



Cardiovascular Disease in Chronic Kidney Disease

Pathophysiological Insights and Therapeutic Options

ABSTRACT: Patients with chronic kidney disease (CKD) exhibit an elevated cardiovascular risk manifesting as coronary artery disease, heart failure, arrhythmias, and sudden cardiac death. Although the incidence and prevalence of cardiovascular events is already significantly higher in patients with early CKD stages (CKD stages 1–3) compared with the general population, patients with advanced CKD stages (CKD stages 4–5) exhibit a markedly elevated risk. Cardiovascular rather than end-stage kidney disease (CKD stage 5) is the leading cause of death in this high-risk population. CKD causes a systemic, chronic proinflammatory state contributing to vascular and myocardial remodeling processes resulting in atherosclerotic lesions, vascular calcification, and vascular senescence as well as myocardial fibrosis and calcification of cardiac valves. In this respect, CKD mimics an accelerated aging of the cardiovascular system. This overview article summarizes the current understanding and clinical consequences of cardiovascular disease in CKD.

Joachim Jankowski¹,
PhD
Jürgen Floege, MD
Danilo Fliser, MD
Michael Böhm², MD
Nikolaus Marx³, MD

Richard Bright, a British physician, was the first to report the association of chronic kidney disease (CKD) with cardiovascular disease (CVD).¹ Patients with CKD exhibit a pronounced risk for cardiovascular events: 50% of all patients with CKD stage 4 to 5 have CVD,² and cardiovascular mortality accounts for ≈40% to 50% of all deaths in patients with advanced CKD (stage 4) as well as end-stage kidney disease (stage 5), compared with 26% in controls with normal kidney function^{3,4} (Figure 1). In addition to the high risk for fatal atherosclerosis-related complications such as myocardial infarction and stroke, cardiovascular death also results from heart failure (HF) and fatal arrhythmias, particularly in advanced CKD stages. In >70 studies in nondialyzed subjects with CKD, correction for classical and even less classical cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, did not neutralize the impact of CKD on cardiovascular risk.⁶ This review summarizes the current knowledge of CVD in patients with CKD, clinical consequences, and treatment options of CVD in CKD (Figure 2). Given space limitations, we will not cover special situations such as extrarenal involvement in vasculitides or the association of autosomal dominant polycystic kidney disease with vascular abnormalities such as intracranial, aortic, or coronary artery aneurysms as well as aortic dissection.⁷

EPIDEMIOLOGY AND PROGNOSIS

The definition and classification of CKD was introduced by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative in 2002,⁸ and the

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Key Words: arrhythmias
■ cardiovascular disease ■ chronic kidney disease ■ clinical aspects ■ heart failure ■ sudden cardiac death

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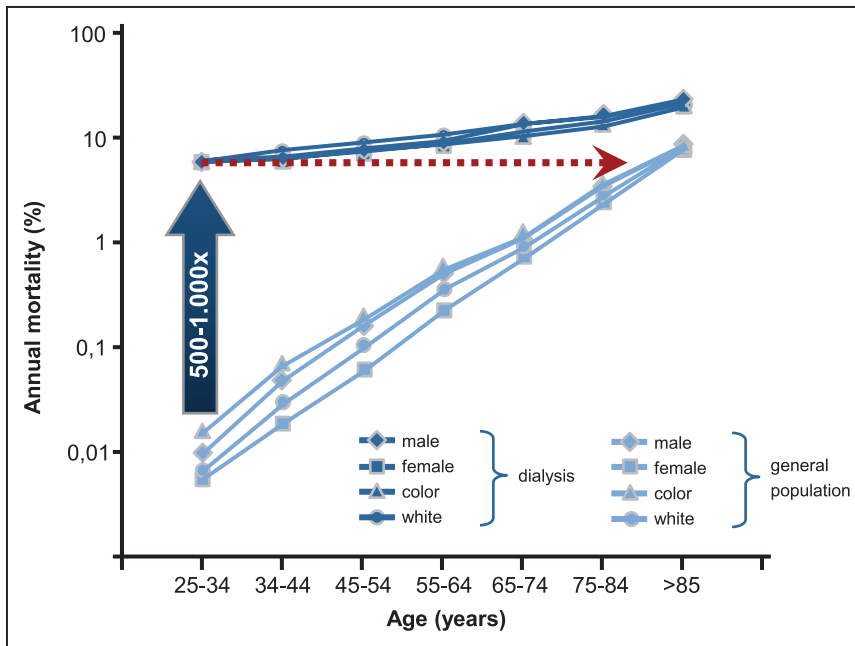


Figure 1. Cardiovascular mortality in the general population and in patients with end-stage kidney disease.

In 25- to 34-year-old patients with end-stage kidney disease, annual mortality is increased 500- to 1000-fold and corresponds to that of the \approx 85-year-old general population. Adapted from Foley et al.⁵

international guideline group Kidney Disease Improving Global Outcomes in 2004.⁹ Kidney damage refers to kidney abnormalities observed during clinical evaluation indicating a reduction in kidney function.^{9,10} Chronic kidney disease is defined as abnormalities in kidney damage or glomerular filtration rate <60 mL/min/1.73 m² that have been present for >3 months and have an impact on health.^{8,11} Kidney damage in many kidney diseases can be ascertained by the presence of albuminuria, defined as albumin-to-creatinine ratio >30 mg/g (Figure 3). Because there is an increasing evidence indicating a continuous relationship between albuminuria and cardiorenal risk in the renal and nonrenal population,^{13,14} albuminuria is considered a prognostic marker for cardiovascular or renal risk, or both.¹⁵ Higher levels of albuminuria indicate a graded increase in risk for mortality independent of eGFR.^{12,16}

CKD is increasingly recognized as a global public health problem¹⁷ imposing huge medical and financial burdens on societies and health care systems with an estimated prevalence of 13.4% globally.¹⁸ The worldwide rise in the prevalence of CKD is accompanied by an increase in patients reaching CKD stage 5 requiring kidney replacement therapy. Currently, about 3 million patients are receiving kidney replacement therapy for CKD stage 5D worldwide out of 10 million who would qualify for kidney replacement therapy; these numbers are expected to grow by 50% to 100% until 2030^{19,20} (Figure 4). Reasons for the increasing incidence and prevalence of advanced CKD, among others, include aging populations, increasing prevalence of type 2 diabetes and hypertension,²² and a low detection rate and therapeutic inertia in the early stages of CKD.^{8,23,24}

Despite the fact that health care resources allocated for the treatment of CKD have significantly

increased in recent years, patients with CKD still exhibit a dramatically reduced life expectancy, with a loss of 25 years of life at advanced stages compared with individuals with normal kidney function.^{25,26} Worldwide, CKD accounted for 2 968 600 (1.1%) of disability-adjusted life-years and 2 546 700 (1.3%) of life-years lost in 2012.⁴ A meta-analysis of the association between nondialysis-dependent CKD and the risk for all-cause and cardiovascular mortality involving 1 371 990 patients demonstrated an exponential increase in absolute risk for death with decreasing kidney function even after adjustment for other established risk factors.²⁷ A meta-analysis of cohort studies involving >1.4 million individuals^{28,29} yielded an association of not only low eGFR but also higher albuminuria with cardiovascular disease (Figure 5).³⁰ Thus, the risk of developing CVD in patients with CKD surpasses the risk of reaching end-stage kidney disease, and therefore, CKD must be considered one of the strongest risk factors for the development of CVD.²⁷

PATHOPHYSIOLOGY OF CVD IN CKD

In general, in addition to traditional risk factors, 2 major mechanisms are thought to contribute to the development of CVD in CKD. On the one hand, the kidney can release hormones,³¹⁻³⁴ enzymes, and cytokines³⁵⁻³⁷ in response to kidney injury or kidney insufficiency, which leads to characteristic changes in the vasculature. On the other hand, CKD-associated mediators as well as hemodynamic alterations contribute to cardiac damage,³⁸ as discussed in the following sections.

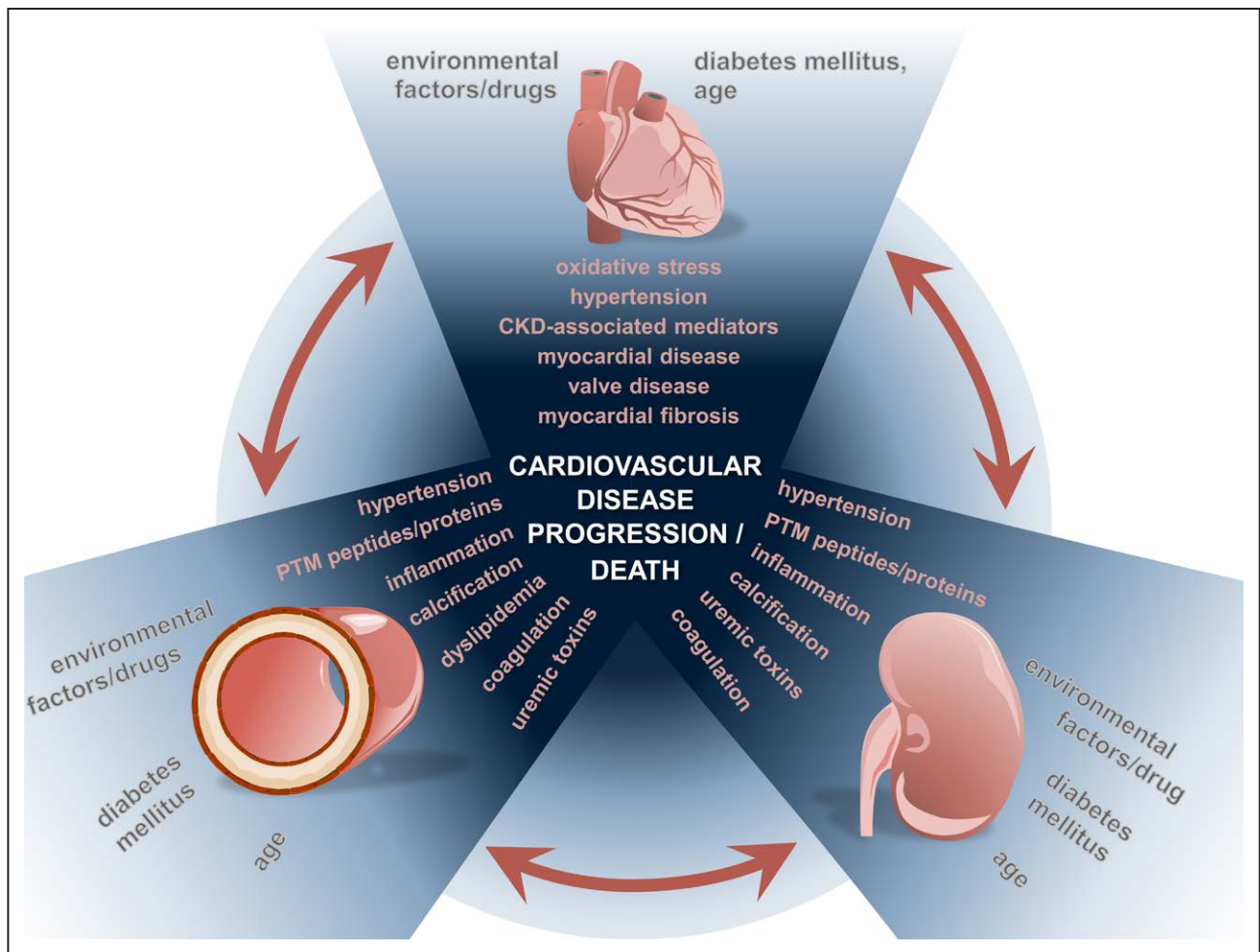


Figure 2. Interaction of cardiovascular disease (CVD) and chronic kidney disease (CKD).

Various mediators and mechanisms in vascular disease, heart failure, and CKD contribute to the progression of CVD and influence the prognosis of patients. PTM indicates post-translational modification.

Traditional Risk Factors of Vascular Disease in CKD

Traditional cardiovascular risk factors are highly prevalent in patients with CKD, and their contribution to atherosclerotic vascular disease is particularly important in earlier CKD stages.^{39,40} Among others, hypertension, insulin resistance/diabetes, dyslipidemia, and smoking contribute not only to atherosclerotic cardiovascular and cerebrovascular sequelae (Table) but also to CKD progression because of their effect on large (eg, kidney artery stenosis) and smaller (eg, nephrosclerosis) kidney vessels.^{49,50} In addition, some of these effects also seem to contribute to the recently described association of CKD with abdominal aortic aneurysms.⁵¹

Hypertension

The elevated cardiovascular risk in CKD cannot solely be explained by the presence of traditional risk factors as shown by data from the ARIC (Atherosclerosis Risk In Communities) and CHS (Cardiovascular Health Study) trials.⁵² In addition, the specific aspects of CKD have not

fully been addressed in studies targeting the modification of these risk factors. However, treatment of hypertension is beneficial in CKD, as recently corroborated by results of the SPRINT trial (Systolic Blood Pressure Intervention Trial), but the optimal target blood pressure in patients with CKD has not yet been established.⁴¹

Diabetes

Hyperglycemia is strongly associated with the development of both CKD and CVD. However, improvement in glycemic control in type 2 diabetes mainly contributes to a reduction in microvascular events such as nephropathy, although various studies failed to show a significant effect on macrovascular events; for example, the ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation⁵³) demonstrated in ~11 000 patients with type 2 diabetes that intensive glucose control compared with standard therapy leads to a reduction in the combined outcome of major macrovascular and microvascular events, but this effect was mainly driven by a reduction in nephropathy with no significant effect

Progression of CKD by GFR and Albuminuria Categories				Albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73m ²) Description and range	G1	Normal to high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	15			

Green: low risk (if no other markers of kidney diseases, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk

Figure 3. Classification and prognosis of chronic kidney disease (CKD) from 2012 KDIGO (Kidney Disease Improving Global Outcomes) guidelines. GFR indicates glomerular filtration rate. Adapted from the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.¹²

on macrovascular events⁴³; the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes)⁵³ was not able to demonstrate that treatment targeting nearly normal glycemic control reduces the risk of cardiovascular events in ≈10 000 patients with type 2 diabetes, and intensive versus standard glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications in VADT (Veterans Affairs Diabetes Trial),⁵⁴ including 1791 patients.

Moreover, data for lifestyle modifications are mostly observational and extrapolated from non-CKD trials. This fact has been clearly exposed by a recent meta-analysis reporting that randomized trials conducted between 2006 to 2014 were less likely to exclude patients with CKD than those between 1985 to 2005 (46% versus 56%).⁵⁵ However, this apparently encouraging trend is not sufficient to close the gap of evidence in patients with CKD.

Dyslipidemia

In addition, patients with CKD exhibit a characteristic lipid pattern of hypertriglyceridemia and low

high-density lipoprotein (HDL) cholesterol levels, but mostly normal low-density lipoprotein cholesterol levels. Recent clinical evidence suggests that vascular effects of HDL can be heterogeneous in different conditions, and that progressive kidney dysfunction dramatically changes the composition and quality of blood lipids, particularly HDL and triglyceride-rich lipoproteins, in favor of a more atherogenic profile.⁴² Adverse endothelial effects of HDL are also detectable in children with CKD, in whom cardiovascular risk factors such as smoking, hypertension, diabetes, and dyslipidemia were not yet present.⁵⁶ Several factors modify the composition of the HDL particle in CKD, including uremic toxins, increased oxidative stress, and the proinflammatory microenvironment. These factors contribute to a pronounced remodeling of HDL particles, altering the proteome and lipidome composition of HDL and inducing posttranslational modifications of HDL's protein cargo. Furthermore, the accumulation of uremic toxins such as symmetrical dimethylarginine in advancing CKD plays a key role in the functional changes of HDL.⁴²

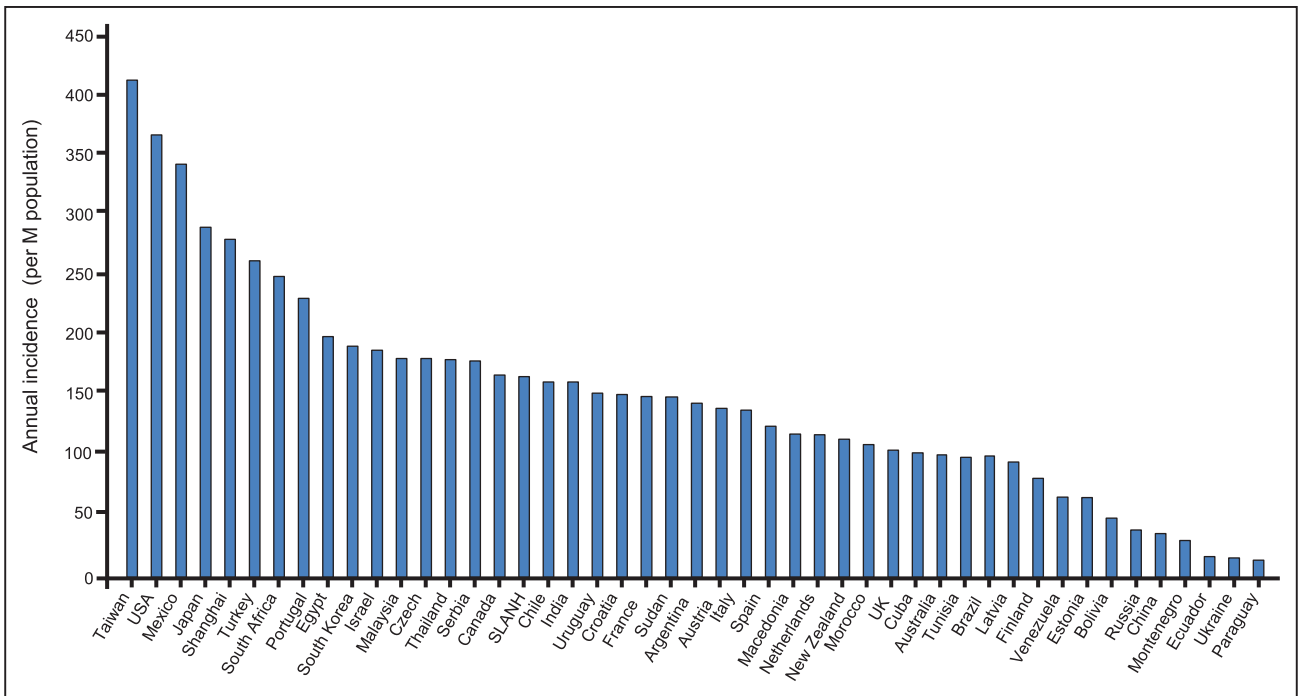


Figure 4. Annual incidence rates of end-stage kidney disease in different countries.
Adapted from Jha et al.²¹

Last, increased albuminuria or proteinuria is a potent risk factor for CVD in both diabetic and nondiabetic patients with CKD (Figure 3), and the incidence of cardiovascular events decreases with the institution of anti-proteinuric measures, in particular renin-angiotensin system (RAS) blockade. However, the pathomechanistic link between albuminuria and CVD may not be a direct one, as systemic but particularly intrarenal hemodynamic effects of RAS blockers affect progression of CKD and thus indirectly of CVD. Therefore, the data

in support of RAS blockers in albuminuric patients are reasonably strong for preventing progression of CKD and less so for CVD protection.⁴⁸

Nontraditional Risk Factors of Vascular Disease in CKD

Vascular Calcification

Vascular smooth muscle cells are the cellular components of the medial layer of the vessels, which can

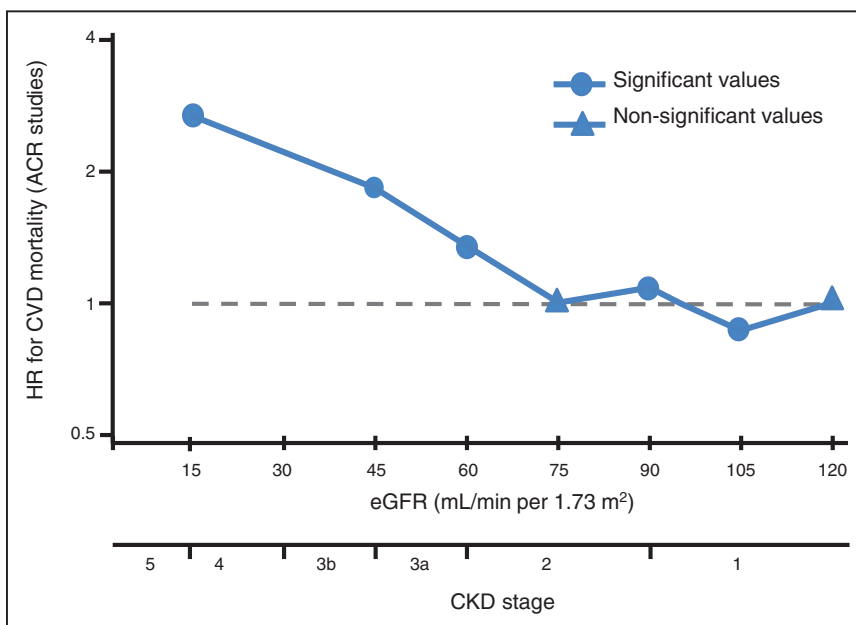


Figure 5. Independent association of kidney function with cardiovascular mortality.
ACR indicates albumin-to-creatinine ratio; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; and HR, hazard ratio. Adapted and modified from Gansevoort et al.³⁰

Table. Traditional and Nontraditional Risk Factors for CVD in CKD

Risk factors for CVD in CKD	Specific aspects/treatment options compared with the non-CKD population	Ref.
Traditional		
Hypertension	Optimal target blood pressure has not yet been established	41
Dyslipidemia	Characteristic lipid pattern of hypertriglyceridemia and HDL cholesterol levels	42
Smoking	—	
Hyperglycemia	Intensive glucose control beneficial to avoid microvascular complications	43
Nontraditional		
Vascular calcifications	Treatment of electrolyte imbalances with magnesium	44, 45
	Vitamin K administration might be beneficial	46
Inflammation	Inhibition of proinflammatory effector molecule interleukin-1 β (IL-1 β) with canakinumab after myocardial infarction	47
Increased proteinuria	RAS blockade	48

CKD indicates chronic kidney disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; and RAS, renin-angiotensin system.

switch from a contractile phenotype to a more synthetic phenotype caused by hemodynamic changes observed in CKD.⁵⁷ Resulting cardiovascular calcifications are markedly accelerated in patients with CKD, and even children with advanced CKD frequently exhibit vascular calcifications.⁵⁸ The histological prevalence of vascular calcifications in radial arteries was 45-fold greater in patients with CKD compared with those without CKD.⁵⁹ In addition to CKD, several common comorbidities, in particular diabetes, further enhance the progression of calcification.

Calcification of central arterial vessels contributes to increased pulse wave velocity, earlier reflection of the pulse wave, increased cardiac afterload, and thus HF.⁶⁰ Resulting hemodynamic alterations induce left ventricular hypertrophy associated with a decrease in coronary perfusion.^{61,62} A particularly severe form of vascular calcification is uremic calcific arteriopathy (calciphylaxis), which is caused by calcium deposition in the media of the dermo-hypodermic arterioles⁶³ leading to skin necrosis and carries a high mortality rate.⁶⁴ The exact mechanism of uremic calcific arteriopathy is unclear: previously, an increase in the calcium-phosphorus product was thought to cause calcification⁶⁵ leading to uremic calcific arteriopathy, but it becomes increasingly clear that calcification involves active cellular processes, not just passive mineralization, because of an increase in calcium-phosphorus concentrations.⁶⁶ However, hemodynamic consequences of medial calcification seem to have an exacerbated risk for left ventricular hypertrophy.⁶⁷

Calcification of cardiac valves, in particular the aortic valve, is a frequent cause of valvular stenosis requiring intervention. The extent and progression rate of vascular calcifications in CKD herald a poor prognosis.⁶⁸ However, the first data raise the hypothesis that repleting patients with vitamin K can retard the progression of valvular calcification⁴⁶; still, negative trials have also been published on this topic.⁶⁹

In addition, electrolyte imbalances like dysmagnesaemia are common in patients with CKD⁷⁰ and contribute to poor patient outcome,⁷¹ and therefore, electrolyte imbalances are potential targets for managing coronary artery calcification. In particular, magnesium, frequently reduced in serum in CKD,⁷⁰ has recently gained interest because of the inhibitory effect on vascular calcification^{44,45}: magnesium interferes with hydroxyapatite crystal formation and can halt vascular calcification progress in advanced CKD.⁷²

Inflammation

Inflammation is a key process observed in patients with CKD, and CKD is considered a systemic inflammatory disease with many causes^{73,74} and has been shown to predict the long-term risk of developing CKD.⁷⁴ Proinflammatory circulatory mediators progressively increase as kidney function declines.⁷⁵ Proinflammatory processes in CKD patients comprise, among others, a variety of infections including periodontal disease, oxidative stress caused by accumulation of advanced glycation end products, metabolic acidosis, reduced cytokine clearance, insulin resistance, posttranslational modifications of blood-borne molecules such as lipoproteins, and epigenetic factors.⁷³

In accordance, the CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcome Study) focusing on \approx 10 000 stable postmyocardial infarction patients with high-sensitivity C-reactive protein demonstrated a benefit of inhibition of proinflammatory effector molecule interleukin-1 β (IL-1 β) with the antibody canakinumab, which was larger in patients with eGFR $<$ 60 mL/min/1.73 m² than in those with eGFR $>$ 60 mL/min/1.73 m²⁴⁷ (Figure 6). However, further studies are needed to firmly establish the pathophysiological mechanisms and potential treatment options for inflammation in patients with CKD.

Myocardial Alterations in CKD

Patients with CKD exhibit characteristic changes in the myocardium with pathological myocardial fibrosis with collagen deposition between capillaries and cardiomyocytes and cardiac hypertrophy the hallmarks of uremic cardiomyopathy.⁷⁶ Left ventricular hypertrophy (LVH) is present in about one-third of all patients with CKD, increasing up to 70% to 80% in patients with end-stage kidney disease. The presence of LVH is an

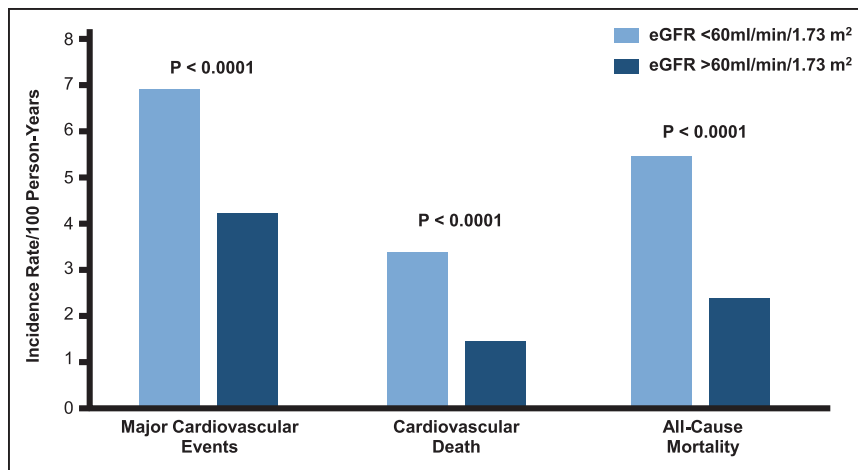


Figure 6. Independent association of kidney function with cardiovascular mortality.

ACR, albumin-to-creatinine ratio; and eGFR, estimated glomerular filtration rate. Adapted and modified from Gansevoort et al.³⁰

independent predictor of survival in patients with CKD, even in those with early-stage CKD. Three main mechanisms are considered to contribute to LVH in CKD: (1) afterload- and (2) preload-related factors as well as (3) nonafterload, nonpreload-related factors.⁷⁷ Afterload-related factors include abnormal arterial stiffness, increased systemic arterial resistance, and systolic hypertension, leading to an initial concentric LVH.⁷⁸ Continuous left ventricular overload subsequently leads to maladaptive changes and cardiomyocyte death, which in turn result in an eccentric hypertrophy and subsequent left ventricular dilatation, systolic dysfunction, and reduced ejection fraction (EF).⁷⁹ Preload-related factors in the pathophysiology of LVH comprise the expansion of intravascular volume in CKD leading to volume overload, length extension of myocardial cells, and eccentric or asymmetrical left ventricular remodeling.⁷⁸ Nonafterload, nonpreload-related factors include intracellular mediators and pathways contributing to progressive LVH.⁸⁰ Essential mechanisms in this context are activation of peroxisome proliferator-activated receptors, stimulation of small G-proteins or the mechanistic target of rapamycin pathway, as well as metabolic changes such as decreased fatty acid oxidation. The second hallmark of uremic cardiomyopathy besides LVH is the development of myocardial fibrosis occurring independently of LVH itself.⁷⁶ Cardiac fibrosis in patients with CKD is characterized by diffuse collagen deposition between capillaries and cardiomyocytes funneling into the maladaptive ventricular hypertrophy with subsequent dilatation of the heart.

Furthermore, there is an epidemiological collinearity of the prevalence and incidence of CKD with aortic and mitral valve disease.⁸¹ Valve disease has a strong impact on the outcome in patients with CKD.⁸² Early CKD stages 1 to 3 are associated with enhanced calcifications of valves and coronary arteries.⁸³ Heart valve calcification occurs in stage 5 CKD in up to 88% to 99% of patients, increasing from 40% of patients in CKD stage 3,⁸⁴ and the final destruction of valves occurs at a 10-fold higher rate in patients with CKD

compared with patients without CKD. Valvular disease in patients with CKD is accelerated by comorbidities like diabetes, arterial hypertension, hyperlipidemia, anemia and ongoing infections of valves, and malnutrition, as well as hypercalcemia, hyperphosphatemia, and hyperparathyroidism.⁸⁵

THERAPY OF CARDIOVASCULAR DISEASE IN CKD

Treatment of Vascular Disease in Patients With CKD

Control of traditional risk factors as well as antiplatelet therapy are cornerstones to reduce cardiovascular risk. As such, current guidelines recommend to lower systolic blood pressure to a range of 130 to 139 mm Hg in patients with diabetic or nondiabetic CKD, and renin-angiotensin-aldosterone inhibitors are first-line agents in CKD.⁸⁶ Given the only moderate effect of glucose control on macrovascular events, hemoglobin A1c targets should be individualized, and side effects such as hypoglycemia should be avoided, in particular in CKD, because hypoglycemic episodes are associated with an increase in mortality in this group of patients. Data from large cardiovascular outcome trials with glucose-lowering sodium-glucose cotransporter 2 (SGLT2) inhibitors or GLP-1 receptor agonists have shown a significant reduction in cardiovascular events in patients with type 2 diabetes at high cardiovascular risk. Thus, various guidelines recommend treatment with these agents in CKD and non-CKD patients with CVD or multiple cardiovascular risk factors.

The effect of lipid-lowering strategies on CV risk reduction in CKD seems to be dependent on the severity of CKD. As such, the SHARP study (Study of Heart and Renal Protection)⁸⁷ examined the effect of simvastatin 20 mg/d versus simvastatin 20 mg/d plus ezetimibe in 9438 patients with advanced chronic kidney disease without a history of myocardial infarction or coronary revascularization and found a significant 17% relative

reduction of the primary end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.⁸⁸ In contrast, both the 4D study (Deutsche Diabetes Dialysis Study)⁸⁹ and the AURORA study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) failed to show a significant reduction of cardiovascular death, nonfatal MI, and nonfatal stroke by atorvastatin or rosuvastatin, respectively, versus placebo in patients with hemodialysis.⁹⁰ These data suggest that the cardiovascular benefit of lipid-lowering therapies is attenuated in subjects with low glomerular filtration rate and limited/absent in patients with end-stage renal disease on hemodialysis.⁹¹

In patients with coronary artery disease without CKD, antiplatelet therapy is well established to reduce cardiovascular risk, but in CKD, the prognostic benefit is less clear. Moreover, these drugs increase the risk of bleeding events in patients with CKD, possibly outweighing the potential benefit.⁹²

The ISCHEMIA-CKD trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches-Chronic Kidney Disease) assessed an invasive or conservative care approach in patients with stable CAD and CKD. A total of 777 patients with advanced kidney disease and moderate or severe ischemia on stress testing were randomly assigned to initial invasive strategy consisting of coronary angiography and revascularization (if appropriate) added to medical therapy or an initial conservative strategy consisting of medical therapy alone and angiography reserved for those in whom medical therapy had failed. After a median follow-up of 2.2 years, there was difference for the primary composite end point of death or nonfatal myocardial infarction between groups. However, the invasive strategy was associated with a significantly higher incidence of stroke than the conservative strategy and with a higher incidence of death or initiation of dialysis.⁹³ In addition, groups did not differ with respect to angina-related health status.⁹⁴

Interestingly, a large registry study in patients with acute myocardial infarction showed that patients with CKD were less likely to receive statins, β -blockers, and antiplatelet therapy compared with those without CKD, suggesting that patients with CKD still receive fewer evidence-based therapies, which may as well contribute to substantially higher mortality rates.⁹⁵

Treatment of Patients With HF and CKD

Current therapeutic options in patients with HF are largely on the basis of cardiovascular outcome trials, which assessed the effect of both medical and interventional therapy to reduce morbidity and mortality. However, patients with CKD have been excluded in

most clinical HF studies, and recommendations for patients with CKD have to be extrapolated from subgroup analyses. There is to date no treatment option available that convincingly reduced morbidity and mortality in patients with HF and preserved EF (left ventricular EF $\geq 50\%$) or moderately impaired left-ventricular function (left ventricular EF 40%–49%) in CKD.

However, at the stage of symptomatically reduced EF (HFrEF; left ventricular EF $< 40\%$), therapy with angiotensin-converting enzyme (ACE) inhibitors and β -blockers is recommended as first-line therapy. ACE inhibitors have been shown to reduce morbidity and mortality in numerous large randomized trials. A clear benefit of ACE inhibitors in patients with CKD stage 1 to 3 has been suggested, but few data are available in patients with advanced CKD stages. In the Swedish Cardiac Insufficiency Registry, a total of 2410 patients with HFrEF and CKD (serum creatinine 2.5 mg/dL or creatinine clearance < 30 mL/min) with or without RAS inhibitor were studied.⁹⁶ Propensity score matching was used to compare 602 patients with and without angiotensin1-receptor blockers or ACE inhibitors. In patients with RAS inhibition, total mortality was significantly lower at 1 year compared with patients without RAS inhibition (hazard ratio, 0.76 [95% CI, 0.67–0.86]).⁹⁶

On the basis of large randomized studies showing a reduction in total mortality, β -blockers are also recommended as first-line therapy in parallel to renin-angiotensin-aldosterone inhibitors to counteract sudden cardiac death and progression of HF in patients with HFrEF.^{97–99} A meta-analysis of intervention studies with β -blockers in patients with CKD stage 3 to 5 clearly demonstrated that these patients benefit from this therapy,¹⁰⁰ suggesting that β -blockers are equally effective in patients with CKD as in non-CKD patients. Recent data underline the benefits of a β -blocker therapy in patients with CKD (CKD stages 3–4) with HF, left ventricular EF $< 50\%$, and sinus rhythm.¹⁰¹ If patients with HFrEF are still symptomatic despite treatment with ACE inhibitors and β -blockers, and if the left ventricular EF is $\leq 35\%$, administration of mineralocorticoid receptor antagonists (MRAs) is indicated, but with particular caution in patients with advanced CKD. Spironolactone and eplerenone improved the prognosis of patients with HFrEF, and this therapy is effective in patients with HF and CKD stages 1 to 3.¹⁰² In the DOHAS study (Dialysis Outcomes Heart Failure Aldactone Study), 309 patients with CKD stage 5D were randomized to either 25 mg spironolactone per day or to standard of care only.¹⁰³ Compared with the control group, the combined primary end point of mortality and cardio- or cerebrovascular hospitalization was significantly reduced in the spironolactone group (hazard ratio, 0.40 [95% CI, 0.20–0.81]). However, cardiovascular efficacy and safety of spironolactone are still uncertain in CKD stage 5. In recent placebo-controlled trials, spironolactone appeared safe in

carefully monitored maintenance CKD stage 5 patient cohorts but it did not affect cardiovascular parameters like diastolic function¹⁰⁴ or left ventricular mass, ambulatory blood pressure, left ventricular EF, 6-minute walk test distance, or New York Heart Association class.¹⁰⁵ Because spironolactone increased the frequency of moderate—albeit not severe—hyperkalemia in patients with CKD stage 4 to 5,^{104,105} MRAs formally are still contraindicated in advanced CKD. The ongoing ALCEMIST trial (ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial) examines the effect of aldosterone on cardiovascular outcome (including HF) in chronic hemodialysis patients. Novel therapeutic strategies with potassium binders may provide an additional option for patients with hyperkalemia.

Diuretics are indicated at New York Heart Association II stage with fluid retention, and generally in New York Heart Association stage III to IV patients, to reduce the risk of decompensation, but no data demonstrating a prognostic benefit of diuretics on mortality are available.

If patients on combination therapy with ACE inhibitors (or angiotensin1-receptor blockers), β -blockers, and MRAs continue to be symptomatic and the ACE inhibitor (or angiotensin1-receptor blocker) was well tolerated, the administration of an angiotensin receptor/neprilysin inhibitor is recommended. Neprilysin inhibitors, such as sacubitril, a relatively new class of drugs, inhibit the enzyme neprilysin, thus prolonging the half-life of vasoactive peptides such as BNP (B-type natriuretic peptide); sacubitril is given in combination with valsartan. For this substance, LCZ 696 (sacubitril and valsartan), a reduction in overall mortality, cardiovascular mortality, and hospitalization compared with enalapril was demonstrated, and this effect was also seen in patients with CKD stages 3 to 5.¹⁰⁶ Thus, angiotensin receptor/neprilysin inhibitors seem effective in patients with HF and CKD.

Therapy with the channel inhibitor ivabradine may be considered once maximally tolerated β -blocker therapy is in place. The evidence for this recommendation is derived from the SHIFT trial (Systolic Heart Failure Treatment with the I[f] Inhibitor Ivabradine Trial), which showed a significant reduction in the combined primary end point of cardiovascular mortality or heart failure hospitalization compared with placebo in patients treated with ivabradine.¹⁰⁷ The incidence of the primary end point was similar in both patients with (CKD stages 3–5) and without CKD.¹⁰⁸

Prevention of Sudden Cardiac Death and Arrhythmias in CKD

More than two-thirds of mortality in advanced CKD stages are a result of sudden cardiac death^{109,110} (Figure 6). Sudden cardiac death refers to the unexpected

natural death from a cardiac cause within 1 hour after onset of symptoms in a person who has no lethal underlying disease. Sudden cardiac death is mainly caused by ventricular arrhythmias.^{111,112} The rate of sudden cardiac death is 59 deaths in 1000 patient-years in the CKD stage 5D population, whereas it is 1 death in 1000 patient-years in the general population.¹¹³

Patients with CKD not only show an increased risk of sudden cardiac death but also have clear differences from the general population in terms of the pathophysiology and cause of sudden cardiac death. In the general population, >80% of sudden cardiac deaths are associated with coronary heart disease.¹¹⁴ Despite the fact that patients with CKD stage 5D have a high incidence of coronary heart disease, the rate of sudden cardiac death is disproportionately high compared with the incidence of coronary heart disease in these patients (Figure 7). Moreover, even a complete revascularization can only partially reduce the risk of sudden cardiac death in patients with CKD.¹¹⁶ According to the current state of knowledge, components of the myocardium, the blood vessels, and the blood as a whole add up to the high risk in these patients. In addition, dialysis itself is a risk factor for sudden cardiac death, with the highest risk of sudden cardiac death within the first 12 hours after dialysis and after a long dialysis-free interval. Potential mechanisms include volume and sudden electrolyte shifts after dialysis as well as volume overload and electrolyte disturbance.¹¹⁷ Accordingly, patients with peritoneal dialysis seem to exhibit a lower risk for sudden cardiac death. To date, noninvasive strategies such as assessment of heart rate variability, late potentials, QT dispersion, or wave alternans failed to adequately predict sudden cardiac death risk in patients with dialysis.¹¹⁸

Compared with drug therapies (eg, antiarrhythmic agents), implantable cardioverter-defibrillators (ICDs) lead to a significant reduction in mortality in cardiovascular patients as primary and secondary prevention, but patients with CKD were again mostly excluded in these studies. A meta-analysis of the effectiveness and importance of implantation of ICDs showed that ICD patients with CKD exhibit an increased mortality, and therefore the value of ICD implantation in this group has been questioned.¹¹⁹

Despite the small number of dialysis patients in clinical studies, current guidelines also recommend primary prophylactic ICD implantation if the EF is $\leq 35\%$. To what extent dialysis patients with an EF $>35\%$ have an increased risk of arrhythmia and may benefit from primary prophylactic ICD implantation is also currently unclear.

Therapy of Valve Disease in CKD

Guideline recommendations for patients with CKD do not differ much from patients without CKD in

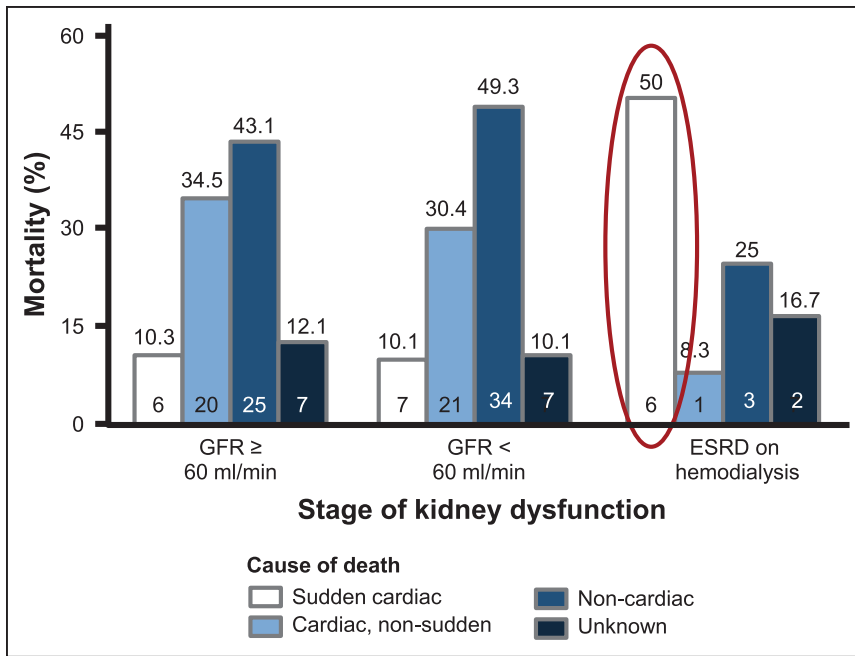


Figure 7. Cause-specific mortality according to varying levels of kidney dysfunction.

For the 3 categories of kidney dysfunction, cause-specific mortality is depicted. Sudden cardiac death was the major cause of death in patients with end-stage renal disease (ESRD) on dialysis (50.0% vs 10.1% [glomerular filtration rate (GFR) <60 mL/min] vs 10.3% [GFR ≥60 mL/min], χ^2 $P=0.010$). Number at the top of each bar is the mortality rate; number within the bar is the n per group. The unknown category was reserved for those patients whose cause of death could not be determined. Adapted from Cheema et al.¹¹⁵

approaches to treat valve disease.⁸¹ In-hospital mortality can rise up to 21% in patients with CKD stage 5.¹²⁰ CKD is a predictor for acute kidney injury and death after valve surgery.¹²¹ Therefore, the Society of Thoracic Surgeons Score, EuroSCORE-II (European System for Cardiac Operative Risk Evaluation), or logistic EuroSCORE have incorporated kidney function as 1 parameter.⁸¹ In patients with low perioperative risk (EuroSCORE-II <4% or logEuroSCORE <10%), surgical aortic valve replacement is recommended.

Transcatheter aortic valve implantation is recommended as a safe and effective treatment option in patients <75 years old at elevated operative risk (Society of Thoracic Surgeons Score >4%). Recent data suggest that in patients at low risk, the all-cause mortality after 24 months decreases by 12% and stroke incidence by 19% compared with surgical aortic valve replacement, which was independent of the preoperative risk before the intervention.¹²² Recently published prospective randomized trials comparing transcatheter aortic valve implantation and surgical aortic valve replacement in patients without CKD showed a superiority of interventional valve treatment compared with operative valve treatment.^{123,124} However, impaired kidney function affects mortality and risk for dialysis after transcatheter aortic valve implantation.¹²⁵ Long-term risk for death and need for introduction of kidney replacement therapy were increased by 51% and 56%, respectively.¹²⁶ Nevertheless, acute kidney injury after transcatheter aortic valve implantation (7%) was less prevalent than surgical aortic valve replacement (12%).¹²⁷

Surgical treatment of mitral valve incompetence with valve reconstruction is superior to valve replacement.⁸¹ Recently, reconstruction of mitral valves in functional

mitral incompetence with the MitraClip system has shown superior results¹²⁸ with a reduction of hospitalization caused by cardiac decompensation in 2 years (hazard ratio, 0.54; $P<0.001$) and extensive reduction of all-cause death¹²⁹ compared with optimal medical treatment. CKD is associated with adverse outcomes in mitral valve interventions. In patients with CKD stage 1 to 2, mortality was 13%; at CKD stage 3, 19%; and CKD stage 4 to 5, 33%.¹³⁰ There was a slight improvement of kidney function by 4.8 mL/min/1.73 m² in CKD stage 4 to 5¹²⁷ after valve replacement, indicating that valve improvement and improvement in myocardial performance might impact kidney function. This improvement was associated with decreased therapy cost and in-hospital treatment duration.¹²⁷

Because valve disease is a common comorbidity in patients with CKD, after echocardiographic evaluation, the decision to treat valve disease with surgery or intervention should be on the basis of the temporary guidelines of the American Heart Association, American College of Cardiology, and European Society of Cardiology. In general, the degree of CKD is associated with increased adverse outcomes risk after interventions and surgery as well as bearing an enhanced intermediate and long-term risk, in particular in patients >75 years of age. In the latter group, aortic valve transcatheter aortic valve implantation should be considered the superior method to be used.

NOVEL THERAPEUTIC APPROACHES

Although CKD is one of the most common comorbidities in CVD, few specific treatment options are available for the high-risk population of patients with advanced

CKD.¹³¹ Finding a balance between the optimization of clinical outcomes in CKD and CVD still requires validation in large prospective, multicenter clinical studies. SGLT2 inhibitors, currently used to treat patients with type 2 diabetes, have shown unprecedented cardiovascular as well as kidney protective effects. In cardiovascular outcome studies such as EMPA REG OUTCOME ([Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) with empagliflozin in >7000 cardiovascular type 2 diabetic patients, the primary end point and cardiovascular mortality were significantly reduced in the SGLT2 group.¹³² A positive effect on cardiovascular morbidity was also demonstrated in cardiovascular outcome studies with canagliflozin and dapagliflozin.^{133,134}

In these studies, the secondary outcome of “HF-related hospitalizations” was less frequent, suggesting a class effect of SGLT2 inhibitors. The use of canagliflozin (CANVAS)¹³³ and empagliflozin (EMPA REG OUTCOME),¹³² in patients with type 2 diabetes, both confirmed the reduction of albuminuria progression by 27% to 38% and the preservation of eGFR, even in advanced CKD stages. Recently, CREDENCE became the first phase III study with an SGLT2 inhibitor in type 2 diabetic patients with CKD (n=4400) with a combined primary kidney end point¹³⁵: within 2 and a half years, canagliflozin significantly reduced the risk of kidney replacement therapy, doubling serum creatinine and death caused by kidney insufficiency by 33%. In addition, most recently, DAPA-CKD, a dedicated trial in patients with CKD (with or without type 2 diabetes), was published. In this placebo-controlled trial, dapagliflozin led to a significant reduction in the primary composite end point of sustained $\geq 50\%$ eGFR decline, renal or cardiovascular death, hospitalization for heart failure, as well as a reduction in all-cause mortality independent of the presence of diabetes.¹³⁶ Initial findings indicate that SGLT2 inhibitors improve kidney function by regulating kidney sodium reabsorption, the resulting glomerular hyperfiltration, and hypertension. On the basis of the promising effects of SGLT2 inhibitors on HF-related end points, various cardiovascular outcomes trials directly assess the efficacy of these agents in HF populations. DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction)—the first study among them to report results—examined the effect of dapagliflozin in HFrEF patients with or without diabetes enrolling patients with an eGFR down to 30 mL/min/1.73 m². Dapagliflozin significantly reduced HF hospitalization, cardiovascular death, and all-cause mortality in patients with and without diabetes.¹³⁷ In EMPEROR-reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction), a trial enrolling HFrEF patients with or without diabetes with an eGFR down to 20 mL/min/1.73 m², empagliflozin significantly reduced the composite end point of time to first event of adjudicated cardiovascular death or

adjudicated hospitalization for heart failure.¹³⁸ Potential mechanisms explaining the beneficial effects of SGLT2 inhibitors in patients with HF or CKD include hemodynamic as well as metabolic effects.¹³⁹ In addition, SGLT2 inhibitors may selectively reduce interstitial fluid, and this may limit the reflex neurohumoral stimulation that occurs in response to intravascular volume contraction with traditional diuretics.¹⁴⁰

MRAs reduce the aldosterone-mediated proinflammatory effects that are involved in the fibrotic remodeling processes. The new selective nonsteroidal MRA finerenone also blocks the damaging effects of the overactivated aldosterone system. In contrast with the MRAs spironolactone and eplerenone, finerenone is equally distributed in myocardial and kidney tissue. Finerenone binds to the same ligand domain but to different amino acids, leading to a different expression pattern of cardiac genes compared with spironolactone and eplerenone. Finerenone also reduced cardiac fibrosis and inflammation more than eplerenone in animal experiments at a comparable dose.

In the phase II ARTS trial (Arterial Revascularization Therapies Study) with >450 patients with CKD and congestive HF, finerenone reduced the urinary albumin-creatinine ratio and NT-proBNP (N-terminal pro-BNP) as potently as spironolactone with significantly lower rates of deteriorating kidney function and hyperkalemia.¹⁴¹ Similarly, in phase IIb, with >800 patients with type 2 diabetes, finerenone reduced albumin—creatinine ratio in urine by up to 38% and was well tolerated.¹⁴² The incidence of severe adverse events, including a 30% glomerular filtration rate decrease, was similar to placebo. Study cessation because of hyperkalemia was rare. In the phase III trials FIDELIO (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease) and FIGARO (Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease), >13 000 type-2 diabetic patients with CKD are currently being tested to determine whether finerenone can reduce cardiovascular morbidity and mortality or prevent progression of kidney disease. The completion of the studies is expected in May 2020 (FIDELIO) and July 2021 (FIGARO), respectively.

CONCLUSIONS

Patients with CKD have high cardiovascular risk, with cardiovascular death being the leading cause of death. Several novel therapies to decrease the risk of cardiovascular diseases in CKD are in clinical development or have been already established, raising the hope that cardiovascular risk in patients with CKD may be modifiable in the future. Still, the lack of data from large cardiovascular outcome trials in the high-risk group of patients with CKD should be a call for action to ensure that novel therapeutic options are assessed in dedicated trials in the CKD

population, in particular in those with advanced CKD, thus paving the way toward a more evidence-based approach to reduce cardiovascular risk in CKD.

ARTICLE INFORMATION

Correspondence

Nikolaus Marx, MD, FESC, FAHA, Department of Internal Medicine I, University Hospital Aachen, Pauwelsstraße 30, D-52074 Aachen, Germany. Email nmarx@ukaachen.de

Affiliations

Institute for Molecular Cardiovascular Research (J.J.), Division of Nephrology and Clinical Immunology (J.F.), Department of Internal Medicine I (Cardiology) (N.M.), University Hospital, Rheinisch-Westfälische Technische Hochschule Aachen (RWTH), Aachen, Germany. School for Cardiovascular Diseases, Maastricht University, The Netherlands (J.J.). Department of Nephrology (D.F.), Department of Cardiology, Angiology and Intensive Care Medicine (M.B.), Saarland University Medical Centre, Homburg, Germany.

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