# Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options

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## BRIEF SUMMARY

This review summarizes the current understanding and clinical consequences of cardiovascular disease in patients with chronic kidney disease.


## ABSTRACT

Patients with chronic kidney disease (CKD) exhibit an elevated cardiovascular risk manifesting as coronary artery disease, heart failure, arrhythmias and sudden cardiac death. While the incidence and prevalence of cardiovascular events is already significantly higher in patients with early CKD stages (CKD stages 1-3) compared to the general population, patients with advanced CKD stages (CKD stages 4-5) exhibit a markedly elevated risk. Importantly, 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 pro-inflammatory 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 ageing of the cardiovascular system.

This overview article summarizes the current understanding and clinical consequences of cardiovascular disease in CKD.


**Keywords:** cardiovascular disease, heart failure, chronic kidney disease, arrhythmias, sudden cardiac death, clinical aspects

### Non-standard abbreviations and acronyms

| | |
|---|---|
| 4D | Deutsche diabetes dialysis Study trial |
| ACCORD | Action to control cardiovascular risk in diabetes trial |
| ADVANCE | Action in diabetes and vascular disease: preterax and diamicron modified release-controlled evaluation trial |
| ALCHEMIST | Aldosterone antagonist chronic hemodialysis interventional survival trial) |
| ARB | Angiotensin1-receptor blockers |
| ARIC | Atherosclerosis risk in communities trial |
| ARNI | Angiotensin receptor/neprilysin inhibitor |
| ARTS-DN | Mineralocorticoid receptor antagonist tolerability diabetic nephropathy study |
| AURORA | A study to evaluate the use of rosuvastatin in subjects on regular hemodialysis: an assessment of survival and cardiovascular events trial |

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|---|---|
| BNP | B-type natriuretic peptide |
| CANTOS | Canakinumab Antiinflammatory Thrombosis Outcome Study trial |
| CHS | Cardiovascular health study trial |
| CKD | Chronic kidney disease |
| CVD | Cardiovascular disease |
| DOHAS | Dialysis outcomes heart failure aldactone study |
| EF | Ejection fraction |
| eGFR | Estimated Glomerular filtration rate |
| EMPA REG OUTCOME | Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients-removing excess glucose |
| ESRD | End-stage renal disease |
| FIDELIO | Finerenone in reducing kidney failure and disease progression in diabetic kidney disease trial |
| FIGARO | Efficacy and safety of finerenone in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease |
| GFR | Glomerular filtration rate |
| GLP-1 | Glucagon-like peptide 1 |
| HbA1c | Hemoglobin A1c |
| HDL | Low high-density lipoprotein |
| HFmrEF | Heart failure and moderately impaired left-ventricular function |
| HFpEF | Heart failure and preserved ejection fraction |
| HFrEF | Heart failure and symptomatically reduced ejection fraction |
| ICD | Implantable cardioverter-defibrillator |
| ISCHEMIA-CKD | International study of comparative health effectiveness with medical and Invasive approaches–chronic kidney disease |
| KDIGO | Kidney Disease Improving Global Outcomes |
| KDOQI | Kidney Disease Outcomes Quality Initiative |
| LDL | Low-density lipoproteins |
| LVH | Left ventricular hypertrophy |
| MRA | Mineralocorticoid receptor antagonist |
| mTOR | Mechanistic target of rapamycin |
| NKF | National Kidney Foundation |
| nsMRA | Nonsteroidal mineralocorticoid receptor antagonist |
| NYHA | New York Heart Association |
| PPAR | Peroxisome proliferator-activated receptor |
| RAS | Renin-angiotensin-system |
| SDMA | Symmetric dimethylarginine |
| SGLT2 | Sodium-glucose cotransporter 2 |
| SHARP | Study of heart and renal protection trial |
| STS | Society of Thoracic Surgeons |
| TAVI | Transcatheter aortic valve implantation |
| VADT | Veterans affairs diabetes trial |

## 1. INTRODUCTION

Dr. 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 4-5 suffer from CVD [2], and cardiovascular mortality accounts for ~40-50% of all deaths in patients with advanced CKD (stage 4) as well as end-stage kidney disease (stage 5), compared to 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 and fatal arrhythmias, particularly in advanced CKD stages. In more than 70 studies in non-dialyzed subjects with CKD, correction for classical and even less classical cardiovascular risk factors, such as hypertension, diabetes mellitus, and dyslipidemia did not neutralize the impact of CKD on cardiovascular risk [6]. This review summarizes the current knowledge of CVD in CKD patients, clinical consequences as well as treatment options of CVD in CKD (**Figure 2**). Given space limitations, we will not cover special situations, for example, 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].

## 2. EPIDEMIOLOGY AND PROGNOSIS

The definition and classification of CKD was introduced by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002 [8], and the international guideline group Kidney Disease Improving Global Outcomes (KDIGO) 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 (GFR) <60 mL/min/1.73 $m^2$ that have been present for more than 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**). Since there is an increasing evidence indicating a continuous relationship between albuminuria and cardiorenal risk in the renal and non-renal population [13, 14], albuminuria considered a prognostic marker for CV 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 three million patients are receiving kidney replacement therapy for CKD stage 5D worldwide out of 10 million that would qualify for kidney replacement therapy; these numbers are expected to grow by 50-100% until 2030 [19, 20] (**Figure 4**). Reasons for the increasing incidence and prevalence of advanced CKD, amongst others, include ageing populations, increasing prevalence of type 2 diabetes mellitus and hypertension [22], as well as low detection rate and therapeutic inertia in 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 to 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 non-dialysis-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 more than 1.4 million individuals [28, 29] yielded an association of not only low estimated GFR (eGFR) but also raised 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 as one of the strongest risk factors for the development of CVD [27].

## 3. PATHOPHYSIOLOGY OF CVD IN CKD

In general, in addition to traditional risk factors, two 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 lead to characteristic changes in the vasculature, while on the other hand, CKD-associated mediators as well as hemodynamic alterations contribute to cardiac damage [38] as discussed in the following chapters.

### 3.1.1. 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 mellitus, dyslipidemia, and smoking not only contribute to atherosclerotic cardiovascular and cerebrovascular sequelae (**Table 1**), but also to CKD progression due to their effect on large (e.g. kidney artery stenosis) and smaller (e.g. 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 CV 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, but the optimal target blood pressure in patients with CKD has not yet been established [41].

*Diabetes mellitus*

Hyperglycemia is strongly associated with both, the development of CKD and as well as CVD. However, improvement in glycemic control in type 2 diabetes mainly contributes to a reduction in microvascular events such as nephropathy while various studies failed to show a significant effect on macrovascular events; for example the ADVANCE ("Action in diabetes and vascular disease: preterax and diamicron modified release controlled evaluation") trial demonstrated in approximately 11,000 patients with type 2 diabetes that intensive glucose control compared to 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 on macrovascular events [43]; the "Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [53] was not able to demonstrate that treatment targeting nearly normal glycaemic control reduces the risk of cardiovascular events in approximately 10,000 type 2 diabetes mellitus patients 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 the "Veterans Affairs Diabetes Trial" (VADT)[54] including 1.791 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 2006-2014 were less likely to exclude patients with CKD

than those between 1985–2005 (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 lipoproteins (LDL) 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 mellitus, and dyslipidemia were not yet present [56]. Several factors modify the composition of the HDL particle in CKD, including uremic toxins, increased oxidative stress as well as the pro-inflammatory micro-environment. These factors contribute to a pronounced remodeling of HDL particles, altering the proteome and lipidome composition of HDL and inducing post-translational modifications of HDL's protein cargo. Furthermore, the accumulation of uremic toxins such as symmetric dimethylarginine (SDMA) in advancing CKD plays a key role in the functional changes of HDL[42].

Finally, increased albuminuria or proteinuria is a potent risk factor for CVD in both diabetic and non-diabetic CKD patients (**Figure 3**) and the incidence of cardiovascular events decreases with the institution of antiproteinuric measures, in particular 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].

### 3.1.2. Non-traditional 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 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 CKD patients compared with those without CKD [59]. In addition to CKD, several common comorbidities, in particular diabetes mellitus, 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 heart failure [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 very 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 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 heralds a poor prognosis [68]. However, 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 CKD patients [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 due to 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 CKD patients, 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]. Pro-inflammatory circulatory mediators progressively increase as kidney function declines[75]. Pro-inflammatory 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, as well as epigenetic factors[73].

In accordance, the CANTOS trial ("Canakinumab Antiinflammatory Thrombosis Outcome Study") focusing on approximately 10,000 stable post-myocardial infarction patients with high-sensitivity C-reactive protein demonstrated a benefit of inhibition of pro-inflammatory effector molecule interleukin-1ß (IL-1ß) with the antibody canakinumab, which was larger in patients with eGFR <60 ml/min/1.73m² than in those with eGFR >60ml/min/1.73 m² [47] (**Figure 6**). However, further studies are needed to firmly establish the pathophysiological mechanisms and potential treatment options for inflammation in patients with CKD.

### 3.2. 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 being the hallmarks of uremic cardiomyopathy [76]. LVH is present in about 1/3 of all patients with CKD, increasing up to 70-80% in patients with end-stage kidney disease. The presence of LVH is an 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: (a) afterload- and (b) preload-related factors as well as (c) non-afterload, non-preload-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, results in an eccentric hypertrophy and subsequent left ventricular dilatation, systolic dysfunction and reduced ejection fraction [79]. Pre-load-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 asymmetric left ventricular remodeling [78]. Non-afterload, non-preload-related factors include intracellular mediators and pathways contributing to progressive LVH [80]. Essential mechanisms in this context are activation of peroxisome proliferator-activated receptors (PPARs), stimulation of small G-proteins or the mechanistic target of rapamycin (mTOR) 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 1-3 are associated with enhanced calcifications of valves and coronary arteries [83]. Heart valve calcification occurs in stage 5 CKD in up to 88-99% of patients, increasing from 40% of patients in CKD stage 3 [84] and the final destruction of valves occurs at a ten-fold higher rate in patients with CKD compared to patients without CKD. Valvular disease in patients with CKD is accelerated by comorbidities like diabetes, arterial hypertension, hyperlipidemia, anemia and ongoing infections of valves, malnutrition as well as hypercalcaemia, hyperphosphataemia and hyperparathyroidism [85].

## 4. THERAPY OF CARDIOVASCULAR DISEASE IN CKD

### 4.1. Treatment of vascular disease in patients with CKD

Control of traditional risk factors as well as antiplatelet therapy are cornerstones to reduce CV risk. As such, current guidelines recommend to lower systolic blood pressure to a range of 130–139 mmHg in patients with diabetic or non-diabetic CKD and RAAS inhibitors are first-line agents in CKD [86]. Given the only moderate effect of glucose control on macrovascular events, HbA1c targets should be individualized and side effects such as hypoglycemia should be avoided in particular in CKD since hypoglycemic episodes are associated with an increase in mortality in this group of patients. Notably, 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 CV risk. Thus, various guidelines recommend treatment with these agents in CKD and non-CKD patients with CVD and/or multiple CV 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 “Study of heart and renal protection” (SHARP) [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 endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularization [88]. In contrast, both the “Deutsche Diabetes Dialysis Study” (4D) [89] as well as the “A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events” (AURORA) failed to show a significant reduction of 3P-MACE (CV death, non-fatal MI, non-fatal stroke) by atorvastatin or rosuvastatin, respectively, versus placebo in patients with hemodialysis [90]. These data suggest that the CV benefit of lipid-lowering therapies is attenuated in subjects with low GFR and very limited / absent in ESRD patients on hemodialysis [91].

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

The ISCHEMIA-CKD trial assessed an invasive or conservative care approach in patients with stable CAD and CKD. 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 endpoint 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 so 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, ß-blockers, and antiplatelet therapy compared to 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].

### 4.2. Treatment of heart failure in patients with CKD

Current therapeutic options in heart failure patients are largely based on cardiovascular outcome trials, which assessed the effect of both medical as well as interventional therapy to reduce morbidity and mortality. However, patients with CKD have been excluded in most clinical heart failure 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 heart failure and preserved ejection fraction (HFpEF; LVEF≥50%) or moderately impaired left-ventricular function (HFmrEF; LVEF 40-49%) in CKD.

However, at the stage of symptomatically reduced ejection fraction (HFrEF; LVEF<40%), therapy with ACE inhibitors and beta-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 1-3 has been suggested, but few data are available in patients with advanced CKD stages. In the Swedish Cardiac Insufficiency Registry, a total of 2,410 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 (ARB) or ACE inhibitors. In patients with RAS inhibition, total mortality was significantly lower at one year compared to patients without RAS inhibition (HR 0.76, 95% CI 0.67-0.86) [96].

Based on large randomized studies showing a reduction in total mortality, beta-blockers are also recommended as first-line therapy in parallel to RAAS inhibitors to counteract sudden cardiac death and progression of heart failure in HFrEF patients [97-99]. A meta-analysis of intervention studies with beta-blockers in patients with CKD stage 3-5 clearly demonstrated that these patients benefit from this therapy [100], suggesting that beta-blockers are equally effective in patients with CKD as in non-CKD patients. Recent data underline the benefits of a beta-blocker therapy in CKD patients (CKD stages 3-4) with heart failure, left ventricular ejection fraction <50% and sinus rhythm [101]. If patients with HFrEF are still symptomatic despite treatment with ACE inhibitors and beta-blockers, and if the LVEF 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 HFrEF patients, and this therapy is effective in patients with heart failure and CKD stages 1-3 [102]. In the DOHAS study, 309 patients with CKD stage 5D were randomized to either 25 mg spironolactone per day or to standard of care only [103]. Compared to the control group, the combined primary endpoint of mortality and cardio- or cerebrovascular hospitalization was significantly reduced in the spironolactone group (HR 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 ejection fraction, 6-minute walk test distance, or NYHA class [105]. Since spironolactone increased the frequency of moderate - albeit not severe - hyperkalemia in patients with CKD stage 4-5 [104, 105], MRAs formally are still contraindicated in advanced CKD. The ongoing ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST trial) examines the effect of aldosterone on CV 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 NYHA II stage with fluid retention, and generally in NYHA III-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 ARB), beta-blockers and mineralocorticoid receptor antagonists (MRA) continue to be symptomatic and the ACE inhibitor (or ARB) was well tolerated, the administration of an angiotensin receptor/neprilysin inhibitor

(ARNI) 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 B-type natriuretic peptide (BNP); 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 to enalapril was demonstrated, and this effect was also seen in patients with CKD stages 3-5 [106]. Thus, ARNIs seem effective in patients with heart failure and CKD.

Therapy with the channel inhibitor ivabradine may be considered once maximally tolerated beta-blocker therapy is in place. The evidence for this recommendation is derived from the SHIFT trial, which showed a significant reduction in the combined primary endpoint in cardiovascular mortality or heat failure hospitalization compared to placebo in patients treated with ivabradine [107].The incidence of the primary endpoint was similar in both patients with (CKD stages 3-5) and without CKD [108].

### 4.1. Prevention of sudden cardiac death and arrhythmias in CKD

More than 2/3 of mortality in advanced CKD stages are due to sudden cardiac death [109, 110] (**Figure 6**). Sudden cardiac death refers to the unexpected natural death from a cardiac cause within one 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 1,000 patient-years in the CKD stage 5D population, while it is one death in 1,000 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, more than 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 to 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 of 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, non-

invasive 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 to drug therapies e.g. antiarrhythmic agents, implantable cardioverter-defibrillators (ICDs) lead to a significant reduction in mortality in cardiovascular patients as primary and secondary prevention, but CKD patients 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 ejection fraction 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.

### 4.2. Therapy of valve disease in CKD

Guideline recommendations for patients with CKD do not differ much from patients without CKD concerning 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 (STS) Score, EuroSCORE-II or logistic EuroSCORE have incorporated kidney function as one parameter [81]. In patients with low perioperative risk (EuroSCORE-II <4% or logEuroSCORE <10%), surgical aortic valve replacement is recommended.

Transcatheter aortic valve implantation (TAVI) is recommended as a safe and effective treatment option in patients <75 years at elevated operative risk (STS 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 to surgical aortic valve replacement, which was independent of the pre-operative risk before the intervention [122]. Recently published prospective randomized trials comparing TAVI and surgical aortic valve replacement in patients without CKD showed a superiority of interventional valve treatment compared to operative valve treatment [123, 124]. However, impaired kidney function affects mortality and risk for dialysis after TAVI [125]. Long-term risk for death and need for introduction of kidney replacement therapy was increased by 51% and 56% respectively [126]. Nevertheless, acute kidney injury post TAVI (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 due to cardiac decompensation in 2 years (hazard ratio 0.54, $p < 0.001$) and extensive reduction of all-cause death [129] compared to optimal medical treatment. CKD is associated with adverse outcomes in mitral valve interventions. In patients with CKD stage 1-2, mortality was 13%, at CKD stage 3 19% and CKD stage 4-5, 33% [130]. There was a slight improvement of kidney function by 4.8 ml/min/1,73 $m^2$ in CKD stage 4/5 [127] after valve replacement indicating that valve improvement and improvement in myocardial performance might impact on kidney function. This improvement was associated with decreased therapy cost and in-hospital treatment duration [127].

Since valve disease is a very common comorbidity in patients with CKD, after echocardiographic evaluation, the decision to treat valve disease with surgery or intervention should be based on 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.

**5. Novel therapeutic approaches**

Even though 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, multi centre 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 with empagliflozin in >7,000 cardiovascular type 2 diabetic patients, the primary endpoint 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 "heart failure-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 27-38% 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 = 4,400) with a combined primary kidney endpoint [135]: Within two and a half years, canagliflozin significantly reduced the risk of kidney replacement therapy, doubling serum creatinine and death due to kidney insufficiency by 33%. In addition, most recently, DAPA-CKD, a dedicated trial in patients with CKD (with or without T2DM) was published. In this placebo-controlled trial, dapagliflozin led to a significant reduction in the primary composite endpoint of sustained ≥50% eGFR decline, ESKD, renal or CV death as well as in CV death or 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. Based on the promising effects of SGLT2 inhibitors on HF-related endpoints, various CVOTs directly assess the efficacy of these agents in HF populations. DAPA-HF - 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 $m^2$. Dapagliflozin significantly reduced HF hospitalization, cardiovascular death and all-cause mortality in patients with and without diabetes [137]. In EMPEROR-reduced, a trial enrolling HFrEF patients with or without diabetes with an eGFR down to 20 ml/min/1.73 $m^2$, empagliflozin significantly reduced the composite endpoint of time to first event of adjudicated CV death or adjudicated HHF [138]. Potential mechanisms explaining the beneficial effects of SGLT2 inhibitors in patients with HF and/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].

Mineralocorticoid receptor antagonists (MRA) reduce the aldosterone-mediated proinflammatory effects that are involved in the fibrotic remodeling processes. The new selective nonsteroidal MRA (nsMRA) finerenone also blocks the damaging effects of the over-activated aldosterone system. In contrast to the MRA 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 to 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 with >450 patients with CKD and congestive heart failure, finerenone reduced the urinary albumin-creatinine ratio and NT-proBNP as potently as spironolactone with significantly lower rates of deteriorating kidney function and hyperkalemia[141]. Similarly, in the 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% GFR decrease, was similar to placebo. Study cessation due to hyperkalemia was very rare. In the phase III trials FIDELIO and FIGARO, over 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.

## 6. Conclusions

Patients with CKD suffer from high cardiovascular risk, with CV death being the leading cause of death. Several novel therapies to decrease the risk of cardiovascular diseases in CKD are in clinical development and/or have been already established raising the hope that CV 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 towards a more evidence-based approach to reduce CV risk in CKD.

## 7. Figure legends

**Figure 1:** Cardiovascular mortality in the general population and in patients with end stage kidney disease (adapted from [5]). In 25-34-year-old patients with end stage kidney disease, annual mortality is increased 500-1000-fold and corresponds to that of the about 85-year old general population.

**Figure 2:** Interaction of cardiovascular disease and chronic kidney disease. Various mediators and mechanisms in vascular disease, heart failure and CKD contribute to the progression of CV disease and influence the prognosis of patients.

**Figure 3:** Classification and prognosis of chronic kidney disease from 2012 KDIGO guidelines (adapted from [12]).

**Figure 4:** Annual incidence rates of end-stage kidney disease in different countries (adapted from [21]).

**Figure 5:** Independent association of kidney function with cardiovascular mortality (ACR=albumin-to-creatinine ratio) (adapted and modified from [30]).

**Figure 6:** Independent association of kidney function with cardiovascular mortality (ACR=albumin-to-creatinine ratio) (adapted and modified from [30]).

**Figure 7:** Cause-specific mortality according to varying levels of kidney dysfunction. For the three categories of kidney dysfunction, cause specific mortality is depicted. Sudden cardiac death was the major cause of death in ESRD patients on dialysis (50.0% versus 10.1% (GFR < 60 mL/min) versus 10.3% (GFR ≥ 60 mL/min), Chi Square P = .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 [115]).

**Table 1**: Traditional and non-traditional risk factors for CVD in CKD

| **Risk factors for CVD in CKD** | | **Specific aspects / treatment options compared to 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 | ---- | |
| | Hyperglycaemia | intensive glucose control beneficial to avoid microvascular complications | 43 |
| **Non-traditional** | Vascular calcifications | treatment of electrolyte imbalances with magnesium | 44, 45 |
| | | vitamin K administration might be beneficial | 46 |
| | Inflammation | inhibition of pro-inflammatory effector molecule interleukin-1ß (IL-1ß) with canakinumab after myocardial infarction | 47 |
| | Increased proteinuria | RAS-blockade | 48 |

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## Conflict of Interest

JJ has given lectures for Bayer and Fresenius Medica Care. In addition, he holds four patents in the topic of the manuscript and is inventor of an additional, already sold patent to Baxter. JF has received consultancy fees from Amgen, Bayer, Calliditas, Retrophin, Omeros, Vifor-Fresenius. In addition, he serves on Data Safety Monitoring Boards of NovoNordisk and Visterra. DF has given lectures for Amgen, Boehringer Ingelheim, Astra-Zeneca and Vifor, and has served as an advisor for Amgen, Astellas, Boehringer Ingelheim, Astra-Zeneca, FMC and Vifor. MB reports fees for lectures and scientifiic advice from Abbott, Amgen, AstraZene-ca, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Servier and Vifor outside the submitted work. In addition, MB served in trial leadership for Boehringer Ingelheim, Astra, Medtronic and ReCor. NM has given lectures for Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, Lilly, NovoNordisk; has received unrestricted research grants from Boehringer Ingelheim, and has served as an advisor for Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, NovoNordisk. In addition, served in trial leadership for Boehringer Ingelheim and NovoNordisk. NM declines all personal compensation from pharma or device companies.

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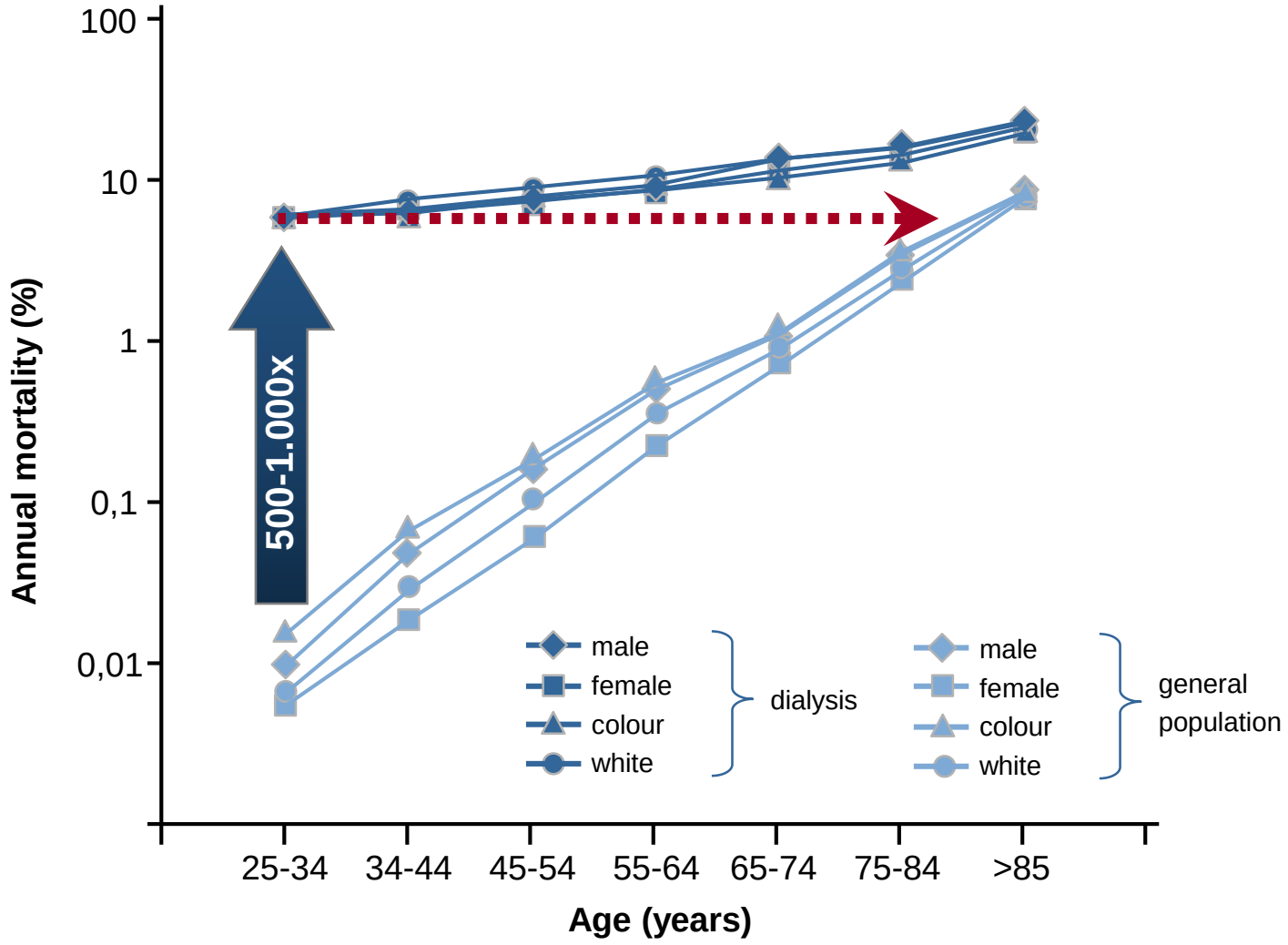
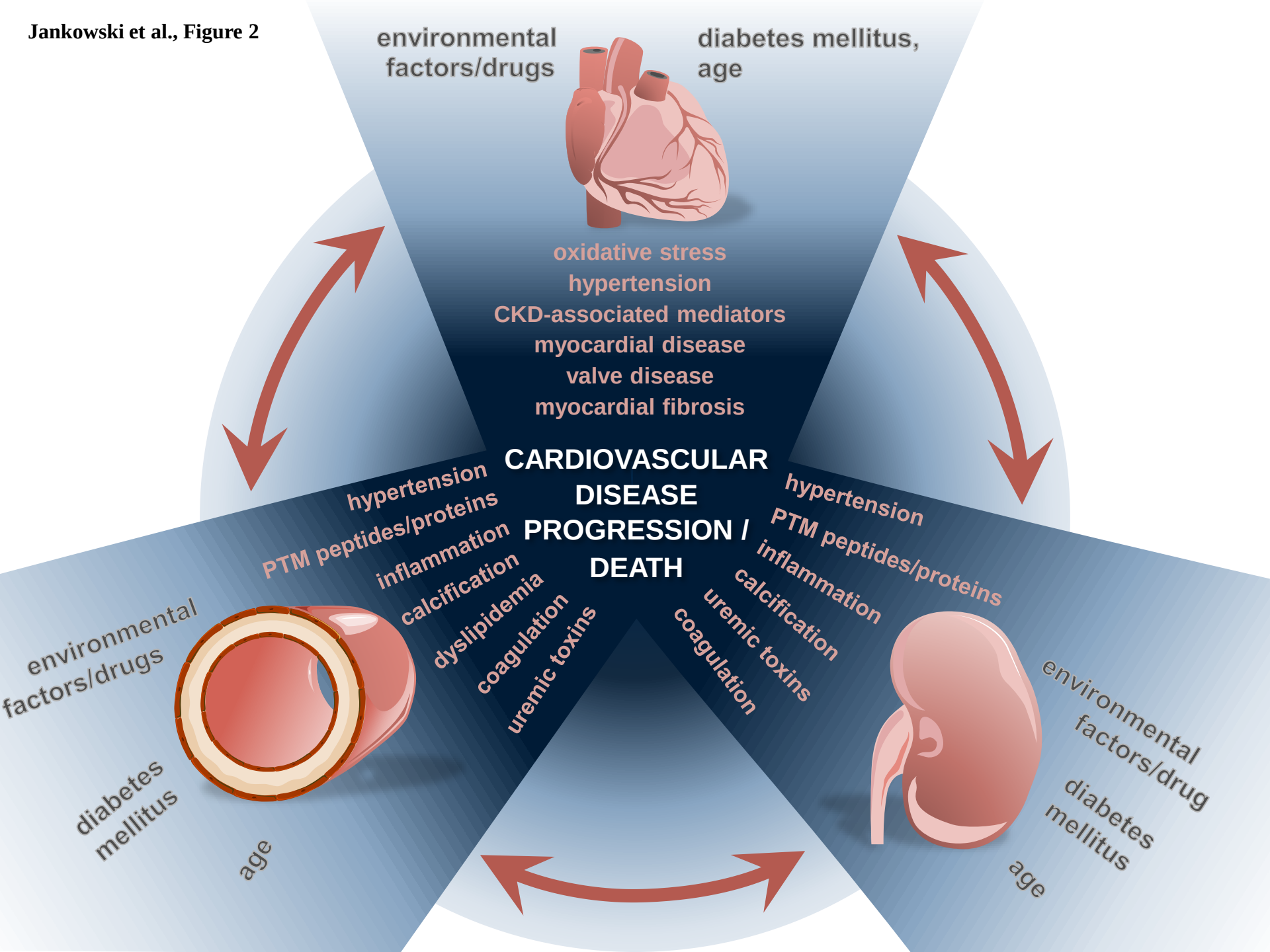
**Jankowski et al., Figure 1**



Jankowski et al., Figure 2



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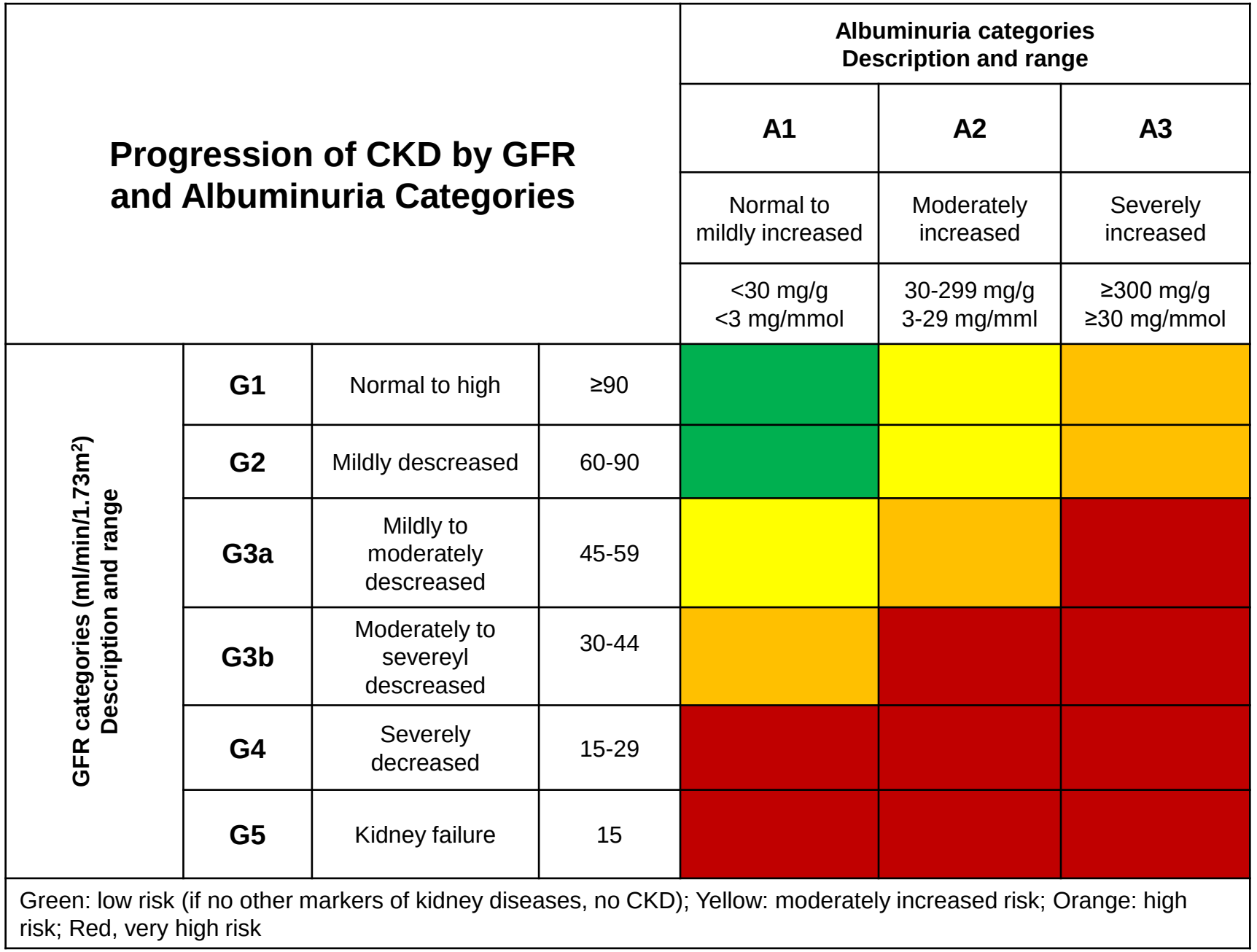

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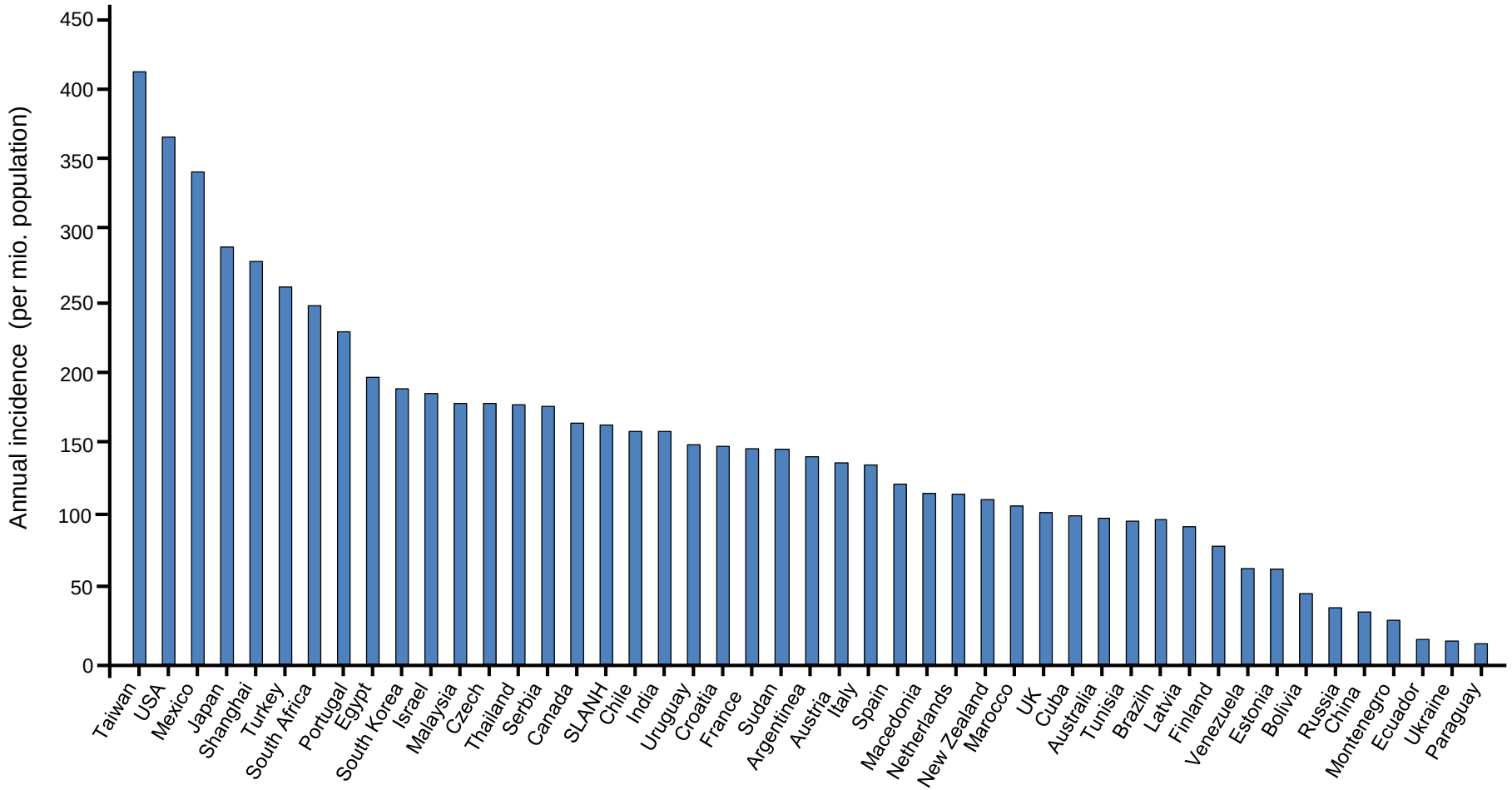

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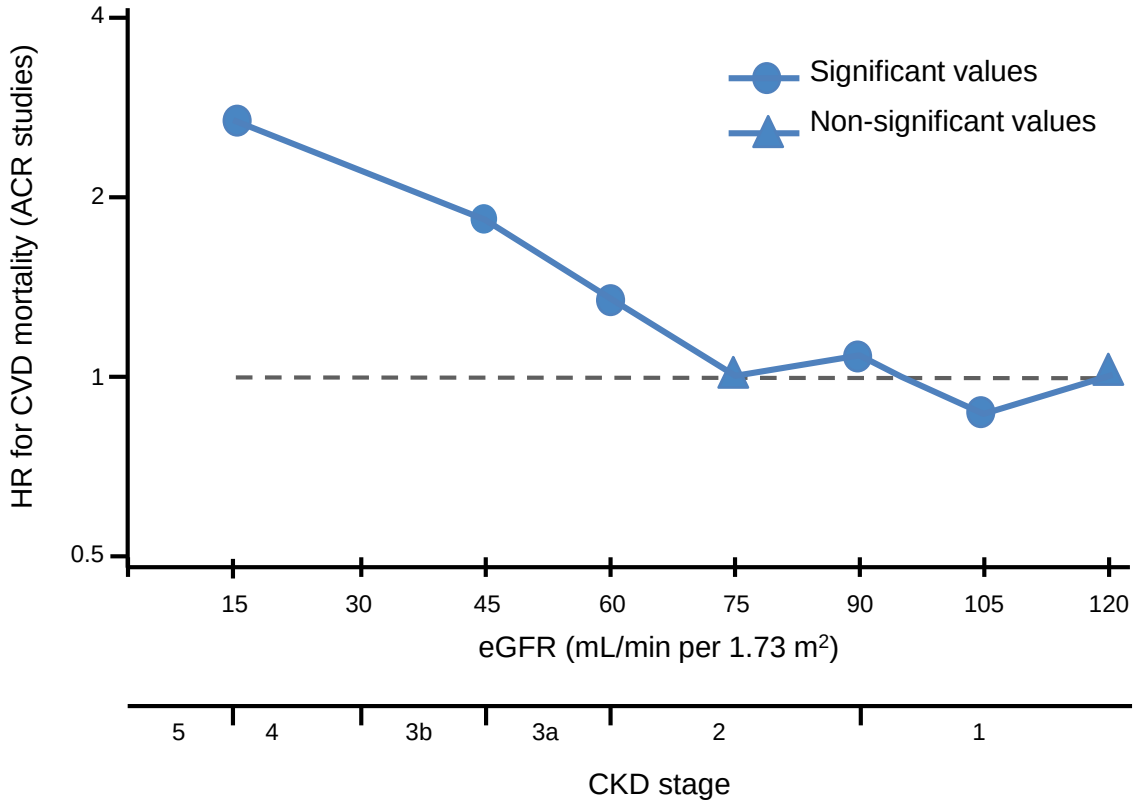

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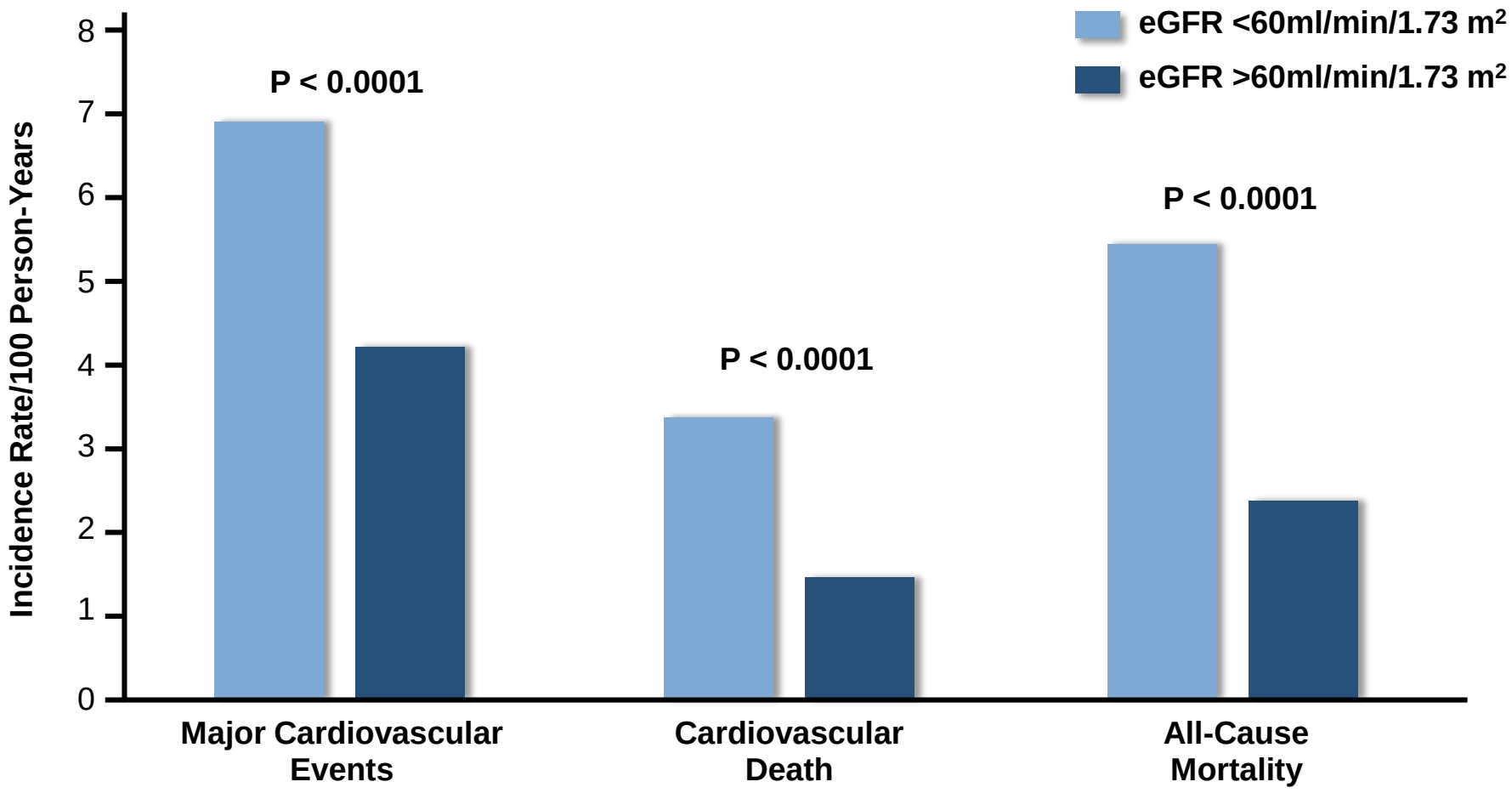

**Jankowski et al., Figure 7**