What Next After Metformin? Part One

Medscape UK X Guidelines
Primary Care Hacks

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This Medscape UK Primary Care Hack is intended to help guide the choice of medication for the management of people living with T2D. As always, take an individualised and holistic approach to the care of people living with T2D.

	Biguanides (Metformin)	**Sulfonylureas** (Gliclazide, Glimepiride, Glipizide)	**Thiazolidinediones** (Pioglitazone)	**DPP-4 Inhibitors or 'Gliptins'** (Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin)
	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, reduces IR, and reduces intestinal glucose absorption	Stimulates insulin secretion from pancreatic beta cells	Insulin-dependent; reduces hepatic and peripheral IR at a molecular level	Increases GLP-1 levels by blocking DPP-4 enzyme that inactivates GLP-1
Expected HbA_{1c} Reduction[1]	11–22 mmol/mol (1–2%)	11–22 mmol/mol (1–2%)	5–15 mmol/mol (0.5–1.4%)	6–9 mmol/mol (0.5–0.8%)
Impact on Weight	Weight loss +	Weight gain ++	Weight gain +++	Weight-neutral
Risk of Hypoglycaemia	Low	High (especially in renal impairment)	Low	Low
Key Advantages	Well established and cost-effective (generic) Reduces IR Legacy effect seen with early metformin therapy;[2] early glycaemic control has durable effects on microvascular outcomes, macrovascular outcomes, and mortality Metformin immediate-release is available in combination with pioglitazone, each of the DPP-4 inhibitors, and each of the SGLT2 inhibitors to reduce pill burden NICE PH38 (2017)[3] also recommends metformin as an adjunct to lifestyle changes in certain people at high risk of developing T2D Metformin is also sometimes used in the management of PCOS, although this use is off label and the evidence base is limited[4] See the related Primary Care Hack on identifying people at high risk of T2D See *Metformin in 2019*, a summary review of the evidence surrounding metformin use See *Metformin Beyond Type 2 Diabetes: Emerging and Potential New Indications* for a review of the future potential of metformin and ongoing research	Well established and cost-effective (generic) Useful as rescue therapy for symptomatic hyperglycaemia (e.g. polydipsia and polyuria) and steroid-induced hyperglycaemia See *Practical Guide to Glucocorticoid Induced Hyperglycaemia and Diabetes*	Well established and cost-effective (generic) Reduces IR Beneficial effects seen in MASLD NICE NG49 (2016)[5] also recommends consideration of pioglitazone for adults with advanced liver fibrosis with or without T2D (unlicensed indication) See the related Primary Care Hack on MASLD/MASH See also *Response to Pioglitazone in Non-alcoholic Fatty Liver Disease Patients With Vs. Without Type 2 Diabetes: A Meta-analysis of Randomized Controlled Trials*	Well tolerated Weight-neutral Safe in CVD Reassuring adverse effect profile Can be prescribed in all stages of renal impairment Generic sitagliptin now available DPP-4 inhibitors have been studied in frail older adults, demonstrating similar efficacy and safety profiles to those in younger adults
Impact on MACE (Composite of Nonfatal MI, Nonfatal Stroke, and CV Death)	Reduction in MI and ACM demonstrated in UKPDS[2,6] and a 2020 reappraisal of clinical trials[7]	No reduction seen in MACE The CAROLINA RCT found that glimepiride was non-nferior 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[8] In relatively recent, robust, high-quality systematic reviews, it has been found that there is no increased risk of ACM in association with sulfonylureas, as compared with other active treatments[9]	Reduction in recurrent stroke and MI in insulin-resistant individuals demonstrated in IRIS study[10]	No reduction seen in MACE[11]
Impact on HF Outcomes **Also see the Primary Care Hacks on HFpEF and HFrEF**	Metformin is safe to use in people living with T2D and HF[12] Some recent evidence suggests that metformin use may be associated with a lower risk of HHF[13]	No reduction seen in hospitalisation or death from HF	Potential harm as a result of fluid retention; contraindicated in HF	No reduction seen in hospitalisation or death from HF (small increase in HHF seen with saxagliptin)[11]
Impact on MARE	No reduction seen in MARE However, evidence from clinical trials[7] has shown that metformin is effective and safe in people with CKD as long as appropriate dose adjustments are used and use is restricted to patients with eGFR >30 ml/min/1.73 m^2	No reduction seen in MARE	No reduction seen in MARE	No reduction seen in MARE
Prescribing in CKD	Please refer to the Primary Care Hacks on **CKD** and **the pharmacological management of hyperglycaemia in people living with T2D and CKD**			
Adverse Effects	GI side effects common; 'start low, go slow' Long-term use can lead to vitamin B12 deficiency, and increases with higher dose; test vitamin B12 serum levels if deficiency is suspected, consider monitoring in patients with risk factors, and administer corrective treatment as appropriate (see MHRA [2022]);[14] check FBC annually	All should have access to SMBG, especially drivers in view of risk of hypoglycaemia Give driving and hypoglycaemia advice; see: *Diabetes: Safe Driving and the DVLA* Poor durability of effect Weight gain 1–4 kg	Peripheral and central oedema; contraindicated in HF and caution in macular oedema Increases fracture risk; avoid in those at increased risk of fracture, e.g. QFracture score ≥10% Weight gain 3–5 kg	GI disturbance. Possible increase in pancreatitis Rarely, anaphylaxis, urticaria, URTIs, angioedema, and arthralgia
Precautions	No specific precautions for metformin LA is rare but is more likely in clinical scenarios of increased lactate production, e.g. sepsis/severe infections, cardiogenic shock, and alcohol dependence Use of iodine-containing contrast medium can also lead to LA: pause metformin at the time of investigation, or 48 hours in advance if eGFR <60 ml/min/1.73 m^2; check eGFR again 48 hours later and restart metformin if stable[15]	Avoid in older people and 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 Increased risk of hypoglycaemia if eGFR <60 ml/min/1.73 m^2; consider reducing dose. Avoid if eGFR <30 ml/min/1.73 m^2. Gliclazide and glipizide are preferred, as they are metabolised in the liver	Possible link with bladder cancer; contraindicated in uninvestigated haematuria and bladder cancer (see the related US FDA Drug Safety Communication); dipstick urine before starting	No specific precautions for gliptins
Sick Day Guidance	Sick day guidance required because of a possible association with LA SADMANS mnemonic a useful clinical aide-mémoire 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**: ARBs **N**: NSAIDs **S**: SGLT2 inhibitors	Advise to increase frequency of SMBG during illness because of the increased risk of hypoglycaemia Give appropriate advice e.g. Trend Diabetes' hypoglycaemia leaflet If unable to eat or drink, an individual with T2D may need to temporarily pause sulfonylurea therapy. If their blood sugar levels are >17 mmol/l and/or they are feeling significantly unwell, advise them to contact an HCP for further advice. Sulfonylurea dose may need to be temporarily increased	No specific sick day guidance required for pioglitazone	No specific sick day guidance required for gliptins

Table based on summaries of product characteristics and the author's clinical experience and appraisal of the literature.

Abbreviations
ACE=angiotensin-converting enzyme; **ACM**=all-cause mortality; **ARB**=angiotensin receptor blocker; **CKD**=chronic kidney disease; **CV**=cardiovascular; **CVD**=cardiovascular disease; **DPP-4**=dipeptidyl peptidase-4; **DVLA**=Driver & Vehicle Licensing Agency; **eGFR**=estimated glomerular filtration rate; **FBC**=full blood count; **FDA**=Food & Drug Administration; **GI**=gastrointestinal; **GLP-1**=glucagon-like peptide-1; **HbA_{1c}**=glycated haemoglobin; **HCP**=healthcare professional; **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; **LA**=lactic acidosis; **MACE**=major adverse cardiovascular events; **MARE**=major adverse renal events; **MASH**=metabolic dysfunction-associated steatohepatitis; **MASLD**=metabolic dysfunction-associated steatotic liver disease; **MHRA**=Medicines and Healthcare products Regulatory Agency; **MI**=myocardial infarction; **NG**=NICE Guideline; **NSAID**=nonsteroidal anti-inflammatory drug; **PCOS**=polycystic ovary syndrome; **PH**=Public Health Guideline; **RCT**=randomised controlled trial; **SADMANS**=sulfonylureas, ACE inhibitors, diuretics, direct renin inhibitors, metformin, ARBs, NSAIDs, SGLT2 inhibitors; **SGLT2**=sodium–glucose co-transporter-2; **SMBG**=self-monitoring of blood glucose; **T2D**=type 2 diabetes; **URTI**=upper respiratory tract infection