What next after metformin? A GPnotebook Shortcut

While metformin is considered to be the first-line glucose-lowering medication of choice in most cases, the decision of which agent to use as second-line therapy is more complicated and requires tailoring to the individual. The array of drug classes available, and their wide variety of effects – both positive and negative – beyond reducing blood glucose levels can make this challenging. This GPnotebook Shortcut will help guide the choice of agent after metformin to ensure that the benefits outweigh the potential harm.

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Recent years have seen a number of new drugs become available for the management of type 2 diabetes, and emerging evidence suggests that many of these agents have benefits beyond their effects on blood glucose control.

Currently, NICE, the American Diabetes Association and the European Association for the Study of Diabetes all recommend metformin as the first-line antidiabetes drug of choice, in conjunction with diet and lifestyle modification. However, if this fails to keep HbA_{1c} at target levels, the question of which medication should be added is more complex.

Reminder: What comes BEFORE metformin is also important

Readers are reminded that healthcare professionals play an important role in the management of type 2 diabetes long before they need to prescribe metformin. Specifically, they should confirm the diagnosis of type 2 diabetes (diabetes is commonly misclassified at diagnosis, which can lead to the wrong treatment; see our previous GPnotebook Shortcut on diagnosis). Providing information and support to lose weight and increase physical activity is the first port of call in managing type 2 diabetes, and newly diagnosed individuals may be encouraged to learn that the condition can be put into remission with sufficient and sustained weight loss (Lean et al, 2019). Finally, reduction of other risk factors, such as blood pressure and cholesterol, should also be considered and appropriate medications offered.

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The decision of which agent to add to metformin therapy should be made in collaboration with the person with diabetes and in accordance with their needs. A host of factors need to be considered, including the individual's health status, priorities, comorbidities and other medications, as well as the new drug's cautions and contraindications, side effects, and beneficial effects beyond glucose lowering.

With so many factors to consider, the GPnotebook Shortcut overleaf will help guide the choice of agent after metformin to ensure that the benefits outweigh the potential harm. ■

Lean MEJ, Leslie WS, Barnes AC et al (2019) Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* **7**: 344–55

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What next after metformin?

GP notebook shortcuts

Reinforce advice on diet, lifestyle and adherence to drug treatment	Biguanides (metformin)	SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin)	GLP-1 RAs (dulaglutide, exenatide, liraglutide, lixisenatide and semaglutide)	DPP-4 inhibitors or "gliptins" (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin)	Thiazolidinediones (pioglitazone)	Sulfonylureas (gliclazide, glimepiride and glipizide)
Mode of action	Decreases hepatic glucose production and reduces insulin resistance	Insulin-independent; inhibits renal glucose reabsorption by blocking SGLT2 transporter	Stimulates glucose-dependent insulin release from the pancreas	Increases incretin (GLP-1) levels by blocking DPP-4 enzyme which inactivates GLP-1	Insulin-dependent; reduces hepatic and peripheral insulin resistance at a molecular level	Stimulates insulin secretion from pancreatic beta-cells
Glycaemic efficacy	Moderate	Moderate	High	Low/moderate	Moderate	High
Impact on weight	Weight loss +	Weight loss ++	Weight loss +++	Weight neutral	Weight gain ++	Weight gain +
Risk of hypoglycaemia	Low	Low	Low	Low	Low	High
Cardiovascular benefits	Yes – ASCVD	Yes – ASCVD and HF	Yes – ASCVD	No	Possible	No
Key advantages	Well established and cost-effective (generic). Reduces insulin resistance. Legacy effect seen with early metformin therapy – reductions in major diabetes complications, MI and all-cause mortality (UK Prospective Diabetes Study; New Engl J Med, 2008)	Reduction in weight and BP. Reduction in MACE and HHF with canagliflozin and empagliflozin. Reduction in HHF and CV mortality composite with dapagliflozin. Slows progression of renal disease	Slows gastric emptying, reduces appetite and weight loss. Reduction in MACE with dulaglutide, liraglutide and semaglutide. Fixed-combination insulin/GLP1-RA products now available	Well tolerated. Weight-neutral. Safe in CVD. Reassuring adverse effect profile	Well established and cost-effective (generic). Reduces insulin resistance. Beneficial effects in fatty liver. Reduced recurrent stroke and MI in insulin-resistant individuals	Well established and cost-effective (generic). Useful as rescue therapy for symptomatic hyperglycaemia (e.g. polydipsia and polyuria) and also for steroid-induced hyperglycaemia
Prescribing in renal impairment (see renal prescribing GPnotebook Shortcut)	Maximum tolerated dose to eGFR 45. Reduce dose to 500 mg *bd* if eGFR 30–45. Avoid if eGFR <30	Do not initiate if eGFR <60. If eGFR subsequently falls to <60, canagliflozin and empagliflozin require dose titration; check current BNF. Avoid all if eGFR <45	Liraglutide can be used in severe renal impairment but no therapeutic experience in ESRD. Dulaglutide and semaglutide can be used down to eGFR 15. Exenatide *bd* and lixisenatide can be used down to eGFR 30. Avoid exenatide *qw* if CrCl <50 mL/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
Precautions and adverse effects	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 lactic acidosis. Temporarily stop the "SADMAN" drugs (S=SGLT2 inhibitors; A=ACE inhibitors; D=Diuretics; M=Metformin; A=ARBs; N=NSAIDs) during any acute dehydrating illness and restart once eating and drinking normally, usually 24–48 hours later	Mycotic genital infections and UTIs. MHRA (2019a) warns of rare reports of Fournier's gangrene; reinforce good personal hygiene and adequate hydration. MHRA (2017) warns of possible class effect of lower limb amputation (predominantly toe); avoid all SGLT2 inhibitors in those with active/past diabetic foot disease or symptomatic peripheral vascular disease. MHRA (2016) warns of euglycaemic DKA; if suspected, check ketones even if BG normal. Sick day guidance required (see metformin)	Injectable. GI side effects common. Contraindicated in multiple endocrine neoplasia type 2 and medullary thyroid cancer. Small increase in cholecystitis with liraglutide. Small worsening of pre-existing retinopathy with semaglutide; monitor if known retinopathy. Possible increase in pancreatitis. Possible DKA if concomitant insulin rapidly reduced or stopped; any reduction in insulin should be done in stepwise manner with careful SMBG (MHRA, 2019b)	GI disturbance. Possible increase in pancreatitis. Rarely, anaphylaxis, urticaria, upper respiratory tract infections, angio-oedema and arthralgia. Small increase in HHF with saxagliptin	Peripheral and central oedema; contraindicated in HF and caution in macular oedema. Increases fracture risk. Possible link with bladder cancer; contraindicated in uninvestigated haematuria and 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 and hypoglycaemia advice. TREND-UK has a useful leaflet: *Diabetes: Safe Driving and the DVLA*

ASCVD: atherosclerotic CVD; **BG:** blood glucose; **BNF:** British National Formulary; **BP:** blood pressure; **CrCl:** creatinine clearance; **CV:** cardiovascular; **CVD:** cardiovascular disease; **DKA:** diabetic ketoacidosis; **DPP-4:** dipeptidyl peptidase-4; **eGFR:** estimated glomerular filtration rate (in mL/min/1.73 m^2); **ESRD:** end-stage renal disease; **FBC:** full blood count; **GI:** gastrointestinal; **GLP-1 RA:** glucagon-like peptide-1 receptor agonist; **HF:** heart failure; **HHF:** hospitalisation for HF; **MACE:** major adverse cardiovascular events (composite of non-fatal MI, non-fatal stroke and cardiovascular death); **MI:** myocardial infarction; **SGLT2:** sodium–glucose cotransporter-2; **SMBG:** self-monitoring of blood glucose; **UTI:** urinary tract infection.

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