## What next after metformin?

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Biguanides (metformin)</th>
<th>SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin &amp; ertugliflozin)</th>
<th>GLP1 receptor agonists (dulaglutide, exenatide, lirolaglutide, lixisenatide &amp; semaglutide)</th>
<th>DPP4 inhibitors or “gliptins” (agliptin, linagliptin, saxagliptin, sitagliptin &amp; vildagliptin)</th>
<th>Thiazolidinediones (pioglitazone)</th>
<th>Sulphonylureas (gliclazide, glimepiride &amp; glipizide)</th>
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<tbody>
<tr>
<td><strong>Decreases hepatic glucose production &amp; reduces IR</strong></td>
<td>Insulin-independent; inhibits renal glucose reabsorption by blocking SGLT2 transporter</td>
<td>Stimulates glucose-dependent insulin release from the pancreas</td>
<td>Increases incretin (GLP1) levels by blocking DPP-4 enzyme which inactivates GLP1</td>
<td>Insulin-dependent; reduces hepatic &amp; peripheral IR at a molecular level</td>
<td>Stimulates insulin secretion from pancreatic beta-cells</td>
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<tr>
<td><strong>Moderate</strong></td>
<td><strong>Moderate</strong></td>
<td><strong>High</strong></td>
<td><strong>Low/moderate</strong></td>
<td><strong>Moderate</strong></td>
<td><strong>High</strong></td>
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<tr>
<td><strong>Weight loss</strong></td>
<td><strong>Weight loss</strong></td>
<td><strong>Weight loss</strong></td>
<td><strong>Weight neutral</strong></td>
<td><strong>Weight gain</strong></td>
<td><strong>Weight gain</strong></td>
<td></td>
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<tr>
<td><strong>Low</strong></td>
<td><strong>Low</strong></td>
<td><strong>Low</strong></td>
<td><strong>Low</strong></td>
<td><strong>Low</strong></td>
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<tr>
<td><strong>Possible</strong></td>
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<td><strong>Well-established &amp; cost-effective (generic).</strong></td>
<td><strong>Reduction in weight &amp; BP. Reduction in MACE &amp; HHF with canagliflozin &amp; empagliflozin. Reduction in HbA1c &amp; CV mortality composite with dapagliflozin. Slows progression of renal disease</strong></td>
<td><strong>Slows gastric emptying, reduces appetite &amp; weight loss. Reduction in MACE with dulaglutide, lirolaglutide &amp; semaglutide</strong></td>
<td><strong>Well-tolerated. Weight-neutral. Safe in CVD. Measuring adverse effect profile</strong></td>
<td><strong>Well-established &amp; cost-effective (generic). Reduces IR. Beneficial effects in fatty liver. Reduced recurrent stroke &amp; MI in insulin-resistant individuals</strong></td>
<td><strong>Well-established &amp; cost-effective (generic). Useful as rescue therapy for symptomatic hyperglycaemia (e.g. polydipsia &amp; polyuria) and also for steroid-induced hyperglycaemia</strong></td>
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<td><strong>Maximum tolerated dose to eGFR 45. Reduce dose to 500mg bd if eGFR 30-45. Avoid if eGFR &lt;30</strong></td>
<td><strong>Do not initiate if eGFR &lt;60. If eGFR subsequently falls &lt;60 canagliflozin &amp; empagliflozin require dose titration; check current BNF. Avoid all if eGFR &lt;45</strong></td>
<td><strong>Dulaglutide, lirolaglutide &amp; semaglutide can be used down to eGFR 15. Exenatide bd &amp; lixisenatide can be used down to eGFR 30. Avoid exenatide qw if CrCl &lt;50ml/min</strong></td>
<td><strong>Can be used down to eGFR&lt;15 with dose titration (no dose titration required for linagliptin)</strong></td>
<td><strong>Can be used down to eGFR&lt;15 but avoid in those on dialysis</strong></td>
<td><strong>Increased risk of hypoglycaemia if eGFR&lt;60; consider reducing dose. Avoid if eGFR&lt;30. Several drug interactions; check current BNF</strong></td>
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<td><strong>GI side-effects common; “start low go slow”. Long-term use can lead to vitamin B12 deficiency; check B12 annually. Sick day guidance required due to possible association with LA</strong></td>
<td><strong>Mycotic genital infections &amp; UTIs; reinforce personal hygiene. Urinary frequency &amp; possible dehydration. Small increase in LLA (predominantly toe) &amp; 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. Euryglycaemic DKA; if suspected check ketones even if BG normal. Sick day guidance required</strong></td>
<td><strong>Injectable. GI side-effects common. Contraindicated MEN2 &amp; MTC. Small increase in cholecystitis with lirolaglutide. Small worsening of pre-existing DR with semaglutide; monitor if known DR. Possible increase in pancreatitis</strong></td>
<td><strong>GI disturbance. Possible increase in pancreatitis. Rarely, anaphylaxis, urticaria, URTIs, angio-oedema &amp; arthralgia. Small increase in HHF with saxagliptin</strong></td>
<td><strong>Peripheral &amp; central oedema; contraindicated in heart failure &amp; caution in macular oedema. Increases fracture risk. Possible link with bladder cancer; contraindicated in uninvestigated haematuria &amp; bladder cancer; dipstick urine before starting</strong></td>
<td><strong>All should have access to SMBG especially drivers in view of risk of hypoglycaemia. Poor durability of effect. Avoid in frailty. Give driving &amp; hypoglycaemia advice</strong></td>
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### Glossary of Abbreviations

- **ACM:** all-cause mortality
- **BG:** blood glucose
- **BP:** blood pressure
- **CrCl:** creatinine clearance
- **CV:** cardiovascular
- **CVD:** cardiovasucular disease
- **DKA:** diabetic ketoacidosis
- **DPP4:** dipeptidyl peptidase-4
- **DR:** diabetic retinopathy
- **eGFR:** estimated glomerular filtration rate
- **FBG:** 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
- **MTC:** medullary thyroid cancer
- **PVD:** peripheral vascular disease
- **SGLT2:** sodium-glucose co-transporter-2
- **SMBG:** self-monitoring of blood glucose
- **URTI:** upper respiratory tract infections
- **UTI:** urinary tract infections
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