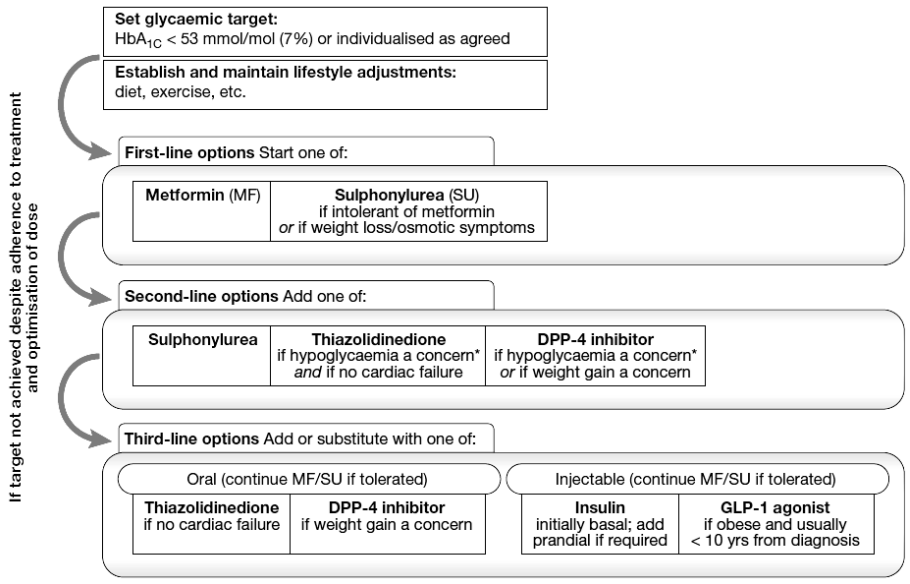
Hypoglycemic drugs

21.27 Effects of drugs used in the treatment of type 2 diabetes

	Insulin	Sulphonylureas and meglitinides	Metformin	Acarbose	Thiazolidinediones (glitazones)	DPP-4 inhibitors (gliptins)	GLP-1 receptor agonists	SGLT2 inhibitors
Fasting blood glucose	↓	↓	↓	↘	↓	↓	↓	↓
Post-prandial blood glucose	↓	↓	↓	↓	↓	↓	↓	↓
Plasma insulin	↑	↑	↓	↓	↓	↑	↑	↓
Body weight	↑	↑	→	→	↑	→	↓	↓
Risk of hypoglycaemia	++	+	–	–	–	–	–	–
Tolerability	Good	Good	Moderate	Moderate	Moderate	Good	Moderate	Limited experience

(DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium and glucose transporter 2)



- **Older drugs** are cheaper and have established benefits for reducing microvascular disease → therefore usually recommended as **first-line therapy** (**M**etformin and **S**ulphonylureas)
- **Newer drugs** using is not supported by evidence for reduction in microvascular disease (because the trials have not yet been done) and they are much more expensive → so are often reserved for later therapy after failure of metformin and sulphonylureas. (One guideline which follows these principles is shown in **(Figure ↑)**

	Mechanism of action	Clinical Use
Biguanides **Metformin** : • It's the only biguanide now available. • It is now widely used *as first-line therapy* for type 2 diabetes, irrespective of body weight. • It given adjunct to insulin therapy in obese patients with type 1 diabetes.	1- Increases insulin sensitivity 'insulin sensitiser' because it lowers insulin levels. 2- It reduces the rate of gluconeogenesis, and hence hepatic glucose output. 3- It has effects on gut glucose uptake and utilisation. 4- At the molecular level, metformin acts as a weak inhibitor of mitochondrial respiration, which ↑(AMP) and ↓ (ATP). This has : a- Direct effects on flux through gluconeogenesis. b- It activates intracellular energy sensor AMP-kinase, which is involved in : - GLUT4 metabolism and - Fatty acid oxidation, BUT its mechanism of action remains unclear at a cellular level. **It does not :** 1- Affect insulin secretion, 2- Induce hypoglycaemia 3- Predispose to weight gain. → helpful on obese people & normal weight. **N.B.** has established benefits in microvascular disease	**Use:** • It is employed as **first-line therapy** in all patients who tolerate it, and • its use is maintained when additional agents are added as glycaemia deteriorates. **Dose:** • Introduced at low dose (500 mg twice daily) to minimise risk of GIT side effects. • The usual maintenance dose is 1 g twice daily. **Side effects :** • GIT side-effects with metformin: - Diarrhoea, - Abdominal cramps, - Bloating - nausea. • Lactic acidosis in →renal impairment , hepatic impairment , alcohol excess : - Dose halved if GFR 30–45 mL/min - Shouldn't used if GFR< 30 mL/min , hepatic impairment , alcohol excess.
Sulphonylureas **insulin secretagogues** **(They promote pancreatic β-cell insulin secretion)** Tolbutamide: Lower maximal efficacy than other sulfonylureas; Short half-life – preferable in elderly; Largely metabolized by liver – can use in renal impairment Glibenclamide: Long biological half-life; Severe hypoglycaemia; Do not use in the elderly Glipizide and Glimepiride: Active metabolites; Renal excretion – avoid in renal impairment	• Their action is to bind to the sulfonylurea receptor on the cell membrane, → which closes ATP-sensitive potassium channels → and blocks potassium efflux → resulting in depolarization which **promotes influx of calcium, a signal for insulin release.** → *They are ineffective in patients without a functional beta-cell mass & their effect wears off as the beta-cell mass declines.* **It does cause :** 1- Hasten beta-cell apoptosis. 2- Induce hypoglycemia. 3- Promote weight gain. **N.B.** has established benefits in microvascular disease.	**Use:** • Often used as an add-on to metformin, if glycaemia is inadequately controlled on metformin alone (see Fig. above). **Dose:** The dose–response of all sulphonylureas is steepest at low doses. **Side effects :** - Weight gain → not preferred to be used in obese individuals. - Hypoglycaemia → Hypoglycaemia occurs because the closure of KATP channels brings about unregulated insulin secretion, even with normal or low blood glucose levels. → *Sulfonylureas should be used with care in patients with liver disease.* → *Patients with renal impairment should only be given those primarily excreted by liver.*
Thiazolidinediones **'glitazones' or 'PPARγ agonists'**	• They reduce insulin resistance by bind and activate **peroxisome proliferator-activated receptor-γ (PPAR γ),** a nuclear receptor present mainly in adipose tissue that regulates the expression of several genes involved in metabolism. 1- TZDs potentiate the effect of endogenous or injected insulin.: - Directly (in the adipose cells) and - Indirectly (by altering release of 'adipokines', such as adiponectin, which alter insulin sensitivity in the liver). 2- Act indirectly via the glucose– fatty acid cycle, lowering free fatty acid levels and thus promoting glucose consumption by muscle. 3- Reduce hepatic glucose production, (effect that is synergistic with that of metformin) **It doesn't & Does cause :** 1- Hypoglycaemia does not occur (Plasma insulin concentrations are not increased) 2- TZDs increase pre-adipocyte differentiation, resulting in an increase in fat mass and in body weight.	**A number of adverse effects become apparent and their use has declined.** **1- Rosiglitazone :** - Increase the risk of MI (withdrawn in 2010). **2- Pioglitazone :** **Uses :** - More effective in insulin-resistant patients. - Has a beneficial effect in reducing fatty liver and NASH - usually added to metformin with or without sulphonylurea therapy - may be given with insulin therapy **Side effects :** (Does not appear to increase the risk of myocardial infarction BUT) - it causes : • Exacerbation of *cardiac failure* by causing fluid retention, • Increases the risk of bone fracture, • Bladder cancer.
Incretin-based therapies: **- GLP-1 analogues** **- DPP-4 inhibitors** **Doesn't cause hypoglycemia :** Unlike sulphonylureas, they only : **promote insulin secretion when there is a glucose 'trigger' for insulin secretion.** Thus, when the blood glucose is normal, the insulin secretion is not augmented and so these agents **do not cause hypoglycaemia.**	**The "incretin effect"** is : • The augmentation of insulin secretion seen when a glucose stimulus is given orally rather than IV, and reflects the release of incretin peptides from the L cells in intestine: **1- Glucagon-like peptide 1 (GLP-1)** **2- Gastric inhibitory polypeptide (GIP).** - **DPP-4 (dipeptidyl peptidase 4)** rapidly inactivates GLP-1. The incretin effect is diminished in type 2 diabetes, and this has stimulated the development of **two incretin-based therapeutic approaches :** **1- 'gliptins', or DPP-4 inhibitors :** - Prevent breakdown → enhance concentrations of endogenous GLP-1 & GIP. - Drugs : 1- **S**itagliptin 2- **V**ildagliptin 3- **S**axagliptin 4-**L**inagliptin. **2- GLP-1 receptor agonists :** - have a similar structure to GLP-1 but have been modified to resist breakdown by DPP-4. - These agents are **not orally active** and have to be **given by subcutaneous injection**. - They have a key advantage over the DPP-4 inhibitors: because the GLP-1 activity achieved is supra-physiological : • it delays gastric emptying and, • at the level of the hypothalamus, decreases appetite. → Thus, injectable GLP-1 analogues lower blood glucose and result in weight loss – an appealing therapy, as the majority of patients with type 2 diabetes are obese. - Drugs: **E**xenatide (twice daily) / **L**iraglutide (once daily).	
SGLT2 inhibitors	**The sodium and glucose transporter 2 (SGLT2) inhibitor**: **Dapagliflozin** (licensed for use in 2012). • Glucose is filtered freely in the renal glomeruli and reabsorbed in the proximal tubules via SGLT2. • Inhibition results in about 25% of the filtered glucose not being reabsorbed → **with consequent glycosuria** → S.E: increased urinary tract and genital fungal infections. • This helps to lower blood glucose AND results in calorie loss and subsequent weight loss.	
α -glucosidase inhibitors	• **α-glucosidase inhibitors** (**Acarbose** taken with each meal) competitively inhibits alpha-glucosidase enzymes situated in the brush border of the intestine, → reducing absorption of dietary carbohydrate → So, undigested starch then enter the large intestine where it will be broken down by fermentation causing (S.E.) : 1- Abdominal discomfort 2- Flatulence 3- Diarrhoea can result	