Chronic Renal Failure and Cardiovascular Disease: A Comprehensive Appraisal

Reviewed by:

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Introduction

Cardiovascular disease (CVD) is the most common cause of death in patients with end-stage renal disease (ESRD). Chronic kidney disease (CKD) has a myriad of direct negative effects on the cardiovascular system. The main causes of morbidity and mortality in patients with CKD are the cardiovascular diseases such as coronary artery disease, congestive heart failure, arrhythmias and sudden cardiac death represent. The condition involves close linkage between heart and kidneys and also traditional and non-traditional cardiovascular risk factors. As per a well-established classification of cardiorenal syndrome, cardiovascular involvement in CKD is known as "type-4 cardiorenal syndrome" (chronic renocardiac syndrome).[1]

Associations Between CKD and CVD

Chronic kidney disease is associated with substantially increased risk for cardiovascular disease morbidity and mortality, independent of traditional cardiovascular risk factors such as diabetes, hypertension, lipoprotein levels, and tobacco use. Besides, certain novel cardiovascular risk factors are more prevalent in persons with chronic kidney disease, including elevated inflammatory and prothrombotic factors (C-reactive protein [CRP], fibrinogen, interleukin 6 [IL-6], and factor VIII), and lipoprotein(a) (Lp[a]), and decreased hemoglobin levels.[2]

The initiation of dialysis for treatment of ESRD exacerbates chronic electrolyte and hemodynamic perturbations. Rapid large shifts in effective intravascular volume and electrolyte concentrations ultimately lead to subendocardial ischemia, increased left ventricular wall mass, and diastolic dysfunction, and can precipitate serious arrhythmias through a complex pathophysiological process. Although these factors are unique to advanced kidney disease and its treatment, they increase the overall incidence of acute coronary syndrome and sudden cardiac death.[3]

Pathophysiology of Cardiorenal Syndrome

The phrase "cardiorenal syndrome" represents the mutual influence of the acute or chronic dysfunction of the heart or kidney on the other organ.[4] As chronic kidney disease progresses, kidney-specific risk factors for cardiovascular events and disease come into play, increasing the risk for cardiovascular disease. The pathophysiology of combined cardiovascular and kidney disease has an interplay and overlapping of several interfaces (Figure 1).[4-6]

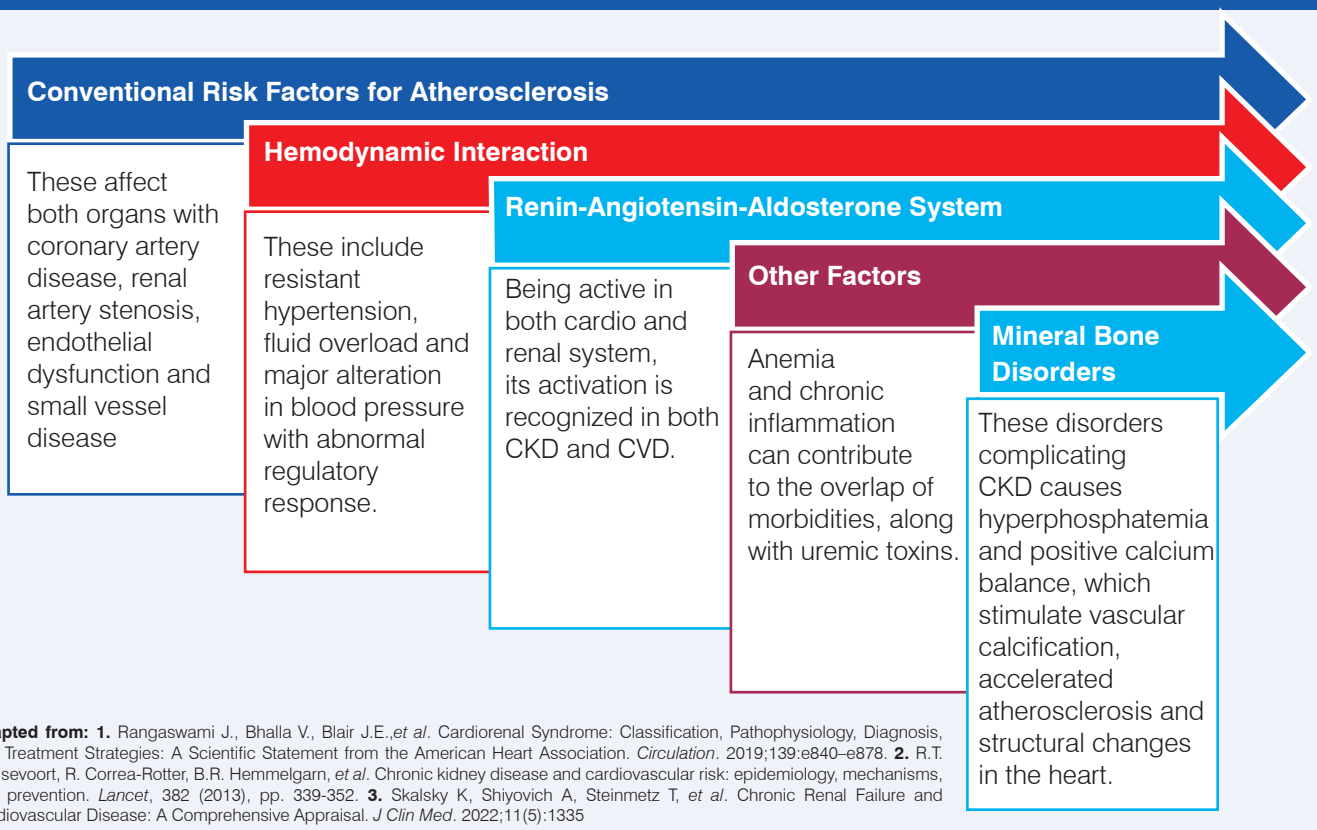
Besides, with progressive CKD, there is progressive volume overload leading to left ventricular hypertrophy (LVH). With initiation of dialysis and progression to ESRD, there is an increased risk of intradialytic hypotension (IDH) leading to subendocardial ischemia in a predisposing hypertrophic myocardium. With thrice weekly dialysis, there is higher risk of sudden cardiac death secondary to arrhythmias likely due to myocardial fibrosis. Thus, there is increased CVD mortality with progressive glomerular filtration rate (GFR) decline.[3]

Pathophysiologic Effects of Hemodialysis on the Cardiovascular System

Other than the direct negative effects of CKD on cardiac system, the hemodialysis poses a big burden on cardiovascular system. Cardiac risk is especially significant upon initiating hemodialysis (HD). In patients with progressive CKD, renal replacement therapy (RRT) is often required for clearance of blood and volume control. Conventional HD takes place over 3 to 4h, 3 times per week. It results in dramatic fluctuations in systolic pressure, intravascular volume status, and electrolytes homeostasis immediately before, during, and for hours after each HD session. In consequence, it produces significant injury to the cardiac myocardium via intradialytic hypotension, myocardial stunning, and electrolyte imbalances.[3]

Risk begins when GFR drops below 60 ml/min and it dramatically increases at GFR <45 ml/min.

Figure 1: Several Interfaces Overlapping in the Pathophysiology of Combined Cardiovascular and Kidney Disease



Adapted from: 1. Rangaswami J., Bhalla V., Blair J.E.,*et al*. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement from the American Heart Association. *Circulation*. 2019;139:e840–e878. **2.** R.T. Gansevoort, R. Correa-Rotter, B.R. Hemmelgarn, *et al*. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*, 382 (2013), pp. 339-352. **3.** Skalsky K, Shiyovich A, Steinmetz T, *et al*. Chronic Renal Failure and Cardiovascular Disease: A Comprehensive Appraisal. *J Clin Med*. 2022;11(5):1335

Clinical Management

Early Surveillance & Diagnosis

Patients with CKD are at an increased risk of cardiac events as they progress toward ESRD. Early identification of CKD can help lead to targeted strategies to limit progression of disease. Social media outreach, such as mass screening and aggressive hypertensive therapies, in at-risk populations are beneficial tools in this regard. Early TTE imaging may help guide management of disease. Those with hypertrophied LVs with small cavities and diastolic dysfunction may not tolerate aggressive diuretic strategies, as they may be dependent on ventricular filling; thus, these patients may benefit more from early usage of calcium-channel blockers (CCBs) or beta-blockers as antihypertensive agents and for reducing LV wall stress. In contrast, those with larger LV cavities may benefit more from angiotensin-converting enzyme inhibitors and diuretic agents to reduce ventricular volume and remodeling as a method of blood pressure control. Figure 2 represents proposed algorithm for early surveillance in CKD.[3]

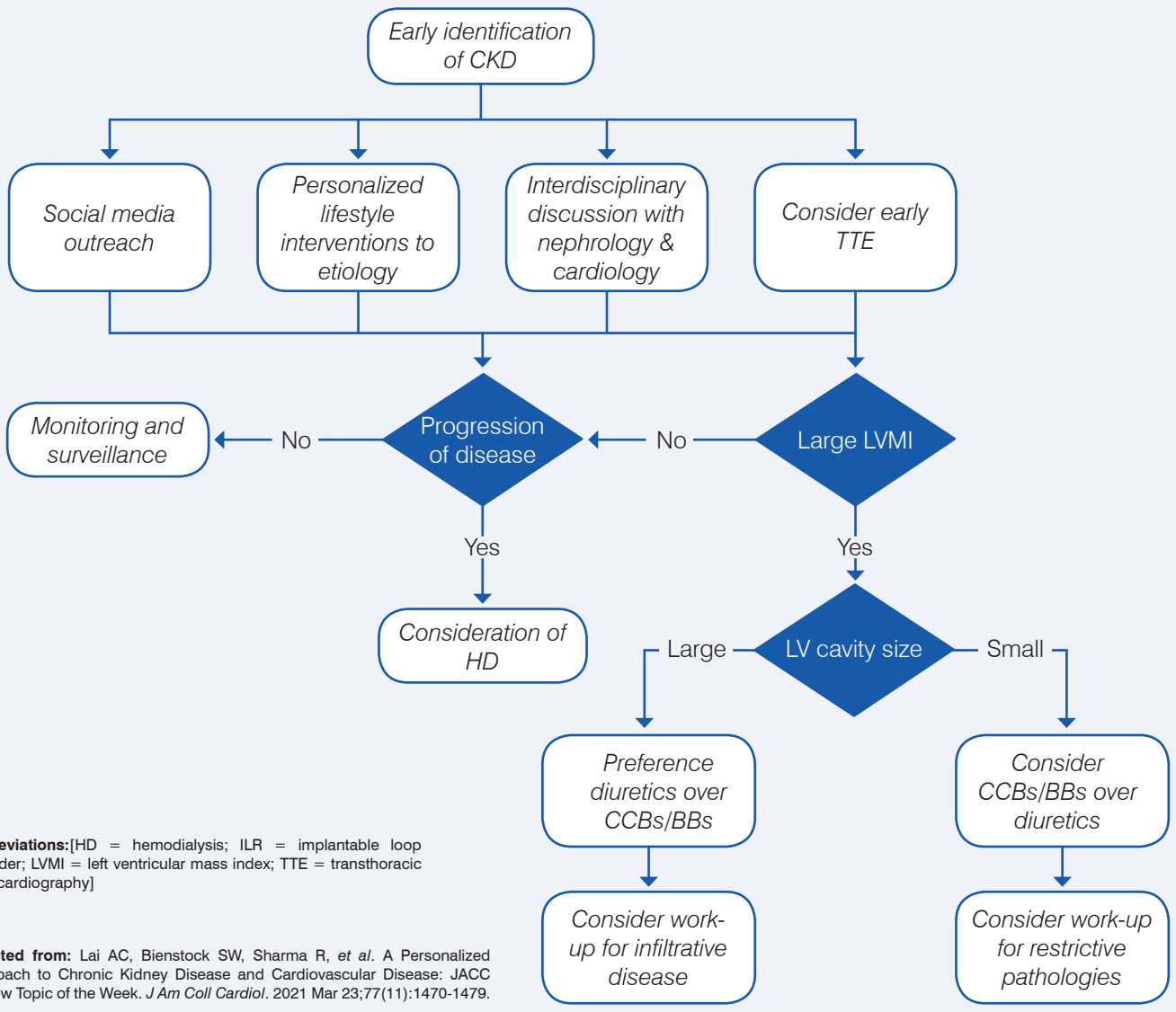
Among patients with CKD, there are limited options for non-invasive diagnostic tests. Key points in relation to diagnosis are as follows.

- ESC guidelines regarding chronic coronary syndrome suggest using either coronary computed tomography angiography (CTA) or functional stress imaging as the preferred methods for risk stratification.
- The next optional non-invasive testing would be the myocardial perfusion single-photon emission computed tomography (SPECT) test and stress echocardiography.
- Since patients with CKD, and especially advanced CKD and dialysis, have limited exercise capacity due to muscle fatigue, peripheral vascular disease, peripheral neuropathy, anemia, volume overload and other comorbidities, the Bruce protocol is not always possible. The alternative would be a dobutamine stress echocardiography (DSE) or SPECT scan with dipyridamole/adenosine infusion.
- DSE and SPECT tests may be both used for the diagnosis of coronary artery disease, although their sensitivity and specificity are relatively low.[3,7]

Treatment Modalities

First recommendation regarding the diagnostic and treatment modalities in CKD patients with suspected chronic coronary syndrome is always a tailored approach with careful consideration of the patient's complaints, medical history, laboratory tests, images, renal function and prognosis. An integrated and multifactorial approach should be followed. The "heart team" forum should consult with nephrologists, diabetologists and primary care physicians on how to optimize the medical care for the heart, the kidneys and the cardiovascular risk factors altogether. This multifactorial approach has been recently validated in diabetic patients

Figure 2: Proposed Algorithm for Early Surveillance in CKD



Abbreviations:[HD = hemodialysis; ILR = implantable loop recorder; LVMI = left ventricular mass index; TTE = transthoracic echocardiography]

Adapted from: Lai AC, Bienstock SW, Sharma R, *et al*. A Personalized Approach to Chronic Kidney Disease and Cardiovascular Disease: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2021 Mar 23;77(11):1470-1479.

with CKD in a multicenter randomized control trial, with a long durability of protection.[6,8]

Revascularization options in patients with CKD include coronary artery bypass grafting (CABG) surgery and percutaneous coronary intervention (PCI). The Dual Antiplatelet Therapy (DAPT) with aspirin and an oral P2Y inhibitor is the mainstay of antithrombotic therapy after PCI. The ESC guidelines published in 2019 on the diagnosis and management of chronic coronary disease suggest four treatment options for combination therapy with aspirin in patients who have a high or moderate risk of ischemic events: clopidogrel, ticagrelor, prasugrel and low dose rivaroxaban.[6,7]

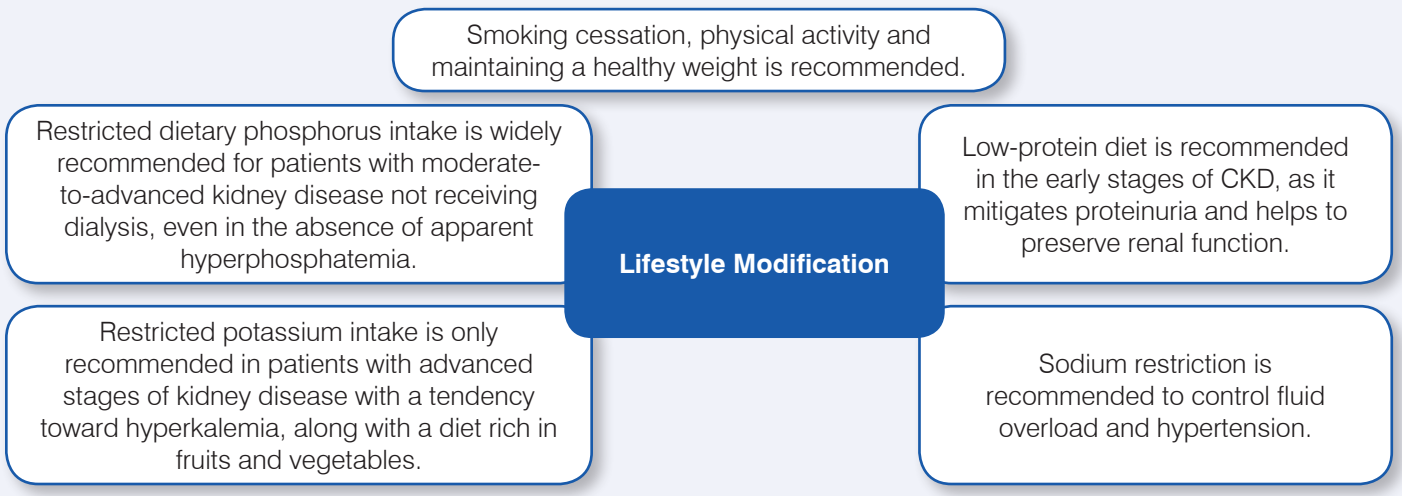
Key messages in the treatment of chronic coronary syndrome and kidney disease are as follows:

- Evidence for the efficacy of cardiac catheterization in the non-acute setting is conflicting.
- The potential damage of iodinated contrast agent to the kidneys should be minimized.
- CABG is superior to PCI in long-term outcomes. The SYNTAX score principles for allocating patients to PCI or CABG is similar to patients with normal or abnormal kidney function.[6]

The patients of advanced CKD can be categorized into three subgroups: pre-dialysis patients, those on renal replacement therapy and renal transplant candidates. Each subgroup has unique features to be considered when choosing the diagnostic studies and treatment options in CAD.

- Pre-dialysis—Patients should be carefully examined to prevent further deterioration of renal function, including avoiding certain drugs and minimizing iodine contrast exposure.
- Dialysis—The consideration of nephrotoxic drugs and iodine contrast exposure are negligible.

Figure 3: Healthy Lifestyle Recommendations to Decrease Cardiovascular Risks among Patients with CKD



Adapted from: Knuuti J., Wijns W., Saraste A., *et al*. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur. *Heart J*. 2020;41:407–477.

- Kidney transplant candidates—The risk assessment should include the potential future damage to the transplanted kidney with the need of coronary revascularization post-surgery.[6]

Prevention of Future Events

Patients with advanced CKD are already considered to be at high or very high risk of cardiovascular disease and there is no need to use risk estimation models. Medical treatment for risk-factor control (lipids, blood pressure and glucose) can improve outcomes. Implementing healthy lifestyle behaviors (as summarized in Figure 3) further decreases cardiovascular risks among patients with CKD. Key highlights are as follows.

- Blood Pressure Control
  - BP should be lowered to <140/90 mmHg and towards systolic BP of <120 mmHg.
- Glycemic Control
  - In CKD stage G1–4, the target of near-normal HbA1c (<7.0%) is recommended.
  - In hemodialysis patients, HbA1c range of 6–8% is preferred.
- Lipid Control
  - The use of statins or statin/ezetimibe combination is recommended in non-dialysis patients with a target LDL of 55 mg/dl.
  - The use of statins among dialysis patients is debatable.[6-8]

End Note

As chronic kidney disease progresses, kidney-specific risk factors for cardiovascular events and disease come into play. As a result, the risk for cardiovascular disease is notably increased in individuals with chronic kidney disease. Yet, cardiovascular disease is frequently underdiagnosed and undertreated in patients with chronic kidney disease. Particular medical attention at an individual level should be given to these patients. In addition, this view should be also be considered in the development of medical guidelines. In brief, better awareness of the challenges and the development of population- and patient-specific approaches to early prevention and identification of at-risk populations is needed.

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