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The Scope of Coronary Heart Disease in Patients With Chronic Kidney Disease

Fadi G. Hage, MD,*† Rajesh Venkataraman, MD,* Gilbert J. Zoghbi, MD,*† Gilbert J. Perry, MD,* Angelo M. DeMattos, MD,‡ Ami E. Iskandrian, MD*

Birmingham, Alabama; and Davis, California

Chronic kidney disease (CKD) affects approximately 13% of the U.S. population and is associated with increased risk of cardiovascular complications. Once renal replacement therapy became available, it became apparent that the mode of death of patients with advanced CKD was more likely than not related to cardiovascular compromise. Further observation revealed that such compromise was related to myocardial disease (related to hypertension, stiff vessels, coronary heart disease, or uremic toxins). Early on, the excess of cardiovascular events was attributed to accelerated atherosclerosis, inadequate control of blood pressure, lipids, or inflammatory cytokines, or perhaps poor glycemia control. In more recent times, outcome research has given us further information that relates even lesser degrees of renal compromise to an excess of cardiovascular events in the general population and in those with already present atherosclerotic disease. As renal function deteriorates, certain physiologic changes occur (perhaps due to hemodynamic, inflammatory, or metabolic changes) that decrease oxygen-carrying capacity of the blood by virtue of anemia, make blood vessels stiffer by altering collagen or through medial calcinosis, raise the blood pressure, increase shearing stresses, or alter the constituents of atherosclerotic plaque or the balance of thrombogenesis and thrombolysis. At further levels of renal dysfunction, tangible metabolic perturbations are recognized as requiring specific therapy to reduce complications (such as for anemia and hyperparathyroidism), although outcome research to support some of our current guidelines is sorely lacking. Understanding the process by which renal dysfunction alters the prognosis of cardiac disease might lead to further methods of treatment. This review will outline the relationship of CKD to coronary heart disease with respect to the current understanding of the traditional and nontraditional risk factors, the role of various imaging modalities, and the impact of coronary revascularization on outcome. (J Am Coll Cardiol 2009;53:2129–40) © 2009 by the American College of Cardiology Foundation

The increasing prevalence of chronic kidney disease (CKD) is staggering. Current estimates from the U.S. show that 13% of the population has CKD, with 341,000 on chronic dialysis and 140,000 with kidney transplants (1–3).§ This epidemic is a direct result of the rising tide of the major causes of CKD, namely, diabetes mellitus (DM) and hypertension (4). Diabetes mellitus has long been recognized as a risk factor for coronary heart disease (CHD) events, but emerging evidence suggests that intensive blood sugar control in patients with type 1 and 2 DM results in delayed reductions of CHD events long after the cessation of intervention, perhaps by slowing the progression of CKD (5–7).

Recent studies suggest that CKD is associated with increased risk of cardiovascular (CV) morbidity and mortality in a manner independent of DM (8,9). This association is even more evident in patients with end-stage renal disease (ESRD), where CV mortality accounts for 45% of all-cause mortality (2). Sudden cardiac death constitutes 62% of the CV mortality in ESRD or a full one-fourth of all-cause mortality (Fig. 1) (10,11). According to another estimate, the annual rate of sudden cardiac death of an ESRD patient receiving dialysis is approximately 7% (11). Although the exact proportion of CKD patients that succumb to sudden death secondary to CHD is unknown, the

From the *Division of Cardiovascular Diseases, University of Alabama at Birmingham, Birmingham, Alabama; †Section of Cardiology, Birmingham Veteran's Administration Medical Center, Birmingham, Alabama; and the ‡Division of Nephrology, University of California Davis, Davis, California. Dr. Iskandrian has served as consultant for Astellas, CV Therapeutics and received research grants from Astellas, CV Therapeutics, and Molecular Imaging. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government. Drs. Hage, Venkataraman, and Zoghbi contributed equally to this report.

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§According to the National Kidney Foundation guidelines, CKD is defined according to the presence or absence of kidney damage and level of kidney function as assessed by the glomerular filtration rate (GFR) (in ml/min/1.73 m^2) into 5 stages; stages 1 and 2 are characterized by kidney damage (structural or functional abnormalities such as proteinuria) with normal or elevated GFR (≥90 in stage 1) or mildly decreased (60 to 89 in stage 2), or by decreased GFR irrespective of kidney damage (GFR 30 to 59, 15 to 29, and <15 or dialysis for stages 3 to 5, respectively). In this review, measured or estimated GFR and creatinine clearance will be designated by GFR for clarity (3).

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CHD = coronary heart disease
CKD = chronic kidney disease
CRP = C-reactive protein
CV = cardiovascular
DM = diabetes mellitus
EF = ejection fraction
ESRD = end-stage renal disease
GFR = glomerular filtration rate
LV = left ventricular
LVH = left ventricular hypertrophy
MI = myocardial infarction
MPI = myocardial perfusion imaging
PCI = percutaneous coronary intervention
RT = renal transplantation

major contributors to this elevated risk of sudden death are CHD, myocardial structural changes, electrolyte imbalance, and autonomic dysfunction (11). CKD is known to affect cardiac structure and function. By the time patients reach ESRD, left ventricular hypertrophy (LVH) is almost universal and left ventricular (LV) mass has been correlated with survival in this patient population. ESRD also results in cardiac fibrosis and in LV systolic and diastolic dysfunction, all of which could be related to the increased incidence of sudden death (12). One of the consequences of decreased glomerular filtration rate (GFR) is increased calcification of both the coronary and the systemic arteries. These could cause coronary artery narrowing but, also of importance, decreased compliance of the aorta and the resultant increase in cardiac afterload (12). Despite this, many if not most CV trials have systematically excluded CKD patients, thus potentially limiting some beneficial therapies from this high-risk population (13). The interaction between the heart and the kidneys is complex and has been reviewed recently in the *Journal* (14); we will outline here the relationship of CKD to CHD with respect to the current understanding of the risk factors, imaging modalities, and coronary revascularization.

CHD Risk Factors

It is now generally accepted that CKD patients are at high risk for CV events. Estimates from several trials indicate that CV disease accounts for more than 50% to 60% of all deaths in patients with CKD before ESRD; most patients with CKD succumb to CV death before developing ESRD (3). Both the mortality and the CV events increase with decreasing GFR below 60 ml/min/1.73 m^2 (adjusted hazard ratio: 1.2, 1.8, 3.2, and 5.9 for death and 1.4, 2.0, 2.8, and 3.4 for CV events for GFR categories 45 to 59, 30 to 44, 15 to 29, and <15 ml/min/1.73 m^2, respectively) (8). Less appreciated is that the mortality of patients with CKD is higher than the general population after incident myocardial infarction (MI) and after undergoing percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or even insertion of an implantable cardiac-defibrillator (Fig. 2) (10,15–17). Therefore, current guidelines consider patients with CKD to be CHD risk equivalent for risk factor management (18). Although almost all traditional risk factors (advanced age, male sex, DM, hypertension, dyslipidemia, tobacco consumption, obesity, sedentary lifestyle, and family history of CHD) show increased prevalence in patients with CKD, there has been doubt over their contribution to risk in this population due to the phenomenon of reverse epidemiology (19). Data from the U.S. Renal Data System in ESRD patients show that overall and CV mortality increase sharply for systolic blood pressures lower than 110 mm Hg but are relatively flat afterward (20). Similarly, mortality is higher in patients with lower cholesterol levels irrespective of the use of lipid-lowering medications (21). The reason for this paradox is now thought to be the prevalence of disease (at least pre-clinical disease) at baseline, which seems to affect the risk factor distribution (19). It is now generally accepted that this reverse association is most likely secondary to confounding factors, whereby patients with ESRD who are predisposed to worse outcome are already malnourished and have higher levels of systemic inflammation, and therefore are underweight and have low cholesterol level and hypotension (22). It is implied then that these risk factors continue to be pathophysiologically important and should be addressed aggressively in patients with CKD. Recent lipid-lowering trials that included patients with CKD have demonstrated that intensive lipid-lowering with statin medications was safe

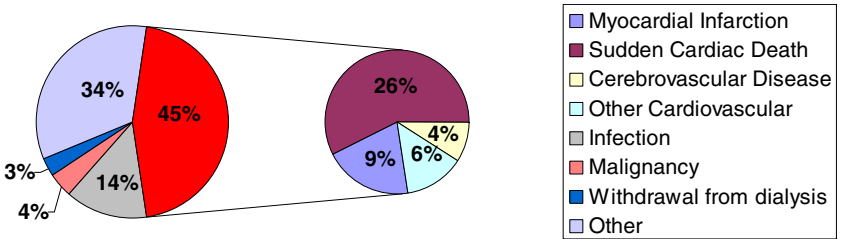

Figure 1 The Distribution of the Causes of Death in Patients With End-Stage Renal Disease in the U.S. Between 2003 and 2005

Cardiovascular disease accounts for 45% of all-cause mortality, including 26% from sudden cardiac death. Data are from the U.S. Renal Data System (10). In the figure, myocardial infarction refers to death that was labeled secondary to acute myocardial infarction or atherosclerotic heart disease, whereas sudden cardiac death refers to those labeled cardiac arrest or cardiac arrhythmias.

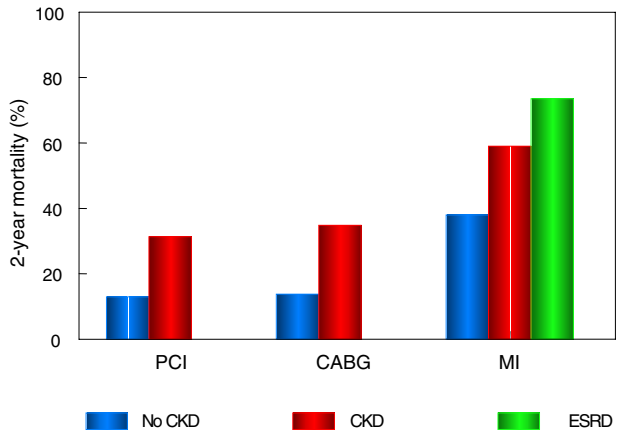

Figure 2 **Mortality Is Increased in CKD Patients After MI, PCI, and CABG**

The 2-year mortality of Medicare patients (age 66 or older on the day of the event or treatment) after receiving first percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) or after incident myocardial infarction (MI) between the years 2000 and 2005 is higher in chronic kidney disease (CKD) patients than non-CKD patients. The mortality of end-stage renal disease (ESRD) patients hospitalized for MI reaches 73% to 74% at 2 years. This figure is based on data from the U.S. Renal Data System. USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the U.S. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2008.

and perhaps even more effective in patients with CKD than in the general population (23). The management of dyslipidemia and hypertension in CKD have been recently reviewed elsewhere and will not be addressed further here, but suffice it to say that early and aggressive control of these risk factors is of paramount importance in improving outcomes (24,25). However, because these traditional risk factors fail to fully account for the elevated CV risk in CKD, there has been a great deal of interest lately in emerging risk factors that are unique to this population (inflammation and C-reactive protein [CRP], oxidative stress, nitric oxide availability, hyperhomocysteinemia, hyperphosphatemia, vascular calcification, increased vascular stiffness, LVH, anemia, endothelial dysfunction, volume overload and electrolyte imbalance, and timing of dialysis) (26), in the hope that modulation of these factors might improve outcomes in CKD patients (Fig. 3).

Systemic inflammation. Atherosclerosis is now considered an inflammatory condition (27). Serum levels of CRP, the prototypical acute phase reactant, have been shown to correlate well with the future development of CHD events in the general population (28). Levels of CRP have been shown to be particularly high when renal function declines to the level of ESRD, where as many as one-third to one-half of the patients have levels in the very-high-risk category, and CRP continues to be an excellent predictor of outcome in this population (29). A recent prospective study followed a cohort of more than 1,000 ESRD patients for a median of 2.5 years and reported that the highest (compared with lowest) tertile of CRP was associated with a 2-fold increased adjusted risk of sudden cardiac death (30). In this study, malnutrition (decreased serum albumin) was also associated with sudden death, but the traditional Framingham risk factors were not (30). The pathogenesis of the extreme elevation of CRP, which is as much as 10-fold higher in ESRD than in the normal population, is not completely understood; but several explanations have been proposed, including some that are directly related to the dialysis procedure itself and others that are linked to uremia, perhaps via increased oxidative stress (31). More recently, CRP has been shown to be elevated in patients with CKD at pre-dialysis stages (32) and that it is a powerful predictor of CV events in this population (33). The major stimulus for increased CRP release by the liver is interleukin-6, which can be produced by the intra-abdominal adipocytes, and thus the association between obesity and increased inflammation in CKD (34). The pathogenic nature of CRP is highly controversial, with a lack of clinical studies showing a direct cause-and-effect relationship and the failure of recent genetic studies to demonstrate a deleterious effect of CRP polymorphisms (35) but strong in vitro and animal data that suggest its direct involvement in the vascular disease process (36). Nonspecific inhibitors of inflammation like aspirin and statin medications are possible therapeutic options, and it seems prudent to avoid preventable causes of inflammation in ESRD patients by using ultra-pure dialysis fluid and more biocompatible dialysis membranes and minimizing infections of access sites in hemodialysis patients and peritonitis in peritoneal dialysis patients, but more specific therapies are currently unavailable (37).

Because inflammation is at the core of the CHD complications of CKD, it is prudent to recognize its interrelation with the other risk factors discussed here, because pathophysiologically it could be related to any or all of them. For example, CRP levels have been shown to be independently associated with anemia (38). Inflammatory mediators inhibit erythrocyte maturation, and inflammation results in the increased production in the liver of hepcidin, a factor that regulates the uptake of dietary iron and its mobilization from hepatic stores (39). Inflammation is also intimately linked to vascular calcification in patients with CKD (40). Furthermore, there is evidence that CRP might be related to progression of CKD, thereby closing the loop between inflammation, CKD, and atherosclerosis (41).

CKD mineral and bone disorder. CKD patients have alterations in their calcium and phosphorus homeostasis that ultimately result in bone disorders and soft tissue and vascular calcifications, a constellation of findings that has been dubbed CKD mineral and bone disorder (42). The intricate mechanisms that regulate these processes and their relation to renal function have been reviewed elsewhere (43). As a result of renal dysfunction, hyperphosphatemia mobilizes calcium from bone through the action of parathyroid hormone. In CKD, the chronic stimulation of the parathyroid gland results in its enlargement, and it ulti-

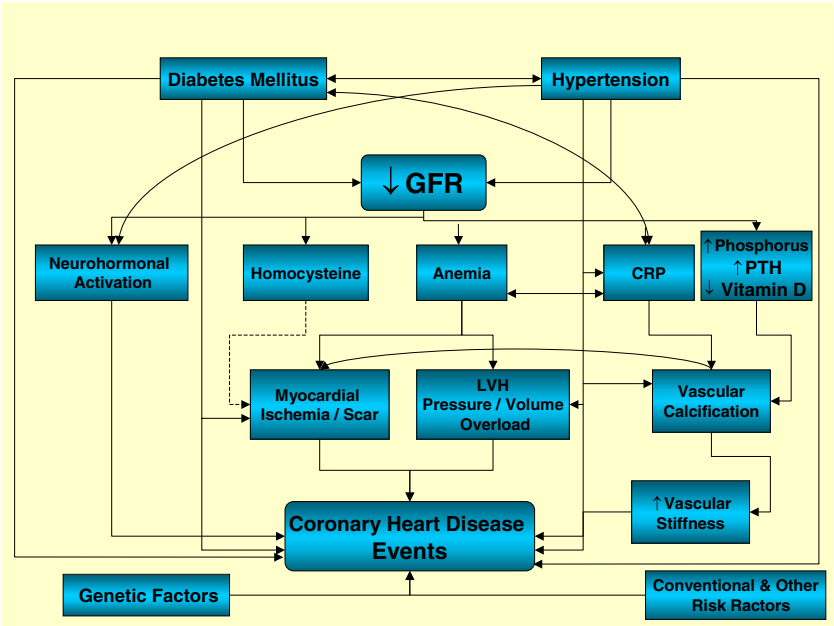

Figure 3 **The Association Between Chronic Kidney Disease and Cardiovascular Events**

The relationship between chronic kidney disease and cardiovascular events is complex and is mediated via multiple pathways that are further explained in the CHD Risk Factors section. "Other risk factors" refers to several risk factors that are not directly related to decreased glomerular filtration rate (GFR) per se but are more common in patients with chronic kidney disease. CRP = C-reactive protein; LVH = left ventricular hypertrophy; PTH = parathyroid hormone.

mately becomes independent from calcium levels (43). This situation is further exaggerated by the high prevalence of nutritional vitamin D deficiency in patients with CKD, thus resulting in an independent stimulus for increasing parathyroid hormone (44).

In 1998, Block et al. (45) analyzed national data from 2 large cohorts that included more than 6,000 ESRD patients and found that mortality risk rose sharply when the phosphorus level increased above 6.5 mg/dl. They further reported that, when the calcium-phosphorus product increased beyond 72 mg^2/dl^2, the risk of death increased by 34% as compared with the reference range of 42 to 52 mg^2/dl^2. Since then, higher phosphorus and calcium-phosphorus product have been more specifically linked to CHD and sudden cardiac deaths (46). Also, quantification of coronary artery calcification with electron-beam computed tomography revealed a direct association with the prevalence of CHD, MI, and angina (47), and the extent of atherosclerotic calcification by ultrasound was strongly associated with all-cause and CV mortality (48). Perhaps even more significantly, in ESRD, coronary artery calcification is almost universal even in the second decade of life, and it progresses quickly over time (49). This rapid progression has also been demonstrated in CKD patients not yet requiring dialysis (50).

The current understanding of atherosclerotic calcification in CKD is that it parallels bone mineralization and occurs in a highly regulated fashion that can be modulated at multiple levels. In the uremic milieu vascular smooth muscle cells are transformed into osteoblast-like cells that express phosphorus transporter Pit-1 and lay down an extracellular matrix capable of concentrating calcium and phosphorus, thereby allowing crystal nucleation to occur and subsequently full mineralization. From there, the progression of mineralization depends on the balance of pro-calcific factors such as the calcium-phosphorus product, parathyroid hormone, and bone morphogenetic protein-2 and inhibitory factors such as the protein fetuin-A, pyrophosphate, osteopontin, osteoprotegerin, and γ-carboxyglutamic acid protein (42,51,52). It is important to note that some of these factors have vascular effects that are distinct from their function in bone. For example, knockout mice for osteoprotegerin develop vascular calcification accompanied by severe osteoporosis (51). Also, because fetuin-A is a negative acute phase reactant, its levels drop with inflammation and it is inversely related to CRP, providing a link between inflammation and vascular calcification (51). Other important factors in the renal regulation of phosphorus that are thought to play important roles in vascular calcification include the bone-derived fibroblast growth factor-23 and a protein that is required for the conversion of its renal receptor, klotho (52).

Although patients with CKD have atherosclerotic calcifications in the vessel intima, they also have calcifications that involve the vascular media. This pattern of calcification (Monckeberg's sclerosis) has also been demonstrated to be a manifestation of accelerated atherosclerosis in patients with

CKD (42). Atherosclerotic calcification is associated with increased vascular stiffness of large capacitive elastic arteries, which contributes to the development and progression of hypertension and LVH. Increasing stiffness of the aorta, as measured by pulse-wave velocity, has been shown to be an independent predictor of CV mortality in this population (53). Even a simple assessment of vascular stiffness, such as pulse pressure, showed a strong association with mortality in a large cohort of more than 30,000 patients with ESRD (12% increase in 1-year mortality for every 10-mm Hg increase in pulse pressure) (54). In this study, although patients with lower systolic blood pressure had worse outcome, increasing pulse pressure within each category of blood pressure was associated with higher mortality (54).

Understanding the pathophysiology of vascular calcifications and its risk factors helps in its prevention and in halting its progression. Current clinical guidelines stress the importance of maintaining phosphorus and parathyroid hormones between strict levels and the use of non–calcium-containing phosphate binders (55). Controlling serum phosphorus levels in ESRD usually requires dietary phosphorus restriction, adequate dialysis, and the use of phosphate binders. Calcium-containing phosphate binders, such as calcium carbonate and calcium acetate, are adequate in controlling the serum phosphorus levels but—due to the high calcium load that they provide (especially with calcium carbonate)—increase the calcium-phosphorus product and stimulate vascular calcification (49).

Despite the apparent detrimental effect of vascular calcification in the CKD population, modulation of this process has been daunting. Because of the differences in calcium load, the studies with calcium carbonate should probably be analyzed separately from those with calcium acetate. The experience with noncalcium-containing phosphorus binders has produced conflicting results, and more studies are still needed (Online Table 1). Furthermore, although initial data suggested that sevelamer could slow atherosclerosis calcification by lowering low-density lipoprotein cholesterol, a recent analysis by McCullough et al. (42) demonstrated that low-density lipoprotein cholesterol reductions in randomized trials of statins and sevelamer did not influence the rate of progression of atherosclerotic calcification. There is some evidence that administration of vitamin D to suppress excessively elevated parathyroid hormone levels might be beneficial. Similarly, other treatments such as calcimimetics, bisphosphonates, and newer noncalcium-containing phosphorus binders (lanthanum carbonate) have been contemplated as potential treatments for vascular calcification (52).

Hyperhomocysteinemia. Almost all patients with ESRD are known to have moderately elevated homocysteine levels due to the decrease in its metabolism by the kidneys. In 1 analysis, elevated homocysteine and fibrinogen levels were able to explain almost 40% of the attributable mortality risk from CKD, and subjects with CKD and homocysteine levels <10 μmol/l had mortality rates similar to those with normal renal function (56). Multiple studies have examined the potential beneficial effect of lowering homocysteine levels with folate and vitamin B combinations, but only a few included patients with CKD (Online Table 2). The totality of evidence points to a strong association of plasma homocysteine with CV outcomes in the general population as well as in the ESRD population after adjustments for confounding factors. Trials that lowered homocysteine by administering folic acid and/or B vitamins have largely been unsuccessful in decreasing coronary events, although their effects on strokes is evident in some trials. In the U.S., enriched grain products have been fortified with folic acid since 1998, mainly because folic acid has been shown to reduce the incidence of neural tube defects in newborns, which resulted in a drop by 10% to 15% in the homocysteine concentration in the entire population (57). It has been suggested that this might have resulted in the decreased incidence of strokes (58).

Anemia. The prevalence of anemia increases with decreasing GFR (59). The pathogenesis of anemia in this setting is multifactorial, in part related to iron deficiency and hemolysis but mostly the result of relative erythropoietin deficiency (60). Anemia has been associated with increased mortality, MI, and coronary revascularization (61,62), but erythropoietin deficiency might also signal a reduction in bone marrow-derived endothelial progenitor cells, and therefore anemia might be a marker of decreased vascular repair in patients with CKD (63). Early trials have suggested that erythropoietin treatment might stimulate the proliferation of these progenitor cells in humans, and ongoing randomized trials are investigating the benefit of erythropoietin administration after MI (64,65). It is particularly interesting that, in the large cohort of more than 37,000 individuals of the National Kidney Foundation's Kidney Early Evaluation Program, anemia and GFR were independently associated with CV disease and survival (66).

Erythropoietin and its derivatives were first administered in patients with ESRD as a means of reducing packed red cell transfusions, but with the advent of observational studies suggesting improved outcomes, their use was liberalized to include patients with higher GFR, and hemoglobin targets were raised to normal values instead of the more conservative partial correction of anemia. This approach has received several setbacks from randomized studies over the last years. Besarab et al. (67) randomized ESRD patients with CHD or heart failure to erythropoietin injections to achieve and maintain hematocrit levels of either 42% (normal hematocrit) or 30% (conventional treatment). After a follow-up of 29 months, the study was stopped early due to concerns about safety. The primary end point of death or nonfatal MI was not different between the 2 groups, but there was a strong trend toward harm in the higher hematocrit group (relative risk: 1.3, 95% confidence interval: 0.9 to 1.9) (67). It is interesting to note that mortality rates decreased with increasing hematocrit levels in both groups, although it was higher for patients in the "normal hemat-

ocrit" versus the "conventional treatment" groups for any attained hematocrit, therefore suggesting that increasing hematocrit is not hazardous in and of itself but rather that erythropoietin and iron administration in high doses carry toxic side effects (67). More recently, 2 trials randomized patients with stages 3 and 4 CKD to partial versus complete correction of anemia with erythropoietin (68,69). Although both trials failed to show a benefit of achieving normal concentrations in this population, the results from Singh et al. (69) indicated a significantly higher risk of the primary outcome of death, MI, hospital stay for heart failure, or stroke in the normal hematocrit group, therefore calming the enthusiasm for the complete correction of anemia in CKD. A recent meta-analysis of all randomized trials has confirmed a higher risk of death in patients treated with higher hemoglobin concentrations in addition to an increased risk of uncontrolled hypertension and arteriovenous access thrombosis (70). Current guidelines endorse the administration of erythropoietin for the partial correction of anemia in CKD with a hemoglobin target of 11 to 12 g/dl and not >13 g/dl (71). Several ongoing trials will expand our understanding of anemia correction in CKD, including the TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) study, which is comparing hemoglobin targets of 13.0 g/dl versus >9.0 g/dl in diabetic patients with CKD stage 2 to 4 on a composite outcome of all-cause mortality and CV morbidity (72).

Cardiovascular Imaging in CKD

The presence of endothelial dysfunction, LVH, and volume and pressure overload in patients with CKD likely affects the accuracy of imaging studies in detecting CHD (Online Table 3). Artifacts unique to this group of patients should be recognized to avoid misinterpretation of the images (73). The use of contrast agents during coronary angiography and computed tomography expose the patients to the risk of contrast-induced acute kidney injury, despite strategies for reducing the risk of this complication, a topic that has been recently reviewed in the *Journal* (74). Several studies have examined the prognostic information provided by imaging modalities (Online Table 4). Patients with abnormal stress myocardial perfusion imaging (MPI) or 2-dimensional echocardiography have higher event rates than those with normal results (75). An abnormal perfusion pattern provides more powerful prognostic data than coronary angiography in the ESRD population (76). In our experience, patients with normal stress MPI and CKD have a higher event rate than that reported in patients without CKD (77). Hakeem et al. (78) found the annual cardiac death rate to be more than 3-fold higher in patients with normal MPI and CKD than in patients with normal MPI and no CKD (2.7% vs. 0.8%). The corresponding numbers in patients with abnormal MPI were much higher (9.5% and 4%, respectively). Furthermore, there was an inverse correlation between extent of perfusion abnormality and GFR (bigger defects in those with lower GFR).

Mark et al. (79) found 2 patterns of scarring by magnetic resonance imaging in patients with ESRD, discrete subendocardial and diffuse. Although both patterns correlated with increased LV mass, only subendocardial fibrosis was associated with CHD risk factors, LV systolic dysfunction, and severe CHD on angiography. The infrequent and yet serious complication of nephrogenic systemic fibrosis related to the use of gadolinium in patients with CKD would likely limit its future use (80).

An interesting study by Nishimura et al. (81), using a hybrid imaging method of perfusion and fatty acid metabolism, showed that patients with ESRD and a mismatch pattern (more severe metabolic than perfusion abnormality) had worse outcome than patients with normal or matched defects. This study suggests that subendocardial ischemia is prevalent in patients with CKD (who likely have LVH) and is prognostically important.

Finally, the high incidence of sudden death in patients with CKD suggests that imaging sympathetic innervation of the heart might provide useful information. In a dog model, innervation–perfusion mismatch was predictive of ventricular tachycardia (82). One would hope that nonimaging predictors of sudden death could be identified, but a recent study in heart failure patients showed that T-wave alternans did not predict sudden death (83). More recently, we have shown that patients with ESRD have lower heart rate response to adenosine infusion than patients with normal renal function, and ESRD patients with a blunted response had a higher mortality rate than ESRD patients with a higher heart rate response (84). The heart rate response to adenosine is thought to be due to sympathetic stimulation. Diabetes mellitus patients also have a blunted heart rate response, most likely due to sympathetic dennervation (85).

LV structural changes are already present in patients with moderate CKD, and they become more prevalent in ESRD (86,87). The presence of LVH is a strong predictor of adverse outcomes, independent of conventional risk factors (Online Table 5). LV ejection fraction (EF) is an even more important predictor of outcome in patients with than without CKD (75,88,89). In 1 study, patients with LVEF ≤40% were twice as likely to die as compared with those with normal LVEF even after adjustment for comorbid conditions (for every 1% decrease in EF the risk of death increased by 2.7%) (Fig. 4) (75).

Revascularization in Patients With CKD

Patients with CKD are usually excluded from prospective randomized controlled trials and are often denied coronary angiography and PCI for fear of worsening renal function. The published studies on patients with CKD who undergo revascularization are usually small, single-centered, and retrospective.

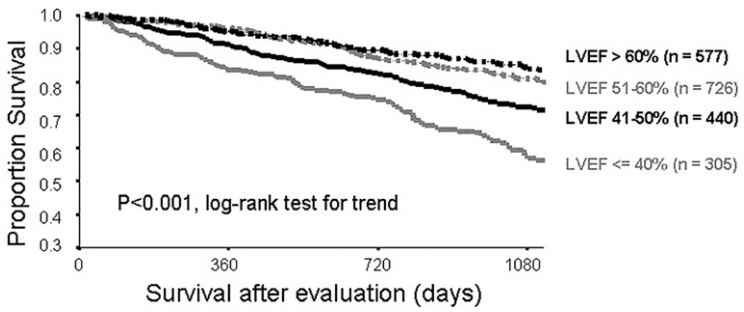

Figure 4 **Survival by Categories of LVEF**

Survival of end-stage renal disease patients evaluated for renal transplantation according to categories of left ventricular ejection fraction (LVEF). There is a stepwise increase in mortality for decreasing ejection fraction. Reproduced with permission from Hage et al. (75).

Percutaneous coronary revascularization. Multiple studies have evaluated the effect of CKD on short- and long-term outcomes after PCI, and these are reviewed in Online Table 6. In general, CKD is a strong predictor of mortality and major adverse cardiac events in a dose-dependent fashion during and after PCI. Despite similar angiographic success rates, procedural and clinical success rates are lower in patients with CKD, driven by higher incidence of death and/or MI, and rates of bleeding and vascular complications are higher. It is important to note that in many of these studies, CKD patients had a higher frequency of risk factors that predisposed them to worse outcome, such as left main, vein graft, or multivessel disease; complex, heavily calcified, or ostial lesions; acute coronary syndrome presentation; DM, hypertension, prior MI, PCI, or CABG; and acute renal failure after PCI. The predictive value of GFR for in-hospital and long-term mortality is irrespective of the presence or absence of DM. The implantation of newer PCI devices such as drug-eluting stents has not negated the detrimental effect of CKD.

Even in acute coronary syndrome CKD is an independent predictor of in-hospital and long-term mortality after PCI (Online Table 6). In 1 large cohort, mortality rates increased incrementally for every 10-ml/min decline in baseline GFR. Contrast-induced acute kidney injury was almost 3-fold more common in patients with a baseline GFR $\leq$60 ml/min/1.73 m^3, and it resulted in relative risks of 13.8 for 30-day mortality and 7.4 for 1-year mortality (90).

The optimal anticoagulation strategy and/or glycoprotein IIb/IIIa inhibitor to be used in CKD patients is not well-defined. In the ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) trial, CKD patients derived a greater magnitude of the treatment effect without an increase in bleeding risk (91). In a study of abciximab during PCI, CKD was associated with increased bleeding risk after PCI in a dose dependent fashion, but the interaction between GFR and major bleeding was of borderline statistical significance (odds ratio: 1.18, p = 0.06) (92). In a meta-analysis of 3 randomized trials (n = 5,035) comparing bivalirudin with heparin during PCI, adverse ischemic and bleeding events increased with decreasing GFR. Bivalirudin was more effective than heparin in decreasing the ischemic and bleeding complications within each stratum of renal impairment (93). The GFR and anemia independently and in combination predicted 30-day and 3-year mortality in several large trials that evaluated the use of abciximab in PCI (94).

Patients with CKD and especially ESRD have higher in-stent restenosis rates with both bare-metal and drug-eluting stents (Online Table 6). This has been attributed to higher incidences of DM, diffuse atherosclerosis, and calcifications in addition to enhanced oxidative stress and granulocyte activation, which increase the risk of in-stent restenosis (95,96).

In summary, the use of stents and particularly drug-eluting stents has decreased the rates of in-stent restenosis, but these rates remain higher than in patients with normal renal function. Although ESRD patients have higher rates of restenosis and major adverse cardiac events, they tend to derive the most benefit from the use of drug-eluting stents compared with bare-metal stents.

Surgical revascularization. The same factors that put CKD patients at increased risk of complications with PCI also put them at increased risk from CABG. Additionally, the presence of ascending aortic calcified plaques increases the operative risk and might require operative modifications (such as use of in situ grafts to avoid aortic manipulations) (97). In patients undergoing CABG, CKD increases bleeding and the risk of blood transfusion, low output syndrome, and requirement for post-operative dialysis and prolongs intensive care stay (98,99).

A sample of studies evaluating the relationship of ESRD with outcome after CABG is reviewed in Online Table 7. Earlier retrospective studies suggested an increased morbidity and mortality in ESRD, and this has now been confirmed in larger cohorts. There are some indications that early outcomes after CABG in ESRD might have improved recently. In 1 retrospective multicenter study, the 30-day

mortality rates of CABG for ESRD patients decreased from 28% in 1989 to 1993 to 7% in 2000 to 2003, although this did not translate into improved long-term prognosis (100).

Multiple studies have now shown that even milder forms of CKD are associated with worse in-hospital and long-term outcomes (Online Table 8). When the outcome of almost half a million patients who underwent isolated CABG was examined, operative mortality increased with declining GFR, from 1.3% for those with normal renal function to 9.3% for patients with severe CKD (101). Improved early outcomes can be achieved with intensive perioperative dialysis and improved late outcomes with extensive usage of arterial grafts (102,103).

Although ESRD patients have worse outcomes after CABG than patients with normal GFR, CABG is associated with improved angina and functional status in patients with ESRD (104–106). Similarly, patients with severe CKD experience more improvement in mental health scores than those without severe CKD, although they might have worse physical function scores (107).

Off-pump CABG decreases invasiveness and allows quicker recovery, and because it avoids cardiopulmonary bypass, it could be useful in patients with CKD who often have heavily calcified aortas. Off-pump CABG in CKD and ESRD patients was compared with on-pump CABG in several studies and showed comparable early and late outcomes in most studies (Online Table 9). Despite some justified concerns, complete revascularization is possible with this strategy, albeit not always achieved, and incomplete revascularization in this population has been linked to lower survival rates. The use of off-pump CABG in patients with CKD has been associated with less hematocrit drop and blood product use; a lower catabolic rate; fewer dialysis requirements after surgery; shorter post-operative ventilation time, intensive care unit stay, and hospital stay length; lower medical cost than on-pump CABG; and in some reports, even lower mortality.

Percutaneous versus surgical revascularization. Several studies compared PCI with surgical revascularization in CKD patients (Online Table 10). Earlier studies showed a long-term advantage of CABG compared with balloon angioplasty due mainly to higher restenosis rate with angioplasty. Survival rates were not significantly different, although patients who underwent CABG had more extensive CHD. The outcomes of PCI have significantly improved with the introduction of newer technologies, although a comparison between the use of drug-eluting stents and CABG in patients with CKD has not yet been performed. Nevertheless, the short- and long-term outcomes of these patients remain worse than patients without CKD who undergo PCI or CABG.

Revascularization versus medical therapy. Few studies compared medical therapy with PCI or CABG in CKD patients (Online Table 11). An analysis from the Duke database showed that CABG was associated with a survival benefit among patients with both normal renal function and CKD compared with medical management. Compared with PCI, CABG was only associated with survival benefit in patients with severe CKD (108). Compared with medical management, PCI was associated with a survival benefit among patients with normal and mildly and moderately impaired renal function but not in patients with severe CKD (108). Another study showed that, compared with medical therapy, CABG was associated with better survival in all categories of GFR, whereas PCI was associated with better survival in non-CKD and in ESRD patients (109). The effect of PCI, CABG, or medical therapy alone on the long-term survival of patients with CKD presenting with acute coronary syndrome was studied in 4,758 patients. Those with severe CKD and not on dialysis had the worst survival. Among patients with significant renal dysfunction, treatment with PCI conferred better survival compared with CABG or medical therapy (110).

The value of revascularization in asymptomatic patients with CKD is less well understood. The ESRD patients who are evaluated for renal transplantation (RT) undergo rigorous evaluation to exclude significant CHD according to the accepted guidelines (111). We examined the evaluation of 3,698 patients with ESRD considered for RT over a 4-year period. Stress MPI was performed on 60% of these patients, due to the presence of risk factors, and coronary angiography was performed on only 7%. During the follow-up of 30 ± 15 months, 17% of the patients died. The presence and severity of CHD by angiography was not predictive of survival, and coronary revascularization did not impact survival except in patients with 3-vessel disease. Importantly, of the entire population, 3-vessel disease was present in only 2% by angiography, thereby limiting the impact of revascularization on survival in this otherwise high-risk population (75).

RT

RT is the ultimate treatment for patients with ESRD; RT results in better survival and better quality of life at a lower overall cost than dialysis (112,113). However, CV disease remains the major cause of death after RT, and RT recipients continue to have a higher incidence of fatal and nonfatal CV events than the general population (10).

The effect of traditional CHD risk factors is presumably similar in RT recipients and the general population, but RT recipients carry a unique baggage of these risk factors. Although, at least in theory, the improvement of GFR after RT should favorably affect blood pressure, the prevalence of hypertension is almost universal in RT recipients (114). This has been linked to immunosuppressant medications such as glucocorticoids and calcineurin inhibitors, and therefore this excess risk is potentially modifiable with more modern regimens (115). These same medications (in addition to sirolimus) have been also associated with dyslipidemia, which is prevalent in more than one-half of RT recipients (114). Treatment with statins in a multicenter,

randomized, double-blind trial in more than 2,000 RT recipients lowered low-density lipoprotein cholesterol and decreased cardiac death and nonfatal MI by one-third over a mean follow-up of 5 years, although the primary combined outcome of cardiac death, nonfatal MI, or coronary revascularization was not different between the treatment and the control groups (116). Notably, the use of fluvastatin in this patient population was demonstrated to be safe, with side effect profile and discontinuation rate similar to placebo. Although this study is in essence a negative study, because the reduction of the primary end point by statin treatment did not meet statistical significance, the consistency of benefit by treatment across multiple subgroups in secondary end points (117) and the similarity of benefits of treatment with statins to other populations combined with the safety outcome in this population resulted in the wide endorsement of this therapy for RT recipients. Clinical practice guidelines consider RT recipients to be CHD-risk equivalent and recommend evaluation for dyslipidemia at presentation, after any change in status (such as a change in immunosuppressive medications) and annually. Treatment recommendations otherwise resemble those in the general population and similarly suggest that initial drug therapy should be with a statin but emphasize the interaction of these medications with immunosuppressive agents (118). Given the tendency of glucocorticoids and calcineurin inhibitors to induce hyperglycemia, the high incidence of post-transplant DM is not surprising (119). This is compounded by the surprisingly high prevalence of obesity at the time of RT, with 60% of recipients being overweight or obese (120). Furthermore, DM has been shown to dramatically increase CHD events as well as mortality after RT, perhaps even more so than in the general population (119).

Many nontraditional risk factors that exacerbate CV risk in patients with CKD and ESRD also operate after RT. Renal allograft dysfunction, proteinuria, anemia, chronic inflammation, hyperhomocysteinemia, hypercoagulation, and LVH have all been linked to CHD risk after RT (114). However, there are also RT-specific risk factors that have been linked to events. For example, prolonged dialysis before RT has been associated with increased mortality after transplantation, perhaps due to the longer exposure to dialysis-related conditions that accelerate CHD (121). Furthermore, mortality and CHD event rates are higher for deceased- than living-donor RT (10). A recent analysis has suggested that these transplant-specific risk factors might in fact interact with the traditional risk factors to modify significantly the risk of CHD events (121).

Aside from affecting risk factors, morbidity, and mortality, RT also favorably affects LV morphology and function (122,123). A decreased EF in ESRD patients continues to predict mortality and the occurrence of CV events even after RT (124). Multiple case reports and at least 1 case series documents an improvement in EF after RT. Wali et al. (122) followed 103 patients who underwent RT with an LVEF <40%. After transplantation, 70% had an improved EF, and an EF >50% alone was a significant marker for lower odds of death or hospital stays.

Conclusions

CKD is a serious health problem worldwide that leads to devastating CHD morbidity and mortality. The mechanisms that lead to these events are diverse and far more complicated than in patients with normal renal function. CHD is uniquely different in CKD from that in the general population, with earlier onset in life, more rapid progression, a closer association with calcification, increased vascular stiffness, resistance to statin medications, higher complications with percutaneous and surgical revascularization, and higher rates of sudden death. This review offers a glimpse of the potential mechanisms of increased CHD risk and current status of treatment options. If we succeed in getting our readers interested in this subject, then we have achieved our goals.

Reprint requests and correspondence: Dr. Fadi G. Hage, Zeigler Research Building 1024, 1530 3rd Avenue South, Birmingham, Alabama 35294-0006. E-mail: fadihage@uab.edu.

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Key Words: chronic kidney disease ■ coronary heart disease ■ imaging ■ revascularization.

APPENDIX

For supplementary tables, please see the online version of this article.