MacLeod Diabetes & Endocrine Centre
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SGLT2 inhibitors in type 2 diabetes

Top line. Useful once-daily pills which also reduce weight and BP a little. They have good evidence of cardiovascular benefit, and in heart failure and CKD. SGLT2i are now often the second choice after metformin, and in many cases may be recommended even if HbA1c is already well controlled. Side effects can include polyuria, thrush and postural hypotension.

Examples

- Canagliflozin 100mg od (can increase to 300mg od for better glucose control)
- Dapagliflozin 10mg od (start at 5mg od in severe hepatic impairment)
- Empagliflozin 10mg od (can increase to 25mg od for better glucose control)
- Ertugliflozin 5mg od (can increase to 15mg od for better glucose control)

Position in type 2 diabetes treatment guideline

In current NICE guidance, SGLT2i will often be the second choice after metformin. They have evidence of benefit in people who have heart failure or cardiovascular disease or chronic kidney disease, regardless of diabetes. This means that an SGLT2i may be added to protect against those diseases, even if HbA1c is already at target. Their use thus becomes similar to statins, which are given to reduce cardiovascular risk regardless of cholesterol levels.

More detailed guidance is available in our other document "Treatment pathway for type 2 diabetes". In brief:

- An SGLT2i is **recommended** (regardless of HbA1c) for people who have established heart failure or atherosclerotic heart disease or urine albumin:creatinine ratio>30.
- An SGLT2i can be **considered** (regardless of HbA1c) for people who are at increased risk of developing cardiovascular disease, or have urine albumin:creatinine ratio 3-30.
- An SGLT2i can also be added, like any other drug, if none of the above apply but HbA1c is above target.

We advise that for people who are at increased cardiovascular risk or have mildly raised urine albumin, "considering" an SGLT2i should mean exactly that, and not "recommended for all". Very nearly 100% of people with type 2 diabetes will meet one of these criteria. An SGLT2i can be considered, taking into account your patient's feelings about taking an extra drug for the purposes of risk reduction. This conversation could be very similar to a discussion about statins for cardiovascular risk reduction, regardless of baseline cholesterol levels.

SGLT2i in renal impairment

The eGFR thresholds for when these drugs are licensed have changed several times, and differ between drugs in the class, and also for the indication for which they are prescribed. This has resulted in this illogical situation at the time of writing:

- One SGLT2i should generally be stopped if eGFR<45 when used for T2DM, but <30 in patients who have established CVD if used for T2DM, and <20 if used for heart failure regardless of diabetes status.
- Another should be used with caution if eGFR<60, and not be started if eGFR<30, but need not be stopped at any level.
- Another should not be started if eGFR<15, but need not be stopped at any level.

We are not going to attempt to justify this, and instead make the following general points:

- If the purpose of prescription is glucose control – expect less benefit if GFR <45-60. The drugs are not harmful, but have less glucose-lowering effect.
- The benefits in heart failure and CKD persist at lower levels of eGFR.
- At present, the Formulary requires prescription in heart failure to be on advice of a heart failure specialist. We cannot contradict that, but if a patient has both T2DM and heart failure, then SGLT2i prescription is already approved under diabetes guidance. If a drug is licensed at a lower eGFR for heart failure, we suggest that it may not be the best use of resources to seek authority from a cardiologist.
- Patients with heart failure or CKD but no diabetes – outside scope of this guidance.

When to avoid SGLT2 inhibitors:

- Type 1 diabetes – do not use.
- Type 2 diabetes – caution if already on insulin, as remote risk of DKA if unrecognised insulin deficiency. Seek advice if features suggest insulin deficiency (slimmer, early progression to insulin). Do not stop insulin without specialist supervision.
- Avoid or use cautiously if active foot disease, e.g. ulceration, severe PVD.
- Caution in elderly, particularly if prone to urosepsis, falls, postural hypotension.

Short-term efficacy

- HbA1c reduction typically 6-11 mmol/mol. Greater reductions can be seen in patients with higher baseline HbA1c.
- Weight reduction typically 2-3kg.

Side effects

- Genital infections (balanitis, vulvovaginitis) – in trials, 5-20% of patients. Urinary tract infections (mainly cystitis) – in trials, 10-15% of patients. Women more at risk. In real-world studies, these side effects seem more frequent.
- Polyuria.
- Dehydration, postural hypotension, falls – more so in the elderly, use with caution.

Driving

- Group 1 licence: no need to notify DVLA unless disabling hypos (very unlikely).
- Group 2 licence: notify DVLA, but should not affect licence, and can continue driving while waiting DVLA assessment. No obligation from DVLA to monitor blood glucose, but they advise monitoring regularly and at times relevant to driving.