Review

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How do We Manage Coronary Artery Disease in Patients with CKD and ESRD?

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Chronic kidney disease (CKD) has been shown to be an independent risk factor for cardiovascular events. In addition, patients with pre-dialysis CKD appear to be more likely to die of heart disease than of kidney disease. CKD accelerates coronary artery atherosclerosis by several mechanisms, notably hypertension and dyslipidemia, both of which are known risk factors for coronary artery disease. In addition, CKD alters calcium and phosphorus homeostasis, resulting in hypercalcemia and vascular calcification, including the coronary arteries. Mortality of patients on long-term dialysis therapy is high, with age-adjusted mortality rates of about 25% annually. Because the majority of deaths are caused by cardiovascular disease, routine cardiac catheterization of new dialysis patients was proposed as a means of improving the identification and treatment of high-risk patients. However, clinicians may be uncomfortable exposing asymptomatic patients to such invasive procedures like cardiac catheterization, thus noninvasive cardiac risk stratification was investigated widely as a more palatable alternative to routine diagnostic catheterization. The effective management of coronary artery disease is of paramount importance in uremic patients. The applicability of diagnostic, preventive, and treatment modalities developed in nonuremic populations to patients with kidney failure cannot necessarily be extrapolated from clinical studies in non-kidney failure populations. Noninvasive diagnostic testing in uremic patients is less accurate than in nonuremic populations. Initial data suggest that dobutamine echocardiography may be the preferred diagnostic method. PCI with stenting is a less favorable alternative to CABG, however, it has a faster recovery time, reduced invasiveness, and no overall mortality difference in nondiabetic and non-CKD patients compared with CABG. CABG is associated with reduced repeat revascularizations, greater relief of angina, and increased long term survival. However, CABG is associated with a higher incidence of post-operative risks. The treatment chosen for each patient should be an individualized decision based upon numerous risk factors. CKD is associated with higher rates of CAD, with 44% of all-cause mortality attributable to cardiac disease and about 20% from acute MI. Optimal treatment including aggressive lifestyle modifications and concomitant medical therapy should be implemented in all patients to maximize benefits from either PCI or CABG. Future prospective randomized controlled trials with newer second or third generation DES and bioabsorbable DES are necessary to determine if PCI may be non-inferior to CABG in the future.

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Introduction

Prevalence of CKD is increasing worldwide. CKD is characterized by a progressive decline in glomerular filtration rate (GFR) over several years resulting in permanent kidney failure requiring dialysis or transplantation. In 2002, the National Kidney Foundation's Kidney Disease

Outcomes Quality Initiative (KDOQI) introduced a conceptual model for CKD. In this model, CKD was defined based on the presence of kidney damage or GFR (GFR <60 ml/min/1.73 m^2) for ≥3 months, irrespective of cause, and was classified into 5 stages based on the level of GFR[1]. Then in 2011, a new classification of CKD was proposed by the Kidney Disease: Improving Global Outcomes (KDIGO). They introduced a two-dimensional staging of the CKD according to the level of albuminuria in addition to the GFR level. Also, the previous CKD stage 3 was subdivided into two stages (G3a and G3b)[2]. When applied this new CKD classification system to the US population studies, about 12% (25 million) are estimated to have CKD[3].

The impact of CKD on cardiovascular and all-cause mortality has been well-established[4]. A one-year mortality rate of patients with end-stage renal disease (ESRD) is approximately 20% in US dialysis population and the single most contributor to this high mortality is cardiovascular disease, which accounts for over 50% of all deaths[3]. Although patients on dialysis are at greatest risk, with age-specific cardiovascular mortality rates of 10-100 times greater than those of the general population, the increased risk also extends to those with milder forms of CKD[5-7]. Coronary artery disease (CAD) is the main cause of death in patients with CKD[3], and the survival of patients with CKD who undergo coronary revascularization is worse than for other patients with CAD[8]. The incidence and severity of obstructive CAD increases as GFR declines[9,10]. In CKD, CAD has been shown to be diffuse multi-vessel involvement with vascular calcification[11]. In the US, about 500,000 patients are on renal replacement therapies (dialysis), but the number of patients with mild to moderate CKD is far greater compared to dialysis patients[3].

In this article, we are going to review epidemiology, pathogenesis, diagnosis, and treatment of CAD in patients with CKD and ESRD.

Epidemiology

Patients with CKD are at substantially higher risk for the development of cardiovascular disease (CVD) than those in the general population without CKD[3,12,13]. CKD has been shown to be an independent risk factor for cardiovascular events, and patients in the earlier stages of CKD are actually far more likely to die from CVD than to progress to ESRD[14]. In a large US community study involving over one million people, an independent, graded relationship was observed between estimated glomerular filtration rate (eGFR) and rates of death, cardiovascular events and hospitalization. Patients with estimated GFRs between 45 to 59, 30 to 44, 15 to 29 and less than 15 mL/min per1.73 m^2, had significantly higher hazard ratios for any cardiovascular event compared to patients with GFR of greater than 60 mL/min per 1.73 m^2 [13]. A similar relationship between eGFR and cardiovascular events was also demonstrated in the VALIANT trial of survivors of acute myocardial infarction complicated by left ventricular dysfunction. Below 81 ml/min, each 10 unit reduction in eGFR was associated with a 10% increase in the relative risk of cardiovascular death and non-fatal events[15]. In patients with CKD, CAD is the well-known leading cause of death[3] and small angiographic studies suggested that the incidence of CAD was more than 50% in unselected CKD 5D patients[16,17]. Among patients with CAD, concomitant CKD worsens the cardiovascular morbidity and mortality which are associated with kidney function inversely and independently, particularly at estimated GFR <15 ml/min per 1.73 m^2 [15,18,19]. CKD is also an independent predictor of mortality in acute coronary syndromes (ACS) without ST segment elevation. An increase in mortality and in re-infarction was evident in an analysis of almost 40,000 patients recorded in the databases of four acute coronary syndrome trials. They showed that a significant proportion of patients who present with ACS have abnormal renal function. Compared with patients with normal renal function, those with abnormal renal function also have more adverse baseline clinical characteristics. Most importantly, abnormal renal function is an independent predictor of adverse outcomes[18]. For dialysis patients, myocardial infarction is a catastrophic event even in the era of advanced reperfusion therapy. Herzog et al.[20] reported that one- and two-year mortality rates

after acute myocardial infarction among patients on long term dialysis were 61% and 74%, respectively. An analysis of the USRDS Dialysis Morbidity and Mortality Study (DMMS) Wave 2 showed that the incidence of hospitalizations for acute coronary syndrome was 29 per 1,000 person years and the incidence of acute myocardial infarction (AMI) was 19 per 1,000 person years and one- and three-year mortality rates were 50% and 80%, respectively[21]. Although the absolute incidence and mortality rate of MI in advanced CKD patients is definitely increased[3], traditional risk factors for CVD are common in CKD. However, the degree to which CKD is associated with the risk of initial MI independently has not been well defined until now.

Pathogenesis

Traditional CVD risk factors are commonly present in CKD patients, but do not fully explain the high incidence of cardiovascular events or increased mortality rates in these patients[22-24] and their association with cardiovascular outcomes could be attenuated or even reversed at the most advanced stages[25]. A wide variety of traditional and non-traditional CV risk factors are present in patients with CKD at all stages, but particularly in those receiving dialysis[14]. Traditional risk factors for CVD in patients with CKD are similar to those for the general population. They include older age, male sex, hypertension, diabetes mellitus, dyslipidemia, cigarette-smoking, physical inactivity, and a family history of premature CVD. A variety of non-traditional CV risk factors, such as hyperhomocysteinemia, increased oxidative stress and inflammation, endothelial cell dysfunction, activation of the renin-angiotensin-aldosterone and the sympathetic nervous systems, vascular calcification due to abnormal calcium and phosphate metabolism, and anemia facilitate CVD risks in CKD. Many of the therapies that are highly effective in reducing CV risk in the general population are ineffective or marginally effective in patients with CKD, particularly those receiving dialysis[26]. Muntner et al.[27] showed that some risk factors for coronary heart disease (CHD) among the general population still remain predictive among patients with CKD and control of these risk factors may have a substantial impact on their excess burden of CHD. Inflammation and oxidative stress have been associated with the pathogenesis of atheromatous plaque formation. Both non-traditional and traditional risk factors are advocated with worse cardiovascular outcomes and the role of inflammation and its principal cause, oxidative stress, are investigated as potential targets of pharmacologic therapy[28,29]. The role of aldosterone in renal and cardiovascular injury, including inflammation, tissue remodeling and fibrosis, has been demonstrated and recently the role of mineralocorticoid excess in the development of cardiovascular complications is increasingly recognized. Aldosterone can exert deleterious effects in the vascular system and kidney independently of angiotensin II[30]. Recently several studies have shown the impact of disordered mineral and bone metabolism on the pathogenesis of CAD in CKD patients[31,32]. Treatment with the active vitamin D analogue calcitriol appears to be associated with significantly greater survival in patients with CKD not yet receiving dialysis[32]. Abnormal vascular pathology in patients with CKD is attributable to two different mechanisms, namely atherosclerosis and arteriosclerosis. Atherosclerosis is an intimal disease that is characterized by fibroatheromatous plaques and occlusive disease[33]. In CKD, there are distinct morphological differences comprised of increased plaque calcification and intimal and medial thickness[34]. These changes promote chronic myocardial ischemia, particularly in the small distal coronary arteries and fibrosis, which may explain the high incidences of sudden cardiac death, heart failure and a lower incidence of acute plaque rupture in patients with CKD[35]. The other characteristic vascular pathology in CKD is the thickening and calcification of the medial arterial layer known as 'arteriosclerosis'. Concomitant increased collagen contents in the vessel wall, hyperplasia and hypertrophy of the vascular smooth muscle cells result in wall hypertrophy and stiffening of large conduit arteries[33]. These changes disturb arterial dampening function and result in increased systolic and pulse pressures. These alte-

rations influence an increased left ventricular afterload and myocardial oxygen demand and also influence altered coronary perfusion and sub-endocardial blood flow distribution. There is little information regarding whether patients with CKD have a high incidence of vulnerable plaques in their coronary arteries. Recently, Nakano et al.[36] reported that elderly patients with CKD have intimal neoangiogenesis and an increased risk of intraplaque hemorrhage in coronary arteries, possibly favored by local accumulation of oxidized low-density lipoprotein (LDL) and vascular endothelial growth factor (VEGF). Kato et al.[37] also compare the coronary plaque characteristics of patients with and without CKD using optical coherence tomography (OCT). They identified 463 non-culprit coronary plaques from 287 patients from the Massachusetts General Hospital OCT registry. Compared to non-CKD patients, the patients with CKD had a larger lipid index with a higher prevalence of calcium, cholesterol crystals and plaque disruption.

Diagnosis

Although coronary heart disease is extremely common in CKD patients, a routine screening test is not currently recommended in the absence of clinical symptoms and signs of cardiovascular disease. Early detection of coronary atheromatous plaque may possibly permit coronary vascular interventions. However, the increased prevalence of CAD among CKD patients diminishes the negative predictive value of diagnostic studies in this population[38]. Also, major cardiovascular disease trials frequently exclude patients with renal disease and do not provide adequate information on the renal function of enrollees or the effect of interventions on patients with renal disease[39]. For these reasons, CKD patients are underrepresented in major cardiac cohort studies evaluating the diagnostic sensitivities and specificities of non-invasive cardiac tests. In patients with CKD and symptomatic coronary heart disease, we usually do cardiac evaluations as in general populations. However, chest pain does not correlate well with CAD in CKD patients and severe CAD is common in asymptomatic patients with CKD, because of autonomic dysfunction secondary to uremia and diabetes[40]. So, CV risk screening in CKD is unique in that there are no definite correlations between anatomic CAD and symptoms of CAD. Diagnosis of ACS may sometimes be problematic in CKD patients because the classic triad of ischemic symptoms such as, chest pain, elevated cardiac biomarkers, and typical electrocardiographic changes is frequently absent. The clinical characteristics of dialysis patients hospitalized for AMI are strikingly different from those of nondialysis AMI patients. There are lower indexes of clinical suspicion for initial diagnosis of ACS, less chest pain, less ST elevation, and twice frequent cardiac arrest in dialysis patients with AMI[41]. Sosnov et al.[42] reported that patients with CKD are more likely to present with shortness of breath and less frequently present with symptoms relating to the arm, shoulder, neck, and chest pain. They concluded that patients with kidney disease experience AMI differently from patients without kidney disease. The etiology of these differences in AMI cannot be determined. However, kidney disease impacts on multiple organ systems, a large number of possible mechanisms exist by which kidney disease might affect the acute symptom profile. In patients with CKD and expecting kidney transplantation, conflicting data exists on the best method of cardiac screening. De Lima et al.[43] evaluated prospectively the accuracy of 2 noninvasive tests and risk stratification in detecting CAD (>or=70% obstruction) and assessing cardiac risk by using coronary angiography (CA). One hundred twenty-six renal transplant candidates underwent myocardial scintigraphy (SPECT), dobutamine stress echocardiography, and coronary angiography. They were followed for 6 to 48 months. The prevalence of CAD was 42%. The sensitivities and negative predictive values for the 2 noninvasive tests and risk stratification were <75%. After 6 to 48 months, there were 18 cardiac events, 9 fatal. Risk stratification ($p=0.007$) and CA ($p=0.0002$) predicted the crude probability of surviving free of cardiac events. The probability of event-free survival at 6, 12, 24, 36, and 48 months were 98%, 98%, 94%, 94%, and 94% in patients with <70% stenosis on CA and 97%, 87%, 61%,

56%, and 54% in patients with >or=70% stenosis. Multivariate analysis showed that the sole predictor of cardiac events was critical coronary lesions (p=0.003). The authors suggested that CA may still be necessary for detecting CAD and may be the best screening method to detect CAD. Other studies have shown that simple clinical risk stratification as well as noninvasive testing is enough to reduce the morbidity and mortality of CV disease after kidney transplantation[44]. Any screening test is associated with false-positive and false-negative results that may lead to the possibility of additional and unnecessary diagnostic procedures. Last year, AHA/ACCF scientific statement released a new guideline. They recommend that noninvasive stress testing may be considered in kidney transplantation candidates with no active cardiac conditions on the basis of the presence of multiple CAD risk factors regardless of functional status. Relevant risk factors include diabetes mellitus, prior CVD, over 1 year on dialysis, left ventricle hypertrophy (LVH), age >60 year, smoking, hypertension, and dyslipidemia; the specific number of risk factors that should be used to prompt testing remains to be determined, but the committee considers >3 to be reasonable[45].

Serum markers such as creatinine kinase (CK), CK-MB isoform, and cardiac troponins (cTns) may be elevated in the absence of true myocardial necrosis, possibly because of myocardial apoptosis or silent micro-infarction due to small vessel disease[46]. Whatever the mechanism involved, serial serum cardiac troponin level elevation is indicative of acute myocardial damage. This mandates careful attention to trends of serum cardiac troponin titers over time. In routine resting electrocardiography (EKG), LVH with a strain pattern which is frequently seen in patients with CKD may mask diagnostic ST depression in ACS. In case of exercise EKG, many CKD patients are not able to exercise fully to a level of diagnostic workload and the ST-segment response is not specific for myocardial ischemia[40,47]. The sensitivity and specificity of non-invasive cardiac tests in CKD patients is much lower than that in the general population. Radionuclide perfusion imaging is more sensitive but less specific than stress echocardiography for diagnosis of significant CAD in patients on renal replacement therapy[40]. Vandenberg et al.[48] retrospectively compared pharmacologic stress thallium scintigraphy with CA and demonstrated 62% sensitivity and 76% specificity for CA stenosis of >75%. Several factors attributed to the lower sensitivity in CKD population. CKD patients have higher levels of basal adenosine resulting in a high resting coronary flow. Pharmacologic myocardial perfusion imaging uses dipyridamole (which works by increasing endogenous adenosine levels) or adenosine as vasodilator to induce stress by challenging the flow reserve. Patel et al.[49] studied 600 patients undergoing pre-KT evaluation and among these, 174 had SPECT imaging done. In these patients, adverse outcomes were predicted by an abnormal SPECT (the only multivariate predictor), whereas event free survival was 97% in patients with a normal SPECT over a 42 month follow-up period. Thus, a negative SPECT carries a very favorable prognostic value in the short and long term prediction of low cardiac events used as an endpoint. A positive SPECT also carries adverse outcomes and warrants aggressive medical therapy and consideration of revascularization if ischemic burden is high. Echocardiography, in conjunction with stress by dobutamine or dipyridamole, is a standard method. However, it should be cautioned that this method may be associated with approximately 2%-4% risk of transient atrial fibrillation in dialysis patients, compared to only 0.5% in the general population. An advantage of echocardiography is that prestress imaging can provide additional information on LV ejection fraction and dimensions, valvular disease, pulmonary artery pressure, and volume status, as well as associated pericardial disease (e.g., pericardial effusion)[50].

Treatment

Patients with CKD on dialysis experience extremely high mortality rates, especially from causes related to CVD[5]. The association of traditional risk factors with better survival in these patients, also termed "reverse epidemiology (RE)", have been described for over a decade and has led to a debate over the plausibility of these findings and

over the benefit of interventions targeting these traditional risk factors in patients on dialysis[51]. The altered relationship of traditional and nontraditional risk factors with cardiovascular outcomes in patients with CKD ensued and there were doubts about the relevance of existing standards of care to these patients[39,52]. The lack of definitive randomized trials to treat CVD in patients with CKD leaves many questions. Currently, treatment decisions are often based on extrapolation from trials in other populations and observational studies in CKD and dialysis patients. These unique features of coronary artery disease in CKD could reduce the absolute benefit of treatment with standard cardiovascular therapies. It is possible that patients with CKD have similar risk-benefit profiles from cardiovascular therapies compared with general population. However, there may be higher absolute benefit in patients with CKD, the absolute risks may also be higher leading to little or no risk-benefit. Evidence of the efficacy of traditional risk factor intervention such as, glycemic control, blood pressure (BP) control, dyslipidemia control, or lifestyle modification to reduce cardiovascular events in patients with advanced CKD remain limited. The role of glycemic control in diabetic ESRD is of growing importance because of the magnitude of the population worldwide and associated worse overall prognosis compared with the general dialysis population. Shurraw et al.[53] reported that in 1,484 incident North American hemodialysis patients during a follow-up of up to 8 years, increased serum glucose and hemoglobin A1c (HbA1c) levels were not independently and directly associated with mortality. Strict glycemic control may not benefit CKD 5D patients with or without diabetes mellitus. Hypertension as a risk factor for CVD in the general population is a well known fact. However, hypertension has not been consistently associated with adverse outcomes and in certain circumstances even seem to be protective. A 'U-shaped' curve has been observed between systolic blood pressure and cardiovascular mortality among patients on dialysis, in contrast to a 'J-shaped' curve in the general population[54,55]. Randomized data on the efficacy of specific BP goals in CKD 5D patients are also lacking. The labile nature of BP and the absence of clear associations between hypertension and adverse cardiovascular outcomes in CKD 5D preclude definitive recommendations about BP control[56]. For example, among incident hemodialysis patients, a low systolic blood pressure was associated with increased mortality during the first 2 years after starting dialysis, while a high systolic blood pressure was associated with increased mortality in patients who survived beyond 3 years[57]. Dyslipidemia is frequently encountered in patients with CKD. KDOQI clinical practice guidelines recommend a treatment goal of LDL-cholesterol level in adult patients with CKD to be less than 100 mg/dL[58]. However, data supporting the benefit of HMG CoA reductase inhibitors for dyslipidemia to reduce cardiovascular risk in patients with CKD are limited. Post hoc subgroup analyses of large statin trials in the general population have suggested that the benefit of statin treatment in people with stage 3 CKD is similar to or greater than that of people with normal renal function. In the Pravastatin Pooling Project, among the 4,491 subjects with moderate CKD, pravastatin (40 mg daily) significantly reduced the incidence of the combined primary outcome of time to myocardial infarction, coronary death, or coronary revascularization (HR=0.77, 95% CI=0.68-0.86) in patients with an eGFR of 30-59 ml/min per 1.73 m^2, similar to the effect of pravastatin on the primary outcome in subjects with normal renal function (HR=0.78, 95% CI=0.65-0.94)[59]. However, in the PREVEND-IT (Prevention of Renal and Vascular End-stage Disease Intervention Trial) study, pravastatin was not associated with a reduction in risk of cardiovascular mortality and hospitalization for cardiovascular morbidity (RR=0.87, 95% CI=0.49-1.57, p=0.649)[60]. Two large clinical trials comparing statins with placebo in hemodialysis patients did not demonstrate any clinical benefit[61,62]. In the randomized 4D study (Die Deutsche Diabetes Dialyze Studie), treatment with atorvastatin (20 mg daily) had no significant effect on the composite primary end point of cardiovascular death, nonfatal myocardial infarction and stroke (RR=0.92, 95% CI=0.77-1.10) compared with placebo, despite a 42% reduction in LDL-cholesterol levels in this high risk pop-

ulation[61]. Investigators in the AURoRA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) trial randomly assigned 2,776 patients on maintenance hemodialysis to rosuvastatin (10 mg daily) or placebo. Despite a 42.9% reduction in LDL-cholesterol levels, from a mean baseline value of 100±35 mg/dL, and an 11.5% reduction in median high sensitivity C reactive protein (CRP) levels, rosuvastatin had no effect on the combined primary end point of death from cardiovascular causes, nonfatal myocardial infarction and nonfatal stroke (HR=0.96, 95% CI=0.84-1.11) or on its individual components[62]. Recently, the SHARP (Study of Heart and Renal Protection) trial results showed that reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced CKD. In the SHARP trial, the combination of simvastatin and ezetimibe in CKD patients (including CKD 5D) reduced major atherosclerotic events by 17%, but did not appear to reduce overall mortality. As no significant harm from statin use was also demonstrated, this reduction in nonfatal events provides a rationale for the use of statins in CKD patients despite the apparent lack of efficacy in reducing the risk of death. After the SHARP trial results, statins may now be the best-studied evidence-based medical therapy in the context of advanced CKD[63]. Lifestyle modifications have not been widely studied in CKD patients; in a small trial, multifactorial intervention that included smoking cessation was not associated with significant cardiovascular benefits[64]. 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 regarding efficacy of prophylactic aspirin in advanced CKD are sparse. Subgroup analyses of randomized trials have demonstrated convincing cardiovascular risk reduction from daily aspirin in individuals with estimated GFR <45 ml/min per 1.73 m^2, including CKD 5D patients, despite higher incidence of bleeding in CKD patients[65,66].

There are no randomized trials of the benefits of reperfusion therapy in CKD. However, there is little reason to believe that renal function impairment diminishes the benefits of immediate reperfusion therapy in acute ST-elevation MI. Randomized controlled trials have demonstrated better outcomes with primary percutaneous coronary intervention (PCI) over fibrinolytic therapy in the treatment of ST segment elevation myocardial infarction (STEMI) patients with normal renal function[67]. Practice guidelines consider primary PCI as the preferred reperfusion strategy for patients presenting with STEMI. A recent retrospective analysis of STEMI patients from 2 large public hospitals in Singapore showed that patients with an admission GFR <60 mL/min per1.73 m^2 who were treated with primary PCI, experienced a lower 30-day unadjusted mortality compared to patients treated with fibrinolysis. Adjusted mortality revealed a point estimate (adjusted OR, 0.7) favoring primary PCI over fibrinolysis; however, this did not achieve statistical significance (p=0.4). In contrast, among patients with an admission GFR ≥60 mL/min per 1.73 m^2, primary PCI was associated with a greater improvement in the point estimate (adjusted OR, 0.4), which achieved statistical significance (p=0.02). The authors suggest the need for randomized trials of primary PCI versus fibrinolytic therapy among patients with renal dysfunction who present with STEMI. However, when immediately available, primary PCI may be the treatment of choice irrespective of CKD status[68]. Among patients with impaired renal function presenting with STEMI, uncertainty remains as to which reperfusion strategy achieves superior outcomes. Although there are no randomized studies comparing primary PCI versus fibrinolytic therapy among STEMI patients with impaired renal function, observational studies have analyzed treatment outcomes associated with either reperfusion strategy in this population[69,70]. In the 2002 Acute Coronary Syndrome Israeli Survey (ACSIS) studied to determine the effect of different myocardial reperfusion modalities on short- and long-term outcomes in 132 STEMI with renal failure patients. Thirty-day crude mortalities were 8.3% in the thrombolysis group, 40.0% in the primary PCI

group, and 29.7% in the no-reperfusion group (p<0.03). Crude and adjusted mortality odds ratios that were observed at 7, 30, and 365 days, with the thrombolysis group as the reference, were 3.1 to 8.1 in the PCI group and 1.5 to 4.6 in the no-reperfusion group. The authors suggest that thrombolysis may represent the preferred modality of reperfusion therapy in patients with renal failure and ST-elevation acute myocardial infarction[69]. In the GRACE (Global Registry of Acute Coronary Events) study, the relative benefit of reperfusion was assessed in 12,532 patients with renal dysfunction and ST-segment elevation/left bundle branch block. As renal function declined, hospital mortality and morbidity increased (both p<0.001) and reperfusion rates decreased. Fibrinolysis was not associated with reduced hospital or 6-month mortality in patients with renal dysfunction. Primary PCI was not associated with lower hospital mortality in patients with renal dysfunction but was associated with lower 6-month mortality in those with moderate dysfunction. Both strategies of reperfusion were associated with higher mortality and outcomes remain poor with severe renal dysfunction, despite receipt of reperfusion therapy[70]. 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. Analysis of 7 contemporary randomized trials in over 8,000 NSTE-ACS patients treated in the era of potent antiplatelet therapy and coronary stents show that early invasive therapy decreases mortality by 25% at a mean of 2 years of follow-up, compared with a more conservative approach. Early invasive therapy also decreases nonfatal myocardial infarction by 17% and recurrent unstable angina requiring rehospitalization by 31%[71]. The survival of patients with CKD who undergo coronary revascularization is worse than for other patients with coronary artery disease. The association between renal dysfunction (RD) and worse outcomes after CABG surgery for patients not on dialysis has been linked closely. Both RD and ESRD are important risk factors for patients undergoing cardiopulmonary bypass. Despite this risk, increasing numbers of patients with RD and ESRD are being referred for coronary revascularization and CABG in particular. Operative mortality rose inversely with declining renal function, from 1.3% for those with normal renal function to 9.3% for patients with severe RD not on dialysis and 9.0% for those who were dialysis dependent. After adjustment for other covariates, preoperative GFR was one of the most powerful predictors of operative mortality and morbidities[72]. Conversely, a recent retrospective analysis of all non-ST-elevation MI patients in Sweden suggested that an early invasive strategy was associated with greater 1-year survival in patients with non-ST-elevation MI and mild to moderate renal insufficiency, but the benefit declines with lower renal function, and harmful for CKD 5 patients[73]. There is a paucity of data regarding revascularization in CKD patients with stable angina. Surgical coronary revascularization is 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[74,75]. No randomized clinical trials directly compare coronary revascularization strategies in advanced CKD patients. For patients with CKD enrolled in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, optimal medical therapy was effective and associated with the same BP and lipid levels as in patients without CKD. A subgroup analysis of the COURAGE trial did not find a benefit from PCI compared with medical therapy in 320 patients with stage 3-4 CKD and predominantly anatomically low-risk, multivessel disease[76]. The ARTS (Arterial Revascularization Therapies Study) trial randomly assigned 1,205 participants with and without CKD to CABG or PCI with multivessel stenting. Among them, 290 participants (25%) had CKD at entry into ARTS. One hundred fifty-one received PCI, and 139 received CABG. No difference was observed in the primary endpoint with CABG or PCI among CKD participants (adjusted HR of CABG versus PCI=0.93; 95% CI=0.54-1.60; p=0.97). However,

CABG was associated with a reduced risk for repeat revascularization (HR=0.28; 95% CI=0.14-0.54; p<0.01). Compared with participants with normal renal function, CKD was associated with a nearly 2-fold risk for the primary outcome (unadjusted HR=1.9; 95% CI=1.4-2.7; p<0.01). After multivariate adjustment, this association remained significant (HR=1.6; 95% CI=1.1-2.4). In this study, treatment with CABG or PCI with multivessel stenting led to similar outcomes of death, MI, or stroke, but CABG was associated with decreased repeat revascularizations. When compared with ARTS participants with normal renal function, those with CKD had a substantially elevated risk of adverse clinical outcomes after coronary revascularization[77]. Observational data consistently show increased risk of serious operative complications in CKD patients. Incidence of operative mortality after CABG rose inversely with declining renal function, from 1.3% for those with normal renal function to 9.3% for patients with severe renal dysfunction not on dialysis and 9.0% for those with dialysis[72]. Charytan and Kuntz[78] reported that in-hospital death occurred in 11.1 % of dialysis patients compared to 3.4% of non-dialysis patients. Operative mortality in dialysis patients still remains high despite recent advances in CABG surgery. However, among CKD patients undergoing coronary revascularization, death is more frequent than ESRD. The incidence of ESRD was lower throughout follow-up after PCI, but long-term risk of death was lower after CABG. Overall clinical outcome with CABG is better than with PCI in CKD patients[79]. Nevertheless, PCI still may be an alternative therapeutic modality because of low perioperative mortality and morbidity compared with CABG surgery. In a study of CKD 5D patients undergoing first revascularization, in-hospital mortality was lower with PCI (4.1% versus 8.6%), but 2-year survival was better with CABG (56.4% versus 48.4%)[80]. Studies in the drug-eluting stent (DES) era provide conflicting evidence on their benefit in CKD patients. A retrospective study by Ishio et al.[81] reported thatwhether DES was superior to bare metal stent (BMS) in 54 dialysis patients with 69 lesions. DES with sirolimus reduced in stent restenosis compared with BMS. However, no statistically significant difference was found for in-segment restenosis or target lesion revascularization. Few published data describes the long-term survival of dialysis patients undergoing surgical versus percutaneous coronary revascularization in the era of DES. Shroff et al.[82] recently conducted a retrospective study of 23,033 US dialysis patients who underwent coronary revascularizations (6,178 coronary artery bypass graftings, 5,011 BMS, 11,844 DES) from 2004 to 2009. In-hospital mortality for coronary artery bypass grafting patients was 8.2%; all-cause survival at 1, 2, and 5 years was 70%, 57%, and 28%, respectively. In-hospital mortality for DES patients was 2.7%; 1-, 2-, and 5-year survival was 71%, 53%, and 24%, respectively. Independent predictors of mortality were similar in both cohorts: age >65 years, white race, dialysis duration, peritoneal dialysis, and congestive heart failure, but not diabetes mellitus. Survival was significantly higher for coronary artery bypass grafting patients who received internal mammary grafts (IMG) (HR=0.83; p<0.0001). The probability of repeat revascularization accounting for the competing risk of death was 18% with BMS, 19% with DES, and 6% with coronary artery bypass graftings at 1 year. They concluded that among dialysis patients undergoing coronary revascularization, in-hospital mortality was higher after coronary artery bypass grafting, but long-term survival was superior with IMG. In-hospital mortality was lower for DES patients, but the probability of repeat revascularization was higher and comparable to that in patients receiving a BMS. The findings from this study support the recently popularized notion of adopting a heart team approach (i.e., deriving input from interventional cardiologists and cardiovascular surgeons to determine an individualized, optimal approach) for coronary revascularization in dialysis patients. DES may be a reasonable consideration in dialysis patients in whom an IMG (typically used to bypass the left anterior descending coronary artery vascular territory) is not an appropriate option in the revascularization strategy or whose overall life expectancy is judged to be limited. Revascularization decisions for dialysis patients should be carefully performed and individualized.

Conclusion

CKD has been shown to be an independent risk factor for cardiovascular events, and patients with pre-dialysis CKD appear to be more likely to die of heart disease than of kidney disease. CKD accelerates coronary artery atherosclerosis by several mechanisms, notably hypertension and dyslipidemia, both of which are known risk factors for coronary artery disease. In addition, CKD alters calcium and phosphorus homeostasis, resulting in hypercalcemia and vascular calcification, including the coronary arteries. Mortality of patients on long-term dialysis therapy is high, with age-adjusted mortality rates of about 25% annually. Because the majority of deaths are caused by cardiovascular disease, routine cardiac catheterization of new dialysis patients was proposed as a means of improving the identification and treatment of high-risk patients. However, clinicians may be uncomfortable exposing asymptomatic patients to invasive procedures such as cardiac catheterization, thus noninvasive cardiac risk stratification was investigated widely as a more palatable alternative to routine diagnostic catheterization. Whether invasive or noninvasive, the premise behind screening dialysis patients is that there is a high frequency of obstructive coronary artery disease (CAD) in this population, even in the absence of classic angina, and that intervention on asymptomatic obstructive coronary lesions could prevent heart attacks and cardiac death in long-term dialysis patients. The effective management of coronary artery disease is of paramount importance in uremic patients. The applicability of diagnostic, preventive, and treatment modalities developed in nonuremic populations to patients with kidney failure cannot necessarily be extrapolated from clinical studies in non-kidney failure populations. Vigorous attempts to treat lipid abnormalities in this population are appropriate, as is attention to other remediable coronary risk factors. Noninvasive diagnostic testing in uremic patients is less accurate than in nonuremic populations. Initial data suggest that dobutamine echocardiography may be the preferred diagnostic method. Although some of the new antiplatelet agents used in ACS require downward dose adjustment or are contraindicated, most anti-angina medications do not require dose adjustments for kidney disease. Erythropoietin therapy is effective in reversing the cardiovascular perturbations that accompany the anemia of kidney failure, but an aggressive approach of normalizing the hematocrit cannot be recommended. Thrombolytic agents are underutilized in the management of MI. Coronary revascularization offers relative clinical advantages over medical therapy similar to non-kidney failure populations. PCI with coronary stenting is the preferred revascularization approach, and conventional balloon PTCA is the least favorable approach. PCI with stenting is a less favorable alternative compared to CABG, however, it has with a faster recovery time, reduced invasiveness, and no overall mortality difference in nondiabetic and non-CKD patients compared with CABG. CABG is associated with reduced repeat revascularizations, greater relief of angina, and increased long term survival. However, CABG is associated with higher incidence of post-operative risks. The treatment chosen for each patient should be an individualized decision based upon numerous risk factors. CKD is associated with higher rates of CAD, with 44% of all-cause mortality attributable to cardiac disease and about 20% from acute MI. Optimal treatment including aggressive lifestyle modifications and concomitant medical therapy should be implemented in all patients to maximize benefits from either PCI or CABG. Future prospective randomized controlled trials with newer second or third generation DES and bioabsorbable DES are necessary to determine, if PCI may be noninferior to CABG in the future.

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