Comment  Useful once-daily pills which also reduce weight and BP, with good evidence of cardiovascular benefit. Side effects can include polyuria, thrush and postural hypotension. We increasingly use SGLT2i as second-line after metformin if heart failure, cardiovascular disease or high risk of CV disease. We might also use SGLT2i second-line for patients at risk of hypos with a sulphonylurea, provided they are not also at risk from side effects of SGLT2i.

Current examples
- Canagliflozin 100mg od (can increase to 300mg od for better glucose control)
- Dapagliflozin 10mg od (reduce to 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)

Which is best?
- Canagliflozin and empagliflozin – both have good evidence of cardiovascular benefit.

Typical uses
- Add to metformin and sulphonylurea if HbA1c>58 mmol/mol (or target appropriate for patient) as alternative to insulin.
- Add to metformin as second-line drug in patients with previous cardiovascular disease (particularly MI, heart failure).
- Add to insulin, if already on large doses of insulin, and increasing insulin doses is unlikely to significantly improve glycaemic control or likely to worsen weight gain.

Other uses
- Alone, if metformin or SU contraindicated or not tolerated.
- Can be combined with virtually any other diabetes drugs.
- NICE has been more prescriptive about combinations, but NICE guidance has been updated so many times over the years that we are no longer trying to reflect it.

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 unreco spected 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.
- We do not routinely use with GLP1 agonists due to high combined cost.

Renal impairment
- Do not initiate with eGFR<60.
- If eGFR falls to 45-60, restrict canagliflozin to 100mg, or empagliflozin to 10mg.
- Stop if eGFR falls <45.
MacLeod Diabetes & Endocrine Centre
Royal Devon & Exeter Hospital

- SGLT2i drugs are less effective in renal impairment, but not harmful.
- A small fall in eGFR may be seen on starting, but there is good evidence that all three drugs delay progression of kidney disease, i.e. they are protective in the long-term.

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 the real-world these side effects seem more frequent.
- Polyuria.
- Dehydration, postural hypotension, falls – more so in the elderly, use with caution.

Long-term efficacy and safety:
- Canagliflozin and empagliflozin have good evidence for overall cardiovascular benefit, heart failure and renal function.
- Dapagliflozin did not show reduction in mortality/MI/stroke, but did show reduction in heart failure and preservation of renal function.

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.