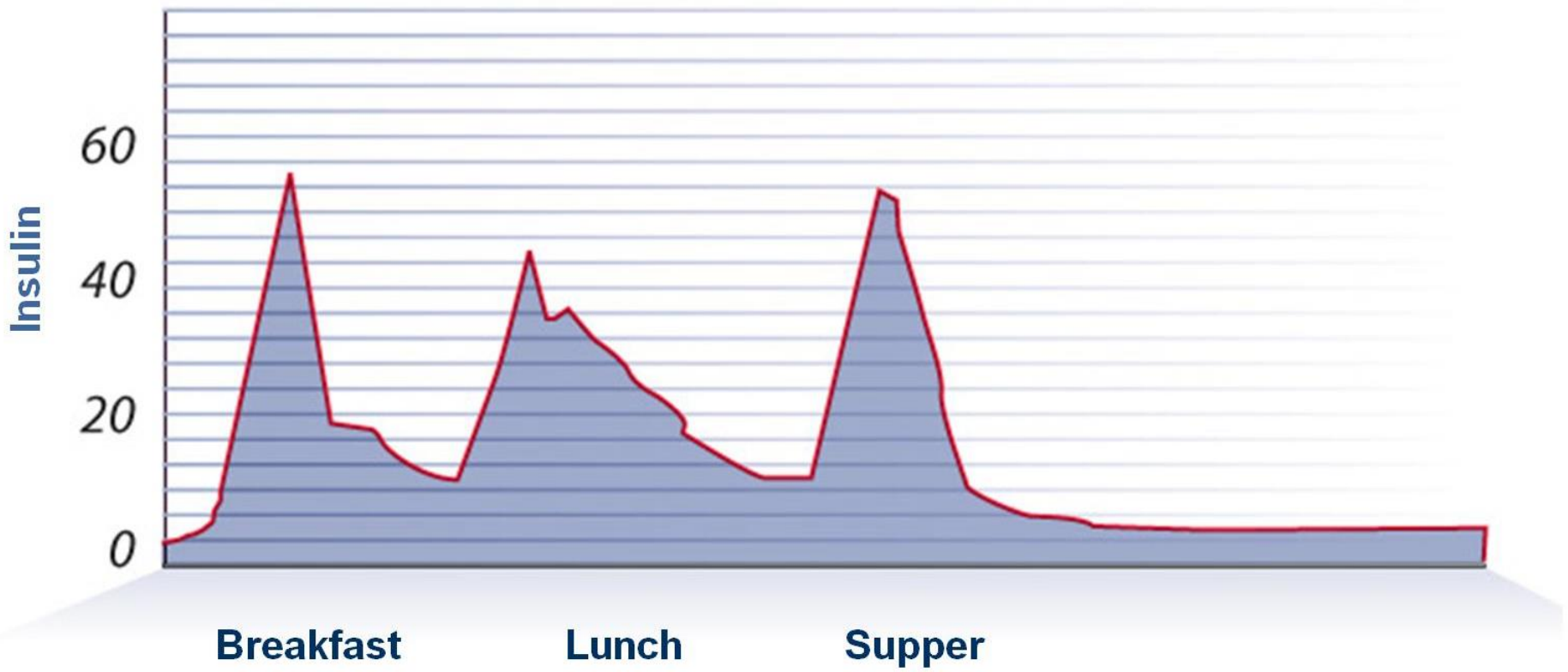
Insulin and non-insulin injectable agents

Hae Jin Kim

Endocrinology & Metabolism
Ajou University School of Medicine

Insulin Therapy

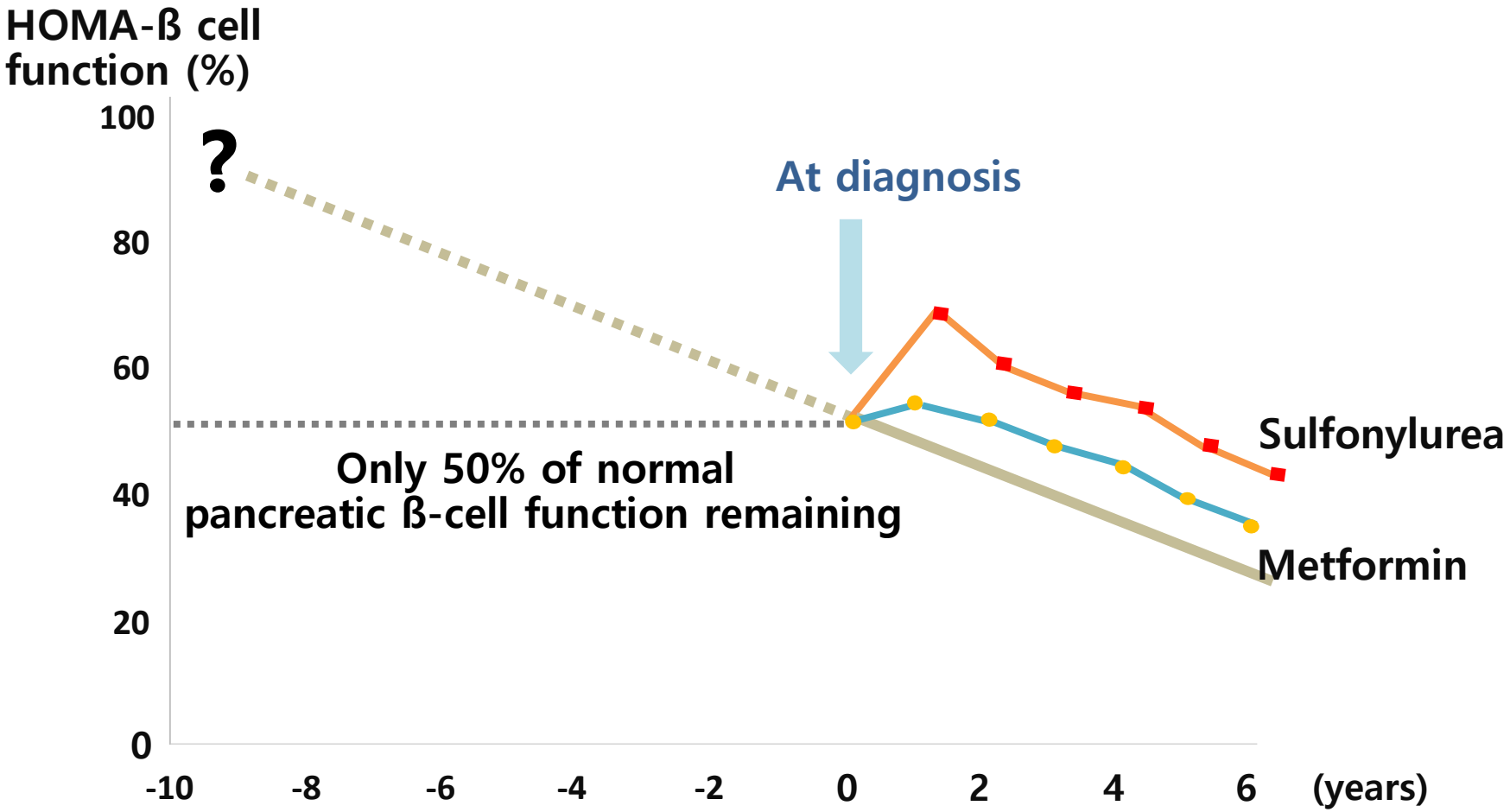
Secretion of Insulin



Indications of Insulin Therapy

- Type 1 diabetes
- In type 2 diabetes, inadequately controlled on glucose-lowering medicines
- Transiently in type 2 diabetes in special situations
- Women with diabetes who become pregnant or are Breastfeeding
- Some women with gestational diabetes

Loss of ß-cell function



HOMA=Homeostasis model assessment

Holman RR. Diabetes Res Clin Pract 1998;40:S21-5

Pros and cons of insulin therapy

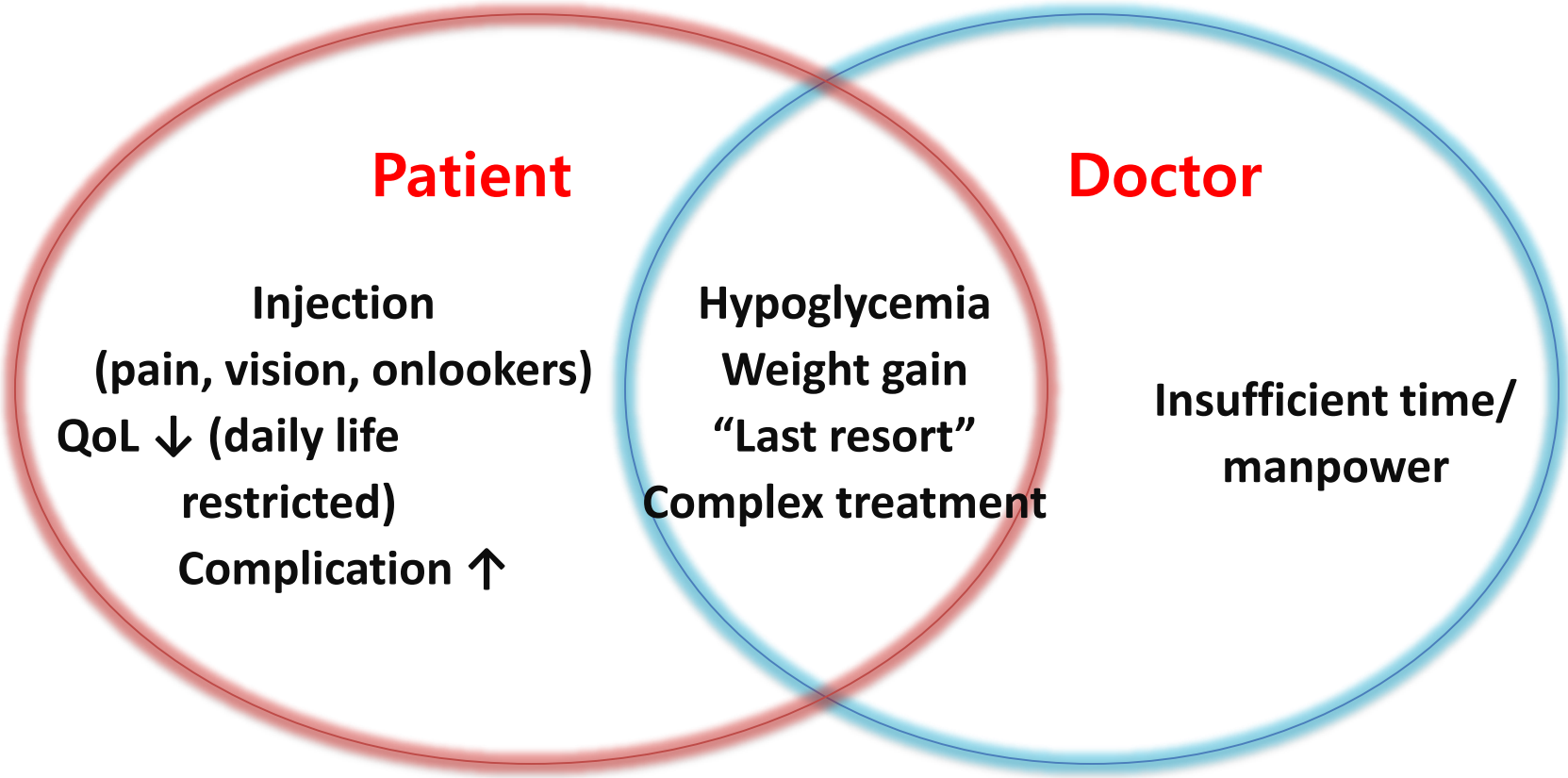
Pros	Cons
Much clinical experience	Weight gain (2~4 kg)
Most rapid hypoglycemic effect	Hypoglycemia
No dose limit	Injection
Improves lipid metabolism (triglyceride, HDL-C)	Self-monitoring of blood glucose

Diabetes Care 2009;32:193-203

Pharmacokinetics of insulin

Insulin	Onset	Peak (hrs)	Duration (hrs)
Bolus insulins			
• Rapid			
Faster Aspart	5 mins	1	3-4
Aspart	10-15 mins	1-1.5	3-5
Lispro		1-2	3.5-4.75
Glulisine		1-1.5	3-5
• Short			
Regular	30 mins	2-3	6.5
Basal insulins			
• Intermediate NPH	1-3 hrs	5-8	Up to 18
• Long acting			
Detemir	90 mins	Flat, no peak	24
Glargine (U100)			24
Degludec	60-90 mins		> 42
Glargine (U300)	6 hrs		> 36
Mixed insulins			
• NPH 70/30			
• Mixed insulin analogues			
Aspart 70/30, 50/50			
Degludec / Aspart 70/30			
Lispro 75/25, 50/50			

Barriers to insulin therapy

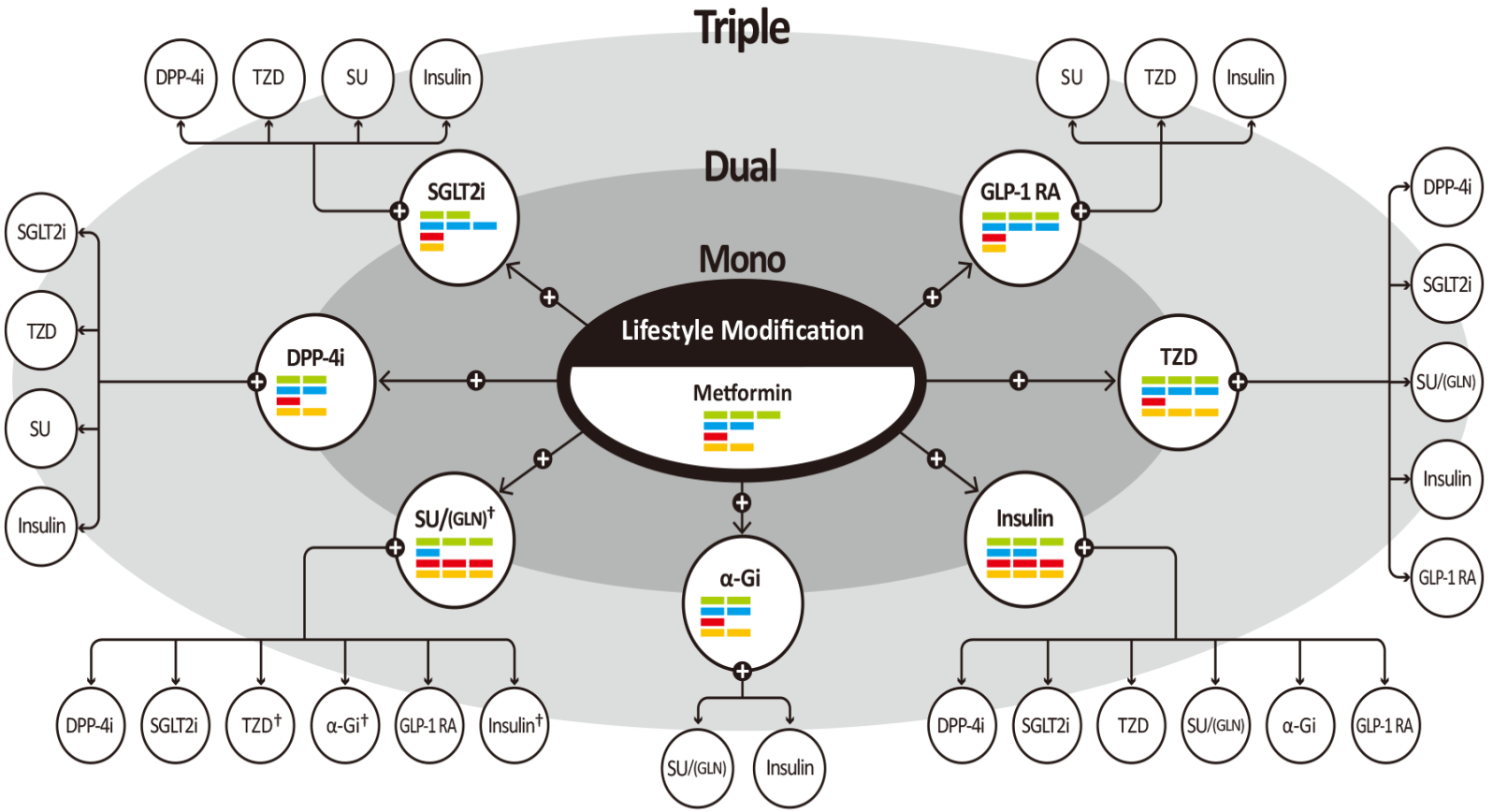


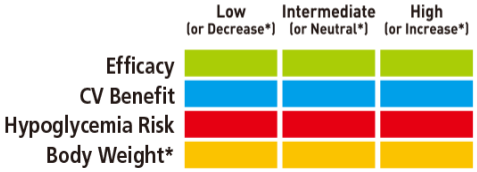
Polonsky WM et al. Diabetes Care 2005;28:2543-5
Hong SH el al. Korean Diabetes J 2008;32:269-279, Karter AJ et al. Diabetes Care 2010;33:733-5

Resolving treatment barrier

Barrier	Solution
Hypo-glycemia	NPH → basal insulin RI → ultrashort-acting analogue Less frequent than type 1 diabetes
Weight gain	Relative to diet intake and insulin dose Basal insulin = less weight gain than NPH Weight managed with diet/exercise
Injection	Less pain than SMBG Pen-type or mixed-type insulin if dosage or mixing difficult
Compli-cation ↑	No increase in complication by insulin itself Thorough glycemic control -> complication ↓
Quality of life ↓	Improve quality of life (energy, sleep, health)! Less complicated than multiple drugs
"Last resort"	Insulin used in every stage of diabetes treatment Most effective glycemic control

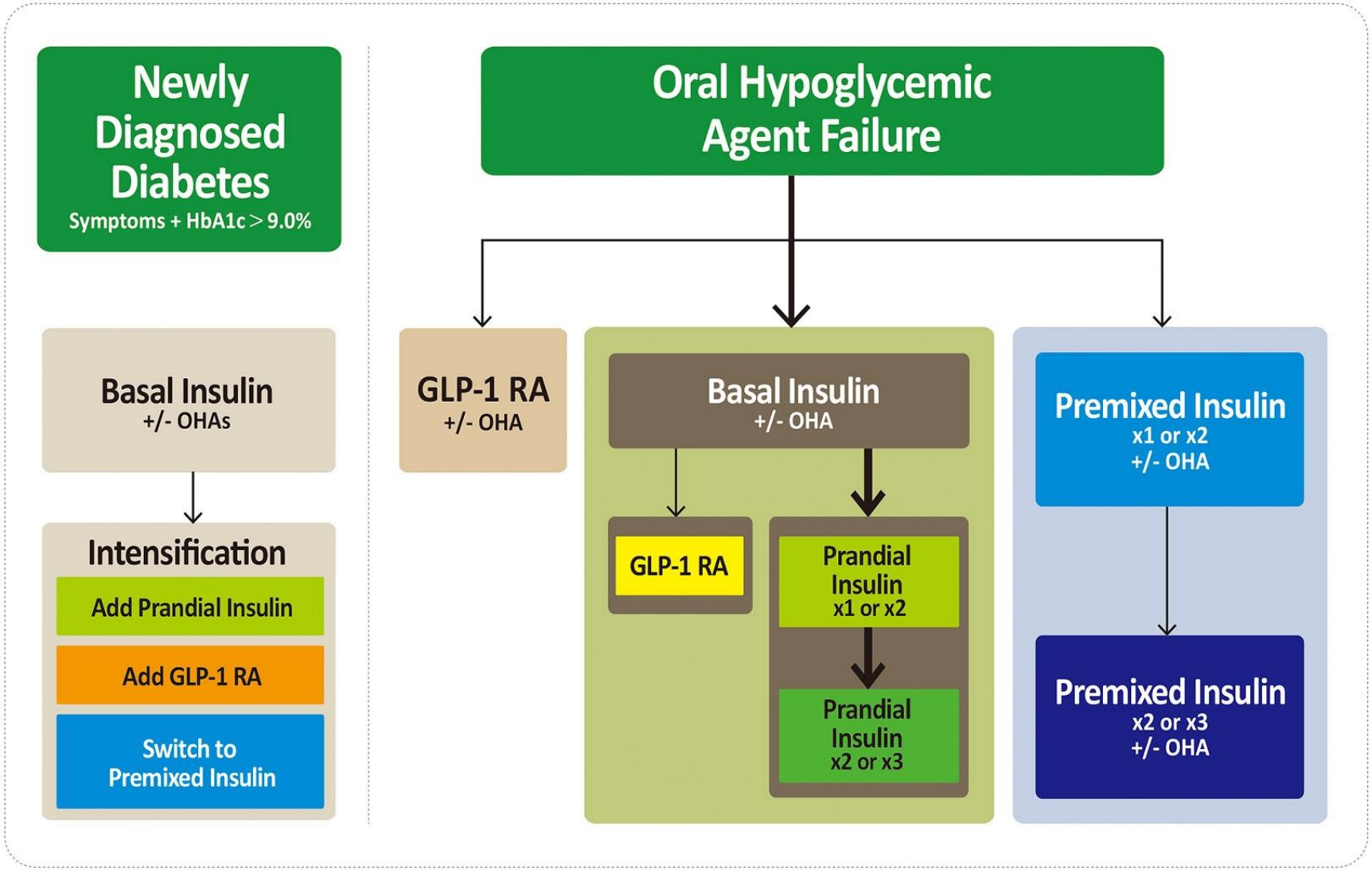
KDA gulideline 2019 (Type 2 DM)





If glycemic target is not achieved within 3 months, add drug:
Mono → Dual → Triple therapy

KDA gulideline 2019 (Type 2 DM)



If HbA1c target is not achieved, consider other regimen at any step.
HbA1c, hemoglobin A1c; GLP-1 RA, glucagon-like peptide 1 receptor agonist;
OHA, oral hypoglycemic agent.

Basal insulin

Pros	**Easy to begin, easy dose adjustment**
	Low risk of hypoglycemia
Cons	**Postprandial glucose difficult to control**
Indictation	**If multiple injection difficult**
	Partially intact insulin secretion
	Elevated fasting glucose, but not severe postprandial glucose

Starting basal insulin in type 2 diabetes

- The most convenient initial regimen
- usually prescribed in conjunction with metformin and possibly one additional noninsulin agent
- Beginning at 10 U or 0.1–0.2 U/kg, depending on the degree of hyperglycemia
  - ✓ Start: 10U/day or 0.1-0.2U/kg/day
  - ✓ Adjust: 10-15% or 2-4U once-twice weekly to reach FBG target
  - ✓ For hypoglycemia: determine and address cause, reduce dose by 4U or 10-20%

ADA-EASD

Oral agents combined with basal insulin

Drug	Mechanism	Pros / Cons
Metformin	**Insulin sensitizer**	• Reduces insulin dosage, minimize weight gain and hypoglycemia • GI complication
Sulfonylurea	**Insulin secretagogue**	•Reduces insulin dose, postprandial glucose. Increases weight gain and hypoglycemia
Glinide	**Insulin secretagogue**	•Improves postprandial glucose, less hypoglycemia. Weight gain
Thiazolidinedione	**Insulin sensitizer**	•Reduces insulin dose •Heart failure, weight gain, edema
DPP-4 inhibitor	**Strengthen incretin**	•Low risk of hypoglycemia •Increased cost, not enough data
α-glucosidase inhibitor	**Dealys sugar absorption**	•Improves postprandial glucose, •Increased cost, GI complications
SGLT2 inhibitor	**Urinary glucose excretion**	•Wt. loss, Low risk of hypoglycemia •Genital infection, dehydration

Mealtime insulins

- Add 1 rapid insulin injection before largest meal
  → if not controlled, consider basal-bolus
  (≥2 rapid insulin injections before meals)
- Start: 4U, 0.1U/kg, or 10% basal dose. If HbA1c<8%, consider ↓ basal by same amount
- Adjust: ↑dose by 1-2U or 10-15% once-twice weekly until SMBG target reached.
- For hypoglycemia: Determine and address cause, ↓corresponding dose by 2-4U or 10-20%

Basal–mealtime insulin regimen

Pros	**Pre- and post-prandial glucose controlled**
Cons	**Increased frequency of injection**
Indication	**Patients desiring strict glucose control**
	Patients wanting to reduce snack (carbohydrate) intake preventing hypoglycemia
	Patients wanting flexible injection schedule (due to irregular mealtime or shift working)

Mixed insulin regimen (± oral medication)

Pros	**Postprandial glucose controlled**
	Injection frequency ↓ **(one injection provide basal and prandial insulin)**
Cons	**↑ risk of hypoglycemia and weight gain than basal insulin**
Indication	**Regular mealtime and meal amount**
	Severe postprandial hyperglycemia

Adjusting insulin for daily changes

Tailored to individual needs

- Lifestyle choices
- Eating more or less
- Exercising more or less
- Stress
- Illness

Steps to interpreting blood glucose diaries

1. Get an overall impression
   - Overall consistent?
2. Look for hypoglycaemia
3. Lifestyle choices
4. Look at fasting levels
5. Look at post prandial
   - How much difference from pre meal?
6. Ask about meal times, activities and variation

GLP-1 Receptor Agonist

GLP-1 actions in type 2 diabetes

Action	GLP-1
Pancreatic beta-cells	
Glucose-dependent insulin release	↑↑
Insulin synthesis	↑
Differentiation into beta cells	↑
Apoptosis	↓
Alpha-cells: glucagon release	↓
Gastric output	↓↓
Postprandial glucose	↓↓
Appetite	↓
Weight	↓

Drucker DJ et al. Lancet 2006;368:1696-705

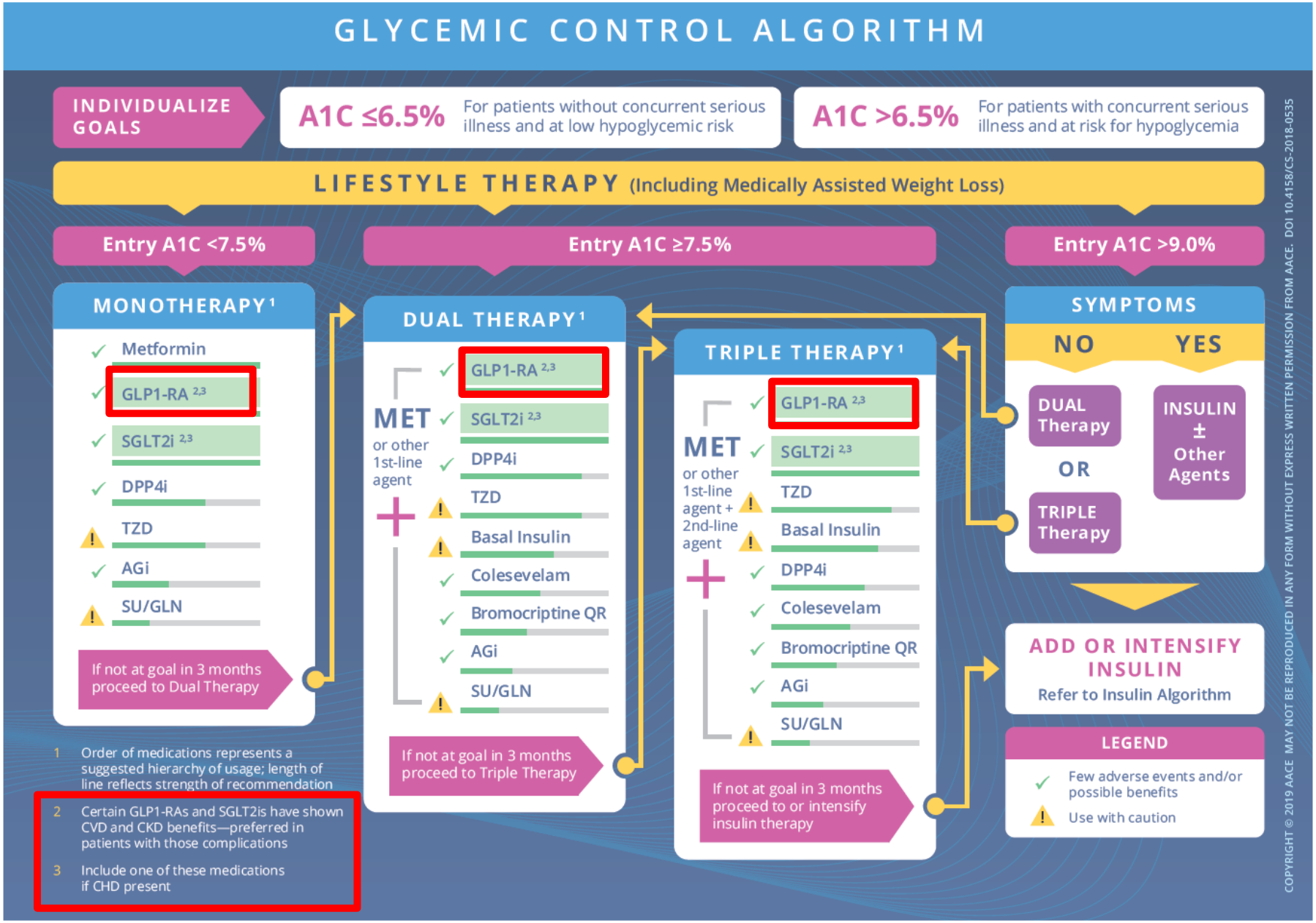
GLP-1 RAs

GLP1RA	Dose	Injection
Exenatide	5-10 ug	Bid
Lixisenatide	10-20 ug	Bid
Liraglutide	0.6-1.8 mg	Qd
Dulaglutide	0.75-1.5 mg	Once weekly
Exenatide LAR	2 mg	Once weekly
Albiglutide	30 -50 mg	Once weekly
Insulin Glargine /Lixisenatide	300 IU/100-150 ug/3 mL	Qd

Pros and cons of GLP-1 analogue

Pros	**Glycemia-dependent insulin release (lower risk of hypoglycemia)**
	Weight loss
	Supression of appetite
	Improves risk factor of CVD (lipid, blood pressure)
Cons	**Injection**
	Costly
	GI side effects such as nausea, vomiting, diarrhea

AACE guideline 2019



GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

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

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW

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 HbA_{1c} 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 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[4]
- SU[6]

NO

WITHOUT ESTABLISHED ASCVD OR CKD

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If HbA_{1c} 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 HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} 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 HbA_{1c} above target

- SGLT2i[2]
- GLP-1 RA with good efficacy for weight loss[8]

If HbA_{1c} 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[6]
- TZD[5]
- Basal insulin

COST IS A MAJOR ISSUE[9-10]

- SU[6]
- TZD[10]

If HbA_{1c} above target

- TZD[10]
- SU[6]

If HbA_{1c} above target

- **Insulin therapy** basal insulin with lowest acquisition cost

OR

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

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

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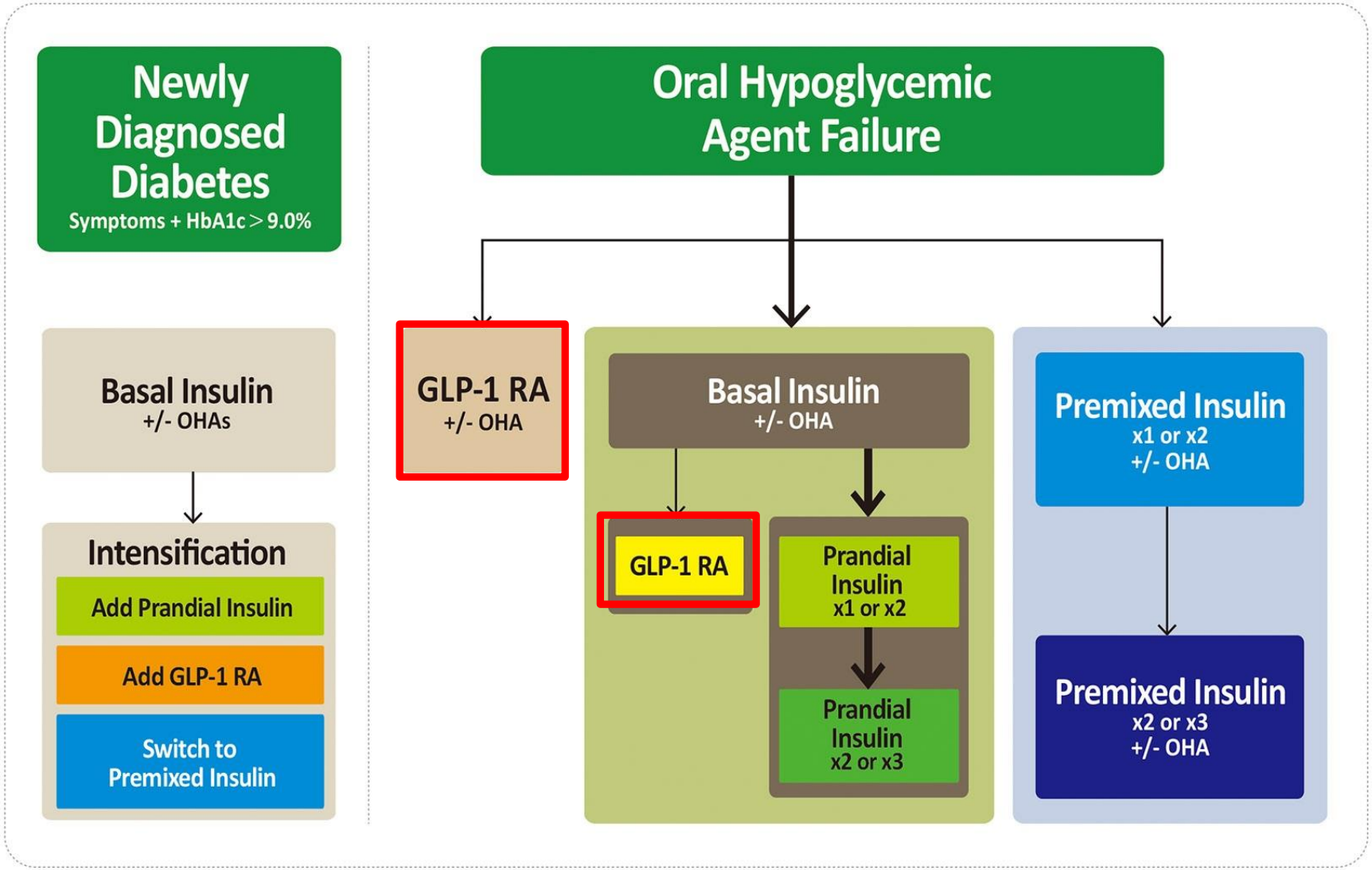

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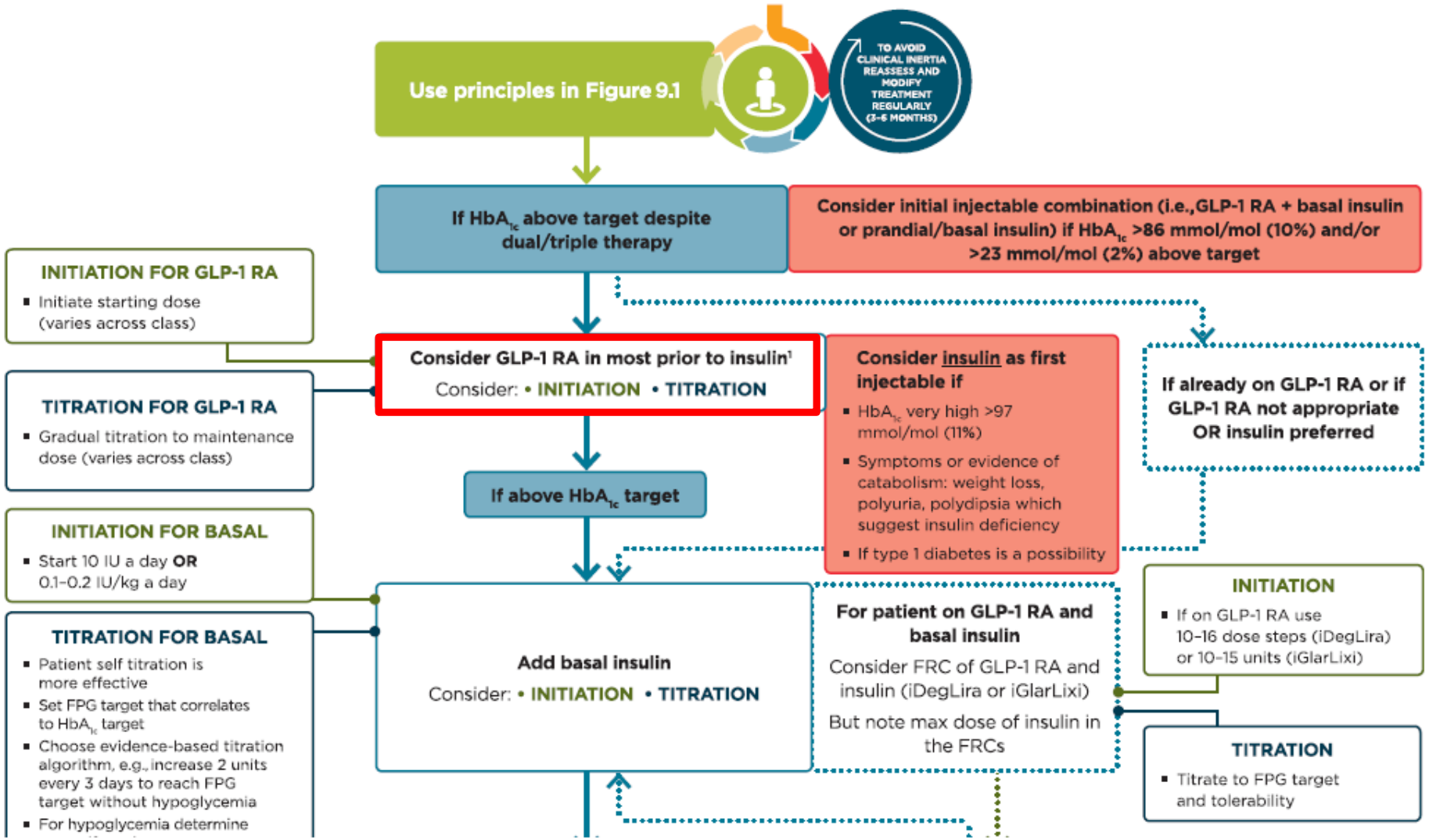
ADA-EASD consensus guideline 2018

Intensifying to Injectable Therapies



GLP-1 RAs
- Safety Issues

- Pancreatitis (rare, but serious)
  - Use with caution in patients with T2D with a history of pancreatitis

- Contraindicated in patients with T2D and a personal or family history of medullary thyroid carcinoma or in patients with MEN 2

- Adverse GI events
  - Nausea is likely to be mild and often resolves in a few weeks to months

Summary

- Insulin is an important therapeutic agent in glycemic control.
- Insulin therapy should not be used as a threat.
- Insulin regimens should be individualized.
  : patient's lifestyle, hyperglycemia pattern (before/after meal), hypoglycemia, etc.
- GLP-1 analogues increase incretin effect and results in postprandial glycemic control, weight loss, and appetite suppression, in addition to improves of cardiovascular risk factors.