



## Coronary artery disease in patients with chronic kidney disease: a brief literature review

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### ABSTRACT

Cardiovascular is the major cause of death in chronic kidney disease and end-stage renal disease. The cardiovascular mortality rate of patients with renal impairment is evaluated to be higher than general population. Coronary artery disease seems to be an important type of cardiovascular complication among patients with chronic kidney disease and end-stage renal disease before the renal replacement therapy. Due to the strong association between chronic kidney disease and the incidence of coronary artery disease, accurate screening, diagnosis, and management of cardiovascular complications would be essential in patients at different stages of renal dysfunction. Despite the need for the comprehensive knowledge about different aspects of coronary artery disease in patients with renal failure, there is not sufficient evidence regarding the pathophysiology, ideal diagnosis, and treatment strategies for coronary heart disease in population with chronic kidney disease. In this study, we briefly reviewed the existing literatures about the possible screening, diagnosis, and the treatment approaches of risk of coronary heart disease in patients with kidney dysfunction.

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### Introduction

A significant association has been identified between chronic kidney disease (CKD) and cardiovascular complications that can result in increased morbidity and mortality rate of patients. CKD is proposed as an important risk factor for cardiovascular diseases such as coronary artery diseases (CAD), congestion heart failure, cerebrovascular disease, and sudden heart death, which increase the coronary artery disease occurrence rate almost 1.5–3 times. CAD is known as the most important cause of morbidity and death among patients with CKD (1). Although a considerable association has been observed between the chronic kidney disease and the incidence rate of coronary heart disease, there is not sufficient in-

formation regarding the histopathological properties of this association. Accurate understanding of the possible risk factors of CAD among patients at different stages of renal impairment, under dialysis or pre-kidney transplant operation would be beneficial in preventing, diagnosis, and treatment of coronary heart disease.

Here, we briefly reviewed the various risk factors of CAD, diagnosis, and treatment strategies for patients with CKD.

### Literature Review

#### *Pathophysiology of CAD*

Based on the study of Lindner et al, coronary heart disease accounts for almost 35% of mor-

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tality rate in patients with advance kidney failure who are under the hemodialysis (2). It is also responsible for more than 50% of mortality among patients with end-stage renal disease (ESRD). Coronary angiography has demonstrated remarkable prevalence of occult coronary artery stenosis in more than 50% of CKD patients with pre-dialysis or prior renal replacement therapy, who had no previous myocardial infarction (3,4). According to American College of Cardiology/American Heart Association (ACC/AHA), CKD should be regarded a CAD equivalent (5), but the reason of this strong association is not accurately clear. Based on the literature, vascular calcification will be increased after an decrease in the renal function in cases with CKD, which leads to the following modifications: reduced coronary microcirculation, decreased arterial elasticity, elevated pulse wave velocity, and developed left ventricular hypertrophy (6). Malnutrition-inflammation-atherosclerosis/calcification (MIAC) syndrome is another possible responsible process of pathogenesis of CAD through a vicious cycle and the important role of cytokines. Epicardial adipose tissue (EAT) is another factor which can be associated with the increased CAD through producing bioactive adipokines such as (tumor necrosis factor) TNF- $\alpha$ , monocyte chemotactic protein (MCP-1), (Interlukin-6) IL-6, and resistin (7).

Comparing the coronary artery plaques of CKD patients with non-uremic controls resulted in statistically different morphology and composition of the lesions in these two groups which might be the origin of further complications in CKD population. In this comparison, the thickness of the media layer was significantly larger in patients with renal impairment compared to control ones. Significantly, higher calcification was observed in coronary atherosclerotic lesions of CKD patients than patients without CKD (8). Although patients with CKD are at higher risk for coronary syndrome compared with those without renal dysfunction, the manner of acute coronary disease clinical representations might be affected in CKD patients. Lower chest, arm, shoulder and neck pain and also more shortness of breath have been observed in CKD patients compared with control ones (9).

### **Risk factors of CAD**

According to the studies, the prevalence of several cardiovascular risk factors might be greater in patients with CKD compared to control ones, which can increase the coronary atherosclerosis occurrence rate. The influence of various coronary atherosclerotic risk factors have been studied in CKD population such as hypertension, increased blood cholesterol

concentration, lipoprotein(a), raised levels of fibrinogen, C-reactive protein, homocysteine, systolic blood pressure, body mass index, leukocyte count, etc (10). Accurate identification of the possible risk factors of coronary atherosclerosis might be beneficial in reducing the incidence rate of coronary heart disease.

The severity of coronary atherosclerosis would gradually increase due to the reduced kidney function and gradual fall of glomerular filtration rate (GFR), which is proposed as a major independent prognostic criterion of CAD. This poor prognosis has been observed even in CKD patients with the history of percutaneous coronary intervention or coronary artery bypass grafting (11). Decreased GFR and proteinuria in CKD patients gradually enhance coronary heart disease and other coronary atherosclerosis risk factors, which may eventually result in increased morbidity and mortality rate. The GFR <15 ml/min per 1.73 m<sup>2</sup> is estimated to be the deteriorative level, which can lead to further coronary complications in CKD patients (12). In one population based study, GFR < 90 mL/min/1.73 m<sup>2</sup> led to the mortality rate of 45.7% in older patients with CKD stage 4 (13). Patients with ESRD are at the highest risk of CAD within the CKD general population.

It has been proposed that various accompanying conditions with reduced renal function including advanced age, hypertension, diabetes mellitus, dyslipidemia, malnutrition, chronic inflammation, bone mineral disorders, endothelial dysfunction and etc. can increase the occurrence rate of advanced coronary atherosclerosis in CKD patients compared to patients without CKD (1,14). Decreased GFR can also result in elevation of other risk parameters of coronary atherosclerosis such as oxidative stress, anemia, and unusual calcium-phosphate metabolism (15).

Various risk factors affect the incidence of coronary heart disease among patients with CKD in different rates due to the dissimilar characteristics of patients such as the stage of renal dysfunction and diverse causes of the disease among patients. According to the studies, a wide range of 60-100 % has been demonstrated for the occurrence of hypertension, 63% for blood cholesterol, 9% for anemia, and higher than 27% for the diabetes in patients with CKD (16-18).

In the study of Acharji et al., 1291 patients had increased baseline levels of troponin among 2179 CKD patients who were included in the study (19). It was demonstrated that elevated baseline cardiac troponin level in CKD patients with acute coronary syndrome can be significantly associated with worse clinical outcome, higher rate of mortality and myocardial infarction in 30 days (HR = 2.05 (1.48–2.83)

and in one year HR = 1.72 (1.36–2.17)) (19).

In another study, it was concluded that the clinical characteristics of advanced CKD patients with myocardial infarction can be similar with clinical presentations of CKD patients without myocardial infarction on admission regarding chest pain, ST elevation and in-hospital mortality (20). In another study, systolic home blood pressure was proposed as a powerful predictor of ESRD and mortality, than clinic blood pressure (21).

### **Diagnosis of CAD**

Using reliable noninvasive screening test would be valuable in early detection of coronary artery disease among CKD patients. Identifying the ideal approach for early detection of coronary heart disease in patients with CKD is still under debate. The sensitivity and specificity of various tests have been studied such as resting and exercise electrocardiography, echocardiography, thallium dipyridamole scintigraphy, coronary angiography, computed tomography coronary angiography, perfusion magnetic resonance imaging, radionuclide perfusion imaging, and pharmacological stress echocardiography. Among all the examined tests, angiography was able to completely reveal the coronary artery disease in high-risk patients with CKD. In one study, performing angiography was suggested only for patients with positive stress test (22). Due to the low sensitivity and specificity of cardiac tests in patients with CKD, direct diagnostic cardiac catheterization was applied for high risk patients in some studies (23).

### **Preventing the CAD**

Because of the low number of randomized trials on CKD cases, evidence is limited regarding the advantageous and disadvantageous of strategies for preventing the coronary atherosclerosis in patients with CKD. Glycemic and blood pressure control, life style modifications such as smoking cessation, exercise, dietary salt reduction, and weight loss are several interventions suggested for CKD patients. According to a small trial, smoking cessation as a life style modification was not significantly beneficial in reducing the risk of coronary artery disease (24).

The efficacy of administering aspirin as a preventive medication has been investigated in some studies. Although bleeding is the possible adverse effect of daily aspirin usage, it has shown beneficial effect in decreasing cardiovascular complications risk in patients with GFR < 45 ml/min per 1.73m<sup>2</sup> (25).

### **Treatment of CAD**

Several drugs such as aspirin, clopidogrel, b-

blockers, and angiotensin-converting enzyme inhibitors (ACEIs)/ARBs (angiotensin receptor blockers) are used as medical therapies and they revealed similar benefits in the treatment of acute coronary artery disease in CKD patients.

Several studies evaluated the influence of using statins for patients in various stages of renal failure in reducing the atherosclerotic events including non-fatal myocardial infarction, coronary death, non-haemorrhagic stroke, etc. In the observational study of Seliger et al. in 2002, the efficacy of statins in reducing the mortality rate of ESRD patients on dialysis was investigated. According to this study a cardiovascular specific mortality reduction was observed among ESRD patients by using statins (aRR=0.63). Similar results were obtained in another observational study such as 23% reduction of cardiac mortality rate in ESRD patients using statins than those not prescribed statins (26). On the contrary, results obtained by one randomized blind controlled trials indicated, no beneficial reduction of mortality and myocardial infarction rate following administering rosuvastatin, 10 mg daily, in ESRD patients undergoing hemodialysis compared to placebo (Hazard ratio 0.96; 95% CI, 0.86 to 1.07; P=0.51) (27). In another randomized study with four years follow up duration, the efficacy of daily atorvastatin 20 mg was compared with placebo in reducing the cardiac mortality rate, myocardial infarction, and stroke in diabetes mellitus patients undergoing dialysis. According to the mentioned study, no beneficial effect was observed regarding the decrease in cardiovascular events (relative risk, 1.12; 95% CI, 0.81 to 1.55; P=0.49) or even mortality rate (relative risk, 0.93; 95% CI, 0.79 to 1.08; P=0.33) by using atorvastatin (28). The effect of using combination of simvastatin 20 mg plus ezetimibe 10 mg per day was evaluated on 4650 patients with moderate to severe renal failure, which compared with placebo on 4620 patients in a median of 4.9 years follow up. Although myocardial infarction or mortality rate were decreased in treatment group, it was not statistically significant (213 [4.6%] simvastatin plus ezetimibe vs. 230 [5.0%] placebo; rate ratio 0.92, 95% CI 0.76-1.11; long rank p=0.37) (29).

According to the Tsai et al., administering some contraindicated antithrombotic drugs such as enoxaparin, eptifibatide or both, for dialytic patients under nonsurgical coronary interventions, can increase the risk of in-hospital bleeding (30).

Conflicting evidence has been obtained through studies compared the efficacy of revascularization in patients with CKD. In CKD patients, the efficacy of several strategies for immediate treating of ST-elevation or non-ST elevation acute coro-

nary syndrome, have been evaluated such as primary percutaneous coronary intervention (PCI) and immediate angiography. According to one retrospective study, performing early invasive procedures can be detrimental in patients with advanced CKD (31).

Some observational studies reported an intense increased risk of complications following operation and procedural risks in CKD and ESRD patients such as coronary artery bypass graft (CABG). Based on mentioned studies, the possibility of death following CABG will be increased 3 to 7 times in patients with CKD compared with general population (32). Similar results were obtained regarding higher mortality rate and also postoperative complications such as sepsis and respiratory failure of CKD or ESRD patients underwent CABG (33). On the contrary, Hemmelgarn et al demonstrated the higher survival of CKD patients underwent CABG compared with medical therapy or PCI (34). In addition, 71% decline in risk of death was observed following CABG compared with PCI in patients with advance CKD in a retrospective study (35).

## Conclusion

Since the CKD patients are at higher risk of coronary artery disease, early identifying, managing, and controlling the cardiovascular risk factors at early stages of the CKD, might be beneficial in diminishing the progression of the coronary artery atherosclerosis of general CKD population. Accurate information about the exact mechanisms of coronary heart complications in CKD patients and the most beneficial strategy, which can be used as the treatment of choice, would be provided by conducting further studies.

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## Conflict of Interest

The authors declare no conflict of interest.

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