《心血管病高危人群筛查及综合干预评价的研究》系列培训

Pharmacological Therapy of Diabetes

Prof. Qiu-Hong Gong

Fuwai Hospital, CAMS & PUMC

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Contents

- **Oral hypoglycaemic drugs**
- Insulin
- GLP-1 receptor agonists
- Principles of Diabetes Medication

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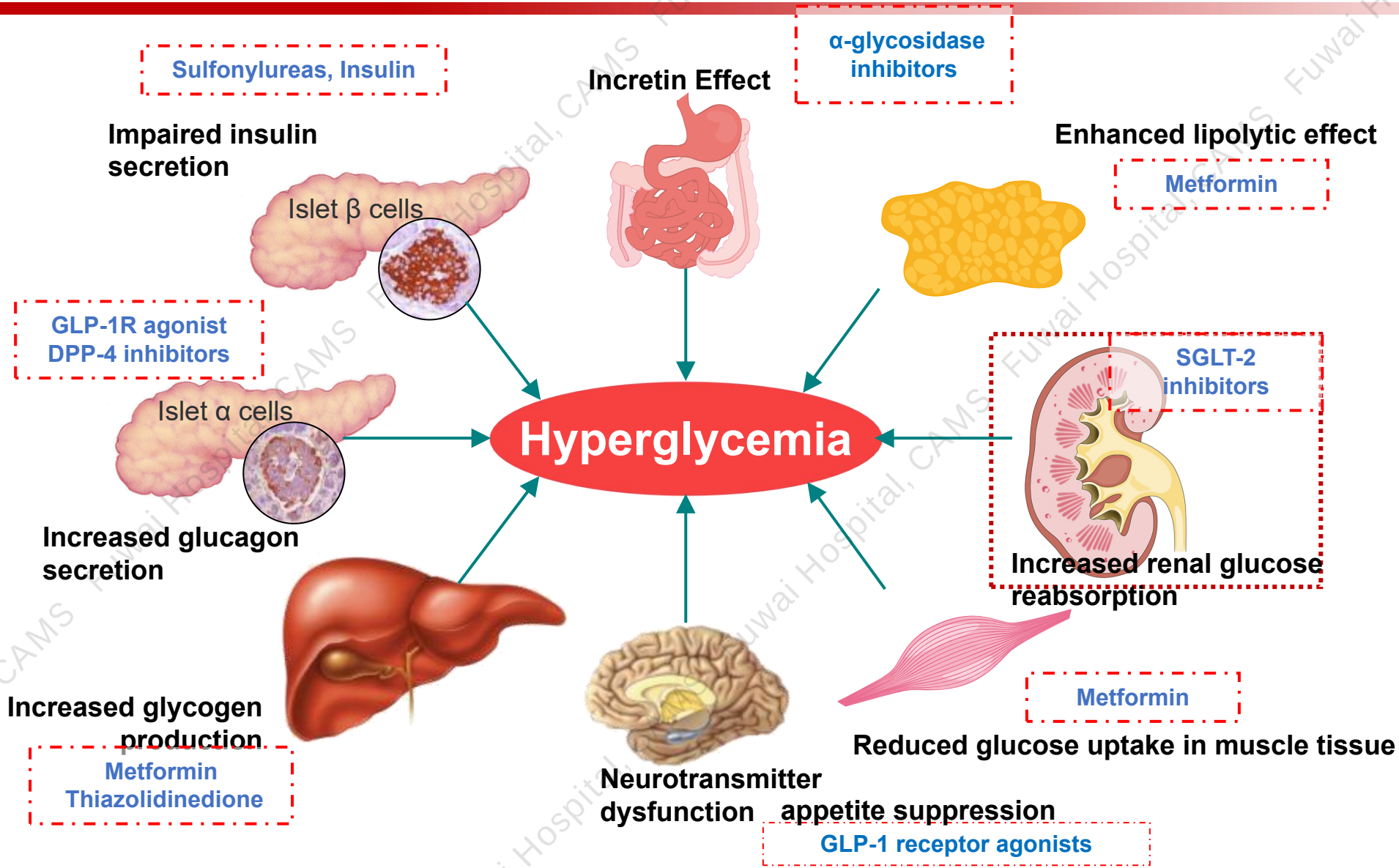
Pathogenesis of diabetes and targets of hypoglycemic agents



Commonly used oral hypoglycemic drugs

- Sulfonylureas.
- 1st Gen: toluenesulfonylurea, chlorosulfonylurea
- 2nd Gen: glibenclamide, gliclazide, glipizide, glipizide
- New Gen: Glimepiride
- Non-sulfonylurea insulin secretagogues (glinides): Repaglinide, nateglinide
- Biguanides: Metformin
- α-Glucosidase inhibitors: acarbose, voglibose, miglitol
- Insulin sensitizers (thiazolidinediones: TZDs): rosiglitazone, pioglitazone
- Enterostatin: GLP-1 analogs (injectable), DPP-4 inhibitors
- SGLT-2: Dagliflozin, Englestrin
- Others: pan-PPAR agonists chiglitazar

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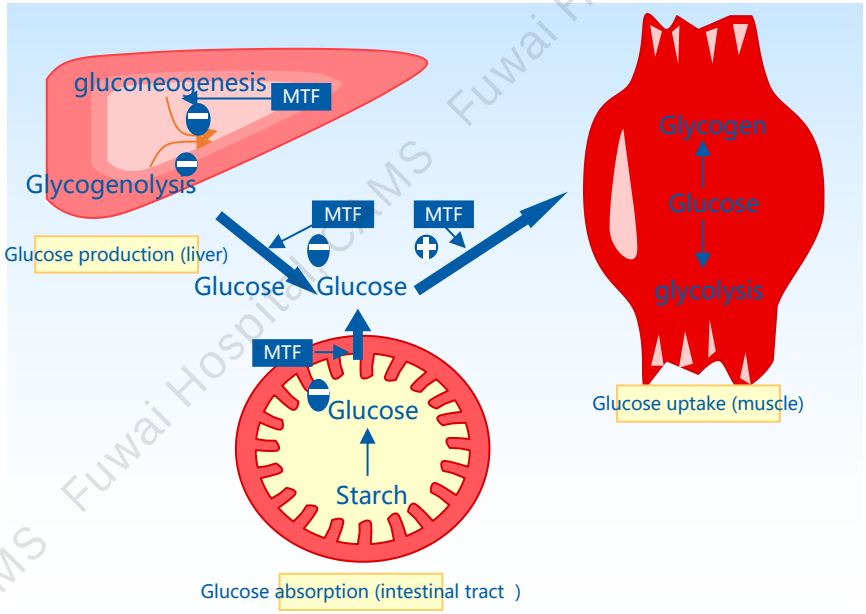
Biguanide - Metformin



First-line drug & Basic drug in the combination therapy

Mechanisms	**Reduces hepatic glucose output Improves peripheral insulin resistance**
Glucose-lowering efficacy	**Decrease HbA1c by 1%-1.5%**
Risk of hypoglycemia	**Does not cause hypoglycemia when used alone. May increase the risk of hypoglycemia when used in combination with insulin or proinsulin secretagogues.**
Other effects	**Reduces CVD events and mortality in obese patients; reduces body weight**
Adverse effects	**Gastrointestinal reactions Lactic acidosis (rare)**

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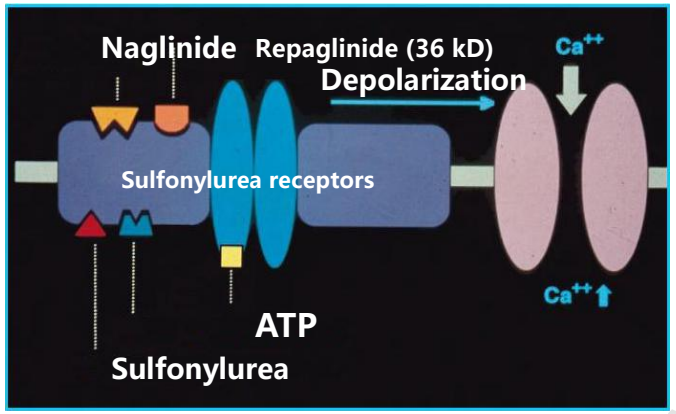
Insulin secretagogues—Sulfonylureas and Glinides



Glinides, like sulfonylureas, act by closing K(ATP) channels
Differences:
Different sites of binding to β-cells, faster binding and dissociation
Repaglinide does not directly stimulate the exocytosis of insulin secretory granules

Mechanisms	**Stimulates early secretion of insulin and increases insulin levels**
Glucose-lowering efficacy	**Decrease HbA1c by 0.5%-1.5%**
Risk of hypoglycemia	**Increase**
Other effects	**Weight gain (hyperinsulinemia), hypoglycemia**

Differences between glinides and sulfonylureas:

- Glinides: "Fast in and fast out", fast absorption, fast onset of action and short duration of action
  - More physiological
  - Less risk and extent of hypoglycemia than sulfonylureas
- Glinides can be used in patients with renal dysfunction

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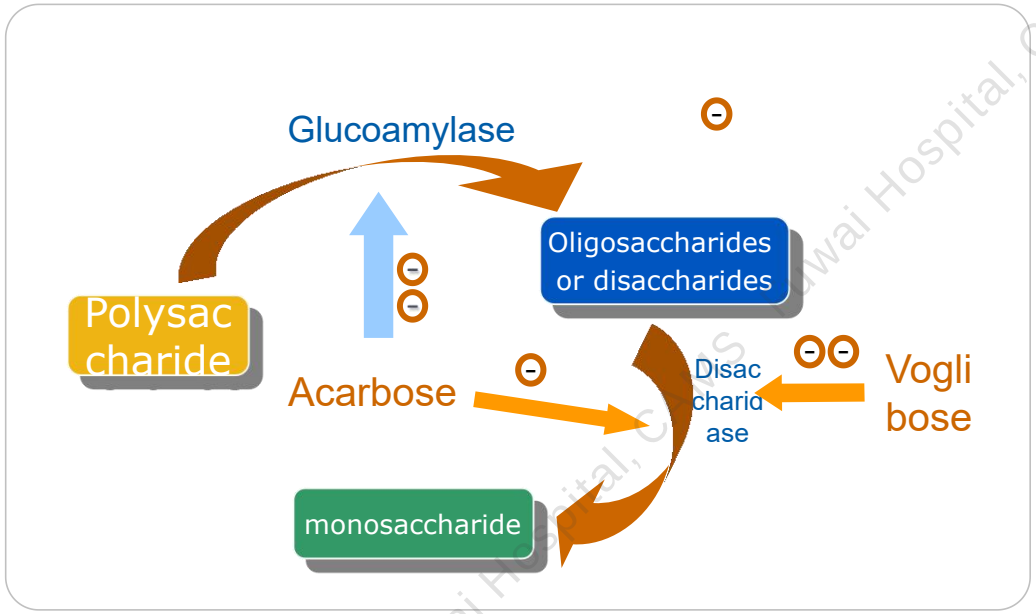
α-Glucosidase inhibitors (Acarbose)



➢ Inhibit carbohydrate absorption in the upper part of the small intestine and decrease postprandial blood glucose

- **Reduces HbA1C by 0.5% to 1.4%**
- **Suitable for T2DM patients with carbohydrate-based food and elevated postprandial glucose**
- **Metabolized by the intestinal tract and does not enter the blood circulation**
- **Does not cause hypoglycemia when used alone**
- **If hypoglycemia occurs, it must be corrected with glucose**
- **Adverse effects:**
  - ✓ Gastrointestinal reactions: abdominal discomfort, flatulence, diarrhea

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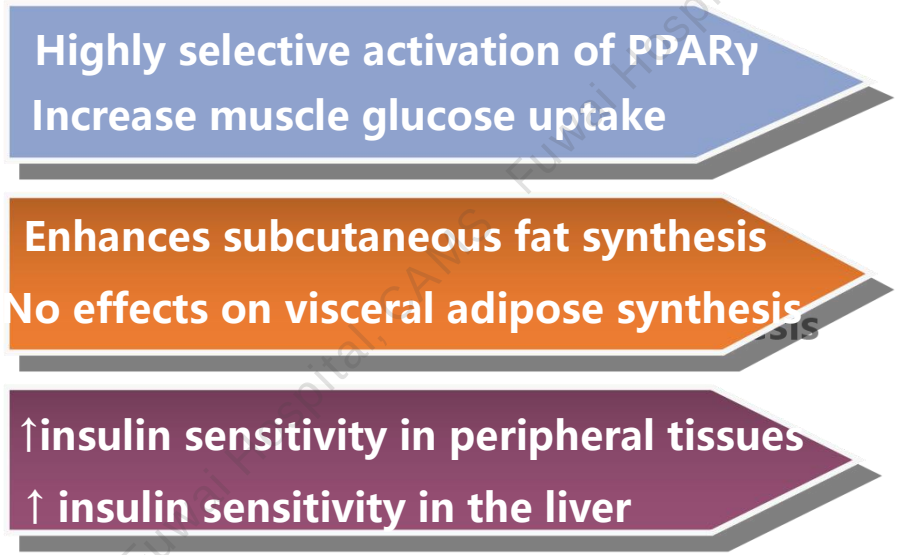
Thiazolidinediones-rosiglitazone

Mechanism- insulin sensitizer



- Hypoglycemia may occur in combination with sulfonylureas and insulin
- Weight gain in some patients
- May increase sodium and water retention
- May increase cardiac load - contraindicated in patients with cardiac insufficiency
- May cause bone fracture

2007-2010 Debate over Rosiglitazone.
Potential for adverse ischemic cardiovascular events
Results: Rosiglitazone Withdrawal

In 2008, the FDA required that all newly developed hypoglycemic drugs be subjected to CVOT trials to ensure their cardiovascular safety

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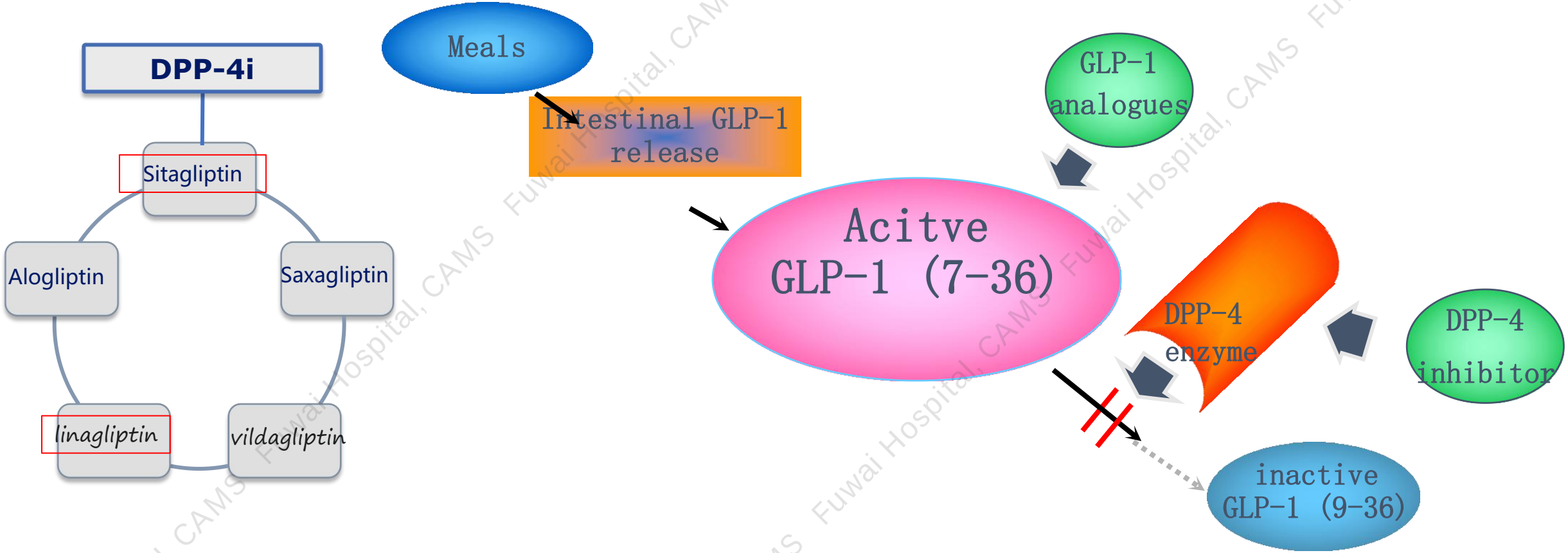
DDP-4i



DPP-IV=dipeptidyl peptidase IV

Adapted from Drucker DJ *Expert Opin Invest Drugs* 2003;12(1):87–100; Ahrén B *Curr Diab Rep* 2003;3:365–372.

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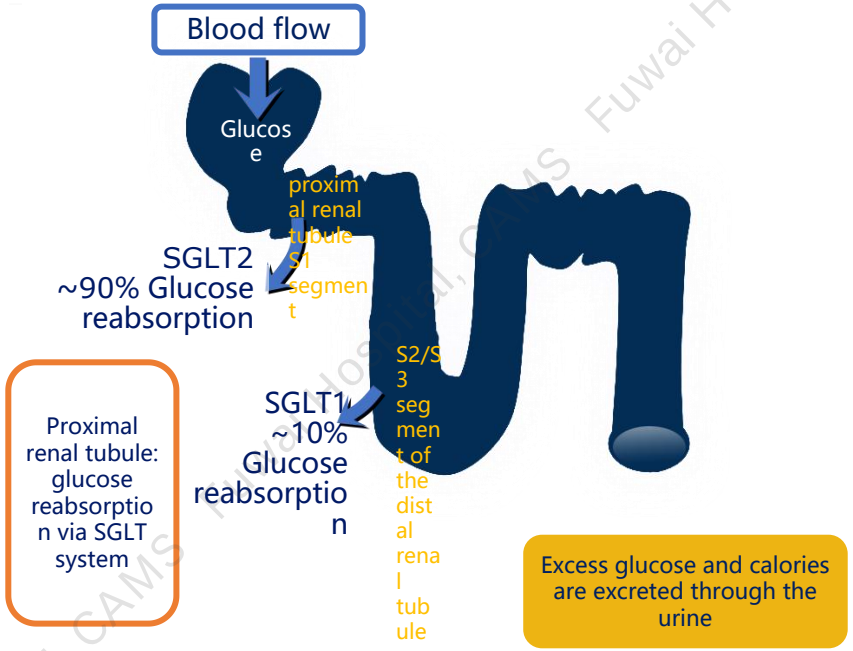
SGLT-2i(sodium-glucose cotransporter 2 inhibitors)

Dapagliflozin, Empagliflozin, and Canagliflozin



- **Mechanisms:** reduce glucose levels by inhibiting renal tubular SGLT2 responsible for glucose reabsorption from urine, reducing the renal glucose threshold and promoting urinary glucose excretion

- **Clinical effects:**
- reduce HbA1c levels by approximately 0.5% to 1.0%,
- reduce body weight by 1.5 to 3.5 kg, and lower systolic blood pressure by 3 to 5 mmHg
- Empagliflozin or Canagliflozin in patients with type 2 diabetes at high cardiovascular risk : reduced the risk of MACE, renal events, and heart failure hospitalizations
- **Main adverse reactions:** mild to moderate urinary and genital tract infections, hypotension (osmotic diuresis), ketoacidosis, acute kidney injury and renal impairment, and possible increased risk of amputation with Canagliflozin (CANVAS & CANVAS-R studies, FDA black box warning)

2Abdul-Ghani MA. *Endocr Pract*. 2008;14:782-790.

1.Knudsen LB et al. J Med Chem 2000;43:1664–1669. 2.闵媛婷, 盛德乔.生命的化学.2015; 35(6): 751-756.3. Diabetes Ther 2013 Dec; 4(2): 195–220.

Mechanism and adverse effects of commonly used oral hypoglycemic drugs

Drugs	Main Mechanism	Adverse Effects
Sulfonylureas	Promotes insulin secretion	Hypoglycemia, weight gain
Glinides	Promotes early insulin secretion	Hypoglycemia, weight gain
Metformin	Reduces hepatic glucose output and increases glucose uptake and utilization by peripheral tissues	Gastrointestinal reactions, lactic acidosis
α-glucosidase inhibitors	Delay absorption of carbohydrates in the gastrointestinal tract	Gastrointestinal reactions
TZDs	Increase insulin sensitivity	Edema, heart failure, fractures, weight gain
DDP-4 inhibitors	Promotes insulin secretion and inhibits glucagon secretion	Hypoglycemia is rare and does not increase body weight

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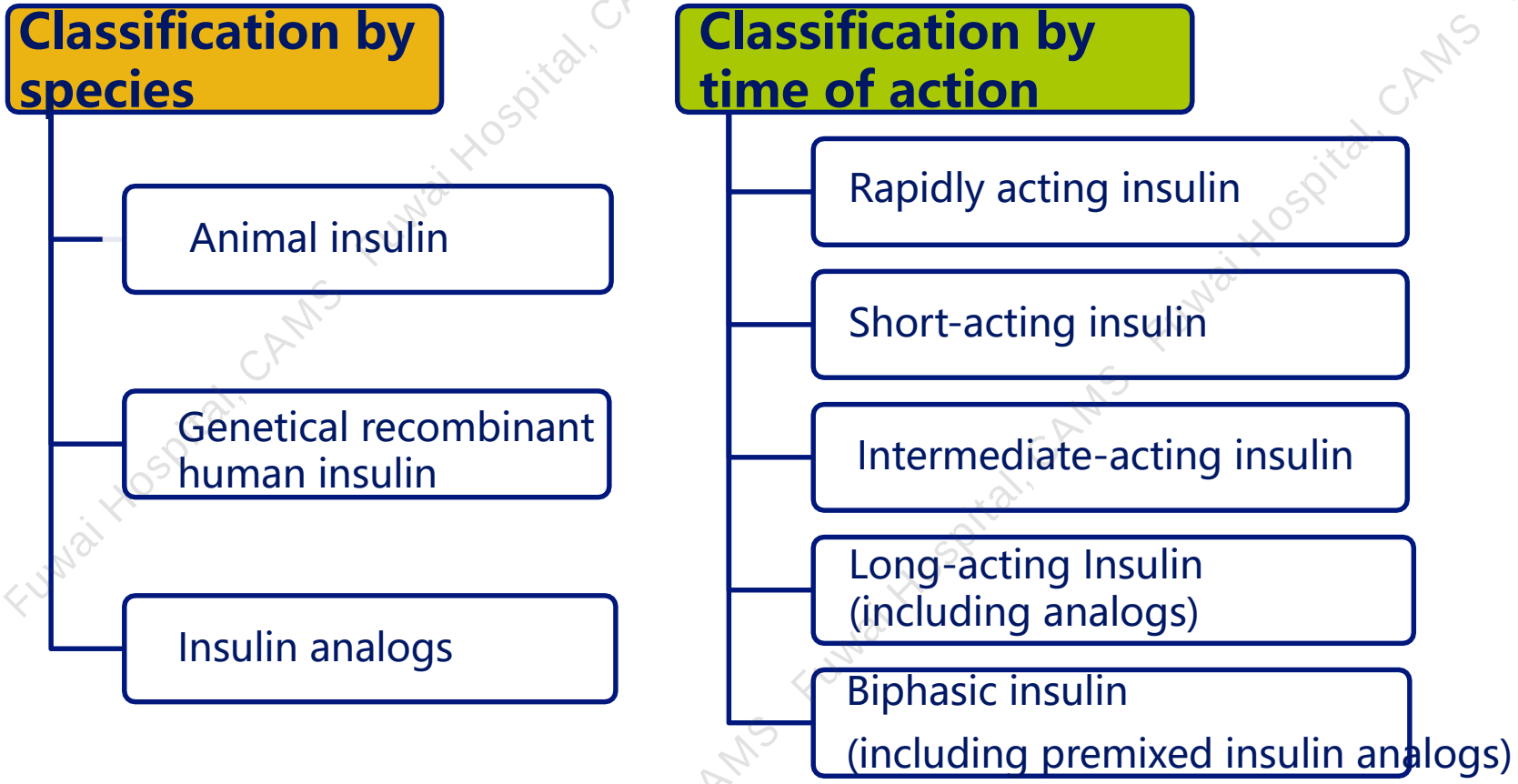
Classification of insulin



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Classification by action characteristics

Bolus Insulin	Rapidly acting insulin analogs	如：诺和锐、优泌乐
	Short-acting insulin	如：诺和灵R、优泌林R
Basal Insulin	Long acting insulin analogs	如：诺和平、来得时、诺和达
	Intermediate-acting insulin	如：诺和灵N、优泌林N
Premixed Insulin	Premixed Insulin analogs	如：诺和锐30、优泌乐25
	Premixed Insulin	如：诺和灵30R、诺和灵50R 优泌林70/30

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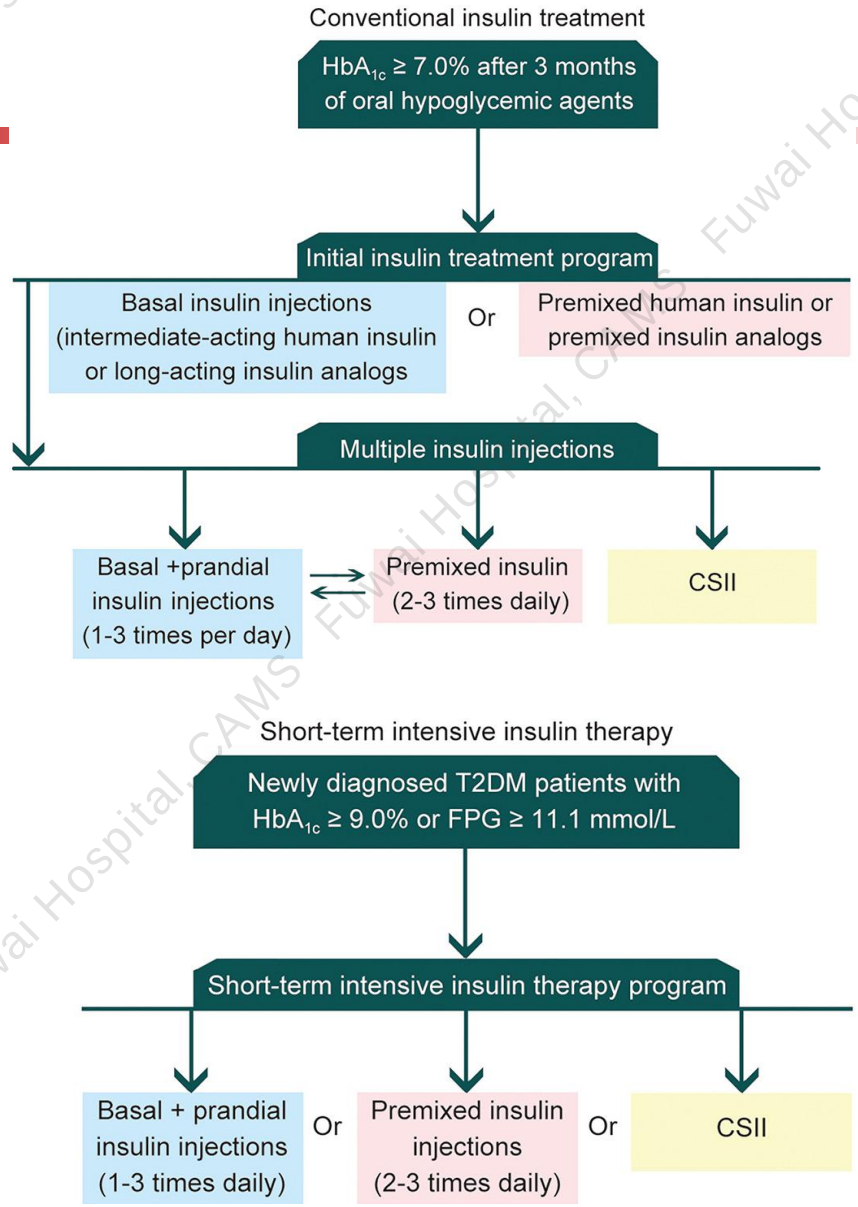
Insulin treatment paths

- **Supplementary treatment**
  - **Basal insulin (intermediate and long-acting insulins)**
  - **Premixed insulin once**
- **Alternative Treatment**
  - **Short-acting (or analogues) and basal insulin: four subcutaneous injections**
  - **Premixed insulin: 2 subcutaneous injections daily**
  - **Premixed insulin analogues: 2 to 3 subcutaneous injections**
- **Intensive insulin therapy for newly diagnosed T2DM** (HbA1c>9% or FPG>11.1mmol/l)



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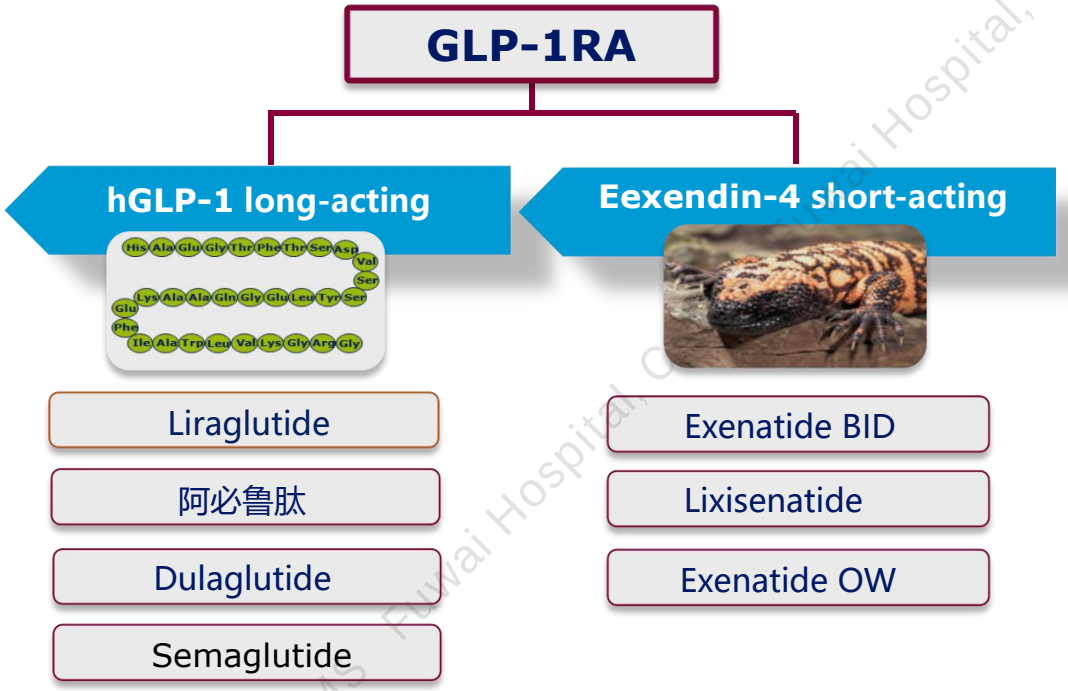
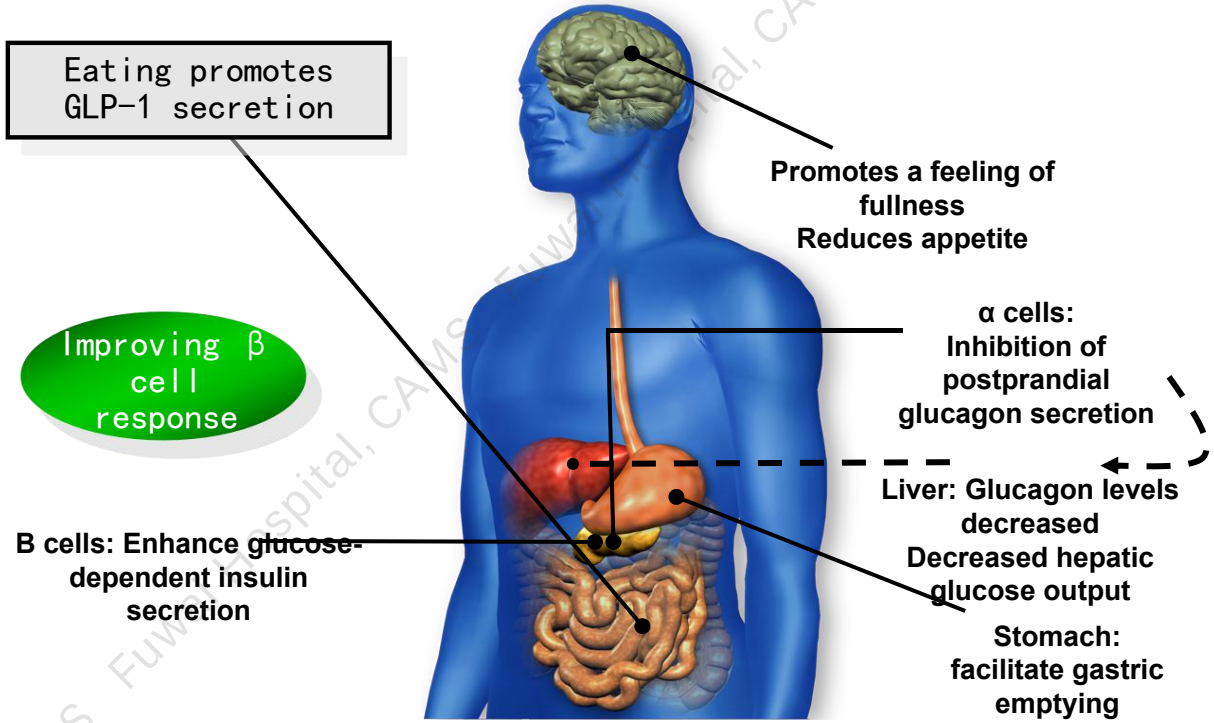
Glucagon-like peptide-1 receptor agonist



Incretin effect



Adapted from Flint A, et al. *J Clin Invest.* 1998;101:515-520; Adapted from Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422; Adapted from Nauck MA, et al. *Diabetologia.* 1996;39:1546-1553; Adapted from Drucker DJ. *Diabetes.* 1998;47:159-169.

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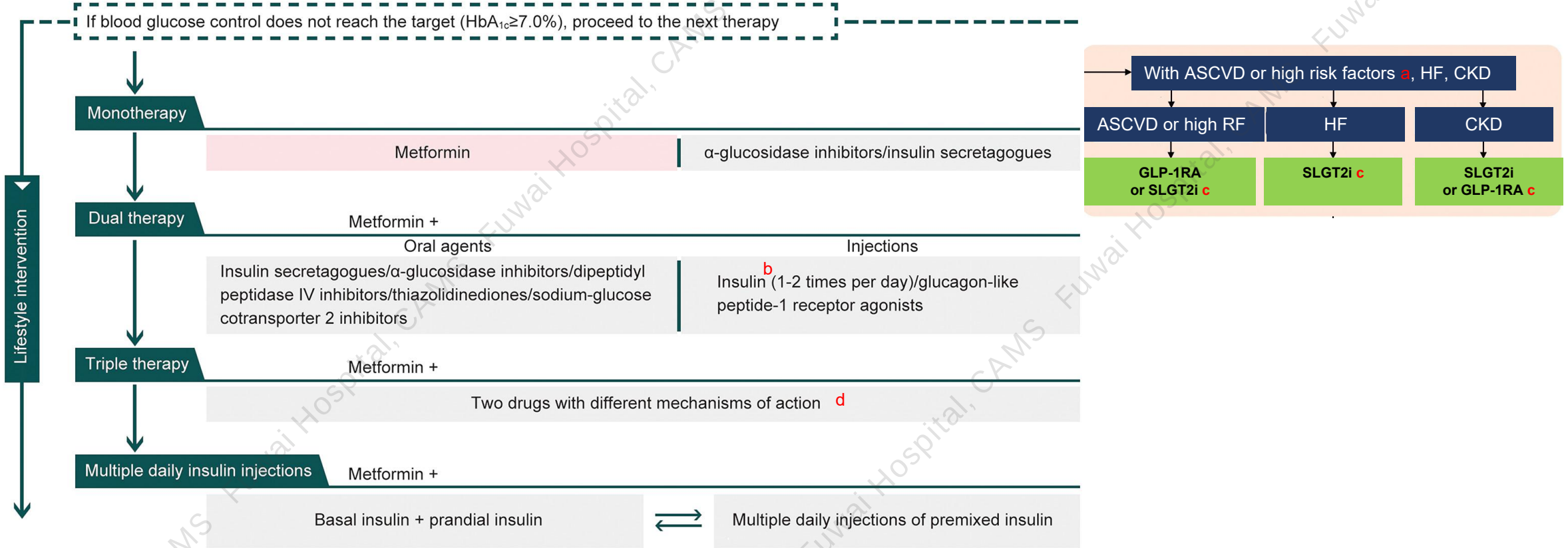
The treatment algorithm for high blood glucose in type 2 diabetes



a. High risk factors refer to age ≥55 years with at least 1 of the following: coronary or carotid artery or lower extremity artery stenosis ≥ 50%, left ventricular hypertrophy;b. basal insulin is usually used;c. GLP- 1RA or SGLT2i with evidence of ASCVD, heart failure or CKD benefit is added; d TZD is not used if heart failure is present

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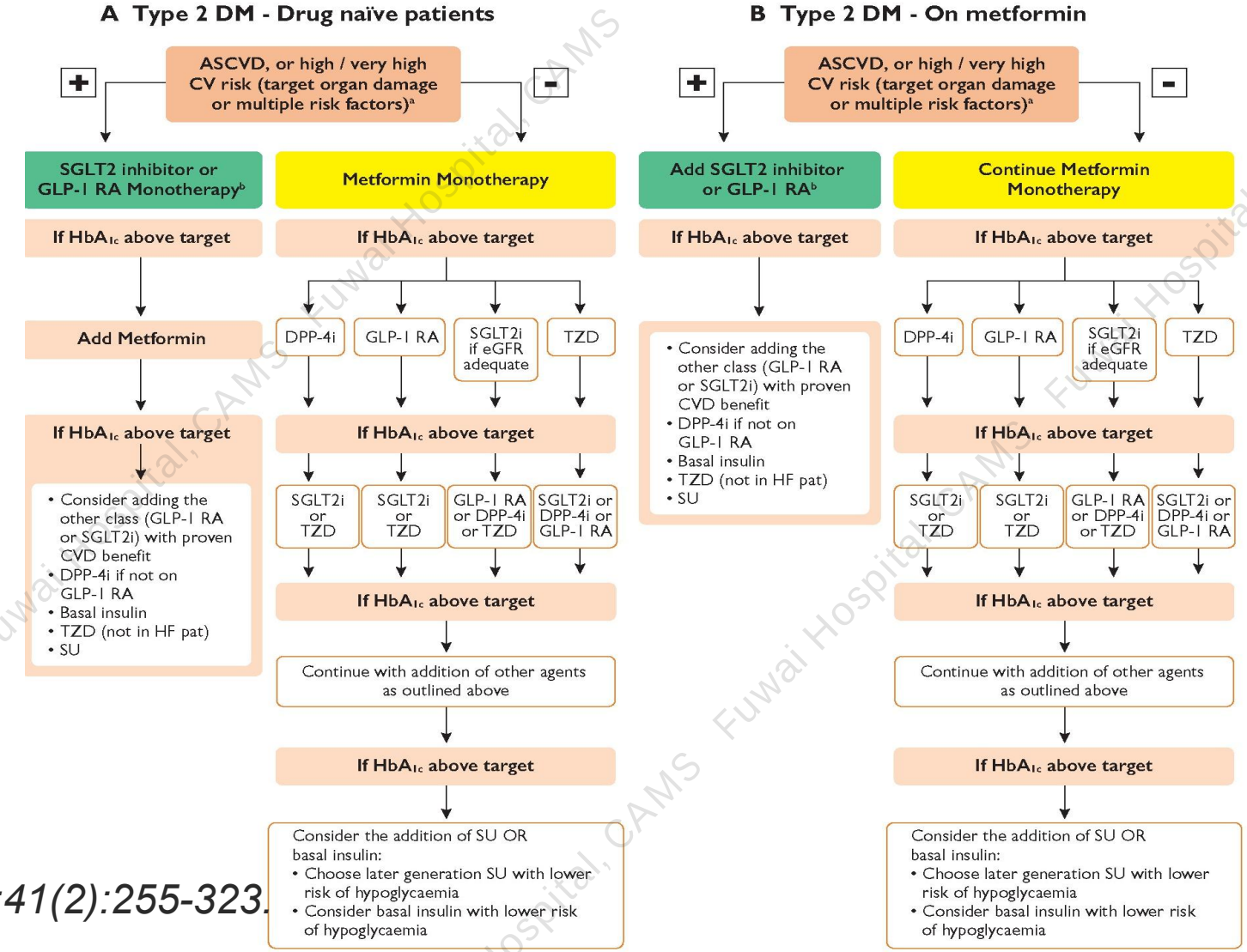
Management of hyperglycemia in Type 2 DM



Eur Heart J. 2020;41(2):255-323.

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Thanks!

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