Type 2 diabetes: treatments by class and action

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Type 2 diabetes is driven by **insulin resistance, progressive pancreatic β-cell dysfunction, inappropriate glucagon secretion, increased hepatic glucose production, altered incretin signalling and increased renal glucose reabsorption**. Treatment should combine lifestyle and weight management with glucose-lowering therapy selected according to cardiovascular disease, heart failure, chronic kidney disease, obesity, hypoglycaemia risk, renal function, cost and patient preference. Current guidance prioritises agents with proven cardiovascular, kidney or weight benefits rather than choosing therapy solely by HbA1c reduction.

Non-pharmacological and procedural treatments

Treatment	Principal action	Typical role
Diabetes education and self-management support	Improves medication use, glucose monitoring, nutrition, problem-solving and complication prevention	Foundation of management at diagnosis and throughout care
Medical nutrition therapy	Reduces total energy and refined carbohydrate intake; improves weight, postprandial glucose and insulin sensitivity	Individualised eating pattern; no single diet is universally superior
Weight-loss programme	Reduces visceral and hepatic fat, improving insulin sensitivity and β-cell function	A sustained loss of ≥5–10% body weight gives meaningful metabolic benefit; larger losses may permit remission
Aerobic exercise	Increases insulin-independent and insulin-mediated skeletal-muscle glucose uptake	Usually ≥150 minutes/week of moderate–vigorous activity, spread across ≥3 days
Resistance exercise	Increases muscle mass and glucose disposal	Usually 2–3 sessions/week
Reduce sedentary time	Improves postprandial glucose and insulin sensitivity	Interrupt sitting approximately every 30 minutes
Adequate sleep and treatment of sleep apnoea	Reduces counter-regulatory stress and may improve insulin sensitivity	Particularly important with obesity or resistant hypertension
Smoking cessation	Reduces macrovascular and microvascular risk	Essential cardiovascular-risk intervention
Metabolic/bariatric surgery	Produces major weight loss and changes gut hormones, bile-acid signalling and insulin sensitivity	Consider for suitable patients with obesity, especially when durable weight loss or diabetes control is not achieved medically

Glucose-lowering medicines

Class	Common agents and usual adult regimen*	Main action	Major advantages	Important cautions/contraindications
Biguanitde	**Metformin:** 500 mg PO od or bid with food; titrate to 1,500–2,000 mg/day	Activates AMP-associated pathways; primarily decreases hepatic gluconeogenesis and improves insulin sensitivity	Effective, inexpensive, weight-neutral or modest loss; minimal hypoglycaemia	**Avoid when eGFR <30 mL/min/1.73 m²;** review/reduce when eGFR 30–44; gastrointestinal effects, vitamin B12 deficiency; temporarily withhold during severe acute illness, hypoxia or significant dehydration
SGLT2 inhibitors	**Empagliflozin** 10–25 mg PO od;	Blocks proximal **renal** sodium–glucose cotransporter-2 → urinary glucose and sodium loss	Low hypoglycaemia risk, modest weight/BP reduction; major heart-failure and kidney protection; selected agents reduce cardiovascular events	Genital fungal infection, volume depletion; rare euglycaemic ketoacidosis; withhold during fasting, major surgery or severe illness; glucose-lowering efficacy declines at low eGFR, although cardiorenal benefit may remain
DPP-4 inhibitors	**Vildagliptin** 50-100mg PO od	Prevents breakdown of endogenous GLP-1 and GIP → modest glucose-dependent insulin increase and glucagon suppression	Oral, weight-neutral and low hypoglycaemia risk	Modest efficacy; possible pancreatitis; severe joint pain; avoid saxagliptin in heart failure and use caution with alogliptin; do not combine with a GLP-1 receptor agonist or tirzepatide
Sulfonylureas	**Gliclazide** 40–80 mg orally daily, titrate to 320 mg/day; glipizide 2.5–5 mg daily, up to 40 mg	Closes pancreatic β-cell ATP-sensitive potassium channels → insulin release independent of glucose	Rapid, effective and inexpensive	Hypoglycaemia and weight gain; caution in older adults, irregular food intake and kidney/liver impairment; avoid long-acting glyburide/glibenclamide where hypoglycaemia risk is high
GLP-1 receptor agonists	Semaglutide 0.25 mg subcutaneously weekly, titrate to 0.5–2 mg; dulaglutide 0.75–1.5 mg weekly, up to 4.5 mg where approved; liraglutide 0.6 mg daily, titrate to 1.2–1.8 mg; oral semaglutide 3 mg daily, then 7–14 mg	Glucose-dependent insulin secretion, reduced glucagon, delayed gastric emptying and increased satiety	High glucose efficacy; substantial weight loss; selected agents reduce cardiovascular events and may provide kidney benefit	Nausea, vomiting, gallbladder disease; avoid in pregnancy; generally avoid with severe gastroparesis; contraindicated for agents carrying the warning in patients with personal/family history of medullary thyroid carcinoma or MEN2
Dual GIP/GLP-1 receptor agonist	**Tirzepatide:** 2.5 mg subcutaneously weekly; increase by 2.5 mg at ≥4-week intervals, usually 5–15 mg weekly	Activates GIP and GLP-1 receptors → glucose-dependent insulin release, reduced glucagon, satiety and delayed gastric emptying	Very high HbA1c efficacy and usually the greatest pharmacological weight loss	Gastrointestinal effects, gallbladder disease; avoid in pregnancy and severe gastroparesis; thyroid C-cell tumour/MEN2 warning; reduce insulin or secretagogue dose if hypoglycaemia occurs
Thiazolidinediones	**Pioglitazone** 15–30 mg orally daily, up to 45 mg	Activates nuclear PPAR-γ receptors → improves adipose, muscle and hepatic insulin sensitivity	Durable glucose lowering; low hypoglycaemia risk; pioglitazone may benefit selected patients with metabolic steatohepatitis	Weight gain, oedema, heart-failure exacerbation and fractures; avoid in symptomatic heart failure or active bladder cancer; slow onset
α-Glucosidase inhibitors	**Acarbose** 25 mg orally with the first bite of meals; titrate to 50–100 mg three times daily; miglitol similar	Delays intestinal carbohydrate digestion and absorption	Targets postprandial glucose; weight-neutral; little hypoglycaemia alone	Flatulence and diarrhoea; avoid in inflammatory bowel disease, intestinal obstruction or significant renal impairment; treat hypoglycaemia with glucose, not sucrose
Dopamine D_2 agonist	**Bromocriptine quick-release:** 0.8 mg orally each morning; titrate to 1.6–4.8 mg within 2 hours of waking	Resets hypothalamic dopaminergic/circadian signalling, reducing hepatic glucose output and insulin resistance	Low hypoglycaemia risk alone	Nausea, dizziness, orthostatic hypotension and syncope; avoid in syncopal migraine and use caution with psychotic illness or dopamine-antagonist therapy
Amylin analogue	**Pramlintide:** generally 60 micrograms subcutaneously before major meals in insulin-treated type 2 diabetes; may increase to 120 micrograms	Reduces postprandial glucagon, slows gastric emptying and increases satiety	Reduces mealtime glucose and may assist weight loss	Requires mealtime insulin reduction because of severe hypoglycaemia risk; avoid in gastroparesis or hypoglycaemia unawareness
Insulin—basal	NPH, glargine, detemir or degludec; commonly start **10 units subcutaneously daily or 0.1–0.2 units/kg/day**, then titrate	Replaces basal insulin; suppresses hepatic glucose production and promotes peripheral glucose uptake	Highest glucose-lowering capacity; works at any HbA1c and in catabolic illness	Hypoglycaemia and weight gain; requires education, glucose monitoring and injection technique review
Insulin—prandial/rapid acting	Aspart, lispro, glulisine or regular insulin; commonly start 4 units or approximately 10% of basal dose before the largest meal, then intensify	Covers meal-related glucose rise and corrects hyperglycaemia	Most powerful control of postprandial glucose	Hypoglycaemia, weight gain and regimen complexity; match dose to carbohydrate intake, glucose and activity

Class	Common agents and usual adult regimen*	Main action	Major advantages	Important cautions/contraindications
Premixed insulin	Biphasic human or analogue insulin, usually before breakfast and evening meal	Fixed combination of basal/intermediate and mealtime insulin	Simpler than basal–bolus treatment	Less flexible meals; greater hypoglycaemia risk than many non-insulin regimens
Fixed-ratio basal insulin/GLP-1 combination	Insulin glargine/lixisenatide or insulin degludec/liraglutide, titrated in product-specific dose steps	Combines fasting glucose control with glucose-dependent postprandial control, satiety and glucagon suppression	Greater HbA1c reduction with less weight gain and hypoglycaemia than intensifying insulin alone	Gastrointestinal effects; product-specific maximum doses; GLP-1 contraindications apply

Insulin should be considered promptly when there is symptomatic hyperglycaemia, ketosis, catabolism, significant unexplained weight loss, suspected insulin deficiency or very high glucose—commonly HbA1c >86 mmol/mol or blood glucose ≥16.7 mmol/L. In most people without severe insulin deficiency, a GLP-1–based treatment is generally considered before starting injectable insulin because it provides effective glucose lowering with less hypoglycaemia and more favourable weight effects.

Choice according to major comorbidity

Clinical priority	Generally prioritised treatment
Established atherosclerotic cardiovascular disease or high cardiovascular risk	GLP-1 receptor agonist and/or SGLT2 inhibitor with demonstrated cardiovascular benefit, independent of metformin use or baseline HbA1c
Heart failure	SGLT2 inhibitor with proven heart-failure benefit; avoid thiazolidinediones
Chronic kidney disease	SGLT2 inhibitor when eGFR permits initiation; add a GLP-1 receptor agonist when further glucose, cardiovascular, kidney or weight benefit is required
Obesity or need for major weight reduction	Tirzepatide or a high-efficacy GLP-1 receptor agonist; consider metabolic surgery where appropriate
Need to avoid hypoglycaemia	Metformin, SGLT2 inhibitor, GLP-1 receptor agonist/tirzepatide, DPP-4 inhibitor or thiazolidinedione
Cost is the dominant issue	Metformin, selected sulfonylureas, pioglitazone and human NPH/regular insulin, balanced against adverse-effect risks
Metabolic dysfunction-associated steatohepatitis	Weight reduction; consider GLP-1–based therapy or pioglitazone in appropriately selected patients

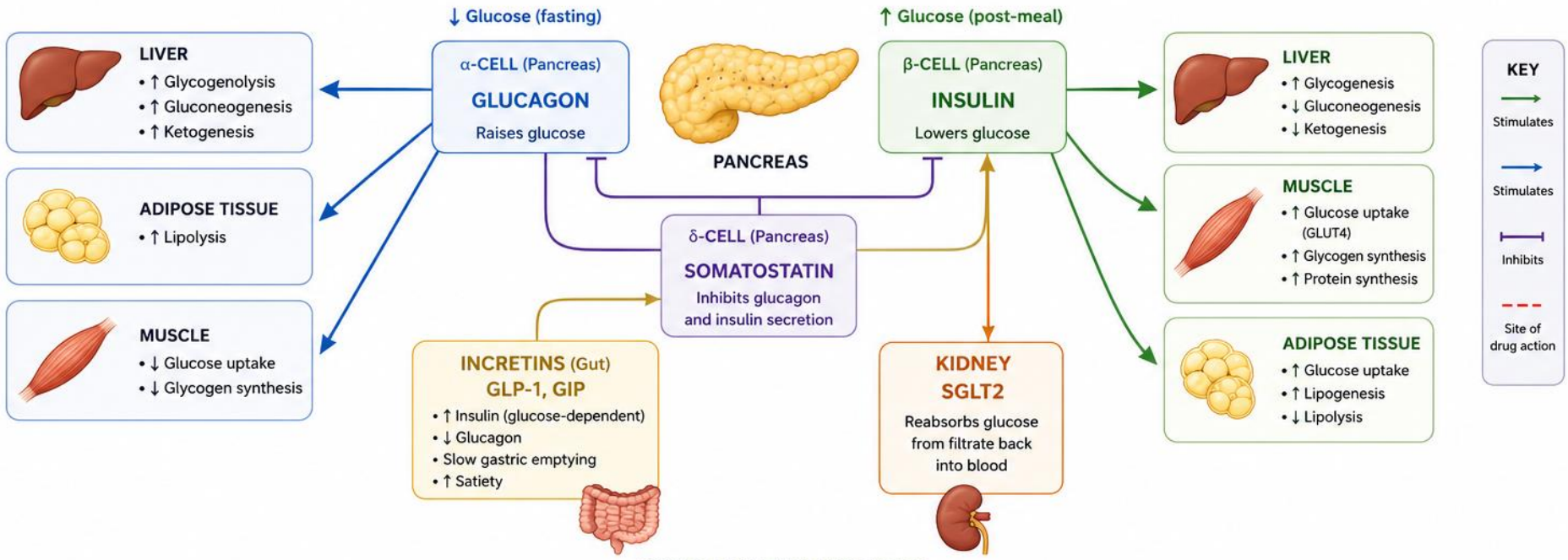
High-yield pearls

- **Metformin:** primarily reduces hepatic glucose output.
- **SGLT2 inhibitors:** remove glucose through urine and protect the heart and kidneys.
- **GLP-1 therapies and tirzepatide:** increase glucose-dependent insulin, suppress glucagon and promote satiety.
- **Sulfonylureas/meglitinides:** directly force insulin release, so hypoglycaemia can occur.
- **Thiazolidinediones:** improve insulin sensitivity but cause fluid retention and weight gain.
- **DPP-4 inhibitors:** well tolerated but modest; never routinely combine them with GLP-1 therapy.
- **Insulin:** has no maximum glucose-lowering effect, but titration is limited by hypoglycaemia and weight gain.
- Do not delay therapy escalation when the individualised HbA1c target is not met, but reassess adherence, nutrition, technique and medication tolerability first.

Simplified treatment algorithm

1. Establish an individualised HbA1c and weight goal; begin education, nutrition, physical activity and cardiovascular-risk management.
2. Screen specifically for atherosclerotic cardiovascular disease, heart failure, kidney disease, obesity and severe insulin deficiency.
3. Start an **SGLT2 inhibitor and/or GLP-1–based therapy** when a cardiorenal or major weight indication exists, regardless of baseline HbA1c or metformin use.
4. Use metformin where appropriate; combine therapies early when HbA1c is substantially above target.
5. Reassess after approximately 3–6 months and add a complementary class rather than duplicating mechanisms.
6. Begin basal insulin promptly for severe or symptomatic hyperglycaemia; otherwise consider GLP-1–based injectable therapy before insulin.
7. If basal insulin is insufficient despite controlled fasting glucose, add GLP-1 therapy or stepwise prandial insulin rather than continuing to escalate basal insulin alone.

HORMONES INVOLVED IN GLUCOSE REGULATION AND SITES OF ACTION OF ORAL DIABETES THERAPIES



WHERE ORAL THERAPIES WORK

	METFORMIN (Biguanide)	SULFONYLUREAS (e.g. gliclazide, glipizide)	MEGLITINIDES (e.g. repaglinide)	DPP-4 INHIBITORS (e.g. sitagliptin, linagliptin)	α-GLUCOSIDASE INHIBITORS (e.g. acarbose)	SGLT2 INHIBITORS (e.g. dapagliflozin, empagliflozin)
Site/Target	LIVER (↓ hepatic glucose production)	PANCREAS (β-cell) (Increases insulin secretion)	PANCREAS (β-cell) (Increases insulin secretion)	INCRETIN PATHWAY (Inhibits DPP-4 enzyme) DPP-4	INTESTINE (Brush border enzymes)	KIDNEY (Proximal tubule) SGLT2 transporter
Mechanism	↓ Gluconeogenesis ↑ Insulin sensitivity	Closes K_{ATP} channels → ↑ Insulin release (Glucose-independent)	Closes K_{ATP} channels → ↑ Insulin release (Short-acting)	↑ Endogenous GLP-1 & GIP → ↑ Insulin (glucose-dependent) → ↓ Glucagon	Delays carbohydrate breakdown & absorption → ↓ Post-prandial glucose	↓ Glucose reabsorption → ↑ Urinary glucose excretion
Key Points	First-line therapy Weight neutral / loss	Risk of hypoglycaemia Weight gain	Take with meals Lower hypoglycaemia risk than sulfonylureas	Weight neutral Low hypoglycaemia risk	GI side effects Weight neutral	Weight loss ↓ BP, CV & renal benefit Genital mycotic infections

Note: All therapies require adequate lifestyle measures. Choice of therapy is individualised based on patient factors, comorbidities, risk of hypoglycaemia, weight goals and cost.

This diagram reflects major hormonal pathways and sites of action of oral agents in type 2 diabetes.