Circulation

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.

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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
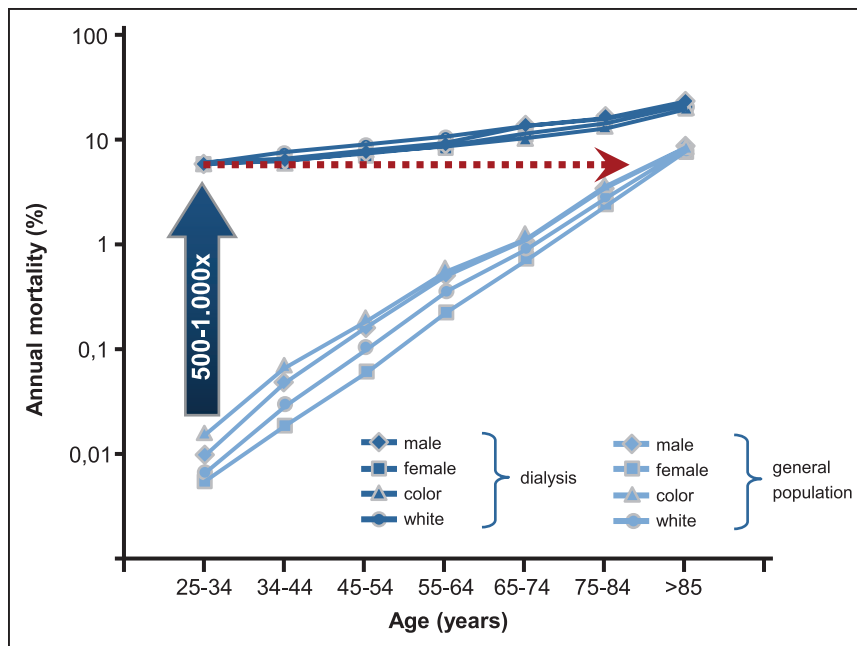
Figure 1. Cardiovascular mortality in the general population and in patients with end-stage kidney disease.
In 25- to 34-year-old patients with end-stage kidney disease, annual mortality is increased 500- to 1000-fold and corresponds to that of the ≈85-year-old general population. Adapted from Foley 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 problem[17] 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 cytokines[35–37] 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.
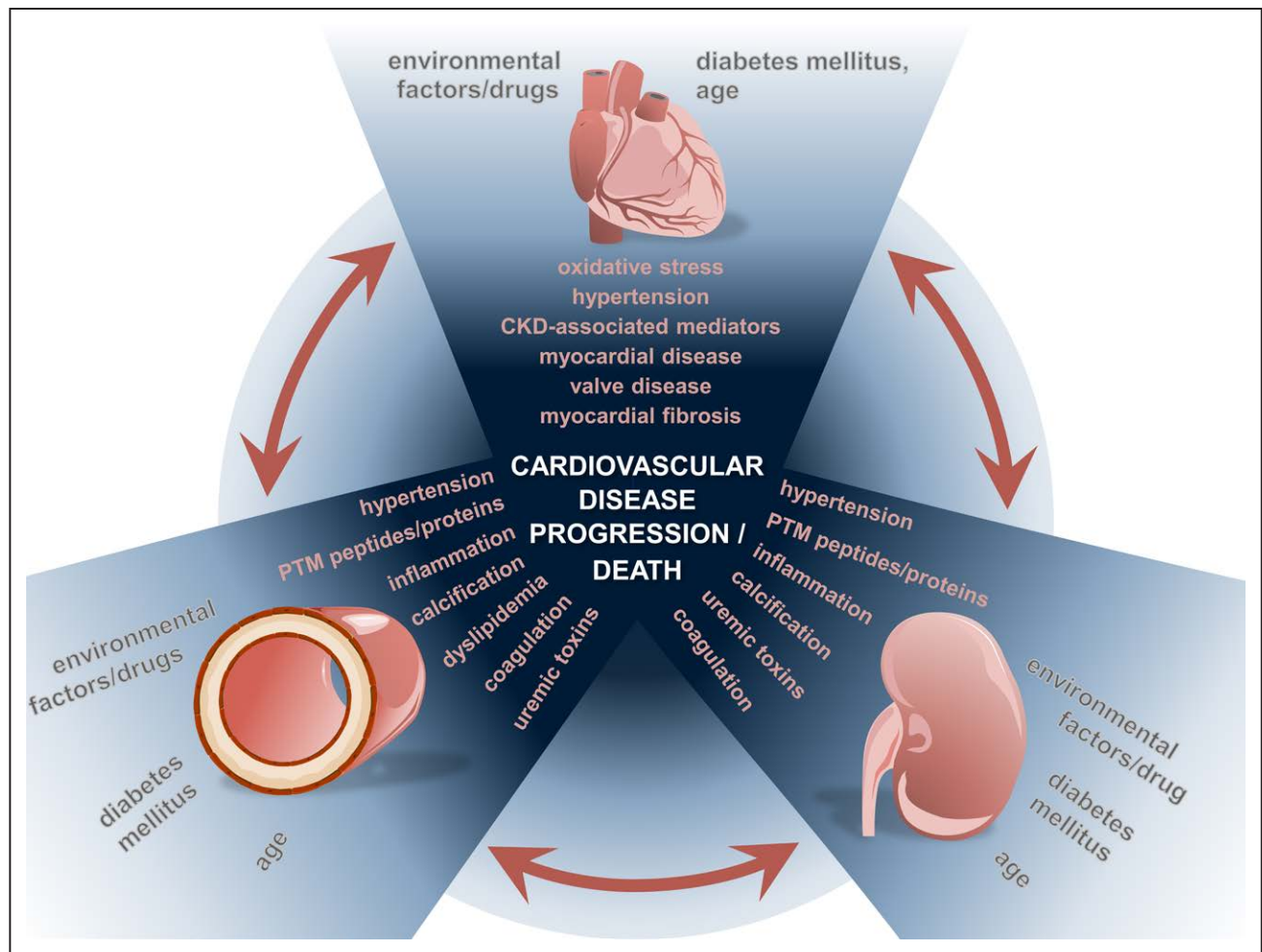
Figure 2. Interaction of cardiovascular disease (CVD) and chronic kidney disease (CKD).
Various mediators and mechanisms in vascular disease, heart failure, and CKD contribute to the progression of CVD and influence the prognosis of patients. PTM indicates post-translational modification.

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 Diamicron Modified Release Controlled Evaluation") 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/1.73m²) 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 events[43]; 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]
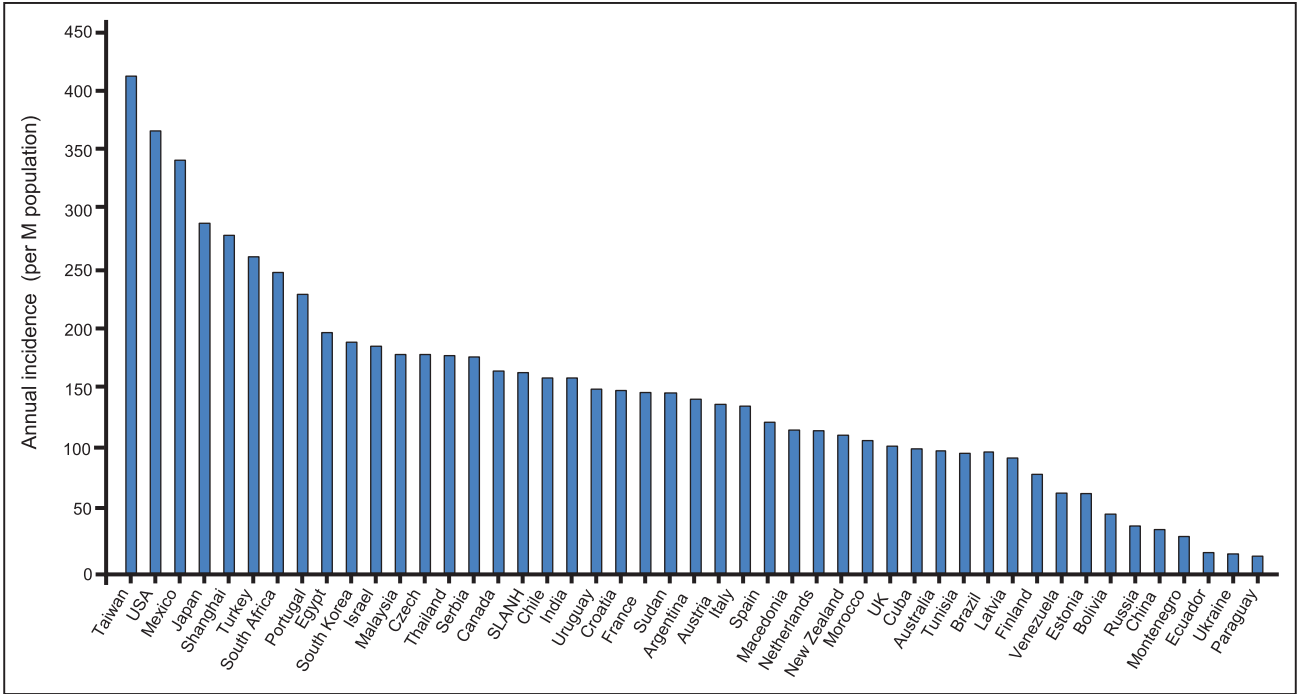
Figure 4. Annual incidence rates of end-stage kidney disease in different countries.
Adapted from Jha et al.[21]

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 antiproteinuric 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
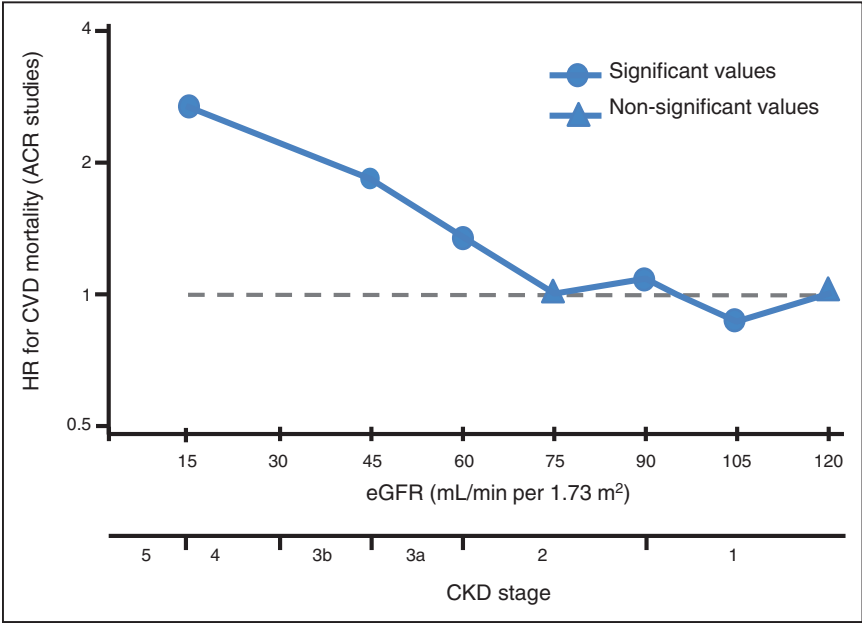

Figure 5. Independent association of kidney function with cardiovascular mortality.
ACR indicates albumin-to-creatinine ratio; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; and HR, hazard ratio. Adapted and modified from Gansevoort et al.[30]

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-1ß (IL-1ß) 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 arteriolopathy (calciphylaxis), which is caused by calcium deposition in the media of the dermo-hypodermic arterioles[63] leading to skin necrosis and carries a high mortality rate.[64] The exact mechanism of uremic calcific arteriolopathy is unclear: previously, an increase in the calcium-phosphorus product was thought to cause calcification[65] leading to uremic calcific arteriolopathy, 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 calcification[46]; still, negative trials have also been published on this topic.[69]

In addition, electrolyte imbalances like dysmagnesemia are common in patients with CKD[70] 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 ≈10 000 stable postmyocardial infarction patients with high-sensitivity C-reactive protein demonstrated a benefit of inhibition of proinflammatory effector molecule interleukin-1β (IL-1β) with the antibody canakinumab, which was larger in patients with eGFR <60 mL/min/1.73 m^2 than in those with eGFR >60 mL/min/1.73 m^2[47] (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
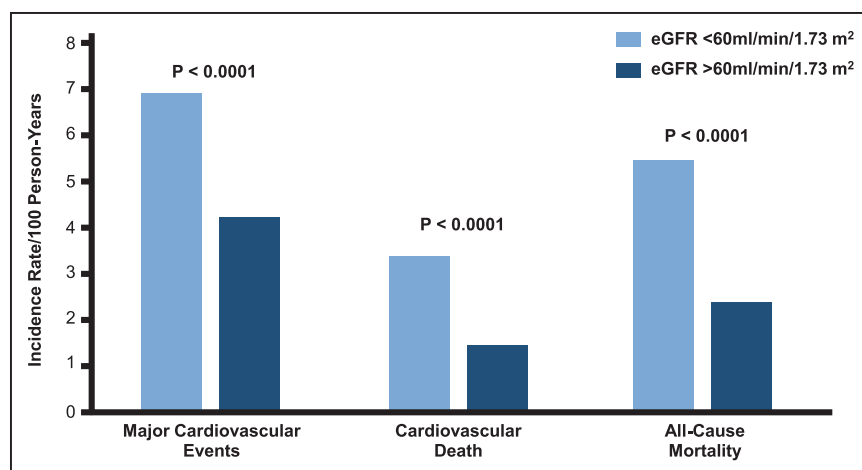
Figure 6. Independent association of kidney function with cardiovascular mortality.
ACR, albumin-to-creatinine ratio; and eGFR, estimated glomerular filtration rate. Adapted and modified from Gansevoort et al.[30]

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 ≥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 ≤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 function[104] 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 ALCHE-MIST 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 heat 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 ≤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
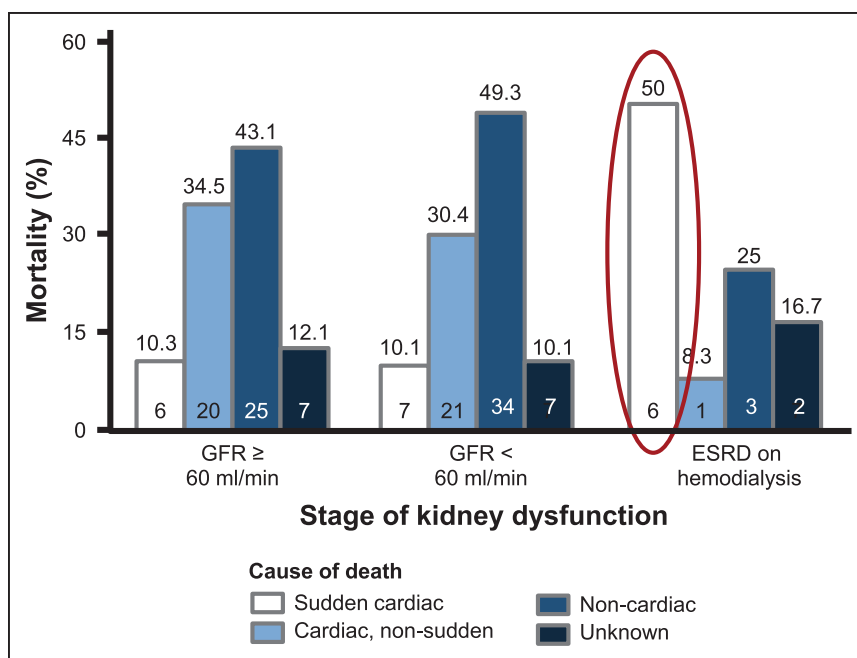
Figure 7. Cause-specific mortality according to varying levels of kidney dysfunction. For the 3 categories of kidney dysfunction, cause-specific mortality is depicted. Sudden cardiac death was the major cause of death in patients with end-stage renal disease (ESRD) on dialysis (50.0% vs 10.1% [glomerular 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 results[128] 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 death[129] 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 5[127] 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 transfemoral 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 (CAN-VAS)[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 point[135]: 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 ≥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 reports 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.

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Disclosures

Dr Jankowski has given lectures for Bayer and Fresenius Medica Care. In addition, he holds 4 patents on the topic of the article and is the inventor of an additional, already sold patent to Baxter. Dr Floege has received consultancy fees from Amgen, Bayer, Calliditas, Retrophin, Omeros, and Vifor-Fresenius. In addition, he serves on Data Safety Monitoring Boards of NovoNordisk and Visterra. Dr Fliser has given lectures for Amgen, Boehringer Ingelheim, AstraZeneca, and Vifor and has served as an advisor for Amgen, Astellas, Boehringer Ingelheim, AstraZeneca, FMC, and Vifor. Dr Böhm reports fees for lectures and scientific advice from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Servier, and Vifor outside the submitted work. In addition, Dr Böhm served in trial leadership for Boehringer Ingelheim, AstraZeneca, Medtronic, and ReCor. Dr Marx has given lectures for Boehringer Ingelheim, Sanofi-Aventis, Merck Sharp & Dohm, Bristol Myers Squibb, AstraZeneca, Lilly, and NovoNordisk; has received unrestricted research grants from Boehringer Ingelheim; and has served as an advisor for Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, and NovoNordisk. In addition, Dr Marx served in trial leadership for Boehringer Ingelheim and NovoNordisk. Dr Marx declines all personal compensation from pharmaceutical or device companies.

REFERENCES

1. Bright R. Cases and observations, illustrative of renal disease, accompanied with the secretion of albuminous urine. *Guy's Hosp Trans.* 1836:338–379.
2. Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R, Hague N, New J, Farmer CK. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney Int.* 2007;72:92–99. doi: 10.1038/sj.ki.5002273
3. Thompson S, James M, Wiebe N, Hemmelgarn B, Manns B, Klarenbach S, Tonelli M; Alberta Kidney Disease Network. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol.* 2015;26:2504–2511. doi: 10.1681/ASN.2014070714
4. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet.* 2017;389:1238–1252. doi: 10.1016/S0140-6736(16)32064-5
5. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998;32(5 suppl 3):S112–S119. doi: 10.1053/ajkd.1998.v32.pm9820470
6. Vanholder R, Argilés A, Baurmeister U, Brunet P, Clark W, Cohen G, De Deyn PP, Deppisch R, Descamps-Latscha B, Henle T, et al. Uremic toxicity: present state of the art. *Int J Artif Organs.* 2001;24:695–725. doi: 10.1177/039139880102401004
7. Kuo IY, Chapman AB. Polycystins, ADPKD, and cardiovascular disease. *Kidney Int Rep.* 2020;5:396–406. doi: 10.1016/j.ekir.2019.12.007
8. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39:S1–266.
9. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2005;67:2089–2100. doi: 10.1111/j.1523-1755.2005.00365.x
10. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med.* 2003;139:137–147. doi: 10.7326/0003-4819-139-2-200307150-00013
11. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3:1–150. doi: 10.1038/kisup.2012.76
12. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Chapter 1: definition and classification of CKD. *Kidney Int Suppl (2011).* 2013;3:19–62. doi: 10.1038/kisup.2012.64
13. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT; Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet.* 2010;375:2073–2081. doi: 10.1016/S0140-6736(10)60674-5
14. Arnlöv J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, Benjamin EJ, D'Agostino RB, Vasan RS. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. *Circulation.* 2005;112:969–975. doi: 10.1161/CIRCULATIONAHA.105.538132
15. Mulè G, Castiglia A, Cusumano C, Scaduto E, Geraci G, Altieri D, Di Natale E, Cacciatore O, Cerasola G, Cottone S. Subclinical kidney damage in hypertensive patients: a renal window opened on the cardiovascular system. Focus on microalbuminuria. *Adv Exp Med Biol.* 2017;956:279–306. doi: 10.1007/5584_2016_85
16. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int.* 2011;80:17–28. doi: 10.1038/ki.2010.483
17. Eckardt KU, Coresh J, Devuyst O, Johnson RJ, Köttgen A, Levey AS, Levin A. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet.* 2013;382:158–169. doi: 10.1016/S0140-6736(13)60439-0
18. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FD. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS One.* 2016;11:e0158765. doi: 10.1371/journal.pone.0158765
19. International Society of Nephrology. ISN Global Health Atlas. 2019. Accessed February 25, 2021. https://www.theisn.org/initiatives/global-kidney-health-atlas
20. United States Renal Data System, Annual Data Report. 2018. Accessed February 25, 2021. https://wwwusrdsorg/2018/view/v2_01aspx
21. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW. Chronic kidney disease: global dimension and perspectives. *Lancet.* 2013;382:260–272. doi: 10.1016/S0140-6736(13)60687-X
22. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. *Nat Rev Nephrol.* 2016;12:73–81. doi: 10.1038/nrneph.2015.173
23. Ma I, Guo M, Muruve D, Benediktsson H, Naugler C. Sociodemographic associations with abnormal estimated glomerular filtration rate (eGFR) in a large Canadian city: a cross-sectional observation study. *BMC Nephrol.* 2018;19:198. doi: 10.1186/s12882-018-0991-5
24. Nissenson AR, Collins AJ, Hurley J, Petersen H, Pereira BJ, Steinberg EP. Opportunities for improving the care of patients with chronic renal insufficiency: current practice patterns. *J Am Soc Nephrol.* 2001;12:1713–1720.
25. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. *Adv Chronic Kidney Dis.* 2016;23:19–28. doi: 10.1053/j.ackd.2015.08.004

26. Mallappallil M, Friedman EA, Delano BG, McFarlane SI, Salifu MO. Chronic kidney disease in the elderly: evaluation and management. *Clin Pract (Lond).* 2014;11:525–535. doi: 10.2217/cpr.14.46

27. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol.* 2006;17:2034–2047. doi: 10.1681/ASN.2005101085

28. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet.* 2010;375:2073-81. doi: 10.1016/S0140-6736(10)60674-5

29. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, de Jong P, Gansevoort RT, van der Velde M, Matsushita K, et al; Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int.* 2011;79:1341–1352. doi: 10.1038/ki.2010.536

30. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet.* 2013;382:339–352. doi: 10.1016/S0140-6736(13)60595-4

31. Buglioni A, Burnett JC Jr. Pathophysiology and the cardiorenal connection in heart failure. Circulating hormones: biomarkers or mediators. *Clin Chim Acta.* 2015;443:3–8. doi: 10.1016/j.cca.2014.10.027

32. Briet M, Barhoumi T, Mian MO, Sierra C, Boutouyrie P, Davidman M, Bercovitch D, Nessim SJ, Frisch G, Paradis P, et al. Effects of recombinant human erythropoietin on resistance artery endothelial function in stage 4 chronic kidney disease. *J Am Heart Assoc.* 2013;2:e000128. doi: 10.1161/JAHA.113.000128

33. Onal EM, Sag AA, Sal O, Yerlikaya A, Afsar B, Kanbay M. Erythropoietin mediates brain-vascular-kidney crosstalk and may be a treatment target for pulmonary and resistant essential hypertension. *Clin Exp Hypertens.* 2017;39:197–209. doi: 10.1080/10641963.2016.1246565

34. Nasrallah R, Hassouneh R, Hébert RL. PGE2, kidney disease, and cardiovascular risk: beyond hypertension and diabetes. *J Am Soc Nephrol.* 2016;27:666–676. doi: 10.1681/ASN.2015050528

35. Tan K, Sethi SK. Biomarkers in cardiorenal syndromes. *Transl Res.* 2014;164:122–134. doi: 10.1016/j.trsl.2014.04.011

36. Sparks MA, Crowley SD, Gurley SB, Mirotsou M, Coffman TM. Classical renin-angiotensin system in kidney physiology. *Compr Physiol.* 2014;4:1201–1228. doi: 10.1002/cphy.c130040

37. Agharazii M, St-Louis R, Gautier-Bastien A, Ung RV, Mokas S, Larivière R, Richard DE. Inflammatory cytokines and reactive oxygen species as mediators of chronic kidney disease-related vascular calcification. *Am J Hypertens.* 2015;28:746–755. doi: 10.1093/ajh/hpu225

38. Fujii H, Goto S, Fukagawa M. Role of uremic toxins for kidney, cardiovascular, and bone dysfunction. *Toxins.* 2018;10:202–220. doi: 10.3390/toxins10050202

39. Ortiz A, Covic A, Fliser D, Fouque D, Goldsmith D, Kanbay M, Mallamaci F, Massy ZA, Rossignol P, Vanholder R, et al; Board of the EURECA-m Working Group of ERA-EDTA. Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure. *Lancet.* 2014;383:1831–1843. doi: 10.1016/S0140-6736(14)60384-6

40. Major RW, Cheng MRI, Grant RA, Shantikumar S, Xu G, Oozeerally I, Brunskill NJ, Gray LJ. Cardiovascular disease risk factors in chronic kidney disease: a systematic review and meta-analysis. *PLoS One.* 2018;13:e0192895. doi: 10.1371/journal.pone.0192895

41. Roehm B, Weiner DE. Blood pressure targets and kidney and cardiovascular disease: same data but discordant guidelines. *Curr Opin Nephrol Hypertens.* 2019;28:245–250. doi: 10.1097/MNH.0000000000000492

42. Zewinger S, Kleber ME, Rohrer L, Lehmann M, Triem S, Jennings RT, Petrakis I, Dressel A, Lepper PM, Scharnagl H, et al. Symmetric dimethylarginine, high-density lipoproteins and cardiovascular disease. *Eur Heart J.* 2017;38:1597–1607. doi: 10.1093/eurheartj/ehx118

43. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, et al; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358:2560–2572. doi: 10.1056/NEJMoa0802987

44. Ter Braake AD, Shanahan CM, de Baaij JHF. Magnesium counteracts vascular calcification: passive interference or active modulation? *Arterioscler Thromb Vasc Biol.* 2017;37:1431–1445. doi: 10.1161/ATVBAHA.117.309182

45. Salem S, Bruck H, Bahlmann FH, Peter M, Passlick-Deetjen J, Kretschmer A, Steppan S, Volsek M, Kribben A, Nierhaus M, et al. Relationship between magnesium and clinical biomarkers on inhibition of vascular calcification. *Am J Nephrol.* 2012;35:31–39. doi: 10.1159/000334742

46. Brandenburg VM, Reinartz S, Kaesler N, Krüger T, Dirrichs T, Kramann R, Peeters F, Floege J, Keszei A, Marx N, et al. Slower progress of aortic valve calcification with vitamin K supplementation: results from a prospective interventional proof-of-concept study. *Circulation.* 2017;135:2081–2083. doi: 10.1161/CIRCULATIONAHA.116.027011

47. Ridker PM, MacFadyen JG, Glynn RJ, Koenig W, Libby P, Everett BM, Lefkowitz M, Thuren T, Cornel JH. Inhibition of interleukin-1β by canakinumab and cardiovascular outcomes in patients with chronic kidney disease. *J Am Coll Cardiol.* 2018;71:2405–2414. doi: 10.1016/j.jacc.2018.03.490

48. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. 2016. Accessed February 25, 2021. https://kdigo.org/wp-con-tent/uploads/2016/10/KDIGO-2012-Blood-Pressure-Guideline-English.pdf

49. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837–1847. doi: 10.1161/01.cir.97.18.1837

50. Centers for Disease Control and Prevention. National Chronic Kidney Disease Fact Sheet, 2017. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2017.

51. Matsushita K, Kwak L, Ballew SH, Grams ME, Selvin E, Folsom AR, Coresh J, Tang W. Chronic kidney disease measures and the risk of abdominal aortic aneurysm. *Atherosclerosis.* 2018;279:107–113. doi: 10.1016/j.atherosclerosis.2018.08.043

52. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, Sarnak MJ. The Framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol.* 2007;50:217–224. doi: 10.1016/j.jacc.2007.03.037

53. Riddle MC. Effects of intensive glucose lowering in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Circulation.* 2010;122:844–846. doi: 10.1161/CIRCULATIONAHA.110.960138

54. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, et al; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med.* 2009;360:129–139. doi: 10.1056/NEJMoa0808431

55. Maini R, Wong DB, Addison D, Chiang E, Weisbord SD, Jneid H. Persistent underrepresentation of kidney disease in randomized, controlled trials of cardiovascular disease in the contemporary era. *J Am Soc Nephrol.* 2018;29:2782–2786. doi: 10.1681/ASN.2018070674

56. Shroff R, Speer T, Colin S, Charakida M, Zewinger S, Staels B, Chinetti-Gbaguidi G, Hettrich I, Rohrer L, O'Neill F, et al. HDL in children with CKD promotes endothelial dysfunction and an abnormal vascular phenotype. *J Am Soc Nephrol.* 2014;25:2658–2668. doi: 10.1681/ASN.2013111212

57. Brunet P, Gondouin B, Duval-Sabatier A, Dou L, Cerini C, Dignat-George F, Jourde-Chiche N, Argiles A, Burtey S. Does uremia cause vascular dysfunction? *Kidney Blood Press Res.* 2011;34:284–290. doi: 10.1159/000327131

58. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med.* 2000;342:1478–1483. doi: 10.1056/NEJM200005183422003

59. O'Neill WC, Lomashvili KA. Recent progress in the treatment of vascular calcification. *Kidney Int.* 2010;78:1232–1239. doi: 10.1038/ki.2010.334

60. Guérin AP, London GM, Marchais SJ, Metivier F. Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant.* 2000;15:1014–1021. doi: 10.1093/ndt/15.7.1014

61. London GM, Guerin AP. Influence of arterial pulse and reflected waves on blood pressure and cardiac function. *Am Heart J.* 1999;138(3 pt 2):220–224. doi: 10.1016/s0002-8703(99)70313-3

62. Gauthier-Bastien A, Ung RV, Larivière R, Mac-Way F, Lebel M, Agharazii M. Vascular remodeling and media calcification increases arterial stiffness in chronic kidney disease. *Clin Exp Hypertens.* 2014;36:173–180. doi: 10.3109/10641963.2013.804541

63. Shetty M, Chowdhury Y, Yegneswaran B. Calcific uremic arteriolopathy. *Cleve Clin J Med.* 2018;85:584–585. doi: 10.3949/ccjm.85a.18009

64. Brandenburg VM, Evenepoel P, Floege J, Goldsmith D, Kramann R, Massy Z, Mazzaferro S, Schurgers LJ, Sinha S, Torregrosa V, et al; ERA-EDTA Working Group on CKD-MBD and EUCALNET. Lack of evidence does not justify neglect: how can we address unmet medical needs in calciphylaxis? *Nephrol Dial Transplant.* 2016;31:1211–1219. doi: 10.1093/ndt/gfw025

65. Shaker JL, Deftos L. Calcium and Phosphate Homeostasis. 2018 Jan 19. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dungan K,

Grossman A, Hershman JM, Hofland J, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Purnell J, Singer F, Stratakis, CA, Trence DL, Wilson DP, eds. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–.

66. Ellis CL, O'Neill WC. Questionable specificity of histologic findings in calcific uremic arteriolopathy. *Kidney Int.* 2018;94:390–395. doi: 10.1016/j.kint.2018.03.016

67. Shobeiri N, Pang J, Adams MA, Holden RM. Cardiovascular disease in an adenine-induced model of chronic kidney disease: the temporal link between vascular calcification and haemodynamic consequences. *J Hypertens.* 2013;31:160–168. doi: 10.1097/HJH.0b013e32835b15bb

68. Raggi P. Cardiovascular disease: coronary artery calcification predicts risk of CVD in patients with CKD. *Nat Rev Nephrol.* 2017;13:324–326. doi: 10.1038/nrneph.2017.61

69. De Vriese AS, Caluwé R, Pyfferoen L, De Bacquer D, De Boeck K, Delanote J, De Surgeloose D, Van Hoenacker P, Van Vlem B, Verbeke F. Multicenter randomized controlled trial of vitamin K antagonist replacement by rivaroxaban with or without vitamin K2 in hemodialysis patients with atrial fibrillation: the Valkyrie Study. *J Am Soc Nephrol.* 2020;31:186–196. doi: 10.1681/ASN.2019060579

70. Floege J. Magnesium in CKD: more than a calcification inhibitor? *J Nephrol.* 2015;28:269–277. doi: 10.1007/s40620-014-0140-6

71. Dhondup T, Qian Q. Electrolyte and acid-base disorders in chronic kidney disease and end-stage kidney failure. *Blood Purif.* 2017;43:179–188. doi: 10.1159/000452725

72. Sakaguchi Y, Hamano T, Obi Y, Monden C, Oka T, Yamaguchi S, Matsui I, Hashimoto N, Matsumoto A, Shimada K, et al. A randomized trial of magnesium oxide and oral carbon adsorbent for coronary artery calcification in predialysis CKD. *J Am Soc Nephrol.* 2019;30:1073–1085. doi: 10.1681/ASN.2018111150

73. Zoccali C, Vanholder R, Massy ZA, Ortiz A, Sarafidis P, Dekker FW, Fliser D, Fouque D, Heine GH, Jager KJ, et al; European Renal and Cardiovascular Medicine (EURECA-m) Working Group of the European Renal Association – European Dialysis Transplantation Association (ERA-EDTA). The systemic nature of CKD. *Nat Rev Nephrol.* 2017;13:344–358. doi: 10.1038/nrneph.2017.52

74. Amdur RL, Feldman HI, Dominic EA, Anderson AH, Beddhu S, Rahman M, Wolf M, Reilly M, Ojo A, Townsend RR, et al; CRIC Study Investigators. Use of measures of inflammation and kidney function for prediction of atherosclerotic vascular disease events and death in patients with CKD: findings from the CRIC Study. *Am J Kidney Dis.* 2019;73:344–353. doi: 10.1053/j.ajkd.2018.09.012

75. Kielstein JT, Veldink H, Martens-Lobenhoffer J, Haller H, Perthel R, Lovric S, Lichtinghagen R, Kliem V, Bode-Böger SM. Unilateral nephrectomy causes an abrupt increase in inflammatory mediators and a simultaneous decrease in plasma ADMA: a study in living kidney donors. *Am J Physiol Renal Physiol.* 2011;301:F1042–F1046. doi: 10.1152/ajprenal.00640.2010

76. Alhaj E, Alhaj N, Rahman I, Niazi TO, Berkowitz R, Klapholz M. Uremic cardiomyopathy: an underdiagnosed disease. *Congest Heart Fail.* 2013;19:E40–E45. doi: 10.1111/chf.12030

77. Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. *Clin J Am Soc Nephrol.* 2009;(4 suppl 1):S79–S91. doi: 10.2215/CJN.04860709

78. Di Lullo L, Gorini A, Russo D, Santoboni A, Ronco C. Left ventricular hypertrophy in chronic kidney disease patients: from pathophysiology to treatment. *Cardiorenal Med.* 2015;5:254–266. doi: 10.1159/000435838

79. Little WC. Heart failure with a normal left ventricular ejection fraction: diastolic heart failure. *Trans Am Clin Climatol Assoc.* 2008;119:93–99; discussion 99.

80. Segall L, Nistor I, Covic A. Heart failure in patients with chronic kidney disease: a systematic integrative review. *Biomed Res Int.* 2014;2014:937398. doi: 10.1155/2014/937398

81. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, et al; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2017;38:2739–2791. doi: 10.1093/eurheartj/ehx391

82. Wang Z, Jiang A, Wei F, Chen H. Cardiac valve calcification and risk of cardiovascular or all-cause mortality in dialysis patients: a meta-analysis. *BMC Cardiovasc Disord.* 2018;18:12. doi: 10.1186/s12872-018-0747-y

83. Abd Alamir M, Radulescu V, Goyfman M, Mohler ER III, Gao YL, Budoff MJ; CRIC Study Investigators. Prevalence and correlates of mitral annular calcification in adults with chronic kidney disease: results from CRIC study. *Atherosclerosis.* 2015;242:117–122. doi: 10.1016/j.atherosclerosis.2015.07.013

84. Rong S, Qiu X, Jin X, Shang M, Huang Y, Tang Z, Yuan W. Risk factors for heart valve calcification in chronic kidney disease. *Medicine (Baltimore).* 2018;97:e9804. doi: 10.1097/MD.0000000000009804

85. Urena-Torres P, D'Marco L, Raggi P, Garcia-Moll X, Brandenburg V, Mazzaferro S, Lieber A, Guirado L, Bover J. Valvular heart disease and calcification in CKD: more common than appreciated. *Nephrol Dial Transplant.* 2019;1:1-8.

86. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J.* 2018;39:3021–3104. doi: 10.1093/eurheartj/ehy339

87. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, et al; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet.* 2011;377:2181–2192. doi: 10.1016/S0140-6736(11)60739-3

88. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, et al; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet.* 2011;377:2181–2192. doi: 10.1016/S0140-6736(11)60739-3

89. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med.* 2005;353:238–248. doi: 10.1056/NEJMoa043545

90. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska et al; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med.* 2009;360:1395–1407. doi: 10.1056/NEJMoa0810177

91. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157:263–275. doi: 10.7326/0003-4819-157-4-201208210-00007

92. Palmer SC, Di Micco L, Razavian M, Craig JC, Perkovic V, Pellegrini F, Copetti M, Graziano G, Tognoni G, Jardine M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med.* 2012;156:445–459. doi: 10.7326/0003-4819-156-6-201203200-00007

93. Bangalore S, Maron DJ, O'Brien SM, Fleg JL, Kretov EI, Briguori C, Kaul U, Reynolds HR, Mazurek T, Sidhu MS, et al; ISCHEMIA-CKD Research Group. Management of coronary disease in patients with advanced kidney disease. *N Engl J Med.* 2020;382:1608–1618. doi: 10.1056/NEJMoa1915925

94. Spertus JA, Jones PG, Maron DJ, Mark DB, O'Brien SM, Fleg JL, Reynolds HR, Stone GW, Sidhu MS, Chaitman BR, et al; ISCHEMIA-CKD Research Group. Health status after invasive or conservative care in coronary and advanced kidney disease. *N Engl J Med.* 2020;382:1619–1628. doi: 10.1056/NEJMoa1916374

95. Washam JB, Herzog CA, Beitelshees AL, Cohen MG, Henry TD, Kapur NK, Mega JL, Menon V, Page RL II, Newby LK; American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, Council on Functional Genomics and Translational Biology, Council on the Kidney in Cardiovascular Disease, and Council on Quality of Care and Outcomes Research. Pharmacotherapy in chronic kidney disease patients presenting with acute coronary syndrome: a scientific statement from the American Heart Association. *Circulation.* 2015;131:1123–1149. doi: 10.1161/CIR.0000000000000183

96. Edner M, Benson L, Dahlström U, Lund LH. Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study. *Eur Heart J.* 2015;36:2318–2326. doi: 10.1093/eurheartj/ehv268

97. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med.* 1996;334:1349–1355. doi: 10.1056/NEJM199605233342101

98. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Rydén L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor,

STATE OF THE ART

lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation.* 1999;100:2312–2318. doi: 10.1161/01.cir.100.23.2312

99. Packer M, Miller AB. Can physicians always explain the results of clinical trials? A case study of amlodipine in heart failure. *Am J Cardiol.* 1999;84:1L–2L. doi: 10.1016/s0002-9149(99)00358-6

100. Badve SV, Roberts MA, Hawley CM, Cass A, Garg AX, Krum H, Tonkin A, Perkovic V. Effects of beta-adrenergic antagonists in patients with chronic kidney disease: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011;58:1152–1161. doi: 10.1016/j.jacc.2011.04.041

101. Kotecha D, Gill SK, Flather MD, Holmes J, Packer M, Rosano G, Böhm M, McMurray JJV, Wikstrand J, Anker SD, et al; Beta-Blockers in Heart Failure Collaborative Group. Impact of renal impairment on beta-blocker efficacy in patients with heart failure. *J Am Coll Cardiol.* 2019;74:2893–2904. doi: 10.1016/j.jacc.2019.09.059

102. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med.* 2011;364:11–21. doi: 10.1056/NEJMoa1009492

103. Matsumoto Y, Mori Y, Kageyama S, Arihara K, Sugiyama T, Ohmura H, Yakushigawa T, Sugiyama H, Shimada Y, Nojima Y, Shio N. Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. *J Am Coll Cardiol.* 2014;63:528–536. doi: 10.1016/j.jacc.2013.09.056

104. Charytan DM, Himmelfarb J, Ikizler TA, Raj DS, Hsu JY, Landis JR, Anderson AH, Hung AM, Mehrotra R, Sharma S, et al; Hemodialysis Novel Therapies Consortium. Safety and cardiovascular efficacy of spironolactone in dialysis-dependent ESRD (SPin-D): a randomized, placebo-controlled, multiple dosage trial. *Kidney Int.* 2019;95:973–982. doi: 10.1016/j.kint.2018.08.034

105. Hammer F, Malzahn U, Donhauser J, Betz C, Schneider MP, Grupp C, Pollak N, Störk S, Wanner C, Krane V; MiREnDa Study Group. A randomized controlled trial of the effect of spironolactone on left ventricular mass in hemodialysis patients. *Kidney Int.* 2019;95:983–991. doi: 10.1016/j.kint.2018.11.025

106. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371:993–1004. doi: 10.1056/NEJMoa1409077

107. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376:875–885. doi: 10.1016/S0140-6736(10)61198-1

108. Voors AA, van Veldhuisen DJ, Robertson M, Ford I, Borer JS, Böhm M, Komajda M, Swedberg K, Tavazzi L; SHIFT investigators. The effect of heart rate reduction with ivabradine on renal function in patients with chronic heart failure: an analysis from SHIFT. *Eur J Heart Fail.* 2014;16:426–434. doi: 10.1002/ejhf.59

109. Ferro CJ, Mark PB, Kanbay M, Sarafidis P, Heine GH, Rossignol P, Massy ZA, Mallamaci F, Valdivielso JM, Malyszko J, et al. Lipid management in patients with chronic kidney disease. *Nat Rev Nephrol.* 2018;14:727–749. doi: 10.1038/s41581-018-0072-9

110. Genovesi S, Boriani G, Covic A, Vernooij RWM, Combe C, Burlacu A, Davenport A, Kanbay M, Kirmizis D, Schnedetz D, et al. Sudden cardiac death in dialysis patients: different causes and management strategies. *Nephrol Dial Transplant.* 2019;1:1–10. doi: 10.1093/ndt/gfz182

111. Basso C, Corrado D, Marcus FI, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. *Lancet.* 2009;373:1289–1300. doi: 10.1016/S0140-6736(09)60256-7

112. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation.* 2010;121:1533–1541. doi: 10.1161/CIRCULATIONAHA.108.840827

113. Green D, Roberts PR, New DI, Kalra PA. Sudden cardiac death in hemodialysis patients: an in-depth review. *Am J Kidney Dis.* 2011;57:921–929. doi: 10.1053/j.ajkd.2011.02.376

114. Bleyer AJ, Hartman J, Brannon PC, Reeves-Daniel A, Satko SG, Russell G. Characteristics of sudden death in hemodialysis patients. *Kidney Int.* 2006;69:2268–2273. doi: 10.1038/sj.ki.5000446

115. Cheema A, Singh T, Kanwar M, Chilukuri K, Maria V, Saleem F, Johnson K, Frank J, Pires L, Hassan S. Chronic kidney disease and mortality in implantable cardioverter-defibrillator recipients. *Cardiol Res Pract.* 2010;2010:989261.

116. Bleyer AJ, Russell GB, Satko SG. Sudden and cardiac death rates in hemodialysis patients. *Kidney Int.* 1999;55:1553–1559. doi: 10.1046/j.1523-1755.1999.00391.x

117. Perl J, Chan CT. Timing of sudden death relative to the hemodialysis procedure. *Nat Clin Pract Nephrol.* 2006;2:668–669. doi: 10.1038/ncpneph0345

118. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ; DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med.* 2004;351:2481–2488. doi: 10.1056/NEJMoa041489

119. Korantzopoulos P, Liu T, Li L, Goudevenos JA, Li G. Implantable cardioverter defibrillator therapy in chronic kidney disease: a meta-analysis. *Europace.* 2009;11:1469–1475. doi: 10.1093/europace/eup282

120. Herzog CA, Ma JZ, Collins AJ. Long-term survival of dialysis patients in the United States with prosthetic heart valves: should ACC/AHA practice guidelines on valve selection be modified? *Circulation.* 2002;105:1336–1341. doi: 10.1161/hc1102.100075

121. Fernando M, Paterson HS, Byth K, Robinson BM, Wolfenden H, Gracey D, Harris D. Outcomes of cardiac surgery in chronic kidney disease. *J Thorac Cardiovasc Surg.* 2014;148:2167–2173. doi: 10.1016/j.jtcvs.2013.12.064

122. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, Pilgrim T, Petrinic T, Nikolakopoulou A, Salanti G, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. *Eur Heart J.* 2019;40:3143–3153. doi: 10.1093/eurheartj/ehz275

123. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, et al; PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med.* 2019;380:1695–1705. doi: 10.1056/NEJMoa1814052

124. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med.* 2019;380:1706–1715. doi: 10.1056/NEJMoa1816885

125. Patel KK, Shah SY, Arrigain S, Jolly S, Schold JD, Navaneethan SD, Griffin BP, Nally JV, Desai MY. Characteristics and outcomes of patients with aortic stenosis and chronic kidney disease. *J Am Heart Assoc.* 2019;8:e009980. doi: 10.1161/JAHA.118.009980

126. Makki N, Lilly SM. Advanced chronic kidney disease: relationship to outcomes post-TAVR, a meta-analysis. *Clin Cardiol.* 2018;41:1091–1096. doi: 10.1002/clc.22993

127. Doshi R, Shlofmitz E, Shah J, Meraj P. Comparison of transcatheter mitral valve repair versus surgical mitral valve repair in patients with advanced kidney disease (from the National Inpatient Sample). *Am J Cardiol.* 2018;121:762–767. doi: 10.1016/j.amjcard.2017.12.015

128. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, et al; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med.* 2018;379:2307–2318. doi: 10.1056/NEJMoa1806640

129. Taramasso M, Pozzoli A, Guidotti A, Nietlispach F, Inderbitzin DT, Benussi S, Alfieri O, Maisano F. Percutaneous tricuspid valve therapies: the new frontier. *Eur Heart J.* 2017;38:639–647. doi: 10.1093/eurheartj/ehv766

130. Shah B, Vemulapalli S, Manandhar P, Amoroso N, Ruiz-Maya T, Staniloae C, Saric M, Williams M. Comparison after transcatheter mitral valve repair in patients with chronic kidney disease: an analysis of 5,241 patients in the United States. *J Am Coll Cardiol.* 2018;71:A1980.

131. Carubelli V, Metra M, Lund LH. Negotiating renal dysfunction when treating patients with heart failure. *Expert Rev Cardiovasc Ther.* 2018;16:113–122. doi: 10.1080/14779072.2018.1422178

132. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720

133. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377:644–657. doi: 10.1056/NEJMoa1611925

134. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380:347–357. doi: 10.1056/NEJMoa1812389

135. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380:2295–2306. doi: 10.1056/NEJMoa1811744

136. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, et al; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383:1436–1446. doi: 10.1056/NEJMoa2024816

137. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381:1995–2008. doi: 10.1056/NEJMoa1911303

138. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, et al; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;383:1413–1424. doi: 10.1056/NEJMoa2022190

139. Lan NSR, Fegan PG, Yeap BB, Dwivedi G. The effects of sodium-glucose cotransporter 2 inhibitors on left ventricular function: current evidence and future directions. *ESC Heart Fail.* 2019;6:927–935. doi: 10.1002/ehf2.12505

140. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia.* 2018;61:2108–2117. doi: 10.1007/s00125-018-4670-7

141. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, Nowack C, Kolkhof P, Kim SY, Zannad F. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur Heart J.* 2013;34:2453–2463. doi: 10.1093/eurheartj/eht187

142. Bakris GL, Agarwal R, Chan JC, Cooper ME, Gansevoort RT, Haller H, Remuzzi G, Rossing P, Schmieder RE, Nowack C, et al; Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA.* 2015;314:884–894. doi: 10.1001/jama.2015.10081