Joined-up strategies for managing cardiac, renal and metabolic complications in type 2 diabetes: Q&A summary

1. **How does diabetes impact renal function and which treatments are best in patients with renal impairment?**
   - Diabetes causes various physiological changes which impact renal function:
     - Macrovascular: reduced circulation to the kidneys and hypertension
     - Microvascular: increased glycaemia causes inflammation and glomerular damage
     - Metabolic: increased hypoxia and oxidative stress in the kidneys.

   Treatment depends on estimated glomerular filtration rate (eGFR, in mL/min/1.73m^2) or severity of chronic kidney disease:

   1. eGFR ≤60 mL/min/1.73m^2 on two readings, 3 months apart: prescribe GLP-1 receptor agonists (GLP-1 RAs) (Buse et al, 2019)
   2. eGFR >60 mL/min/1.73m^2 plus microalbuminuria (≥30 mg) on ≥2 samples: prescribe sodium-glucose co-transporter-2 (SGLT2) inhibitors. Start if eGFR >60 mL/min/1.73m^2; continue if eGFR remains >44 mL/min/1.73m^2; discontinue if eGFR drops ≥25%. SGLT2 inhibitor licenses may change due to EMPA-REG (Zinman et al, 2015), CREDENCE (Perkovic et al, 2019) and DAPA-HF (Ponikowski, 2020) findings for use at lower eGFR.

   - All medications that reduce glucose levels impact eGFR. Start with an SGLT2 inhibitor, or if eGFR falls consistently <60 mL/min/1.73m^2, a glucagon-like peptide-1 receptor agonist (GLP-1 RA) can be used. GLP-1 RAs can also be used when SGLT2 inhibitors cannot be introduced due to contraindications or tolerability issues.
   - Caution:
     - SGLT2 inhibitors may increase the risk of diabetic ketoacidosis (DKA). If there are concernsabout ketosis, measure blood ketones.
     - GLP-1 RAs have been linked to increased risk of pancreatitis and pancreatic cancer; do not prescribe if the patient is at high risk of pancreatitis (e.g. high triglycerides).

2. **When should GLP-1 RAs and SGLT2 inhibitors be used?**
   - Consider using GLP-1 RAs and SGLT2 inhibitors to improve glycaemic control, reduce weight and as early second-line therapy in people with type 2 diabetes and established chronic kidney disease or cardiovascular disease (Buse et al, 2019).
   - GLP-1 RAs should be used in people with BMI ≥35 kg/m^2 or BMI ≥30 kg/m^2 plus comorbidity; they can be initiated at a lower BMI in ethnic minorities (NICE, 2015). GLP-1 RAs can be used in people with type 2 diabetes and liver disease (Takahashi et al, 2020).
   - SGLT2 inhibitors can be used for primary (Ponikowski, 2020) and secondary (Zinman et al, 2015) prevention of cardiovascular disease and heart failure and for renal protection (Neal et al, 2017, Perkovic et al, 2019). SGLT2 inhibitors can reduce high blood sugars quickly, so consider use early on in treatment. (NB: HbA_{1c} reductions taper as eGFR falls but cardiac and renal benefits remain).
   - Monitor and ensure patients are benefiting from treatments prescribed.
   - As GLP-1 RAs and SGLT2 inhibitors use different mechanisms of action, they can be used together.

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3. **What considerations should be taken into account when prescribing SGLT2 inhibitors?**
    - Side-effects: Educate the patient about good hygiene and increased fluid intake to reduce risk of thrush and urinary tract infections; discontinue if problematic.
    - Increased risk of DKA: Educate the patient about DKA and sick day rules.
    - Heart failure: Consider halving the dose of loop diuretic when initiating an SGLT2 inhibitor; monitor closely and increase diuretic dose if needed.

4. **Which treatments have cardiac benefits and should be considered for patients with diabetes?**
    - Consider reasons for use and benefits before prescribing medications. For example, glucose lowering; blood pressure control; prevention of kidney failure, myocardial infarction (MI) and stroke; reduction in hospitalisation and mortality for heart failure.
    - Review medications currently being taken: Would an alternative treatment offer better cardiovascular protection?
    - ACE inhibitors and angiotensin II receptor blockers (ARBs): although clinical studies cannot be directly compared, results suggest both classes have similar cardiorenal benefits. With ACE inhibitors, start on a low dose and uptitrate to maximum tolerated dose based on symptoms, hypotension and potassium level (continue prescribing if potassium ≤6 mmol/L but if ≥6 mmol/L consider reducing/stopping treatment). Switch to an ARB if ACE inhibitor causes cough or allergy or is not tolerated.
    - GLP-1 RAs and SGLT2 inhibitors: see question 2 for information on when to use these products.
    - If a person with type 2 diabetes is at high risk of heart failure or presents with chronic fatigue and shortness of breath, refer for B-type natriuretic peptide, X-ray, ECG and echocardiogram and prescribe based on findings:
        - Heart failure with preserved ejection fraction:
            - Caused by fibrosis and stiffening of the heart
            - Doesn't respond to beta-blockers; some early response to diuretics; controversy around use of ACE inhibitors
            - Prevention is goal: lifestyle changes and early treatment (SGLT2 inhibitors, GLP-1 RAs, ACE inhibitors) in high-risk patients
        - Heart failure with reduced ejection fraction:
            - Caused by myocardial damage and ischaemia
            - Improved with beta-blockers, ACE inhibitors, mineralocorticoids, GLP-1 RAs and SGLT2 inhibitors

5. **Can lipid management impact metabolic risk and when would you advise young adults with high cholesterol to start treatment?**
    - Statins can worsen/hasten onset of diabetes. The number needed to harm with a statin is 598 versus 115 needed to treat to prevent 1 heart attack, so statins are beneficial.
    - Recommend starting statins in:
        - Type 1 diabetes: at age 40 or duration of type 1 diabetes >10 years or established nephropathy or other cardiovascular risk factors (NICE, 2014)
        - Type 2 diabetes:
            - At age 40 (due to high cardiovascular risk; Bailey et al, 2004)
            - <40 years if there is a strong family history or significant dyslipidaemia or fatty liver disease.

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6. **At what level of HbA_{1c} and blood pressure would you say diabetes and hypertension are in remission?**
   - Diabetes and hypertension are in remission if patient is off all treatment and:
     - HbA_{1c} 48 mmol/mol (6.5%) for >6 months (Nagi et al, 2019)
     - Blood pressure: No specific measurement. The lower the better, if there are no hypotensive symptoms.

7. **Can ARBs, ACE inhibitors and SGLT2 inhibitors be prescribed in patients with COVID-19?**
   - ARBs and ACE inhibitors increase the number of cell receptors COVID-19 can bind to, and so may increase viral load. However, they also bind to soluble receptors, causing competitive antagonism with the virus. When COVID-19 attacks a cell, it triggers inflammation, increasing angiotensin II levels and leading to vasoconstriction and leaky capillaries, which can cause adult respiratory distress syndrome. Both ARBs and ACE inhibitors reduce angiotensin II, reducing fluid on the lungs (Gupta et al, 2020). As such, their use should be continued in patients with COVID-19 (NICE, 2020).
   - COVID-19 damages the lungs, increasing pulmonary oedema and issues with fluid regulation; SGLT2 inhibitors seem to worsen control and outcomes in patients with COVID-19 (Mirabelli et al, 2020) However, they improve glycaemic control, reduce weight and increase time-in-range, reducing the risk of poor outcomes in patients without COVID-19. Guidelines urge caution, counselling patients on sick day rules and temporarily stopping treatment if COVID-19 symptoms develop (Bornstein et al, 2020).

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