Insulin Therapy
ADA – EASD 2019

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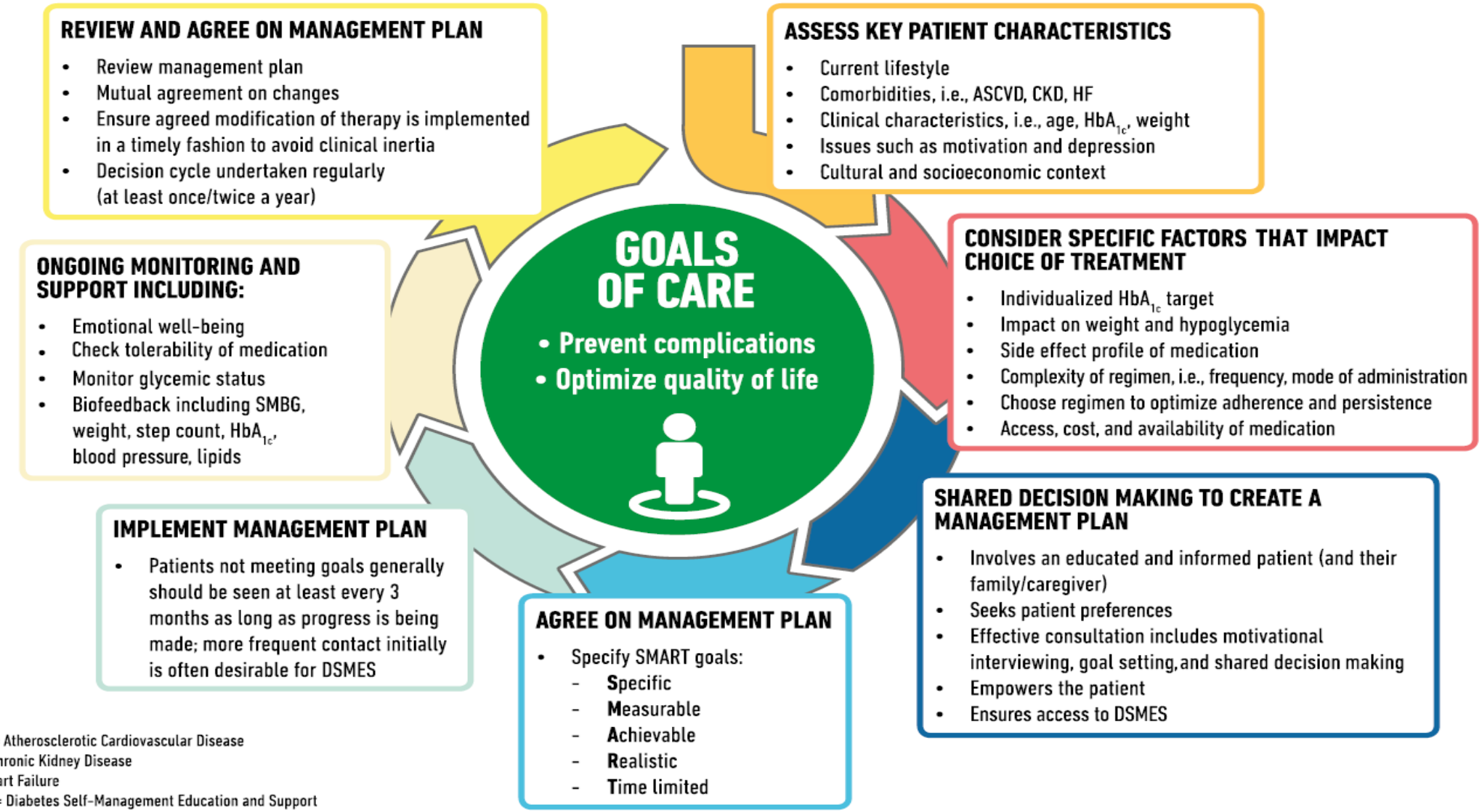
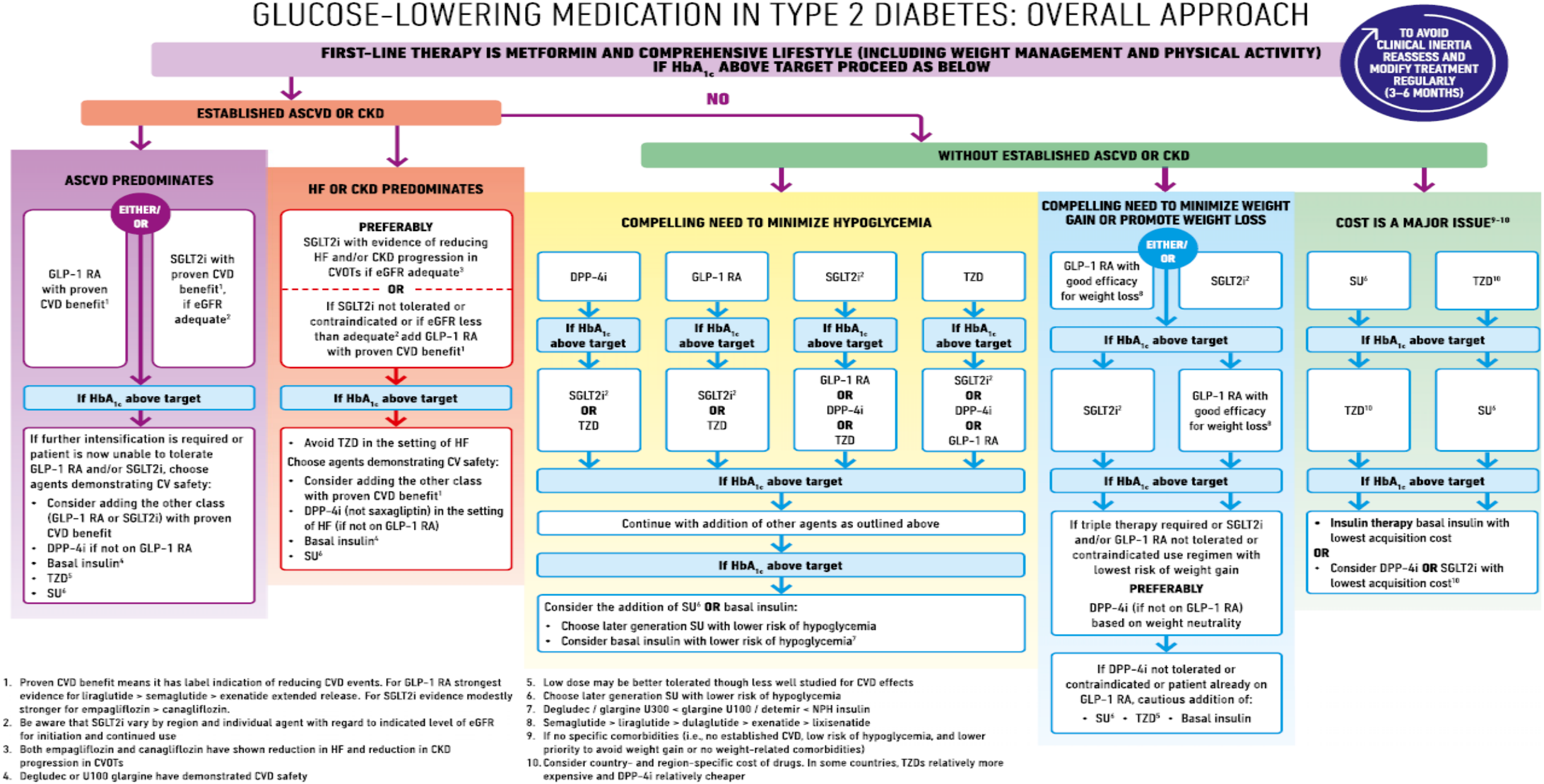
DECISION CYCLE FOR PATIENT-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

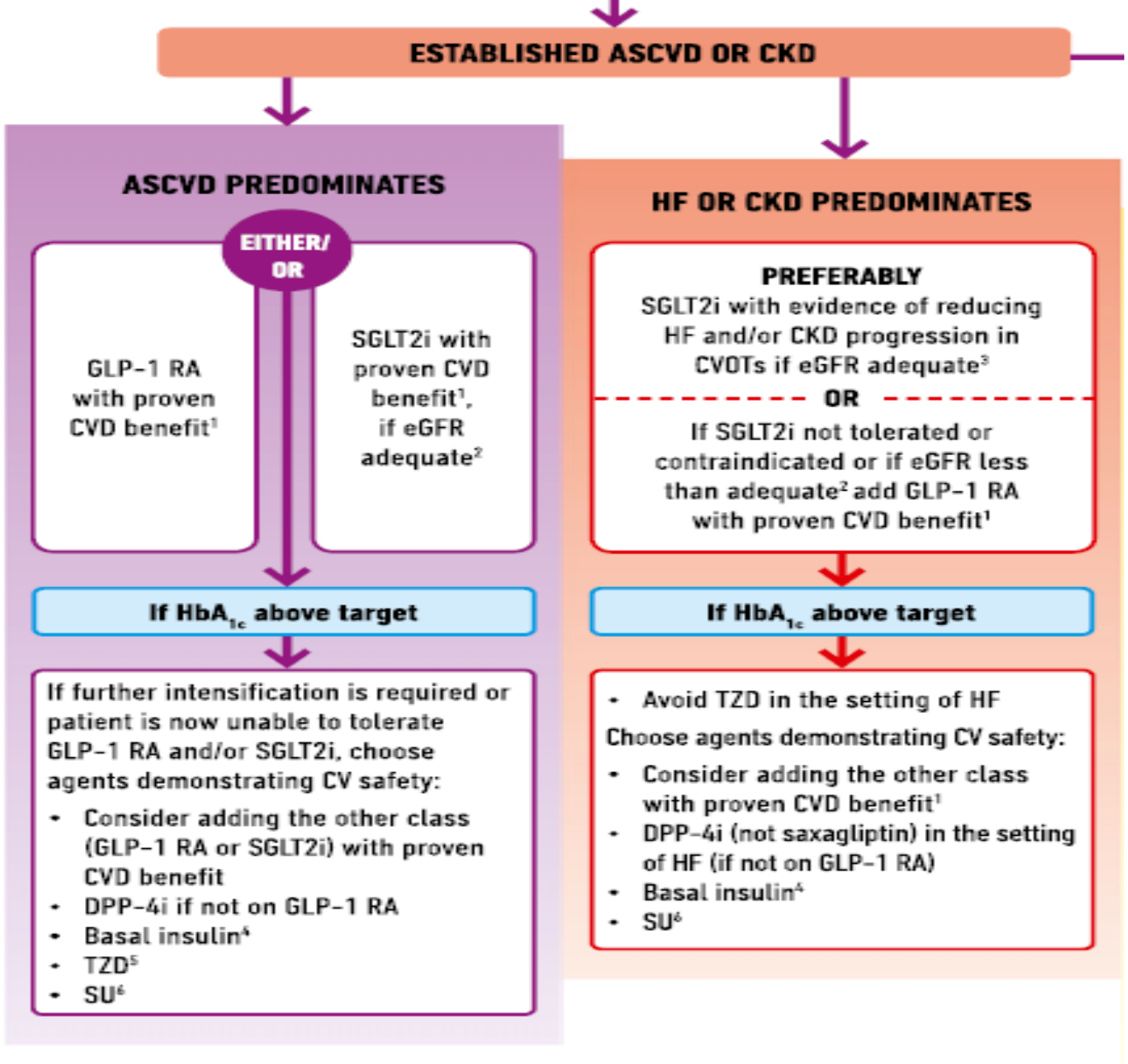
Figure 1—Decision cycle for patient-centered glycemic management in type 2 diabetes.

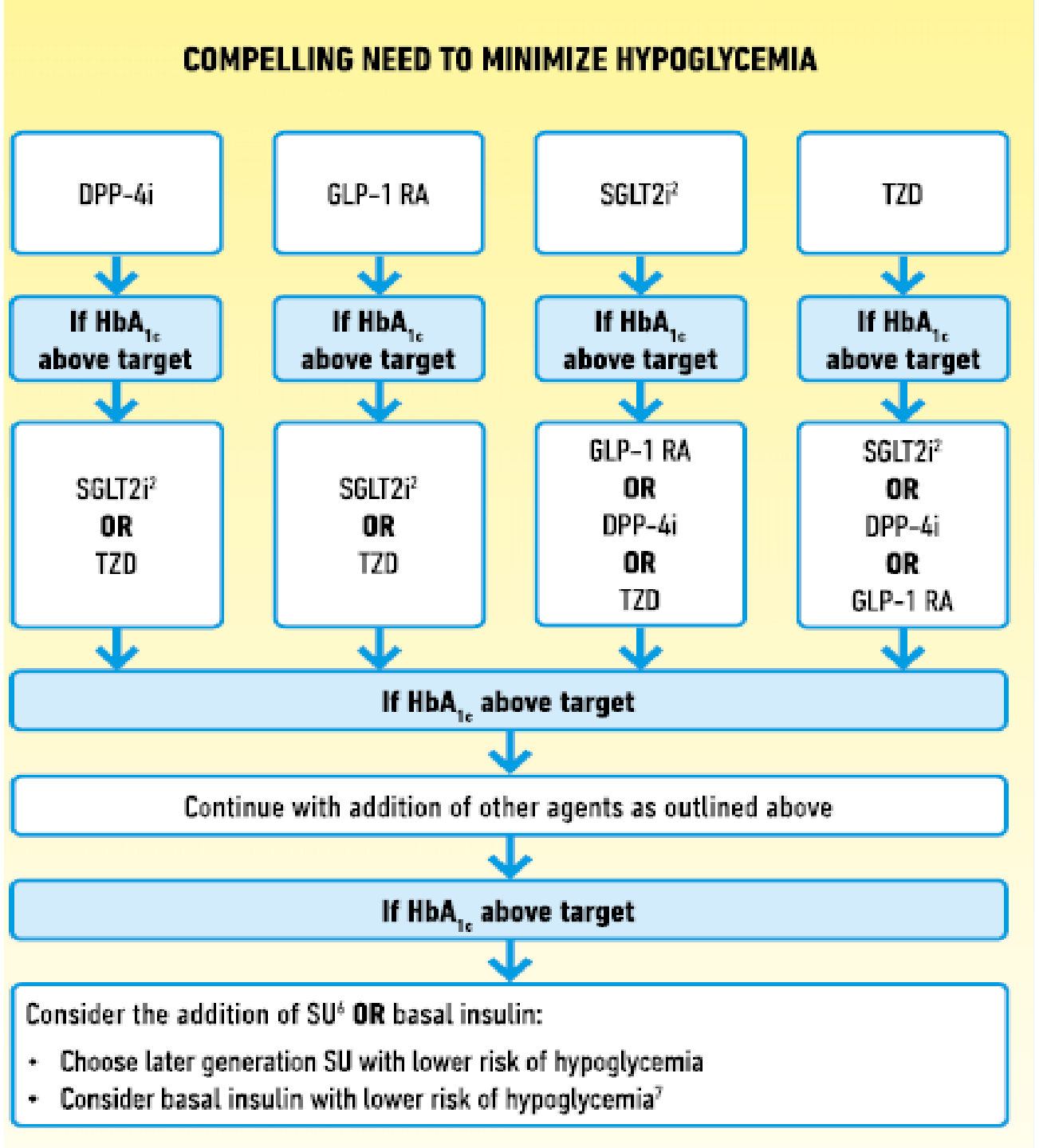
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

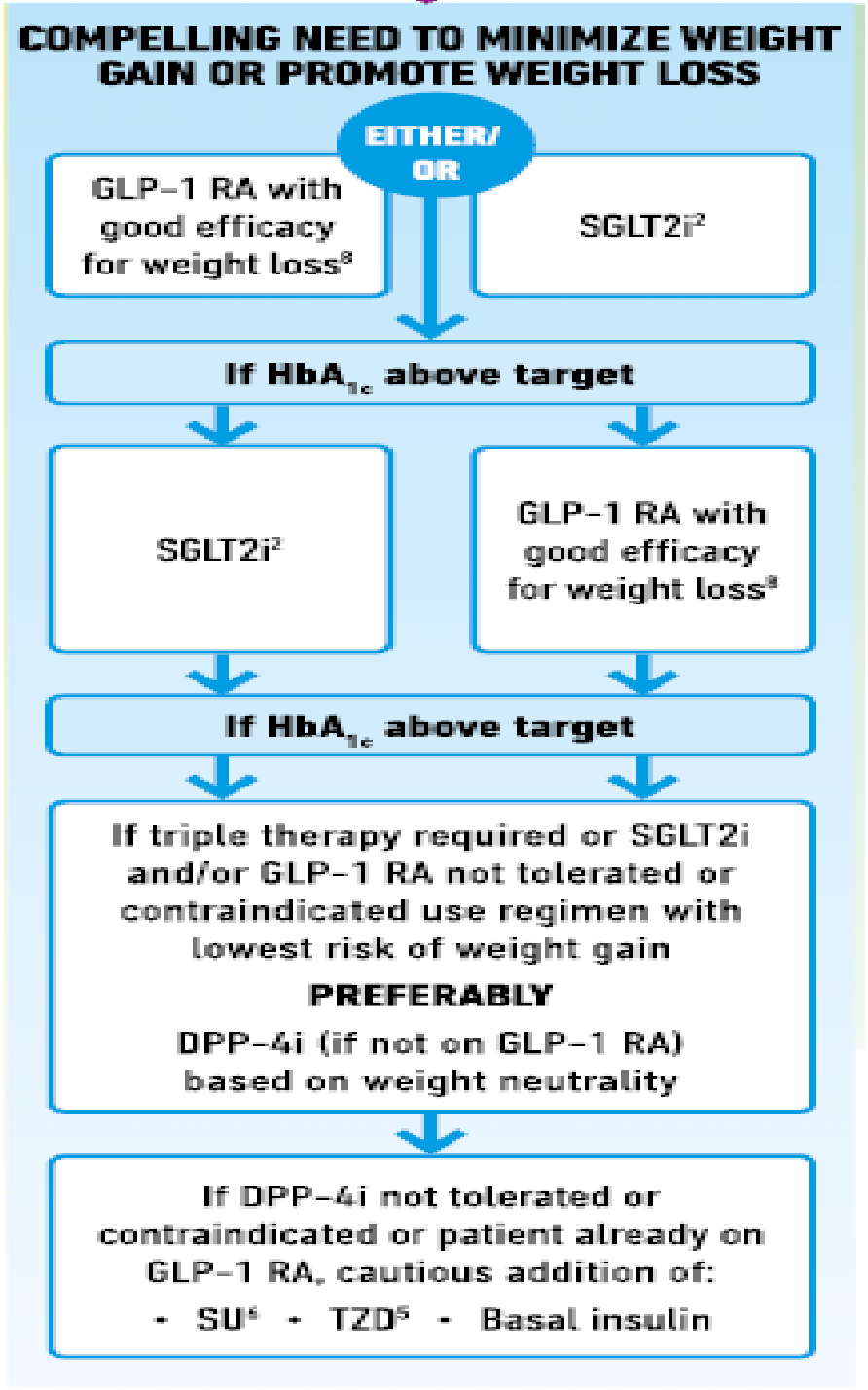


1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent 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

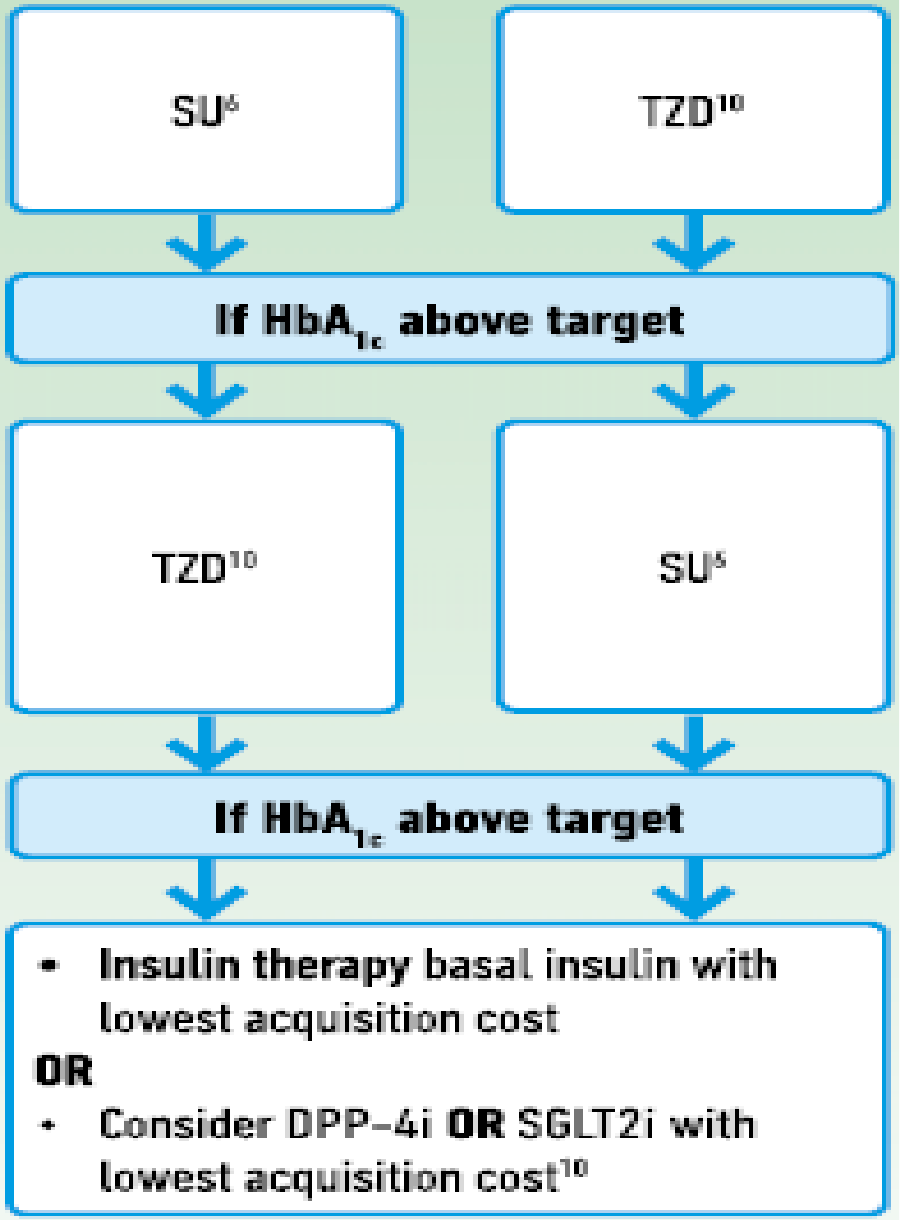
Figure 2—Glucose-lowering medication in type 2 diabetes: overall approach. CV, cardiovascular; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 SU, sulfonylurea.


ESTABLISHED ASCVD OR CKD
ASCVD PREDOMINATES
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1], if eGFR adequate[2]
If HbA1c above target
If further intensification is required or patient is now 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
• DPP-4i if not on GLP-1 RA
• Basal insulin[4]
• TZD[5]
• SU[6]
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]
If HbA1c 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[4]
• SU[6]


COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i[2]
TZD
If HbA1c above target
If HbA1c above target
If HbA1c above target
If HbA1c above target
SGLT2i[2] OR TZD
SGLT2i[2] OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i[2] OR DPP-4i OR GLP-1 RA
If HbA1c above target
Continue with addition of other agents as outlined above
If HbA1c above target
Consider the addition of SU[6] OR basal insulin:
• Choose later generation SU with lower risk of hypoglycemia
• Consider basal insulin with lower risk of hypoglycemia[7]

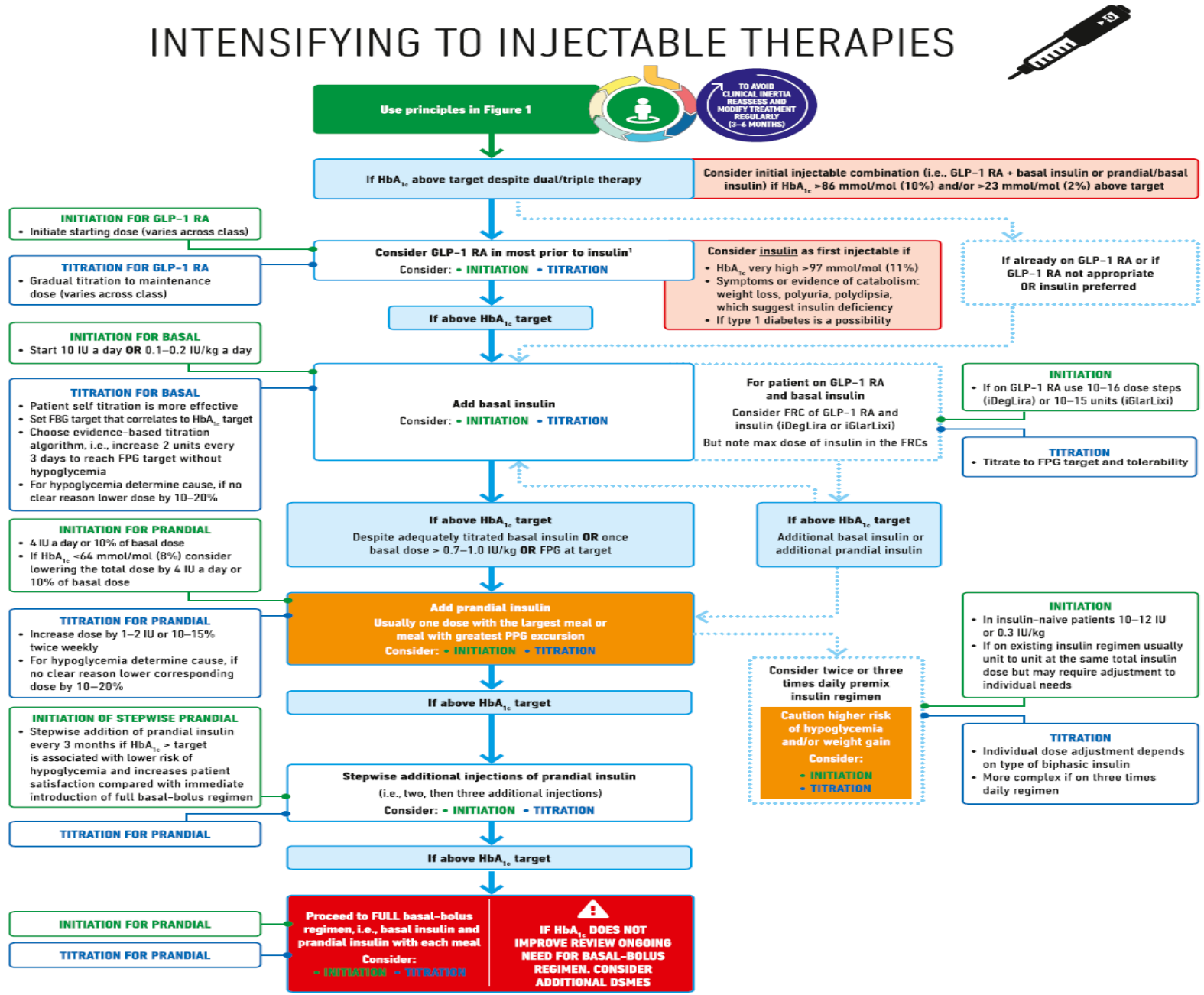

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/ OR
GLP–1 RA with good efficacy for weight loss[8]
SGLT2i[2]
If HbA1c above target
SGLT2i[2]
GLP–1 RA with good efficacy for weight loss[8]
If HbA1c above target
If triple therapy required or SGLT2i and/or GLP–1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain
PREFERABLY
DPP–4i (if not on GLP–1 RA) based on weight neutrality
If DPP–4i not tolerated or contraindicated or patient already on GLP–1 RA, cautious addition of:
• SU[4] • TZD[5] • Basal insulin

COST IS A MAJOR ISSUE[9-10]



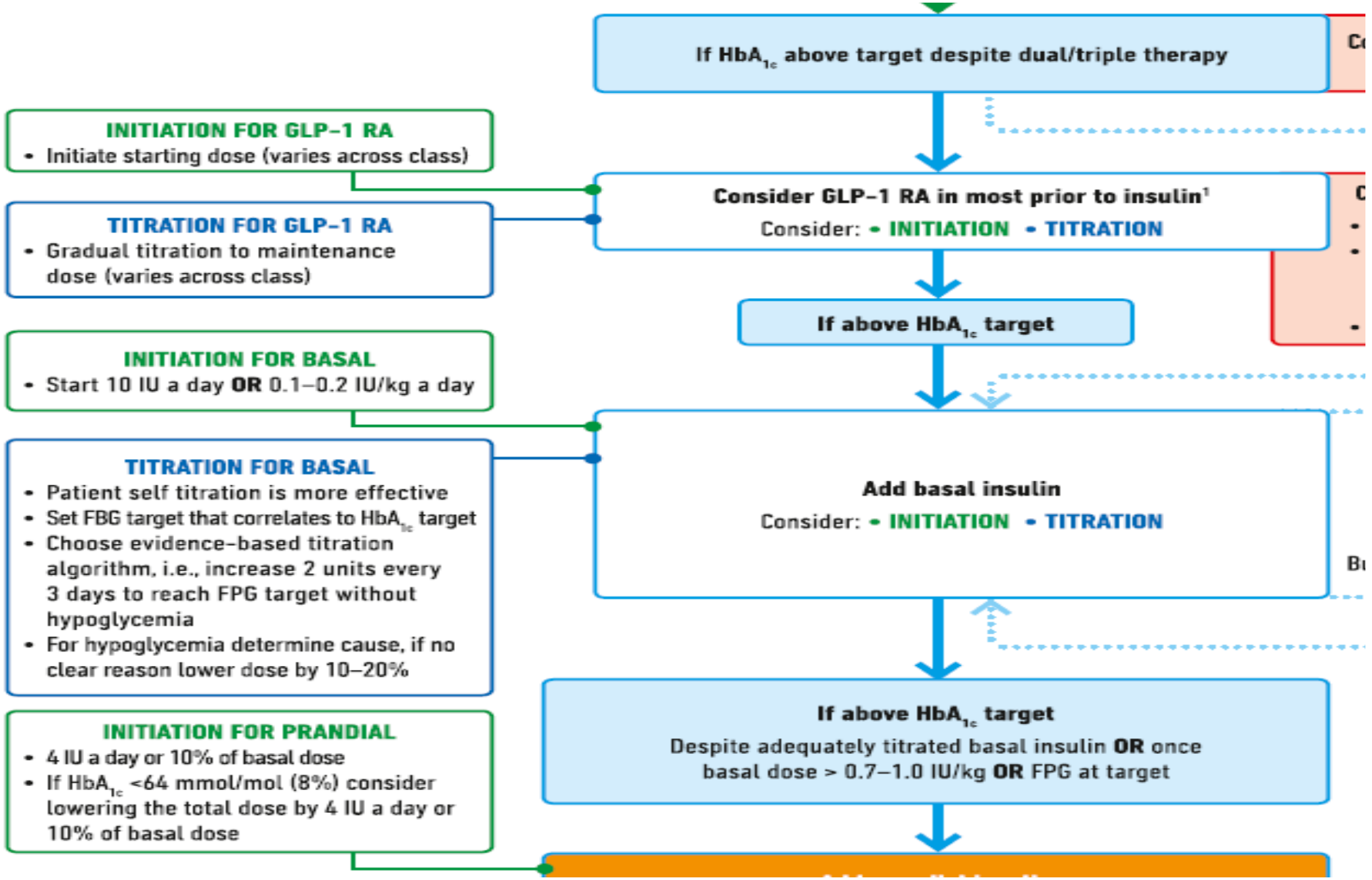

Lantus SoloStar
100 Units/ml
Solution for injection in a pre-filled pen
insuline glargine/insulin glargine
NovoRapid FlexPen
100 U/ml
Solution for injection
insulin aspart
Apidra SoloStar
100 Units/ml
Solution for injection in a pre-filled pen
insuline glulisine/insulin glulisine

INTENSIFYING TO INJECTABLE THERAPIES



1. Consider choice of GLP–1 RA considering: patient preference, HbA_{1c} lowering, weight–lowering effect, or frequency of injection. If CVD, consider GLP–1 RA with proven CVD benefit

Figure 7—Intensifying to injectable therapies. FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide 1 receptor agonist; FBG, fasting blood glucose; FPG, fasting plasma glucose; max, maximum; PPG, postprandial glucose.


If HbA1c above target despite dual/triple therapy
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
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
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

9.8 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**

9.9 Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥1.5% (12.5 mmol/mol) above their glycemic tar-

Basal Insulin

Basal insulin alone is the **most convenient** initial insulin regimen and can be added to metformin and other oral agents.

Starting doses can be estimated based on body weight (e.g., ***10 units a day or 0.1–0.2*** **units/kg/day) and the degree of hyperglycemia, with individualized** titration over days to weeks as needed.

The principal action of basal insulin is to restrain hepatic glucose production, with a goal of maintaining euglycemia overnight and between meals

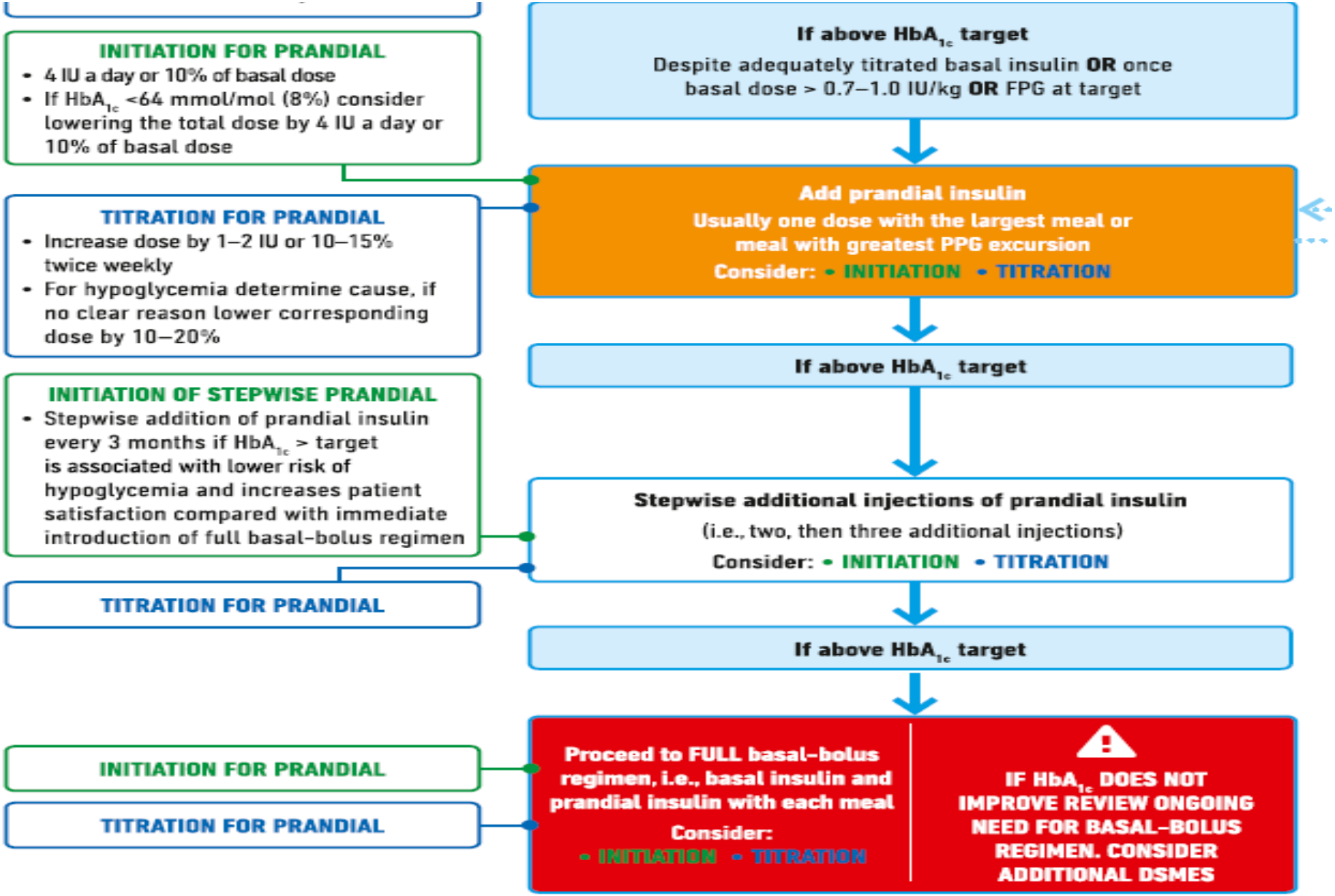
Basal insulin dose and titration schedules

	ADA/EASD[4]	AACE[3]
Initial dose when:		
• HbA1c is 7%-<8%	0.1-0.2 U/kg	0.1-0.2 U/kg
• HbA1c is ≥8% (Severe hyperglycemia)	0.3-0.4 U/kg	0.2-0.3 U/kg
Target blood glucose	Fasting/premeal: <130 mg/dL; prebedtime: <180 mg/dL	Fasting/premeal: <110 mg/dL*
Titration schedule	Increase by 1-2 U twice weekly	Increase by 2 U every 2-3 days

Lantus dose adjustment instructions

- If your average blood sugar reading was below 140 do not change dose.
- If your average blood sugar reading was between 140 –179 increase by 4 units
- If your average blood sugar reading was between 180 -240 increase by 6 units
- If your average blood sugar reading was greater- than 241 increase by 8 units

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

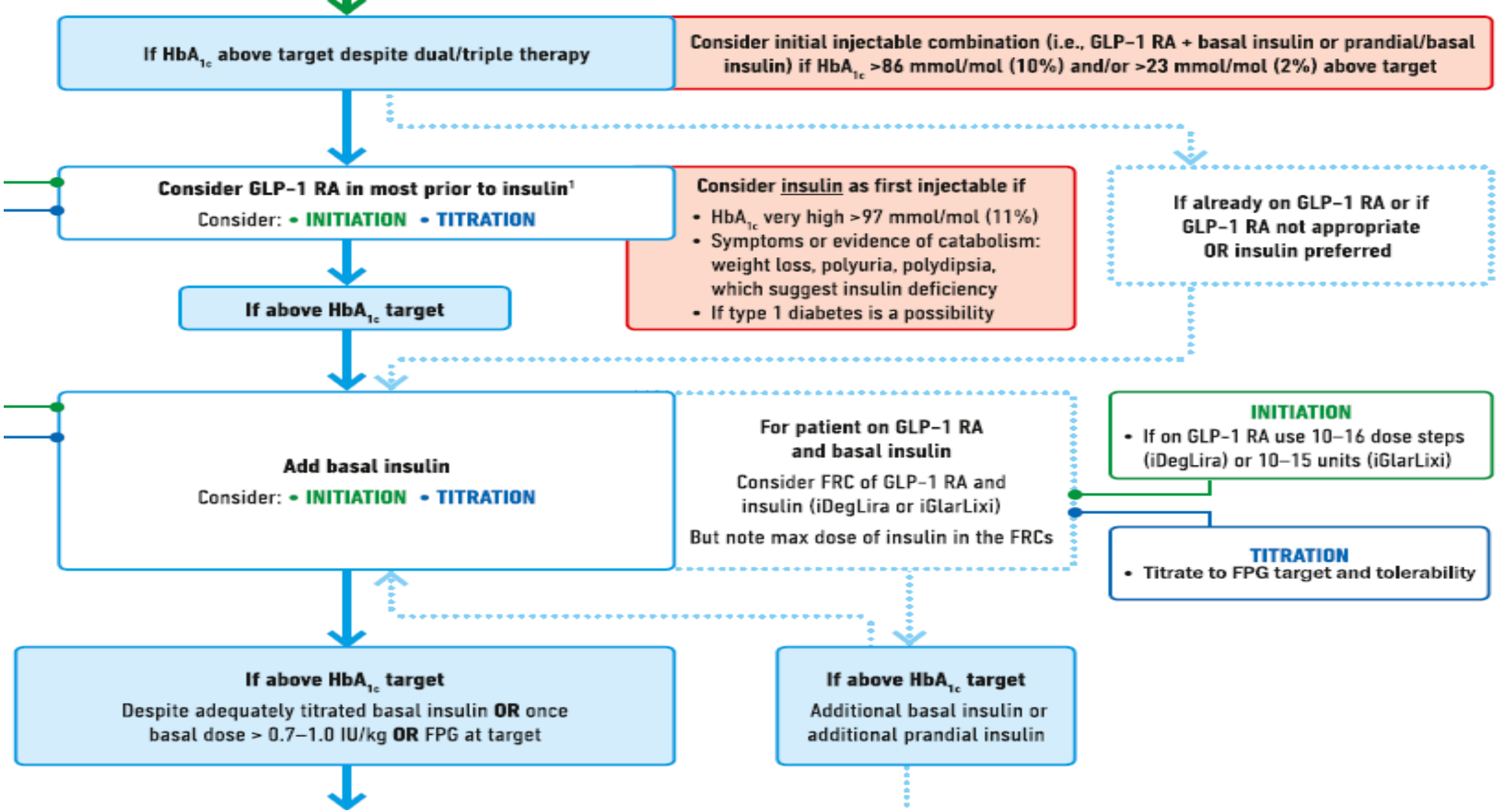

If above HbA1c target
Despite adequately titrated basal insulin OR once basal dose > 0.7–1.0 IU/kg OR FPG at target
INITIATION FOR PRANDIAL
• 4 IU a day or 10% of basal dose
• If HbA1c <64 mmol/mol (8%) consider lowering the total dose by 4 IU a day or 10% of basal dose
Add prandial insulin
Usually one 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

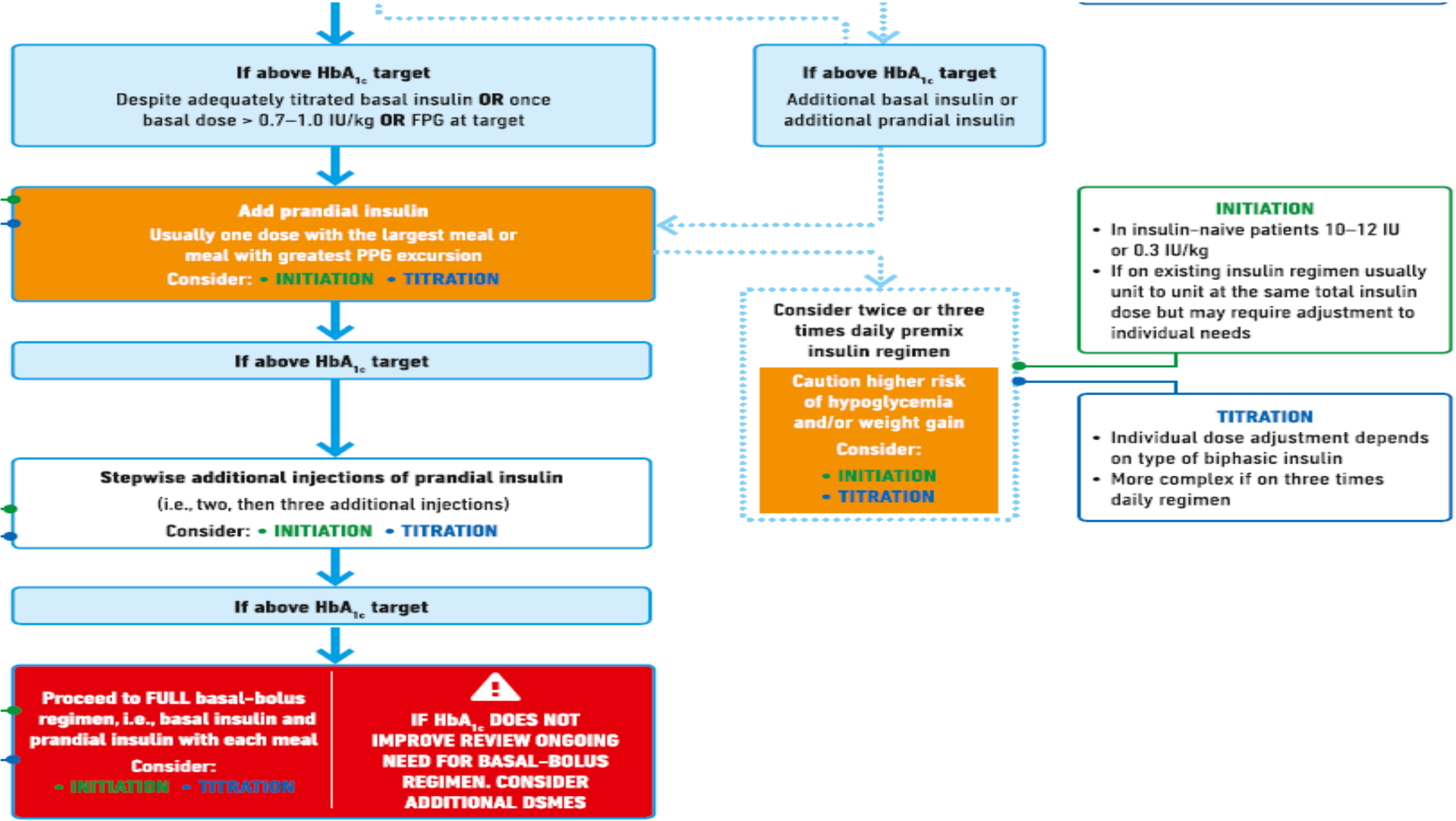
Prandial Insulin

Individuals with type 2 diabetes may require doses of insulin before meals in addition to basal insulin.

The recommended starting dose of mealtime insulin is either 4 units or 10% of the basal dose at each meal.

Titration is done based on home glucose monitoring or A1C.


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
Consider GLP–1 RA in most prior to insulin[1]
Consider: • INITIATION • TITRATION
Consider insulin as first injectable if
• HbA_{1c} 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 HbA_{1c} target
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
If above HbA_{1c} target
Despite adequately titrated basal insulin OR once basal dose > 0.7–1.0 IU/kg OR FPG at target
If above HbA_{1c} target
Additional basal insulin or additional prandial insulin

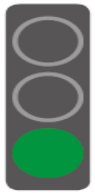

If above HbA1c target
Despite adequately titrated basal insulin OR once basal dose > 0.7–1.0 IU/kg OR FPG at target
If above HbA1c target
Additional basal insulin or additional prandial insulin
Add prandial insulin
Usually one dose with the largest meal or meal with greatest PPG excursion
Consider: • INITIATION • TITRATION
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
If above HbA1c target
Consider twice or three times daily premix insulin regimen
Caution higher risk of hypoglycemia and/or weight gain
Consider:
• INITIATION
• TITRATION
TITRATION
• Individual dose adjustment depends on type of biphasic insulin
• More complex if on three times daily regimen
Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)
Consider: • INITIATION • TITRATION
If above HbA1c target
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

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

In patients with suboptimal blood glucose control, especially those requiring large insulin doses, 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.

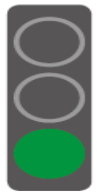
CONSIDERING ORAL THERAPY IN COMBINATION WITH INJECTABLE THERAPIES

METFORMIN



Continue treatment with metformin

SGLT2i



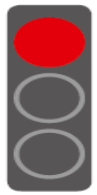
If on SGLT2i, continue treatment

Consider adding SGLT2i if

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

TZD[1]

Stop TZD when commencing insulin OR reduce dose

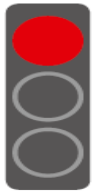


Beware

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

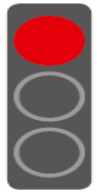
SULFONYLUREA

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



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

DPP-4i



Stop DPP-4i if GLP-1 RA initiated

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

Figure 8—Considering oral therapy in combination with injectable therapies. DKA, diabetic ketoacidosis; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

Thanks