

HOW TO INITIATE AND INTENSIFY INSULIN THERAPY

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DISCLOSURES:

Speakers Bureau- Novo Nordisk, Jansenn, Xeris Pharmaceuticals

Advisory Board- Xeris Pharmaceuticals,

AT THE END OF
THIS SESSION,
PARTICIPANTS
SHOULD BE
ABLE TO:

- ▶ Discuss the need for patient-centered care and shared decision-making to formulate the best treatment plan for individual patients
- ▶ Discuss when to initiate and intensify injectable or insulin therapy based on current American Diabetes Association (ADA) Standards of Medical Care
- ▶ Calculate an initial basal insulin dose and explain how to titrate basal insulin to meet fasting glycemic target
- ▶ Identify when intensification of insulin therapy is necessary and how to initiate and titrate prandial insulin

Glycemic Recommendations for Many Non-Pregnant Adults with Diabetes

A1C	<7.0%* # (53 mmol/mol)
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (<10.0 mmol/L)

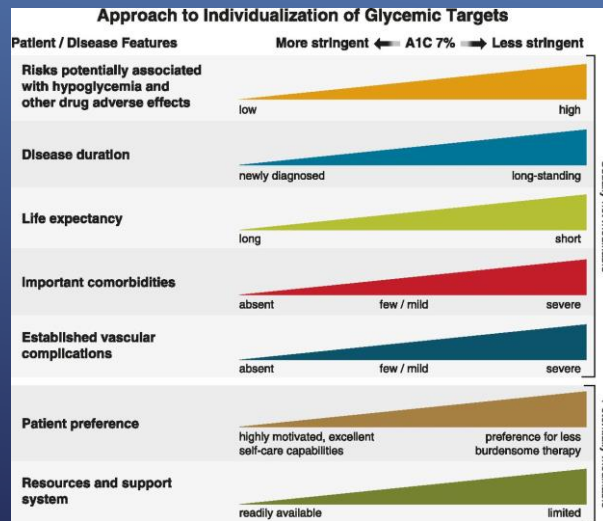
*More or less stringent glycemic goals may be appropriate for individual patients.

CGM may be used to assess glycemic target

† Postprandial glucose may be targeted if A1C goal is not met despite reaching preprandial glucose goals. Should be made 1–2 hours after the beginning of the meal, generally peak levels in patients with diabetes.

American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes 2021. Diabetes Care 2021;44(Suppl. 1):S73–S84

Patient and disease factors used to determine optimal glycemic targets.

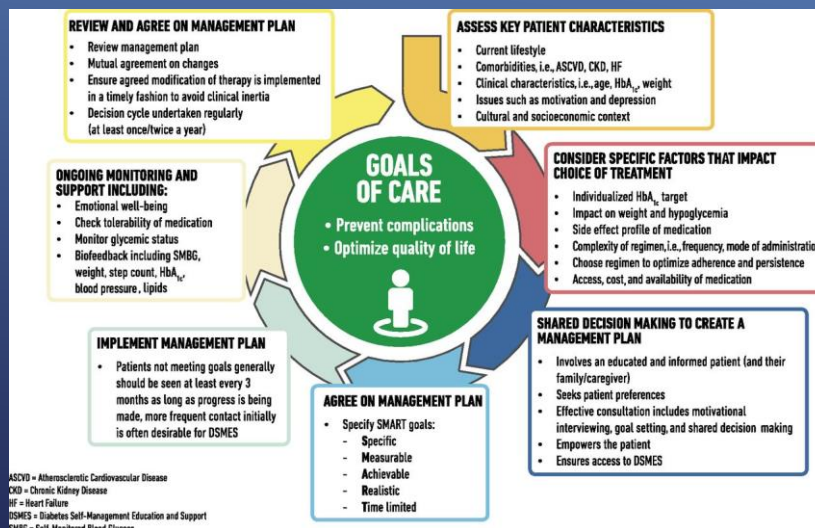


American Diabetes Association Dia Care 2021;44:S73-S84

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Decision Cycle for Patient-Centered Glycemic Management in Type 2 Diabetes



American Diabetes Association. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities Diabetes Care: Standards of Medical Care in Diabetes 2021;44(Suppl. 1):S40–S52.

Natural History of Type 2 Diabetes

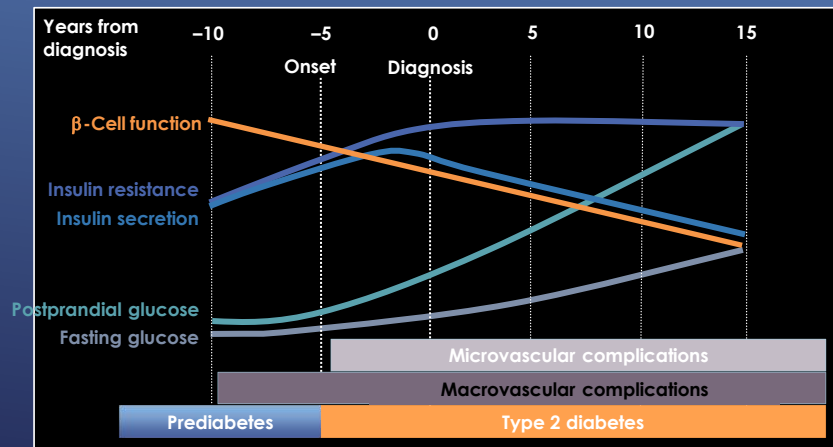
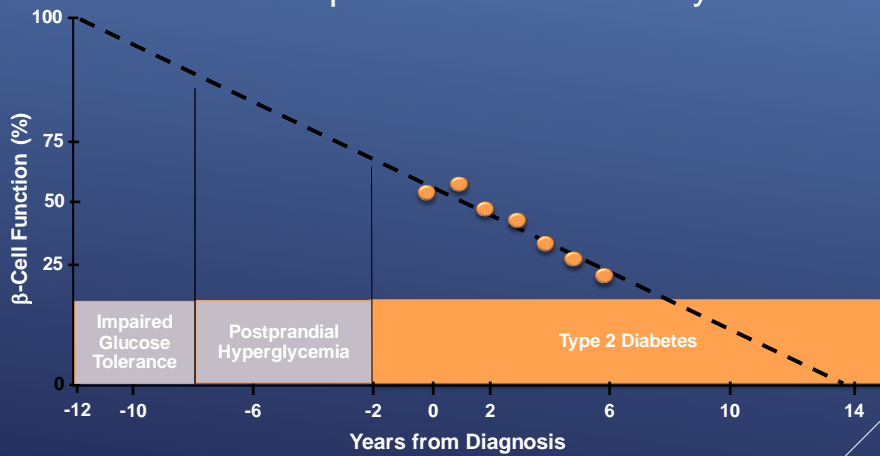


Figure courtesy of CADRE. Accessed from www.aace.com, January 2019. Adapted from Holman RR. Diabetes Res Clin Pract 1998;40(Suppl.):S21–S25; Ramlo-Halsted BA, Edelman SV. Prim Care 1999;26:771 – 789; Nathan DM. N Engl J Med 2002;347:1342–1349; UK Prospective Diabetes Study Group. Diabetes 1995;44:1249–1258

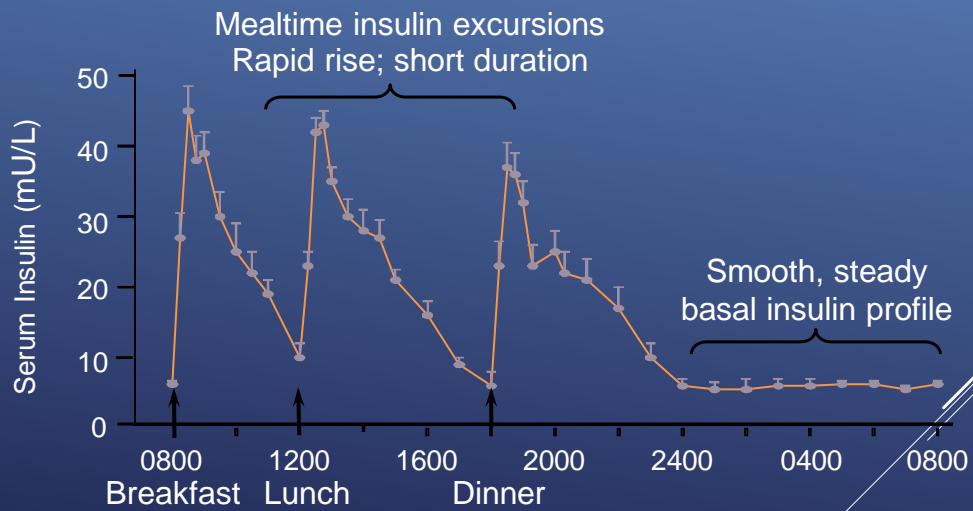
β -CELL LOSS OVER TIME

UK Prospective Diabetes Study



Dashed line = extrapolation based on homeostasis model assessment (HOMA) data. Data points from obese UKPDS population, determined by HOMA model. Accessed from www.aace.com January 2019. Holman RR. Diabetes Res Clin Pract. 1998;40(Suppl.):S21-S25

THE PHYSIOLOGIC INSULIN PROFILE

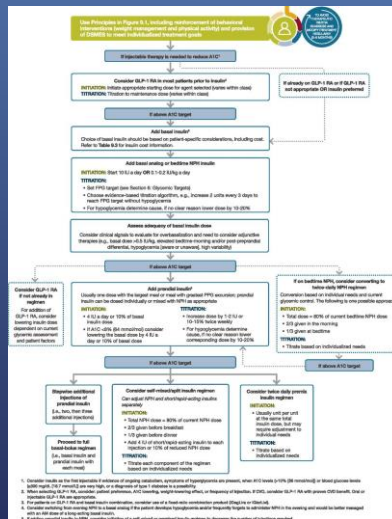


Kruszynska YT, Home PD, Hanning I, Alberti KG. Diabetologia 1987;30:16–21; Daly A, Powers MA. Medical nutrition therapy. In *Therapy for Diabetes Mellitus and Related Disorders*. 6th ed. Umptierrez GE, Ed. Alexandria, VA, American Diabetes Association, 2014; *Medical Management of Type 2 Diabetes*. 7th ed. Burant CF, Ed. Alexandria, VA, American Diabetes Association, 2012.

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

- ▶ **9.1** Most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **A**
- ▶ **9.10** In patients with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. **A**
- ▶ **9.7** The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥ 300 mg/dL [16.7 mmol/L]) are very high. **E**

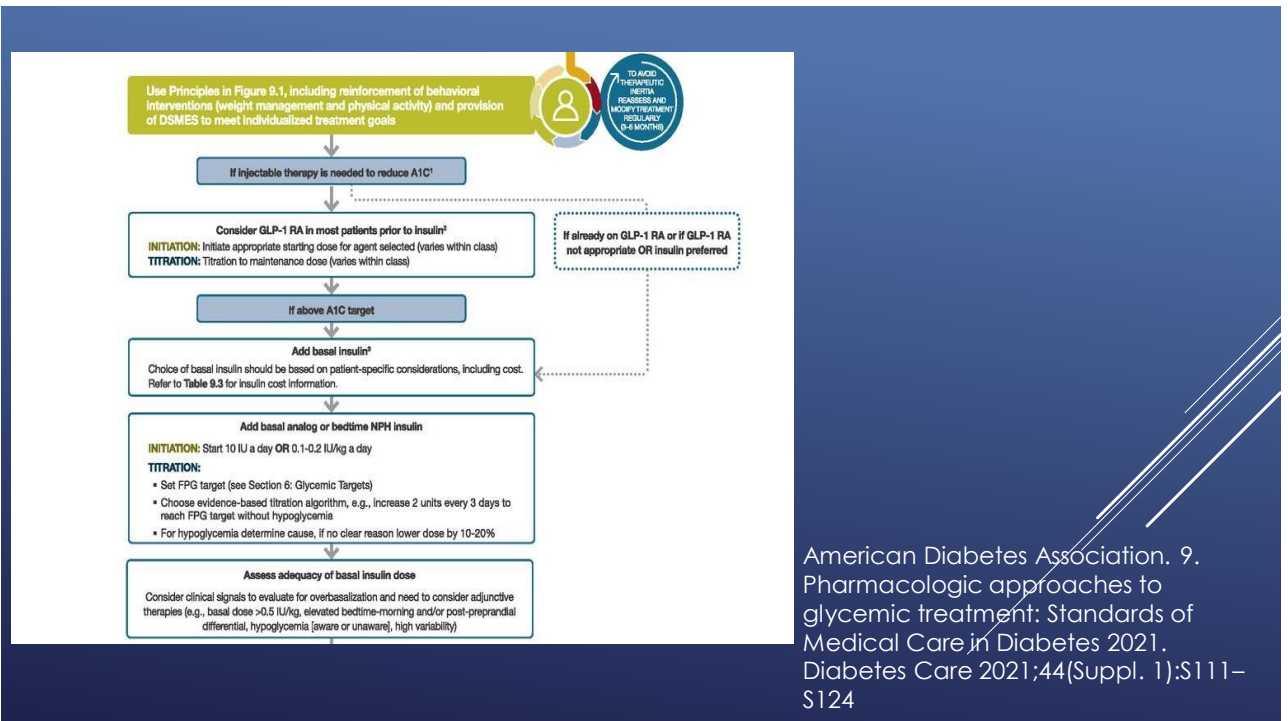
Intensifying to injectable therapies.



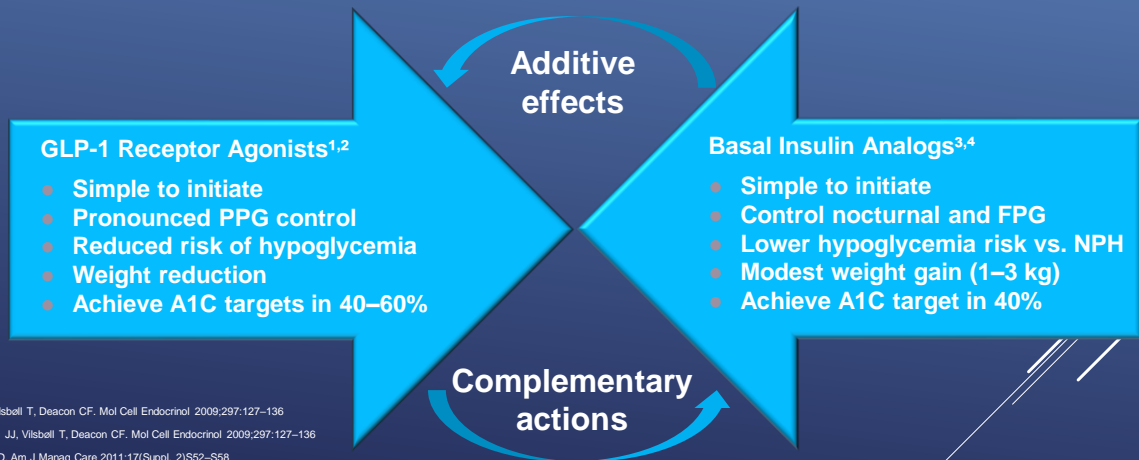
American Diabetes Association Dia Care 2021;44:S111-S124

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SCIENTIFIC RATIONALE FOR COMBINING A GLP-1 RECEPTOR AGONIST WITH BASAL INSULIN



¹Holst JJ, Vilsbøll T, Deacon CF. Mol Cell Endocrinol. 2009;297:127–136

²Calabro Holst JJ, Vilsbøll T, Deacon CF. Mol Cell Endocrinol. 2009;297:127–136

³Calabrese D. Am J Manag Care. 2011;17(Suppl. 2):S52–S58

⁴Liebl A. Curr Med Res Opin. 2007;23:129–132

⁵Giugliano D, Maiorino MI, Bellastella G, Chiodini P, Ceriello A, Esposito K. Diabetes Care. 2011;34:510–517

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TYPES OF INSULIN/GLP-1 RECEPTOR AGONIST COMBINATION PRODUCTS

Fixed-Ratio Combination Product	Starting Dose	Titration	Maximum Dose	Titration Based on:
Degludec/liraglutide 100/3.6	16 units	2 units every 3–4 days	50 units	Fasting glycemic target
Glargine/lixisenatide 100/33	If on <30 units basal insulin before, start at 15 units; if on 30–60 units basal insulin before, start at 30 units	2–4 units every week	60 units	Fasting glycemic target

Adapted from U.S. Food and Drug Administration-approved package inserts for each product.

Basal Insulins

Type of Insulin	Onset of Action	Peak of Action	Duration of Action	Presentation
Insulin, intermediate-acting				
NPH	2–4 hours	4–10 hours	10–16 hours	Vial, pen/cartridge
Insulin, long-acting				
Insulin glargine U-100	2–4 hours	No peak	18–26 hours	Pen/Vial
Insulin detemir	2–4 hours	No peak	22–24 hours	Pen/Vial
Insulin, ultra-long-acting				
Insulin degludec ²	6–8 hours	No peak	>42 hours	Pen/Vial
Insulin glargine U-300 ¹	2–4 hours	No peak	36 hours	Pen

Adapted from U.S. Food and Drug Administration-approved package inserts for each preparation

WHAT IS THE PREFERRED FIRST LINE
INJECTABLE IN MOST CASES IN PATIENTS
WITH TYPE 2 DIABETES?

- A. Basal insulin
- B. Prandial Insulin
- C. GLP1 RA
- D. Combination Therapy GLP-1RA and Basal insulin

WHAT IS THE PREFERRED FIRST LINE INJECTABLE IN MOST CASES IN PATIENTS WITH TYPE 2 DIABETES?

The Correct Answer is: **C. GLP1 RA**

According to ADA Standards of Medical Care,

9.10 In patients with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. **A**

INITIATION OF BASAL INSULIN

Add basal analog or bedtime NPH insulin

Start 10 units a day or 0.1-0.2 units/kg a day

*Choice of basal insulin should be based on patient-specific considerations, including cost.
Refer to **Table 9.3** for insulin cost information

American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2021. *Diabetes Care* 2021;44(Suppl. 1):S111-S124

EXAMPLE OF CALCULATING BASAL INSULIN

- ▶ 53 year old patient who weighs 253 lbs is ready to start basal insulin
- ▶ **10 units** initiation dose
- ▶ Or calculate weight-based dose

253 divided by 2.2= 115 kg

115 kg x 0.2 units= **23 units**

Base your starting dose on individual factors per patient

TITRATION OF BASAL INSULIN

START

Basal Insulin
Daily dose: 10 units or 0.1–0.2 units/kg
Set Individualized FPG target



Check
FPG daily with SMBG

ADJUST

Choose evidence-based titration algorithm
(e.g., increase 2 units every 3 days) to reach
FPG target without hypoglycemia



For hypoglycemia determine
cause, if no clear reason lower
dose by 10-20%



Continue regimen and
check A1C every 3 months

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EXAMPLE OF TITRATING BASAL INSULIN

Patient's target A1C less than 7%. Patient's fasting target is 130 mg/dl or less

Fasting SMBG	Dose of Insulin	Decision-Making
220 mg/dl	10 units	
190 mg/dl	10 units	
175 mg/dl	10 units	Increase by 2 units
165 mg/dl	12 units	
152 mg/dl	12 units	
146 mg/dl	12 units	Increase by 2 units
126 mg/dl	14 units	
122 mg/dl	14 units	
116 mg/dl	14 units	Remain at current dose

ASSESS ADEQUACY OF BASAL INSULIN DOSE

- ▶ Consider clinical signals to evaluate **overbasalization**
 - ▶ Basal dose > 0.5units/kg
 - ▶ Elevated bedtime-morning and/or post-preprandial differential
 - ▶ Hypoglycemia (aware or unaware)
 - ▶ High variability

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WHAT WOULD THE WEIGHT-BASED
STARTING DOSE OF BASAL INSULIN BE FOR
A PATIENT WHO WEIGHS 184 LBS?

- A. 10 units
- B. 20 units
- C. 12 units
- D. 17 units

WHAT WOULD THE WEIGHT-BASED
STARTING DOSE OF BASAL INSULIN BE FOR
A PATIENT WHO WEIGHS 184 LBS?

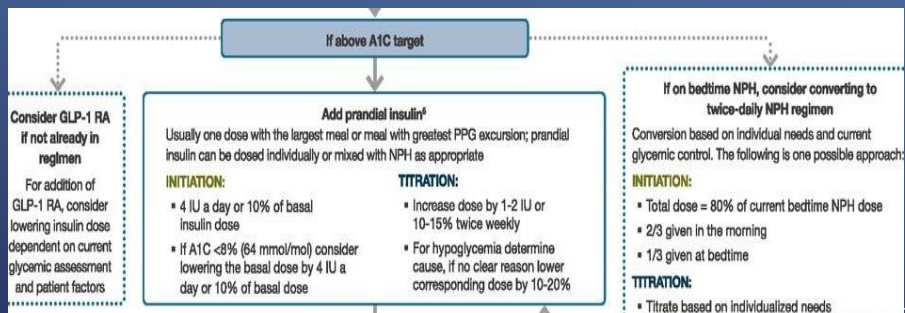
The Correct Answer is: **D. 17 units**

184 lbs divided by 2.2= 83.6 kg

84 kg x 0.2 u/kg= 16.8 units

17 units

INTENSIFYING TO PRANDIAL THERAPY



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CONVERTING NPH TO TWICE DAILY REGIMEN

Conversion based on individual needs and current glycemic control

Initiation:

Total dose= 80% of current bedtime NPH dose

2/3 given in the morning

1/3 given at bedtime

Example: Total once daily basal dosage is **36 units**

24 units in the morning

12 units at bedtime

Titration:

Based on individualized needs and SMBG results

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TYPES OF INSULIN: PRANDIAL (MEAL-RELATED)

<i>Type of Insulin</i>	<i>Presentation</i>
<i>Rapid-acting insulin analog</i>	
Insulin Lispro (U100, U200)	Vial or pen
Insulin Glulisine	Vial or pen
Insulin Aspart	Vial or pen
Inhaled insulin	Inhaler
<i>Ultra Rapid-acting analog</i>	
Insulin Aspart(faster acting)	Vial or Pen
Insulin lispro-aabc	Vial or Pen
<i>Short-acting insulin</i>	
Regular, human	Vial

Adapted from U.S. Food and Drug Administration-approved package inserts for each preparation.

INITIATION OF PRANDIAL INSULIN

- ▶ Initiation:
 - ▶ 4 units/day or 10% of basal dose
 - ▶ One largest meal or meal with the greatest post prandial excursion
 - ▶ Prandial insulin can be **dosed individually** or **mixed with NPH as appropriate**
 - ▶ If A1C is <8% (64 mmol/mol), consider decreasing the basal dose by 4 units a day or 10% of basal dose

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EXAMPLE OF ADDING PRANDIAL

A1C is > 8% and patient is on 36 units of basal insulin:

36 units basal at bedtime

4 units prandial with largest meal of day (most cases evening meal)

A1C is <8% and patient is on 36 units of basal insulin:

32 units of basal at bedtime

4 units of prandial with largest meal of day (most cases evening meal)

TITRATION OF PRANDIAL INSULIN

Titration:

- ▶ Increase dose by 1–2 units or 10–15% twice weekly
- ▶ Test plasma glucose levels using SMBG just before and 2 hours after largest meal

Signs or symptoms of hypoglycemia:

- ▶ Determine and address cause
- ▶ If no clear reason lower corresponding dose by 10–20%

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EXAMPLE OF TITRATING PRANDIAL INSULIN

Patient's fasting 2 hour post prandial target is 180 mg/dl or less

Pre meal SMBG	Post meal SMBG	Prandial Insulin	Decision-Making
135 mg/dl	250 mg/dl	4 units	
120 mg/dl	220 mg/dl	4 units	
122 mg/dl	215 mg/dl	4 units	Increase by 1 units
114 mg/dl	200 mg/dl	5 units	
124 mg/dl	195 mg/dl	5 units	
117 mg/dl	186 mg/dl	5 units	Increase by 1 units
126 mg/dl	180 mg/dl	5 units	
122 mg/dl	172 mg/dl	5 units	
116 mg/dl	166 mg/dl	5 units	Remain at current dose

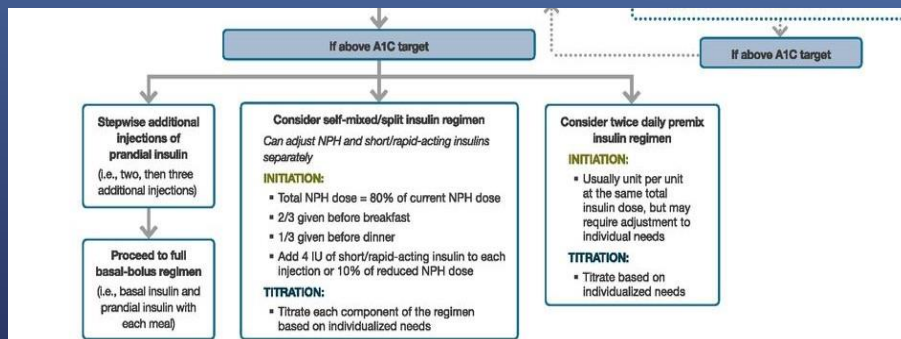
IF FASTING GLUCOSE IS TO GOAL WITH
BASAL INSULIN BUT A1C IS STILL ELEVATED,
HOW WOULD YOU INTENSIFY THERAPY?

- A. Add prandial insulin to largest meal
- B. Add a GLP1 RA
- C. Convert NPH from once daily to twice daily
- D. All of the above

IF FASTING GLUCOSE IS TO GOAL WITH
BASAL INSULIN BUT A1C IS STILL ELEVATED,
HOW WOULD YOU INTENSIFY THERAPY?

The Correct Answer is: **D. All of the above**

3 MONTHS LATER IF STILL ABOVE A1C TARGET



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PRANDIAL INSULIN IN A STEPWISE APPROACH

Stepwise approach:

Add prandial insulin to a second meal based off of post prandial readings

Individualized to the patient based off of SMBG

May be breakfast or lunch

Start 4 units and titrate as previously demonstrated

May need to add to third meal after 3 months if necessary to full basal/bolus

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SELF- MIXED/SPLIT INSULIN REGIMEN

- ▶ Can adjust NPH and short/rapid-acting insulins separately
- ▶ INITIATION:
 - ▶ Total NPH dose= 80% of current NPH dose
 - ▶ 2/3 given before breakfast and 1/3 before dinner
 - ▶ Add 4 IU of short/rapid-acting insulin to each injection or 10%of reduced NPH dose
 - ▶ Example: NPH 36 units
 - 36 units x 0.80 = 28 units of NPH
 - 2/3 before breakfast= 19 units and 1/3 before dinner= 9 units
 - Regular insulin 4 units before breakfast and 4 units before dinner (mixed in syringe with NPH)
- TITRATION:
 - Titrate each component of the regimen based on individualized needs
 - If fasting is not to target increase NPH 2 units every 3 days until target
 - If post prandial is not to target increase the Regular 1 unit every 3 days until target

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TWICE DAILY PREMIX INSULIN REGIMEN

Initiation:

- ▶ Usually unit to unit at the same total insulin dose, but may require adjustment to individual needs

Example: 50 units of basal insulin

Change to twice daily premix to 25 units twice daily

Titration:

- ▶ Titrate based on individualized needs

Fasting glucose in AM elevated increase evening dose 2 units every 3 days

If pre dinner glucose is elevated increase morning dose by 2 units every 3 days

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American Diabetes Association. Diabetes Care 2020;43(Suppl. 1):S98–S110

PREMIX INSULINS

- ▶ NPH/regular 70/30
- ▶ Lispro 50/50
- ▶ Lispro 75/25
- ▶ Aspart 70/30

- ▶ All available in pen and vial

ALTERNATIVE OPTIONS FOR BASAL/BOLUS TO REDUCE INJECTION BURDEN

- ▶ VGo Wearable Insulin Delivery Device (Disposable Patch Pump)
- ▶ Continuous Subcutaneous Insulin Infusion (CSII)/Insulin Pumps
 - ▶ Type 1 diabetes coverage is good
 - ▶ Type 2 diabetes coverage has improved
 - ▶ Sensor-augmented insulin pumps may be used to mitigate hypoglycemia

CONTINUOUS GLUCOSE MONITORS (CGM)

- ▶ Real-time CGM (rtCGM)- measures and displays glucose continuously
- ▶ Intermittently scanned CGM (isCGM)- measures continuously but only displays glucose levels when scanned with reader or phone app
- ▶ Professional CGM- placed on patients in the office and worn for 7 to 14 days. Data may be visible or blinded to patient depending of device. Used to assess glycemic trends and adjust therapy
- ▶ Coverage has improved. Often need to be testing glucose 4 x daily and be on 3 or more injections of insulin/day or insulin pump for coverage

CONSIDERING ORAL THERAPY IN COMBINATION WITH INJECTABLE THERAPIES

METFORMIN



Continue treatment with metformin

SGLT2i



If on SGLT2i, continue treatment
 Consider adding SGLT2i if

- Established CVD
- If HbA_{1c} above target or as weight reduction aid

TZD¹



Stop TZD when commencing insulin OR reduce dose



Beware

- DKA (euglycemic)
- Instruct on sick-day rules
- Do not down-titrate insulin over-aggressively

SULFONYLUREA



If on SU, stop or reduce dose by 50% when basal insulin initiated

DPP-4i



Stop DPP-4i if GLP-1 RA initiated



Consider stopping SU if prandial insulin initiated or on a premix regimen

¹Contraindicated in some countries, consider lower dose. This combination has a high risk of fluid retention and weight gain

Davies MJ, D'Alessio DA, Fradkin J, et al. Diabetes Care 2018;41:2669–2701

CVD,
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SUMMARY

- ▶ Insulin therapy is often a necessary intervention for patients with type 2 diabetes due to the progressive nature of the disease
- ▶ GLP1 RA in most cases is the preferred first injectable
- ▶ Basal insulin should be initiated at 10 units/day or 0.2 units/kg/day and titrated with evidence-based algorithm until fasting target is reached
- ▶ Intensification of insulin therapy after basal insulin can be done in a step-wise approach with one prandial dose of insulin therapy daily at first and further intensification if A1C not to goal

RESOURCES:

- ▶ professional.diabetes.org
- ▶ American Diabetes Association. Standards of Medical Care in Diabetes 2021. Diabetes Care 2021;44(Suppl. 1)

THANK YOU!