Summary of Revisions : Standards of Medical Care in Diabetes - 2019

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Section 2. Classification and Diagnosis of Diabetes

- Based on new data, the criteria for the diagnosis of diabetes was changed to include two abnormal test results from *the same sample* (i.e., fasting plasma glucose and A1C from same sample).

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Table 2.6—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130 mg/dL, 135 mg/dL, or 140 mg/dL (7.2 mmol/L, 7.5 mmol/L, or 7.8 mmol/L, respectively), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two* of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h during OGTT) are met or exceeded:

	Carpenter-Coustan (86)	or	NDDG (87)
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group

*ACOG notes that one elevated value can be used for diagnosis (82).

POSTTRANSPLANTATION DIABETES MELLITUS

- The **oral glucose tolerance test** is the preferred test to make a diagnosis of posttransplantation diabetes mellitus. B

Section 3. Prevention or Delay of Type 2 Diabetes

- The nutrition section was updated to highlight the importance of **weight loss** for those at high risk for developing type 2 diabetes who have overweight or obesity.

- Because **smoking** may increase the risk of type 2 diabetes, a section on tobacco use and cessation was added.

Section 5. Lifestyle Management

- A recommendation was modified to encourage people with diabetes to decrease consumption of both sugar sweetened and nonnutritive-sweetened beverages and use other alternatives, with an emphasis on ***water intake***.

- The sodium consumption / Restriction
- Physical Activity
- E – cigarrete

Noninsulin Treatments for Type 1 Diabetes

- Pramlintide
- The addition of **metformin** to adults with type 1 diabetes caused small reductions in body weight and lipid levels but ***did not improve A1C***
- The addition of the glucagon-like peptide 1 (GLP-1) receptor agonists ***liraglutide*** and ***exenatide*** to insulin therapy caused small (0.2%) reductions in A1C compared with insulin alone in people with type 1 diabetes and also reduced body weight by #3 kg

Noninsulin Treatments for Type 1 Diabetes

- Similarly, the addition of a sodium–glucose cotransporter 2 (SGLT2) inhibitor to insulin therapy has been associated with improvements in A1C and body weight when compared with insulin alone ; however, SGLT2 inhibitor use is also associated with more adverse events including **ketoacidosis**.

Sotagliflozin

- The dual SGLT1/2 inhibitor sotagliflozin is currently under consideration by the FDA and, if approved, would be the first adjunctive oral therapy in type 1 diabetes.

- **Gabapentin** was added to the list of agents to be **considered** for the treatment of neuropathic pain in people with diabetes based on data on efficacy and the potential for cost savings.

- The recommendation for patients with diabetes to have their feet inspected at every visit was modified to only include *those at **high risk** for ulceration*.

- Annual examinations remain recommended for everyone.

Section 14. Management of Diabetes in Pregnancy

- Greater emphasis has been placed on the use of **insulin** as the preferred medication for treating hyperglycemia in gestational diabetes mellitus as it does not cross the placenta to a measurable extent and how **metformin** and **glyburide** should not be used **as first line agents** as both **cross the placenta** to the fetus.

PHARMACOLOGIC THERAPY FOR T2DM

- ***Metformin*** is the preferred initial pharmacologic agent for the treatment of type 2 diabetes./ A

- Once initiated, **metformin** should be continued as long as it is **tolerated** and **not contraindicated** ; other agents, including insulin, should be added to metformin. /A

Metformin

- Long-term use of metformin may be associated with biochemical *vitamin B12 deficiency*, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, **especially** in those with *anemia* or *peripheral neuropathy*. / B

Dual therapy in T2DM

- Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C $\geq$ 1.5% , (12.5 mmol/ mol) above their glycemic target. / E

- A comparative effectiveness meta-analysis suggests that each new class of noninsulin agents **added** to initial therapy generally lowers A1C approximately 0.7–1.0%

Insulin therapy in T2DM

- 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

Combination Therapy

- In trials comparing the addition of **GLP-1 receptor** agonists or **insulin** in patients needing further glucose lowering, the **efficacy** of the two treatments was **similar**

PHARMACOLOGIC THERAPY FOR T2DM

- key patient factors:
  1) important comorbidities such as atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and heart failure (HF),
  2) hypoglycemia risk,
  3) effects on body weight,
  4) side effects,
  5) cost
  6) patient preferences

Glucose – lowering Medications

- Therefore, an important early step in this new approach (Fig. 3) is to consider the presence or absence of **ASCVD**, **HF**, and **CKD**, conditions in aggregate affecting **15–25%** of the population with type 2 diabetes.

Drugs in ASCVD

- Among patients with type 2 diabetes who have established ASCVD , ***SGLT2 inhibitors*** or ***GLP-1 receptor agonists*** with proven cardiovascular benefit are recommended **as part of glycemic management.** (Figs. 2 and 3)

ASCVD

- Taken together, it appears that among patients with established **CVD**, some **GLP-1** receptor agonists may provide cardiovascular benefit, with the evidence of benefit strongest for **liraglutide**, favorable for **semaglutide**, and less certain for **exenatide**.

- There is no evidence of cardiovascular benefit with **lixisenatide** .

ASCVD

- For the SGLT2 inhibitors studied to date, it appears that among patients with established **CVD**, there is likely cardiovascular benefit, with the evidence of benefit **modestly stronger** for **empagliflozin** than **canagliflozin .**

- While the evidence of an **ASCVD** outcomes benefit for **GLP-1** receptor agonists and **SGLT2** inhibitors has been demonstrated for people with established ASCVD, the evidence of benefit **beyond glucose lowering** has **not** been **demonstrated** in those **without ASCVD**.

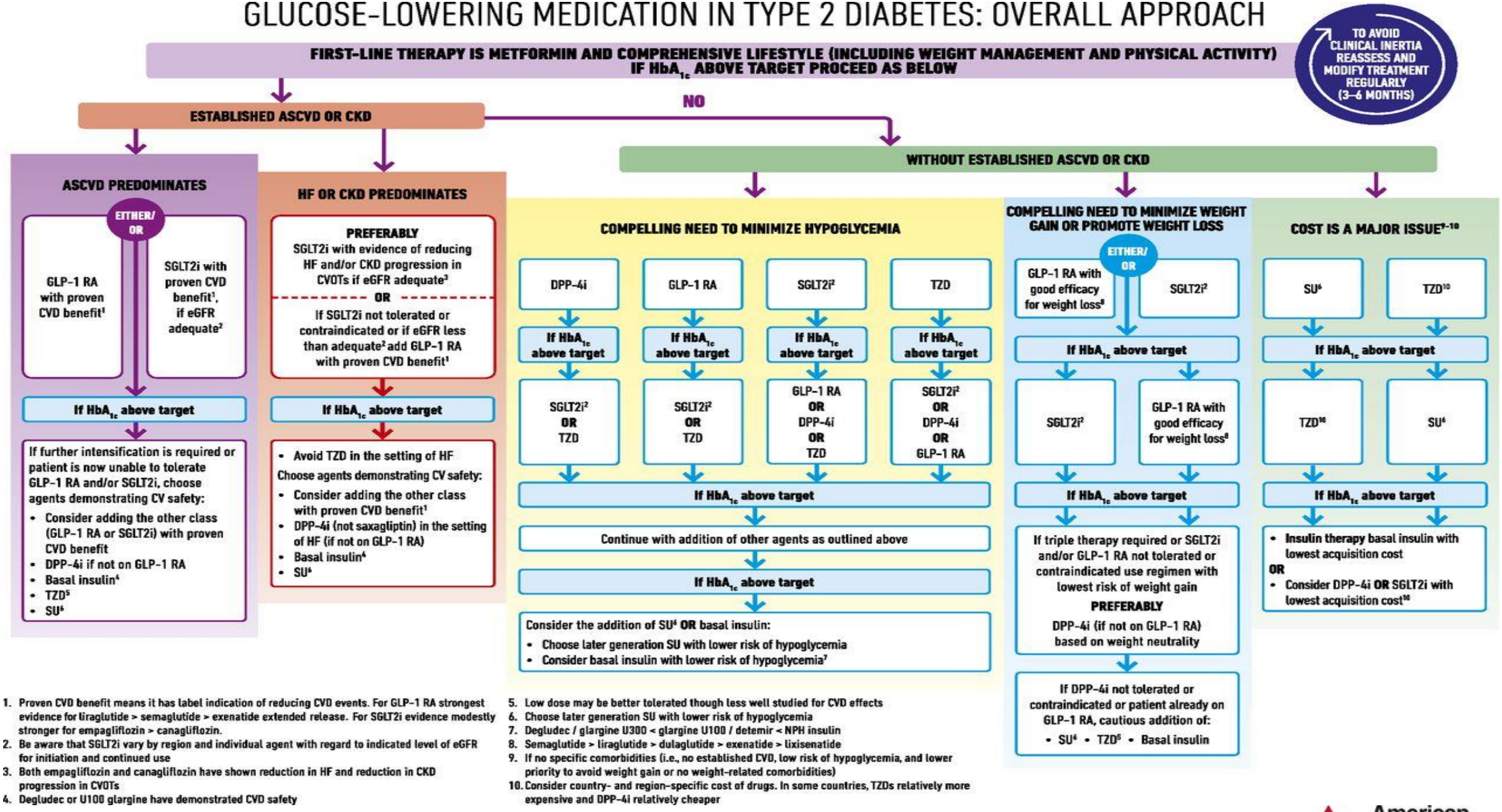
- Indeed, in subgroup analyses of these trials, **lower-risk individuals** have **not** been observed to have an **ASCVD benefit.**

PHARMACOLOGIC THERAPY FOR T2DM

- Among patients with atherosclerotic cardiovascular disease at high risk of **heart failure** or in whom **heart failure coexists**, sodium–glucose cotransporter 2 inhibitors are preferred. / C

- For patients with type 2 diabetes and **chronic kidney disease**, consider use of a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, **or both**./ C

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

Melanie J. Davies et al. Dia Care 2018;41:2669-2701

American Diabetes Association.

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)

Use principles in Figure 1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit[1] (see below)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (see below)

OR reconsider/lower individualized target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3-month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target

ASCVD predominates

HF or CKD predominates

ASCVD predominates

GLP-1 RA with proven CVD benefit[1]

EITHER/ OR

SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit[1]
- DPP-4i if not on GLP-1 RA
- Basal insulin[5]
- TZD[6]
- SU[7]

HF or CKD predominates

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1,4]

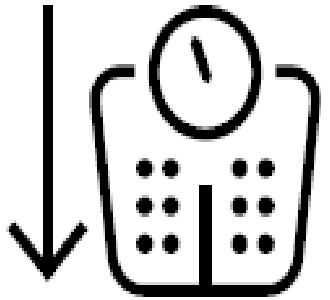
If HbA_{1c} above target

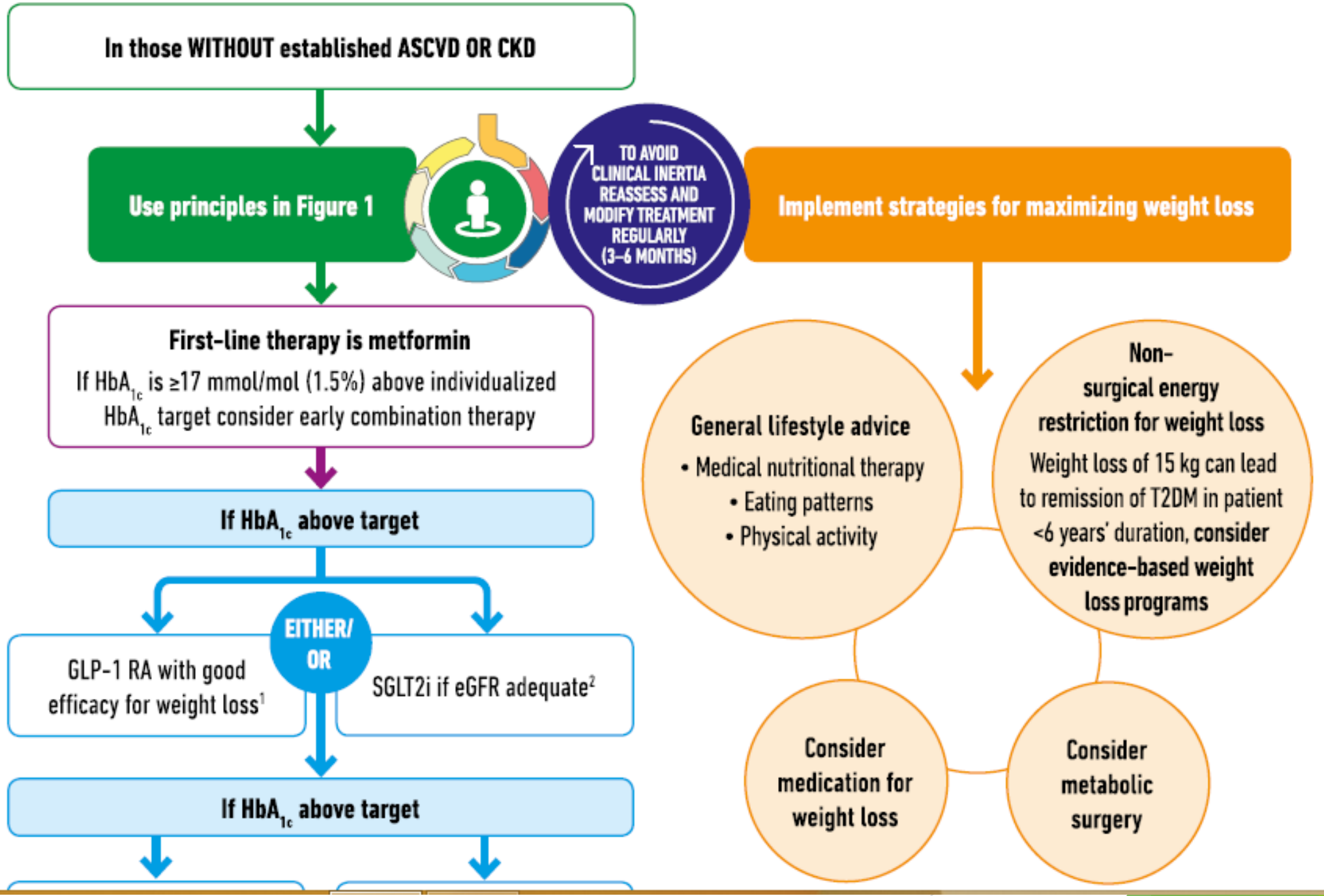
- Avoid TZD in the setting of HF

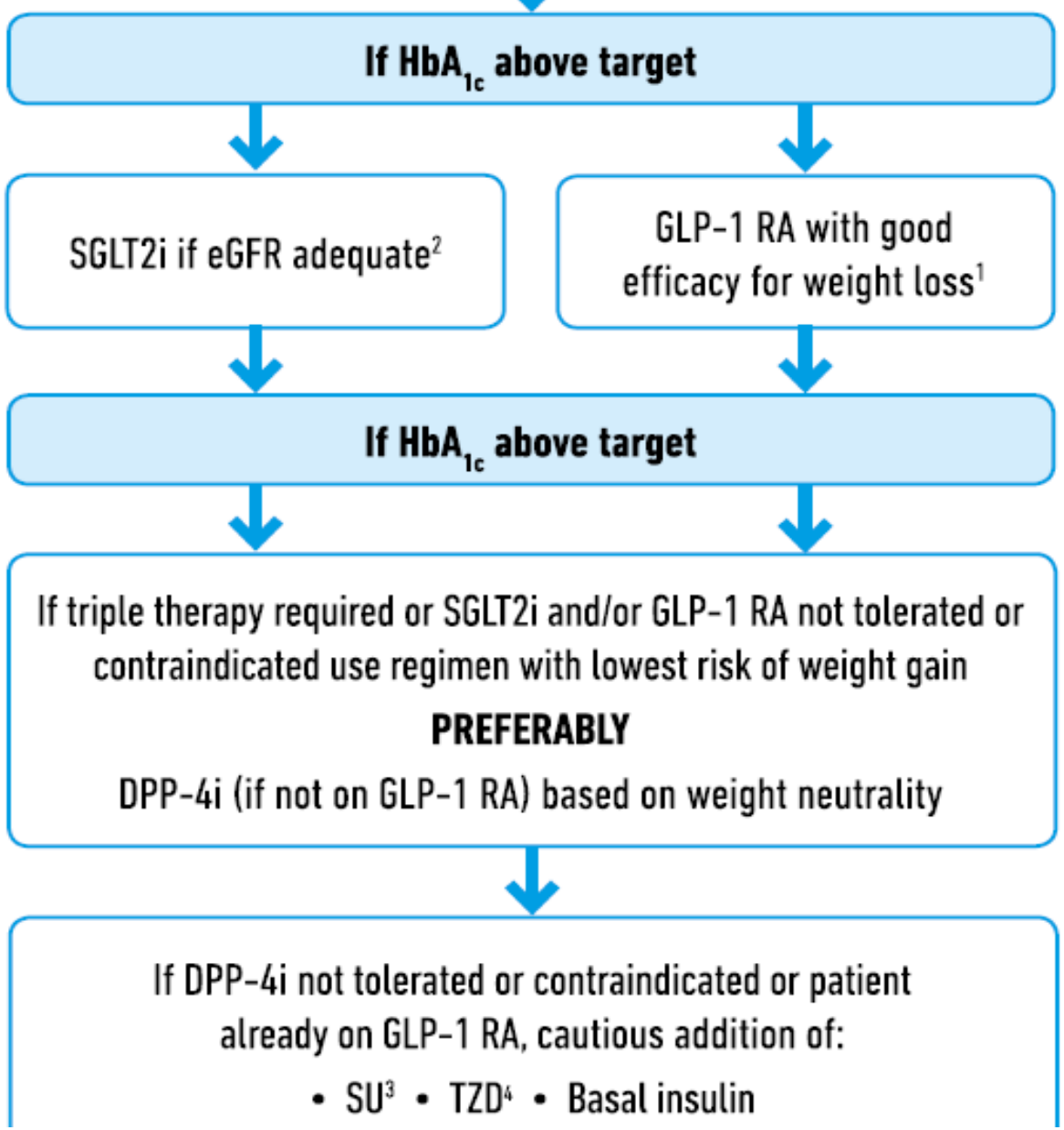
Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[5]
- SU[7]

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

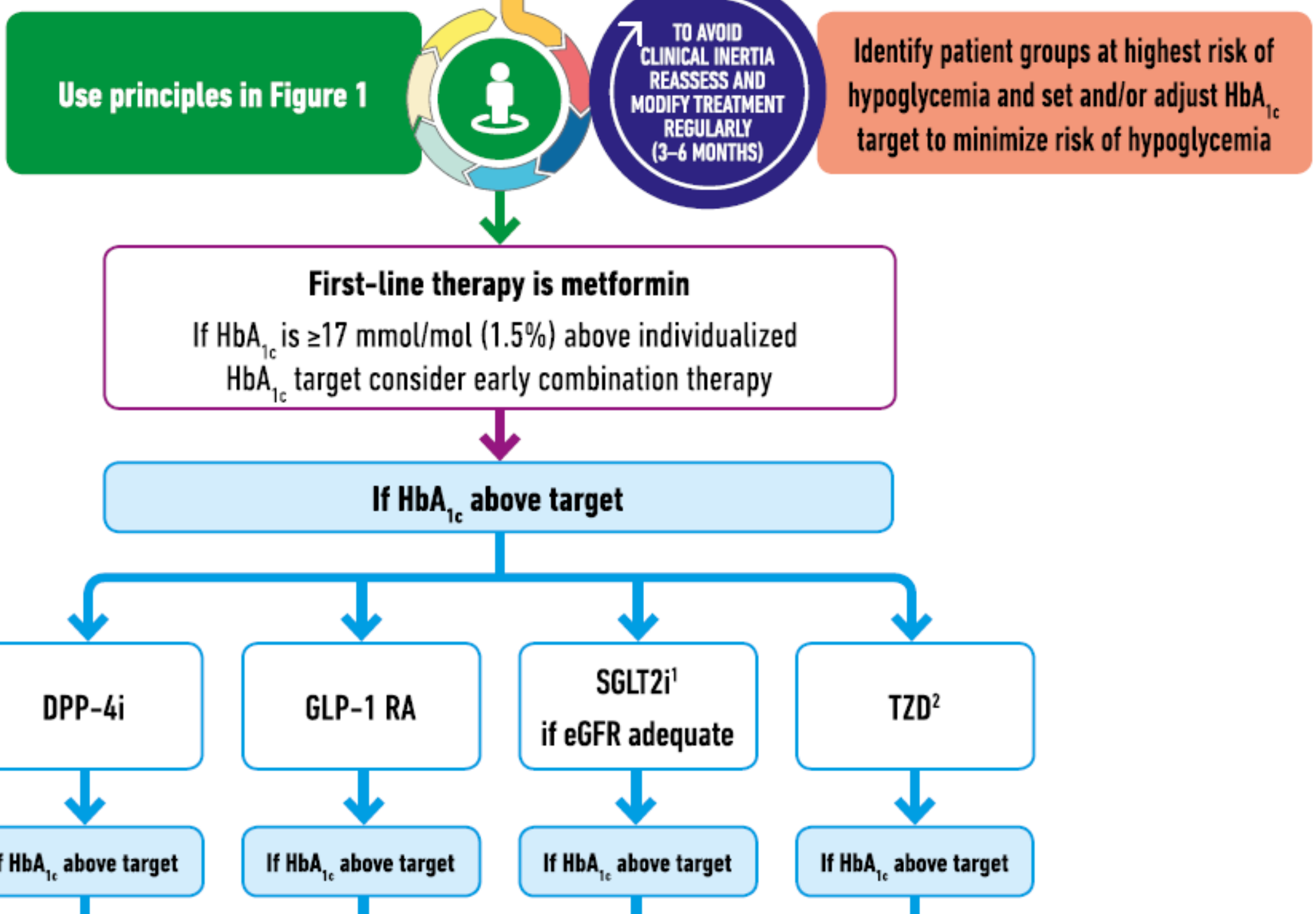


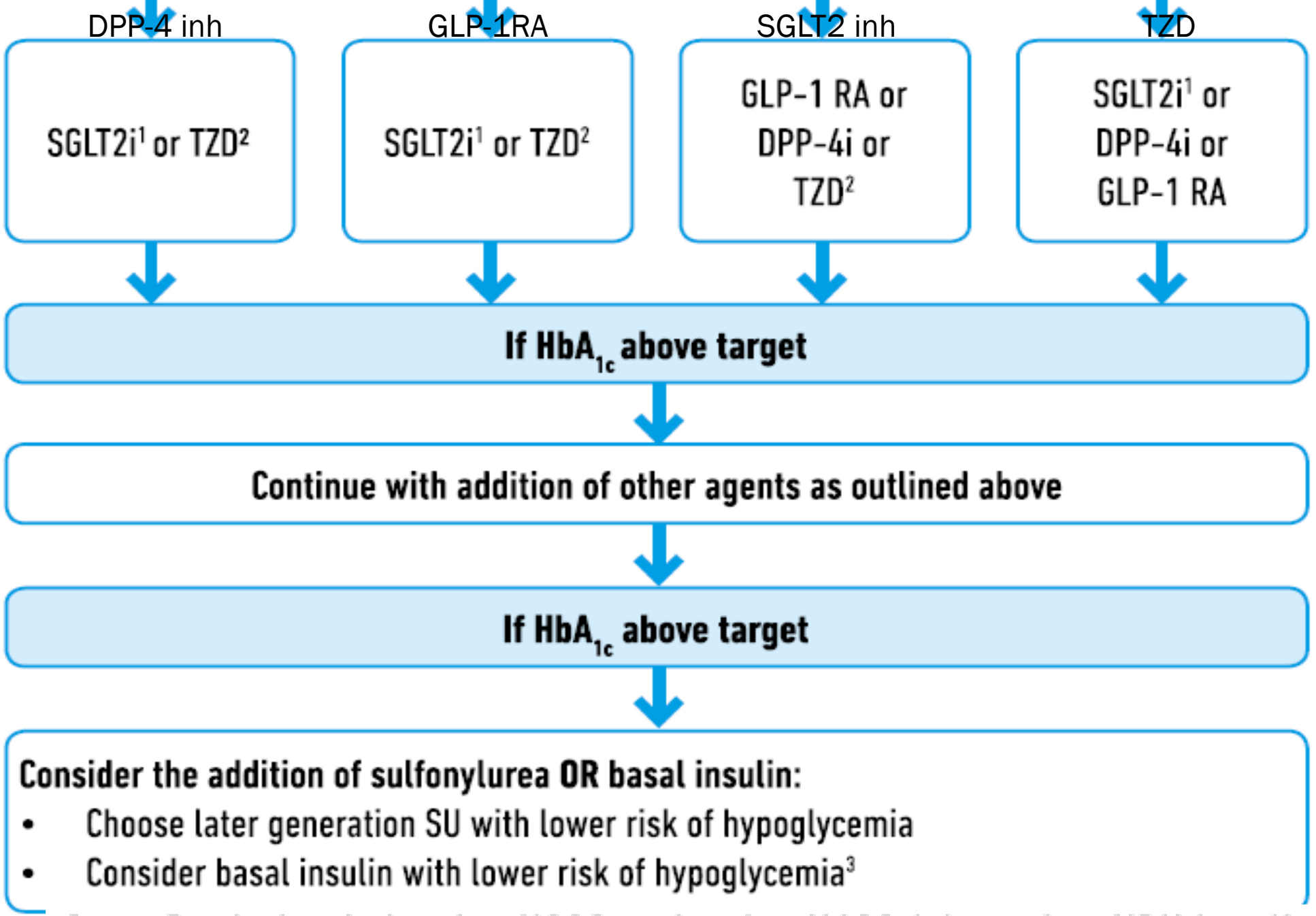

In those WITHOUT established ASCVD OR CKD
Use principles in Figure 1
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
Implement strategies for maximizing weight loss
First-line therapy is metformin
If HbA1c is ≥17 mmol/mol (1.5%) above individualized HbA1c target consider early combination therapy
If HbA1c above target
EITHER/ OR
GLP-1 RA with good efficacy for weight loss[1]
SGLT2i if eGFR adequate[2]
If HbA1c above target
General lifestyle advice
• Medical nutritional therapy
• Eating patterns
• Physical activity
Non-surgical energy restriction for weight loss
Weight loss of 15 kg can lead to remission of T2DM in patient <6 years' duration, consider evidence-based weight loss programs
Consider medication for weight loss
Consider metabolic surgery



1. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Choose later generation SU with lower risk of hypoglycemia
4. Low dose may be better tolerated though less well studied for CVD effects

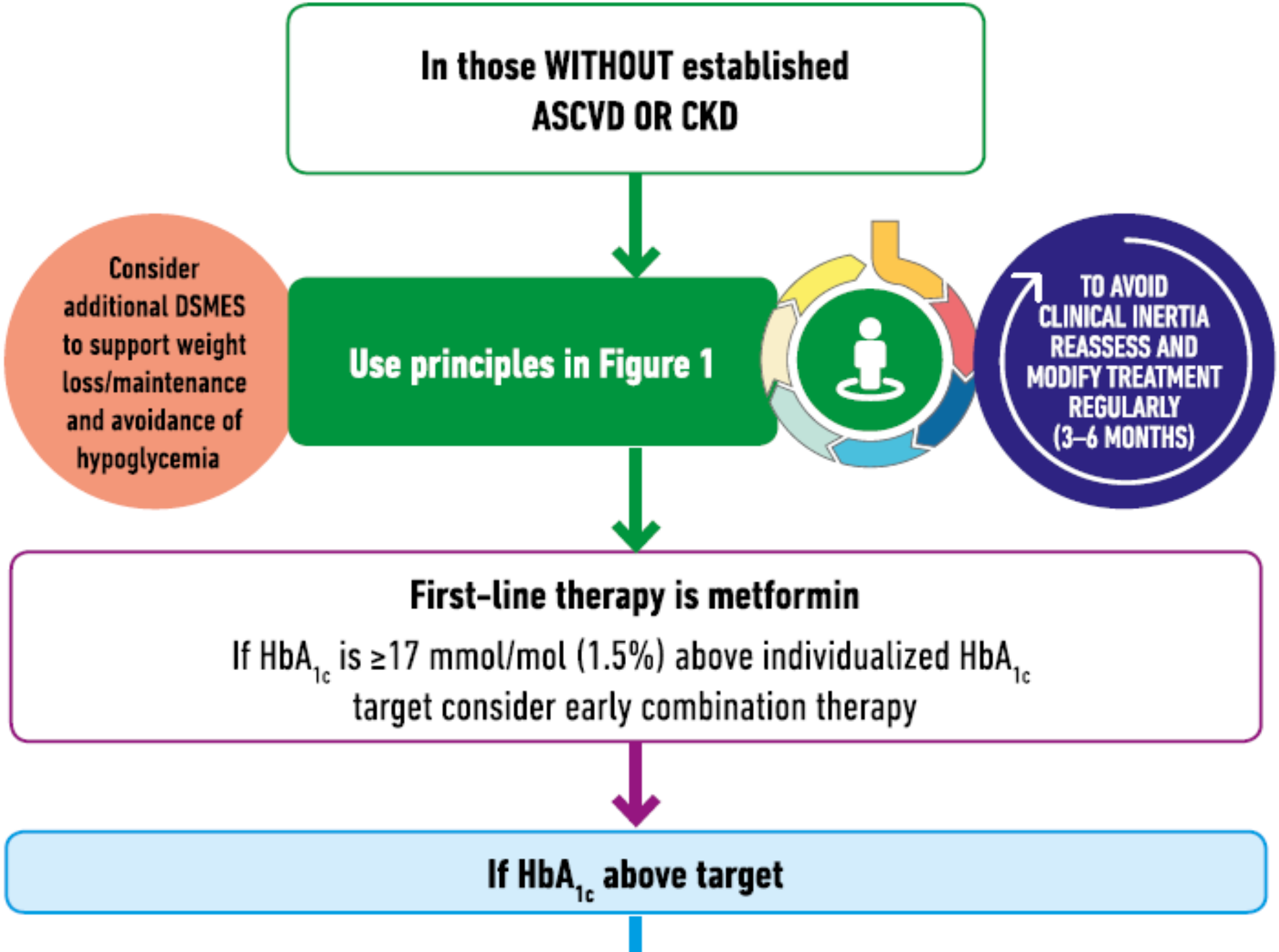
CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

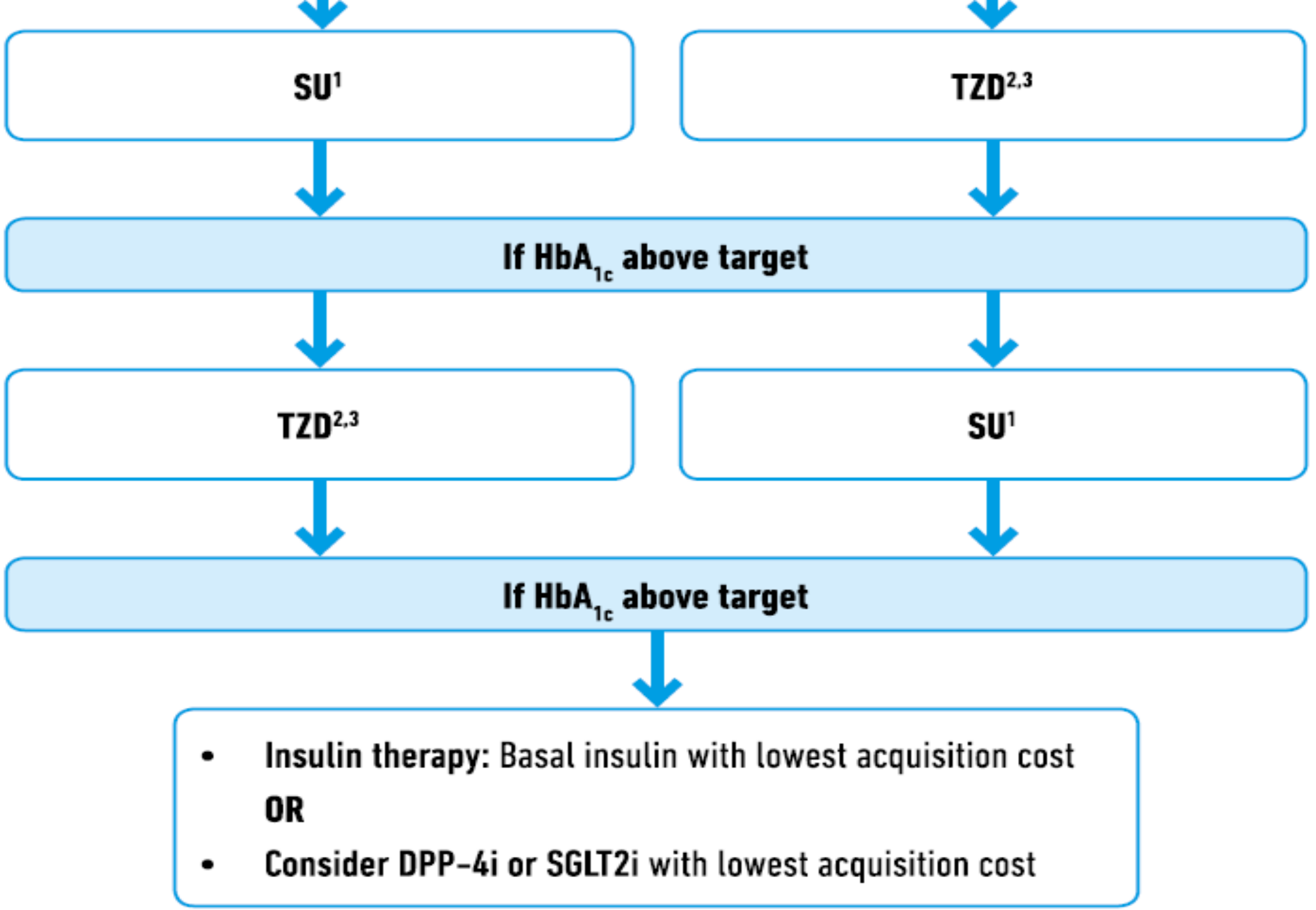

Use principles in Figure 1
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
Identify patient groups at highest risk of hypoglycemia and set and/or adjust HbA1c target to minimize risk of hypoglycemia
First-line therapy is metformin
If HbA1c is ≥17 mmol/mol (1.5%) above individualized HbA1c target consider early combination therapy
If HbA1c above target
DPP-4i
GLP-1 RA
SGLT2i[1] if eGFR adequate
TZD[2]
If HbA1c above target
If HbA1c above target
If HbA1c above target
If HbA1c above target



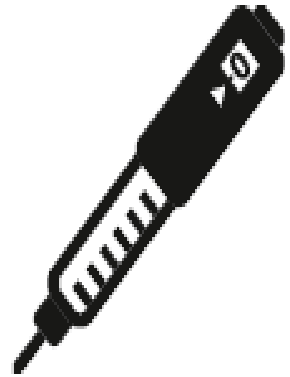
3. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin

CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE

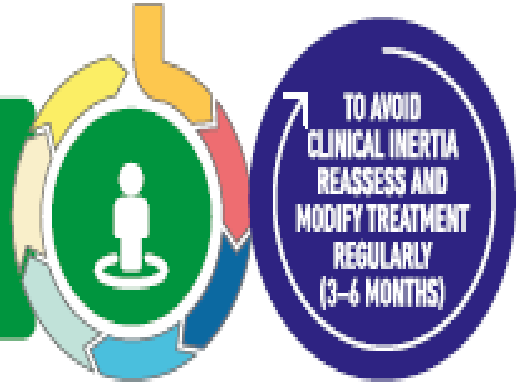

In those WITHOUT established ASCVD OR CKD
Consider additional DSMES to support weight loss/maintenance and avoidance of hypoglycemia
Use principles in Figure 1
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
First-line therapy is metformin
If HbA1c is ≥17 mmol/mol (1.5%) above individualized HbA1c target consider early combination therapy
If HbA1c above target


SU[1]
TZD[2,3]
If HbA1c above target
TZD[2,3]
SU[1]
If HbA1c above target
• Insulin therapy: Basal insulin with lowest acquisition cost
OR
• Consider DPP-4i or SGLT2i with lowest acquisition cost

INTENSIFYING TO INJECTABLE THERAPIES

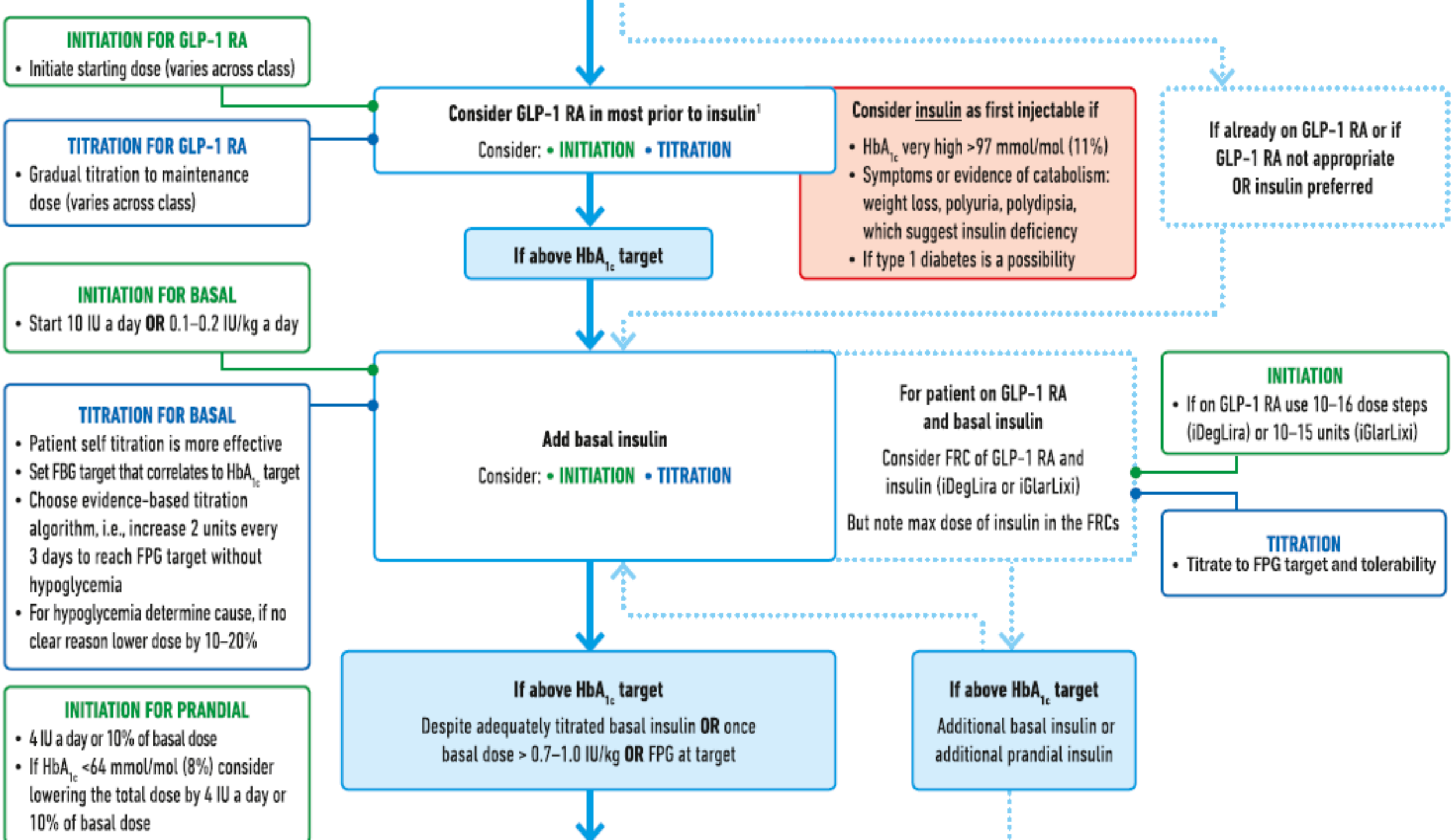


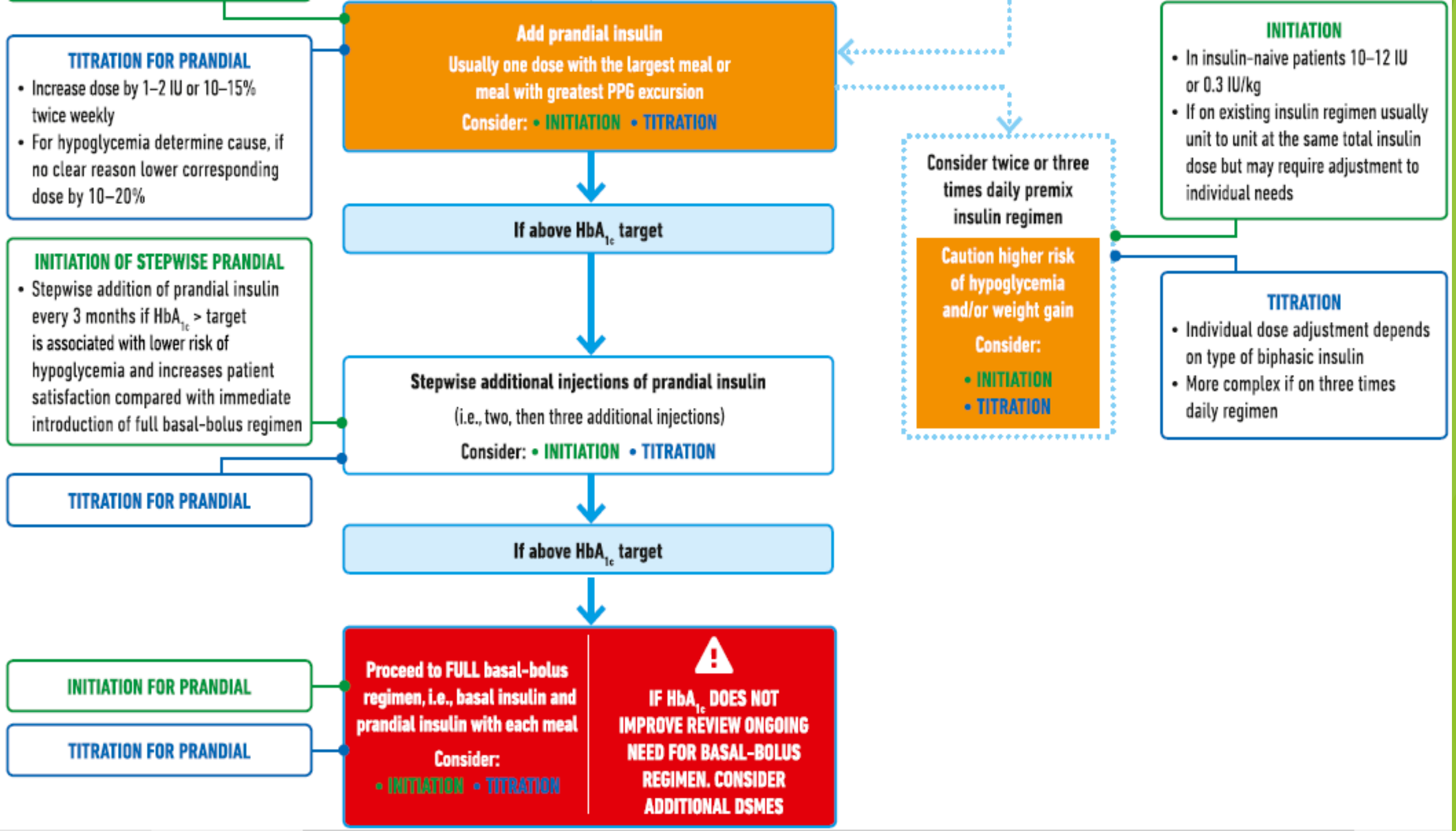
Use principles in Figure 1



If HbA_{1c} above target despite dual/triple therapy

Consider initial injectable combination (i.e., GLP-1 RA + basal insulin or prandial/basal insulin) if HbA_{1c} >86 mmol/mol (10%) and/or >23 mmol/mol (2%) above target


INITIATION FOR GLP-1 RA
• Initiate starting dose (varies across class)
TITRATION FOR GLP-1 RA
• Gradual titration to maintenance dose (varies across class)
Consider GLP-1 RA in most prior to insulin[1]
Consider: • INITIATION • TITRATION
Consider insulin as first injectable if
• HbA1c very high >97 mmol/mol (11%)
• Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia, which suggest insulin deficiency
• If type 1 diabetes is a possibility
If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred
If above HbA1c target
INITIATION FOR BASAL
• Start 10 IU a day OR 0.1–0.2 IU/kg a day
TITRATION FOR BASAL
• Patient self titration is more effective
• Set FBG target that correlates to HbA1c target
• Choose evidence-based titration algorithm, i.e., 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%
Add basal insulin
Consider: • INITIATION • TITRATION
For patient on GLP-1 RA and basal insulin
Consider FRC of GLP-1 RA and insulin (iDegLira or iGlarLixi)
But note max dose of insulin in the FRCs
INITIATION
• If on GLP-1 RA use 10–16 dose steps (iDegLira) or 10–15 units (iGlarLixi)
TITRATION
• Titrate to FPG target and tolerability
INITIATION FOR PRANDIAL
• 4 IU a day or 10% of basal dose
• If HbA1c <64 mmol/mol (8%) consider lowering the total dose by 4 IU a day or 10% of basal dose
If above HbA1c target
Despite adequately titrated basal insulin OR once basal dose > 0.7–1.0 IU/kg OR FPG at target
If above HbA1c target
Additional basal insulin or additional prandial insulin


Add prandial insulin
Usually one dose with the largest meal or meal with greatest PPG excursion
Consider: • INITIATION • TITRATION
TITRATION FOR PRANDIAL
• 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 above HbA1c target
INITIATION OF STEPWISE PRANDIAL
• Stepwise addition of prandial insulin every 3 months if HbA1c > target is associated with lower risk of hypoglycemia and increases patient satisfaction compared with immediate introduction of full basal-bolus regimen
Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)
Consider: • INITIATION • TITRATION
TITRATION FOR PRANDIAL
If above HbA1c target
INITIATION FOR PRANDIAL
TITRATION FOR PRANDIAL
Proceed to FULL basal-bolus regimen, i.e., basal insulin and prandial insulin with each meal
Consider:
• INITIATION • TITRATION
IF HbA1c DOES NOT IMPROVE REVIEW ONGOING NEED FOR BASAL-BOLUS REGIMEN. CONSIDER ADDITIONAL DSMES
Consider twice or three times daily premix insulin regimen
Caution higher risk of hypoglycemia and/or weight gain
Consider:
• INITIATION
• TITRATION
INITIATION
• In insulin-naive patients 10–12 IU or 0.3 IU/kg
• If on existing insulin regimen usually unit to unit at the same total insulin dose but may require adjustment to individual needs
TITRATION
• Individual dose adjustment depends on type of biphasic insulin
• More complex if on three times daily regimen

Basal Insulin

- For many patients with type 2 diabetes (e.g., individuals with relaxed A1C goals, low rates of hypoglycemia, and prominent insulin resistance, as well as those with cost concerns), human insulin (NPH and Regular) may be the appropriate choice of therapy, and clinicians should be familiar with its use

Prandial Insulin

- Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in patients with type 2 diabetes have not reported important differences in A1C or hypoglycemia

Concentrated Insulin Products

- U-500 regular insulin is, by definition, five times more concentrated than U-100 regular insulin.
- U-300 glargine and U-200 degludec are three and two times as concentrated, respectively, as their U-100 formulations and allow higher doses of basal insulin administration per volume used.
- U-300 glargine has a longer duration of action than U-100 glargine

Concentrated Insulin Products

- TheFDA has also approved a concentrated formulation of rapid-acting **insulin lispro , U-200** (200 units/mL).

- These concentrated preparations may be more convenient and comfortable for patients to inject and may improve adherence in those with insulin resistance who ***require large doses of insulin***.

Combination Injectable Therapy

- Two different **once-daily** fixed-dual combination products containing basal insulin plus a GLP-1 receptor agonist are available: (**FRC**)

  - **insulin glargine** plus **lixisenatide** and
  - **insulin degludec** plus **liraglutide.**

Combination Injectable Therapy

- When initiating combination **injectable therapy**, ***metformin*** therapy should be **maintained** while sulfonylureas and DPP-4 inhibitors are typically **discontinued**.

- Adjunctive use of a ***thiazolidinedione*** or an ***SGLT2 inhibitor*** may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered.