Insulin therapy for type 2 diabetes

General principles of insulin therapy in diabetes mellitus

- Many patients with type 2 diabetes will require insulin as their beta-cell function declines over time.
- Clinical features that, if present **in a patient with diabetes at any age**, suggest the ***need for insulin therapy*** include:
  - Marked and otherwise unexplained ***recent weight loss*** (irrespective of the initial weight)
  - Short history with ***severe symptoms***
  - Presence of ***moderate to heavy ketonuria.***

Normal patterns of insulin secretion

- Insulin is ***secreted in a pulsatile*** manner; pulses occur under basal (unstimulated) conditions and in ***response to meals***.
- **Basal insulin** secretion represents approximately **50 percent** of 24-hour insulin production, with the remainder accounted for by prandial (mealtime) excursions.

Cont…

- **"conventional insulin therapy"**
  - simpler insulin regimens, such as ***single daily injections*****, or** ***two injections per day of regular and NPH insulin*****,** ***mixed together*** in the same syringe and given in fixed amounts before breakfast and dinner.
- **"intensive insulin therapy"**
  - More **complex regimens** that **separate basal insulin delivery** (given as one to two daily injections of intermediate- or long-acting insulin) with **superimposed doses of short-acting or rapid-acting insulins three or more times daily**.
  - ***For patients with type 1 diabetes*****,** they are now frequently used for patients with type **2** diabetes, as well.

Addressing patient resistance to insulin therapy for patients with type 2 diabetes

- **Patient concerned with pain from injection**
  - Minimal with thinner, smaller needles
  - Use of insulin pens
- **Patient worried that starting insulin signifies worsening diabetes**
  - Diabetes is a progressive disease
  - Taking insulin will control blood glucose and help prevent complications
  - Taking insulin **may slow down the rate of beta cell failure**

Cont…

- **Patient fears low blood sugar reactions**
  - Explain that **severe hypoglycemia is rare in type 2 diabetes**
  - Self-monitoring glucose levels
  - Explain how to avoid and how to treat hypoglycemia
- **Patient believes that insulin will decrease his/her quality of life**
  - Benefits from glucose control: more energy, better sleep, overall well-being
- **Patient thinks insulin will lead to diabetic complications**
- **Patient concerned that he/she will be treated differently by friends and family**
- **Patient has heard insulin causes weight gain**
  - Role of diet and exercise

INSULIN PREPARATIONS

1. Biosynthetic ***human*** insulin (eg, neutral protamine hagedorn [NPH], regular)
2. Synthetic insulin ***analog*** (eg, glargine, lispro).
3. ***Animal***-sourced insulins (derived from the pancreas of cows and pigs)

Cont..

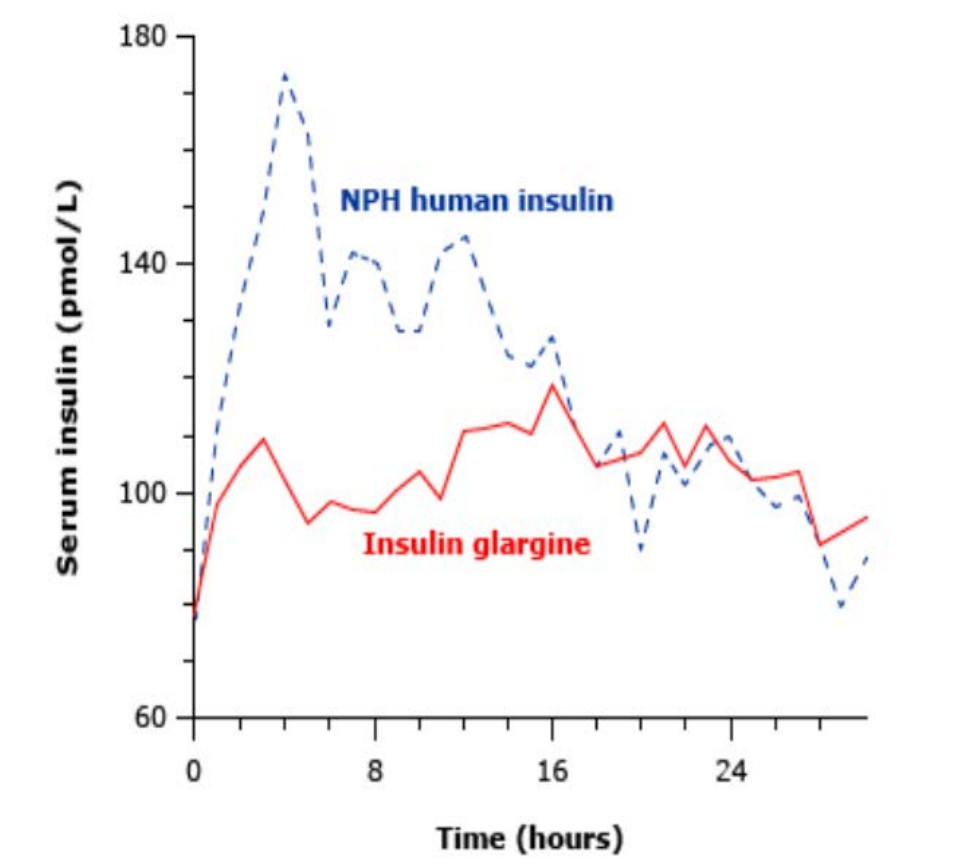
- In type 2 diabetes, insulin is generally provided in three ways:
- As a **basal supplement** with an intermediate- to long-acting preparation (NPH, glargine, detemir, or the very-long-acting degludec) to ***suppress hepatic glucose production and maintain near normoglycemia in the fasting state***.
- As a **premeal (prandial) bolus dose** of short-acting (regular) or rapid-acting (lispro, aspart, glulisine) ***insulin to cover the extra requirements after food is absorbed***
- As a **premixed** combination of intermediate-acting and short- or rapid-acting insulin

Pharmacokinetics of the most commonly used insulin preparations

Insulin type	Onset of action	Peak effect	Duration of action
Lispro, aspart, glulisine	5 to 15 minutes	45 to 75 minutes	Two to four hours
Regular	About 30 minutes	Two to four hours	Five to eight hours
NPH	About two hours	4 to 12 hours	18 to 28 hours
Insulin glargine	About two hours	No peak	20 to >24 hours
Insulin detemir	About two hours	Three to nine hours	6 to 24 hours*
NPL	About two hours	Six hours	15 hours
Insulin degludec	About two hours	No peak	>40 hours

NPH: neutral protamine hagedorn; NPL: neutral protamine lispro.
*Duration of action is dose-dependent. **At higher doses (≥0.8 units/kg)**, mean **duration** of action **is longer and less variable (22 to 23 hours)**.

Time-action profiles for NPH and insulin glargine

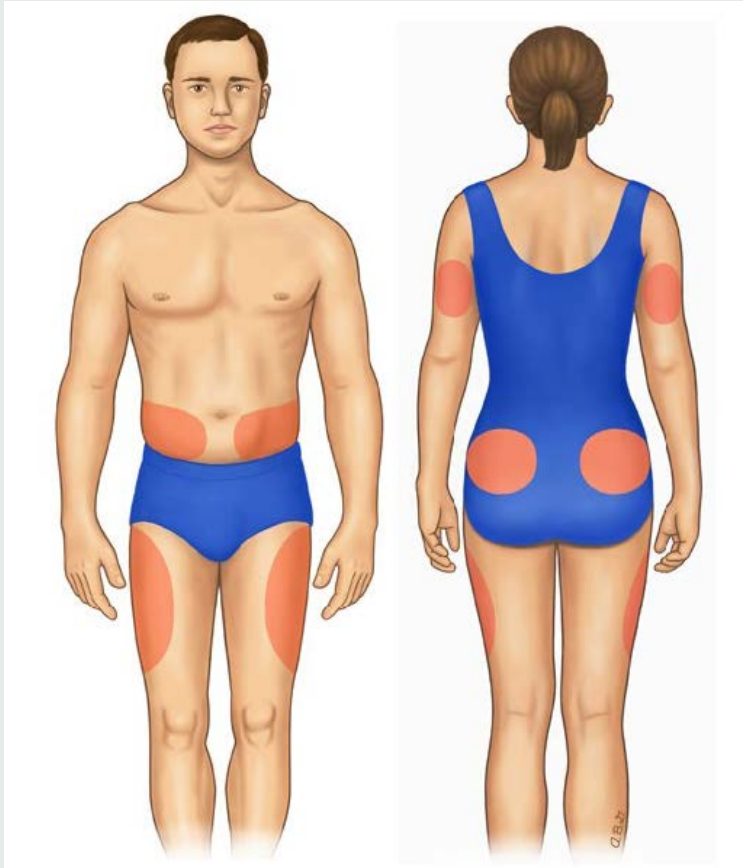


DETERMINANTS OF INSULIN EFFICACY

- **Type of insulin**
  - the degree of absorption of any dose, both among patients and in the same patient, can vary from day to day by as much as **25 to 50 percent,** leading to unexplained fluctuations in glycemic control.
- ***Size of subcutaneous depot***
- **Injection technique**
- **Alterations in *subcutaneous blood flow***
  - Insulin absorption is **reduced by smoking** and **increased by any increases in skin temperature** induced by exercise, saunas or hot baths, and local massage.
  - ***These variations*** are ***more marked*** with ***regular and rapid-acting insulins*** than with longer-acting insulins

Site of injection

- Random rotation of injection sites
- Insulin is ***absorbed fastest*** from the ***abdominal wall***
- ***Slowest*** from the ***leg and buttock***
- ***Intermediate*** rate from ***the arm***
- At any of these sites, the **rapidity of insulin absorption** varies **inversely** ***with subcutaneous fat thickness.***



Disadvantages

- **Weight gain**
  - The magnitude of the ***weight gain depends*** upon the ***intensity of regimen*** (dose and frequency of insulin)

- **Hypoglycemia**
  - Patients with ***type 2 diabetes*** experience ***less hypoglycemia***.
  - ***Basal insulin*** is associated with ***less hypoglycemia than prandial insulin***.
  - Among basal insulin preparations, insulin ***glargine, detemir, and degludec*** may have some relatively modest clinical advantages ***over NPH*** (***less symptomatic and nocturnal hypoglycemia)*** with the important disadvantage of high cost

Indications for insulin

- ***Persistent hyperglycemia on oral agents***
- ***Initial therapy***
  - ***severity of the baseline metabolic disturbance***.
- ***Difficulty distinguishing type of diabetes***
  - patients who are underweight, are losing weight, or are ketotic

DESIGNING AN INSULIN REGIMEN

- ***Add insulin to oral medication***
  - By **suppressing hepatic glucose production,** the patient can retain the convenience of oral agents while minimizing total insulin requirements and weight gain.
  - The addition of ***basal insulin*** will ***improve nocturnal and fasting blood glucose*** **(FBG)**
  - ***we suggest initiating basal rather than prandial insulin***.
  - Either insulin **NPH or detemir** given at bedtime**,** or insulin **glargine or degludec** given in the morning or at bedtime**,** is a reasonable initial regimen.
  - The ***timing of daily insulin glargine or degludec*** is based on ***patient preference*** and when the patient is less likely to miss a dose.
  - A ***morning rather than a bedtime dose*** of insulin glargine may provide better glycemic control in patients with type 2 diabetes who are also treated with a sulfonylurea.

DESIGNING AN INSULIN REGIMEN

- **SWITCHING TO INSULIN MONOTHERAPY**
- **INSULIN AS INITIAL THERAPY**
  - when blood glucose is ≥300 mg/dL (16.7 mmol/L) or ***A1C is ≥10%*** (86 mmol/mol) or if the patient ***has symptoms of hyperglycemia*** (i.e., polyuria or polydipsia).
  - By inducing near normoglycemia with intensive insulin therapy, both endogenous insulin secretion and insulin sensitivity improve.
  - Insulin can be considered as initial therapy for all patients with type 2 diabetes and can result in **remission for one year or longer**.
  - The improvement in insulin secretion is presumably due to the **elimination of the deleterious effects of hyperglycemia on beta cell secretory function**, and, in some patients, it results in better glycemic control that can then be maintained with diet and exercise for many months or even years.

Basal versus bolus

- **Basal:**
  - Intermediate- to long-acting preparations (NPH, NPL, detemir, glargine, or degludec)
  - Continuous infusion of a short- or rapid-acting insulin via an insulin pump
- **Bolus** :
  - Short-acting (regular) insulin
  - Rapid-acting (lispro, aspart, or glulisine)

Basal Insulin

- Basal insulin alone is the most convenient initial insulin regimen***, beginning at 10 units per day or 0.1–0.2 units/kg/day, depending on the degree of hyperglycemia.***
- Basal insulin is usually prescribed in conjunction with **metformin** and sometimes one additional noninsulin agent.
- When basal insulin is added to antihyperglycemic agents in patients with type 2 diabetes, **long-acting basal analogs** (U-100 glargine or detemir) can be used instead of NPH to **reduce** the risk of **symptomatic** and **nocturnal** hypoglycemia.

- **Longer acting basal analogs** (**U-300 glargine** or **degludec**) may additionally convey a ***lower hypoglycemia risk compared with U-100 glargine*** when used in combination with oral antihyperglycemic agents.

- While there is evidence for reduced hypoglycemia with newer, longer-acting basal insulin analogs, **people without a history of hypoglycemia are at decreased risk and could potentially be switched to human insulin safely**.

Bolus Insulin

- Many individuals with type 2 diabetes may require mealtime bolus insulin dosing in addition to basal insulin.
- **Rapid** acting analogs are **preferred** due to their prompt onset of action after dosing.
- The recommended **starting dose** of mealtime insulin is **4 units**, **0.1 units/kg**, or **10% of the basal dose**.
- **If A1C is < 8%** when starting mealtime bolus insulin, consideration should be given to **decreasing the basal insulin dose**.

Premixed Insulin

- Premixed insulin products **contain both a basal and prandial component**, allowing coverage of both basal and prandial needs with a single injection.
- NPH/Regular 70/30 insulin, for example, is composed of 70% NPH insulin and 30% regular insulin.
- Insulin **glargine** and insulin **detemir** *should not be mixed* with other insulins due to the low pH of the diluents.
- ***After mixing NPH with regular insulin, the formulation should be used immediately***.
- Rapid-acting insulin can be mixed with NPH.
- When this is done, the ***mixture should be injected within 15 minutes prior to a meal.***

Inhaled Insulin

- Inhaled insulin is available for **prandial use** with amore limited dosing range.
- It is **contraindicated** in patients with chronic lung disease such as asthma and chronic obstructive pulmonary disease and is **not recommended** in patients who smoke or who recently stopped smoking.
- It requires spirometry (FEV1) testing to identify potential lung disease in all patients prior to and after starting therapy.

Combination Injectable Therapy

- Consider advancing to ***combination injectable therapy If:***
  - ❖ Basal insulin has been titrated to an acceptable fasting blood glucose level or
  - ❖ If the dose is.0.5 units/kg/day
  - ❖ and A1C remains above target
- When initiating combination injectable therapy, metformin therapy should be maintained while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens.

Cont…

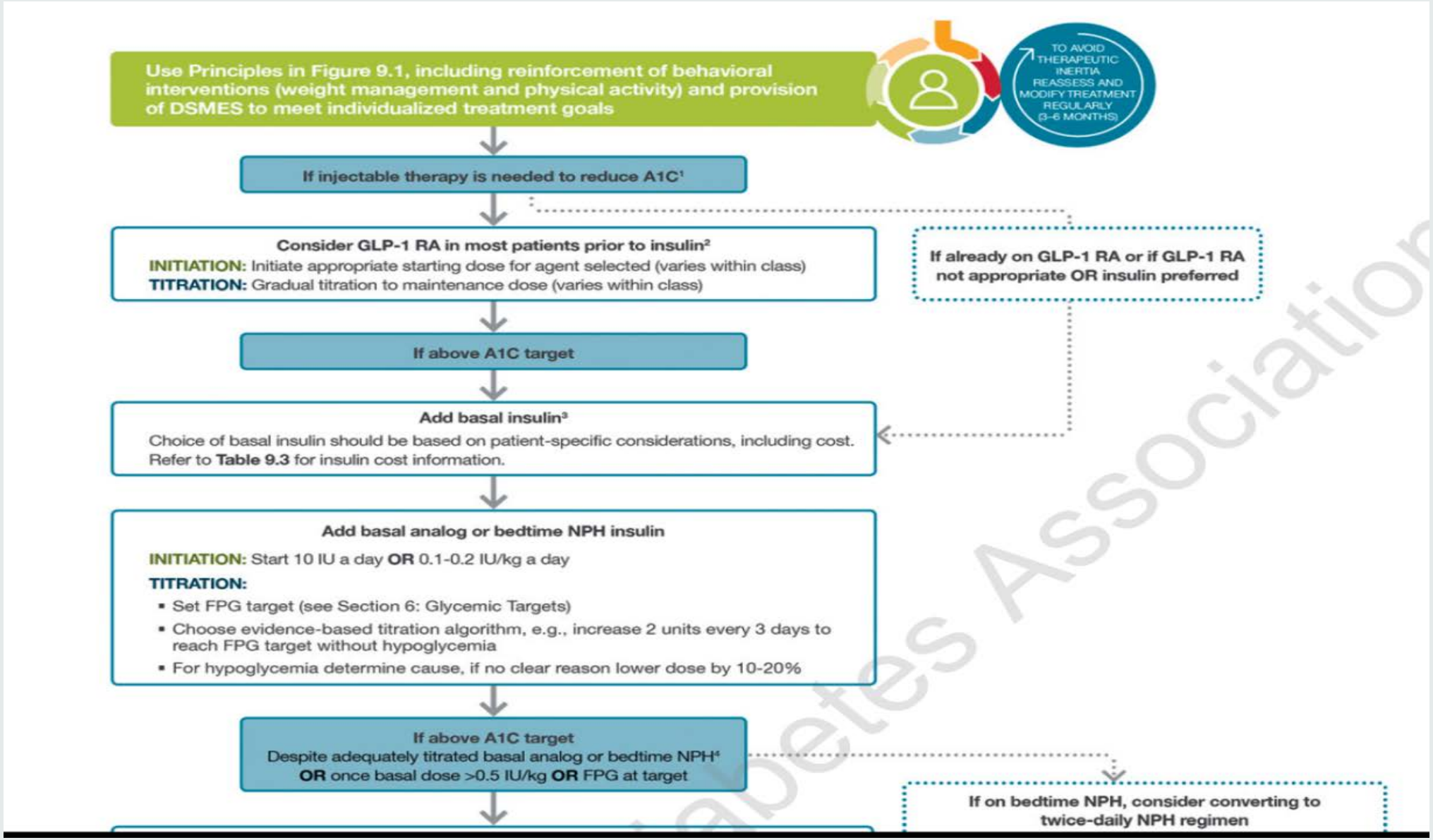
- In general, **GLP-1 receptor agonists** should **not be discontinued** with the initiation of **basal** insulin.
- **Sulfonylureas**, **DPP-4 inhibitors**, and **GLP- 1 receptor agonists** are typically stopped once **more complex insulin regimens beyond basal are used**.

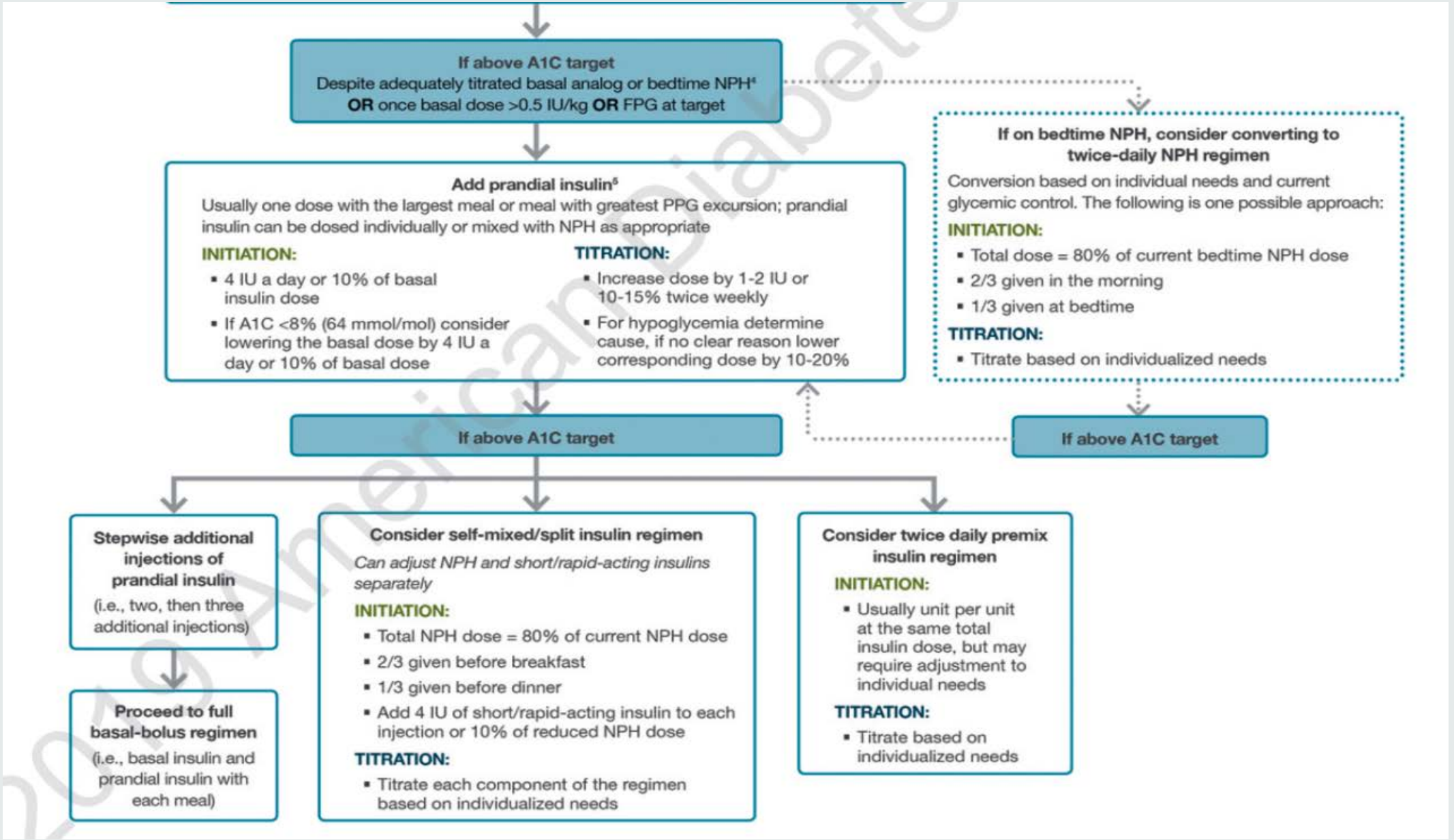
Cont…

- In patients with suboptimal blood glucose control, ***especially those requiring large insulin doses:***
  - Adjunctive use of a **thiazolidinedione** or **SGLT2 inhibitor** may ***help to improve control and reduce the amount of insulin needed,*** though potential side effects should be considered.

Options for treatment intensification

1. **Basal insulin plus GLP-1 receptor agonists** are associated with less hypoglycemia and with weight loss instead of weight gain but may be less tolerable and have a greater cost.
   - In November2016, the FDA approved two different once-daily fixed-dual combination products containing basal insulin plus a GLP-1 receptor agonist: insulin glargine plus lixisenatide and insulin degludec plus liraglutide.
2. **Adding a single injection of rapid-acting** insulin analog (lispro, aspart, or glulisine) before the largest meal
3. Stopping the basal insulin and **initiating a premixed** (or biphasic)


Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If injectable therapy is needed to reduce A1C[1]
Consider GLP-1 RA in most patients prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Gradual titration to maintenance dose (varies within class)
If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred
If above A1C target
Add basal insulin[3]
Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 9.3 for insulin cost information.
Add basal analog or bedtime NPH insulin
INITIATION: Start 10 IU a day OR 0.1-0.2 IU/kg a day
TITRATION:
Set FPG target (see Section 6: Glycemic Targets)
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%
If above A1C target
Despite adequately titrated basal analog or bedtime NPH[4]
OR once basal dose >0.5 IU/kg OR FPG at target
If on bedtime NPH, consider converting to twice-daily NPH regimen


If above A1C target
Despite adequately titrated basal analog or bedtime NPH[4]
OR once basal dose >0.5 IU/kg OR FPG at target
Add prandial insulin[5]
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate
INITIATION:
4 IU a day or 10% of basal insulin dose
If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 IU a day or 10% of basal dose
TITRATION:
Increase dose by 1-2 IU or 10-15% twice weekly
For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10-20%
If on bedtime NPH, consider converting to twice-daily NPH regimen
Conversion based on individual needs and current glycemic control. The following is one possible approach:
INITIATION:
Total dose = 80% of current bedtime NPH dose
2/3 given in the morning
1/3 given at bedtime
TITRATION:
Titrate based on individualized needs
If above A1C target
If above A1C target
Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)
Proceed to full basal-bolus regimen
(i.e., basal insulin and prandial insulin with each meal)
Consider 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
1/3 given before dinner
Add 4 IU of short/rapid-acting insulin to each injection or 10% of reduced NPH dose
TITRATION:
Titrate each component of the regimen based on individualized needs
Consider twice daily premix insulin regimen
INITIATION:
Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs
TITRATION:
Titrate based on individualized needs