بسم الله الرحمن الرحيم

Cardiovascular disease in chronic kidney disease.

Dr PARISA JAVADIAN

Assistant professor of nephrology

SHAHREKORD university of medical sciences

- Cardiovascular morbidity and mortality in patients with
- chronic kidney disease (CKD) is high, and the presence of
- CKD worsens outcomes of cardiovascular disease (CVD)

- As originally proposed patients with an eGFR <60 ml/min per 1.73 m2 (i.e., stage 3 or higher) have 2 to 16 times higher risk of MACE compared with patients with an eGFR >60 ml/min per 1.73 m
- Moreover, for those patients with CKD not yet requiring renal replacement therapy, the rate of developing MACE is much higher than reaching end-stage renal disease (ESRD) and requiring renal replacement therapy.

KDIGO (Kidney Disease: Improving Global Outcomes)

- (1) coronary artery disease (CAD) and myocardial infarction (MI)
- (2) congestive heart failure (CHF)
- (3)cerebrovascular disease, stroke, atrial fibrillation, peripheral
- arterial disease (PAD)
- (4) sudden cardiac death (SCD).

- unlike the general population ,a multitude of risk factors, some traditional (e.g., hypercholesterolemia and presence of diabetes) and others nontraditional (e.g., vascular calcification and myocardial fibrosis), predispose patients with CKD to cardiovascular events.

CAD AND MI
Epidemiology and pathophysiology

- The incidence and severity of obstructive CAD increases as
- glomerular filtration rate (GFR) declines.
- CAD shows a pattern of diffuse multi-vessel involvement with coronary Calcification
- small angiographic studies suggest that this incidence exceeds 50% in unselected CKD 5D patients.

- The amount of atheromatous plaques in CKD patients appears to be similar to those found in non-CKD patients.
- However, the atheromatous plaques were more calcified, with the presence of hydroxyapatite (i.e., calcium phosphate) and the presence of medial calcification in patients with CKD (i.e., pre dialysis and on hemodialysis) compared with those without CKD

- Patients with eGFR <60 ml/min per 1.73 m2 were 4.1 times as likely
- (relative risk, 4.1; 95% confidence interval, 3–5.5) to have 3-
- vessel disease as patients with eGFR $60 ml/min per 1.73 m2.
- Patients with eGFR <60 ml/min per 1.73 m2 had more prevalent CAD (1–3 vessels) compared with those with eGFR $60 ml/min per 1.73 m2 (87% vs 71%, respectively

- Standard cardiovascular risk factors are common in CKD, but do not fully explain the high incidence of cardiovascular events or increased
- mortality rates
- their association with cardiovascular outcomes is attenuated or even reversed at the most advanced CKD stages

- Inflammation and oxidative stress have been linked to the pathogenesis of plaque formation and plaque rupture; both are associated with worse cardiovascular outcomes.
- The role of mineralocorticoid excess in the development of cardiovascular complications is increasingly recognized.
- Recent studies have implicated disordered mineral and bone metabolism in the pathogenesis of coronary disease and CVD in CKD patients.

Diagnosis

- Although early detection of coronary plaque may permit
- risk factor modification and pharmacological intervention,
- the increased prevalence of CAD among CKD patients
- diminishes the negative predictive value of diagnostic studies
- in this population. CKD patients are underrepresented in
- cohort studies evaluating the diagnostic sensitivities and
- specificities of non-invasive tests

- **Exercise electrocardiography** is limited by lack of specificity of the ST-segment response and by inability of many CKD patients to exercise
- to a diagnostic workload.
- The risks of contrast agents limit the use of perfusion magnetic resonance imaging and computed tomography coronary angiography, and the latter is compromised by a high prevalence of coronary calcification among CKD patients

- **Radionuclide perfusion imaging** is more sensitive but less specific than stress echocardiography, but may be problematic in the setting of elevated left-ventricular (LV) mass index and frank LV hypertrophy (LVH) because limited spatial resolution and disturbed coronary flow reserve may lead to false results

- The accuracy of exercise and of pharmacological myocardial perfusion
- imaging is reduced in CKD patients compared with the
- general population, and sensitivities and specificities 80%
- have been reported. Conversely, stress echocardiography
- may be compromised by small LV cavity size in patients with elevated LV mass index.Sensitivity and specificity for pharmacological stress echocardiography is 69–95% and 76–94%, respectively

Noninvasive detection of ASCVD in the CKD population

- All of our currently available tools for detecting ASCVD—
- typical symptoms, electrocardiogram, and cardiac stress
- testing—are less reliable in patients with CKD compared with
- those without.
- In ACS, chest pain is the most common presentation in patients with CKD (pre-ESRD or ESRD).

- Diagnosis of acute coronary syndrome may also be problematic in CKD. The classic triad of ischemic symptoms,
- elevated cardiac biomarkers, and electrocardiographic
- changes is frequently absent in CKD patients, who are
- more likely to present with systolic or diastolic dysfunction
- causing heart failure symptoms, or with syncope

- LVH with a strain pattern may mask diagnostic ST depression.
- Conversely, creatine kinase MB isoform and cardiac troponins
- (cTns) may be elevated in the absence of true myocardial
- necrosis, possibly because of myocardial apoptosis or small
- vessel disease. This mandates careful attention to trends
- over time and reduces the value of single tests, a problem that
- may be exacerbated by increased sensitivity of next-generation
- troponin assays.

- In ACS, chest pain is the most common presentation in patients with CKD (pre-ESRD or ESRD).
- However, when compared with patients without CKD, those
- with CKD are more likely to have atypical symptoms, specifically
- shortness of breath

- Nevertheless, the presence of CKD is associated with the presence of ASCVD, at least in adults, suggesting that CKD is an ASCVD equivalent

Prevention

- The altered relationship of typical risk factors with cardiovascular outcomes[41–43] and the routine exclusion of patients
- with advanced CKD from most clinical trials testing CVD
- therapies[44,45] engender doubt about the relevance of existing
- standards of care to these patients.

- Evidence of the efficacy of glycemic or blood pressure (BP) control or lifestyle modification to reduce cardiovascular events in patients with
- advanced CKD remains limited.
- Strict glycemic control may not benefit CKD 5D patients.
- Randomized data on the efficacy of specific BP goals in CKD 5D patients are lacking.

- Nevertheless, smoking cessation, exercise, dietary salt reduction,
- and weight loss are reasonable interventions at all CKD
- stages, and control of hypertension to usual goals or lower is
- indicated to slow CKD progression in patients with predialysis
- CKD.

- Data are sparse regarding efficacy of prophylactic **aspirin**
- in advanced CKD. Subgroup analyses of randomized
- trials have demonstrated convincing cardiovascular risk
- reduction from daily aspirin in individuals with estimated
- GFRo45 ml/min per 1.73m2, including CKD 5D patients,
- despite higher incidence of bleeding in CKD patients

- **statins** may now be the best-studied medical therapy in the context of advanced CKD. Nevertheless, debate continues regarding their appropriate role. A subgroup analysis of several randomized
- clinical trials suggests benefit in patients with moderate
- CKD

Treatment

- Randomized data on treatment of **acute MI in CKD** patients are sparse, but treatment approaches using aspirin, clopidogrel,
- b-blockers, and angiotensin-converting enzyme inhibitors
- (ACEIs)/ARBs (angiotensin receptor blockers) seem to have similar benefits in CKD and non-CKD patients

- There is little reason to believe that kidney impairment
- diminishes the benefits of immediate reperfusion therapy in
- acute ST-elevation MI, but there are no randomized trials
- of reperfusion therapy in CKD

- A recent analysis suggests that, when immediately available, primary percutaneous coronary intervention (PCI) should be the treatment of
- choice irrespective of CKD status

- Among patients with non-ST elevation acute coronary
- syndrome (unstable angina and non-ST-elevation MI), the
- primary decision is between immediate angiography and
- a conservative approach. In the general population, an early
- invasive strategy reduces post-acute coronary syndrome
- morbidity and mortality by 20–30%,61 and guidelines
- recommend early angiography in high-risk patients

- A recent meta-analysis suggested similar benefits in CKD 3–4
- patients, but CKD 4 was underrepresented (no300) and
- CKD 5D patients were not included. Conversely, a recent
- retrospective analysis of all non-ST-elevation MI patients in
- Sweden suggested that an early invasive strategy was harmful
- for CKD 5 patients

Medical management of SIHD in CKD.

- In addition to lifestyle modifications, advancements in the medical management of SIHD have led to considerable reductions in
- morbidity and mortality in the general population.

- **statins**, meta-analyses of patients with CKD within large general population studies have identified a reduction in mortality as well as cardiovascular events.
- As such, the Kidney Disease: Improving Global Outcomes lipid guidelines recommended the use of statins in all patients with CKD who are older than age 50 years, and in those at high risk for ASCVD aged 18 to 49 years

- Altered platelet reactivity seems to be a common feature of
- patients with CKD. The available evidence seems to suggest
- that there is a baseline higher reactivity of platelets to adenosine
- diphosphate among individuals with CKD compared with those with normal renal function

- Furthermore, patients with CKD exhibit less reduction in platelet reactivity to P2Y12 inhibitors such as clopidogrel than do patients with
- normal renal function. Other studies have also shown that
- patients with CKD are more likely to bleed. Thus, patients
- with CKD are not only at high risk for thrombotic events, but
- also for bleeding events

- This has 2 major implications in regard to SIHD in patients with CKD. First, the role of antiplatelet therapy, notably aspirin, for the primary prevention of SIHD is limited in patients with CKD to prevention of MI
- but not for mortality.
- Second, an advance in medical management of SIHD in the general population is the availability of potent antiplatelet regimens to maintain stent patency following percutaneous coronary intervention (PCI).

- The limitation in efficacy of the P2Y12 inhibitors and aspirin
- in CKD is likely a strong contributor to the reduction in
- benefit following PCI in individuals with CKD, especially
- given that in-stent thrombosis has been implicated as a major
- concern in individuals with CKD.

- There is a paucity of data regarding revascularization in CKD patients with stable angina.
- Surgical coronary revascularization s generally recommended for non-CKD patients with high-risk features such as left-main CAD, and PCI is typically recommended for symptomatic single- or two-vessel CAD or when a significant amount of myocardium is at risk.
- No randomized clinical trials compare coronary revascularization strategies in advanced CKD patients

- COURAGE and BARI 2D demonstrated that an
- initial strategy of revascularization by PCI or coronary artery
- bypass graft surgery is not superior to an initial strategy of
- optimal medical therapy alone in reducing all-cause mortality
- or myocardial infarction in patients with SIHD. Patients with
- CKD were largely excluded in those studies

- Thus, the data on how to manage SIHD in the CKD population are lacking and derived
- mainly by observational studies with consequent selection
- and ascertainment bias .

- In summary, there is currently lack of robust evidence to
- support revascularization over optimal medical therapy alone
- in patients with SIHD and CKD.

- Patients with CKD appear to have better outcomes with drug-eluting stents compared with bare-metal stents. In addition, for those patients with <3-vessel disease, drug-eluting stent have allowed for similar outcomes compared with coronary artery bypass graft surgery, especially when the later-generation drug-eluting stent are used

- Observational data consistently show increased risk
- of serious operative complications in CKD patients.
- Incidence of operative death after CABG is 9–12.2% for CKD
- 5D patients, and 3- to 7-fold higher in CKD 4–5ND patients
- than in non-CKD patients. PCI may be an alternative,
- but may pose the added risk of contrast-induced nephropathy.

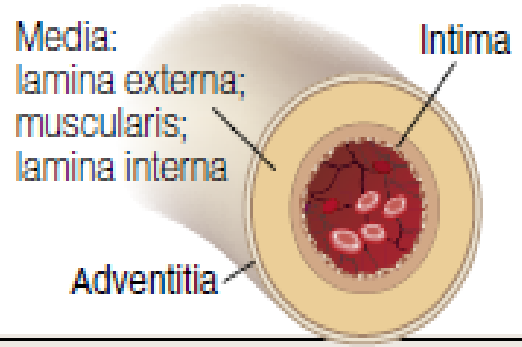
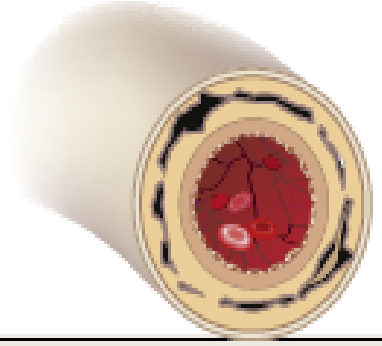
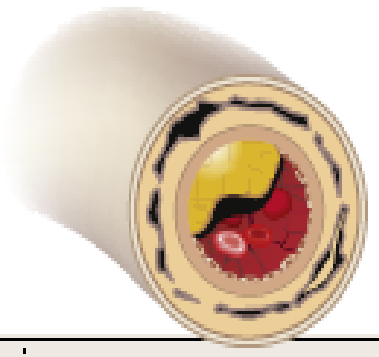
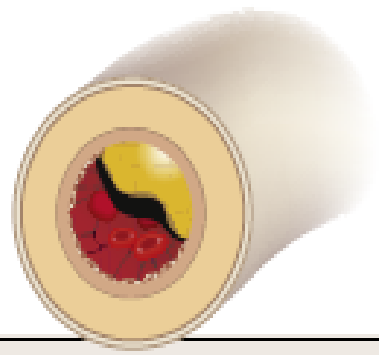
- Special considerations for coronary angiography in
- CKD. Likely the single most important concern in patients
- with CKD being considered for angiography is the development
- of contrast-associated acute kidney injury (C-AKI)

- The clinical outcomes of patients who experience C-AKI also tend to be worse than those who do not experience C-AKI. Two factors may mitigate this concern.
- First, strategies have been developed to minimize the risk of C-AKI, notably minimizing and even eliminating the amount of contrast administered, using low or iso-osmolar contrast agents, and maintaining adequate hydration before contrast administration.
- Second, the benefit of coronary angiography and possibly intervention in the appropriate candidate may outweigh the risk of C-AKI

Pathophysiologic considerations in ASCVD in CKD

- The atherosclerotic plaque is the central therapeutic target in CAD. Revascularization for critical lesions associated with ACS and stabilization of atherosclerotic plaques with medical therapy with agents such as statins remain the cornerstone of therapy.
- However, these therapeutic agents have provided limited benefits in terms of reduction of MACE among patients with CKD. A number of observations, some of those mentioned above, point to a more complex set of contributors to ASCVD in patients with CKD

- First, calcification of the atherosclerotic plaque is accelerated
- by CKD, but calcification is also enhanced in the medial layers of the arteries, which is not seen in patients with preserved renal function (Figure 1). A contributor to vascular calcification, especially medial calcification, is secondary hyperparathyroidism of renal origin.

	Normal coronary artery	Chronic kidney disease–related CAD		Non–chronic kidney disease CAD
				
Intima / plaque	No calcification. No plaque. Contains normal endothelial cells.	Coronary artery without atherosclerotic plaque	Heavily calcified atherosclerotic plaque	Calcified atherosclerotic plaque
Media	No calcification. Smooth muscles organized.	Calcification present*	Calcification present	Typically no medial calcification
Effect on CAC score	No CAC on computed tomography.	Both intimal and medial calcification coexist in patients with CKD. This results in significantly higher CAC readings among patients with CKD, especially when atherosclerotic plaque is present, as compared to controls.		In patients without CKD, CAC score correlates with presence of athero-sclerotic plaque as the plaque is uniquely calcified, in comparison to the normal, noncalcified vessel wall.

- Second, patients with advanced CKD often display additional
- ASCVD risk factors, including albuminuria and generalized increase in inflammatory markers.
- Rein et ali dentified that the presence of albuminuria is associated with a higher likelihood of finding significant coronary artery stenosis ($ 50%) on angiography; they also found a direct correlation between the amount of albuminuria and the number of vessels with significant stenosis

- Third, myocardial fibrosis is prominent among patients with
- CKD and ESRD. The cardiac fibrosis of renal disease consists of
- Inter myocyte fibrosis that leads to a reduction in capillary to myocyte ratio.
- Mediators identified as important in CKD related cardiac fibrosis include

- increased fibroblast growth factor,
- reduced klotho levels,
- increased phosphorus levels.
- Many of these mediators ultimately result in potentiating transforming growth factor–b1-induced fibrosis within the myocardium. Interestingly cardiac fibrosis is also an end result of myocardial ischemia

- Finally, kidney transplantation; that is, correction of the uremic milieu, leads to much greater reductions in clinical ASCVD events than coronary artery revascularization. This is connected to multiple pathophysiologic processes that require functioning nephrons to correct .
- The inflammation associated with uremia is also corrected and may in part be related to the reductions in ASCVD events seen after transplantation

- An important caveat is that poorly controlled CKD parameters and uremia-related inflammation pre transplantation leads to worse cardiovascular outcomes post transplantation, highlighting the importance of CKD control pre transplantation

Conclusions

- Cardiovascular disease remains the leading cause of morbidity
- and mortality in patients with CKD, and ASCVD remains a contributor to cardiovascular events, as it does in the general population.
- Two important aspects of ASCVD are markedly altered in patients with CKD compared with those with normal renal function
- ASCVD is clearly present in all stages of CKD; however, the atherosclerotic plaque is heavily calcified, even more so than in elderly populations with normal renal function

- The coronary vessel wall, the medial layer, is also calcified, resulting in altered vaso reactivity.
- In addition, the ability to suppress platelet reactivity is altered in patients
- with CKD. These characteristics have limited the utility of our available therapeutics for ASCVD in CKD populations.
- Currently, reversal of uremia with renal transplantation appears
- to be the best way to improve the cardiovascular outcomes associated with ESRD, but cardiovascular outcomes still remain worse than the general population in patients with functioning renal transplant.

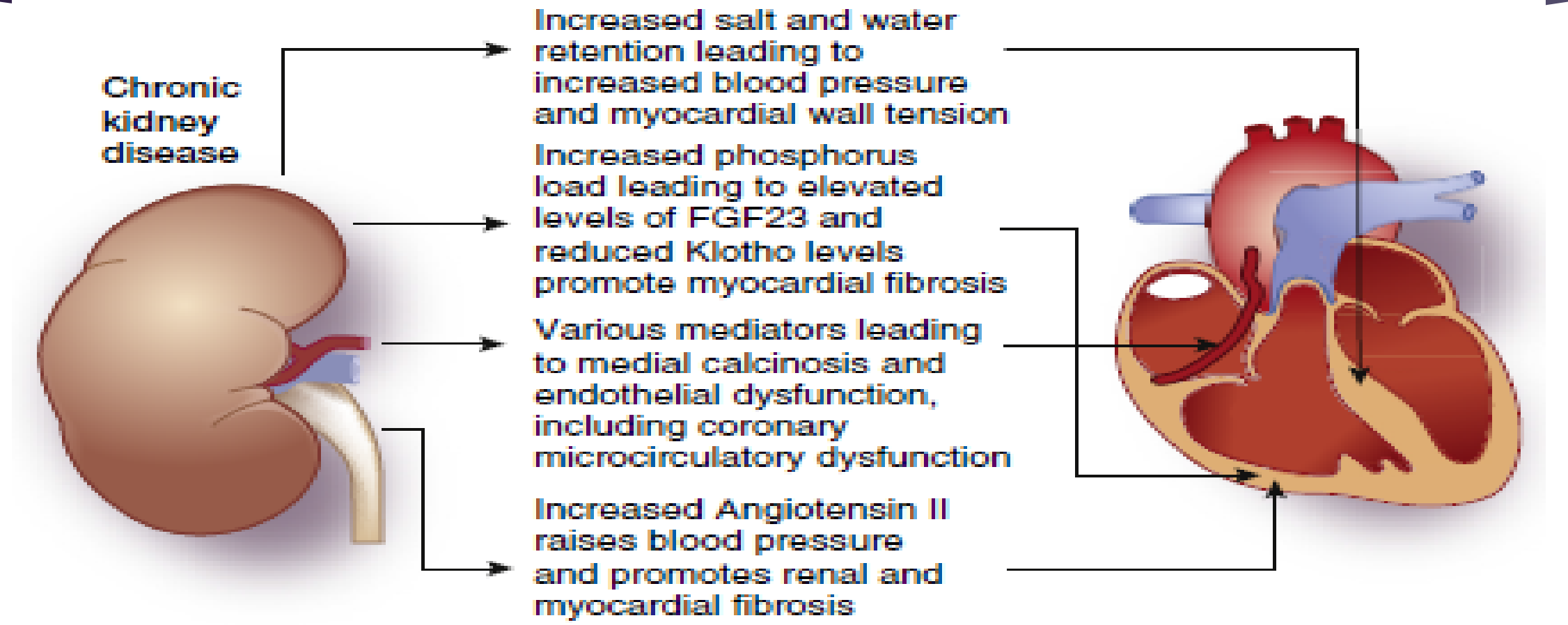
CONGESTIVE HEART FAILURE
Epidemiology

- CKD is associated with increased prevalence of concomitant CHF, ischemic heart disease, cardiac arrhythmias (most commonly atrial fibrillation), and valvular calcification.
- In observational studies, CHF prevalence increases with declining kidney function. CHF is the leading cardiovascular condition in CKD patients, with mortality slightly higher for diastolic than for systolic CHF

- **Pathophysiology**
- CKD exposes the heart to three major mechanisms that facilitate the development of cardiomyopathy and induce LV failure: pressure overload, volume overload, and CKD associated non-hemodynamic factors that alter the myocardium

- **Diagnosis**
- The clinical syndrome of CHF in CKD, heralded by effort intolerance, fatigue, and edema, is difficult to distinguish from volume overload. Echocardiography (including tissue Doppler imaging) has a key role in diagnosing LVH, diastolic and systolic LV dysfunction, and global assessment of cardiovascular prognosis.

- The cTns T and I, biomarkers of cardiomyocyte damage, accumulate in CHF. Although the clinical significance of increased cTn concentrations in CKD patients with CHF is unclear, they are strong predictors of all-cause mortality in CKD 5D, and the US FDA (Food and Drug Administration) approved cTnT for risk stratification in CKD 5D patients


Chronic kidney disease
Increased salt and water retention leading to increased blood pressure and myocardial wall tension
Increased phosphorus load leading to elevated levels of FGF23 and reduced Klotho levels promote myocardial fibrosis
Various mediators leading to medial calcinosis and endothelial dysfunction, including coronary microcirculatory dysfunction
Increased Angiotensin II raises blood pressure and promotes renal and myocardial fibrosis