What Next After Metformin?

Medscape UK X Guidelines
Primary Care Hacks

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This Medscape UK Primary Care Hack is intended to help guide our choice of medication for the management of people living with type 2 diabetes. As always, we should take an individualised and holistic approach to the care of people living with type 2 diabetes.

	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)	Sulfonylureas (Gliclazide, Glimepiride, Glipizide)
	Reinforce the importance of 24-hour physical behaviours for T2D. See: *Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association and the European Association for the Study of Diabetes*					
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 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, macrovascular outcomes, and mortality	Secondary benefits of weight loss and BP reduction Average reduction of around 4 mmHg systolic/2 mmHg diastolic seen in ambulatory BP monitoring studies Certain SGLT2 inhibitors have also demonstrated benefits in ASCVD, HFrEF, HFpEF, and CKD NICE NG28 (2022)[1] now recommends early combination therapy with metformin + SGLT2 inhibitor for those with chronic HF, established ASCVD, or a QRISK2 score of ≥10%	Slows gastric emptying, reduces appetite, and can facilitate significant weight reduction Predominantly injectable therapies; however, oral semaglutide is now available—needs counselling regarding correct administration to optimise oral absorption Certain GLP-1 receptor agonists have demonstrated CV benefits in those with established ASCVD and also in the presence of multiple CV risk factors	Well-tolerated Weight-neutral Safe in CVD Reassuring adverse effect profile Can be prescribed in all stages of renal impairment	Well-established and cost-effective (generic) Reduces IR Beneficial effects in fatty liver disease NICE NG49 (2016)[2] also recommends consideration of pioglitazone for adults with advanced liver fibrosis with or without T2D (unlicensed indication)	Well-established and cost-effective (generic) Useful as rescue therapy for symptomatic hyperglycaemia (e.g. polydipsia and polyuria) and steroid-induced hyperglycaemia
Impact on MACE **See also *Primary Care Hacks: Extra-Glycaemic Indications of SGLT2 Inhibitors***	Reduction in MI and ACM demonstrated in UKPDS[3]	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 injectable semaglutide	No reduction seen in MACE	Reduction in recurrent stroke and MI in insulin-resistant individuals demonstrated in IRIS study[4]	No reduction seen in MACE The CAROLINA RCT demonstrated that glimepiride was non-inferior to linagliptin with respect to the risk of adverse CV outcomes, i.e., glimepiride use appears to be safe in the context of elevated CV risk[5]
Impact on HF Outcomes **See also *Primary Care Hacks: Extra-Glycaemic Indications of SGLT2 Inhibitors***	No reduction seen in hospitalisation or death from HF	Reduction in HHF seen with all SGLT2 inhibitors Dapagliflozin and empagliflozin have demonstrated significant reductions in HHF and CV mortality composite in HFrEF and are both licensed for HFrEF in people living with and without T2D Dapagliflozin has demonstrated a CV mortality benefit in HFrEF in people living with and without T2D Dapagliflozin and empagliflozin have demonstrated significant reductions in HHF and CV mortality composite in HFpEF Empagliflozin is licensed for HFpEF in people living with and without T2D	No reduction seen in hospitalisation or death from HF	No reduction seen in hospitalisation or death from HF (small increase in HHF seen with saxagliptin)	Potential harm due to fluid retention; contraindicated in HF	No reduction seen in hospitalisation or death from HF
Impact on MARE **See also *Primary Care Hacks: Extra-Glycaemic Indications of SGLT2 Inhibitors***	No reduction seen in MARE	Reduction in MARE seen with canagliflozin, dapagliflozin, and empagliflozin in people living with T2D Dapagliflozin and empagliflozin have demonstrated a reduction in MARE in people without T2D Dapagliflozin is licensed for the treatment of CKD in people living with and without T2D	No reduction seen in MARE	No reduction seen in MARE	No reduction seen in MARE	No reduction seen in MARE
Prescribing in Chronic Kidney Disease	Please refer to the Medscape UK Primary Care Hacks tool ***The Pharmacological Management of Hyperglycaemia in People Living with Type 2 Diabetes and Chronic Kidney Disease***					
Precautions and Adverse Effects (For Which Drugs to Temporarily Pause During Any Incurrent Illness)	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 SAD MANS mnemonic useful clinical aide memoire for which drugs to temporarily pause during any significant intercurrent illness; see the Canadian Diabetes Association's Sick Day Medications List **S**: sulfonylureas **A**: ACE inhibitors **D**: diuretics, direct renin inhibitors **M**: metformin **A**: angiotensin receptor blockers **N**: nonsteroidal anti-inflammatory drugs **S**: SGLT2 inhibitors	Mycotic genital infections and UTIs—reinforce good personal hygiene and adequate fluid intake MHRA (2019)[6] warns of rare association between SGLT2 inhibitors and Fournier's gangrene. Advise patients to seek urgent medical attention if they experience severe pain, tenderness, erythema, or swelling in the genital or perineal area, accompanied by fever or malaise Urinary frequency and possible volume depletion/dehydration Euglycaemic DKA—if suspected, check ketones even if BG normal. Sick day guidance required— SAD MANS clinical mnemonic for drugs to temporarily pause during significant intercurrent illness. See the Canadian Diabetes Association's Sick Day Medications List See *The Place and Value of Sodium–Glucose Cotransporter 2 Inhibitors in the Evolving Treatment Paradigm for Type 2 Diabetes Mellitus: a Narrative Review* for an SGLT2 inhibitor prescribing tool with associated clinical summaries	Counsel about GI side-effects (e.g. nausea, diarrhoea and constipation, early satiety, dyspepsia), but most of these effects generally decrease with time Eating smaller meals more frequently and stopping eating when starting to feel full can ease these side-effects Additionally, escalating dosing of GLP-1 receptor agonists over time can improve GI tolerability Contraindicated in 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)[6] 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 See *Glucagon-Like Peptide 1 Receptor Agonist Usage in Type 2 Diabetes in Primary Care for the UK and Beyond: A Narrative Review* for a GLP-1 receptor agonist prescribing tool	GI disturbance. Possible increase in pancreatitis Rarely, anaphylaxis, urticaria, URTIs, angio-oedema, and arthralgia	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; see *Diabetes and Frailty: An Expert Consensus Statement on the Management of Older Adults with Type 2 Diabetes* for advice on managing diabetes in the older person with frailty Give driving and hypoglycaemia advice; see: *Diabetes: Safe Driving and the DVLA*

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

Abbreviations
ACM=all-cause mortality; **BG**=blood glucose; **BP**=blood pressure; **CAROLINA**=Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes; **CKD**=chronic kidney disease; **CV**=cardiovascular; **CVD**=cardiovascular disease; **DKA**=diabetic ketoacidosis; **DPP-4**=dipeptidyl peptidase-4; **DR**=diabetic retinopathy; **FBC**=full blood count; **GI**=gastrointestinal; **GLP-1**=glucagon-like peptide-1; **HF**=heart failure; **HFpEF**=heart failure with preserved ejection fraction; **HFrEF**=heart failure with reduced ejection fraction; **HHF**=hospitalisation for heart failure; **IR**=insulin resistance; **IRIS**=Insulin Resistance Intervention after Stroke; **LA**=lactic acidosis; **MACE**=major adverse cardiovascular events (composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death); **MARE**=major adverse renal events; **MHRA**=Medicines and Regulatory products Healthcare Agency; **MEN2**=multiple endocrine neoplasia type 2; **MI**=myocardial infarction; **MTC**=medullary thyroid cancer; **NG**=NICE Guideline; **QRISK2**=Cardiovascular Risk Score 2; **RCT**=randomised controlled trial; **SAD MANS**=sulfonylureas, angiotensin-converting enzyme inhibitors, diuretics, direct renin inhibitors, metformin, angiotensin receptor blockers, nonsteroidal anti-inflammatory, SGLT2 inhibitors; **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

References

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