What Next After Metformin?

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Reinforce advice on diet, lifestyle and adherence to drug treatment	Biguanides (metformin)	SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	GLP-1 receptor agonists (dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide)	DPP-4 inhibitors or "gliptins" (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin)	Thiazolidinediones (pioglitazone)	Sulphonylureas (gliclazide, glimepiride, glipizide)
Mode of action	Decreases hepatic glucose production and reduces IR	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 that inactivates GLP-1	Insulin-dependent; reduces hepatic and peripheral IR at a molecular level	Stimulates insulin secretion from pancreatic beta-cells
Glycaemic efficacy	Moderate/high	Moderate/high	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
Key advantages	Well-established and cost-effective (generic). Reduces IR. Legacy effect seen with early metformin therapy: early glycaemic control has durable effects on microvascular outcomes, microvascular outcomes and mortality	Reduction in weight and BP. Secondary benefits of weight loss and BP reduction of around 4/2 mmHg	Slows gastric emptying, reduces appetite and can facilitate significant weight reduction. Injectable therapies; however, oral semaglutide now available, but needs careful counselling regarding administration to optimise exposure	Well-tolerated. Weight-neutral. Safe in CVD. Reassuring adverse effect profile	Well-established and cost-effective (generic). Reduces IR. Beneficial effects in fatty liver	Well-established and cost-effective (generic). Useful as rescue therapy for symptomatic hyperglycaemia (e.g. polydipsia and polyuria) and steroid-induced hyperglycaemia
Impact on major adverse cardiovascular events	Reduced MI and ACM demonstrated in UKPDS	Reduction in MACE with canagliflozin and empagliflozin. CV mortality benefit with empagliflozin. Reduction in HHF and CV mortality composite with dapagliflozin	Reduction in MACE with dulaglutide, liraglutide and semaglutide SC	No	Reduced recurrent stroke and MI in insulin-resistant individuals demonstrated in IRIS study	No
Impact on heart failure events	No	Reduction in HHF seen with all SGLT2 inhibitors. Dapagliflozin and empagliflozin have also demonstrated benefits in those without T2D	No	No (small increase in HHF with saxagliptin)	Potential harm; contraindicated in HF	No
Impact on major adverse renal events	No	Reduction in major adverse renal events with canagliflozin and dapagliflozin. Dapagliflozin has also demonstrated benefits in those without T2D	No	No	No	No
Prescribing in renal impairment (see GPnotebook Shortcut "Prescribing for people living with type 2 diabetes and renal impairment")	Maximum tolerated dose to eGFR 45. Reduce dose to 500 mg bd if eGFR 30–45. Avoid if eGFR <30	Due to significant differences within class, please refer to GPnotebook Shortcut Prescribing for people living with type 2 diabetes and renal impairment	Dulaglutide, liraglutide and semaglutide (SC and oral) can be used down to eGFR 15. Exenatide (bd and qw) and lixisenatide can be used down to eGFR 30	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
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 LA. SADMANS mnemonic useful clinical aide memoire for which drugs to temporarily pause; see: https://guidelines.diabetes.ca/docs/cpg/Appendix-8.pdf	Mycotic genital infections and UTIs; reinforce personal hygiene. Urinary frequency and possible dehydration. Small increase in LLA (predominantly toe) and fractures with canagliflozin but has not been borne out in more recent RCTs; avoid all SGLT2 inhibitors 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; see "How to use SGLT2 inhibitors safely and effectively" in *Diabetes & Primary Care*: https://www.diabetesonthenet.com/journals/issue/631/article-details/how-use-sglt2-inhibitors-safely-and-effectively	GI side-effects common. Contraindicated MEN2 and MTC. Small increase in cholecystitis with liraglutide. Small worsening of pre-existing DR with semaglutide in those with suboptimal glycaemic control at baseline and treated with insulin; monitor for progression of DR in these individuals. MHRA (2019) warns of reports of DKA when concomitant insulin is rapidly reduced or discontinued alongside GLP-1 receptor agonists; any dose reduction of insulin should be done in a stepwise manner with careful SMBG, particularly when GLP-1 receptor agonist therapy is initiated	GI disturbance. Possible increase in pancreatitis. Rarely, anaphylaxis, urticaria, URTIs, angio-oedema and arthralgia	Peripheral and central oedema; contraindicated in heart failure 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; see https://trenddiabetes.online/wp-content/uploads/2018/03/A5_6pp_Driving_TREND_CONNECT.pdf

Table based on Summaries of Product Characteristics and the author's clinical experience and appraisal of the literature.

Abbreviations

ACM: all-cause mortality; **bd:** twice daily; **BG**: blood glucose; **BP:** blood pressure; **CV:** cardiovascular; **CVD:** cardiovascular disease; **DKA:** diabetic ketoacidosis; **DPP-4:** dipeptidyl peptidase-4; **DR:** diabetic retinopathy **eGFR:** estimated glomerular filtration rate; **FBC:** full blood count; **GI:** gastrointestinal; **GLP-1:** glucagon-like peptide-1; **HHF:** hospitalisation for heart failure; **IR:** insulin resistance; **IRIS:** Insulin Resistance Intervention after Stroke **LA:** lactic acidosis; **LLA:** lower limb amputations; **MACE:** major adverse cardiovascular events (composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death); **MEN:** multiple endocrine neoplasia; **MI:** myocardial infarction; **MTC:** medullary thyroid cancer; **PVD:** peripheral vascular disease; **qw:** once weekly; **RCT:** randomised controlled trial; **SADMANS:** sulphonylureas, angiotensin-converting enzyme inhibitors, diuretics, direct renin inhibitors, metformin, angiotensin receptor blockers, nonsteroidal anti-inflammatory, SGLT2 inhibitors; **SC:** subcutaneous; **SGLT2:** sodium-glucose co-transporter-2; **SMBG:** self-monitoring of blood glucose; **T2D:** type 2 diabetes; **UKPDS:** UK Prospective Diabetes Study; **URTIs:** upper respiratory tract infections; **UTIs:** urinary tract infection

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