled with only one basal insulin injection per day."* *Diabet Med. 2017 Sep;*
  - And this is without treatment with GLP1RA or SGLT2i
- *"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.
      - These patients will need higher preprandial insulin doses because of their fasting hyperglycemia.
    - Preprandial insulin will have relatively little effect on meeting FPG targets.
      - Exception might be high BG at bedtime



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
- 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)
  - Glinides (Starlix, Prandin)
  - 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 (endogenous)
      - inhibit glucagon secretion (reduce glucose from liver)
      - slow gastric emptying (reduce pp spike)
      - increase satiety
  - Amylin receptor agonist (Symlin (pramlintide))
  - **SGLT2i** helps reduce height of postprandial rise

Prandial (mealtime) Coverage

- Many individuals with ***type 2 diabetes*** require **mealtime insulin**, in addition to basal insulin, to reach glycemic targets.
  - If the individual is not already being treated with a GLP-1 RA, a **GLP-1 RA or Dual agent should be considered prior to prandial insulin** to
    - further address ***prandial control*** (addresses multiple components)
    - ***minimize the risks of hypoglycemia and weight gain*** associated with insulin therapy.
    - ***minimize burden/complexity & fewer injections***
      - "The use of prandial insulin requires extensive patient education on topics such as meal timing and the relationship between insulin doses and carbohydrate intake and also requires increased glucose monitoring and additional injection burden" https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7364465

Adding Tirzepatide to Basal Insulin Cuts HbA1c in Poorly Controlled T2D — Results with the GIP/GLP-1 receptor agonist were statistically superior to added insulin lispro

European Association for the Study of Diabetes (EASD) meeting

- In patients on an insulin glargine regimen, the estimated mean change from baseline in HbA1c at week 52 was
  - -2.1% for those assigned to one of three different doses of **tirzepatide**
    - 68% achieved A1c <7% (resulted in Mean HbA1c of 6.7%)
    - Mean weight change - loss of 9 kg (19.9 lb)
    - Hypoglycemia/severe hypoglycemia – 0.4 events/patient-year
    - Ave 46u/d Insulin → average 13u/d Insulin [20% able to dc Insulin]
  - -1.1% for those randomized to **insulin lispro**
    - 36% achieved A1c <7% (resultant Mean HbA1c 7.7%)
    - Mean weight change – gain of 3.2kg (7.1 lb)
    - Hypoglycemia/severe hypoglycemia – 4.4 events/patient-year
    - Ave 46u/d Insulin → 62u/d insulin lispro + 42u/d insulin glargine (104u/d)

Baseline A1c 8.8%
Metformin + glargine

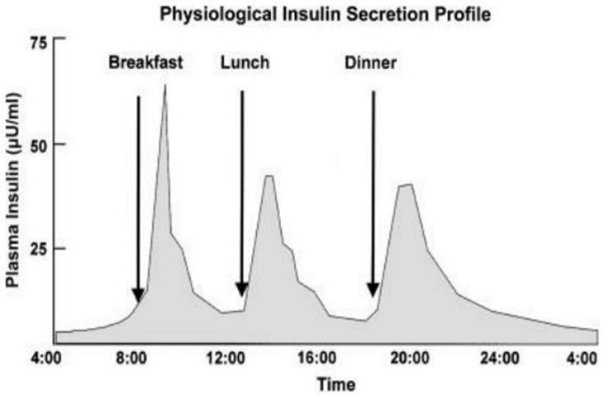
Insulins

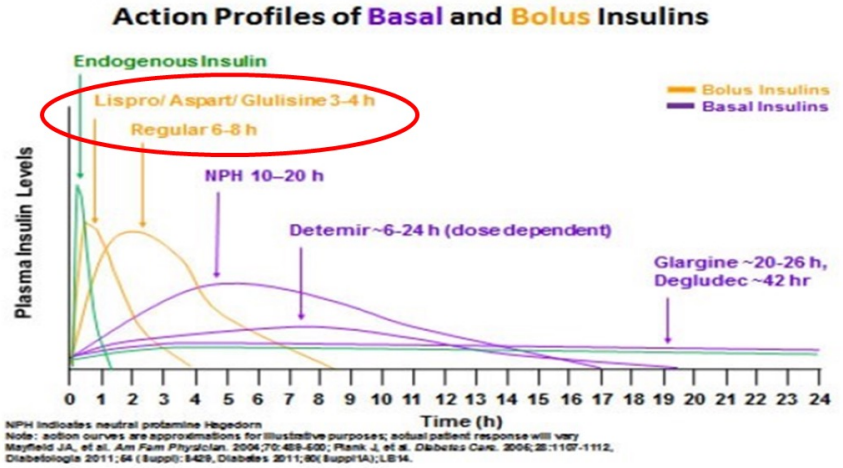
- Dosing to try to replace /mimic the natural secretion of insulin
  - **Basal insulin** is designed to *suppress hepatic glucose production and improve basal (fasting) hyperglycemia*
  - **Bolus (mealtime, prandial) Insulin** –as rapid-acting insulin - limits hyperglycemia after *meals(covers food carbs)* – 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





Prandial Insulin for T2D
2024 ADA Standards of Care

- **Bolus (mealtime, prandial) Insulin** – limits hyperglycemia after meals(*covers food carbs*) – should hold if NPO or not eating
- For individuals who advance to prandial insulin, ***one*** prandial insulin dose of ***4 units (5u) or 10% of the amount of basal insulin*** at the ***largest meal*** or the ***meal with the greatest postprandial excursion*** is a safe estimate for *initiating* therapy.
  - With ***significant additions to the prandial insulin dose***, particularly with the *evening meal*, consideration should be given to **decreasing basal insulin** (begin by decreasing by 4u or 10% of basal dose)
  - Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in type 2 diabetes have *not reported important differences* in A1C or hypoglycemia.
  - *Titration* can be based on home self-monitored blood glucose or CGM.
  - The prandial insulin plan can then be *intensified based on individual needs*.

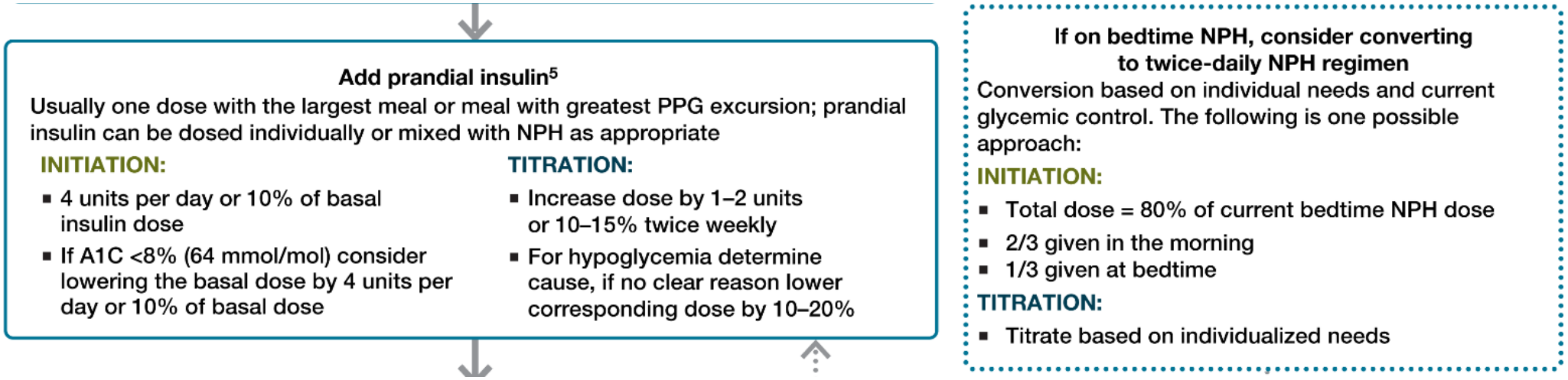


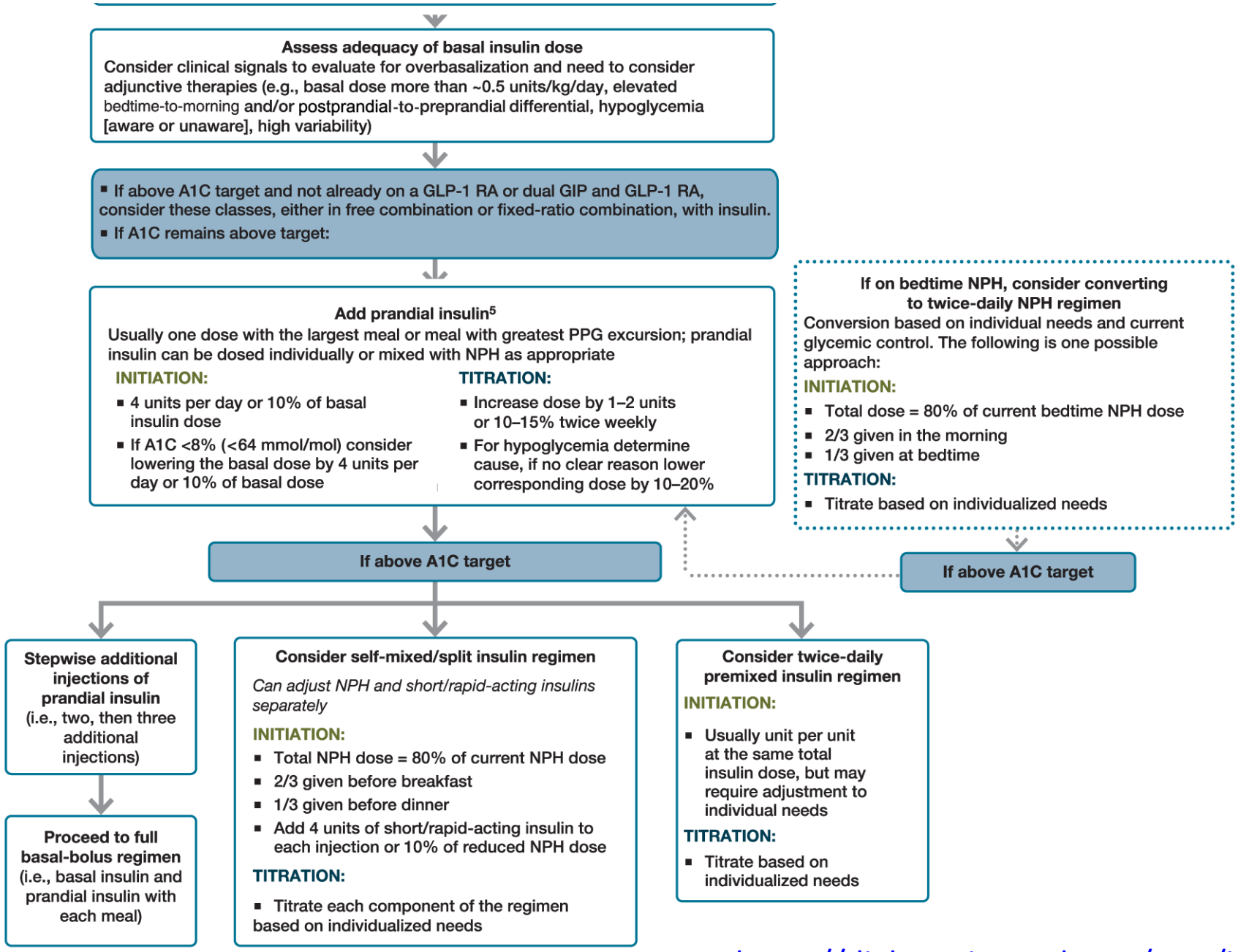
Figure Legend: Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (43).

Treatment Intensification for Type 2 Diabetes

- Can add prandial insulin to basal insulin in a ***stepwise*** manner, usually by *starting with a patient's largest meal of the day (or meal with largest pp rise)*
  - The term **'basal-plus therapy'** describes a regimen of one basal insulin injection and the *stepwise addition* of one to three preprandial short-acting insulin injections per day
    - Over 60% need 2 or less prandial injections,
      - Patients not on GLP1 RA med (or SGLT2i)
    - First meal of day often highest – can be more convenient for patient (give injection at home)
  - **Full basal-bolus therapy** = basal insulin plus three short-acting insulin injections per day

- For some patients - Premixed Insulin
  - Premixed insulin (e.g., NPH/regular or analog 70/30) is administered either before the largest meal of the day or, more commonly, as two injections per day before breakfast and dinner
    - Less costly
    - Patients must eat regular meals - higher risk of hypoglycemia
    - Less flexibility with dosing

Choice is patient specific (accounting for eating habits, preferences, convenience, and cost)



https://diabetesjournals.org/care/issue/47/Supplement_1

Adjusting prandial (rapid-acting) insulin – the Insulin-to-Carb Ratio (ICR)

- The **insulin-to-carb ratio (ICR)** is a way to get closer to the right amount of insulin for the carbohydrates in a meal (or snack) for any individual patient
  - More critical in patients with less endogenous insulin (e.g., T1D, T3cD)
  - It means the patient will take ***1 unit of insulin for a certain amount of carbohydrate***
    - This is usually expressed as "1 unit of insulin covers XX grams of carbs" or 1:XX
  - The ICR depends on how sensitive or resistant the patient is to insulin –
    - The more sensitive they are to insulin the more grams of carb 1 unit of insulin will cover
    - The goal is to limit postprandial BG rise to no more than 50 points or BG of 180 (200)
      - Prandial insulin doses often *vary* meal to meal
      - Insulin sensitivity can vary according to the *time of day*, from person to person, and is affected by *physical activity and stress*

The **ICR** can be **calculated using the 500 rule (500/TDI)** or can be **based on weight**

Calculating Insulin Dose :: Diabetes Education Online (ucsf.edu)

Calculating TDI & ICR

- **Total Daily Insulin (TDI)** Requirement (in units of insulin) =

  Weight in Pounds ÷ 4 *or* **Weight in Kilograms x 0.55**

  - Example 1: Body weight in pounds with weight of 160 lbs.
    - TOTAL DAILY INSULIN DOSE = 160 lb ÷ 4 = 40 units of insulin/day
  - Example 2: Body weight in kilograms with weight of 70Kg.
    - TOTAL DAILY INSULIN DOSE = 0.55 x 70 Kg = 38.5 units of insulin/day
  - If very resistant to insulin, may require a higher dose – If very sensitive to insulin, may require a lower insulin dose.

- **Insulin to Carb Ratio (ICR)** ("carbohydrate coverage ratio"):
- This can be calculated using the Rule of "500" (Carbohydrate Bolus Calculation)
  - **500 ÷ Total Daily Insulin Dose** = 1 unit insulin covers so many grams of carbohydrate
  - Example: if TDI = 40 units then ICR = 500 ÷ TDI (40 units) = 1unit insulin/ 12 g CHO (1:12)

Estimating an Insulin to Carb Ratio

Based on Total Daily Dose

- 8—11 units 1:50
- 12—14 units 1:40
- 15—18 units 1:30
- 19—21 units 1:25
- 22—27 units 1:20
- 28—35 units 1:15
- 36—45 units 1:12
- 46—55 units 1:10
- 56—65 units 1:8
- 66—80 units 1:6
- 81—120 units 1:5
- >120 units 1:4

Based on the 500 Rule

Based on Body Weight

- <60 lb. 1:30
- 60—80 lb. 1:25
- 81—100 lb. 1:20
- 101—120 lb. 1:18
- 121—140 lb. 1:15
- 141—170 lb. 1:12
- 171—200 lb. 1:10
- 201—230 lb. 1:8
- 231—270 lb. 1:6
- >270 lb. 1:5

Fails to consider body composition & insulin resistance or other meds

With patient taking GLP1 RA would go with a lower (weaker) ICR and titrate as needed – e.g., 1:10 instead of 1:6

Covering Meal Carbs

- Even if eating **fixed amounts of carb** at a meal – you need to base the prescribed **fixed meal insulin dose** on an ICR that is appropriate to the patient
  - No need for the patient to do carb counting but having an idea of the correct ICR to base meal dose on for any given patient can help improve the response to insulin therapy

- E.g. - If the estimated insulin-to-carb ratio (ICR) is 1 unit of insulin for every 10 grams of carbohydrate (written 1:10) - will take 1 unit of insulin for every 10 grams of carbohydrate eaten – if eat 30 grams will take 3units; if eat 60 grams will take 6 units vs
  - If ICR is 1:15 – will take 1 unit for every 15 grams of carb eaten
    - If eat 30 grams will take 2units; if eat 60 grams of Carb will take 4 units
- For fixed meal doses – e.g., patient eats ~45 grams of carb each meal and weighs ~120# with estimated ICR of 1:15 - will take 3 units with each meal [if 280# -ICR 1:5 – 9u/45g]
  - Or if patient eats 30g Carb with Breakfast, 45 grams with Lunch & 60 grams with Dinner – would take 2u with B, 3u with L and 4 units with D [6u-9u-12u if ICR 1:5]
- For varying meal amounts - you can get an estimate of what a “smaller”, “usual” or “larger” meal is for that patient (e.g., 30 grams CHO, 60 grams CHO, 90 grams CHO)
  - Utilize the patient’s ICR to estimate dose for each (e.g., 1:10)
  - Give 3 units for a small meal, 6 for a medium meal and 9 for a large meal
  - Can add *correction insulin* if pre-meal BG is above target

Adding prandial (rapid-acting) insulin – usually need both meal coverage & correction insulin

- **Bolus (mealtime, prandial) Insulin** (“carbohydrate coverage”)
  - as rapid-acting insulin - limits hyperglycemia after meals(covers food carbs)
  - should ***hold if NPO or not eating***

Correction Insulin (“High Blood Sugar Correction Dose”) = ***extra rapid-acting insulin given for high blood glucose*** to decrease BG levels to ***target range*** – based on patient’s “sensitivity or correction factor” -

- The dose of “correction insulin” is the amount of insulin needed to lower the BG from its current level to the target level over the time of insulin action – depends on how sensitive the patient is to insulin

Correction Insulin –March 2024 Tribal Diabetes ECHO

Titrating Mealtime Insulin dose

- Can monitor glucose
  - before and 2 hours after meal (after beginning of meal)
    - Goal <50 mg/dl above premeal or < 180 (200)
  - ***before next meal or bedtime*** if mealtime insulin is dosed at evening meal (T2D)
    - Goal = in target range 80-130 before next meal or 125-150 at bedtime
  - CGM data

- Adjust mealtime insulin by
  - 1-2units or 10% of dose – increase if above target/reduce if below target
  - 1 gram of carb in ICR – if glucose above goal → reduce grams of CHO/ if low, increase
    - E.g., ICR from 1:10 to 1:9 for glucose above goal
    - works well if pump but can generate math challenges & partial units that are difficult for injections

- If opt to start mealtime insulin with *all* meals – each meal may require different adjustments –
  - Recommend adjust one meal at a time
  - Immediate attention if glucose low after a mealtime dose (check for missed meal, increased activity) [for 2h ppg <180 may end up with low BG at 3-4h – may need to adjust *timing* of bolus]

When Mealtime Insulin is Taken:	When to Test Blood Sugar:	If the Blood Sugar Results Are: Then You Should:	When:
At Lunch	Before Dinner	**Under 80** Subtract 2 Units from Mealtime Dose **80 – 130** Do Not Adjust Mealtime Insulin Dose **Over 130** Add 2 Units to Mealtime Dose	Before Lunch the Next Day
At Dinner	Before Bed	**Under 125** Subtract 2 Units from Mealtime Dose **125 – 150** Do Not Adjust Mealtime Insulin Dose **Over 150** Add 2 Units to Mealtime Dose	Before Dinner the Next Day

Example of Algorithm:

- Start with 4 units before largest meal
- Increase or decrease dose before that meal based on BG before next meal or bedtime
- As get closer to target can adjust by 1 unit

https://www.endocrine.org/improving-practice/aid/mealtime

Timing of Mealtime Prandial Insulin

- Multiple studies and clinical practice guidelines have suggested that the optimal time to administer a ***rapid-acting insulin analog*** is 15–20 minutes before the start of a meal.
  - Premeal bolusing of rapid-acting insulin analogs 15-20 minutes before mealtime resulted in lower PPG excursions and more time spent in the euglycemic range without increased risk of hypoglycemia.
  - Taking **insulin after meals** increases the risk of *early postprandial hyperglycemia* followed by *delayed hypoglycemia*.
- ***Regular insulin*** may be used instead and is given 30 to 45 minutes before meals.
- Additional need to *individualize*:
  - Postprandial glucose excursions are best controlled by a well-timed injection of prandial insulin. The ***optimal time to administer prandial insulin varies***, based on:
    - the pharmacokinetics of the formulation (regular, RAA, inhaled)
    - the premeal blood glucose level
    - carbohydrate consumption
    - rate of gastric emptying (rapid gastric emptying – earlier & higher pp spike)

Gastric Emptying in Diabetes

- Abnormally *rapid* gastric (stomach) emptying has been reported in [many] patients with diabetes
  - This can contribute to a postprandial BG spike
  - Slowing down gastric emptying can reduce this spike (therapeutic effect)
- Glycemic values impact rate of stomach emptying:
  - Hyperglycemia delays stomach emptying, so the nutrients are propelled more slowly for absorption at the intestinal level
  - Hypoglycemia accelerates gastric emptying and increases the nutrient absorption speed, thus allowing for a prompter correction of glycemic levels
- GLP-1 induces an inhibitory feedback effect, delaying gastric emptying – [GLP1 RA effect can help reduce pp BG spike]

Timing of Mealtime Prandial Insulin

- People with **gastroparesis** have a slower postmeal rise in blood glucose levels resulting from delayed gastric emptying, *administering prandial insulin* ***after meals*** instead of before can better match the timing of the postprandial glucose excursion.
- GLP1 RA meds delay gastric emptying – should the timing of prandial insulin be delayed if the patient is treated with a GLP1 RA agent?
  - Studies show ~30% reduction in dose needed for mealtime insulin with GLP1 RA med
  - Should timing be adjusted as well?

- Instructions for using Symlin (pramlintide -synthetic amylin) with insulin: *"Take Symlin 5-10 minutes before your meal* and *take your insulin 5-10 minutes after your meal."*
  - Reduced rate of gastric emptying
  - Reduced intake (enhanced satiety)

Summary – Key Points

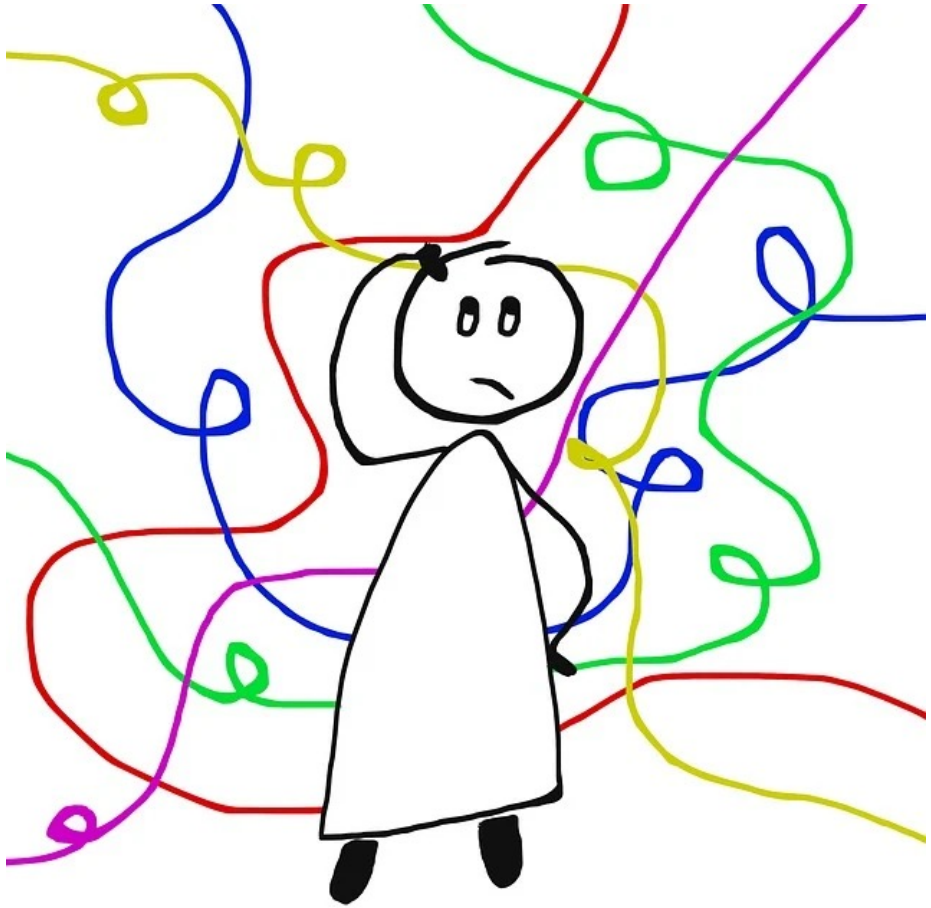
- Mealtime insulin is a critical component of insulin therapy for T1D & other insulin deficient states
- The pathophysiology of postprandial hyperglycemia is complex
  - For T2D - GLP1 RA therapy (&/or Amylin replacement therapy) addresses many of these issues and is preferred over mealtime insulin when possible
- For T2D -Mealtime insulin can be initiated in a stepwise fashion, starting with one meal per day
  - Usually, the largest meal or meal with the highest pp glucose excursion (often breakfast)
- Even for people with T2D, estimating & utilizing an Insulin-to-Carbohydrate Ratio (ICR) can improve the response to mealtime insulin therapy
  - Use it to help determine more appropriate dose, patient does not need to do carb counting
- Traditionally, timing of mealtime insulin administration prior to meals provides better glycemia than with or after meals
  - Do we need to consider delaying the administration of mealtime insulin with therapeutic delays to gastric emptying rates?

Post-Question - which two options are correct?

- Meal-time (Prandial) Insulin therapy
  A. Should always be divided equally between 3 meals per day
  B. Is a critical component of insulin treatment for type 1 diabetes
  C. For people with type 2 diabetes, can be added to cover one meal at a time
  D. Should always be administered 15-20 minutes before first bite of meal

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

Questions, Comments, Clarifications, etc.



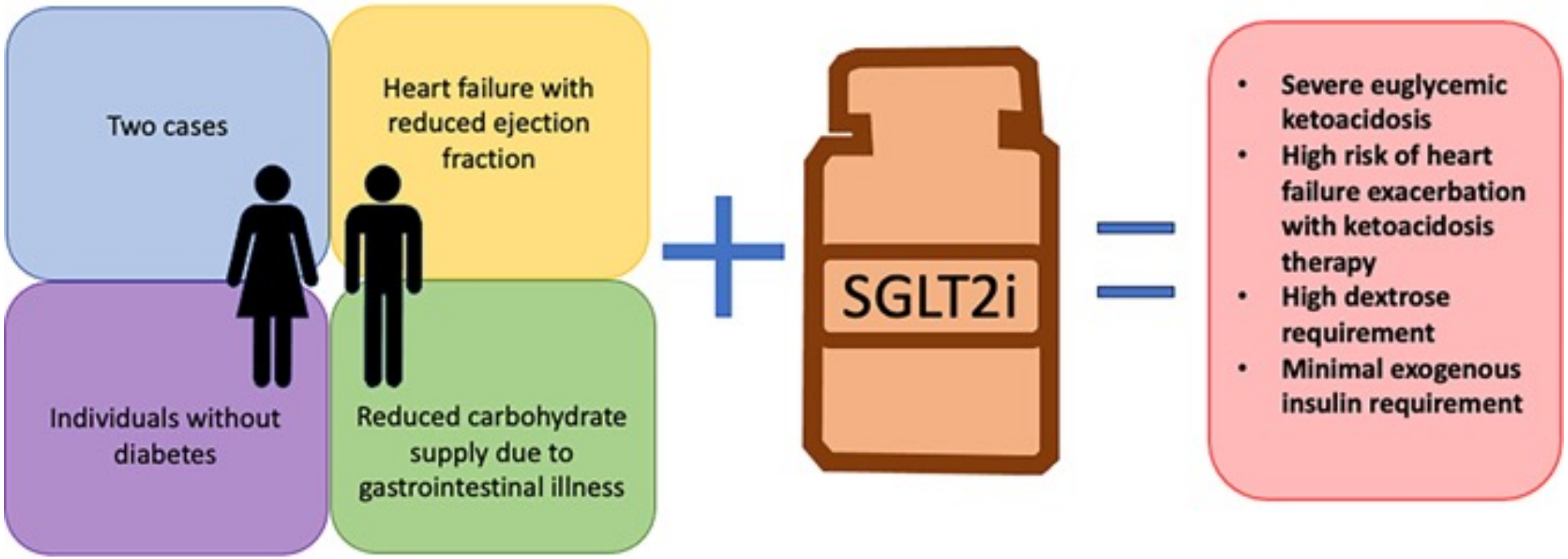
Extra Slides

Trial Data vs Real World Experience

- Metformin & GLP1 RA induced GI symptoms/ side effects
  - Real World experience – reducing metformin dose can reduce GI side effects
  - Trial data – no impact of metformin on GLP1 RA related GI side effects
    - Diabetes Care 2024; 47: 280-284

- Euglycemic Keto-Acidosis in people *without* Diabetes treated with SGLT2i medications (for HF and/or CKD)
  - Trial data – no Keto-Acidosis seen in people without diabetes
  - Real World experience Diabetes Care. 2023;47(1):140-143. doi:10.2337/dc23-1163
  - **Euglycemic Ketoacidosis in Two Patients Without Diabetes After Introduction of Sodium–Glucose Cotransporter 2 Inhibitor for Heart Failure With Reduced Ejection Fraction** Euglycemic Ketoacidosis in Two Patients Without Diabetes After Introduction of Sodium–Glucose Cotransporter 2 Inhibitor for Heart Failure With Reduced Ejection Fraction | Diabetes Care | American Diabetes Association (diabetesjournals.org)

Two Case Reports of Euglycemic Ketoacidosis in Individuals Without Diabetes Treated With SGLT2i For Heart Failure



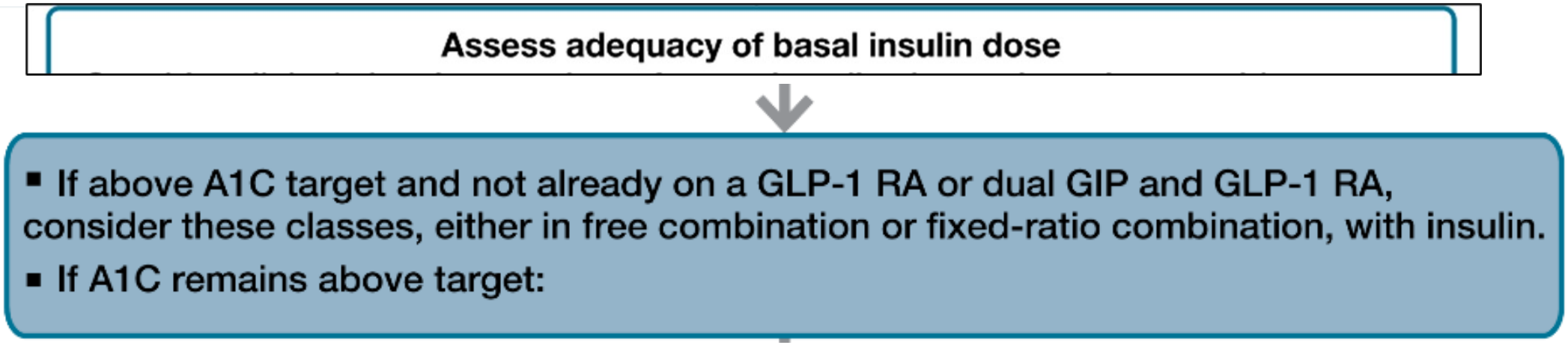
Reference:

- https://diabetesjournals.org/care/issue/47/Supplement_1
  - 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2024 | Diabetes Care | American Diabetes Association (diabetesjournals.org)

- https://www.aafp.org/pubs/afp/issues/2011/0715/p183.html#afp20110715p183-b29

American Diabetes Association

https://diabetesjournals.org/care/issue/47/Supplement_1



A9.24 **If insulin is used, combination therapy with a GLP-1 RA, including a dual GIP and GLP-1 RA, is recommended** for greater glycemic effectiveness as well as beneficial effects on weight and hypoglycemia risk for adults with type 2 diabetes. Insulin dosing should be reassessed upon addition or dose escalation of a GLP-1 RA or dual GIP and GLP-1 RA. ADA/EASD

AACE/ACE: For most persons who need **intensification of glycemic control and who are already undergoing 3 to 4 oral therapies**, a GLP-1 RA or GIP/GLP-1 RA should be the initial choice, if not already in use https://www.endocrinepractice.org/article/S1530-891X(23)00034-4/fulltext

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).

ADA 2024 Standards of Care

- 9.23 In adults with type 2 diabetes, a GLP-1 RA, including a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, is preferred to insulin (Fig. 9.4). A

- 9.24 If insulin is used, combination therapy with a GLP-1 RA, including a dual GIP and GLP-1 RA, is recommended for greater glycemic effectiveness as well as beneficial effects on weight and hypoglycemia risk for adults with type 2 diabetes. Insulin dosing should be reassessed upon addition or dose escalation of a GLP-1 RA or dual GIP and GLP-1 RA. A

- https://diabetesjournals.org/care/issue/47/Supplement_1

Adding Tirzepatide to Basal Insulin Cuts HbA1c in Poorly Controlled T2D — Results with the GIP/GLP-1 receptor agonist were statistically superior to added insulin lispro

European Association for the Study of Diabetes (EASD) meeting

- To be included, all participants had to have their **type 2 diabetes inadequately controlled with once- or twice-daily basal insulin**, including insulin NPH, insulin glargine, insulin detemir, or insulin degludec, with a maximum combination of two oral antidiabetics including metformin, sulfonylurea, or a DPP-4 inhibitor. ***Oral agents except for metformin were discontinued at baseline***
  - Mean baseline A1c 8.8%
  - Patients with type 1 diabetes, an eGFR under 30 mL/min/ 1.73 m2 or under 45 mL/min/1.73 m2 for those on metformin, and ***proliferative diabetic retinopathy, diabetic macular edema, or nonproliferative diabetic retinopathy requiring immediate treatment were excluded***.
- After randomization, 708 patients received prandial **thrice-daily insulin lispro** and 243, 238, and 236 patients received **5, 10, and 15 mg once-weekly tirzepatide injection**, respectively.
- There was a target fasting glucose of 100-125 mg/dL during the trial.
  - Most common adverse effects – GI adverse events were mild to moderate gastrointestinal symptoms, including nausea, diarrhea, and vomiting.

Adding Tirzepatide to Basal Insulin Cuts HbA1c in Poorly Controlled T2D — Results with the GIP/GLP-1 receptor agonist were statistically superior to added insulin lispro

European Association for the Study of Diabetes (EASD) meeting

- In patients on an insulin glargine regimen, the estimated mean change from baseline in HbA1c at week 52 was
  - -2.1% for those assigned to one of three different doses of **tirzepatide**
    - 68% achieved A1c <7% (resulted in Mean HbA1c of 6.7%)
    - Mean weight change - loss of 9 kg (19.9 lb)
    - Hypoglycemia/severe hypoglycemia – 0.4 events/patient-year
    - Ave 46u/d Insulin → average 13u/d Insulin [20% able to dc Insulin]
  - -1.1% for those randomized to **insulin lispro**
    - 36% achieved A1c <7% (resultant Mean HbA1c 7.7%)
    - Mean weight change – gain of 3.2kg (7.1 lb)
    - Hypoglycemia/severe hypoglycemia – 4.4 events/patient-year
    - Ave 46u/d Insulin → 62u/d insulin lispro + 42u/d insulin glargine (104u/d)

Guidance on Adding A GLP1/Dual Receptor Agonist Medication to Insulin

- Adding a GLP1 or Dual RA medication to Basal Insulin:
  - Reduce the dose of basal insulin by 10-20% in patients with an HbA1c ≤8 % (8.5%)
  - Reduce dose of basal insulin by 30% when begin tirzepatide

- Adding a GLP1 RA medication to Basal-Bolus Insulin:
  - Reduce Bolus insulin dose by ½ with initial dose of the GLP1/ Dual RA
  - Stop Bolus insulin as increase GLP1 Dual RA dose –
  - Titrate GLP1/Dual RA to max tolerated dose, adjust Basal insulin as needed
  - Add back bolus insulin to meals with high pp BG

References

- https://diabetesjournals.org/care/issue/47/Supplement_1
- https://diabetesjournals.org/care/article/46/Supplement_1/S140/148057/9-Pharmacologic-Approaches-to-Glycemic-Treatment
- Diabet Med. 2017 Sep; 34(9): 1193–1204.Review of basal-plus insulin regimen options for simpler insulin intensification in people with Type 2 diabetes mellitus D. Raccah et al https://diabetesjournals.org/clinical/article/39/4/411/137699/The-Clinical-Definition-of-Overbasalization
- ADA/EASD Standards of Care https://diabetesjournals.org/care/article/46/Supplement_1/S140/148057/9-Pharmacologic-Approaches-to-Glycemic-Treatment
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7364465

- https://www.aafp.org/pubs/afp/issues/2011/0715/p183.html
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8603317/
- https://diabetesjournals.org/care/article/46/Supplement_1/S140/148057/9-Pharmacologic-Approaches-to-Glycemic-Treatment

- https://diabetesjournals.org/care/article/43/10/2509/35858/Impact-of-a-Weekly-Glucagon-Like-Peptide-1

- Tirzepatide vs mealtime insulin https://pubmed.ncbi.nlm.nih.gov/37786396/
- Calculating Insulin Dose :: Diabetes Education Online (ucsf.edu)

- Mealtime insulin https://www.wcu.edu/WebFiles/PDFs/6403AdvancedInsulinManagementFinal.pdf
- https://www.endocrine.org/improving-practice/aid/mealtime
-

T1D

Insulin Therapy for Type 1 Diabetes

- In general, individuals with type 1 diabetes require approximately 30–50% of their daily insulin as basal and the remainder as prandial.
  - This proportion is dependent on a number of factors, including but not limited to carbohydrate consumption, age, pregnancy status, and puberty stage.
- Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day.

Improved Outcomes for T1D

- Because the hallmark of type 1 diabetes is absent or near-absent β-cell function, insulin treatment is essential for individuals with type 1 diabetes.
  - In addition to hyperglycemia, insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening.
- Severe metabolic decompensation can be, and was, mostly prevented with once- or twice-daily injections for the six or seven decades after the discovery of insulin.
- However, over the past three decades, evidence has accumulated supporting more intensive insulin replacement, using **multiple daily injections (MDI) of insulin or continuous subcutaneous administration through an insulin pump,** as providing the **best combination of effectiveness and safety for people with type 1 diabetes**.
- The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes.

https://diabetesjournals.org/care/article/46/Supplement_1/S140/148057/9-Pharmacologic-Approaches-to-Glycemic-Treatment

- Typical multidose regimens for individuals with type 1 diabetes combine premeal use of shorter-acting insulins with a longer-acting formulation.
  - The long-acting basal dose is titrated to regulate overnight and fasting glucose.
  - Postprandial glucose excursions are best controlled by a **well-timed injection of prandial insulin**. Recommendations for prandial insulin dose administration should therefore be ***individualized***.
  - The ***optimal time to administer prandial insulin varies***, based on
    - the pharmacokinetics of the formulation (regular, RAA, inhaled)
    - the premeal blood glucose level
    - carbohydrate consumption
  - Physiologic insulin secretion varies with glycemia, meal size, meal composition, and tissue demands for glucose.
    - Education on how to adjust prandial insulin to account for carbohydrate intake, premeal glucose levels, and anticipated activity can be effective and should be offered to most individuals .

Impact of Fat & Protein on PP glucose

- Carbohydrate counting has been shown to be an important determining factor of postprandial hypoglycemia and hyperglycemia.
- More recently, continuous glucose monitor (CGM) data revealed the PPG patterns in T1D, including rapid glucose spikes with high glycemic index carbohydrates and late postprandial hyperglycemia with increases in dietary fat and protein.
  - High-fat meals
    - may alter gastric emptying, often contributing to late blood glucose elevations that can occur as late as 4 to 5 h after the meal
    - can increase free fatty acid levels that impair insulin sensitivity, and further contribute to higher glucose values.
  - Higher protein intake has also been shown to increase PPG levels 3–5 h postmeal.
  - A high-fat and high-protein meal consisting of similar amounts of carbohydrates require more insulin to lower PPG when compared with low-fat, low-protein meals in T1D.

Additional factors to consider for PPG

- There are also data to suggest that **food order** has a significant role to play.
  - A study showed that when protein and fat were consumed 15 min before carbohydrates, the mean PPG levels were lower by 28.6%, 36.7%, and 16.8% at 30, 60, and 120 min, respectiv
- The **glycemic index** of food may also affect PPG levels
  - foods with a high glycemic index have been shown to result in even greater and more rapid increase in blood glucose following a meal.
  - foods with a lower glycemic index result in lesser fluctuations in blood glucose.
- Therapeutic approaches for T1D management during **exercise** also need to account for the residual effects of meals, insulin dose, and the impact of activity on glucose turnover, insulin mobilization, glucagon, and sympathetic response.
  - Several types of exercises are associated with rapid reductions in glucose (walking and jogging)
  - other forms of exercises may result in rapid increase in plasma glucose (weight training and high-intensity intervals)
  - Duration and type of exercise must also be considered in preventing exercise-induced hypoglycemia and postexercise hyperglycemia.

Insulin Therapy in T1D

- In general, individuals with type 1 diabetes require 50% of their daily insulin as basal and 50% as prandial,
  - but this is dependent on a number of factors, including whether the individual consumes lower or higher carbohydrate meals.
- Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day.
  - Higher amounts are required during puberty, pregnancy, and medical illness.
- The American Diabetes Association/JDRF Type 1 Diabetes Sourcebook notes 0.5 units/kg/day as a typical starting dose in individuals with type 1 diabetes who are metabolically stable, with half administered as prandial insulin given to control blood glucose after meals and the other half as basal insulin to control glycemia in the periods between meal absorption;
  - this guideline provides detailed information on intensification of therapy to meet individualized needs.
  - In addition, the American Diabetes Association (ADA) position statement “Type 1 Diabetes Management Through the Life Span” provides a thorough overview of type 1 diabetes treatment.

T1D Therapy

- Insulin replacement regimens typically consist of basal insulin, mealtime insulin, and correction insulin.
  - Basal insulin includes NPH insulin, long-acting insulin analogs, and continuous delivery of rapid-acting insulin via an insulin pump.
  - Basal insulin analogs have longer duration of action with flatter, more constant plasma concentrations and activity profiles than NPH insulin; longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in individuals with type 1 diabetes. Despite the advantages of insulin analogs in individuals with type 1 diabetes, for some individuals the expense and/or intensity of treatment required for their use is prohibitive.
  - Rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin. In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain as well as lower A1C compared with human insulins.
- There are multiple approaches to insulin treatment, and the central precept in the management of type 1 diabetes is that some form of insulin be given in a planned regimen tailored to the individual to keep them safe and out of diabetic ketoacidosis and to avoid significant hypoglycemia, with every effort made to reach the individual's glycemic targets.

Postprandial BG targets

- Current recommendations are neither well established nor consistently individualized for individuals with T1D; however,
  - the recommended 2-h PPG level <140 mg/dL has been suggested by the American Association of Clinical Endocrinologists (AACE)
  - values <180 mg/dL have been put forth by the American Diabetes Association (ADA)
  - targets of <160–180 mg/dL were recommended by European Association for the Study of Diabetes (EASD)
  - <160 mg/dL was the suggested target provided by International Diabetes Federation
  - all targeting these values with no increase in associated rates of significant hypoglycemia.
- [cg – the new “hybrid closed-loop”/AID insulin delivery [*more adjustability]* systems significantly help safely achieve tight pp glucose targets.]

From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023**

Diabetes Care. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009

Representative relative attributes of insulin delivery approaches in people with type 1 diabetes[1]

Injected insulin regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	+++
Less-preferred, alternative injected insulin regimens			
MDI with NPH + RAA or URAA	++	++	++
MDI with NPH + short-acting (regular) insulin	++	+	+
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	+

Continuous insulin infusion regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
Hybrid closed-loop technology	+++++	+++++	++++++
Insulin pump with threshold/ predictive low-glucose suspend	++++	++++	+++++
Insulin pump therapy without automation	+++	+++	++++

Mealtime Insulin Algorithms

Algorithm to Titrate Mealtime Insulin doses for T2D

https://www.endocrine.org/improving-practice/aid/mealtime

When Mealtime Insulin is Taken:	When to Test Blood Sugar:	If the Blood Sugar Results Are: Then You Should:	When:
At Breakfast	Before Lunch	**Under 80** Subtract 2 Units from Mealtime Dose **80 – 130** Do Not Adjust Mealtime Insulin Dose **Over 130** Add 2 Units to Your Mealtime Dose	Before Breakfast the Next Day

When Mealtime Insulin is Taken:	When to Test Blood Sugar:	If the Blood Sugar Results Are: Then You Should:	When:
At Lunch	Before Dinner	**Under 80** Subtract 2 Units from Mealtime Dose **80 – 130** Do Not Adjust Mealtime Insulin Dose **Over 130** Add 2 Units to Mealtime Dose	Before Lunch the Next Day
At Dinner	Before Bed	**Under 125** Subtract 2 Units from Mealtime Dose **125 – 150** Do Not Adjust Mealtime Insulin Dose **Over 150** Add 2 Units to Mealtime Dose	Before Dinner the Next Day

From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023**

Diabetes Care. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009

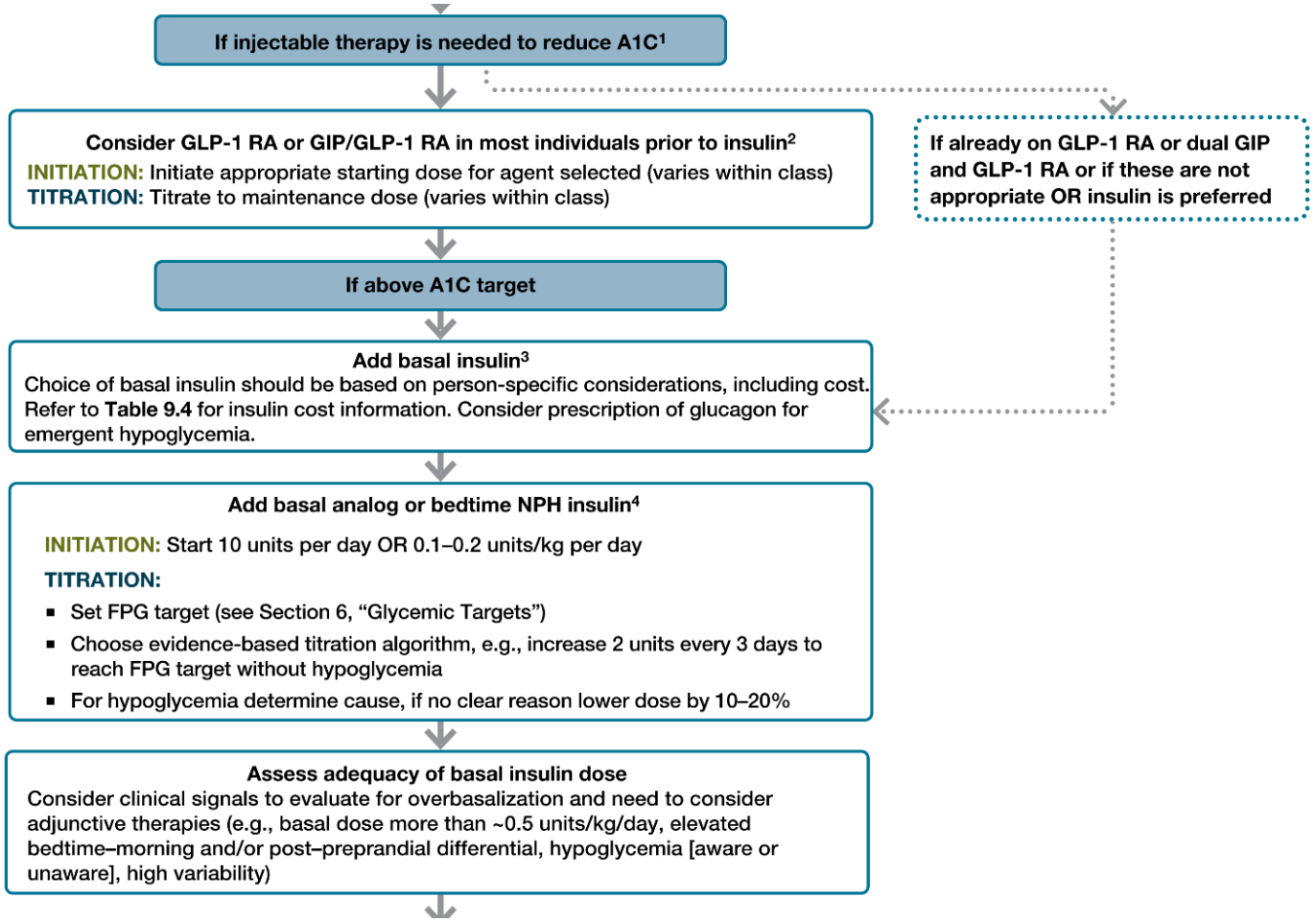
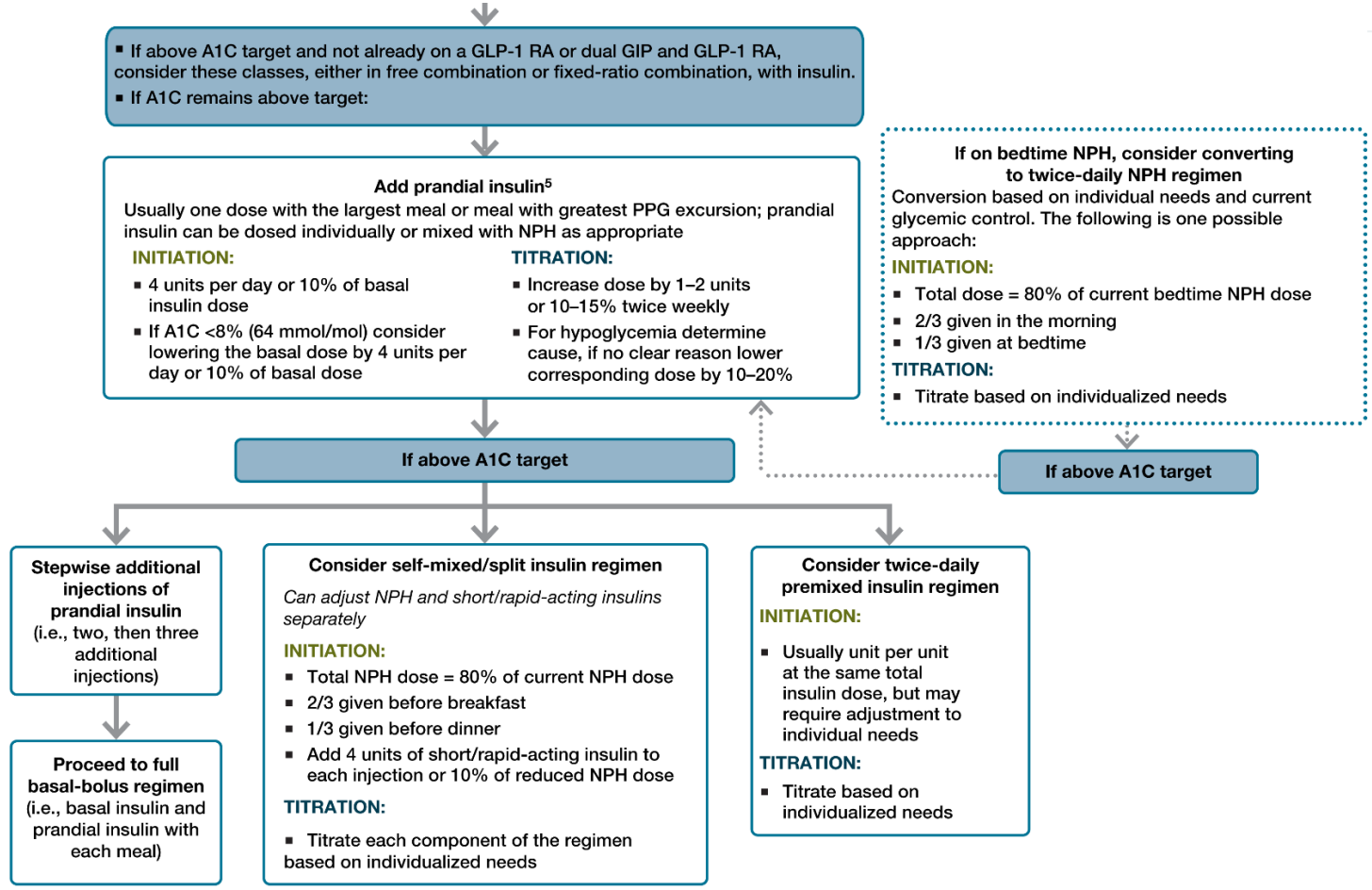


Figure Legend: Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (43).

American Diabetes Association®

From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023**



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider individual preference, A1C lowering, weight-lowering effect, or fequency of injection. If CVD is present, consider GLP-1 RA with proven CVD benefit. Oral or injectable GLP-1 RA are appropriate.
3. For people on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (IDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an A.M. dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

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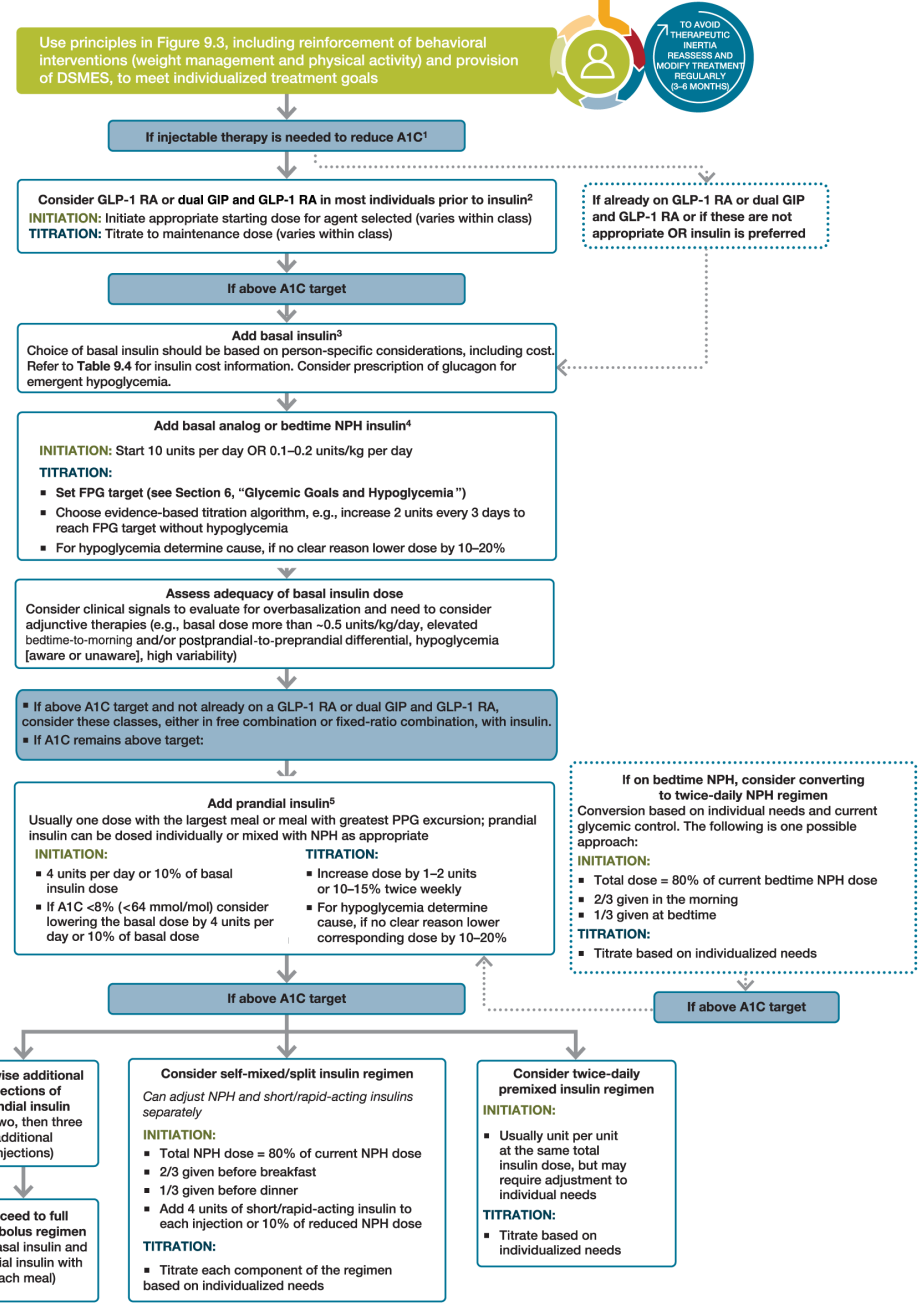

1. Consider insulin as the first injectable if evidence of ongoing catabolism is present, symptoms of hyperglycemia are present, when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]), or when a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RAs, consider individual preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVO is present. consider GLP-1 RA with proven CVO benefit. Oral or injectable GLP-1 RAs are appropriate.
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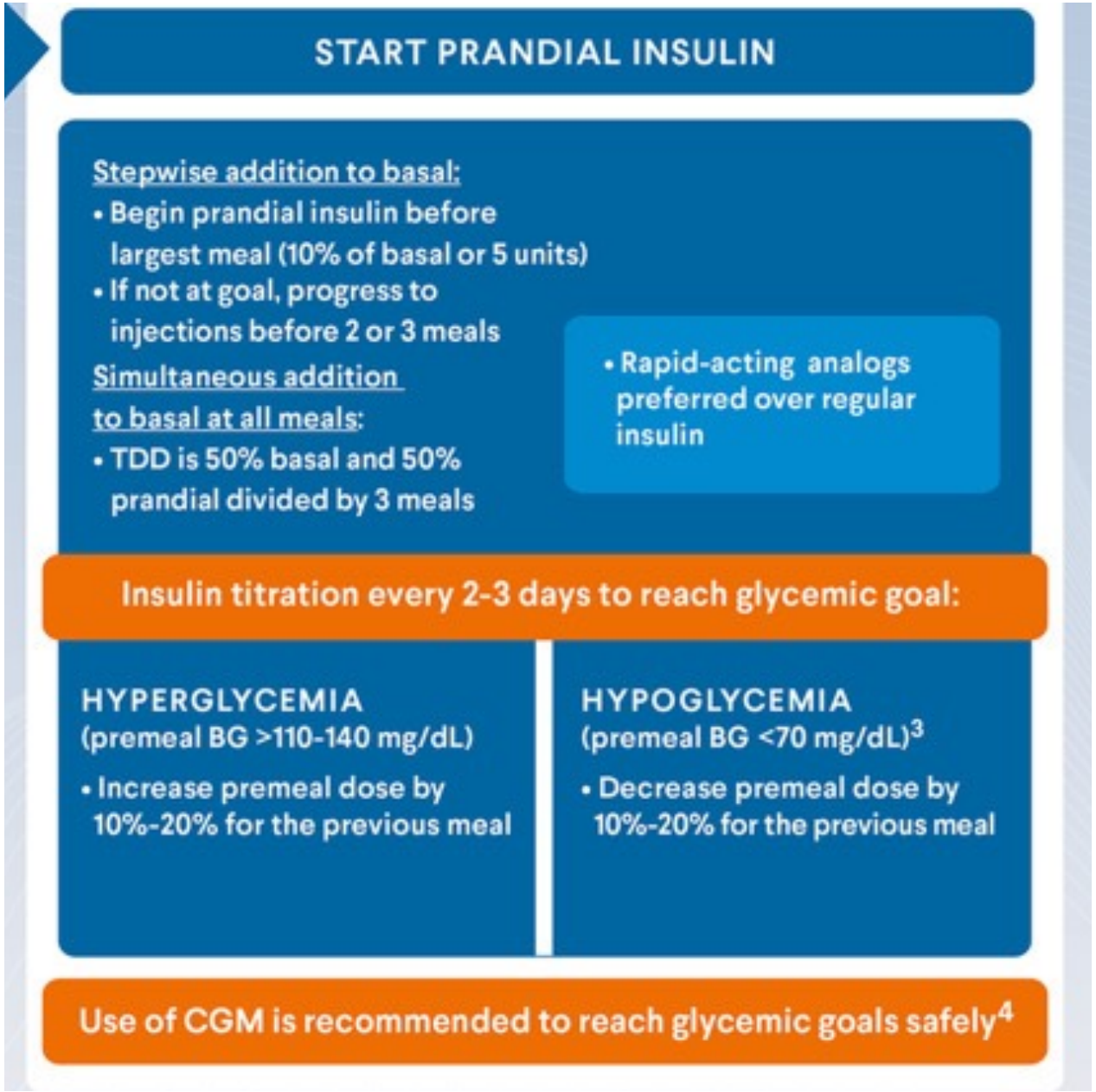
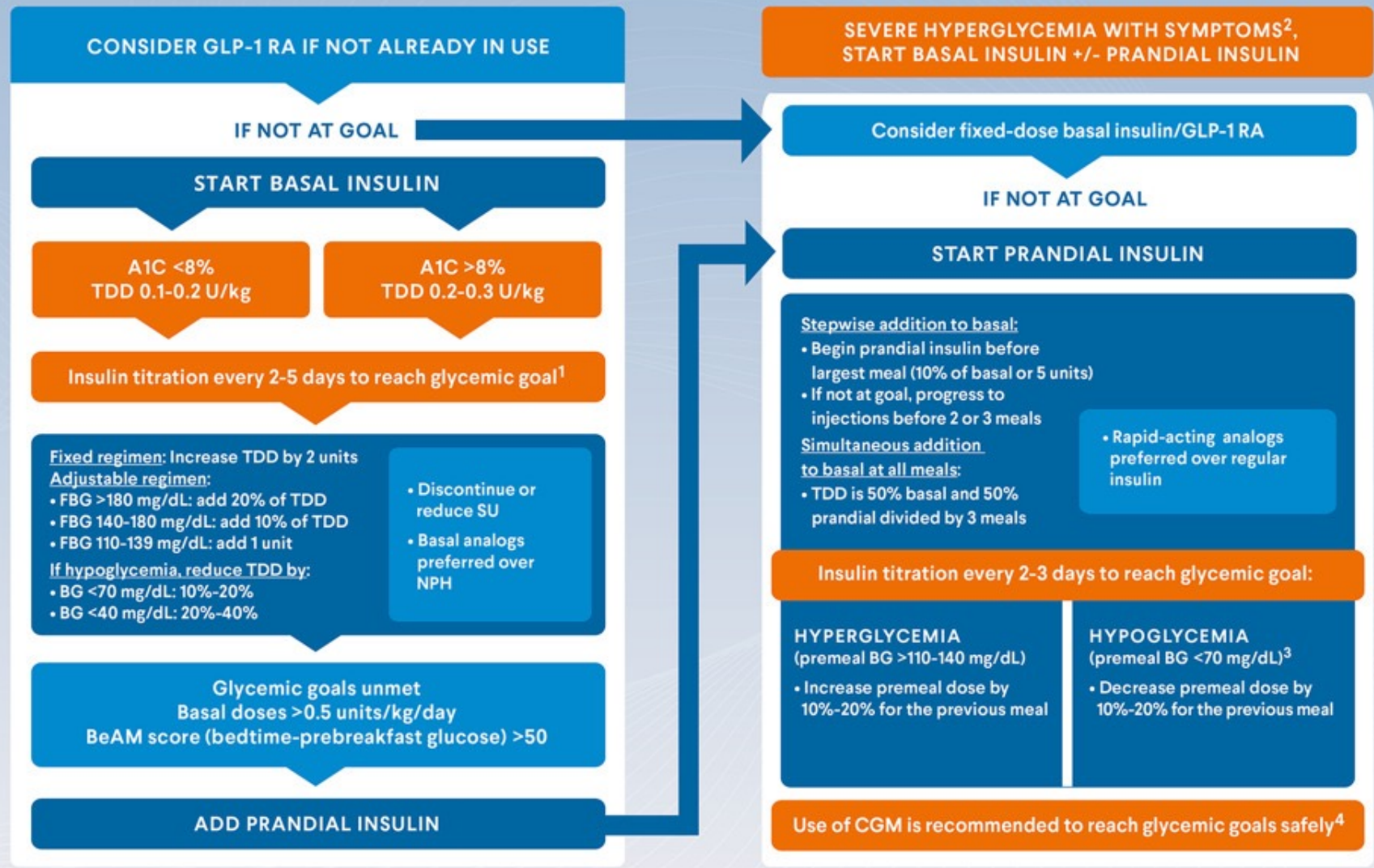
AACE/ACE Guidelines



ALGORITHM FOR ADDING/INTENSIFYING INSULIN



[1]Glycemic goals: A1C ≤6.5%-7% without hypoglycemia, fasting and premeal glucose <110 mg/dL, A1C should be individualized in people with comorbidities and at high adverse consequences of hypoglycemia and/or limited life expectancy. Longer-acting basal insulins (e.g., glargine U300, degludec U100 or U200) require slower titration ≥3 days because of a longer time to steady state. [2]For symptomatic hyperglycemia with A1C >10% and/or BG ≥300 mg/dL, reduce glucose/A1C as promptly and safely as possible. Consider testing for autoimmune diabetes. GLP-1 RA requires titration phase which can delay glycemic control. [3]Oral administration of rapidly absorbed source of glucose (tablet, fruit juice) if person can safely swallow. If unresponsive or unable to swallow, subcutaneous/Intramuscular/intranasal glucagon or glucagon analogue can be given by a trained member of the household. [4]See also American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons with Diabetes Mellitus.

Algorithm Figure 8-Adding/Intensifying Insulin

Gastric Emptying

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1993989/

- Gastric emptying in patients with diabetes is often accelerated compared with healthy individuals.
  - This may, at least in part, be due to deficient amylin secretion in response to meals.
  - Since gastric emptying is the rate-limiting step for glucose entering the circulation, accelerated gastric emptying may exacerbate postprandial glucose excursions in patients with diabetes.

Linda E Watson, Cong Xie, Xuyi Wang, Ziyi Li, Liza K Phillips, Zilin Sun, Karen L Jones, Michael Horowitz, Christopher K Rayner, Tongzhi Wu, Gastric Emptying in Patients With Well-Controlled Type 2 Diabetes Compared With Young and Older Control Subjects Without Diabetes, The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 8, August 2019, Pages 3311–3319, https://doi.org/10.1210/jc.2018-02736

- The rate of gastric emptying, which exhibits substantial interindividual but low intraindividual variation in both health and diabetes, is a major determinant of the glycemic response to a glucose drink or a solid meal containing carbohydrate.
- Interventions that slow gastric emptying, including glucagon-like peptide-1 (GLP-1) receptor agonists, pramlintide, acarbose, and nutrient preloads, have the capacity to attenuate postprandial glycemic excursions in type 2 diabetes (T2DM).
- The baseline rate of gastric emptying is likely to be an important determinant of the response to therapy.
  - The reduction in postprandial glycemia with GLP-1 receptor agonists is related to the magnitude of the slowing of gastric emptying such that when baseline gastric emptying is relatively more rapid, the reduction of postprandial glycaemia is greater.

Linda E Watson, Cong Xie, Xuyi Wang, Ziyi Li, Liza K Phillips, Zilin Sun, Karen L Jones, Michael Horowitz, Christopher K Rayner, Tongzhi Wu, Gastric Emptying in Patients With Well-Controlled Type 2 Diabetes Compared With Young and Older Control Subjects Without Diabetes, The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 8, August 2019, Pages 3311–3319, https://doi.org/10.1210/jc.2018-02736

- therapies that slow gastric emptying are effective in reducing postprandial glycemic excursions in patients who have normal or rapid emptying at baseline but have minimal impact in those in whom emptying is already delayed. Therefore, our findings are of high clinical relevance because the subset of patients with relatively good glycemic control (HbA1c <7.9%) is most likely to benefit from interventions that target postprandial glycemia

- Https://link.springer.com/article/10.1007/s00125-022-05796-1#Sec4

- Normal and disordered gastric emptying in diabetes: recent insights into (patho)physiology, management and impact on glycaemic control
- Published: 04 October 2022
- volume 65, pages1981–1993 (2022)

More on beginning the First mealtime insulin Before Breakfast

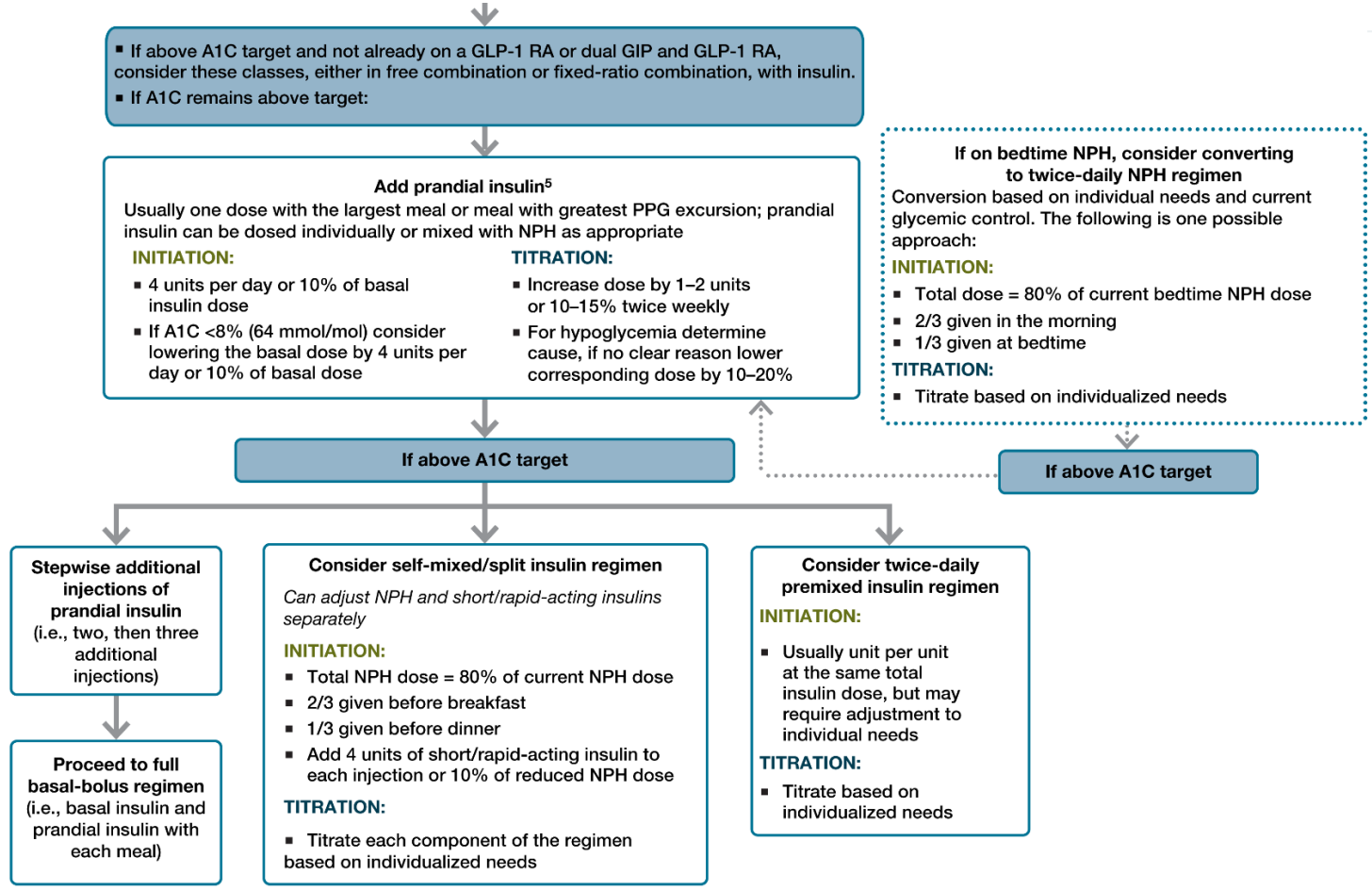
Timing of meal insulin boluses to achieve optimal postprandial glycemic control in patients with type 1 diabetes

Diabetes Technol Ther. 2010 Mar;12(3):173-7.

- Abstract
- Objective: This study determined the optimal timing of insulin bolus administration in relation to meal consumption in adolescents and adults with type 1 diabetes.
- Study design and methods: Twenty-three subjects participated in this crossover study consisting of three treatment arms: delivering an insulin glulisine bolus by insulin pump 20 min prior to a meal ("PRE"), immediately before the meal ("START"), and 20 min after meal initiation ("POST"). Blood glucose levels were measured every 30 min for a total of 240 min post-meal initiation. Mean blood glucose levels at 1 and 2 h after meal initiation, blood glucose area under the curve (AUC), and maximum blood glucose levels were analyzed.
- Results: At both 60 and 120 min after meal initiation, the PRE arm showed significantly lower glycemic excursions than the START arm (P = 0.0029 and 0.0294, respectively) and the POST arm (P = 0.001 and 0.0408, respectively). Glycemic AUC was significantly less in the PRE arm versus both the START and POST arms (159.5 +/- 58.9 mg/dL vs. 187.0 +/- 43.1 mg/dL [P = 0.0297] and 184.5 +/- 33.2 mg/dL [P = 0.0463], respectively). Peak blood glucose levels were significantly lower in the PRE arm compared to the START arm (P = 0.0039) and the POST arm (P = 0.0027).
- Conclusions: **A bolus of rapid-acting insulin 20 min prior to a meal results in significantly better postprandial glucose control than when the meal insulin bolus is given just prior to the meal or 20 min after meal initiation.**

American Diabetes Association®

From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023**



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
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3. For people on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (IDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an A.M. dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

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).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5599968/#:~:text=Full%20basal%E2%80%90bolus%20therapy%20comprises,%2C%2021%2C%2022%2C%2023.

- Basal insulin is designed to suppress hepatic glucose production and improve fasting hyperglycaemia. The basal insulin dose needs to be optimized before adding prandial insulin
  - if basal insulin is properly titrated, only ~60% of patients will require the addition of prandial insulin (this is without GLP1 RA or SGLT2i)
  - a full basal-bolus regimen is probably not necessary for the majority of patients at the time of insulin intensification after appropriate basal insulin titration.
- In the STEP study 20, when the main meal was defined as the one with the largest post-meal glucose increase (ExtraStep), a higher percentage of participants received a bolus injection at breakfast, whereas when the main meal was defined as the largest self-reported meal, a higher percentage of participants received injections at lunch and dinner. Even in patients who ate light breakfasts, the mean blood glucose values after breakfast were not very different from those after lunch and dinner, suggesting that administering the first injection at breakfast might result in a similar improvement in glycaemic control as administration at lunch or dinner 26.

Mealtime Insulin - Highest Excursion after Breakfast

- beginning with a dose with the first meal of the day, resulted in significant improvements in glycaemic control, with ~50% of participants achieving HbA1c ≤53 mmol/mol (7.0%) 42.

- These findings suggest that, for patients who eat breakfast, this may be a suitable and convenient meal at which to administer the first prandial insulin injection after optimization of insulin glargine. For patients who do not eat breakfast, the first injection could be taken at lunch 42 or with their evening meal if the largest of the day, based on social and cultural habits.
- Pre-meal values thus appear easier in daily life for patients to measure and offer less variability in measurement than post-meal tests. If the time between meals is very long, however, and especially for people with Type 2 diabetes in Spain and other countries who eat a late evening meal, 2-h post-meal glycaemic values may be more appropriate.

Mealtime Insulin - Highest Excursion after Breakfast

- The first critical step is to optimize basal insulin dosing to reach a fasting glucose of ~6.7 mmol/l; this allows ~40% of patients with baseline HbA1c >75 mmol/mol (9%) to be controlled with only one basal insulin injection per day.
- Breakfast appears to be the best choice both from a glycaemic point of view (as it is the meal with the highest glycaemic excursion) and from a practical point of view, as the person can usually inject at home; however, some flexibility is needed for people taking no or very light breakfasts, with the first injection then taken at lunch or at supper, whichever is the largest meal of the day, based on cultural or social habits.
- Postprandial glycaemia measurement appears to be more complicated for people with Type 2 diabetes and potentially more variable in real life than preprandial glycaemia. Since preprandial and postprandial glycaemia give equivalent results, preprandial glucose levels appear more practical in daily practice; however, in countries where there is usually a long interval between meals, as with a late supper, titration based on 2-h postprandial glycaemia may be more appropriate.

Edelman SV, Liu R, Johnson J, Glass LC. AUTONOMY: The first randomized trial comparing two patient-driven approaches to initiate and titrate prandial insulin lispro in type 2 diabetes. Diabetes Care 2014; 37: 2132–2140.

- Approximately 61% of participants required ≤2 doses of prandial insulin rather than a full basal-bolus regimen