

# Reducing cardiovascular risk by treating chronic kidney dysfunction

## Prevention and treatment

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**Abstract-** Chronic kidney disease (CKD) is a complex public health issue with high incidence, prevalence, and expensive management. It is linked to increased cardiovascular events, such as heart attacks, strokes, heart failure, and death, due to the gradual decline in glomerular filtration rate (eGFR). To reduce the frequency of critical cardiovascular events, clinicians should focus on preventing renal function deterioration. Early detection and targeted therapy are crucial to prevent the illness from progressing to severe stages. Most CKD patients were treated for a long time by controlling risk factors like diabetes and hypertension, and using renin-angiotensin aldosterone system inhibitors. However, this approach was only partially successful due to the steady decline in renal function. Innovative antidiabetic medications, such as gliflozins and incretins, have been shown to reduce eGFR, reduction in CKD patients and significantly impact cardiovascular prognosis by lowering clinical incidents.

**Keywords:** Chronic kidney disease (CKD), glomerular filtration rate, renin-angiotensin aldosterone system inhibitors, gliflozins, incretins, cardiovascular prognosis.

### Abbreviations:

CKD – Chronic Kidney Disorder  
CV – Cardio Vascular  
GFR – Glomerular Filtration Rate  
CHS – Cardiovascular Health Study  
ARIC – Atherosclerosis Risk in Communities  
CAD – Coronary Artery Disease  
MI – Myocardial Infarction  
LVH – Left Ventricle Hypertrophy  
LV – Left Ventricle  
PCI – Percutaneous Coronary Intervention  
ACEI - Angiotensin-Converting Enzyme Inhibitor  
CABG - Coronary Artery Bypass Grafting  
COURAGE- Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation  
CHF - Concomitant Heart Failure  
KDOQI- Kidney Disease Outcomes Quality Initiative

### **Introduction:**

Chronic kidney disease (CKD) is a clinical syndrome secondary to the definitive change in function and/or structure of the kidney and is characterized by its irreversibility and slow and progressive evolution. Another important aspect is the pathology represents a higher risk of complications and mortality, especially cardiovascular-related<sup>1</sup>.

Chronic kidney disease (CKD)<sup>2</sup> is defined as persistent kidney damage and/or glomerular filtration rate (GFR) below 60 mL/min/1.73m<sup>2</sup> for more than three months.<sup>2</sup> Patients with CKD experience higher mortality and adverse cardiovascular (CV) event rates,<sup>3-5</sup> which remain significant after adjustment for conventional coronary risk factors. This progressive CV risk associated with worsening renal function may be explained by other factors that become increasingly important with renal decline.<sup>6-7</sup> More investigation into nonconventional factors, such as inflammation, albuminuria, reduced vascular compliance, and homocysteine, is needed. CKD patients often experience "therapeutic nihilism," where there is a lack of appropriate risk factor modification and intervention.<sup>8</sup> Evidence-based cardiovascular therapies and strategies may benefit these individuals, but more educational efforts are needed to reduce this therapeutic gap.

### **Causes :**

The most frequent causes of chronic kidney disease (CKD) are diabetes and high blood pressure. In order to determine the cause of your kidney illness, your doctor will examine your medical history and perhaps do certain tests. The kind of treatment you get may depend on what caused your kidney condition.

- **Diabetes** -

Blood with excessive glucose, sometimes referred to as sugar, damages the kidney filters. Over time, your kidneys may sustain significant harm, making it challenging for them to efficiently filter waste materials and extra fluid from your blood. The presence of protein in your urine is typically the first sign of diabetic kidney damage. When the filters are broken, a vital protein called albumin that you need to maintain good health escapes out of your blood and into your urine. In a healthy kidney, albumin cannot transfer from the blood into the urine. Diabetic renal disease is the medical term for kidney damage brought on by diabetes.<sup>9</sup>

- **High blood pressure -**

Factors, as shown in ARIC and CHS trials<sup>10</sup>. Studies targeting modification of risk factors have not fully addressed specific aspects of CKD. Treatment of hypertension is beneficial, but optimal target blood pressure remains unestablished.<sup>11</sup>

**Risk Factors :**

- **Heart Disease** - Eating a diet high in saturated fats, trans fat, and cholesterol has been linked to heart disease and related conditions, such as atherosclerosis. Also, too much salt (sodium) in the diet can raise blood pressure. Not getting enough physical activity can lead to heart disease.
- **Smoking** - Even people who smoke fewer than five cigarettes a day may show signs of early CVD. The risk of CVD increases with the number of cigarettes smoked per day, and when smoking continues for many years. Smoking cigarettes with lower levels of tar or nicotine does not reduce the risk for cardiovascular disease. More than 33,000 non-smokers die every year in the United States from coronary heart disease caused by exposure to second-hand smoke.
- **Obesity** - Excess weight can lead to fatty material building up in your arteries (the blood vessels that carry blood to your organs). If the arteries that carry blood to your heart get damaged and clogged, it can lead to a heart attack.
- **Family history of kidney disease** - Family history is the biggest risk factor for hereditary kidney disease. But other health problems may impact how severe your symptoms are and if you'll suffer complications like kidney failure, which further leads to cardiovascular risk.

**Symptoms :**

Signs and symptoms of chronic kidney disease develop over time if kidney damage progress slowly. Loss of kidney function can cause a buildup of fluid or body waste or electrolyte problems. Depending on how severe is loss of kidney function can cause :

- |                        |   |
|------------------------|---|
| • Nausea               | • Urinating more or less                          |
| • Vommiting            | • Decreased mental sharpness                      |
| • Loss of appetite     | • Swelling of feet and ankles                     |
| • Fatigue and weakness | • Dry, itchy skin                                 |
| • Sleep problems       | • High blood pressure that's difficult to control |

Signs and symptoms of kidney disease are often non specific. This means that they can also be caused by other illness. Because your kidney are able to make for lost function, you might not develop signs and symptoms until irreversible damage has occurred.<sup>12</sup>

**1. Coronary Artery Disease & Myocardial Infarction:**

**Epidemiology and Pathophysiology:**

As glomerular filtration rate (GFR) decreases, obstructive CAD incidence and severity rise.<sup>14</sup> Small angiographic investigations imply that this prevalence approaches 50% in unselected CKD 5D patients;<sup>15-16</sup> CAD has a pattern of diffuse multi-vessel involvement with coronary calcification.<sup>17</sup> A poorer prognosis is predicted for people with CAD who also have concurrent CKD. Particularly with estimated GFR  $< 15$  ml/min per  $1.73 \text{ m}^2$ ,<sup>18-20</sup> renal function is negatively and independently correlated with cardiovascular morbidity and death. Although the absolute incidence and mortality rate of MI are unquestionably higher in advanced CKD, typical cardiovascular risk factors are frequently present in this scenario, and it is unclear to what extent CKD is independently related with the risk of first MI. Common cardiovascular risk factors are present in CKD but do not entirely explain the high prevalence of cardiovascular events or rising death rates; in the most severe stages of CKD, their connection with cardiovascular outcomes is diminished or even reversed.<sup>21-23</sup> Plaque rupture and inflammation have both been connected to poorer cardiovascular outcomes.<sup>24</sup> Oxidative stress and inflammation have also been linked to the pathophysiology of plaque development. More people are becoming aware of how excess mineralocorticoids might lead to cardiovascular issues.<sup>25</sup> Disordered mineral and bone metabolism has been linked in recent research to the etiology of coronary disease and CVD in CKD patients.<sup>26</sup>

**Diagnosis:**

The higher frequency of CAD among CKD patients reduces the negative predictive value of diagnostic investigations in this population, even if early diagnosis of coronary plaque may allow risk factor reduction and pharmaceutical intervention. In cohort studies examining the diagnostic sensitivity and specificity of non-invasive diagnostics, CKD patients are underrepresented. Exercise electrocardiography has limitations due to the ST-segment coronary flow reserve's lack of specificity, which can produce inaccurate results.<sup>27</sup> The precision of myocardial perfusion measurements and exercise. Sensitivities and specificities of 80% have been documented,<sup>28</sup> although imaging is less common in CKD patients than in the general population In

individuals with increased LV mass index, however, a small LV cavity size may impair the results of a stress echocardiogram.<sup>29</sup> Pharmacological stress echocardiography has a sensitivity and specificity of 69-95% and 76-94%, respectively.<sup>30</sup> Acute coronary syndrome diagnosis in CKD patients may also be challenging. In CKD patients, who are more prone to present with systolic or diastolic dysfunction causing heart failure symptoms, or with syncope, the typical trio of ischemia symptoms, increased cardiac biomarkers, and electrocardiographic abnormalities is commonly missing.<sup>31</sup> A strain pattern in the LVH might conceal diagnostic ST depression. On the other hand, myocardial apoptosis or small vessel disease may cause cardiac troponins (cTns) and creatine kinase MB isoform to be increased in the absence of actual myocardial necrosis.<sup>32</sup> This necessitates paying close attention to patterns over time and diminishes the utility of single tests, a situation that may be made worse by the greater sensitivity of next-generation troponin assays and the fact that many CKD patients are unable to exercise to a high enough level. diagnostic effort. Perfusion magnetic resonance imaging and computed tomography coronary angiography are less often used due to the dangers of contrast agents, and the latter is hampered by the high prevalence of coronary calcification among CKD patients. In the presence of a high left ventricular (LV) mass index and frank LV hypertrophy (LVH), radionuclide perfusion imaging is more sensitive but less specific than stress echocardiography. However, owing of its poor spatial resolution and disrupted.

### **Prevention:**

There is some question about the applicability of current guidelines of treatment to these patients given the altered connection between usual risk variables and cardiovascular outcomes<sup>33-34</sup> and the frequent exclusion of patients with severe CKD from the majority of clinical trials investigating CVD therapies.<sup>35</sup> There is still a lack of proof that glycemic, blood pressure (BP), or lifestyle modifications can effectively lower cardiovascular events in people with advanced CKD. Patients with CKD 5D might not benefit from strict glycemic control.<sup>36</sup> There are few randomized studies on the effectiveness of particular BP goals in patients with CKD 5D. Definitive advice for BP control are not possible due to the labile nature of blood pressure and the lack of connections between hypertension and negative cardiovascular outcomes in CKD 5D.<sup>37</sup> Patients with CKD have not been extensively examined about lifestyle changes; A small trial, multifactorial intervention, which included quitting smoking, was not linked to any notable cardiovascular advantages.<sup>38</sup> Nevertheless, weight loss, dietary salt reduction, exercise, and cessation of smoking are all feasible therapies at all CKD stages, and control of hypertension to typical targets or lower is advised to decrease the progression of CKD in individuals with predialysis CKD. There is a lack of information on preventive aspirin's effectiveness in advanced CKD. Despite the greater incidence of bleeding in CKD patients, subgroup analysis of randomized trials have shown substantial cardiovascular risk reduction from daily aspirin in people with estimated GFR<sub>045</sub> ml/min per 1.73 m<sup>2</sup>, including CKD 5D patients.<sup>39</sup> Statins may now be the most thoroughly researched medicinal treatment in the world following the release of preliminary findings from the SHARP (Study of Heart and Renal Protection) study. with regard to advanced CKD.<sup>40</sup> Nevertheless, there is ongoing discussion about their proper function. Several randomized clinical trials' subgroup analyses point to benefits for patients with moderate CKD.<sup>40</sup> On the other hand, two sizable trials that compared statins to a placebo in hemodialysis patients failed to show any effect.<sup>41</sup> More recently, in the SHARP trial, simvastatin with ezetimibe reduced major atherosclerotic events in CKD patients (including CKD 5D) by 17% but did not appear to lower overall mortality. This decrease in non-fatal events provides a justification for the use of statins in CKD patients despite the apparent lack of efficacy in lowering the risk of death because no significant damage from statin usage was revealed in any of the trials.

### **Treatment:**

There are few randomized studies on the treatment of acute MI in CKD patients, however angiotensin-converting enzyme inhibitors (ACEIs)/ARBs (angiotensin receptor blockers) and b-blockers as well as aspirin and clopidogrel seem to have similar benefits in CKD and non-CKD patients.<sup>42</sup> Low-molecular weight heparins and eptifibatide may not be safe in CKD 5D patients since they are There are no randomized trials of reperfusion therapy in CKD, although there is little reason to think that renal disease reduces the advantages of early reperfusion therapy in acute ST-elevation MI. According to a recent analysis, primary percutaneous coronary intervention (PCI), regardless of CKD status,<sup>43</sup> should be the preferred treatment when it is immediately accessible.<sup>60</sup> among those with The main choice is between urgent angiography and a cautious strategy for non-ST elevation acute coronary syndrome (unstable angina and non-ST-elevation MI). Early invasive treatment lowers post-acute coronary syndrome morbidity and death by 20–30% in the general population,<sup>44</sup> and early angiography is advised in high-risk patients. Similar advantages were seen in CKD 3–4 patients in a recent meta-analysis,<sup>45</sup> but CKD 4 was underrepresented (no300), and patients with CKD 5D were not included. A recent retrospective investigation of all non-ST-elevation MI patients in Sweden, on the other hand, revealed that an early invasive technique was deleterious for CKD 5 patients.<sup>46</sup> Information on revascularization in CKD patients with stable angina is scarce. For non-CKD patients with high-risk characteristics such left-main CAD and PCI, surgical coronary revascularization is typically advised. is frequently advised for symptomatic single- or two-vessel CAD or when a sizable portion of the myocardium is in danger.<sup>47,48</sup> Advanced CKD patients have no randomized clinical trials that compare different coronary revascularization approaches.

In patients with CKD 3–4 and predominately structurally low-risk, multivessel disease, a subgroup analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial did not reveal a benefit from PCI compared with conventional therapy. The Arterial Revascularization Therapies Study, or ARTS-1 study, discovered There is no discernible difference between the primary outcome (death, Between PCI and coronary artery bypass graft, MI, stroke 290 individuals underwent (CABG) surgery with a creatinine clearance 60ml/min.<sup>49</sup> The revascularization rate, however, was lower in the CABG arm noticeably. Consistently, observational data demonstrate higher risk of a skilled operator complications in people with CKD. For CKD, the rate of operational death following CABG is 9.2–12.2%. 3–7 times greater in CKD 4-5ND patients and patients with 5D patients than in those without CKD.<sup>50,51</sup> PCI could be a substitute nevertheless could come with the additional

risk of contrast-induced nephropathy. In a study of patients with CKD 5D undergoing first In-hospital mortality was decreased with revascularization. PCI (4.1 vs. 8.6%), although CABG had a superior 2-year survival rate.(56.4 vs 48.4%).<sup>52</sup> In a similar vein, a more recent retrospective research indicated that CABG was connected to a risk of developing CKD 5D.Compared to PCI, there is a 71% decrease in the chance of death.Thus, available research offer mixed evidence about the advantages of PCI and CABG in relation to CKD patients.<sup>53,54</sup>

## **2. Congestive Heart Failure:**

### **Epidemiology :**

CKD increases the prevalence of concomitant heart failure (CHF), ischemic heart disease, cardiac arrhythmias, and valvular calcification.<sup>55,56</sup> CHF is the leading cardiovascular condition in CKD patients, with mortality slightly higher for diastolic CHF.<sup>57</sup> Terminal events include pump failure and sudden arrhythmic death.

### **Pathophysiology :**

CKD increases the prevalence of concomitant heart failure (CHF), ischemic heart disease, cardiac arrhythmias, and valvular calcification. CHF is the leading cardiovascular condition in CKD patients, with mortality slightly higher for diastolic CHF. Terminal events include pump failure and sudden arrhythmic death.Hemodialysis can lead to ischemic heart disease or severe hemodynamic stress, causing repetitive hemodynamic instability, myocardial ischemia, prolonged systolic dysfunction, and adverse outcomes. Other factors include inappropriate renin-angiotensin system activation, iron-dependent oxidative stress, inflammation, and prohypertrophic and profibrogenic factors.<sup>58-62</sup>

### **Diagnosis :**

CHF in chronic kidney disease (CKD) is characterized by effort intolerance, fatigue, and edema, which is difficult to differentiate from volume overload. Echocardiography is crucial for diagnosing LVH, diastolic and systolic LV dysfunction, and global assessment of cardiovascular prognosis.<sup>63</sup> The Current Kidney Disease Outcomes Quality Initiative (KDOQI) recommends echocardiograms for all CKD 5D patients 1-3 months after renal replacement therapy initiation and at subsequent 3-year intervals. Serial examinations at closer intervals may increase prognostic value.<sup>64</sup> B-type natriuretic peptides (BNP and NT-proBNP) are less clear in diagnosing and managing CHF, but their concentration is influenced by kidney function and severity.<sup>65</sup> C-type natriuretic peptides (cTns T and I) accumulate in CHF, but their clinical significance is unclear. Other cardiac and renal biomarkers include neutrophil-gelatinase-associated lipocalin, kidney injury molecule 1, interleukin-18, galectin-3, mid-regional pro-adrenomedullin, catalytic iron, and markers of oxidative stress. The critical issue is the independence of GFR in these markers.<sup>66</sup>

### **Prevention & Treating :**

Prevention of chronic kidney failure (CHF) in CKD patients relies on blood pressure and volume control, as well as modifying risk factors for progression. Treatment using European Society of Cardiology guidelines is reasonable,<sup>67</sup> but these strategies are not based on strong evidence. Dietary salt restriction should be a mainstay of clinical counseling. Pharmacological treatment should consider kidney dysfunction,<sup>68</sup> as CHF patients with kidney dysfunction often require more intensive diuretic treatment. Aldosterone antagonists should be used with caution due to potential hyperkalemia. Despite strong evidence from randomized clinical trials, there is little equivalent evidence for CKD patients. Randomized clinical trials of CHF management with ACEIs, ARBs,<sup>69</sup> new direct renin inhibitors, and mineralocorticoid receptor blockers are required for CKD patients. Specialist supervision is recommended for patients with GFR levels below B30 ml/min per 1.73 m<sup>2</sup>. Other management strategies include correcting anemia and minimizing vascular calcification.<sup>70</sup> Control of calcium and phosphate concentrations is instrumental in minimizing vessel calcification,<sup>71,72</sup> but non-calcium-containing phosphate binders may be advantageous.<sup>73</sup> Achieving adequate vitamin D status and avoiding excessively high or low parathyroid hormone concentrations are reasonable treatment goals, although their efficacy has not been demonstrated. Ultrafiltration should be combined with dietary sodium restriction and lower dialysate sodium concentrations for CKD 5D patients with CHF.<sup>74,75</sup>

## **3. Sudden Cardiac Death :**

### **Epidemiology :**

Sudden death (SCD) is defined as sudden, unexpected death within an hour of symptom onset or unwitnessed death without obvious non-cardiac cause in patients known to be well within the past 24 hours.<sup>76,77</sup> In CKD 5D patients, determining the unexpectedness of death is problematic due to their high burden of comorbidity and disproportionate time spent in healthcare facilities. SCD accounts for about one-fourth of dialysis patient deaths, with an annual rate of 5.5%.<sup>78-80</sup> SCD accounts for 22-26% of all-cause mortality in dialysis patients.<sup>81-83</sup> Further studies are needed to understand regional differences in SCD and comparative SCD rates in patients using non-conventional hemodialytic techniques. The relationship between less severe CKD stages and SCD risk has been explored, with studies finding an incremental risk of SCD with decreasing baseline GFR.<sup>84,85</sup>

### **Pathophysiology :**

The association between CKD 5D and sudden cardiac death (SCD) is complex and multifactorial, likely involving vulnerable myocardial substrate and transient triggers. CAD is prevalent among CKD patients, producing structural heart disease and triggering events, leading to terminal arrhythmias.<sup>86</sup> However, the pathophysiology of CAD as the main determinant of SCD risk is problematic among CKD patients. In clinical trials, only 9% of deaths were directly attributable to CAD, while SCD accounted for 26%.<sup>87-89</sup> The degree to which unique dialysis-specific complications and non-cardiac mechanisms contribute to the overall

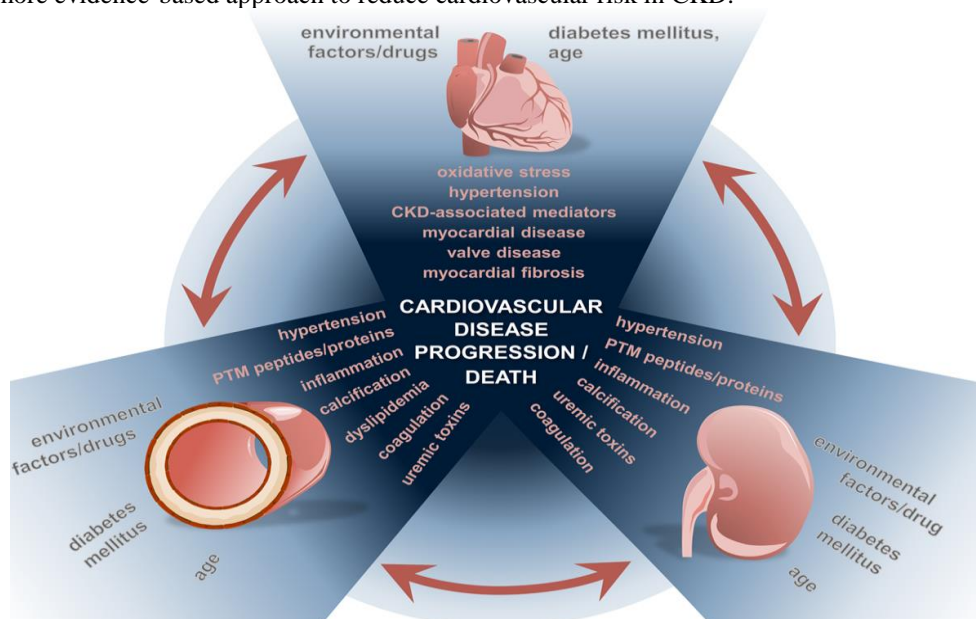
sudden death rate is unknown, and few autopsy data are available. Characterizing primary arrhythmias responsible for sudden death in CKD patients is important, as non-ventricular arrhythmias would not respond to traditional resuscitative measures.<sup>90</sup> Implantable loop recorders could be useful, but a coordinated effort is necessary due to low enrollment rates in such studies.

### **Prevention :**

Preventive strategies for stroke in CKD 5D patients should be a major public health concern. Efficacy of these strategies relies on reasonable risk-stratification data, which is challenging due to the wide range of events and risk factors associated with stroke. Dilated GFR alone should be considered a significant risk factor, and CKD 5D confers additional risk.<sup>91</sup> Most studies of SCD risk factors in CKD patients focus on retrospective and small observational prospective cohorts, which are limited by small sample size, inherent limitations in adjudication of end points, and failure to examine a wide range of candidate variables. An important and consistent observation is increased SCD occurrence in CKD 5HD patients on the first hemodialysis day following the long intradialytic period.<sup>92-94</sup> Exposure to low-potassium and calcium dialysate, volume removal on dialysis, and pre-dialysis hyperkalemia and hypokalemia have been consistently associated with increased risk of intradialytic SCD.<sup>95-97</sup> Obstructive sleep apnea, disordered nocturnal breathing, structural heart disease, and other non-invasive cardiac markers have been insufficiently studied in this population to be of clinical utility. Serum biomarkers, particularly cTnT, have been associated with all-cause mortality and SCD and may serve as markers for cardiac apoptosis and CHF. Other biomarkers associated with SCD among CKD 5D patients include markers of inflammation and nutrition, but these have not been validated across cohorts. Multinational observational cohorts including diverse populations of CKD ND and CKD 5D patients and examining a broad spectrum of potential risk factors and risk-stratification techniques are desirable.

### **Conclusion :**

Patient with CKD have high cardiovascular risk, with cardiovascular death being the leading cause of death. Several novel therapies to decrease the risk of cardiovascular disease in CKD are in clinical development or have 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 patient 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.



**Fig no. 1 :Interaction of cardiovascular disease (CVD) and chronic kidney disease (CKD).**

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