

## What next after metformin?



Reinforce advice on diet, lifestyle & adherence to drug treatment	Biguanides (metformin)	SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin & ertugliflozin)	GLP1 receptor agonists (dulaglutide, exenatide, liraglutide, lixisenatide & semaglutide)	DPP4 inhibitors or "gliptins" (alogliptin, linagliptin, saxagliptin, sitagliptin & vildagliptin)	Thiazolidinediones (pioglitazone)	Sulphonylureas (gliclazide, glimepiride & glipizide)
<b>Mode of action</b>	Decreases hepatic glucose production & reduces IR	Insulin-independent; inhibits renal glucose reabsorption by blocking SGLT2 transporter	Stimulates glucose-dependent insulin release from the pancreas	Increases incretin (GLP1) levels by blocking DPP-4 enzyme which inactivates GLP1	Insulin-dependent; reduces hepatic & peripheral IR at a molecular level	Stimulates insulin secretion from pancreatic beta-cells
<b>Glycaemic efficacy</b>	Moderate	Moderate	High	Low/moderate	Moderate	High
<b>Impact on weight</b>	Weight loss	Weight loss	Weight loss	Weight neutral	Weight gain	Weight gain
<b>Risk of hypoglycaemia</b>	Low	Low	Low	Low	Low	High
<b>Cardiovascular benefits</b>	Yes	Yes	Yes	No	Possible	No
<b>Key advantages</b>	Well-established & cost-effective (generic). Reduces IR. Legacy effect seen with early metformin therapy - reductions in major diabetes complications, MI & ACM	Reduction in weight & BP. Reduction in MACE & HHF with canagliflozin & empagliflozin. Reduction in HHF & CV mortality composite with dapagliflozin. Slows progression of renal disease	Slows gastric emptying, reduces appetite & weight loss. Reduction in MACE with dulaglutide, liraglutide & semaglutide	Well-tolerated. Weight-neutral. Safe in CVD. Reassuring adverse effect profile	Well-established & cost-effective (generic). Reduces IR. Beneficial effects in fatty liver. Reduced recurrent stroke & MI in insulin-resistant individuals	Well-established & cost-effective (generic). Useful as rescue therapy for symptomatic hyperglycaemia (e.g. polydipsia & polyuria) and also for steroid-induced hyperglycaemia
<b>Prescribing in renal impairment (see GPnotebook Shortcut)</b>	Maximum tolerated dose to eGFR 45. Reduce dose to 500mg bd if eGFR 30-45. Avoid if eGFR <30	Do not initiate if eGFR<60. If eGFR subsequently falls <60 canagliflozin & empagliflozin require dose titration; check current BNF. Avoid all if eGFR <45	Dulaglutide, liraglutide & semaglutide can be used down to eGFR 15. Exenatide bd & lixisenatide can be used down to eGFR 30. Avoid exenatide qw if CrCl <50ml/min	Can be used down to eGFR<15 with dose titration (no dose titration required for linagliptin)	Can be used down to eGFR<15 but avoid in those on dialysis	Increased risk of hypoglycaemia if eGFR<60; consider reducing dose. Avoid if eGFR<30. Several drug interactions; check current BNF
<b>Precautions &amp; adverse effects</b>	GI side-effects common; "start low go slow". Long-term use can lead to vitamin b12 deficiency; check FBC annually. Sick day guidance required due to possible association with LA	Mycotic genital infections & UTIs; reinforce personal hygiene. Urinary frequency & possible dehydration. Small increase in LLA (predominantly toe) & fractures with canagliflozin but has not been borne out in more recent RCTs; avoid all SGLT2is in those with active/past diabetic foot disease or symptomatic PVD. Euglycaemic DKA; if suspected check ketones even if BG normal. Sick day guidance required	Injectable. GI side-effects common. Contraindicated MEN2 & MTC. Small increase in cholecystitis with liraglutide. Small worsening of pre-existing DR with semaglutide; monitor if known DR. Possible increase in pancreatitis	GI disturbance. Possible increase in pancreatitis. Rarely, anaphylaxis, urticaria, URTIs, angio-oedema & arthralgia. Small increase in HHF with saxagliptin	Peripheral & central oedema; contraindicated in heart failure & caution in macular oedema. Increases fracture risk. Possible link with bladder cancer; contraindicated in uninvestigated haematuria & bladder cancer; dipstick urine before starting	All should have access to SMBG especially drivers in view of risk of hypoglycaemia. Poor durability of effect. Avoid in frailty. Give driving & hypoglycaemia advice

### Glossary of Abbreviations

**ACM:** all-cause mortality; **BG:** blood glucose; **BP:** blood pressure; **CrCl:** creatinine clearance; **CV:** cardiovascular; **CVD:** cardiovascular disease; **DKA:** diabetic ketoacidosis; **DPP4:** dipeptidyl peptidase-4; **DR:** diabetic retinopathy **eGFR:** estimated glomerular filtration rate; **FBC:** full blood count; **GI:** gastrointestinal; **GLP1:** glucagon-like peptide-1; **HHF:** hospitalisation for heart failure; **IR:** insulin resistance; **LA:** lactic acidosis; **LLA:** lower limb amputations; **MACE:** major adverse cardiovascular events (composite of non-fatal myocardial infarction, non-fatal stroke & cardiovascular death) **MEN:** multiple endocrine neoplasia; **MI:** myocardial infarction; **MI:** myocardial infarction; **MTC:** medullary thyroid cancer; **PVD:** peripheral vascular disease; **SGLT2:** sodium-glucose co-transporter-2; **SMBG:** self-monitoring of blood glucose; **URTIs:** upper respiratory tract infections; **UTIs:** urinary tract infections