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STATE OF THE ART REVIEW
Diabetes and metabolic disorders

Cardiovascular disease in chronic kidney disease

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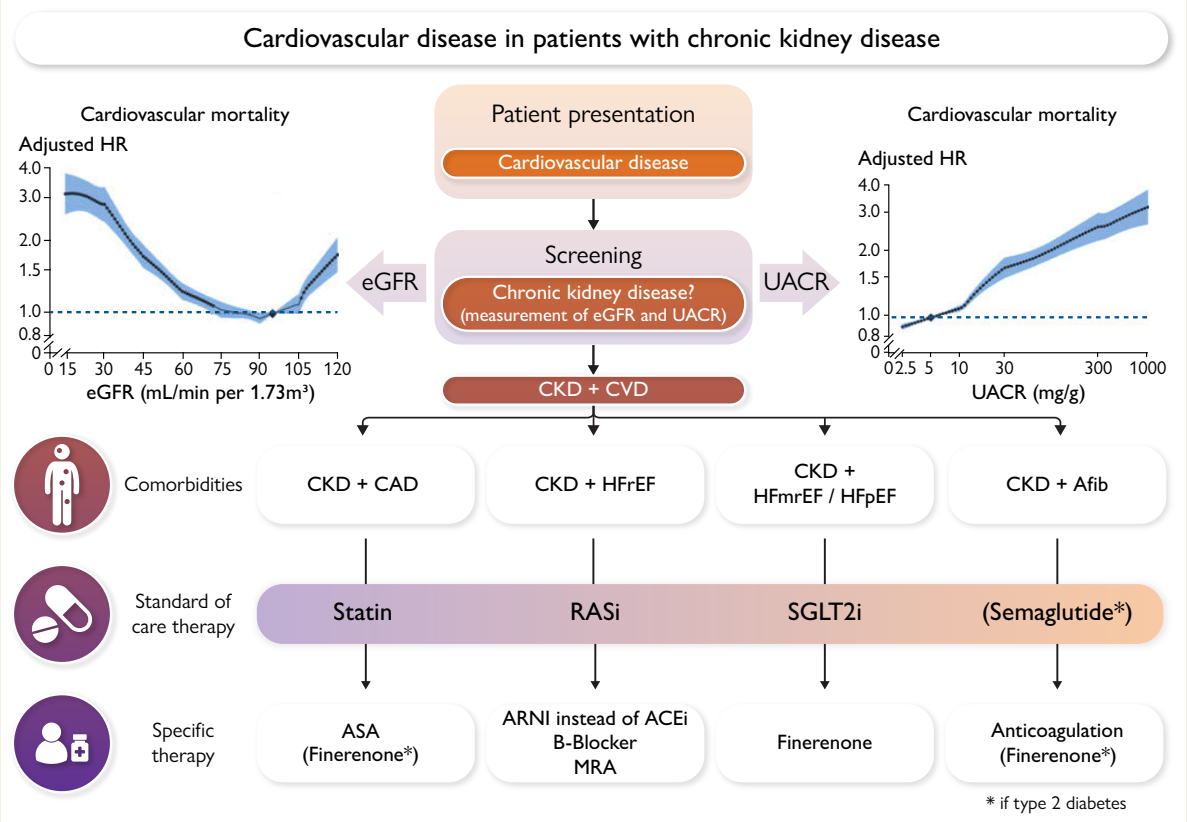
Graphical Abstract



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Abstract

Individuals with chronic kidney disease (CKD) exhibit an increased risk for the development of cardiovascular disease (CVD) with its manifestations coronary artery disease, stroke, heart failure, arrhythmias, and sudden cardiac death. The presence of both, CVD and CKD has a major impact on the prognosis of patients. This association likely reflects the involvement of several pathophysiological mechanisms, including shared risk factors (e.g. diabetes and hypertension), as well as other factors such as inflammation, anaemia, volume overload, and the presence of uraemic toxins. Identifying and characterizing CKD is crucial for appropriate CVD risk prediction. Mitigating CVD risk in patients with CKD mandates a multidisciplinary approach involving cardiologists, nephrologists, and other health care professionals. The present State-of-the-Art Review addresses the current understanding on the pathophysiological link between CVD and CKD, clinical implications and challenges in the treatment of these patients.

Keywords Chronic kidney disease • Cardiovascular disease • SGLT2 inhibitors • GLP-1 receptor agonists • Non-steroidal MRAs • CV risk

Patients with chronic kidney disease (CKD) exhibit an elevated risk to develop cardiovascular disease (CVD) with its different manifestations of coronary artery disease (CAD), stroke, heart failure (HF), or arrhythmias and sudden cardiac death. In addition, the presence of CKD has a major impact on the prognosis of patients with CVD, leading to an increased morbidity and mortality if both comorbidities are present. Therapeutic options including medical therapy as well as interventional treatment are often limited in patients with advanced CKD and in most cardiovascular outcome trials (CVOTs) patients with advanced CKD have been excluded. Thus, in many patients, treatment strategies for CVD need to be extrapolated from trials conducted in patients without CKD. The current overview article addresses aspects on the diagnosis of CKD, the pathophysiology of CVD in CKD and provides an update on CV risk reduction in CKD as well as treatment strategies in CKD patients with the most frequent CVD manifestations of CAD, HF, and arrhythmias.

Diagnosis and classification of CKD

Chronic kidney disease is defined as a change in kidney structure or function that has existed for >3 months with implications for health. Chronic kidney disease stages are categorized by glomerular filtration rate (GFR) and albuminuria categories (*Figure 1*). The CKD Epidemiology Collaboration (CKD-EPI) has developed eGFR equations based on measurements of creatinine and/or cystatin C. Even if an eGFR is ≥60 mL/min/1.73 m^2, the presence of albuminuria or other evidence of kidney disease can define CKD. A sustained decrease in eGFR <60 mL/min/1.73 m^2 (i.e. CKD stages G3–5) is sufficient to make the diagnosis of CKD. The most advanced stage of CKD, G5, is characterized by an eGFR of <15 mL/min/1.73 m^2. Albuminuria is an early marker of nephropathy and has a predictive value for the risk of kidney failure as well as for CVD and all-cause mortality, regardless of eGFR. Measurement of the urinary albumin creatinine ratio (UACR) in spontaneously voided urine allows for efficient identification and quantification of albuminuria.[1] Of note, albuminuria measurement can potentially provide false positive results e.g. after exercise or during infection.

Epidemiology, prognosis

The prevalence of CKD is estimated to be ~10–20% in many countries.[2–5] Approximately 5 million individuals are estimated to require renal replacement therapy (i.e. dialysis or kidney transplantation) globally.[6] The composition of primary causes of CKD varies considerably across countries and regions, but diabetes and hypertension are considered as the two leading causes of CKD worldwide.[7] Given these two factors as leading risk factors of CVD, it is not surprising that individuals with CKD have a higher risk of CVD compared with those without.[8] Chronic kidney disease is associated with an elevated risk of many CVD types [atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), aortic disease, arrhythmias, and venous thrombosis)[9] and particularly with severe phenotypes (e.g. CVD mortality), as detailed below.[8]

An international consortium including data from ~80 cohorts from ~50 countries, the CKD Prognosis Consortium, has conducted a series of individual-level data meta-analysis to quantify the association of the two key measures of CKD, eGFR, and albuminuria, with major CV outcomes (i.e. CAD, stroke, HF, and CV mortality).[8] As shown in *Figure 2*, lower eGFR and higher albuminuria are associated with all CVD outcomes, independently of traditional risk factors such as age, blood pressure, and diabetes. Importantly, the associations appeared stronger for CV mortality and HF compared with CAD and stroke.

Several studies have reported the robust association of CKD with the risk of developing atrial fibrillation (Afib).[10–12] A US study applied 2-week electrocardiogram in community-dwelling older adults and showed that CKD is also associated with Afib burden (i.e. percent time with Afib).[13] This study also uniquely identified other arrhythmias related to CKD (e.g. non-sustained ventricular tachycardia and long pause). Several studies have also shown the independent association of CKD with sudden cardiac death.[14] The presence of Afib in patients with advanced CKD is associated with increased CV morbidity and mortality. A Dutch observational study showed that of 12 394 patients presenting as outpatients, 699 had Afib, 2752 had CKD, and 325 had Afib and CKD. After adjustment, patients with CKD and Afib had a 3.0-fold increased risk of bleeding (95% CI: 2.0–4.4), a 4.2-fold increased risk of ischaemic stroke (95% CI: 3.0–6.0), and a 2.2-fold increased risk of mortality (95% CI: 1.9–2.6) compared to people without Afib and without CKD.[15]

CVD risk prediction in CKD

Despite a body of evidence linking CKD with elevated CVD risk, major prediction tools used in clinical guidelines have not directly incorporated CKD measures (e.g. SCORE2 and SCORE2-OP in Europe and the Pooled Cohort Equation in the US).[16,17] However, a group of experts developed an add-on tool ('CKD Add-on'; https://ckdpcrisk.org) to calibrate predicted risk according to CKD measured on top of those established prediction tools.[18,19] For example, a 62-year-old man in a

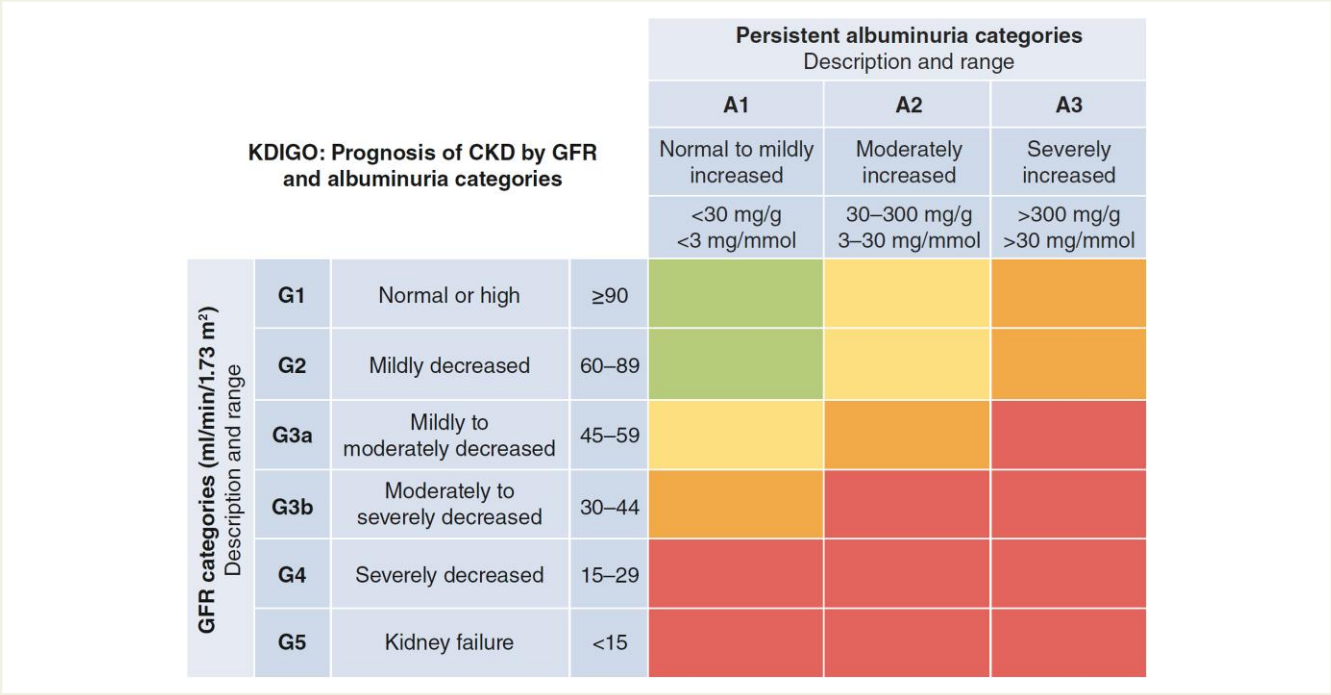

Figure 1 Current chronic kidney disease nomenclature used by KDIGO. KDIGO staging system for chronic kidney disease based on categories of glomerular filtration rate and urinary albumin creatinine ratio. The colours represent the risk of developing a need for dialysis or other relevant outcomes including cardiovascular disease. Green indicates low risk (and represents no chronic kidney disease if there is no structural or histological evidence of kidney disease). Compared with low risk (estimated at 0.04/1000 patient-years), yellow indicates chronic kidney disease with moderately increased risk (at least ~5-fold), orange indicates chronic kidney disease with high risk (at least ~20-fold), and red indicates chronic kidney disease with very high risk (at least ~150-fold). From[1].

European moderate-risk region with no smoking history, no diabetes, systolic blood pressure (SBP) of 128 mmHg, total cholesterol of 4.5 mmol/L, and high-density lipoprotein cholesterol of 1.6 mmol/L has a 10-year predicted risk of 5.9% based on the original SCORE2. If he has eGFR of 25 mL/min/1.73 m^2 and ACR of 500 mg/g, with the CKD Add-on, this person's risk is predicted to be 23%.[19]

In the US, the American Heart Association, in collaboration with the CKD Prognosis Consortium, has recently proposed a new risk prediction tool, PREVENT, to predict the risk of a composite of CVD (myocardial infarction, stroke, and HF) in US adults aged 30–79 years.[20] This equation uniquely includes eGFR in the primary model together with other traditional risk factors such as lipids, blood pressure, diabetes, and smoking. The equation provides an option to include information on ACR (https://professional.heart.org/en/guidelines-and-statements/prevent-calculator).

Pathophysiology of CVD in CKD

The development of CVD in CKD is a complex, multifactorial process caused by traditional risk factors such as hypertension, diabetes, or dyslipidaemia, as well CKD-associated factors like inflammation, oxidative stress, activation of the renin-angiotensin-aldosterone-system, fluid overload and haemodynamic alterations, mineral and bone disorders, and accumulation of uraemic toxins as well as CKD-specific post-translational modifications.[21] These factors lead to characteristic changes in the vasculature and in the heart.

In the vasculature, calcification is a typical finding in CKD. Vascular smooth muscle cells in the medial layer of blood vessels can shift from a contractile to a synthetic phenotype due to haemodynamic changes associated with CKD and this transition accelerates vascular calcifications, which are notably prevalent even in children with advanced CKD.[22] Moreover, dysregulation of mineral metabolism with increased phosphate as well as elevated levels of parathyroid hormone and fibroblast growth factor 23 (FGF23) promote vascular but also valvular calcification.[23] Although previously attributed solely to elevated calcium-phosphorus product levels, it is now understood that active cellular processes also play a significant role in vascular and valvular calcification. All stages of CKD are associated with enhanced valvular calcifications: up to 99% of patients with CKD stage G5 experience valvular calcification compared with only 40% at CKD stage 3.[24]

Inflammation plays a critical role in CKD. Proinflammatory mediators increase as kidney function declines and these mediators exhibit direct effects in the vasculature, contributing to endothelial dysfunction and recruitment of inflammatory cells into the vessel wall.[25] The importance of inflammation in this context is underscored by results from the CANTOS trial demonstrating CVD risk reduction by inhibiting interleukin-1β (IL-1β) using canakinumab, particularly among patients with reduced eGFR.[26]

Myocardial alterations in CKD manifest as pathological fibrosis and cardiac hypertrophy—hallmarks of uraemic cardiomyopathy.[27] Approximately one-third of CKD patients exhibit left ventricular hypertrophy (LVH), which rises to 70–80% among those with end-stage kidney disease. Left ventricular hypertrophy serves as an independent predictor of survival across all stages of CKD. Contributing mechanisms include afterload-related factors such as arterial stiffness and systemic resistance leading to concentric LVH, while preload-related factors involve volume overload causing eccentric remodelling.[28,29] Myocardial fibrosis in CKD is characterized by collagen deposition

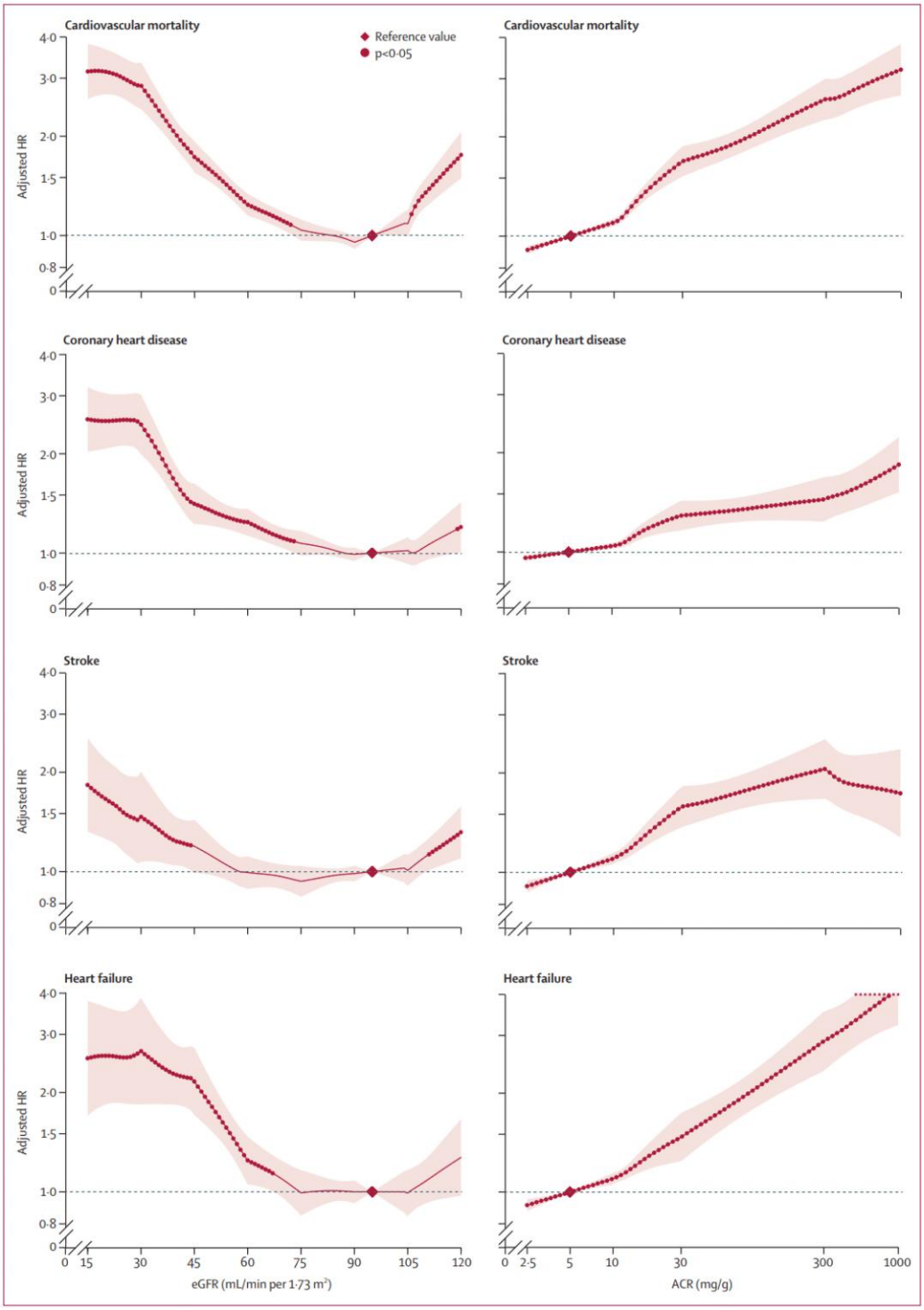

Figure 2 Adjusted hazard ratios and 95% CIs (shaded areas or whisker plots) of cardiovascular mortality (top row), coronary heart disease (second row), stroke (third row), and heart failure (bottom row) according to estimated glomerular filtration rate (left column) and albumin-to-creatinine ratio (right column) in the combined general population and high-risk cohorts. The reference is estimated glomerular filtration rate 95 mL/min/1.73 m^2 and albumin-to-creatinine ratio 5 mg/g (diamond). Dots represent statistical significance ($P < .05$). *Adjustments were for age, sex, race/ethnicity, smoking, systolic blood pressure, antihypertensive drugs, diabetes, total and high-density lipoprotein cholesterol concentrations, and albuminuria (albumin-to-creatinine ratio or dipstick) or estimated glomerular filtration rate, as appropriate. In the analyses of estimated glomerular filtration rate, there were 629 776 participants for cardiovascular mortality, 144 874 for coronary heart disease, 137 658 for stroke, and 105 127 for heart failure. In the analyses of albumin-to-creatinine ratio, there were 120 148 participants for cardiovascular mortality, 91 185 for coronary heart disease, 82 646 for stroke, and 55 855 for heart failure. Figure from Matsushita et al.[8]

between capillaries and cardiomyocytes, funneling into maladaptive ventricular hypertrophy and subsequent heart dilation. Still, the diagnosis of myocardial fibrosis in CKD e.g. by MRI is challenging and is so far not included in treatment decisions.

Overall, various mediators and mechanisms contribute to the development and progression of CVD in patients with CKD and a complex interaction of factors characterizes the multifaceted organ cross talk between the CV system and the kidney in the setting of CKD (*Figure 3*). The different pathophysiological aspects of CVD development in individuals with CKD compared with those without are further emphasized by the fact that recent CVOTs in this patient population demonstrated mainly a reduction in HF-related outcomes but to a lesser extent in atherosclerosis-related endpoints.

Reduction of CV risk in CKD

Cardiovascular and kidney failure risk reduction in CKD includes management of traditional risk factors and—based on more recent evidence—treatment strategies with sodium–glucose cotransporter 2 (SGLT2) inhibitors, the non-steroidal mineralocorticoid receptor antagonist Finerenone and Glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

Risk factor management in CKD

Management of risk factors including blood pressure lowering, glucose as well as lipid management is mandatory to reduce CVD risk in CKD.

Blood pressure management

Arterial hypertension is a major risk factor for CVD and CKD, and lowering blood pressure is effective in reducing CVD as well as kidney failure risk in patients with CKD. Per 10 mmHg decrease in SBP, CVD risk reduction is more pronounced in patients with an initial SBP of ≥140 mmHg, but even among those with an SBP <140 mmHg, further reductions can lead to decreased risks of stroke and albuminuria.[30] However, there is still disagreement as to whether SBP should be reduced to values <120 mmHg. This uncertainty has led to different blood pressure recommendations from different medical societies. The 2024 KDIGO guidelines adopted the results of the SPRINT study[31] and recommend lowering SBP to <120 mmHg in CKD patients, when tolerated, using standardized office BP measurement.[1] The 2024 ESC guidelines recommend a target SBP of 120–129 mmHg for adults with moderate to severe CKD and an eGFR >30 mL/min/1.73 m^2 if tolerated[32]; individualized blood pressure targets are recommended for patients with a lower eGFR or for kidney transplant patients. For details on BP management in CKD, we refer to the recently published 2024 ESC guidelines on the management of blood pressure.[32]

Glucose management

Diabetes mellitus is a strong risk factor for both CVD and CKD. Tight glycaemic control is effective in reducing microvascular complications such as diabetic nephropathy or retinopathy in patients with type 1 and type 2 diabetes, regardless of the blood glucose-lowering medication used.[33,34] Personalized HbA1c targets between 6.5% and 7.5% (48–58 mmol/mol) are recommended for people with diabetes and CKD; in principle, the best possible HbA1c level—even <7.0% (<53 mmol/mol)—should be achieved, unless this goal is achieved by accepting hypoglycaemia.[35,36]

Lipid management

Four studies in patients with varying degrees of CKD severity confirmed the safety of intensive LDL-C lowering with statins alone (atorvastatin, rosuvastatin, fluvastatin) or with statin in combination with ezetimibe (simvastatin) and demonstrated a reduction of serious atherosclerotic events, but did not show a significant effect on the progression of CKD.[37–39] In contrast, in patients on haemodialysis, neither the 'German Diabetes Dialysis Study' (4D study)[40] nor the A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events' (AURORA study)[41] found a significant reduction in three-point MACE with atorvastatin or rosuvastatin, respectively, compared with placebo. For PCSK9 inhibitors, subgroup analyses from the FOURIER study of the PCSK9 inhibitor evolocumab showed that the LDL-C-lowering effect is maintained in patients with CKD stage G3 and that CV benefits are independent of baseline eGFR.[39]

The ESC guidelines recommend LDL-C targets of <70 mg/dL for CKD stage G3 and LDL-C < 55 mg/dL for CKD stages G4/5 without dialysis in combination with at least a 50% reduction in baseline LDL-C.[42] Initiation of statin therapy is not recommended in patients requiring dialysis but should be continued if previously prescribed.[42] Kidney transplant recipients should also receive statin therapy (note interaction with e.g. calcineurin inhibitors, e.g. rosuvastatin with tacrolimus possible, fluvastatin with ciclosporin possible), although this is only supported by limited study results.[43]

Cardiovascular risk reduction by SGLT2 inhibitors

Four randomized control trials have been conducted in dedicated CKD cohorts, designed to investigate the effect of SGLT2 inhibitors on either the kidney composite outcome of CKD progression, HF hospitalization, and CV and CKD death[44–46] or the CV composite of urgent HF visits, HF hospitalization, and CV death.[47] Treatment effects on other CV endpoints were evaluated through secondary analyses. A recent meta-analysis evaluated the effect of SGLT2 inhibition on a three-point MACE composite in 11 randomized control trials from participants with diabetes at high ASCVD risk, HF, and CKD.[48] Across the three trial populations ($n = 78\,607$), SGLT2 inhibition reduced the rate of MACE by 9%. In the subgroup of participants from dedicated CKD trials (CREDENCE, DAPA-CKD, EMPA-Kidney; $n = 15\,314$), SGLT2 inhibition similarly lowered the incidence of MACE by 13% [HR: 0.87 (95% CI: 0.77–0.98)]. This reduction in MACE was also consistent across numerous subgroup analyses, including those stratified by established ASCVD, diabetes status, eGFR, albuminuria, and KDIGO risk classifications.[48]

Another meta-analysis evaluated the impact of SGLT2 inhibition on CKD progression in 13 randomized control trials from participants with diabetes at high ASCVD risk, HF, and CKD.[35] Across the three trial populations ($n = 90\,409$), SGLT2 inhibition demonstrated a 37% reduction in the risk of CKD progression [HR: 0.63 (95% CI: 0.58–0.69)], consistent in the subgroup from dedicated CKD trial population [HR: 0.62 (95% CI: 0.56–0.69)] and irrespective of diabetes status.[35]

Cardiovascular risk reduction by non-steroidal-MRAs

A recent study in individuals with CKD stage G3b could not demonstrate a reduction in CV events by the steroidal MRA spironolactone but showed an increased risk for side effects such as hyperkalaemia.[49]

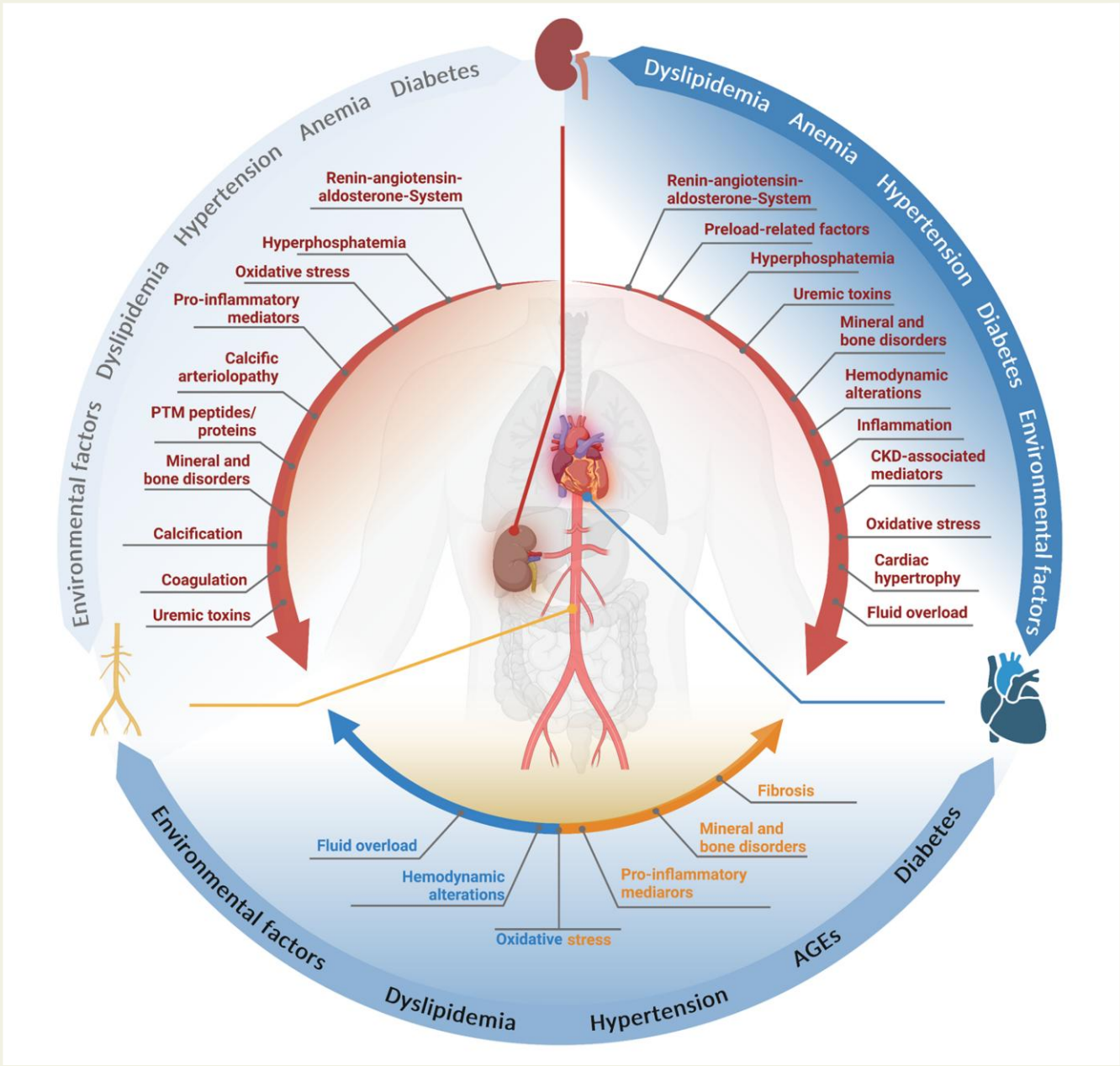

Figure 3 Organ cross talk between the kidney and the cardiovascular system in chronic kidney disease. Various mediators and mechanisms contribute to the development and progression of cardiovascular disease in patients with chronic kidney disease and a complex interaction of factors characterizes the multifaceted organ cross talk between the CV system and the kidney in the setting of chronic kidney disease. AGE, advanced glycation end products; PTM, posttranslational modification.

The effect of the non-steroidal MRA finerenone on kidney and CV composite endpoints in adults with diabetic CKD on maximally tolerable RAS inhibitors was examined in the FIDELIO-DKD and FIGARO-DKD trials.[50,51] These complementary trials, employing similar trial designs, were subsequently pooled into the prespecified FIDELITY analysis, to elicit more robust estimates of finerenone efficacy in terms of both kidney and CV outcomes.[52] In the 13 026 CKD participants with diabetes included in FIDELITY, finerenone demonstrated a 14% reduction in the composite CV endpoint of CV death, non-fatal MI, non-fatal stroke, or HF hospitalization [HR: 0.86 (95% CI: 0.76–0.98)], which was largely driven by treatment effects on the incidence of HF hospitalization. The exclusion of participants with symptomatic HF with reduced ejection fraction (HFrEF) and low prevalence of participants with a history of HF (7.7%) highlights the efficacy for finerenone in the prevention of new-onset HF.[53] Finerenone also demonstrated a 23% lower incidence in the composite renal endpoint of end-stage kidney disease (ESKD), sustained eGFR <15 mL/min/1.73 m^2, sustained ≥57% decline in eGFR, or CKD death [HR: 0.77 (95% CI: 0.67–0.88)]. Hyperkalaemia-related treatment discontinuation was higher in participants receiving finerenone compared with placebo, with a low overall risk over 3-years of follow-up (1.7% vs 0.6%).

Since concomitant use of SGLT2 inhibitors (6.7%) and GLP1-RAs (7.2%) within the FIDELITY analysis were low, the additive benefits of finerenone when added to more contemporary background care remains unclear and is the topic of ongoing trials (NCT05254002). Despite the low number of participants on background SGLT2 inhibition, secondary subset analysis of FIDELITY found that SGLT2 inhibition, either prescribed prior to enrollment or during the trial, did not affect risk reduction for the CV or kidney composite with finerenone,[54] although a signal for an interactive treatment effect in favour of combined finerenone and SGLT2 inhibition on HF hospitalization was observed.[53,54] Lastly, the reductions in the composite CV endpoint were similar in participants with or without pre-existing ASCVD, demonstrating that finerenone is an important 'primary and secondary preventive' therapy in diabetic CKD,[55] and across the spectrum of baseline eGFR and UACR.[56] The ongoing CONFIDENCE trial is investigating whether dual therapy with finerenone and an sodium–glucose co-transporter-2 inhibitor is superior to either agent alone on relative change in UACR.[57]

An important consideration is that efficacy of finerenone for the treatment of non-diabetic CKD is not yet known. The ongoing phase III FIND-CKD trial (NCT05047263) aims to evaluate finerenone on the primary endpoint of total eGFR slope, and the secondary cardiorenal composite endpoint of ESKD, sustained eGFR <15 mL/min/1.73 m^2, sustained ≥57% decline in eGFR, HF hospitalization, or CV death in 1584 patients with nondiabetic CKD.[58] An additional trial in people with type 1 diabetes and CKD called FINE-ONE is underway and is designed to assess the impact of finerenone on UACR.[59]

Cardiovascular risk reduction by GLP1-RA

Meta-analyses of large CVOTs performed in individuals with diabetes or obese individuals without diabetes demonstrated that GLP1-RA reduce the rate of the three-point MACE composite of CV death, MI, or stroke by 14% [HR: 0.86 (95% CI: 0.80–0.93)].[60] No treatment heterogeneity was observed in secondary subgroup analyses when participants were dichotomized according to baseline eGFR above or below 60 mL/min/1.73 m^2[60] or across the spectrum of eGFR and UACR in pooled analyses of the SUSTAIN-6 and PIONEER-6 trials.[61] In addition, secondary analyses from these CVOTs have individually reported a lower incidence of composite kidney outcomes, which was largely driven by the reduction in macroalbuminuria progression, rather than worsening eGFR or ESKD due to low event rates in non-CKD diabetic populations.[62–66]

The FLOW trial was the first dedicated kidney outcome trial enrolling 3534 adults with diabetic CKD.[67] Compared with placebo, semaglutide led to a 24% lower incidence of the primary renal composite endpoint of kidney failure, sustained 50% decline in eGFR, or CV or CKD death [HR: 0.76 (95% CI: 0.66–0.88)]. Further, an 18% relative risk reduction in the three-point MACE was also observed [HR: 0.82 (95% CI: 0.68–0.98)]. These CVD risk reductions aligned with observations from a non-CKD cohort at high CVD risk from the SELECT trial, which included non-diabetic individuals with overweight/obesity. In SELECT, a 20% risk reduction in the three-point MACE was reported.[68] Secondary analyses of the FLOW trial also demonstrated that semaglutide lowered the risk of HF events or CVD death by 17%, irrespective of HF history at baseline, with no treatment heterogeneity in subgroup analyses by KDIGO risk classification.[69] Lastly, concomitant use of SGLT2 inhibitors was relatively low in the FLOW trial (15.6%) with secondary subset analyses demonstrating that concomitant SGLT2 inhibitor use did not alter treatment effects of semaglutide on kidney and CVD composite endpoints.[70] A recent meta-analysis of CVOTs with GLP-1 RA including FLOW and SELECT suggests that GLP-1 RA reduce kidney disease progression in T2DM or overweight/obesity regardless of CKD status.[71]

Future therapeutic approaches to reduce CV risk in individuals with CKD include anti-inflammatory strategies such as treatment with ziltivecimab, a fully human monoclonal antibody directed against IL-6 ligand, which is currently tested in the ZEUS trial in individuals with ASCVD and CKD (NCT05021835).

Figure 4 summarizes the clinical approach for the reduction of CVD risk in patients with CVD and CKD without (*Figure 4A*) and with type 2 diabetes (*Figure 4B*).

Treatment of coronary artery disease in CKD

Medical therapy for ACS and CCS in patients with CKD

According to current guidelines, drug therapy in patients with acute coronary syndrome (ACS)[72] or chronic coronary syndrome (CCS)[73] with CKD should not differ from therapy in non-CKD patients, but renally excreted drugs used in CCS should be dose adjusted for kidney function.

Revascularization for CAD

ACS

Given the poor prognosis of patients with ACS and CKD and the fact that CKD patients are less likely to receive appropriate therapy, current guidelines recommend that patients with ACS and CKD should be treated as aggressively as patients without CKD.[72]

CCS

The ISCHEMIA-CKD trial examined the effect of coronary revascularization in patients with CKD and CCS in 777 patients with eGFR <30 mL/min/1.73 m^2 and moderate to severe myocardial ischaemia.[74] Patients were randomized to early angiography and revascularization [either by percutaneous coronary intervention (PCI) or coronary bypass surgery] in addition to optimal medical therapy or to optimal medical therapy only. During a mean follow-up of 2.2 years, there was no difference between the two study groups in the combined primary endpoint of death from any cause or non-fatal myocardial infarction nor in all-cause mortality or CV mortality. Strokes were more frequent in the invasive group [22 vs 6 events; HR: 3.76 (95% CI: 1.52–9.32)], as was kidney failure requiring dialysis (36 vs 29 events; $P = 0.14$). There was no difference in procedure-related acute kidney injury (7.8% vs 5.4%; $P = 0.26$), but the median time to dialysis initiation was shorter in the invasive group (6 months vs 18.2 months).[74] There was no difference in primary outcome between the invasively and conservatively treated groups in patients listed for kidney transplantation [25% of all participants; HR: 0.91 (95% CI: 0.54–1.54)] compared to unlisted [HR: 1.03 (95% CI: 0.78–1.37)] patients. These results do not support routine coronary angiography or revascularization in patients with advanced CKD and CCS before inclusion on the waiting list for kidney transplantation.

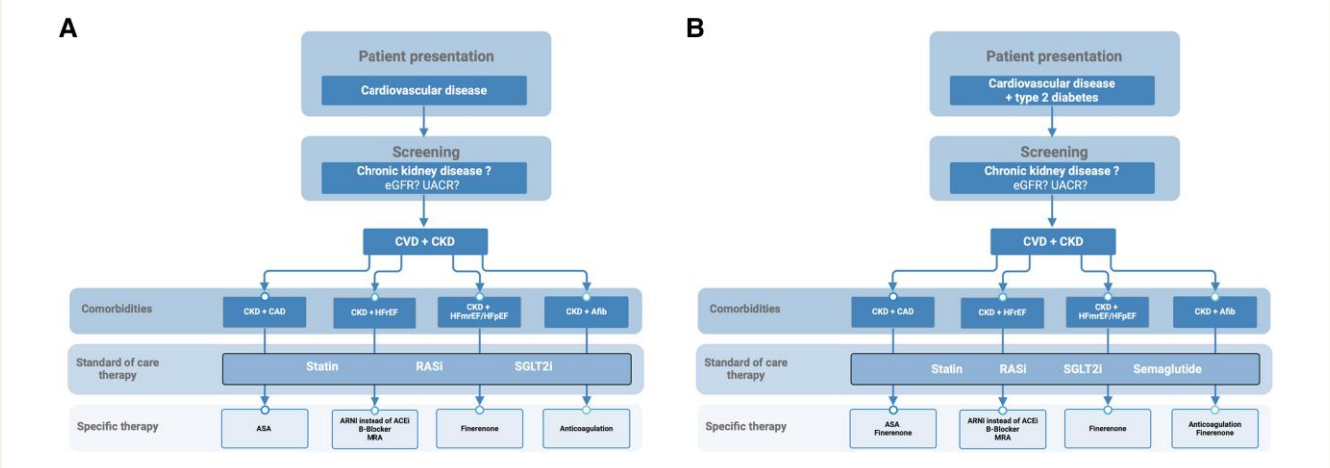

Figure 4 Clinical approach for the management of cardiovascular disease in patients with chronic kidney disease not on haemodialysis. *A*, All patients with cardiovascular disease need screening for the presence of chronic kidney disease by measurement of estimated glomerular filtration rate (eGFR) as well as urine albumin-to-creatinine ratio (UACR) assessment in the spot urine. Patients with both cardiovascular disease and chronic kidney disease benefit from standard treatment with a statin, RAS inhibition (angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker) as well as a sodium–glucose co-transporter-2 inhibitor on top of stringent blood pressure control with a systolic blood pressure < 130 mmHg. In addition, depending on the cardiovascular disease manifestation (coronary artery disease, heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction/preserved ejection fraction (HFmrEF/HFpEF), or atrial fibrillation, additional specific therapies need to be implemented). *B*, All patients with cardiovascular disease and type 2 diabetes need screening for the presence of chronic kidney disease by measurement of eGFR as well as UACR assessment in the spot urine. Patients with cardiovascular disease, type 2 diabetes and chronic kidney disease benefit from standard treatment with a statin, semaglutide, RAS inhibition (angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker) as well as an sodium–glucose cotransporter 2 inhibitor on top of stringent blood pressure control (systolic blood pressure < 130 mmHg). In addition, depending on the cardiovascular disease manifestation (chronic kidney disease, HFrEF, HFmrEF/HFpEF, or atrial fibrillation, additional specific therapies need to be implemented. Afib, atrial fibrillation; ASA, acetylsalicylic acid; B-blocker, beta-blocker; MRA, mineralocorticoid-receptor antagonist.

Treatment of HF in CKD

Treatment of HFrEF in CKD

Based on the data of large CVOTs in patients with HFrEF, current treatment strategies are based on 4 foundational therapies: angiotensin receptor–neprilysin inhibitor (ARNI)/ACE-I, beta blockers, MRAs, and SGLT2 inhibitors. All these agents have a class I recommendation in current European and American guidelines for the reduction of CV morbidity and mortality. Patients with CKD Stages G4 and 5 were excluded in many of these guideline-relevant HF studies and thus recommendations for this patient population must be extrapolated from data in HFrEF patients without advanced CKD. According to current guidelines, all 4 prognosis-improving drugs should ideally be implemented simultaneously and uptitrated within 6 weeks while monitoring kidney function and potassium,[75,76] based on data from the Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testinG, of Heart Failure Therapies (STRONG-AF) study.[77]

ACE inhibitors

Angiotensin-converting enzyme inhibitor were the first class of drugs that demonstrated a reduction in mortality and morbidity in patients with HFrEF but in these trials only patients with CKD stage G1 to 3 were included. Data derived from the Swedish Heart Failure Registry including 2410 patients with HFrEF and CKD (serum creatinine 2,5 or above or creatinine clearance <30 mL/min/1.73 m^2) with or without RAS-inhibition suggest that overall mortality after 1 year was significantly lower in patients receiving RAS-inhibition compared to patients without RAS-inhibition.[78] Interestingly, registry data from Japan ($n =$ 6965, eGFR 10–60 mL/min/1.73 m^2) suggests that permanent discontinuation of an ACE-I or ARB due to side effects was associated with an increased risk of kidney outcomes and mortality.[79]

ARNI

The ARNI Sacubitril Valsartan was examined in a large outcome trial in HFrEF patients compared with the ACE-I enalapril. In patients with CKD stage G1 to 3, the ARNI was effective in significantly reducing the primary endpoint of CV death and HF hospitalization. This benefit was also observed in patients with an eGFR of 30–60 mL/min/1.73 m^2[80] suggesting that ARNIs are effective in HFrEF in CKD Stage G1–3. Reliable evidence for the use of ARNIs in CKD Stage G4–5 is missing and these drugs may be used at reduced doses in an individualized approach considering potential side effects such as hypotension as well as an increase in potassium and/or creatinine values.

Beta blockers

Various clinical trials have demonstrated a reduction in morbidity and mortality in patients treated with beta blockers in HFrEF including patients at CKD Stage G3. A meta-analysis of 6 studies analyzing the effect of beta blocker therapy in HFrEF and CKD Stages G3–5 suggest positive effects for patients with advanced CKD.[81] Moreover, a large retrospective analysis from Canada demonstrated that beta blocker therapy, with bisoprolol, carvedilol, and metoprolol was associated with reduced mortality in patients with HF in CKD including patients with CKD Stage G4.[82,83]

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, have been shown to be effective in reducing mortality and HF hospitalization in patients with HFrEF. However, only patients with CKD Stages G1–3 were included in these studies.[84,85] In the RALES study, spironolactone showed a comparable risk reduction for all-cause mortality and the combined endpoint of all-cause mortality and HF hospitalization in patients with impaired compared to patients with normal kidney function. However, there was an increased risk of hyperkalaemia and worsening kidney function in patients with CKD.[86] Similar efficacy was shown in a secondary analysis of the EMPHASIS-HF trial in patients with an eGFR of 30 to 60 mL/min/1.73 m^2 for eplerenone in reducing CV death or HF hospitalization, regardless of kidney function but with an increased risk of hyperkalaemia.[87]

SGLT2 inhibitors

Two large CVOTs in patients with HFrEF with or without diabetes showed that dapagliflozin[88] or empagliflozin[89] significantly reduced the combined endpoint of CV death or HF hospitalization compared with placebo. The results were driven by a significant reduction in HF hospitalization and a non-significant reduction in CV deaths. In addition, these SGLT2 inhibitors have been shown to reduce kidney endpoints and worsening nephropathy. As these studies included patients with eGFRs as low as 30 mL/min/1.73 m^2 (DAPA-HF) or 20 mL/min/1.73 m^2 (EMPEROR-Reduced), these agents appear to be effective in HFrEF patients with CKD Stages G3 and 4.

Diuretics

Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.[75] Diuretics are effective in patients with HFrEF and CKD, but there are no specific endpoint data for patients with CKD. A recent consensus document from the HF Association of the European Society of Cardiology suggests a practical approach for initiation and uptitration of multilevel, guideline-directed medical therapy for different levels of eGFR in patients with HFrEF[90] (see *Figure 5*).

Treatment of heart failure with mildly reduced or preserved ejection fraction (HFmrEF; HFpEF)

In patients with HFmrEF/HFpEF (left ventricular ejection fraction ≥40%), the CVOTs EMPEROR-preserved[91] and DELIVER[92] demonstrated a significant reduction combined endpoint of HF hospitalization or CV with the SGLT2 inhibitors empagliflozin or dapagliflozin, respectively, compared with placebo. Both trials enrolled patients with an eGFR down to 20 mL/min/1.73 m^2 (EMPEROR-preserved) and 25 mL/min/1.73 m^2 (DELIVER). In prespecified subgroup analyses, no significant difference was found between patients with eGFR <60 mL/min/1.73 m^2 and eGFR ≥60 mL/min/1.73 m^2, suggesting that patients with HFmrEF/HFpEF and CKD benefit from treatment with one of these SGLT2 inhibitors.

The FINEARTS-HF study investigated the efficacy and safety of finerenone in patients with HF and LVEF ≥ 40% including patients with an eGFR down to 25 mL/min/1.73 m^2. Over a median period of 32 months, finerenone led to a significant 16% relative reduction of the combined primary endpoint of total (first and recurrent HF events) and CV deaths; these results were mainly driven by a significant reduction in the total number of HF exacerbations (HR: 0.82; 95% CI: 0.71–0.94; $P = .006$). The reduction in CV death was not significant. There was no difference between the finerenone and placebo groups in all-cause mortality or a composite kidney endpoint. Serious adverse events were comparable in both groups (finerenone: 38.7%; placebo: 40.5%). Finerenone increased the risk of investigator-reported hyperkalaemia (9.7% vs 4.2%) but decreased the risk of hypokalaemia (4.4% vs 9.7%). Forty-eight percent of patients in this study had an eGFR < 60 mL/min/1.73 m^2; there was no significant difference for the primary endpoint in the subgroups with and without CKD.[93] FINEHEART, a prespecified analysis of FIDELIO-CKD, FIGARO-CKD, and FINEARTS-HF showed consistent benefits of finerenone on cardio-kidney outcomes in patients with a high burden of cardio-kidney-metabolic conditions.[94]

Management of atrial fibrillation in CKD

Key aspects in the management of Afib include the avoidance of stroke and thromboembolism as well as the reduction of symptoms by rate or rhythm control.[95]

Anticoagulation for Afib and CKD

Scores for assessing the risk of thromboembolic events or bleeding have not been validated for higher-grade CKD, and the currently most frequently used CHA_2DS_2-VA score does not include eGFR or albuminuria despite the fact that individuals with CKD exhibit an elevated risk for both thromboembolism and bleeding.[96] There are no published, dedicated randomized trials on the clinical risks and benefits of anticoagulation in patients with advanced CKD. Observational studies suggest that vitamin K antagonist treatment with warfarin reduces the relative risk of ischaemic stroke or systemic embolism in Afib and CKD Stage G3 by 76%.[97] In contrast, the effect of warfarin for stroke prevention in dialysis patients is controversial due to the increased risk of bleeding. In addition, a meta-analysis in a population of stroke patients showed that the relative frequency of haemorrhagic strokes increases with decreasing kidney function.[98]

A meta-analysis of six randomized controlled trials and 19 observational studies suggest that direct oral anti-coagulants (DOACs) are associated with better efficacy in early CKD compared with vitamin K antagonists and appear to be associated with a better safety profile in advanced CKD Stages G4/5.[99] Data from three small, randomized trials comparing DOACs vs vitamin K antagonists are now available for haemodialysis patients, indicating an acceptable safety profile for the DOACs apixaban and rivaroxaban.[99–101] Of note, due to partial kidney excretion, the dose of DOACs should be adjusted in patients with advanced CKD.

If there are contraindications to antithrombotic therapy, atrial appendage occlusion can be a treatment option with registry data suggesting an acceptable safety profile for the procedure in higher-grade CKD.[102]

Rhythm vs rate control

A recent meta-analysis demonstrated a 2.3-fold increased risk of recurrence of Afib after catheter ablation in individuals with CKD compared with those without CKD.[103]

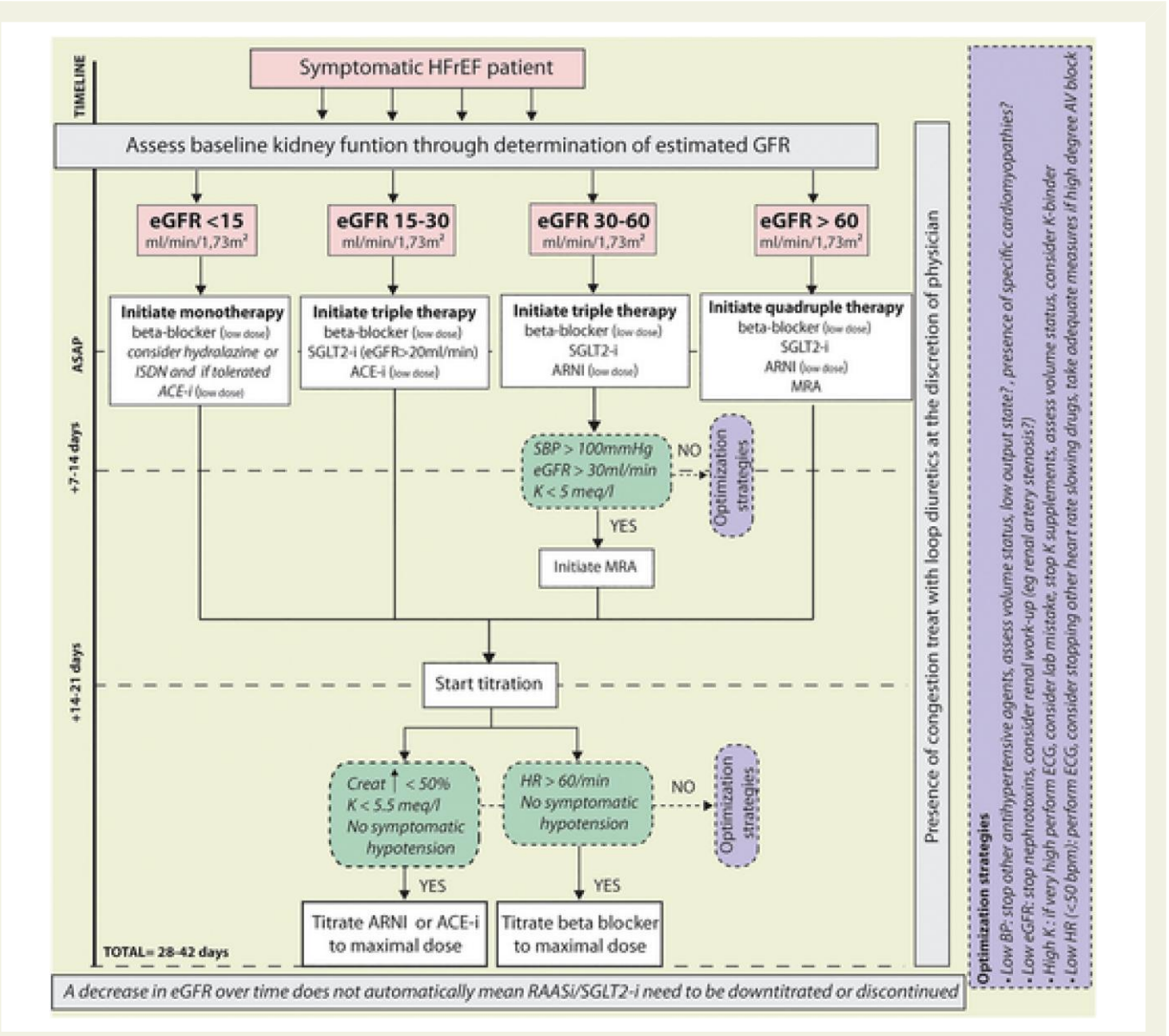

Figure 5 Renal-based approach to initiation and titrating of multilevel guideline-directed medical therapy. Proposed flowchart for titrating guideline-directed medical therapy in the setting of chronic kidney disease. During titration the lower threshold of blood pressure should be individualized based on the presence of activity limiting hypotension rather than pure blood pressure values itself. ACE-I, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor–neprilysin inhibitor; AV, atrioventricular; BP, blood pressure; Creat, creatinine; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HR, heart rate; ISDN, isosorbide dinitrate; K, potassium; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor; SBP, systolic blood pressure; SGLT2-i, sodium–glucose cotransporter 2 inhibitor. From Mullens et al.[90]

Concluding key messages for the clinician for the management of CVD in CKD

Screening of all patients with CVD for the presence of CKD

All patients with CVD should be screened for the presence of CKD by assessing eGFR defined by CKD-EPI and UACR in the spot urine since the presence of both comorbidities has a major impact on the prognosis as well as the implementation of additional CVD risk reducing therapies.

CV risk reduction in patients with CVD and CKD

Patients with CVD and CKD should receive the following standard therapy to reduce CVD risk: stringent blood pressure control (SBP < 130 mmHg), statin therapy, RASi with ACE-I or ARBs, as well as SGLT2 inhibitor treatment. In patients with CVD, CKD, and type 2

diabetes, additional therapy with finerenone and semaglutide is indicated to further reduce the risk of CVD and kidney failure.

Interdisciplinary, patient-centered management

Overall, the management of CVD in patients with CKD requires an interdisciplinary approach including cardiologists, nephrologists, general practitioners, as well as other health care providers to implement evidence-based, person-centred strategies to reduce the burden of disease in each patient and to improve the prognosis. In addition, patient education and raising awareness are key elements for successful management of these group of high-risk individuals.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

K.M.-S. has received personal fees for lectures from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, MSD, Novo Nordisk, Novartis, OmniaMed and served as an advisor for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim and Novo Nordisk. D.Z.I.C. has received consulting fees or speaking honorarium, or both, from AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim-Lilly, Bristol-Myers Squibb, Janssen, JNJ, MAZE, Merck & Co., Inc., Mitsubishi-Tanabe, Novo Nordisk, Otsuka, Prometic, and Sanofi; has received operating funds from AstraZeneca, Boehringer Ingelheim-Lilly, Janssen, Merck & Co., Inc., Novo Nordisk, and Sanofi; and has served as a scientific advisor or member of AstraZeneca, Boehringer Ingelheim, Janssen, Merck & Co., Inc., Novo Nordisk, and Sanofi. K.M. received funding from NIH and Resolve to Save Lives and personal fees from Fukuda Denshi, Kowa Company, AMGA, and RhythmX AI outside of the submitted work. N.M. has given lectures for Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, Lilly, NovoNordisk; has received unrestricted research grants from Boehringer Ingelheim, and has served as an advisor for Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, NovoNordisk. In addition, served in trial leadership for Boehringer Ingelheim and NovoNordisk. N.M. declines all personal compensation from pharma or device companies.

Data Availability

No data were generated or analysed for or in support of this paper.

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