necessitate the need to start maintenance kidney replacement therapy (KRT).[677]

Albuminuria is an early marker of nephropathy and predicts both risk of kidney failure and CVD independently of eGFR.[43,682] Nephropathy caused by diabetes is a leading cause of CKD globally, and screening patients with diabetes for CKD is recommended at least annually.[676,677] A spot urine sample measuring UACR is an efficient method to identify and quantify albuminuria.[677,683] Changes in UACR or GFR slope are used as surrogate trial endpoints for nephroprotection, but more definitive evidence for reducing risk of kidney failure in patients with diabetes generally requires categorical endpoints based on a ≥40% sustained decline in GFR.[684,685]

9.2. Management of cardiovascular disease risk and kidney failure in patients with chronic kidney disease and diabetes

Risk of CVD increases progressively with lower levels of eGFR and, in those with advanced CKD, structural abnormalities of the heart, HF, and sudden death are particular features.[679,680,686–688] Increased risk of CAD also accompanies CKD, often with calcification of atherosclerotic plaques.[679,689] Accelerated vascular media calcification with increased vascular stiffness is also a feature of CKD and attributed to disordered calcium–phosphate metabolism, referred to as CKD-mineral bone disorder (CKD-MBD).[690,691] Managing CVD risk in patients with CKD and diabetes may, therefore, need to consider multiple interventions and both traditional and CKD-specific risk factors.[361,692–694]

All patients with diabetes and CKD should be offered standard advice on smoking, nutrition, and exercise.[45] A raised BMI is independently associated with risk of CKD, and behavioural interventions to promote weight loss in people with T2DM reduce the risk of developing very high-risk CKD over the long-term.[57,695,696] Management of people with diabetes and CKD is then based on sequentially initiating and titrating doses of pharmacological interventions with proven efficacy (*Figure 18*).

Statin-based therapy reduces the risk of major atherosclerotic events (i.e. coronary death, non-fatal MI, ischaemic stroke, and coronary revascularization) in patients with CKD, but does not meaningfully slow progression of CKD.[248,697–699] Trials of statin-based therapy, combined in collaborative meta-analyses, show a trend towards smaller relative reductions per mmol/L reduction in LDL-C on major atherosclerotic events as eGFR declines, with uncertainty about benefits among patients on dialysis.[697] This diminution in RR reduction at decreased eGFR implies that more intensive LDL-C-lowering regimens are required to maximize benefits.[697] The goal in patients with CKD and diabetes should be to achieve the largest possible absolute reduction in LDL-C safely.[697,700]

Four large trials recruiting different types of patients with CKD have confirmed the safety of intensive LDL-C lowering with statins alone (atorvastatin, rosuvastatin, fluvastatin), or combining a moderate dose of simvastatin with ezetimibe.[698,701–704] Although there is no dedicated, large-scale trial of a PCSK9 inhibitor in patients with CKD, sub-group analyses by CKD stage from the FOURIER trial of the PCSK9 inhibitor evolocumab found its LDL-C-lowering effect was preserved in patients with stage G3 CKD, and CV benefits on atherosclerotic events appeared unmodified by baseline eGFR.[699]

Several drugs developed to manage CVD risk or hyperglycaemia have been shown to reduce the risk of CKD progression in large trials that recruited patients with T2DM and CKD (*Figure 18*). These include RAS inhibitors, SGLT2 inhibitors, and finerenone. There is increasing evidence that these interventions should be started early to prevent end-organ damage in at-risk patients.

Blocking RAS with an ACE-I (captopril) or ARBs (irbesartan/losartan) prevented kidney failure in patients with diabetes and overt nephropathy in dedicated clinical outcomes trials.[705–707] ARBs (irbesartan/telmisartan) also slowed progression from microalbuminuria (albuminuria stage A2) to overt nephropathy.[708,709] These RAS inhibitors are therefore recommended in patients with diabetes as soon as CKD is clinically diagnosed. Combining an ARB with an ACE-I, however, is not recommended, as large trials have identified an increased risk of hyperkalaemia and acute kidney injury, without demonstrable additional benefits of such 'dual-blockade' on risk of kidney failure or CVD.[710]

In contrast, combining an SGLT2 inhibitor with an ACE-I or ARB has clear beneficial effects on risk of kidney failure and hospitalization for HF in patients with CKD and T2DM.[153,542] The CREDENCE, DAPA-CKD, and EMPA-KIDNEY placebo-controlled trials were all stopped early for efficacy while testing canagliflozin, dapagliflozin, and empagliflozin, respectively.[153,543,711] All three trials found the RR reductions for kidney disease progression were unmodified by baseline eGFR, with EMPA-KIDNEY reporting clear benefits in patients with eGFR 20–30 mL/min/1.73 m^2.[153,542,543,712,713] EMPA-KIDNEY included 254 patients with an eGFR <20 mL/min/1.73 m^2 at randomization, and once initiated, SGLT2 inhibitors could be continued until the need of KRT. As patients with decreased eGFR are at the highest absolute risk of kidney disease progression, these trials' results should encourage the initiation of SGLT2 inhibitors in patients with CKD down to at least an eGFR of 20 mL/min/1.73 m^2 with continued use until the need for KRT (despite low eGFR substantially attenuating their HbA1c-lowering effect). Meta-analysis of all the large SGLT2 inhibitor trials shows benefits of SGLT2 inhibitors on the risk of HF hospitalization or CV death are also unmodified by eGFR (at a trial level; *Figure 19*).[714] The combined SGLT1/2 inhibitor sotagliflozin was analysed vs. placebo in the SCORED trial in patients with T2DM and CKD (eGFR 25–60 mL/min/1.73 m^2); sotagliflozin reduced the primary composite of the total number of CV deaths, hospitalizations for HF, and urgent visits for HF by 26% vs. placebo (HR 0.74; 95% CI, 0.63–0.88; $P < 0.001$).[150] Initiating an SGLT2 inhibitor alongside an ACE-I or ARB is therefore recommended in patients with T2DM following the first clinical evidence of CKD. In patients with T1DM and CKD, the absence of large trials with sufficient follow-up means it is unclear whether the absolute benefits of SGLT2 inhibitors on kidney failure and CVD outcomes are outweighed by the high absolute risk of ketoacidosis with SGLT2 inhibitors.[715,716]

MRAs reduce BP and albuminuria in patients with CKD.[717] The placebo-controlled FIDELIO-DKD (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease) and FIGARO-DKD (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease) trials demonstrated for the non-steroidal MRA finerenone that these effects translate into reduced risk of kidney failure and a reduction of the combined CV outcome of CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF in patients with CKD and T2DM who are already on maximum ACE-I or ARB.[718–720] FIDELIO-DKD demonstrated reduced risk of a categorical kidney outcome, a primary composite outcome combining kidney failure, a sustained decline in eGFR of at least 40%, or death from renal causes, in patients with eGFR 25–60 mL/min/1.73 m^2 and UACR of 34–567 mg/mmol (30–5000 mg/g), or eGFR 60–75 mL/min/1.73 m^2 with UACR of 34–567 mg/mmol (300–5000 mg/g; mean eGFR 43 ± 13 mL/min/1.73 m^2; median UACR 96 mg/mmol [852 mg/g]).[719]