

Insulin Titrations

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University of Washington
Cardiometabolic
ECHO

Disclosures

- None

Objectives

- Define the classes of insulin and the pharmacodynamics
- Explain insulin titration to achieve glycemic goals in type 2 diabetes
- Explain the use of insulin with insulin sparing agents
- Identify diabetes technology tools to enhance diabetes control
- Use insurance formularies for prescribing diabetes medications
- Use patient assistance programs for patients having problems with affording their diabetes medications



Insulin Classes

- Rapid
- Short
- Intermediate
- Concentrated human regular
- Long
- Premixed
- Premixed/GLP- 1

Rapid- Acting Insulin

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- Lispro follow-on product
- Lispro
- Lispro-aabc
- Glulisine
- Aspart
- Aspart (fast acting)



Rapid-Acting Insulins Pharmacodynamics

Insulin	Onset	Peak (hr.)	Duration (hr.)	Appearance
Lispro	Within 15 min	~ 1	3-5	Clear
Aspart	Within 15 min	~ 1	3-5	Clear
Glulisine	Within 15-30 min	~0.5 – 1	4	Clear
Aspart (Fast Acting)	Within 5 min	~ 1	3-4	Clear
Lispro-aabc	Within 17 min	~ 1 -2	4-6	Clear

Technosphere Insulin

- Onset within 5 min
- Peak 15 min
- Duration 3 hrs
- Powder

Short -Acting Regular Insulin

- Onset 1 hr
- Peak 2–4 hrs
- Duration 5 - 8 hrs
- Clear

Intermediate Acting NPH Insulin

- Onset 1 – 2 hrs
- Peak 4 – 10 hrs
- Duration 14 hrs
- Cloudy

Long-Acting Insulin

- Determir
- Glargine
- Degludec
- Insulin glargine -yfgn



Long-Acting Insulins Pharmacodynamics

Insulin	Onset (hr.)	Peak (hr.)	Duration (hr.)	Appearance
Detemir	3-4	6-8 (relatively flat)	Up to 20-24	Clear
Glargine	1.5	Flat	24	Clear
Degludec	1	9	42	Clear
Glargine-yfgn	1.5	Flat	24	Clear

Insulin Mixtures

- NPH/Regular (70%/30%)
- Protamine/Lispro (50%/50%)
- Protamine/Lispro (75%/25%)
- Protamine/ Aspart (70%/30%)



Insulin Mixtures Pharmacodynamics

Insulin	Onset	Peak (hr.)	Duration (hr.)	Appearance
Lispro Mix 50/50	15-30 min	0.5-3	14-24	Cloudy
Lispro Mix 75/25	15-30 min	0.5-2.5	14-24	Cloudy
Aspart Mix 70/30	6-12 min	1-4	18-24	Cloudy
NPH/Regular 70/30	30 min	2-12	Up to 24	Cloudy

Concentrated Insulin

- U-500 regular insulin
- U-200 degludec
- U-300 glargine
- U-200 lispro
- U-200 lispro -aabc

Premixed Insulin/ GLP-1 RA

- Glargin/ Lixisenatide
- Degluded/Liraglutide

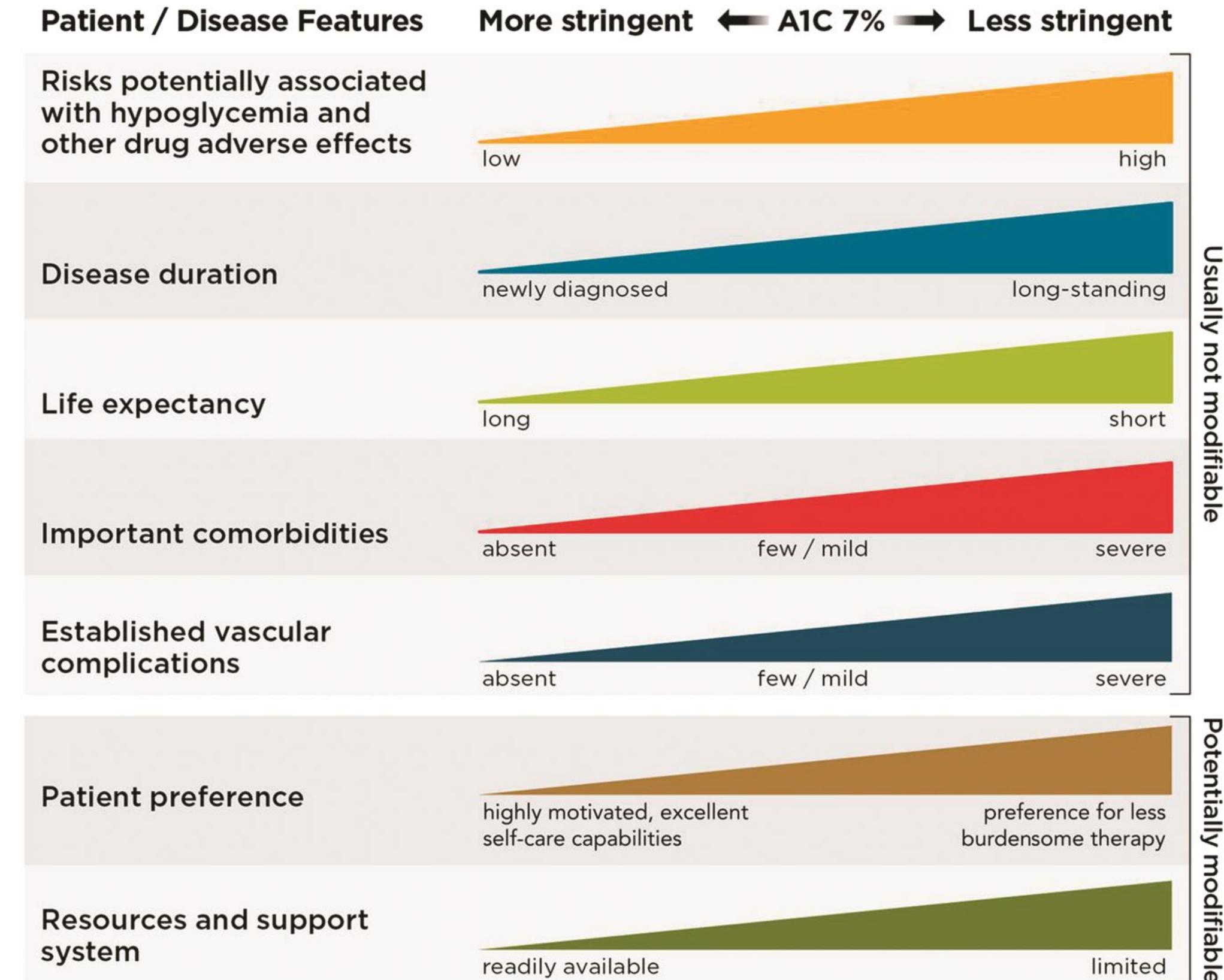
When to Use Insulin

- Type 1 diabetes
- Gestational diabetes not meeting glycemic goals
- Type 2 diabetes
 - Symptomatic hyperglycemia at the time of diagnosis
 $BG > 300 \text{ mg\%}$
 - Not reaching glycemic goals despite maximally tolerated oral agents and non -insulin injectables
 - Check for immune mediated diabetes antibodies (islet cell, glutamic acid decarboxylase, insulin, tyrosine phosphatase islet antigen 2 and zinc transporter 8)
 - Glucocorticoids, certain medications, or severe stress from illness
 - Progressive beta cell loss

Glycemic Goal

- A1c and FPG targets may be adjusted based on patient's age
- Duration of diabetes
- Presence of comorbidities
- Diabetes complications
- Hypoglycemia risk

Approach to Individualization of Glycemic Targets



Insulinopenia

- Insulinopenia is defined as a fasting c-peptide that is less than or equal to 110% of the lowest limit for the lab with a simultaneous blood glucose of < 225 mg/dl (CMS Guidelines) or glucagon stimulated c-peptide of < 0.2 nmol/l (Diab Ther 2017 June 8; (3): 475 -487)



Clinical Inertia in Starting Insulin

Patient Barriers

- Inconvenience
- Need for more frequent SBGM
- Hypoglycemia fear
- Weight gain
- Injection pain
- Psychological fear of failing at diabetes management
- Insulin leads to dialysis, amputations and blindness

Provider Barriers

- Hypoglycemia fear
- Patient resistance
- Lack of confidence in patient's ability to manage insulin therapy
- Lack of integrated care
- Uncertainty regarding insulin type, the complexity to be managed in a PCP's office

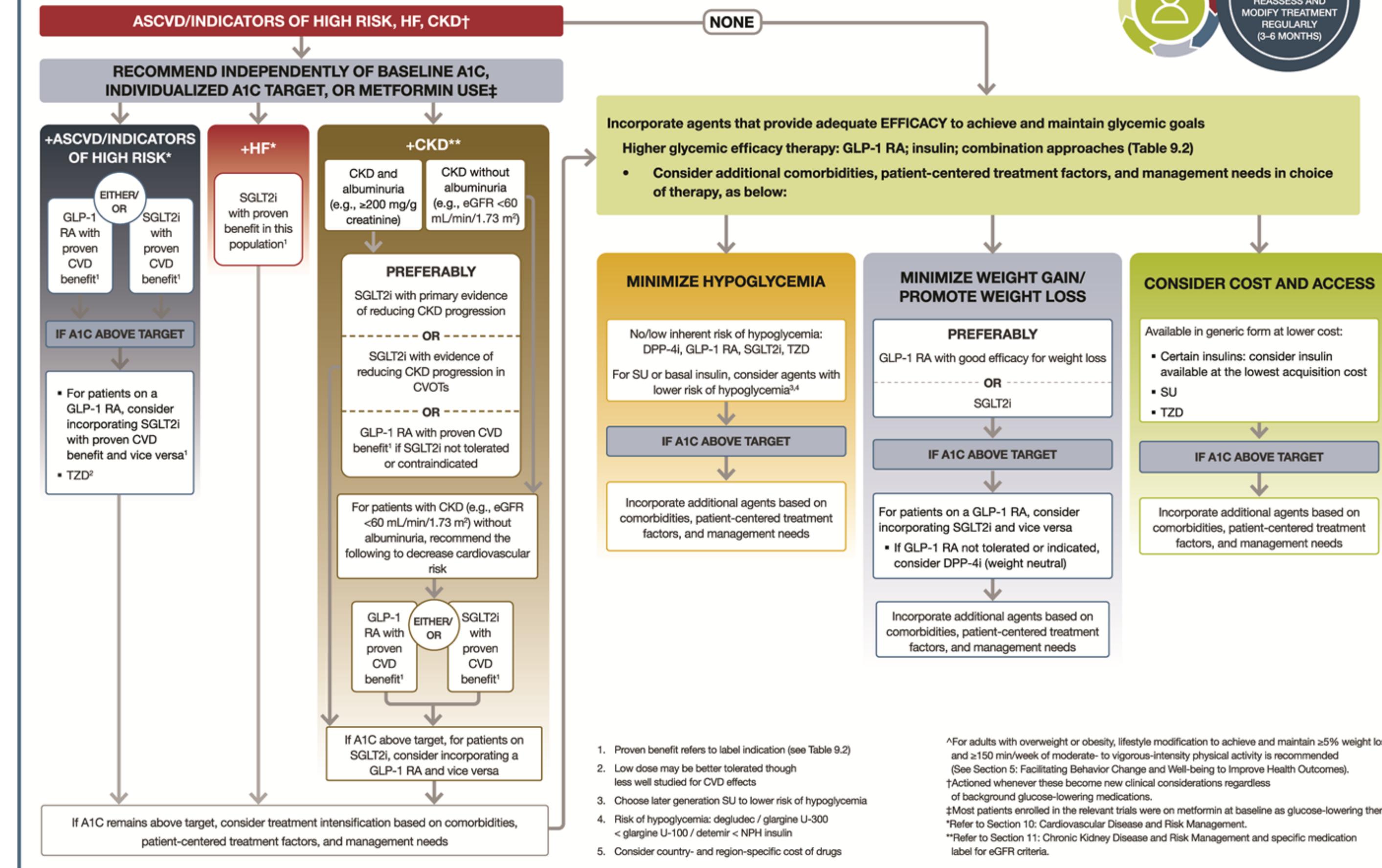
Basal Insulin Titration





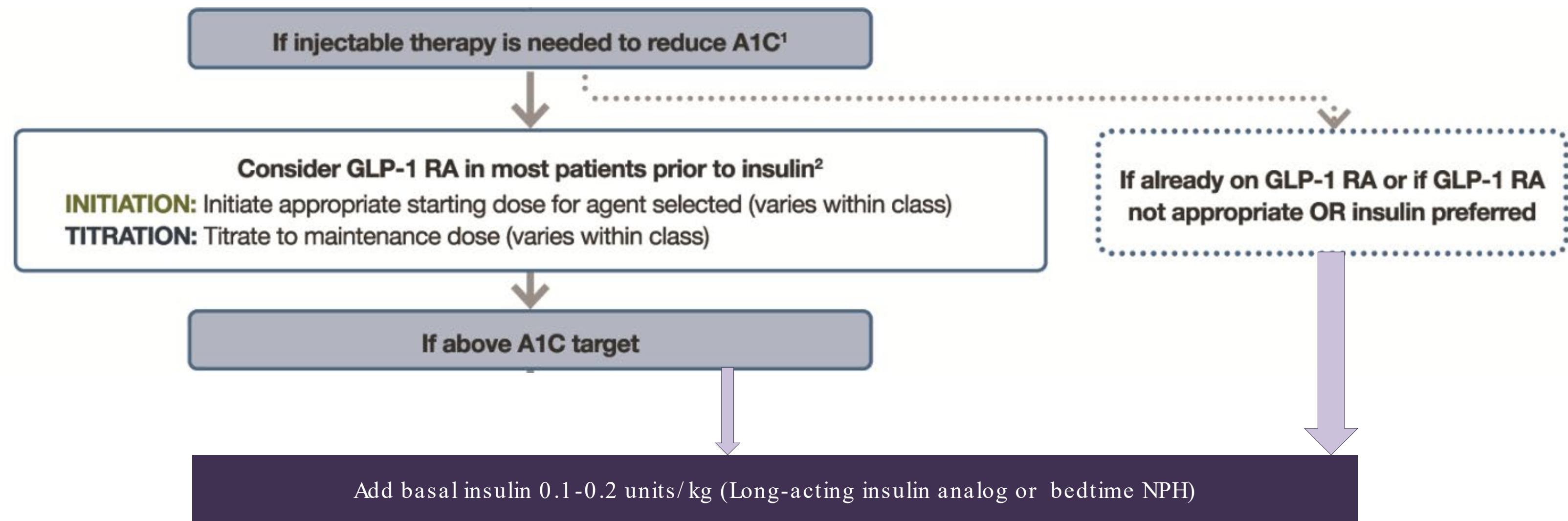
PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES

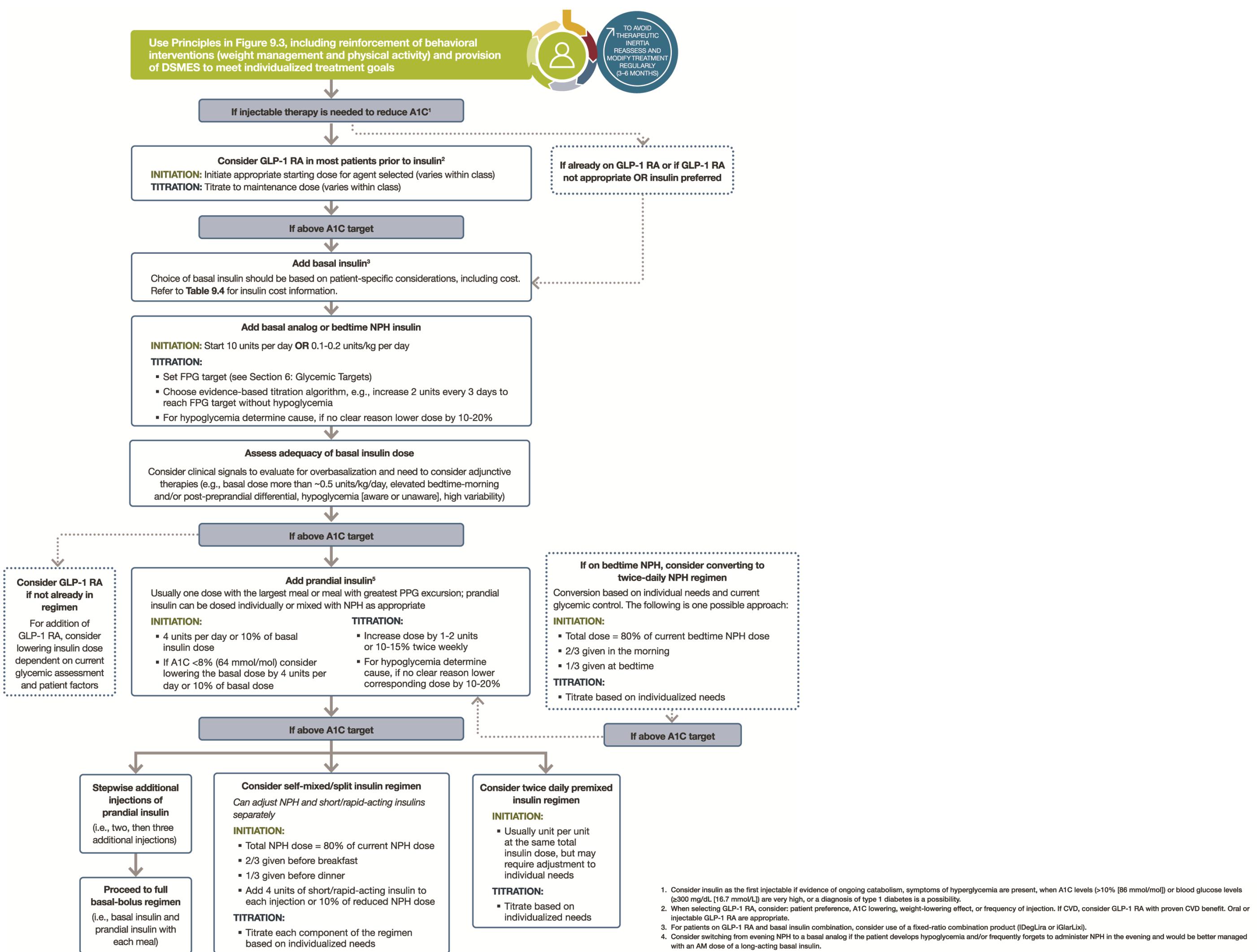
FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification[^]





Reinforce weight management through diet and exercise
Refer to Diabetes Self-Management Education Support







Target fasting BG to 80-130 mg/dl range. Adjust target BG higher if comorbidities put patient at risk for hypoglycemia

Forced Titration Algorithm

Fasting Glucose the past 3 days	Increase in Basal Insulin (units)
80 – 130	0
130 – 159	2
160 – 189	4
190 – 220	6
Over 220	8

Decrease dose by 2-4 units for any glucose level < 80

<https://www.ncbi.nlm.nih.gov/books/NBK278938/#!po=14.5833>

Do not increase basal insulin to more than 0.5 units/kg day.
Add prandial insulin



Titration Algorithms Evaluated in Clinical Trials

Treat-to-Target

- Gla-100 titration
- Increase Gla-100 dose by
 - 8 units FPG \geq 180 mg/dl
 - 6 units FPG \geq 140 - 180 mg/dl
 - 4 units FPG \geq 120 - 140 mg/dl
 - 2 units FPG \geq 100 - 120 mg/dl

Predictive Study

- Decrease insulin detemir by 3 units FPG < 80mg/dl
- Keep detemir dose same FPG 80 - 100
- Increase insulin detemir by 3 units FPG > 110 mg/dl

Diabetes Care 2003;26:3080 -3086

Diabetes Obes Metab 2007;9:902 -913



Basal Insulin Forced Titration Algorithm

Time	Breakfast	Lunch	Dinner	Bedtime
	Blood Glucose	Extra Units of Short or Rapid-acting insulin	Extra Units of Short or Rapid-acting insulin	Extra Units of Short or Rapid-acting insulin
80 – 150	0	0	0	0
151 – 200	2	2	2	0
201 – 250	4	4	4	2
251 – 300	6	6	6	4
301 – 350	8	8	8	6
351 – 400	10	10	10	8
Over 400	12	12	12	10

Prandial Insulin Titration





Add 1 rapid-acting insulin injection before largest meal

Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount

Adjust: ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached

For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

If A1C not controlled,
advance to basal-bolus

Add ≥2 rapid-acting insulin injections before meals ('basal-bolus')

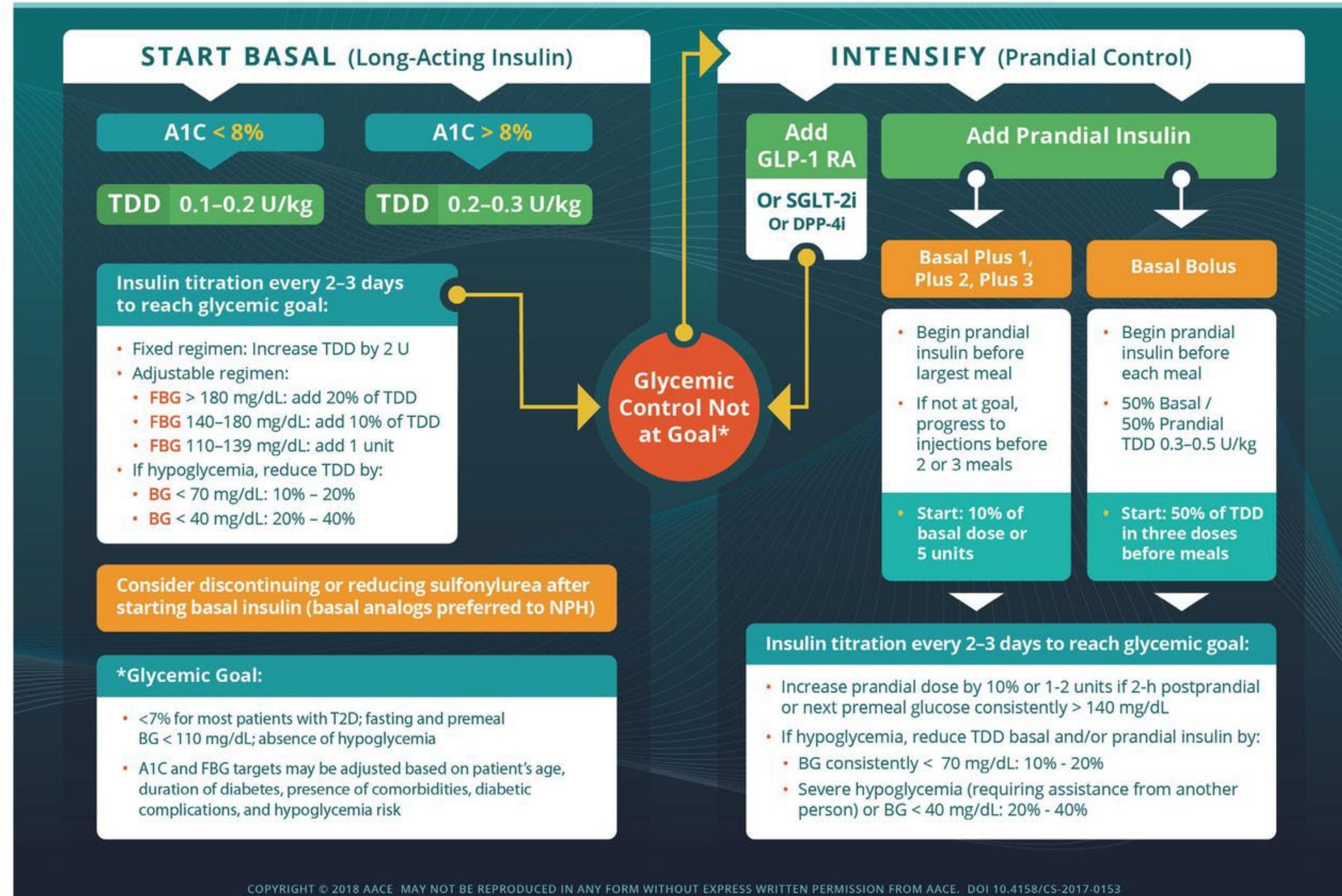
Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount

Adjust: ↑ dose(s) by 1-2 units or 10-15% once or twice weekly to achieve SMBG target

For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%



Algorithm for Adding/Intensifying Insulin

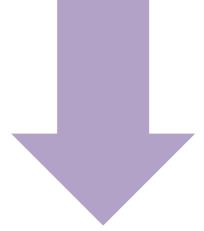


Prandial Insulin Titration

American Diabetes Association	American Association of Clinical Endocrinologist
<p>Add rapid acting insulin to largest meal</p> <ol style="list-style-type: none">1. Start 4 units, 0.1 U/kg, or 10% basal dose. If A1c <8%, consider ↓ basal insulin by same amount.2. Adjust by 1-2 units or 10-15% once or twice a week3. Hypo: Determine cause. If no cause ↓ corresponding dose by 2-4 units or 10-20%	<p>Add Prandial Insulin</p> <ol style="list-style-type: none">1. Begin prandial insulin before largest meal at 10% of basal dose or 5 units2. If not at goal progress to injections before 2 or 3 meals3. Titrate every 2-3 days to reach glycemic goal by increasing prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently >140 mg/dl4. If hypoglycemia reduce TDD basal and/or prandial insulin by:<ol style="list-style-type: none">1. BG < 70 mg/dl: 10-20%2. BG < 40 mg/dl: 20-40%

Basal-Bolus

1. Begin prandial insulin before each meal
2. 50% Basal/50% prandial
3. Prandial dose divided into 3 doses TDD 0.3-0.5 u/kg



1. Titrate every 2-3 days to reach glycemic goal by increasing prandial dose by 10% or 1 -2 units if 2 -h postprandial or next premeal glucose consistently >140 mg/dl
2. If hypoglycemia reduce TDD basal and/or prandial insulin by:
 - a) BG < 70 mg/dl: 10 -20%
 - b) BG < 40 mg/dl: 20 -40%



Intensifying Insulin – Bedtime NPH

Consider twice daily NPH regimen

1. Start with 80% of bedtime NPH
2. 2/3 given in the morning
3. 1/3 given in the evening

Consider self-mixed/split insulin regimen

*Either NPH and short/rapid -acting insulin
separately*

1. 80% of total NPH with 2/3 before breakfast and 1/3 before dinner
2. Add 4 units of short/rapid -acting insulin to each injection or 10% of reduced NPH dose

Consider twice daily premixed insulin regimen

1. Start with 2/3 before breakfast and 1/3 before dinner
2. Adjust based on individualized needs



Use of Weight Based Insulin with CHO ratio and Correction Algorithms

1. Start 0.5 U/kg day for TDD
2. $\frac{1}{2}$ dose will be basal insulin
3. Use the rule of 500 to calculate the Insulin: CHO ratio (ICR)
4. Calculate insulin sensitivity factor (ISF) using 1800/TDD to reach a target correction of 100 mg/dl before meals

Example

Weight is 100 kg

$$0.5 \text{ U/kg} \times 100 \text{ kg} = 50 \text{ units}$$

Basal insulin 25 units

ICR: $500/50 = 10$ (1 unit for every 10 gm of CHO consumed)

ISF: $1800/50 = 36$

(Current BG-Target BG/ISF) is the correction algorithm

$$200 - 100/36 = 2.7 \text{ units} \sim 2\text{u added to ICR to maintain target BG}$$

Connected Pen Device

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Connected Pen Prescription

Insulin Settings

Maximum Calculated Dose u

Duration of Insulin Action hh:mm

TIME OF DAY - OFF

Time of Day OFF

Target Blood Glucose mg/dL

Insulin Sensitivity Factor mg/dL/u

TIME OF DAY - ON

Time of Day AM/PM

Target Blood Glucose mg/dL

Insulin Sensitivity Factor mg/dL/u

Select ONE Meal Therapy Mode

Carb Counting Meal Estimation Fixed Dose

Insulin to Carb Ratio g/u

*Time of Day AM/PM

Low Medium High
Carb Carb Carb

	Low Carb	Medium Carb	High Carb
Breakfast	<u>u</u>	<u>u</u>	<u>u</u>
Lunch	<u>u</u>	<u>u</u>	<u>u</u>
Dinner	<u>u</u>	<u>u</u>	<u>u</u>
Snack	<u>u</u>	<u>u</u>	<u>u</u>

Long - Acting

Insulin Type _____

Doses per day _____

Dose 1

Usual Amount u

Time hh:mm

Dose 2

Usual Amount u

Time hh:mm



Insulin Pumps and Continuous Glucose Sensors



Continuous Glucose Monitors



CGM Devices

Type of CGM	Description
Real-time CGM	CGM systems that measure and display glucose levels continuously
Intermittently scanned CGM	CGM systems that measure glucose levels continuously but only display glucose values when swiped by a reader or a smartphone
Professional CGM	CGM devices that are placed on the patient in the provider's office (or with remote instruction) and worn for a discrete period of time (generally 7 – 14 days). Data may be blinded or visible to the person wearing the device. The data are used to assess glycemic patterns and trends. These devices are not fully owned by the patient – they are a clinic-based device, as opposed to the patient -owned real-time or intermittently scanned CGM devices.



Key points included in standard AGP report

AGP Report

GLUCOSE STATISTICS AND TARGETS

14 days % Sensor Time

Glucose Ranges

	Targets [% of Readings (Time/Day)]
Target Range 70–180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL.....	Less than 5% (1h 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

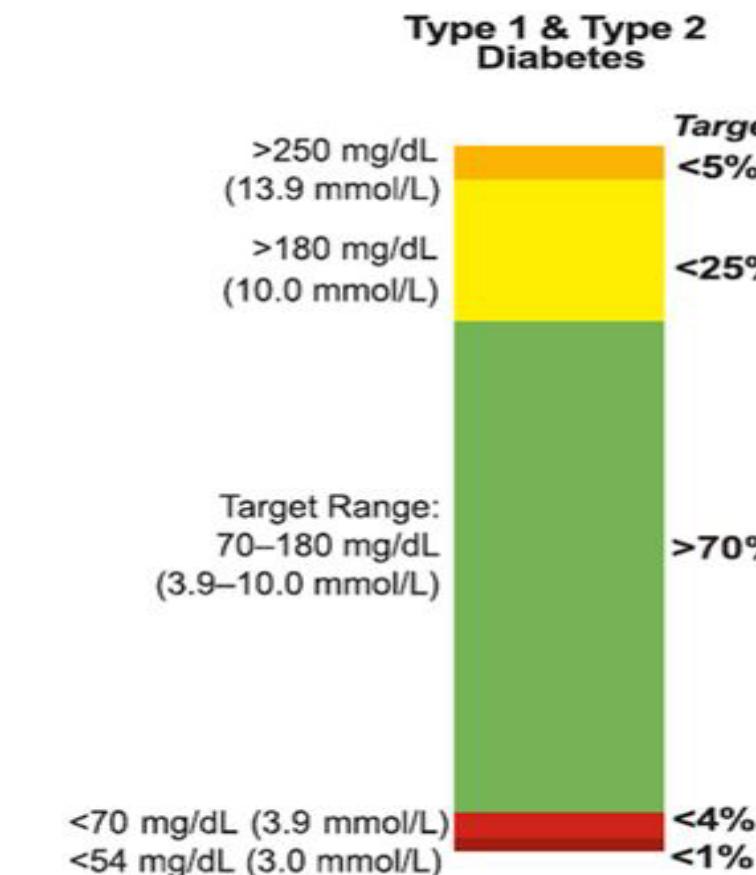
Average Glucose Glucose Management Indicator (GMI) Glucose Variability

Defined as percent coefficient of variation (%CV); target ≤36%

Name _____

MRN _____

TIME IN RANGES



Digital Health Tools

Average Diabetes Medication Costs





Non-Insulin Costs

Medication	\$ Cost (30-day supply)
Sulfonylurea	3-12
Thiazolidinediones	5
Metformin	2 (ER 102)
Alpha-Glucosidase Inhibitors	26
DPP-4 Inhibitors	166-471
SGLT2 Inhibitors	297-526
GLP-1 Receptor Agonists	727-975
Bromocriptine	1,036
Pramlintide	2702





Insulin Costs

Medication	\$ Cost (per 1000 unit)
Regular insulin (10 ml vial)	132-167
NPH (10 ml vial, 3ml pen)	133-167
Pre-Mix (10 ml vial, 3ml pen)	133-338
Rapid Acting (10 ml vial, 3ml pen)	132-339
U 500 concentrated human regular (vial, pen)	143 - 184
Long Acting (10 ml vial, 3ml pen)	96-325
Long Acting + GLP1 (3ml pen)	495-732
Inhaled Insulin	847





Walmart

Insulin	Dispense	Cost \$
ReliOn NPH	Vial	25
ReliOn Regular	Vial	25
ReliOn 70/30	vial	25
ReliOn	Syringes #100	4.99
ReliOn	Meter	9.00
ReliOn	Test strips #100	7.88
ReliOn	Lancets #100	1.62
Total	Vials + supplies	73.49

Insulin	Dispense	Cost \$
ReliOn Novolog	Vial	72.88
ReliOn Novolog	(5) 3ml pens	85.88
ReliOn	Syringes #100	4.99
ReliOn	Meter	9.00
ReliOn	Test strips #100	7.88
ReliOn	Lancets #100	1.62
ReliOn	Pen needles #50	5.87
Total	Vials + supplies	121.37
Total	Vial + pen +supplies	140.24



Patient Assistance Program Eligibility

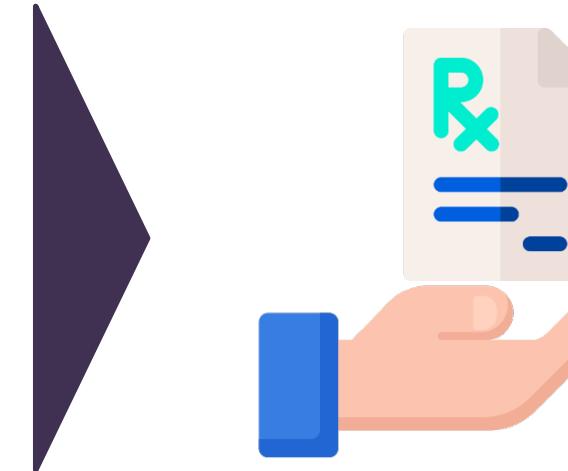
- No private insurance
- No Medicaid
- Proof of income
- Medicare only receives Part D benefits
- May qualify for Low Income Subsidy

Private Insurance Copay Assistance Cards

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Print your FREE card now
Using the button above.



Present it at your pharmacy
the next time you need a
prescription filled.



Collect your savings right away.
No receipts or claim forms to
submit!

Images: flaticon.com

Patient Assistance Program by Manufacturer

- [https://www.astrazeneca - us.com/medicines/Affordability.html#!](https://www.astrazeneca-us.com/medicines/Affordability.html#!)
- [https://www.boehringer -ingelheim.us/our - responsibility/patient -assistance-program](https://www.boehringer-ingelheim.us/our-responsibility/patient-assistance-program)
- <https://www.lillycares.com/>
- <https://www.merckhelps.com/>
- [https://www.novocare.com/diabetes - overview/let -us-help/pap.html](https://www.novocare.com/diabetes-overview/let -us-help/pap.html)
- [https://www.sanofipatientconnection.com/ patient-assistance-connection](https://www.sanofipatientconnection.com/patient-assistance-connection)

Medicaid Formularies

How to use the Apple Health PDL

The Apple Health PDL has products listed in groups by drug class. To obtain authorization for a nonpreferred drug, a client must have tried and failed, or is intolerant to, a designated number of preferred drugs within the drug class unless contraindicated or not clinically appropriate. The designated number of preferred drugs is listed on the Apple Health PDL.

In addition to approval criteria for nonpreferred products, some drugs have additional criteria that must be met. The requirement for additional criteria is noted in the columns on the Apple Health PDL.

Note: For continuity of care, all plans will use the same PA criteria, step therapy edits, and quantity limits developed by HCA.

Are you a pharmacist or prescriber? See what drugs are preferred and whether they need a prior authorization (PA).

[View the Apple Health PDL](#)



Prescribing Apps



Coverage Search 4+

MMIT

Designed for iPad

★★★★★ 4.3 • 383 Ratings

Free



Fingertip Formulary (DRG)

Trusted formulary intelligence

Decision Resources Group

Designed for iPad

★★★★★ 3.7 • 6 Ratings

Free

Formulary Medical



Questions?



Cardiometabolic teleECHO™ Clinic

Patient Recommendation Form

Presentation Date: June 29, 2022

Presenter name: Pratha Muthia, MD

Presenter Facility: Sea Mar CHC

Case Report Recap: 66 y/o, widowed, African American female with sub-optimally managed diabetes (hba1c 5/23/22 9.0), HLD, HTN and BMI 30.3 (wt. 188 lbs, ht 5'6) with anxiety around taking medications and insulin. Prescribed glargine 45 qhs, Lispro 14 U before meals, exenatide ER 2mg, irbesartan 300mg, diclofenac. Previously reported intolerance to losartan, lisinopril, metformin, atorvastatin and Jardiance. Barriers include health literacy (misunderstanding of medication side effect), infrequent home glucose checks, unclear if adherent to medications and need to care for her grandchild which takes away from self-care. Patient has established good rapport with current PCP.

Case Recommendations:

1. Evaluate for Type 1 diabetes with GAD-65 antibody testing due to history of DKA.
2. Basal insulin typically does not need adjustment once patient starts exenatide ER, but given patient's fasting blood sugars are close to goal, consider a 10-15% reduction based on response in the first few weeks.
3. If professional (blinded) CGM available, can provide a visual pattern for pt to better understand her glucose trends; personal CGM is covered under Medicare – intermittent scanned CGM (Freestyle Libre2) is a good option
4. Do PHQ-9/GAD-7. If a positive result, refer to behavioral health services for a further evaluation for treatment recommendations. Improved mental health care might help patient manage anxiety around her medications. With her obesity rule out vitamin D deficiency.
5. Evaluate sleep patterns since this can impact mood, weight, and insulin resistance. Screen for sleep apnea with a STOP-BANG and refer if positive.

Nicole Ehrhardt, MD

Physician Signature: *Nicole Ehrhardt*

Please Re-present case: **