Non-Insulin

Clinical Pearls

- SGLT2 inhibitors (e.g. empagliflozin, dapagliflozin) cause an initial increase in serum creatinine of up to 25-30%, similar to starting an ACEI or an ARB. This is expected and may even be a marker of renal benefit. It is recommended to check labs (e.g. renal function, electrolytes) 2-4 weeks after SGLT2 inhibitor initiation to ensure the rise in SCr is <30%. If a patient's eGFR <30 mL/min (or even <45), refer to nephrology.
- While nausea with GLP1 agonists (e.g. semaglutide, liraglutide) is common, tolerance often develops over the course of several months when these agents are titrated slowly. Emphasize this to patients when starting.
- Avoid combining DPP4 inhibitors and GLP1 agonists. These agents work similarly, and combining could result in an additive risk of pancreatitis.
- The vast majority of patients, perhaps greater than 90%, are able to tolerate metformin when the dose is started low and titrated slowly. If unsuccessful, extended-release (ER) metformin **GLUMETZA** has a lower rate of nausea and diarrhea than immediate-release metformin, and can be a way of overcoming metformin intolerance. Drug plan coverage for metformin ER is often a barrier, but some patients may be good candidates for a combination product (e.g. sitagliptin/metformin XR - **JANUMET XR**[EDS in SK]).

Links & Resources

- Shared Decision Making - Mayo Clinic shareddecisions.mayoclinic.org

Metformin remains the bedrock of pharmacologic glycemic control due to favourable outcome data, the potential for weight loss, a low risk of hypoglycemia, the availability of combination products, its low cost, and decades of real-world experience. Page 13 describes some tips and tricks to overcoming metformin intolerance and managing contraindications.

Table 1: Effect of therapies on A1c

Intervention	A1c lowering (approx.)
metformin	↓ 1-1.5%
sulfonylureas	↓ 1-1.5%
repaglinide	↓ 1-1.5%
GLP1 agonists	↓ 1-1.5%
thiazolidinediones	↓ 1%
SGLT2 inhibitors	↓ 0.5-0.8%
DPP4 inhibitors	↓ 0.5-0.7%

What drug comes after metformin? This question does not have a one-size-fits-all answer. Many options are reasonable.

- A comparison of available diabetes agents is found on page 14.
- Numerous patient factors that might be considered when choosing an agent are described on page 4, Table 2.
- A Shared Decision Making Tool that can be used to help explore what's important to a patient, and guide the decision of which diabetes agent might be best for them is found on page 33. Patients are asked to consider which of six factors is most important to them (cost, convenience, oral vs injection, adverse effects, cardiovascular protection, and renal protection). Then a side-by-side comparison on page 34 can be used to make an informed decision.

Large outcome trials have suggested cardiovascular and renal benefits with some GLP1 agonists; and cardiovascular, renal, and heart failure benefits with some SGLT2 inhibitors. Two important considerations come to mind when considering this data:

- Some benefits appear to be **agent-specific**. For example, some GLP1 agonists may prevent heart attacks, while others may not. See page 19 for more details.
- Benefits have been predominately shown in **people with established risk**. For example, the renal benefit of SGLT2 inhibitors is clearest in patients with established renal disease.

Other new agents with large outcome trials are also available. See page 14 for more details.

- finerenone **KERENDIA**
- tirzepatide **MOUNJARO**